Synthesis of New Uracil Non-nucleoside Derivatives As Potential Inhibitors of HIV-1

Farag A. El-Essawy, Nasser R. El-Brollosy and Erik B. Pedersen*

Nucleic Acid Center , Department of Chemistry, University of Southern Denmark, Campusvej 55, DK-5230 Odense M, Denmark

Claus Nielsen

Retrovirus Laboratory, Department of Virology, State Serum Institute, Artillerivej 5, DK-2300 Copenhagen, Denmark

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6-(2-Phenylethyl) and 6-cyclohexyl 5-cyanouracils (**1a,b**) were synthesized and reacted with chloromethyl ethyl ether, benzyl chloromethyl ether, chloromethyl methyl sulfide and (2-acetoxyethoxy)methyl bromide. New uracil analogues of (*S*)-DHPA were synthesized by reaction of compounds (**1a,b**) with ((*S*)-2,2-dimethyl-1,3-dioxolane-4-yl) alkyl *p*-toluenesulfonate.

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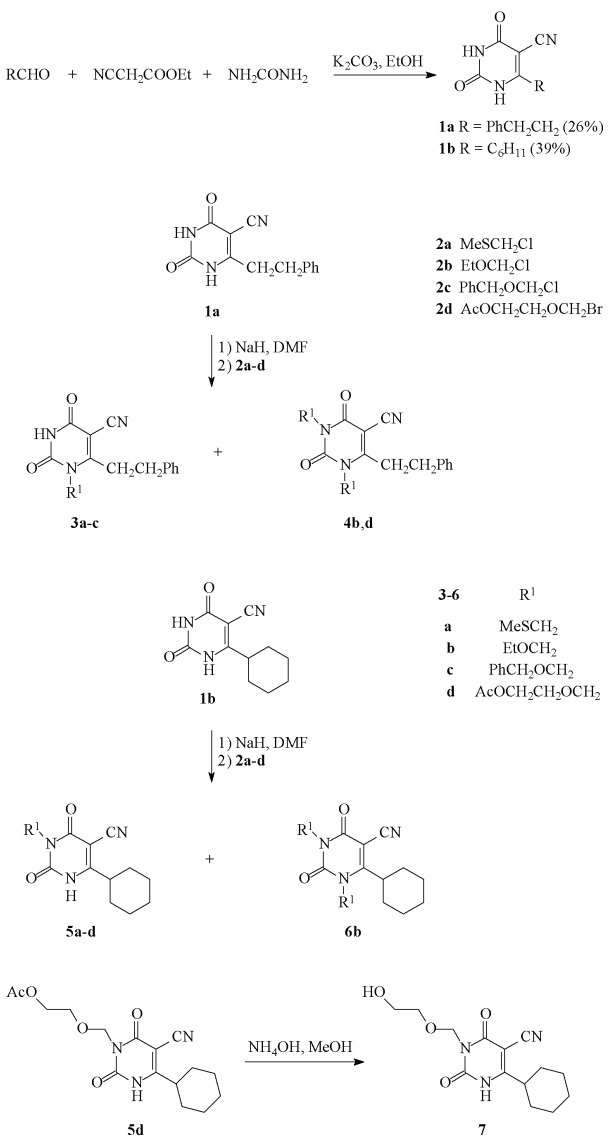
In the fight against human immunodeficiency virus type 1 (HIV-1), the causative agent of the acquired immunodeficiency syndrome (AIDS), several classes of compounds have been identified as highly specific inhibitors of HIV-1 [1]. Among the compounds, a cyclic 6-substituted uracil derivative 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)-thymine (HEPT) is an HIV-1 specific reverse transcriptase inhibitor [2]. This has led to the synthesis of many new analogues [3-6] of which 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil (MKC-442) has been chosen as a candidate for clinical trials with AIDS patients [7]. Structure activity relationship studies showed that a ring structure at C-6 position of the pyrimidine moiety is an important determinant for the anti-HIV-1 activity. On the other hand, De Clercq *et al*. [8,9] reported the antiviral activity of (*S*)-9-(2,3-dihydroxypropyl)adenine (*S*-DHPA). Several viruses including vaccinia, HSV-1 and HSV-2 were inhibited by (*S*)-DHPA. Several acyclonucleosides of DHPA analogues were investigated [10]. Thus, in this report, as a continuation of our interest, in this area [11], we describe a practical synthesis of 5-cyano-6-phenylethyl and 6-cyclohexyl analogues of HEPT and MKC-442.

The commercial aldehydes, 3-phenylpropanal and cyclohexanecarboxaldehyde react with ethyl cyanoacetate and urea according to the procedure of Kambe *et al*. [12], to afford the uracil derivatives **1a,b**. N-1 alkylation was achieved when 5-cyano-6-(2-phenylethyl)uracil (**1a**) was treated with sodium hydride and chloromethyl methylsulfide (**2a**) or benzyl chloromethyl ether (**2c**) in anhydrous DMF. 5-Cyano-1-(methylthiomethyl)-6-(2-phenylethyl)-uracil (**3a**) and 1-benzyloxymethyl-5-cyano-6-(2-phenylethyl)uracil (**3c**) were obtained in 50% and 42% yields, respectively. Alkylation with chloromethyl ethyl ether (**2b**) afforded the corresponding N-1 alkylated **3b** and 1,3-dialkylated **4b** products in 53% and 33% yields, respectively. On alkylation with 2-(acetoxyethoxy)methyl bromide (**2d**) the corresponding 1,3-bis(acetoxyethoxymethyl)uracil

Scheme 1



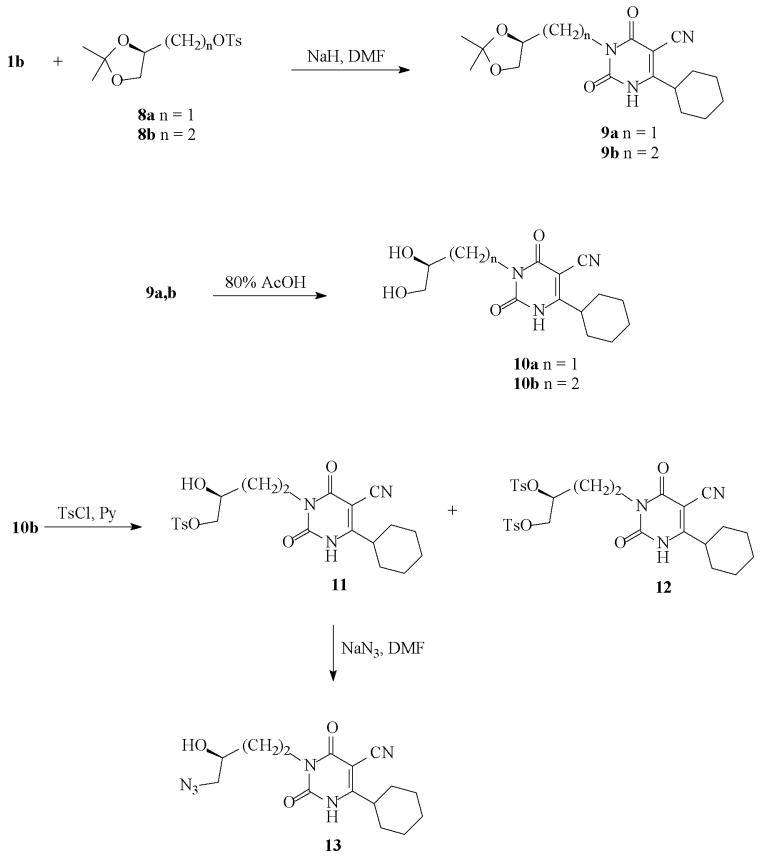
4d was obtained without observing the monoalkylated product. 5-Cyano-6-cyclohexyluracil (**1b**) has more steric hindrance around N-1 than **1a**. Therefore **1b** upon reaction with **2a,c,d** under the same reaction conditions gave the N-3 substituted compounds 5-cyano-6-cyclohexyl-3-(methylthiomethyl)uracil (**5a**), 3-benzyloxymethyl-5-cyano-6-cyclohexyluracil (**5c**) and 3-(acetoxyethoxymethyl)-5-cyano-6-cyclohexyluracil (**5d**), respectively. The product **5d** was deblocked with methanolic ammonia at room temperature to give the 3-(2-hydroxylethoxymethyl) substituted uracil **7** in 60% yield (Scheme 1). Alkylation of **1b** with chloromethyl ethyl ether (**2b**) after treatment with NaH in anhydrous DMF afforded again a 1,3-dialkylated product **6b** together with an N-3 monoalkylated product **5b**. Due to steric hindrance by the 6-cyclohexyl group the N-1 monoalkylated product was never observed.

Compound **1b** was treated with NaH in anhydrous DMF followed by (*R*)-2,2-dimethyl-1,3-dioxolan-4-methyl toluene-4-sulfonate (**8a**), and the homologous 2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl toluene-4-sulfonate (**8b**) to afford the (*S*)-N-3 substituted uracil derivatives **9a**,**b**. Their deprotection was performed by treatment with aqueous acetic acid (80%) at room temperature to afford the corresponding 5-cyano-6-cyclohexyl-3-((*S*)-2,3-dihydroxypropyl)uracil (**10a**), and 5-cyano-6-cyclohexyl-3-((*S*)-3,4-dihydroxybutyl)uracil (**10b**), respectively (Scheme 2). Compound **10b** was tosylated by reaction with tosyl chloride in dry pyridine at 4° to give the monotosylate **11** and the ditosylate **12** after silica chromatography with $CHCl_3$:EtOAc. The monotosylate **11** was treated with sodium azide in dry DMF at 80° to afford the corresponding 3-((*S*)-4-azido-3-hydroxybutyl)-5-cyano-6-cyclohexyluracil (**13**) in 60% yield which showed the azido group at 2102 cm^{-1} in the ir spectrum.

The N-1 alkylated compound **3b** was confirmed by nuclear overhouser effect (NOE) of Ph-CH_2-CH_2 (4%) on irradiation of OCH_2N, while on irradiation of the cyclohexyl protons of compound **5b**, no NOE enhancement of OCH_2N was observed confirming N-3 alkylation in case of the bulky cyclohexyl substitutent in the 6 position of the uracil ring. ^{13}C nmr spectra of compounds **3b**, **5b**, **4b** and **6b** showed O*C*H_2N at N-1 at lower field (73.20-74.13 ppm) and O*C*H_2N at N-3 at higher field (70.63-71.46 ppm).

The test for activity against HIV-1 was performed in MT4 cell cultures infected with either wild type HIV-1 or strain N119 that harboured a substitution of cysteine for tyrosine at position 181. No compounds exhibited activity against HIV-1, except 1-benzyloxymethyl-5-cyano-6-(2-

Scheme 2



phenylethyl)uracil (**3c**) which showed activity (ED_{50} = 1.3 µM; CD_{50} = 25 µM) against wild type HIV-1.

EXPERIMENTAL

Nmr Spectra were recorded at 300 MHz for ^1H and 75 MHz for ^{13}C on a Varian Gemini 2000 NMR 300 MHz spectrometer or on a Bruker AC-250 FT spectrometer at 250 MHz for ^1H and at 62.9 MHz for ^{13}C; δ values are in ppm relative to tetramethylsilane as an internal standard. EI mass spectra were recorded on a Finnigan MAT SSQ 710. MALDI mass spectra were recorded on a Kratos MS50RF spectrometer. Analytical silica gel (tlc) was performed on Merck precoated 60 F_{254} plates. The silica gel (0.040 x 0.063 mm) used for column chromatography was purchased from Merck.

General Procedure for the Preparation of 5-Cyano-6-substituted Uracils (**1a,b**).

A mixture of ethyl cyanoacetate (10.6 g, 0.1 mole), an appropriate aldehyde (0.1 mole), urea (6 g, 0.1 mole) in absolute ethanol (100 ml) containing anhydrous potassium carbonate (13.82 g, 0.1 mole) was heated under reflux for 5 hours. The potassium salt of **1a,b** that precipitates during the reaction was collected by filtration and washed with ethanol. The crude salt was dissolved in warm water and after cooling the solution was acidified with acetic acid, and the precipitate was collected by filtration, washed with water, dried, and recrystallised from acetic acid to give **1a,b**.

5-Cyano-6-(2-phenylethyl)uracil (**1a**).

This compound was obtained as yellow crystals, yield 6.3 g (26%); mp 294-296°; ^1H nmr (DMSO-d_6): δ 2.81-2.85, 2.93-2.98 (2 x m, 4 H, 2 x CH_2), 7.22-7.35 (m, 5 H, H_{arom}), 11.73 (brs, 2 H, 2 x NH); ^{13}C nmr (DMSO-d_6): δ 33.11, 34.04 (2 x CH_2), 86.45 (C-5), 114.33 (CN), 126.53, 128.21, 128.51, 139.09 (Ar), 149.85 (C-2); 161.08 (C-4), 165.63 (C-6); EI ms: m/z 241($M^{+\cdot}$).

5-Cyano-6-cyclohexyluracil (**1b**).

This compound was obtained as yellow crystals, yield 8.5 g (39%); mp 284-286°; ^1H nmr (DMSO-d_6): δ 1.17-1.25, 1.66-1.82 (2 x m, 10 H, 5 x CH_2), 2.66-2.73 (m, 1 H, CH), 11.70 (brs, 2 H, 2 x NH); ^{13}C nmr (DMSO-d_6): δ 24.61, 25.35, 28.35, 42.40 (cyclohexyl), 85.11 (C-5), 114.53 (CN), 150.05 (C-2), 161.34 (C-4), 169.46 (C-6); EI ms: m/z 219 ($M^{+\cdot}$).

General Procedure for the Preparation of Compounds **3a-c**, **4b**,**d**, **5a-d** and **6b**.

To a stirred solution of **1a,b** (1 mmole) in dry *N*,*N*-dimethylformamide (10 ml), 0.04 g (1 mmole) of sodium hydride (60% dispersion in mineral oil) was added. When liberation of hydrogen had ceased (1 hour), the appropriate ether (**2a-d**, 1.1 mmoles) was added, and the reaction mixture was stirred at room temperature for 10-15 hours. The solvent was evaporated *in vacuo*, and the compounds were purified by silica gel column chromatography with chloroform:ethyl acetate (2:1, v/v). Fractions with dialkylated derivatives **4b**,**d** and **6b** were eluated faster than their mono-alkylated counterparts **3a-c** and **5a-d**.

5-Cyano-1-(methylthiomethyl)-6-(2-phenylethyl)uracil (**3a**).

This compound was obtained as colorless crystals, yield 0.15 g (50%); mp 228-230°; ^1H nmr (DMSO-d_6): δ 2.24 (s, 3 H, CH_3), 3.01-3.04 (m, 2 H, CH_2), 3.07-3.12 (m, 2 H, CH_2), (s, 2 H, CH_2), 7.25-7.37 (m, 5 H, H_{arom}), 12.14 (s, 1 H, NH); ^{13}C nmr (DMSO-d_6): δ 14.37 (CH_3), 33.50 (CH_2), 33.93 (CH_2), 47.47 (CH_2), 89.77 (C-5), 114.35 (CN), 126.00, 128.31, 128.52, 138.98 (Ar), 149.95 (C-2), 159.42 (C-4), 165.69 (C-6); EI ms: m/z 301 ($M^{+\cdot}$).

5-Cyano-1-(ethoxymethyl)-6-(2-phenylethyl)uracil (**3b**).

This compound was obtained as colorless crystals, yield 0.16 g (53%); mp 197-200°; ^1H nmr (DMSO-d_6): δ 1.13 (t, 3 H, J = 7.0 Hz, CH_3), 2.94-2.98 (m, 2 H, CH_2), 2.99-3.04 (m, 2 H, CH_2), 3.58 (q, 2 H, J = 7.0 Hz, CH_2), 5.57 (s, 2 H, CH_2), 7.23-7.38 (m, 5 H, H_{arom}), 12.09 (s, 1 H, NH); ^{13}C nmr (DMSO-d_6): δ 14.76 (CH_3), 33.82 (CH_2), 33.87 (CH_2), 64.21 (CH_2), 73.20 (CH_2), 89.74 (C-5), 114.25 (CN), 126.61, 128.16, 128.58, 139.31 (Ar), 150.27 (C-2), 159.09 (C-4), 166.58 (C-6). HRms (MALDI): m/z 322 (M + Na^+): *Anal*. Calcd. for $C_{16}H_{17}N_3NaO_3$: 322.1162. Found: 322.1166.

1-Benzyloxymethyl-5-cyano-6-(2-phenylethyl)uracil (**3c**).

This compound was obtained as colorless crystals, yield 0.15 g (42%); mp 160-163°; ^1H nmr (DMSO-d_6): δ 2.80-2.86 (m 2 H, CH_2), 2.91-2.97 (m, 2 H, CH_2), 4.59 (s, 2 H, CH_2), 5.29 (s, 2 H, CH_2), 7.20-7.38 (m, 10 H, H_{arom}); ^{13}C nmr (DMSO-d_6): δ 33.02 (CH_2), 34.03 (CH_2), 69.76 (CH_2), 70.99 (CH_2), 86.21 (C-5), 114.12 (CN), 126.54, 127.28, 127.46, 128.12, 128.16, 128.49, 137.81, 139.05 (Ar), 149.89 (C-2), 160.32 (C-4), 164.79 (C-6). HRms (MALDI): m/z 384 (M + Na^+): *Anal*. Calcd. for $C_{22}H_{21}N_3NaO_3$: 384.1324. Found: 384.1325.

5-Cyano-6-cyclohexyl-3-(methylthiomethyl)uracil (**5a**).

This compound was obtained as colorless crystals, yield 0.1 g (37%); mp 246-249°; ^1H nmr (deuteriochloroform): δ 1.28-1.89 (m, 10 H, 5 x CH_2), 2.13 (s, 3 H, CH_3), 2.91-2.99 (m, 1 H, CH), 4.99 (s, 2 H, CH_2), 10.42 (bs, 1 H, NH); ^{13}C nmr (deuteriochloroform): δ 16.64 (CH_3), 25.13, 25.48, 29.52, 42.30 ($C_{cyclohexyl}$), 44.98 (CH_2), 87.84 (C-5), 112.75 (CN), 151.24 (C-2), 159.47 (C-4), 167.12 (C-6). HRms (MALDI): m/z 302 (M + Na^+): *Anal.* Calcd. for $C_{13}H_{17}N_3NaO_2S$: 302.0934. Found: 302.0943.

5-Cyano-6-cyclohexyl-3-(ethoxymethyl)uracil (**5b**).

This compound was obtained as colorless crystals, yield 0.12 g (43%); mp 194-195°; ^1H nmr (deuteriochloroform): δ 1.18 (t, 3 H, J = 7.0 Hz, CH_3), 1.33-1.94 (m, 10 H, 5 x CH_2), 2.94-2.99 (m, 1 H, CH), 3.63 (q, 2 H, J = 7.0 Hz, CH_2), 5.39 (s, 2 H, CH_2), 10.7 (s, 1 H, NH); ^{13}C nmr (deuteriochloroform): δ 15.05 (CH_3), 25.01, 25.48, 29.44, 42.32 ($C_{cyclohexyl}$), 66.23 (CH_2), 70.63 (CH_2), 87.58 (C-5), 112.80 (CN), 151.62 (C-2), 159.81 (C-4), 167.60 (C-6). HRms (MALDI): m/z 300 (M + Na^+): *Anal.* Calcd. for $C_{14}H_{19}N_3NaO_3$: 300.1319. Found: 300.1327.

3-(Benzyloxymethyl)-5-cyano-6-cyclohexyluracil (**5c**).

This compound was obtained as colorless crystals, yield 0.17 g (50%); mp 139-142°; ^1H nmr (deuteriochloroform): δ 1.26-1.89 (m, 10 H, 5 x CH_2), 2.87-2.95 (m, 1 H, CH), 4.69 (s, 2 H, CH_2), 5.48 (s, 2 H, CH_2), 7.23-7.44 (m, 5 H, H_{arom}), 10.33 (brs, 1 H, NH); ^{13}C nmr (deuteriochloroform): δ 25.02, 25.44, 29.39, 42.26 ($C_{cyclohexyl}$), 70.62 (CH_2), 72.68 (CH_2), 87.68 (C-5), 112.77 (CN), 127.36, 127.92, 128.36, 137.33 (Ar), 151.40 (C-2), 159.85 (C-4), 167.51 (C-6). HRms (MALDI): m/z 362 (M + Na^+): *Anal.* Calcd. for $C_{19}H_{21}N_3NaO_3$: 362.1475. Found: 362.1482.

3-[(2-Acetoxyethoxy)methyl]-5-cyano-6-cyclohexyluracil (**5d**).

This compound was obtained as colorless crystals, yield 0.1 g (33%); mp 159-161°; ^{1}H nmr (deuteriochloroform): δ 1.31-1.91 (m, 10 H, 5 x CH_2), 2.06 (s, 3 H, CH_3), 2.94 (m, 1 H, CH), 3.84 (t, 2 H, J = 4.9 Hz, CH_2), 4.18 (t, 2 H, J = 4.9 Hz, CH_2), 5.43 (s, 2 H, CH_2), 10.32 (brs, 1 H, NH); ^{13}C nmr (deuteriochloroform): δ 20.80 (CH_3), 25.01, 25.43, 29.47, 42.29 ($C_{cylclohexyl}$), 63.11 (CH_2), 68.79 (CH_2), 71.06 (CH_2), 87.76 (C-5), 112.70 (CN), 151.26 (C-2), 159.85 (C-4), 167.67 (C-6), 170.84 (CO). HRms (MALDI): m/z 358 (M + Na^+): *Anal.* Calcd. for $C_{16}H_{21}N_3NaO_5$: 358.1373. Found: 358.1380.

1,3-Bis(ethoxymethyl)-5-cyano-6-(2-phenylethyl)uracil (**4b**).

This compound was obtained as colorless crystals, yield 0.15 g (42%); mp 124-126°; ^{1}H nmr (deuteriochloroform): δ 1.19, 1.22 (2 x t, 6 H, J = 7.0 Hz, 2 x CH_3), 3.04-3.09 (m, 2 H, CH_2), 3.17-3.23 (m, 2 H, CH_2), 3.64, 3.65 (2 x q, 4 H, J = 7.0 Hz, 2 x CH_2), 5.35 (s, 2 H, CH_2), 5.42 (s, 2 H, CH_2), 7.24-7.37 (m, 5 H, H_{arom}): ^{13}C nmr (deuteriochloroform): δ 14.95, 15.08 (2 x CH_3), 34.24 (CH_2), 34.90 (CH_2), 65.90, 66.34 (2 x CH_2), 71.46 (CH_2), 74.43 (CH_2), 90.93 (C-5), 113.17 (CN), 127.22, 128.31, 128.95, 138.37 (Ar), 150.88 (C-2), 158.77 (C-4), 165.40 (C-6); EI ms: m/z 357 ($M^{+\cdot}$).

1,3-Bis(ethoxymethyl)-5-cyano-6-cyclohexyluracil (**6b**).

This compound was obtained as colorless crystals, yield 0.11 g (33%); mp 119-120°; ^{1}H nmr (deuteriochloroform): δ 1.19, 1.20 (2 x t, 6 H, J = 7.0 Hz, 2 x CH_3), 1.33-2.26 (m, 10 H, 5 x CH_2), 3.01-3.06 (m, 1 H, CH), 3.62, 3.64 (2 x q, 4 H, J = 7.0 Hz, 2 x CH_2), 5.41 (s, 2 H, CH_2), 5.49 (s, 2 H, CH_2); ^{13}C nmr (deuteriochloroform): δ 14.94, 15.04 (2 x CH_3), 24.75, 26.10, 28.89, 40.92 ($C_{cyclohexyl}$), 65.32, 66.33 (2 x CH_2), 71.49, 74.13 (2 x CH_2), 87.85 (C-5), 113.76 (CN), 150.95 (C-2), 159.59 (C-4), 170.23 (C-6). HRms (MALDI): m/z 358 (M + Na^+): *Anal.* Calcd. for $C_{17}H_{25}N_3NaO_4$: 358.1737. Found: 358.1750.

1,3-Bis[(2-acetoxyethoxy)methyl]-5-cyano-6-(2-phenylethyl)uracil (**4d**).

This compound was obtained as an viscous oil, yield 0.2 g (45%); ^{1}H nmr (deuteriochloroform): δ 2.00 (s, 3 H, CH_3), 2.06 (s, 3 H, CH_3), 3.05-3.11 (m, 2 H, CH_2), 3.16-3.22 (m, 2 H, CH_2), 3.85-3.89 (m, 4 H, OCH_2CH_2O), 4.18-4.23 (m, 4 H, OCH_2CH_2O), 5.42 (s, 2 H, CH_2), 5.46 (s, 2 H, CH_2), 7.26-7.37 (m, 5 H, H_{arom}); ^{13}C nmr (deuteriochloroform): δ 20.26, 20.74 (2 x CH_3), 34.23, 34.63 (2 x CH_2), 90.94 (C-5), 112.96 (CN), 127.17, 128.21, 128.88, 138.19 (Ar), 150.48 (C-2), 158.62 (C-4), 165.36 (C-6), 170.54, 170.73 (2 x *C*OCH_3). HRms (MALDI): m/z 496 (M + Na^+): *Anal.* Calcd. for $C_{23}H_{27}N_3NaO_8$: 496.1690. Found: 496.1672.

5-Cyano-6-cyclohexyl-3-(2-hydroxyethoxymethyl)uracil (**7**).

Compound **5d** (60 mg, 0.2 mmole) was dissolved in 50% methanolic ammonia (10 ml) and the mixture was stirred for 5 hours at 50-60°. The solvent was evaporated *in vacuo* and the residue was purified by silica gel column chromatography with chloroform:methanol (95:5, v/v) as the eluent to give **7** (30 mg, 60%) as a colorless viscous oil; ^{1}H nmr (DMSO-d_6): δ 1.19-1.81 (m, 10 H, 5 x CH_2), 2.64-2.68 (m, 1 H, CH), 3.41-3.47 (m, 2 H, CH_2), 3.58-3.62 (m, 2 H, CH_2), 4.62 (br s, 1 H, OH), 5.11 (s, 2 H, CH_2); ^{13}C nmr (DMSO-d_6): δ 24.64, 25.31, 28.39, 42.50 ($C_{cyclohexyl}$), 60.06 (CH_2), 70.19 (CH_2),71.58 (NCH_2O), 84.39 (C-5), 114.77 (CN), 150.78 (C-2), 160.91 (C-4), 169.38 (C-6).

General Procedure for the Preparation of Compounds (**9a,b**).

To a stirred solution of **1b** (0.22 g, 1 mmole) in dry *N*,*N*-dimethylformamide (10 ml), 0.04 g (1mmole) of sodium hydride (60% dispersion in mineral oil) was added. After evolution of hydrogen has completed (1 hour), the appropriate 2,2-dimethyl-1,3-dioxolane-4-yl alkyl *p*-toluenesulfonate (**8a,b**, 1.1 mmoles) was added in one portion, and the reaction mixture was stirred for additional 8-10 hours at 100°. The reaction mixture was cooled to room temperature, and the solvent was evaporated *in vacuo*. The compounds were purified by silica gel column chromatography with chloroform:ethyl acetate (95:5, v/v).

5-Cyano-6-cyclohexyl-3-((*S*)-2,2-dimethyl-1,3-dioxolan-4-ylmethyl)uracil (**9a**).

This compound was obtained as colorless crystals, yield 0.2 g (17%); mp 123-125°; ^{1}H nmr (deuteriochloroform): δ 1.21 (s, 3 H, CH_3), 1.47 (s, 3 H, CH_3), 1.23-1.91 (m, 10 H, 5 x CH_2), 2.94-3.05 (m, 1 H, CH), 3.79 (dd, 1 H, J = 5.3, 8.9 Hz, CH_2), 3.88 (dd, 1 H, J = 4.9, 12.9 Hz, CH_2), 4.06 (dd, 1 H, J = 6.4, 8.8 Hz, CH_2), 4.24 (dd, 1 H, J = 7.3, 12.9 Hz, CH_2), 4.42-4.51 (m, 1 H, CH), 10.55 (brs, 1 H, NH); ^{13}C nmr (deuteriochloroform): δ 25.08, 26.65, 29.47, 42.21 ($C_{cyclohexyl}$), 25.29 (CH_3), 25.45 (CH_3), 44.23 (CH_2), 67.46 (CH_2), 72.46 (CH), 87.85 (C-5), 109.87 ($C(CH_3)_2$), 112.87 (CN), 151.78 (C-2), 159.70 (C-4), 166.90 (C-6).

5-Cyano-6-cyclohexyl-3-[2-((*S*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethyl]uracil (**9b**).

This compound was obtained as colorless crystals, yield 0.1 g (66%); mp 189-191°; ^{1}H nmr (deuteriochloroform): δ 1.30 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 1.30-1.99 (m, 10 H, 5 x CH_2), 2.90-3.01 (m, 1 H, $CH_{cyclohexyl}$), 3.53-3.58 (m, 2 H, CH_2), 3.93-4.27 (m, 5 H, CH, CH_2CH_2), 10.68 (brs, 1 H, NH); ^{13}C nmr (deuteriochloroform): δ 25.15, 26.81, 29.46, 42.15 ($C_{cyclohexyl}$), 25.44, 25.45 (2 x CH_3), 31.02 (CH_2), 38.72 (CH_2), 69.03 (CH_2), 73.94 (CH), 87.68 (C-5), 109.05 ($C(CH_3)_2$), 112.97 (CN), 151.68 (C-2), 159.74 (C-4), 166.72 (C-6).

General Procedure for the Deprotection of Compounds (**9a,b**).

Compound **9a** or **9b** (1mmole) was dissolved in 80% aqueous acetic acid (10 ml) and the solution was stirred overnight at room temperature. The volatiles were evaporated *in vacuo* and the residue was coevaporated with water (3 x 5 ml), and finally with ethanol (3 x 5 ml). The compounds **10a,b** were purified by silica gel column chromatography with chloroform:methanol (95:5, v/v).

5-Cyano-6-cyclohexyl-3-((*S*)-2,3-dihydroxypropyl)uracil (**10a**).

This compound was obtained as a colorless viscous oil, yield 61 mg (60%); ^{1}H nmr (DMSO-d_6): δ 1.17-1.91 (m, 10 H, 5 x CH_2), 2.67-2.72 (m, 1 H, CH), 3.67-3.91 (m, 5 H, CH, 2 x CH_2), 4.78 (brs, 2 H, 2 x OH); ^{13}C nmr (DMSO-d_6): δ 24.73, 25.40, 28,64, 42.50 ($C_{cyclohexyl}$), 43.66 (CH_2), 64.16 (CH_2), 68.18 (CH), 83.89 (C-5), 115.37 (CN), 151.69 (C-2), 161.41 (C-4), 169.19 (C-6). HRms (MALDI): m/z 316 (M + Na^+): *Anal.* Calcd. for $C_{14}H_{19}N_3O_4Na$: 316.1268. Found: 316.1264.

5-Cyano-6-cyclohexyl-3-((*S*)-3,4-dihydroxybutyl)uracil (**10b**).

This compound was obtained as a colorless viscous oil, yield 60 mg (86%); ^{1}H nmr (DMSO-d_6): δ 1.18-1.81(m, 10 H, 5 x CH_2), 2.68-2.72 (m, 1 H, CH), 3.21-3.45 (m, 3 H, CH, CH_2), 3.70-3.79, 3.89-3.98 (2 x m, 2 H, CH_2), 4.53 (brs, 2 H, 2 x OH); ^{13}C nmr (DMSO-d_6): δ 24.14, 24.88, 27.86, 41.75 ($C_{cyclohexyl}$),

30.68 (CH_2), 37.70 (CH_2), 65.33 (CH_2), 69.11 (CH), 84.42 (C-5), 114.15 (CN), 149.53 (C-2), 159.95 (C-4), 167.09 (C-6). HRms (MALDI): m/z 330 ($M + Na^+$): *Anal.* Calcd. for $C_{15}H_{21}N_3O_4Na$: 330.1424. Found: 330.1422.

Toluene-4-sulfonic Acid (*S*)-4-(5-Cyano-6-cyclohexyluracil-3-yl)-2-hydroxybutyl Ester (**11**).

4-Toluenesulfonyl chloride (0.29 g, 1.5 mmoles) was added to an ice cooled solution of compound **10b** (0.19 g, 0.75 mmole) in dry pyridine (10 ml) and left it to stand overnight at 4°, and then 4 hours at room temperature. The pyridine was evaporated *in vacuo*, and the resulting gum was purified by silica gel column chromatography with chloroform:ethyl acetate (1:1, v/v) to give **11**, yield 0.17 g (48%), and **12** yield 0.2 g (40%).

Compound **11** has ^{1}H nmr (deuteriochloroform): δ 1.21-1.93 (m, 12 H, 6 x CH_2), 2.46 (s, 3 H, CH_3), 2.91-2.99 (m, 1 H, CH), 3.25 (brs, 1 H, OH), 3.82-3.85 (m, 1 H, CH), 3.94 (d, 2 H, J = 5.1 Hz,CH_2), 4.07-4.09 (m, 2 H, CH_2), 7.34 (d, 2 H, J = 8.2 Hz, H_{arom}), 7.75 (d, 2 H, J = 8.2 Hz, H_{arom}); ^{13}C nmr (deuteriochloroform): δ 21.66 (CH_3), 25.13, 25.47, 29.67, 42.19 ($C_{cyclohexyl}$), 30.77 (CH_2), 38.15 (CH_2), 66.67 (CH_2), 73.03 (CH), 87.59 (C-5), 112.89 (CN), 127.92, 129.98, 132.37, 145.22 (C_{arom}), 151.07 (C-2), 160.66 (C-4), 167.09 (C-6). HRms (MALDI): m/z 484 ($M + Na^+$): *Anal.* Calcd for $C_{22}H_{27}N_3O_6SNa$: 484.5263. Found: 484.5262.

Compound **12** has ^{1}H nmr (deuteriochloroform): δ 1.26-2.09 (m, 12 H, 6 x CH_2), 2.45, 2.46 (2 x s, 6 H, 2 x CH_3), 2.90-2.98 (m, 1 H, CH), 3.90-3.92 (m, 2 H, CH_2), 4.02-4.11 (m, 2 H, CH_2), 4.68-4.71 (m, 1 H, CH), 7.26-7.35 (m, 4 H, H_{arom}), 7.66-7.70 (m, 4 H, H_{arom}), 9.95 (s, 1 H, NH); ^{13}C nmr (deuteriochloroform): δ 21.69 (2 x CH_3), 25.25, 25.48, 29.65, 42.24 ($C_{cyclohexyl}$), 28.65 (CH_2), 37.37 (CH_2), 68.84 (CH_2), 76.58 (CH), 87.51 (C-5), 112.98 (CN), 127.92, 127.93, 129.99 132.04, 132.94, 145.38 (C_{arom}), 150.83 (C-2), 159.88 (C-4), 167.07 (C-6). HRms (MALDI): m/z 638 ($M + Na^+$): *Anal.* Calcd. for $C_{29}H_{33}N_3O_8S_2Na$: 638.7147. Found: 638.2998.

3-((*S*)-4-Azido-3-hydroxybutyl)-5-cyano-6-cyclohexyluracil (**13**).

A mixture of compound **11** (1 mmole) and sodium azide (1 mmole) in dry *N*,*N*-dimethylformamide (5 ml) was heated for 2 hours at 80°. The solvent was removed *in vacuo* and the remaining syrup was triturated with ice-water. A white precipitate was collected by filtration, and washed with ice-water. The product was recrystallised from ethanol as colorless crystals, 0.03 g (60%); mp 129-131°; ir (KBr): CN 2232, N_3 2102 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.12-1.94 (m, 12 H, 6 x CH_2), 2.90-2.98 (m, 1 H, CH), 3.25-3.30 (m, 2 H, CH_2), 3.71 (brs, 1 H, OH), 4.09-4.16 (m, 2 H, CH_2), 9.81 (brs, 1 H, NH); ^{13}C nmr (deuteriochloroform): δ 25.13, 25.47, 29.71, 42.16 ($C_{cyclohexyl}$), 32.15 (CH_2), 38.36 (CH_2), 56.35 (CH_2), 67.98 (CH), 87.73 (C-5), 112.77 (CN), 151.19 (C-2), 160.62 (C-4), 166.99 (C-6). HRms (MALDI): m/z 638 ($M + Na^+ - N_2$): *Anal.* Calcd for $C_{15}H_{20}N_4O_3Na$: 327.1428. Found: 327.1429.

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* To whom correspondence should be addressed.

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