Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

First synthesis of orthogonally 1,7-diprotected cyclens

Fabio Travagin,[a,b] Luciano Lattuada[a] and Giovanni B. Giovenzana*[b]

[a] *Bracco Imaging S.p.A., Bracco Research Centre, Via Ribes 5, I-10100 Colleretto Giacosa (TO), Italy.*

[b] *Dipartimento di Scienze del Farmaco, Università del Piemonte Orientale "A. Avogadro", Largo Donegani 2/3, I-28100 Novara, Italy.*

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Experimental section

General Information: Solvents and starting materials were purchased from Sigma-Aldrich or TCI Europe and used without further purification. All aqueous solutions were prepared from ultrapure laboratory grade water (18 MΩ ▪ cm) obtained from Millipore/MilliQ purification system. ^1H and ^{13}C NMR spectra were recorded at 300 MHz on a Jeol Eclipse ECP300 spectrometer. Chemical shifts are reported in ppm with the protic impurities of the deuterated solvent as the internal reference. Mass spectra were obtained with a Finnigan LCQ ion trap spectrometer equipped with an electrospray source. High resolution mass spectra were registered on a ThermoScientific Q-Exactive Plus spectrometer. TLC were performed with silica gel (MN Kieselgel 60F254) and visualized by UV or sprayed with Dragendorff reagent or alkaline $KMnO_4$. *N*-Monoformylcyclen **3** was prepared following the procedure reported in literature.[1]

***tert*-Butyl 7-formyl-1,4,7,10-tetraazacyclododecane-1-carboxylate (4)**. A solution of compound **3** (1.11 g, 5.54 mmol, 1 eq), in a mixture of water (4 mL) and THF (10 mL) is acidified to pH 5 with conc. HCl. A solution of di-*tert*-butyl dicarbonate (3.87 g, 1.77 mmol, 3.2 eq) in THF (6 mL) is slowly added with vigorous stirring and the pH is kept at 5 continuously adding $NaHCO_3$ during 9h. After complete conversion of the substrate (monitored by TLC), the solution is extracted 3 times with petroleum ether. The aqueous layer is basified with Na_2CO_3 and extracted 3 times with CH_2Cl_2. The solvent is dried over Na_2SO_4 and Na_2CO_3, filtered and removed *in vacuo* to give compound **4** as a yellow oil (1.12 g, 67 %). ^1H NMR (300 MHz, $CDCl_3$, 333 K) δ 7.99 (s, 1H), 3.30 – 3.14 (m, 8H), 2.85 – 2.66 (m, 8H), 1.30 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 333 K) δ 164.0 (CH), 156.0 (C), 79.6 (C), 50.0 (CH_2), 49.7 (CH_2), 47.5 (CH_2), 45.2 (CH_2), 28.4 (CH_3) ppm. MS (ESI^+): *m*/*z* = 301.11 (100%, $[M+H]^+$), 201.28 (80%, $[M+H]^+$). Anal. Calc. for $C_{14}H_{28}N_4O_3$: 300.40. HRMS (ESI^+): *m*/*z* = 301.22327 (100%, $[M+H]^+$). Anal. Calc. for $C_{14}H_{28}N_4O_3$: 300.21614.

***tert*-Butyl 1,4,7,10-tetraazacyclododecanecarboxylate (5)**. Compound **4** (1.67 g, 3.88 mmol) is dissolved in isopropyl alcohol (10 mL), then a solution of sodium hydroxide 1 M in water (10 mL) is added. The reaction is heated at 80°C and the conversion of the substrate is monitored by TLC ($CH_2Cl_2/MeOH/NH_3$ 6:3.1). After 40h, isopropyl alcohol is removed by vacuum evaporation, and the aqueous layer is extracted 3 times with CH_2Cl_2. The solvent is dried over Na_2SO_4 and Na_2CO_3, filtered and removed under vacuum to give compound **5** as a yellow oil (1.01 g, 96 %). ^1H NMR (300 MHz, $CDCl_3$, 333 K) δ 3.17 – 3.13 (m, 4H), 2.58 – 2.51 (m, 8H), 2.43 – 2.40 (m, 5H), 1.20 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 333 K) δ 156.2 (C), 79.1 (C), 49.0 (CH_2), 48.7 (CH_2), 48.1 (CH_2), 46.5 (CH_2), 28.1 (CH_3) ppm. MS (ESI^+): *m*/*z* (100%) = 273.23 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{28}N_4O_2$: 272.39.

1-Allyl 7-*tert*-butyl 1,4,7,10-tetraazacyclododecane-1,7-dicarboxylate (6). A solution of compound **5** (0.869 g, 3.19 mmol, 1 eq) in a mixture of water (10 mL) and THF (8 mL) is acidified to pH 5.0 with conc. HCl. A solution of allyl chloroformate (0.37 mL, 3.48 mmol, 1.1 eq) in THF (2 mL) is slowly added with vigorous stirring and the pH is maintained at 5.0 continuously adding $NaHCO_3$ during 5h. After complete conversion of the substrate (monitored by TLC), the solution is extracted 3 times with petroleum ether. The aqueous layer is basified with Na_2CO_3 and extracted 3 times with CH_2Cl_2. The solvent is dried over Na_2SO_4 and Na_2CO_3, filtered and removed under vacuum to give compound **6** as a yellow oil (0.860 g, 76 %). ^1H NMR (300 MHz, $CDCl_3$, 333 K) δ 6.36 (br s, 2H), 5.89 – 5.76 (m, 1H), 5.21 – 5.11 (m, 2H), 4.52 (d, *J* = 5.1 Hz, 2H), 3.59 – 3.50 (m, 8H), 2.92 (br s, 8H), 1.37 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 333 K) δ 156.0 (C), 155.4 (C), 132.4 (CH), 117.9 (CH_2), 80.7 (C), 66.3 (CH_2), 49.6 (4 CH_2), 28.3 (CH_3) ppm. MS (ESI^+): *m*/*z* = 357.12 (79%, $[M+H]^+$), 257.27 (100%, $[M+H]^+$). Anal. Calc. for $C_{17}H_{32}N_4O_4$: 356.47. HRMS (ESI^+): *m*/*z* = 357.24918 (100%, $[M+H]^+$). Anal. Calc. for $C_{17}H_{32}N_4O_4$: 356.24236.

1-Allyl 7-formyl-1,4,7,10-tetraazacyclododecane-1-carboxylate (7). A solution of compound **3** (1.02 g, 5.09 mmol, 1 eq) in a mixture of water (2 mL) and THF (4 mL) is acidified to pH 3 with conc. HCl. A solution of allyl chloroformate (1.35 mL, 12.7 mmol, 2.5 eq) in THF (4 mL) is added with vigorous stirring over 30 min. The pH is kept at 3 continuously adding $NaHCO_3$ in little portion for 10h. After complete conversion of the substrate (monitored by TLC, $CH_2Cl_2/MeOH/NH_3$ 6:3.1), the solution is extracted 3 times with petroleum ether, the aqueous layer is basified with Na_2CO_3 and extracted 3 times with CH_2Cl_2. The solvent is dried over Na_2SO_4 and Na_2CO_3, filtered and removed *in vacuo* to give compound **7** as a yellow oil (1.07 g, 74 %). ^1H NMR (300 MHz, $CDCl_3$, 333 K) δ 7.70 (s, 1H), 5.57 – 5.45 (m, 1H), 4.85 (d, *J* = 17.2 Hz, 1H), 4.76 (d, *J* = 10.4 Hz, 1H), 4.14 (s, 2H), 3.07 – 2.91 (m, 8H), 2.43 – 2.37 (m, 10H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 333 K) δ 163.2 (CH), 155.6 (C), 132.4 (CH), 116.3 (CH_2), 64.9 (CH_2), 49.3 (CH_2), 47.8 (CH_2), 46.8 (CH_2), 44.6 (CH_2) ppm. MS (ESI^+): *m*/*z* (100%) = 285.26 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{24}N_4O_3$: 284.36. HRMS (ESI^+): *m*/*z* = 285.19193 (100%, $[M+H]^+$). Anal. Calc. for $C_{13}H_{24}N_4O_3$: 284.18484.

1-Benzyl 7-formyl-1,4,7,10-tetraazacyclododecane-1-carboxylate (8). A solution of compound **3** (1.98 g, 9.89 mmol, 1 eq) in a mixture of water (4mL) and THF (6 mL) is acidified to pH 3 with conc. HCl. A solution of benzyl chloroformate (4.2 mL, 29.7 mmol, 3 eq) in THF (10mL) is added dropwise with vigorous stirring and the pH is maintained at 3 by continuous addition of $NaHCO_3$ during for 2h. When the pH is stable at 3 the solution is stirred at RT for 18h. After complete conversion of the substrate (monitored by TLC, $CH_2Cl_2/MeOH/NH_3$ 6:3.1), the mixture is extracted 3 times with petroleum ether, then the aqueous layer is basified with Na_2CO_3 and extracted 3 times with CH_2Cl_2. The solvent is dried over Na_2SO_4 and Na_2CO_3, filtered and removed under vacuum to give compound **8** as a yellow oil (3.06 g, 93 %). ^1H NMR (300 MHz, $CDCl_3$, 333 K) δ 7.98 (s, 1H), 7.18 (br s, 5H), 4.98 (s, 2H), 3.27 – 3.22 (m, 10H), 2.76 – 2.64 (m, 8H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 333 K) δ 163.8 (CH), 156.4 (C), 136.5 (C), 128.2 (CH), 127.6 (CH), 127.5 (CH), 66.8 (CH_2), 49.8 (CH_2), 48.4 (CH_2), 47.3 (CH_2), 45.1 (CH_2) ppm. MS (ESI$^+$): *m*/z = 335.25 (100%, $[M+H]^+$). Anal. Calc. for $C_{17}H_{26}N_4O_3$: 334.42. HRMS (ESI$^+$): *m*/z = 335.20752 (100%, $[M+H]^+$). Anal. Calc. for $C_{17}H_{26}N_4O_3$: 334.20049.

Benzyl 1,4,7,10-tetraazacyclododecanecarboxylate·3HCl (9·3HCl). Compound **8** (509 mg, 1.52 mmol) was dissolved in HCl 1 M and the solution was stirred at 50 °C for 20 h. The solvent was evaporated under vacuum, the residue was dissolved in boiling ethanol, filtrated, cooled to room temperature, and precipitated with diethyl ether. The product was isolated by vacuum filtration to yield compound **9**·3HCl as a white solid (486 mg, 77%). ^1H NMR (300 MHz, D_2O, 333 K) δ 7.28 (br s, 5H), 5.02 (s, 2H), 3.51 (br t, *J* = 4.8 Hz, 4H), 3.28 – 3.06 (m, 12H) ppm. ^{13}C NMR (75 MHz, D_2O, 333 K) δ 157.9 (C), 135.4 (C), 128.6 (CH), 128.3 (CH), 128.0 (CH), 68.3 (CH_2), 45.7 (CH_2), 44.9 (CH_2), 43.0 (CH_2), 42.6 (CH_2) ppm. MS (ESI$^+$): *m*/z (100%) = 307.22 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{26}N_4O_2$: 306.41.

1-Benzyl 7-*tert*-butyl 1,4,7,10-tetraazacyclododecane-1,7-dicarboxylate (10). A solution of compound **9** (1.44 g, 3.46 mmol, 1 eq) in a mixture of water (5 mL) and THF (3 mL) is acidified to pH 5 with conc. HCl. A solution of di-*tert*-butyl dicarbonate (1.51 g, 6.91 mmol, 2 eq) in THF (2 mL) is added dropwise and the pH is kept at 5 continuously adding $NaHCO_3$ in little portion for 10h. After complete conversion of the substrate (monitored by TLC, $CH_2Cl_2/MeOH/NH_3$ 6:3.1), the solution is extracted 3 times with petroleum ether, the aqueous layer is basified with Na_2CO_3 and extracted 3 times with CH_2Cl_2. The solvent is dried over Na_2SO_4 and Na_2CO_3, filtered and removed *in vacuo* to give compound **10** as a yellow oil (1.08 g, 77 %). ^1H NMR (300 MHz, $CDCl_3$, 333 K) δ 7.05 – 7.03 (m, 5H), 4.84 (s, 2H), 3.12 – 3.04 (m, 8H), 2.77 (br s, 2H), 2.53 (br s, 8H), 1.18 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 333 K) δ 156.0 (C), 155.4 (C), 136.5 (C), 127.8 (CH), 127.2 (CH), 127.1 (CH), 78.7 (C), 66.3 (CH_2), 49.6 (2 CH_2), 48.3 (2 CH_2), 27.9 (CH_3) ppm. MS (ESI$^+$): *m*/z = 429.15 (21%, $[M+Na]^+$), 407.16 (100%, $[M+H]^+$), 307.30 (23%). Anal. Calc. for $C_{21}H_{34}N_4O_4$: 406.53. HRMS (ESI$^+$): *m*/z = 407.26487 (100%, $[M+H]^+$). Anal. Calc. for $C_{21}H_{34}N_4O_4$: 406.25801.

1-Allyl 7-benzyl 1,4,7,10-tetraazacyclododecane-1,7-dicarboxylate (11). A solution of compound **9** (1.47 g, 3.54 mmol, 1 eq), water (5 mL) and THF (3 mL) is acidified to pH 3 with HCl and stirred. Then a solution of allyl chloroformate (0.76 mL, 7.08 mmol, 2 eq) and THF (2 mL) is slowly added and the pH is maintained at 3 continuously adding $NaHCO_3$ for 10h. After complete conversion of the substrate (monitored by TLC, $CH_2Cl_2/MeOH/NH_3$ 6:3.1), the solution is extracted 3 times with Pet, the aqueous layer is basified with solid Na_2CO_3 and extracted 3 times with CH_2Cl_2. The solvent is dried over Na_2SO_4 and Na_2CO_3, filtered and removed under vacuum to give compound **11** as a yellow oil (1.19 g, 86 %). ^1H NMR (300 MHz, $CDCl_3$, 333 K) δ 7.04 (s, 5H), 5.68 – 5.60 (m, 1H), 4.99 (d, *J* = 17.2 Hz, 1H), 4.91 – 4.85 (m, 3H), 4.31 (d, *J* = 2.2 Hz, 2H), 3.23 – 3.13 (m, 10H), 2.56 (br s, 8H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 333 K) δ 155.9 (C), 155.7 (C), 136.3 (C), 132.6 (CH), 127.8 (CH), 127.2 (CH), 127.0 (CH), 116.4 (CH_2), 66.3 (CH_2), 65.1 (CH_2), 49.9 (2 CH_2), 48.5 (CH_2), 47.9 (CH_2) ppm. MS (ESI$^+$): *m*/z (100%) = 391.27 $[M+H]^+$. Anal. Calc. for $C_{20}H_{30}N_4O_4$: 390.48. HRMS (ESI$^+$): *m*/z = 391.23333 (100%, $[M+H]^+$). Anal. Calc. for $C_{20}H_{30}N_4O_4$: 390.48400.

[1] A-C. Ferrand, D. Imbert, A-S. Chauvin, C. D. B. Vandevyver and J-C. G. Bünzli, *Chem. Eur. J.*, 2007, **13**, 8678.

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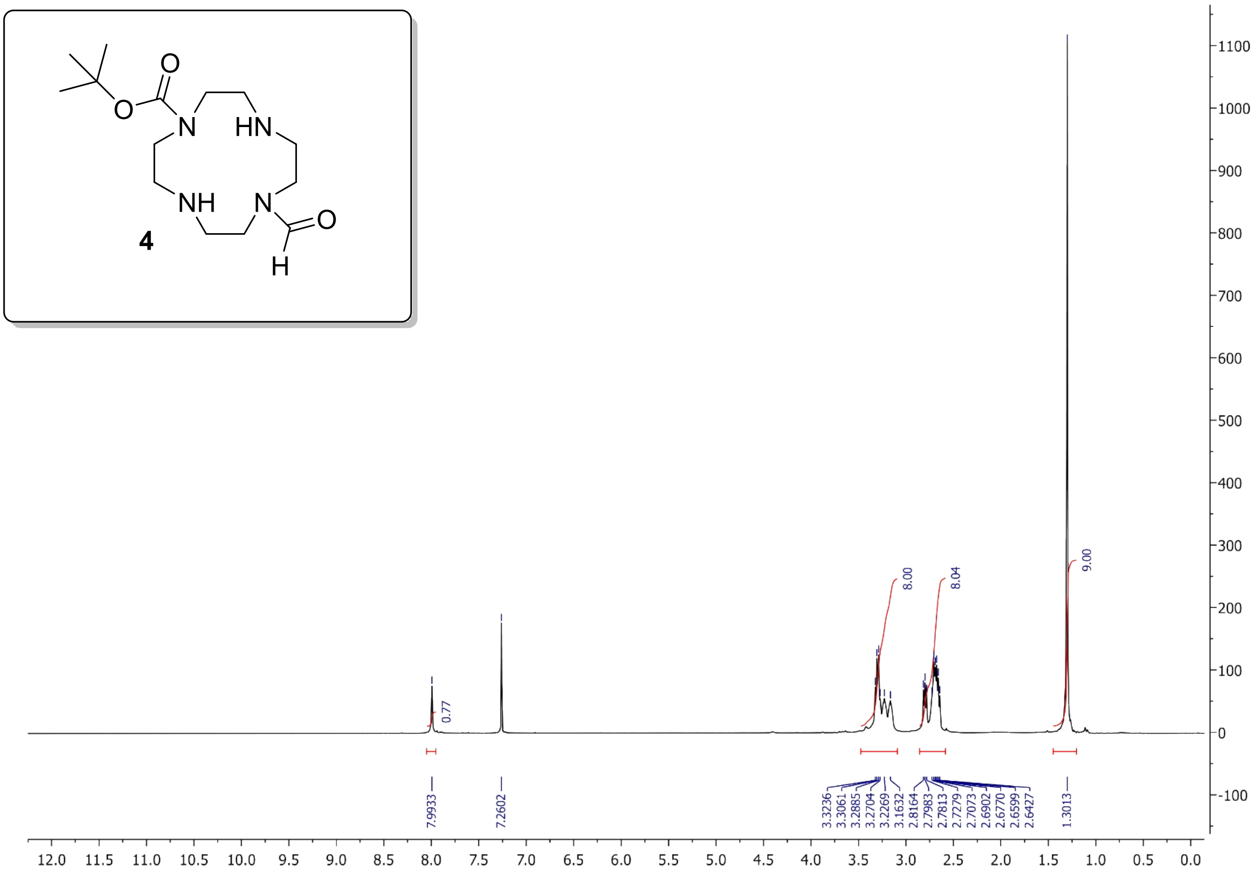


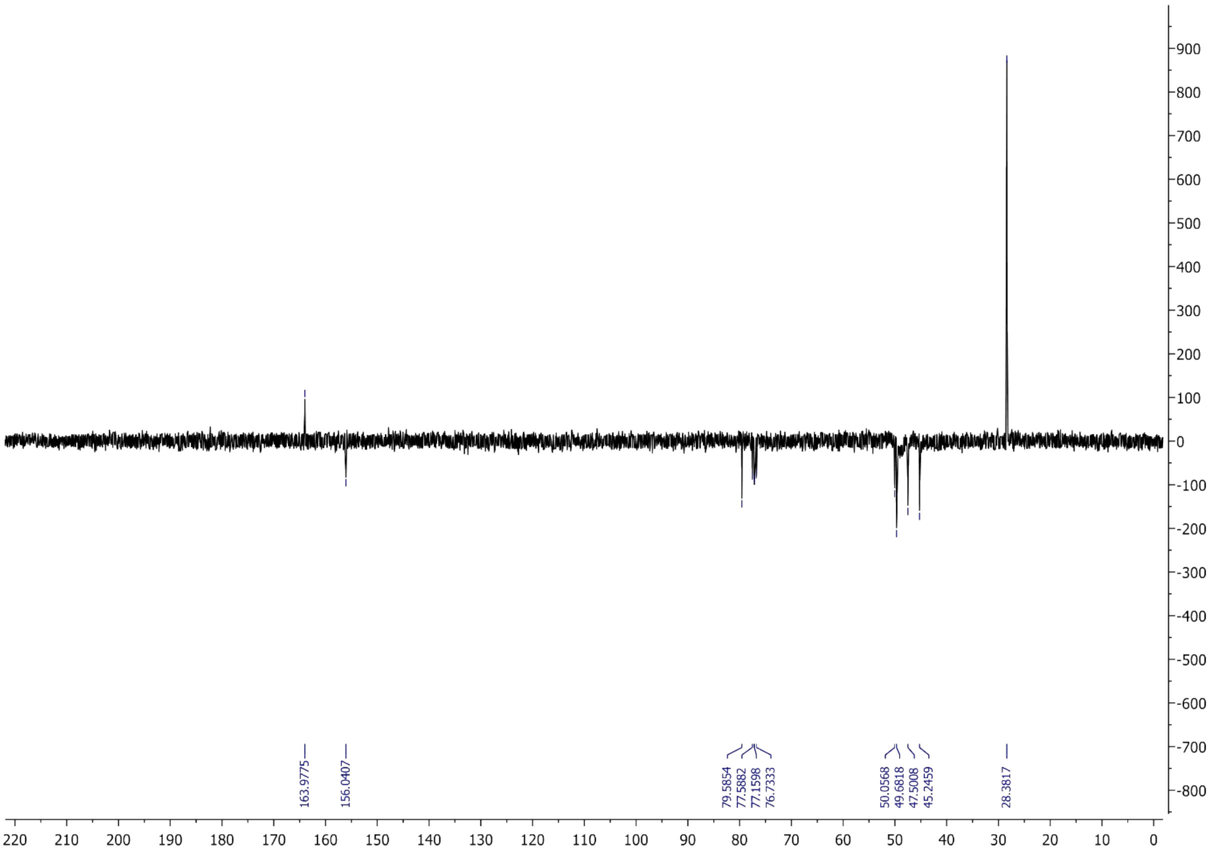
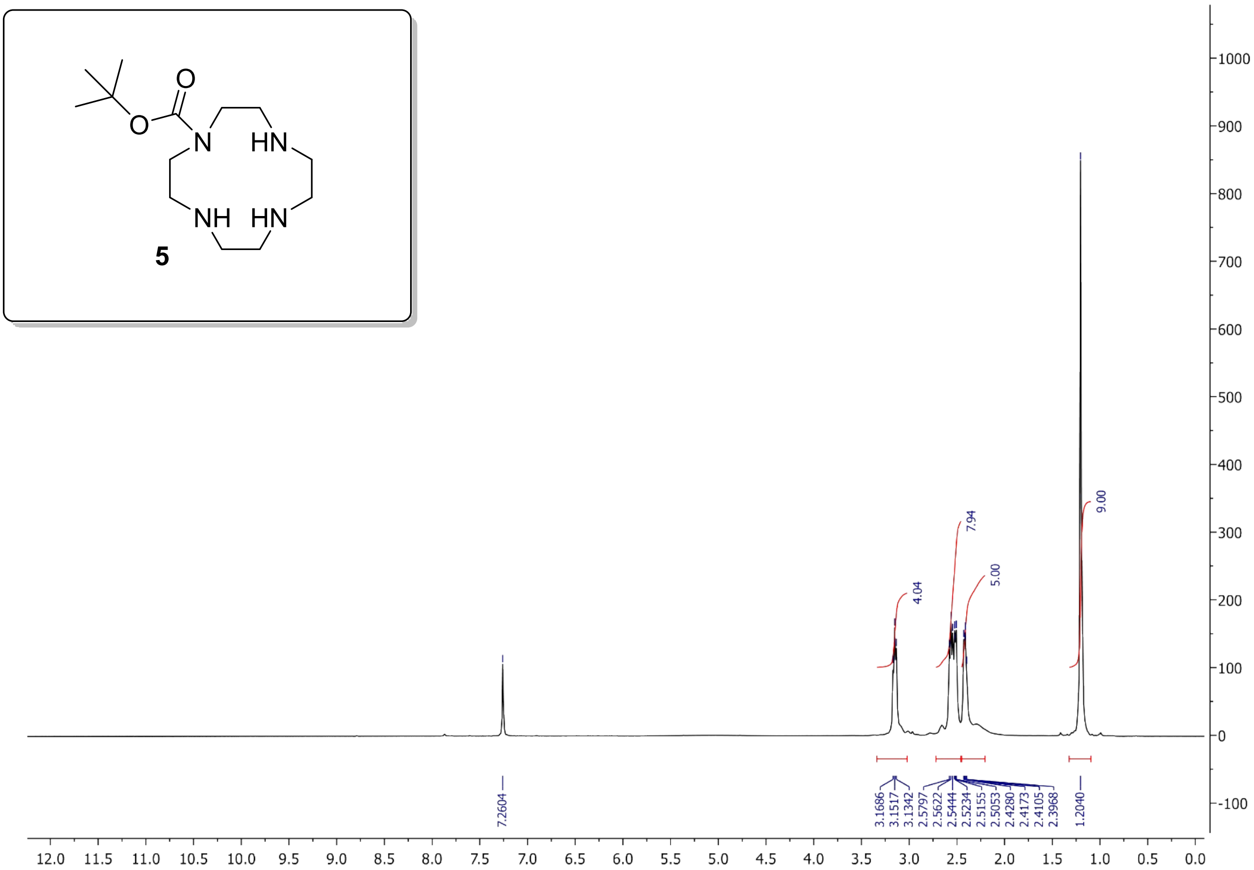


Figure S1 – ^{1}H NMR spectrum of compound **4**

Figure S2 – ^{13}C APT NMR spectrum of compound **4**



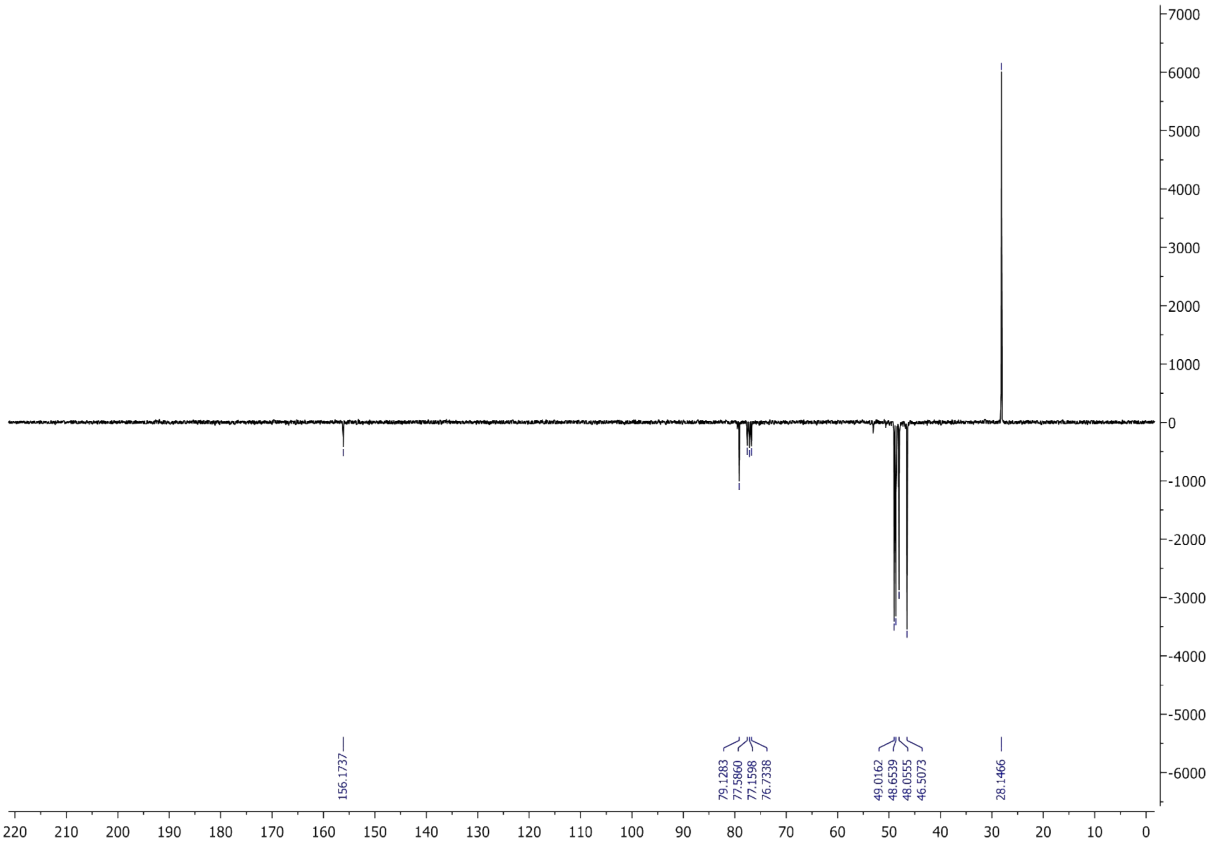


Figure S3 – ^{1}H NMR spectrum of compound **5**

Figure S4 – ^{13}C APT NMR spectrum of compound **5**

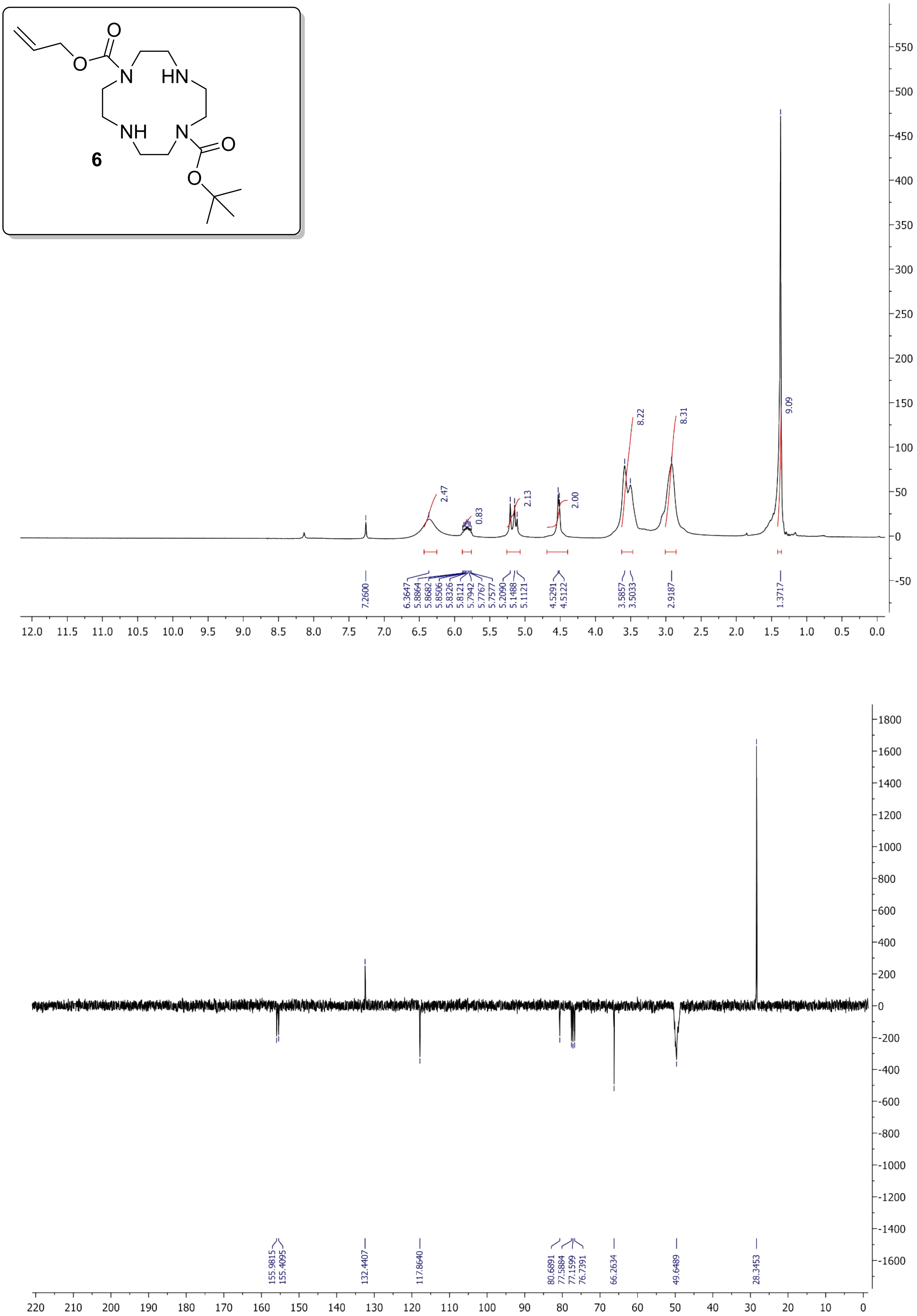
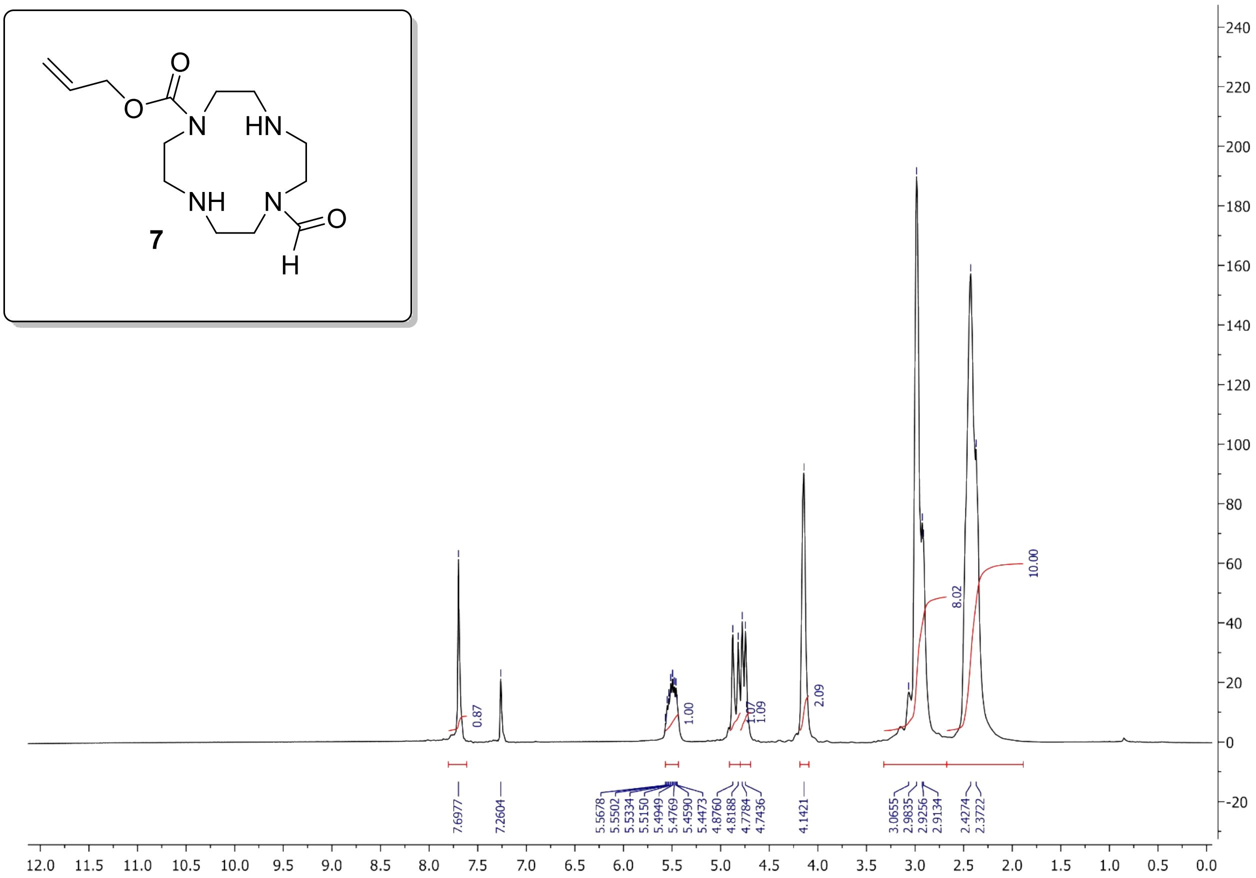


Figure S5 – ^{1}H NMR spectrum of compound **6**

Figure S6 – ^{13}C APT NMR spectrum of compound **6**



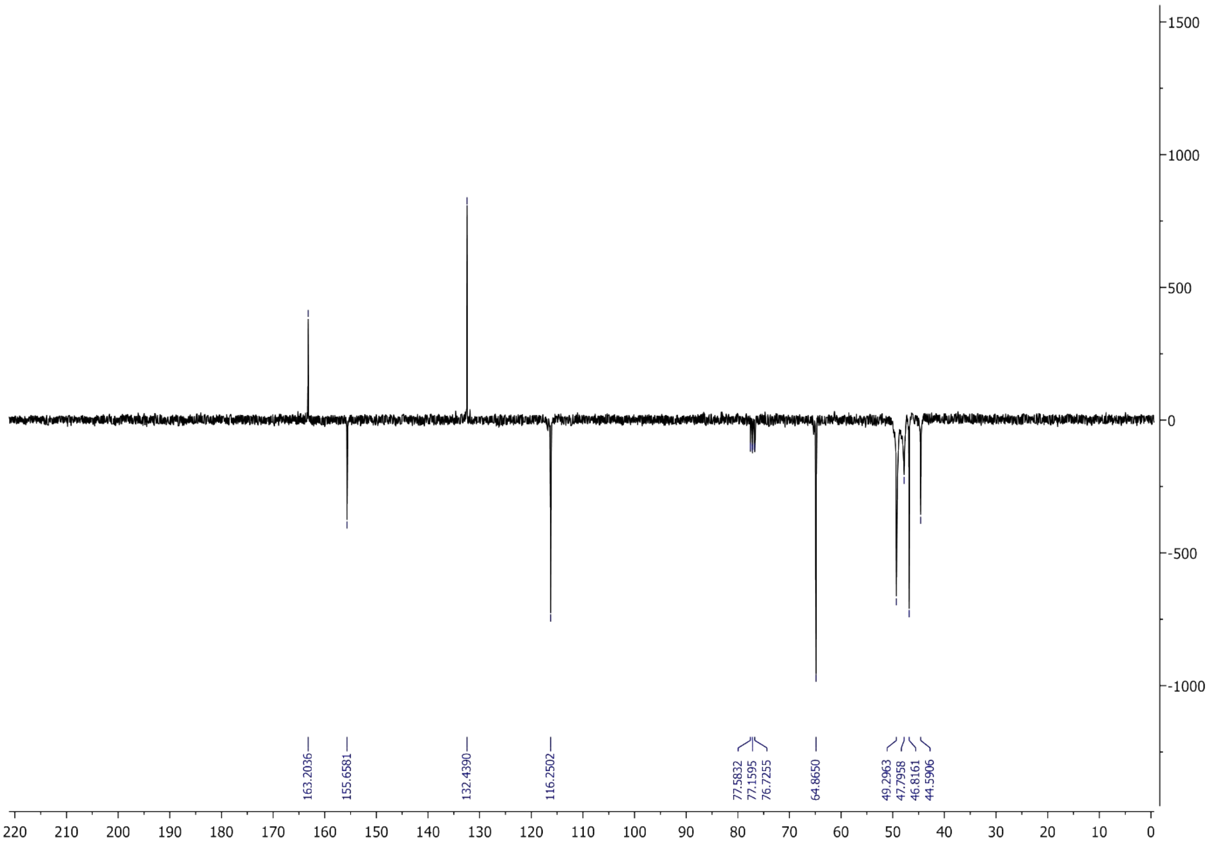
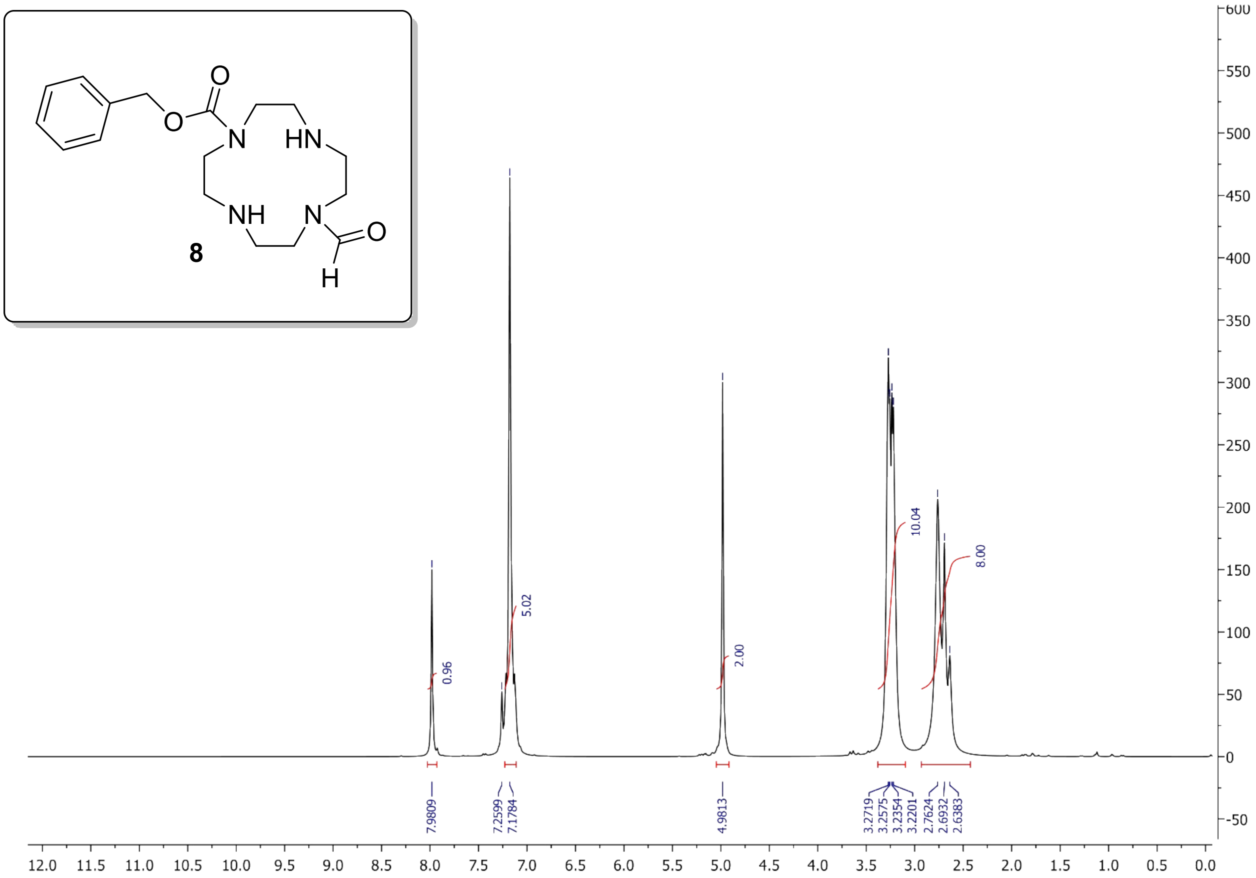


Figure S7 – ^{1}H NMR spectrum of compound **7**

Figure S8 – ^{13}C APT NMR spectrum of compound **7**



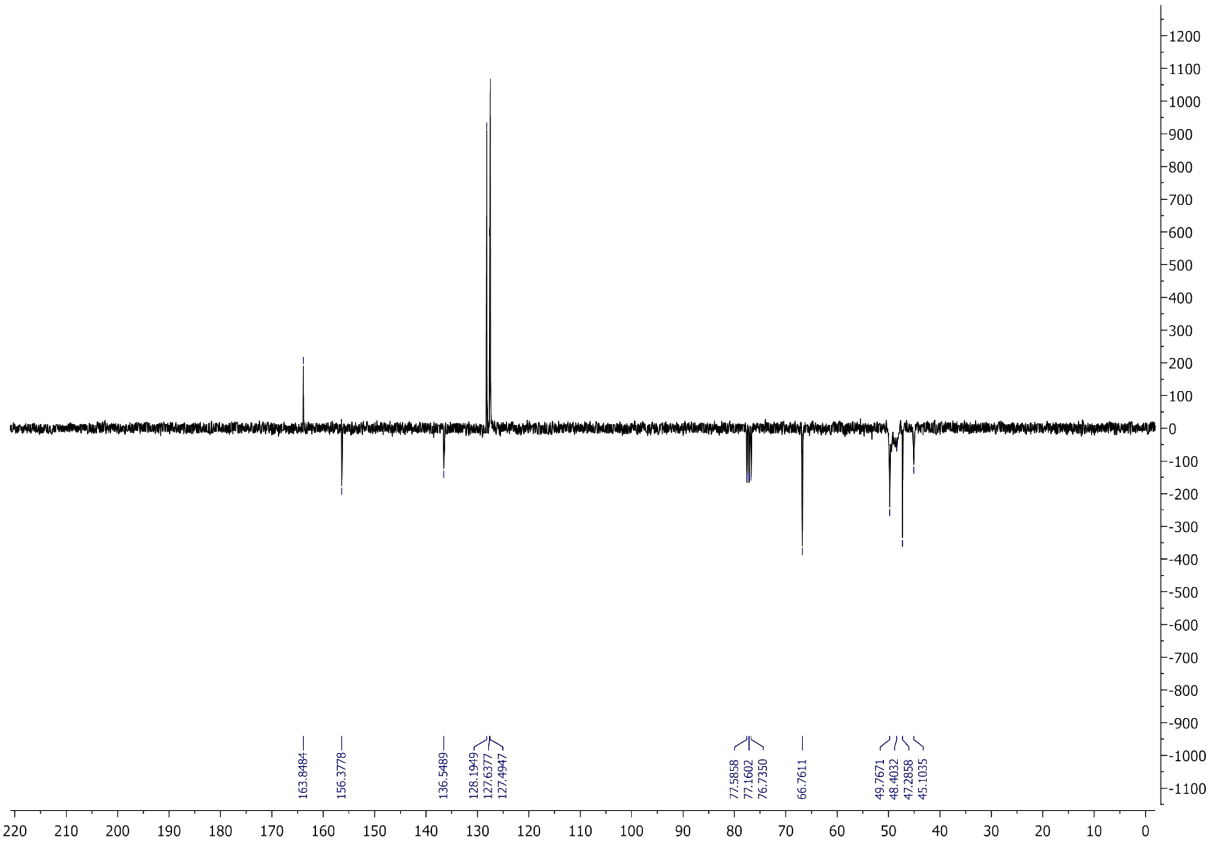


Figure S9 – ^{1}H NMR spectrum of compound **8**

Figure S10 – ^{13}C APT NMR spectrum of compound **8**

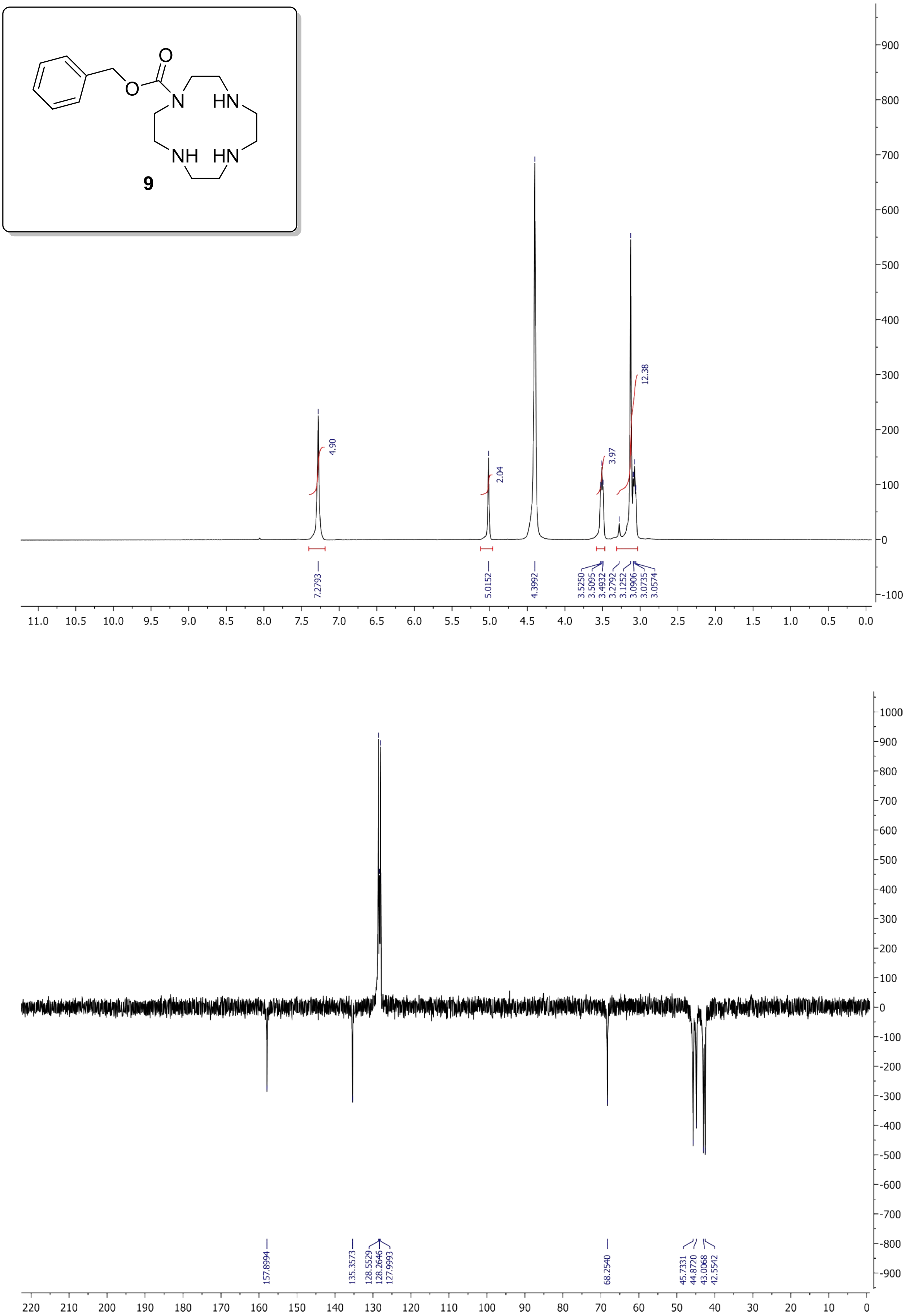
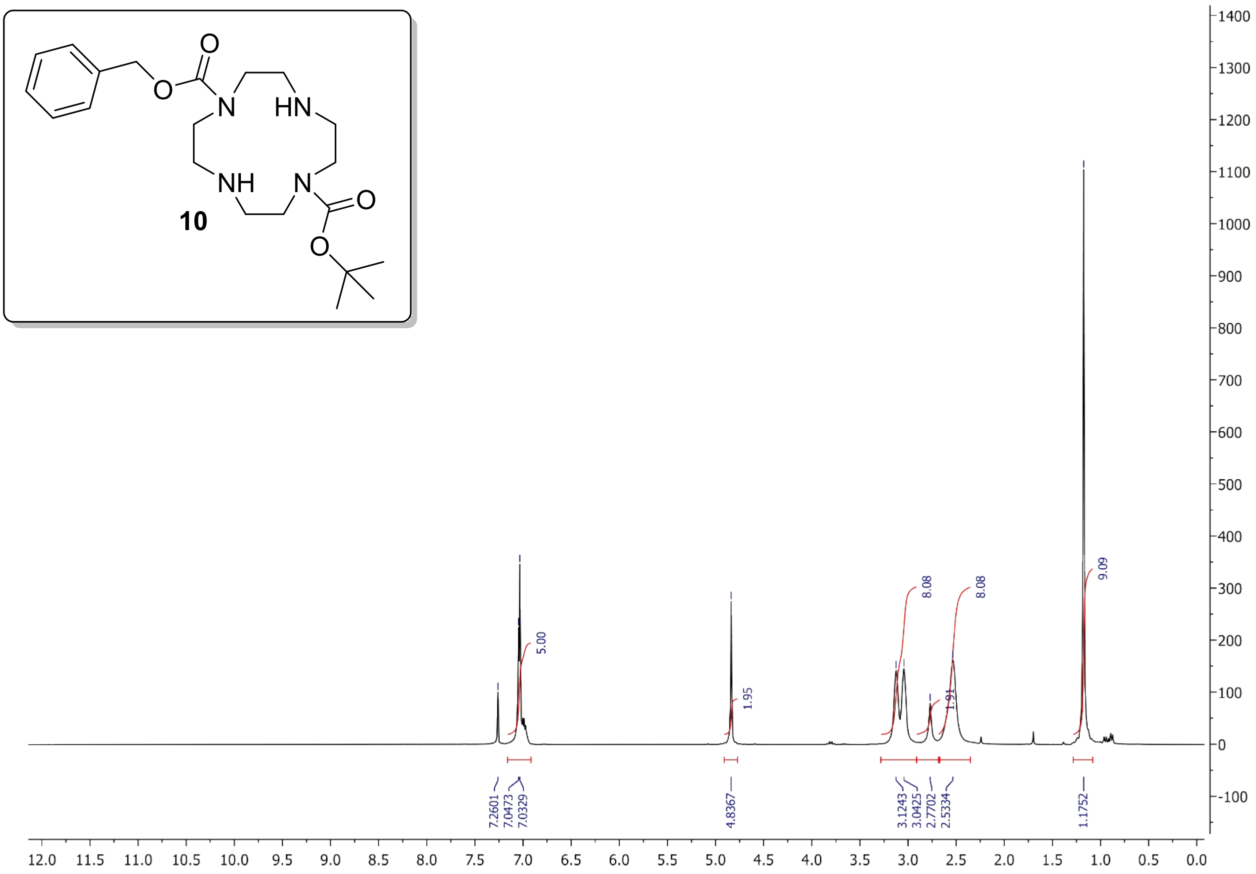


Figure S11 – ^{1}H NMR spectrum of compound **9**

Figure S12 – ^{13}C APT NMR spectrum of compound **9**



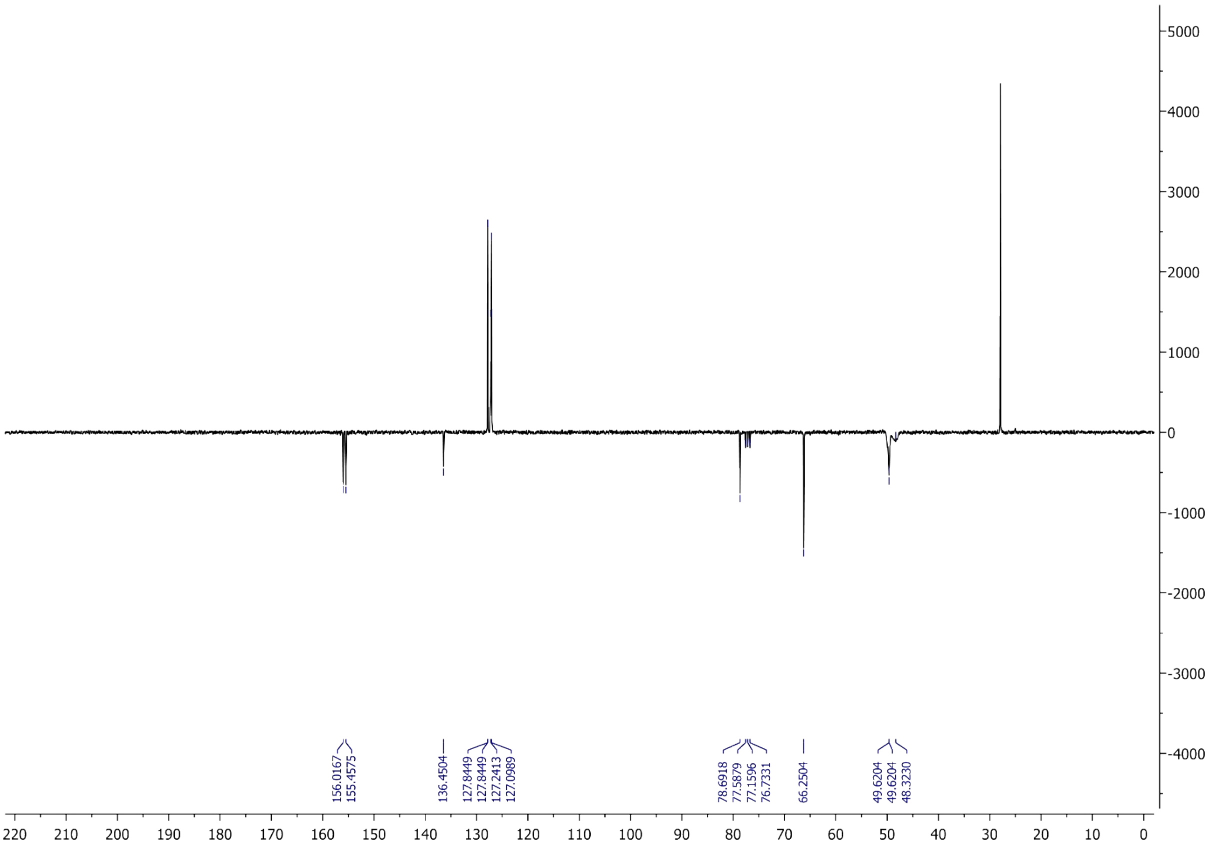
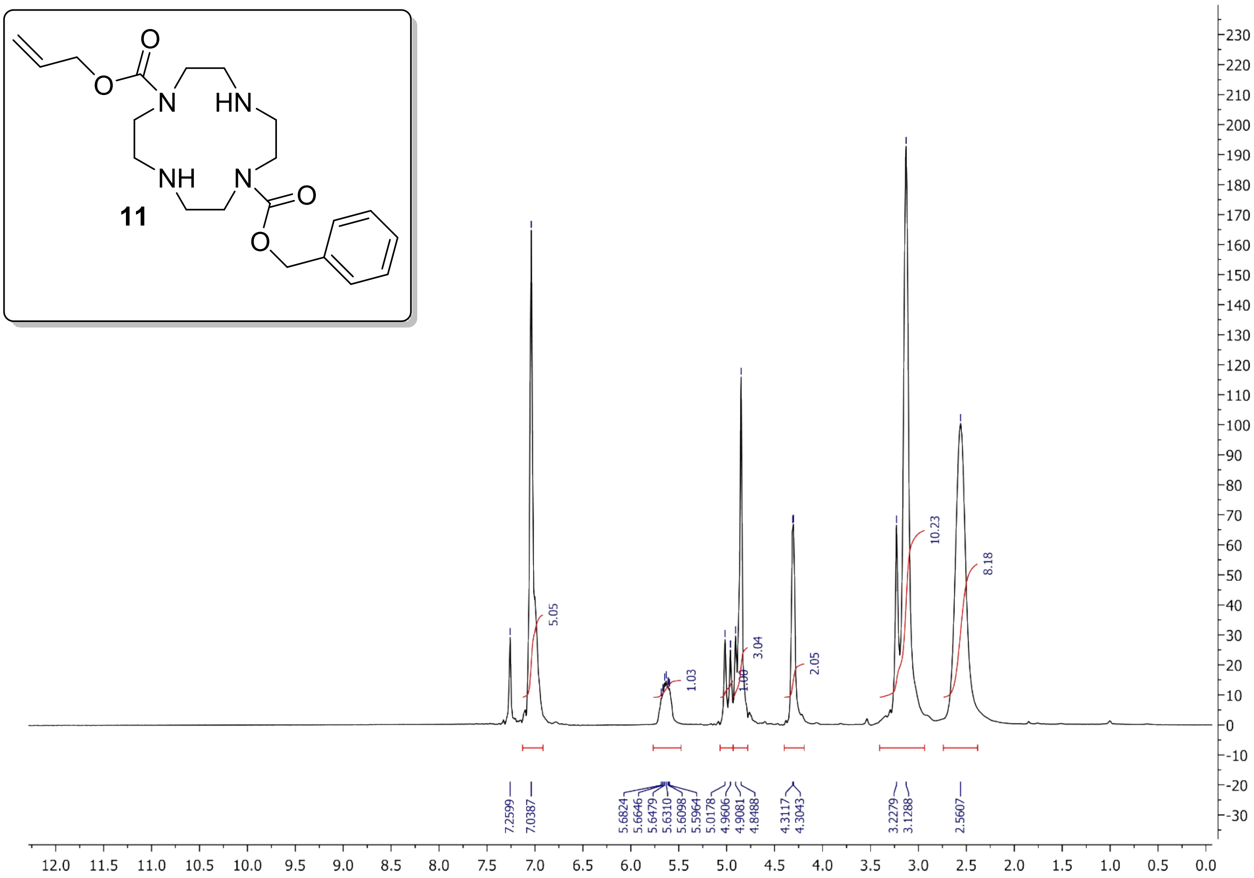


Figure S13 – ^{1}H NMR spectrum of compound **10**

Figure S14 – ^{13}C APT NMR spectrum of compound **10**



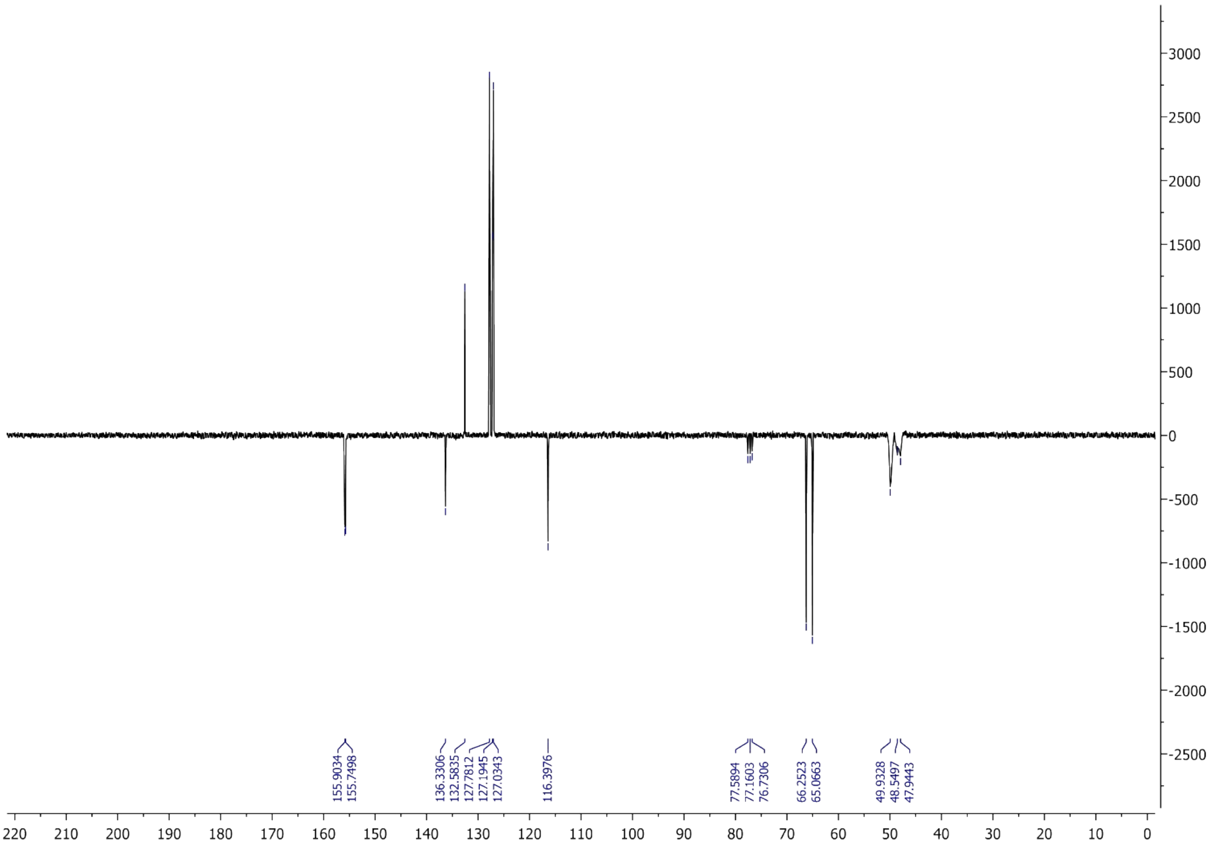


Figure S15 – ^{1}H NMR spectrum of compound **11**

Figure S16 – ^{13}C APT NMR spectrum of compound **11**

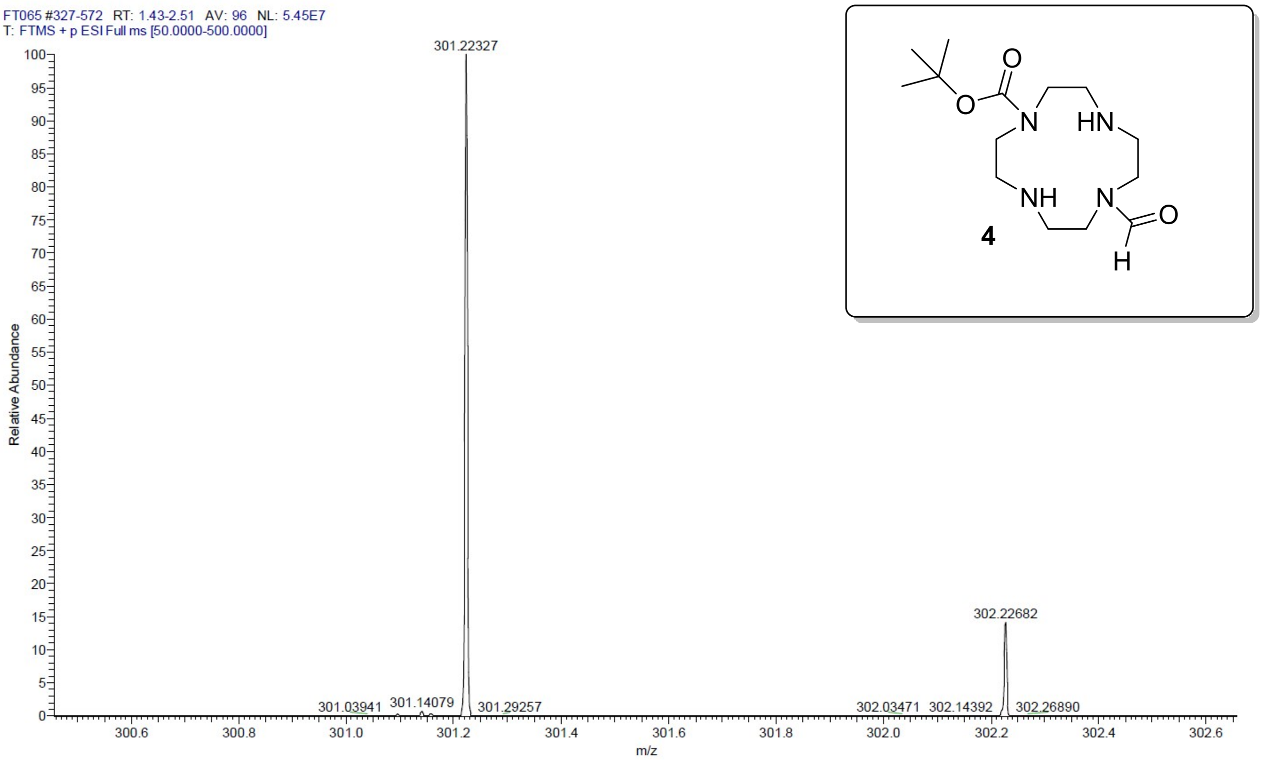


Figure S17 – High resolution mass spectrum of compound **4**

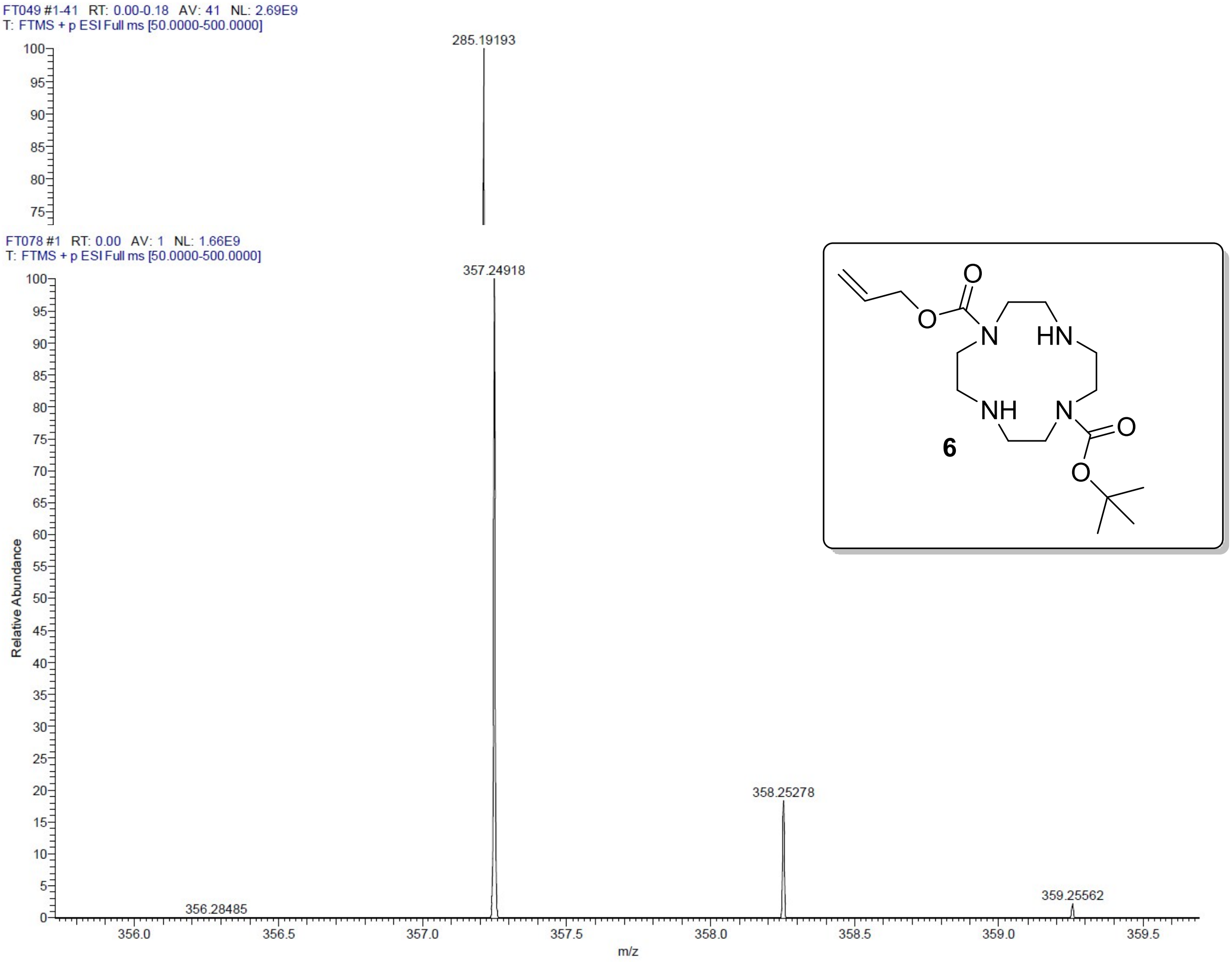


Figure S18 – High resolution mass spectrum of compound **6**

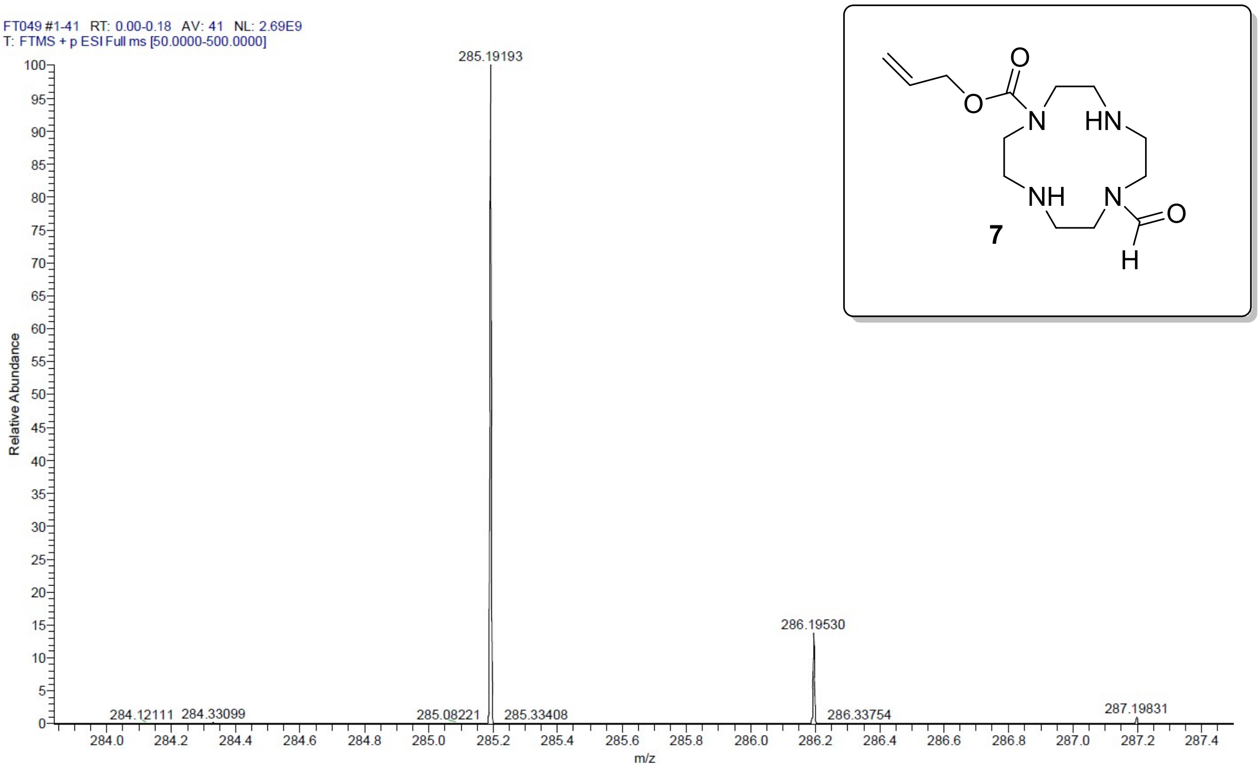


Figure S19 – High resolution mass spectrum of compound **7**

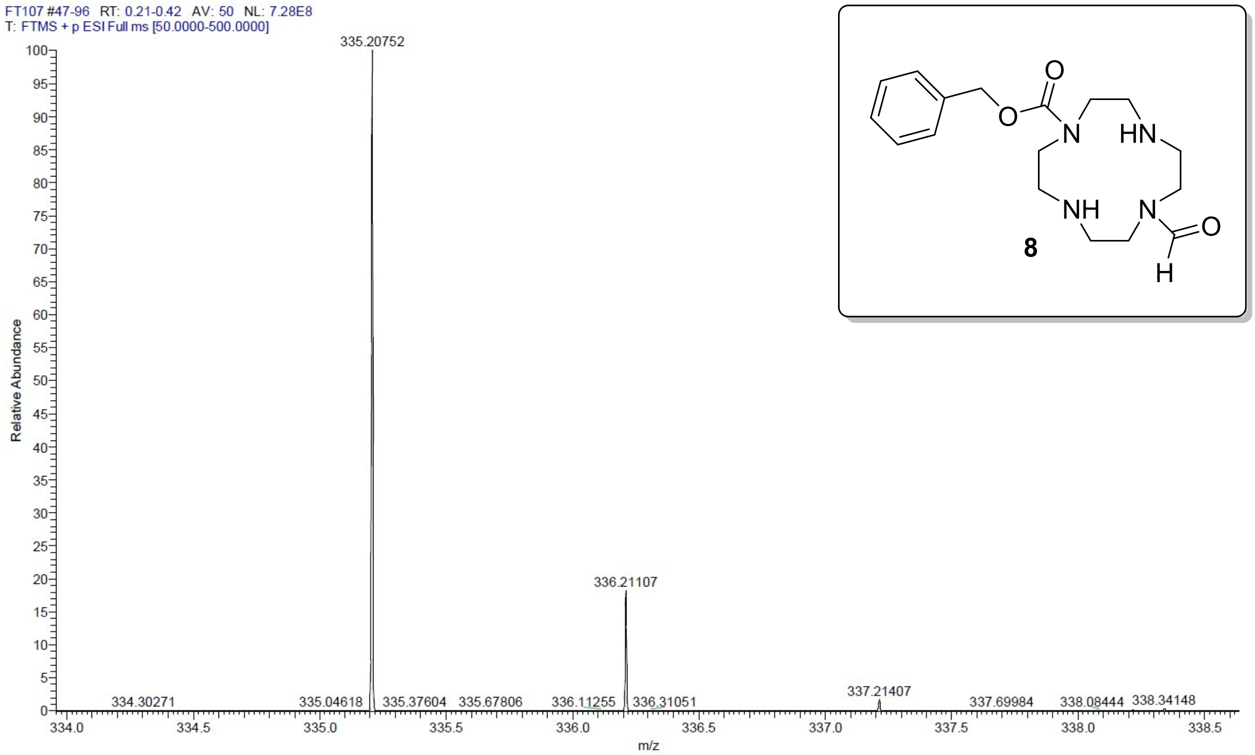


Figure S20 – High resolution mass spectrum of compound **8**

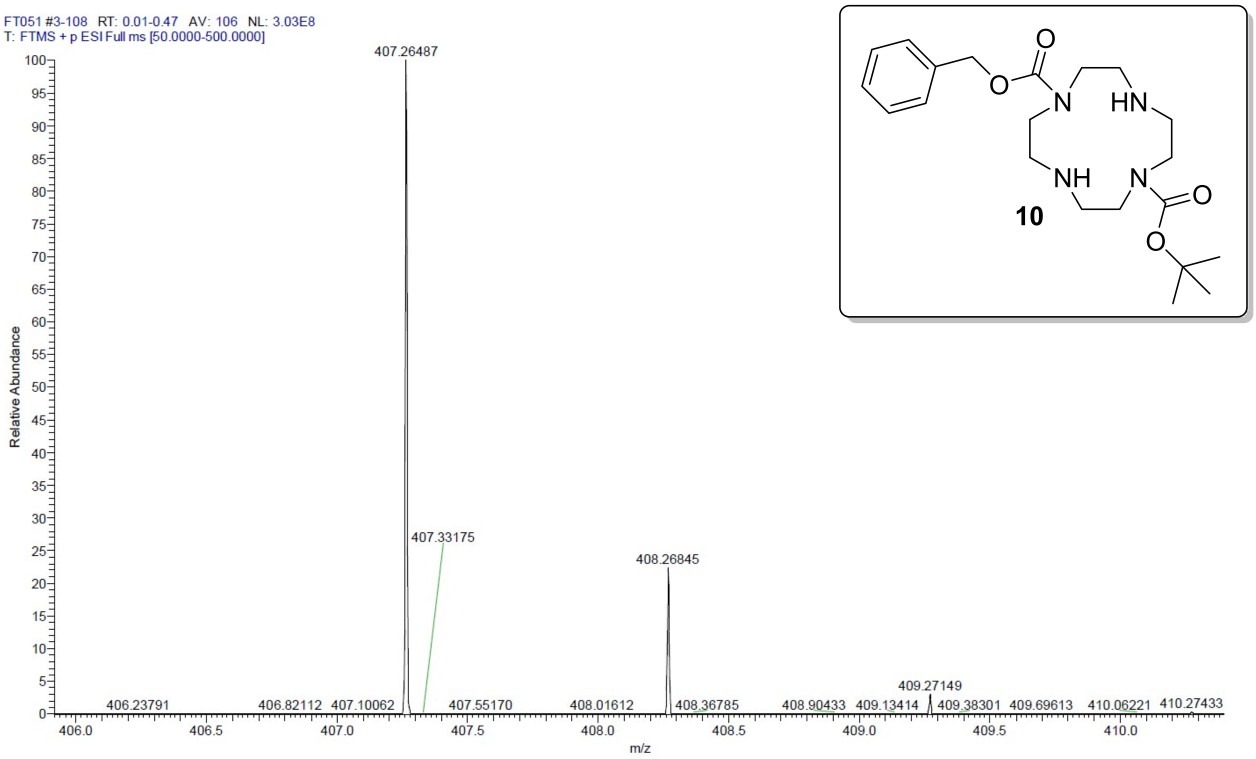


Figure S21 – High resolution mass spectrum of compound **10**

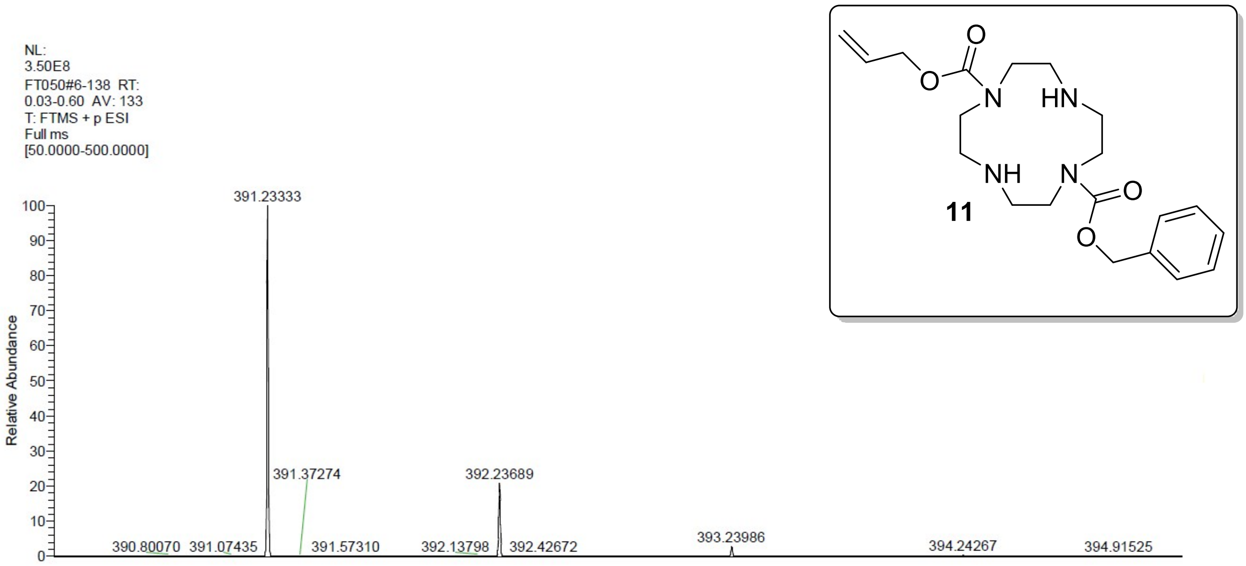


Figure S22 – High resolution mass spectrum of compound **11**