Synthesis and Anti-HIV-1 Activity of 1,3-Phenylene Bis-Uracil Analogues of MKC-442

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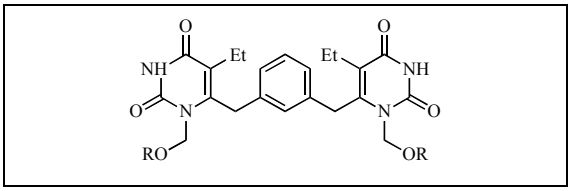

Reaction of 1,3-phenylenediacetonitrile with the zinc organometallic reagent of ethyl 2-bromobutyrate afforded the 1,3-phenylene-bis(acetoacetate) **2** which was used as the starting material for the synthesis of 1,3-phenylene-bis[6-(2-thiouracil)] **4**. Desulphurization of **4** gave the corresponding bis-uracil **6**, which after silylation was N-1 alkylated with bis(allyoxy)methane using TMS-triflate as the catalyst or with chloromethyl ethyl ether to give the MKC-442 analogues **7** and **9**. The amino-DABO and S-DABO derivatives **11**, **12a**,**b** and **14** were also synthesized. The anti-HIV-1 activity test showed that when MKC-442 analogues were constructed with 1,3-phenylene in all cases they were detrimental to have activity against HIV-1.

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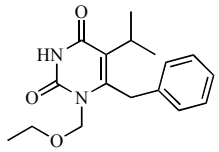
INTRODUCTION

Since the synthesis of 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT) by Miyasaka *et al.* [1] in 1989, there has been a growing interest in non-nucleoside reverse transcriptase inhibitors (NNRTIs). HEPT was further developed into 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil (MKC-442, emivirine, Figure 1) [2], which was brought into phase III clinical trials. However, Triangle Pharmaceuticals halted development of MKC-442 in January 2002 when a comparative study showed emivirine to be less potent than other antiretrovirals [3].



MKC-442

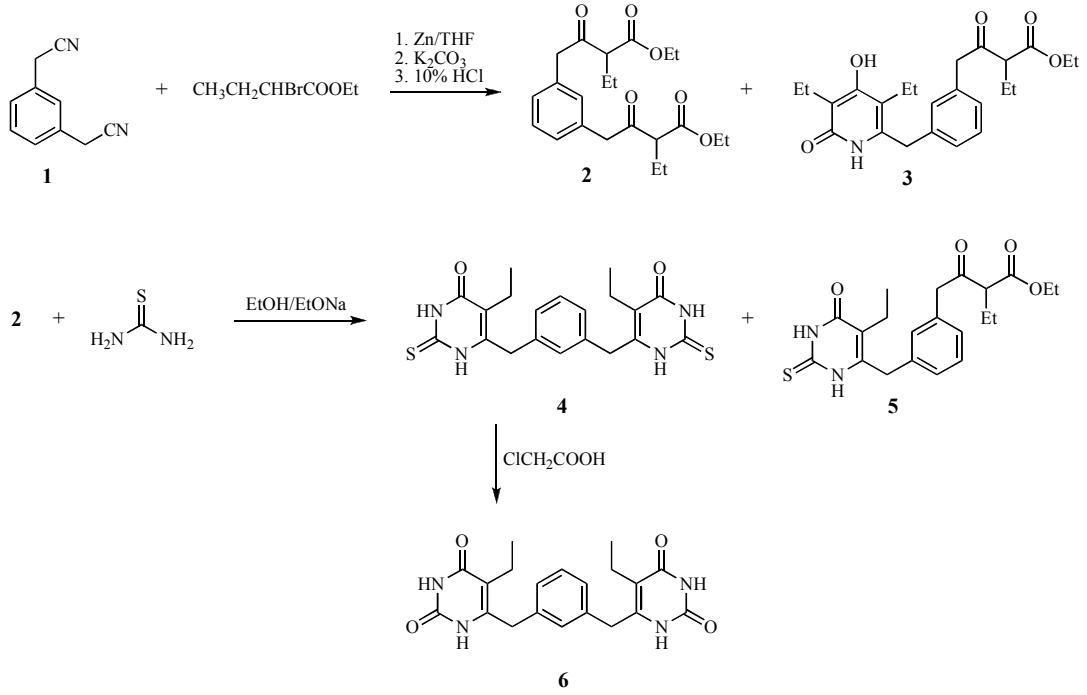
Figure 1

MKC-442 inhibits reverse transcriptase (RT) of the HIV-1 virus allosterically, as it binds to the enzyme in a hydrophobic pocket outside the active site and thereby changes the conformation of the active site, making RT inactive. The inhibitor is mainly held in place in the pocket by hydrogen bonds and hydrophobic bonds to the nearby amino acids [4]. The importance of finding new analogues with higher binding affinity is obvious, because HIV-1 strain with RT mutations are shown to emerge rapidly upon treatment with existing drugs [5]. Therefore, it is of interest to study whether MKC-442 analogues with an extra nucleobase of the MKC-442 type attached to the benzylic part of MKC-442 will show better or comparable anti HIV-1 activity towards wild-type and Y181C or Y181C+K103N mutated HIV-1 strains. The perspective could be that an asymmetric pair of nucleobases substituted in this type of derivatives could result in compounds with activity against a broader range of HIV resistant mutant viruses.

RESULTS AND DISCUSSION

In order to synthesis the benzylic base pair at C-6 a route was chosen in which the β-ketoester **2** would be a key intermediate as in the synthesis of MKC-442 by Danel *et al.* [6]. Commercially available 1,3-phenylene-diaceto-nitrile (**1**) was reacted with zinc organometallic reagent of ethyl 2-bromobutyrate in anhydrous THF to afford the bis-β-ketoester **2** in 38% yield and the pyridinone **3** as by-product in 3% yield. Compound **2** was used as the starting material for the synthesis of the bis-thiouracil **4** in a ring closure reaction with thiourea and sodium ethoxide using the method of Danel *et al.* [6] to afford this compound as the major product in 42% yield and 2-thio-pyrimidine-benzylic-β-ketoester **5** as minor product in 18% yield. Desulphurization of **4** using chloroacetic acid [7,8] gave the benzylic bis-uracil **6** in 63% yield (Scheme 1).

Scheme 1

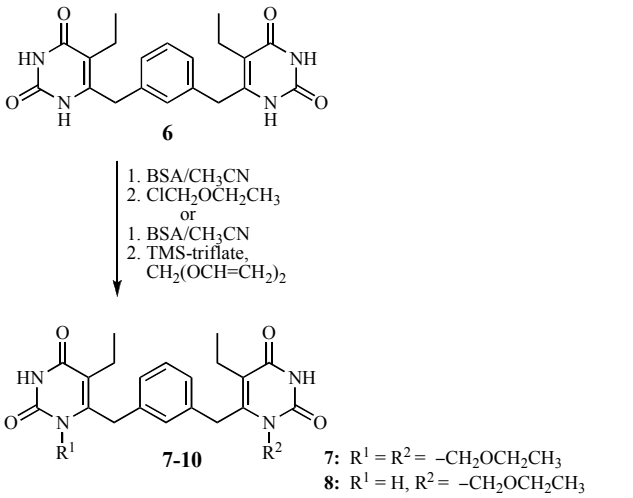


Compound **6** was silylated using bis-(trimethylsilyl)-acetamide (BSA) and it was subsequently N-1 alkylated using chloromethyl ethyl ether [7] to give the bis-non-nucleoside analogues **7** in 23% yield and the N-1 mono-alkylated by-product **8** in 11% yield. The benzylic bis-uracils **6** was also reacted with bis(allyloxy)methane [9] in the presence of trimethylsilyl trifluoromethanesulfonate (TMS triflate) as a Lewis acid catalyst [10] to give the bis-non-nucleoside analogue **9** in 34% yield and the N-1 mono-alkylated derivative **10** in 22% yield (Scheme 2).

Having the bis-β-ketoester **2** readily available as a starting material, it was straight forward also to synthesis the corresponding amino-DABO and S-DABO analogues. These are 2-amino and 2-alkylthio analogues respectively, of uracils and they are highly active against HIV when properly substituted [11].

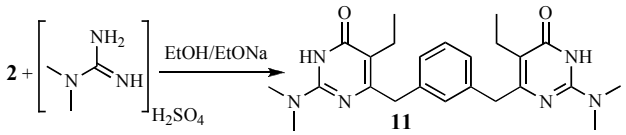
For the synthesis of an amino-DABO derivatives the □-ketoester **2** was reacted with *N*,*N*-dimethylguanidinium sulphate in EtONa to afford compound **11** in 18% yield (Scheme 3).

Scheme 2



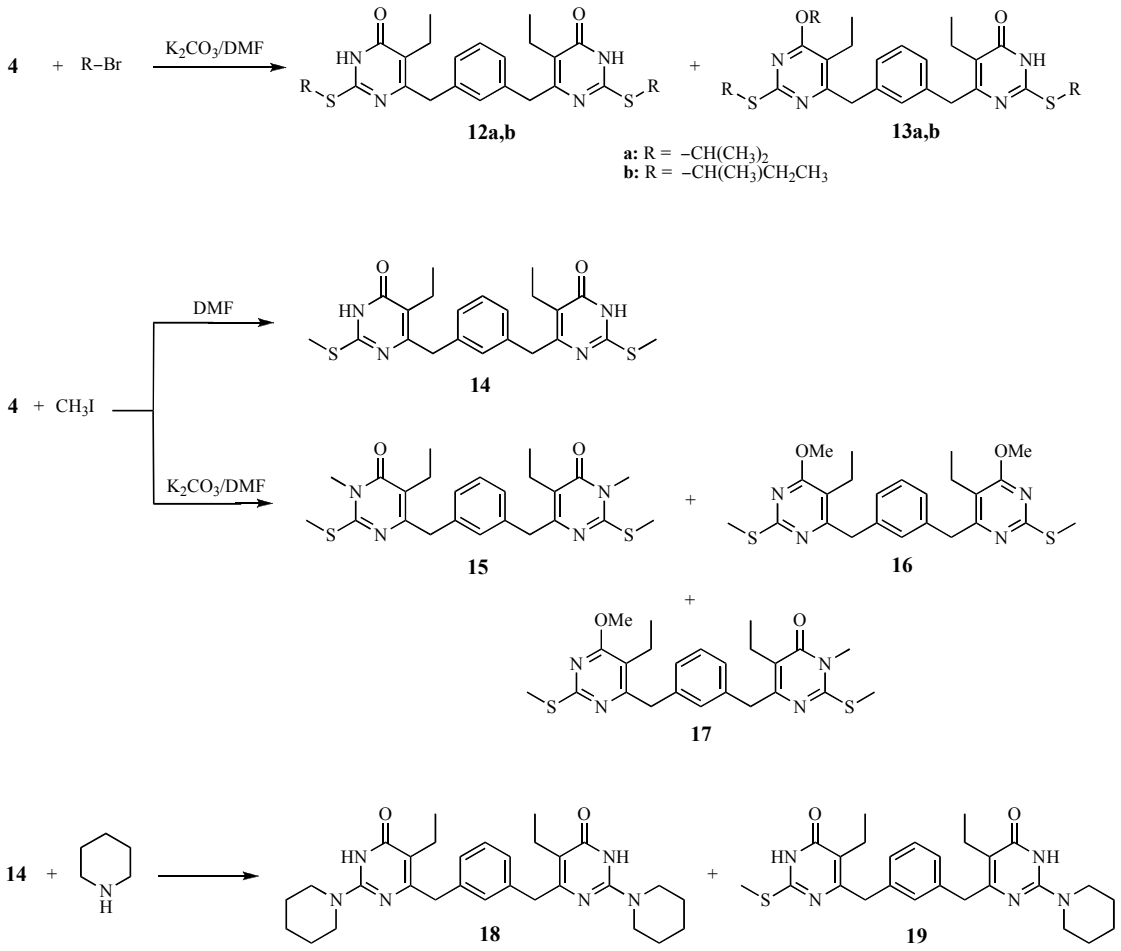
7: $R^1 = R^2 = -CH_2OCH_2CH_3$
8: $R^1 = H, R^2 = -CH_2OCH_2CH_3$
9: $R^1 = R^2 = -CH_2OCH_2CH{=}CH_2$
10: $R^1 = H, R^2 = -CH_2OCH_2CH{=}CH_2$

Scheme 3



Alkylation of **4** with isopropyl bromide or isobutyl bromide in the presence of K_2CO_3 in dry DMF gave S-alkylated products **12a,b** in 23-33% yield and O- and S-bisalkylated products **13a,b** in 12-22% yield. The reaction of compound **4** with CH_3I however, gave different results depending on the reaction conditions. When **4** was reacted with CH_3I in DMF at room temperature, the expected S-alkylated product **14** was obtained in 82% yield, while reaction of **4** with CH_3I in DMF in the presence of K_2CO_3 at room temperature afforded a mixtures of polymethyl-ated compounds **15**-**17** in 11-28% yields (Scheme 4).

Scheme 4



Compound **14** was reacted with excess of piperidine to give the bis-piperidinyl derivative **18** in 32% yield and the mono-piperidinyl derivative **19** in 26% yield (Scheme 4) which are additional examples of amino-DABOs.

Antiviral activity.

The anti-HIV-1 activity and cytotoxicity of the synthesized MKC-442 analogues **3-18** are summarized in Table 1. In general, the introduction of a base at the meta-position of the benzyl group in MKC-442 as well as in amino-DABO or S-DABO was detrimental to the activity against HIV-1, when compared with the activity of MKC-442. Only compounds **7**-**10, 12a** and **16** showed moderate activity against wild-type HIV-1 but was totally inactive against resistant mutant viruses.

EXPERIMENTAL

Nmr Spectra were recorded on a Varian Gemini 2000 spectrometer at 300 MHz for ^{1}H and 75 MHz for ^{13}C; δ values are in ppm relative to tetramethylsilane as an internal standard. Accurate-ion mass determinations were performed using the 4.7 T Ultima Fourier transform (FT) mass spectrometer (Ion Spec,

Table 1

Cytotoxicity and anti-HIV-1 activity of compounds **3-18** in MT-4 cells[a]

Compound No.	CC_{50} (μM)[b]	EC_{50} (μM)[c]			
		WT	EFV^R	Y181C	K103N+Y181C
3	100±1	>100	>100	>100	>100
4	>100	>100	>100	>100	>100
6	>100	>100	>100	>100	>100
7	>100	14±1	>100	>100	>100
8	>100	47±3	>100	>100	>100
9	>100	34±2	>100	>100	>100
10	>100	11±0.1	>100	>100	>100
11	>100	>100	>100	>100	>100
12a	36±1	14±5	>36	>36	>36
12b	27±2	>27	>27	>27	>27
13a	43±2	>43	>43	>43	>43
14	>100	>100	>100	>100	>100
15	>100	>100	>100	>100	>100
16	>100	41±11	>100	>100	>100
17	80±20	>80	>80	>80	>80
18	75±25	>75	>75	>80	>80
MKC-442	>100	0.03	100	20	>100

[a]Data represent mean values of at least two separate experiments; [b]Compound dose required to reduce the viability of mock-infected cells by 50%, as determined by the MTT method; [c]Compond dose required to achieve 50% protection of MT-4 cells from HIV-1- induced cytopathogenicity, as determined by the MTT method

Irvine, CA). The (M + H^+) and (M + Na^+) ions were peak matched using ions derived from the 2,5-dihydroxybenzoic acid matrix. Thin-layer chromatography (tlc) analyses were performed on Merck precoated 60 F_{254} plates. The silica gel (0.040–-0.063 mm) used for column chromatography was purchased from Merck. Solvents used for column chromatography were distilled prior to use, while reagents were used as purchased.

General Procedure for the Preparation of Compounds 2 and 3. Zn dust 25–30 g was activated by stirring with 4 M HCl (100 ml) for 5 minutes. The zinc dust was filtered and washed sequentially with water, ethyl alcohol, and ether. Dried by evaporation under reduced pressure at 80° for 5 hours and kept in vacuo overnight. The active Zn was suspended in dry THF 300 ml and heated to reflux. A few drops of ethyl 2-bromobutyrate were added and the mixture was refluxed until a green colour appeared. 1,3-Phenylenediacetontrile 10.03 g (66 mmoles) was added in one portion and ethyl 2-bromobutyrate 50.6 g (260 mmoles) in 20 ml THF was added dropwise. After complete addition the reaction mixture was refluxed for 5 hours, cooled and diluted with THF (300 ml) and subsequently quenched by addition of saturated aqueous K_2CO_3 (100 ml). The mixture was stirred for 1 hour and the THF layer was decanted and the residue was washed with THF (3 × 100 ml). The combined THF fractions were stirred with 10% aqueous HCl (90 ml) for 45 minutes. The solution was concentrated under reduced pressure and diluted with CH_2Cl_2 (300 ml). The organic phase was washed with saturated aqueous $NaHCO_3$ (2 × 100 ml), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was chromatographed on a silica gel column using petroleum ether (60–80°):ethyl acetate (8:2, v/v) to give **2** and **3**.

4-[3-(3-Ethoxycarbonyl-2-oxo-pentyl)-phenyl]-2-ethyl-3-oxo-butyric acid ethyl ester (2). Yield 4.5 g (38%); oil; ^{1}H nmr (deuteriochloroform): δ 0.84-0.88 (m, 6H, 2 × C*H*$_3$CH$_2$), 1.24-1.28 (m, 6H, 2 × C*H*$_3$CH$_2$O), 1.82-1.89 (m, 4H, 2 × C*H*$_2$CH$_3$), 3.46 (t, 2H, J = 7.3 Hz, 2 × COC*H*CO), 3.80 (s, 4H, 2 × ArC*H*$_2$), 4.12-4.19 (m, 4H, 2 × OC*H*$_2$CH$_3$), 7.03-7.26 (m, 4H, Ar); ^{13}C nmr (deuteriochloroform): δ 11.70, 14.01 (4 × CH$_3$), 21.43 (2 × *C*H$_2$CH$_3$), 48.69 (2 × *C*H$_2$Ar), 59.57 (2 × CO*C*HCO), 61.24 (2 × O*C*H$_2$CH$_3$), 128.40, 128.82, 130.85, 133.64 (C$_{arom}$), 169.47 (2 × *C*OOEt), 202.37 (2 × *C*OCH$_2$Ar). HRms (MALDI, peak matching): m/z 413.1931 [$C_{22}H_{30}O_6$ + Na^+], requires m/z 413.1935.

4-[3-(3,5-Diethyl-4-hydroxy-6-oxo-1,6-dihydro-pyridin-2-ylmethyl)-phenyl]-2-ethyl-3-oxo-butyric acid ethyl ester (3). Yield 0.4 g (3%); mp 112-114°; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ 0.68-1.09 (m, 12H, 4 × CH$_3$), 1.60-1.71 (m, 2H, CHC*H*$_2$CH$_3$), 2.28-2.38 (m, 4H, 2 × CH$_2$), 3.54 (t, 1H, J = 7.22 Hz, COCHCO), 3.71, 3.76 (2s, 4H, 2 × PhC*H*$_2$), 3.98-4.03 (m, 2H, OCH$_2$), 6.93-7.18 (m, 4H, Ar); 9.04-9.07 (br s, 1H, OH), 11.08 (br s, 1H, NH); ^{13}C nmr (dimethyl sulfoxide-d$_6$): δ 11.48, 13.05, 13.86, 14.19 (4 × CH$_3$), 16.03, 17.94, 20.87(3 × CH$_2$), 34.98 (*C*H$_2$Ar), 48.06 (Ar*C*H$_2$CO), 58.80 (CO*C*HCO), 60.69 (OCH$_2$), 110.97, 111.22 (C-3, C-5), 126.50, 127.75, 128.34, 129.32, 134.03, 138.52 (C$_{arom}$), 139.14 (C-6), 161.55 (C=O), 163.14 (C-4), 169.09 (CO), 202.84 (CO). HRms (MALDI, peak matching): m/z 436.2115 [$C_{24}H_{31}NO_5$ + Na^+], requires m/z 436.2094. *Anal.* Calcd. for ($C_{24}H_{31}NO_5$ × 0.25H_2O): C, 68.96; H, 7.60; N, 3.35. Found: C, 69.13; H, 7.59; N, 3.53.

Synthesis of Compounds 4 and 5. Na (50.2 g, 2.2 moles) was dissolved in 800 ml absolute ethanol. Thiourea 116.46 g (1.54 moles) was added, and the mixture was heated to reflux. The β-ketoester **2** (19.89 g, 0.015 mole) was added dropwise and the mixture was refluxed for 20 hours. Ethanol was evaporated *in vacuo*, and the residue was dissolved in 500 ml of water, the thiouracil **4** and **5** were precipitated by neutralization with HCl. The precipitate was filtered off, washed with water and chromatographed on a silica gel column using petroleum ether (60–80°):ethyl acetate (1:1, v/v) to give **4** and **5**.

5-Ethyl-6-{3-[(5-ethyl-6-oxo-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-yl)methyl]benzyl}-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-one (4). Yield 8.84 g (42%); mp 254-256°; ^{1}H nmr (deuteriochloroform): δ 0.70 (t, 6H, J = 7.3 Hz, 2 × C*H*$_3$CH$_2$), 2.15-2.17 (m, 4H, 2 × C*H*$_2$CH$_3$), 3.74 (s, 4H, 2 × C*H*$_2$Ar), 6.99-7.05 (m, 4H, Ar), 12.10, 12.30 (2s, 2H, 2 × NH); ^{13}C nmr (deuteriochloroform): δ 12.75 (2 × CH$_3$), 17.71 (2 × *C*H$_2$CH$_3$), 34.41 (2 × *C*H$_2$Ar), 117.14 (C-5), 126.68, 127.66, 128.90, 137.11 (C$_{arom}$), 148.92 (C-6), 161.38 (CO), 174.14 (C=S). HRms (MALDI, peak matching): m/z 415.1266 [$C_{20}H_{22}N_4O_2S_2$ + H^+], requires m/z 415.1257. *Anal.* Calcd. for ($C_{20}H_{22}N_4O_2S_2$ × 0.25H_2O): C, 57.35; H, 5.41; N, 13.37. Found: C, 57.35; H, 5.50; N, 13.43.

4-[3-(5-Ethyl-6-oxo-2-thioxo-2,3-dihydropyrimidin-4(1*H*)-ylmethyl)-phenyl]-2-ethyl-3-oxo-butyric acid ethyl ester (5). Yield 1.09 g (18%); semisolid; ^{1}H nmr (deuteriochloroform): δ 0.85-1.05 (m, 9H, 3 × CH$_3$), 1.55-1.62 (m, 2H, CH$_2$ at C-5), 2.43-2.48 (m, 2H, C*H*$_2$CH$_3$), 3.58 (t, 1H, J = 7.3 Hz, C*H*CH$_2$), 3.69, 3.86 (2s, 4H, 2 × C*H*$_2$Ar), 4.10-4.13 (m, 2H, OCH$_2$), 7.02-7.28 (m, 4H, Ar), 10.88, 11.20 (2s, 2H, 2 × NH); ^{13}C nmr (deuteriochloroform): δ 13.10, 13.56, 13.57 (3 × CH$_3$), 17.09, 18.23 (2 × *C*H$_2$CH$_3$), 35.35, 44.24 (2 × *C*H$_2$Ar), 49.54 (CO*C*H.CO), 65.99 (OCH$_2$), 118.71 (C-5), 126.58, 128.77, 129.14, 129.79, 134.87, 135.14 (C$_{arom}$), 148.86 (C-6), 151.76, 161.81 (2 × CO), 173.85 (C=S), 208.47 (CO).

5-Ethyl-6-{3-[(5-ethyl-2,6-dioxopyrimidin-4-(1*H*,3*H*)-yl)-methyl]benzyl}pyrimidine-2,4(1H,3H)-dione (6). Thiouracil **4** (3.82 g, 9.2 mmoles) was suspended in 300 ml 10% aqueous chloroacetic acid. The suspension was refluxed overnight and filtered after cooling. The precipitate was washed with cold ethanol and dried *in vacuo* to give compound **6**. Yield 2.2 g (63%); mp 335-337°; ^{1}H nmr (deuteriochloroform): δ 0.70 (t, 6H, J = 7.27 Hz, C*H*$_3$CH$_2$), 2.09-2.17 (m, 4H, C*H*$_2$CH$_3$), 3.74 (s, 4H, CH$_2$Ar), 7.04-7.23 (m, 4H, Ar), 12.10, 12.30 (2s, 2H, 2 × NH); ^{13}C nmr (deuteriochloroform): δ 13.34 (2 × CH$_3$), 17.58 (2 × *C*H$_2$CH$_3$), 34.89 (2 × *C*H$_2$Ar), 111.34 (C-5), 126.65, 127.66, 128.80, 137.23 (C$_{arom}$), 148.43 (C-6), 150.88, 164.44 (2 × CO). HRms (MALDI, peak matching): m/z 383.1728 [$C_{20}H_{22}N_4O_4$ + H^+], requires m/z 383.1714. *Anal.* Calcd. for ($C_{20}H_{22}N_4O_4$ × 0.25H_2O): C, 62.08; H, 5.86; N, 14.48. Found: C, 62.31; H, 5.68; N, 14.43.

General Procedure for the Synthesis of Compounds 7 and 8. N,O-*Bis*-(trimethylsilyl)-acetamide (BSA, 6.2 ml, 2.5 mmoles) was dissolved in 30 ml dry MeCN under nitrogen and compound **6** (3.82 g, 10 mmoles) was added. After 10 minutes the reaction mixture become a clear solution and chloromethyl ethyl ether (3 ml, 30 mmoles) was added. The reaction mixture was stirred overnight at room temperature under nitrogen, quenched with 25 ml ice cold saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (2 × 50 ml). The organic layer was dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by silica gel column chromatography using chloroform:methanol (9:1, v/v) to give compounds **7** and **8**.

5-Ethyl-1-ethoxymethyl-6-{3-[(5-ethyl-1-ethoxymethyl-2,6-dioxopyrimidin-4(1*H*,3*H*)-yl)methyl]benzyl}pyrimidine-

2,4(1*H*,3*H*)-dione (7). Yield 1.15 g (23%); white foam; ^{1}H nmr (deuteriochloro-form): δ 1.03 (t, 6H, J = 7.3 Hz, 2 × C*H*$_3$ at C-5), 1.15 (t, 6H, J = 7.0 Hz, 2 × C*H*$_3$CH$_2$), 2.40-2.45 (m, 4H, 2 × C*H*$_2$CH$_3$ at C-5), 3.50-3.63 (m, 4H, 2 × OC*H*$_2$CH$_3$), 4.14 (s, 4H, 2 × C*H*$_2$Ar), 5.09 (s, 4H, NCH$_2$O), 6.90-7.30 (m, 4H, Ar), 10.06 (s, 2H, 2 × NH); ^{13}C nmr (deuteriochloroform): δ 13.69 (2 × CH$_3$ at C-5), 14.95 (2 × *C*H$_3$CH$_2$), 19.08 (2 × *C*H$_2$CH$_3$), 33.18 (2 × *C*H$_2$Ar), 64.94 (2 × OCH$_2$CH$_3$), 72.61 (NCH$_2$O), 117.05 (C-5), 126.08, 126.36, 130.02, 136.48 (C$_{arom}$), 148.53 (2 × C-6), 151.96 (2 × CO), 163.41(2 × CO). *Anal.* Calcd. for (C$_{26}$H$_{34}$N$_4$O$_6$ × 0.5H$_2$O): C, 61.52; H, 6.95; N, 11.12. Found: C, 61.79; H, 6.95; N, 10.97.

5-Ethyl-1-ethoxymethyl-6-{3-[(5-ethyl-2,6-dioxopyrimidin-4(1*H*,3*H*)-yl)methyl]benzyl}pyrimidine-2,4(1*H*,3*H*)-dione (8). Yield 0.48 g (11%); oil; ^{1}H nmr (deuteriochloroform): δ 1.21-1.28 (m, 9H, 3 × CH$_3$), 2.03-2.10 (m, 4H, 2 × C*H*$_2$CH$_3$ at C-5), 3.53, 3.56 (2s, 4H, 2 × C*H*$_2$Ar), 3.57-3.60 (m, 2H, OC*H*$_2$CH$_3$), 4.69 (s, 2H, NCH$_2$O), 7.06-7.31 (m, 4H, Ar), 9.82, 10.08, 10.16 (3s, 3H, 3 × NH); ^{13}C nmr (deuteriochloroform): δ 13.55, 13.62, 14.94 (3 × CH$_3$), 18.14, 18.99 (2 × *C*H$_2$CH$_3$), 33.13, 35.70 (2 × *C*H$_2$Ph), 63.73 (OCH$_2$CH$_3$), 69.71 (NCH$_2$O), 113.45, 116.87 (2 × C-5), 126.40, 127.20, 127.39, 129.69, 136.11, 136.52 (C$_{arom}$), 147.99, 148.75 (2 × C-6), 151.94, 163.54, 164.58, 170.90 (4 × CO).

General Procedure for the Synthesis of Compounds 9 and 10. Compound **6** (0.38 g, 1.0 mmole) was dissolved in 30 ml dry CH$_3$CN under nitrogen and BSA (1.74 ml, 3.5 mmoles) was added. The reaction was cooled to –30° and TMS-triflate (trimethylsilyl trifluoromethanesulfonate, 0.18 ml, 1.0 mmole) was added dropwise followed by addition of bis(allyloxy)-methane (0.76 ml, 4.0 mmoles). The reaction mixture was stirred at room temperature for 2 days and quenched by a saturated solution of NaHCO$_3$ (10 ml). CH$_3$CN was evaporated under reduced pressure and the residue was extracted with chloroform (2 × 50 ml) and dried over MgSO$_4$. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography using chloroform:methanol (9:1, v/v) to give compounds **9** and **10**.

5-Ethyl-1-allyloxymethyl-6-{3-[(5-ethyl-3-allyloxymethyl-2,6-dioxopyrimidin-4(1*H*,3*H*)-yl)methyl]benzyl}pyrimidine-2,4(1*H*,3*H*)-dione (9). Yield 0.18 g (34%); white foam; ^{1}H nmr (deuteriochloro-form): δ 1.04 (t, 6H, J = 7.3 Hz, 2 × C*H*$_3$CH$_2$), 2.43-2.48 (m, 4H, 2 × C*H*$_2$CH$_3$), 4.09 (s, 4H, 2 × C*H*$_2$Ar), 4.10-4,13 (m, 4 H, 2 × OCH$_2$), 5.12 (s, 4H, NCH$_2$O), 5.15 (m, 2H, C*H*$_2$=CH), 5.19 (m, 2H, C*H*$_2$=CH), 5.82-5.88 (m, 2H, 2 × C*H*=CH$_2$), 7.02-7.31 (m, 4H, Ar), 10.16 (s, 2H, 2 × NH); ^{13}C nmr (deuteriochloroform): δ 13.71 (2 × CH$_3$), 19.08 (2 × *C*H$_2$CH$_3$), 33.23 (2 × *C*H$_2$Ar), 70.45 (OCH$_2$), 72.41 (NCH$_2$O), 117.76 (C-5), 117.76 (*C*H$_2$=CH), 133.45 (*C*H=CH$_2$), 126.13, 126.39, 130.05, 136.41 (C$_{arom}$), 148.40 (C-6), 151.99, 163.41 (2 × CO). HRms (MALDI, peak matching): m/z 545.2364 [C$_{28}$H$_{34}$N$_4$O$_6$ + Na$^+$], requires m/z 545.2371. *Anal.* Calcd. for (C$_{28}$H$_{34}$N$_4$O$_6$ × 0.25H$_2$O): C, 63.80; H, 6.60; N, 10.63. Found: C, 63.60; H, 6.47; N, 10.57.

5-Ethyl-6-{3-[(5-ethyl-1-allyloxymethyl-2,6-dioxopyrimidin-4(1*H*,3*H*)-yl)methyl]benzyl}pyrimidine-2,4(1*H*,3*H*)-dione (10). Yield 0.1 g (22%); foam; ^{1}H nmr (deuteriochloroform): δ 1.11-1.66 (m, 6H, 2 × C*H*$_3$CH$_2$), 2.34-2.38 (m, 4H, 2 × C*H*$_2$CH$_3$), 3.98, 4.09 (2s, 4H, 2 × C*H*$_2$Ar), 4.13-4.18 (m, 2H, OC*H*$_2$CH), 5.20 (s, 2H, NCH$_2$O), 5.33-5.36 (m, 2H, C*H*$_2$=CH), 5.75-5.86 (m, 1H, C*H*=CH$_2$), 7.05-7.32 (m, 4H, Ar), 9.96, 10.38 (2s, 2H, 2 × NH); ^{13}C nmr (deuteriochloroform): δ 13.63, 13.70 (2 × CH$_3$), 18.25, 19.02 (2 × *C*H$_2$CH$_3$), 33.27, 35.81 (2 × *C*H$_2$Ar), 70.36 (OCH$_2$), 72.52 (NCH$_2$O), 113.56, 117.03 (2 × C-5), 117.66 (*C*H$_2$=CH), 133.51 (*C*H=CH$_2$), 126.56, 129.70, 136.05, 136.71 (C$_{arom}$), 148.25, 148.79 (2 × C-6), 152.08, 152.30, 163.75, 164.77 (4 × CO). *Anal.* Calcd. for (C$_{24}$H$_{28}$N$_4$O$_5$): C, 63.70; H, 6.24; N, 12.38, Found: C, 63.45; H, 6.20; N, 12.11.

6-(3-((2-(dimethylamino)-5-ethyl-1,6-dihydro-6-oxopyrimidin-4-yl)methyl)benzyl)-2-(dimethylamino)-5-ethylpyrimidin-4(3*H*)-one (11). The β-ketoester **2** (1.23 g, 3.15 mmoles) was dissolved in EtONa (Na, 0.28g, 12.6 mmoles in 50 ml absolute ethanol). *N*,*N*-Dimethylguanidinium sulphate (2.34 g, 8.6 mmoles) was added and the reaction mixture was refluxed for 3 days, then cooled and the mixture was filtered, and ethanol was removed to half volume *in vacuo*. The residue was poured onto water and extracted with chloroform. The organic layer was washed with water (2 × 50 ml), dried over MgSO$_4$ and evaporated *in vacuo*. The residue was purified by silica gel column chromatography using chloroform:methanol (95:5, v/v) to give compound **11**. Yield 0.25 g (18%); mp: 286-288°; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ 0.78 (t, 6H, J = 7.1 Hz, 2 × C*H*$_3$CH$_2$), 2.21-2.37 (m, 4H, 2 × C*H*$_2$CH$_3$), 2.87 (s, 12H, 4 × NCH$_3$), 3.58 (s, 4H, 2 × C*H*$_2$Ar), 6.96-7.16 (m, 4H, Ar), 11.10 (s, 2H, 2 × NH); ^{13}C nmr (dimethyl sulfoxide-d$_6$): δ 13.76 (2 × CH$_3$), 17.94 (2 × *C*H$_2$CH$_3$), 36.77 (4 × NCH$_3$), 43.35 (2 × *C*H$_2$Ph), 111.61 (C-5), 126.43, 127.83, 130.43, 138.84 (C$_{arom}$), 152.56 (2 × C-6), 161.67 (2 × CO), 164.09 (2 × C-2). HRms (MALDI, peak matching): m/z 437.2642 [C$_{24}$H$_{32}$N$_6$O$_2$ + H$^+$], requires m/z 437.2660. *Anal.* Calcd. for (C$_{24}$H$_{32}$N$_6$O$_2$ × 0.25H$_2$O): C, 65.36; H, 7.43; N, 19.05. Found: C, 65.32, H, 7.31; N, 18.63.

General Procedure for the Synthesis of Compounds 12a,b and 13a,b. Compound **4** (0.81 g, 2 mmoles) was dissolved in 20 ml dry DMF, K$_2$CO$_3$ (0.55 g, 4 mmoles) and isopropyl bromide or isobutyl bromide (4.8 mmoles) were added, the reaction mixture was stirred at room temperature for 3 days. The DMF was evaporated under reduced pressure, and the residue was chromatographed using ethyl acetate:petroleum ether (60-80°) (1:1, v/v) to afford **12a,b** and **13a,b**.

5-Ethyl-2-isopropylsulfanyl-6-{3-[(5-ethyl-2-isopropylsulfanyl-pyrimidin-4(1*H*,3*H*)-yl)methyl]benzyl}pyrimidine-2,4-(1*H*,3*H*)-one (12a). Yield 0.3 g (33%); mp 198-200°; ^{1}H nmr (dimethyl sulfoxide-d$_6$): δ 0.93 (t, 6H, J = 7.2 Hz, 2 × C*H*$_3$CH$_2$), 1.22 (d, 12H, J = 6.7 Hz, 4 × CH$_3$[Pr^i]), 2.41-2.48 (m, 4H, 2 × C*H*$_2$CH$_3$), 3.69-3.76 (m, 2H, 2 × SCH), 3.80 (s, 4H, 2 × C*H*$_2$Ar), 7.09-7.20 (m, 4H, Ar), 12.43 (s, 2H, 2 × NH); ^{13}C (dimethyl sulfoxide-d$_6$): δ 13.02 (2 × CH$_3$), 18.07 (2 × *C*H$_2$CH$_3$), 22.34 (4 × CH$_3$[Pr^i]), 35.42 (2 × SCH), 40.77 (2 × *C*H$_2$Ar), 120.80 (C-5), 126.82, 128.00, 129.28, 138.38 (C$_{arom}$), 156.73 (2 × C-6), 159.99, 162.71 (C-2 and C-4). HRms (MALDI, peak matching): m/z 521.1994 [C$_{26}$H$_{34}$N$_4$O$_2$S$_2$ + Na$^+$], requires *m/z* = 521.2015.

5-Ethyl-2-isopropylsulfanyl-4-isopropyloxy-6-{3-[(5-ethyl-2-isopropylsulfanyl-4-isopropyloxy-pyrimidin-4(1*H*,3*H*)-yl)-methyl]benzyl}pyrimidine-2,4(1*H*,3*H*)-one (13a). Yield 0.2 g (19%); oil; ^{1}H nmr (deuteriochloroform): δ 0.90-1.14 (m, 6H, 2 × C*H*$_3$CH$_2$), 1.22-1.38 (m, 18H, 6 × CH$_3$[Pr^i]), 2.44-2.59 (m, 4H, 2 × C*H*$_2$CH$_3$), 3.79-3.87 (m, 2H, 2 × SCH) 3.94 (s, 4H, 2 × C*H*$_2$Ar), 5.30-5.38 (m, 1H, OCH), 7.05-7.26 (m, 4H, Ar), 12.10 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 13.12, 13.16 (2 × CH$_3$), 18.23, 18,67 (2 × *C*H$_2$CH$_3$), 21.88, 22.72, 23.03 (6 × CH$_3$[Pr^i]), 35.56, 36.51 (2 × SCH), 40.33, 40.44 (2 × *C*H$_2$Ar), 68.98 (OCH), 116.55, 122.01 (2 × C-5), 126.80, 126.92, 128.23, 129.54, 138.35, 138.60 (C$_{arom}$), 156.46, 161.67 (2 × C-6),

164.80, 165.42, 166.88, 167.09 (C-2 and C-4). HRms (MALDI, peak matching): m/z 563.2480 [$C_{29}H_{40}N_4O_2S_2$ + Na^+], requires m/z 563.2485.

5-Ethyl-2-secbutylsulfanyl-6-{3-[(5-ethyl-2-secbutylsulfanyl-pyrimidin-4(1*H*,3*H*)-yl)methyl]benzyl}pyrimidine-2,4-(1*H*,3*H*)-one (12b). Yield 0.23 g (23%); mp 181-183°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 0.84 (t, 6H, J = 7.2 Hz, 2 × C*H*$_3$CH$_2$ at C-5), 0.93 (t, 6H, J = 7.4 Hz, 2 × C*H*$_3$CH$_2$[sec-Bu]), 1.22 (d, 6H, J = 6.8, 2 × C*H*$_3$CH[sec-Bu]), 1.50-1.60 (m, 4H, 2 × C*H*$_2$CH$_3$[sec-Bu]), 2.40-2.51 (m, 4H, 2 × C*H*$_2$CH$_3$ at C-5), 3.60-3.66 (m, 2H, 2 × SCH), 3.79 (s, 4H, 2 × C*H*$_2$.Ar), 7.08-7.20 (m, 4H, Ar), 12.43 (s, 1H, NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 11.01 (2 × CH$_3$ at C-5), 13.03 (2 × CH$_3$[sec-Bu]), 18.09 (2 × *C*H$_2$.CH$_3$ at C-5), 19.91 (2 × *C*H$_3$CH[sec-Bu]), 28.59 (2 × *C*H$_2$CH$_3$[sec-Bu]), 39.52 (2 × SCH), 40.57 (2 × *C*H$_2$Ar), 120.86 (2 × C-5), 126.82, 127.95, 129.32. 138.40 (C_{arom}), 156.77 (2 × C-6), 159.91, 162.72 (C-2 and C-4). HRms (MALDI, peak matching): m/z 549.2329 [$C_{28}H_{38}N_4O_2S_2$ + Na^+], requires m/z 549.2328. *Anal.* Calcd. for ($C_{28}H_{38}N_4O_2S_2$): C, 63.84; H, 7.27; N, 10.64. Found: C, 63.59; H, 7.37, N, 10.40.

5-Ethyl-2-secbutylsulfanyl-4-secbutyloxy-6-{3-[(5-ethyl-2-secbutylsulfanyl-4-secbutyloxy-pyrimidin-4(1*H*,3*H*)-yl)methyl]benzyl}pyrimidine-2,4(1*H*,3*H*)-one (13b). Yield 0.26 g (22%); oil; ^{1}H nmr (deuteriochloroform): δ 0.90-1.07 (m, 15H, 5 × CH$_3$), 1.27, 1.36 (2d, 9H, J = 7.8Hz, 3 × C*H*$_3$CH[sec-Bu]), 1.53-1.80 (m, 6H, 3 × C*H*$_2$CH[sec-Bu]), 2.45-2.59 (m, 4H, 2 × C*H*$_2$CH$_3$ at C-5), 3.67-3.80 (m, 2H, 2 × SCH[sec-But]), 3.84, 3.95 (2s, 2 × C*H*$_2$Ar), 4.08-4.15 (m, 1H, OCH[sec-But]), 7.06-7.20 (m, 4H, Ar), 11.99 (s, 1H, NH); ^{13}C nmr ($CDCl_3$): δ 9.66, 11.32 (2 × CH$_3$ at C-5), 11.53, 13.19, 13.23 (3 × CH$_3$[sec-But]), 18.28, 19.25 (2 × *C*H$_2$CH$_3$ at C-5), 20.35, 20.44, 20.55 (3 × *C*H$_3$CH[sec-But]), 28.87, 29.24, 29.46 (3 × *C*H$_2$CH[sec-But]), 40.37, 40.49 (2 × SCH[sec-But]), 41.87, 42.80 (2 × *C*H$_2$Ar), 73.56 (OCH), 116.55, 122.07 (2 × C-5), 126.85, 126.95, 128.26, 129.59, 138.42, 138.65 (C_{arom}), 156.62, 161.60 (2 × C-6), 164.76, 165.46, 167.12, 167.24 (C-2 and C-4). HRms (MALDI, peak matching): m/z 605.2965 [$C_{32}H_{46}N_4O_2S_2$ + Na^+], requires m/z 605.2954.

5-Ethyl-2-methylthio-6-{3-[(5-ethyl-2-methylthio-pyrimidin-4(1*H*,3*H*)-yl)methyl]benzyl}pyrimidine-2,4(1*H*,3*H*)-one (14). Compound **4** (0.8 g, 2 mmoles) was dissolved in 30 ml dry DMF under nitrogen and CH$_3$I (0.56 g, 0.26 ml, 4 mmoles) was added. The reaction mixture was stirred at room temperature for 24 hours and poured onto cold water. The product was collected by filtration, washed three times with water and chromatographed using ethyl acetate:petroleum ether (60-80°) (1:1, v/v) to give **14**.

Yield 0.7 g (82%); mp 266-268°; ^{1}H nmr (deuteriochloroform): δ 0.80 (t, 6H, J = 7.3 Hz, 2 × C*H*$_3$CH$_2$), 2.29 (s, 6H, 2 × SCH$_3$), 2.31-2.36 (m, 4H, 2 × C*H*$_2$CH$_3$), 3.72 (s, 4H, 2 × C*H*$_2$Ar), 6.02-7.14 (m, 4H, Ar), 12.41 (s, 2H, 2 NH); ^{13}C nmr (deuteriochloroform): δ 12.50 (2 × CH$_3$), 12.98 (2 × SCH$_3$), 18.13 (2 × *C*H$_2$CH$_3$), 39.62 (2 × *C*H$_2$Ar), 120.79 (C-5), 126.79, 128.14, 129.06, 138.43 (C_{arom}), 157.62 (C-6), 159.91, 162.74 (C-2 and C-4). HRms (MALDI, peak matching): m/z 465.1372 [$C_{22}H_{26}N_4O_2S_2$ + Na^+], requires m/z 465.1389. *Anal.* Calcd. for ($C_{22}H_{26}N_4O_2S_2$ × 0.5H$_2$O): C, 58.51; H, 6.03; N, 12.41. Found: C, 58.85; H, 6.33; N, 12.15.

General Procedure for the Synthesis of Compounds 15, 16 and 17. Compound **4** (0.81 g, 2 mmoles) was dissolved in 20 ml dry DMF, and K_2CO_3 (0.54 g, 4 mmoles) and CH$_3$I (0.62 g, 4 mmoles) were added. The reaction mixture was stirred at room temperature for 48 hours. The DMF was evaporated under reduced pressure. The products **15, 16** and **17** were isolated after column chromatography using chloroform:petroleum ether (60-80°) (7:3, v/v).

5-Ethyl-2-methylthio-3-methyl-6-{3-[(5-ethyl-2-methylthio-3-methyl-pyrimidin-4(1*H*,3*H*)-yl)methyl]benzyl}pyrimidine-2,4(1*H*,3*H*)-one (15). Yield 0.2 g (28%); mp 175-177°; ^{1}H nmr (deuteriochloro-form): δ 1.04 (t, 6H, J = 7.2 Hz, 2 × C*H*$_3$CH$_2$), 2.41 (s, 6H, 2 × SCH$_3$), 2.53-2.60 (m, 4H, 2 × C*H*$_2$CH$_3$), 3.46 (s, 6H, 2 × NCH$_3$), 3.84 (s, 4H, 2 × C*H*$_2$Ar), 7.11-7.26 (m, 4H, Ar); ^{13}C nmr (deuteriochloroform): δ 13.09 (2 × CH$_3$), 14..64 (2 × SCH$_3$), 19.46 (2 × *C*H$_2$CH$_3$), 30.30 (2 × NCH$_3$), 40.22 (2 × *C*H$_2$Ar), 120.76 (C-5), 127.06, 128.12, 129.62, 138.47 (C_{arom}), 158.17 (C-6), 158.37, 162.73 (C-2 and C-4). HRms (MALDI, peak matching): m/z 471.1872 [$C_{24}H_{30}N_4O_2S_2$ + H^+], requires m/z 471.1883. *Anal.* Calcd. for ($C_{24}H_{30}N_4O_2S_2$ × 0.25H$_2$O): C, 60.67; H, 6.47; N, 11.79. Found: C, 60.65; H, 5.94; N, 11.51.

5-Ethyl-2-methylthio-4-methoxy-6-{3-[(5-ethyl-2-methylthio-4-methoxy-pyrimidin-4(1*H*,3*H*)-yl)methyl]benzyl}pyrimidine-2,4(1*H*,3*H*) (16). Yield 0.1 g (11%); oil; ^{1}H nmr (deuteriochloroform): δ 0.88-0.97 (m, 6H, 2 × C*H*$_3$CH$_2$), 2.50 (s, 6H, 2 × SCH$_3$), 2.52-2.54 (m, 4H, 2 × C*H*$_2$CH$_3$), 3.95 (s, 6H, 2 × OCH$_3$), 3.96 (s, 4H, 2 × C*H*$_2$Ar), 7.05-7.25 (m, 4H, Ar); ^{13}C nmr (deuteriochloroform): δ 13.19 (2 × CH$_3$), 14.06 (2 × SCH$_3$), 18.18 (2 × *C*H$_2$CH$_3$), 40.35 (2 × *C*H$_2$Ar), 53.81 (2 × OCH$_3$), 116.52 (2 × C-5), 126.75, 128.34, 129.25, 138.56 (C_{arom}), 158.70 (2 × C-6), 165.46, 167.73 (C-2 and C-4). HRms (MALDI, peak matching): m/z 471.1897 [$C_{24}H_{30}N_4O_2S_2$ + H^+], requires m/z 471.1883.

5-Ethyl-2-methylthio-3-methyl-6-{3-[(5-ethyl-2-methylthio-4-methoxy-pyrimidin-4(1*H*,3*H*)-yl)methyl]benzyl}pyrimidine-2,4(1*H*,3*H*)-one (17). Yield 0.15 g (18%); oil; ^{1}H nmr (deuteriochloroform): δ 0.89-1.08 (m, 6H, 2 × C*H*$_3$CH$_2$), 2.40, 2.51 (2s, 6H, 2 × SCH$_3$), 2.52-2.57 (m, 4H, 2 × C*H*$_2$CH$_3$), 3.46 (s, 3H, NCH$_3$), 3.82, 3.99 (2s, 4H, 2 × C*H*$_2$Ph), 3.95 (s, 3H, OCH$_3$), 7.06-7.26 (m, 4H, Ar); ^{13}C nmr (deuteriochloroform): δ 13.07, 13.13 (2 × CH$_3$), 13.99, 14.69 (2 × SCH$_3$), 18.51, 19.43 (2 × *C*H$_2$CH$_3$), 30.25 (NCH$_3$), 40.18, 40.34 (2 × *C*H$_2$Ar), 53.78 (OCH$_3$), 116.40, 120.71 (2 × C-5), 126.75, 127.00, 128.21, 129.39, 138.44, 138.53 (C_{arom}), 158.13, 158.36 (2 × C-6), 162.73, 165.41 (2 × C-2), 167.41, 167.66 (2 × C-4). HRms (MALDI, peak matching): m/z 471.1892 [$C_{24}H_{30}N_4O_2S_2$ + H^+], requires m/z 471.1883.

Synthesis of Compounds 18 and 19. Compound **14** (2.2 g, 5 mmoles) was dissolved in piperidine (4.2 g, 50 mmoles). The reaction mixture was refluxed for 24 hours, cooled and poured onto cold water. The solid formed was collected by filtration and washed with water. The products **18** and **19** were isolated after column chromatography using chloroform:methanol (95:5, v/v).

5-Ethyl-2-piperidinyl-6-{3-[(5-ethyl-2-piperidinyl-pyrimidin-4(1*H*,3*H*)-yl)methyl]benzyl}pyrimidine-2,4(1*H*,3*H*)-one (18). Yield 32%; mp 263-265°; ^{1}H nmr (deuteriochloroform): δ 0.83-0.91 (m, 6H, 2 × C*H*$_3$CH$_2$), 1.44-1.56 (m, 12H, piperidino), 2.29-2.41 (m, 4H, 2 × C*H*$_2$CH$_3$), 3.45-3.49 (m, 8H, piperidino), 3.66 (s, 4H, 2 × C*H*$_2$Ar), 7.08-7.18 (m, 4H, Ar), 11.32 (s, 2H, 2 × NH); ^{13}C nmr (deuteriochloroform): δ 13.69 (2 × CH$_3$), 17.95 (2 × *C*H$_2$CH$_3$), 23.90, 24.92, 44.98 (piperidino), 30.60 (2 × *C*H$_2$Ar), 112.07 (2 × C-5), 126.41, 127.53, 128.95, 138.82 (C_{arom}), 152.10 (2 × C-6), 158.18, 164.37 (C-2 and C-4). HRms (MALDI, peak matching): m/z 539.3092 [$C_{30}H_{40}N_6O_2$ + Na^+], requires m/z 539.3105.

5-Ethyl-2-methylthio-6-{3-[(5-ethyl-2-piperidinyl-pyrimid-in-4(1*H*,3*H*)-yl)methyl]benzyl}pyrimidine-2,4(1*H*,3*H*)-one (19). Yield 26%; mp 248-250°; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 0.80-0.85 (m, 6H, 2 × C*H*$_3$CH$_2$), 1.39-1.57 (m, 6H, piperidino), 2.29-2.35 (m, 4H, 2 × C*H*$_2$CH$_3$), 2.29 (s, 3H, SCH$_3$), 3.43-3.61 (m, 4H, piperidino), 3.71 (s, 4H, 2 × C*H*$_2$Ar), 7.02-7.12 (m, 4H, Ar), 7.85, 8.16 (2s, 2H, 2 × NH); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 12.66, 13.71 (2 × CH$_3$), 13.14 (SCH$_3$), 18.01, 18.32 (2 × *C*H$_2$CH$_3$), 22.61, 24.62, 45.02 (piperidino), 39.62, 43.63 (2 × *C*H$_2$Ar), 112.22, 119.95 (2 × C-5), 126.61, 126.52, 128.04, 129.09, 138.72 (C$_{arom}$), 152.17 (2 × C-6), 159.36, 159.73, 164.53, 165.27 (C-2 and C-4). HRms (MALDI, peak matching): m/z 480.2415 [$C_{26}H_{33}N_5O_2S + H^+$], requires m/z 480.2428.

Cell-based Assays

Compounds. Compounds were dissolved in DMSO at 100 mM and then diluted in culture medium.

Cells and Viruses. Cell lines were purchased from American Type Culture Collection (ATCC). The absence of mycoplasma contamination was checked periodically by the Hoechst staining method. Cell lines supporting the multiplication of RNA viruses were the CD4$^+$ human T-cells containing an integrated HTLV-1 genome (MT-4).

Cytotoxicity Assays. For cytotoxicity evaluations, exponentially growing cells derived from human haematological tumors [CD4$^+$ human T-cells containing an integrated HTLV-1 genome (MT-4)] were seeded at an initial density of 1x10^5 cells/ml in 96 well plates in RPMI-1640 medium supplemented with 10% fetal calf serum (FCS), 100 units/mL penicillin G and 100 μg/mL streptomycin. Cell cultures were then incubated at 37 °C in a humidified, 5% CO_2 atmosphere in the absence or presence of serial dilutions of test compounds. Cell viability was determined after 96 hrs at 37 °C by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide (MTT) method [12].

Antiviral Assays. Activity of compounds against Human Immunodeficiency virus type-1 (HIV-1) was based on inhibition of virus-induced cytopathogenicity in MT-4 cells acutely infected with a multiplicity of infection (m.o.i.) of 0.01. Briefly, 50 μL of RPMI containing 1x10^4 MT-4 were added to each well of flat-bottom microtitre trays containing 50 μL of RPMI, without or with serial dilutions of test compounds. Then, 20 μL of an HIV-1 suspension containing 100 CCID$_{50}$ were added. After a 4-day incubation, cell viability was determined by the MTT method.

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REFERENCES AND NOTES

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