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Synthesis of Spacered Cyclopropyl Nucleoside Analogues as Potential Antiviral Agents

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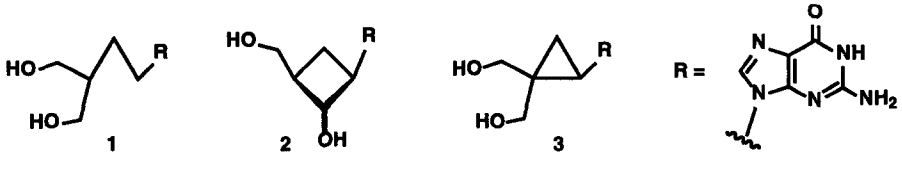
Abstract

Novel spacered cyclopropane nucleoside analogues possessing both a hydroxyethyl group and an additional methylene spacer between the base and the ring were synthesized starting from 3-buten-1-ol. After tetrahydropyranylation, cyclopropanation, and reduction the target molecules were obtained by Mitsunobu reactions followed by two consecutive deprotection steps.

Keywords: Cyclopropanes; Nucleosides; Antivirals

Introduction

Acyclonucleosides, e.g. penciclovir **1** [1-3], have been studied extensively as antiviral agents and several of them have emerged as potent and selective anti-herpes virus agents. Their cyclobutyl [4] **2** and cyclopropyl [5] analogues **3** have been prepared and screening of their antiviral activity revealed potent activity for the former and no activity against *herpes simplex* 1 and 2, *varicella zoster* virus and *cytomegalo* virus for the latter [1-5].



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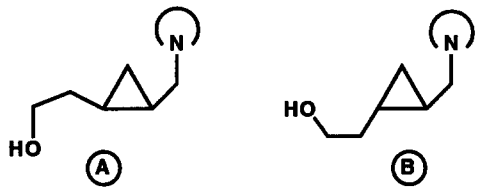
Results and Discussion

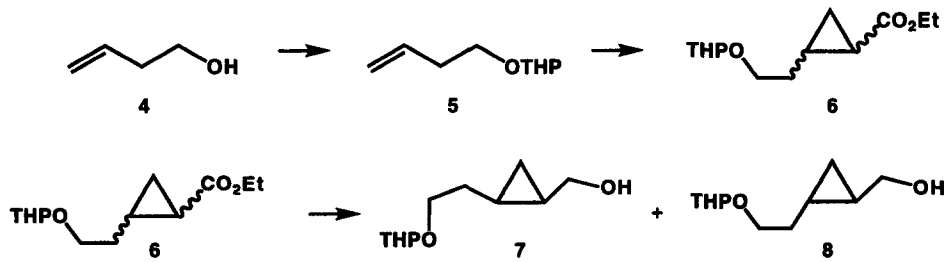
In order to explain these somewhat unexpected results it was assumed that the lacking antiviral activity of **3** might be due to a decreased conformational flexibility as a consequence of the rather rigid cyclopropyl ring [1]. Rigidity seems to be unfavourable either for the interaction with phosphorylating enzymes or for the interaction of the corresponding triphosphate with viral DNA polymerases.

To obtain higher flexibilty in the cyclopropanoid nucleoside analogues series [6] the synthesis of compounds of type **A** and type **B** was planned [7-10]. To avoid lengthy routes a strategy was to be developed that should allow in a forthcoming project the chosen strategy to be easily transferred into a combinatorial approach using parallel synthesis on beads.



Thus, commercially available 3-buten-1-ol (**4**) was tetrahydropyranylated [11-13] to afford **5** that was subjected to a cyclopropanation reaction with ethyl diazoacetate in the presence of catalytic amounts of dimeric rhodium acetate. [14, 15] A mixture of the *cis* and *trans* configurated cyclopropanes **6** was obtained that could not be separated by chromatography under a variety of different conditions nor by fractional distillation.

Hence **6** was reduced to the corresponding primary alcohols **7** and **8** in 83% yield. Albeit chromatography allowed the separation of *cis*-**7** from *trans*-**8**, no separation of the tetrahydropyranyl based diastereomers could be achieved. *Cis*-**7** is characterized by the presence of a broad signal in the IR spectrum at $\nu = 3422\ cm^{-1}$ indicative for the presence of an hydroxy group that is found in the corresponding ^1H NMR spectrum at $\delta = 4.50$ ppm as an D_2O exchangeable signal. The hydroxymethyl group was found in the ^{13}C NMR spectrum at $\delta = 68.14$ ppm whereas for the *trans* configurated **8** this signal is observed at $\delta = 72.72$ ppm.

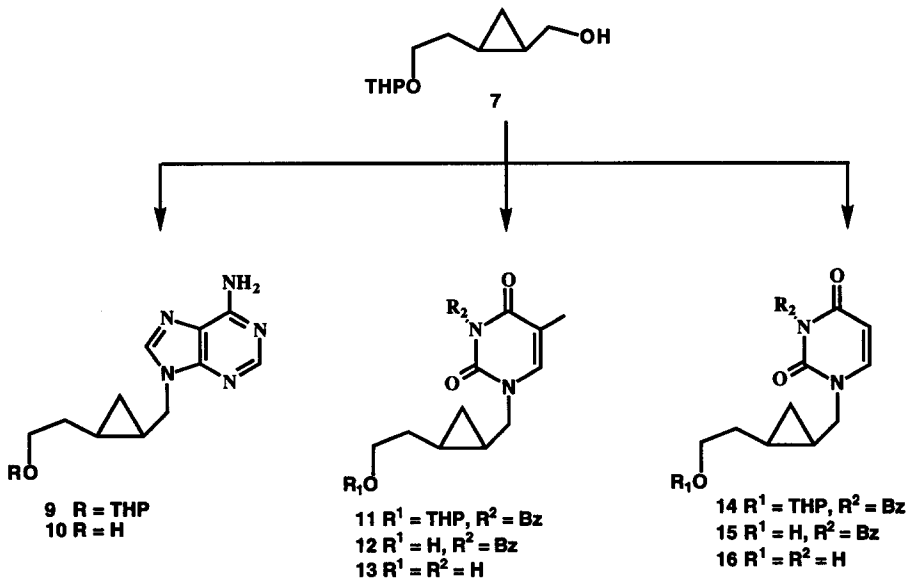


Compounds **7** and **8** are optimal starting materials for straightforward syntheses of the target compounds by convenient two step strategies consisting of an attachment of suitable protected heterocycles under *Mitsunobu* conditions [16] followed by a one or two step deprotection sequence.

Thus, treatment of **7** with adenine in the presence of triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD) gave 41% of **9**. Deprotection of **9** with 10% aqueous hydrochloric acid at room temperature [17] finally gave the adenosine analogue **10** that is characterized by the presence of D_2O exchangeable signals in the ^1H NMR spectrum at δ = 7.12 and 4.44 ppm, the former of which being indicative for the presence of an amino group whereas the latter was assigned to the hydroxyl moiety. The cyclopropane ring shows in the ^{13}C NMR spectrum its characteristic signals at δ = 15.02 [C(2)], 13.10 [C(1)] and 9.61 [C(3)] ppm, respectively.

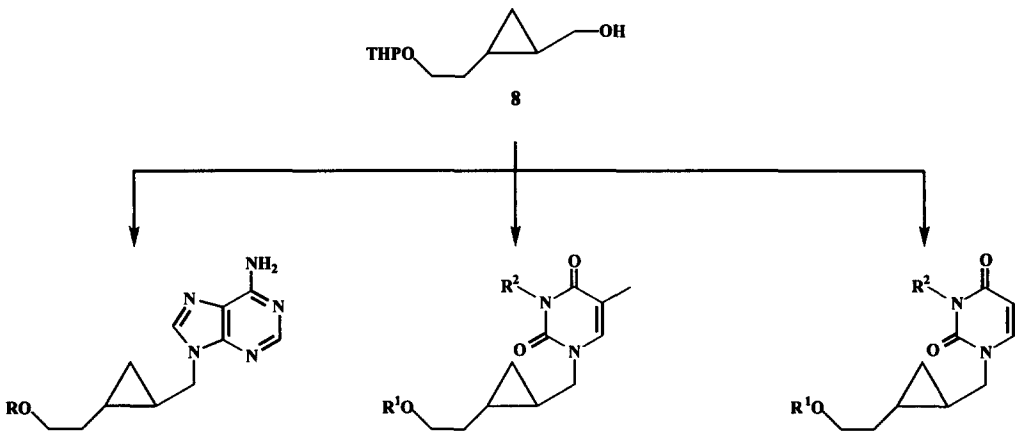
Treatment of **7** with N^3-benzoyl-thymine [18, 19] under the same conditions gave **11** whose reaction with methanolic hydrochloric acid gave 95% of **12**. Cleavage of the benzoyl group was achieved by the reaction with 8 N sodium hydroxide in 1,4-dioxane leading to the target compound **13**; these conditions were shown to be superior as compared to the deprotection with ammonium hydroxide that invariably led to the formation of side products.

Finally, the reaction of **7** with N^3-benzoyl-uracil [18, 20] gave **14**. Treatment of **14** with methanolic hydrochloric acid fortunately gave 71% of final **16** together with 23% of partially protected **15**.



As far as the series of the corresponding *trans*-configurated compounds is concerned, the strategy employed for the synthesis of **16** could be easily adopted. Thus, **8** gave upon *Mitsunobu* reaction **17** whose deprotection under acidic conditions afforded 85% of **18**.

Comparison of the spectral data of **19** to those obtained for **10** revealed a shift both in the ^1H and ^{13}C NMR spectra to lower fields for the CH_2-N moiety for the *cis*-configurated derivative.



17 R = THP
18 R = H

19 R^1 = THP, R^2 = Bz
20 R^1 = H, R^2 = Bz
21 R^1 = R^2 = H

22 R^1 = THP, R^2 = Bz
23 R^1 = H, R^2 = Bz
24 R^1 = R^2 = H

As compared to the *cis*-series a significant raise in yields could be obtained for the synthesis of **19** from **8**. Again, dehydropyranylation was performed by methanolic hydrochloric acid and the resulting benzoylated **20** was debenzoylated under basic conditions to yield the thymine analogue **21**. *Mitsunobu* reaction of **8** with N^3-benzoyl-uracil gave **22** albeit at somewhat low yields. It's deprotection under acidic conditions afforded the final uracil analogue **24** together with 57% of partially deprotected **23**.

In order to establish the relative configuration of the products exhaustive NOE experiments were performed. Thus, for both **15** and **16** H-C(2) showed a strong NOE to H-C(1) and, in addition, for **15** a strong NOE was found for H_A-C(3) and the *cis*-oriented H-C(1). For the *trans*-configurated compounds **23** and **24** NOE's were found between H-C(2) and H_A-C(3) whilst H_B-C(3) gave an analogous effect with H-C(1) therefore establishing a *trans* orientation of H-C(1) and H-C(2); similar observations were made for **10** and **18**.

Experimental

General [18]; in addition, NMR spectra (internal Me_4Si) were recorded using the Varian spectrometers Gemini 200, Gemini 2000 or Unity 500 (δ given in ppm, *J* in Hz, internal Me_4Si for ^1H and ^{13}C NMR spectra, C' correspond to the atoms of the heterocycle, C" correspond to the atoms of the ethyl group, C"' correspond to the atoms of the tetrahydropyranyl fragment), GC-MS spectra were taken on a Hewlett Packard 5890/5972.

*2-(3-Butenyloxy)tetrahydro-2*H*-pyran (5).* A mixture of 3-buten-1-ol (27.29 g, 0.38 mol) and 3,4-dihydro-2*H*-pyran (34.34 g, 0.41 mol) was cooled to 5 °C and conc. hydrochloric acid (37%, 3 drops) was added. The mixture was allowed to warm to room temperature and stirred overnight, then neutralized with $NaHCO_3$ and filtered. The crude product was purified by column chromatography (silica gel, ethyl acetate/hexane 1:8) to afford **5** (54.2 g, 91%) as a colorless oil; R_F (ethyl acetate/hexane 1:10) 0.58; IR (film): *v* 3078*w*, 2942*s*, 2871*m*, 1642*w*, 1466*w*, 1454*w*, 1442*w*, 1384*w*, 1352*m*, 1324*w*, 1261*w*, 1202*m*, 1184*w*, 1162*m*, 1136*m*, 1122*s*, 1079*s*, 1035*s*; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85-5.74 (*m*, 1 H, H-C(3)), 5.08-4.96 (*m*, 2 H, H_2-C(4)), 4.56-4.54 (*m*, 1 H, H-C(2‴)), 3.86-3.79 (*m*, 1 H, H_A-C(6‴)), 3.76-3.71 (*m*, 1 H, H_A-C(1)), 3.48-3.36 (*m*, 2 H, H_B-C(6‴), H_B-C(1)), 2.34-2.28 (*m*, 2 H, H_2-C(2)), 1.82-1.74 (*m*, 1 H, H_A-C(4‴)), 1.69-1.62 (*m*, 1 H, H_A-C(3‴)), 1.57-1.44 (*m*, 4 H, H_B-C(3‴), H_B-C(4‴), H_2-C(5‴)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.35 (*d*, C(3)), 116.23 (*t*, C(4)), 98.70 (*d*, C(2‴)), 66.68 (*t*, C(1)), 62.13 (*t*, C(6‴)), 34.04 (*t*, C(2)), 30.53 (*t*, C(3‴)), 25.32 (*t*, C(5‴)), 19.38 (*t*, C(4‴)); GC-MS: 156 (0.05%), 155 (0.3%), 128 (0.8%), 115 (3.5%), 101 (8.4%), 100 (3.8%), 85 (100.0%); HRMS calcd. for $C_9H_{16}O_2$: 156.1150; found: 156.1150; Anal. calcd. for $C_9H_{16}O_2$ (156.22): C, 69.20; H, 10.32; found: C, 69.01; H, 10.39.

(±)-Ethyl-(1 RS, *2* RS*)*-cis-*2-[2-(tetrahydro-2*H*-2-pyranyloxy)ethyl]-1-cyclopropane carboxylate and (±)-ethyl-(1* RS, *2* SR*)*-trans-*2-[2-(tetrahydro-2*H*-2-pyranyloxy)ethyl]-1-cyclopropane carboxylate* [(±)-**6**]. Ethyl diazoacetate (7.62 g, 66.78 mmol) was added at a controlled rate over a 12 h period to a stirred mixture of **5** (5.20 g, 33.29 mmol) and dirhodium(II) tetraacetate (0.19 g, 0.43 mmol) at room temperature. Work up was performed by fractional bulb-to-bulb distillation (0.1 mbar, 100-125 °C) to afford **6** (5.20 g, 64%) as a yellowish oil; R_F (ethyl acetate/hexane 1:2) *cis*: 0.74, *trans*: 0.69; IR (film): *v* 2941*m*, 2871*m*, 1726*s*, 1453*w*, 1409*m*, 1382*m*, 1368*w*, 1352*m*, 1323*w*, 1264*m*, 1202*m*, 1179*s*, 1136*m*, 1121*m*, 1078*m*, 1063*m*, 1034*s*; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.55-4.54 (*m*, 1 H, H-C(2‴)), 4.11-4.02 (*m*, 2 H, CH_2-Ethyl), 3.85-3.60 (*m*, 2 H, H_A-C(6‴), H_A-C(2‟), 3.47-3.33 (*m*, 2 H, H_B-C(6‴), H_B-C(2‟)), 1.87-1.71 (*m*, 1 H, H_A-C(1‟)), 1.69-1.63 (*m*, 1 H, H_A-C(3‴)), 1.61-1.42 (*m*, 5 H, H_B-C(1‟), H_B-C(3‴), H_2-C(5‴), H_A-C(4‴)), 1.41-1.31 (*m*, 1 H, H_B-C(4‴)), 1.23-1.19 (*m*, 3 H, CH_3), 1.16-1.10 (*m*, 1 H, H-C(1)), 1.01-0.96 (*m*, 1 H, H-C(2)), 0.93-0.88 (*m*, 1 H, H_A-C(3)), 0.72 (*m*, 1 H, H_B-C(3)); ^{13}C NMR (100 MHz, $CDCl_3$): data for *cis* (±)-**3**: δ 173.04 (*s*, CO), 98.59 (*d*, C(2‴)), 66.55 (*t*, C(6‴)), 61.90 (*t*, C(2‟)), 60.14 (*t*, CH_2-ethyl), 33.06 (*t*, C(1‟)), 30.47 (*t*, C(3‴)), 25.30 (*t*, C(5‴)), 19.26 (*t*, C(4‴)), 18.68 (*d*, C(1)), 17.74 (*d*, C(2)), 14.07 (*t*, C(3)), 12.85 (*q*, CH_3); data for *trans* (±)-**3**: δ 174.40 (*s*, CO), 98.66 (*d*, C(2‴)), 66.99 (*t*, C(6‴)), 61.90 (*t*, C(2‟)), 60.14 (*t*, CH_2-ethyl), 33.06 (*t*, C(1‟)), 30.49 (*t*, C(3‴)), 27.12 (*t*, C(5‴)), 19.79 (*t*, C(4‴)), 19.18 (*d*, C(1)), 17.74 (*d*, C(2)), 14.79 (*t*, C(3)), 12.85 (*q*, CH_3); MS (e.i., 70 eV): 242 (3.6%), 241 (5.7%), 224 (7.1%), 213 (25.7%), 197 (4.3%), 157 (7.1%), 141 (30.0%), 128 (5.0%), 113 (30.7%), 101 (17.9%), 85 (100.0%); Anal. calcd. for $C_{13}H_{22}O_4$ (242.32): C, 64.44; H, 9.15; found: C, 64.53; H, 9.01.

(±)-{(1 RS, *2* RS*)*-cis-*2-[2-(Tetrahydro-2*H*-2-pyranyloxy)ethyl]cyclopropyl}methanol* [(±)-**7**] *and (±)-{(1* RS, *2* SR*)*-trans-*2-[2-(tetrahydro-2*H*-2-pyranyloxy)ethyl]cyclopropyl} methanol* [(±)-**8**]. To a -60°C cooled solution of DIBAH (100 *ml*, 1.2 M in toluene, 120 mmol, Fluka, used as received) a solution of (±)-**6** (6.80 g, 28.07 mmol) in dry toluene (20 *ml*) was slowly added at this temperature over a period of 60 min. Stirring at –60 °C was continued for additional 3 h and then the reaction was quenched by the successive addition of methanol (20 *ml* of a 10% solution in toluene), methanol (2 *ml*) and finally water (20 *ml*). The mixture was allowed to warm to 25 °C, the white precipitate was filtered off and washed with

ethyl acetate (500 *ml*). The washings and the filtrate were combined, dried ($MgSO_4$), the solvent was removed under reduced pressure and the residue subjected to column chromatography (ethyl acetate/hexane 1:2→ 2:1) to afford (±)-**7** (2.25 g, 40%) and (±)-**8** (2.43 g, 43%), respectively.

Data for (±)-**7**: Colorless oil; R_F (ethyl acetate/hexane 2:1) 0.56; IR (film): *v* 3422*brw*, 3064*w*, 2993*w*, 2942*m*, 2871*m*, 1441*w*, 1385*w*, 1353*w*, 1323*w*, 1260*w*, 1201*m*, 1184*w*, 1121*m*, 1077*m*, 1033*s*; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.59-4.56 (*m*, 1 H, H-C(2‴)), 4.50 (*brs*, 1 H, OH), 3.84-3.72 (*m*, 1 H, CH_2-OH), 3.48-3.32 (*m*, 4 H, H_2-C(6‴), H_2-C(2‟)), 3.21-3.14 (*m*, 1 H, CH_2-OH), 1.87-1.64 (*m*, 3 H, H_A-C(4‴), H_A-C(3‴), H_A-C(1‟)), 1.56-1.41 (*m*, 5 H, H_B-C(4‴), H_B-C(3‴), H_B-C(1‟), H_2-C(5‴)), 1.20-1.11 (*m*, 1 H, H-C(1)), 0.80-0.72 (*m*, 1 H, H-C(2)), 0.63-0.57 (*m*, 1 H, H_A-C(3)), -0.13-(-)0.18 (*m*, 1 H, H_B-C(3)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 99.06 (*d*, C(2‴)), 68.14 (*t*, CH_2-OH), 62.14 (*t*, C(6‴)), 62.04 (*t*, C(2‟)), 30.02 (*t*, C(1‟)), 27.82 (*t*, C(3‴)), 25.05 (*t*, C(5‴)), 19.11 (*t*, C(4‴)), 18.32 (*d*, C(1)), 13.74 (*d*, C(2)), 7.14 (*t*, C(3)); GC-MS: 199 (0.04%), 183 (0.1%), 169 (0.7%), 155 (1.0%), 141 (0.8%), 127 (1.1%), 115 (5.0%), 101 (9.5%), 85 (100%); Anal. calcd. for $C_{11}H_{20}O_3$ (200.28): C, 65.97; H, 10.07; found: C, 65.99; H, 10.14.

Data for (±)-**8**: Colorless oil; R_F (ethyl acetate/hexane 2:1) 0.48; IR (film): *v* 3413*m*, 3065*w*, 2996*w*, 2941*s*, 2869*m*, 1728*w*, 1454*w*, 1441*w*, 1384*w*, 1353*m*, 1323*w*, 1261*w*, 1201*m*, 1184*w*, 1166*m*, 1136*m*, 1120*m*, 1075*m*, 1033*s*; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.59-4.56 (*m*, 1 H, H-C-(2‴)), 3.88-3.43 (*m*, 6 H, CH_2-OH, H_2-C(6‴), H_2-C(2‟)), 2.25 (*s*, 1 H, OH), 1.82-1.61 (*m*, 4 H, H_2-C(1‟), H_A-C(4‴), H_A-C(3‴)), 1.53-1.47 (*m*, 4 H, H_B-C(4‴), H_B-C(3‴), H_2-C(5‴)), 0.92-0.81 (*m*, 1 H, H-C(1)), 0.76-0.55 (*m*, 1 H, H-C(2)), 0.43-0.32 (*m*, 2 H, H_2-C(3)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 100.48 (*d*, C(2‴)), 72.72 (*t*, CH_2-OH), 68.30 (*t*, C(6‴)), 63.83 (*t*, C(2‟)), 34.51 (*t*, C(1‟)), 31.67 (*t*, C(3‴)), 26.55 (*t*, C(5‴)), 21.52 (*t*, C(4‴)), 20.39 (*d*, C(1)), 15.48 (*d*, C(2)), 10.10 (*t*, C(3)); GC-MS 199 (0.1%), 183 (0.1%), 169 (0.7%), 155 (0.8%), 141 (0.7%), 127 (1.0%), 115 (2.0%), 101 (9.6%), 85 (100%); Anal. calcd. for $C_{11}H_{20}O_3$ (200.28): C, 65.97; H, 10.07; found: C, 65.72; H, 10.22.

(±)-9-{(1 RS, *2* RS*)*-cis-*2-[2-(Tetrahydro-2*H*-2-pyranyloxy)ethyl]cyclopropyl}methyl)-9*H*-6-purinamine* [(±)-**9**]. To a mixture of **7** (0.7 g, 3.5 mmol), triphenylphosphine (2.0 g, 7.62 mmol) and adenine (1.04 g, 7.70 mmol) in dry 1,4-dioxane (20 *ml*) a solution of DEAD (1.25 g, 7.18 mmol) in dry 1,4-dioxane (20 *ml*) was added dropwise at room temperature over a period of 2.5 h. The solution was stirred overnight, the solvent was removed *in vacuo* and the remaining yellowish oil was purified by column chromatography (silica gel, ethyl acetate/methanol 10:1) to afford **9** (0.451 g, 41%) as a white solid; mp: 127.9-128.5 °C; R_F (ethyl acetate/methanol 3:1) 0.22; UV (methanol): λ_{max}= 263 nm (log ε = 4.26); IR (KBr): *v* 3272*brm*, 3125*brm*, 2939*m*, 2870*w*, 1675*s*, 1605*s*, 1573*m*, 1479*m*, 1416*m*, 1310*m*, 1244*m*, 1203*m*, 1120*m*, 1075*m*, 1021*m*; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.29 (*s*, 1 H, H-C(2‘)), 7.88 (*s*, 1 H, H-C(8‘)), 6.29 (*s*, 2 H, NH_2), 4.53 (*dd*, *J* = 4.33, 7.59, 1 H, H-C(2‴)), 4.23 (*dd*, *J* = 8.40, 14.44, 1 H, H_A-C-N), 4.06 (*dd*, *J* = 8.16, 14.36, 1 H, H_B-C-N), 3.83-3.74 (*m*, 2 H, H_A-C(6‴), OCH_A), 3.47-3.37 (*m*, 2 H, H_B-C(6‴), OCH_B), 1.98-1.43 (*m*, 8 H, H_2-C (1‟), H_2-C(3‴), H_2-C(4‴), H_2-C(5‴)), 1.41-1.34 (*m*, 1 H, H-C(1)), 1.08-1.01 (*m*, 1 H, H-C(2)), 0.83-0.79 (*m*, 1 H, H_A-C(3)), 0.20 (*ddd*, *J* = 5.51, 5.51, 6.57, 1 H, H_B-C(3)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.83 (*s*, C(6‘)), 152.93 (*d*, C(2‘)), 150.15 (*s*, C(4‘)), 139.96 (*d*, C(8‘)), 119.62 (*s*, C(5‘)), 98.90 (*d*, C(2‴)), 67.24 (*t*, C(6‴)), 62.22 (*t*, OCH_2), 43.88 (*t*, CH_2-N), 30.51 (*t*, C(1‟)), 28.77 (*t*, C(3‴)), 25.24 (*t*, C(5‴)), 19.43 (*t*, C(4‴)), 14.96 (*d*, C(1)), 13.59 (*d*, C(2)), 10.27 (*t*, C(3)); MS (e.i., 70 eV): 317 (4.3%), 288 (2.9%), 232 (100.0%); HRMS

calcd. for $C_{16}H_{23}N_5O_2$: 317.18516; found: 317.18516; Anal. calcd. for $C_{16}H_{23}N_5O_2$ (317.39): C, 60.55; H, 7.30; N, 22.07; found: C, 60.43; H, 7.12; N, 22.13.

(±)-2-{(1 RS, *2* RS*)-cis-2-[(6-Amino-9*H*-9-purinyl)methyl]cyclopropyl}-1-ethanol* [(±)-**10**]. A solution of **9** (0.805 g, 2.54 mmol) in aqueous hydrochloric acid (20 *ml*, 10%) was stirred at room temperature for 12 h. The reaction mixture was cooled to 5 °C, adjusted to pH 7 with 8 N NaOH and the mixture was extracted with diethyl ether (3 x 50 *ml*) to remove impurities. The resulting aqueous solution was adjusted to pH=10 by an addition of 8 N NaOH to afford **10** (0.49 g, 83%) as a white solid; mp: 164.1-165.3 °C; R_F (ethyl acetate/methanol 3:1) 0.27; UV (methanol) λ_{max}= 264 nm (log ε = 4.13); IR (KBr): *ν* 3304*brm*, 3128*brs*, 2929*m*, 2871*w*, 1669*s*, 1601*s*, 1573*m*, 1481*m*, 1416*m*, 1380*w*, 1332*m*, 1308*m*, 1248*m*, 1210*m*, 1140*w*, 1074*m*, 1009*m*; ^{1}H NMR (500 MHz, d_6-DMSO): δ 8.17 (*s*, 1 H, H-C(8')), 8.12 (*s*, 1 H, H-C(2')), 7.12 (*s*, 2 H, NH_2), 4.44 (*t*, *J* = 5.20, 1H, OH), 4.23 (*dd*, *J* = 7.03, 14.26, 1 H, H_A-C-N), 4.00 (*dd*, *J* = 8.40, 14.26, 1 H, H_B-C-N), 3.44-3.38 (*m*, 2 H, OCH_2), 1.61-1.41 (*m*, 2 H, H_2-C(2")), 1.40-1.36 (*m*, 1 H, H-C(2)), 0.99-0.89 (*m*, 1 H, H-C(1)), 0.65 (*ddd*, *J* = 4.20, 4.20, 12.40, 1 H, H_A-C(3)), 0.22-0.18 (*m*, 1 H, H_B-C(3)), ^{13}C NMR (100 MHz, d_6-DMSO): δ 156.12 (*s*, C(6')), 152.52 (*d*, C(2')), 149.71 (*s*, C(4')), 140.66 (*d*, C(8')), 118.86 (*s*, C(5')), 61.11 (*t*, OCH_2), 43.11 (*t*, CH_2-N), 31.41 (*d*, C(2")), 15.03 (*d*, C(2)), 13.10 (*d*, C(1)), 9.61 (*t*, C(3)); MS (e.i., 70 eV): 233 (23.6%), 232 (8.6%), 216 (4.3%), 202 (100.0%), 188 (17.5%), 177 (11.4%), 163 (11.4%), 149 (21.4%), 148 (20.4%), 135 (58.6%), 108 (23.6%); HRMS calcd. for $C_{11}H_{15}N_5O$: 233.12765; found: 233.12766; Anal. calcd. for $C_{11}H_{15}N_5O$ (233.27): C, 56.64; H, 6.48; N, 30.02; found: C, 56.49; H, 6.29; N, 29.92.

(±)-3-Benzoyl-5-methyl-1-({(1 RS, *2* RS*)*-cis-*2-[2-(tetrahydro-2*H*-2-pyranyloxy)ethyl] cyclopropyl}methyl)-1,2,3,4-tetrahydro-2,4-pyrimidinedione* [(±)-**11**]. The reaction was performed as described for the preparation of compound **9** using **7** (2.0 g, 10 mmol) in dry 1,4-dioxane (20 *ml*), N^3-benzoylthymine (4.6 g, 20 mmol), triphenylphosphine (5.2 g, 19.82 mmol) and DEAD (3.49 g, 20 mmol) in 1,4-dioxane (20 *ml*). After stirring overnight, the solvent was evaporated, the residue was purified by column chromatography (silica gel, ethyl acetate/hexane 1:1) to obtain **11** (0.89 g, 22%) as a colorless oil contaminated with some impurities that were easily separated in the next reaction step; an analytical sample was obtained by column chromatography (silica gel RP-18, methanol/water 8:3); R_F (ethyl acetate/hexane 10:1) 0.75; UV (methanol): λ_{max}= 256 nm, (log ε = 4.28); IR (film): *ν* 3067*brw*, 2944*s*, 1748*s*, 1652*s*, 1599*m*, 1436*s*, 1353*s*, 1251*s*, 1201*m*, 1164*m*, 1120*s*, 1076*m*, 1032*s*; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86-7.84 (*m*, 2 H, H_2-C_{ortho} phenyl), 7.58-7.54 (*m*, 1 H, H-C_{para} phenyl), 7.43-7.39 (*m*, 2 H, H_2-C_{meta} phenyl), 4.52-4.50 (*m*, 1 H, H-C(2"')), 3.86-3.66 (*m*, 2 H, CH_2-N), 3.61-3.52 (*m*, 2 H, H_A-C(6"'), OCH_A), 3.45-3.33 (*m*, 2 H, H_B-C(6"'), OCH_B), 1.88 (*s*, 3 H, CH_3), 1.77-1.60 (*m*, 2 H, H_A-C(3"'), H_A-C(4"')), 1.54-1.42 (*m*, 6 H, H_2-C(1"), H_B-C(3"'), H_B-C(4"'), H_2-C(5"')), 1.19-1.09 (*m*, 1 H, H-C(1)), 1.02-0.93 (*m*, 1 H, H-C(2)), 0.78-0.74 (*m*, 1 H, H_A-C(3)), 0.14-0.10 (*m*, 1 H, H_B-C(3)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.24 (*s*, CO benzoyl), 163.13 (*s*, C(4')), 149.94 (*s*, C(2')), 139.87 (*d*, C(6')), 134.81 (*s*, C_q phenyl), 131.62 (*d*, C_{para} phenyl), 130.25 (*d*, C_{ortho} phenyl), 128.99 (*d*, C_{meta} phenyl), 110.28 (*s*, C(5')), 98.90 (*d*, C(2"')), 67.18 (*t*, C(6"')), 62.18 (*t*, OCH_2), 48.07 (*t*, CH_2-N), 30.42 (*t*, C(1")), 28.82 (*t*, C(3")), 25.12 (*t*, C(5")), 19.37 (*t*, C(4"')), 17.29 (*d*, C(1)), 14.27 (*d*, C(2)), 12.05 (*q*, CH_3), 9.82 (*t*, C(3)); MS (e.i., 70 eV): 412 (0.4%), 383 (1.4%), 328 (5.7%), 311 (5.0%), 297 (7.9%), 224 (11.4%), 223 (12.9%), 207 (24.3%), 193 (11.4%), 179 (6.4%), 165 (5.0%), 140 (5.0%), 127 (8.6%), 105 (100.0%); HRMS calcd. for

$C_{23}H_{28}N_2O_5$: 412.19981; found: 412.19980; Anal. calcd. for $C_{23}H_{28}N_2O_5$:(412.49): C, 66.97; H, 6.84; N, 6.79; found: C, 66.87; H, 6.92; N, 6.81.

(±)-3-Benzoyl-1-{[(1 RS, *2* RS*)*-cis-*2-(2-hydroxyethyl)cyclopropyl]methyl}-5-methyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione* [(±)-**12**]. A solution of **11** (0.81 g, 1.97 mmol) in methanol (60 *ml*) and conc. aqueous hydrochloric acid (80 *ml*, 10%) was stirred at room temperature for 12 h. The reaction mixture was cooled to 5 °C, adjusted to pH 7-8 by the addition of 8 N NaOH and the mixture was extracted with ethyl acetate (10 x 50 *ml*). The combined organic phases were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 10:1) to afford **12** (0.62 g, 95%) as a colorless oil; R_F (ethyl acetate/hexane 10:1) 0.36; UV (methanol): λ_{max}= 256 nm (log ε = 4.18); IR (film): *v* 3469*brm*, 3068*m*, 2931*s*, 2543*m*, 1745*s*, 1652*s*, 1558*s*, 1435*s*, 1354*s*, 1247*s*, 1180*s*, 1120*s*, 1032*s*; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90-7.88 (*m*, 2 H, H_2-C_{ortho} phenyl), 7.63-7.59 (*m*, 1 H, H-C_{para} phenyl), 7.49-7.44 (*m*, 2 H, H_2-C_{meta} phenyl), 7.21 (*s*, 1 H, H-C(6')), 3.85 (*dd*, *J* = 6.84, 14.45, 1 H, H_A-C-N), 3.69-3.58 (*m*, 3 H, H_B-C-N, OCH_2), 1.93 (*s*, 3 H, CH_3), 1.90 (*s*, 1 H, OH), 1.71-1.64 (*m*, 1 H, H-C(1")), 1.48 (*dddd*, *J* = 5.71, 6.84, 7.23, 14.21, 1 H, H-C(1")), 1.16 (*ddddd*, 1 H, *J* = 5.06, 5.77, 6.99, 8.05, 11.74, H-C(1)), 0.99 (*ddddd*, *J* = 4.55, 4.75, 5.86, 6.85, 11.74, 1 H, H-C(2)), 0.82 (*ddd*, *J* = 4.55, 6.74, 8.05, 1 H, H_A-C(3)), 0.15 (*ddd*, *J* = 4.75, 5.77, 6.74, 1 H, H_B-C(3)); ^{13}C NMR (100 MHz; $CDCl_3$): δ 169.36 (*s*, CO benzoyl), 163.27 (*s*, C(4')), 150.15 (*s*, C(2')), 139.84 (*d*, C(6')), 135.02 (*s*, C_q phenyl), 131.74 (*d*, C_{para} phenyl), 130.44 (*d*, C_{ortho} phenyl), 129.16 (*d*, C_{meta} phenyl), 110.68 (*s*, C(5')), 62.73 (*t*, OCH_2), 48.05 (*t*, CH_2-N), 31.58 (*t*, C(1")), 14.29 (*d*, C(1)), 13.19 (*d*, C(2)), 12.25 (*q*, CH_3), 9.86 (*t*, C(3)); MS (e.i., 70 eV): 328 (1.4%), 311 (0.4%), 297 (6.1%), 256 (1.4%), 223 (3.6%), 193 (7.1%), 127 (4.3%), 105 (100.0%); HRMS calcd. for $C_{18}H_{20}N_2O_4$: 328.14229; found: 328.14229; Anal. calcd. for $C_{18}H_{20}N_2O_4$ (328.27): C, 65.84; H, 6.14; N, 8.53; found: C, 65.74; H, 6.00; N, 8.73.

(±)-1-{[(1 RS, *2* RS*)*-cis-*2-(2-Hydroxyethyl)cyclopropyl]methyl}-5-methyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione* [(±)-**13**]. A solution of **12** (0.55 g, 1.67 mmol) in 1,4-dioxane (20 *ml*) was treated with sodium hydroxide (8 N, 10 *ml*) for 12 h. The reaction mixture was cooled to 5 °C, neutralized with 10% aqueous hydrochloric acid and extracted with ethyl acetate (10 x 50 *ml*). The combined organic phases were dried over $MgSO_4$ and evaporated under reduced pressure. The remaining oil was purified by column chromatography (silica gel, ethyl acetate) to afford **13** (0.35 g, 95%) as a white solid; mp: 113.5-113.8 °C; R_F (ethyl acetate/methanol 10:1) 0.44; UV (methanol): λ_{max}= 274 nm (log ε = 3.94); IR (film): *v* 3401*brm*, 3176*brm*, 2998*m*, 2931*s*, 2537*brm*, 2357*m*, 2068*w*, 1771*m*, 1682*brs*, 1470*s*, 1370*s*, 1332*s*, 1252*s*, 1225*s*, 1170*m*, 1120*m*, 1056*s*; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.42 (*brs*, 1 H, NH), 7.12 (*s*, 1 H, H-C(6')), 3.88 (*dd*, *J* = 7.05, 14.34, 1 H, H_A-C-N), 3.71 (*ddd*, *J* = 6.59, 6.59, 10.48, 2 H, OCH_2), 3.61 (*dd*, *J* = 7.69, 14.42, 1 H, H_B-C-N), 2.20 (*brs*, 1 H, OH), 1.92 (*s*, 3 H, CH_3), 1.79-1.72 (*m*, 1 H, H_A-C(1")), 1.60-1.53 (*m*, 1 H, H_B-C(1")), 1.26-1.13 (*m*, 1 H, H-C(1)), 1.03-0.95 (*m*, 1 H, H-C(2)), 0.83 (*ddd*, *J* = 4.81, 8.45, 8.45, 1 H, H_A-C(3)), 0.18-0.15 (*m*, 1 H, H_B-C(3)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.38 (*s*, C(4')), 151.35 (*s*, C(2')), 139.98 (*d*, C(6')), 110.84 (*s*, C(5')), 62.72 (*t*, OCH_2), 47.67 (*t*, CH_2-N), 31.65 (*t*, C(1")), 14.37 (*d*, C(1)), 13.16 (*d*, C(2)), 12.21 (*q*, CH_3), 9.85 (*t*, C(3)); MS (e.i., 70 eV): 224 (32.9%), 207 (4.3%), 194 (16.4%), 193 (100.0%); HRMS calcd. for $C_{11}H_{16}N_2O_3$: 224.11608; found: 224.11609; Anal. calcd. for $C_{11}H_{16}N_2O_3$ (224.26): C, 58.91; H, 7.19; N, 12.49; found: C, 58.69; H, 6.86; N, 12.63.

(±)-3-Benzoyl-1-({(1 RS, *2* RS*)*-cis-*2-[2-(tetrahydro-2H-2-pyranyloxy)ethyl]cyclopropyl}methyl)-1,2,3,4-tetrahydro-2,4-pyrimidinedione* [(±)-**14**]. Following the procedure given for the preparation of compound **9** using **7** (2.01 g, 10.05 mmol), triphenylphosphine (5.73 g, 21.85 mmol), dry 1,4-dioxane (50 *ml*), N^3-benzoyluracil (4.73 g, 21.88 mmol) and DEAD (3.50 g, 20.10 mmol) in 1,4-dioxane (20 *ml*) **14** (1.90 g, 48%) was obtained after purification by column chromatography (silica gel, ethyl acetate/hexane 1:1 and ethyl acetate/acetonitrile 5:1) as a yellowish oil; R_F (ethyl acetate/hexane 2:1) 0.40; UV (methanol): λ_{max}= 255 nm (log ε = 4.28); IR (film): *v* 3494*w*, 3351*w*, 3088*m*, 2943*s*, 2870*m*, 1748*s*, 1704*s*, 1668*s*, 1598*s*, 1519*w*, 1441*s*, 1375*s*, 1351*s*, 1246*s*, 1201*s*, 1179*s*, 1162*s*, 1120*s*, 1075*s*, 1032*m*; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.92-7.87 (*m*, 2 H, H_2-C_{ortho} phenyl), 7.65-7.57 (*m*, 1 H, H-C_{para} phenyl), 7.49-7.38 (*m*, 3 H, H_2-C_{meta} phenyl, 1 H-C(6')), 5.76 (*d*, *J* = 8.0, 1 H, H-C(5')), 4.56-4.54 (*m*, 1 H, H-C(2"')), 3.93-3.57 (*m*, 4 H, CH_2-N, H_A-C(6"') and OCH_A), 3.49-3.35 (*m*, 2 H, H_B-C(6"'), OCH_B), 1.86-1.61 (*m*, 2 H, H_A-C(3"'), H_A-C(4"')), 1.57-1.50 (*m*, 6 H, H_2-C(1"), H_B-C(3"'), H_B-C(4"'), H_2-C(5"')), 1.18-1.02 (*m*, 2 H, H-C(1), H-C(2)), 0.81 (*ddd*, *J* = 4.93, 8.35, 8.35, 1 H, H_A-C(3)), 0.19-0.11 (*m*, 1 H, H_B-C(3)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.89 (*s*, CO benzoyl), 162.39 (*s*, C(4')), 149.90 (*s*, C(2')), 143.68 (*d*, C(6')), 134.96 (*s*, C_q phenyl), 131.42 (*d*, C_{para} phenyl), 130.33 (*d*, C_{meta} phenyl), 129.04 (*d*, C_{ortho} phenyl), 101.83 (*d*, C(5')), 99.02 (*d*, C(2"')), 67.24 (*t*, C(6"')), 62.36 (*t*, OCH_2), 48.62 (*t*, CH_2-N), 30.61 (*t*, C(1")), 29.00 (*t*, C(3"')), 25.31 (*t*, C(5"')), 19.61 (*t*, C(4"')), 14.32 (*d*, C(1)), 13.66 (*d*, C(2)), 10.04 (*t*, C(3)); MS (e.i., 70 eV): 398 (1.4%), 369 (10.0%), 359 (5.0%), 313 (1.4%), 298 (3.6%), 283 (3.6%), 216 (9.3%), 209 (7.9%), 193 (14.3%), 179 (2.1%), 106 (7.9%), 105 (100.0%); HRMS calcd. for $C_{22}H_{26}N_2O_5$: 398.18416; found: 398.18415; Anal. calcd. for $C_{22}H_{26}N_2O_5$ (398.46): C, 66.32; H, 6.58; N, 7.03; found: C, 66.17; H, 6.45; N, 6.87.

(±)-3-Benzoyl-1-{[(1 RS, *2* RS*)*-cis-*2-(2-hydroxyethyl)cyclopropyl]methyl}-1,2,3,4-tetrahydro-2,4-pyrimidinedione* [(±)-**15**] and *(±)-1-{[(1* RS, *2* RS*)*-cis-*2-(2-hydroxyethyl)cyclopropyl]methyl}-1,2,3,4-tetrahydro-2,4-pyrimidinedione* [(±)-**16**]. The same experimental procedure as given for **12** starting from **14** (1.06 g, 4.018 mmol), methanol (20 *ml*) and hydrochloric acid (50 *ml*, 10%) led to the crude products. Column chromatography (ethyl acetate/hexane 10:1) of the residue gave **15** (0.30 g, 23%) and **16** (0.6 g, 71%), respectively.

Data for **15**: colorless oil; R_F (ethyl acetate/methanol 10:1) 0.63; UV (methanol): λ_{max}= 269 nm (log ε = 3.81); IR (film): *v* 3400*brs*, 3055*s*, 2939*m*, 2876*m*, 1682*s*, 1575*m*, 1464*s*, 1386*s*, 1353*s*, 1251*s*, 1158*m*, 1054*m*; ^{1}H NMR (400 MHz; $CDCl_3$): δ 7.83-7.81 (*m*, 2 H, H_2-C_{ortho} phenyl), 7.51-7.49 (*m*, 1 H, H-C_{para} phenyl), 7.45-7.41 (*m*, 2 H, H_2-C_{meta} phenyl), 7.33 (*d*, *J* = 7.81, 1 H, H-C(6')), 5.71 (*d*, *J* = 8.0, 1H, H-C(5')), 3.88 (*dd*, *J* = 7.03, 7.23, 1 H, H_A-C-N), 3.79-3.61 (*m*, 3 H, H_B-C-N, OCH_2), 1.77-1.70 (*m*, 1 H, H_A-C(1")), 1.59-1.50 (*m*, 1 H, H_B-C(1")), 1.18 (*ddddd*, *J* = 5.49, 6.97, 7.62, 8.40, 8.79, 1 H, H-C(1)), 1.00 (*ddddd*, *J* = 5.97, 6.62, 7.63, 8.10, 8.40, 1 H, H-C(2)), 0.83 (*ddd*, *J* = 4.89, 8.10, 8.79, 1 H, H_A-C(3)), 0.17 (*ddd*, *J* = 4.89, 5.49, 5.97, 1 H, H_B-C(3)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.76 (*s*, CO benzoyl), 163.95 (*s*, C(4')), 151.34 (*s*, C(2')), 144.00 (*s*, C(6')), 132.07 (*d*, C_{para} phenyl), 128.66 (*d*, C_{meta} phenyl), 127.46 (*d*, C_{ortho} phenyl), 102.26 *d*, C(5')), 62.77 (*t*, OCH_2), 48.10 (*t*, CH_2-N), 31.65 (*t*, C(1")), 14.20 (*d*, C(1)), 13.17 (*d*, C(2)), 9.92 (*t*, C(3)); MS (e.i., 70 eV): 283 (1.4%), 210 (18.6%), 180 (22.9%), 179 (100.0%); HRMS calcd. for $C_{17}H_{18}N_2O_4$: 314.12664; found: 314.12665; Anal. calcd. for $C_{17}H_{18}N_2O_4$ (314.34): C, 64.96; H, 5.77; N, 8.91; found: C, 64.75; H, 5.71; N, 8.99.

Data for **16**: yellowish solid; mp: 199-200 °C; R_F (ethyl acetate/methanol 10:1) 0.40; UV (methanol): λ_{max}= 270 nm (log ε = 3.54); IR (film): *v* 3401*brs*, 1674*s*, 1608*m*, 1538*s*, 1416*s*, 1252*m*, 1025*m*; ^{1}H NMR (400 MHz, d_6-DMSO): δ 11.19 (*s*, 1 H, NH), 7.70 (*d*, *J* = 7.82, 1 H, H-C(6')), 5.54 (*d*, *J* = 7.81, 1 H, H-C(5')), 3.85 (*dd*, *J* = 6.45, 14.06, 1 H, H_A-C-N), 3.50-3.40 (*m*, 3 H, H_B-C-N, OCH_2), 1.73 (*s*, 1 H, OH), 1.49 (*dddd*, *J* = 6.86, 6.89, 17.21, 46.56, 2 H, H_2-C(1")), 1.18-1.09 (*m*, 1 H, H-C(1)), 0.93-0.84 (*m*, 1 H, H-C(2)), 0.62 (*dddd*, *J* = 4.25, 6.20, 10.40, 1 H, H_A-C(3)), 0.15-0.11 (*m*, 1 H, H_B-C(3)); ^{13}C NMR (100 MHz, d_6-DMSO): δ 163.87 (*s*, C(4')), 151.22 (*s*, C(2')), 145.63 (*d*, C(6')), 100.82 (*d*, C(5')), 61.02 (*t*, OCH_2), 47.34 (*t*, CH_2-N), 31.51 (*t*, C(1")), 14.17 (*d*, C(1)), 12.75 (*d*, C(2)), 9.23 (*t*, C(3)); MS (e.i., 70 eV): 212 (13.6%), 211 (7.9%), 210 (2.1%), 182 (10.7%), 181 (16.5%), 180 (100.0%), 179 (17.9%), 167 (14.3%), 155 (5.7%), 139 (22.1%), 126 (17.9%), 115 (24.3%), 114 (47.9%), 113 (23.6%), 95 (22.1%), 82 (72.9%), 81 (22.9%), 69 (25.0%), 67 (47.1%); HRMS calcd. for $C_{10}H_{14}N_2O_3$: 210.10043; found: 210.10043; Anal. calcd. for $C_{10}H_{14}N_2O_3$ (210.23): C, 57.13; H, 6.71; N, 13.32; found: C, 57.00; H, 6.43; N, 13.68.

(±)-9-{(1 RS, *2* SR*)*-trans-*2-[2-(Tetrahydro-2*H*-2-pyranyloxy)ethyl]cyclopropyl}methyl)-* 9H*-6-purinamine* [(±)-**17**]. The reaction was performed under the conditions as described for **9** using **8** (1.36 g, 6.78 mmol), triphenylphosphine (3.64 g, 13.88 mmol), adenine (1.9 g, 14.06 mmol), 1,4-dioxane (20 *ml*) and DEAD (2.43 g, 13.95 mmol) in 1,4-dioxane (20 *ml*). Evaporation of the solvents and purification of the residue by column chromatography (silica gel, ethyl acetate/methanol 10:1) gave **17** (1.2 g, 56%) as a white solid; mp: 87.6-87.9 °C; R_F (ethyl acetate/methanol 3:1) 0.22; UV (methanol): λ_{max}= 264 nm (log ε = 4.09); IR (KBr): *v* 3295*s*, 3142*s*, 2939*s*, 2870*m*, 1668*s*, 1602*s*, 1572*s*, 1512*w*, 1477*s*, 1415*s*, 1352*m*, 1324*s*, 1309*s*, 1240*s*, 1201*m*, 1184*m*, 1119*s*, 1074*s*, 1022*s*; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (*s*, 1 H, HC(2')), 7.87 (*s*, 1 H, H-C(8')), 6.18 (*s*, 2 H, NH_2), 4.44 (*dd*, *J* = 7.42, 21.09, 1 H, H-C(2"')), 4.07-3.95 (*m*, 2 H, CH_2-N), 3.79 (*ddd*, *J* = 3.47, 3.47, 14.80, 1 H, OCH_A), 3.75-3.65 (*m*, 1 H, H_A-C(6"')), 3.45-3.40 (*m*, 1 H, OCH_B), 3.36-3.24 (*m*, 1 H, H_B-C(6"')), 1.77-1.71 (*m*, 1 H, H_A-C(4"')), 1.66-1.60 (*m*, 1 H, H_A-C(3"')), 1.59-1.42 (*m*, 6 H, H_2-C(1,), H_B-C(3"'), H_B-C(4"'), H_2-C(5"')), 1.24-1.05 (*m*, 1 H, H-C(1)), 0.98-0.84 (*m*, 1 H, H-C(2)), 0.61-0.56 (*m*, 1 H, H_A-C(3)), 0.48-0.43 (*m*, 1 H, H_B-C(3)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.77 (*s*, C(6')), 152.99 (*d*, C(2')), 150.14 (*s*, C(4')), 140.11 (*d*, C(8')), 119.60 (*s*, C(5')), 98.94 (*d*, C(2"')), 66.82 (*t*, C(6"')), 62.32 (*t*, OCH_2), 47.73 (*t*, CH_2-N), 33.34 (*t*, C(1")), 30.56 (*t*, C(3"')), 25.27 (*t*, C(5"')), 19.51 (*t*, C(4"')), 18.07 (*d*, C(1)), 15.67 (*d*, C(2)), 10.95 (*t*, C(3)); MS (e.i., 70 eV): 317 (1.4%), 288 (3.6%), 233 (23.6%), 232 (100.0%), 217 (20.7%), 216 (12.1%), 203 (16.4%), 202 (92.8%), 189 (8.6%), 188 (13.6%), 175 (12.1%), 174 (22.9%), 162 (5.7%), 161 (6.4%), 149 (13.6%), 148 (15.0%), 136 (51.4%), 135 (54.3%); HRMS calcd. for $C_{16}H_{23}N_5O_2$: 317.18516; found: 317.18515; Anal. calcd. for $C_{16}H_{23}N_5O_2$ (317.39): C, 60.55; H, 7.30; N, 22.07; found: C, 60.25; H, 7.18; N, 22.25.

(±)-2-{(1 RS, *2* SR*)*-trans-*2-[(6-Amino-9*H*-9-purinyl)methyl]cyclopropyl}-1-ethanol* [(±)-**18**]. A solution of **17** (1.0 g, 3.15 mmol) in aqueous hydrochloric acid (20 *ml*, 10%) was stirred at room temperature for 10 h. The reaction mixture was cooled to 5 °C and adjusted to pH 7-8 with 8 N NaOH to afford **18** (0.623 g, 85%) as a white precipitate; mp: 189.6-191.1 °C; R_F (ethyl acetate/methanol 3:1) 0.27; UV (methanol): λ_{max}= 263 nm, (log ε = 3.99); IR (KBr): *v* 3272*brm*, 3101*brm*, 2934*w*, 2878*w*, 1679*m*, 1604*m*, 1575*m*, 1486*w*, 1419*m*, 1391*w*, 1341*m*, 1306*m*, 1244*w*, 1205*w*, 1078*w*, 1013*m*; ^{1}H NMR (500 MHz, d_6-DMSO): δ 8.16 (*s*, 1 H, H-C(8')), 8.12 (*s*, 1 H, H-C(2')), 7.14 (*s*, 2 H, NH_2), 4.45 (*d*, *J* = 4.59, 1 H, OH), 4.02-3.94 (*m*, 2 H, CH_2-N), 3.29-3.23 (*m*, 2 H, OCH_2), 1.38-1.34 (*m*, 1 H, H_A-C(2")), 1.24-1.19

(*m*, 1 H, H_B-C(2")), 1.05-1.01 (*m*, 1 H, H-C(2)), 0.85-0.84 (*m*, 1 H, H-C(1)), 0.54 (*ddd*, *J* = 4.43, 4.43, 8.70, 1 H, H_A-C(3)), 0.30 (*ddd*, *J* = 4.79, 4.79, 8.27, 1 H, H_B-C(3)); ^{13}C NMR (125 MHz, d_6-DMSO): δ 155.91 (*s*, C(6')), 152.45 (*d*, C(2'), 149.49 (*s*, C(4')), 140.82 (*d*, C(8')), 118.69 (*s*, C(5')), 60.67 (*t*, OCH_2), 46.93 (*t*, CH_2-N), 36.28 (*t*, C(2")), 18.34 (*d*, C(2)), 14.91 (*d*, C(1)), 10.41 (*t*, C(3)); MS (e.i., 70 eV): 233 (17.9%), 202 (100.0%); HRMS calcd. for $C_{11}H_{15}N_5O$: 233.12764; found: 233.12765; Anal. calcd. for $C_{11}H_{15}N_5O$ (233.27): C, 56.64; H, 6.48; N, 30.02; found: C, 56.43; H, 6.38; N, 30.12.

(±)-3-Benzoyl-5-methyl-1-({(1 RS, *2* SR*)*-trans-*2-[2-(tetrahydro-2*H*-2-pyranyloxy) ethyl]cyclopropyl}methyl)-1,2,3,4-tetrahydro-2,4-pyrimidinedione* [(±)-**19**]. The reaction was performed under the conditions as described for **9** using **8** (1.5 g, 7.49 mmol) in dry 1,4-dioxane (40 *ml*), triphenylphosphine (3.9 g, 14.87 mmol), N^3-benzoylthymine (3.45 g, 14.99 mmol) and DEAD (2.61 g, 14.99 mmol) in dry 1,4-dioxane (20 *ml*). After evaporation of the solvents and purification by column chromatography (silica gel, ethyl acetate/hexane 1:1) **19** (1.99 g, 64%) was obtained as a colorless oil contaminated with some impurities that were separated in the next reaction step; an analytical sample was obtained by column chromatography (silica gel RP-18, methanol/water 8:3); R_F (ethyl acetate/hexane 10:1) 0.75; UV (methanol): λ_{max}= 256 nm (log ε = 4.18); IR (film): *v* 3488*brw*, 3068*w*, 2943*s*, 2868*m*, 2249*w*, 1748*s*, 1694*s*, 1652*s*, 1599*m*, 1436*s*, 1354*s*, 1254*s*, 1201*m*, 1166*m*, 1120*s*, 1076*s*, 1032*s*; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91-7.89 (*m*, 2 H, H_2-C_{ortho} phenyl), 7.63-7.60 (*m*, 1 H, H-C_{para} phenyl), 7.49-7.45 (*m*, 2 H, H_2-C_{meta} phenyl), 4.55-4.53 (*m*, 1 H, H-C(2"')), 3.84 (*dd*, *J* = 7.33, 11.04, 1 H, H_A-C-N), 3.77 (*dd*, *J* = 6.55, 9.67, 1 H, H_B-C-N), 3.61-3.58 (*m*, 2 H, H_A-C(6"'), OCH_A), 3.49-3.41 (*m*, 2 H, H_B-C(6"'), OCH_B)), 1.94 (*s*, 3 H, CH_3), 1.81-1.78 (*m*, 1 H, H_A-C(4"')), 1.71-1.67 (*m*, 1 H, H_A-C(3"')), 1.58-1.47 (*m*, 6 H, H_2-C(1"), H_B-C(3"'), H_B-C(4"'), H_2-C(5"')), 0.98-0.95 (*m*, 1 H, H-C(1)), 0.88-0.85 (*m*, 1 H, H-C(2)), 0.54-0.51 (*m*, 1 H, H_A-C(3)), 0.48-0.43 (*m*, 1 H, H_B-C(3)); ^{13}C NMR (100 MHz; $CDCl_3$): δ 170.37 (*s*, CO benzoyl), 164.35 (*s*, C(4')), 151.13 (*s*, C(2')), 141.10 (*d*, C(6')), 135.99 (*s*, C*q* phenyl), 132.87 (*d*, C_{para} phenyl), 131.48 (*d*, C_{ortho} phenyl), 130.19 (*d*, C_{meta} phenyl), 111.46 (*s*, C(5')), 100.14 (*d*, C(2"')), 68.03 (*t*, C(6"')), 63.56 (*t*, OCH_2), 53.26 (*t*, CH_2-N), 34.45 (*t*, C(1")), 31.72 (*t*, C(3"')), 26.32 (*t*, C(5"')), 20.68 (*t*, C(4"')), 18.30 (*d*, C(1)), 16.28 (*d*, C(2)), 13.26 (*q*, CH_3), 11.50 (*t*, C(3)); MS (e.i.; 70 eV): 412 (0.4%), 397 (0.4%), 328 (2.9%), 307 (3.6%), 277 (2.9%), 223 (1.4%), 207 (5.9%), 127 (2.9%), 105 (100.0%); HRMS calcd. for $C_{23}H_{28}N_2O_5$: 412.19981; found: 412.19981; Anal. calcd. for $C_{23}H_{28}N_2O_5$ (412.49); C, 66.97; H, 6.84; N, 6.79; found: C, 66.81; H, 6.59; N, 6.95.

(±)-3-Benzoyl-1-{[(1 RS, *2* SR*)*-trans-*2-(2-hydroxyethyl)cyclopropyl]methyl}-5-methyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione* [(±)-**20**]. The reaction was performed under the conditions as described for **12** using **19** (1.85 g, 4.48 mmol), methanol (40 *ml*) and hydrochloric acid (80 *ml*, 10%). After evaporation of the solvents under reduced pressure the residue was purified by column chromatography (silica gel, ethyl acetate/hexane 10:1) to afford compound **20** (1.03 g, 70%) as a white solid; mp: 133.4-134.2 °C; R_F (ethyl acetate/hexane 10:1) 0.36; UV (methanol): λ_{max}= 256 nm (log ε = 4.02); IR (KBr): *v* 3480*brs*, 1746*s*, 1694*s*, 1652*s*, 1599*m*, 1443*m*, 1357*m*, 1255m, 1180*w*, 1044*w*; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91-7.89 (*m*, 2 H, H_2-C_{ortho} phenyl), 7.63-7.59 (*m*, 1 H, H-C_{para} phenyl), 7.48-7.44 (*m*, 2 H, H_2-C_{meta} phenyl), 7.19 (*s*, 1 H, H-C(6')), 3.69-3.59 (*m*, 3 H, H_A-C-N, OCH_2), 3.52 (*dd*, *J* = 7.61, 14.26, 1 H, H_B-C-N), 1.92 (*s*, 3 H, CH_3), 1.83 (*s*, 1 H, OH), 1.62-1.54 (*m*, 1 H, H_A-C(1")), 1.35-1.28 (*m*, 1 H, H_B-C(1")), 0.94-0.83 (*m*, 2 H, H-C(1), H-C(2)), 0.51 (*ddd*, *J* = 4.69, 4.69, 8.98, 1 H, H_A-C(3)), 0.43 (*ddd*, *J* = 5.27, 5.27, 8.21, 1 H, H_B-C(3)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.41 (*s*, CO benzoyl), 163.35 (*s*, C(4')), 150.21 (*s*, C(2')), 140.23 (*d*,

C(6')), 135.03 (*s*, C_q phenyl), 131.75 (*d*, C_{para} phenyl), 130.47 (*d*, C_{ortho} phenyl), 129.16 (*d*, C_{meta} phenyl), 110.53 (*s*, C(5')), 62.33 (*t*, OCH_2), 52.45 (*t*, CH_2-N), 36.04 (*t*, C(1")), 17.19 (*d*, C(1)), 15.28 (*d*, C(2)), 12.17 (*q*, CH_3), 10.06 (*t*, C(3)); MS (e.i., 70 eV): 328 (0.7%), 297 (3.6%), 284 (1.4%), 223 (5.0%), 193 (4.3%), 126 (3.6%), 105 (100.0%); HRMS calcd. for $C_{18}H_{20}N_2O_4$: 328.14229; found: 328.14229; Anal. calcd. for $C_{18}H_{20}N_2O_4$ (328.36): C, 65.84; H, 6.14; N, 8.53; found: C, 65.79; H, 6.11; N, 9.12.

(±)-1-{[(1 RS, *2* SR*)*-trans-*2-(2-Hydroxyethyl)cyclopropyl]methyl}-5-methyl-1,2,3,4-tetrahydro-2,4-pyrimidinedione* [(±)-**21**]. According to the preparation of **13** from **20** (0.81 g, 2.47 mmol), 1,4-dioxane (20 *ml*), sodium hydroxide (8 N, 10 *ml*) **21** (0.42 g, 76%) was obtained as a white solid; mp: 144.9-146.0 °C; R_F (ethyl acetate/methanol 10:1) 0.44; UV (methanol): λ_{max}= 274 nm (log ε = 3.98); IR (KBr): *ν* 3445*s*, 3175*m*, 3049*m*, 2917*m*, 2817*w*, 1662*s*, 1471*m*, 1358*m*, 1322*w*, 1257*w*, 1212*w*, 1074*w*, 1027*w*; ^{1}H NMR (500 MHz, CD_3OD): δ 7.46 (*s*, 1 H, H-C(6')), 3.66 (*dd*, *J* = 6.89, 14.14, 1 H, H_A-C-N), 3.62-3.51 (*m*, 3 H, H_B-C-N, OCH_2), 1.87 (*s*, 3 H, CH_3), 1.56-1.49 (*m*, 1 H, H_A-C(1")), 1.41-1.34 (*m*, 1 H, H_B-C(1")), 1.00-0.94 (*m*, 1 H, H-C(1)), 0.90-0.83 (*m*, 1 H, H-C(2)), 0.56 (*ddd*, *J* = 4.71, 4.71, 8.63, 1 H, H_A-C(3)), 0.40 (*ddd*, *J* = 5.0, 5.0, 8.36, 1 H, H_B-C(3)); ^{13}C NMR (100 MHz, CD_3OD): δ 167.16 (*s*, C(4')), 153.30 (*s*, C(2')), 143.32 (*d*, C(6')), 111.10 (*s*, C(5')), 62.79 (*t*, OCH_2), 52.96 (*t*, CH_2-N), 37.42 (*t*, C(1")), 18.61 (*d*, C(1)), 15.76 (*d*, C(2)), 12.08 (*q*, CH_3), 10.71 (*t*, C(3)); MS (e.i., 70 eV): 224 (7.1%), 207 (2.1%), 194 (15.0%), 193 (70.0%), 180 (8.6%), 179 (8.6%), 165 (4.3%), 152 (14.3%), 150 (10.7%), 139 (15.0%), 127 (22.1%), 126 (55.7%), 109 (10.0%), 98 (14.3%), 96 (50.0%), 83 (27.1%), 81 (85.0%), 79 (27.1%), 68 (35.0%), 67 (95.0%), 55 (100.0%); HRMS calcd. for $C_{11}H_{16}N_2O_3$ 224.11608; found: 224.11607; Anal. calcd. for $C_{11}H_{16}N_2O_3$ (224.26): C, 58.91; H, 7.19; N, 12.49; found: C, 58.79; H, 6.88; N, 12.63.

(±)-3-Benzoyl-1-({(1 RS, *2* SR*)*-trans-*2-[2-(tetrahydro-2*H*-2-pyranyloxy)ethyl]cyclopropyl}-methyl)-1,2,3,4-tetrahydro-2,4-pyrimidinedione* [(±)-**22**]. Similarly as described for compound **9** from **8** (2.08 g, 10.39 mmol), triphenylphosphine (5.55 g, 21.17 mmol), dry 1,4-dioxane (40 *ml*), N^3-benzoyluracil (4.6 g, 21.28 mmol) and DEAD (3.66 g, 21.02 mmol) in dry 1,4-dioxane (20 *ml*) **22** (1.55 g, 38%) was obtained as a colorless oil after column chromatography (silica gel, ethyl acetate/hexane 1:1 and ethyl acetate/acetonitrile 5:1). R_F (ethyl acetate/hexane 2:1) 0.37; UV (methanol) λ_{max}= 256 nm (log ε = 4.49); IR (film): *ν* 3451*brs*, 2942*m*, 2868*w*, 1748*s*, 1703*s*, 1663*s*, 1598*m*, 1439*m*, 1384*m*, 1350*m*, 1254*m*, 1200*m*, 1179*m*, 1119*m*, 1075*m*, 1031*m*; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92-7.90 (*m*, 2 H, H_2-C_{ortho} phenyl), 7.63-7.60 (*m*, 1 H, H-C_{para} phenyl), 7.48-7.45 (*m*, 2 H, H_2-C_{meta} phenyl), 7.38 (*d*, *J* = 8.00; 1 H, H-C(6')), 5.76 (*d*, *J* = 7.81, 1H, H-C(5')), 4.53 (*brs*, 1 H, H-C(2"')), 3.85-3.73 (*m*, 2 H, CH_2-N), 3.67-3.55 (*m*, 2 H, H_A-C(6"'), OCH_A), 3.48-3.38 (*m*, 2 H, H_B-C(6"'), OCH_B), 1.79-1.78 (*m*, 1 H, H_A-C(4"')), 1.72-1.68 (*m*, 1 H, H_A-C(3"')), 1.61-1.44 (*m*, 6 H, H_2-C(1"), H_B-C(3"'), H_B-C(4"'), H_2-C(5"')), 0.96-0.84 (*m*, 2 H, H-C(1), H-C(2)), 0.54-0.44 (*m*, 2 H, H-C(3)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.09 (*s*, CO benzoyl), 163.64 (*s*, C(4')), 151.11 (*s*, C(2')), 144.97 (*d*, C(6')), 136.11 (*s*, C_q phenyl), 132.70 (*d*, C_{para} phenyl), 131.53 (*d*, C_{ortho} phenyl), 130.24 (*d*, C_{meta} phenyl), 102,98 (*d*, C(5')), 100.30 (*d*, C(2"')), 68.02 (*t*, C(6"')), 67.97 (*t*, OCH_2), 53.55 (*t*, CH_2-N), 34.41 (*t*, C(1")), 31.76 (*t*, C(3"')), 26.32 (*t*, C(5"')), 20.74 (*t*, C(4"')), 18.09 (*d*, C(1)), 16.51 (*d*, C(2)), 11.50 (*t*, C(3)); MS (e.i., 70 eV): 398 (5.0%), 369 (1.4%), 313 (8.6%), 293 (26.4%), 283 (10.0%), 209 (3.9%), 193 (22.1%), 179 (4.3%), 105 (100.0%); HRMS calcd. for $C_{22}H_{26}N_2O_5$: 398.18415; found: 398.18416; Anal. calcd. for $C_{22}H_{26}N_2O_5$ (398.46): C, 66.32; H, 6.58; N, 7.03; found: C, 66.09; H, 6.39; N, 6.91.

(±)-3-Benzoyl-1-{[(1 RS, *2* SR*)*-trans-*2-(2-hydroxyethyl)cyclopropyl]methyl}-1,2,3,4-tetrahydro-2,4-pyrimidinedione* [(±)-**23**] and *(±)-1-{[(1* RS, *2* SR*)*-trans-*2-(2-hydroxyethyl)cyclopropyl]methyl}-1,2,3,4-tetrahydro-2,4-pyrimidinedione* [(±)-**24**].
According to the preparation of **10** compound **22** (1.44 g, 3.62 mmol) was dissolved in hydrochloric acid (50 *ml*, 10%) and stirred at room temperature for 12 h. The reaction mixture was cooled to 5 °C, adjusted to pH 7-8 with 8 N NaOH and extracted with ethyl acetate (10 x 50 *ml*). The combined organic phases were dried ($MgSO_4$) and evaporated to afford **23** (0.65 g, 57%) and **24** (0.22 g, 28%) after column chromatography (silica gel, ethyl acetate/methanol 10:1).

Data for **23**: white solid; mp: 195-196 °C; R_F (ethyl acetate/methanol 10:1) 0.63; UV (methanol): λ_{max}= 256 nm (log ε = 4.25); IR (film): *v* 3436*brm*, 3088*w*, 2999*w*, 2930*m*, 1747*s*, 1699*s*, 1652*s*, 1598*m*, 1446*s*, 1385*m*, 1350*m*, 1254*s*, 1179*m*, 1042*m*; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93-7.90 (*m*, 2 H, H_2-C_{ortho} phenyl), 7.64-7,60 (*m*, 1 H, H-C_{para} phenyl), 7.49-7.45 (*m*, 2 H, H_2-C_{meta} phenyl), 7.37 (*d*, *J* = 8.01, 1 H, H-C(6')), 5.75 (*d*, *J* = 8.00, 1 H, H-C(5')), 3.69 (*dd*, *J* =6.35, 13.97, 1 H, CH_2-N), 3.62-3.59 (*m*, 2 H, OCH_2), 3.52 (*dd*, *J* = 7.71, 14.16, 1 H, CH_2-N), 2.02-2.01 (*m*, 1 H, OH), 1.62-1.54 (*m*, 1 H, H_A-C(1")), 1.27 (*dddd*, *J* = 7.11, 7.45, 13.06, 26.88,1 H, H_B-C(1")), 0.96-0.80 (*m*, 2 H, H-C(1), H-C(2)), 0.50 (*ddd*, *J* = 4.98, 4.98, 8.69, 1 H, H_A-C(3)), 0.43 (*ddd*, *J* = 5.27, 5.27, 8.30, 1 H, H_B-C(3)); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.18 (*s*, CO benzoyl), 162.72 (*s*, C(4')), 150.17 (*s*, C(2')), 144.30 (*d*, C(6')), 135.17 (*d*, C_{para} phenyl), 131.55 (*s*, C_q phenyl), 130.49 (*d*, C_{ortho} phenyl), 129.21 (*d*, C_{meta} phenyl), 101.82 (*d*, C(5')), 62.25 (*t*, OCH_2), 52.75 (*t*, CH_2-N), 35.92 (*t*, C(1")), 17.08 (*d*, C(1)), 15.25 (*d*, C(2)), 10.13 (*t*, C(3)); MS (e.i., 70 eV): 314 (0.7%), 283 (9.3%), 270 (3.6%), 209 (15.7%), 179 (12.9%), 113 (8.6%), 106 (7.9%), 105 (100.0%); HRMS calcd. for $C_{17}H_{18}N_2O_4$: 314.12664; found: 314.12665; Anal. calcd. for $C_{17}H_{18}N_2O_4$ (314.34): C, 64.96; H, 5.77; N, 8.91; found: C, 64.76; H, 5.43; N, 8.99.

Data for **24**: white solid; mp: 123.0-123.6 °C; R_F (ethyl acetate/methanol 10:1) 0.40; UV (methanol): λ_{max}= 270 nm (log ε = 3.96); IR (KBr): *v* 3490*brm*, 3014*brw*, 1687*s*, 1660*s*, 1472*w*, 1431*w*, 1389*w*, 1372*w*, 1357*w*, 1258*w*, 1165*w*, 1029*w*, 1008*w*; ^{1}H NMR (400 MHz, d_6-DMSO): δ 11.83 (*s*, 1 H, NH), 7.65 (*d*, *J* = 7.81, 1 H, H-C(6')), 5.51 (*d*, *J* = 7.82, 1 H, H-C(5')), 3.55 (*dd*, *J* = 6.94, 13.97, 1 H, H_A-C-N), 3.45 (*dd*, *J* = 7.52, 13.97, 1 H, H_B-C-N), 3.34-3.32 (*m*, 2 H, OCH_2), 1.97 (*s*, 1 H, OH), 1.40-1.34 (*m*, 1 H, H_A-C(1")), 1.26-1.19 (*m*, 1 H, H_B-C(1")), 0.88-0.84 (*m*, 1 H, H-C(1)), 0.79-0.75 (*m*, 1 H, H-C(2)), 0.45 (*ddd*, *J* = 4.43, 4.43, 8.64, 1 H, H_A-C(3)), 0.28 (*ddd*, *J* = 4.15, 4.15, 8.93, 1 H, H_B-C(3)); ^{13}C NMR (100 MHz, d_6-DMSO): δ 163.94 (*s*, C(4')), 151.22 (*s*, C(2')), 145.75 (*d*, C(6')), 100.71 (*d*, C(5')), 60.69 (*t*, OCH_2), 50.99 (*t*, CH_2-N), 36.24 (*t*, C(1")), 17.25 (*d*, C(1)), 14.17 (*d*, C(2)), 9.66 (*t*, C(3)); MS (e.i., 70 eV): 210 (8.6%), 193 (2.9%), 179 (56.4%), 167 (10.7%), 149 (15.7%), 138 (12.1%), 126 (10.0%), 113 (44.3%), 112 (21.4%), 98 (12.9%), 95 (17.9%), 82 (48.6%), 81 (40.0%), 69 (40.0%), 67 (100.0%), 55 (59.3%), 53 (49.3%); HRMS calcd. for $C_{10}H_{14}N_2O_3$: 210.10043; found: 210.10043; Anal. calcd. for $C_{10}H_{14}N_2O_3$ (210.23): C, 57.13; H, 6.71; N, 13.3; found: C, 57.00; H, 6.51; N, 13.52.

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