Supplementary Material (ESI) for Chemical Communications

Supporting Information

Sheet-Forming Abiotic Foldamers

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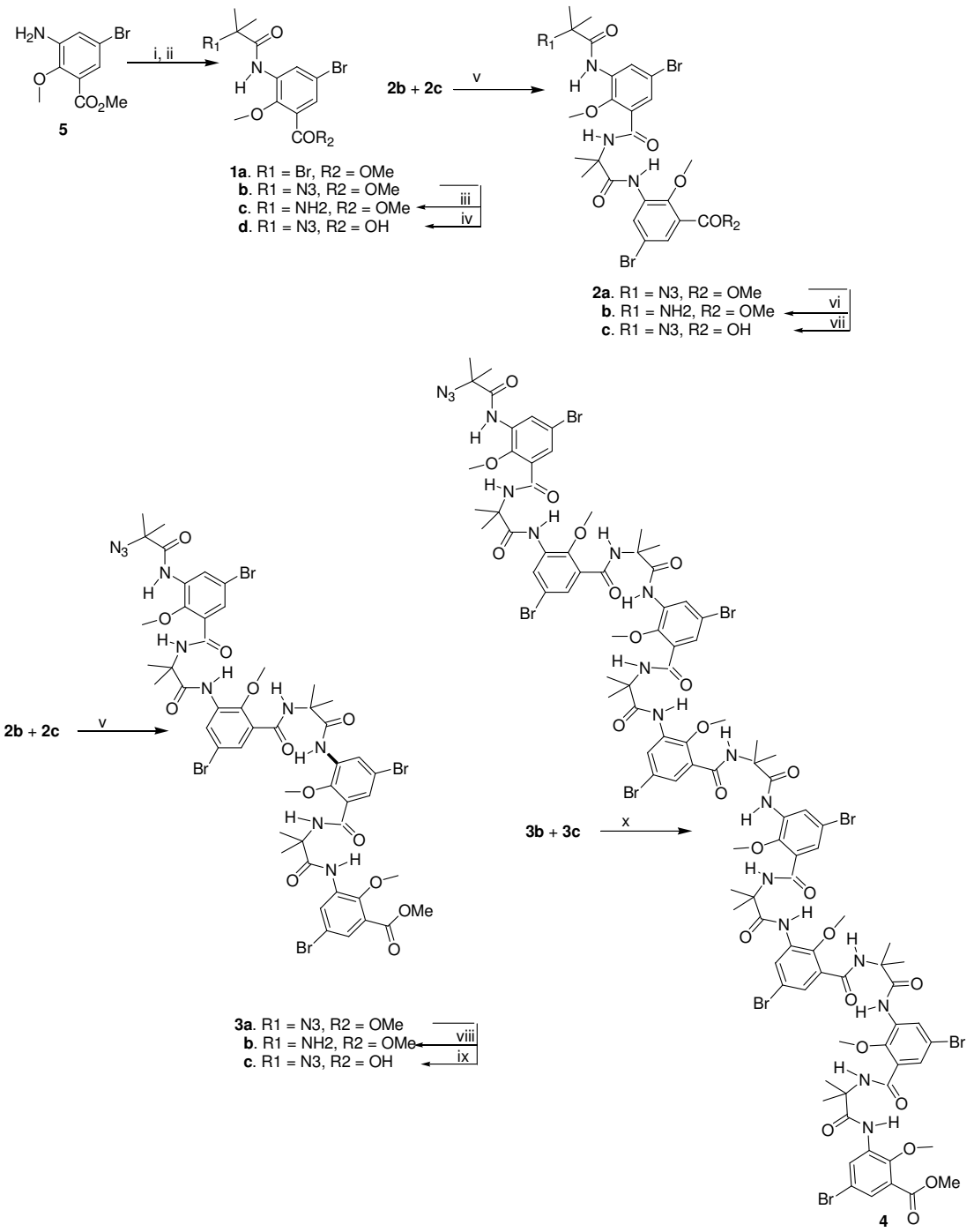
General Methods. Unless otherwise stated, starting materials were obtained from commercial suppliers and used without further purification. Dry dichloromethane (DCM) was freshly prepared by distillation over P_2O_5. Dry dimethyl sulphoxide (DMSO) and acetonitrile (MeCN) were freshly distilled over CaH_2. Dry reactions were performed under argon atmosphere. Purification by column chromatography was performed in 100-200-mesh silica, unless otherwise stated. Electrospray ionization mass spectrometry (ESI-MS) was carried out on a Finnigan MAT-1020 mass spectrometer and MALDI-TOF mass spectra on a Voyager-DE STR mass spectrometer. IR spectra, recorded in $CHCl_3$ or nujol were obtained from Perkin–Elmer 68515 PC-FTIR spectrophotometer. Combustion data were recorded on Elmentar-Vario-EL (Heraeus Company Ltd., Germany). Melting points were measured on Buchi 535 melting point apparatus and are uncorrected. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates. Single crystal X-ray data were collected on a Bruker SMART APEX CCD diffractometer with graphite-monochromatized (Mo Kα=0.71073Å) radiation at room temperature. All the data were corrected for Lorentzian, polarization and absorption effects using Bruker's SAINT and SADABS programs. SHELX-97[3] was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model. NMR spectra were recorded in $CDCl_3$ and d6-DMSO on AC 200MHz and DRX-400 MHz Bruker NMR spectrometers. The oligomers deposited on carbon coated polymer film were analyzed by transmission electron microscopy (TEM) on a JEOL 1200EX instrument.

Synthetic scheme:



Reagent and condition: (i) Bromo isobutyryl bromide, DIPEA, DCM; (ii) LiN_3, DMSO, 40^0C, 48 hrs.; (iii) 2 equiv. $SnCl_2.2H_2O$, MeOH, 40^0C, 5 hrs.; (iv) 1.5 equiv. $LiOH.H_2O$, aq. MeOH, 18 hrs.; (v) TBTU, MeCN, DIPEA, rt, 12 hrs.; (vi) $SnCl_2.2H_2O$, MeOH, 60^0C, 5 hrs.; (vii) 2.5 equiv. $LiOH.H_2O$, aq. MeOH, 18 hrs.; (viii) 6 equiv. $SnCl_2.2H_2O$, MeOH, reflux, 48 hrs.; (ix) 3 equiv. $LiOH.H_2O$, MeOH, dioxane, water, 24 hrs.; (x) TBTU, MeCN, DCM, DIPEA, rt, 12 hrs.

Experimental Section:

Crystallographic data for **2**. ($C_{25}H_{28}Br_2N_6O_7$): M= 684.35, crystal size, 0.84 x 0.14 x 0.13 mm^3, T = 297(2) K, crystal system, monoclinic, space group $P2_1/c$; a = 18.553(4), b = 16.680(4), c = 9.608(2) Å, β = 101.480(4)°, V = 2913.8(11) $Å^3$, Z = 4, F(000) = 1384, d calc [g cm^{-3}] = 1.560, μ [mm^{-1}] = 2.835, absorption correction, multi-scan, T_{min} = 0.1990; T_{max} = 0.7130; 20883 reflection collected, 5136 unique reflections, 4077 observed reflections, 368 refined parameters, R_1 [I>2σ(I)] = 0.0370, WR_2 = 0.0873 (all data R = 0.0512, wR2 = 0.0942), goodness of fit, 1.008, $\Delta\rho_{max}$, $\Delta\rho_{min}$ (e $Å^{-3}$)= 0.575, -0.528. Crystallographic data of **2** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-640754. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK.

Methyl 5-bromo-3-(2-bromo-2-methylpropanamido)-2-methoxybenzoate 1a: To a ice cold solution of hydrochloride salt of methyl 3-amino-5-bromo-2-methoxybenzoate **5** (3.30 g, 11.2 mmol, 1 equiv) and N,N'-diisopropylethylamine, DIPEA (5.72 mL, 33.3 mmol, 3 equiv) in dry DCM (10 mL) was added slowly bromo isobutyryl bromide (1.65 mL, 13.4 mmol, 1.2 equiv). The reaction mixture was allowed to come at room temperature and stirred for additional 12 hrs. The reaction mixture was diluted with DCM (100 mL) and washed sequentially with saturated sodium bicarbonate, dil. HCl and brine solution. The organic layer was dried over Na_2SO_4, filtered and solvent was stripped off under reduced pressure. The crude product was purified by column chromatography. Yield 4.28 g (93.8%); mp 41 ^{0}C; IR ($CHCl_3$) ν (cm^{-1}): 3367.48, 3107.11, 3022.25, 2985.60, 2950.89, 1731.96, 1693.38, 1514.02, 1421.44, 1317.29, 1274.86, 1226.64, 1149.50, 991.34; ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.27 (s, 1H), 8.73 (d, *J* = 2.52 Hz, 1H),

7.73 (d, *J* = 2.53 Hz, 1H), 3.94 (s, 3H), 3.93 (s, 3H), 2.05 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.92, 164.16, 148.23, 133.38, 128.64, 126.05, 124.60, 116.82, 62.51, 62.17, 52.42; ESI Mass: 411.2 (M^+); Anal. Calcd. For $C_{13}H_{15}Br_2NO_4$: C = 38.17, H = 3.70, N = 3.42; Found: C = 38.27, H = 3.51, N = 3.57.

Methyl 3-(2-azido-2-methylpropanamido)-5-bromo-2-methoxybenzoate 1b: To a solution of **1a** (4.09 g, 10 mmol, 1 equiv) in dry DMSO (15 mL) was added lithium azide (2.45 g, 50 mmol, 5 equiv) and the reaction mixture was heated at 40 ^{0}C for 48 hrs. The reaction mixture was cooled and added to water. The water layer was extracted with ethyl acetate. The combined organic layer was given water and brine wash. The organic layer was dried over Na_2SO_4, filtered and solvent was stripped off under reduced pressure. The crude product was purified by column chromatography. Yield 3.2 g (86.2%); mp 60-61 ^{0}C; IR ($CHCl_3$) ν (cm^{-1}): 3377.12, 3022.25, 2979.82, 2952.81, 2115.77, 1731.96, 1693.38, 1514.02, 1421.44, 1315.36, 1269.07, 1149.50, 991.34; ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.07 (s, 1H), 8.76 (d, *J* = 2.53 Hz, 1H), 7.71 (d, *J* = 2.52 Hz, 1H), 3.93 (s, 3H), 3.90 (s, 3H), 1.63 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.31, 164.09, 148.20, 133.02, 128.43, 126.13, 124.56, 116.58, 64.57, 62.12, 52.25, 24.22; ESI Mass: 371.3 (M + 1), 393.4 (M + Na); Anal. Calcd. For $C_{13}H_{15}BrN_4O_4$: C = 42.07, H = 4.07, N = 15.09; Found: C = 42.26, H = 4.23, N = 15.28.

Methyl 3-(2-amino-2-methylpropanamido)-5-bromo-2-methoxybenzoate 1c: To a stirred suspension of $SnCl_2.2H_2O$ (3.29 g, 14.6 mmol, 2 equiv.) in methanol (15 mL) was added **1b** (2.71 g, 7.3 mmol, 1 equiv.) and the reaction mixture was heated at 40 ^{0}C for 5 hrs. Methanol was removed under reduced pressure. The residue was dissolved in ethyl acetate (50 mL) and slowly added to a saturated sodium bicarbonate solution. Filtered

through celite and organic layer separated. The water layer was further extracted with ethyl acetate (2 x 30 mL). The combined organic layer was given water and brine wash (2 x 50 mL each). The organic layer was dried over Na_2SO_4 and used for next step without further purification. Yield 2.46 g (97.6%).

3-(2-azido-2-methylpropanamido)-5-bromo-2-methoxybenzoic acid 1d: To a solution of **1b** (2.71 g, 7.3 mmol, 1 equiv.) in methanol (25 mL) was added $LiOH.H_2O$ (0.63 g, 15 mmol, 1.5 equiv.) in water (5 mL) and stirred for 18 hrs. The solvent was stripped off under reduced pressure. To the residue was added water (50 mL) and acidified with dilute HCl. The water layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layer was given water and brine wash, dried over Na_2SO_4 and used for next reaction without further purification. Yield 2.52 g (96.6%).

Methyl 3-(2-(3-(2-azido-2-methylpropanamido)-5-bromo-2-methoxybenzamido)-2-methylpropanamido)-5-bromo-2-methoxybenzoate 2a: To an ice-cold stirred solution of the acid **1d** (2.5 g, 7 mmol, 1 equiv.) and amine **1c** (2.42 g, 7 mmol, 1 equiv.) in dry acetonitrile (15 mL), DIPEA (1.80 mL, 10.5 mmol, 1.5 equiv.) was added followed by the addition of TBTU (2.70 g, 8.4 mmol, 1.2 equiv.). The resulting reaction mixture was stirred overnight at room temperature. The solvent was stripped off under reduced pressure; the residue was dissolved in dichloromethane (100 mL) and washed sequentially with dilute HCl, saturated sodium bicarbonate, and water. Drying and concentration in vacuum yielded the crude ester, which was purified by column chromatography to furnish **2a**. Yield 3.42 g (71.3%); mp 163-164^{0}C; IR ($CHCl_3$) ν (cm^{-1}): 3375.20, 3020.32, 2977.89, 2943.17, 2117.69, 1730.03, 1697.24, 1517.87, 1411.80, 1315.36, 1217.00, 1149.50, 987.49; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.10 (s, 1H), 8.92 (s,

1H), 8.78 (d, *J* = 2.26 Hz, 1H), 8.72 (d, *J* = 2.51 Hz), 8.05 (s, 1H), 7.89 (d, *J* = 2.51 Hz, 1H), 7.71 (d, *J* = 2.51 Hz, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.86 (s, 3H), 1.79 (s, 6H), 1.67 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.07, 170.44, 164.37, 163.28, 148.27, 146.26, 133.72, 132.33, 128.54, 128.38, 127.23, 126.85, 126.32, 124.61, 118.46, 116.80, 64.77, 62.48, 62.37, 58.38, 52.40, 25.16, 24.41; ESI Mass: 685.1 (M + 1), 707.0 (M + Na), 723.0 (M + K); Anal. Calcd. For $C_{25}H_{28}Br_2N_6O_7$: C = 43.88, H = 4.12, N = 12.28; Found: C = 43.73, H = 4.21, N = 12.19.

Methyl 3-(2-(3-(2-amino-2-methylpropanamido)-5-bromo-2-methoxybenzamido)-2-methylpropanamido)-5-bromo-2-methoxybenzoate 2b: To a stirred suspension of $SnCl_2.2H_2O$ (2.87 g, 12.7 mmol, 2 equiv.) in methanol (20 mL) was added **2a** (2.9 g, 4.2 mmol, 1equiv.) and the reaction mixture was heated at 60 ^{0}C for 5 hrs. Methanol was removed under reduced pressure. The residue was dissolved in ethyl acetate (70 mL) and slowly added to a saturated sodium bicarbonate solution. Filtered through celite and organic layer separated. The water layer was further extracted with ethyl acetate (2 x 30 mL). The combined organic layer was given water and brine wash (2 x 50 mL each). The organic layer was dried over Na_2SO_4 and used for next step without further purification. Yield 2.65 g (95%).

3-(2-(3-(2-azido-2-methylpropanamido)-5-bromo-2-methoxybenzamido)-2-methylpropanamido)-5-bromo-2-methoxybenzoic acid 2c: To a solution of **2a** (2.95 g, 4.3 mmol, 1 equiv.) in methanol (40 mL) was added $LiOH.H_2O$ (0.45 g, 10.8 mmol, 2.5 equiv.) in water (5 mL) and stirred for 18 hrs. The solvent was stripped off under reduced pressure. To the residue was added water (50 mL) and acidified with dilute HCl. The water layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layer

was given water and brine wash, dried over Na_2SO_4 and used for next reaction without further purification. Yield 2.75 g (95.2%).

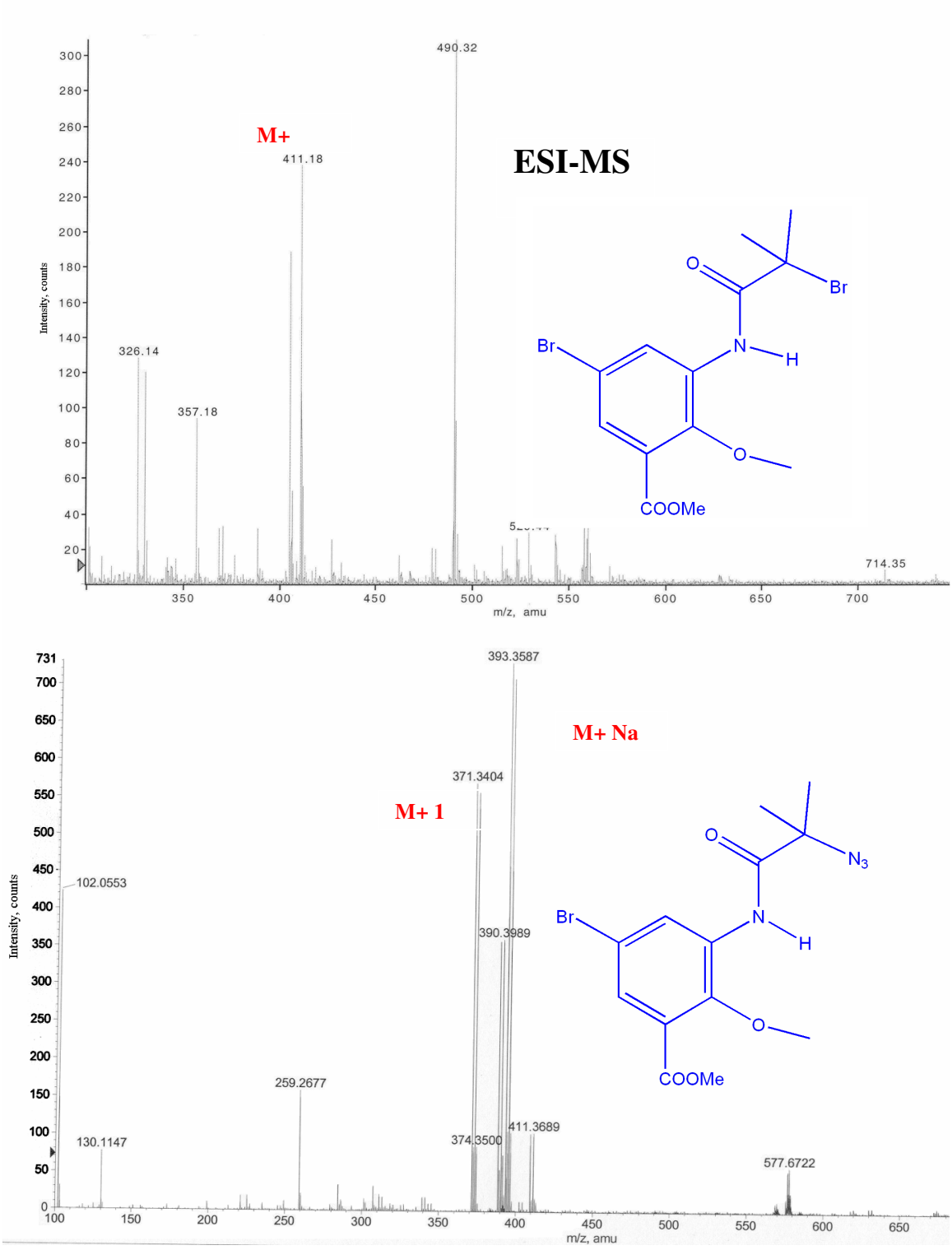
Methyl 3-(2-(3-(2-(3-(2-(3-(2-azido-2-methylpropanamido)-5-bromo-2-methoxybenzamido)-2-methylpropanamido)-5-bromo-2-methoxybenzamido)-2-methylpropanamido)-5-bromo-2-methoxybenzamido)-2-methylpropanamido)-5-bromo-2-methoxybenzoate 3a: To an ice-cold stirred solution of the acid **2c** (2.63 g, 3.9 mmol, 1equiv.) and amine **2b** (2.58 g, 3.9 mmol, 1 equiv.) in dry acetonitrile (15 mL), DPIEA (1 mL, 5.9 mmol, 1.5 equiv.) was added followed by the addition of TBTU (1.51 g, 4.7 mmol, 1.2 equiv.). The resulting reaction mixture was stirred overnight at room temperature. The solvent was stripped off under reduced pressure; the residue was dissolved in dichloromethane (100 mL) and washed sequentially with dilute HCl, saturated sodium bicarbonate, and water. Drying and concentration in vacuum yielded the crude ester, which was purified by column chromatography to furnish **3a**. Yield 3.52 g (68.4%); mp 213-215^{0}C; IR ($CHCl_3$) ν (cm^{-1}): 3371.34, 3018.39, 2977.89, 2941.24, 2117.69, 1693.38, 1668.31, 1514.02, 1456.16, 1409.87, 1313.48, 1215.07, 981.70; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (s, 1H), 9.69 (s, 1H), 9.45 (s, 1H), 9.36 (d, J = 2.51, 1H), 9.31 (m, 2H), 9.14 (d, J = 2.51, 1H), 8.73 (s, 1H), 8.22 (d, J = 2.51, 1H), 8.19 (d, J = 2.51, 1H), 8.15 (d, J = 2.51, 1H), 7.80 (d, J = 2.51, 1H), 7.67 (s, 1H), 7.65 (s, 1H), 7.55 (s, 1H), 3.74 (s, 3H), 3.57 (s, 3H), 3.56 (s, 3H), 3.45 (s, 3H), 3.25 (s, 3H), 1.64 (s, 6H), 1.60 (s, 6H), 1.57 (s, 6H), 1.34 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 170.5, 164.4, 164.0, 163.9, 163.5, 148.3, 146.5, 146.4, 146.3, 133.8, 133.3, 133.2, 132.4, 128.4, 128.3, 128.2, 127.4, 127.2, 127.1, 127.0, 126.8, 126.6, 124.6, 118.6, 118.43, 118.36, 116.8, 64.8, 62.64, 62.62, 62.5, 62.4, 58.63, 58.62, 58.4, 52.4, 25.33, 25.30, 25.25, 24.44;

MALDI-TOF: 1334.0 (M + Na), 1350.0 (M + K); Anal. Calcd. For $C_{49}H_{54}Br_4N_{10}O_{13}$: C = 44.90, H = 4.15, N = 10.69; Found: C = 45.13, H = 4.24, N = 10.43.

Methyl 3-(2-(3-(2-(3-(2-(3-(2-amino-2-methylpropanamido)-5-bromo-2-methoxybenzamido)-2-methylpropanamido)-5-bromo-2-methoxybenzamido)-2-methylpropanamido)-5-bromo-2-methoxybenzamido)-2-methylpropanamido)-5-bromo-2-methoxybenzoate 3b: To a stirred suspension of $SnCl_2.2H_2O$ (0.41 g, 1.8 mmol, 6 equiv.) in methanol (20 mL) was added **3a** (0.40 g, 0.3 mmol, 1equiv.) and the reaction mixture was refluxed for 48 hrs. Methanol was removed under reduced pressure. The residue was dissolved in ethyl acetate (50 mL) and slowly added to a saturated sodium bicarbonate solution. Filtered through celite and organic layer separated. The water layer was further extracted with ethyl acetate (2 x 30 mL). The combined organic layer was given water and brine wash (2 x 50 mL each). The organic layer was dried over Na_2SO_4 and used for next step without further purification. Yield 2.65 g (90%).

3-(2-(3-(2-(3-(2-(3-(2-azido-2-methylpropanamido)-5-bromo-2-methoxybenzamido)-2-methylpropanamido)-5-bromo-2-methoxybenzamido)-2-methylpropanamido)-5-bromo-2-methoxybenzamido)-2-methylpropanamido)-5-bromo-2-methoxybenzoic acid 3c: To a solution of **3a** (0.40 g, 0.3 mmol, 1equiv.) in a mixture of methanol (15 mL) and dioxane (15 mL) was added $LiOH.H_2O$ (0.38 g, 0.9 mmol, 3 equiv.) in water (3 mL) and stirred for 24 hrs. The solvent was stripped off under reduced pressure. To the residue was added water (50 mL) and acidified with dilute HCl. The water layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layer was given water and brine wash, dried over Na_2SO_4 and used for next reaction without further purification. Yield 2.75 g (95.2%).

Methyl 3-(2-(3-(2-(3-(2-(3-(2-(3-(2-(3-(2-(3-(2-azido-2-methylpropanamido)-5-bromo-2-methoxybenzamido)-2-methylpropanamido)-5-bromo-2-methoxybenzamido)-2-methylpropanamido)-5-bromo-2-methoxybenzamido)-2-methylpropanamido)-5-bromo-2-methoxybenzamido)-2-methylpropanamido)-5-bromo-2-methoxybenzamido)-2-methylpropanamido)-5-bromo-2-methoxybenzamido)-2-methylpropanamido)-5-bromo-2-methoxybenzoate 4: To an ice-cold stirred solution of the acid **3c** (0.38 g, 0.3 mmol, 1equiv.) and amine **3b** (0.38 g, 0.3 mmol, 1 equiv.) in a mixture of dry acetonitrile (10 mL) and dry DCM (10 mL), DPIEA (0.1 mL, 0.6 mmol, 2 equiv.) was added followed by the addition of TBTU (0.14 g, 0.4 mmol, 1.5 equiv.). The resulting reaction mixture was stirred overnight at room temperature. The solid precipitate obtained was filtered, washed with DCM, dilute HCl, saturated sodium bicarbonate, and water. Dried over P_2O_5 vacuum desiccator to furnish **4**. Yield 0.28 (36.9%); mp > 300^0C; IR (Nujol) ν (cm^{-1}): 3400.27, 3274.9, 2115.77, 1706.88, 1647.1, 1521.73, 1508.23, 1461.94, 1377.08, 1321.15, 1147.57, 997.13; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.42 (s, 1H), 9.31 (s,1H), 9.25 (m, 6H), 8.94 (m, 7H), 8.28 (m, 1H), 8.20 (m, 6H), 8.07 (m, 1H), 7.64 (m, 1H), 7.61 (m, 1H), 7.58 (m, 1H), 7.57 (m, 5H), 3.85 (s, 3H), 3.79 (s, 3H), 3.70 (m, 21H), 1.56 (m, 48H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.2, 173.1, 171.1, 164.8, 164.7, 164.5, 149.8, 149.0, 147.8, 134.4, 133.4, 132.6, 131.3, 131.1, 131.0, 128.7, 1218.1, 128.0, 127.9, 126.8, 126.6, 126.2, 115.2, 115.0, 64.6, 62.2, 62.0, 59.9, 57.5, 52.8, 24.7, 24.3; MALDI-TOF: 2562.8 (M+), 2586.1 (M + Na); Anal. Calcd. For $C_{97}H_{106}Br_8N_{18}O_{25}$: C = 45.45, H = 4.17, N = 9.84; Found: C = 45.62, H = 4.21, N = 9.56.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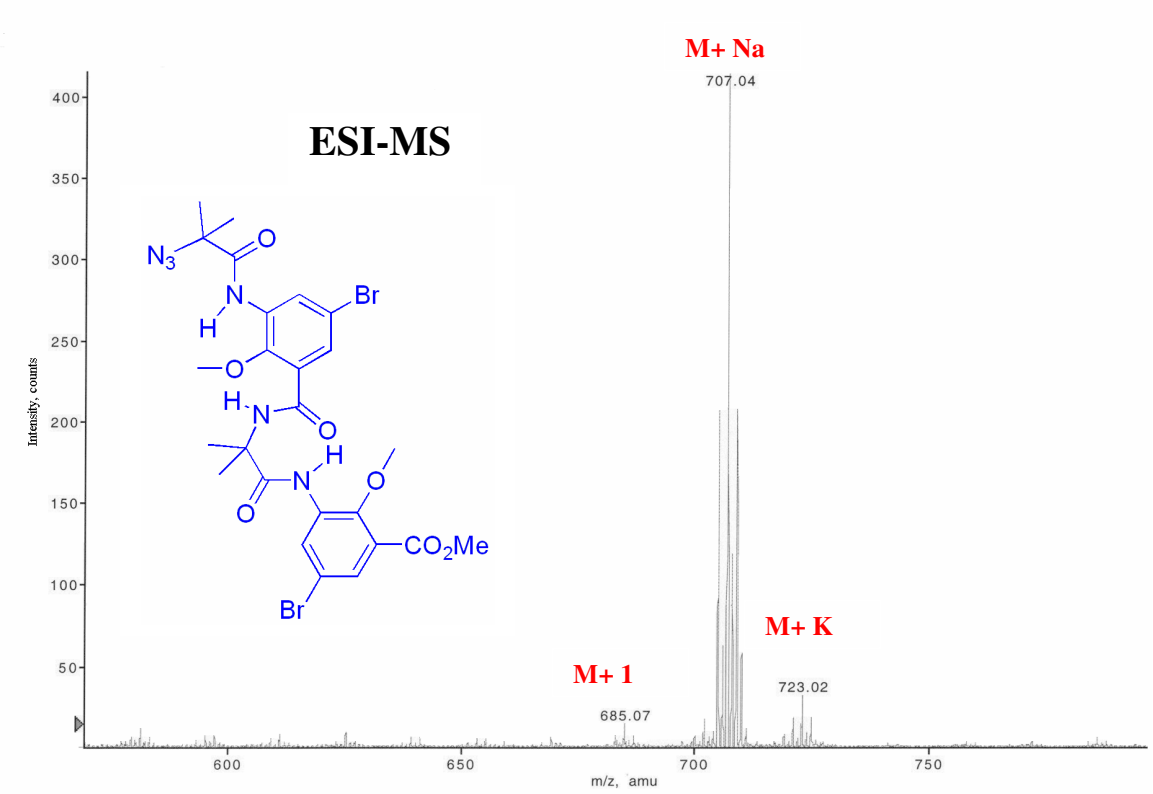
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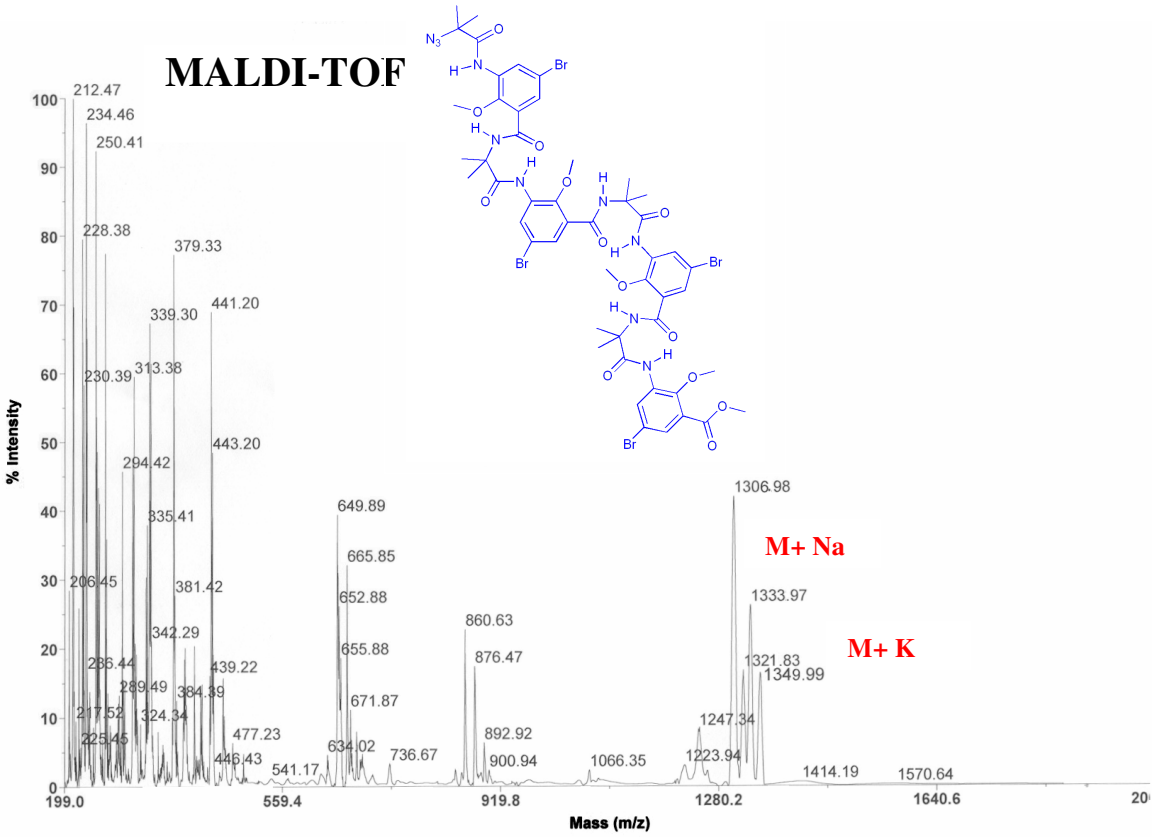
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% Intensity
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339.30
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313.38
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443.20
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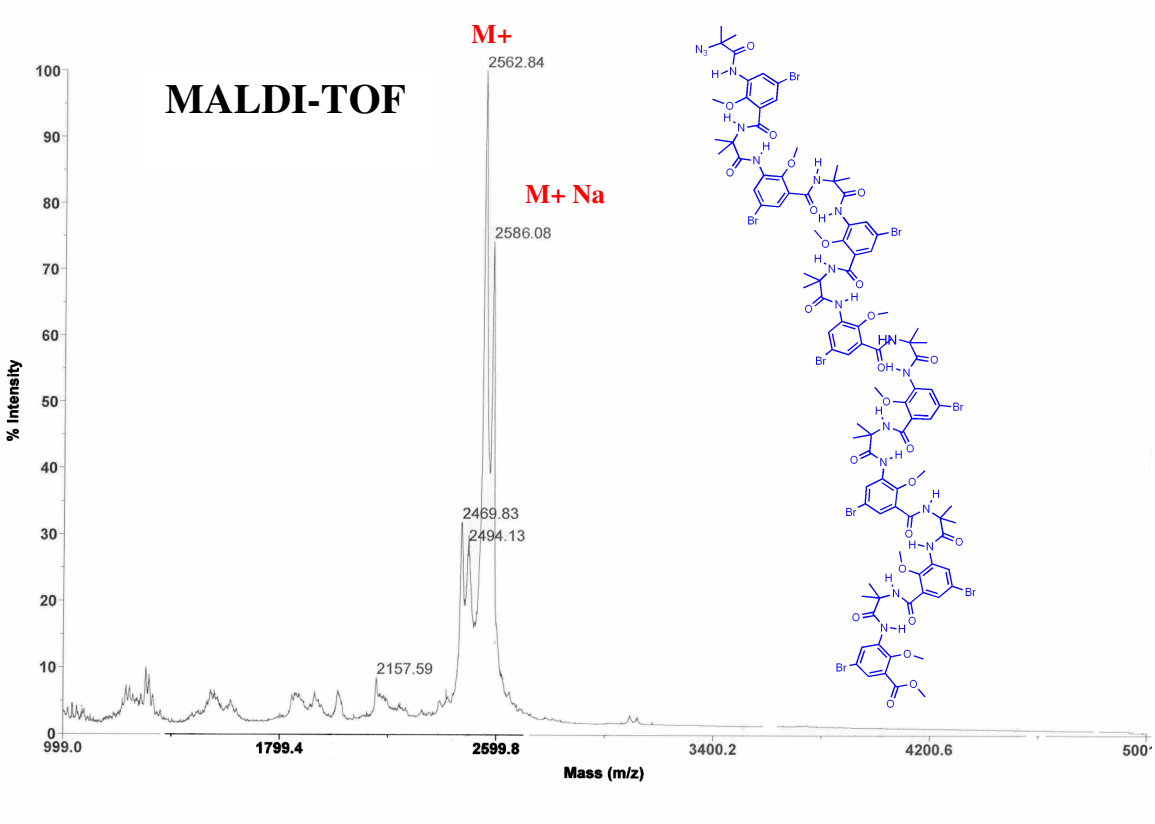
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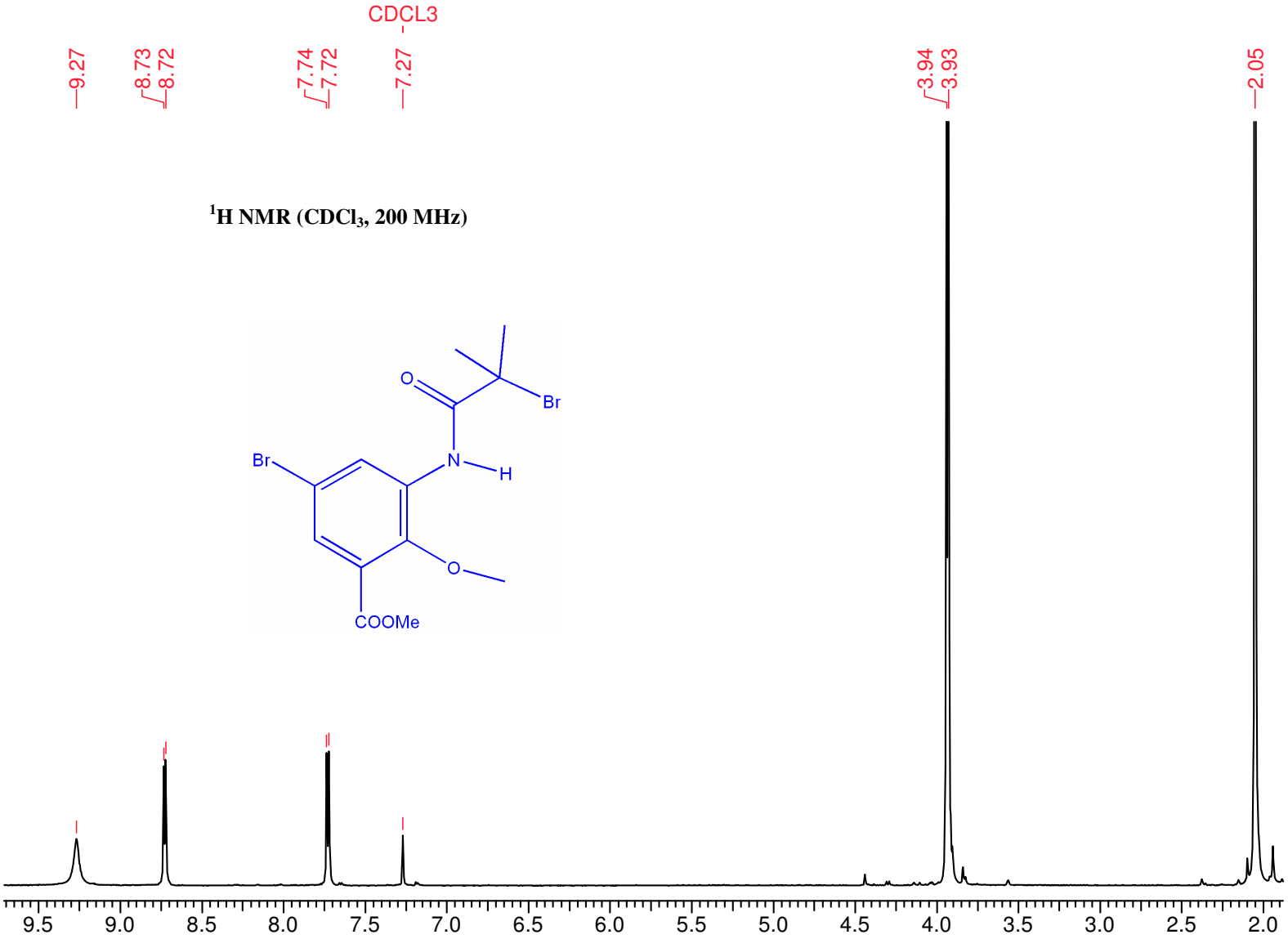
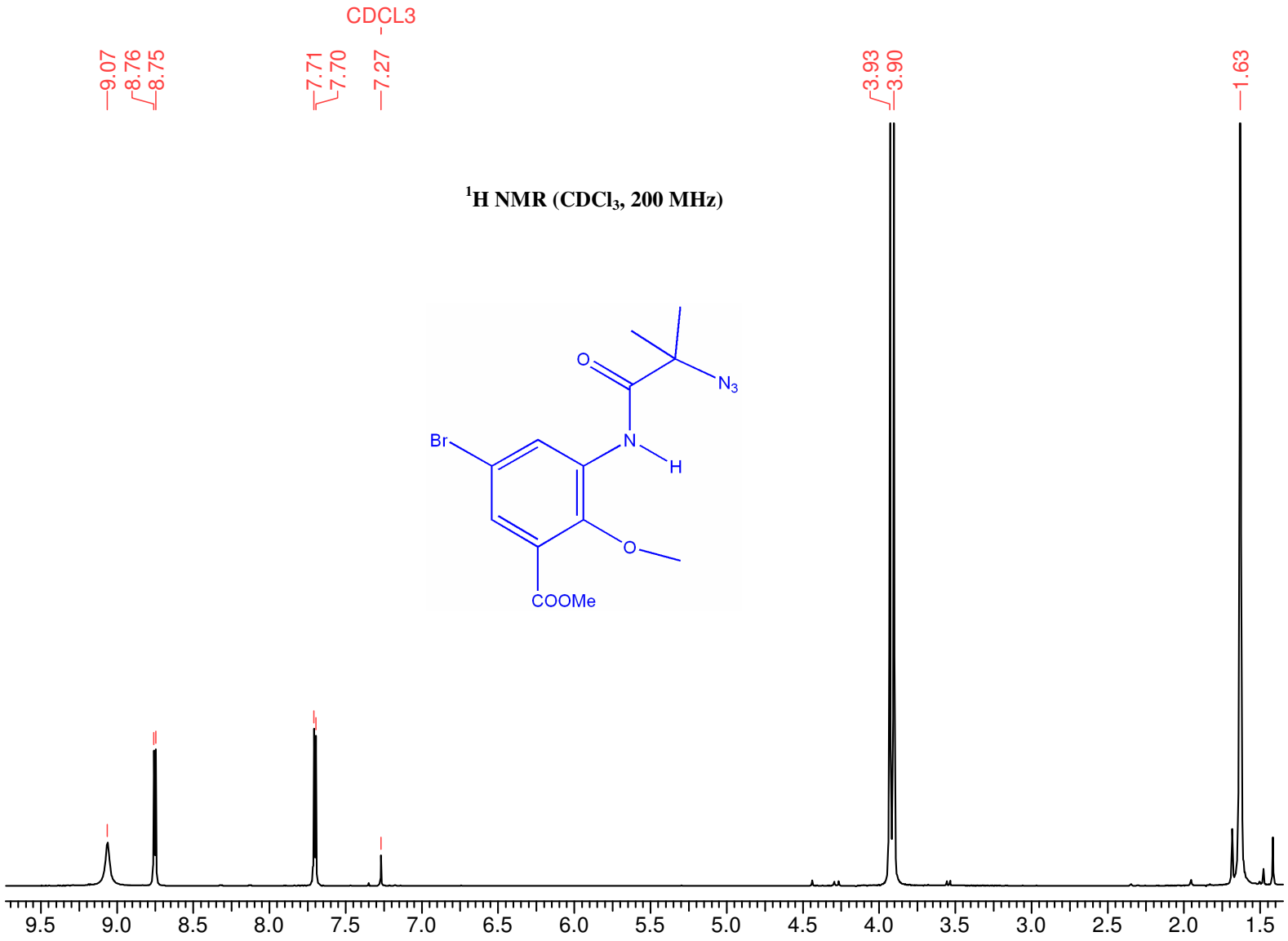
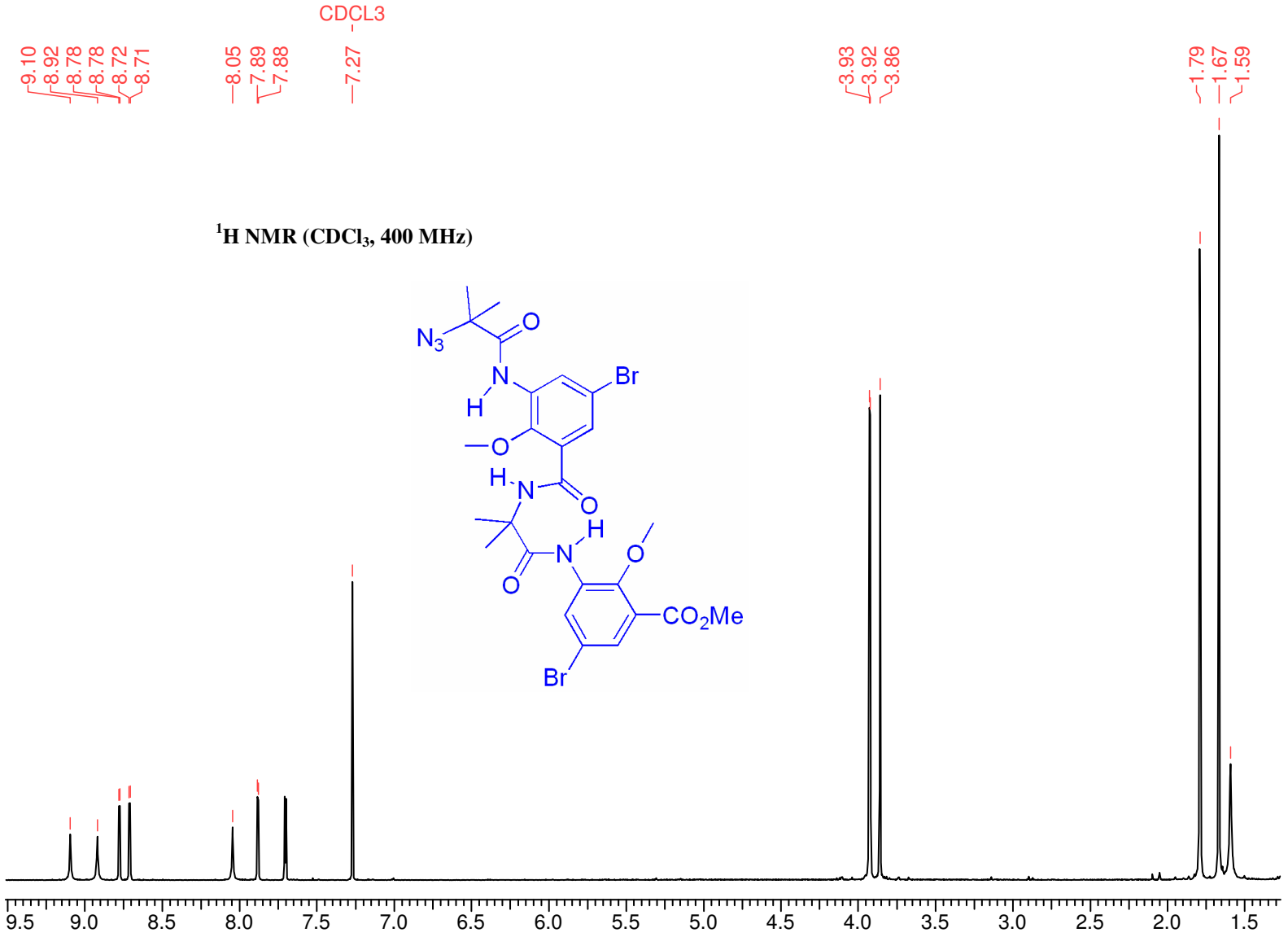
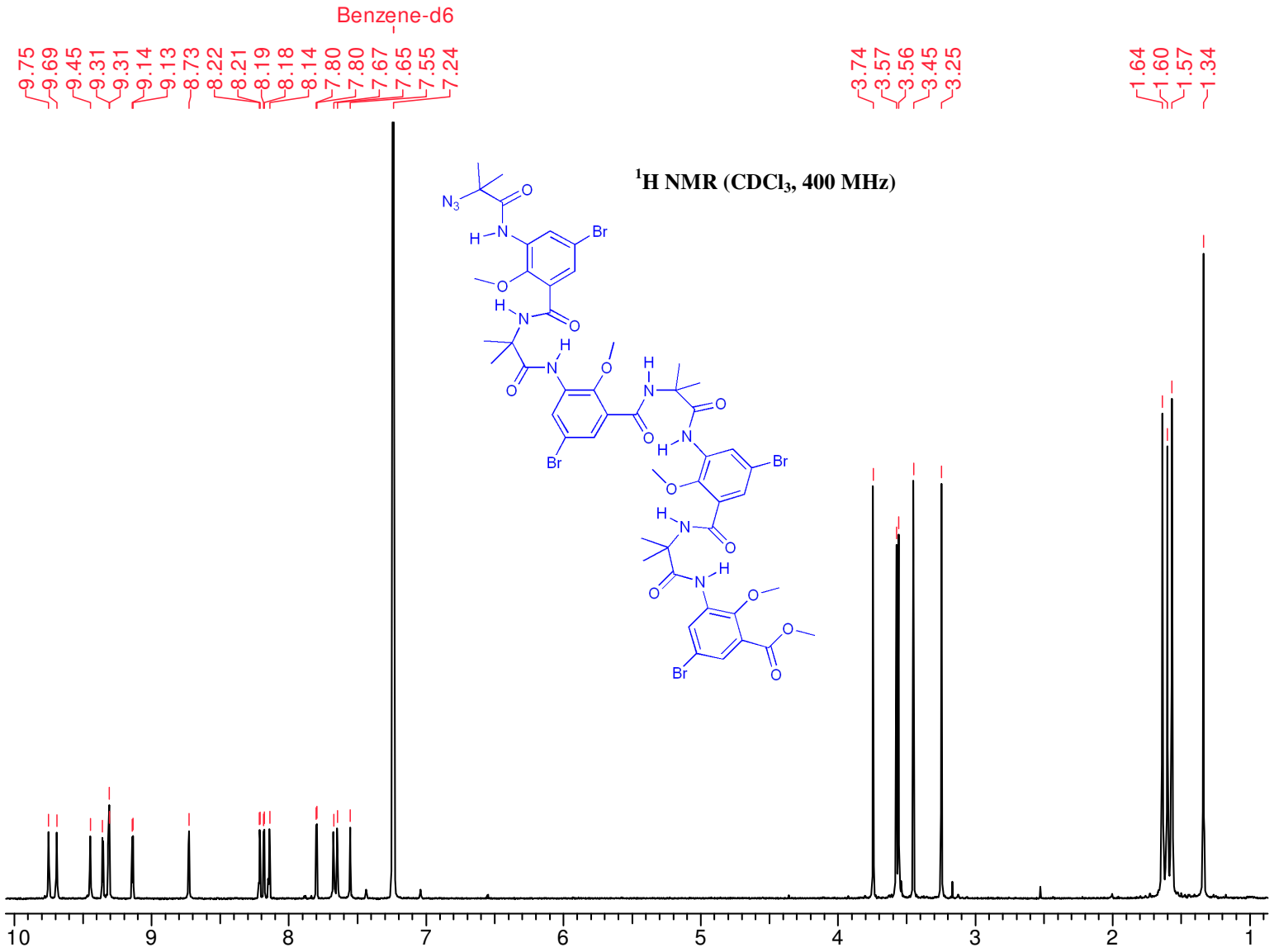




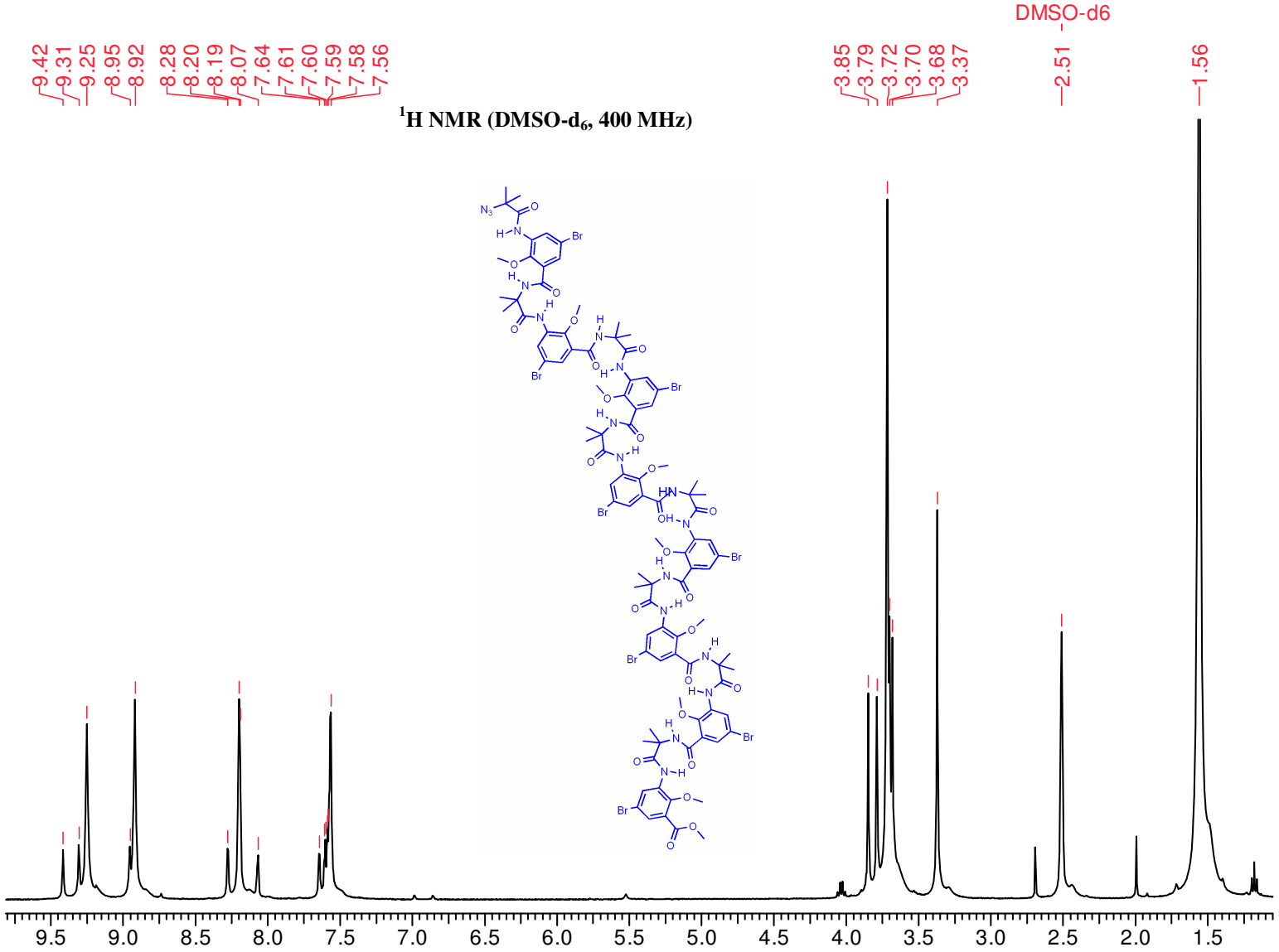
^{1}H NMR ($CDCl_3$, 200 MHz)

^{1}H NMR ($CDCl_3$, 400 MHz)



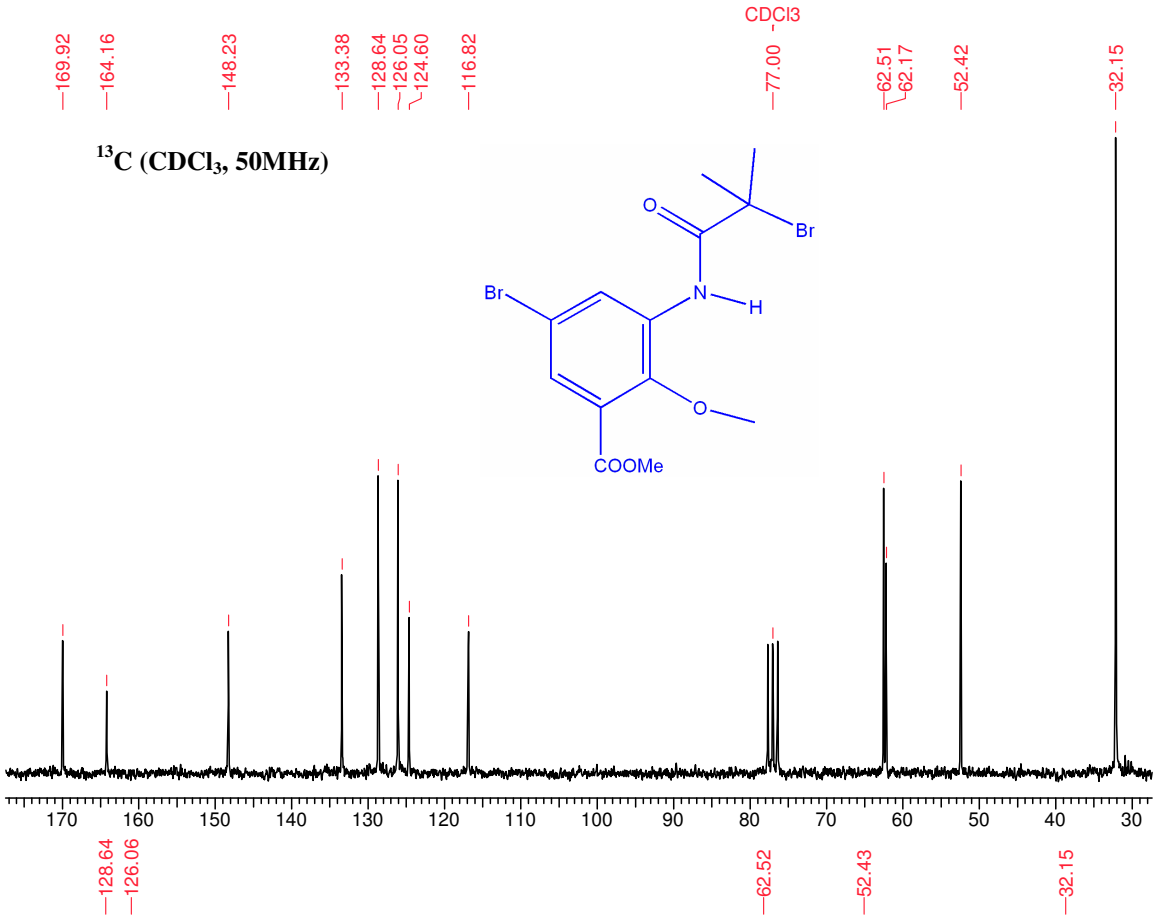


^{1}H NMR ($CDCl_3$, 400 MHz)

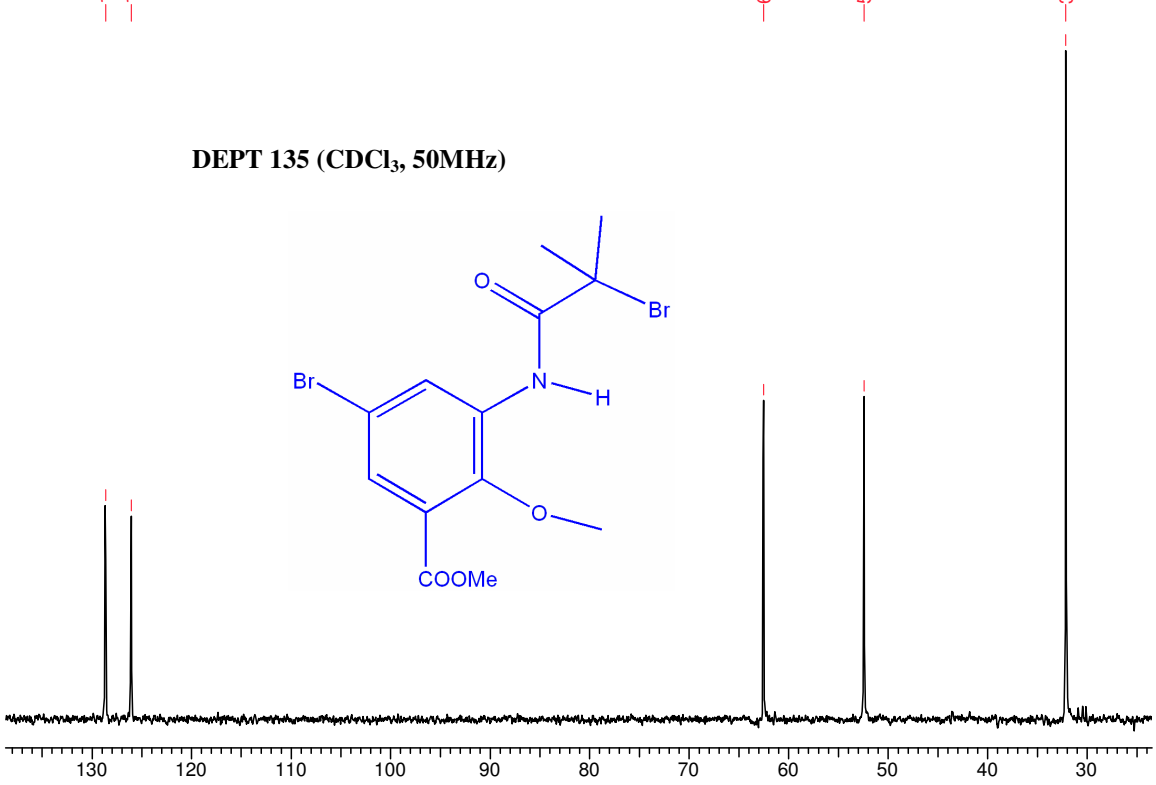


^{1}H NMR (DMSO-d$_6$, 400 MHz)

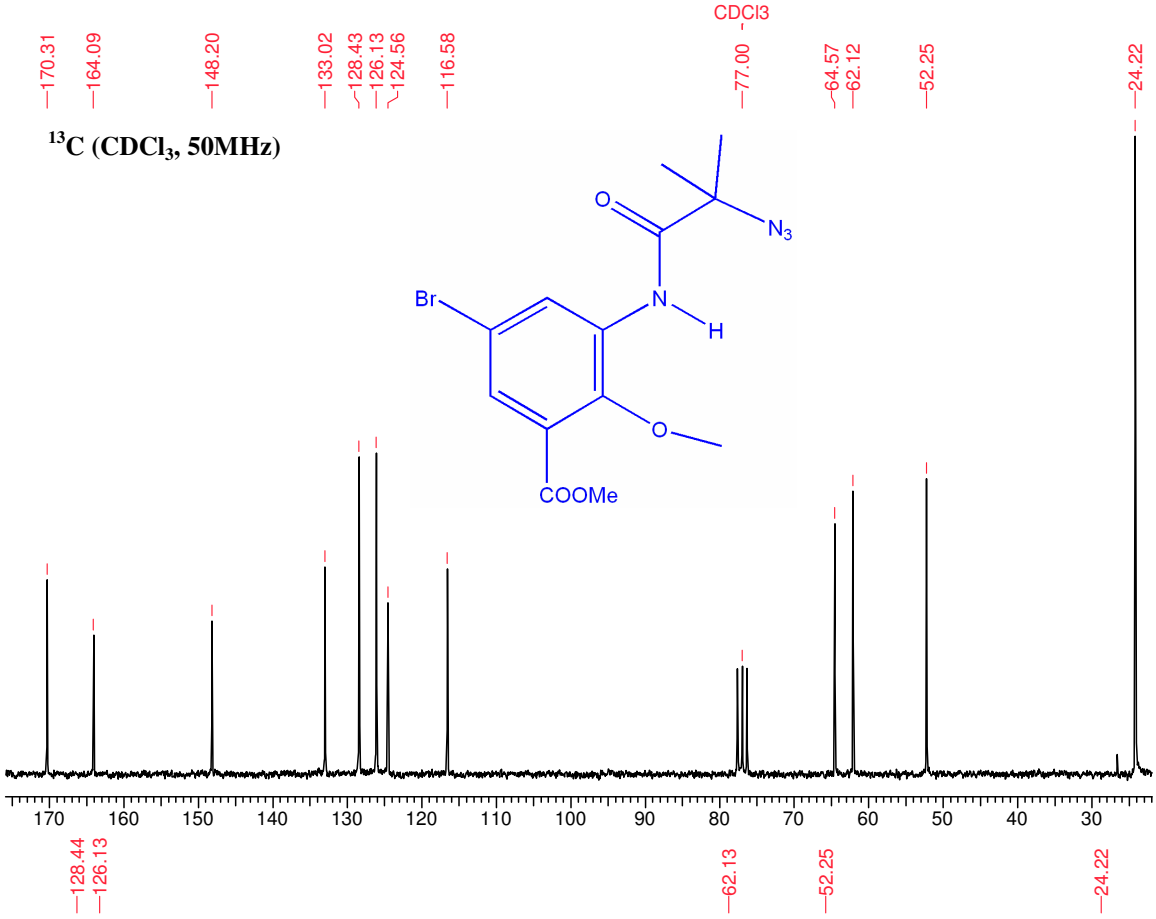
^{13}C ($CDCl_3$, 50MHz)



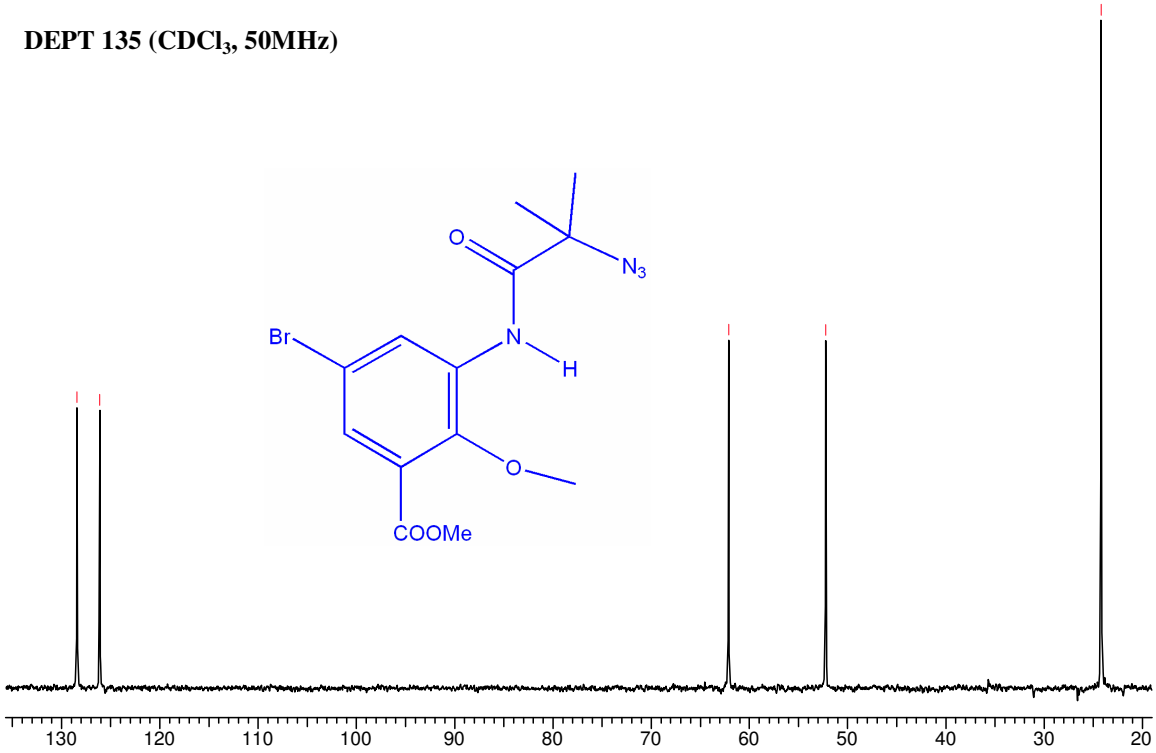
DEPT 135 ($CDCl_3$, 50MHz)



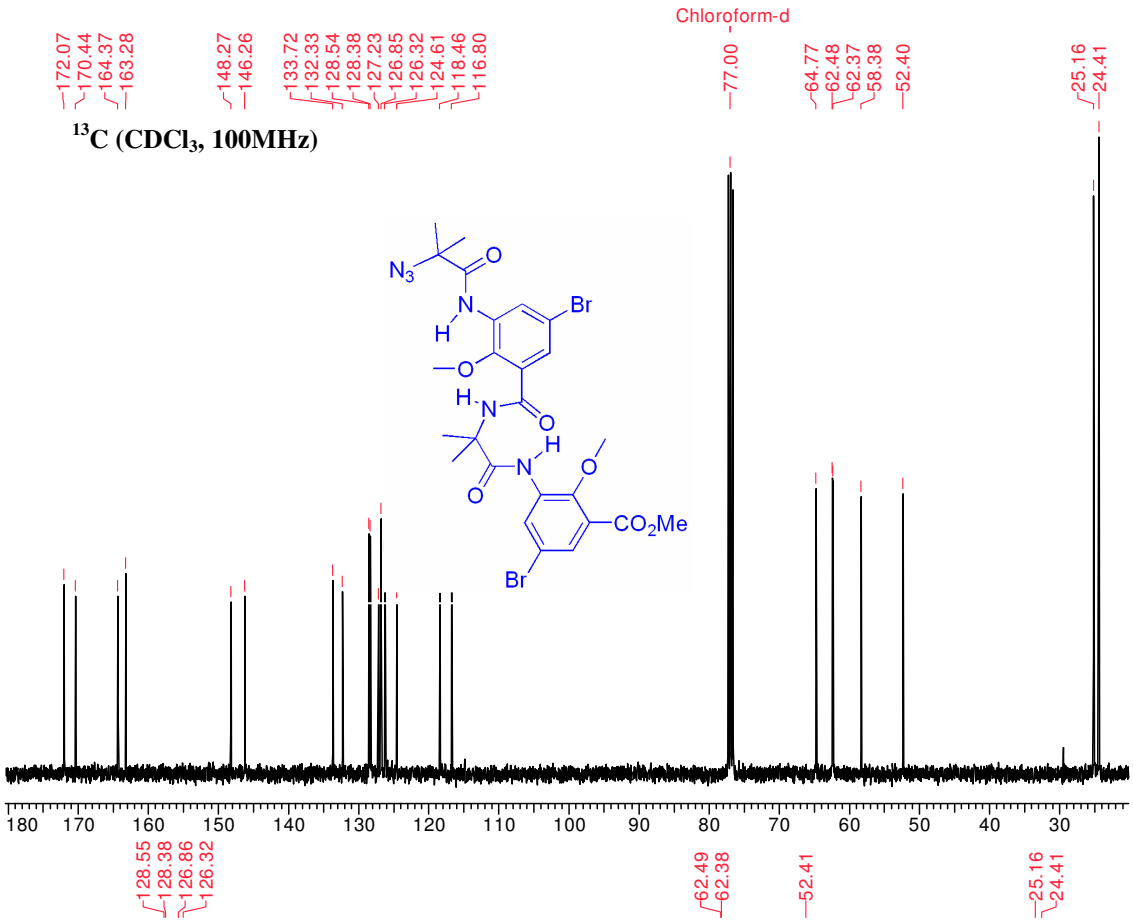
^{13}C ($CDCl_3$, 50MHz)



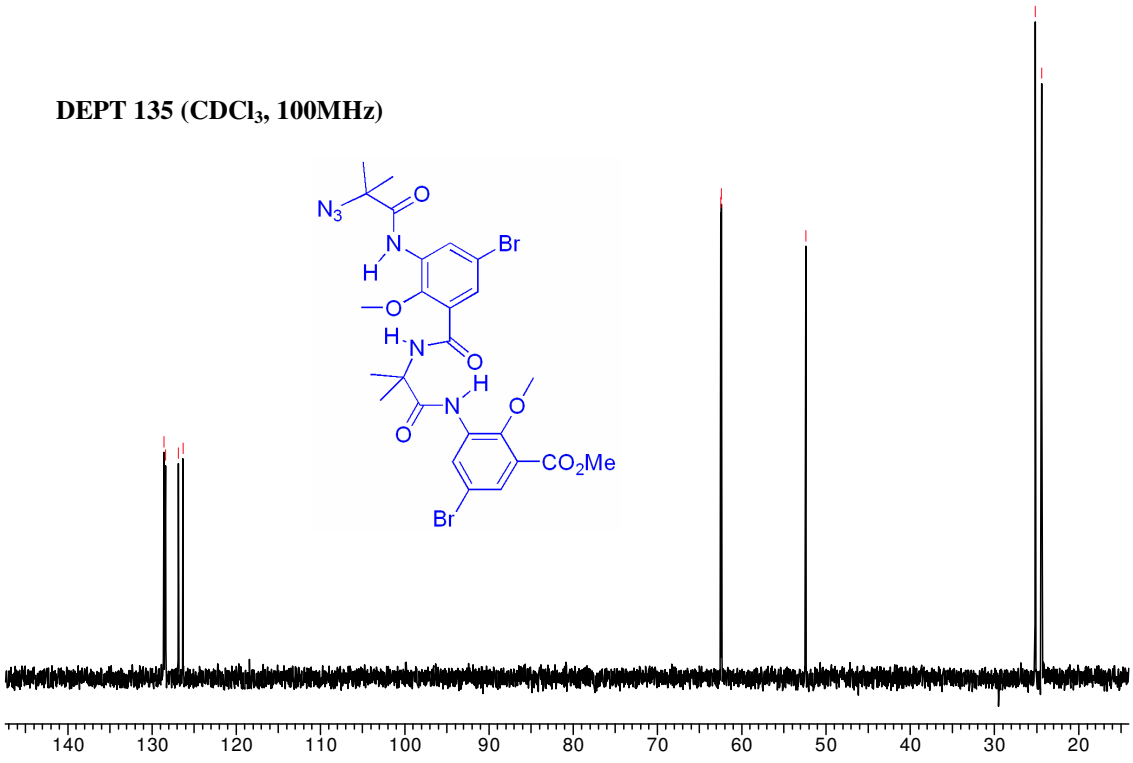
DEPT 135 ($CDCl_3$, 50MHz)

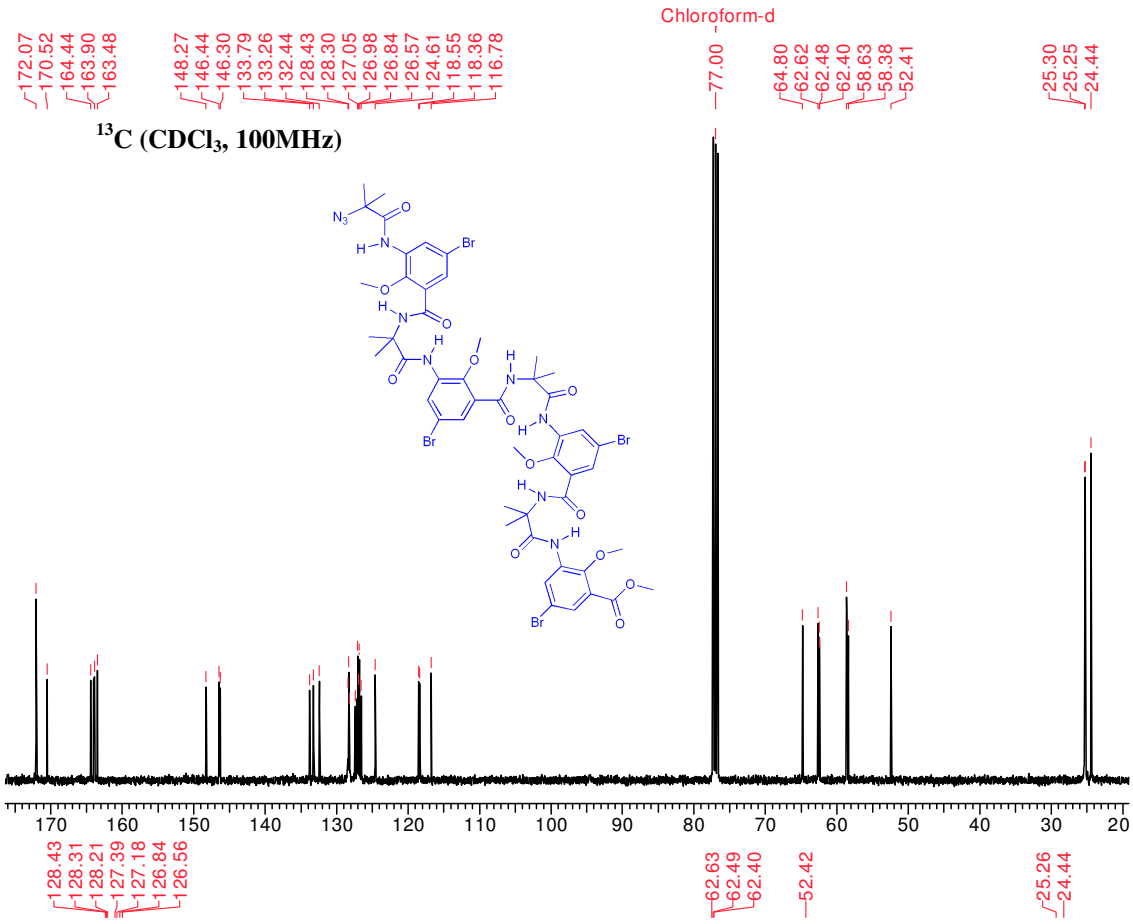


^{13}C ($CDCl_3$, 100MHz)



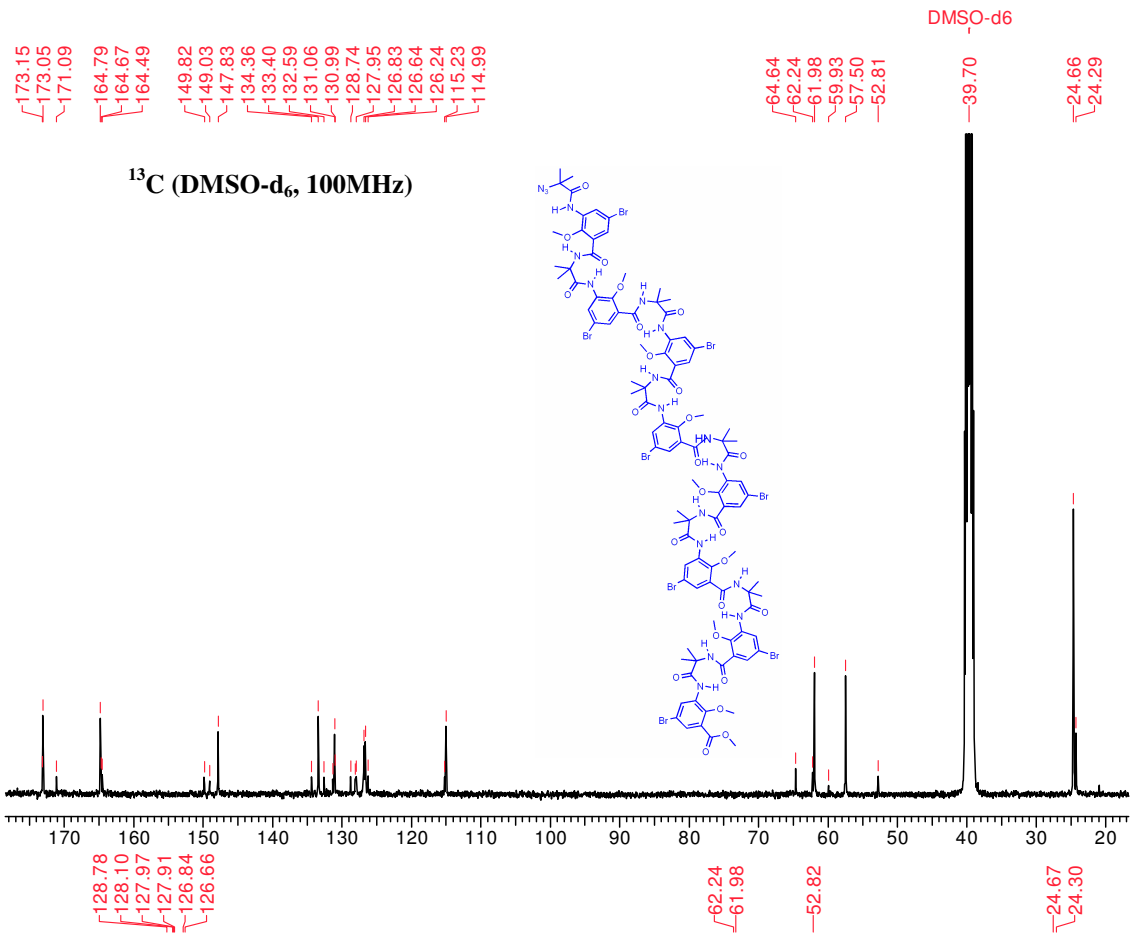
DEPT 135 ($CDCl_3$, 100MHz)



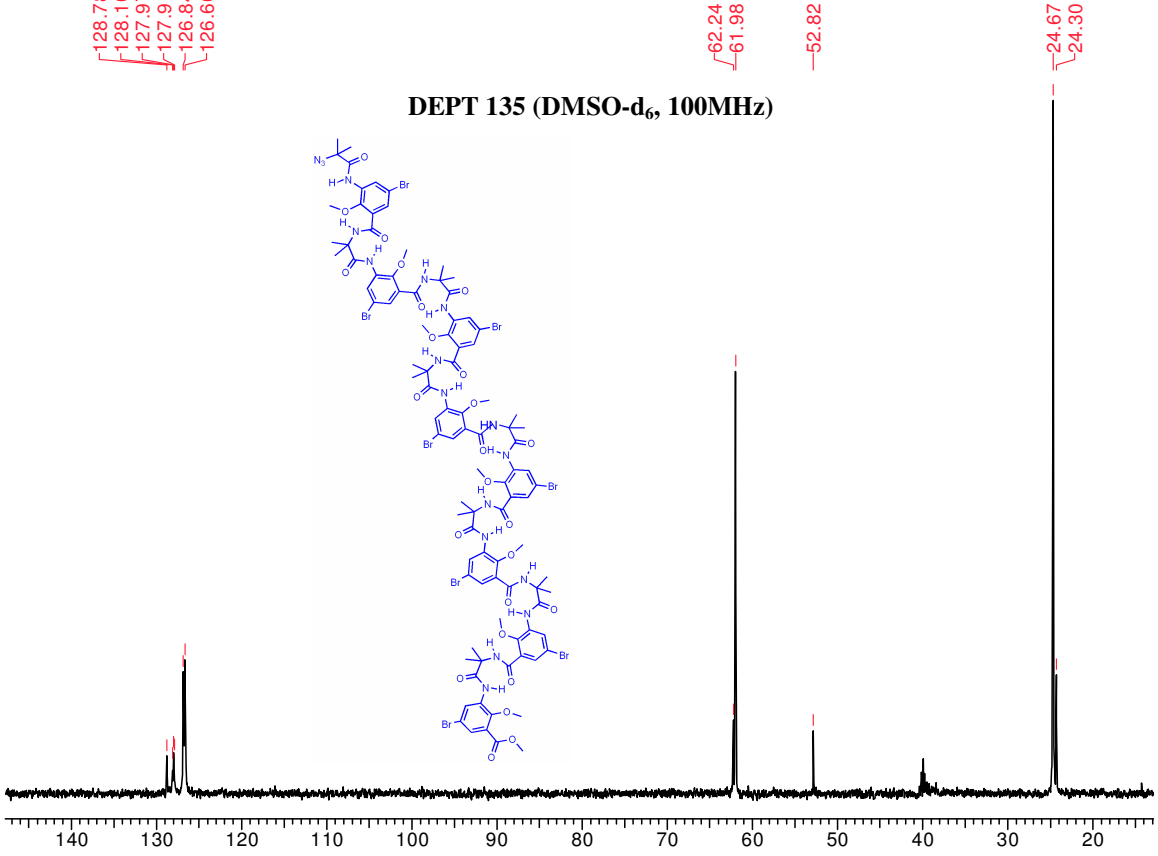


^{13}C ($CDCl_3$, 100MHz)

DEPT 135 ($CDCl_3$, 100MHz)

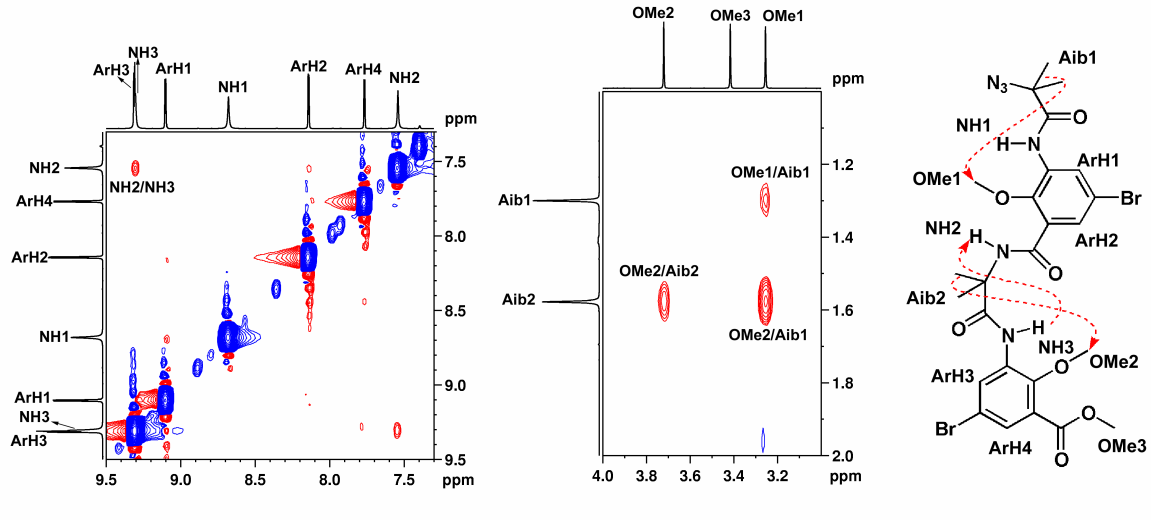


^{13}C (DMSO-d$_6$, 100MHz)

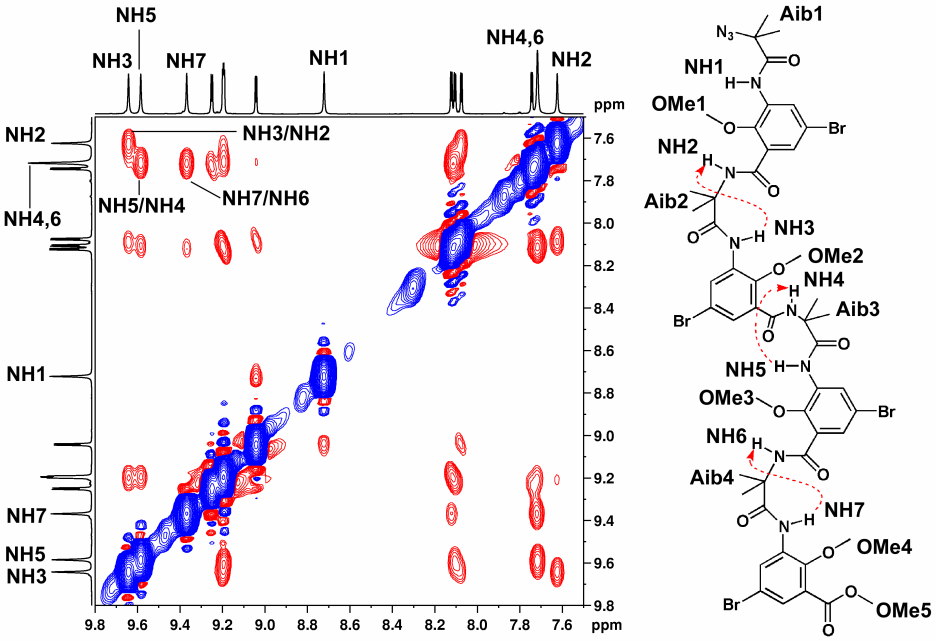


DEPT 135 (DMSO-d$_6$, 100MHz)

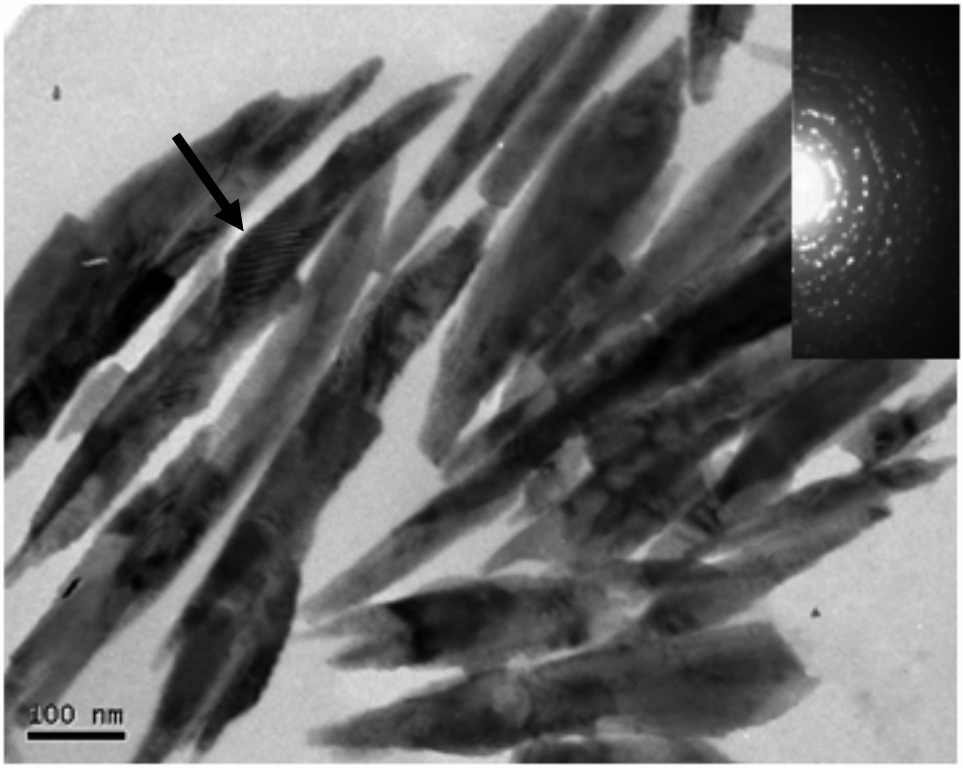
Partial 2D NMR of tetrapeptide foldamer 2a:



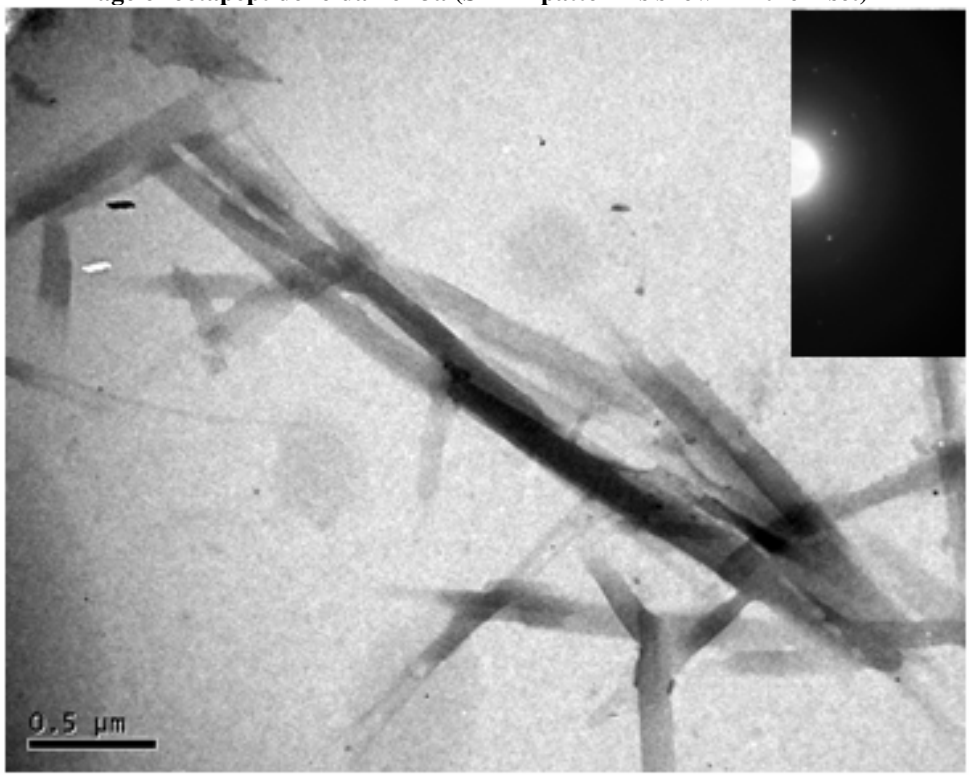
Partial 2D NMR of octapeptide foldamer 3a:



TEM image of tetrapeptide foldamer 2a (SAED pattern is shown in the inset)



TEM image of octapeptide foldamer 3a (SAED pattern is shown in the inset)



TEM image of hexadecapeptide foldamer 4 (SAED pattern is shown in the inset)

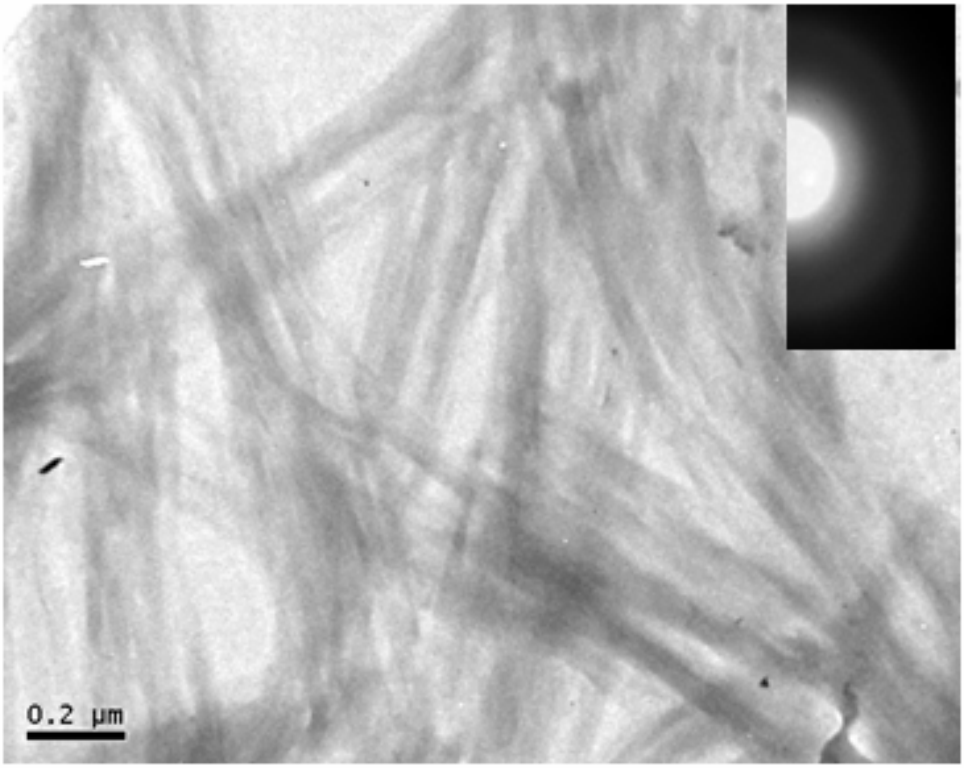
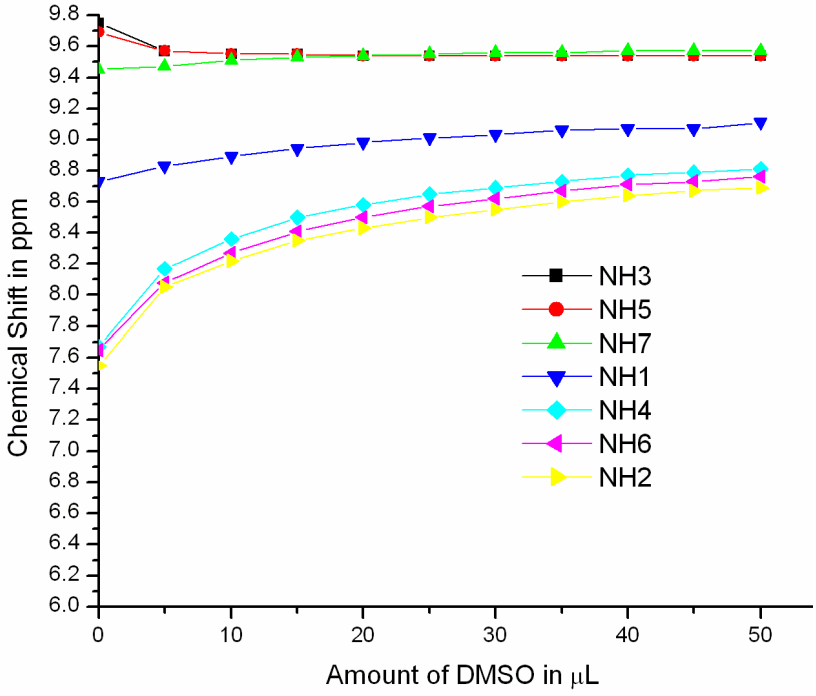
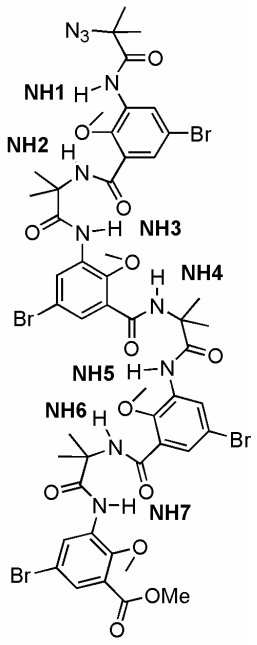


Table -1. DMSO-D6 Titration for octapeptide 3 in Benzene-d6

Amount of DMSO in mL	Chemical shift in ppm (NH3)	Chemical shift in ppm (NH5)	Chemical shift in ppm (NH7)	Chemical shift in ppm (NH1)	Chemical shift in ppm (NH4)	Chemical shift in ppm (NH6)	Chemical shift in ppm (NH2)
0	9.75	9.69	9.45	8.73	7.67	7.65	7.55
5	9.57	9.57	9.47	8.83	8.17	8.08	8.05
10	9.55	9.55	9.51	8.89	8.36	8.27	8.22
15	9.55	9.55	9.53	8.94	8.5	8.41	8.35
20	9.54	9.54	9.54	8.98	8.58	8.5	8.43
25	9.54	9.54	9.55	9.01	8.65	8.57	8.5
30	9.54	9.54	9.56	9.03	8.69	8.62	8.55
35	9.54	9.54	9.56	9.06	8.73	8.67	8.6
40	9.54	9.54	9.57	9.07	8.77	8.71	8.64
45	9.54	9.54	9.57	9.07	8.79	8.73	8.67
50	9.54	9.54	9.57	9.11	8.81	8.76	8.69

DMSO-D6 Titration graph for octapeptide 3 in Benzene-d6:





Octapeptide Foldamer 3