Synthesis and Anti-HIV Activity of HEPT and S-DABO-analogues with 5-Benzyl and 5-Phenyl Substituents

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6-Benzyl-5-phenyluracil (**4**) and 5,6-dibenzyluracil (**9**) were synthesised from diphenyl acetone (**1**) and ethyl 3-oxo-4-phenylbutyrate (**6**), respectively. The uracils were alkylated to afford the 1-alkoxymethyl-uracils **5**, **10** and **11**. Furthermore, S-alkylated dihydroalkoxybenzyloxopyrimidine (S-DABO) analogues were prepared by alkylating 5,6-dibenzyl-2-thiouracil (**8**) on sulfur to yield compounds **12a-f**. All compounds were tested for their inhibition of HIV-1 reverse transcriptase, and moderate activity was found for 6-benzyl-1-(ethoxymethyl)-5-phenyluracil (**5**).

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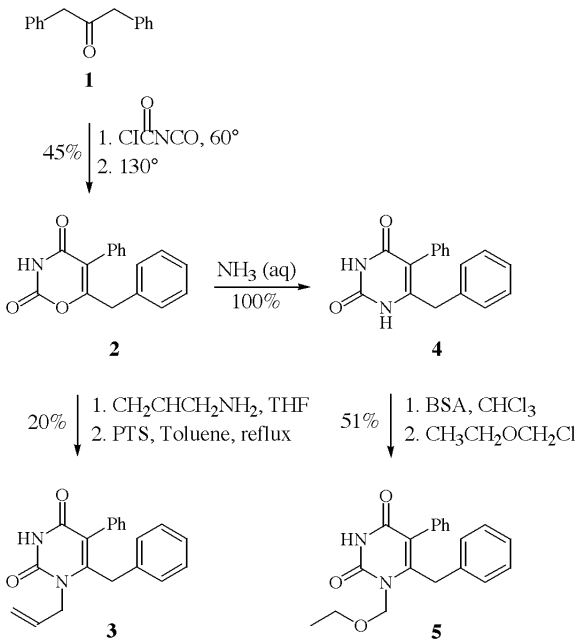
1-[2-(Hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) was synthesised in 1989 by Miyasaka *et al.* [1] and the compound showed moderate activity against Human Immunodeficiency Virus 1 (HIV-1). HEPT was then chosen as a lead for further investigations, and 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil (MKC-442) [2], a highly active analogue of HEPT, was synthesised in 1995. The background for the increased activity is that the 5-substituent in the uracil ring of MKC-442 induces a Tyr181 switch in the reverse transcriptase enzyme and thereby opens a possibility for hydrophobic interactions between the 6-benzyl ring of the inhibitor and the enzymatic Tyr181 [3]. Although extensive structure activity relationships on the anti-HIV activity have been performed, only few investigations have been dealing with the variation of the 5-substituent in the uracil ring. The highest activities are obtained with 5-ethyl and 5-isopropyl substituents whereas no or little information is available about aromatic and more bulky substituents. In this investigation, 5-phenyl and 5-benzyl groups are used as examples of aromatic substituents and when they are compared with the 5-isopropyl group in MKC-442, they also represent more bulky substituents. 5,6-Dibenzyl-2-thiouracil is also S-alkylated to give new S-DABO (dihydroalkoxybenzyloxopyrimidine) analogues of compounds that have shown remarkably high activity against HIV-1 [4].

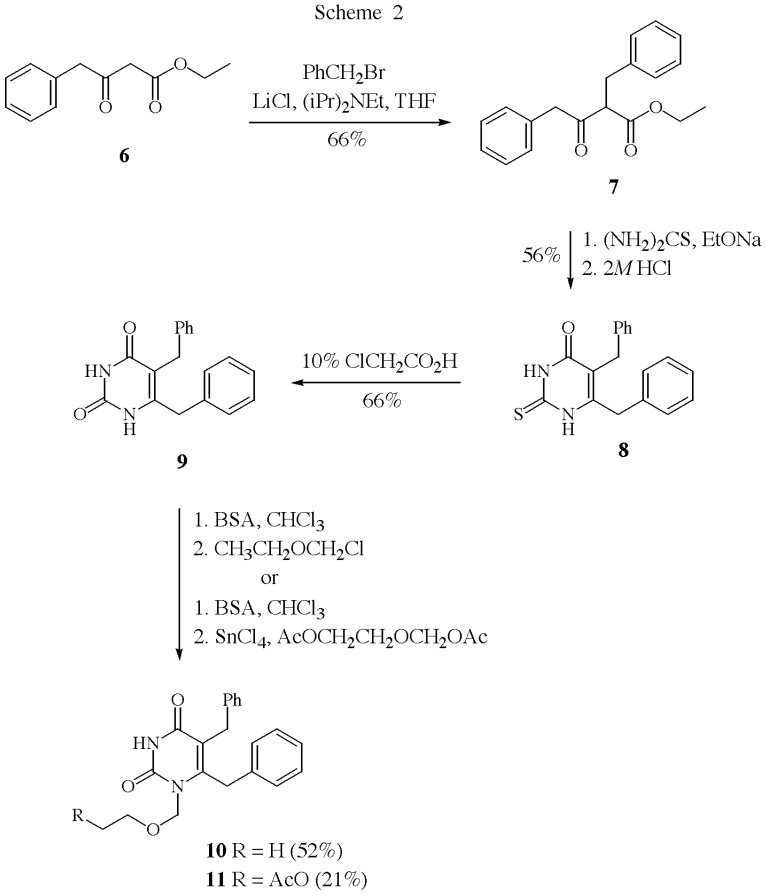
Scheme 1



A new strategy of synthesising 5-substituted analogues of MKC-442 is used. *N*-(chlorocarbonyl) isocyanate was reacted with diphenyl acetone (**1**) at 60-130° under nitrogen, to give 6-benzyl-5-phenyl-1,3-oxazine-2,4(*3H*)-dione (**2**) in 45% yield, using the method of Jaeger *et al.* [5]. Compound **2** was reacted directly with allyl amine according to literature procedures [6,7] to give the *N*-1 alkylated pyrimidine-dione-analogue **3** in 20% yield. The synthesis of the MKC-442 analogue containing the ethoxymethyl group at N-1 was not possible by this procedure because the ethoxymethyl amine is unstable and cannot be isolated. Therefore **2** was reacted with aqueous ammonia under reflux to yield the corresponding 6-benzyl-5-phenyl-uracil (**4**) in a quantitative yield. Compound **4** was then silylated using *N*,*O*-bis-(trismethylsilyl)acetamide (BSA) in chloroform and subsequently alkylated with chloromethyl ethyl ether to obtain the desired 6-benzyl-1-(ethoxymethyl)-5-phenyluracil (**5**) in 51% yield after column chromatography (Scheme 1).

For compound **5** we observed exactly the same ^{13}C nmr chemical shift for the N-1-CH_2 as was previously observed for similar compounds with substituents in the 6-position of the uracil ring [8]. For the isomeric N-3 substituted derivative the corresponding shift of N-3-CH_2 is to be 10 ppm upfield [9].

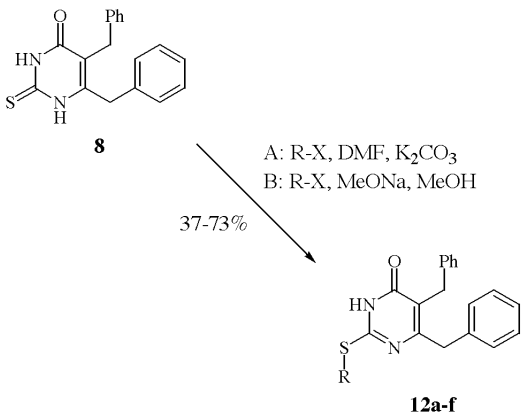
Scheme 2



The above mentioned reaction pathway was used without complications because the starting ketone **1** was symmetric, but in case of unsymmetric ketones one has to expect the most stable enol form to produce the major product. Therefore another pathway was chosen in order to synthesise 5,6-dibenzyluracil (**9**). Ethyl 3-oxo-4-phenyl-butyrate (**6**) was synthesised according to literature procedures in a high yield [10] and alkylated by the method of Nicolai *et al*. [11] with benzyl bromide using lithium chloride and *N*,*N*-diisopropylethylamine as base to give **7** in 66% yield. Compound **7** was condensed with thiourea using sodium ethoxide and the uracil **8** was precipitated in 56% yield from an aqueous solution by acidifying with 2 *M* hydrochloric acid. Transchalogenation of the thione **8** was carried out by refluxing **8** in aqueous chloroacetic acid for 24 hours to give 5,6-dibenzyluracil (**9**) in 66% yield. Compound **9** was silylated using BSA and alkylated with chloromethyl ethyl ether or with 2-acethoxyethyl acethoxymethyl ether using stannane (IV) chloride as a Lewis acid catalyst to give **10** and **11** in 52% and 21% yield, respectively (Scheme 2).

Compound **8** could also be used for the synthesis of new potential anti-HIV S-DABO analogues, and compound **8** was therefore alkylated on sulfur with alkyl halides to give the desired analogues **12 a-f** in 37-73% yield (Scheme 3).

Scheme 3



12	R	X	Method	Yield (%)
a	Me	I	A	53
b	Et	I	A	53
c	Sec-Butyl	Br	B	37
d	Cyclopentyl	Br	B	46
e	Benzyl	Br	A	54
f	-CH_2SCH_3	Cl	A	73

The compounds **2-5**,**8-11**,**12a-f** were tested for their activity against HIV-1 in MT-4 cells using HIV antigen detection ELISA for quantifying expression of HIV in culture medium. However only compound **5** (ED_{50} = 7 μ*M*, CD_{50} > 100 μ*M*) showed activity against HIV-1, but at a considerably higher concentration than the reference compound, MKC-442 (ED_{50} = 0.005 μ*M*).

The biological results clearly shows that introducing a bulky aromatic substituents does not improve the biological activity of these compounds, although it is interesting that compound **5** shows activity in the same range as HEPT (ED_{50} = 7 μ*M*).

EXPERIMENTALS

Nmr Spectra were recorded at 300 MHz for ^{1}H and 75 MHz for ^{13}C on a Varian Gemini 2000 NMR 300 MHz spectrometer; δ values are in ppm relative to tetramethylsilane as an internal standard. EI mass spectra were recorded on a Finnigan MAT SSQ 710. Fast atom bombardment mass spectra (FAB ms) were recorded on a Kratos 50TC spectrometer. Analytical silica gel (tlc) was performed on Merck precoated 60 F_{254} plates. The silica gel (0.040–0.063 mm) used for column chromatography was purchased from Merck. Microanalysis was carried out at the H. C. Ørsted Institute, Copenhagen University.

6-Benzyl-5-phenyl-1,3-oxazine-2,4(3*H*)-dione (**2**).

Diphenyl acetone (**1**) (2.0 g, 9.5 mmoles) was mixed with *N*-(chlorocarbonyl) isocyanate (1.02 g, 9.5 mmoles) under nitrogen and the mixture was heated in an oil bath at 60° for 2 hours. After additional heating at 130° for 1 hour and cooling to room temperature, the mixture was taken up in 100 ml ethyl acetate and the organic phase was washed with a saturated aqueous solution of sodium hydrogencarbonate (2 x 50 ml) followed by water (2 x 50 ml). The organic phase was dried over sodium sulfate, and evaporated *in vacuo* to an oily product which was purified by silica gel column chromatography with ethyl acetate:petroleum ether (bp. 60-80°, 1:1, v/v) as the eluent to give 2 (1.19 g, 45%); mp 133-38° (lit. 136-138° [5]); ^{1}H nmr (deuteriochloroform): δ 3.60 (s, 2 H, CH_2Ph), 7.14-7.50 (m, 10 H, Ar), 9.45 (brs, 1 H, NH); ^{13}C nmr (deuteriochloroform): δ 36.98 (CH_2Ph), 114.92 (C-5), 128.65, 129.50, 130.61, 134.39 (Ar), 147.33 (C-2), 162.51 (C-6), 164.41 (C-4); EI ms: m/z 279 (M^+).

1-Allyl-6-benzyl-5-phenyluracil (**3**).

To a solution of 6-benzyl-5-phenyl-1,3-oxazine-2,4(*3H*)-dione (2) (0.5 g, 1.80 mmoles) in tetrahydrofuran (50 ml) was added allylamine (0.13 ml, 1.80 mmoles) and the mixture was heated at 45° for 2 hours. Tlc showed complete reaction and the solvent was evaporated *in vacuo* and the oily product redissolved in dry toluene (50 ml). *p*-Toluenesulfonic acid (PTS, 2 crystals) was added and the mixture was refluxed for 1 hour after which a new product was formed (according to tlc). The reaction mixture was evaporated *in vacuo* and the semisolid was purified by silica gel column chromatography with methanol:methylene chloride (5:95, v/v) as the eluent to give **3** as a white solid (0.12 g, 20%); mp 234-238°; ^{1}H nmr (deuteriochloroform): δ 3.87 (s, 2 H, CH_2Ph), 4.33 (m, 2 H, NCH_2), 5.25 (m, 2 H, CH_2=CH), 5.84 (m, 1 H, C*H*=CH_2), 7.10-7.37 (m, 10 H, Ar), 9.10 (brs, 1 H, NH); ^{13}C nmr (deuteriochloroform): δ 35.61 (CH_2Ph), 46.35 (NCH_2), 116.95 (*C*H_2=CH), 117.25 (C-5), 127.85, 128.05, 128.87, 129.45, 130.01, 132.12, 132.40 (Ar), 135.71 (*C*H=CH_2), 151.29, 151.99 (C-2 , C-6), 162.61 (C-4); EI ms: m/z 318 (M^+).

6-Benzyl-5-phenyluracil (**4**).

The 6-Benzyl-5-phenyl-1,3-oxazine-2,4(*3H*)-dione (**2**) (1.0 g, 3.58 mmoles) was suspended in 50 ml of conc. aqueous ammonia and the mixture was refluxed overnight. Evaporation of the solvent *in vacuo* and subsequent washing with ether (50 ml) gave the uracil in quantitative yield (0.98 g); mp 210-215° (lit. 218-222° [5]); ^{1}H nmr (DMSO-d_6): δ 3.63 (s, 2 H, CH_2Ph), 7.01-7.47 (m, 10 H, Ar), 11.00 (s, 1 H, NH), 11.10 (s, 1 H, NH); ^{13}C nmr (DMSO-d_6): δ 35.59 (CH_2Ph), 112.5 (C-5), 127.31, 127.67, 128.19, 128.51, 131.22, 133.17, 136.77 (Ar), 150.32, 151.17 (C-2, C-6), 164.06 (C-4); EI ms: m/z 278 (M^+).

6-Benzyl-1-(ethoxymethyl)-5-phenyluracil (**5**).

To a suspension of the uracil **4** (0.5 g, 1.80 mmoles) in dry chloroform (15 ml) was added *N*,*O*-bis-(trimethylsilyl)-acetamid (BSA) (1.05 ml, 3.6 mmoles) and stirring was continued until all the starting material had dissolved. Then chloromethyl ethyl ether (0.17 ml, 1.8 mmoles) was added and the reaction mixture was stirred until tlc showed no change in the amount of starting material. After evaporation of the solvent *in vacuo* the product was purified by silica gel column chromatography with methanol:methylene chloride (5:95, v/v) as the eluent to obtain the pure *N*-1 alkylated product (0.31 g, 51%), white solid; mp 231-235°; ^{1}H nmr (deuteriochloroform): δ 1.22 (t, 3 H, J = 7.0 Hz, CH_3), 3.64 (q, 2 H, J = 7.0 Hz, CH_2), 4.05 (s, 2 H, CH_2Ph), 5.15 (s, 2 H, NCH_2O), 7.11-7.35 (m, 10 H, Ar), 9.54 (brs, 1 H, NH); ^{13}C nmr (deuteriochloroform): δ 14.90 (CH_3), 34.75 (CH_2Ph), 65.10 (CH_2O), 72.81 (NCH_2), 117.92 (C-5), 128.23, 128.51, 129.10, 129.70, 132.56, 135.95 (Ar), 150.99, 151.99 (C-2, C-6), 162.81 (C-4); EI ms: m/z 336 (M^+).

Anal. Calcd. for $C_{20}H_{20}N_2O_3$ (336): C, 71.41; H, 5.99; N, 8.33. Found: C, 71.44; H, 6.06; N, 8.20.

Ethyl 2-benzyl-3-oxo-4-phenylbutyrate (**7**).

To a solution of ethyl 3-oxo-4-phenylbutyrate [14] (15.0 g, 0.073 mole) and benzylbromide (7.13 ml, 0.073 mole) in dry tetrahydrofuran (100 ml) were added *N*,*N*-diisopropyl-ethylamine (25.3 ml, 0.145 mole) and lithium chloride (3.08 g, 0.073 mole). The mixture was refluxed for 15 hours and then concentrated *in vacuo*. The residue was taken up in water and extracted with ethyl acetate. The organic layer was washed with 1 *M* hydrochloric acid and with water, dried over magnesium sulfate, and evaporated *in vacuo* to furnish an oily brownish residue which was purified by silica gel column chromatography with ether:petroleum ether (bp. 60-80°, 7:3, v/v) as the eluent to give **7** (14.3 g, 66%); ^{1}H nmr (DMSO-d_6): δ 1.06 (t, 3 H, J = 7.06 Hz, CH_2CH_3), 3.05 (m, 2 H, CH_2Ph), 3.86 (m, 2 H, CH_2Ph), 4.08 (q, 2 H, J = 7.17 Hz, CH_2CH_3), 4.12 (t, 1 H, J = 7.60 Hz, C*H*CH_2), 7.05-7.30 (m, 10 H, Ar); ^{13}C nmr (DMSO-d_6): δ 13.68 (CH_3), 33.29 (Ph*C*H_2CH), 48.34 (CH_2Ph), 59.06 (CH), 60.81 (OCH_2), 126.48, 126.76, 128.3, 128.36, 128.8, 129.76, 133.82, 138.20 (Ar), 168.70 (COOEt), 202.59 (C=O).

5,6-Dibenzyl-2-thiouracil (**8**).

Sodium (26.0 g, 1.13 moles) was dissolved in anhydrous ethanol (570 ml) and thiourea (59.0 g, 0.78 mole) and compound **7** (15.0 g, 0.05 mole) were added to obtain a clear solution. The mixture was refluxed for 18 hours and evaporated *in vacuo* at 30-40° to leave a nearly dry residue which was redissolved in the least amount of water (200 ml). The title compound was precipitated by addition of 4 *M* hydrochloric acid (300 ml). Yield 8.62 g (56%); mp 190-191°; ^{1}H nmr (DMSO-d_6): δ 3.63 (s, 2 H, CH_2Ph), 3.84 (s, 2 H, CH_2Ph), 7.07-7.29 (m, 10 H, Ar), 12.43 (brs, 2 H, 2 x NH); ^{13}C nmr (DMSO-d_6): δ 29.21 (CH_2Ph), 34.70 (CH_2Ph), 114.72 (C-5), 126.03, 126.86, 128.03, 128.29, 128.69, 136.22, 139.29 (Ar), 150.88 (C-2, C-6), 161.91 (C=O), 174.73 (C=S); EI ms: m/z 308 (M^+).

Anal. Calcd. for $C_{18}H_{16}N_2OS$ (308): C, 70.10; H, 5.23; N, 9.08. Found: C, 70.20; H, 5.27; N, 9.09.

5,6-Dibenzyluracil (**9**).

5,6-Dibenzyl-2-thiouracil (**8**) (2.0 g, 6.5 mmoles) was suspended in 10% aqueous chloroacetic acid (200 ml) and subsequently refluxed for 24 hours. After cooling to room temperature the precipitate was filtered off, washed with cold ethanol and finally dried *in vacuo* to afford the title compound. Yield 1.25 g (66%); mp 210°; ^{1}H nmr (DMSO-d_6): δ 3.46 (s, 2 H, CH_2Ph), 3.59 (s, 2 H, CH_2Ph), 6.94-7.15 (m, 10 H, Ar), 10.73 (br, 1 H, NH), 10.99 (br, 1 H, NH); ^{13}C nmr (DMSO-d_6): δ 29.13 (CH_2Ph), 35.18 (CH_2Ph), 108.89 (C-5), 125.73, 126.68, 127.62, 136.18, 140.01 (Ar), 150.91, 151.03 (C-2, C-6), 164.76 (C-4); EI ms: m/z 292 (M^+).

Anal. Calcd. for $C_{18}H_{16}N_2O_2$ (292): C, 73.96; H, 5.52; N, 9.58. Found: C, 73.74; H, 5.54; N, 9.57.

1-(Ethoxymethyl)-5,6-dibenzyluracil (**10**).

Compound **9** (0.29 g, 1 mmole) was suspended in anhydrous chloroform (15 ml), and *N,O*-bis(trimethylsilyl)acetamide (BSA) (0.6 ml, 2.5 mmoles) was added dropwise under nitrogen After stirring 10 minutes, chloromethyl ethyl ether (0.14 ml, 1.5 mmoles) was added to the clear solution and the mixture was stirred at room temperature overnight. The mixture was quenched, and neutralised by addition of saturated aqueous sodium hydrogencarbonate (7 ml) and ethanol (20 ml), and was evaporated *in vacuo* to afford the title compound which was purified by silica gel column chromatography with ethyl acetate:petroleum ether (bp. 60-80°, 3:10, v/v) as the eluent to give **10** (183 mg, 52%); mp133-134°; ^{1}H nmr (deuteriochloroform): δ 1.16 (t, 3 H, J = 7.11 Hz, CH_3), 3.60 (q, 2 H, J = 7.07 Hz, CH_2O), 3.82 (s, 2 H, CH_2Ph), 4.15 (s, 2 H, CH_2Ph), 5.12 (s, 2 H, OCH_2), 7.03-7.33 (m, 10 H, Ar), 8.77 (brs, 1 H, NH); ^{13}C nmr (deuteriochloroform): δ 15.01 (CH_3CH_2), 30.64 (CH_2Ph), 33.98 (CH_2Ph), 65.80 (OCH_2), 72.88 (OCH_2N), 114.35 (C-5), 126.37, 127.27, 127.33, 128.11, 128.54, 129.21, 134.56, 138.98 (Ar), 151.35, 151.56 (C-2, C-6), 163.26 (C-4); FAB ms: (DMSO+3-nitrobenzyl alcohol) m/z 351 ($M+H^+$).

Anal. Calcd. for $C_{21}H_{22}N_2O_3$ (350): C, 71.98; H, 6.33; N, 7.99. Found: C, 72.00; H, 6.34; N, 7.99.

1-[(2-Acetoxyethoxy)methyl]-5,6-dibenzyluracil (**11**).

N,O-Bis(trimethylsilyl)acetamide (3 ml, 0.012 mole) was added dropwise under nitrogen to a stirred mixture of 5,6-dibenzyluracil (**9**) (1.46 g, 0.005 mole) and 2-acetoxyethyl acetoxymethyl ether (1.35 g, 0.0075 mole) in anhydrous methylene chloride (15 ml). After 3 hours with stirring at room temperature the clear solution was cooled to 0° and stannane (IV) chloride (0.1 ml, 0.001 mole) was added. The mixture was then allowed to warm to room temperature, and was stirred overnight. The mixture was poured into a mixture of cold saturated aqueous sodium hydrogencarbonate (50 ml). The resulting emulsion was filtered through Celite and separated. The aqueous layer was extracted further with ethyl acetate (3 x 25 ml) and the combined organic phases were dried over anhydrous sodium sulfate and evaporated under reduced pressure. The remaining oily residue was triturated with ether to furnish the crude oily product which was purified by silica gel column chromatography with ethyl acetate:petroleum ether (bp. 60-80°, 1:1, v/v) as the eluent to give **11** (429 mg, 21%); mp 71-72°; ^{1}H nmr (deuteriochloroform): δ 1.97 (s, 3 H, CH_3), 3.78 (t, 2 H, J = 2.91 Hz, CH_2OCH_2), 3.83 (s, 2 H, 2 x CH_2Ph), 4.15 (t, 2 H, J = 4.59 Hz, OCH_2CH_2), 5.17 (s, 2 H, OCH_2), 7.03-7.32 (m, 10 H, Ar), 10.15 (br, 1 H, NH); ^{13}C nmr (deuteriochloroform): δ 20.69 (CH_3), 30.51 (CH_2Ph), 33.81 (CH_2Ph), 63.06 (OCH_2), 67.47 (OCH_2CH_2), 73.05 (OCH_2N), 114.63 (C-5), 126.45, 127.35, 127.48, 128.01, 128.67, 129.41, 134.78, 138.59 (Ar), 150.97 (C-2, C-6), 163.78 (C-4), 170.73 (C=O); FAB ms: (DMSO+3-nitrobenzyl alcohol) m/z 409 ($M+H^+$).

Anal. Calcd. for $C_{23}H_{24}N_2O_5$ (408): C, 66.90; H, 5.98; N, 6.78. Found: C, 66.79; H, 5.89; N, 6.71.

General Procedure for the Preparation of Compounds (**12a-f**).

Method A: Compound **8** (1.0 mmole) was mixed with the appropriate halogen compound (1.0 mmole) and anhydrous potassium carbonate (1.0 mmole) in anhydrous *N,N*-dimethylformamide (3 ml). Method B: Compound **8** was mixed with (2.2 mmoles) of the appropriate halo compound and sodium (1.1 mmoles) in methanol (3 ml). The mixture was stirred overnight at room temperature. After treatment with water (60 ml), the solution was extracted with ethyl acetate (3 x 50 ml), dried over anhydrous sodium sulfate and evaporated *in vacuo* to afford the corresponding crude 2-alkylthio derivatives. The compounds **12a-f** were purified by the procedures describes for each compound.

5,6-Dibenzyl-2-(methylthio)pyrimidine-4(3*H*)-one (**12a**).

The compound was recrystallised from ethanol. Yield 70 mg (53%); mp 195-196°; ^{1}H nmr (DMSO-d_6): δ 2.45 (s, 3 H, CH_3), 3.89 (s, 2 H, CH_2Ph), 3.94 (s, 2 H, CH_2Ph), 7.13-7.25 (m, 10 H, Ar), 12.55 (brs, 1 H, NH); ^{13}C nmr (DMSO-d_6): δ 13.24 (CH_3), 30.39 (CH_2Ph), 40.76 (CH_2Ph), 119.39 (C-5), 126.06, 126.39, 128.27, 128.39, 128.45, 129.09, 137.72, 139.78 (Ar), 158.03 (C-6), 163.22 (C-2), 165.26 (C-4); EI ms: m/z 322 (M^+).

Anal. Calcd. for $C_{19}H_{18}N_2OS$ (322): C, 70.78; H, 5.63; N, 8.68. Found: C, 70.60; H, 5.59; N, 8.69.

5,6-Dibenzyl-2-(ethylthio)pyrimidine-4(3*H*)-one (**12b**).

The compound was recrystallised from ethanol. Yield 178 mg (53%); mp 134°; ^{1}H nmr (deuteriochloroform): δ 1.22 (t, 3 H, J = 7.20 Hz, CH_3), 3.05 (q, 2 H, J = 7.50 Hz, CH_2), 3.88 (s, 2 H, CH_2Ph), 3.95 (s, 2 H, CH_2Ph), 7.11-7.27 (m, 10 H, Ar); ^{13}C nmr (deuteriochloroform): δ 14.48 (CH_3CH_2), 25.05 (CH_2CH_3), 30.37 (CH_2Ph), 40.71 (CH_2Ph), 119.36 (C-5), 126.34, 126.61, 128.22, 128.39, 128.89, 129.55, 137.65, 139.20 (Ar), 157.55 (C-6), 163.26 (C-2), 165.39 (C-4); EI ms: m/z 336 (M^+).

Anal. Calcd. for $C_{20}H_{20}N_2OS$ (336): C, 71.40; H, 5.99; N, 8.33. Found: C, 71.52; H, 6.02; N, 8.42.

2-(*sec*-Butylthio)-5,6-dibenzylpyrimidin-4(3*H*)-one (**12c**).

The compound was recrystallised from ethanol-water. Yield 134 mg (37%); mp 128-129°; ^{1}H nmr (deuteriochloroform): δ 0.91 (t, 3 H, J = 7.29 Hz, CH_3), 1.26 (d, 3 H, J = 7.11 Hz, CH_3), 1.60 (m, 2 H, CH_2), 3.75 (m, 1 H, CH), 3.87 (s, 2 H, CH_2Ph), 3.95 (s, 2 H, CH_2Ph), 7.10-7.30 (m, 10 H, Ar), 12.27 (brs, 1 H, NH); ^{13}C nmr (deuteriochloroform): δ 11.33 (CH_3CH_2), 20.29 (CH_3CH), 29.23 (CH_2CH_3), 30.40 (CH), 40.69 (CH_2Ph), 42.88 (CH_2Ph), 119.33 (C-5), 126.05, 126.32, 128.21, 128.39, 128.53, 129.17, 137.87, 139. 93 (Ar), 157.74 (C-6), 163.23 (C-2), 165.16 (C-4); EI ms: m/z 364 (M^+).

Anal. Calcd. for $C_{22}H_{24}N_2OS$ (364): C, 72.49; H, 6.64; N, 7.69. Found: C, 72.49; H, 6.62; N, 7.70.

2-(Cyclopentylthio)-5,6-dibenzylpyrimidin-4(3*H*)-one (**12d**).

The compound was recrystallised from ethanol. Yield 173 mg (46%); mp 142-143°; ^{1}H nmr (deuteriochloroform): δ 1.45-2.03 (m, 9 H, cyclopentyl), 3.87 (s, 2 H, CH_2Ph), 3.95 (s, 2 H, CH_2Ph), 7.11-7.30 (m, 10 H, Ar), 12.62 (brs, 1 H, NH); ^{13}C nmr (deuteriochloroform): δ 24.66 (Cγ), 30.35 (CH_2Ph), 33.00 (C_β), 40.71 (CH_2Ph), 43.90 (SCH), 119.18 (C-5), 126.02, 126.28, 128.18, 128.37, 128.53, 129.21, 137.90, 139.94 (Ar), 158.34 (C-6), 163.38 (C-2), 165.33 (C-4); EI ms: m/z 376 (M^+).

Anal. Calcd. for $C_{23}H_{24}N_2OS$ (376): C, 73.37; H, 6.42; N, 7.44. Found: C, 73.62; H, 6.43; N, 7.43.

2-(Benzylthio)-5,6-dibenzylpyrimidin-4(3*H*)-one (**12e**).

The compound was recrystallised from ethanol. Yield 214 mg (54%); mp 155-156°; ^{1}H nmr (deuteriochloroform): δ 3.92 (s, 4 H, 2 x CH_2Ph), 4.29 (s, 2 H, SCH_2), 7.09-7.48 (m, 15 H, Ar), 12.63 (brs, 1 H, NH); ^{13}C nmr (deuteriochloroform): δ 30.41 (CH_2Ph), 34.41 (CH_2Ph), 40.72 (SCH_2), 119.82 (C-5), 126.07, 126.44, 127.34, 128.13, 128.21, 128.52, 128.61, 129.01, 129.15, 136.90, 137.73, 139.70 (Ar), 157.04 (C-6), 163.16 (C-2), 165.31 (C-4); EI ms: m/z 398 (M^+).

Anal. Calcd. for $C_{25}H_{22}N_2OS$ (398): C, 75.35; H, 5.56; N, 7.03. Found: C, 75.17; H, 5.57; N, 7.11.

5,6-Dibenzyl-2-(methylthiomethyl)thiouracil (**12f**).

The compound was purified by silica gel column chromatography with ethyl acetate:petroleum ether (bp. 60-80°, 1:8, v/v) as the eluent. Yield 268 mg (73%); mp 126-128°; ^{1}H nmr (deuteriochloroform): δ 2.11 (s, 3 H, CH_3), 3.91 (s, 2 H, CH_2Ph), 3.95 (s, 2 H, CH_2Ph), 4.23 (s, 2 H, SCH_2), 7.12-7.28 (m, 10 H, Ar), 12.50 (br, 1 H, NH); ^{13}C nmr (deuteriochloroform): δ 15.38 (CH_3), 30.36 (CH_2Ph), 36.48 (CH_2Ph), 40.58 (SCH_2), 119.88 (C-5), 126.17, 126.50, 128.36, 128.47, 128.54, 129.21, 137.60, 139.63 (Ar),156.42 (C-6), 163.06 (C-2), 165.23 (C-4); EI ms: m/z 368 (M^+).

Anal. Calcd. for $C_{20}H_{20}N_2OS_2$ (368): C, 65.19; H, 5.47; N, 7.60. Found: C, 65.35; H, 5.62; N, 7.53.

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