Supporting Information for:

Stimulus Responsive Self-assembly of Gemini AmphiphilicPseudopeptides

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General

Reagents and solvents were purchased from commercial suppliers (Adrich, Fluka or Merck) and were used without further purification. The C_2 symmetrical bis(amidoamines) were prepared as previously described (see reference 71 of the manuscript)

Electron microscopy

Scanning Electron Microscopy was performed either in a LEO 440I or in a JEOL 7001F microscope with a digital camera. Samples were obtained by slow evaporation of a solution of the compounds (~1-2 mg/ml) directly onto the sample holder, and were conventionally coated previous to the measurement. Transmission Electron Microscopy was carried out in a in a JEOL 2100 microscope at 120 KV. The micrographs were obtained from ~1 mg/ml solutions onto a holey carbon copper grid. The samples were sonicated for 10 minutes previous to the measurement, one drop added onto the grid and collected directly without staining.

NMR spectroscopy

The NMR experiments were carried out on a Varian INOVA 500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C) or on a Varian UNITY 300 (300 MHz for ^{1}H and 75 MHz for ^{13}C). Chemical shifts are reported in ppm using TMS as a reference.

Infrared spectroscopy

FT-IR spectra were acquired in a JASCO 6200 equipment having a MIRacle Single Reflection ATR Diamond / ZnSe accessory. A 20 mM sample of the corresponding pseudopeptide was prepared and seeded onto the ATR sample holder. The FT-IR spectra were sequentially collected until the complete solvent evaporation. The raw IR data were processed with the JASCO spectral manager software and the deconvolution of the bands was performed with the Origin software, using Gaussian-shaped ideal peaks.

UV and CD spectroscopy

Spectra were recorded with a JASCO J-810 spectropolarimeter at RT. The normalized CD spectra were obtained by transforming the molar circular dichroic absorption data ($\Delta\varepsilon$, cm^2 $mmol^{-1}$) using the formula: $\Delta\varepsilon = \theta/(32980Cl)$, in which θ is the measured ellipticity (in mdeg), C is the cincentration (in M) and l is the pathlength (in cm). Molar extinction coeficients of the UV spectra were obtained by linear regresion between the measured absorbance and the sample concentration.

Steady-state fluorescence spectroscopy

Steady-state fluorescence spectra were recorded in a Spex Fluorog 3-11 equipped with a 450 W xenon lamp. Fluorescence spectra were recorded in the front face mode. All the samples were measured in aerated conditions otherwise stated.

Molecular Modeling

All the theoretical calculations were performed with Spartan 06 sofware, using the MMFF level of theory for the geometry optimizations.

General procedure for the reductive amination reaction

Synthesis of A2Val_a10obenz. The corresponding pseudopeptidic bis(amidoamine) precursor (216.0 mg, 0.836 mmol) was dissolved in 5 mL of $CHCl_3$ and the solution was placed inside a flask under nitrogen atmosphere. Then, 4-decyloxybenzaldehyde (476.1 µL, 452.3 mg, 1.672 mmol) was dissolved in 5 mL of $CHCl_3$, this solution was added over the solution of the diamine and afterwards**,** 7 mL of $CHCl_3$ were added until a final volume of 17 mL (0.05 M final concentration each). The mixture was stirred overnight, then a large excess of Py·BH_3 (889.0 µL, 817.9 mg, 8.36 mmol) was carefully added at 35 ºC, and the mixture was allowed to react for 24 h before being hydrolyzed (conc. HCl, to acidity) and evaporated to dryness. The residue obtained was dissolved in water, basified with 1N NaOH, and extracted with $CHCl_3$. The combined organic layers were dried ($MgSO_4$) and evaporated in vacuum. The product was purified by flash chromatography on silica gel using CH_2Cl_2 as eluent, increasing slowly the polarity with MeOH and several drops of aqueous ammonia.

Yield = 63%; mp 95-104 ºC; $[\alpha]_D^{25}$ = -27.0 (c = 0.01, $CHCl_3$); IR (ATR) 3303, 2921, 2851, 1641, 1555, 1513 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.79 (m, 18H), 0.86 (m, 24H), 1.23 (m, 4H), 1.38 (s, 2H), 1.48 (m, 4H), 1.7 (m, 2H), 2.01 (m, 2H), 2.87 (m, 4H), 3.35 (dd, 2H, J = 5.2, 8.1 Hz), 3.45 (dd, 2H, J = 5.4, 8.2 Hz), 3.61 (t, 4H, J=6.6 Hz), 6.77 (d, 4H, J = 6.77 Hz), 7.10 (d, 4H, J = 7.10 Hz), 7.53 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.3, 18.0, 19.8, 22.9, 26.3, 29.5, 29.8, 29.9, 31.5, 32.1, 39.6, 53.1, 68.0, 68.3, 114.8, 129.5, 131.7, 158.7, 174.7; HRMS (ESI-TOF)$^+$ measured for $C_{46}H_{78}N_4O_4$ $(M + H)^+$: 751.6101; found 751.6102; Anal. Calcd. for $C_{46}H_{78}N_4O_4 \cdot H_2O$: C, 71.93; H, 11.17; N, 6.70; found: C, 71.83; H, 10.98; N, 6.90. A small ammount of the monoalkylated by-product was also isolated: Yield = 5%; mp 78-82 ºC; $[\alpha]_D^{25}$ = –2.5 (c = 0.01, $CHCl_3$); IR (ATR) 3299, 2958, 2852, 1631, 1553, 1513, 1467, 1244 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.81 (d, 6H, J = 6.7 Hz), 0.87 (m, 3H), 0.95 (d, 6H, J = 6.0 Hz), 1.30 (m, 12H), 1.43 (m, 2H), 1.65 (m, 2H), 1.76 (td, 1H, J = 6.6, 13.0 Hz), 2.08 (m, 1H), 2.25 (m, 1H), 2.96 (s, 1H), 3.19 (s, 1H), 3.40 (t, 4H, J = 12.5 Hz), 3.55 (d, 1H, J = 12.8 Hz), 3.69 (d, 1H, J = 11.4 Hz), 3.93 (t, 2H, J = 6.5 Hz), 6.84 (m, 2H), 7.19 (m, 2H), 7.61 (s, 2H), 7.69 (s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.3, 16.4, 18.1, 19.7, 22.9, 26.3, 29.5, 29.6, 29.8, 31.0, 31.4, 32.1, 39.3, 39.8, 52.9, 60.4, 67.9, 68.3, 114.8, 129.6, 131.4, 158.8, 174.7, 175.1; HRMS (ESI-TOF)$^+$ calcd. for $C_{29}H_{52}N_4O_3$ $(M + H)^+$: 505.4118; found 505.4114; Anal. Calcd. for $C_{29}H_{52}N_4O_3$: C, 69.01; H, 10.38; N, 11.10; found: C, 68.85; H, 10.70; N, 11.43.

A3Val_a10obenz. Yield = 68%; mp 89-94 ºC; [α]D25 = -35.6 (c = 0.01, CHCl3); IR (ATR) 3323, 2852, 1631, 1547, 1512, 1467 cm-1; ^{1}H-NMR (500 MHz, CDCl3) δ 0.88 (t, 6H, J = 6.9 Hz), 0.92 (d, 6H, J = 6.6 Hz), 0.96 (d, 6H, J = 6.9 Hz), 1.30 (m, 24H), 1.44 (m, 4H), 1.67 (m, 2H), 1.76 (m, 4H), 2.15 (td, 2H, J = 13.4, 26.9 Hz), 3.06 (s, 2H), 3.30 (m, 4H), 3.64 (d, 2H, J = 2.9 Hz), 3.77 (d, 2H, J = 12.8 Hz), 3.92 (t, 4H, J = 6.6 Hz), 6.84 (d, 4H, J = 8.4 Hz), 7.25 (d, 4H, J = 8.5 Hz), 7.64 (s, 2H); ^{13}C-NMR (125 MHz, CDCl3) 14.3, 18.3, 19.6, 22.9, 26.3, 29.5, 29.6, 29.7, 29.8, 29.9, 30.2, 31.2, 32.1, 36.1, 52.8, 67.8, 68.3, 114.2, 129.9, 130.0, 158.9, 173.9; HRMS (ESI-TOF)$^+$ calc for $C_{47}H_{80}N_4O_4$ $(M + H)^+$: 765.6258; found 765.6264; Anal. Calcd. for $C_{47}H_{80}N_4O_4 \bullet 2H_2O$: C, 70.46; H, 10.57; N, 6.99; found: C, 70.01; H, 10.53; N, 7.13. Monoalkylated by-product: Yield = 15 %; mp 72-78 ºC; $[\alpha]_D^{25}$ = –26.3 (c = 0.01, $CHCl_3$); IR (ATR) 3299, 2954, 2922, 2867, 1637, 1542, 1509, 1467, 1245 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.86 (m, 3H), 0.94 (d, 6H, J = 6.9 Hz), 0.99 (d, 6H, J = 6.9 Hz), 1.30 (m, 12H), 1.44 (m, 2H), 1.66 (m, 2H), 1.76 (m, 2H), 2.09 (m, 2H), 2.27 (m, 1H), 2.96 (d, 2H, J = 4.6 Hz), 3.29 (m, 4H), 3.57 (d, 1H, J = 12.9 Hz), 3.70 (d, 1H, J = 12.8 Hz), 3.93 (t, 2H, J = 6.6 Hz), 6.84 (d, 2H, J = 8.7 Hz), 7.20 (d, 2H, J = 8.6 Hz), 7.57 (t, 2H, J = 6.3 Hz), 7.69 (d, 2H, J = 5.5 Hz); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.3, 16.7, 18.1, 19.8, 22.9, 26.3, 29.5, 29.6, 29.8, 30.2, 31.2, 31.4, 32.1, 36.0, 53.1, 60.5, 68.0, 68.3, 114.8, 129.7, 131.2, 158.7, 173.2, 174.3; HRMS (ESI-TOF)$^+$ calcd. for $C_{30}H_{54}N_4O_3$ $(M + H)^+$: 519.4274; found 519.4273; Anal. Calcd. for $C_{30}H_{54}N_4O_3$: C, 69.46; H, 10.49; N, 10.80; found: C, 69.27; H, 10.84; N, 10.85.

A4Val_a10obenz. Yield = 66%; mp 85-89 ºC; $[\alpha]_D^{25}$ = -17.8 (c = 0.01, $CHCl_3$); IR (ATR) 3302, 2921, 2852, 1632, 1549, 1513 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.87 (m, 12H), 0.93 (d, 6H, J = 6.9 Hz), 1.30 (m, 24H), 1.44 (m, 4H), 1.55 (m, 4H), 1.76 (m, 4H), 1.88 (s, 2H), 2.10 (dt, 2H, J = 6.8, 13.5 Hz), 2.97 (d, 2H, J = 4.3 Hz), 3.29 (tdd, 4H, J = 5.98, 12.1, 24.1 Hz), 3.56 (d, 2H, J = 12.9 Hz), 3.68 (d, 2H, J = 12.9 Hz), 3.92 (t, 4H, J = 6.6 Hz), 6.84 (d, 4H, J = 8.4 Hz), 7.17 (d, 4H, J = 8.3 Hz), 7.35 (s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.3, 18.0, 19.8, 22.9, 26.3, 27.5, 29.5, 29.6, 29.8, 29.9, 31.4, 32.1, 38.7, 53.1, 68.0, 68.3, 114.8, 129.6, 131.4, 158.8, 173.6; HRMS (ESI-TOF)$^+$ calc for $C_{48}H_{82}N_4O_4$ $(M + H)^+$: 779.6414; found 779.6421; Anal. Calcd. for $C_{48}H_{82}N_4O_4 \cdot H_2O$: C, 72.32; H, 10.62; N, 7.03; found: C, 72.44; H, 10.71; N, 7.02. Monoalkylated by-product: Yield = 19 %; mp 65-67 ºC; $[\alpha]_D^{25}$ = –25.3 (c = 0.01, $CHCl_3$); IR (ATR) 3300, 2940, 2865, 1637, 1542, 1509, 1457, 1245 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.81 (d, 3H, J = 6.9 Hz), 0.86 (m, 6H), 0.93 (d, 3H, J = 6.9 Hz), 0.97 (d, 3H, J

= 7.0 Hz), 1.31 (m, 12H), 1.43 (m, 2H), 1.53 (m, 4H), 1.76 (m, 2H), 1.88 (s, 1H), 2.08 (m, 1H), 2.27 (qd, 1H, J = 6.7, 13.5 Hz), 2.94 (d, 2H, J = 4.4 Hz), 3.26 (m, 4H), 3.55 (d, 1H, J = 12.8 Hz), 3.66 (d, 1H, J = 12.9 Hz), 3.93 (t, 2H, J = 6.6 Hz), 6.84 (d, 2H, J = 8.4 Hz), 7.16 (d, 2H, J = 8.3 Hz), 7.34 (t, 2H, J = 5.6 Hz), 7.41 (s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.3, 16.5, 18.0, 19.8, 22.9, 26.3, 27.3, 27.6, 29.5, 29.6, 29.8, 31.0, 31.4, 31.4, 32.1, 38.7, 38.8, 53.1, 60.3, 68.0, 68.3, 114.8, 129.5, 131.6, 158.7, 173.7, 174.2; HRMS (ESI-TOF)$^+$ calcd. for $C_{31}H_{56}N_4O_3$ $(M + H)^+$: 533.4431; found 533.4431; Anal. Calcd. for $C_{31}H_{56}N_4O_3 \cdot 2H_2O$: C, 65.46; H, 10.63; N, 9.85; found: C, 65.52; H, 10.89; N, 9.36.

A5Val_a10obenz. Yield = 38%; mp 95-96 ºC; [α]D25 = -21.2 (c = 0.01, CHCl3); IR (ATR) 3310, 2957, 2921, 2851, 1682, 1641, 1510 cm-1; 1H-NMR (500 MHz, CDCl3) δ 0.86 (m, 12H), 0.92 (d, 6H, J = 6.7 Hz), 1.26 (m, 26H), 1.42 (m, 4H). 1.53 (m, 4H), 1.75 (m, 4H), 2.08 (m, 2H), 2.94 (d, 2H, J = 3.8 Hz), 3.25 (m, 4H), 3.55 (d, 2H, J = 12.8 Hz), 3.67 (d, 2H, J = 12.9 Hz), 3.92 (t, 4H, J = 6.3 Hz), 6.84 (d, 4H, J = 8.1 Hz), 7.17 (d, 4H, J = 8.0 Hz), 7.29 (s, 2H); 13C-NMR (125 MHz, CDCl3) δ 14.1, 17.8, 19.6, 22.6, 24.3, 26.0, 29.3, 29.4, 29.4, 29.4, 29.5, 29.5, 31.2, 31.9, 38.7, 52.9, 67.8, 68.0, 114.5, 129.3, 131.4, 158.5, 173.3; HRMS (ESI-TOF)+ calc for C49H84N4O4 (M + H)+: 793.6571; found 793.6565; Anal. Calcd. for $C_{49}H_{84}N_4O_4$: C, 74.19; H, 10.67; N, 7.06; found: C, 74.38; H, 10.33; N, 7.36. Monoalkylated by-product: Yield = 19%; mp 67-68 ºC; $[\alpha]_D^{25}$ = -29.0 (c = 0.01, $CHCl_3$); IR (ATR) 3296, 2955, 2920, 2852, 1638, 1549, 1511 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.77 (d, 3H, J = 6.9 Hz), 0.83 (m, 6H), 0.89 (d, 3H, J = 6.9 Hz), 0.92 (d, 3H, J = 7.0 Hz), 1.29 (m, 14H), 1.40 (m, 2H), 1.49 (m, 4H), 1.72 (m, 2H), 2.03 (m, 1H), 2.22 (m, 1H), 2.89 (d, 2H, J = 4.6 Hz), 3.14 (d, 2H, J = 3.8 Hz), 3.21 (m, 4H), 3.51 (d, 1H, J = 12.9 Hz), 3.63 (d, 1H, J = 12.9 Hz), 3.89 (t, 2H, J = 6.6 Hz), 6.81 (d, 2H, J = 8.5 Hz), 7.13 (d, 2H, J = 8.5 Hz), 7.27 (s, 1H), 7.32 (s, 1H) ; ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.0, 16.1, 17.8, 19.6, 19.6, 22.6, 24.2, 26.0, 29.2, 29.3, 29.4, 29.4, 29.5, 29.5, 29.5, 30.8, 31.2, 31.8, 38.6, 38.7, 52.8, 60.1, 67.8, 68.0, 114.5, 129.2, 131.5, 158.4, 173.5, 174.2; HRMS (ESI-TOF)$^+$ calc for $C_{32}H_{58}N_4O_3$ $(M + H)^+$: 547.4587; found 547.4594; Anal. Calcd. for $C_{32}H_{58}N_4O_3 \cdot H_2O$: C, 68.04; H, 10.71; N, 9.92; found: C, 67.92; H, 10.87; N, 9.94.

A6Val_a10obenz. Yield = 67%; mp 93-95 ºC; $[\alpha]_D^{25}$ = -3.2 (c = 0.01, $CHCl_3$); IR (ATR) 3293, 2954, 2922, 2852, 1638, 1553, 1510 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.88 (m, 12H), 0.94 (d, 6H, J = 6.5 Hz), 1.31 (m, 28H), 1.44 (m, 4H), 1.51 (m, 4H), 1.76 (m, 4H), 2.12 (m, 2H), 2.99 (m, 2H), 3.26 (m, 4H), 3.59 (d, 2H, J = 12.8 Hz), 3.70 (d, 2H, J = 12.8 Hz), 3.93 (t, 4H, J = 6.1 Hz), 6.85 (d, 4H, J = 7.9 Hz), 7.19 (d, 4H, J = 7.9 Hz), 7.33 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.1, 17.9, 19.5, 22.6, 26.0, 26.4, 29.3, 29.3, 29.4, 29.5, 29.5, 29.7, 31.1, 31.9, 38.7, 52.7, 67.7, 68.1, 114.6, 129.4, 158.6, 172.9; HRMS (ESI-TOF)$^+$ calc for $C_{50}H_{86}N_4O_4$ $(M + H)^+$: 807.6121; found 807.6129; Anal. Calcd. for $C_{50}H_{86}N_4O_4$: C, 74.39; H, 10.74; N, 6.94; found: C, 74.44; H, 10.64; N, 6.91. Monoalkylated by-product: Yield = 9%; $[\alpha]_D^{25}$ = -5.3 (c = 0.01, $CHCl_3$); IR (ATR) 3310, 2953, 2922, 2853, 1641, 1613, 1550, 1510 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.79 (d, 3H, J = 6.9 Hz), 0.84 (m, 6H), 0.91 (d, 3H, J = 7.0 Hz), 0.95 (d, 3H, J = 7.0 Hz), 1.29 (m, 16H), 1.44 (m, 6H), 1.65 (td, 1H, J = 5.6, 11.2 Hz), 1.74 (m, 2H), 2.05 (m, 1H), 2.25 (m, 1H), 2.91 (d, 1H, J = 4.5 Hz), 3.23 (m, 4H), 3.53 (d, 1H, J = 12.9 Hz), 3.65 (d, 1H, J = 12.9 Hz), 3.91 (t, 2H, J = 6.5 Hz), 6.83 (d, 2H, J = 8.4 Hz), 7.15 (d, 2H, J = 8.5 Hz), 7.31 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.1, 16.1, 17.7, 19.6, 19.7, 22.6, 26.0, 26.4, 26.5, 29.3, 29.4, 29.5, 29.5, 29.5, 29.6, 29.7, 30.8, 31.2, 31.8, 38.6, 38.7, 52.9, 60.2, 67.8, 68.0, 114.5, 129.2, 131.6, 158.4, 173.5, 174.3; HRMS (ESI-TOF)$^+$ calc for $C_{33}H_{60}N_4O_3$ $(M + H)^+$: 561.4744; found 561.4752; Anal. Calcd. for $C_{33}H_{60}N_4O_3$: C, 70.67; H, 10.78; N, 9.99; found: C, 71.00; H, 10.51; N, 10.02.

A2Phe_a10obenz. Yield = 66%; mp 131-136 ºC; $[\alpha]_D^{25}$ = -33.4 (c = 0.01, $CHCl_3$); IR (ATR) 3345, 3278, 2920, 2851, 1652, 1511, 1468 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.89 (t, 6H, J = 6.6 Hz), 1.32 (m, 24H), 1.42 (m, 4H), 1.75 (m, 4H), 2.77 (m, 2H), 3.15 (d, 2H, J= 13.8 Hz),

3.38 (m, 6H), 3.45 (m, 2H), 3.63 (d, 2H, J = 13.0 Hz), 3.89 (t, 4H, J = 6.5 Hz), 6.76 (d, 4H, J = 8.4 Hz), 6.99 (d, 4H, J = 6.6 Hz), 7.13 (d, 4H, J = 7.3 Hz), 7.20 (t, 4H, J = 7.2 Hz), 7.26 (t, 2H, J = 7.3 Hz), 7.43 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.1, 22.6, 25.9, 29.1, 29.3, 29.5, 30.2, 31.4, 31.9, 35.1, 38.6, 52.8, 60.2, 68.1, 114.8, 123.9, 124.4, 127.8, 129.0, 129.7, 131.9, 160.1, 171.9; HRMS (ESI-TOF)$^+$ calc for $C_{54}H_{78}N_4O_4$ $(M + H)^+$: 847.6101; found 847.6115; Anal. Calcd. for $C_{54}H_{78}N_4O_4 \cdot 6H_2O$: C, 67.89; H, 9.50; N, 5.86; found: C, 67.85; H, 8.86; N, 5.65. Monoalkylated by-product: Yield = 21%; mp 110-112 ºC; $[\alpha]_D^{25}$ = –26.3 (c = 0.01, $CHCl_3$); IR (ATR) 3281, 2922, 2854, 1648, 1509, 1245 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 6.6 Hz), 1.30 (m, 14H), 1.43 (s, 1H), 1.75 (m, 2H), 2.15 (s, 2H), 2.73 (m, 2H), 3.19 (m, 2H), 3.34 (m, 4H), 3.50 (d, 1H, J = 13.2 Hz), 3.59 (m, 1H), 3.65 (d, 1H, J = 13.1 Hz), 3.89 (t, 2H, J = 6.6 Hz), 6.77 (d, 2H, J = 8.5 Hz), 7.00 (d, 2H, J = 8.3 Hz), 7.14 (d, 2H, J = 7.5 Hz), 7.19 (d, 2H, J = 7.5 Hz), 7.23 (m, 4H), 7.29 (m, 2H), 7.52 (s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.3, 22.9, 26.3, 29.5, 29.6, 29.8, 29.9, 30.4, 31.6, 32.1, 39.3, 39.6, 41.1, 52.1, 56.7, 63.1, 68.3, 114.7, 127.1, 127.1, 128.9, 129.0, 129.4, 129.4, 129.5, 137.4, 137.9, 158.7, 164.3, 174.7; HRMS (ESI-TOF)$^+$ calcd. for $C_{37}H_{52}N_4O_3$ $(M + H)^+$: 601.4117; found 601.4111; Anal. Calcd. for $C_{37}H_{52}N_4O_3$: C, 73.96; H, 8.72; N, 9.32; found: C, 75.61; H, 8.57; N, 9.13.

A3Phe_a10obenz. Yield = 61%; mp 81-83 ºC; $[\alpha]_D^{25}$ = -50.8 (c = 0.01, $CHCl_3$); IR (ATR) 3310, 2922, 2852, 1638, 1611, 1541, 1509, 1471, 1245 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 6H, J = 6.5 Hz), 1.27 (m, 24H), 1.43 (m, 4H), 1.58 (m, 2H), 1.68 (s, 2H), 1.75 (m, 4H), 2.75 (dd, 2H, J = 9.3 Hz), 3.18 (m, 6H), 3.37 (dd, 2H, J = 4.3, 9.0 Hz), 3.48 (d, 2H, J = 13.1 Hz), 3.66 (d, 2H, J = 13.1 Hz), 3.91 (t, 4H, J = 6.5 Hz), 6.77 (d, 4H, J = 8.3 Hz), 7.00 (d, 4H, J = 8.2 Hz), 7.16 (d, 4H, J = 6.9 Hz), 7.25 (m, 6H), 7.54 (t, 2H, J = 5.3 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.1, 22.6, 26.0, 29.3, 29.4, 29.6, 29.6, 30.0, 31.9, 35.6, 39.3, 52.1, 63.1, 68.1, 114.5, 126.8, 128.7, 129.1, 131.1, 137.5, 158.3, 174.0; HRMS (ESI-TOF)$^+$ calc for $C_{55}H_{80}N_4O_4$ $(M + H)^+$: 861.6258; found 861.6262; Anal. Calcd. for $C_{55}H_{80}N_4O_4$: C, 76.70; H, 9.36; N, 6.51; found: C, 76.72; H, 9.68; N, 6.25. Monoalkylated by-product: Yield = 19 %; mp 73-76 ºC; $[\alpha]_D^{25}$ = –19.0 (c = 0.01, $CHCl_3$); IR (ATR) 3305, 2921, 2850, 1640, 1543, 1510, 1444, 1241 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 6.8 Hz), 1.29 (m, 12H), 1.43 (s, 2H), 1.59 (m, 2H), 1.75 (m, 2H), 2.12 (s, 2H), 2.76 (td, 2H, J = 9.4, 13.7 Hz), 3.19 (m, 6H), 3.39 (dd, 2H, J = 4.4, 9.1 Hz), 3.49 (d, 1H, J = 13.1 Hz), 3.65 (d, 1H, J = 13.2 Hz), 3.90 (m, 2H), 6.77 (d, 2H, J = 8.3 Hz), 6.99 (d, 2H, J = 8.3 Hz), 7.15 (d, 2H, J = 7.1 Hz), 7.26 (m, 8H), 7.56 (s, 1H), 7.63 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.1, 22.6, 26.0, 29.3, 29.3, 29.4, 29.5, 29.5, 29.7, 31.9, 35.7, 39.2, 41.0, 52.1, 56.6, 63.0, 68.1, 114.5, 126.8, 128.6, 128.7, 129.1, 129.2, 129.3, 130.8, 137.3, 137.8, 158.4, 174.0, 174.2 ; HRMS (ESI-TOF)$^+$ calc for $C_{38}H_{54}N_4O_3$ $(M + H)^+$: 615.4274; found 615.4278; Anal. Calcd. for $C_{38}H_{54}N_4O_3 \cdot 4H_2O$: C, 66.44; H, 9.10; N, 8.16; found: C, 66.06; H, 9.01; N, 8.55.

A4Phe_a10obenz. Yield = 74%; mp 100-104 ºC; $[\alpha]_D^{25}$ = -47.3 (c = 0.01, $CHCl_3$); IR (ATR) 3332, 3286, 2919, 2851, 1631, 1612, 1534, 1509, 1466 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.89 (t, 6H, J = 6.9 Hz), 1.31 (m, 24H), 1.43 (m, 8H), 1.76 (m, 4H), 2.31 (s, 2H), 2.76 (dd, 2H, J = 9.1, 13.8 Hz), 3.18 (d, 2H, J = 4.4 Hz), 3.24 (m, 4H), 3.40 (dd, 2H, J = 4.5, 8.8 Hz), 3.49 (d, 2H, J = 13.1 Hz), 3.62 (d, 2H, J = 13.1 Hz), 3.89 (t, 4H, J = 6.6 Hz), 6.77 (d, 4H, J = 8.5 Hz), 6.98 (d, 4H, J = 8.4 Hz), 7.15 (d, 4H, J = 6.9 Hz), 7.22 (m, 2H), 7.27 (m, 4H), 7.35 (t, 2H, J = 5.6 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 26.0, 27.0, 29.3, 29.3, 29.4, 29.5, 29.6, 31.9, 38.6, 39.1, 52.0, 63.0, 68.0, 114.5, 126.8, 128.5, 128.7, 129.1, 129.1, 137.3, 158.4, 173.2; HRMS (ESI-TOF)$^+$ calc for $C_{56}H_{82}N_4O_4$ $(M + H)^+$: 875.6414; found 875.6419; Anal. Calcd. for $C_{56}H_{82}N_4O_4$: C, 78.17; H, 11.21; N, 5.46; found: C, 77.76; H, 11.30; N, 5.85. Monoalkylated by-product: Yield = 23 %; mp 97-104 ºC; $[\alpha]_D^{25}$ = –44.6 (c = 0.01, $CHCl_3$); IR (ATR) 3292, 2920, 2852, 1639, 1529, 1509, 1466, 1244 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 6.7 Hz), 1.29 (m, 12H), 1.44 (m, 6H), 1.75 (m, 2H), 1.99 (m, 3H), 2.72 (m,

2H), 3.18 (m, 2H), 3.24 (m, 4H), 3.36 (dd, 2H, J = 4.3, 9.1 Hz), 3.47 (d, 1H, J = 13.1 Hz), 3.60 (d, 1H, J = 13.2 Hz), 3.90 (t, 2H, J = 6.6 Hz), 6.77 (d, 2H, J = 8.5 Hz), 6.96 (d, 2H, J = 8.5 Hz), 7.14 (d, 2H, J = 6.9 Hz), 7.22 (m, 6H), 7.27 (m, 2H), 7.50 (s, 2H), 7.54 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.1, 22.6, 26.0, 26.9, 27.1, 29.3, 29.3, 29.4, 29.5, 29.5, 31.9, 38.6, 38.7, 39.2, 41.0, 52.1, 56.5, 63.0, 68.1, 114.5, 126.8, 126.8, 128.6, 128.7, 129.0, 129.1, 129.3, 131.0, 137.4, 137.9, 158.4, 173.6, 174.1; HRMS (ESI-TOF)$^+$ calcd. for $C_{39}H_{56}N_4O_3$ (M + H)$^+$: 629.4431; found 629.4435; Anal. Calcd. for $C_{39}H_{56}N_4O_3$: C, 75.77; H, 9.20; N, 7.52; found: C, 75.45; H, 9.50; N, 7.63.

A2Val_a8. Yield = 26%; mp 100-105 ºC; $[\alpha]_D^{25}$ = -65.0 (c = 0.01, $CHCl_3$); IR (ATR) 3288, 3085, 2957, 2921, 2853, 1632, 1556, 1450 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.87 (m, 12H), 0.97 (d, 6H, J = 6.9 Hz), 1.32 (m, 24H), 1.44 (s, 2H), 2.08 (m, 2H), 2.49 (t, 4H, J = 6.9 Hz), 2.86 (d, 2H, J = 3.0 Hz), 3.39 (m, 4H), 7.64 (s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.3, 18.0, 19.8, 22.9, 27.5, 29.5, 29.7, 30.4, 31.5, 32.0, 39.4, 49.9, 68.7, 175.0; HRMS (ESI-TOF)$^+$ calc for $C_{28}H_{58}N_4O_2$ (M + H)$^+$: 483.4638; found 483.4635; Anal. Calcd. for $C_{28}H_{58}N_4O_2$: C, 69.66; H, 12.11; N, 11.60; found: C, 70.00; H, 12.29; N, 11.30.

A3Val_a8. Yield = 21%; mp 89-90 ºC; $[\alpha]_D^{25}$ = -37.8 (c = 0.01, $CHCl_3$); IR (ATR) 3284, 2955, 2923, 2854, 1638, 1557, 1542 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.87 (t, 6H, J = 6.6 Hz), 0.98 (d, 12H, J = 6.9 Hz), 1.27 (m, 20H), 1.36 (s, 2H), 1.44 (td, 4H, J = 6.1, 12.4 Hz), 1.67 (m, 2H), 2.10 (m, 2H), 2.51 (m, 4H), 2.86 (d, 2H, J = 4.5 Hz), 3.29 (m, 4H), 7.57 (s, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.3, 18.0, 19.9, 22.8, 27.5, 29.5, 29.7, 30.4, 31.5, 32.0, 35.9, 49.9, 68.9, 174.6; HRMS (ESI-TOF)$^+$ calc for $C_{29}H_{60}N_4O_2$ (M + H)$^+$: 497.4795; found 497.4799; Anal. Calcd. for $C_{29}H_{60}N_4O_2$: C, 70.11; H, 12.17; N, 11.28; found: C, 70.45; H, 12.40; N, 10.93.

A4Val_a8. Yield = 32%; mp 84-87 ºC; $[\alpha]_D^{25}$ = -30.3 (c = 0.01, $CHCl_3$); IR (ATR) 3281, 2921, 2851, 1637, 1542, 1509, 1466, 1245 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.87 (m, 12H), 0.97 (m, 6H), 1.29 (m, 24H), 1.43 (m, 2H), 1.54 (m, 4H), 2.10 (m, 2H), 2.46 (m, 4H), 2.81 (d, 1H, J = 4.3 Hz), 2.86 (d, 1H, J = 4.3 Hz), 3.23 (m, 2H), 3.33 (m, 2H), 7.35 (m, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.0, 17.6, 19.6, 22.6, 27.2, 27.3, 29.2, 29.4, 30.2, 31.2, 31.8, 38.4, 49.7, 68.6, 173.9; HRMS (ESI-TOF)$^+$ calc for $C_{30}H_{62}N_4O_2$ (M + H)$^+$: 511.4951; found 511.4958; Anal. Calcd. for $C_{30}H_{62}N_4O_2$: C, 70.54; H, 12.23; N, 10.97; found: C, 70.45; H, 12.57; N, 10.52.

A4Ala_a10obenz . Yield = 48%; mp 101-103 ºC; $[\alpha]_D^{25}$ = 20.2 (c = 0.01, $CHCl_3$); IR (ATR) 3299, 2952, 2918, 2850, 1638, 1622, 1549, 1511 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.81 (t, 6H, J = 6.9 Hz), 1.21 (m, 28H), 1.37 (m, 4H), 1.46 (m, 6H), 1.69 (m, 4H), 3.14 (q, 2H, J = 6.9 Hz), 3.19 (q, 4H, J = 5.9 Hz), 3.55 (d, 2H, J = 12.9 Hz), 3.55 (d, 2H, J = 13.0 Hz), 3.85 (t, 4H, J = 6.6 Hz), 6.77 (d, 4H, J = 8.5 Hz), 7.09 (d, 4H, J = 8.5 Hz), 7.25 (t, 2H, J = 5.8 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.1, 19.9, 22.6, 26.0, 27.2, 29.3, 29.4, 29.4, 29.5, 29.5, 31.9, 38.5, 52.1, 57.7, 68.1, 114.6, 129.1, 131.4, 158.4, 174.9; HRMS (ESI-TOF)$^+$ calc for $C_{44}H_{74}N_4O_4$ (M + H)$^+$: 723.5788; found 723.5790; Anal. Calcd. for $C_{44}H_{74}N_4O_4$: C, 73.09; H, 10.32; N, 7.75; found: C, 72.94; H, 10.11; N, 7.37. Monoalkylated by-product: Yield = 26%; mp 79-82 ºC; $[\alpha]_D^{25}$ = 60.7 (c = 0.01, $CHCl_3$); IR (ATR) 3290, 2923, 2857, 1640, 1543, 1519, 1466 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.75 (t, 3H, J = 6.8 Hz), 1.14 (m, 18H), 1.31 (m, 2H), 1.39 (m, 4H), 1.62 (m, 2H), 1.85 (s, 3H), 3.07 (m, 5H), 3.30 (dd, 1H, J = 6.9, 13.8 Hz), 3.48 (d, 1H, J = 12.9 Hz), 3.52 (d, 1H, J = 13.0 Hz), 3.79 (t, 2H, J = 6.5 Hz), 6.70 (d, 2H, J = 8.4 Hz), 7.04 (d, 2H, J = 8.4 Hz), 7.36 (t, 1H, J = 5.7 Hz), 7.42 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.0, 19.6, 21.6, 22.5, 25.9, 26.8, 27.0, 29.1, 29.2, 29.2, 29.4, 29.4, 31.7, 38.4, 38.5, 50.6, 51.8, 57.4, 67.9, 114.4, 129.0, 131.4, 158.2, 175.0, 175.8; ; HRMS (ESI-TOF)$^+$ calc for $C_{27}H_{48}N_4O_3$ (M + H)$^+$: 477.3805; found 477.3807; Anal. Calcd. for $C_{27}H_{48}N_4O_3$: C, 68.03; H, 10.15; N, 11.75; found: C, 68.43; H, 10.38; N, 11.57.

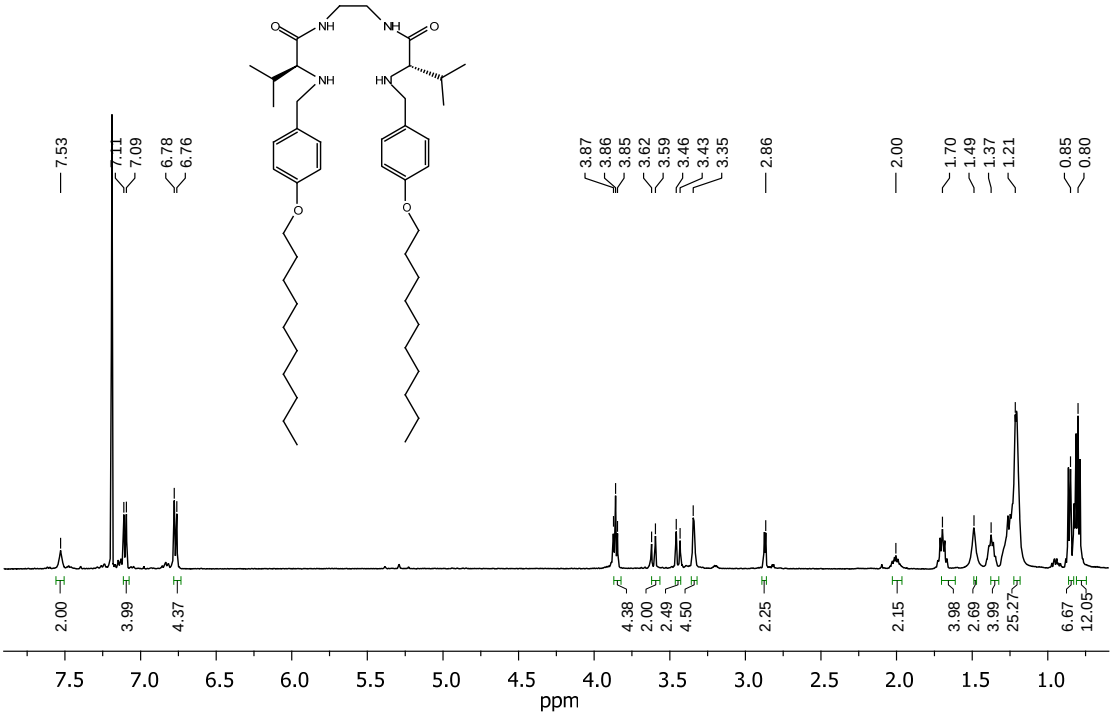
A4Leu_a10obenz. Yield = 63%; mp 98-99 ºC; $[\alpha]_D^{25}$ = -19.3 (c = 0.01, $CHCl_3$); IR (ATR) 3329, 2956, 2921, 2852, 1643, 1629, 1546, 1509 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.83 (d, 6H, J = 6.2 Hz), 0.89 (m, 12H), 1.38 (m, 28H), 1.60 (m, 6H), 1.76 (m, 4H), 3.17 (dd, 2H, J = 4.2, 8.3 Hz), 3.27 (m, 4H), 3.56 (d, 2H, J = 12.9 Hz), 3.67 (d, 2H, J = 12.9 Hz), 3.91 (t, 4H, J = 6.3 Hz), 6.84 (d, 4H, J = 8.1 Hz), 7.17 (d, 4H, J = 8.1 Hz), 7.38 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 14.1, 21.8, 22.6, 23.2, 25.1, 26.0, 27.2, 29.3, 29.3, 29.4, 29.5, 29.6, 31.9, 38.5, 42.9, 52.2, 60.8, 68.1, 114.6, 129.3, 131.0, 158.5, 174.5; HRMS (ESI-TOF)$^+$ calc for $C_{50}H_{86}N_4O_4$ $(M + H)^+$: 807.6727; found 807.6735; Anal. Calcd. for $C_{50}H_{86}N_4O_4 \cdot H_2O$: C, 72.77; H, 10.75; N, 6.75; found: C, 72.73; H, 10.68; N, 6.37. Monoalkylated by-product: Yield = 12%; mp 65-70 ºC; $[\alpha]_D^{25}$ = -192.6 (c = 0.01, $CHCl_3$); IR (ATR) 3326, 2925, 2858, 1631, 1541, 1518 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.83 (m, 15H), 1.38 (m, 15H), 1.53 (m, 4H), 1.63 (m, 5H), 2.06 (s, 3H), 3.11 (m, 1H), 3.23 (m, 4H), 3.32 (m, 1H), 3.52 (d, 1H, J = 12.9 Hz), 3.63 (d, 1H, J = 12.6 Hz), 3.90 (t, 2H, J = 6.3 Hz), 6.81 (d, 2H, J = 8.1 Hz), 7.13 (d, 2H, J = 8.1 Hz), 7.34 (s, 1H), 7.40 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 15.8, 23.2, 23.5, 24.4, 25.0, 25.1, 26.6, 26.8, 27.8, 28.7, 29.0, 31.0, 31.0, 31.1, 31.3, 31.3, 33.6, 40.2, 40.3, 44.8, 45.9, 54.0, 55.3, 62.6, 69.8, 116.3, 130.9, 133.2, 160.2, 176.7, 177.3; HRMS (ESI-TOF)$^+$ calc for $C_{33}H_{60}N_4O_3$ $(M + H)^+$: 561.4744; found 561.4750; Anal. Calcd. for $C_{33}H_{60}N_4O_3$: C, 70.67; H, 10.78; N, 9.99; found: C, 70.73; H, 10.88; N, 10.02.

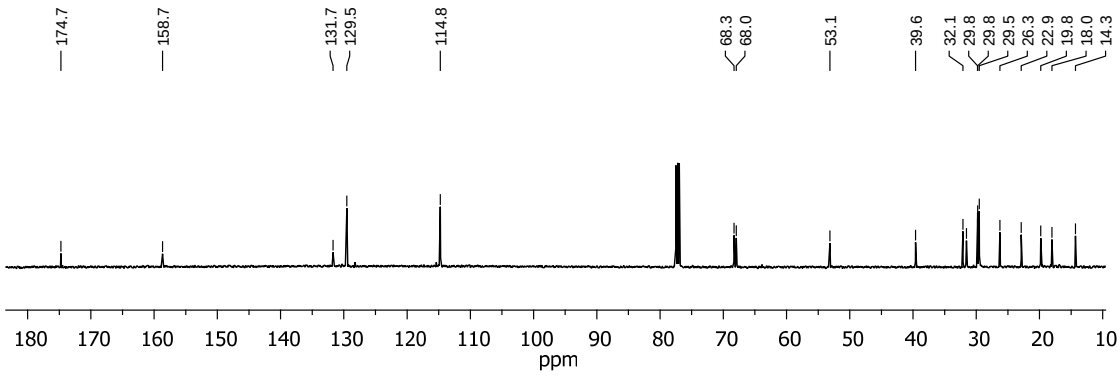
A4Val_a1obenz. Yield = 77%; mp 115-117 ºC; $[\alpha]_D^{25}$ = -36.1 (c = 0.01, $CHCl_3$); IR (ATR) 3303, 2934, 2822, 1634, 1547, 1513, 1455, 1364, 1298, 1242 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.86 (d, 6H, J = 6.8 Hz), 0.93 (d, 6H, J = 6.8 Hz), 1.53 (m, 4H), 2.09 (dd, 2H, J = 6.4, 11.5 Hz), 2.96 (d, 2H, J = 4.1 Hz), 3.27 (dd, 4H, J = 5.9, 14.8Hz), 3.57 (d, 2H, J = 12.9), 3.68 (d, 2H, J= 12.9 Hz), 3.78 (s, 6H), 6.85 (d, 4H, J = 8.2Hz), 7.18 (d, 4H, J = 8.2Hz), 7.33 (s, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 17.8, 19.5, 27.3, 31.2, 38.5, 52.8, 55.2, 67.7, 113.9, 129.4, 131.4, 158.9, 173.3; HRMS (ESI-TOF)$^+$ calc for $C_{30}H_{46}N_4O_4$ $(M + H)^+$: 527.3597; found 527.3596; Anal. Calcd. for $C_{30}H_{46}N_4O_4$: C, 68.41; H, 8.80; N, 10.64; found: C, 68.64; H, 8.26; N, 10.34.

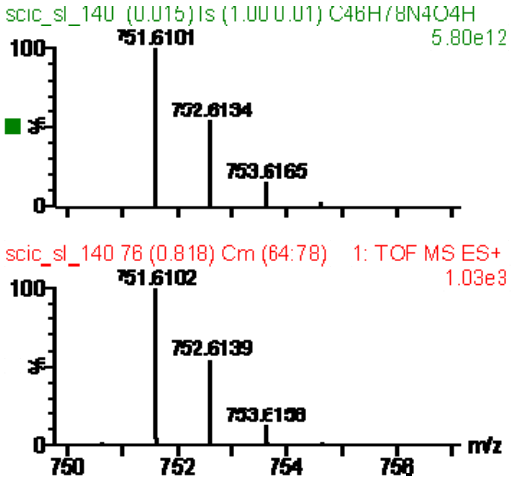
A4Val_a4obenz. Yield = 70%; mp 98-100 ºC; $[\alpha]_D^{25}$ = -28.95 (c = 0.01, $CHCl_3$); IR (ATR) 3307, 2939, 2871, 1633, 1544, 1518, 1459 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.84 (d, 6H, J = 6.9 Hz), 0.93 (m, 12H), 1.46 (q, 4H, J = 7.4, 14.7 Hz), 1.52 (m, 4H), 1.73 (q, 4H, J = 6.5, 14.3 Hz), 1.84 (s, 2H), 2.06 (q, 2H, J = 6.9, 11.6 Hz), 2.92 (d, 2H, J = 4.6 Hz), 3.26 (q, 4H, J = 6.2, 13.1 Hz), 3.53 (d, 2H, J = 12.9 Hz), 3.65 (d, 2H, J = 12.9 Hz), 3.91 (t, 4H, J = 6.5 Hz), 6.82 (d, 4H, J = 8.6 Hz), 7.15 (d, 4H, J = 8.6 Hz), 7.33 (t, 2H, J = 5.7 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.8, 17.8, 19.2, 19.6, 27.3, 31.2, 31.3, 38.5, 52.9, 67.7, 67.8, 114.5, 129.3, 131.4, 158.4, 173.5; HRMS (ESI-TOF)$^+$ calc for $C_{36}H_{58}N_4O_4$ $(M + H)^+$: 611.4536; found 611.4538; Anal. Calcd. for $C_{36}H_{58}N_4O_4$: C, 70.78; H, 9.57; N, 9.17; found: C, 71.01; H, 9.43; N, 9.19. Monoalkylated by-product: Yield = 12%; mp 65-68 ºC; $[\alpha]_D^{25}$ = -36.41 (c = 0.01, $CHCl_3$); IR (ATR) 3294, 3083, 2952, 2871, 1635, 1546, 1518 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.80 (d, 3H, J = 6.9 Hz), 0.85 (d, 3H, J = 6.9 Hz), 0.94 (m, 9H), 1.47 (m, 2H), 1.53 (m, 4H), 1.74 (m, 5H), 2.07 (m, 1H), 2.25 (m, 1H), 2.92 (d, 1H, J = 4.5 Hz), 3.20 (m, 1H), 3.27 (m, 4H), 3.54 (d, 1H, J = 12.9 Hz), 3.65 (d, 1H, J = 12.9 Hz), 3.93 (t, 2H, J = 6.5 Hz), 6.84 (d, 2H, J = 8.6 Hz), 7.16 (d, 2H, J = 8.5 Hz), 7.33 (t, 1H, J = 5.7 Hz), 7.39 (s, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 13.8, 16.1, 17.7, 19.2, 19.6, 19.6, 27.1, 27.3, 30.8, 31.2, 31.3, 38.5, 38.5, 52.9, 60.1, 67.7, 67.8, 114.5, 129.2, 131.5, 158.4, 173.6, 174.2; HRMS (ESI-TOF)$^+$ calc for $C_{25}H_{44}N_4O_3$ $(M + H)^+$: 449.3492; found 449.3500; Anal. Calcd. for $C_{25}H_{44}N_4O_3$: C, 66.93; H, 9.89; N, 12.49; found: C, 66.98; H, 9.52; N, 12.26.

Copies of the NMR and ESI-MS spectra

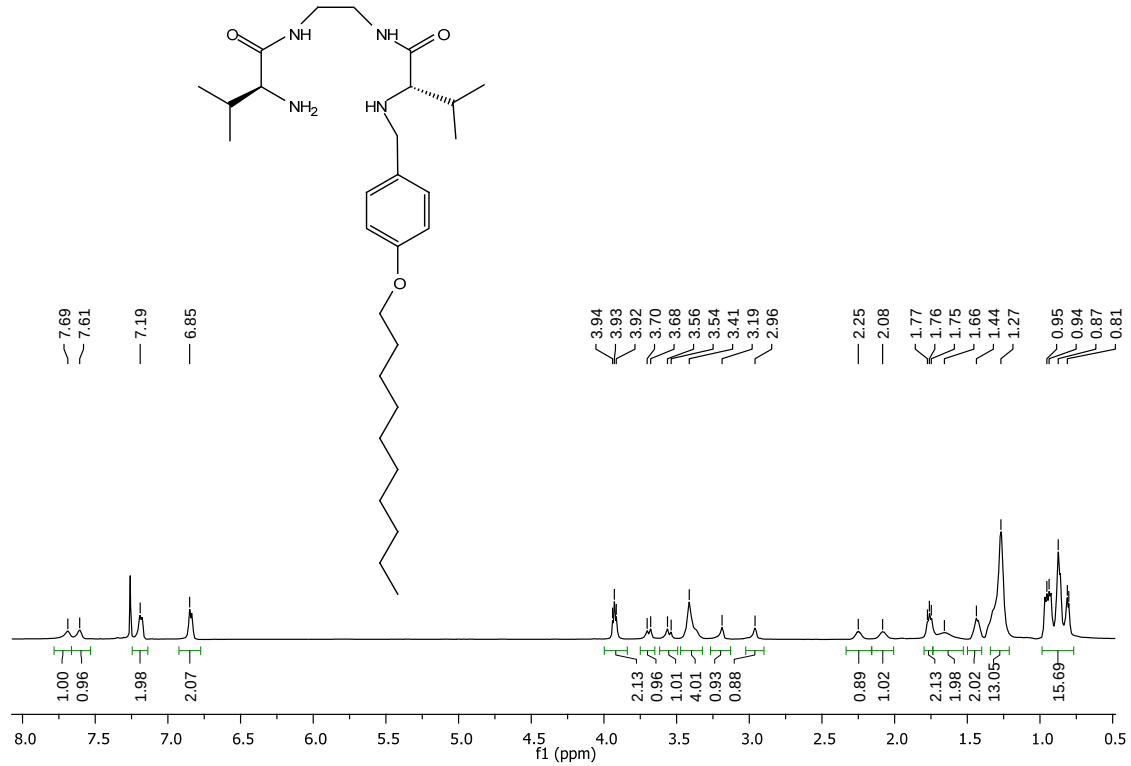
A2Val_a10obenz (1)

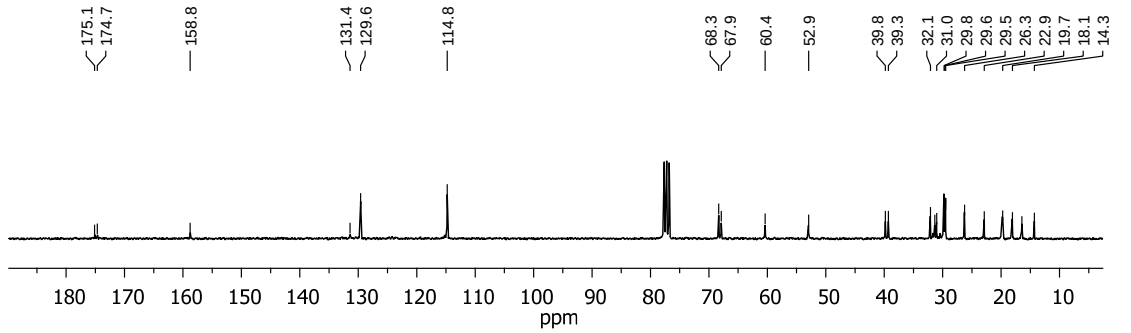


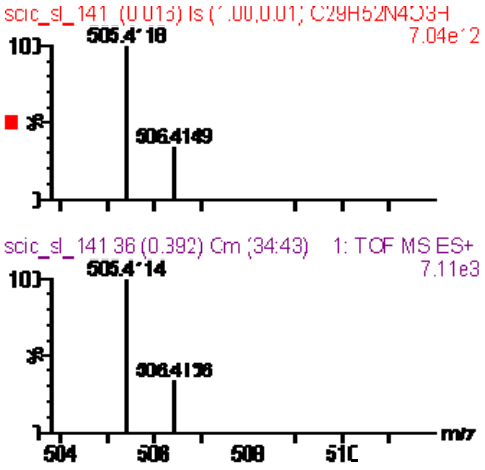




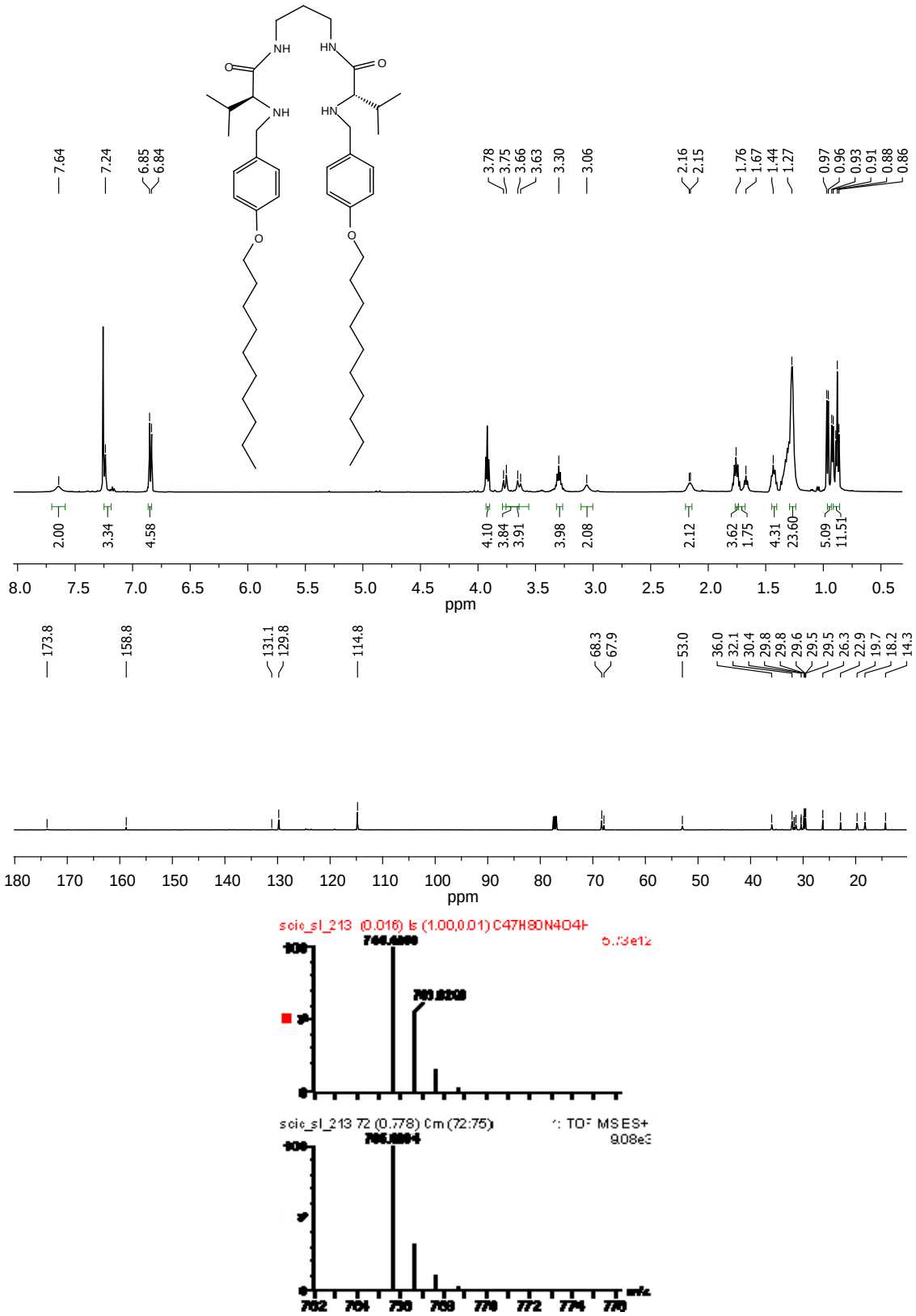
A2Val_a10obenz_m (1)[b]



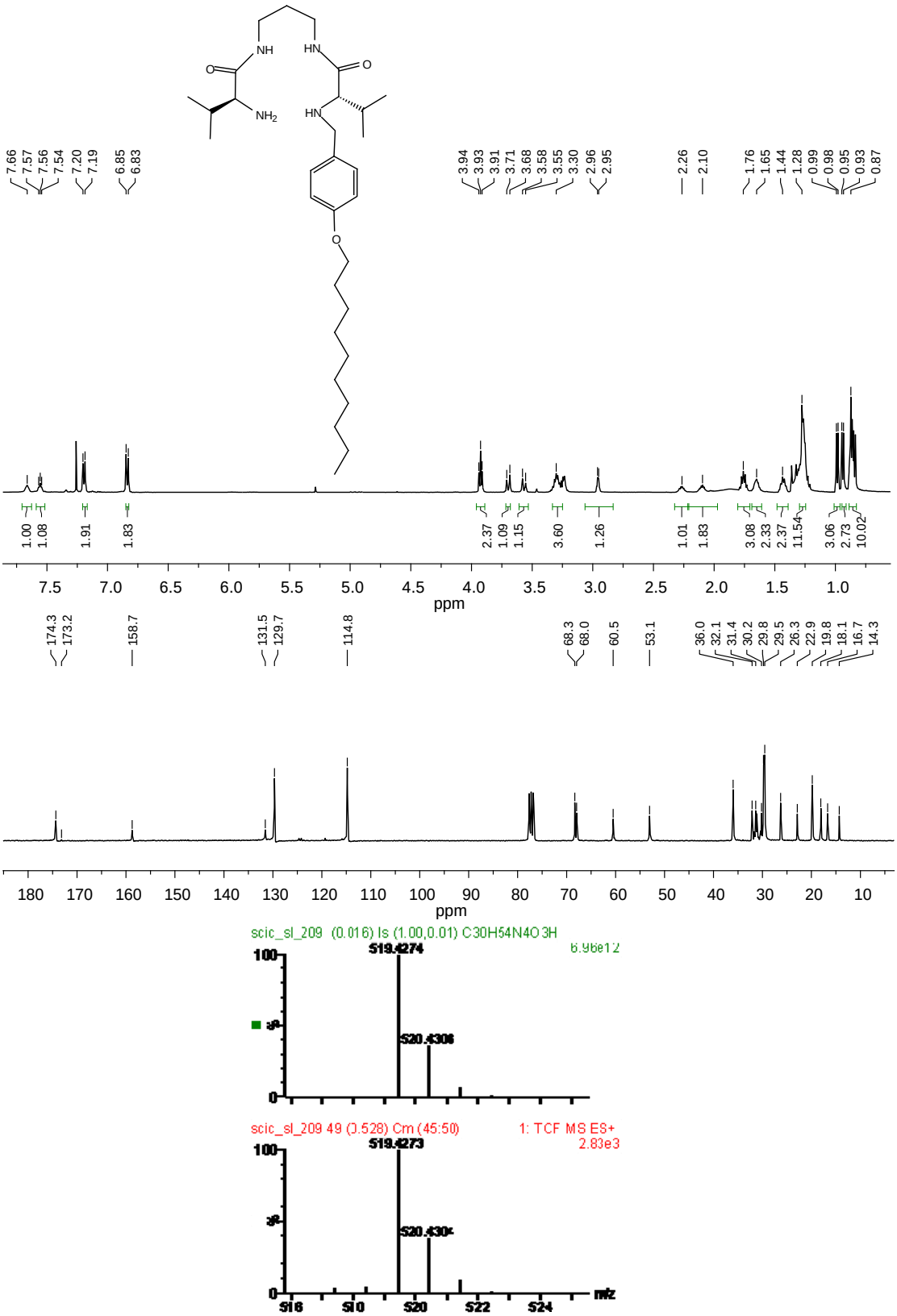




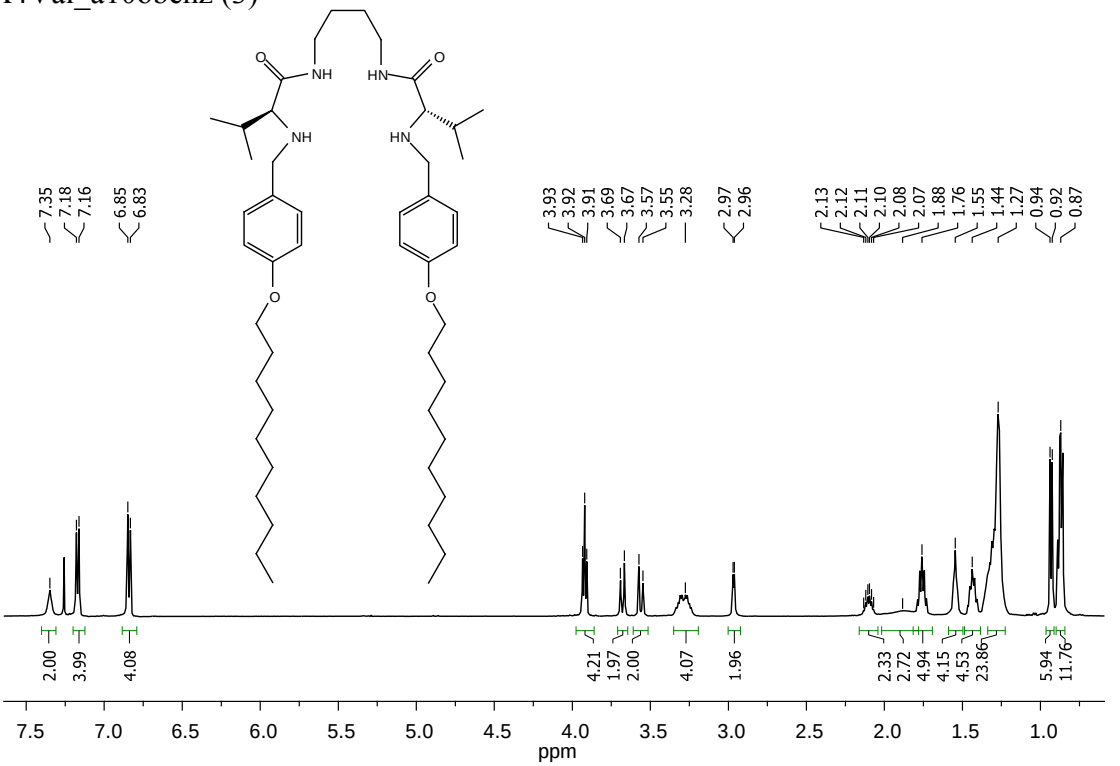
A3Val_a10obenz (2)

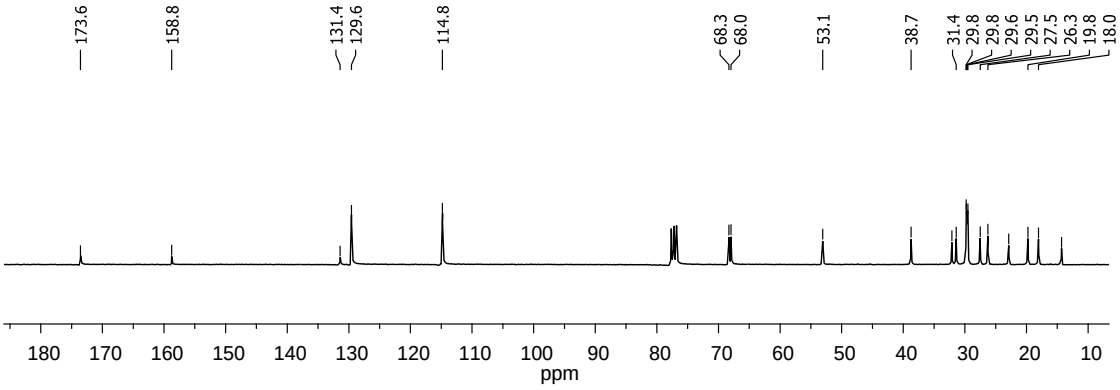


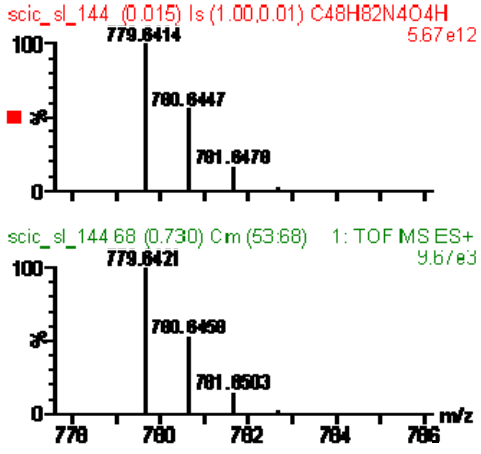
A3Val_a10obenz_m (2)[b]



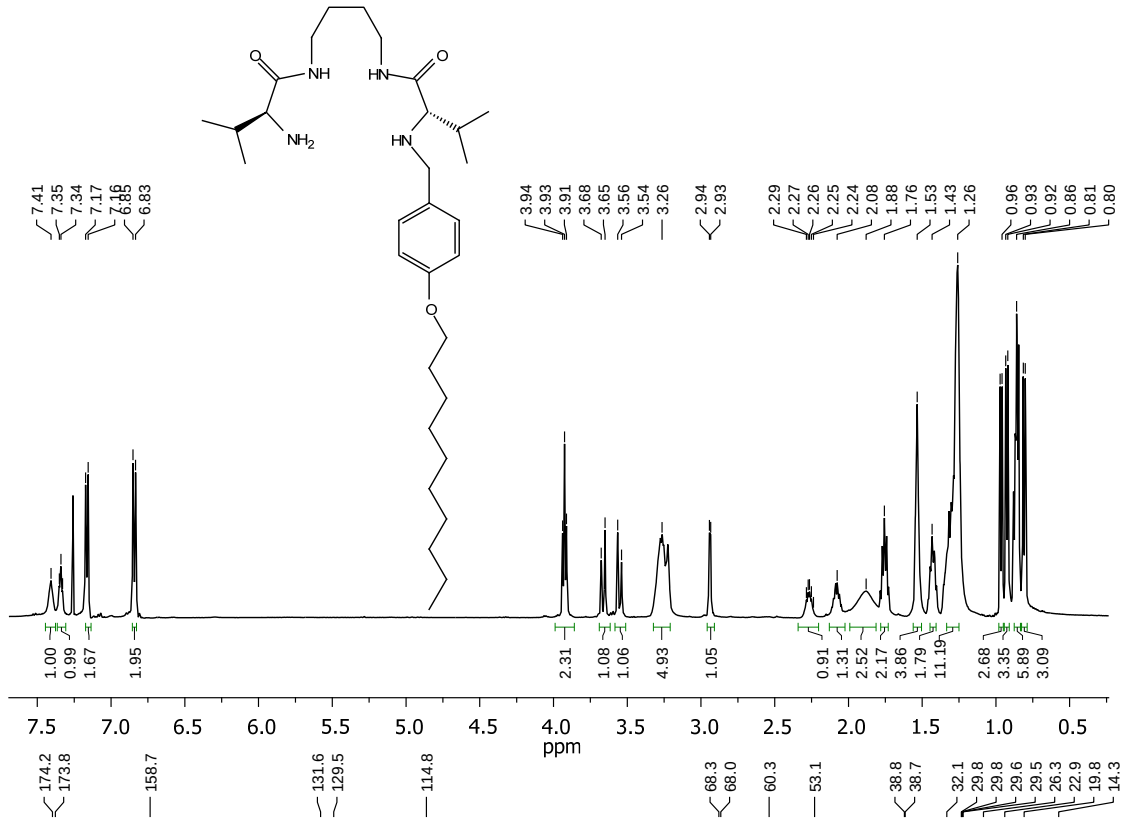
A4Val_a10obenz (3)

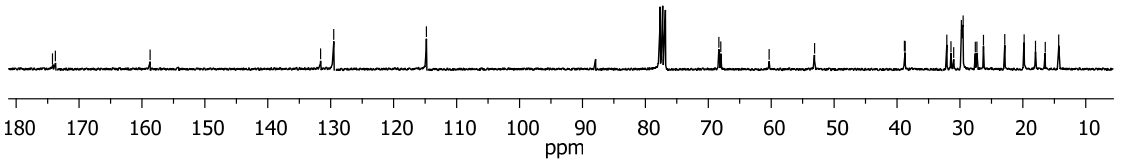


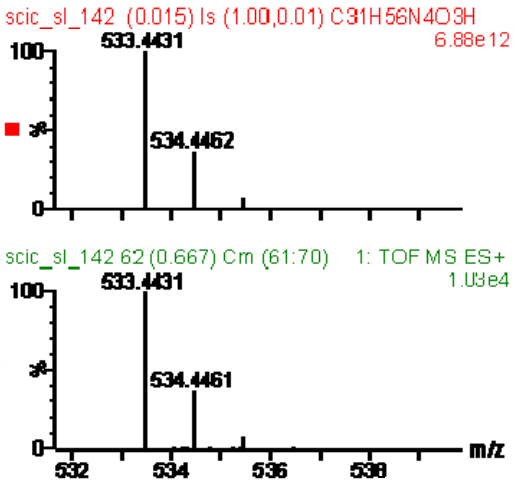




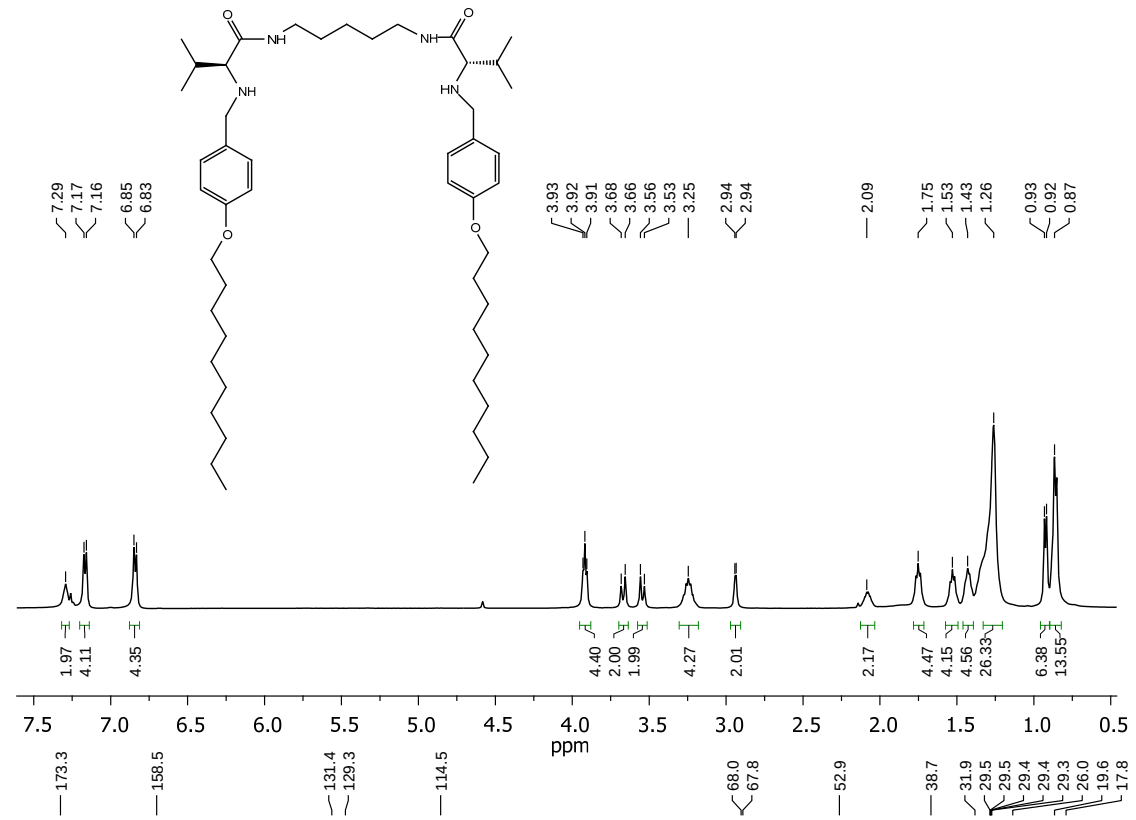
A4Val_a10obenz_m (3)[b]

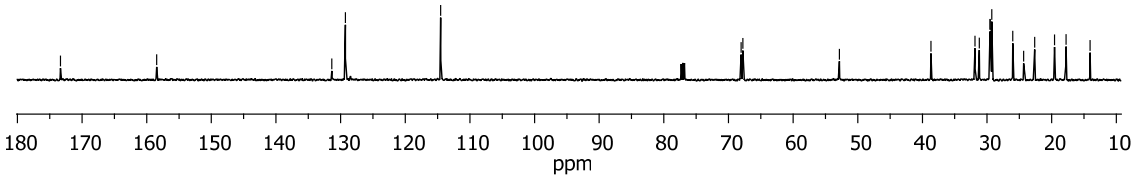


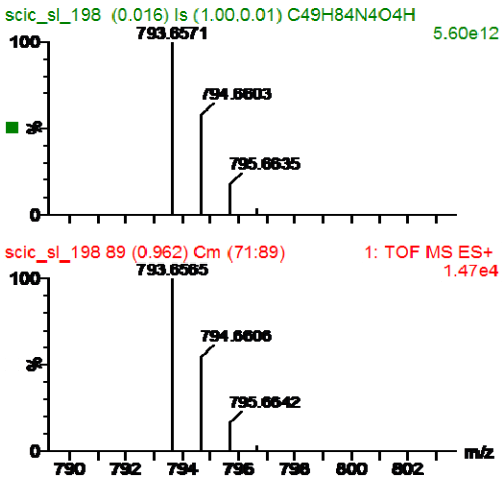




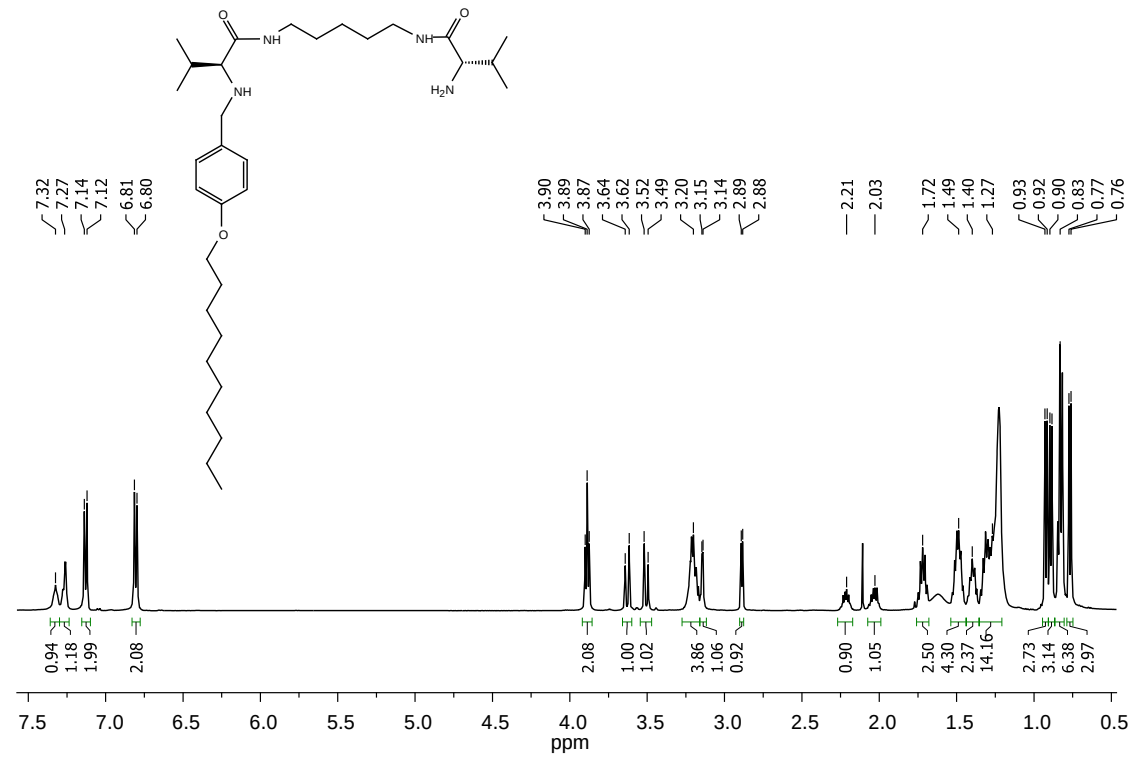
A5Val_a10obenz (4)

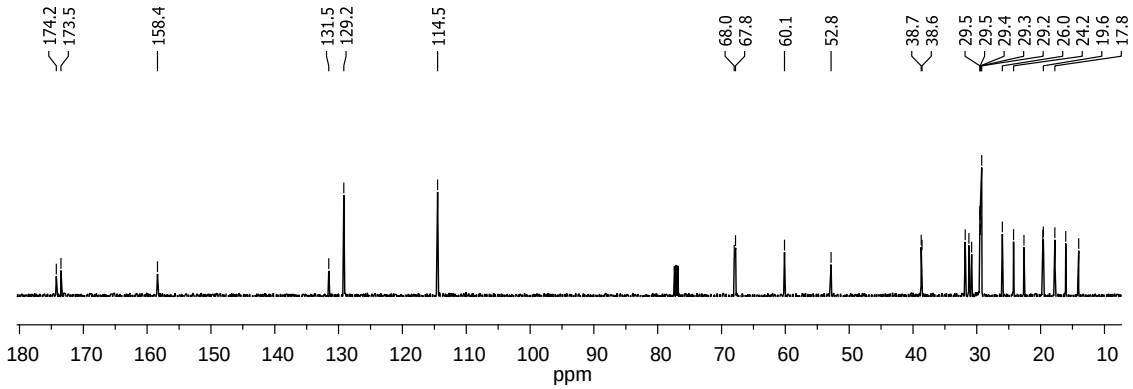


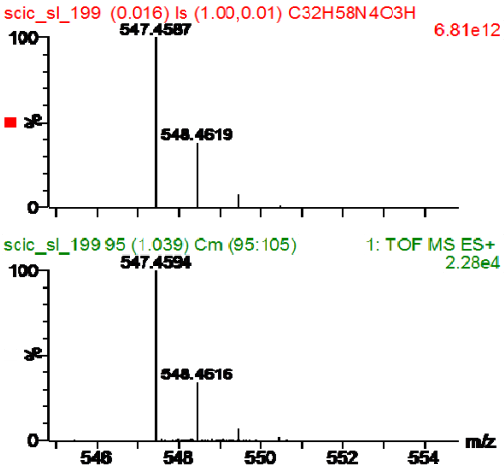




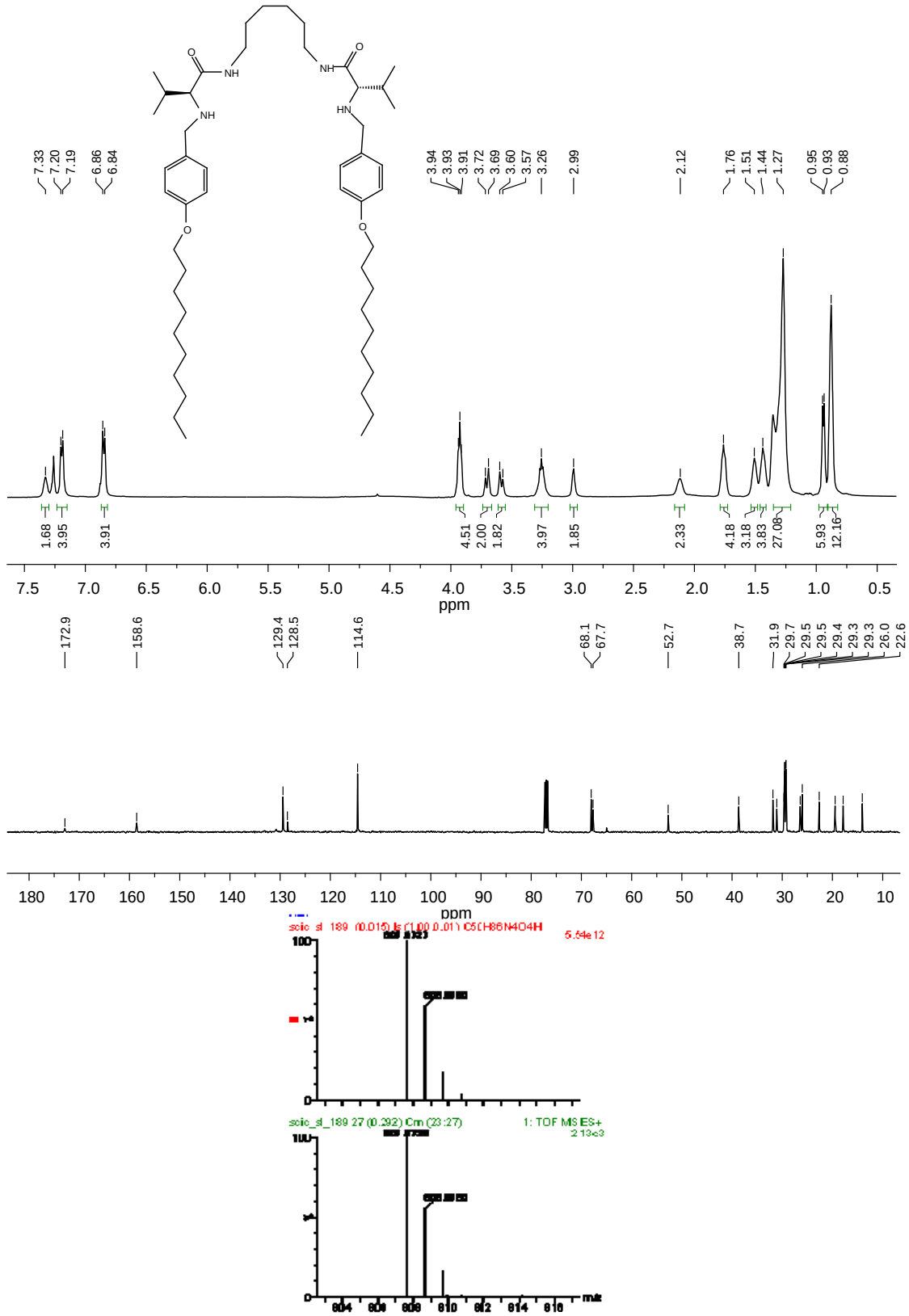
A5Val_a10obenz_m (4)[b]



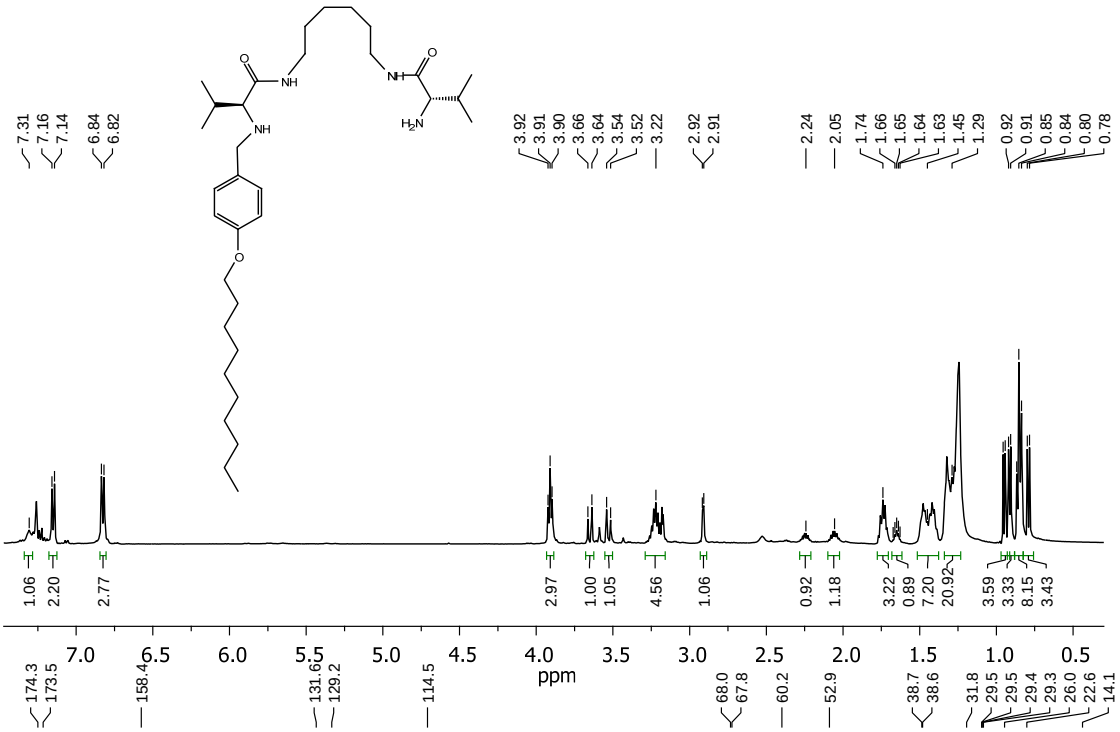


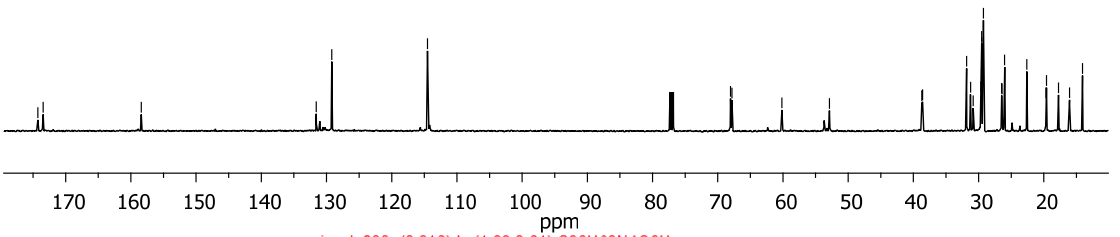


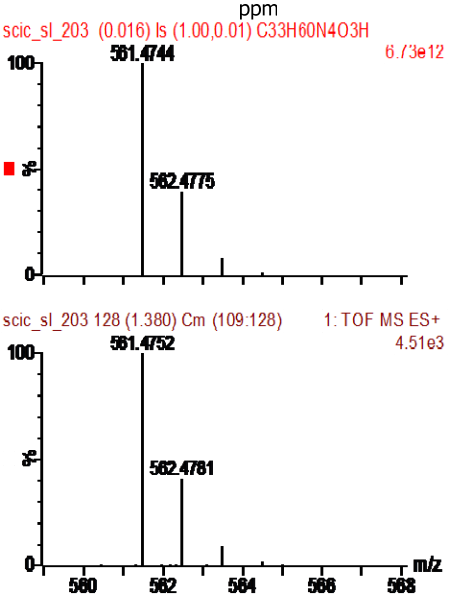
A6Val_a10obenz (5)



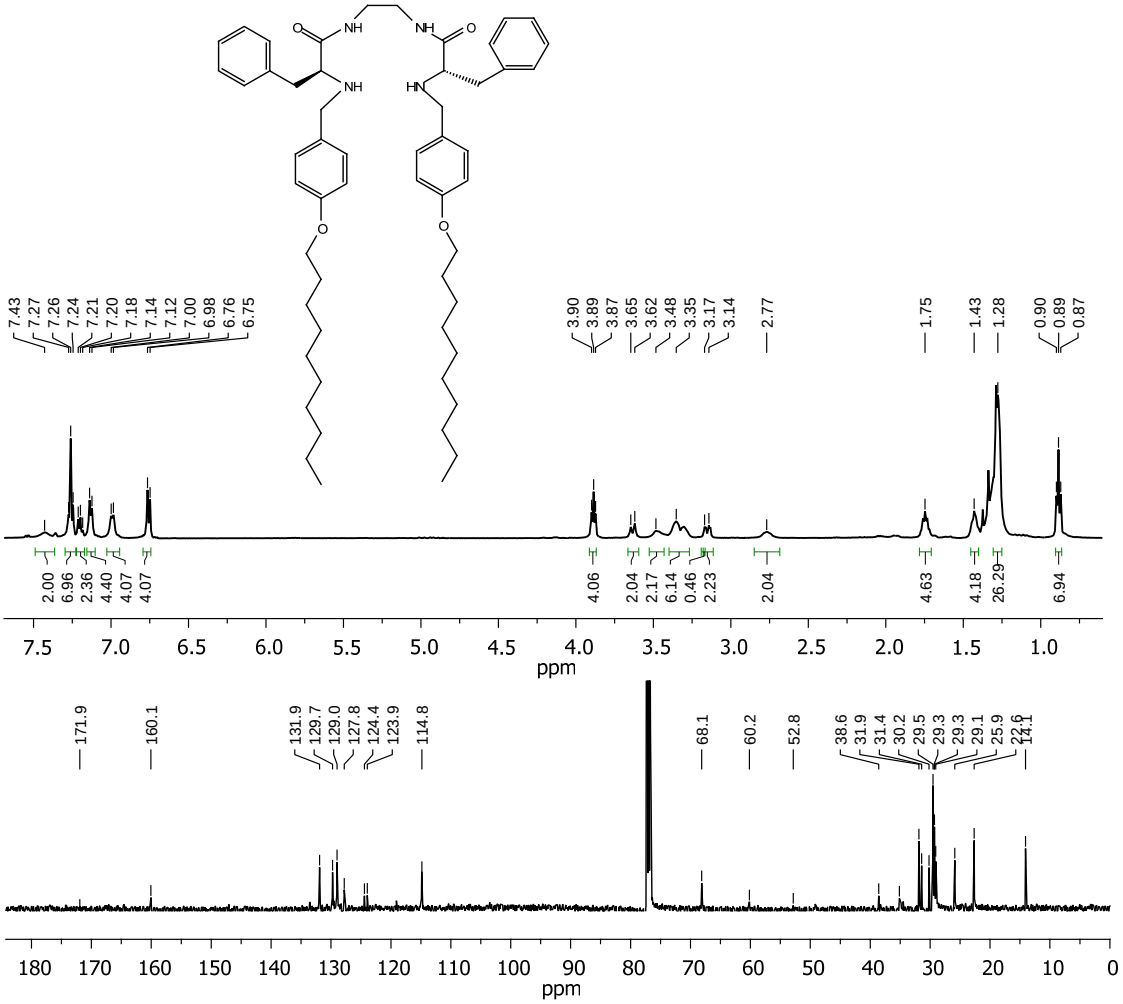
A6Val_a10obenz_m (5)[b]

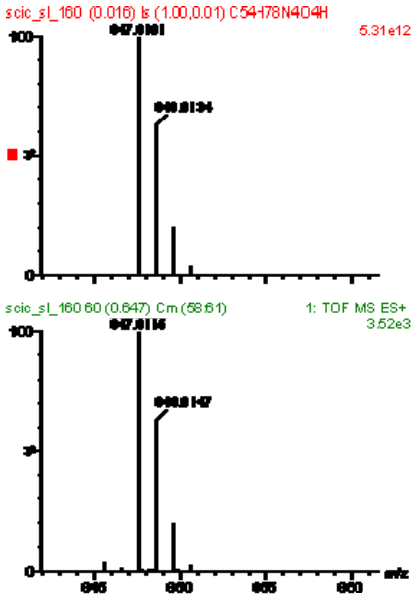




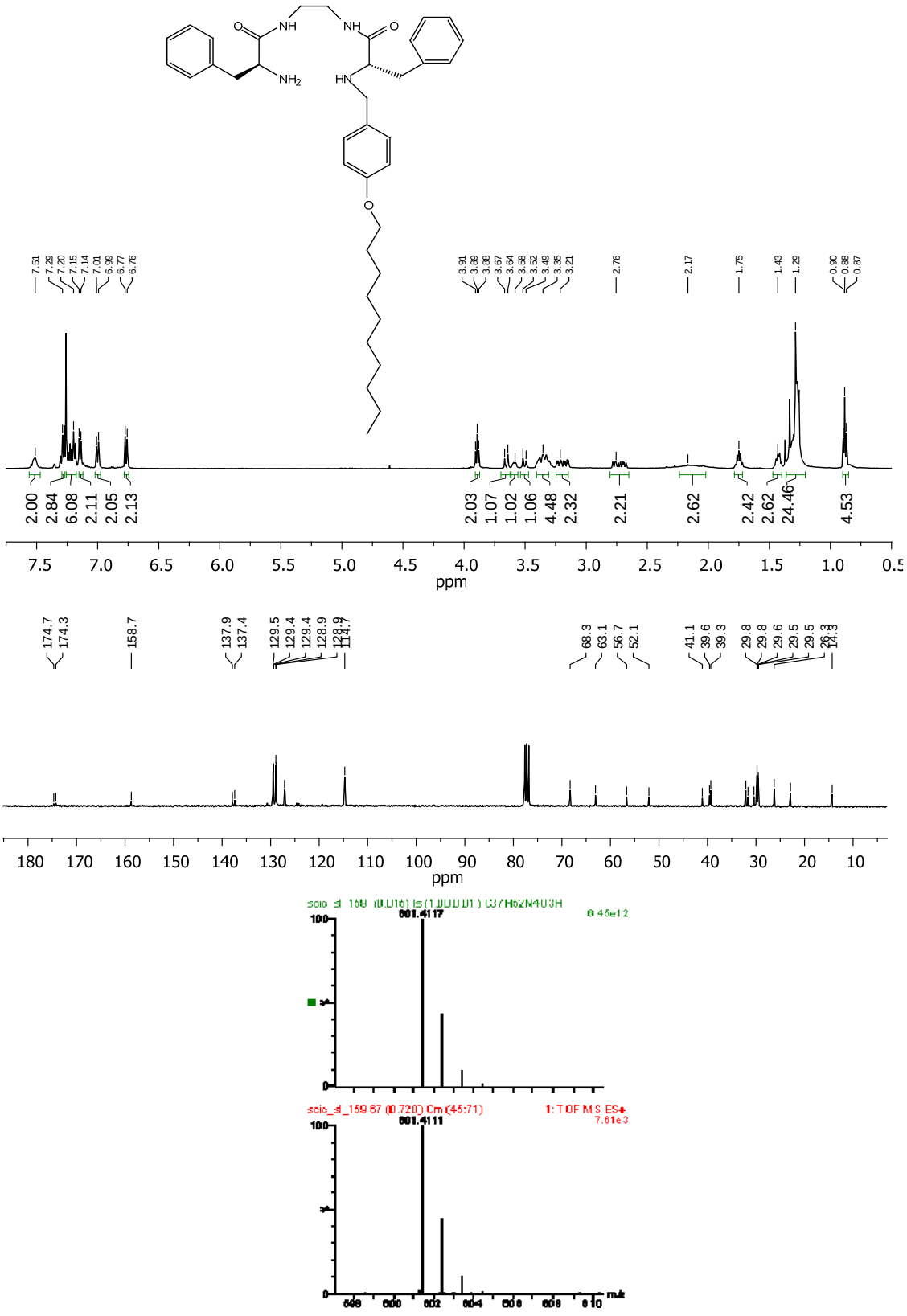


A2Phe_a10obenz (6)

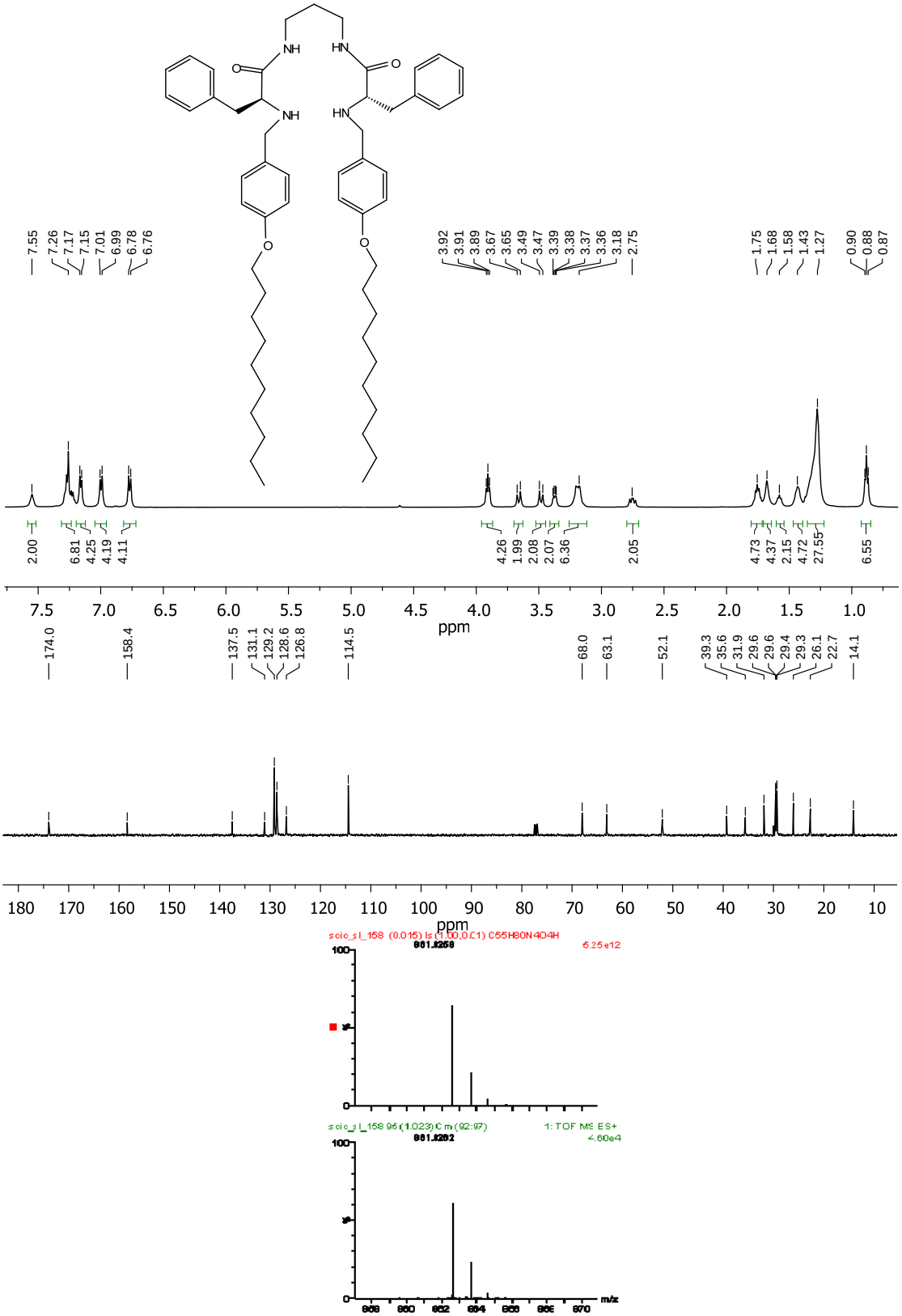




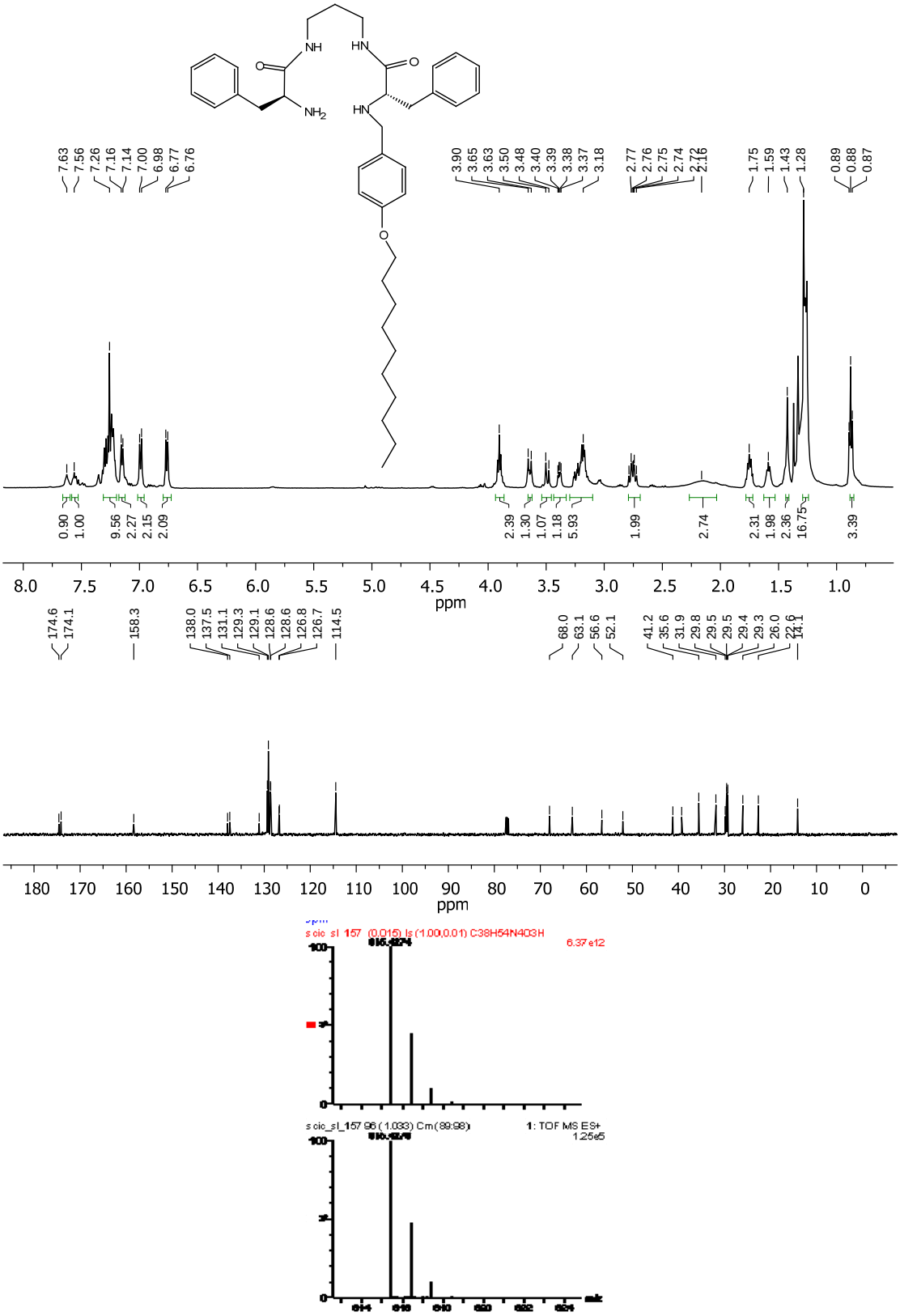
A2Phe_a10obenz_m (6)[b]



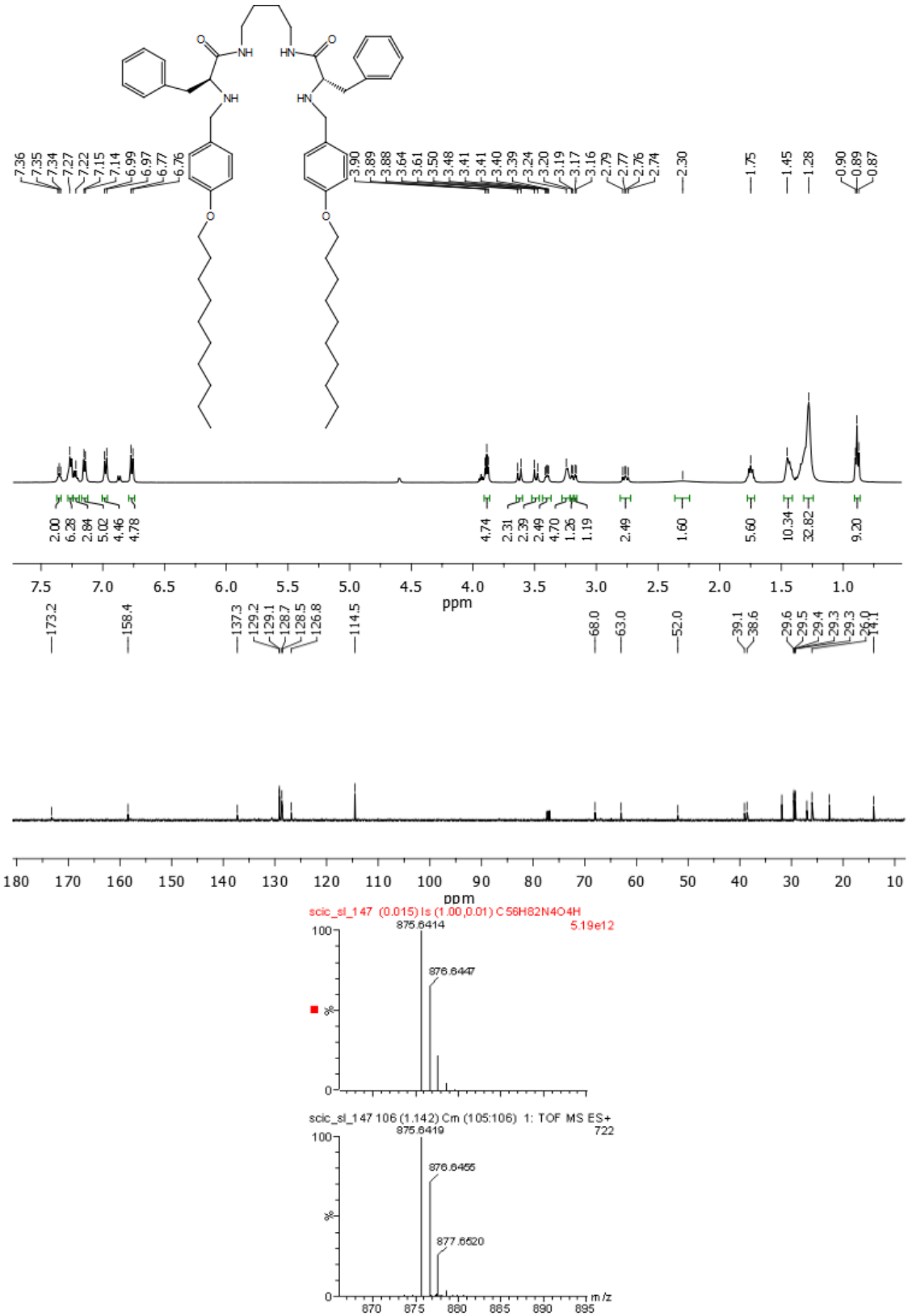
A3Phe_a10obenz (7)



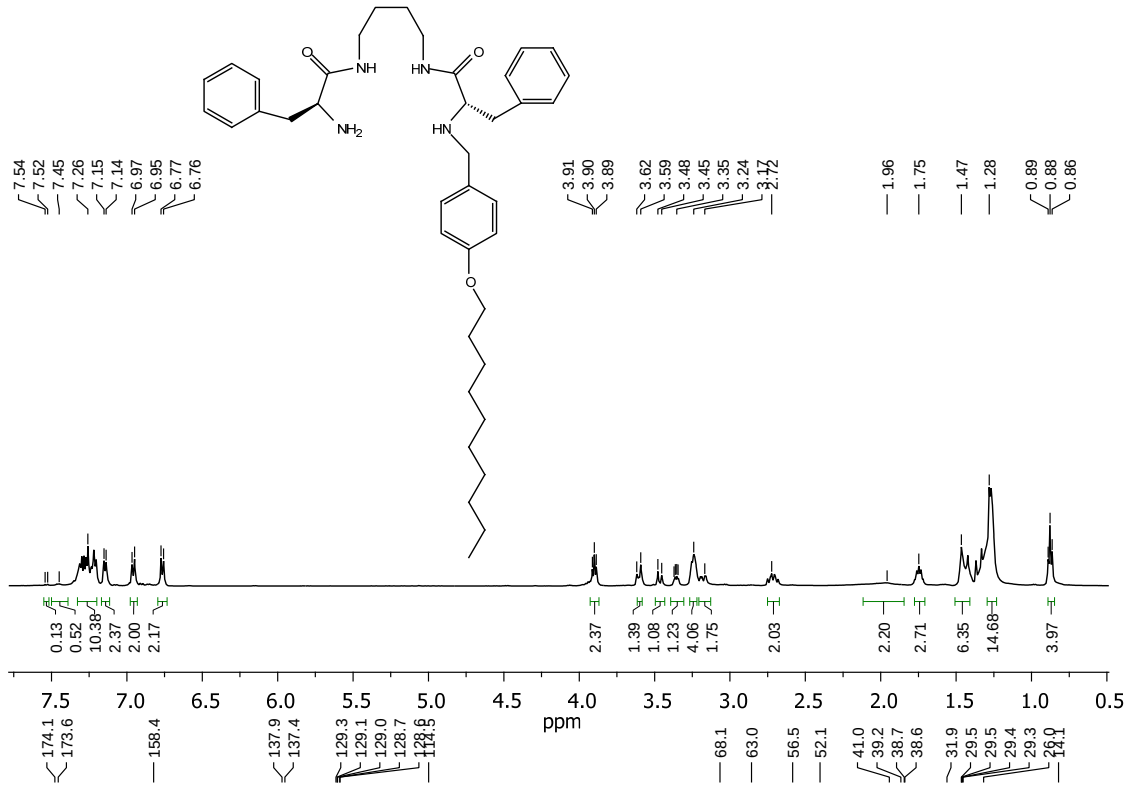
A3Phe_a10obenz_m (7)[b]

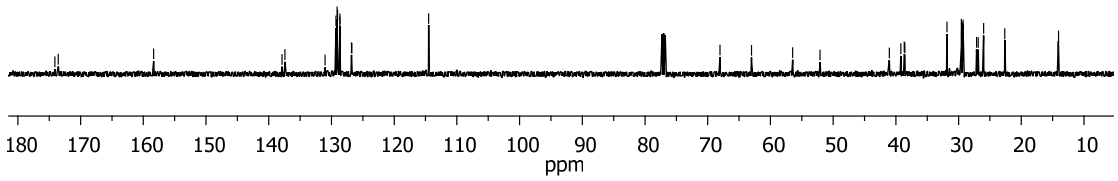


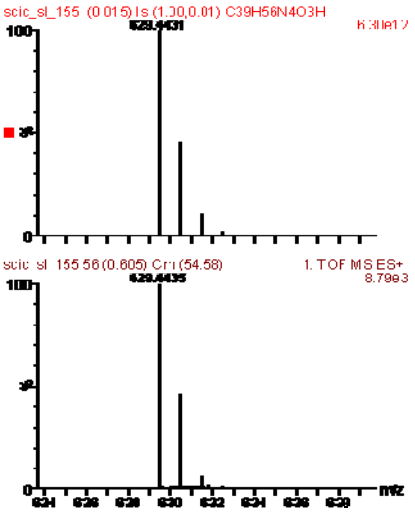
A4Phe_a10obenz (8)



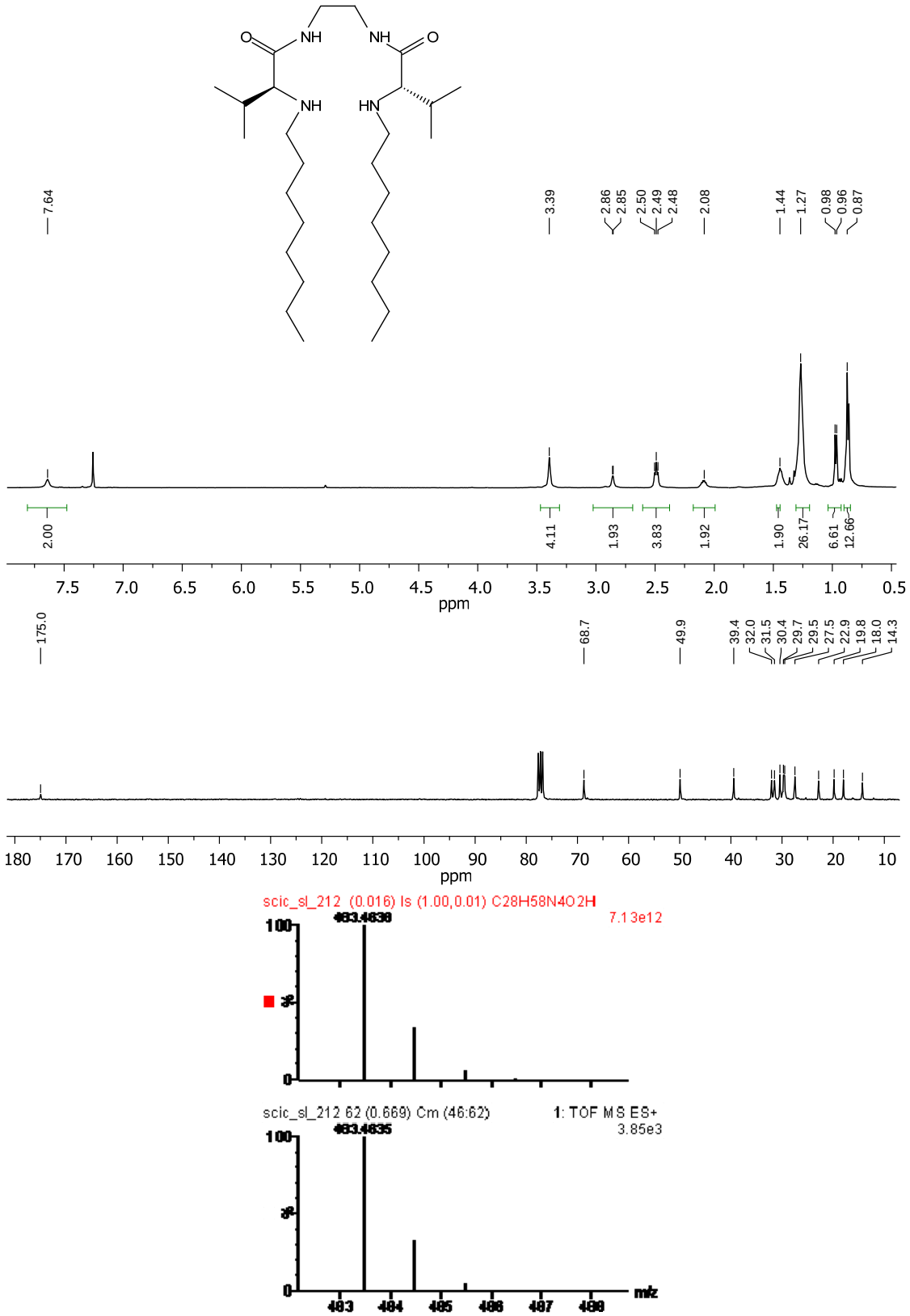
A4Phe_a10obenz_m (8)[b]



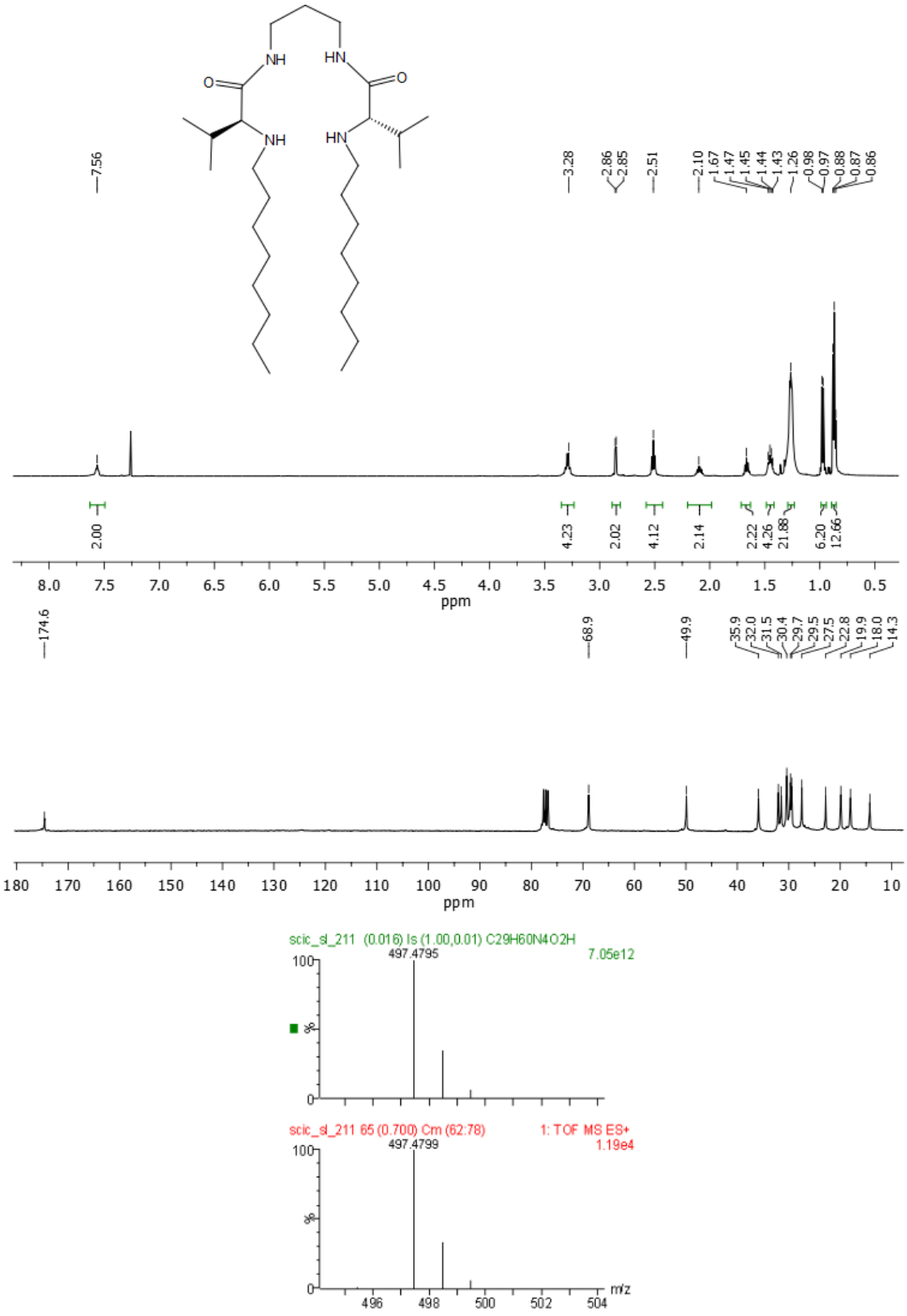




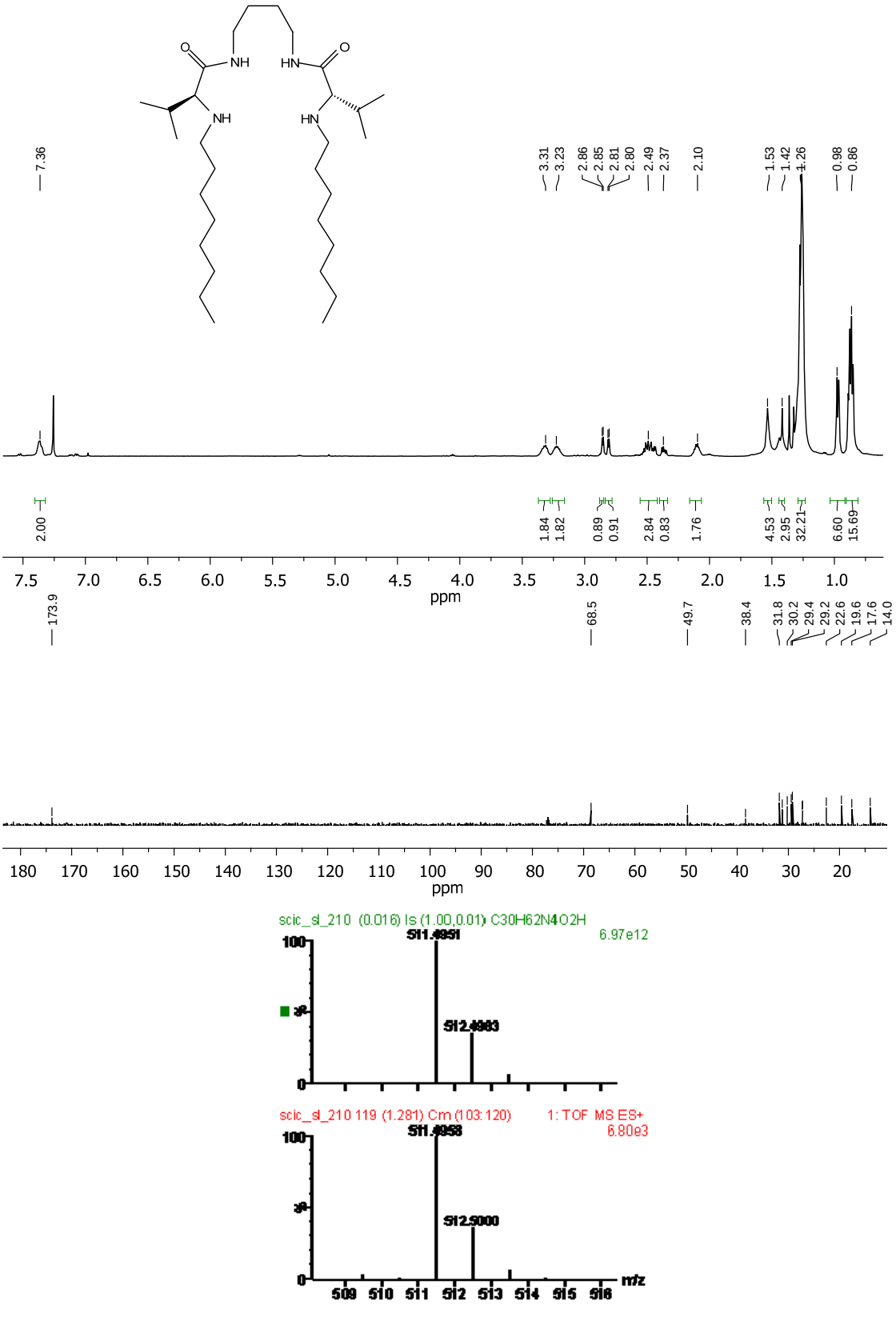
A2Val_a8 (9)


NH
NH
NH
HN
O
O
7.64
3.39
2.86
2.85
2.50
2.49
2.48
2.08
1.44
1.27
0.98
0.96
0.87
2.00
4.11
1.93
3.83
1.92
1.90
26.17
6.61
12.66
ppm
175.0
68.7
49.9
39.4
32.0
31.5
30.4
29.7
29.5
27.5
22.9
19.8
18.0
14.3
ppm
scic_sl_212 (0.016) Is (1.00,0.01) C28H58N4O2H
483.4838
7.13e12
scic_sl_212 62 (0.669) Cm (46:62)
1: TOF MS ES+
483.4835
3.85e3
m/z

A3Val_a8 (10)

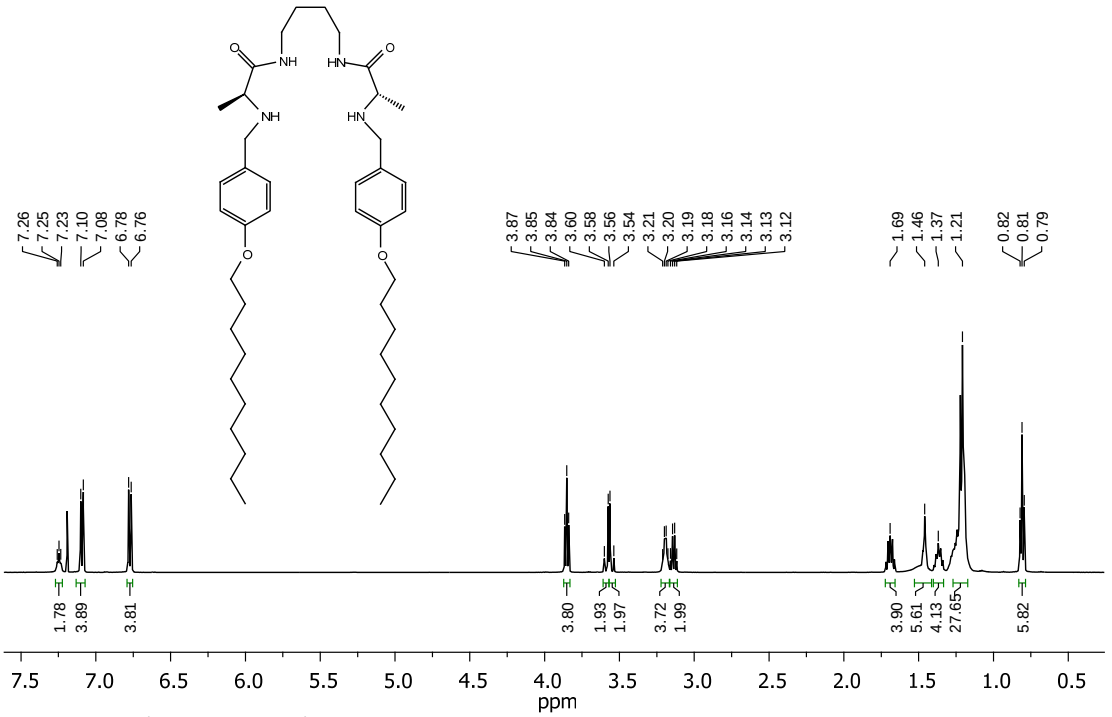

NH
HN
O
O
NH
HN
7.56
3.28
2.86
2.85
2.51
2.10
1.67
1.47
1.45
1.44
1.43
1.26
0.98
0.97
0.88
0.87
0.86
2.00
4.23
2.02
4.12
2.14
2.22
4.26
21.88
6.20
12.66
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm
174.6
68.9
49.9
35.9
32.0
31.5
30.4
29.7
29.5
27.5
22.8
19.9
18.0
14.3
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm
scic_sl_211 (0.016) Is (1.00,0.01) C29H60N4O2H
497.4795
7.05e12
100
%
0
scic_sl_211 65 (0.700) Cm (62:78)
1: TOF MS ES+
1.19e4
497.4799
100
%
0
m/z
496 498 500 502 504

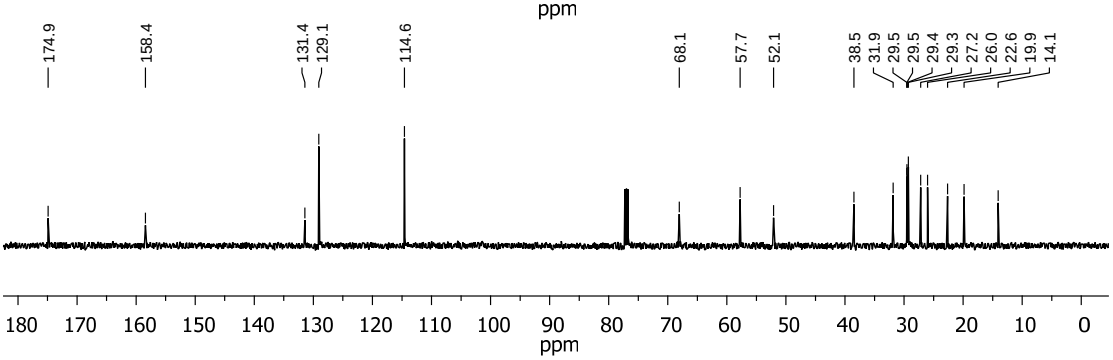
A4Val_a8 (11)

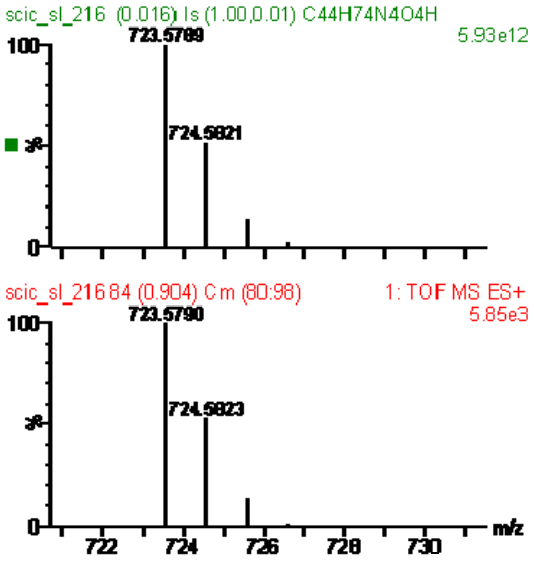

O
NH
HN
O
NH
HN
7.36
3.31
3.23
2.86
2.85
2.81
2.80
2.49
2.37
2.10
1.53
1.42
1.26
0.98
0.86
2.00
1.84
1.82
0.89
0.91
2.84
0.83
1.76
4.53
2.95
32.21
6.60
15.69
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
ppm
173.9
68.5
49.7
38.4
31.8
30.2
29.4
29.2
22.6
19.6
17.6
14.0
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

scic_sl_210 (0.016) Is (1.00,0.01) C30H62N4O2H
511.4951
6.97e12
100
%
512.4983
0
scic_sl_210 119 (1.281) Cm (103:120)
1: TOF MS ES+
511.4958
6.80e3
100
%
512.5000
0
m/z
509 510 511 512 513 514 515 516

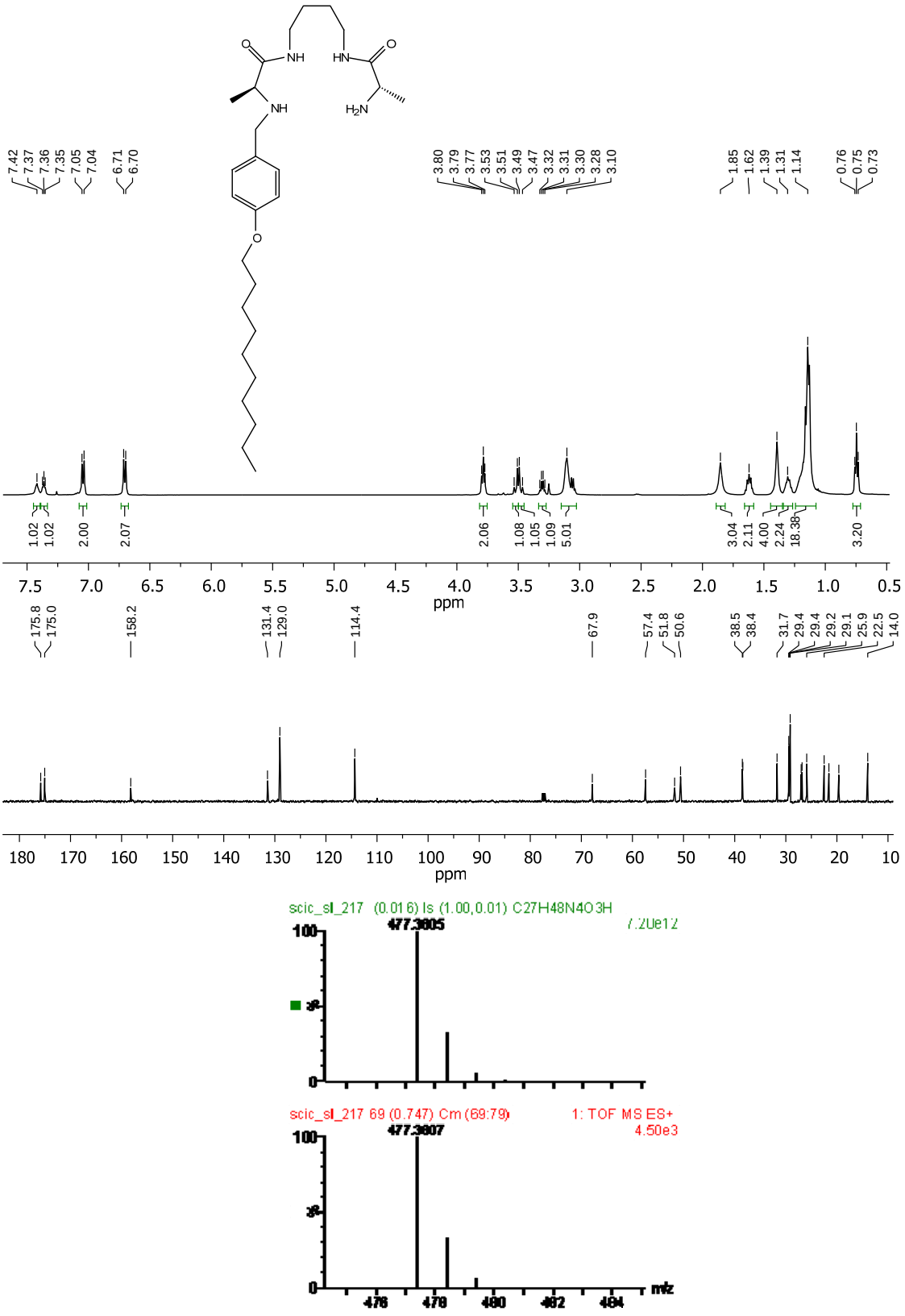
A4Ala_a10obenz (12)



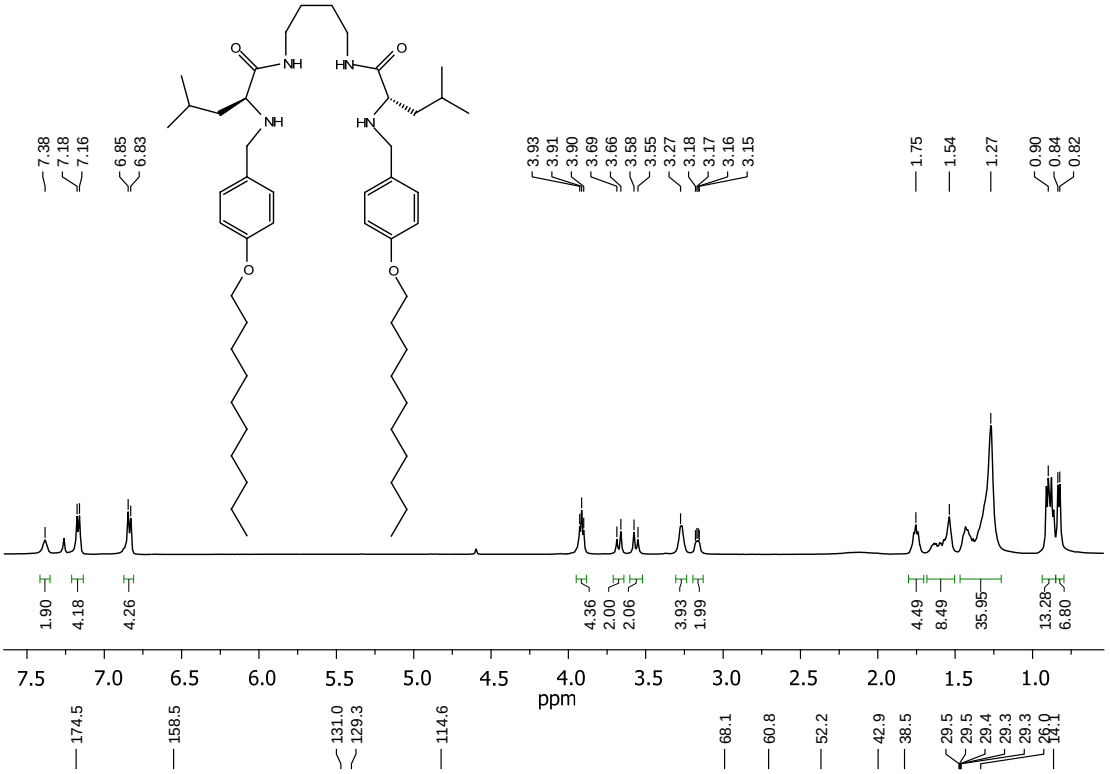


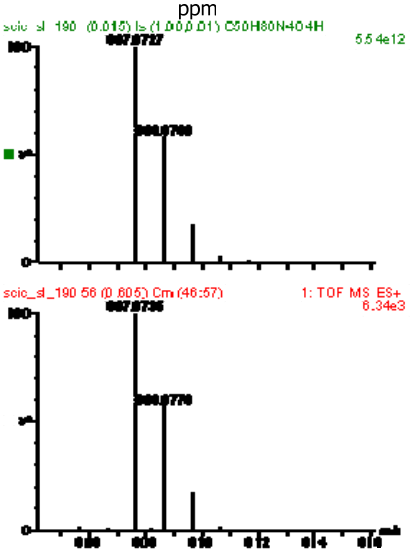


A4Ala_a10obenz_m (12)[b]

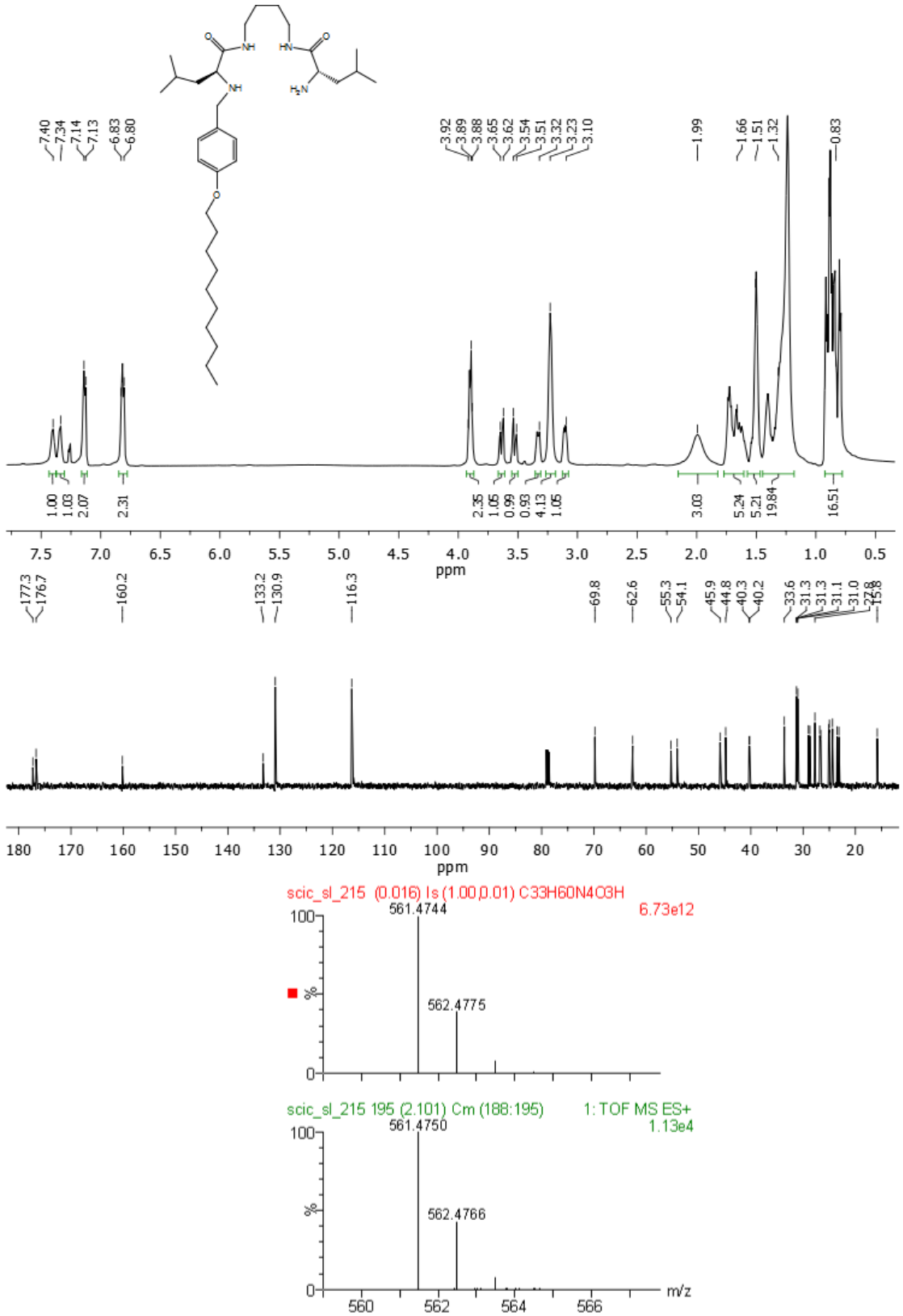


A4Leu_a10obenz (13)

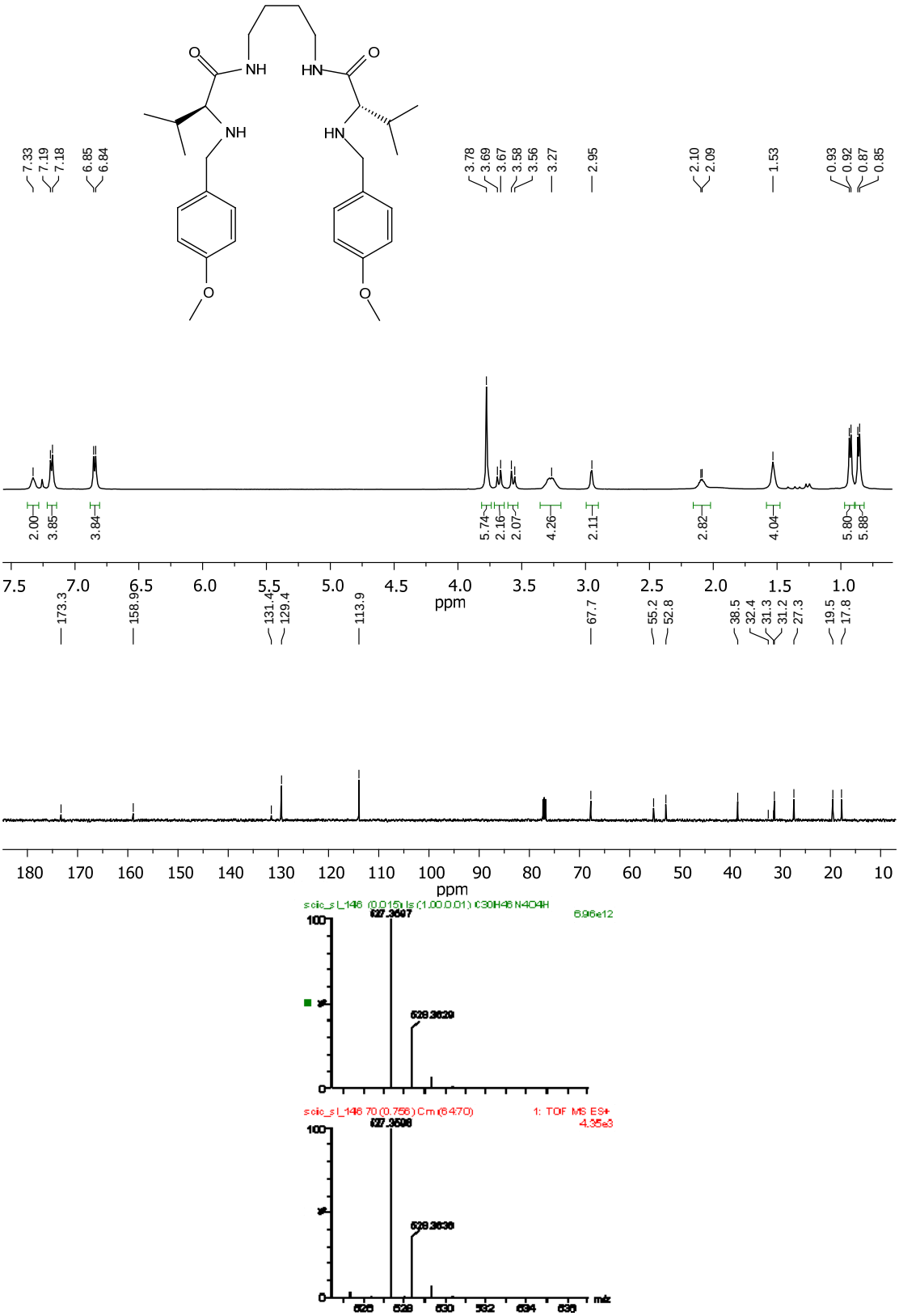




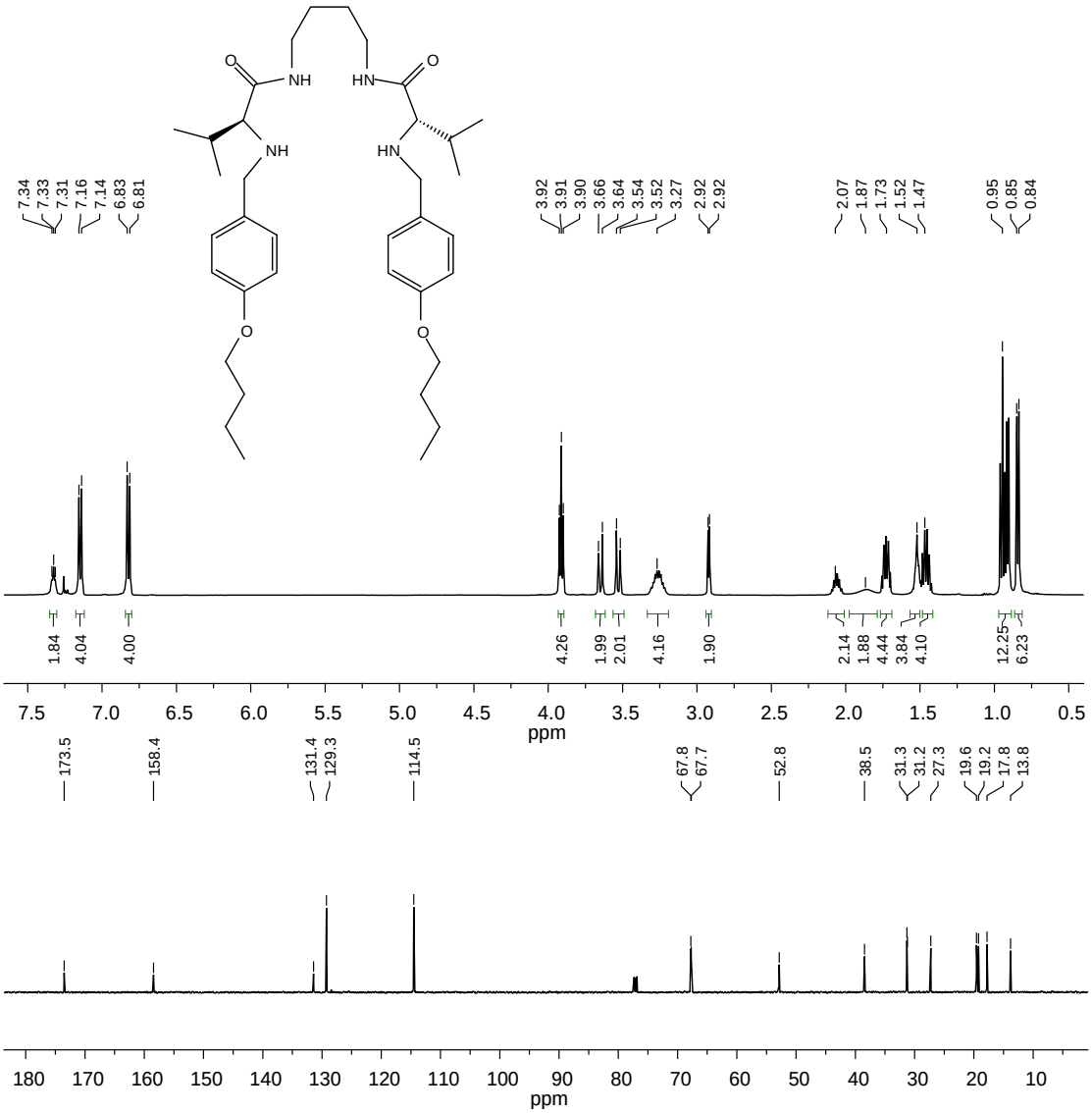
A4Leu_a10obenz_m (13)[b]

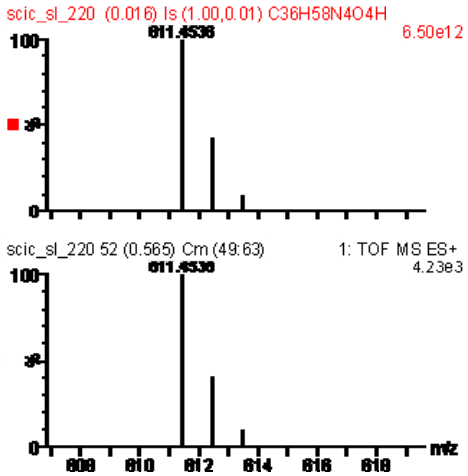


A4Val_a1obenz (14)

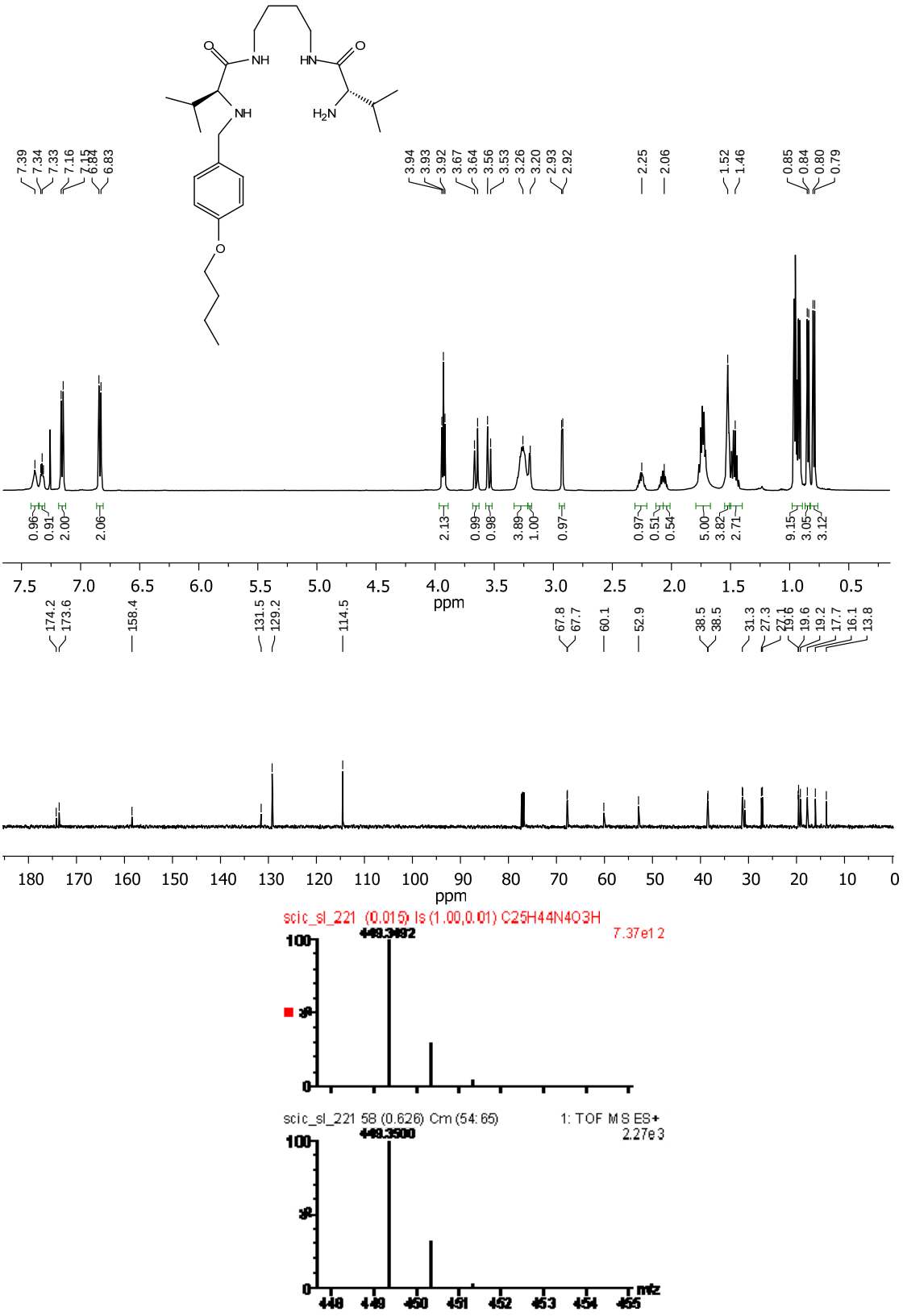


A4Val_a4obenz (15)





A4Val_a4obenz_m (15)[b]



SEM micrographs of compounds from chloroform solutions:

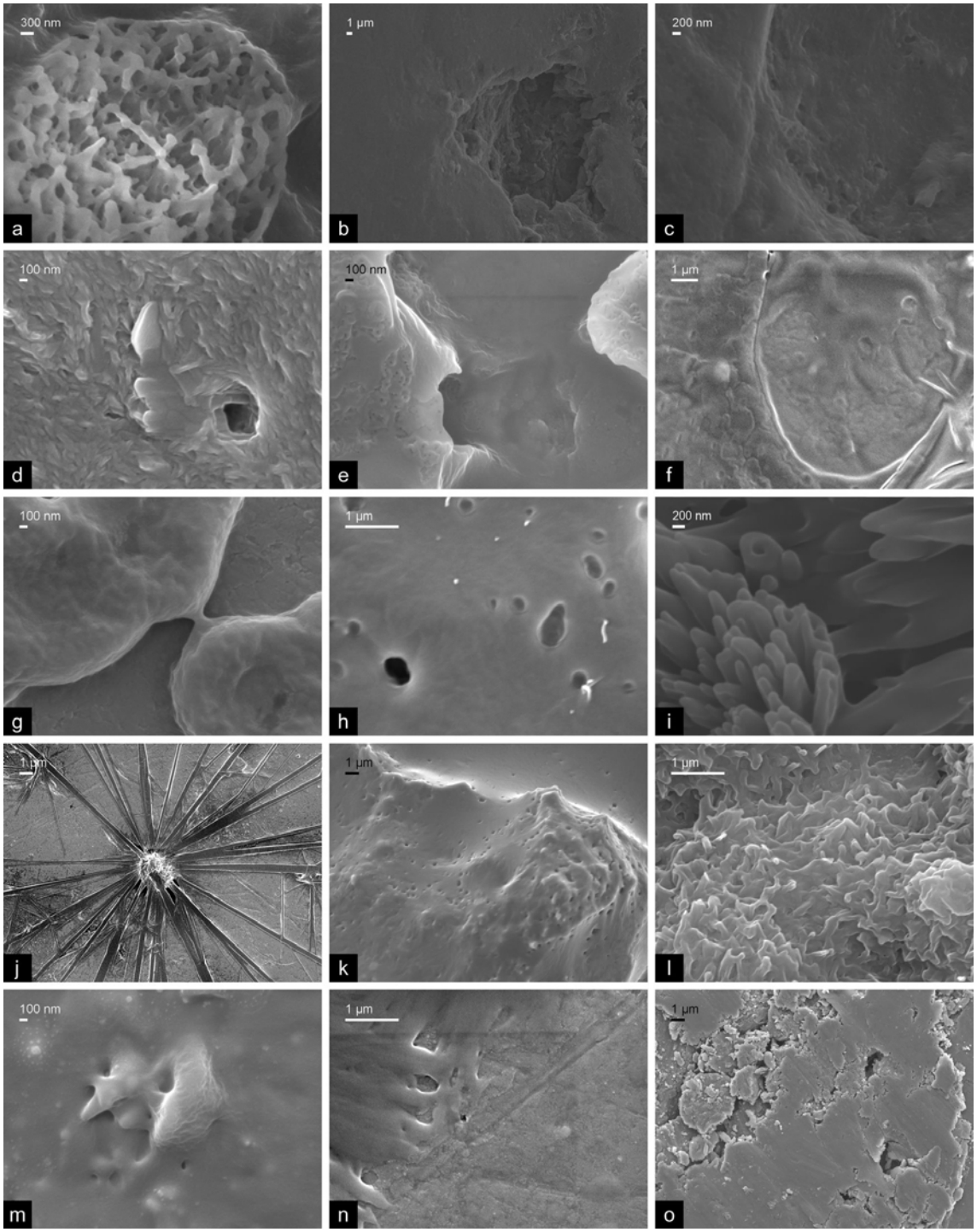


Figure S1. SEM micrographs of (a) A2Val_a10obenz, (b) A3Val_a10obenz, (c) A4Val_a10obenz, (d) A5Val_a10obenz, (e) A6Val_a10obenz, (f) A2Phe_a10obenz, (g) A3Phe_a10obenz, (h) A4Phe_a10obenz, (i) A2Val_a8, (j) A3Val_a8, (k) A4Val_a8, (l) A4Ala_a10obenz, (m) A4Leu_a10obenz, (n) A4Val_a1obenz and (o) A4Val_a4obenz, grown from $CHCl_3$ solutions. The corresponding scale bars are shown for every picture.

SEM micrographs of compounds from MeOH solutions:

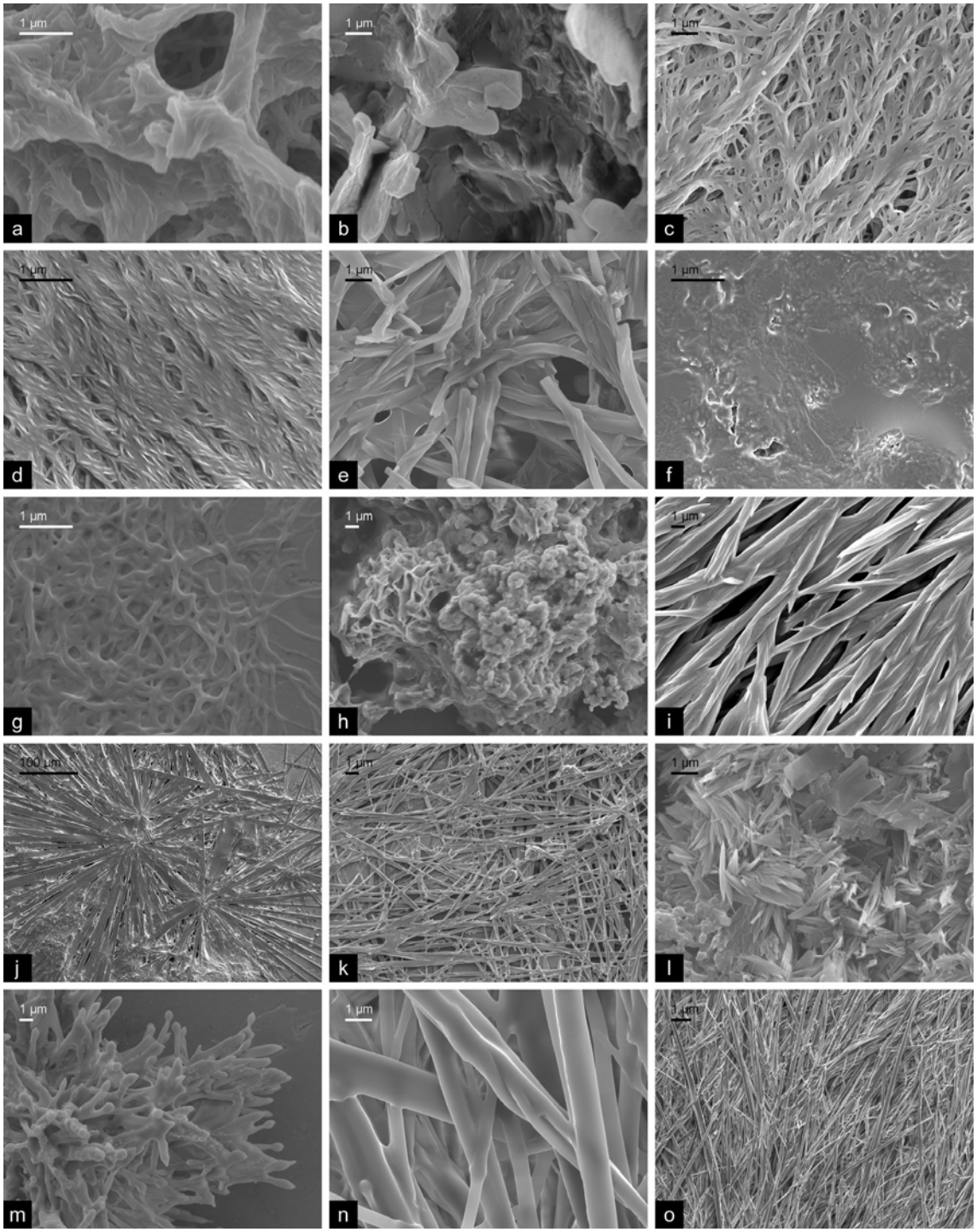


Figure S2. SEM micrographs of (a) A2Val_a10obenz, (b) A3Val_a10obenz, (c) A4Val_a10obenz, (d) A5Val_a10obenz, (e) A6Val_a10obenz, (f) A2Phe_a10obenz, (g) A3Phe_a10obenz, (h) A4Phe_a10obenz, (i) A2Val_a8, (j) A3Val_a8, (k) A4Val_a8, (l) A4Ala_a10obenz, (m) A4Leu_a10obenz, (n) A4Val_a1obenz and (o) A4Val_a4obenz, grown from MeOH solutions. The corresponding scale bars are shown for every picture.

SEM micrographs of compounds from 2 : 1 MeOH : H_2O solutions:

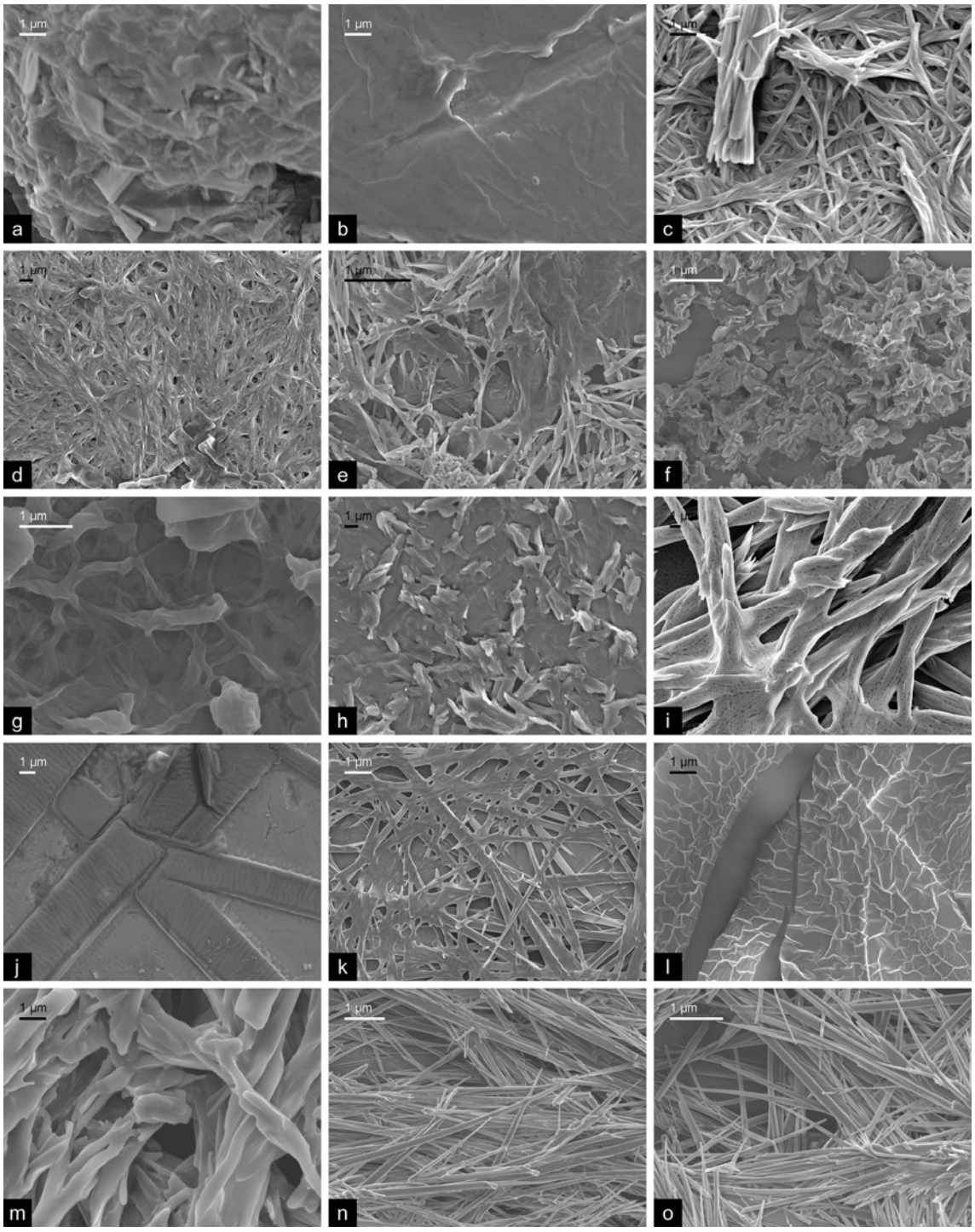


Figure S3. SEM micrographs of (a) A2Val_a10obenz, (b) A3Val_a10obenz, (c) A4Val_a10obenz, (d) A5Val_a10obenz, (e) A6Val_a10obenz, (f) A2Phe_a10obenz, (g) A3Phe_a10obenz, (h) A4Phe_a10obenz, (i) A2Val_a8, (j) A3Val_a8, (k) A4Val_a8, (l) A4Ala_a10obenz, (m) A4Leu_a10obenz, (n) A4Val_a1obenz and (o) A4Val_a4obenz, grown from 2 : 1 MeOH : H_2O solutions. The corresponding scale bars are shown for every picture.

SEM micrographs of compounds from 2 : 1 MeOH : H_2O solutions in the presence of acid (HCl):

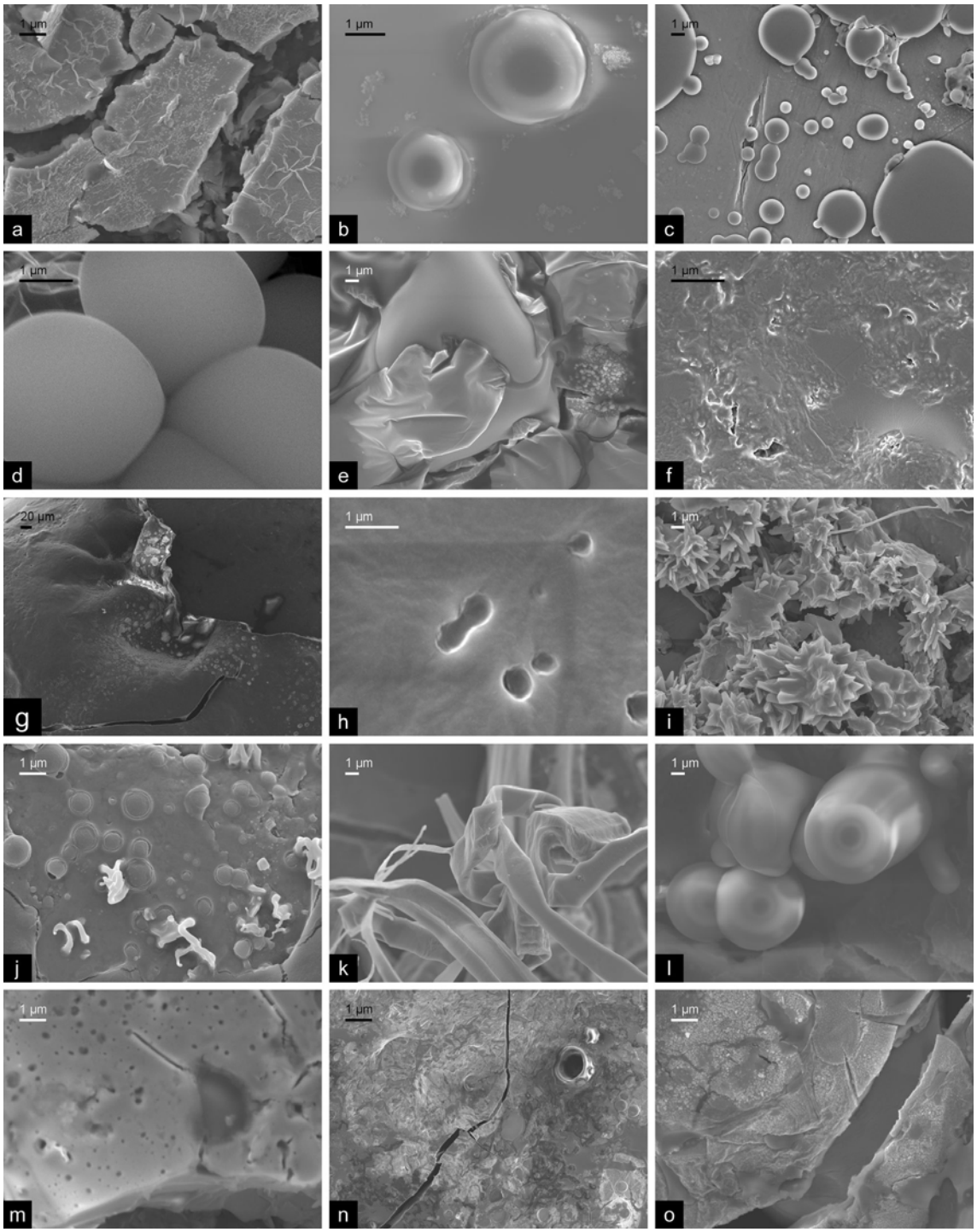


Figure S4. SEM micrographs of (a) A2Val_a10obenz, (b) A3Val_a10obenz, (c) A4Val_a10obenz, (d) A5Val_a10obenz, (e) A6Val_a10obenz, (f) A2Phe_a10obenz, (g) A3Phe_a10obenz, (h) A4Phe_a10obenz, (i) A2Val_a8, (j) A3Val_a8, (k) A4Val_a8, (l) A4Ala_a10obenz, (m) A4Leu_a10obenz, (n) A4Val_a1obenz and (o) A4Val_a4obenz, grown from 2 : 1 MeOH : H_2O solutions in the presence of acid (HCl). The corresponding scale bars are shown for every picture.

NMR spectra of A4Val_a10obenz (3) at different conditions:

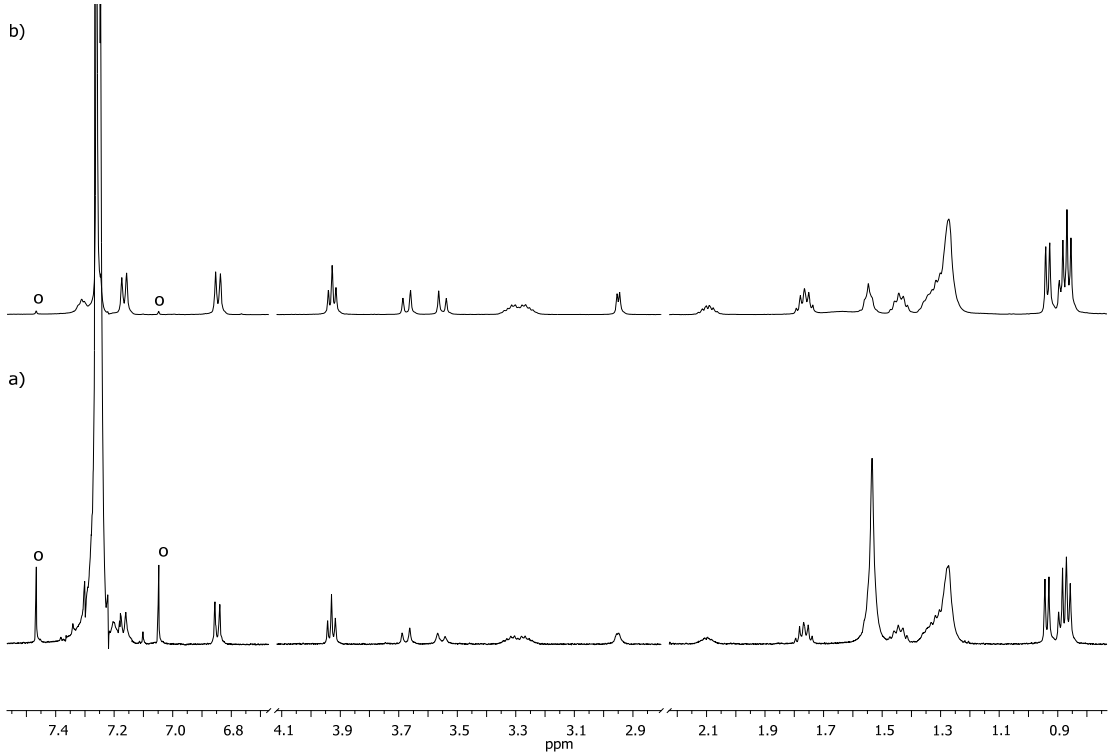


Figure S5. ^{1}H NMR spectra of A4Val_a10obenz (3) (500 MHz, 303 K, in CD_3OD) at 1 mM (a), and 20 mM (b).

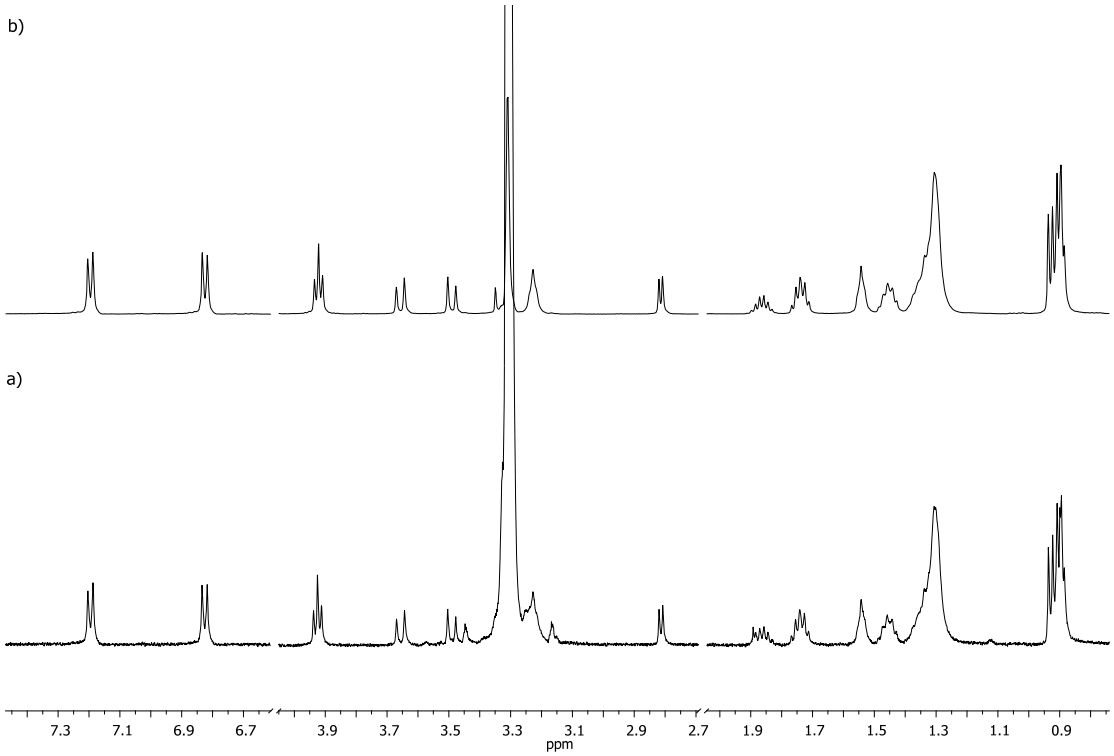


Figure S6. ^{1}H NMR spectra of A4Val_a10obenz (3) (500 MHz, 303 K, in CD_3OD) at 1 mM (a), and 20 mM (b).

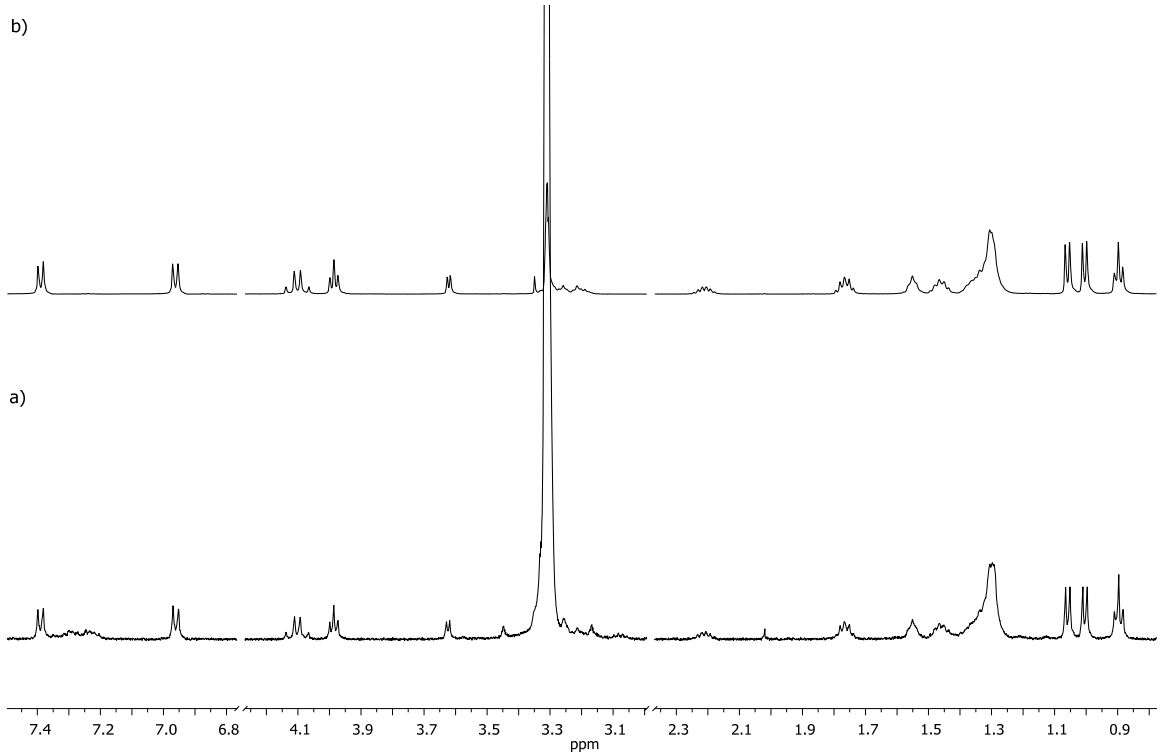


Figure S7. ^{1}H NMR spectra of A4Val_a10obenz (3) (500 MHz, 303 K, in CD_3OD + DCl) at 1 mM (a), and 20 mM (b).

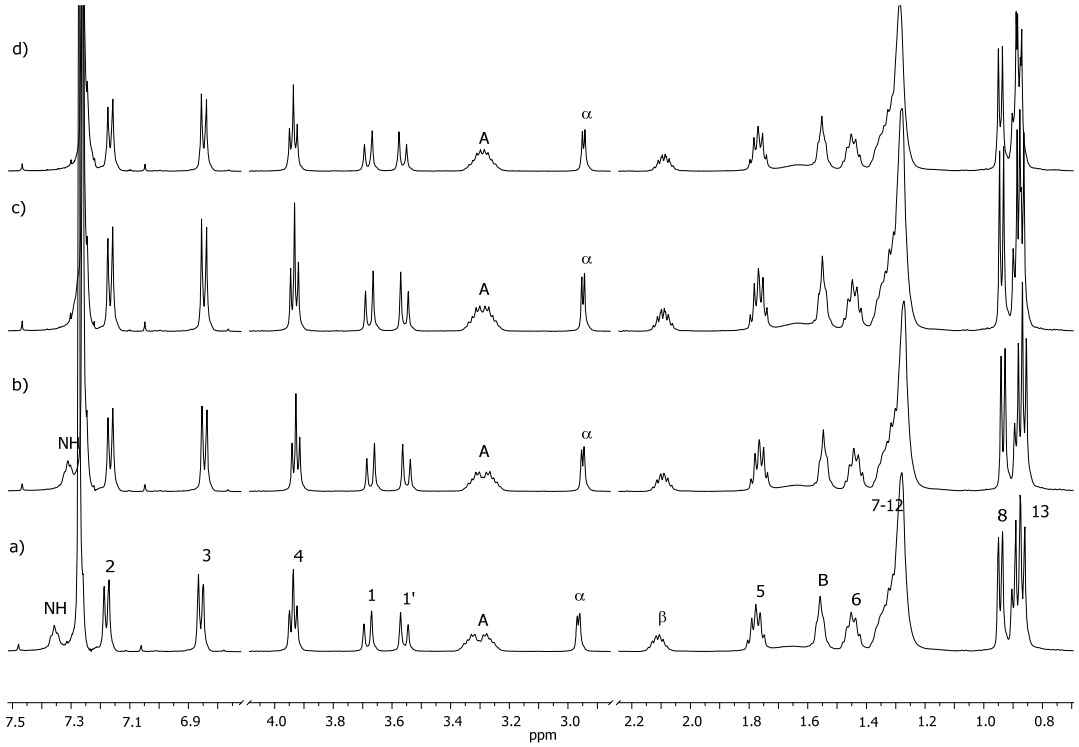


Figure S8. ^{1}H NMR spectra of A4Val_a10obenz (3) (500 MHz, 20 mM, in $CDCl_3$) at 294 K (a), 303 K (b), 313 K (c) and 323 K (d). Assignations of the signals experiencing changes are shown following the arbitrary lettering of the chemical substructure.

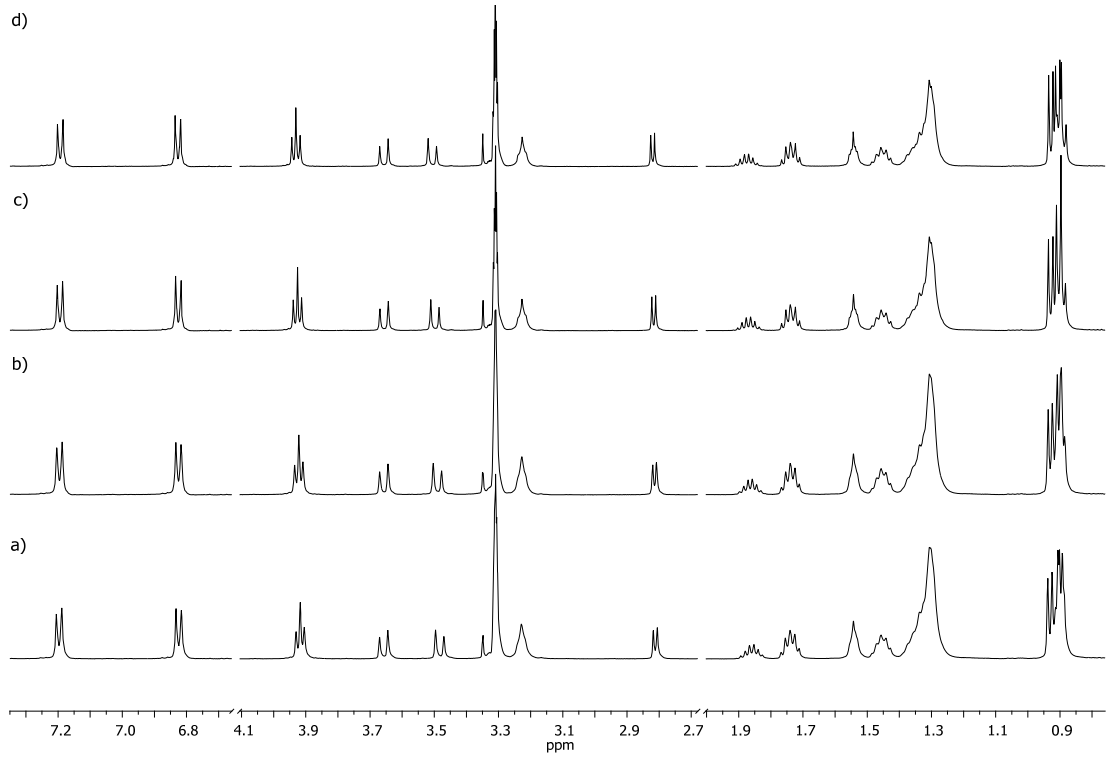


Figure S9. ^{1}H NMR spectra of A4Val_a10obenz (3) (500 MHz, 20 mM, in CD_3OD) at 294 K (a), 303 K (b), 313 K (c) and 323 K (d).

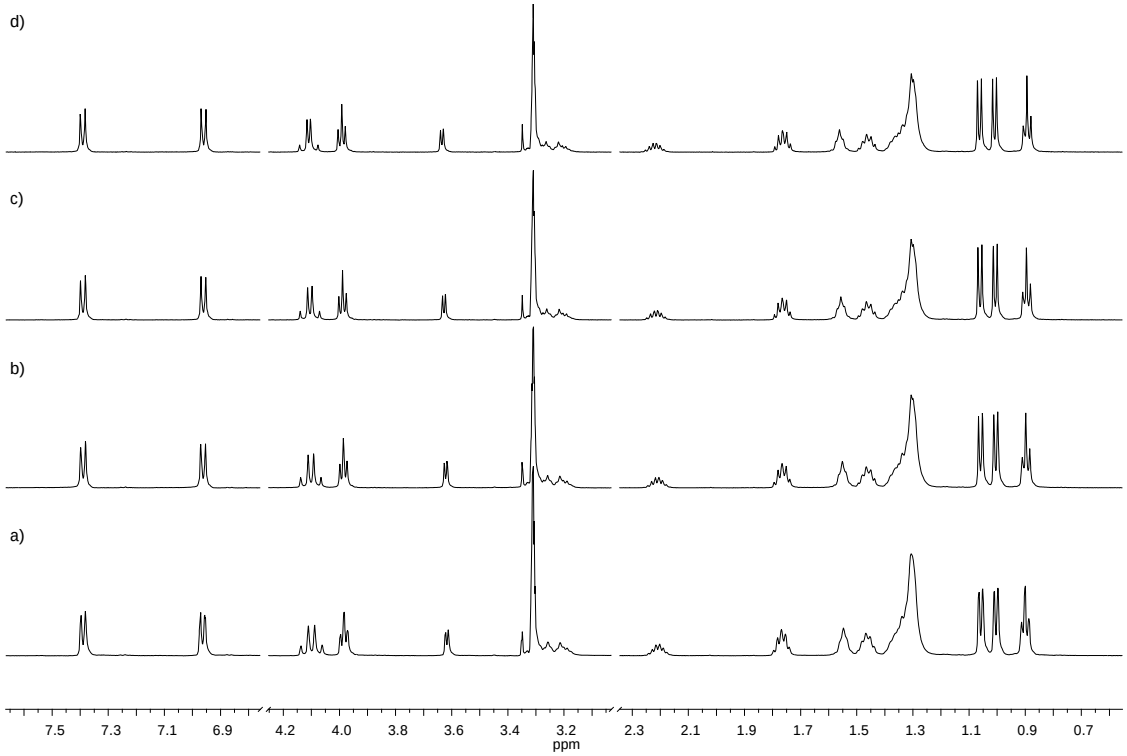


Figure S10. ^{1}H NMR spectra of A4Val_a10obenz (3) (500 MHz, 20 mM, in CD_3OD + DCl) at 294 K (a), 303 K (b), 313 K (c) and 323 K (d).

NMR studies to check similar trends of compounds:

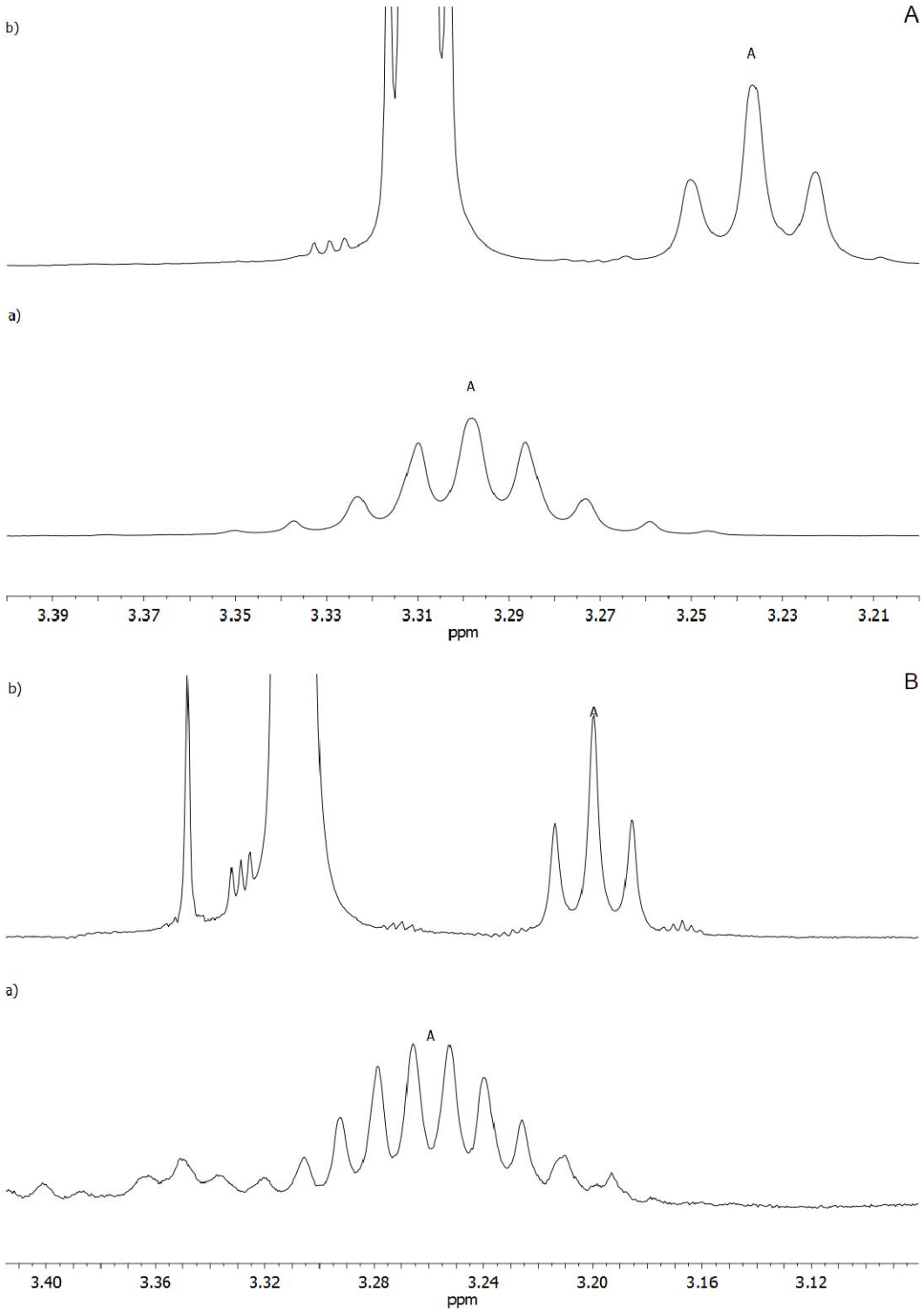


Figure S11. Selected partial ^{1}H NMR spectra (500 MHz, 303 K, 20 mM) of compound A3Val_a10obenz (2) in $CDCl_3$ (a) and CD_3OD (b) (A) and compound A5Val_a10obenz (4) in in $CDCl_3$ (a) and CD_3OD (b) (B). Assignations of the signals are shown following the arbitrary lettering of the chemical substructure.

Table S1. Deshielding values for different GAPs obtained after protonation of the system. From MeOD to MeOD + DCl.

		Deshielding (ppm)							
	Compound	H1	H1'	H2	H3	H4	Hα	Hβ	Hγ
1	A2Val_a10obenz	0.48	0.61	0.23	0.14	0.05	0.88	0.35	0.15
2	A3Val_a10obenz	0.48	0.58	0.19	0.13	0.06	0.80	0.34	0.12
3	A4Val_a10obenz	0.47	0.59	0.20	0.14	0.07	0.81	0.33	0.13
4	A5Val_a10obenz	0.48	0.59	0.20	0.12	0.06	0.82	0.35	0.13
5	A6Val_a10obenz	0.47	0.58	0.19	0.13	0.06	0.79	0.35	0.12

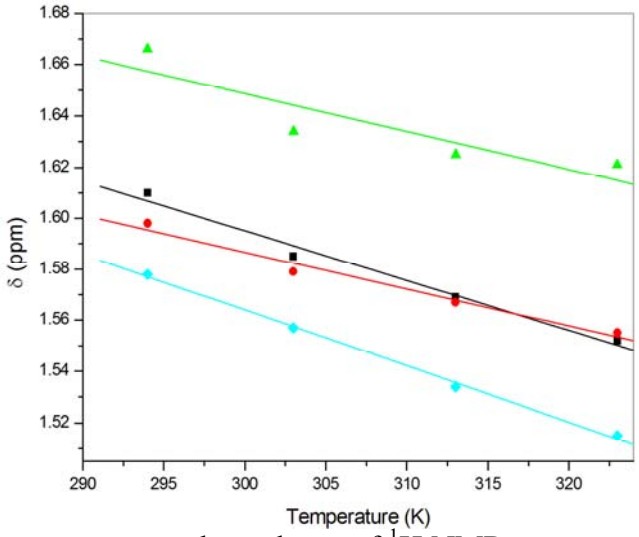


Figure S12. Plot of the temperature dependence of ^{1}H NMR spectroscopic data of the amine NH protons of A2Val_a10obenz (1) (black), A3Val_a10obenz (2) (red), A4Val_a10obenz (3) (green) and A6Val_a10obenz (5) (cyan) (all at 500 MHz, 20 mM) in $CDCl_3$.

Table S2. Temperature factors for the amine NH protons.

	Compound	ΔδNHamine/Δ*T* (ppb/K)
1	A2Val_a10obenz	-3.8
2	A3Val_a10obenz	-4.0
3	A4Val_a10obenz	-2.7
5	A6Val_a10obenz	-3.8

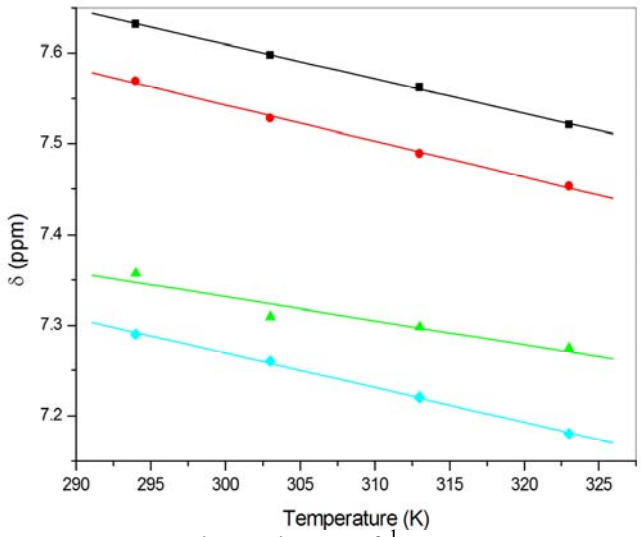


Figure S13. Plot of the temperature dependence of ^{1}H NMR spectroscopic data of the amide NH protons of A2Val_a10obenz (1) (black), A3Val_a10obenz (2) (red), A4Val_a10obenz (3) (green) and A6Val_a10obenz (5) (cyan) (all at 500 MHz, 20 mM) in $CDCl_3$.

Table S3. Temperature factors for the amide NH protons.

	Compound	ΔδNHamide/Δ*T* (ppb/K)
1	A2Val_a10obenz	-2.0
2	A3Val_a10obenz	-1.5
3	A4Val_a10obenz	-1.6
5	A6Val_a10obenz	-2.2

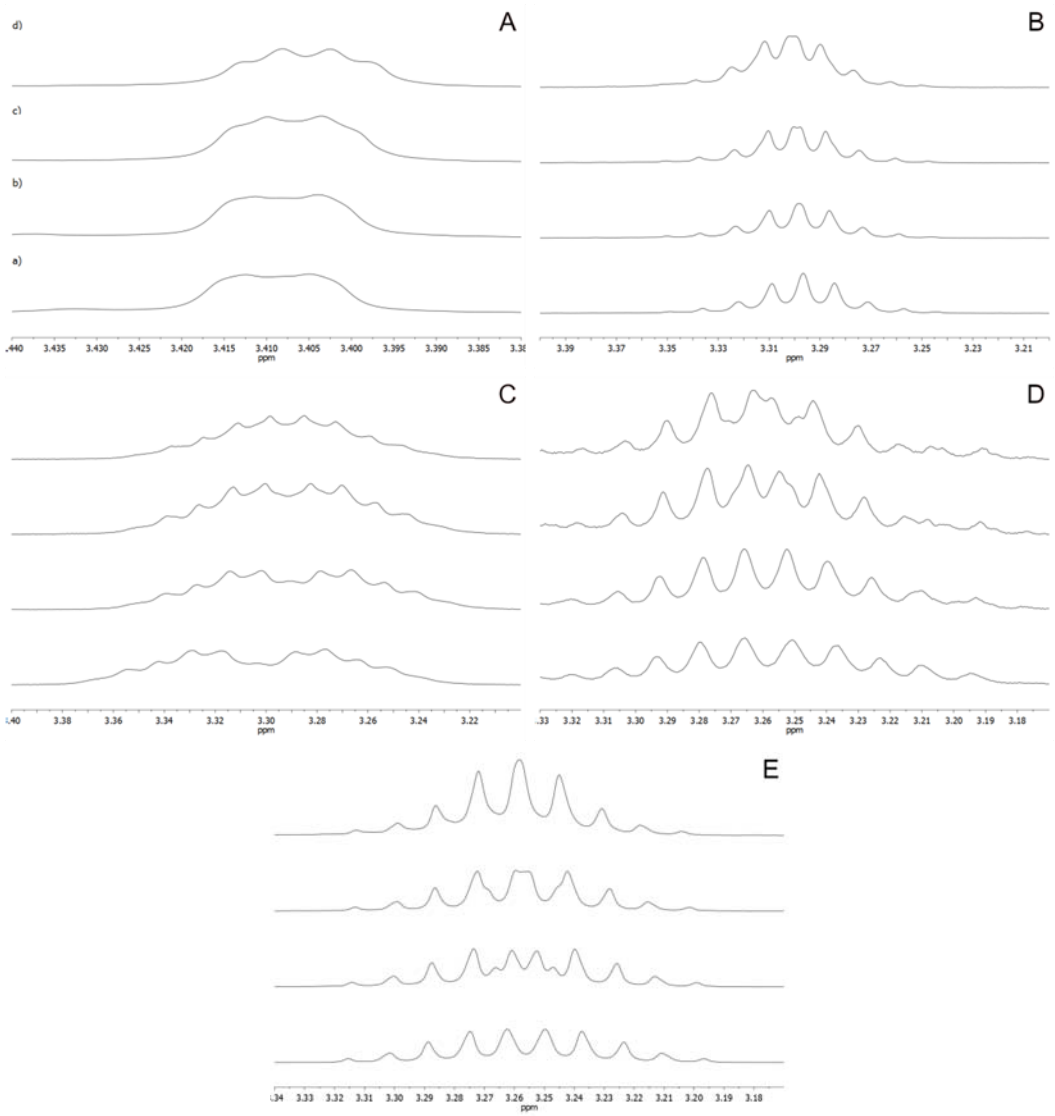


Figure S14. Selected partial ^{1}H NMR spectra (A signal, 500 MHz, 20 mM, $CDCl_3$) of compounds A2Val_a10obenz (A), A3Val_a10obenz (B), A4Val_a10obenz (C), A5Val_a10obenz (D) and A6Val_a10obenz (E) at 294 K (a), 303 K (b), 313 K (c) and 323 K (d).

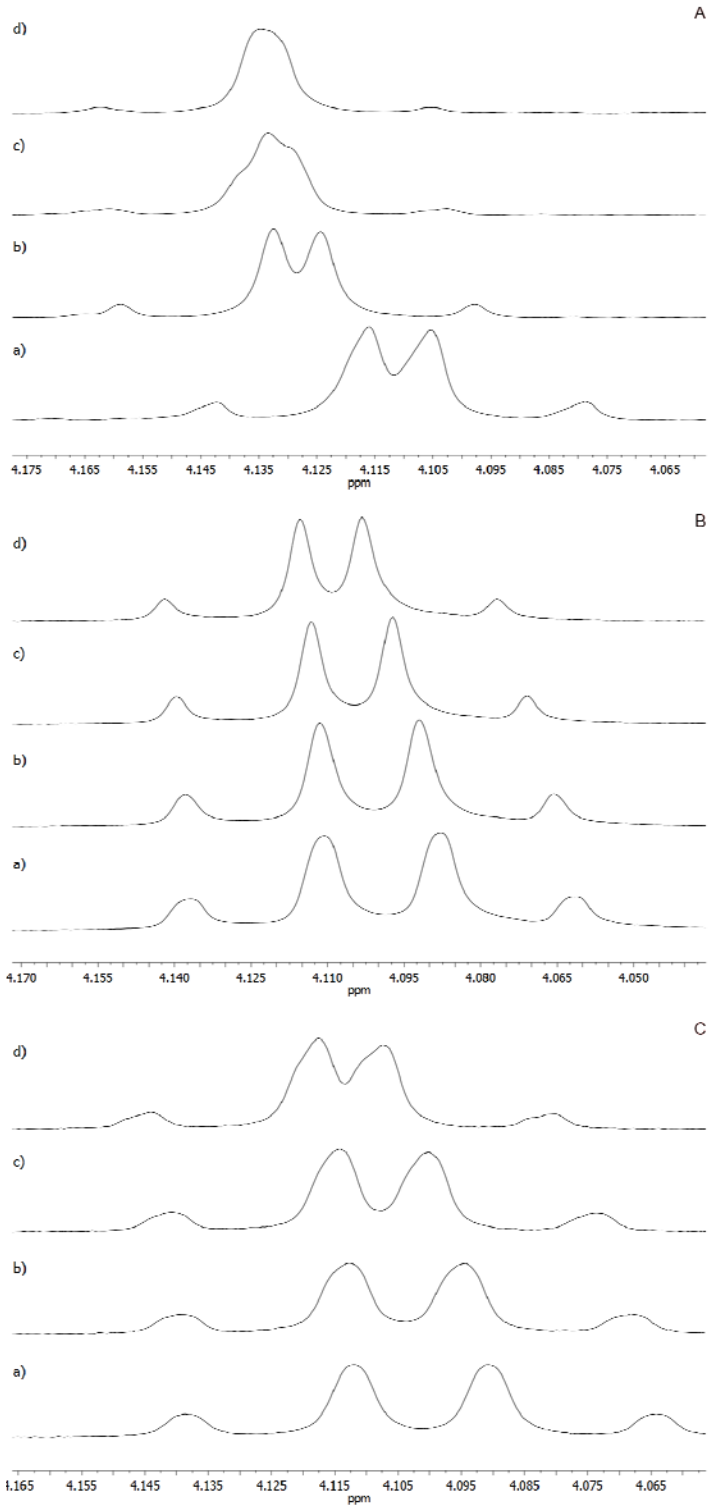


Figure S15. Selected partial ^{1}H NMR spectra (H1 signal, 500 MHz, 20 mM, CD_3OD + DCl) of compounds A2Val_a10obenz (A), A4Val_a10obenz (B) and A6Val_a10obenz (C) at 294 K (a), 303 K (b), 313 K (c) and 323 K (d).

UV spectra of A4Val_a10obenz (3) in MeOH at different concentrations:

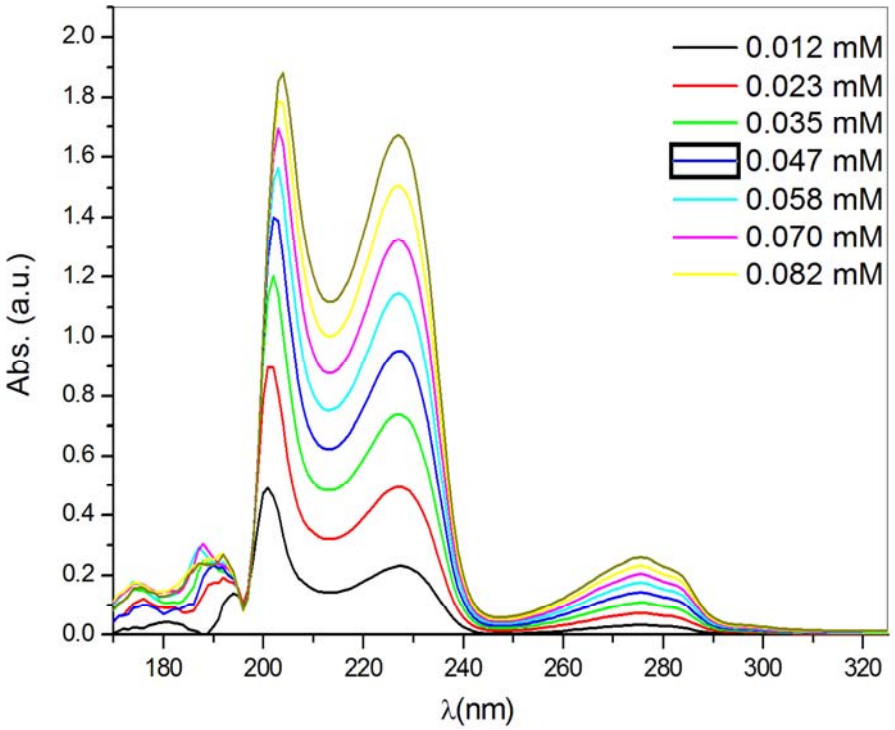


Figure S16. UV spectra of the A4Val_a10obenz (3) in MeOH at different concentrations.

UV study of compounds at different concentrations in MeOH in the presence of acid:

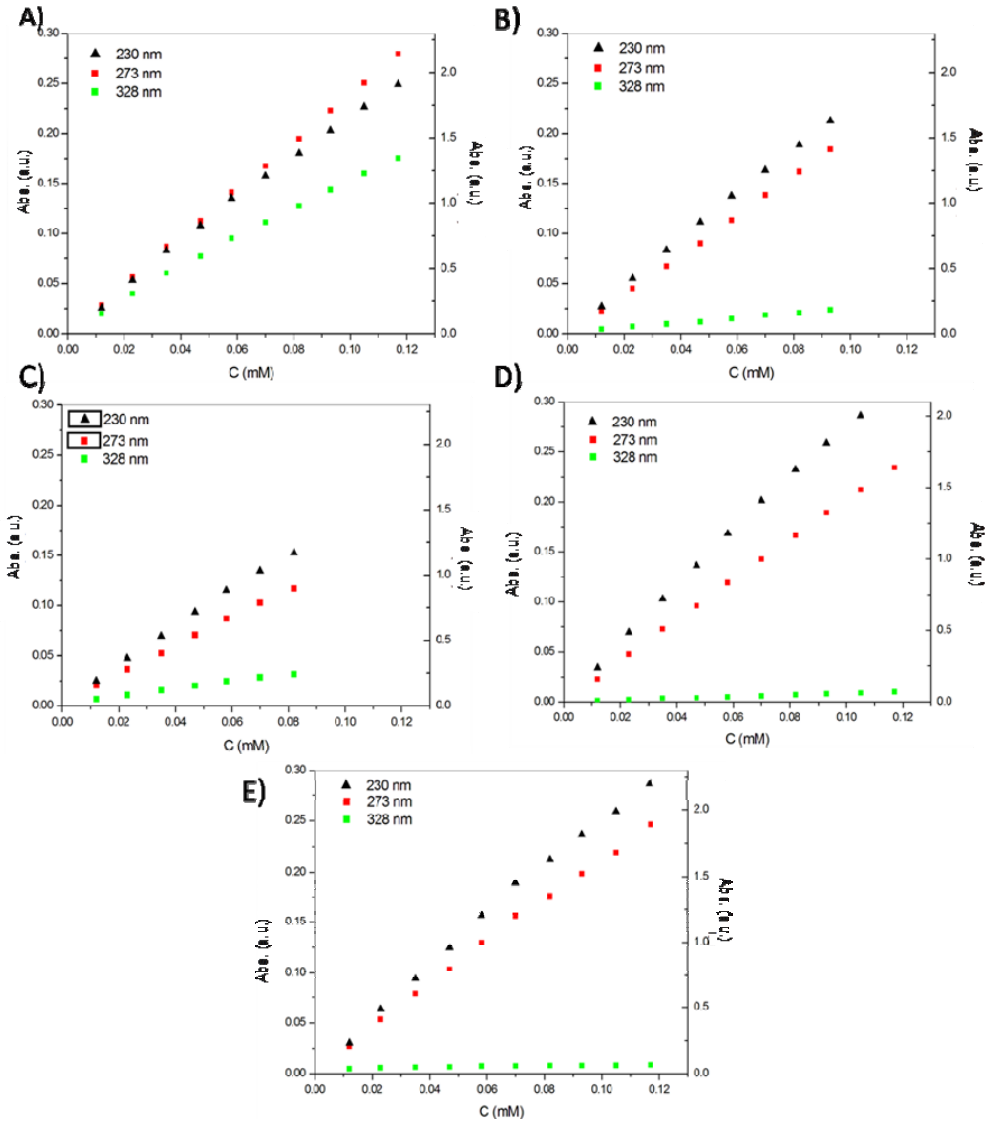


Figure S17. Plot of the UV absorbance at the corresponig π-π* transition (black triangle, right axis), n-π* transition (red square, left axis) and CT band (green square, left axis) in MeOH at acid pH; A2Val_a10obenz (1) (A), A3Val_a10obenz (2) (B), A4Val_a10obenz (3) (C), A5Val_a10obenz (4) (D) and A6Val_a10obenz (5) (E).

UV study of compounds with different long aliphatic tail:

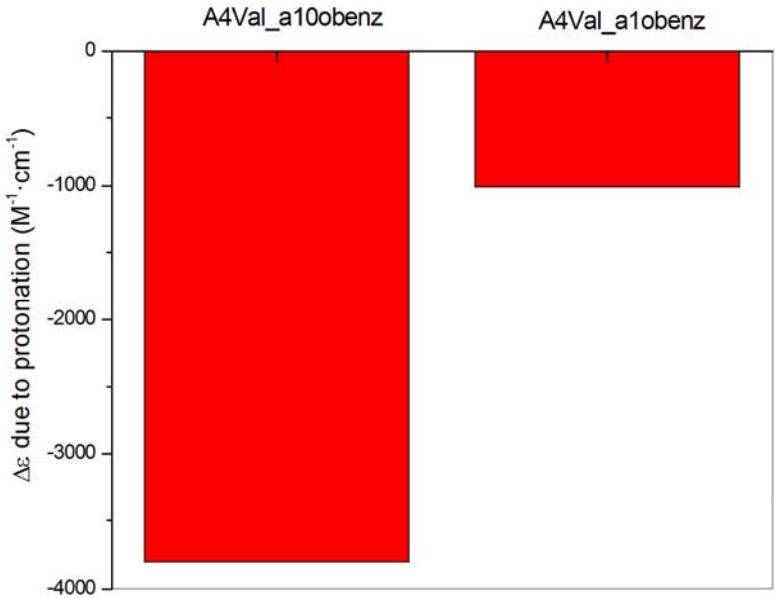


Figure S18. Plot of the variation o UV extinction coefficients at the corresponding maxima due to protonation for A4Val_a10obenz and A4Val_a1obenz.

UV study of compounds with different amino acid side chain:

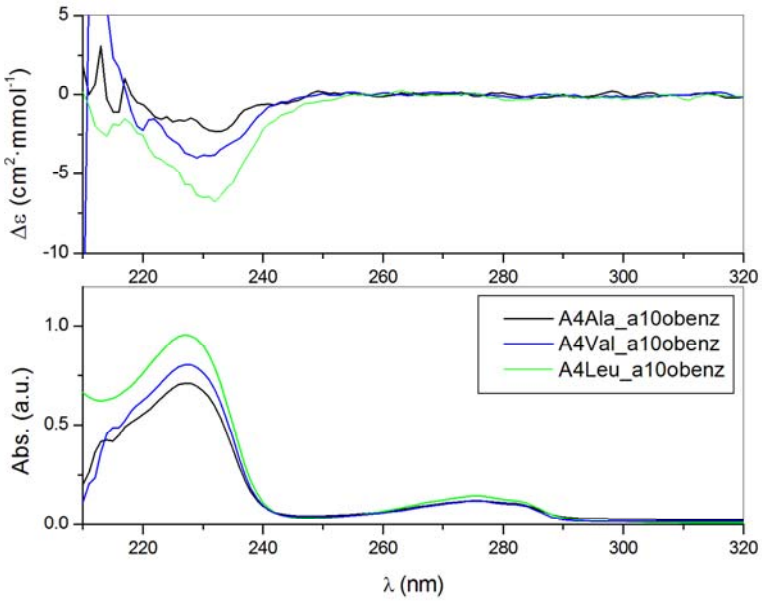


Figure S19. UV-CD spectra of A4Xxx_a10obenz (Xxx = Ala, Val and Leu) in MeOH.

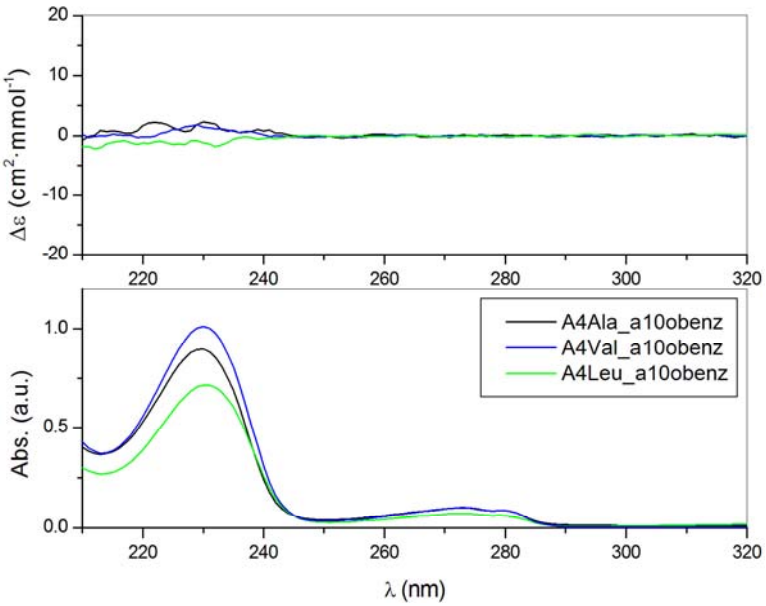


Figure S20. UV-CD spectra of A4Xxx_a10obenz (Xxx = Ala, Val and Leu) in MeOH in the presence of acid.

UV extinction coefficients at the corresponding maxima for several compounds:

Compound	Media	λ_{max} (nm)	ε ($M^{-1}\cdot cm^{-1}$)	R
A2Val_a10obenz	MeOH, acid	230	16200 ± 300	0.99876
		273	2373 ± 13	0.99989
		328	1466 ± 24	0.99894
	MeOH	230	10414 ± 16	0.9979
		273	3231 ± 7	0.9987
A3Val_a10obenz	MeOH, acid	230	17500 ± 200	0.99961
		273	1993 ± 14	0.99985
		328	240 ± 6	0.99822
	MeOH	230	15056 ± 12	0.9994
		273	2258.9 ± 0.7	0.9996
A4Val_a10obenz	MeOH, acid	230	14100 ± 300	0.99882
		273	1400 ± 20	0.99949
		328	365 ± 11	0.99762
	MeOH, basic	226	8050 ± 90	0.99969
		276	1447 ± 18	0.99962
	MeOH	226	17900 ± 700	0.992
		276	2840 ± 90	0.9941
	$CHCl_3$	238	5470 ± 130	0.99778
		276*	3000 ± 300	0.93275
	MeOH, acid5%H_2O	230*	2820 ± 110	0.98592
		273	399 ± 3	0.99953
		328	273.6 ± 0.5	0.99652
	MeOH, acid10%H_2O	230*	3200 ± 500	0.82072
		273	1584 ± 15	0.99917
A5Val_a10obenz	MeOH, acid	230	19000 ± 300	0.99907
		273	2010 ± 13	0.99983
	MeOH	227	18130 ± 210	0.99945
		276	2752 ± 17	0.99984
A6Val_a10obenz	MeOH, acid	230	18700 ± 400	0.99786
		273	2070 ± 30	0.99919
	MeOH	226	16220 ± 180	0.99951
		275	2390 ± 30	0.99935
A4Val_a1obenz	$CHCl_3$	238	4090 ± 80	0.998
		276	2721 ± 13	0.9991
	MeOH, acid	226	14770 ± 90	0.99984
		275	2242 ± 16	0.99979
		276	2226 ± 16	0.99979
	MeOH, basic	226	14000 ± 100	0.99972
		276	2082 ± 18	0.99969
	MeOH	226	15780 ± 80	0.99989
		276	2383 ± 15	0.99983
A4Ala_a10obenz	MeOH, acid	230	18190 ± 230	0.99935
		273	2131 ± 19	0.99967
	MeOH	227	14860 ± 140	0.99966
		276	2349 ± 18	0.99977
A4Leu_a10obenz	MeOH, acid	227	18600 ± 400	0.99793
		275	2640 ± 50	0.99871
	MeOH	230	20700 ± 400	0.99875
		273	2185 ± 12	0.99988

Selected bands of the ATR FT-IR spectra of A4Val_a10obenz at different conditions:

Evolution of the ATR FT-IR spectra of A4Val_a10obenz: we monitored the IR spectrum from $CHCl_3$, MeOH and acidic MeOH solutions until complete evaporation of the solvent to dryness. The spectra were normalized considering the area of the analyzed bands in every region.

Amide II (N-H bending) region

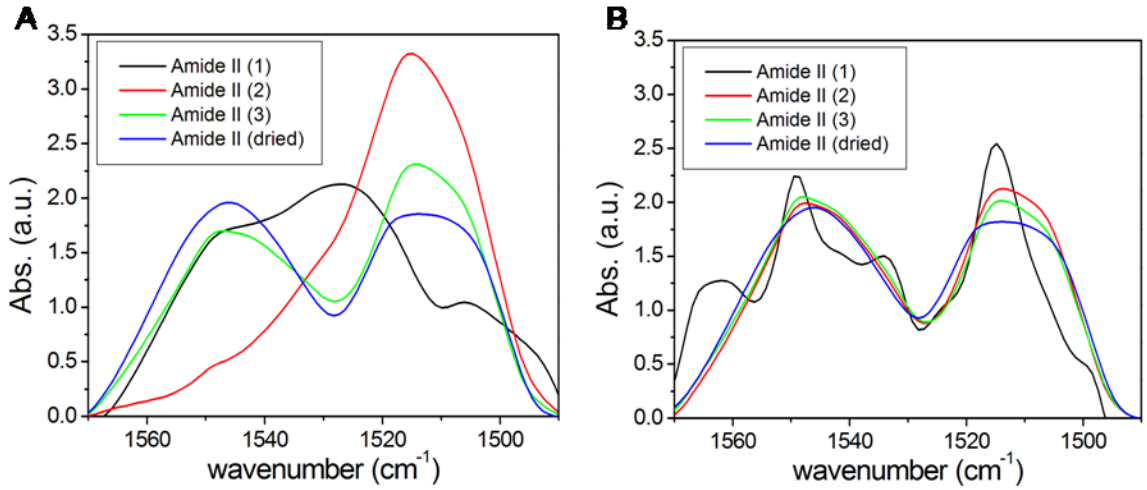


Figure S21. Selected regions of several ATR FT-IR spectra of A4Val_a10obenz: (A) amide II in $CHCl_3$ and (B) amide II in MeOH.

Amide A (N-H stretching) region

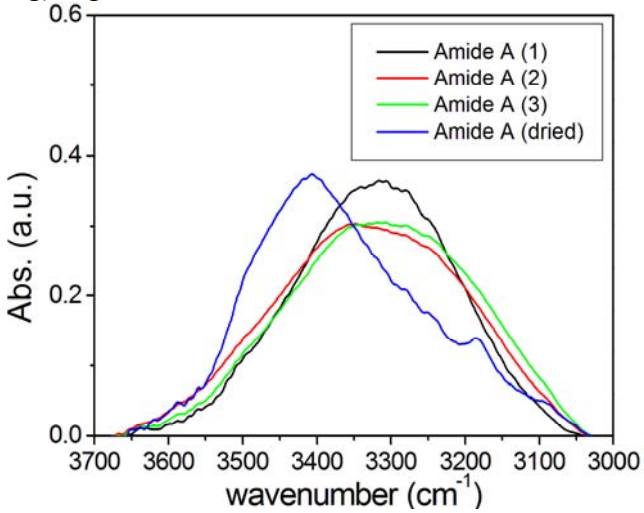


Figure S22. ATR FT-IR spectra (amide A region) evolution of 4Val_a10obenz in acidic MeOH.

Amide I (C=O stretching) and Amide II (N-H bending) regions.

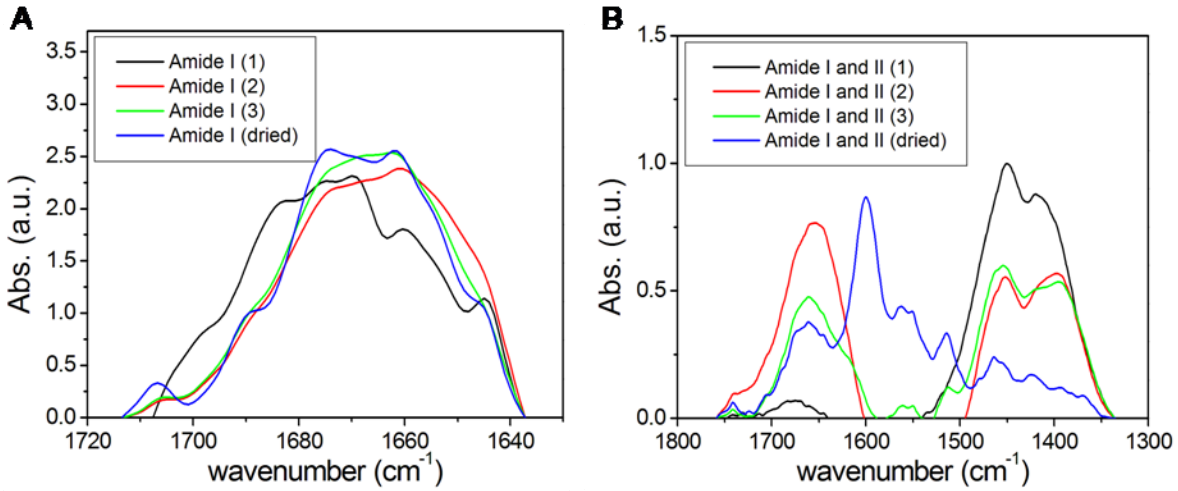


Figure S23. Selected regions of several ATR FT-IR spectra of A4Val_a10obenz: (A) amide I and (B) amide I and II in MeOH with acid.

Evolution of the ATR FT-IR spectra of A4Val_a10obenz upon evaporation of the solvent to dryness.

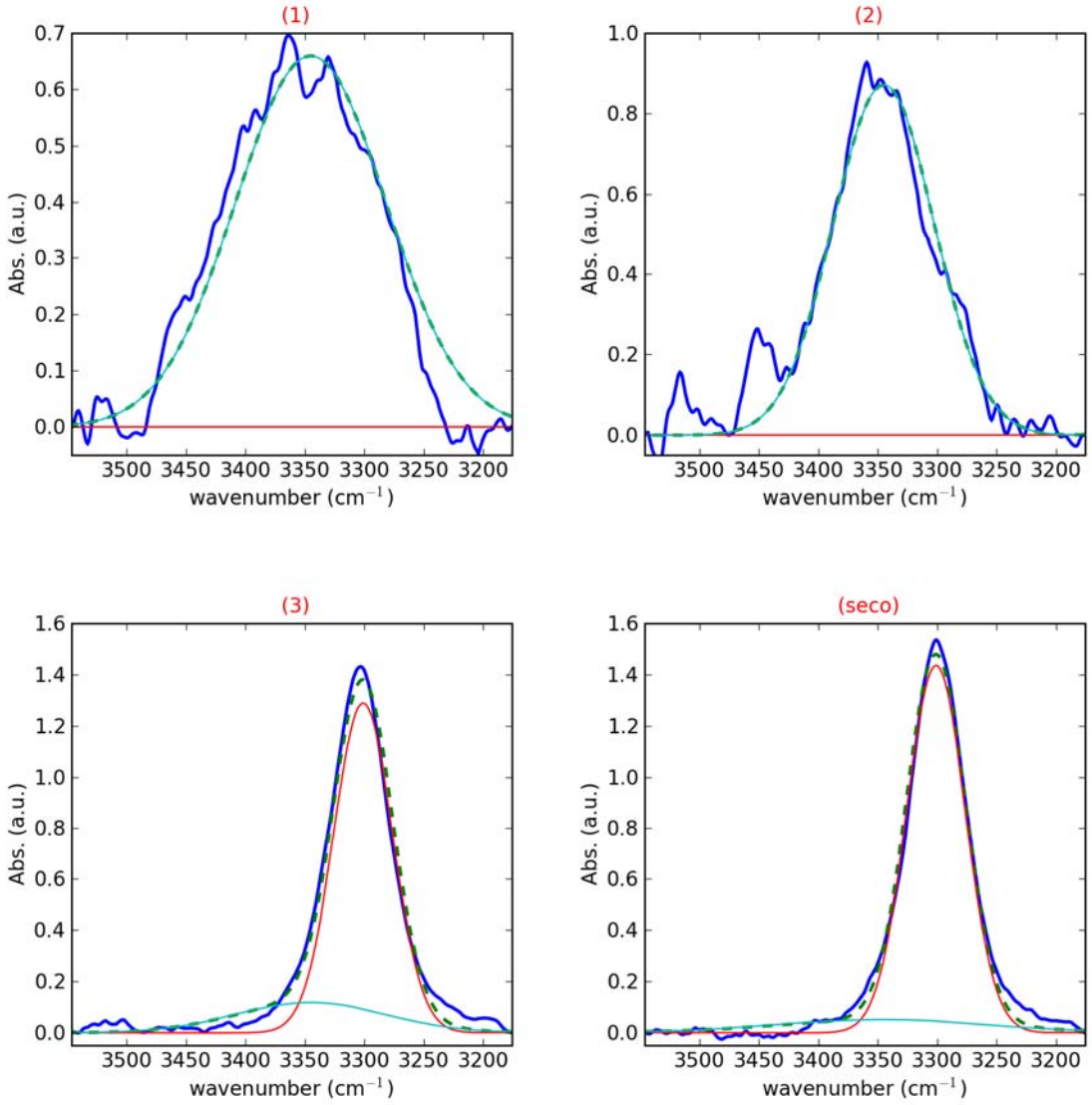


Figure S24. Solvent evaporation evolution for amide A for A4Val_a10obenz in $CHCl_3$.

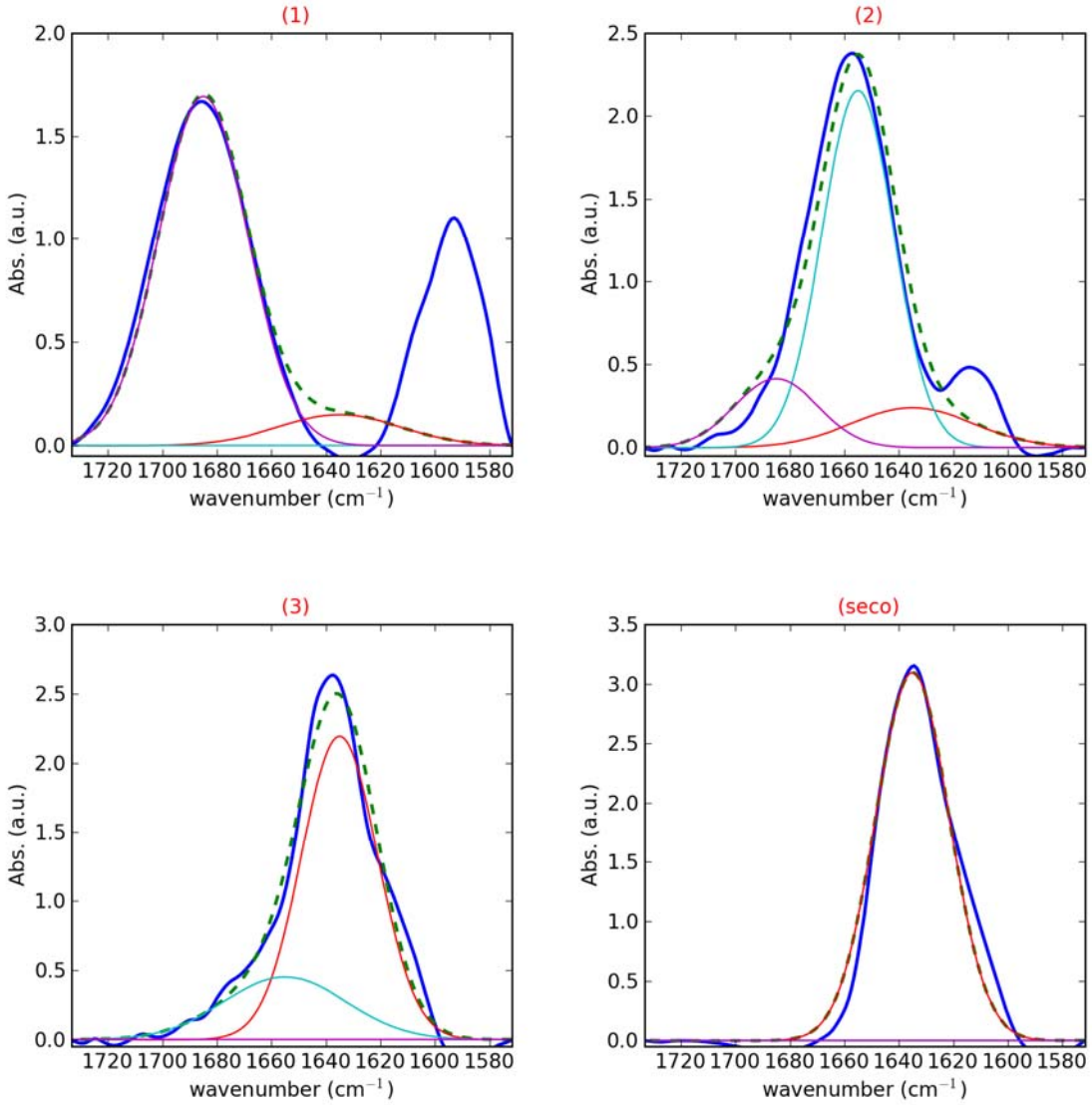


Figure S25. Solvent evaporation evolution for amide I for A4Val_a10obenz in $CHCl_3$.

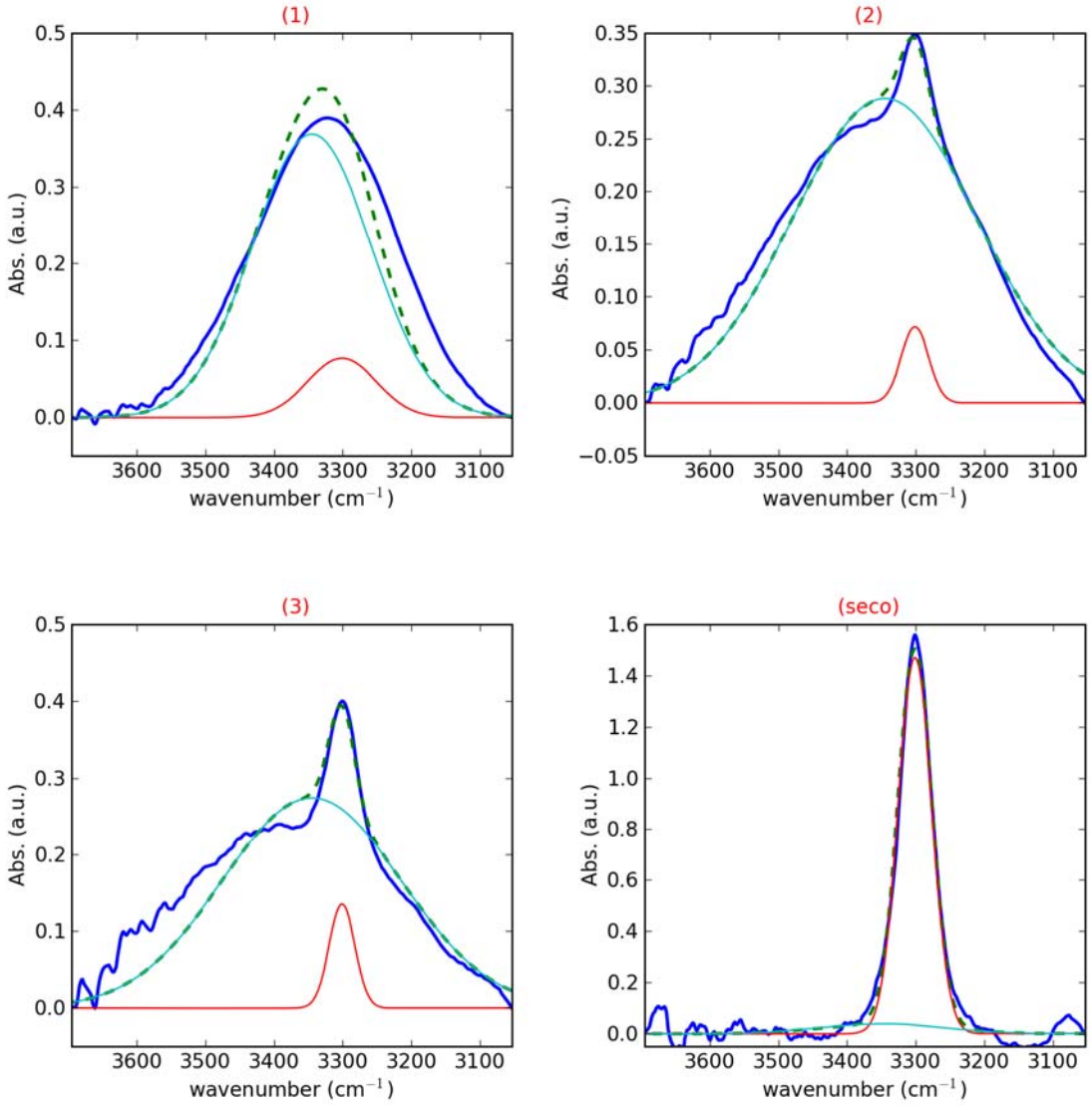


Figure S26. Solvent evaporation evolution for amide A for A4Val_a10obenz in MeOH.

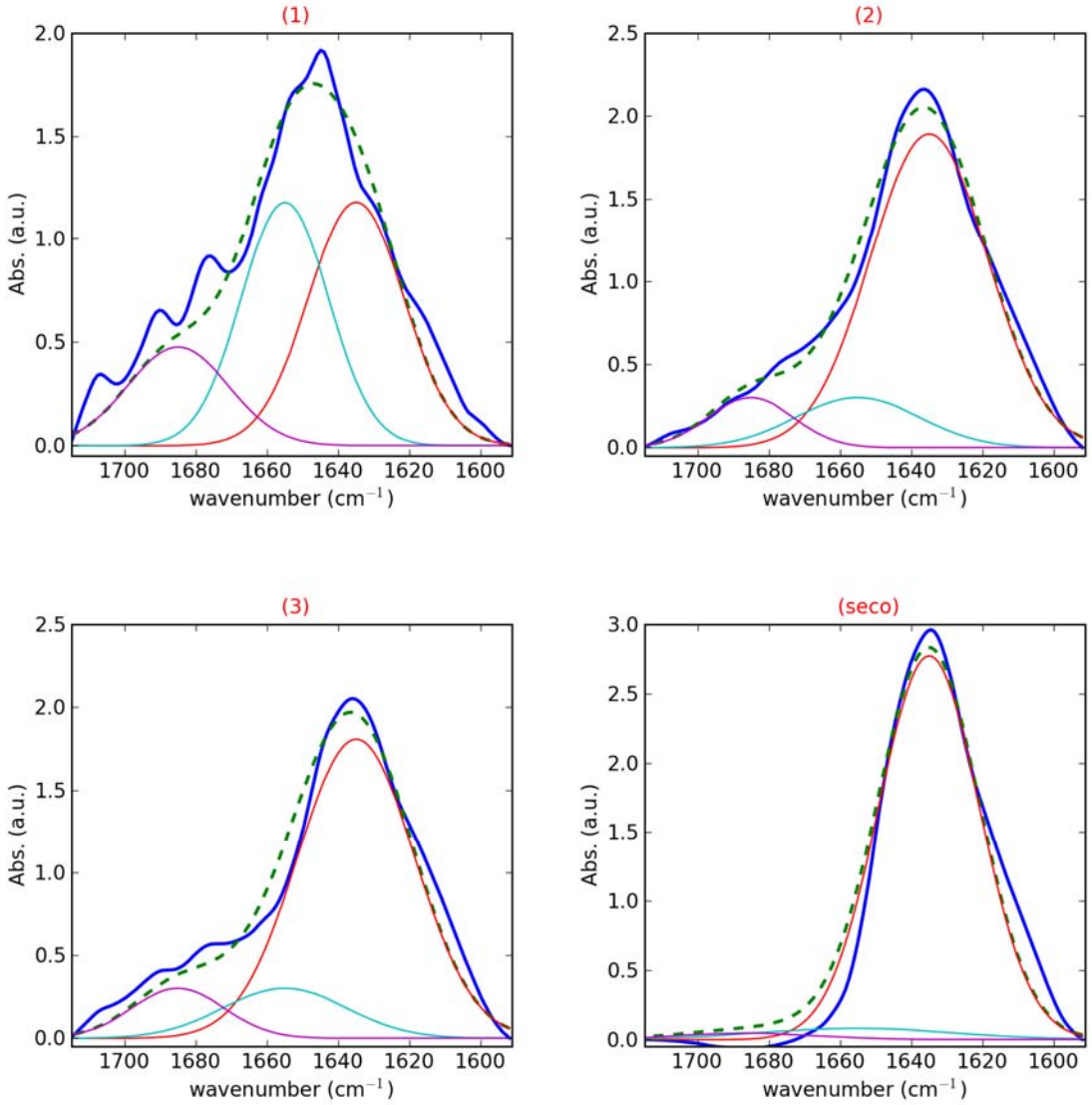


Figure S27. Solvent evaporation evolution for amide I for A4Val_a10obenz in MeOH.

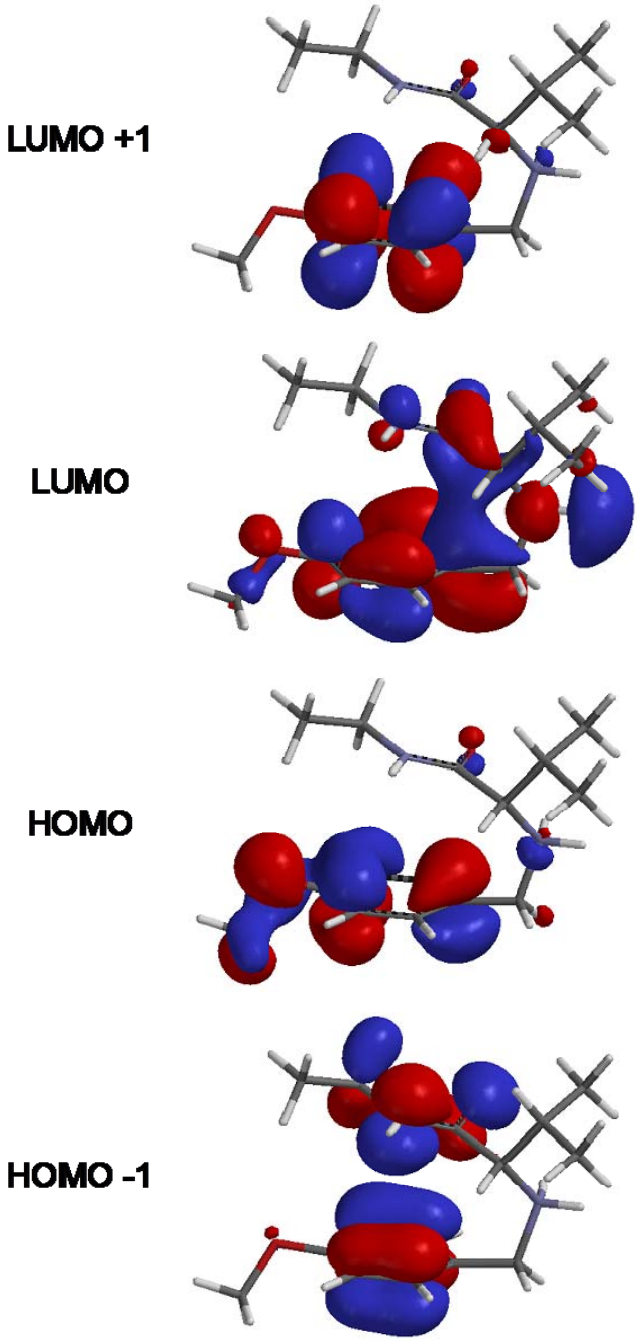


Figure S28. Frontier orbitals (B3LYP/6-31G*) for a simplified fragment of the GAPs.