

Anti-HIV Active Naphthyl Analogues of HEPT and DABO

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5-Ethyl-6-(1-naphthylmethyl)uracil and 5-ethyl-6-(1-naphthylmethyl)-2-thiouracil were alkylated to give, respectively, *N*-1 and *S*², ethoxymethyl and methylthiomethyl uracil derivatives. 5-Ethyl-6-(1-naphthylmethyl)-2-thiouracil was also *S*² alkylated with methyl bromoacetate. The products showed activity against HIV-1, and the *N*-1 alkylated derivatives were indeed highly active.

Several classes of compounds have been identified as highly specific reverse transcriptase (RT) inhibitors of human immunodeficiency virus type 1 (HIV-1), the causative agent of the acquired immune deficiency syndrome (AIDS). They are either substrate analogues, such as 3'-azido-3'-deoxythymidine (AZT),¹ 2',3'-dideoxycytidine (DDC), and 2',3'-dideoxyinosine (DDI),² currently used in AIDS therapy, or non-substrate analogues such as tetrahydroimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one and -thione (TIBO),^{3,4} and 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HEPT)^{5,6} which were the first non-substrate analogues reported as specific HIV-1 inhibitors of viral RT. The substrate analogues are less specific and inhibit both the HIV-1 and the HIV-2 RTs by competing with natural substrate and causing chain termination⁷ whereas the non-substrate analogues inhibit HIV-1 replication by virtue of a specific (allosteric)⁸ interaction with a non-substrate binding site of the enzyme. For a precise and detailed understanding of the important inhibitor–protein interactions the crystal structures for a number of different non-substrate analogues have been determined.^{9–12} As a result, the presence of a flexible, highly hydrophobic pocket has been shown, in which the non-substrate analogues must fit snugly.^{13–15} In a recent molecular modelling study on HEPT derivatives¹⁶ it was postulated that replacement of the 6-(phenylthio) group with a naphthylmethyl group might be favorable. Also, various thio analogues of dihydroalkoxybenzoxypyrimidines (DABOs),¹⁷ a new class of non-substrate analogues, have recently been found to inhibit selectively HIV-1 replication *in vitro*.

In an attempt to obtain more potent and selective compounds against HIV-1 and to confirm the above-mentioned findings from molecular modelling, we

decided to synthesize a series of derivatives bearing a resemblance to HEPT and DABO by introducing a naphthylmethyl as a fused aromatic system at C-6 of the pyrimidine ring and also in the DABO type of compounds by modifying substituents at C-2. Also we would like to emphasize that new compounds within these two classes of compounds can easily be synthesized from the same precursors.

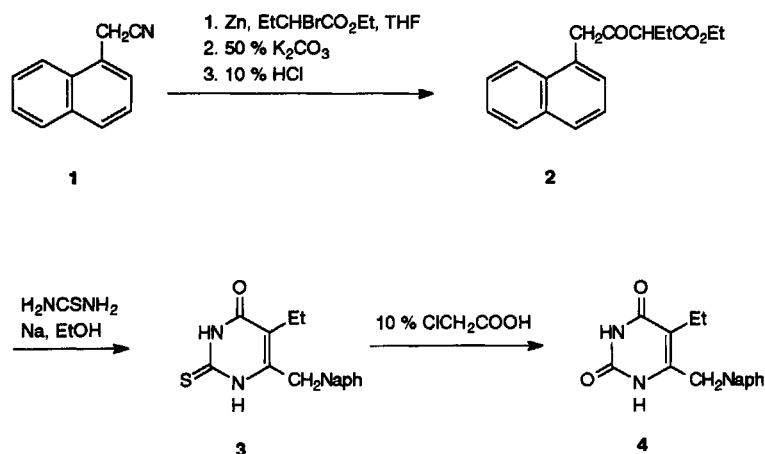
Results and discussion

Ethyl 2-ethyl-4-(1-naphthyl)-3-oxobutyrates **2** was obtained from commercially available 1-naphthylacetonitrile **1** by the method previously described.^{18,19} The β -keto ester **2** was condensed with thiourea²⁰ in the presence of sodium ethoxide to furnish the corresponding thiouracil **3**, which, in boiling aqueous chloroacetic acid, afforded the uracil **4** by exchanging sulfur with oxygen.²¹ Even though the β -keto ester **2** was impure, it could be used as a raw material in the synthesis of **3**. The NMR spectra of crude compound **2** 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 compound as an impurity in the raw material of **3**. However, pure compound **3** was easily obtained by recrystallization.

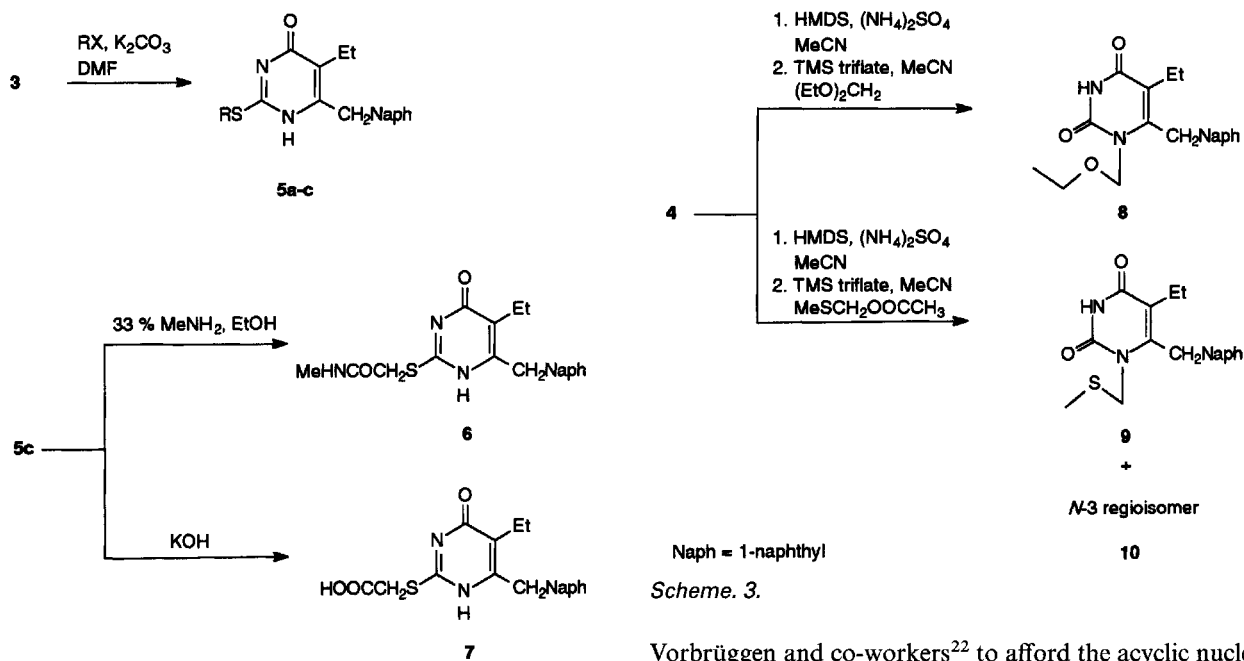
Reaction of **3** with alkylthiomethyl chloride or methyl bromoacetate in *N,N*-dimethylformamide (DMF) in the presence of potassium carbonate afforded 2-(alkylthio)-6-naphthylmethylpyrimidin-4(1*H*)-ones **5**. The amide **6** was obtained quantitatively upon treatment of **5c** in 33% ethanolic methylamine. The ester **5c** was also hydrolyzed to the corresponding acid **7** in hot aqueous potassium hydroxide.

The pyrimidine **4** was silylated by heating at reflux in 1,1,1,3,3,3-hexamethyldisilazane (HMDS) and under-

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Scheme 1.



Scheme 3.

Naph = 1-naphthyl

5	R
a	MeSCH ₂
b	EtSCH ₂
c	MeOOCCH ₂

Scheme 2.

went alkylation by treatment with diethoxymethane or methylthiomethyl acetate in the presence of trimethylsilyl trifluoromethanesulfonate (TMS triflate) according to

Vorbrüggen and co-workers²² to afford the acyclic nucleosides **8** and **9** in 60 and 61% yield, respectively. Compound **8** could also be obtained in 51% yield from **4** by treatment with *N,O*-bis(trimethylsilyl)acetamide (BSA) in chloroform and subsequent addition of chloromethyl ethyl ether. *N*-1 Substitution was proved by the NOE enhancement in one of the naphthyl protons when 1-CH₂ was irradiated. The *N*-3 regioisomer could also be isolated when methylthiomethyl acetate was used as the alkylating agent.

Antiviral activity. For the compounds synthesized in the present study we used the HIV-1 strain HTLV-III_B and MT-4 cells in our assay to investigate the anti-HIV-1 activity. From Table 1 it can be seen that the DABO analogues **5** showed only moderate activity against HIV-1

compared with AZT. When the ester group of **5c** was replaced with an amide the activity completely disappeared (compound **6**).

Table 1. Antiviral activity of compounds **5–9**, MKC-442 and AZT against HIV-1 in MT-4 cells.

Compd.	ED ₅₀ /μM ^a	CD ₅₀ /μM ^b	SI ^c
5a	4.6	> 100	> 22
5b	2.7	> 100	> 37
5c	5.2	> 100	> 19
6	> 100		
8	0.05	46	920
9	0.37	27	73
AZT	0.04	52	1300
MKC-442	0.005	141	28000

^aEffective dose of compound, achieving 50% inhibition of HIV-1 antigen production in MT-4 cultures. ^bCytotoxic dose of compound required to reduce the proliferation of normal uninfected MT-4 cells by 50%. ^cSelectivity index: ratio CD₅₀/ED₅₀. ED₅₀ and CD₅₀ are expressed as the mean values of three independent determinations.

The HEPT analogues **8** and **9** were highly active. In fact, the activity of compound **8** was comparable to that of AZT, but lower than that of 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil (MKC-442) which is the HEPT analogue chosen as a candidate for clinical trials with AIDS patients.²³ For all compounds in this investigation, the selectivity indices are lower than those of both AZT and MKC-442. However, variation of the 5- and 1-substituents of the uracil may very well lead to even higher activities against HIV-1 and selectivity indices than the ones we have found for the naphthyl analogue **8**.

To conclude, experimental evidence has confirmed the molecular modelling studies¹⁶ that 6-naphthyl analogues of HEPT are possible leads for new compounds with activity against HIV-1.

Experimental

NMR spectra were recorded on a Bruker AC-250 FT NMR spectrometer at 250 MHz for ¹H and 62.9 MHz for ¹³C with TMS as an internal standard. Analytical silica gel TLC plates 60 F₂₅₄ and the silica gel (0.040–0.063) used for column chromatography were purchased from Merck. THF was distilled from sodium-benzophenone prior to use. Microanalyses were carried out at the H. C. Ørsted Institute, Universitetsparken 5, DK-2100 Copenhagen.

Ethyl 2-ethyl-4-(1-naphthyl)-3-oxobutyrates (2). Activated zinc dust (zinc dust washed sequentially with 3 M aq. HCl, distilled H₂O, EtOH, Et₂O, and then dried *in vacuo*; 45 g, 0.69 mol) was suspended in refluxing THF (400 ml) under nitrogen. A few drops of ethyl 2-bromobutyrate were added to initiate the reaction. After the appearance of a green colouration (approx. 60 min), 1-naphthylacetonitrile (23 g, 0.14 mol) was

added in one portion, followed by slow addition (60 min) of ethyl 2-bromobutyrate (70.4 g, 0.36 mol). The mixture was refluxed for an additional 20 min. After cooling and dilution with THF (1240 ml) aq. 50% K₂CO₃ (180 ml) was added and the mixture vigorously stirred. The top layer of the two distinct layers was decanted and the residue extracted with THF (3 × 100 ml). The combined organic fractions were treated with 10% aq. HCl (150 ml) at room temperature for 45 min. The mixture was concentrated *in vacuo*. Dichloromethane was added and the solution washed with sat. NaHCO₃, dried over sodium sulfate and evaporated under reduced pressure to furnish the crude oxo-ester **2** (51 g) which was used without further purification. Analytically pure **2** was obtained by preparative TLC (10% EtOAc in petroleum ether). ¹H NMR (CDCl₃): δ 0.77 (t, *J* = 7.4 Hz, 3 H, CH₃), 1.18 (t, *J* = 7.1 Hz, 3 H, CH₃), 1.85 (m, 2 H, CH₂), 3.49 (t, *J* = 7.2 Hz, 1 H, CH), 4.07 (q, *J* = 7.1 Hz, 2 H, OCH₂), 4.23 (s, 2 H, CH₂), 7.32–7.87 (m, 7 H, naphthyl); ¹³C NMR (CDCl₃): δ 11.6 (CH₃), 13.9 (CH₃), 21.5 (CH₂), 47.4 (CH₂), 58.7 (OCH₂), 61.1 (CH), 123.8–133.8 (naphthyl), 169.5 (C=O), 202.6 (C=O). Anal. C₁₇H₂₀O₃: C, H.

5-Ethyl-6-(1-naphthylmethyl)-2-thiouracil (3). The crude compound **2** (51 g) was added to a solution of sodium (9.3 g, 0.40 mol) and thiourea (21.3 g, 0.28 mol) in EtOH (200 ml). The mixture was heated at reflux overnight. After cooling, the solvent was removed *in vacuo* and the residue dissolved in water and neutralized with HCl. The precipitate was collected, washed with water and recrystallized from EtOH (twice) to afford the title compound as white crystals. M.p. 188–191 °C. Yield 10.0 g (24%). ¹H NMR (DMSO-*d*₆): δ 0.81 (t, *J* = 7.3 Hz, 3 H, CH₃), 2.19 (q, *J* = 7.3 Hz, 2 H, CH₂), 4.32 (s, 2 H, CH₂), 7.08–8.14 (m, 7 H, naphthyl), 12.38–12.42 (br s, 2 H, 2 × NH); ¹³C NMR (DMSO-*d*₆): δ 12.9 (CH₃), 17.7 (CH₂), 31.7 (CH₂), 118.2 (C-5), 123.3–133.2 (naphthyl), 148.7 (C-6), 161.3 (C-4), 174.3 (C-2). Anal. C₁₇H₁₆N₂OS · 0.5 H₂O: C, H, N.

5-Ethyl-6-(1-naphthylmethyl)uracil (4). The crude thiouracil **3** (5.0 g) was suspended in boiling 10% aq. chloroacetic acid and heating was continued until disappearance of the starting material (TLC). After cooling, the precipitate was collected, washed with water and recrystallized from EtOH to afford 2.5 g of **4**, m.p. 207–210 °C. ¹H NMR (DMSO-*d*₆): δ 0.82 (t, *J* = 7.3 Hz, 3 H, CH₃), 2.18 (q, *J* = 7.3 Hz, 2 H, CH₂), 4.25 (s, 2 H, CH₂), 7.16–8.16 (m, 7 H, naphthyl), 10.76 (s, 1 H, NH), 11.12 (s, 1 H, NH); ¹³C NMR (DMSO-*d*₆): δ 13.4 (CH₃), 17.6 (CH₂), 32.2 (CH₂), 112.5 (C-5), 123.2–133.2 (naphthyl), 148.1 (C-6), 151.0 (C-2), 164.4 (C-4). Anal. C₁₇H₁₆N₂O₂: C, H, N.

Preparation of 5a,b. A mixture of **3** (296 mg, 1 mmol), alkyl chloromethyl sulfide (1 mmol), and K₂CO₃ (138 mg, 1 mmol) in anhydr. DMF (5 ml) was stirred overnight at room temperature. After treatment with

water (100 ml), the solution was extracted with EtOAc (3 × 50 ml). The combined extracts were washed with sat. NaCl (2 × 50 ml), dried (MgSO₄), filtered and concentrated *in vacuo* to give the crude products **5a** and **5b** which were purified by column chromatography (CHCl₃).

5-Ethyl-2-[(methylthiomethyl)thio]-6-(1-naphthylmethyl)pyrimidin-4(1H)-one (5a). Yield 281 mg (79%), m.p. 174–175 °C (EtOH). ¹H NMR (CDCl₃): δ 1.11 (t, *J* = 7.3 Hz, 3 H, CH₃), 1.92 (s, 3 H, SCH₃), 2.63 (q, *J* = 7.3 Hz, 2 H, CH₂), 3.93 (s, 2 H, CH₂), 4.37 (s, 2 H, SCH₂), 7.22–8.10 (m, 7 H, naphthyl), 12.70 (s, 1 H, NH); ¹³C NMR (CDCl₃): δ 12.7 (CH₃), 15.1 (SCH₃), 18.7 (CH₂), 36.2 (CH₂C₁₀H₇), 37.3 (SCH₂), 122.8 (C-5), 124.1–134.2 (naphthyl), 155.5 (C-6), 161.4 (C-4), 165.0 (C-2). Anal. C₁₉H₂₀N₂O₂S₂: C, H, N.

5-Ethyl-2-[(ethylthiomethyl)thio]-6-(1-naphthylmethyl)pyrimidin-4(1H)-one (5b). Yield 320 mg (86%), m.p. 142–144 °C (EtOH). ¹H NMR (CDCl₃): δ 1.06 (t, *J* = 7.4 Hz, 3 H, CH₃), 1.07 (t, *J* = 7.4 Hz, 3 H, CH₃), 2.43 (q, *J* = 7.4 Hz, 2 H, CH₂), 2.63 (q, *J* = 7.4 Hz, 2 H, CH₂), 3.98 (s, 2 H, SCH₂), 4.36 (s, 2 H, CH₂), 7.22–8.01 (m, 7 H, naphthyl); ¹³C NMR (CDCl₃): δ 13.0 (CH₃), 14.0 (CH₃), 18.8 (CH₂), 25.8 (SCH₂), 33.7 (CH₂C₁₀H₇), 37.4 (SCH₂S), 122.9 (C-5), 124.1–134.3 (naphthyl), 155.8 (C-6), 161.5 (C-4), 165.1 (C-2). Anal. C₂₀H₂₂N₂O₂S₂: C, H, N.

5-Ethyl-2-[(methoxycarbonylmethyl)thio]-6-(1-naphthylmethyl)pyrimidin-4(1H)-one (5c). To a solution of thiouracil **3** (592 mg, 2 mmol) in anhydr. DMF (5 ml) were added methyl bromacetate (306 mg, 2 mmol), and K₂CO₃ (276 mg, 2 mmol). The mixture was stirred overnight and filtered. The solid was washed with a small amount of DMF (3 ml). The combined organic fractions were evaporated *in vacuo*. The residue was coevaporated with toluene (2 × 10 ml). The remaining solid was recrystallized from EtOAc–petroleum ether to furnish slightly pink crystals. Yield 320 mg (45%), m.p. 138–141 °C. ¹H NMR (DMSO-*d*₆): δ 0.94 (t, *J* = 7.3 Hz, 3 H, CH₃), 2.51 (q, *J* = 7.3 Hz, 2 H, CH₂), 3.43 (s, 3 H, OCH₃), 3.79 (s, 2 H, SCH₂), 4.31 (s, 2 H, CH₂), 7.20–8.33 (m, 7 H, naphthyl), 12.72 (s, 1 H, NH); ¹³C NMR (DMSO-*d*₆): δ 12.8 (CH₃), 18.3 (CH₂), 31.6 (CH₂C₁₀H₇), 36.8 (SCH₂), 52.0 (OCH₃), 121.5 (C-5), 124.0–134.5 (naphthyl), 156.5 (C-6), 160.2 (C-4), 163.1 (C-2), 168.7 (C=O). Anal. C₂₀H₂₀N₂O₃S: C, H, N.

5-Ethyl-2-[(methylcarbamoylmethyl)thio]-6-(1-naphthylmethyl)pyrimidin-4(1H)-one (6). The ester **5c** (100 mg, 0.282 mmol) was dissolved in 33% methylamine in EtOH (5 ml). When TLC showed no more starting material, the solution was evaporated *in vacuo* to dryness to give the amide. Yield 103 mg (100%), m.p. 213–214 °C. ¹H NMR (DMSO-*d*₆): δ 0.93 (t, *J* = 7.3 Hz, 3 H, CH₃), 2.37 (d, *J* = 4.5 Hz, 3 H, NHCH₃), 2.43 (q, *J* = 7.3 Hz, 2 H,

CH₂), 3.52 (s, 2 H, SCH₂), 4.30 (s, 2 H, CH₂), 7.20–8.20 (m, 7 H, naphthyl); ¹³C NMR (DMSO-*d*₆): δ 13.1 (CH₃), 18.6 (CH₂), 25.7 (NCH₃), 33.2 (CH₂C₁₀H₇), 36.8 (SCH₂), 120.0 (C-5), 124.0–135.2 (naphthyl), 159.6 (C-6), 160.8 (C-4), 168.1 (C-2), 168.8 (C=O). Anal. C₂₀H₂₁N₃O₂S: C, H, N.

2-[(Carboxymethyl)thio]-5-ethyl-6-(1-naphthylmethyl)pyrimidin-4(1H)-one (7). The ester **5c** (450 mg, 1.22 mmol) was dissolved in hot (80 °C) aq. KOH (3.5 M, 3 ml). The solution was kept at this temperature for 5 min. After cooling, water was added (3 ml) and the pH adjusted to 7 with 4 M HCl. The precipitate was collected, washed with cold water and dried to furnish the acid **7** (420 mg, 97%), m.p. 185–188 °C (EtOH–H₂O). ¹H NMR (DMSO-*d*₆): δ 0.90 (t, *J* = 7.3 Hz, 3 H, CH₃), 2.46 (q, *J* = 7.3 Hz, 2 H, CH₂), 3.80 (s, 3 H, SCH₂), 4.32 (s, 2 H, CH₂), 7.25–8.24 (m, 7 H, naphthyl), 12.61–12.73 (br s, 1 H, COOH); ¹³C NMR (DMSO-*d*₆): δ 12.7 (CH₃), 18.3 (CH₂), 32.1 (CH₂C₁₀H₇), 37.0 (SCH₂), 121.5 (C-5), 124.1–134.4 (naphthyl), 156.8 (C-6), 160.2 (C-4), 163.1 (C-2), 169.5 (C=O). Anal. C₁₉H₁₈N₂O₃S · H₂O: C, H, N.

1-(Ethoxymethyl)-5-ethyl-6-(1-naphthylmethyl)uracil (8). 5-Ethyl-6-(1-naphthylmethyl)uracil **4** (0.84 g, 3 mmol) was silylated with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) (5 ml) in the presence of (NH₄)₂SO₄ (10 mg). When the silylation was complete, the excess of HMDS was evaporated *in vacuo* to yield a translucent yellow oil which was dissolved in anhydr. MeCN (10 ml) and cooled to –35 °C. Trimethylsilyl trifluoromethanesulfonate (TMS triflate) (0.62 g, 2.79 mmol) was added in one portion, followed by the dropwise addition of diethoxymethane (3.1 g, 30 mmol). After this, the mixture was stirred for 3 h at –35 °C. When the reaction was finished (TLC analysis), the mixture was quenched with ice cold sat. NaHCO₃ (10 ml) and evaporated to near dryness by coevaporation with ethanol (2 × 50 ml). The resulting solid was suspended in Et₂O (200 ml) and the mixture stirred for 1 h. After filtration the residue was extracted with Et₂O (100 ml) and the combined organic fractions were evaporated to furnish crude **8** (1.7 g). Column chromatography (10 → 25% EtOAc in petroleum ether) gave 0.74 g of a white foam which was recrystallized (EtOH–EtOAc) to give 0.61 g (60%) of **8** as a white powder, m.p. 170–172 °C (EtOH–AcOEt). ¹H NMR (DMSO-*d*₆): δ 0.92 (t, *J* = 7.3 Hz, 3 H, CH₃), 0.99 (t, *J* = 7.3 Hz, 3 H, CH₃), 2.29 (q, *J* = 7.2 Hz, 2 H, CH₂), 3.44 (q, *J* = 7.0 Hz, 2 H, OCH₂), 4.51 (s, 2 H, CH₂), 4.95 (s, 2 H, NCH₂), 7.10–8.20 (m, 7 H, naphthyl), 10.59 (s, 1 H, NH); ¹³C NMR (DMSO-*d*₆): δ 13.5 (CH₃), 14.6 (CH₃), 18.5 (CH₂), 30.1 (CH₂C₁₀H₇), 63.7 (OCH₂), 72.1 (NCH₂), 115.9 (C-5), 125.9–133.3 (naphthyl), 148.3 (C-6), 151.5 (C-2), 162.8 (C-4). Anal. C₂₀H₂₂N₂O₃: C, H, N.

5-Ethyl-1-(methylthiomethyl)-6-(1-naphthylmethyl)uracil (**9**). The uracil **4** (840 mg, 3 mmol) was silylated by being refluxed in HMDS (10 ml) in the presence of $(\text{NH}_4)_2\text{SO}_4$ (15 mg). After evaporation of the solvent, the resulting solid was dissolved in anhydr. MeCN (10 ml). The mixture was cooled to -40°C and trimethylsilyl trifluoromethanesulfonate (667 mg, 3 mmol) was added in one portion. Methylthiomethyl acetate (420 mg, 3.5 mmol) was added dropwise. The temperature of the reaction was raised gradually to -5°C and the stirring continued at this temperature overnight. The reaction was quenched at this temperature by adding cold sat. aq. NaHCO_3 (15 ml). The mixture was evaporated *in vacuo* to near dryness. EtOH (50 ml) was added and the resulting suspension evaporated *in vacuo* one more time. The solid was triturated with CHCl_3 and the solvent was removed *in vacuo* to afford a slightly yellow foam. Purification by silica gel column chromatography (CHCl_3) gave the acyclic nucleoside **9**. Yield 627 mg (61%), m.p. $175\text{--}177^\circ\text{C}$ (EtOH-AcOEt). ^1H NMR (DMSO- d_6): δ 0.92 (t, $J=7.4$ Hz, 3 H, CH_3), 2.13 (s, 3 H, SCH_3), 2.33 (q, $J=7.3$ Hz, 2 H, CH_2), 4.56 (s, 2 H, CH_2), 4.63 (s, 2 H, NCH_2), 7.12–8.32 (m, 7 H, naphthyl), 11.60 (s, 1 H, NH); ^{13}C NMR (DMSO- d_6): δ 13.7 (CH_3), 14.9 (CH_3), 18.7 (CH_2), 30.6 ($\text{CH}_2\text{C}_{10}\text{H}_7$), 46.5 (NCH_2), 116.2 (C-5), 122.8–133.3 (naphthyl), 147.9 (C-6), 151.3 (C-2), 162.6 (C-4). Anal. $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2\text{S} \cdot 0.25 \text{H}_2\text{O}$: C, H, N.

5-Ethyl-3-(methylthiomethyl)-6-(1-naphthylmethyl)uracil (**10**). This compound was isolated during purification of compound **9** by chromatography. Oil. Yield 65 mg (6%). ^1H NMR (CDCl_3): δ 1.08 (t, $J=7.4$ Hz, 3 H, CH_3), 2.08 (s, 3 H, SCH_3), 2.48 (q, $J=7.4$ Hz, 2 H, CH_2), 4.18 (s, 2 H, CH_2), 4.72 (s, 2 H, NCH_2), 7.19–7.90 (m, 7 H, naphthyl), 9.14 (br s, 1 H, NH); ^{13}C NMR (CDCl_3): δ 13.5 (CH_3), 16.3 (SCH_3), 18.7 (CH_2), 32.9 ($\text{CH}_2\text{C}_{10}\text{H}_7$), 43.9 (NCH_2), 113.3 (C-5), 122.6–133.8 (naphthyl), 145.6 (C-6), 151.3 (C-2), 162.9 (C-4).

Antiviral assay procedure. For inhibition of HIV-1 we used the HTLV-IIIB strain and MT-4 cells as previously described.²⁴

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