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Supporting Information

Fourfold Symmetric MCR's via the Tetraisocyanide 1,3-diisocyano-2,2-bis(isocyanomethyl)propane

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General information

Reagents were available from commercial suppliers (Sigma Aldrich, ABCR, Acros and AK Scientific) and used without any purification unless otherwise noted. Thin-layer chromatography was performed on Fluka precoated silica gel plates (0.20 mm thick, particle size 25 µm). Flash chromatography was performed on a Teledyne ISCO Combiflash Rf, using RediSep Rf Normal-phase Silica Flash Columns (Silica Gel 60 Å, 230 – 400 mesh) and on a Reveleris® X2 Flash Chromatography, using Grace® Reveleris Silica flash cartridges (40 grams, 24 grams, 12 grams and 3 grams). All microwave irradiation reactions were carried out in a Biotage Initiator+. Infrared spectroscopy was conducted on a Thermo Fisher scientific Nicolet 380 FT-IR. Nuclear magnetic resonance spectra were recorded on a Bruker Avance 500 spectrometer. Chemical shifts for ^{1}H NMR were reported relative to TMS (δ = 0 ppm) or the corresponding solvent peak ($CDCl_3$ δ = 7.26 ppm, DMSO-d_6 δ = 2.50 ppm, CD_3OD δ = 3.31 ppm) and coupling constants were reported in Hertz (Hz). The following abbreviations were used for spin multiplicity: s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, ddd = doublet of doublet of doublets, td = triplet of doublets, t = triplet, q = quartet, dq = doublet of quartets, p = quintet and m = multiplet. Chemical shifts for ^{13}C NMR were reported in ppm relative to the solvent peak ($CDCl_3$ δ = 77.2 ppm, CD_3OD δ = 49.0 ppm, CF_3COOD (TFA-*d*) δ = 164.2 ppm, DMSO-d_6 δ = 39.5 ppm). High-resolution mass spectra (HRMS) were recorded using an Orbitrap-Velos Pro at a resolution of 60,000. Melting points were obtained on a melting point apparatus and were uncorrected.

Experimental procedures and analytical data

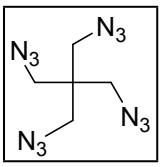
Procedure A: General procedure for the U4C-reaction

A microwave vial was charged with acid (1.0 mmol) and amine (1.0 mmol) in 2,2,2-trifluoroethanol (1 mL). The mixture was stirred at room temperature for 30 min. Thereafter, paraformaldehyde (1.0 mmol) and 1,3-diisocyano-2,2-bis(isocyanomethyl)propane (**1**, 0.25 mmol) where added. After sealing the microwave vial, the reaction vessel was heated (microwave-assisted heating) to 120 °C for 2 hours. After cooling to ambient temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography using DCM–EtOH as eluent system.

Procedure B: General procedure for the P3C-reaction

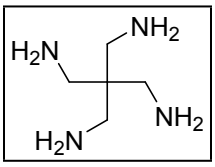
A microwave glass vial was charged with acid (1.0 mmol) and triethylamine (1.0 mmol) in 2,2,2-trifluoroethanol (1 mL). The mixture was stirred at room temperature for 30 min. Thereafter, paraformaldehyde (1.0 mmol) and 1,3-diisocyano-2,2-bis(isocyanomethyl)propane (**1**, 0.25 mmol) where added. After sealing the microwave glass vial, the reaction vessel was heated (microwave-assisted heating) to 120 °C for 2 hours. After cooling to ambient temperature, the solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography using PE-EA or DCM-EtOH as eluent system.

1,3-Diazido-2,2-bis(azidomethyl)propane (6)



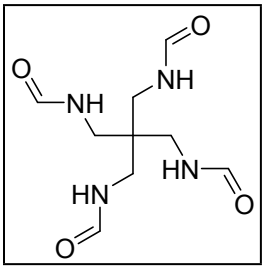
A round bottom flask was charged with 1,3-dibromo-2,2-bis(bromomethyl)propane (13.4 g, 34.6 mmol), sodium azide (27.0 g, 415 mmol), and 200 mL of DMF. The reaction mixture was stirred at 80 °C for 12 h. The reaction mixture was diluted with 1.5 L of water and extracted thrice with 150 mL diethyl ether. The combined organic layers were dried over magnesium sulfate and the solvent was removed under reduced pressure. The resulting oil was purified by column chromatography (petroleum ether 100%) to afford the product **6** (7.18 g, 30.4 mmol, 88%) as colourless crystals; m.p.: 46 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ = 3.34 (s, 8H); ^{13}C NMR (126 MHz, chloroform-*d*) 51.5, 44.0; The analytical data corresponds with the data in the literature.[1]

2,2-Bis(aminomethyl)propane-1,3-diamine (7)



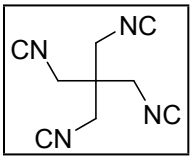
A glass reactor was charged under N_2 atmosphere with **6** (7.18 g, 30.4 mmol), 50 mL methanol, and 10% Pd/C (8.09 g, 7.60 mmol). The reactor was attached to a Paar apparatus. The reaction mixture was shaken at 40 °C for 20 h exposed to 3 bar of hydrogen. Afterwards, the mixture was filtered over Celite and the solvent was removed under reduced pressure to yield in **7** (3.98 g, 30.1 mmol, 99%) as a colourless oil; ^{1}H NMR (500 MHz, DMSO-d_6) δ = 2.33 (s, 8H); ^{13}C NMR (126 MHz, DMSO-d_6) δ = 43.3, 42.8.

***N,N'*-(2,2-bis(formamidomethyl)propane-1,3-diyl) diformamide (8)**



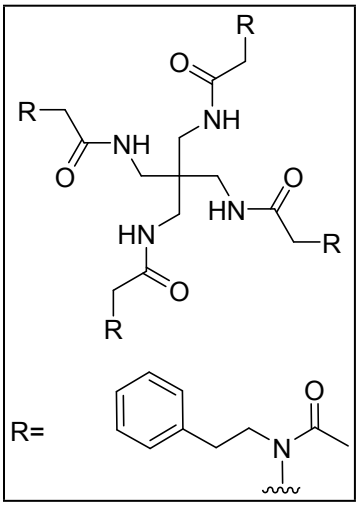
A round bottom flask was charged with **7** (3.98 g, 30.1 mmol) and 150 mL ethyl formate. The reaction mixture was stirred at 60 °C for 48 h and the solvent was then removed under reduced pressure. The residue was washed with cold methanol resulting in **8** (6.77 g, 27.7 mmol, 92%) as a colourless solid; m.p.: 202-205 °C (decomp.); ^{1}H NMR (500 MHz, DMSO-d_6) (mixture of rotamers) δ = 8.16 – 8.09 (m, 4H), 7.97 (t, *J* = 6.5 Hz, 1H), 7.89 – 7.84 (m, 3H), 2.97 (d, *J* = 6.7 Hz, 8H), 2.89 (d, *J* = 6.8 Hz, 1H, minor); ^{13}C NMR (126 MHz, methanol-d_4) δ = 165.7, 45.4, 38.8; HRMS (ESI) m/z calculated for $C_9H_{15}N_4O_4$ $[M-H]^-$: 243,1099, found $[M-H]^-$: 243.1100.

1,3-Diisocyano-2,2-bis(isocyanomethyl)propane (1)



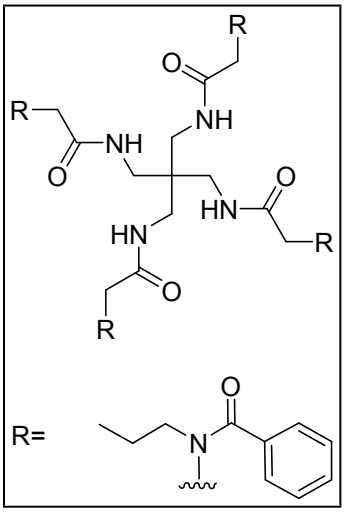
A round bottom flask was charged with **8** (2.04 g, 8.35 mmol), triethylamine (29.2 mL, 209 mmol) and 100 mL DCM. The suspension was stirred at -20 °C for 30 min. $POCl_3$ (3.50 mL, 37.6 mmol) was added dropwise over 1 h. The reaction mixture was stirred at rt. for 18 h. Carefully, 12 mL sat. $NaHCO_{3(aq.)}$ was added to the reaction mixture and stirred for further 2 h at rt. The aqueous layer was extracted twice with 50 mL DCM and the combined organic layers were then freed of solvents under reduced pressure. The residue was washed once with cold DCM and thrice with cold water resulting in **1** (791 mg, 4.59 mmol, 55%) as an off-white solid; m.p.: 215-219 °C (decomp.); IR [cm^{-1}] ν = 2982, 2951, 2148, 2117, 1446, 1360, 1310, 1290, 1160, 979, 961, 890, 660;^{1}H NMR (500 MHz, DMSO-d_6) δ = 3.83 (s, 8H); ^{13}C NMR (126 MHz, DMSO-d_6) δ = 160.9, 42.7, 39.1; HRMS (ESI) m/z calculated for $C_9H_7N_8$ $[M-H]^-$: 171,0676, found $[M-H]^-$: 171.0663.

***N,N'*-(2,2-bis((2-(*N*-phenethylacetamido)acetamido)methyl)propane-1,3-diyl) bis(2-(*N*-phenethylacetamido)acetamide) (12)**



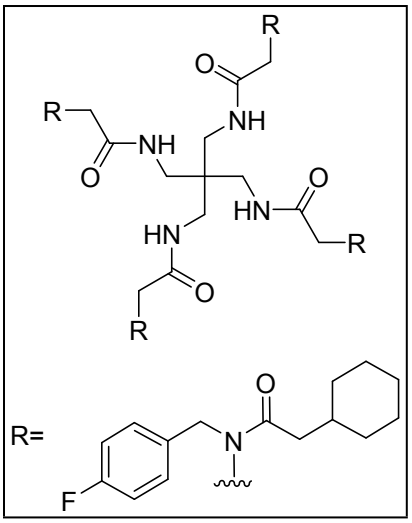
Synthesis according to procedure **A** afforded **12** (137 mg, 58%) as a colourless solid; m.p.: 82 °C ^{1}H NMR (500 MHz, methanol-d_4) (mixture of rotamers) δ = 7.99 – 7.67 (m, 2H), 7.30 (t, *J* = 7.5 Hz, 8H), 7.26 – 7.18 (m, 14H), 4.08 (s, 1H, minor), 3.92 (s, 8H), 3.69 (t, *J* = 7.2 Hz, 8H), 3.56 (t, *J* = 7.8 Hz, 1H, minor), 2.92 (t, *J* = 7.2 Hz, 8H), 2.88 – 2.72 (m, 10H), 2.03 (s, 2H, minor), 1.93 (d, *J* = 1.9 Hz, 12H); ^{13}C NMR (126 MHz, methanol-d_4) (mixture of rotamers; only signals of major rotamer are reported) δ = 174.6, 172.1, 139.6, 130.1, 129.8, 127.8, 53.3, 51.4, 47.4, 38.7, 35.8, 21.1; HRMS (ESI) m/z calculated for $C_{53}H_{69}N_8O_8$ $[M+H]^+$: 945.5233, found $[M+H]^+$: 945.5238.

***N,N'*-(2,2-bis((2-(*N*-propylbenzamido)acetamido)methyl)propane-1,3-diyl) bis(2-(*N*-propyl-benzamido)acetamide) (13a)**



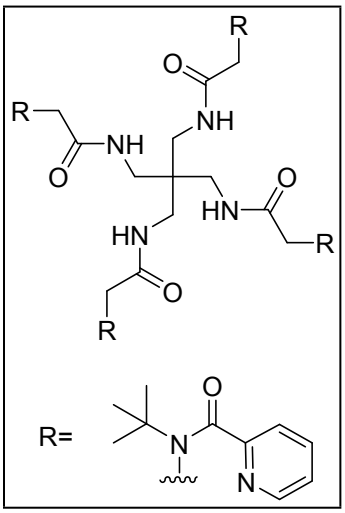
Synthesis according to procedure **A** afforded **13a** (194 mg, 82%) as a colourless solid; m.p.: 90 °C ^{1}H NMR (500 MHz, methanol-d_4) (mixture of rotamers) δ = 8.22 – 7.96 (m, 2H), 7.65 – 7.54 (m, 8H), 7.51 – 7.34 (m, 16H), 4.29 – 4.06 (m, 10H), 3.61 – 3.47 (m, 2H, minor), 3.38 (t, *J* = 8.0 Hz, 8H), 3.14 – 2.71 (m, 10H), 1.69 (q, *J* = 7.7 Hz, 10H), 1.05 – 0.92 (m, 3H, minor), 0.77 (t, *J* = 7.4 Hz, 12H); ^{13}C NMR (126 MHz, methanol-d_4) (mixture of rotamers; only signals of major rotamer are reported) δ = 175.2, 172.3, 137.0, 131.0, 129.6, 128.1, 54.3, 51.3, 47.5, 39.4, 22.9, 11.3; HRMS (ESI) m/z calculated for $C_{53}H_{69}N_8O_8$ $[M+H]^+$: 945.5233, found $[M+H]^+$: 945.5231.

***N,N'*-(((2,2-bis((2-(2-cyclohexyl-*N*-(4-fluorobenzyl)acetamido)acetamido)methyl)propane-1,3-diyl)bis(azanediyl))bis(2-oxoethane-2,1-diyl)) bis(2-cyclohexyl-*N*-(4-fluorobenzyl)acetamide) (13b)**



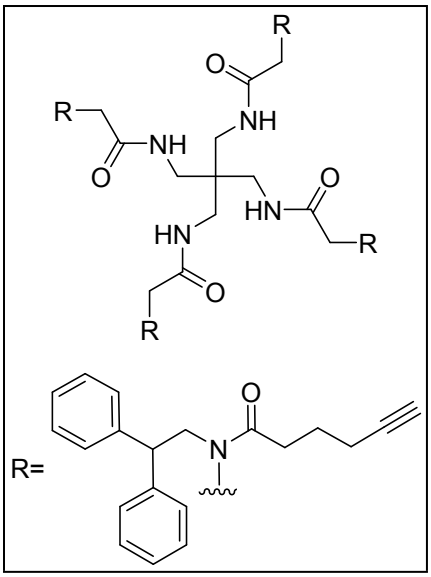
Synthesis according to procedure **A** afforded **13b** (168 mg, 52%) as a yellow solid; m.p.: 71 °C; ^{1}H NMR (500 MHz, DMSO-d_6) (mixture of rotamers) δ = 7.87 – 7.63 (m, 6H), 7.37 – 7.24 (m, 13H), 7.20 (t, *J* = 8.7 Hz, 8H), 7.12 (t, *J* = 8.9 Hz, 5H, minor), 4.68 (t, *J* = 10.9 Hz, 8H), 4.52 (t, *J* = 8.1 Hz, 5H, minor), 4.06 (t, *J* = 23.6 Hz, 5H, minor), 3.88 (t, *J* = 6.2 Hz, 8H), 2.95 – 2.60 (m, 13H), 2.26 (m, 8H), 2.17 (d, *J* = 6.6 Hz, 5H, minor), 1.83 – 1.43 (m, 40H), 1.26 – 0.97 (m, 20H), 0.95 – 0.73 (m, 13H); ^{13}C NMR (126 MHz, chloroform-*d*) (mixture of rotamers; only signals of major rotamer are reported) δ = 174.0, 170.2, 163.4 & 161.5 (d, J_{CF} = 247 Hz), 132.0 (d, J_{CF} = 3.2 Hz), 130.2 (d, J_{CF} = 7.8 Hz), 128.3 (t, J_{CF} = 7.8 Hz), 116.1 (dd, J_{CF} = 21.7 Hz, 4.4 Hz), 51.9, 50.2, 46.3, 40.5, 38.0, 34.3, 33.5, 26.3, 26.2; HRMS (ESI) m/z calculated for $C_{73}H_{97}F_4N_8O_8$ $[M+H]^+$: 1289.7360, found $[M+H]^+$: 1289.7355.

***N,N'*-(((2,2-bis((2-(*N*-(*tert*-butyl)picolinamido)acetamido)methyl)propane-1,3-diyl)bis(azanediyl))bis(2-oxoethane-2,1-diyl)) bis(*N*-(*tert*-butyl)picolinamide) (13c)**



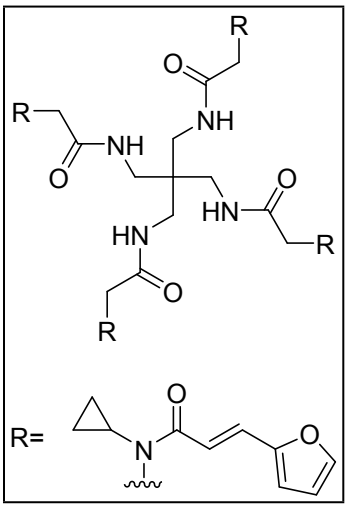
Synthesis according to procedure **A** afforded **13c** (173 mg, 69%) as a colourless solid; m.p.: 258 °C; ^{1}H NMR (500 MHz, methanol-d_4) δ = 8.48 (d, *J* = 4.9 Hz, 4H), 7.83 (td, *J* = 7.7 Hz, 1.5 Hz, 4H), 7.65 (d, *J* = 7.7 Hz, 4H), 7.43 (ddd, *J* = 7.7 Hz, 4.9 Hz, 1.5 Hz, 4H), 4.17 (s, 8H), 2.95 (s, 8H), 1.53 (s, 36H); ^{13}C NMR (126 MHz, TFA-*d*) δ = 175.5, 162.5, 151.7, 145.5, 143.1, 133.4, 128.2, 48.5, 46.3, 42.1, 28.1; HRMS (ESI) m/z calculated for $C_{53}H_{73}N_{12}O_8$ $[M+H]^+$: 1005.5669, found $[M+H]^+$: 1005.5668.

***N,N'*-(((2,2-bis((2-(*N*-(2,2-diphenylethyl)hex-5-ynamido)acetamido)methyl)propane-1,3-diyl)bis(azanediyl))bis(2-oxoethane-2,1-diyl)) bis(*N*-(2,2-diphenylethyl)hex-5-ynamide) (13d)**



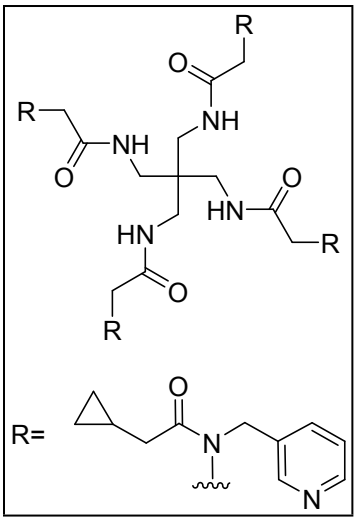
Synthesis according to procedure **A** afforded **13d** (255 mg, 70%) as a colourless solid; m.p.: 94 °C; ^{1}H NMR (500 MHz, methanol-d_4) (mixture of rotamers) δ = 7.49 – 7.12 (m, 50H), 4.44 (td, *J* = 8.0 Hz, 3.0 Hz, 1H, minor), 4.37 (q, *J* = 7.5 Hz, 4H), 4.14 (t, *J* = 6.9 Hz, 8H), 4.10 – 4.04 (m, 2H, minor), 3.87 – 3.65 (m, 10H), 2.84 – 2.49 (m, 10H), 2.39 – 2.24 (m, 10H), 2.21 (q, *J* = 2.8 Hz, 4H), 2.13 (td, *J* = 6.9 Hz, 2.6 Hz, 2H, minor), 2.07 – 2.00 (m, 8H), 1.71 (p, *J* = 7.1 Hz, 2H), 1.63 – 1.49 (m, 8H); ^{13}C NMR (126 MHz, methanol-d_4) (mixture of rotamers; only signals of major rotamer are reported) δ = 176.3, 172.0, 143.2, 129.8, 129.4, 128.1, 84.6, 70.4, 55.8, 52.5, 51.8, 47.3, 38.6, 32.4, 24.9, 18.6; HRMS (ESI) m/z calculated for $C_{93}H_{101}N_8O_8$ $[M+H]^+$: 1457.7737, found $[M+H]^+$: 1457.7734.

(2*E*,2'*E*)-*N,N'*-(((2,2-bis((2-((*E*)-*N*-cyclopropyl-3-(furan-2-yl)acrylamido)acetamido)methyl)-propane-1,3-diyl)bis(azanediyl))bis(2-oxoethane-2,1-diyl)) bis(*N*-cyclopropyl-3-(furan-2-yl)-acrylamide) (13e)



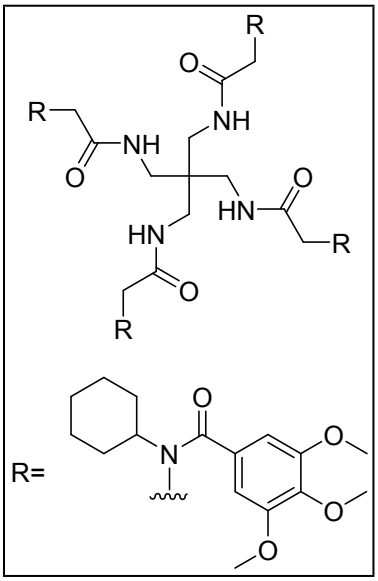
Synthesis according to procedure **A** afforded **13e** (160 mg, 64%) as an orange solid; m.p.: 162 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ = 7.82 (s, 4H), 7.64 (t, *J* = 6.6 Hz, 4H), 7.30 (d, *J* = 15.5 Hz, 4H), 7.14 (d, *J* = 15.5 Hz, 4H), 6.86 (d, *J* = 3.4 Hz, 4H), 6.61 (dd, *J* = 3.4 Hz, 1.8 Hz, 4H), 3.94 (s, 8H), 3.05 – 2.89 (m, 4H), 2.70 (d, *J* = 6.6 Hz, 8H), 0.96 – 0.75 (m, 16H); ^{13}C NMR (126 MHz, DMSO-d_6) δ = 170.4, 168.1, 151.1, 145.1, 128.1, 115.9, 114.9, 112.6, 51.9, 45.8, 37.6, 31.0, 9.1; HRMS (ESI) m/z calculated for $C_{53}H_{61}N_8O_{12}$ $[M+H]^+$: 1001.4404, found $[M+H]^+$: 1001.4403.

***N,N'*-(((2,2-bis((2-(2-cyclopropyl-*N*-(pyridin-3-ylmethyl)acetamido)acetamido)methyl)propane-1,3-diyl)bis(azanediyl))bis(2-oxoethane-2,1-diyl)) bis(2-cyclopropyl-*N*-(pyridin-3-ylmethyl)-acetamide) (13f)**



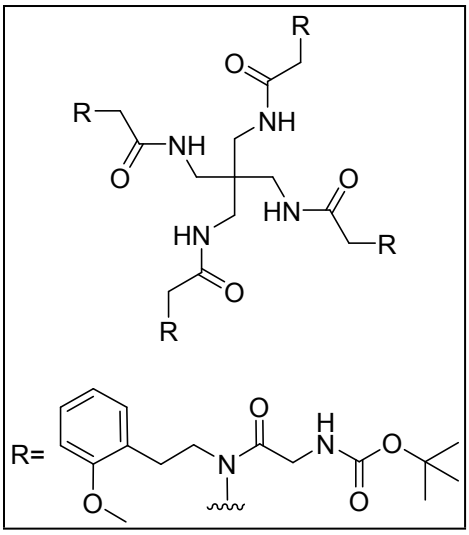
Synthesis according to procedure **A** afforded **13f** (155 mg, 59%) as a colourless oil; ^{1}H NMR (500 MHz, chloroform-*d*) (mixture of rotamers) δ = 8.64 (s, 8H), 7.93 – 7.11 (m, 18H), 4.74 (t, *J* = 14.6 Hz, 8H), 4.63 – 4.50 (m, 5H, minor), 4.25 – 3.99 (m, 5H, minor), 3.92 (t, *J* = 9.1 Hz, 8H), 2.90 – 2.65 (m, 13H), 2.38 (q, *J* = 7.1 Hz, 8H), 2.28 (d, *J* = 6.7 Hz, 5H, minor), 1.08 – 0.85 (m, 7H), 0.50 – 0.38 (m, 5H, minor), 0.38 (q, *J* = 7.7 Hz, 8H), 0.09 (q, *J* = 5.0 Hz, 5H, minor), 0.00 (d, *J* = 5.0 Hz, 8H); ^{13}C NMR (126 MHz, chloroform-*d*) (mixture of rotamers; only signals of major rotamer are reported) δ = 174.3, 169.9, 149.7, 148.6, 134.5, 134.4, 131.9, 123.9, 50.6, 50.5, 46.6, 38.5, 37.9, 6.9, 4.6, 0.1; HRMS (ESI) m/z calculated for $C_{57}H_{73}N_{12}O_8$ $[M+H]^+$: 1053.5669, found $[M+H]^+$: 1053.5668.

***N,N'*-(((2,2-bis((2-(*N*-cyclohexyl-3,4,5-trimethoxybenzamido)acetamido)methyl)propane-1,3-diyl)bis(azanediyl))bis(2-oxoethane-2,1-diyl)) bis(*N*-cyclohexyl-3,4,5-trimethoxybenzamide) (13g)**



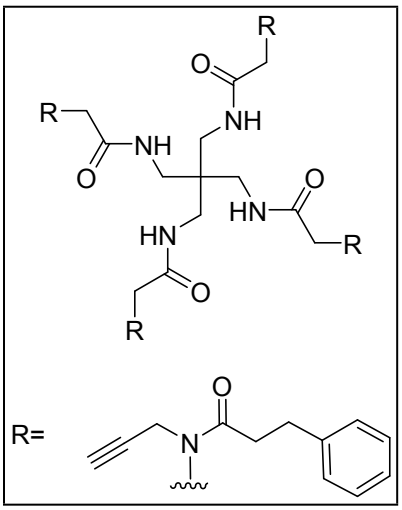
Synthesis according to procedure **A** afforded **13g** (304 mg, 83%) as a colourless solid; m.p.: 114 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ = 8.17 – 7.95 (m, 4H), 6.94 (s, 8H), 4.09 – 3.96 (m, 4H), 3.94 – 3.74 (m, 44H), 3.31 (dd, *J* = 14.0 Hz, 9.2 Hz, 4H), 2.48 (d, *J* = 14.0 Hz, 4H), 2.17 (d, *J* = 7.9 Hz, 4H), 1.90 – 1.76 (m, 10H), 1.61 (d, *J* = 12.6 Hz, 4H), 1.33 (q, *J* = 12.0 Hz, 9H), 1.16 (dq, *J* = 26.5 Hz, 13.1 Hz, 12.6 Hz, 9H), 1.08 – 0.93 (m, 4H); ^{13}C NMR (126 MHz, chloroform-*d*) (mixture of rotamers; only signals of major rotamer are reported) δ = 172.9, 170.6, 153.3, 139.0, 131.3, 104.4, 61.0, 58.8, 56.3, 53.6, 46.3, 38.2, 31.6, 31.0, 25.6, 25.2; HRMS (ESI) m/z calculated for $C_{77}H_{109}N_8O_{20}$ $[M+H]^+$: 1465.7753, found $[M+H]^+$: 1465.7745.

Di-*tert*-butyl (3,13-bis(2-methoxyphenethyl)-8,8-bis(5-(2-methoxyphenethyl)-11,11-dimethyl-3,6,9-trioxo-10-oxa-2,5,8-triazadodecyl)-2,5,11,14-tetraoxo-3,6,10,13-tetraazapentadecane-1,15-diyl)dicarbamate (13h)



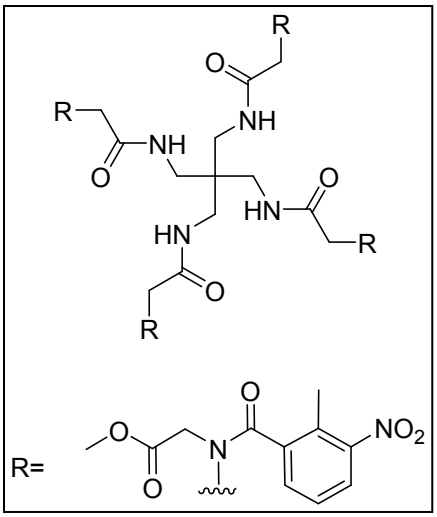
Synthesis according to procedure **A** afforded **13h** (134 mg, 35%) as a colourless solid; m.p.: 96 °C ^{1}H NMR (500 MHz, methanol-d_4) δ = 7.22 (td, *J* = 8.0 Hz, 1.7 Hz, 4H), 7.15 (dd, *J* = 7.4 Hz, 1.7 Hz, 4H), 6.92 (d, *J* = 8.0 Hz, 4H), 6.87 (t, *J* = 7.4 Hz, 4H), 4.02 (s, 8H), 3.92 (s, 8H), 3.82 (s, 12H), 3.57 (t, *J* = 7.6 Hz, 8H), 2.93 (t, *J* = 7.6 Hz, 8H), 2.84 – 2.68 (m, 8H), 1.43 (s, 36H); ^{13}C NMR (126 MHz, methanol-d_4) δ = 172.5, 172.1, 159.0, 158.0, 131.7, 129.5, 127.1, 121.8, 111.6, 80.4, 55.8, 51.8, 49.9, 47.3, 42.9, 38.9, 31.1, 28.8; HRMS (ESI) m/z calculated for $C_{77}H_{113}N_{12}O_{20}$ $[M+H]^+$: 1525.8189, found $[M+H]^+$: 1525.8185.

***N,N'*-(((2,2-bis((2-(3-phenyl-*N*-(prop-2-yn-1-yl)propanamido)acetamido)methyl)propane-1,3-diyl)bis(azanediyl))bis(2-oxoethane-2,1-diyl)) bis(3-phenyl-*N*-(prop-2-yn-1-yl)propanamide) (13i)**



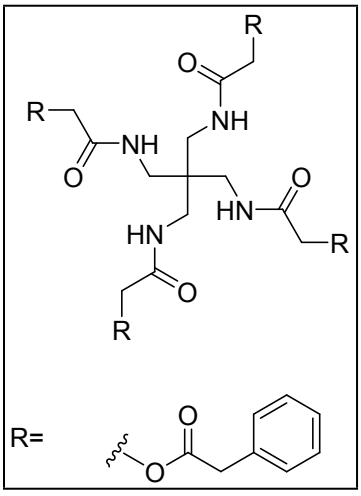
Synthesis according to procedure **A** afforded **13i** (122 mg, 47%) as a colourless oil; ^{1}H NMR (500 MHz, methanol-d_4) (mixture of rotamers) δ = 7.98 – 7.65 (m, 2H), 7.31 – 7.06 (m, 26H), 4.36 – 4.21 (m, 10H), 4.18 (d, *J* = 3.0 Hz, 2H, minor), 4.04 (d, *J* = 3.6 Hz, 8H), 2.97 – 2.81 (m, 23H), 2.79 – 2.68 (m, 11H), 2.66 – 2.53 (m, 2H, minor); ^{13}C NMR (126 MHz, methanol-d_4) (mixture of rotamers; only signals of major rotamer are reported) δ = 175.6, 171.9, 142.4, 129.6, 129.5, 127.2, 79.0, 75.1, 51.2, 47.3, 39.9, 36.9, 35.8, 31.7; HRMS (ESI) m/z calculated for $C_{61}H_{69}N_8O_8$ $[M+H]^+$: 1041.5233, found $[M+H]^+$: 1041.5232.

D**imethyl-8,8-bis((2-(*N*-(2-methoxy-2-oxoethyl)-2-methyl-3-nitrobenzamido)acetamido)methyl)-3,13-bis(2-methyl-3-nitrobenzoyl)-5,11-dioxo-3,6,10,13-tetraazapentadecanedioate (13j)**



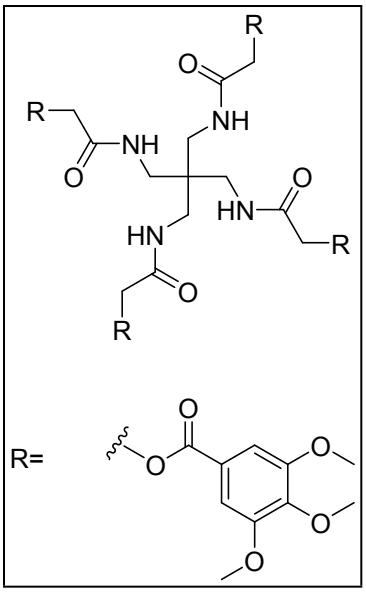
Synthesis according to procedure **A** afforded **13j** (189 mg, 58%) as a colourless solid; m.p.: 124 °C; ^{1}H NMR (500 MHz, DMSO-d_6) (mixture of rotamers) δ = 7.97 (dd, *J* = 7.6 Hz, 2.0 Hz, 7H), 7.93 – 7.84 (m, 2H), 7.80 – 7.65 (m, 4H), 7.60 – 7.52 (m, 2H), 7.51 – 7.42 (m, 10H), 4.53 (br s, 4H), 4.33 – 3.77 (m, 22H), 3.71 (s, 12H), 3.60 (s, 7H, minor), 3.08 – 2.72 (m, 12H), 2.41 (t, *J* = 2.9 Hz, 12H), 2.33 (d, *J* = 2.2 Hz, 7H, minor); ^{13}C NMR (126 MHz, chloroform-*d*) (mixture of rotamers; only signals of major rotamer are reported) δ = 169.8, 168.9, 150.8, 137.5, 130.6, 130.4, 127.4, 125.5, 52.9, 52.1, 47.3, 46.0, 38.9, 16.1; HRMS (ESI) m/z calculated for $C_{57}H_{65}N_{12}O_{24}$ $[M+H]^+$: 1301,4229, found $[M+H]^+$: 1301.4292.

***((2,2-Bis((2-(2-phenylacetoxy)acetamido)methyl)propane-1,3-diyl)bis(azanediyl)) bis(2-oxo-ethane-2,1-diyl)bis(2-phenylacetate)* (14a)**



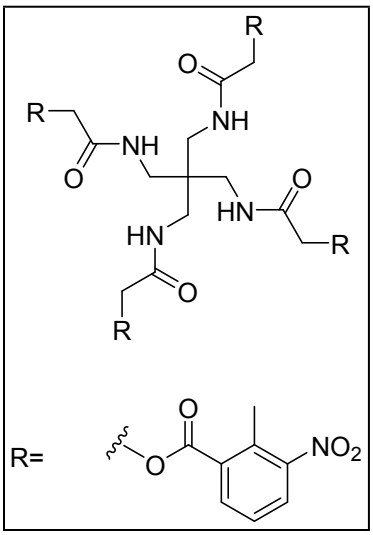
Synthesis according to procedure **B** afforded **14a** (161 mg, 77%) as a colourless oil; ^{1}H NMR (500 MHz, DMSO-d_6) δ = 8.02 (t, *J* = 6.7 Hz, 2H), 7.37 – 7.14 (m, 20H), 4.65 (s, 8H), 3.85 (s, 8H), 2.89 – 2.78 (m, 8H); ^{13}C NMR (126 MHz, DMSO-d_6) δ = 171.1, 168.9, 133.8, 129.6, 128.4, 127.0, 62.8, 45.3, 37.8, 37.7; HRMS (ESI) m/z calculated for $C_{45}H_{49}N_4O_{12}$ $[M+H]^+$: 837.3342, found $[M+H]^+$: 837.3340.

((2,2-Bis((2-((3,4,5-trimethoxybenzoyl)oxy)acetamido)methyl)propane-1,3-diyl)-bis(azanediyl)) bis(2-oxoethane-2,1-diyl)bis(3,4,5-trimethoxybenzoate) **(14b)**



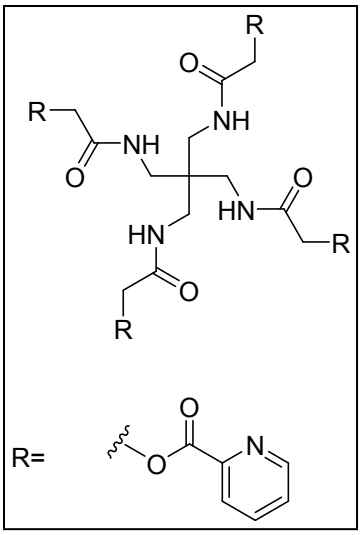
Synthesis according to procedure **B** afforded **14b** (171 mg, 60%) as a colourless solid; m.p.: 228 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ = 8.42 (t, *J* = 6.8 Hz, 4H), 7.46 (s, 8H), 4.81 (d, *J* = 15.6 Hz, 4H), 4.70 (d, *J* = 15.6 Hz, 4H), 3.94 (s, 24H), 3.93 (s, 12H), 3.56 – 3.47 (m, 4H), 2.49 (d, *J* = 13.0 Hz, 4H); ^{13}C NMR (126 MHz, chloroform-*d*) δ = 169.4, 165.7, 153.1, 143.0, 123.7, 107.6, 63.6, 61.1, 56.5, 46.0, 38.5; HRMS (ESI) m/z calculated for $C_{53}H_{65}N_4O_{24}$ $[M+H]^+$: 1141.3983, found $[M+H]^+$: 1141.3991.

((2,2-Bis((2-((2-methyl-3-nitrobenzoyl)oxy)acetamido)methyl)propane-1,3-diyl)bis(azanediyl)) bis(2-oxoethane-2,1-diyl)bis(2-methyl-3-nitrobenzoate) **(14c)**



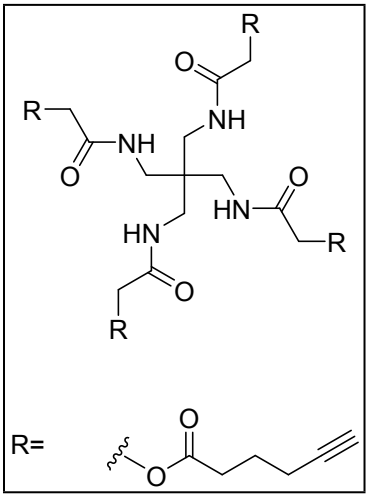
Synthesis according to procedure **B** afforded **14c** (89 mg, 35%) as a colourless solid; m.p.: 239 °C; ^{1}H NMR (500 MHz, chloroform-*d*) δ = 8.21 – 8.10 (m, 8H), 7.98 (d, *J* = 8.2 Hz, 4H), 7.47 (t, *J* = 8.0 Hz, 4H), 4.83 (s, 8H), 3.06 (d, *J* = 6.6 Hz, 8H), 2.46 (s, 12H); ^{13}C NMR (126 MHz, chloroform-*d*) δ = 169.0, 165.4, 152.2, 134.6, 134.2, 131.5, 127.5, 126.6, 63.8, 45.9, 38.7, 16.2; HRMS (ESI) m/z calculated for $C_{45}H_{45}N_8O_{20}$ $[M+H]^+$: 1017.2745, found $[M+H]^+$: 1017.2744.

((2,2-bis((2-(picolinoyloxy)acetamido)methyl)propane-1,3-diyl)bis(azanediyl))bis(2-oxoethane-2,1-diyl) dipicolinate **(14d)**



Synthesis according to procedure **B** afforded **14d** (133 mg, 68%) as a red solid; m.p.: 217-221 °C (decomp.); ^{1}H NMR (500 MHz, chloroform-*d*) δ = 8.77 (dd, *J* = 4.8 Hz, 1.1 Hz, 4H), 8.34 (dt, *J* = 7.8 Hz, 1.1 Hz, 4H), 8.22 (t, *J* = 6.7 Hz, 4H), 7.83 (tt, *J* = 7.8 Hz, 1.7 Hz, 4H), 7.53 – 7.46 (m, 4H), 4.82 (s, 8H), 2.99 (s, 8H); ^{13}C NMR (126 MHz, chloroform-*d*) δ = 168.8, 164.4, 150.1, 146.9, 137.3, 127.5, 126.0, 63.9, 45.8, 38.6; HRMS (ESI) m/z calculated for $C_{37}H_{37}N_8O_{12}$ $[M+H]^+$: 785.2526, found $[M+H]^+$: 785.2524.

((2,2-bis((2-(hex-5-ynoyloxy)acetamido)methyl)propane-1,3-diyl)bis(azanediyl))bis(2-oxoethane-2,1-diyl) bis(hex-5-ynoate) **(14e)**

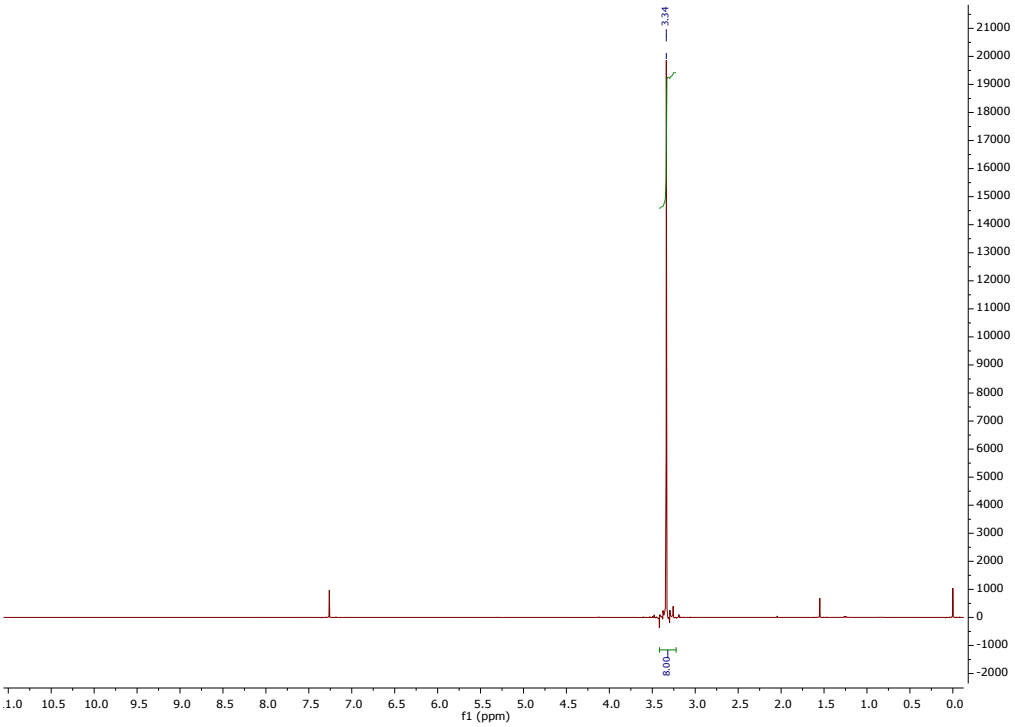


Synthesis according to procedure **B** afforded **14e** (130 mg, 70%) as a colourless oil; ^{1}H NMR (500 MHz, chloroform-*d*) δ = 8.02 (t, *J* = 6.8 Hz, 4H), 4.87 – 4.22 (m, 8H), 3.31 (br s, 4H), 2.76 – 2.60 (m, 8H), 2.42 – 2.30 (m, 3H), 2.28 (td, *J* = 6.9 Hz, 2.7 Hz, 8H), 1.99 (t, *J* = 2.7 Hz, 4H), 1.89 (p, *J* = 6.9 Hz, 8H); ^{13}C NMR (126 MHz, chloroform-*d*) δ = 172.8, 169.4, 83.3, 69.3, 62.7, 45.8, 38.1, 32.4, 23.5, 17.9; HRMS (ESI) m/z calculated for $C_{37}H_{49}N_4O_{12}$ $[M+H]^+$: 741.3342, found $[M+H]^+$: 741.3344.

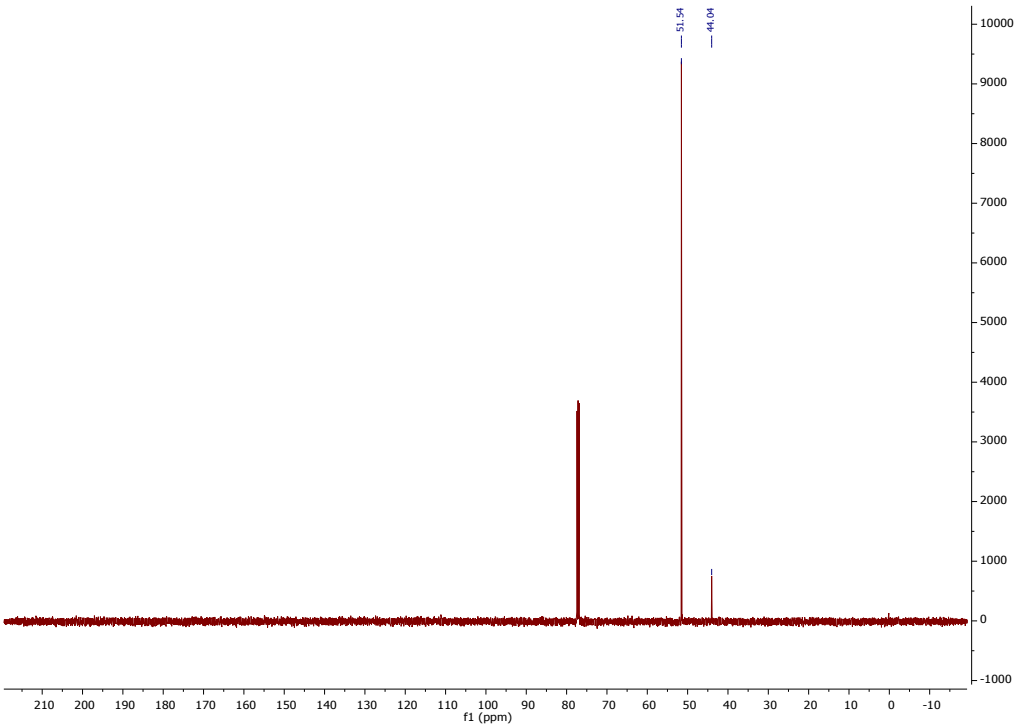
NMR spectra

1,3-Diazido-2,2-bis(azidomethyl)propane **(6)**

^{1}H-NMR

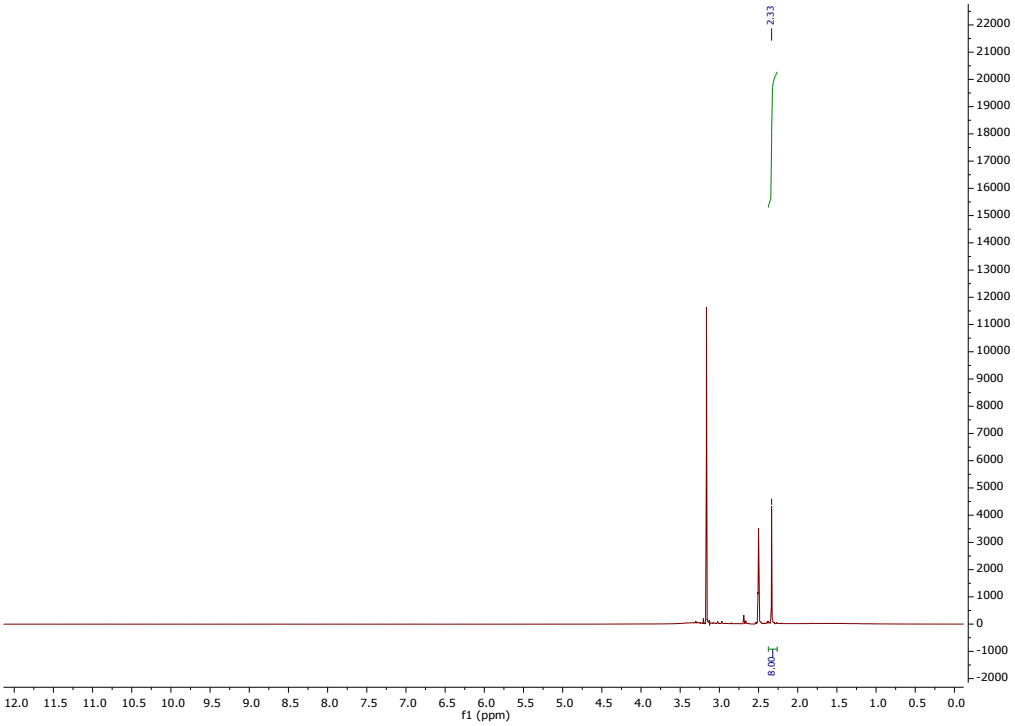


^{13}C-NMR

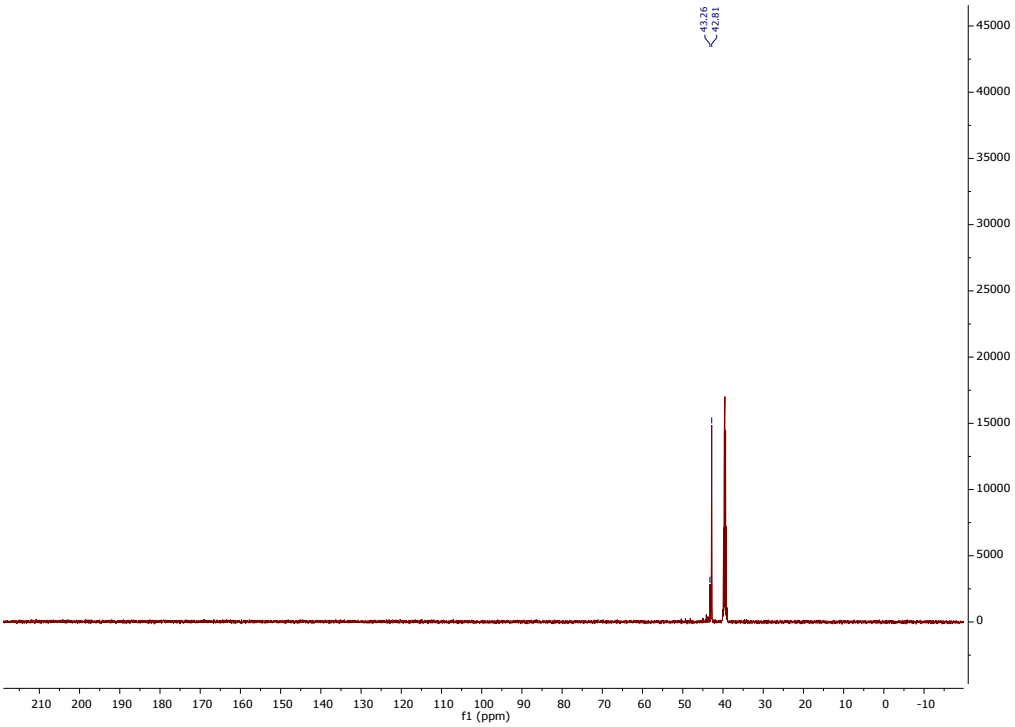


***2,2-Bis(aminomethyl)propane-1,3-diamine* (7)**

^{1}H-NMR

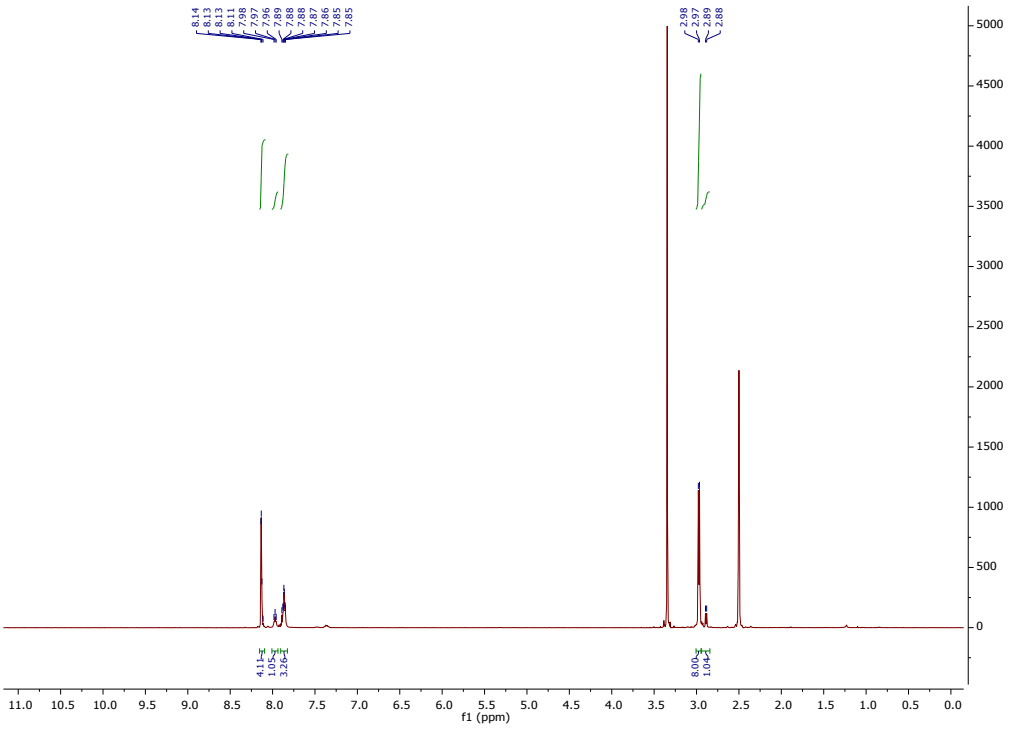


^{13}C-NMR

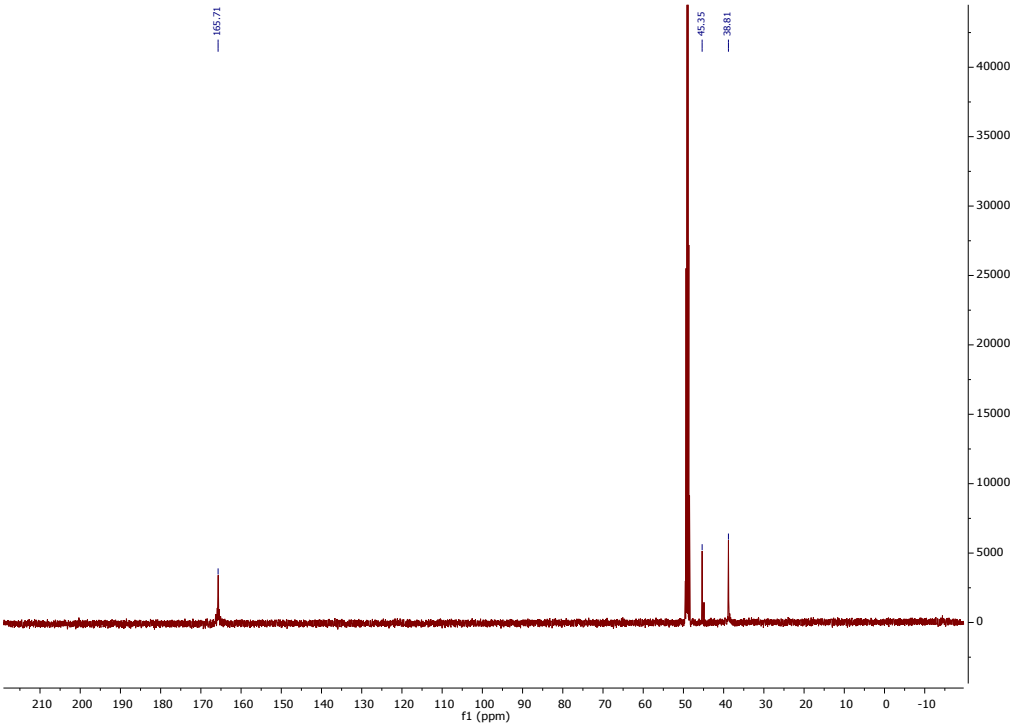


***N,N'-(2,2-bis(formamidomethyl)propane-1,3-diyl) diformamide* (8)**

^{1}H-NMR

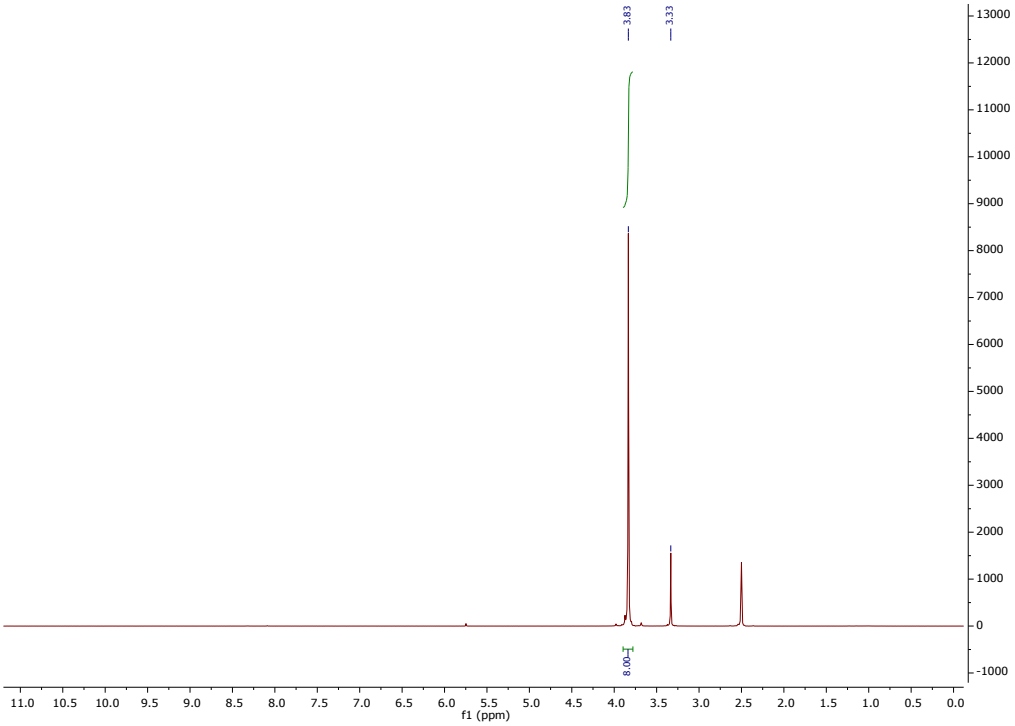


^{13}C-NMR

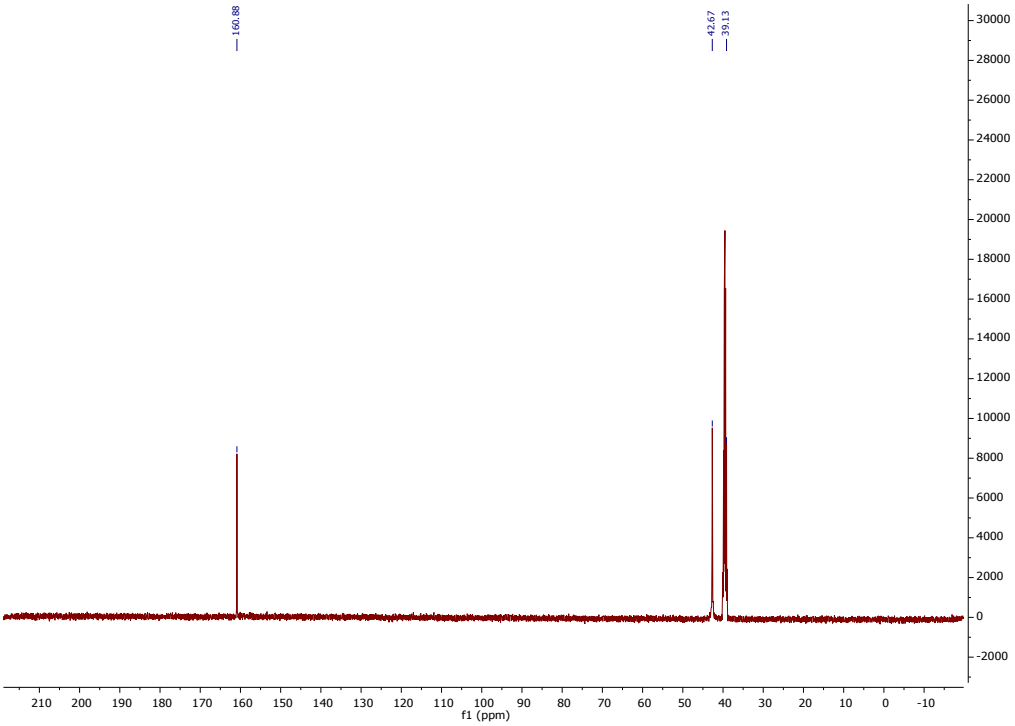


1,3-Diisocyano-2,2-bis(isocyanomethyl)propane (1)

^{1}H-NMR

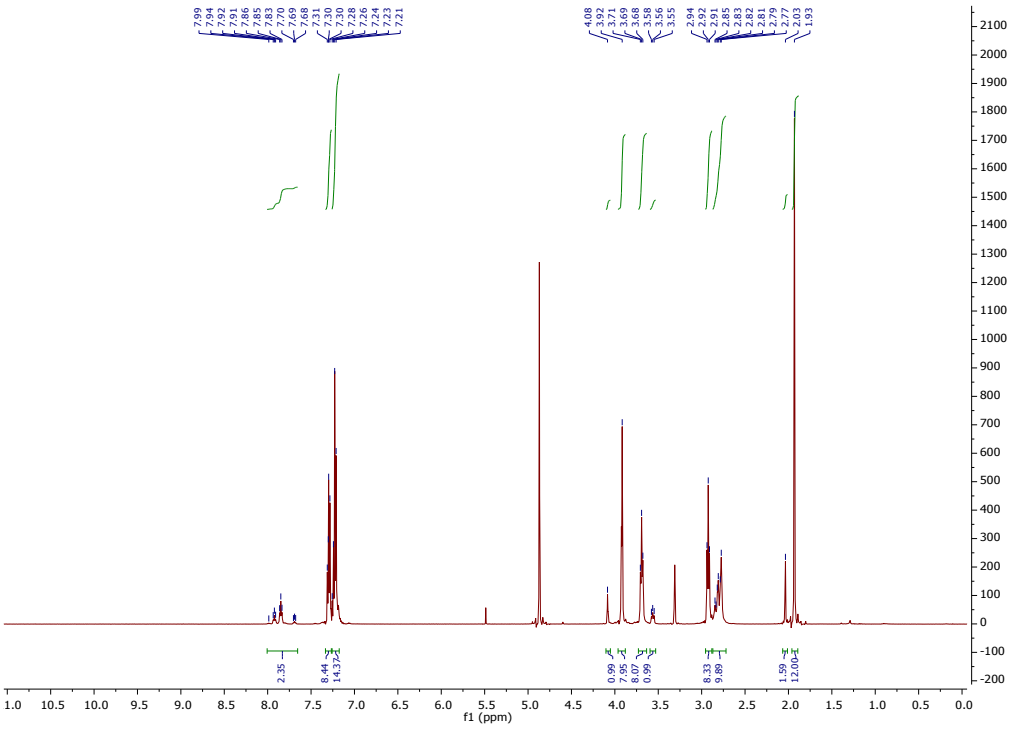


^{13}C-NMR

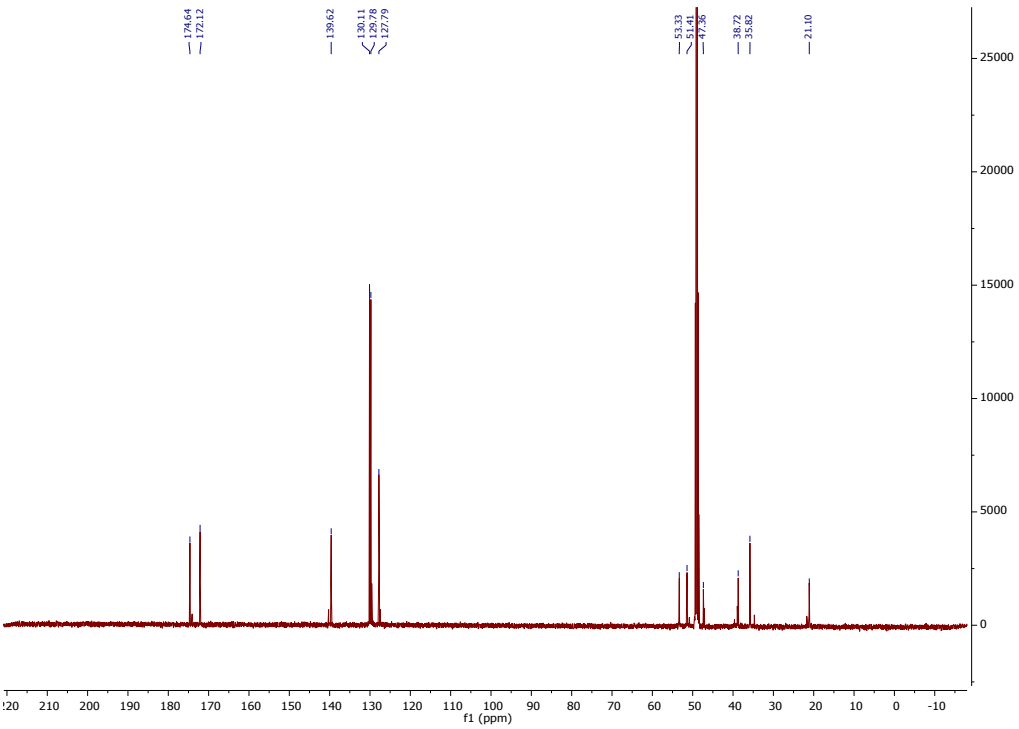


***N,N'*-(2,2-bis((2-(*N*-phenethylacetamido)acetamido)methyl)propane-1,3-diyl) bis(2-(*N*-phenethylacetamido)acetamide) (12)**

^{1}H-NMR

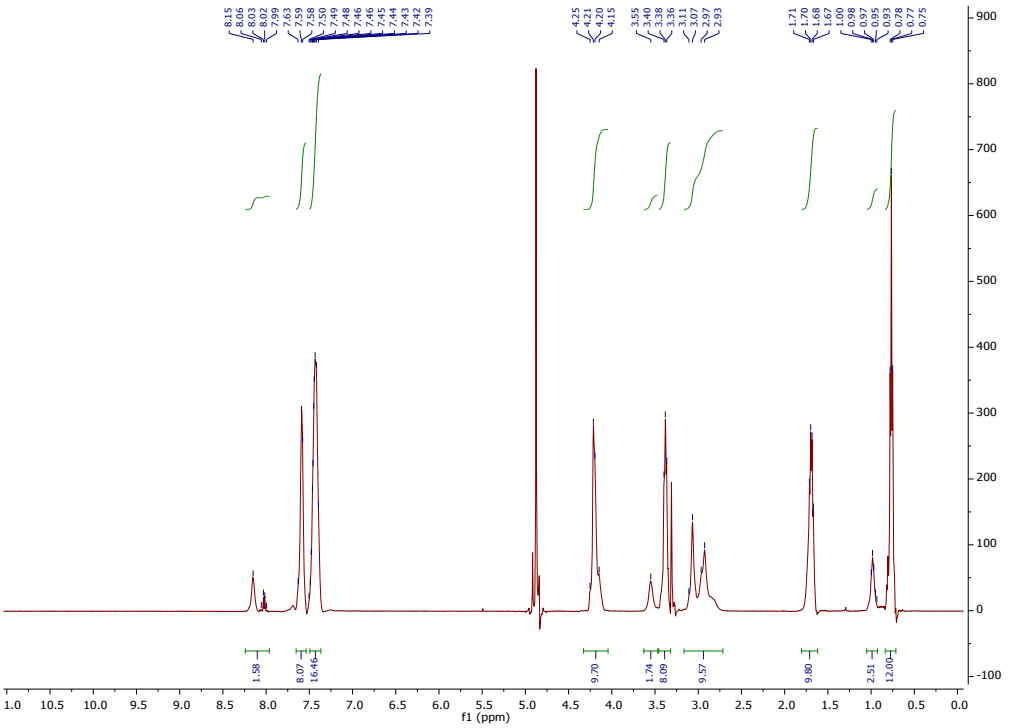


^{13}C-NMR

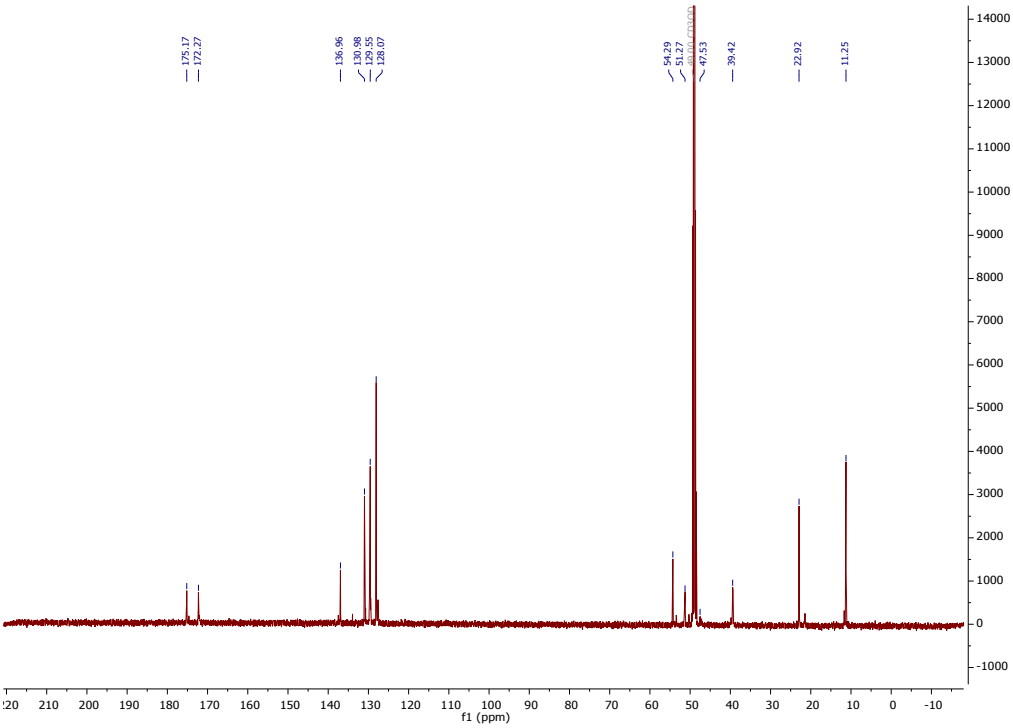


***N,N'*-(2,2-bis((2-(*N*-propylbenzamido)acetamido)methyl)propane-1,3-diyl) bis(2-(*N*-propylbenzamido)acetamide) (13a)**

^{1}H-NMR

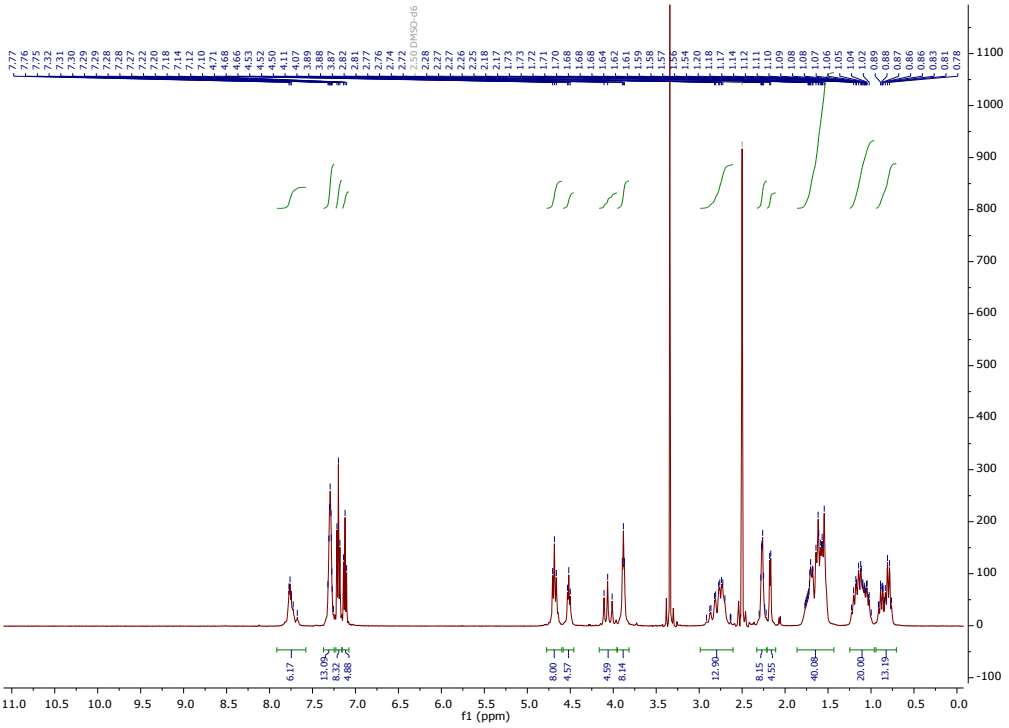


^{13}C-NMR

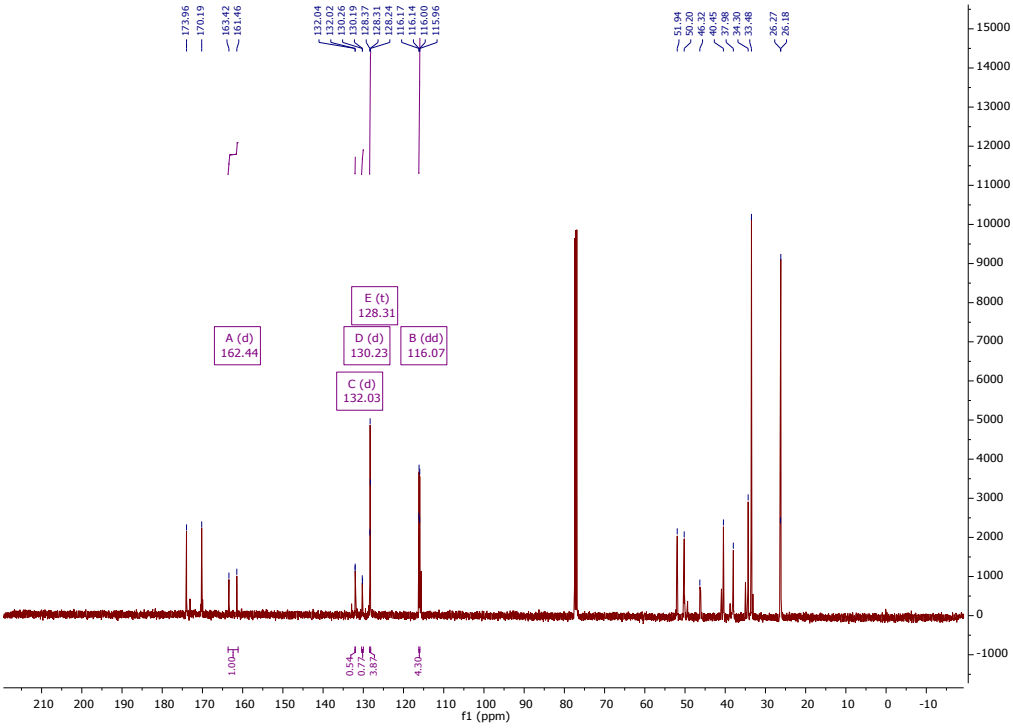


***N,N'*-((2,2-bis((2-(2-cyclohexyl-*N*-(4-fluorobenzyl)acetamido)acetamido)methyl)-propane-1,3-diyl)bis(azanediyl))bis(2-oxoethane-2,1-diyl) bis(2-cyclohexyl-*N*-(4-fluorobenzyl)acetamide) (13b)**

^{1}H-NMR

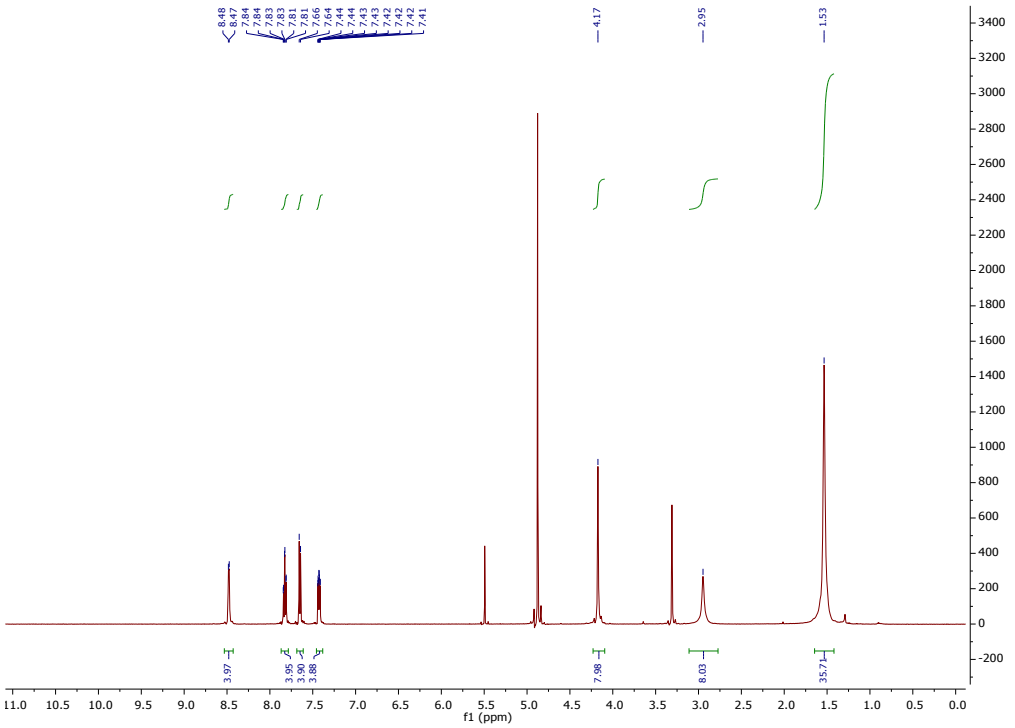


^{13}C-NMR

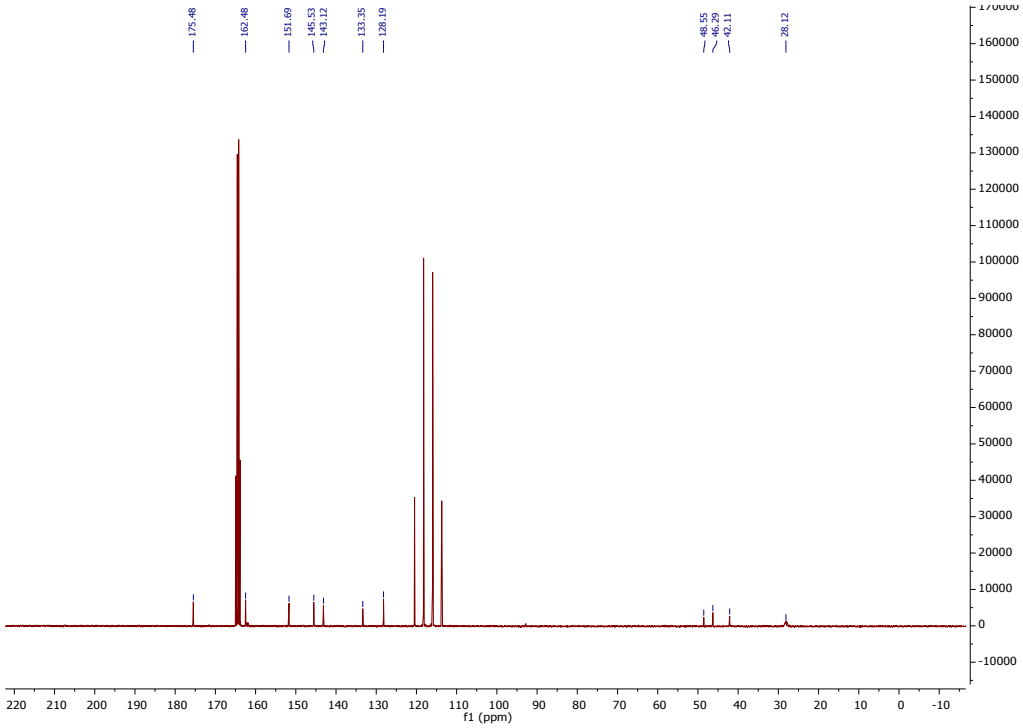


***N,N'*-(((2,2-bis((2-(N-(*tert*-butyl)picolinamido)acetamido)methyl)propane-1,3-diyl)bis(azanediyl))bis(2-oxoethane-2,1-diyl))bis(*N*-(*tert*-butyl)picolinamide) (13c)**

^{1}H-NMR

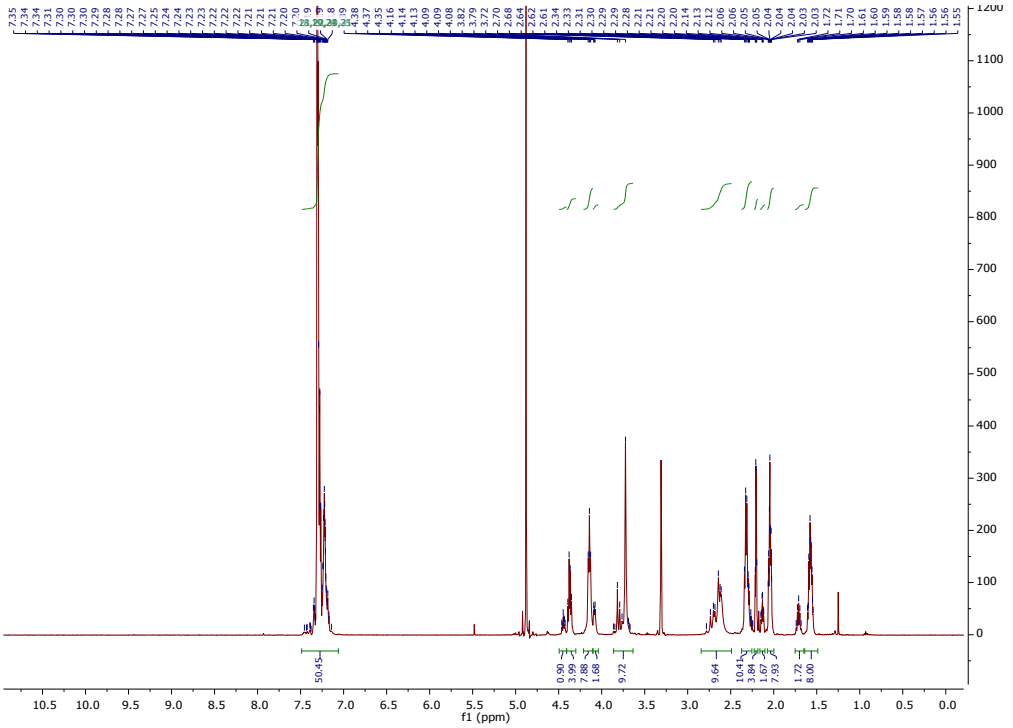


^{13}C-NMR

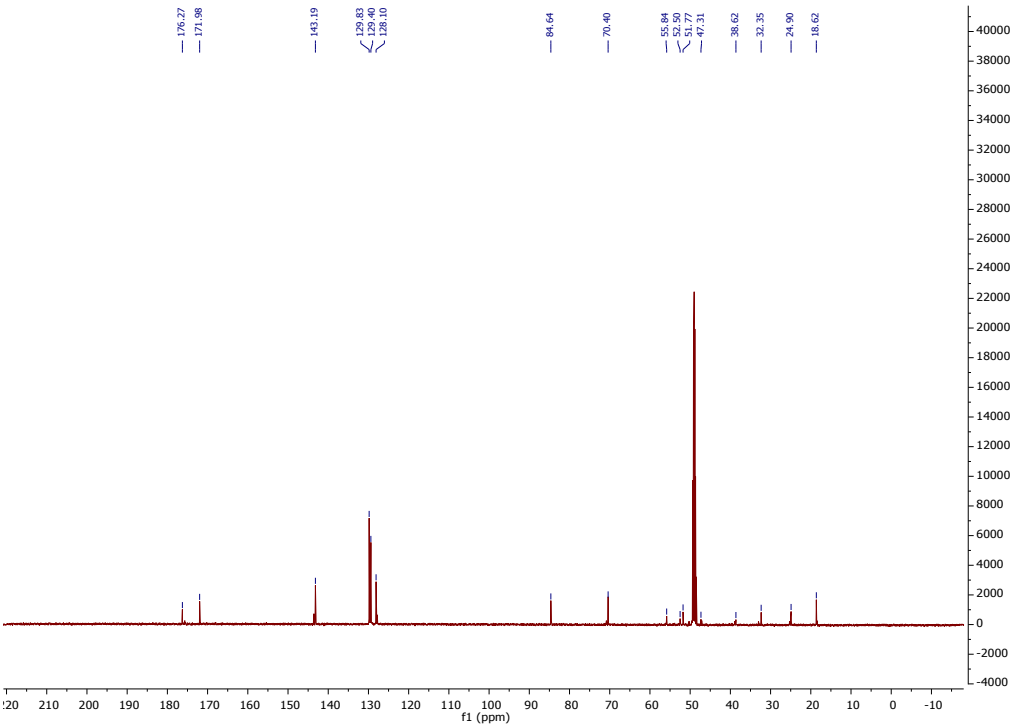


***N,N'*-(((2,2-bis((2-(*N*-(2,2-diphenylethyl)hex-5-ynamido)acetamido)methyl)propane-1,3-diyl)bis(azanediyl))bis(2-oxoethane-2,1-diyl)) bis(*N*-(2,2-diphenylethyl)hex-5-ynamide) (13d)**

^{1}H-NMR

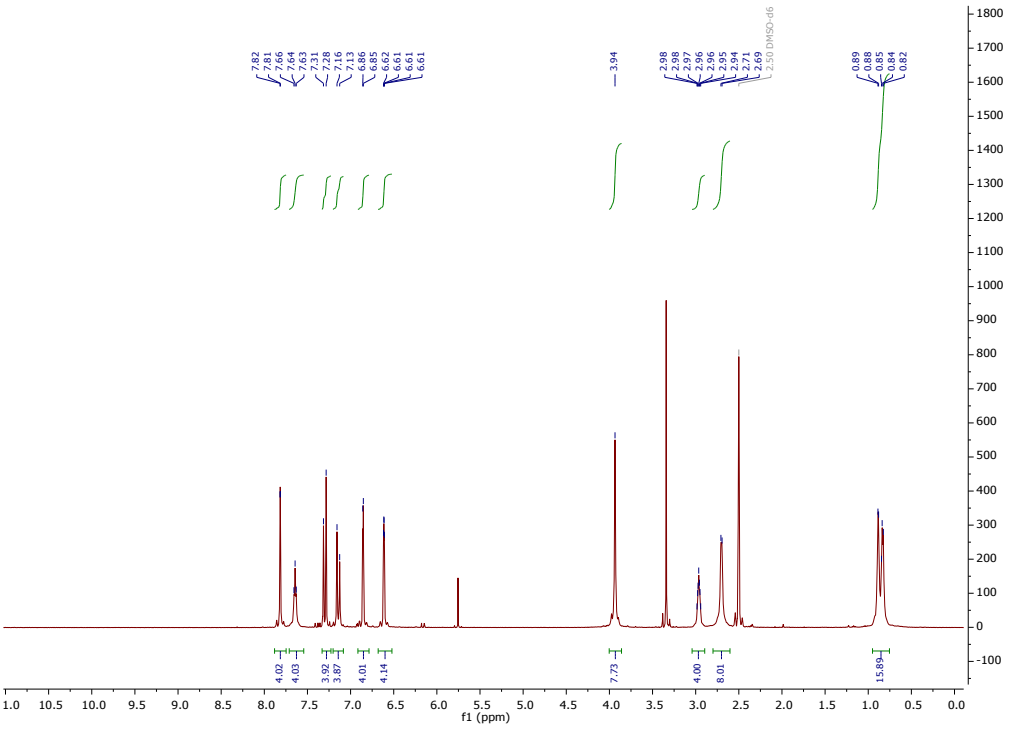


^{13}C-NMR

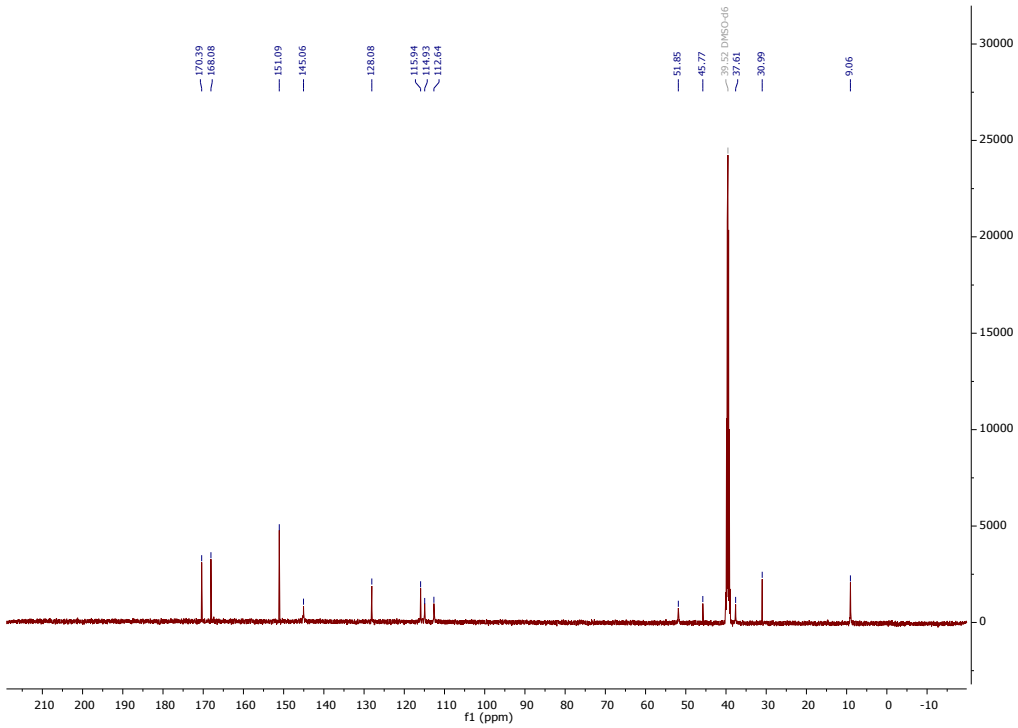


(2*E*,2'*E*)-*N*,*N*'-(((2,2-bis((2-((*E*)-*N*-cyclopropyl-3-(furan-2-yl)acrylamido)acetamido)-methyl)propane-1,3-diyl)bis(azanediyl))bis(2-oxoethane-2,1-diyl))bis(*N*-cyclopropyl-3-(furan-2-yl)acrylamide) (13e)

^{1}H-NMR

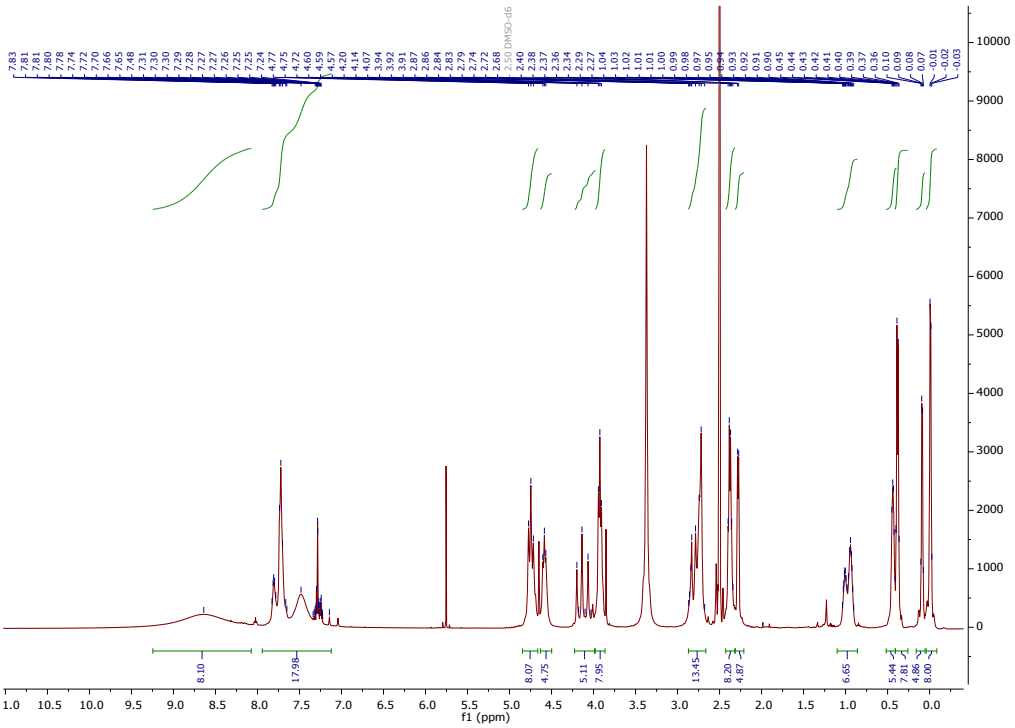


^{13}C-NMR

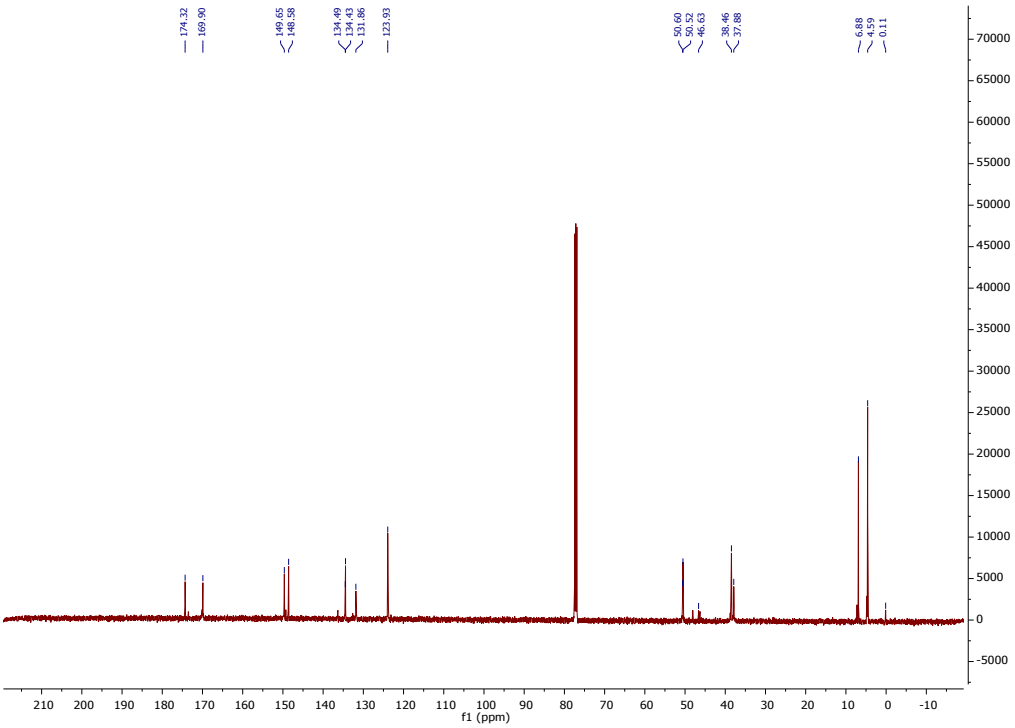


***N,N'*-(((2,2-bis((2-(2-cyclopropyl-*N*-(pyridin-3-ylmethyl)acetamido)acetamido)methyl)-propane-1,3-diyl)bis(azanediyl))bis(2-oxoethane-2,1-diyl))bis(2-cyclopropyl-*N*-(pyridin-3-ylmethyl)acetamide) (13f)**

^{1}H-NMR

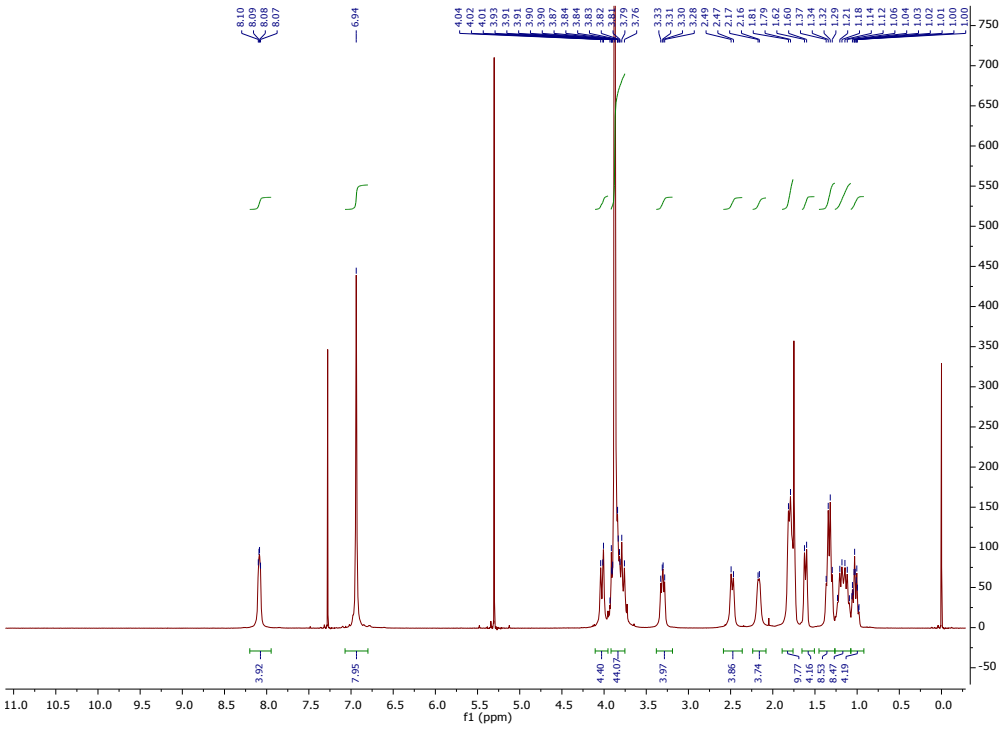


^{13}C-NMR

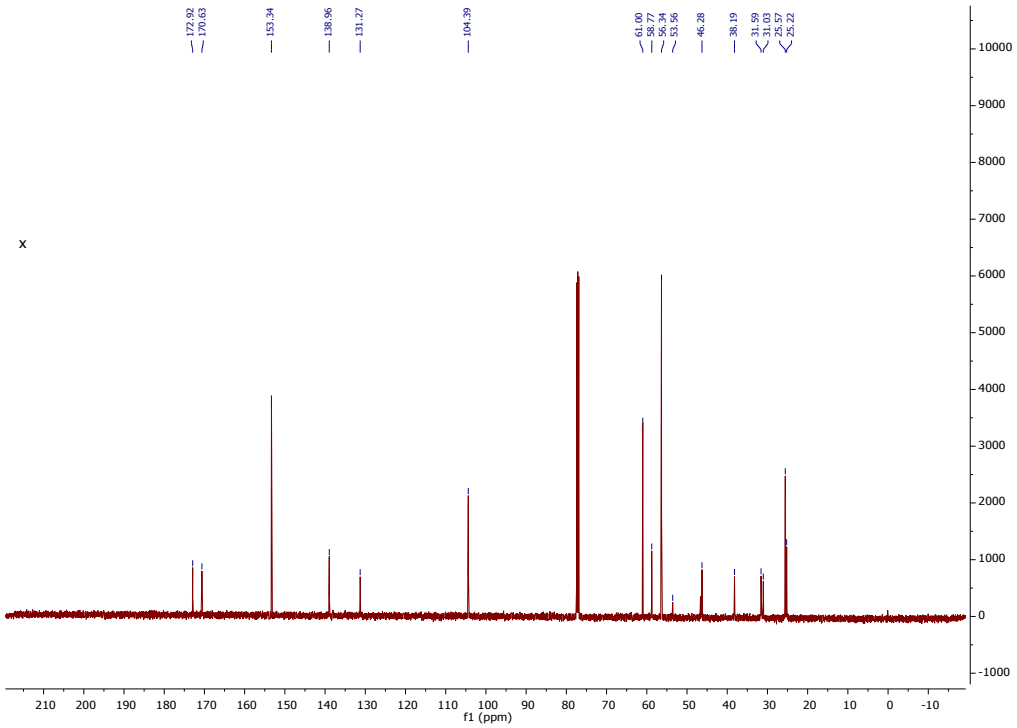


***N,N'*-(((2,2-bis((2-(*N*-cyclohexyl-3,4,5-trimethoxybenzamido)acetamido)methyl)propane-1,3-diyl)bis(azanediyl))bis(2-oxoethane-2,1-diyl))bis(*N*-cyclohexyl-3,4,5-trimethoxybenzamide) (13g)**

^{1}H-NMR

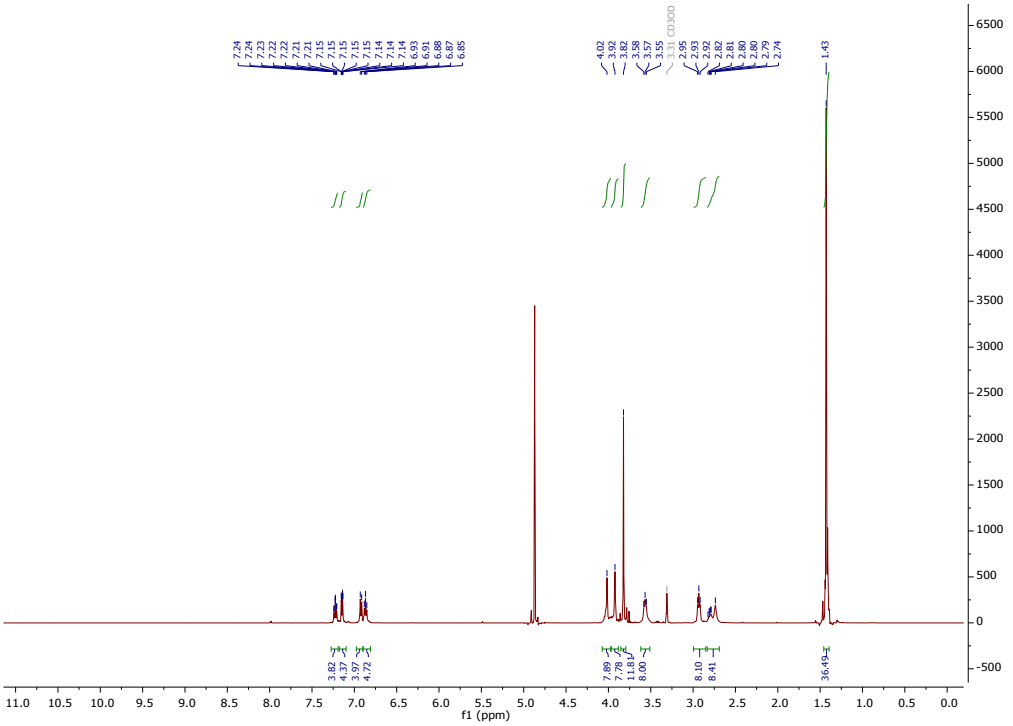


^{13}C-NMR

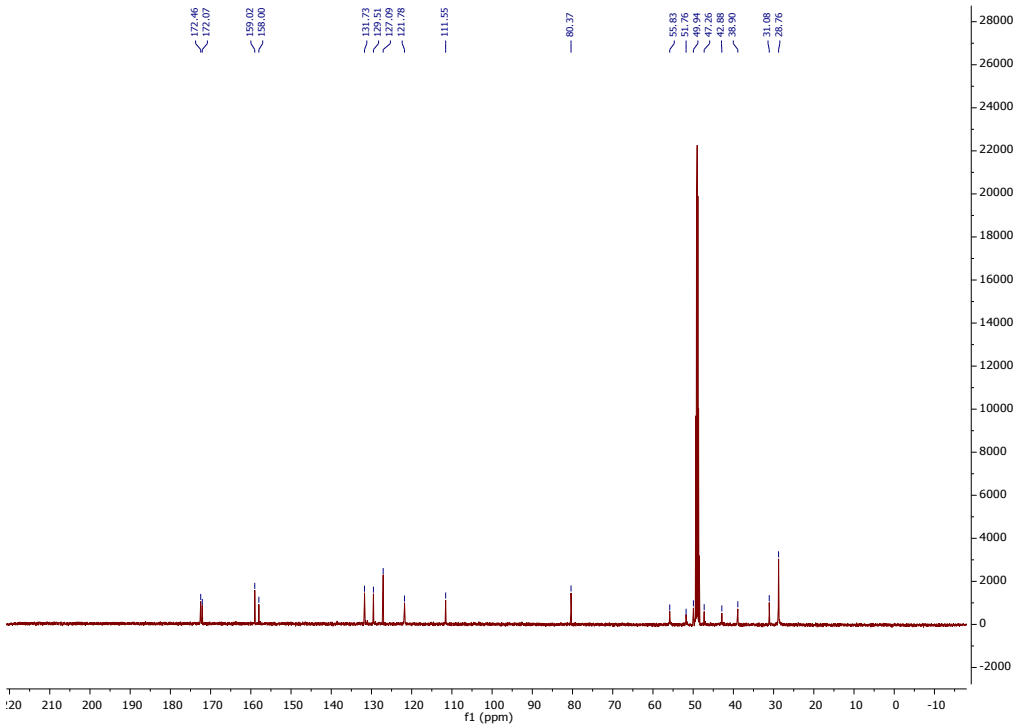


Di-*tert*-butyl-(3,13-bis(2-methoxyphenethyl)-8,8-bis(5-(2-methoxyphenethyl)-11,11-dimethyl-3,6,9-trioxo-10-oxa-2,5,8-triazadodecyl)-2,5,11,14-tetraoxo-3,6,10,13-tetraazapentadecane-1,15-diyl)dicarbamate (13h)

^{1}H-NMR

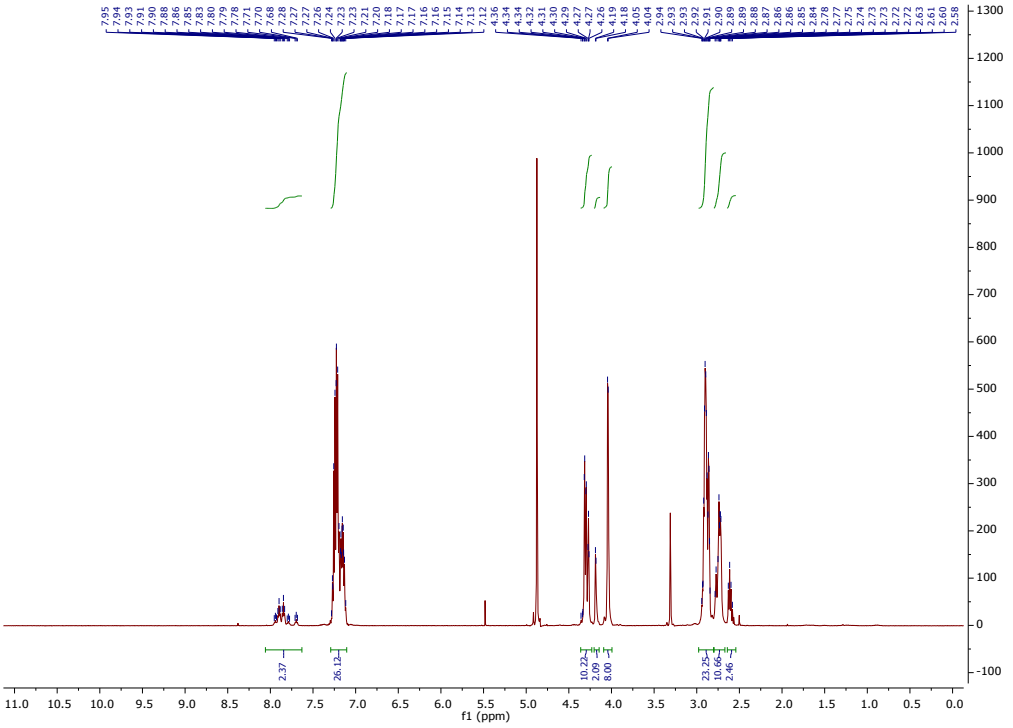


^{13}C-NMR

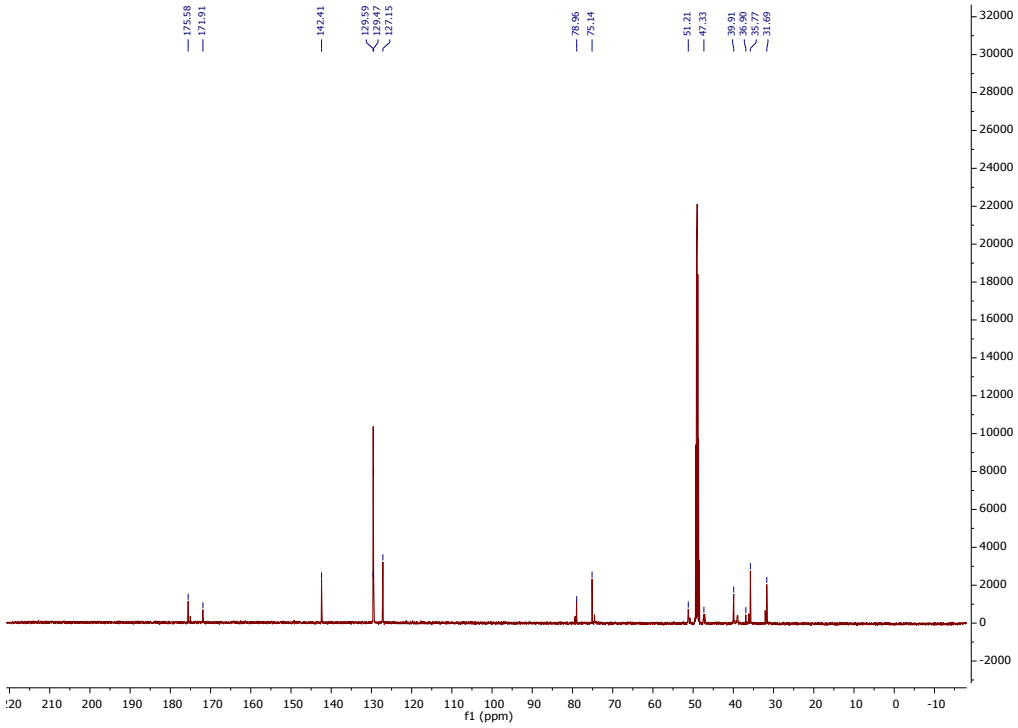


***N,N'*-(((2,2-bis((2-(3-phenyl-*N*-(prop-2-yn-1-yl)propanamido)acetamido)methyl)-propane-1,3-diyl)bis(azanediyl))bis(2-oxoethane-2,1-diyl))bis(3-phenyl-*N*-(prop-2-yn-1-yl)propanamide) (13i)**

^{1}H-NMR

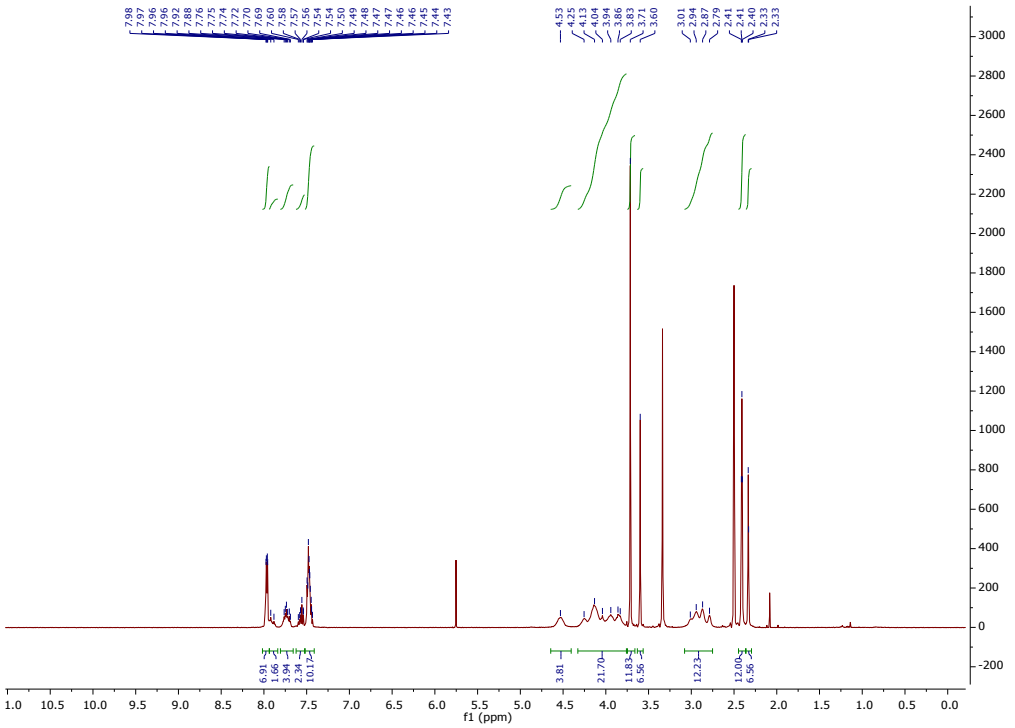


^{13}C-NMR

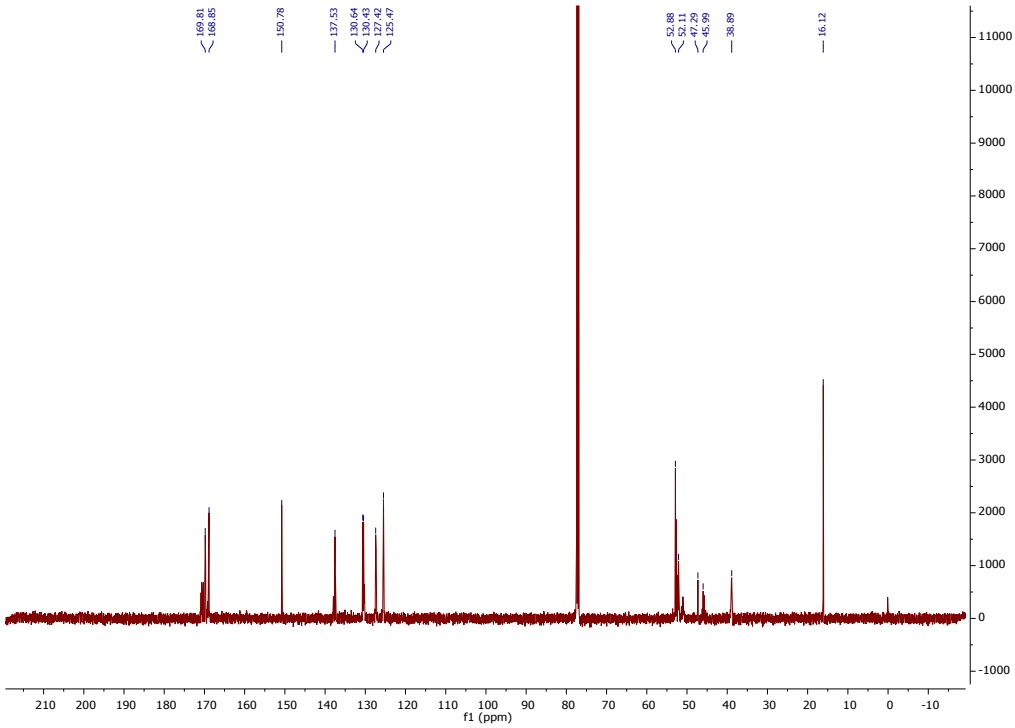


Dimethyl-8,8-bis((2-(*N*-(2-methoxy-2-oxoethyl)-2-methyl-3-nitrobenzamido)acetamido)-methyl)-3,13-bis(2-methyl-3-nitrobenzoyl)-5,11-dioxo-3,6,10,13-tetraazapentadecanedioate (13j)

^{1}H-NMR

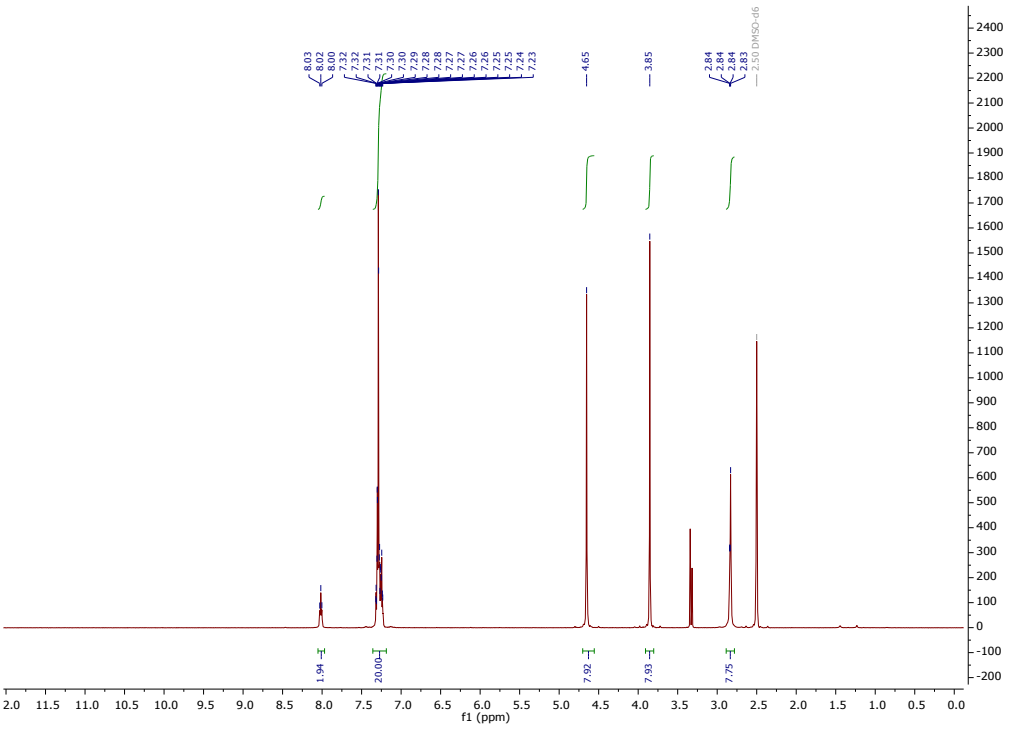


^{13}C-NMR

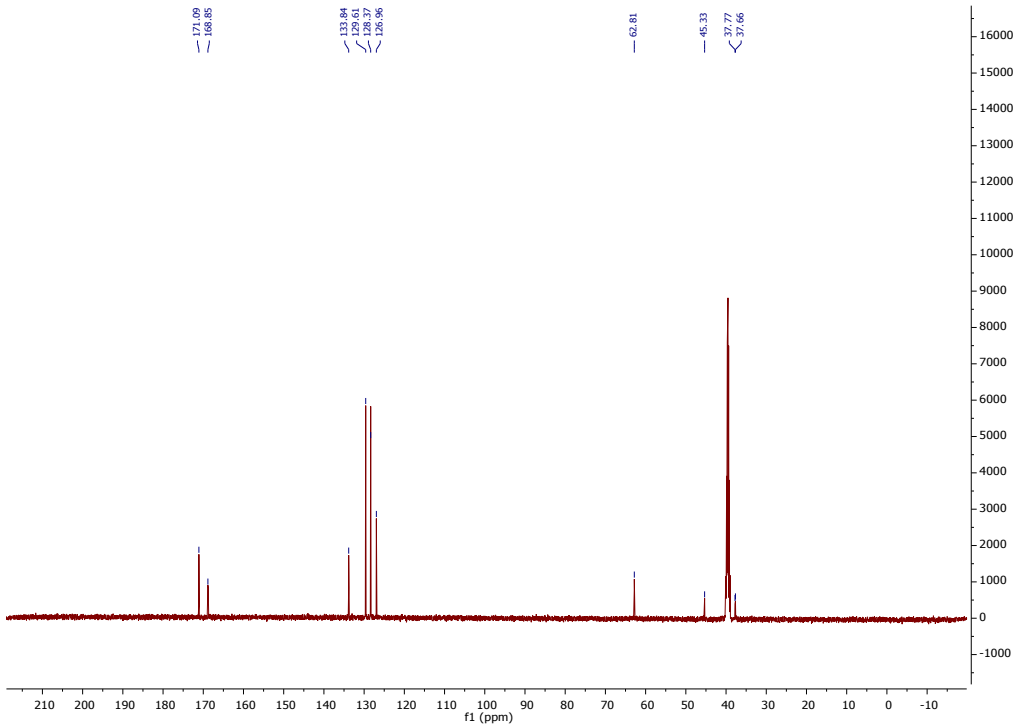


((2,2-Bis((2-(2-phenylacetoxy)acetamido)methyl)propane-1,3-diyl)bis(azanediyl))bis(2-oxoethane-2,1-diyl) bis(2-phenylacetate) (14a)

^{1}H-NMR

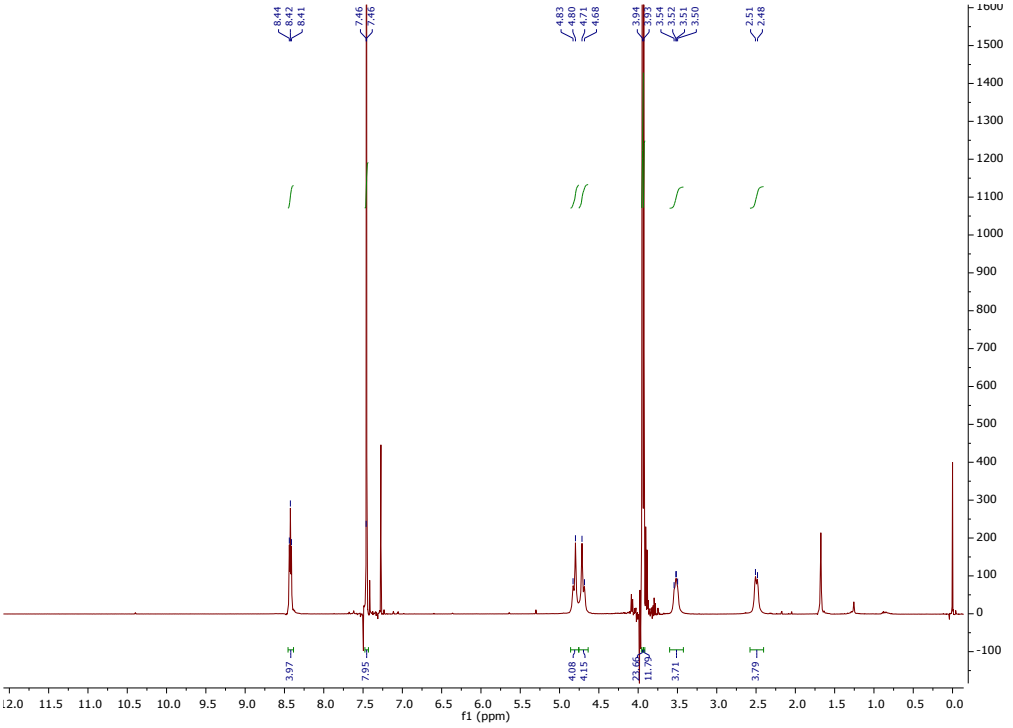


^{13}C-NMR

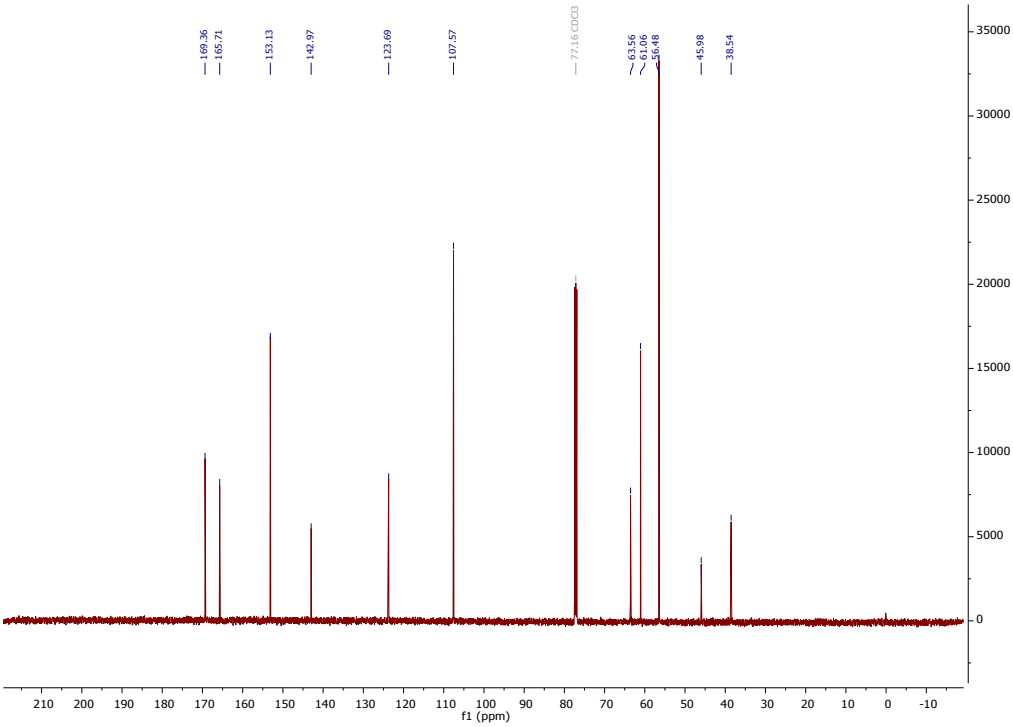


((2,2-bis((2-((3,4,5-trimethoxybenzoyl)oxy)acetamido)methyl)propane-1,3-diyl)bis(azanediyl))bis(2-oxoethane-2,1-diyl) bis(3,4,5-trimethoxybenzoate) (14b)

^{1}H-NMR

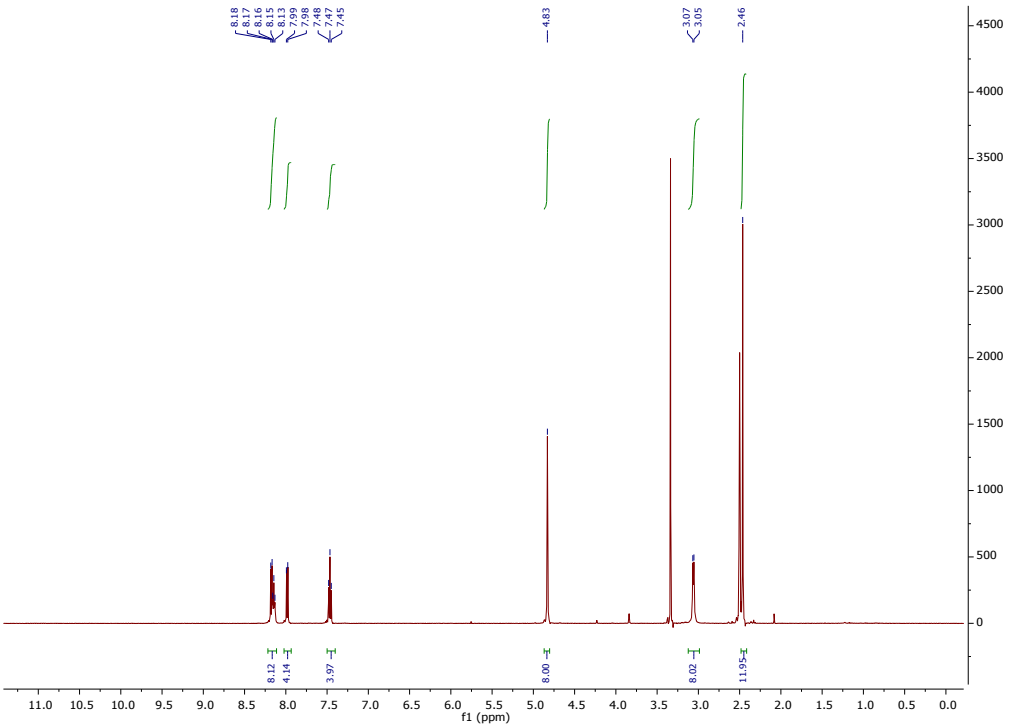


^{13}C-NMR

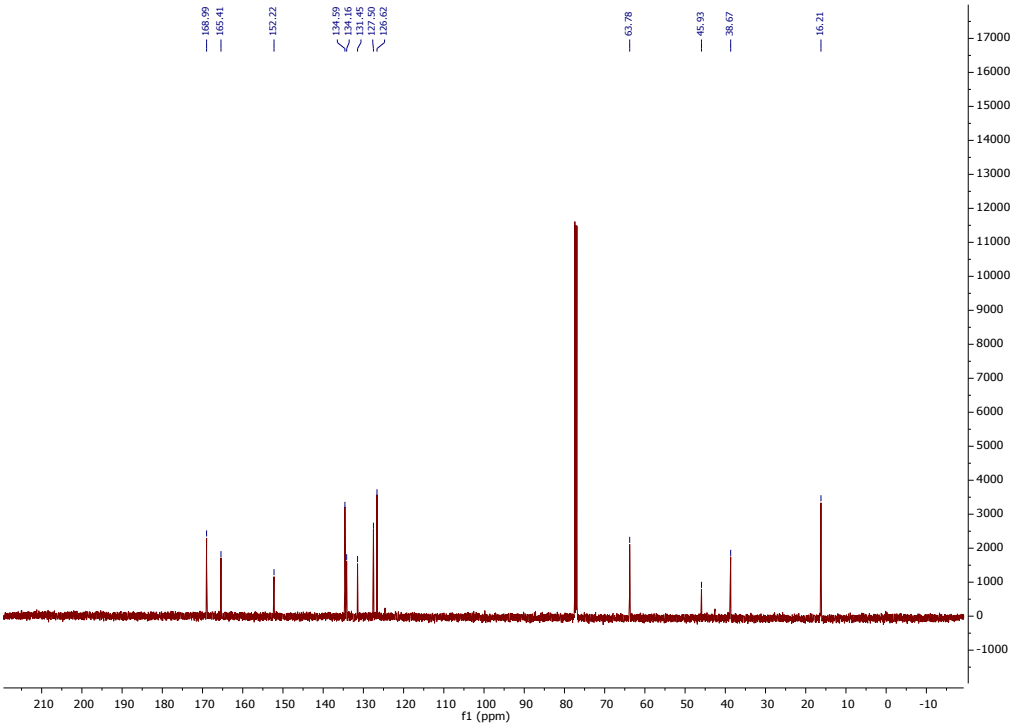


((2,2-bis((2-((2-methyl-3-nitrobenzoyl)oxy)acetamido)methyl)propane-1,3-diyl)bis(azanediyl))bis(2-oxoethane-2,1-diyl) bis(2-methyl-3-nitrobenzoate) (14c)

^{1}H-NMR

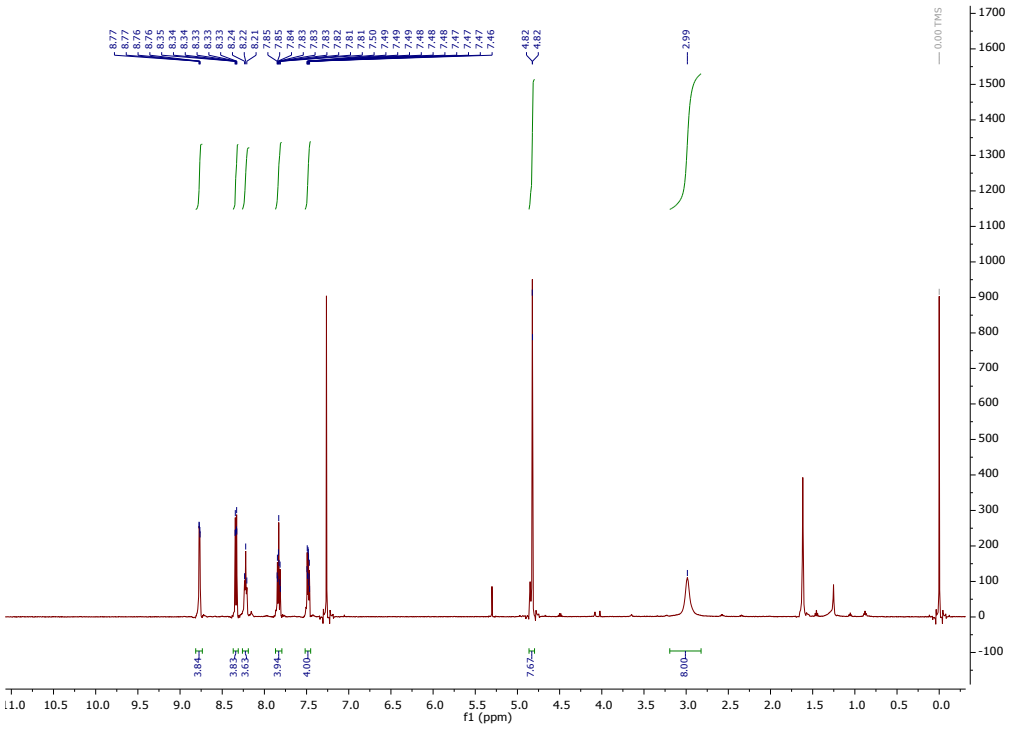


^{13}C-NMR

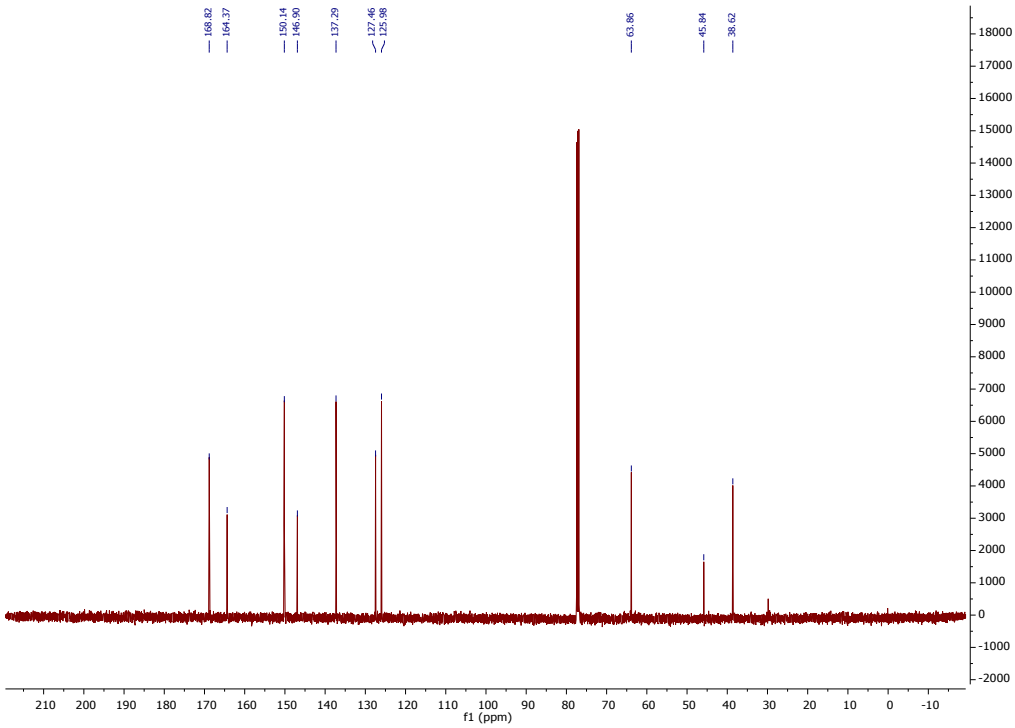


((2,2-bis((2-(picolinoyloxy)acetamido)methyl)propane-1,3-diyl)bis(azanediyl))bis(2-oxoethane-2,1-diyl) dipicolinate (14d)

^{1}H-NMR

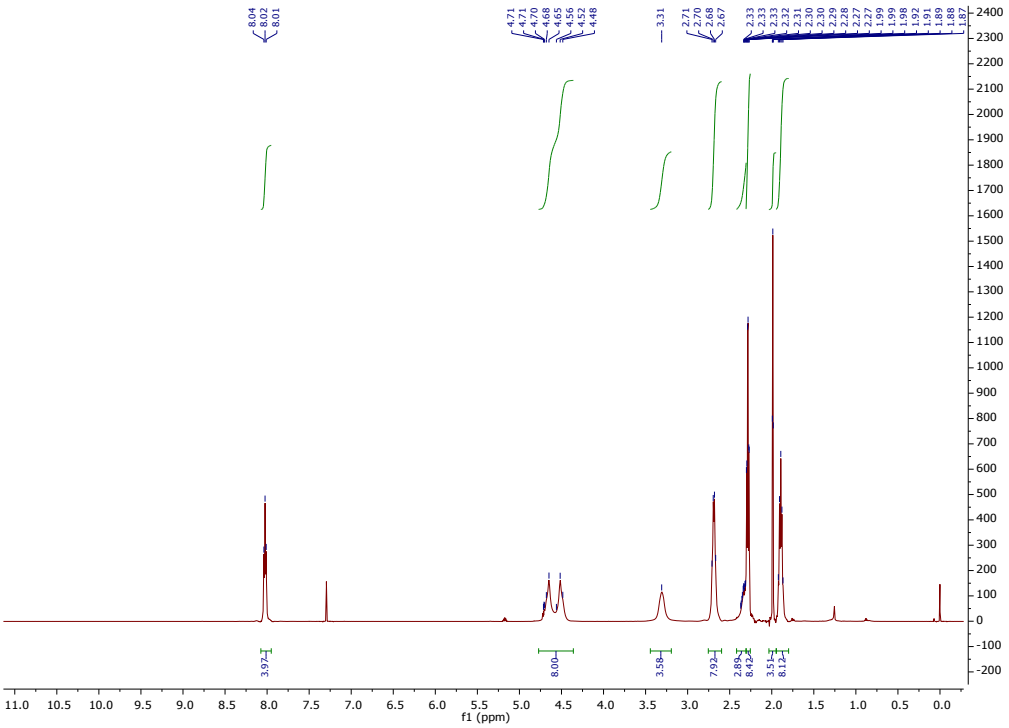


^{13}C-NMR

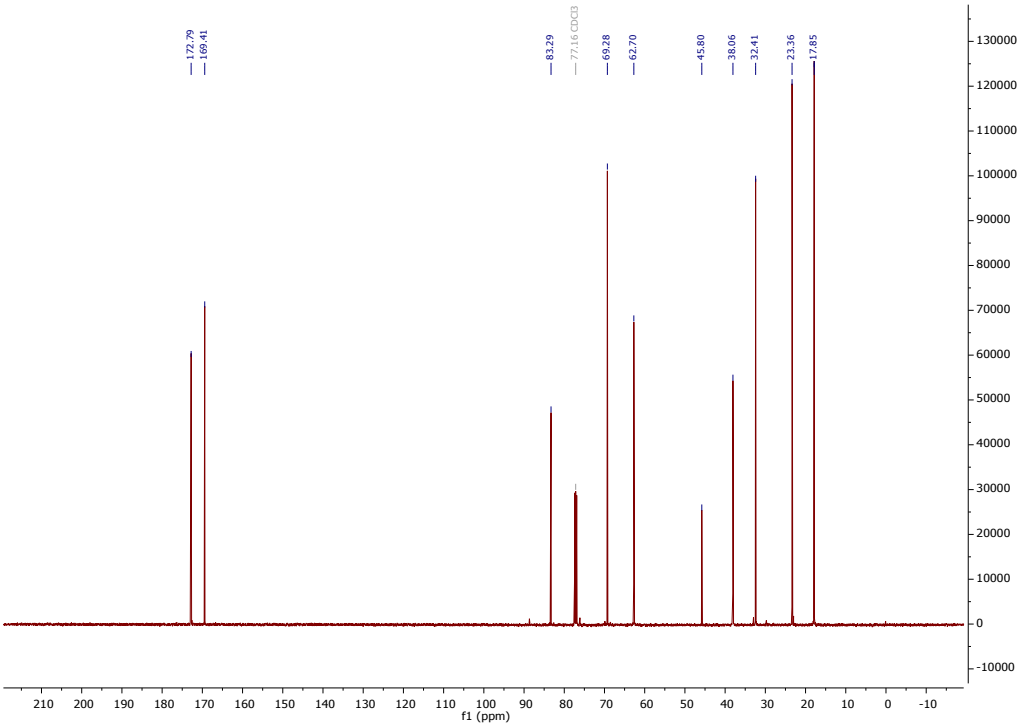


((2,2-bis((2-(hex-5-ynoyloxy)acetamido)methyl)propane-1,3-diyl)bis(azanediyl))bis(2-oxoethane-2,1-diyl) bis(hex-5-ynoate) (14e)

^{1}H-NMR

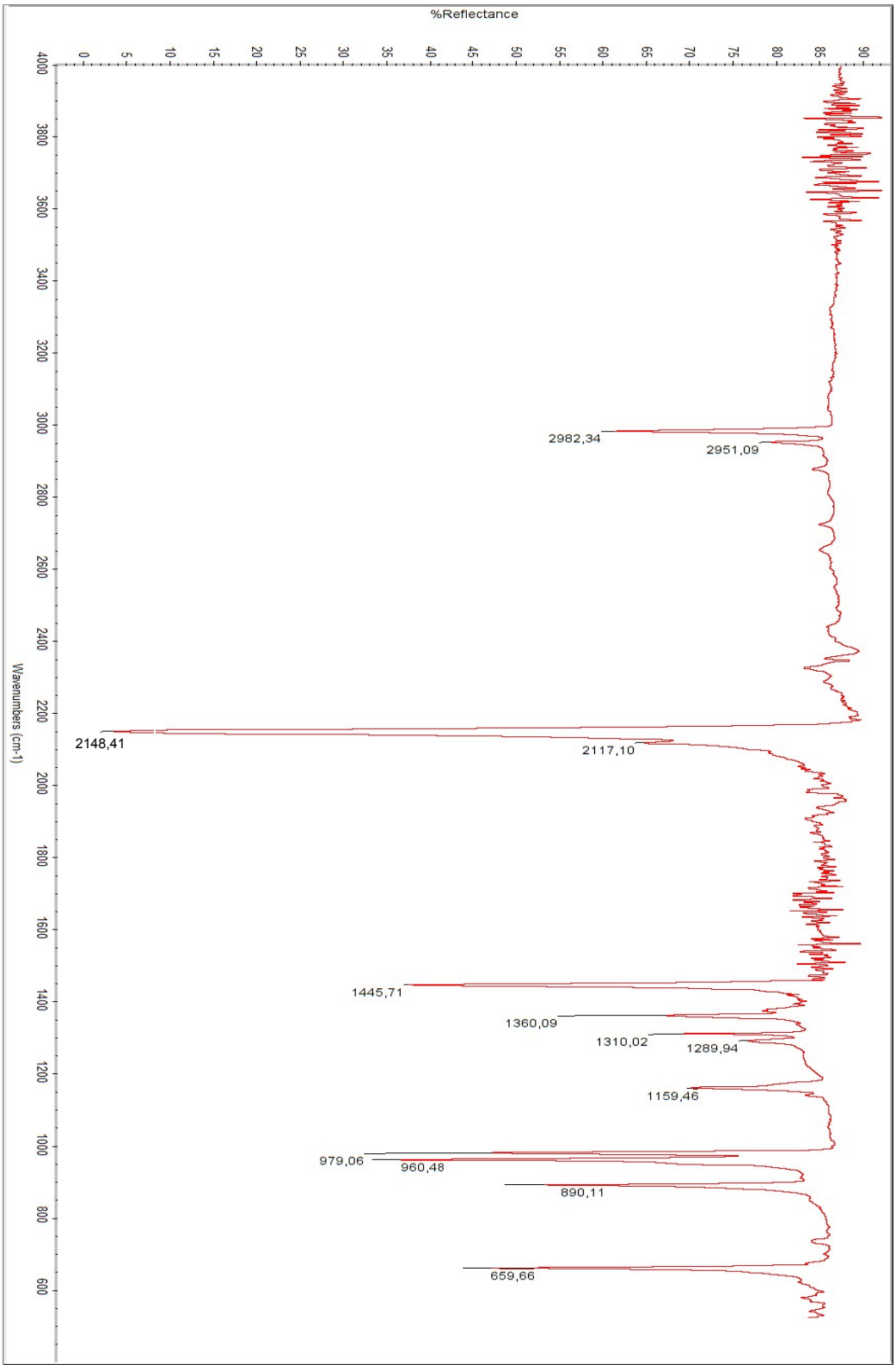


^{13}C-NMR



IR-spectrum

1,3-Diisocyano-2,2-bis(isocyanomethyl)propane (1)



Crystal structure determination

X-ray diffraction data for single crystals of compounds **1**, **13e**, and **13b** were collected using XtalLAB Synergy-S. Each crystal was measured using SuperNova (Rigaku - Oxford Diffraction) four circle diffractometers with a mirror monochromator and a microfocus CuKα radiation source (λ = 1.5418 Å). Additionally, the diffractometer was equipped with the cryostat system allowing low-temperature experiments, performed at 100(2) K (**13e** and **13b**) and 130(2) K (**1**). The obtained data sets were processed with CrysAlisPro software.[2] The phase problem was solved with direct methods using SIR2014 [3] (**13e** and **13b**) or SUPERFLIP [4] (**1**). Parameters of obtained models were refined by full-matrix least-squares on F^2 using SHELXL-2014/6 .[5] Calculations were performed using WinGX integrated system (ver. 2014.1).[6] Figures were prepared with Mercury 4.0 software.[7]

All non-hydrogen atoms were refined anisotropically. All hydrogen atoms attached to carbon atoms were positioned with the idealised geometry and refined using the riding model with the isotropic displacement parameter $U_{iso}[H] = 1.2\ U_{eq}[C]$ for all but methyl groups, where $U_{iso}[H] = 1.5\ U_{eq}[C]$ was applied. The difference Fourier map was inspected in order to localise hydrogens linked to nitrogen atoms. Crystal data and refinement results are shown in table S1. The molecular geometry observed in crystal structures are shown in figure S1.

All presented compounds are highly symmetric organic molecules with 4-fold axis symmetry at C1 atom. This symmetry led to the positioning of the mentioned carbon atom at the special position in the crystal structure (a rotoinversion 4-fold axis parallel to [001] direction) in the case of **13b** and **1**. Thus, the asymmetric unit of mentioned crystal structures consists of a quarter of the molecule. Additionally, in the crystal structure of **13b** a highly disordered solvent molecule (ethyl acetate) is observed, with one carbon atom occupying the special position (a rotoinversion 4-fold axis parallel to [001] direction). In figure S2 two of the several alternative positions of the disordered solvent is shown. However, due to the unresolved disorder model and unstable refinement, a PLATON SQUEEZE [8] procedure was applied. Despite the high molecular symmetry of the investigated compound **13e**, it crystallises in the triclinic system. This is related to three deuterated methanol molecules incorporated in the crystal lattice, which are responsible for breaking the higher symmetry of the crystal. They form a solvent channel propagated along [100] direction, by forming a hydrogen bond system.

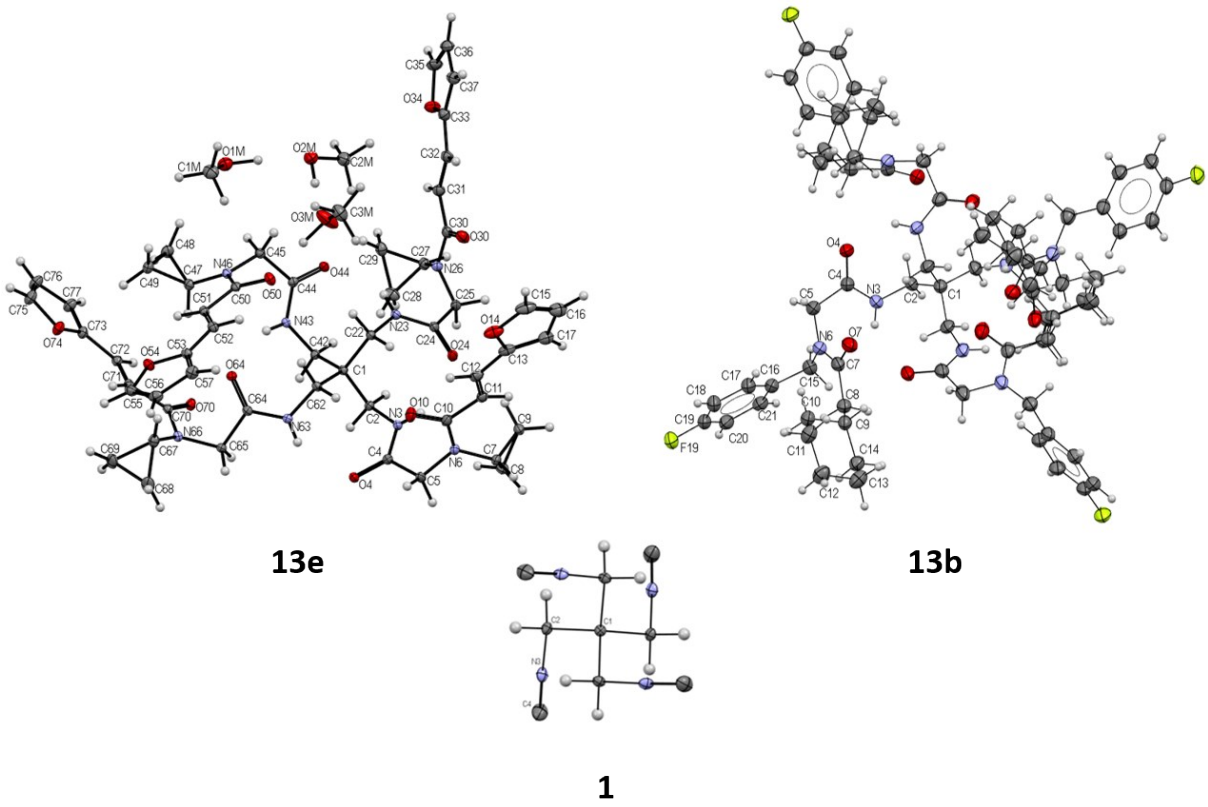


Figure S1. Molecular geometry observed in crystal structures of compounds **13e**, **13b**, and **1** showing the atom labelling scheme only for the asymmetric unit. The C1 carbon atom in structures **13b** and **1** occupies the special position (a rotoinversion 4-fold axis parallel to [001] direction) and asymmetric unit consists of a quarter of the molecule. Displacement ellipsoids of non-hydrogen atoms are drawn at the 30% probability level. H atoms are presented as small spheres with an arbitrary radius.

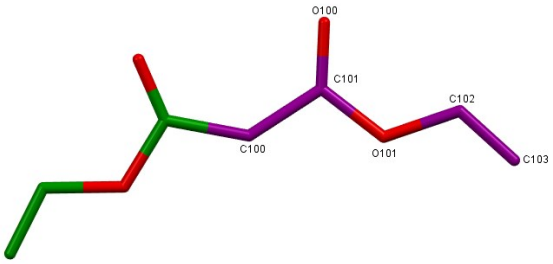


Figure S2. Two of the several alternative orientations of the highly disordered ethyl acetate molecule in the crystal structure of **13b**. The C100 carbon atom occupies a special position - a rotoinversion 4-fold axis parallel to [001] direction.

Table S1. Crystal data and structure refinement results for compounds **13e**, **13b**, and **1**.

Compound	**13e**	**13b**	**1**
Empirical moiety formula	$C_{53}\ H_{60}\ N_8\ O_{12}$, $3(CD_3OD)$	$C_{73}\ H_{96}\ F_4\ N_8\ O_8$	$C_9\ H_8\ N_4$
Formula weight [g/mol]	1109.29	1289.57	172.19
Crystal system	Triclinic	Tetragonal	Tetragonal
Space group	$P\bar{1}$	$I4_1/a$	$P4_2/n$
Unite cell dimensions	a = 10.2036(1) Å b = 14.4428(1) Å c = 19.7614 (1) Å α= 79.654(1)° β= 84.510(1)° γ= 75.810(1)°	a = 15.6151(1) Å b = 15.6151(1) Å c = 33.2923(3) Å α= 90.0° β= 90.0° γ= 90.0°	a = 8.3584(6) Å b = 8.3584(6) Å c = 6.7005(9) Å α= 90.0° β= 90.0° γ= 90.0°
Volume [Å^3]	2773.37(4)	8117.71(13)	468.12(9)
Z	2	4	2
D_{calc} [Mg/m^3]	1.328	1.055	1.222
μ [mm^{-1}]	0.795	0.613	0.644
F(000)	1168	2760	180
Crystal size [mm^3]	0.5 x 0.4 x 0.2	0.5 x 0.4 x 0.2	0.3 x 0.2 x 0.2
Θ range	2.28° to 77.62°	4.89° to 76.53°	8.48° to 70.85°
Index ranges	-12 ≤ h ≤ 11, -18 ≤ k ≤ 18, -24 ≤ l ≤ 24	-19 ≤ h ≤ 19, -19 ≤ k ≤ 19, -40 ≤ l ≤ 41	-9 ≤ h ≤ 10, -7 ≤ k ≤ 8, -7 ≤ l ≤ 2
Refl. collected	89827	126535	671
Independent reflections	11349 [R(int) = 0.0425]	4260 [R(int) = 0.0436]	435 [R(int) = 0.0136]
Completeness [%] to Θ = 67.68°	99.8	99.9	98.8
Absorption correction	Multi-scan	Multi-scan	Multi-scan
Tmin. and Tmax.	0. 683 and 1.000	0. 321 and 1.000	0. 254 and 1.000
Data/ restraints/parameters	11349 / 0 / 777	4260 / 0 / 215	435 / 0 / 31
GooF on F2	1.076	1.098	1.176
Final R indices [I>2sigma(I)]	R1= 0.0460, wR2= 0.1194	R1= 0.0336, wR2= 0.1691	R1= 0.0665, wR2= 0.1693
R indices (all data)	R1= 0.0506, wR2= 0.1270	R1= 0.0654, wR2= 0.1703	R1= 0.0678, wR2= 0.1706
$\Delta\rho_{max}$, $\Delta\rho_{min}$ [e·Å^{-3}]	0.74 and -0.68	0.24 and -0.16	0.35 and -0.47

Literature:

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