Supplementary Material (ESI) for Organic & Biomolecular Chemistry

A Click Chemistry Approach to C-3 Symmetric, G-Quadruplex Stabilising Ligands

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General Experimental

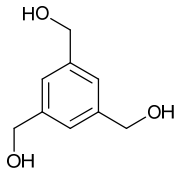
Melting points were determined on a Stuart SMP3 machine and are uncorrected. High resolution mass spectra were recorded on VG Micron Autospec or Bruker Micro TOF. Fourier Transform Infrared Spectroscopy (FT-IR) spectra were obtained on Perkin Elmer 1600 series or Bruker Tensor 27 spectrometer. NMR spectra were recorded on Bruker AV(III) 400, Bruker AV 400 or Bruker DPX 400 at 400 and 101 MHz, for ^{1}H and ^{13}C NMR respectively, or on a JEOL 270 spectrometer at 270 and 70 Hz, for ^{1}H and ^{13}C NMR respectively. Coupling constant are given in hertz (Hz), the shifts are given as parts per million (ppm) using tetramethylsilane as an internal standard. The following notations indicate the multiplicity of the signals: s (singlet), d (doublet), br s (broad signal), t (triplet), q (quartet), m (multiplet). Thin layer chromatography was performed on Merck precoated silica gel aluminium plates (60F-254) and visualised using UV absorption and/or an appropriate stain. Column chromatography was performed using Merck silica gel 60 (230-400 mesh). All solvents and reagents were used as received from commercial suppliers. Petrol ethers refers to petroleum ethers 40 - 60 $^{\circ}C$. Dry THF was distilled from sodium wire/benzophenone and dry CH_2Cl_2 from CaH_2 immediately prior to use. Microwave reactions were conducted on a CEM Discover Explorer microwave reactor.

Molecular Modelling: Automated docking studies were carried out using the AutoDock program. v4.0 (D. S. Goodsell, G. M. Morris and A. J. Olson. *J. Mol. Recogn*. 1996, **9**, 1). A Lamarckian genetic algorithm (LGA) was applied to investigate the plausible interactions between the ligand and G-quadruplex DNA. Values for all other docking parameters were kept as default. A total of 250 independent docking runs were undertaken to enhance the reliability of the docking process (R. Wang, Y. Lu and S. Wang. *J. Med. Chem*. 2003, **46**, 2287). Cluster analysis was carried out on the docked results using a root mean square (RMS) tolerance of 1.0 Å. The AMBER 9.0 suite (W. D. Cornell, P. Cieplak, C. I. Bayly, I. R. Gould, K. M. Merz Jr., D. M. Ferguson, D. C. Spellmeyer, T. Fox, J. W. Caldwell and P. A. Kollman, *J. Am. Chem. Soc.* 1995, **117**, 5179; http://ambermd.org).was used for all subsequent

calculations. Positions of the K^+ ions located within the central electronegative channel in the crystal structures were retained. Additional cations (K^+) were added to the system such that the net -ve charge was zero. The ligand complex was then solvated in a waterbox whose boundary was at least 10 Å away from the solute. Equilibration step involved 220 ps of minimisation and dynamics followed by 20 ns of unrestrained MD simulation using the ParmBSC forcefield for nucleic acids.

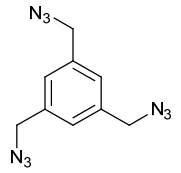
Experimental Procedures

1,3,5-Tris(hydroxymethyl)benzene, 5[1]



A solution of 1,3,5-tris(carbomethoxy)benzene (14.0 g, 55.5 mmol) in dry THF (80 mL) was added to a suspension of LAH (4.72 g, 124.2 mmol) in dry THF (100 mL). The resulting mixture was stirred at rt for 1 h then reflux for 10 h. The reaction was cooled to 0 °C and H_2O was added carefully. When gas evolution had ceased a saturated solution of Rochelle's salt was added and stirred overnight. The layers were separated and the aqueous layer was extracted repeatedly with EtOAc which was dried ($MgSO_4$), filtered and concentrated. The residue was recrystallised from EtOAc to give 1,3,5-tris(hydroxymethyl)benzene **5** as fine colourless needles (4.49 g, 27.0 mmol, 49 %). mp 75 °C, (Lit.[1] mp 77 °C); δ_H (d_6-DMSO, 400 MHz) 7.12 (3 H, s), 5.13 (3 H, t, *J* 5.7), 4.48 (6 H , d, *J* 5.7,); δ_C (*d*-DMSO, 70 MHz) 142.6, 123.5, 63.6.

1,3,5-Tris(azidomethyl)benzene, 6[2]



1,3,5-Tris(hydroxymethyl)benzene **5** (2.01 g, 12.0 mmol) was suspended in dry ether (110 mL) under an N_2 atmosphere. PBr_3 (2.90 mL, 30.9 mmol) was then added dropwise and the reaction was stirred at rt for 20 h before being cooled to 0 °C. A saturated solution of $NaHCO_3$ (30 mL) was added cafefully and the reaction neutralised by the careful addition of solid

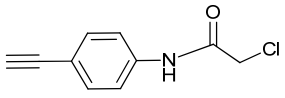
$NaHCO_3$. The layers were separated and the aqueous layer was extracted with Et_2O (2 × 50 mL). The organics were combined, dried ($MgSO_4$), filtered and concentrated to give 1,3,5-tris(bromomethyl)benzene as a colourless solid, which was used without further purification.

A mixture of 1,3,5-tris(bromomethyl)benzene (1.00 g, 2.81 mmol) and NaN_3 (586 mg, 9.01 mmol) in DMF (12 mL) was stirred at 80 °C for 4 h. The reaction was cooled to rt then poured into brine (15 mL), which was extracted with EtOAc (3 × 20). The combined organics were washed with brine (20 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo.* The crude product was purified by flash chromatography (9:1 to 4:1, petrol ethers-EtOAc) to afford the title compound **6** as a colourless oil (626 mg, 2.58 mmol, 92 % over 2 steps). ν_{max}/cm^{-1} 3007, 2102, 1634; δ_H ($CDCl_3$, 400 MHz) 7.26 (3 H, s), 4.41 (6 H, s); δ_C ($CDCl_3$, 101 MHz) 137.0, 127.5, 54.3; HRMS (ESI) calcd for $C_9H_9N_9Na$ $[M+Na]^+$ 226.0870, found 226.0873.

General procedure for the preparation of the 4-ethynylaniline amides 8 and 9

4-Ethynylaniline **7** (1 eq) was dissolved in THF (2 mL/mmol) and cooled to 0 °C with stirring. To this solution was added Et_3N (1 eq), followed by dropwise addition of the acid chloride (2 eq) in THF (2 ml/mmol). The reaction mixture was then allowed to warm to rt and stirred until the reaction had reached completion. The reaction was concentrated *in vacuo* and partitioned between water and EtOAc. The product was extracted with EtOAc (twice) and the combined organic layers were washed with water, brine and dried (Na_2SO_4). Removal of the solvent gave the crude product, which was used in the next step without further purification.

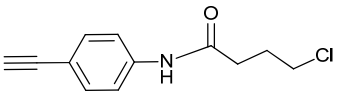
Chloro-*N*-(4-ethynylphenyl)-acetamide, 8



Yellow solid (72 %). ν_{max}/cm^{-1} 3400, 3301, 3011, 1692, 1589; δ_H ($CDCl_3$, 400 MHz) 8.32 (1 H, s), 7.54 (4 H, m), 4.22 (2 H, s), 3.10 (1 H, s); δ_C ($CDCl_3$, 101 MHz) 163.8, 137.1, 133.1,

119.7, 118.8, 83.1, 76.7, 42.9; HRMS (ESI) calcd for $C_{10}H_8NOClNa$ $[M+Na]^+$ 216.0187, found 216.0187.

4-Chloro-*N*-(4-ethynylphenyl)-butyramide, 9

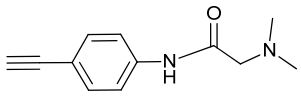


Yellow solid (74 %). ν_{max}/cm^{-1} 3430, 3301, 3009, 1696, 1607, 1586; δ_H ($CDCl_3$, 400 MHz) 7.49 (4 H, m), 7.37 (1 H, s), 3.67 (2 H, m), 3.07 (1 H, s), 2.59 (2 H, m), 2.21 (2 H, m); δ_C ($CDCl_3$, 101 MHz) 170.0, 138.1, 133.0, 119.4, 117.8, 83.3, 76.7, 44.4, 34.2, 27.8; HRMS (ESI) calcd for $C_{12}H_{12}ClNNaO$ $[M+Na]^+$ 244.0500, found 244.0507.

General procedure for the preparation of tertiary amines 10 – 19

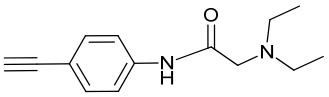
The appropriate secondary amine (2 eq) was added dropwise to a solution of the alkyl chloride (**8** or **9**, 1 eq) in MeOH (3 mL/mmol). The resulting mixture was stirred at rt, or under heating conditions, until the reaction was complete. The reaction was concentrated *in vacuo* and partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc (twice) and the combined organic layers were washed with a saturated solution of $NaHCO_3$, water and brine. The organics were dried ($MgSO_4$) and concentrated *in vacuo* to give the desired amine which was used without further purification.

Dimethylamino-*N*-(4-ethynylphenyl)-acetamide, 10



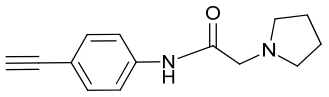
Yellow oil (94 %). ν_{max}/cm^{-1} 3300, 3011, 2952, 2835, 2790, 1690, 1606, 1579; δ_H ($CDCl_3$, 400 MHz) 9.26 (1 H, s), 7.47-7.61 (4 H, m), 3.13 (2 H, s), 3.07 (1 H, s), 2.43 (6 H, s); δ_C ($CDCl_3$, 101 MHz) 168.7, 138.2, 133.0, 119.0, 117.5, 83.5, 76.7, 63.5, 46.0; HRMS (ESI) calcd for $C_{12}H_{15}N_2O$ $[M+H]^+$ 203.1779, found 203.1774.

Diethylamino-*N*-(4-ethynylphenyl)-acetamide, 11



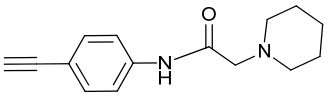
Brown oil (80 %). ν_{max}/cm^{-1} 3300, 2975, 2825, 1686, 1605, 1578; δ_H ($CDCl_3$, 400 MHz) 9.52 (1 H, s), 7.47-7.59 (4 H, m), 3.18 (2 H, s), 3.07 (1 H, s), 2.67 (4 H, q, *J* 7.2), 1.11 (6 H, t, *J* 7.2); δ_C ($CDCl_3$, 101 MHz) 170.2, 138.2, 133.0, 118.9, 117.4, 83.5, 76.8, 58.1, 48.9, 12.4; HRMS (ESI) calcd for $C_{14}H_{19}N_2O$ $[M+H]^+$ 231.1492, found 231.1503.

Pyrrolidino-*N*-(4-ethynylphenyl)-acetamide, 12



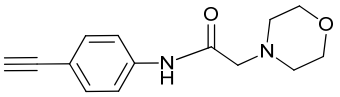
Brown oil (97 %). ν_{max}/cm^{-1} 3300, 3011, 2819, 1687, 1605, 1579; δ_H ($CDCl_3$, 400 MHz) 9.19 (1 H, s), 7.44-7.60 (4 H, m), 3.28 (2 H, s), 3.04 (1 H, s), 2.69 (4 H, m), 1.86 (4 H, m); δ_C ($CDCl_3$, 101 MHz) 169.3, 138.2, 133.0, 119.0, 117.4, 83.5, 76.7, 59.8, 54.6, 24.1; HRMS (ESI) calcd for $C_{14}H_{17}N_2O$ $[M+H]^+$ 229.1335, found 229.1335.

Piperidino-*N*-(4-ethynylphenyl)-acetamide, 13



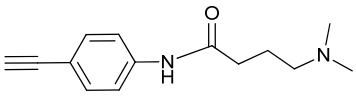
Pale yellow solid (95 %). ν_{max}/cm^{-1} 3300, 3011, 2942, 1687, 1605, 1579; δ_H ($CDCl_3$, 400 MHz) 9.38 (1 H, s), 7.52 (4 H, m), 3.09 (2 H, s), 3.06 (1 H, s), 2.57 (4 H, m), 1.67 (4 H, q, *J* 5.6), 1.51 (2 H, m); δ_C ($CDCl_3$, 101 MHz) 170.5, 140.5, 135.2, 121.2, 119.7, 85.8, 78.9, 65.0, 57.2, 28.6, 25.9; HRMS (ESI) calcd for $C_{15}H_{19}N_2O$ $[M+H]^+$ 243.1492, found 243.1507.

Morpholino-*N*-(4-ethynylphenyl)-acetamide, 14



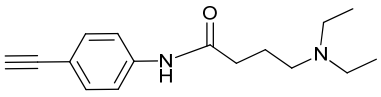
Yellow oil (98 %). ν_{max}/cm^{-1} 3305, 3011, 2816, 1690, 1580; δ_H ($CDCl_3$, 400 MHz) 9.10 (1 H, s), 7.54 (4 H, m), 3.78 (4 H, t, *J* 4.8), 3.14 (2 H, s), 3.06 (1 H, s), 2.78 (4 H, t, *J* 4.8); δ_C ($CDCl_3$, 101 MHz) 168.0, 137.9, 133.0, 119.0, 117.7, 83.4, 76.7, 67.0, 62.5, 53.8; HRMS (ESI) calcd for $C_{14}H_{17}N_2O_2$ $[M+H]^+$ 245.1285, found 245.1297.

4-Dimethylamino-*N*-(4-ethynylphenyl)-butyramide, 15



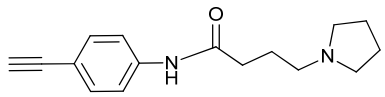
Orange oil (53 %). ν_{max}/cm^{-1} 3301, 3011, 2827, 1683, 1601; δ_H ($CDCl_3$, 400 MHz) 10.26 (1 H, s), 7.41-7.51 (4 H, m), 3.03 (1 H, s), 2.51 (2 H, t, *J* 6.0), 2.45 (2 H, t, *J* 6.0), 2.32 (6 H, s), 1.86 (2 H, m); δ_C ($CDCl_3$, 101 MHz) 171.7, 139.5, 132.9, 118.9, 116.8, 83.6, 76.4, 59.2, 45.1, 37.3, 22.6; HRMS (ESI) calcd for $C_{14}H_{19}N_2O$ $[M+H]^+$ 231.1492, found 231.1497.

4-Diethylamino-*N*-(4-ethynylphenyl)-butyramide, 16



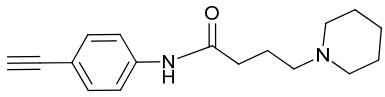
Brown oil (46 %). ν_{max}/cm^{-1} 3301, 2975, 1681, 1601; δ_H ($CDCl_3$, 400 MHz) 10.42 (1 H, s), 7.41-7.51 (4 H, m), 3.04 (1 H, s), 2.53-2.69 (8 H, m), 1.88 (2 H, m), 1.17 (6 H, t, *J* 7.2); δ_C ($CDCl_3$, 101 MHz) 171.7, 139.4, 132.9, 119.3, 116.8, 83.6, 76.4, 52.9, 46.8, 37.9, 22.7, 10.9; HRMS (ESI) calcd for $C_{16}H_{23}N_2O$ $[M+H]^+$ 259.1805, found 259.1820.

4-Pyrrolidino-*N*-(4-ethynylphenyl)-butyramide, 17



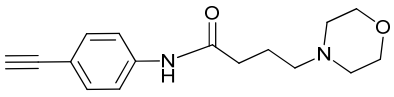
Orange oil (50 %). ν_{max}/cm^{-1} 3674, 3461, 3300, 3011, 2970, 2812, 1682, 1599; δ_H ($CDCl_3$, 400 MHz) 10.07 (1 H, s), 7.48 (4 H, m), 3.06 (1 H, s), 2.54-2.67 (8 H, m), 1.85-1.96 (6 H, m); δ_C ($CDCl_3$, 101 MHz) 171.8, 139.4, 132.9, 119.1, 116.9, 83.6, 76.4, 55.9, 54.0, 37.3, 23.8, 23.6; HRMS (ESI) calcd for $C_{16}H_{21}N_2O_3$ $[M+H]^+$ 257.1648, found 257.1658.

4-Piperidino-*N*-(4-ethynylphenyl)-butyramide, 18



Orange oil (44 %). ν_{max}/cm^{-1} 3432, 3300, 3011, 2941, 2812, 1685, 1595; δ_H ($CDCl_3$, 400 MHz) 9.38 (1 H, s), 7.47 (4 H, m), 3.04 (1 H, s), 2.32-2.48 (8 H, m), 1.83-1.93 (2 H, m), 1.49-1.67 (6 H, m); δ_C ($CDCl_3$, 101 MHz) 171.8, 139.0, 132.9, 119.4, 117.1, 83.6, 76.5, 57.3, 54.3, 36.1, 25.9, 24.4, 22.0; HRMS (ESI) calcd for $C_{17}H_{23}N_2O[M+H]^+$ 271.1805, found 271.1790.

4-Morpholino-*N*-(4-ethynylphenyl)-butyramide, 19

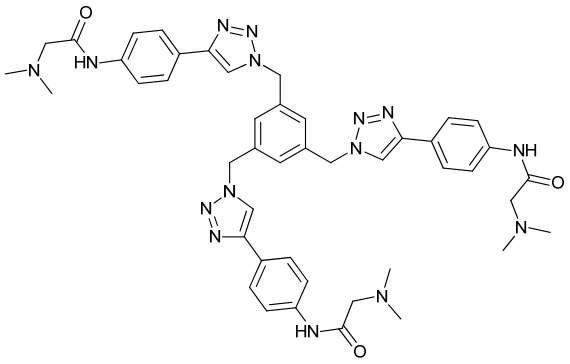


Orange oil (44 %). ν_{max}/cm^{-1} 3431, 3301, 3011, 2967, 2860, 1691, 1587; δ_H ($CDCl_3$, 400 MHz) 8.68 (1 H, s), 7.39-7.48 (4 H, m), 3.69 (4 H, t, *J* 4.8), 3.04 (1 H, s), 2.40 (8 H, m), 1.87 (2 H, m); δ_C ($CDCl_3$, 101 MHz) 171.6, 138.7, 132.8, 119.3, 117.4, 83.4, 76.8, 66.6, 57.6, 53.5, 35.2, 21.9; HRMS (ESI) calcd for $C_{16}H_{21}N_2O_2$ $[M+H]^+$ 273.1598, found 273.1591.

General procedure for the preparation of tristriazole ligands 20 – 24 and 27 - 29

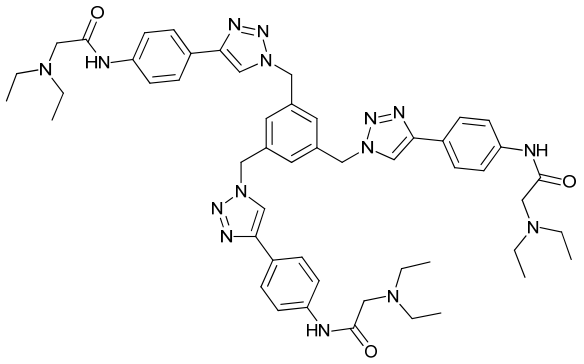
A microwave tube was charged with the mixture of **6** (0.2 mmol), the desired alkyne (**10** – **19**, 0.6 mmol), $CuSO_4.5H_2O$ (0.06 mmol) in DMF (2 mL) and a freshly made solution of sodium ascorbate (0.36 mmol) in H_2O (2 mL). The mixture was stirred and heated in a microwave reactor for 15 min at 120 ^oC. The reaction mixture was then cooled and diluted with H_2O (5 mL), filtered and the solid was washed with water, EtOH and Et_2O successively then dried *in vacuo*. A sample was purified by preparative HPLC (*vide infra*) for biological testing.

2-Dimethylamino-*N*-{4-[1-(3-{4-[4-(2-dimethylamino-acetylamino)-phenyl]-[1,2,3]triazol-1-yl}-5-{4-[4-(2-dimethylamino-acetylamino)-phenyl]-[1,2,3]triazol-1-ylmethyl}-benzyl)-1*H*-[1,2,3]triazol-4-yl]-phenyl}-acetamide, 20



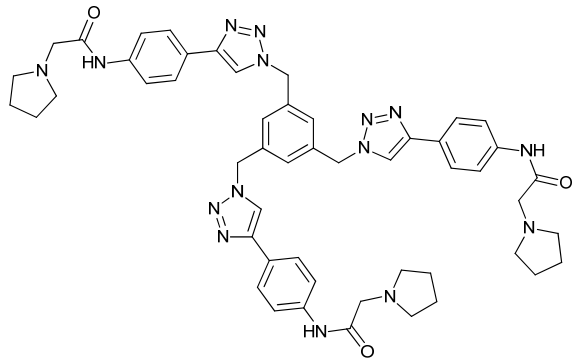
Yellow powder (54 %). δ_H (d_6-DMSO, 400 MHz) 9.80 (3 H, s), 8.52 (3 H, s), 7.73 (12 H, m), 7.34 (3 H, s), 5.64 (6 H, s), 3.09 (6 H, s), 2.30 (18 H, s); δ_C (d_6-DMSO, 101 MHz) 169.1, 147.0, 138.9, 137.8, 127.8, 126.1, 126.0, 121.5, 120.2, 63.2, 53.0, 45.8; HRMS (ESI) calcd for $C_{45}H_{52}N_{15}O_3$ $[M+H]^+$ 850.4372, found 850.4337.

2-Diethylamino-*N*-{4-[1-(3-{4-[4-(2-diethylamino-acetylamino)-phenyl]-[1,2,3]triazol-1-yl}-5-{4-[4-(2-diethylamino-acetylamino)-phenyl]-[1,2,3]triazol-1-ylmethyl}-benzyl)-1*H*-[1,2,3]triazol-4-yl]-phenyl}-acetamide, 21



Yellow solid (45 %). δ_H ($CDCl_3$, 400 MHz) 9.49 (3 H, s), 7.74 (6 H, d, *J* 8.8), 7.72 (6 H, d, *J* 8.8), 7.23 (3 H, s), 5.41 (6 H, s), 3.17 (6 H, s), 2.67 (12 H, q, *J* 7.2), 1.11 (18 H, t, *J* 7.2); δ_C ($CDCl_3$, 101 MHz) 170.2, 148.0, 137.8, 137.1, 127.5, 126.4, 126.0, 119.6, 119.5, 58.1, 53.4, 48.9, 12.4; HRMS (ESI) calcd for $C_{51}H_{64}N_{15}O_3$ $[M+H]^+$ 934.5311, found 934.5306.

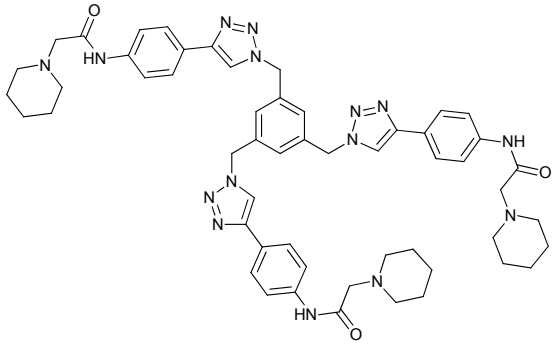
2-Pyrrolidin-1-yl-*N*-{4-[1-(3-{4-[4-(2-pyrrolidin-1-yl-acetylamino)-phenyl]-[1,2,3]triazol-1-yl}-5-{4-[4-(2-pyrrolidin-1-yl-acetylamino)-phenyl]-[1,2,3]triazol-1-ylmethyl}-benzyl)-1*H*-[1,2,3]triazol-4-yl]-phenyl}-acetamide, 22



Yellow solid (45 %). δ_H (d_6-DMSO, 400 MHz) 9.78 (3 H, s), 8.51 (3 H, s), 7.69-7.81 (12 H, m), 7.33 (3 H, s), 5.64 (6 H, s), 3.27-3.47 (6 H, s), 2.61 (6 H, br s), 1.75 (12 H, br s), 1.13-1.10 (6 H, m); δ_C (d_6-DMSO, 101 MHz) 168.3, 147.0, 138.9, 137.8, 127.8, 126.1, 126.0,

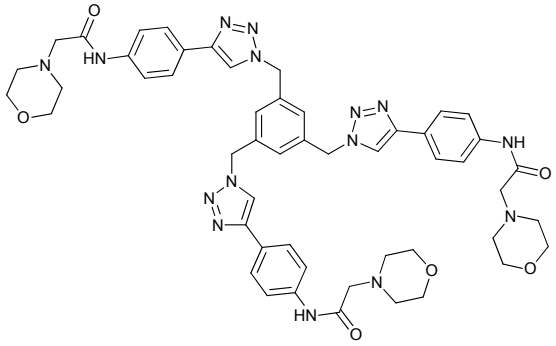
121.5, 120.2, 56.5, 53.4, 53.0, 23.8; HRMS (ESI) calcd for $C_{51}H_{57}N_{15}NaO_3$ $[M+Na]^+$ 950.4661, found 950.4619.

2-Piperidin-1-yl-*N*-{4-[1-(3-{4-[4-(2-piperidin-1-yl-acetylamino)-phenyl]-[1,2,3]triazol-1-yl}-5-{4-[4-(2-piperidin-1-yl-acetylamino)-phenyl]-[1,2,3]triazol-1-ylmethyl}-benzyl)-1*H*-[1,2,3]triazol-4-yl]-phenyl}-acetamide, 23



Yellow solid (41 %). δ_H (d_6-DMSO, 400 MHz) 9.72 (3 H, s), 8.51 (3 H, s), 7.72 (12 H, m), 7.33 (3 H, s), 5.64 (6 H, s), 3.07 (6 H, s), 2.49 (12 H, br s), 1.57 (18 H, m); δ_C (d_6-DMSO, 101 MHz) 169.1, 147.0, 138.7, 137.7, 127.8, 126.2, 126.0, 121.5, 120.1, 63.1, 54.6, 53.0, 25.9, 24.0; HRMS (ESI) calcd for $C_{54}H_{64}N_{15}O_3$ $[M+H]^+$ 970.5311, found 970.5301.

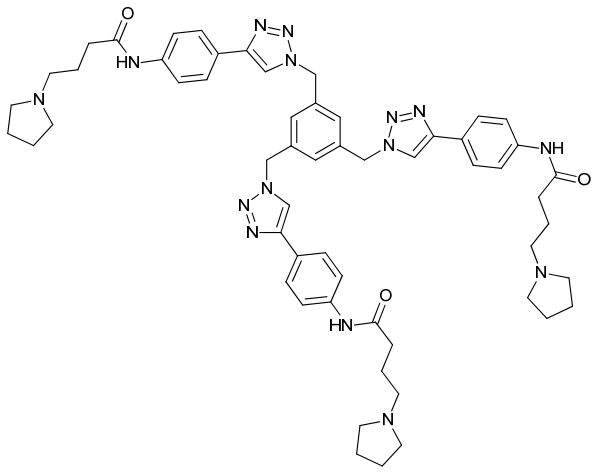
2-Morpholin-4-yl-*N*-{4-[1-(3-{4-[4-(2-morpholin-4-yl-acetylamino)-phenyl]-[1,2,3]triazol-1-yl}-5-{4-[4-(2-morpholin-4-yl-acetylamino)-phenyl]-[1,2,3]triazol-1-ylmethyl}-benzyl)-1*H*-[1,2,3]triazol-4-yl]-phenyl}-acetamide, 24



Yellow solid (56 %). δ_H ($CDCl_3$, 400 MHz) 9.18 (3 H, s), 7.77 (6 H, d, *J* 8.4), 7.70 (3 H, s), 7.64 (6 H, d, *J* 8.4), 7.25 (3 H, s), 5.55 (6 H, s), 3.83 (12 H, t, *J* 4.4), 3.19 (6 H, s), 2.68 (12 H,

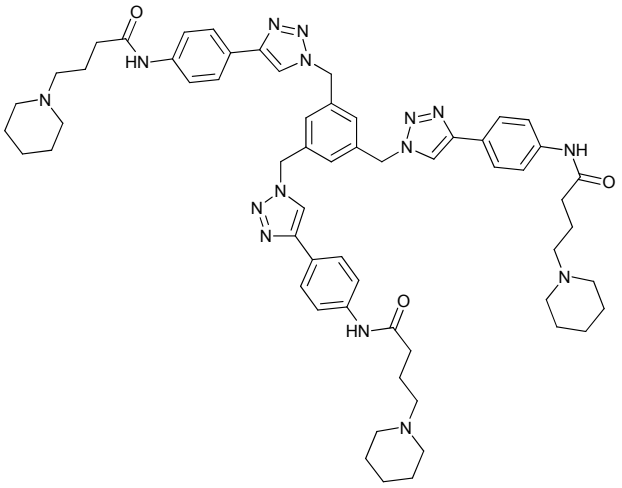
t, *J* 4.4); δ_C ($CDCl_3$, 101 MHz) 168.1, 148.1, 137.6, 137.1, 127.4, 126.4, 126.2, 119.8, 119.4, 67.0, 62.5, 53.8, 53.4; HRMS (ESI) calcd for $C_{51}H_{58}N_{15}O_6$ $[M+H]^+$ 976.4689, found 976.4740.

4-Pyrrolidin-1-yl-*N*-{4-[1-(3-{4-[4-(4-pyrrolidin-1-yl-butyrylamino)-phenyl]-[1,2,3]triazol-1-yl}-5-{4-[4-(4-pyrrolidin-1-yl-butyrylamino)-phenyl]-[1,2,3]triazol-1-ylmethyl}-benzyl)-1*H*-[1,2,3]triazol-4-yl]-phenyl}-butyramide, 27



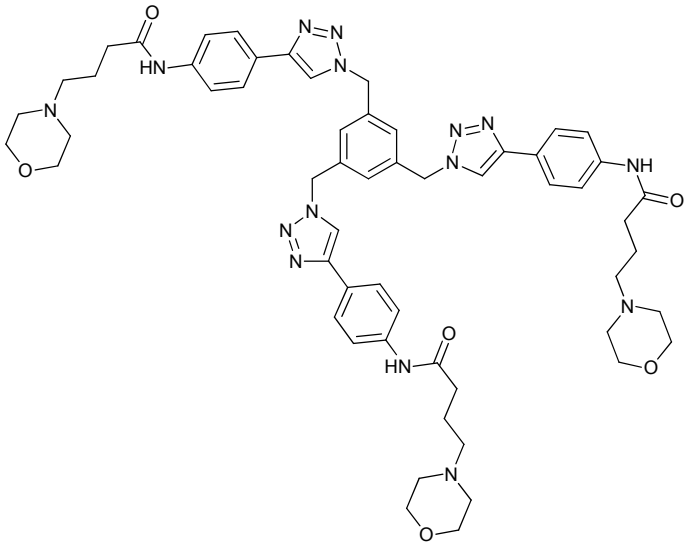
Yellow solid (34 %). δ_H (*d*$_6$-DMSO, 400 MHz) 9.92 (3 H, s), 8.45 (3 H, s), 7.68 (6 H, d, *J* 8.8), 7.60 (6 H, d, *J* 8.8), 7.28 (3 H, s), 5.59 (6 H, s), 2.23-2.42 (24 H, m), 1.58-1.75 (18 H, m); δ_C (*d*$_6$-DMSO, 101 MHz) 171.7, 147.0, 139.6, 137.8, 127.8, 126.0, 125.7, 121.4, 119.7, 55.6, 54.0, 53.0, 35.0, 24.8, 23.6; HRMS (ESI) calcd for $C_{57}H_{69}N_{15}NaO_3$ $[M+Na]^+$ 1034.5600, found 1034.5594.

4-Piperidin-1-yl-*N*-{4-[1-(3-{4-[4-(4-piperidin-1-yl-butyrylamino)-phenyl]-[1,2,3]triazol-1-yl}-5-{4-[4-(4-piperidin-1-yl-butyrylamino)-phenyl]-[1,2,3]triazol-1-ylmethyl}-benzyl)-1*H*-[1,2,3]triazol-4-yl]-phenyl}-butyramide, 28



Yellow solid (42 %). δ_H (d_6-DMSO, 400 MHz) 9.95 (3 H, s), 8.51 (3 H, s), 7.74 (6 H, d, *J* 8.4), 7.66 (6 H, d, *J* 8.4), 7.34 (3 H, s), 5.67 (6 H, s), 2.23-2.36 (24 H, m), 1.75 (6 H, m), 1.37-1.50 (18 H, m); δ_C (d_6-DMSO, 101 MHz) 171.7, 147.0, 139.6, 137.8, 127.8, 126.0, 125.7, 121.4, 119.7, 58.6, 54.5, 53.0, 35.0, 26.1, 24.7, 22.8; HRMS (ESI) calcd for $C_{60}H_{76}N_{15}O_3$ $[M+H]^+$ 1054.6250, found 1054.6196.

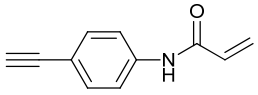
4-Morpholin-4-yl-*N*-{4-[1-(3-{4-[4-(4-morpholin-4-yl-butyrylamino)-phenyl]-[1,2,3]triazol-1-yl}-5-{4-[4-(4-morpholin-4-yl-butyrylamino)-phenyl]-[1,2,3]triazol-1-ylmethyl}-benzyl)-1*H*-[1,2,3]triazol-4-yl]-phenyl}-butyramide, 29



Yellow solid (67 %). δ_H (d_6-DMSO, 400 MHz) 9.95 (3 H, s), 8.51 (3 H, s), 7.74 (6 H, d, *J* 8.4), 7.66 (6 H, d, *J* 8.4), 7.34 (3 H, s), 5.67 (6 H, s), 3.55 (12 H, t, *J* 4.5), 2.27-2.40 (24 H, m), 1.76

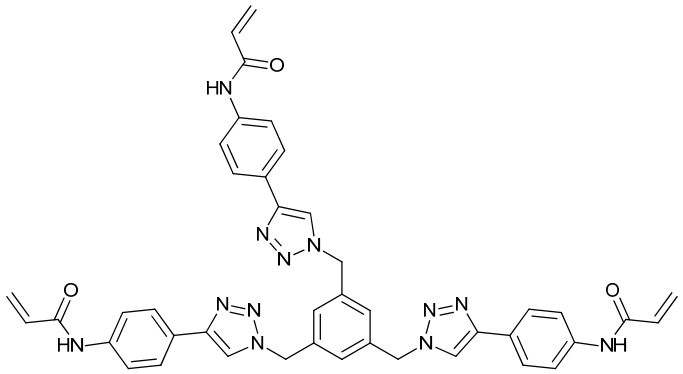
(6 H, m); δ_C (d_6-DMSO, 101 MHz) 171.7, 147.0, 139.6, 137.8, 127.8, 126.1, 125.7, 121.4, 119.7, 66.7, 58.2, 53.8, 53.0, 34.9, 22.3; HRMS (ESI) calcd for $C_{57}H_{70}N_{15}O_6$ $[M+H]^+$ 1060.5628, found 1060.5618.

***N*-(4-Ethynyl-phenyl)-acrylamide, 30**



To a solution of 4-ethynylaniline **7** (2.00 g, 17.1 mmol) in dry CH_2Cl_2 (25 mL) at 0 ˚C under N_2, was added acryloyl chloride (1.67 mL, 20.5 mmol) dropwise. Dry Et_3N (2.90 mL, 20.8 mmol) was then added dropwise and the reaction was stirred 1 h at 0 ˚C then 1 h at rt. MeOH (1 mL) was added and the reaction was stirred a further 1 h before the solution was washed with H_2O (2 × 10 mL), brine (10 mL) and dried ($MgSO_4$). The crude product was purified by flash chromatography (9:1 to 4:1, petrol ethers-EtOAc) to afford *N-(4-ethynyl-phenyl)-acrylamide* **30** as a colourless solid (2.50 g, 14.6 mmol, 85 %). R_F 0.29 (7:3, petrol ether-EtOAc); ν_{max}/cm^{-1} 3429, 3301, 3012, 2108, 1689, 1634, 1586; δ_H (400 MHz, $CDCl_3$) 7.83 (2 H, d, *J* 9.6), 7.72 (2 H, d, *J* 9.7), 7.56 (1 H, br s), 6.60 (1 H, dd, *J* 18.7, 1.5), 6.35 (1 H, dd, *J* 18.7, 11.3), 5.87 (1 H, dd, *J* 11.3, 1.5), 2.83 (1 H, s); δ_C (101 MHz, $CDCl_3$) 163.6, 138.2, 133.0, 130.9, 128.4, 127.2, 119.6, 118.0, 83.3; *m/z* (ESI) 194 ($[M+Na]^+$ 12 %), 172 (51); HRMS (ESI) calcd for $C_{11}H_{10}NO$ $[M+H]^+$ 172.0762, found 172.0755.

***N*-[4-(1-{3,5-Bis-[4-(4-acryloylamino-phenyl)-[1,2,3]triazol-1-ylmethyl]-benzyl}-1*H*-[1,2,3]triazol-4-yl)-phenyl]-acrylamide, 31**



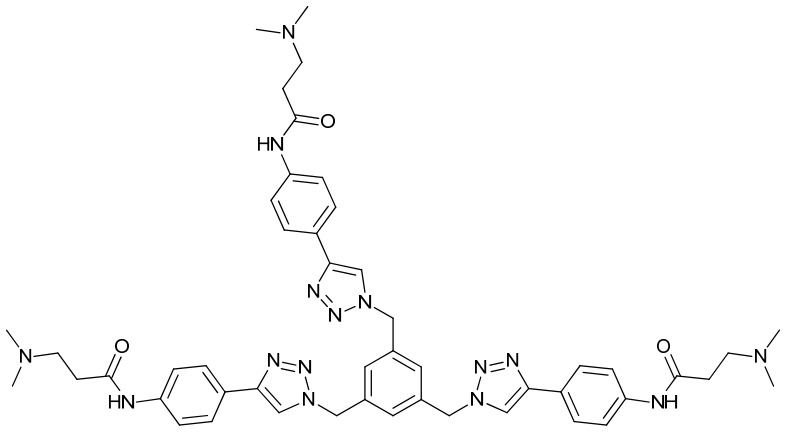
1,3,5-Tris(azidomethyl)benzene **6** (301 mg, 1.24 mmol), **30** (633 mg, 3.70 mmol), 2,6-lutidine (140 µL, 1.22 mmol) and $CuSO_4.5H_2O$ (10 mol%, 31 mg, 0.123 mmol) were

added to DMSO (15 mL). Sodium ascorbate (436 mg, 2.20 mmol) was dissolved in water/DMSO (1:1, 4 mL) and added to the rest of the mixture which was then stirred for 2 min. The reaction was sealed, placed in a microwave reactor and heated at 120 ˚C for 20 min. The reaction was cooled to rt, then water (25 mL) was added and the solid was filtered, washing consecutively with H_2O, MeOH then EtOAc. The product **31** was dried in a vacuum oven and used without further purification.

General procedure for tristriazole ligands 32 - 36

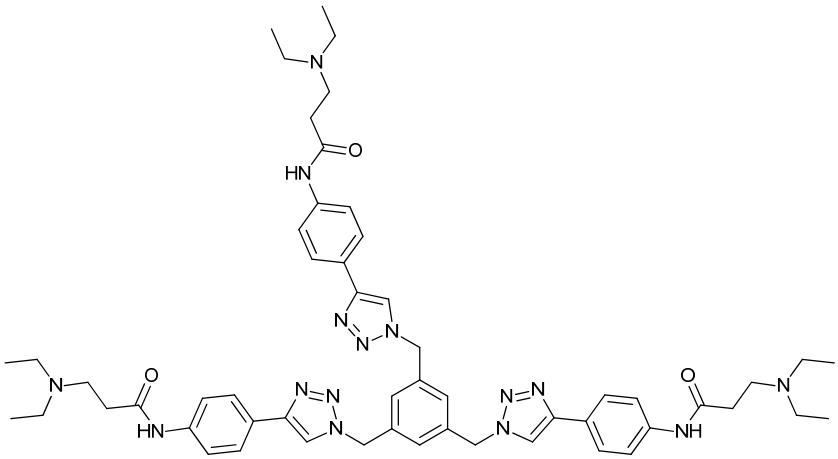
The crude tristriazole **31** (1 eq) was dissolved in DMSO (0.1 M solution) and filtered. The amine (8 eq) was added and the reaction was heated to 70 ˚C (40 ˚C in the case of **32** and **33**) until mass spectrometry indicated the reaction had finished. The reaction was cooled to rt then brine (3 volumes) and H_2O (2 volumes) were added. The mixture was cooled to 0 ˚C for ½ h then filtered and washed with H_2O. A sample was purified by HPLC for spectroscopic analysis and biological testing.

***N*-{4-[1-(3,5-Bis-{4-[4-(3-dimethylamino-propionylamino)-phenyl]-[1,2,3]triazol-1-ylmethyl}-benzyl)-1*H*-[1,2,3]triazol-4-yl]-phenyl}-3-dimethylamino-propionamide, 32**



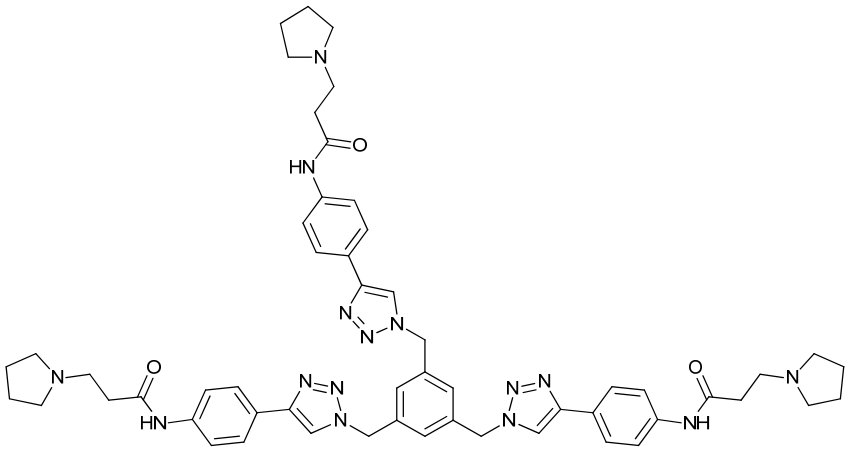
Obtained as a brown solid (157 mg, 0.176 mmol, 57 % over 2 steps). δ_H (400 MHz, MeOD) 8.33 (3 H, s), 7.76 (6 H, d, *J* 8.4), 7.68 (6 H, d, *J* 8.4), 7.36 (3 H, s), 5.68 (6 H, s), 3.53 (6 H, t, *J* 6.4), 2.97 (24 H, m); δ_C (101 MHz, MeOD) 168.7, 147.5, 138.3, 137.4, 127.2, 126.1, 125.8, 120.8, 119.9, 53.8, 53.0, 42.3, 30.0; *m/z* (ESI) 892 ($[M+H]^+$ 100 %), 649 (5); HRMS (ESI) calcd for $C_{48}H_{58}N_{15}O_3$ $[M+H]^+$ 892.4842, found 892.4806.

_N_-{4-[1-(3,5-Bis-{4-[4-(3-diethylamino-propionylamino)-phenyl]-[1,2,3]triazol-1-ylmethyl}-benzyl)-1_H_-[1,2,3]triazol-4-yl]-phenyl}-3-diethylamino-propionamide, 33



Obtained as a brown solid (57 mg, 0.054 mmol, 18 % over 2 steps). δ_H (400 MHz, MeOD) 8.34 (3 H, s), 7.77 (6 H, d, *J* 8.7), 7.69 (6 H, d, *J* 8.7), 7.37 (3 H, s), 5.68 (6 H, s), 3.55 (6 H, t, *J* 6.6), 3.32 (12 H, q, *J* 7.3), 2.96 (6 H, t, *J* 6.6), 1.40 (18 H, t, *J* 7.3); δ_C (101 MHz, MeOD) 168.6, 147.5, 138.4, 137.4, 127.2, 126.1, 125.8, 120.8, 119.9, 95.0, 53.0, 47.3, 47.4, 29.8; *m/z* (ESI) 977 ($[M+H]^+$ 100 %), 721 (5); HRMS (ESI) calcd for $C_{54}H_{69}N_{15}O_3$ $[M+H]^+$ 976.5781, found 976.5731.

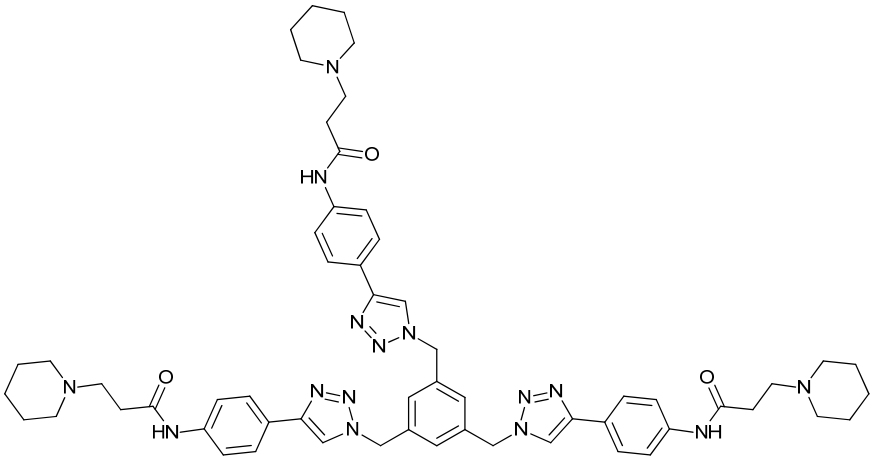
_N_-{4-[1-(3,5-Bis-{4-[4-(3-pyrrolidin-1-yl-propionylamino)-phenyl]-[1,2,3]triazol-1-ylmethyl}-benzyl)-1_H_-[1,2,3]triazol-4-yl]-phenyl}-3-pyrrolidin-1-yl-propionamide, 34



Obtained as a brown solid (120 mg, 0.124 mmol, 60 % over 2 steps). δ_H (400 MHz, MeOD) 8.32 (3 H, s), 7.75 (6 H, d, *J* 8.6), 7.67 (6 H, d, *J* 8.6), 7.35 (3 H, s), 5.67 (6 H, s), 3.75 (6 H, br s), 3.59 (6 H, t, *J* 6.5), 3.18 (6 H, br s), 2.96 (6 H, t, *J* 6.5), 2.19 (6 H, br s), 2.09 (6 H, br s);

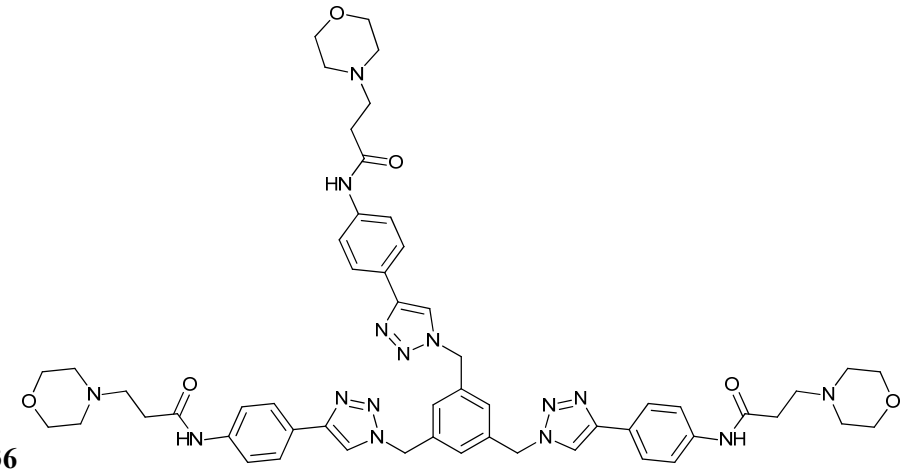
δ_C (101 MHz, MeOD) 168.5, 147.5, 138.4, 137.4, 127.1, 126.1, 125.8, 120.8, 119.9, 54.1, 53.0, 50.9, 31.5, 22.6; *m/z* (ESI) 971 ($[M+H]^+$ 100 %); HRMS (ESI) calcd for $C_{54}H_{64}N_{15}O_3$ $[M+H]^+$ 970.5311, found 970.5332.

_N_-{4-[1-(3,5-Bis-{4-[4-(3-piperidin-1-yl-propionylamino)-phenyl]-[1,2,3]triazol-1-ylmethyl}-benzyl)-1_H_-[1,2,3]triazol-4-yl]-phenyl}-3-piperidin-1-yl-propionamide, 35



Obtained as a brown solid (171 mg, 0.169 mmol, 53 % over 2 steps). δ_H (400 MHz, MeOD) 8.32 (3 H, s), 7.75 (6 H, d, *J* 8.8), 7.66 (6 H, d, *J* 8.8), 7.35 (3 H, s), 5.67 (6 H, s), 3.63 (6 H, m), 3.50 (6 H, t, *J* 6.8), 3.03 (6 H, m), 2.97 (6 H, t, *J* 6.8), 2.00 (6 H, m), 1.83 (9 H, m), 1.57 (3 H, m); δ_C (101 MHz, MeOD) 168.4, 147.5, 138.4, 137.4, 127.2, 126.1, 125.8, 120.8, 119.9, 53.2, 53.0, 52.7, 30.0, 22.8, 21.2; *m/z* (ESI) 1013 ($[M+H]^+$ 25 %), 539 (18), 507 (100); HRMS (ESI) calcd for $C_{57}H_{70}N_{15}O_3$ $[M+H]^+$ 1012.5781, found 1012.5738.

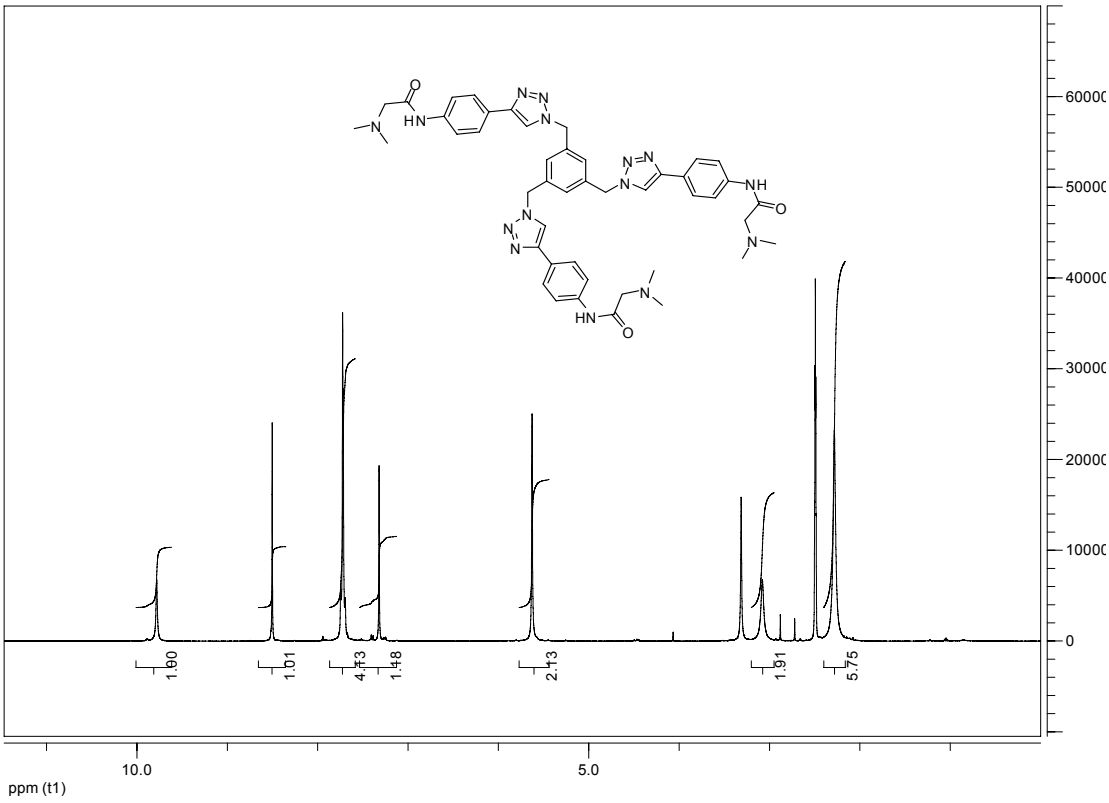
***N*-{4-[1-(3,5-Bis-{4-[4-(3-morpholin-4-yl-propionylamino)-phenyl]-[1,2,3]triazol-1-ylmethyl}-benzyl)-1*H*-[1,2,3]triazol-4-yl]-phenyl}-3-morpholin-4-yl-propionamide,**

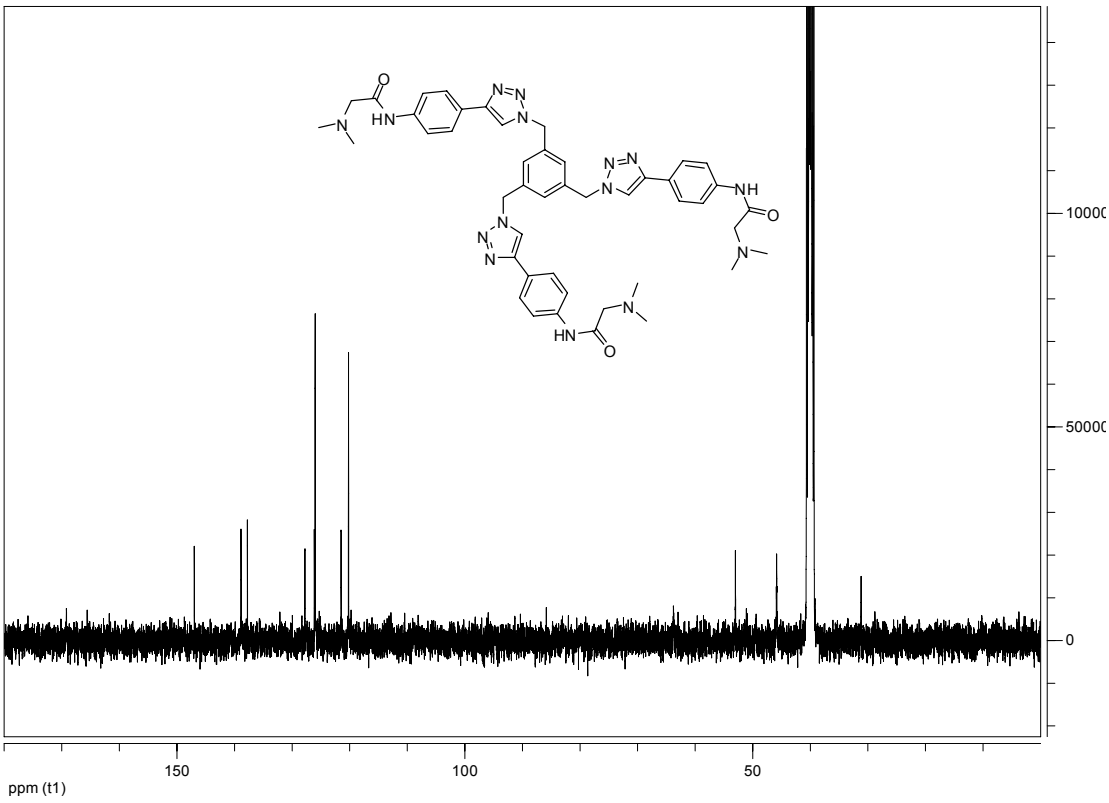


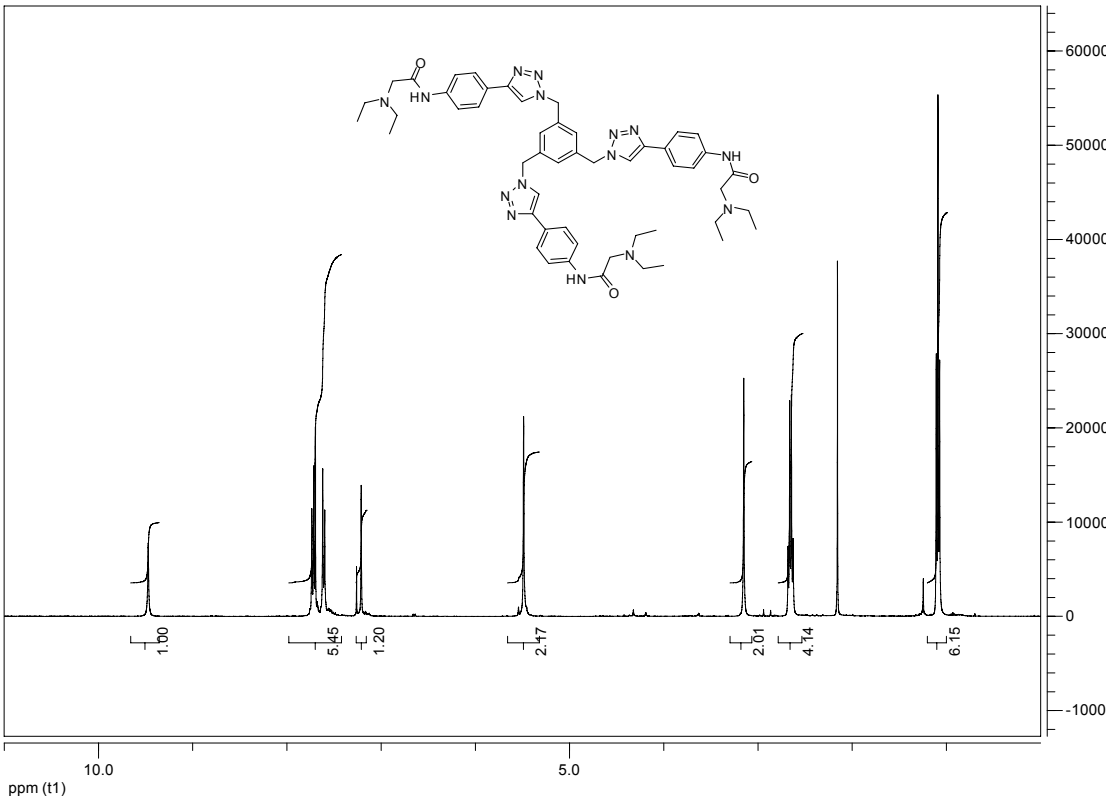
36

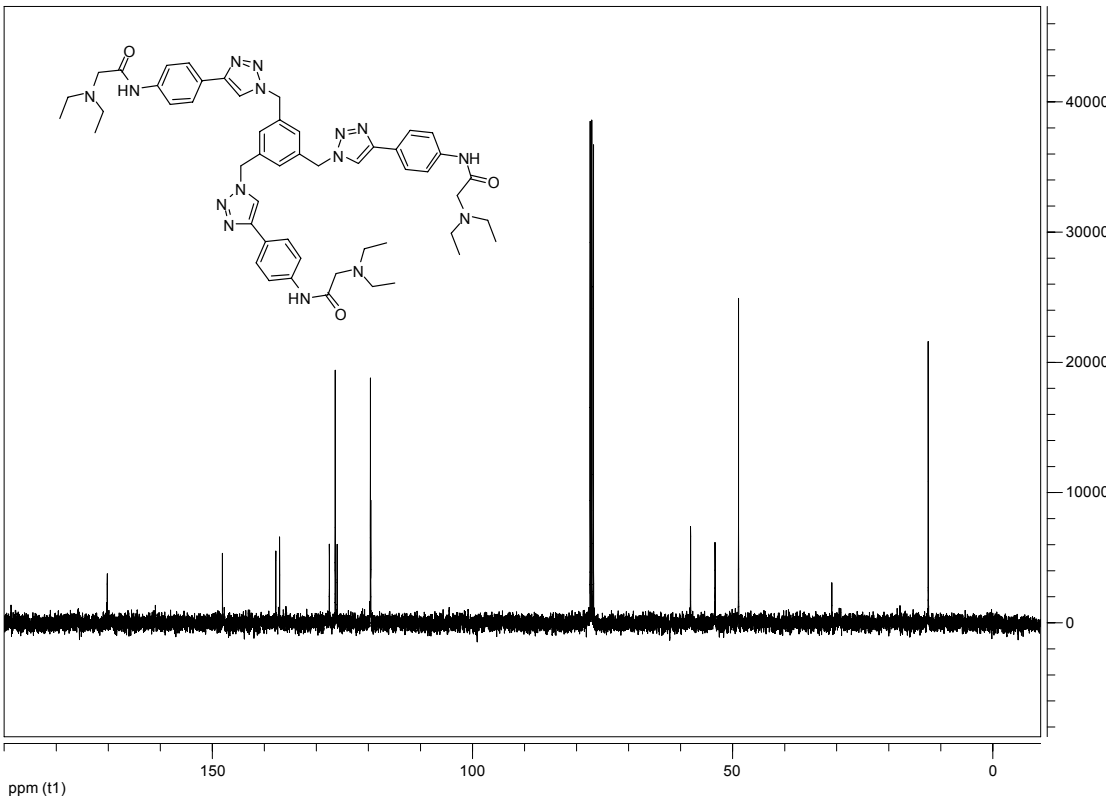
Obtained as a brown solid (96 mg, 0.094 mmol, 36 % over 2 steps). δ_H (400 MHz, MeOD) 8.32 (3 H, s), 7.76 (6 H, d, *J* 8.8), 7.68 (6 H, d, *J* 8.7), 7.37 (3 H, s), 5.68 (6 H, s), 4.10 (6 H, br s), 3.85 (6 H, br s), 3.59 (12 H, t, *J* 6.7), 3.25 (6 H, br s), 3.00 (6 H, t, *J* 6.6); δ_C (101 MHz, MeOD) 168.3, 147.5, 138.4, 137.4, 127.2, 126.1, 125.8, 120.8, 119.9, 63.6, 53.0, 53.0, 52.0, 29.6; *m/z* (ESI) 1019 ($[M+H]^+$ 19 %), 589 (3), 510 (100); HRMS (ESI) calcd for $C_{54}H_{64}N_{15}O_6$ $[M+H]^+$ 1018.5159, found 1018.5104.

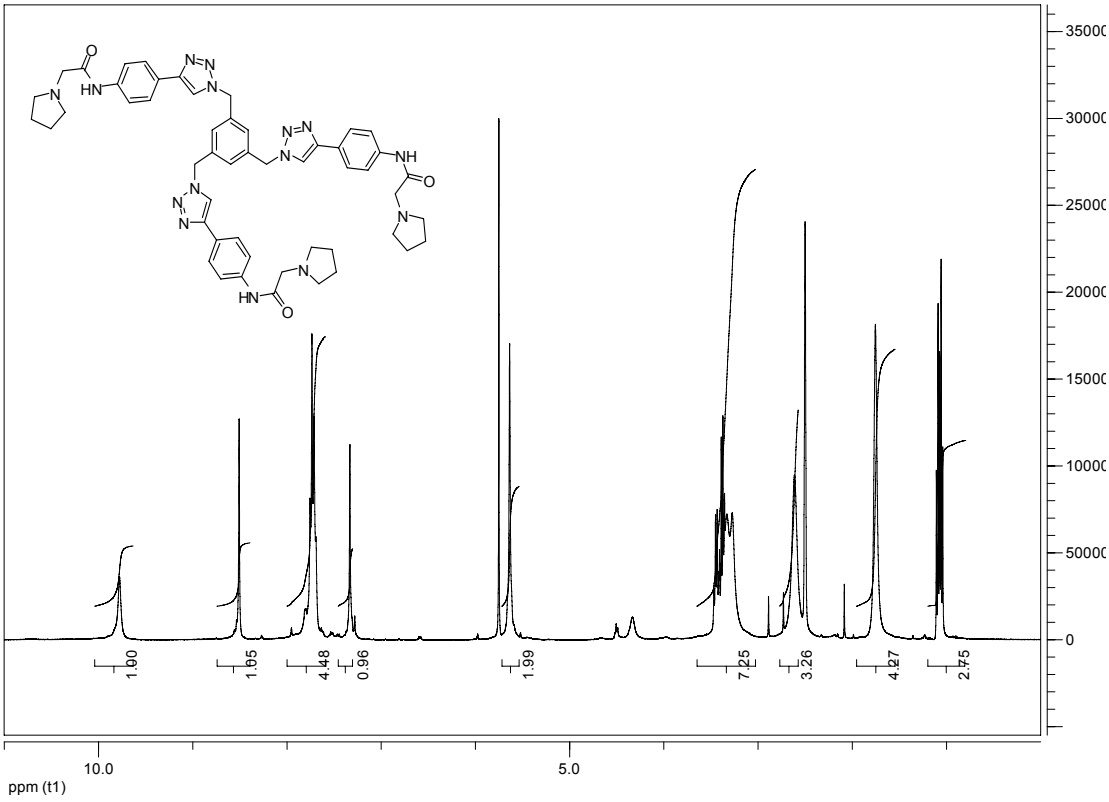
NMR Spectra

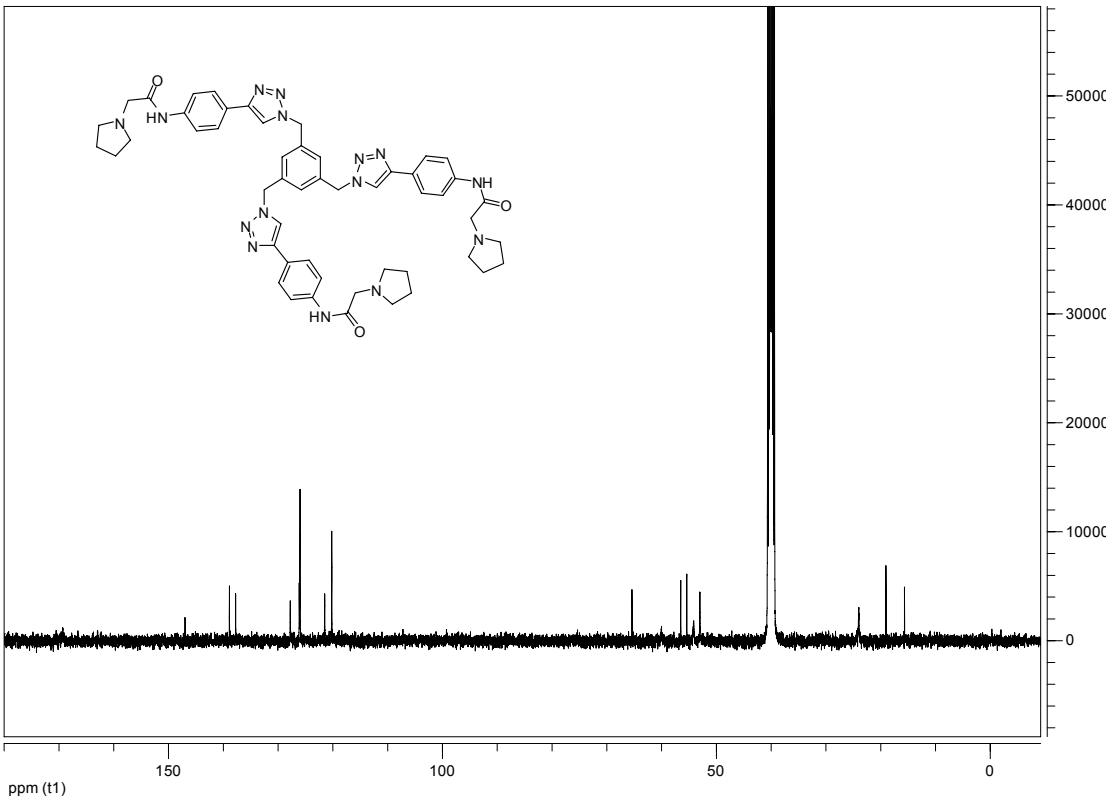


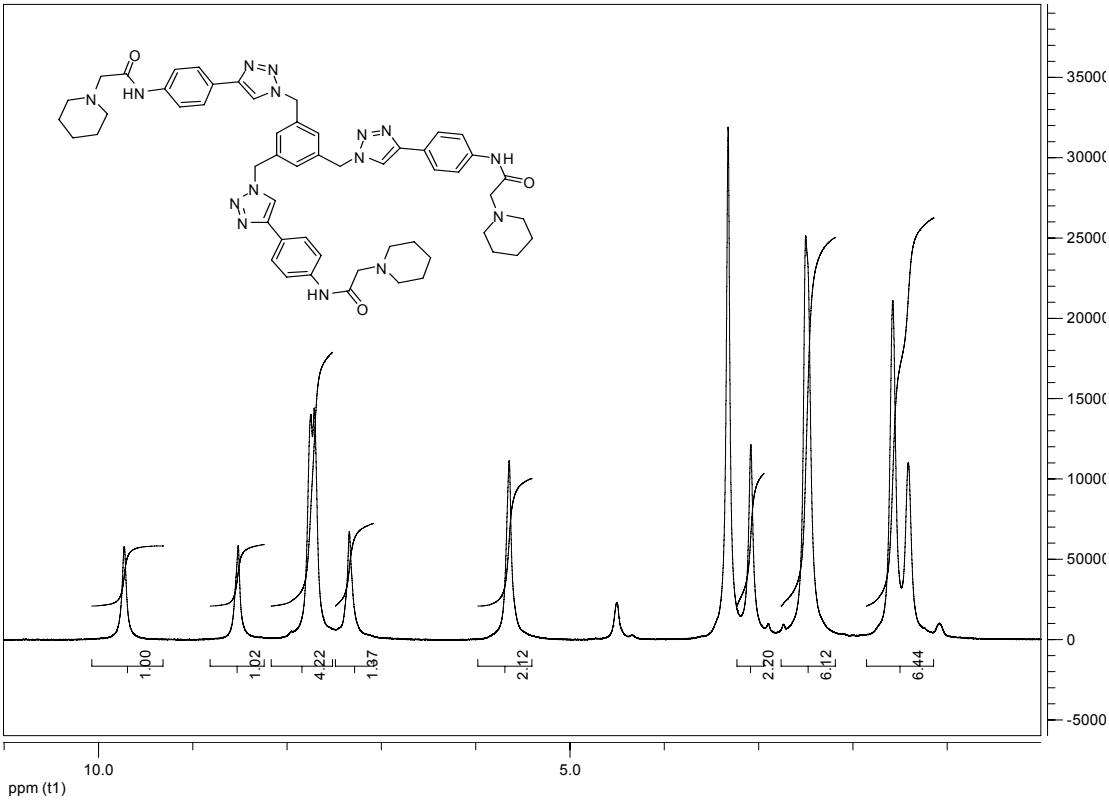


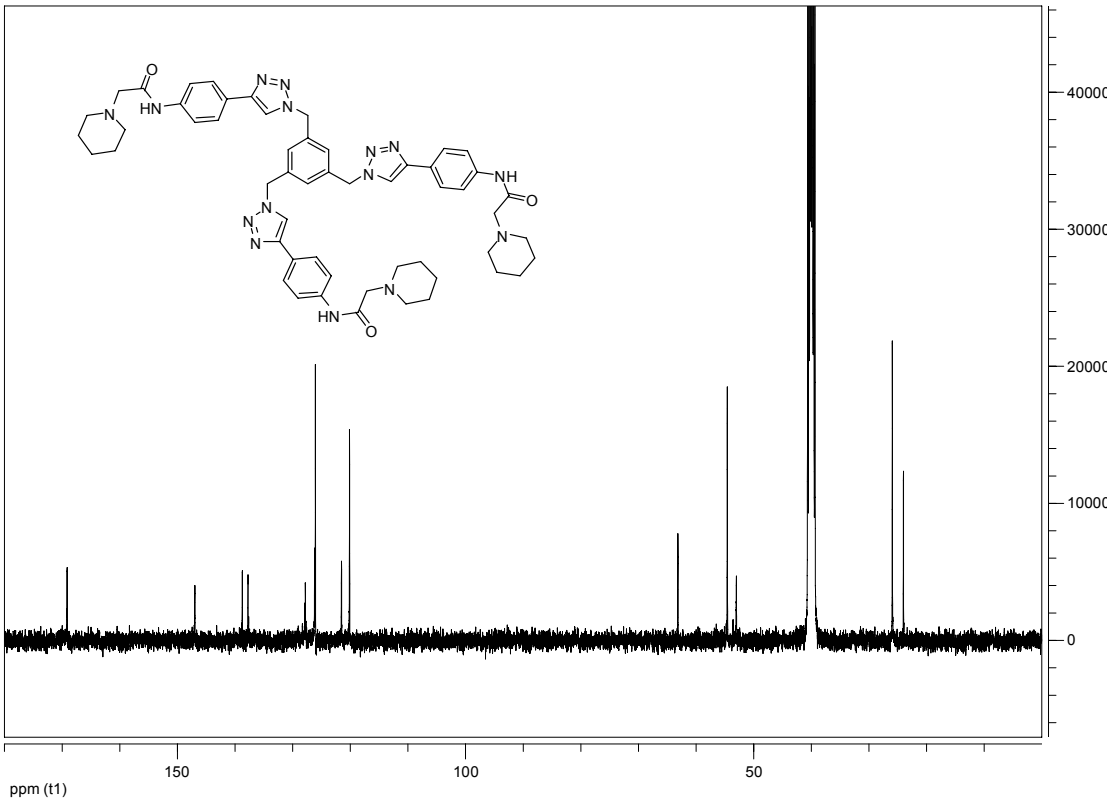


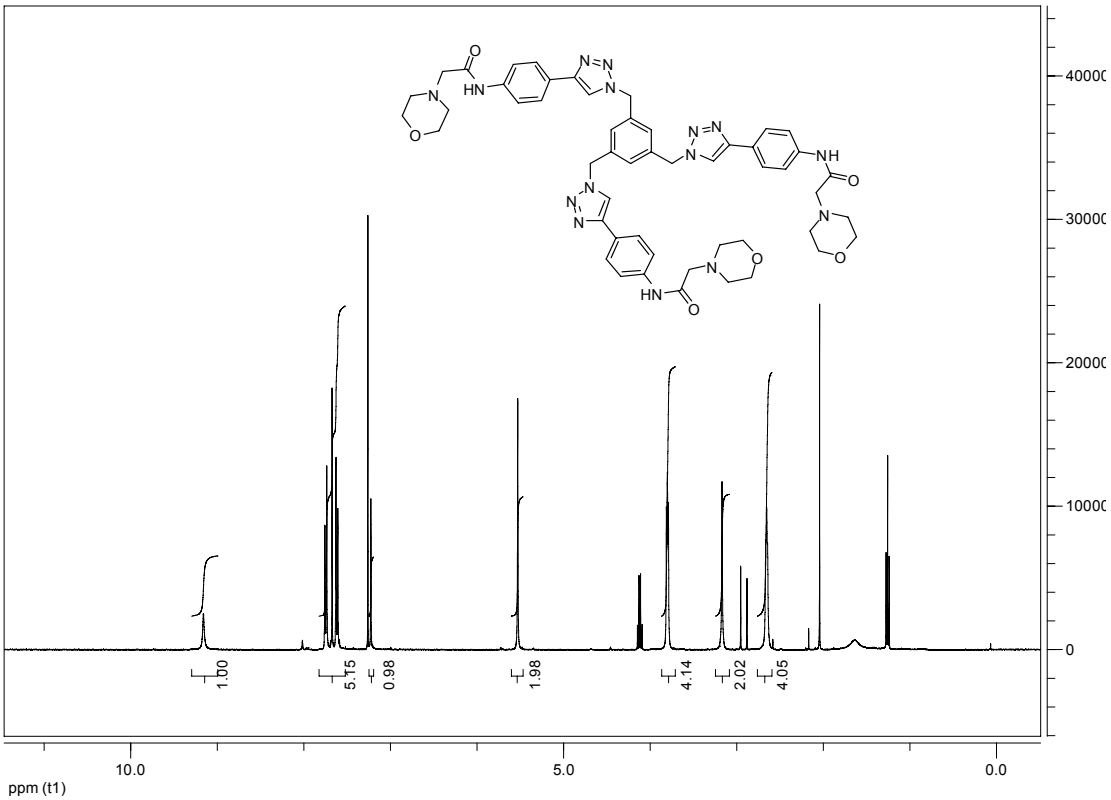


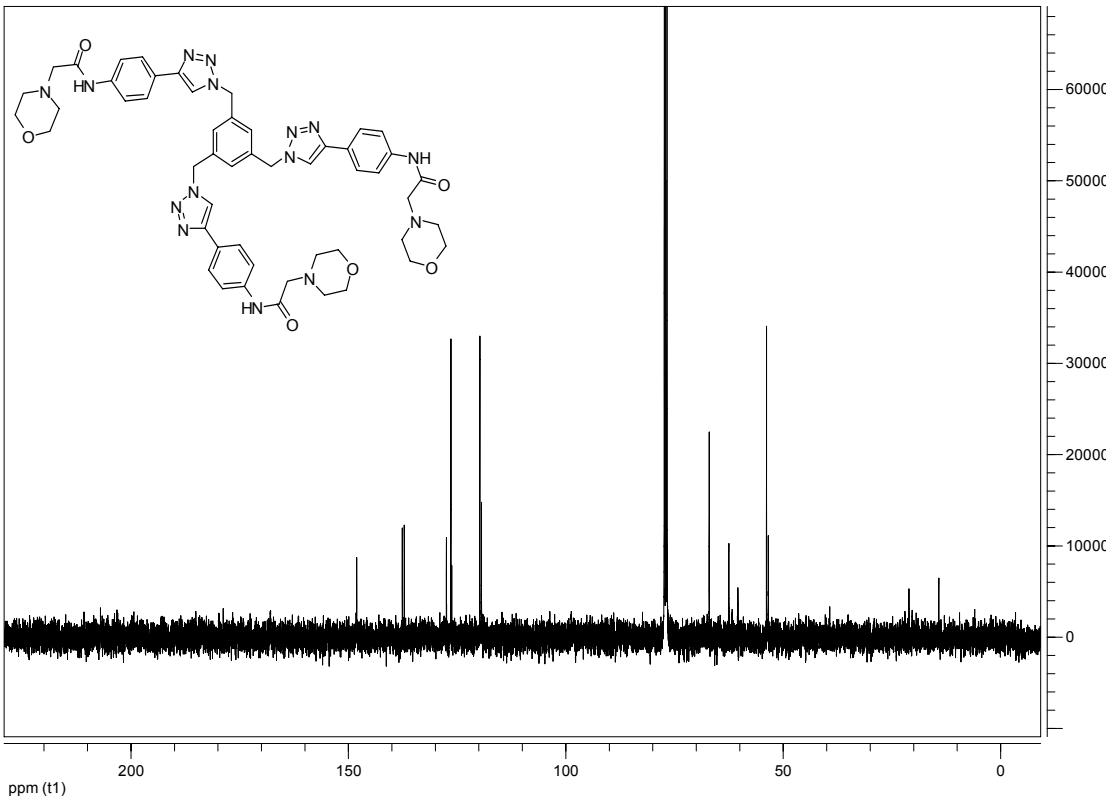


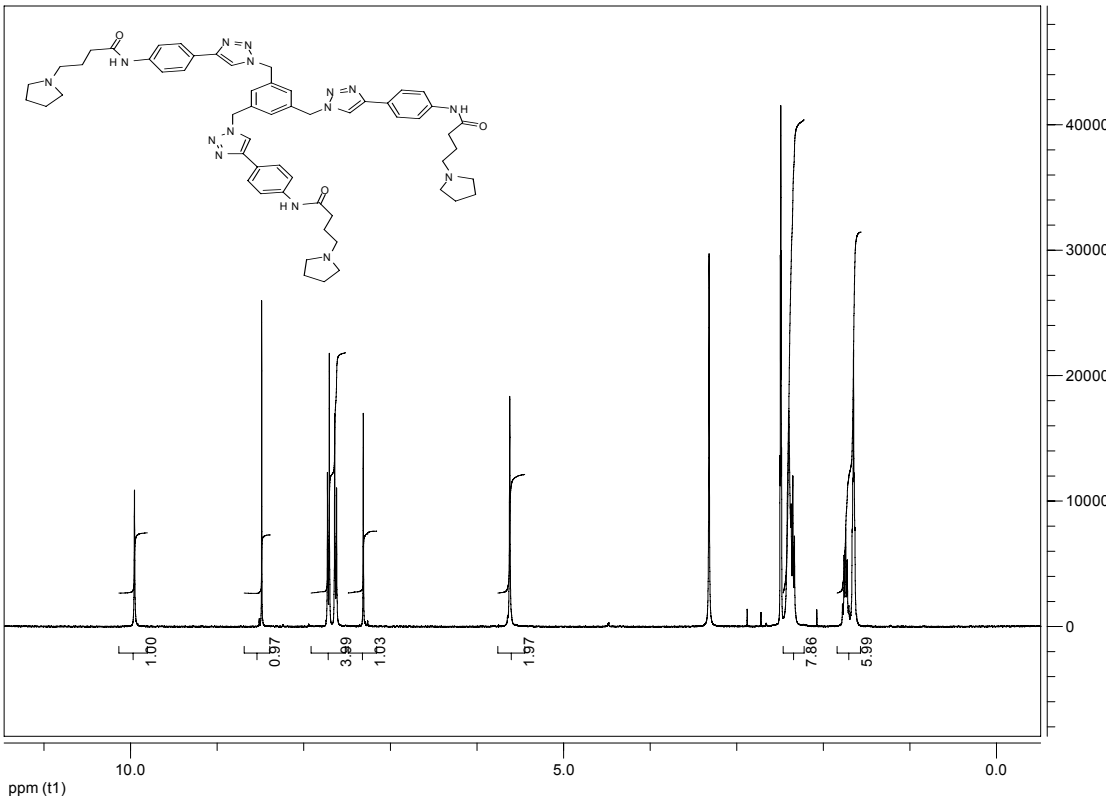


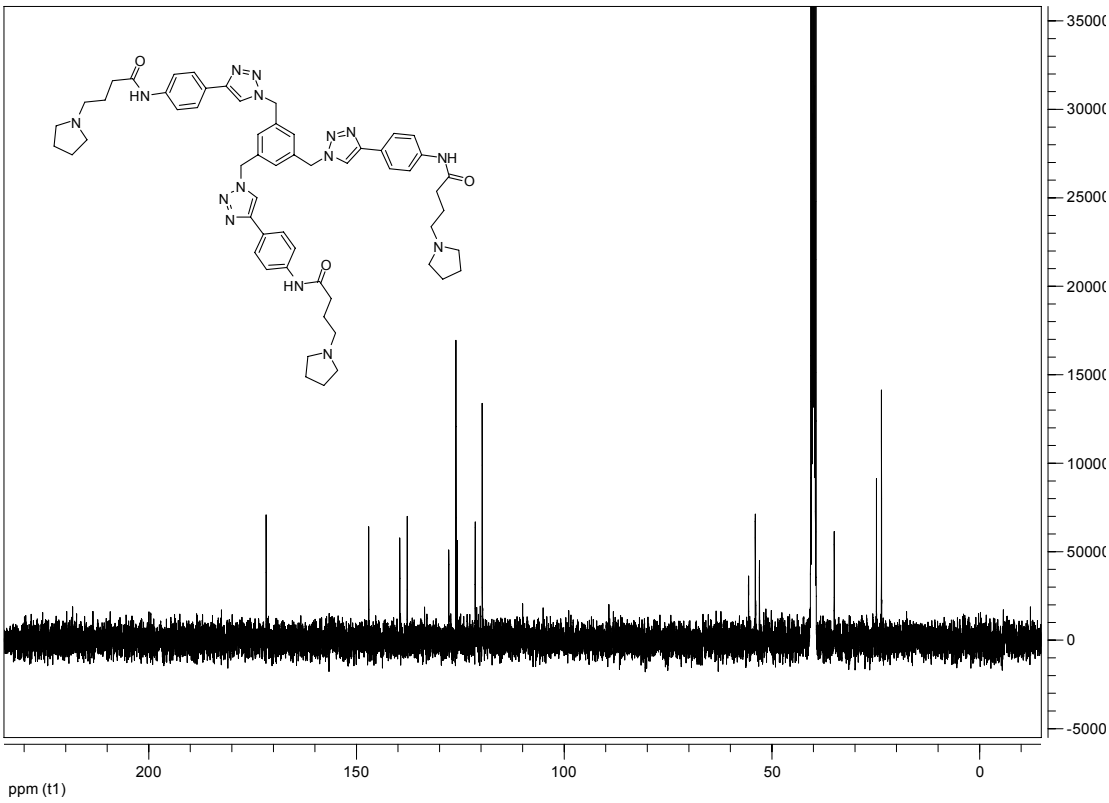


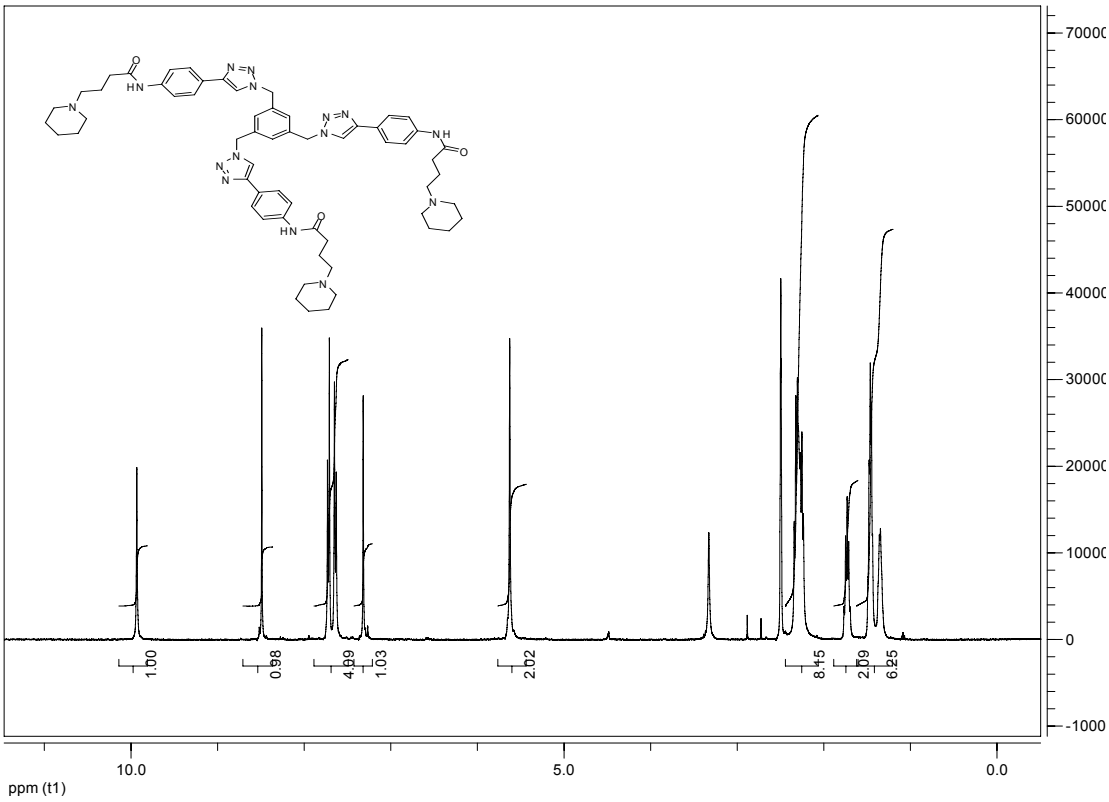


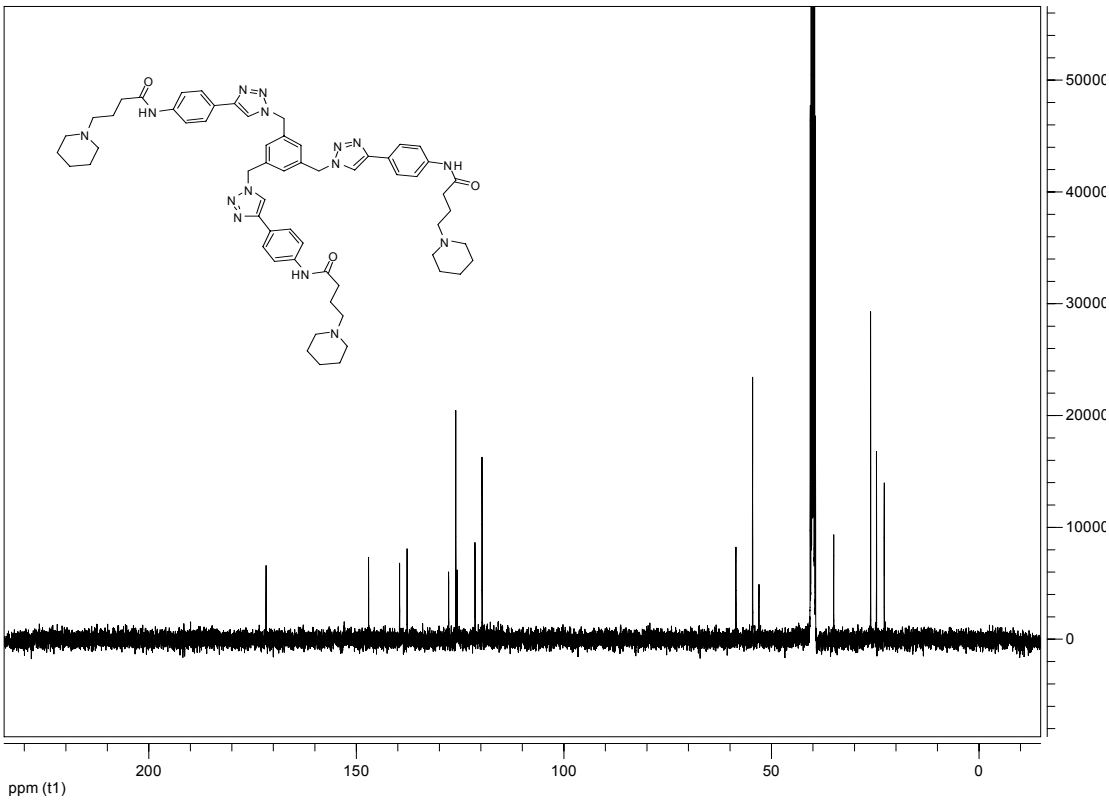


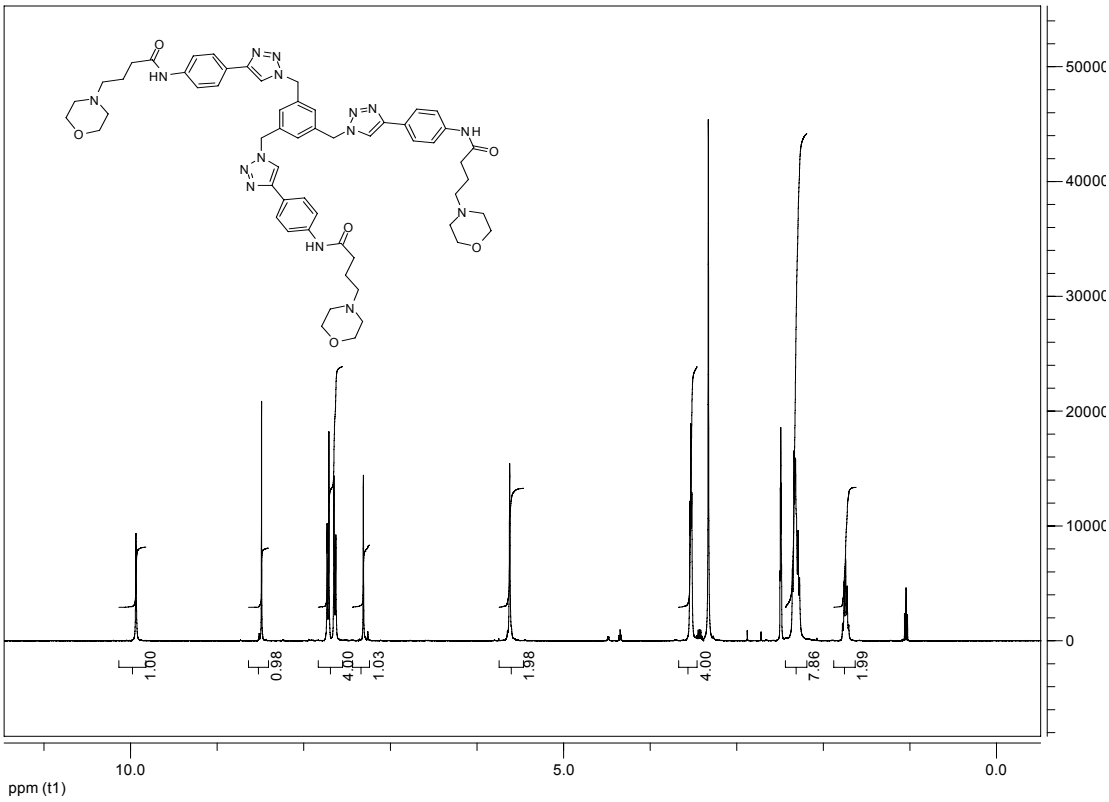


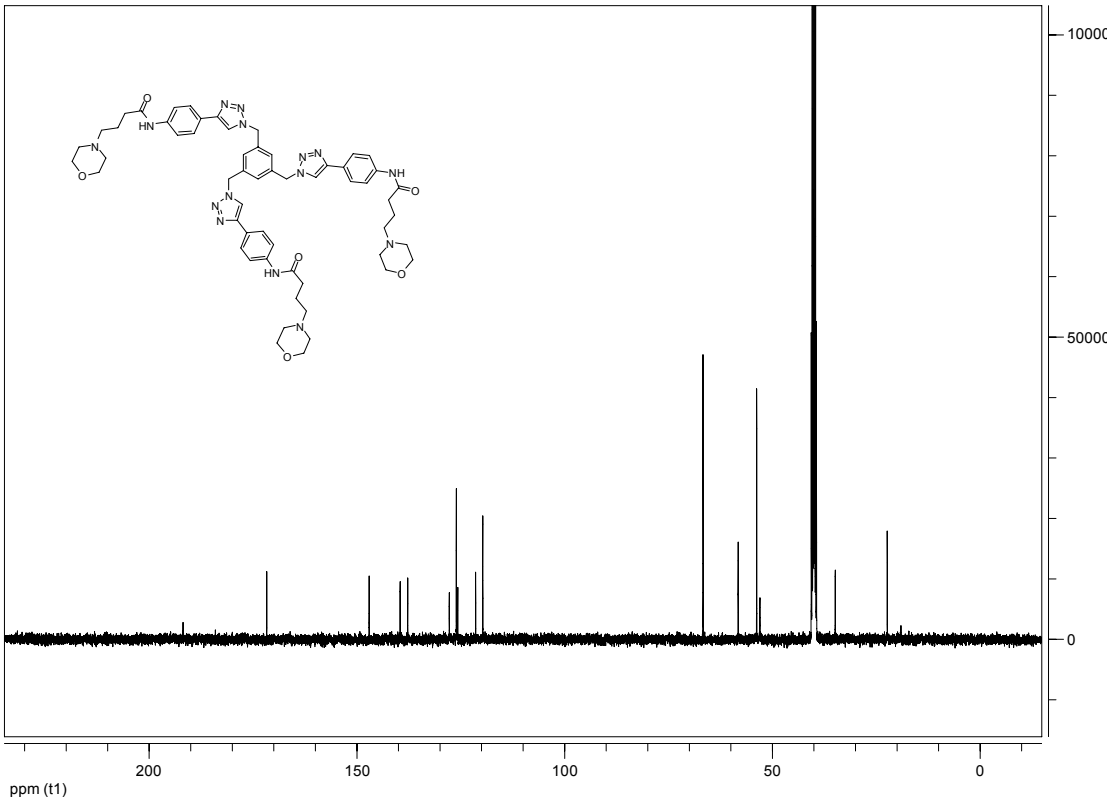


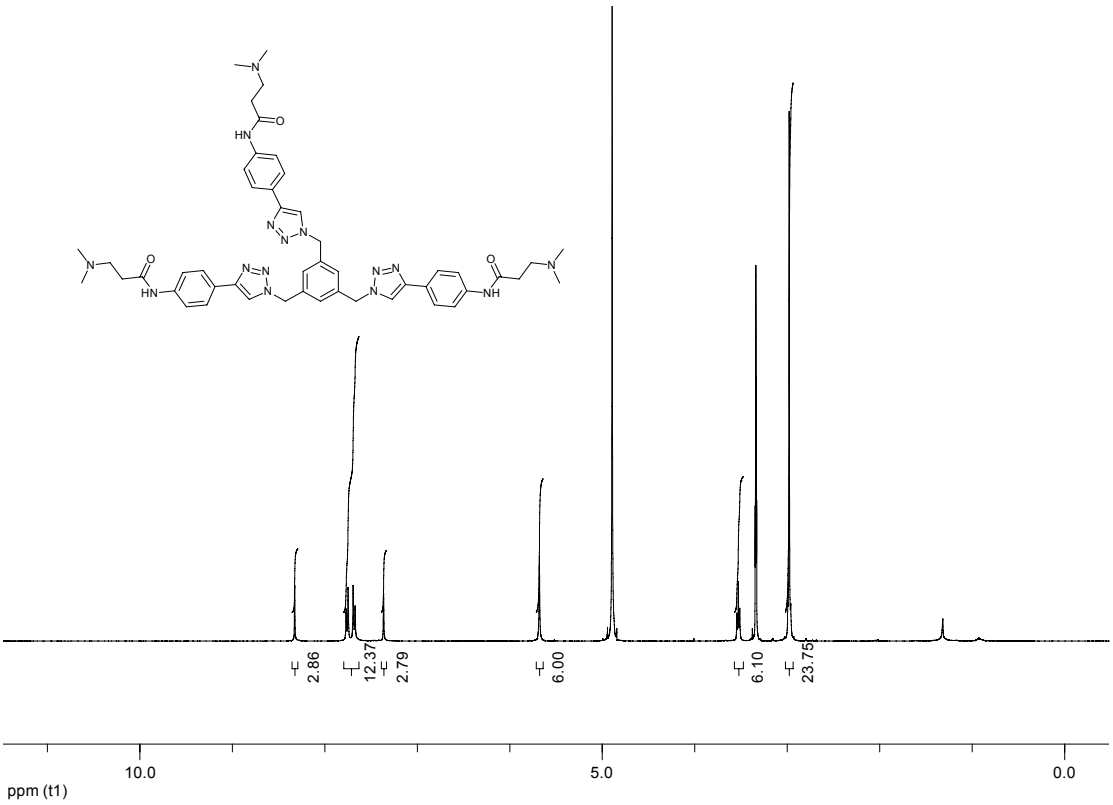


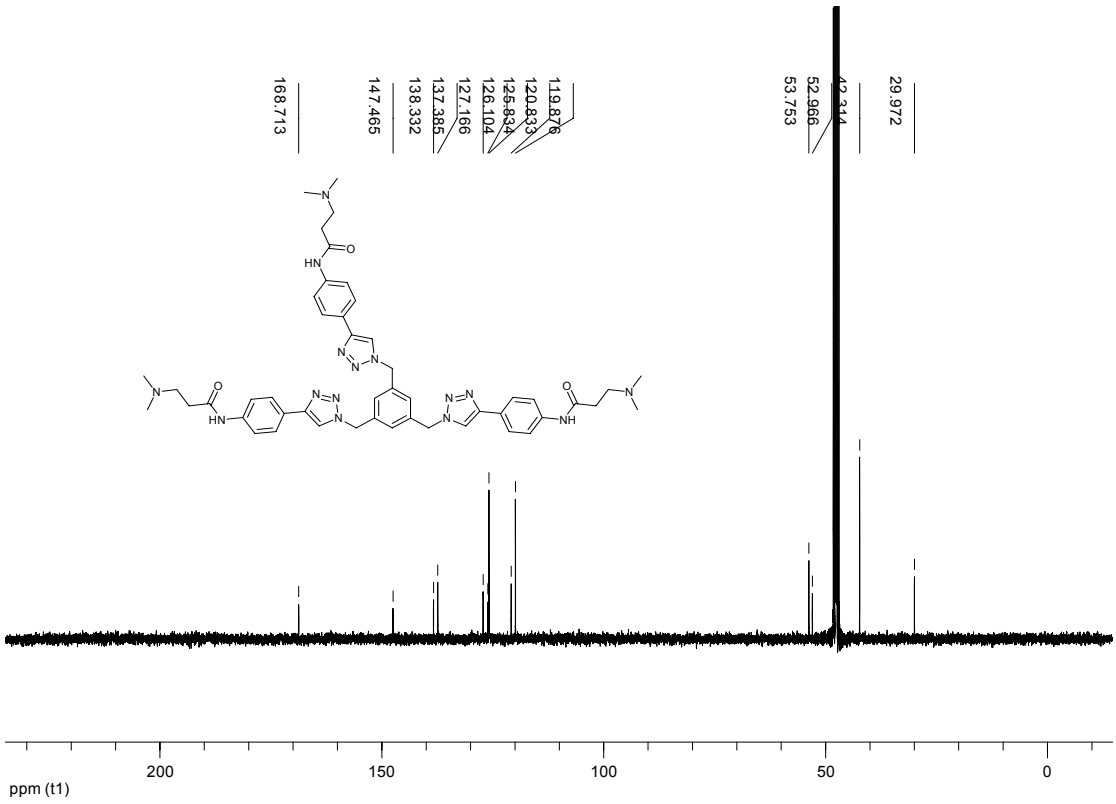


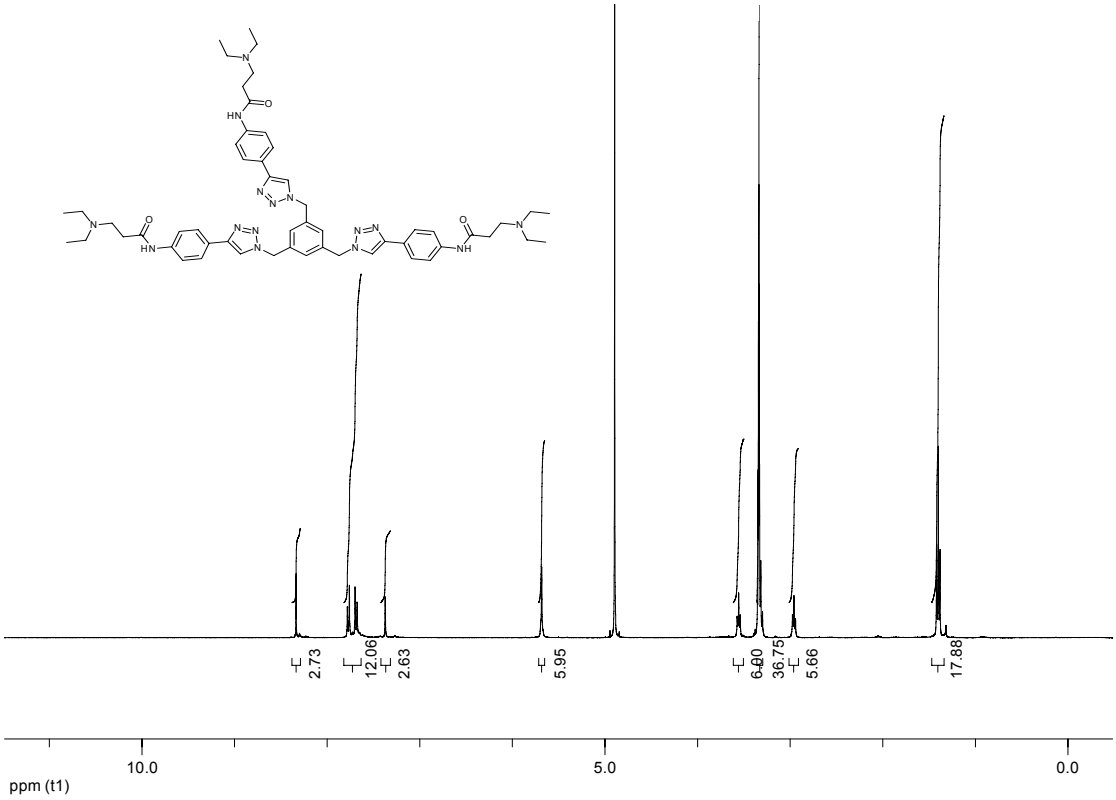


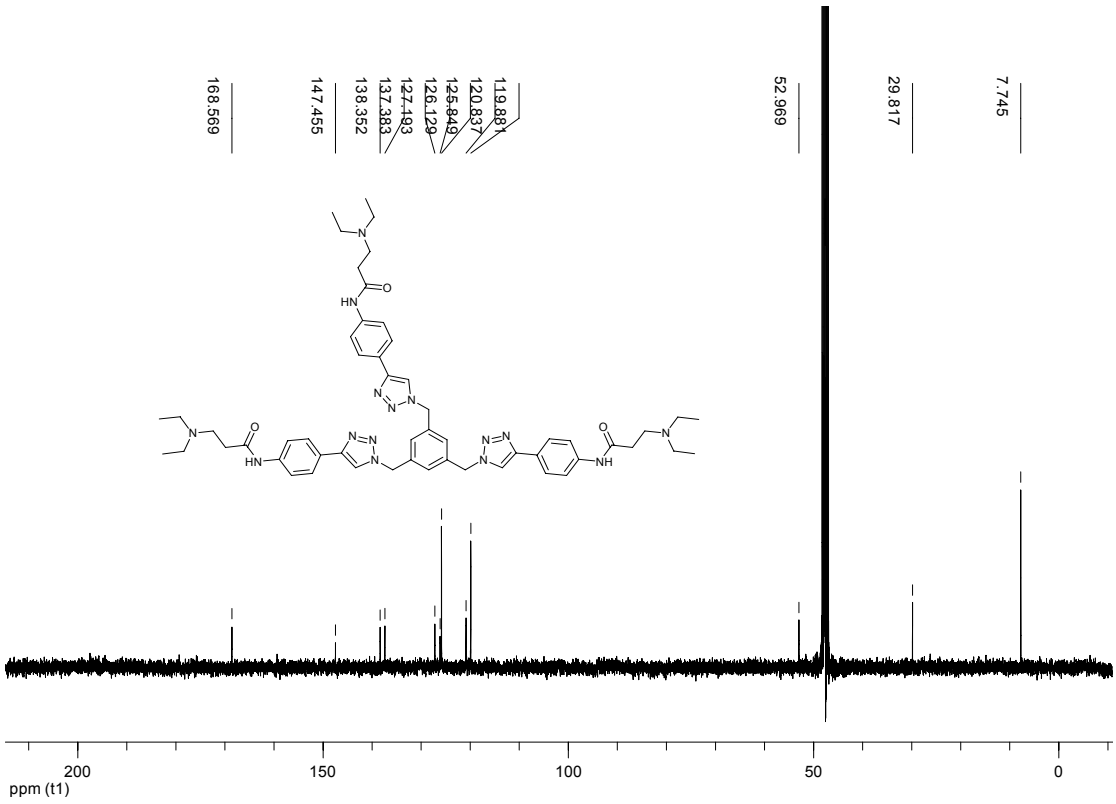


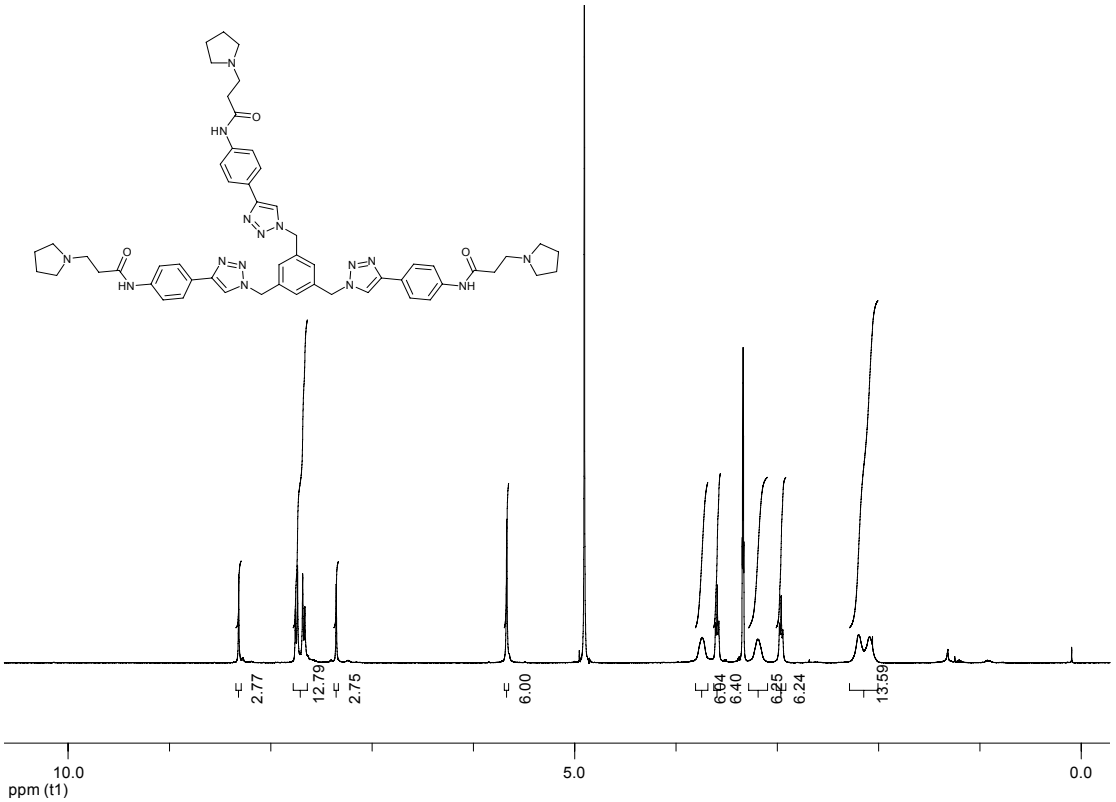


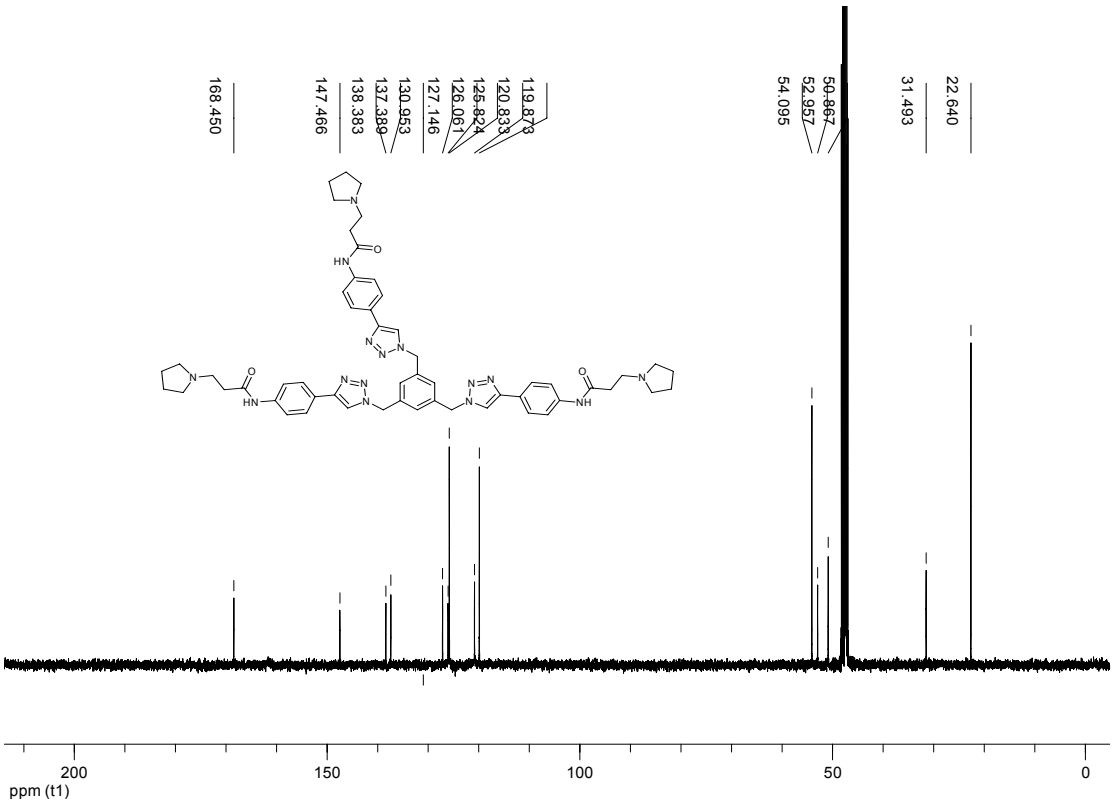


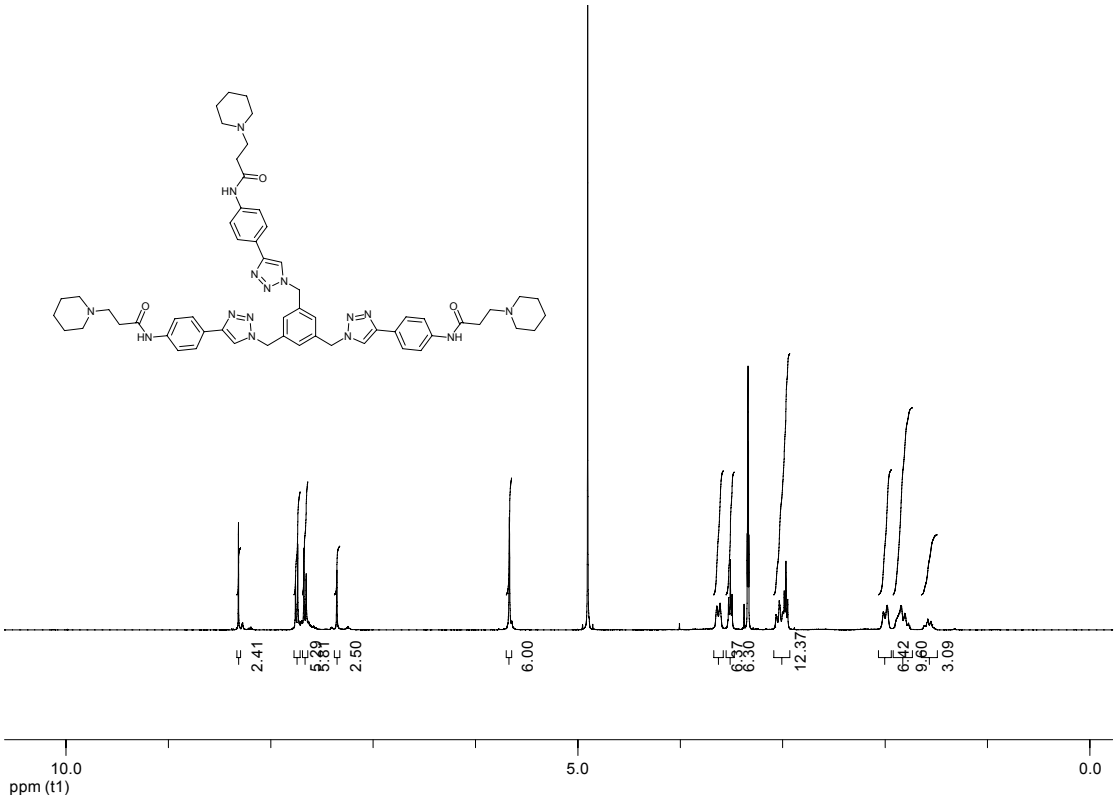


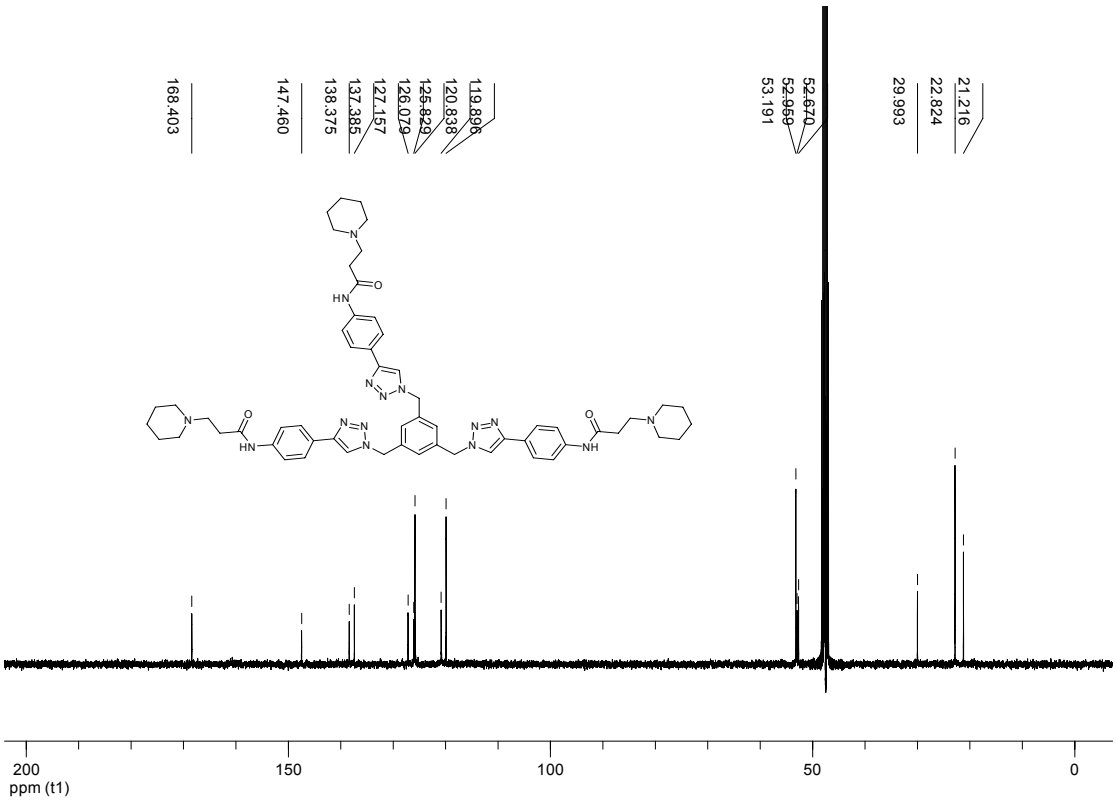


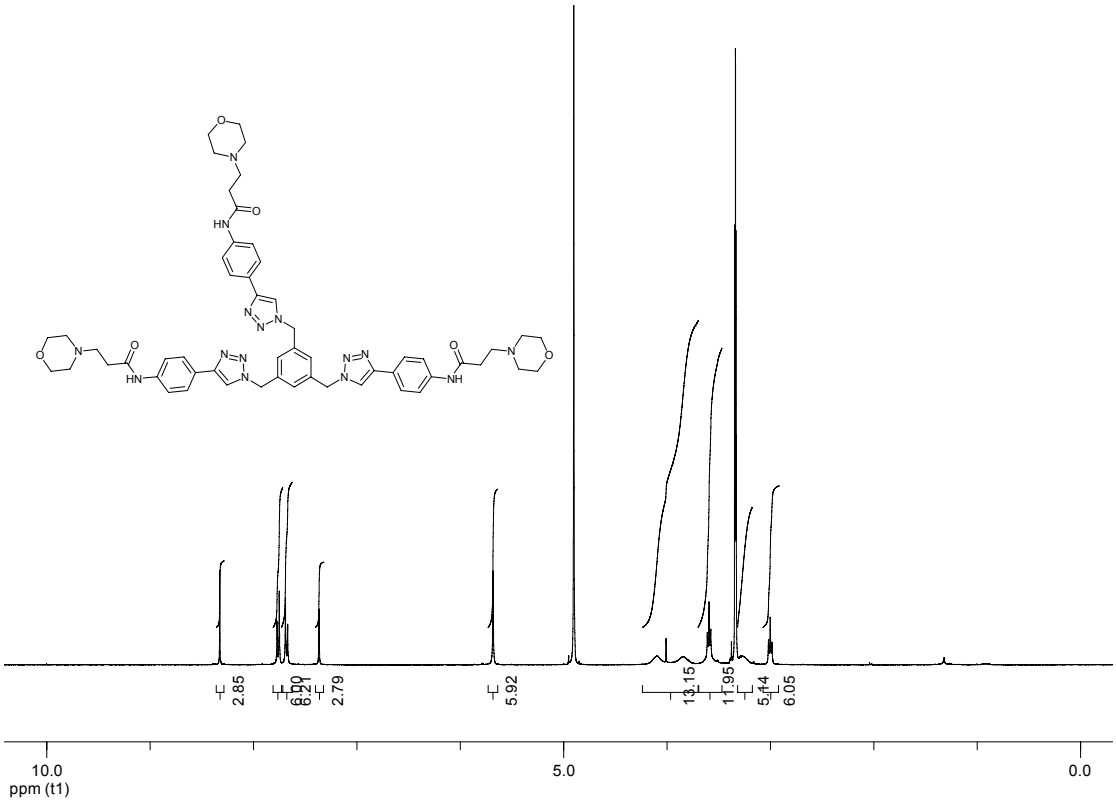


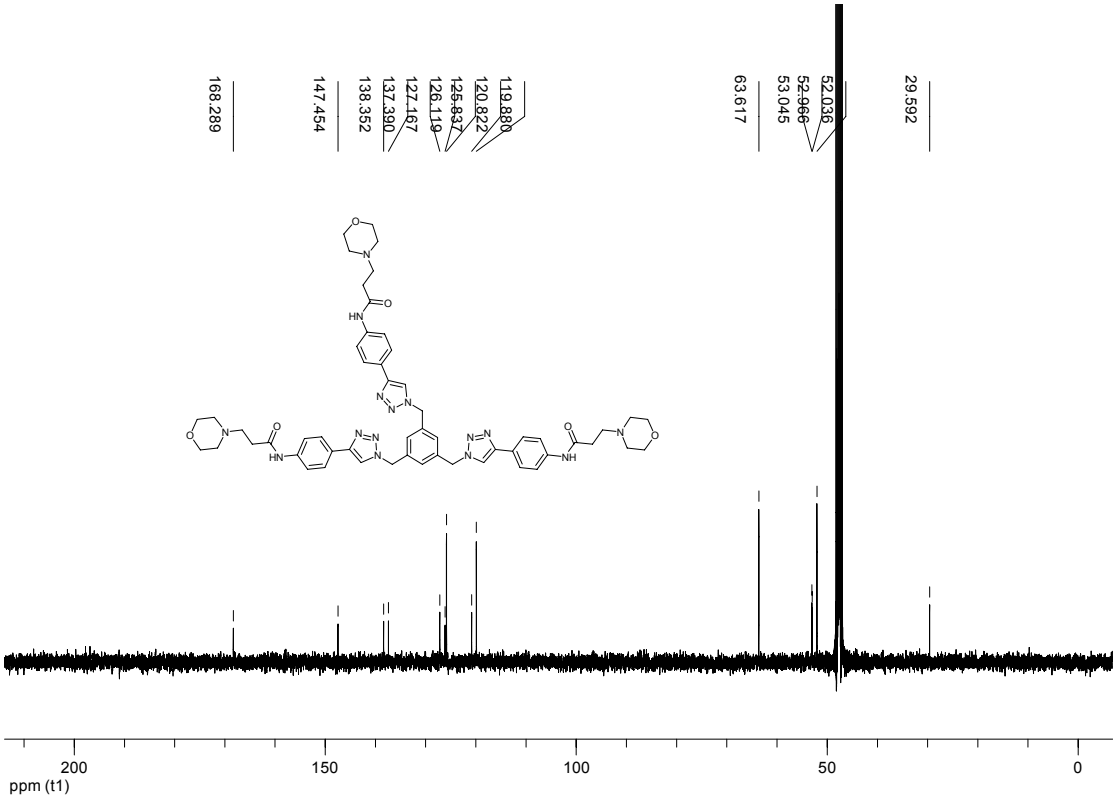












HPLC Procedures

Preparative HPLC was performed with an Agilent Technologies 1200 series system using a reverse phase column (YMC Co., Ltd., YMC-Pack R&D ODS-A, 100 × 20 mm I.D., particle size S-5 μm, 12 nm). Analytical HPLC was carried out on using the same instrument as for preparative HPLC, using a reverse phase column (YMC Co., Ltd., YMC-Pack R&D ODS-A, 100 × 4.6 mm I.D., particle size S-5 μm, 12 nm). Solvents were HPLC grade purchased from Fischer Scientific.

Solvents

Solvent A: MeOH/0.1% TFA

Solvent B: H_2O/0.1% TFA

Preparative HPLC

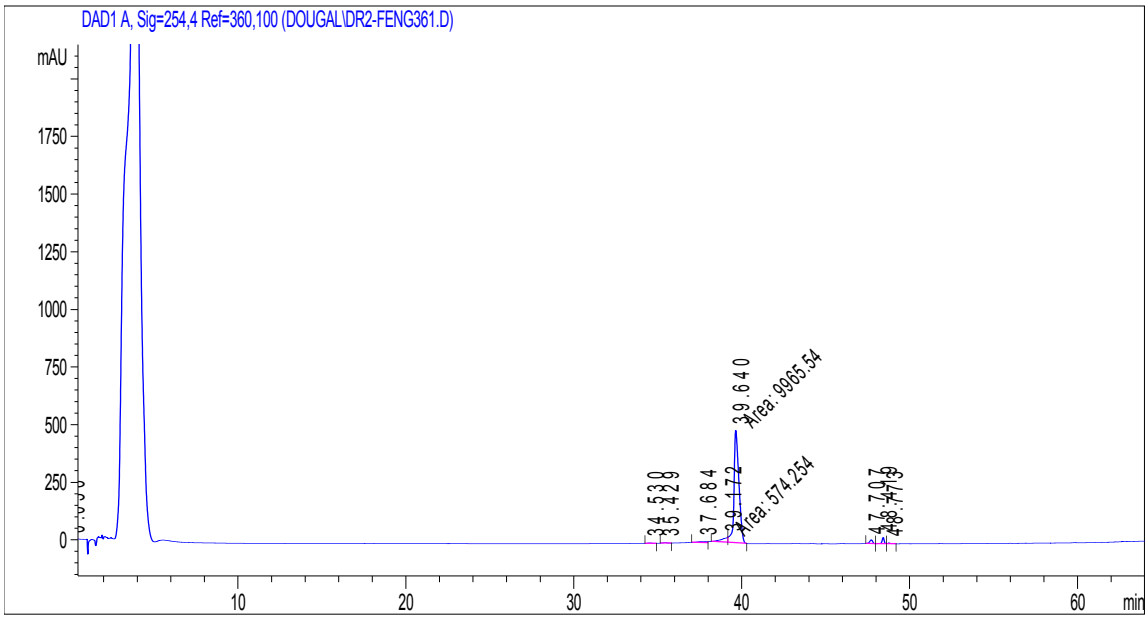
Flow rate: 3.5 mL/min; Run program: 0-2 min, 10% solvent A. 2-40 min, gradient from 10% solvent A to 35% solvent A. 40-60 min, gradient from 35% solvent A to 75% solvent A. 60-70 min, gradient from 75% solvent A to 100% solvent A. 70-80 min, 100% solvent A.

Analytical HPLC

Flow rate: 1.25mL/min; Run program: 0-2 min, 10% solvent A. 2-40 min, gradient from 10% solvent A to 35% solvent A. 40-55 min, gradient from 35% solvent A to 75% solvent A. 55-60 min, gradient from 75% solvent A to 100% solvent A.

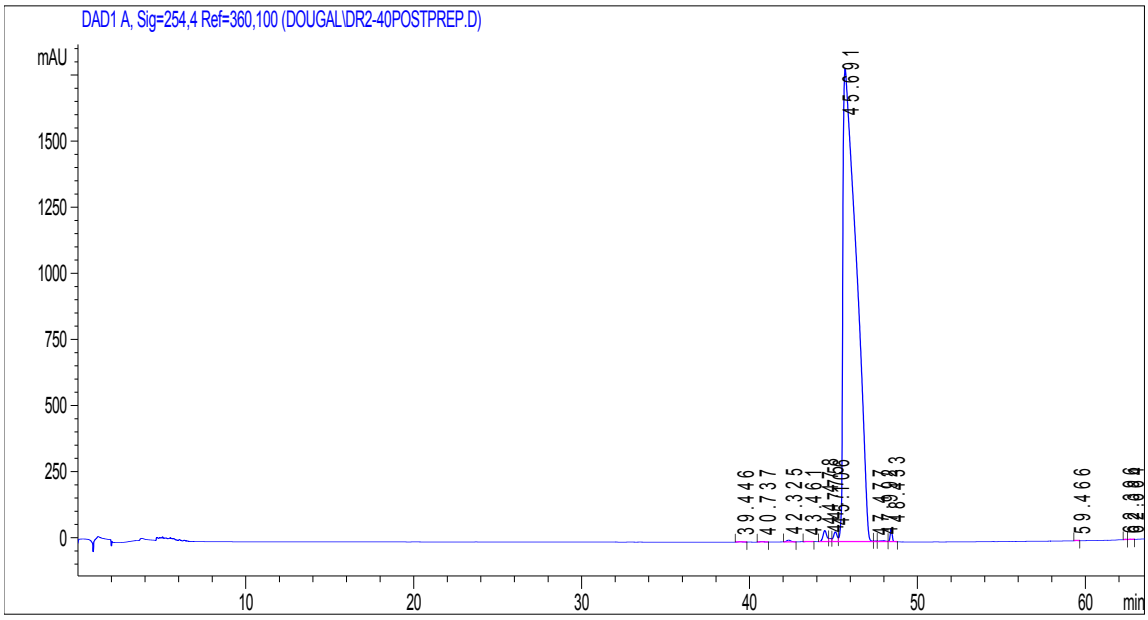
HPLC Traces

Ligand **20**



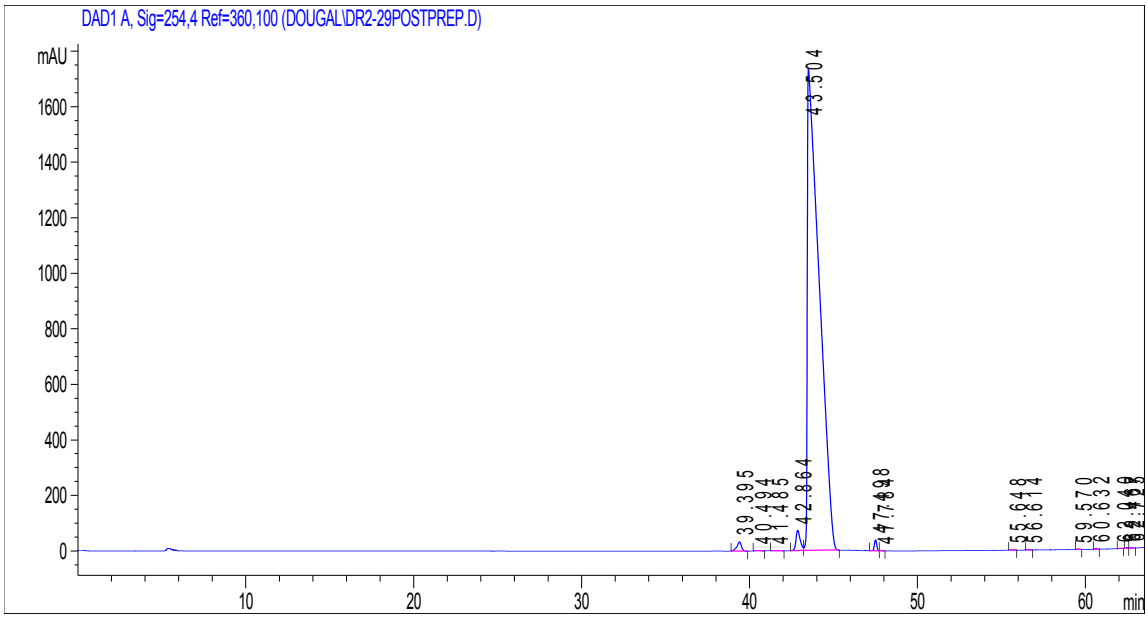
#	Time	Area	Height	Width	Area%	Symmetry
1	3.62E-26.8		1.6	0.073	0.060	0.412
2	34.53	28.2	1.9	0.2299	0.250	1.258
3	35.429	32.4	2.3	0.2222	0.287	1.354
4	37.684	203.7	5.6	0.4895	1.804	1.233
5	39.172	574.3	22.2	0.4319	5.085	0
6	39.64	9965.5	487.9	0.3404	88.243	0.571
7	47.707	209.3	16.8	0.1892	1.853	1.21
8	48.419	236.1	27.2	0.1313	2.090	1.149
9	48.773	36.9	4.1	0.1323	0.327	0.903

Ligand **21**



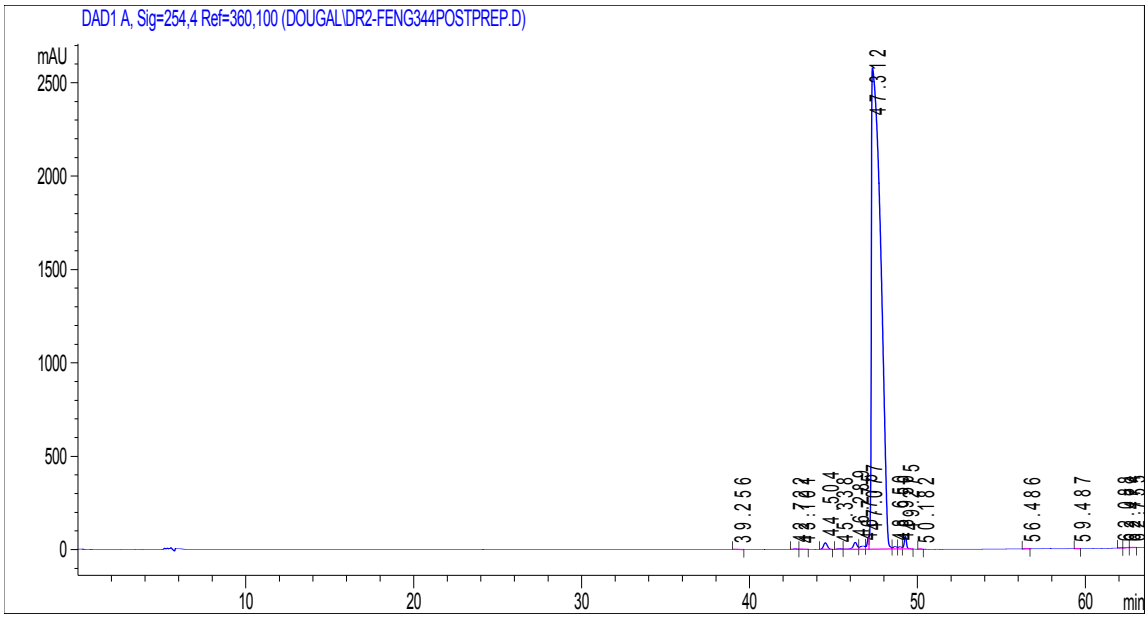
#	Time	Area	Height	Width	Area%	Symmetry
1	39.446	27.4	1.9	0.2318	0.027	0.939
2	40.737	41.7	2.7	0.2366	0.041	0.915
3	42.325	124.9	7.1	0.2701	0.124	0.856
4	43.461	19.2	1.2	0.2391	0.019	0.631
5	44.478	669.6	42.5	0.2379	0.664	0.89
6	44.775	135.5	12.9	0.1542	0.134	0.585
7	45.106	567.1	37.7	0.2274	0.562	1.016
8	45.691	98613.5	1790.5	0.7226	97.802	0.188
9	47.477	40.8	3.4	0.1751	0.040	0.843
10	47.992	127.6	4.7	0.3447	0.127	1.843
11	48.433	434.4	51.8	0.1299	0.431	0.955
12	59.466	9	1.1	0.1224	0.009	0.916
13	62.396	12.3	2	0.0965	0.012	1.001
14	62.664	6.9	1.1	0.0968	0.007	0.995

Ligand **22**



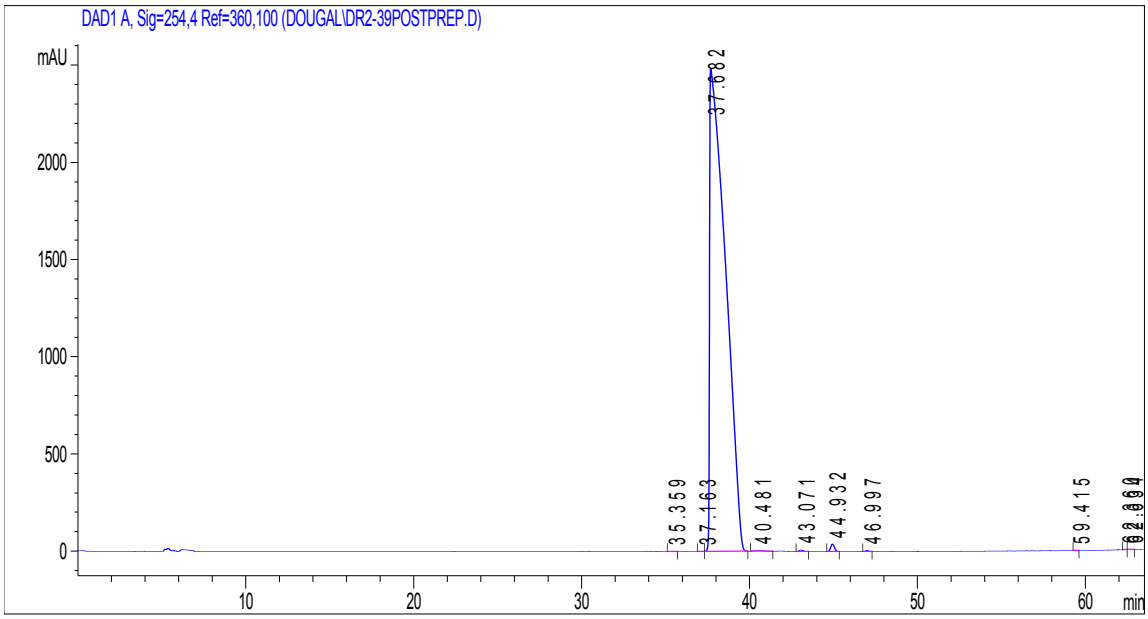
#	Time	Area	Height	Width	Area%	Symmetry
1	39.395	618.7	33.3	0.2731	0.709	1.364
2	40.494	25.4	1.6	0.2394	0.029	1.047
3	41.485	38.2	1.7	0.3141	0.044	0.602
4	42.864	1317.5	73.8	0.2624	1.511	0.67
5	43.504	84707.4	1738.6	0.6384	97.121	9.92E-2
6	47.498	400.2	39.8	0.1573	0.459	0.944
7	47.784	9	1.2	0.1176	0.010	0.679
8	55.648	14.5	1.3	0.1737	0.017	0.905
9	56.614	19.4	1.8	0.1565	0.022	0.803
10	59.57	11.7	1.6	0.116	0.013	0.922
11	60.632	19.6	2.8	0.109	0.023	1.144
12	62.04	8	1.2	0.1027	0.009	0.816
13	62.467	15	2.3	0.0986	0.017	0.846
14	62.725	14.2	1.9	0.1092	0.016	0.796

Ligand **23**



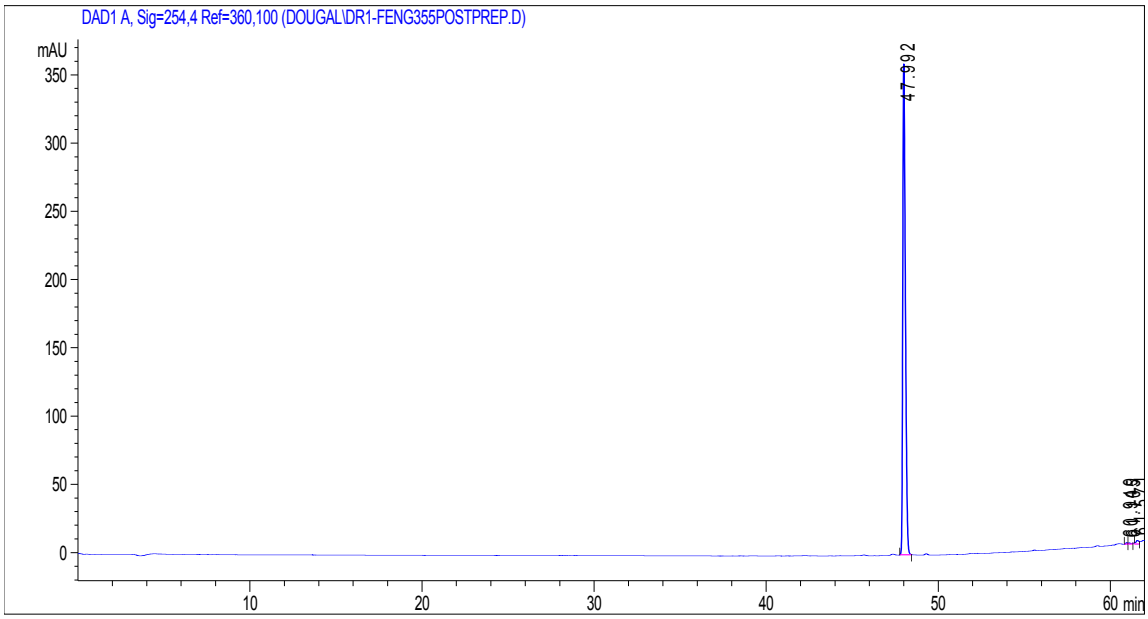
#	Time	Area	Height	Width	Area%	Symmetry
1	39.256	28.7	2	0.2321	0.028	0.936
2	42.722	65.7	4.4	0.2338	0.065	0.887
3	43.101	34	2.3	0.2276	0.033	0.953
4	44.504	580.2	36	0.2522	0.571	0.861
5	45.338	75.7	4.4	0.261	0.074	0.98
6	46.289	658.8	37.9	0.2568	0.648	1.295
7	46.775	369	17.7	0.2807	0.363	2
8	47.077	500	67.4	0.1105	0.492	2.828
9	47.312	98223.3	2577.4	0.6686	96.592	0.133
10	48.65	231.7	14.5	0.2425	0.228	0.938
11	48.95	182.9	13.3	0.2127	0.180	0.912
12	49.275	672.7	68.4	0.1507	0.661	1.01
13	50.182	10.5	1.3	0.1273	0.010	1.016
14	56.486	11.3	1	0.1672	0.011	1.308
15	59.487	8.1	1	0.1197	0.008	0.937
16	62.088	7.7	1.1	0.1041	0.008	0.893
17	62.474	18.3	2.9	0.0974	0.018	0.89
18	62.755	10.3	1.5	0.0996	0.010	0.841

Ligand **24**



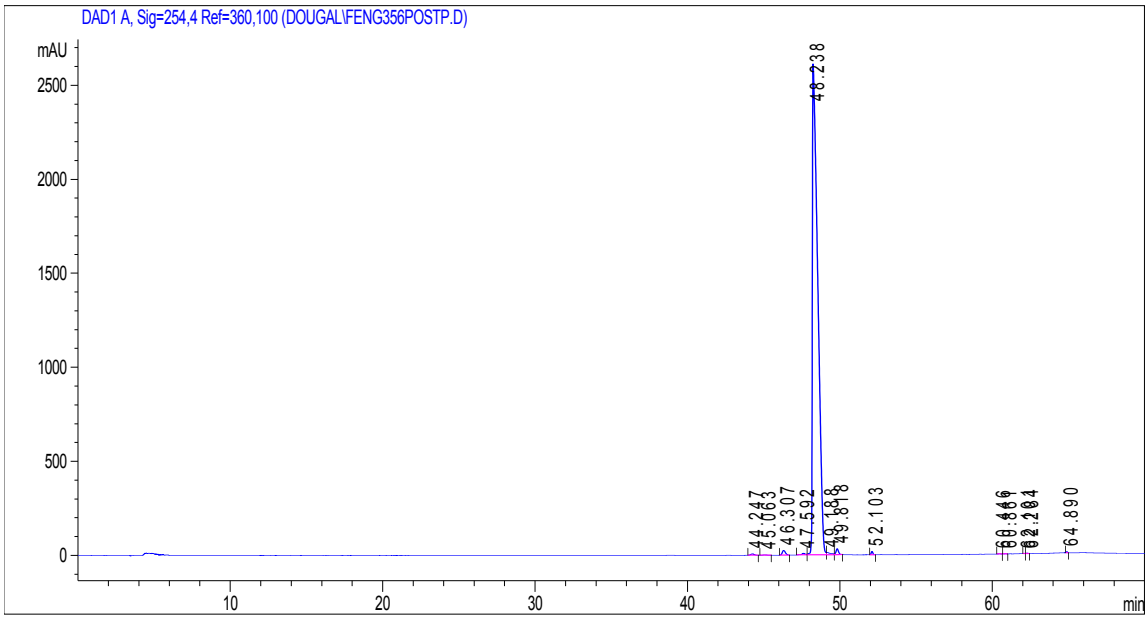
#	Time	Area	Height	Width	Area%	Symmetry
1	35.359	17.1	1.2	0.2218	0.011	0.996
2	37.163	20.8	1.6	0.2022	0.013	1.081
3	37.682	162027.6	2485.2	0.8006	99.390	7.17E-2
4	40.481	104.4	3.5	0.4223	0.064	0.634
5	43.071	125.3	8	0.2427	0.077	0.916
6	44.932	606.6	39.3	0.2403	0.372	0.874
7	46.997	80.4	7.1	0.1766	0.049	0.972
8	59.415	13.5	1.7	0.1219	0.008	0.9
9	62.36	16.1	2.5	0.0994	0.010	0.933
10	62.634	9.6	1.3	0.1103	0.006	0.906

Ligand **27**



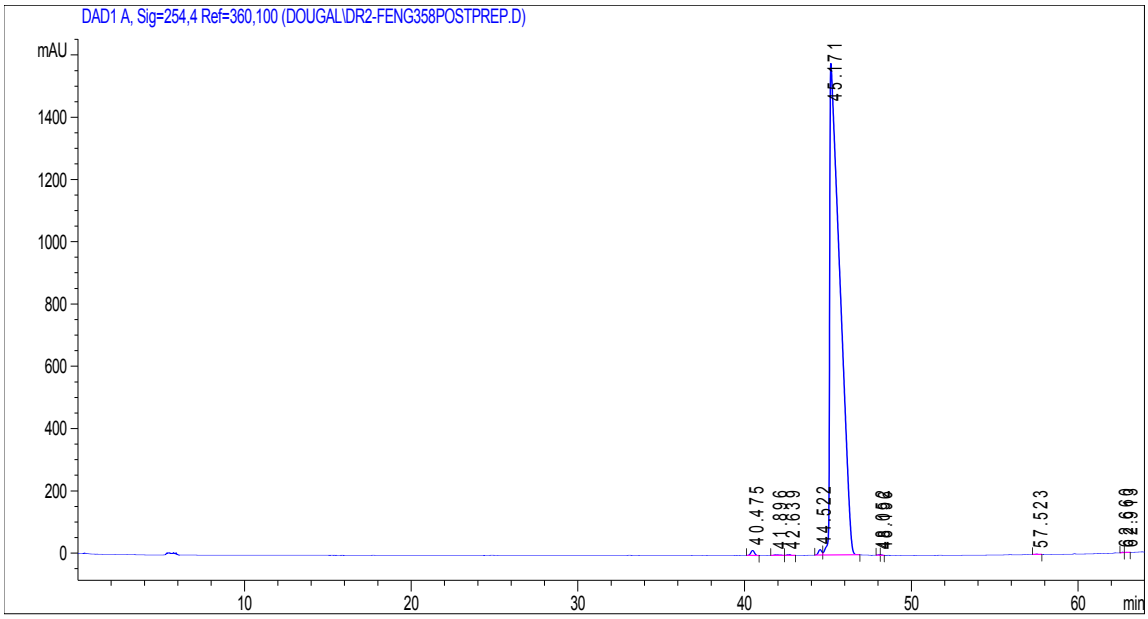
#	Time	Area	Height	Width	Area%	Symmetry
1	47.992	3794.5	360.2	0.1609	98.469	0.568
2	60.949	9.2	1.3	0.1045	0.239	0.979
3	61.105	13.9	1.1	0.171	0.360	0.373
4	61.571	35.9	3	0.1659	0.932	0.988

Ligand **28**



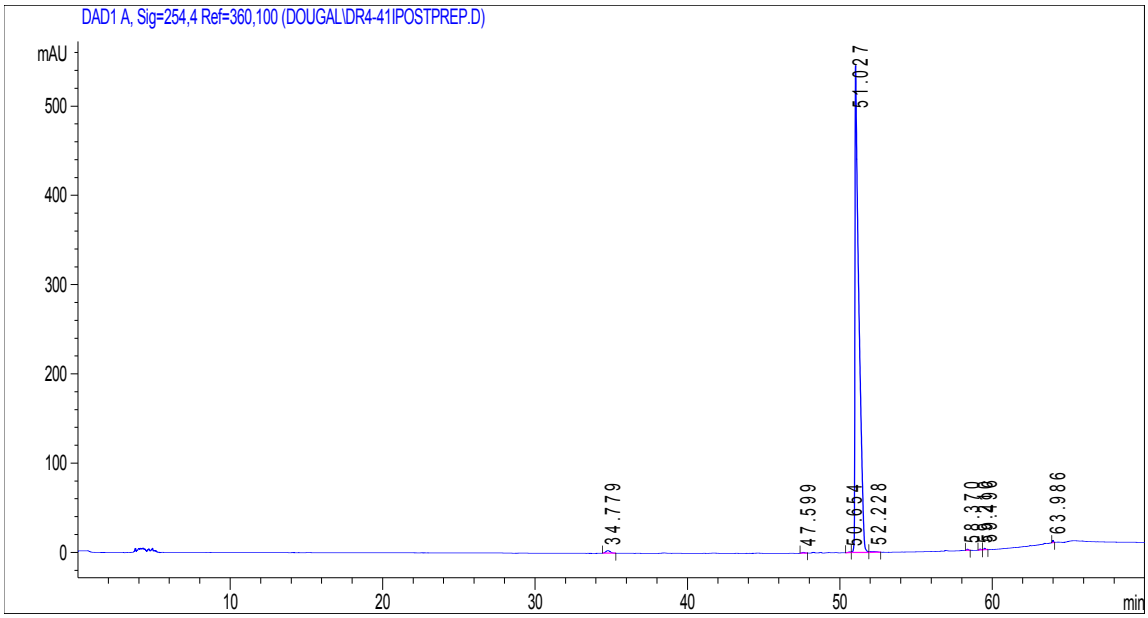
#	Time	Area	Height	Width	Area%	Symmetry
1	44.247	114.8	7.2	0.2463	0.177	0.845
2	45.063	31.9	2	0.254	0.049	0.833
3	46.307	361.4	25.2	0.2212	0.556	0.783
4	47.592	152.7	9.6	0.2203	0.235	0.752
5	48.238	63457	2612.1	0.3934	97.662	0.16
6	49.188	255.5	11.9	0.2756	0.393	0.202
7	49.818	380.8	32.7	0.172	0.586	0.872
8	52.103	139.8	18.2	0.1194	0.215	0.954
9	60.446	13.1	1.8	0.1121	0.020	0.947
10	60.861	11.2	1.4	0.1209	0.017	1.046
11	62.101	7.2	1.2	0.0877	0.011	1.096
12	62.284	22.1	4	0.0868	0.034	1.068
13	64.89	28.8	7.1	0.0615	0.044	0.954

Ligand **29**



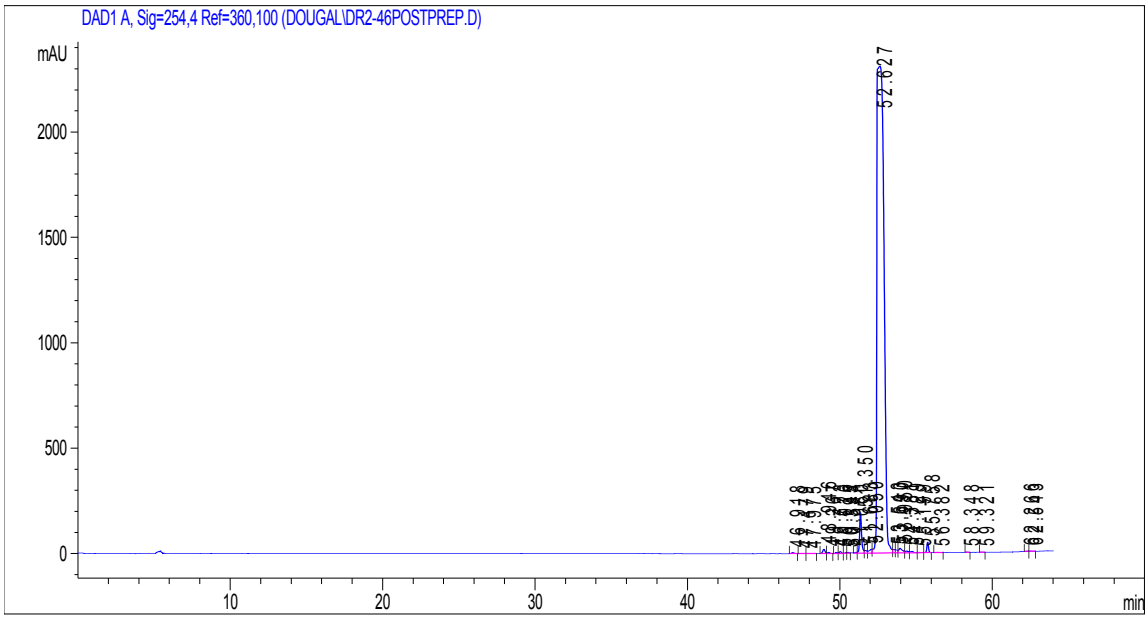
#	Time	Area	Height	Width	Area%	Symmetry
1	40.475	258.9	16.8	0.2381	0.383	1.015
2	41.896	81.1	3.1	0.3657	0.120	0.47
3	42.639	56.8	3.6	0.2439	0.084	1.016
4	44.522	255	1 7.9	0.2179	0.377	0.986
5	45.171	66888.9	1578.4	0.5484	98.918	0.129
6	48.052	20.2	2.2	0.1352	0.030	1.04
7	48.196	13.6	1.8	0.1182	0.020	0.568
8	57.523	23.9	2.2	0.1672	0.035	1.245
9	62.66	13.7	2.4	0.0896	0.020	0.959
10	62.913	8.2	1.4	0.0903	0.012	1.015

Ligand **32**



#	Time	Area	Height	Width	Area%	Symmetry
3	50.654	12.4	1	0.1639	0.127	1.842
4	51.027	9605.9	545.6	0.2314	98.333	0.176
5	52.228	30.6	1.2	0.3271	0.313	1.174
6	58.37	11.6	1.6	0.109	0.118	0.819
7	59.21	9.8	1.3	0.1171	0.101	0.791
8	59.496	14.3	1.9	0.1109	0.146	0.85
9	63.986	11.8	2.7	0.067	0.121	0.842

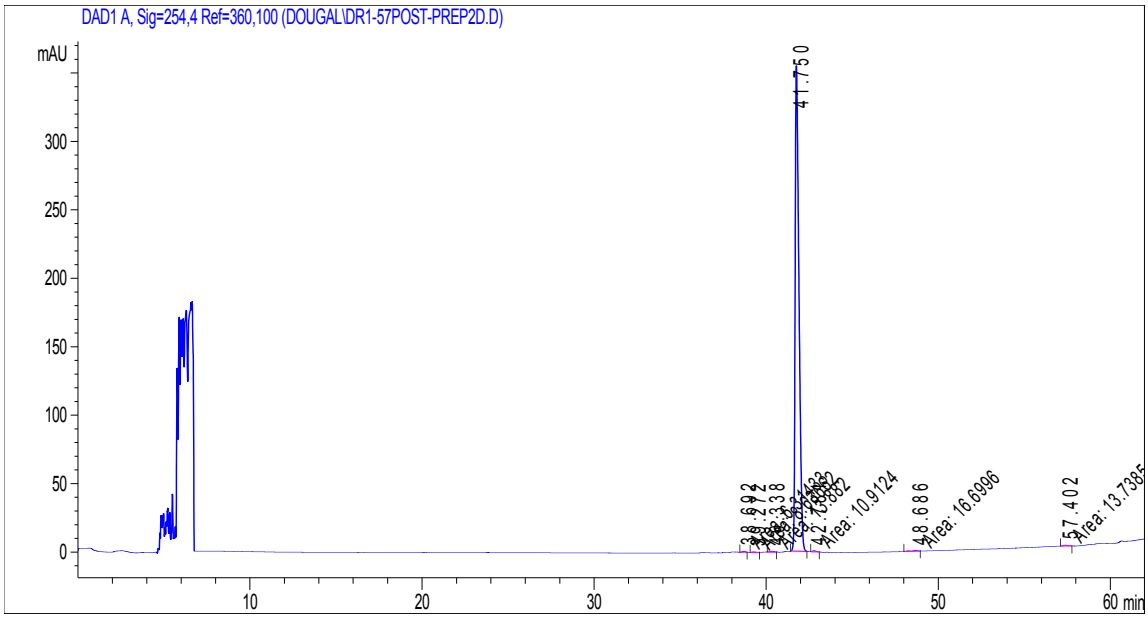
Ligand **33**



#	Time	Area	Height	Width	Area%	Symmetry
1	46.918	70.2	5.9	0.1859	0.091	1.02
2	47.479	16	1.3	0.1897	0.021	0.828
3	47.975	19.6	1.2	0.2318	0.025	0.731
4	48.946	222.3	20.8	0.1648	0.288	0.962
5	49.267	65.3	6.3	0.1576	0.085	0.877
6	49.773	52.6	5.4	0.1467	0.068	0.857
7	50.026	91.7	9.2	0.1484	0.119	1.004
8	50.395	32.1	4	0.1196	0.042	1.686
9	50.544	55.9	5.7	0.1423	0.073	0.807
10	51.06	58.2	5.8	0.1459	0.076	1.662
11	51.35	1730.9	192	0.1372	2.246	0.761
12	51.683	142.4	13.2	0.156	0.185	0.689
13	52.05	246.6	19	0.1757	0.320	3.098
14	52.62	72803.8	2310.8	0.4636	94.457	0.724
15	53.543	161.5	16	0.144	0.210	0.805
16	53.69	139.2	14.6	0.1371	0.181	0.436
17	53.95	380.4	22.9	0.2216	0.493	0.538
18	54.381	136.7	9.6	0.1962	0.177	0.777
19	54.729	125.4	6.8	0.2597	0.163	0.753
20	55.199	51.6	2.8	0.2448	0.067	0.465
21	55.758	385.3	50.7	0.1166	0.500	0.971
22	56.382	37.8	1.9	0.2686	0.049	0.547
23	58.348	13.4	1.8	0.1107	0.017	0.88

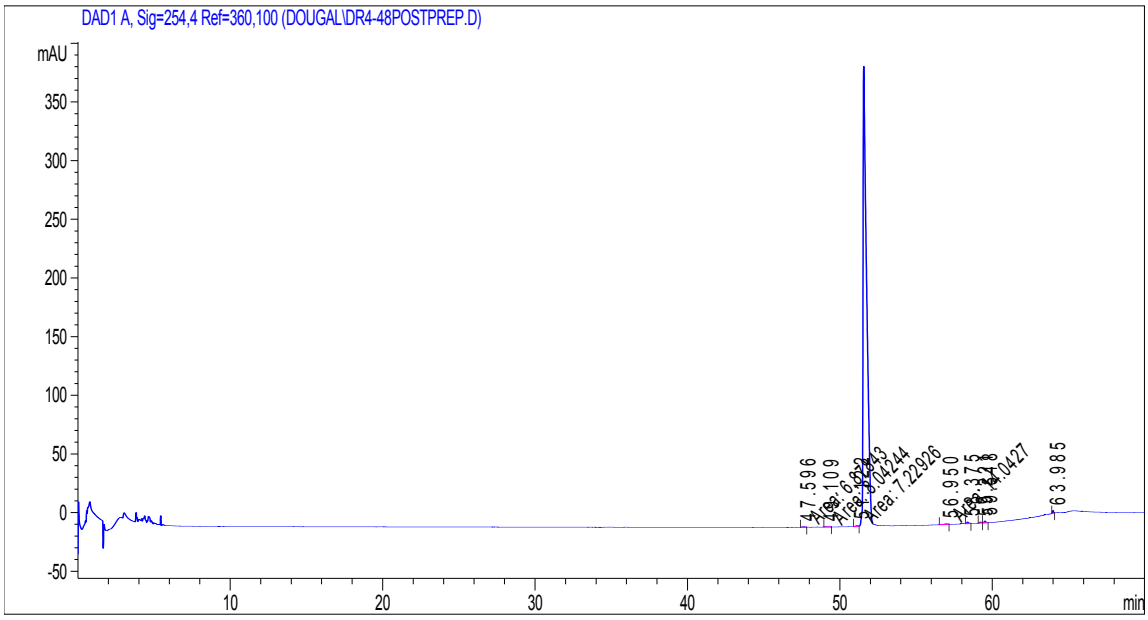
24	59.321	9	1.2	0.1177	0.012	0.932
25	62.266	14	2.2	0.0977	0.018	0.904
26	62.543	14.4	1.8	0.1152	0.019	0.725

Ligand **34**



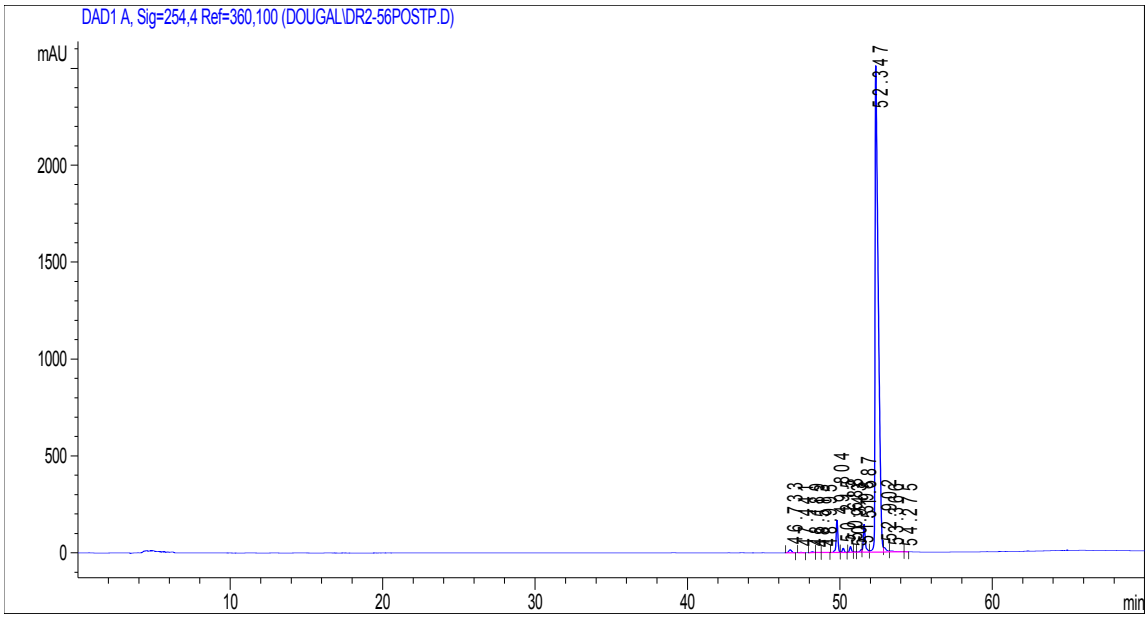
#	Time	Area	Height	Width	Area%	Symmetry
1	38.692	6.3	5.9E-1	0.1794	0.114	0.906
2	39.272	8.6	4.8E-1	0.3027	0.156	0.692
3	40.338	13.9	7.4E-1	0.3111	0.251	1.212
4	41.75	5452.2	355	0.2332	98.729	0.461
5	42.781	10.9	8.7E-1	0.2088	0.198	1.015
6	48.686	16.7	6.6E-1	0.4248	0.302	1.808
7	57.402	13.7	7.5E-1	0.3047	0.249	0.821

Ligand **35**



#	Time	Area	Height	Width	Area%	Symmetry
1	47.596	6.9	6.2E-1	0.186	0.107	0.781
2	49.109	8	4.5E-1	0.2947	0.125	0.527
3	51.122	7.2	7.2E-1	0.1667	0.112	1.725
4	51.559	6346.6	391.8	0.27	98.760	0.232
5	56.95	14	8.2E-1	0.2856	0.219	0.945
6	58.375	11	1.5	0.1135	0.171	0.792
7	59.221	9.1	1.2	0.1172	0.141	0.821
8	59.518	12.6	1.7	0.1121	0.196	0.878
9	63.985	10.8	2.5	0.0651	0.168	0.822

Ligand **36**



#	Time	Area	Height	Width	Area%	Symmetry
1	46.733	213.4	15.6	0.2116	0.525	0.937
2	47.441	48.4	3.6	0.1998	0.119	1.038
3	48.189	71.1	5.3	0.2113	0.175	0.861
4	48.513	11.4	1.2	0.1504	0.028	0.906
5	48.995	19.1	1.5	0.2005	0.047	0.966
6	49.804	1379.7	167.8	0.1259	3.393	0.938
7	50.215	202	22.8	0.1333	0.497	0.914
8	50.688	272.4	30.6	0.1357	0.670	0.83
9	50.943	37.5	4.2	0.127	0.092	0.604
10	51.398	137.7	14.7	0.133	0.339	2.67
11	51.587	1355.8	145.1	0.1391	3.334	0.664
12	52.347	36417.2	2511.7	0.2092	89.561	0.258
13	52.902	294.2	23.7	0.1751	0.723	0.189
14	53.366	189.9	6.4	0.4043	0.467	0.265
15	54.275	12	1.3	0.1363	0.029	0.478

MS Experimental Procedures

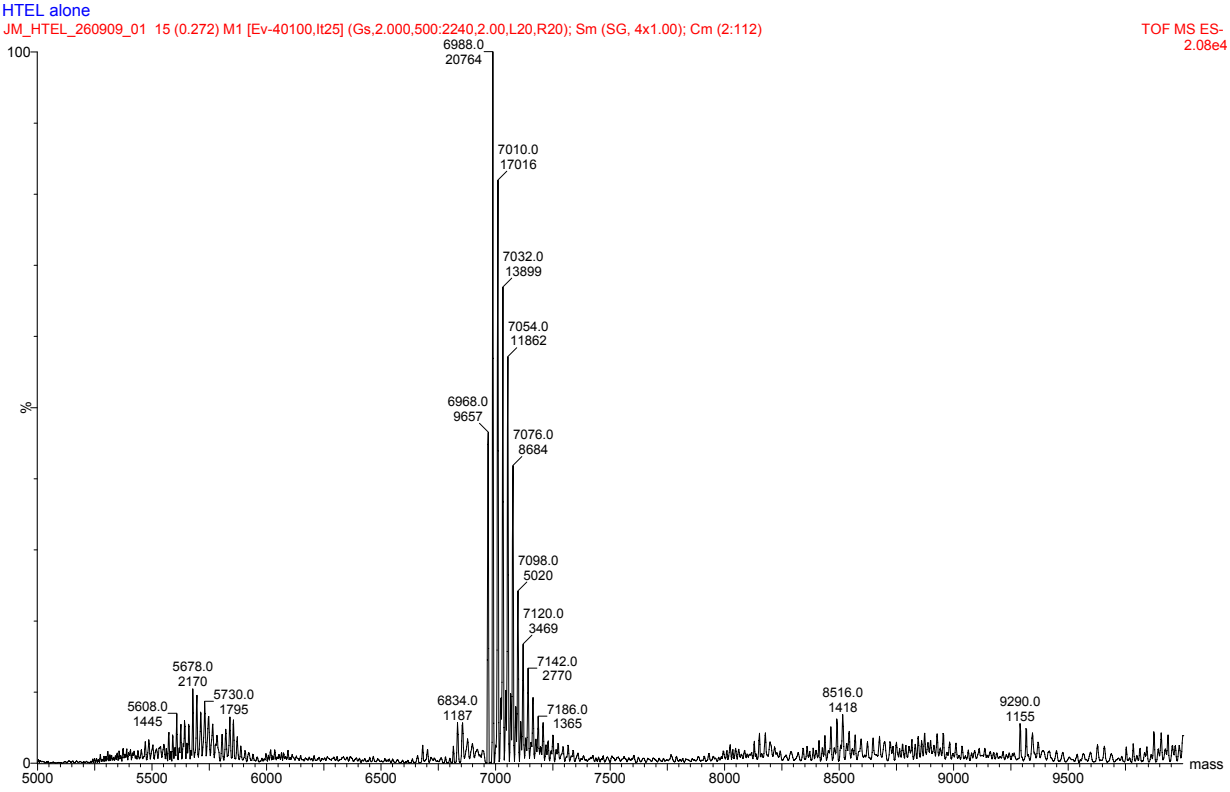
Electrospray ionization mass spectrometry was performed on a Waters (Altrincham, UK) Synapt High Definition Mass Spectrometer (HDMS) - a hybrid quadrupole/ion mobility/orthogonal acceleration time of flight (oa-TOF) instrument operated in the negative ion mode. Samples were infused to the standard electrospray (z-spray) source using a Harvard apparatus 22 dual syringe pump, model 55-2222 and 100 μL Hamilton syringes, at infusion rates between 3-5 μL/min. The capillary of the ESI source was held at -2.5 kV, and the sample cone operated at -10-20V, required to preserve non-covalent interactions. The oa-TOF-MS was operated over the scanning range of *m/z* 500-10000 at a pressure of 1.8 x 10^{-6} mbar.

Sample preparation

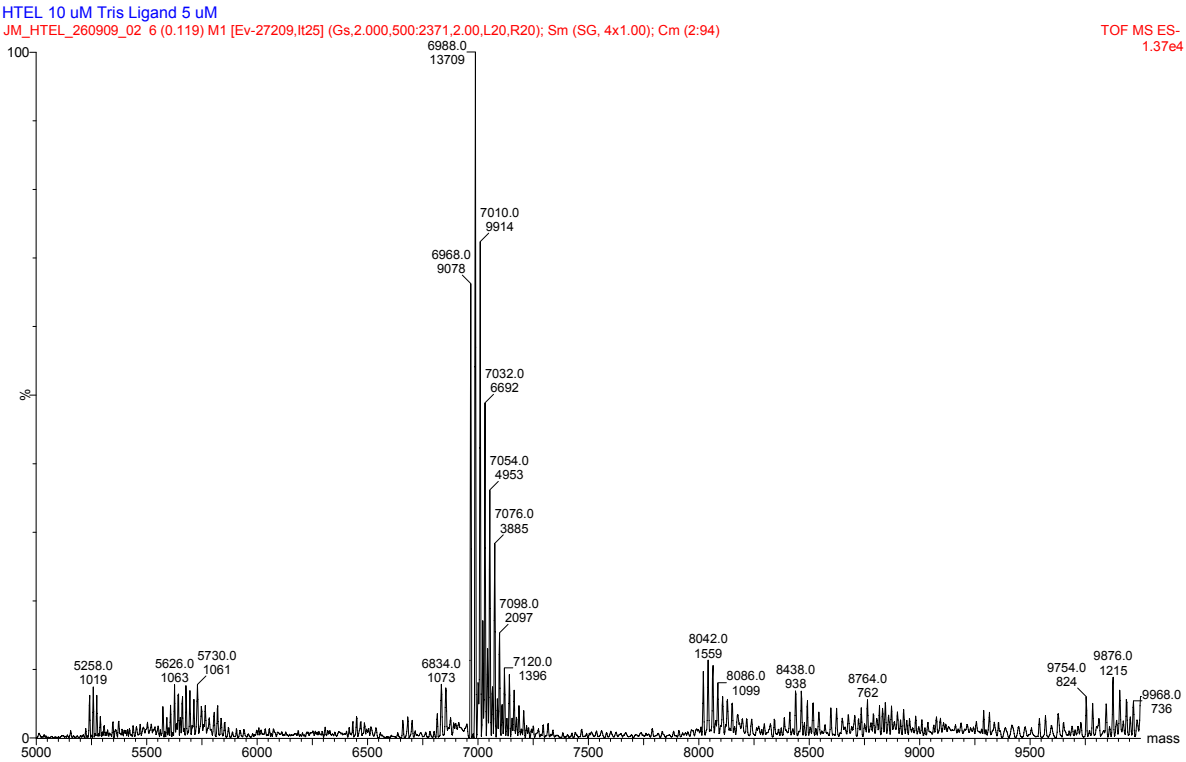
G-Quadruplex samples were prepared in ammonium acetate buffer (25 mM, pH 7) at 10 μM. Triazole ligand **28** was titrated in to the solution to give final concentrations between 5 and 25 μM.

Mass Spectra

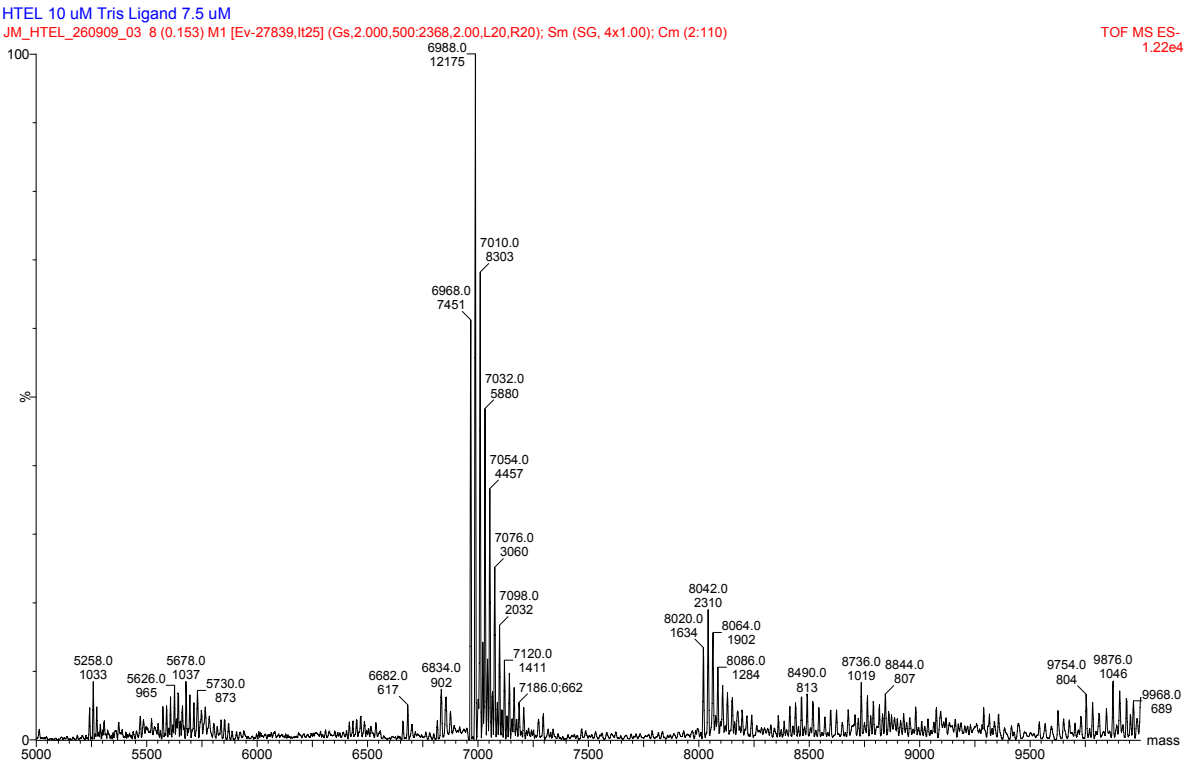
10 μM *h*-Tel



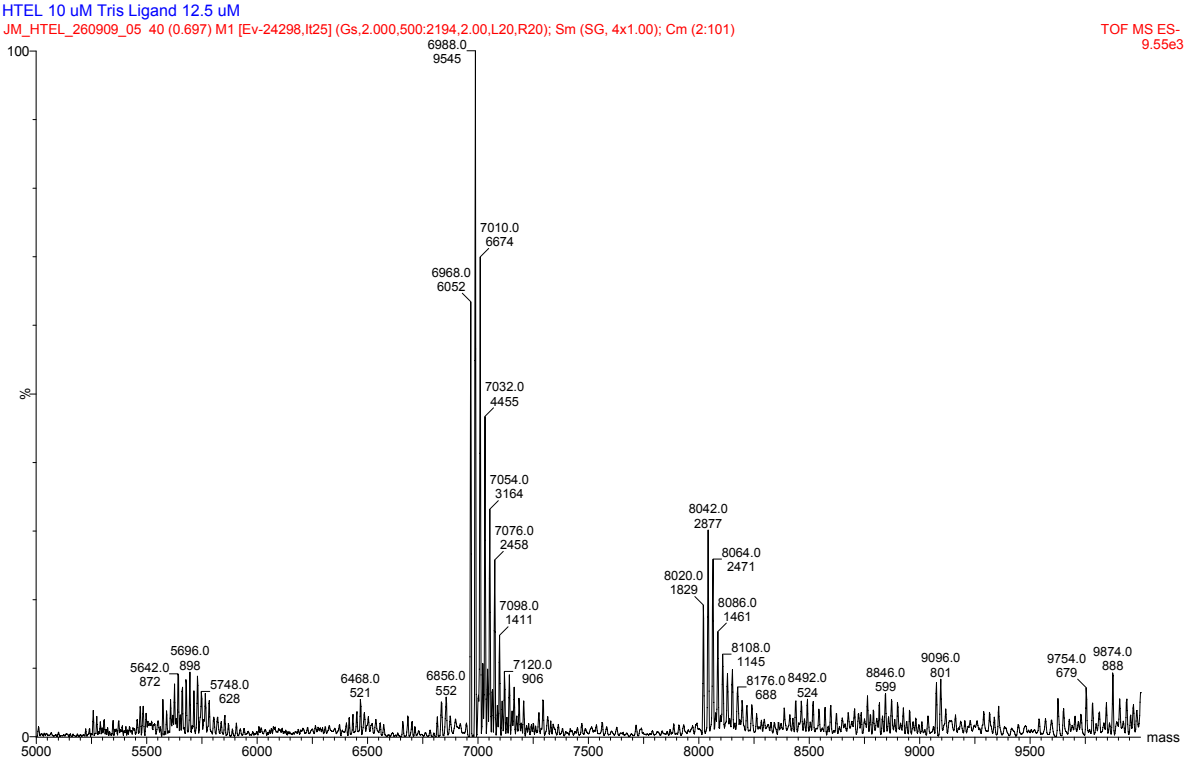
10 μM *h*-Tel + 5 μM ligand **28**



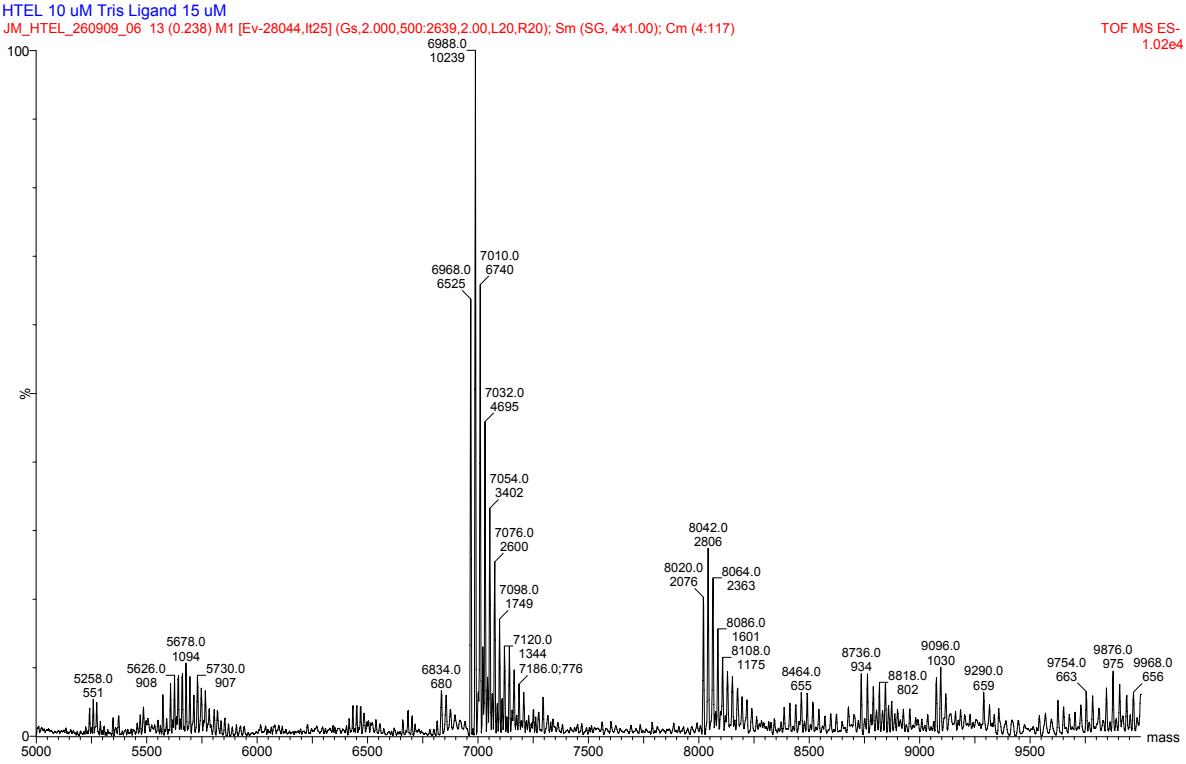
10 μM *h*-Tel + 7.5 μM ligand **28**



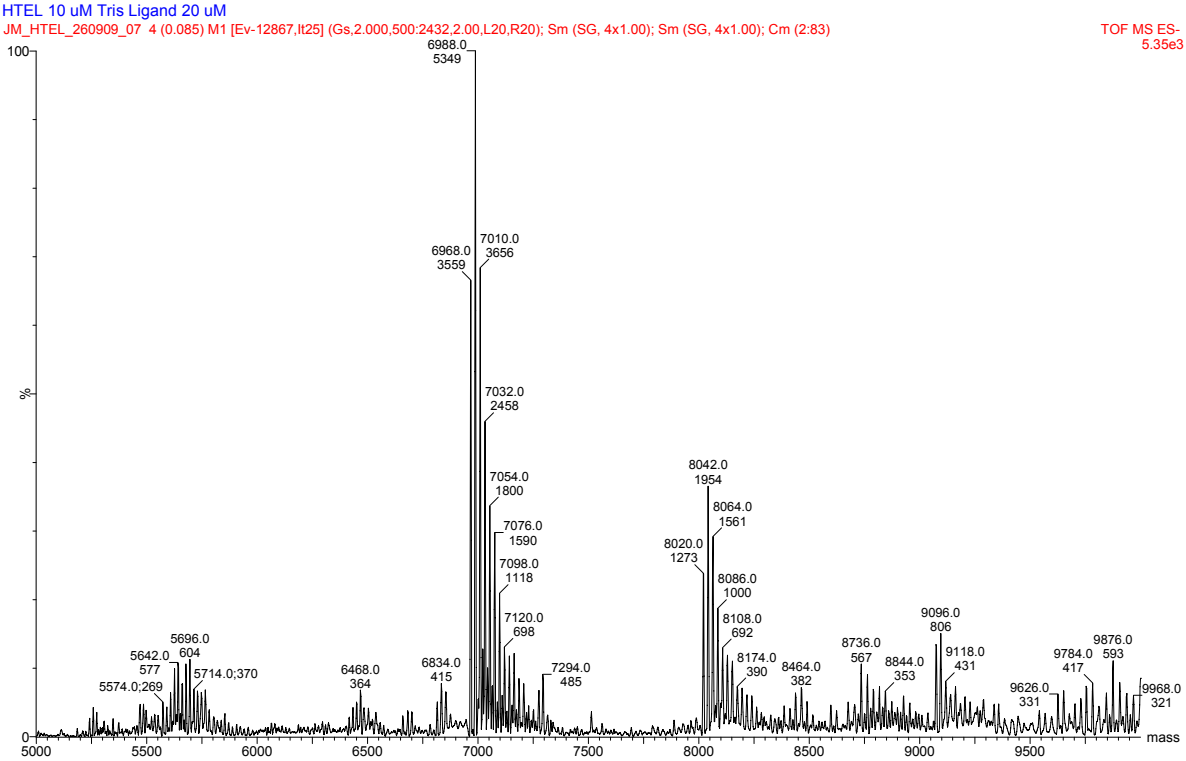
10 μM *h*-Tel + 12.5 μM ligand **28**



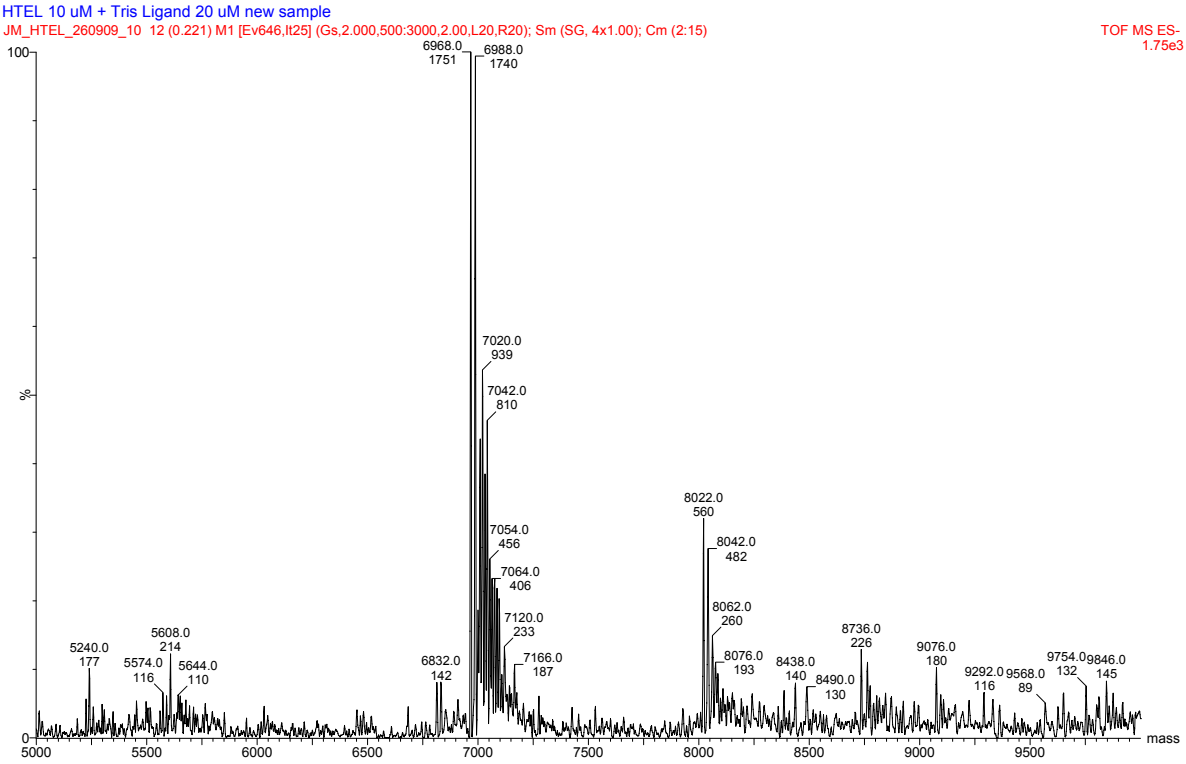
10 μM *h*-Tel + 15 μM ligand **28**



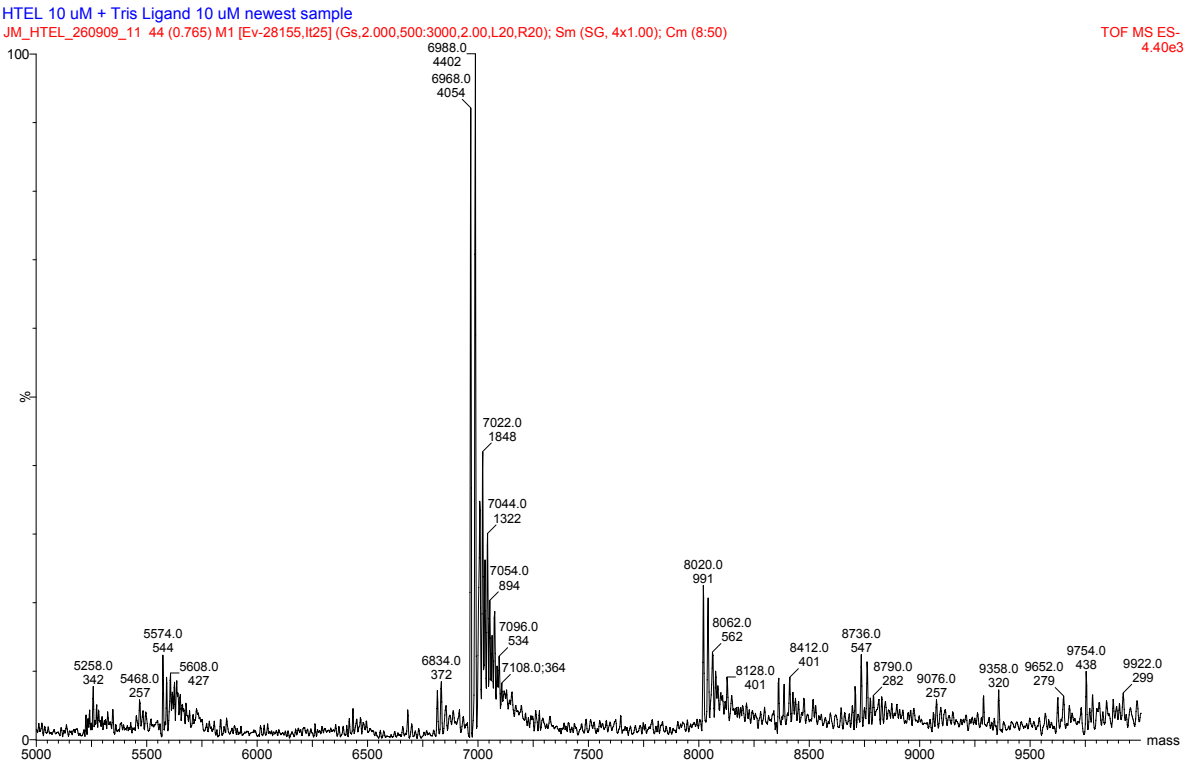
10 μM *h*-Tel + 20 μM ligand **28**



10 μM *h*-Tel + 20 μM ligand **28** Repeat



10 μM *h*-Tel + 10 μM ligand **28** Repeat



MS Plots

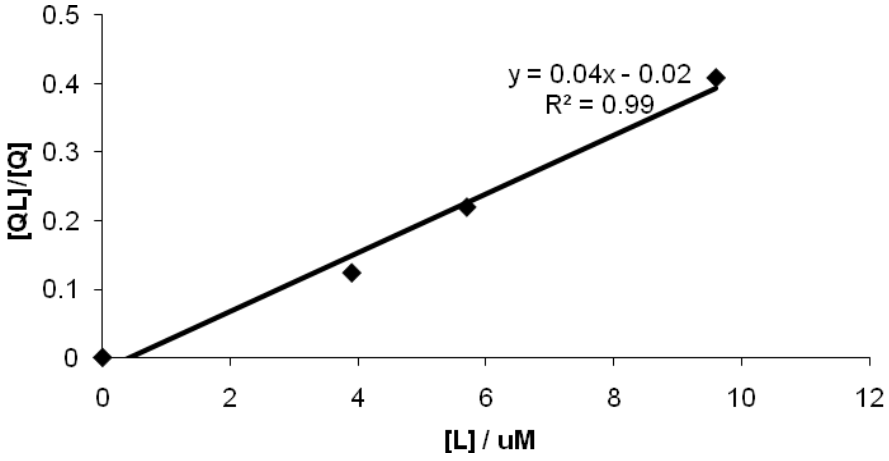


Fig. S1 Plot of G-quadruplex:**28** complex ([QL]) over free G-quadruplex concentration ([G]) vs concentration of **28** in solution ([L]), revealing a K_D of 23 μM (reciprocal of the slope) for the first binding event. Data derived from ESI-MS titration measurements.

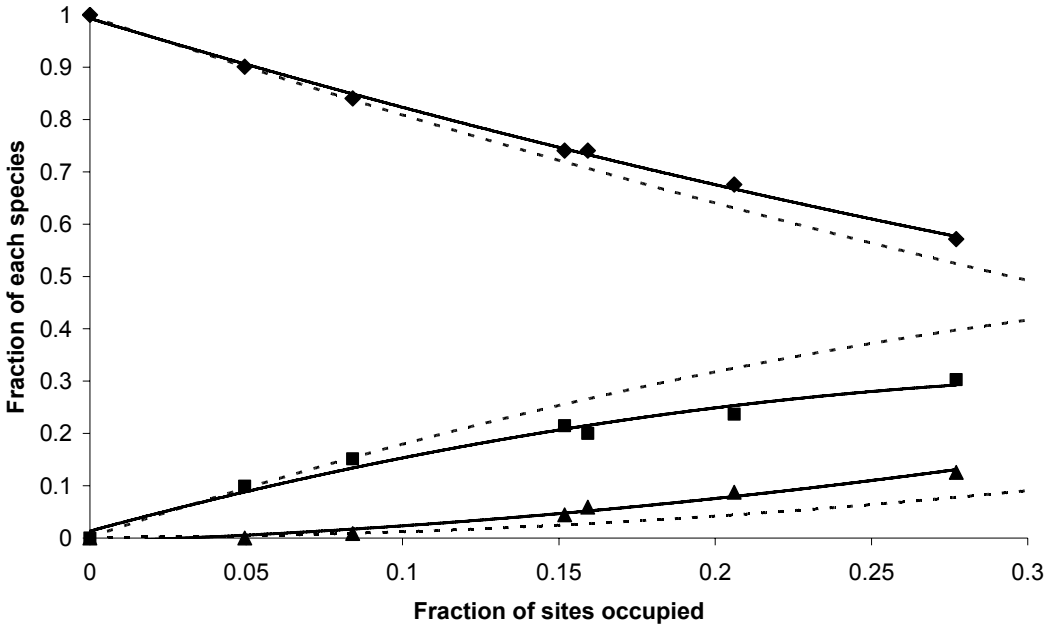


Fig. S2 A plot of fraction of each species (G-quadruplex = diamonds; G-quadruplex:**28** = squares; G-quadruplex:(**28**)$_2$ = triangles) *vs* fraction of sites occupied. Data derived from ESI-MS analysis of the G-quadruplex:**28** complex.

References

1) W. P. Cochrane, P. L. Pauson and T. S. Stevens, *J. Chem. Soc. C.,* 1968, 603.

2) Y. Song, E. K. Kohlmeir and T. J. Meade, *J. Am. Chem. Soc.,* 2008, **130**, 6662.