Electronic Supplementary Material (ESI) for ChemComm.

The discovery of 9/8-ribbons, β/γ-peptides with curved shapes governed by a combined configuration-conformation code

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SUPPORTING INFORMATION

I. SYNTHESIS OF PEPTIDES 1-6 AND I-III

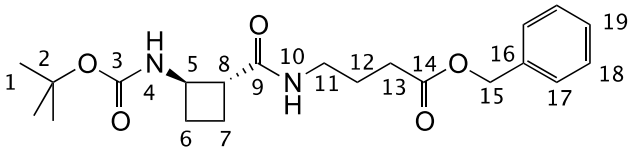
1. General Information

(1*R*,2*R*)-2-(*tert*-butyloxyamino)cyclobutane-1-carboxylic acid (Boc-*t*ACBC-OH) was obtained according to the published procedure.[1] Dichloromethane was dried over activated alumina, DMF was distilled from CaH_2. All other reagents and solvents were of commercial grade and were used without further purification. Flash chromatography was performed using Combiflash (Teledyne ISCO) with columns of 15−40 µm silica gel (SI60, Merck Chimie SAS). Analytical thin-layer chromatography was performed with 0.25 mm commercial silica gel plates (EMD, Silica Gel $60F_{254}$). TLC plates were visualized by UV fluorescence at 254 nm then revealed using a ninhydrin solution (14 mM in EtOH); retention factors (R_f) are given for such analyses. Routine nuclear magnetic resonance (NMR) data were acquired on Bruker spectrometers operating at 360, 400 or 600 MHz for ^{1}H and at 90 or 100 MHz for ^{13}C. Chemical shifts (δ) are reported in parts per million from tetramethylsilane. Splitting patterns for ^{1}H NMR signals are designated as: s (singlet), d (doublet), t (triplet), bs (broad singlet) and m (multiplet). Coupling constants (*J*) are reported in hertz. High-resolution mass spectrometry (HRMS) data were recorded using the electrospray ionization technique in positive mode (ESI+) with a MicroTOF-Q (Bruker) analyzer. Fourier-transform infrared absorption spectroscopy (IR) was performed for solutions in $CDCl_3$ (10 mM) retained in a 0.2 mm path length NaCl solution cell with a $CDCl_3$ background; spectra were recorded on a Spectrum One (Perkin-Elmer) spectrometer. Maximum absorbances (ν_{max}) are reported for significant bands in cm^{-1}. Melting points were obtained in open capillary tubes using a Büchi B-545 melting point apparatus. Optical rotations were measured on a Specord 205 instrument (Analytik-Jena) using a 10 cm quartz cell; values for $[\alpha]_D^T$ were obtained with the D-line of sodium at the indicated temperature *T*, using solutions of concentration (c) in units of $g \cdot 100\ mL^{-1}$.

2. Synthetic procedures for the preparation of peptides ***1***-***6*** and ***I***-***III***

*Linear synthetic procedure for peptides **1**, **3**, **5**, **I** and **II***

Boc-*t*ACBC-GABA-OBn (1):

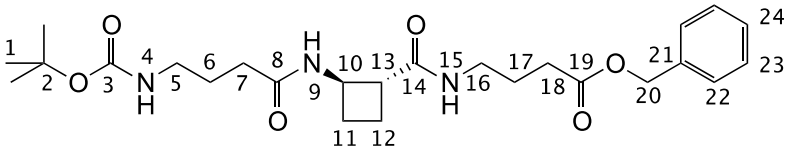


To a solution of Boc-*t*ACBC-OH (430 mg, 2 mmol, 1 eq.) in a 4 : 1 mixture of CH_2Cl_2 and DMF (4 mL : 1 mL) was added DIPEA (629 µL, 476 mg, 4 mmol, 2 eq.) followed by HATU (788 mg, 2.1 mmol, 1.05 eq.) The resulting mixture was stirred for 10 min at room temperature and the solution became brownish. After this, a solution of H-GABA-OBn (386 mg, 2 mmol, 1 eq.) and DIPEA (2.09 mL, 1.55 g, 12 mmol, 6 eq.) in CH_2Cl_2 (6 mL) was added and the reaction mixture was stirred overnight. Solvents were removed under reduced pressure. The crude product was dissolved in EtOAc and the resulting solution washed successively with a saturated solution of $NaHCO_3$, brine, 1 M HCl, then brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (gradient from 10/90 to 100/0: EtOAc/PE) to give Boc-*t*ACBC-GABA-OBn (**1**) as a white solid (483 mg, 62%). Mp: 116 °C; R_f 0.14 (50/50: EtOAc/PE); $[a]_D^{21}$ = −10 (*c.* 0.50, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.42 (s, 9H, 9H-1), 1.70-1.78 (m, 1H, H-6), 1.85-1.92 (m, 3H, H-7, 2H-12), 2.08-2.22 (m, 2H, H-7', H-6'), 2.46 (t, 2H, *J* = 7.6 Hz, 2H-13), 2.85-2.92 (m,

[1] V. Declerck and D. J. Aitken, *Amino Acids*, 2011, **41**, 587.

1H, H-8), 3.22-3.27 (m, 1H, H-11), 3.34-3.39 (m, 1H, H-11'), 4.05-4.13 (m, 1H, H-5), 4.91 (bs, 1H, H-4), 5.12 (s, 2H, 2H-15), 7.32-7.36 (m, 5H, 2H-17, 2H-18, H-19), 8.12 (bs, 1H, H-10); ^{13}C NMR (90 MHz, $CDCl_3$) δ 18.6 (C-7), 24.7 (C-6, C-12), 28.3 (C-1), 31.2 (C-13), 38.6 (C-11), 48.8 (C-5), 50.1 (C-8), 66.2 (C-15), 80.5 (C-2), 128.2, 128.2, 128.5 (C-17, C-18, C-19), 136.0 (C-16), 156.3 (C-3), 173.1, 173.1 (C-9, C-14); IR ($CDCl_3$) ν_{max} 1499, 1562, 1649, 1692, 1730, 3297 (br), 3447 cm^{-1}; HRMS (ESI): $[M+Na]^+$, theor. 413.2047 (calc. for $C_{21}H_{30}N_2NaO_5$), meas. 413.2065.

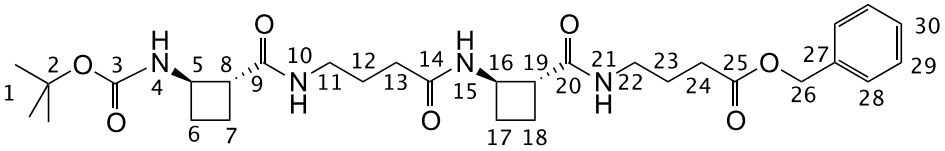
Boc-GABA-*t*ACBC-GABA-OBn (I):



To a solution of Boc-*t*ACBC-GABA-OBn (**1**) (483 mg, 1.2 mmol, 1 eq.) in CH_2Cl_2 (30 mL) was added TFA (2.85 mL, 4.24 g, 37 mmol, 30 eq.) at room temperature under argon atmosphere. The resulting yellowish mixture was stirred for 3 h. CH_2Cl_2 was then evaporated under reduced pressure. Toluene was added to co-evaporate the excess of TFA to leave TFA·H-*t*ACBC-GABA-OBn. This material was engaged directly in the coupling reaction.

To a solution of Boc-GABA-OH (258 mg, 1.2 mmol, 1 eq.) in a 4 : 1 mixture of CH_2Cl_2 and DMF (2 mL : 0.5 mL) was added DIPEA (415 µL, 310 mg, 2.4 mmol, 2 eq.) followed by HATU (473 mg, 1.3 mmol, 1.05 eq.). The resulting mixture was stirred for 10 min at room temperature and the solution became brownish. After this, a solution of TFA·H-*t*ACBC-GABA-OBn (see above, 1 eq.) and DIPEA (1.250 mL, 929 mg, 7.2 mmol, 6 eq.) in CH_2Cl_2 (4 mL) was added and the reaction mixture was stirred overnight. Solvents were removed under reduced pressure. The crude product was dissolved in EtOAc and the resulting solution washed successively with a saturated solution of $NaHCO_3$, brine, 1 M HCl, then brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (gradient from 10/90 to 100/0: EtOAc/PE) to give Boc-GABA-*t*ACBC-GABA-OBn (**I**) as a white solid (435 mg, 76%). Mp: 85 °C; R_f 0.57 (EtOAc); $[a]_D^{23}$ = –15 (*c*. 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H, 9H-1), 1.71-1.82 (m, 2H, 2H-6), 1.86-1.98 (m, 4H, H-11, H-12, 2H-17), 2.11-2.16 (m, 2H, H-11', H-12'), 2.23 (t, 1H, *J* = 6.5 Hz, H-18), 2.44 (t, 1H, *J* = 7.5 Hz, H-18'), 2.94-3.01 (m, 1H, H-13), 3.12 (bs, 2H, 2H-5), 3.29 (dt, 2H, *J* = 6.3 Hz, *J* = 6.5 Hz, 2H-16), 4.24-4.31 (m, 1H, H-10), 5.03 (bs, 1H, H-4), 5.11 (s, 2H, 2H-20), 7.34 (m, 5H, 2H-22, 2H-23, H-24), 7.59 (bs, 1H, H-9), 8.81 (bs, 1H, H-15); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 23.7 (C-11, C-12), 24.3 (C-17), 26.2 (C-6), 28.2 (C-1), 31.5 (C-18), 32.7 (C-7), 38.7 (C-16), 39.2 (C-5), 47.8 (C-10), 49.1 (C-13), 66.1 (C-20), 79.4 (C-2), 128.0, 128.1, 128.4 (C-22, C-23, C-24), 135.7 (C-21), 156.6 (C-3), 172.9 (C-8), 173.9 (C-14), 174.2 (C-19); IR ($CDCl_3$) ν_{max} 1514, 1565, 1647, 1697, 1729, 2980, 3280 (br), 3452 cm^{-1}; HRMS (ESI): $[M+Na]^+$, theor. 498.2575 (calc. for $C_{25}H_{37}N_3NaO_6$), meas. 498.2581.

Boc-[*t*ACBC-GABA]$_2$-OBn (3):

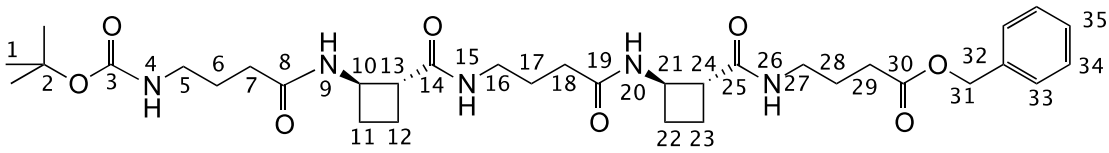


To a solution of Boc-GABA-*t*ACBC-GABA-OBn (**I**) (435 mg, 0.9 mmol, 1 eq.) in dry CH_2Cl_2 (22 mL) was added TFA (2.07 mL, 3.08 g, 27 mmol, 30 eq.) at room temperature under argon atmosphere. The resulting

yellowish mixture was stirred for 2 h. CH_2Cl_2 was then evaporated under reduced pressure. Toluene was added to co-evaporate the excess of TFA to give TFA·H-GABA-*t*ACBC-GABA-OBn. This material was engaged directly in the coupling reaction.

To a solution of Boc-*t*ACBC-OH (194 mg, 0.9 mmol, 1 eq.) in a 3 : 1 mixture of CH_2Cl_2 and DMF (1.5 mL : 0.5 mL) was added DIPEA (310 µL, 232 mg, 1.8 mmol, 2 eq.) followed by HATU (356 mg, 1 mmol, 1.05 eq.). The resulting mixture was stirred for 10 min at room temperature and the solution became brownish. After this, a solution of TFA·H-GABA-*t*ACBC-GABA-OBn (see above, 1 eq.) and DIPEA (940 µL, 696 mg, 5.4 mmol, 6 eq.) in CH_2Cl_2 (4 mL) was added and the reaction mixture was stirred overnight. Solvents were removed under reduced pressure. The crude product was dissolved in EtOAc and the resulting solution washed successively with a saturated solution of $NaHCO_3$, brine, 1 M HCl, then brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (gradient from 10/90 to 100/0: EtOAc/PE then gradient from 0/100 to 10/90: CH_3OH/CH_2Cl_2) to give Boc-[*t*ACBC-GABA]$_2$-OBn (**3**) as a white solid (300 mg, 58%). Mp: 197 °C; R_f 0.60 (10/90: CH_3OH/CH_2Cl_2); $[a]_D^{22}$ = –19 (*c.* 0.50, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.44 (s, 9H, 9H-1), 1.69-1.70 (m, 1H, H-12), 1.83-1.95 (m, 4H, H-6, H-12', 2H-23), 1.98-2.06 (m, 5H, 2H-7, H-17, 2H-18), 2.16-2.22 (m, 4H, H-6', 2H-13, H-17'), 2.46 (t, 2H, *J* = 7.5 Hz, 2H-24), 2.84-2.87 (m, 1H, H-8), 3.00-3.05 (m, 1H, H-19), 3.11-3.14 (bs, 1H, H-11), 3.29-3.32 (m, 2H, 2H-22), 3.43-3.45 (bs, 1H, H-11'), 4.21-4.24 (m, 1H, H-5), 4.35-4.37 (m, 1H, H-16), 5.11 (s, 2H, 2H-26), 5.58 (d, 1H, *J* = 7.3 Hz , H-4), 7.32-7.35 (m, 5H, 2H-28, 2H-29, H-30), 7.57 (bs, 1H, H-10), 7.91 (d, 1H, *J* = 6.7 Hz, H-15), 8.63 (t, 1H, *J* = 5.2 Hz, H-21); ^{13}C NMR (90 MHz, $CDCl_3$) δ 18.2, 18.3 (C-7, C-18), 24.4 (C-17), 24.8 (C-23), 25.1 (C-6), 26.2 (C-12), 28.3 (C-1), 29.7, 31.8 (C-24), 32.3 (C-13), 37.2 (C-11), 38.5 (C-22), 48.1 (C-16), 48.9 (C-5), 49.6 (C-19), 50.2 (C-8), 66.1 (C-26), 80.4 (C-2), 128.1, 128.5 (C-28, C-29, C-30), 136.0 (C-27), 156.1 (C-3), 173.3, 173.1 (C-14, C-20), 173.4 (C-25), 173.7 (C-9); IR ($CDCl_3$) ν_{max} 1469, 1499, 1560, 1600, 1647, 1692, 1704, 1717, 1731, 1793, 1812, 2982, 3280 (br), 3349, 3444 cm^{-1}; HRMS (ESI): $[M+Na]^+$, theor. 595.3102 (calc. for $C_{30}H_{44}N_4NaO_7$), meas. 595.3100.

Boc-GABA-[*t*ACBC-GABA]$_2$-OBn (II):

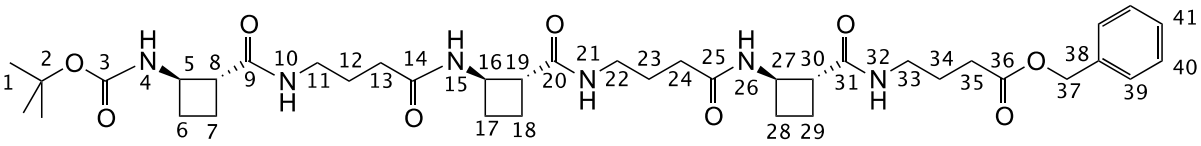


To a solution of Boc-[*t*ACBC-GABA]$_2$-OBn (**3**) (220 mg, 0.38 mmol, 1 eq.) in CH_2Cl_2 (10 mL) was added TFA (883 µL, 1.32 g, 11.5 mmol, 30 eq.) at room temperature under argon atmosphere. The resulting yellowish mixture was stirred for 2 h. CH_2Cl_2 was then evaporated under reduced pressure. Toluene was added to co-evaporate the excess of TFA to give TFA·H-[*t*ACBC-GABA]$_2$-OBn. This material was engaged directly in the coupling reaction.

To a solution of Boc-GABA-OH (82 mg, 0.38 mmol, 1 eq.) in a 1 : 2 mixture of CH_2Cl_2 and DMF (0.5 mL : 1 mL) was added DIPEA (120 µL, 90 mg, 0.76 mmol, 2 eq.) followed by HATU (150 mg, 0.40 mmol, 1.05 eq.). The resulting mixture was stirred for 10 min at room temperature and the solution became brownish. After this, a solution of TFA·H-[*t*ACBC-GABA]$_2$-OBn (see above, 1 eq.) and DIPEA (360 µL, 270 mg, 2.28 mmol, 6 eq.) in CH_2Cl_2 (3 mL) was added and the reaction mixture was stirred overnight. Solvents were removed under reduced pressure. The crude product was dissolved in EtOAc and the resulting solution washed successively with a saturated solution of $NaHCO_3$, brine, 1 M HCl, then brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (gradient from 10/90 to 100/0: EtOAc/PE then gradient from 0/100 to 20/80: CH_3OH/CH_2Cl_2) to give Boc-GABA-[*t*ACBC-GABA]$_2$-OBn (**II**) as a white solid (163 mg, 65%). Mp: 185 °C; R_f 0.53 (10/90: CH_3OH/CH_2Cl_2); $[a]_D^{23}$ = –23 (*c.* 0.50, CH_3OH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.45 (s, 9H, 9H-1), 1.73-1.82 (m, 4H, 2H-6, 2H-17), 1.82-2.03 (m,

6H, 2H-28, H-11, H-12, H-22, H-23), 2.08-2.29 (m, 8H, 2H-7, H-11', H-12', 2H-18, H-22', H-23'), 2.91-2-96 (m, 2H, H-13, H-24), 3.13-3.23 (m, 3H, 2H-5, H-16), 3.23-3.36 (m, 3H, H-16', 2H-27), 4.27-4.33 (m, 1H, H-21), 4.33-4.38 (m, 1H, H-10), 4.85 (m, 1H, H-4), 5.10 (s, 2H, 2H-31), 7.26-7.35 (m, 5H, 2H-33, 2H-34, H-35), 7.50 (m, 1H, H-9), 8.08 (m, 1H, H-20), 8.30 (m, 1H, H-15), 8.64 (m, 1H, H-26); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 18.7, 24.1, 24.2, 24.8 (C-11, C-12, C-22, C-23, C-28), 26.3, 26.7 (C-6, C-17), 28.4 (C-1), 31.8 (C-29), 32.8, 32.9 (C-18, C-7), 37.3, 39.1 (C-5, C-16), 38.6 (C-27), 48.1, 48.3 (C-10, C-21), 49.8, 49.9 (C-13, C-24), 66.2 (C-31), 79.9 (C-2), 128.2, 128.5 (C-33, C-34, C-35), 136.0 (C-32), 157.0 (C-3), 173.1 (C-30), 173.5, 173.7, (C-14, C-25), 173.9, 173.9 (C-8, C-19); IR ($CDCl_3$) ν_{max} 1447, 1515, 1567, 1647, 1695, 1731, 2879, 2939, 2980, 3073, 3278 (br), 3442 cm^{-1}; HRMS (ESI): $[M+Na]^+$, theor. 680.3630 (calc. for $C_{34}H_{51}N_5NaO_8$), meas. 680.3625.

Boc-[*t*ACBC-GABA]$_3$-OBn (5):

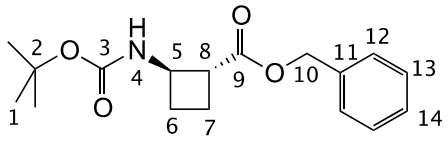


To a solution of Boc-GABA-[*t*ACBC-GABA]$_2$-OBn (**II**) (126 mg, 0.19 mmol, 1 eq.) in CH_2Cl_2 (5 mL) was added TFA (440 µL, 656 mg, 5.75 mmol, 30 eq.) at room temperature under argon atmosphere. The resulting yellowish mixture was stirred for 3 h. CH_2Cl_2 was then evaporated under reduced pressure. Toluene was added to co-evaporate the excess of TFA to give TFA·H-GABA-[*t*ACBC-GABA]$_2$-OBn. This material was engaged directly in the coupling reaction.

To a solution of Boc-*t*ACBC-OH (41 mg, 0.19 mmol, 1 eq.) in a 1 : 2 mixture of CH_2Cl_2 and DMF (0.5 mL : 1 mL) was added DIPEA (65 µL, 49 mg, 0.38 mmol, 2 eq.) followed by HATU (75 mg, 0.20 mmol, 1.05 eq.). The resulting mixture was stirred for 10 min at room temperature and the solution became brownish. After this, a solution of TFA·H-GABA-[*t*ACBC-GABA]$_2$-OBn (see above, 1 eq.) and DIPEA (200 µL, 147 mg, 1.14 mmol, 6 eq.) in DMF (4 mL) was added and the reaction mixture was stirred overnight. Solvents were removed under reduced pressure. The crude product was dissolved in EtOAc and the resulting solution washed successively with a saturated solution of $NaHCO_3$, brine, 1 M HCl, then brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (gradient from 10/90 to 100/0: EtOAc/PE then gradient from 0/100 to 20/80: CH_3OH/CH_2Cl_2) to give Boc-[*t*ACBC-GABA]$_3$-OBn (**5**) as a white solid (104 mg, 75%). Mp: 246 °C; R_f 0.51 (10/90: CH_3OH/CH_2Cl_2); $[a]_D^{23}$ = –16 (*c.* 0.50, CH_3OH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.47 (s, 9H, 9H-1), 1.65-1.71 (m, 4H, 2H-12, 2H-23), 1.78-1.88 (m, 4H, 2H-6, 2H-34), 1.91-2.04 (m, 8H, 2H-7, H-13, H-17, H-18, H-24, H-28, H-29), 2.08-2.29 (m, 7H, H-6', H-13', H-17', H-18', H-24', H-28', H-29'), 2.48 (t, 2H, *J* = 7.5 Hz, 2H-35), 2.76-2.80 (m, 1H, H-8), 2.96-3.04 (m, 2H, H-19, H-30), 3.07-3.11 (m, 2H, H-11, H-22), 3.28-3.36 (m, 2H, 2H-33), 3.55-3.59 (m, 2H, H-11', H-22'), 4.25-4.28 (m, 1H, H-5), 4.32-4.34 (m, 1H, H-27), 4.45-4.48 (m, 1H, H-16), 5.12 (d, 1H, *J* = 7.3 Hz, H-4), 5.13 (s, 2H, H-37), 6.81-6.83 (m, 1H, H-10), 7.33-7.38 (m, 5H, 2H-39, 2H-40, H-41), 8.02 (d, 1H, *J* = 7.7 Hz, H-15), 8.13 (t, 1H, *J* = 5.1 Hz, H-21), 8.24 (d, 1H, *J* = 6.9 Hz, H-26), 8.67 (t, 1H, *J* = 5.4 Hz, H-32). ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1, 18.1, 18.3 (C-7, C-18, C-29), 24.0, 24.8, 25.4, 25.5, 26.3, 28.3, 32.6 (C-6, C-12, C-13, C-17, C-23, C-24, C-28), 31.2 (C-35), 36.6, 37.1 (C-11, C-22), 38.5 (C-33), 48.1 (C-16, C-27), 48.9 (C-5), 49.8 (C-19, C-30), 50.5 (C-8), 66.0 (C-37), 80.5 (C-2), 128.0, 128.0, 128.4 (C-39, C-40, C-41), 136.3 (C-38), 155.7 (C-3), 172.5, 173.3, 173.4, 173.9 (C-9, C-14, C-20, C-25, C-31, C-36); IR ($CDCl_3$) ν_{max} 1443, 1453, 1501, 1560, 1648, 1698, 1730, 2879, 2943, 2981, 3072, 3286, 3329 (br), 3443 cm^{-1}; HRMS (ESI): $[M+Na]^+$, theor. 777.4157 (calc. for $C_{39}H_{58}N_6NaO_9$), meas. 777.4115.

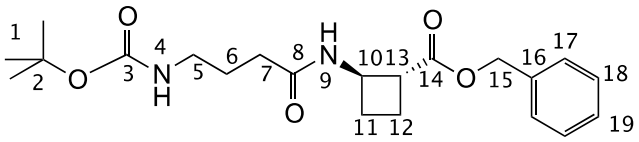
*Convergent synthetic procedure for peptides **2**, **4**, **6** and **III***

Boc-*t*ACBC-OBn (III):



To a solution of Boc-*t*ACBC-OH (800 mg, 3.72 mmol, 1 eq.) in DMF (12 mL) was added Cs_2CO_3 (7.23 g, 22.3 mmol, 6 eq.) followed by BnBr (665 µL, 954 mg, 5.58 mmol, 1.5 eq.) under argon atmosphere. The resulting white suspension was stirred overnight at room temperature. Water (10 mL) and EtOAc (20 mL) were added to the reaction mixture. The organic layer was extracted, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The crude product was purified by flash chromatography (gradient from 0/100 to 30/70: EtOAc/PE) to give Boc-*t*ACBC-OBn (**III**) as a white solid (850 mg, 75%). Mp: 100 °C; R_f 0.80 (30/70: EtOAc/PE); $[a]_D^{23}$ = –36 (*c.* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40 (s, 9H, 9H-1), 1.94-2.00 (m, 3H, H-6, 2H-7), 2.26-2.28 (m, 1H, H-6'), 3.06 (bs, 1H, H-8), 4.30 (bs, 1H, H-5), 4.88 (bs, 1H, H-4), 5.15 (s, 2H, 2H-10), 7.36-7.37 (m, 5H, 2H-12, 2H-13, H-14); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1 (C-7), 27.4 (C-6), 28.4 (C-1), 47.1 (C-8), 48.9 (C-5), 66.3 (C-10), 79.5 (C-2), 128.1, 128.1, 128.5 (C-12, C-13, C-14), 136.0 (C-11), 154.6 (C-3), 172.8 (C-9); IR ($CDCl_3$) ν_{max} 1456, 1504, 1713, 1725, 2871, 2932, 2982, 3003, 3446 cm^1; HRMS (ESI): $[M+Na]^+$, theor. 328.1519 (calc. for $C_{17}H_{23}NaNO_4$), meas. 328.1521.

Boc-GABA-*t*ACBC-OBn (2):

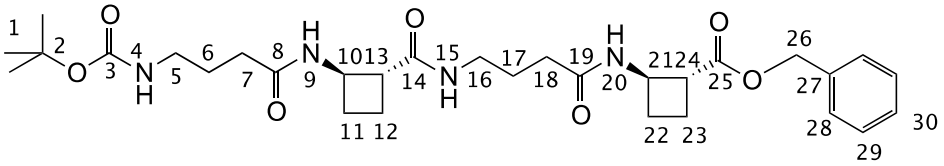


To a solution of Boc-*t*ACBC-OBn (**III**) (160 mg, 0.52 mmol, 1 eq.) in CH_2Cl_2 (10 mL) was added TFA (1.21 mL, 1.79 g, 15.7 mmol, 30 eq.) at room temperature under argon atmosphere. The resulting yellowish mixture was stirred for 2 h. CH_2Cl_2 was then evaporated under reduced pressure. Toluene was added to co-evaporate the excess of TFA to give TFA·H-*t*ACBC-OBn. This material was engaged directly in the coupling reaction.

To a solution of Boc-GABA-OH (112 mg, 0.52 mmol, 1 eq.) in a 4 : 1 mixture of CH_2Cl_2 and DMF (2 mL : 0.5 mL) was added DIPEA (163 µL, 124 mg, 1.04 mmol, 2 eq.) followed by HATU (206 mg, 0.55 mmol, 1.05 eq.). The resulting mixture was stirred for 10 min at room temperature and the solution became brownish. After this, a solution of TFA·H-*t*ACBC-OBn (see above, 1 eq.) and DIPEA (545 µL, 402 mg, 3.12 mmol, 6 eq.) in CH_2Cl_2 (2 mL) was added and the reaction mixture was stirred overnight. Solvents were removed under reduced pressure. The crude product was dissolved in EtOAc and the resulting solution washed successively with a saturated solution of $NaHCO_3$, brine, 1 M HCl, then brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (gradient from 10/90 to 50/50: EtOAc/PE) to give Boc-GABA-*t*ACBC-OBn (**2**) as a white solid (155 mg, 76%). Mp 109 °C**;** R_f 0.10 (90/10: EtOAc/PE); $[a]_D^{22}$ = –16 (*c*. 0.50, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$) δ 1.45 (s, 9H, 9H-1), 1.71-1.80 (m, 2H, 2H-6), 1.93-2.05 (m, 3H, H-11, 2H-12), 2.15-2.31 (m, 3H, 2H-7, H-11'), 3.02-3.18 (m, 3H, 2H-5, H-13), 4.50-4.63

(m, 1H, H-10), 4.72-4.90 (m, 1H, H-4), 5.13 (s, 2H, 2H-15), 6.93 (bs, 1H, H-9), 7.29-7.37 (m, 5H, 2H-17, 2H-18, H-19); ^{13}C NMR (90 MHz, $CDCl_3$) δ 18.6 (C-12), 26.3 (C-6), 27.0 (C-11), 28.4 (C-1), 33.2 (C-7), 39.5 (C-5), 46.7 (C-13), 47.4 (C-10), 66.4 (C-15), 79.5 (C-2), 128.1, 128.1, 128.5 (C-17, C-18, C-19), 136.0 (C-16), 156.7 (C-3), 172.1 (C8), 172.8 (C-14); IR ($CDCl_3$) ν_{max} 1455, 1512, 1670, 1699, 1723, 2871, 2934, 2981, 3312 (br), 3451 cm^{1}; HRMS (ESI): $[M+Na]^+$, theor. 413.2047 (calc. for $C_{21}H_{30}N_2NaO_5$), meas. 413.2032.

Boc-[GABA-*t*ACBC]$_2$-OBn (4):

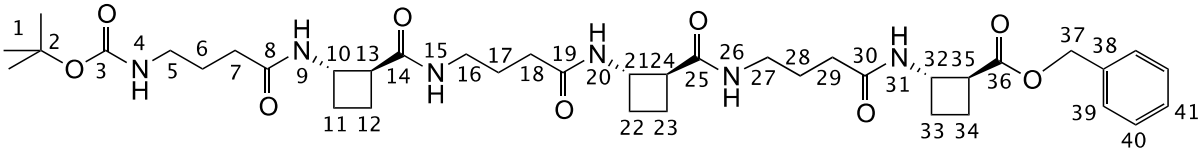


To a solution of Boc-GABA-*t*ACBC-OBn (**2**) (75 mg, 0.19 mmol, 1 eq.) in CH_2Cl_2 (5 mL) was added TFA (440 µL, 657 mg, 5.77 mmol, 30 eq.) at room temperature under argon atmosphere. The resulting yellowish mixture was stirred for 2 h. CH_2Cl_2 was then evaporated under reduced pressure. Toluene was added to co-evaporate the excess of TFA to give TFA·H-GABA-*t*ACBC-OBn. This material was engaged directly in the coupling reaction.

To a solution of Boc-GABA-*t*ACBC-OBn (**2**) (75 mg, 0.19 mmol, 1 eq.) in CH_2Cl_2 (3 mL) was added 10% Pd-C (60 mg). The black suspension was stirred for 2 h under H_2 atmosphere. The mixture was then filtered through Celite and CH_2Cl_2 was evaporated under reduced pressure to afford Boc-GABA-*t*ACBC-OH. This material was engaged directly in the coupling reaction.

To a solution of Boc-GABA-*t*ACBC-OH (see above, 1 eq.) in a 2 : 1 mixture of CH_2Cl_2 and DMF (1 mL : 0.5 mL) was added DIPEA (65 µL, 49 mg, 0.38 mmol, 2 eq.) followed by HATU (206 mg, 0.55 mmol, 1.05 eq.). The resulting mixture was stirred for 10 min at room temperature and the solution became brownish. After this, a solution of TFA·H-GABA-*t*ACBC-OBn (see above, 1 eq.) and DIPEA (198 µL, 147 mg, 1.14 mmol, 6 eq.) in CH_2Cl_2 (2 mL) was added and the reaction mixture was stirred overnight. Solvents were removed under reduced pressure. The crude product was dissolved in EtOAc and the resulting solution washed successively with a saturated solution of $NaHCO_3$, brine, 1 M HCl, then brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (gradient from 10/90 to 100/0: EtOAc/PE) to give Boc-[GABA-*t*ACBC]$_2$-OBn (**4**) as a white solid (65 mg, 58%). Mp: 141 °C; R_f 0.45 (10/90: CH_3OH/CH_2Cl_2); $[a]_D^{16}$ = –32 (*c.* 0.50, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.42 (s, 9H, 9H-1), 1.73-1.79 (m, 5H, 2H-6, 2H-17, H-23), 1.93-2.00 (m, 4H, H-11, H-12, H-22, H-23'), 2.07-2.24 (m, 7H, 2H-7, H-11', H-12', 2H-18, H-22'), 2.89-2.94 (m, 1H, H-13), 3.11-3.14 (m, 4H, 2H-5, H-16, H-24), 3.19-3.24 (m, 1H, H-16'), 4.27-4.32 (m, 1H, H-10), 4.53-4.58 (m, 1H, H-21), 5.07-5.11 (m, 3H, H-4, 2H-26), 7.28-7.32 (m, 5H, 2H-28, 2H-29, H-30), 7.65 (d, *J* = 6.3 Hz, 1H, H-9), 7.81 (d, *J* = 8.1 Hz, 1H, H-20), 8.36 (t, *J* = 5.6 Hz, 1H, H-15); ^{13}C NMR (90 MHz, $CDCl_3$) δ 18.5, 18.7 (C-11, C-12), 24.1 (C-22), 26.2, 26.5, 26.9 (C-6, C-17, C-23), 28.4 (C-1), 33.0, 33.2 (C-7, C-18), 37.5 (C-16), 39.3 (C-5), 46.6 (C-21), 47.4 (C-24), 48.1 (C-10), 49.7 (C-13), 66.3 (C-26), 79.6 (C-2), 128.0, 128.1, 128.5 (C-28, C-29, C-30), 136.0 (C-27), 156.8 (C-3), 172.4, 173.1, 173.6 (C-8, C-14, C-19), 174.1 (C-25); IR ($CDCl_3$) ν_{max} 1470, 1515, 1560, 1603, 1646, 1695, 2902, 2984, 3072, 3155, 3283 (br), 3451 cm^{-1}; HRMS (ESI): $[M+Na]^+$, theor. 595.3102 (calc. for $C_{30}H_{44}N_4NaO_7$), meas. 595.3081.

Boc-[GABA-*t*ACBC]$_3$-OBn (6):



To a solution of Boc-[GABA-*t*ACBC]$_2$-OBn (**4**) (60 mg, 0.10 mmol, 0.8 eq.) in CH_2Cl_2 (3 mL) was added TFA (230 µL, 342 mg, 3 mmol, 24 eq.) at room temperature under argon atmosphere. The resulting yellowish mixture was stirred for 3 h. CH_2Cl_2 was then evaporated under reduced pressure. Toluene was added to co-evaporate the excess of TFA to give TFA·H-[GABA-*t*ACBC]$_2$-OBn. This material was engaged directly in the coupling reaction.

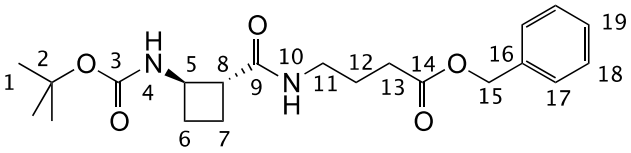
To a solution of Boc-GABA-*t*ACBC-OBn (**2**) (60 mg, 0.12 mmol, 1 eq.) in CH_2Cl_2 (3 mL) was added 10% Pd-C (60 mg). The black suspension was stirred for 2 h under H_2 atmosphere. The mixture was then filtered through celite and CH_2Cl_2 was evaporated under reduced pressure to afford Boc-GABA-*t*ACBC-OH. This material was engaged directly in the coupling reaction.

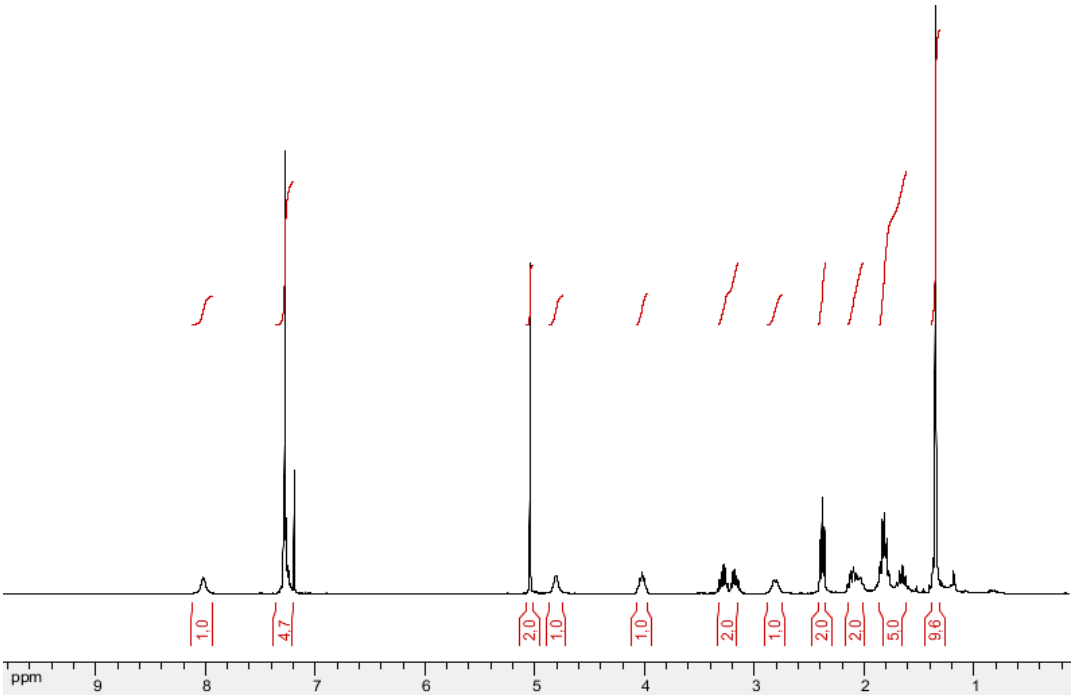
To a solution of Boc-GABA-*t*ACBC-OH (see above, 1 eq.) in a 2 : 1 mixture of CH_2Cl_2 and DMF (1 mL : 0.5 mL) was added DIPEA (40 µL, 31 mg, 0.24 mmol, 2 eq.) followed by HATU (47 mg, 0.13 mmol, 1.05 eq.). The resulting mixture was stirred for 10 min at room temperature and the solution became brownish. After this, a solution of TFA·H-[GABA-*t*ACBC]$_2$-OBn (see above, 0.8 eq.) and DIPEA (198 µL, 147 mg, 1.14 mmol, 6 eq.) in CH_2Cl_2 (2 mL) was added and the reaction mixture was stirred overnight. Solvents were removed under reduced pressure. The crude product was dissolved in EtOAc and the resulting solution washed successively with a saturated solution of $NaHCO_3$, brine, 1 M HCl, then brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (gradient from 10/90 to 100/0: EtOAc/PE then gradient from 0/100 to 20/80: CH_3OH/CH_2Cl_2) to give Boc-[GABA-tACBC]$_3$-OBn (**6**) as a white solid (42 mg, 56%). Mp: 215 °C; R_f 0.50 (10/90: CH_3OH/CH_2Cl_2); $[\alpha]_D^{21}$ = –25 (*c.* 0.50, CH_3OH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.47 (s, 9H, 9H-1), 1.76-1.92 (m, 7H, 2H-6, 2H-17, 2H-28, H-34), 1.92-2.03 (m, 6H, H-11, H-12, H-22, H-23, H-33, H-34'), 2.05-2.17 (m, 3H, H-12', H-22', H-23'), 2.19-2.27 (m, 8H, 2H-7, H-11', 2H-18, 2H-29, H-33'), 2.91-3.00 (m, 2H, H-13, H-24), 3.13-3.23 (m, 5H, 2H-5, H-16, H-27, H-35), 3.28 (bs, 1H, H-27'), 3.42 (bs, 1H, H-16'), 4.32-4.41 (m, 2H, H-10, H-21), 4.57-4.63 (m, 1H, H-32), 4.81 (bs, 1H, H-4), 5.13 (s, 2H, 2H-37), 7.31-7.36 (m, 5H, 2H-39, 2H-40, H-41), 7.92 (bs, 1H, H-31), 8.11 (bs, 1H, H-15), 8.25 (bs, 1H, H-20), 8.51 (bs, 1H, H-26); ^{13}C NMR (100 MHz, $CDCl_3$ / CD_3OD : 1 / 1) δ 18.2, 18,3 (C-12, C-23), 24.0 (C-22), 25.5, 25.8, 25.8, 26.1 (C-6, C-17, C-28, C-34), 26.6 (C-11, C-33), 28.2 (C-1), 32.5, 32.8, 33.1 (C-7, C-18, C-29), 37.5 (C-16), 37.7 (C-27), 39.3 (C-5), 46.4 (C-35), 47.2 (C-32), 47.8 (C-10, C-21), 49.4 (C-24), 49.5 (C-13), 66.3 (C-37), 79.6 (C-2), 128.0, 128.0, 128.4 (C-39, C-40, C-41), 135.8 (C-38), 156.9 (C-3), 172.9, 173.1, 173.1, 174.1 (C-8, C-14, C-19, C-25, C-30, C-36). IR (10 mmol/L, $CDCl_3$) ν_{max} 1443, 1456, 1517, 1551, 1646, 1692, 1725, 2870, 2940, 2980, 3038, 3083, 3283 (br), 3442 cm^{-1}; HRMS (ESI): [M+Na]$^+$, theor. 777.4163 (calc. for $C_{39}H_{58}N_6NaO_9$), meas. 777.4189.

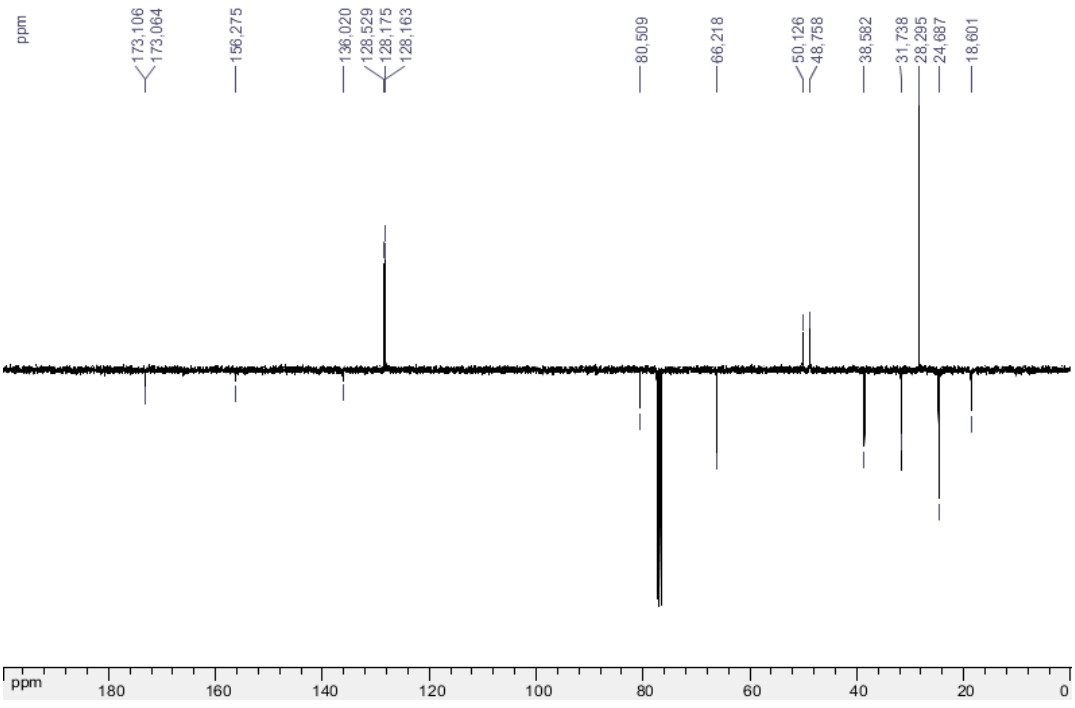
II. SPECTROSCOPIC ANALYSES OF PEPTIDES 1-6 AND I-III

1. ^{1}H and ^{13}C NMR spectra

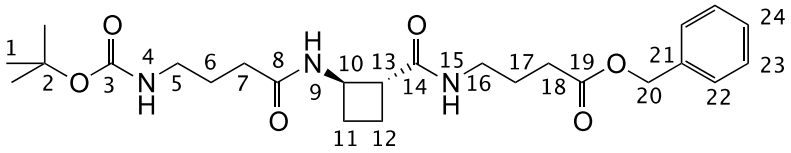
Boc-*t*ACBC-GABA-OBn (1)

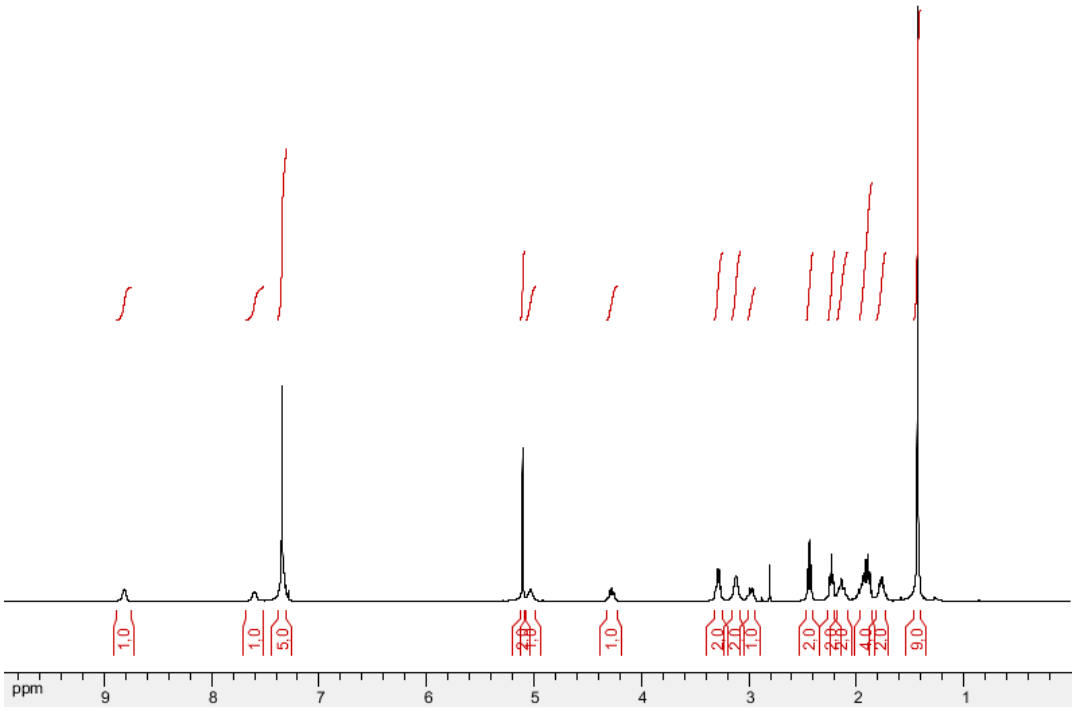


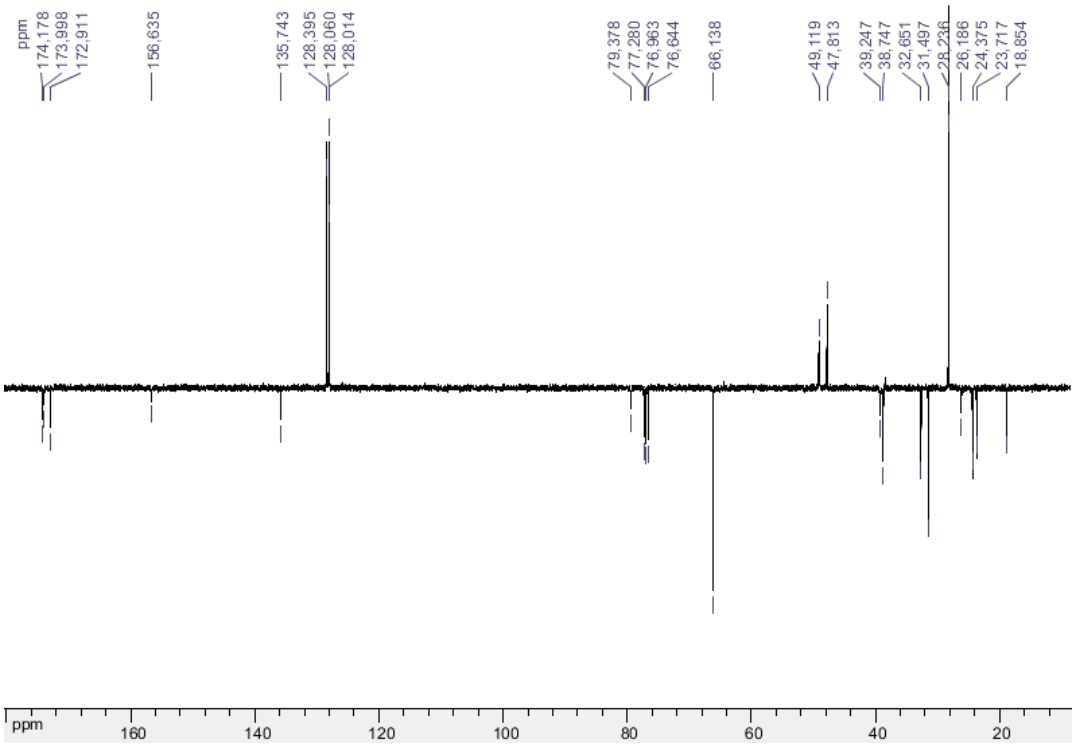




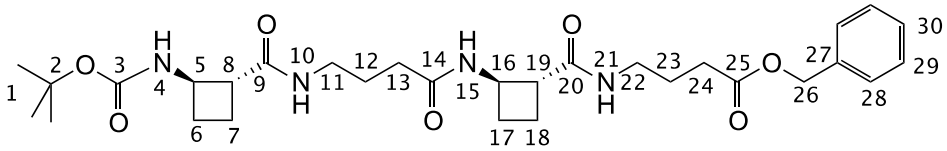
Boc-GABA-*t*ACBC-GABA-OBn (I)

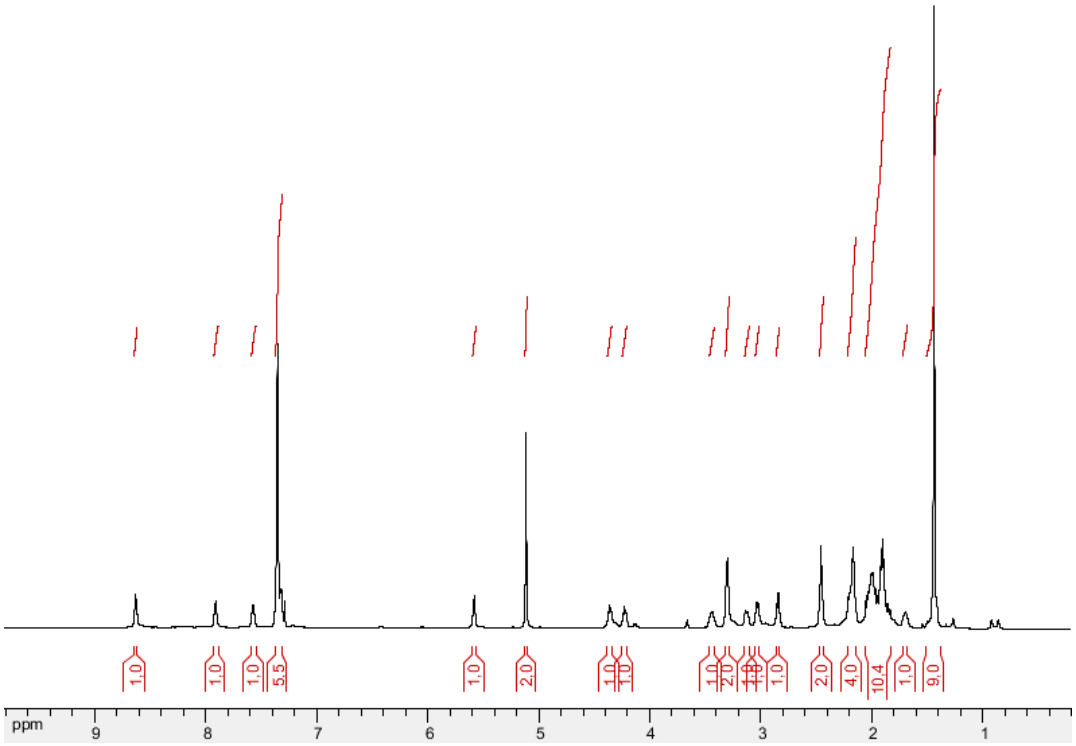


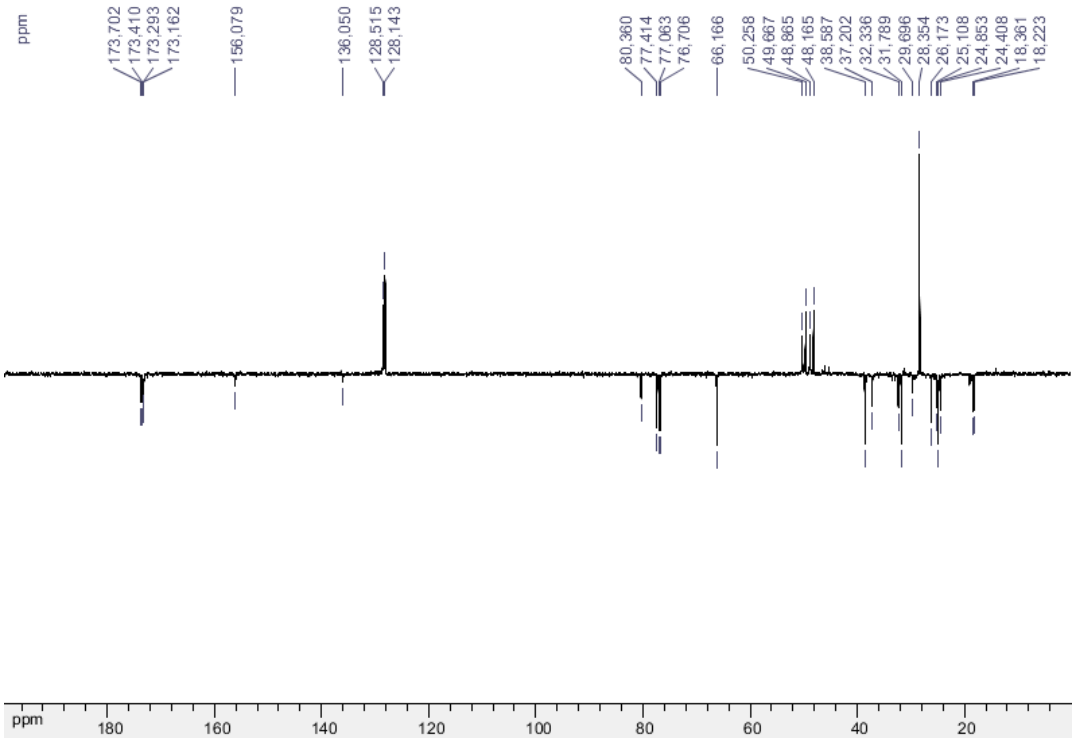




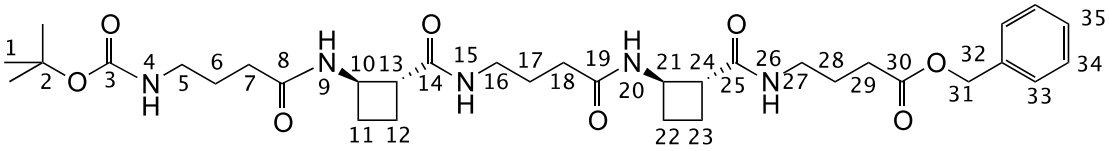
Boc-[*t*ACBC-GABA]$_2$-OBn (3)

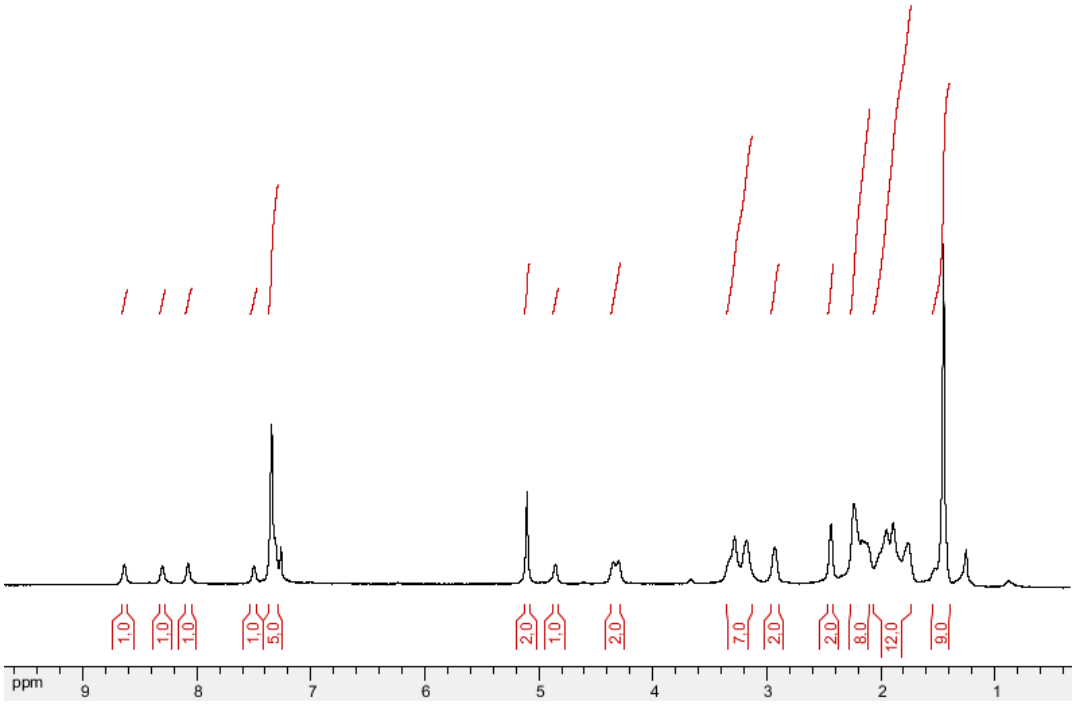


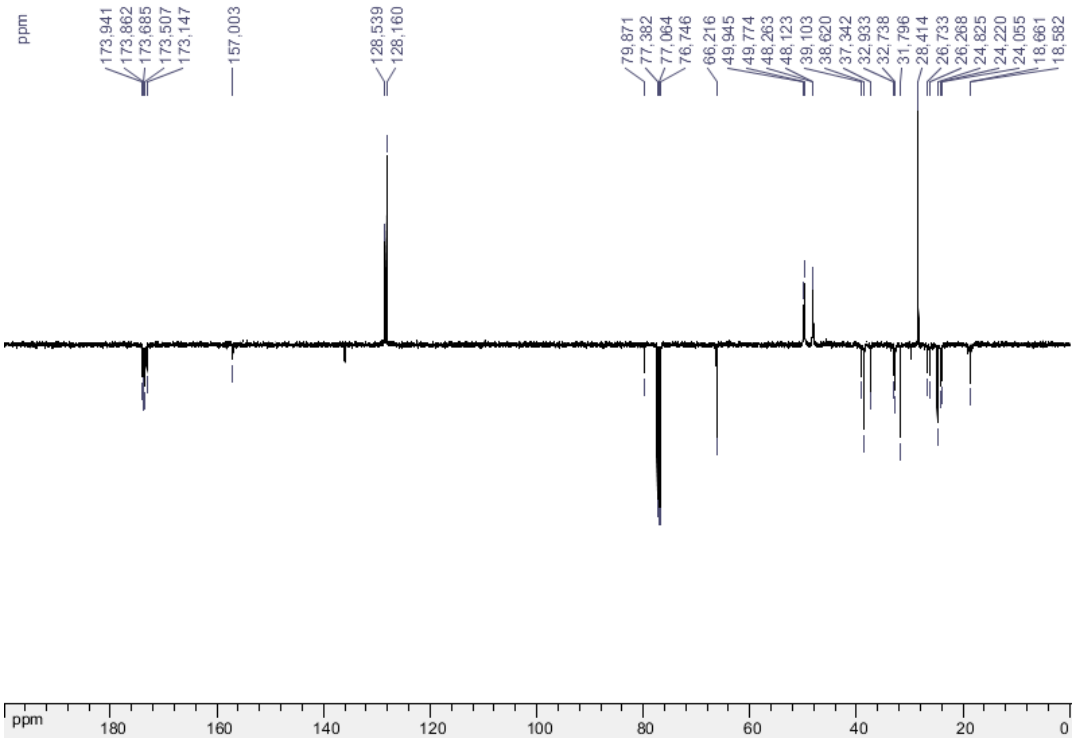




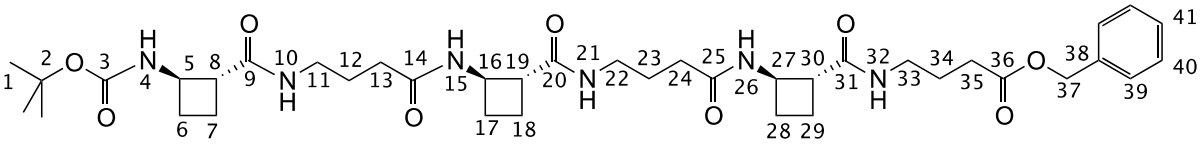
Boc-GABA-[*t*ACBC-GABA]$_2$-OBn (II)

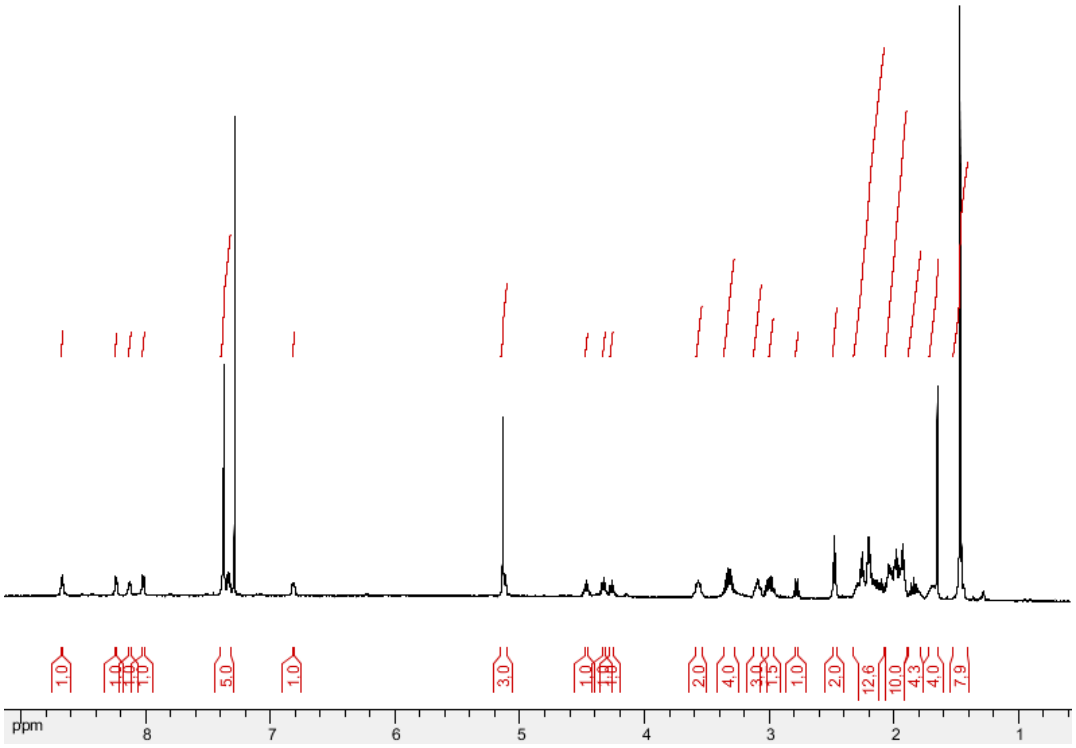


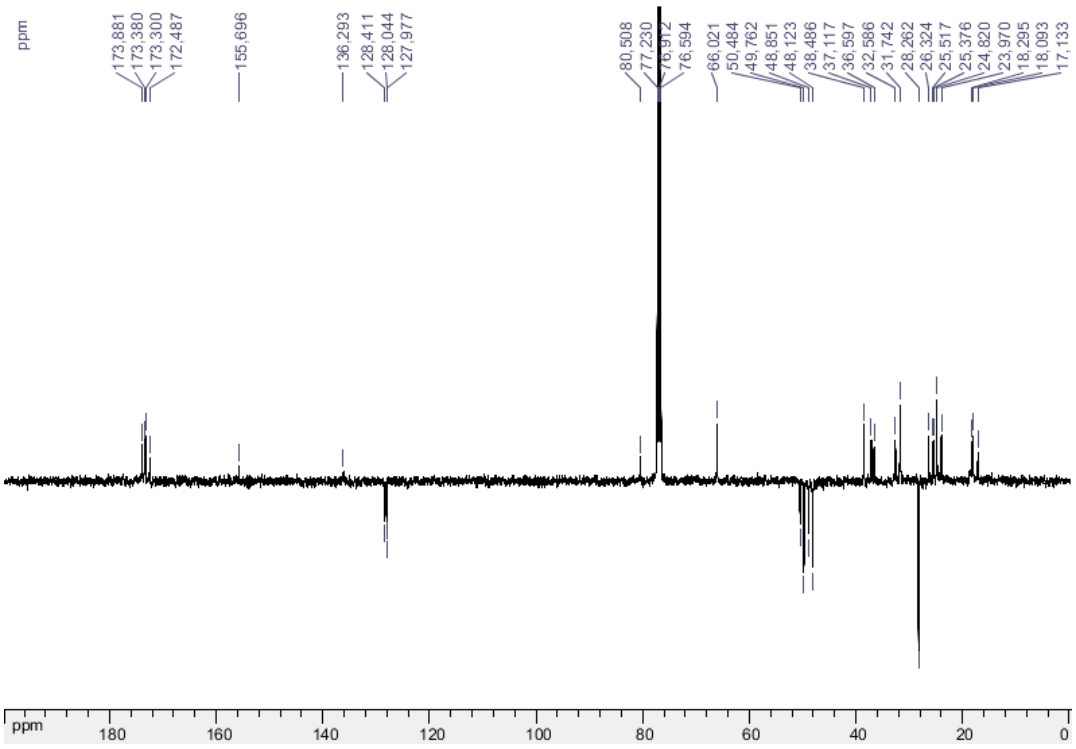




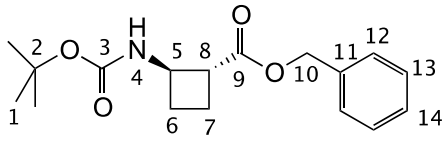
Boc-[*t*ACBC-GABA]$_3$-OBn (5)

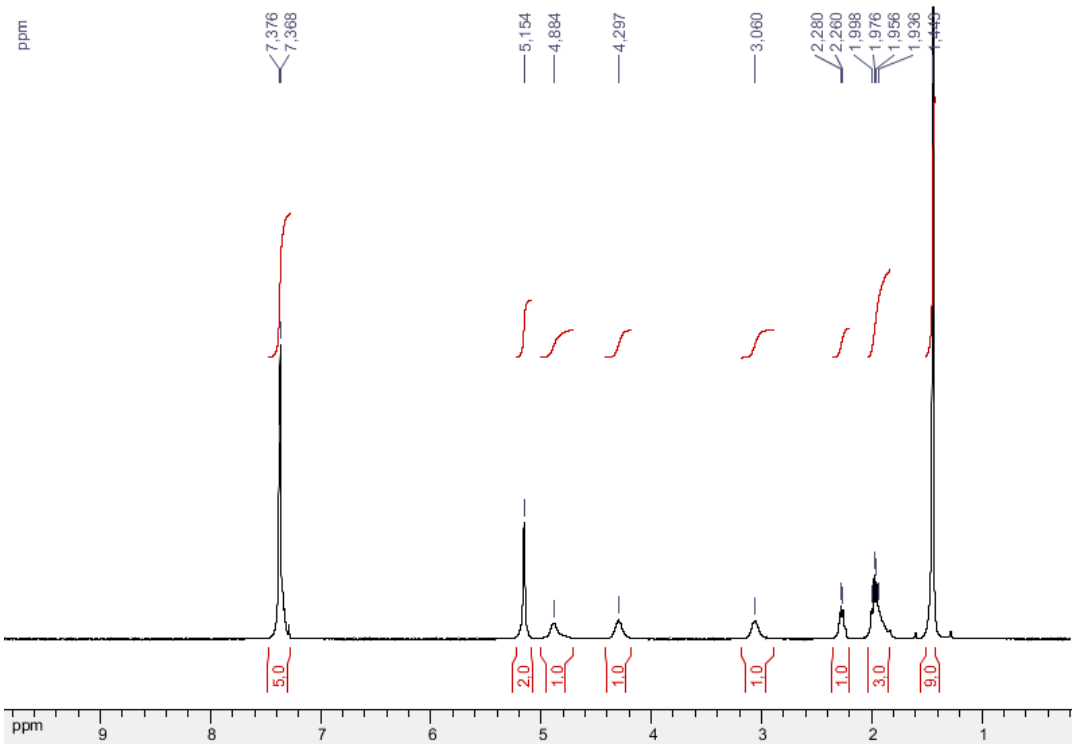


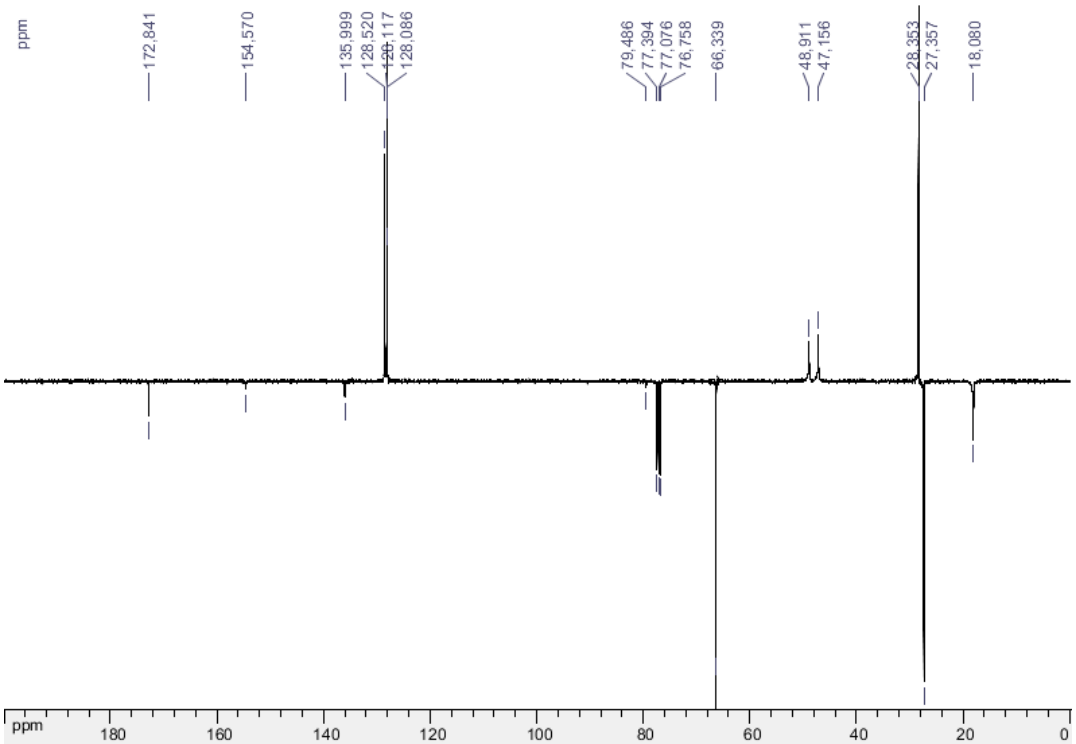




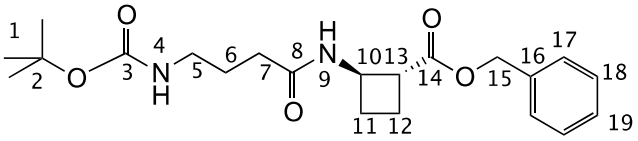
Boc-*t*ACBC-OBn (III)

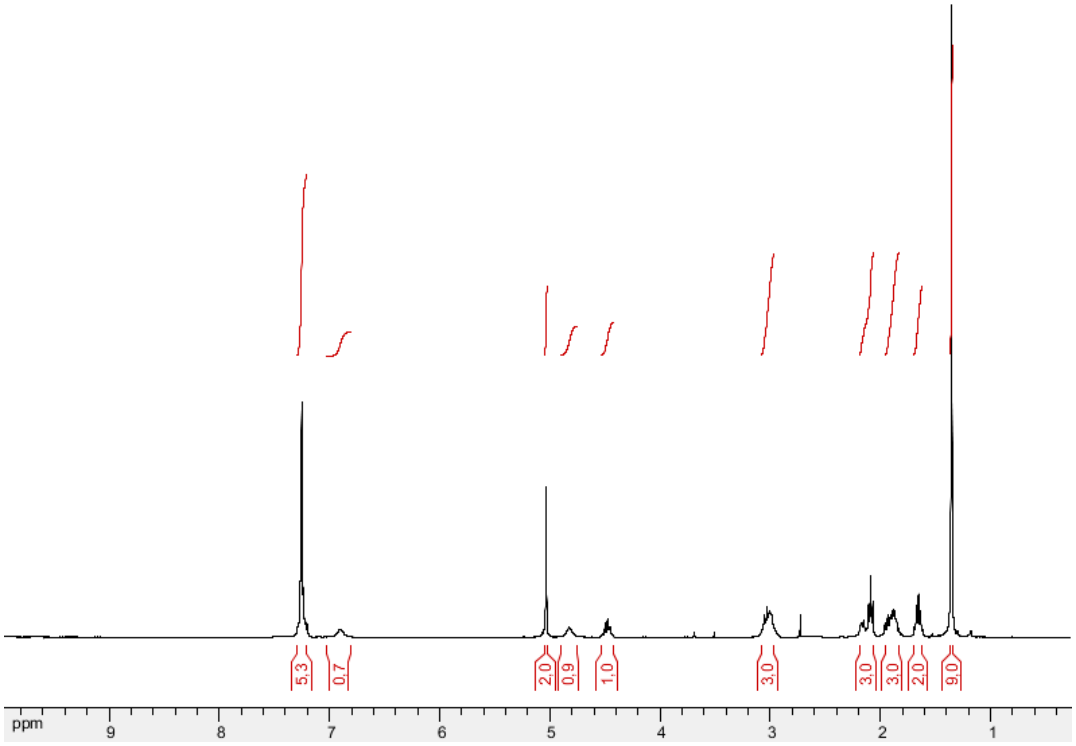


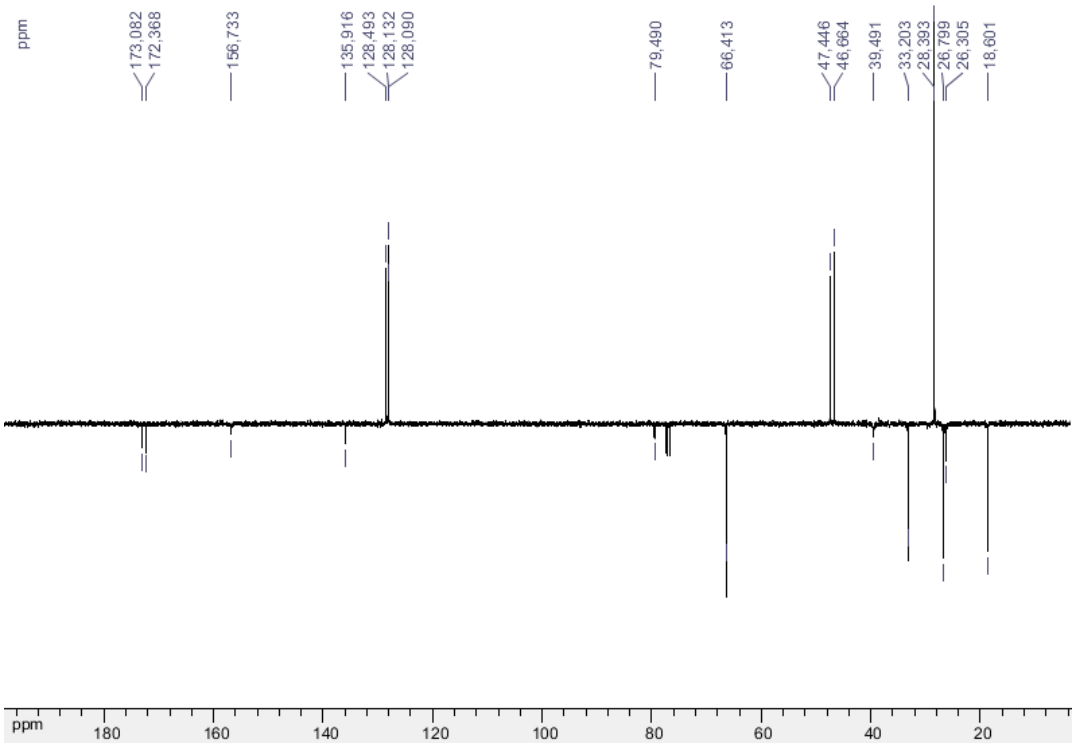




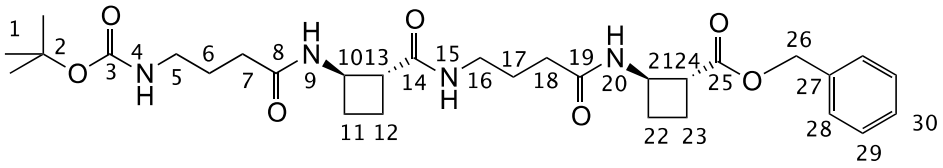
Boc-GABA-*t*ACBC-OBn (2)

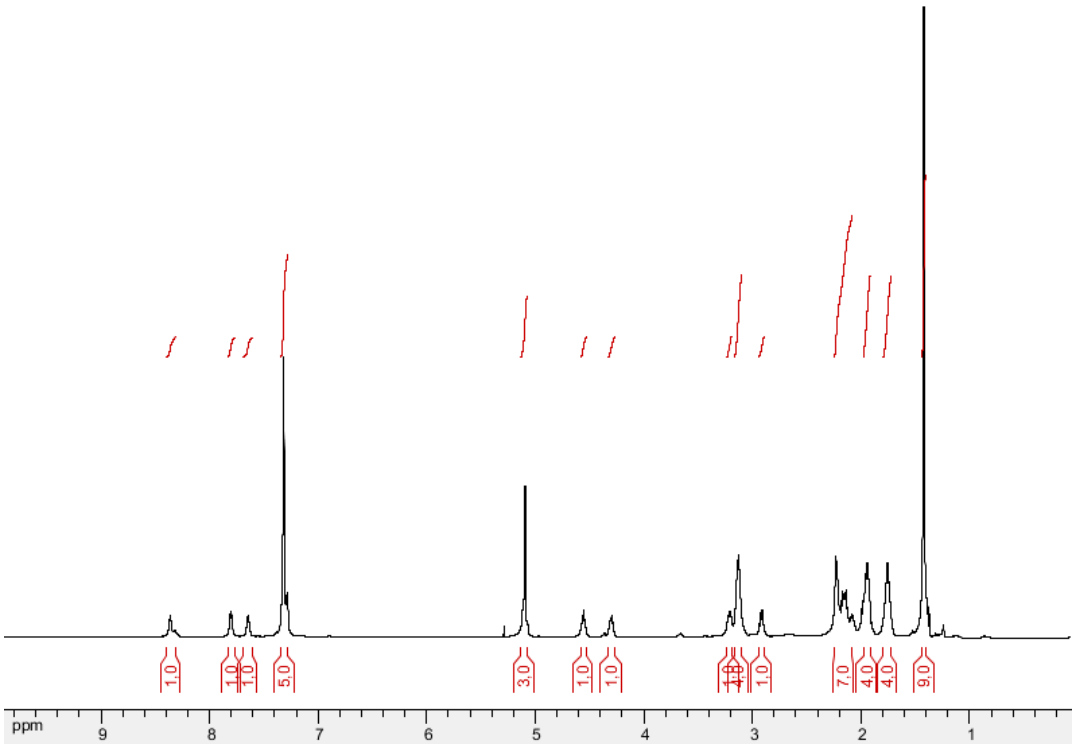


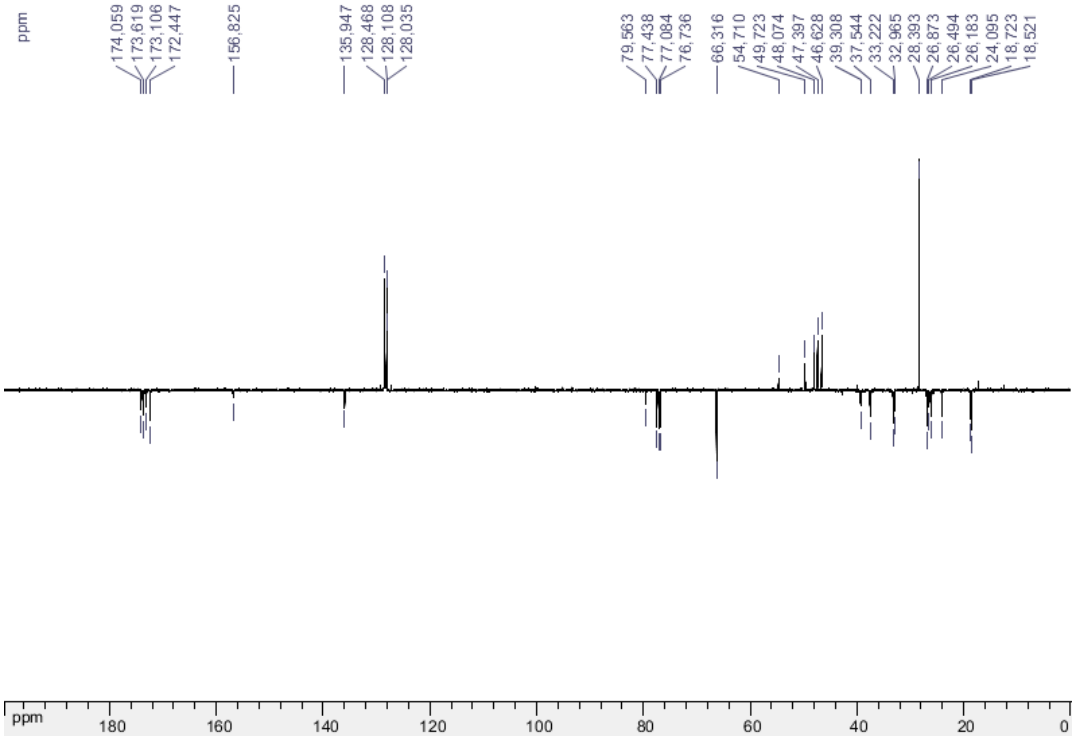




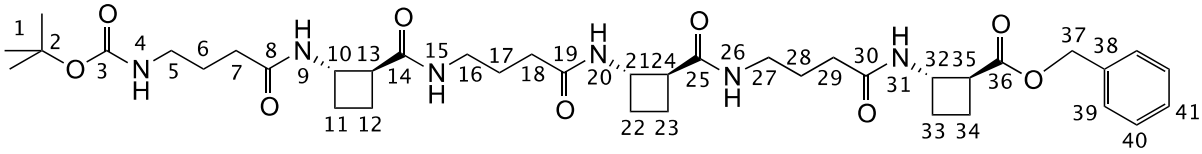
Boc-[GABA-*t*ACBC]$_2$-OBn (4)

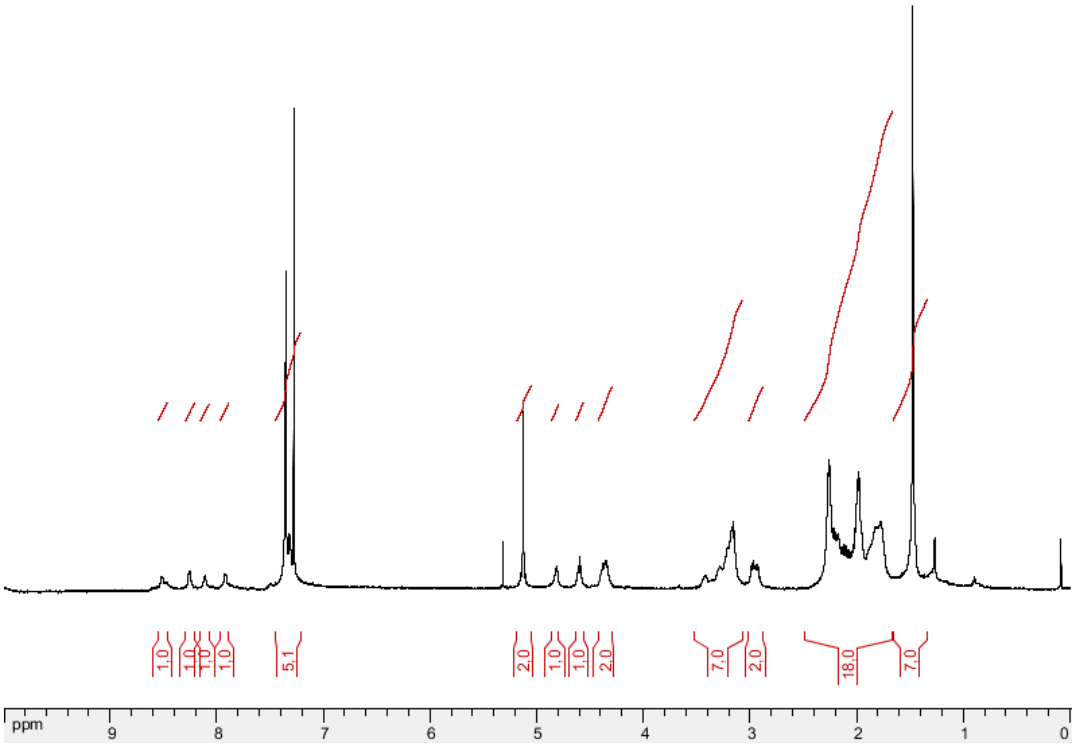


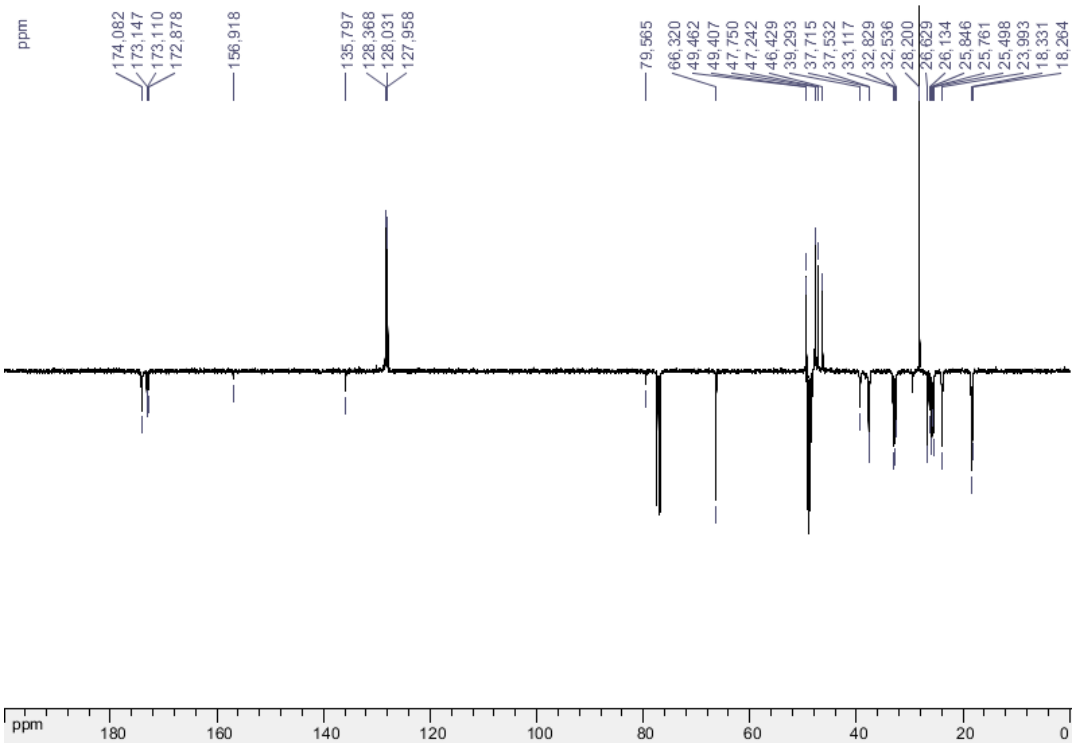




Boc-[GABA-*t*ACBC]$_3$-OBn (6)

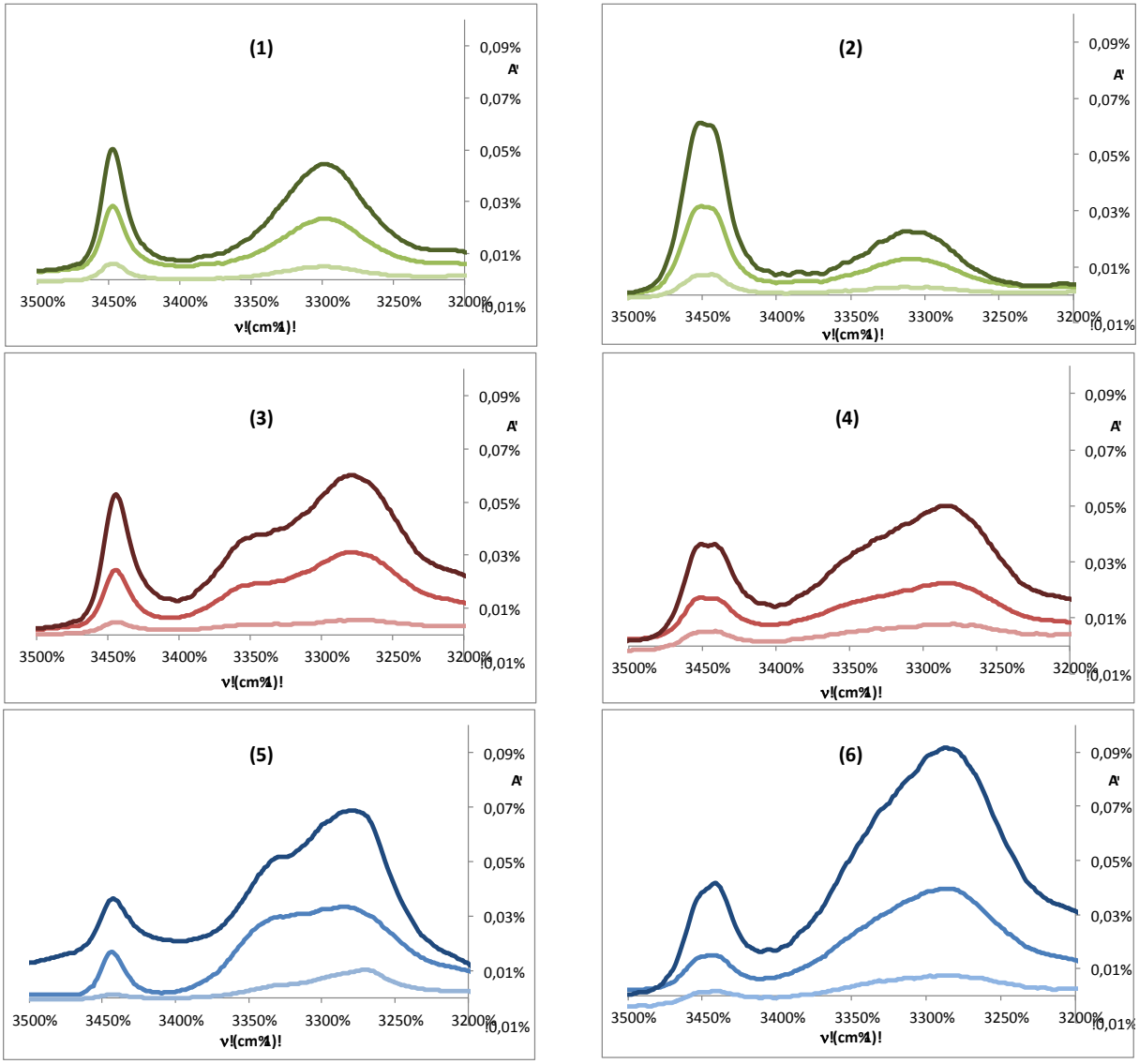






2. *Infrared studies*

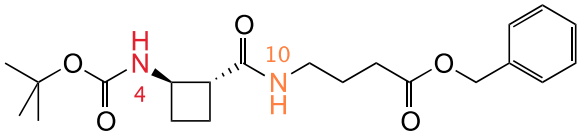
Infrared spectra were recorded in chloroform at three different concentrations (1, 5 and 10 mM). For each peptide, the concentration is indicated by the color graduation of the spectral plot (light, medium and dark, respectively).



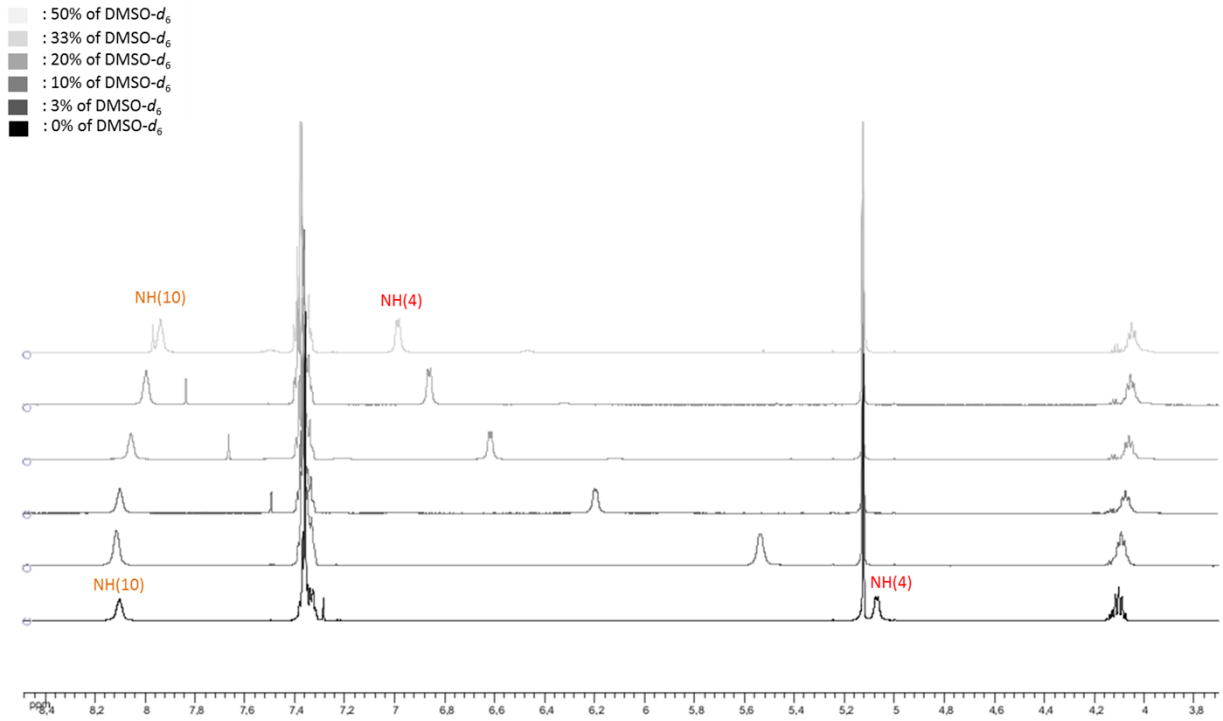
3. *DMSO-d_6 titrations*

^{1}H spectra were recorded at 300 K on a Bruker 600 MHz spectrometer. Samples were dissolved in $CDCl_3$ (600 µL) to give solutions of concentration 10 mM. Aliquots of DMSO-d_6 (20 µL, 40 µL, 60 µL, 80 µL and 100 µL) were added successively to the NMR tube followed, after each addition, by rapid agitation then re-recording of the ^{1}H spectra.

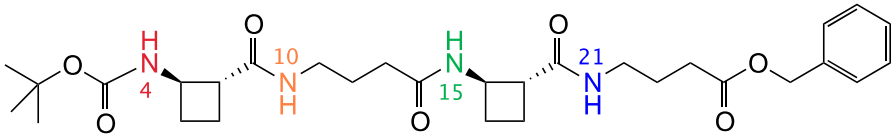
Boc-*t*ACBC-GABA-OBn (1)



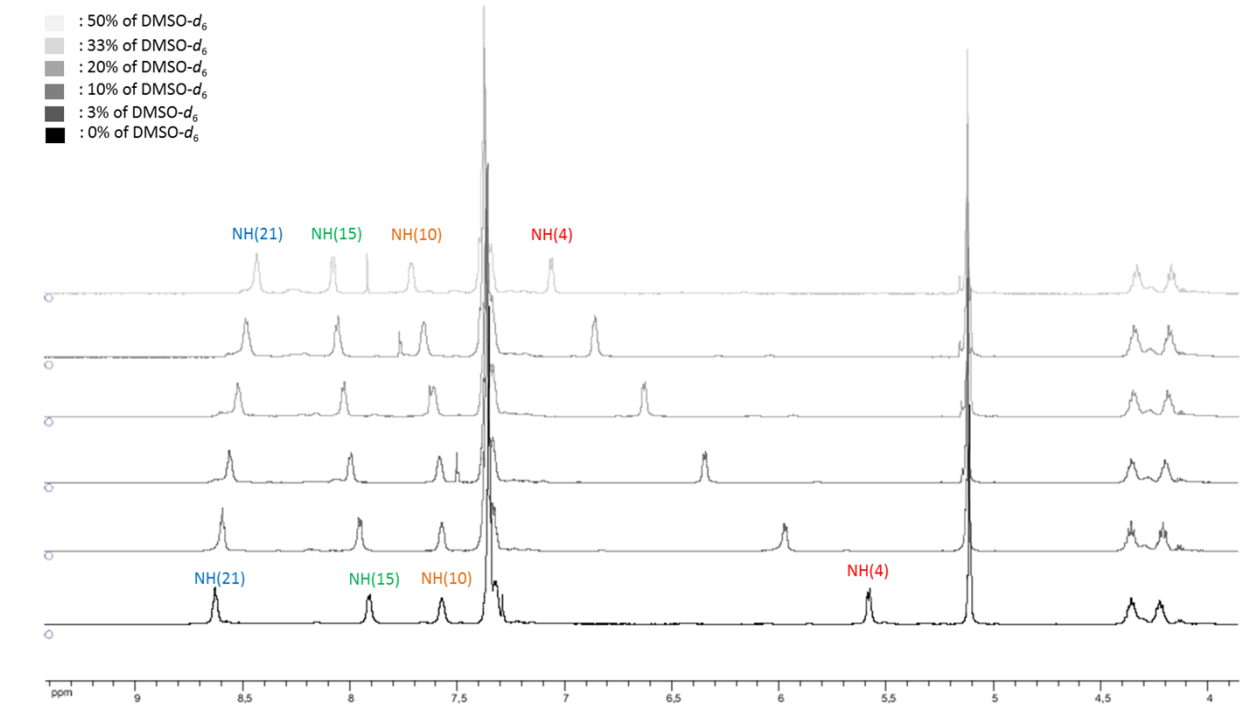
	DMSO-d_6 (%, v/v)						
NH	**0%**	**3%**	**10%**	**20%**	**33%**	**50%**	Δδ
NH(4)	5.06	5.54	6.19	6.61	6.85	6.99	1.93
NH(10)	8.11	8.11	8.11	8.06	8.00	7.93	0,18



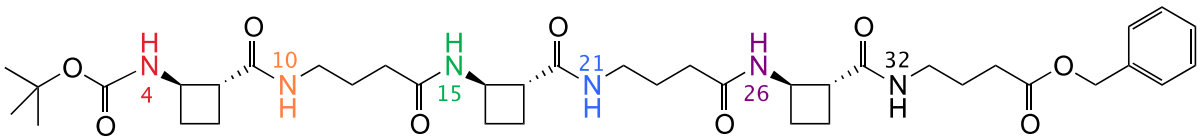
Boc-[*t*ACBC-GABA]$_2$-OBn (3)



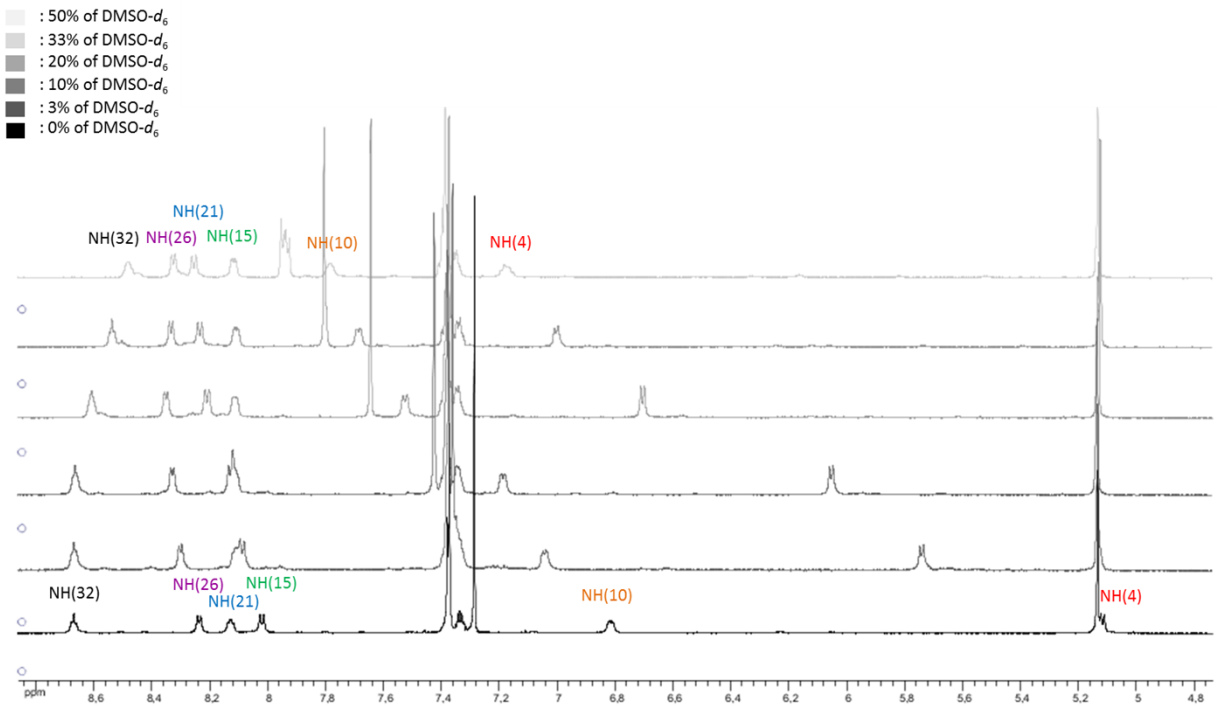
	DMSO-d_6 (%, v/v)						
HN	**0%**	**3%**	**10%**	**20%**	**33%**	**50%**	Δδ
NH(4)	5.57	5.96	6.34	6.63	6.84	7.07	1.5
NH(10)	7.57	7.57	7.6	7.6	7.65	7.71	0.14
NH(15)	7.91	7.94	7.98	8.01	8.04	8.06	0.15
NH(21)	8.63	8.6	8.55	8.51	8.48	8.42	-0.21



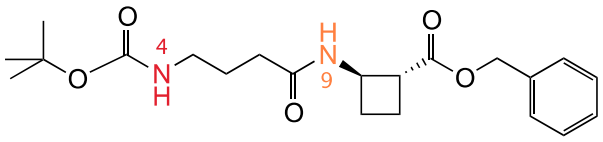
Boc-[*t*ACBC-GABA]$_3$-OBn (5)



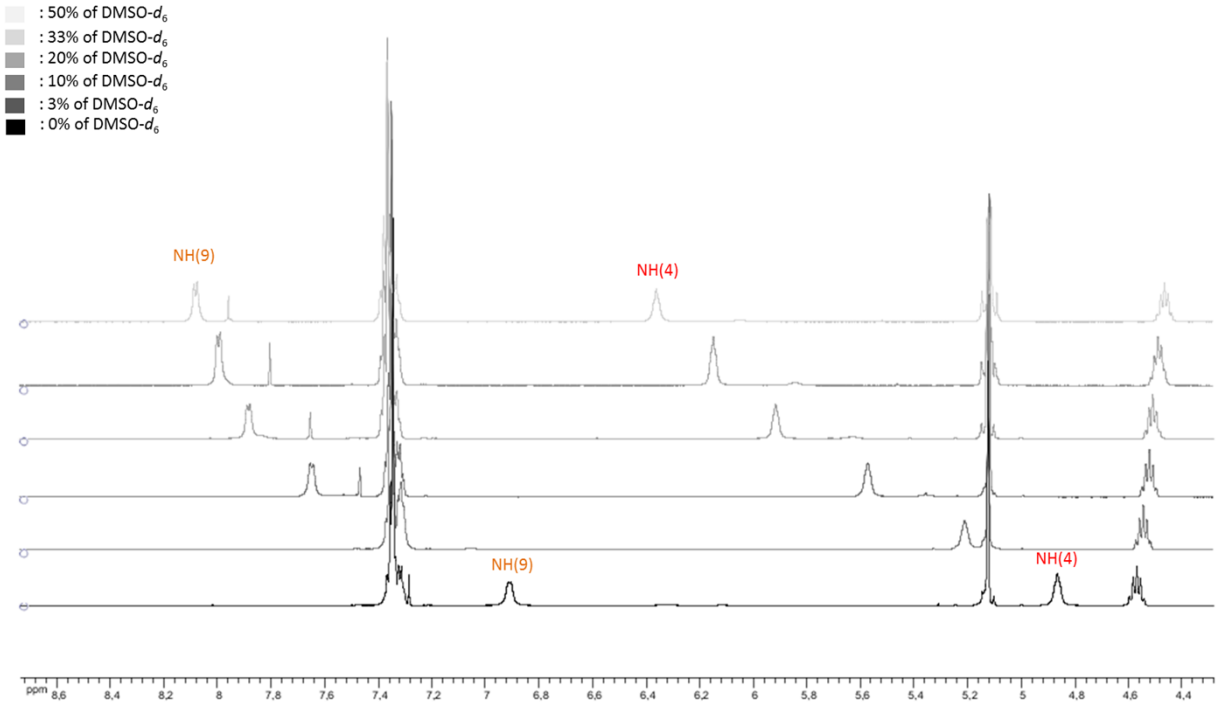
	DMSO-d_6 (%, v/v)						
NH	**0%**	**3%**	**10%**	**20%**	**33%**	**50%**	**Δδ**
NH(4)	5.13	5.73	6.04	6.7	7.01	7.17	2,04
NH(10)	6.82	7.03	7.18	7.52	7.7	7.78	0.96
NH(15)	8.09	8.12	8.2	8.24	8.24	8.25	0.16
NH(21)	8.12	8.12	8.12	8.12	8.12	8.12	0
NH(26)	8.24	8.3	8.32	8.35	8.34	8.32	0.08
NH(32)	8.67	8.66	8.66	8.6	8.55	8.49	-0,18



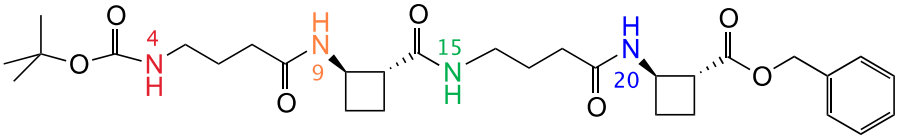
Boc-GABA-*t*ACBC-OBn (2)



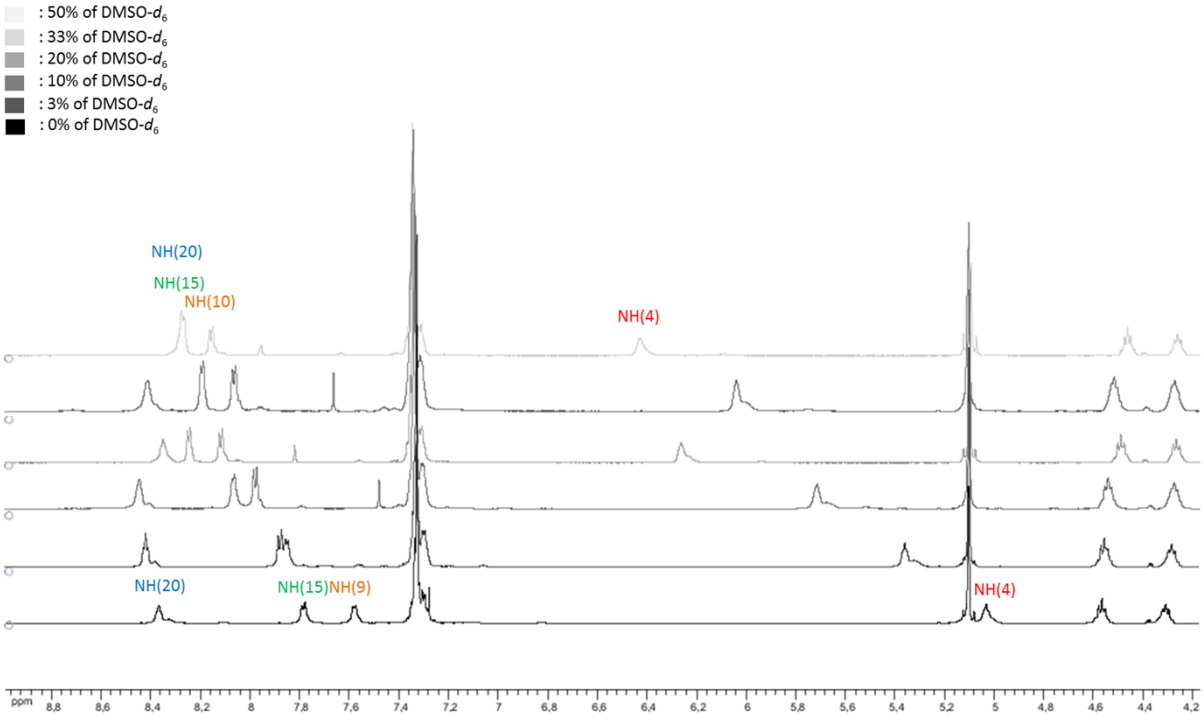
	DMSO-d_6 (%, v/v)						
NH	**0%**	**3%**	**10%**	**20%**	**33%**	**50%**	**Δδ**
NH(4)	4.87	5.21	5.57	5.92	6.15	6.36	1.49
NH(9)	6.91	7.31	7.64	7.88	8	8.08	1.17



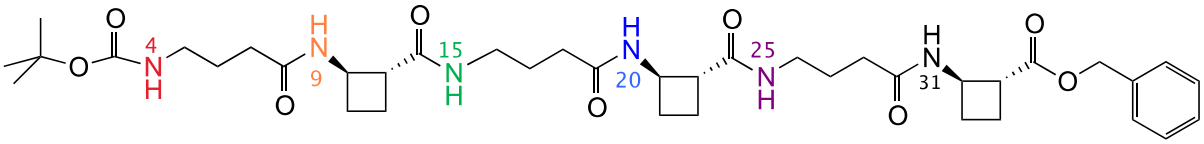
Boc-[GABA-*t*ACBC]$_2$-OBn (4)



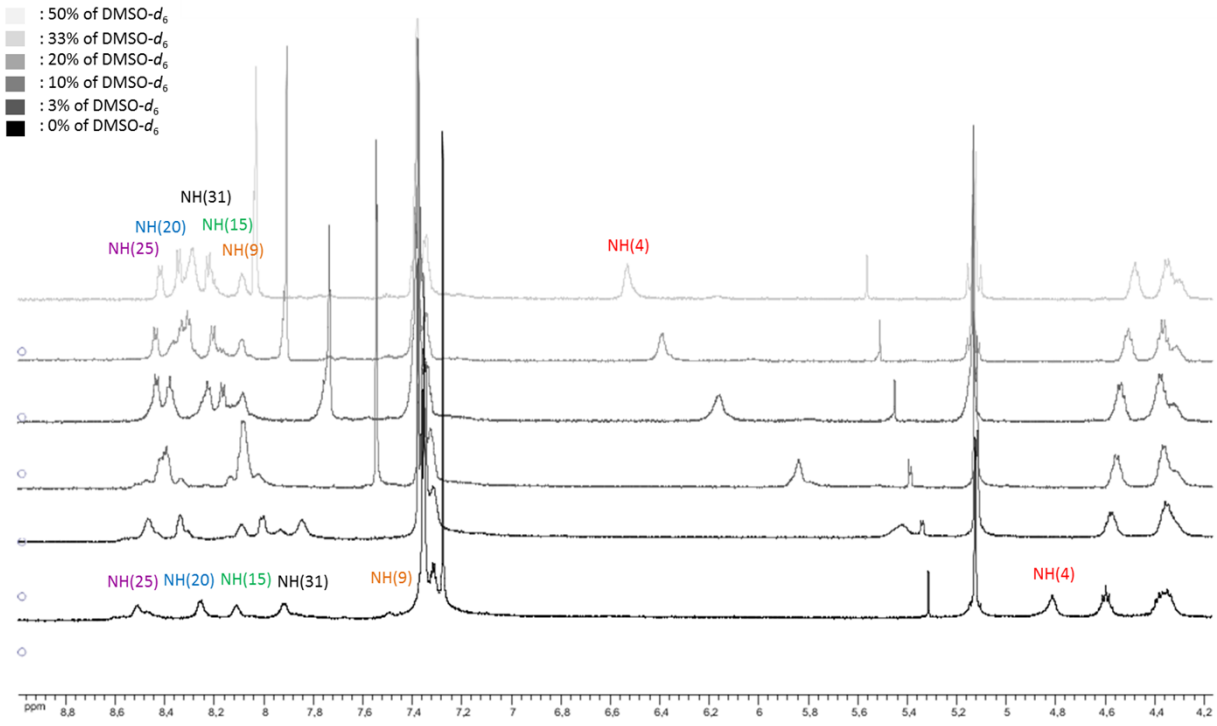
DMSO-d_6 (%, v/v)							
NH	**0%**	**3%**	**10%**	**20%**	**33%**	**50%**	**Δδ**
NH(4)	5.03	5.35	5.71	6.03	6.26	6.42	1.39
NH(9)	7.57	7.84	8.06	8.19	8.23	8.26	0.69
NH(15)	8.37	8.42	8.44	8.41	8.34	8.27	-0.1
NH(20)	7.78	7.87	7.98	8.05	8.11	8.16	0.38



Boc-[GABA-*t*ACBC]$_3$-OBn (6)



	DMSO-d_6 (%. v/v)						
NH	**0%**	**3%**	**10%**	**20%**	**33%**	**50%**	**Δδ**
NH(4)	4.81	5.42	5.84	6.16	6.39	6.53	1.72
NH(9)	7.36	7.85	8.08	8.23	8.3	8.33	0.97
NH(15)	8.09	7.99	8.06	8.06	8.08	8.08	-0.01
NH(20)	8.25	8.33	8.37	8.42	8.42	8.41	0.16
NH(25)	8.5	8.46	8.4	8.38	8.34	8.34	-0.16
NH(31)	7.91	8	8.08	8.16	8.21	8.22	0.31



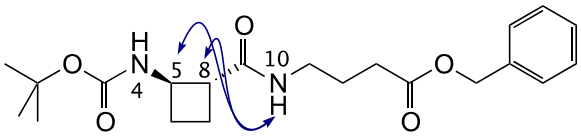
4. ROESY correlations

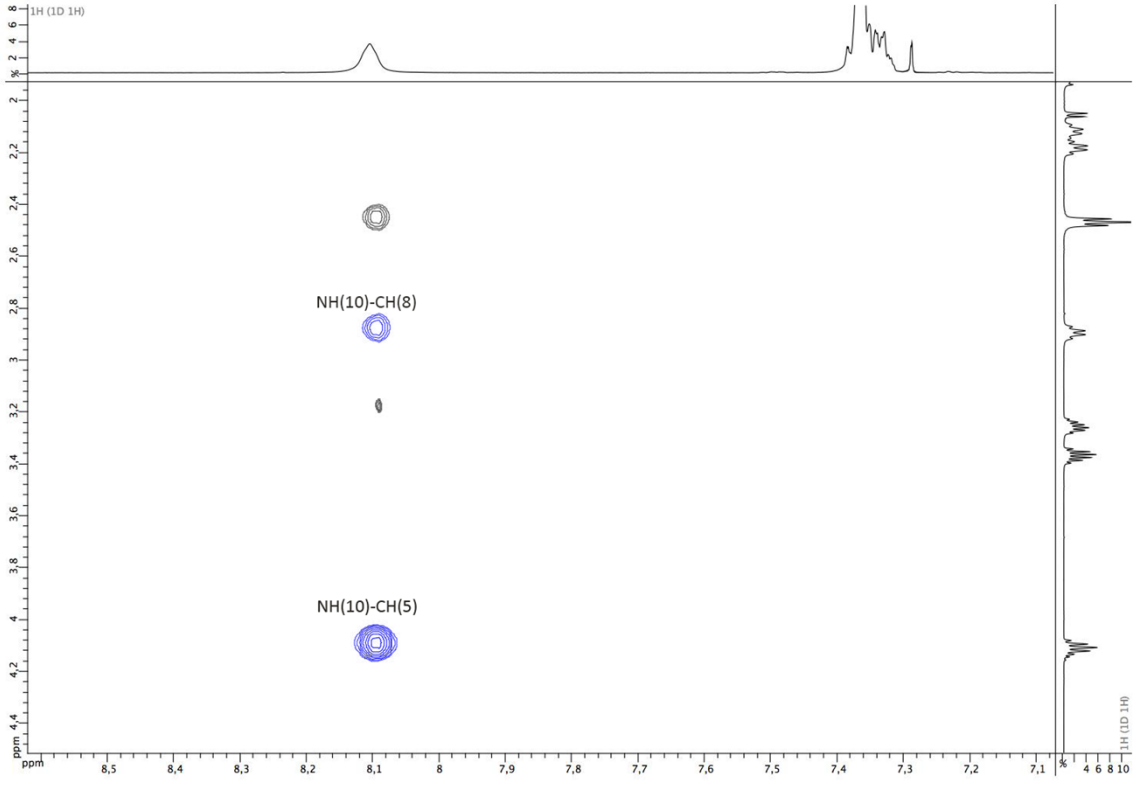
ROESY spectra were recorded at 300 K on a Bruker 600 MHz spectrometer. Samples were prepared in $CDCl_3$ at a concentration of 10 mM. The pulse sequence was roesyph. ROESY experiments employed a pulse spinlock of 200 ms. All experiments were performed by collecting 6492 points in f1 and 256 points (for **2**, **3**, **4**) or 512 points (for **5**, **6**) in f2.

ROESY correlations representative of the 9H-membered ring (C9): ⟷

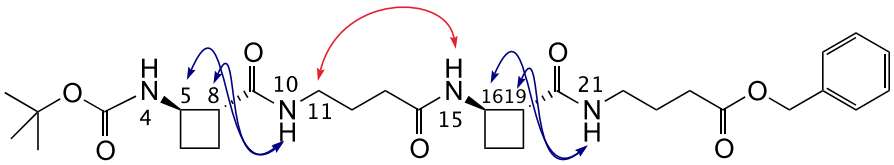
ROESY correlations representative of the 8H-membered ring (C8): ⟷

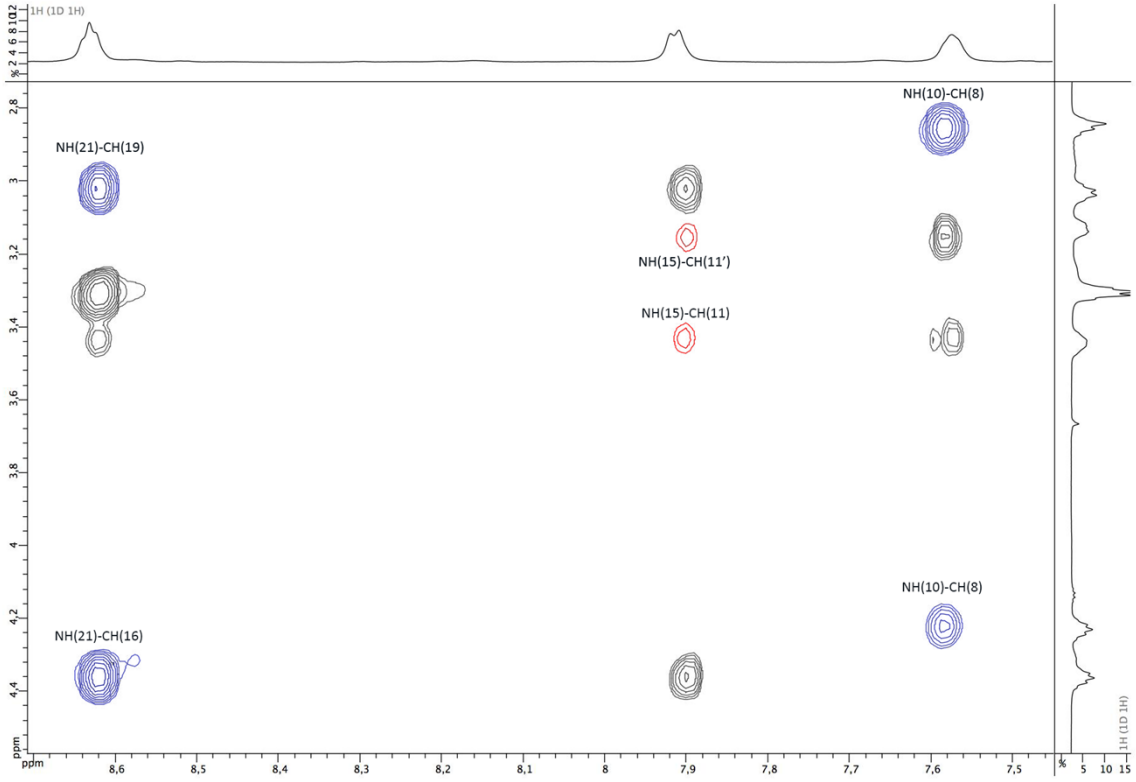
Boc-*t*ACBC-GABA-OBn (1)



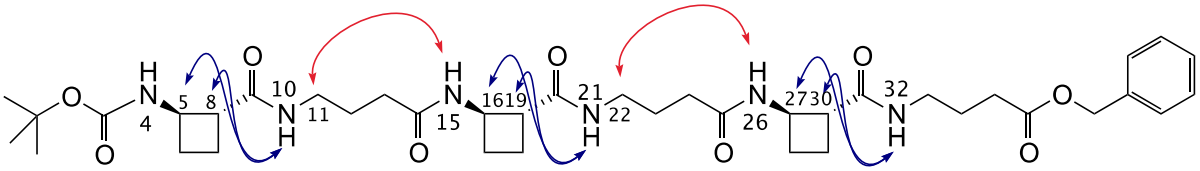


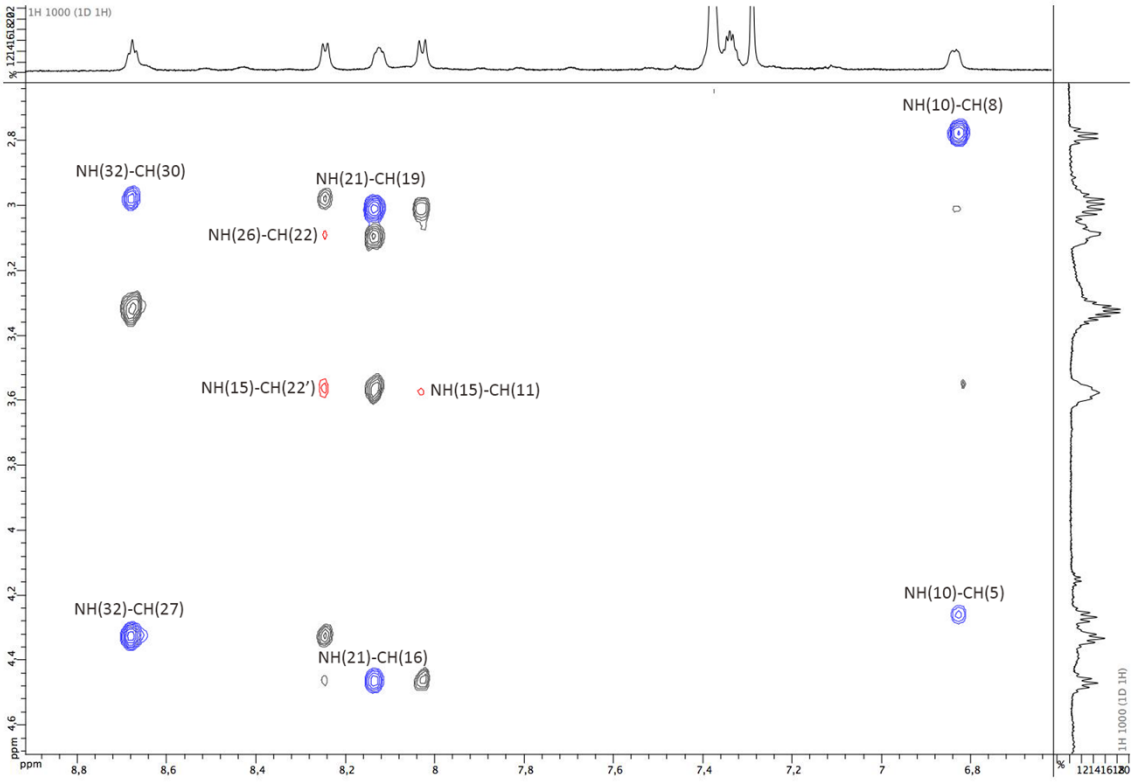
Boc-[*t*ACBC-GABA]$_2$-OBn (3)



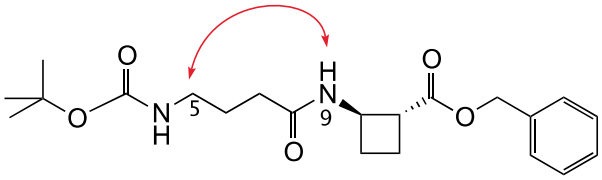


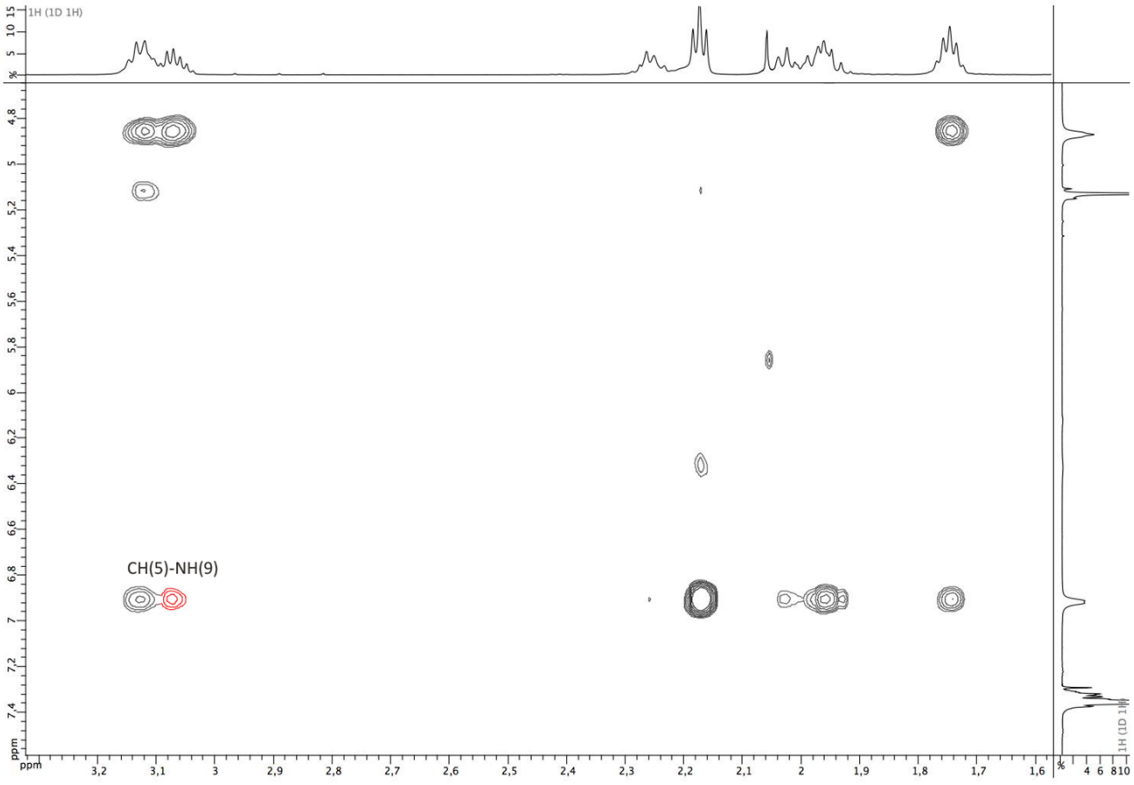
Boc-[*t*ACBC-GABA]$_3$-OBn (5)



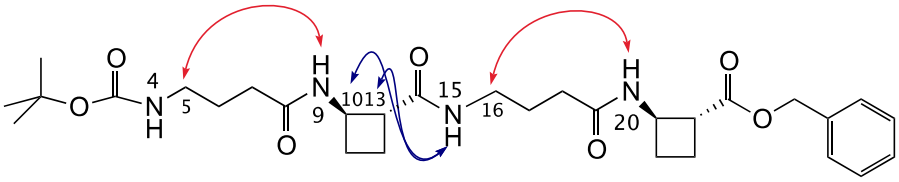


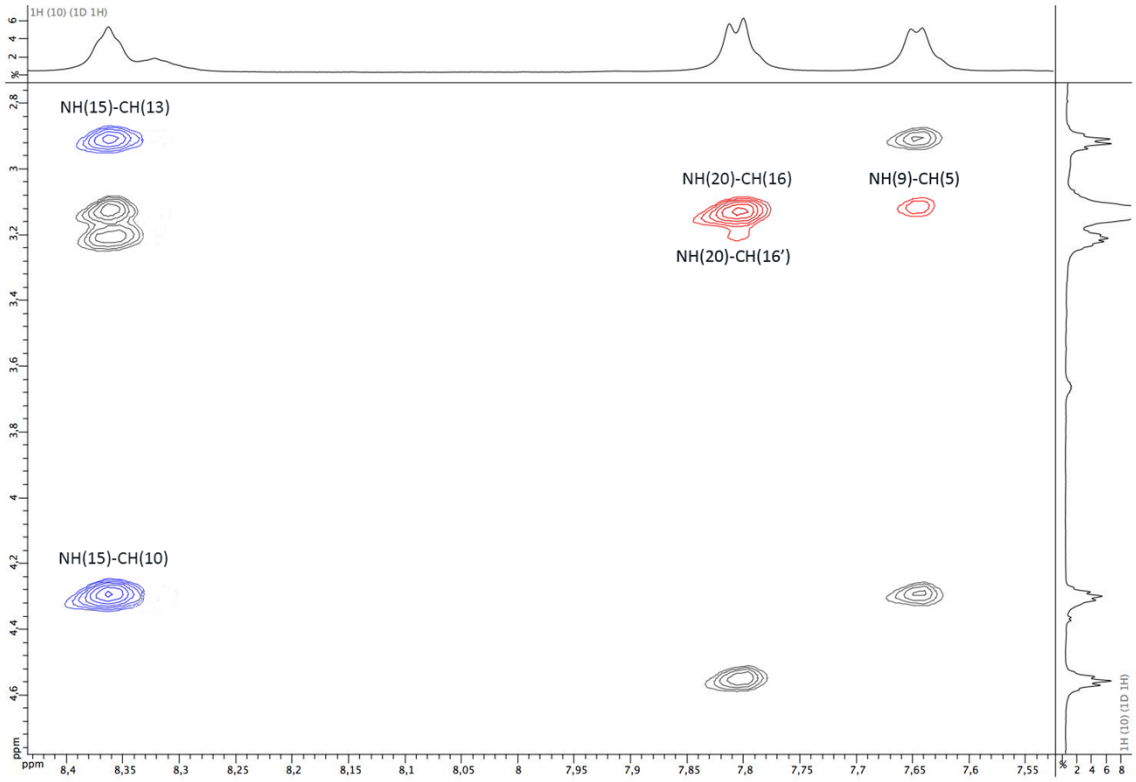
Boc-GABA-*t*ACBC-OBn (2)



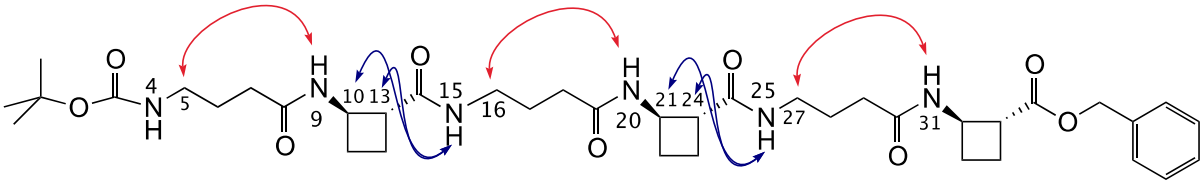


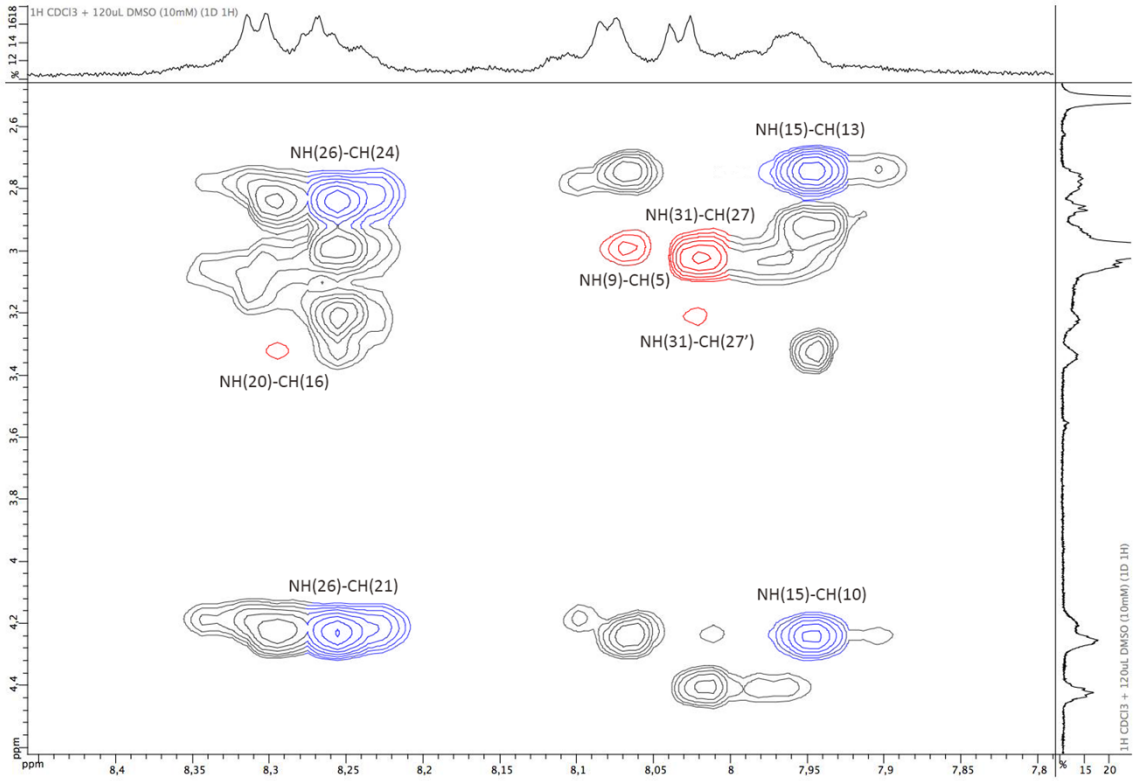
Boc-[GABA-*t*ACBC]$_2$-OBn (4)





Boc-[GABA-*t*ACBC]$_3$-OBn (6)





III. MOLECULAR MODELLING OF 3, 4, 5 AND 6

1. *Conformations obtained from a hybrid MCMM calculation*

A hybrid Monte Carlo Molecular Mechanics (MCMM) conformational search was carried out on **3, 4**, **5** and **6** in a chloroform medium using Macromodel 04 from Schrödinger software and the MMFF force field without restraints. 10 000 conformers were generated by MCMM. Low energy conformers (up to 10 kJ.mol^{-1} of relative energy) were retained. Different types of conformations were observed and were sorted according to the hydrogen-bonded (H-bonded) ring systems they possessed:

- the 9/8-ribbon type conformer is composed of an uninterrupted sequence of alternating and distinctive 9- and 8-membered H-bonded rings (C9 and C8).

- the other conformers are composed of 8-, 9-, 13- and 18-membered H-bonded rings. The discreet, successive rings are separated by the symbol "-" (*e.g.* 8-9). The 13- and 18-membered H-bonded rings implicate a carbonyl oxygen that is bifurcated between two amide hydrogens, thus forming two rings wherein the larger ring includes the smaller; the combined system is noted with the symbol ","(*e.g.* 8,13).

	Number of conformers < 10 kJ.mol^{-1}	Abundance of each conformer family (number of conformers of that family / total number of conformers; expressed as %)							
tetrapeptides		9/8-ribbon	8-9,13	9-8,13					
3	261	98%	2%	-					
4	616	94%	-	6%					
hexapeptides		9/8-ribbon	8-9-8-9,13	8-9-8,13-9	9-8-9-8,13	9-8-9,13-9	9-13-13-13	9-8,13-8,17	17,8-8,17
5	827	92%	5%	3%	-	-	-	-	-
6	961	75%	-	-	16%	2%	3%	2%	2%

2. *DFT optimization of conformers and Boltzmann distributions*

The geometries of the lowest energy conformers were optimized by DFT using GAUSSIAN 09 and the B3LYP/6-311G(d,p) basis set in a chloroform medium. When the optimization converged, the Gibbs free energy was calculated allowing determination of Boltzmann distributions at 300 K.

Boc-[*t*ACBC-GABA]$_2$-OBn (**3**)

Conformations	Relative Gibbs energy (kJ.mol^{-1})	Boltzmann distribution (%)
9/8-ribbon	0	100
8-9,13	13.6	0

Boc-[GABA-*t*ACBC]$_2$-OBn (**4**)

Conformations		Relative Gibbs energy (kJ.mol^{-1})	Boltzmann distribution (%)	
9/8-ribbon	A	0.20	25	99
	B	0	27	
	C	0.44	22	
	D	0.21	25	
9-8,13		7.30	1	

Boc-[*t*ACBC-GABA]$_3$-OBn (**5**)

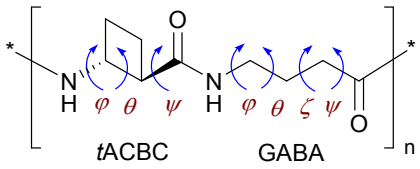
Conformations	Relative Gibbs energy (kJ.mol^{-1})	Boltzmann distribution (%)
9/8-ribbon	0	88.9
8-9-8-9,13	5.30	10.6
8-9-8,13-9	13.1	0.5

Boc-[GABA-*t*ACBC]$_3$-OBn (**6**)

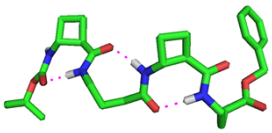
Conformations		Relative Gibbs energy (kJ.mol^{-1})	Boltzmann distribution (%)	
9/8-ribbon	A	0.07	12	93
	B	0.38	11	
	C	0.46	11	
	D	0.58	10	
	E	0.19	12	
	F	0.15	12	
	G	0.15	12	
	H	0	13	
9-8-9-8,13		1.48	7	
9-8-9,13-9		8.71	0	
9-13-13-13		10.5	0	
9-8,13-8,17		17.1	0	
17,8-8,17		did not converge	0	

3. *Lists of dihedral angles of the 9/8-ribbon conformers*

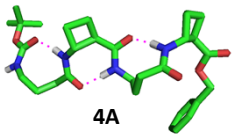
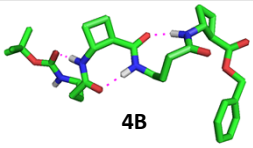
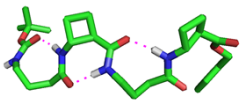
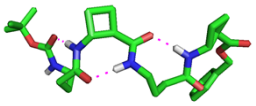
Dihedral angles are defined conventionally, as shown:



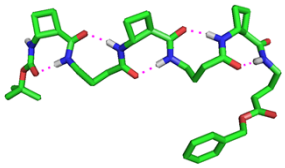
Boc-[*t*ACBC-GABA]$_2$-OBn (**3**)

Conformer (top-view)	residue	φ(°)	θ(°)	ζ(°)	ψ(°)
	*t*ACBC-1	88.4	–101.1		31.5
	GABA-2	–98.9	67.4	74.6	–87.7
	*t*ACBC-3	89.1	–101.1		29.5
	GABA-4	–109.1	60.3	64.9	–151.1

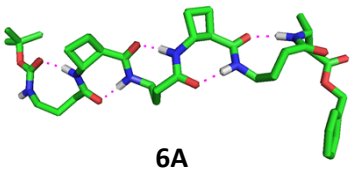
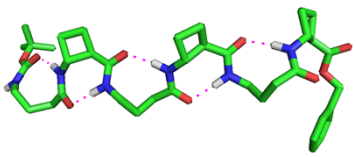
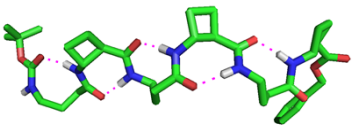
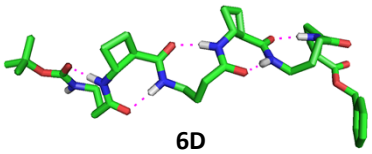
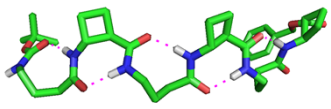
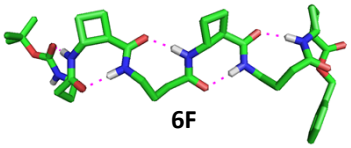
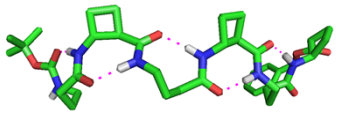
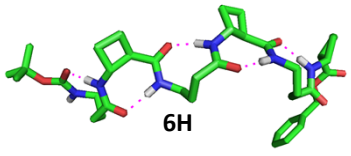
Boc-[GABA-*t*ACBC]$_2$-OBn (**4**)

Conformers (top-view)	residue	φ(°)	θ(°)	ζ(°)	ψ(°)
 **4A**	GABA-1	–98.6	66.1	74.5	–86.5
	*t*ACBC-2	87.4	–102.1		32.1
	GABA-3	99.8	–67.0	–74.4	89.4
	*t*ACBC-4	117.2	–97.6		91.9
 **4B**	GABA-1	100.8	–67.1	–75.0	94.3
	*t*ACBC-2	86.5	–100.9		30.5
	GABA-3	101.1	–68.5	–73.3	93.0
	*t*ACBC-4	93.5	–99.7		99.3
 **4C**	GABA-1	–101.3	67.3	74.8	–89.5
	*t*ACBC-2	88.0	–101.1		29.7
	GABA-3	–99.6	68.0	74.5	–88.4
	*t*ACBC-4	100.1	–99.1		95.9
 **4D**	GABA-1	100.2	–67.5	–74.2	94.1
	*t*ACBC-2	85.5	–101.4		30.5
	GABA-3	–99.8	67.2	75.1	–87.9
	*t*ACBC-4	104.0	–99.1		91.3

Boc-[*t*ACBC-GABA]$_3$-OBn (**5**)

Conformer (top-view)	residue	φ(°)	θ(°)	ζ(°)	ψ(°)
	*t*ACBC-1	88.6	–101.1		32.1
	GABA-2	–98.5	68.2	73.9	–89.3
	*t*ACBC-3	87.5	–101.4		32.6
	GABA-4	100.4	–68.8	–72.9	95.1
	*t*ACBC-5	87.8	–100.0		28.2
	GABA-6	–85.5	–56.4	–67.3	170.0

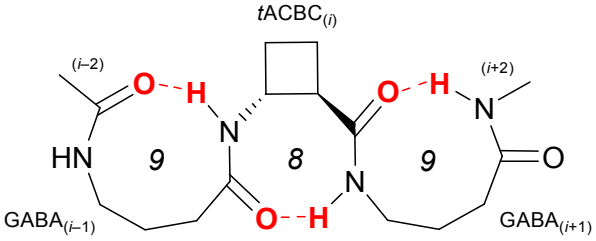
Boc-[GABA-*t*ACBC]$_3$-OBn (**6**)

Conformers (top-view)	residue	φ	θ	ζ	ψ
 **6A**	GABA-1	–100.6	66.8	75.4	–89.3
	*t*ACBC-2	88.6	–101.9		31.4
	GABA-3	101.5	–67.4	–73.7	93.1
	*t*ACBC-4	86.5	–101.3		31.9
	GABA-5	101.7	–67.3	–74.0	91.8
	*t*ACBC-6	95.9	–99.3		95.9
 **6B**	GABA-1	–101.0	67.2	74.9	–89.3
	*t*ACBC-2	87.9	–101.2		29.9
	GABA-3	–99.5	67.5	73.8	–87.8
	*t*ACBC-4	88.4	–101.1		30.7
	GABA-5	101.3	–67.5	–74.2	90.7
	*t*ACBC-6	90.4	–99.4		102.1
 **6C**	GABA-1	–99.7	68.0	74.4	–91.7
	*t*ACBC-2	87.3	–101.7		31.2
	GABA-3	100.3	–67.1	–74.4	90.1
	*t*ACBC-4	84.3	–102.3		31.5
	GABA-5	–100.0	67.6	74.6	–87.8
	*t*ACBC-6	96.5	–99.0		98.4
 **6D**	GABA-1	100.3	–67.6	–74.5	95.7
	*t*ACBC-2	87.4	–100.2		30.5
	GABA-3	101.2	–67.8	–73.4	93.5
	*t*ACBC-4	86.7	–101.1		32.1
	GABA-5	102.1	–67.5	–73.8	92.4
	*t*ACBC-6	96.3	–99.4		95.4
 **6E**	GABA-1	–100.4	66.9	74.5	–88.4
	*t*ACBC-2	88.6	–100.2		28.0
	GABA-3	–100.0	66.6	74.5	–87.1
	*t*ACBC-4	88.0	–100.8		29.2
	GABA-5	–99.4	67.5	74.9	–88.3
	*t*ACBC-6	101.9	–98.6		93.1
 **6F**	GABA-1	100.8	–67.4	–74.7	93.5
	*t*ACBC-2	85.5	–101.5		31.1
	GABA-3	–99.0	67.7	73.9	–88.0
	*t*ACBC-4	88.5	–101.2		31.1
	GABA-5	101.7	–67.5	–73.9	91.8
	*t*ACBC-6	98.2	–100.0		95.3
 **6G**	GABA-1	100.8	–67.6	–74.4	94.0
	*t*ACBC-2	85.9	–101.0		29.1
	GABA-3	–100.0	66.7	74.4	–87.2
	*t*ACBC-4	87.9	–101.0		29.6
	GABA-5	–99.3	67.6	74.8	–87.7
	*t*ACBC-6	100.9	–98.6		93.9
 **6H**	GABA-1	100.3	–67.0	–75.0	93.5
	*t*ACBC-2	85.6	–101.6		32.5
	GABA-3	100.8	-67.4	–74.0	92.5
	*t*ACBC-4	85.8	–101.2		31.1
	GABA-5	–99.5	67.3	75.1	–86.5
	*t*ACBC-6	103.3	–98.5		92.0

4. *Relationship between GABA local conformations and global molecular shape*

For any conformer, a GABA conformation set is expressed in terms of + or –, to represent G^+ or G^-, where G^+ represents a GABA residue having g^+ conformations for both the θ and ζ torsion angles and G^- represents a GABA residue having g^- conformations for both the θ and ζ torsion angles (data are taken from the tables in Section III.3 above).

For the same conformer, the relationship between successive H-bonded rings which constitute a C9/C8/C9 system centered around a residue *t*ACBC$_{(i)}$ is conveniently expressed in terms of the dihedral angle defined by the four-atom sets CO$_{(i-2)}$–HN$_{(i)}$–CO$_{(i-1)}$–HN$_{(i+2)}$ for the C9→C8 relationship and CO$_{(i-1)}$–HN$_{(i+1)}$–CO$_{(i)}$–HN$_{(i+2)}$ for the C8→C9 relationship, as illustrated below:



Only two value ranges are observed. For the C9→C8 relationship, these are from 164° to 178° which constitutes a "straight" (–) segment of the molecular architecture, or from 122° to 136° which constitutes a "bent" (∩) segment. For the C8→C9 relationship, the observed value ranges are from 160° to 168° for a "straight" (–) segment, or from –136° to –144° for a "bent" (∩) segment.

To determine the topology set for any C9/C8/C9 system, the 2-component GABA conformation set codes for a specific two-component topology set as follows:

2-Component GABA conformation set	Topology set
+ –	– –
– –	∩ –
+ +	– ∩
– +	∩ ∩

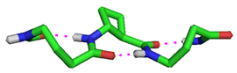
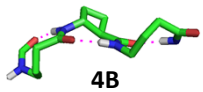
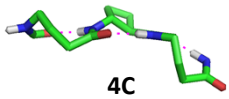
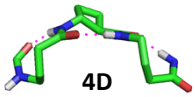
No C9/C8/C9 system is present in peptide **3**.

One 2-component GABA conformation set is prevalent in peptides **4** and **5**, since there is one C9/C8/C9 system in each peptide; these leads to a two-component topology set.

In peptide **6**, two successive 2-component GABA conformation sets are in evidence, leading to a four-component topology set.

By extension, the hypothetical octapeptide Boc-[GABA-*t*ACBC]$_4$-OBn, with three successive 2-component GABA conformation sets, would have a six-component topology set to describe the six distinct relationships between the seven successive H-bonded rings in the putative C9/C8/C9/C8/C9/C8/C9 system.

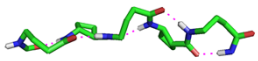
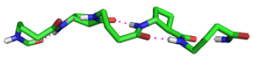
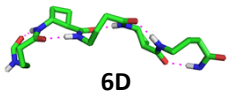
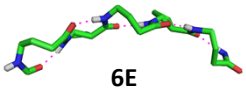
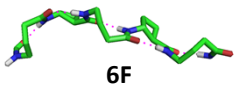
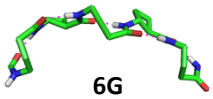
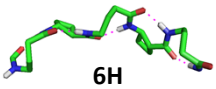
Boc-[GABA-*t*ACBC]$_2$-OBn (**4**)

Conformer (side-view, showing H-bonded core)	GABA conformation set	C9→C8 relationship (°)	C8→C9 relationship (°)	Topology set
 **4A**	+ –	164.7	164.7	– –
 **4B**	– –	126.3	166.8	∩ –
 **4C**	+ +	174.7	–140.8	– ∩
 **4D**	– +	127.5	–139.4	∩ ∩

Boc-[*t*ACBC-GABA]$_3$-OBn (**5**)

Conformer (side-view, showing H-bonded core)	GABA conformation set	C9→C8 relationship (°)	C8→C9 relationship (°)	Topology set
	+ –	172.2	163.8	– –

Boc-[GABA-*t*ACBC]$_3$-OBn (**6**)

Conformer (side-view, showing H-bonded core)	GABA conform-ation set	First C9→C8 relation-ship (°)	First C8→C9 relation-ship (°)	Second C9→C8 relation-ship (°)	Second C8→C9 relation-ship (°)	Topology set
 **6A**	+ − −	171.9	162.9	125.4	161.5	− − ∩ −
 **6B**	+ + −	173.9	–141.5	170.8	166.1	− ∩ − −
 **6C**	+ − +	178.0	167.3	135.6	–139.7	− − ∩ ∩
 **6D**	− − −	122.3	164.7	125.1	160.1	∩ − ∩ −
 **6E**	+ + +	170.3	–136.3	169.7	–138.1	− ∩ − ∩
 **6F**	− + −	128.1	–143.8	170.1	163.5	∩ ∩ − −
 **6G**	− + +	127.2	–136.8	170.0	–139.4	∩ ∩ − ∩
 **6H**	− − +	128.4	163.7	128.5	–142.8	∩ − ∩ ∩