Synthesis of Cyclopropanoid Nucleoside Analogues Possessing a Flexible Side Chain

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A novel class of cyclopropanoic nucleoside analogues containing an hydroxyethyl residue instead of a hydroxymethyl side chain has been prepared in an easy sequence. These compounds showed weak antitumor activity. The resolution of the racemates on an analytical scale was performed by HPLC using chiral stationary phases.

Key words: Nucleoside Analogues, Cyclopropanes, HPLC

Introduction

An attractive strategy in the development of new antitumor and/or antiviral active compounds consists in the introduction of carbocyclic units into nucleosides [1]. This concept has successfully been used for the synthesis of numerous cyclobutane [2] and cyclopentane [3] analogues of nucleosides, the so-called carbocyclic nucleosides analogues among which the cyclopropanoid derivatives play a most prominent role [4 – 6]. Besides antitumor activity many of these cyclopropanoic compounds have been shown to be excellent inhibitors of various enzymes.

Results and Discussion

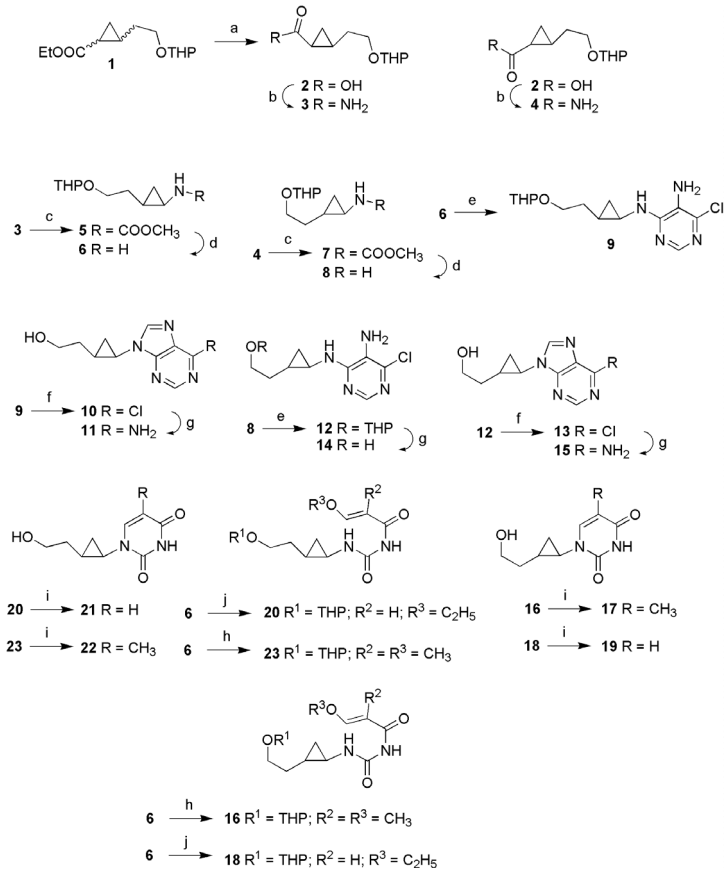
To obtain higher flexibility in the difluoro cyclopropanoid nucleoside analogues series the synthesis of compounds possessing a flexible chain chain was planned. During ongoing QSAR studies of antitumor active cyclopropanoid nucleoside analogues we became interested in the synthesis and biological evaluation of hydroxyethyl substituted derivatives.

The synthesis of *cis* as well as of *trans* configurated compounds (with respect to the relative configuration at the cyclopropane ring) started from well known (±)-ethyl 2-[2-(tetrahydro-2*H*-2-pyranyloxy)ethyl]-1-cyclopropanoate (**1**) [6] as a racemic 1:1 mixture of the corresponding *cis*/*trans* diastereomers to afford after saponification the acids **2**. The relative configuration of these comnpounds has been determined by NMR spectroscopy [6]. Whereas a *Curtius* degradation of **2** under different reaction conditions invariably afforded low yields of complex mixtures of stereomeric products that could not be separated by chromatography, its treatment with ethyl chloroformate in the presence of dry triethylamine followed by the reaction with ammonia at −5 °C gave a mixture of the diastereomeric carboxamides *cis*-**3** and *trans*-**4** that were easily separated by chromatography. *Hofmann* degradation of (±)-**3** using di(acetoxyiodo)-benzene/methanolic potassium hydroxide gave the corresponding methyl carbamate **5** that was conveniently hydrolysed to the amine (±)-**6** [7, 8].

In an analogous manner from **3** *via* the methyl carbamate **7** in good yields the amine **8** was obtained. To obtain heterocycles of the purine type, (±)-**6** was treated with 5-amino-4,6-dichloropyrimidine in the presence of *n*-butanol and triethylamine to yield **9** followed by the reaction with triethyl orthoformate/conc. hydrochloric acid [(±)-**10**]. Finally after treatment with ammonia at 50 bar at 76 °C in an autoclave, 97% of the adenine analogue (±)-**11** were obtained [5].

Similarly for the synthesis of the trans-configurated compounds, reaction of amine **8** with 5-amino-4,6-dichloropyrimidine as described above gave **12** whose cyclization afforded the 6-chloro-purine (±)-**13** and **14** as a by-product. Treatment of (±)-**13** with ammonia in an autoclave finally afforded the adenine derivative (±)-**15**.

A thymine nucleoside analogue was synthesized in the *cis*-series starting from the amine (±)-**6** that was allowed to react with *in situ* prepared (3-methoxy-2-



Scheme 1. Reactions and conditions: a) NaOH; b) $ClCO_2Et/NH_3$; c) di(acetoxyiodo)benzene/KOH; d) KOH/MeOH; e) 5-amino-4,6-dichloro-pyrimidine, *n*-BuOH, NEt_3; f) $C(COEt)_3/HCl$; g) NH_3; h) 3-methoxy-2-methyl-acryloyl chloride/AgOCN; i) H_2SO_4; j) 3-ethoxy-acryloyl chloride/AgOCN.

methyl-acryloyl)isocyanate [9] to afford (±)-**16** followed by a ring closure reaction mediated by 2 N sulphuric acid to yield the thymine derivative (±)-**17**. Following this strategy the *trans* amine (±)-**8** gave under the same conditions *via* (±)-**18** the thymine derivative (±)-**19**. The uracil analogues were obtained by the reaction of the amines with *in situ* prepared (3-ethoxy-acryloyl)isocyanate (to afford (±)-**20** and **18**, respectively) [9] followed by acid-mediated ring closure that gave the *cis*-configurated uracil analogue (±)-**21** and *trans* (±)-**19**, respectively.

Preliminary biological screening of racemic **11**, **15**, **17**, **19**, **21** and **22** revealed weak antitumor activity for several of these compounds. Since it is well established that the biological activity of many nucleoside analogues resides only in one enantiomer [10], the analytical separation of the corresponding enantiomers was accomplished by HPLC using chiral stationary phases.

The chromatographic separation of the enantiomers of (±)-**11**, (±)-**25**, (±)-**17**, (±)-**19**, (±)-**21** and (±)-**22** was performed by HPLC on a Daicel Chiralcel OD column using a hexane/2-propanol mixture or on a Daicel Chiralpak AD column using methanol as the eluent. The better results for these compounds were obtained with the Chiralpak AD column. The results of these separations are summarized in Tables 1 and 2.

Table 1. HPLC conditions for the separation of the enantiomers.

Column	Chiralpak AD	Chiralcel OD
Flow	0.5 ml/min	1.0 ml/min
Pressure	15.7 – 16.7 bar	25.5 bar
Detection	UV/vis, λ = 267, 271, 276 nm	UV/vis, λ = 271, 276 nm
Eluent	methanol	hexane/2-propanol 80:20
Temperature	20 °C	20 °C

For compound (±)-**11** a semi-preparative separation using an analytical Chiralpak AD column was performed using approx. 5 mg/2 ml of (±)-**11** per injection. Thus, sufficient enantiomerically pure material could be obtained; the CD-spectra of (+)-**11** and (−)-**11** are shown in Fig. 1 and are listed in Table 3.

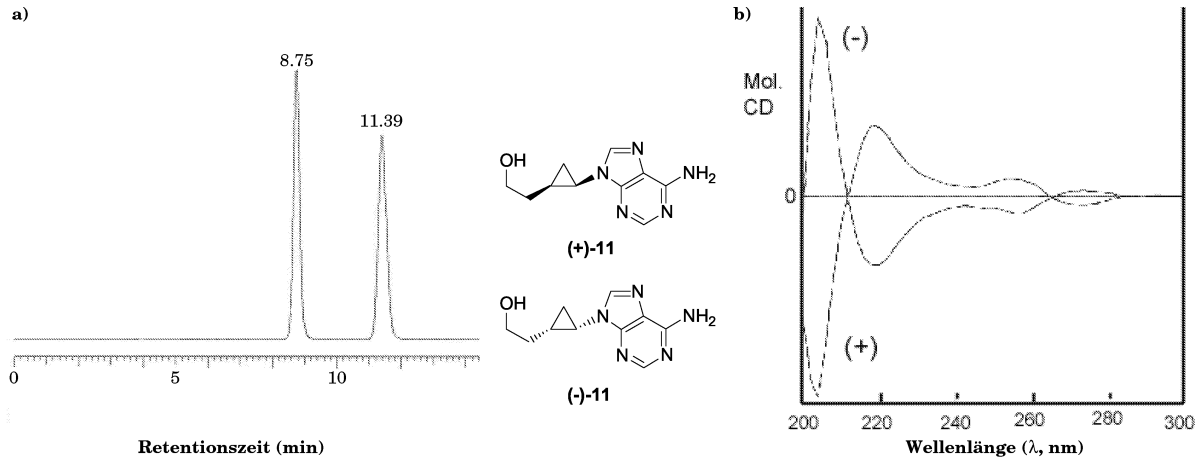


Fig. 1. a) Typical chromatogram for the analytical separation of the enantiomers of (±)-**11** by HPLC (Daicel, Chiralpak AD); b) CD-spectra of (+)-**11** and (−)-**11**.

Table 2. HPLC separation of the enantiomers.

Compound	Column	t_R (+) [min]	t_R (–) [min]
11	Chiralpak AD	8.75	11.39
15	Chiralpak AD	13.71	24.99
22	Chiralpak AD	12.72	28.27
17	Chiralcel OD	61.49	96.27
21	Chiralpak AD	18.29	77.33
19	Chiralcel OD	134.88	155.44

Table 3. Representative optical data for **(-)-11** and **(+)-11**.

Compound	$[\alpha]_D^{20}$	$\Delta\varepsilon$	ee
(+)–11	+6.1	−0.14 (226 nm)	> 99%
(–)–11	−6.2	+0.2 (230 nm)	> 99%

Presently the separation of all enantiomeric forms and their biological testing as well as a chemoenzymatic approach for the synthesis of the pure enantiomers is under investigation in our labs.

Experimental Section

General methods: Melting points are uncorrected (*Leica* hot stage microscope), optical rotations were obtained using a Perkin-Elmer 341 polarimeter (1 cm micro cell), 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 tetrahydropyranyl fragment), IR spectra (film or KBr pellet) were measured on a Perkin-Elmer FT-IR spectrometer Spectrum 1000, MS spectra were taken on a Intectra GmbH AMD 402 (electron impact, 70 eV) or on a Finnigan MAT LCQ 7000 (electrospray, voltage 4.5 kV, under nitrogen) instrument; for elemental analysis a Foss-Heraeus Vario EL instrument was used. TLC was performed on silica gel (Merck 5554, detection by treatment with a solution of 10% sulfuric acid, ammonium molybdate and cerium$^{(IV)}$ sulfate followed by gentle heating or by UV/vis absorption); column chromatography was performed on silica gel 60 (FLUKA, 0.04 – 0.06 mm). HPLC was performed on a Merck-Hitachi L6200A/L4000/D2500 instrument using either a Chiralcel OD (Daicel Chemical Industries, 4.6 × 250 mm, 10 μm) or a Chiralpak AD (Daicel Chemical Industries, 4.6 × 250 mm, 10 μm) column.

*(±)-(1 RS, 2 RS)-cis-2-[2-(Tetrahydro-2H-2-pyranyloxy)-ethyl]-1-cyclopropanecarboxylic acid (**cis**-(±)-**2**) and (±)-(1 RS, 2 SR)-trans-2-[2-(tetrahydro-2H-2-pyranyloxy)-ethyl]-1-cyclopropanecarboxylic acid (**trans**-(±)-**2**)*

A solution of (±)-ethyl(1 *RS*, 2 *RS*)-*cis*-2-[2-(tetrahydro-2*H*-2-pyranyloxy)ethyl]-1-cyclopropanecarboxylate (**cis**-(±)-**1**) and (±)-ethyl(1 *RS*, 2 *SR*)-*trans*-2-[2-(tetrahydro-2*H*-2-pyranyloxy)ethyl]-1-cyclopropanecarboxylate (**trans**-(±)-**1**) (9.65 g, 39.82 mmol) in ethanol (50 ml) was heated under reflux. To this mixture a solution of NaOH (3.02 g, 75.51 mmol) in water (15 ml) was added dropwise over a period of 2 h and stirring was continued for 1 h. After cooling to room temperature the mixture was concentrated, water was added (20 ml) and the mixture was concentrated again. The yellowish residue was suspended in water (20 ml) and extracted with diethyl ether (3 × 50 ml). After adjusting the pH of the aqueous phase to 3 by the addition of HCl (10%), the mixture was extracted with diethyl ether (5 × 50 ml). The combined organic phases were dried over $MgSO_4$ and evaporated under reduced pressure to obtain **2** (8.42 g, 99%) as a yellowish oil. – R_F (ethyl acetate/hexane 3:1), **cis-2**: 0.52, **trans-2**: 0.44. – IR (film): ν = 2944s,

2872m, 1694s, 1456m, 1434m, 1385m, 1353m, 1324m, 1261m, 1228m, 1201s, 1185s, 1137s, 1120s, 1077m, 1034s cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$): δ = 7.99 (s, 1 H, OH), 4.59 – 4.58 (m, 1 H, 2”-H), 3.87 – 3.64 (m, 2 H, 6”-H_A, OCH_A), 3.53 – 3.35 (m, 2 H, 6”-H_B, OCH_B), 1.90 – 1.37 (m, 8 H, 3”-H_2, 4”-H_2, 5”-H_2, CH_2-ethyl), 1.26 – 0.94 (m, 3 H, 2-H, 1-H, 3-H_A), 0.85 – 0.76 (m, 1 H, 3-H_B). – ^{13}C NMR (50 MHz, $CDCl_3$): data for **cis-2**: δ = 178.94 (s, CO), 98.59 (d, C-2”), 66.50 (t, C-6”), 61.89 (t, OCH_2), 33.02 (t, CH_2-ethyl), 30.49 (t, C-3”), 27.10 (t, C-5”), 25.32 (t, C-4”), 19.24 (d, C-1) , 17.69 (d, C-2), 13.81 (t, C-3); data for **trans-2**: δ = 180.09 (s, CO), 98.62 (d, C-2”), 66.90 (t, C-6”), 61.94 (t, OCH_2), 33.02 (t, CH_2-ethyl), 30.49 (t, C-3”), 27.10 (t, C-5”), 25.32 (t, C-4”), 19.91 (d, C-1), 17.69 (d, C-2), 13.81 (t, C-3). – MS (EI, 70 eV): *m/z* (%) = 213 (0.7), 196 (2.1), 168 (0.7), 156 (0.7), 141 (3.6), 129 (2.1), 113 (33.6), 101 (23.6), 95 (12.9), 85 (100.0). – HRMS calcd. for $C_{11}H_{18}O_4$: 214.12050; found: 214.12050. – Analysis for $C_{11}H_{18}O_4$ (214.26): calcd. C 61.66, H 8.47; found C 61.72, H 8.49.

*(±)-(1 RS, 2 RS)-cis-2-[2-(Tetrahydro-2H-2-pyranyloxy)-ethyl]-1-cyclopropanecarboxamide ((±)-**3**) and (±)-(1 RS, 2 SR)-trans-2-[2-(tetrahydro-2H-2-pyranyloxy)ethyl]-1-cyclopropanecarboxamide ((±)-**4**)*

To a stirred solution of **2** (5.00 g, 23.34 mmol), triethylamine (3.9 ml, 28.06 mmol) in dry THF (100 ml) ethyl chloroformate (2.7 ml, 28.37 mmol) was added dropwise at −5 °C and stirring was continued for 1 h at −5 °C. A saturated solution of NH_3 in THF (250 ml) was then added carefully at this temperature and stirring was pursued for 1 h at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for an additional 2 h and filtered. The filtrate was concentrated and the residue was purified by column chromatography (silica gel, ethyl acetate/hexane 1:2 → 2:1) to obtain **3** (2.01 g, 40%) and **4** (2.03 g, 40%). – Data for (±)-**3**: white solid. – M. p. 103.6 – 104.8 °C. – R_F (ethyl acetate/hexane 3:1) 0.21. – IR (KBr): ν = 3360s, 3186m, 2941m, 2869m, 2359w, 1353m, 1324w, 1301m, 1260w, 1201m, 1183w, 1166m, 1139m, 1120m, 1080m, 1060m, 1036s cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 5.57 (s, 1 H, NH), 5.31 (s, 1 H, NH), 4.57 (dd, *J* = 7.37, 3.13 Hz, 1 H, 2”-H), 3.88 – 3.83 (m, 1 H, OCH_A), 3.79 – 3.74 (m, 1 H, 6”-H_A), 3.50 – 3.41 (m, 2 H, OCH_B, 6”-H_B), 1.89 – 1.76 (m, 4 H, 4”-H_2, 3”-H_2), 1.72 – 1.67 (m, 1 H, CH_A-ethyl), 1.57 – 1.48 (m, 4 H, 1-H, CH_B-ethyl, 5”-H_2), 1.37 – 1.24 (m, 1 H, 2-H), 1.00 – 0.92 (m, 2 H, 3-H_2). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.23 (s, CO), 99.89 (d, C-2”), 68.21 (t, C-6”), 63.35 (t, OCH_2), 31.67 (t, CH_2-ethyl), 28.08 (t, C-3”), 26.37 (t, C-5”), 20.57 (t, C-4”), 20.02 (d, C-1), 19.17 (d, C-2), 12.62 (t, C-3). – MS (EI, 70 eV): *m/z* (%) = 184 (8.6), 142 (0.7), 128 (28.6), 113 (19.3), 112 (100.0). – HRMS calcd. for $C_{11}H_{19}NO_3$: 213.13648; found: 213.13648. – Analysis for $C_{11}H_{19}NO_3$ (213.27): calcd. C 61.95, H 8.98, N 6.57; found C 61.85, H 9.02, N 6.63.

Data for (±)-**4**: white solid. – M. p. 77.1 – 77.7 °C. – R_F (ethyl acetate/hexane 3:1) 0.16. – IR (KBr): ν = 3406 brm, 3204w, 2943m, 2871w, 1661m, 1622m, 1456w, 1428w, 1380w, 1353w, 1324w, 1284w, 1201w, 1184w, 1136m, 1120m, 1077w, 1030m cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 5.79 (s, 2 H, NH_2), 4.54 (dd, *J* = 4.32, 4.32 Hz, 1 H, 2”-H), 3.84 – 3.74 (m, 2 H, OCH_A, 6”-H_A), 3.48 – 3.39 (m, 2 H, OCH_B, 6”-H_B), 1.81 – 1.73 (m, 1 H, 4”-H_A), 1.69 – 1.61 (m, 1 H, 3”-H_A), 1.60 – 1.41 (m, 6 H, 4”-H_B, 3”-H_B, 5”-H_2), CH_2-ethyl), 1.40 – 1.33 (m, 1 H, 2-H), 1.22 (ddd, *J* = 8.16, 6.44, 4.18 Hz, 1 H, 1-H), 1.12 (ddd, *J* = 10.95, 4.31, 2.19 Hz, 1 H, 3-H_A), 0.63 (ddd, *J* = 7.96, 6.24, 4.11 Hz, 1 H, 3-H_B). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.13 (s, CO), 99.98 (d, C-2”), 67.87 (t, OCH_2), 63.28 (t, C-6”), 34.19 (t, CH_2-ethyl), 31.62 (t, C-3”), 26.33 (t, C-5”), 22.21 (d, C-1), 20.46 (d, C-2), 20.07 (t, C-4”), 15.07 (t, C-3). – MS (EI, 70 eV): *m/z* (%) = 212 (0.7), 184 (4.3), 158 (2.1), 141 (6.4), 130 (23.6), 113 (58.6), 99 (28.6), 85 (100.0). – HRMS calcd. for $C_{11}H_{19}NO_3$: 213.13648; found: 213.13648. – Analysis for $C_{11}H_{19}NO_3$ (213.27): calcd. C 61.95, H 8.98, N 6.57; found C 61.83, H 9.00, N 6.68.

*(±)-Methyl(1 RS, 2 RS)-cis-2-[2-(tetrahydro-2H-2-pyranyloxy)ethyl]-1-cyclopropylcarbamate ((±)-**5**)*

To a stirred solution of **3** (1.96 g, 9.19 mmol), KOH (1.35 g, 24.06 mmol) in methanol (60 ml), di(acetoxyiodo)benzene (4.0 g, 12.42 mmol) was added in one portion at 5°C. The solution was stirred at ice-bath temperature for 15 min followed by warming to room temperature for an additional 2 h. Methanol was removed under reduced pressure and the residue was partitioned between water (70 ml) and dichloromethane (30 ml). The aqueous layer was extracted with dichloromethane (4 × 30 ml). The combined organic phases were washed with water (50 ml) and brine (50 ml), dried ($MgSO_4$), evaporated and the residue was subjected to column chromatography (silica gel, hexane → ethyl acetate/hexane 1:2 → 2:1) to afford **5** (2.02 g, 90%) as a white solid. – M. p. 65.1 – 66.3 °C. – R_F (ethyl acetate/hexane 1:1) 0.54. – IR (KBr): ν = 3288m, 2949m, 2869m, 1712s, 1691s, 1540m, 1454w, 1354w, 1324w, 1274m, 1236m, 1202m, 1186w, 1137m, 1119m, 1095m, 1078m, 1063m, 1033m cm^{-1}. – ^1H NMR (200 MHz, $CDCl_3$): δ = 5.79 (s, 1 H, NH), 4.60 – 4.57 (m, 1 H, 2″-H), 3.96 – 3.64 (m, 2 H, 6″-H_A, OCHA), 3.60 (s, 3 H, OCH_3), 3.51 – 3.23 (m, 2 H, 6″-H_B), OCH_B), 2.51 (ddd, *J* = 10.89, 5.52, 5.52 Hz, 1 H, 1-H), 1.90 – 1.67 (m, 2 H, 3″-H_A, 4″-H_A), 1.64-1.50 (m, 6 H, 3″H_B, 4″-H_B, 5″-H_2), CH_2-ethyl), 0.96 – 0.77 (m, 2 H, 2-H, 3-H_A), 0.18 – 0.35 (m, 1 H, 3-H_B). – ^{13}C NMR (50 MHz, $CDCl_3$): δ = 158.12 (s, CO), 99.47 (d, C-2″), 67.30 (t, OCH_2), 61.77 (t,

C-6″), 51.78 (q, CH_3), 30.46 (t, CH_2-ethyl), 28.65 (t, C-3″), 26.76 (d, C-1), 25.26 (t, C-5″), 19.29 (t, C-4″), 15.32 (d, C-2), 12.82 (t, C-3); MS (EI, 70 eV): *m/z* (%) = 159 (19.3), 142 (11.4), 128 (7.1), 114 (13.6), 110 (2.9), 100 (2.1), 88 (7.9), 85 (100.0). – HRMS calcd. for $C_{12}H_{21}NO_4$: 243.14705; found: 243.14704. – Analysis for $C_{12}H_{21}NO_4$ (243.30): calcd. C 59.24, H 8.70, N 5.76; found C 59.17, H 8.89, N 5.87.

(±)-(1 RS, 2 RS)-cis-2-[2-(Tetrahydro-2H-2-pyranyl-oxy)-ethyl]-1-cyclopropylamine ((±)-6)

A solution of **5** (3.36 g, 13.81 mmol), KOH (14.6 g, 260.2 mmol), methanol (100 ml) and water (30 ml) was heated under reflux for 48 h. The solvents were removed under reduced pressure and water (50 ml) was added. The aqueous layer was extracted with dichloromethane (5 × 50 ml). The combined organic phases were washed with brine (50 ml), dried ($MgSO_4$) and evaporated *in vacuo* to obtain **6** (2.12 g, 83%) as a colorless oil. – R_F (ethyl acetate/hexane 1:1) 0.05. – IR (film): ν = 3375w, 3068w, 2942s, 2870m, 1576m, 1442m, 1384m, 1352m, 1323m, 1284m, 1261m, 1201m, 1184m, 1164m, 1136s, 1119s, 1076m, 1033s cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.58 – 4.57 (m, 1 H, 2”-H), 3.87 – 3.74 (m, 2 H, 6″-H_A, OCH_A), 3.47 – 3.39 (m, 2 H, 6″-H_B, OCH_B), 2.31 (ddd, *J* = 13.33, 6.10, 5.03 Hz, 1 H, 1-H), 1.81 – 1.65 (m, 4 H, 3″-H_2, 4″-H_2), 1.58 – 1.37 (m, 4 H, CH_2-ethyl, 5″-H_2), 0.70 – 0.59 (m, 2 H, 2-H, 3-H_A), −0.06 (ddd, *J* = 7.62, 3.42, 3.42 Hz, 1 H, 3-H_B). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 98.61 (d, C-2″), 67.69 (t, OCH_2), 61.97 (t, C-6″), 30.59 (t, CH_2-ethyl), 27.74 (t, C-3″), 27.11 (d, C-1), 25.36 (t, C-5″), 19.41 (t, C-4″), 14.96 (d, C-2), 13.00 (t, C-3); MS (EI, 70 eV): *m/z* (%) = 186 (1.4), 168 (0,7), 154 (1.4), 140 (3.6), 126 (3.6), 112 (4.3), 101 (16.4), 100 (32.1), 85 (100.0). – HRMS calcd. for $C_{10}H_{19}NO_2$: 185.14157; found: 185.14158. – Analysis for $C_{10}H_{19}NO_2$ (185.26): calcd. C 64.83, H 10.34, N 7.56; found C 64.69, H 10.18, N 7.31.

(±)-Methyl(1 RS, 2 SR)-trans-2-[2-(tetrahydro-2H-2-pyranyloxy)ethyl]-1-cyclopropylcarbamate ((±)-7)

Following the procedure given for the preparation of compound **5** using **4** (5.23 g, 24.52 mmol), KOH (3.45 g, 61.49 mmol), methanol (75 ml) and bis(acetoxy)iodobenzene (8.10 g, 25.15 mmol) **7** (5.67 g, 95%) was obtained after purification by column chromatography (silica gel, hexane → ethyl acetate/hexane 1:2 → 2:1) as a colorless oil. – R_F (ethyl acetate/hexane 1:1) 0.54. – IR (film): ν = 3323m, 2944m, 2869m, 1708s, 1527m, 1455m, 1354m, 1264m, 1217m, 1201m, 1136m, 1119m, 1076m, 1064m, 1032s cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.87 (s, 1 H, NH), 4.57 – 4.54 (m, 1 H, 2″-H), 3.86 – 3.76 (m, 2 H, 6″-H_A), OCH_A), 3.62 (s, 3 H, OCH_3), 3.50 – 3.44 (m, 2 H, 6″-H_B, OCH_B), 2.38 – 2.50 (m, 1 H, 1-H), 1.81 – 1.74 (m, 1 H, 4″-H_A), 1.71 – 1.63 (m, 1 H, 3″-H_A), 1.58 – 1.42 (m, 6 H, 3″-H_B, 4″-H_B, 5″-H_2), CH_2-ethyl), 0.95 – 0.87 (m, 1 H, 2-H), 0.64 (ddd, *J* = 9.23, 4.54, 4.54 Hz, 1 H, 3-H_A), 0.57 – 0.52 (m, 1 H, 3-H_B). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.69 (s, CO), 98.94 (d, C-2″), 66.64 (t, OCH_2), 62.31 (t, C-6″), 51.94 (q, CH_3), 32.37 (t, CH_2-ethyl), 30.63 (t, C-3″), 29.34 (d, C-1), 25.33 (t, C-5″), 19.53 (t, C-4″), 17.71 (d, C-2), 13.47 (t, C-3). – MS (EI, 70 eV): *m/z* (%) = 242 (5.7), 212 (2.1), 184 (2.1), 159 (18.6), 142 (3.6), 128 (8.6), 114 (20.7), 110 (2.9), 101 (2.9), 88 (8.6), 85 (100.0). – HRMS calcd. for $C_{12}H_{21}NO_4$: 243.14706; found: 243.14706. – Analysis for $C_{12}H_{21}NO_4$ (243.30): calcd. C 59.24, H 8.70, N 5.76; found C 58.98, H 8.70, N 5.89.

(±)-(1 RS, 2 SR)-trans-2-[2-(Tetrahydro-2H-2-pyranyl-oxy)-ethyl]-1-cyclopropylamine ((±)-8)

According to the preparation of **6** from **7** (2.00 g, 8.22 mmol), KOH (8.72 g, 155.41 mmol), methanol (40 ml) and water (10 ml) **8** (1.41 g, 93%) was obtained as a colorless oil. – R_F (ethyl acetate/hexane 1:1) 0.05. – IR (film): ν = 3361w, 3071w, 2941s, 2869m, 2360w, 1578w, 1454m, 1353m, 1323w, 1261w, 1201m, 1184w, 1165m, 1136m, 1120m, 1077m, 1033s cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.53 – 4.48 (m, 1 H, 2″-H), 3.85 – 3.68 (m, 2 H, 6″-H_A, OCH_A), 3.47 – 3.34 (m, 2 H, 6″-H_B, OCH_B), 2.02 (ddd, *J* = 6.78, 3.37, 3.37 Hz, 1 H, 1-H), 1.80 – 1.58 (m, 2 H, 3″-H_A, 4″-H_A), 1.55 – 1.29 (m, 6 H, 3″-H_B, 4″-H_B, 5″-H_2, CH_2-ethyl), 0.74 – 0.67 (m, 1 H, 2-H), 0.42 (ddd, *J* = 10.98, 4.88, 2.78 Hz, 1 H, 3-H_A), 0.24 (ddd, *J* = 7.18, 4.74, 4.74 Hz, 1 H, 3-H_B). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 98.81 (d, C-2″), 67.06 (t, OCH_2), 62.14 (t, C-6″), 32.62 (t, CH_2-ethyl), 30.71 (t, C-3″), 30.57 (d, C-1), 25.30 (t, C-5″), 19.35 (t, C-4″), 18.45 (d, C-2), 14.27 (t, C-3). – MS (EI, 70 eV): *m/z* (%) = 184 (1.4), 149 (0.7), 126 (1.4), 112 (0,7), 101 (2.9), 100 (19.3), 85 (100.0). – HRMS calcd. for $C_{10}H_{19}NO_2$: 185.14157; found: 185.14157. – Analysis for $C_{10}H_{19}NO_2$ (185.26): calcd. C 64.83, H 10.34, N 7.56; found C 64.78, H 10.54, N 7.69.

(±)-4N-{(1 RS, 2 RS)-cis-2-[2-(Tetrahydro-2H-2-pyranyl-oxy)ethyl]cyclopropyl}-6-chloro-4,5-pyrimidine-diamine ((±)-9)

A suspension of **6** (2.0 g, 10.8 mmol), triethylamine (25 ml), 5-amino-4,6-dichloro-pyrimidine (3.55 g, 21.65 mmol) in *n*-butanol (50 ml) was heated under reflux for 24 h. After cooling to room temperature the solvent was removed under reduced pressure and the remaining oil subjected to column chromatography (silica gel, ethyl acetate/hexane 1:1 → 2:1) to afford **9** (3.15 g, 93%) as a yellowish oil. – R_F (ethyl acetate/hexane 3:1) 0.5. – UV/vis (methanol): λ_{max} (lg ε) = 302 nm (4.28). – IR (film):

ν = 3354s, 2942s, 2870m, 1733m, 1644m, 1574s, 1495s, 1454s, 1418s, 1358s, 1244m, 1202m, 1184m, 1119s, 1074s, 1032s cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, J = 7.81 Hz,1 H, 2′-H), 6.03 (s, 2 H, NH_2), 4.62 (s, 1 H, NH), 4.52 (dd, J = 6.64, 2.34 Hz, 1 H, 2″-H), 3.96 – 3.80 (m, 2 H, 6″-H_A, OCH_A), 3.61 – 3.46 (m, 2 H, 6″-H_B, OCH_B), 2.77 (ddd, J = 9.27, 4.30, 3.52 Hz, 1 H, 1-H), 1.98 – 1.47 (m, 8 H, 3″-H_2), 4″-H_2, 5″-H_2, CH_2-ethyl), 1.11 – 1.05 (m, 2 H, 2-H, 3-H_A), 0.23 – 0.20 (m, 1 H, 3-H_B). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.30 (s, C-6′), 148.97 (d, C-2′), 141.01 (s, C-4′), 122.74 (s, C-5′), 101.56 (d, C-2″), 69.16 (t, OCH_2), 64.38 (t, C-6″), 30.85 (t, CH_2-ethyl), 29.11 (t, C-3″), 27.65 (d, C-1), 25.10 (t, C-5″), 20.68 (t, C-4″), 15.83 (d, C-2), 13.27 (t, C-3). – MS (EI, 70 eV): *m/z* (%) = 312 (9.3), 239 (6.4), 227 (25.0), 211 (21.4), 201 (15.7), 183 (15.0), 156 (27.7), 144 (15.7), 130 (5.7), 101 (5.7), 85 (100.0). – HRMS calcd. for $C_{14}H_{21}ClN_4O_2$: 312.13529; found: 312.13529. – Analysis for $C_{14}H_{21}ClN_4O_2$ (312.80): calcd. C 53.76, H 6.77, Cl 11.33, N 17.91; found C 53.49, H 6.86; Cl 11.56, N 17.64.

(±)-2-[(1 RS, 2 RS)-cis-2-(6-Chloro-9H-9-purinyl)cyclopropyl]-1-ethanol ((±)-10)

A suspension of **9** (2.38 g, 7.61 mmol) in triethyl orthoformate (18.0 g, 121.46 mmol) and hydrochloric acid (36%, 0.9 g, 9.0 mmol) was stirred for 4 h at room temperature. By addition of sodium hydrogen carbonate and water (50 ml) the pH of the reaction mixture was adjusted to 7 – 8 and the aqueous solution was extracted with ethyl acetate (5 × 100 ml), the combined organic phases were dried ($MgSO_4$) and the solvent was removed. The crude product was purified by column chromatography (silica gel, ethyl acetate → ethyl acetate/methanol 10:1) to obtain **10** (0.97 g, 53%) as a white solid. – M. p. 122.4 – 122.9 °C; UV/vis (methanol): λ_{max} (lg ε) = 269 nm (4.23). – R_F(ethyl acetate/methanol 10:1) 0.52. – IR (KBr): ν = 3343m, 3103w, 2939w, 2863w, 1594s, 1569m, 1498w, 1441m, 1404m, 1342s, 1234m, 1150w, 1045m cm^{-1}. – ^1H NMR (500 MHz, $CDCl_3$): δ = 8.71 (s, 1 H, 2′-H), 8.10 (s, 1 H, 8′-H), 3.69 – 3.64 (m, 2 H, OCH_2), 3.55 (ddd, J = 7.36, 7.36, 4.16 Hz, 1 H, 2-H), 2.31 (brs, 1 H, OH), 1.59 – 1.52 (m, 2 H, CH_A-ethyl, 1-H), 1.46 (ddd, J = 7.64, 5.96, 3.81 Hz, 1 H, 3-H_A), 1.15 (ddd, J = 6.28, 6.28, 4.36 Hz, 1 H, 3-H_B), 1.00 (dddd, J = 17.98, 8.38, 4.50, 4.26 Hz, 1 H, CH_B-ethyl). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.19 (s, C-6′), 152.16 (d, C-2′), 151.34 (s, C-4′), 146.68 (d, C-8′), 131.94 (s, C-5′), 61.70 (t, OCH_2), 30.63 (d, C-2), 30.08 (t, CH_2-ethyl), 15.10 (d, C-1), 10.26 (t, C-3). – MS (EI, 70 eV): *m/z* (%) = 239 (3.6), 237 (2.9), 221 (3.6), 219 (3.6), 209 (11.4), 207 (67.1), 205 (7.1), 194 (25.0), 183 (5.7), 167 (7.9), 157 (37.1), 155 (100.0). – HRMS calcd. for $C_{10}H_{11}ClN_4O$: 238.06213; found: 238.06214. – Analysis for $C_{10}H_{11}ClN_4O$ (238.68): calcd. C 50.32, H 4.65, Cl 14.85, N 23.47; found C 50.21, H 4.81, Cl 15.02, N 23.51.

(±)-2-[(1 RS, 2 RS)-cis-2-(6-Amino-9H-9-purinyl)cyclopropyl]-1-ethanol ((±)-11)

A solution of **10** (0.9 g, 3.77 mmol) in liquid ammonia (100 ml) was heated at 76 °C for 20 h in an autoclave (50 bar). After removal of the ammonia the residue was dissolved in methanol. The solvent was removed *in vacuo* to afford **11** (0.80 g, 97%) as a white solid. – M. p. 185.4 – 186.1 °C. – R_F(ethyl acetate/methanol 10:1) 0.23. – UV/vis (methanol): λ_{max} (lg ε) = 264 nm (4.28). – IR (KBr): ν = 3296s, 3125s, 2931m, 1677s, 1608s, 1577m, 1480m, 1404m, 1335m, 1307m, 1262w, 1194w, 1111w, 1048m cm^{-1}. – ^1H NMR (500 MHz, CD_3OD): δ = 8.21 (s, 1 H, 2′-H), 8.08 (s, 1 H, 8′-H), 4.79 (s, 1 H, OH), 3.60 – 3.52 (m, 3 H, 2-H, OCH_2), 1.59 – 1.52 (m, 1 H, CH_A-ethyl), 1.48 – 1.35 (m, 2 H, 1-H, 3-H_A), 1.21 (ddd, J = 7.29, 4.21, 4.21 Hz, 1 H, 3-H_B), 0.89 – 0.83 (m, 1 H, CH_B-ethyl). – ^{13}C NMR (100 MHz, d_6-DMSO): δ = 156.15 (s, C-6′), 152.67 (d, C-2′), 151.20 (s, C-4′), 141.77 (d, C-8′), 119.18 (s, C-5′), 60.26 (t, OCH_2), 30.75 (d, C-2), 29.28 (t, CH_2-ethyl), 14.34 (d, C-1), 9.20 (t, C-3). – MS (EI, 70 eV): *m/z* (%) = 219 (41.4), 202 (7.9), 189 (33.6), 188 (100.0). – HRMS calcd. for $C_{10}H_{13}N_5O$: 219.11199; found: 219.11200. – Analysis for $C_{10}H_{13}N_5O$ (219.25): calcd. C 54.78, H 5.98, N 31.94; found C 54.52, H 5.71, N 31.69.

(±)-N4-{trans-2-[2-(Tetrahydro-2H-2-pyranyloxy)-ethyl]-cyclopropyl}-6-chloro-4,5-pyrimidinediamine ((±)-12)

The reaction was performed under the conditions as described for **9** using **8** (2.00 g, 10.80 mmol), triethylamine (50 ml), 5-amino-4,6-dichloro-pyrimidine (2.93 g, 17.87 mmol) in *n*-butanol (100 ml). After evaporation of the solvents and purification by column chromatography (silica gel, ethyl acetate/hexane 1:1 → 2:1) **12** (2.94 g, 87%) was obtained as a yellowish oil. – R_F(ethyl acetate/hexane 3:1) 0.5. – UV/vis (methanol): λ_{max} (lg ε) = 302 nm (3.98). – IR (film): ν = 3355s, 3251s, 2941s, 2870m, 1737m, 1644m, 1574s, 1496s, 1467s, 1450s, 1419s, 1342m, 1299m, 1238m, 1200m, 1184m, 1162m, 1119s, 1075s, 1030s cm^{-1}. – ^1H NMR (400 MHz, $CDCl_3$): δ = 8.07 (s, 1 H, 2′-H), 5.37 (s, 1 H, NH), 4.55 (dd, J = 4.59, 2.83 Hz, 1 H, 2″-H), 3.88 – 3.80 (m, 2 H, 6″-H_A, OCH_A), 3.66 – 3.42 (m, 2 H, 6″-H_B, OCH_B), 2.59 (ddd, J = 7.91, 5.57, 3.22 Hz, 1 H, 1-H), 1.81 – 1.45 (m, 8 H, 3″-H_2, 4″-H_2, 5″-H_2, CH_2-ethyl), 1.03 – 0.94 (m, 1 H, 2-H), 0.73 – 0.67 (m, 2 H, 3-H_2). – ^{13}C NMR (100 MHz, $CDCl_3$): ν = 155.71 (s, C-6′), 149.54 (d, C-2′), 142.44 (s, C-4′), 122.15 (s, C-5′), 99.34 (d, C-2″), 66.97 (t, OCH_2), 62.70 (t, C-6″), 32.45 (t, CH_2-ethyl), 30.67 (t, C-3″), 30.46 (d, C-1), 25.30 (t, C-5″), 19.73 (t, C-4″), 17.83 (d, C-2), 13.99 (t, C-3). – MS (EI, 70 eV): *m/z* (%) = 312 (14.3), 239 (7.9), 228 (32.9), 212 (27.1), 197 (20.7), 183 (21.4), 175 (19.3), 169 (25.0), 156 (30.0), 144 (18.6), 130 (6.4), 119 (4.3), 101 (5.0), 85 (100.0). – HRMS calcd.

for $C_{14}H_{21}ClN_4O_2$: 312.13529; found: 312.13527. – Analysis for $C_{14}H_{21}ClN_4O_2$ (312.80): calcd. C 53.76, H 6.77, Cl 11.33, N 17.91; found C 53.41, H 6.82, Cl 11.49, N 17.69.

(±)-2-{(1 RS, 2 SR)-trans-2-(6-Chloro-9H-9-purinyl)-cyclopropyl}-1-ethanol ((±)-13) and (±)-2-{(1 RS, 2 SR)-trans-2-(5-Amino-6-chloro-4-pyrimidinyl-amino)cyclopropyl}-1-ethanol ((±)-14)

The same experimental procedure as given for **10** starting from **12** (2.72 g, 8.70 mmol), triethyl orthoformate (21.47 g, 144.87 mmol) and hydrochloric acid (36%, 1.11 g, 11.10 mmol) led to the crude products. Column chromatography (silica gel, ethyl acetate → ethyl acetate/methanol 10:1) of the residue yielded **13** (0.31 g, 15%) and **14** (1.05 g, 53%).

Data for (±) – **13**: yellowish oil. – R_F(ethyl acetate/methanol 10:1) 0.52. – UV/vis (methanol): λ_{max} (lg ε) = 270 nm (3.70). – IR (film): ν = 3346brm, 3061w, 2933m, 2239w, 1797w, 1724m, 1592s, 1564s, 1496m, 1438m, 1412m, 1337m, 1226s, 1172m, 1120m, 1094m, 1063m cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74 (s, 1 H, 8′-H), 8.13 (s, 1 H, 2′-H), 3.73 – 3.63 (m, 2 H, OCH_2), 3.57 (ddd, J = 7.32, 7.32, 4.30 Hz, 1 H, 2-H), 2.29 (s, 1 H, OH), 1.61 – 1.45 (m, 3 H, 1-H, 3-H_A), CH_A-ethyl), 1.16 (ddd, J = 6.98, 5.23, 5.22 Hz, 1 H, 3-H_B), 1.06 – 1.00 (m, 1 H, CH_B-ethyl). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.24 (s, C-6′), 153.20 (d, C-2′), 152.39 (s, C-4′), 147.70 (d, C-8′), 132.99 (s, C-5′), 62.75 (t, OCH_2), 31.67 (d, C-2), 31.13 (t, CH_2-ethyl), 16.15 (d, C-1), 11.30 (t, C-3). – MS (EI, 70 eV): *m/z* (%) = 239 (2.9), 238 (0.7), 237 (3.6), 221 (2.1), 219 (2.9), 209 (21.4), 207 (59.3), 205 (6.4), 194 (24.3), 183 (12.5), 167 (21.8), 157 (38.2), 155 (100.0), 129 (7.9), 119 (8.6), 104 (15.0), 84 (4.3), 77 (4.6). – HRMS calcd. for $C_{10}H_{11}ClN_4O$: 238.06213; found: 238.06213. – Analysis for $C_{10}H_{11}ClN_4O$ (238.68): calcd. C 50.32, H 4.65, N 23.47; found C 50.21, H 4.39, N 23.23.

Data for (±) – **14**: yellowish solid. – M. p. 161.2 – 163.0 °C. – R_F(ethyl acetate/methanol 10:1) 0.56. – UV/vis (methanol): λ_{max} (lg ε) = 272 nm (3.74). – IR (KBr): ν = 3447m, 3351m, 3254m, 2941m, 2864w, 1668m, 1636m, 1592s, 1503m, 1475m, 1449m, 1414m, 1396w, 1341m, 1300m, 1236m, 1198w, 1164w, 1100m, 1068m, 1010w cm^{-1}. – ^{1}H NMR (400 MHz, CD_3OD): δ = 7.79 (s, 1 H, 2′-H), 4.84 (s, 1 H, OH), 3.84 – 3.71 (m, 2 H, OCH_2), 2.55 (ddd, J = 7.18, 3.57, 3.57 Hz, 1 H, 2-H), 1.97 – 1.91 (m, 1 H, CH_A-ethyl), 1.10 (dddd, J = 15.65, 9.01, 4.37, 4.37 Hz, 1 H, CH_B-ethyl), 0.87 (ddd, J = 9.18, 5.28, 3.90 Hz, 1 H, 3-H_A), 0.80 – 0.72 (m, 1 H, 1-H), 0.63 (ddd, J = 7.37, 5.52, 5.52 Hz, 1 H, 3-H_B). – ^{13}C NMR (100 MHz, CD_3OD): δ = 155.09 (s, C-6′), 146.96 (d, C-2′), 138.66 (s, C-4′), 125.63 (s, C-5′), 63.51 (t, OCH_2), 36.36 (t, CH_2-ethyl), 31.23 (d, C-2), 20.54 (d, C-1), 11.62 (t, C-3). – MS (EI, 70 eV): *m/z* (%) = 229 (12.9), 228 (6.1), 227 (3.6), 213 (12.1), 211 (30.0), 199 (21.4), 197 (65.0), 186 (30.7), 184 (95.7), 171 (37.1), 169 (100.0). – HRMS calcd. for $C_9H_{13}ClN_4O$: 228.07778; found: 228.07777. – Analysis for $C_9H_{13}ClN_4O$ (228.68): calcd. C 47.27, H 5.73, N 24.50; found C 47.03, H 5.53, N 24.34.

(±)-2-{(1 RS, 2 SR)-trans-2-(6-Amino-9H-9-purinyl)-cyclopropyl}-1-ethanol ((±)-15

A solution of **13** (0.29 g, 1.22 mmol) in liquid ammonia (25 ml) was heated at 76 °C for 20 h in an autoclave (30 bar). After removal of the ammonia the residue was dissolved in methanol. The solvent was removed *in vacuo* and the residue was subjected to column chromatography (silica gel, ethyl acetate/methanol 10:1) to obtain **15** (0.17 g, 64%) as a yellowish solid. – M. p. 192.2 – 193.0 °C. – R_F(ethyl acetate/methanol 10:1) 0.23. – UV/vis (methanol): λ_{max} (lg ε) = 266 nm (3.90). – IR (KBr): ν = 3284s, 3135s, 2930m, 2872m, 1728m, 1675s, 1608s, 1573m, 1515w, 1480m, 1457m, 1422m, 1404m, 1382m, 1336m, 1300s, 1256m, 1198m, 1120m, 1064m, 1026m, 1006m cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.33 (s, 1 H, 2′-H), 7.76 (s, 1 H, 8′-H), 5.91 (s, 2 H, NH_2), 3.95 – 3.86 (m, 2 H, OCH_2), 3.20 (ddd, J = 7.05, 3.53, 3.53 Hz, 1 H, 2-H), 1.30 – 1.21 (m, 2 H, CH_A-ethyl, 1-H), 1.10 – 1.02 (m, 1 H, 3-H_A), 0.96 (ddd, J = 7.94, 4.33, 3.05 Hz, 1 H, 3-H_B), 0.91 – 0.85 (m, 1 H, CH_B-ethyl). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.76 (s, C-6′), 153.97 (d, C-2′), 152.17 (s, C-4′), 142.13 (d, C-8′), 120.63 (s, C-5′), 62.64 (t, OCH_2), 35.83 (d, C-2), 31.49 (t, CH_2-ethyl), 19.18 (d, C-1), 11.91 (t, C-3). – MS (EI, 70 eV): *m/z* (%) = 219 (35.0), 202 (7.9), 189 (65.7), 188 (100.0). – HRMS calcd. for $C_{10}H_{13}N_5O$: 219.11200; found: 219.11201. – Analysis for $C_{10}H_{13}N_5O$ (219.25): calcd. C 54.78, H 5.98, N 31.94; found C 54.92, H 5.99, N 31.85.

(±)-{(1 RS, 2 SR)-trans-2-[2-(Tetrahydro-2H-2-pyranyl-oxy)ethyl]cyclopropyl}-3-(3-methoxy-2-methyl-acryloyl)-urea ((±)-16)

Following the procedure given for the preparation of compound **23** using 3-methoxy-2-methylacryloyl chloride (1.80 g, 13.38 mmol), silver cyanate (2.30 g, 15.34 mmol) in dry benzene (15 ml) and **8** (0.80 g, 4.32 mmol), compound **16** (1.02 g, 72%) was obtained after purification by column chromatography (silica gel, ethyl acetate/hexane 1:1) as a yellowish oil. – R_F(ethyl acetate/hexane 1:1) 0.19. – UV/vis (methanol): λ_{max} (lg ε) = 259 nm (4.13). – IR (film): δ = 3270m, 2941m, 2869m, 1689s, 1615m, 1538s, 1454m, 1402m, 1369w, 1352m, 1295m, 1244s, 1184m, 1130s, 1076m, 1034s cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71 (s, 1 H, OCNHCO), 8.64 (s, 1 H, NH), 7.33 (d, J = 1.17 Hz, 1 H, CH=), 4.56 – 4.53 (m, 1 H, 2″-H), 3.84 – 3.74 (m, 2 H, 6″-H_A, OCH_A), 3.81 (s, 3 H, OCH_3), 3.48 – 3.40 (m, 2 H, 6″-H_B, OCH_B), 2.46 (ddd, J = 5.66, 4.49,

2.54 Hz, 1 H, 1-H), 1.80 – 1.74 (m, 2 H, 4″-H_2), 1.72 (d, J = 0.98 Hz, 3 H, CH_3), 1.70 – 1.61 (m, 1 H, 3″-H_A), 1.55 – 1.44 (m, 5 H, 3″-H_B, 5″-H_2, CH_2-ethyl), 1.00 – 0.93 (m, 1 H, 2-H), 0.69 (ddd, J = 9.28, 5.37, 3.91 Hz, 1 H, 3-H_A), 0.56 (ddd, J = 9.37, 9.37, 3.71 Hz, 1 H, 3-H_B). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.63 (s, CO), 158.40 (d, CH=), 155.43 (s, NHCONH), 107.50 (s, C_q), 98.75 (d, C-2″), 66.48 (t, OCH_2), 62.09 (t C-6″), 61.27 (q, OCH_3), 32.49 (t, CH_2-ethyl), 30.57 (t, C-3″), 28.59 (d, C-1), 25.32 (t, C-5″), 19.37 (t, C-4″), 17.16 (d, C-2), 13.19 (t, C-3), 8.56 (q, CH_3). – MS (EI, 70 eV): *m/z* (%) = 327 (3.6), 311 (4.3), 279 (0.7), 243 (2.9), 227 (5.7), 211 (3.6), 197 (7.9), 178 (4.3), 159 (39.3), 141 (7.1), 116 (7.1), 99 (100.0). – HRMS calcd. for $C_{16}H_{26}N_2O_5$: 326.18416; found: 326.18417. – Analysis for $C_{16}H_{26}N_2O_5$ (326.39): calcd. C 58.88, H 8.03, N 8.58; found C 58.97, H 7.85, N 8.55.

(±)-1-{(1 RS, 2 SR)-trans-2-(2-Hydroxyethyl)cyclopropyl}-5-methyl-1,2,3,4-tetrahydro-pyrimidine-2,4-dione ((±)-17)

According to the preparation of **22** from **16** (0.47 g, 1.44 mmol) and sulfuric acid (2 N, 20 ml), compound **17** (0.21 g, 68%) was obtained as a yellowish solid. – M. p. 196.4 – 197.0 °C. – R_F (ethyl acetate/methanol 10:1) 0.59. – UV/vis (methanol): λ_{max} (lg ε) = 275 nm (4.11). – IR (film): ν = 3382s, 3156m, 3016m, 2923s, 1667s, 1454m, 1425m, 1387m, 1321m, 1297m, 1163m, 1074m, 1018m cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.17 (s, 1 H, NH), 7.05 (s, 1 H, 6′-H), 3.83 – 3.78 (m, 2 H, OCH_2), 2.87 (ddd, J = 7.11, 3.51, 3.51 Hz, 1 H, 1-H), 2.07 – 2.03 (m, 1 H, CH_A-ethyl), 1.88 (s, 3 H, CH_3), 1.18 – 1.14 (m, 1 H, 2-H), 1.07 – 1.01 (m, 1 H, CH_B-ethyl), 0.96 (ddd, J = 9.80, 6.12, 3.73 Hz, 1 H, 3-H_A), 0.80 – 0.76 (m, 1 H, 3-H_B). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.80 (s, C-4′), 152.87 (s, C-2′), 140.78 (d, C-6′), 111.16 (s, C-5′), 61.97 (t, OCH_2), 36.47 (d, C-1), 35.21 (t, CH_2-ethyl), 19.63 (d, C-2), 12.13 (q, CH_3), 11.30 (t, C-3). – MS (EI, 70 eV): *m/z* (%) = 210 (13.6), 182 (17.1), 180 (7.9), 166 (12.1), 154 (2.9), 140 (6.1), 136 (16.4), 127 (100.0). – HRMS calcd. for $C_{10}H_{14}N_2O_3$: 210.10043; found: 210.10042. – Analysis for $C_{10}H_{14}N_2O_3$ (210.23): calcd. C 57.13, H 6.71, N 13.33; found C 57.33, H 6.58, N 12.87.

(±)-{(1 RS, 2 SR)-trans-2-[2-(Tetrahydro-2H-2-pyranyl-oxy)ethyl]cyclopropyl}-3-(3-ethoxy-acryloyl)urea ((±)-18)

Similarly as described for compound **23** using 3-ethoxy-acryloyl chloride (2.00 g, 14.86 mmol), silver cyanate (3.36 g, 22.42 mmol) in dry benzene (20 ml) and **8** (1.09 g, 5.88 mmol), **18** (1.39 g, 72%) was obtained as a yellowish solid. – M. p. 102.6 – 103.9 °C. – R_F (ethyl acetate/hexane 3:1) 0.45. – UV/vis (methanol): λ_{max} (lg ε) = 252 nm (4.25). – IR (KBr): δ 3272m, 3091m, 2940m, 2869m, 1704s, 1676s, 1606s, 1537s, 1499s, 1473m, 1455m, 1396m, 1370w, 1345m, 1325m, 1244s, 1184s, 1151s, 1076m, 1062m, 1031s, 1000m cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.97 (s, 1 H, OCNHCO), 8.64 (s, 1 H, NH), 7.56 (d, J = 12.30 Hz, 1 H, OCH=), 5.36 (d, J = 12.30 Hz, 1 H, CH=), 4.54 – 4.52 (m, 1 H, 2″-H), 3.91 (q, J = 6.40 Hz, 2 H, OCH_2-ethyl), 3.83 – 3.73 (m, 2 H, 6″-H_A, OCH_A), 3.47 – 3.39 (m, 2 H, 6″-H_B, OCH_B), 2.44 (ddd, J = 3.42, 3.42, 2.05 Hz, 1 H, 1-H), 1.79 – 1.71 (m, 1 H, 4″-H_A), 1.69 – 1.62 (m, 2 H, 3″-H_A, CH_A-ethyl), 1.52 – 1.35 (m, 5 H, 3″-H_B, 4″-H_B, 5″-H_2, CH_B-ethyl), 1.28 (t, J = 4.69 Hz, 3 H, CH_3), 1.00 – 0.93 (m, 1 H, 2-H), 0.70 (ddd, J = 9.28, 5.27, 4.10 Hz, 1 H, 3-H_A), 0.57 – 0.53 (m, 1 H, 3-H_B). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.38 (s, CO), 162.54 (d, OCH=), 156.48 (s, NHCONH), 98.74 (d, OC-CH=), 98.06 (d, C-2″), 67.01 (t, OCH_2-ethyl), 66.45 (t, OCH_2), 62.08 (t, C-6″), 32.43 (t, CH_2-ethyl), 30.53 (t, C-3″), 28.45 (d, C-1), 25.27 (t, C-5″), 19.35 (t, C-4″), 17.31 (d, C-2), 14.20 (q, CH_3), 12.92 (t, C-3). – MS (EI, 70 eV): *m/z* (%) = 327 (0.4), 297 (0.7), 285 (0.7), 256 (0.4), 242 (44.3), 226 (4.3), 211 (8.6), 197 (6.4), 185 (6.4), 172 (5.7), 159 (100.0). – HRMS calcd. for $C_{16}H_{26}N_2O_5$: 326.18416; found: 326.18416. – Analysis for $C_{16}H_{26}N_2O_5$ (326.39): calcd. C 58.88, H 8.03, N 8.58; found C 58.71, H 7.98, N 8.48.

(±)-1-[(1 RS, 2 SR)-trans-2-(2-Hydroxyethyl)cyclopropyl]-1,2,3,4-tetrahydro-pyrimidine-2,4-dione ((±)-19)

The reaction was performed under the conditions as described for **21** using **18** (0.80 g, 2.46 mmol) in sulfuric acid (2 N, 25 ml). After neutralisation and evaporation of the solvents under reduced pressure, the residue was extracted with ethyl acetate (300 ml). The combined organic phases were dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by column chromatography (silica gel, ethyl acetate/methanol 10:1) to afford compound **19** (0.32 g, 66%) as a yellowish solid. – M. p. 227 – 228 °C. – R_F (ethyl acetate/methanol 10:1) 0.50. – UV/vis (methanol): λ_{max} (lg ε) = 270 nm (3.91). – IR (KBr): ν = 3376m, 3134m, 3010m, 2957m, 2876w, 2810m, 1675s, 1616m, 1470m, 1420m, 1396m, 1354w, 1320m, 1298s, 1238w, 1192w, 1123w, 1093w, 1075m, 1022w cm^{-1}. – ^{1}H NMR (500 MHz, d_6-DMSO): δ = 11.16 (s, 1 H, NH), 7.49 (d, J = 8.01 Hz, 1 H, 6′-H), 5.47 (d, J = 7.91 Hz, 1 H, 5′-H), 3.56 – 3.51 (m, 2 H, OCH_2), 2.77 (ddd, J = 7.24, 3.66, 3.64 Hz, 1 H, 1-H), 1.58 – 1.52 (m, 1 H, CH_A-ethyl), 1.38-1.31 (m, 1 H, CH_B-ethyl), 1.14-1.10 (m, 1 H, 2-H), 0.97 (ddd, J = 9.71, 5.81, 3.91 Hz, 1 H, 3-H_A), 0.76 – 0.72 (m, 1 H, 3-H_B). – ^{13}C NMR (100 MHz, d_6-DMSO): δ = 163.66 (s, C-4′), 152.03 (s, C-2′), 145.63 (d, C-6′), 100.72 (d, C-5′), 60.25 (t, OCH_2), 36.12 (d, C-1), 34.67 (t, CH_2-ethyl), 17.42 (d, C-2), 12.10 (t, C-3). – MS (EI, 70 eV): *m/z* (%) = 196 (7.1), 179 (1.4), 168 (20.7), 152 (12.9), 140 (3.6), 122 (13.6), 113 (100.0). – HRMS calcd. for $C_9H_{12}N_2O_3$: 196.08478; found: 196.08477. – Analysis for $C_9H_{12}N_2O_3$

(196.20): calcd. C 55.10, H 6.16, N 14.28; found C 55.18, H 6.32, N 14.09.

(±)-{(1 RS, 2 RS)-cis-2-[2-(Tetrahydro-2H-2-pyranyl-oxy)-ethyl]cyclopropyl}-3-(3-ethoxy-acryloyl)urea ((±)-20)

The reaction was performed under the conditions as described for **23** using 3-ethoxy-acryloyl chloride (1.79 g, 13.2 mmol), silver cyanate (2.6 g, 17.28 mmol) in dry benzene (20 ml) and the amine **6** (0.8 g, 4.32 mmol). After evaporation of the solvents and purification by column chromatography (silica gel, ethyl acetate/hexane 1:1) **20** (1.06 g, 75%) was obtained as a yellowish solid. – M. p. 78.9 – 79.3 °C. – R_F (ethyl acetate/hexane 3:1) 0.45. – UV/vis (methanol): λ_{max} (lg ε) = 252 nm (4.29). – IR (film): ν = 3233m, 3088m, 2942s, 2868m, 2247w, 1707s, 1673s, 1606s, 1548s, 1496s, 1396m, 1346m, 1246s, 1162s, 1076m, 1060m, 1032s cm^{-1}. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.19 (s, 1 H, OCNHCO), 8.63 (s, 1 H, NH), 7.60 (d, J = 12.30 Hz, 1 H, OCH=), 5.32 (d, J = 12.30 Hz, 1 H, CH=), 4.59 (dd, J = 12.30, 7.23 Hz, 1 H, 2″-H), 3.95 (q, J = 7.13 Hz, 2 H, OCH_2-ethyl), 3.86 – 3.80 (m, 2 H, 6″-H_A, OCH_A), 3.49 – 3.44 (m, 2 H, 6″-H_B, OCH_B), 2.79 (ddd, J = 7.37, 7.37, 4.05 Hz, 1 H, 1-H), 1.82 – 1.65 (m, 3 H, 3″-H_A, 4″-H_A, CH_A-ethyl), 1.61 – 1.46 (m, 5 H, 3″-H_B, 4″-H_B, 5′-H_2, CH_B-ethyl), 1.32 (t, J = 7.13 Hz, 3 H, CH_3), 1.07 – 0.88 (m, 2 H, 2-H, 3-H_A), 0.28 (ddd, J = 6.44, 5.76, 3.03 Hz, 1 H, 3-H_B). – ^{13}C NMR (100 MHz, $CDCl_3$): ν = 168.13 (s, CO), 162.82 (d, OCH=), 156.44 (s, NHCONH), 98.93 (d, OC-CH=), 98.09 (d, C-2″), 67.18 (t, OCH_2-ethyl), 66.99 (t, OCH_2), 61.96 (t, C-6″), 30.58 (t, CH_2-ethyl), 28.19 (t, C-3″), 26.53 (d, C-1), 25.38 (t, C-5″), 19.41 (t, C-4″), 14.52 (d, C-2), 14.32 (q, CH_3), 11.63 (t, C-3). – MS (EI, 70 eV): *m/z* (%) = 327 (0.4), 242 (32.9), 225 (6.4), 213 (7.1), 197 (6.8), 185 (4.3), 172 (3.6), 159 (100.0). – HRMS calcd. for $C_{16}H_{26}N_2O_5$: 326.18416; found: 326.18416. – Analysis for $C_{16}H_{26}N_2O_5$ (326.39): calcd. C 58.88, H 8.03, N 8.58; found C 58.66, H 8.25, N 8.69.

(±)-1-[(1 RS, 2 RS)-cis-2-(2-Hydroxyethyl)cyclopropyl]-1,2,3,4-tetrahydro-pyrimidine-2,4-dione ((±)-21)

A solution of **20** (0.86 g, 2.63 mmol) in sulfuric acid (2 N, 20 ml) was stirred for 2 h at 75 °C then cooled to 5 °C neutralised with NaOH (8 N) and concentrated under reduced pressure. The precipitate was washed with ethyl acetate (300 ml). The washings were dried ($MgSO_4$), the solvent was removed *in vacuo* and the residue subjected to column chromatography (silica gel, ethyl acetate/methanol 10:1) to afford **21** (0.37 g, 71%) as a yellowish solid. – M. p. 142.7 – 143.5 °C. – R_F (ethyl acetate/methanol 10:1) 0.49. – UV/vis (methanol): λ_{max} (lg ε) = 271 nm (4.00). – IR (KBr): ν = 3412s, 3162w, 3087w, 3036m, 2932w, 2877w, 1731s, 1666s, 1462w, 1427w, 1387m, 1364w, 1306m, 1247w, 1120w, 1058w, 1023m cm^{-1}. – ^{1}H NMR (500 MHz, d_6-DMSO): δ = 7.52 (d, J = 7.91 Hz, 1 H, 6′-H), 5.47 (d, J = 7.91, 1 H, 5′-H), 3.44 – 3.41 (m, 2 H, OCH_2), 3.06 (ddd, J = 7.49, 7.49, 4.43, 1 H, 1-H), 1.55 – 1.49 (m, 1 H, CH_A-ethyl), 1.19 – 1.15 (m, 1 H, C-2), 1.01 (ddd, J = 9.51, 5.71, 5.71, 1 H, 3-H_A), 0.91 – 0.84 (m, 1 H, CH_B-ethyl), 0.73 (ddd, J = 6.33, 6.33, 4.53, 1 H, 3-H_B). – ^{13}C NMR (100 MHz, d_6-DMSO): δ = 163.77 (s, C-4′), 152.07 (s, C-2′), 146.23 (d, C-6′), 100.41 (d, C-5′), 60.47 (t, OCH_2), 34.98 (d, C-1), 30.58 (t, CH_2-ethyl), 15.06 (d, C-2), 9.61 (t, C-3). – MS (EI, 70 eV): *m/z* (%) = 196 (2.5), 179 (1.4), 168 (6.4), 166 (6.4), 151 (7.9), 140 (2.5), 126 (4.3), 122 (18.6), 113 (100.0). – HRMS calcd. for $C_9H_{12}N_2O_3$: 196.08478; found: 196.08478. – Analysis for $C_9H_{12}N_2O_3$ (196.20): calcd. C 55.10, H 6.16, N 14.28; found C 55.13, H 6.23, N 14.00.

(±)-1-[(1 RS, 2 RS)-cis-2-(2-Hydroxyethyl)cyclopropyl]-5-methyl-1,2,3,4-tetrahydro-pyrimidine-2,4-dione ((±)-22)

Compound **23** (0.6 g, 1.84 mmol) was dissolved in sulfuric acid (2 N, 20 ml) and stirred for 2 h at 76 °C. After cooling in an ice-bath the mixture was neutralised with NaOH (8 N) and concentrated under reduced pressure. The residue was extracted with ethyl acetate (300 ml). The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The remaining residue was purified by column chromatography (silica gel, ethyl acetate/methanol 10:1) to obtain **22** (0.33 g, 85%) as a white solid. – M. p. 145.3 – 145.9 °C. – R_F (ethyl acetate/methanol 10:1) 0.48. – UV/vis (methanol): λ_{max} (lg ε) = 276 nm (4.28). – IR (KBr): ν = 3491s, 3148m, 3085m, 3019m, 2940m, 2885m, 2820m, 2360w, 1704s, 1652s, 1474m, 1454m, 1426m, 1399w, 1373m, 1355m, 1306s, 1246w, 1192w, 1142w, 1111w, 1065m, 1032m cm^{-1}. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.60 (s, 1 H, NH), 7.02 (s, 1 H, 6′-H), 3.70 – 3.68 (m, 2 H, OCH_2), 3.12 (ddd, J = 7.41, 7.41, 4.50, 1 H, 1-H), 2.62 (s, 1 H, OH), 1.86 (s, 3 H, CH_3), 1.69 – 1.62 (m, 1 H, CH_A-ethyl), 1.36 – 1.30 (m, 1 H, 2-H), 1.26 – 1.21 (m, 1 H, CH_B-ethyl), 1.17 (ddd, J = 14.81, 7.36, 7.36, 1 H, 3-H_A), 0.62 (ddd, J = 6.38, 6.38, 4.67, 1 H, 3-H_B). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.34 (s, C-4′), 153.60 (s, C-2′), 142.09 (d, C-6′), 111.47 (s, C-5′), 63.04 (t, OCH_2), 36.70 (d, C-1), 31.55 (t, CH_2-ethyl), 17.09 (d, C-2), 13.21 (q, CH_3), 11.27 (t, C-3). – MS (EI, 70 eV): *m/z* (%) = 210 (9.6), 193 (1.4), 182 (17.1), 179 (9.3), 165 (20.0), 154 (3.6), 149 (5.0), 140 (6.4), 136 (21.4), 127 (100.0). – HRMS calcd. for $C_{10}H_{14}N_2O_3$: 210.10043; found: 210.10043. – Analysis for $C_{10}H_{14}N_2O_3$ (210.23): calcd. C 57.13, H 6.71, N 13.33; found C 57.09, H 6.80, N 12.96.

(±)-[(1 RS,2 RS)-cis-2-[2-(Tetrahydro-2H-2-pyranyl-oxy)-ethyl]cyclopropyl]-3-(3-methoxy-2-methylacryloyl)-urea ((±)-23)

A suspension of 3-methoxy-2-methylacryloyl chloride (1.73 g, 12.86 mmol) and silver cyanate (2.3 g, 15.27 mmol)

in dry benzene (10 ml) was heated under reflux for 30 min. The mixture was cooled to 0 °C and the supernatant liquor was rapidly added to the amine **6** (0.8 g, 4.32 mmol). The solution was stirred for 20 h at room temperature and concentrated. The residue was purified by column chromatography (silica gel, ethyl acetate/hexane 1:1) to yield **23** (0.95 g, 67%) as a yellowish solid. – M. p. 93.3 – 94.0 °C. – R_F (ethyl acetate/hexane 1:1) 0.18. – UV/vis (methanol): λ_{max} (lg ε) = 259 nm (4.27). – IR (KBr): ν = 3362m, 3258s, 3072w, 2947s, 2870m, 2786w, 2651w, 2361w, 1687s, 1659s, 1543s, 1489s, 1455s, 1405m, 1370m, 1296s, 1247s, 1159s, 1078s, 1068m, 1036s, 1024m cm^{-1} – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.07 (s, 1 H, OCNHCO), 8.79 (brs, 1 H, NH), 7.40 (d, J = 1.17, 1 H, CH=), 4.54 (dd, J = 7.42, 7.42, 1 H, 2″-H), 3.83 – 3.74 (m, 2 H, 6″-H_A, OCH_A), 3.80 (s, 3 H, OCH_3), 3.46 – 3.39 (m, 2 H, 6″-H_B, OCH_B), 2.74 (ddd, J = 7.37, 7.37, 4.05, 1 H, 1-H), 1.78 – 1.72 (m, 1 H, 4″-H_A), 1.70 (s, 3 H, CH_3), 1.68 – 1.63 (m, 2 H, 3″-H_A, CH_A-ethyl), 1.60 – 1.42 (m, 5 H, 3″-H_B, 4″-H_B, 5′′-H_2, CH_B-ethyl), 0.99 – 0.87 (m, 2 H, 2-H, 3-H_A), 0.23 (ddd, J = 4.83, 4.83, 2.39, 1 H, 3-H_B). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.82 (s, CO), 158.26 (d, CH), 156.25 (s, NHCONH), 107.26 (s, C_q), 98.78 (d, C-2″), 67.03 (t, OCH_2), 61.87 (t, C-6″), 61.12 (q, OCH_3), 30.48 (t, CH_2-ethyl), 28.09 (t, C-3″), 26.42 (d, C-1), 25.29 (t, C-5″), 19.30 (t, C-4″), 14.26 (d, C-2), 11.56 (t, C-3), 8.50 (q, CH_3). – MS (EI, 70 eV): *m/z* (%) = 327 (0.7), 242 (21.4), 225 (6.1), 211 (4.3), 197 (2.9), 159 (65.0), 116 (8.2), 100 (14.3), 99 (100.0). – HRMS calcd. for $C_{16}H_{26}N_2O_5$: 326.18416; found: 326.18415. – Analysis for $C_{16}H_{26}N_2O_5$ (326.39): calcd. C 58.88, H 8.03, N 8.58; found C 58.80, H 8.15, N 8.32.

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