Aza-β^3-Cyclotetrapeptides

Arnaud Salaün,[†] Clémence Mocquet,[†] Romain Perochon,[†] Aurélien Lecorgne,[†] Barbara Le Grel,[†]

Michel Potel,[‡] and Philippe Le Grel.*[,†]

†ICMV, UMR CNRS 6226, Université de Rennes I, 263 avenue du Général Leclerc 35042 Rennes Cedex. ‡CSM, UMR CNRS 6226, Université de Rennes I, 263 avenue du Général Leclerc 35042 Rennes Cedex.

philippe.legrel@univ-rennes1.fr

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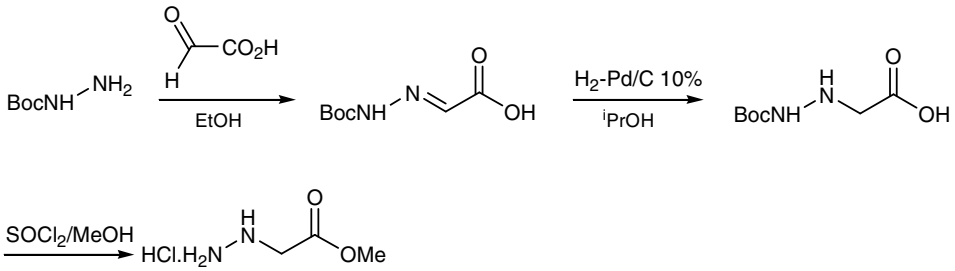
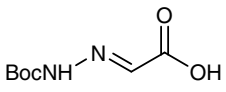
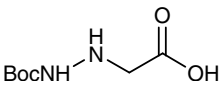
All other monomers were prepared and assembled following our previous publications excepted for the following compounds.

Synthesis and characterization of monomer HCl. H-(aza-β^3-Gly)-OMe.

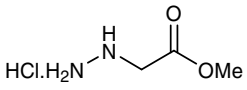




Tertio butyl carbazate (33g, 0,25 mol) and glyoxylic acid monohydrate (23 g, 0,25 mol) were dissolved in EtOH 95 % (100 mL). The mixture was stirred for 12 h at room temperature. Evaporation gave a crude powder that was filtrated after trituration in Et_2O (44.7g, 95%). ^{1}H NMR (200 MHz, DMSO-d_6) δ 1.48 (s, 9H, 3xCH_3), 7.33 (s, 1H, CH), 11.37 (broad, 1H, NH).



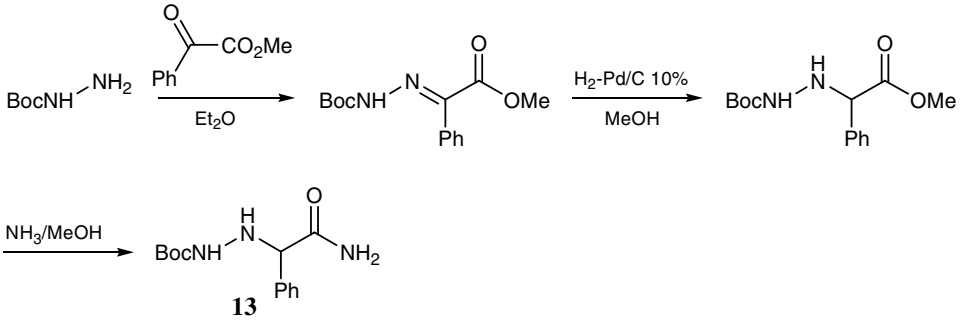
To a solution of hydrazone (44.7g, 0.24 mole) in *i*-PrOH (500 mL) was added 10% Pd/C (400 mg). After 12 h of stirring under H_2 atmosphere, the solution was filtered on Celite and evaporated. The residue precipitated by addition of dichloromethane to give a white solid which was filtered to afford Boc-hydrazinoacetic acid (41.8g, 93%). ^{1}H NMR (200 MHz, 298 K, DMSO-d_6) δ 1.40 (s, 9H, 3xCH_3), 3.42 (s, 2H, CH_2), 8.19 (broad, 1H, NH). mp144°C.



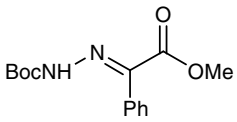
$SOCl_2$ (1.25g, 0.021 mole) is added dropwise to a solution of Boc-hydrazinoacetic acid (2g, 0.0105 mole) in methanol. After 8 h stirring, the solvent is evaporated under reduced pressure. The crude methyl hydrazinoacetic ester hydrochloride (2g, 95%) is filtrated after trituration in ether. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.68 (s, 3H, CH_3), 3.79 (s, 2H, CH_2).

The coupling of methyl hydrazinoacetic ester hydrochloride is performed in the same conditions as other monomers except that it is pre-dissolved in DCM in the presence of a 3 fold excess of NEt_3 before the addition of HOBT, the acid partner, and EDCI.

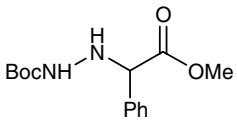
Synthesis and characterization of compound 13.



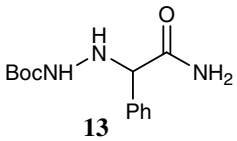
13



To a solution of Tertio butyl carbazate (6.6g, 50 mmol) in Et_2O (500 mL), was added methyl benzoylformate (8.2g, 50 mmol). Two drops of acetic acid were added and the mixture was stirred at room temperature for 12 h. Organic layer was dried (Na_2SO_4) and filtered. The solvent was removed *in vacuo* affording intermediate hydrazone (11.97g, 90%). ^{1}H NMR (200 MHz, 298 K, $CDCl_3$) δ 1.51 (s, 9H, 3xCH_3), 3.87 (s, 3H, CH_3), 7.27-7.32 (m, 2H, 2xCH), 7.51-7.56 (m, 3H, 3xCH), 8.07 (s, 1H, NH).



To a solution of hydrazone (6.65g, 25 mmol) in MeOH (50 mL) was added 10% Pd/C (300 mg). After 12 h of stirring under H_2 atmosphere, the solution was filtered on Celite and the solvent was evaporated to afford the crude ester as pale yellow oil. ^{1}H NMR (200 MHz, 298 K, $CDCl_3$) δ 1.48 (s, 9H, 3xCH_3), 3.72 (s, 3H, CH_3), 4.50 (sl, 1H, NH), 4.87 (s, 1H, CH), 6.45 (sl, 1H, NH), 7.30-7.48 (m, 5H, C_6H_5).



13

The crude ester (2.68g, 10 mmol) was dissolved in a 7 N NH_3/MeOH 40% solution (30 mL). The solution was stirred at ambient temperature for 36 h. Excess of NH_3/MeOH was evaporated. Trituration in Et_2O affords **13** as white solid (2.15g, 85 %). **13** was crystallized from acetonitrile. mp 191°C. ^{1}H NMR (500 MHz, 298 K, $CDCl_3$) δ 1.49 (s, 9H, 3xCH_3), 4.36 (broad, 1H, CH), 4.62 (s, 1H, CH), 5.53 (broad, 1H, NH), 6.19 (broad, 1H, NH), 7.07 (broad, 1H, NH), 7.34-7.48 (m, 5H, C_6H_5). Anal. Calcd: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.89; H, 7.22; N, 15.91.

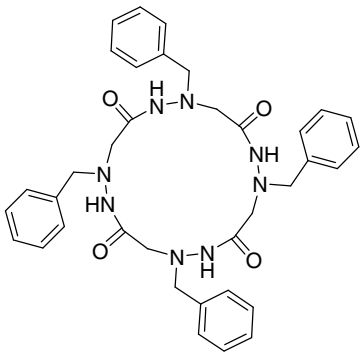
General macrocyclization procedure for compounds 1-11.

Typically, a Boc-aza-β^3-OH tetramer (1 mmol) was treated with a mixture of DCM/TFA (6 mL/4 mL) during 12 h. The excess of TFA was then co-evaporated under reduced pressure with toluene (3 x 20 mL) then ether (3 x 20 mL) until a white foam appeared. The crude residue was dissolved in 20 mL of DCM and 10 mmoles of triethylamine were added. This solution is poured drop by drop to a solution of EDCI (8 mmol) and HOBT (8 mmol) in 1.5 L of DCM. The reaction is stirred vigorously for 72 h (unoptimized). The volume is then reduced to around 100 mL. The addition of 20 mL of 1 N HCl under stirring gives rise to the apparition of a white solid (HOBT, HCl) which is filtrated by succion. The solution was then washed successively with 20 mL 1 N HCl, twice 20 mL water, twice 20 mL 1 N $NaHCO_3$, dried on Na_2SO_4, and evaporated. In the cases of compounds **1**-**5**, **8**, and **9**, the crude reaction product was obtained as an off white powder which was purified by flash chromatography (DCM/ EtOAc 50/50) and crystallized in EtOAc.

Purification of compounds **6**, **7**, **10**, and **11** was performed on silica gel (DCM, then AcOEt/EtOH 80/20). Monocrystals for **11** were obtained in AcOEt.

Synthesis of **6** starting from **5**: Macrocycle **5** (1g) is dissolved in 20 mL of methanol containing two drops of acetic acid. 10% Pd/C (50 mg) was added, and the mixture was stirred for 12 h under hydrogen atmosphere. After filtration on celite, methanol is evaporated. The residue is further co-evaporated with toluene (twice 10 mL) then with DCM (twice 10 mL) to afford **6** quantitatively as a white powder.

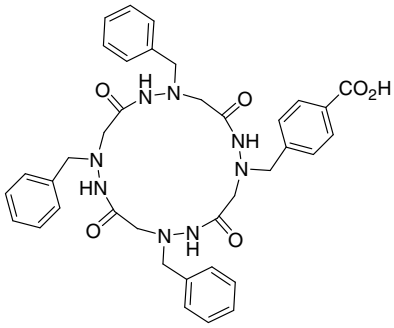
Characterization of macrocycles of compounds 1-11



1

Characterization data for 1. mp 208-210°C.

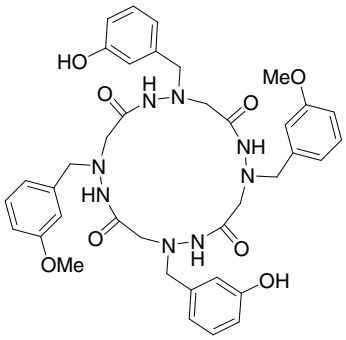
^{1}H NMR (500 MHz, 298 K, $CDCl_3$, 10 mM) δ 3.31 (s, 8H), 3.83 (d, *J* = 12.6 Hz, 4H), 3.87 (d, *J* = 12.6 Hz, 4H), 7.34-7.35 (m, 20H), 8.88 (s, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 58.2, 63.3, 128.6, 128.9, 130.0, 135.5, 168.2. ESI$^+$ HRMS 687.2817, calcd for $C_{36}H_{40}N_8O_4K$ 687.2810.



2

Characterization data for 2. mp 145–147°C.

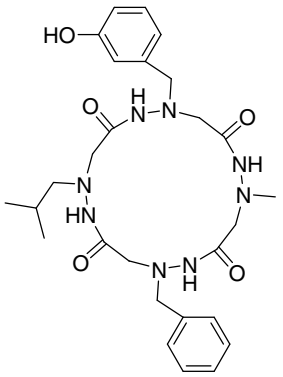
^{1}H NMR (500 MHz, 298 K, $CDCl_3$, 10 mM) δ 3.30-3.43 (m, 8H), 3.81-3.93 (m, 8H), 7.33-7.37 (m, 15H), 7.45 (d, *J* = 8.5 Hz, 2H), 8.05 (d, *J* = 8.5 Hz, 2H), 8.88 (s, 1H), 8.90 (s, 1H), 8.92 (s, 1H), 8.98 (s, 1H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 57.8, 58.4, 62.5, 62.8, 62.8, 128.2, 128.5, 129.5, 129.5, 129.6, 129.6, 130.2, 134.9, 135.0, 135.1, 140.7, 167.6, 167.9, 168.0, 168.1, 169.4. ESI$^+$ HRMS 715.2969, calcd for $C_{37}H_{40}N_8O_6Na$ 715.29685.



3

Characterization data for 3. mp 224–226°C.

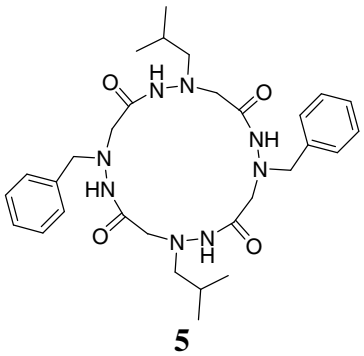
^{1}H NMR (500 MHz, 298 K, DMSO-d_6, 10 mM) δ 3.03 (m, 4H), 3.34 (m, 2H), 3.47 (m, 2H), 3.74 (s, 12H), 3.78 (m, 2H), 3.86 (m, 2H), 6.72 (dd, *J* = 6 Hz, *J* = 2 Hz, 2H), 6.74 (d, *J* = 7.6 Hz, 2H), 6.79 (s, 2H), 6.90 (d, *J* = 7.6 Hz, 2H), 6.96 (d, *J* = 2 Hz, 2H), 7.12 (t, *J* = 7.8 Hz, 2H), 7.25 (t, *J* = 7.8 Hz, 2H), 8.70 (s, 2H), 8.67 (s, 2H), 9.42 (s, 2H). ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 31.1, 55.4, 58.2, 58.7, 62.2, 113.7, 115.0, 115.1, 116.6, 120.3, 121.9, 129.6, 129.7, 137.1, 137.4, 157.8, 159.6, 167.3, 167.4. ESI$^+$ HRMS 779.2906, calcd for $C_{38}H_{44}N_8O_8K$ 779.29192.



4

Characterization data for 4. mp 220–222°C

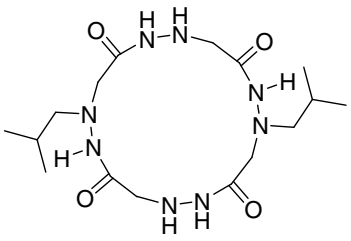
^{1}H NMR (500 MHz, 298 K, $CDCl_3$, 10 mM) δ 0.91 (d, *J* = 6.7 Hz, 3H), 1.00 (d, *J* = 6.5 Hz, 3H), 1.58 (n, *J* = 6.8 Hz, 1H), 2.44 (dd, *J* = 12.1 Hz, *J* = 8.6 Hz, 1H), 2.57 (dd, *J* = 12.2 Hz, *J* = 5.6 Hz, 1H), 2.63 (s, 3H), 3.27 (d, *J* = 16.2 Hz, 1H), 3.33 (d, *J* = 16.4 Hz, 1H), 3.35 (d, *J* = 16.4 Hz, 1H), 3.42 (d, *J* = 16.5 Hz, 1H), 3.42 (d, *J* = 16.4 Hz, 1H), 3.44 (d, *J* = 16.2 Hz, 1H), 3.46 (d, *J* = 16.4 Hz, 1H), 3.49 (d, *J* = 16.5 Hz, 1H), 3.86 (d, *J* = 12.8 Hz, 1H), 3.86 (d, *J* = 13 Hz, 1H), 3.87 (d, *J* = 13 Hz, 1H), 3.92 (d, *J* = 12.8 Hz, 1H), 6.47 (sl, 1H), 6.82 (dd, *J* = 8.0 Hz, *J* = 1.7 Hz, 1H), 6.89 (d, *J* = 7.5 Hz, 1H), 6.96 (s, 1H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.31-7.36 (m, 3H), 7.41 (d, *J* = 7.0 Hz, 2H), 8.70 (s, 1H), 8.75 (s, 1H), 8.91 (s, 1H), 8.98 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.9, 21.2, 26.6, 47.0, 58.3, 58.5, 60.4, 61.6, 63.1, 63.3, 67.6, 115.9, 116.9, 121.2, 128.5, 128.8, 129.6, 130.0, 135.5, 136.6, 157.3, 167.9, 168.5, 168.5.ESI$^+$ HRMS 593.2594, calcd for $C_{27}H_{38}N_8O_5K$ 593.26022.



5

Characterization data for 5. mp 184−185°C.

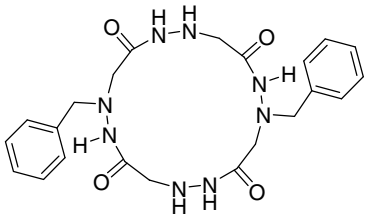
^{1}H NMR (500 MHz, 298 K, $CDCl_3$, 10 mM) δ 0.91 (d, *J* = 6.7 Hz, 6H), 1.01 (d, *J* = 6.5 Hz, 6H), 1.59 (n, *J* = 6.6 Hz, 2H), 2.42 (dd, *J* = 8.7 Hz, 12 Hz, 2H), 2.57 (dd, *J* = 5.5 Hz, 12.1 Hz, 2H), 3.30 (d, *J* = 16.9 Hz, 2H), 3.35 (d, *J* = 16.9 Hz, 2H), 3.41 (d, *J* = 16.9 Hz, 2H), 3.44 (d, *J* = 16.9 Hz, 2H), 3.91 (s, 4H), 7.31-7.39 (m, 10H), 8.67 (s, 2H), 8.95 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.5, 20.8, 26.3, 58.1, 60.2, 62.9, 67.3, 128.1, 128.5, 129.4, 135.0, 168.0, 168.1. ESI$^+$ HRMS 603.3388, calcd for $C_{30}H_{44}N_8O_4Na$ 603.33832.



6

Characterization data for 6. mp 220–222°C.

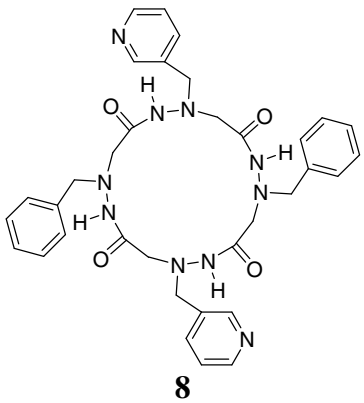
^{1}H NMR (500 MHz, 298 K, $CDCl_3$, 10 mM) δ 0.92 (d, *J* = 6.7 Hz, 6H), 1.04 (d, *J* = 6.4 Hz, 6H), 1.65 (n, *J* = 6.7 Hz, 2H), 2.43 (dd, *J* = 11.9 Hz, *J* = 9.5 Hz, 2H) 2.62 (dd, *J* = 12 Hz, *J* = 4.9 Hz, 2H), 3.46 (d, *J* = 16.5 Hz, 2H), 3.51 (d, *J* = 16.5 Hz, 2H), 3.60 (dd, *J* = 16.3 Hz, *J* = 2.7 Hz, 2H), 3.70 (d, *J* = 16.8 Hz, 2H), 3.87 (broad, 2H), 8.71 (s, 2H), 9.10 (broad, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.5, 20.8, 26.2, 53.9, 60.4, 67.3, 168.3, 169.5. ESI$^+$ HRMS 423.2441, calcd for $C_{16}H_{32}N_8O_4Na$ 423.24442.



7

Characterization data for 7. mp 133–135°C.

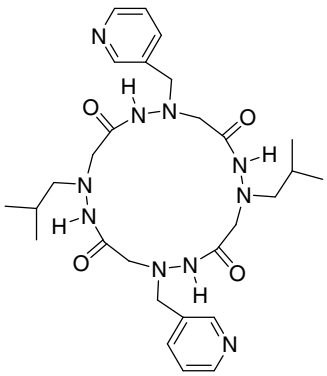
^{1}H NMR (500 MHz, 298 K, $CDCl_3$, 10 mM) δ 3.41 (d, *J* = 16.2 Hz, 2H), 3.46 (d, *J* = 16.2 Hz, 2H), 3.51 (d, *J* = 17.1 Hz, 2H), 3.66 (d, *J* = 17.1 Hz, 2H), 3.79 (s, 2H), 3.86 (d, *J* = 12.4 Hz, 2H), 3.94 (d, *J* = 12.4 Hz, 2H), 7.29-7.41 (m, 10H), 8.99 (s, 2H), 9.03 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.2, 58.4, 63.3, 128.5, 128.7, 128.9, 135.5, 168.4, 169.6. ESI$^+$ HRMS calcd for 491.2131. Found $C_{22}H_{28}N_8O_4Na$ 491.2134.



8

Characterization data for 8. mp 226–228°C.

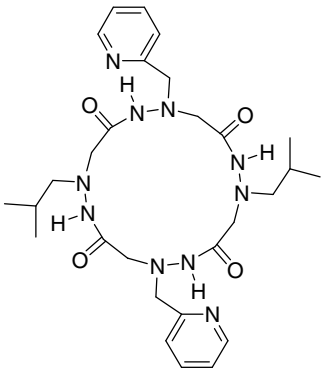
^{1}H NMR (500 MHz, 298 K, $CDCl_3$, 10 mM) δ 3.28 (s, 4H), 3.30 (d, *J* = 16.5 Hz, 2H), 3.39 (d, *J* = 16.2 Hz, 2H), 3.83 (d, *J* = 12.6 Hz, 2H), 3.85 (d, *J* = 12.6 Hz, 2H), 3.85 (d, *J* = 13.0 Hz, 2H), 3.88 (d, *J* = 13.0 Hz, 2H), 7.26 (dd, *J* = 4.9 Hz, *J* = 7.48 Hz, 2H), 7.31-7.35 (m, 10H), 7.72 (d, *J* = 7.7 Hz, 2H), 8.57 (m, 4H), 8.80 (s, 2H), 8.94 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 57.8, 58.2, 60.19, 62.8, 123.26, 128.2, 128.5, 129.3, 130.7, 134.8, 136.9, 149.6, 150.4, 167.31, 167.9. ESI$^+$ HRMS 673.2977, calcd for $C_{34}H_{38}N_{10}O_4Na$ 673.29752.



9

Characterization data for 9. mp 213–215°C.

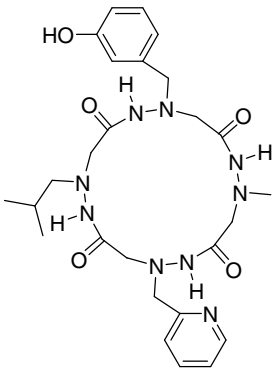
^{1}H NMR (500 MHz, 298 K, $CDCl_3$, 10 mM) δ 0.91 (d, *J* = 6.6 Hz, 6H), 1.01 (d, *J* = 6.6 Hz, 6H), 1.59 (n, *J* = 6.8 Hz, 2H), 2.41 (dd, *J* = 8.7 Hz, *J* = 12.1 Hz, 2H), 2.56 (dd, *J* = 5.5 Hz, *J* = 12.1 Hz, 2H,), 3.22 (d, *J* = 16.7 Hz, 2H), 3.38 (d, *J* = 16.7 Hz, 2H), 3.46 (d, *J* = 16.5 Hz, 2H), 3.48 (d, *J* = 16.7 Hz, 2H), 3.89 (d, *J* = 13.2 Hz, 2H), 3.96 (d, *J* = 13.2 Hz, 2H), 7.30 (dd, *J* = 4.9 Hz, *J* = 7.5 Hz, 2H), 7.83 (d, *J* = 7.9 Hz, 2H), 8.56 (broad, 4H), 8.61 (s, 2H), 8.99 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.43, 20.74, 26.32, 58.72, 59.96, 60.26, 67.22, 123.41, 130.68, 137.09, 149.68, 150.42, 167.07, 168.08. ESI$^+$ HRMS 605.3286, calcd for $C_{28}H_{42}N_{10}O_4Na$ 605.32882.



10

Characterization data for 10. mp 148–150°C.

^{1}H NMR (500 MHz, 298 K, $CDCl_3$, 10 mM) δ 0.92 (d, *J* = 6.7 Hz, 6H), 1.04 (d, *J* = 6.5 Hz, 6H), 1.61 (n, *J* = 5.6 Hz, 2H), 2.49 (dd, *J* = 12 Hz, *J* = 8.9 Hz, 2H), 2.51 (dd, *J* = 12 Hz, *J* = 5.3 Hz, 2H), 3.33 (d, *J* = 16.5 Hz, 2H), 3.45 (d, *J* = 16.5 Hz, 2H), 3.47 (d, *J* = 16.5 Hz, 2H), 3.52 (d, *J* = 16.5 Hz, 2H), 4.05 (d, *J* = 14 Hz, 2H), 4.16 (d, *J* = 14 Hz, 2H), 7.25 (ddd, *J* = 5.0 Hz, *J* = 4.9 Hz, *J* = 0.8 Hz, 2H), 7.45 (d, *J* = 7.8 Hz, 2H), 7.70 (ddd, *J* = 7.7 Hz, *J* = 7.5 Hz, *J* = 1.8 Hz, 2H), 8.61 (d, *J* = 4.0 Hz, 2H), 8.67 (s, 2H), 9.32 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4, 20.7, 26.3, 58.8, 60.2, 63.7, 67.2, 122.9, 123.5, 136.6, 149.4, 155.4, 167.7, 168.0. ESI$^+$ HRMS 605.3299, calcd for $C_{28}H_{42}N_{10}O_4Na$ 605.32882.

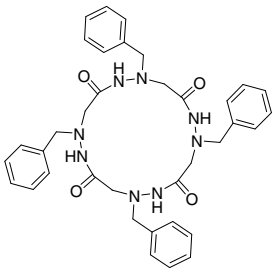


11

Characterization data for 11. mp 182–184°C.

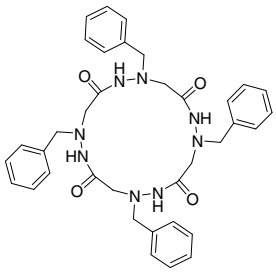
^{1}H NMR (500 MHz, 298 K, $CDCl_3$, 10 mM) δ 0.90 (d, *J* = 6.7 Hz, 3H), 0.99 (d, *J* = 6.5 Hz, 3H), 1.58 (n, *J* = 6.5 Hz, 1H), 2.42 (dd, *J* = 8.5 Hz, *J* = 12.1 Hz, 1H), 2.57 (dd, *J* = 7 Hz, *J* = 12.1 Hz, 1H), 2.59 (s, 3H), 3.25-3.52 (m, 8H), 3.84 (d, *J* = 13 Hz, 1H), 3.87 (d, *J* = 13 Hz, 1H), 4.06 (d, *J* = 14 Hz, 1H), 4.10 (d, *J* = 14 Hz), 6.83 (dd, *J* = 2 Hz, *J* = 7.8 Hz, 2H), 6.98 (t, *J* = 1.8 Hz, 1H), 7.18 (t, 7.8 Hz, 1H), 7.24 (ddd, *J* = 1.1 Hz, *J* = 4.9 Hz, *J* = 7.5Hz, 1H), 7.48 (d, *J* = 8 Hz, 1H), 7.70 (ddd, 1.8 Hz, *J* = 7.7 Hz, 1H), 8.00 (broad, 1H), 8.59 (ddd, 1H, *J* = 1.1 Hz, *J* = 6.5 Hz, 1H), 8.73 (s, 1H), 8.87 (s, 1H), 8.96 (s, 1H,), 9.01 (s, 1H); ^{13}C NMR 125MHz, $CDCl_3$) δ 20.5, 20.8, 26.3, 46.7, 58.1, 59.0, 60.2, 61.3, 62.8, 63.9, 67.2, 115.6, 116.3, 121.0, 123.0, 123.6, 129.7, 136.3, 136.9, 149.3, 155.5, 156.9, 167.7, 167.9, 168.0, 168.2. ESI$^+$ HRMS 594.2562, calcd for $C_{26}H_{37}N_9O_5K$ 594.25547.

^{1}H NMR (500 MHz) spectrum of compound 1 (10 mM in $CDCl_3$ at 298K).



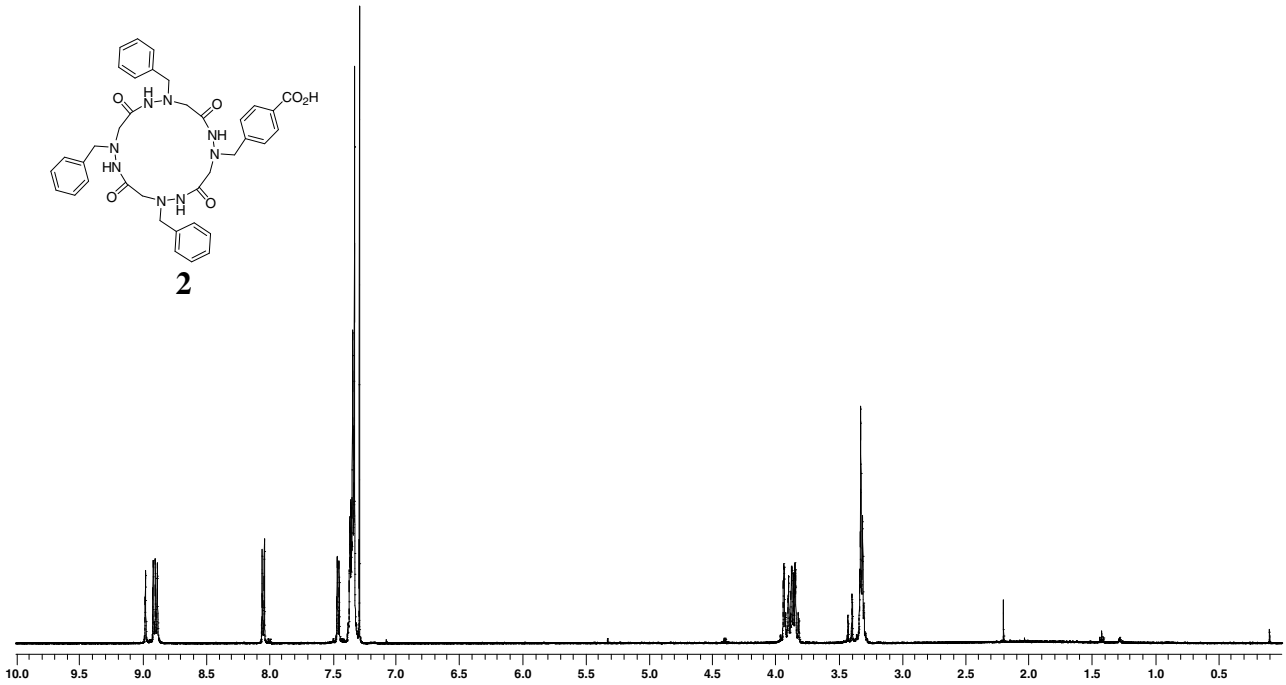
1

^{13}C NMR (50 MHz) spectrum of compound 1 ($CDCl_3$ at room temperature).



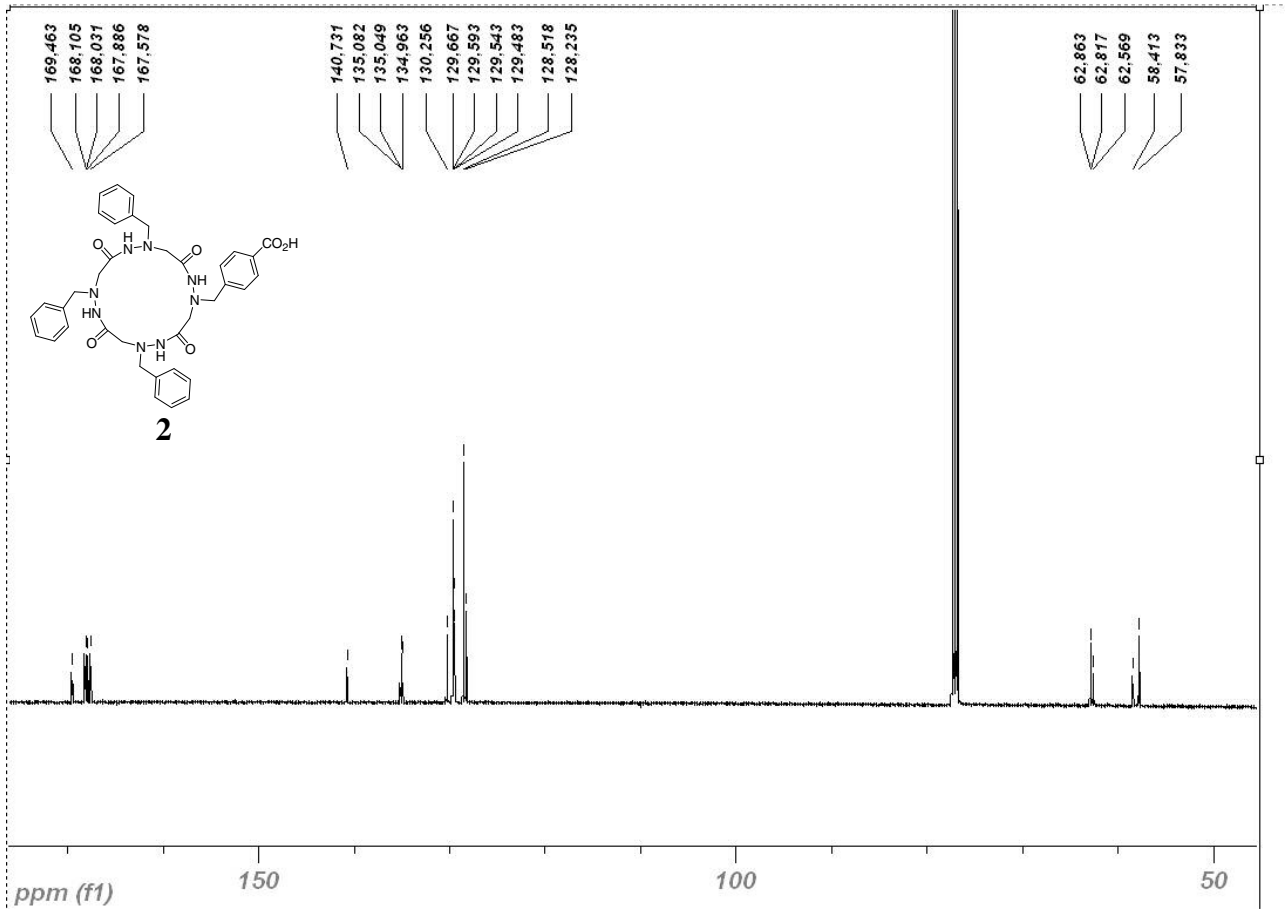
1

^{1}H NMR (500 MHz) spectrum of compound 2 (10 mM in $CDCl_3$ at 298K).



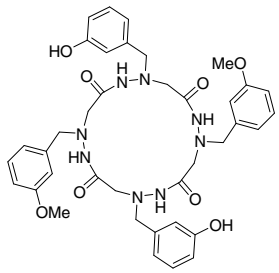
2

^{13}C NMR (125 MHz) spectrum of compound 2 ($CDCl_3$ at room temperature).



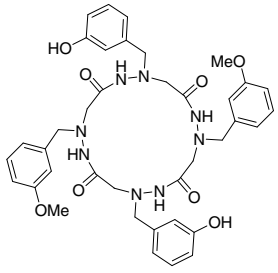
2

^{1}H NMR (500 MHz) spectrum of compound 3 (10 mM in DMSO-d_6 at 298K).



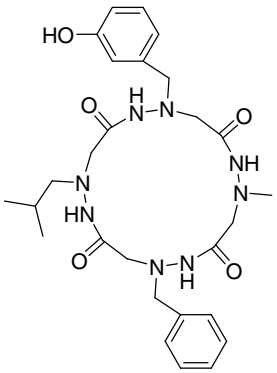
3

^{13}C NMR (125 MHz) spectrum of compound 3 (DMSO-d_6 at 298K).



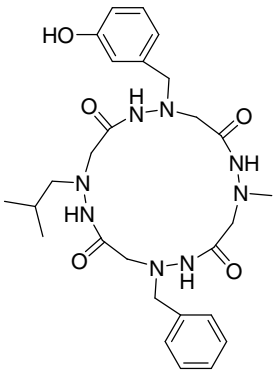
3

^{1}H NMR (500 MHz) spectrum of compound 4 (10 mM in $CDCl_3$ at 298K).



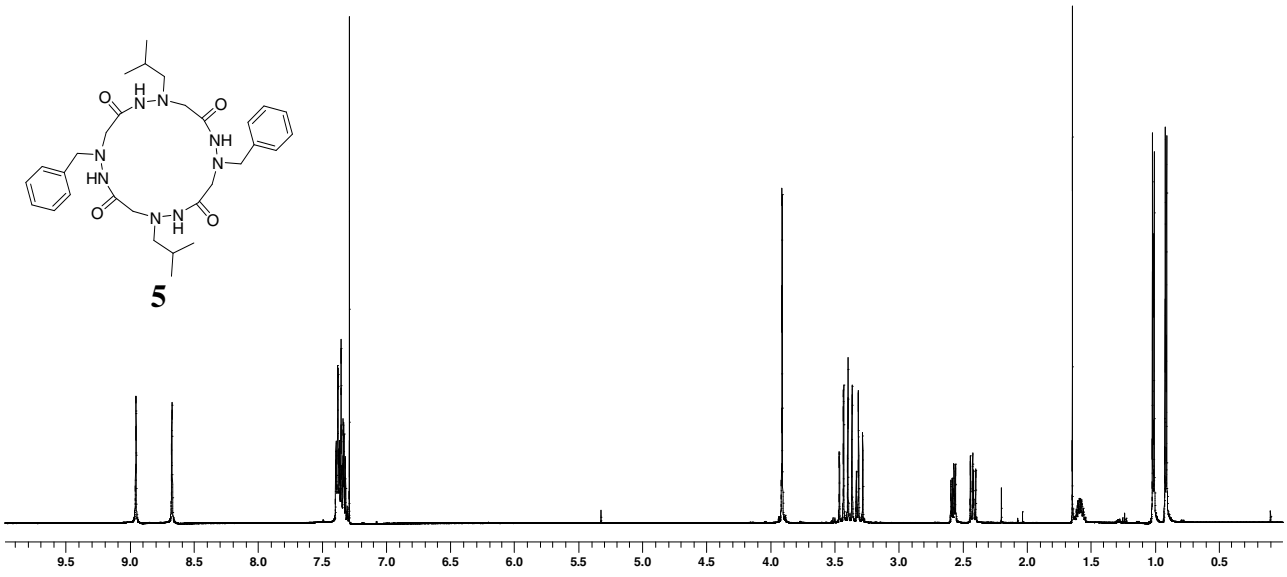
4

^{13}C NMR (50 MHz) spectrum of compound 4 ($CDCl_3$ at room temperature).

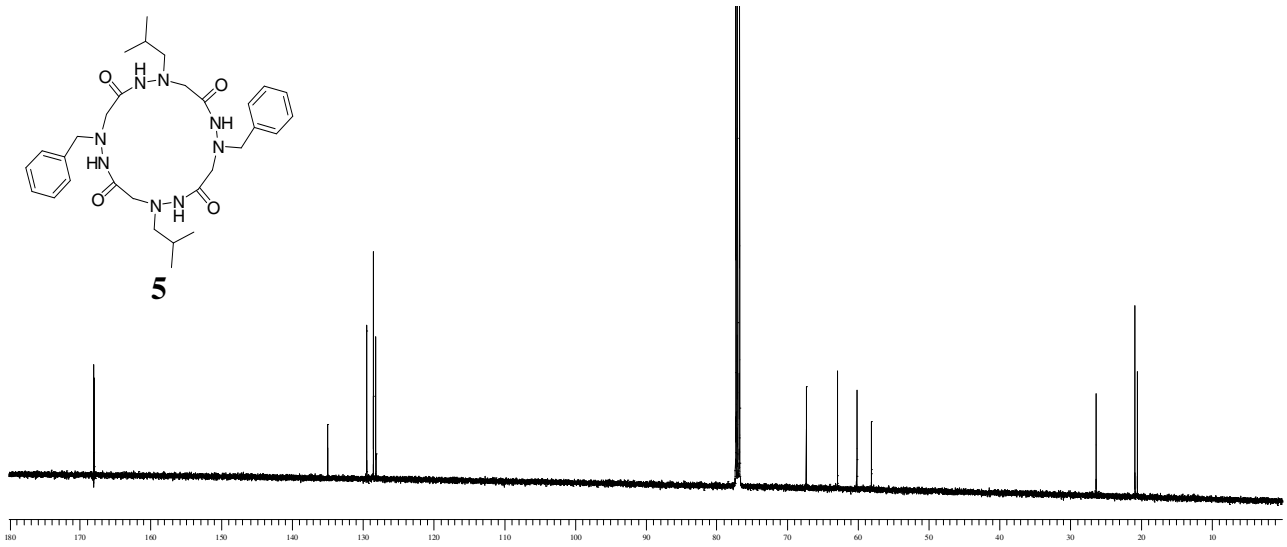


4

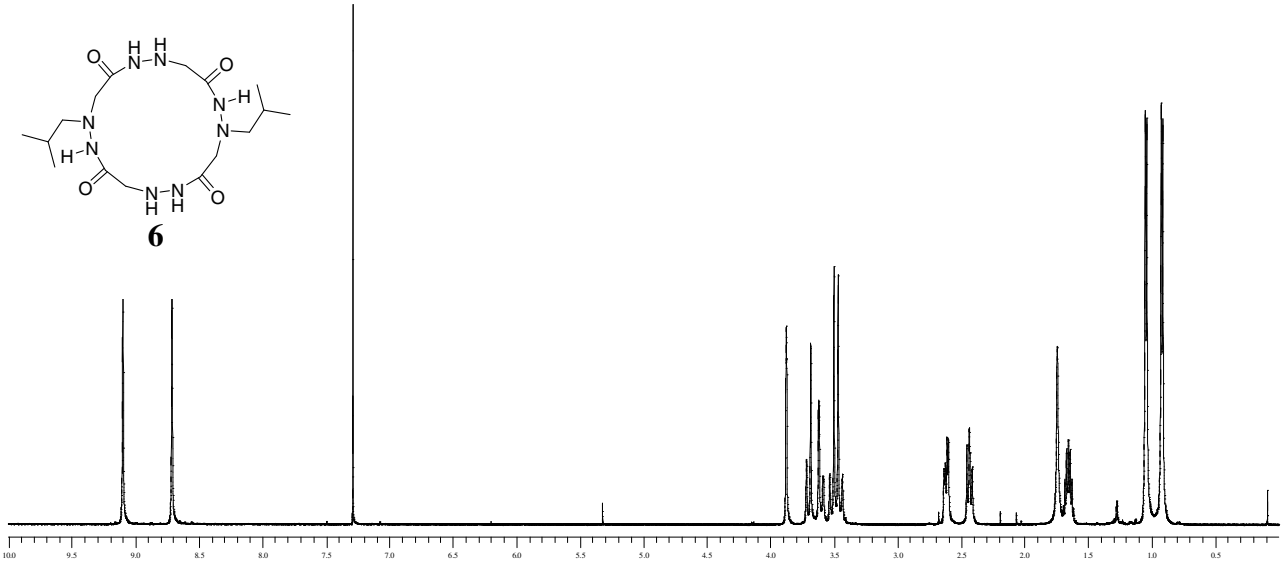
^{1}H NMR (500 MHz) spectrum of compound 5 (10 mM in $CDCl_3$ at 298K).



^{13}C NMR (125 MHz) spectrum of compound 5 ($CDCl_3$ at 298K).

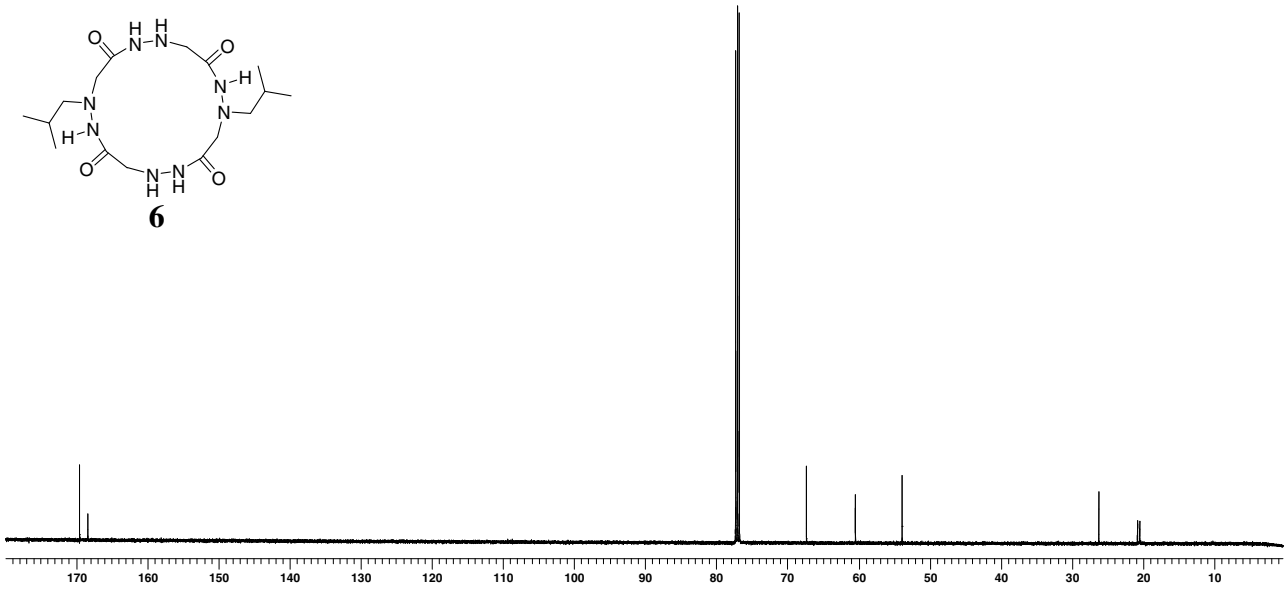


^{1}H NMR (500 MHz) spectrum of compound 6 (10 mM in $CDCl_3$ at 298K).



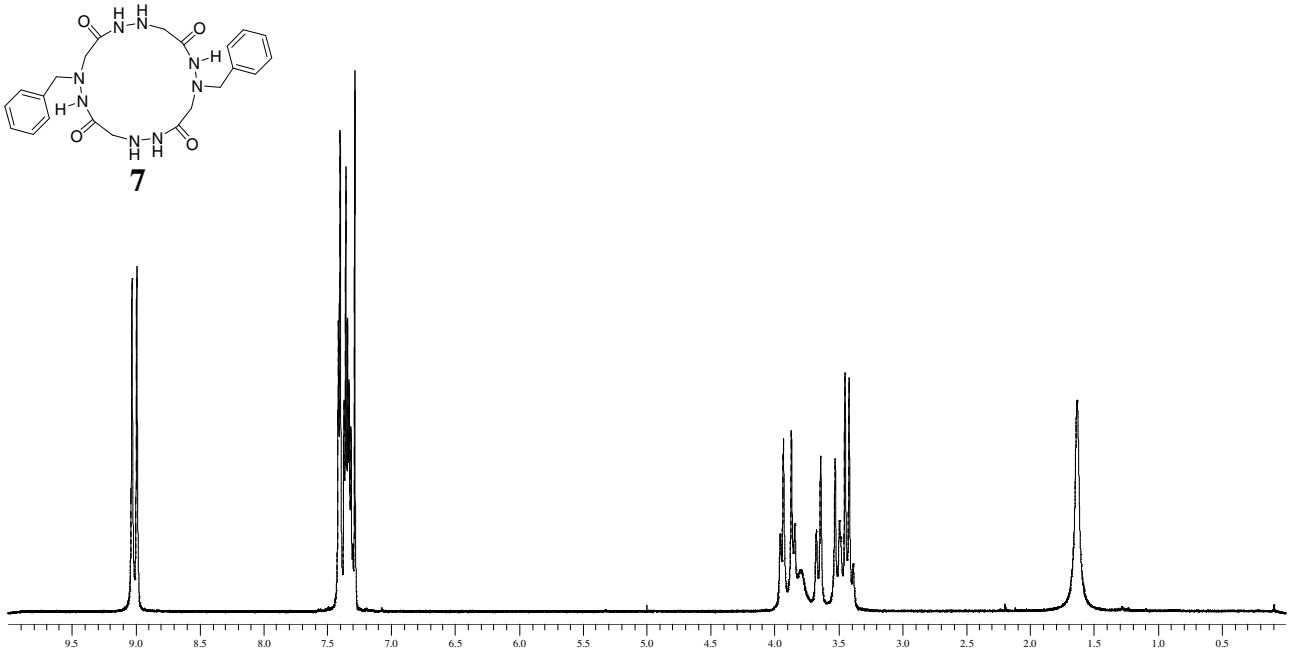
6

^{13}C NMR (125 MHz) spectrum of compound 6($CDCl_3$ at room temperature).

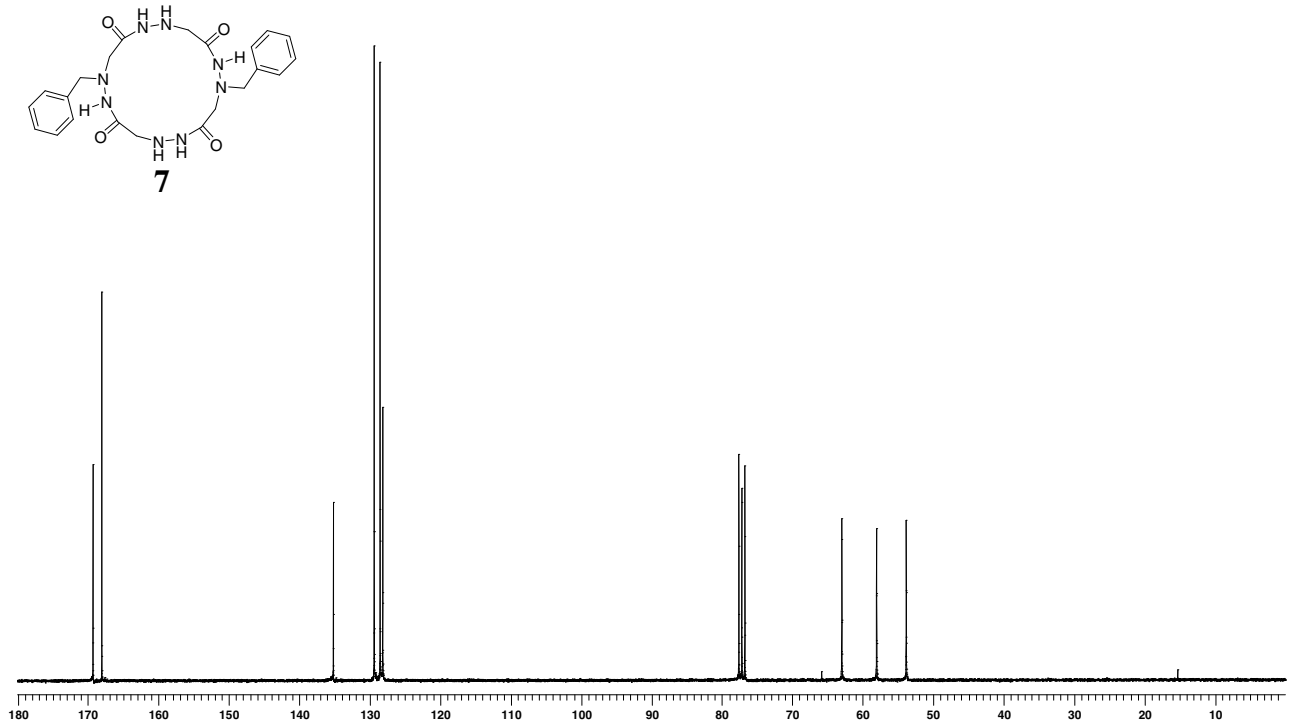


6

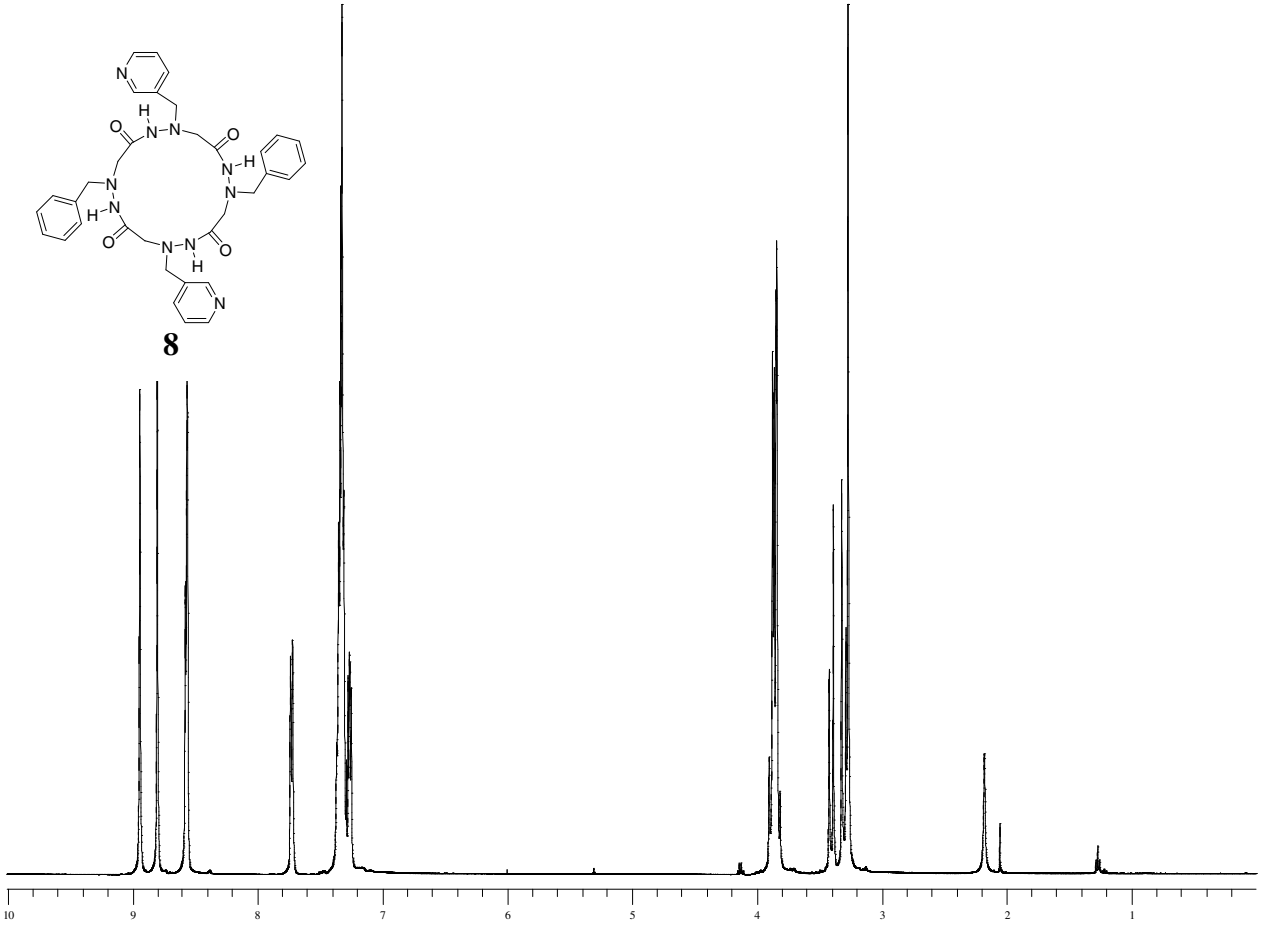
^{1}H NMR (500 MHz) spectrum of compound 7 (10 mM in $CDCl_3$ at 298K).



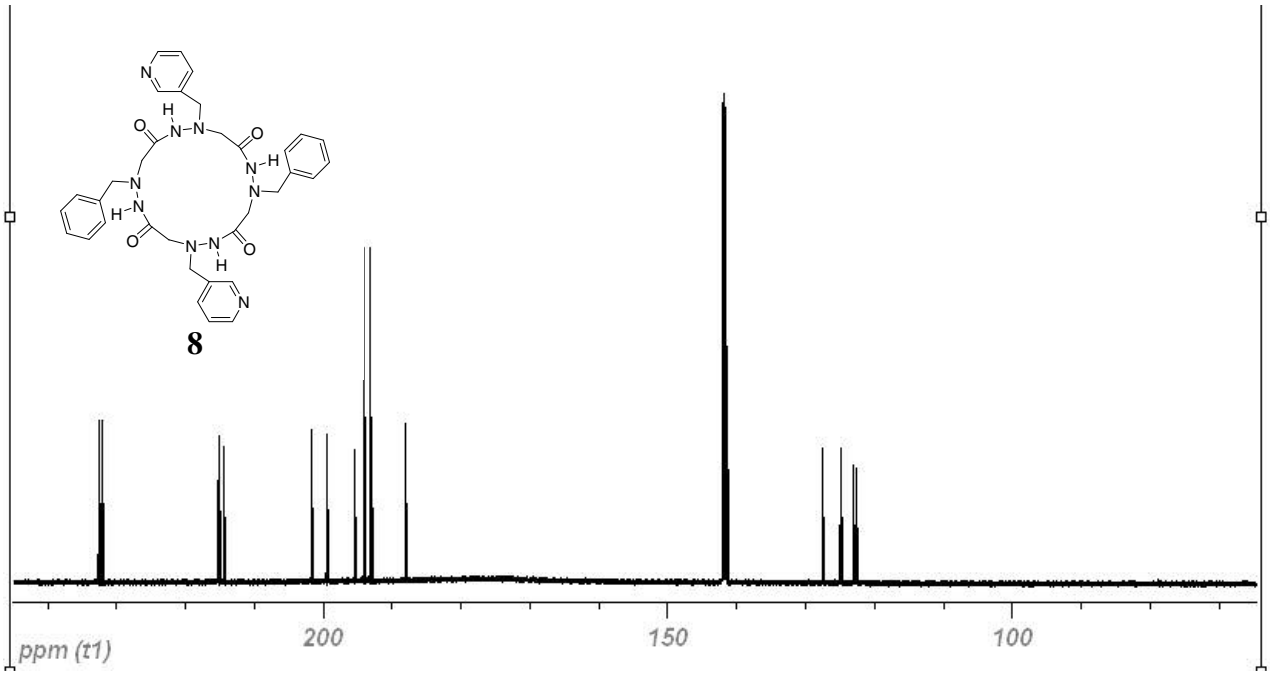
^{13}C NMR (75 MHz) spectrum of compound 7 ($CDCl_3$ at room temperature).



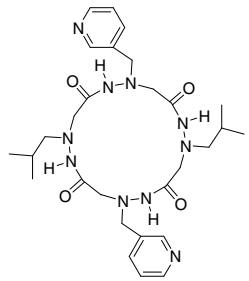
^{1}H NMR (500 MHz) spectrum of compound 8 (10 mM in $CDCl_3$ at 298K).



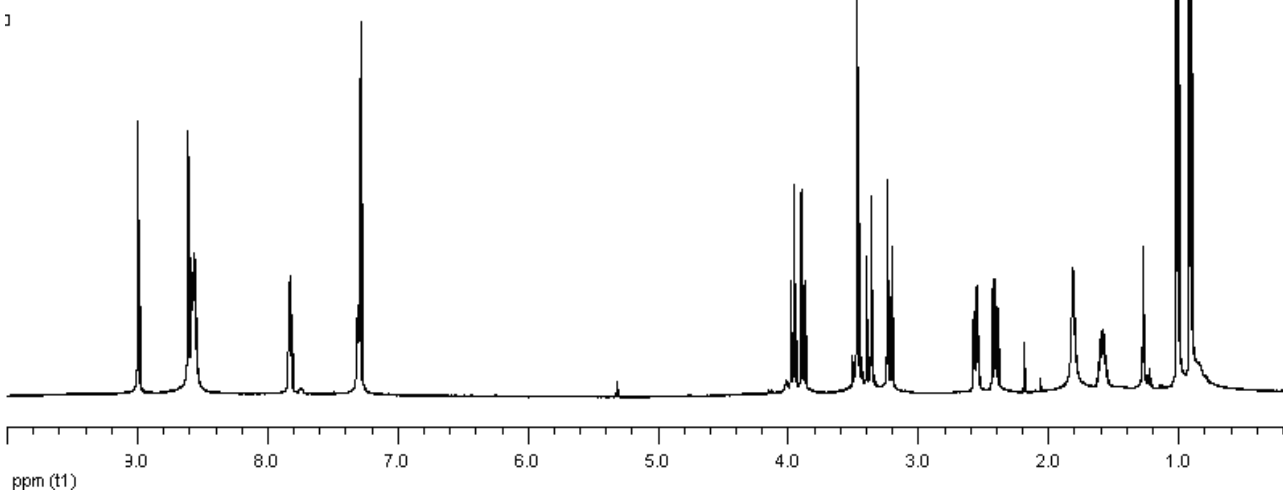
^{13}C NMR (125 MHz) spectrum of compound 8 ($CDCl_3$ at room temperature).



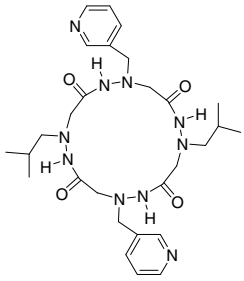
^{1}H NMR (500 MHz) spectrum of compound 9 (10 mM in $CDCl_3$ at 298K).



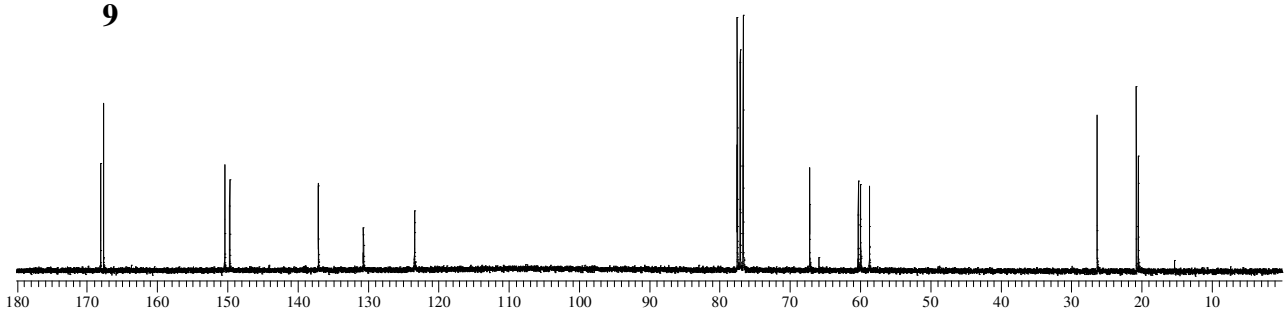
9



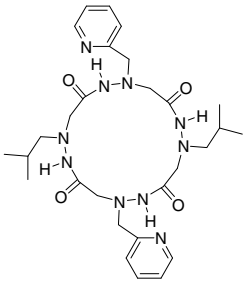
^{13}C NMR (75 MHz) spectrum of compound 9 ($CDCl_3$ at room temperature).



9

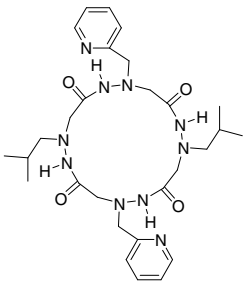


^{1}H NMR (500 MHz) spectrum of compound 10 (10 mM in $CDCl_3$ at 298K).



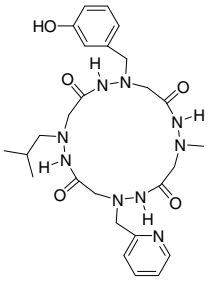
10

^{13}C NMR (75 MHz) spectrum of compound 10 ($CDCl_3$ at room temperature).



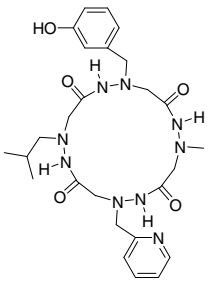
10

^{1}H NMR (500 MHz) spectrum of compound 11 (10 mM in $CDCl_3$ at 298K).



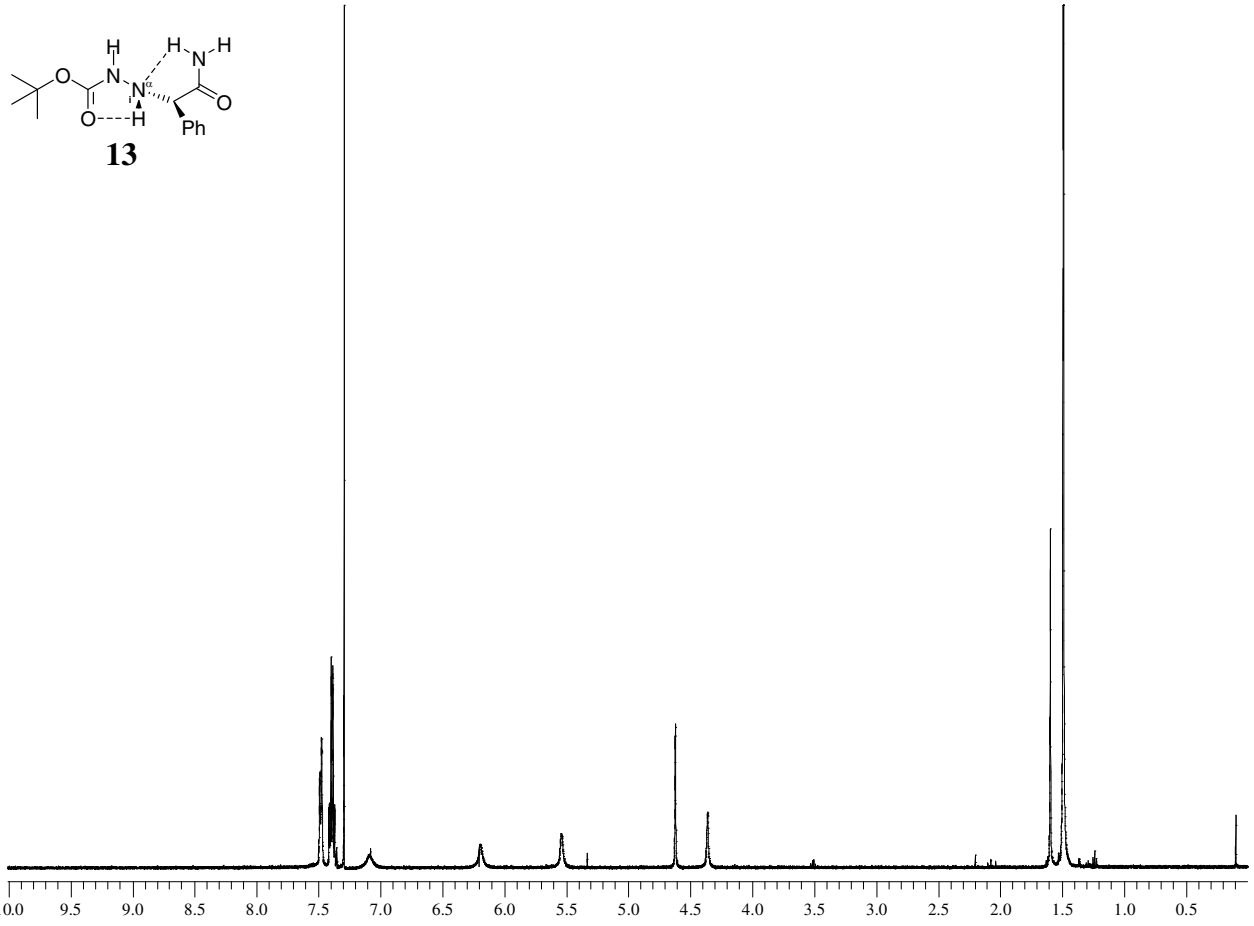
11

^{13}C NMR (125 MHz) spectrum of compound 11 ($CDCl_3$ at room temperature).

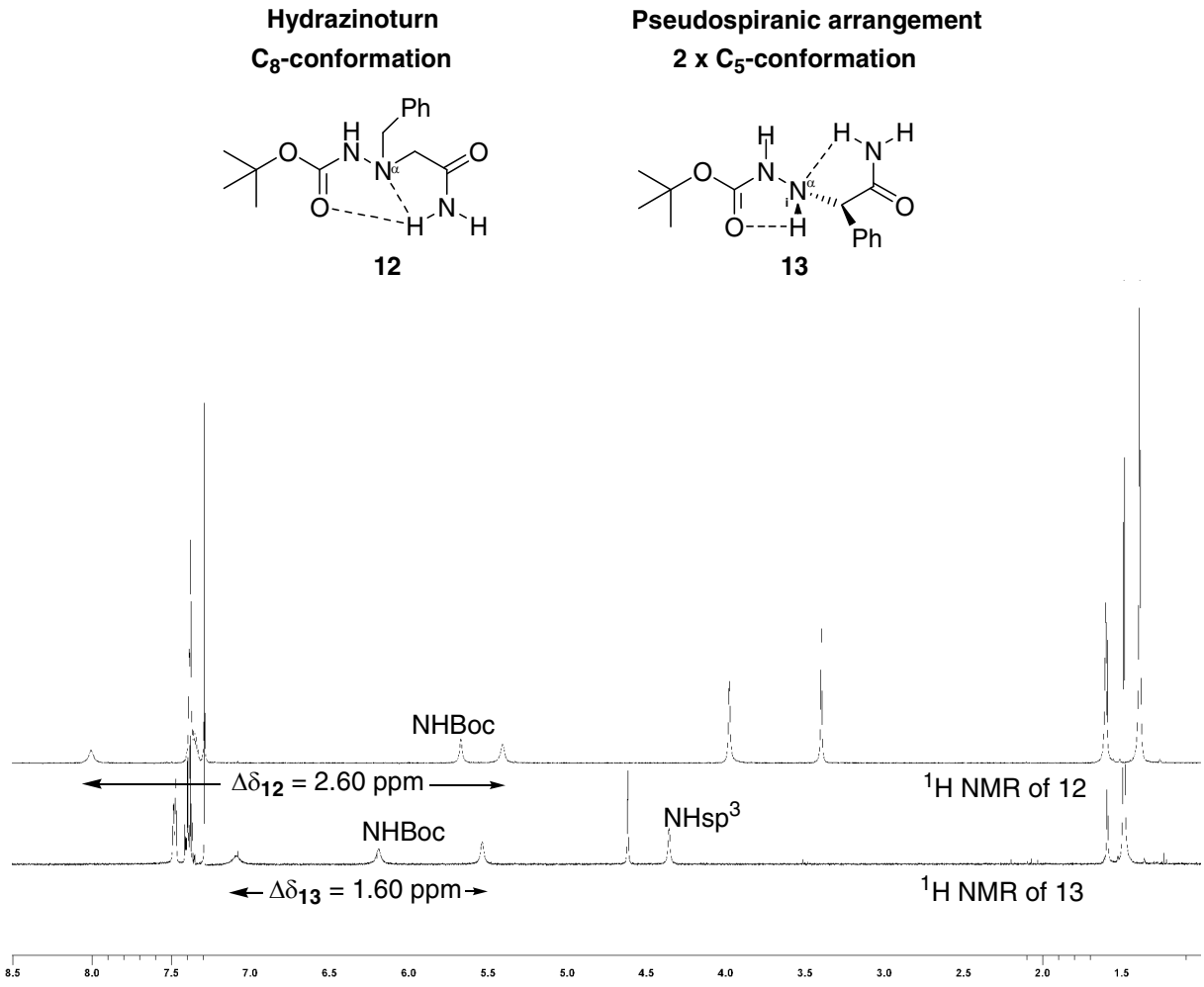


11

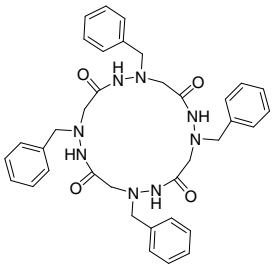
^{1}H NMR (500 MHz) spectrum of compound 13 (10 mM in $CDCl_3$ at 298K).



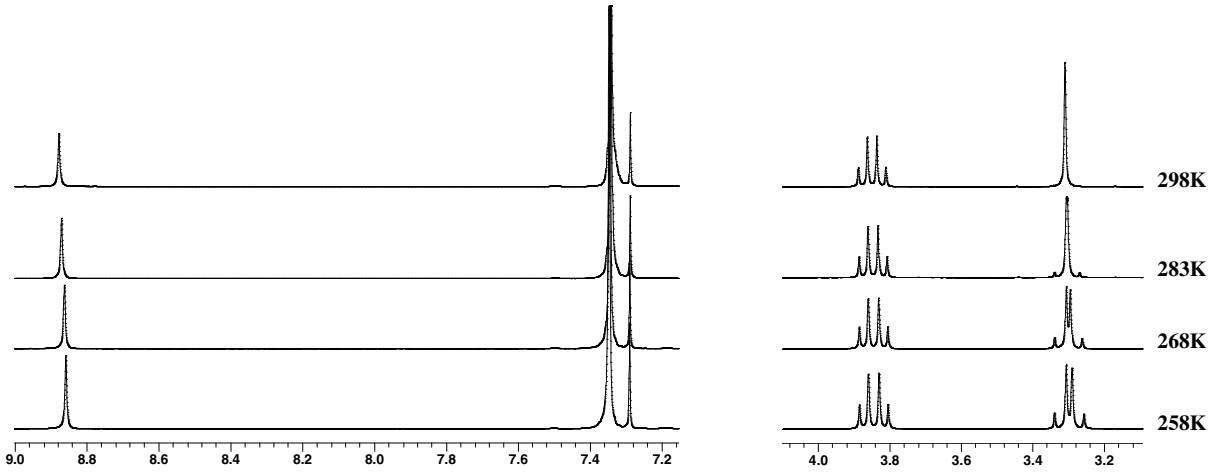
^{1}H NMR (500 MHz) spectrum of compounds 12 (top) and 13 (bottom) (10 mM in $CDCl_3$).

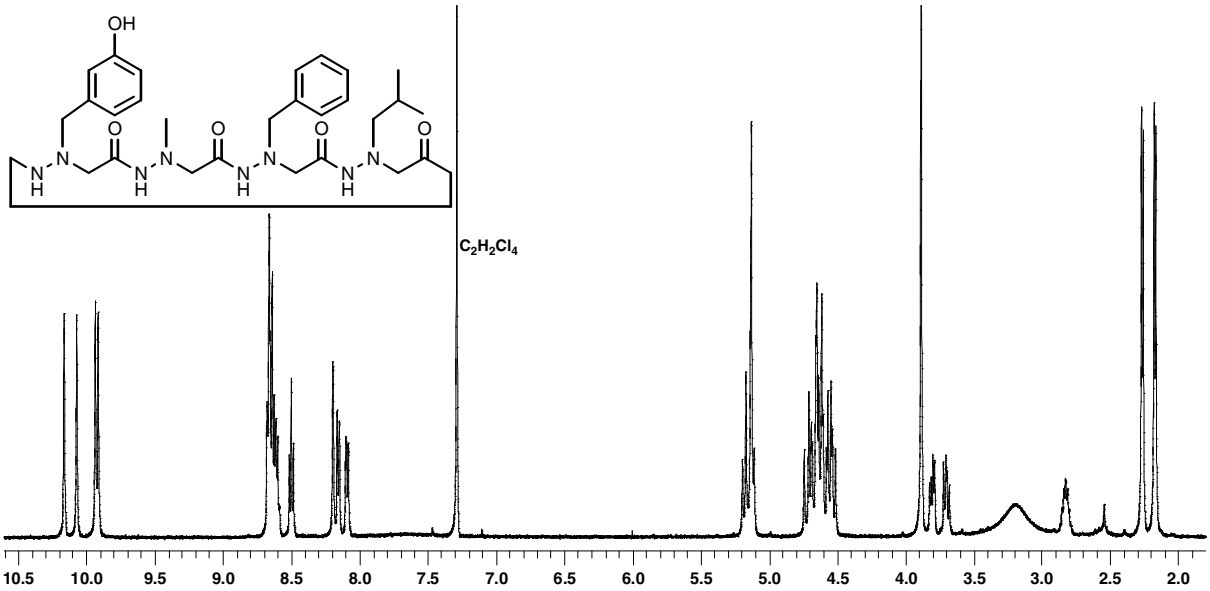


^{1}H NMR (300 MHz) spectra of compound 1 (aza-β^3-Phe)$_4$ between 298K and 258K (10 mM in $CDCl_3$).

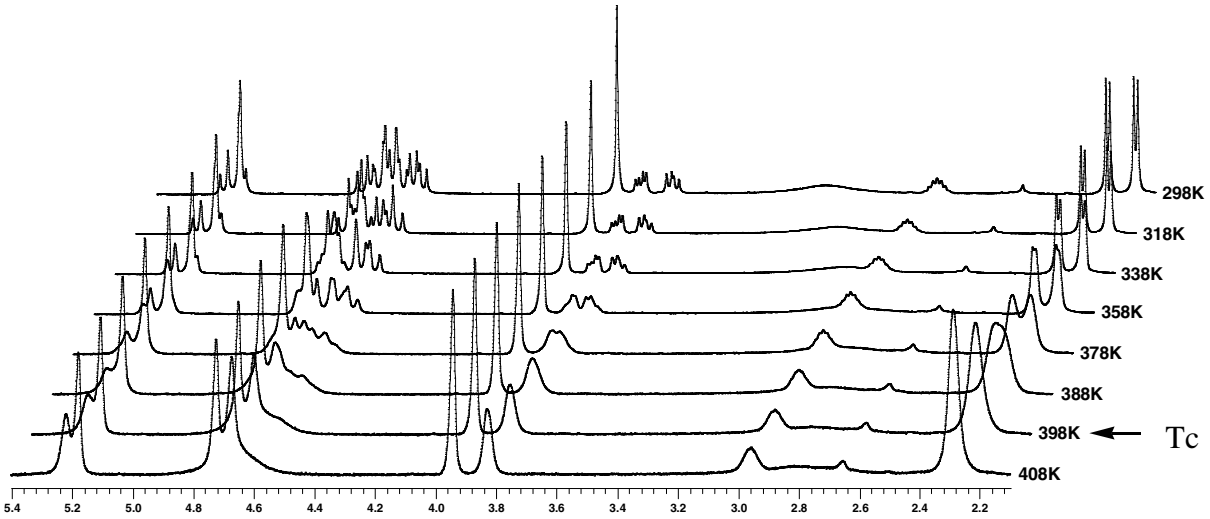


1

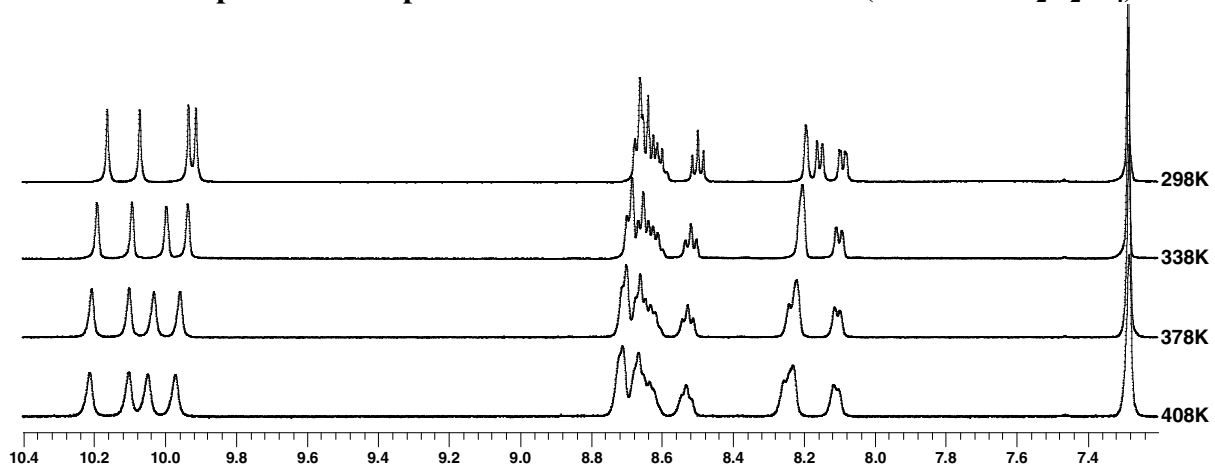




^{1}H NMR (500 MHz) spectrum of compound 4 (10 mM in $C_2D_2Cl_4$ at 298K).

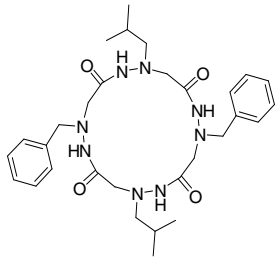


^{1}H NMR spectra of compound 4 between 298K and 408K (10 mM in $C_2D_2Cl_4$).



^{1}H NMR spectra of compound 4 between 298K and 408K. Hydrazidic NHs region of overlaid ^{1}H NMR spectra of 4.

Influence of the dilution and the addition of increasing amounts of DMSO-d_6 for aza-β^3-cyclotetramer 5 (aza-β^3-Phe-aza-β^3-Leu)$_2$.



5

a) Chemical shifts of hydrazidic NHs of compound **5** at different concentrations in $CDCl_3$ (from 1 mM to 100 mM).

	δNH (ppm)/$CDCl_3$/298K of compound **5**	
	NH(aza-β^3-Phe)	NH(aza-β^3-Leu)
Concentration : 10^{-3} M	**8.952**	**8.666**
Concentration : 10^{-2} M	**8.950**	**8.664**
Concentration : 10^{-1} M	**8.942**	**8.658**

b) Graphics showing the variation of the chemical shifts of NHs as a function of the concentration of DMSO-d_6 (0-8%) in a 10 mM solution of compound **5** (1 mL in $CDCl_3$ at room temperature).