# Synthesis and biological evaluation of conformationally restricted $\sigma_1$ receptor ligands with 7,9-diazabicyclo[4.2.2]decane scaffold

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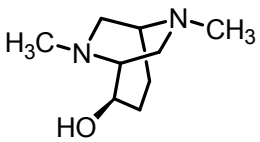
## Conformational analysis

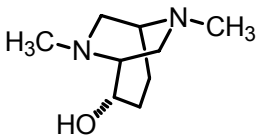
3D-Structures were generated with MOE (Molecular Operating Environment), Version 2009.10, Chemical computing group AG (CCG, Montreal, Canada). Stochastic conformational search was carried out at standard conditions. Method: Stochastic, Rejection Limit: 100, Iteration Limit 10000, RMS Gradient: 0.005, MM Iteration Limit: 500, RMSD Limit: 0.25, Strain cutoff: 7 kcal/mol, Conformation Limit: 10000). Table 6-9 present the relative energies and dihedral angels of all calculated conformers.

Table 6: Relative energies and dihedral angles of the energetically most favored conformations (ΔE < 7 kcal/mol) of the model compound (1*R*,2*R*,5*S*)-**A**.



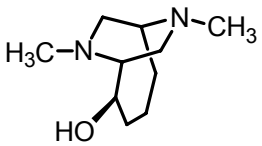

| conformation | ΔE (kcal/mol) | dihedral angle $N^8$-$C^1$-$C^2$-OH |
|---|---|---|
| 1 | 0.00 | 157° |
| 2 | 0.69 | -158° |
| 3 | 3.03 | 166° |
| 4 | 3.04 | -153° |
| 5 | 3.29 | 162° |
| 6 | 3.59 | -156° |
| 7 | 4.74 | 167° |
| 8 | 4.81 | -150° |
| 9 | 5.12 | 170° |
| 10 | 6.28 | 174° |

Table 7: Relative energies and dihedral angles of the energetically most favored conformations (ΔE < 7 kcal/mol) of the model compound (1*R*,2*S*,5*S*)-**B**.



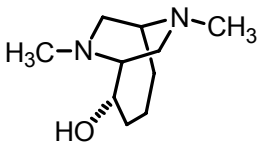

| Conformation | ΔE (kcal/mol) | dihedral angle $N^8$-$C^1$-$C^2$-O |
|---|---|---|
| 1 | 0.00 | -83° |
| 2 | 0.57 | -35° |
| 3 | 2.99 | -74° |
| 4 | 4.29 | -85° |
| 5 | 6.15 | -88° |
| 6 | 6.27 | -54° |
| 7 | 6.94 | -81° |

Table 8: Relative energies and dihedral angles of the energetically most favored conformations (ΔE < 7 kcal/mol) of the model compound (1*R*,2*R*,6*S*)-**C**.




| Conformation | ΔE (kcal/mol) | dihedral angle $N^9$-$C^1$-$C^2$-OH |
|---|---|---|
| 1 | 0.00 | -165° |
| 2 | 2.90 | 164° |
| 3 | 4.01 | 169° |
| 4 | 5.74 | -161° |
| 5 | 6.16 | -163° |

Table 9: Relative energies and dihedral angles of the energetically most favored conformations (ΔE < 7 kcal/mol) of the model compound (1*R*,2*S*,6*S*)-**D**.




| Conformation | ΔE (kcal/mol) | dihedral angle $N^9$-$C^1$-$C^2$-OH |
|---|---|---|
| 1 | 0.00 | -51° |
| 2 | 3.44 | -81° |
| 3 | 5.75 | -47° |
| 4 | 6.01 | -60° |

## Synthetic procedures

### 1. (1RS,2SR,6RS)-7-Benzyl-2-ethoxy-9-(4-methoxybenzyl)-7,9-diazabicyclo[4.2.2] decane-8,10-dione (15c)

Under $N_2$ **15a** (0.12 g, 0.3 mmol) and $CH_3CH_2I$ (0.05 mL, 0.6 mmol) were added to a solution of NaH (0.12 g, 3.4 mmol, 60 % in paraffin oil) in dry THF (15 mL) under ice-cooling. The mixture was warmed to rt and stirred at the same temperature for 3 h. Excess NaH was destroyed with $H_2O$ (3 mL) under ice-cooling. The reaction mixture was washed with 2M NaOH (15 mL). The aqueous layer was extracted with $CH_2Cl_2$ (5 x 20 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$ and the solvent was evaporated in vacuum. The crude solid was purified by fc (cyclohexane/ethyl acetate = 1/1, 2 cm, 13 cm, 10 mL, $R_f$ = 0.22) to obtain colorless crystals, mp 143 – 146 °C, yield 0.07 g (72 %). $C_{25}H_{30}N_2O_4$ (422.2). Purity (HPLC, method B): 98.9 %, $t_R$ = 17.8 min. $^1$H NMR ($CDCl_3$): δ (ppm) = 1.10 (t, *J* = 6.7 Hz, 3H, $OCH_2CH_3$), 1.26-1.37 (m, 1H, 4-H), 1.50-1.67 (m, 3H, 4-H, 3-H), 1.74-1.83 (m, 1H, 5-H), 1.90-1.98 (m, 1H, 5-H), 3.31 (qd, *J* = 8.9/2.1 Hz, 1H, $OCH_2CH_3$), 3.37-3.40 (m, 1H, 2-H), 3.59 (qd, *J* = 8.9/2.1 Hz, 1H, $OCH_2CH_3$), 3.74 (s, 3H, $C_6H_4OCH_3$), 3.98 (dd, *J* = 4.8/3.0 Hz, 1H, 6-H), 4.03 (d, *J* = 14.8 Hz, 1H, $NCH_2C_6H_4OCH_3$), 4.16 (d, *J* = 4.8 Hz, 1H, 1-H), 4.24 (d, *J* = 14.6 Hz, 1H, $NCH_2C_6H_5$), 4.69 (d, *J* = 14.6 Hz, 1H, $NCH_2C_6H_5$), 4.99 (d, *J* = 14.8 Hz, 1H, $NCH_2C_6H_4OCH_3$), 6.80 (d, *J* = 8.5 Hz, 2H, 3-H, 5-$H_{methoxybenzyl}$), 7.12 (d, *J* = 8.5 Hz, 2H, 2-H, 6-$H_{methoxybenzyl}$), 7.16-7.27 (m, 5H, 2-H, 3-H, 4-H, 5-H, 6-$H_{benzyl}$). $^{13}$C NMR ($CDCl_3$): δ (ppm) = 15.5 (1C, $OCH_2CH_3$), 17.8 (1C, C-4), 29.5 (1C, C-3), 32.0 (1C, C-5), 47.6 (1C, $CH_2C_6H_4OCH_3$), 48.4 (1C, $CH_2C_6H_5$), 55.5 (1C, $C_6H_4OCH_3$), 59.6 (1C, C-6), 60.9 (1C, C-1), 65.2 (1C, $OCH_2CH_3$), 79.9 (1C, C-2), 114.6 (2C, C-3, C-5$_{methoxybenzyl}$), 127.9 (1C, C-4$_{benzyl}$), 128.2 (1C, C-1$_{methoxybenzyl}$), 128.5 (2C, C-3, C-5$_{benzyl}$), 129.1 (2C, C-2, C-6$_{benzyl}$), 130.1 (2C, C-2, C-6$_{methoxybenzyl}$), 136.2 (1C, C-1$_{benzyl}$), 159.8 (1C, C-4$_{methoxybenzyl}$), 165.4 (1C, carbonyl), 168.9 (1C, carbonyl). MS (EI): m/z (%) = 421.8 [$(M)^+$, 4], 121.0 [$(methoxybenzyl)^+$, 100], 91.1 [$(benzyl)^+$, 22]. IR (neat): ν ($cm^{-1}$) = 1650 (C=O), 1508 (C=C aromatic), 1240 (C-O).

### 2. (1RS,2SR,6RS)-7-Benzyl-9-(4-methoxybenzyl)-2-propoxy-7,9-diazabicyclo[4.2.2] decane-8,10-dione (15d)

Under $N_2$ **15a** (0.15 g, 0.38 mmol) and $CH_3CH_2CH_2I$ (0.07 mL, 0.76 mmol) were added slowly to a solution of NaH (0.15 g, 3.8 mmol, 60 % in paraffin oil) in dry THF (18 mL) under ice-cooling. The mixture was warmed to rt and stirred at the same temperature for 24 h. The excess NaH was destroyed

with $H_2O$ (3 mL) under ice-cooling. The reaction mixture was washed with 2M NaOH (15 mL). The aqueous layer was extracted with $CH_2Cl_2$ (5 x 20 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$ and the solvent was evaporated in vacuum. The crude solid was purified by fc (cyclohexane/ethyl acetate = 7/3, 2.5 cm, 14 cm, 8 mL, $R_f$ = 0.05) to obtain colorless crystals, mp 118 – 122 °C, yield 0.103 g (62 %). $C_{26}H_{32}N_2O_4$ (436.2). Purity (HPLC, method B): 98.6 %, $t_R$ = 18.66 min. $^1$H NMR ($CDCl_3$): δ (ppm) = 0.87 (t, *J* = 7.4 Hz, 3H, $OCH_2CH_2CH_3$), 1.29-1.38 (m, 1H, 4-H), 1.49-1.57 (m, 2H, $OCH_2CH_2CH_3$), 1.59-1.72 (m, 3H, 4-H, 3-H), 1.72-1.85 (m, 1H, 5-H), 1.95-2.02 (m, 1H, 5-H), 3.24 (td, *J* = 8.9/6.7 Hz, 1H, $OCH_2CH_2CH_3$), 3.39-3.42 (m, 1H, 2-H), 3.52 (td, *J* = 8.9/6.7 Hz, 1H, $OCH_2CH_2CH_3$), 3.79 (s, 3H, $C_6H_4OCH_3$), 4.03 (dd, *J* = 4.8/3.1 Hz, 1H, 6-H), 4.09 (d, *J* =, 14.7 Hz, 1H, $NCH_2C_6H_4OCH_3$), 4.20 (d, *J* = 4.8 Hz, 1H, 1-H), 4.29 (d, *J* =, 14.5 Hz, 1H, $NCH_2C_6H_5$), 4.73 (d, *J* =, 14.5 Hz, 1H, $NCH_2C_6H_5$), 5.01 (d, *J* = 14.7 Hz, 1H, $NCH_2C_6H_4OCH_3$), 6.84 (d, *J* = 8.6 Hz, 2H, 3-H, 5-$H_{methoxybenzyl}$), 7.17 (d, *J* = 8.6Hz, 2H, 2-H, 6-$H_{methoxybenzyl}$), 7.21-7.31 (m, 5H, 2-H, 3-H, 4-H, 5-H, 6-$H_{benzyl}$). $^{13}$C NMR ($CDCl_3$): δ (ppm) = 10.73 (1C, $OCH_2CH_2CH_3$), 17.9 (1C, C-4), 22.8 (1C, $OCH_2CH_2CH_3$), 29.4 (1C, C-3), 32.0 (1C, C-5), 47.7 (1C, $CH_2C_6H_4OCH_3$), 48.4 (1C, $CH_2C_6H_5$), 55.5 (1C, $C_6H_4OCH_3$), 59.6 (1C, C-6), 61.0 (1C, C-1), 71.6 (1C, $OCH_2CH_2CH_3$), 79.8 (1C, C-2), 114.6 (2C, C-3, C-5$_{methoxybenzyl}$), 127.9 (1C, C-4$_{benzyl}$), 128.1 (1C, C-1$_{methoxybenzyl}$), 128.5 (2C, C-3, C-5$_{benzyl}$), 129.0 (2C, C-2, C-6$_{benzyl}$), 130.1 (2C, C-2, C-6$_{methoxybenzyl}$), 136.2 (1C, C-1$_{benzyl}$), 159.8 (1C, C-4$_{methoxybenzyl}$), 165.4 (1C, carbonyl), 168.8 (1C, carbonyl). Exact mass (ESI): *m/z* = calculated for $C_{26}H_{32}N_2O_4Na^+$ 459.2260, found 459.2254. IR (neat): ν ($cm^{-1}$) = 1651 (C=O), 1515 (C=C aromatic), 1239 (C-O).

### 3. (1RS,2SR,6RS)-7-Benzyl-2-butyloxy-9-(4-methoxybenzyl)-7,9-diazabicyclo[4.2.2] decane-8,10-dione (15e)

Under $N_2$ **15a** (0.1 g, 0.25 mmol), $CH_3CH_2CH_2CH_2Br$ (0.28 mL, 2.5 mmol) and n-$Bu_4N^+I^-$ (0.9 g, 2.5 mmol) were slowly added to a solution of NaH (0.05 g, 1.27 mmol, 60 % in paraffin oil) in dry THF (10 mL) one after the other under ice-cooling. The mixture was warmed to rt and stirred at the same temperature for 12.5 h. The reaction mixture was cooled to 0 °C and excess NaH was destroyed with $H_2O$ (3 mL). The reaction mixture was washed with 2M NaOH (5 mL). The aqueous layer was extracted with $CH_2Cl_2$ (6 x 10 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$ and the solvent was evaporated in vacuum. The crude solid was purified by fc (cyclohexane/ethyl acetate = 7/3, 3.5 cm, 16 cm, 30 mL, $R_f$ = 0.075) to obtain colorless crystals, mp 117 – 120 °C, yield 0.085 g (75 %). $C_{27}H_{34}N_2O_4$ (450.2). Purity (HPLC, method B): 97.8 %, $t_R$ = 19.5

min. $^1$H NMR ($CDCl_3$): δ (ppm) = 0.83 (t, *J* = 7.3 Hz, 3H, $OCH_2CH_2CH_2CH_3$), 1.23-1.35 (m, 3H, 5-H, $OCH_2CH_2CH_2CH_3$), 1.41-1.48 (m, 2H, $OCH_2CH_2CH_2CH_3$), 1.57-1.66 (m, 3H, 4-H, 5-H), 1.73-1.80 (m, 1H, 3-H), 1.90-1.97 (m, 1H, 3-H), 3.23 (td, *J* = 9.0/6.6 Hz, 1H, $OCH_2CH_2CH_2CH_3$), 3.35 (td, *J* = 6.6/4.2 Hz, 1H, 2-H), 3.51 (td, *J* = 9.0/6.5 Hz, 1H, $OCH_2CH_2CH_2CH_3$), 3.74 (s, 3H, $C_6H_4OCH_3$), 3.98 (dd, *J* = 4.8/3.1 Hz, 1H, 6-H), 4.11 (d, *J* = 14.7 Hz, 1H, $NCH_2C_6H_4OCH_3$), 4.14 (d, *J* = 4.8 Hz, 1H, 1-H), 4.31 (d, *J* =, 14.5 Hz, 1H, $NCH_2C_6H_5$), 4.75 (d, *J* =, 14.5 Hz, 1H, $NCH_2C_6H_5$), 5.03 (d, *J* = 14.7 Hz, 1H, $NCH_2C_6H_4OCH_3$), 6.80 (d, *J* = 8.6 Hz, 2H, 3-H, 5-$H_{methoxybenzyl}$), 7.12 (d, *J* = 8.6 Hz, 2H, 2-H, 6-$H_{methoxybenzyl}$), 7.16-7.18 (m, 3H, 2-H, 4-H, 6-$H_{benzyl}$), 7.21-7.25 (m, 2H, 3-H, 5-$H_{benzyl}$). $^{13}$C NMR ($CDCl_3$): δ (ppm) = 12.8 (1C, $OCH_2CH_2CH_2CH_3$), 16.6 (1C, C-5), 18.2 (1C, $OCH_2CH_2CH_2CH_3$), 28.2 (1C, C-4), 30.7 (2C, C-3, $OCH_2CH_2CH_2CH_3$), 46.4 (1C, $CH_2C_6H_4OCH_3$), 47.2 (1C, $CH_2C_6H_5$), 54.3 (1C, $C_6H_4OCH_3$), 58.4 (1C, C-6), 59.8 (1C, C-1), 68.5 (1C, $OCH_2CH_2CH_2CH_3$), 78.6 (1C, C-2), 113.3 (2C, C-3, C-$5_{methoxybenzyl}$), 126.6 (1C, C-$4_{benzyl}$), 126.9 (1C, C-$1_{methoxybenzyl}$), 127.3 (2C, C-3, C-$5_{benzyl}$), 127.8 (2C, C-2, C-$6_{benzyl}$), 128.8 (2C, 2C, C-2, C-$6_{methoxybenzyl}$), 135.0 (1C, C-$1_{benzyl}$), 158.5 (1C, C-$4_{methoxybenzyl}$), 164.1 (1C, carbonyl), 167.6 (1C, carbonyl). Exact mass (ESI): *m/z* = calculated for $C_{27}H_{34}N_2O_4Na^+$ 473.2416, found 473.2411. IR (neat): ν ($cm^{-1}$) = 1655 (C=O), 1512 (C=C aromatic), 1247 (C-O).

## 4. (1RS,2SR,6RS)-7-Benzyl-2-isopentyloxy-9-(4-methoxybenzyl)-7,9-diazabicyclo[4.2.2]decane-8,10-dione (15f)

Under $N_2$ **15a** (0.12 g, 0.3 mmol), $(CH_3)_2CHCH_2CH_2Br$ (0.1 mL, 0.76 mmol) and n-$Bu_4N^+I^-$ (0.28 g, 0.76 mmol) were slowly added to a solution of NaH (0.12 g, 3.0 mmol, 60 % in paraffin oil) in dry THF (15 mL) one after the other under ice-cooling. The mixture was warmed to rt and stirred under reflux for 24 h. The reaction mixture was cooled to 0 °C and excess NaH was destroyed with $H_2O$ (3 mL). The reaction mixture was washed with 2M NaOH (15 mL). The aqueous layer was extracted with $CH_2Cl_2$ (5 x 20 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$ and the solvent was evaporated in vacuum. The crude solid was purified by fc (cyclohexane/ethyl acetate = 85/15, 2 cm, 13 cm, 7 mL, $R_f$ = 0.02) to obtain colorless crystals, mp 96 – 99 °C, yield 0.094 g (67 %). $C_{28}H_{36}N_2O_4$ (464.2). Purity (HPLC, method B): 95.6 %, $t_R$ = 20.2 min. $^1$H NMR ($CDCl_3$): δ (ppm) = 0.81 (dd, *J* = 6.6/5.1 Hz, 7H, $OCH_2CH_2CH(CH_3)_2$), 1.36 (dt, *J* = 6.9/6.8 Hz, 2H, $OCH_2CH_2CH(CH_3)_2$), 1.53-1.66 (m, 5H, 3-H, 4-H, $OCH_2CH_2CH(CH_3)_2$), 1.72-1.80 (m, 1H, 5-H), 1.90-1.97 (m, 1H, 5-H), 3.25 (td, *J* = 9.1/6.9 Hz, 1H, $OCH_2CH_2CH(CH_3)_2$), 3.33-3.36 (m, 1H, 2-H), 3.52 (td, *J* = 9.1/6.9 Hz, 1H, $OCH_2CH_2CH(CH_3)_2$), 3.74 (s, 3H, $C_6H_4OCH_3$), 3.98 (dd, *J* = 4.8/3.1 Hz,

1H, 6-H), 4.04 (d, *J* = 14.7 Hz, 1H, NC*H*$_2$C$_6$H$_4$OCH$_3$), 4.14 (d, *J* = 4.8 Hz, 1-H), 4.25(d, *J* = 14.5 Hz, 1H, NC*H*$_2$C$_6$H$_5$), 4.68 (d, *J* = 14.5 Hz, 1H, NC*H*$_2$C$_6$H$_5$), 4.96 (d, *J* = 14.7 Hz, 1H, NC*H*$_2$C$_6$H$_4$OCH$_3$), 6.80 (d, *J* = 8.7 Hz, 2H, 3-H, 5-H$_{methoxybenzyl}$), 7.12 (d, *J* = 8.7 Hz, 2H, 2-H, 6-H$_{methoxybenzyl}$), 7.15-7.18 (m, 2H, 2-H, 6-H$_{benzyl}$), 7.20-7.27 (m, 3H, 3-H, 4-H, 5-H$_{benzyl}$). $^{13}$C NMR (CDCl$_3$): δ (ppm) = 16.9 (1C, C-4), 21.5 (1C, OCH$_2$CH$_2$CH(*C*H$_3$)CH$_3$), 21.6 (1C, OCH$_2$CH$_2$CH(*C*H$_3$)CH$_3$), 23.9 (1C, OCH$_2$CH$_2$*C*H(CH$_3$)$_2$, 28.2 (1C, C-3), 30.7 (1C, C-5), 37.4 (1C, OCH$_2$*C*H$_2$CH(CH$_3$)$_2$), 46.4 (1C, *C*H$_2$C$_6$H$_4$OCH$_3$), 47.2 (1C, *C*H$_2$C$_6$H$_5$), 54.3 (1C, C$_6$H$_4$O*C*H$_3$), 58.4 (1C, C-6), 59.8 (1C, C-1), 67.2 (1C, O*C*H$_2$CH$_2$CH(CH$_3$)$_2$), 78.7 (1C, C-2), 113.3 (2C, C-3, C-5$_{methoxybenzyl}$), 126.6 (1C, C-4$_{benzyl}$), 126.9 (1C, C-1$_{methoxybenzyl}$), 127.3 (2C, C-3, C-5$_{benzyl}$), 127.8 (2C, C-2, C-6$_{benzyl}$), 128.8 (2C, C-2, C-6$_{methoxybenzyl}$), 135.0 (1C, C-1$_{benzyl}$), 158.5 (1C, C-4$_{methoxybenzyl}$), 164.1 (1C, carbonyl), 167.6 (1C, carbonyl). Exact mass (ESI): *m/z* = calculated for C$_{28}$H$_{36}$N$_2$O$_4$Na$^+$ 487.2573$^+$, found 487.2567. IR (neat): ν (cm$^{-1}$) = 1650 (C=O), 1511 (C=C aromatic), 1242 (C-O).

**5. (1RS,2SR,6RS)-7-Benzyl-2-benzyloxy-9-(4-methoxybenzyl)-7,9-diazabicyclo[4.2.2]decane-8,10-dione (15g)**

Under N$_2$ **15a** (0.20 g, 0.5 mmol) and C$_6$H$_5$CH$_2$Br (0.1 mL, 0.76 mmol) were added to a solution of NaH (0.2 g, 5.0 mmol, 60 % in paraffin oil) in dry THF (21 mL) slowly one after the other under ice-cooling. The mixture was then warmed to rt and stirred at the same temperature for 1.5 h. The excess NaH was destroyed with H$_2$O (3 mL) under ice-cooling. The reaction mixture was washed with 2M NaOH (15 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (5 x 20 mL). The combined organic layers were washed with brine, dried over Na$_2$SO$_4$ and the solvent was evaporated in vacuum. The crude solid was purified by fc (cyclohexane/ethyl acetate = 1/1, 2.5 cm, 13 cm, 10 mL, R$_f$ = 0.32) to obtain colorless crystals, mp 135 – 139 °C, yield 0.23 g (94 %). C$_{30}$H$_{32}$N$_2$O$_4$ (484.2). Purity (HPLC, method B): 96.6 %, t$_R$ = 18.7 min. $^1$H NMR (CDCl$_3$): δ (ppm) = 1.25-1.34 (m, 1H, 4-H), 1.44-1.51 (m, 1H, 3-H), 1.59-1.71 (m, 2H, 3-H, 4-H), 1.77-1.84 (m, 1H, 5-H), 1.88-1.96 (m, 1H, 5-H), 3.47 (ddd, *J* = 6.0/5.9/3.4 Hz, 1H, 2-H), 3.73 (s, 3H, C$_6$H$_4$OC*H*$_3$), 3.98 (dd, *J* = 5.2/2.7 Hz, 1H, 6-H), 4.12 (d, *J* =14.5 Hz, 1H, NC*H*$_2$C$_6$H$_5$), 4.14 (d, *J* =14.7 Hz, 1H, NC*H*$_2$C$_6$H$_4$OCH$_3$), 4.17 (d, *J* = 4.2 Hz, 1-H), 4.53 (d, *J* = 12.4 Hz, 1H, OC*H*$_2$C$_6$H$_5$), 4.66 (d, *J* = 12.4 Hz, 1H, OC*H*$_2$C$_6$H$_5$), 4.67 (d, *J* =14.5 Hz, 1H, NC*H*$_2$C$_6$H$_5$), 5.05 (d, *J* =14.7 Hz, 1H, NC*H*$_2$C$_6$H$_4$OCH$_3$), 6.73 (d, *J* = 8.7 Hz, 2H, 3-H, 5-H$_{methoxybenzyl}$), 6.98 (d, *J* = 8.7 Hz, 2H, 2-H, 6-H$_{methoxybenzyl}$), 7.17-7.30 (m, 10H, 2-H, 3-H, 4-H, 5-H, 6-H$_{O\text{-}benzyl,\ N\text{-}benzyl}$). $^{13}$C NMR (CDCl$_3$): δ (ppm) = 17.6 (1C, C-4), 29.1 (1C, C-3), 32.3 (1C, C-5), 47.7 (1C, N*C*H$_2$C$_6$H$_4$OCH$_3$), 48.3 (1C, N*C*H$_2$C$_6$H$_5$), 55.5 (1C, C$_6$H$_4$O*C*H$_3$), 59.6 (1C, C-6), 60.8 (1C, C-1),

71.2 (1C, O*C*H$_2$C$_6$H$_5$), 77.8 (1C, C-2), 114.5 (2C, C-3, C-5$_{methoxybenzyl}$), 127.6 (1C, C-4$_{N\text{-}benzyl}$), 128.0 (2C, C-4$_{O\text{-}benzyl}$, C-1$_{methoxybenzyl}$), 128.2 (2C, C-2, C-6$_{O\text{-}benzyl}$), 128.5 (2C, C-2, C-6$_{N\text{-}benzyl}$), 128.7 (2C, C-3, C-5$_{N\text{-}benzyl}$), 129.0 (2C, C-3, C-5$_{O\text{-}benzyl}$), 130.0 (1C, C-2, C-6$_{methoxybenzyl}$), 136.2 (1C, C-1$_{N\text{-}benzyl}$), 138.0 (1C, C-1$_{O\text{-}benzyl}$), 159.6 (1C, C-4$_{methoxybenzyl}$), 165.5 (1C, carbonyl), 168.9 (1C, carbonyl). Exact mass (ESI): *m/z* = calculated for $C_{30}H_{32}N_2O_4Na^+$ 507.2259, found 507.2254. IR (neat): ν (cm$^{-1}$) = 1650 (C=O), 1514 (C=C aromatic), 1247 (C-O).

**6. (1RS,2RS,6SR)-7-Benzyl-2-ethoxy-9-(4-methoxybenzyl)-7,9-diazabicyclo[4.2.2] decane (16c)**

Under $N_2$ $LiAlH_4$ (0.012 g, 0.48 mmol) was added slowly to a solution of **15c** (60 mg, 0.15 mmol) in dry THF (14 mL) under ice-cooling. The mixture was warmed to rt and stirred under reflux for 17 h. Excess $LiAlH_4$ was destroyed with $H_2O$ (1 mL) under ice-cooling. The mixture was again stirred under reflux for 1 h. The solution was cooled to rt and filtered through a sintering funnel. The precipitate was washed with $CH_2Cl_2$ (50 mL). The solvent was evaporated in vacuum. The crude oil was purified by fc (ethyl acetate/petroleum ether = 1/9, 1.5 cm, 13 cm, 10 mL, $R_f$ = 0.5 (ethyl acetate/cyclohexane = 1/4)). Colorless oil, yield 20 mg (32 %). $C_{25}H_{34}N_2O_2$ (394.2). Purity (HPLC, method B): 97.2 %, $t_R$ = 17.5 min. $^1$H NMR ($CDCl_3$): δ (ppm) = 0.90 (t, *J* = 7.0 Hz, 3H, OCH$_2$C*H$_3$*), 1.22-1.28 (m, 1H, 5-H), 1.34-1.43 (m, 1H, 5-H), 1.55-1.63 (m, 1H, 4-H), 1.82-1.89 (m, 1H, 3-H), 2.07-2.20 (m, 1H, 4-H), 2.34 (q, *J* = 11.1 Hz, 1H, 3-H), 2.55 (dd, *J* = 10.9/1.7 Hz, 1H, 10-H), 2.76-2.79 (m, 3H, 1-H, 6-H, 8-H), 2.94-2.99 (m, 3H, 2-H, 8-H, 10-H), 3.02-3.14 (m, 2H, OC*H$_2$*CH$_3$), 3.43 (d, *J* = 12.3 Hz, 2H, C*H$_2$*C$_6$H$_5$, C*H$_2$*C$_6$H$_4$OCH$_3$), 3.52 (d, *J* = 12.5 Hz, 1H, C*H$_2$*C$_6$H$_5$), 3.61 (d, *J* = 13.1 Hz, 1H, C*H$_2$*C$_6$H$_4$OCH$_3$), 3.72 (s, 3H, C$_6$H$_4$OC*H$_3$*), 6.77 (d, *J* = 8.7 Hz, 2H, 3-H, 5-H$_{methoxybenzyl}$), 7.11-7.22 (m, 5H, 2-H, 6-H$_{methoxybenzyl}$, 2-H, 4-H, 6-H$_{benzyl}$), 7.27-7.30 (m, 2H, 3-H, 5-H$_{benzyl}$). Exact mass (ESI): *m/z* = calculated for $C_{25}H_{34}N_2O_2H^+$ 395.2699, found 395.2693. IR (neat): ν (cm$^{-1}$) = 1512 (C=C aromatic), 1241 (C-O), 1094 (C-O).

**7. (1RS,2RS,6SR)-7-Benzyl-9-(4-methoxybenzyl)-2-propoxy-7,9-diazabicyclo[4.2.2]decane (16d)**

Under $N_2$ $LiAlH_4$ (0.03 g, 0.8 mmol) was added slowly to a solution of **15d** (0.09 g, 0.2 mmol) in dry THF (10 mL) under ice-cooling. The mixture was warmed to rt and then stirred under reflux for 18 h. Excess $LiAlH_4$ was destroyed with $H_2O$ (1mL) under ice-cooling. The mixture was again stirred under reflux for 1 h. The solution was cooled to rt and filtered through a sintering funnel. The precipitate was washed with $CH_2Cl_2$ (50 mL). The solvent was evaporated in vacuum. The crude oil was purified by fc

(petroleum ether/ethyl acetate = 95/5, 1.5 cm, 13 cm, 7 mL, $R_f$ = 0.53 (ethyl acetate/cyclohexane = 1/4)). Colorless oil, yield 0.054 g (65 %). $C_{26}H_{36}N_2O_2$ (408.3). Purity (HPLC, method A): 96.2 %, $t_R$ = 21.9 min. $^1$H NMR ($CDCl_3$): δ (ppm) = 0.67 (t, *J* = 7.4 Hz, 3H, $OCH_2CH_2CH_3$), 1.18-1.29 (m, 3H, 5-H, $OCH_2CH_2CH_3$), 1.35-1.44 (m, 1H, 5-H), 1.54-1.62 (m, 1H, 4-H), 1.81-1.89 (m, 1H, 3-H), 2.12 (qd, *J* = 13.4/4.9 Hz, 1H, 4-H), 2.33 (q, *J* = 11.0 Hz, 1H, 3-H), 2.56 (dd, *J* = 10.9/1.8 Hz, 1H, 10-H), 2.75-2.80 (m, 3H, 1-H, 6-H, 8-H), 2.90-3.00 (m, 5H, 2-H, 8-H, 10-H, $OCH_2CH_2CH_3$), 3.42 (d, *J* = 12.5 Hz, 1H, $CH_2C_6H_5$), 3.44 (d, *J* = 13.1 Hz, 2H, $CH_2C_6H_4OCH_3$), 3.53 (d, *J* = 12.5 Hz, 1H, $CH_2C_6H_5$), 3.61 (d, *J* = 13.1 Hz, 2H, $CH_2C_6H_4OCH_3$), 3.72 (s, 3H, $C_6H_4OCH_3$), 6.77 (d, *J* = 8.7 Hz, 2H, 3-H, 5-$H_{methoxybenzyl}$), 7.12-7.22 (m, 5H, 2-H, 6-$H_{methoxybenzyl}$, 2-H, 4-H, 6-$H_{benzyl}$), 7.27-7.30 (m, 2H, 3-H, 5-$H_{benzyl}$). $^{13}$C NMR ($CDCl_3$): δ (ppm) = 10.6 (1C, $OCH_2CH_2CH_3$), 22.2 (1C, C-4), 23.3 (1C, $OCH_2CH_2CH_3$), 30.7 (1C, C-3), 36.3 (1C, C-5), 45.5 (1C, C-8), 50.8 (1C, C-10), 55.5 (1C, $C_6H_4OCH_3$), 57.4 (1C, C-6), 59.9 (1C, C-1), 62.8 (1C, $CH_2C_6H_5$), 63.1 (1C, $CH_2C_6H_4OCH_3$), 70.7 (1C, $OCH_2CH_2CH_3$), 82.0 (1C, C-2), 113.6 (2C, C-3, C-$5_{methoxybenzyl}$), 126.9 (1C, C-$4_{benzyl}$), 128.2 (1C, C-$1_{methoxybenzyl}$), 129.3 (2C, C-3, C-$5_{benzyl}$), 130.7 (2C, C-2, C-$6_{benzyl}$), 131.8 (2C, C-2, C-$6_{methoxybenzyl}$), 140.1 (1C, C-$1_{benzyl}$), 158.8 (1C, C-$4_{methoxybenzyl}$). Exact mass (ESI): *m/z* = calculated for $C_{26}H_{36}N_2O_2H^+$ 409.2855, found 409.2850. IR (neat): ν ($cm^{-1}$) = 1508 (C=C aromatic), 1239 (C-O), 1092 (C-O).

**8. (1RS,2RS,6SR)-7-Benzyl-2-butyloxy-9-(4-methoxybenzyl)-7,9-diazabicyclo[4.2.2]decane (16e)**

Under $N_2$ $LiAlH_4$ (1.0 M in THF, 0.75 mL, 0.75 mmol) was added slowly to a solution of **15e** (0.085 g, 0.19 mmol) in dry THF (5 mL) under ice-cooling. The mixture was warmed to rt and then stirred under reflux for 14 h. Excess $LiAlH_4$ was destroyed with $H_2O$ (1mL) under ice-cooling. The mixture was again stirred under reflux for 1 h. The solution was cooled to rt and filtered through a sintering funnel. The precipitate was washed with $CH_2Cl_2$ (50 mL). The solvent was evaporated in vacuum. The crude oil was purified by fc (petroleum ether/ethyl acetate = 97/3, 1.5 cm, 22 cm, 5 mL, $R_f$ = 0.36 (ethyl acetate/cyclohexane = 1/9)). Colorless oil, yield 0.018 g (23 %). $C_{28}H_{42}N_2O_2$ (423.3). Purity (HPLC, method B): 98 %, $t_R$ = 18.5 min. $^1$H NMR ($CDCl_3$): δ (ppm) = 0.75 (t, *J* = 7.3 Hz, 3H, $OCH_2CH_2CH_2CH_3$), 1.11 (qd, *J* = 7.3/2.9 Hz, 2H, $OCH_2CH_2CH_2CH_3$), 1.18-1.24 (m, 2H, $OCH_2CH_2CH_2CH_3$), 1.26 (s(b), 1H, 5-H), 1.36-1.43 (m, 1H, 5-H), 1.57-1.63 (m, 1H, 4-H), 1.81-1.89 (m, 1H, 3-H), 2.07-2.18 (m, 1H, 4-H), 2.32 (q, *J* = 11.1 Hz, 1H, 3-H), 2.56 (d (b), *J* = 10.2 Hz, 1H, 10-H), 2.75-2.80 (m, 3H, 1-H, 6-H, 8-H), 2.90-3.04 (m, 5H, 2-H, 8-H, 10-H, $OCH_2CH_2CH_2CH_3$), 3.40-3.46 (m, 2H, $CH_2C_6H_5$, $CH_2C_6H_4OCH_3$), 3.53 (d, *J* = 12.2 Hz, 1H, $CH_2C_6H_5$), 3.61 (d, *J* = 13.1 Hz, 1H, $CH_2C_6H_4OCH_3$), 3.72 (s, 3H, $C_6H_4OCH_3$), 6.77 (d, *J* = 8.6 Hz, 2H, 3-H, 5-$H_{methoxybenzyl}$), 7.12-7.22

(m, 5H, 2-H, 6-$H_{methoxybenzyl}$, 2-H, 4-H, 6-$H_{benzyl}$), 7.29 (d, *J* = 7.3 Hz, 2H, 3-H, 5-$H_{benzyl}$). $^{13}$C NMR ($CDCl_3$): δ (ppm) = 14.1 (1C, $OCH_2CH_2CH_2\mathit{C}H_3$), 19.4 (1C, $OCH_2CH_2\mathit{C}H_2CH_3$), 22.2 (1C, C-4), 30.7 (1C, C-3), 32.3 (1C, $OCH_2\mathit{C}H_2CH_2CH_3$), 36.4 (1C, C-5), 45.5 (1C, C-8), 50.9 (1C, C-10), 55.5 (1C, $C_6H_4O\mathit{C}H_3$), 57.5 (1C, C-6), 59.9 (1C, C-1), 62.8 (1C, $\mathit{C}H_2C_6H_5$), 63.2 (1C, $\mathit{C}H_2C_6H_4OCH_3$), 68.8 (1C, $O\mathit{C}H_2CH_2CH_2CH_3$), 82.0 (1C, C-2), 113.6 (2C, C-3, C-$5_{methoxybenzyl}$), 126.9 (1C, C-$4_{benzyl}$), 128.2 (1C, C-$1_{methoxybenzyl}$), 129.3 (2C, C-3, C-$5_{benzyl}$), 130.7 (2C, C-2, C-$6_{benzyl}$), 131.8 (2C, C-2, C-$6_{methoxybenzyl}$), 140.1 (1C, C-$1_{benzyl}$), 158.8 (1C, C-$4_{methoxybenzyl}$). Exact mass (ESI): *m/z* = calculated for $C_{28}H_{42}N_2O_2H^+$ 423.3012, found 423.3017. IR (neat): ν ($cm^{-1}$) = 1506 (C=C aromatic), 1242 (C-O), 1089 (C-O).

## 9. (1RS,2RS,6SR)-7-Benzyl-2-isopentyloxy-9-(4-methoxybenzyl)-7,9-diazabicyclo[4.2.2]decane (16f)

Under $N_2$ $LiAlH_4$ (1.0 M in THF, 1.0 mL, 1 mmol) was added slowly to a solution of **15f** (0.09 g, 0.2 mmol) in dry THF (5 mL) under ice-cooling. The mixture was warmed to rt and then stirred under reflux for 12 h. Excess $LiAlH_4$ was destroyed with $H_2O$ (1mL) under ice-cooling. The mixture was again stirred under reflux for 1 h. The solution was cooled to rt and filtered through a sintering funnel. The precipitate was washed with $CH_2Cl_2$ (50 mL). The solvent was evaporated in vacuum. The crude oil was purified by fc (petroleum ether/ethyl acetate = 97/3, 1.5 cm, 22 cm, 5 mL, $R_f$ = 0.39 (ethyl acetate/cyclohexane = 1/9)). Colorless oil, yield 0.025 g (30 %). $C_{28}H_{40}N_2O_2$ (436.3). Purity (HPLC, method B): 96.0 %, $t_R$ = 19.0 min. $^1$H NMR ($CDCl_3$): δ (ppm) = 0.72 (t, *J* = 6.5 Hz, 6H, $OCH_2CH_2CH(C\mathit{H}_3)_2$), 1.12-1.18 (m, 2H, $OCH_2C\mathit{H}_2CH(CH_3)_2$), 1.26 (d (b), *J* = 13.8 Hz, 1H, 5-H), 1.35-1.48 (m, 2H, 5-H, $OCH_2CH_2C\mathit{H}(CH_3)_2$), 1.53-1.62 (m, 1H, 4-H), 1.81-1.88 (m, 1H, 3-H), 2.07-2.18 (m, 1H, 4-H), 2.32 (q, *J* = 11.1 Hz, 1H, 3-H), 2.56 (d (b), *J* = 10.1 Hz, 1H, 10-H), 2.76-2.80 (m, 3H, 1-H, 6-H, 8-H), 2.88-3.05 (m, 5H, 2-H, 8-H, 10-H, $OC\mathit{H}_2CH_2CH(CH_3)_2$), 3.39-3.46 (m, 2H, $C\mathit{H}_2C_6H_5$, $C\mathit{H}_2C_6H_4OCH_3$), 3.53 (d, *J* = 12.5 Hz, 1H, $C\mathit{H}_2C_6H_5$), 3.61 (d, *J* = 13.1 Hz, 1H, $C\mathit{H}_2C_6H_4OCH_3$), 3.72 (s, 3H, $C_6H_4OC\mathit{H}_3$), 6.77 (d, *J* = 8.5 Hz, 2H, 3-H, 5-$H_{methoxybenzyl}$), 7.12-7.22 (m, 5H, 2-H, 6-$H_{methoxybenzyl}$, 2-H, 4-H, 6-$H_{benzyl}$), 7.28 (d, *J* = 7.3 Hz, 2H, 3-H, 5-$H_{benzyl}$). $^{13}$C NMR ($CDCl_3$): δ (ppm) = 22.2 (1C, C-4), 22.7 (1C, $OCH_2CH_2CH(\mathit{C}H_3)_2$), 22.8 (1C, $OCH_2CH_2CH(\mathit{C}H_3)_2$), 25.2 (1C, $OCH_2CH_2\mathit{C}H(CH_3)_2$), 30.7 (1C, C-3), 36.4 (1C, C-5), 39.1 (1C, $OCH_2\mathit{C}H_2CH(CH_3)_2$), 45.5 (1C, C-8), 50.9 (1C, C-10), 55.5 (1C, $C_6H_4O\mathit{C}H_3$), 57.5 (1C, C-6), 59.9 (1C, C-1), 62.8 (1C, $\mathit{C}H_2C_6H_5$), 63.2 (1C, $\mathit{C}H_2C_6H_4OCH_3$), 67.5 (1C, $O\mathit{C}H_2CH_2CH(CH_3)_2$), 82.0 (1C, C-2), 113.6 (2C, C-3, C-$5_{methoxybenzyl}$), 126.9 (1C, C-$4_{benzyl}$), 128.2 (1C, C-$1_{methoxybenzyl}$), 129.3 (2C, C-3, C-$5_{benzyl}$), 130.7

(2C, C-2, C-$6_{benzyl}$), 131.8 (2C, C-2, C-$6_{methoxybenzyl}$), 140.1 (1C, C-$1_{benzyl}$), 158.8 (1C, C-$4_{methoxybenzyl}$). Exact mass (ESI): *m/z* = calculated for $C_{28}H_{41}N_2O_2H^+$ 437.3168, found 437.3163. IR (neat): ν ($cm^{-1}$) = 1506 (C=C aromatic), 1242 (C-O), 1089 (C-O).

**10. (1RS,2RS,6SR)-7-Benzyl-2-benzyloxy-9-(4-methoxybenzyl)-7,9-diazabicyclo[4.2.2]decane (16g)**

Under $N_2$ $LiAlH_4$ (0.07, 1.8 mmol) was added slowly to a solution of **15g** (0.22 g, 0.44 mmol) in dry THF (22 mL) under ice-cooling. The mixture was warmed to rt and then stirred under reflux for 16 h. Excess $LiAlH_4$ was destroyed with $H_2O$ (1mL) under ice-cooling. The mixture was again stirred under reflux for 1 h. The solution was cooled to rt and filtered through a sintering funnel. The precipitate was washed with $CH_2Cl_2$ (100 mL). The solvent was evaporated in vacuum. The crude oil was purified by fc (petroleum ether/ethyl acetate = 95/5, 2 cm, 13 cm, 10 mL, $R_f$ = 0.58). Colorless oil, yield 0.06 g (30 %). $C_{30}H_{36}N_2O_2$ (456.3). Purity: 95.6 % (HPLC, method A), $t_R$ = 22.5 min. $^1$H NMR ($CDCl_3$): δ (ppm) = 1.35-1.45 (s (b), 1H, 4-H), 1.53-1.68 (s (b), 2H, 4-H, 5-H), 1.91 (s (b), 1H, 3-H), 2.06-2.17 (m, 1H, 5-H), 2.40 (q, *J* = 10.8 Hz, 1H, 3H), 2.56 (d, *J* = 9.7 Hz, 1H, 10-H), 2.78 (s (b), 2H, 6-H, 8-H), 2.87 (s, 1H, 1-H), 2.98-3.10 (m (b), 3H, 2-H, 8-H, 10-H), 3.40 (d, *J* = 12.3 Hz, 1H, NC*H*$_2$C$_6$H$_4$OCH$_3$), 3.49 (t, *J* = 14.9 Hz, 2H, NC*H*$_2$C$_6$H$_5$), 3.61 (d, *J* = 12.3 Hz, 1H, NC*H*$_2$C$_6$H$_4$OCH$_3$), 3.72 (s, 3H, C$_6$H$_4$OC*H*$_3$), 4.07 (d, *J* = 12.5 Hz, 1H, OC*H*$_2$C$_6$H$_5$), 4.17 (d, *J* = 12.4 Hz, 1H, OC*H*$_2$C$_6$H$_5$), 6.76 (d, *J* = 8.4 Hz, 2H, 3-H, 5-H$_{methoxybenzyl}$), 7.05 (d, *J* = 8.7 Hz, 2H, 2-H, 6-H$_{methoxybenzyl}$), 7.14-7.30 (m, 10H, 2-H, 3-H, 4-H, 5-H, 6-H$_{O\text{-}benzyl,\ N\text{-}benzyl}$). $^{13}$C NMR ($CDCl_3$): δ (ppm) = 22.1 (1C, C-4), 30.1 (1C, C-5), 36.3 (1C, C-3), 45.4 (1C, C-8), 50.9 (1C, C-10), 55.4 (1C, O*C*H$_3$), 57.5 (1C, C-6), 60.1 (1C, C-1), 62.8 (N*C*H$_2$C$_6$H$_5$), 63.1 (1C, N*C*H$_2$C$_6$H$_4$OCH$_3$), 70.8 (1C, O*C*H$_2$C$_6$H$_5$), 81.7 (1C, C-2), 113.7 (2C, C-3, C-$5_{methoxybenzyl}$), 126.9 (1C, C-$4_{N\text{-}benzyl}$), 127.3 (2C, C-2, C-$6_{O\text{-}benzyl}$), 127.5 (1C, C-$4_{O\text{-}benzyl}$), 128.2 (2C, C-2, C-$6_{N\text{-}benzyl}$), 128.3 (2C, C-3, C-$5_{N\text{-}benzyl}$), 129.3 (2C, C-3, C-$5_{O\text{-}benzyl}$), 130.3 (1C, C-$1_{methoxybenzyl}$), 132.6 (2C, C-2, C-$6_{methoxybenzyl}$), 139.6 (1C, C-$1_{N\text{-}benzyl}$), 139.8 (1C, C-$1_{O\text{-}benzyl}$), 158.8 (1C, C-$4_{methoxybenzyl}$). Exact mass (ESI): *m/z* = calculated for $C_{30}H_{37}N_2O_2H^+$ 457.2855, found 457.2850. I.R. (neat): ν ($cm^{-1}$) = 2922 (C-H), 1509 (C-O), 1246 (C-O), 731 (C=C), 698 (C=C).

**11. [(1RS,2RS,6SR)-7-Benzyl-9-(4-methoxybenzyl)-7,9-diazabicyclo[4.2.2]dec-2-yl] 4-Nitro-benzoate (21)**

Under $N_2$ triphenylphosphine (4.02 g, 15.3 mmol) and p-nitrobenzoic acid (1.7 g, 10.2 mmol) were added to a solution of **16a** (1.25 g, 3.4 mmol) in THF (35 mL). Diisopropyl azodicarboxylate (3.04

mL, 15.3 mmol) was added dropwise to this mixture under ice-cooling.The mixture was stirred at rt for 16 h. The solvent was evaporated in vacuum. The crude mixture was purified by fc (ethyl acetate/cyclohexane = 3/97, 8 cm, 13 cm, 100 mL, $R_f$ = 0.89) to obtain *p*-nitrobenzoate **21** as pale yellow solid, mp 101 – 105 °C, yield 1.22 g (69 %). $C_{30}H_{33}N_3O_5$ (515.6). Purity% (HPLC, method A): 99.2 %, $t_R$ = 20.3 min. $^1$H NMR ($CDCl_3$): δ (ppm) = 1.41 (ddd, *J* = 13.6/7.3/2.9 Hz, 1H, 5-H), 1.62-1.70 (m, 1H, 5-H), 1.70-1.81 (m, 1H, 4-H), 2.11-2.18 (m, 1H, 3-H), 2.31-2.42 (m, 1H, 4-H), 2.57 (d, *J* = 10.9 Hz, 1H, 8-H), 2.67 (q, *J* = 11.3 Hz, 1H, 3-H), 2.82 (*J* = 11.4/3.5 Hz, 1H, 10-H), 2.91 (*J* = 11.6/1.5 Hz, 2H, 6-H, 10-H), 3.00-3.03 (m, 2H, 1-H, 8-H), 3.54 (d, *J* = 12.8 Hz, 1H, NC*H*$_2$C$_6$H$_5$), 3.60 (d, *J* = 12.9 Hz, 1H, NC*H*$_2$C$_6$H$_4$OCH$_3$), 3.74 (d, *J* = 12.9 Hz, 1H, NC*H*$_2$C$_6$H$_4$OCH$_3$), 3.75 (d, *J* = 12.8 Hz, 1H, NC*H*$_2$C$_6$H$_5$), 3.79 (s, 3H, C$_6$H$_4$OC*H*$_3$), 5.07 (dt, *J* = 5.8/4.9 Hz, 1H, 2-H), 6.84 (d, *J* = 8.7 Hz, 2H, 3-H, 5-H$_{methoxybenzyl}$), 7.24 (d, *J* = 8.7 Hz, 2H, 2-H, 6-H$_{methoxybenzyl}$), 7.29-7.34 (m, 3H, 3-H, 4-H, 5-H$_{benzyl}$), 7.38-7.40 (m, 2H, 2-H, 6-H$_{benzyl}$), 7.96 (d, *J* = 8.9 Hz, 2H, 2-H, 6-H$_{nitrobenzoyl}$), 8.18 (d, *J* = 8.9 Hz, 2H, 3-H, 5-H$_{nitrobenzoyl}$). $^{13}$C NMR ($CDCl_3$): δ (ppm) = 21.7 (1C, C-4), 30.2 (1C, C-5), 31.1 (1C, C-3), 35.9 (1C, C-8), 44.9 (1C, C-10), 49.7 (1C, C-6), 55.4 (1C, O*C*H$_3$), 58.2 (1C, C-1), 61.2 (1C, *C*H$_2$C$_6$H$_5$), 62.7 (1, *C*H$_2$C$_6$H$_4$OCH$_3$), 63.0 (1C, C-2), 113.8 (2C, C-3, C-5$_{methoxybenzyl}$), 123.5 (2C, C-3C-5$_{nitrobenzoyl}$), 127.1 (1C, C-4$_{benzyl}$), 128.4 (1C, C-1$_{methoxybenzyl}$), 129.2 (2C, C-3, C-5$_{benzyl}$), 130.2 (2C, C-2, C-6$_{benzyl}$), 130.7 (2C, C-2, C-6$_{methoxybenzyl}$), 131.2 (2C. C-2, C-6$_{nitrobenzoyl}$), 136.6 (1C, C-1$_{benzyl}$), 140.0 (1C, C-1$_{nitrobenzoyl}$), 150.5 (1C, C-6$_{nitrobenzoyl}$), 158.9 (1C, C-6$_{methoxybenzyl}$), 163.9 (1C, carbonyl). Exact mass (ESI): *m/z* = calculated for $C_{30}H_{33}N_3O_5H^+$ 516.2498, found 516.2492. I.R. (neat): ν ($cm^{-1}$) = 2908 (C-H), 1718 (C=O), 1522 (O=N-O), 1512 (C-O), 1306 (O=N-O), 1249 (C-O), 717 (C=C).

**12. (1RS,2SR,6SR)-7-Benzyl-2-ethoxy-9-(4-methoxybenzyl)-7,9-diazabicyclo[4.2.2] decane (25c)**

Under $N_2$ NaH (4 mg, 0.14 mmol, 60 % in paraffin oil) was slowly added to a solution of **25a** (35 mg, 0.095 mmol) and $CH_3CH_2I$ (0.02 mL, 0.2 mmol) in dry DMF (2 mL) under ice-cooling. The reaction mixture was stirred for 3 h at rt. The excess NaH was destroyed with $H_2O$ (5 mL) under ice-cooling. The aqueous layer was extracted with ethyl acetate (7 x 10 mL). The combined organic layers were washed with brine, dried over $K_2CO_3$ and the solvent was evaporated in vacuum. The crude viscous oil was purified by fc (ethyl acetate/petroleum ether = 5/95 + 0.05 % N,N-dimethylethylamine, 1.5 cm, 13 cm, 10 mL, $R_f$ = 0.44 (ethyl acetate/cyclohexane = 1/4)) to obtain a colorless viscous oil, yield 0.027 g (72 %). $C_{25}H_{34}N_2O_2$ (394.2). Purity: 93.5 % (HPLC, method B), $t_R$ = 17.0 min. $^1$H NMR ($CDCl_3$): δ (ppm) = 1.07 (t, *J* = 6.98 Hz, 3H, OCH$_2$C*H*$_3$), 1.10-1.15 (m, 1H, 5-H), 1.45 (dt, *J* = 12.9/5.6 Hz, 1H, 5-

H), 1.56-1.63 (m, 1H, 4-H), 1.96 (ddd, *J* = 11.9/6.4/4.2 Hz, 1H, 3-H), 2.03-2.12 (m, 2H, 3-H, 4-H), 2.28 (d, *J* = 10.7 Hz, 1H, 10-H), 2.50 (d, *J* = 11.0 Hz, 1H, 8-H), 2.74 (s(b), 1H, 6-H), 2.79 (dd, *J* = 10.7/3.1 Hz, 1H, 10-H), 2.85 (dd, *J* = 11.1/4.4 Hz, 1H, 8-H), 3.06 (dd, *J* = 5.9/2.4 Hz, 1H, 2-H), 3.08 (s(b), 1H, 1-H), 3.36 (dq, *J* = 14.5/6.8 Hz, Hz, 2H, OC*H*$_2$CH$_3$), 3.45 (d, *J* = 12.8 Hz, 1H, C*H*$_2$C$_6$H$_4$OCH$_3$), 3.53 (s, 2H, C*H*$_2$C$_6$H$_5$), 3.72 (s, 3H, C$_6$H$_4$OC*H*$_3$), 3.77 (d, *J* = 12.8 Hz, 1H, C*H*$_2$C$_6$H$_4$OCH$_3$), 6.77 (d, *J* = 8.7 Hz, 2H, 3-H, 5-H$_{methoxybenzyl}$), 7.11-7.22 (m, 5H, 2-H, 6-H$_{methoxybenzyl}$, 2-H, 4-H, 6-H$_{benzyl}$), 7.27-7.30 (m, 2H, 3-H, 5-H$_{benzyl}$). $^{13}$C NMR (CDCl$_3$): δ (ppm) = 16.0 (1C, OCH$_2$*C*H$_3$), 20.6 (1C, C-4), 31.2 (1C, C-3), 35.7 (1C, C-5), 49.9 (1C, C-10), 50.2 (1C, C-8), 55.4 (1C, C$_6$H$_4$O*C*H$_3$), 57.7 (1C, C-6), 61.6 (1C, C-1), 63.3 (1C, O*C*H$_2$CH$_3$), 63.7 (1C, *C*H$_2$C$_6$H$_5$), 63.8 (1C, *C*H$_2$C$_6$H$_4$OCH$_3$), 84.6 (1C, C-2), 113.5 (2C, C-3, C-5$_{methoxybenzyl}$), 126.9 (1C, C-4$_{benzyl}$), 128.3 (1C, C-1$_{methoxybenzyl}$), 129.1 (2C, C-2, C-6$_{benzyl}$), 130.3 (2C, C-3, C-5$_{benzyl}$), 132.7 (2C, C-2, C-6$_{methoxybenzyl}$), 140.3 (1C, C-1$_{benzyl}$), 158.6 (1C, C-4$_{methoxybenzyl}$). Exact mass (ESI): *m/z* = calculated for C$_{25}$H$_{35}$N$_2$O$_2$H$^+$ 395.2698, found 395.2693. I.R. (neat): ν (cm$^{-1}$) = 2904 (C-H), 1509 (C-O), 1243 (C-O), 697 (C=C).

## 13. (1RS,2SR,6SR)-7-Benzyl-2-benzyloxy-9-(4-methoxybenzyl)-7,9-diazabicyclo[4.2.2]decane (25g)

Under N$_2$ NaH (0.01 g, 0.22 mmol, 60 % in paraffin oil) was slowly added to a solution of **25a** (55 mg, 0.15 mmol) and C$_6$H$_5$CH$_2$Br (0.04 mL, 0.3 mmol) in dry DMF (2 mL) under ice-cooling. The reaction mixture was stirred for 3 h at rt. The excess NaH was destroyed with H$_2$O (5 mL) under ice-cooling. The aqueous layer was extracted with ethyl acetate (7 x 10 mL). The combined organic layers were washed with brine, dried over K$_2$CO$_3$ and the solvent was evaporated in vacuum. The crude viscous oil was purified by fc (ethyl acetate/petroleum ether = 5/95+0.05 % N,N-dimethylethylamine, 1.5 cm, 13 cm, 10 mL, R$_f$ = 0.15 (ethyl acetate/cyclohexane = 1/9)) to obtain a colorless viscous oil, yield 38 mg (55 %). C$_{30}$H$_{36}$N$_2$O$_2$ (456.3). Purity: 88.3 % (HPLC, method B), t$_R$ = 18.4 min. $^1$H NMR (CDCl$_3$): δ (ppm) = 1.11-1.17 (m, 1H, 5-H), 1.41-1.46 (m, 1H, 5-H), 1.55-1.63 (m, 1H, 4-H), 2.01-2.17 (m, 3H, 3-H, 4-H), 2.31 (d, *J* = 10.4 Hz, 1H, 10-H), 2.48 (d, *J* = 11.1 Hz, 1H, 8-H), 2.76 (s(b), 1H, 6-H), 2.81 (dd, *J* = 10.8/3.2 Hz, 1H, 10-H), 2.86 (dd, *J* = 11.2/4.4 Hz, 1H, 8-H), 3.16-3.20 (m, 2H, 1-H, 2-H), 3.48 (d, *J* = 12.7 Hz, 1H, NC*H*$_2$C$_6$H$_4$OCH$_3$), 3.52 (s, 2H, NC*H*$_2$C$_6$H$_5$), 3.71 (s, 3H, C$_6$H$_4$OC*H*$_3$), 3.85 (d, *J* = 12.7 Hz, 1H, NC*H*$_2$C$_6$H$_4$OCH$_3$), 4.39 (d, *J* =12.3 Hz, 1H, OC*H*$_2$C$_6$H$_5$), 4.47 (d, *J* = 12.3 Hz, 1H, OC*H*$_2$C$_6$H$_5$), 6.75 (d, *J* = 8.6 Hz, 2H, 3-H, 5-H$_{methoxybenzyl}$), 7.12-7.17 (m, 2H 2-H, 6-H$_{methoxybenzyl}$), 7.18-7.25 (m, 10H, 2-H, 3-H, 4-H, 5-H, 6-H$_{O\text{-}benzyl,\ N\text{-}benzyl}$). $^{13}$C NMR (CDCl$_3$): δ (ppm) = 20.5 (1C, C-4), 30.5 (1C, C-3), 35.7 (1C, C-5), 49.9 (1C, C-10), 50.0 (1C, C-8), 55.4 (1C, NC$_6$H$_4$O*C*H$_3$), 57.7 (1C,

C-6), 62.1 (1C, C-1), 63.3 (1C, N*C*H$_2$C$_6$H$_5$), 63.8 (1C, N*C*H$_2$C$_6$H$_4$OCH$_3$), 70.3 (1C, O*C*H$_2$C$_6$H$_5$), 84.3 (1C, C-2), 113.5 (2C, C-3, C-5$_{N\text{-methoxybenzyl}}$), 127.0 (1C, C-4$_{N\text{-benzyl}}$), 127.2 (2C, C-2, C-6$_{O\text{-benzyl}}$), 127.4 (1C, C-4$_{O\text{-benzyl}}$), 128.3 (2C, C-2, C-6$_{O\text{-benzyl}}$), 128.4 (2C, C-3, C-5$_{N\text{-benzyl}}$), 129.1 (2C, C-2, C-6$_{N\text{-benzyl}}$), 130.3 (1C, C-1$_{N\text{-methoxybenzyl}}$), 132.6 (2C, C-2, C-6$_{N\text{-methoxybenzyl}}$), 139.9 (1C, C-1$_{N\text{-benzyl}}$), 140.2 (1C, C-1$_{O\text{-benzyl}}$), 158.6 (1C, C-4$_{N\text{-methoxybenzyl}}$). Exact mass (ESI): *m/z* = calculated for $C_{30}H_{37}N_2O_2H^+$ 457.2855 $(M+H)^+$, found 457.2850 $(M+H)^+$. I.R. (neat): ν ($cm^{-1}$) = 2906 (C-H), 1509 (C-O), 1244 (C-O), 731 (C=C) 696 (C=C).

## 14. [(1RS,2SR,6RS)-7-Benzyl-2-hydroxy-9-(4-methoxybenzyl)-2-methyl-7,9-diazabicyclo[4.2.2]-decane-8,10-dione (28)

Under $N_2$ $CH_3MgBr$ (1.0 M in THF, 0.4 mL, 0.4 mmol) was added to a solution of **14** (0.10 g, 0.25 mmol) in THF (6 mL) at -78 °C. The mixture was stirred at -78 °C for 10 h and at rt for 24 h. 1M HCl (5 mL) was added to the reaction mixture under ice-cooling followed by washing with sat. $NaHCO_3$ (10 mL) solution. The aqueous layer was extracted with EtOAc (5 x 10 mL). The combined organic layers were washed with brine, dried ($Na_2SO_4$) and the solvent was evaporated in vacuum to obtain a colorless viscous oil. Purification by fc (ethyl acetate/cyclohexane = 2/3, 2 cm, 15 cm, 10 mL, 0.07 (ethyl acetate/cyclohexane = 7/3) ) gave **28** as a colorless viscous oil. Yield 50 mg (48 %). $C_{24}H_{28}N_2O_3$ (408.5). $^1$H NMR ($CDCl_3$): δ (ppm) = 1.43 (s, 3H, C*H$_3$*), 1.48-1.60 (m, 2H, 4-H, 5-H), 1.63-1.70 (m, 2H, 4-H, 5-H), 1.87-1.95 (m, 1H, 3-H), 2.01-2.07 (m, 1H, 3-H), 3.46 (s (broad), 1H, O*H*), 3.80 (d, *J* = 14.8 Hz, 1H, NC*H$_2$*C$_6$H$_4$OCH$_3$), 3.81 (s, 3H, OC*H$_3$*), 3.84 (s, 1H, 1-H), 3.98 (d, *J* = 14.8 Hz, 1H, NC*H$_2$*C$_6$H$_5$), 4.07 (dd, *J* = 5.0/3.0 Hz, 1H, 6-H), 5.13 (d, *J* = 14.8 Hz, 1H, NC*H$_2$*C$_6$H$_5$), 5.51 (d, *J* = 14.8 Hz, 1H, NC*H$_2$*C$_6$H$_4$OCH$_3$), 6.86 (d, *J* = 8.8 Hz, 2H, 3-H, 5-H$_{methoxybenzyl}$), 7.07 (d, *J* = 8.6 Hz, 2H, 2-H, 6-H$_{methoxybenzyl}$), 7.17 (dd, *J* = 7.3/1.8 Hz, 2H, 2-H, 6-H$_{benzyl}$), 7.30-7.35 (m, 3H, 3-H, 4-H, 5-H$_{benzyl}$). Exact mass (ESI): *m/z* = calculated for $C_{24}H_{28}N_2O_3Na^+$ 431.1946, found 431.1941. IR (neat): ν ($cm^{-1}$) = 3439 (O-H), 1651 (C=O), 1511 (C=C), 1242 (C-O), 734 (C-H).

## 15. (1RS,6RS)-7-Benzyl-9-(4-methoxybenzyl)-2-methyl-7,9-diazabicyclo[4.2.2]dec-2-ene-8,10-dione (29) and (1RS,6RS)-7-Benzyl-9-(4-methoxybenzyl)-2-methylene-7,9-diazabicyclo[4.2.2]decane-8,10-dione (30)

Under $N_2$ $P_4O_{10}$ (0.7 g, 2.44 mmol) was added to a solution of **28** (0.10 g, 0.24 mmol) in toluene (10 mL) and stirred at 90 °C for 12 h. The mixture was filtered through a sintering funnel and the

precipitate was washed several times with EtOAc. The organic solvent was evaporated in vacuum to obtain a colorless viscous oil. Purification by fc (ethyl acetate/cyclohexane = 1/1, 2 cm, 15 cm, 10 mL, $R_f$ = 0.22) gave a mixture of **29** and **30** (**29 : 30** = 40 : 60 according to $^1$H NMR spectrum) as a colorless viscous oil, yield 30 mg (32 %). $C_{24}H_{26}N_2O_3$ (390.4). $^1$H NMR ($CDCl_3$): δ (ppm) = 1.10-1.15 (m, 1H, 4-$H_{maj + min}$), 1.62-1.70 (m, 1H, 4-$H_{maj + min}$), 1.73 (s, 3 x 0.4H, C$H_{3\ min}$), 1.79 (dd, *J* = 14.8/9.0 Hz, 0.6H, 3-$H_{maj}$), 1.88-1.92 (m, 2 x 0.6H, 5-$H_{maj}$), 2.01-2.08 (m, 0.4H, 4-$H_{min}$), 2.21 (t, *J* = 13.8 Hz, 0.4H, 4-$H_{min}$), 2.30 (dd, *J* = 15.2/9.1 Hz, 0.6H, 3-$H_{maj}$), 3.62 (d, *J* = 14.8 Hz, 0.6H, NC$H_2C_6H_4OCH_{3\ maj}$), 3.74 (s, 3H, OC$H_{3\ maj+min}$), 4.01-4.07 (m, 1.8H, 1-$H_{min}$, 6-$H_{maj+min}$, NC$H_2C_6H_4OCH_{3\ min}$), 4.11 (d, *J* = 14.6 Hz, 0.6H, NC$H_2C_6H_{5\ maj}$), 4.13 (d, *J* = 14.4 Hz, 0.4H, NC$H_2C_6H_{5\ min}$), 4.31 (s, 0.6H, 1-$H_{maj}$), 4.77 (d, *J* = 14.4 Hz, 0.4H, NC$H_2C_6H_{5\ min}$), 4.83 (d, *J* = 14.5 Hz, 0.4H, NC$H_2C_6H_4OCH_{3\ min}$), 4.85 (d, *J* = 14.4 Hz, 0.6H, NC$H_2C_6H_{5\ maj}$), 5.04 (d, *J* = 14.8 Hz, 0.6H, NC$H_2C_6H_4OCH_{3\ maj}$), 5.05 (s, 2 x 0.6H, C=C$H_{2\ maj}$), 5.47 (dd, *J* = 9.0/4.2 Hz, 0.4H, 3-$H_{min}$), 6.78 (d, *J* = 8.6 Hz, 2H, 3-H, 5-$H_{methoxybenzyl\ maj+min}$), 7.08 (d, *J* = 8.6 Hz, 2 x 0.6H, 2-H, 6-$H_{methoxybenzyl\ maj}$), 7.11 (d, *J* = 8.5 Hz, 2 x 0.4H, 2-H, 6-$H_{methoxybenzyl\ min}$), 7.14-7.19 (m, 2H, 2-H, 6-$H_{benzyl\ maj+min}$), 7.22-7.28 (m, 3H, 3-H, 4-H, 5-$H_{benzyl\ maj+min}$). $^{13}$C NMR ($CDCl_3$): δ (ppm) = 23.1 (1C, C-$4_{maj}$), 23.2 (1C, C-$4_{min}$), 25.5 (1C, *C*$H_{3\ min}$), 32.3 (1C, C-$3_{maj}$), 32.8 (2C, C-$5_{maj+min}$), 46.8 (1C, N*C*$H_2C_6H_4OCH_{3\ maj}$), 48.1 (1C, N*C*$H_2C_6H_{5\ maj}$), 48.3 (1C, N*C*$H_2C_6H_4OCH_{3\ min}$), 48.6 (1C, N*C*$H_2C_6H_{5\ min}$), 55.5 (2C, O*C*$H_{3\ maj+min}$), 59.2 (1C, C-$6_{maj}$), 59.6 (1C, C-$6_{min}$), 64.1 (1C, C-$1_{\ min}$), 65.4 (1C, C-$1_{maj}$), 114.4 (2C, C-3, C-$5_{methoxybenzyl\ maj}$), 114.5 (2C, C-3, C-$5_{methoxybenzyl\ min}$), 118.6 (C=*C*$H_{2\ maj}$), 126.2 (1C, C-$3_{min}$), 127.2 (1C, C-$2_{min}$), 127.5 (1C, C-$2_{maj}$), 128.2 (1C, C-$4_{benzyl\ min}$), 128.3 (1C, C-$4_{benzyl\ maj}$), 128.5 (1C, C-$1_{methoxybenzyl\ maj}$), 128.6 (1C, C-$1_{methoxybenzyl\ min}$), 129.1 (2C, C-3, C-$5_{benzyl\ maj+min}$), 130.2 (4C, C-2, C-$6_{benzyl\ maj+min}$), 135.8 (2C, C-2, C-$6_{methoxybenzyl\ min}$), 136.2 (2C, C-2, C-$6_{methoxybenzyl\ maj}$), 145.6 (2C, C-$1_{benzyl\ maj+min}$), 159.6 (1C, C-$4_{methoxybenzyl\ maj}$), 159.7 (1C, C-$4_{methoxybenzyl\ min}$), 166.1 (1C, carbonyl$_{min}$), 166.9 (1C, carbonyl$_{maj}$), 167.8 (1C, carbonyl$_{min}$), 168.9 (1C, carbonyl$_{maj}$). Exact mass (ESI): *m/z* = calculated for $C_{24}H_{26}N_2O_3Na^+$ 413.1841, found 413.1836. IR (neat): ν ($cm^{-1}$) = 1662 (C=O), 1611 (C=C), 1511 (C=C), 1245 (C-O), 701 (C-H).

**16. (1RS,6RS)-7-Benzyl-9-(4-methoxybenzyl)-2-methylene-7,9-diazabicyclo[4.2.2]decane (32)**

Under $N_2$ $LiAlH_4$ (6 mg, 0.16 mmol) was added to a solution of mixture of **29** and **30** (20 mg, 0.05 mmol) in THF (5 mL) under ice-cooling. The mixture was stirred under reflux for 12 h. The excess $LiAlH_4$ was destroyed with $H_2O$ (1 mL) under ice-cooling. The mixture was refluxed for an additional hour. The mixture was cooled to rt and filtered. The filtrate was concentrated in vacuum to obtain a colorless viscous oil. Purification by fc (ethyl acetate/petroleum ether = 3/97, 1.5 cm, 15 cm, 5 mL, $R_f$

= 0.51 (ethyl acetate/cyclohexane = 1/4)) gave **32** as colorless oil, yield 10 mg (54 %). $C_{24}H_{30}N_2O$ (362.2). Purity (HPLC, method A): 93.6 %, $t_R$ = 20.6 min. $^1$H NMR ($CDCl_3$): δ (ppm) = 1.29-1.35 (m, 1H, 5-H), 1.51-1.58 (m, 1H, 5-H), 1.74-1.82 (m, 1H, 4-H), 1.86-1.95 (m, 1H, 4-H), 2.37 (d, *J* = 10.0 Hz, 1H, 10-H), 2.53 (dd, *J* = 10.0/8.0 Hz, 2H, 3-H), 2.60 (d, *J* = 10.1 Hz, 1H, 8-H), 2.84 (s, 1H, 6-H), 2.93 (dd, *J* = 10.8/3.8 Hz, 1H, 10-H), 3.01 (dd, *J* = 10.7/3.9 Hz, 1H, 8-H), 3.28 (s, 1H, 1-H), 3.50 (d, *J* = 12.9 Hz, 1H, NC*H*$_2$C$_6$H$_4$OCH$_3$), 3.53 (d, *J* = 11.8 Hz, NC*H*$_2$C$_6$H$_5$), 3.58 (d, *J* = 12.4 Hz, NC*H*$_2$C$_6$H$_5$), 3.61 (d, *J* = 12.6 Hz, 1H, NC*H*$_2$C$_6$H$_4$OCH$_3$), 3.72 (s, 3H, OC*H*$_3$), 4.33 (s, 1H, C=C*H*$_2$), 4.54 (s, 1H, C=C*H*$_2$), 6.81 (d, *J* = 8.8 Hz, 2H, 3-H,5-H$_{methoxybenzyl}$), 7.14 (d, *J* = 7.9 Hz, 2H, 2-H,6-H$_{methoxybenzyl}$ ), 7.20-7.26 (m, 5H, 2-H, 3-H, 4-H, 5-H, 6-H$_{benzyl}$). $^{13}$C NMR ($CDCl_3$): δ (ppm) = 24.3 (1C, C-4), 32.7 (1C, C-3), 35.0 (1C, C-5), 49.3 (1C, C-10), 50.2 (1C, C-8), 54.2 (1C, O*C*H$_3$), 56.1 (1C, C-6), 60.5 (1C, N*C*H$_2$C$_6$H$_5$), 61.8 (1C, N*C*H$_2$C$_6$H$_4$OCH$_3$), 63.8 (1C, C-1), 107.8 (1C, C=*C*H$_2$), 112.3 (2C, C-3, C-5$_{methoxybenzyl}$), 125.7 (1C, C-4$_{benzyl}$), 127.0 (1C, C-1$_{methoxybenzyl}$), 127.8 (2C, C-3, C-5$_{benzyl}$,), 128.6 (2C, C-2, C-6$_{benzyl}$), 130.8 (2C, C-2, C-6$_{methoxybenzyl}$), 138.9 (1C, C-1$_{benzyl}$), 154.8 (2C, C-4$_{methoxybenzyl}$, C-2). Exact mass (ESI): *m/z* = calculated for $C_{24}H_{30}N_2OH^+$ 363.2436, found 363.2431. IR (neat): ν (cm$^{-1}$) = 1611 (C=C), 1511 (C=C), 1451 (C-N), 1244 (C-O), 699 (C-H).

### 17. (1RS,6SR)-7-Benzyl-2,2-difluoro-9-(4-methoxybenzyl)-7,9-diazabicyclo[4.2.2]decane-8-10-dione (33) and (1RS,6SR)-7-Benzyl-2-fluoro-9-(4-methoxybenzyl)-7,9-diazabicyclo[4.2.2]dec-2-ene-8-10-dione (34)

Diethylaminosulfur trifluoride (DAST, 0.06 mL, 0.5 mmol) was added to a solution of ketone **14** (0.10 g, 0.25 mmol) in $CH_2Cl_2$ (5 mL) at -78 °C and the mixture was stirred for 12 h at -78 °C. The reaction mixture was washed with sat. $NaHCO_3$ solution (5 mL) and the aqueous layer was extracted with $CH_2Cl_2$ (5 x 10 mL). The combined organic layers were dried ($Na_2SO_4$) and the solvent was evaporated in vacuum to obtain a colorless viscous oil. Purification by fc (ethyl acetate/cyclohexane = 1/1, 2 cm, 15 cm, 10 mL, $R_f$ = 0.26) resulted in a mixture of **33** and **34** as a colorless viscous oil. Yield 0.85 g (**33** : **34** = 3 : 1). **33** - $C_{23}H_{24}F_2N_2O_3$ (414.4) and **34** - $C_{23}H_{23}FN_2O_3$ (394.4). Purity (HPLC, method A): 25.2 %, $t_R$ = 20.2 min (**34**), 74.6 %, $t_R$ = 20.3 min (**33**). $^1$H NMR ($CDCl_3$): δ (ppm) = 1.39 (ddd, *J* = 27.2/11.3/3.8 Hz, 1H, 4-H$_{maj}$), 1.57-1.66 (m, 1H, 4-H$_{maj}$), 1.76-2.03 (m, 4.2 H, 3-H, 2 x 5-H$_{maj}$, 2 x 4-H, 2 x 5-H$_{min}$), 2.07-2.22 (m, 1H, 3-H$_{maj}$), 3.71 (d, *J* = 15.0 Hz, 1H, NC*H*$_2$C$_6$H$_4$OCH$_{3,\ maj}$), 3.74 (s, 3.9 H, OC*H*$_{3,\ maj}$, OC*H*$_{3,\ min}$), 3.98 (d, *J* = 14.8 Hz, 0.3H, NC*H*$_2$C$_6$H$_4$OCH$_{3,\ min}$), 4.06-4.10 (m, 1.6 H, 6-H$_{maj}$, 6-H$_{min}$, NC*H*$_2$C$_6$H$_{5,\ min}$), 4.16 (d, *J* = 14.7 Hz, 1H, NC*H*$_2$C$_6$H$_{5,\ maj}$), 4.23 (d, *J* = 12.2 Hz,

1H, 1-$H_{maj}$), 4.31 (dd, *J* = 12.5/1.4 Hz, 0.3H, 1-$H_{min}$), 4.83 (d, *J* = 14.7 Hz, 1H, NC$H_2$C$_6$H$_{5\ maj}$), 4.88 (d, *J* = 14.7 Hz, 0.3H, NC$H_2$C$_6$H$_{5,\ min}$), 5.00 (d, *J* = 14.6 Hz, 0.3H, NC$H_2$C$_6$H$_4$OCH$_{3,\ min}$), 5.36 (d, *J* = 14.7 Hz, 1H, NC$H_2$C$_6$H$_4$OCH$_{3,\ maj}$), 5.31-5.40 (m, 0.3H, 3-$H_{min}$), 6.80 (d, *J* = 8.8 Hz, 2.6H, 3-H, 5-$H_{methoxybenzyl\ maj}$, 3-H, 5-$H_{methoxybenzyl\ min}$), 7.05 (d, *J* = 8.8 Hz, 2.6H, 2-H, 6-$H_{methoxybenzyl\ maj}$, 2-H, 6-$H_{methoxybenzyl\ min}$), 7.10-7.16 (m, 3.9 H, 2-H, 5-H, 6-$H_{benzyl\ maj}$, 2-H, 5-H, 6-$H_{benzyl\ min}$). Exact mass (ESI): *m/z* = calculated for $C_{23}H_{24}F_2N_2O_3Na^+$ (**31**+Na)$^+$ 437.1652, found 437.1647, calculated for $C_{23}H_{23}FN_2O_3Na^+$ (**32**+Na)$^+$ 417.1590, found 451.1589.

**18. (1RS,6SR)-7-Benzyl-2-fluoro-9-(4-methoxybenzyl)-7,9-diazabicyclo[4.2.2]dec-2-ene (35)**

Under $N_2$ $LiAlH_4$ (10 mg, 0.24 mmol) was added to a solution of **33** and **34** (3 : 1 mixture, 50 mg, 0.12 mmol) in THF (10 mL) under ice-cooling. The mixture was heated to reflux for 12 h. The mixture was filtered through a sintering funnel and the solvent was evaporated in vacuum to obtain a colorless oil. Purification by fc (ethyl acetate/petroleum ether = 5/95, 1.5 cm, 15 cm, 5 mL, $R_f$ = 0.40 (ethyl acetate/cyclohexane = 1/4)) gave a colorless viscous oil, yield 24 mg (54 %). $C_{23}H_{27}FN_2O$ (366.4). Purity (HPLC, method A): 93.5 %, $t_R$ = 18.9 min. $^1$H NMR ($CDCl_3$): δ (ppm) = 0.72-0.83 (m, 1H, 5-H), 1.40-1.44 (m, 1H, 5-H), 1.67-1.74 (m, 1H, 4-H), 1.88-1.94 (m, 1H, 4-H), 2.62 (d, *J* = 9.2 Hz, 1H, 8-H), 2.81-2.89 (m, 2H, 8-H, 10-H), 2.99-3.03 (m, 2H, 6-H, 10-H), 3.30 (d, *J* = 9.0 Hz, 1H, 1-H), 3.59 (s, 2H, NC$H_2$C$_6$H$_5$), 3.67 (d, *J* = 13.5 Hz, 1H, NC$H_2$C$_6$H$_4$OCH$_3$), 3.72 (s, 3H, OC$H_3$), 3.76 (d, *J* = 13.5 Hz, 1H, NC$H_2$C$_6$H$_4$OCH$_3$), 5.44 (ddd, *J* = 23.0/8.9/6.5 Hz, 1H, 3-H), 6.31 (d, *J* = 8.8 Hz, 2H, 3-H, 5-$H_{methoxybenzyl}$), 7.18 (d, *J* = 8.2 Hz, 2H, 2-H, 6-$H_{methoxybenzyl}$), 7.21-7.29 (m, 5H, 2-H, 3-H, 4-H, 5-H, 6-$H_{benzyl}$). Exact mass (ESI): *m/z* = calculated for $C_{23}H_{27}FN_2OH^+$ 367.2185, found 367.2179.

## X-ray crystal structure analyses

### 1. Compound 15b

Crystal data for $C_{24}H_{28}N_2O_4$ (**15b**), $M$ = 408.48, monoclinic, space group $P2_1/c$ (No. 14), $a$ = 12.0559(4), $b$ = 8.3214(3), $c$ = 21.4645(9) Å, $\beta$ = 101.963(2)°, $V$ = 2106.59(14) Å$^3$, $D_c$ = 1.288 g cm$^{-3}$, $\mu$ = 0.710 mm$^{-1}$, $Z$ = 4, $\lambda$ = 1.54178 Å, $T$ = 223(2) K, 18311 reflections collected ($\pm h$, $\pm k$, $\pm l$), [(sinθ)/λ] = 0.60 Å$^{-1}$, 3745 independent ($R_{int}$ = 0.037), and 3571 observed reflections [I ≥ 2σ($I$)], 273 refined parameters, $R$ = 0.039, w$R^2$ = 0.109. CCDC .

### 2. Compound 15c

Crystal data for $C_{25}H_{30}N_2O_4$ (**15c**), $M$ = 422.51, triclinic, space group $P$1bar (No. 2), $a$ = 8.7032(3), $b$ = 14.2662(5), $c$ = 18.1661(7) Å, $\alpha$ = 87.240(3), $\beta$ = 89.706(3), $\gamma$ = 79.745(2)°, $V$ = 2216.91(14) Å$^3$, $D_c$ = 1.266 g cm$^{-3}$, $\mu$ = 0.691 mm$^{-1}$, $Z$ = 4, $\lambda$ = 1.54178 Å, $T$ = 223(2) K, 29302 reflections collected ($\pm h$, $\pm k$, $\pm l$), [(sinθ)/λ] = 0.60 Å$^{-1}$, 7822 independent ($R_{int}$ = 0.037), and 7423 observed reflections [I ≥ 2σ($I$)], 563 refined parameters, $R$ = 0.041, w$R^2$ = 0.105. CCDC .

### 3. Compound 21

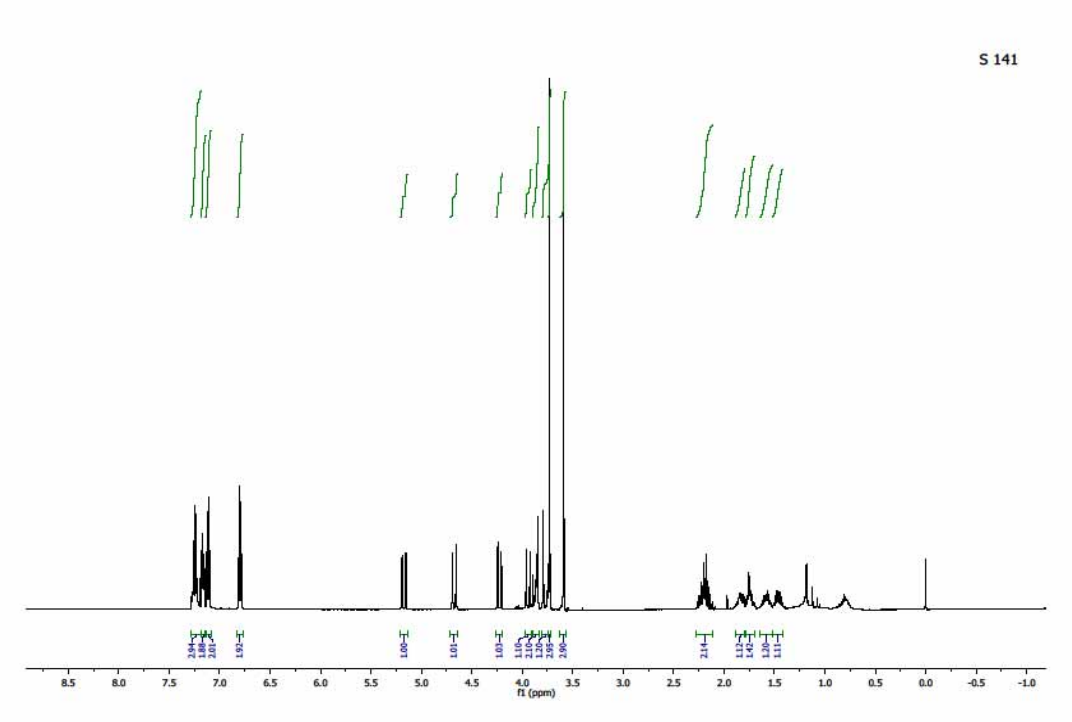
Crystal data for $C_{30}H_{33}N_3O_5$ (**21**), $M$ = 515.59, triclinic, space group $P$1bar (No. 2), $a$ = 10.4650(1), $b$ = 12.3120(2), $c$ = 12.3680(2) Å, $\alpha$ = 106.693(1), $\beta$ = 100.898(1), $\gamma$ = 109.321(1)°, $V$ = 1367.44(3) Å$^3$, $D_c$ = 1.252 g cm$^{-3}$, $\mu$ = 0.696 mm$^{-1}$, $Z$ = 2, $\lambda$ = 1.54178 Å, $T$ = 223(2) K, 14795 reflections collected ($\pm h$, $\pm k$, $\pm l$), [(sinθ)/λ] = 0.60 Å$^{-1}$, 4634 independent ($R_{int}$ = 0.034), and 4297 observed reflections [I ≥ 2σ($I$)], 344 refined parameters, $R$ = 0.056, w$R^2$ = 0.144. CCDC .

### 4. General

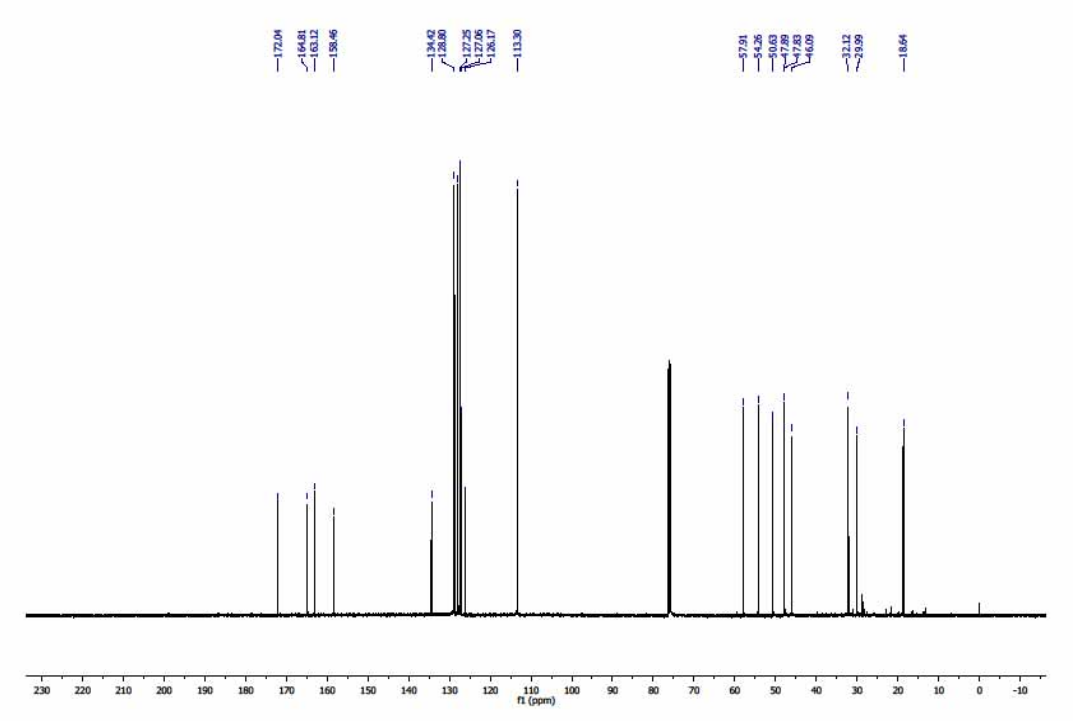
Data sets were collected with a Nonius KappaCCD diffractometer. Programs used: data collection COLLECT (Nonius B.V., 1998), data reduction Denzo-SMN (Z. Otwinowski, W. Minor, *Methods in Enzymology*, **1997**, *276*, 307-326), absorption correction Denzo (Z. Otwinowski, D. Borek, W. Majewski, W. Minor, *Acta Cryst.* **2003**, *A59*, 228-234), structure solution SHELXS-97 (G.M. Sheldrick, *Acta Cryst.* **1990**, *A46*, 467-473), structure refinement SHELXL-97 (G.M. Sheldrick, *Acta Cryst.* **2008**, *A64*, 112-122), graphics SCHAKAL (E. Keller, Univ. Freiburg, 1997). R-values are given for the observed reflections, w$R^2$-values for all. See http://www.rsc.org/suppdata/…… for crystallographic data in cif or other electronic format.

# NMR sSpetra and HPLC chromatrograms of important compounds

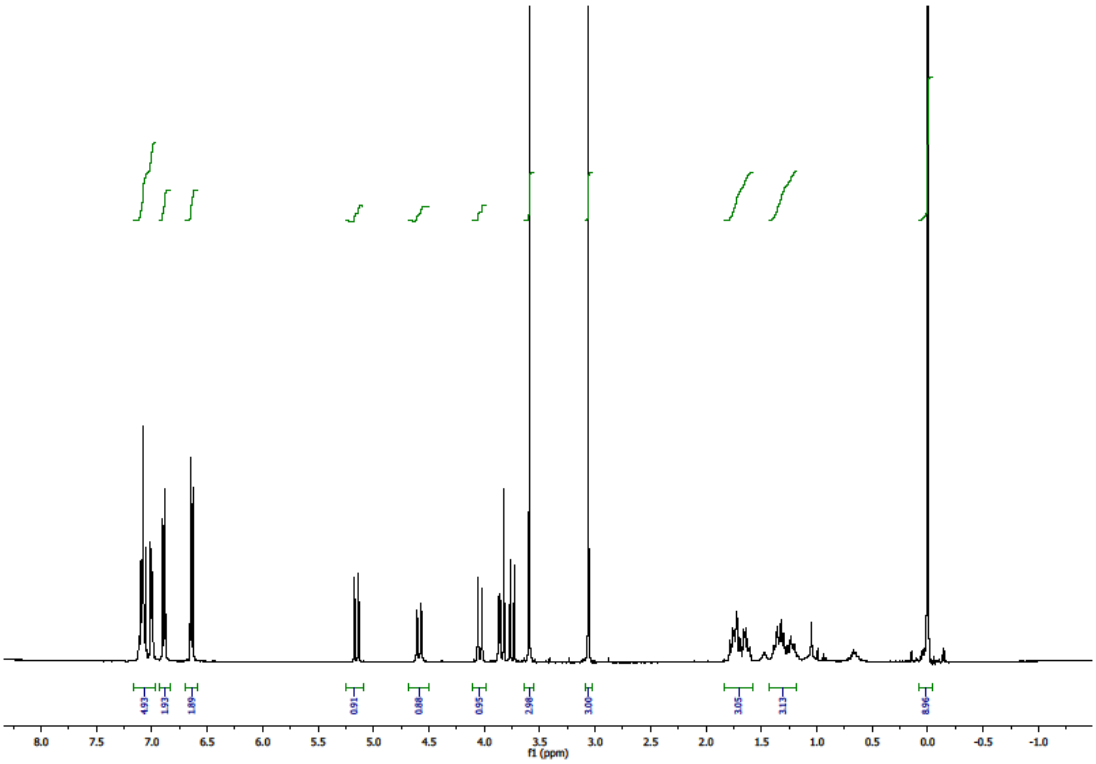
$^{1}$H NMR spectrum of Compound **11**



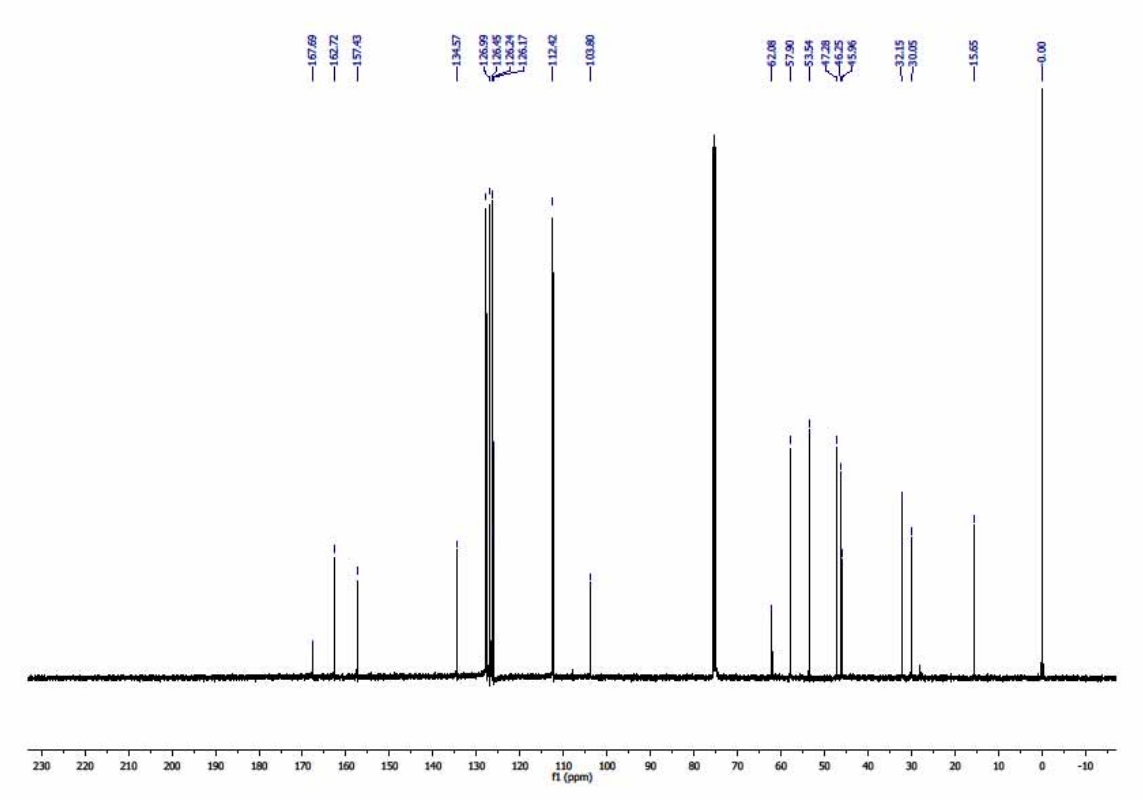

$^{13}$C NMR spectrum of compound **11**



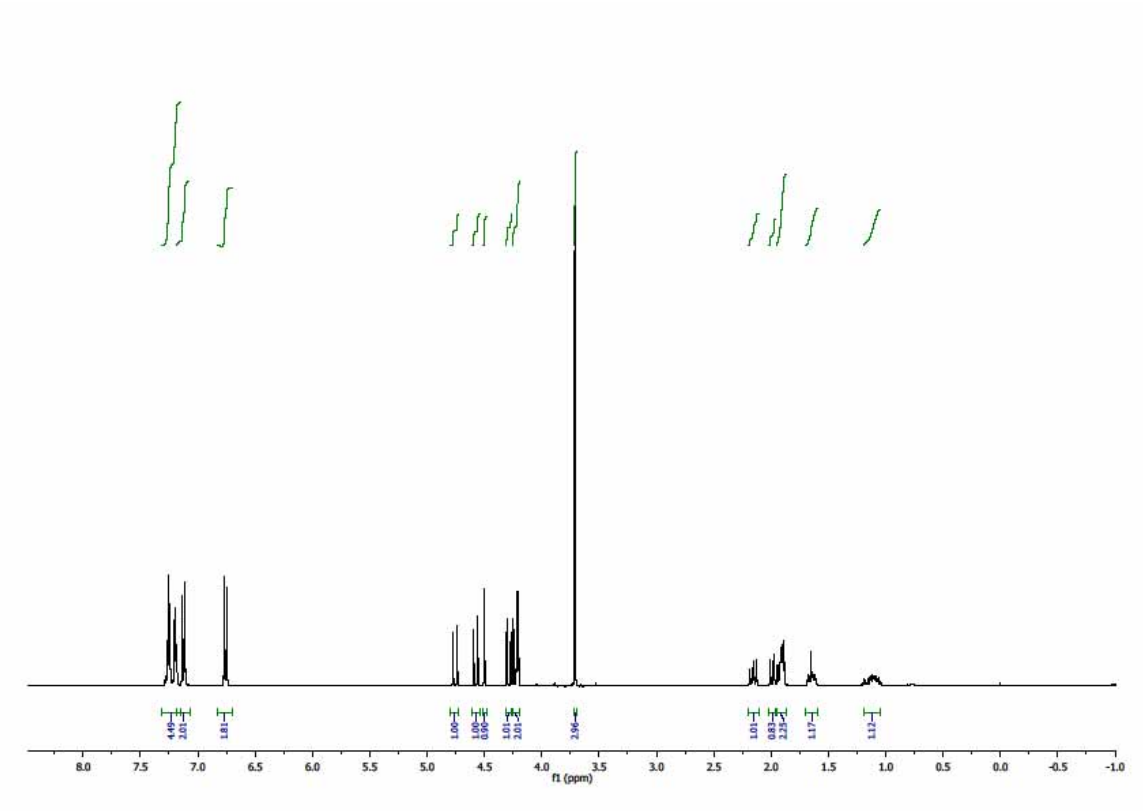
$^{1}$H NMR spectrum of **13**



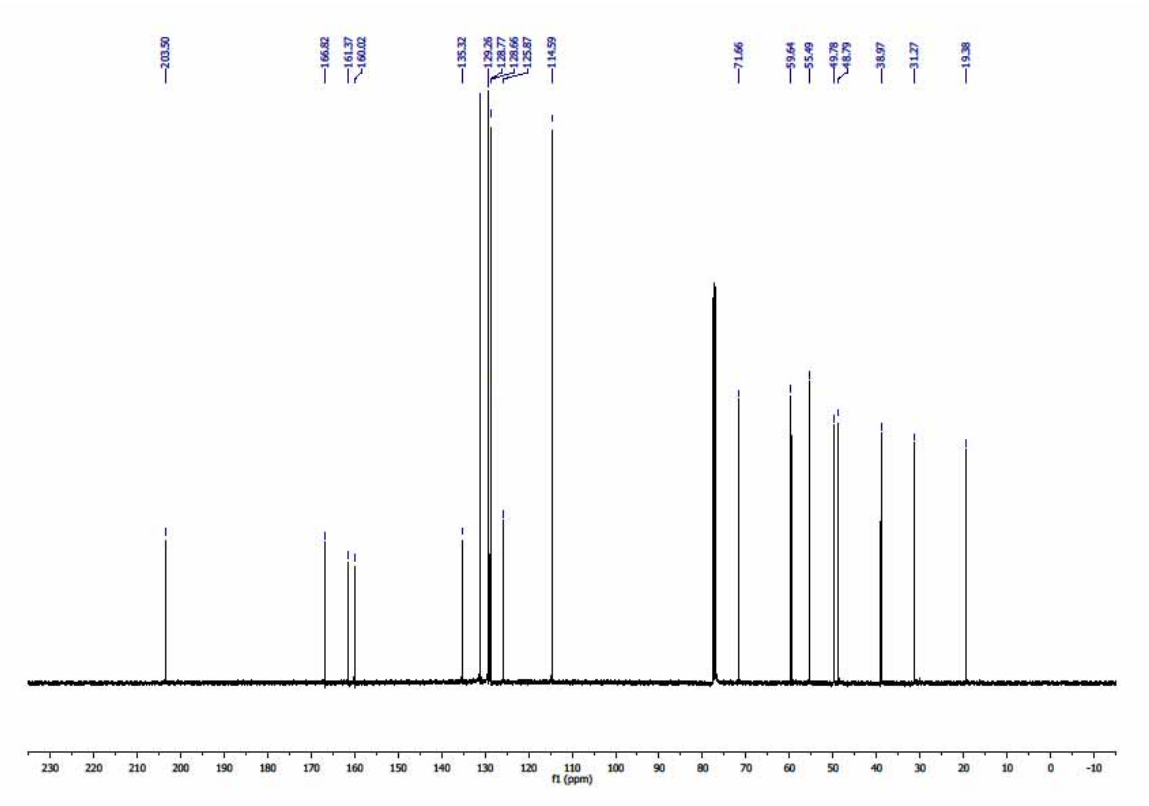

$^{13}$C NMR spectrum of **13**



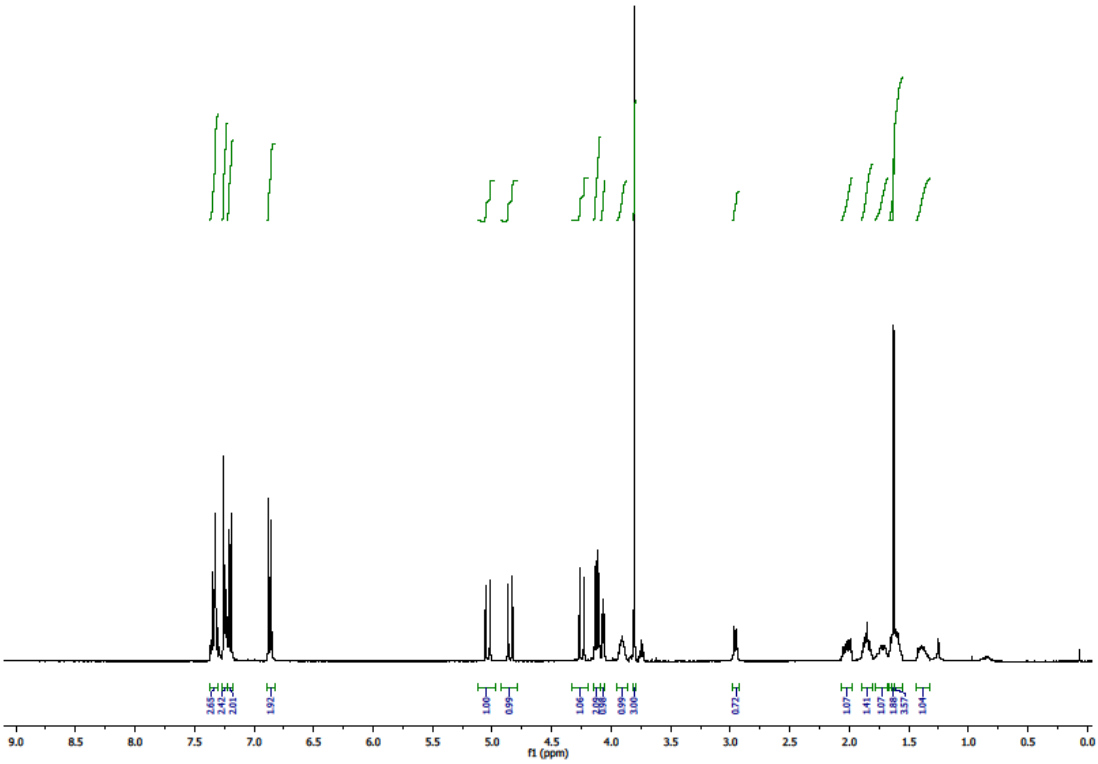
$^{1}$H NMR spectrum of **14**



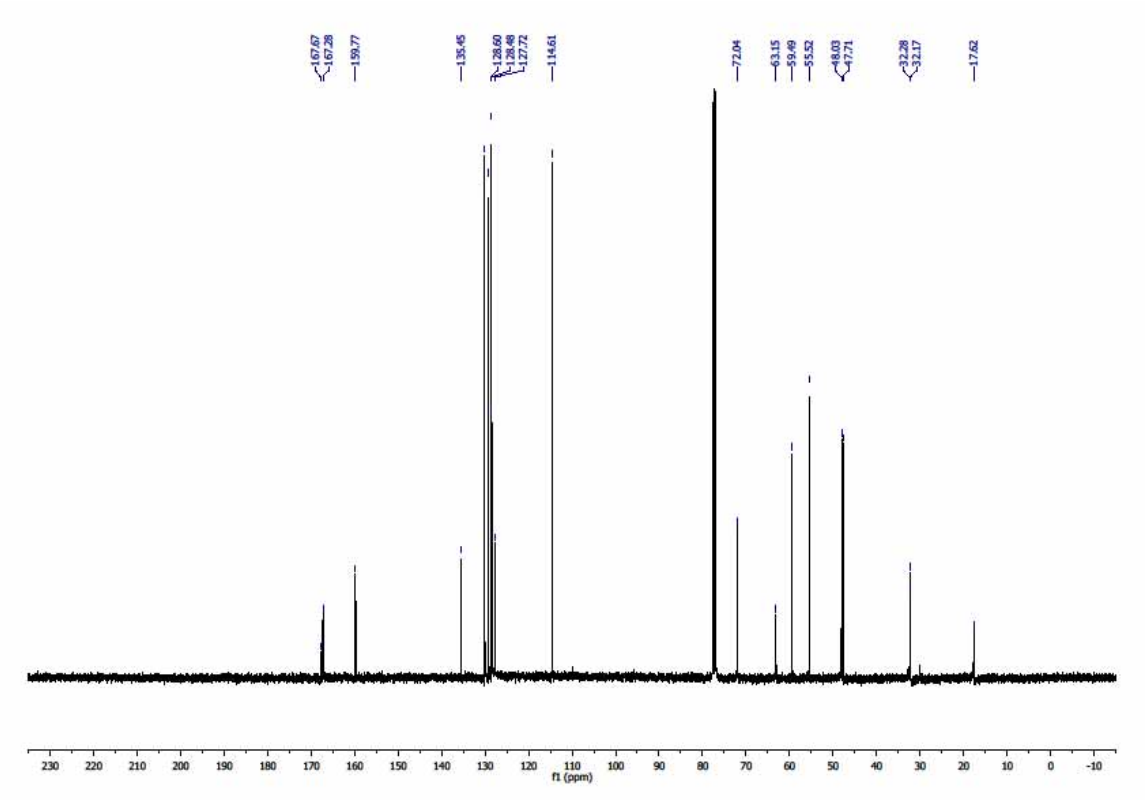

$^{13}$C NMR spectrum of **14**



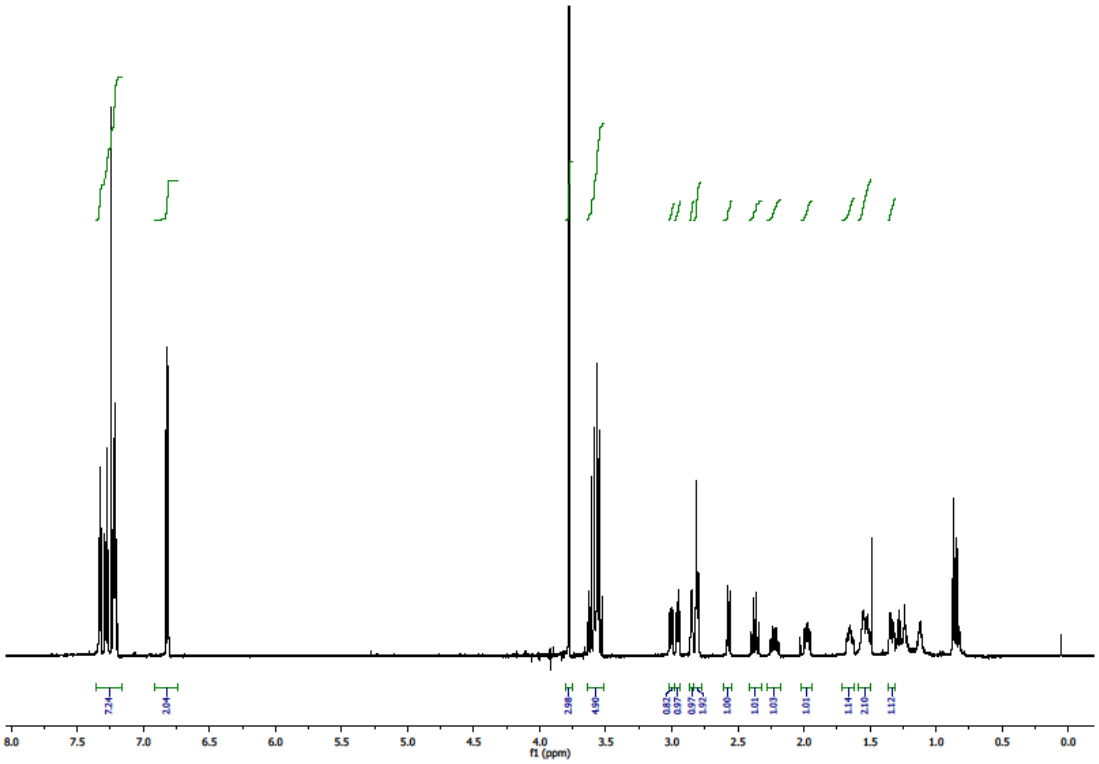
$^{1}$H NMR spectrum of **15a**



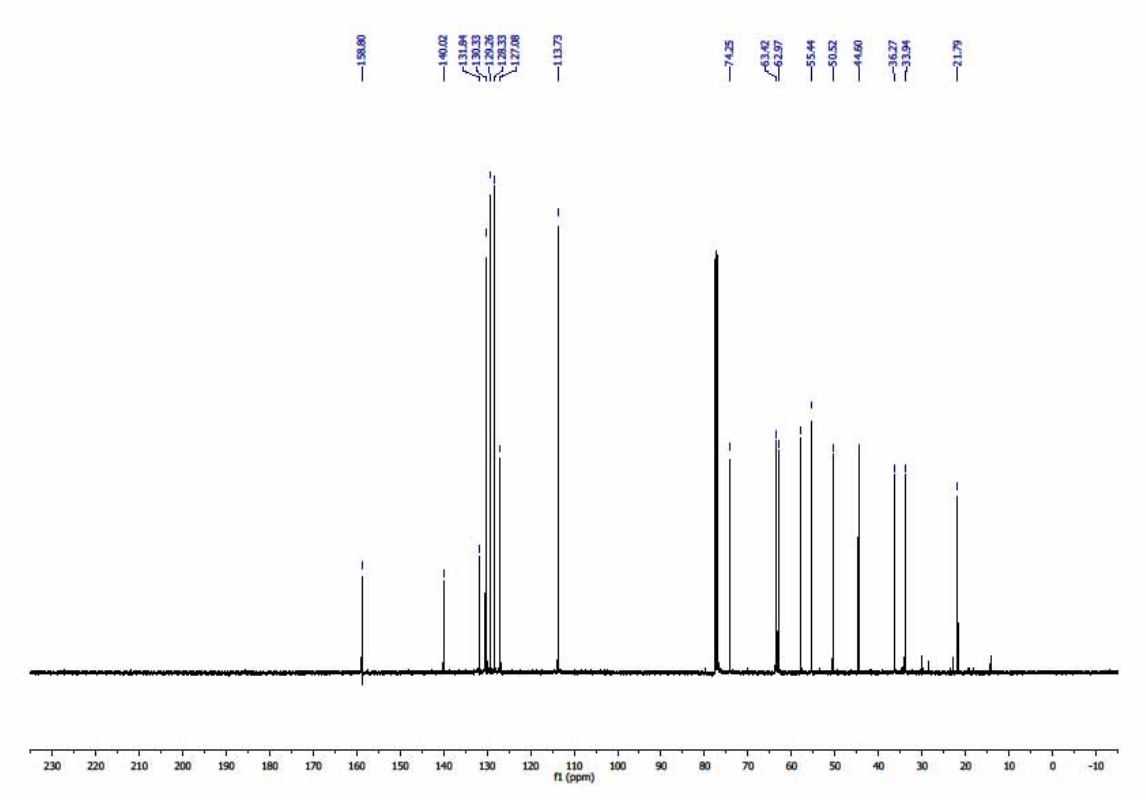

$^{13}$C NMR spectrum of **15a**



$^{1}$H NMR spectrum of **16a**




$^{13}$C NMR spectrum of **16a**



HPLC Chromatogram of **16a**

# HPLC

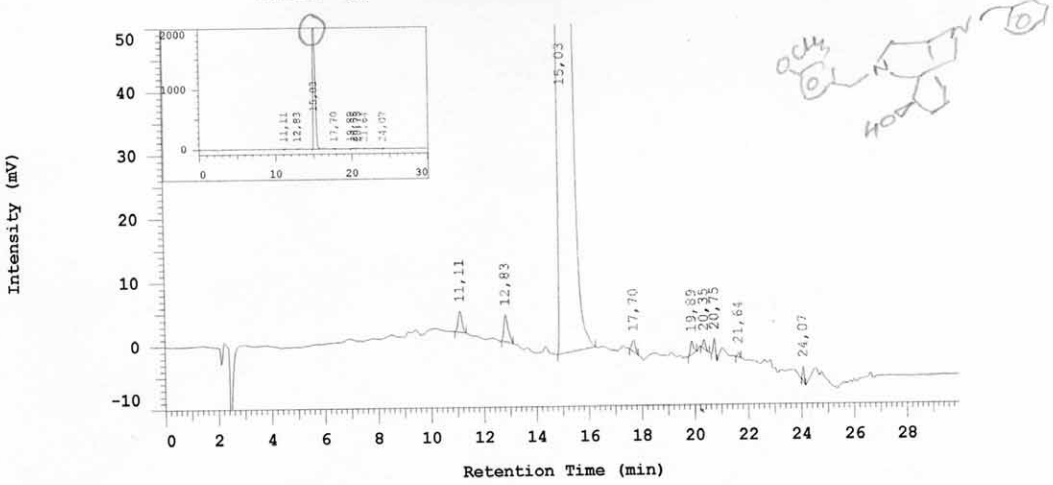
Analyzed: 28.05.09 13:55

Data Path: D:\WIN32APP\HSM\Chromni\DATA\0255\
Application: Chromni
**Sample Name: S108**
Injection from this vial: 1 of 1

Reported: 29.05.09 09:04
Processed: 29.05.09 09:04

Series:0255
Vial Number: 2
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1




**Acquisition Method: Chromni MeOH**
Blank Subtr Sample Name: MeOH
Column Type: 010
Solvent A: Wasser + 0,05%TFA

Developed by: Christian
Solvent C: MeOH +0,05% TFA

| No. | RT | Area | Conc 1 | BC |
|---|---|---|---|---|
| 1 | 11,11 | 32671 | 0,082 | MC |
| 2 | 12,83 | 46240 | 0,115 | MC |
| 3 | 15,03 | 39950547 | 99,665 | MC |
| 4 | 17,70 | 16774 | 0,042 | BB |
| 5 | 19,89 | 15521 | 0,039 | BB |
| 6 | 20,35 | 8738 | 0,022 | MC |
| 7 | 20,75 | 0 | 0,000 | |
| 8 | 21,64 | 3815 | 0,010 | MC |
| 9 | 24,07 | 10538 | 0,026 | BB |
| | | 40084844 | 100,000 | |

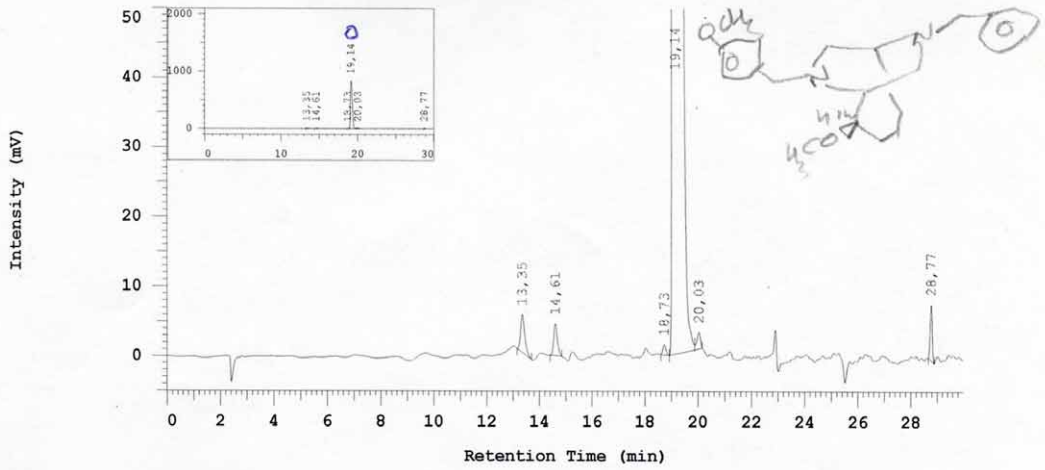
Peak rejection level: 0

HPLC Chromatogram of **16b**

# HPLC

Analyzed: 31.07.08 01:37
Reported: 31.07.08 16:29
Processed: 31.07.08 16:29

Data Path: D:\WIN32APP\HSM\Christoph\DATA\1487\
Application: Christoph
Series:1487
**Sample Name: S178**
Vial Number: 11
Injection from this vial: 1 of 1
Vial Type: UNK
Volume: 5,0 ul
Chrom Type: HPLC Channel : 1




**Acquisition Method: Chromni**
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

| No. | RT | Area | Conc 1 | BC |
|---|---|---|---|---|
| 1 | 13,35 | 59731 | 0,455 | BB |
| 2 | 14,61 | 43652 | 0,332 | MC |
| 3 | 18,73 | 11753 | 0,090 | BB |
| 4 | 19,14 | 12951785 | 98,626 | MC |
| 5 | 20,03 | 22374 | 0,170 | MC |
| 6 | 28,77 | 42965 | 0,327 | MC |
| | | 13132260 | 100,000 | |

Peak rejection level: 0

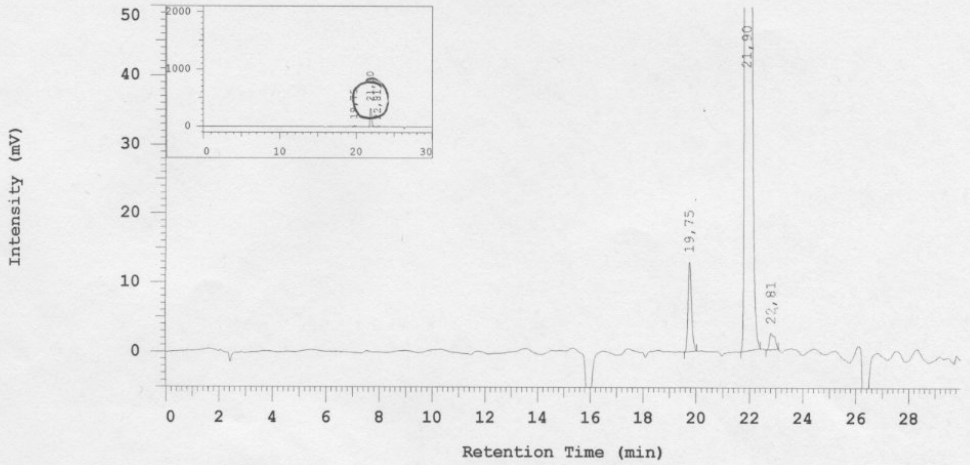
HPLC Chromatogram of **16d**

# HPLC

Analyzed: 24.04.08 00:05
Reported: 24.04.08 09:52
Processed: 24.04.08 09:52

Data Path: D:\WIN32APP\HSM\Christoph\DATA\1223\
Application: Christoph
Series:1223
**Sample Name: S119**
Vial Number: 6
Injection from this vial: 1 of 1
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1




**Acquisition Method: Chromni**
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

| No. | RT | Area | Conc 1 | BC |
|---|---|---|---|---|
| 1 | 19,75 | 115464 | 2,903 | MC |
| 2 | 21,90 | 3828937 | 96,264 | MC |
| 3 | 22,81 | 33143 | 0,833 | MC |
| | | 3977544 | 100,000 | |

Peak rejection level: 0

HPLC Chromatogram of **16e**

# HPLC

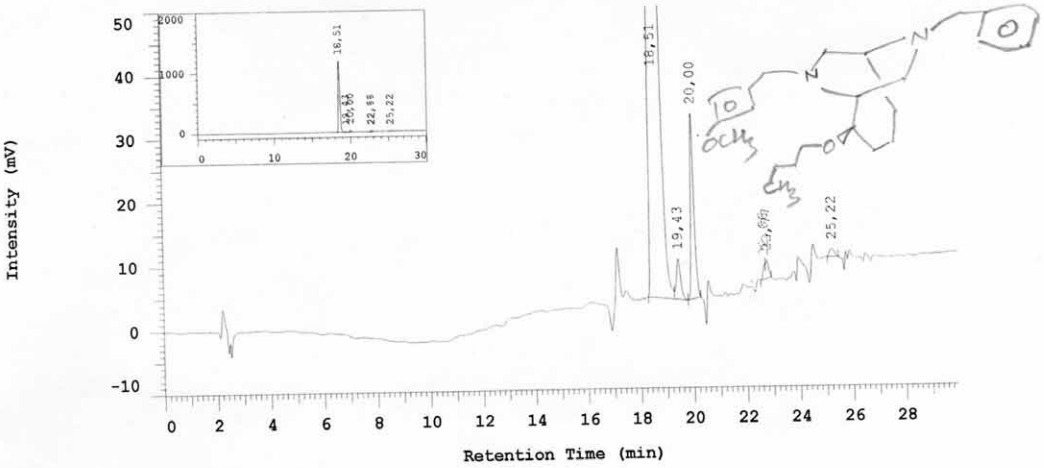
Analyzed: 22.07.09 23:22

Data Path: D:\WIN32APP\HSM\Chromni\DATA\0417\
Application: Chromni
**Sample Name: S338**
Injection from this vial: 1 of 1

Reported: 23.07.09 19:24
Processed: 23.07.09 19:24

Series:0417
Vial Number: 5
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1




**Acquisition Method: Chromni MeOH**
Blank Subtr Sample Name: MeOH
Column Type: 010
Solvent A: Wasser + 0,05%TFA

Developed by: Christian
Solvent C: MeOH +0,05% TFA

| No. | RT | Area | Conc 1 | BC |
|---|---|---|---|---|
| 1 | 18,51 | 15390100 | 97,682 | MC |
| 2 | 19,43 | 67691 | 0,430 | MC |
| 3 | 20,00 | 249072 | 1,581 | MC |
| 4 | 22,66 | 12407 | 0,079 | MC |
| 5 | 22,77 | 21326 | 0,135 | VB |
| 6 | 25,22 | 14756 | 0,094 | MC |
| | | 15755352 | 100,000 | |

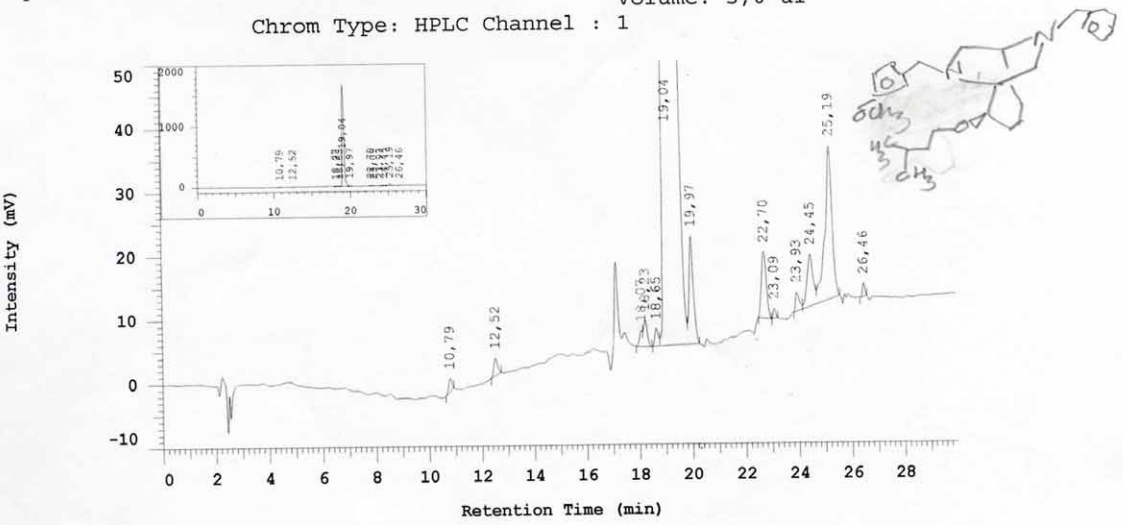
Peak rejection level: 0

HPLC Chromatogram of **16f**

# HPLC

Analyzed: 23.07.09 00:09
Reported: 23.07.09 19:29
Processed: 23.07.09 19:29

Data Path: D:\WIN32APP\HSM\Chromni\DATA\0418\
Application: Chromni
**Sample Name: S340**
Injection from this vial: 1 of 1
Series:0418
Vial Number: 6
Vial Type: UNK
Volume: 5,0 ul
Chrom Type: HPLC Channel : 1




**Acquisition Method: Chromni MeOH**
Blank Subtr Sample Name: MeOH
Column Type: 010
Developed by: Christian
Solvent A: Wasser + 0,05%TFA
Solvent C: MeOH +0,05% TFA

| No. | RT | Area | Conc 1 | BC |
|---|---|---|---|---|
| 1 | 10,79 | 16045 | 0,060 | MC |
| 2 | 12,52 | 26992 | 0,100 | MC |
| 3 | 18,07 | 17525 | 0,065 | MC |
| 4 | 18,23 | 42798 | 0,159 | VB |
| 5 | 18,65 | 24201 | 0,090 | MC |
| 6 | 19,04 | 25837716 | 96,002 | MC |
| 7 | 19,97 | 189061 | 0,702 | MC |
| 8 | 22,70 | 133118 | 0,495 | MC |
| 9 | 23,09 | 9729 | 0,036 | MC |
| 10 | 23,93 | 28993 | 0,108 | MC |
| 11 | 24,45 | 126980 | 0,472 | MC |
| 12 | 25,19 | 447733 | 1,664 | MC |
| 13 | 26,46 | 12774 | 0,047 | MC |
| | | 26913665 | 100,000 | |

Peak rejection level: 0

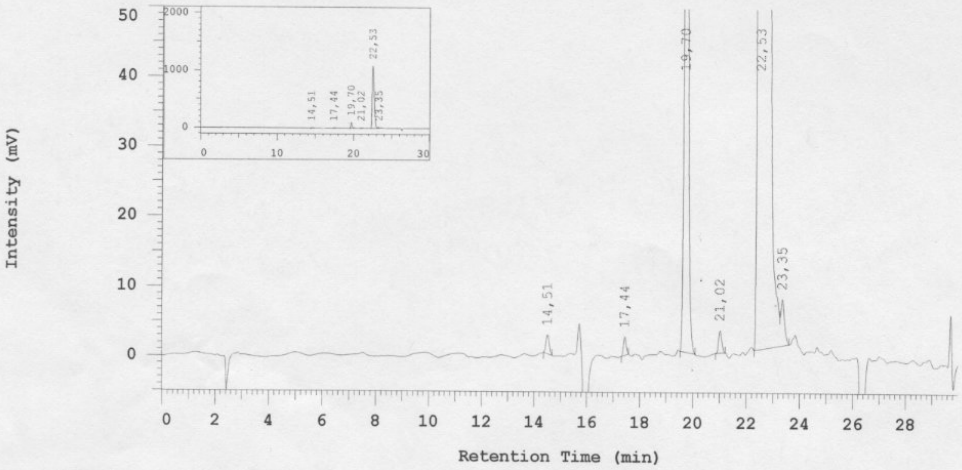
HPLC Chromatogram of **16g**

# HPLC

Analyzed: 23.04.08 23:24
Reported: 24.04.08 09:51
Processed: 24.04.08 09:50

Data Path: D:\WIN32APP\HSM\Christoph\DATA\1222\
Application: Christoph
Series:1222
**Sample Name: S118**
Vial Number: 5
Injection from this vial: 1 of 1
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1




**Acquisition Method: Chromni**
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

| No. | RT | Area | Conc 1 | BC |
|---|---|---|---|---|
| 1 | 14,51 | 23472 | 0,120 | MC |
| 2 | 17,44 | 18688 | 0,095 | MC |
| 3 | 19,70 | 960193 | 4,902 | MC |
| 4 | 21,02 | 26320 | 0,134 | MC |
| 5 | 22,53 | 18491832 | 94,413 | MC |
| 6 | 23,35 | 65532 | 0,335 | MC |
| | | 19586037 | 100,000 | |

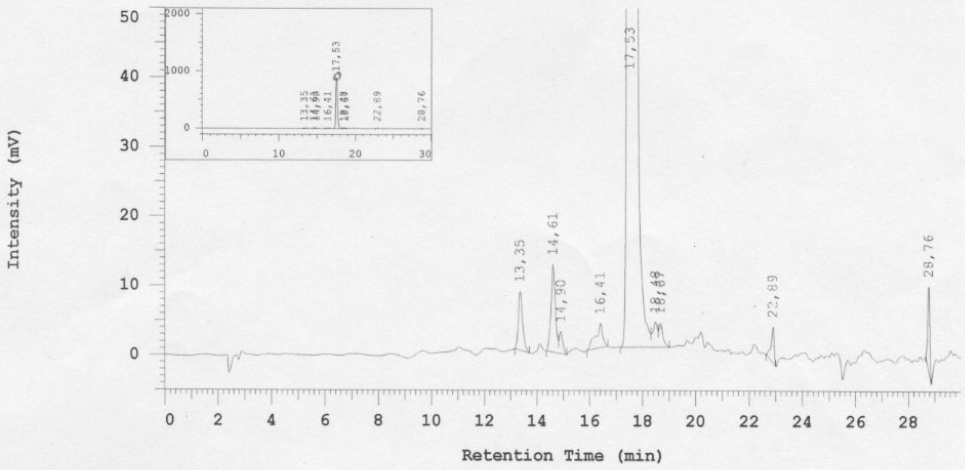
Peak rejection level: 0

HPLC Chromatogram of **24**

# HPLC

Analyzed: 31.07.08 00:56
Reported: 31.07.08 16:25
Processed: 31.07.08 16:25

Data Path: D:\WIN32APP\HSM\Christoph\DATA\1486\
Application: Christoph
Series:1486
**Sample Name: S174**
Vial Number: 10
Injection from this vial: 1 of 1
Vial Type: UNK
Volume: 5,0 ul
Chrom Type: HPLC Channel : 1




**Acquisition Method: Chromni**
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

| No. | RT | Area | Conc 1 | BC |
|---|---|---|---|---|
| 1 | 13,35 | 92900 | 0,708 | MC |
| 2 | 14,61 | 143531 | 1,094 | MC |
| 3 | 14,90 | 30483 | 0,232 | MC |
| 4 | 16,41 | 65989 | 0,503 | MC |
| 5 | 17,53 | 12603794 | 96,024 | MC |
| 6 | 18,48 | 45381 | 0,346 | MC |
| 7 | 18,67 | 37459 | 0,285 | MC |
| 8 | 22,89 | 41045 | 0,313 | BB |
| 9 | 28,76 | 65123 | 0,496 | MC |
| | | 13125705 | 100,000 | |

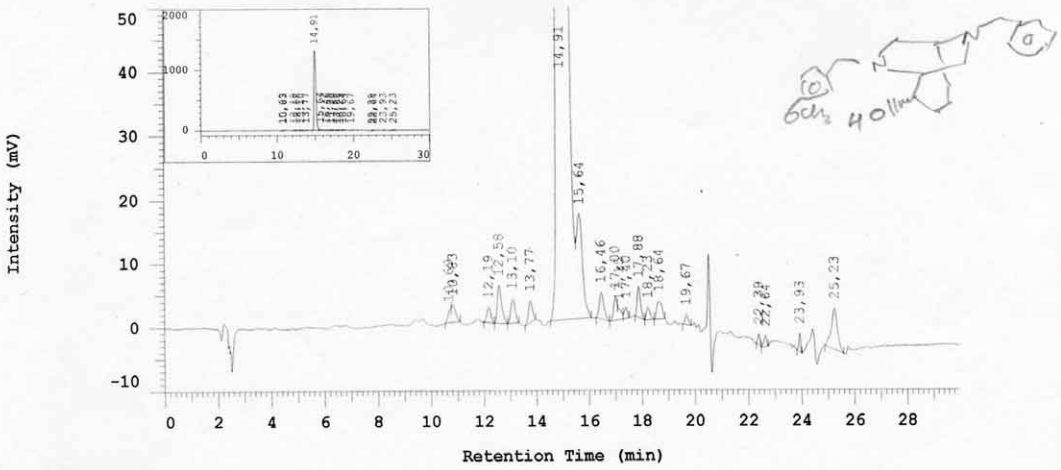
Peak rejection level: 0

HPLC Chromatogram of **25a**

# HPLC

Analyzed: 23.07.09 00:55
Reported: 23.07.09 19:32
Processed: 23.07.09 19:32

Data Path: D:\WIN32APP\HSM\Chromni\DATA\0419\
Application: Chromni
Series:0419
**Sample Name: S3671**
Vial Number: 7
Vial Type: UNK
Injection from this vial: 1 of 1
Volume: 5,0 ul
Chrom Type: HPLC Channel : 1




**Acquisition Method: Chromni MeOH**
Blank Subtr Sample Name: MeOH
Column Type: 010
Developed by: Christian
Solvent A: Wasser + 0,05%TFA
Solvent C: MeOH +0,05% TFA

| No. | RT | Area | Conc 1 | BC |
|---|---|---|---|---|
| 1 | 10,69 | 15273 | 0,068 | MC |
| 2 | 10,83 | 29712 | 0,133 | MC |
| 3 | 12,19 | 25600 | 0,115 | BB |
| 4 | 12,58 | 66222 | 0,296 | BB |
| 5 | 13,10 | 42761 | 0,191 | BB |
| 6 | 13,77 | 35386 | 0,158 | MC |
| 7 | 14,91 | 21486497 | 96,183 | MC |
| 8 | 15,64 | 272962 | 1,222 | MC |
| 9 | 16,46 | 50802 | 0,227 | MC |
| 10 | 17,00 | 31077 | 0,139 | BV |
| 11 | 17,15 | 17788 | 0,080 | MC |
| 12 | 17,40 | 14495 | 0,065 | BB |
| 13 | 17,88 | 41733 | 0,187 | MC |
| 14 | 18,23 | 18296 | 0,082 | MC |
| 15 | 18,64 | 39123 | 0,175 | MC |
| 16 | 19,67 | 12624 | 0,057 | MC |
| 17 | 22,39 | 10086 | 0,045 | MC |
| 18 | 22,64 | 11753 | 0,053 | MC |
| 19 | 23,93 | 13091 | 0,059 | BB |
| 20 | 25,23 | 103857 | 0,465 | MC |
| | | 22339138 | 100,000 | |

Peak rejection level: 0

HPLC Chromatogram of **25b**

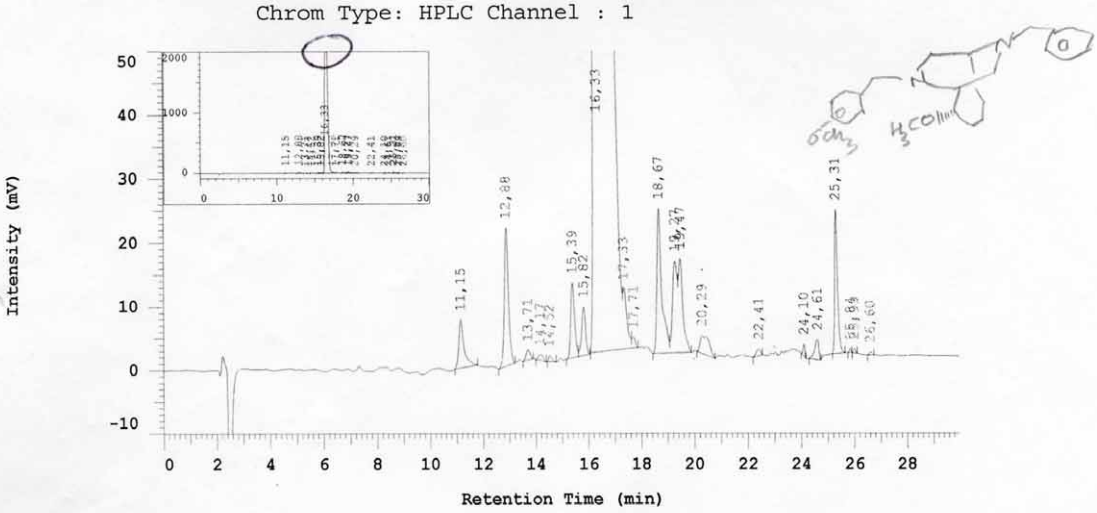
# HPLC

Analyzed: 24.06.09 20:12
Reported: 25.06.09 08:28
Processed: 25.06.09 08:28

Data Path: D:\WIN32APP\HSM\Chromni\DATA\0329\
Application: Chromni
**Sample Name: S368**
Injection from this vial: 1 of 1

Series:0329
Vial Number: 2
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1




**Acquisition Method: Chromni MeOH**
Blank Subtr Sample Name: MeOH
Column Type: 010
Developed by: Christian
Solvent A: Wasser + 0,05%TFA
Solvent C: MeOH +0,05% TFA

| No. | RT | Area | Conc 1 | BC |
|---|---|---|---|---|
| 1 | 11,15 | 104306 | 0,175 | MC |
| 2 | 12,88 | 229732 | 0,386 | BB |
| 3 | 13,71 | 16343 | 0,027 | BB |
| 4 | 14,17 | 10996 | 0,018 | MC |
| 5 | 14,52 | 7291 | 0,012 | MC |
| 6 | 15,39 | 119531 | 0,201 | MC |
| 7 | 15,82 | 78579 | 0,132 | MC |
| 8 | 16,33 | 57910854 | 97,265 | MC |
| 9 | 17,33 | 105967 | 0,178 | MC |
| 10 | 17,71 | 16386 | 0,028 | MC |
| 11 | 18,67 | 288180 | 0,484 | MC |
| 12 | 19,27 | 174670 | 0,293 | MC |
| 13 | 19,47 | 178491 | 0,300 | MC |
| 14 | 20,29 | 68636 | 0,115 | BB |
| 15 | 22,41 | 11197 | 0,019 | MC |
| 16 | 24,10 | 8431 | 0,014 | MC |
| 17 | 24,61 | 33858 | 0,057 | MC |
| 18 | 25,31 | 166664 | 0,280 | MC |
| 19 | 25,84 | 2686 | 0,005 | MC |
| 20 | 25,99 | 3466 | 0,006 | MC |
| 21 | 26,60 | 2958 | 0,005 | MC |
| | | 59539222 | 100,000 | |

Peak rejection level: 0

HPLC Chromatogram of **25c**

# HPLC

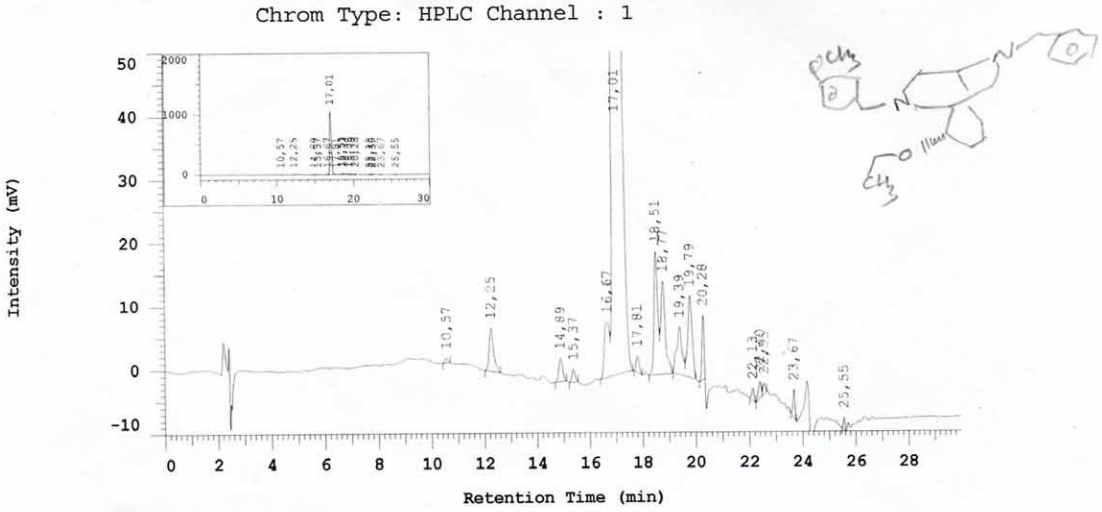
Analyzed: 01.07.09 22:54

Reported: 02.07.09 11:25
Processed: 02.07.09 11:25

Data Path: D:\WIN32APP\HSM\Chromni\DATA\0349\
Application: Chromni
**Sample Name: S371**
Injection from this vial: 1 of 1

Series:0349
Vial Number: 5
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1




**Acquisition Method: Chromni MeOH**
Blank Subtr Sample Name: MeOH
Column Type: 010
Developed by: Christian
Solvent A: Wasser + 0,05%TFA
Solvent C: MeOH +0,05% TFA

| No. | RT | Area | Conc 1 | BC |
|---|---|---|---|---|
| 1 | 10,57 | 5810 | 0,038 | MC |
| 2 | 12,25 | 77567 | 0,501 | MC |
| 3 | 14,89 | 35912 | 0,232 | MC |
| 4 | 15,37 | 17090 | 0,110 | MC |
| 5 | 16,67 | 115669 | 0,748 | MC |
| 6 | 17,01 | 14469361 | 93,520 | MC |
| 7 | 17,81 | 21185 | 0,137 | MC |
| 8 | 18,51 | 184918 | 1,195 | MC |
| 9 | 18,77 | 170564 | 1,102 | MC |
| 10 | 19,39 | 104110 | 0,673 | MC |
| 11 | 19,79 | 146840 | 0,949 | MC |
| 12 | 20,28 | 52276 | 0,338 | MC |
| 13 | 22,13 | 11901 | 0,077 | MC |
| 14 | 22,40 | 18683 | 0,121 | BB |
| 15 | 22,55 | 9697 | 0,063 | BB |
| 16 | 23,67 | 22102 | 0,143 | BB |
| 17 | 25,55 | 8268 | 0,053 | MC |
| | | 15471953 | 100,000 | |

Peak rejection level: 0

HPLC Chromatogram of **25g**

# HPLC

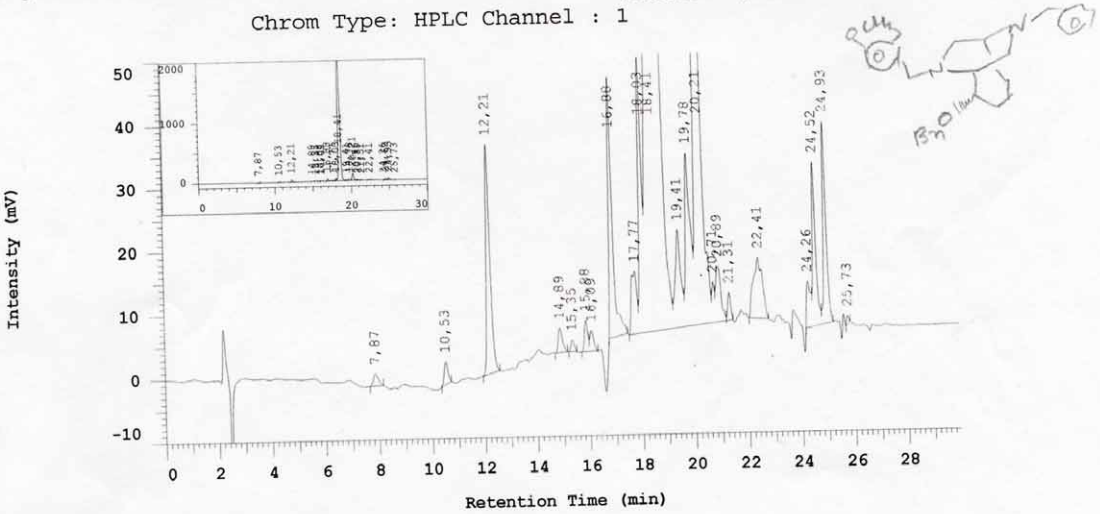
Analyzed: 01.07.09 22:08

Reported: 02.07.09 11:23
Processed: 02.07.09 11:23

Data Path: D:\WIN32APP\HSM\Chromni\DATA\0348\
Application: Chromni
**Sample Name: S369**
Injection from this vial: 1 of 1

Series:0348
Vial Number: 4
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1




**Acquisition Method: Chromni MeOH**
Blank Subtr Sample Name: MeOH
Column Type: 010
Solvent A: Wasser + 0,05%TFA

Developed by: Christian
Solvent C: MeOH +0,05% TFA

| No. | RT | Area | Conc 1 | BC |
|---|---|---|---|---|
| 1 | 7,87 | 24109 | 0,060 | MC |
| 2 | 10,53 | 34487 | 0,085 | MC |
| 3 | 12,21 | 368411 | 0,910 | MC |
| 4 | 14,89 | 41666 | 0,103 | MC |
| 5 | 15,35 | 15094 | 0,037 | MC |
| 6 | 15,88 | 42121 | 0,104 | MC |
| 7 | 16,09 | 32457 | 0,080 | MC |
| 8 | 16,88 | 399527 | 0,987 | MC |
| 9 | 17,77 | 140606 | 0,347 | MC |
| 10 | 18,03 | 378163 | 0,934 | MC |
| 11 | 18,41 | 35752816 | 88,289 | MC |
| 12 | 19,41 | 224388 | 0,554 | MC |
| 13 | 19,78 | 367631 | 0,908 | MC |
| 14 | 20,21 | 1698430 | 4,194 | MC |
| 15 | 20,71 | 43275 | 0,107 | MC |
| 16 | 20,89 | 119544 | 0,295 | MC |
| 17 | 21,31 | 32619 | 0,081 | MC |
| 18 | 22,41 | 220867 | 0,545 | MC |
| 19 | 24,26 | 78323 | 0,193 | MC |
| 20 | 24,52 | 220223 | 0,544 | MC |
| 21 | 24,93 | 254044 | 0,627 | MC |
| 22 | 25,73 | 6547 | 0,016 | MC |
| | | 40495348 | 100,000 | |

Peak rejection level: 0

HPLC Chromatogram of **26**

# HPLC

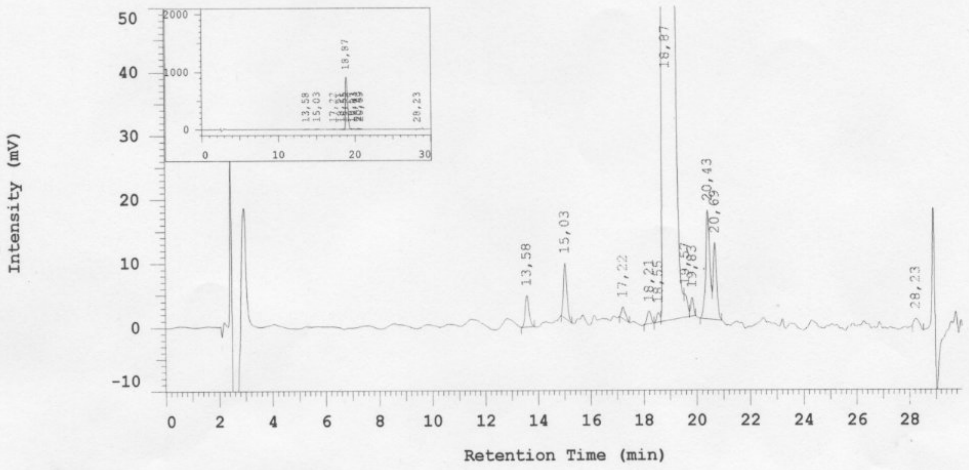
Acetonitril - Methode

Analyzed: 06.08.09 12:30
Reported: 06.08.09 15:03
Processed: 06.08.09 15:03

Data Path: D:\WIN32APP\HSM\Chromni\DATA\0497\
Application: Chromni
**Sample Name: S156**
Injection from this vial: 1 of 1

Series:0497
Vial Number: 21
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1




**Acquisition Method: Chromni**
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

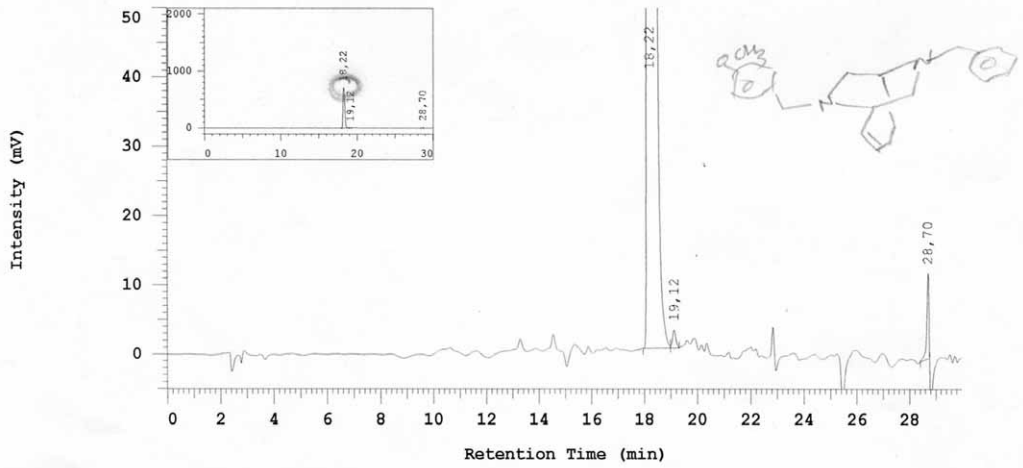
| No. | RT | Area | Conc 1 | BC |
|---|---|---|---|---|
| 1 | 13,58 | 49837 | 0,293 | MC |
| 2 | 15,03 | 76779 | 0,452 | MC |
| 3 | 17,22 | 18309 | 0,108 | BB |
| 4 | 18,21 | 20230 | 0,119 | MC |
| 5 | 18,55 | 11756 | 0,069 | MC |
| 6 | 18,87 | 16479777 | 96,946 | MC |
| 7 | 19,57 | 31671 | 0,186 | MC |
| 8 | 19,83 | 21092 | 0,124 | MC |
| 9 | 20,43 | 182055 | 1,071 | MC |
| 10 | 20,69 | 107416 | 0,632 | MC |
| 11 | 28,23 | 0 | 0,000 | |
| | | 16998922 | 100,000 | |

Peak rejection level: 0

HPLC Chromatogram of **27**

# HPLC

Analyzed: 29.07.08 21:32
Reported: 30.07.08 09:21
Processed: 30.07.08 09:21
Data Path: D:\WIN32APP\HSM\Christoph\DATA\1468\
Application: Christoph
Series:1468
**Sample Name: S177**
Vial Number: 9
Vial Type: UNK
Injection from this vial: 1 of 1
Volume: 5,0 ul
Chrom Type: HPLC Channel : 1




**Acquisition Method: Chromni**
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

| No. | RT | Area | Conc 1 | BC |
|---|---|---|---|---|
| 1 | 18,22 | 10424015 | 99,157 | BB |
| 2 | 19,12 | 21875 | 0,208 | MC |
| 3 | 28,70 | 66781 | 0,635 | MC |
| | | 10512671 | 100,000 | |

Peak rejection level: 0

HPLC Chromatogram of **31**

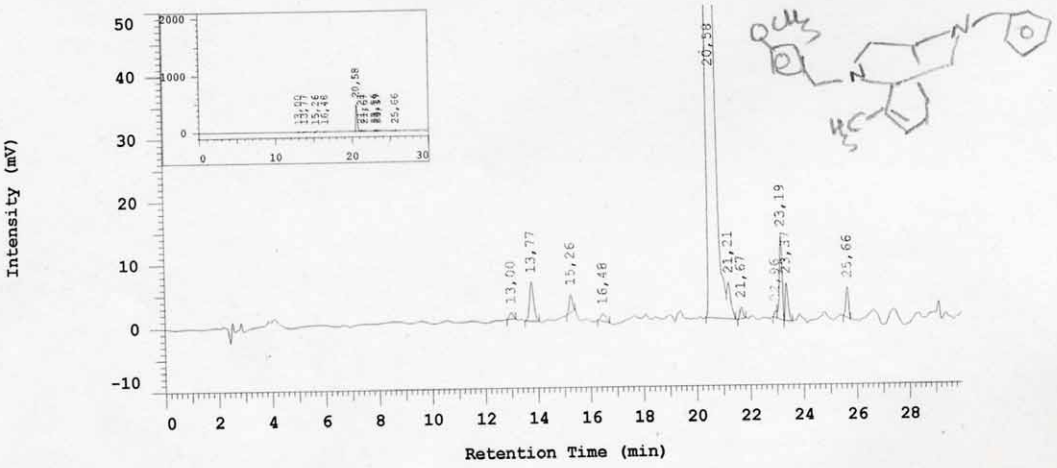
# HPLC

Analyzed: 12.01.10 16:50
Reported: 04.06.10 11:51
Processed: 12.01.10 18:25

Data Path: D:\WIN32APP\HSM\Chromni\DATA\1010\
Application: Chromni
**Sample Name: 454-1**
Injection from this vial: 1 of 1

Series:1010
Vial Number: 4
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1




**Acquisition Method: Chromni**
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

| No. | RT | Area | Conc 1 | BC |
|---|---|---|---|---|
| 1 | 13,00 | 9902 | 0,172 | BB |
| 2 | 13,77 | 66713 | 1,162 | MC |
| 3 | 15,26 | 23063 | 0,402 | MC |
| 4 | 16,48 | 16806 | 0,293 | MC |
| 5 | 20,58 | 5376983 | 93,628 | MC |
| 6 | 21,21 | 58579 | 1,020 | MC |
| 7 | 21,67 | 14570 | 0,254 | MC |
| 8 | 22,96 | 6452 | 0,112 | MC |
| 9 | 23,19 | 92765 | 1,615 | MC |
| 10 | 23,37 | 43289 | 0,754 | BB |
| 11 | 25,66 | 33823 | 0,589 | MC |
| | | 5742945 | 100,000 | |

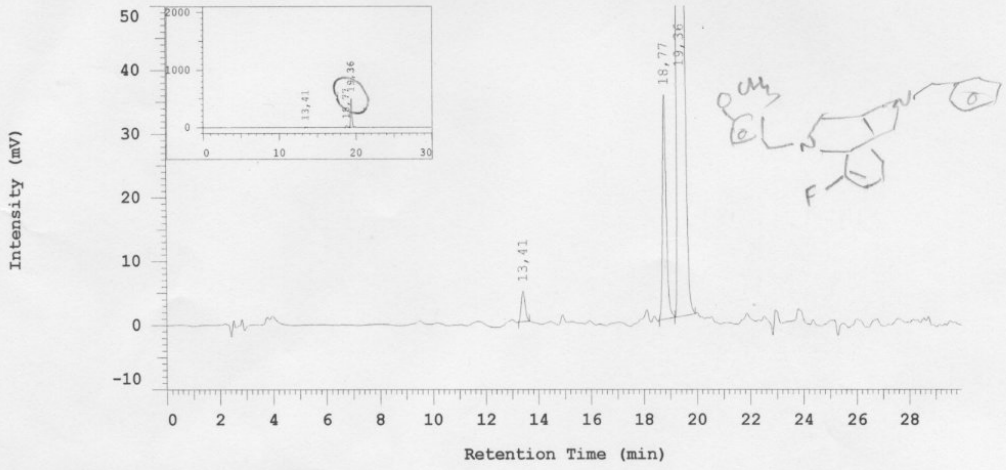
Peak rejection level: 0

HPLC Chromatogram of **35**

# HPLC

Analyzed: 18.01.10 15:45
Reported: 18.01.10 17:59
Processed: 18.01.10 17:59

Data Path: D:\WIN32APP\HSM\Chromni\DATA\1054\
Application: Chromni
Series:1054
**Sample Name: 4573**
Vial Number: 6
Injection from this vial: 1 of 1
Vial Type: UNK
Volume: 5,0 ul
Chrom Type: HPLC Channel : 1




**Acquisition Method: Chromni**
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

| No. | RT | Area | Conc 1 | BC |
|---|---|---|---|---|
| 1 | 13,41 | 47817 | 0,792 | MC |
| 2 | 18,77 | 330776 | 5,482 | MC |
| 3 | 19,36 | 5655197 | 93,725 | MC |
| | | 6033790 | 100,000 | |

Peak rejection level: 0

HPLC Chromatogram of **36**

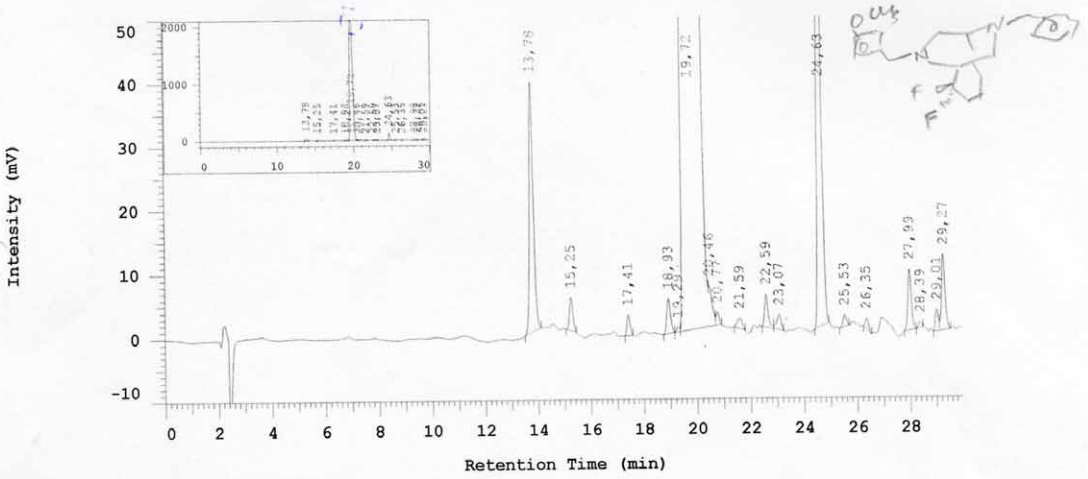
# HPLC

Analyzed: 17.12.09 06:57
Reported: 17.12.09 13:43
Processed: 17.12.09 13:43

Data Path: D:\WIN32APP\HSM\Chromni\DATA\0967\
Application: Chromni
**Sample Name: S441**
Injection from this vial: 1 of 1

Series:0967
Vial Number: 16
Vial Type: UNK
Volume: 5,0 ul

Chrom Type: HPLC Channel : 1




**Acquisition Method: Chromni**
Blank Subtr Sample Name: ACN
Column Type: 010
Developed by: Jens
Solvent A: Wasser + 0,05%TFA
Solvent B: ACN + 0,05%TFA

| No. | RT | Area | Conc 1 | BC |
|---|---|---|---|---|
| 1 | 13,78 | 408824 | 0,691 | BB |
| 2 | 15,25 | 45410 | 0,077 | MC |
| 3 | 17,41 | 25554 | 0,043 | MC |
| 4 | 18,93 | 53434 | 0,090 | BB |
| 5 | 19,29 | 6066 | 0,010 | MC |
| 6 | 19,72 | 57069280 | 96,450 | BV |
| 7 | 20,46 | 63776 | 0,108 | MC |
| 8 | 20,77 | 16143 | 0,027 | MC |
| 9 | 21,59 | 20549 | 0,035 | MC |
| 10 | 22,59 | 46522 | 0,079 | MC |
| 11 | 23,07 | 26064 | 0,044 | MC |
| 12 | 24,63 | 1128445 | 1,907 | MC |
| 13 | 25,53 | 15759 | 0,027 | MC |
| 14 | 26,35 | 13562 | 0,023 | MC |
| 15 | 27,99 | 85730 | 0,145 | BB |
| 16 | 28,39 | 7550 | 0,013 | BB |
| 17 | 29,01 | 26342 | 0,045 | BV |
| 18 | 29,27 | 110821 | 0,187 | VB |
| | | 59169831 | 100,000 | |

Peak rejection level: 0