Supporting Information

Modular and Chromatography-Free Synthesis of Natural Linear Polyamines

Masato Takahashi,[a*] Teruyuki Kobayashi,[a] Takuya Noguchi,[a] Seisuke Mimori,[a] Masakiyo Hosokawa,[a] Takashi Fukui,[b] Akira Takagi,[b] Nobuaki Okumura,[c] Hiroshi Kawabe,[c] Takanori Yano,[d] Naomi Ohta,[e] Akihisa Hata,[e] Ryoji Mitsui,[d] Noboru Fujitani[f]

[a] Department of Pharmacy, Faculty of Pharmacy, Chiba Institute of Science, 15-8, Shiomi-cho, Choshi, Chiba 288-0025, Japan
[b] Department of Health and Medical Sciences, Faculty of Risk and Crisis Management, Chiba Institute of Science, 15-8 Shiomi, Choshi, Chiba 288-0025, Japan
[c] Institute for Bee Products and Health Science, Yamada Bee Company Inc., 194 Ichiba, Kagamino-cho, Tomata-gun, Okayama 708-0393, Japan
[d] Department of Bioscience, Faculty of Lifescience, Okayama University of Science, 1-1 Ridaicho, Kita-ku, Okayama-shi, Okayama 700-0005, Japan
[e] Faculty of Veterinary Medicine, Okayama University of Science, 1-3, Ikoinooka, Imabari, Ehime 797-8555, Japan
[f] Biomedical Science Examination and Research Center, Okayama University of Science, 1-3, Ikoinooka, Imabari, Ehime 797-8555, Japan

*Corresponding author
Masato Takahashi, PhD
Faculty of Pharmacy, Chiba Institute of Science, 15-8, Shiomi-cho, Choshi, Chiba, 288-0025, Japan
Tel: +81 479 30 4680; E-mail: matakahashi@cis.ac.jp

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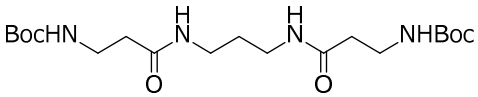
General Information.

All reactions were carried out under ambient air unless otherwise noted. All reagents and solvents were of reagent grade and used without further purification. An oil bath was employed as the heating source for reactions requiring elevated temperatures. Unless otherwise stated, reaction mixtures were stirred using a magnetic stirrer. All organic solvents were removed under reduced pressure using a rotary evaporator. Yields are reported immediately prior to the subsequent reaction step and after recrystallization of the final products, unless otherwise noted.

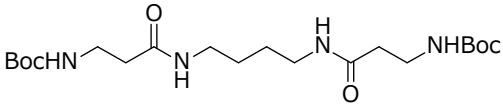
^{1}H- and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on an Ascend^{TM} 400 spectrometer (Bruker, MA, USA) in $CDCl_3$, DMSO-*d6*, CD_3OD, or D_2O, as indicated. Chemical shifts (δ) are reported in parts per million (ppm). Residual solvent signals were used as internal references for spectra recorded in $CDCl_3$ (δH = 7.26 ppm, δC = 77.0 ppm), DMSO-*d6* (δH = 2.51 ppm, δC = 39.5 ppm), and CD_3OD (δH = 3.31 ppm, δC = 49.0 ppm). For spectra measured in D_2O, the residual HDO signal (δH = 4.79 ppm) was used as the reference for ^{1}H NMR; no internal reference was used for ^{13}C NMR. Signal multiplicities are designated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = double doublet, dt = double triplet. High-resolution mass spectra (HRMS) were obtained using electrospray ionization (ESI) in positive/negative mode on a LIT-q-TOF tandem mass spectrometer (NanoFrontier LD) coupled to a liquid chromatograph (Hitachi High-Tech Corporation, Japan).

Synthesis of **23a**



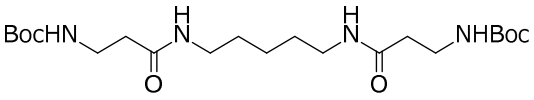
*di-tert-Butyl ((propane-1,3-diylbis(azanediyl))bis(3-oxopropane-3,1-diyl))dicarbamate (**23a**).* A mixture of *N*-Boc-β-alanine (**21a**) (1135 mg, 6.0 mmol), propane-1,3-diamine (**22a**) (148 mg, 2.0 mmol), EDC·HCl (1150 mg, 6.0 mmol), and DMAP (24 mg, 0.2 mmol) in DMF (10 mL) was stirred at 50 °C for 3 h. After cooling in an ice bath, 5% aqueous $NaHCO_3$ (30 mL) was added, stirred for 10 min at the same temperature, and the precipitate was collected by filtration using a Kiriyama funnel and washed with hexane/ethyl acetate (10:1). The resulting colorless solid **23a** (802 mg, 96.3%) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.52 (br s, 2H), 5.28 (br s, 2H), 3.40 (dt, *J* = 6.0, 6.0 Hz, 4H), 3.28 (dt, *J* = 6.0, 6.0 Hz, 4H), 2.42 (t, *J* = 6.0 Hz, 4H), 1.66–1.60 (m, 2H), 1.43 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.0, 156.2, 79.4, 36.8, 36.5, 35.8, 29.5, 28.4; HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{37}N_4O_6$ $[M+H]^+$ 417.2708, found 417.2701.

Synthesis of **23b**



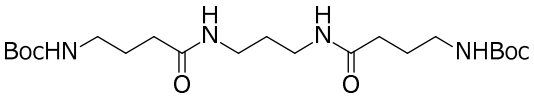
di-tert-Butyl ((butane-1,4-diylbis(azanediyl))bis(3-oxopropane-3,1-diyl))dicarbamate ***(23b)***. A mixture of *N*-Boc-β-alanine (**21a**) (1140 mg, 6.0 mmol), butane-1,4-diamine (**22b**) (176 mg, 2.0 mmol), EDC·HCl (1155 mg, 6.0 mmol), and DMAP (24 mg, 0.2 mmol) in DMF (10 mL) was stirred at 50 °C for 3 h. After cooling in an ice bath, 5% aqueous $NaHCO_3$ (30 mL) was added, stirred for 10 min at the same temperature, and the precipitate was collected by filtration using a Kiriyama funnel and washed with hexane/ethyl acetate (10:1). The resulting colorless solid **23b** (833 mg, 96.7%) was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.81 (t, *J* = 5.2 Hz, 2H), 6.73 (t, *J* = 5.2 Hz, 2H), 3.11 (dt, *J* = 6.8, 6.8 Hz, 4H), 3.02–3.01 (m, 4H), 2.20 (t, *J* = 7.2 Hz, 4H), 1.40–1.35 (m, 22H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-*d6*) δ 170.1, 155.4, 77.5, 38.1, 36.8, 35.8, 28.2, 26.5; HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{39}N_4O_6$ $[M+H]^+$ 431.2864, found 431.2865.

Synthesis of **23c**



di-tert-Butyl ((pentane-1,5-diylbis(azanediyl))bis(3-oxopropane-3,1-diyl))dicarbamate ***(23c)***. A mixture of *N*-Boc-β-alanine (**21a**) (1137 mg, 6.0 mmol), pentane-1,5-diamine (**22c**) (204 mg, 2.0 mmol), EDC·HCl (1149 mg, 6.0 mmol), and DMAP (24 mg, 0.2 mmol) in DMF (10 mL) was stirred at 50 °C for 3 h. After cooling in an ice bath, 5% aqueous $NaHCO_3$ (30 mL) was added, stirred for 10 min at the same temperature, and the precipitate was collected by filtration using a Kiriyama funnel and washed with hexane/ethyl acetate (10:1). The resulting colorless solid **23c** (871 mg, 98.0%) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13 (br s, 2H), 5.34 (br s, 2H), 3.39 (dt, *J* = 6.0, 6.0 Hz, 4H), 3.25 (dt, *J* = 6.0, 6.0 Hz, 4H), 2.40 (t, *J* = 6.0 Hz, 4H), 1.55–1.48 (m, 4H), 1.42 (s, 18H), 1.37–1.30 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 171.5, 156.3, 79.3, 39.0, 36.8, 36.4, 28.9, 28.4, 23.7; HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{41}N_4O_6$ $[M+H]^+$ 445.3021, found 445.3027.

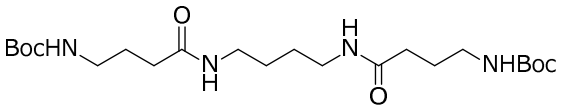
Synthesis of **23d**



di-tert-Butyl ((propane-1,3-diylbis(azanediyl))bis(4-oxobutane-4,1-diyl))dicarbamate ***(23d)***. A mixture of *N*-Boc-γ-aminobutyric acid (**21b**) (1219 mg, 6.0 mmol), propane-1,3-diamine (**22a**) (148 mg, 2.0 mmol), EDC·HCl (1150 mg, 6.0 mmol), and DMAP (24 mg, 0.2 mmol) in DMF (10 mL) was stirred at 50 °C for 3 h. After cooling in an ice bath, 5% aqueous $NaHCO_3$ (30 mL) was added, stirred for 10 min at the same temperature, and the precipitate was collected by filtration using a Kiriyama funnel and washed with hexane/diethyl ether (10:1). The resulting colorless solid **23d** (866 mg, 97.4%) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.81 (br s, 2H),

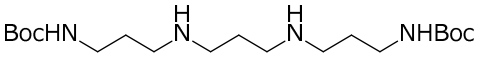
4.88 (br s, 2H), 3.28 (dt, *J* = 6.0, 6.0 Hz, 4H), 3.18 (dt, *J* = 6.0, 6.0 Hz, 4H), 2.24 (t, *J* = 7.2 Hz, 4H), 1.84–1.77 (m, 4H), 1.68–1.62 (m, 2H), 1.43 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 173.2, 156.3, 78.9, 39.7, 35.9, 33.5, 29.3, 28.2, 26.1; HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{41}N_4O_6$ $[M+H]^+$ 445.3021, found 445.3026.

Synthesis of **23e**



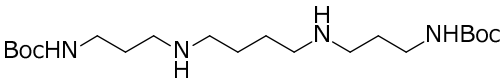
*di-tert-Butyl ((butane-1,4-diylbis(azanediyl))bis(4-oxobutane-4,1-diyl))dicarbamate (**23e**)*. A mixture of *N*-Boc-γ-aminobutyric acid (**21b**) (1220 mg, 6.0 mmol), butane-1,4-diamine (**22b**) (176 mg, 2.0 mmol), EDC·HCl (1150 mg, 6.0 mmol), and DMAP (24 mg, 0.2 mmol) in DMF (10 mL) was stirred at 50 °C for 3 h. After cooling in an ice bath, 5% aqueous $NaHCO_3$ (30 mL) was added, stirred for 10 min at the same temperature, and the precipitate was collected by filtration using a Kiriyama funnel and washed with hexane/ethyl acetate (10:1). The resulting colorless solid **23e** (909 mg, 99.1%) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.63 (br s, 2H), 4.93 (br s, 2H), 3.27 (dt, *J* = 6.0, 6.0 Hz, 4H), 3.15 (dt, *J* = 6.0, 6.0 Hz, 4H), 2.22 (t, *J* = 6.8 Hz, 4H), 1.83–1.77 (m, 4H), 1.58–1.52 (m, 4H), 1.43 (s, 18H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 172.9, 156.5, 79.3, 39.7, 39.0, 33.6, 28.4, 26.7, 26.4; HRMS (ESI-TOF) *m/z* calcd for $C_{22}H_{43}N_4O_6$ $[M+H]^+$ 459.3177, found 459.3179.

Synthesis of **24a**



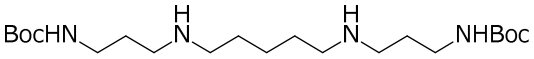
*di-tert-Butyl ((propane-1,3-diylbis(azanediyl))bis(3-oxopropane-3,1-diyl))dicarbamate (**24a**)*. A 3.6 M solution of Red-Al in toluene (2.0 mL, 7.2 mmol) was slowly added to a solution of diamide **23a** (250 mg, 0.6 mmol) in toluene/THF (2:1, 10 mL) at 0 °C. The reaction mixture was stirred at 40 °C for 3 h. After cooling to 0 °C, 1.0 M aqueous NaOH (10 mL) was added slowly. The mixture was stirred for 5 min and extracted with toluene (20 mL). The organic layer was washed with H_2O (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting colorless solid **24a** (227 mg, 97.1%) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (br s, 2H), 3.16–3.12 (m, 4H), 2.62–2.59 (m, 8H), 1.64–1.54 (m, 6H), 1.39 (s, 20H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 156.0, 78.8, 48.2, 47.7, 39.1, 30.2, 29.8, 28.4; HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{41}N_4O_4$ $[M+H]^+$ 389.3122, found 389.3117.

Synthesis of **24b**



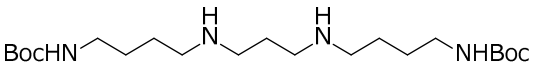
*di-tert-Butyl ((butane-1,4-diylbis(azanediyl))bis(propane-3,1-diyl))dicarbamate (**24b**).* A 3.6 M solution of Red-Al in toluene (1.3 mL, 4.7 mmol) was slowly added to a solution of diamide **23b** (172 mg, 0.4 mmol) in toluene/THF (2:1, 10 mL) at 0 °C. The reaction mixture was stirred at 40 °C for 3 h. After cooling to 0 °C, 1.0 M aqueous NaOH (10 mL) was added slowly. The mixture was stirred for 5 min and extracted with toluene (20 mL). The organic layer was washed with H_2O (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting colorless oil **24b** (143 mg, 89.0%) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.21 (br s, 2H), 3.16–3.11 (m, 4H), 2.60 (t, *J* = 6.8 Hz, 4H), 2.57–2.52 (m, 4H), 1.62–1.55 (m, 4H), 1.47–1.44 (m, 4H), 1.38 (s, 18H); NH protons (2H) were not observed; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.0, 78.8, 49.7, 47.6, 39.1, 29.8, 28.3, 27.7; HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{43}N_4O_4$ $[M+H]^+$ 403.3279, found 403.3274.

Synthesis of **24c**



*di-tert-Butyl ((pentane-1,5-diylbis(azanediyl))bis(propane-3,1-diyl))dicarbamate (**24c**).* A 3.6 M solution of Red-Al in toluene (2.0 mL, 7.2 mmol) was slowly added to a solution of diamide **23c** (267 mg, 0.6 mmol) in toluene/THF (2:1, 10 mL) at 0 °C. The reaction mixture was stirred at 40 °C for 3 h. After cooling to 0 °C, 1.0 M aqueous NaOH (10 mL) was added slowly. The mixture was stirred for 5 min and extracted with toluene (20 mL). The organic layer was washed with H_2O (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting pale yellow oil **24c** (234 mg, 93.7%) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.24 (br s, 2H), 3.13–3.12 (m, 4H), 2.59 (t, *J* = 6.8 Hz, 4H), 2.53–2.50 (m, 4H), 1.61–1.53 (m, 4H), 1.47–1.38 (m, 24H); NH protons (2H) were not observed; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.0, 78.7, 49.7, 47.7, 39.1, 29.9, 29.8, 28.3, 24.9; HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{45}N_4O_4$ $[M+H]^+$ 417.3435, found 417.3438.

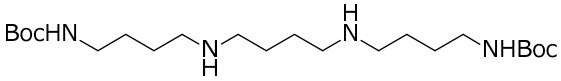
Synthesis of **24d**



*di-tert-Butyl ((propane-1,3-diylbis(azanediyl))bis(butane-4,1-diyl))dicarbamate (**24d**).* A 3.6 M solution of Red-Al in toluene (2.0 mL, 7.2 mmol) was slowly added to a solution of diamide **23d** (267 mg, 0.6 mmol) in toluene/THF (2:1, 10 mL) at 0 °C. The reaction mixture was stirred at 40 °C for 3 h. After cooling to 0 °C, 1.0 M aqueous NaOH (10 mL) was added slowly. The mixture was stirred for 5 min and extracted with toluene (20 mL). The organic layer was washed with H_2O (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting colorless oil **24d** (245 mg, 98.1%) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (br s, 2H), 3.04–3.02 (m, 4H), 2.57 (t, *J* = 6.4 Hz, 4H), 2.54–2.48 (m, 4H), 1.62–1.55

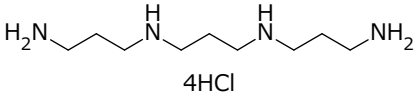
(m, 2H), 1.43–1.42 (m, 8H), 1.35 (s, 18H); NH protons (2H) were not observed; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 155.9, 78.7, 49.4, 48.3, 40.3, 30.1, 28.3, 27.8, 27.3; HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{45}N_4O_4$ $[M+H]^+$ 417.3435, found 417.3434.

Synthesis of **24e**



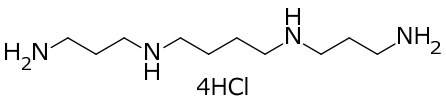
*di-tert-Butyl ((butane-1,4-diylbis(azanediyl))bis(butane-4,1-diyl))dicarbamate (**24e**)*. A 3.6 M solution of Red-Al in toluene (2.0 mL, 7.2 mmol) was slowly added to a solution of diamide **23e** (275 mg, 0.6 mmol) in toluene/THF (2:1, 10 mL) at 0 °C. The reaction mixture was stirred at 40 °C for 3 h. After cooling to 0 °C, 1.0 M aqueous NaOH (10 mL) was added slowly. The mixture was stirred for 5 min and extracted with toluene (20 mL). The organic layer was washed with H_2O (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting colorless solid **24e** (225 mg, 87.2%) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (br s, 2H), 3.04–3.03 (m, 4H), 2.54–2.49 (m, 8H), 1.47–1.39 (m, 12H), 1.36 (s, 18H); NH protons (2H) were not observed; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 155.9, 78.7, 49.6, 49.3, 40.3, 28.3, 27.74, 27.68, 27.2; HRMS (ESI-TOF) *m/z* calcd for $C_{22}H_{47}N_4O_4$ $[M]^+$ 431.3592, found 431.3591.

Synthesis of **6**



*Norspermine tetrahydrochloride (**6**)*. A 4.0 M solution of HCl in 1,4-dioxane (0.75 mL, 3.0 mmol) was added to a solution of the di-Boc compound **24a** (116 mg, 0.3 mmol) in 1,4-dioxane (5.0 mL) at 0 °C. The reaction mixture was stirred at 50 °C for 3 h. After removal of the solvent under reduced pressure, the crude residue was recrystallized from MeOH to afford a colorless solid **6** (73 mg, 73.3%). ^{1}H NMR (400 MHz, D_2O) δ 3.21 (m, 8H), 3.13 (m, 4H), 2.20–2.08 (m, 6H); $^{13}C\{^{1}H\}$ NMR (100 MHz, D_2O) δ 44.7, 44.6, 36.6, 23.7, 22.7; HRMS (ESI-TOF) *m/z* calcd for $C_9H_{25}N_4$ $[M+H]^+$ 189.2074, found 189.2072.

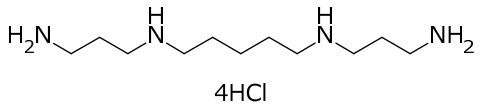
Synthesis of **7**



*Spermine tetrahydrochloride (**7**)*. A 4.0 M solution of HCl in 1,4-dioxane (0.75 mL, 3.0 mmol) was added to a solution of the di-Boc compound **24b** (121 mg, 0.3 mmol) in 1,4-dioxane (5.0 mL) at 0 °C. The reaction mixture was stirred at 50 °C for 3 h. After removal of the solvent under reduced pressure, the crude residue was recrystallized from MeOH to afford a colorless solid **7** (58 mg, 55.7%). ^{1}H NMR

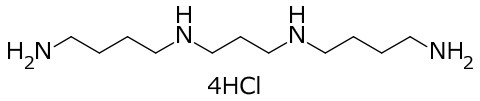
(400 MHz, D_2O) δ 3.18–3.09 (m, 12H), 2.13–2.06 (m, 4H), 1.85–1.74 (m, 4H); $^{13}C\{^1H\}$ NMR (100 MHz, D_2O) δ 47.0, 44.6, 36.6, 23.8, 22.8; HRMS (ESI-TOF) *m/z* calcd for $C_{10}H_{27}N_4$ $[M+H]^+$ 203.2230, found 203.2228.

Synthesis of **8**



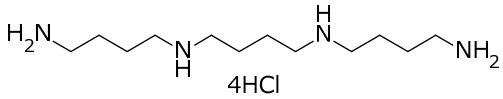
*bis(Aminopropyl)cadaverine tetrahydrochloride (**8**)*. A 4.0 M solution of HCl in 1,4-dioxane (0.75 mL, 3.0 mmol) was added to a solution of the di-Boc compound **24c** (125 mg, 0.3 mmol) in 1,4-dioxane (5.0 mL) at 0 °C. The reaction mixture was stirred at 50 °C for 12 h. After removal of the solvent under reduced pressure, the crude residue was recrystallized from MeOH to afford a colorless solid **8** (78 mg, 71.4%). ^1H NMR (400 MHz, D_2O) δ 3.18–3.07 (m, 12H), 2.14–2.06 (m, 4H), 1.78–1.71 (m, 4H), 1.51–1.43 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, D_2O) δ 47.5, 44.5, 36.6, 25.1, 23.8, 22.8; HRMS (ESI-TOF) *m/z* calcd for $C_{11}H_{29}N_4$ $[M+H]^+$ 217.2387, found 217.2389.

Synthesis of **9**



*Canavalmine tetrahydrochloride (**9**)*. A 4.0 M solution of HCl in 1,4-dioxane (0.75 mL, 3.0 mmol) was added to a solution of the di-Boc compound **24d** (208 mg, 0.5 mmol) in 1,4-dioxane (5.0 mL) at 0 °C. The reaction mixture was stirred at 50 °C for 3 h. After removal of the solvent under reduced pressure, the crude residue was recrystallized from MeOH to afford a colorless solid **9** (76 mg, 70.1%). ^1H NMR (400 MHz, D_2O) δ 3.19–3.04 (m, 12H), 2.17–2.09 (m, 2H), 1.85–1.70 (m, 8H); $^{13}C\{^1H\}$ NMR (100 MHz, D_2O) δ 47.1, 44.5, 38.8, 23.9, 22.8, 22.7; HRMS (ESI-TOF) *m/z* calcd for $C_{11}H_{29}N_4$ $[M+H]^+$ 217.2387, found 217.2389.

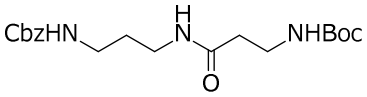
Synthesis of **10**



*Homospermine tetrahydrochloride (**10**)*. A 4.0 M solution of HCl in 1,4-dioxane (1.0 mL, 4.0 mmol) was added to a solution of the di-Boc compound **24e** (172 mg, 0.4 mmol) in 1,4-dioxane (3.0 mL) at 0 °C. The reaction mixture was stirred at 50 °C for 3 h. After removal of the solvent under reduced pressure, the crude residue was recrystallized from MeOH to afford a colorless solid **10** (100 mg, 66.6%). ^1H NMR (400 MHz, D_2O) δ 3.12–3.03 (m, 12H), 1.83–1.82 (m, 12H); $^{13}C\{^1H\}$ NMR (100 MHz, D_2O) δ 46.9, 46.9, 38.8, 23.9, 22.80, 22.76; HRMS (ESI-TOF) *m/z* calcd for $C_{12}H_{31}N_4$ $[M+H]^+$

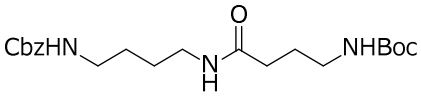
231.2543, found 231.2548.

Synthesis of **26a**



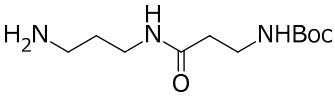
*tert-Butyl (3-((3-(((benzyloxy)carbonyl)amino)propyl)amino)-3-oxopropyl)carbamate (**26a**)*. A mixture of *N*-Cbz-propane-1,3-diamine hydrochloride (**25a**) (734 mg, 3.0 mmol), *N*-Boc-β-alanine (**21a**) (851 mg, 4.5 mmol), EDC·HCl (863 mg, 4.5 mmol), and DMAP (36 mg, 0.3 mmol) in Et_3N (0.6 mL, 4.3 mmol), DMF (10 mL) was stirred at 50 °C for 3 h. After cooling in an ice bath, 5% aqueous $NaHCO_3$ (30 mL) was added, stirred for 10 min at the same temperature, and the precipitate was collected by filtration using a Kiriyama funnel and washed with hexane/diethyl ether (10:1). The resulting colorless solid **26a** (1086 mg, 95.4%) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.30 (m, 5H), 6.30 (br s, 1H), 5.29 (br s, 1H), 5.19 (br s, 1H), 5.10 (s, 2H), 3.41–3.21 (m, 6H), 2.41–2.39 (m, 2H), 1.67–1.61 (m, 2H), 1.43 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 171.9, 157.0, 156.2, 136.5, 128.5, 128.1, 128.0, 79.4, 66.7, 37.6, 36.7, 36.3, 35.9, 29.8, 28.3; HRMS (ESI-TOF) *m/z* calcd for $C_{19}H_{30}N_3O_5$ $[M+H]^+$ 380.2180, found 380.2183.

Synthesis of **26b**



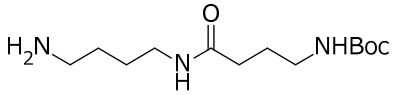
*tert-Butyl (4-((4-(((benzyloxy)carbonyl)amino)butyl)amino)-4-oxobutyl)carbamate (**26b**)*. A mixture of *N*-Cbz-butane-1,4-diamine hydrochloride (**25b**) (776 mg, 3.0 mmol), *N*-Boc-γ-aminobutyric acid (**21b**) (915 mg, 4.5 mmol), EDC·HCl (863 mg, 4.5 mmol), and DMAP (36 mg, 0.3 mmol) in Et_3N (0.6 mL, 4.3 mmol), DMF (10 mL) was stirred at 50 °C for 3 h. After cooling in an ice bath, 5% aqueous $NaHCO_3$ (30 mL) was added, stirred for 10 min at the same temperature, and the precipitate was collected by filtration using a Kiriyama funnel and washed with hexane/diethyl ether (10:1). The resulting colorless solid **26b** (1163 mg, 95.1%) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) 7.38–7.29 (m, 5H), 6.32 (br s, 1H), 5.09 (s, 2H), 4.98 (br s, 1H), 4.78 (br s, 1H), 3.28–3.13 (m, 6H), 2.20 (t, *J* = 6.8 Hz, 2H), 1.82–1.76 (m, 2H), 1.58–1.52 (m, 4H), 1.43 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.7, 156.5 (2C), 136.6, 128.5 (2C), 128.1, 79.4, 66.6, 40.6, 39.6, 39.0, 33.6, 28.4, 27.3, 26.6, 26.5; HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{34}N_3O_5$ $[M+H]^+$ 408.2493, found 408.2487.

Synthesis of **27a**



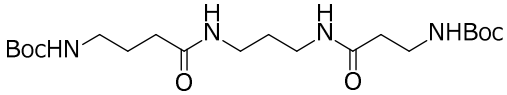
*tert-Butyl (3-((3-aminopropyl)amino)-3-oxopropyl)carbamate (**27a**)*. A mixture of amide **26a** (759 mg, 2.0 mmol) and 10% Pd/C (76 mg, 10 wt%) in MeOH (10 mL) was stirred at room temperature for 5 h under hydrogen atmosphere. The mixture was filtered through Celite and concentrated under reduced pressure to give the desired compound as a colorless solid **27a** (487 mg, 99.3%), which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (br s, 1H), 5.43 (br s, 1H), 3.33–3.24 (m, 4H), 2.71 (t, *J* = 6.4 Hz, 2H), 2.32 (t, *J* = 6.0 Hz, 2H), 1.61–1.51 (m, 4H), 1.35 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 171.4, 156.1, 79.0, 39.8, 37.5, 36.7, 36.2, 32.1, 28.3; HRMS (ESI-TOF) *m/z* calcd for $C_{11}H_{24}N_3O_3$ $[M+H]^+$ 246.1812, found 246.1816.

Synthesis of **27b**



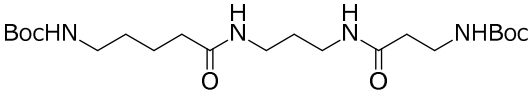
*tert-Butyl (4-((4-aminobutyl)amino)-4-oxobutyl)carbamate (**27b**)*. A mixture of amide **26b** (815 mg, 2.0 mmol) and 10% Pd/C (76 mg, 10 wt%) in MeOH (10 mL) was stirred at room temperature for 5 h under hydrogen atmosphere. The mixture was filtered through Celite and concentrated under reduced pressure to give the desired compound as a colorless solid **27b** (543 mg, 99.3%), which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (br s, 1H), 4.98 (br s, 1H), 3.28–2.70 (m, 8H), 2.20 (t, *J* = 6.8 Hz, 2H), 1.81–1.74 (m, 2H), 1.60–1.50 (m, 4H), 1.41 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.8, 156.5, 79.3, 41.2, 39.8, 39.2, 33.6, 29.7, 28.4, 26.8, 26.4; HRMS (ESI-TOF) *m/z* calcd for $C_{13}H_{28}N_3O_3$ $[M+H]^+$ 274.2125, found 274.2127.

Synthesis of **28a**



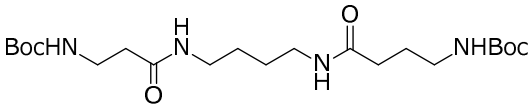
*tert-Butyl (2,2-dimethyl-4,8,14-trioxo-3-oxa-5,9,13-triazaheptadecan-17-yl)carbamate (**28a**)*. A mixture of amine **27a** (487 mg, 2.0 mmol), *N*-Boc-4-aminobutylic acid (**21b**) (610 mg, 3.0 mmol), EDC·HCl (575 mg, 3.0 mmol), and DMAP (24 mg, 0.2 mmol) in DMF (10 mL) was stirred at 50 °C for 3 h. After cooling in an ice bath, 5% aqueous $NaHCO_3$ (30 mL) was added, stirred for 10 min at the same temperature, and the precipitate was collected by filtration using a Kiriyama funnel and washed with hexane/ethyl acetate (10:1). The resulting colorless solid **28a** (820 mg, 95.3%) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92–6.85 (m, 2H), 5.33 (br s, 1H), 4.99 (br s, 1H), 3.37–3.34 (m, 2H), 3.25–3.24 (m, 4H), 3.13–3.12 (m, 2H), 2.41–2.20 (m, 4H), 1.81–1.75 (m, 2H), 1.64–1.61 (m, 2H), 1.41 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.4, 172.0, 156.5, 156.2, 79.3 (2C), 39.7, 36.8, 36.4, 35.9, 33.6, 29.5, 29.4, 28.4 (2C), 26.3; HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{39}N_4O_6$ $[M+H]^+$ 431.2864, found 431.2859.

Synthesis of **28b**



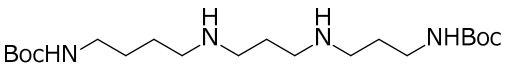
*tert-Butyl (2,2-dimethyl-4,8,14-trioxo-3-oxa-5,9,13-triazaoctadecan-18-yl)carbamate (**28b**)*. A mixture of amine **27a** (491 mg, 2.0 mmol), *N*-Boc-5-aminopentanoic acid (**21c**) (652 mg, 3.0 mmol), EDC·HCl (575 mg, 3.0 mmol), and DMAP (24 mg, 0.2 mmol) in DMF (10 mL) was stirred at 50 °C for 3 h. After cooling in an ice bath, 5% aqueous $NaHCO_3$ (30 mL) was added, stirred for 10 min at the same temperature, and the precipitate was collected by filtration using a Kiriyama funnel and washed with hexane/ethyl acetate (10:1). The resulting colorless solid **28b** (852 mg, 95.8%) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (br s, 1H), 6.45 (br s, 1H), 5.27 (br s, 1H), 4.78 (br s, 1H), 3.41–3.10 (m, 8H), 2.43–2.40 (m, 2H), 2.24–2.21 (m, 2H), 1.70–1.58 (m, 4H), 1.54–1.42 (m, 20H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.6, 172.0, 156.19, 156.15, 79.3, 79.2, 39.8, 36.7, 36.4, 35.9, 35.8, 29.62, 29.58, 29.5, 28.39, 28.37, 22.7; HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{41}N_4O_6$ $[M+H]^+$ 445.3021, found 445.3013.

Synthesis of **28c**



*tert-Butyl (2,2-dimethyl-4,8,15-trioxo-3-oxa-5,9,14-triazaoctadecan-18-yl)carbamate (**28c**)*. A mixture of amine **27b** (543 mg, 2.0 mmol), *N*-Boc-β-alanine (**21a**) (566 mg, 3.0 mmol), EDC·HCl (575 mg, 3.0 mmol), and DMAP (24 mg, 0.2 mmol) in DMF (10 mL) was stirred at 50 °C for 3 h. After cooling in an ice bath, 5% aqueous $NaHCO_3$ (30 mL) was added, stirred for 10 min at the same temperature, and the precipitate was collected by filtration using a Kiriyama funnel and washed with hexane/ethyl acetate (10:1). The resulting colorless solid **28c** (847 mg, 95.3%) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77–6.68 (m, 2H), 5.36 (br s, 1H), 5.05 (br s, 1H), 3.36–3.10 (m, 8H), 2.41–2.13 (m, 4H), 1.81–1.70 (m, 2H), 1.54–1.32 (m, 22H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.9, 171.7, 156.5, 156.2, 79.2 (2C), 39.7, 38.9 (2C), 36.8, 36.2, 33.5 (2C), 28.3, 26.8, 26.6, 26.4; HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{41}N_4O_6$ $[M+H]^+$ 445.3021, found 445.3013.

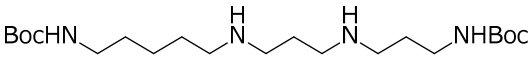
Synthesis of **29a**



*tert-Butyl (2,2-dimethyl-4-oxo-3-oxa-5,10,14-triazaheptadecan-17-yl)carbamate (**29a**)*. A 3.6 M solution of Red-Al in toluene (5.0 mL, 18 mmol) was slowly added to a solution of diamide **28a** (431 mg, 1.0 mmol) in toluene/THF (2:1, 10 mL) at 0 °C. The reaction mixture was stirred at 40 °C for 3 h. After cooling to 0 °C, 1 M aqueous NaOH (10 mL) was added slowly. The mixture was stirred for 5

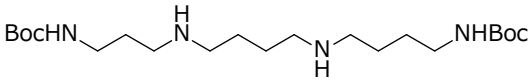
min and extracted with toluene (20 mL). The organic layer was washed with H_2O (10 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting colorless solid (353 mg, 87.6%) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.25 (br s, 1H), 5.04 (br s, 1H), 3.12–3.00 (m, 4H), 2.58–2.50 (m, 8H), 1.60–1.52 (m, 4H), 1.43–1.34 (m, 22H); NH protons (2H) were not observed; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 155.94, 155.89, 78.6 (2C), 49.4, 48.21, 48.19, 47.6, 40.3, 39.0, 30.1, 29.8, 28.3 (2C), 27.7, 27.3; HRMS (ESI-TOF) *m/z* calcd for $C_{20}H_{43}N_4O_4$ $[M+H]^+$ 403.3279, found 403.3272.

Synthesis of **29b**



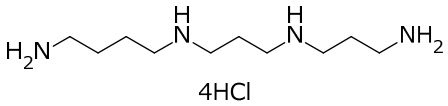
*tert-butyl (2,2-dimethyl-4-oxo-3-oxa-5,9,13-triazaoctadecan-18-yl)carbamate (**29b**)*. A 3.6 M solution of Red-Al in toluene (5.0 mL, 18 mmol) was slowly added to a solution of diamide **28b** (445 mg, 1.0 mmol) in toluene/THF (2:1, 20 mL) at 0 °C. The reaction mixture was stirred at 40 °C for 3 h. After cooling to 0 °C, 1 M aqueous NaOH (10 mL) was added slowly. The mixture was stirred for 5 min and extracted with toluene (20 mL). The organic layer was washed with H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting colorless solid (395 mg, 94.9%) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19 (br s, 1H), 4.66 (br s, 1H), 3.15–3.06 (m, 4H), 2.63–2.50 (m, 8H), 1.69–1.51 (m, 4H), 1.45–1.33 (m, 24H); NH protons (2H) were not observed; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.1, 156.0, 78.9, 78.8, 49.8, 48.3 (2C), 47.6, 40.4, 39.1, 30.2, 29.9 (2C), 29.6, 28.4 (2C), 24.5; HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{45}N_4O_4$ $[M+H]^+$ 417.3435, found 417.3428.

Synthesis of **29c**



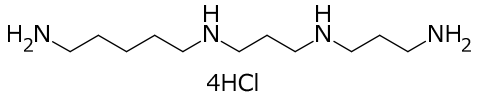
*tert-butyl (2,2-dimethyl-4-oxo-3-oxa-5,9,14-triazaoctadecan-18-yl)carbamate (**29c**)*. A 3.6 M solution of Red-Al in toluene (7.5 mL, 27 mmol) was slowly added to a solution of diamide **28c** (667 mg, 1.5 mmol) in toluene/THF (2:1, 20 mL) at 0 °C. The reaction mixture was stirred at 40 °C for 3 h. After cooling to 0 °C, 1 M aqueous NaOH (10 mL) was added slowly. The mixture was stirred for 5 min and extracted with toluene (20 mL). The organic layer was washed with H_2O (10 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting colorless solid (595 mg, 95.2%) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.19 (br s, 1H), 4.94 (br s, 1H), 3.62–3.60 (m, 1H), 3.24–3.23 (m, 1H), 3.18–3.07 (m, 4H), 2.64–2.54 (m, 8H), 1.64–1.56 (m, 2H), 1.48–1.46 (m, 8H), 1.40 (m, 18H); NH protons (2H) were not observed; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.04, 155.98, 78.8 (2C), 49.8, 49.7, 49.5, 47.7, 40.4, 39.2, 32.8, 29.9, 28.4, 28.3, 27.83, 27.81, 27.4; HRMS (ESI-TOF) *m/z* calcd for $C_{21}H_{45}N_4O_4$ $[M+H]^+$ 417.3435, found 417.3436.

Synthesis of **11**



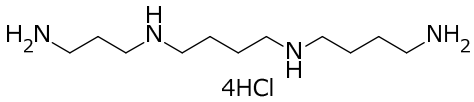
*Thermospermine tetrahydrochloride (**11**).* A 4.0 M solution of HCl in 1,4-dioxane (1.0 mL, 4.0 mmol) was added to a solution of the di-Boc compound **29a** (242 mg, 0.6 mmol) in 1,4-dioxane (5.0 mL) at 0 °C. The reaction mixture was stirred at 50 °C for 3 h. After removal of the solvent under reduced pressure, the crude residue was recrystallized from MeOH to afford a colorless solid **11** (134 mg, 64.0%). ^{1}H NMR (400 MHz, D_2O) δ 3.22–3.03 (m, 12H), 2.18–2.07 (m, 4H), 1.84–1.72 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, D_2O) δ 47.1, 44.7, 44.6, 44.5, 38.8, 36.6, 23.9, 23.8, 22.8, 22.7; HRMS (ESI-TOF) *m/z* calcd for $C_{10}H_{27}N_4$ $[M+H]^+$ 203.2230, found 203.2231.

Synthesis of **12**



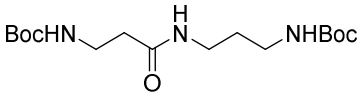
*Aminopentylnorspermidine tetrahydrochloride (**12**).* A 4.0 M solution of HCl in 1,4-dioxane (1.0 mL, 4.0 mmol) was added to a solution of the di-Boc compound **29b** (250 mg, 0.6 mmol) in 1,4-dioxane (5.0 mL) at 0 °C. The reaction mixture was stirred at 50 °C for 3 h. After removal of the solvent under reduced pressure, the crude residue was recrystallized from MeOH to afford a colorless solid **12** (161 mg, 74.1%). ^{1}H NMR (400 MHz, D_2O) δ 3.21–2.99 (m, 12H), 2.17–2.07 (m, 4H), 1.78–1.68 (m, 4H), 1.50–1.43 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, D_2O) δ 47.5, 44.73, 44.65, 44.4, 39.2, 36.5, 26.3, 25.1, 23.8, 22.8, 22.7; HRMS (ESI-TOF) *m/z* calcd for $C_{11}H_{29}N_4$ $[M+H]^+$ 217.2387, found 217.2386.

Synthesis of **13**



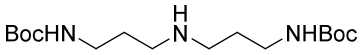
*Aminopropylhomospermidine tetrahydrochloride (**13**).* A 4.0 M solution of HCl in 1,4-dioxane (1.5 mL, 6.0 mmol) was added to a solution of the di-Boc compound **29c** (417 mg, 0.6 mmol) in 1,4-dioxane (10.0 mL) at 0 °C. The reaction mixture was stirred at 50 °C for 3 h. After removal of the solvent under reduced pressure, the crude residue was recrystallized from MeOH to afford a colorless solid **13** (304 mg, 83.8%). ^{1}H NMR (400 MHz, D_2O) δ 3.19–3.03 (m, 12H), 2.14–2.06 (m, 2H), 1.83–1.70 (m, 8H); ^{13}C{^{1}H} NMR (100 MHz, D_2O) δ 47.0, 46.93, 46.86, 44.6, 38.8, 36.6, 23.9, 23.8, 22.80, 22.78, 22.76; HRMS (ESI-TOF) *m/z* calcd for $C_{11}H_{29}N_4$ $[M+H]^+$ 217.2387, found 217.2389.

Synthesis of **31**



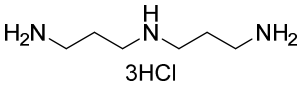
*tert-butyl (3-((3-((tert-butoxycarbonyl)amino)propyl)amino)-3-oxopropyl)carbamate (**31**)*. A mixture of *N*-Boc-propane-1,3-diamine (**30**) (174 mg, 1.0 mmol), *N*-Boc-β-alanine (**21a**) (227 mg, 1.2 mmol), EDC·HCl (230 mg, 1.2 mmol), and DMAP (12 mg, 0.1 mmol) in DMF (5.0 mL) was stirred at 50 °C for 3 h. After cooling in an ice bath, 5% aqueous $NaHCO_3$ (20 mL) was added, stirred for 10 min at the same temperature, and the precipitate was collected by filtration using a Kiriyama funnel and washed with hexane/ethyl acetate (10:1). The resulting colorless solid **31** (332 mg, 96.0%) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (br s, 1H), 5.29 (br s, 1H), 5.00 (br s, 1H), 3.38 (dd, *J* = 12.0, 6.0 Hz, 2H), 3.27 (dd, *J* = 12.4, 6.0 Hz, 2H), 3.14 (dd, *J* = 12.0, 6.0 Hz, 2H), 2.39 (t, *J* = 6.0 Hz, 2H), 1.62–1.56 (m, 2H), 1.42 (s, 9H), 1.41 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 171.7, 156.6, 156.1, 79.4, 79.2, 37.0, 36.7, 36.2, 35.8, 30.1, 28.3 (2C); HRMS (ESI-TOF) *m/z* calcd for $C_{16}H_{32}N_3O_5$ $[M+H]^+$ 346.2337, found 346.2345.

Synthesis of **32**



*di-tert-butyl (azanediylbis(propane-1,3-diyl))dicarbamate (**32**)*. A 3.6 M solution of Red-Al in toluene (1.5 mL, 5.4 mmol) was slowly added to a solution of amide **31** (345 mg, 4.0 mmol) in toluene/THF (2:1, 15 mL) at 0 °C. The reaction mixture was stirred at 40 °C for 3 h. After cooling to 0 °C, 1 M aqueous NaOH (10 mL) was added slowly. The mixture was stirred for 5 min and extracted with toluene (20 mL). The organic layer was washed with H_2O (10 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting colorless solid **32** (312 mg, 94.2%) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (br s, 2H), 3.13–3.06 (m, 4H), 2.53 (t, *J* = 6.4 Hz, 4H), 1.57–1.48 (m, 4H), 1.48 (s, 18H); NH proton (1H) was not observed; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.0, 78.6, 47.1, 38.6, 29.5, 28.2; HRMS (ESI-TOF) *m/z* calcd for $C_{16}H_{34}N_3O_4$ $[M+H]^+$ 332.2544, found 332.2547.

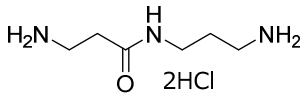
Synthesis of **1**



*Norspermidine trihydrochloride (**1**)*. A 4.0 M solution of HCl in 1,4-dioxane (1.0 mL, 4.0 mmol) was added to a solution of the di-Boc compound **32** (265 mg, 0.8 mmol) in 1,4-dioxane (3.0 mL) at 0 °C. The reaction mixture was stirred at 50 °C for 2 h. After removal of the solvent under reduced pressure, the crude residue was recrystallized from MeOH/iPrOH to afford a colorless solid **1** (111 mg, 71.9%). ^{1}H NMR (400 MHz, D_2O) δ 3.10–2.90 (m, 8H), 2.12–1.88 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, D_2O)

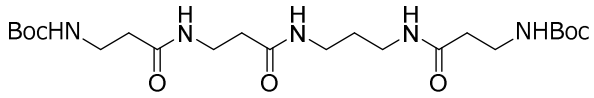
δ 44.6, 36.5, 23.7; HRMS (ESI-TOF) *m/z* calcd for $C_6H_{18}N_3$ $[M+H]^+$ 132.1495, found 132.1492.

Synthesis of **33**



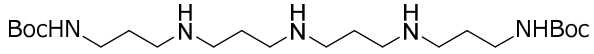
*3-amino-N-(3-aminopropyl)propanamide dihydrochloride (**33**)*. A 4.0 M solution of HCl in 1,4-dioxane (3.0 mL, 12.0 mmol) was added to a solution of the di-Boc compound **31** (1038 mg, 3.0 mmol) in 1,4-dioxane (3.0 mL) at 0 °C. The reaction mixture was stirred at 50 °C for 2 h. After removal of the solvent under reduced pressure. The resulting colorless solid **33** (648 mg, 99.1%) was used in the next step without further purification. ^{1}H NMR (400 MHz, D_2O) δ 3.31 (t, *J* = 6.8 Hz, 2H), 3.27 (t, *J* = 6.8 Hz, 2H), 3.01 (t, *J* = 7.6 Hz, 2H), 2.68 (t, *J* = 6.8 Hz, 2H), 1.91–1.84 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, D_2O) δ 172.5, 37.0, 36.1, 35.7, 31.9, 26.6; HRMS (ESI-TOF) *m/z* calcd for $C_6H_{16}N_3O$ $[M+H]^+$ 146.1288, found 146.1285.

Synthesis of **34**



*tert-butyl (2,2-dimethyl-4,8,12,18-tetraoxo-3-oxa-5,9,13,17-tetraazaicosan-20-yl)carbamate (**34**)*. A mixture of diamine (**33**) (218 mg, 1.0 mmol), *N*-Boc-β-alanine (**21a**) (454 mg, 2.4 mmol), EDC·HCl (460 mg, 2.4 mmol), and DMAP (12 mg, 0.1 mmol) in DMF (10 mL) and Et_3N (0.35 mL, 2.5 mmol) was stirred at 50 °C for 3 h. After cooling in an ice bath, 5% aqueous $NaHCO_3$ (20 mL) was added, stirred for 10 min at the same temperature, and the precipitate was collected by filtration using a Kiriyama funnel and washed with hexane/ethyl acetate (10:1). The resulting colorless solid **34** (410 mg, 84.1%) was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.92–7.85 (m, 3H), 6.78–6.75 (m, 2H), 3.22–3.03 (m, 10H), 2.22–2.19 (m, 6H), 1.52–1.49 (m, 2H), 1.37 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-*d6*) δ 170.31 (2C), 170.27, 155.5 (2C), 77.6 (2C), 36.81, 36.78, 36.2 (2C), 35.9, 35.8, 35.5, 35.3, 29.1, 28.3 (2C); HRMS (ESI-TOF) *m/z* calcd for $C_{22}H_{42}N_5O_7$ $[M+H]^+$ 488.3079, found 488.3071.

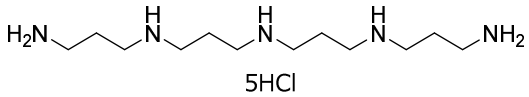
Synthesis of **35**



*di-tert-butyl (((azanediylbis(propane-3,1-diyl))bis(azanediyl))bis(propane-3,1-diyl))dicarbamate (**35**)*. A 3.6 M solution of Red-Al in toluene (2.8 mL, 10.1 mmol) was slowly added to a solution of amide **34** (322 mg, 0.66 mmol) in toluene/THF (2:1, 15 mL) at 0 °C. The reaction mixture was stirred at 40 °C for 3 h. After cooling to 0 °C, 1 M aqueous NaOH (10 mL) was added slowly. The mixture was

stirred for 5 min and extracted with CH_2Cl_2 (20 mL×2). The organic layer was washed with H_2O (10 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting colorless solid **35** (232 mg, 79.1%) was used in the next step without further purification. ^{1}H NMR (400 MHz, CD_3OD) δ 3.09 (t, *J* = 6.4 Hz, 4H), 2.66–2.58 (m, 12H), 1.75–1.63 (m, 8H), 1.43 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 158.6, 79.9, 47.8, 39.1, 30.7, 29.9, 28.8; Two carbon signals overlap with the solvent signal; HRMS (ESI-TOF) *m/z* calcd for $C_{22}H_{48}N_5O_4$ $[M+H]^+$ 446.3701, found 446.3705.

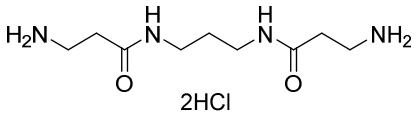
Synthesis of **14**



*Caldopentamine pentahydrochloride **(14)***. A 4.0 M solution of HCl in 1,4-dioxane (0.5 mL, 2.0 mmol) was added to a solution of the di-Boc compound **35** (265 mg, 0.4 mmol) in 1,4-dioxane (2.0 mL) at 0 °C. The reaction mixture was stirred at 50 °C for 2 h. After removal of the solvent under reduced pressure, the crude residue was recrystallized from EtOH/H_2O to afford a colorless solid **14** (110 mg, 64.3%). ^{1}H NMR (400 MHz, D_2O) δ 3.20–3.08 (m, 16H), 2.16–2.05 (m, 8H); ^{13}C{^{1}H} NMR (100 MHz, D_2O) δ 44.7, 44.6, 44.5, 36.5, 23.7, 22.6; HRMS (ESI-TOF) *m/z* calcd for $C_{12}H_{32}N_5$ $[M+H]^+$ 246.2652, found 246.2657.

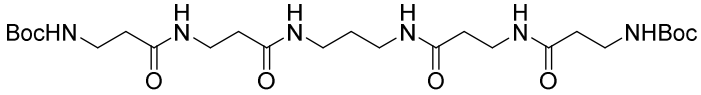
The ^{1}H NMR (400 MHz, D_2O) and ^{13}C NMR (100 MHz, D_2O) data of caldopentamine pentahydrochloride were in good agreement with those reported in the literature (ref. 49).

Synthesis of **36**



*N,N'-(propane-1,3-diyl)bis(3-aminopropanamide) dihydrochloride **(36)***. A 4.0 M solution of HCl in 1,4-dioxane (1.5 mL, 6.0 mmol) was added to a solution of the di-Boc compound **23a** (416 mg, 1.0 mmol) in 1,4-dioxane (10 mL) at 0 °C. The reaction mixture was stirred at 50 °C for 3 h. After removal of the solvent under reduced pressure, the resulting colorless solid **36** (281 mg, 97.2%) was used in the next step without further purification. ^{1}H NMR (400 MHz, D_2O) δ 3.28–3.15 (m, 8H), 2.61 (t, *J* = 6.4 Hz, 4H), 1.70–1.63 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, D_2O) δ 172.0, 36.5, 35.7, 32.0, 27.7; HRMS (ESI-TOF) *m/z* calcd for $C_9H_{20}N_4O_2$ $[M+H]^+$ 217.1659, found 217.1656.

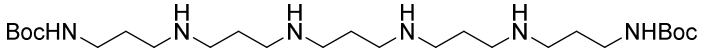
Synthesis of **37**



*di-tert-butyl (3,7,13,17-tetraoxo-4,8,12,16-tetraazanonadecane-1,19-diyl)dicarbamate **(37)***. A

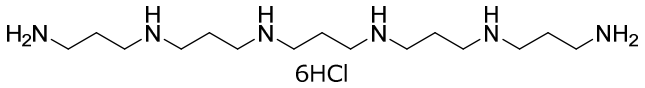
mixture of diamine (**36**) (578 mg, 2.0 mmol), *N*-Boc-β-alanine (**21a**) (1135 mg, 6.0 mmol), EDC·HCl (1150 mg, 6.0 mmol), and DMAP (24 mg, 0.2 mmol) in EtOH (12 mL) and 1 M aqueous NaOH (6.0 mL, 6.0 mmol) was stirred at 50 °C for 12 h. After removal of the EtOH under reduced pressure, and the precipitate was collected by filtration using a Kiriyama funnel and washed with H_2O and hexane/ethyl acetate (10:1). The resulting colorless solid **37** (969 mg, 86.7%) was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.91–7.83 (m, 4H), 6.75–6.72 (m, 2H), 3.24–3.20 (m, 4H), 3.13–3.02 (m, 8H), 2.23–2.18 (m, 8H), 1.55–1.48 (m, 2H), 1.37 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-*d6*) δ 170.3 (2C), 155.4, 77.6, 36.7, 36.1, 35.7, 35.5, 35.3, 29.1, 28.2; HRMS (ESI-TOF) *m/z* calcd for $C_{25}H_{47}N_6O_8$ $[M+H]^+$ 559.3450, found 559.3455.

Synthesis of **38**



*di-tert-butyl (4,8,12,16-tetraazanonadecane-1,19-diyl)dicarbamate (**38**)*. A 3.6 M solution of Red-Al in toluene (5.6 mL, 20.2 mmol) was slowly added to a solution of amide **37** (559 mg, 1.0 mmol) in toluene/THF (2:1, 20 mL) at 0 °C. The reaction mixture was stirred at 40 °C for 5 h. After cooling to 0 °C, 1 M aqueous NaOH (10 mL) was added slowly. The mixture was stirred for 5 min and extracted with CH_2Cl_2 (20 mL×2). The organic layer was washed with H_2O (10 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting colorless solid (374 mg, 74.4%) was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35–5.09 (m, 4H), 3.18–3.17 (m, 4H), 2.66–2.59 (m, 16H), 1.70–1.62 (m, 10H), 1.43 (s, 18H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.1, 79.0, 48.44, 48.36, 48.3, 47.7, 39.1, 30.2, 29.9, 28.4, 22.2; HRMS (ESI-TOF) *m/z* calcd for $C_{25}H_{55}N_6O_4$ $[M+H]^+$ 503.4279, found 503.4270.

Synthesis of **17**



*Caldohexamine hexahydrochloride (**17**)*. A 4.0 M solution of HCl in 1,4-dioxane (1.0 mL, 4.0 mmol) was added to a solution of the di-Boc compound **38** (251 mg, 0.50 mmol) in 1,4-dioxane (5.0 mL) at 0 °C. The reaction mixture was stirred at 50 °C for 3 h. After removal of the solvent under reduced pressure, the crude residue was recrystallized from EtOH/H_2O to afford a colorless solid **17** (143 mg, 54.8%). ^{1}H NMR (400 MHz, D_2O) δ 3.09–2.98 (m, 20H), 2.06–1.95 (m, 10H); ^{13}C{^{1}H} NMR (100 MHz, D_2O) δ 66.6, 44.7, 44.60 (2C), 44.58, 36.5, 23.7, 22.7; HRMS (ESI-TOF) *m/z* calcd for $C_{15}H_{39}N_6$ $[M+H]^+$ 303.3231, found 303.3221.

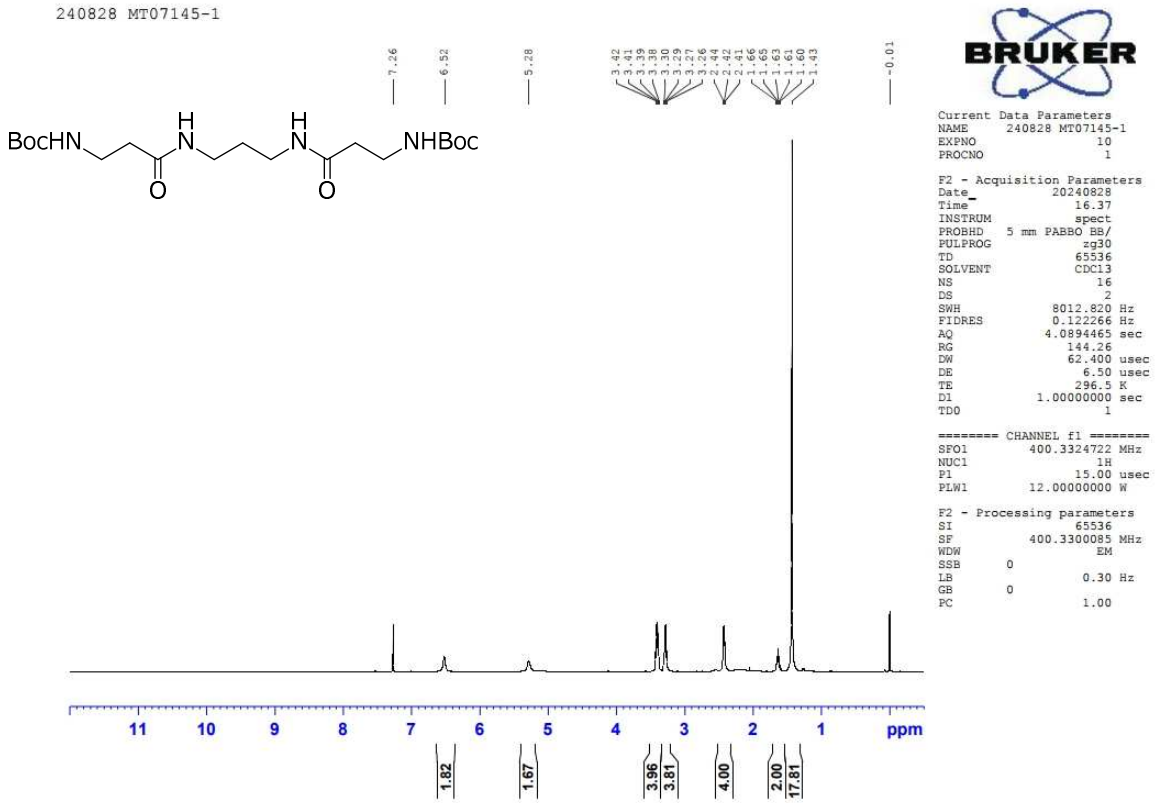
The ^{1}H NMR (400 MHz, D_2O) data of caldohexamine hexahydrochloride was in good agreement with those reported in the literature (ref. 49).

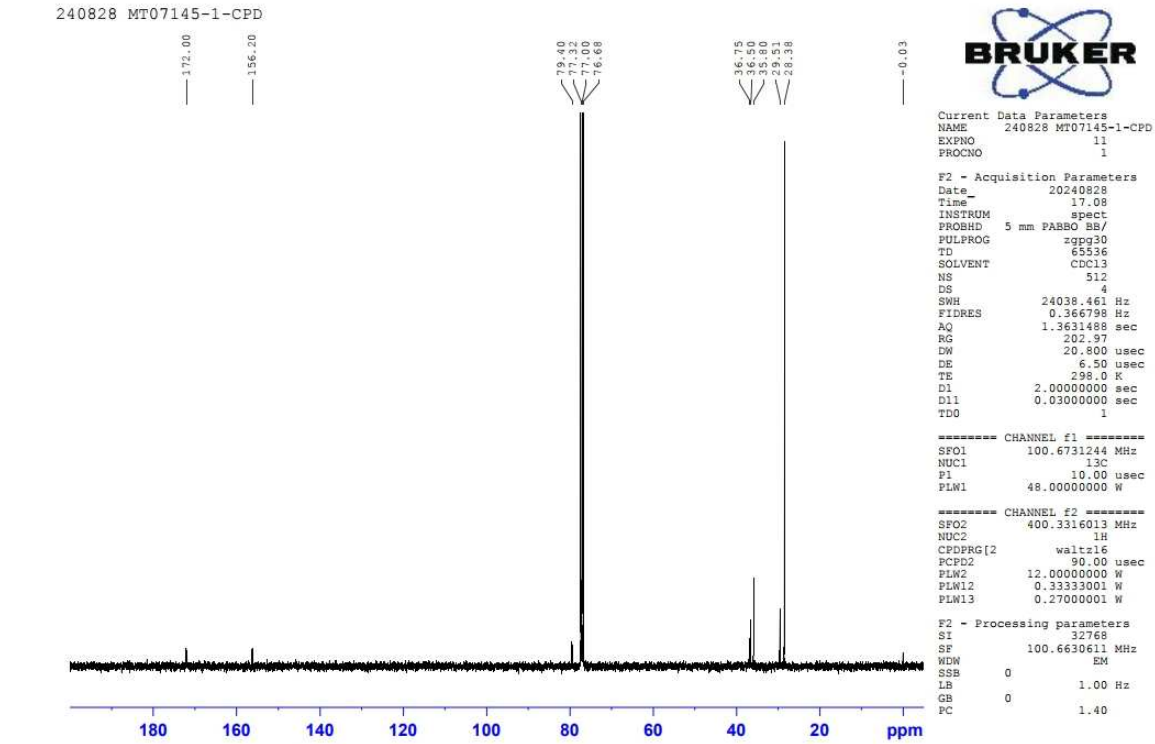
Table S1. Comparison of the present polyamine synthesis with previously reported methods.

Method	Key reagents / steps	Number of steps	purification	Notes
Niitsu, M. *et al*. (ref. 12)	Gabriel synthesis (phthalimide alkylation, hydrazinolysis)	**14**: 8 steps **15**: 7 steps	Column chromatography, recrystallisation	First chemical synthesis of compounds **14** and **15**; establishment of a series of ten pentaamines
Oshima, T. *et al*. (ref. 49)	Gabriel synthesis (phthalimide alkylation, hydrazinolysis)	**14**: 3 steps **17**: 10 steps	Column chromatography, recrystallisation	Compound **14** synthesized in 3 steps from commercially available compound **6**; costly starting material; compound **17** with synthetic route and ^{1}H NMR only
Kariya, Y. *et al*. (ref. 13)	Ns chemistry (nosyl-protected amines, reductive removal)	**6**,**7**: 5 steps **11**: 11 steps	Column chromatography, solid-phase final purification	High purity via solid-phase workflow; simple final purification
This work	EDC amidation and Red-Al reduction	**1**, **6**–**10**: 3 steps **11**–**14**, **17**: 5 steps	Recrystallisation	Chromatography-free synthesis; short and modular routes; first full characterization of compound **17**

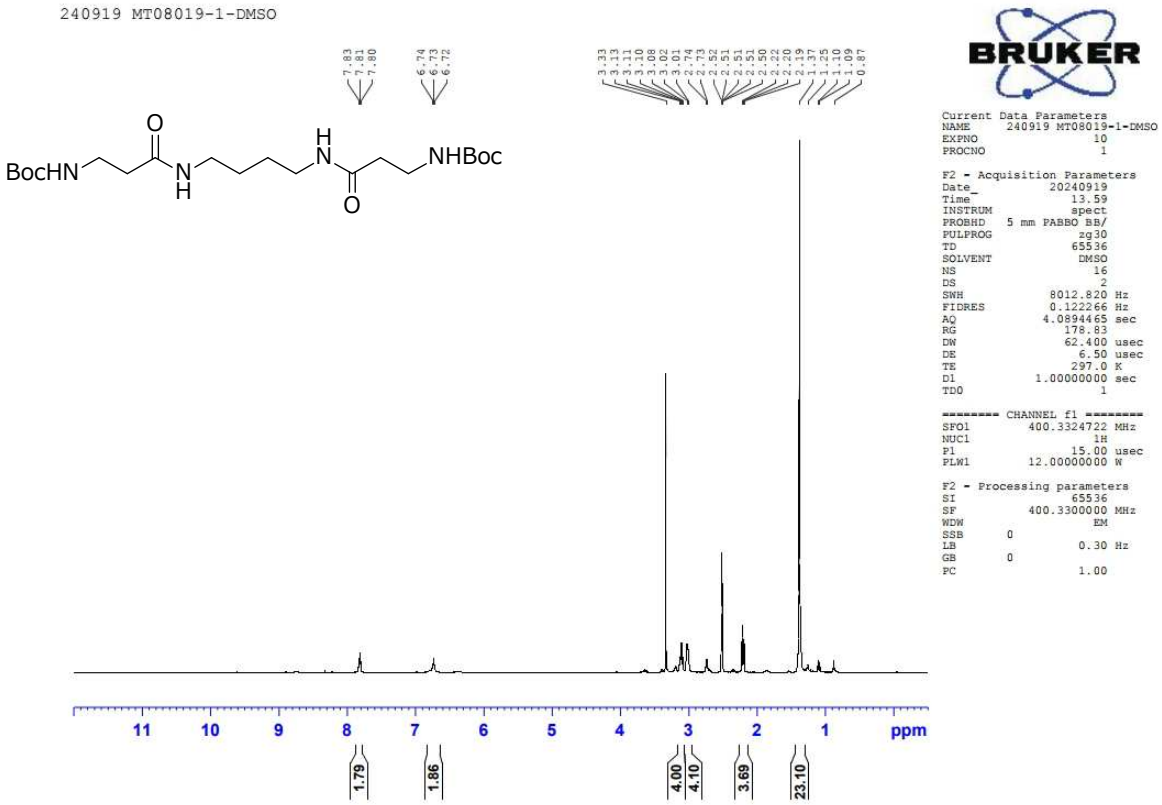
Compound names and numbers (same as in the main text): norspermidine (**1**); norspermine (**6**); spermine (**7**); bis(aminopropyl)cadaverine (**8**); canavalmine (**9**); homospermine (**10**); thermospermine (**11**); aminopentylnorspermidine (**12**); aminopropylhomospermidine (**13**); caldopentamine (**14**); homocaldopentamine (**15**); caldohexamine (**17**).

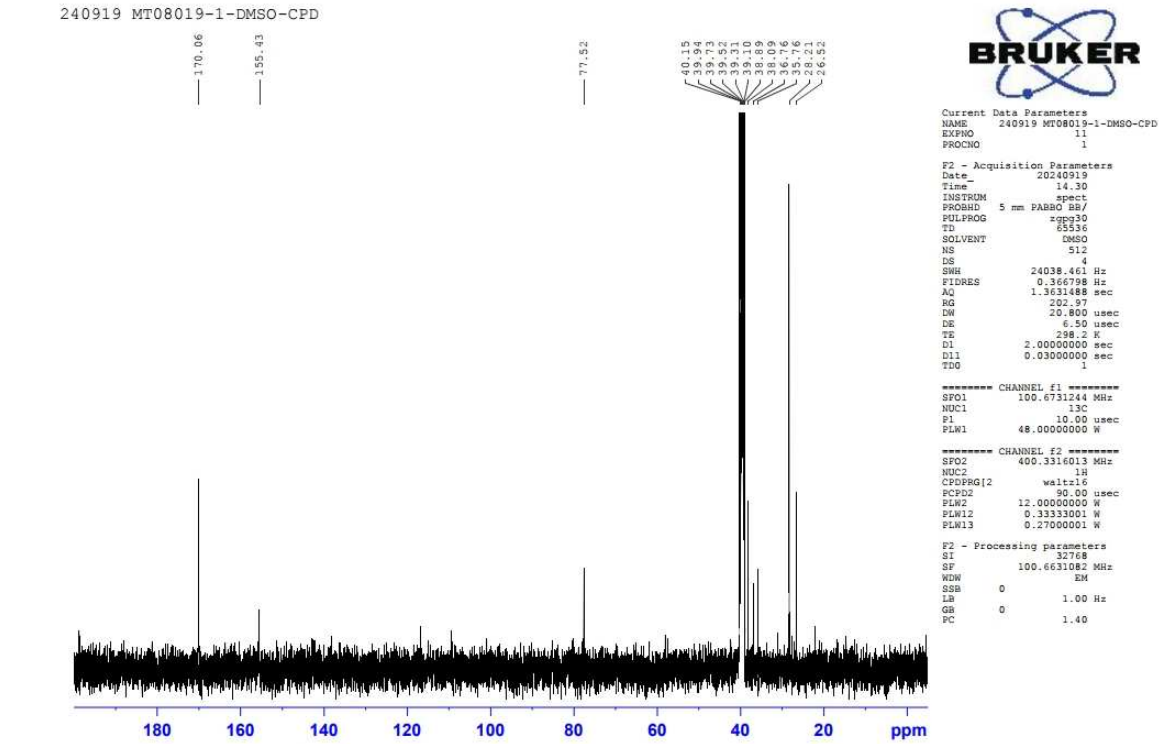
NMR chart of **23a**



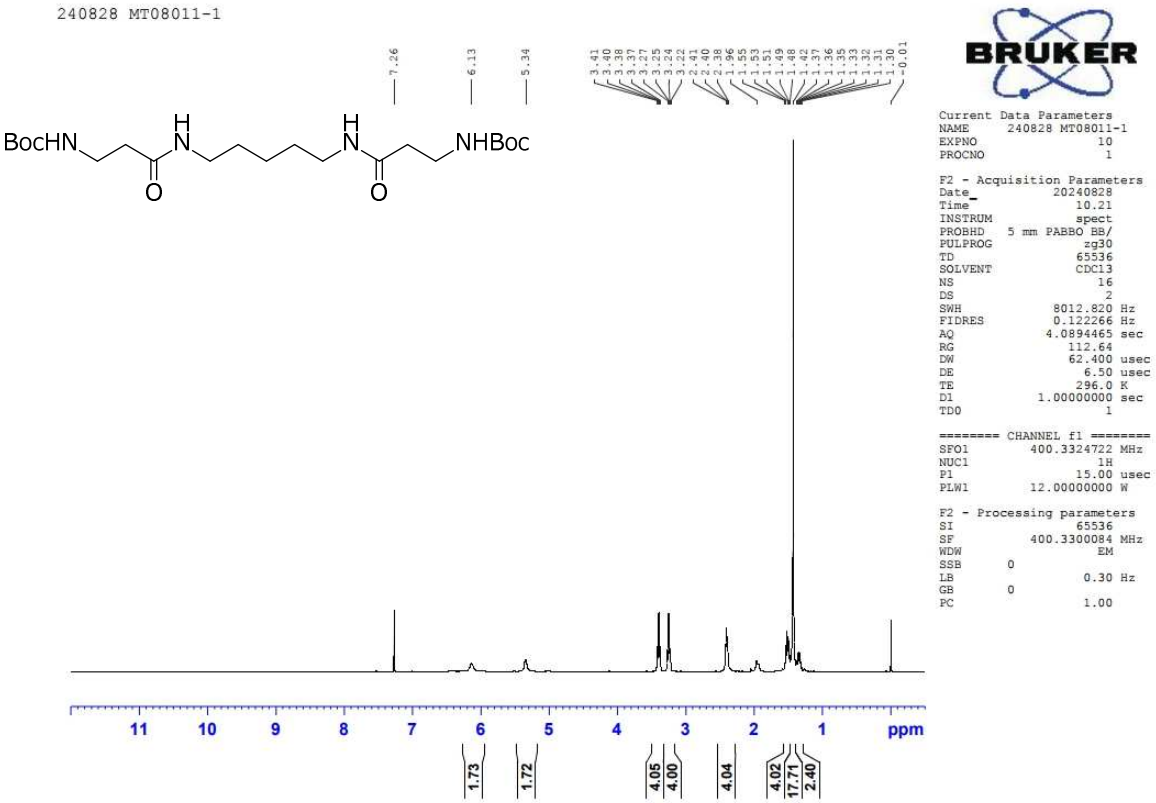


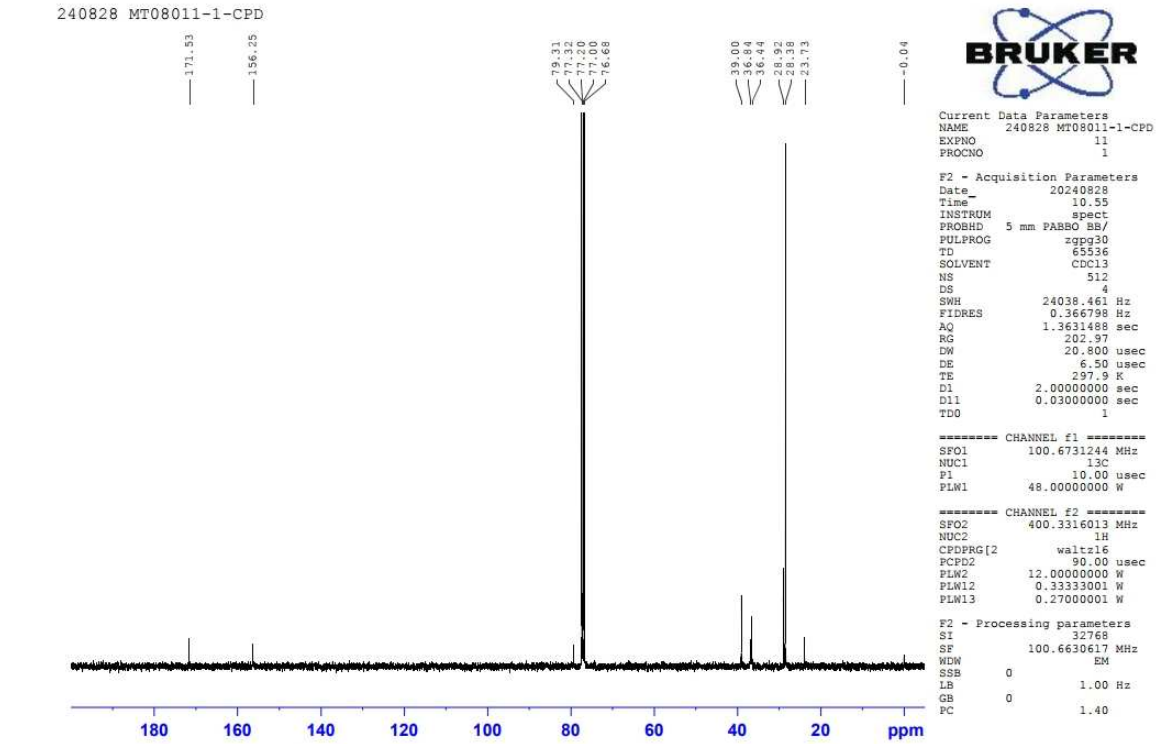
NMR chart of **23b**



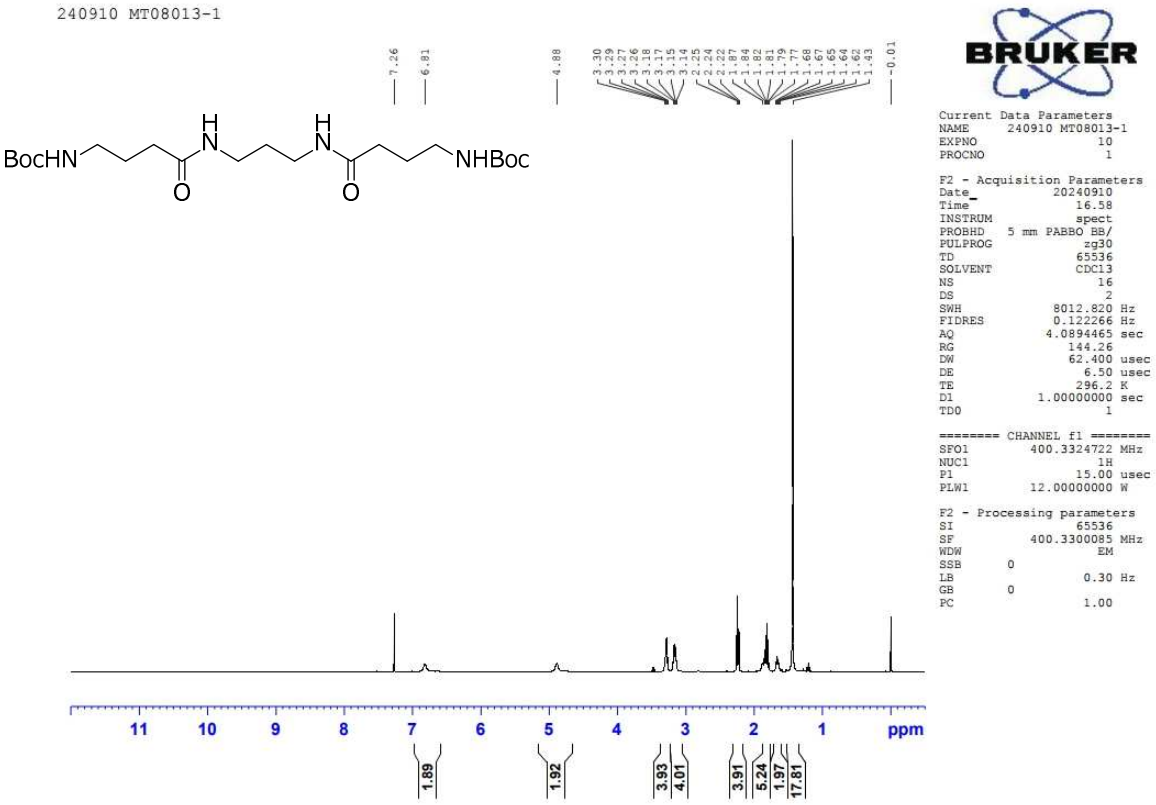


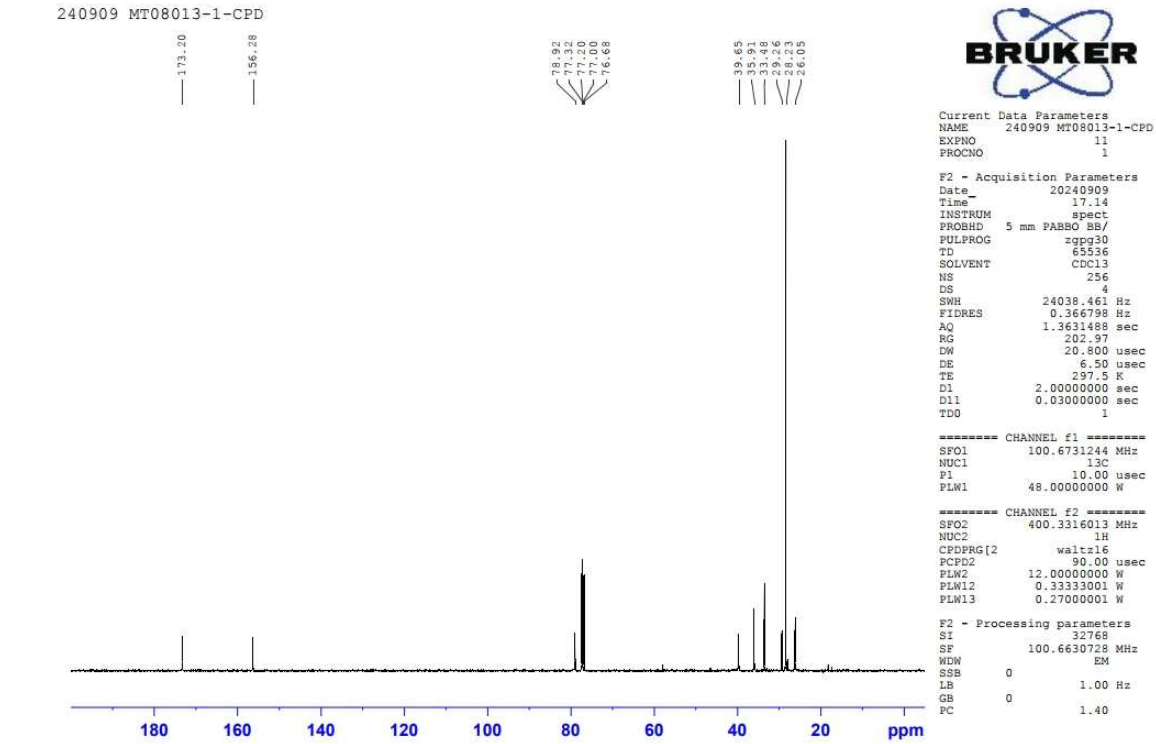
NMR chart of **23c**



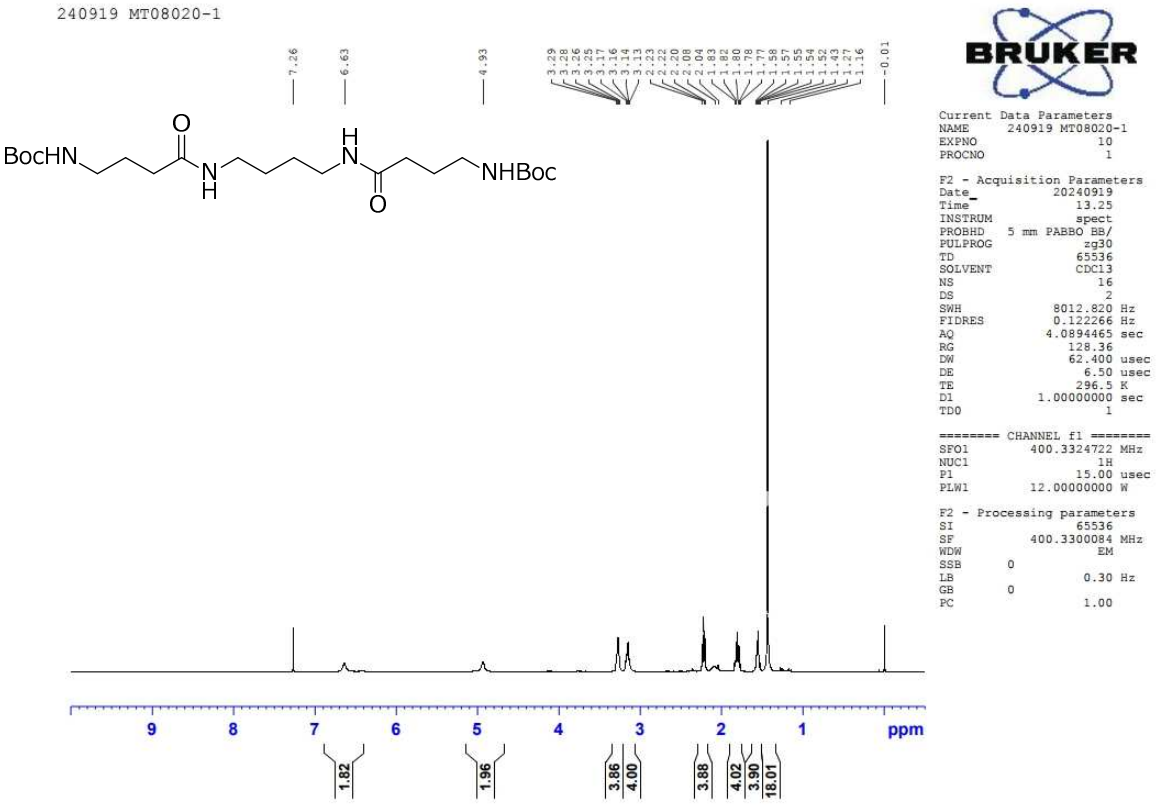


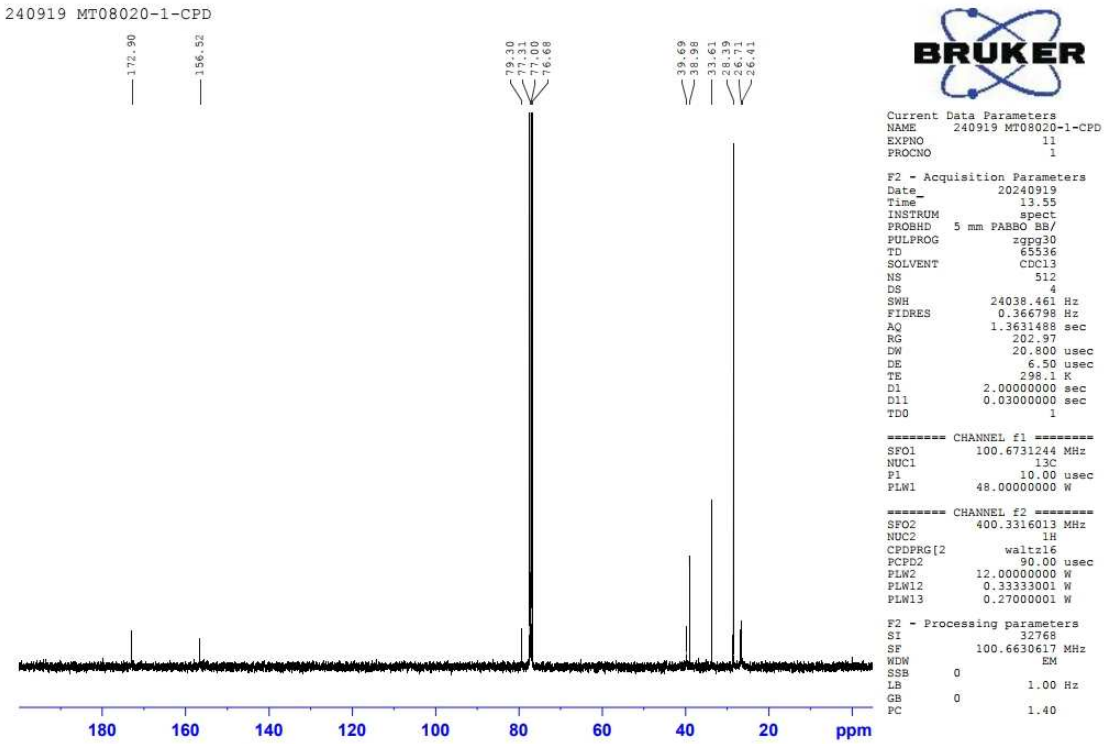
NMR chart of **23d**



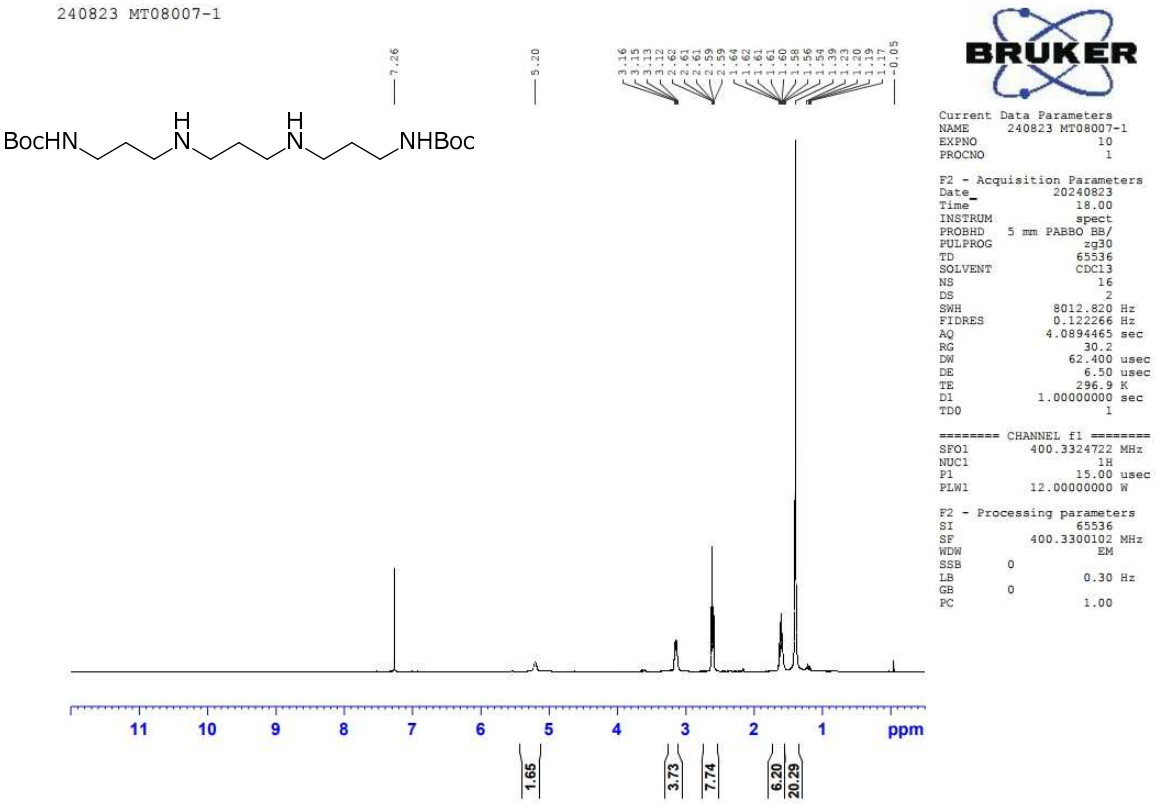


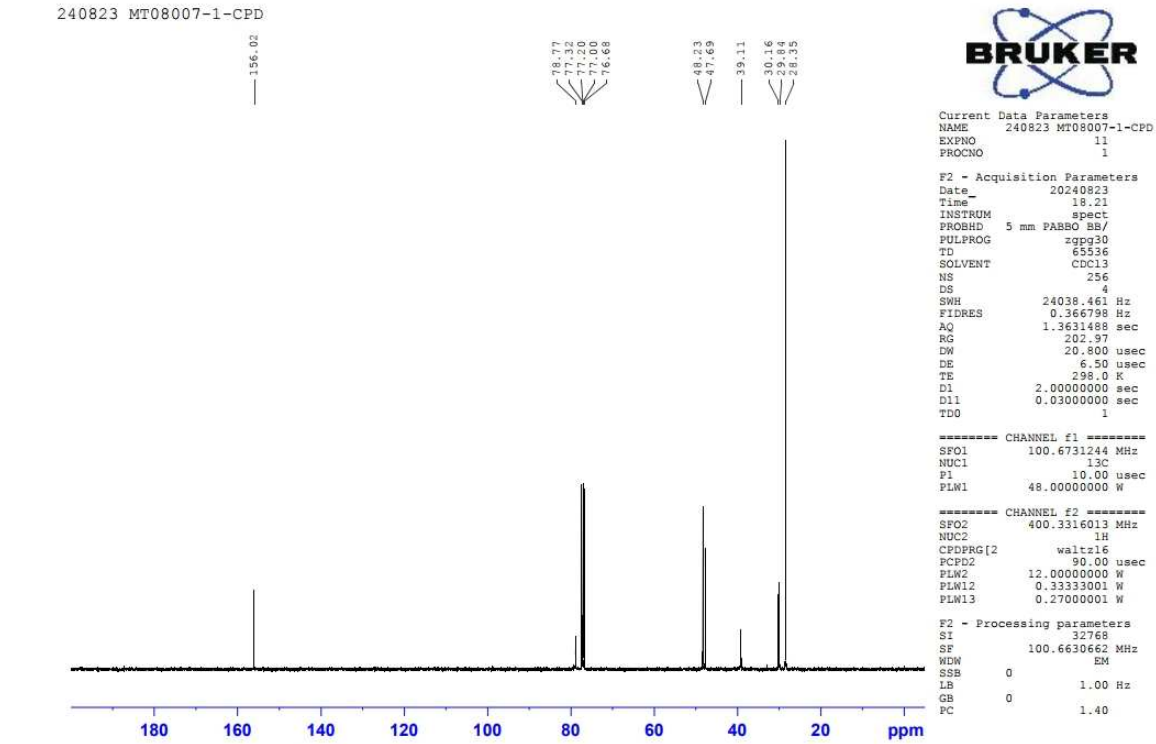
NMR chart of **23e**



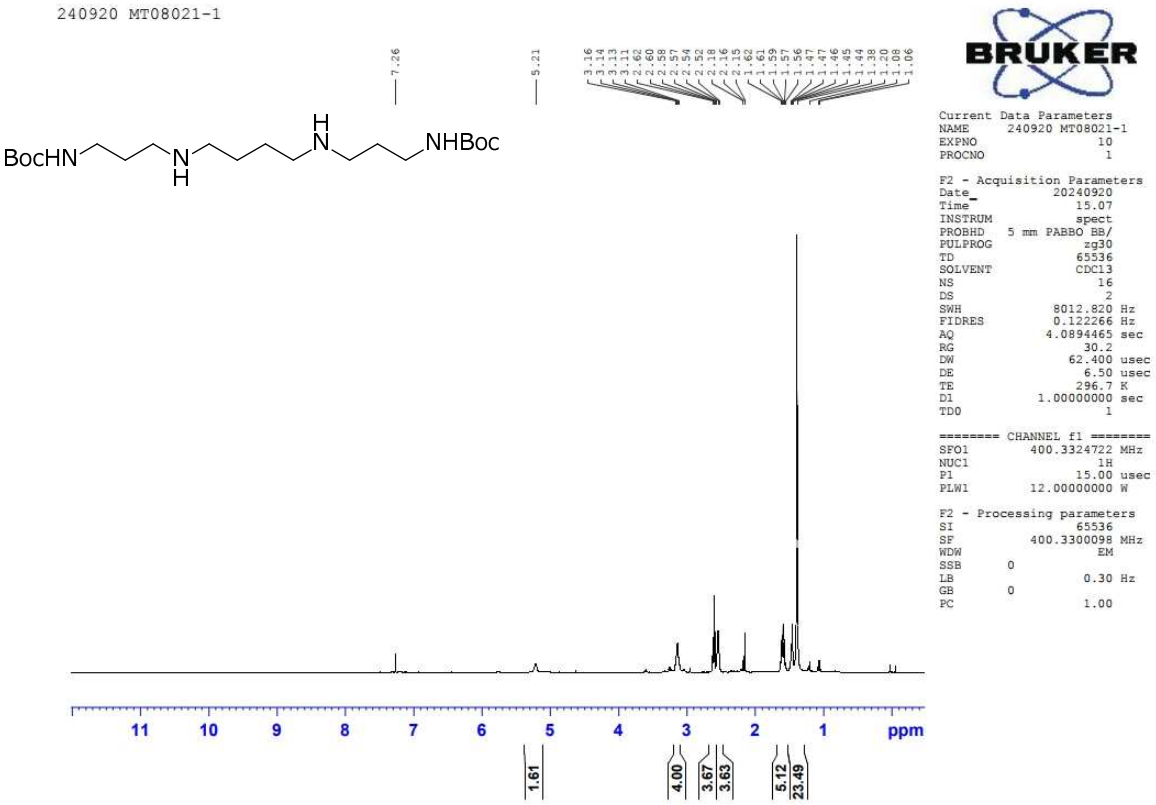


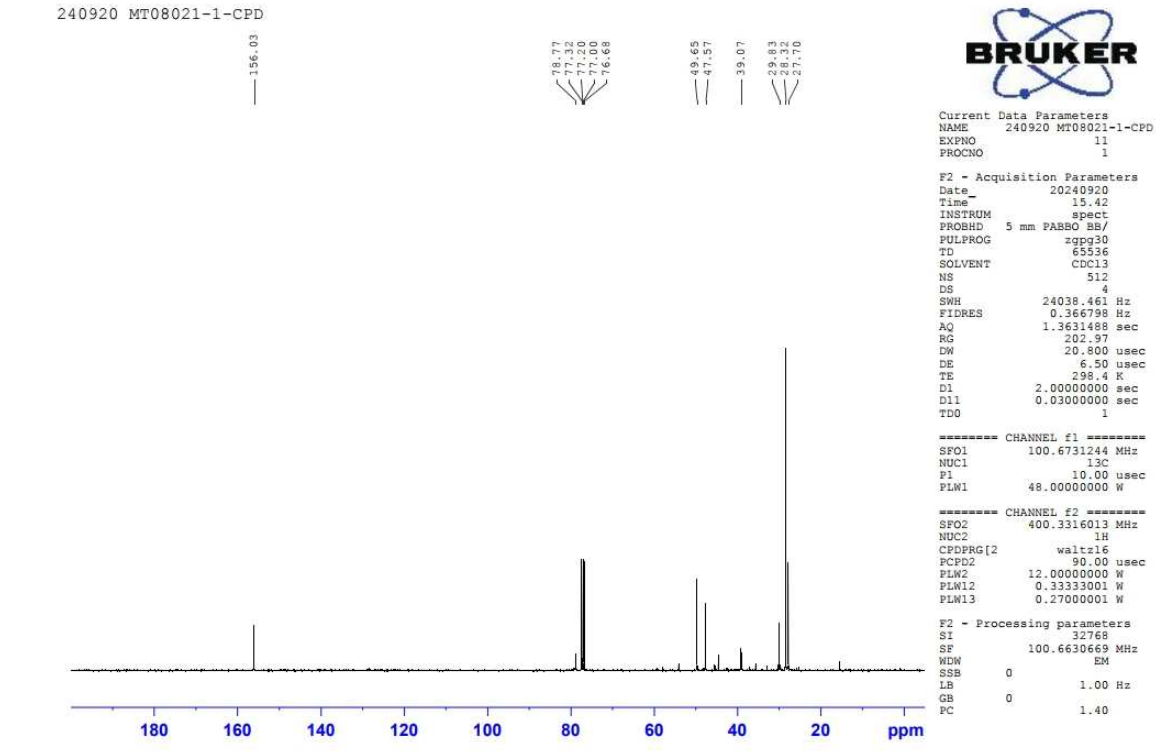
NMR chart of **24a**



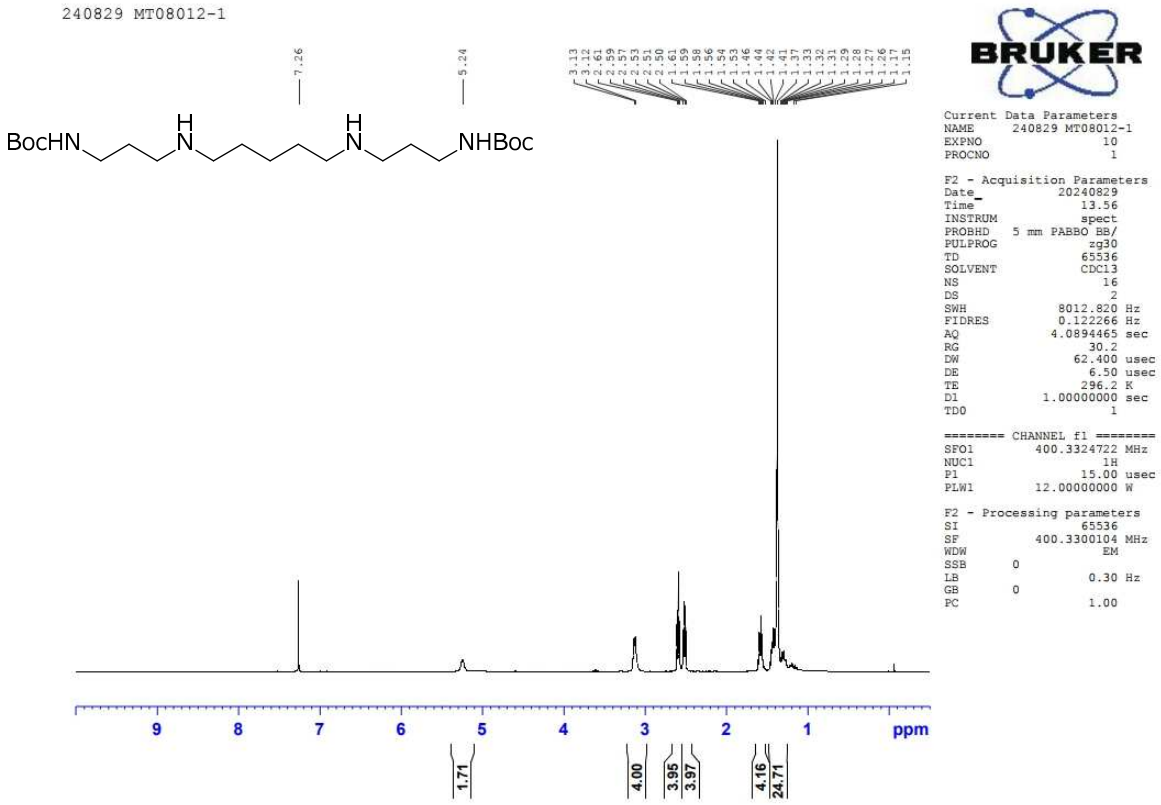


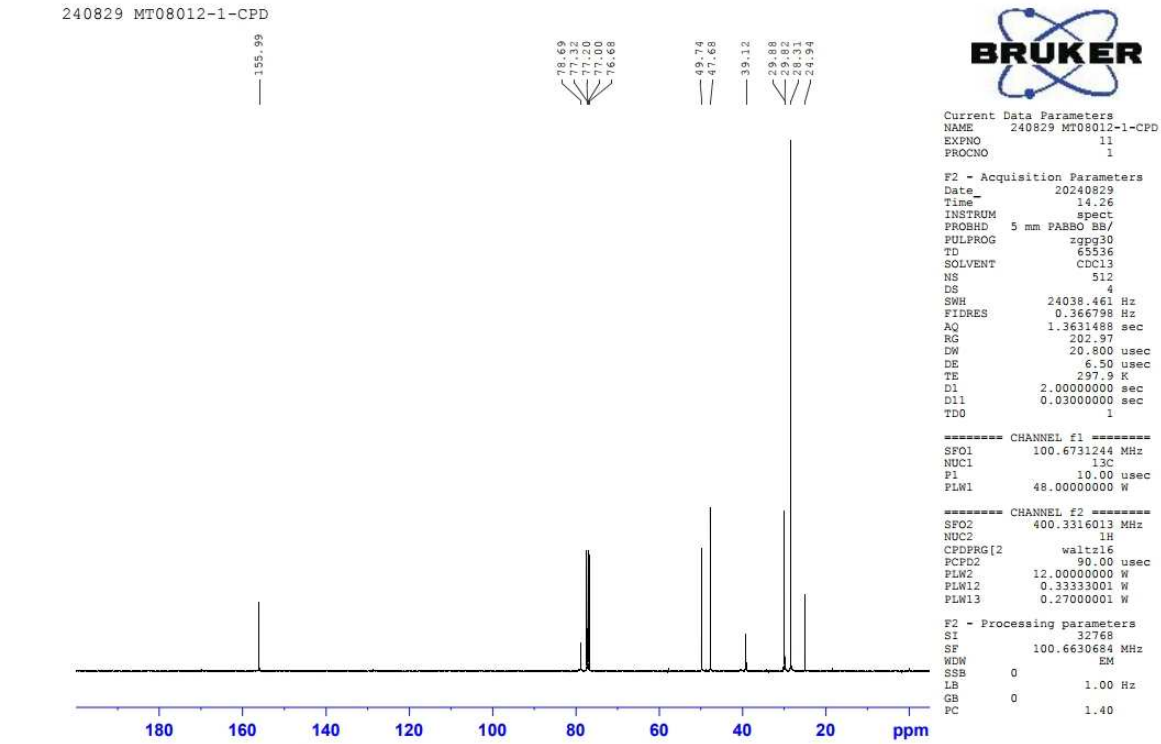
NMR chart of **24b**



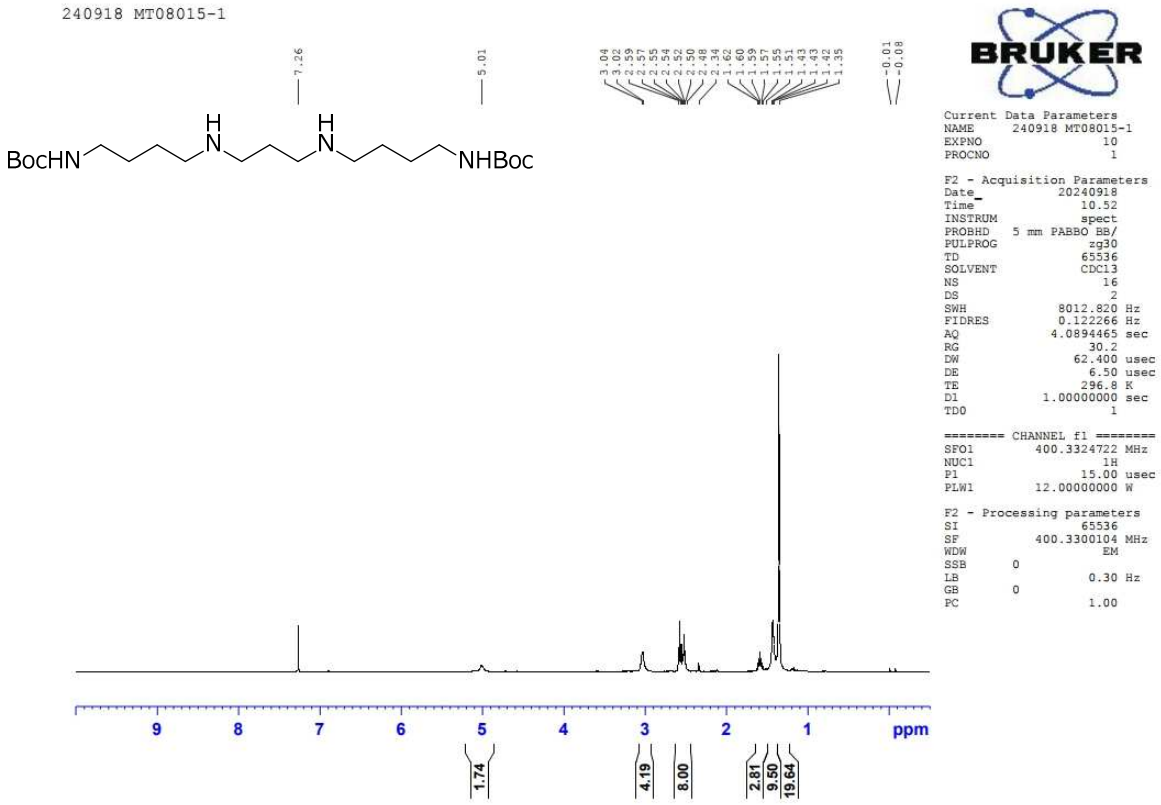


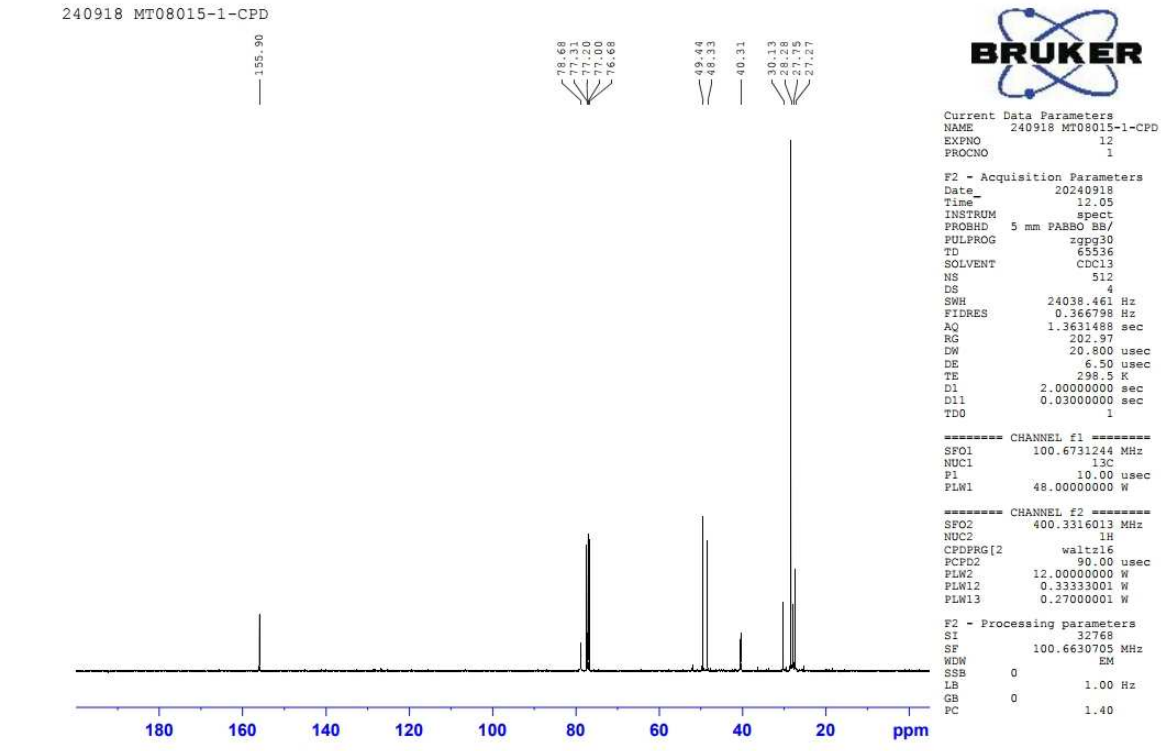
NMR chart of **24c**



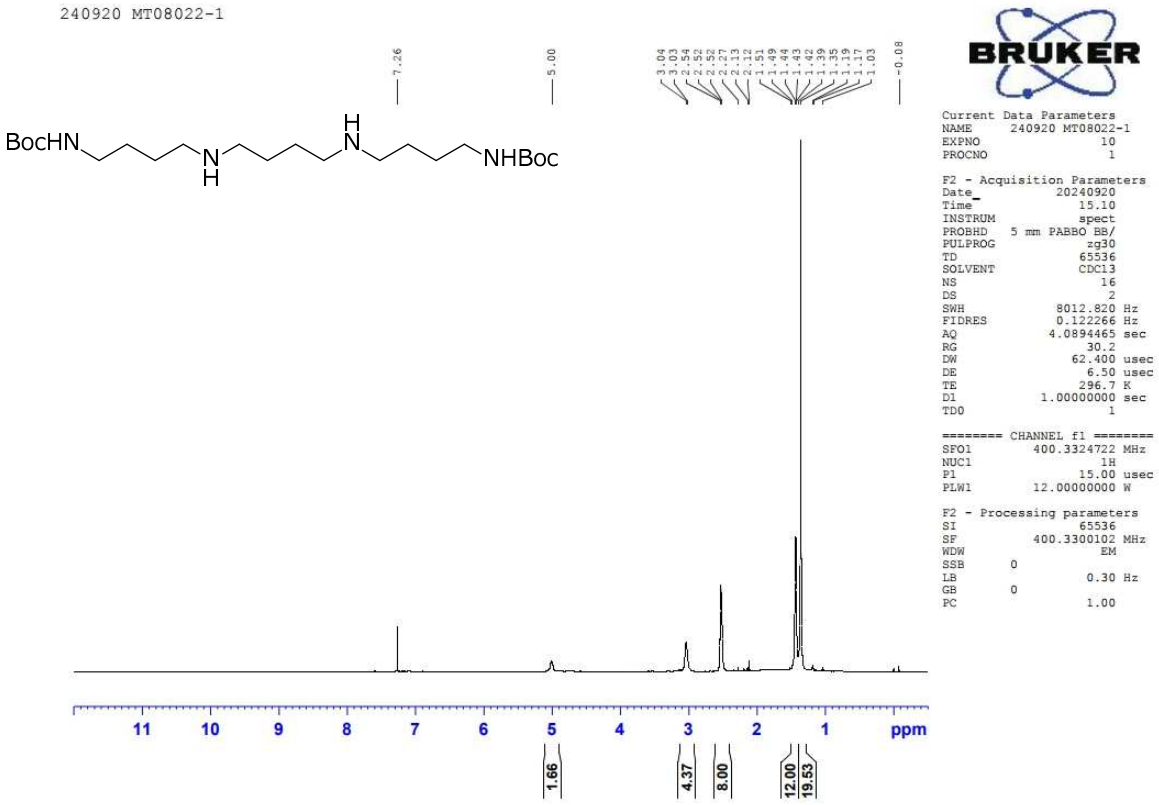


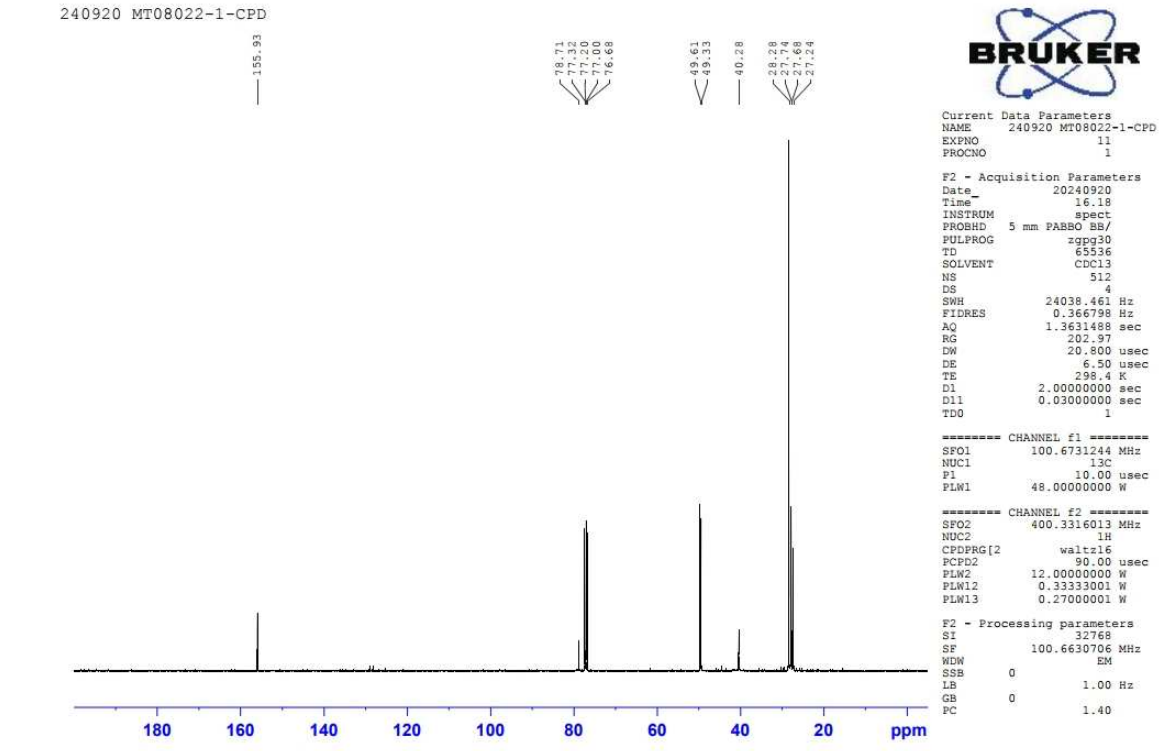
NMR chart of **24d**



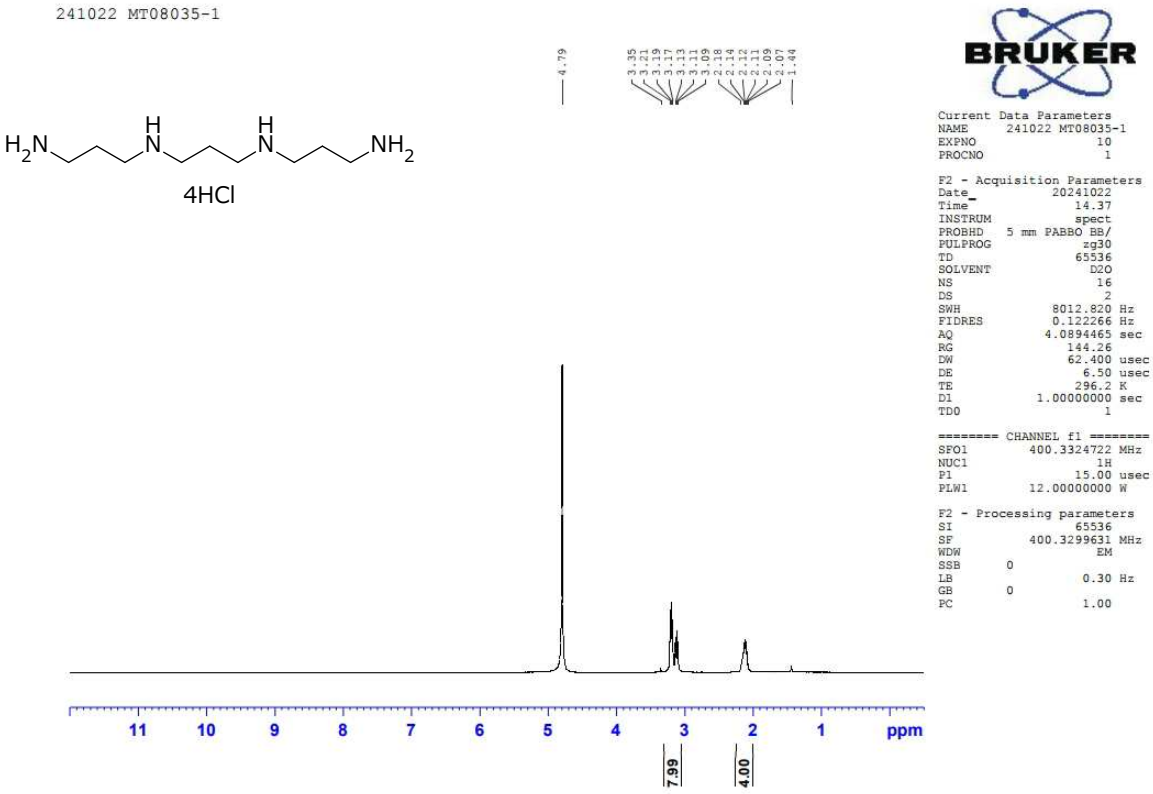


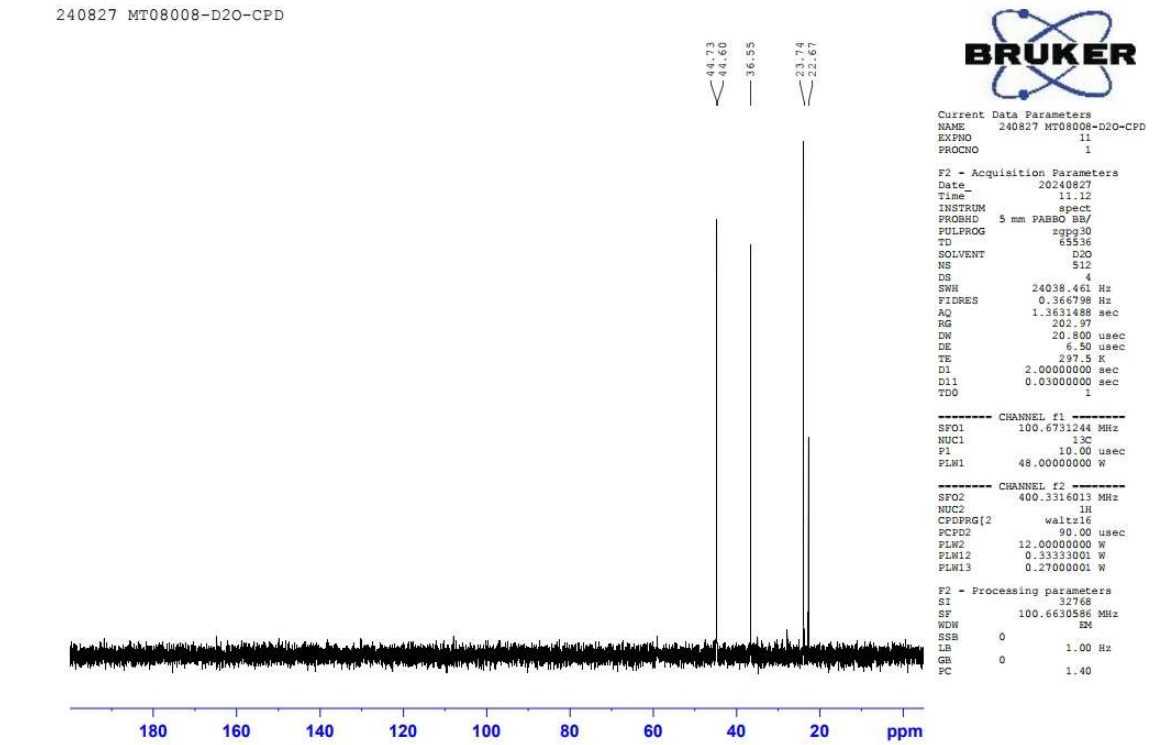
NMR chart of **24e**



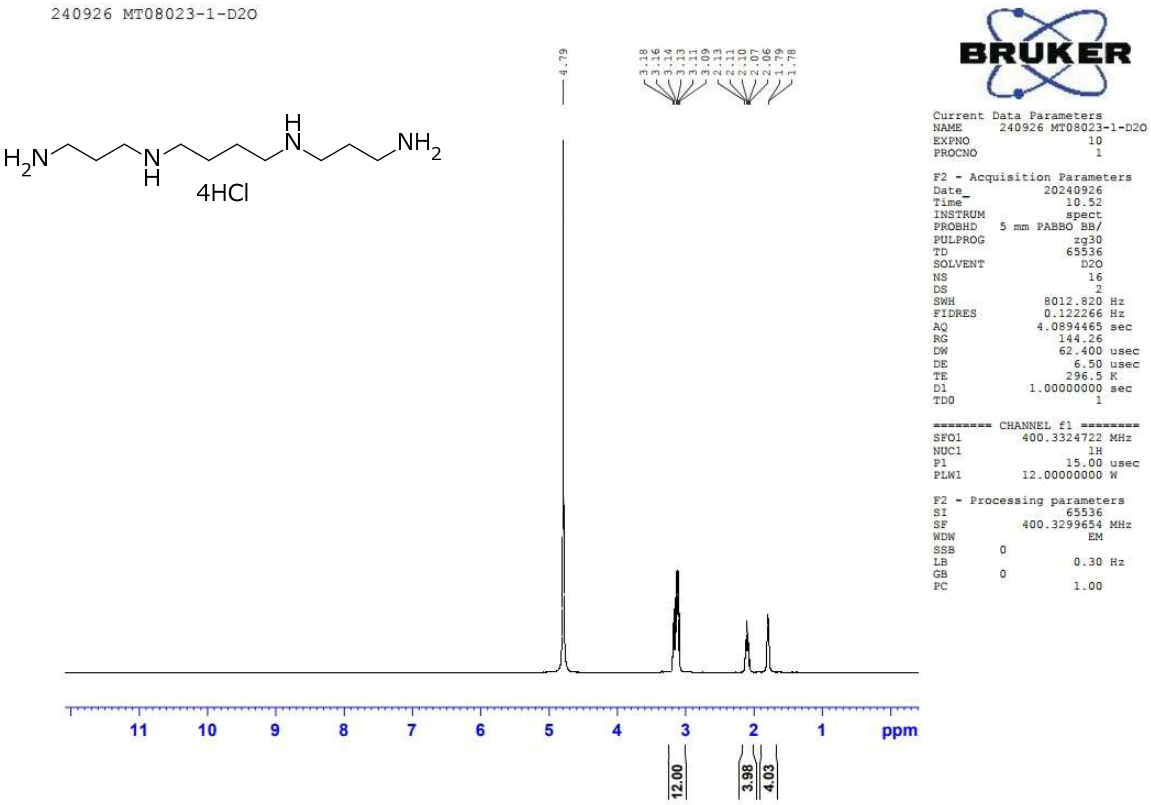


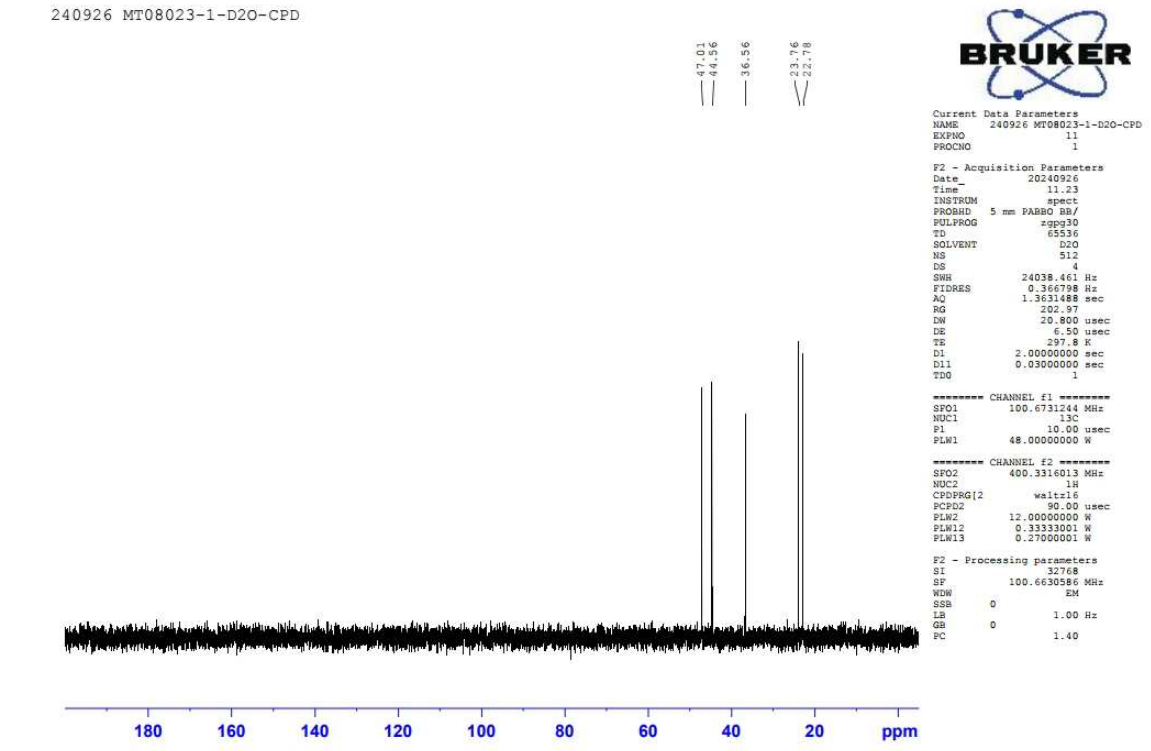
NMR chart of **6**





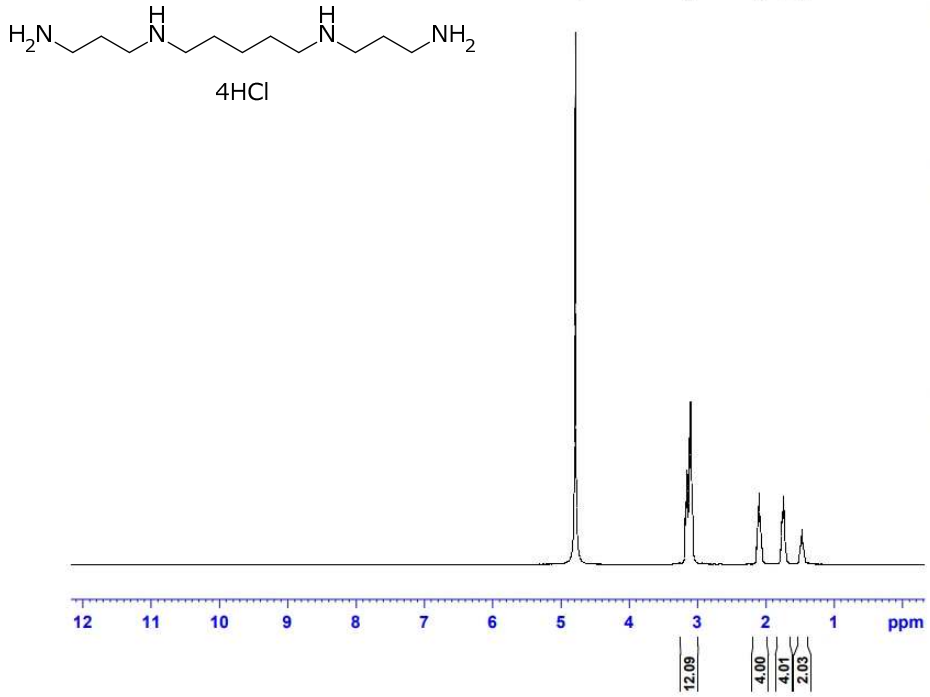
NMR chart of **7**





NMR chart of **8**

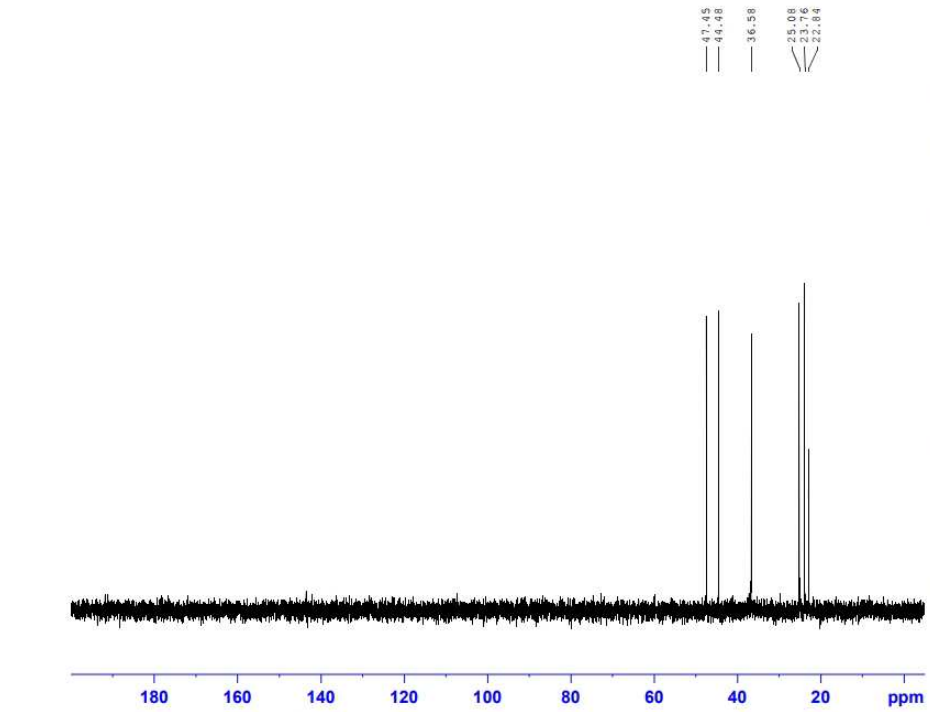
240828 MT08010-1-rec



H_2N NH_2 4HCl

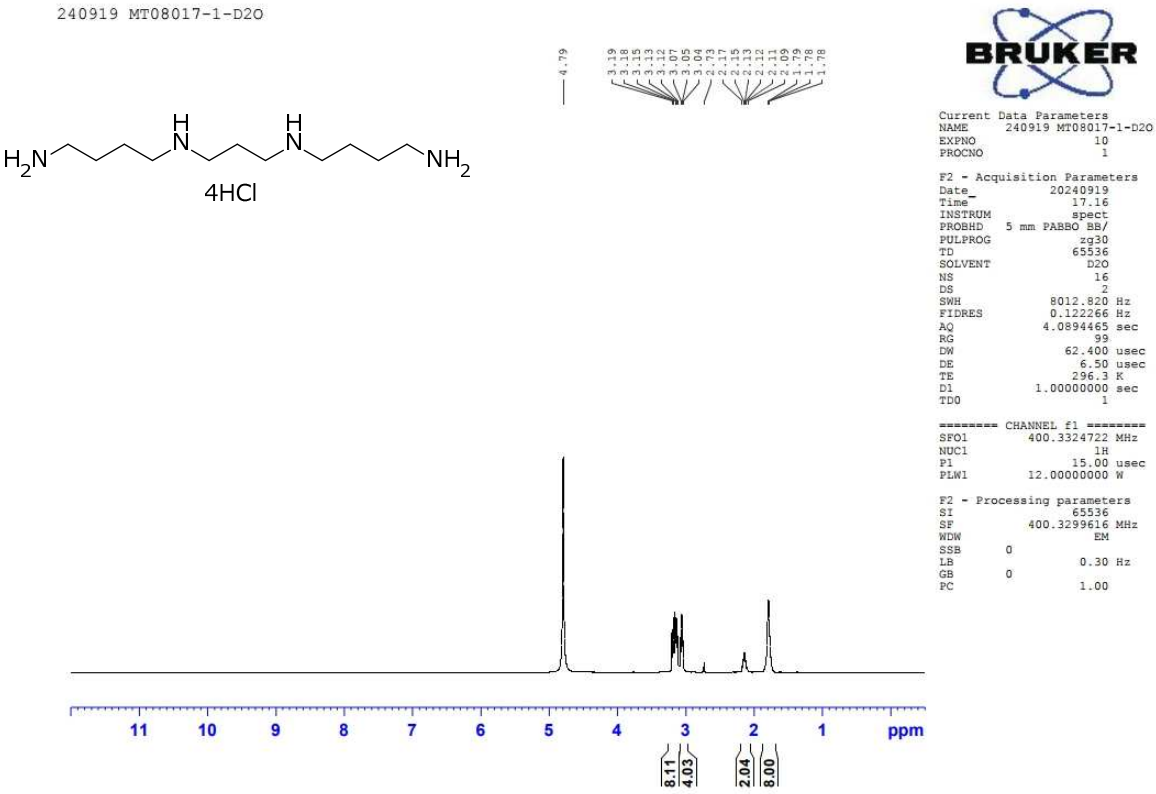
```
Current Data Parameters
NAME      240828 MT08010-1-rec
EXPNO             10
PROCNO             1

F2 - Acquisition Parameters
Date_          20240828
Time              18.19
INSTRUM           spect
PROBHD    5 mm PABBO BB/
PULPROG           zg30
TD               65536
SOLVENT            D2O
NS                  16
DS                   2
SWH            8012.820 Hz
FIDRES         0.122266 Hz
AQ             4.0894465 sec
RG                128.36
DW                62.400 usec
DE                 6.50 usec
TE                296.3 K
D1             1.00000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1          400.3324722 MHz
NUC1                 1H
P1                15.00 usec
PLW1          12.00000000 W

F2 - Processing parameters
SI               65536
SF            400.3299654 MHz
WDW                 EM
SSB       0
LB                0.30 Hz
GB        0
PC                1.00
```

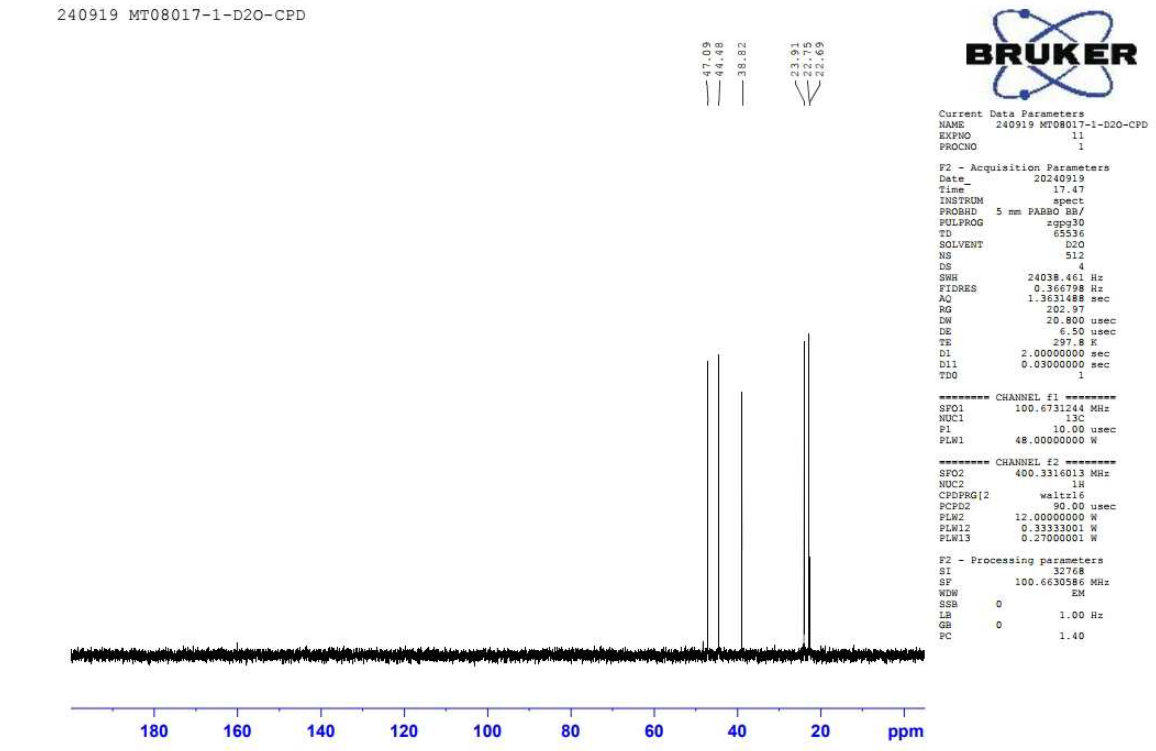
240828 MT08010-1-rec-CPD



```
Current Data Parameters
NAME      240828 MT08010-1-rec-CPD
EXPNO             11
PROCNO             1

F2 - Acquisition Parameters
Date_          20240828
Time              18.51
INSTRUM           spect
PROBHD    5 mm PABBO BB/
PULPROG         zgpg30
TD               65536
SOLVENT            D2O
NS                 512
DS                   4
SWH           24038.461 Hz
FIDRES         0.366798 Hz
AQ             1.3631488 sec
RG                202.97
DW                20.800 usec
DE                 6.50 usec
TE                297.8 K
D1             2.00000000 sec
D11            0.03000000 sec
TD0                  1

======== CHANNEL f1 ========
SFO1          100.6731244 MHz
NUC1                 13C
P1                10.00 usec
PLW1          48.00000000 W

======== CHANNEL f2 ========
SFO2          400.3316013 MHz
NUC2                 1H
CPDPRG[2          waltz16
PCPD2             90.00 usec
PLW2          12.00000000 W
PLW12          0.33333001 W
PLW13          0.27000001 W

F2 - Processing parameters
SI               32768
SF            100.6630586 MHz
WDW                 EM
SSB       0
LB                1.00 Hz
GB        0
PC                1.40
```

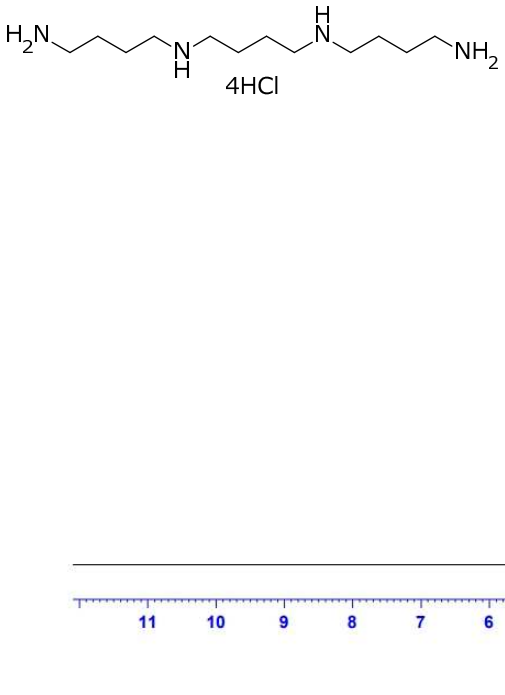
NMR chart of **9**

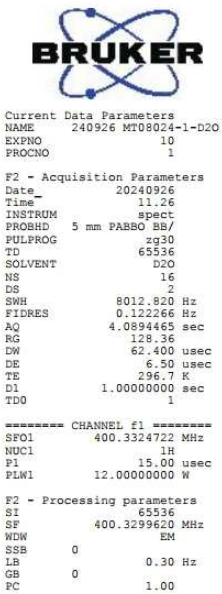




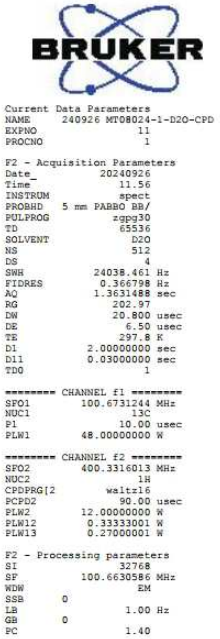
NMR chart of **10**

240926 MT08024-1-D2O

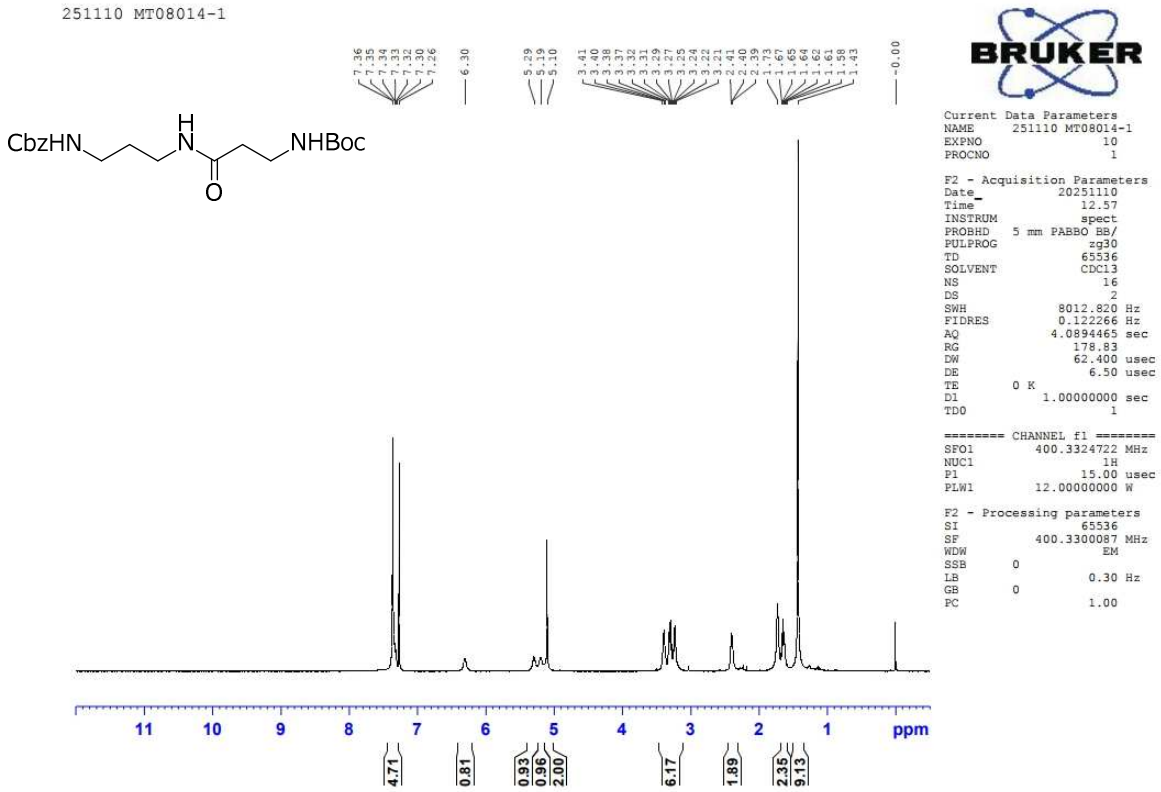


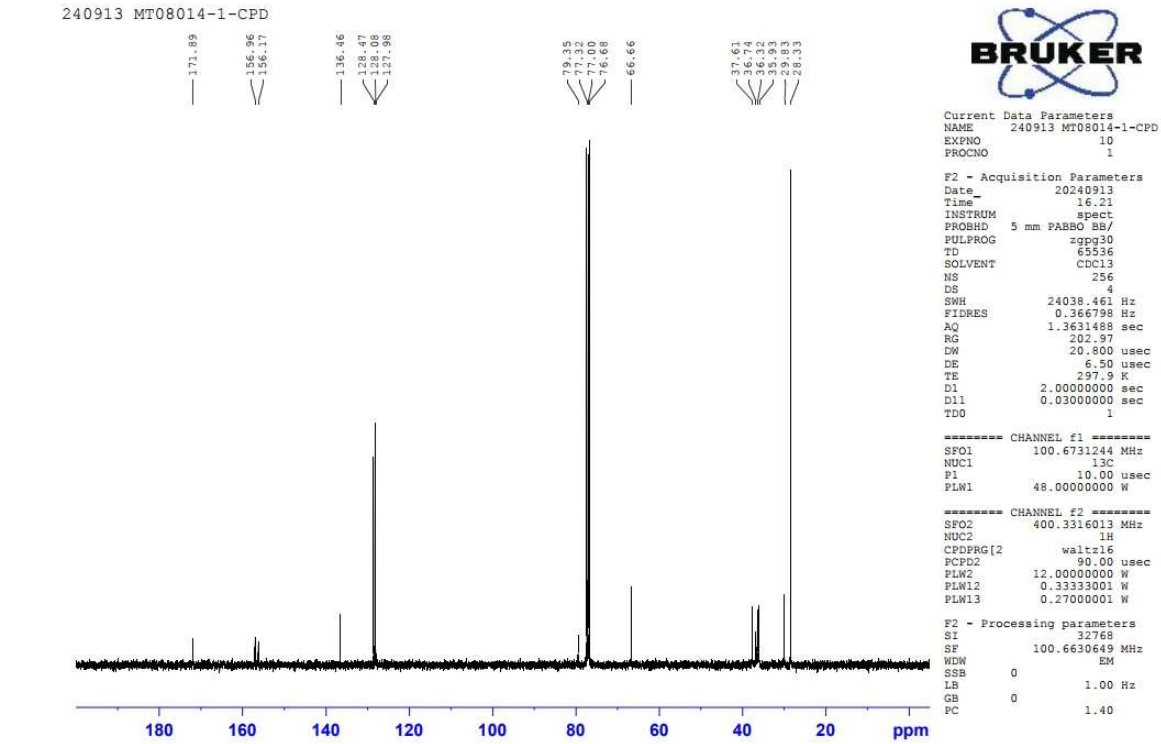


240926 MT08024-1-D2O-CPD

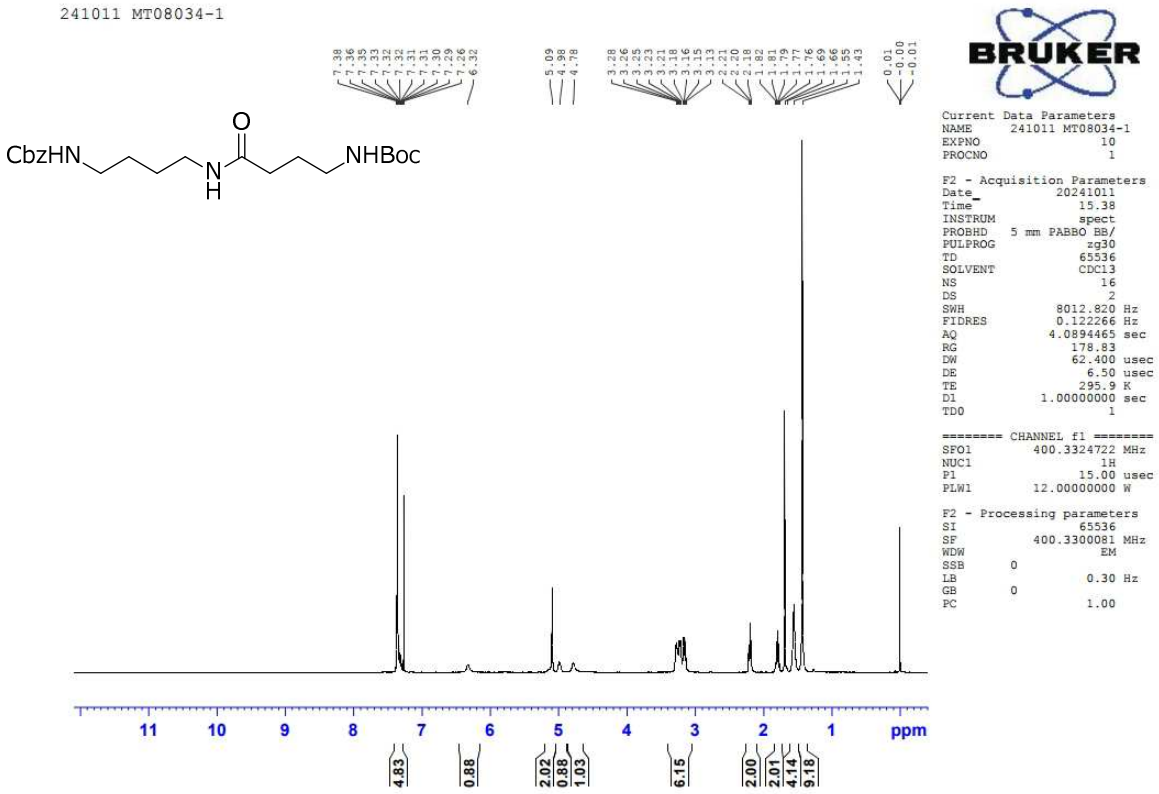


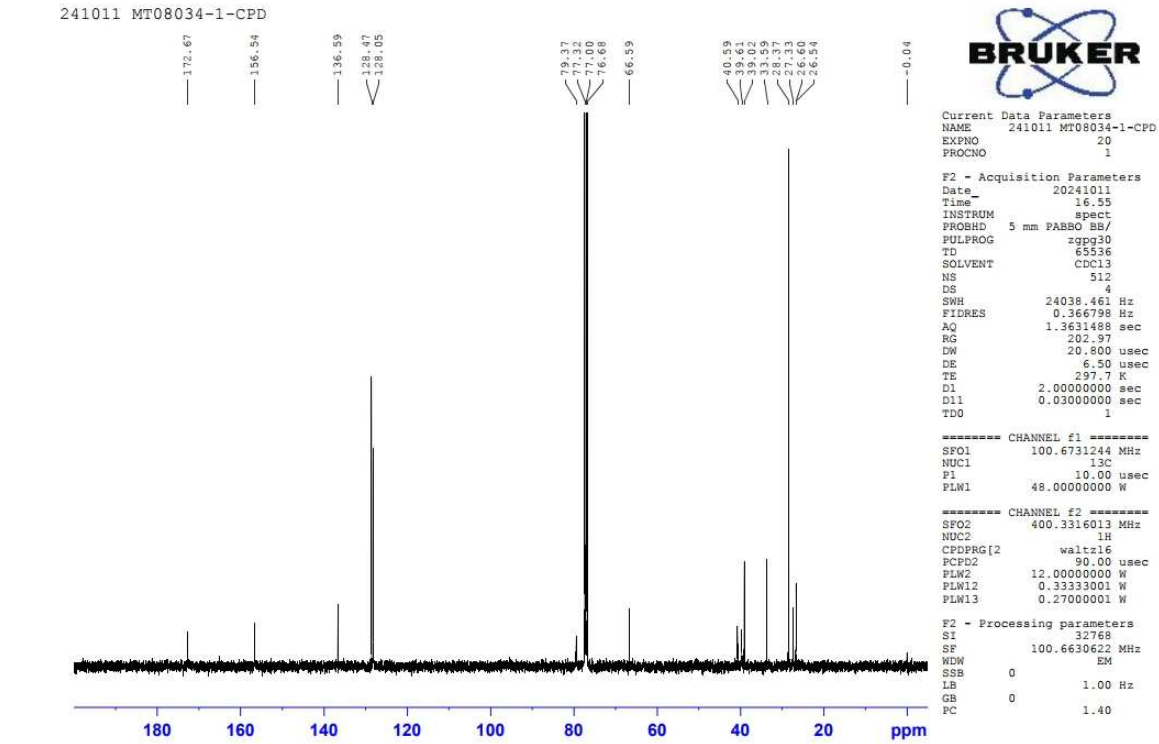
NMR chart of **26a**



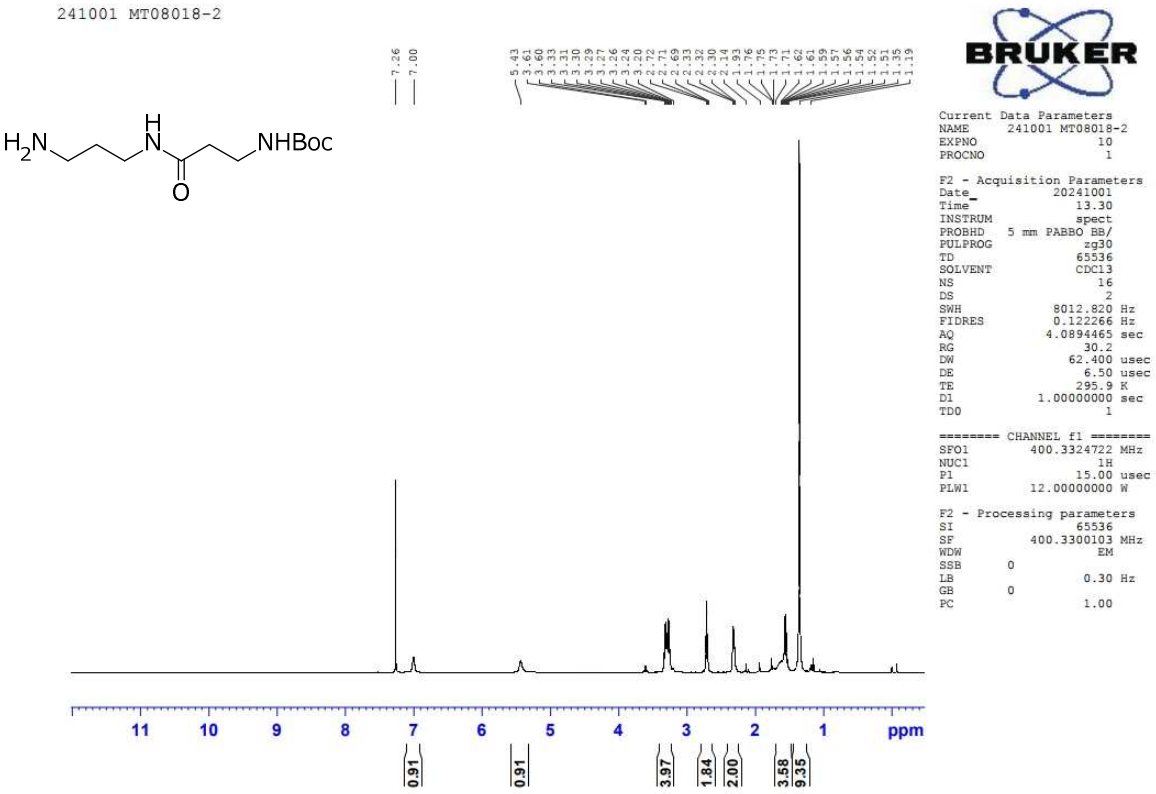


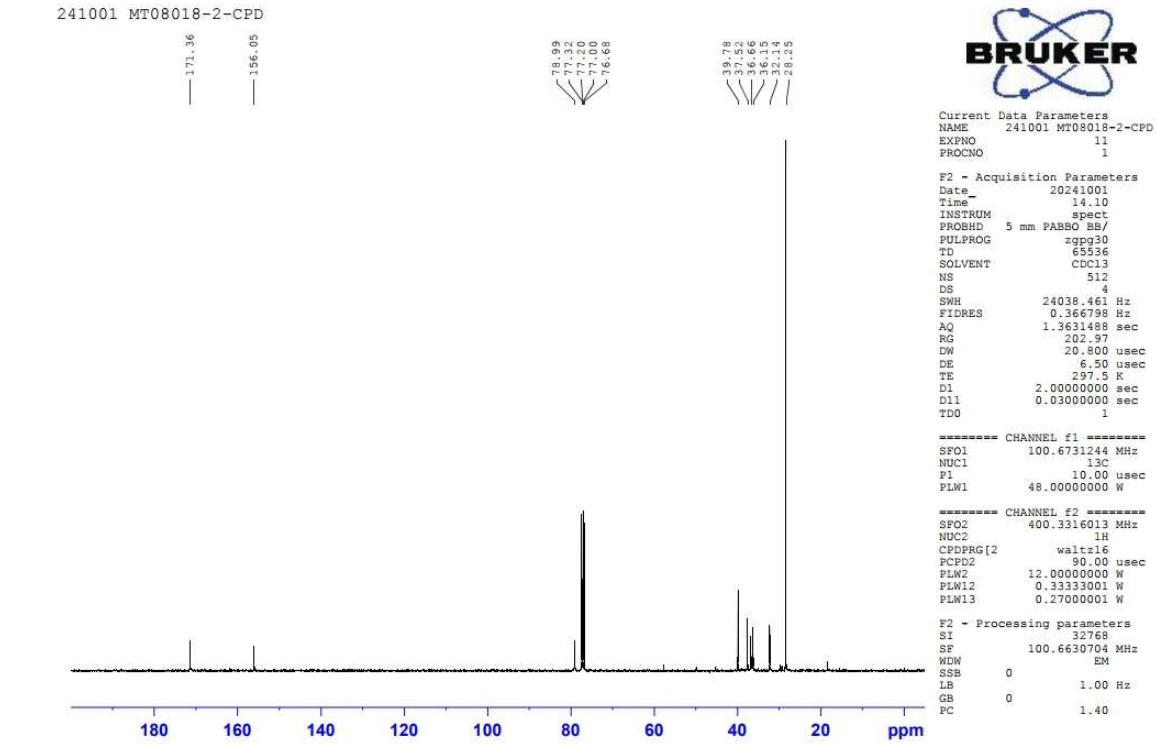
NMR chart of **26b**



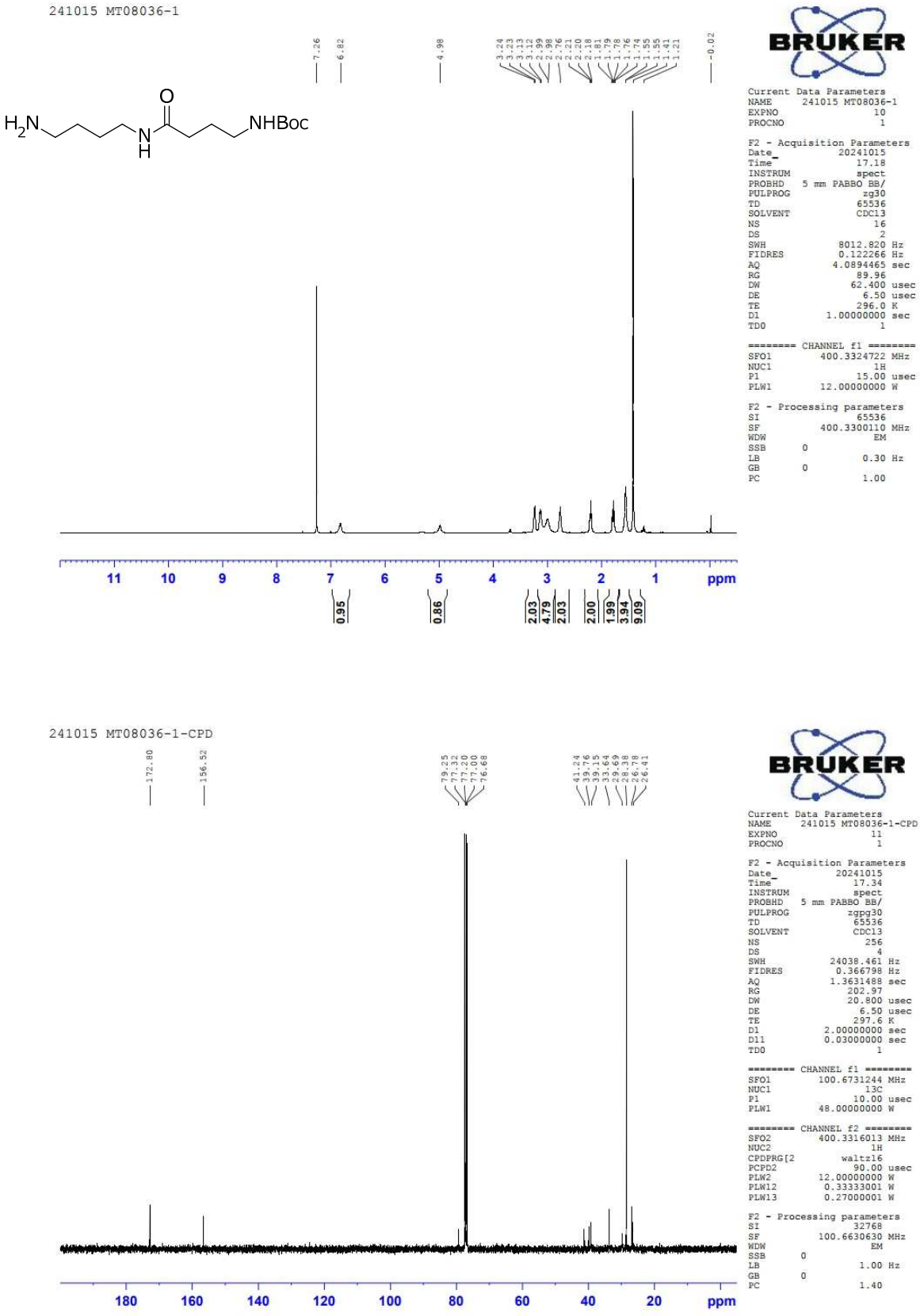


NMR chart of **27a**

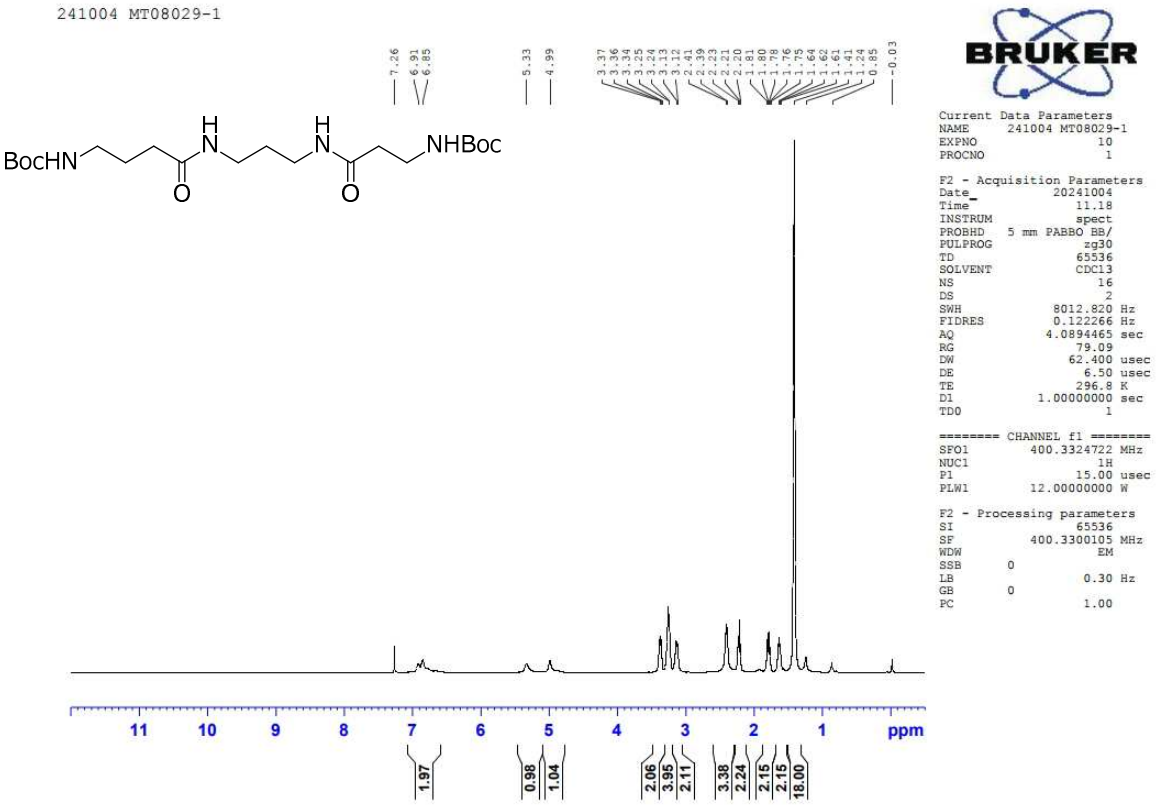


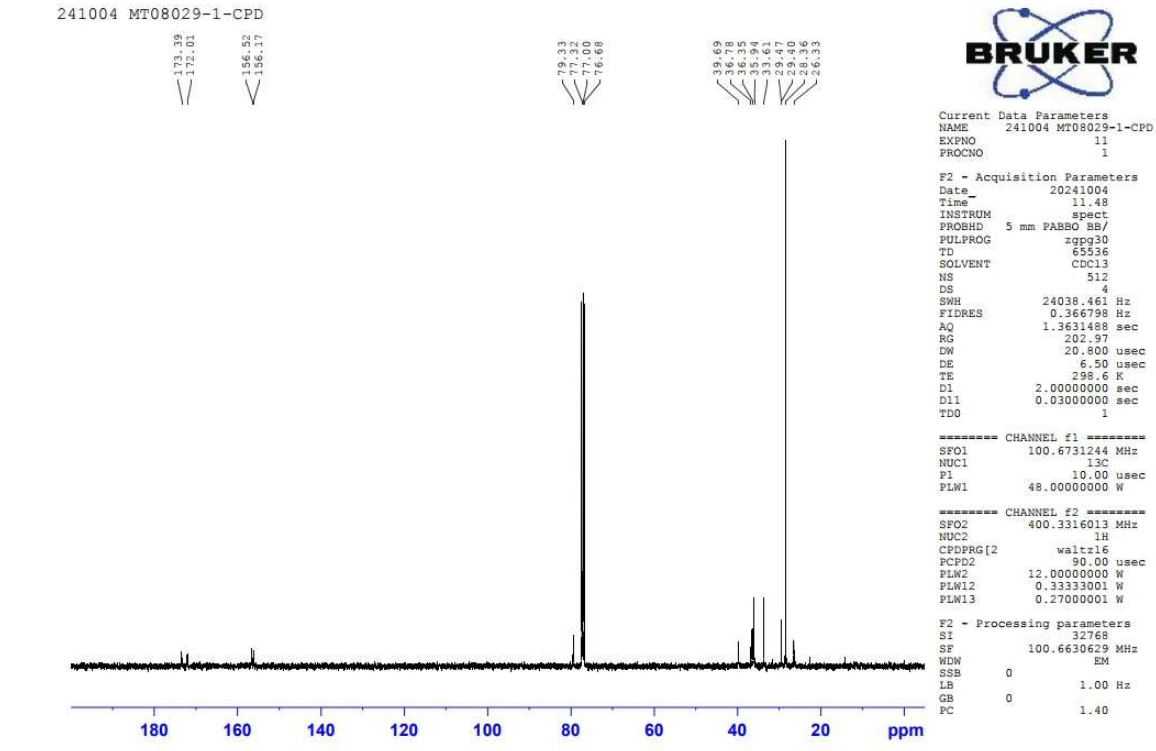


NMR chart of **27b**

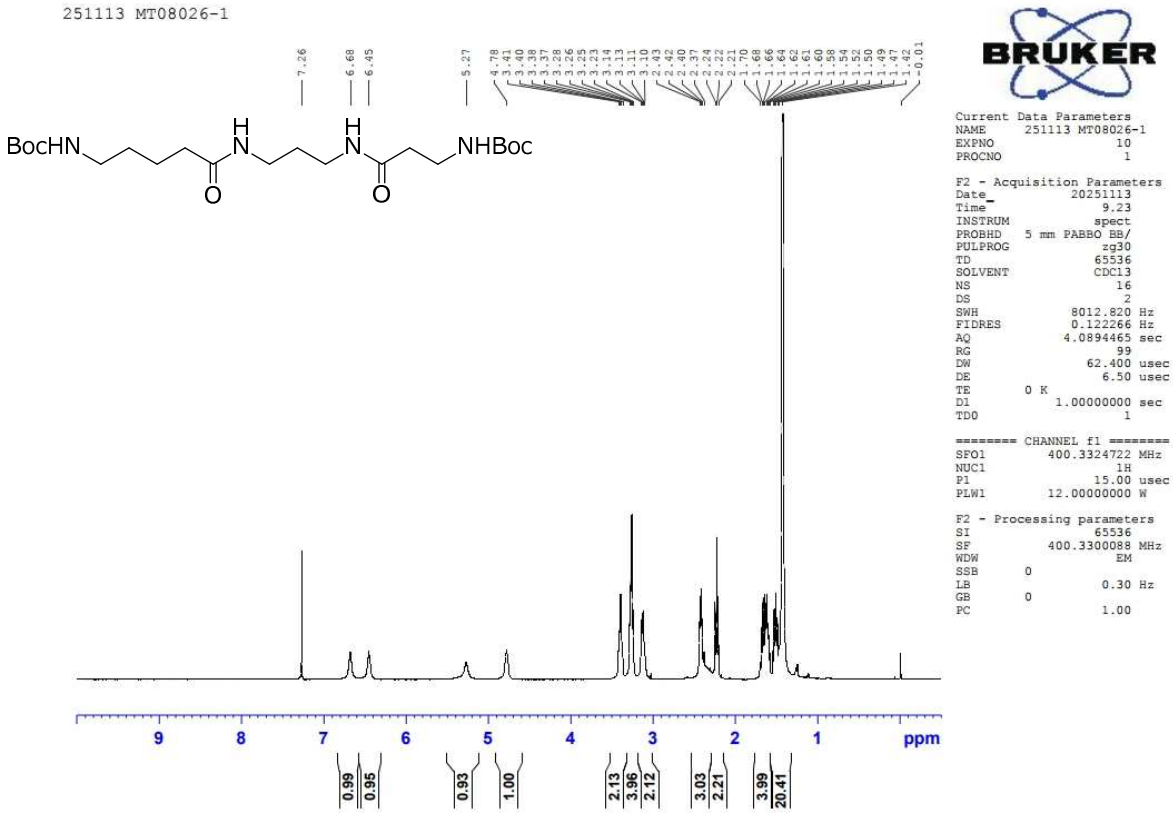


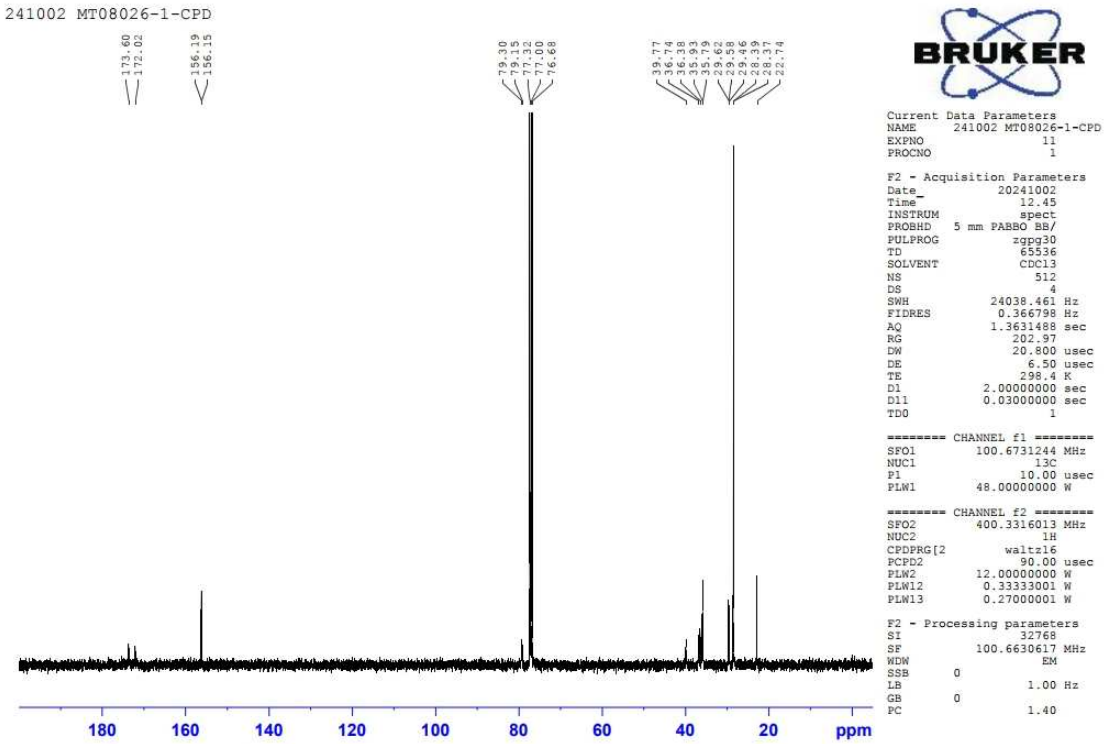
NMR chart of **28a**



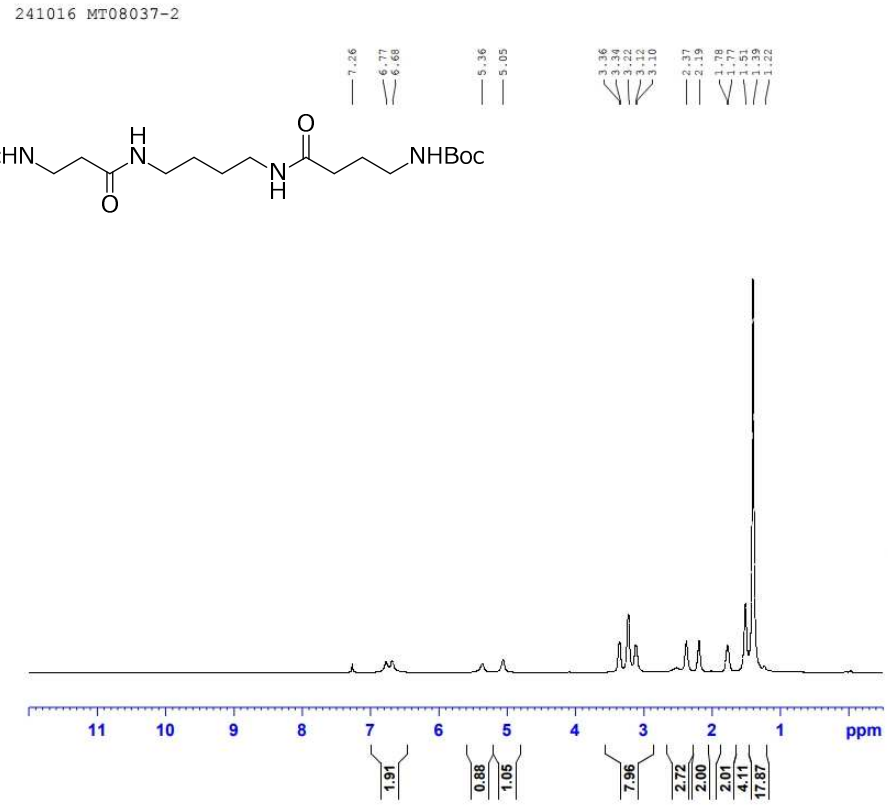


NMR chart of **28b**

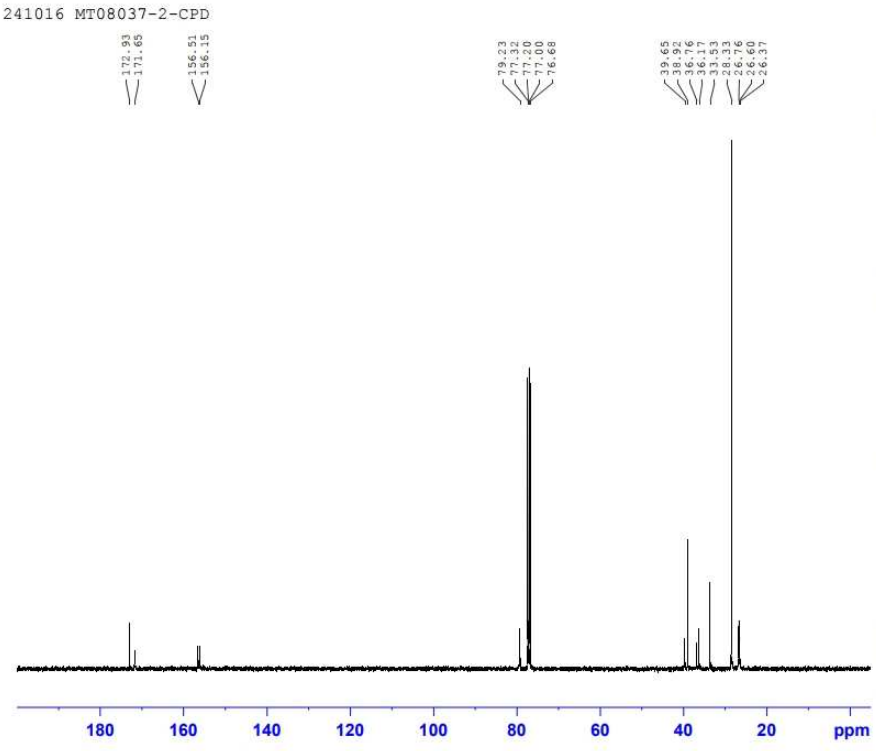




NMR chart of **28c**

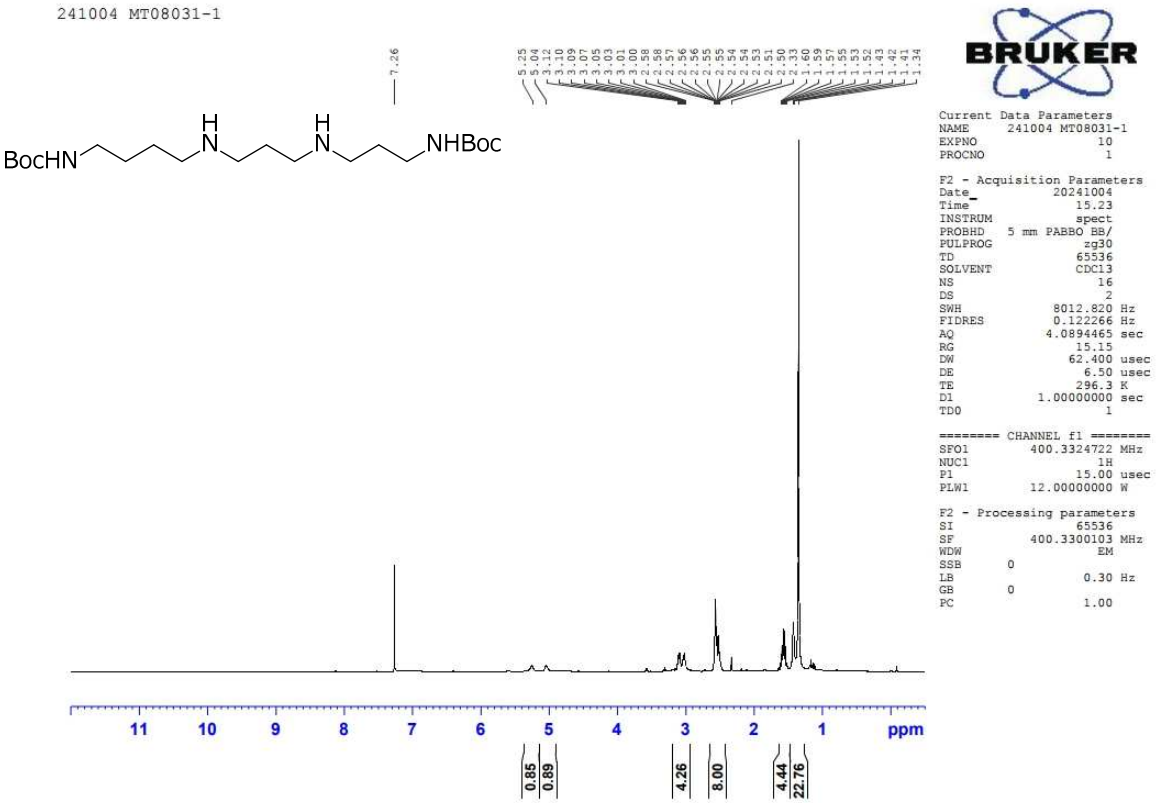


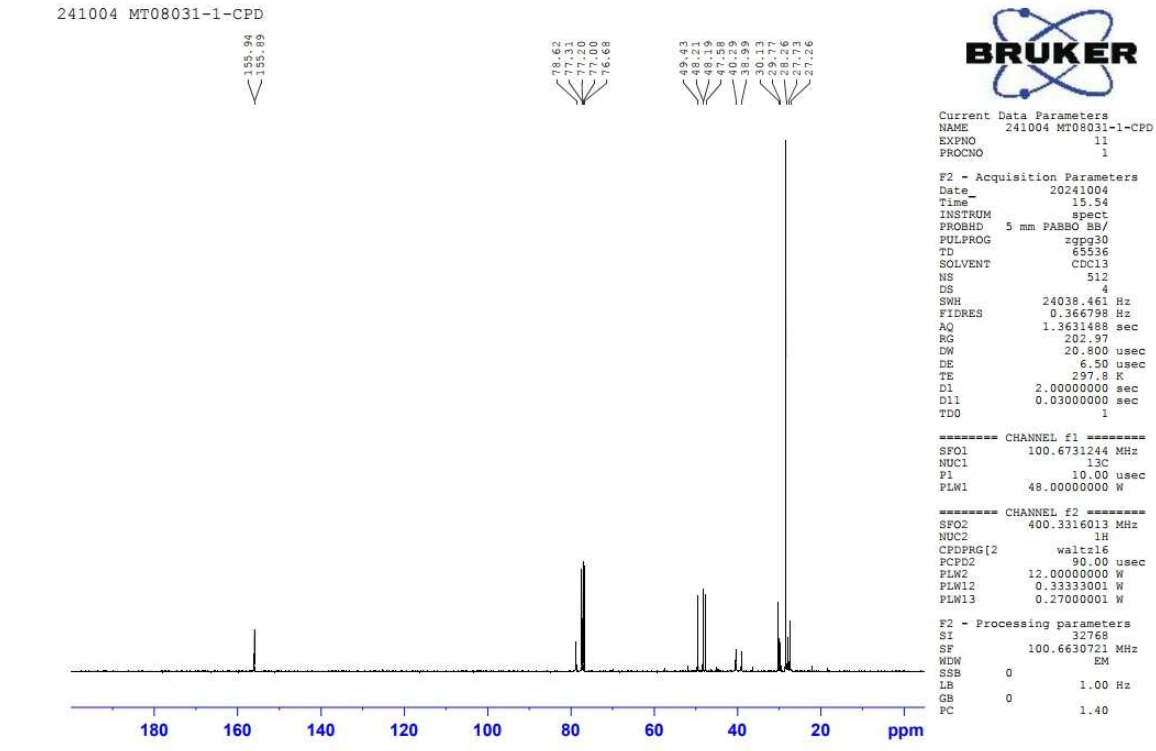

```
Current Data Parameters
NAME      241016 MT08037-2
EXPNO              12
PROCNO              1

F2 - Acquisition Parameters
Date_           20241016
Time              15.46
INSTRUM           spect
PROBHD   5 mm PABBO BB/
PULPROG           zg30
TD               65536
SOLVENT          CDCl3
NS                  64
DS                   2
SWH           8012.820 Hz
FIDRES        0.122266 Hz
AQ            4.0894465 sec
RG                49.9
DW              62.400 usec
DE               6.50 usec
TE              296.0 K
D1           1.00000000 sec
TD0                 1

======== CHANNEL f1 ========
SFO1        400.3324722 MHz
NUC1               1H
P1               15.00 usec
PLW1        12.00000000 W

F2 - Processing parameters
SI               65536
SF          400.3300105 MHz
WDW                EM
SSB       0
LB               0.30 Hz
GB        0
PC               1.00
```



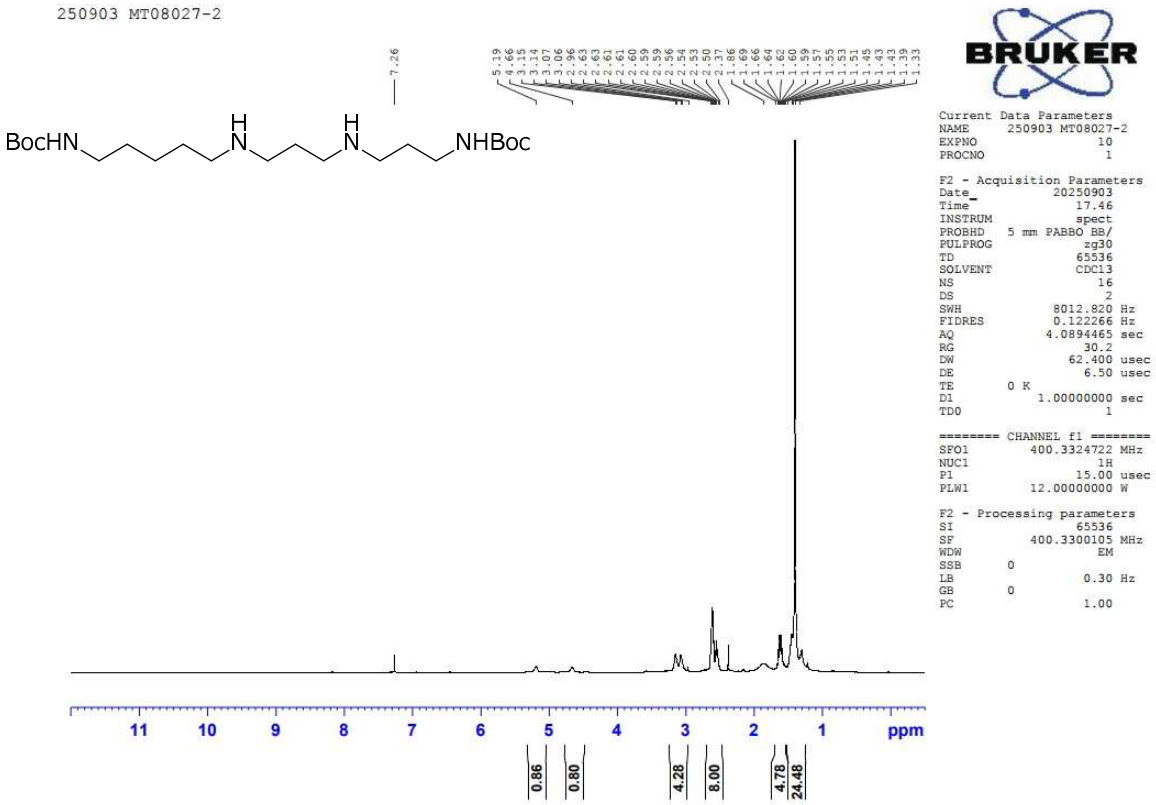

```
Current Data Parameters
NAME      241016 MT08037-2-CPD
EXPNO              14
PROCNO              1

F2 - Acquisition Parameters
Date_           20241016
Time              16.17
INSTRUM           spect
PROBHD   5 mm PABBO BB/
PULPROG         zgpg30
TD               65536
SOLVENT          CDCl3
NS                 512
DS                   4
SWH          24038.461 Hz
FIDRES        0.366798 Hz
AQ            1.3631488 sec
RG                202.97
DW              20.800 usec
DE               6.50 usec
TE              297.7 K
D1           2.00000000 sec
D11          0.03000000 sec
TD0                 1

======== CHANNEL f1 ========
SFO1        100.6731244 MHz
NUC1               13C
P1               10.00 usec
PLW1        48.00000000 W

======== CHANNEL f2 ========
SFO2        400.3316013 MHz
NUC2               1H
CPDPRG[2         waltz16
PCPD2            90.00 usec
PLW2        12.00000000 W
PLW12        0.33333001 W
PLW13        0.27000001 W

F2 - Processing parameters
SI               32768
SF          100.6630654 MHz
WDW                EM
SSB       0
LB              1.00 Hz
GB        0
PC               1.40
```

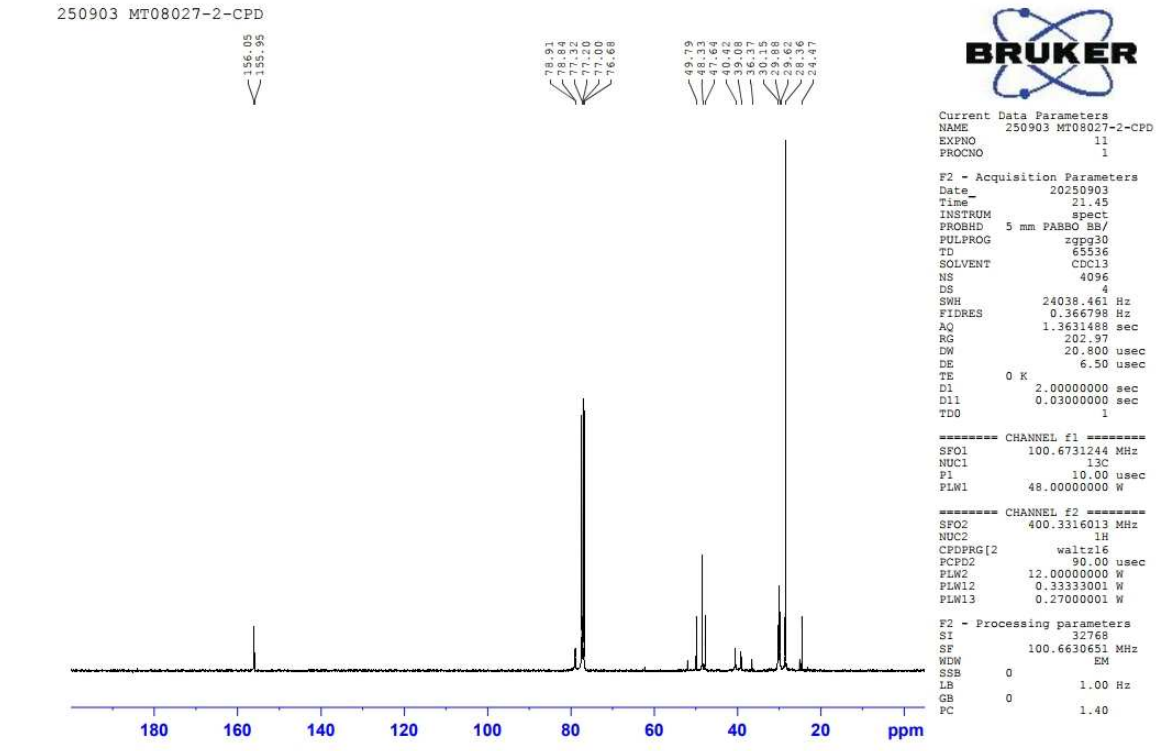
NMR chart of **29a**



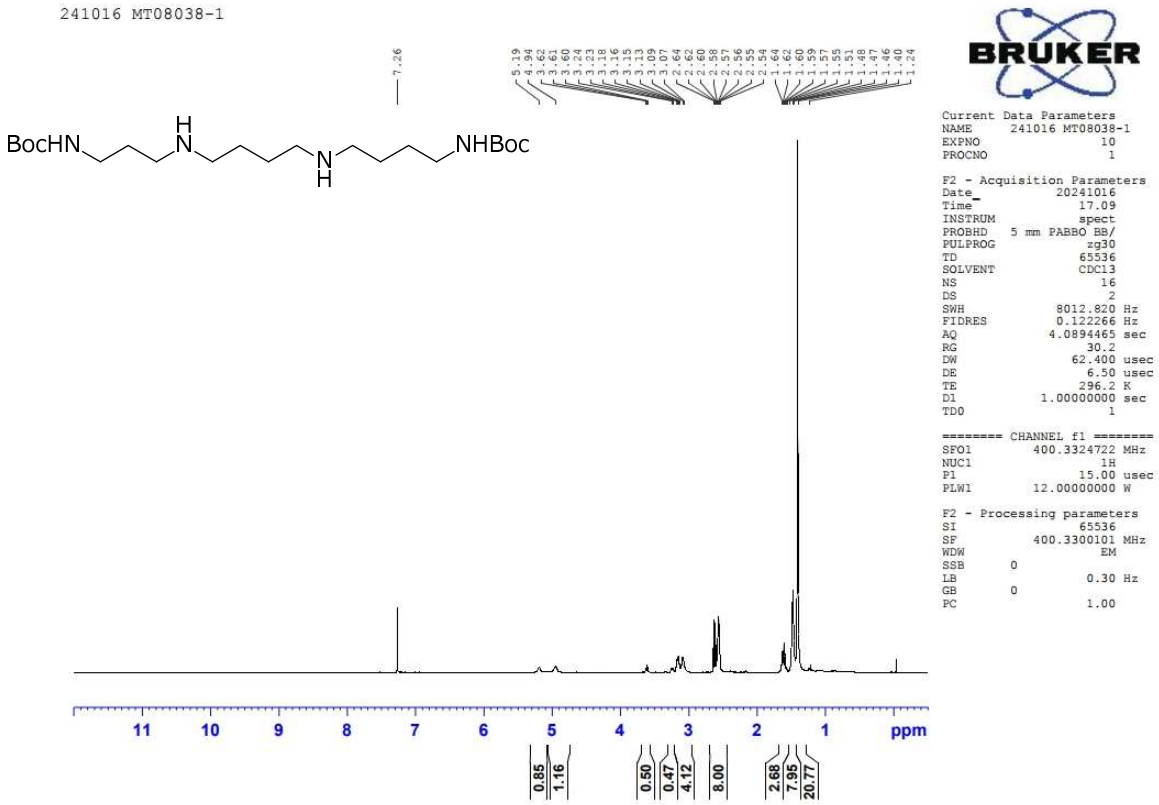


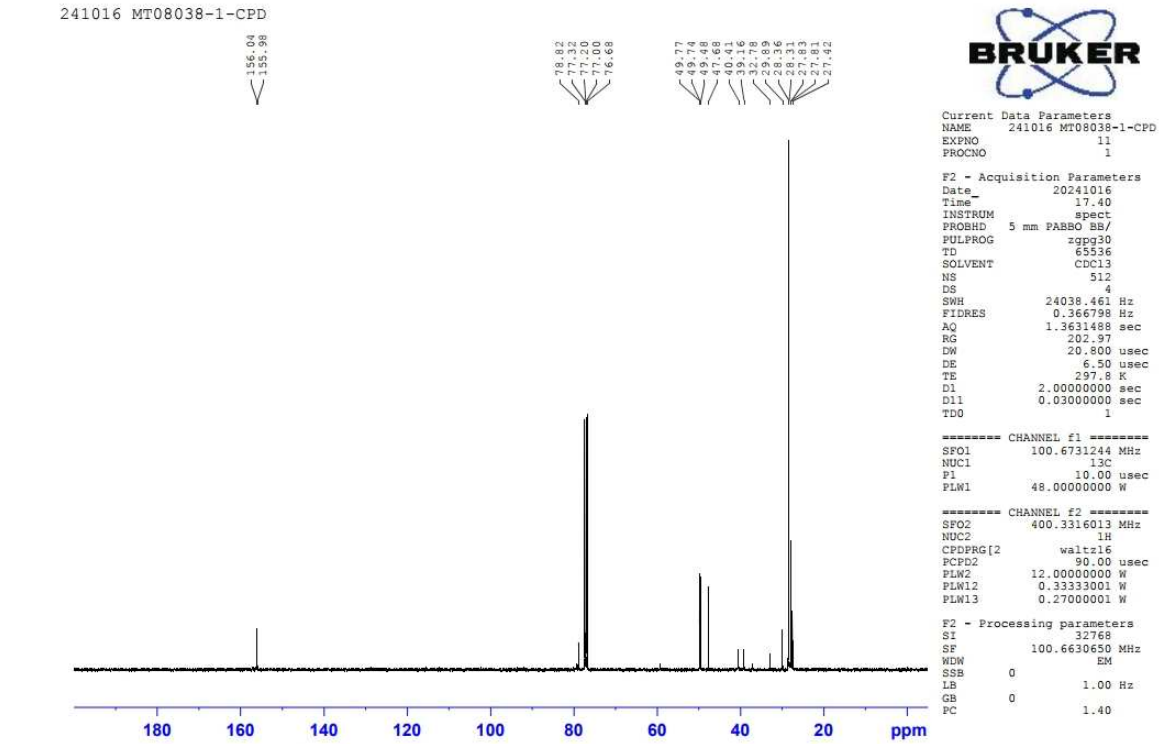
NMR chart of **29b**



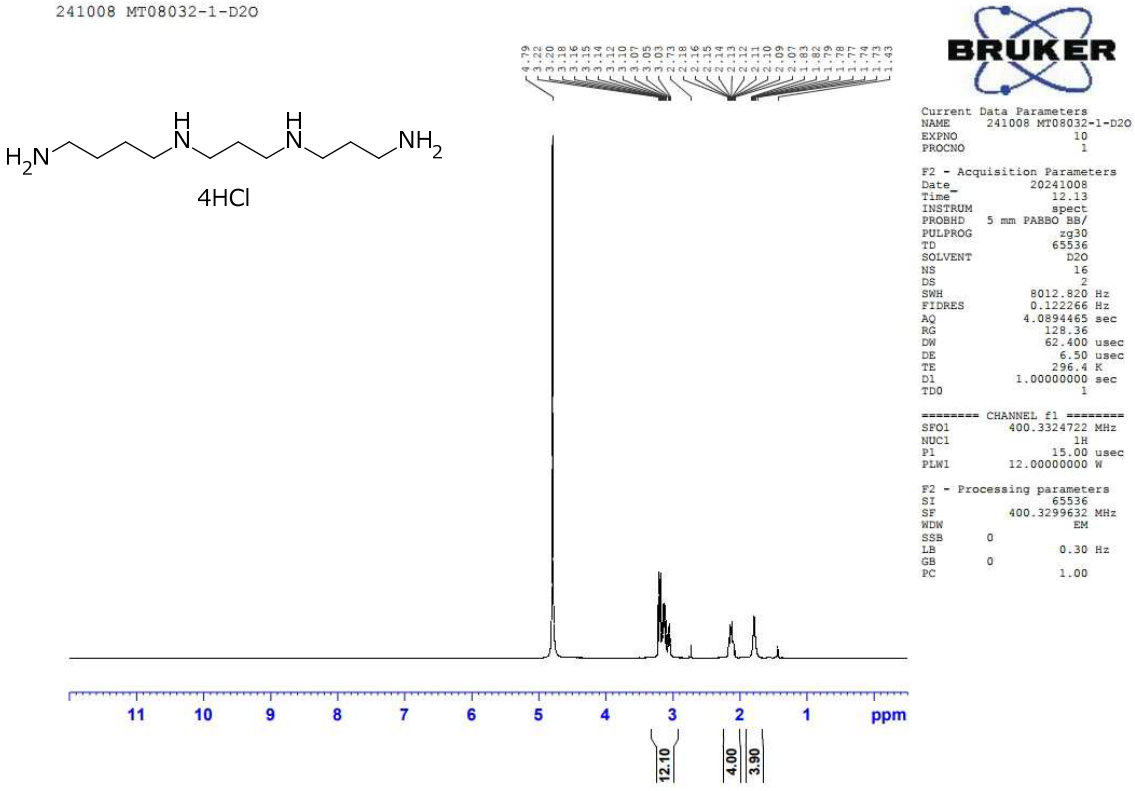


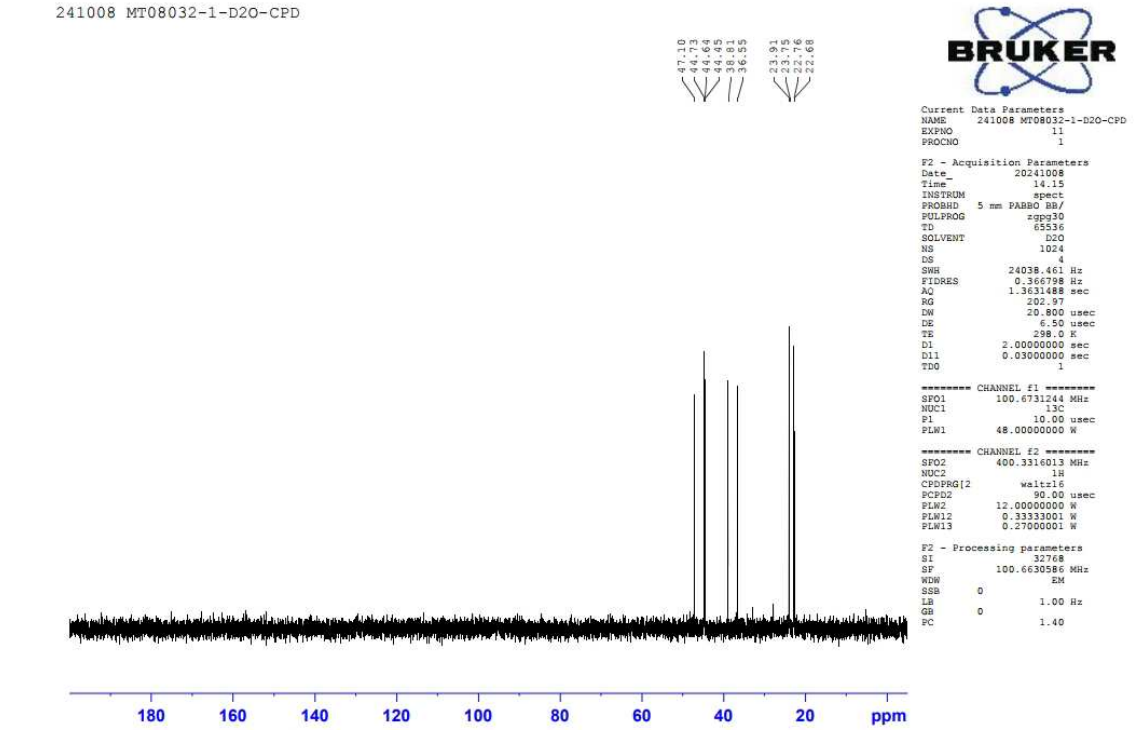
NMR chart of **29c**



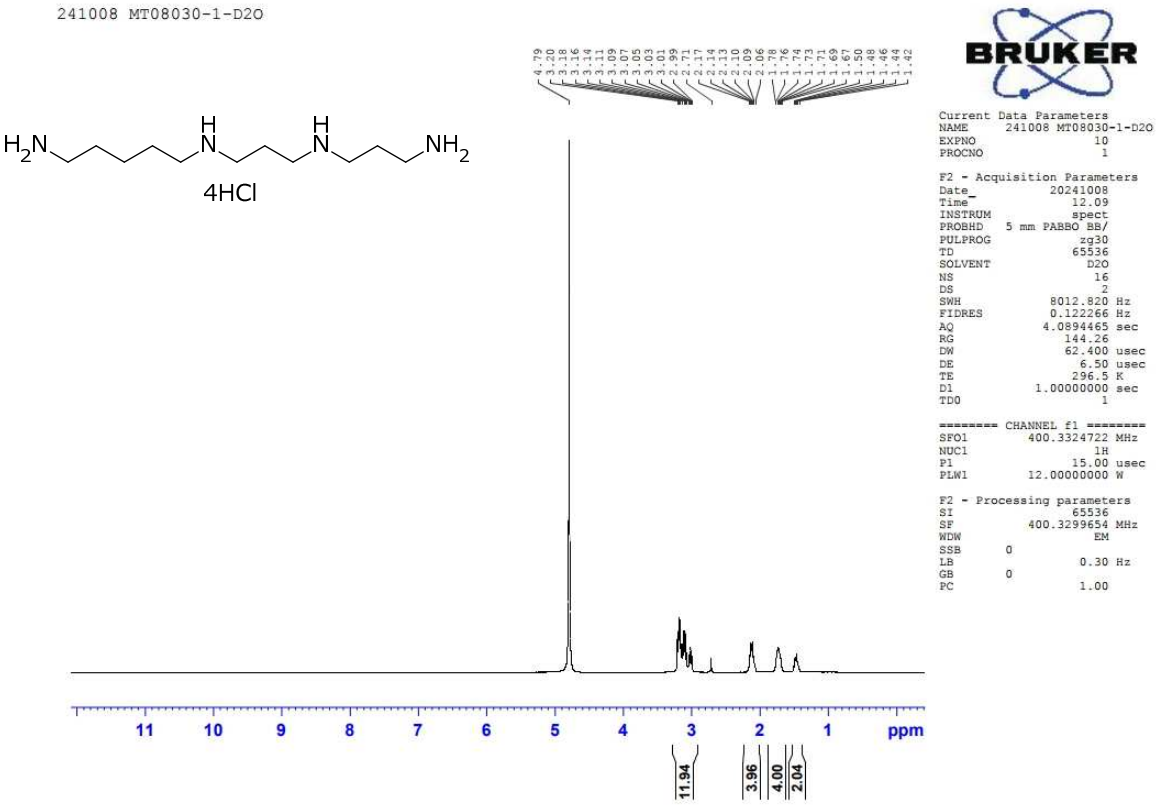


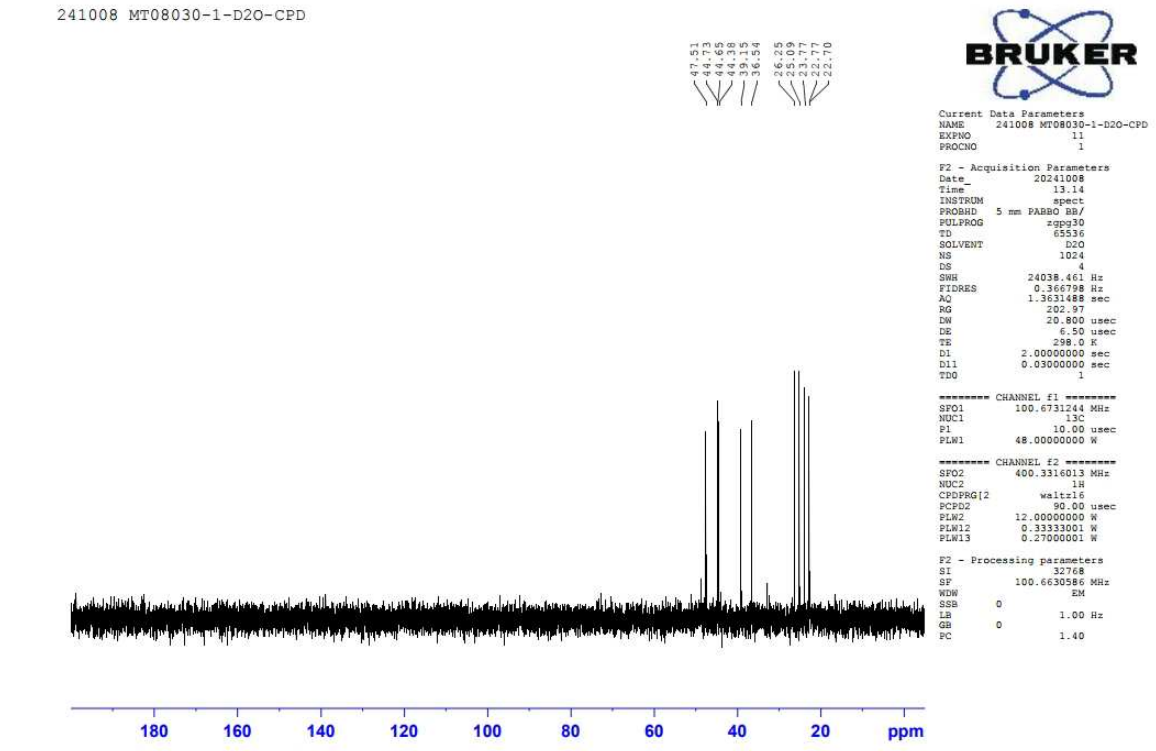
NMR chart of **11**



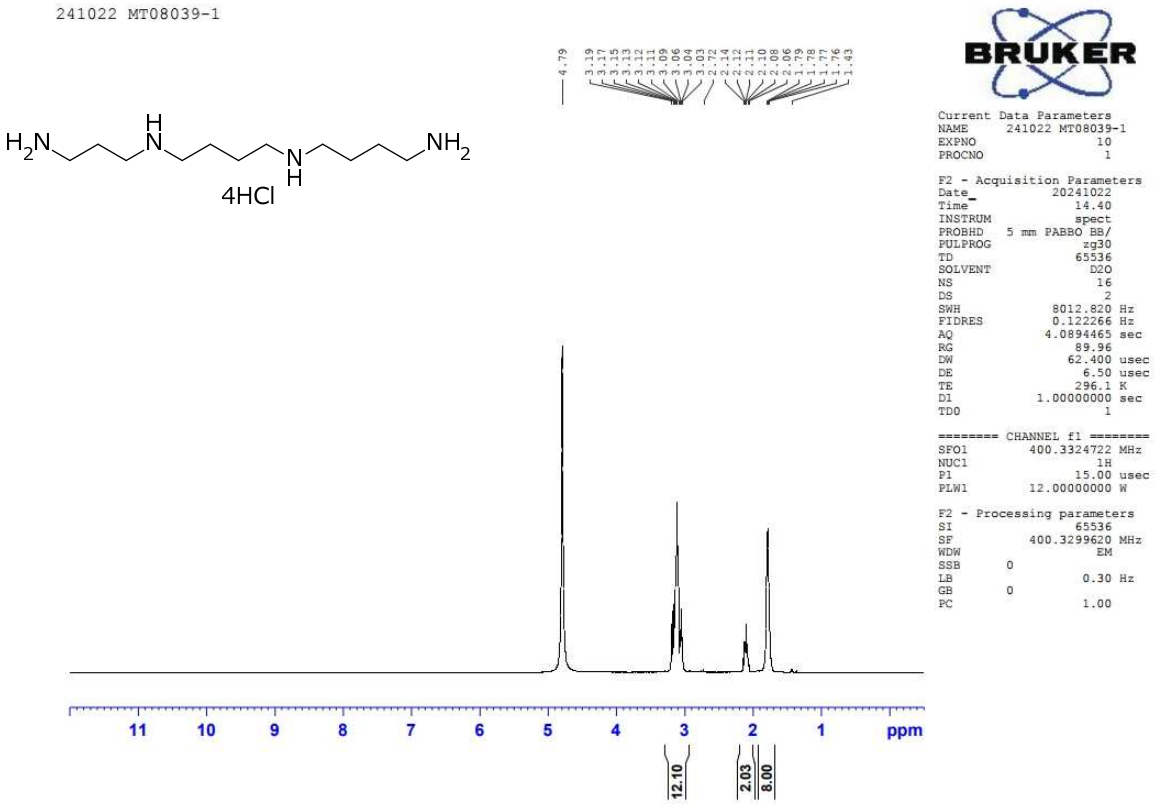


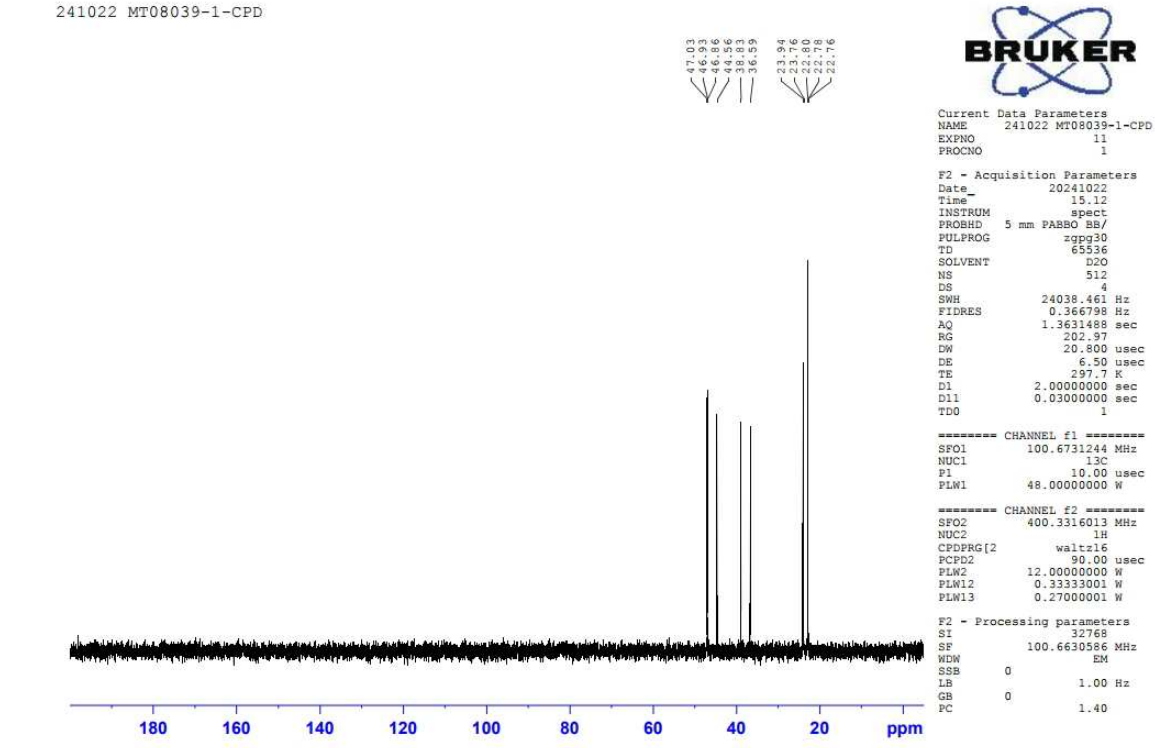
NMR chart of **12**



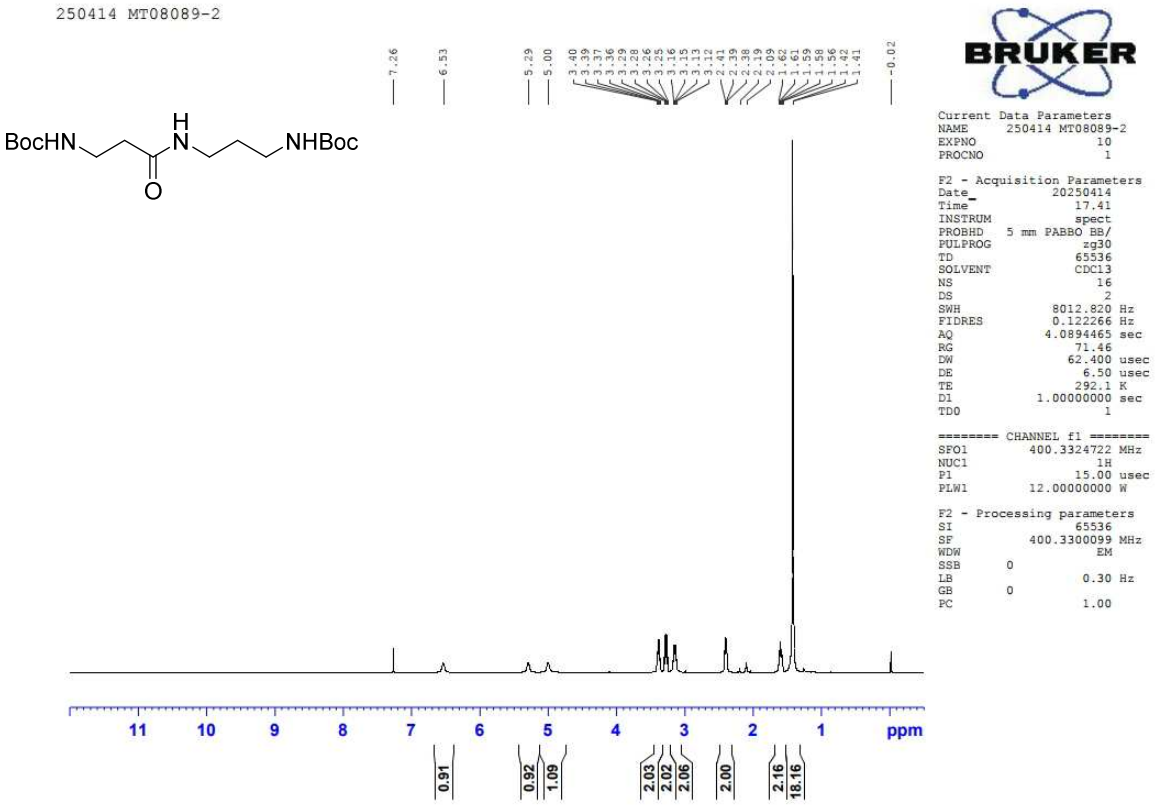


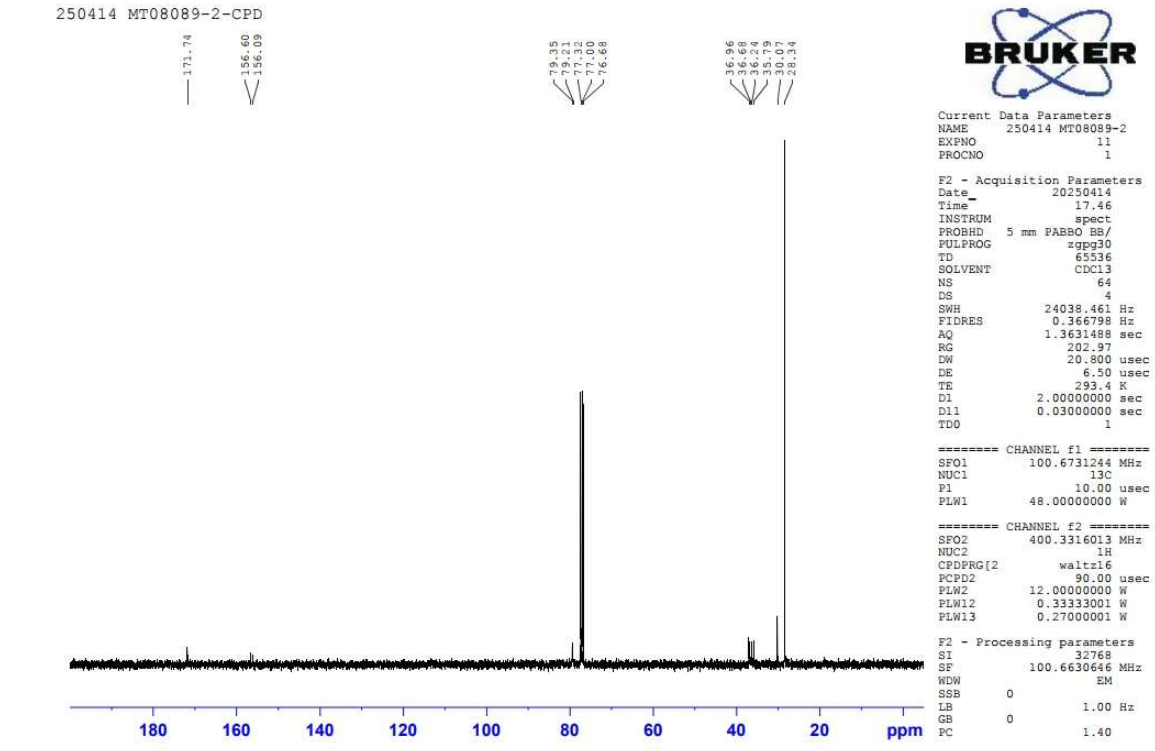
NMR chart of **13**



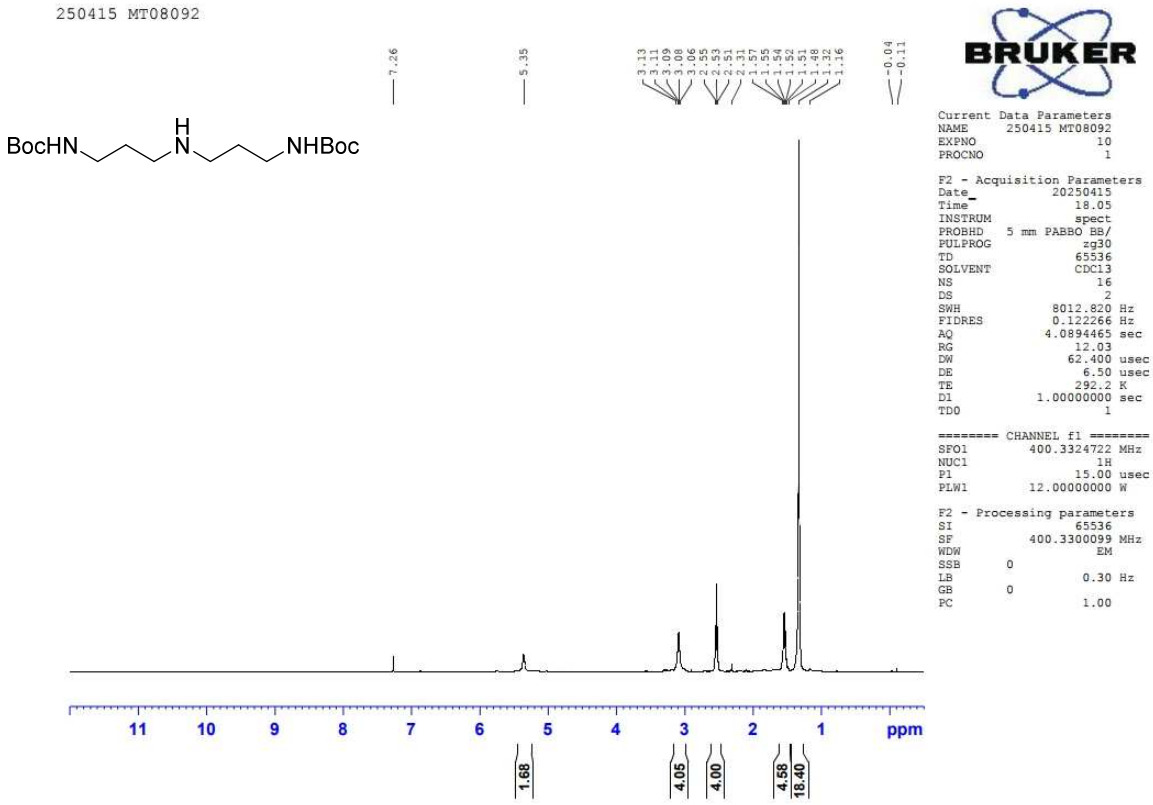


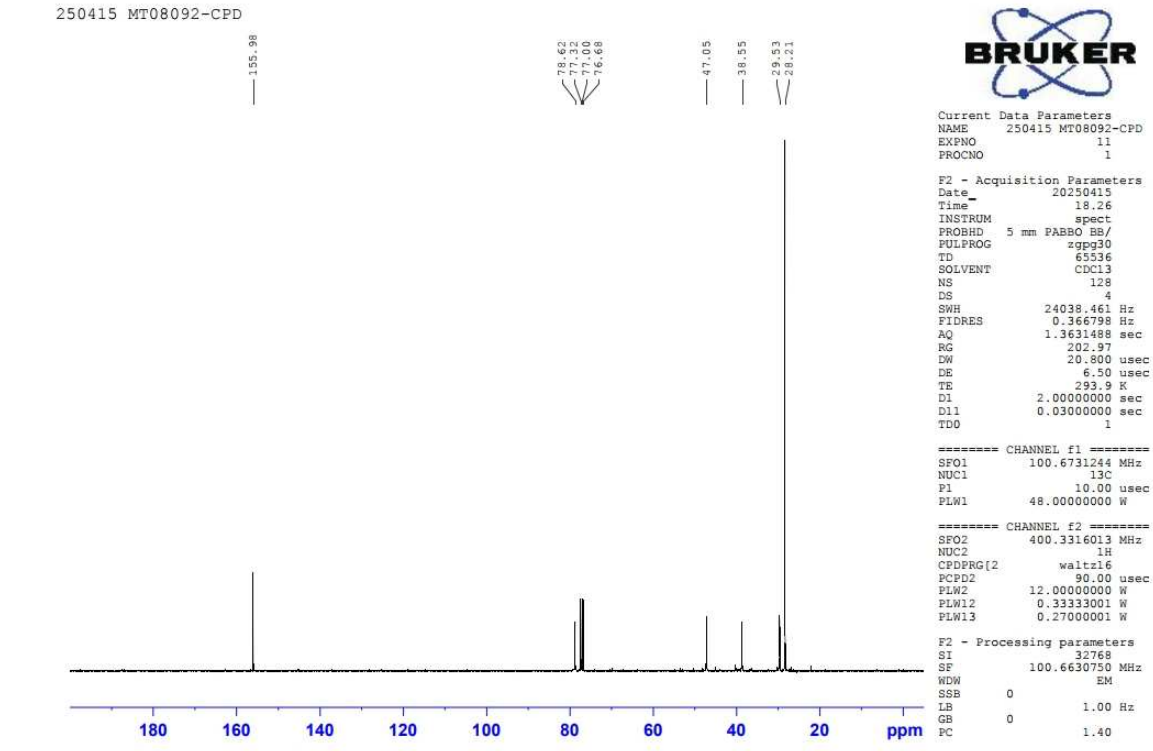
NMR chart of **31**



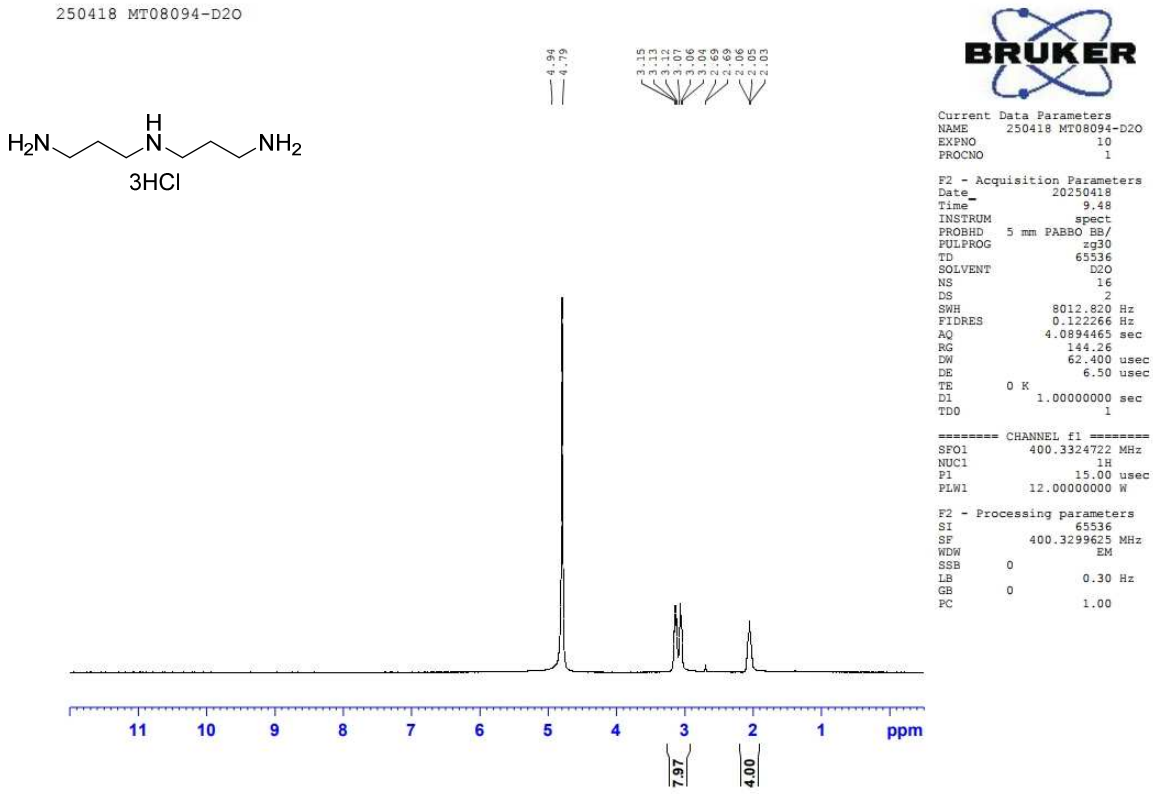


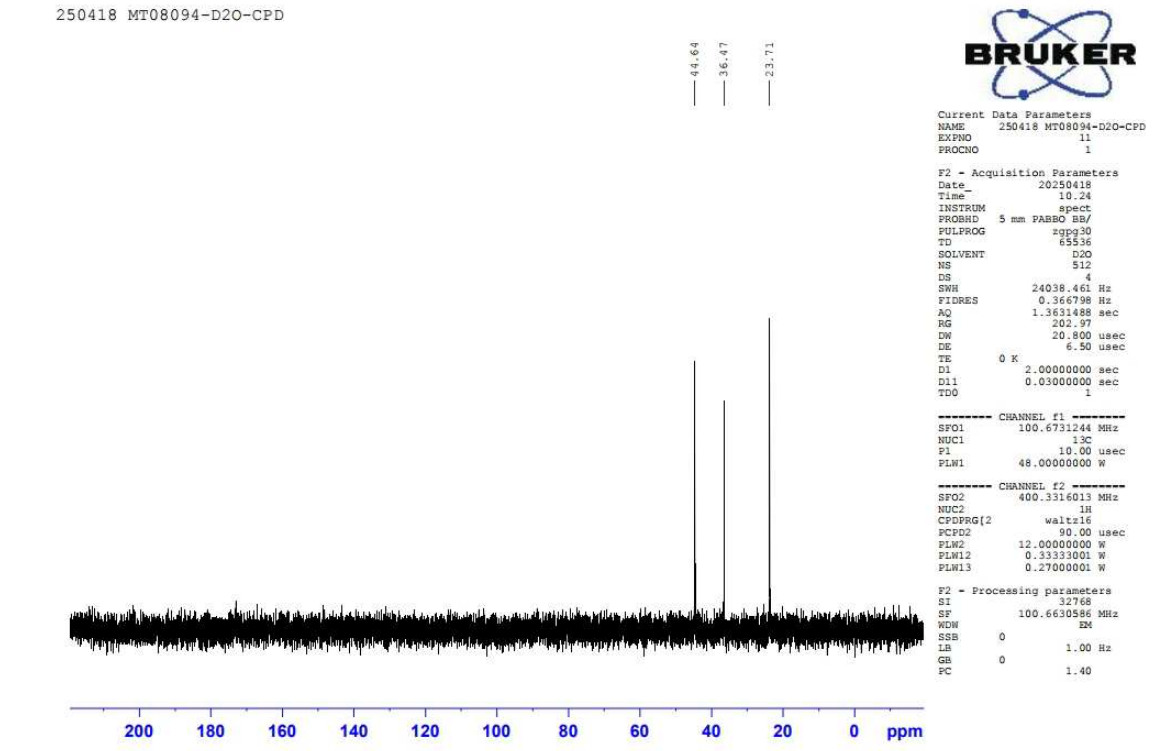
NMR chart of **32**



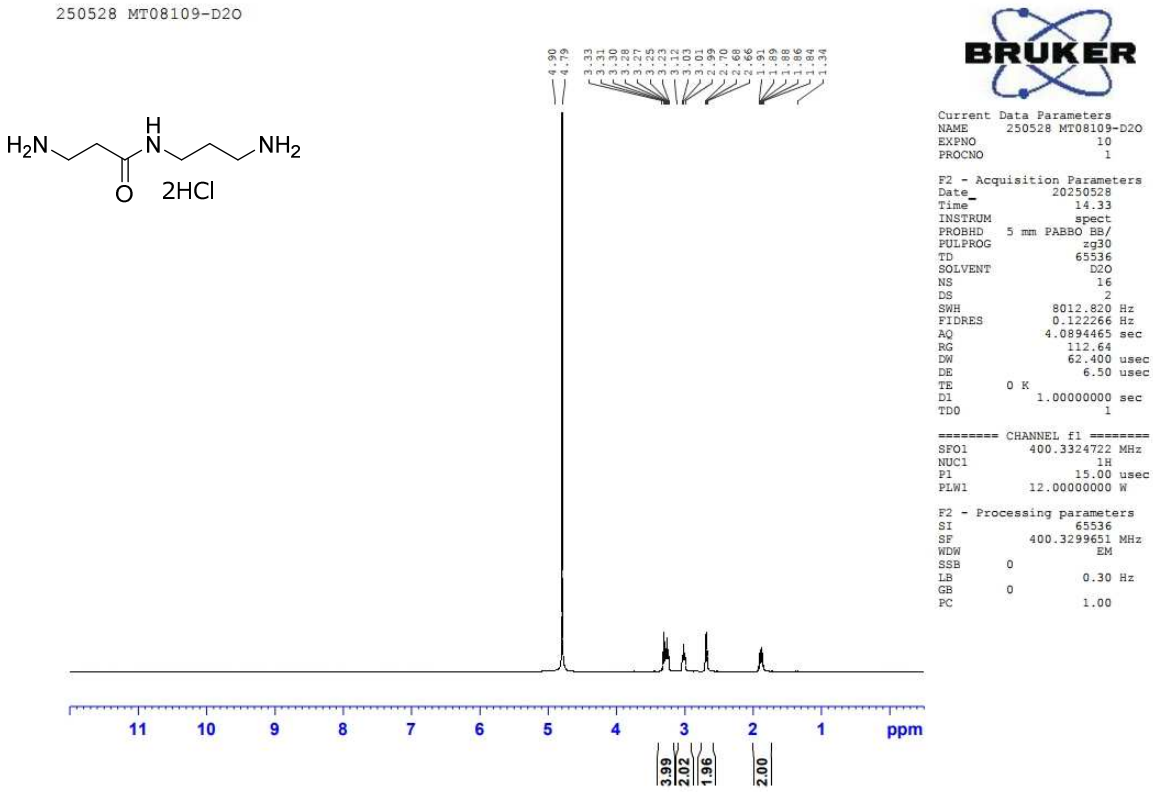


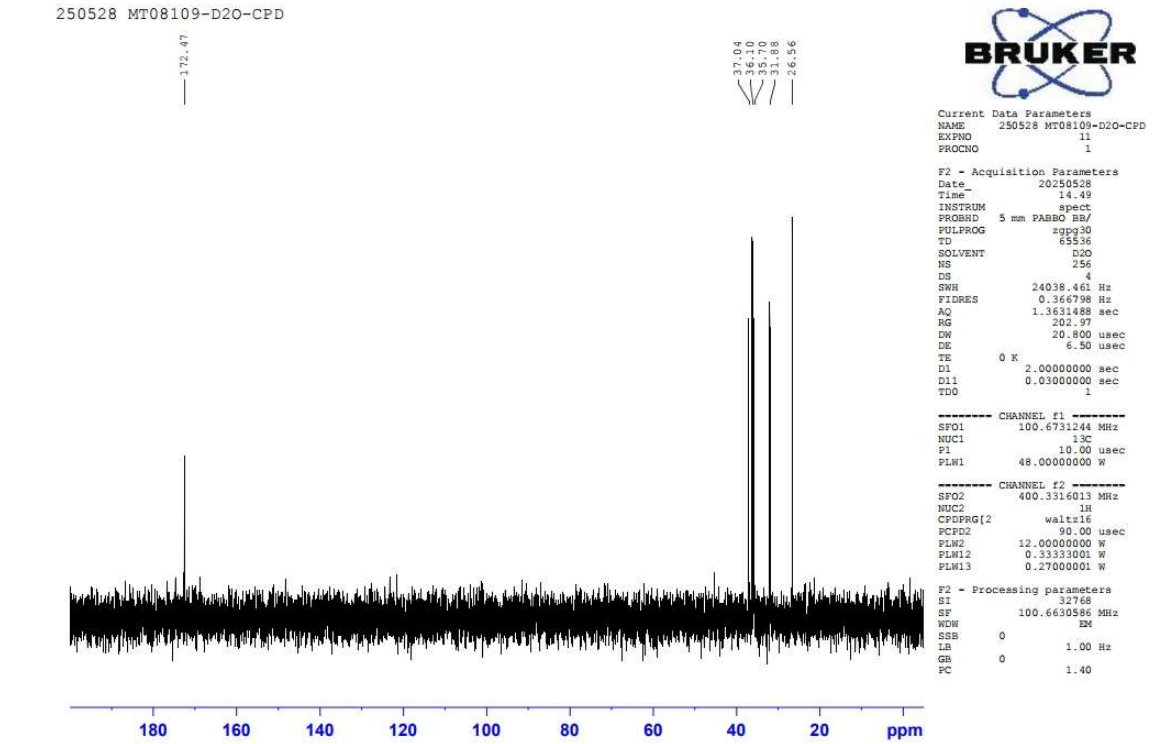
NMR chart of **1**



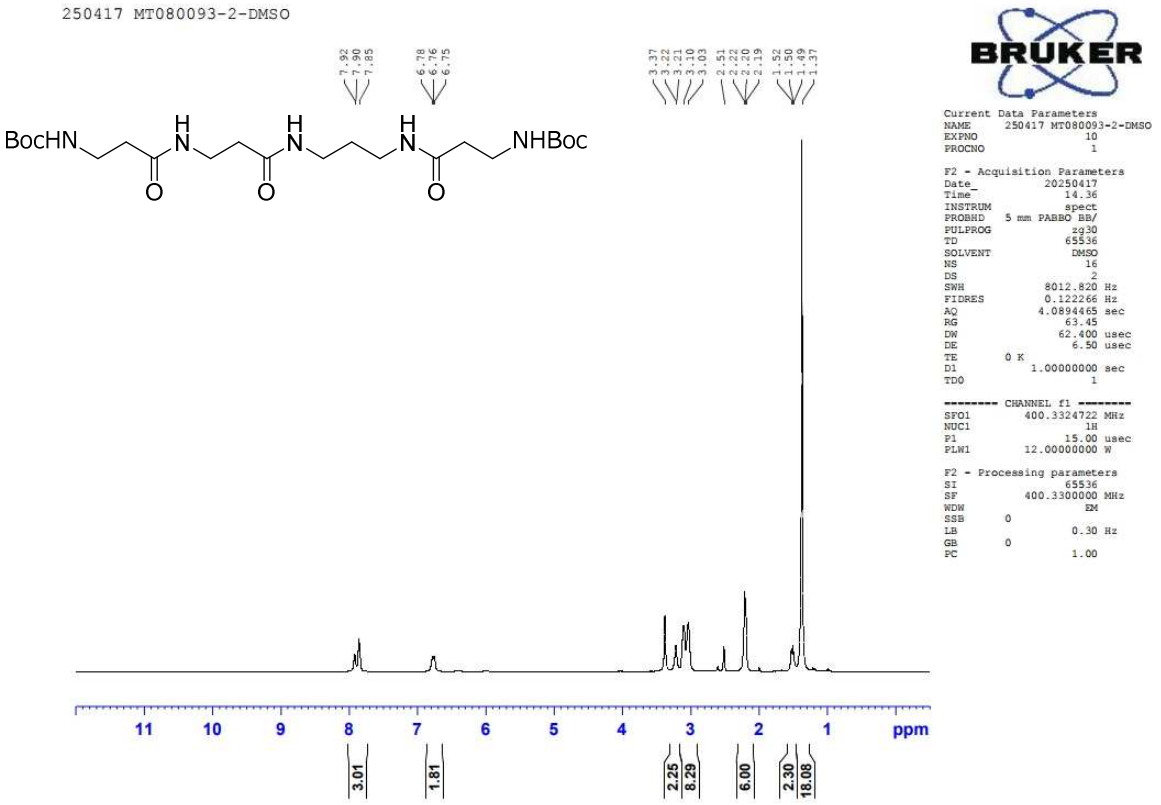


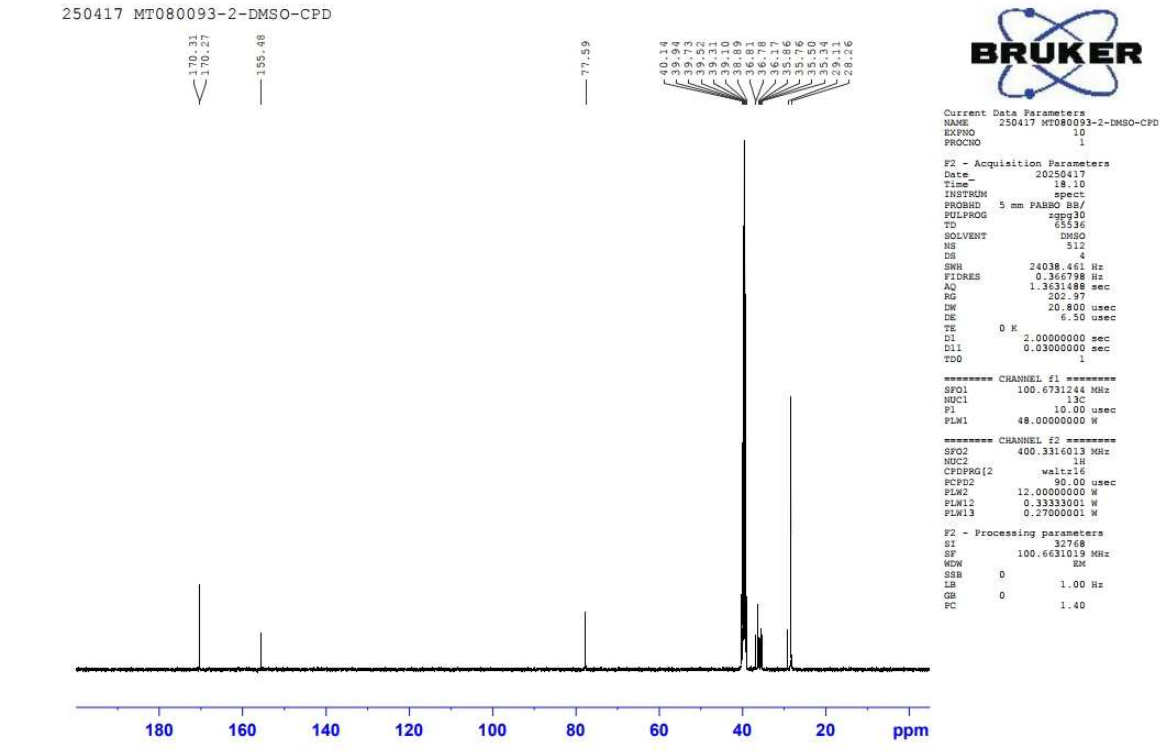
NMR chart of **33**



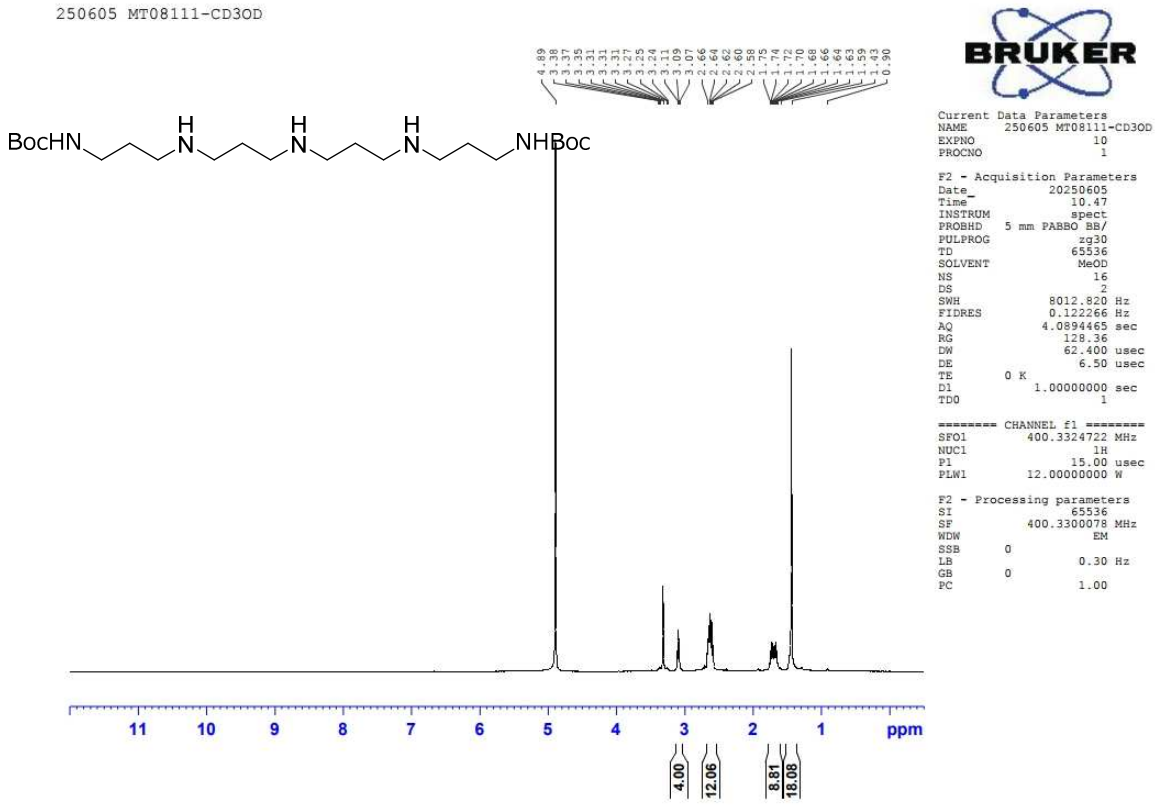


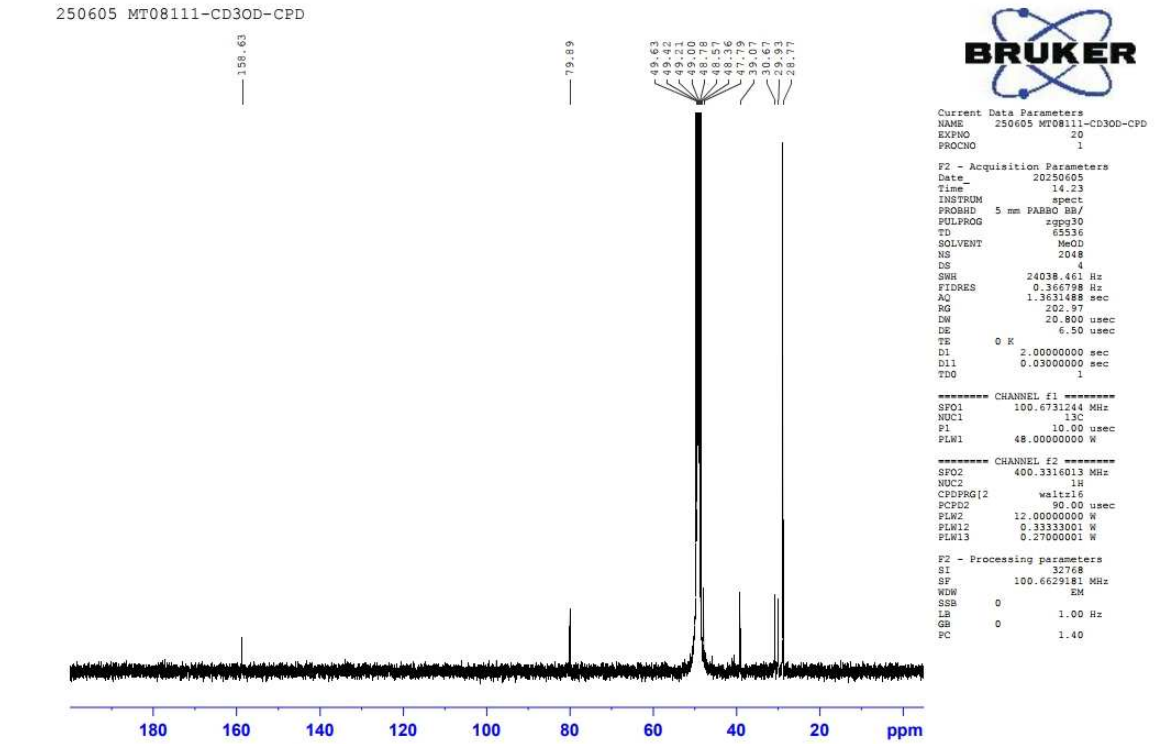
NMR chart of **34**



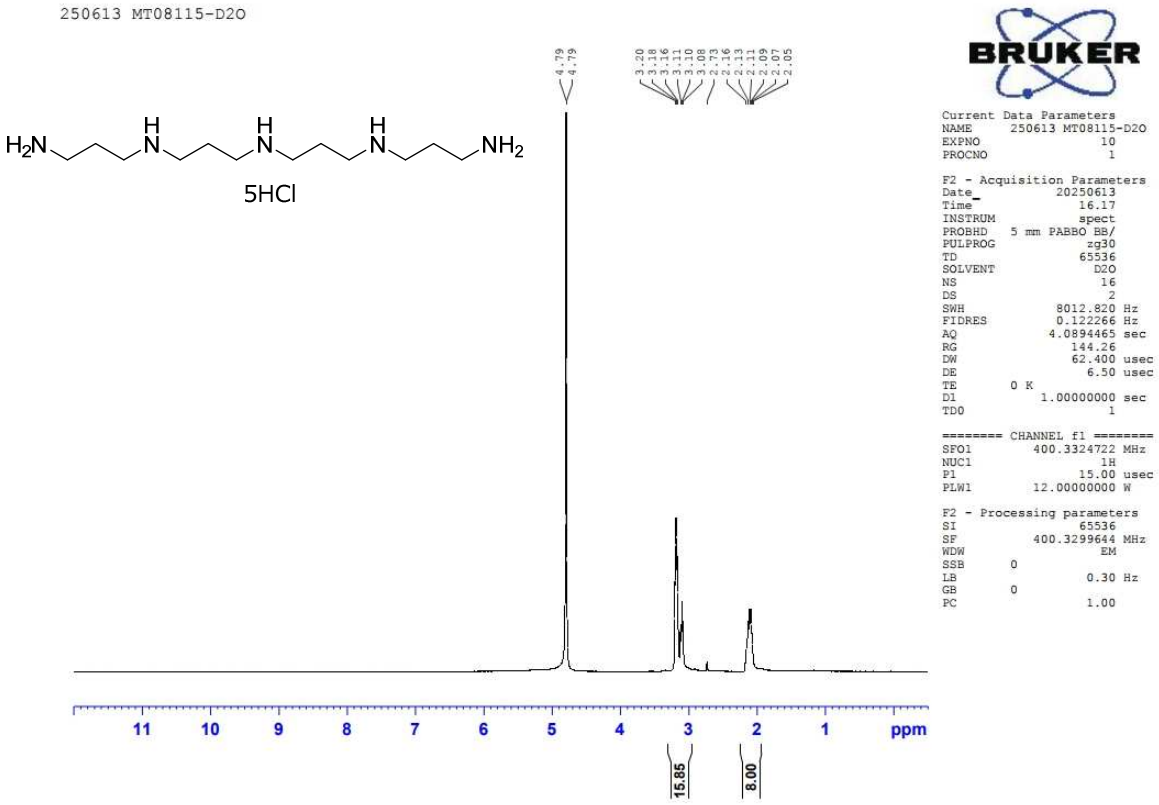


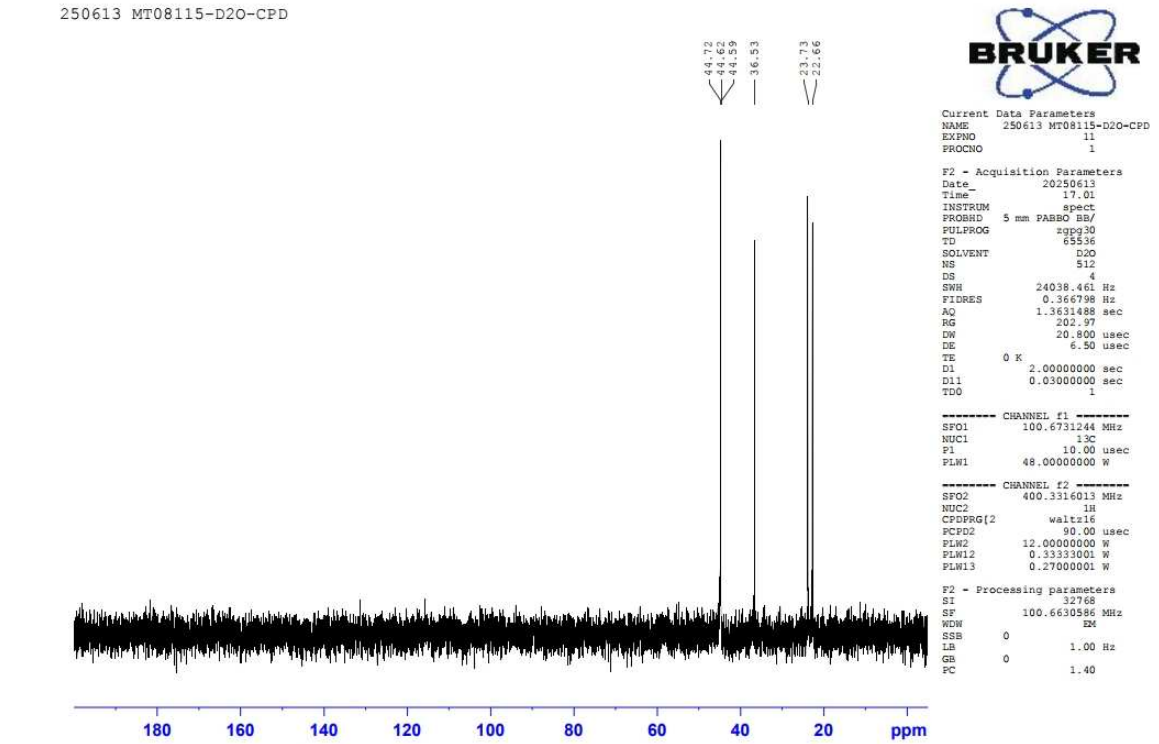
NMR chart of **35**



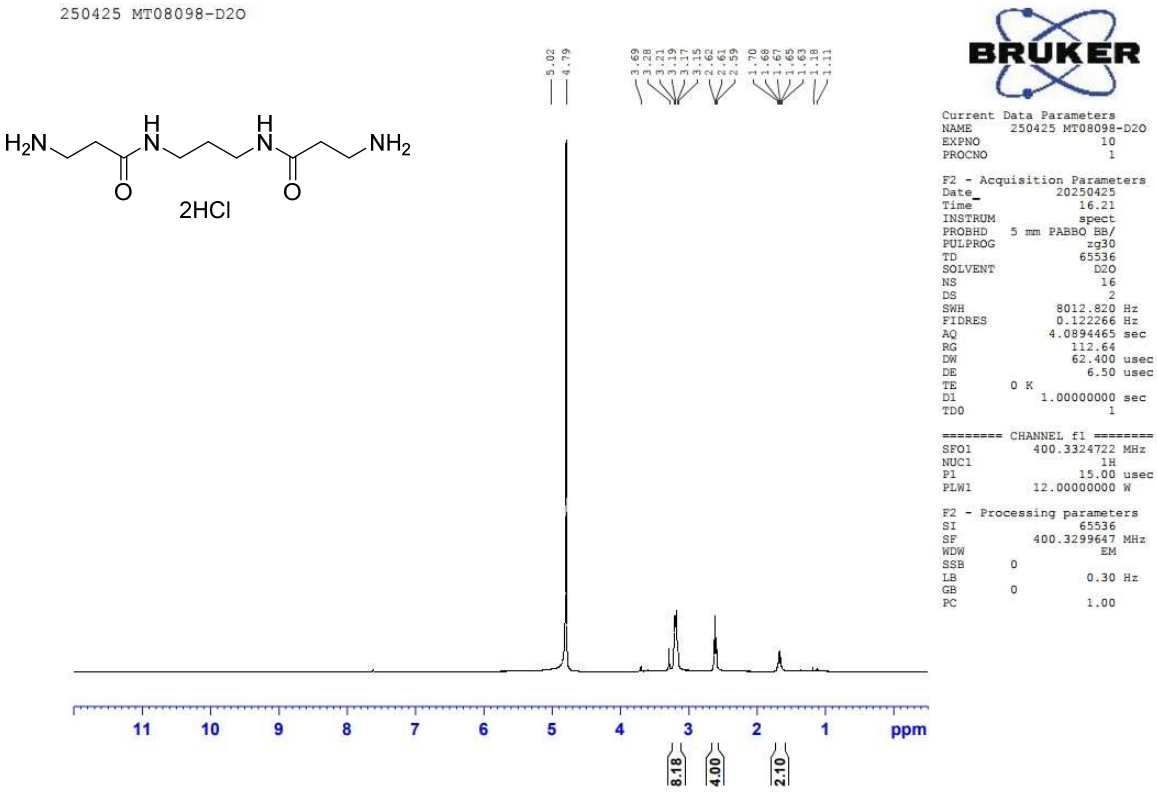


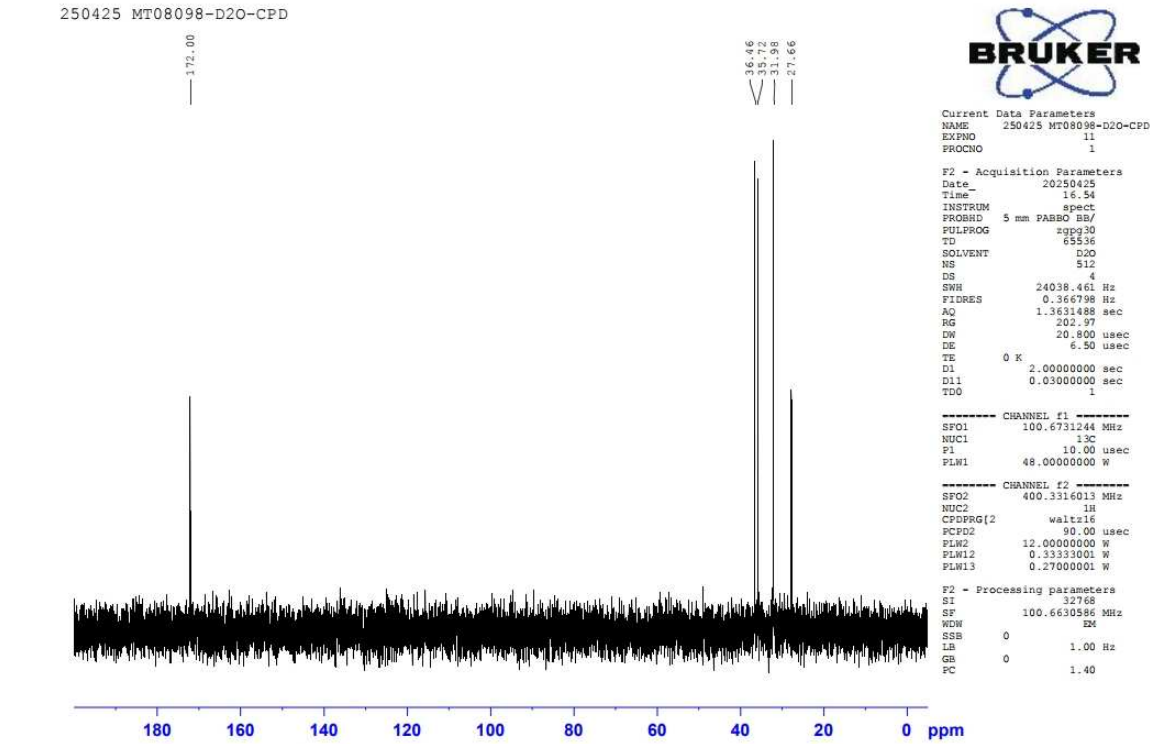
NMR chart of **14**



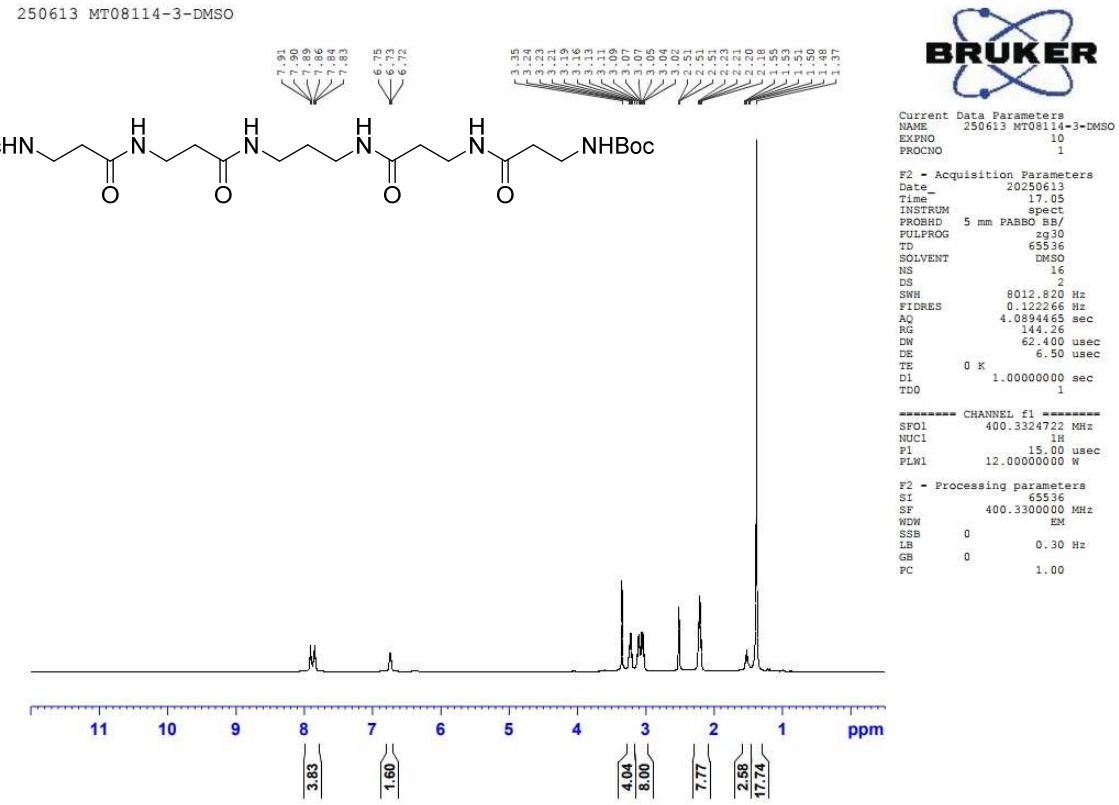


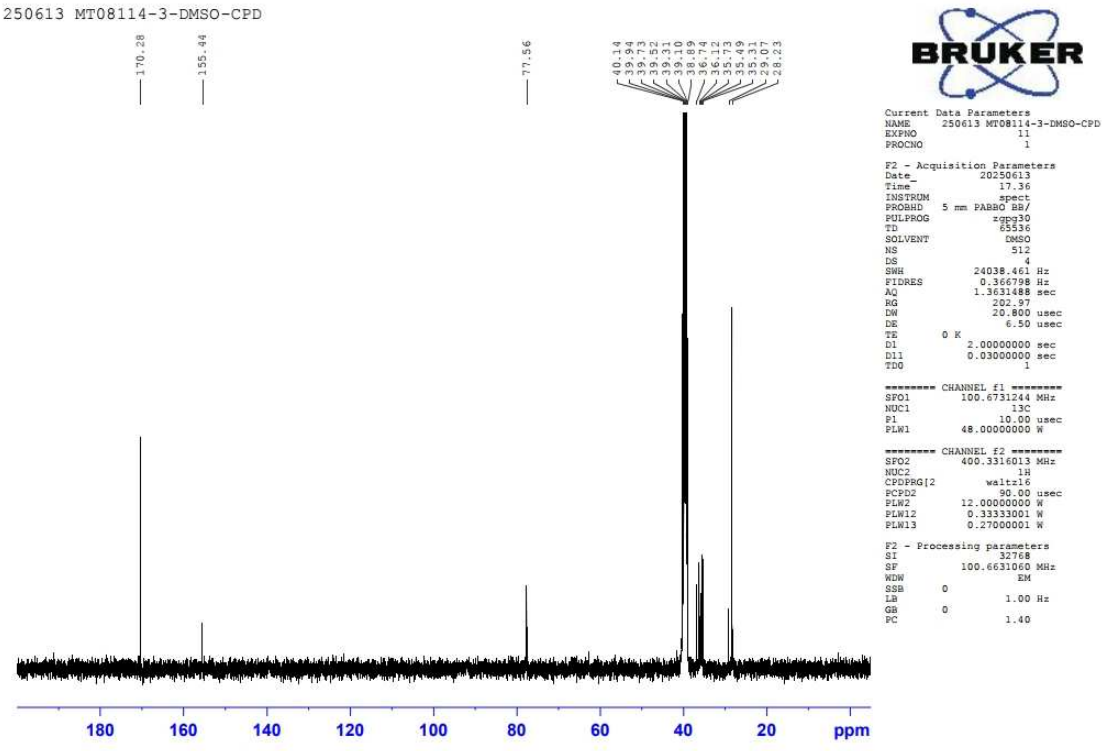
NMR chart of **36**



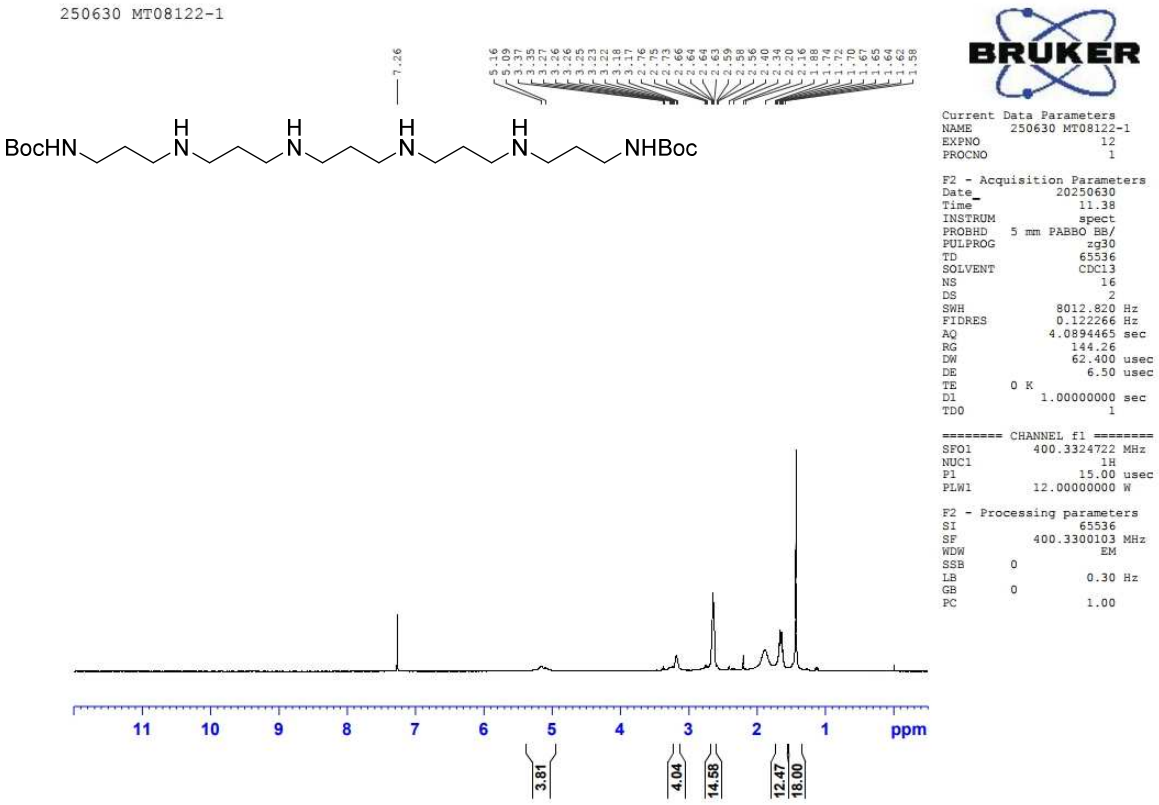


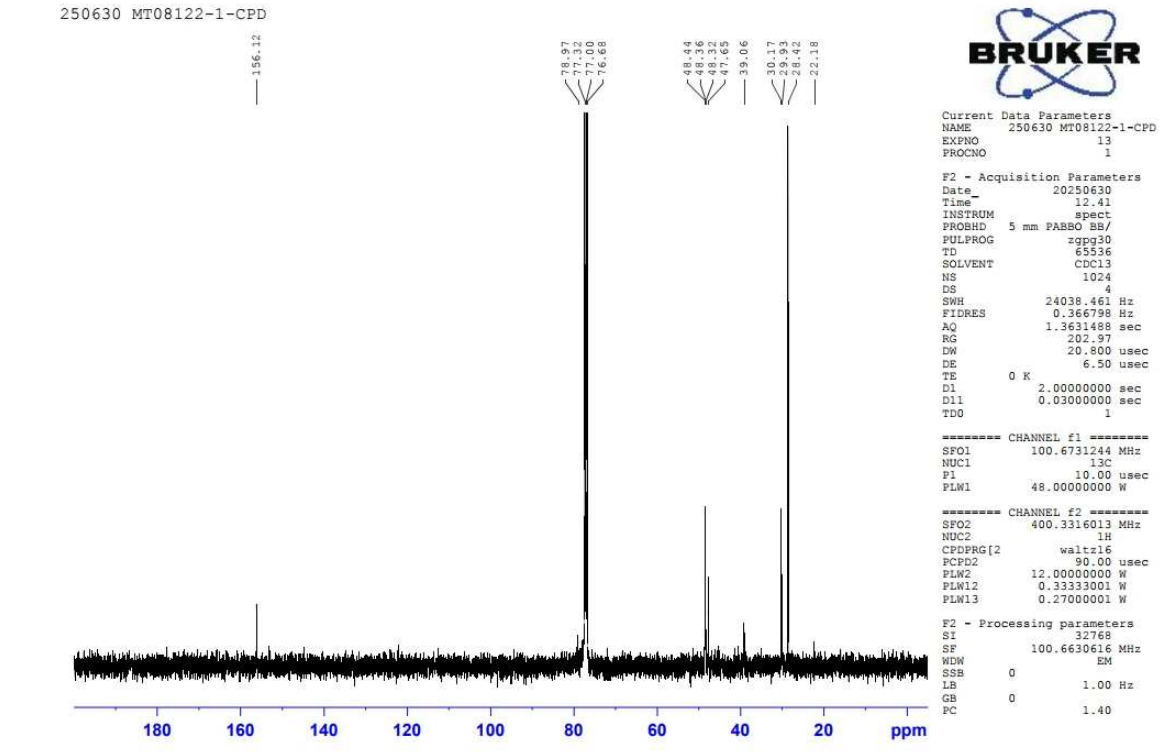
NMR chart of **37**





NMR chart of **38**





NMR chart of **17**