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Synthesis of 5-acyl-6-[2-hydroxy-3-(amino)propylamino]-1,3-dialkyl-1*H*-pyrimidine-2,4-diones†

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A stepwise synthetic approach involving substitution of 6-chloro-1,3-dialkyluracils (**5** and **6**) with 3-(*tert*-amino)-2-hydroxypropylamines and subsequent acylation at C5 of uracil has been used to synthesize pyrimidinediones **27–33** in 61–89% overall yield. The conformational aspects of the new molecules based upon NMR data have been discussed.

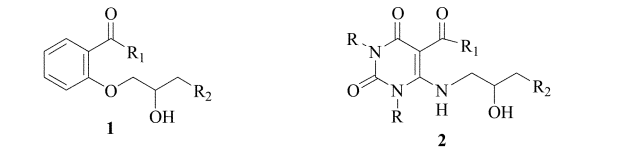
Introduction

One major objective of organic synthesis is to design and synthesize molecules with potential bioactivities. Multi-drug resistance (MDR) is a major limiting factor in the development of drug candidates. In recent years, the development of means to control MDR has become important – even more important than the development of new drug molecules. It is well established that MDR comes into play due to the over-expression of p-glycoprotein (p-gp).[1,2] A number of MDR modulators are being used along with the drugs which bind competitively to p-gp and thereby inhibit the p-gp-mediated transport of drug molecules out of the cell.[1–3] Propafenone (**1a**) and its derivatives (**1b**–**g**), as well as its heterocyclic analogues that have pyrazole in place of benzene[13] have been extensively explored[4–12,13] for their MDR-modulating properties. Most of the MDR modulators have appropriately placed aromatic ring(s) and a basic tertiary nitrogen. Uracil, a unique molecule due to its functionalities and reactivity pattern, is widespread in natural as well as synthetic systems. The pyrimidinedione ring constitutes the basic skeleton of a number of clinically used drugs, many of which face the problem of multi-drug resistant organisms. The use of uracil-based MDR modulators can create competition between the MDR modulators and anti-cancer drugs for binding to p-gp, reducing the level of multi-drug resistance. The acceptability of the uracil moiety in biological systems and the presence of a greater number of H-binding sites in comparison to propafenone(s) prompted us to design and synthesize pyrimidinedione-based molecules (**2a**–**g**). These molecules could be considered as structural analogues of propafenone (**1a**), formed by replacement of the benzene moiety and the ethereal oxygen of propafenone with pyrimidinedione and NH respectively (Scheme 1).

Results and discussion

Herein we present the syntheses of the new designed pyrimidine-2,4-dione derivatives **2a**–**g**. The conformational features of some of the molecules have been described on the basis of coupling constants of various protons in the ^{1}H NMR spectra, and NOE experiments.

A direct approach for the syntheses of compounds **2a**–**g** by the reaction of epichlorohydrin with 1,3-dimethyl-6-aminouracil (**3**)



1

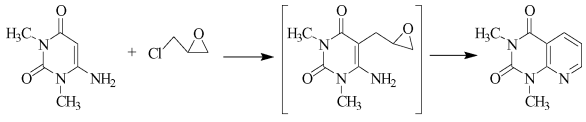
a, R_1= CH_2CH_2Ph, R_2 = $NHCH_2CH_2CH_3$
b, R_1 = Ph, R_2 = 4-morpholinyl
c, R_1 = Ph, R_2 = 1-piperidinyl
d, R_1 = Ph, R_2 = 1-pyrrolidinyl
e, R_1 = CH_2CH_2Ph, R_2 = 4-morpholinyl
f, R_1 = CH_2CH_2Ph, R_2 = 1-piperidinyl
g, R_1 = CH_2CH_2Ph, R_2 = 1-pyrrolidinyl

2

a, R = CH_3, R_1=Ph, R_2 = 4-morpholinyl
b, R = CH_3, R_1=Ph, R_2 = 1-piperidinyl
c, R = CH_3, R_1=Ph, R_2 = 1-pyrrolidinyl
d, R = CH_2Ph, R_1=Ph, R_2 = 4-morpholinyl
e, R = CH_2Ph, R_1=Ph, R_2 = 1-piperidinyl
f, R = CH_2Ph, R_1=Ph, R_2 = 1-pyrrolidinyl
g, R= CH_3, R_1=CH_2CH_2Ph, R_2=4-morpholinyl

Scheme 1

in DMF using K_2CO_3 as base gave a solid compound [M^+ *m/z* 191], in 40% yield (lit.[14] 14%), mp 163–64 °C (lit.[15] mp 164–165 °C), which was identified as 1,3-dimethylpyrido[2,3-*d*]pyrimidin-2,4-dione (**4**) by comparison with reported data (Scheme 2). This is probably a result of epichlorohydrin reacting at C5 of the uracil followed by epoxide ring-opening by the 6-NH_2 group and oxidation/dehydrogenation.



3 **4**

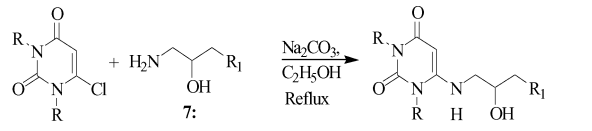
Scheme 2

In another synthetic approach, 6-amino-5-benzoyl-1,3-dimethyluracil[16] failed to react with epichlorohydrin under various reaction conditions, using *e.g.* K_2CO_3, potassium *tert*-butoxide, triethylamine, NaH and NaOH as bases in CH_3CN, DMF and methanol.

Therefore, an alternative approach was followed, whereby 1,3-dialkyl-6-chlorouracils (**5**, **6**) were made to react with hydroxy amines **7**.[17,18] 6-Chloro-1,3-dimethyluracil (**5**) (10 mmol) on refluxing with 3-morpholino-2-hydroxypropylamine (**7a**) (10 mmol) in absolute ethanol in the presence of Na_2CO_3 gave **8** as yellow oil (87%), [M^+ + 1, *m/z* 299] (Scheme 3). In the ^{1}H NMR spectrum of **8**, most of the protons are magnetically non-equivalent and the spectrum shows a 4H multiplet at δ 2.43–2.48, a 2H multiplet at δ 2.63, two 1H double double doublets at δ 3.00 and 3.21, two 3H singlets at δ 3.29 and 3.40, a broad 1H signal (exchangeable with D_2O) at δ 3.35, a 4H multiplet at

† Electronic supplementary information (ESI) available: ^{1}H NMR spectra of **12** and **18**. See DOI: 10.1039/b509775d

DOI:10.1039/b509775d



5, R = CH_3
6, R = CH_2Ph

a, R_1 = 4-morpholinyl
b, R_1 = 1-piperidinyl
c, R_1 = 1-pyrrolidinyl

7:

8-13

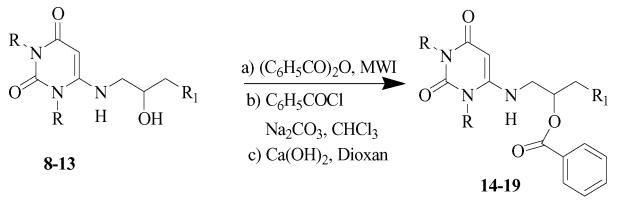
8, R = CH_3, R_1 = 4-morpholinyl (87%)
9, R = CH_3, R_1 = 1-piperidinyl (84%)
10, R = CH_3, R_1 = 1-pyrrolidinyl (84%)
11, R = CH_2Ph, R_1 = 4-morpholinyl (78%)
12, R = CH_2Ph, R_1 = 1-piperidinyl (77%)
13, R = CH_2Ph, R_1 = 1-pyrrolidinyl (76%)

Scheme 3

δ 3.72, a 1H multiplet at δ 4.0, a singlet at δ 4.81 and a broad 1H triplet (exchangeable with D_2O) at δ 5.21. The assignments of these signals to specific protons have been made on the basis of coupling constants of various signals, their decouplings, NOE and ^1H–^{13}C HETCOR NMR experiments. Decoupling of the multiplet at δ 4.0 converts the two double double doublets to their respective double doublets, and the most upfield signal at δ 2.44 is converted to a singlet, which shows that the 1H multiplet at δ 4.0 belongs to H_d and that the 4H multiplet at δ 2.43–2.48 contains the 2 C10 protons (Fig. 1a). On D_2O exchange, the signal at δ 5.21 disappears and the two double double doublets are converted to two double doublets. This indicates that the exchangeable signal at δ 5.21 belongs to NH (H_a) and two double double doublets at δ 3.00 and 3.21 belong to the H_c and H_b protons at C8, and that the appearance of the double double doublets is due to geminal coupling and two vicinal couplings with the CH and NH protons. Decoupling of the 4H signal at δ 3.72 transforms the left part of the multiplet at δ 2.43–2.48 to a singlet. This shows that the 4H multiplet at δ 2.43–2.48 contains the two protons at C12/C16 and that the signal at δ 3.72 belongs to the 4 protons at C13 and C15. These assignments have also been confirmed by the ^1H–^{13}C HETCOR NMR spectrum. The other two protons of C12/C16 appear at δ 2.63 as a multiplet. The observation of an NOE between H_d and the multiplet signal at δ 2.63 indicates that the equatorial protons of the C12/C16 carbons appear at δ 2.63, while the axial protons of C12/C16 appear at δ 2.43 (the energy-minimized structure of **8** also shows that H_d and the equatorial proton of C16 are in close proximity). The geminal coupling constant of each proton of the ddd ($J_{H_b-H_c}$) is 12.6 Hz. The proton at δ 3.21 (H_b) shows a coupling of 3.6 Hz with H_d and a coupling of 3.9 Hz with NH (H_a) proton. The proton at δ 3.00 (H_c) shows a 6.9 Hz coupling with H_d and a coupling of 6.6 Hz with the NH (H_a) proton. On the basis of the dependence of coupling constant on dihedral angle, it is predicted that H_a, H_b, and H_d are *syn* to each other, while the proton H_c is *anti* to the H_a and H_d protons. Based upon these NMR investigations, configurations of the chiral carbon center present in compound **8** have been shown in Fig. 1a ; its energy-minimized structure (Fig. 1b) also corresponds to the structure predicted from the NMR data. It seems that the part of the substituent at C6 near to the uracil ring *i.e.*, the NH–C8–C9 fragment, shows slow conformational changes on the NMR scale, while the distal part of the chain (C10 and the morpholine moiety) is flexible.

In similar reactions, the 6-chloro-1,3-dialkyluracils **5** and **6**, on reaction with appropriately synthesized amino alcohols **7a–c**, provide respective uracil derivatives **9–13** in 76–84% yields (Scheme 3). The ^1H NMR spectra of **9–13** show similar coupling features to those for **8**. In compounds **11–13**, the benzylic protons at N1 and N3 appear as doublets with a strong geminal coupling constant of 15 Hz.

Heating of a mixture of **8** and benzoic anhydride (2 equiv.) in a microwave oven for 3 minutes, after work-up and column chromatography, gave a yellow oil in 95% yield, [$M^+ + 1$ m/z 403], which contained a benzoyl group. The downfield shift of the H_d proton to δ 5.42 (presence of the electron-withdrawing group on C9), the absence of an exchangeable (OH) proton in the region δ 3–4, and the appearance of an ester absorption peak at 1709 cm^{-1} in the IR spectrum support the formation of compound **14**. (Scheme 4).



8-13

14-19

	conditions		
	a	b	c
14, R = CH_3, R_1 = 4-morpholinyl	95%	92%	81%
15, R = CH_3, R_1 = 1-piperidinyl	91%	88%	75%
16, R = CH_3, R_1 = 1-pyrrolidinyl	90%	88%	73%
17, R = CH_2Ph, R_1 = 4-morpholinyl	82%	81%	70%
18, R = CH_2Ph, R_1 = 1-piperidinyl	80%	80%	72%
19, R = CH_2Ph, R_1 = 1-pyrrolidinyl	79%	75%	70%

Scheme 4

The chemical shifts to all the protons of **14** have been assigned on the basis of decoupling, NOE and ^1H–^{13}C HETCOR NMR experiments. The C8 protons appear as double double doublets at δ 3.41 and 3.53 (Fig. 2) as in compound **8**. In contrast to compound **8**, the C10 protons appear as a doublet at δ 2.77, not overlapping with the C12/C16 protons. Similarly,

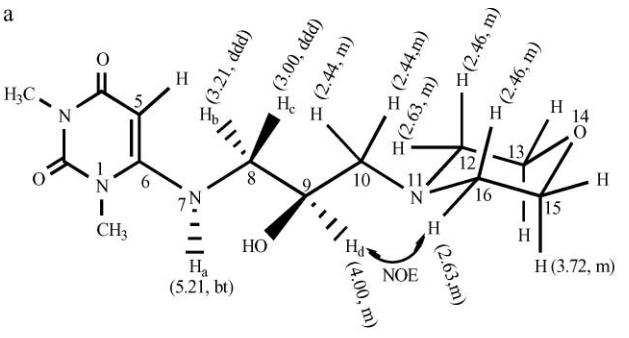


Fig. 1 a) NMR spectral assignment and relative configurations at NH, C8 and C9 of **8**. b) Energy-minimized structure of **8**.[19]

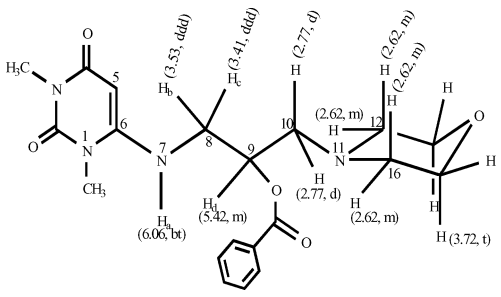
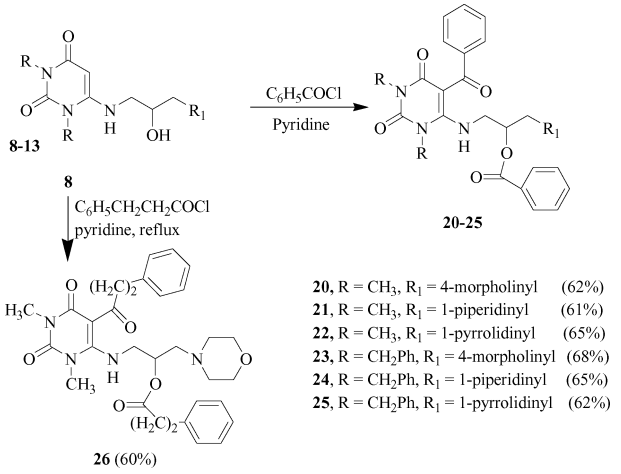


Fig. 2 NMR spectral assignment of **14**.

compounds **9–13** on treatment with benzoic anhydride under microwave irradiation provide compounds **15–19** in excellent yield (Scheme 4).

In order to get C5-benzoylated products, alternative reaction conditions were tried. Treatment of **8** with benzoyl chloride in chloroform/Na_2CO_3 or dioxan/$Ca(OH)_2$ gave compound **14** in 92% and 81% yields respectively; no C5-benzoylated product was formed. Compounds **9–13** also undergo a similar type of reaction to give the respective compounds **15–19** (Scheme 4, conditions b and c). Therefore, under all the reaction conditions shown in Scheme 4, compounds **8–13** underwent regioselective benzoylation at OH. However, on treatment with benzoyl chloride in pyridine, **8** gave an oily product [$M^+ + 1$ m/z 507]. The mass difference of 208 units from **8** indicated that two benzoyl groups had been introduced. The conspicuous absence of the C5 proton in the δ 4–5 region of the ^{1}H NMR spectrum indicated the formation of compound **20** (Scheme 5). The downfield shifting of NH protons to δ 9.6 in compound **20** must be due to strong intramolecular H-bonding with the C=O group at C5.



Scheme 5

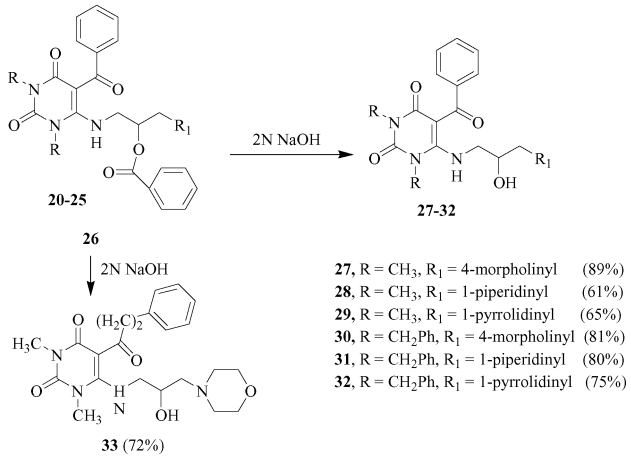
Similarly, refluxing of **9–13** with benzoyl chloride in pyridine gave the compounds **21–25**, respectively (Scheme 5). Compound **8** also underwent diacylation with 3-phenylpropionyl chloride in pyridine to gave compound **26** in 60% yield, [$M^+ + 1$ m/z 563] (Scheme 5).

In order to achieve the target 5-benzoylated-6-substituted uracils, the hydrolysis of compounds **20–26** was carried out. On treatment with 2 N NaOH, compound **20** gave a yellowish oil [$M^+ + 1$ m/z 403]. The molecular mass is 104 units less than **20**, which clearly indicates the removal of one benzoyl group. Its ^{1}H NMR spectrum shows an exchangeable broad 1H triplet at δ 9.50, another exchangeable proton at δ 2.79, and the absence of the C5 proton in the δ 4–5 region, along with the other signals. The H_d proton appears at δ 3.91 (similar to the H_d proton of **8**). Based upon NMR spectral data, formation of compound **27** was confirmed (Scheme 6). The downfield shift of NH proton to δ 9.50 is due to strong intramolecular H-bonding with the C=O group at C5.

The energy-minimized structure of **27** shows the close proximity of the NH proton to the carbonyl oxygen at C5 (1.85 Å) (Fig. 3b). The chemical shifts and splitting pattern of the protons of **27** are shown in Fig. 3a. Similarly, the hydrolysis of **21–26** gave compounds **28–33** respectively (Scheme 6).

Conclusion

A stepwise synthesis leads to the formation of 5-benzoyl-6-substituted pyrimidin-2,4-diones in moderate to high yields. The target of introducing acyl and hydroxy amine groups



Scheme 6

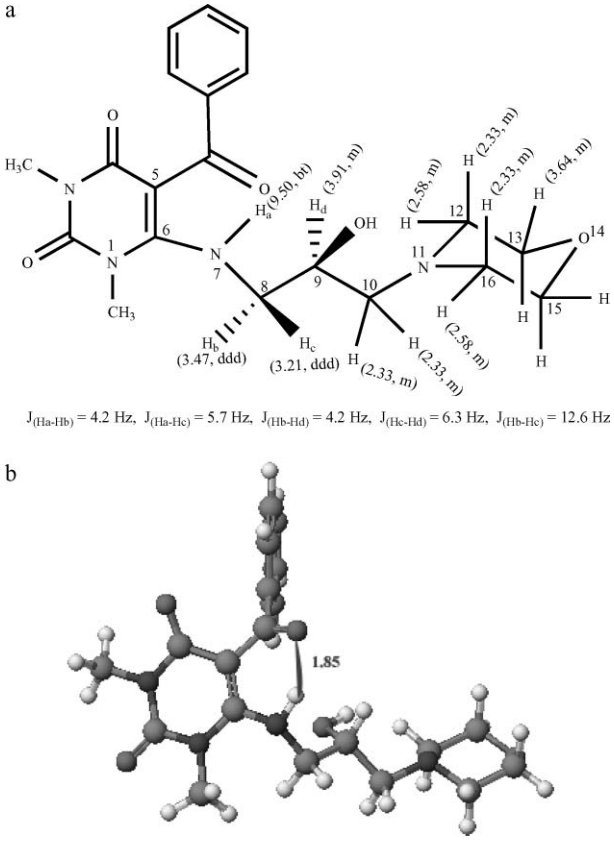


Fig. 3 a) ^{1}H NMR spectral assignments of various protons in **27**. The chemical shifts and splitting pattern are given in parentheses. b) Energy-minimized structure of **27**.

on adjacent carbons of uracil, similar to the groups present on adjacent carbons of benzene in propafenone, has been achieved.

Experimental

General

All melting points are uncorrected. Column chromatography was carried out using silica gel (60–120 mesh). All eluents were distilled prior to use. The ^{1}H NMR spectra were recorded on Bruker 300 MHz and JEOL JNM 300 MHz NMR spectrometers, and ^{13}C NMR spectra at 75 MHz on the same spectrometers in deuterated chloroform; chemical shifts are quoted in ppm against tetramethylsilane, and coupling constants in Hertz. In ^{13}C NMR spectral data, +ve signals correspond to CH_3

and CH carbons and −ve signals correspond to CH_2 carbons in the DEPT-135 NMR spectrum. The FAB mass spectra were recorded on a JEOL SX 102/DA-6000 Mass Spectrometer/Data System using argon/xenon (6 kV, 10 mA) as the FAB gas. Infrared spectra were recorded on an FTIR Shimadzu 8400 spectrometer on a thin dispersed film (from chloroform).

6-(2-Hydroxy-3-morpholin-4-ylpropylamino)-1,3-dimethyl-1*H*-pyrimidin-2,4-dione (8)

A solution of 6-chloro-1,3-dimethyluracil (1.745 g, 10 mmol), 3-morpholino-2-hydroxypropylamine (1.47 g, 10 mmol) and sodium carbonate (1.06 g, 10 mmol) in absolute ethanol (10 ml) was refluxed. After 7–10 h of refluxing, the reaction mixture was filtered while hot and concentrated under vacuum. The residue was purified by column chromatography using $CHCl_3$–MeOH (7 : 3) as eluent, giving rise to **8** (2.25 g, 87%) as a yellowish oil. (Found: C, 52.51; H, 7.55; N, 18.65. $C_{13}H_{22}N_4O_4$ requires C, 52.34; H, 7.43; N, 18.78%); ν_{max} ($CHCl_3$)/cm^{-1}: 3200 (NH), 1613, 1692 (C=O); δ_H(300 MHz, $CDCl_3$, Me_4Si) 2.44 (2H, m, C10-H_2), 2.46 (2H, m, C12-H_2/C16-H_2), 2.63 (2H, m, C12-H_2/C16-H_2), 3.00 (1H, ddd, $^2J_{H_c-H_b}$ = 12.6 Hz, $^3J_{H_c-H_d}$ = 7.0 Hz, $^3J_{H_c-H_a}$ = 6.6 Hz, H_c), 3.21 (1H, ddd, $^2J_{H_b-H_c}$ = 12.6 Hz, $^3J_{H_b-H_a}$ = 3.9 Hz, $^3J_{H_b-H_d}$ = 3.6 Hz, H_b), 3.29 (3H, s, NCH_3), 3.35 (1H, bs, OH, exchanges with D_2O), 3.40 (3H, s, NCH_3), 3.72 (4H, m, C13-H_2, C15-H_2), 4.00 (1H, m, H_d), 4.81 (1H, s, C5-H), 5.21 (1H, t, J = 4.2 Hz, H_a, exchanges with D_2O); δ_C(75.4 MHz, $CDCl_3$, Me_4Si): 27.8 (+ve, NCH_3), 28.7 (+ve, NCH_3), 46.8 (−ve, C8), 53.8 (−ve, C12,16), 62.0 (−ve, C10), 63.9 (+ve, C9-H), 66.8 (−ve, C13,15), 75.8 (+ve, C5), 151.8 (C2), 153.2 (C6), 163.1 (C4); ^{1}H–^{13}C HETCOR: The ^{1}H NMR signal at δ 2.43–2.48 corresponds to the two carbon signals at δ 53.8 (C12,16) and 62.0 (C10). The ^{1}H NMR signal at δ 2.63 also corresponds to the carbon signal at δ 53.8 (C12, C16). The 2 × ddd at δ 3.00 and 3.21 correspond to one carbon at δ 46.8 (C8). NOE: irradiation of the 1H signal at δ 5.21 shows an NOE between N1-CH_3 and H_d. Irradiation of the 1H signal at δ 4.00 shows an NOE between the protons at δ 5.21 and 2.63; m/z (FAB) 299 ($M^+ + 1$).

6-(2-Hydroxy-3-piperidin-1-ylpropylamino)-1,3-dimethyl-1*H*-pyrimidin-2,4-dione (9)

According to the preparation of **8**, **9** was obtained from **5** (1.745 g, 10 mmol) as a yellowish oil. Yield: 2.15 g, 84%; (Found: C, 56.71; H, 7.95; N, 18.72. $C_{14}H_{24}N_4O_3$ requires C, 56.74; H, 8.16; N, 18.90%); ν_{max} ($CHCl_3$)/cm^{-1}: 3220 (NH), 1632, 1692 (C=O); δ_H(300 MHz, $CDCl_3$, Me_4Si) 1.46 (2H, m, C14-H_2), 1.57 (4H, m, C13-H_2, C15-H_2), 2.36 (2H, m, C12-H_2/C16-H_2), 2.38 (2H, d, ^2J = 6 Hz, C10-H_2), 2.57 (2H, m, C12-H_2/C16-H_2), 3.00 (1H, dt, $^2J_{H_c-H_b}$ = 12.6 Hz, $^3J_{H_c-H_d}$ = 6.3 Hz, $^3J_{H_c-H_a}$ = 4.2 Hz, H_c), 3.16 (1H, dt, $^2J_{H_b-H_c}$ = 12.6 Hz, $^3J_{H_b-H_d}$ = 4.2 Hz, $^3J_{H_b-H_a}$ = 4.2 Hz, H_b), 3.29 (3H, s, NCH_3), 3.40 (3H, s, NCH_3), 3.50 (1H, bs, OH, exchanges with D_2O), 3.98 (1H, m, H_d), 4.81 (1H, s, C5-H), 5.44 (1H, t, J = 4.2 Hz, H_a, exchanges with D_2O); δ_C(75.4 MHz, $CDCl_3$, Me_4Si): 24.0 (−ve, C14), 26.0 (−ve, C13,15), 27.8 (+ve, NCH_3), 28.7 (+ve, NCH_3), 47.2 (−ve, C8), 54.9 (−ve, C12,16), 62.4 (−ve, C10), 63.9 (+ve, C9), 75.7 (+ve, C5), 151.9 (C2), 153.3 (C6), 163.1(C4); m/z (FAB) 297 ($M^+ + 1$).

6-(2-Hydroxy-3-pyrrolidin-1-ylpropylamino)-1,3-dimethyl-1*H*-pyrimidin-2,4-dione (10)

According to the preparation of **8**, **10** was obtained from **5** (1.745 g, 10 mmol) as a yellowish oil. Yield: 2.05 g, 84%; (Found: C, 55.43; H, 7.75; N, 19.75. $C_{13}H_{22}N_4O_3$ requires C, 55.30; H, 7.85; N, 19.84%); ν_{max} ($CHCl_3$)/cm^{-1}: 3200 (NH), 1613, 1692 (C=O); δ_H(300 MHz, $CDCl_3$, Me_4Si) 1.81 (4H, m, C13-H_2, C14-H_2), 2.56 (1H, dd, ^2J = 12.3 Hz, ^3J = 4.8 Hz, C10-H), 2.61 (2H, m, C12-H_2/C15-H_2), 2.77–2.84 (3H, m, 2H of C12-H_2/C15-H_2, 1H of C10), 3.11 (1H, ddd, $^2J_{H_c-H_b}$ = 12.3 Hz, $^3J_{H_c-H_d}$ = 4.8 Hz, $^3J_{H_c-H_a}$ = 4.2 Hz, H_c), 3.19 (1H, dt, $^2J_{H_b-H_c}$ = 12.3 Hz, $^3J_{H_b-H_d}$ = 4.8 Hz, $^3J_{H_b-H_a}$ = 4.5 Hz, H_b), 3.30 (3H, s, NCH_3), 3.35 (1H, bs, OH, exchanges with D_2O), 3.37 (3H, s, NCH_3), 4.01 (1H, m, H_d), 4.81 (1H, s, C5-H), 5.98 (1H, bs, H_a, exchanges with D_2O); δ_C(75.4 MHz, $CDCl_3$, Me_4Si): 23.6 (−ve, $C_{13,14}$), 27.8 (+ve, NCH_3), 28.6 (+ve, NCH_3), 47.7 (−ve, C8), 54.4 (−ve, C12,15), 60.0 (−ve, C10), 65.5 (+ve, C9), 75.4 (+ve, C5), 151.9 (C2), 153.3 (C6), 163.2 (C4); ^{1}H–^{13}C HETCOR: The 2 × ddd at δ 3.11 and 3.19 belong to one carbon at δ 47.7. The carbon signal at δ 54.4 corresponds to two proton signals: a multiplet at δ 2.61 and part of a multiplet at δ 2.77–2.84. The carbon signal at δ 60.0 corresponds to two proton signals, a dd at δ 2.56 and part of multiplet at δ 2.77–2.84; m/z (FAB) 283 ($M^+ + 1$).

1,3-Dibenzyl-6-(2-hydroxy-3-morpholin-4-ylpropylamino)-1*H*-pyrimidin-2,4-dione (11)

According to the preparation of **8**, **11** was obtained from **6** (3.105 g, 10 mmol) as a yellowish oil. Yield: 3.4 g, 78%; (Found: C, 66.60; H, 6.75; N, 12.45. $C_{25}H_{30}N_4O_4$ requires C, 66.65; H, 6.71; N, 12.44%); ν_{max} ($CHCl_3$)/cm^{-1}: 3378 (NH), 1627, 1691 (C=O); δ_H(300 MHz, $CDCl_3$, Me_4Si) 2.09 (1H, dd, ^2J = 12.6 Hz, ^3J = 10.2 Hz, C10-H), 2.21 (1H, dd, ^2J = 12.6 Hz, ^3J = 3.9 Hz, C10-H), 2.29 (2H, m, C12-H_2, C16-H_2), 2.55 (2H, m, C12-H_2, C16-H_2), 2.81 (1H, dt, ^2J = 12.6 Hz, ^3J = 5.4 Hz, H_c), 3.12 (1H, dt, ^2J = 12.6 Hz, ^3J = 5.7 Hz, H_b), 3.67 (4H, m, C13-H_2, C15-H_2), 3.82 (1H, m, H_d), 4.82 (1H, s, C5-H), 4.93 (1H, d, J = 16.6 Hz, PhCH_2), 5.15 (1H, d, J = 14.0 Hz, PhCH_2), 5.18 (1H, d, J = 14.0 Hz, PhCH_2), 5.37 (1H, d, J = 16.6 Hz, PhCH_2), 7.24–7.48 (10H, m, 2 × Ph); δ_C(75.4 MHz, $CDCl_3$, Me_4Si): 44.3 (−ve, PhCH_2), 45.7 (−ve, C8), 46.0 (−ve, PhCH_2), 53.5 (−ve, C12,16), 61.2 (−ve, C10), 63.6 (+ve, C9), 66.8 (−ve, C13,15), 76.3 (+ve, C5), 126.6 (+ve, ArCH), 127.3 (+ve, ArCH), 128.2 (+ve, ArCH), 128.3 (+ve, ArCH), 128.6 (+ve, ArCH), 129.2 (+ve, ArCH), 135.1 (ArC), 137.6 (ArC), 152.2 (C2), 153.0 (C6), 162.6 (C4); ^{1}H–^{13}C HETCOR: 2 × dd at δ 2.09 and 2.21 correspond to carbon signal at δ 61.2, two multiplets at δ 2.29 and 2.55 belong to carbon signal at δ 53.5, 2 × dt at δ 2.81 and 3.12 correspond to carbon signal at δ 45.7, two doublets at δ 4.93 and 5.37 belong to carbon signal at δ 46.0 and two doublets at δ 5.15 and 5.18 belong to carbon signal at δ 44.3; m/z (FAB) 451 ($M^+ + 1$).

1,3-Dibenzyl-6-(2-hydroxy-3-piperidin-1-ylpropylamino)-1*H*-pyrimidin-2,4-dione (12)

According to the preparation of **8**, **12** was obtained from **6** (3.105 g, 10 mmol) as a yellowish oil. Yield: 3.3 g, 77%; (Found: C, 69.52; H, 7.15; N, 12.44. $C_{26}H_{32}N_4O_3$ requires C, 69.62; H, 7.19; N, 12.49%); ν_{max} ($CHCl_3$)/cm^{-1}: 3296 (NH), 1635, 1689 (C=O); δ_H(300 MHz, $CDCl_3$, Me_4Si): 1.43 (2H, m, C14-H_2), 1.54 (4H, m, C13-H_2, C15-H_2), 2.08 (1H, dd, ^2J = 12.3 Hz, ^3J = 9.9 Hz, C10-H), 2.18 (1H, dd, ^2J = 12.6 Hz, ^3J = 3.9 Hz, C10-H), 2.23 (2H, m, C12-H_2/C16-H_2), 2.50 (2H, m, C12-H_2/C16-H_2), 2.80 (1H, dt, ^2J = 12.6 Hz, ^3J = 5.4 Hz, H_c), 3.10 (1H, dt, ^2J = 12.0 Hz, ^3J = 4.2 Hz, H_b), 3.82 (1H, m, H_d), 4.82 (1H, s, C5-H), 4.93 (1H, d, J = 16.5 Hz, PhCH_2), 5.15 (1H, d, J = 14.1 Hz, PhCH_2), 5.18 (1H, d, J = 14.1 Hz, PhCH_2), 5.35 (1H, d, J = 16.5 Hz, PhCH_2), 7.25–7.46 (10H, m, 2 × Ph); δ_C(75.4 MHz, $CDCl_3$, Me_4Si): 23.9 (−ve, C14), 25.7 (−ve, C13,15), 44.3 (−ve, PhCH_2), 45.9 (−ve, C8), 46.0 (−ve, PhCH_2), 54.6 (−ve, C12,16), 61.3 (−ve, C10), 63.6 (+ve, C9), 76.1 (+ve, C5), 126.6 (+ve, ArCH), 127.2 (+ve, ArCH), 128.2 (+ve, ArCH), 128.3 (+ve, ArCH), 128.5 (+ve, ArCH), 129.2 (+ve, ArCH), 135.1 (ArC), 137.7 (ArC), 152.2 (C2), 153.2 (C6), 162.8 (C4); m/z (FAB) 449 ($M^+ + 1$).

1,3-Dibenzyl-6-(2-hydroxy-3-pyrrolidin-1-yl-propylamino)-1*H*-pyrimidin-2,4-dione (13)

According to the preparation of **8**, **13** was obtained from **6** (3.105 g, 10 mmol) as a yellowish oil. Yield: 3.2 g, 76%; (Found:

C, 69.01; H, 7.05; N, 12.85. $C_{25}H_{30}N_4O_3$ requires C, 69.10; H, 6.96; N, 12.89%); ν_{max} ($CHCl_3$)/cm^{-1}: 3016 (NH), 1627, 1689 (C=O); δ_H(300 MHz, $CDCl_3$, Me_4Si): 1.93 (4H, m, C13-H_2, C14-H_2), 2.34 (1H, dd, ^2J = 12.0 Hz, ^3J = 2.4 Hz, C10-H), 2.48 (1H, dd, ^2J = 11.4 Hz, ^3J = 3.9 Hz, C10-H), 2.54 (2H, m, C12-H_2/C15-H_2), 2.64 (2H, m, C12-H_2/C15-H_2), 2.92 (1H, m, H_c), 3.07 (1H, m, H_b), 3.87 (1H, m, H_d), 4.82 (1H, s, C5-H), 4.97 (1H, d, J = 16.4 Hz, PhCH_2), 5.09 (1H, d, J = 14.0 Hz, PhCH_2), 5.13 (1H, d, J = 16.4 Hz, PhCH_2), 5.33 (1H, d, J = 14.0 Hz, PhCH_2), 5.62 (1H, bs, H_a), 7.21–7.54 (10H, m, 2 × Ph); δ_C(75.4 MHz, $CDCl_3$, Me_4Si): 23.0 (−ve, $C_{13,14}$), 44.3 (−ve, PhCH_2), 45.4 (−ve, C8), 45.7 (−ve, PhCH_2), 54.6 (−ve, C12,15), 58.3 (−ve, C10), 64.5 (+ve, C9), 75.6 (+ve, C5), 126.0 (+ve, ArCH), 127.2 (+ve, ArCH), 127.7 (+ve, ArCH), 128.0 (+ve, ArCH), 128.3 (+ve, ArCH), 128.8 (+ve, ArCH), 135.4 (ArC), 137.5 (ArC), 152.0 (C2), 153.1 (C6), 163.2 (C4); *m/z* (FAB) 435 ($M^+ + 1$).

Benzoic acid 2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-ylamino)-1-(morpholin-4-ylmethyl)ethyl ester (14)

Compound **8** (2.98 g, 10 mmol), on mixing with benzoic anhydride (4.52 g, 20 mmol) was heated in a microwave oven for 3 min. After stirring with a saturated solution of $NaHCO_3$, the reaction mixture was extracted with $CHCl_3$. Removal of $CHCl_3$ left a thick liquid which was purified by column chromatography using chloroform–methanol (8 : 2) as eluents, to give **14** (3.8 g, 95%) as a yellowish oil. (Found: C, 59.60; H, 6.55; N, 13.95. $C_{20}H_{26}N_4O_5$ requires C, 59.69; H, 6.51; N, 13.92%); ν_{max} ($CHCl_3$)/cm^{-1}: 3438 (NH), 1709, 1672 (C=O); δ_H(300 MHz, $CDCl_3$, Me_4Si): 2.62 (4H, m, C12-H_2, C16-H_2), 2.77 (2H, d, J = 6.0 Hz, C10-H_2), 3.30 (3H, s, NCH_3), 3.40 (3H, s, NCH_3), 3.40 (1H, merged with NCH_3, H_c), 3.53 (1H, dt, ^2J = 12.9 Hz, ^3J = 4.2 Hz, H_b, on D_2O exchange it becomes a dd with coupling constants of 12.9 and 4.2 Hz), 3.72 (4H, t, J = 4.8 Hz, C13-H_2, C15-H_2), 4.88 (1H, s, C5-H), 5.42 (1H, m, H_d), 6.06 (1H, bt, J = 5.4 Hz, H_a), 7.47–8.01 (5H, m, Ph); δ_C(75.4 MHz, $CDCl_3$, Me_4Si): 27.7 (+ve, NCH_3), 28.9 (+ve, NCH_3), 47.3 (−ve, C8), 54.4 (−ve, C12,16), 60.8 (−ve, C10), 66.8 (−ve, C13,15), 69.9 (+ve, C9), 75.6 (+ve, C5), 128.7 (+ve, ArCH), 129.0 (ArC), 129.8 (+ve, ArCH), 133.9 (+ve, ArCH), 151.9 (C2), 152.8 (C6), 163.0 (C4), 167.3 (C=O); ^{1}H–^{13}C HETCOR: The ^{1}H NMR signal at δ 3.40 corresponds to two carbon signals at δ 28.9 and 47.3, and the 1H signal at δ 3.53 also corresponds to a carbon signal at δ 47.3. NOE: irradiation of the 1H signal at δ 6.06 shows an NOE between N1-CH_3 and H_d; *m/z* (FAB) 403 ($M^+ + 1$).

Alternative procedures

(i) A mixture of **8** (2.98 g, 10 mmol), benzoyl chloride (1.405 g, 10 mmol) and sodium carbonate (1.06 g, 10 mmol) in 10 ml of chloroform was refluxed for 5 h. After cooling and filtration, the solvent was removed under vacuum and the crude residue was purified by column chromatography using chloroform–methanol as eluent.

(ii) A mixture of **8** (10 mmol), benzoyl chloride (10 mmol) and $Ca(OH)_2$ in dioxan was refluxed until the completion of the reaction (TLC). After filtration, the solvent was removed under vacuum and the crude residue was purified by column chromatography using chloroform–methanol as eluent.

Benzoic acid 2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-ylamino)-1-(piperidin-1-ylmethyl)ethyl ester (15). According to the preparation of **14**, **15** was obtained from **9** (2.96 g, 10 mmol) as a white solid. Yield: 3.7 g, 91%; mp 202–204 °C; (Found: C, 62.99; H, 7.10; N, 13.92. $C_{21}H_{28}N_4O_4$ requires C, 62.98; H, 7.05; N, 13.99%); ν_{max} (KBr)/cm^{-1}: 3218 (NH), 1710, 1699 (C=O); δ_H(300 MHz, $CDCl_3$, Me_4Si): 1.77 (2H, m, C14-H_2), 2.49 (4H, m, C13-H_2, C15-H_2), 3.00 (2H, m, C12-H_2/C16-H_2), 3.38 (2H, m, C12-H_2/C16-H_2), 3.07 (3H, s, NCH_3), 3.24 (3H, s, NCH_3), 3.46 (2H, dd, ^2J = 9.6 Hz, ^3J = 6.0 Hz, C8-H_2), 3.56 (2H, dd, ^2J = 9.2 Hz, ^3J = 6.2 Hz, C10-H_2), 5.07 (1H, s, C5-H), 5.57 (1H, m, H_d), 7.16 (1H, bt, J = 6.0 Hz, H_a), 7.53–8.03 (5H, m, Ph); δ_N(30.4 MHz, $CDCl_3$): 117.4 (N1), 142.9 (N3), 73.8 (N7), 50.7 (N11); δ_C(75.4 MHz, $CDCl_3$, Me_4Si): 21.0 −ve, C14), 22.1 (−ve, C13,15), 27.1 (+ve, NCH_3), 29.5 (+ve, NCH_3), 42.9 (−ve, C8), 53.1 (−ve, C12,16), 56.2 (−ve, C10), 66.8 (+ve, C9), 74.2 (+ve, C5), 128.6 (+ve, ArCH), 129.2 (ArC), 129.6 (+ve, ArCH), 133.6 (+ve, ArCH), 151.4 (C2), 153.1 (C6), 161.6 (C4), 165.2 (C=O); *m/z* (FAB) 401 ($M^+ + 1$).

Benzoic acid 2-(1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-ylamino)-1-(pyrrolidin-1-ylmethyl)ethyl ester (16). According to the preparation of **14**, **16** was obtained from **10** (2.82 g, 10 mmol) as a white solid. Yield: 4.45 g, 90%; mp 180–82 °C; (Found: C, 62.12; H, 6.80; N, 14.55. $C_{20}H_{26}N_4O_4$ requires C, 62.16; H, 6.78; N, 14.50%); ν_{max} (KBr)/cm^{-1}: 3288 (NH), 1720, 1662 (C=O); δ_H(300 MHz, $CDCl_3$, Me_4Si): 1.91 (4H, m, C13-H_2, C14-H_2), 3.07 (3H, s, NCH_3), 3.22 (4H, m, C12-H_2, C15-H_2), 3.23 (3H, s, NCH_3), 3.48 (2H, dd, ^2J = 8.4 Hz, ^3J = 6.0 Hz, C8-H_2), 3.59 (2H, dd, ^2J = 6.0 Hz, ^3J = 4.2 Hz, C10-H_2), 5.04 (1H, s, C5-H), 5.54 (1H, m, H_d), 7.15 (1H, t, J = 6.0 Hz, H_a), 7.50–8.05 (5H, m, Ph); 1D TOCSY: irradiation of the multiplet at δ 5.54 (H_d) shows signals at δ 3.48 (C8-H_2), 3.58 (C10-H_2) and 7.15 (NH) indicating that these protons are part of a one-spin system; δ_C(75.4 MHz, $CDCl_3$, Me_4Si): 22.6 (−ve, $C_{13,14}$), 27.1 (+ve, NCH_3), 29.5 (+ve, NCH_3), 42.8 (−ve, C8), 54.2 (−ve, C12,15), 54.3 (−ve, C10), 67.9 (+ve, C9), 74.1 (+ve, C5), 128.6 (+ve, ArCH), 129.2 (ArC), 129.7 (+ve, ArCH), 133.6 (+ve, ArCH), 151.4 (C2), 153.1 (C6), 161.6 (C4), 165.2 (C=O); *m/z* (FAB) 387 ($M^+ + 1$).

Benzoic acid 2-(1,3-dibenzyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-ylamino)-1-(morpholin-4-ylmethyl)ethyl ester (17). According to the preparation of **14**, **17** was obtained from **11** (4.50 g, 10 mmol) as a yellowish oil. Yield: 4.5 g, 82%; (Found: C, 69.32; H, 6.15; N, 10.15. $C_{32}H_{34}N_4O_5$ requires C, 69.30; H, 6.18; N, 10.10%); ν_{max} ($CHCl_3$)/cm^{-1}: 3300 (NH), 1710, 1629 (C=O); δ_H(300 MHz, $CDCl_3$, Me_4Si): 2.47 (2H, m, C12-H, C16-H), 2.50 (2H, d, J = 7.2 Hz, C10-H and C12-H/C16-H), 2.57 (2H, d, J = 5.4 Hz, C10-H and C12-H/C16-H), 3.29 (1H, ddd, $^2J_{H_c-H_b}$ = 13.2 Hz, $^3J_{(H_c-H_d)}$ = 5.1 Hz, $^3J_{H_c-H_a}$ = 3.3 Hz, H_c), 3.44 (1H, ddd, $^2J_{H_b-H_c}$ = 13.2 Hz, $^3J_{H_b-H_d}$ = 4.2 Hz, $^3J_{H_b-H_a}$ = 3.6 Hz, H_b), 3.61 (4H, t, J = 4.5 Hz, C13-H_2, C15-H_2), 4.97 (1H, s, C5-H), 5.11 (2H, d, J = 16.8 Hz, N1-CH_2Ph), 5.15 (2H, s, N3-CH_2Ph), 5.26 (1H, m, C9-H_d), 7.15–7.46 (15H, m, 3 × Ph); δ_C(75.4 MHz, $CDCl_3$, Me_4Si): 44.2 (−ve, PhCH_2), 45.8 (−ve, PhCH_2), 45.9 (−ve, C8), 54.2 (−ve, C12,16), 59.6 (−ve, C10), 66.7 (−ve, C13,15), 69.9 (+ve, C9), 76.5 (+ve, C5), 126.0 (+ve, ArCH), 127.2 (+ve, ArCH), 128.0 (+ve, ArCH), 128.3 (+ve, ArCH), 128.5 (+ve, ArCH), 128.6 (+ve, ArCH), 129.1 (+ve, ArCH), 129.2 (ArC), 134.8 (ArC), 137.6 (ArC), 152.0 (C2), 152.8 (C6), 162.6 (C4), 166.5 (C=O); ^{1}H–^{13}C HETCOR: The carbon signal at δ 54.2 shows cross-peaks with three proton signals at δ 2.47, 2.50 and 2.57, and the carbon signal at δ 59.6 also shows a cross-peak with the proton signals at δ 2.50 and 2.57. The 2 × ddd at δ 3.29 and 3.44 show cross-peaks with the carbon signal at δ 45.9. The ^{1}H NMR signals at δ 5.11 and 5.15 correspond to the carbon signals at δ 45.8 and 44.2 respectively; *m/z* (FAB) 555 ($M^+ + 1$).

Benzoic acid 2-(1,3-dibenzyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-ylamino)-1-(piperidin-1-ylmethyl)ethyl ester (18). According to the preparation of **14**, **18** was obtained from **12** (4.48 g, 10 mmol) as a yellowish oil. Yield: 4.4 g, 80%; (Found: C, 71.75; H, 6.50; N, 10.15. $C_{33}H_{36}N_4O_4$ requires C, 71.72; H, 6.57; N, 10.14%); ν_{max} ($CHCl_3$)/cm^{-1}: 3033 (NH), 1715, 1631 (C=O); δ_H(300 MHz, $CDCl_3$, Me_4Si): 1.37 (2H, m, C14-H_2), 1.50 (4H, m, C13-H_2, C15-H_2), 2.44 (4H, m, C12-H_2, C16-H_2), 2.56 (2H, dd, ^2J = 8.2 Hz, ^3J = 5.8 Hz, C10-H_2), 3.33 (1H, ddd, $^2J_{H_c-H_b}$ = 12.3 Hz, $^3J_{H_c-H_d}$ = 8.4 Hz, $^3J_{H_c-H_a}$ = 3.9 Hz, H_c), 3.44 (1H, ddd, $^2J_{H_b-H_c}$ = 12.3 Hz, $^3J_{H_b-H_d}$ = 6.3 Hz, $^3J_{H_b-H_a}$ = 4.2 Hz, H_b), 4.96

(1H, s, C5-H), 5.12 (2H, s, PhCH_2), 5.14 (2H, s, PhCH_2), 5.27 (1H, m, C9-H_d), 7.19–7.90 (15H, m, 3 × Ph); δ_C(75.4 MHz, $CDCl_3$, Me_4Si): 23.8 (−ve, C14), 25.5 (−ve, C13,15), 44.2 (−ve, PhCH_2), 45.7 (−ve, PhCH_2), 46.2 (−ve, C8), 55.3 (−ve, C12,16), 60.0 (−ve, C10), 69.9 (+ve, C9), 76.4 (+ve, C5), 126.1 (+ve, ArCH), 127.2 (+ve, ArCH), 127.9 (+ve, ArCH), 128.3 (+ve, ArCH), 128.5 (+ve, ArCH), 128.6 (+ve, ArCH), 129.0 (+ve, ArCH), 129.2 (ArC), 129.7 (+ve, ArCH), 133.6 (+ve, ArCH), 135.0 (ArC), 137.6 (ArC), 152.1 (C2), 152.9 (C6), 162.6 (C4), 166.4 (C=O); *m/z* (FAB) 553 ($M^+ + 1$).

Benzoic acid 2-(1,3-dibenzyl-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-ylamino)-1-(pyrrolidin-1-ylmethyl)ethyl ester (19). According to the preparation of **14**, **19** was obtained from **13** (4.34 g, 10 mmol) as a yellowish oil. Yield: 4.73 g, 75%; (Found: C, 71.55; H, 6.80; N, 10.55. $C_{32}H_{34}N_4O_4$ requires C, 71.35; H, 6.36; N, 10.40%); ν_{max} ($CHCl_3$) (cm^{-1}): 3233 (NH), 1710 (C=O); δ_H(300 MHz, $CDCl_3$, Me_4Si): 1.81 (4H, m, C13-H_2, C14-H_2), 2.92 (2H, dd, ^2J = 7.2 Hz, ^3J = 3.2 Hz, C10-H_2), 3.30 (4H, m, C12-H_2, C15-H_2), 3.55 (2H, dd, ^2J = 7.5 Hz, ^3J = 5.6 Hz, C8-H_2), 4.82 (1H, s, C5-H), 5.07 (2H, d, J = 15.2 Hz, PhCH_2), 5.28 (2H, d, J = 14.4 Hz, PhCH_2), 5.43 (1H, m, H_d), 7.25–7.37 (15H, m, 3 × Ph); δ_C(75.4 MHz, $CDCl_3$, Me_4Si): 23.2 (−ve, $C_{13,14}$), 44.3 (−ve, PhCH_2), 45.6 (−ve, C8), 45.7 (−ve, PhCH_2), 55.6 (−ve, C12,15), 58.5 (−ve, C10), 70.1 (+ve, C9), 75.9 (+ve, C5), 126.2 (+ve, ArCH), 126.8 (+ve, ArCH), 127.2 (+ve, ArCH), 127.7 (+ve, ArCH), 127.9 (+ve, ArCH), 128.0 (+ve, ArCH), 128.3 (+ve, ArCH), 128.8 (+ve, ArCH), 129.0 (ArC), 135.4 (ArC), 137.5 (ArC), 152.0 (C2), 153.1 (C6), 163.2 (C4), 166.5 (C=O); *m/z* (FAB) 539 ($M^+ + 1$).

Benzoic acid 2-(5-benzoyl-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydro-pyrimidin-4-ylamino)-1-(morpholin-4-ylmethyl)ethyl ester (20). A mixture of **8** (2.98 g, 10 mmol) and benzoyl chloride (2.81, 20 mmol) in pyridine (10 ml) was refluxed at 115 °C for 4 h. The solvent was removed under vacuum and treated with a saturated solution of sodium bicarbonate to remove traces of benzoic acid. The aqueous part was extracted with ether and dried over anhydrous sodium sulfate. Removal of the solvent provided a crude product which was purified by column chromatography using hexane–ethyl acetate (3 : 7) as eluent giving rise to compound **20** (3.2 g, 62%) as a yellowish oil; (Found: C, 64.12; H, 6.05; N, 11.20. $C_{27}H_{30}N_4O_6$ requires C, 64.02; H, 5.97; N, 11.06%); ν_{max} ($CHCl_3$)/cm^{-1}: 3209 (NH), 1655, 1719 (C=O); δ_H(300 MHz, $CDCl_3$, Me_4Si): 2.50 (4H, m, C12-H_2, C16-H_2), 2.63 (2H, d, J = 6.6 Hz, C10-H_2), 3.19 (3H, s, NCH_3), 3.56 (3H, s, NCH_3), 3.62 (4H, t, J = 4.5 Hz, C13-H_2, C15-H_2), 3.69 (2H, m, C8-H_2), 5.31 (1H, m, H_d), 7.39–7.95 (10H, m, 2 × Ph), 9.62 (1H, t, J = 5.4 Hz, H_a, exchanges with D_2O)); δ_C(75.4 MHz, $CDCl_3$, Me_4Si): 28.1 (+ve, NCH_3), 34.8 (+ve, NCH_3), 48.4 (−ve, C8), 54.2 (−ve, C12,16), 58.7 (−ve, C10), 66.8 (−ve, C13,15), 70.6 (+ve, C9), 94.5 (C5), 127.8 (+ve, ArCH), 128.5 (+ve, ArCH), 129.1 (ArC), 129.7 (+ve, ArCH), 131.1 (+ve, ArCH), 133.6 (+ve, ArCH), 141.2 (ArC), 151.5 (C2), 160.5 (C6), 161.3 (C4), 166.1 (C=O), 195.5 (C=O); *m/z* (FAB) 507 ($M^+ + 1$).

Benzoic acid 2-(5-benzoyl-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-ylamino)-1-(piperidin-1-ylmethyl)ethyl ester (21). According to the preparation of **20**, **21** was obtained from **9** (2.96 g, 10 mmol) as a yellowish oil. Yield: 5.1 g, 61%; (Found: C, 66.52; H, 6.40; N, 11.10. $C_{28}H_{32}N_4O_5$ requires C, 66.65; H, 6.39; N, 11.10%); ν_{max} ($CHCl_3$)/cm^{-1}: 3230 (NH), 1720, 1656 (C=O); δ_H(300 MHz, $CDCl_3$, Me_4Si): 1.41 (2H, m, C14-H_2), 1.52 (4H, m, C13-H_2, C15-H_2), 2.42 (2H, m, C12-H_2/C16-H_2), 2.51 (2H, m, C12-H_2/C16-H_2), 2.61 (2H, dd, ^2J = 3.6 Hz, ^3J = 1.2 Hz, C10-H_2), 3.21 (3H, s, NCH_3), 3.58 (3H, s, NCH_3), 3.66 (2H, m (distorted triplet), J = 5.1 Hz, C8-H_2), 5.30 (1H, m, H_d), 7.33–7.98 (10H, m, 2 × Ph), 9.63 (1H, t, J = 6.4 Hz, H_a, exchanges with D_2O); δ_C(75.4 MHz, $CDCl_3$, Me_4Si): 23.9 (−ve, C14), 25.9 (−ve, C13,15), 28.0 (+ve, NCH_3), 34.6 (+ve, NCH_3), 48.8 (−ve, C8), 55.4 (−ve, C12,16), 59.1 (−ve, C10), 70.6 (+ve, C9), 94.1 (C5), 127.8 (+ve, ArCH), 127.9 (+ve, ArCH), 128.5 (+ve, ArCH), 129.2 (ArC), 129.7 (+ve, ArCH), 131.0 (+ve, ArCH), 133.5 (+ve, ArCH), 141.3 (ArC), 151.5 (C2), 160.1 (C6), 161.4 (C4), 165.9 (C=O), 195.3 (C=O); 2D TOCSY, HMBC and HSQC experiments of this compound also confirm all the above assignments to various protons and carbons; *m/z* (FAB) 505 ($M^+ + 1$).

Benzoic acid 2-(5-benzoyl-1,3-dimethyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-ylamino)-1-(pyrrolidin-1-ylmethyl)ethyl ester (22). According to the preparation of **20**, **22** was obtained from **10** (2.82 g, 10 mmol) as a yellowish oil. Yield: 3.4 g, 65%; (Found: C, 66.12; H, 6.10; N, 11.52. $C_{27}H_{30}N_4O_5$ requires C, 66.11; H, 6.16; N, 11.42%); ν_{max} ($CHCl_3$)/cm^{-1}: 3328 (NH), 1710, 1670 (C=O); δ_H(300 MHz, $CDCl_3$, Me_4Si): 1.95 (4H, m, C13-H_2, C14-H_2), 2.87 (2H, dd, ^2J = 8.4 Hz, ^3J = 6.0 Hz, C10-H_2), 3.10 (3H, s, NCH_3), 3.15 (4H, m, C12-H_2, C15-H_2), 3.24 (3H, s, NCH_3), 3.60 (2H, dd, ^2J = 8.4 Hz, ^3J = 6.5 Hz, C8-H_2), 5.44 (1H, m, H_d), 7.51–8.01 (10H, m, 2 × Ph), 9.52 (1H, t, J = 6.0 Hz, H_a); δ_C(75.4 MHz, $CDCl_3$, Me_4Si): 22.5 (−ve, $C_{13,14}$), 27.3 (+ve, NCH_3), 29.0 (+ve, NCH_3), 46.8 (−ve, C8), 55.2 (−ve, C12,15), 58.3 (−ve, C10), 69.9 (+ve, C9), 94.1 (C5), 127.3 (+ve, ArCH), 127.6 (+ve, ArCH), 128.7 (+ve, ArCH), 129.5 (ArC), 129.7 (+ve, ArCH), 131.8 (+ve, ArCH), 132.5 (+ve, ArCH), 141.6 (ArC), 151.5 (C2), 158.1 (C6), 161.8 (C4), 165.2 (C=O), 194.8 (C=O); *m/z* (FAB) 491 ($M^+ + 1$).

Benzoic acid 2-(5-benzoyl-1,3-dibenzyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-ylamino)-1-(morpholin-4-ylmethyl)ethyl ester (23). According to the preparation of **20**, **23** was obtained from **11** (4.50 g, 10 mmol) as a yellowish oil. Yield: 4.5 g, 68%; (Found: C, 71.00; H, 5.80; N, 8.71. $C_{39}H_{38}N_4O_6$ requires C, 71.11; H, 5.81; N, 8.51%); ν_{max} ($CHCl_3$)/cm^{-1}: 3386 (NH), 1716, 1635 (C=O); δ_H(300 MHz, $CDCl_3$, Me_4Si): 2.30 (4H, m, C12-H_2, C16-H_2), 2.41 (2H, d, J = 5.6 Hz, C10-H_2), 3.41 (1H, ddd, $^2J_{H_c-H_b}$ = 12.4 Hz, $^3J_{H_c-H_d}$ = 9.0 Hz, $^3J_{H_c-H_a}$ = 4.4 Hz, H_c), 3.59 (1H, ddd, $^2J_{H_b-H_c}$ = 12.4 Hz, $^3J_{H_b-H_d}$ = 8.4 Hz, $^3J_{H_b-H_a}$ = 4.0 Hz, H_b), 3.86 (4H, t, J = 4.5 Hz, C13-H_2, C15-H_2), 5.05 (2H, d, J = 16.2 Hz, PhCH_2), 5.10 (2H, d, J = 14.4 Hz, PhCH_2), 5.11 (1H, m, H_d), 7.01–8.04 (20H, m, 4 × Ph); δ_C(75.4 MHz, $CDCl_3$, Me_4Si): 44.3 (−ve, PhCH_2), 46.8 (−ve, PhCH_2), 46.9 (−ve, C8), 54.4 (−ve, C12,16), 59.2 (−ve, C10), 66.2 (−ve, C13,15), 69.6 (+ve, C9), 94.2 (C5), 126.2 (+ve, ArCH), 126.5 (+ve, ArCH), 127.0 (+ve, ArCH), 127.3 (+ve, ArCH), 127.5 (+ve, ArCH), 127.9 (+ve, ArCH), 128.4 (+ve, ArCH), 128.6 (+ve, ArCH), 129.1 (ArC), 129.5 (+ve, ArCH), 130.0 (+ve, ArCH), 131.1 (+ve, ArCH), 131.5 (+ve, ArCH) 131.8 (ArC), 133.0 (ArC), 137.1 (ArC), 152.0 (C2), 162.9 (C6), 165.6 (C4), 174.7 (C=O), 195.3 (C=O); *m/z* (FAB) 659 ($M^+ + 1$).

Benzoic acid 2-(5-benzoyl-1,3-dibenzyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-ylamino)-1-(piperidin-1-ylmethyl)ethyl ester (24). According to the preparation of **20**, **24** was obtained from **12** (4.48 g, 10 mmol) as a yellowish oil. Yield: 4.27 g, 65%; (Found: C, 73.12; H, 6.30; N, 8.85. $C_{40}H_{40}N_4O_5$ requires C, 73.15; H, 6.14; N, 8.53%); ν_{max} ($CHCl_3$)/cm^{-1}: 3200 (NH), 1725, 1633 (C=O); δ_H(300 MHz, $CDCl_3$, Me_4Si): 1.40 (2H, m, C14-H_2), 1.49 (4H, m, C13-H_2, C15-H_2), 2.44 (4H, m, C12-H_2, C16-H_2), 2.62 (2H, d, J = 6.3 Hz, C10-H_2), 3.66 (1H, dd, ^2J = 10.8 Hz, ^3J = 8.1 Hz, C8-H), 3.88 (1H, d, J = 13.5 Hz, C8-H), 5.11 (2H, d, J = 15.9 Hz, PhCH_2), 5.16 (2H, d, J = 13.2 Hz, PhCH_2), 5.32 (1H, m, H_d), 7.21–8.02 (20H, m, 4 × Ph), 14.30 (1H, bs, H_a, exchanges with D_2O); δ_C(75.4 MHz, $CDCl_3$, Me_4Si): 23.2 (−ve, C14), 24.5 (−ve, C13,15), 44.1 (−ve, PhCH_2), 45.0 (−ve, PhCH_2), 45.1 (−ve, C8), 54.9 (−ve, C12,16), 60.2 (−ve, C10), 68.2 (+ve, C9), 94.4 (C5), 125.9 (+ve, ArCH), 126.3 (+ve, ArCH), 126.9 (+ve, ArCH), 128.3 (+ve, ArCH), 128.5 (+ve, ArCH), 128.6 (+ve, ArCH), 128.9 (ArC), 129.0 (+ve, ArCH), 129.2 (+ve, ArCH), 129.3 (+ve, ArCH), 129.8 (+ve, ArCH), 130.9 (ArC), 133.8 (ArC), 137.7 (ArC), 148.3

(C2), 151.1 (C6), 157.3 (C4), 162.6 (C=O), 194.3 (C=O); *m/z* (FAB) 657 ($M^+ + 1$).

Benzoic acid 2-(5-benzoyl-1,3-dibenzyl-2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-ylamino)-1-(pyrrolidin-1-ylmethyl)ethyl ester (25). According to the preparation of **20**, **25** was obtained from **13** (4.34 g, 10 mmol) as a yellowish oil. Yield: 3.9 g, 62%; (Found: C, 72.72; H, 5.60; N, 8.55. $C_{39}H_{38}N_4O_5$ requires C, 72.88; H, 5.96; N, 8.72%); ν_{max} ($CHCl_3$)/cm^{-1}: 3345 (NH), 1710, 1660 (C=O); δ_H(300 MHz, $CDCl_3$, Me_4Si): 1.80 (4H, m, C13-H_2, C14-H_2), 2.63 (2H, dd, ^2J = 7.2 Hz, ^3J = 3.0 Hz, C10-H_2), 2.79 (2H, m, C12-H_2/C15-H_2) 2.90 (2H, m, C12-H_2/C15-H_2), 3.08 (2H, dd, ^2J = 7.5 Hz, ^3J = 3.8 Hz, C8-H_2), 5.07 (2H, d, J = 16.8 Hz, PhCH_2), 5.12 (2H, d, J = 14.8 Hz, PhCH_2), 5.41 (1H, m, H_d), 7.07–7.91 (20H, m, 4 × Ph), 8.61 (1H, bs, H_a, exchanges with D_2O); δ_C(75.4 MHz, $CDCl_3$, Me_4Si): 23.8 (−ve, $C_{13,14}$), 44.1 (−ve, PhCH_2), 45.2 (−ve, C8), 45.7 (−ve, Ph*C*H_2), 56.0 (−ve, C12,15), 58.9 (−ve, C10), 69.1 (+ve, C9), 94.6 (C5), 126.2 (+ve, ArCH), 126.4 (+ve, ArCH), 126.8 (+ve, ArCH), 127.2 (+ve, ArCH), 127.4 (+ve, ArCH), 127.7 (+ve, ArCH), 127.9 (+ve, ArCH), 128.0 (+ve, ArCH), 128.3 (+ve, ArCH), 128.5 (ArC), 128.8 (+ve, ArCH), 129.0 (ArC), 135.4 (ArC), 137.5 (ArC), 152.8 (C2), 153.3 (C6), 163.2 (C4), 163.0 (C=O), 194.6 (C=O); *m/z* (FAB) 643 ($M^+ + 1$).

3-Phenyl-propionic acid 2-[1,3-dimethyl-2,6-dioxo-5-(3-phenylpropionyl)-1,2,3,6-tetrahydropyrimidin-4-ylamino)-1-(morpholin-4-ylmethyl)ethyl ester (26). According to the preparation of **20**, **26** was obtained from **8** (2.98 g, 10 mmol) as a yellowish oil by using 3-phenylpropionyl chloride. Yield: 3.4 g, 60%; (Found: C, 66.12; H, 6.80; N, 9.70. $C_{31}H_{38}N_4O_6$ requires C, 66.17; H, 6.81; N, 9.96%); ν_{max} ($CHCl_3$)/cm^{-1}: 3243 (NH), 1700, 1650 (C=O); δ_H(300 MHz, $CDCl_3$, Me_4Si): 2.29–2.43 (6H, m, C10-H_2, C12-H_2, C16-H_2), 2.70 (2H, dt, J = 7.8 Hz, 6.9 Hz, CH_2), 2.92 (4H, m, 2 × CH_2), 3.31 (3H, s, NCH_3), 3.32 (2H, m, CH_2), 3.40 (3H, s, NCH_3), 3.50 (2H, dd, ^2J = 8.0 Hz, ^3J = 4.2 Hz, C8-H_2), 3.60 (4H, t, J = 4.5 Hz, C13-H_2, C15-H_2), 5.12 (1H, m, H_d), 7.15–7.30 (10H, m, 2 × Ph), 11.68 (1H, t, J = 5.4 Hz, H_a, exchanges with D_2O); δ_C(75.4 MHz, $CDCl_3$, Me_4Si): 28.1 (+ve, NCH_3), 30.6 (+ve, NCH_3), 30.7 (−ve, CH_2), 35.3 (−ve, CH_2), 35.6 (−ve, CH_2), 36.5 (−ve, CH_2), 47.6 (−ve, C8), 54.0 (−ve, C12,16), 58.2 (−ve, C10), 66.5 (−ve, C13,15), 69.4 (+ve, C9), 94.9 (C5), 125.7 (+ve, ArCH), 126.3 (+ve, ArCH), 128.2 (+ve, ArCH), 128.4 (+ve, ArCH), 128.5 (+ve, ArCH), 140.0 (ArC), 141.8 (ArC), 151.3 (C2), 161.6 (C4), 162.7 (C6), 172.0 (C=O), 200.4 (C=O); *m/z* (FAB) 563 ($M^+ + 1$).

5-Benzoyl-6-(2-hydroxy-3-morpholin-4-ylpropylamino)-1,3-dimethyl-1*H*-pyrimidin-2,4-dione (27). Compound **20** (2.53 g, 5 mmol) was stirred with 2 N aqueous sodium hydroxide (10 ml) in ethanol (10 ml) at room temperature for 2 h. Extraction with ether, drying over sodium sulfate and solvent removal afforded a thick liquid which was purified by column chromatography using ethyl acetate–methanol (8 : 2) as eluent to give **27** (1.82 g, 89%) as a yellowish oil. (Found: C, 59.68; H, 6.40; N, 13.85. $C_{20}H_{26}N_4O_5$ requires C, 59.70; H, 6.46; N, 13.93%); ν_{max} ($CHCl_3$)/cm^{-1}: 3393 (NH), 1638, (C=O); δ_H(300 MHz, $CDCl_3$, Me_4Si): 2.33 (2H, m, C12-H_2/C16-H_2), 2.34 (2H, m, C10-H_2), 2.58 (2H, m, C12-H_2/C16-H_2), 2.79 (1H, bs, OH, exchanges with D_2O), 3.21 (1H, ddd, $^2J_{H_c-H_b}$ = 12.6 Hz, $^3J_{H_c-H_d}$ = 6.3 Hz, $^3J_{H_c-H_a}$ = 5.7 Hz, H_c), 3.26 (3H, s, NCH_3), 3.47 (1H, dt, $^2J_{H_b-H_c}$ = 12.9 Hz, $^3J_{H_b-H_a}$ = 4.2 Hz, $^3J_{(Hb-Hd)}$ = 4.2 Hz, H_b), 3.54 (3H, s, CH_3), 3.64 (4H, m, C13-H_2, C15-H_2), 3.91 (1H, m, H_d), 7.37–7.54 (5H, m, Ph), 9.50 (1H, t, J = 4.5 Hz, H_a); δ_C(75.4 MHz, $CDCl_3$, Me_4Si): 28.1 (+ve, NCH_3), 34.8 (+ve, NCH_3), 50.3 (−ve, C8), 53.6 (−ve, C12,16), 61.1 (−ve, C10), 65.4 (+ve, C9), 66.7 (−ve, C13,15), 94.4 (C5), 127.7 (+ve, ArCH), 127.9 (+ve, ArCH), 131.1 (+ve, ArCH), 141.5 (ArC), 151.7 (C2), 160.6 (C6), 161.4 (C4), 195.8 (C=O); ^1H–^{13}C HETCOR: The two multiplets at δ 2.33 and 2.58 correspond to the carbon signal at δ 53.6. The 2H multiplet at δ 2.34 belongs to the carbon signal at δ 61.1. The signals at δ 3.21 and 3.47 correspond to the carbon signal at δ 50.3; *m/z* (FAB) 403 ($M + 1$).

5-Benzoyl-6-(2-hydroxy-3-piperidin-1-ylpropylamino)-1,3-dimethyl-1*H*-pyrimidin-2,4-dione (28). According to the preparation of **27**, **28** was obtained from **21** (2.52 g, 5 mmol) as a yellowish oil. Yield: 2.6 g, 61%; (Found: C, 63.01; H, 6.98; N, 14.02. $C_{21}H_{28}N_4O_4$ requires C, 63.00; H, 7.00; N, 14.00%); ν_{max} ($CHCl_3$)/cm^{-1}: 3131 (NH), 1647 (C=O); δ_H(300 MHz, $CDCl_3$, Me_4Si): 1.47 (2H, m, C14-H_2), 1.58 (4H, m, C13-H_2, C15-H_2), 2.55 (2H, m, C12-H_2/C16-H_2), 2.67 (2H, m, C12-H_2/C16-H_2), 2.79 (2H, d, J = 5.1 Hz, C10-H_2), 2.90 (1H, bs, OH, exchanges with D_2O), 3.03 (1H, ddd, $^2J_{H_c-H_b}$ = 12.3 Hz, $^3J_{H_c-H_d}$ = 7.4 Hz, $^3J_{H_c-H_a}$ = 4.0 Hz, H_c), 3.20 (1H, ddd, $^2J_{H_b-H_c}$ = 12.3 Hz, $^3J_{H_b-H_d}$ = 5.4 Hz, $^3J_{H_b-H_a}$ = 4.2 Hz, H_b), 3.30 (3H, s, NCH_3), 3.42 (3H, s, NCH_3), 4.09 (1H, m, H_d), 7.36–8.03 (5H, m, Ph), 8.59 (1H, bs, H_a); δ_C(75.4 MHz, $CDCl_3$, Me_4Si): 23.5 (−ve, C14), 26.1 (−ve, C13,15), 28.2 (+ve, NCH_3), 34.8 (+ve, NCH_3), 49.8 (−ve, C8), 55.1 (−ve, C12,16), 60.1 (−ve, C10), 64.3 (+ve, C9), 94.3 (C5), 127.8 (+ve, ArCH), 127.9 (+ve, ArCH), 131.0 (+ve, ArCH), 141.3 (ArC), 151.8 (C2), 160.3 (C6), 161.3 (C4), 195.3 (C=O); *m/z* (FAB) 401 ($M^+ + 1$).

5-Benzoyl-6-(2-hydroxy-3-pyrrolidin-1-ylpropylamino)-1,3-dimethyl-1*H*-pyrimidin-2,4-dione (29). According to the preparation of **27**, **29** was obtained from **22** (2.45 g, 5 mmol) as a yellowish oil. Yield: 1.25 g, 65%; (Found: C, 66.40; H, 6.70; N, 14.51. $C_{20}H_{26}N_4O_4$ requires C, 66.32; H, 6.73; N, 14.50%); ν_{max} ($CHCl_3$)/cm^{-1}: 3335 (NH), 1700, 1680 (C=O); δ_H(300 MHz, $CDCl_3$, Me_4Si): 1.97 (4H, m, C13-H_2, C14-H_2), 2.85 (2H, dd, ^2J = 8.4 Hz, ^3J = 6.0 Hz, C10-H_2), 2.90 (4H, m, C12-H_2, C15-H_2), 3.25 (3H, s, NCH_3), 3.40 (3H, s, NCH_3), 3.44 (2H, dd, ^2J = 8.4 Hz, ^3J = 6.5 Hz, C8-H_2), 3.99 (1H, m, H_d), 7.46–7.95 (5H, m, Ph), 9.60 (1H, t, J = 6.0 Hz, H_a): δ_C(75.4 MHz, $CDCl_3$, Me_4Si): 22.8 (−ve, $C_{13,14}$), 28.1 (+ve, NCH_3), 29.1 (+ve, NCH_3), 47.0 (−ve, C8), 55.4 (−ve, C12,15), 58.9 (−ve, C10), 64.9 (+ve, C9), 94.8 (C5), 127.1 (+ve, ArCH), 129.7 (+ve, ArCH), 130.8 (+ve, ArCH), 141.8 (ArC), 151.7 (C2), 159.1 (C6), 161.1 (C4), 194.8 (C=O); *m/z* (FAB) 387 ($M^+ + 1$).

5-Benzoyl-1,3-dibenzyl-6-(2-hydroxy-3-morpholin-4-ylpropylamino)-1*H*-pyrimidin-2,4-dione (30). According to the preparation of **27**, **30** was obtained from **23** (3.29 g, 5 mmol) as a yellowish oil. Yield: 2.25 g, 81%; (Found: C, 69.28; H, 6.32; N, 10.04. $C_{32}H_{34}N_4O_5$ requires C, 69.31; H, 6.31; N, 10.10%); ν_{max} ($CHCl_3$)/cm^{-1}: 3231 (NH), 1637 (C=O); δ_H(300 MHz, $CDCl_3$, Me_4Si): 2.17 (2H, m, C10-H_2), 2.20 (2H, m, C12-H_2/C16-H_2), 2.46 (2H, C12-H_2/C16-H_2), 2.87 (1H, ddd, $^2J_{H_c-H_b}$ = 12.6 Hz, $^3J_{H_c-H_d}$ = 6.3 Hz, $^3J_{H_c-H_a}$ = 4.2 Hz, H_c), 3.08 (1H, dt, $^2J_{H_b-H_c}$ = 12.92 Hz, $^3J_{H_b-H_d}$ = 3.6 Hz, $^3J_{H_b-H_a}$ = 4.0 Hz, H_b), 3.60 (4H, t, J = 4.6 Hz, C13-H_2, C15-H_2), 3.66 (1H, m, H_d), 5.12 (2H, d, J = 16.2 Hz, PhCH_2), 5.30 (2H, d, J = 14.4 Hz, PhCH_2), 7.17–7.77 (15H, m, 3 × Ph); δ_C(75.4 MHz, $CDCl_3$, Me_4Si): 44.3 (−ve, Ph*C*H_2), 48.6 (−ve, Ph*C*H_2), 49.6 (−ve, C8), 53.3 (−ve, C12,16), 60.8 (−ve, C10), 64.5 (−ve, C13,15), 66.3 (+ve, C9), 92.9 (C5), 125.9 (+ve, ArCH), 126.4 (+ve, ArCH), 127.0 (+ve, ArCH), 128.0 (+ve, ArCH), 128.2 (+ve, ArCH), 128.8 (ArC), 129.2 (+ve, ArCH), 129.8 (+ve, ArCH), 133.4 (+ve, ArCH), 134.1 (+ve, ArCH), 137.5 (ArC), 140.2 (ArC), 151.4 (C2), 156.5 (C6), 161.1 (C4), 194.4 (C=O); (FAB) *m/z* 555 ($M^+ + 1$).

5-Benzoyl-1,3-dibenzyl-6-(2-hydroxy-3-piperidin-1-ylpropylamino)-1*H*-pyrimidin-2,4-dione (31). According to the preparation of **27**, **31** was obtained from **24** (3.28 g, 5 mmol) as a yellowish oil. Yield: 2.2 g, 80%; (Found: C, 71.52; H, 6.49; N, 10.12. $C_{33}H_{36}N_4O_4$ requires C, 71.73; H, 6.52; N, 10.14%); ν_{max} ($CHCl_3$)/cm^{-1}: 3330 (NH), 1640 (C=O); δ_H(300 MHz, $CDCl_3$, Me_4Si): 1.49 (2H, m, C14-H_2), 1.67 (4H, m, C13-H_2, C15-H_2), 2.18 (2H, m, C12-H_2/C16-H_2), 2.69 (2H, m, C12-H_2/C16-H_2), 2.70 (2H, d, J = 6.8 Hz, C10-H_2), 3.01 (1H, ddd, $^2J_{H_c-H_b}$ = 12.3 Hz, $^3J_{H_c-H_d}$ = 7.4 Hz, $^3J_{H_c-H_a}$ = 3.8 Hz, H_c), 3.14 (1H, ddd,

$^2J_{H_b-H_c}$ = 12.3 Hz, $^3J_{H_b-H_d}$ = 4.2 Hz, $^3J_{H_b-H_a}$ = 4.2 Hz, H_b), 3.96 (1H, m, H_d), 5.06 (2H, d, J = 14.8 Hz, PhCH_2), 5.17 (2H, d, J = 16.2 Hz, PhCH_2), 7.11–7.52 (15H, m, 3 × Ph); δ_C(75.4 MHz, $CDCl_3$, Me_4Si): 22.6 (−ve, C14), 23.8 (−ve, C13,15), 44.0 (−ve, PhCH_2), 45.2 (−ve, PhCH_2), 46.2 (−ve, C8), 54.5 (−ve, C12,16), 60.6 (−ve, C10), 63.1 (+ve, C9), 93.2 (C5), 125.9 (+ve, ArCH), 126.9 (+ve, ArCH), 127.6 (+ve, ArCH), 128.3 (+ve, ArCH), 128.5 (+ve, ArCH), 128.8 (ArC), 129.2 (+ve, ArCH), 130.9 (+ve, ArCH), 133.4 (+ve, ArCH), 137.5 (ArC), 144.5 (ArC), 151.1 (C2), 155.0 (C6), 157.1 (C4), 194.2 (C=O); *m/z* (FAB) 553 ($M^+ + 1$).

5-Benzoyl-1,3-dibenzyl-6-(2-hydroxy-3-pyrrolidin-1-yl-propylamino)-1*H*-pyrimidin-2,4-dione (32). According to the preparation of **27**, **32** was obtained from **25** (3.16 g, 5 mmol) as a yellowish oil. Yield: 2.02 g, 75%; (Found: C, 71.32; H, 6.32; N, 10.38. $C_{32}H_{34}N_4O_4$ requires C, 71.37; H, 6.31; N, 10.40%); ν_{max} ($CHCl_3$)/cm^{-1}: 3231 (NH), 1652 (C=O); δ_H(300 MHz, $CDCl_3$, Me_4Si): 1.93 (4H, m, C13-H_2, C14-H_2), 2.67 (2H, dd, ^2J = 7.0 Hz, ^3J = 3.8 Hz, C10-H_2), 2.81 (2H, m, C12-H_2/C15-H_2), 2.90 (2H, m, C12-H_2/C15-H_2), 3.13 (2H, dd, ^2J = 8.0 Hz, ^3J = 4.2 Hz, C8-H_2), 4.11 (1H, m, H_d), 5.23 (2H, d, J = 15.9 Hz, PhCH_2), 5.52 (2H, d, J = 14.1 Hz, PhCH_2), 7.19–7.72 (15H, m, 3 × Ph): δ_C(75.4 MHz, $CDCl_3$, Me_4Si): 24.0 (−ve, $C_{13,14}$), 44.1 (−ve, PhCH_2), 45.4 (−ve, C8), 45.9 (−ve, PhCH_2), 56.5 (−ve, C12,15), 59.9 (−ve, C10), 62.8 (+ve, C9), 93.6 (C5), 126.2 (+ve, ArCH), 126.8 (+ve, ArCH), 127.2 (+ve, ArCH), 127.7 (+ve, ArCH), 127.9 (+ve, ArCH), 128.0 (+ve, ArCH), 128.3 (+ve, ArCH), 128.5 (ArC), 128.8 (+ve, ArCH), 135.4 (ArC), 137.5 (ArC), 152.2 (C2), 153.8 (C6), 158.2 (C4), 194.8 (C=O); *m/z* (FAB) 539 ($M^+ + 1$).

6-(2-Hydroxy-3-morpholin-4-ylpropylamino)-1,3-dimethyl-5-(3-phenylpropionyl)-1*H*-pyrimidin-2,4-dione (33). According to the preparation of **27**, **33** was obtained from **26** (2.81 g, 5 mmol) as a yellowish oil. Yield: 1.55 g, 72%; (Found: C, 61.35; H, 6.87; N, 13.01. $C_{22}H_{30}N_4O_5$ requires C, 61.39; H, 6.97; N, 13.02%); ν_{max} ($CHCl_3$)/cm^{-1}: 3313 (NH), 1680 (C=O); δ_H(300 MHz, $CDCl_3$, Me_4Si): 2.53 (2H, dd, ^2J = 8.1 Hz, ^3J = 3.0 Hz, C10-H_2), 2.64 (2H, m, C12-H_2/C16-H_2), 2.77 (2H, m, C12-H_2/C16-H_2), 2.95 (2H, t, J = 7.4 Hz, CH_2), 3.32 (3H, s, NCH_3), 3.33 (1H, merged with NCH_3, H_c), 3.42 (2H, t, J = 7.4 Hz, CH_2), 3.48 (3H, s, NCH_3), 3.53 (1H, dt, ^2J = 12.6 Hz, ^3J = 4.2 Hz, ^3J = 3.9 Hz, H_b), 3.80 (4H, m, C13-H_2, C15-H_2), 4.02 (1H, m, H_d), 7.16–7.25 (5H, m, Ph), 11.77 (1H, t, J = 4.2 Hz, NH_a); δ_C(75.4 MHz, $CDCl_3$, Me_4Si): 28.1 (+ve, NCH_3), 30.9 (−ve, CH_2), 36.4 (+ve, NCH_3), 44.6 (−ve, CH_2), 50.5 (−ve, C8), 53.7 (−ve, C12,16), 61.4 (−ve, C10), 65.5 (+ve, C9), 66.0 (−ve, C13,15), 94.9 (C5), 125.7 (+ve, ArCH), 128.2 (+ve, ArCH), 128.5 (+ve, ArCH), 141.9 (ArC), 151.4 (C2), 161.7 (C4), 162.7 (C6), 200.4 (C=O); *m/z* (FAB) 431 ($M^+ + 1$).

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References

1 E. Teodori, S. Dei, S. Scapecchi and F. Gultieri, *Farmaco*, 2002, **57**, 385–415.
2 R. Krishna and L. D. Mayer, *Eur. J. Pharm. Sci.*, 2000, **11**, 265–283.
3 M. Kawase and N. Motohashi, *Curr. Drug Targets*, 2003, **4**, 31–43.
4 P. Chiba, S. Rebitzer, E. Richter, M. Hitzler and G. Ecker, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 829–832.
5 P. Chiba, D. Annibali, M. Hitzler, E. Richter and G. Ecker, *Farmaco*, 1998, **53**, 357–364.
6 G. Ecker, P. Chiba, M. Hitzler, D. Schimd, K. Visser, H. P. Cordes, J. Sollei, J. K. Seydel and K.-J. Schaper, *J. Med. Chem.*, 1996, **39**, 4767–4774.
7 P. Chiba, S. Burghofer, E. Richter, B. Tell, A. Moser and G. Ecker, *J. Med. Chem.*, 1995, **38**, 2789–2793.
8 K. Pleban, C. Hoffer, S. Kopp, M. Peer, P. Chiba and G. Ecker, *Arch. Pharm. Pharmacol. Med. Chem.*, 2004, **337**, 328–334.
9 T. Langer, M. Eder, R. D. Hoffman, P. Chiba and G. Ecker, *Arch. Pharm. Pharmacol. Med. Chem.*, 2004, **337**, 317–327.
10 D. Schmid, D. L. Staudacher, H. G. Loew, P. G. Spieckermann, G. Ecker, S. Kopp and P. Chiba, *J. Pharmacol. Exp. Ther.*, 2003, **307**, 589–596.
11 G. Ecker, M. Huber, D. Schmid and P. Chiba, *Mol. Pharmacol.*, 1999, **56**, 791–796.
12 D. Annibali, G. Ecker, W. Fleishhacker, T. Helml, W. Holzer and C. R. Noe, *Monatsh. Chem.*, 2000, **131**, 375–382.
13 P. Chiba, W. Holzer, M. Landau, G. Bechmann, K. Lorenz, B. Plagens, M. Hitzler, E. Richter and G. Ecker, *J. Med. Chem.*, 1998, **41**, 4001–4011.
14 T.-L. Su and K. A. Watanabe, *J. Heterocycl. Chem.*, 1984, **21**, 1543–1547.
15 A. C. Mclean and F. S. Spring, *J. Chem. Soc.*, 1949, 2582–2585.
16 J. L. Bernier, A. Lefebvre, J. P. Henichart, R. Honssin and C. Lespagnol, *Bull. Soc. Chim. Fr.*, 1976, **3**, 616–620.
17 H. Gilman, C. S. Sharman, C. C. Price, R. C. Elderfield, J. T. Maynard, R. H. Reitsema, L. Tolman, S. P. Massie, F. J. Marshall and L. Goldman, *J. Am. Chem. Soc.*, 1946, **68**, 1291–1293.
18 D. L. Heywood and B. Phillips, *J. Am. Chem. Soc.*, 1958, **80**, 1257–1259.
19 The energy minimizations and theoretical predictions of MDR modulating properties were performed using the BioMed CaChe Worksystem Pro 6.1 molecular modeling software.