Supporting Information

Rigidity versus flexibility: is this an issue in σ_1 (sigma-1) receptor ligand affinity and activity?

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Purity data of prepared compounds

compound	purity by HPLC	exact MS calcd.	exact MS found
9a	97.9%	402.2393	402.2423
9b	99.8%	-	-
10a	92.0%	343.2022	343.2068
10b	93.1%	-	-
11b	97.9%	-	-
12a	92.1%	445.2523	445.2576
ent-**12a**	98.8%	445.2523	445.2553
12b	98.6%	-	-
12c	95.9%	-	-
ent-**12c**	95.5%	-	-
12d	94.6%	-	-
ent-**12d**	97.1%	-	-
13a	86.8%	341.1865	341.1885
ent-**13a**	88.5%	-	-
13b	75.6%	-	-
13c	73.6%	391.2022	391.1997
ent-**13c**	98.3%	391.2022	391.2077
13d	82.2%	417.2179	417.2156
ent-**13d**	85.3%	-	-
14a	98.9%	315.2436	315.2486
ent-**14a**	96.2%	315.2436	315.2431
14b	97.3%	233.1654	233.1612
14c	95.9%	365.2593	365.2604
ent-**14c**	97.4%	365.2593	365.2595
14d	96.2%	391.2751	391.2742
ent-**14d**	99.5%	391.2751	391.2744
15a	96.7%	315.2436	315.2431
ent-**15a**	96.7%	315.2436	315.2431
15b	96.3%	233.1654	233.1629
15c	95.6%	365.2593	365.2608
ent-**15c**	95.5%	-	-

15d	97.7%	391.2751	391.2751
ent-**15d**	98.5%	391.2751	391.2785
17·HCl	-	-	-
18	97.1%	342.1108	342.1097
19	99.4%	387.2284	387.2308
20	95.9%	459.2679	459.2649
21	97.4%	355.2021	355.1982
22	95.1%	329.2592	329.2566
23	96.6%	329.2592	329.2552

Experimental data

Chemistry, general

Moisture sensitive reactions were conducted under dry nitrogen. THF was dried with sodium/benzophenone and was freshly distilled before use. Thin layer chromatography: Silica gel 60 F254 plates (Merck). Flash chromatography (fc): Silica gel 60, 40–43 µm (Merck); parentheses include: diameter of the column, eluent, R_f value. In order to obtain high yields some compounds were adsorbed on silica gel by addition of silica gel to a solution of the compound in an appropriate solvent, removal of the solvent in vacuo and giving the mixture on top of the column. Melting point: Melting point apparatus SMP 3 (Stuart Scientific), uncorrected. ^{1}H NMR (600 MHz, 400 MHz), ^{13}C NMR (151 MHz, 100 MHz): Agilent 600-MR, Agilent 400-MR and Mercury Plus AS 400 NMR spectrometer (Varian); δ in ppm related to tetramethylsilane; coupling constants are given with 0.5 Hz resolution; the assignments of ^{13}C and ^{1}H NMR signals were supported by 2D NMR techniques. MS: MAT GCQ (Thermo-Finnigan): EI, MAT LCQ (Thermo Finnigan): ESI, MicroTOF-QII (Bruker Daltonics): APCI. IR: IR spectrophotometer 480Plus FT-ATR-IR (Jasco) or FT/IR Prestige 21 (Shimadzu). Polarimetry: Polarimeter 341 (Perkin Elmer), sample length 1 dm, λ = 589 nm, +20 °C. The purity of all test compounds was determined by HPLC analysis (purity >95%). HPLC (method ACN): Merck Hitachi Equipment; UV detector: L-7400; autosampler:L-7200; pump: L-7100; degasser: L-7614; column: LiChrospher® 60 RP-select B (5 µm); LiCroCART® 250-4 mm cartridge; flow rate: 1.0 mL/min; injection volume: 5.0 µL; detection at λ = 210 nm; solvents: A: demineralized H_2O with 0.05% (v/v) trifluoroacetic acid; B: acetonitrile with 0.05% (v/v) trifluoroacetic acid: gradient elution: 0.0 min: 90.0% of A, 10.0% of B; 4.0 min: 90.0% of A, 10.0% of B; 29.0 min: 0.0% of A, 100.0% of B; 31.0 min: 0.0% of A, 100.0% of B; 31.5 min: 90.0% of A, 10.0% of B; 40.0 min: 90.0% of A, 10.0% of B.

General Procedure A: Under N_2, 1 equivalent of the bibyclic piperazinedione was dissolved in THF abs. and the mixture was cooled down to 0 °C. At this temperature, $LiAlH_4$ (6 equivalents) was added. The reaction mixture was stirred at 0 °C for 10 min and then heated to reflux for 16 h. Finally H_2O was added under ice-cooling until H_2 liberation was finished. The mixture was stirred at 0 °C for 10 min and then heated to

reflux for 30 min. After cooling to room temperature, the mixture was filtered and the solvent was removed in vacuo. The residue was purified by fc.

Synthesis of starting material

The synthesis of Dimethyl (*S*)-2-aminobutanedioate hydrochloride (**6**·HCl) and dimethyl (*R*)-2-aminobutanedioate hydrochloride (*ent*-**6**·HCl) is reported in reference[1].

The synthesis of the following compounds is reported in reference[2]:
Dimethyl (*S*)-2-[*N*-benzyl-*N*-(2-chloroacetyl)amino]butanedioate (**7a)**
Dimethyl (*R*)-2-[*N*-benzyl-*N*-(2-chloroacetyl)amino]butanedioate (*ent*-**7a**)
Dimethyl (*S*)-2-[*N*-(chloroacetyl)-*N*-(naphthalen-1-ylmethyl)amino]butandioate (**7c**)
Dimethyl (*R*)-2-[*N*-(chloroacetyl)-*N*-(naphthalen-1-ylmethyl)amino]butanedioate (*ent*-**7c**)
Dimethyl (*S*)-2-[*N*-(biphenyl-4-ylmethyl)-*N*-(2-chloroacetyl)amino]butanedioate (**7d**)
Dimethyl (*R*)-2-[*N*-(biphenyl-4-ylmethyl)-*N*-(2-chloroacetyl)amino]butanedioate (*ent*-**7d**)
Methyl (*S*)-2-[1-benzyl-4-(cyclohexylmethyl)-3,6-dioxopiperazin-2-yl]acetate (**8a**)
Methyl (*R*)-2-[1-benzyl-4-(cyclohexylmethyl)-3,6-dioxopiperazin-2-yl]acetate (*ent*-**8a**)
Methyl (*S*)-2-(1-benzyl-4-methyl-3,6-dioxopiperazin-2-yl)acetate (**8b**)
Methyl (*S*)-2-[4-(cyclohexylmethyl)-1-(naphthalen-1-ylmethyl)-3,6-dioxo-piperazin-2-yl]acetate (**8c**)
Methyl (*R*)-2-[4-(cyclohexylmethyl)-1-(naphthalen-1-ylmethyl)-3,6-dioxo-piperazin-2-yl]acetate (*ent*-**8c**)
Methyl (*S*)-2-[1-(biphenyl-4-ylmethyl)-4-(cyclohexylmethyl)-3,6-dioxopiperazin-2-yl]acetate (**8d**)
Methyl (*R*)-2-[1-(biphenyl-4-ylmethyl)-4-(cyclohexylmethyl)-3,6-dioxopiperazin-2-yl]acetate (*ent*-**8d**)

The synthesis of Dimethyl (*S*)-2-aminopentanedioate hydrochloride (**17**·HCl) is reported in reference[3].

The synthesis of Dimethyl (*S*)-2-[*N*-benzyl-*N*-(2-chloroacetyl)amino]pentanedioate (**18**) is reported in reference[4].

Synthetic procdures

(*S*)-2-[1-Benzyl-4-(cyclohexylmethyl)-3,6-dioxopiperazin-2-yl]-*N*-methoxy-*N*-methylacetamide (9a)

N,*O*-Dimethylhydroxylamine hydrochloride (393 mg, 4.03 mmol) was dissolved in CH_2Cl_2 abs (12 mL) and cooled to 0 °C. Trimethylaluminium solution (2 M in toluene, 2 mL, 4.03 mmol) was added and the mixture was stirred at room temperature for 30 min. Then a solution of **8a** (500 mg, 1.34 mmol) in CH_2Cl_2 abs (5 mL) was added and the reaction mixture was stirred for 5 h at room temperature. For work-up, the mixture was filled up with aqueous sodium potassium tartrate solution (10%, 7 mL) and stirred for additional 1 h. The resulting suspension was filtered through Celite and washed with CH_2Cl_2 for several times. The filtrate was concentrated under reduced pressure and the residue was purified by fc (∅ 3 cm, h = 18 cm, v = 20 mL, C_6H_{12}/EtOAc = 1/1, R_f = 0.12). Colorless solid, mp 92 – 95 °C, yield 340 mg (63%). $C_{22}H_{31}N_3O_4$, M_r = 401.4. HPLC (method ACN): t_R = 18.9 min, purity 97.9%. Specific rotation: $[\alpha]_D^{20}$ = +41.7 (c = 0.94; EtOAc). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.89 – 1.00 (m, 2H, $NCH_2C_6H_{11}$), 1.12 – 1.29 (m, 3H, $NCH_2C_6H_{11}$), 1.61 – 1.71 (m, 6H, $NCH_2C_6H_{11}$), 2.95 (dd, J = 17.7 / 3.8 Hz, 1H, $CHCH_2CON(OCH_3)CH_3$), 3.06 (dd, J = 17.7 / 3.8 Hz, 1H, $CHCH_2CON(OCH_3)CH_3$), 3.13 (dd, J = 13.5 / 7.3 Hz, 1H, $NCH_2C_6H_{11}$), 3.16 (s, 3H, NCH_3), 3.22 (dd, J = 13.5 / 6.9 Hz, 1H, $NCH_2C_6H_{11}$), 3.46 (s, 3H, $NOCH_3$), 3.92 (d, J = 17.0 Hz, 1H, $O=CCH_2N$), 4.15 (t, J = 3.9 Hz, 1H, $CHCH_2C\ ON(OCH_3)CH_3$, 4.40 (d, J = 15.4 Hz, 1H, NCH_2Ar), 4.42 (d, J = 16.9 Hz, 1H, $O=CCH_2N$), 4.91 (d, J = 15.1 Hz, 1H, NCH_2Ar), 7.19 – 7.36 (m, 5H, Ar-*H*). ^{13}C NMR ($CDCl_3$): δ [ppm] = 25.8 (1C, $NCH_2C_6H_{11}$), 26.3 (1C, $NCH_2C_6H_{11}$), 26.4 (1C, $NCH_2C_6H_{11}$), 30.7 (1C, $NCH_2C_6H_{11}$), 30.8 (1C, $NCH_2C_6H_{11}$), 32.1 (1C, NCH_3), 32.9 (1C, $CHCH_2CON(OCH_3)CH_3$), 35.6 (1C, $NCH_2C_6H_{11}$), 47.8 (1C, NCH_2Ar), 51.1 (1C, $O=CCH_2N$), 52.7 (1C, $NCH_2C_6H_{11}$), 56.6 (1C, $CHCH_2CON(OCH_3)CH_3$), 61.2 (1C, OCH_3), 127.9 (1C, Ar-*C*), 128.0 (2C, Ar-*C*), 128.9 (2C, Ar-*C*), 136.2 (1C, Ar-C_q), 165.2 (1C, *C*=O), 166.4 (1C, *C*=O), 170 ($O=CN(OCH_3)CH_3$). MS (EM, APCI): m/z = calcd for $C_{22}H_{32}N_3O_4$ 402.2393 (M+H), found 402.2423. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2924, 2850 (C-H $_{aliph.}$), 1647 (C=O $_{amide}$), 721, 698 (arom. monosubst.).

(*S*)-2-(1-Benzyl-4-methyl-3,6-dioxopiperazin-2-yl)-*N*-methoxy-*N*-methylacetamide (9b)

N,*O*-Dimethylhydroxylamine hydrochloride (505 mg, 5.17 mmol) was dissolved in CH_2Cl_2 abs (15 mL) and cooled to 0 °C. Trimethylaluminium solution (2 M in toluene, 2.6 mL, 5.17 mmol) was added and the mixture was stirred at room temperature for 30 min. Then a solution of **8b** (500 mg, 1.72 mmol) in CH_2Cl_2 abs (8 mL) was added and the reaction mixture was stirred for 5 h at room temperature. For work-up, the mixture was filled up with aqueous sodium potassium tartrate solution (10%, 5 mL) and stirred for additional 1 h. The resulting suspension was filtered through Celite and washed with CH_2Cl_2 for several times. The filtrate was concentrated under reduced pressure and the residue was purified by fc (∅ 3 cm, h = 18 cm, v = 20 mL, acetone/ EtOAc = 4/1, R_f = 0.17). Colorless solid, mp 131 – 134 °C, yield 482 mg (88%). $C_{16}H_{21}N_3O_4$, M_r = 319.4. HPLC (method ACN): t_R = 13.8, purity 99.8%. Specific rotation: $[\alpha]_D^{20}$ = 000 (c = 000; EtOAc). ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.97 (s, 3H, NC*H*$_3$), 3.01 – 3.06 (m, 2H, CHC*H*$_2$CON(OCH$_3$)CH$_3$), 3.08 (s, 3H, NC*H*$_3$), 3.48 (s, 3H, NOC*H*$_3$), 3.93 (d, J = 16.9 Hz, 1H, O=CC*H*$_2$N), 4.10 (t, J = 3.9 Hz, 1H, C*H*CH$_2$CON(OCH$_3$)CH$_3$), 4.30 (d, J = 15.2 Hz, 1H, NC*H*$_2$Ar), 4.42 (d, J = 16.9 Hz, 1H; O=CC*H*$_2$N), 4.99 (d, J = 15.2 Hz, 1H, NC*H*$_2$Ar), 7.23 – 7.34 (m, 5H, Ar-*H*). MS (EI): m/z [%] = 217 (M – CHCON(OCH$_3$)CH$_3$, 54), 91 (M – CH$_2$Ph, 77). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2924, 2360 (C-H $_{aliph.}$), 1649 (C=O $_{amide}$), 722, 669 (arom. monosubst.).

(*S*)-4-Benzyl-3-(2-hydroxyethyl)-1-methylpiperazine-2,5-dione (10b)

Under N_2, **8b** (100 mg, 0.34 mmol) was dissolved in THF abs. (10 mL) and the mixture was cooled down to -30 °C. Then, 4 equivalents of $LiBH_4$ solution (1 M in THF, 1.36 mL, 1.36 mmol) were added dropwise and the mixture was stirred for 2.5 h at -30 °C. To complete the reaction, additional $LiBH_4$ solution (1 M in THF, 1.36 mL, 1.36 mmol) was added and the mixture was stirred for another 2.5 h at the same temperature. The reaction mixture was warmed to room temperature, then HCl (1 M, 10 mL) was added carefully. The mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed in vacuo. Purification of the residue by fc (∅ 2 cm, h = 19 cm, v = 10 mL, EtOAc /acetone = 9/1, R_f = 0.14). Colorless oil, yield 36.9 mg (41%). $C_{14}H_{18}N_2O_3$, M_r = 262.3.

HPLC (method ACN): t_R = 11.3 min, purity 97.9%. Specific rotation: $[\alpha]_D^{20}$ = +25.5 (c = 0.70; EtOAc). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.85 – 1.89 (m, 1H, CHC*H*$_2$CH$_2$OH), 2.02 – 2.16 (m, 1H, CHC*H*$_2$CH$_2$OH), 2.90 (s, 3H, NC*H*$_3$), 3.59 – 3.65 (m, 1H, CHCH$_2$C*H*$_2$OH), 3.66 – 3.73 (m, 1H, CHCH$_2$C*H*$_2$OH), 3.92 (d, J = 17.2 Hz, 1H, O=CC*H*$_2$N), 3.95 (d, J = 14.7 Hz, 1H, NC*H*$_2$Ar), 4.00 (dd, J = 8.6 / 3.8 Hz, 1H, C*H*CH$_2$CH$_2$OH), 4.18 (d, J = 17.2 Hz, 1H, O=CC*H*$_2$N), 5.28 (d, J = 14.9 Hz, 1H, NC*H*$_2$Ar), 7.23 – 7.34 (m, 5H, Ar-*H*). MS (ESI): m/z [%] = 263 (M + H, 100). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3402 (O-H), 2931, 2882 (C-H $_{aliph.}$), 1736 (C=O $_{ester}$), 1647 (C=O $_{amide}$) 725, 698 (arom. monosubst.).

(*S*)-2-[1-Benzyl-4-(cyclohexylmethyl)-3,6-dioxopiperazin-2-yl]acetaldehyde (11a)

Under N_2, **9a** (200 mg, 0.50 mmol) was dissolved in THF abs. (10 mL) and cooled down to -78°C. At this temperature, 1.5 equivalents of $LiAlH_4$ solution (1 M in THF, 0.75 ml, 0.75 mmol) were added slowly and the mixture was stirred for 16 h. For work-up, the mixture was treated with HCl (1 M, 6 mL) and warmed to room temperature. The aqueous layer was extracted with Et_2O (5 x 10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuo (H_2O bath temperature ≤ 30 °C). The crude product was purified by fc (∅ 3 cm, h = 20 cm, v = 20 mL, C_6H_{12}/EtOAc = 1/1, R_f = 0.23). Colorless solid, mp 99 – 102 °C, yield 109 mg (64%). $C_{20}H_{26}N_2O_3$, M_r = 342.4. HPLC (method ACN): t_R = 17.6 min, purity 92.0%. Specific rotation: $[\alpha]_D^{20}$ = +47.9 (c = 1.02; EtOAc). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.90 – 0.98 (m, 2H, NCH$_2$C$_6$*H*$_{11}$), 1.00 – 1.22 (m, 3H, NCH$_2$C$_6$*H*$_{11}$), 1.64 – 1.75 (m, 6H, NCH$_2$C$_6$*H*$_{11}$), 2.92 (ddd, J = 18.7 / 5.1 / 0.9 Hz, 1H, CHC*H*$_2$CHO), 3.08 (dd, J = 18.6 / 4.0 Hz, 1H, CHC*H*$_2$CHO), 3.16 (dd, J = 13.5 / 6.8 Hz, 1H, NC*H*$_2$C$_6$H$_{11}$), 3.30 (dd, J = 13.5 / 7.8 Hz, 1H, NC*H*$_2$C$_6$H$_{11}$), 3.96 (d, J = 17.3 Hz, 1H, O=CC*H*$_2$N), 4.12 (t, J = 4.5 Hz, 1H, C*H*CH$_2$CHO), 4.35 (d, J = 15.1 Hz, 1H, NC*H*$_2$Ar), 4.42 (d, J = 17.2 Hz, 1H O=CC*H*$_2$N), 4.89 (d, J = 15.2 Hz, 1H, NC*H*$_2$Ar), 7.20 – 7-35 (m, 5H, Ar-*H*), 9.52 (s, 1H, C*H*O). MS (EM, APCI): m/z = calcd. for $C_{20}H_{27}N_2O_3$ 343.2022 (M+H), found 343.2068. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2920 (C-H $_{aliph.}$), 2847 (C-H $_{aldehyde}$), 1728 (C=O $_{ester}$), 1651 (C=O $_{aldehyde}$ / C=O $_{amide}$), 779, 698 (arom. monosubst.).

(*S*)-2-(1-Benzyl-4-methyl-3,6-dioxopiperazin-2-yl)acetaldehyde (11b)

Under N_2, **9b** (100 mg, 0.31 mmol) was dissolved in THF abs. (10 mL) and cooled down to -78°C. At this temperature, 1.25 equivalents of $LiAlH_4$ solution (1 M in THF, 0.4 mL, 0.39 mmol) were added slowly and the mixture was stirred for 16 h. For work-up, the mixture was treated with HCl (1 M, 4 mL) and warmed to room temperature. The aqueous layer was extracted with CH_2Cl_2 (7 x 10 ml). The combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuo (H_2O bath temperature ≤ 30 °C). The crude product was purified by fc (∅ 2 cm, h = 22 cm, v = 10 mL, CH_2Cl_2/ C_6H_{12}/MeOH = 2.5/7/0.5.; R_f = 0.23 (CH_2Cl_2/C_6H_{12}/MeOH = 5/4.5/0.5)). Pale yellow oil, yield 42.4 mg (53%). $C_{14}H_{16}N_2O_3$, M_r = 260.3. HPLC (method ACN): t_R = 10.3, purity 93.1%. Specific rotation: $[\alpha]_D^{20}$ = +17.6 (c = 0.21; EtOAc). ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.96 (dd, J = 18.8 / 4.6 Hz, 1H, CHC*H*$_2$CHO), 2.97 (s, 3H, NC*H*$_3$), 3.12 (dd, J = 18.9 / 3.9 Hz, 1H, CHC*H*$_2$CHO), 3.99 (d, J = 17.2 Hz, 1H, O=CC*H*$_2$N), 4.08 (t, J = 4.2 Hz, 1H, C*H*CH$_2$CHO), 4.28 (d, J = 15.1 Hz, 1H, NC*H*$_2$Ar), 4.43 (d, J = 17.2 Hz, 1H, O=CC*H*$_2$N), 4.96 (d, J = 15.1 Hz, 1H, NC*H*$_2$Ar), 7.23 – 7.36 (m, 5H, Ar-*H*), 9.53 (s, 1H, C*H*O). MS (EM, APCI): m/z = calcd. for $C_{14}H_{17}N_2O_3$ 261.1239 (M+H), found 261.1205. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2932 (C-H aliph), 1728 (C=O $_{ester}$), 1652 (C=O $_{aldehyde}$ / C=O $_{amide}$), 728, 698 (arom. monosubst.).

(1*S*,4*S*,7*R*)-5-Benzyl-2-(cyclohexylmethyl)-7-methoxy-7-(trimethylsilyloxy)-2,5-diazabicyclo[2.2.2]octane-3,6-dione (12a)

Under N_2, **8a** (2.68 g, 7.20 mmol) was dissolved in THF abs (50 mL) and the mixture was cooled down to -78 °C. Then a 1 M solution of sodium hexamethyldisilazane in THF (21.6 mL, 21.6 mmol) was added dropwise. After stirring at -78 °C for 40 min, the mixture was treated with chlorotrimethylsilane (2.27 mL, 17.99 mmol) and stirred for additional 1 h at -78 °C and at room temperature for 2 h. Then, an aqueous solution of $NaHCO_3$ (35 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was adsorbed on silica gel and given on a silica column (∅ 5.5 cm, h = 20 cm, v = 65 mL, C_6H_{12}/EtOAc = 4/1, R_f = 0.39). Colorless solid, mp 138 – 141 °C, yield 540 mg (17%). $C_{24}H_{36}N_2O_4Si$, M_r = 444.5. HPLC (method ACN): t_R = 22.5 min, purity 92.1%. Specific rotation: $[\alpha]_D^{20}$ = -2.12 (c = 0.39;

EtOAc). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.20 (s, 9H, $OSi(CH_3)_3$), 0.85 – 0.96 (m, 2H, $NCH_2C_6H_{11}$), 1.08 – 1.27 (m, 3H, $NCH_2C_6H_{11}$), 1.51 – 1.72 (m, 6H, $NCH_2C_6H_{11}$), 1.84 (dd, J = 13.6 / 3.9 Hz, 1H, 8-*H*), 2.07 (dd, J = 13.6 / 2.0 Hz, 1H, 8-*H*), 2.74 (dd, J = 13.8 / 6.6 Hz, 1H, $NCH_2C_6H_{11}$), 3.21 (s, 3H, OCH_3), 3.60 (dd, J = 13.8 / 7.7 Hz, 1H, $NCH_2C_6H_{11}$), 3.82 (dd, J = 3.9 / 2.0 Hz, 1H, 4-*H*), 3.95 (s, 1H, 1-*H*), 4.25 (d, J = 14.8 Hz, 1H, NCH_2Ar), 4.83 (d, J = 14.8 Hz, 1H, NCH_2Ar), 7.24 – 7.34 (m, 5H, Ar-*H*). ^{13}C NMR ($CDCl_3$): δ [ppm] = 1.61 (3C, $OSi(CH_3)_3$), 25.8 (1C, $NCH_2C_6H_{11}$), 25.9 (1C, $NCH_2C_6H_{11}$), 26.4 (1C, $NCH_2C_6H_{11}$), 30.5 (1C, $NCH_2C_6H_{11}$), 30.9 (1C, $NCH_2C_6H_{11}$), 37.1 (1C, $NCH_2C_6H_{11}$), 39.3 (1C, *C*-8), 48.3 (1C, NCH_2Ar), 50.4 (1C, OCH_3), 51.9 (1C, $NCH_2C_6H_{11}$), 58.8 (1C, *C*-4), 67.6 (1C, *C*-1), 102.8 (1C, *C*-7), 128.1 (1C, Ar-*C*), 128.5 (2C, Ar-*C*), 128.9 (2C, Ar-*C*), 136.0 (1C, Ar-C_q), 167.7 (1C, C=O), 168.9 (1C, *C*=O). MS (EM, APCI): m/z = calcd. for $C_{24}H_{37}N_2O_4Si$ 445.2523 (M+H), found 445.2576. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2924, 2851 (C-H $_{aliph.}$), 1681 (C=O $_{amide}$), 1096 (Si-O), 740, 698 (arom. monosubst.).

(1*R*,4*R*,7*S*)-5-Benzyl-2-(cyclohexylmethyl)-7-methoxy-7-(trimethylsilyloxy)-2,5-diazabicyclo[2.2.2]octane-3,6-dione (*ent*-12a)

Ent-**12a** was synthesized according to the same procedure as **12a**: Under N_2, *ent*-**8a** (1.04 g, 2.79 mmol) was reacted with a solution of sodium hexamethyldisilazane (1 M in THF, 8.4 mL, 8.38 mmol) and chlorotrimethylsilane (0.9 mL, 6.98 mmol) in THF abs. (30 mL). The crude product was adsorbed on silica gel and given on a silica column (∅ 4.0 cm, h = 20 cm, v = 20 mL, C_6H_{12}/EtOAc = 4/1, R_f = 0.39). Colorless solid, mp 141 – 146 °C, yield 225.3 mg (18%). $C_{24}H_{36}N_2O_4Si$, M_r = 444.5. HPLC (method ACN): t_R = 19.3 min, purity 98.8%. Specific rotation: $[\alpha]_D^{20}$ = +2.27 (c = 0.38; EtOAc). MS (EM, APCI): m/z = calcd. for $C_{24}H_{37}N_2O_4Si$ 445.2523 (M+H), found 445.2553.

(1*S*,4*S*,7*R*)-5-Benzyl-7-methoxy-2-methyl-7-(trimethylsilyloxy)-2,5-diazabicyclo[2.2.2]octane-3,6-dione (12b)

Under N_2, **8b** (540 mg, 1.86 mmol) was dissolved in THF abs (25 mL) and the mixture was cooled down to -78 °C. Then a 1 M solution of sodium hexamethyldisilazane in THF (5.6 mL, 5.58 mmol) was added dropwise. After stirring at -78 °C for 40 min, the mixture was treated with chlorotrimethylsilane (0.6 mL, 4.65

mmol) and stirred for additional 1 h at -78 °C and at room temperature for 2 h. Then an aqueous solution of $NaHCO_3$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was adsorbed on silica gel and given on a silica column (∅ 3.5 cm, h = 16 cm, v = 20 mL, C_6H_{12}/EtOAc = 2/1, R_f = 0.10). Colorless solid, mp 170 – 175 °C, yield 229 mg (34%). $C_{18}H_{26}N_2O_4Si$, M_r = 362.5. HPLC (method ACN): t_R = 13.7 min, purity 98.6%. Specific rotation: $[\alpha]_D^{20}$ = +24.6 (c = 0.71; EtOAc). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.20 (s, 9H, $OSi(CH_3)_3$), 1.82 (dd, J = 13.6 / 3.8 Hz, 1H, 8-*H*), 2.07 (dd, J = 13.6 / 2.0 Hz, 1H, 8-*H*), 3.01 (s, 3H, NCH_3), 3.27 (s, 3H, OCH_3), 3.82 (dd, J = 3.8 / 2.0Hz, 1H, 4-*H*), 3.93 (s, 1H, 1-*H*), 4.14 (d, J = 14.8 Hz, 1H, NCH_2Ar), 4.94 (d, J = 14.8 Hz, 1H, NCH_2Ar), 7.24 – 7.35 (m, 5H, Ar-*H*). ^{13}C NMR ($CDCl_3$): δ [ppm] = 1.59 (3C, $OSi(CH_3)_3$), 33.0 (1C, NCH_3), 39.9 (1C, *C*-8), 48.3 (1C, NCH_2Ar), 50.4 (1C, OCH_3), 58.7 (1C, *C*-4), 68.8 (1C, *C*-1), 102.8 (1C, C-7), 128.2 (1C, Ar-*C*), 128.5 (2C, Ar-*C*), 129.0 (2C, Ar-*C*), 135.8 (1C, Ar-C_q), 167.7 (1C, *C*=O), 168.8 (1C, *C*=O). MS (ESI): m/z [%] = 363 (M + H, 100). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2924 (C-H $_{aliph.}$), 1683 (C=O $_{amide}$), 1099 (Si-O), 732, 695 (arom. monosubst.).

(1*S*,4*S*,7*R*)-2-(Cyclohexylmethyl)-7-methoxy-5-(naphthalen-1-ylmethyl)-7-(trimethylsilyloxy)-2,5-diazabicyclo[2.2.2]octane-3,6-dione (12c)

Under N_2, **8c** (530 mg, 1.25 mmol) was dissolved in THF abs (25 mL) and the mixture was cooled down to -78 °C. Then a 1 M solution of sodium hexamethyldisilazane in THF (3.8 mL, 3.76 mmol) was added dropwise. After stirring at -78 °C for 40 min, the mixture was treated with chlorotrimethylsilane (0.4 mL, 3.14 mmol) and stirred for additional 1 h at -78 °C and at room temperature for 2 h. Then an aqueous solution of $NaHCO_3$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was adsorbed on silica gel and given on a silica column (∅ 2.5 cm, h = 20.5 cm, v = 10 mL, C_6H_{12}/EtOAc = 4/1, R_f = 0.26). Colorless oil, yield 82.3 mg (13%). $C_{28}H_{38}N_2O_4Si$, M_r = 494.7. HPLC (method ACN): t_R = 20.9 min, purity 95.9%. Specific rotation: $[\alpha]_D^{20}$ = -4.18 (c = 0.37; EtOAc). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.15 (s, 9H, $OSi(CH_3)_3$), 0.84 – 0.97 (m, 2H, $NCH_2C_6H_{11}$), 1.10 – 1.24 (m, 2H, $NCH_2C_6H_{11}$), 1.51 – 1.59 (m, 3H, $NCH_2C_6H_{11}$), 1.66 – 1.75 (m, 5H, $NCH_2C_6H_{11}$, 8-*H*), 1.99 (dd, J = 13.6 / 2.1 Hz, 1H, 8-*H*), 2.72 (dd, J = 13.9 / 6.6 Hz,

1H, NC*H*$_2$C$_6$H$_{11}$), .20 (s, 3H, OC*H*$_3$), 3.59 (dd, J = 13.9 / 7.7 Hz, 1H, NC*H*$_2$C$_6$H$_{11}$), 3.86 (dd, J = 3.8 / 2.1 Hz, 1H, 4-*H*), 3.97 (s, 1H, 1-*H*), 4.76 (d, J = 14.7 Hz, 1H, NC*H*$_2$Ar), 5.23 (d, J = 14.7 Hz, 1H, NC*H*$_2$Ar), 7.42 – 7.44 (m, 2H, Ar-*H*), 7.50 – 7.53 (m, 2H, Ar-*H*), 7.83 – 7.87 (m, 2H, Ar-*H*), 8.09 – 8.11 (m, 1H, Ar-*H*). ^{13}C NMR ($CDCl_3$): δ [ppm] = 1.59 (3C, OSi(*C*H$_3$)$_3$), 25.8 (1C, NCH$_2$*C*$_6$H$_{11}$), 25.9 (1C, NCH$_2$*C*$_6$H$_{11}$), 26.5 (1C, NCH$_2$*C*$_6$H$_{11}$), 30.5 (1C, NCH$_2$*C*$_6$H$_{11}$), 30.9 (1C, NCH$_2$*C*$_6$H$_{11}$), 37.1 (1C, NCH$_2$*C*$_6$H$_{11}$), 38.9 (1C, *C*-8), 46.0 (1C, N*C*H$_2$Ar), 50.3 (1C, O*C*H$_3$), 52.0 (1C, N*C*H$_2$C$_6$H$_{11}$), 57.6 (1C, *C*-4), 67.8 (1C, *C*-1), 102.7 (1C, *C*-7), 123.9 (1C, Ar-*C*), 125.3 (1C, Ar-*C*), 126.3 (1C, Ar-*C*), 127.0 (1C, Ar-*C*), 128.3 (1C, Ar-*C*), 128.8 (1C, Ar-*C*), 129.4 (1C, Ar-*C*), 131.3 (1C, Ar-*C*$_q$), 131.6 (1C, Ar-*C*$_q$), 134.0 (1C, Ar-*C*$_q$), 167.5 (1C, C=O), 168.9 (1C, *C*=O). MS (ESI): m/z [%] = 495 (M + H, 100). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2924, 2851 (C-H $_{aliph.}$), 1686 (C=O $_{amide}$), 1099 (Si-O), 741, 698 (arom. monosubst.).

(1*R*,4*R*,7*S*)-2-(Cyclohexylmethyl)-7-methoxy-5-(naphthalen-1-ylmethyl)-7-(trimethylsilyloxy)-2,5-diazabicyclo[2.2.2]octane-3,6-dione (*ent*-12c)

As described for **12c**, *ent*-**12c** (1.01 g, 2.39 mmol) was reacted with a solution of sodium hexamethyldisilazane (1 M in THF, 7.1 mL, 7.17 mmol) and chlorotrimethylsilane (0.75 mL, 5.98 mmol) in THF abs. (30 mL). The crude product was adsorbed on silica gel and given on a silica column (∅ 5.0 cm, h = 18 cm, v = 30 mL, C_6H_{12}/EtOAc = 4/1, R_f = 0.25). $C_{28}H_{38}N_2O_4Si$, M_r = 494.7. HPLC (method ACN): t_R = 20.9 min, purity 95.9%. Specific rotation: $[\alpha]_D^{20}$ = +4.18 (c = 0.37; EtOAc) MS (ESI): m/z [%] = 495 (M + H, 100).

(1*S*,4*S*,7*R*)-5-(Biphenyl-4-ylmethyl)-2-(cyclohexylmethyl)-7-methoxy-7-(trimethylsilyloxy)-2,5-diazabicyclo[2.2.2]octane-3,6-dione (12d)

Under N_2, **8d** (500 mg, 1.12 mmol) was dissolved in THF abs (25 mL) and the mixture was cooled down to -78 °C. Then a 1 M solution of sodium hexamethyldisilazane in THF (3.3 mL, 3.34 mmol) was added dropwise. After stirring at -78 °C for 40 min, the mixture was treated with chlorotrimethylsilane (0.35 mL, 2.79 mmol) and stirred for additional 1 h at -78 °C and at room temperature for 2 h. Then, an aqueous solution of $NaHCO_3$ (19 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried

(Na_2SO_4), filtered and concentrated in vacuo. The residue was adsorbed on silica gel and given on a silica column (∅ 2.5 cm, h = 20 cm, v = 10 mL, C_6H_{12}/EtOAc = 4/1, R_f = 0.35). Colorless solid, mp 150.9 °C, yield 127.5 mg (22%). $C_{30}H_{40}N_2O_4Si$, M_r = 520.7. HPLC (method ACN): t_R = 25.9 min, purity 94.6%. ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.22 (s, 9H, $OSi(CH_3)_3$), 0.85 – 0.98 (m, 2H, $NCH_2C_6H_{11}$), 1.12 – 1.23 (m, 3H, $NCH_2C_6H_{11}$), 1.54 – 1.74 (m, 6H, $NCH_2C_6H_{11}$), 1.90 (dd, J = 13.6 / 3.9 Hz, 1H, 8-*H*), 2.10 (dd, J = 13.6 / 2.0 Hz, 1H, 8-*H*), 2.76 (dd, J = 13.8 / 6.6 Hz, 1H, $NCH_2C_6H_{11}$), 3.25 (s, 3H, OCH_3), 3.62 (dd, J = 13.8 / 7.6 Hz, 1H, $NCH_2C_6H_{11}$), 3.87 (dd, J = 3.8 / 2.0 Hz, 1H, 4-*H*), 3.98 (s, 1H, 1-*H*), 4.29 (d, J = 14.8 Hz, 1H, NCH_2Ar), 4.89 (d, J = 14.8 Hz, 1H, NCH_2Ar), 7.32 – 7.37 (m, 3H, Ar-*H*), 7.41 – 7.46 (m, 2H, Ar-*H*), 7.53 – 7.59 (m, 4H, Ar-*H*). ^{13}C NMR ($CDCl_3$): δ [ppm] = 1.58 (3C, $OSi(CH_3)_3$), 25.8 (1C, $NCH_2C_6H_{11}$), 25.9 (1C, $NCH_2C_6H_{11}$), 26.5 (1C, $NCH_2C_6H_{11}$), 30.5 (1C, $NCH_2C_6H_{11}$), 30.9 (1C, $NCH_2C_6H_{11}$), 37.1 (1C, $NCH_2C_6H_{11}$), 39.4 (1C, *C*-8), 48.3 (1C, NCH_2Ar), 50.4 (1C, OCH_3), 52.0 (1C, $NCH_2C_6H_{11}$), 58.9 (1C, *C*-4), 67.6 (1C, *C*-1), 102.8 (1C, *C*-7), 127.2 (2C, Ar-*C*), 127.6 (1C, Ar-*C*), 127.6 (2C, Ar-*C*), 128.9 (2C, Ar-*C*), 129.0 (2C, Ar-*C*), 135.0 (1C, Ar-C_q), 140.7 (1C, Ar-C_q), 141.1 (1C, Ar-C_q), 167.7 (1C, C=O), 168.9 (1C, *C*=O). MS (ESI): m/z [%] = 521 (M + H, 100). **IR** (neat): $\tilde{\nu}$ [cm^{-1}] = 2924, 2851 (C-H $_{aliph.}$), 1682 (C=O $_{amide}$), 1099 (Si-O), 732, 694 (arom. monosubst.).

(1*R*,4*R*,7*S*)-5-(Biphenyl-4-ylmethyl)-2-(cyclohexylmethyl)-7-methoxy-7-(trimethylsilyloxy)-2,5-diazabicyclo[2.2.2]octane-3,6-dione (*ent*-12d)

As described for **12d**, *ent*-**8d** (1.0 g, 2.23 mmol) was reacted with a solution of sodium hexamethyldisilazane (1 M in THF, 6.7 mL, 6.69 mmol) and chlorotrimethylsilane (0.7 mL, 5.57 mmol) in THF abs. (50 mL). The crude product was adsorbed on silica gel and given on a silica column (∅ 4 cm, h = 18 cm, v = 30 mL, C_6H_{12}/ EtOAc = 4/1, R_f = 0.35). Colorless solid, mp 151.5 °C, yield 76 mg (7%). $C_{30}H_{40}N_2O_4Si$, M_r = 520.7. HPLC (method ACN): t_R = 26.1 min, purity 97.1%. MS (ESI): m/z [%] = 521 (M + H, 100).

(1*S*,4*S*)-5-Benzyl-2-(cyclohexylmethyl)-2,5-diazabicyclo[2.2.2]octane-3,6,7-trione (13a)

12a (450 mg, 1,01 mmol) was dissolved in a mixture of THF/0.5 M HCl (9/1, 150 mL) and the reaction mixture was stirred for 16 h at room temperature. For work-up, H_2O

was added (12 mL) and the mixture was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was adsorbed on silica gel and given on a silica column (∅ 3 cm, h = 18 cm, v = 20 mL, C_6H_{12}/EtOAc = 3/2, R_f = 0.23). Colorless solid, mp 151 – 155 °C, yield 339 mg (99.6%). $C_{20}H_{24}N_2O_3$, M_r = 340.4. HPLC (method ACN): t_R = 16.2 min, purity 86.8%. Specific rotation: $[\alpha]_D^{20}$ = -14.7 (c = 0.22; MeOH). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.84 – 0.95 (m, 2H, $NCH_2C_6H_{11}$), 1.07 – 1.25 (m, 3H, $NCH_2C_6H_{11}$), 1.51 – 1.71 (m, 6H, $NCH_2C_6H_{11}$), 2.20 (dd, J = 18.6 / 3.3 Hz, 1H, 8-*H*), 2.52 (dd, J = 18.5 / 2.1 Hz, 1H, 8-*H*), 3.16 (dd, J = 13.9 / 6.9 Hz, 1H, $NCH_2C_6H_{11}$), 3.36 (dd, J = 13.9 / 6.8 Hz, 1H, $NCH_2C_6H_{11}$), 4.11 (dd, J = 3.3 / 2.1 Hz, 1H, 4-*H*), 4.21 (s, 1H, 1-*H*), 4.37 (d, J = 14.6 Hz, 1H, NCH_2Ar), 4.89 (d, J = 14.6 Hz, 1H, NCH_2Ar), 7.23 – 7.33 (m, 5H, Ar-*H*). MS (EM, APCI): m/z = calcd. for $C_{20}H_{25}N_2O_3$ 341.1865 (M+H), found 341.1885. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2920, 2851 (C-H $_{aliph.}$), 1748 (C=O $_{ketone}$), 737, 698 (arom. monosubst.).

(1*R*,4*R*)-5-Benzyl-2-(cyclohexylmethyl)-2,5-diazabicyclo[2.2.2]octane-3,6,7-trione (*ent*-13a)

As described for **13a**, *ent*-**12a** (200 mg, 0.45 mmol) was reacted in a mixture of THF/0.5 M HCl (9/1, 100 mL). For purification, the crude product was adsorbed on silica gel and given on a silica column (∅ 2 cm, h = 18 cm, v = 10 mL, C_6H_{12}/EtOAc = 3/2, R_f = 0.25). Colorless solid, mp 150 – 154 °C, yield 150 mg (98%). $C_{20}H_{24}N_2O_3$, M_r = 340.4. HPLC (method ACN): t_R = 16.0min, purity 88.5%. Specific rotation: $[\alpha]_D^{20}$ = +15.6 (c = 0.27; MeOH). MS (ESI): m/z [%] = 341 (M + H, 100).

(1*S*,4*S*)-5-Benzyl-2-methyl-2,5-diazabicyclo[2.2.2]octane-3,6,7-trione (13b)

12b (300 mg, 0.83 mmol) was dissolved in a mixture of THF/0.5 M HCl (9/1, 120 mL) and the reaction mixture was stirred for 16 h at room temperature. For work-up, H_2O was added (10 mL) and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was adsorbed on silica gel and given on a silica column (∅ 3 cm, h = 17 cm, v = 20 mL, C_6H_{12}/EtOAc = 3/7, R_f = 0.11). Colorless solid, mp 175 – 177 °C, yield 202 mg (94%). $C_{14}H_{14}N_2O_3$, M_r = 258.3. HPLC (method ACN): t_R =

14.1min, purity 75.6%. Specific rotation: $[\alpha]_D^{20}$ = +6.92 (c = 0.38; MeOH). ^{1}H NMR ($CDCl_3$): δ [ppm] = 2.18 (dd, J = 18.5 / 3.3 Hz, 1H, 8-*H*), 2.51 (dd, J = 18.5 / 2.0 Hz, 1H, 8-*H*), 3.07 (s, 3H, NCH_3), 4.10 (dd, J = 3.2 / 2.2 Hz, 1H, 4-*H*), 4.20 (s, 1H, 1-*H*), 4.29 (d, J = 14.6 Hz, 1H, NCH_2Ar), 4.97 (d, J = 14.6 Hz, 1H, NCH_2Ar), 7.22 – 7.35 (m, 5H, Ar-*H*). MS (EI): m/z [%] = 91 (CH_2Ar, 100). IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2953 (C-H $_{aliph.}$), 1745 (C=O $_{ketone}$), 733, 699 (arom. monosubst.).

(1*S*,4*S*)-2-(Cyclohexylmethyl)-5-(naphthalen-1-ylmethyl)-2,5-diazabicyclo[2.2.2] octane-3,6,7-trione (13c)

12c (250 mg, 0.51 mmol) was dissolved in a mixture of THF/0.5 M HCl (9/1, 100 mL) and the reaction mixture was stirred for 16 h at room temperature. For work-up, H_2O was added (10 mL) and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was adsorbed on silica gel and given on a silica column (∅ 2.5 cm, h = 23 cm, v = 20 mL, C_6H_{12}/EtOAc = 1/1, R_f = 0.50). Colorless solid, mp 100 – 104 °C, yield 186.6 mg (94%). $C_{24}H_{26}N_2O_3$, M_r = 390.5. HPLC (method ACN): t_R = 17.7 min, purity 73.6%. Specific rotation: $[\alpha]_D^{20}$ = +31.1 (c = 0.18; MeOH). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.87 – 0.95 (m, 2H, NC$H_2C_6H_{11}$), 1.09 – 1.22 (m, 3H, NC$H_2C_6H_{11}$), 1.48 – 1.57 (m, 3H, NC$H_2C_6H_{11}$), 1.62 -. 1.72 (m, 3H, NC$H_2C_6H_{11}$), 1.70 (dd, J = 18.6 / 3.4 Hz, 1H, 8-*H*), 2.29 (dd, J = 18.5 / 1.9 Hz, 1H, 8-*H*), 3.15 (dd, J = 13.9 / 7.0 Hz, 1H, NC$H_2C_6H_{11}$), 3.33 (dd, J = 13.8 / 6.8 Hz, 1H, NC$H_2C_6H_{11}$), 4.07 – 4.09 (m, 1H, 4-*H*), 4.22 (s, 1H, 1-*H*), 4.63 (d, J = 14.5 Hz, 1H, NCH_2Ar), 5.53 (d, J = 14.5 Hz, 1H, NCH_2Ar), 7.46 – 7.48 (m, 2H, Ar-*H*), 7.52 – 7.54 (m, 2H, Ar-*H*), 7.87 – 7.93 (m, 3H, Ar-*H*). MS (EM, APCI): m/z = calcd. for $C_{24}H_{27}N_2O_3$ 391.2022 (M+H), found 391.1997. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2924, 2851 (C-H $_{aliph.}$), 1751 (C=O $_{ketone}$), 737, 698 (arom. monosubst.).

(1*R*,4*R*)-2-(Cyclohexylmethyl)-5-(naphthalen-1-ylmethyl)-2,5-diazabicyclo[2.2.2] octane-3,6,7-trione (*ent*-13c)

As described for **13c**, *ent*-**12c** (250 mg, 0.51 mmol) was reacted in a mixture of THF/0.5 M HCl (9/1, 100 mL). For purification, the crude product was adsorbed on silica gel and given on a silica column (2 cm, h = 18 cm, v = 10 mL, C_6H_{12}/EtOAc = 1/1, R_f = 0.50). Colorless solid, mp 103 – 104 °C, yield 198.0 mg (99%). $C_{24}H_{26}N_2O_3$,

M_r = 390.5. HPLC (method ACN): t_R = 17.7 min, purity 98.3%. Specific rotation: $[\alpha]_D^{20}$ = -33.2 (c = 0.18; MeOH). MS (EM, APCI): m/z = calcd. for $C_{24}H_{27}N_2O_3$ 391.2022 (M+H), found 391.2077.

(1*S*,4*S*)-5-(Biphenyl-4-ylmethyl)-2-(cyclohexylmethyl)-2,5-diazabicyclo[2.2.2]octane-3,6,7-trione (13d)

12d (209 mg, 0.40 mmol) was dissolved in a mixture of THF/0.5 M HCl (9/1, 100 mL) and the reaction mixture was stirred for 16 h at room temperature. For work-up, H_2O was added (10 mL) and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was adsorbed on silica gel and given on a silica column (∅ 3 cm, h = 20 cm, v = 20 mL, C_6H_{12}/EtOAc = 1/1, R_f = 0.37). Colorless solid, mp 208.6 °C, yield 73 mg (44%). $C_{26}H_{28}N_2O_3$, M_r = 416.5. HPLC (method ACN): t_R = 19.7 min, purity 82.2%. ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.86 – 0.95 (m, 3H, $NCH_2C_6H_{11}$), 1.13 – 1.22 (m, 3H, $NCH_2C_6H_{11}$), 1.51 – 1.71 (m, 5H, $NCH_2C_6H_{11}$), 2.27 (dd, J = 18.5 / 3.3 Hz, 1H, 8-*H*), 2.56 (dd, J = 18.5 / 2.1 Hz, 1H, 8-*H*), 3.18 (dd, J = 13.9 / 6.9 Hz, 1H, $NCH_2C_6H_{11}$), 3.37 (dd, J = 13.9 / 6.8 Hz, 1H, $NCH_2C_6H_{11}$), 4.16 (dd, J = 3.3 / 2.1 Hz, 1H, 4-*H*), 4.23 (s, 1H, 1-*H*), 4.40 (d, J = 14.7 Hz, 1H, NCH_2Ar), 4.94 (d, J = 14.7 Hz, 1H, NCH_2Ar), 7.30 – 7.38 (m, 3H, Ar-*H*), 7.43 – 7.46 (m, 2H, Ar-*H*), 7.56 – 7.59 (m, 4H, Ar-*H*). ^{13}C NMR ($CDCl_3$): δ [ppm] = 25.6 (1C, $NCH_2C_6H_{11}$), 25.7 (1C, $NCH_2C_6H_{11}$), 26.3 (1C, $NCH_2C_6H_{11}$), 30.5 (1C, $NCH_2C_6H_{11}$), 30.6 (1C, $NCH_2C_6H_{11}$), 37.0 (1C, $NCH_2C_6H_{11}$), 37.1 (1C, *C*-8), 48.3 (1C, NCH_2Ar), 52.1 (1C, $NCH_2C_6H_{11}$), 58.2 (1C, *C*-4), 72.3 (1C, *C*-1), 127.2 (2C, Ar-*C*), 127.8 (2C, Ar-*C*), 128.0 (1C, Ar-*C*), 129.0 (2C, Ar-*C*), 129.3 (2C, Ar-*C*), 133.7 (1C, Ar-C_q), 140.3 (1C, Ar-C_q), 141.7 (1C, Ar-C_q), 164.6 (1C, C=O), 167.1 (1C, *C*=O), 197.1 (1C, *C*-7). MS (EM, APCI): m/z = calcd. for $C_{26}H_{28}N_2O_3$ 417.2179 (M+H), found 417.2156. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2920, 2851 (C-H $_{aliph.}$), 1744 (C=O $_{ketone}$), 729, 694 (arom. monosubst.).

(1*R*,4*R*)-5-(Biphenyl-4-ylmethyl)-2-(cyclohexylmethyl)-2,5-diazabicyclo[2.2.2]octane-3,6,7-trione (*ent*-13d)

As described for **13d**, *ent*-**12d** (140 mg, 0.27 mmol) was reacted in a mixture of THF/0.5 M HCl (9/1, 100 mL). For purification, the crude product was adsorbed on silica gel and given on a silica column (∅ 2.5 cm, h = 20 cm, v = 10 mL, C_6H_{12}/EtOAc

= 1/1, R_f = 0.37). Colorless solid, mp 207.5 °C, yield 45.3 mg (78%). $C_{26}H_{28}N_2O_3$, M_r = 416.5.HPLC (method ACN): t_R = 19.7 min, purity 85.3%. MS (EI): m/z [%] = 417 (M + H).

(1*R*,4*S*,7*S*)-5-Benzyl-2-(cyclohexylmethyl)-2,5-diazabicyclo[2.2.2]octan-7-ol (14a)

(1*R*,4*S*,7*R*)-5-Benzyl-2-(cyclohexylmethyl)-2,5-diazabicyclo[2.2.2]octan-7-ol (15a)

14a and **15a** were synthesized according to **General Procedure A: 13a** (310 mg, 0.91 mmol) was reacted with $LiAlH_4$ solution (1M in THF, 5.46 mL, 5.46 mmol) in THF abs. (30 mL). The crude product was purified by fc (∅ 3 cm, h = 20 cm, v = 10 mL, C_6H_{12}/EtOAc = 9.5/0.5 + 0.5% *N*,*N*-dimethylethylamine). $C_{20}H_{30}N_2O$, M_r = 314.5. **14a:** (R_f = 0.49) Colorless solid, mp 68 – 72 °C, yield 45.8 mg (16%). HPLC (method ACN): t_R = 13.0 min, purity 98.9%. Specific rotation: $[\alpha]_D^{20}$ = +15.3 (c = 0.79; EtOAc). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.84 – 0.94 (m, 2H, $NCH_2C_6H_{11}$), 1.14 – 1.29 (m, 4H, $NCH_2C_6H_{11}$), 1.38 – 1.43 (m, 2H, $NCH_2C_6H_{11}$, 8-*H*), 1.68 – 1.74 (m, 4H, $NCH_2C_6H_{11}$), 1.87 (d, J = 13.5 Hz, 1H, O-*H*), 2.29 (dd, J = 11.8 / 8.8 Hz, 1H, $NCH_2C_6H_{11}$), 2.37 – 2.44 (m, 1H, 8-*H*), 2.51 – 2.55 (m, 2H, $NCH_2C_6H_{11}$, 4-*H*), 2.58 – 2.62 (m, 2H, NCH_2, 1-*H*), 2.72 (dt, J = 10.2 / 2.2 Hz, 1H, NCH_2), 2.98 – 3.07 (m, 2H, NCH_2), 3.60 (d, J = 13.4 Hz, 1H, NCH_2Ar), 3.64 (d, J = 13.1 Hz, 1H, NCH_2Ar), 3.92 (dt, J = 8.8 / 2.8 Hz, 1H, 7-*H*), 7.21 – 7.36 (m, 5H, Ar-*H*). ^{13}C NMR ($CDCl_3$): δ [ppm] = 26.23 / 26.3 / 27.0 / 31.5 / 32.0 / 36.2 (6C, $NCH_2C_6H_{11}$), 37.0 (1C, *C*-8), 49.0 (1C, NCH_2), 50.5 (1C, *C*-1), 53.6 (1C, NCH_2), 58.4 (1C, *C*-4), 59.5 (1C, NCH_2Ar), 63.0 (1C, $NCH_2C_6H_{11}$), 67.6 (1C, *C*-7), 127.0 (1C, Ar-*C*), 128.4 (2C, Ar-*C*), 128.6 (2C, Ar-*C*), 139.5 (1C, Ar-C_q). MS (EM, APCI): m/z = calcd. for $C_{20}H_{31}N_2O$ 315.2436 (M+H), found 315.2486. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3264 (O-H), 2920, 2847 (C-H $_{aliph.}$), 732, 698 (arom. monosubst.). **15a:** (R_f = 0.36) Colorless oil, yield 119.7 mg (42%). HPLC (method ACN): t_R = +13.6 min, purity 95.0%. Specific rotation: $[\alpha]_D^{20}$ = +9.04 (c = 0.65; EtOAc). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.78 – 0.91 (m, 2H, $NCH_2C_6H_{11}$), 1.13 – 1.20 (m, 3H, $NCH_2C_6H_{11}$), 1.31 - 1.42 (m, 1H, $NCH_2C_6H_{11}$), 1.65 – 1.80 (m, 6H, $NCH_2C_6H_{11}$, 8-*H*), 2.10 (ddd, J = 13.7 / 8.8 / 1.7 Hz, 1H, 8-*H*), 2.34 (dd, J = 11.8 / 6.7 Hz, 1H, $NCH_2C_6H_{11}$), 2.41 (dd, J = 11.8 / 6.7 Hz, 1H, $NCH_2C_6H_{11}$), 2.62 – 2.65 (m, 2H, NCH_2,

4-*H*), 2.66 – 2.69 (m, 1H, 1-*H*), 2.74 – 2.78 (m, 2H, NCH_2), 3.08 (dd, J = 10.8 / 2.9 Hz, 1H, NCH_2), 3.64 (d, J = 14.0 Hz, 1H, NCH_2Ar), 3.67 (d, J = 13.7 Hz, 1H, NCH_2Ar), 4.03 – 4.07 (m, 1H, 7-*H*), 7.21 – 7.35 (m, 5H, Ar-*H*). The signal for the proton of the OH group is not seen. ^{13}C NMR ($CDCl_3$): δ [ppm] = 26.3 / 26.4 / 27.1 / 31.7 / 32.0 / 36.5 (6C, $NCH_2C_6H_{11}$), 38.3 (1C, *C*-8), 47.2 (1C, NCH_2), 50.5 (1C, NCH_2), 51.1 (1C, *C*-1), 56.4 (1C, *C*-4), 59.3 (1C, NCH_2Ar), 62.4 (1C, N$CH_2C_6H_{11}$), 68.0 (1C, *C*-7), 127.1 (1C, Ar-*C*), 128.4 (2C, Ar-*C*), 128.7 (2C, Ar-*C*), 139.3 (1C, Ar-C_q). MS (EM, APCI): m/z = calcd. for $C_{20}H_{31}N_2O$ 315.2436 (M+H), found 315.2489. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3391 (O-H), 2920, 2847 (C-H $_{aliph.}$), 729, 698 (arom. monosubst.).

(1*S*,4*R*,7*R*)-5-Benzyl-2-(cyclohexylmethyl)-2,2-diazabicyclo[2.2.2]octan-7-ol (*ent*-14a)

(1*S*,4*R*,7*S*)-5-Benzyl-2-(cyclohexylmethyl)-2,5-diazabicyclo[2.2.2]octan-7-ol (*ent*-15a)

Ent-**14a** and *ent*-**15a** were synthesized according to **General Procedure A:** *ent*-**13a** (150 mg, 0.44 mmol) was reacted with $LiAlH_4$ solution (1M in THF, 2.64 mL, 2.64 mmol) in THF abs. (10 mL). The crude product was purified by fc (∅ 2 cm, h = 20 cm, v = 10 mL, C_6H_{12}/EtOAc = 9.75/0.25 + 0.5% *N*,*N*-dimethylethylamine). $C_{20}H_{30}N_2O$, M_r = 314.5. *ent*-**14a:** (R_f = 0.38) Colorless solid, mp 79 – 83 °C, yield 27.6 mg (20%). HPLC (method ACN): t_R = 12.1 min, purity 96.2%. Specific rotation: $[\alpha]_D^{20}$ = -14.6 (c = 0.79; EtOAc). MS (EM, APCI): m/z = calcd. for $C_{20}H_{31}N_2O$ 315.2436 (M+H), found 315.2431. *ent*-**15a:** (R_f = 0.23) Colorless oil, yield 46.5 mg (34%). HPLC (method ACN): t_R = 12.7 min, purity 96.7%. Specific rotation: $[\alpha]_D^{20}$ = -8.68 (c = 0.64; EtOAc). MS (EM, APCI): m/z = calcd. for $C_{20}H_{31}N_2O$ 315.2436 (M+H), found 315.2431.

(1*R*,4*S*,7*S*)-5-Benzyl-2-methyl-2,5-diazabicyclo[2.2.2]octan-7-ol (14b)

(1*R*,4*S*,7*R*)-5-Benzyl-2-methyl-2,5-diazabicyclo[2.2.2]octan-7-ol (15b)

14b and **15b** were synthesized according to **General Procedure A: 13b** (210 mg, 0.81 mmol) was reacted with $LiAlH_4$ solution (1M in THF, 4.9 mL, 4.88 mmol) in THF abs. (20 mL). The crude product was purified by fc (∅ 2 cm, h = 18 cm, v = 10 mL, EtOAc / MeOH = 9.5/0.5 + 0.5% *N*,*N*-dimethylethylamine). $C_{14}H_{20}N_2O$, M_r = 232.3.

14b: (R_f = 0.16). Pale yellow oil, yield 41.4 mg (22%). HPLC (method ACN): t_R = 4.02 min, purity 97.3%. Specific rotation: $[\alpha]_D^{20}$ = +22.2 (c = 0.54; EtOAc). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.40, (dt, J = 13.7 / 2.6 Hz, 1H, 8-*H*), 2.38 – 2.43 (m, 1H, 8-*H*), 2.45 (s, 3H, NCH_3), 2.48 – 2.51 (m, 1H, 1-*H*), 2.57 – 2.65 (m, 2H, NCH_2, 4-*H*), 2.71 – 2.75 (m, 1H, NCH_2), 3.03 – 3.07 (m, 2H, NCH_2), 3.56 (d, J = 15.7 Hz, 1H, NCH_2Ar), 3.60 (d, J = 15.7 Hz, 1H, NCH_2Ar), 3.96 (dt, J = 9.1 / 3.0 Hz, 1H, 7-*H*), 7.21 – 7.36 (m, 5H, Ar-*H*). The signal for the proton of the OH group is not seen. ^{13}C NMR ($CDCl_3$): δ [ppm] = 36.5 (1C, *C*-8), 46.4 (1C, N*C*H_3), 48.0 (1C, N*C*H_2), 50.6 (1C, *C*-4), 54.7 (1C, N*C*H_2), 59.2 (1C, N*C*H_2Ar), 59.4 (1C, *C*-1), 67.7 (1C, *C*-7), 127.2 (1C, Ar-*C*), 128.5 (2C, Ar-*C*), 128.7 (2C, Ar-*C*), 139.1 (1C, Ar-C_q). MS (EM, APCI): m/z = calcd. for $C_{14}H_{21}N_2O$ 233.1654 (M+H), found 233.1612. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3379 (O-H), 2936, 2874 (C-H $_{aliph.}$), 729, 698 (arom. monosubst.). **15b:** (R_f = 0.11) Colorless oil, yield 87.8 mg (47%). HPLC (method ACN): t_R = 4.72 min, purity 96.3%. Specific rotation: $[\alpha]_D^{20}$ = +19.8 (c = 0.40; EtOAc). ^{1}H NMR ($CDCl_3$): δ [ppm] = 1.74 – 1.79 (m, 1H, 8-*H*), 2.11 (ddd, J = 13.9 / 8.7 / 1.6 Hz, 1H, 8-*H*), 2.45 (s, 3H, NCH_3), 2.64 – 2.66 (m, 1H, 4-*H*), 2.71 – 2.74 (m, 2H, NCH_2, 1-*H*), 2.77 – 2.81 (m, 2H, NCH_2), 3.08 (dd, J = 11.0 / 3.0 Hz, 1H, NCH_2), 3.66 (d, J = 13.9 Hz, 1H, NCH_2Ar), 3.70 (d, J = 13.7 Hz, 1H, NCH_2Ar), 4.12 – 4.15 (m, 1H, 7-*H*), 7.24 – 7.36 (m, 5H, Ar-*H*). The signal for the proton of the OH group is not seen. ^{13}C NMR ($CDCl_3$): δ [ppm] = 37.8 (1C, *C*-8), 42.1 (1C, N*C*H_3), 45.9 (1C, N*C*H_2), 51.1 (1C, *C*-1), 51.7 (1C, N*C*H_2), 57.8 (1C, *C*-4), 59.2 (1C, N*C*H_2Ar), 67.6 (1C, *C*-7), 127.2 (1C, Ar-*C*), 128.5 (2C, Ar-*C*), 128.7 (2C, Ar-*C*), 139.1 (1C, Ar-C_q). MS (EM, APCI): m/z = calcd. for $C_{14}H_{21}N_2O$ 233.1654 (M+H), found 233.1629. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3329 (O-H), 2930, 2843 (C-H $_{aliph.}$), 729, 698 (arom. monosubst.).

(1*R*,4*S*,7*S*)-2-(Cyclohexylmethyl)-5-(naphthalen-1-ylmethyl)-2,5-diazabicyclo-[2.2.2]octan-7-ol (14c)

(1*R*,4*S*,7*R*)-2-(Cyclohexylmethyl)-5-(naphthalen-1-ylmethyl)-2,5-diazabicyclo-[2.2.2]octan-7-ol (15c)

14c and **15c** were synthesized according to **General Procedure A: 13c** (180 mg, 0.46 mmol) was reacted with $LiAlH_4$ solution (1M in THF, 2.7 mL, 2.77 mmol) in THF abs. (10 mL). The crude product was purified by fc (∅ 2 cm, h = 19 cm, v = 10 mL,

C_6H_{12}/EtOAc = 7/3). $C_{24}H_{32}N_2O$, M_r = 364.5. **14c:** (R_f = 0.14, C_6H_{12}/EtOAc 4/1 + 0.5% *N*,*N*-dimethylethylamine) Colorless oil, yield 45.6 mg (28%). HPLC (method ACN): t_R = 17.7 min, purity 95.9%. Specific rotation: $[\alpha]_D^{20}$ = +7.00 (c = 0.22; EtOAc). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.82 – 0.95 (m, 2H, $NCH_2C_6H_{11}$), 1.12 – 1.24 (m, 3H, $NCH_2C_6H_{11}$), 1.39 – 1.44 (m, 2H, $NCH_2C_6H_{11}$,8-*H*), 1.66 – 1.74 (m, 4H, $NCH_2C_6H_{11}$), 1.85 – 1.89 (m, 1H, $NCH_2C_6H_{11}$), 2.30 – 2.35 (m, 1H, $NCH_2C_6H_{11}$), 2.39 – 2.46 (m, 1H, 8-*H*), 2.54 – 2.58 (m, 2H, $NCH_2C_6H_{11}$, 4-*H*), 2.66 – 2.68 (m, 2H, NCH_2, 1-*H*), 2.75 – 2.79 (m, 1H, NCH_2), 3.04 (dd, J = 10.3 / 2.7 Hz, 1H, NCH_2), 3.14 (dt, J = 11.1 / 2.0 Hz, 1H, NCH_2), 3.93 (dt, J = 9.0 / 2.9 Hz, 1H, 7-*H*), 4.02 (d, J = 13.6 Hz, 1H, NCH_2Ar), 4.06 (d, J = 13.2 Hz, 1H, NCH_2Ar), 7.26 – 7.39 (m, 2H, Ar-*H*), 7.41 – 7.51 (m, 2H, Ar-*H*), 7.75 – 7.78 (m, 1H, Ar-*H*), 7.83 – 7.85 (m, 1H, Ar-*H*), 8.26 – 8.29 (m, 1H, Ar-*H*). The signal for the proton of the OH group is not seen. ^{13}C NMR ($CDCl_3$): δ [ppm] = 26.2 / 26.3 / 27.0 / 31.5 / 32.0 / 36.2 (6C, $NCH_2C_6H_{11}$), 36.8 (1C, *C*-8), 48.9 (1C, NCH_2), 50.5 (1C, *C*-1), 53.8 (1C, NCH_2), 57.8 (1C, NCH_2Ar), 58.5 (1C, *C*-4), 63.0 (1C, $NCH_2C_6H_{11}$), 67.6 (1C, *C*-7), 124.6 (1C, Ar-C), 125.3 (1C, Ar-C), 125.8 (1C, Ar-C), 125.9 (1C, Ar-C), 126.7 (1C, Ar-C), 128.0 (1C, Ar-C), 128.6 (1C, Ar-C), 132.4 (1C, Ar-C_q), 134.0 (1C, Ar-C_q), 134.9 (1C, Ar-C_q). MS (EM, APCI): m/z = calcd. for $C_{24}H_{33}N_2O$ 365.2593 (M+H), found 365.2604. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3425 (O-H), 2920, 2847 (C-H $_{aliph.}$), 733, 698 (arom. monosubst.). **15c:** (R_f = 0.10, C_6H_{12}/EtOAc 4/1 + 0.5% *N*,*N*-dimethylethylamine) Colorless oil, yield 70 mg (43%). HPLC (method ACN): t_R = 17.8 min, purity 95.6%. Specific rotation: $[\alpha]_D^{20}$ = +5.22 (c = 1.00; EtOAc). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.82 – 0.92 (m, 2H, $NCH_2C_6H_{11}$), 1.11 – 1.29 (m, 4H, $NCH_2C_6H_{11}$), 1.34 – 1.45 (m, 1H, $NCH_2C_6H_{11}$), 1.76 – 1.81 (m, 6H, $NCH_2C_6H_{11}$, 8-*H*, O-*H*), 2.10 (ddd, J = 13.7 / 8.7 / 1.7 Hz, 1H, 8-*H*), 2.39 (dd, J = 11.9 / 7.6 Hz, 1H, $NCH_2C_6H_{11}$), 2.46 (dd, J = 11.9 / 6.7 Hz, 1H, $NCH_2C_6H_{11}$), 2.67 – 2.73 (m, 2H, NCH_2, 4-*H*), 2.80 – 2.88 (m, 3H, NCH_2, 1-*H*), 3.06 (dd, J = 10.8 / 3.0 Hz, 1H, NCH_2), 4.04 (d, J = 13.0 Hz, 1H, NCH_2Ar), 4.05 – 4.07 (m, 1H, 7-*H*), 4.15 (d, J = 13.1 Hz, 1H, NCH_2Ar), 7.30 – 7.51 (m, 4H, Ar-*H*), 7.76 – 7.78 (m, 1H, Ar-*H*), 7.82 – 7.86 (m, 1H, Ar-*H*), 8.25 – 8.28 (m, 1H, Ar-*H*). ^{13}C NMR ($CDCl_3$): δ [ppm] = 26.3 / 26.4 / 27.0 / 31.7 / 32.0 / 35.7 (6C, $NCH_2C_6H_{11}$), 38.2 (1C, *C*-8), 46.8 (1C, NCH_2), 50.6 (1C, NCH_2), 51.4 (1C, *C*-1), 56.5 (1C, *C*-4), 57.4 (1C, NCH_2Ar), 62.4 (1C, $NCH_2C_6H_{11}$), 68.0 (1C, *C*-7), 124.3 (1C, Ar-C), 125.3 (1C, Ar-C), 125.8 (1C, Ar-C), 126.0 (1C, Ar-C), 127.1 (1C, Ar-C), 128.1 (1C, Ar-C), 128.7 (1C, Ar-C), 132.4 (1C, Ar-C_q), 134.0 (1C, Ar-C_q),

134.5 (1C, Ar-C_q). MS (EM, APCI): m/z = calcd. for $C_{24}H_{33}N_2O$ 365.2593 (M+H), found 365.2608. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3379 (O-H), 2920, 2845 (C-H $_{aliph.}$), 768, 717 (arom. monosubst.).

(1*S*,4*R*,7*R*)-2-(Cyclohexylmethyl)-5-(naphthalen-1-ylmethyl)-2,5-diazabicyclo-[2.2.2]octan-7-ol (*ent*-14c)

(1*S*,4*R*,7*S*)-2-(Cyclohexylmethyl)-5-(naphthalen-1-ylmethyl)-2,5-diazabicyclo-[2.2.2]octan-7-ol (*ent*-15c)

As described for **14c** and **15c**, *ent*-**14c** and *ent*-**15c** were synthesized according to **General Procedure A:** *ent*-**13c** (160 mg, 0.41 mmol) was reacted with $LiAlH_4$ solution (1M in THF, 2.5 mL, 2.46 mmol) in THF abs. (20 mL). The crude product was purified by fc (∅ 2 cm, h = 20 cm, v = 10 mL, C_6H_{12}/EtOAc = 7/3). $C_{24}H_{32}N_2O$, M_r = 364.5. *ent*-**14c**: (R_f = 0.23, C_6H_{12}/EtOAc 4/1 + 1% *N*,*N*-dimethylethylamine). Colorless oil, yield 36.2 mg (24%). HPLC (method ACN): t_R = 18.7 min, purity 97.4%. Specific rotation: $[\alpha]_D^{20}$ = - 8.23 (c = 0.62; EtOAc). MS (EM, APCI): m/z = calcd. for $C_{24}H_{33}N_2O$ 365.2593 (M+H), found 365.2595. *ent*-**15c:** (R_f = 0.16, C_6H_{12}/EtOAc 4/1 + 1% *N*,*N*-dimethylethylamine). Colorless oil, yield 50.4 mg (34%). HPLC (method ACN): t_R = 17.5 min, purity 95.9%. Specific rotation: $[\alpha]_D^{20}$ = - 6.81 (c = 0.53; EtOAc). MS (ESI): m/z [%] = 365 (M+H, 100).

(1*R*,4*S*,7*S*)- 5-(Biphenyl-4-ylmethyl)-2-(cyclohexylmethyl)-2,5-diazabicyclo[2.2.2]octan-7-ol (14d)

(1*R*,4*S*,7*R*)- 5-(biphenyl-4-ylmethyl)-2-(cyclohexylmethyl)-2,5-diazabicyclo[2.2.2]octan-7-ol (15d)

14d and **15d** were synthesized according to **General Procedure A: 13d** (60 mg, 0.14 mmol) was reacted with $LiAlH_4$ solution (1M in THF, 0.86 mL, 0.86 mmol) in THF abs. (10 mL). The crude product was purified by fc (∅ 2 cm, h = 21 cm, v = 10 mL, C_6H_{12}/EtOAc = 7/3). $C_{26}H_{34}N_2O$, M_r = 390.6. **14d:** (R_f = 0.18, C_6H_{12}/EtOAc 4/1 + 0.5% *N*,*N*-dimethylethylamine). Colorless oil, yield 15.2 mg (28%). HPLC (method ACN): t_R = 17.6 min, purity 96.2%. MS (EM, APCI): m/z = calcd. for $C_{26}H_{34}N_2O$ 391.2751 (M+H), found 391.2742. **15d:** (R_f = 0.13, C_6H_{12}/EtOAc 4/1 + 0.5% *N*,*N*-

dimethylethylamine). Colorless oil, yield 17.5 mg (32%). HPLC (method ACN): t_R = 17.9 min, purity 97.7%. MS (EM, APCI): m/z = calcd. for $C_{26}H_{34}N_2O$ 391.2751 (M+H), found 391.2751.

(1*S*,4*R*,7*R*)- 5-(Biphenyl-4-ylmethyl)-2-(cyclohexylmethyl)-2,5-diazabicyclo[2.2.2]octan-7-ol (*ent*-14d)

(1*S*,4*R*,7*S*)- 5-(biphenyl-4-ylmethyl)-2-(cyclohexylmethyl)-2,5-diazabicyclo[2.2.2]octan-7-ol (*ent*-15d)

As described for **14d** and **15d**, *ent*-**14d** and *ent*-**15d** were synthesized according to **General Procedure A:** *ent*-**13d** (120 mg, 0.29 mmol) was reacted with $LiAlH_4$ solution (1M in THF, 1.7 mL, 1.73 mmol) in THF abs. (20 mL). The crude product was purified by fc (∅ 2.5 cm, h = 22 cm, v = 10 mL, C_6H_{12}/EtOAc = 7/3). $C_{26}H_{34}N_2O$, M_r = 390.6. *ent*-**14d:** (R_f = 0.18 C_6H_{12}/EtOAc = 4/1 + 0.5% *N*,*N*-dimethylethylamine). Colorless oil, yield 25.2 mg (22%). HPLC (method ACN): t_R = 17.7 min, purity 99.5%. ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.81 – 1.01 (m, 3H, $NCH_2C_6H_{11}$), 1.15 – 1.46 (m, 5H, $NCH_2C_6H_{11}$), 1.59 – 1.78 (m, 4H, $NCH_2C_6H_{11}$, 8-*H*), 1.77 – 1.82 (m, 1H, 8-*H*), 2.38 (dd, J = 12.0, 7.4 Hz, 1H, $NCH_2C_6H_{11}$), 2.51 (dd, J = 12.2, 7.0 Hz, 1H, $NCH_2C_6H_{11}$), 2.58 – 2.63 (m, 2H, NCH_2), 2.80 – 2.92 (m, 3H, NCH_2, 4-*H*), 3.18 – 3.36 (m, 1H, 1-*H*), 3.77 – 3.82 (m, 2H, NCH_2Ar), 4.12 (d, J = 10.5 Hz, 1H, 7-*H*), 7.35 – 7.39 (m, 1H, Ar-*H*), 7.40 – 7.48 (m, 4H, Ar-*H*), 7.61 – 7.72 (m, 4H, Ar-*H*). The signal for the proton of the OH group is not seen. ^{13}C NMR ($CDCl_3$): δ [ppm] = 26.2 / 26.3 / 27.2 / 31.8 / 31.9 / 36.4 (6C, $NCH_2C_6H_{11}$), 37.4 (1C, *C*-8), 47.4 (1C, *C*-1), 50.6 (1C, NCH_2), 51.0 (1C, *C*-4), 56.2 (1C, NCH_2), 58.9 (1C, NCH_2Ar), 62.5 (1C, $NCH_2C_6H_{11}$), 67.1 (1C, *C*-7), 127.1 (1C, Ar-C), 127.2 (1C, Ar-C), 127.3 (2C, Ar-C), 127.4 (1C, Ar-C), 128.8 (3C, Ar-C), 129.5 (1C, Ar-C), 131.0 (1C, Ar-C_q), 140.8 (1C, Ar-C_q), 140.9 (1C, Ar-C_q). MS (EM, APCI): m/z = calcd. for $C_{26}H_{34}N_2O$ 391.2751 (M+H), found 391.2744. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3325 (O-H), 2924, 2851 (C-H $_{aliph.}$), 756, 698 (arom. monosubst.). *ent*-**15d:** (R_f = 0.11 C_6H_{12}/EtOAc = 4/1 + 0.5% *N*,*N*-dimethylethylamine). Colorless oil, yield 18.5 mg (16%). HPLC (method ACN): t_R = 18.0 min, purity 98.5%. ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.84 – 0.92 (m, 3H, $NCH_2C_6H_{11}$), 1.15 – 1.40 (m, 6H, $NCH_2C_6H_{11}$), 1.65 – 1.73 (m, 3H, $NCH_2C_6H_{11}$, 8-*H*), 1.75 – 1.80 (m, 1H, 8-*H*), 2.39 (dd, J = 12.0, 7.6 Hz, 1H, $NCH_2C_6H_{11}$), 2.46 (dd, J = 11.6, 7.2 Hz, 1H, $NCH_2C_6H_{11}$), 2.71 (d, J = 11.5 Hz, 2H, NCH_2), 2.80 – 2.92 (m, 3H, NCH_2, 4-*H*), 3.18 – 3.35 (m, 1H, 1-*H*), 3.77 – 3.82 (m,

2H, NC*H*$_2$Ar), 4.12 (d, J = 10.5 Hz, 1H, 7-*H*), 7.33 – 7.36 (m, 1H, Ar-*H*), 7.42 – 7.49 (m, 4H, Ar-*H*), 7.53 – 7.59 (m, 4H, Ar-*H*). The signal for the proton of the OH group is not seen. ^{13}C NMR ($CDCl_3$): δ [ppm] = 26.2 / 26.3 / 27.0 / 31.7 / 31.9 / 36.4 (6C, NCH$_2$*C*$_6$H$_{11}$), 37.3 (1C, *C*-8), 47.4 (1C, *C*-1), 50.4 (1C, N*C*H$_2$), 51.1 (1C, *C*-4), 56.2 (1C, N*C*H$_2$), 58.8 (1C, N*C*H$_2$Ar), 62.5 (1C, N*C*H$_2$C$_6$H$_{11}$), 67.1 (1C, *C*-7), 127.1 (1C, Ar-C), 127.2 (1C, Ar-C), 127.3 (2C, Ar-C), 127.4 (1C, Ar-C), 128.9 (3C, Ar-C), 129.5 (1C, Ar-C), 131.0 (1C, Ar-C$_q$), 140.8 (1C, Ar-C$_q$), 140.9 (1C, Ar-C$_q$). MS (EM, APCI): m/z = calcd. for $C_{26}H_{34}N_2O$ 391.2751 (M+H), found 391.2785. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3321 (O-H), 2920, 2850 (C-H $_{aliph.}$), 733, 698 (arom. monosubst.).

Methyl (*S*)-3-[1-benzyl-4-(cyclohexylmethyl)-3,6-dioxopiperazin-2-yl]propanoate (19)

18 (2.5 g, 7.31 mmol) was dissolved in dry acetonitrile (molecular sieves 3 Å, 25 mL) and triethylamine (1.2 mL, 8.78 mmol) and cyclohexylmethylamine (1.2 mL, 9.51 mmol) were added slowly. The reaction mixture was stirred at room temperature for 16 h. For workup, the solvent was evaporated in vacuo and the residue was dissolved in EtOAc (30 mL). The organic layer was washed with 0.5 M HCl (2 x 10 mL), 0.5 M NaOH (1 x 10 mL) and brine (1 x 10 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by fc (∅ 8 cm, h = 16 cm, v = 65 mL, C_6H_{12}/EtOAc = 7/3, R_f = 0.16). Colorless oil, yield 1.8 g (64%). $C_{22}H_{30}N_2O_4$, M_r = 386.5. HPLC (method ACN): t_R = 19.7 min, purity 99.4%. Specific rotation: $[\alpha]_D^{20}$ = +19.6 (c = 1.06; EtOAc). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.91 – 1.00 (m, 2H, NCH$_2$C$_6$*H*$_{11}$), 1.13 – 1.22 (m, 2H, NCH$_2$C$_6$*H*$_{11}$), 1.57 – 1.74 (m, 7H, NCH$_2$C$_6$*H*$_{11}$), 1.97 – 2.09 (m, 1H, CHC*H*$_2$CH$_2$CO$_2$CH$_3$), 2.16 – 2.22 (m, 1H, CHC*H*$_2$CH$_2$CO$_2$CH$_3$), 2.35 – 2.50 (m, 2H, CHCH$_2$C*H*$_2$CO$_2$CH$_3$), 3.12 (dd, J = 13.5 / 6.9 Hz, 1H, NC*H*$_2$C$_6$H$_{11}$), 3.30 (dd, J = 13.5 / 7.7 Hz, 1H, NC*H*$_2$C$_6$H$_{11}$), 3.67 (s, 3H, OC*H*$_3$), 3.86 – 3.89 (m, 1H, C*H*CH$_2$CH$_2$CO$_2$CH$_3$), 3.89 (d, J = 17.5 Hz, 1H, O=CC*H*$_2$N), 4.01 (d, J = 14.8 Hz, 1H, NC*H*$_2$Ar), 4.15 (d, J = 17.2 Hz, 1H, O=CC*H*$_2$N), 5.26 (d, J = 14.8 Hz, 1H, NC*H*$_2$Ar), 7.25 – 7.35 (m, 5H, Ar-*H*). ^{13}C NMR ($CDCl_3$): δ [ppm] = 25.7 (1C, NCH$_2$*C*$_6$H$_{11}$), 25.8(1C, NCH$_2$*C*$_6$H$_{11}$), 26.3 (1C, NCH$_2$*C*$_6$H$_{11}$), 26.6 (1C, CH*C*H$_2$CH$_2$CO$_2$CH$_3$), 29.4 (1C, CHCH$_2$*C*H$_2$CO$_2$CH$_3$), 30.6 (1C, NCH$_2$*C*$_6$H$_{11}$), 30.8 (1C, NCH$_2$*C*$_6$H$_{11}$), 35.6 (1C, NCH$_2$*C*$_6$H$_{11}$), 47.2 (1C, N*C*H$_2$Ar), 50.5 (1C, O=C*C*H$_2$N), 52.1 (1C, O*C*H$_3$), 52.5 (1C, N*C*H$_2$C$_6$H$_{11}$), 58.7 (1C, *C*HCH$_2$CH$_2$CO$_2$CH$_3$), 128.2 (1C, Ar-*C*), 128.4 (2C, Ar-*C*),

129.0 (2C, Ar-*C*), 135 7 (1C, Ar-C_q), 164.3 (1C, *C*=O), 165.9 (1C, *C*=O), 172.8 (CO_2CH_3). MS (EM, APCI): m/z = calcd. for $C_{22}H_{31}N_2O_4$ 387.2284 (M+H), found 387.2308. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2920, 2850 (C-H $_{aliph.}$), 1721 (C=O $_{ester}$), 1647 (C=O $_{amide}$), 771, 694 (arom. monosubst.).

(1*S*,2*R*,5*S*)-6-Benzyl-8-(cyclohexylmethyl)-2-methoxy-2-(trimethylsilyloxy)-6,8-diazabicyclo[3.2.2]nonane-7,9-dione (20)

Under N_2, **19** (980 mg, 2.54 mmol) was dissolved in THF abs (50 mL) and the mixture was cooled down to -78 °C. Then a 1 M solution of sodium hexamethyldisilazane in THF (7.6 mL, 7.61 mmol) was added dropwise. After stirring at -78 °C for 40 min, the mixture was treated with chlorotrimethylsilane (0.8 mL, 6.34 mmol) and stirred for additional 1 h at -78 °C and at room temperature for 2 h. Then an aqueous solution of $NaHCO_3$ (20 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was adsorbed on silica gel and given on a silica column (∅ 5 cm, h = 22 cm, v = 65 mL, C_6H_{12}/EtOAc = 8.5/1.5, R_f = 0.22). Colorless solid, mp 112 – 113 °C, yield 698 mg (61%). $C_{25}H_{38}N_2O_4Si$, M_r = 458.7. HPLC (method ACN): t_R = 22.9 min, purity 95.9%. Specific rotation: $[\alpha]_D^{20}$ = +39.3 (c = 0.90; EtOAc). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.21 (s, 9H, $OSi(CH_3)_3$), 0.86 – 0.99 (m, 2H, $NCH_2C_6H_{11}$, 3-*H*, 4-*H*), 1.13 – 1.26 (m, 3H, $NCH_2C_6H_{11}$, 3-*H*, 4-*H*), 1.45 – 1.51 (m, 1H, $NCH_2C_6H_{11}$, 3-*H*, 4-*H*), 1.55 – 1.75 (m, 6H, $NCH_2C_6H_{11}$, 3-*H*, 4-*H*), 1.80 – 1.89 (m, 3H, $NCH_2C_6H_{11}$, 3-*H*, 4-*H*), 2.69 (dd, J = 13.6 / 6.3 Hz, 1H, $NCH_2C_6H_{11}$), 3.24 (s, 3H, OCH_3), 3.77 (dd, J = 13.7 / 7.7 Hz, 1H, $NCH_2C_6H_{11}$), 3.81 – 3.83 (m, 1H, 5-*H*), 3.95 (s, 1H, 1-*H*), 4.41 (d, J = 14.6 Hz, 1H, NCH_2Ar), 4.66 (d, J = 14.7 Hz, 1H, NCH_2Ar), 7.23 – 7.32 (m, 5H, Ar-*H*). ^{13}C NMR ($CDCl_3$): δ [ppm] = 1.75 (3C, $OSi(CH_3)_3$), 24.5 / 25.8 / 25.9 / 26.4 / 30.3 / 31.1 / 33.1 / 36.7 (8C, $NCH_2C_6H_{11}$, *C*-3, *C*-4), 49.0 (1C, NCH_2Ar), 49.3 (1C, OCH_3), 51.9 (1C, $NCH_2C_6H_{11}$), 59.6 (1C, *C*-5), 68.3 (1C, *C*-1), 98.9 (1C, *C*-2), 128.1 (1C, Ar-*C*), 128.6 (2C, Ar-*C*), 128.9 (2C, Ar-*C*), 136.3 (1C, Ar-C_q), 166.4 (1C, *C*=O), 168.8 (1C, *C*=O). MS (EM, APCI): m/z = calcd. for $C_{25}H_{39}N_2O_4Si$ 459.2679 (M+H), found 459.2649. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2920, 2851 (C-H $_{aliph.}$), 1682 (C=O $_{amide}$), 1072 (Si-O), 759, 694 (arom. monosubst.).

(1*S*,5*S*)-6-benzyl-8-(cyclohexylmethyl)-6,8-diazabicyclo[3.2.2]nonane-2,7,9-trione (21)

20 (500 mg, 1.09 mmol) was dissolved in a mixture of THF/0.5 M HCl (9/1, 70 mL) and the reaction mixture was stirred for 16 h at room temperature. For work-up, H_2O was added (12 mL) and the mixture was extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The residue was adsorbed on silica gel and given on a silica column (∅ 3 cm, h = 16 cm, v = 20 mL, C_6H_{12}/EtOAc = 7/3, R_f = 0.16). Colorless solid, mp 135 - 140 °C, yield 354.7 mg (91%). $C_{21}H_{26}N_2O_3$, M_r = 354.4. HPLC (method ACN): t_R = 18.0 min, purity 97.4%. Specific rotation: $[\alpha]_D^{20}$ = +88.5 (c = 0.19; MeOH). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.87 – 1.02 (m, 2H, $NCH_2C_6H_{11}$), 1.12 – 1.26 (m, 3H, $NCH_2C_6H_{11}$), 1.54 – 1.73 (m, 6H, $NCH_2C_6H_{11}$), 2.82 – 2.34 (m, 1H, 4-*H*), 2.46 – 2.51 (m, 1H, 4-*H*), 2.48 (ddd, J = 15.6 / 7.2 / 4.3 Hz, 1H, 3-*H*), 2.74 (dt, J = 15.6 / 8.4 Hz, 1H, 3-*H*), 2.92 (dd, J = 13.8 / 6.5 Hz, 1H, $NCH_2C_6H_{11}$), 3.61 (dd, J = 13.8 / 7.4 Hz, 1H, $NCH_2C_6H_{11}$), 4.05 (dd, J = 4.2 / 3.2 Hz, 1H, 5-*H*), 4.22 (s, 1H, 1-*H*), 4.55 (d, J = 14.6 Hz, 1H, NCH_2Ar), 4.70 (d, J = 14.6 Hz, 1H, NCH_2Ar), 7.24 – 7.37 (m, 5H, Ar-*H*). MS (EM, APCI): m/z = calcd. for $C_{21}H_{27}N_2O_3$ 355.2021 (M+H), found 355.1982. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 2974, 2920, 2851 (C-H $_{aliph.}$), 1728 (C=O $_{ketone}$), 733, 698 (arom. monosubst.).

(1*R*,2*S*,5*S*)-6-Benzyl-8-(cyclohexylmethyl)-6,8-diazabicyclo[3.2.2]nonan-2-ol (22)

(1*R*,2*R*,5*S*)-6-Benzyl-8-(cyclohexylmethyl)-6,8-diazabicyclo[3.2.2]nonan-2-ol (23)

22 and **23** were synthesized according to **General Procedure A: 21** (340 mg, 0.96 mmol) was reacted with $LiAlH_4$ solution (1M in THF, 5.8 mL, 5.76 mmol) in THF abs. (30 mL). The crude product was purified by fc (∅ 2 cm, h = 25 cm, v = 10 mL, C_6H_{12}/EtOAc = 9.5/0.5). $C_{21}H_{32}N_2O$, M_r = 328.5. **22:** (R_f = 0.30) Colorless oil, yield 69.4 mg (22%). HPLC (method ACN): t_R = 14.7 min, purity 95.1%. Specific rotation: $[\alpha]_D^{20}$ = +18.6 (c = 0.47; EtOAc). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.87 – 0.96 (m, 2H, $NCH_2C_6H_{11}$), 1.14 – 1.27 (m, 4H, $NCH_2C_6H_{11}$), 1.46 - 1.53 (m, 1H, $NCH_2C_6H_{11}$), 1.57 – 1.79 (m, 7H, $NCH_2C_6H_{11}$ (4H), 3-*H,* 4-*H*, O-*H*), 1.88 – 1.93 (m, 1H, 3-*H* or 4-*H*), 2.10 – 2.17 m, 1H, 3-*H* or 4-*H*), 2.25 (t, J = 10.4 Hz, 1H, $NCH_2C_6H_{11}$), 2.62 – 2.69 (m, 3H, $NCH_2C_6H_{11}$, NCH_2, 1-*H*), 2.72 – 2.92 (m, 4H, 5-*H*, NCH_2), 3.70 (s, broad, 2H,

NC*H*$_2$Ar), 3.79 – 3.82 (m, 1H, 2-*H*), 7.21 – 7.34 (m, 5H, Ar-*H*). ^{13}C NMR ($CDCl_3$): δ [ppm] = 26.1 / 26.2 / 26.9 / 28.0 / 30.2 / 30.9 / 32.1 / 35.8 (8C, $NCH_2C_6H_{11}$, *C*-3, *C*-4), 49.1 (1C, N*C*H$_2$), 51.3 (1C, N*C*H$_2$), 53.8 (1C, *C*-5), 60.7 (1C, N*C*H$_2$Ar), 62.0 (1C, *C*-1), 65.4 (1C, N*C*H$_2$C$_6$H$_{11}$), 70.7 (1C, *C*-2), 127.0 (1C, Ar-*C*), 128.4 (2C, Ar-*C*), 128.5 (2C, Ar-*C*), 140.0 (1C, Ar-C_q). MS (EM, APCI): m/z = calcd. for $C_{21}H_{33}N_2O$ 329.2592 (M+H), found 329.2566. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3364 (O-H), 2920, 2845 (C-H $_{aliph.}$), 729, 698 (arom. monosubst.). **23:** (R_f = 0.14) Colorless oil, yield 131.6 mg (42%). HPLC (method ACN): t_R = 16.1 min, purity 96.6%. Specific rotation: $[\alpha]_D^{20}$ = +18.5 (c = 0.65; EtOAc). ^{1}H NMR ($CDCl_3$): δ [ppm] = 0.81 – 0.92 (m, 2H, $NCH_2C_6H_{11}$), 1.17 – 1.26 (m, 3H, $NCH_2C_6H_{11}$), 1.33 - 1.43 (m, 1H, $NCH_2C_6H_{11}$), 1.64 – 1.85 (m, 9H, $NCH_2C_6H_{11}$ (5H), 3-*H,* 4-*H* (2H), O-*H*), 2.14 – 2.21 (m, 1H, 3-*H*), 2.31 – 2.40 (m, 2H, NC*H*$_2$C$_6$H$_{11}$), 2.72 – 2.80 (m, 4H, NC*H*$_2$, 1-*H*), 2.86 – 2.89 (m, 1H, 5-*H*), 3.11 – 3.14 (m, 1H, NC*H*$_2$), 3.72 (d, J = 13.3 Hz, 1H, NC*H*$_2$Ar), 3.77 (d, J = 13.4 Hz, 1H, NC*H*$_2$Ar), 4.02 – 4.06 (m, 1H, 2-*H*), 7.26 – 7.40 (m, 5H, Ar-*H*). ^{13}C NMR ($CDCl_3$): δ [ppm] = 26.3 / 26.4 / 27.1 / 29.6 / 30.8 / 31.5 / 32.0 / 36.4 (8C, $NCH_2C_6H_{11}$, *C*-3, *C*-4), 47.2 (1C, N*C*H$_2$), 51.3 (1C, N*C*H$_2$), 54.7 (1C, *C*-5), 61.1 (1C, N*C*H$_2$Ar), 62.1 (1C, *C*-1), 64.7 (1C, N*C*H$_2$C$_6$H$_{11}$), 75.2 (1C, *C*-2), 127.1 (1C, Ar-*C*), 128.4 (2C, Ar-*C*), 128.7 (2C, Ar-*C*), 139.6 (1C, Ar-C_q). MS (EM, APCI): m/z = calcd. for $C_{21}H_{33}N_2O$ 329.2592 (M+H), found 329.2552. IR (neat): $\tilde{\nu}$ [cm^{-1}] = 3345 (O-H), 2916, 2847 (C-H $_{aliph.}$), 729, 698 (arom. monosubst.).

Chiral HPLC

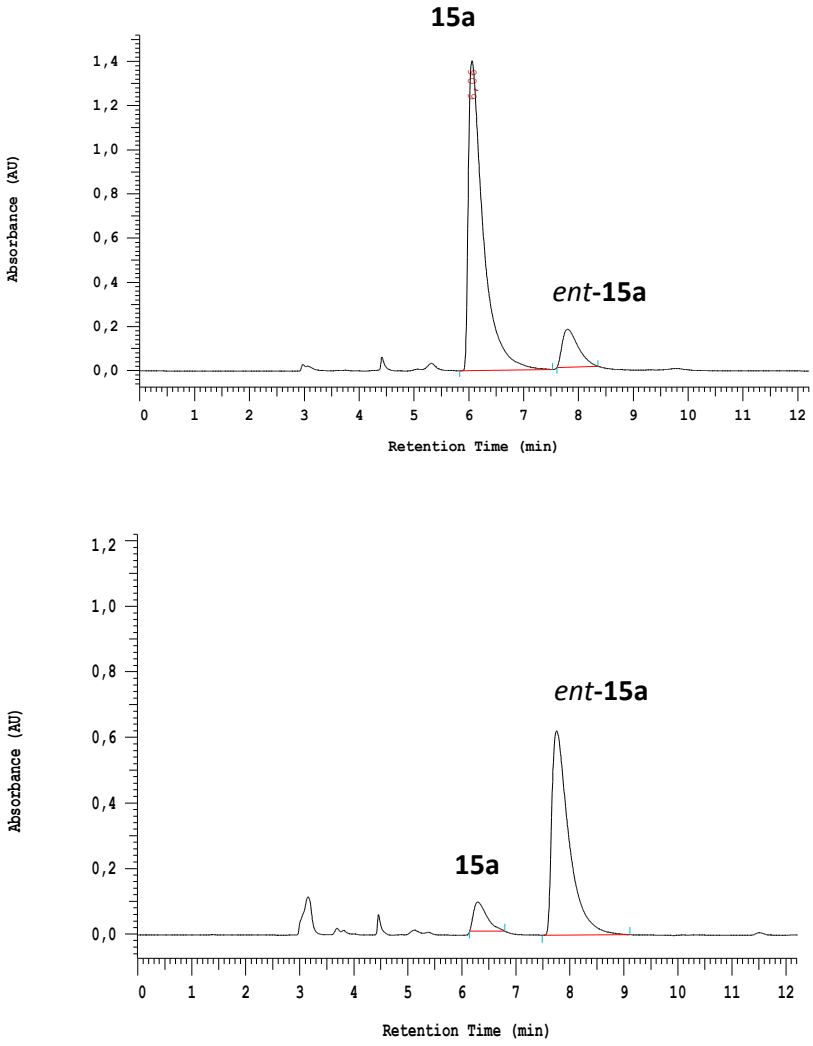

Figure S1; Chromatograms of HPLC analyses of **15a** (top) and *ent*-**15a** (bottom): Chiralpak® IA, isohexane : ethanol = 90 : 10, flow rate 1.0 mL/min, UV detection λ = 210 nm. Both compounds contain approximately 10 % the enantiomer.

Receptor binding studies

Fragments of guinea pig brain served as receptor source for the investigation of binding to the animal σ_1 receptor. Membrane preparation of human RPMI 8226 cells was used in case of the cellbased σ_1 assay. Both assays were performed with [^{3}H]-(+)-pentazocine as radioligand. The non-specific binding in the guinea pig assay was determined with unlabeled (+)-pentazocine, the cell-based assay was performed with haloperidol. The σ_2 assay was carried out with rat liver homogenates. The assay was performed with [^{3}H]DTG as radioligand in presence of non-labeled (+)-pentazocine for selective mask of the σ_1 receptors, because DTG is not selective for σ_2 receptors. Non-tritiated DTG was employed for investigation of non-specific binding. Usually, all experiments were carried out in triplicates using standard 96-well-multiplates (Diagonal). Six serially diluted stock solutions were used to determine the competition curves. The IC_{50} values were calculated with the program GraphPad Prism® 3.0 (GraphPad Software) by non-linear regression analysis. The K_i values were calculated according to Cheng and Prusoff.[5] The K_i values of highly affine compounds are given as mean values ± SEM from three independent experiments.

Materials

Guinea pig brains and rat livers were commercially available (Harlan-Winkelmann, Germany). The cell line RPMI 8226 used for the human σ_1 assay was acquired from the DSMZ (Heidelberg, Germany). Homogenizers: Elvehjem Potter (B. Braun Biotech International, Melsungen, Germany) and Soniprep 150, MSE, London, UK). Centrifuges: Cooling centrifuge model Rotina 35R (Hettich, Tuttlingen, Germany) and High-speed cooling centrifuge model Sorvall RC-5C plus (Thermo Fisher Scientific, Langenselbold, Germany). Multiplates: standard 96-well multiplates (Diagonal, Muenster, Germany). Shaker: self-made device with adjustable temperature and tumbling speed (scientific workshop of the institute). Harvester: MicroBeta FilterMate-96 Harvester. Filter: Printed Filtermat Typ A and B. Scintillator: Meltilex (Typ A or B) solid state scintillator. Scintillation analyzer: MicroBeta Trilux (all Perkin Elmer LAS, Rodgau-Jügesheim, Germany).

Protein determination

The protein concentration was determined by the method of Bradford, modified by Stoscheck.[6,7] The Bradford solution was prepared by dissolving 5 mg of Coomassie Brilliant Blue G 250 in 2.5 mL of EtOH (95%, v/v). 10 mL deionized H_2O and 5 mL phosphoric acid (85%, m/v) were added to this solution, the mixture was stirred and filled to a total volume of 50.0 mL with deionized H_2O. The calibration was carried out using bovine serum albumin as a standard in 9 concentrations (0.1, 0.2, 0.4, 0.6, 0.8, 1.0, 1.5, 2.0 and 4.0 mg /mL). In a 96-well standard multiplate, 10 µL of the calibration solution or 10 µL of the membrane receptor preparation were mixed with 190 µL of the Bradford solution, respectively. After 5 min, the UV absorption of the protein-dye complex at λ = 595 nm was measured with a platereader (Tecan Genios, Tecan, Crailsheim, Germany).

General procedures for the binding assays

The test compound solutions were prepared by dissolving approximately 10 µmol (usually 2-4 mg) of test compound in DMSO so that a 10 mM stock solution was obtained. To obtain the required test solutions for the assay, the DMSO stock solution was diluted with the respective assay buffer. The filtermats were presoaked in 0.5% aqueous polyethylenimine solution for 2 h at room temperature before use. All binding experiments were carried out in duplicates in the 96-well multiplates. The concentrations given are the final concentration in the assay. Generally, the assays were performed by addition of 50 µL of the respective assay buffer, 50 µL test compound solution in various concentrations (10^{-5}, 10^{-6}, 10^{-7}, 10^{-8}, 10^{-9} and 10^{-10} mol/L), 50 µL of corresponding radioligand solution and 50 µL of the respective receptor preparation into each well of the multiplate (total volume 200 µL). The receptor preparation was always added last. During the incubation, the multiplates were shaken at a speed of 500-600 rpm at the specified temperature. Unless otherwise noted, the assays were terminated after 120 min by rapid filtration using the harvester. During the filtration each well was washed five times with 300 µL of H_2O. Subsequently, the filtermats were dried at 95 °C. The solid scintillator was melted on the dried filtermats at a temperature of 95 °C for 5 minutes. After solidifying of the scintillator at room temperature, the trapped radioactivity in the filtermats was measured with the scintillation analyzer. Each position on the filtermat

corresponding to one well of the multiplate was measured for 5 min with the [^{3}H]-counting protocol. The overall counting efficiency was 20%. The IC_{50} values were calculated with the program GraphPad Prism® 3.0 (GraphPad Software, San Diego, CA, USA) by non-linear regression analysis. Subsequently, the IC_{50} values were transformed into K_i values using the equation of Cheng and Prusoff.[5]

Determination of the σ_1 receptor affinity

Preparation of membrane homogenates from guinea pig brain

5 guinea pig brains were homogenized with the potter (500-800 rpm, 10 up-and-down strokes) in 6 volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1200 x *g* for 10 min at 4 °C. The supernatant was separated and centrifuged at 23500 x *g* for 20 min at 4 °C. The pellet was resuspended in 5-6 volumes of buffer (50 mM TRIS, pH 7.4) and centrifuged again at 23500 x g (20 min, 4 °C). This procedure was repeated twice. The final pellet was resuspended in 5-6 volumes of buffer and frozen (−80 °C) in 1.5 mL portions containing about 1.5 mg protein/mL.

Performance of the assay

The assay was performed with the radioligand [^{3}H]-(+)-Pentazocine (22.0 Ci/mmol; Perkin Elmer). The thawed membrane preparation of guinea pig brain cortex (about 100 µg of the protein) was incubated with various concentrations of test compounds, 2 nM [^{3}H]-(+)-Pentazocine, and TRIS buffer (50 mM, pH 7.4) at 37 °C. The non-specific binding was determined with 10 µM unlabeled (+)-Pentazocine. The K_d-value of (+)-Pentazocine is 2.9 nM.[8]

Cell culture and membrane preparation of RPMI 8226 cells

The cell line RPMI 8226 used for this assay, was obtained from *Leibniz Institute DSMZ-German Collection of Microorganisms and Cell Cultures (DSMZ),* Braunschweig, Germany. The cells were grown in RPMI 1640 medium. After detaching adherent cells with the cell scraper, the harvesting of the cells was performed by centrifugation (1000 rpm, 5 min, 4 °C). The resulting pellet was washed with 10 mL PBS and resuspended in a defined volume of Tris buffer (pH 7.4, 50 mM) to gain a suspension containing 6,000,000 cells / mL. The cells were lysed and

homogenized by sonication at volumes between 25 mL and 30 mL (3 x 10 s cycles with interceptions of 10 s).[9]

Performance of the assay

The radioligand [^{3}H]-(+)-pentazocine in TRIS buffer (pH 7.4, 50 mM) was used at a concentration of 2 nM for the association and also for the competition experiment. Cell membrane preparations (50 µL, approximately 300,000 cells per well) were incubated in 96-well-plates (total volume: 200 µL per well). A single well contained 50 µL of [^{3}H]-(+)-pentazocine and 50 µL of the cell membrane preparation. 50 µL of buffer and 50 µL of haloperidol (final concentration 10 µM per well) were added for the determination of non-specific binding. Total binding was determined by addition of 100 µL buffer. Filtration follows the incubation step, using filter mats (Filtermat B), which were pre-soaked in 0.2% aqueous polyethylenimine for 2 h at room temperature. Each well was washed with 300 µL of H_2O at RT for 8 times. After drying of the filter mats, solid scintillator (MeltiLex® B) was melted on the mats at 95 °C. The bound radioactivity was counted in the scintillation analyzer after solidification. The overall counting efficiency was 20%.[9]

Determination of the σ_2 receptor affinity

Preparation of membrane homogenates from rat liver

Two rat livers were cut into small pieces and homogenized with the potter (500-800 rpm, 10 up-and-down strokes) in 6 volumes of cold 0.32 M sucrose. The suspension was centrifuged at 1,200 x *g* for 10 min at 4 °C. The supernatant was separated and centrifuged at 31,000 x *g* for 20 min at 4 °C. The pellet was resuspended in 5-6 volumes of buffer (50 mM TRIS, pH 8.0) and incubated at room temperature for 30 min. After the incubation, the suspension was centrifuged again at 31,000 x *g* for 20 min at 4 °C. The final pellet was resuspended in 5-6 volumes of buffer and stored at -80,°C in 1.5 mL portions containing about 2 mg protein/mL.

Performance of the assay

The assay was performed with the radioligand [^{3}H]DTG (specific activity 50 Ci/mmol; ARC, St. Louis, MO, USA). The thawed membrane preparation (about 100 µg protein) was incubated with various concentrations of the test compound, 3 nM

[^{3}H]DTG and buffer containing (+)-pentazocine (500 nM (+)-pentazocine in 50 mM TRIS, pH 8.0) at room temperature. The non-specific binding was determined with 10 µM non-labeled DTG. The K_d value is 17.9 nM.[10]

Cytotoxicity assay

The cytotoxic effects of the test compounds were investigated in seven cell lines. In case of the suspension-cell line HL 60, the test compounds were tested in a MTT-Assay. 5000 cells/well were seeded out in 50 µL medium and the test compounds were added in five serially diluted concentrations. After an incubation time of 48 h, 20 µL of a freshly prepared solution of MTT in PBS (2.5 mg/mL) was added to each well and the plates were incubated again under protection from light. After 6 h, 100 µL 0.04 N HCl in isopropanol was added to each well to dissolve the MTT-formazan product and the optical density was measured at λ = 570 nm with the Anthos plate reader and the SpectraMax Plus 384 microplate reader (Molecular Devices).

The adherent cell lines were tested in a panel included the cell lines 5637 (bladder cancer), RT-4 (bladder cancer), A427 (small cell lung cancer), LCLC 103H (large cell lung cancer), MCF-7 (breast cancer), DAN-G (pancreas cancer). All cell lines were obtained from the German Collection of Microbiology and Cell Culture (DSMZ, Braunschweig, FRG). Except for LCLC 103H, which was seeded out at 500 cells/well in 100 µL medium, every other cell lines were plated out at 1000 cells/well in 100 µL medium. In the primary screening the tumor cells were incubated with a 20 µM solution of the test compound at 37 °C and 5% CO_2. After 96 h the medium was removed and the density of adherent cells was measured by staining with crystal violet as reported earlier.[10] To determine the IC_{50} values, five serially diluted stock solutions of the test compound in DMSO were used in the studies; concentrations giving T/C_{corr} values between 10-90% were used to estimate the IC_{50} values, which were calculated by least squares of the dose-response curves.[11]

Induction of apoptosis

The induction of apoptosis was determined by staining the cells with annexin V and propidium iodide by using the Annexin V-FITC kit (Miltenyi Biotech, Teterow, Germany). The staining procedure was carried out according to the kit instructions as described previously.[12] Adaptations were made for the use of the adherent A427 cell line. Briefly, 5.0 x 10^5 cells were seeded in T25 flasks and incubated for 24 h to allow for attachment and growth. Afterwards, the cells were treated for 24 h and 48 h with substances using concentrations 2-fold higher the IC_{50} values determined in the crystal violet proliferation assay, more precisely 5.6 µM (*ent*-**14a**), 3.4 µM (*ent*-**14c**), 8.7 µM (*ent*-**15c**), and 7.4 µM (*ent*-**14d**), respectively. Following the treatment, the cells were harvested by trypsinization, washed with binding buffer and stained with annexin V for 15 min in the dark. After washing with binding buffer, the cells were stained with propidium iodide (PI) and subsequently analyzed by flow cytometry using the Macs Quant flow cytometer (Miltenyi Biotech, Bergisch Gladbach, Germany). The FITC channel ($\lambda_{Ex/Em}$ = 488/530 nm) was used for detection of Annexin V-positive cells, whereas late apoptotic/necrotic and dead cells were detected with the PI channel ($\lambda_{Ex/Em}$ = 488/690 nm). Data analysis was performed with the Macs Quantify Software (Miltenyi Biotech, Bergisch Gladbach, Germany).

Sequence alignment of the human and the guinea pig σ_1 receptor

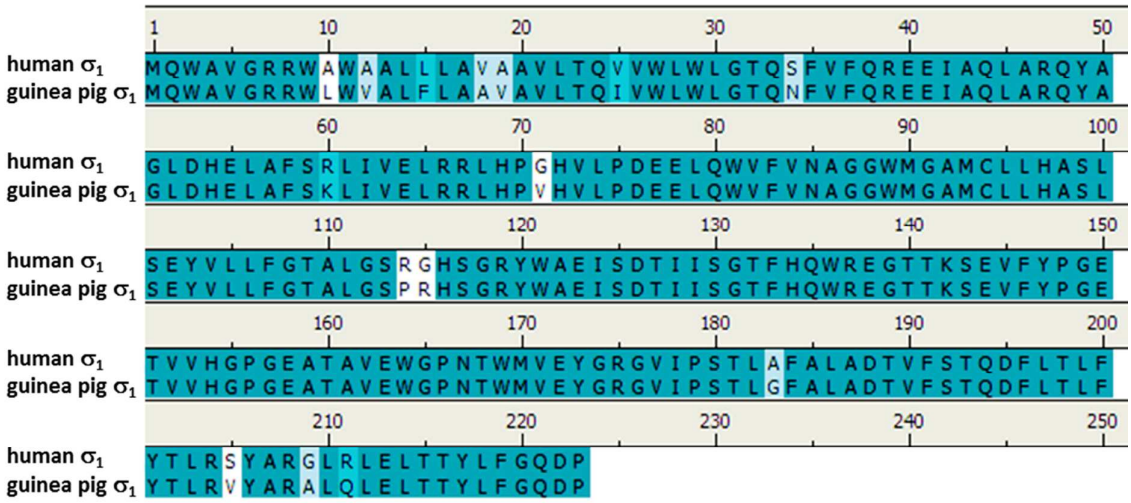

Figure S2. Sequence alignment of the human σ_1 receptor with the guinea pig σ_1 receptor.

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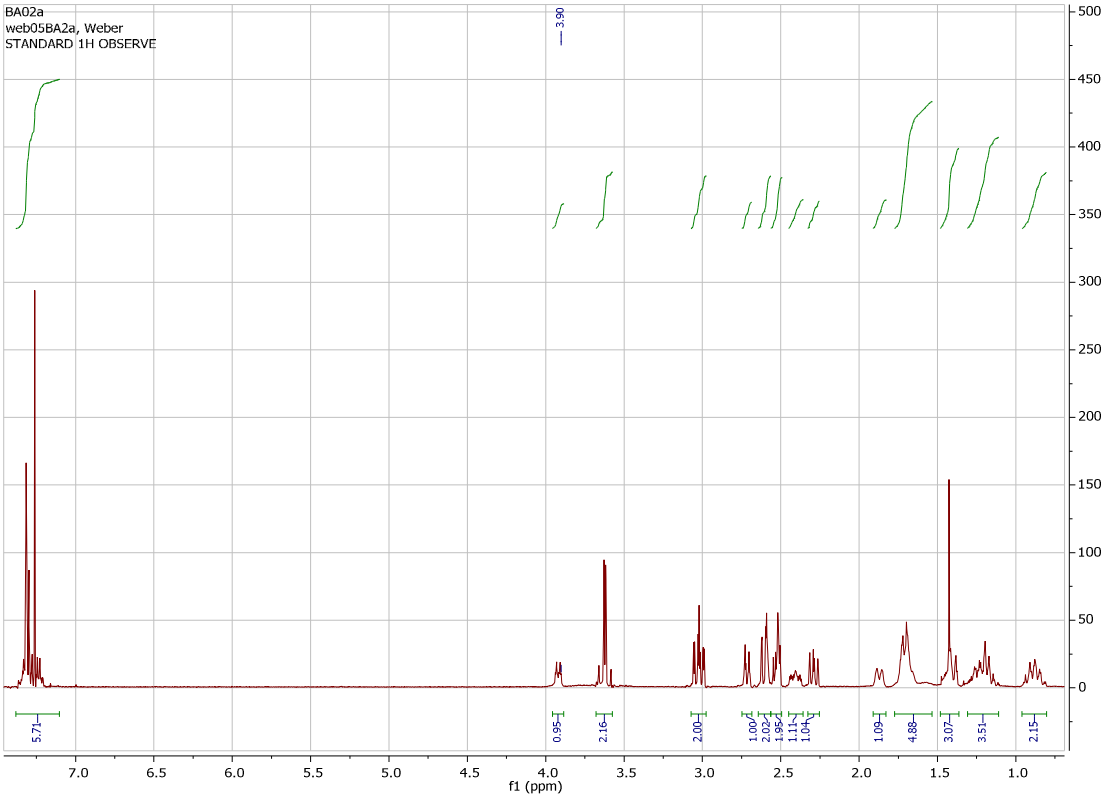
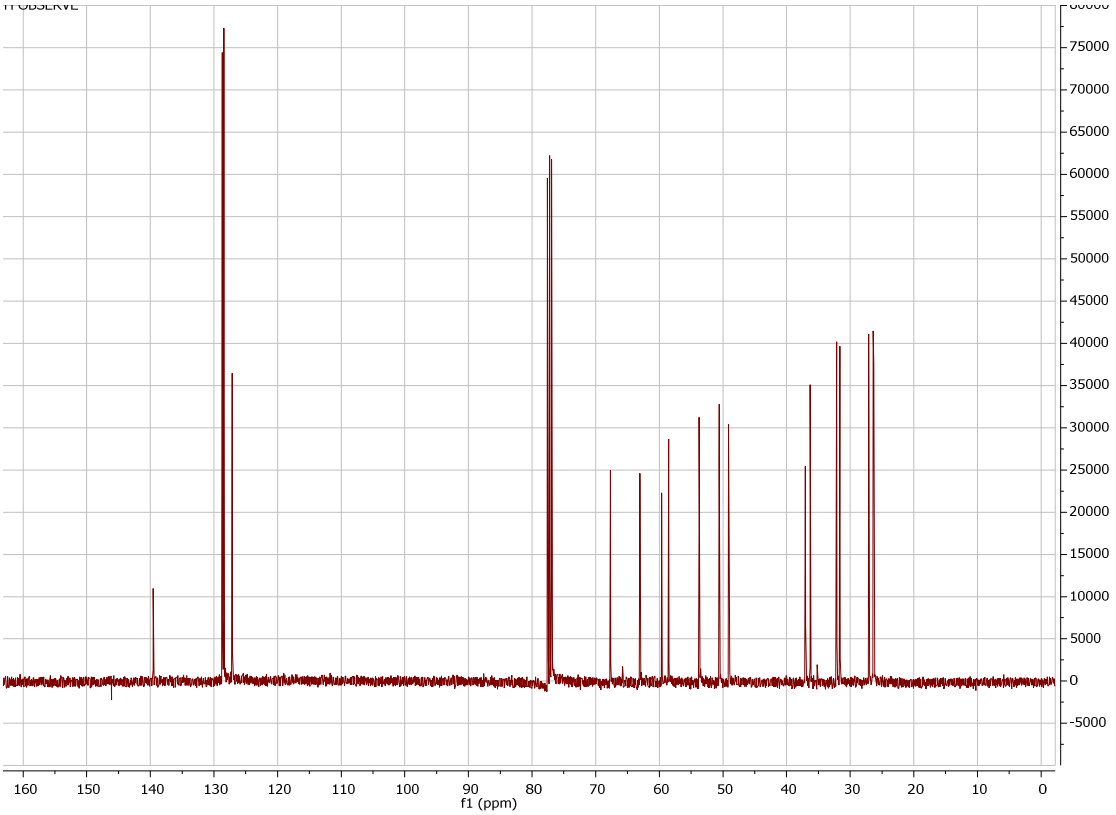
NMR spectra



^{1}H NMR spectrum ($CDCl_3$) of **14a**



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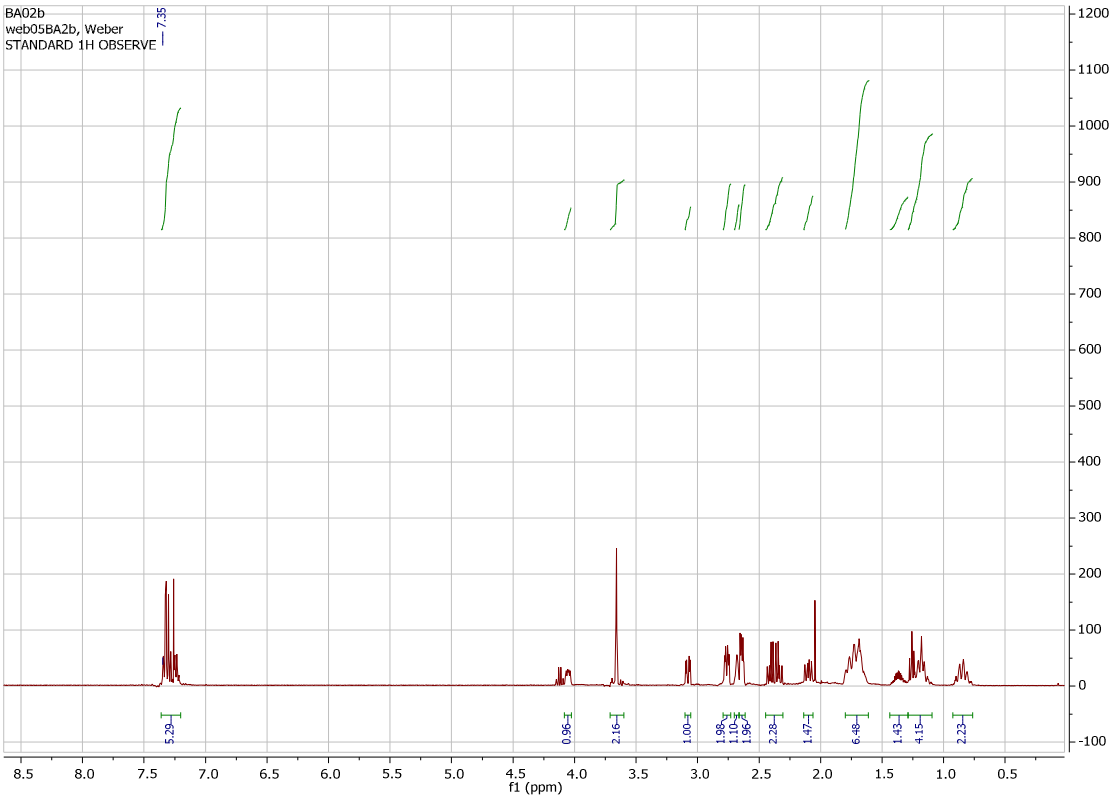

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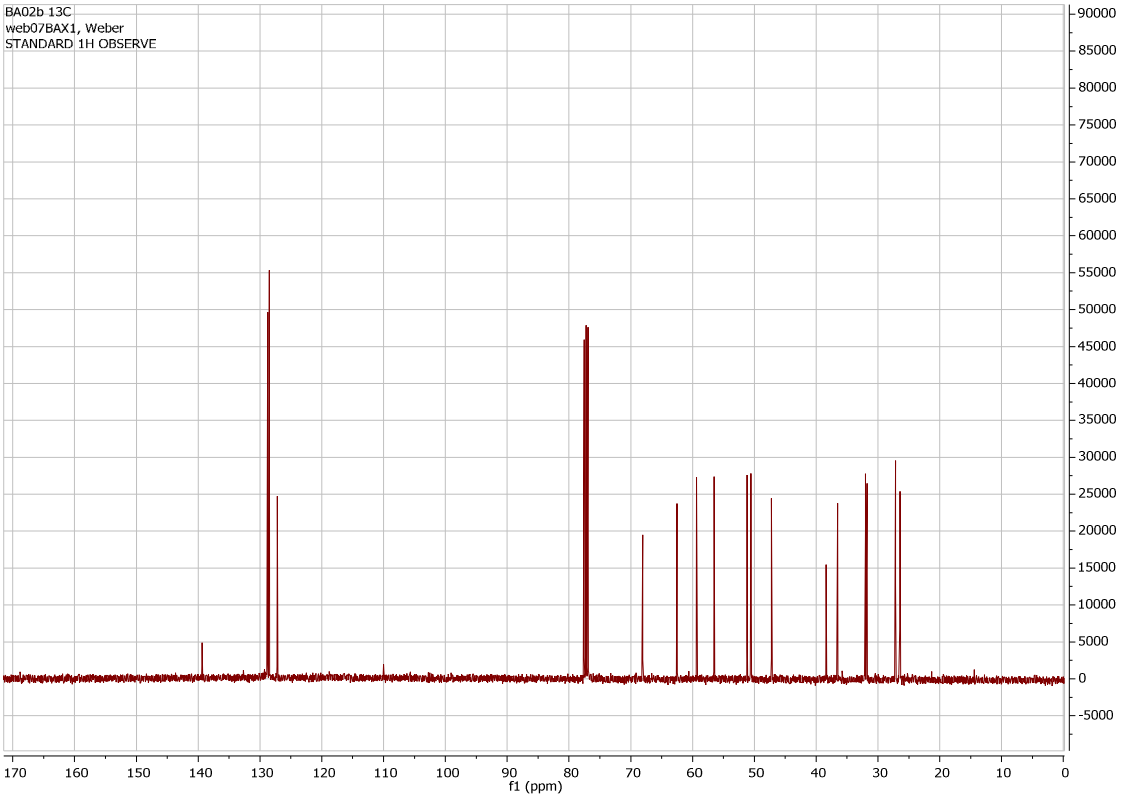

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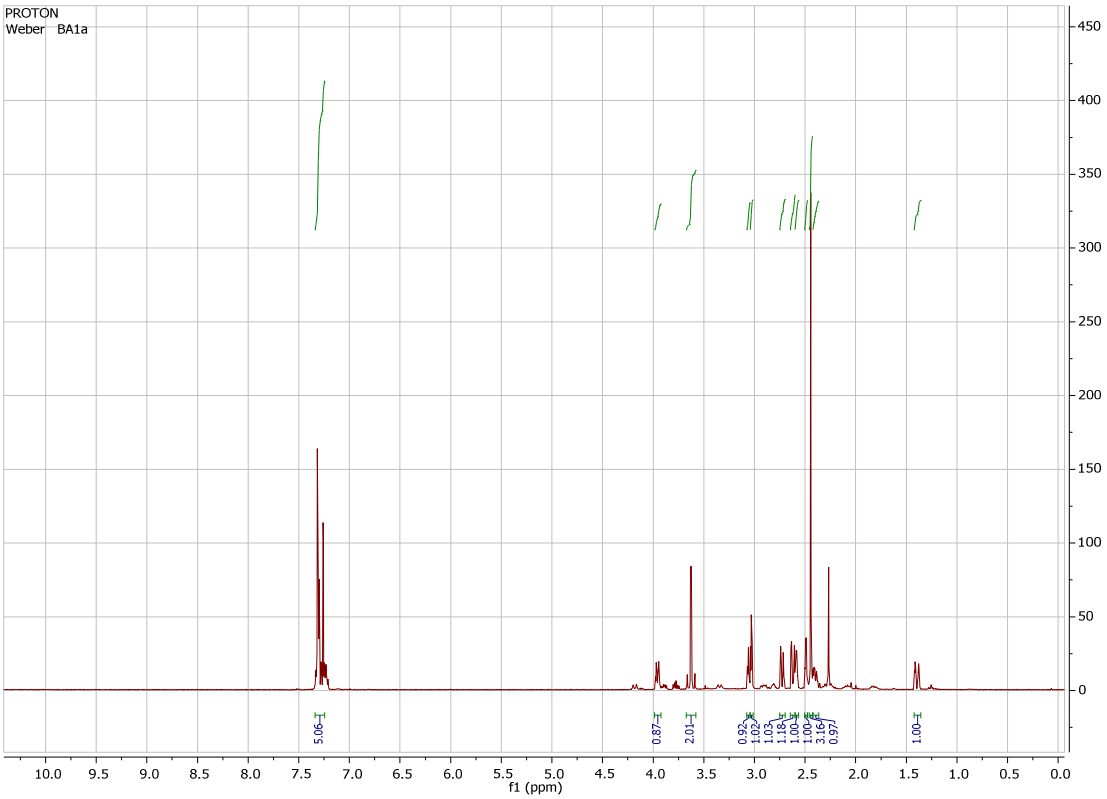

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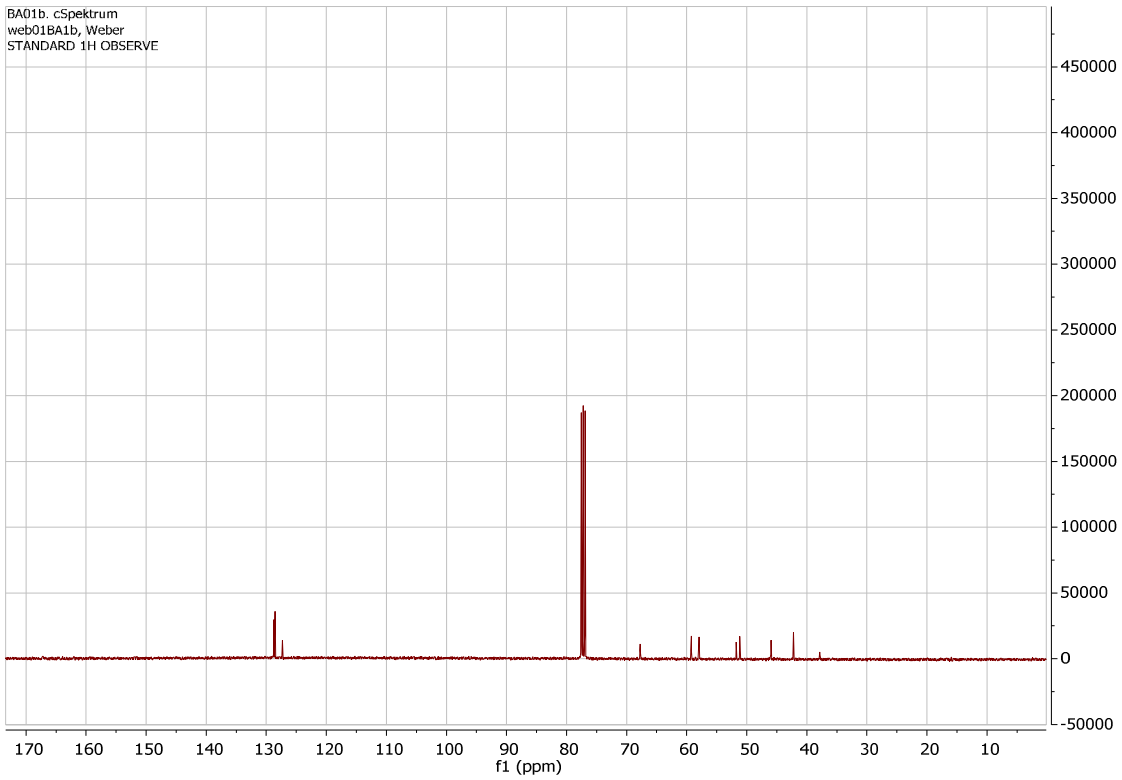

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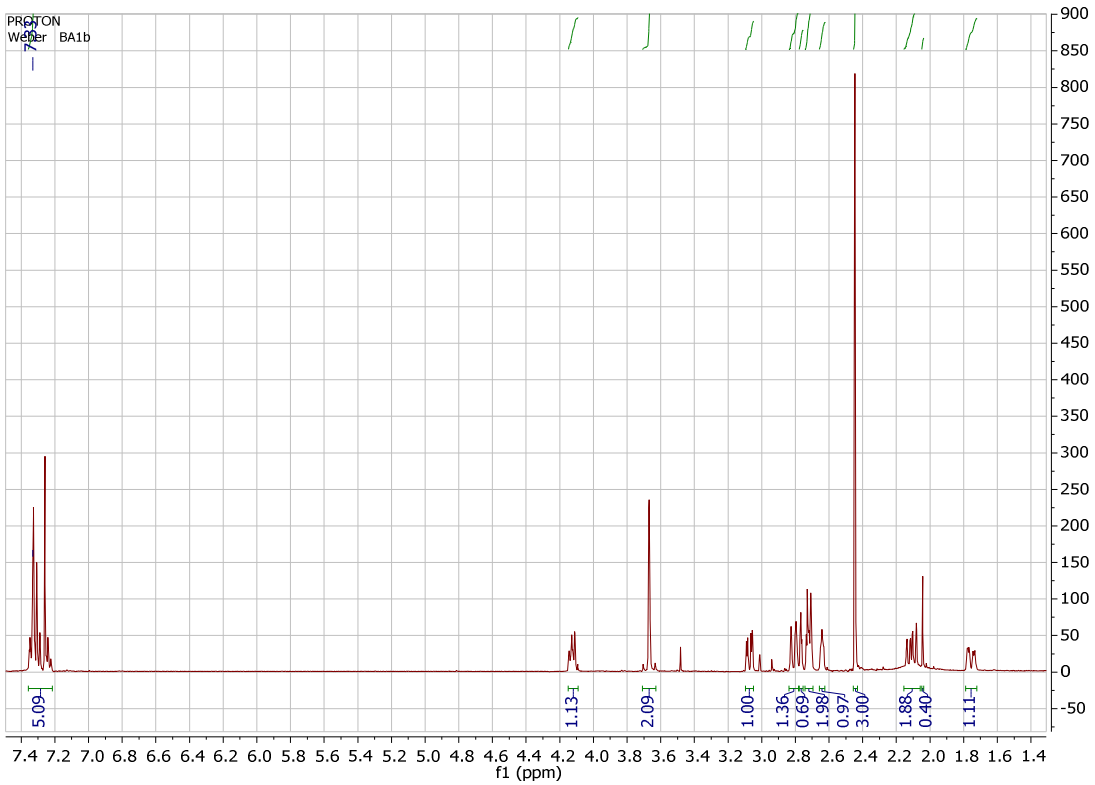

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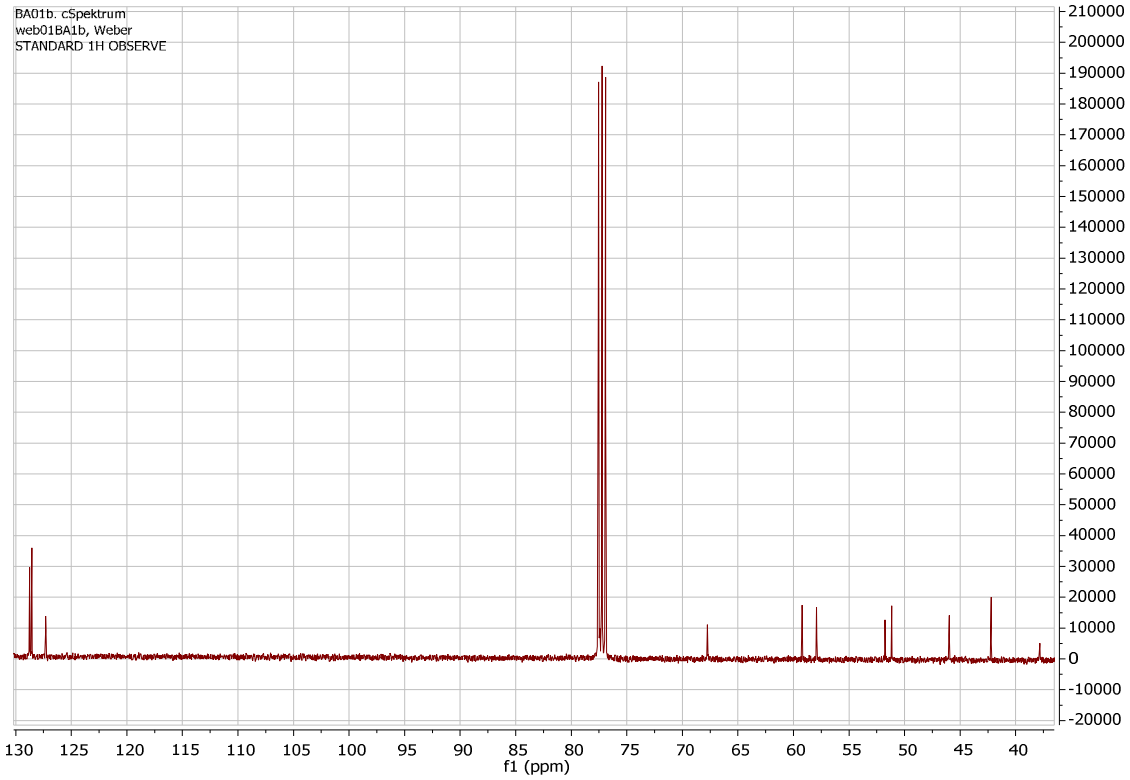

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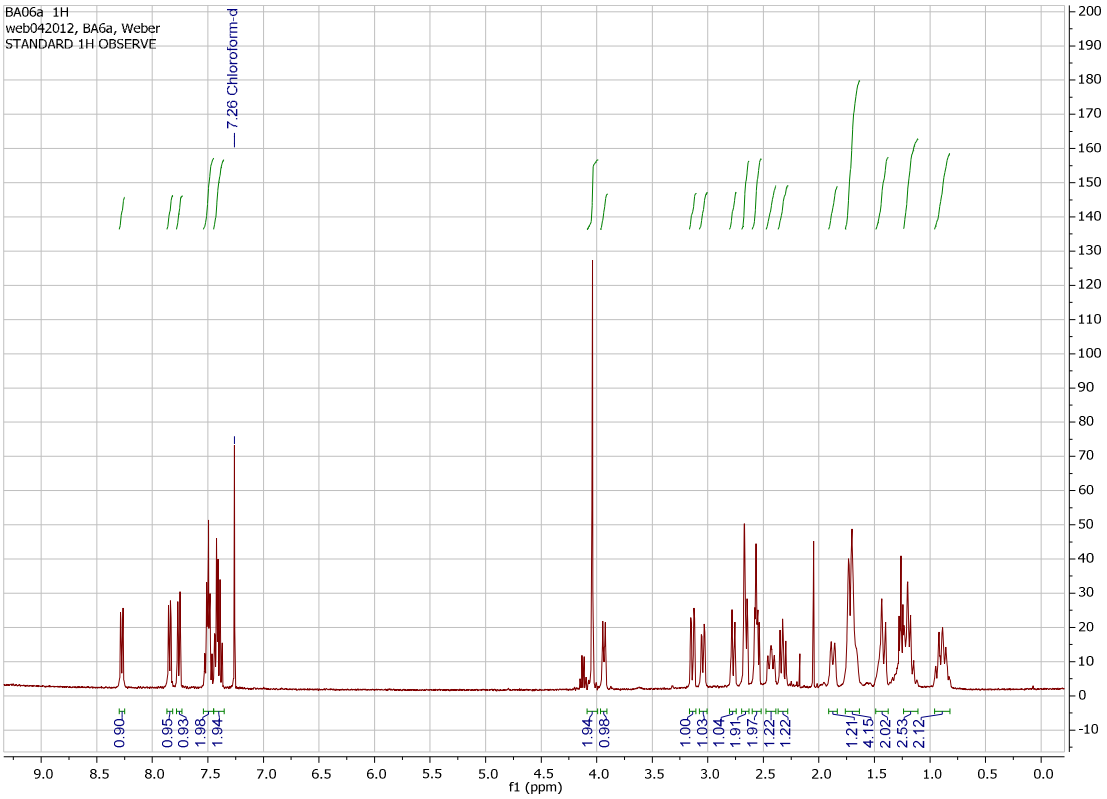

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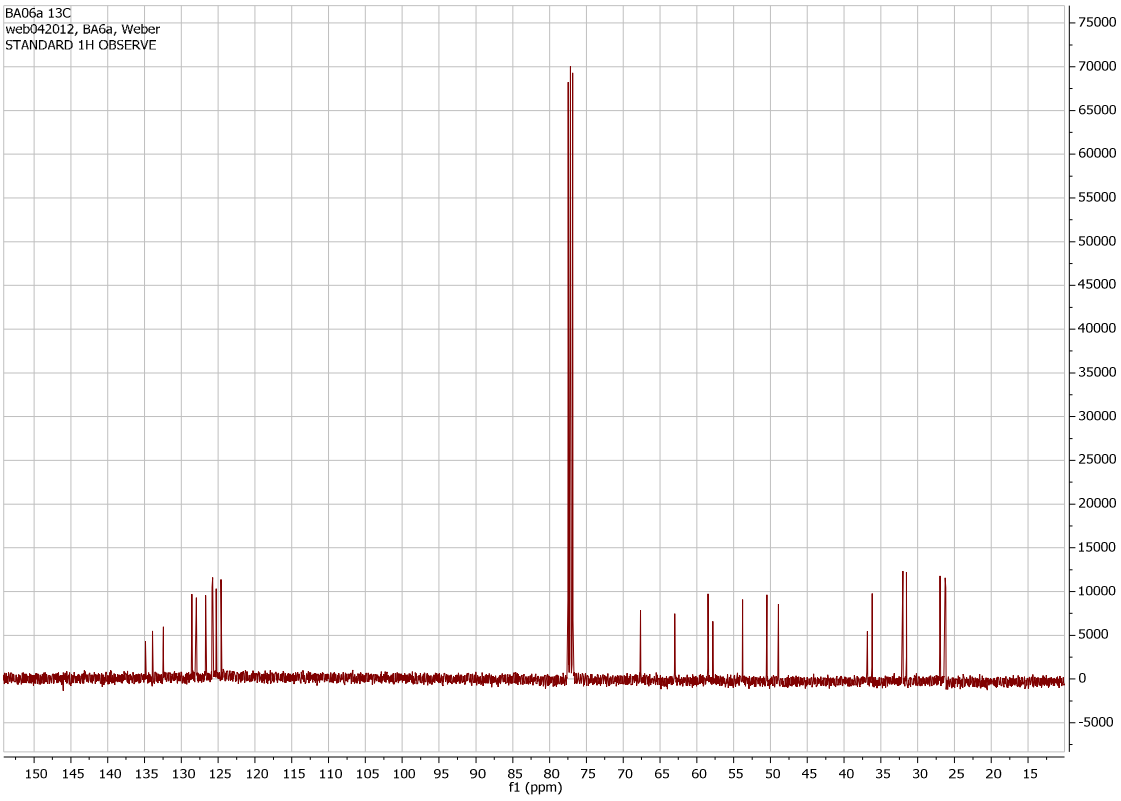

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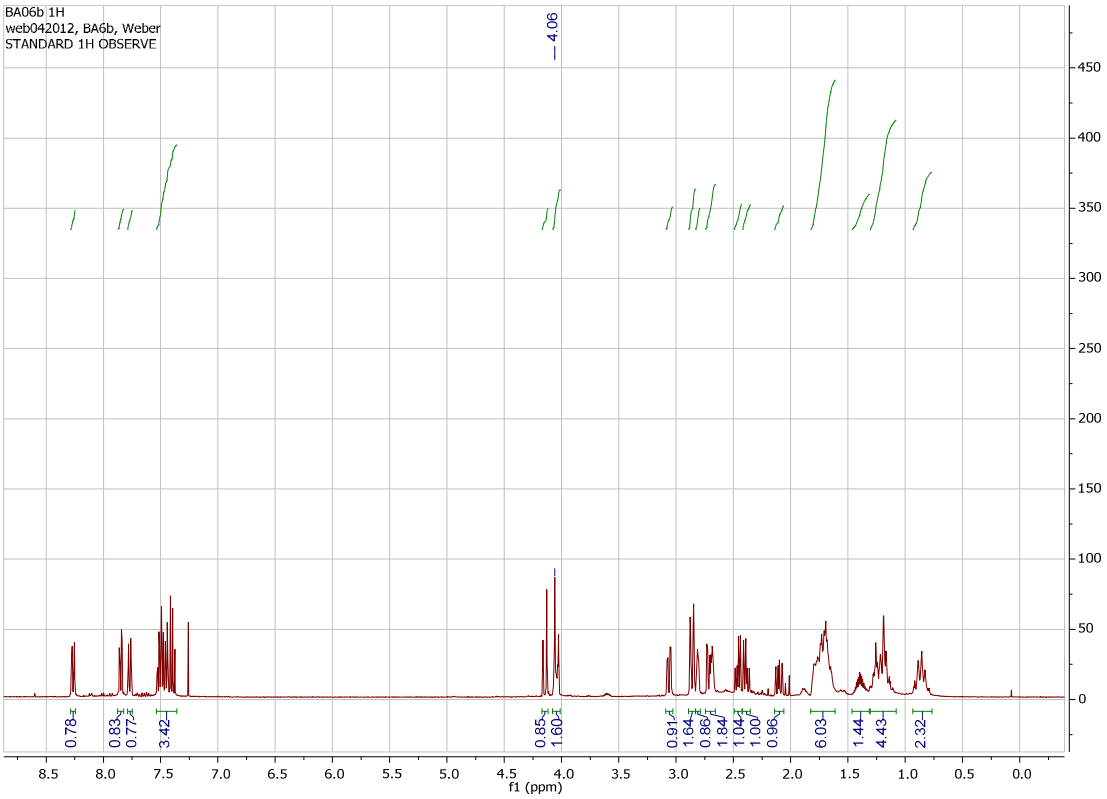

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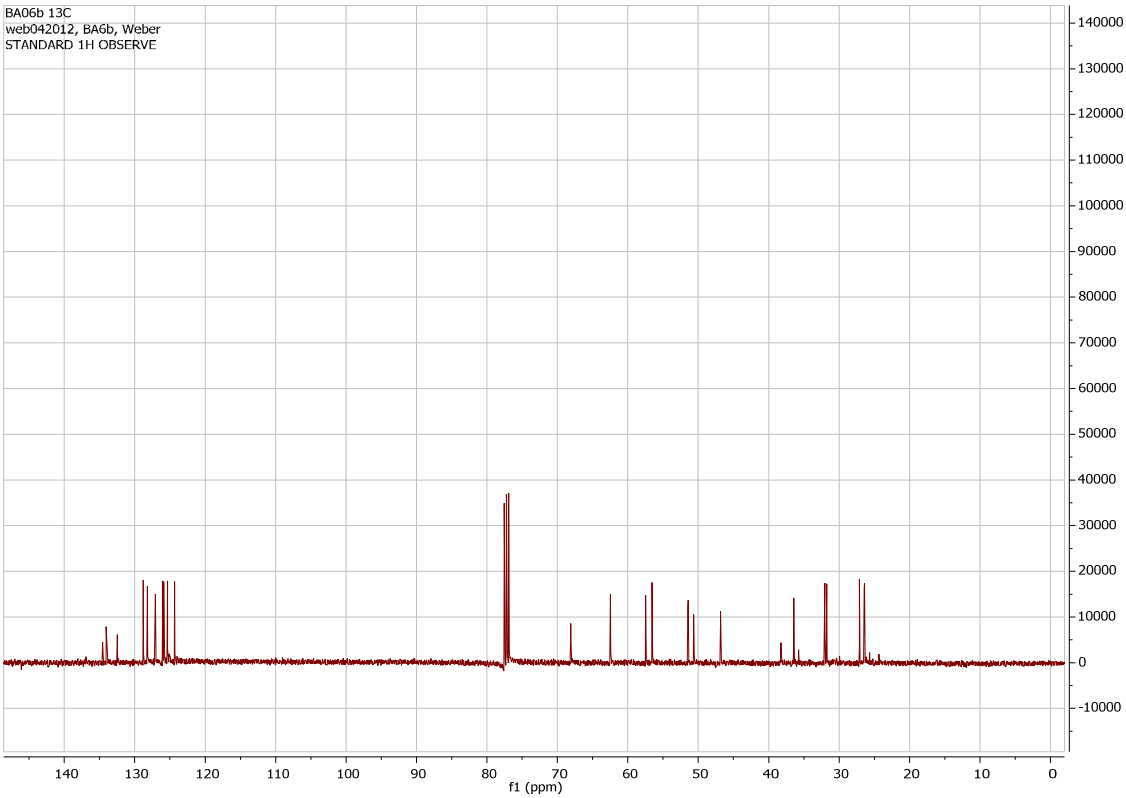

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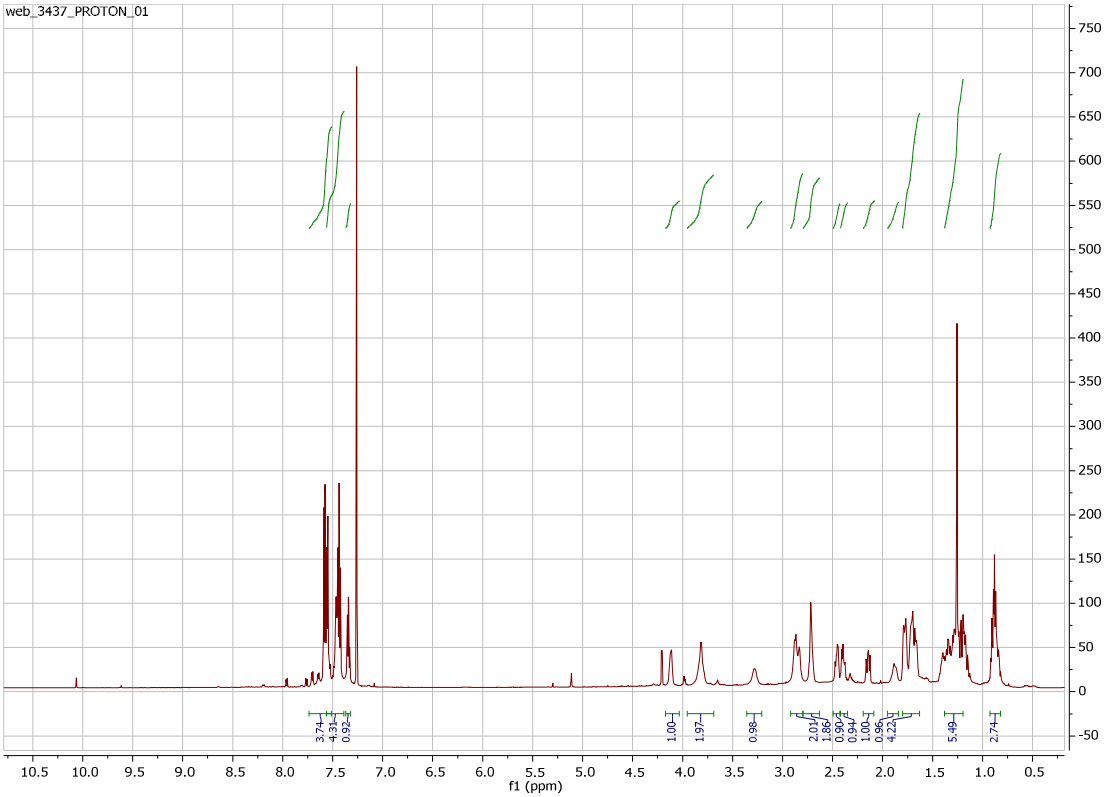

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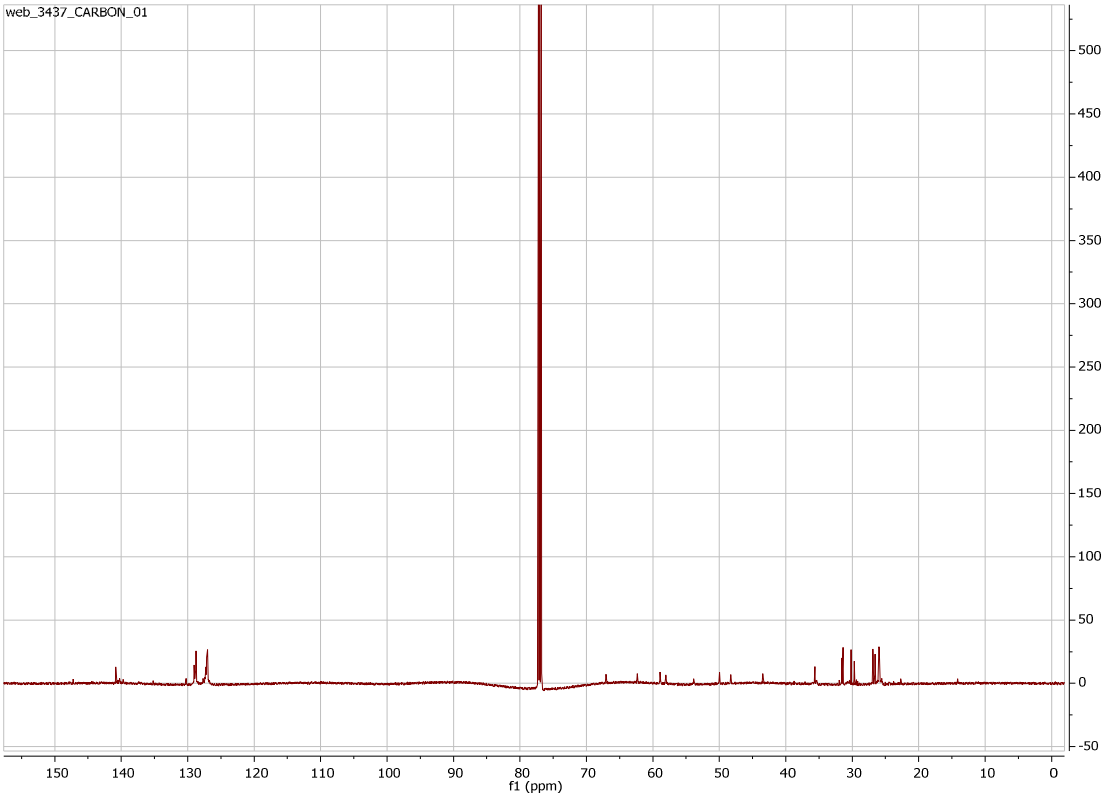

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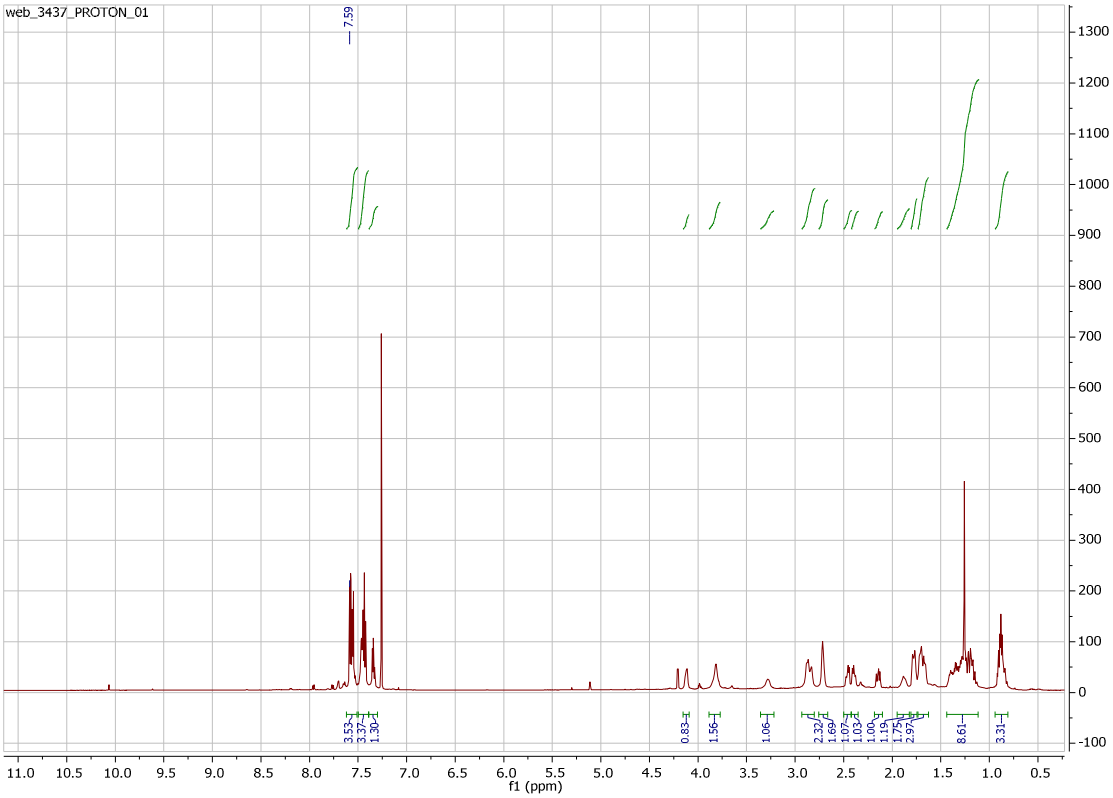

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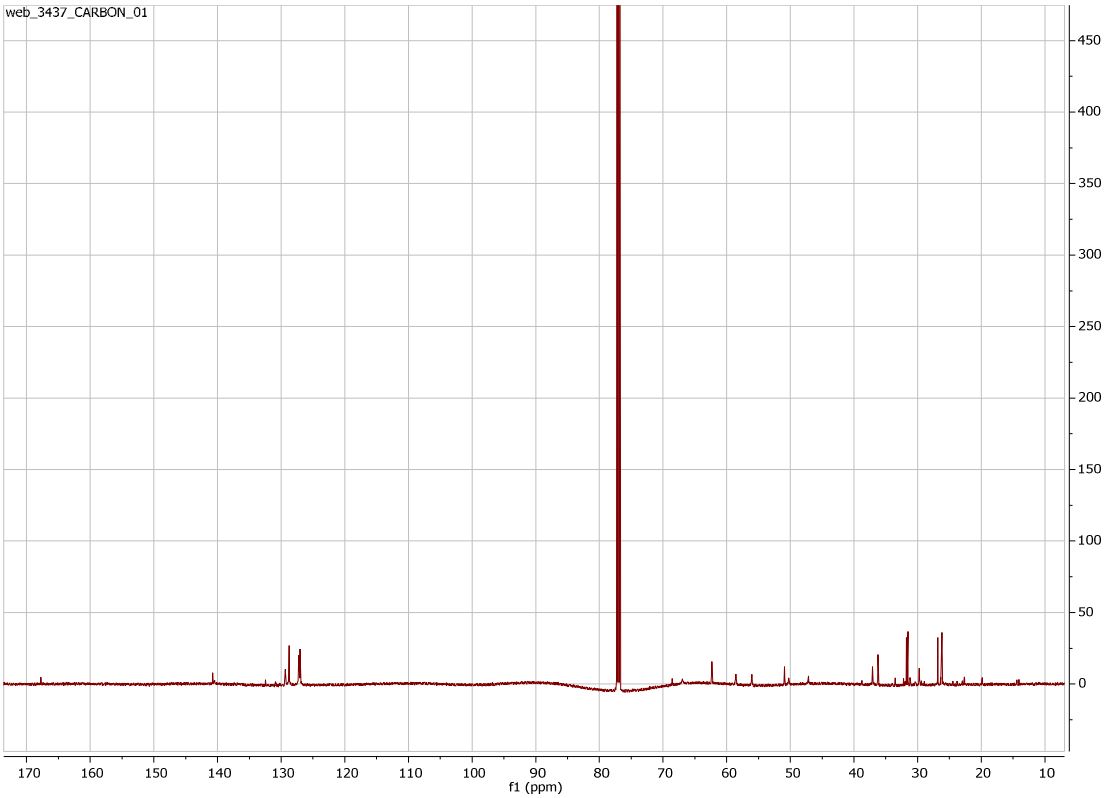

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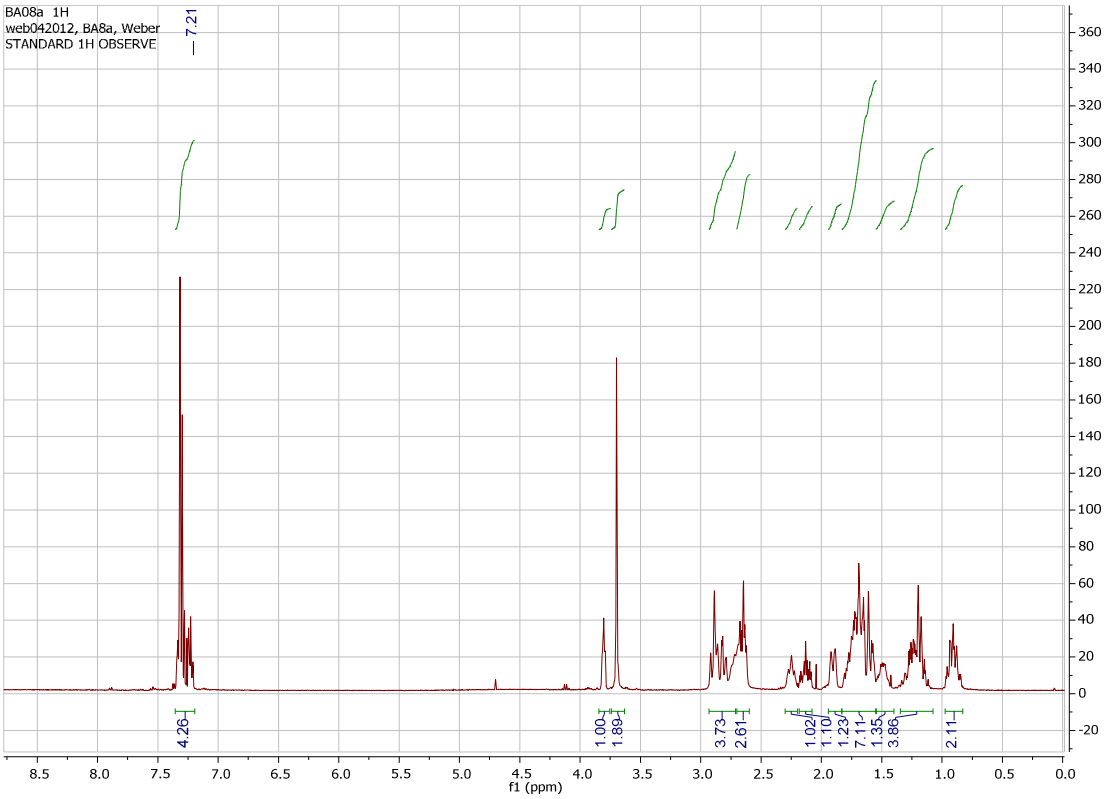

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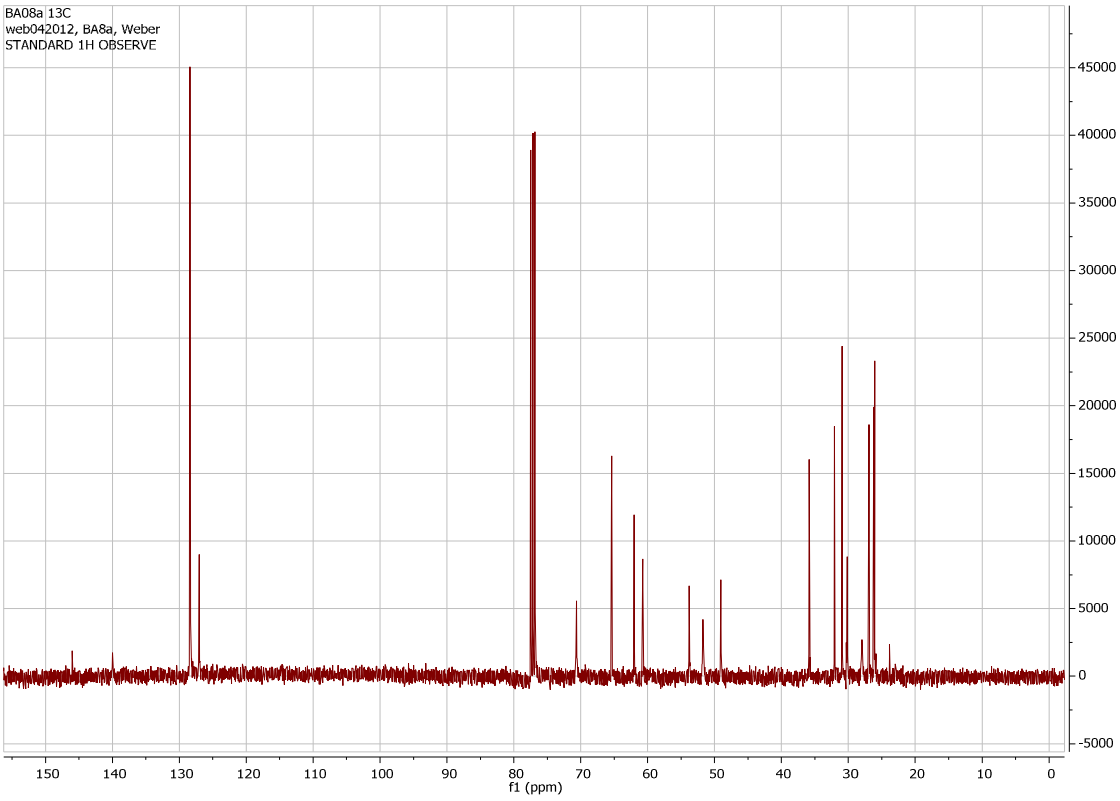

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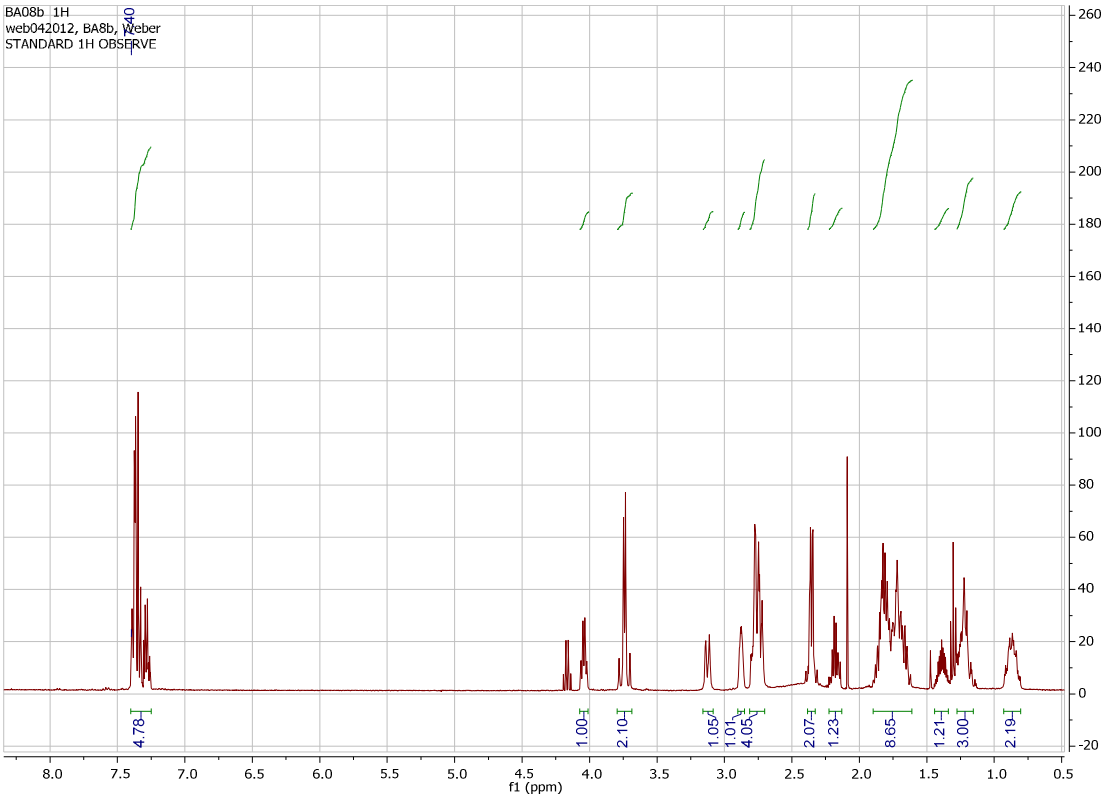

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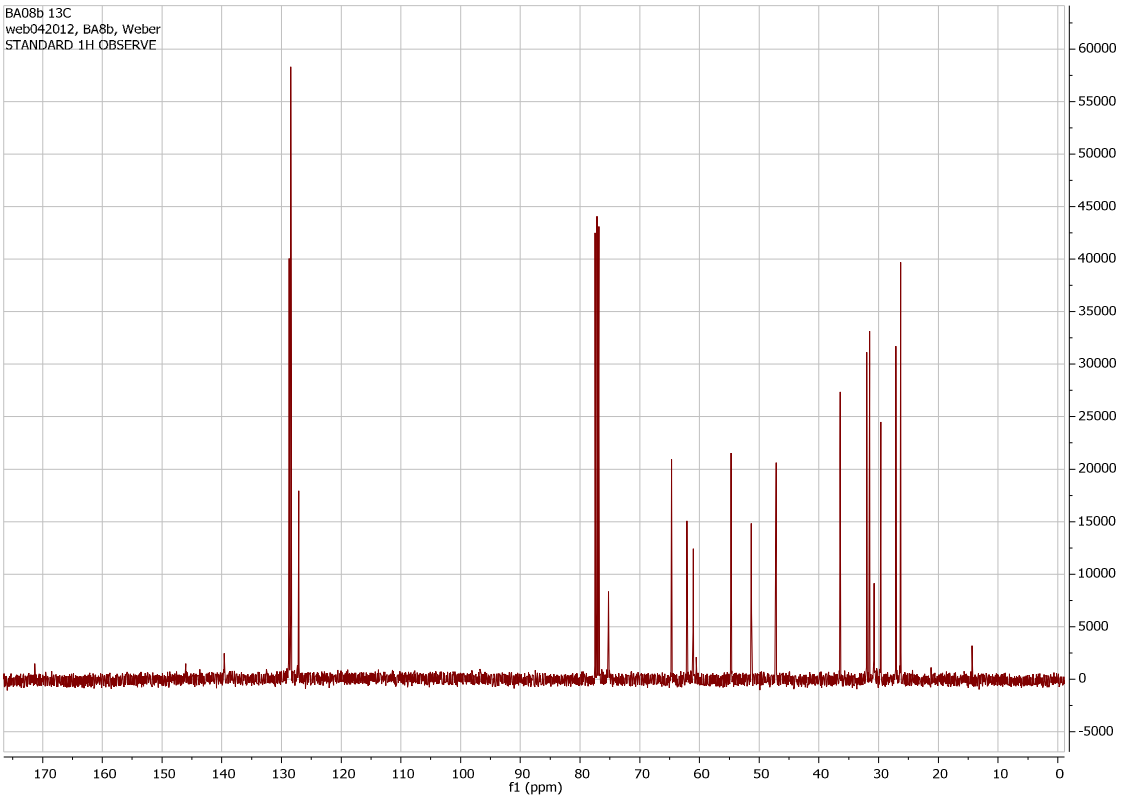

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