Synthesis of novel uracil non-nucleosides analogues of 3,4-dihydro-2-alkylthio-6-benzyl-4-oxopyrimidines and 6-benzyl-1-ethoxymethyl-5-isopropyluracil

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A series of new uracil non-nucleosides analogues of S-DABO's was synthesised by reaction of 5-alkyl-6-(*p*-chlorobenzyl)-2-thiouracils with chloroethyl dialkylamine hydrochloride, *N*-(2-chloroethyl)-pyrrolidine hydrochloride, *N*-(2-chloroethyl)-piperidine hydrochloride or appropriate haloethers. Novel emivirine analogues were synthesised by silylation of 5-alkyl-6-(*p*-chlorobenzyl)uracils and treatment with bromomethyl methyl ether, chloromethyl ethyl ether or benzyl chloromethyl ether. Compounds 6-(*p*-chlorobenzyl)-5-ethyl-1-ethyloxymethyluracil (**9e**) and 1-benzyloxymethyl-6-(4-chlorobenzyl)-5-ethyluracil (**9f**) showed activity against wild-type HIV-1 strain III B in MT-4 cells.

Keywords: non-nucleosides, reverse transcriptase inhibitors, HIV drugs, S-DABOs, Emivirine analogues

Acquired immunodeficiency syndrome (AIDS) which is caused by the human immunodeficiency virus type-1 (HIV-1), has become a major worldwide pandemic. Three main classes of compounds are used in the treatment of AIDS; fusion inhibitors (FIs), protease inhibitors (PIs) and reverse transcriptase inhibitors (RTIs). HIV-1 reverse transcriptase (RT) is a key target for inhibition of HIV-1 replication and the majority of drugs used clinically are RTIs.[1-3]

RTIs can be divided into two groups; nucleoside reverse transcriptase inhibitors (NRTIs), such as 3'-azido-3'-deoxythymidine (AZT)[4], 2',3'-dideoxycytidine (DDC)[5] and 2',3'-dideoxyinosine (DDI)[6], which act as chain terminators to block the elongation of the HIV-1 viral DNA strand; and non-nucleoside reverse transcriptase inhibitors (NNRTIs), which in contrast to NRTIs, are highly specific as their binding site is a hydrophobic pocket located approximately 10 Å from polymerase active site.[7] They bind allosterically forcing the RT-subunit into an inactive conformation.[8]

Among the representatives of the NNRTIs, 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)-thymine (HEPT)[9,10] and S-DABOs, the thio analogues of dihydroalkyloxybenzyloxopyrimidines (DABOs).[11,12]

Although HEPT did not show very high activity against HIV-1, it was considered as interesting lead compound for the synthesis of new analogues. Among them 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil (Emivirine, formerly MKC-442)[13] which showed high activity against HIV-1,

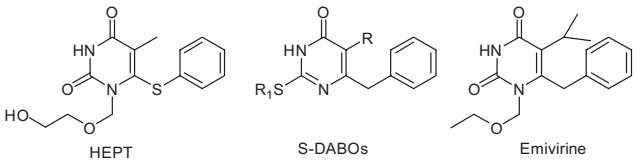
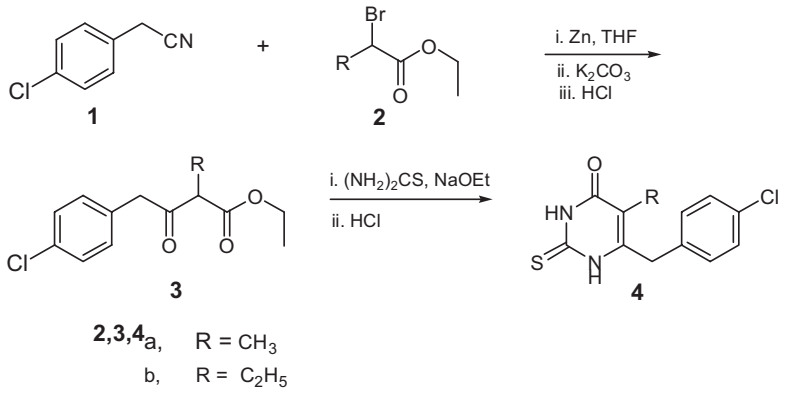


Fig. 1

but unfortunately in phase III clinical trials it was also found to activate a liver enzyme in the P_{450} family which metabolises protease inhibitors.[14]

Structure-activity relationship (SAR) studies on S-DABOs showed that the presence of the C-2 alkylthio side chain is a structural determinant for the antiviral activity of these compounds. Unlike the length and type of substituent at C-2, the substituents at C-5 have modulatory effects on potency. However, modification of the pyrimidine base such as N-3 alkylation, shift of benzyl group from C-6 to C-5, decrease or increase the distance between the pyrimidine and the phenyl ring, or replacement of the C-6 benzyl with smaller substituents have led to substantial loss of activity.[12]

In the present work, and as a part of our continuing interest in the chemistry of NNRTIs,[15-21] the synthesis and anti-HIV evaluation of novel S-DABO and Emivirine analogues have been investigated. Herein, we describe synthesis of new S-DABOs bearing substituted aminoalkylthio and substituted



Scheme 1

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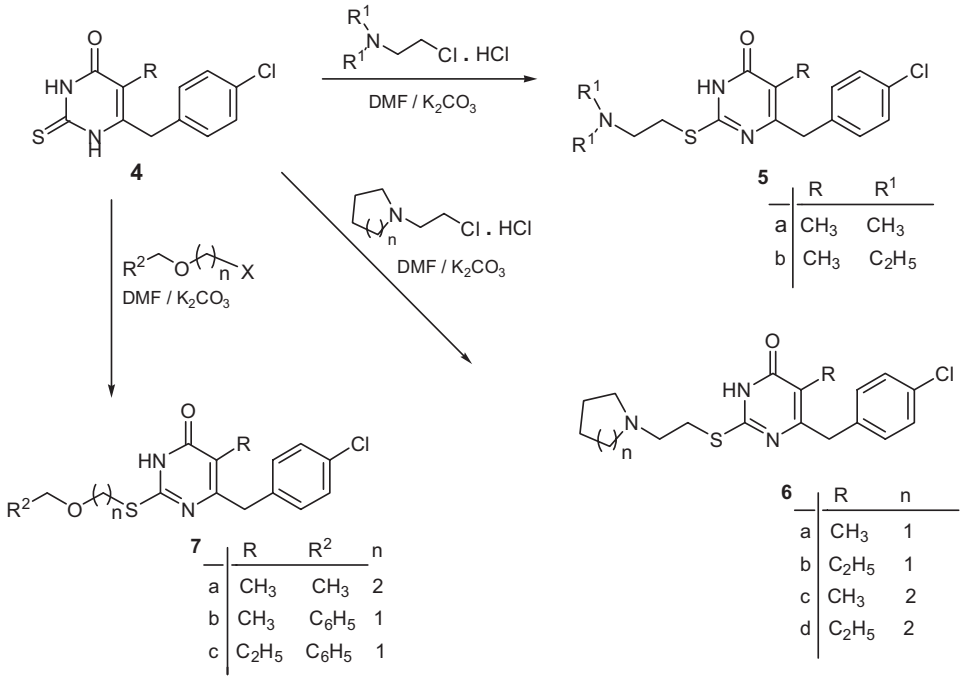


Scheme 2

alkyloxyalkylthio moieties at C-2. The objective was to investigate whether substitution with electron-rich groups at C-2 of the pyrimidine ring could lead to an improved activity against HIV-1. In addition, the synthesis of new HEPT analogues would also provide information to the ongoing investigation of the NNRTI binding site.

Results and discussions

p-Chlorophenylacetonitrile was reacted with ethyl 2-bromopropionate or ethyl 2-bromobutyrate in anhydrous THF in the presence of activated zinc to give the corresponding 2-alkyl-4-(*p*-chlorophenyl)-3-oxo esters **3a,b** in good yields. 5-Alkyl-6-(*p*-chlorobenzyl)-2-thiouracils (**4a,b**) were synthesised from **3a,b** according to the procedure described by Danel *et al.*[22] by treatment with thiourea in boiling ethanol in the presence of sodium ethoxide.

The NMR spectra of crude compound **3b** showed an impurity identified as another β-keto ester resulting from self-condensation of ethyl 2-bromobutyrate. On reaction with thiourea, this β-keto ester impurity also formed a pyrimidine as an impurity in the raw material of **4b**.[23] However, pure compound **4b** was easily obtained by recrystallisation from aqueous ethanol.

Compound **4a** was treated with 2-chloroethyl dimethylamine hydrochloride or 2-chloroethyl diethylamine hydrochloride in DMF in the presence of anhydrous potassium carbonate to afford 6-(*p*-chlorobenzyl)-2-dimethylaminoethylthio-5-methyl-pyrimidin-4(*3H*)-one (**5a**) and its diethylaminoethylthio derivative **5b** in 55% and 68% yields, respectively.

Pyrrolidinylethylthio and piperidinylethylthiouracils **6a–d** were prepared in good yields from **4a,b** by reaction with *N*-(2-chloroethyl)-pyrrolidine hydrochloride or *N*-(2-chloroethyl)-piperidine hydrochloride in DMF. On the other hand, the *S*-DABOs analogues **7a–c** were synthesised by treatment of compounds **4a,b** with bromoethyl ethyl ether or benzyl chloromethyl ether in DMF in the presence of anhydrous potassium carbonate.

Desulfurisation of 2-thiouracils **4a,b** was achieved by reaction with boiling aqueous chloroacetic acid to give 5-alkyl-6-(p-chlorobenzyl)uracils (**8a,b**) in good yields. Silylation of compounds **8a,b** with *N,O*-bis-(trimethylsilyl) acetamide (*BSA*) in anhydrous chloroform followed by treatment with bromomethyl methyl ether, chloromethyl ethyl ether or benzyl chloromethyl ether in the presence of cesium iodide gave the Emivirine analogues **9a–f** and their 1,3-bis-alkylated derivatives **10a–d** in 18–48% and 31–52% yields, respectively.

The newly synthesised *S*-DABOs and Emivirine analogues **5b**, **6a–d**, **7a–d** and **9b–f** were tested against wild-type HIV-1 strain III B in MT-4 cells. No compounds exhibited activity against HIV-1 except 6-(*p*-chlorobenzyl)-5-ethyl-1-ethyloxymethyluracil (**9e**) and 1-benzyloxymethyl-6-(*p*-chlorobenzyl)-5-ethyluracil (**9f**) which showed activities (ED_{50} = 44 μM; CD_{50} = > 100 μM) and (ED_{50} = 5 μM; CD_{50} = > 100 μM), respectively.

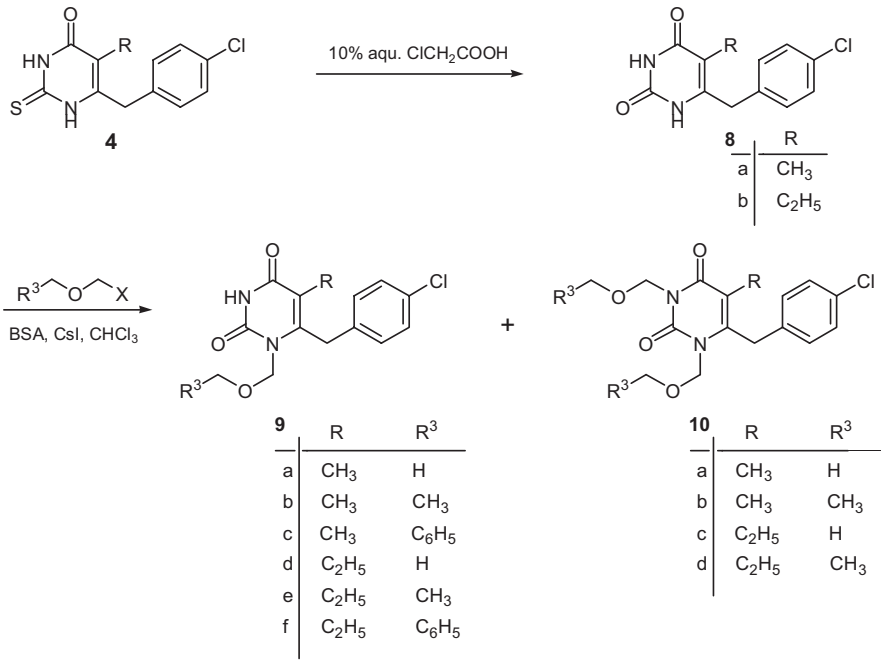
Virus and cells

The inhibitory activity against HIV-1 infection was evaluated using MT-4 cells[24] as target cells and the HIV-1 strain HTLV-IIIB[25] as infectious virus. The virus was propagated in H9[24] cells at 37°C, 5% CO_2 using RPMI 1640 with 10% heat-inactivated fetal calf serum (FCS) and antibiotics (growth medium). Culture supernatant was filtered (0.45 nm), aliquoted, and stored at –80°C until use.

Experimental

NMR spectra were recorded on a Varian Brüker AC 500 Ultra Shield NMR spectrometer at 500 MHz for ^{1}H and 125 MHz for ^{13}C with TMS as an internal standard. Chemical shifts are reported in ppm (δ), and signals are expressed as s (singlet), d (doublet), t (triplet), q (quartet) or m (multiplet). Electron impact mass spectra were recorded on Shimadzu GC-MS-QP 5000 instrument, all compounds showed fragments corresponding to the typical pattern of chlorine isotopes (^{35}Cl and ^{37}Cl). Melting points (uncorrected) were determined on a Gallenkamp melting point apparatus. The progress of reactions was monitored by TLC (DC-alufolio 60 F_{254}) from Merck. For column chromatography Merck silica gel (0.040–0.063 mm) was used.

Ethyl 2-alkyl-4-(p-chlorophenyl)-3-oxobutyrates **3a** *and* **3b**: Zinc dust (14 g) was activated by stirring with 4M HCl (30 cm^3) for 5 min. The zinc dust was filtered, washed sequentially with H_2O, EtOH and dry Et_2O then dried. The active zinc was suspended in dry THF



Scheme 2

(60 cm^3) and heated to reflux. A few drops of ethyl 2-bromopropionate or ethyl 2-bromobutyrate were added and the mixture was refluxed for 10 min. *p*-Chlorophenylacetonitrile (4.55 g, 0.03 mol) was added in one portion and ethyl 2-bromopropionate or ethyl 2-bromobutyrate (0.06 mol) was added dropwise. After the addition was completed, the mixture was refluxed for 30 min, then it was diluted THF (150 cm^3) and quenched by addition of sat. aq. K_2CO_3 (60 cm^3). The mixture was stirred for 1 h at room temperature. The THF layer was decanted and the residue was washed with THF (3 × 30 cm^3). The combined THF fractions were stirred with 10% aq. HCl (40 cm^3) for 30 min. The solution was concentrated under reduced pressure and diluted with CH_2Cl_2 (100 cm^3). The organic phase was washed with sat. aq. $NaHCO_3$ (2 × 60 cm^3), dried (Na_2SO_4) and evaporated under reduced pressure to give the product that was used for further synthesis without purification.

Ethyl 4-(p-chlorophenyl)-2-methyl-3-oxobutyrate (**3a**): Faint yellow oil[26]; yield 7.4 g (97%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.28 (t, *J* = 7.5 Hz, 3H, CH_3), 1.34 (d, *J* = 7.0 Hz, 3H, CH_3), 3.68 (q, *J* = 7.0 Hz, 1H, CH), 3.89 (s, 2H, CH_2), 4.17 (q, *J* = 7.5 Hz, 2H, CH_2); 7.14, 7.30 (2 × d, *J* = 8.0 Hz, 4H, H_{arom}) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 12.87 (CH_3), 14.26 (CH_3), 47.64 (CH_2), 52.12 (CH_2), 61.77 (CH), 128.69, 130.96, 131.89, 133.17 (C_{arom}), 170.30 (CO), 202.87 (CO) ppm; MS (EI): *m/z* (%) = 254 (M^+, 6), 208 (4), 152 (33), 129 (42), 125 (100).

Ethyl 4-(p-chlorophenyl)-2-ethyl-3-oxobutyrate (**3b**): Faint yellow oil; yield 7.7 g (96%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.93 (t, *J* = 7.0 Hz, 3H, CH_3), 1.26 (t, *J* = 7.5 Hz, 3H, CH_3), 1.89 (m, 2H, CH_2), 3.46 (t, *J* = 7.5 Hz, 1H, CH), 3.80 (s, 2H, CH_2), 4.18 (q, *J* = 7.0 Hz, 2H, CH_2), 7.14, 7.30 (2 × d, *J* = 8.0 Hz, 4H, H_{arom}) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 12.84 (CH_3), 13.53 (CH_3), 18.47 (CH_2), 42.02 (CH_2), 60.72 (CH_2), 61.98 (CH), 128.67, 130.99, 131.77, 133.17 (C_{arom}), 162.56 (CO), 202.31 (CO) ppm; MS (EI): *m/z* (%) = 268 (M^+, 11), 222 (3), 213 (5), 186 (2), 152 (33), 143 (72), 125 (100).

5-Alkyl-6-(p-chlorobenzyl)-2-thiouracils **4a** *and* **4b**: Na (9.84 g, 0.434 mol) was dissolved in absolute EtOH (150 cm^3). Thiourea (22.84 g, 0.3 mol) was added and the mixture was heated to reflux. Compounds **3a** or **3b** (0.02 mol) was added dropwise and the mixture was refluxed for 90 min. The solvent was evaporated to dryness under reduced pressure and the residue was redissolved in H_2O (150 cm^3). The product was precipitated by addition of conc. HCl (16 cm^3) and then glacial acetic acid till pH = 4. The precipitate was filtered off, washed with H_2O dried and crystallised from aq. EtOH.

6-(p-Chlorobenzyl)-5-methyl-2-thiouracil (**4a**): White solid; yield 3.3 g (62%); m.p. 261–262°C (lit. 262–263°C)[26]; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.78 (s, 3H, CH_3), 3.84 (s, 2H, CH_2), 7.26, 7.38 (2 × d, *J* = 8.0 Hz, 4H, H_{arom}), 12.28, 12.45 (2 × s, 2H, 2 × NH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 10.33 (CH_3), 34.65 (CH_2), 111.93 (C-5), 128.89, 130.56, 131.92, 135.82 (C_{arom}), 149.61 (C-6), 162.39 (C-4), 174.55 (C-2) ppm; MS (EI): *m/z* (%) = 266 (M^+, 8).

6-(p-Chlorobenzyl)-5-ethyl-2-thiouracil (**4b**): White solid; yield 3.6 g (64%); m.p. 218–220°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.80 (t, *J* = 7.3 Hz, 3H, CH_3), 2.23 (q, *J* = 7.3 Hz, 2H, CH_2), 3.84 (s, 2H, CH_2), 7.26, 7.39 (2 × d, *J* = 8.0 Hz, 4H, H_{arom}), 12.36 (bs, 2H, 2 × NH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.39 (CH_3), 18.19 (CH_2), 34.25 (CH_2), 117.03 (C-5), 129.06, 130.50, 131.88, 136.34 (C_{arom}), 149.36 (C-6), 161.96 (C-4), 174.71 (C-2) ppm; MS (EI): *m/z* (%) = 280 (M^+, 42), 265 (9), 206 (5), 155 (39), 141 (3), 125 (61); Anal. Calcd. for $C_{13}H_{13}ClN_2OS$ (280.77): C 55.6, H 4.7, N 10.0. Found: C 55.5, H 4.6, N 9.7%.

6-(p-Chlorobenzyl)-2-(N,N-dialkylamino)ethylthio-5-methyl-pyrimidin-4(3H)-ones **5a** *and* **5b**: 6-(*p*-Chlorobenzyl)-5-methyl-2-thiouracil (**4a**, 0.266 g, 0.001 mol) was dissolved in anhydrous DMF (3 cm^3). Anhydrous potassium carbonate (0.304 g, 0.0022 mol) was added followed by addition of chloroethyl dimethylamine hydrochloride or chloroethyl diethylamine hydrochloride (0.0011 mol). The mixture was stirred at room temperature for 24 h, then was diluted with H_2O (100 cm^3) and extracted with ether (3 × 50 cm^3). The combined organic extract was washed with H_2O (3 × 50 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel column with $CHCl_3$ to afford **5a** and **5b**.

6-(p-Chlorobenzyl)-2-(N,N-dimethylamino)ethylthio-5-methyl-pyrimidin-4(3H)-one (**5a**): White solid; yield 0.185 g (55%); m.p. 136–138°C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 1.93 (s, 3H, CH_3), 2.12 (s, 6H, 2 × CH_3); 2.44 (br s, 2H, CH_2), 3.12 (br s, 2H, CH_2), 3.83 (s, 2H, CH_2), 7.26, 7.33 (2 × d, *J* = 8.0 Hz, 4H, H_{arom}) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 10.86 (CH_3), 28.22 (CH_3), 39.56 (CH_2), 45.07 (CH_2), 58.61 (CH_2), 115.64 (C-5), 128.70, 131.08, 131.36, 137.81 (C_{arom}), 157.94 (C-6), 160.35 (C-4), 164.03 (C-2) ppm; MS (EI): *m/z* (%) = 337 (M^+, 2), 322 (4), 291 (9), 267 (5), 248 (4), 220 (3), 192 (14), 143 (11), 125 (100); Anal. Calcd. for $C_{16}H_{20}ClN_3OS$ (337.87): C 56.9, H 6.0, N 12.4. Found: C 56.9, H 5.9, N 12.3%.

6-(p-Chlorobenzyl)-2-(N,N-diethylamino)ethylthio-5-methyl-pyrimidin-4(3H)-one (**5b**): White solid; yield 0.25 g (68%); m.p. 122–124°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.16 (t, *J* = 7.0 Hz, 6H, 2 × CH_3), 2.03 (s, 3H, CH_3), 2.76 (q, *J* = 7.0 Hz, 4H, 2 × CH_2), 2.94–2.96 (m, 2H, CH_2), 3.06–3.08 (m, 2H, CH_2), 3.85 (s, 2H, CH_2), 7.17, 7.25 (2 × d, *J* = 8.0 Hz, 4H, H_{arom}), 13.51 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 10.38 (CH_3), 10.72 (CH_3), 31.27 (CH_2), 40.22 (CH_2), 47.13 (CH_2), 55.17 (CH_2), 117.68 (C-5), 128.51, 130.03, 132.16, 136.57 (C_{arom}), 157.65 (C-6), 160.62 (C-4), 165.88 (C-2) ppm; MS (EI): *m/z* (%) = 365 (M^+, 2), 354 (2), 330 (1), 297 (3), 192 (5), 125 (11), 99 (71); Anal. Calcd. for $C_{18}H_{24}ClN_3OS$ (365.92): C 59.1, H 6.6, N 11.5. Found: C 59.0, H 6.6, N 11.4.

5-Alkyl-6-(p-chlorobenzyl)-2-pyrrolidin-1-ylethylthiopyrimidin-4(3H)-ones (**6a,b**) *and 5-Alkyl-6-(p-chlorobenzyl)-2-piperidin-1-ylethylthiopyrimidin-4(3H)-ones* (**6c,d**): To a solution of compound **4a,b** (0.001 mol) in anhydrous DMF (3 cm^3), was added anhydrous potassium carbonate (0.304 g, 0.0022 mol) followed by N-chloroethylpyrrolidine hydrochloride or N-chloroethylpiperidine hydrochloride (1.1 mmol). The mixture was stirred at room temperature for 24 h, then was diluted with H_2O (100 cm^3) and extracted with ether (3 × 50 cm^3). The combined ether extract was washed with H_2O (3 × 50 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel column with $CHCl_3$ to give **6a–d**.

6-(p-Chlorobenzyl)-5-methyl-2-pyrrolidin-1-ylethylthiopyrimidin-4(3H)-ones (**6a**): White solid, yield 0.26 g (72%); m.p. 153-155°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.03-2.04 (m, 9H, CH_3, 2 × CH_2), 2.81-2.82 (m, 4H, 2 × CH_2), 3.08-3.09 (m, 4H, 2 × CH_2), 3.86 (s, 2H, CH_2), 7.17, 7.25 (2 × d, *J* = 8.0 Hz, 4H, H_{arom}), 12.31 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 10.81 (CH_3), 23.74, 54.15 ($C_{pyrrolidine}$), 31.71 (CH_2), 40.21 (CH_2), 58.87 (CH_2), 117.53 (C-5), 128.52, 130.01, 132.12, 136.58 (C_{arom}), 157.78 (C-6), 160.70 (C-4), 165.59 (C-2) ppm; MS (EI): *m/z* (%) = 363 (M^+, 3), 291 (9), 266 (4), 234 (3), 192 (5), 163 (7), 143 (4), 125 (32); Anal. Calcd. for $C_{18}H_{22}ClN_3OS$ (363.90): C 59.4, H 6.1, N 11.55. Found: C 59.2, H 5.9, N 11.4.

6-(p-Chlorobenzyl)-5-ethyl-2-pyrrolidin-1-ylethylthiopyrimidin-4(3H)-ones (**6b**): White solid; yield 0.285 g (75%); m.p. 142–144°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.01 (t, *J* = 7.3 Hz, 3H, CH_3), 2.01–2.02 (m, 4H, 2 × CH_2), 2.47 (q, *J* = 7.3 Hz, 2H, CH_2), 2.78–2.79 (m, 4H, 2 × CH_2), 3.05–3.06 (m, 4H, 2 × CH_2), 7.16, 7.24 (2 × d, *J* = 8.0 Hz, 4H, H_{arom}), 11.81 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.13 (CH_3), 18.83 (CH_2), 23.68, 54.11 ($C_{pyrrolidine}$), 31.05 (CH_2), 39.50 (CH_2), 58.72 (CH_2), 123.36 (C-5), 128.40, 130.02, 132.03, 136.95 (C_{arom}), 157.76 (C-6), 160.09 (C-4), 164.90 (C-2) ppm; MS (EI): *m/z* (%) = 377 (M^+, 3), 344 (2), 325 (2), 307 (2), 280 (3), 248 (2), 206 (2), 141 (4), 125 (9); Anal. Calcd. for $C_{19}H_{24}ClN_3OS$ (377.93): C 60.4, H 6.4, N 11.1. Found: C 60.2, H 6.4, N 11.1.

6-(p-Chlorobenzyl)-5-methyl-2-piperidin-1-ylethylthiopyrimidin-4(3H)-ones (**6c**): White solid; yield 0.27 g (72%); m.p. 137–139°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.55 (br s, 2H, CH_2), 1.89–1.90 (m, 4H, 2 × CH_2), 2.04 (s, 3H, CH_3), 2.64–2.65 (m, 4H, 2 × CH_2), 2.84 (t, *J* = 4.1 Hz, 2H, CH_2), 3.06 (t, *J* = 4.1 Hz, 2H, CH_2), 3.86 (s, 2H, CH_2), 7.18, 7.26 (2 × d, *J* = 8.0 Hz, 4H, H_{arom}), 11.32 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 10.84 (CH_3), 23.97, 24.28, 55.44 ($C_{piperdine}$), 29.97 (CH_2), 40.21 (CH_2), 61.71 (CH_2), 117.79 (C-5), 128.54, 130.03, 132.17, 136.51 (C_{arom}), 157.66 (C-6), 160.56 (C-4), 165.10 (C-2) ppm; MS (EI): *m/z* (%) = 377 (M^+, 2), 356 (1), 342 (2), 318 (2), 291 (1), 192 (3), 163 (2), 143 (3), 125 (9), 111 (100); Anal. Calcd. for $C_{19}H_{24}ClN_3OS$ (377.93): C 60.4, H 6.4, N 11.1. Found: C 60.3, H 6.2 N 10.9%.

6-(p-Chlorobenzyl)-5-ethyl-2-piperidin-1-ylethylthiopyrimidin-4(3H)-ones (**6d**): White solid; yield 0.301 g (77%); m.p. 119–121°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.02 (t, *J* = 7.4 Hz, 3H, CH_3), 1.53 (br s, 2H, CH_2), 1.86–1.87 (m, 4H, 2 × CH_2), 2.48 (q, *J* = 7.4 Hz, 2H, CH_2), 2.62–2.63 (m, 4H, 2 × CH_2), 2.81 (t, *J* = 4.0 Hz, 2H, CH_2), 3.04 (t, *J* = 4.0 Hz, 2H, CH_2), 3.83 (s, 2H, CH_2), 7.16, 7.24 (2 × d, *J* = 8.0 Hz, 4H, H_{arom}), 10.97 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.15 (CH_3), 18.88 (CH_2), 23.96, 24.31, 55.40 ($C_{piperidine}$), 29.93 (CH_2), 39.54 (CH_2), 61.63 (CH_2), 123.62 (C-5), 128.44, 130.05, 132.09, 136.89 (C_{arom}), 157.69 (C-6), 159.97 (C-4), 164.47 (C-2) ppm; MS (EI): *m/z* (%) = 391 (M^+, 2), 354 (1), 307 (3), 218 (4), 170 (2), 149 (3), 111 (32); Anal. Calcd. for $C_{20}H_{26}ClN_3OS$ (391.96): C 61.3, H 6.7, N 10.7. Found: C 61.3, H 6.7, N 10.6%.

General Procedure for Preparation of S-DABOs analogues **7a–7c**: To a solution of compound **4a,b** (0.001 mol) in anhydrous DMF (3 cm^3), was added anhydrous potassium carbonate (0.152 g, 0.0011 mol) followed by addition of bromoethyl ethyl ether or benzyl chloromethyl ether (0.0011 mol). The mixture was stirred at room temperature for 24 h, then was diluted with H_2O (100 cm^3) and extracted with ether (3 × 50 cm^3). The combined ether extract was washed with H_2O (3 × 50 cm^3), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel column with $CHCl_3$ to furnish **7a–c**.

6-(p-Chlorobenzyl)-2-ethyloxyethylthio-5-methylpyrimidin-4(3H)-one (**7a**): White solid; yield 0.213 g (63%); m.p. 169–171°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.19 (t, *J* = 7.1 Hz, 3H, CH_3), 2.07 (s, 3H, CH_3), 3.26 (t, *J* = 6.0 Hz, 2H, CH_2), 3.51 (q, *J* = 7.1 Hz, 2H, CH_2), 3.61 (t, *J* = 6.0 Hz, CH_2), 3.84 (s, 2H, CH_2), 7.17, 7.26 (2 × d, *J* = 8.0 Hz, 4H, H_{arom}); 12.36 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 10.64 (CH_3), 15.04 (CH_3), 30.74 (CH_2), 40.20 (CH_2), 66.72 (CH_2), 69.33 (CH_2), 116.80 (C-5), 128.51, 130.25, 132.31, 136.43 (C_{arom}), 156.39 (C-6), 161.20 (C-4), 164.76 (C-2) ppm; MS (EI): *m/z* (%) = 338 (M^+, 2), 293 (2), 266 (37), 251 (2), 231 (4), 192 (5), 143 (3), 125 (18); Anal. Calcd. for $C_{16}H_{19}ClN_2O_2S$ (338.85): C 56.7, H 5.65, N 8.3. Found: C 56.5, H 5.5, N 8.1.

2-Benzyloxymethylthio-6-(p-chlorobenzyl)-5-methylpyrimidin-4(3H)-one (**7b**): White solid; yield 0.255 g (66%); m.p. 185–186°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.01 (s, 3H, CH_3), 3.91 (s, 2H, CH_2), 4.57 (s, 2H, CH_2), 5.43 (s, 2H, CH_2), 7.18–7.28 (m, 9H, H_{arom}), 12.34 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 10.31 (CH_3), 39.86 (CH_2), 71.23 (CH_2), 71.83 (CH_2), 117.41 (C-5), 127.21, 127.99, 128.52, 128.60, 130.26, 133.01, 137.12, 137.84 (C_{arom}), 156.17 (C-6), 161.73 (C-4), 164.92 (C-2) ppm; MS (EI): *m/z* (%) = 386 (M^+, 2), 356 (4), 339 (5), 295 (3), 280 (4), 267 (5), 143 (3), 125 (11), 91 (100); Anal. Calcd. for $C_{20}H_{19}ClN_2O_2S$ (386.90): C 62.1, H 4.95, N 7.2. Found: C 62.1, H 5.0, N 7.2.

2-Benzyloxymethylthio-6-(p-chlorobenzyl)-5-ethylpyrimidin-4(3H)-one (**7c**): White solid; yield 0.244 g (61%); m.p. 236–238°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.06 (t, *J* = 7.0 Hz, 3H, CH_3), 2.57 (q, *J* = 7.0 Hz, 2H, CH_2), 3.91 (s, 2H, CH_2), 4.34 (s, 2H, CH_2), 5.21 (s, 2H, CH_2), 7.16-7.40 (m, 9H, H_{arom}), 12.31 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.21 (CH_3), 18.77 (CH_2), 39.67 (CH_2), 70.85 (CH_2), 71.15 (CH_2), 122.64 (C-5); 127.44, 128.50, 128.55, 128.92, 130.37, 132.32, 136.77, 136.91 (C_{arom}), 156.23 (C-6), 160.89 (C-4), 164.48 (C-2) ppm; MS (EI): *m/z* (%) = 400 (M^+, 3), 371 (19), 357 (16), 338 (14), 306 (14), 280 (15), 248 (19), 190 (24), 155 (37); Anal. Calcd. for $C_{21}H_{21}ClN_2O_2S$ (400.92): C 62.9, H 5.3, N 7.0. Found: C 62.7, H 5.2, N 6.9%.

5-Alkyl-6-(p-chlorobenzyl)-uracils **8a** *and* **8b**: Compound **4a,b** (0.01 mol) was suspended in 10% aq. $ClCH_2CO_2H$ (200 cm^3). The suspension was refluxed for overnight and filtered after cooling. The precipitate was washed with H_2O, cold EtOH then Et_2O and dried.

6-(p-Chlorobenzyl)-5-methyluracil (**8a**): White solid; yield 2.2 g (88%); m.p. 285–287 (dec.); ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 1.75 (s, 3H, CH_3); 3.74 (s, 2H, CH_2), 7.28, 7.38 (2 × d, *J* = 8.0 Hz, 4H, H_{arom}), 10.78, 11.03 (2 × s, 2H, 2 × NH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 10.12 (CH_3), 35.15 (CH_2), 105.78 (C-5), 129.03, 130.53, 131.87, 136.00 (C_{arom}), 149.01 (C-6), 151.35 (C-2), 165.37 (C-4) ppm; MS (EI): *m/z* (%) = 250 ($M^{+,}$ 6), 235 (2), 224 (3), 215 (8), 196 (2), 173 (4), 138 (5), 125 (13); Anal. Calcd. for $C_{12}H_{11}ClN_2O_2$ (250.68): C 57.5, H 4.4, N 11.2. Found: C 57.3, H 4.4, N 11.0%.

6-(p-Chlorobenzyl)-5-ethyluracil (**8b**): White solid; yield 2.15 g (81%); m.p. 261–263°C; ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 0.81 (t, *J* = 7.4 Hz, 3H, CH_3), 2.23 (q, *J* = 7.4 Hz, 2H, CH_2), 3.84 (s, 2H, CH_2), 7.28, 7.38 (2 × d, *J* = 8.0 Hz, 4H, H_{arom}), 10.76, 11.04 (2 × s, 2H, 2 × NH) ppm; ^{13}C NMR (DMSO-d_6, 125 MHz): δ = 14.00 (CH_3), 18.05 (CH_2), 34.73 (CH_2), 111.94 (C-5), 129.02, 130.45, 131.21, 136.42 (C_{arom}), 148.70 (C-6), 151.39 (C-2), 164.95 (C-4) ppm; MS (EI): *m/z* (%) = 264 (M^+, 100), 249 (82), 206 (31), 181 (42), 178 (18), 139 (65), 125 (66); Anal. Calcd. for $C_{13}H_{13}ClN_2O_2$ (264.71): C 59.0, H 4.95, N 10.6. Found: C 58.7, H 4.9, N 10.4.

Emivirine analogues (**9a–f**) *and their 1,3- bis-alkylated derivatives* (**10a–d**): *N,O*-Bis(trimethylsilyl)acetamide (*BSA*) (0.87 cm^3, 0.0035 mol) was added to a suspension of **8a,b** (0.001 mol) in anhydrous $CHCl_3$ (20 cm^3) and the mixture was stirred at room temperature under nitrogen. After a clear solution was obtained (10 min), the appropriate haloethers namely, bromomethyl methyl ether, chloromethyl ethyl ether or benzyl chloromethyl ether (0.015 mol) and CsI (0.26 g, 0.001 mol) were added. The reaction mixture was stirred at room temperature under nitrogen for 3–4 h. Sat. aq. $NaHCO_3$ (20 cm^3) was added and mixture was extracted with CH_2Cl_2 (3 × 50 cm^3). The organic phase was collected, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed on silica gel column using $CHCl_3$ to give **9a–f** and **10a–d**.

6-(p-Chlorobenzyl)-5-methyl-1-methyloxymethyluracil (**9a**): White solid; yield 0.062 g (21%); m.p. 201–202°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.05 (s, 3H, CH_3), 3.45 (s, 3H, CH_3), 3.78 (s, 2H, CH_2), 5.37 (s, 2H, CH_2), 7.21, 7.31 (2 × d, *J* = 8.0 Hz, 4H, H_{arom}), 10.01 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 10.79 (CH_3), 35.91 (CH_2), 57.91 (CH_3), 71.81 (CH_2), 107.47 (C-5), 129.26, 130.04, 133.23, 133.67 (C_{arom}), 146.51 (C-6), 152.57 (C-2), 164.01 (C-4) ppm; MS (EI): *m/z* (%) = 294 (M^+, 5), 279 (7), 264 (6), 251 (62), 229 (3), 199 (5), 125 (17); $C_{14}H_{15}ClN_2O_3$ (294.73): C 57.05, H 5.1, N 9.5. Found: C 56.8, H 5.0, N 9.3%.

6-(p-Chlorobenzyl)-1-ethyloxymethyl-5-methyluracil (**9b**): White solid; yield 0.090 g (29%); m.p. 214–215°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.18 (t, *J* = 7.0 Hz, 3H, CH_3), 2.02 (s, 3H, CH_3), 3.61 (q, *J* = 7.0 Hz, 2H, CH_2), 4.15 (s, 2H, CH_2), 5.15 (s, 2H, CH_2), 7.07,

7.29 (2 × d, J = 8.0 Hz, 4H, H_{arom}), 9.54 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 10.91 (CH_3), 14.99 (CH_3), 33.41 (CH_2), 65.03 (CH_2), 72.82 (CH_2), 111.07 (C-5), 128.67, 129.42, 133.29, 133.31 (C_{arom}), 149.10 (C-6), 151.73 (C-2), 163.55 (C-4) ppm; MS (EI): *m/z* (%) = 308 (M^+, 3), 262 (6), 249 (4), 227 (32), 215 (4), 143 (5), 125 (18); Anal. Calcd. for $C_{15}H_{17}ClN_2O_3$ (308.76): C 58.35, H 5.55, N 9.1. Found: C 58.1, H 5.5, N 8.9%.

1-Benzyloxymethyl-6-(p-chlorobenzyl)-5-methyluracil (**9c**): White solid; yield 0.152 g (41%); m.p. 128–129°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.01 (s, 3H, CH_3), 4.13 (s, 2H, CH_2), 4.66 (s, 2H, CH_2), 5.23 (s, 2H, CH_2), 7.01–7.36 (m, 9H, H_{arom}), 9.67 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 10.92 (CH_3), 33.43 (CH_2), 71.71 (CH_2), 72.79 (CH_2), 111.15 (C-5), 127.89, 128.23, 128.67, 129.42, 130.04, 133.18, 133.32, 137.11 (C_{arom}), 148.92 (C-6), 151.77 (C-2), 163.53 (C-4) ppm; MS (EI): *m/z* (%) = 370 (M^+, 2), 264 (5), 215 (3), 201 (7), 143 (2), 125 (14), 91 (100), 77 (16); Anal. Calcd. for $C_{20}H_{19}ClN_2O_3$ (370.83): C 64.8, H 5.2, N 7.55. Found: C 64.7, H 5.1, N 7.2%.

6-(p-Chlorobenzyl)-5-ethyl-1-methyloxymethyluracil (**9d**): White solid; yield 0.055 g (18%), m.p. 171–172°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.08 (t, J = 7.0 Hz, 3H, CH_3), 2.52 (q, J = 7.0 Hz, 2H, CH_2), 3.39 (s, 3H, CH_3), 3.78 (s, 2H, CH_2), 5.34 (s, 2H, CH_2), 7.22, 7.30 (2 × d, J = 8.0 Hz, 4H, H_{arom}), 9.82 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.70 (CH_3), 18.88 (CH_2), 35.38 (CH_2), 57.93 (CH_3), 71.71 (CH_2), 113.59 (C-5), 129.25, 130.08, 133.29, 133.68 (C_{arom}), 146.14 (C-6), 152.49 (C-2), 163.50 (C-4) ppm; MS (EI): *m/z* (%) = 308 (M^+, 4), 293 (3), 278 (3), 265 (27), 153 (5), 125 (17); Anal. Calcd. for $C_{15}H_{17}ClN_2O_3$ (308.76): C 58.35, H 5.55, N 9.1. Found: C 58.1, H 5.4, N 8.9%.

6-(p-Chlorobenzyl)-5-ethyl-1-ethyloxymethyluracil (**9e**): White solid; yield 0.126 g (39%); m.p. 135–136°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.08 (t, J = 7.5 Hz, 3H, CH_3), 1.18 (t, J = 7.0 Hz, 3H, CH_3), 2.45 (q, J = 7.5 Hz, 2H, CH_2); 3.60 (q, J = 7.0 Hz, 2H, CH_2), 4.14 (s, 2H, CH_2), 5.12 (s, 2H, CH_2), 7.07, 7.29 (2 × d, J = 8.0 Hz, 4H, H_{arom}), 9.60 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.74 (CH_3), 15.00 (CH_3), 19.18 (CH_2), 32.83 (CH_2), 65.06 (CH_2), 72.76 (CH_2), 117.11 (C-5), 128.66, 129.38, 133.28, 133.83 (C_{arom}), 148.54 (C-6), 151.83 (C-2), 163.17 (C-4) ppm; MS (EI): *m/z* (%) = 322 (M^+, 3), 265 (4), 249 (3), 241 (19), 228 (2), 213 (4), 125 (16); Anal. Calcd. for $C_{16}H_{19}ClN_2O_3$ (322.79): C 59.5, H 5.9, N 8.7. Found: C 59.35, H 5.8, N 8.5%.

1-Benzyloxymethyl-6-(p-chlorobenzyl)-5-ethyluracil (**9f**): White solid; yield 0.185 g (48%); m.p. 137–138°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.05 (t, J = 7.0 Hz, 3H, CH_3), 2.43 (q, J = 7.0 Hz, 2H, CH_2), 4.12 (s, 2H, CH_2), 4.66 (s, 2H, CH_2), 5.20 (s, 2H, CH_2), 7.02–7.39 (m, 9H, H_{arom}), 9.61 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.76 (CH_3), 19.16 (CH_2), 32.85 (CH_2), 71.85 (CH_2), 72.80 (CH_2), 117.18 (C-5), 127.59, 128.07, 128.52, 128.67, 129.39, 133.31, 133.68, 137.21 (C_{arom}), 148.35 (C-6), 151.87 (C-2), 163.12 (C-4) ppm; MS (EI): *m/z* (%) = 384 (M^+, 2), 370 (2), 356 (2), 333 (2), 278 (5), 201 (7), 125 (12), 91 (100), 77 (13); Anal. Calcd. for $C_{21}H_{21}ClN_2O_3$ (384.86): C 65.5, H 5.5, N 7.3. Found: C 65.5, H 5.5, N 7.2%.

1,3-Bis-(methyloxymethyl)-6-(p-chlorobenzyl)-5-methyluracil (**10a**): White solid; yield 0.145 g (43%); m.p. 92–93°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.03 (s, 3H, CH_3), 3.41 (s, 3H, CH_3), 3.48 (s, 3H, CH_3), 4.12 (s, 2H, CH_2), 5.12 (s, 2H, CH_2), 5.45 (s, 2H, CH_2), 7.05, 7.28 (2 × d, J = 8.0 Hz, 4H, H_{arom}) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 11.51 (CH_3), 33.41 (CH_2), 57.05 (CH_3), 57.94 (CH_3), 72.77 (CH_2), 75.06 (CH_2), 110.52 (C-5), 128.66, 129.26, 133.28, 133.32 (C_{arom}), 147.69 (C-6), 152.57 (C-2), 163.02 (C-4) ppm; MS (EI): *m/z* (%) = 338 (M^+, 4), 295 (6), 234 (7), 211 (5), 199 (8), 155 (11), 125 (14); Anal. Calcd. for $C_{16}H_{19}ClN_2O_4$ (338.79): C 56.7, H 5.65, N 8.3. Found: C 56.5, H 5.5, N 8.0%.

1,3-Bis-(ethyloxymethyl)-6-(p-chlorobenzyl)-5-methyluracil (**10b**): Colourless oil; yield 0.19 g (52%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.17 (t, J = 7.0 Hz, 3H, CH_3), 1.22 (t, J = 7.1 Hz, 3H, CH_3), 2.22 (s, 3H, CH_3), 3.51 (m, 4H, 2 × CH_2), 4.13 (s, 2H, CH_2), 4.77 (s, 2H, CH_2), 4.90 (s, 2H, CH_2), 7.06, 7.31 (2 × d, J = 8.0 Hz, 4H, H_{arom}) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 11.50 (CH_3), 14.97 (CH_3), 15.17 (CH_3), 33.45 (CH_2), 65.08 (CH_2), 65.92 (CH_2), 71.26 (CH_2), 73.59 (CH_2), 110.42 (C-5), 128.69, 129.38, 133.26, 133.38 (C_{arom}), 147.73 (C-6), 152.48 (C-2), 163.06 (C-4) ppm; MS (EI): *m/z* (%) = 366 (M^+, 3), 322 (18), 309 (11), 279 (8), 263 (24), 241 (9), 234 (22), 211 (3), 199 (16), 169 (7), 125 (23); Anal. Calcd. for $C_{18}H_{23}ClN_2O_4$ (366.84): C 58.9, H 6.3, N 7.6. Found: C 59.1, H 6.1, N 7.45%.

1,3-Bis-(methyloxymethyl)-6-(p-chlorobenzyl)-5-ethyluracil (**10c**): Colourless oil; yield 0.11 g (31%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.05 (t, J = 7.0 Hz, 3H, CH_3), 2.45 (q, J = 7.0 Hz, 2H, CH_2), 3.40 (s, 3H, CH_3), 3.49 (s, 3H, CH_3), 4.10 (s, 2H, CH_2), 5.08 (s, 2H, CH_2), 5.44 (s, 2H, CH_2), 7.06, 7.31 (2 × d, J = 8.0 Hz, 4H, H_{arom}) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.69 (CH_3), 19.74 (CH_2), 32.85 (CH_2), 57.11 (CH_3), 57.97 ((CH_3), 72.68 (CH_2), 74.99 (CH_2), 116.48 (C-5), 128.65, 129.41, 133.30, 133.74 (C_{arom}), 147.18 (C-6), 152.61 (C-2), 162.54 (C-4) ppm; MS (EI): *m/z* (%) = 352 (M^+, 4), 337 (2), 309 (4), 277 (9), 248 (11), 220 (7), 204 (3), 155 (7), 125 (12); Anal. Calcd. for $C_{17}H_{21}ClN_2O_4$ (352.81): C 57.9, H 6.0, N 7.9. Found: C 57.5, H 5.8, N 7.7.

1,3-Bis-(ethyloxymethyl)-6-(p-chlorobenzyl)-5-ethyluracil (**10d**): Colourless oil; yield 0.167 g (44%); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.05 (t, J = 7.5 Hz, 3H, CH_3), 1.16 (t, J = 7.0 Hz, 3H, CH_3), 1.24 (t, J = 7.2 Hz, 3H, CH_3); 2.45 (q, J = 7.5 Hz, 2H, CH_2), 3.59 (q, J = 7.0 Hz, 2H, CH_2), 3.69 (q, J = 7.2 Hz, 2H, CH_2), 4.12 (s, 2H, CH_2), 5.12 (s, 2H, CH_2), 5.47 (s, 2H, CH_2), 7.06, 7.30 (2 × d, J = 8.0 Hz, 4H, H_{arom}) ppm; ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 13.69 (CH_3), 15.00 (CH_3), 15.19 (CH_3), 19.74 (CH_2), 32.88 (CH_2), 65.12 (CH_2), 65.95 (CH_2), 71.17 (CH_2), 73.51 (CH_2), 116.36 (C-5), 128.68, 129.35, 133.22, 133.85 (C_{arom}), 147.23 (C-6), 152.52 (C-2), 162.58 (C-4) ppm; MS (EI): *m/z* (%) = 380 (M^+, 2), 336 (9), 323 (5), 277 (16), 255 (7), 248 (9), 220 (4), 169 (11), 141 (6), 125 (27); Anal. Calcd. for $C_{19}H_{25}ClN_2O_4$ (380.87): C 59.9, H 6.6, N 7.4. Found: C 59.8, H 6.5, N 7.1%.

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