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Regioselective synthesis of 1-allyl- and 1-arylmethyl uracil and thymine derivatives

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Abstract—2,4-Bis(trimethylsiloxy) pyrimidines **1** with allyl halides and arylmethyl halides in 1,2-dichloroethane in the presence of I_2 regioselectively provide 1-allyl-/1-arylmethyl-uracil and thymine derivatives. The secondary aryl alkyl and diaryl methyl halides with **1** provide chiral 1-arylalkyl/1-(diarylmethyl) uracil/thymine derivatives. The procedure has been extended to the synthesis of fluorescent uracil/thymine derivatives.

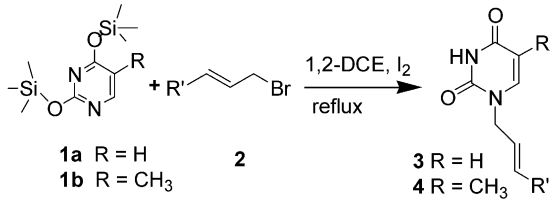
1. Introduction

The nucleoside analogues have been cornerstones for chemotherapy of cancer and viral diseases.[1] However, the clinical toxicities arising due to the various reasons, limited uptake, high susceptibility to catabolism and rapid emergence of resistance towards virus or cancer cells has led to diversification to non-nucleoside inhibitors (NNIs).[2] The NNIs do not interact at the catalytic site of the enzyme but interact in a hydrophobic pocket through π–π or π–HC interactions.[3] These feeble interactions through their multiple interacting features become significant structural force to inhibit the functioning of enzyme.[4] The role of π–π interactions is emphasized in the development of new multi drug resistance modulators[5] as well as in the interactions of olefinic and arene moieties of aromatic amino acids (phenylalanine, tyrosine, tryptophane, which constitute ~8% of the known protein sequence) with the most prevalent biological cations[6,7] Na^+ and K^+. Distinctly, in NNIs the phosphorylation is not an obligatory step for their ability to block the DNA replication and cell growth.

This role of arene moieties and π-bonds in effective participation in biological systems has drawn the attention to the development of synthetic procedures for arene/allyl substituted nucleic bases—uracil and thymine, etc. Such 1-allyl-and 1-arylmethyl nucleobases can prove vital synthons for the development of new drug molecules. However, their synthesis has found scarce attention[8] and available methodologies through base mediated allylation of free nucleic bases[9–11] or Lewis acid catalysed allylation of 2,4-bis(trimethylsiloxy)pyrimidines[2b] suffer with non-regioselectivity of reactions at N-1 and N-3 and poor yields.

2. Results and discussion

In the present manuscript, a simple and general approach for the synthesis of pyrimidine-2,4-diones bearing allyl, arylmethyl, alkyl aryl methyl, diarylmethyl substituents at N-1 is presented (Scheme 1).



Scheme 1.

Refluxing of a solution of **1a**[12] with allyl bromide (1.2 equiv) in 1,2-dichloroethane in the presence of I_2 (5 mol%, catalyst), after usual reaction workup regioselectively provides **3a** (93%), mp 109 °C (lit.[11] mp 110 °C)., M^+ (*m/z*) 152. The structure of **3a** was confirmed by the presence of H-5 and H-6 doublets at δ 5.74 and 7.16 and one 2H doublet at δ 4.38 due to NCH_2 along with the olefinic protons and exchangeable NH (δ 9.68) in its ^1H NMR spectrum. Similarly, **1b** with allyl bromide in 1,2-DCE and I_2 gave **4a** (68%), mp 77 °C, M^+ *m/z* 166. On

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using benzene as solvent, the yields of **3a** (54%) and **4a** (52%) were lowered and in solvents like CH_3CN and $CHCl_3$ the allylation product was not formed. In these reactions, the formation of 1,3-diallyluracil/thymine was not observed even in traces (tlc). Similarly, **1a/1b**[12] with cinnamyl bromide, ethyl 4-bromocrotonate and 1-bromo-2-butene provide respective compounds **3b–d** and **4b–d** in 64–85% yields. (Table 1, entries 2–8).

Table 1. Synthesis of 1-allyluracil and 1-allylthymine derivatives

S. no	R in **1**	R′ in **2/3/4**	Reaction time (h)	Product (yield %)
1	H	H	24	**3a** (93)
2	H	CH_3	24	**3b** (85)
3	H	C_6H_5	36	**3c** (75)
4	H	$CO_2C_2H_5$	36	**3d** (70)
5	CH_3	H	24	**4a** (68)
6	CH_3	CH_3	36	**4b** (67)
7	CH_3	C_6H_5	36	**4c** (68)
8	CH_3	$CO_2C_2H_5$	36	**4d** (64)

The earlier reported Pd (0) catalyzed allylation of uracil and derivatives performed in DMSO[10] or organic aqueous medium (H_2O–CH_3CN) or (H_2O–THF) in the presence of base DBU, and water soluble sulphonated triphenylphosphine P(C_6H_4-m-$SO_3Na)_3$,[11] gave mixture of 1-allyl- and 1,3-diallyluracil derivatives and in general, large excess (4–8 equiv) of the allylating reagent has to be used.

Therefore, the present procedure which requires only equivalent amounts of expensive allylating reagent and provides regioselectively 1-allyl products irrespective of the nature of allyl halide, provides a general and economical procedure for the synthesis of 1-allyl uracil/thymine derivatives.

The presence of benzyl group on the nucleobase due to its higher participation in cation-π and π–π interactions can provide more opportunities for their interactions in biological systems.[13] Further, it is possible to tune these interactions by the presence of electron-withdrawing or electron-donating groups on the aryl rings and the bulk of the substituents. So, the above methodology was extended for the synthesis of 1-(arylmethyl) uracil derivatives.

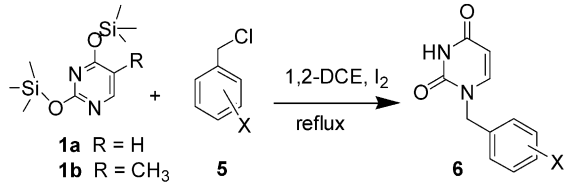
2,4-Bis(trimethylsiloxy) pyrimidine (**1a**) on refluxing with phenylmethyl chloride in 1,2-dichloroethane gave 1-phenylmethyluracil **6a** (87%) mp 160 °C, M^+ *m/z* 203 (Table 2, entry 1) (Scheme 2). Similarly, **1a** and **1b** with substituted aryl-methyl halides provided respective 1-arylmethyluracil/thymine derivatives **6b–6j** in 68–87% yields. In all these cases, the assignment of H-5 and H-6 signals was made on the basis of decoupling of H-5 which appeared at δ 5.54–6.10. It is observed that in cases of **6a–6g** H-6 is present at δ 7.14–7.20 and in **6h**, the C-6H signal is shifted considerably upfield (δ 6.66) which may be attributed to the increased shielding by phenyl ring to H-6 due to the presence of three electron-donating methyl groups at the phenyl moiety.

The reactions of **1** with secondary alkyl halides would provide an opportunity to synthesize the chiral uracil molecules. The role of 4-chlorophenyl methyl group in cetirizine defines the importance of such moieties and the present approach can provide synthons for developing uracil based isosteres of cetirizine.[14] **1** on reaction with secondary chiral and achiral halides provided respective 1-substituted uracil derivatives **9** in 65–80% yields (Table 3, Scheme 3).

Table 2. Synthesis of 1-arylmethyluracil and 1-arylmethylthymine derivatives

S. no	R in **1** and **6**	X in **5/6**	Time (h)	Yield (%)
1	H	H	24	**6a** (87)
2	H	2-Cl[a]	48	**6b** (74)
3	H	3-Cl	72	**6c** (81)
4	H	4-Cl	48	**6d** (81)
5	H	4-F	48	**6e** (70)
6	H	2,4-diCl[a]	36	**6f** (69)
7	H	2-NO_2	36	**6g** (68)
8	H	2,4,6-triMe	36	**6h** (62)
9	CH_3	2-Cl	36	**6i** (87)
10	CH_3	2,4-diCl	36	**6j** (85)

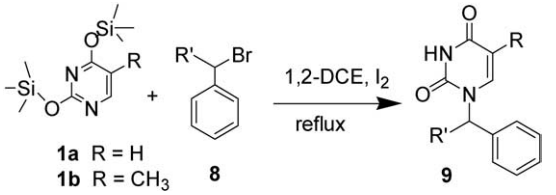
[a] In these cases 1,3-bis(2-chlorophenylmethyl)uracil (**7a**) and 1,3-bis(2,4-dichlorophenylmethyl)uracil (**7b**) derivatives were isolated in <3% yields.



Scheme 2.

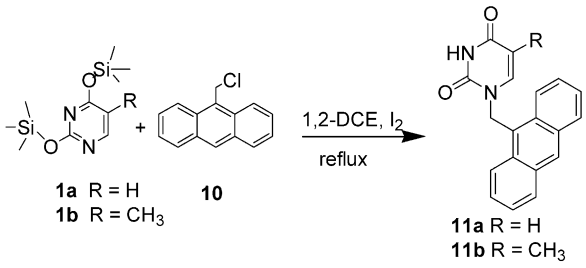
Table 3. Synthesis of 1-diarylalkyl/1-alkyaryl uracil/thymine derivatives

S. no.	R	R′	Reaction time (h)	Yield (%)
1	H	CH_3	36	**9a** (69)
2	H	C_6H_5	36	**9b** (70)
3	H	4-ClC_6H_5	48	**9c** (65)
4	CH_3	CH_3	36	**9d** (78)
5	CH_3	C_6H_5	36	**9e** (80)



Scheme 3.

The presence of a fluorescent moiety[15] on the pyrimidine base could provide a handle to study the interactions of nucleobases through fluorescence measurements. **1a/1b** on reaction with 9-anthracenylmethyl chloride **10** provided **11a** (84%), mp 240 °C, M^+ (*m/z*) 302 and **11b** (80%), mp 260 °C, M^+ *m/z* 316 (Scheme 4). An upfield shift of C-6H ((δ 6.86) from their normal position, i.e. δ 7.14 clearly showed the shielding of H-6 by anthracene moiety. Compounds **11** in their UV–vis spectra showed λ_{max} at 387, 367, 349, 333 nm and their fluorescence spectra gave



Scheme 4.

λ_{max} at 412, 390, 363 nm, the characteristic spectral features of anthracene moiety. On excitation at λ_{max} 365 nm, the solutions of compounds **11** in acetonitrile gave $\phi_f = 0.23 \pm 0.01$.

3. Conclusions

2,4-Bis(trimethylsiloxy)pyrimidines **1** on refluxing with allyl halides and primary and secondary arylalkyl halides provide a simple and general methodology for 1-allyl- and 1-arylmethyl- and 1-diarylmethyl- uracil/thymine derivatives.

4. Experimental

4.1. General

The melting points were determined in capillaries and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC 200 MHz and JEOL JNM 300 MHz machines. High resolution mass spectra were recorded on micromass (using GC–MS).

4.2. General procedure for the preparation of 1-substituted uracil/thymine derivatives

A solution of 2,4-bis-(trimethylsiloxy)pyrimidine (0.01 mol), allyl/arylmethyl/arylalkyl halide (0.012 mol) and I_2 (20 mg) in 1,2-DCE (20 ml) was refluxed. After completion of the reaction (tlc), the cooled reaction mixture was treated with ethanol (10 ml). The solid separated was filtered and recrystallized from ethanol or acetonitrile to get pure 1-substituted uracil/thymine derivative. In case of reactions with 2-chloro- and 2,4-dichloroarylmethyl chloride, the respective 1,3-bis (arylmethyl)uracils were isolated from filtrate by column chromatography using ethyl acetate and hexane mixtures as eluents.

4.2.1. 1-Allyl-1*H*-pyrimidine-2,4-dione (3a). 93%; White solid, mp 109 °C (ethanol) (lit.[11] mp 110 °C); ^{1}H NMR ($CDCl_3$,): δ 4.38 (d, 2H, $J=7.0$ Hz, NCH_2), 5.22–5.34 (m, 2H, $=CH_2$), 5.74 (1H, d, $J=7.8$ Hz, H-5), 5.81–5.95 (1H, m, =CH), 7.16 (1H, d, $J=7.8$ Hz, H-6), 9.68 (1H, bs, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 47.24 (−ve, CH_2), 99.37 (+ve, CH-5), 115.71 (−ve, $=CH_2$), 130.76 (+ve, CH), 143.18 (+ve, CH-6), 148.83 (ab, C), 161.87 (ab, C); ν_{max} (KBr) cm^{-1}: 1693 (C=O), 3566 (NH); HRMS: found 152.0588, $C_7H_8N_2O_2$ requires 152.0586.

4.2.2. 1-But-2-enyl-1*H*-pyrimidine-2,4-dione (3b). 85%; White solid, mp 88 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 1.76 (3H, d, $J=6.4$ Hz, CH_3), 4.27 (2H, d, $J=6.2$ Hz, NCH_2), 5.46–5.57 (1H, m, =CH), 5.71 (1H, d, $J=8$ Hz, H-5), 5.73–5.83 (1H, m, =CH), 7.18 (1H, d, $J=8$ Hz, H-6), 9.58 (1H, bs, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT) ($CDCl_3$): δ 17.65 (+ve, CH_3), 49.39 (−ve, CH_2), 102.16 (+ve, CH-5), 124.20 (+ve, =CH), 131.74 (+ve, =CH), 143.78 (+ve, CH-6), 151.02 (ab, C), 164.28 (ab, C); ν_{max} (KBr) cm^{-1}: 1683 (C=O), 3486 (NH); HRMS found: 166.0745, $C_8H_{10}N_2O_2$ requires 166.0742.

4.2.3. 1-(3-Phenyl-allyl)-1*H*-pyrimidine-2,4-dione (3c). 75%; Light yellow crystals, mp 170 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 4.52 (2H, d, $J=6.2$ Hz, NCH_2), 5.75 (1H, d, $J=8.0$ Hz, H-5), 6.23 (1H, dt, $J_1=6.2$ Hz, $J_2=16$ Hz, =CH), 6.65 (1H, d, $J=16$ Hz, =CH), 7.24 (1H, d, $J=8.0$ Hz, H-6), 7.26–7.38 (5H, m, ArH), 8.77 (1H, b, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 47.52 (−ve, CH_2), 100.12 (+ve, CH-5), 121.88 (+ve, CH), 124.82 (+ve, ArCH), 126.34 (+ve, =CH), 126.94 (+ve, ArCH), 131.65 (+ve, =CH), 134.25 (ab, C),143.05 (+ve, CH-6), 149.40 (ab, C), 162.40 (ab, C); ν_{max} (KBr) (cm^{-1}): 1685 (C=O), 3480 (NH); HRMS found: 228.0898, $C_{13}H_{12}N_2O_2$ requires 228.0899.

4.2.4. 1-(3-Ethoxycarbonyl-allyl)-1*H*-pyrimidine-2,4-dione (3d). 70%; White solid, mp 110 °C (ethanol); ^{1}H NMR ($CDCl_3$,): δ 1.28 (3H, t, $J=7.2$ Hz, CH_3), 4.23 (2H, q, $J=7.2$ Hz, OCH_2), 4.49 (2H, d, $J=6.0$ Hz, NCH_2), 5.76 (1H, d, $J=8.0$ Hz, H-5), 5.87 (1H, d, $J=16$ Hz, =CH), 6.89 (1H, dt, $J_1=6.0$ Hz, $J_2=16$ Hz, =CH), 7.11 (d, $J=8.0$ Hz, H-6), 9.43 (1H, bs, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 14.09 (+ve, CH_3), 48.24 (−ve, CH_2), 60.83 (−ve, CH_2), 103.01 (+ve, CH-5), 124.02 (+ve, =CH), 140.14 (+ve, =CH), 143.70 (+ve, CH-6) 150.64 (ab, C), 163.80 (ab, C), 165.16 (ab, C). HRMS found: 224.0798, $C_{10}H_{12}N_2O_4$ requires 224.0797.

4.2.5. 1-Allyl-5-methyl-1*H*-pyrimidine-2,4-dione (4a). 68%; White solid, mp 77 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 1.90 (3H, s, CH_3). 4.32 (2H, d, $J=6.8$ Hz, NCH_2), 5.21–5.33 (2H, m, $=CH_2$), 5.79–5.88 (1H, m, =CH), 6.95 (1H, s, H-6), 8.35 (1H, s, NH, exchanges with D_2O.); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 12.25 (+ve, CH_3), 49.70 (−ve, CH_2), 110.92 (ab, C-5), 119.08 (−ve, $=CH_2$), 131.70 (+ve, =CH), 141.21 (+ve, CH-6), 150.99 (ab, C), 164.47 (ab, C); HRMS found: 166.0743, $C_8H_{10}N_2O_2$ requires 166.0742.

4.2.6. 1-But-2-enyl-5-methyl-1*H*-pyrimidine-2,4-dione (4b). 67%; White solid, mp 110 °C (ethanol); ^{1}H NMR ($CDCl_3$,): δ 1.74(3H, d, $J=6.4$ Hz, CH_3), 1.93 (3H, s, CH_3), 4.32 (2H, dd, $J_1=7.0$ Hz, $J_2=24$ Hz NCH_2), 5.31–5.47 (1H, m, =CH), 5.65–5.83 (1H, m, =CH), 6.98 (1H, s, H-6), 8.68 (1H, bs, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 12.24 (+ve, CH_3), 17.64 (+ve, CH_3), 49.15 (−ve, CH_2), 110.55 (ab, C-5), 124.55 (+ve, =CH), 131.23 (+ve, =CH), 139.76 (+ve, CH-6), 151.49

(ab, C), 164.65 (ab, C); HRMS found: 180.0898 $C_9H_{12}N_2O_2$ requires 180.0899.

4.2.7. 1-(3-Phenyl-allyl)-5-methyl-1*H*-pyrimidine-2,4-dione (4c). 68%; Light yellow crystals, mp 208 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 1.86 (3H, s, CH_3), 4.49 (d, J=6.4 Hz, 2H, NCH_2), 6.24 (1H, dt, J_1=6.4 Hz, J_2=15.8 Hz, =CH), 6.62 (1H, d, J=15.8 Hz, =CH), 7.04 (1H, s, H-6), 7.21–7.34 (5H, m, ArH), 8.68 (1H, bs, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 11.83 (+ve, CH_3), 48.74 (−ve, CH_2), 109.94 (ab, C-5), 122.75 (+ve, ArCH), 126.03 (+ve, ArCH), 127.61 (+ve, =CH), 128.13 (+ve, ArCH), 133.29 (+ve, =CH), 135.45 (ab, C), 139.63 (+ve, CH-6), 150.82 (ab, C), 164.42 (ab, C); HRMS found: 241.1051 $C_{14}H_{14}N_2O_2$ requires 241.1055.

4.2.8. 1-(3-Ethoxycarbonyl-allyl)-5-methyl-1*H*-pyrimidine-2,4-dione (4d). 64%; White solid, mp 105 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 1.30 (3H, t, J=7.2 Hz, CH_3), 1.92 (3H, s, CH_3), 4.20 (2H, q, J=7.2 Hz, OCH_2), 4.48 (2H, dd, J_1=5.2 Hz, J_2=1.8 Hz, NCH_2), 5.91 (1H, dt, J_1=1.8 Hz, J_2=16 Hz, =CH), 6.88 (1H, dt, J_1=5.2 Hz, J_2=16 Hz, =CH), 6.96 (1H, s, H-6), 8.50 (1H, bs, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 12.18 (+ve, CH_3), 14.05 (+ve, CH_3), 50.44 (−ve, CH_2), 60.67 (−ve, CH_2), 110.99 (ab, C-5), 123.69 (+ve, CH), 139.58 (+ve, CH), 140.58 (+ve, CH), 150.82 (ab, C), 164.57 (ab, C), 165.45 (ab, C); HRMS found: 238.0957 $C_{11}H_{14}N_2O_4$ requires 238.0954.

4.2.9. 1-Benzyl-1*H*-pyrimidine-2,4-dione (6a). 87%; White solid, mp 160 °C (ethanol), ^{1}H NMR ($CDCl_3$): δ 4.94 (2H, NCH_2), 5.72 (1H, d, J=7.9 Hz, H-5), 7.17 (1H, d, J=7.9 Hz, H-6), 7.31–7.42 (5H, m, ArH), 9.01 (1H, bs, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$+TFA): δ 52.30 (−ve, CH_2), 102.67 (+ve, CH-5), 128.16 (+ve, ArCH), 129.17 (+ve, ArCH), 129.37 (+ve, ArCH), 133.48 (ab, ArC), 146.04 (+ve, CH-6), 151.94 (ab, C), 166.19 (ab, C); HRMS found: 202.0741, $C_{11}H_{10}N_2O_2$ requires 202.0742.

4.2.10. 1-(2-Chlorobenzyl)-1*H*-pyrimidine-2,4-dione (6b). 74%; White solid, mp 210 °C (ethanol); ^{1}H NMR ($CDCl_3$+TFA): δ 5.11 (2H, s, NCH_2), 6.04 (1H, d, J=7.8 Hz, H-5), 7.25–7.47 (4H, m, ArH), 7.54 (1H, d, J=7.8 Hz, H-6); ^{13}C (normal/DEPT-135) ($CDCl_3$+TFA): δ 49.98 (−ve, CH_2), 102.28 (+ve, CH-5), 127.70 (+ve, ArCH), 130.23 (+ve, ArCH), 130.74 (+ve, ArCH), 131.09 (ab, ArC), 131.34 (+ve, ArCH), 133.86 (ab, ArC), 146.23(+ve, CH-6), 151.66 (ab, C), 166.17 (ab, C); HRMS found: 236.0358 $C_{11}H_9^{35}ClN_2O_2$ requires 236.0353. found 238.0327 $C_{11}H_9^{37}ClN_2O_2$ requires 238.0323.

4.2.11. 1-(3-Chlorobenzyl)-1*H*-pyrimidine-2,4-dione (6c). 81%; White solid, mp 140 °C (ethanol); ^{1}H NMR ($CDCl_3$+TFA): δ 4.87 (2H, s, NCH_2), 5.69 (1H, d, J=7.8 Hz, H-5), 7.18 (1H, d, J=7.8 Hz, H-6), 7.25–7.35 (4H, m, ArH); ^{13}C (normal/DEPT-135) ($CDCl_3$+TFA): δ 51.84 (−ve, CH_2), 102.96 (+ve, CH-5), 126.24 (+ve, ArCH), 128.23 (+ve, ArCH), 129.51 (+ve, ArCH), 130.77 (+ve, ArCH), 131.5 (ab, ArC), 135.41 (ab, ArC), 146.09 (+ve, CH-6), 152.00 (ab, C), 166.40 (ab, C); HRMS found: 236.0351, $C_{11}H_9^{35}ClN_2O_2$ requires 236.0353. found 238.0323 $C_{11}H_9^{37}ClN_2O_2$ requires 238.0323.

4.2.12. 1-(4-Chlorobenzyl)-1*H*-pyrimidine-2,4-dione (6d). 81%; White solid, mp 180 °C (ethanol); ^{1}H NMR ($CDCl_3$+TFA): δ 4.94 (2H, s, NCH_2), 5.97 (1H, d, J=7.8 Hz, H-5), 7.25–7.37 (5H, m, 4×ArH, H-6); ^{13}C (normal/DEPT-135) ($CDCl_3$+TFA): δ 51.83 (−ve, NCH_2), 102.76 (+ve, CH-5), 129.59 (+ve, ArCH), 129.63(+ve, ArCH), 131.98 (ab, ArC), 135.40 (ab, ArC), 146.27 (+ve, CH-6), 151.99 (ab, C), 166.47 (ab, C); HRMS found: 236.0352, $C_{11}H_9^{35}ClN_2O_2$ requires 236.0353. found 238.0325 $C_{11}H_9^{37}ClN_2O_2$ requires 238.0323.

4.2.13. 1-(4-Fluorobenzyl)-1*H*-pyrimidine-2,4-dione (6e). 70%; White solid, mp 230 °C (ethanol); ^{1}H NMR ($CDCl_3$+TFA): δ 4.97 (2H, s, NCH_2), 6.04 (1H, d, J=7.8 Hz, H-5), 7.10 (2H, t, J=8.4 Hz, $(CH)_2CF$), 7.28–7.38 (2H, m, 2×ArH), 7.43 (1H, d, J=7.8 Hz, H-6); ^{13}C (normal/DEPT-135) ($CDCl_3$+TFA): δ 51.71 (−ve, NCH_2), 102.71 (+ve, CH-5), 116.34 (+ve, d, J=21.6 Hz, ^{2}CH-CF), 129.40 (ab, d, J=3 Hz, ^{4}C-F), 130.29 (+ve, d, J=8.7 Hz, ^{3}CH-CF), 145.98 (+ve, CH-6), 151.90 (ab, C), 161.452, 164.75 (ab, d, J=247 Hz, C-F), 166.33 (ab, C); HRMS found: 220.0645, $C_{11}H_9FN_2O_2$ requires 220.0648.

4.2.14. 1-(2,4-Dichlorobenzyl)-1*H*-pyrimidine-2,4-dione (6f). 69%; White solid, mp 140 °C (ethanol); ^{1}H NMR ($CDCl_3$+TFA): δ 5.09 (2H, s, NCH_2), 6.00 (1H, d, J=7.8 Hz, H-5), 7.25–7.46 (3H, m, ArH), 7.51 (1H, d, J=7.8 Hz, H-6); ^{13}C(normal/DEPT-135) ($CDCl_3$+TFA): δ 49.72 (−ve, NCH_2), 102.32 (+ve, CH-5), 128.03 (+ve, ArCH), 129.70 (ab, ArC), 130.08 (+ve, ArCH), 132.29 (+ve, ArCH), 134.54 (ab, ArC), 136.18 (ab, ArC), 146.23 (+ve, CH-6), 151.61(ab, C), 166.12 (ab, C); HRMS found: 292.9853 (M^++Na) $C_{11}H_8^{35}Cl_2N_2O_2Na$ requires 292.9855.

4.2.15. 1-(2-Nitrobenzyl)-1*H*-pyrimidine-2,4-dione (6g). 68%; Light yellow solid, mp 120 °C (ethanol); ^{1}H NMR ($CDCl_3$+TFA) δ: 5.12 (2H, s, NCH_2), 6.04 (1H, d, J=7.8 Hz, H-5), 7.41 (1H, d, J=8.0 Hz, ArH-3), 7.55 (1H, d, J=7.8 Hz, H-6), 7.59 (1H, t, J=8.0 Hz, ArH-4), 772 (1H, t, J=8.0 Hz, ArH-5), 8.15 (1H, t, J=8.0 Hz, ArH-3); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$+TFA) δ: 50.09 (−ve, CH_2), 102.82 (+ve, C-5), 125.88 (+ve, ArCH), 130.17 (+ve, ArCH), 130.36 (+ve, ArCH), 134.56 (+ve, ArCH), 135.08 (ab, ArC), 146.86 (+ve, CH-6), 147.87 (ab, C), 151.62 (ab, C), 166.26 (ab, C); HRMS found: 247.0654 $C_{11}H_9N_3O_4$ requires 247.0593.

4.2.16. 1-(2,4,6-Trimethylbenzyl)-1*H*-pyrimidine-2,4-dione (6h). 62%; White solid, mp 230 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 2.24 (6H, s, 2×CH_3), 2.30 (3H, s, CH_3), 4.90 (2H, s, NCH_2), 5.54 (1H, d, J=8.0 Hz, H-5), 6.66 (1H, d, J=8.0 Hz, H-6), 6.93 (2H, s, ArH), 9.12 (1H, b, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 19.73 (+ve, CH_3), 21.02 (+ve, CH_3), 44.81 (−ve, CH_2), 101.94 (+ve, CH-5), 126.27 (ab, ArC), 129.82 (+ve, ArCH), 138.27 (ab, ArC), 139.24 (ab, ArC), 141.36 (+ve, CH-6), 151.68 (ab, C), 162.08 (ab, C); HRMS found: 244.1213, $C_{14}H_{16}N_2O_2$ requires 244.1212.

4.2.17. 1-(2-Chlorobenzyl)-5-methyl-1*H*-pyrimidine-2,4-dione (6i). 87%; White soild, mp 132 °C (ethanol); ^{1}H NMR ($CDCl_3$+TFA): δ 1.97 (3H, s, CH_3), 5.12 (2H, s, NCH_2), 7.28–7.51 (5H, m, 4×ArH+H-6); ^{13}C (normal/DEPT-135) ($CDCl_3$+TFA): δ 11.94 (+ve, CH_3), 50.01 (−ve, CH_2), 112.32 (ab, C-5), 127.82 (+ve, ArCH), 130.38 (+ve, ArCH), 130.90 (+ve, ArCH), 131.10 (ab, ArC), 133.90 (ab, ArC), 142.66 (+ve, CH-6), 152.46 (ab, C), 166.66 (ab, C); HRMS found: 250.0513 $C_{12}H_{11}^{35}ClN_2O_2$ requires 250.0509. found: 252.0488 $C_{12}H_{11}^{37}ClN_2O_2$ requires 252.0479.

4.2.18. 1-(2,4-Dichlorobenzyl)-5-methyl-1*H*-pyrimidine-2,4-dione (6j). 85%; White solid, mp 140 °C (ethanol); ^{1}H NMR ($CDCl_3$+TFA): δ 1.99 (3H, s, CH_3), 5.09 (2H, s, NCH_2), 7.32–7.51 (5 H, m, 4×ArH+H-6); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$+TFA): δ 11.98 (+ve, CH_3), 49.48 (−ve, CH_2), 108.73 (ab, C-5), 127.95 (+ve, ArCH), 129.85 (ab, ArC), 129.98 (+ve, ArCH), 131.81 (+ve, ArCH), 134.53 (ab, ArC), 136.24 (ab, ArC), 142.29 (+ve, CH-6), 152.33 (ab, C), 166.41 (ab, C); HRMS found: 284.0119, $C_{12}H_{10}^{35}Cl_2N_2O_2$ requires 284.0119. found 286.0094, $C_{12}H_{10}^{35}Cl^{37}ClN_2O_2$ requires 286.0089.

4.2.19. 1,3-Bis(2-chlorobenzyl)-1*H*,3*H*-pyrimidine-2,4-dione (7a). White solid, mp 74 °C; FAB Mass *m/z* 361, 363, 365 (100: 62: 10) (M^+); ^{1}H NMR ($CDCl_3$): δ 4.97 (2H, s, CH_2), 5.22 (2H, s, CH_2), 5.74 (1H, d, J=7.8 Hz, 5-H), 6.91–7.01(1H, m, ArH), 7.11–7.17 (2H, m, ArH), 7.24–7.43 (4H, m, 5 ArH, C-6H), ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 42.23 (−ve, CH_2), 49.95 (−ve, CH_2), 101.81 (+ve, CH), 126.59 (+ve, ArCH), 126.73 (+ve, ArCH), 127.42 (+ve, ArCH), 128.23 (+ve, ArCH), 129.55 (+ve, ArCH), 129.97 (+ve, ArCH), 130.57 (+ve, ArCH), 132.94 (+ve, ArCH), 132.58 (ab, C), 132.94 (ab, C),133.58 (ab, C), 133.93 (ab, C), 142.31 (+ve, CH), 151.49 (ab, C), 162.63 (ab, C).(found: C, 59.63; H, 3.62; N, 7.42%; $C_{18}H_{14}Cl_2N_2O_2$ requires C, 59.66; H, 3.86; N, 7.73%).

4.2.20. 1,3-Bis(2,4-dichlorobenzyl)-1*H*,3*H*-pyrimidine-2,4-dione (7b). 72%; White solid, mp 72 °C; FAB mass *m/z* 429, 431, 433, 435 (78:100: 50:12) (M^+); ^{1}H NMR ($CDCl_3$): δ 5.01 (2H, s, CH_2), 5.21 (2H, s, CH_2), 5.85 (1H, d, J=7.8 Hz, C5H), 6.91(1H, d, J=8.0 Hz, ArH), 7.15 (1H, d, J=8.0 Hz, ArH), 7.24–7.51 (5H, m, 4×ArH, C-6H). The decoupling of C-5H doublet at δ 5.85 converts δ 7.37 doublet into singlet; ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 41.88 (−ve, CH_2), 49.71 (−ve, CH_2), 101.97 (+ve, CH), 127.07 (+ve, ArCH), 127.80 (+ve, ArCH), 127.99 (+ve, ArCH), 129.41 (+ve, ArCH), 129.82 (+ve, ArCH), 131.11 (ab, C), 131.71 (+ve, ArCH), 132.31 (ab, C), 133.46 (ab, C), 133.73 (ab, C), 134.28 (ab, C), 135.39 (ab, C), 142.40 (+ve, CH), 151.41 (ab, C), 162.49 (ab, C). (Found: C, 49.84; H, 2.42; N, 6.21%. $C_{18}H_{12}Cl_4N_2O_2$ requires C, 50.12; H, 2.78; N, 6.50%).

4.2.21. 1-(1-Phenyl-ethyl)-1*H*-pyrimidine-2,4-dione (9a). 69%; White solid, mp 85 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 1.70 (3H, d, J=7.2 Hz, CH_3), 5.66 (1H, d, J=8.0 Hz, H-5), 5.99 (1H, q, J=7.2 Hz, CH), 7.03 (1H, d, J=8.0 Hz, H-6), 7.24-7.37 (5H, m, ArH), 9.26 (1H, bs, NH, exchanges with D_2O); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 18.33 (+ve, CH_3), 53.20 (+ve, CH), 102.66 (+ve, CH-5), 127.18 (+ve, ArCH), 128.32 (+ve, ArCH), 128.99 (+ve, ArCH), 138.57 (ab, ArC), 141.05 (+ve, CH-6), 151.28 (ab, C), 163.72 (ab, C); HRMS found: 216.0901 $C_{12}H_{12}N_2O_2$ requires 216.0899.

4.2.22. 1-Benzhydryl-1*H*-pyrimidine-2,4-dione (9b). 70%; White solid, mp 180 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 5.67 (1H, d, J=7.8 Hz, H-5), 7.07 (1H, d, J=7.0 Hz, H-6), 7.13–7.36 (11H, m, ArH+CH), 9.53 (1H, bs, ArH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$) δ: 62.19 (+ve, CH), 102.06 (+ve, C-5), 128.38 (+ve, ArCH), 128.44 (+ve, ArCH), 129.00 (+ve, ArCH), 137.49 (ab, C), 142.39 (+ve, CH-6), 151.21 (ab, C), 163.71 (ab, C; HRMS found: 278.1055, $C_{17}H_{14}N_2O_2$ requires 278.1055.

4.2.23. 1-(4-Chlorophenyl phenyl methyl)-1*H*-pyrimidine-2,4-dione (9c). 65%; Thick yellow oil; ^{1}H NMR ($CDCl_3$): δ 5.68 (1H, d, J=8.4 Hz, H-5), 7.06 (1H, d, J=8.4 Hz, CH-6), 7.11–7.42 (10H, m, 9×ArH+CH), 9.47(1H, bs, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 61.32 (+ve, CH), 102.31 (+ve, CH-5), 126.49 (+ve, ArCH), 128.38 (+ve, ArCH), 128.74 (+ve, ArCH), 129.21 (+ve, ArCH), 129.60 (+ve, ArCH), 134.45 (ab, ArC), 136.06 (ab, ArC), 141.95 (+ve, CH-6) 151.13 9 (ab, C), 163.46 (ab, C).

4.2.24. 1-(1-Phenyl-ethyl)-5-methyl-1*H*-pyrimidine-2,4-dione (9d). 78%; White solid, mp 110 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 1.69 (3H, d, J=7.0 Hz, CH_3), 1.84 (3H, s, CH_3), 6.02 (1H, q, J=7.0 Hz, CH), 6.82 (1H, s, H-6), 7.27–7.39 (5H, m, ArH), 9.58 (1H, bs, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 11.94 (+ve, CH_3), 17.99 (+ve, CH_3), 55.66 (+ve, CH), 112.67 (ab, C-5), 127.38 (+ve, ArCH), 129.42 (+ve, ArCH), 129.60 (+ve, ArCH), 137. 37 (ab, ArC), 140.35 (+ve, CH-6), 152.58 (ab, C=O)), 166.80 (ab, C=O); HRMS found: 230.1057 $C_{13}H_{14}N_2O_2$ requires 230.1055.

4.2.25. 1-Benzhydryl-5-methyl-1*H*-pyrimidine-2,4-dione (9e). 80%; White solid, mp 180 °C (ethanol); ^{1}H NMR ($CDCl_3$): δ 1.93 (3H, s, CH_3), 6.88 (1H,s, CH), 7.07 (1H, s, H-6), 7.14–7.41 (10H, m, ArH), 9.52 (1H, b, NH, exchanges with D_2O); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$): δ 12.18 (+ve, CH_3), 64.19 (+ve, CH), 111.96 (ab, C-5), 128.51 (+ve, ArCH), 129.26 (+ve, ArCH), 129.50 (+ve, ArCH), 136.28 (ab, ArC), 143.02 (+ve, CH-6), 152.61 (ab, C=O), 166.53 (ab, C=O); HRMS found: 292.1214, $C_{18}H_{16}N_2O_2$ requires 292.1212.

4.2.26. 1-Anthracen-9-ylmethyl-1*H*-pyrimidine-2,4-dione (11a). 84%; Yellow solid, mp 240 °C (ethanol); UV–vis (CH_3CN): λ_{max} 387(ε 6300), 367(ε 7100), 349(ε 4800), 333(ε 2400); ^{1}H NMR ($CDCl_3$+TFA) δ: 5.71 (1H, d, J=7.8 Hz, H-5), 5.97 (2H, s, NCH_2), 6.86 (1H, d, J=8.0 Hz, H-6), 7.56-7.68 (4H, m, ArH), 8.06 (2H, d, J=8.4 Hz, ArH), 8.10 (2H, d, J=8.4 Hz, ArH), 8.64 (1H, s, ArH); ^{13}C (normal/DEPT-135) ($CDCl_3$+TFA): δ 43.34 (−ve, NCH_2), 102.01 (+ve, CH-5), 120.95 (ab, ArC), 122.07 (+ve, ArCH), 125.90 (+ve, ArCH), 128.70 (+ve, ArCH), 130.04 (+ve, ArCH), 131.18 (+ve, ArCH), 131.56 (ab, ArC), 131.68 (ab, ArC), 145.21(+ve, CH-6), 153.47 (ab, C=O), 167.47 (ab, C=O); HRMS found: 302.1056, $C_{19}H_{14}N_2O_2$ requires 302.1055.

4.2.27. 1-Anthracen-9-ylmethyl-5-methyl-1*H*-pyrimidine-2,4-dione (11b). 80%; Yellow solid, mp 260 °C (ethanol); UV–vis (CH_3CN): λ_{max} 387(ε 7500), 367(ε 7800), 349(ε 4800), 333(ε 1600); ^1H NMR ($CDCl_3$+TFA): δ 1.58 (3H, s, CH_3), 5.92 (2H, s, NCH_2), 6.65 (1H, s, H-6), 7.53–7.69 (4H, m, ArH), 8.06 (4H, t, J=8.4 Hz, ArH), 8.64 (1H, s, ArH); ^{13}C NMR (normal/DEPT-135) ($CDCl_3$+TFA): δ 11.95 (+ve, CH_3), 43.22 (−ve, CH_2), 111.96 (ab, CH-5), 121.85 (ab,ArC), 122.20 (+ve, ArCH), 125.61 (+ve, ArCH), 128.32 (+ve, ArCH), 129.74 (+ve, ArCH), 130.67 (+ve, ArCH), 131.44 (ab, ArC), 131.46 (ab, ArC), 140.01 (+ve, CH-6), 152.40 (ab, C=O), 166.21 (ab, C=O); HRMS found: 316.1207, $C_{20}H_{16}N_2O_2$ requires 316.1212.

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