SYNTHESIS OF RACEMIC 2-HYDROXY-4- AND 2-HYDROXY-5-(HYDROXYMETHYL)CYCLOHEXANE PYRIMIDINE *C*-NUCLEOSIDE ANALOGUES

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The oxirane ring opening of 3-[(benzyloxy)methyl]-7-oxabicyclo[4.1.0]heptane with sodium salt of diethyl malonate followed by treatment with TsOH gave (3a*R**,6*R**,7a*S**)-6-[(benzyloxy)methyl]hexahydro-1-benzofuran-2(3*H*)-one (**3a**) and (3a*R**,5*R**,7a*S**)-5-[(benzyloxy)methyl]hexahydro-1-benzofuran-2(3*H*)-one (**3b**). Lactones **3a** and **3b** were formylated and then treated with thiourea or guanidine to give, after deprotection, racemic 5-[2-hydroxy-4- and 2-hydroxy-5-(hydroxymethyl)cyclohexyl]-2-thiouracil (**5a** and **5b**) or -isocytosine (**12a** and **12b**). Simple transformations of the 2-thiouracil derivative led to uracil (**7a** and **7b**), 4-thiouracil (**9a** and **9b**), and cytosine derivatives (**10a** and **10b**).

Keywords: Carbanucleosides; Carbocyclic nucleosides; Nucleosides; Cyclohexanes; *C*-Nucleosides; Pyrimidines.

Syntheses of new modified nucleosides as antiviral and cytostatic agents has remained a very active field of research. *C*-Nucleosides are a class of nucleosides in which the heterocycle is connected to a sugar moiety by a C–C bond instead of the C–N bond. This modification results in resistance to the chemical and the enzymatic hydrolytic cleavage of the glycosidic bond. Moreover, naturally occurring *C*-nucleosides[1] such as showdomycin, formycins, oxazinomycin, and pyrazomycin exhibit interesting biological activities. Also, several biologically active *C*-nucleosides such as 9-deazaadenosine[2], pseudoisocytidine[3], and thiazofurin[4] were synthesized. As the hexitol nucleosides exhibit antiviral activity[5], a variety of their carbocyclic congeners and cyclohexene analogues were prepared[6]. Recently, a potent antiviral activity of such compounds was found[6j,6k]. On the basis of interesting chemical and biological properties of these carbocyclic nucleosides and *C*-nucleosides, it was of interest to synthesize carbocyclic *C*-nucleosides.

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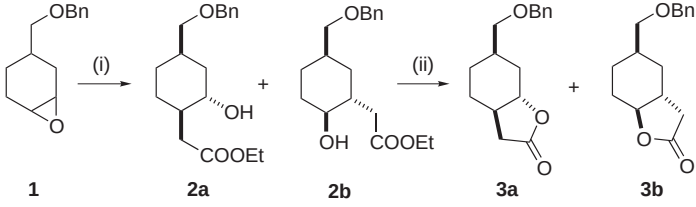
Only a few carbocyclic *C*-nucleosides have been synthesized[7]. No carbahexopyranosyl nucleoside analogues have been reported so far.

This communication is a part of our program[8,6r,6s] aimed at the syntheses and structure–antiviral activity study of carbocyclic nucleosides, dealing with the synthesis of racemic 5-[2-hydroxy-4- and 2-hydroxy-5-(hydroxymethyl)cyclohexyl]pyrimidine *C*-nucleosides as a novel group of unconvential nucleoside analogues not yet synthesized.

Our synthetic strategy was based on nucleophilic opening of oxirane ring with sodium salt of diethyl malonate and on subsequent construction of the 5-substituted pyrimidine base. As a starting material was chosen racemic 3-[(benzyloxy)methyl]-7-oxabicyclo[4.1.0]heptane (**1**), which is easily available as a mixture of *exo* and *endo* isomers[9b]. Oxirane **1** was refluxed with sodium salt of diethyl malonate in ethanol to afford a mixture of racemic acetic acid derivatives **2a** and **2b** (Scheme 1). None of the expected malonate diester derivative was found in the reaction mixture (cf. analogous reaction in[10]). Attempts to separate this mixture using chromatographic techniques were not successful. The mixture of hydroxy esters was converted to lactones **3a** and **3b** by heating with TsOH in toluene. Lactones **3a** (35%) and **3b** (41%) were separated by chromatography on a silica gel column. The regioselectivity of the ring opening reaction and ratio of the isomers was consistent with literature data[9].



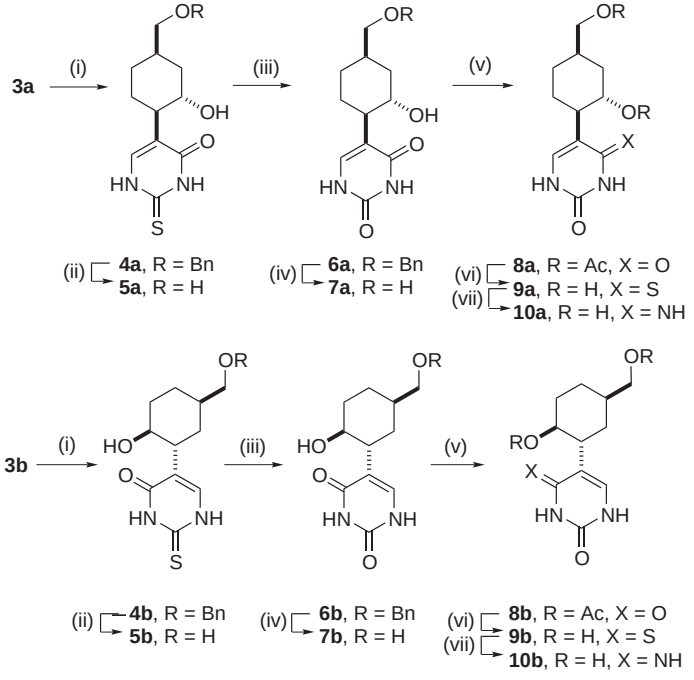
(i) diethyl malonate, EtONa/EtOH, reflux, 52% of mixture **2a** and **2b**
(ii) TsOH/toluene, 125 °C, 35% of **3a**, 41% of **3b**.

SCHEME 1

The key intermediates **4a** and **4b** were prepared in two steps (Scheme 2). Condensation of lactone **3a** or **3b** with ethyl formate in the presence of *t*-BuOK followed by the treatment with thiourea in refluxing propan-2-ol and then in DMF at 145 °C afforded thiouracil **4a** (55%) or **4b** (56%). Deprotection of the benzyl derivatives **4a** and **4b** with ethane-1,2-dithiol and boron trifluoride[11] gave free nucleosides **5a** (38%) and **5b** (23%), respectively. Hydrolysis of the 2-thiouracils **4a** and **4b** with chloroacetic acid

led to uracils **6a** and **6b**. Free nucleoside analogues **7a** and **7b** were easily obtained by transfer hydrogenation[12].

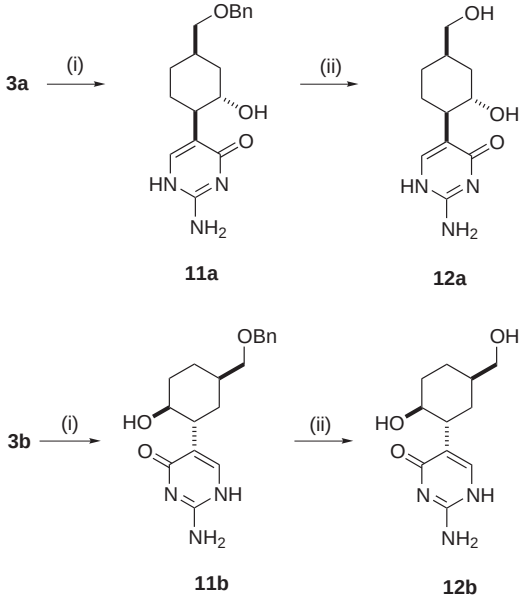
Nucleosides **7a** and **7b** served as a starting material for the synthesis of 4-thiouracils **9a**, **9b** and cytosines **10a**, **10b**. Acetylation of the compound **7a** or **7b** afforded acetate **8a** (91%) or **8b** (88%) which was thionated with Lawesson's reagent in 1,2-dichloroethane and then deprotected with methanolic sodium methoxide to give 4-thiouracil **9a** (53%) or **9b** (54%). As methanolysis of acetyl groups proceeded slowly, the reaction was performed at elevated temperature (55 °C). Compounds **9a** and **9b** were treated with liquid ammonia in an autoclave at 85 °C to yield cytosines **10a** (56%) and **10b** (52%), respectively.



(i) 1. HCOOEt, *t*-BuOK/Et_2O, r.t., 2. thiourea/*i*-PrOH, reflux, then DMF, 145 °C, 55% of **4a**, 56% of **4b**;
(ii) ethane-1,2-dithiol, BF_3-Et_2O, r.t., 38% of **5a**, 23% of **5b**;
(iii) chloroacetic acid/H_2O–DMF, reflux, 78% of **6a**, 83% of **6b**;
(iv) cyclohexene, $Pd(OH)_2$/DMF, 80 °C, 75% of **7a**, 78% of **7b**;
(v) Ac_2O/DMAP/CH_3CN, r.t., 91% of **8a**, 88% of **8b**;
(vi) 1. Lawesson's reagent/dichloroethane, reflux, 2. MeONa/MeOH, 55 °C, 53% of **9a**, 54% of **9b**;
(vii) liq. NH_3, MeOH, 85 °C, 56% of **10a**, 52% of **10b**

SCHEME 2

Lactones **3a** and **3b** were also used for preparation of isocytosines **12a** and **12b** (Scheme 3). Lactones **3a** or **3b** was formylated with ethyl formate in the presence of *t*-BuOK and then treated with guanidine (generated from guanidine hydrochloride in situ). The obtained isocytosines **11a** (44%) and **11b** (45%) were easily deprotected by transfer hydrogenation.



(i) 1. HCOOEt, *t*-BuOK/Et_2O, r.t., 2. guanidine hydrochloride, *t*-BuOK/*i*-PrOH, reflux, 44% of **11a**, 45% of **11b**; (ii) cyclohexene, $Pd(OH)_2$/DMF, 80°C, 79% of **12a**, 85% of **12b**.

SCHEME 3

Assignment of the relative configuration to the structures of prepared compounds was accomplished by analysis of coupling constants in ^{1}H NMR spectra (cf. lit.[6r]). Assignment of the signals to protons and carbon atoms in NMR spectra of compounds **10a** and **10b** was also confirmed by HETCOR.

The target nucleoside analogues **5a**, **5b**, **7a**, **7b**, **9a**, **9b**, **10a**, **10b**, **12a**, and **12b** were tested for cytostatic activity (inhibition of cell growth of the following cell cultures: mouse leukemia L1210 cells, human promyeolocytic leukemia HL60 cells, human cervix carcinoma HeLaS3 cells). All the compounds were inactive[13]. Further antiviral testing of this series of compounds is under way.

In conclusion, new racemic 2-hydroxy-4- and 2-hydroxy-5-(hydroxymethyl)cyclohexane analogues of pseudouridine, 2-thiopseudouridine, pseudoisocytidine, and pseudocytidine were prepared from 3-(benzyloxy)methyl-7-oxabicyclo[4.1.0]heptane. The obtained results demonstrate that inexpensive cyclohexane epoxides may be used in some cases as starting material for the synthesis of racemic carbocyclic nucleosides.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. NMR spectra (δ, ppm; *J*, Hz) were measured on a Varian Unity 500 instrument (500 MHz for ^{1}H and 125.7 MHz for ^{13}C) in hexadeuteriated dimethyl sulfoxide and referenced to the solvent signal (δ 2.50 and 39.70, respectively). Mass spectra were measured on a ZAB-EQ (VG Analytical) spectrometer using the FAB (ionization with Xe, accelerating voltage 8 kV, thioglycerol–glycerol (3:1) mixture or bis(2-hydroxyethyl) disulfide was used as a matrix). Column chromatography was performed on Silica gel 60 (Fluka) and thin-layer chromatography (TLC) on Silufol UV 254 foils (Kavalier, Votice). Solvents were evaporated at 2 kPa and bath temperature 30–60 °C; compounds were dried at 13 Pa and 50 °C.

Ethyl {(1*R**,2*S**,4*R**)-4-[(Benzyloxy)methyl]-2-hydroxycyclohexyl}acetate (**2a**) and
Ethyl {(1*R**,2*S**,5*R**)-5-[(Benzyloxy)methyl]-2-hydroxycyclohexyl}acetate (**2b**)

Oxirane **1** (9.8 g, 45 mmol) was co-evaporated with toluene (3 × 15 ml) and dissolved in absolute ethanol (30 ml). This solution was added in three portions during 1 h to the solution of sodium salt of diethyl malonate in ethanol, which was previously prepared from ethanol (80 ml), sodium (1.85 g, 80.4 mmol) and diethyl malonate (14 ml, 92 mmol). The reaction mixture was refluxed in argon atmosphere for 12 h. After cooling, the reaction mixture was neutralized with 9% aqueous H_2SO_4 and partitioned between water (100 ml) and ethyl acetate (300 ml). The water layer was extracted with ethyl acetate (2 × 300 ml). Combined organic layers were dried over anhydrous sodium sulfate and evaporated. The residue was chromatographed on a silica gel column (780 g) in toluene–ethyl acetate (2:1). It was obtained 7.08 g (52%) of colorless oil as a mixture of isomers **2a** and **2b**. For $C_{18}H_{26}O_4$ (306.4) calculated: 70.56% C, 8.55% H; found: 70.45% C, 8.65% H. FAB MS, *m*/*z* (rel.%): 307 (20) [M + H], 289 (30) [M + H – H_2O], 91 (100) [Bn]. ^{1}H NMR: 1.05–2.15 m, 20 H (2 × cyclohexane, 2 × C**H**$_2$COOEt); 1.15 t, 3 H, *J* = 7.3 and 1.16 t, 3 H, *J* = 7.3 (2 × CH_3); 3.11–3.42 m, 6 H (2 × OCH_2, 2 × H-2); 4.03 q, 2 H, *J* = 7.3 and 4.04 q, 2 H, *J* = 7.3 (2 × $COCH_2$); 4.44 s, 1 H and 4.45 s, 1 H (OCH_2Ph); 4.52 d, 1 H, *J* = 4.3 and 4.54 d, 1 H, *J* = 4.3 (2 × OH); 7.22–7.40 m, 10 H (2 × Ph).

(3a*R**,6*R**,7a*S**)-6-[(Benzyloxy)methyl]hexahydro-1-benzofuran-2(3*H*)-one (**3a**) and
(3a*R**,5*R**,7a*S**)-5-[(Benzyloxy)methyl]hexahydro-1-benzofuran-2(3*H*)-one (**3b**)

A mixture of **2a** and **2b** (2.1 g, 6.86 mmol) and TsOH (85 mg, 0.49 mmol) in toluene (125 ml) was heated (bath 125 °C) for 3 h. The formed ethanol was continuously distilled off. After cooling, the reaction mixture was washed with saturated aqueous sodium hydrogencarbonate (2 × 50 ml). The organic layer was dried over anhydrous sodium sulfate and evap-

orated. The residue was chromatographed on a silica gel column (350 g) in toluene–ethyl acetate (7:1) to give pure isomers and a mixture of isomers. The mixed fraction was re-chromatographed under the same conditions. It was obtained 630 mg (35%) lactone **3a** and 730 mg (41%) lactone **3b**, both as colorless oils.

(3aR,6R*,7aS*)-6-[(Benzyloxy)methyl]hexahydro-1-benzofuran-2(3H)-one* (**3a**): for $C_{16}H_{20}O_3$ (260.3) calculated: 73.82% C, 7.74% H; found: 73.32% C, 7.94% H. FAB MS, *m/z* (rel.%): 261 (1) [M + H], 91 (100) [Bn], 77 (5) [Ph]. ^{1}H NMR: 1.38 brqd, 1 H, *J*(4ax,3a ax) = 11.2, *J*(4ax,5eq) = 3.7, *J*(4ax,5ax) = J_{gem} = 13.6 (H-4ax); 1.49 tdd, 1 H, *J*(5ax,4eq) = 3.8, *J*(5ax,6eq) = 5.5, (H-5ax); 1.60 td, 1 H, *J*(7ax,6eq) = 5.6, *J*(7ax,7a ax) = J_{gem} = 12.1 (H-7ax); 1.70 m, 2 H (H-5eq, H-6eq); 1.86 m, 1 H, *J*(3a ax,4eq) = 3.2, *J*(3a ax,7a ax) = 10.7 (H-3a ax); 2.16 ddt, 1 H, *J*(7eq,5eq) = *J*(7eq,6eq) = 2.1, *J*(7eq,7a ax) = 4.0 (H-7eq); 2.27 m, 1 H (H-6eq); 2.31 dd, 2 H, *J*(C**H**HCO,3a ax) = 12.6, J_{gem} = 16.0 (C**H**HCO); 2.37 dd, 2 H, *J*(CH**H**CO,3a ax) = 7.0 (CH**H**CO); 3.45 dd and 3.47 dd, 2 H, *J*(CH_2,6eq) = 7.6, J_{gem} = 12.6 (CH_2OBn); 4.00 ddd, 1 H (H-7a ax); 4.52 s, 2 H (OCH_2Ph); 7.23–7.40 m, 5 H (Ph).

(3aR,5R*,7aS*)-5-[(Benzyloxy)methyl]hexahydro-1-benzofuran-2(3H)-one* (**3b**): for $C_{16}H_{20}O_3$ (260.3) calculated: 73.82% C, 7.74% H; found: 73.50% C, 8.03% H. FAB MS, *m/z* (rel.%): 261 (1) [M + H], 91 (100) [Bn], 77 (5) [Ph]. ^{1}H NMR: 1.45 ddd, 1 H, *J*(4ax,5eq) = 5.3, *J*(4ax,3a ax) = 12.2, J_{gem} = 12.7 (H-4ax); 1.54 m, 2 H (H-6ax, H-7ax); 1.82 brdq, 1 H, *J*(6eq,4eq) ≈ *J*(6eq,5eq) ≈ *J*(6eq,7eq) ≈ 2.6, J_{gem} = 12.4 (H-6eq); 1.88 ddt, 1 H, *J*(4eq,5eq) = 2.1, *J*(4eq,3a ax) = 4.0 (H-4eq); 1.91 ddd, 1 H, *J*(7eq,7a ax) = 3.9, J_{gem} = 13.2 (H-7eq); 1.98 m, 1 H, *J*(3a ax,C**H**HCO) = 7.2, *J*(3a ax,7a ax) = 10.6, *J*(3a ax,CH**H**CO) = 12.2 (H-3a ax); 2.05 m, 1 H (H-5eq); 2.28 dd, 1 H, J_{gem} = 16.0 (C**H**HCO); 2.33 dd, 1 H (CH**H**CO); 3.46 d, 2 H, *J*(CH_2,5eq) = 7.7 (CH_2OBn); 3.83 td, 1 H, *J*(7a ax,5eq) = 3.9, *J*(7a ax,7ax) = 10.6 (H-7a ax); 4.52 s, 2 H (OCH_2Ph); 7.23–7.41 m, 5 H (Ph).

5-{(1*R**,2*S**,4*R**)-4-[(Benzyloxy)methyl]-2-hydroxycyclohexyl}-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-one (**4a**) and 5-{(1*R**,2*S**,5*R**)-5-[(Benzyloxy)methyl]-2-hydroxycyclohexyl}-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-one (**4b**)

Lactone **3a** or **3b** (550 mg, 2.12 mmol) was co-evaporated with toluene (3 × 15 ml). A solution of lactone and ethyl formate (0.86 ml, 10.6 mmol) in ether (20 ml) was added dropwise with stirring to a suspension potassium *tert*-butoxide (832 mg, 7.42 mmol) in ether (25 ml) in an argon atmosphere at 0 °C. The solution was stirred at room temperature for 22 h and evaporated. The residue was dissolved in propan-2-ol (40 ml), thiourea (322 mg, 4.23 mmol) was added and the reaction mixture was refluxed in an argon atmosphere for 9 h and then evaporated. The residue was dissolved in dimethylformamide (40 ml) and the solution was heated (bath 145 °C) in argon atmosphere for 10 h. After cooling, the reaction mixture was neutralized with 10% hydrochloric acid and evaporated. The residue was decanted with water (3 × 75 ml) and the solid precipitate was filtered off and crystallized from ethanol.

5-{(1R,2S*,4R*)-4-[(Benzyloxy)methyl]-2-hydroxycyclohexyl}-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-one* (**4a**): yield 403 mg (55%), m.p. 251–254 °C (with decomposition). For $C_{18}H_{22}N_2O_3S$ (346.4) calculated: 62.40% C, 6.40% H, 8.09% N, 9.26% S; found: 62.39% C, 6.56% H, 7.97% N, 9.11% S. FAB MS, *m/z* (rel.%): 347 (25) [M + H], 329 (5) [M + H – H_2O], 91 (100) [Bn]. ^{1}H NMR: 1.32 ddd, 1 H, *J*(3′ax,4′) = 5.0, *J*(3′ax,2′) = 11.0, J_{gem} = 12.8 (H-3′ax); 1.38 tt, 1 H, *J*(5′ax,6′eq) = *J*(5′ax,4′) = 4.5, *J*(5′ax,6′ax) = J_{gem} = 13.1 (H-5′ax); 1.46 dq, 1 H, *J*(6′eq,5′eq) = 3.5, *J*(6′eq,1′) = 4.2, J_{gem} = 13.2 (H-6′eq); 1.53 btdd, 1 H, *J*(6′ax,5′eq) = 3.2, *J*(6′ax,1′) = 12.2 (H-6′ax); 1.60 dm, 1 H, *J*(5′eq,3′eq) ≈ 3.0, *J*(5′eq,4′) ≈ 4.0 (H-5′eq); 1.88 dm,

1 H, *J*(3′eq,4′) = 3.0, *J*(3′eq,2′) = 4.5 (H-3′eq); 2.11 m, 1 H (H-4′); 2.28 brtd, 1 H, *J*(1′,2′) = 10.0 (H-1′); 3.46 dd, 1 H, *J*(CH,4′) = 7.9, J_{gem} = 9.5 (OC**H**H); 3.49 dd, 1 H, *J*(CH,4′) = 7.3 (OCH**H**); 3.71 brtt, 1 H, *J*(2′,OH) = 5.1 (H-2′); 4.42 d, 1 H (OH); 4.47 s, 2 H (OCH_2Ph); 7.17 d, 1 H, *J*(CH,NH-1) = 5.2 (H-6); 7.25–7.45 m, 5 H (Ph); 12.19 brd, 1 H (NH-1); 12.30 s, 1 H (NH-3).

5-{(1R,2S*,5R*)-5-[(Benzyloxy)methyl]-2-hydroxycyclohexyl}-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-one* (**4b**): yield 411 mg (56%), m.p. 256–258 °C (with decomposition). For $C_{18}H_{22}N_2O_3S \cdot 1/3\ H_2O$ (352.5) calculated: 61.34% C, 6.48% H, 7.95% N, 9.10% S; found: 61.47% C, 6.46% H, 7.89% N, 9.35% S. FAB MS, *m/z* (rel.%): 347 (13) [M + H], 91 (100) [Bn]. ^{1}H NMR: 1.26 tdd, 1 H, *J*(3′ax,4′eq) = 4.2, *J*(3′ax,2′) = 10.2, *J*(3′ax,4′ax) = J_{gem} = 13.6 (H-3′ax); 1.47 tt, 1 H, *J*(4′ax,3′eq) = *J*(4′ax,5′) = 4.3, J_{gem} = 13.6 (H-4′ax); 1.60 ddd, 1 H, *J*(6′ax,5′) = 4.5, *J*(6′ax,1′) = 10.6, J_{gem} = 13.6 (H-6′ax); 1.66 m, 1 H (H-6′eq); 1.66 m, 1 H (H-3′eq); 1.69 dm, 1 H (H-4′eq); 1.93 m, 1 H (H-5′); 2.41 td, 1 H, *J*(1′,6′eq) = 5.6, *J*(1′,2′) = 9.8 (H-1′); 3.42 dd, 1 H, *J*(CH,5′) = 7.8, J_{gem} = 9.2 (OC**H**H); 3.46 dd, 1 H, *J*(CH,5′) = 7.3 (OCH**H**); 3.57 brtt, 1 H, *J*(2′,3′eq) = 4.8, *J*(2′,OH) = 5.1 (H-2′); 4.46 d, 1 H (OH); 4.49 s, 2 H (OCH_2Ph); 7.11 s, 1 H (H-6); 7.25–7.45 m, 5 H (Ph); 12.17 brs and 12.30 brs, 2 × 1 H (2 × NH).

5-[(1*R**,2*S**,4*R**)-2-Hydroxy-4-(hydroxymethyl)cyclohexyl]-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-one (**5a**) and 5-[(1*R**,2*S**,5*R**)-2-Hydroxy-5-(hydroxymethyl)cyclohexyl]-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-one (**5b**)

Thiouridine **4a** or **4b** (250 mg, 0.72 mmol) was suspended in ethane-1,2-dithiol (6 ml) and to the mixture BF_3–Et_2O (1 ml, 7.9 mmol) was added. The reaction mixture was stirred for 5.5 h, then water was added and mixture was evaporated. The residue was co-evaporated with methanol (2 × 10 ml) and DMF (2 × 15 ml). The product was isolated by chromatography on a silica gel column (40 g) in ethyl acetate–acetone–ethanol–water (100:15:6:4) and crystallization.

5-[(1R,2S*,4R*)-2-Hydroxy-4-(hydroxymethyl)cyclohexyl]-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-one* (**5a**): yield 71 mg (38%) after crystallization from propan-2-ol, m.p. > 260 °C. For $C_{11}H_{16}N_2O_3S$ (256.3) calculated: 51.54% C, 6.29% H, 10.93% N, 12.51% S; found: 51.40% C, 6.74% H, 10.52% N, 12.15% S. FAB MS, *m/z* (rel.%): 257 (18) [M + H], 91 (100). ^{1}H NMR: 1.27 ddd, 1 H, *J*(3′ax,4′) = 5.6, *J*(3′ax,2′) = 11.0, J_{gem} = 13.4 (H-3′ax); 1.31 tt, 1 H, *J*(5′ax,6′eq) ≈ *J*(5′ax,4′) ≈ 4.4, *J*(5′ax,6′ax) ≈ J_{gem} ≈ 13.2 (H-5′ax); 1.42 brdq, 1 H, *J*(6′eq,5′eq) = 3.5, *J*(6′eq,1′) ≈ *J*(6′eq,5′ax) ≈ 4.0, J_{gem} = 13.2 (H-6′eq); 1.54 tdd, 1 H, *J*(6′ax,5′eq) = 3.6, *J*(6′ax,1′) = 12.0 (H-6′ax); 1.61 dm, 1 H, *J*(5′eq,3′eq) ≈ 2.6, *J*(5′eq,4′) ≈ 3.8 (H-5′eq); 1.86 dm, 1 H, *J*(3′eq,4′) = 2.7, *J*(3′eq,2′) = 4.3 (H-3′eq); 1.87 m, 1 H (H-4′); 2.24 ddd, 1 H, *J*(1′,2′) = 9.9 (H-1′); 3.38 ddd, 1 H, *J*(CH,OH) = 5.2, *J*(CH,4′) = 7.9, J_{gem} = 10.5 (OC**H**H); 3.43 ddd, 1 H, *J*(CH,4′) = 7.0 (OCH**H**); 3.70 dddd, 1 H, *J*(2′,OH) = 5.2 (H-2′); 4.37 d, 1 H (OH); 4.42 t, 1 H (CH_2OH); 7.16 s, 1 H (H-6); 12.20 brs and 12.30 brs, 2 × 1 H (2 × NH). ^{13}C NMR: 26.20 (C-5′); 26.38 (C-6′); 36.74 (C-3′); 36.88 (C-4′); 45.20 (C-1′); 63.00 (OCH_2); 66.41 (C-2′); 120.68 (C-5); 138.96 (C-6); 162.39 (C-4); 174.86 (C-2).

5-[(1R,2S*,5R*)-2-Hydroxy-5-(hydroxymethyl)cyclohexyl]-2-thioxo-1,2,3,4-tetrahydropyrimidin-4-one* (**5b**): yield 43 mg (23%) after crystallization from ethanol, m.p. > 260 °C. For $C_{11}H_{16}N_2O_3S$ (256.3) calculated: 51.54% C, 6.29% H, 10.93% N, 12.51% S; found: 51.11% C, 6.30% H, 10.74% N, 12.15% S. FAB MS, *m/z* (rel.%): 257 (100) [M + H], 239 (28) [M + H – H_2O]. HRMS (FAB): for $C_{11}H_{16}N_2O_3S$ calculated: 257.0959; found: 257.0960. ^{1}H NMR: 1.28 tdd, 1 H, *J*(3′ax,4′eq) = 3.6, *J*(3′ax,2′) = 10.0, *J*(3′ax,4′ax) ≈ J_{gem} ≈ 13.2 (H-3′ax);

1.41 tt, 1 H, *J*(4′ax,3′eq) ≈ *J*(4′ax,5′) ≈ 4.4, J_{gem} = 13.0 (H-4′ax); 1.58 m, 2 H (H-6′ax, H-6′eq); 1.62 brdq, 1 H, *J* ≈ 4.2 (3×) (H-3′eq); 1.67 m, 1 H (H-5′); 1.68 m, 1 H, *J* ≈ 3.4 (4×) (H-4′eq); 2.41 td, 1 H, *J*(1′,6′ax) ≈ *J*(1′,6′eq) = 8.0, *J*(1′,2′) = 9.8 (H-1′); 3.37 ddd, 1 H, *J*(CH,OH) = 5.4, *J*(CH,5′) = 7.8, J_{gem} = 10.5 (OC**H**H); 3.43 ddd, 1 H, *J*(CH,5′) = 7.1 (OCH**H**); 3.56 brtt, 1 H, *J*(2′,3′eq) ≈ *J*(2′,OH) ≈ 4.4 (H-2′); 4.41 d, 1 H (OH); 4.43 t, 1 H (CH_2OH); 7.13 s, 1 H (H-6); 12.17 brs and 12.30 brs, 2 × 1 H (2 × NH). ^{13}C NMR: 25.35 (C-4′); 30.84 (C-3′); 31.52 (C-6′); 35.43 (C-5′); 39.37 (C-1′); 62.37 (OCH_2); 70.79 (C-2′); 120.68 (C-5); 138.85 (C-6); 162.35 (C-4); 174.74 (C-2).

5-{(1*R**,2*S**,4*R**)-4-[(Benzyloxy)methyl]-2-hydroxycyclohexyl}pyrimidine-2,4(1*H*,3*H*)-dione (**6a**) and 5-{(1*R**,2*S**,5*R**)-5-[(Benzyloxy)methyl]-2-hydroxycyclohexyl}pyrimidine-2,4(1*H*,3*H*)-dione (**6b**)

A suspension of **4a** or **4 b** (120 mg, 0.35 mmol) in 10% aqueous chloroacetic acid (10 ml) and dimethylformamide (2 ml) was refluxed with stirring for 19 h (suspension dissolved). After cooling to room temperature, the solid precipitate was filtered off and washed with water, ether and dried. Recrystallization from acetone gave analytically pure sample.

5-{(1R,2S*,4R*)-4-[(Benzyloxy)methyl]-2-hydroxycyclohexyl}pyrimidine-2,4(1H,3H)-dione* (**6a**): yield 89 mg (78%), m.p. 232–236 °C. For $C_{18}H_{22}N_2O_4$ (330.4) calculated: 65.44% C, 6.71% H, 8.48% N; found: 65.00% C, 6.78% H, 8.35% N. FAB MS, *m/z* (rel.%): 331 (31) [M + H], 313 (5) [M + H – H_2O], 91 (100) [Bn]. ^{1}H NMR: 1.22–1.72 m, 3 H (H-5′eq, H-6′ax, H-6′eq); 1.32 ddd, 1 H, *J* = 4.9, 11.0, 12.9 (H-3′ax); 1.37 tt, 1 H, *J* = 4.8, 13.0 (H-5′ax); 1.87 m, 1 H (H-3′eq); 2.10 m, 1 H (H-4′); 2.24 td, 1 H, *J* = 5.0, 10.9, 11.0 (H-1′); 3.45 dd, 1 H, *J*(CH,4′) = 7.7, J_{gem} = 9.5 (OC**H**H); 3.48 dd, 1 H, *J*(CH,4′) = 7.1 (OCH**H**); 3.70 brtt, 1 H, *J* = 4.8, *J*(2′,OH) = 5.4, *J* = 10.0 (H-2′); 4.32 d, 1 H (OH); 4.47 s, 2 H (OCH_2Ph); 7.10 s, 1 H (H-6); 7.24–7.45 m, 5 H (Ph); 10.63 s and 10.90 brs, 2 × 1 H (2 × NH).

5-{(1R,2S*,5R*)-5-[(Benzyloxy)methyl]-2-hydroxycyclohexyl}pyrimidine-2,4(1H,3H)-dione* (**6b**): yield 95 mg (83%), m.p. 233–235.5 °C. For $C_{18}H_{22}N_2O_4$ (330.4) calculated: 65.44% C, 6.71% H, 8.48% N; found: 64.99% C, 6.72% H, 8.31% N. FAB MS, *m/z* (rel.%): 331 (21) [M + H], 313 (1) [M + H – H_2O], 91 (100) [Bn]. ^{1}H NMR: 1.26 tdd, 1 H, *J*(3′ax,4′eq) = 3.7, *J*(3′ax,2′) = 10.2, *J*(3′ax,4′ax) = J_{gem} = 13.0 (H-3′ax); 1.46 tt, 1 H, *J*(4′ax,3′eq) = 3.7, *J*(4′ax,5′) = 4.2, J_{gem} = 13.0 (H-4′ax); 1.50 ddd, 1 H, *J*(6′ax,5′) = 4.9, *J*(6′ax,1′) = 10.0, J_{gem} = 13.6 (H-6′ax); 1.64 m, 2 H (H-6′eq, H-3′eq); 1.69 dm, 1 H (H-4′eq); 1.92 m, 1 H (H-5′); 2.37 td, 1 H, *J*(1′,6′eq) = 5.7, *J*(1′,2′) = 9.9 (H-1′); 3.42 dd, 1 H, *J*(CH,5′) = 7.8, J_{gem} = 9.4 (OC**H**H); 3.47 dd, 1 H, *J*(CH,5′) = 7.2 (OCH**H**); 3.55 brtt, 1 H, *J*(2′,3′eq) = 4.0, *J*(2′,OH) = 5.2 (H-2′); 4.37 d, 1 H (OH); 4.49 s, 2 H (OCH_2Ph); 7.06 d, 1 H, *J*(CH,NH-1) = 5.6 (H-6); 7.25–7.45 m, 5 H (Ph); 10.61 d, 1 H (NH-1); 10.90 s, 1 H (NH-3).

5-[(1*R**,2*S**,4*R**)-2-Hydroxy-4-(hydroxymethyl)cyclohexyl]pyrimidine-2,4(1*H*,3*H*)-dione (**7a**) and 5-[(1*R**,2*S**,5*R**)-2-Hydroxy-5-(hydroxymethyl)-cyclohexyl]pyrimidine-2,4(1*H*,3*H*)-dione (**7b**)

A mixture of **6a** or **6b** (50 mg, 0.15 mmol) and $Pd(OH)_2$/C (20% Pd, 70 mg) in DMF (3 ml) and cyclohexene (3 ml) was heated at 80 °C in argon atmosphere. After cooling, the catalyst was filtered off and washed with ethanol. The combined filtrates were evaporated and the residue was chromatographed on a silica gel column (10 g) in ethyl acetate–acetone–ethanol–water (17:3:3:2) and crystallized from ethanol.

5-[(1R,2S*,4R*)-2-Hydroxy-4-(hydroxymethyl)cyclohexyl]pyrimidine-2,4(1H,3H)-dione* (**7a**): yield 27 mg (75%), m.p. > 260 °C. For $C_{11}H_{16}N_2O_4$ (240.3) calculated: 54.99% C, 6.71% H, 11.66% N; found: 54.38% C, 6.85% H, 11.30% N. FAB MS, *m/z* (rel.%): 241 (40) [M + H], 215 (46), 110 (56), 91 (100). ^{1}H NMR: 1.26 ddd, 1 H, *J*(3′ax,4′) = 5.0, *J*(3′ax,2′) = 10.9, J_{gem} = 13.4 (H-3′ax); 1.31 tt, 1 H, *J*(5′ax,6′eq) = *J*(5′ax,4′) = 4.5, *J*(5′ax,6′ax) = J_{gem} = 13.2 (H-5′ax); 1.43 dq, 1 H, *J*(6′eq,1′) ≈ *J*(6′eq,5′eq) ≈ 4.0, J_{gem} = 13.2 (H-6′eq); 1.51 d pent, 1 H, *J*(5′eq,3′) ≈ 3.0, *J*(5′eq,6′ax) ≈ *J*(5′eq,4′) ≈ 3.5 (H-5′eq); 1.54 tdd, 1 H, *J*(6′ax,1′) = 12.6 (H-6′ax); 1.85 dm, 1 H (H-3′eq); 1.86 m, 1 H (H-4′); 2.20 ddd, 1 H, *J*(1′,2′) = 10.0 (H-1′); 3.38 ddd, 1 H, *J*(CH,OH) = 5.3, *J*(CH,4′) = 7.9, J_{gem} = 10.6 (OC**H**H); 3.47 ddd, 1 H, *J*(CH,4′) = 7.2 (OCH**H**); 3.69 dddd, 1 H, *J*(2′,3′eq) = 4.0, *J*(2′,OH) = 5.4 (H-2′); 4.26 d, 1 H (OH); 4.41 t, 1 H (CH_2O**H**); 7.10 s, 1 H (H-6); 10.61 brs, 1 H (NH); 10.89 brs, 1 H (NH). ^{13}C NMR: 26.44 (C-5′); 26.58 (C-6′); 36.80 (C-3′); 36.83 (C-4′); 47.70 (C-1′); 62.98 (OCH_2); 66.51 (C-2′); 114.89 (C-5); 138.66 (C-6); 151.96 (C-2); 165.28 (C-4).

5-[(1R,2S*,5R*)-2-Hydroxy-5-(hydroxymethyl)cyclohexyl]pyrimidine-2,4(1H,3H)-dione* (**7b**): yield 28 mg (78%), m.p. > 260 °C. For $C_{11}H_{16}N_2O_4 \cdot 1/2\ C_2H_5OH$ (263.3) calculated: 54.74% C, 7.27% H, 10.64% N; found: 54.39% C, 7.24% H, 10.73% N. FAB MS, *m/z* (rel.%): 241 (45) [M + H], 215 (25), 110 (30), 91 (100). ^{1}H NMR: 1.29 tdd, 1 H, *J*(3′ax,4′eq) = 3.4, *J*(3′ax,2′) = 10.2, *J*(3′ax,4′ax) ≈ J_{gem} ≈ 12.8 (H-3′ax); 1.40 tdd, 1 H, *J*(4′ax,3′eq) = 4.0, *J*(4′ax,5′) = 4.4, J_{gem} = 13.4 (H-4′ax); 1.58 m, 2 H (H-6′ax, H-6′eq); 1.62 ddt, 1 H, *J*(3′eq,4′eq) = 3.4, *J*(3′eq,2′) = 4.2 (H-3′eq); 1.67 m, 1 H (H-5′); 1.68 dm, 1 H (H-4′eq); 2.38 dt, 1 H, *J*(1′,6′ax) ≈ *J*(1′,6′eq) ≈ 8.0, *J*(1′,2′) = 9.8 (H-1′); 3.37 ddd, 1 H, *J*(CH,OH) = 5.3, *J*(CH,5′) = 7.8, J_{gem} = 10.4 (OC**H**H); 3.43 ddd, 1 H, *J*(CH,5′) = 6.8 (OCH**H**); 3.53 brtdd, 1 H, *J*(2′,OH) = 5.3 (H-2′); 4.33 d, 1 H (OH); 4.40 t, 1 H (CH_2O**H**); 7.07 s, 1 H (H-6); 10.61 s, 1 H (NH); 10.89 s, 1 H (NH). ^{13}C NMR: 25.53 (C-4′); 31.03 (C-3′); 32.17 (C-6′); 35.64 (C-5′); 39.31 (C-1′); 62.71 (OCH_2); 71.33 (C-2′); 115.25 (C-5); 139.13 (C-6); 152.21 (C-2); 165.67 (C-4).

[(1*R**,3*S**,4*R**)-3-Acetoxy-4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-cyclohexyl]methyl Acetate (**8a**) and [(1*R**,3*R**,4*S**)-4-Acetoxy-3-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)cyclohexyl]methyl Acetate (**8b**)

Acetic anhydride (2.5 ml, 26.5 mmol) and 4-(dimethylamino)pyridine (35 mg, 0.29 mmol) were added to a stirred suspension of **7a** or **7b** (410 mg, 1.71 mmol) in acetonitrile (40 ml). After 22-h stirring, methanol (5 ml) was added, the reaction mixture was set aside for 15 min and taken down. The residue was partitioned between ethyl acetate (150 ml) and water (50 ml), the aqueous layer was extracted with ethyl acetate (150 ml). Combined organic layers were evaporated. The residue was dissolved in methanol–water (40 ml, 1:1 v/v) at 60 °C, $KHCO_3$ (100 mg, 1 mmol) was added. The solution was set aside for 20 min and evaporated. The residue was chromatographed on a silica gel column (50 g) in ethyl acetate–acetone–ethanol–water (125:15:6:4).

[(1R,3S*,4R*)-3-Acetoxy-4-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)cyclohexyl]methyl acetate* (**8a**): yield 510 mg (91%) after crystallization from absolute ethanol, m.p. 203–205 °C. For $C_{15}H_{20}N_2O_6$ (324.3) calculated: 55.55% C, 6.22% H, 8.64% N; found: 55.18% C, 6.39% H, 8.31% N. FAB MS, *m/z* (rel.%): 325 (35) [M + H], 205 (77), 125 (100), 91 (16). ^{1}H NMR: 1.47 tdd, 1 H, *J*(6ax,5eq) = 4.0, *J*(6ax,1) = 4.6, *J*(6ax,5ax) = J_{gem} = 13.2 (H-6ax); 1.49 m, 1 H (H-2ax); 1.59 dm, 1 H, J_{gem} = 13.2 (H-6eq); 1.51 dq, 1 H, *J*(5eq,4) = *J*(5eq,6eq) = 4.0, J_{gem} = 12.6 (H-5eq); 1.88 brdt, 1 H, *J*(2eq,5eq) = 2.0, *J*(2eq,3) ≈ *J*(2eq,1) ≈ 4.2, J_{gem} = 12.8 (H-2eq); 1.74 brqd, 1 H, *J*(5ax,6eq) = 3.2, *J*(5ax,4) ≈ 12.4 (H-5ax); 1.88 s, 3 H (CH_3CO);

2.02 s, 3 H (CH_3CO); 2.15 m, 1 H (H-1); 2.57 ddd, 1 H, *J*(4,3) = 10.6 (H-4); 4.06 dd, 1 H, *J*(C**H**H,1) = 7.2, J_{gem} = 11.0 (OC**H**H); 4.14 dd, 1 H, *J*(CH**H**,1) = 8.3 (CH**H**); 5.07 td, 1 H, *J*(3,2ax) = 10.6 (H-3); 7.29 d, 1 H, *J*(6,NH-1) = 5.8 (H-6′); 10.69 dd, 1 H, *J*(NH-1,NH-3) = 2.0 (NH-1); 10.98 d, 1 H (NH-3).

[(1R,3R*,4S*)-4-Acetoxy-3-(2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)cyclohexyl]methyl acetate* (**8b**): yield 482 mg (88%) as a foam. For $C_{15}H_{20}N_2O_6 \cdot 1/5\ H_2O$ (327.9) calculated: 54.94% C, 6.27% H, 8.54% N; found: 54.90% C, 6.29% H, 8.31% N. FAB MS, *m/z* (rel.%): 325 (32) [M + H], 205 (73), 125 (100), 91 (20). ^{1}H NMR: 1.45 tdd, 1 H, *J*(6ax,5eq) = 3.9, *J*(6ax,1) = 4.1, J_{gem} = 13.2 (H-6ax); 1.65 brd pent, 1 H, *J*(6eq,5eq) ≈ *J*(6eq,1) ≈ *J*(6eq,2eq) ≈ 2.8, J_{gem} = 13.6 (H-6eq); 1.75 dq, 1 H, *J*(5eq,4) = 4.2 (H-5eq); 1.88 m, 2 H (H-2ax, H-2eq); 1.88 s, 3 H (CH_3CO); 2.00 m, 1 H (H-1); 2.01 s, 3 H (CH_3CO); 2.72 ddd, 1 H, *J*(3,2eq) = 3.9, *J*(3,4) = 10.6, *J*(3,2ax) = 12.1 (H-3); 4.02 dd, 1 H, *J*(C**H**H,1) = 8.4, J_{gem} = 11.0 (OC**H**H); 4.13 dd, 1 H, *J*(CH**H**,1) = 7.2 (CH**H**); 4.94 td, 1 H (H-4); 7.21 s, 1 H (H-6′); 10.68 s, 1 H (NH); 10.98 s, 1 H (NH).

5-[(1*R**,2*S**,4*R**)-2-Hydroxy-4-(hydroxymethyl)cyclohexyl]-4-thioxo-1,2,3,4-tetrahydropyrimidin-4-one (**9a**)

Stirred suspension of **8a** (366 mg, 1.13 mmol) and Lawesson's reagent (350 mg, 0.85 mmol) in 1,2-dichloroethane (23 ml) was refluxed for 15 h. Two additional portions of Lawesson's reagent (each 350 mg, 0.85 mmol) were added every 5 h. After cooling, the precipitate was filtered off and dried. The mother liquor was chromatographed on silica gel column (200 g) in ethyl acetate–toluene (10:1) to afford another portion of the intermediate. The combined precipitate (270 mg) and residue after chromatography (30 mg) were dissolved in methanolic 0.15 M sodium methoxide (30 ml) and the solution was heated at 55 °C (bath) for 3 h. The solution was neutralized with Dowex 50 (H^+ form), filtered and the filtrate was taken down. The residue was chromatographed on a silica gel column (50 g) in ethyl acetate–acetone–ethanol–water (100:15:6:4) and crystallized from propan-2-ol to afford 160 mg (53%) of **9a**, m.p. > 260 °C. For $C_{11}H_{16}N_2O_3S$ (256.3) calculated: 51.54% C, 6.29% H, 10.93% N, 12.51% S; found: 51.41% C, 6.43% H, 10.54% N, 12.22% S. FAB MS, *m/z* (rel.%): 257 (58) [M + H], 239 (44) [M + H – H_2O], 214 (39), 91 (100). ^{1}H NMR: 1.19 m, 1 H (H-6′ax); 1.31 tt, 1 H, *J*(5′ax,4′) ≈ *J*(5′ax,6′eq) ≈ 4.5, *J*(5′ax,6′ax) ≈ J_{gem} ≈ 13.2 (H-5′ax); 1.33 ddd, 1 H, *J*(3′ax,4′) = 4.9, *J*(3′ax,2′) = 10.7, J_{gem} = 12.8 (H-3′ax); 1.62 dm, 1 H (H-5′eq); 1.65 m, 1 H (H-6′eq); 1.90 m, 1 H (H-4′); 1.91 brdq, 1 H, *J*(3′eq,2′) ≈ *J*(3′eq,4′) ≈ *J*(3′eq,5′eq) ≈ 3.0 (H-3′eq); 2.90 m, 1 H (H-1′); 3.40 ddd, 1 H, *J*(C**H**H,OH) = 5.0, *J*(C**H**H,4′) = 7.1, J_{gem} = 10.6 (OC**H**H); 3.45 ddd, 1 H, *J*(CH**H**,4′) = 8.0 (OCH**H**); 3.70 m, 1 H (H-2′); 4.26 d, 1 H, *J*(OH,2′) = 5.2 (OH); 4.39 t, 1 H (CH_2O**H**); 7.23 s, 1 H (H-6); 11.47 s, 1 H (NH); 12.34 s, 1 H (NH). ^{13}C NMR: 26.36 (C-5′); 27.09 (C-6′); 36.75 (C-4′); 36.90 (C-3′); 45.88 (C-1′); 62.47 (OCH_2); 66.03 (C-2′); 123.04 (C-5); 136.50 (C-6); 148.31 (C-2); 191.86 (C-4).

5-[(1*R**,2*S**,5*R**)-2-Hydroxy-5-(hydroxymethyl)cyclohexyl]-4-thioxo-1,2,3,4-tetrahydropyrimidin-4-one (**9b**)

To a stirred suspension of **8b** (445 mg, 1.37 mmol) in 1,2-dichloroethane (22 ml) Lawesson's reagent (417 mg, 1.03 mmol) was added. The reaction mixture was refluxed for 5 h. Then another portion of Lawesson's reagent (417 mg, 1.03 mmol) was added and the reaction mixture was refluxed for additional 5 h. After cooling, the solution was chromatographed on a silica gel column (200 g) in ethyl acetate–toluene (10:1). Obtained acetate (394 mg) was

dissolved in methanolic 0.15 M sodium methoxide (40 ml). The solution was heated at 55 °C (bath) for 3 h and neutralized with Dowex 50 (H^+ form). The resin was filtered off and the filtrate was taken down. The residue was chromatographed on a silica gel column (50 g) in ethyl acetate–acetone–ethanol–water (100:15:6:4) and crystallized from ethanol to afford 190 mg (54%) of **9b**, m.p. > 260 °C. For $C_{11}H_{16}N_2O_3S$ (256.3) calculated: 51.54% C, 6.29% H, 10.93% N, 12.51% S; found: 51.27% C, 6.36% H, 10.81% N, 12.67% S. FAB MS, *m/z* (rel.%): 257 (27) [M + H], 239 (11) [M + H – H_2O], 91 (8), 75 (100). ^{1}H NMR: 1.20 m, 1 H (H-6′ax); 1.36 tdd, 1 H, *J*(3′ax,4′eq) = 3.0, *J*(3′ax,2′) = 10.5, *J*(3′ax,4′ax) ≈ J_{gem} ≈ 12.6 (H-3′ax); 1.41 brtt, *J*(4′ax,3′eq) ≈ *J*(4′ax,3′eq) ≈ 4.4, J_{gem} ≈ 13.2 (H-4′ax); 1.67 m, 2 H (H-3′eq, H-4′eq); 1.77 brdq, 1 H, *J*(6′eq,1′) ≈ *J*(6′eq,5′) ≈ *J*(6′eq,4′eq) ≈ 2.5, J_{gem} = 12.6 (H-6′eq); 1.78 m, 1 H (H-5′); 3.10 brt, 1 H, *J*(1′,2′) ≈ *J*(1′, 6′ax) ≈ 10.0 (H-1′); 3.40 ddd, 1 H, *J*(C**H**H,OH) = 4.8, *J*(C**H**H,5′) = 7.0, J_{gem} = 10.5 (OC**H**H); 3.53 ddd, 1 H, *J*(CH**H**,5′) = 9.0 (OCH**H**); 3.53 m, 1 H (H-2′); 4.33 brt, 1 H (CH_2O**H**); 4.35 d, 1 H, *J*(OH,2′) = 5.4 (OH); 7.18 s, 1 H (H-6); 11,47 s, 1 H (NH); 12.35 s, 1 H (NH). ^{13}C NMR: 24.80 (C-4′); 30.80 (C-3′); 33.27 (C-6′); 35.59 (C-5′); 40.54 (C-1′); 61.88 (OCH_2); 70.53 (C-2′); 123.13 (C-5); 136.24 (C-6); 148.27 (C-2); 191.89 (C-4).

4-Amino-5-[(1*R**,2*S**,4*R**)-2-hydroxy-4-(hydroxymethyl)cyclohexyl]pyrimidin-2(1*H*)-one (**10a**) and 4-Amino-5-[(1*R**,2*S**,5*R**)-2-hydroxy-5-(hydroxymethyl)-cyclohexyl]pyrimidin-2(1*H*)-one (**10b**)

Thiouridine **9a** or **9b** (150 mg, 0.59 mmol) was heated with liquid ammonia (10 ml) and methanol (2 ml) in an autoclave at 85 °C for 48 h. After cooling the mixture was dissolved in hot water (15 ml) and the solution was decolorized with charcoal, filtered and evaporated to dryness. The residue was applied onto a Dowex 50 (H^+ form, 7 ml). The column was eluted with water (100 ml) and then with 2.5% aqueous ammonia. UV absorbing fractions containing the product were evaporated and the residue was crystallized from 95% aqueous methanol.

4-Amino-5-[(1R,2S*,4R*)-2-hydroxy-4-(hydroxymethyl)cyclohexyl]pyrimidin-2(1H)-one* (**10a**): yield 78 mg (56%), m.p. 250–252 °C. For $C_{11}H_{17}N_3O_3 \cdot 1/2\ H_2O$ (248.3) calculated: 53.21% C, 7.31% H, 16.92% N; found: 53.01% C, 7.25% H, 16.47% N. FAB MS, *m/z* (rel.%): 240 [M + H]. ^{1}H NMR: 1.25 tdd, 1 H, *J*(6′ax,5′eq) = 3.4, *J*(6′ax,1′) = 11.2, *J*(6′ax,5′ax) = 11.2, *J*(6′ax,5′ax) = J_{gem} = 12.8 (H-6′ax); 1.38 ddd, 1 H, *J*(3′ax,4′) = 5.6, *J*(3′ax,2′) = 10.5, J_{gem} = 13.6 (H-3′ax); 1.47 tdd, 1 H, *J*(5′ax,6′eq) = 4.0, *J*(5′ax,4′) = 4.4, J_{gem} = 12.8 (H-5′ax); 1.51 dq, 1 H, *J*(6′eq,1′) ≈ *J*(6′eq,5′eq) ≈ 3.0 (H-6′eq); 1.57 brd pent, 1 H, *J*(5′eq,4′) ≈ *J*(5′eq,3′eq) ≈ 2.5 (H-5′eq); 1.87 m, 2 H (H-3′eq, H-4′); 2.21 ddd, 1 H, *J*(1′,2′) = 9.6 (H-1′); 3.38 ddd, 1 H, *J*(C**H**H,OH) = 5.3, *J*(C**H**H,4′) = 7.1, J_{gem} = 10.6 (OC**H**H); 3.41 ddd, 1 H, *J*(CH**H**,4′) = 7.8 (OCH**H**); 3.52 dddd, 1 H, *J*(2′,3′eq) = 4.0, *J*(2′,OH) = 5.4 (H-2′); 4.42 t, 1 H (CH_2O**H**); 4.45 d, 1 H (OH); 6.65 s, 1 H and 6.95 s, 1 H (NH_2); 7.12 s, 1 H (H-6); 10.40 brs, 1 H (NH). ^{13}C NMR: 25.98 (C-5′); 27.25 (C-6′); 36.42 (C-4′); 36.68 (C-3′); 42.22 (C-1′); 62.65 (OCH_2); 67.72 (C-2′); 107.27 (C-5); 139.13 (C-6); 156.46 (C-2); 166.70 (C-4).

4-Amino-5-[(1R,2S*,5R*)-2-hydroxy-5-(hydroxymethyl)cyclohexyl]pyrimidin-2(1H)-one* (**10b**): yield 73 mg (52%), m.p. 253–256 °C. For $C_{11}H_{17}N_3O_3 \cdot 1/2\ H_2O$ (248.3) calculated: 53.21% C, 7.31% H, 16.92% N; found: 52.90% C, 7.12% H, 16.58% N. FAB MS, *m/z* (rel.%): 240 [M + H]. ^{1}H NMR: 1.37 ddd, 1 H, *J*(6′ax,5′) = 4.4, *J*(6′ax,1′) = 11.8, J_{gem} = 13.2 (H-6′ax); 1.42 m, 1 H (H-3′ax); 1.45 tdd, 1 H, *J*(4′ax,3′eq) = 3.2, *J*(4′ax,5′) = 4.4, *J*(4′ax,3′ax) = J_{gem} = 13.2 (H-4′ax); 1.62 brd pent, 1 H, *J* = 2.6 (4×) (H-4′eq); 1.63 dq, 1 H, *J*(3′eq,4′eq) ≈ *J*(3′eq,2′) ≈ 3.2 (H-3′eq); 1.68 dt, 1 H, *J*(6′eq,1′) ≈ *J*(6′eq,5′) ≈ 2.8 (H-6′eq); 1.71 m, 1 H (H-5′); 2.33 ddd, 1 H,

J(1′,2′) = 9.6 (H-1′); 3.34 m, 1 H (H-2′); 3.45 dd, 2 H, *J*(CH_2,OH) = 5.3, *J*(CH_2,5′) = 7.7 OCH_2); 4.50 t, 1 H (CH_2O**H**); 4.54 d, 1 H, *J*(OH,2′) = 5.1 (OH); 6.43 s, 1 H and 7.00 s, 1 H (NH_2); 7.13 s, 1 H (H-6); 10.30 brs, 1 H (NH). ^{13}C NMR: 25.00 (C-4′); 30.91 (C-3′); 31.88 (C-6′); 35.22 (C-5′); 37.07 (C-1′); 61.97 (OCH_2); 72.55 (C-2′); 107.49 (C-5); 139.22 (C-6); 156.40 (C-2); 166.81 (C-4).

2-Amino-5-{(1*R**,2*S**,4*R**)-4-[(benzyloxy)methyl]-2-hydroxycyclohexyl}-pyrimidin-4(1*H*)-one (**11a**) and 2-Amino-5-{(1*R**,2*S**,5*R**)-5-[(benzyloxy)-methyl]-2-hydroxycyclohexyl}pyrimidin-4(1*H*)-one (**11b**)

Lactone **3a** or **3b** (420 mg, 1.62 mmol) was co-evaporated with toluene (3 × 15 ml). A solution of lactone and ethyl formate (0.65 ml, 8.1 mmol) in ether (20 ml) was added dropwise with stirring to a suspension of potassium *tert*-butoxide (636 mg, 5.67 mmol) in ether (20 ml) in argon atmosphere at 0 °C. The solution was stirred at room temperature for 22 h and evaporated. Guanidine hydrochloride (310 mg, 3.24 mmol) was dissolved in a solution of potassium *tert*-butoxide (364 mg, 3.24 mmol) in propan-2-ol (30 ml) and the solution was stirred for 10 min. This solution was added to the residue and the reaction mixture was refluxed in argon atmosphere for 8 h. After cooling, the reaction mixture was neutralized with 10% acetic acid and evaporated. The residue was decanted with water (3 × 75 ml), the solid precipitate was filtered off and then crystallized from water–ethanol (5:1). The filtrate after decantation was washed with ethyl acetate (3 × 75 ml), combined organic extracts were dried over anhydrous sodium sulfate and evaporated. The residue combined with mother liquors after crystallization was chromatographed on a silica gel column (50 g) in ethyl acetate–acetone–ethanol–water (17:3:3:2) to obtain another portion of the product.

2-Amino-5-{(1R,2S*,4R*)-4-[(benzyloxy)methyl]-2-hydroxycyclohexyl}pyrimidin-4(1H)-one* (**11a**): total yield 235 mg (44%), m.p. 183–186 °C. For $C_{18}H_{23}N_3O_3 \cdot 1/3\ H_2O$ (335.4) calculated: 64.46% C, 7.11% H, 12.53% N; found: 64.26% C, 7.11% H, 12.27% N. EI MS, *m/z* (rel.%): 329 (2) [M], 311 (7), 238 (1), 220 (30), 190 (10), 176 (9), 150 (10), 138 (14), 124 (79), 112 (7), 91 (100) [Bn], 82 (15), 65 (14), 43 (25). ^{1}H NMR: 1.34 ddd, 1 H, *J*(3′ax,4′) = 5.0, *J*(3′ax,2′) = 10.5, J_{gem} = 12.8 (H-3′ax); 1.39 tt, 1 H, *J*(5′ax,6′ax) = 4.0, *J*(5′ax,4′) = 4.6, *J*(5′ax,6′ax) = J_{gem} = 13.8 (H-5′ax); 1.46 dq, 1 H, *J*(6′eq,1′) ≈ *J*(6′eq,5′eq) ≈ 4.0, J_{gem} = 13.4 (H-6′eq); 1.59 m, 2 H (H-5′eq, H-6′ax); 1.86 m, 1 H (H-3′eq); 2.11 m, 1 H (H-4′); 2.26 ddd, 1 H, *J*(1′,2′) = 9.9, *J*(1′,6′ax) = 10.5 (H-1′); 3.44 dd, 1 H, *J*(CH,4′) = 7.8, J_{gem} = 9.4 (OC**H**H); 3.47 dd, 1 H, *J*(CH,4′) = 7.2 (OCH**H**); 3.76 td, 1 H, *J*(2′,3′eq) = 4.0 (H-2′); 4.30 brs, 1 H (OH); 4.47 s, 2 H (OCH_2Ph); 6.54 brs, 2 H (NH_2); 7.25–7.40 m, 6 H (Ph, H-6); 11.10 brs, 1 H (NH).

2-Amino-5-{(1R,2S*,5R*)-5-[(benzyloxy)methyl]-2-hydroxycyclohexyl}pyrimidin-4(1H)-one* (**11b**): total yield 240 mg (45%), m.p. 181–183 °C. For $C_{18}H_{23}N_3O_3 \cdot 1/2\ H_2O$ (338.4) calculated: 63.89% C, 7.15% H, 12.42% N; found: 63.92% C, 7.17% H, 12.31% N. FAB MS, *m/z* (rel.%): 330 (100) [M + H], 91 (39) [Bn]. ^{1}H NMR: 1.27 tdd, 1 H, *J*(3′ax,4′eq) = 3.2, *J*(3′ax,2′) = 9.9, *J*(3′ax,4′ax) ≈ J_{gem} ≈ 13.1 (H-3′ax); 1.46 tt, 1 H, *J*(4′ax,3′eq) ≈ *J*(4′ax,5′) ≈ 4.2, *J*(4′ax,3′ax) ≈ J_{gem} ≈ 13.4 (H-4′ax); 1.59 dm, 1 H (H-4′eq); 1.64 dq, 1 H, *J*(3′eq,4′eq) ≈ *J*(3′eq,2′) ≈ 4.2 (H-3′eq); 1.68 m, 2 H (H-6′eq, H-6′ax); 1.92 m, 1 H (H-5′); 2.39 ddd, 1 H, *J*(1′,6′eq) = 4.2, *J*(1′,2′) = 9.8, *J*(1′,6′ax) = 11.9 (H-1′); 3.42 dd, 1 H, *J*(CH,5′) = 8.1, J_{gem} = 9.2 (OC**H**H); 3.47 dd, 1 H, *J*(CH,5′) = 7.1 (OCH**H**); 3.60 brtd, 1 H (H-2′); 4.29 brs, 1 H (OH); 4.48 s, 2 H (OCH_2Ph); 6.44 brs, 2 H (NH_2); 7.25–7.40 m, 5 H (Ph); 7.32 s, 1 H (H-6); 11.00 brs, 1 H (NH).

2-Amino-5-[(1*R**,2*S**,4*R**)-2-hydroxy-4-(hydroxymethyl)cyclohexyl]pyrimidin-4(1*H*)-one (**12a**) and 2-Amino-5-[(1*R**,2*S**,5*R**)-2-hydroxy-5-(hydroxymethyl)-cyclohexyl]pyrimidin-4(1*H*)-one (**12b**)

A mixture of **11a** or **11b** (115 mg, 0.35 mmol), $Pd(OH)_2/C$ (20%, 150 mg) in DMF (12 ml) and cyclohexene (12 ml) was heated at 80 °C in argon atmosphere. After cooling, the catalyst was filtered off and washed with ethanol. The combined filtrates were evaporated and the residue was chromatographed on a silica gel column (25 g) in ethyl acetate–acetone–ethanol–water 15:3:4:3. The obtained white solid was macerated with hot ethyl acetate, filtered off and dried.

2-Amino-5-[(1R,2S*,4R*)-2-hydroxy-4-(hydroxymethyl)cyclohexyl]pyrimidin-4(1H)-one* (**12a**): yield 66 mg (79%), m.p. 162–164 °C. For $C_{11}H_{17}N_3O_3 \cdot 1/2\ H_2O$ (248.3) calculated: 53.21% C, 7.31% H, 16.92% N; found: 53.34% C, 7.42% H, 16.55% N. FAB MS, *m/z* (rel.%): 240 (100) [M + H], 222 (10) [M + H – H_2O]. ^{1}H NMR: 1.27 ddd, 1 H, J(3′ax,4′) = 4.8, J(3′ax,2′) = 10.6, J_{gem} = 13.8 (H-3′ax); 1.32 tt, 1 H, J(5′ax,6′eq) ≈ J(5′ax,4′) ≈ 4.5, J(5′ax,6′ax) = J_{gem} = 13.6 (H-5′ax); 1.41 dq, 1 H, J(6′eq,5′eq) ≈ 3.8, J(6′eq,1′) ≈ 4.4, J_{gem} = 12.8 (H-6′eq); 1.59 dm, 1 H (H-5′eq); 1.62 tdd, 1 H, J(6′ax,5′eq) = 3.8, J(6′ax,1′) = 11.2 (H-6′ax); 1.83 dm, 1 H, J(3′eq,5′eq) = 2.0, J(3′eq,2′) ≈ J(3′eq,4′) ≈ 4.2 (H-3′eq); 1.86 m, 1 H (H-4′); 2.20 ddd, 1 H, J(1′,2′) = 10.0 (H-1′); 3.37 ddd, 1 H, J(CH,OH) = 4.6, J(CH,4′) = 8.1, J_{gem} = 10.6 (OC**H**H); 3.41 ddd, 1 H, J(CH,4′) = 7.2 (OCH**H**); 3.75 brtt, 1 H, J(2′,OH) = 4.6 (H-2′); 4.17 d, 1 H (OH); 4.41 t, 1 H (CH_2O**H**); 6.40 brs, 2 H (NH_2); 7.33 s, 1 H (H-6); 10.90 brs, 1 H (NH). ^{13}C NMR: 26.04 (C-5′); 26.22 (C-6′); 36.89 (C-4′); 37.01 (C-3′); 44.91 (C-1′); 63.16 (OCH_2); 66.84 (C-2′); 117.09 (C-5); 151.26 (C-6); 154.64 (C-2); 163.29 (C-4).

2-Amino-5-[(1R,2S*,5R*)-2-hydroxy-5-(hydroxymethyl)cyclohexyl]pyrimidin-4(1H)-one* (**12b**): yield 71 mg (85%), m.p. 166–169 °C. For $C_{11}H_{17}N_3O_3 \cdot 1/2\ H_2O$ (248.3) calculated: 53.21% C, 7.31% H, 16.92% N; found: 53.39% C, 7.55% H, 16.59% N. FAB MS, *m/z* (rel.%): 240 (100) [M + H], 222 (14) [M + H – H_2O]. ^{1}H NMR: 1.30 tdd, 1 H, J(3′ax,4′eq) = 4.3, J(3′ax,2′) = 9.9, J(3′ax,4′ax) ≈ J_{gem} ≈ 13.0 (H-3′ax); 1.40 tt, 1 H, J(4′ax,3′eq) ≈ J(4′ax,5′) ≈ 4.0, J(4′ax,3′ax) ≈ J_{gem} ≈ 13.0 (H-4′ax); 1.56 brdm, 1 H (H-4′eq); 1.63 brdq, 1 H, J(3′eq,4′eq) ≈ J(3′eq,2′) ≈ 4.0 (H-3′eq); 1.68 m, 3 H (H-5′, H-6′eq, H-6′ax); 2.40 td, 1 H, J(1′,6′eq) = 3.8, J(1′,2′) = 10.0, J(1′,6′ax) = 11.0 (H-1′); 3.36 m, 1 H and 3.43 m, 1 H (OCH_2); 3.58 brtt, 1 H, J(2′,OH) ≈ 4.5 (H-2′); 4.25 brd, 1 H (OH); 4.39 brt, 1 H, J(CH,OH) ≈ 5.0 (CH_2OH); 6.43 brs, 2 H (NH_2); 7.33 s, 1 H (H-6); 10.98 brs, 1 H (NH). ^{13}C NMR: 25.66 (C-4′); 31.27 (C-3′); 32.24 (C-6′); 35.76 (C-5′); 39.36 (C-1′); 62.89 (OCH_2); 71.61 (C-2′); 117.90 (C-5); 151.28 (C-6); 155.20 (C-2); 165.04 (C-4).

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