Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 5944–5951
Tetrahedron

Unique chlorine effect in regioselective one-pot synthesis of 1-alkyl-/allyl-3-(*o*-chlorobenzyl) uracils: anti-HIV activity of selected uracil derivatives

Vaishalli Malik, Palwinder Singh* and Subodh Kumar*

Department of Chemistry, Guru Nanak Dev University, Amritsar 143005, India

Received 27 January 2006; revised 24 March 2006; accepted 6 April 2006
Available online 3 May 2006

Abstract—2,4-Bis(trimethylsilyloxy)pyrimidines **1/2** on reaction with *o*-chlorobenzyl chlorides in 1,2-dichloroethane in the presence of I_2 undergo single step 1,3-dibenzylation to provide 1,3-bis(*o*-chlorobenzyl)pyrimidine-2,4-diones. The reactions of **1** with allyl/alkyl bromide followed by subsequent addition of *o*-chlorobenzyl chloride provide a simple one-pot synthesis of 1,3-unsymmetrical pyrimidine-2,4-diones. Amongst these, 1,3-bis(*o*-chlorobenzyl)uracil (**6a**) shows anti-HIV-1 activity.

1. Introduction

Due to the clinical toxicities involved in the use of nucleoside inhibitors of reverse transcriptase (NRTIs)[1] and high frequency of viral mutations, the use of non-nucleoside inhibitors of reverse transcriptase (NNRTIs)[2] (enzyme responsible for encoding viral RNA to host DNA) has been overcoming the use of nucleoside inhibitors. The presence of hydrophobic residues lining the non-nucleoside binding pocket (NNBP) of HIV-1 RT has necessitated the development of NNIs with allyl/benzyl/alkyl groups at suitable sites of nucleobases which could facilitate the π–π or π–CH interactions with the amino acid residues of the enzyme.[3,4] The presence of these moieties generally enhances the potency profile of lead drug molecules e.g., the presence of allyl/amidophenyl/thiophenyl/aminophenyl moieties at the end of N-1 chain of HEPT along with a thiophenyl/benzyl group at C-6 of pyrimidine has led to higher anti-HIV-1 activity than that observed with HEPT.[5,6] It was envisaged that the presence of hydrophobic moieties at N-1 and N-3 of pyrimidinedione might enhance the anti-HIV activities of the resulting compounds. 1,3-Disubstituted pyrimidinediones are little explored for their anti-HIV activities, which might be due to the difficulty in synthesis of such compounds. This led us to design and synthesise new molecules with an allyl/alkyl/benzyl substituent at N-1 and a benzyl group at N-3 of the pyrimidinedione.

During the synthesis of N-1, N-3 unsymmetrically substituted pyrimidine-2,4-diones, we have observed that the alkylation of 2,4-bis(trimethylsilyloxy)pyrimidine (**1**) stops at N-1 substitution stage.[7] The present work shows that alkylation of **1** with *o*-chlorobenzyl chlorides on prolonged heating provide N-1 and N-3 dialkylated products. This unique ability of N-3 *o*-chlorobenzylation has been exploited for the synthesis of 1-allyl-/alkyl-/benzyl-3-(*o*-chlorobenzyl) pyrimidine-2,4-diones. The mechanism for such unique ability of *o*-chlorobenzyl chlorides to promote the benzylation at N-3 of 1-substituted pyrimidine-2,4-diones has been discussed. The selected 1,3-substituted pyrimidine-2,4-diones have been evaluated for their in vitro anti-HIV activities.

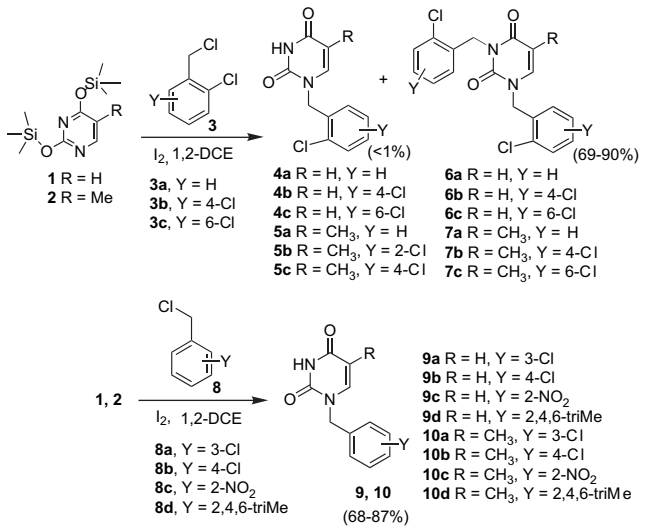
2. Results and discussion

2,4-Bis(trimethylsilyloxy)pyrimidine (**1**) on refluxing with 2-chlorobenzyl chloride (**3a**) (3 equiv) in 1,2-dichloroethane (1,2-DCE) in the presence of I_2 (0.1 equiv) for 96 h, after the usual work-up and column chromatography gave two compounds **4a** (<1%) and **6a** (74%). Compound **6a**, mp 72 °C, M^+ *m/z* 361, 363, 365 (100:60:10), shows the signals of H-5 and H-6 protons as doublets at δ 5.74 and 7.24 and N-1 and N-3 CH_2 as singlets at δ 4.97 and 5.22 along with aromatic protons in its ^{1}H NMR spectrum and the presence of 10 positive (due to CH), two negative (due to CH_2) and six quaternary carbons in ^{13}C normal and DEPT-135 spectra, which corroborate the structure **6a** (Scheme 1).

Similarly, the refluxing of solutions of **1** with 2,4-dichlorobenzyl chloride **3b** and 2,6-dichlorobenzyl chloride **3c** in 1,2-DCE in the presence of I_2 for 96 h gave 1,3-disubstituted

Keywords: Uracil; Thymine; N_1-Alkylation; *o*-Chlorobenzyl chloride; 1,3-Unsymmetrical dialkylation.
* Corresponding authors. Tel.: +91 183 2258802-09x3206; fax: +91 183 2258820/2258819; e-mail addresses: palwinder_singh_2000@yahoo.com; subodh_gndu@yahoo.co.in

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.04.018



Scheme 1.

uracil derivatives **6b** and **6c**, respectively. In these reactions, only traces (<1%) of **4b** and **4c** were isolated (Table 1). Furthermore, the reactions of 2,4-bis(trimethylsilyloxy)-5-methylpyrimidine (**2**) with **3a–c** gave the respective 1,3-bis(*o*-chlorobenzyl)thymines **7a–7c** along with small amounts of **5a–5c** (Scheme 1, Table 1).

However, the reactions of **1** and **2** with 3-chloro-/4-chloro-/2-nitro-/2,4,6-trimethyl-benzyl chlorides (**8a–8d**) (3 equiv) did not provide respective 1,3-disubstituted uracil/thymine derivatives even on prolonged refluxing (7 days) and the reactions stopped at the 1-substituted stage yielding N_1-substituted uracils **9(a–d)** and **10(a–d)** (Scheme 1, Table 1).

Amongst various substituted benzyl halides **3(a–c)** and **8(a–d)**, which were made to react with **1** and **2**, only **3(a–c)** gave dibenzylated products **6** and **7**, while in all other cases the reaction stops at the N_1-substitution stage. These results clearly point to the unique role of *o*-chlorine in benzyl halides **3(a–c)** in yielding 1,3-dibenzyl pyrimidine-2,4-diones **6** and **7**. The reasons for this differential reactivity remain unexplained.

The monitoring of reactions of **1** with **3a/3b/3c** by ^{1}H NMR spectroscopy unravels the plausible mechanism in transferring *o*-chlorobenzyl group at N-3. The ^{1}H NMR spectrum of the reaction mixture of **1** and 2-chlorobenzyl chloride **3a**, recorded by quenching the reaction after 48 h, shows two sets of signals each due to H-5 (at δ 5.74 and 5.89), N_1-CH_2 (two singlets δ 4.97 and 5.06) and two singlets due to N_3-CH_2 (at δ 5.22 and 5.47) in the 96:4 ratio (entry 1, Table 2). The major component on the basis of ^{1}H NMR spectrum has been assigned the structure **6a**. The minor component could be due to **11a/12a** formed due to O-alkylation at C_2=*O* or C_4=*O* (Scheme 2). Similarly, the reaction of **1** with 2,4-dichlorobenzyl chloride **3b** on work-up after 48 h, in its ^{1}H NMR spectrum shows two sets of signals each due to H-5 (δ 5.85 and 5.95), N_1-CH_2 (δ 5.01 and 5.12) and N_3-CH_2 (δ 5.21 and 5.48) protons in 75:25 ratio (entry 2, Table 2). The ^{1}H NMR spectrum of the reaction of **1** with 2,6-dichlorobenzyl chloride **3c** recorded after 48 h of reaction shows three singlets each due to N_1-CH_2 at δ 5.20, 5.28 and 5.35, N_3-CH_2 at δ 5.40, 5.46 and 5.68 in the ratio 27:24:49 indicating it to be a mixture of three components.

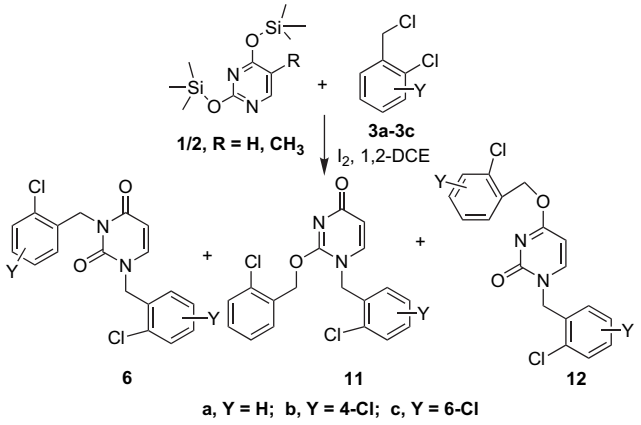
Table 1. Reactions of 1/2 with substituted 2-chlorobenzyl chlorides

Entry	R in 1/2	Benzyl halide	Rx time (h)	N_1-alkylated, yield %	N_1,N_3-alkylated, yield %
1	H	**3a**	96	**4a** (<1)	**6a** (74)
2	H	**3b**	96	**4b** (<1)	**6b** (82)
3	H	**3c**	96	**4c** (<1)	**6c** (89)
4	CH_3	**3a**	96	**5a** (<1)	**7a** (72)
5	CH_3	**3b**	96	**5b** (<1)	**7b** (76)
6	CH_3	**3c**	96	**5c** (<1)	**7c** (67)
7	H	**8a**	96	**9a** (74)	—
8	H	**8b**	96	**9b** (78)	—
9	H	**8c**	96	**9c** (74)	—
10	H	**8d**	96	**9d** (68)	—
11	CH_3	**8a**	96	**10a** (79)	—
12	CH_3	**8b**	96	**10b** (82)	—
13	CH_3	**8c**	96	**10c** (82)	—
14	CH_3	**8d**	96	**10d** (87)	—

Table 2. Product distribution ratio for the reaction of 1/2 with substituted benzyl chlorides quenched after 48 h (Scheme 2)

Entry	R in **1/2**	Benzyl halide	Product ratio (**6**: **11**+**12**)	Product **6** (yield %[a])
1	H	**3a**	96:4	**6a** (70)
2	H	**3b**	75:25	**6b** (70)
3	H	**3c**	27:73	**6c** (72)

[a] Yield after work-up with 4 M HCl.



Scheme 2.

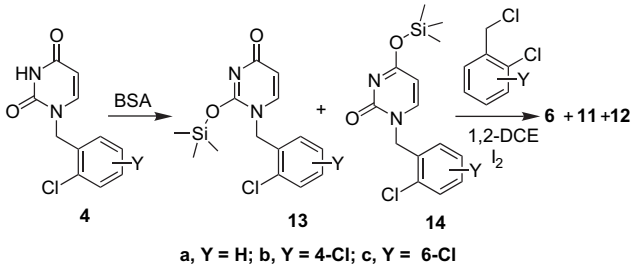
However, TLC of these mixtures shows the presence of only one component and even on repeated chromatography these could not be separated.

The crude reaction mixtures obtained after 48 h of refluxing of **1** with **3(a–c)** on further heating with 4 M HCl at 80 °C for 1 h gave pure products **6a–6c** (Table 2) along with small quantities of respective 1-(*o*-chlorobenzyl)uracil derivatives **4(a–c)** (<1%). Alternatively, these reaction mixtures on further heating in 1,2-DCE for >24 h underwent rearrangement to 1,3-disubstituted uracil derivatives **6a–6c**.

These observations indicate that probably after N-1 alkylation, the *ortho*-chlorobenzyl promotes N-3, C_2=O and C_4=O alkylation to provide mixture of N_3-alkyl derivative

6 and *O*-alkyl derivatives **11** and **12** (Scheme 2), which on heating in HCl or 1,2-DCE undergo rearrangement to provide **6**.

The participation of intermediates **11** and **12** has been further confirmed by silylation of **4**(**a**–**c**) and subsequent alkylation with *o*-chlorobenzyl chlorides **3**(**a**–**c**). Compound **4a** on heating with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) gave a clear solution, which confirms its complete silylation. ^{1}H NMR ($CDCl_3$) spectrum of this silylated mixture shows the presence of two NCH_2 signals at δ 4.93 and 5.07 and two H-5 doublets at δ 5.61 and 5.79 in 22:78 ratio and confirms it to be a mixture of C_2=O and C_4=O silylated derivatives **13** and **14** (Scheme 3). The mixture of **13** and **14** on refluxing with 2-chlorobenzyl chloride in the presence of I_2 on work-up after 48 h provided a mixture of **6a** and **11/12**. Similarly, **4b** and **4c** on silylation showed the presence of **13b**, **14b** and **13c**, **14c** in their ^{1}H NMR spectra. The silylated pyrimidines **13** and **14** on subsequent refluxing with *o*-chlorobenzyl chlorides for 48 h provided mixtures of **6**, **11** and **12** in nearly similar ratios as observed in direct alkylation of **1** as given in Table 2.

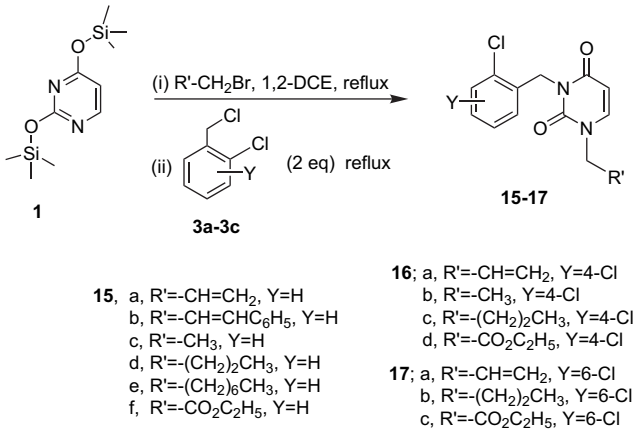


Scheme 3.

Therefore, **1** initially undergoes regioselective alkylation at N-1 and then 2-chloro-/2,4-dichloro-/2,6-dichloro-benzyl chloride causes alkylation at N-3, C_2=O and C_4=O to provide a mixture of **6**, **11** and **12**, which on heating undergoes rearrangement to the respective 1,3-disubstituted uracil derivatives **6a**–**6c**. This provides a simple approach for the 1,3-disubstituted uracil and thymine derivatives under neutral or mild acidic conditions. Significantly, in the case of reactions of **2** with 2-chlorobenzyl chlorides **3a**–**3c**, even after work-up at different intervals of time, the formation of respective *O*-alkylated products **11** and **12** was not observed.

This ability of *o*-chlorobenzyl chlorides to promote N_3-benzylation of *O*-silylated uracil derivatives has been advantageously used for the one-pot synthesis of 1-alkyl/allyl/3-(*o*-chlorobenzyl) uracil derivatives (Scheme 4). The reactions of **1** with various alkyl/allyl/benzyl halides and subsequent in situ reactions with *o*-chlorobenzyl chlorides provide 1,3-unsymmettrically substituted uracil derivatives.

The refluxing of **1** with allyl bromide (1.5 equiv) in 1,2-DCE containing I_2 (0.1 equiv) provided *O*-silylated derivatives of 1-allyluracil (TLC comparison with authentic sample). Then, **3a** (2 equiv) was added to the reaction mixture and refluxing was continued (Scheme 4). The reaction mixture on work-up and column chromatography gave a pale yellow liquid **15a** (73%), [M^+ *m*/*z* 277, 279 (3:1)] (entry 1, Table 3,). Similarly, the reaction of **1** with allyl bromide (1.5 equiv) followed by subsequent reaction with **3b** and **3c** (2 equiv)



Scheme 4.

Table 3. Percentage yield and melting points of 1-allyl/arylmethyl/alkyl-3-(*o*-chlorobenzyl) uracil derivatives (**15**–**17**)

Entry	Y	R′	Yield (%)	Mp (°C)
1	H	$CH{=}CH_2$	**15a** (73)	liq
2	H	$CH{=}CHC_6H_5$	**15b** (72)	110
3	H	CH_3	**15c** (63)	liq
4	H	$(CH_2)_2CH_3$	**15d** (78)	liq
5	H	$(CH_2)_6CH_3$	**15e** (67)	liq
6	H	$CO_2C_2H_5$	**15f** (64)	liq
7	4-Cl	$CH{=}CH_2$	**16a** (62)	94
8	4-Cl	CH_3	**16b** (70)	98
9	4-Cl	$(CH_2)_2CH_3$	**16c** (63)	94
10	4-Cl	$CO_2C_2H_5$	**16d** (64)	120
11	6-Cl	$CH{=}CH_2$	**17a** (65)	110
12	6-Cl	$(CH_2)_2CH_3$	**17b** (62)	140
13	6-Cl	$CO_2C_2H_5$	**17c** (62)	120

provided the respective compounds **16a** and **17a** (entries 7 and 11, Table 3).

To check the competition between the allyl bromide and *o*-chlorobenzyl chloride for N-3 alkylation, **1** was refluxed with 1.2 equiv of allyl bromide for 24 h and then 2 equiv each of allyl bromide and *o*-chlorobenzyl chloride was added and the reaction mixture was refluxed for 48 h. The reaction mixture on work-up provided only **15a** (73%). 1,3-Diallyluracil was not isolated from the reaction mixture. The reaction of **1** with cinnamyl bromide (1.5 equiv) and subsequent alkylation with 2-chlorobenzyl chloride gave uracil derivative **15b** (72%). Similarly, the reactions of **1** with various alkyl/alkyl ester halides followed by addition of 2 equiv of **3a/3b/3c** provided respective compounds **15**–**17** (Scheme 4, Table 3).

2.1. In vitro anti-HIV activities

The in vitro anti-HIV activities of the six selected compounds in terms of 50% effective concentration against HIV cytopathic effects and 50% inhibitory concentration for cell growth have been evaluated against human immunodeficiency virus (HIV). The biological results as inhibition of HIV-1 replication in T4 lymphocytes (CEM-SS cell line) are given in Table 4.

Among the compounds tested (**6a**–**6c**, **15a**, **16a**, **17a**) for anti-HIV-1 activity, **6a** possessing 2-chlorobenzyl groups

Table 4. Inhibition of HIV-1 replication in T4 lymphocytes (CEM-SS cell line) by compounds **6a–6c** and **15a**, **16a**, **17a**

Compd	IC_{50}[a] (μM)	EC_{50}[b] (μM)	TI[c]
6a	36.4	9.19	3.65
6b	35.5	>200	<0.17
6c	35.4	>200	<0.17
15a	121	>200	<0.6
16a	111	>200	<0.5
17a	42.7	>200	<0.2
HEPT	740	7	106
AZT	20	0.016	1250

[a] Concentration of compound required to achieve 50% inhibition of cell growth.
[b] Compound dose required to achieve 50% protection of T4 lymphocyte cells from HIV-1 induced cytopathogenecity.
[c] Therapeutic Index (TI=IC_{50}/EC_{50}).

at N-1 and N-3 of uracil shows highest anti-HIV-1 activity with EC_{50}=9.19 μM, which is comparable to HEPT (7.0 μM) but lacks the selectivity. The replacement of *o*-chlorobenzyl group at N-1 with allyl moiety (**15a**, **16a**, **17a**) results in total loss of anti-HIV activity. The presence of another chlorine atom at 4 or 6 positions of the benzyl group in **6b** and **6c** increases the effective concentration required to achieve 50% protection of HIV infected cells while the IC_{50} values of these compounds are parallel with **6a**. It seems as if the presence of a phenyl moiety at N-1 is the essential requirement for these compounds to exhibit anti-HIV-1 activities.

3. Conclusions

2,4-Bis(trimethylsilyloxy)pyrimidines **1** on reaction with allyl/arylmethyl/alkyl/alkoxycarbonylmethyl halides followed by reactions with 2-chloro/2,4-dichloro-/2,6-dichloro benzyl chlorides provides simple one-pot methodology for the synthesis of 1-allyl-/alkyl-/benzyl-3-(*o*-chlorobenzyl) uracil derivatives.

4. Experimental

4.1. General

Melting points were determined in capillaries and are uncorrected. ^1H and ^{13}C NMR spectra were run on JEOL JNM-AL spectrometer at 300 MHz and 75 MHz, respectively, using $CDCl_3$ as solvent and TMS as an internal standard. In ^{13}C NMR spectral data, +ve signals correspond to CH_3 and CH and −ve signals correspond to CH_2 carbons in DEPT-135 spectrum. *J* values are given in Hertz. Mass spectra were recorded at CDRI, Lucknow. IR spectra were recorded by using $CHCl_3$ or KBr (solid) as medium. CHN analysis was performed on thermoelectron CHN analyser EA1112.

4.2. General procedure for the reactions of 1/2 with benzyl chlorides 3(a–c) and 8(a–d)

Procedure **A**: A solution of 2,4-bis-(trimethylsilyloxy)pyrimidine (**1/2**) (0.01 mol), the appropriate benzyl chloride (0.03 mol) and I_2 (0.001 mol) in 1,2-DCE (20 ml) was refluxed for 96 h. After completion of the reaction (TLC), the cooled reaction mixture was treated with ethanol (10 ml). The solvent was distilled off under vacuum and the residue was column chromatographed over silica-gel using ethyl acetate and hexane mixtures as eluents to isolate the pure compounds.

4.2.1. 1-(2-Chlorobenzyl)-1*H*-pyrimidine-2,4-dione (4a). <1%; White solid, mp 209 °C (lit.[7] mp 210 °C).

4.2.2. 1,3-Bis(2-chlorobenzyl)-1*H*-pyrimidine-2,4-dione (6a). 74%; White solid, mp 72 °C (CH_3CN); FAB mass *m/z* 361, 363, 365 (100:62:10) (M^+); ^1H NMR ($CDCl_3$): δ 4.97 (2H, s, CH_2), 5.22 (2H, s, CH_2), 5.74 (1H, d, *J*=7.8 Hz, C5-H), 6.91–7.01 (1H, m, ArH), 7.11–7.17 (2H, m, ArH), 7.24–7.43 (6H, m, 5ArH, C-6H); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 42.23 (−ve, CH_2), 49.95 (−ve, CH_2), 101.81 (+ve, 5-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-6), 151.49 (ab, C), 162.63 (ab, C); ν_{max} (KBr)/cm^{-1}: 3100, 1708, 1670, 1658, 742, 798; (Found: C, 59.6; H, 4.0; N, 7.9. $C_{18}H_{14}Cl_2N_2O_2$ requires C, 59.85; H, 3.91; N, 7.76%).

4.2.3. 1-(2,4-Dichlorobenzyl)-1*H*-pyrimidine-2,4-dione (4b). <1%; White solid, mp 140 °C (lit.[7] mp 140 °C).

4.2.4. 1,3-Bis(2,4-dichlorobenzyl)-1*H*-pyrimidine-2,4-dione (6b). 82%; White solid, mp 72 °C (CH_3CN); FAB mass *m/z* 429, 431, 433, 435 (78:100:50:12) (M^+); ^1H NMR ($CDCl_3$): δ 5.01 (2H, s, CH_2), 5.21 (2H, s, CH_2), 5.85 (1H, d, *J*=7.8 Hz, C-5H), 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 signal at δ 5.85 gives a singlet at δ 7.37; ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 41.88 (−ve, CH_2), 49.71 (−ve, CH_2), 101.97 (+ve, 5-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, 6-CH), 151.41 (ab, C), 162.49 (ab, C); ν_{max} (KBr)/cm^{-1}: 3200, 1708, 1654, 727, 813; (Found: C, 50.3; H, 2.6; N, 6.2. $C_{18}H_{12}Cl_4N_2O_2$ requires C, 50.26; H, 2.81; N, 6.51%).

4.2.5. 1-(2,6-Dichlorobenzyl)-1*H*-pyrimidine-2,4-dione (4c). <1%; White solid, mp 256 °C (CH_3CN); FAB mass *m/z* 270, 272, 274 (100:60:10) (M^+); ^1H NMR ($CDCl_3$+TFA): δ 5.34 (2H, s, CH_2), 6.00 (1H, d, *J*=8.0 Hz, C5-H), 7.19 (1H, d, *J*=8.0 Hz, C6-H), 7.39–7.49 (3H, m, ArH); ^{13}C (normal/DEPT-135) ($CDCl_3$+TFA): δ 46.83 (−ve, CH_2), 102.38 (+ve, 5-CH), 128.56 (ab, C), 129.24 (+ve, ArCH), 131.83 (+ve, ArCH), 137.14 (ab, C), 144.80 (+ve, 6-CH), 151.78 (ab, C), 166.45 (ab, C); ν_{max} (KBr)/cm^{-1}: 3029, 1691,1658, 781, 767; (Found: C, 48.42; H, 2.89; N, 10.15. $C_{11}H_8Cl_2N_2O_2$ requires C, 48.7; H, 2.95; N, 10.33%).

4.2.6. 1,3-Bis(2,6-dichlorobenzyl)-1*H*-pyrimidine-2,4-dione (6c). 89%; White solid, mp 120 °C (CH_3CN); FAB mass *m/z* 429, 431, 433, 435 (78:100:50:12) (M^+); ^1H NMR ($CDCl_3$): δ 5.20 (2H, s, CH_2), 5.42 (2H, s, CH_2), 5.63 (1H, d, *J*=8.0 Hz, C5-H), 6.78 (1H, d, *J*=8.0 Hz, C6-H), 7.12 (1H, t, *J*=8.0 Hz, ArH), 7.16–7.41 (5H, m,

ArH). The decoupling of the C-5H signal at δ 5.63 converts the doublet at δ 6.78 to a singlet; ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 41.16 (−ve, CH_2), 46.18 (−ve, CH_2), 101.79 (+ve, 5-CH), 128.48 (+ve, ArCH), 128.76 (+ve, ArCH), 128.91 (+ve, ArCH), 130.10 (ab, C), 130.20 (ab, C), 130.96 (+ve, ArCH), 131.88 (ab, C), 139.73 (+ve, 6-CH), 135.82 (ab, C), 137.05 (ab, C), 151.05 (ab, C), 162.49 (ab, C); ν_{max} (KBr)/cm^{-1}: 3100, 1716, 1668, 759, 777; (Found C, 49.9; H, 2.4; N, 6.8%. $C_{18}H_{12}Cl_4N_2O_2$ requires C, 50.26; H, 2.81; N, 6.51%).

4.2.7. 1-(2-Chlorobenzyl)-5-methyl-1H-pyrimidine-2,4-dione (5a). <1%; White solid, mp 130 °C (lit.[7] mp 132 °C).

4.2.8. 1,3-Bis[(2-chlorobenzyl]-5-methyl-1*H*-pyrimidine-2,4-dione (7a). 72%; White solid, mp 136 °C (CH_3CN); FAB mass *m/z* 375, 377, 379 (100:62:10) (M^+); ^{1}H NMR ($CDCl_3$): δ 1.93 (3H, s, CH_3), 5.05 (2H, s, CH_2), 5.29 (2H, s, CH_2), 6.94–6.99 (1H, m, ArH), 7.13–7.27 (3H, m, ArH), 7.29–7.44 (5H, m, ArH, C6-H); ^{13}C (normal/DEPT) ($CDCl_3$): δ 13.12 (+ve, CH_3), 42.46 (−ve, CH_2), 49.54 (−ve, CH_2), 110.24 (ab, C-5), 126.73 (+ve, ArCH), 126.79 (+ve, ArCH), 127.40 (+ve, ArCH), 128.19 (+ve, ArCH), 129.54 (+ve, ArCH), 129.75 (+ve, ArCH), 129.91 (+ve, ArCH), 130.13 (+ve, ArCH), 133.01 (ab, C), 133.41 (ab, C), 133.85 (ab, C), 138.37 (+ve, C-6H), 151.58 (ab, C), 163.43 (ab, C); ν_{max} (KBr)/cm^{-1}: 3066, 2360, 2339, 1703, 1643, 748; (Found C, 60.88; H, 4.31; N, 7.26%. $C_{19}H_{16}Cl_2N_2O_2$ requires C, 60.88; H, 4.26; N, 7.46%).

4.2.9. 1-(2,4-Dichlorobenzyl)-5-methyl-1*H*-pyrimidine-2,4-dione (5b). <1%; White solid, mp 138 °C (lit.[7] mp 140 °C).

4.2.10. 1,3-Bis(2,4-dichlorobenzyl)-5-methyl-1*H*-pyrimidine-2,4-dione (7b). 76%; White solid, mp 152 °C (CH_3CN); FAB mass *m/z* 443, 445, 447, 449 (78:100:50:12) (M^+); ^{1}H NMR ($CDCl_3$): δ 1.95 (3H, s, CH_3), 5.01 (2H, s, CH_2), 5.23 (2H, s, CH_2), 6.92 (1H, d, J=8.0 Hz, ArH), 7.12–7.17 (2H, m, ArH), 7.27–7.28 (2H, m, ArH), 7.38–7.45 (2H, m, ArH, C6-H); ^{13}C (normal/DEPT) ($CDCl_3$): δ 13.11 (+ve, CH_3), 42.07 (−ve, CH_2), 49.25 (−ve, CH_2), 110.45 (ab, C-5), 127.05 (+ve, ArCH), 127.76 (+ve, ArCH), 128.14 (+ve, ArCH), 129.37 (+ve, ArCH), 129,75 (+ve, ArCH), 131.24 (+ve, ArCH), 131.54 (ab, C), 132.57 (ab, C), 133.38 (ab, C), 133.76 (ab, C), 134.10 (ab, C), 135.12 (ab, C), 138.35 (+ve, C-6H), 151.46 (ab, C), 163.27 (ab, C); ν_{max} (KBr)/cm^{-1}: 2360, 2339, 1704, 1666, 1643, 775; (Found C, 51.12; H, 3.12; N, 6.11%. $C_{19}H_{14}Cl_4N_2O_2$ requires C, 51.3; H, 3.15; N, 6.30%).

4.2.11. 1-(2,6-Dichlorobenzyl)-5-methyl-1*H*-pyrimidine-2,4-dione (5c). <1%; White solid, mp 240 °C (CH_3CN); ^{1}H NMR ($CDCl_3$+TFA): δ 1.93 (3H, s, CH_3), 5.30 (2H, s, CH_2), 6.93 (1H, s, C6-H), 7.31–7.47 (3H, m, ArH); ^{13}C (normal/DEPT-135) ($CDCl_3$+TFA): δ 12.02 (+ve, CH_3), 46.24 (−ve, CH_2), 129.07 (+ve, ArCH), 112.19 (ab, C-5), 128.88 (ab, C), 129.21 (+ve, ArCH), 131.65 (+ve, ArCH), 137.04 (ab, C), 140.32 (+ve, 6-CH), 151.95 (ab, C), 166.20 (ab, C). ν_{max} (KBr)/cm^{-1}: 3002, 2829, 1703, 1658, 784, 756; HRMS found 284.0119, $C_{12}H^{35}_{10}Cl_2N_2O_2$ requires 284.0119; found 286.0091, $C_{12}H^{35}_{10}Cl^{37}ClN_2O_2$ requires 286.0089; (Found: C, 50.23; H, 3.53; N, 9.69. $C_{12}H_{10}Cl_2N_2O_2$ requires C, 50.52; H, 3.50; N, 9.82%).

4.2.12. 1,3-Bis(2,6-dichlorobenzyl)-5-methyl-1*H*-pyrimidine-2,4-dione (7c). 67%; White solid, mp 128 °C (CH_3CN); FAB mass *m/z* 443, 445, 447, 449 (76:100:48:12) (M^+); ^{1}H NMR ($CDCl_3$): δ 1.81 (3H, s, CH_3), 5.22 (2H, s, CH_2), 5.45 (2H, s, CH_2), 6.65 (1H, s, C6-H), 7.07–7.15 (1H, m, ArH), 7.29–7.42 (5H, m, ArH); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 13.26 (+ve, CH_3), 41.47 (−ve, CH_2), 110.08 (ab, C-5), 128.47 (+ve, ArCH), 128.74 (+ve, ArCH), 128.92 (+ve, ArCH), 130.43 (ab, C), 130.82 (+ve, ArCH), 132.04 (ab, C), 135.81 (ab, C), 135.88 (+ve, C6-H), 136.98 (ab, C), 151.91 (ab, C), 163.33 (ab, C); ν_{max} (KBr)/cm^{-1}: 1710, 1662, 1649, 775, 763; (Found C, 51.12; H, 3.13; N, 6.11%. $C_{19}H_{14}Cl_4N_2O_2$ requires C, 51.3; H, 3.15; N, 6.30%).

4.2.13. 1-(3-Chlorobenzyl)-1*H*-pyrimidine-2,4-dione (9a). 74%; White solid, mp 140 °C (lit.[7] mp 140 °C).

4.2.14. 1-(4-Chlorobenzyl)-1*H*-pyrimidine-2,4-dione (9b). 78%; white solid, mp 178 °C (lit.[7] mp 180 °C).

4.2.15. 1-(2-Nitrobenzyl)-1*H*-pyrimidine-2,4-dione (9c). 74%; white solid, mp 119 °C (lit.[7] mp 120 °C).

4.2.16. 1-(2,4,6-Trimethylbenzyl)-1H-pyrimidine-2,4-dione (9d). 68%; White solid, mp 230 °C (CH_3CN) (lit.[7] mp 230 °C).

4.2.17. 1-(3-Chlorobenzyl)-5-methyl-1*H*-pyrimidine-2,4-dione (10a). 79%; White solid, mp 140 °C (CH_3CN); ^{1}H NMR ($CDCl_3$+TFA): δ 1.93 (3H, s, CH_3), 4.92 (2H, s, CH_2), 7.15–7.38 (6H, m, ArH+C6-H); ^{13}C (normal/DEPT-135) ($CDCl_3$+TFA): δ 11.80 (+ve, CH_3), 51.64 (−ve, CH_2), 112.90 (ab, C-5), 126.20 (+ve, ArCH), 128.13 (+ve, ArCH), 129.41 (+ve, ArCH), 130.75 (+ve, ArCH), 135.38 (ab, C), 135.78 (ab, C), 142.25 (+ve, C-6), 152.38 (ab, C), 166.58 (ab, C); ν_{max} (KBr)/cm^{-1}: 3022, 2999, 1685, 1656, 775; HRMS found: 250.0513, $C_{12}H^{35}_{11}ClN_2O_2$ requires 250.0509; found: 252.0488, $C_{12}H^{37}_{11}ClN_2O_2$ requires 252.0479; (Found: C, 57.1; H, 4.29; N, 11.20. $C_{12}H_{11}ClN_2O_2$ requires C, 57.4; H, 4.39; N, 11.2%).

4.2.18. 1-(4-Chlorobenzyl)-5-methyl-1*H*-pyrimidine-2,4-dione (10b). 82%; White solid, mp 160 °C (CH_3CN); FAB mass *m/z* 251, 253 (3:1) (M^+); ^{1}H NMR ($CDCl_3$+TFA): δ 1.95 (3H, s, CH_3), 4.95 (2H, s, CH_2), 7.23–7.25 (3H, m, ArH+C6-H), 7.37–7.40 (2H, m, ArH); ^{13}C (normal/DEPT-135) ($CDCl_3$+TFA): δ 11.89 (+ve, CH_3), 51.56 (−ve, CH_2), 112.80 (ab, C5-H), 129.51 (+ve, ArCH), 129.65 (+ve, ArCH), 132.26 (ab, C), 135.37 (ab, C), 142.00 (+ve, C6-H), 152.32 (ab, C), 166.43 (ab, C); ν_{max} (KBr)/cm^{-1}: 3170, 2358, 1702, 1656, 746, 692; (Found: C, 56.68; H, 4.23; N, 11.4. $C_{12}H_{11}ClN_2O_2$ requires C, 57.4; H, 4.39; N, 11.2%).

4.2.19. 1-(2-Nitrobenzyl)-5-methyl-1*H*-pyrimidine-2,4-dione (10c). 82%; White solid, mp 242 °C (CH_3CN); FAB mass *m/z* 262 (M^++1); ^{1}H NMR ($CDCl_3$+TFA): δ 1.99 (3H, s, CH_3), 5.40 (2H, s, CH_2), 7.35 (1H, d, J=9.0 Hz, ArH), 7.40 (1H, s, C6-H), 7.60 (1H, t, J=9.0 Hz, ArH), 7.72 (1H, t, J=9.0 Hz, ArH), 8.18 (1H, d, J=9.0 Hz, ArH);

^{13}C (normal/DEPT-135) ($CDCl_3$+TFA): δ 11.75 (+ve, CH_3), 49.83 (−ve, CH_2), 112.58 (ab, C-5), 125.89 (+ve, ArCH), 129.56 (+ve, ArCH), 129.62 (+ve, ArCH), 129.93 (ab, C), 134.74 (+ve, ArCH), 142.85 (+ve, 6-CH), 147.72 (ab, C), 152.42 (ab, C), 166.58 (ab, C); ν_{max} (KBr)/cm^{-1}: 3039, 1691, 1517, 1353, 727; (Found: C, 54.97; H, 4.18; N, 15.83. $C_{12}H_{11}N_3O_4$ requires C, 55.2; H, 4.21; N, 16.09%).

4.2.20. 1-(2,4,6-Trimethyl)-5-methyl-1*H*-pyrimidine-2,4-dione (10d). 87%; White solid, mp 210 °C (CH_3CN); FAB mass *m*/*z* 259 (M^++1); ^{1}H NMR ($CDCl_3$): δ 1.77 (3H, s, CH_3), 2.25 (6H, s, 2×CH_3), 2.33 (3H, s, CH_3), 4.93 (2H, s, CH_2), 6.48 (1H, s, C6-H), 6.94 (2H, s, ArH), 8.91 (1H, br s, NH); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 12.51 (+ve, CH_3), 19.76 (+ve, CH_3), 20.99 (+ve, CH_3), 44.38 (−ve, CH_2), 110.52 (ab, C5), 126.82 (ab, ArCH), 129.75 (+ve, ArCH), 137.16 (+ve, 6-CH), 138.16 (ab, C), 138.92 (ab, C), 151.24 (ab, C), 163.90 (ab, C); ν_{max} (KBr)/cm^{-1}: 3033, 2385, 1701, 1676, 864; (Found: C, 69.56; H, 6.84; N, 10.83. $C_{15}H_{18}N_2O_2$ requires C, 69.7; H, 6.97; N, 10.85%).

4.3. N_3-(*o*-Chlorobenzylation) of 4a–4c

Procedure **B**: **4a** (2.36 g, 1 mmol) was heated with *N*,*O*-bis-(trimethylsilyl)acetamide (BSA) at 110 °C in an oil bath and a clear solution was obtained in 3–4 h. **3a** (2 equiv) and 1,2-DCE (10 ml) were added to the above solution and refluxing was continued for 48 h. The reaction mixture was treated with ethanol (10 ml). The solvent was distilled off under vacuum and the residue was column chromatographed over silica-gel column using hexane–ethyl acetate mixture as eluent to isolate mixture of **6a**, **11a** and **12a**. Similarly, **4b** and **4c** on silylation with BSA followed by reactions with **3b** and **3c** gave respective mixtures of **6b+11b+12b** and **6c+11c+12c**.

4.4. General procedure for the synthesis of 1-allyl/alkyl/ethoxycarbonylmethyl 3-(2-Cl/2,4-diCl/2,6-diCl-benzyl-2,4-1*H*,3*H*-pyrimidine-2,4-dione derivatives

Procedure **C**: A solution of 2,4-bis-(trimethylsilyloxy)pyrimidine (**1**) (0.01 mol), alkyl/allyl halide (0.15 mol) and I_2 (127 mg, 0.001 mol) in 1,2-DCE (20 ml) was refluxed for 24–48 h. Then appropriately substituted *o*-chlorobenzyl chloride (0.02 mol) was added and the refluxing was continued. After completion of the reaction (TLC), it was cooled and treated with ethanol (10 ml). The solvent was distilled off under vacuum and the residue was column chromatographed over silica-gel column using hexane–ethyl acetate as eluents to isolate the pure compounds.

4.4.1. 1-Allyl-3-(2-chlorobenzyl)-1*H*-pyrimidine-2,4-dione (15a). 73%; Pale yellow liquid, FAB mass *m*/*z* 277, 279 (3:1) (M^+); ^{1}H NMR ($CDCl_3$): δ 4.30 (2H, d, *J*=6.2 Hz, CH_2), 5.24 (2H, s, CH_2), 5.29–5.35 (2H, m, =CH_2), 5.88 (1H, d, *J*=8.0 Hz, C5-H), 5.91–5.95 (1H, m, =CH), 6.96–7.11 (1H, m, ArH), 7.15–7.35 (4H, m, ArH+C6-H). The decoupling of 5-H doublet at δ 5.88 gives a sharp singlet at δ 7.24 embedded into a multiplet; ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 41.76 (−ve, CH_2), 50.95 (−ve, CH_2), 101.45 (+ve, 5-CH), 117.53 (−ve, CH_2), 126.46 (+ve, ArCH), 126.62 (+ve, ArCH), 127.89 (+ve, ArCH), 129.42 (+ve, ArCH), 131.52 (+ve, CH), 133.27 (ab, C), 135.45 (ab, C), 143.98 (+ve, 6-CH), 150.85 (ab, C), 162.48 (ab, C); ν_{max} ($CHCl_3$)/cm^{-1}: 3104, 1712, 1643, 752, 810; (Found C, 60.9; H, 4.76; N, 9.97%. $C_{14}H_{13}ClN_2O_2$ requires C, 60.7; H, 4.70; N, 10.12%).

4.4.2. 1-Cinnamyl-3-(2-chlorobenzyl)-1*H*-pyrimidine-2,4-dione (15b). 72%; Light yellow solid, mp 110 °C (CH_3CN); FAB mass *m*/*z* 353, 355 (3:1) (M^+); ^{1}H NMR ($CDCl_3$): δ 4.53 (2H, d, *J*=6.0 Hz, CH_2), 5.17 (2H, s, CH_2), 5.84 (1H, d, *J*=7.8 Hz, C5-H), 6.22 (1H, dt, J_1=16.0 Hz, J_2=6.0 Hz, =CH), 6.87 (1H, d, *J*=16.0 Hz, =CH), 7.15–7.51 (10H, m, ArH+C6-H); ^{13}C (normal, DEPT-135) ($CDCl_3$): δ 42.14 (−ve, CH_2), 50.78 (−ve, CH_2), 101.75 (+ve, 5-CH), 122.14 (+ve, ArCH), 126.54 (+ve, ArCH), 126.74 (+ve, ArCH), 126.77 (+ve, ArCH), 128.22 (+ve, ArCH), 128.37 (+ve, ArCH), 128.62 (+ve, ArCH), 129.51 (+ve, CH), 132.94 (ab, C), 133.68 (ab, C), 135.04 (+ve, CH), 135.47 (ab, C), 141.93 (+ve, 6-CH), 151.22 (ab, C), 162.78 (ab, C); ν_{max} (KBr)/cm^{-1}: 3050, 1706, 1643, 752; (Found C, 67.9; H, 5.0; N, 8.2%. $C_{20}H_{17}ClN_2O_2$ requires C, 68.09; H, 4.86; N, 7.94%).

4.4.3. 1-Ethyl-3-[(2-chlorobenzyl)-1*H*-pyrimidine-2,4-dione (15c). 63%; Transparent liquid, FAB mass *m*/*z* 265, 267 (3:1) (M^+); ^{1}H NMR ($CDCl_3$): δ 1.27 (3H, t, *J*=7.8 Hz, CH_3), 3.82 (2H, q, *J*=7.8 Hz, CH_2), 5.25 (2H, s, CH_2), 5.82 (1H, d, *J*=7.8 Hz, C-5H), 6.94–6.98 (1H, m, ArH), 7.12–7.46 (4H, m, ArH+C6-H); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 14.24 (+ve, CH_3), 41.86 (−ve, CH_2), 44.89 (−ve, CH_2), 101.51 (+ve, 5-CH), 126.59 (+ve, ArH), 126.74 (+ve, ArH), 128.17 (+ve, ArH), 129.47 (+ve, ArH), 131.63 (ab, C), 133.48 (ab, C), 142.31 (+ve, 6-CH), 150.99 (ab, C), 162.88 (ab, C); ν_{max} ($CHCl_3$)/cm^{-1}: 3050, 2900, 2950, 1710, 1618, 810; (Found: C, 58.92; H, 5.02; N, 9.86. $C_{13}H_{13}ClN_2O_2$ requires C, 58.97; H, 4.95; N, 10.59%).

4.4.4. 1-Butyl-3-(2-chlorobenzyl)-1*H*-pyrimidine-2,4-dione (15d). 78%; Transparent liquid, FAB mass *m*/*z* 293, 295 (3:1) (M^+); ^{1}H NMR ($CDCl_3$): δ 0.98 (3H, t, *J*=7.2 Hz, CH_3), 1.32 (2H, hextet, *J*=7.2 Hz, CH_2), 1.68 (2H, quintet, *J*=7.2 Hz, CH_2), 3.74 (2H, t, *J*=7.2 Hz, CH_2), 5.28 (2H, s, CH_2), 5.84 (1H, d, *J*=8.0 Hz, C5-H), 6.97–7.01 (1H, m, ArH), 7.13–7.48 (4H, m, ArH+C6-H); The decoupling of the C5-H signal at δ 5.84 gives a singlet at δ 7.19 embedded into a multiplet; ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 13.56 (+ve, CH_3), 19.61 (−ve, CH_2), 30.97 (−ve, CH_2), 42.04 (−ve, CH_2), 49.63 (−ve, CH_2), 101.32 (+ve, 5-CH), 126.61 (+ve, ArH), 126.72 (+ve, ArH), 128.16 (+ve, ArH), 129.51 (+ve, ArH), 132.97 (ab, C), 133.76 (ab, C), 142.62 (+ve, 6-CH), 151.23 (ab, C), 162.96 (ab, C); ν_{max} ($CHCl_3$)/cm^{-1}: 3050, 2958, 1708, 1662, 810 cm^{-1}; (Found C, 61.5; H, 5.68; N, 9.38%. $C_{15}H_{17}ClN_2O_2$ requires C, 61.5; H, 5.81; N, 9.57%).

4.4.5. 1-Octyl-3-(2-chlorobenzyl)-1*H*-pyrimidine-2,4-dione (15e). 67%; Transparent liquid, FAB mass *m*/*z* 349, 351 (3:1) (M^+); ^{1}H NMR ($CDCl_3$): δ 0.87 (3H, t, *J*=7.2 Hz, CH_3), 1.27–1.29 (8H, m, 4×CH_2), 1.64–1.68 (4H, m, 2×CH_2), 3.74 (2H, t, *J*=7.2 Hz, CH_2), 5.25 (2H, s, CH_2), 5.80 (1H, d, *J*=8.0 Hz, C5-H), 6.93–6.98 (1H, m, ArH), 7.24 (1H, d, *J*=8.0 Hz, C6-H), 7.26–7.38 (3H, m, ArH); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 13.99 (+ve, CH_3), 22.52 (−ve, CH_2), 26.43 (−ve, CH_2), 29.03 (−ve,

CH_2), 31.65 (−ve, CH_2), 49.89 (−ve, CH_2), 101.31 (+ve, 5-CH), 126.62 (+ve, ArH), 126.91 (+ve, ArH), 128.15 (+ve, ArH), 129.35 (+ve, ArH), 132.99 (ab, C), 133.80 (ab, C), 142.6 (+ve, 6-CH), 150.99 (ab, C), 162.87 (ab, C); ν_{max} ($CHCl_3$)/cm^{-1}: 3043, 2923, 1689, 1641, 813; (Found: C, 65.48; H, 7.23; N, 7.87. $C_{19}H_{25}ClN_2O_4$ requires C, 65.41; H, 7.22; N, 8.03).

4.4.6. 1-(Ethoxycarbonylmethyl)-3-(2-chlorobenzyl)-1*H*-pyrimidine-2,4-dione (15f). 64%; Transparent liquid, FAB mass *m/z* 323, 325 (3:1) (M^+); ^1H NMR ($CDCl_3$): δ 1.29 (3H, t, J=7.2 Hz, CH_3), 4.22 (2H, q, J=7.2 Hz, CH_2), 4.46 (2H, s, CH_2), 5.24 (2H, s, CH_2), 5.85 (1H, d, J=7.8 Hz, C5-H), 6.95–7.51 (5H, m, ArH+C6-H); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 13.98 (+ve, CH_3), 42.11 (−ve, CH_2), 49.87 (−ve, CH_2), 62.09 (−ve, CH_2), 102.13 (+ve, CH-5), 126.65 (+ve, ArH), 127.50 (+ve, ArH), 129.44 (+ve, ArH), 129.64 (+ve, ArH), 132.92 (ab, C), 133.43 (ab, C), 142.52 (+ve, CH-6), 151.34 (ab, C), 162.62 (ab, C), 167.29 (ab, C); ν_{max} ($CHCl_3$)/cm^{-1}: 3064, 2987, 1747, 1704, 1658, 1207, 811; (Found: C, 55.79; H, 4.77; N, 8.60. $C_{15}H_{15}ClN_2O_4$ requires C, 55.80; H, 4.65; N, 8.60).

4.4.7. 1-Allyl-3-(2,4-dichlorobenzyl)-1*H*-pyrimidine-2,4-dione (16a). 62%; Solid, mp 94 °C (CH_3CN); FAB mass *m/z* 311, 313, 315 (100:62:1) (M^+); ^1H NMR ($CDCl_3$): δ 4.36 (2H, d, J=8 Hz, CH_2), 5.21 (2H, s, CH_2), 5.25–5.35 (2H, m, =CH_2), 5.72 (1H, d, J=8.0 Hz, C5-H), 5.79–5.90 (1H, m, =CH), 6.96 (1H, d, J=8.0 Hz, Ar-6′H), 7.12 (1H, dd, J_1=8.0 Hz, J_2=1.2 Hz, Ar-5′H) 7.21 (1H, d, J=8.0 Hz, C6-H), 7.78 (1H, d, J=1.2 Hz, Ar-3′H); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 41.75 (−ve, CH_2), 51.09 (−ve, CH_2), 101.63 (+ve, 5-CH), 119.58 (−ve, =CH_2), 127.06 (+ve, ArCH), 128.02 (+ve, ArCH), 129.32 (+ve, ArCH), 131.27 (+ve, CH), 131.43 (ab, C), 132.40 (ab, C), 133.37 (ab, C), 142.27 (+ve, 6-CH), 151.06 (ab, C), 162.97 (ab, C); ν_{max} (KBr)/cm^{-1}: 3089, 1708, 1658, 808; (Found: C, 53.9; H, 3.9; N, 9.3. $C_{14}H_{12}Cl_2N_2O_2$ requires C, 54.04; H, 3.89; N, 9.00%).

4.4.8. 1-Ethyl-3-(2,4-dichlorobenzyl)-1*H*-pyrimidine-2,4-dione (16b). 70%; White solid, mp 98 °C (CH_3CN); FAB mass *m/z* 299, 301 (100: 62:1) (M^+); ^1H NMR ($CDCl_3$): δ 1.27 (3H, t, J=7.2 Hz, CH_3), 3.81 (2H, q, J=7.2 Hz, CH_2), 5.19 (2H, s, CH_2), 5.83 (1H, s, J=7.8 Hz, C5-H), 6.92 (1H, d, J=8.4 Hz, Ar6′-H); 7.14 (1H, dd, J_1=8.4 Hz, J_2=1.8 Hz, Ar-5′H), 7.23 (1H, d, J=7.8 Hz, C6-H), 7.37 (1H, d, J=1.8 Hz, Ar-3′H); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 14.25 (+ve, CH_3), 41.68 (−ve, CH_2), 45.03 (−ve, CH_2), 101.42 (+ve, 5-CH), 127.05 (+ve, ArCH), 128.09 (+ve, ArCH), 129.31 (+ve, ArCH), 132.45 (ab, C), 133.39 (ab, C), 133.76 (ab, C), 142.51 (+ve, 6-CH), 150.94 (ab, C), 163.28 (ab, C); ν_{max} (KBr)/cm^{-1}: 3087, 3060, 2897, 1708, 1656, 808 cm^{-1}; (Found: C, 51.9; H, 3.8; N, 9.5. $C_{13}H_{12}Cl_2N_2O_2$ requires C, 52.19; H, 4.04; N, 9.36%).

4.4.9. 1-Butyl-3-(2,4-dichlorobenzyl)-1*H*-pyrimidine-2,4-dione (16c). 63%; White solid, mp 60 °C (CH_3CN); FAB mass *m/z* 327, 329, 331 (100:62:1) (M^+); ^1H NMR ($CDCl_3$): δ 0.98 (3H, t, CH_3), 1.25–1.42 (2H, m, CH_2), 1.62–1.72 (2H, m, CH_2), 3.76 (2H, t, CH_2), 5.17 (2H, s, CH_2), 5.83 (1H, d, J=8.0 Hz, C5-H), 6.94 (1H, d, J=8.0 Hz, C6-H), 7.13–7.48 (3H, m, ArH); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 13.59 (+ve, CH_3), 19.63 (−ve, CH_2), 30.90 (−ve, CH_2), 41.64 (−ve, CH_2), 49.67 (−ve, CH_2), 101.32 (+ve, 5-CH), 127.02 (+ve, ArH), 127.96 (+ve, ArH), 131.38 (+ve, ArH), 131.75 (absent, C), 133.38 (absent, C), 133.78 (absent, C), 142.8 (+ve, 6-CH), 151.18 (absent, C), 163.04 (absent, C); ν_{max} (KBr)/cm^{-1}: 3056, 2960, 1703, 1672, 811; HRMS found: 327.0662, $C_{15}H_{17}^{35}Cl_2N_2O_2$ requires 327.0659.

4.4.10. 1-(Ethoxycarbonylmethyl)-3-(2,4-dichlorobenzyl)-1*H*-pyrimidine-2,4-dione (16d). 64%; White solid, mp 120 °C (CH_3CN); FAB mass *m/z* 357, 359, 361 (100:70:10) (M^+); ^1H NMR ($CDCl_3$): δ 1.28 (3H, t, J=7.2 Hz, CH_3), 4.23 (2H, q, J=7.2 Hz, OCH_2), 4.64 (2H, s, NCH_2), 5.20 (2H, s, CH_2), 5.83 (1H, d, J=8.0 Hz, C-5H), 6.93 (1H, d, J=8.0 Hz, C-6H), 7.07–7.38 (3H, m, ArH); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 14.04 (+ve, CH_3), 41.62 (−ve, CH_2), 49.76 (−ve, CH_2), 62.05 (−ve, CH_2), 102.03 (+ve, 5-CH), 127.03 (+ve, ArCH), 127.90 (+ve, ArCH), 129.28 (+ve, ArCH), 132.40 (ab, C), 133.57 (ab, C), 133.86 (ab, C), 142.32 (+ve, 6-CH), 151.26 (ab, C), 162.28 (ab, C), 167.10 (ab, C); ν_{max} (KBr)/cm^{-1}: 3074, 2995, 2958, 1743, 1720, 1683, 1236, 779; (Found: C, 50.3; H, 3.9; N, 7.8. $C_{15}H_{14}Cl_2N_2O_4$ requires C, 50.44; H, 3.95; N, 7.84%).

4.4.11. 1-Allyl-3-(2,6-dichlorobenzyl)-1*H*-pyrimidine-2,4-dione (17a). 65%; White solid, mp 110 °C (CH_3CN); FAB mass *m/z* 311, 313, 315 (100: 62:1) (M^+); ^1H NMR ($CDCl_3$): δ 4.30 (2H, d, J=6.0 Hz, CH_2), 5.13–5.23 (2H, m, =CH_2), 5.41 (2H, s, CH_2), 5.72–5.87 (1H, m, =CH), 5.88 (1H, d, J=8.0 Hz, C5-H), 7.12 (1H, d, J=8.0 Hz, C6-H), 7.17 (1H, t, J=8.0 Hz, Ar-4′H), 7.37 (2H, d, J=8.0 Hz, Ar-3′/5′H); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 40.93 (−ve, CH_2), 50.77 (−ve, CH_2), 101.73 (+ve, 5-CH), 118.99 (−ve, CH_2), 128.53 (+ve, ArCH), 128.79 (+ve, ArCH), 131.61 (+ve, =CH), 131.87 (ab, C), 135.73 (ab, C), 141.74 (+ve, CH), 150.99 (ab, C), 162.73 (ab, C); ν_{max} (KBr)/cm^{-1}: 3050, 1708, 1656, 736; (Found: C, 53.9; H, 3.7; N, 9.1. $C_{14}H_{12}Cl_2N_2O_2$ requires C, 54.04; H, 3.89; N, 9.00%).

4.4.12. 1-Butyl-3-(2,6-dichlorobenzyl)-1*H*-pyrimidine-2,4-dione (17b). 62%; Solid, mp 140 °C (CH_3CN); FAB mass *m/z* 327, 329, 331 (100: 72:1) (M^+); ^1H NMR ($CDCl_3$): δ 0.98 (3H, t, J=7.2 Hz, CH_3), 1.25–1.37 (2H, m, CH_2), 1.40–1.72 (2H, m, CH_2), 3.73 (2H, t, J=7.2 Hz, CH_2), 5.18 (2H, s, CH_2), 5.80 (1H, d, J=9.0 Hz, C5-H), 6.92 (1H, d, J=9.0 Hz, C6-H), 7.09–7.45 (3H, m, ArH); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 13.56 (+ve, CH_3), 19.54 (−ve, CH_2), 30.93 (−ve, CH_2), 40.87 (−ve, CH_2), 49.46 (−ve, CH_2), 101.23 (+ve, 5-CH), 128.50 (+ve, ArCH), 128.68 (+ve, ArCH), 131.94 (ab, C), 135.65 (ab, C), 142.35 (+ve, 6-CH), 151.03 (ab, C), 162.87 (ab, C); ν_{max} (KBr)/cm^{-1}: 3070, 2952, 1712, 1656, 800; (Found: C, 55.36; H, 4.60; N, 8.19. $C_{15}H_{16}Cl_2N_2O_2$ requires C, 55.04; H, 4.89; N, 8.56%).

4.4.13. 1-Ethoxycarbonylmethyl-3-(2,6-dichlorobenzyl)-1*H*-pyrimidine-2,4-dione (17c). 62%; White solid, mp 120 °C (CH_3CN); FAB mass *m/z* 357, 359, 361 (100: 62:1) (M^+); ^1H NMR ($CDCl_3$): δ 1.29 (3H, t, J=7.2 Hz, CH_3),

4.14 (2H, q, J=7.2 Hz, OCH_2), 4.39 (2H, s, CH_2), 5.38 (2H, s, CH_2), 5.78 (1H, d, J=7.8 Hz, C5-H), 7.06 (1H, d, J=7.8 Hz, C6-H), 7.08–7.27 (3H, m, ArH); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 14.00 (+ve, CH_3), 40.88 (−ve, CH_2), 49.55 (−ve, CH_2), 61.86 (−ve, CH_2), 101.98 (+ve, 5-CH), 128.37 (+ve, ArCH), 128.60 (+ve, ArCH), 131.89 (ab, C), 136.00 (ab, C), 141.90 (+ve, 6-CH), 151.05 (ab, C), 162.31 (ab, C), 167.13 (ab, C); ν_{max} (KBr)/cm^{-1}: 3083, 2985, 2958, 1743, 1720, 1683, 1236, 779 (Found: C, 49.8; H, 3.8; N, 7.8. $C_{15}H_{14}Cl_2N_2O_4$ requires C, 50.04; H, 3.95; H, 7.84%).

Acknowledgements

We thank CSIR, New Delhi for financial assistance and DST, New Delhi for the FIST programme. NIH, Bethesda USA is gratefully acknowleged for evaluating anti-HIV activites.

References and notes

1. (a) Richman, D. D. *Antimicrob. Agents Chemother.* **1993**, *37*, 1207; (b) Mitsuya, H.; Border, S. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1911–1915; (c) Yarchoan, R.; Mitsuya, H.; Thomas, R. V.; Pluda, J. M.; Hartman, N. R.; Perno, C.-F.; Marczyk, K. S.; Allain, J.-P.; Johns, D. G.; Border, S. *Science* **1989**, *245*, 412–415; (d) Tantillo, C.; Ding, J.; Jacobo-Holina, A.; Nanni, R. G.; Boyer, P. L.; Hughes, S. H.; Pauwels, R.; Andries, K.; Janssen, P. A.; Arnold, E. *J. Mol. Biol.* **1994**, *243*, 369–387.
2. (a) Ragno, R.; Mai, A.; Sbardella, G.; Artico, M.; Massa, S.; Musiu, C.; Mura, M.; Marturana, F.; Cadeddu, A.; Colla, P. L. *J. Med. Chem.* **2004**, *47*, 928–934; (b) Pederson, O. S.; Pederson, E. B. *Antiviral Chem. Chemother.* **1999**, *10*, 285–314; (c) De Clercq, E. *Antiviral Res.* **1998**, *38*, 153–179; (d) De Clercq, E. *J. Med. Chem.* **1995**, *38*, 2491–2517; (e) Isobe, Y.; Tobe, M.; Inoue, Y.; Sobe, M.; Tsuchiya, M.; Hayashi, H. *Bioorg. Med. Chem.* **2003**, *11*, 4933–4940.
3. (a) Smerdon, S. J.; Jager, J.; Wang, J.; Kohlstaedt, L. A.; Chirino, A. J.; Frieduan, J. M.; Rice, P. A.; Steitz, T. A. *Proc. Natl. Acad. Sci. U.S.A.* **1994**, *91*, 3911–3915; (b) Spence, R. A.; Kati, W. M.; Anderson, K. S.; Johnson, K. A. *Science* **1995**, *267*, 988–993; (c) Ding, J.; Das, K.; Moereels, H.; Koyuans, L.; Andries, K.; Janssen, P. A. J.; Hughes, S. H.; Arnold, E. *Nat. Struct. Biol.* **1995**, *2*, 407–415 and references therein; (d) Ren, J.; Esnouf, R.; Garman, E.; Somers, S.; Ross, C.; Kirby, I.; Keeling, J.; Darby, G.; Jones, Y.; Stuart, D.; Stanners, D. *Nat. Struct. Biol.* **1995**, *2*, 293–302.
4. Nisho, M.; Hirota, M.; Umerzawa, Y. *The CH–π interactions*; Wiley-VCH: New York, NY, 1988.
5. Pontikis, R.; Benhida, R.; Aubertin, A.-M.; Grierson, D. S.; Monheret, C. *J. Med. Chem.* **1997**, *40*, 1845–1854.
6. El-Brollosy, N. R.; Jorgensen, P. T.; Daha, B.; Boel, A. M.; Pederson, E. B.; Nielsen, C. *J. Med. Chem.* **2002**, *45*, 5721–5726.
7. Malik, V.; Singh, P.; Kumar, S. *Tetrahedron* **2005**, *61*, 4009–4014.