

Effects of turn-structure on folding and entanglement in artificial molecular overhand knots

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-Supporting Information-

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S1. ABBREVIATIONS

BCR backbone-to-crossing ratio; Bn benzyl; Boc *tert*-butoxycarbonyl; COSY correlation spectroscopy; DEPT distortionless enhancement by polarization transfer; DIPEA *N,N*-diisopropylethylamine; DMF *N,N*-dimethylformamide; DMSO dimethylsulfoxide; EDC 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide; HATU hexafluorophosphate azabenzotriazole tetramethyl uronium; HMBC heteronuclear multiple-bond correlation; HOBt hydroxybenzotriazole; HRMS high-resolution mass spectrometry; HSQC heteronuclear single quantum coherence; MALDI-TOF matrix assisted laser desorption/ionization time-of-flight; MeCN acetonitrile; NMR nuclear magnetic resonance; RT room temperature; THF tetrahydrofuran; TLC thin layer chromatography.

S2. GENERAL EXPERIMENTAL

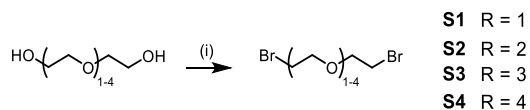
Unless stated otherwise, reagents were obtained from commercial sources and used without purification. Reactions were carried out in anhydrous solvents under an N₂ atmosphere. Anhydrous solvents were obtained by passing the solvent through an activated alumina column on a Phoenix SDS (solvent drying system; JC Meyer Solvent Systems, CA, USA). Compounds **S1**¹, **S2**², **S3**³, **S4**³, **S5**⁴, **S14**⁵, **S15**⁶, **S17**⁶, **S18**⁷, **S20**⁸, **A1**⁵, **A2**⁶, **2**⁶, **5**⁸ and **2**•[Lu]⁶ were synthesized as previously described. ¹H NMR spectra were recorded on a Bruker Avance III with an Oxford AS600 magnet equipped with a cryoprobe [5mm CPDCH ¹³C-¹H/D] (600 MHz) or a Bruker Ascend 500 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) from high-to-low frequency using the residual solvent peak as the internal reference (CDCl₃ = 7.26 ppm, (CD₃)₂SO = 2.50 ppm, CD₃CN = 1.94 ppm). All ¹H resonances are reported to the nearest 0.01 ppm. The multiplicity of ¹H signals are indicated as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad; app = apparent. Coupling constants (J) are quoted in Hz and reported to the nearest 0.1 Hz. Where appropriate, averages of the signals from peaks displaying multiplicity were used to calculate the value of the coupling constant. ¹³C NMR spectra were recorded on the same spectrometer with the central resonance of the solvent peak as the internal reference (CD₃CN = 118.26 ppm, CDCl₃ = 77.16 ppm, and (CD₃)₂SO = 39.52 ppm). All ¹³C resonances are reported to the nearest 0.01 ppm. DEPT, COSY, HSQC and HMBC experiments were used to aid structural determination and spectral assignment. Fully characterized compounds were chromatographically homogeneous. DOSY measurements were performed using the standard Bruker pulse program dstebpgp3s. Smoothed square gradients were used with a total duration of 1.6 ms. The gradient recovery delay was 200 μs, and diffusion time Δ = 10 ms was used for the experiments. Ten gradient increments were acquired, ranging from 5.9–53.2 G•cm⁻¹ in equal steps of gradient squared.

Microwave-assisted reactions were carried out using the CEM Focused Microwave™ Synthesis System, Discover® SP (CEM, North Carolina, USA). Flash column chromatography was carried out using Silica 60 Å (particle size 40–63 μm, Sigma Aldrich, UK) as the stationary phase. Size exclusion chromatography was carried out using Sephadex LH-20 (MeOH) and Bio-Beads SX-1 (CH₂Cl₂) as the stationary phase. TLC was performed on precoated silica gel plates (0.25 mm thick, 60 F₂₅₄, Merck, Germany) and visualized using both short and long wave ultraviolet light in combination with standard laboratory stains (basic potassium permanganate, acidic ammonium molybdate and ninhydrin). Low resolution ESI mass spectrometry was performed on a Thermo Scientific LCQ Fleet Ion Trap Mass Spectrometer or an Agilent Technologies 1200 LC system with either an Agilent 6130 single quadrupole MS detector or an Advion Expression LCMS single quadrupole MS detector. CD and UV/Vis

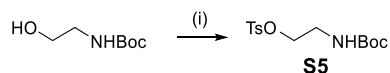
spectroscopy was measured on an Applied Photophysics Ltd Chirascan CD Spectrometer. High-resolution mass spectrometry (HRMS) and MALDI-TOF (matrix assisted laser desorption/ionization time-of-flight) was carried out by staff at the Mass Spectrometry Service, Department of Chemistry, The University of Manchester and the Mass Spectrometry Service, East China Normal University.

S3. REACTIONS SCHEMES

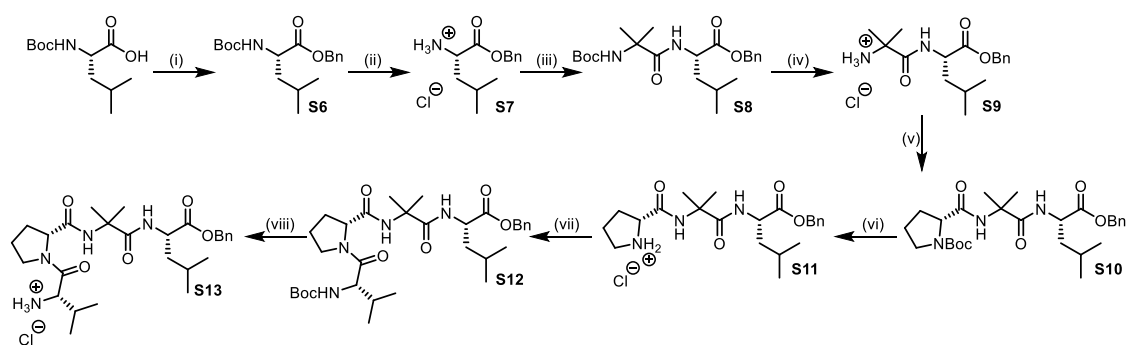
3.1. Synthesis of linkers



Scheme S1. Synthesis of polyethylene glycol linkers **S1-S4**. Reagents and conditions: CBr_4 , PPh_3 , THF, 0°C to RT, 16 h, 57% / 73% / 52% / 48% (for **S1/S2/S3/S4**).

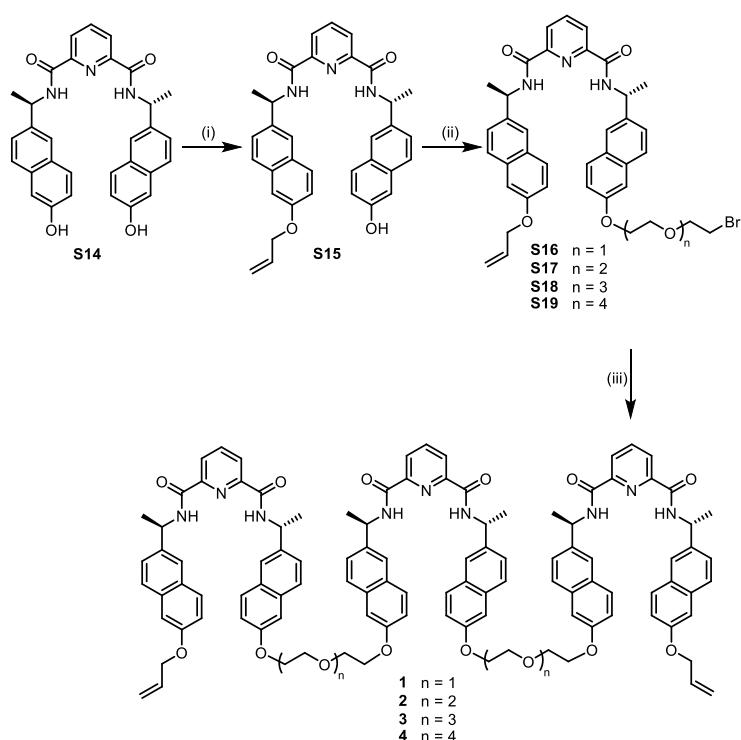


Scheme S2. Synthesis of intermediate linker **S5**. Reagents and conditions: (i) *p*-toluenesulfonyl chloride, NEt_3 , CH_2Cl_2 , RT, 3 h, 74%.

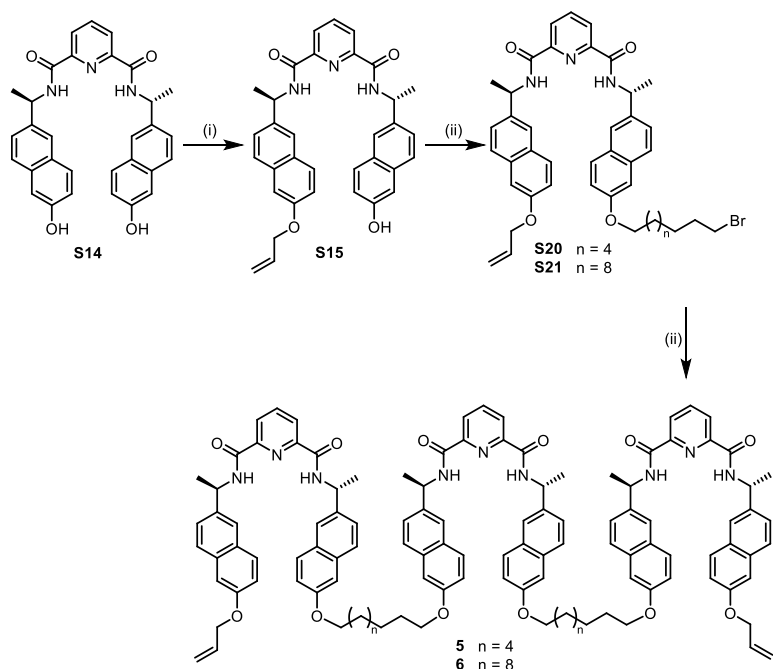


Scheme S3. Synthesis of tetrapeptide hairpin **S13**. Reagents and conditions: (i) BnBr , Cs_2CO_3 , DMF, 0°C to RT overnight, 72%; (ii) HCl (4 M), 1,4-dioxane, RT, 1 h; (iii) 2-(Boc-amino)isobutyric acid, $\text{HOBt} \cdot \text{H}_2\text{O}$, $\text{EDC} \cdot \text{HCl}$, DIPEA, CH_2Cl_2 , RT, 4 h, 86% over two steps; (iv) HCl (4 M), 1,4-dioxane, 1 h; (v) *N*-Boc-D-proline, HATU, DIPEA, RT, 2 h, 82% over two steps; (vi) HCl (4 M), 1,4-dioxane, RT, 1 h; (vii) *N*-Boc-L-valine, HATU, DIPEA, RT, 2 h, 82% over two steps; (viii) HCl (4 M), 1,4-dioxane, RT, 1 h, quant.

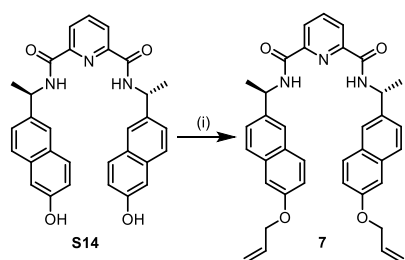
3.2 Synthesis of ligands 1-7



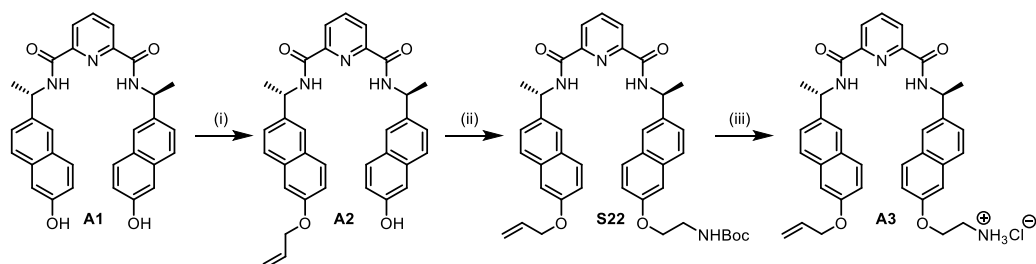
Scheme S4. Synthesis of tridentate ligands 1-4. Reagents and conditions: (i) allyl bromide, K_2CO_3 , DMF, $80^\circ C$, 2 h, 43%. (ii) **S1/S2/S3/S4**, K_2CO_3 , DMF, $80^\circ C$, 4 h (for **S16**, **S17**, **S18**) or RT, 16 h (**S19**), 42% / 73% / 49% / 72% (for **S16/S17/S18/S19**). (iii) **S14**, K_2CO_3 , DMF, $80^\circ C$, 16-24 h, 38% / 68% / 43% / 68% (for **1/2/3/4**).



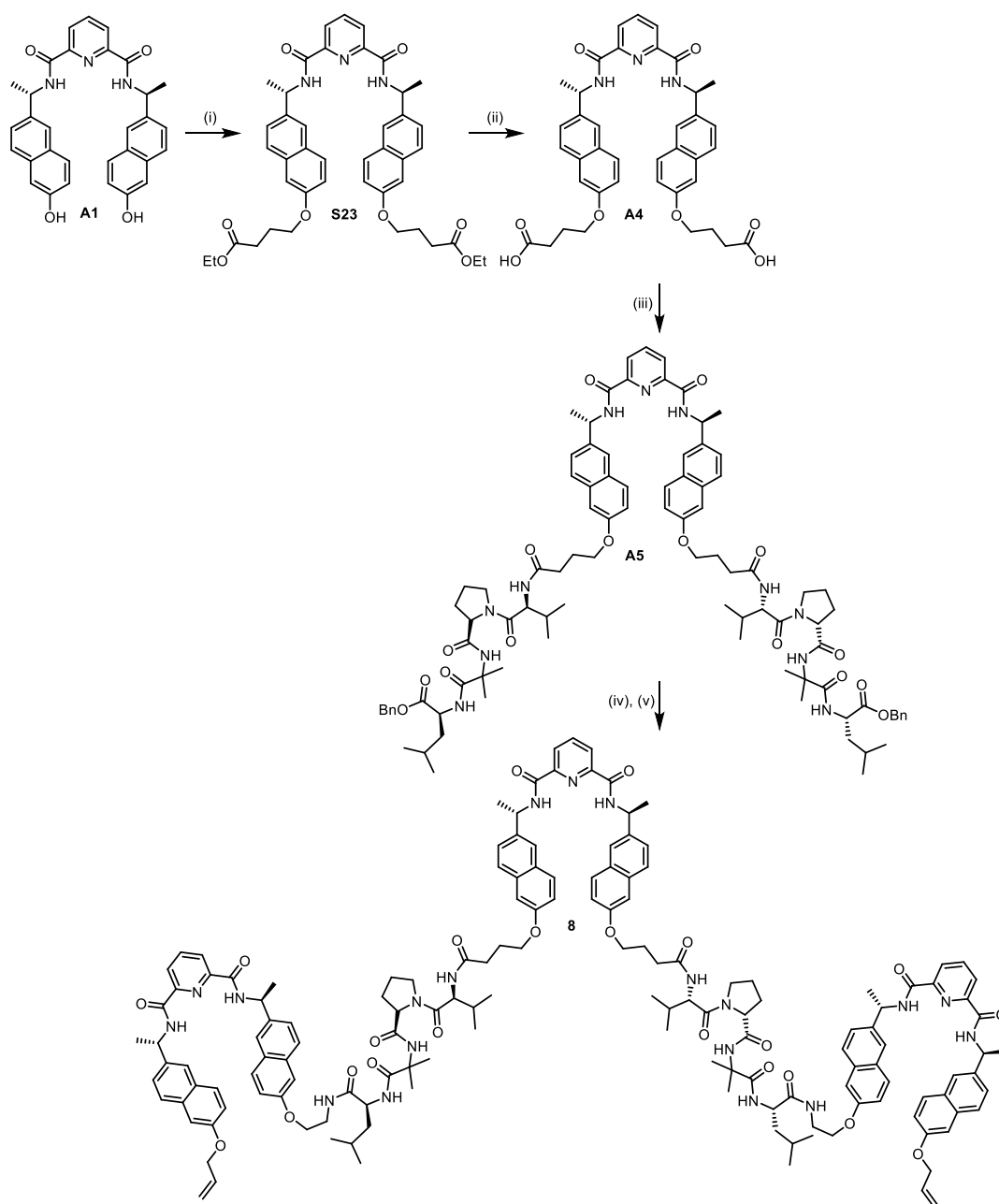
Scheme S5. Synthesis of tridentate ligands 5-6. Reagents and conditions: (i) allyl bromide, K_2CO_3 , DMF, $80^\circ C$, 2 h, 43%. (ii) 1,8-dibromo-octane or 1,12-dibromo-dodecane, K_2CO_3 , DMF, RT, 72h, 72% / 72% (for **S20/S21**). (iii) **S14**, K_2CO_3 , DMF, $80^\circ C$, 16 h, 52% / 74% (for **5/6**).



Scheme S6. Synthesis of ligand **7**. Reagents and conditions: (i) allyl bromide, K_2CO_3 , DMF, RT, 16 h, 63%.

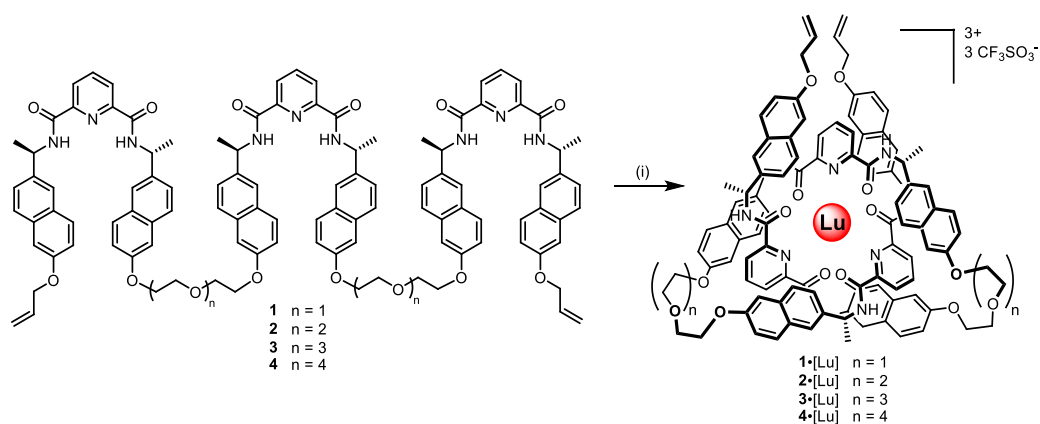


Scheme S7. Synthesis of amine-appended ligand intermediate **A3**. Reagents and conditions: (i) allyl bromide, K_2CO_3 , DMF, $80^\circ C$, 2 h, 43% or allyl bromide, NaOH (s, ground), DMF, $60^\circ C$, overnight, 46%. (ii) **S5**, Cs_2CO_3 , DMF, $80^\circ C$, 16 h, 98%. (iii) HCl (4 M), 1,4-dioxane, 1 h, quant.

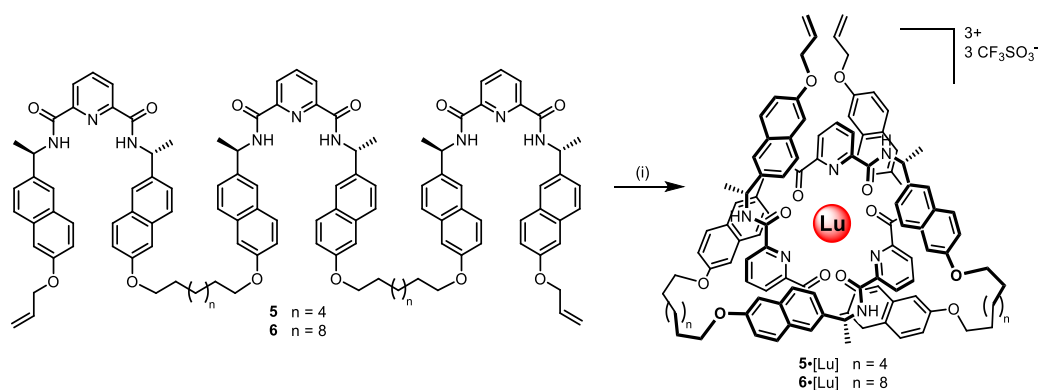


Scheme S8. Synthesis of metallopeptide ligand **8**. Reagents and conditions: (i) ethyl-4-bromobutyrate, Cs_2CO_3 , DMF, RT, overnight, 81%; (ii) NaOH, EtOH/H₂O/THF (1:1:1), 40 °C, 3 h; (iii) **S13**, HATU, DIPEA, DMF, 4 h, 67%; (iv) $\text{Pd}(\text{OH})_2/\text{C}$, MeOH, 35 °C, overnight; (v) **A3**, HATU, DIPEA, DMF, 5 h, 78%.

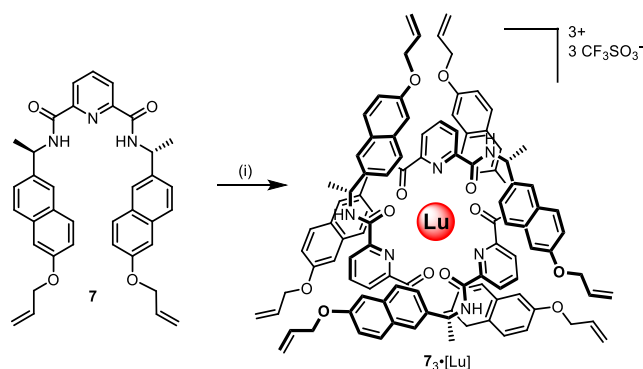
3.3 Synthesis of overhand knots and circular helicates



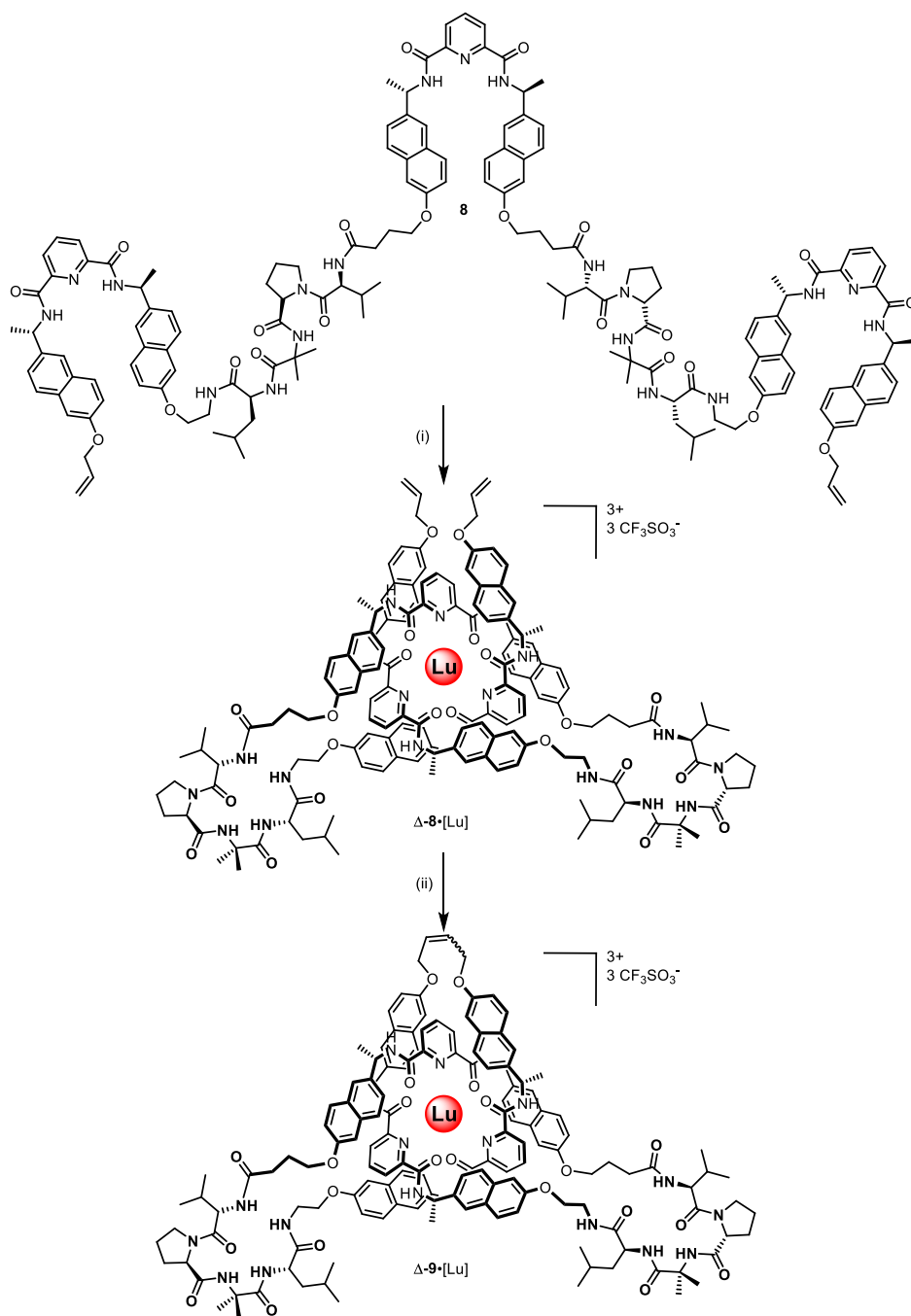
Scheme S9. Synthesis of overhand knots **1•[Lu]**, **2•[Lu]**, **3•[Lu]** and **4•[Lu]**. Reagents and conditions: $\text{Lu}(\text{CF}_3\text{SO}_3)_3$, MeCN, 80 °C, 16 h, 12% / 90% / 76% / 64% (for **1•[Lu]**/**2•[Lu]**/**3•[Lu]**/**4•[Lu]**).



Scheme S10. Synthesis of overhand knots **5•[Lu]** and **6•[Lu]**. Reagents and conditions: $\text{Lu}(\text{CF}_3\text{SO}_3)_3$, MeCN, 80 °C, 16 h, 53% / 52% (for **5•[Lu]**/**6•[Lu]**).



Scheme S11. Synthesis of circular helicate **7₃•[Lu]**. Reagents and conditions: (i) $\text{Lu}(\text{CF}_3\text{SO}_3)_3$, MeCN, RT, 16 h, 86%.



Scheme S12. Synthesis of metallopeptide overhand knot $8\bullet[\text{Lu}]$ and covalent capture conditions. Reagents and conditions: (i) $\text{Lu}(\text{CF}_3\text{SO}_3)_3$, MeCN , MW (80 W, 80 °C), 8 h, 97%. (ii) Hoveyda-Grubbs 2nd generation catalyst, $\text{CH}_2\text{Cl}_2/\text{MeNO}_2$ 3:2, 50 °C, 24 h, 90%.

S4. EXPERIMENTAL PROCEDURES

S4.1. Synthetic procedures and characterization

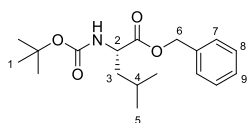
General method A for deprotection of *tert*-butoxycarbonyl (Boc) group:

The Boc-protected starting material was dissolved in a solution of hydrochloric acid in 1,4-dioxane (4.0 M) and the resulting mixture was left stirring at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure after diluting with dichloromethane and the crude product was carried through to the next step without further purification.

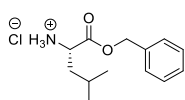
General method B for amino acid coupling:

A mixture of carboxylic acid and appropriate coupling reagents was stirred in CH₂Cl₂ or DMF for 10 min, after which the amine in CH₂Cl₂ was added. The resulting solution was stirred for 10 min followed by the dropwise addition of di-*isopropylethylamine* (DIPEA). The reaction mixture was left stirring at room temperature for the appropriate amount of time. The reaction mixture was diluted by CH₂Cl₂ and washed successively with citric acid (aq, 10%), sodium bicarbonate (sat. aq.) and brine. The combined organic phases were dried over sodium sulphate and concentrated under reduced pressure to give the crude product. Flash column chromatography, eluting with hexane and EtOAc in the appropriate ratio, was used to yield the pure products.

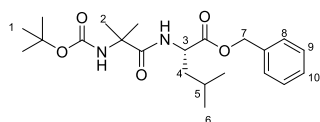
S6



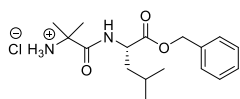
A solution of *N*-Boc-L-leucine (2.5 g, 10.03 mmol) and caesium carbonate (6.53 g, 20.06 mmol) in DMF (40 mL) was stirred at 0 °C for 1 h, after which benzyl bromide (1.78 mL, 15.04 mmol) was added. The resulting solution was left stirring at room temperature overnight after which it was concentrated under reduced pressure to give the crude product as a yellow oil. Flash column chromatography (hexane/EtOAc 7:1) yielded the pure compound **S6** as a colourless oil (2.31 g, 72%). **¹H NMR** (500 MHz, CDCl₃) δ = 7.38 – 7.31 (m, 5H, H_{7,8,9}), 5.19 (d, *J* = 12.5 Hz, 1H, H₆), 5.13 (d, *J* = 12.5 Hz, 1H, H₆), 4.89 (d, *J* = 8.9 Hz, 1H, *N*-H), 4.36 (td, *J* = 8.9, 5.2 Hz, 1H, H₂), 1.72 – 1.58 (m, 2H, H₃), 1.52 – 1.48 (m, 1H, H₄), 1.43 (s, 9H, H₁), 0.93 (d, *J* = 4.1 Hz, 3H, H₅), 0.91 (d, *J* = 4.1, 3H, H₅); **¹³C NMR** (126 MHz, CDCl₃) δ = 173.48, 155.54, 135.65, 128.69, 128.44, 128.30, 80.03, 67.02, 52.34, 41.87, 28.45, 24.91, 22.96, 22.10. **HRMS** (ESI⁺): Calcd. for C₁₈H₂₇NO₄Na⁺ 344.1828, found 344.1832 [M+Na]⁺.

S7

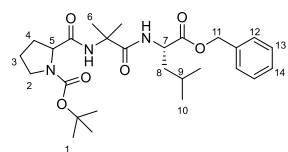
Using the general method A, the compound **S6** (2.31 g, 7.19 mmol) was converted into the title compound as a colourless solid. The crude compound was carried through to the next step without further purification.

S8

Using the general method B, the compound **S7** (1.85 g, 7.19 mmol) was converted into the title compound (2.51 g, 86%) as a colourless solid in the presence of 2-(Boc-amino)isobutyric acid (1.60 g, 7.91 mmol), HOBT·H₂O (1.16 g, 8.63 mmol), EDC·HCl (1.70 g, 8.63 mmol) and DIPEA (3.0 mL, 17.27 mmol). **¹H NMR** (500 MHz, CDCl₃) δ = 7.41-7.29 (m, 5H, H_{8,9,10}), 6.88 (m, 1H, *N-H*), 5.17 (d, *J* = 12.3, 1H, H₇), 5.12 (d, *J* = 12.3, 1H, H₇), 4.93 - 4.80 (m, 1H, *N-H*), 4.66-4.59 (m, 1H, H₃), 1.72 - 1.59 (m, 2H, H₄), 1.59 - 1.52 (m, 1H, H₅), 1.50 (app s, 3H, H₂), 1.45 (app s, 3H, H₂), 1.43 (app s, 9H, H₁), 0.92 (d, *J* = 6.2, 3H, H₆), 0.90 (d, *J* = 6.2, 3H, H₆); **¹³C NMR** (126 MHz, CDCl₃) δ = 174.48, 173.03, 154.73, 135.60, 128.70, 128.48, 128.36, 80.35, 67.08, 56.90, 51.02, 41.69, 28.39, 24.83, 23.03, 21.95. **HRMS** (ESI⁺): Calcd. for C₂₂H₃₅N₂O₅ 407.2536, found 407.2540 [M+H]⁺.

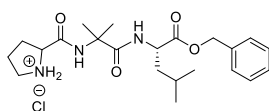
S9

Using the general method A, the compound **S8** (2.46 g, 3.61 mmol) was converted into the title compound as a white foam. The crude compound was carried through to the next step without further purification.

S10

Using the general method B, the compound **S9** (2.0 g, 5.85 mmol) was converted into the title compound (2.40 g, 82%) as a colourless solid by the addition of *N*-Boc-D-proline (1.26 g, 5.85 mmol), HATU (2.22 g, 5.85 mmol) and DIPEA (2.2 mL, 12.86 mmol). **¹H NMR** (500 MHz, CDCl₃) δ = 7.40 - 7.29 (m, 6H, H_{12,13,14,N-H}), 6.71 (s, 1H, *N-H*), 5.20 - 5.06 (m, 2H, H₁₁), 4.63 - 4.51 (m, 1H, H₇), 4.18 - 4.12 (m, 1H, H₅), 3.48 - 3.40 (m, 2H, H₂), 2.13 - 2.07 (m, 2H, H₄), 1.88 (dt, *J* = 12.2, 6.9, 2H, H₃), 1.74 - 1.61 (m, 5H, H_{6,8}), 1.55 (s, 3H, H₆), 1.46 (s, 9H, H₁), 1.43 (m, 1H, H₉), 0.90 (m, 6H, H₁₀); **¹³C NMR** (126 MHz, CDCl₃) δ = 174.29, 173.05, 171.54, 156.05, 135.87, 128.62, 128.28, 81.07, 66.81, 61.30, 57.28, 51.33, 47.40, 40.69, 28.47, 26.95, 24.81, 24.49, 23.11, 21.70. **HRMS** (ESI⁺): Calcd. for C₂₇H₄₂N₃O₆: 504.3068, found 504.3064 [M+H]⁺.

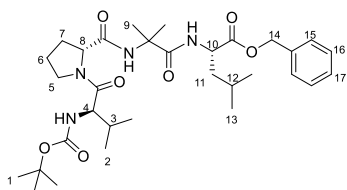
S11



purification.

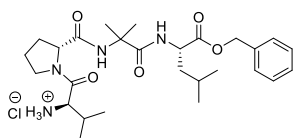
Using the general method A, the compound **S10** (2.40 g, 4.77 mmol) was converted into the title compound as a white foam. The crude compound was carried through to the next step without further

S12



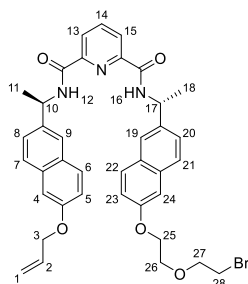
Using the general method B, the compound **S11** (2.0 g, 4.59 mmol) was converted into the title compound (2.27 g, 82%) as a colourless solid by the addition of *N*-Boc-L-valine (1.0 g, 4.59 mmol), HATU (1.75 g, 4.59 mmol) and DIPEA (1.8 mL, 10.1 mmol). **¹H NMR** (500 MHz, CDCl₃) δ = 7.36 – 7.31 (m, 5H, H_{15,16,17}), 7.23 - 7.19 (m, 1H, *N*-H), 6.73 (s, 1H, *N*-H), 5.41 (d, *J* = 8.5, 1H, *N*-H), 5.17 (d, *J* = 12.4, 1H, H₁₄), 5.10 (d, *J* = 12.4, 1H, H₁₄), 4.65 - 4.58 (m, 1H, H₁₀), 4.37 - 4.32 (m, 1H, H₈), 4.18 (dd, *J* = 8.6, 7.4, 1H, H₄), 3.93 - 3.86 (m, 1H, H₅), 3.62 - 3.53 (m, 1H, H₅), 2.29 - 2.19 (m, 1H, H₇), 2.13 - 2.06 (m, 1H, H₇), 2.04 - 1.94 (m, 3H, H_{3,6}), 1.70 - 1.61 (m, 2H, H₁₁), 1.58 - 1.56 (m, 1H, H₁₂), 1.50 (app s, 3H, H₉), 1.42 (app s, 3H, H₉), 1.42 (s, 9H, H₁), 0.97 (d, *J* = 6.7, 6H, H_{2/13}), 0.90 (d, *J* = 6.2, 6H, H_{2/13}); **¹³C NMR** (126 MHz, CDCl₃) δ = 174.12, 173.32, 172.57, 170.66, 156.14, 135.87, 128.63, 128.29, 79.92, 66.86, 61.19, 57.77, 57.43, 50.99, 47.67, 41.27, 30.75, 28.53, 28.42, 26.00, 25.52, 25.03, 24.89, 23.14, 21.88, 19.78, 18.02. **HRMS** (ESI⁺): Calcd. for C₃₂H₅₁N₄O₇: 603.3713, found 603.3748 [M+H]⁺.

S13

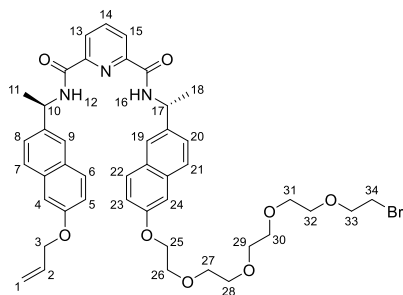


purification.

Using the general method A, the compound **S12** (1.01 g, 4.88 mmol) was converted into the title compound as a white foam. The crude compound was carried through to the next step without further

S16

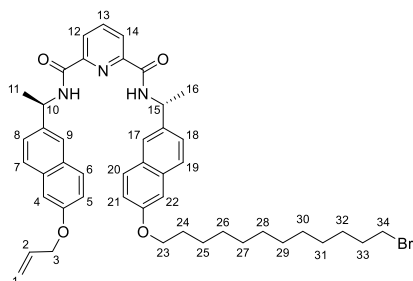
To a solution of **S15** (39 mg, 71.9 μ mol) and potassium carbonate (40 mg, 288 μ mol) in degassed DMF (2.5 mL) was added **S1** (66 mg, 288 μ mol). The solution was heated to 80 $^{\circ}$ C for 4 h after which it was concentrated under reduced pressure. Flash column chromatography (CH_2Cl_2 to $\text{CH}_2\text{Cl}_2/\text{EtOAc}$, 3:1) yielded the pure compound **S16** as a colourless solid (21 mg, 42 %). **^1H NMR** (600 MHz, CDCl_3) δ 8.38 (d, J = 7.8 Hz, 2H, $\text{H}_{13,15}$), 8.05 (t, J = 7.8 Hz, 1H, H_{14}), 7.89 (d, J = 8.1 Hz, 2H, $\text{H}_{12,16}$), 7.75 (s, 2H, $\text{H}_{9,19}$), 7.70 (d, J = 9.0 Hz, 2H, $\text{H}_{6,22}$), 7.66 (m, 2H, $\text{H}_{7,21}$), 7.45 (m, 2H, $\text{H}_{8,20}$), 7.21 (dd, J = 8.9, 2.5 Hz, 2H, $\text{H}_{5,23}$), 7.16 – 7.13 (m, 2H, $\text{H}_{4,24}$), 6.15 (ddt, J = 17.0, 10.5, 5.3 Hz, 1H, H_2), 5.53 – 5.43 (m, 3H, $\text{H}_{1(\text{trans}),10,17}$), 5.36 – 5.33 (m, 1H, $\text{H}_{1(\text{cis})}$), 4.69 – 4.65 (m, 2H, H_3), 4.32 – 4.27 (m, 2H, H_{25}), 4.00 – 3.97 (m, 2H, H_{26}), 3.94 (t, J = 6.3 Hz, 2H, H_{27}), 3.54 (t, J = 6.3 Hz, 2H, H_{28}), 1.68 (d, J = 6.8 Hz, 6H, $\text{H}_{11,18}$). **^{13}C NMR** (151 MHz, CDCl_3) δ 162.55, 156.88, 156.77, 148.81, 139.07, 137.97, 137.89, 133.90, 133.86, 133.05, 129.40, 128.91, 128.84, 127.58, 127.55, 125.16, 124.93, 124.90, 124.58, 119.51, 119.49, 117.89, 106.90, 106.69, 71.45, 69.64, 68.86, 67.49, 49.06, 30.23, 21.67, 21.62; Due to high degree of apparent symmetry, several ^{13}C signals overlap. **HRMS** (ESI $^{+}$): Calcd. for $\text{C}_{38}\text{H}_{38}\text{O}_5\text{BrN}_3\text{Na}$: 718.1887, found 718.1869 $[\text{M}+\text{Na}]^{+}$.

S19

To a solution of **S15** (33 mg, 0.06 mmol) and potassium carbonate (34 mg, 0.24 mmol) in degassed DMF (2.0 mL) was added **S4** (88 mg, 0.24 mmol). The solution was stirred at room temperature for 16 h after which it was concentrated under reduced pressure. Flash column chromatography (CH_2Cl_2 to EtOAc) yielded the pure compound **S19** as a colourless solid (36 mg, 72%). **^1H NMR** (600 MHz, CDCl_3) δ 8.39 (d, J = 7.8 Hz, 2H, $\text{H}_{13,15}$), 8.05 (t, J = 7.8 Hz, 1H, H_{14}), 7.88 (d, J = 8.1 Hz, 2H, $\text{H}_{12,16}$), 7.77 – 7.74 (m, 2H, $\text{H}_{9,19}$), 7.72 – 7.65 (m, 4H, $\text{H}_{6,7,21,22}$), 7.48 – 7.44 (m, 2H, $\text{H}_{8,20}$), 7.23 – 7.20 (m, 2H, $\text{H}_{5,23}$), 7.16 – 7.13 (m, 2H, $\text{H}_{4,24}$), 6.15 (ddt, J = 17.2, 10.6, 5.3 Hz, 1H, H_2), 5.53 – 5.43 (m, 3H, $\text{H}_{1(\text{trans}),10,17}$), 5.37 – 5.34 (m, 1H, $\text{H}_{1(\text{cis})}$), 4.70 – 4.65 (m, 2H, H_3), 4.28 (t, J = 4.9 Hz, 2H, H_{25}), 3.98 – 3.94 (m, 2H, H_{26}), 3.81 (t, J = 6.4 Hz, 2H, H_{33}), 3.80 – 3.78 (m, 2H, H_{27}), 3.74 – 3.72 (m, 2H, H_{32}), 3.70 – 3.68 (m, 4H, $\text{H}_{28,31}$), 3.68 (br s, 4H, $\text{H}_{29,30}$), 3.47 (t, J = 6.3 Hz, 2H, H_{34}), 1.71 – 1.67 (m, 6H, $\text{H}_{11,18}$); **^{13}C NMR** (151 MHz, CDCl_3) δ 162.54, 157.02, 156.76, 148.80, 139.09, 137.89, 137.87, 133.89, 133.04, 129.41, 129.35, 128.83, 127.56, 125.17, 124.92, 124.87, 124.59, 119.58, 119.52, 117.91, 106.86, 106.55, 71.19, 70.91, 70.67, 70.60, 70.54,

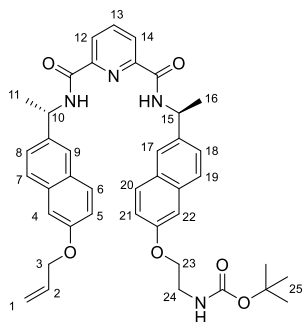
69.73, 68.85, 67.48, 49.06, 30.35, 21.67, 21.63; Due to high degree of apparent symmetry, several ^{13}C signals overlap; **HRMS** (ESI⁺): Calcd. for $\text{C}_{44}\text{H}_{50}\text{O}_8\text{BrN}_3\text{Na}$: 850.2673, found 850.2662 $[\text{M}+\text{Na}]^+$.

S21



To a solution of **S15** (136 mg, 0.25 mmol) and potassium carbonate (103 mg, 0.75 mmol) in degassed DMF (25 mL) was added 1,12-dibromododecane (245 mg, 0.75 mmol). The reaction was stirred for 3 days at room temperature, after which the mixture was concentrated under reduced pressure. Flash column chromatography (CH_2Cl_2 to $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 3:1) yielded the pure compound **S21** as a colourless solid (318 mg, 72 %). **^1H NMR** (600 MHz, CDCl_3) δ 8.38 (t, J = 7.4 Hz, 2H, $\text{H}_{12,14}$), 8.05 (t, J = 7.7 Hz, 1H, H_{13}), 7.88 (d, J = 8.0 Hz, 2H, $N\text{-H}$), 7.72 (s, 2H, $\text{H}_{9,17}$), 7.70 (d, J = 9.0 Hz, 1H, $\text{H}_{6/20}$), 7.66 (d, J = 8.9 Hz, 1H, $\text{H}_{6/20}$), 7.65 (m, 1H, $\text{H}_{7,19}$), 7.44 (m, 2H, $\text{H}_{8,18}$), 7.21 (dd, J = 2.5, 8.9 Hz, 1H, $\text{H}_{5/21}$), 7.16 (dd, J = 2.5, 8.9 Hz, 1H, $\text{H}_{5/21}$), 7.14 (m, 1H, $\text{H}_{4/22}$), 7.12 (m, 1H, $\text{H}_{4/22}$), 6.18 – 6.10 (m, 1H, H_2), 5.49 (m, 1H, $\text{H}_{1\text{trans}}$), 5.43 (q, J = 7.3 Hz, 2H, $\text{H}_{10,15}$), 5.34 (m, 1H, $\text{H}_{1\text{cis}}$), 4.66 (d, J = 5.3 Hz, 2H, H_3), 4.08 (t, J = 6.5 Hz, 2H, H_{23}), 3.42 (t, J = 6.8 Hz, 2H, H_{34}), 1.90 – 1.84 (m, 4H, $\text{H}_{24,33}$), 1.64 (d, J = 6.8 Hz, 6H, $\text{H}_{11,16}$), 1.56 – 1.49 (m, 2H, $\text{H}_{25,32}$), 1.48 - 1.30 (m, 12H, $\text{H}_{26,27,28,29,30,31}$); **^{13}C NMR** (151 MHz, CDCl_3) δ 162.89, 157.73, 157.12, 149.18, 149.16, 139.42, 138.24, 137.98, 134.37, 134.25, 133.39, 129.74, 129.62, 129.18, 129.03, 127.92, 127.83, 125.49, 125.23, 125.16, 124.93, 119.93, 119.86, 118.23, 107.23, 106.78, 69.21, 68.44, 49.43, 34.43, 33.18, 29.91, 29.89, 29.87, 29.78, 29.77, 29.60, 29.12, 28.52, 26.46, 22.00, 21.97. Due to high degree of apparent symmetry, several ^{13}C signals overlap. **HRMS** (ESI⁺): Calcd. for $\text{C}_{46}\text{H}_{55}\text{N}_3\text{O}_4\text{Br}$: 792.3370, found 792.3384 $[\text{M}+\text{H}]^+$.

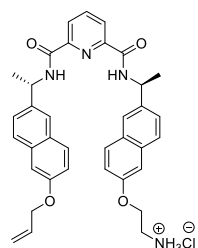
S22



To a stirred mixture of **A2** (190 mg, 0.35 mmol) and caesium carbonate (568 mg, 1.74 mmol) in degassed DMF (3 mL) was added **S5** (549 mg, 1.74 mmol) in degassed DMF (3 mL). The reaction mixture was stirred at 80 °C for 16 h, cooled to room temperature and diluted with EtOAc (15 mL). The resulting mixture was washed with lithium chloride (aq, 5%, 10 mL) and extracted with EtOAc (3 $\times$ 10 mL). The combined organics were dried over sodium sulphate and concentrated under reduced pressure to give the crude compound as a yellow oil. Flash column chromatography ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 5:1) yielded the pure compound **S22** as a colourless

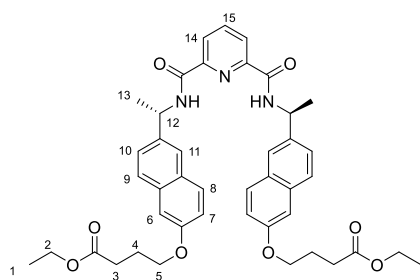
solid (236 mg, 98%). **¹H NMR** (500 MHz, CDCl₃) δ = 8.36 (d, J = 7.8, 2H, H_{12,14}), 8.03 (t, J = 7.8, 1H, H₁₃), 7.87 (d, J = 2.6, 1H, *N-H*), 7.85 (d, J = 2.6, 1H, *N-H*), 7.73 (m, 2H, H_{9,17}), 7.71 – 7.61 (m, 4H, H_{6,7,19,20}), 7.49 – 7.38 (m, 2H, H_{8,18}), 7.19 (dd, J = 8.9, 2.5, 1H, H_{5/21}), 7.15 (dd, J = 8.9, 2.5 Hz, 1H, H_{5/21}), 7.13 (d, J = 2.5, 1H, H_{4/22}), 7.09 (d, J = 2.5, 1H, H_{4/22}), 6.13 (m, 1H, H₂), 5.53 – 5.40 (m, 3H, H_{1trans,10,15}), 5.36 – 5.32 (m, 1H, H_{1cis}), 4.68 – 4.65 (m, 2H, H₃), 4.15 (t, J = 5.4, 2H, H₂₃), 3.64 – 3.58 (m, 2H, H₂₄), 1.67 (d, J = 6.9, 3H, H_{11/16}), 1.66 (d, J = 6.9, 3H, H_{11/16}), 1.46 (app s, 9H, H₂₅); **¹³C NMR** (126 MHz, CDCl₃) δ = 162.70, 156.93, 148.96, 139.24, 138.18, 138.04, 134.06, 133.19, 133.19, 129.61, 129.55, 129.00, 127.74, 127.71, 125.32, 125.08, 124.75, 124.72, 119.66, 119.35, 118.05, 107.06, 106.76, 79.75, 69.02, 67.42, 49.14, 40.66, 28.56, 21.76. Due to high degree of apparent symmetry, several ¹³C signals overlap. **HRMS** (ESI⁺): Calcd. for C₄₁H₄₄N₄O₆Na⁺: 711.3153, found 711.3146 [M+Na]⁺.

A3



Using the general method A, **S22** (50 mg, 0.073 mmol) was converted into the title compound as an off-white solid. The crude compound was carried through to the next step without further purification

S23

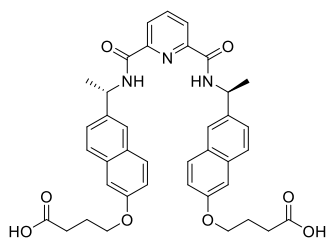


To a stirred solution of compound **A1** (311 mg, 0.62 mmol) and caesium carbonate (0.8 g, 2.46 mmol) in degassed DMF (8 mL) was added ethyl-4-bromobutyrate (0.2 mL, 1.35 mmol). The reaction mixture was stirred at room temperature overnight, after which it was diluted with EtOAc (15 mL). The resulting solution was washed with lithium chloride (aq, 5%, 10 mL) and extracted with EtOAc (3 × 15 mL). The combined

organics were dried over sodium sulphate and concentrated under reduced pressure to give the crude compound as a yellow oil. Flash column chromatography (CH₂Cl₂/EtOAc 5:1) yielded the pure compound **S23** as a white solid (366 mg, 81%). **¹H NMR** (500 MHz, CDCl₃) δ = 8.35 (d, J = 7.8, 2H, H₁₄), 8.02 (t, J = 7.8, 1H, H₁₅), 7.91 – 7.86 (m, 2H, *N-H*), 7.72 (d, J = 1.7, 2H, H₁₁), 7.67 (d, J = 9.0, 2H, H₈), 7.65 (d, J = 9.0, 2H, H₉), 7.43 (dd, J = 8.5, 1.8, 2H, H₁₀), 7.14 (dd, J = 8.9, 2.5 Hz, 2H, H₇), 7.10 (d, J = 2.5, 2H, H₆), 5.44 (quintet, J = 7.0 Hz, 2H, H₁₂), 4.20 – 4.11 (m, 8H, H_{2,5}), 2.56 (t, J = 7.3, 4H, H₃), 2.18 (quintet, J = 7.3, 4H, H₄), 1.67 – 1.62 (m, 6H, H₁₃), 1.26 (t, J = 7.1, 6H, H₁); **¹³C NMR** (126 MHz, CDCl₃) δ = 173.35, 162.70, 157.19, 148.96, 139.20, 138.98, 134.08, 129.48, 128.92, 127.66, 125.03, 124.71, 119.55,

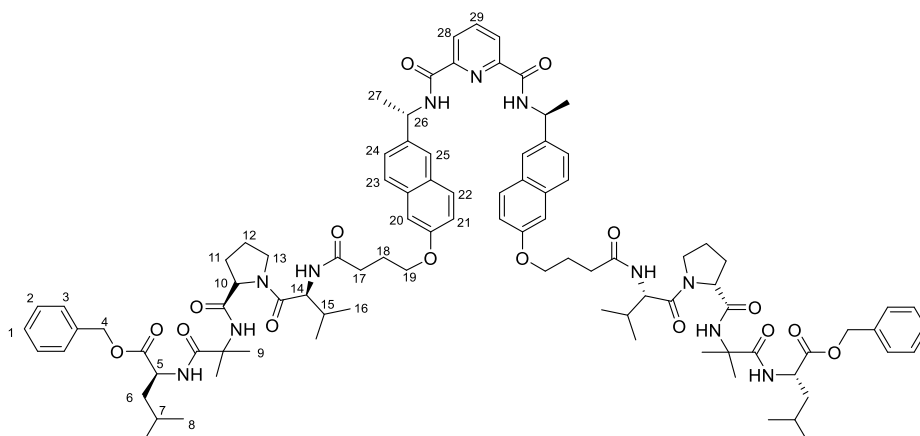
106.65, 66.96, 60.63, 49.17, 31.01, 24.77, 21.78, 14.39. **HRMS** (ESI+): Calcd. for $C_{43}H_{47}N_3O_8Na^+$: 756.3255, found 756.3249 $[M+Na]^+$.

A4



A mixture of **S23** (366 mg, 0.50 mmol) and sodium hydroxide (80 mg, 2.0 mmol) was stirred in THF (6 mL), EtOH (6 mL) and H₂O (6 mL) at 40 °C for 3 h. The reaction mixture was concentrated under reduced pressure and the resulting solid was dissolved in H₂O (25 mL). The solution was washed with hexane (30 mL) and acidified with hydrochloric acid (aq, 2.0 M, 25 mL). The aqueous phase was extracted with ethyl acetate (3×40 mL). The combined organic layers were dried over sodium sulphate and concentrated under reduced pressure to give the title compound as a colourless solid, which was carried through crude to the next step without further purification. **HRMS** (ESI+): Calcd. for $C_{39}H_{39}N_3O_8Na^+$: 700.2629, found 700.2623 $[M+Na]^+$.

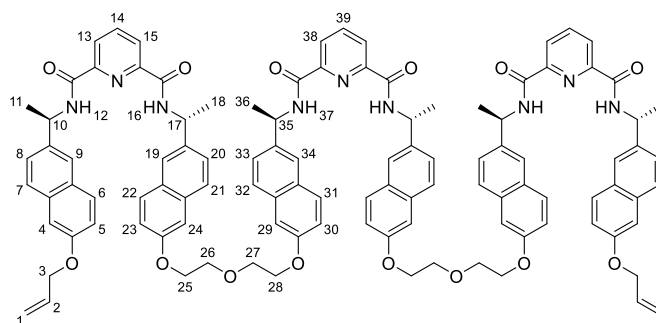
A5



To a stirred solution of **A4** (100 mg, 0.148 mmol) and HATU (128.7 mg, 0.302 mmol) in DMF (2 mL) was added **S13** (178 mg, 0.330 mmol) in DMF (2 mL) and DIPEA (0.1 mL, 0.518 mmol). The reaction mixture was stirred at room temperature for 4 hours, after which the reaction mixture was diluted with EtOAc (10 mL). The solution was washed with lithium chloride (aq., 5%, 5 mL) and extracted with EtOAc (3 ×10 mL). The combined organics were washed with lithium chloride (aq., 5%, 5 mL), dried over sodium sulphate and concentrated under reduced pressure to give the crude product as a yellow oil. Flash column chromatography (CH₂Cl₂/EtOAc 4:1) yielded the pure compound **A5** as a colourless solid (161 mg, 67%). **¹H NMR** (500 MHz, CDCl₃) δ = 8.36 (d, J = 7.8, 2H, H₂₈), 8.03 (t, J = 7.8, 1H, H₂₉), 7.87 (dd, J = 7.9, 2H, $N-H$), 7.72 (d, J = 1.7, 2H, H₂₅), 7.65 (d, J = 8.6, 4H, H_{22,23}), 7.44 (dd, J = 8.6, 1.5, 2H,

H₂₄), 7.31 – 7.23 (m, 12H, H_{1,2,3,N-H}), 7.13 - 7.08 (m, 4H, H_{20,21}), 6.56 - 6.52 (m, 2H, *N-H*), 6.48 (s, 2H, *N-H*), 5.44 (quintet, *J* = 7.1, 2H, H₂₆), 5.10 (d, *J* = 12.5, 2H, H₄), 5.03 (d, *J* = 12.5, 2H, H₄), 4.65 - 4.59 (m, 2H, H₅), 4.32 - 4.24 (m, 4H, H_{10,14}), 4.11 - 4.01 (m, 6H, H_{13,19}), 3.65 - 3.56 (m, 2H, H₁₃), 2.50 (t, *J* = 7.4, 4H, H₁₇), 2.19 – 1.93 (m, 14H, H_{11,12,15,18}), 1.77 – 1.69 (m, 4H, H₆), 1.67 - 1.63 (m, 6H, H₂₇), 1.61-1.57 (m, 2H, H₇), 1.55 (s, 6H, H₉), 1.44 (s, 6H, H₉), 0.97 (d, *J* = 6.7, 6 H, H₁₆), 0.95 (d, *J* = 6.7, 6H, H₁₆), 0.91-0.87 (m, 12H, H₈); ¹³C NMR (126 MHz, CDCl₃) δ = 174.53, 173.91, 173.87, 172.08, 170.84, 162.70, 157.15, 148.97, 139.23, 138.05, 134.09, 129.51, 128.95, 128.60, 128.24, 127.93, 127.67, 125.35, 125.01, 124.71, 119.46, 106.74, 67.14, 66.71, 61.77, 57.47, 51.04, 49.16, 47.93, 40.97, 32.53, 30.32, 29.27, 29.17, 26.78, 25.20, 25.08, 24.97, 24.78, 23.20, 21.87, 21.69, 19.34, 18.91. Due to the apparent symmetry, two ¹³C signals overlap. HRMS (ESI⁺): Calcd. for C₉₃H₁₂₀N₁₁O₁₆: 1646.8870, found 1646.8884 [M+H]⁺.

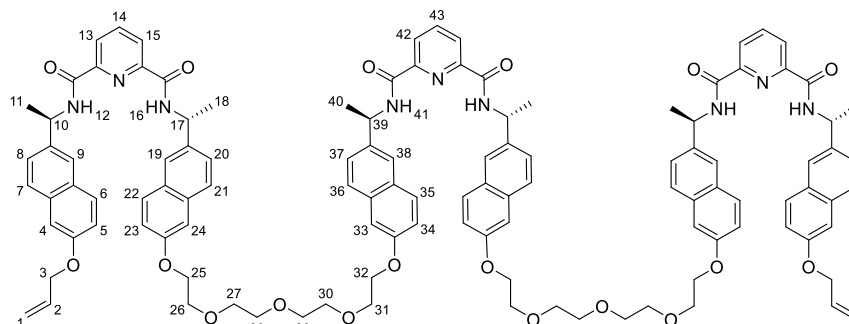
1



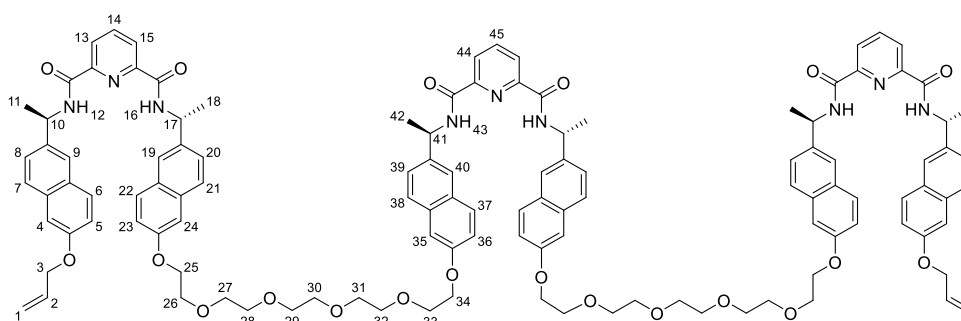
To a solution of **S16** (21 mg, 0.03 mmol) and potassium carbonate (4.2 mg, 0.03 mmol) in degassed DMF (3.0 mL) was added **S14** (7.6 mg, 0.015 mmol). The solution was stirred at 80 °C for 24 h after which the mixture was concentrated under reduced pressure. Flash column chromatography (CH₂Cl₂/EtOAc, 2:1 to CH₂Cl₂/CH₃OH, 20:1) followed by size exclusion chromatography (Bio-Beads SX-1, CH₂Cl₂) yielded the pure compound **1** as a colourless solid (10 mg, 38%). ¹H NMR (600 MHz, CDCl₃) δ 8.37 – 8.30 (m, 6H, H_{13,15,38}), 8.02 – 7.94 (m, 9H, H_{12,14,16,37,39}), 7.69 – 7.66 (m, 6H, H_{9,19,34}), 7.66 – 7.61 (m, 12H, H_{6,7,21,22,31,32}), 7.44 - 7.39 (m, 6H, H_{8,20,33}), 7.20 – 7.14 (m, 6H, H_{5,23,30}), 7.13 – 7.10 (m, 6H, H_{4,24,29}), 6.14 (ddt, *J* = 17.2, 10.6, 5.3 Hz, 2H, H₂), 5.52 - 5.32 (m, 10H, H_{1(trans),1(cis),10,17,35}), 4.68 - 4.65 (m, 4H, H₃), 4.33 - 4.28 (m, 8H, H_{25,28}), 4.07 – 4.01 (m, 8H, H_{26,27}), 1.63 (d, *J* = 6.8 Hz, 6H, H_{11/18/36}), 1.57 (d, *J* = 6.8 Hz, 6H, H_{11/18/36}), 1.54 (d, *J* = 6.8 Hz, 6H, H_{11/18/36}); ¹³C NMR (151 MHz, CDCl₃) δ 162.64, 162.63, 156.93, 156.92, 156.71, 148.76, 148.73, 138.96, 138.93, 137.95, 137.94, 137.93, 133.81, 133.05, 129.33, 129.30, 128.82, 128.76, 127.50, 127.46, 125.12, 125.02, 124.49, 124.47, 119.51, 119.49, 119.47, 117.88, 106.85, 106.68, 106.66, 70.01, 68.84, 67.53, 48.93, 48.90, 48.88, 21.48, 21.43, 21.40; Due to high degree of apparent symmetry, several ¹³C

signals overlap; **HRMS** (ESI⁺): Calcd. for C₁₀₇H₁₀₁O₁₄N₉Na: 1758.7360, found 1758.7388 [M+Na]⁺.

3



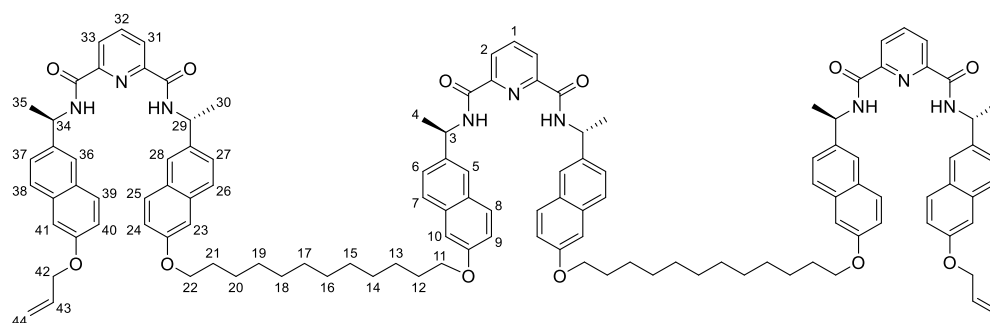
To a solution of **S18** (50 mg, 0.064 mmol) and potassium carbonate (8.8 mg, 0.064 mmol) in degassed DMF (3.2 mL) was added **S14** (61 mg, 0.032 mmol). The solution was stirred at 80 °C for 16 h after which the mixture was concentrated under reduced pressure. Flash column chromatography (EtOAc to CH₂Cl₂/CH₃OH, 20:1) followed by size exclusion chromatography (Bio-Beads SX-1, CH₂Cl₂) yielded the pure compound **3** as a colourless solid (26 mg, 43%). **¹H NMR** (600 MHz, CDCl₃) δ 8.33 (d, *J* = 7.7 Hz, 2H, H_{13/15/42}), 8.33 (d, *J* = 7.7 Hz, 2H, H_{13/15/42}), 8.29 (d, *J* = 7.8 Hz, 2H, H_{13/15/42}), 8.05 – 7.99 (m, 6H, H_{12,16,41}), 7.97 (t, *J* = 7.7 Hz, 2H, H₁₄), 7.93 (t, *J* = 7.8 Hz, 1H, H₄₃), 7.69 – 7.59 (m, 18H, H_{6,7,9,19,21,22,35,36,38}), 7.43 – 7.37 (m, 6H, H_{8,20,37}), 7.20 – 7.14 (m, 6H, H_{5,23,34}), 7.11 – 7.07 (m, 6H, H_{4,24,33}), 6.14 (ddt, *J* = 17.3, 10.5, 5.3 Hz, 2H, H₂), 5.51 – 5.47 (m, 2H, H_{1(trans)}), 5.46 – 5.32 (m, 8H, H_{1(cis),10,17,39}), 4.68 – 4.64 (m, 4H, H₃), 4.23 (t, *J* = 4.8 Hz, 8H, H_{25,32}), 3.92 (t, *J* = 4.8 Hz, 8H, H_{26,31}), 3.78 – 3.75 (m, 8H, H_{27,30}), 3.74 – 3.71 (m, 8H, H_{28,29}), 1.62 (d, *J* = 6.9 Hz, 6H, H₁₁), 1.56 – 1.52 (m, 12H, H_{18,40}); **¹³C NMR** (151 MHz, CDCl₃) δ 162.70, 162.69, 156.95, 156.93, 156.69, 148.74, 148.71, 148.68, 138.86, 138.81, 137.96, 133.79, 133.76, 133.07, 129.30, 129.27, 129.24, 128.76, 128.72, 127.44, 127.42, 127.41, 125.08, 125.06, 125.03, 125.01, 124.44, 124.42, 119.48, 119.44, 117.86, 106.82, 106.56, 70.87, 70.71, 69.71, 68.83, 67.45, 48.84, 48.79, 21.49, 21.40, 21.38; Due to high degree of apparent symmetry, several ¹³C signals overlap; **HRMS** (ESI⁺): Calcd. for C₁₁₅H₁₁₇O₁₈N₉Na: 1934.8409, found 1934.8364 [M+Na]⁺.



To a solution of **S19** (34 mg, 0.04 mmol) and potassium carbonate (5.7 mg, 0.04 mmol) in degassed DMF (4.0 mL) was added **S14** (10.4 mg, 0.02 mmol). The solution was stirred at 80 °C for 16 h after which the mixture was concentrated under reduced pressure. Flash column chromatography (EtOAc to CH₂Cl₂/CH₃OH, 20:1) followed by size exclusion chromatography (Bio-Beads SX-1, CH₂Cl₂) yielded the pure compound **4** as a colourless solid (28 mg, 68%).

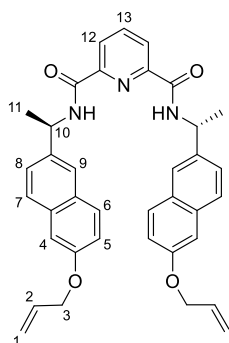
¹H NMR (600 MHz, CDCl₃) δ 8.34 - 8.31 (m, 4H, H_{13/15/44}), 8.29 (d, *J* = 7.8 Hz, 2H, H_{13/15/44}), 8.06 – 7.99 (m, 6H, H_{12,16,43}), 7.98 (t, *J* = 7.8 Hz, 2H, H₁₄), 7.93 (t, *J* = 7.8 Hz, 1H, H₄₅), 7.69 – 7.59 (m, 18H, H_{6,7,9,19,21,22,37,38,40}), 7.44 – 7.39 (m, 6H, H_{8,20,39}), 7.21 – 7.14 (m, 6H, H_{5,23,36}), 7.12 – 7.07 (m, 6H, H_{4,24,35}), 6.14 (ddt, *J* = 17.1, 10.6, 5.3 Hz, 2H, H₂), 5.51 - 5.47 (m, 2H, H_{1(trans)}), 5.46 – 5.37 (m, 6H, H_{10,17,41}), 5.36 – 5.32 (m, 2H, H_{1(cis)}), 4.68 - 4.64 (m, 4H, H₃), 4.23 (t, *J* = 4.3 Hz, 8H, H_{25,34}), 3.92 (t, *J* = 4.8 Hz, 8H, H_{26,33}), 3.77 – 3.73 (m, 8H, H_{27,32}), 3.71 – 3.69 (m, 8H, H_{28,31}), 3.68 (br s, 8H, H_{29,30}), 1.61 (d, *J* = 6.8 Hz, 6H, H₁₁), 1.57 – 1.53 (m, 12H, H_{18,42});

¹³C NMR (151 MHz, CDCl₃) δ 162.63, 162.61, 156.97, 156.95, 156.71, 148.76, 148.70, 138.95, 138.88, 137.93, 137.91, 133.83, 133.80, 133.06, 129.33, 129.29, 129.26, 128.79, 128.76, 127.48, 127.47, 127.44, 125.11, 125.07, 124.99, 124.95, 124.48, 124.45, 119.51, 119.49, 119.46, 117.86, 106.84, 106.55, 70.89, 70.66, 69.70, 68.83, 67.46, 48.92, 48.88, 48.84, 21.57, 21.48, 21.45; Due to high degree of apparent symmetry, several ¹³C signals overlap; **HRMS** (ESI⁺): Calcd. for C₁₁₉H₁₂₅O₂₀N₉Na₂: 1022.9413, found 1022.9395 [M+2Na]⁺.



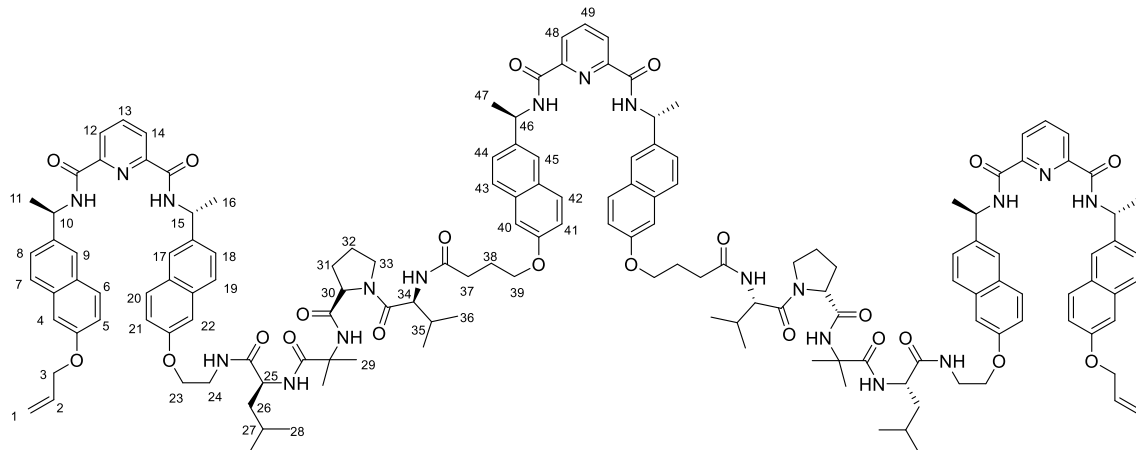
To a solution of **S21** (69 mg, 0.087 mmol) and potassium carbonate (60 mg, 0.43 mmol) in degassed DMF (8.7 mL) was added **S14** (22 mg, 0.043 mmol). The reaction was stirred for 16 hours at 80 °C. The mixture was allowed to cool to room temperature and concentrated under reduced pressure. Flash column chromatography (EtOAc to CH₂Cl₂/MeOH 9:1) yielded the pure compound **6** as a colourless solid (47 mg, 74 %). **¹H NMR** (600 MHz, CDCl₃) δ 8.36 – 8.32 (m, 6H, H_{2,31,33}), 8.02 – 7.94 (m, 9H, *N-H*, H_{1,32}), 7.72 – 7.67 (m, 6H, H_{5,28,36}), 7.65 – 7.60 (m, 12H, H_{7,8,25,26,38,39}), 7.44 – 7.39 (m, 6H, H_{6,27,37}), 7.21 – 7.14 (m, 6H, H_{9,24,40}), 7.12 – 7.08 (m, 6H, H_{10,23,41}), 6.19 – 6.10 (m, 2H, H₄₃), 5.49 (m, 2H, H_{44trans}), 5.47 – 5.39 (m, 6H, H_{3,29,34}), 5.35 (m, 2H, H_{44cis}), 4.67 (d, *J* = 5.3 Hz, 4H, H₄₂), 4.10 – 4.06 (m, 8H, H_{11,22}), 1.89 – 1.83 (m, 8H, H_{12,21}), 1.65 – 1.57 (m, 18H, H_{4,30,35}), 1.55 – 1.48 (m, 8H, H_{13,20}), 1.43 – 1.37 (m, 24H, H_{14,15,16,17,18,19}); **¹³C NMR** (151 MHz, CDCl₃) δ 162.94, 157.68, 157.07, 149.14, 149.10, 139.32, 138.26, 138.02, 134.32, 134.18, 133.39, 129.69, 129.58, 129.12, 128.98, 127.85, 127.78, 125.46, 125.44, 125.29, 125.22, 125.20, 124.86, 119.89, 119.82, 118.22, 107.19, 106.75, 69.19, 68.40, 49.31, 29.91, 29.89, 29.73, 29.57, 26.44, 21.91, 21.89, 21.87. Due to high degree of apparent symmetry many ¹³C signals overlap. **HRMS** (ESI⁺): Calcd. for C₁₂₃H₁₃₄N₉O₁₂: 1930.0180, found 1930.0123 [M+H]⁺.

7



To a solution of **S14** (65 mg, 0.13 mmol) and potassium carbonate (88 mg, 0.64 mmol) in degassed DMF (13 mL) was added allyl bromide (32 μ L, 0.38 mmol). The reaction was stirred for 16 h at room temperature, after which the mixture was concentrated under reduced pressure. Flash column chromatography ($\text{CH}_2\text{Cl}_2/\text{EtOAc}$ 3:1) yielded the pure compound **7** as a colourless solid (47 mg, 63 %). ^1H NMR (600 MHz, CDCl_3) δ 8.37 (d, J = 7.8 Hz, 2H, H_{12}), 8.04 (t, J = 7.8 Hz, 1H, H_{13}), 7.85 (d, J = 8.1 Hz, 2H, $N\text{-H}$), 7.74 (s, 2H, H_9), 7.69 (d, J = 8.9 Hz, 2H, H_6), 7.64 (d, J = 8.5 Hz, 2H, H_7), 7.44 (dd, J = 1.9, 8.5 Hz, 2H, H_8), 7.20 (dd, J = 2.5, 8.9 Hz, 2H, H_5), 7.13 – 7.12 (m, 2H, H_4), 6.18 – 6.10 (m, 2H, H_2), 5.84 (m, 2H, $\text{H}_{1\text{trans}}$), 5.44 (quintet, J = 7.3 Hz, 2H, H_{10}), 5.34 (m, 2H, $\text{H}_{1\text{cis}}$), 4.68 – 4.66 (m, 4H, H_3), 1.67 (d, J = 6.9 Hz, 6H, H_{11}); ^{13}C NMR (151 MHz, CDCl_3) δ 162.80, 157.02, 149.06, 139.31, 138.13, 134.14, 133.28, 129.64, 129.08, 127.80, 125.40, 125.14, 124.83, 119.76, 118.13, 107.13, 69.10, 49.31, 21.87. Due to high degree of apparent symmetry many ^{13}C signals overlap. HRMS (ESI $^-$): Calcd. for $\text{C}_{37}\text{H}_{36}\text{N}_3\text{O}_4$: 586.2700, found 586.2700 $[\text{M}+\text{H}]^+$

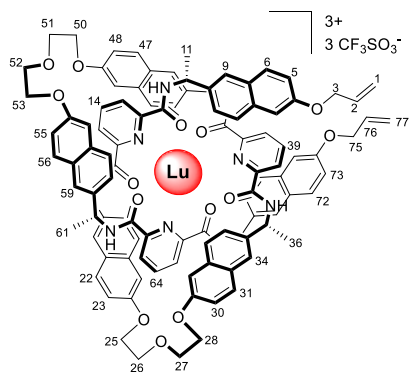
8



The compound **A5** (253 mg, 0.15 mmol) and $\text{Pd}(\text{OH})_2$ on carbon (35 wt%) were stirred overnight in MeOH (10 mL) at 35 $^\circ\text{C}$ under an atmosphere of H_2 . The reaction mixture was filtered through Celite $^\circ$ and concentrated under reduced pressure to give the deprotected peptide as a colourless solid, which was carried through crude to the next step without further purification. To a stirred solution of the crude product and HATU (118 mg, 0.31 mmol) in DMF (4 mL) was added **A3** (222.6 mg, 0.36 mmol) in DMF (4 mL), followed by DIPEA (112 μ L, 0.64 mmol). The reaction mixture was left stirring at room temperature for 5 hours, after which the mixture was diluted with ethyl acetate (10 mL). The suspension was washed with lithium chloride (aq 5%, 5 mL). and extracted with fresh EtOAc (3 $\times$ 10 mL), followed by drying over

sodium sulphate and concentration under reduced pressure to give the crude product as a yellow oil. Flash column chromatography (CH₂Cl₂/MeOH 35:1) yielded the pure compound **8** as an off-white solid (234 mg, 78%). ¹H NMR (500 MHz, DMSO-*d*₆) δ = 9.43 (d, *J* = 8.4, 6H, *N*-H), 8.31 (br s, 1H, *N*-H), 8.24 – 8.22 (m, 2H, H₄₈), 8.22 – 8.21 (m, 4H, H_{12,14}), 8.19 – 8.14 (m, 3H, H_{13,49}), 7.87 – 7.76 (m, 20H, H_{6,7,9,17,18,19,20,42,43,45}), 7.58 – 7.53 (m, 6H, H_{8,18,44}), 7.42 (m, 2H, *N*-H), 7.31 (d, *J* = 2.4, 2H, H₄₀), 7.26 (m, 4H, H_{4,22}), 7.17 (m, 2H, H₄₁), 7.15 – 7.07 (m, 4H, H_{5,21}), 6.10 (m, 2H, H₂), 5.48 – 5.34 (m, 8H, H_{1trans,10,15,46}), 5.29 (m, 2H, H_{1cis}), 4.67 (m, 4H, H₃), 4.36 (app t, *J* = 7.8, 2H, H₃₀), 4.21 (m, 2H, H₃₄), 4.15 (m, 2H, H₂₅), 4.08 – 4.01 (m, 8H, H_{23,39}), 3.72 – 3.68 (m, 2H, H₃₃), 3.61 – 3.54 (m, 2H, H₃₃), 3.48 (m, 2H, H₂₄), 3.38 – 3.35 (m, 2H, H₂₄), 2.45 (m, 2H, H₃₇), 2.31 (m, 2H, H₃₇), 2.02 – 1.90 (m, 12H, H_{31,32,38}), 1.78 – 1.74 (m, 2H, H₃₅), 1.69 – 1.62 (m, 22H, H_{11,16,26,47}), 1.58 – 1.53 (m, 2H, H₂₇), 1.33 (s, 6H, H₂₉), 1.31 (s, 6H, H₂₉), 0.89 – 0.79 (m, 24H, H_{28,36}); ¹³C NMR (126 MHz, DMSO-*d*₆) δ = 174.48, 174.26, 173.77, 172.66, 172.34, 171.87, 170.74, 162.84, 156.38, 156.24, 155.93, 149.13, 139.37, 139.00, 138.91, 138.85, 133.59, 133.29, 133.24, 129.64, 129.22, 129.11, 129.07, 128.22, 128.20, 128.13, 126.89, 126.83, 125.54, 125.49, 124.73, 124.04, 118.85, 117.58, 106.91, 106.58, 106.44, 68.21, 67.00, 66.32, 65.82, 59.91, 56.09, 51.42, 48.13, 47.36, 38.34, 31.26, 29.80, 29.08, 29.02, 26.55, 26.34, 24.79, 24.50, 24.46, 24.01, 23.13, 21.68, 21.11, 20.44, 19.02, 18.23. Due to high degree of apparent symmetry many ¹³C signals overlap; MALDI-TOF (+): Calcd. for C₁₅₁H₁₇₅N₁₉O₂₂Na: 2629.3, found 2628.8 [M+Na]⁺.

1•[Lu]

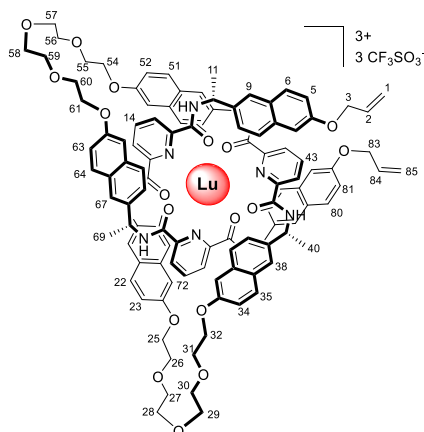


To a solution of **1** (30 mg, 0.017 mmol) in MeCN (17 mL) was added lutetium trifluoromethanesulfonate (10.7 mg, 0.017 mmol). The solution was stirred at 80 °C for 16 h. The mixture was allowed to cool to room temperature, filtered and concentrated under reduced pressure. The crude was purified using size exclusion chromatography (Sephadex LH-20, MeOH) to give **1•[Lu]** as a colourless solid (5 mg, 12 %). The yield is representative of the size exclusion fractions

of the highest purity. ¹H NMR (600 MHz, CD₃CN) δ 8.43 (d, *J* = 4.8 Hz, 2H, H_{12/16/37/41/62/66}), 8.39 (d, *J* = 3.8 Hz, 2H, H_{12/16/37/41/62/66}), 8.22 (d, *J* = 4.8 Hz, 2H, H_{12/16/37/41/62/66}), 7.65 (d, *J* = 8.8 Hz, 2H, H_{6/22/31/47/56/72}), 7.60 (d, *J* = 8.0 Hz, 2H, H_{38,40}), 7.54 (d, *J* = 8.5 Hz, 2H, H_{7/21/32/46/57/71}), 7.52 – 7.47 (m, 4H, H_{6/22/31/47/56/72, 7/21/32/46/57/71}), 7.34 – 7.20 (m, 15H, H_{4/24/29/49/54/74, 5/23/30/48/55/73, 6/22/31/47/56/72, 7/21/32/46/57/71, 8/20/33/45/58/70, 39}), 7.11 (dd, *J* = 8.9, 2.1 Hz, 2H, H_{5/23/30/48/55/73}), 7.00 (s, 2H, H_{4/24/29/49/54/74}), 6.95 (s, 2H, H_{9/19/34/44/59/69}), 6.92 (s, 2H, H_{9/19/34/44/59/69}), 6.90 – 6.83 (m, 6H,

H_{8/20/33/45/58/70}, 9/19/34/44/59/69, 13/15/63/65), 6.66 (d, *J* = 7.3 Hz, 2H, H_{13/15/63/65}), 6.57 (d, *J* = 7.4 Hz, 2H, H_{8/20/33/45/58/70}), 6.24 (ddt, *J* = 17.9, 10.5, 5.2 Hz, 2H, H_{2,76}), 5.82 (t, *J* = 7.9 Hz, 2H, H_{14,64}), 5.57 (app dd, *J* = 17.3, 1.6 Hz, 2H, H_{1,77(trans)}), 5.40 (app dd, *J* = 10.6, 1.4 Hz, 2H, H_{1,77(cis)}), 4.80 – 4.72 (m, 6H, H_{3,35,42,75}), 4.67 – 4.61 (m, 4H, H_{10,17,60,67}), 4.56 – 4.51 (m, 2H, H_{25/28/50/53}), 4.47 – 4.42 (m, 2H, H_{25/28/50/53}), 4.38 – 4.29 (m, 4H, H_{25/28/50/53}), 4.15 – 4.0 (m, 8H, H_{26,27,51,52}), 1.62 (d, *J* = 7.1 Hz, 6H, H_{11/18/36/43/61/68}), 1.56 (d, *J* = 7.1 Hz, 6H, H_{11/18/36/43/61/68}), 1.46 (d, *J* = 7.0 Hz, 6H, H_{11/18/36/43/61/68}); **¹³C NMR** (151 MHz, CD₃CN) δ 167.22, 166.93, 166.66, 157.32, 157.23, 157.12, 145.09, 144.06, 143.92, 141.61, 139.10, 139.08, 139.03, 138.74, 134.19, 134.13, 133.92, 133.45, 129.75, 129.39, 128.93, 128.92, 128.49, 127.75, 127.71, 127.38, 124.88, 124.26, 123.72, 123.50, 123.10, 119.98, 119.87, 119.76, 107.82, 107.61, 70.04, 69.81, 69.32, 68.09, 68.04, 54.17, 53.59, 52.59, 23.38, 23.09, 21.71. Due to high degree of apparent symmetry many ¹³C signals overlap. **HRMS** (ESI⁺): Calcd. for C₁₀₈H₁₀₁N₉O₁₇F₃SLu: 1029.8192, found 1029.8151 [M-(CF₃SO₃)₂]²⁺.

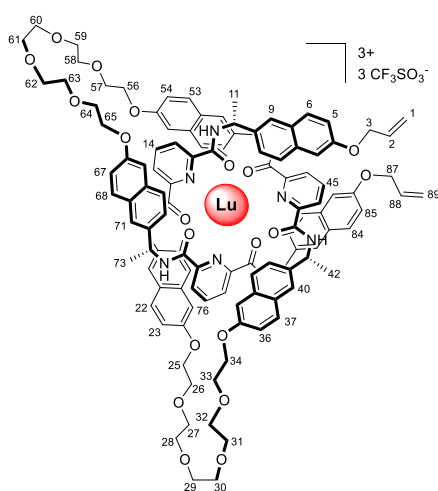
3•[Lu]



To a solution of **3** (1.5 mg, 0.785 μmol) in MeCN (0.5 mL) was added lutetium trifluoromethanesulfonate (0.5mg, 0.785 μmol). The solution was stirred at 80 °C for 48 h. The mixture was allowed to cool to room temperature, filtered, concentrated and triturated twice with CH₂Cl₂ to give **3•[Lu]** as a colourless solid (1.2 mg, 76% yield). **¹H NMR** (600 MHz, CD₃CN) δ 8.58 - 8.55 (m, 4H, H_{12/16/41/45/70/74}), 8.50 (d, *J* = 5.8 Hz, 2H, H_{12/16/41/45/70/74}), 7.64 (d, *J* = 8.9 Hz, 2H, H_{6/22/35/51/64/80}), 7.59 – 7.55 (m, 4H, H_{6/22/35/51/64/80}), 7.59 – 7.54 (m, 4H, H_{7/21/36/50/65/79}), 7.54 – 7.52 (m, 2H, H_{42,44}), 7.40 - 7.35 (m, 4H, H_{4/7/21/24/33/36/50/53/62/65/79/82}), 7.34 – 7.25 (m, 6H, H_{5,23,34,52,63,81}), 7.25 – 7.23 (m, 2H, H_{9/19/38/48/67/77}), 7.20 – 7.15 (m, 4H, H_{4/24/33/53/62/82}), 7.11 – 7.06 (m, 4H, H_{13,15,71,73}), 7.06 – 7.05 (m, 1H, H₄₃), 7.05 – 6.96 (m, 4H, H_{9/19/38/48/67/77}), 6.83 - 6.78 (m, 4H, H_{8/20/37/49/66/78}), 6.67 (dd, *J* = 8.4, 1.8 Hz, 2H, H_{8/20/37/49/66/78}), 6.31 – 6.24 (m, 2H, H_{2,84}), 6.20 (t, *J* = 7.9 Hz, 2H, H_{14,72}), 5.63 - 5.58 (m, 2H, H_{1,85(trans)}), 5.45 - 5.41 (m, 2H, H_{1,85(cis)}), 4.83 - 4.77 (m, 8H, H_{3,17,39,46,68,83}), 4.71 (quintet, *J* = 6.4 Hz, 2H, H_{10,75}), 4.44 – 4.37 (m, 4H, H_{25/32/54/61}), 4.32 – 4.25 (m, 4H, H_{25/32/54/61}), 4.14 – 4.08 (m, 4H, H_{26/31/55/60}), 4.01 – 3.96 (m, 4H, H_{26/31/55/60}), 3.83 – 3.79 (m, 8H, H_{27,30,56,59}), 3.78 – 3.72 (m, 8H, H_{28,29,57,58}), 1.59 (d, *J* = 7.1 Hz, 6H, H_{11/18/40/47/69/76}), 1.55 (d, *J* = 7.1 Hz, 6H, H_{11/18/40/47/69/76}), 1.52 (d, *J* = 7.1 Hz, 6H, H_{11/18/40/47/69/76}); **¹³C NMR** (151 MHz, CD₃CN) δ 166.61, 166.41, 166.24, 157.10, 157.01, 156.78, 149.44, 144.38, 143.82, 143.77, 140.68, 139.52,

138.38, 138.34, 138.12, 137.75, 133.65, 133.60, 133.47, 133.30, 129.93, 129.89, 129.18, 129.10, 129.01, 128.97, 128.96, 128.48, 128.40, 128.36, 128.22, 127.23, 127.21, 127.06, 125.84, 125.39, 124.19, 124.07, 123.43, 123.33, 123.18, 122.83, 122.72, 122.39, 122.26, 121.95, 119.83, 119.46, 119.40, 107.28, 106.97, 70.68, 70.57, 70.26, 70.23, 69.44, 69.40, 68.76, 67.99, 52.78, 52.46, 51.98, 22.22, 22.12, 21.17; Due to the symmetry of the molecule, several carbon signals could not be distinguished due to overlapping peaks; **HRMS** (ESI⁺): Calcd. for C₁₁₆H₁₁₇N₉O₂₁F₃SLu: 1117.8717, found 1117.8670 [M-(CF₃SO₃)₂]²⁺.

4•[Lu]

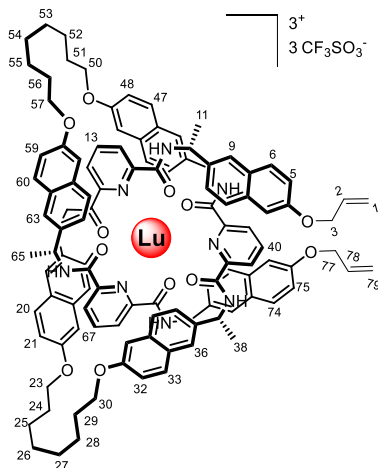


To a solution of **4** (7.0 mg, 3.5 μ mol) in MeCN(1.75 mL) was added lutetium trifluoromethanesulfonate (2.2 mg, 3.5 μ mol). The solution was stirred at 80 °C for 48 h. The mixture was allowed to cool to room temperature, filtered, concentrated and triturated twice with CH₂Cl₂ to give **4•[Lu]** as a colourless solid (4.9 mg, 64% yield). **¹H NMR** (600 MHz, CD₃CN) δ 8.59 (d, *J* = 5.9 Hz, 2H, H_{12/16/43/47/74/78}), 8.47 (d, *J* = 6.0 Hz, 2H, H_{12/16/43/47/74/78}), 8.47 (d, *J* = 6.0 Hz, 2H, H_{12/16/43/47/74/78}), 7.59 (dd, 4H, H_{6/22/37/53/68/84}), 7.54 (d, *J* = 8.0 Hz, 2H, H_{44,46}), 7.50 (d, *J*

= 8.7 Hz, 4H, H_{7/21/38/52/69/83}), 7.38 (d, *J* = 8.5 Hz, 2H, H_{6/22/37/53/68/84}), 7.31 – 7.28 (m, 6H, H_{5,23,36,54,67,85}), 7.26 – 7.21 (m, 6H, H_{4,24,35,55,66,86}), 7.18 (dd, *J* = 8.9, 2.5 Hz, 2H, H_{7/21/38/52/69/83}), 7.14 (d, *J* = 8.0 Hz, 2H, H_{13/15/75/77}), 7.07 (t, *J* = 8.0 Hz, 1H, H₄₅), 7.03 (d, *J* = 4.0 Hz, 2H, H_{13/15/75/77}), 7.02 – 6.98 (m, 4H, H_{9/19/40/50/71/81}), 6.90 (d, *J* = 2.2 Hz, 1H, H_{9/19/40/50/71/81}), 6.78 – 6.74 (m, 5H, H_{8/20/39/51/70/82,9/19/40/50/71/81}), 6.68 (dd, *J* = 8.5, 1.9 Hz, 2H, H_{8/20/39/51/70/82}), 6.56 (t, *J* = 7.9 Hz, 2H, H_{14,76}), 6.28 (ddt, *J* = 17.3, 10.6, 5.3 Hz, 2H, H_{2,88}), 5.62 - 5.58 (m, 2H, H_{1,89(trans)}), 5.45 - 5.41 (m, 2H, H_{1,89(cis)}), 4.82 - 4.77 (m, 6H, H_{3,10/17/41/48/72/79/87}), 4.75 – 4.68 (m, 4H, H_{10/17/41/48/72/79}), 4.41 – 4.33 (m, 8H, H_{25,34,56,65}), 4.04 – 3.98 (m, 8H, H_{26,33,57,64}), 3.82 – 3.78 (m, 8H, H_{27,32,58,63}), 3.76 – 3.70 (m, 8H, H_{28,31,59,62}), 3.69 - 3.67 (m, 8H, H_{29,30,60,61}), 1.57 (d, *J* = 7.0 Hz, 6H, H_{11/18/42/49/73/80}), 1.55 – 1.51 (m, 12H, H_{11/18/42/49/73/80}); **¹³C NMR** (151 MHz, CD₃CN) δ 166.44, 166.36, 166.22, 157.02, 156.97, 156.80, 149.42, 144.40, 143.91, 143.82, 140.21, 138.30, 138.28, 137.94, 137.74, 133.61, 133.44, 133.34, 129.89, 129.17, 129.01, 128.95, 128.93, 128.48, 128.39, 128.26, 128.19, 127.24, 127.21, 127.17, 125.84, 125.39, 124.20, 123.50, 123.47, 123.25, 122.89, 122.46, 122.32, 119.49, 119.37, 119.30, 107.24, 107.03, 106.99, 70.64, 70.47, 70.44, 69.29, 68.76, 67.66, 67.63, 52.28, 52.22, 51.94, 21.79, 21.03, 19.88; Due to the symmetry of the molecule, several carbon signals could not be distinguished

due to overlapping peaks; **HRMS** (ESI⁺): Calcd. for C₁₂₀H₁₂₅N₉O₂₃F₃SLu: 1161.8979, found 1161.8921 [M-(CF₃SO₃)₂]²⁺.

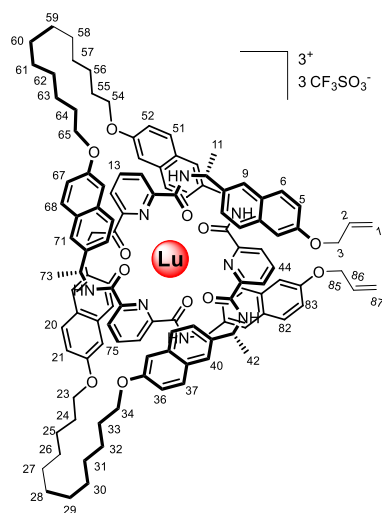
5•[Lu]



To a vigorously stirred solution of **5** (80 mg, 0.045 mmol) in MeCN (44 mL) was added lutetium trifluoromethanesulfonate (27.4 mg, 0.045 mmol). The reaction was stirred at 80 °C for 48 h. The mixture was allowed to cool to room temperature, filtered and concentrated under reduced pressure. The solid was repeatedly triturated with dichloromethane to give **5•[Lu]** as an off-white powder (57 mg, 53 %). ¹H NMR (600 MHz, CD₃CN) δ 8.60 (d, *J* = 5.2 Hz, 2H, *N-H*), 8.48 – 8.43 (m, 4H, *N-H*), 7.69 – 7.58 (m, 6H, H_{6,39,41,61,73,74}), 7.55 – 7.48 (m, 4H, H_{7,19,20,60}), 7.36 – 7.19 (m, 14H, H_{5,21,22,31,33,34,36,44,46,47,49,58,59,75}),

7.16 (t, *J* = 7.9 Hz, 1H, H₄₀), 7.13 – 7.08 (m, 4H, H_{4,32,48,76}), 7.06 – 7.03 (m, 2H, H_{12/14/66/68}), 6.99 (s, 2H, H_{9/17/63/71}), 6.96 – 6.92 (m, 2H, H_{12/14/66/68}), 6.91 (s, 2H, H_{9/17/63/71}), 6.85 – 6.81 (m, 4H, H_{8,18,62,72}), 6.73 – 6.69 (m, 2H, H_{35,45}), 6.31 – 6.23 (m, 6H, H_{2,13,67,78}), 5.60 (m, 2H, H_{1,79trans}), 5.43 (m, 2H, H_{1,79cis}), 4.84 – 4.77 (m, 6H, H_{3,37,42,77}), 4.74 – 4.67 (m, 4H, H_{10,15,64,69}), 4.33 – 4.22 (m, 4H, H_{23/30/50/57}), 4.19 – 4.09 (m, 4H, H_{23/30/50/57}), 2.13 – 2.05 (m, 4H, H_{24/29/51/56}), 2.01 – 1.92 (m, 4H, H_{24/29/51/56}), 1.80 – 1.68 (m, 12H, H_{25/26/27/28/52/53/54/55}), 1.64 – 1.59 (m, 10H, H_{11/16/38/43/65/70/25/26/27/28/52/53/54/55}), 1.56 (d, *J* = 7 Hz, 6H, H_{11/16/38/43/65/70}), 1.52 (d, *J* = 7 Hz, 6H, H_{11/16/38/43/65/70}); ¹³C NMR (151 MHz, CD₃CN) δ 167.00, 166.81, 166.59, 157.73, 157.61, 157.22, 144.89, 144.23, 144.08, 141.20, 139.62, 138.59, 138.57, 138.41, 134.05, 133.86, 133.66, 129.61, 129.26, 129.09, 128.83, 128.54, 128.37, 127.63, 127.47, 124.73, 124.00, 123.72, 123.66, 123.46, 123.35, 122.06, 122.01, 119.97, 119.92, 119.81, 107.69, 107.07, 69.18, 68.59, 68.57, 53.24, 52.92, 52.40, 49.33, 29.60, 27.91, 27.87, 27.62, 27.57, 25.45, 25.42, 22.52, 22.47, 21.44. Due to high degree of apparent symmetry many ¹³C signals overlap. **HRMS** (ESI⁺): Calcd. for C₁₁₅H₁₁₇N₉O₁₂Lu: 663.9415, found 663.9401 [M-3(CF₃SO₃)]³⁺.

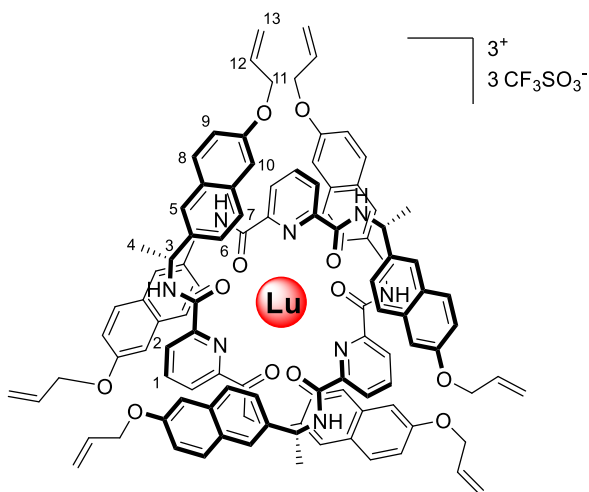
6•[Lu]



To a vigorously stirred solution of **6** (8.8 mg, 4.5 μmol) in MeCN (4.5 mL) was added lutetium trifluoromethanesulfonate (2.8 mg, 4.5 μmol). The reaction was stirred at 80 $^{\circ}\text{C}$ for 2 days. The mixture was allowed to cool to room temperature, filtered and concentrated under reduced pressure. The solid was repeatedly triturated with dichloromethane to give **6•[Lu]** as an off-white powder (6.1 mg, 52%). ^1H NMR (600 MHz, CD_3CN) δ 8.61 – 8.55 (m, 6H, *N-H*), 7.52 – 7.37 (m, 14H, $\text{H}_{6,7,19,20,38,43,45,48,50,51,68,69,81,82}$), 7.31 – 7.13 (m, 18H, $\text{H}_{4,5,12,14,21,22,35,36,37,40,52,53,66,67,74,76,83,84}$), 7.08 (s, 4H, $\text{H}_{9,17,71,79}$), 7.00 – 6.96 (t, $J = 7.9$ Hz, 1H, H_{44}), 6.76 – 6.70 (m, 4H,

$\text{H}_{13,75,8/18/39/49/70/80}$), 6.67 – 6.64 (m, 2H, $\text{H}_{8/18/39/49/70/80}$), 6.62 – 6.59 (m, 2H, $\text{H}_{8/18/39/49/70/80}$), 6.31 – 6.22 (m, 2H, $\text{H}_{2,86}$), 5.60 (m, 2H, $\text{H}_{1,87\text{trans}}$), 5.43 (m, 2H, $\text{H}_{1,87\text{cis}}$), 4.83 – 4.73 (m, 10H, $\text{H}_{3,10,15,41,46,72,77,85}$), 4.26 – 4.19 (m, 8H, $\text{H}_{23,34,54,65}$), 2.02 – 1.92 (m, 8H, $\text{H}_{24,33,55,64}$), 1.70 – 1.62 (m, 8H, $\text{H}_{25,32,56,63}$), 1.58 – 1.53 (m, 18H, $\text{H}_{11,16,42,47,73,78}$), 1.52 – 1.45 (m, 24H, $\text{H}_{26,27,28,29,30,31,57,58,59,60,61,62}$). ^{13}C NMR (151 MHz, CD_3CN) δ 167.35, 167.25, 167.23, 158.29, 158.26, 157.71, 145.33, 145.15, 145.09, 141.55, 141.09, 138.90, 138.84, 138.83, 134.57, 134.53, 134.51, 134.49, 130.06, 129.89, 129.30, 129.10, 129.07, 128.15, 128.08, 128.04, 125.04, 124.75, 124.70, 124.35, 124.15, 124.10, 124.03, 123.50, 120.47, 120.43, 120.41, 108.15, 107.69, 69.70, 69.16, 52.99, 52.91, 52.88, 29.61, 29.57, 29.16, 29.13, 28.87, 28.83, 28.51, 26.22, 26.19, 22.33, 22.08. Due to high degree of apparent symmetry many ^{13}C signals overlap. HRMS (ESI $^{+}$): Calcd. for $\text{C}_{123}\text{H}_{133}\text{N}_9\text{O}_{12}\text{Lu}$: 701.3166, found 701.3143[M-3(CF $_3$ SO $_3$)] $^{3+}$.

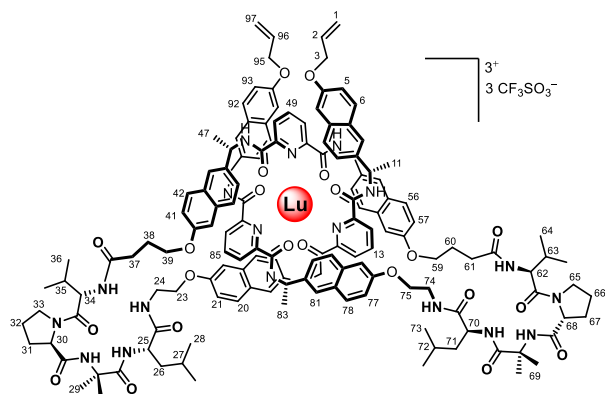
7₃•[Lu]



To a vigorously stirred solution of **7** (56 mg, 0.095 mmol) in MeCN (6.33 mL) was added lutetium trifluoromethanesulfonate (19.5 mg, 0.031 mmol). The reaction was stirred overnight at room temperature. The solution was concentrated and the solid was repeatedly triturated with dichloromethane to give **7₃•[Lu]** as an off-white powder (65 mg, 86%). ¹H NMR (600 MHz, CD₃CN) δ 8.54 (d, *J* = 6.4 Hz, 6H, *N-H*), 7.45 – 7.41 (m, 12H, H_{7,8}), 7.35 (d, *J* = 8.0 Hz, 6H, H₂), 7.23 – 7.21 (m,

6H, H₅), 7.20 – 7.17 (m, 6H, H₆), 7.10 (s, 6H, H₁₀), 6.87 (t, *J* = 7.9 Hz, 3H, H₁), 6.67 – 6.65 (m, 6H, H₉), 6.28 – 6.19 (m, 6H, H₁₂), 5.57 (m, 6H, H_{13trans}), 5.40 (m, 6H, H_{13cis}), 4.79 – 4.70 (m, 18H, H_{3,11}), 1.50 (d, *J* = 7.0 Hz, 18H, H₄); ¹³C NMR (151 MHz, CD₃CN) δ 167.25, 157.69, 145.30, 141.41, 138.87, 134.57, 134.46, 130.04, 129.27, 128.12, 124.91, 124.30, 123.91, 120.37, 108.12, 69.69, 52.93, 22.12. Due to high degree of apparent symmetry many ¹³C signals overlap. HRMS (ESI⁺): Calcd. for C₁₁₁H₁₀₅N₉O₁₂Lu [M-3(CF₃SO₃)]³⁺: 643.9105, found 643.9082.

8•[Lu]



A mixture of **8** (10 mg, 3.83 μmol) and lutetium trifluoromethanesulfonate (2.4 mg, 3.83 μmol) in MeCN was stirred at 80 $^{\circ}\text{C}$ for 8 h under microwave conditions (80 W). The mixture was allowed to cool to room temperature and concentrated under reduced pressure to give the title compound as an off-white solid (12 mg, 97%). ^1H NMR (500 MHz, CD_3CN) δ = 8.60 – 8.51 (m, 6H,

N-H), 7.61 - 7.55 (m, 4H, $\text{H}_{6,92,N-H}$), 7.54 – 7.42 (m, 12H, $\text{H}_{7,19,20,42,48,50,56,78,79,91,N-H}$), 7.40 - 7.34 (m, 2H, $\text{H}_{43,55}$), 7.28 - 7.13 (m, 18H, $\text{H}_{4,5,9/17/81/89,21,22,40,41,45,53,57,58,76,77,93,94,N-H}$), 7.10 - 6.97 (m, 7H, $\text{H}_{9/17/81/89,12,14,49,84,86}$), 6.87 - 6.76 (m, 4H, $\text{H}_{8,18,80,90}$), 6.62 - 6.58 (m, 2H, $\text{H}_{44,54}$), 6.41 (t, J = 7.8, 2H, $\text{H}_{13,85}$), 6.31 - 6.21 (m, 2H, $\text{H}_{2,96}$), 5.63 - 5.56 (m, 2H, $\text{H}_{1,97(\text{trans})}$), 5.45 - 5.41 (m, 2H, $\text{H}_{1,97(\text{cis})}$), 4.83 – 4.63 (m, 10H, $\text{H}_{3,10,15,46,51,82,87,95}$), 4.51 (t, J = 7.5, 2H, $\text{H}_{34,62}$), 4.38 - 4.18 (m, 12H, $\text{H}_{23,25,30,39,59,68,70,75}$), 3.96 - 3.80 (m, 4H, $\text{H}_{24,33,65,74}$), 3.77 - 3.70 (m, 4H, $\text{H}_{33,65}$), 3.60 – 3.51 (m, 4H, $\text{H}_{24,74}$), 2.63 (m, 4H, $\text{H}_{37,61}$), 2.33 - 2.25 (m, 4H, $\text{H}_{38,60}$), 2.21 - 2.13 (m, 10H, $\text{H}_{31,32,35,63,66,67}$), 1.85 - 1.77 (m, 4H, $\text{H}_{26,71}$), 1.63 - 1.50 (m, 26H, $\text{H}_{11,16,27,47,52,72,83,88,29/69}$), 1.43 (s, 6H, $\text{H}_{29/69}$), 1.02 - 0.99 (m, 12H, $\text{H}_{36,64}$), 0.96 - 0.87 (m, 12H, $\text{H}_{28,73}$). ^{13}C NMR (126 MHz, CD_3CN) δ = 175.69, 175.04, 174.33, 174.22, 173.72, 172.17, 167.47, 167.36, 167.18, 157.96, 157.73, 157.70, 150.24, 145.34, 144.70, 144.67, 139.90, 139.89, 139.66, 139.00, 138.90, 134.57, 134.50, 134.35, 134.19, 130.75, 130.11, 130.04, 129.84, 129.26, 129.17, 128.78, 128.13, 128.09, 128.04, 125.00, 124.47, 124.09, 124.04, 124.02, 123.88, 123.51, 123.48, 123.45, 123.35, 123.24, 121.78, 121.40, 121.26, 119.25, 108.67, 108.25, 108.14, 104.78, 69.69, 68.66, 67.73, 61.89, 57.99, 57.45, 53.85, 53.29, 52.89, 48.82, 40.76, 34.11, 32.59, 31.35, 30.31, 30.30, 30.25, 30.14, 30.02, 29.95, 29.81, 29.73, 27.30, 25.77, 25.56, 24.50, 23.35, 21.51, 19.69. Due to high degree of apparent symmetry many ^{13}C signals overlap. HRMS (ESI $^{+}$): Calcd. for $\text{C}_{151}\text{H}_{175}\text{N}_{19}\text{O}_{22}\text{Lu}$ [$\text{M}-3(\text{CF}_3\text{SO}_3)$] $^{3+}$: 927.4207, found 927.4195.

S4.2. Ring-closing metathesis for covalent capture of 8•[Lu]

All alkene-terminated molecular overhand knots can be ring-closed as previously described by us.⁶ For metallopeptide knot **8•[Lu]**, the procedure is as follows. Compound **8•[Lu]** (9.0 mg, 1.0 eq) and Hoveyda-Grubbs 2nd Generation catalyst (1.75 mg, 1.0 eq) were dissolved in a mixture of freshly degassed CH_2Cl_2 and MeNO_2 (3:2, 5 mL). The resulting mixture was left

stirring at 50°C for 24 hours (monitored by ESI-MS). The reaction was quenched with ethyl vinyl ether (1 mL), stirred for 1 h and the reaction mixture was then concentrated under reduced pressure. The residue was washed three times with a mixture of CH₂Cl₂ and diethyl ether, redissolved in methanol and concentrated under reduced pressure. This yielded the target molecule Δ -9•[Lu], characterised by ¹H NMR spectroscopy (Figure S1) and ESI-MS (Figure S2) which shows full conversion to the desired product.

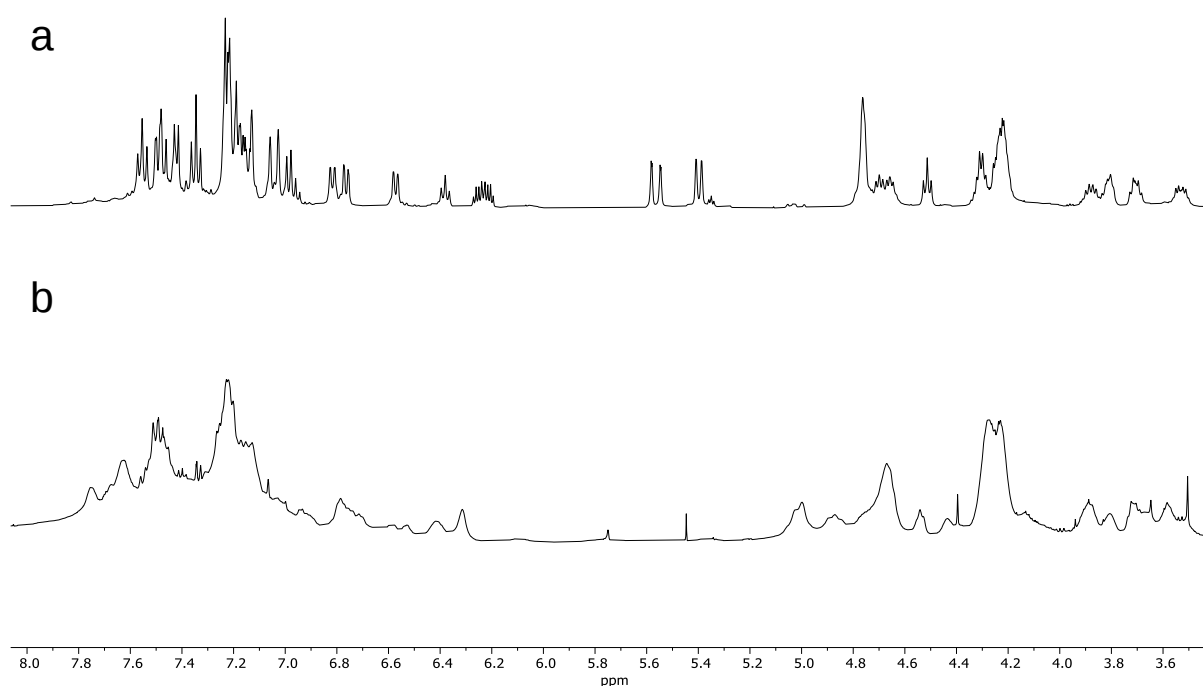


Figure S1. a) ¹H NMR spectrum (500 MHz, 298 K, CD₃CN) of metallopeptide overhand knot Δ -8•[Lu]. b) ¹H NMR spectrum (500 MHz, 298 K, CD₃CN) of ring-closed metallopeptide knot Δ -9•[Lu].

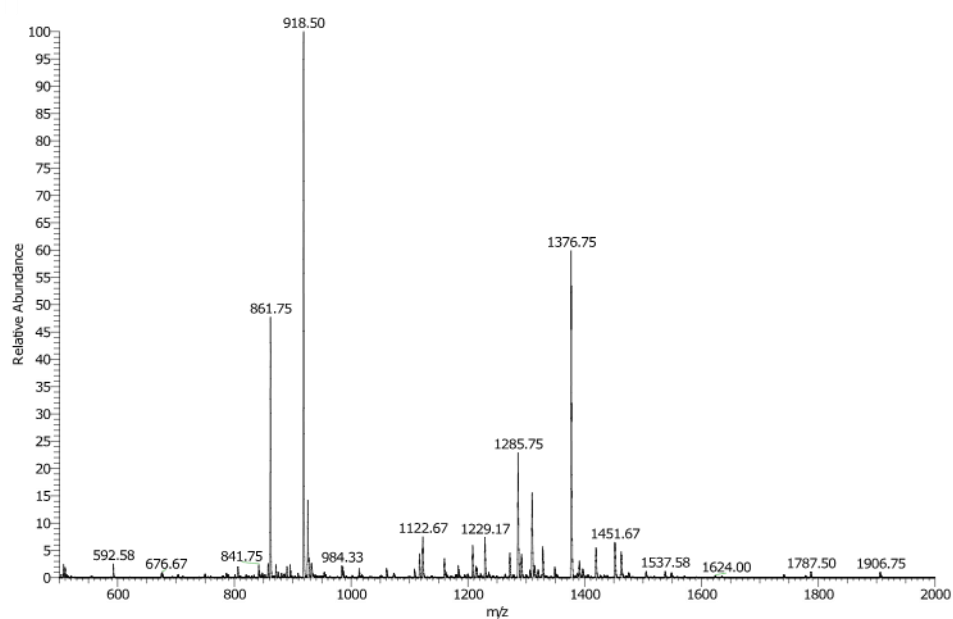


Figure S2. Low resolution ESI-MS (positive mode) of **9•[Lu]** after completion of the ring-closing olefin metathesis reaction. The main peak at m/z 918.5 corresponds to the $[M-n(CF_3SO_3)]^{3+}$ adduct.

S5. MASS SPECTRA

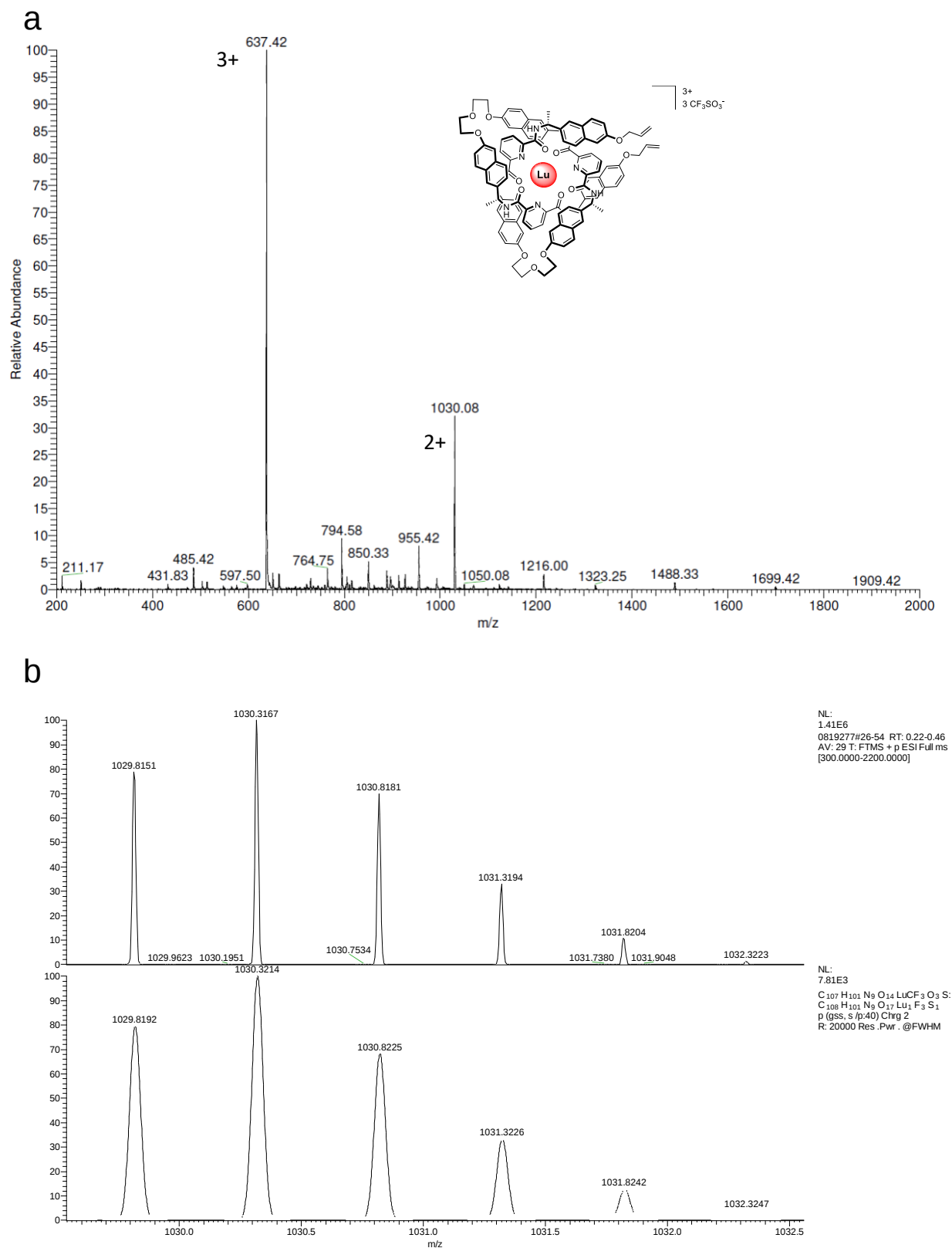


Figure S3. a) Low resolution ESI-MS (positive mode) of **1**•[Lu] (all peaks observed as the $[\text{M}-n(\text{CF}_3\text{SO}_3)]^{n+}$ adducts). b) High-resolution ESI-MS isotopic distribution of **1**•[Lu] $[\text{M}+(\text{CF}_3\text{SO}_3)]^{2+}$, with observed spectra above and predicted below.

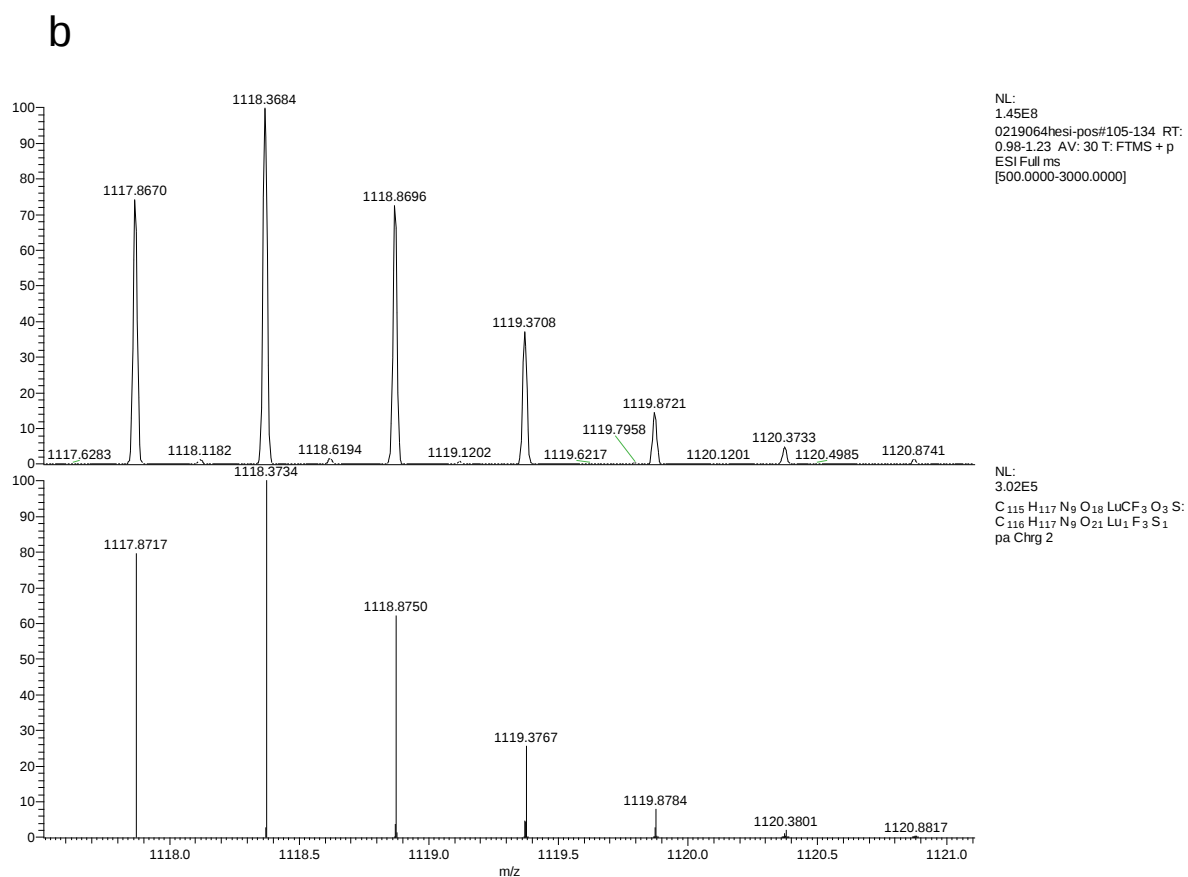
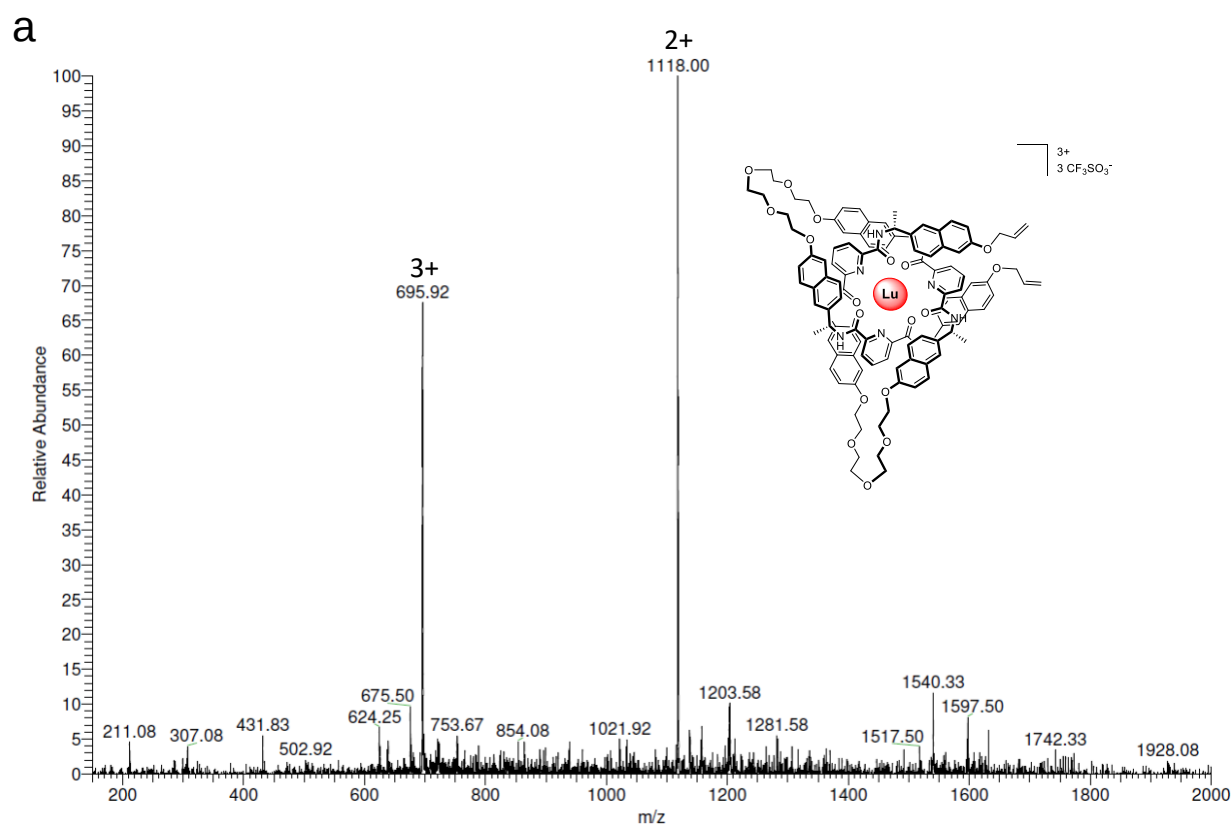


Figure S4. a) Low resolution ESI-MS (positive mode) of $3\bullet[\text{Lu}]$ (all peaks observed as the $[\text{M}-n(\text{CF}_3\text{SO}_3)]^{n+}$ adducts). b) High-resolution ESI-MS isotopic distribution of $3\bullet[\text{Lu}]$ $[\text{M}+(\text{CF}_3\text{SO}_3)]^{2+}$, with observed spectra above and predicted below.

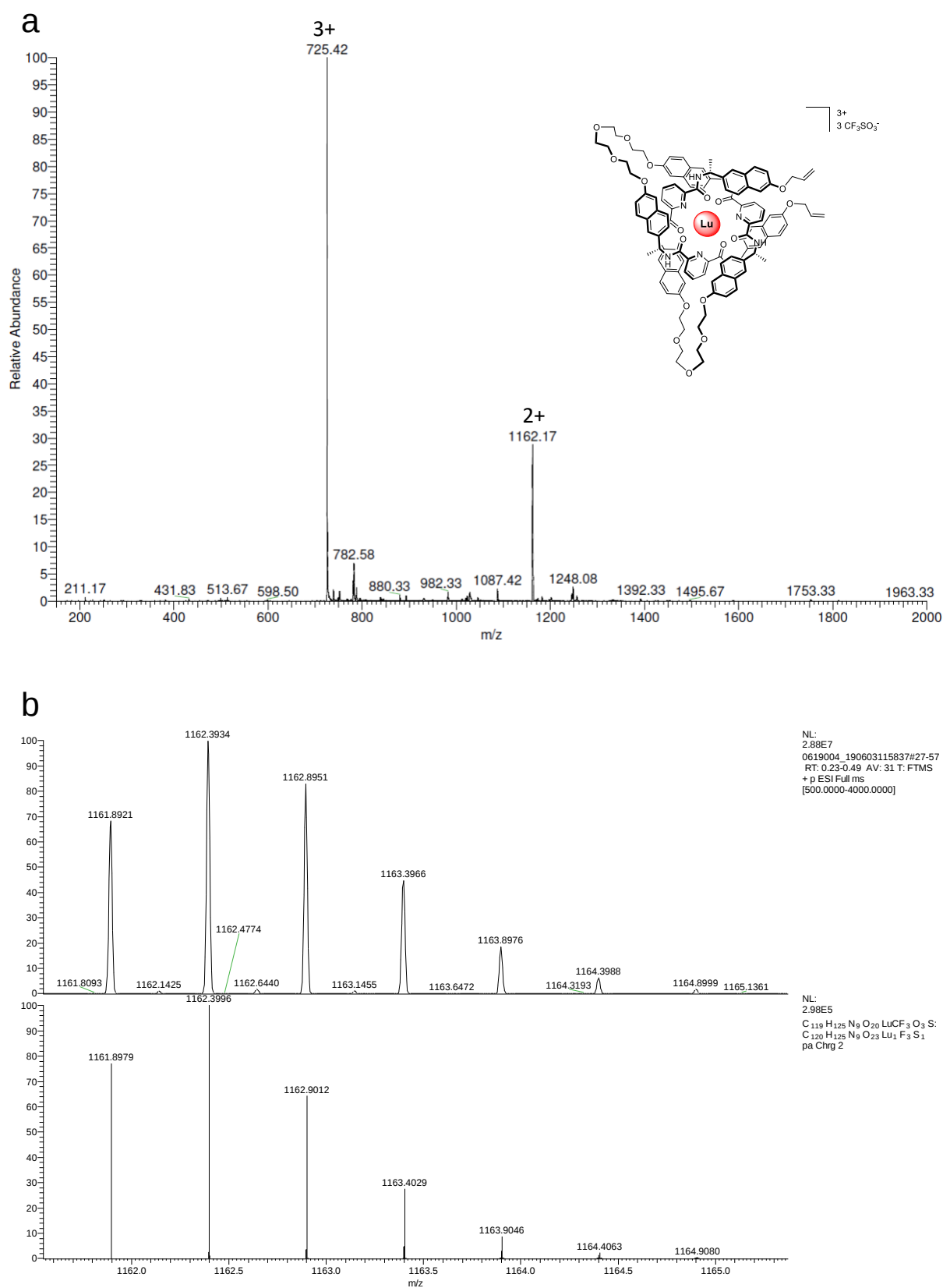


Figure S5. a) Low resolution ESI-MS (positive mode) of **4**•[Lu] (all peaks observed as the $[M-n(\text{CF}_3\text{SO}_3)]^{n+}$ adducts). b) High-resolution ESI-MS isotopic distribution of **4**•[Lu] $[M+(\text{CF}_3\text{SO}_3)]^{2+}$, with observed spectra above and predicted below.

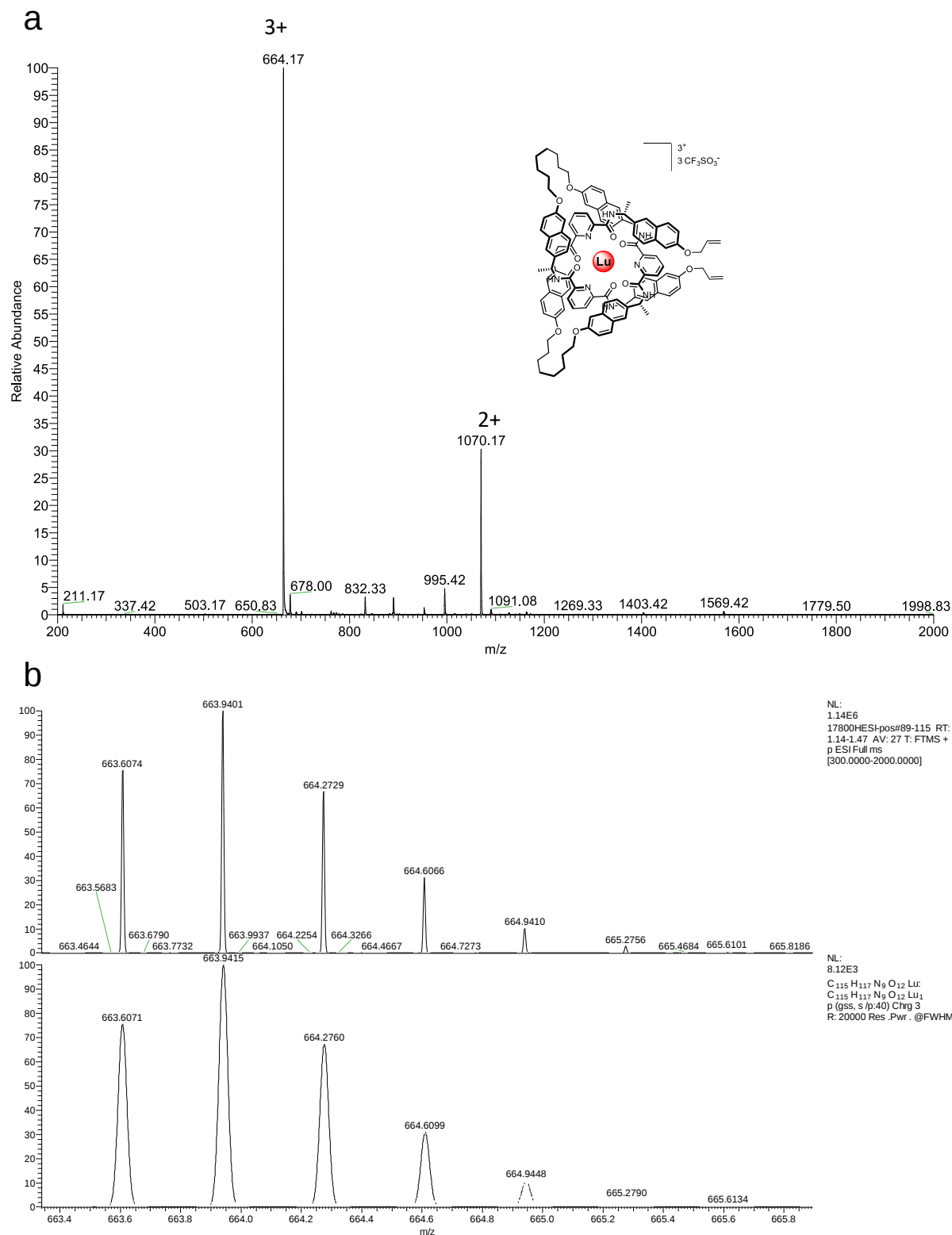


Figure S6. a) Low resolution ESI-MS (positive mode) of **5**•[Lu] (all peaks observed as the $[M-n(\text{CF}_3\text{SO}_3)]^{n+}$ adducts). b) High-resolution ESI-MS isotopic distribution of **5**•[Lu] $[M+(\text{CF}_3\text{SO}_3)]^{2+}$, with observed spectra above and predicted below.

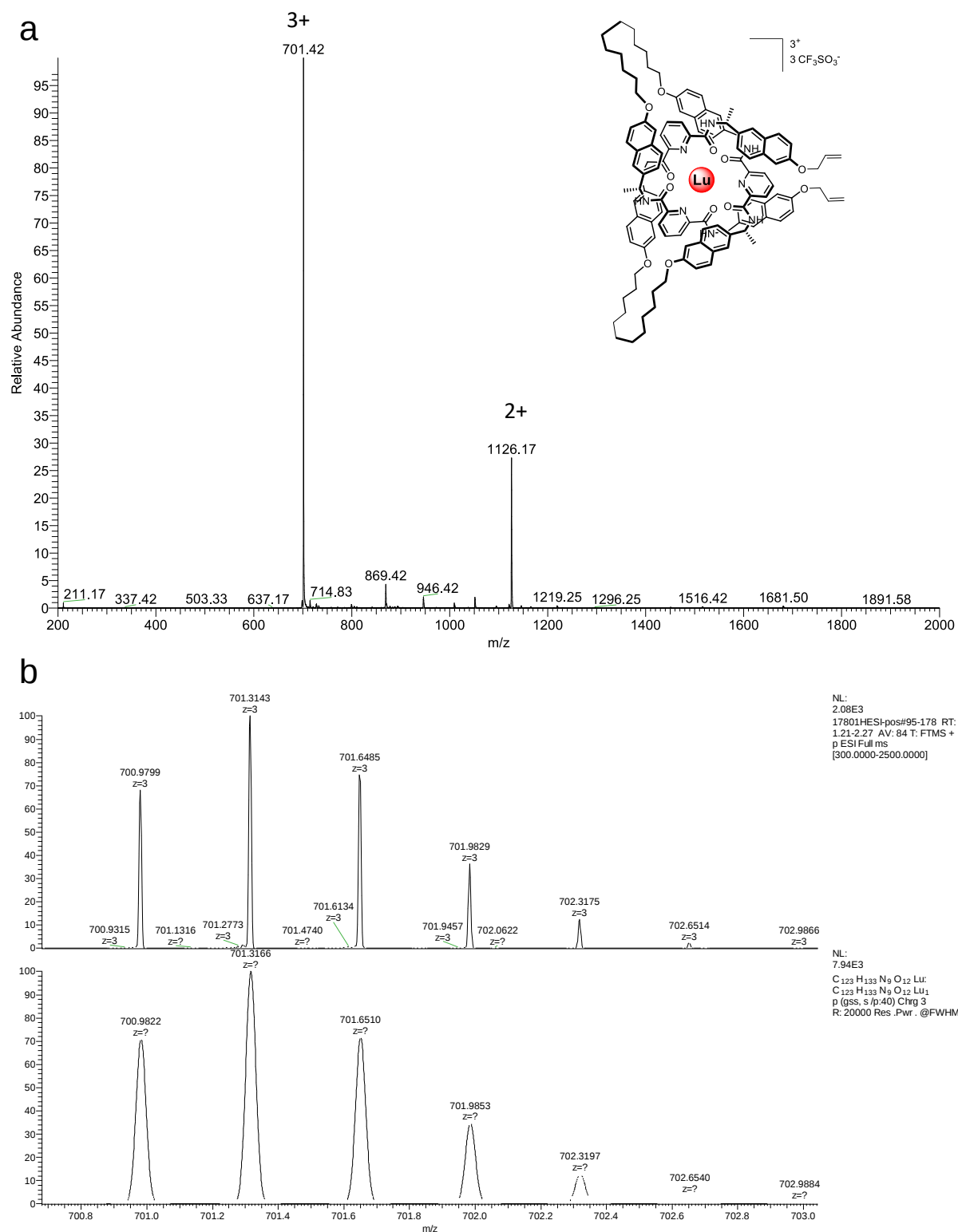


Figure S7. a) Low resolution ESI-MS (positive mode) of **6•[Lu]** (all peaks observed as the $[M-n(\text{CF}_3\text{SO}_3)]^{n+}$ adducts). b) High-resolution ESI-MS isotopic distribution of **6•[Lu]** $[M+(\text{CF}_3\text{SO}_3)]^{2+}$, with observed spectra above and predicted below.

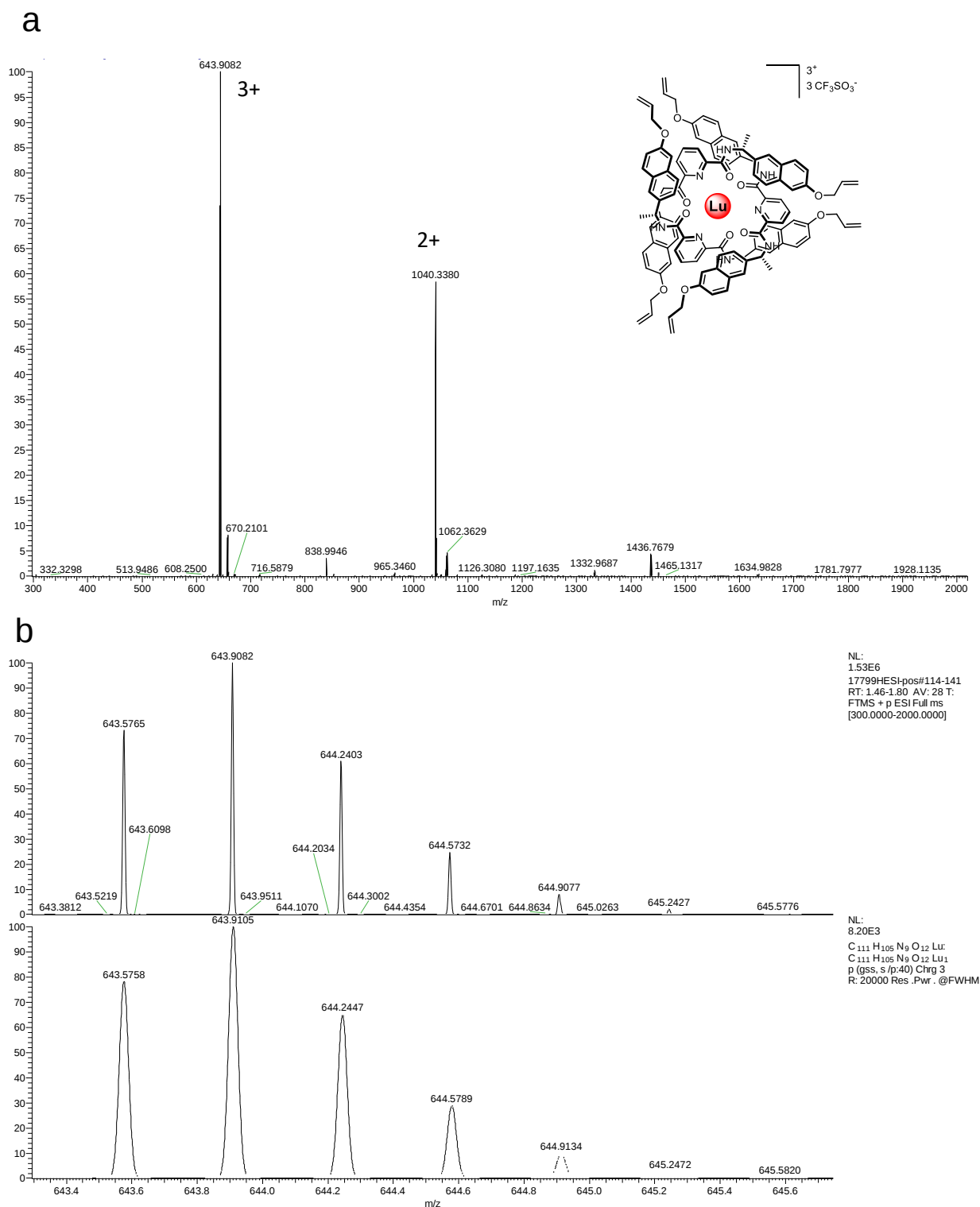


Figure S8. a) Low resolution ESI-MS (positive mode) of **73•[Lu]** (all peaks observed as the $[M - n(\text{CF}_3\text{SO}_3)]^{n+}$ adducts). b) High-resolution ESI-MS isotopic distribution of **73•[Lu]** $[M + (\text{CF}_3\text{SO}_3)]^{2+}$, with observed spectra above and predicted below.

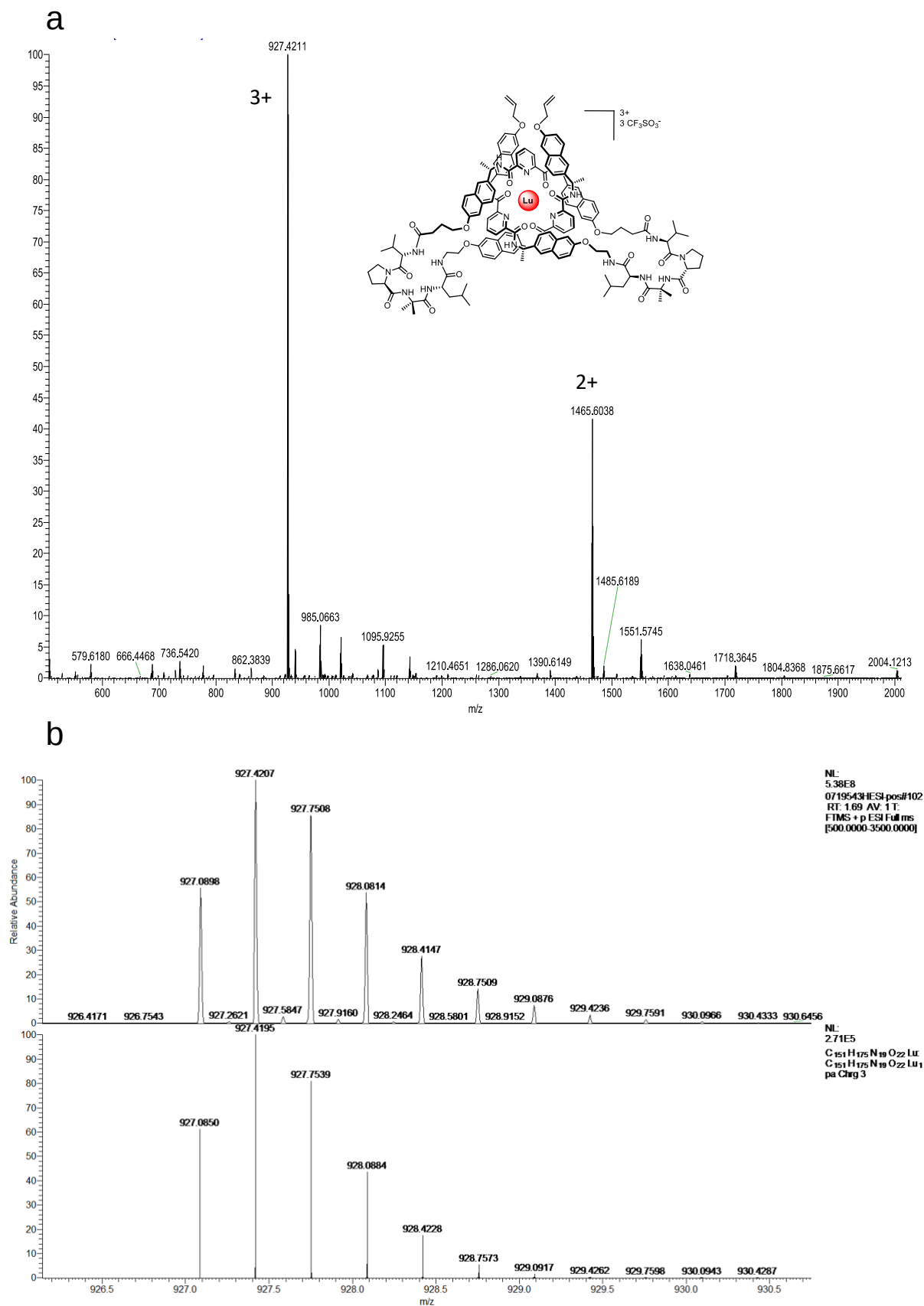


Figure S9. a) Low resolution ESI-MS (positive mode) of $8\bullet[\text{Lu}]$ (all peaks observed as the $[\text{M}-n(\text{CF}_3\text{SO}_3)]^{n+}$ adducts). b) High-resolution ESI-MS isotopic distribution of $8\bullet[\text{Lu}]$

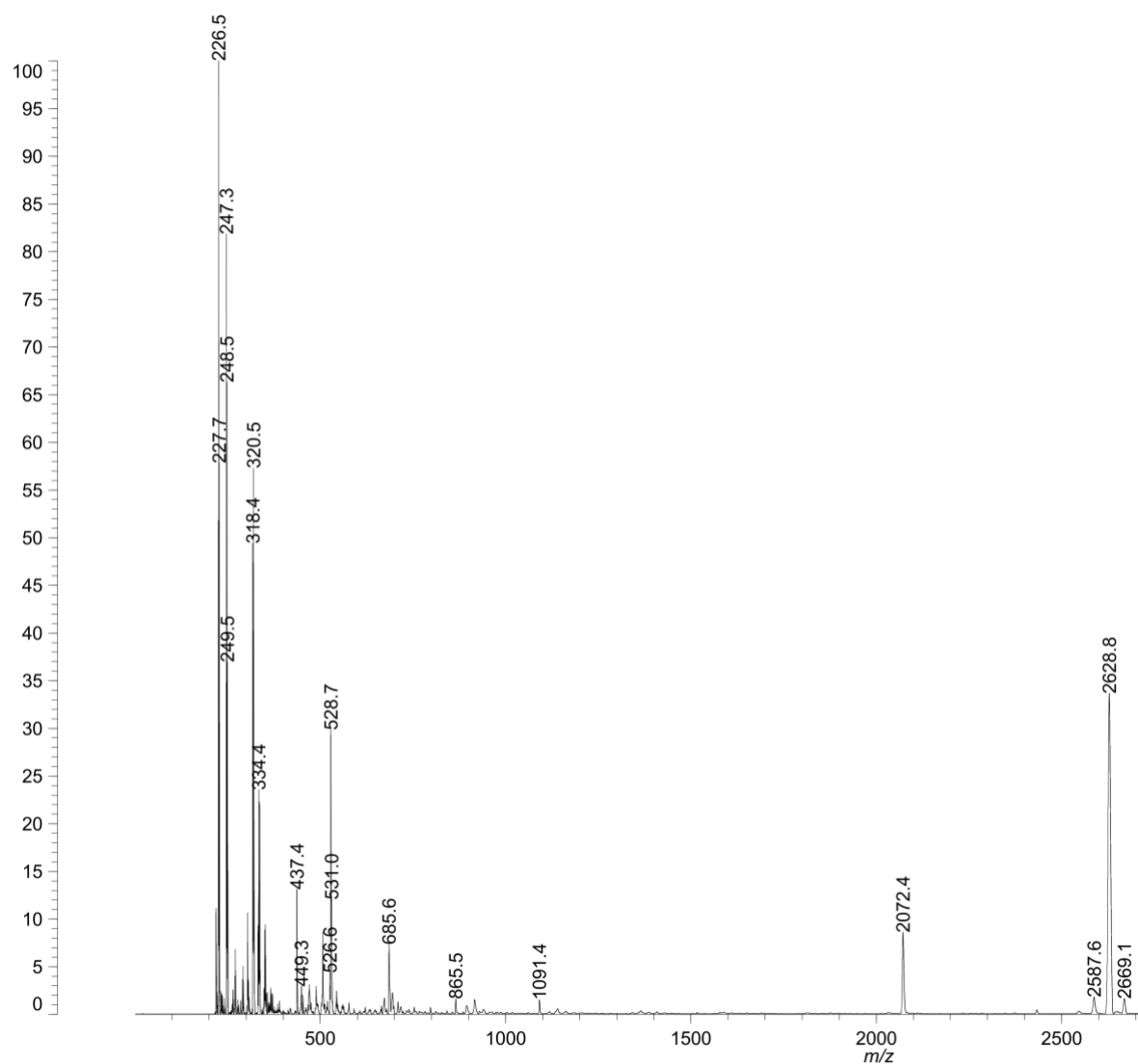
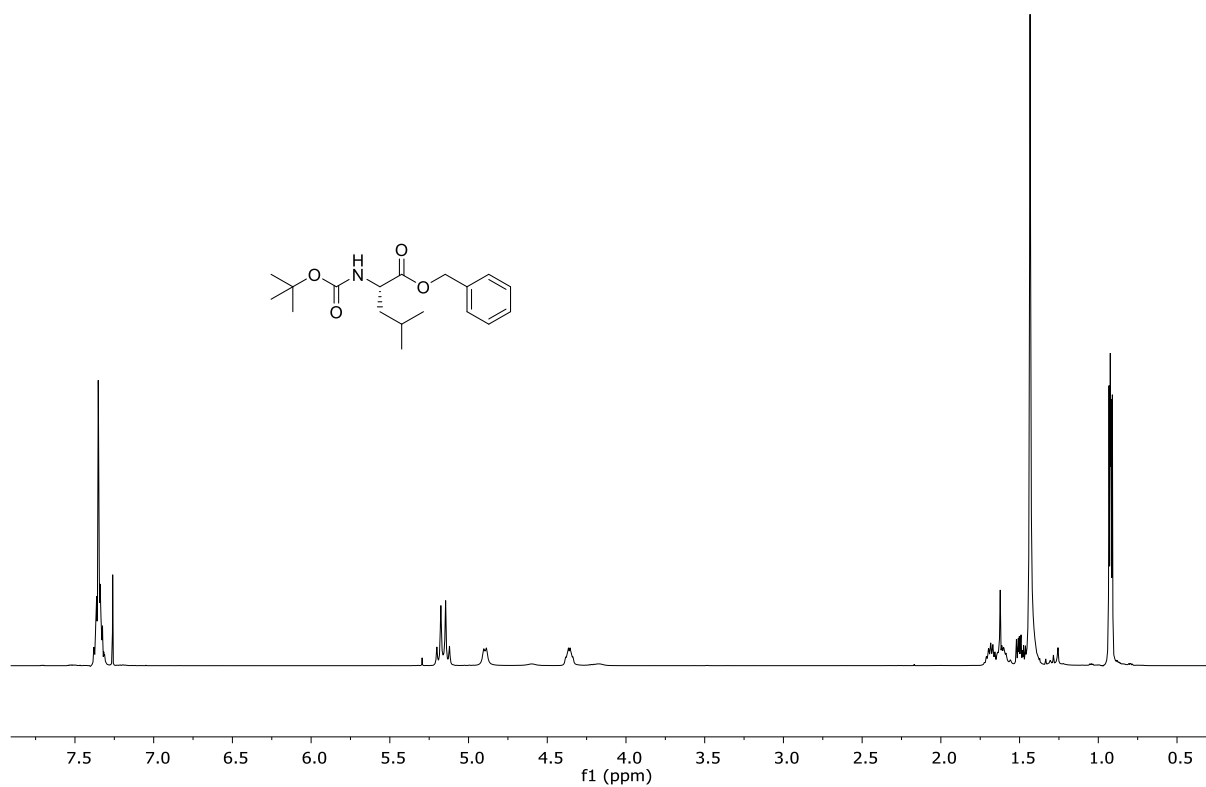
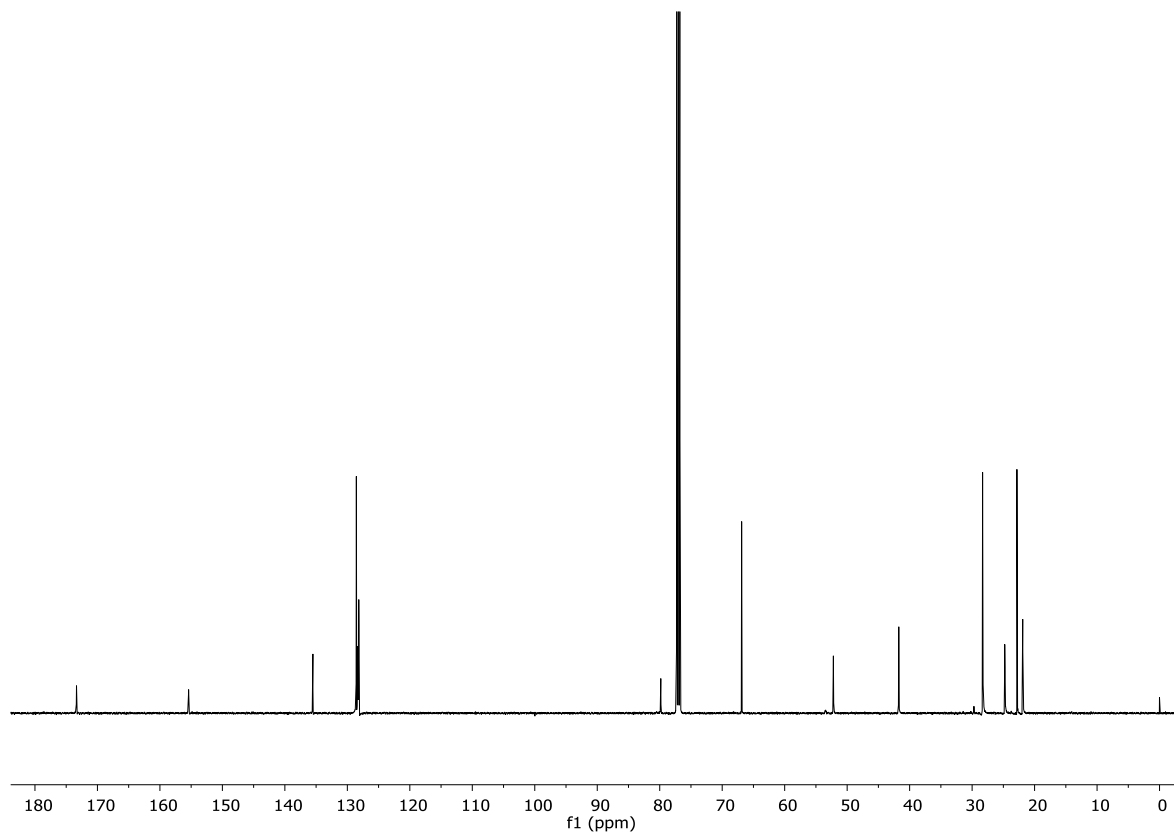


Figure S10. MALDI-TOF MS (positive mode, dithranol matrix) of ligand **8**. Peak observed as the $[M+Na]^+$ adduct. Calculated peak (m/z): 2629.3.

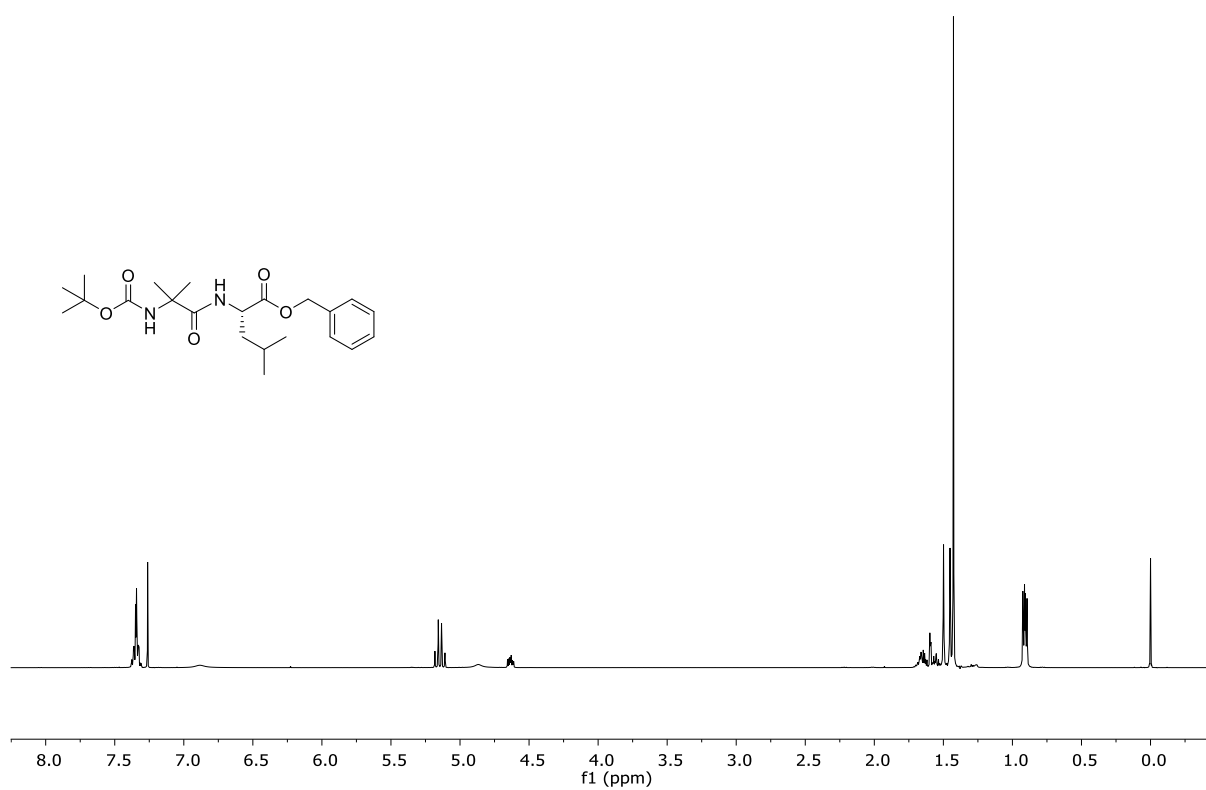
S6. NMR SPECTRA



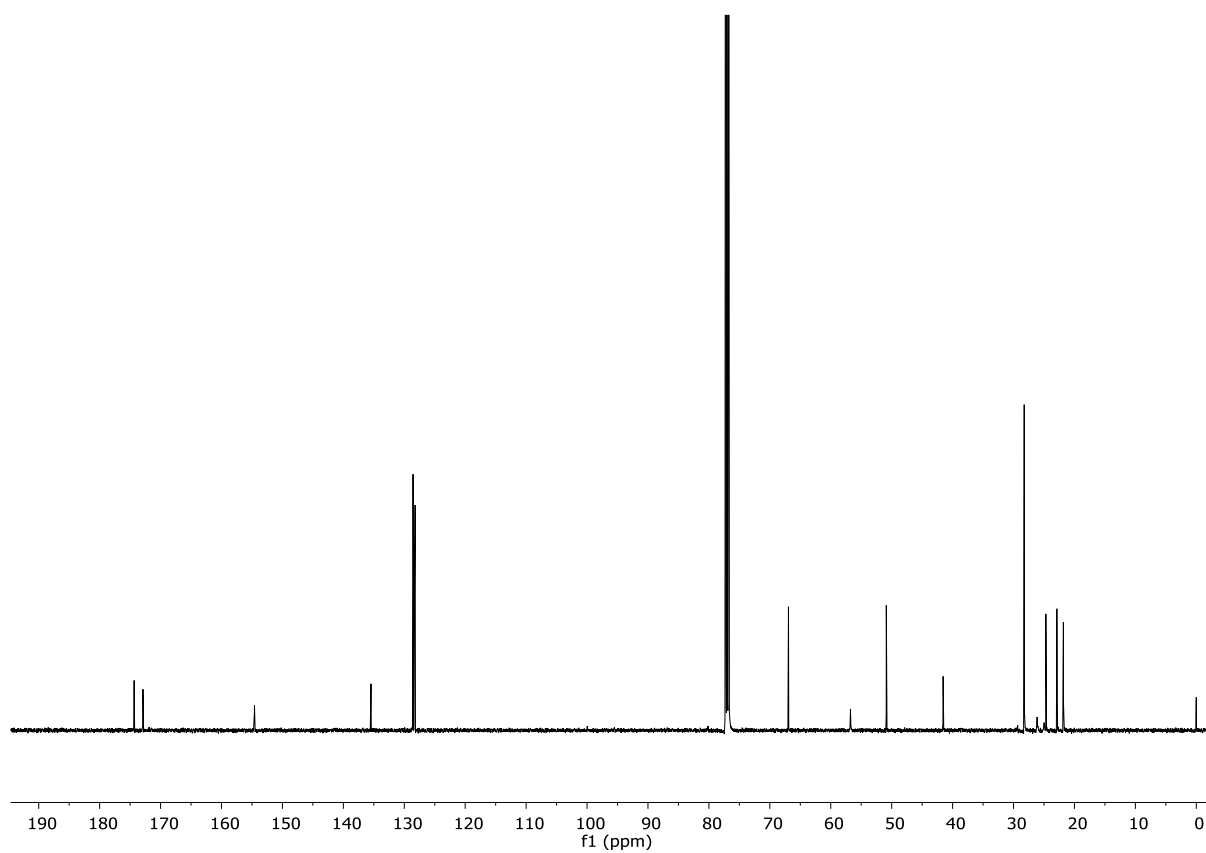
Spectrum S1. ¹H-NMR (500 MHz, CDCl₃, 298 K) of **S6**.



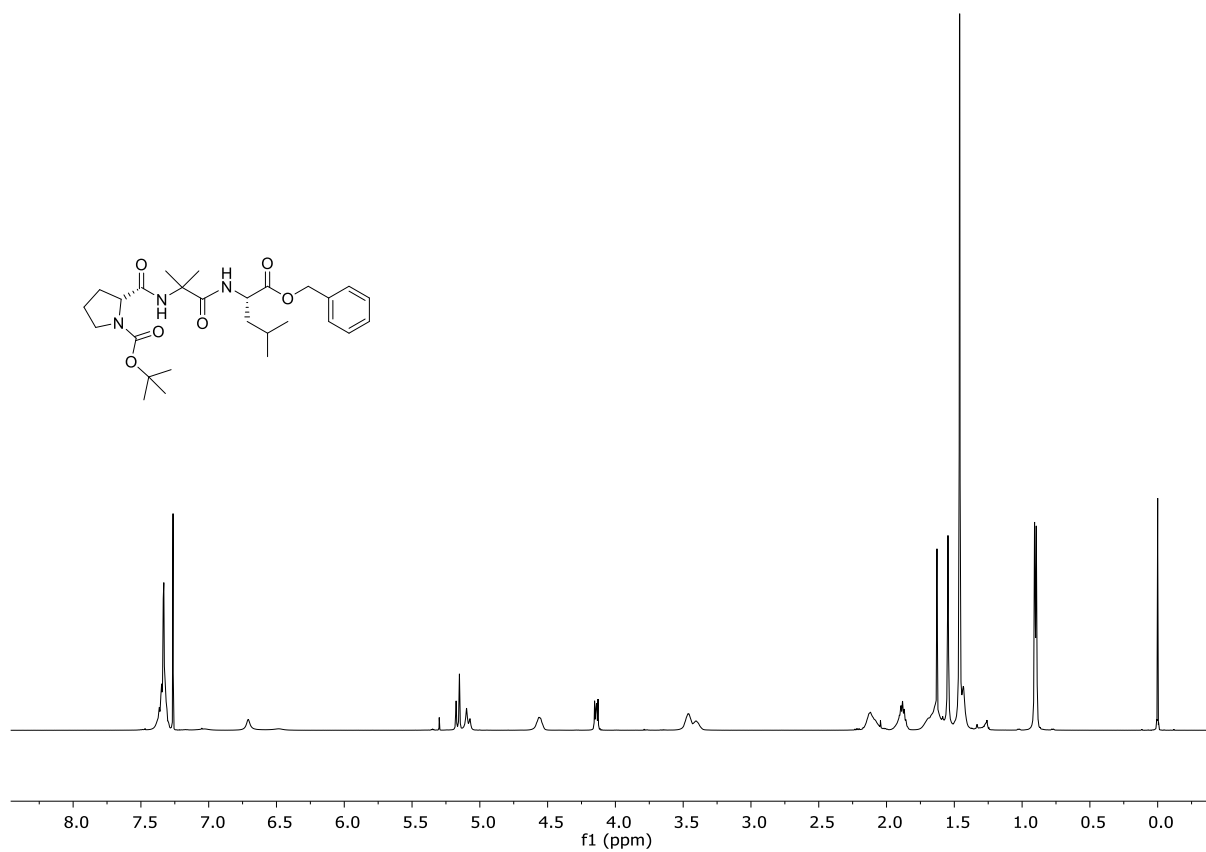
Spectrum S2. ¹³C-NMR (125 MHz, CDCl₃, 298 K) of **S6**.



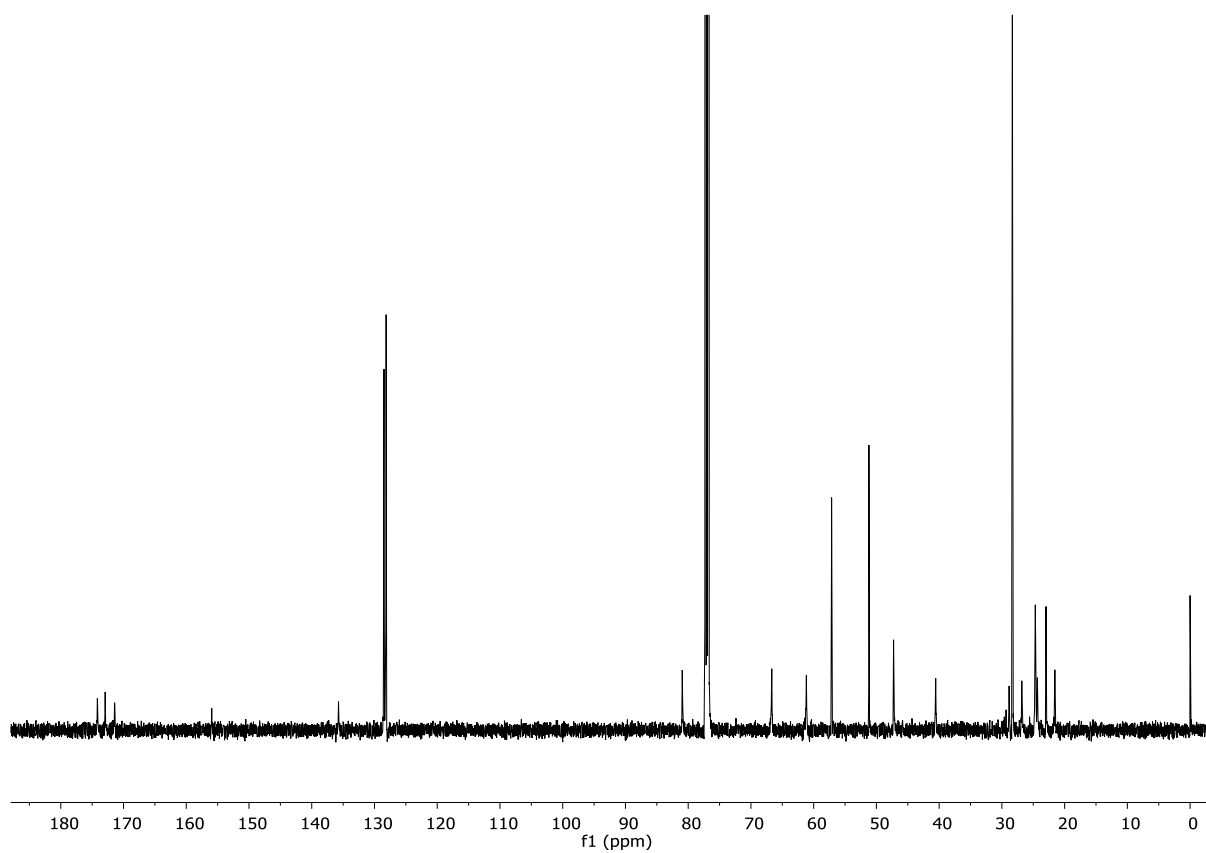
Spectrum S3. ¹H-NMR (500 MHz, CDCl₃, 298 K) of **S8**.



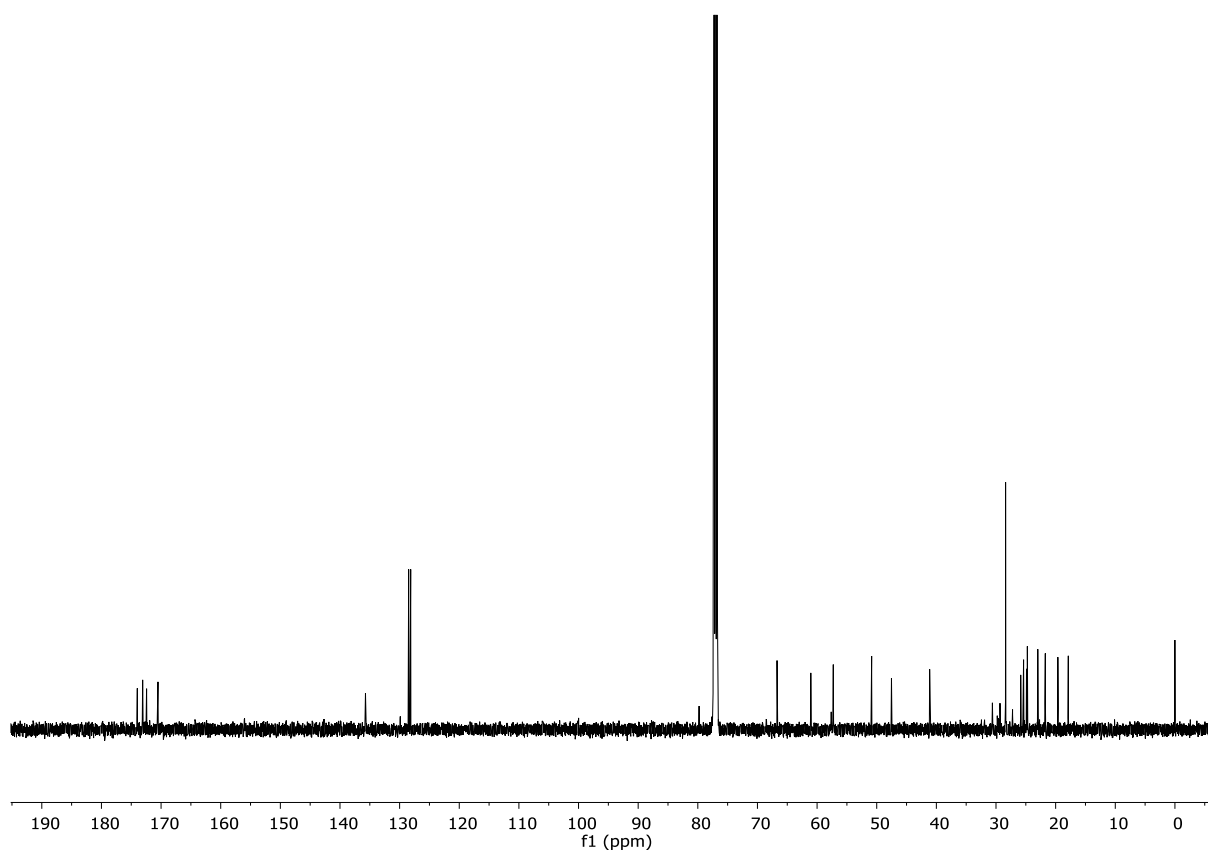
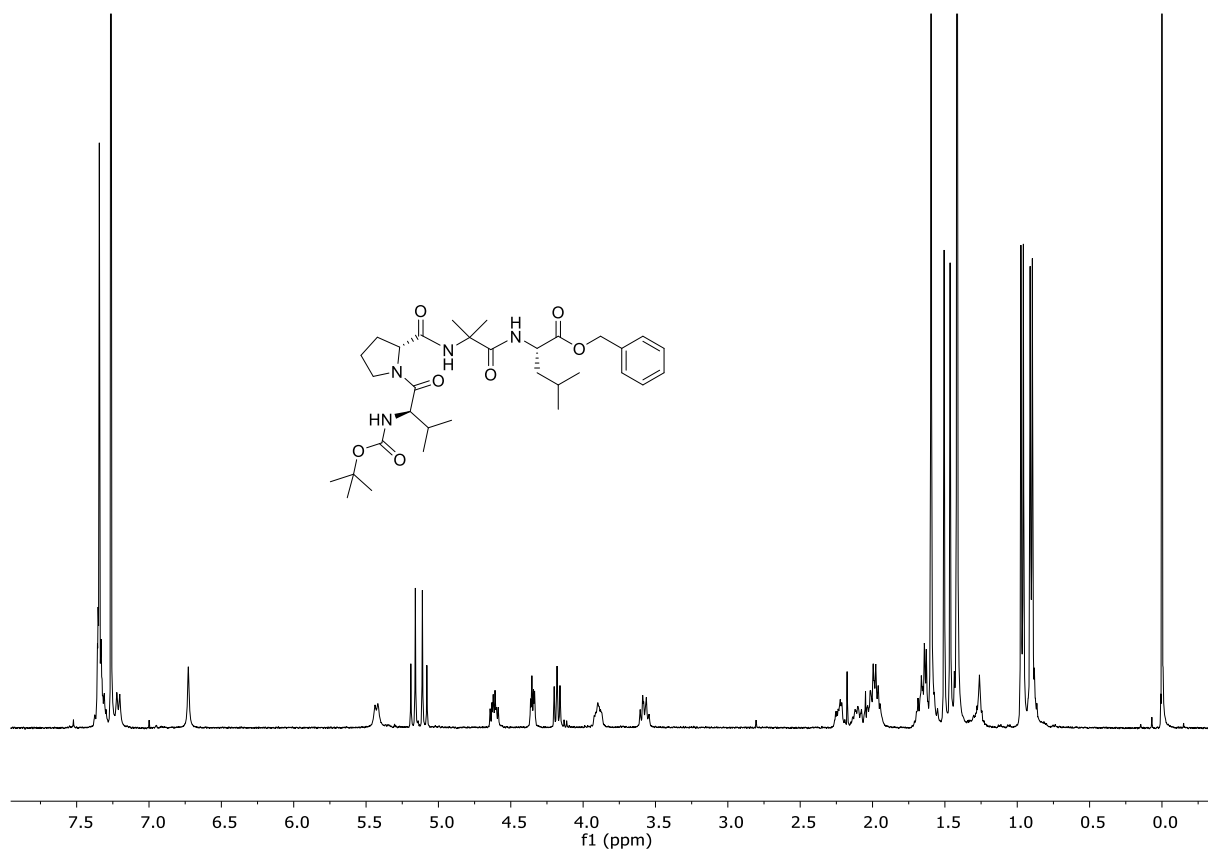
Spectrum S4. ¹³C-NMR (125 MHz, CDCl₃, 298 K) of **S8**.

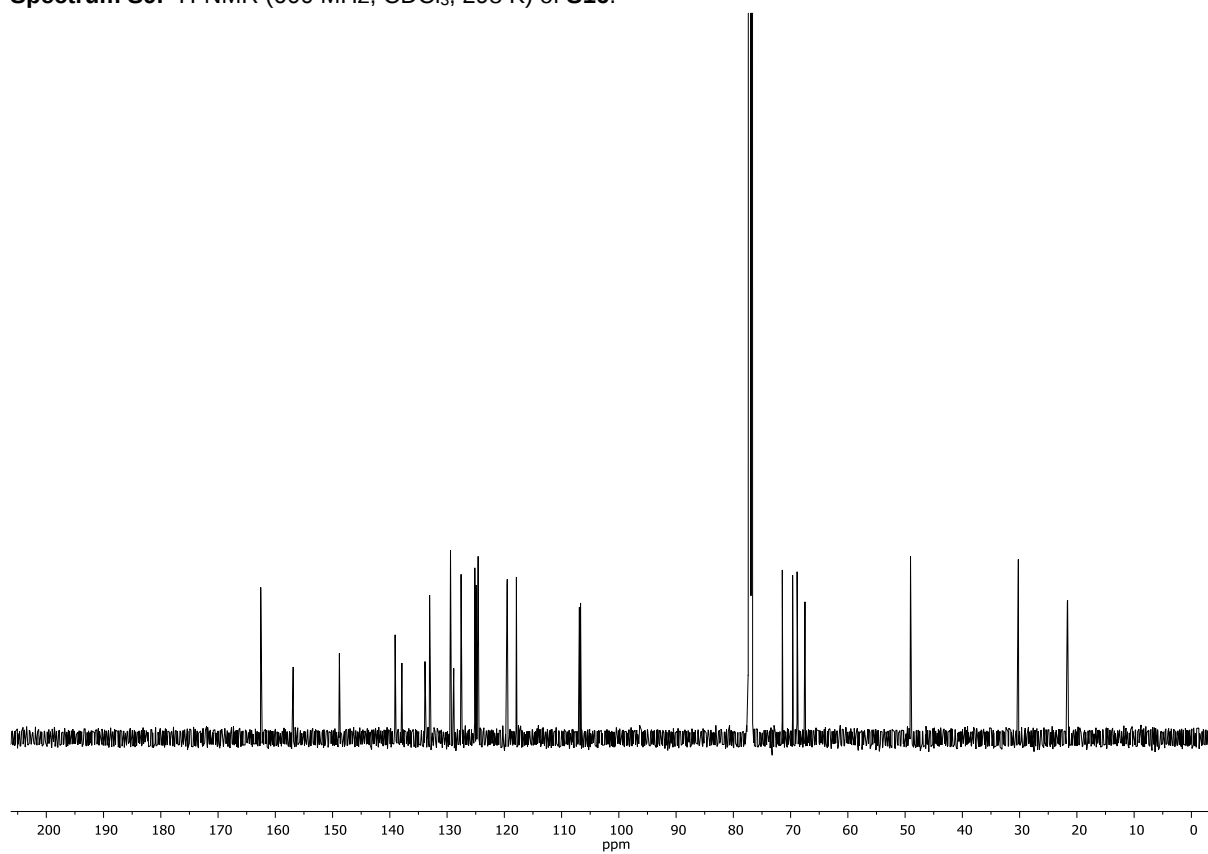
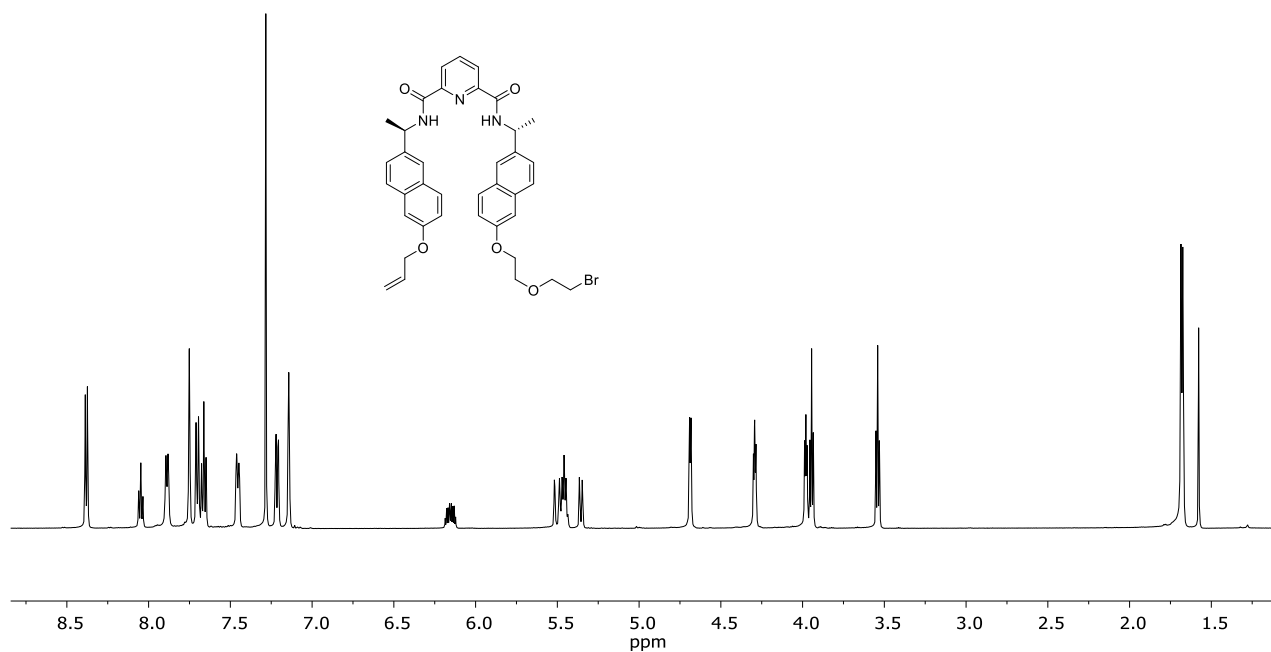


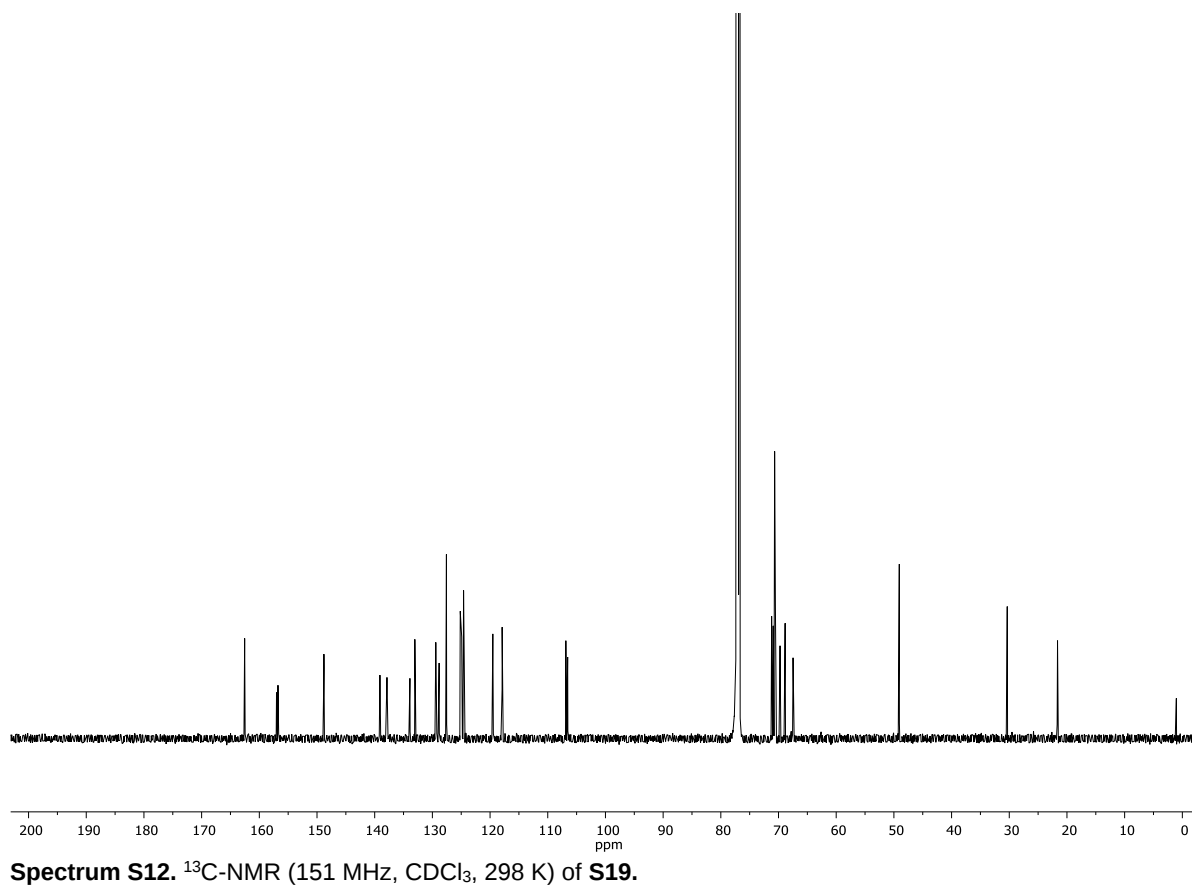
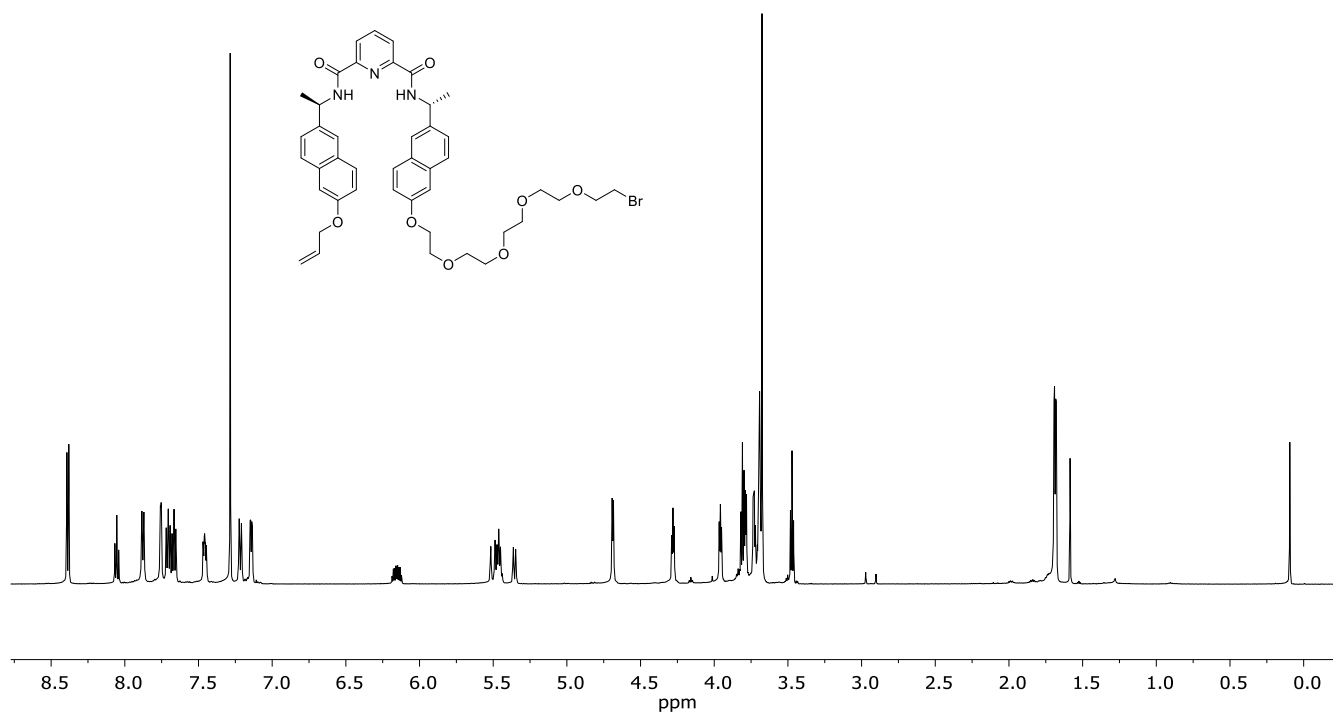
Spectrum S5. ¹H-NMR (500 MHz, CDCl₃, 298 K) of **S10**.

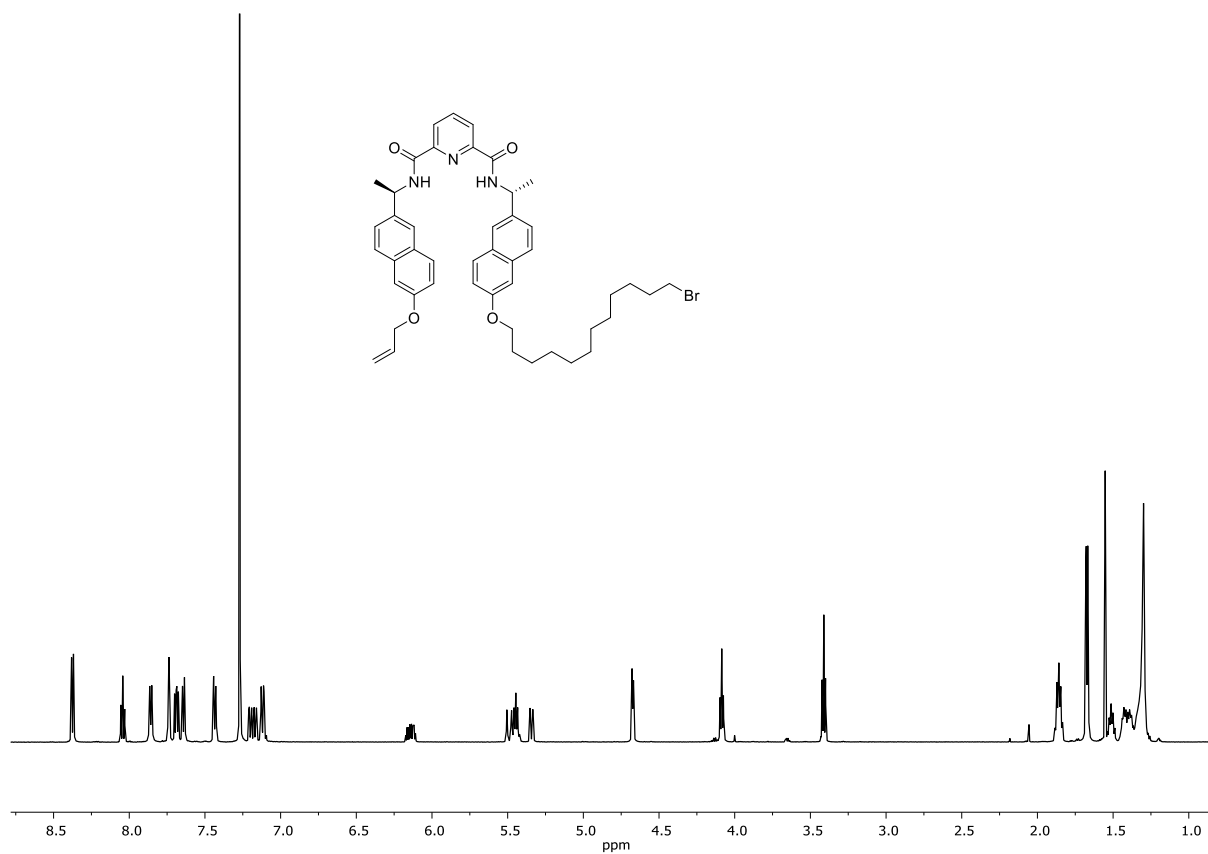


Spectrum S6. ¹³C-NMR (125 MHz, CDCl₃, 298 K) of **S10**.

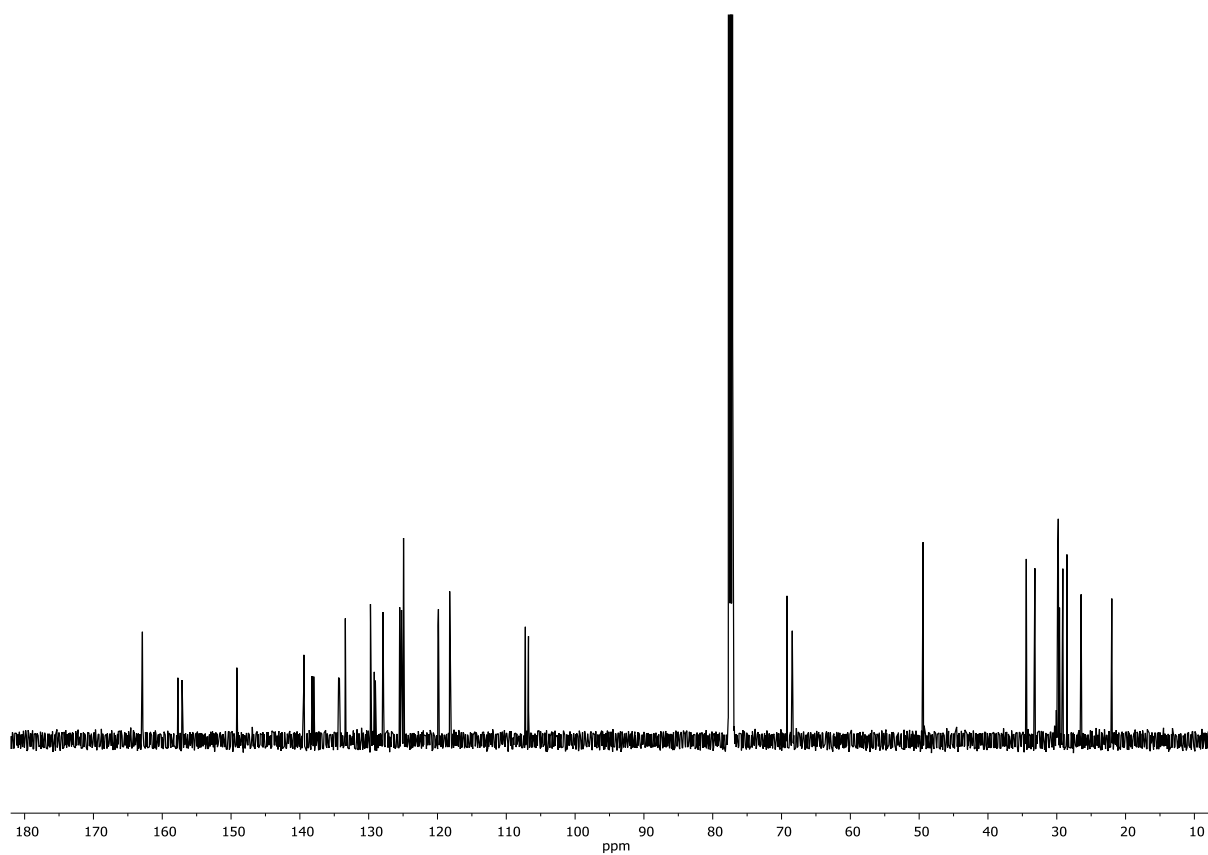




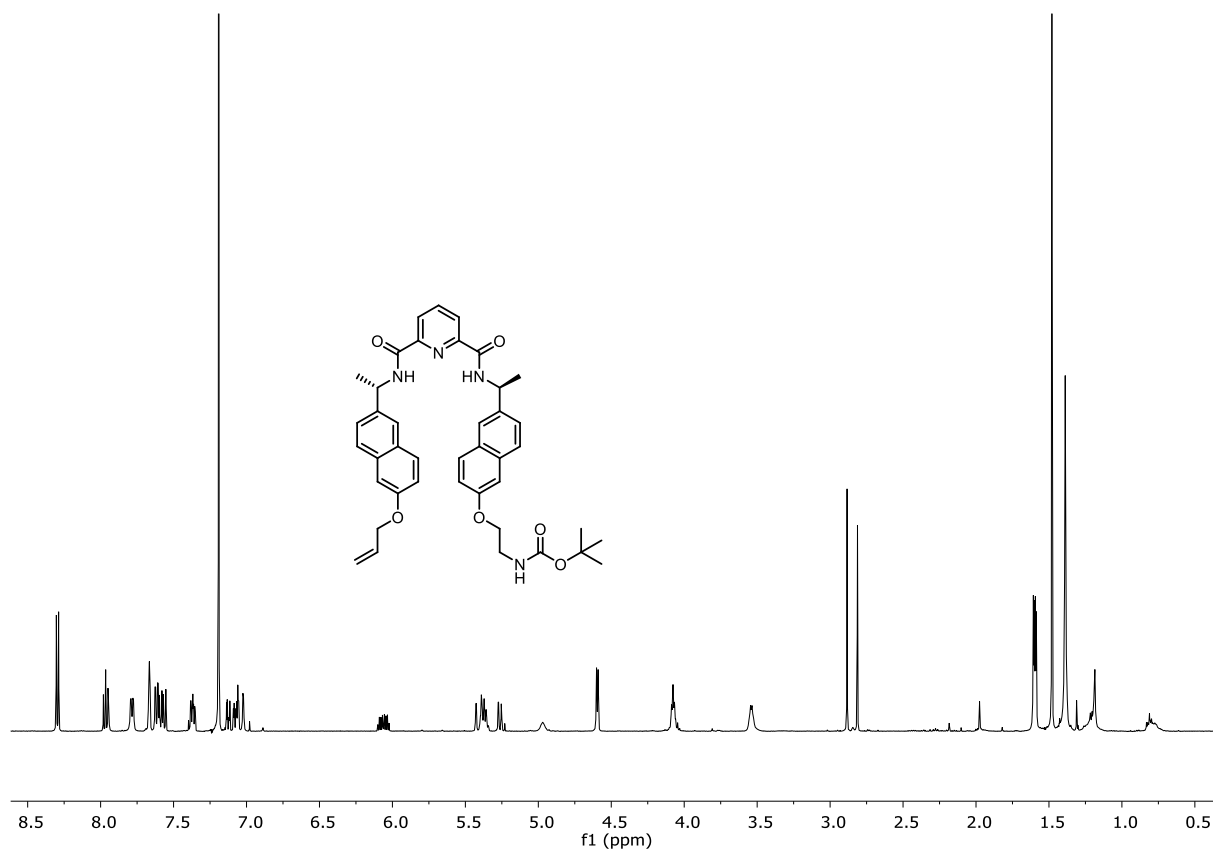




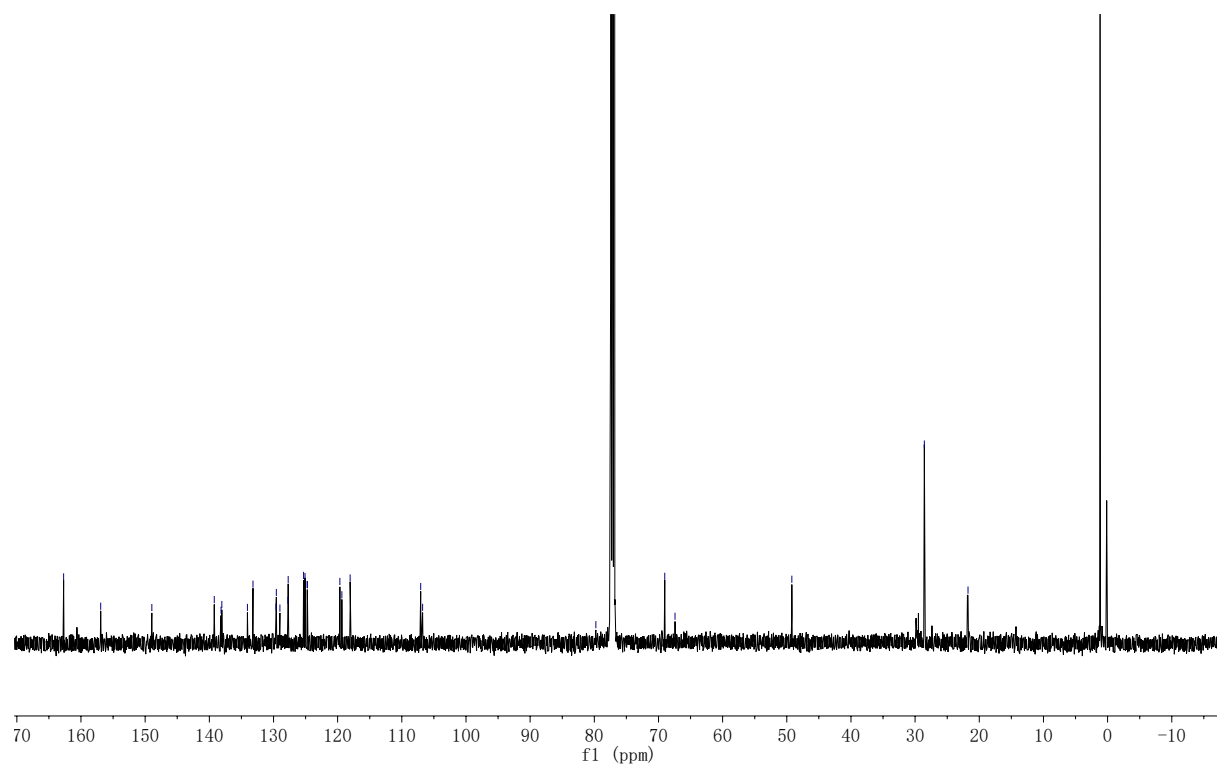
Spectrum S13. ^1H -NMR (600 MHz, CDCl_3 , 298 K) of **S21**.



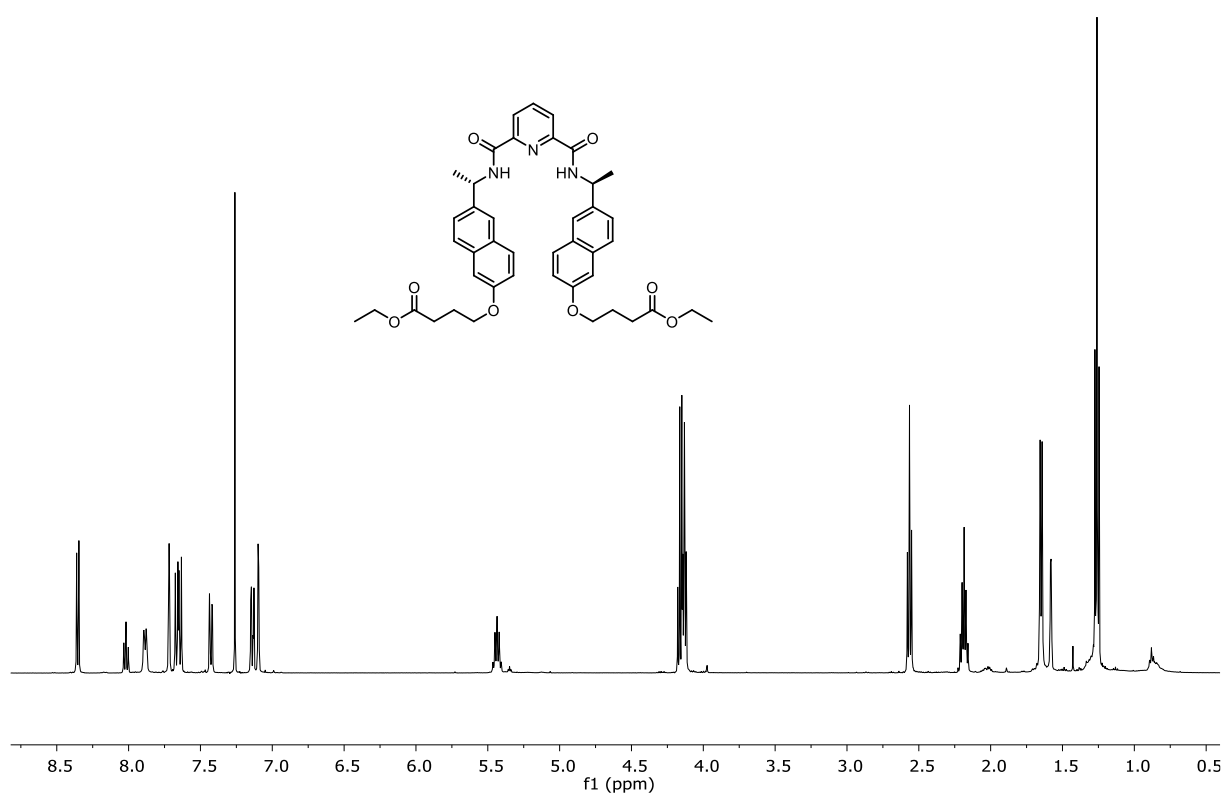
Spectrum S14. ^{13}C -NMR (151 MHz, CDCl_3 , 298 K) of **S21**.



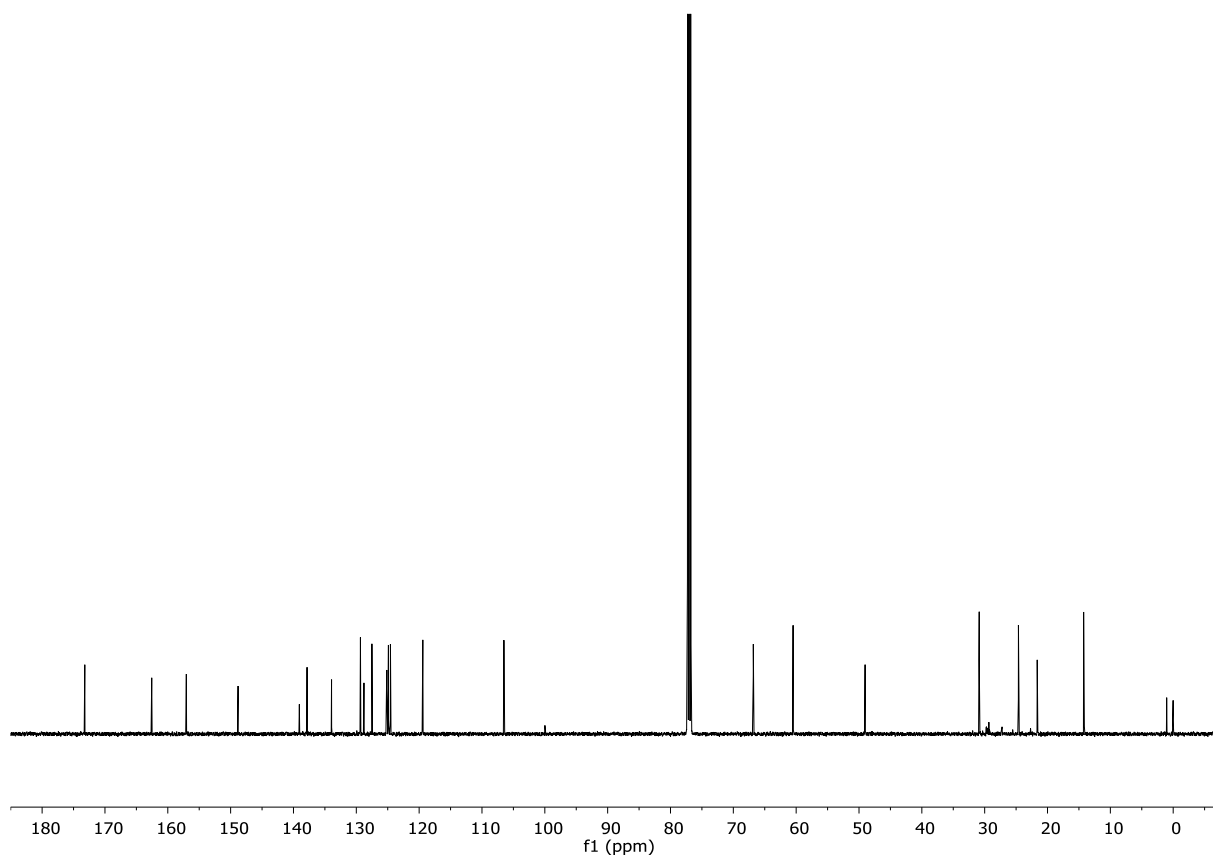
Spectrum S15. ¹H-NMR (500 MHz, CDCl₃, 298 K) of S22.



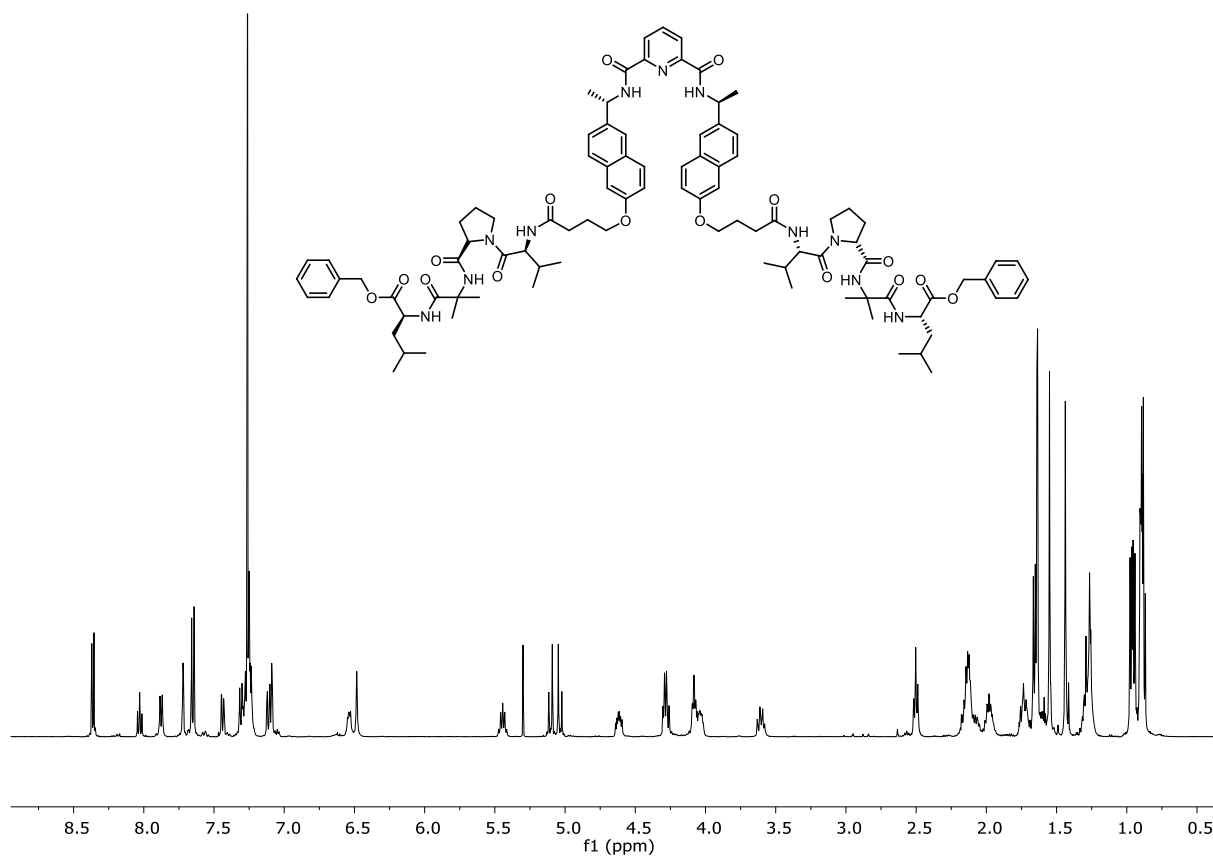
Spectrum S16. ¹³C-NMR (125 MHz, CDCl₃, 298 K) of S22.



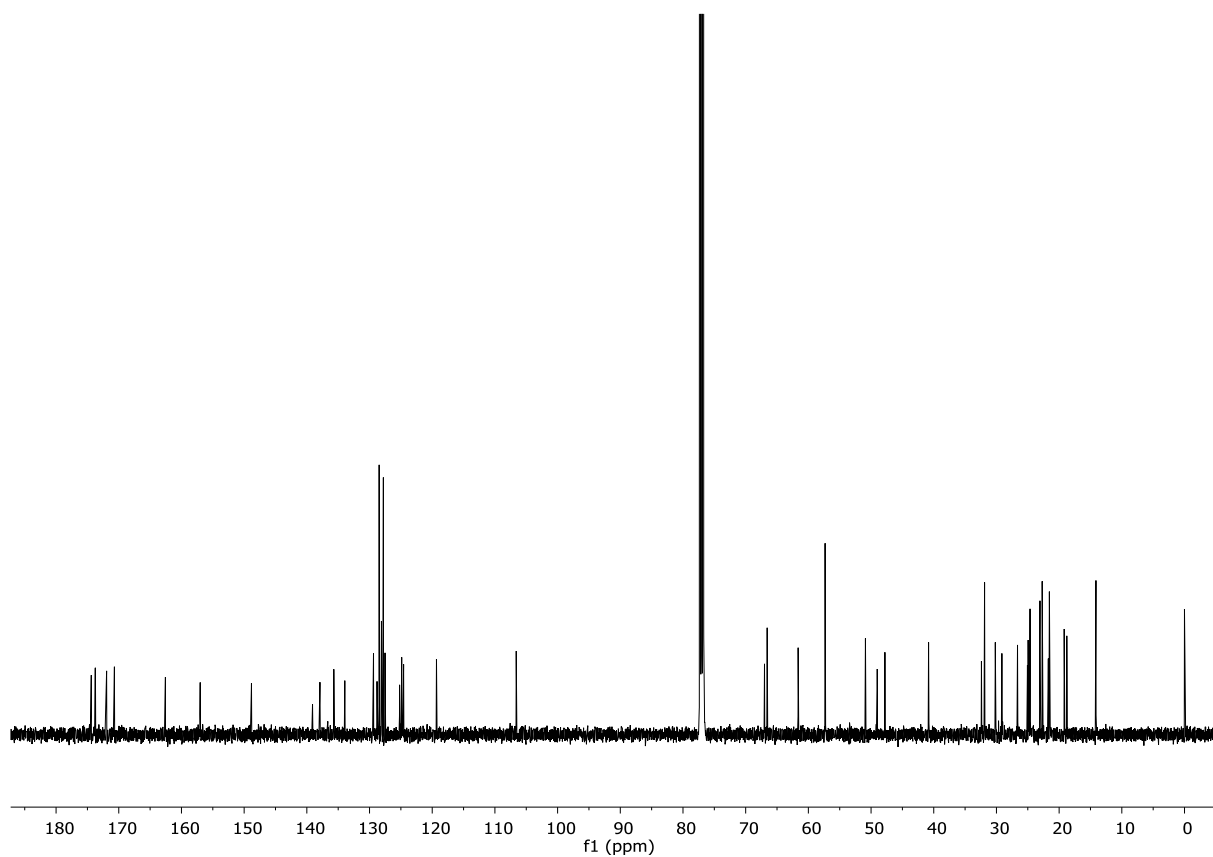
Spectrum S17. ¹H-NMR (500 MHz, CDCl₃, 298 K) of **S23**.



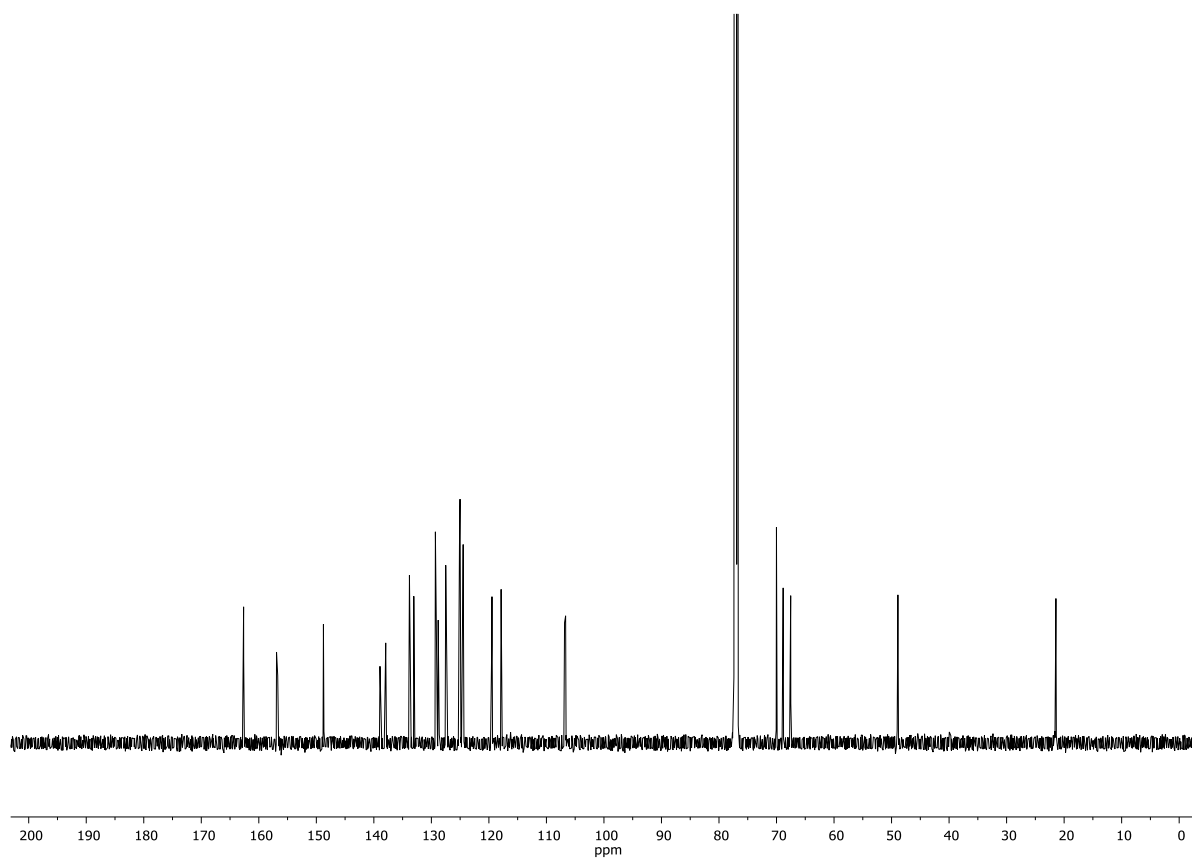
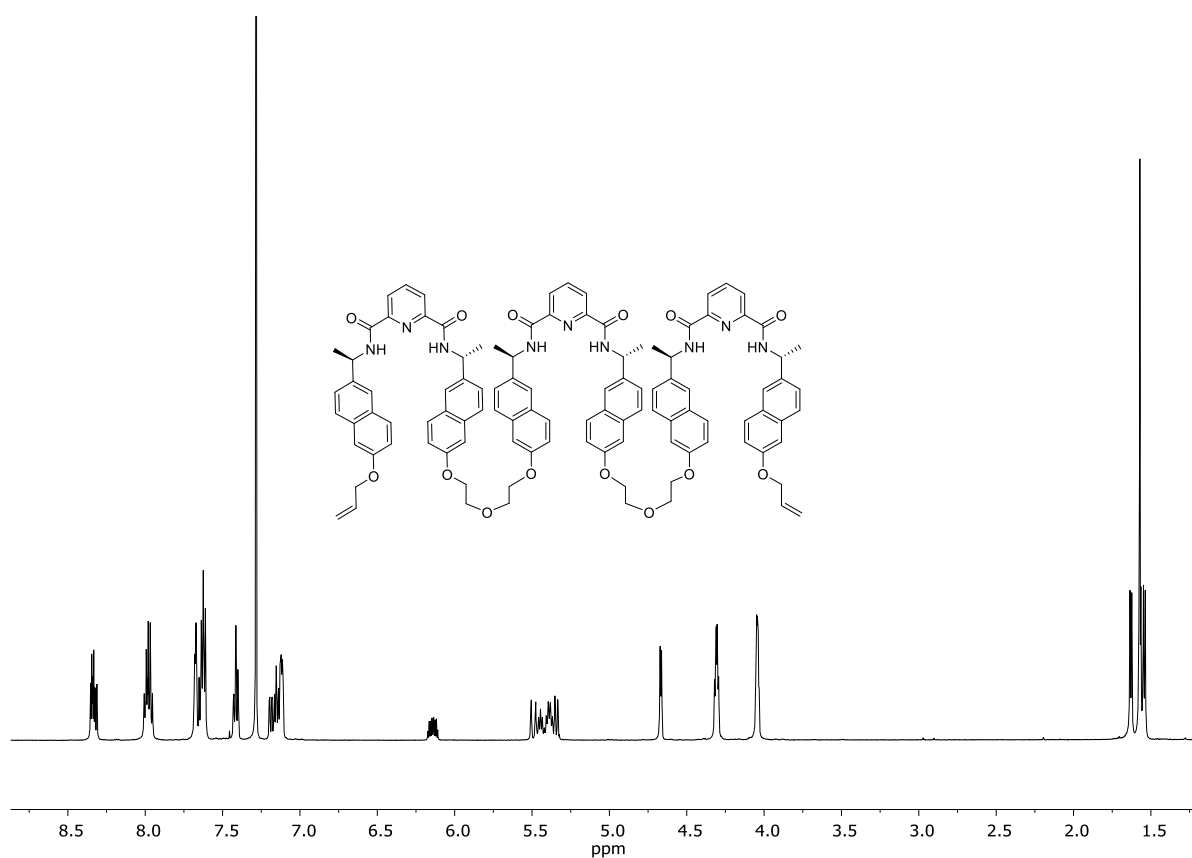
Spectrum S18. ¹³C-NMR (125 MHz, CDCl₃, 298 K) of **S23**.

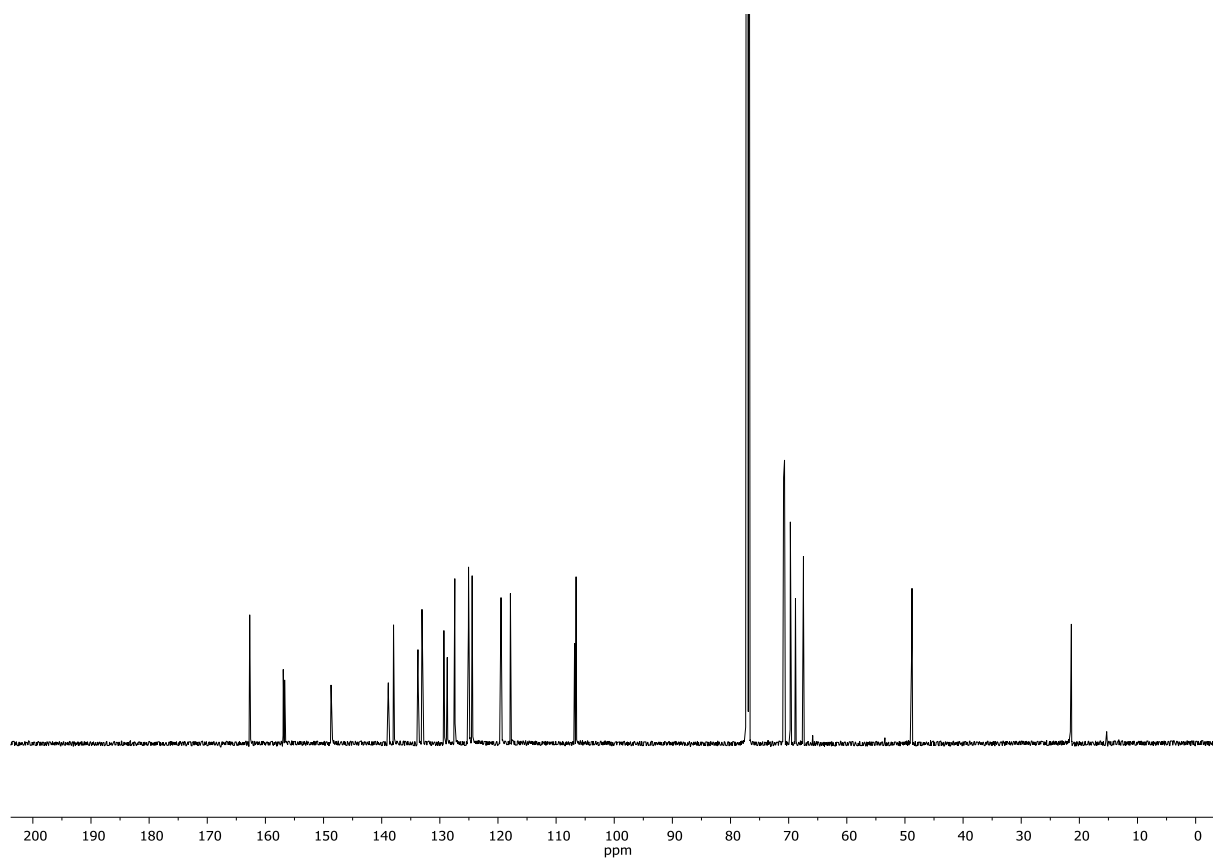
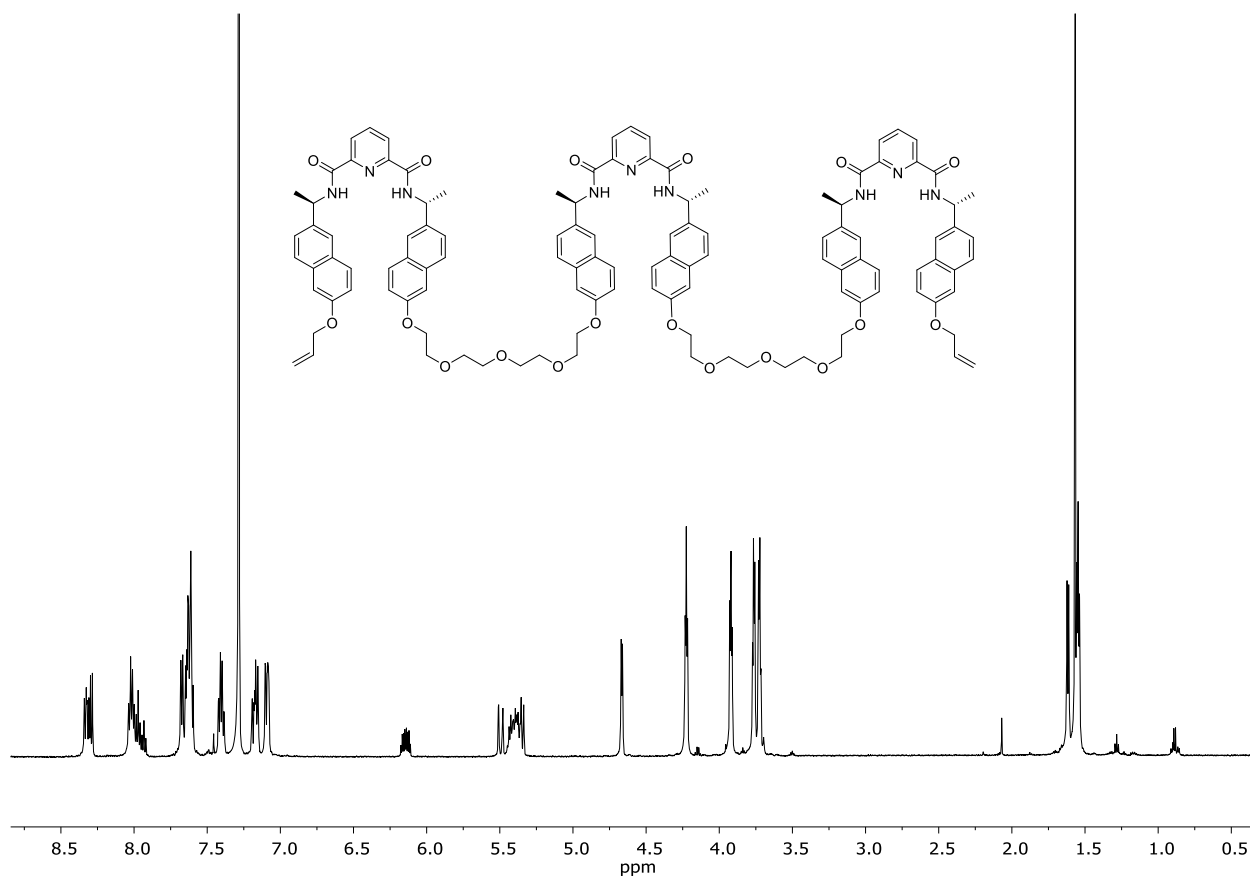


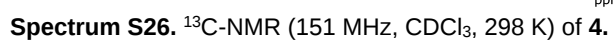
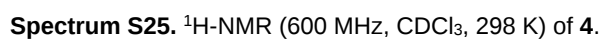
Spectrum S19. ^1H -NMR (500 MHz, CDCl_3 , 298 K) of **A5**.

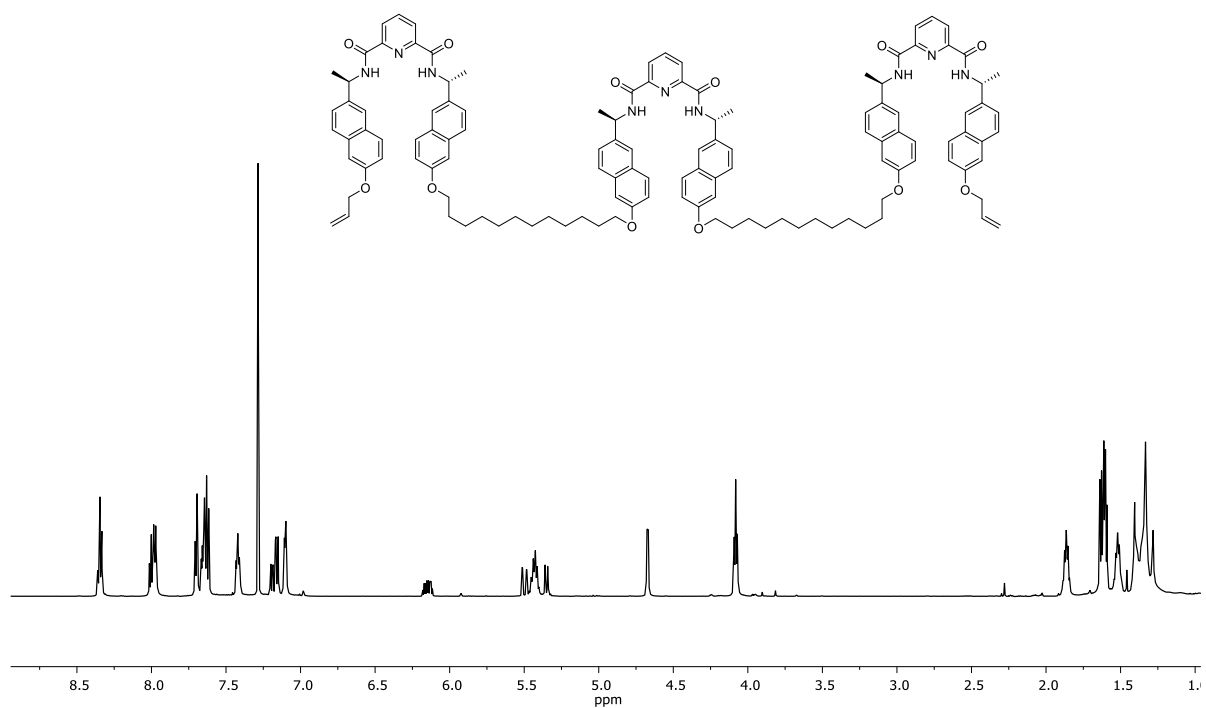


Spectrum S20. ^{13}C -NMR (125 MHz, CDCl_3 , 298 K) of **A5**.

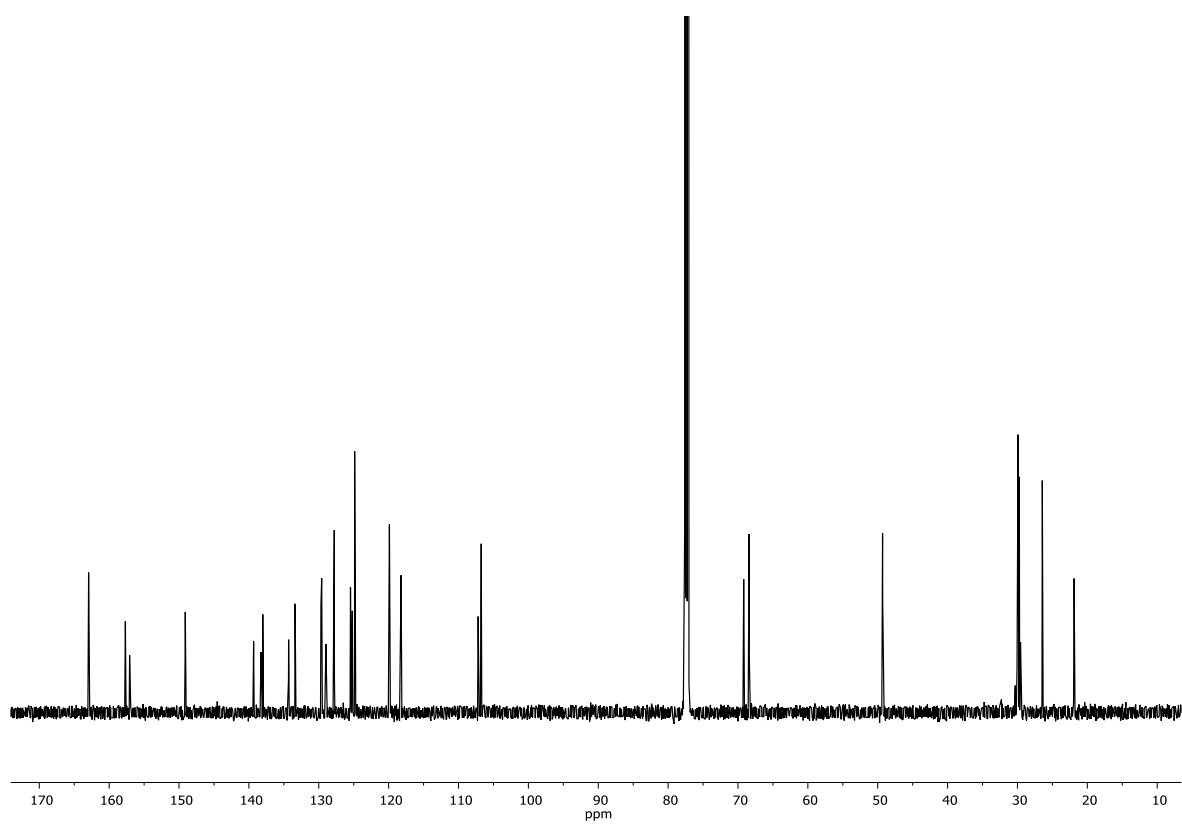




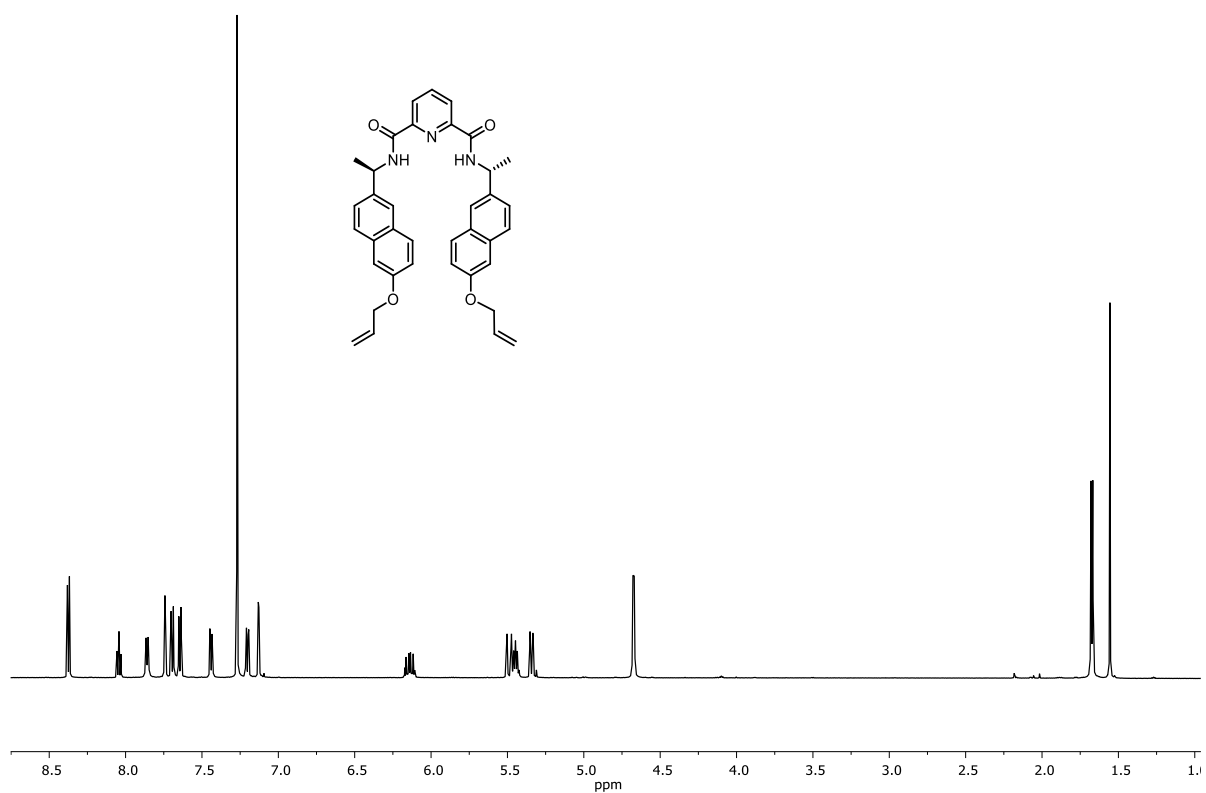




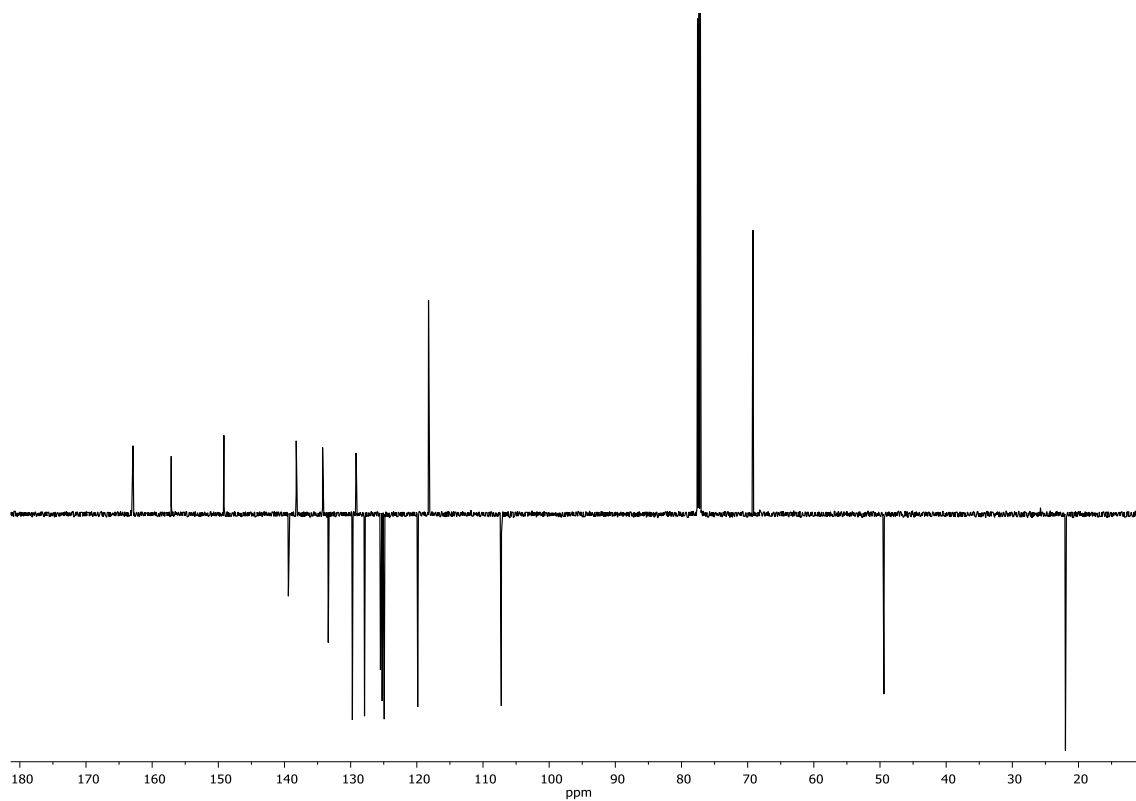
Spectrum S27. ^1H -NMR (600 MHz, CDCl_3 , 298 K) of **6**.



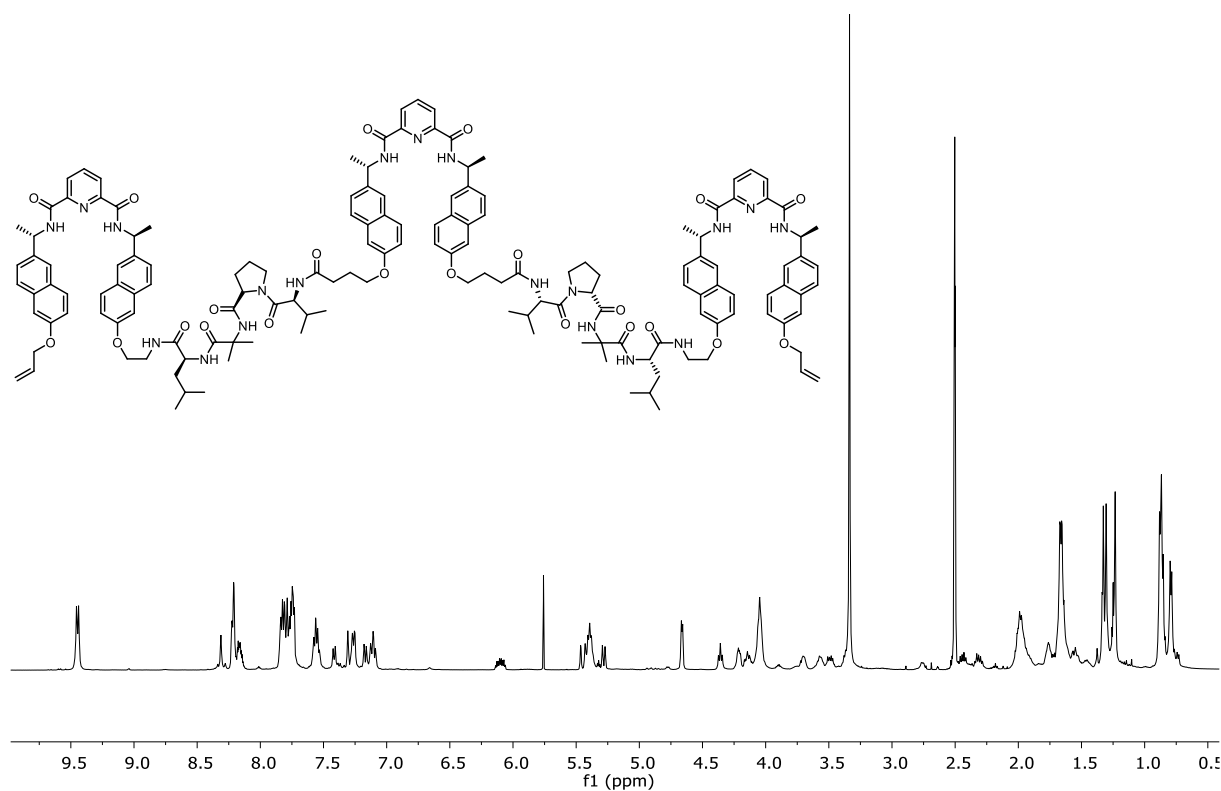
Spectrum S28. ^{13}C -NMR (151 MHz, CDCl_3 , 298 K) of **6**.



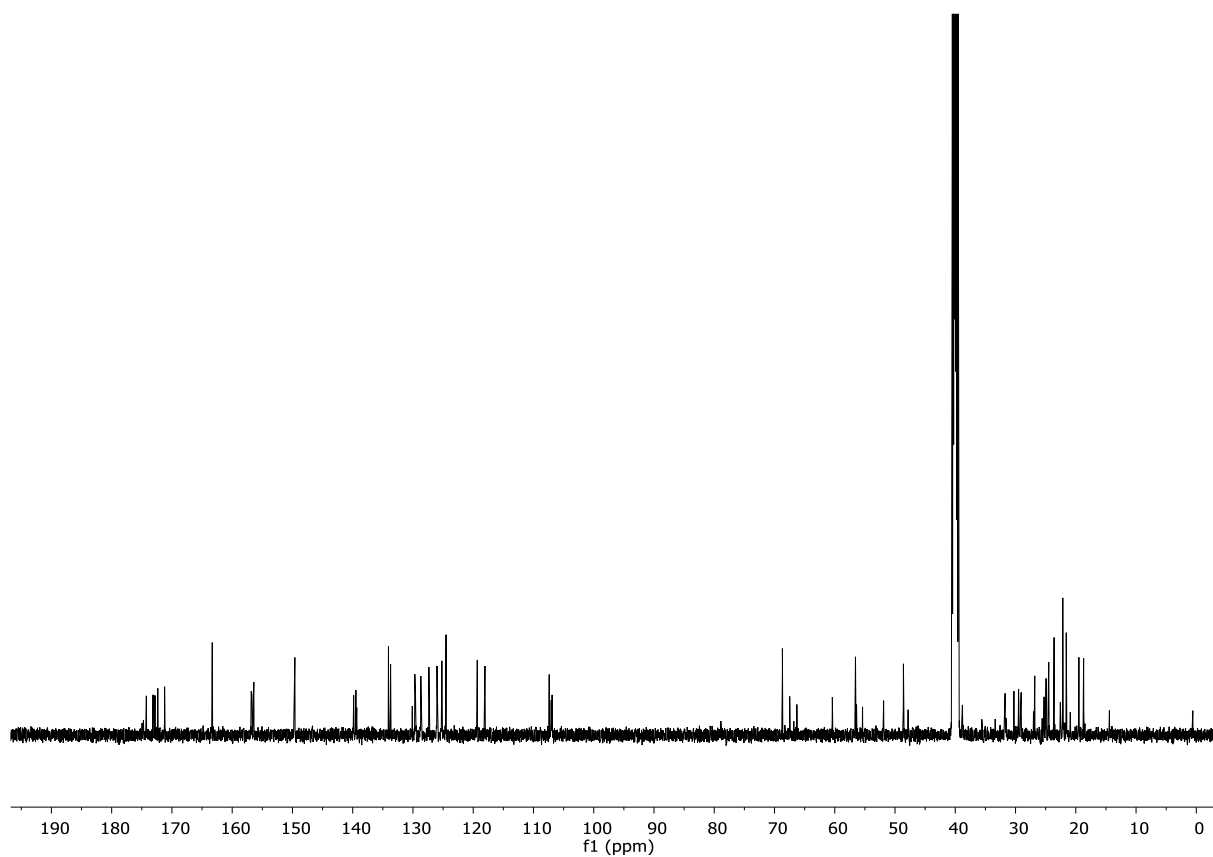
Spectrum S29. ¹H-NMR (600 MHz, CDCl₃, 298 K) of 7.



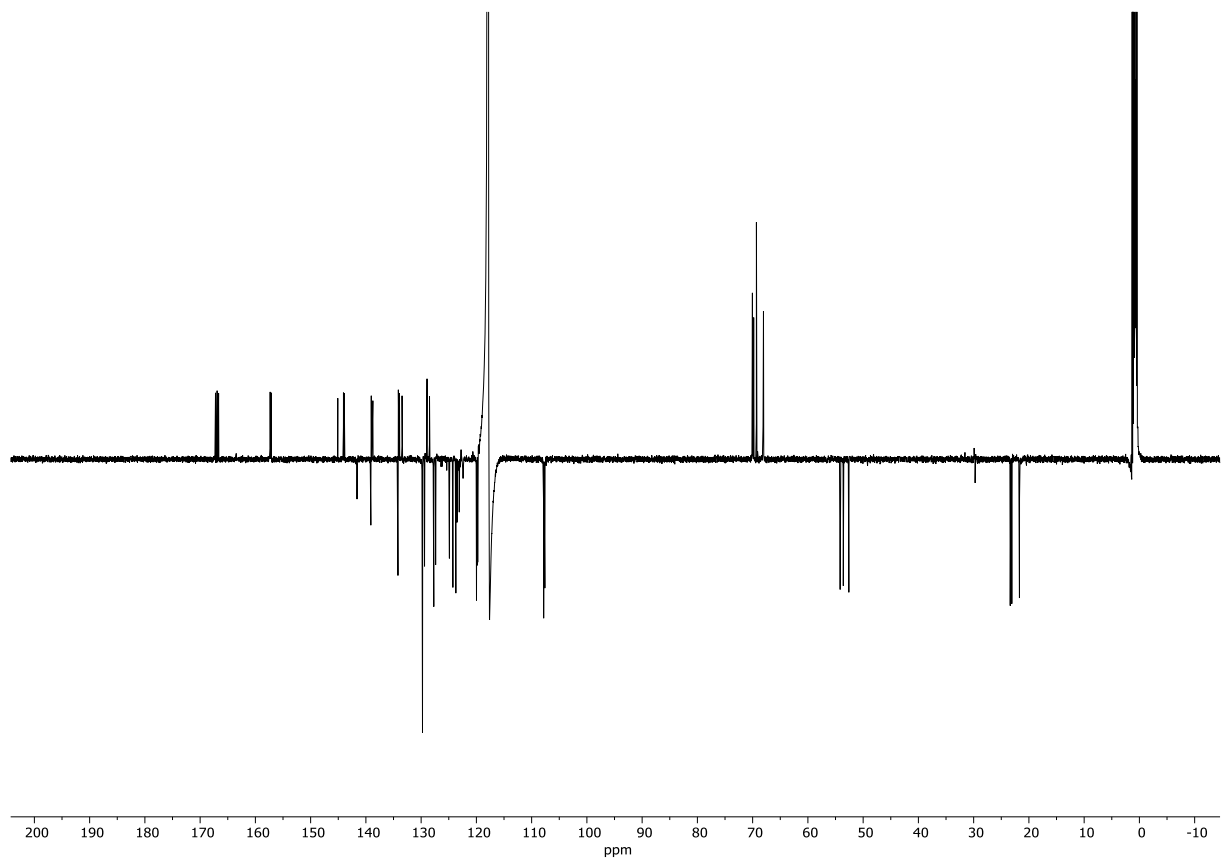
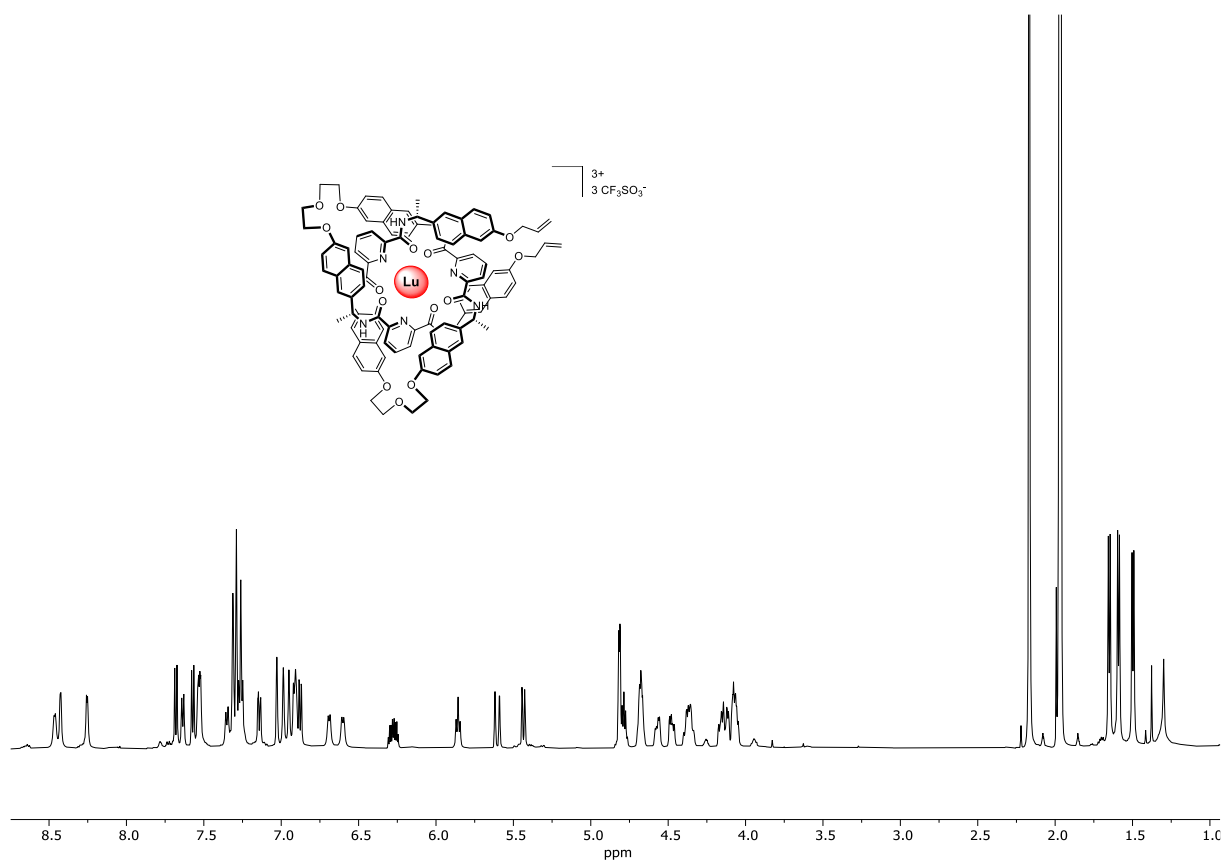
Spectrum S30. ¹³C DEPT-NMR (151 MHz, CD₃CN, 298 K) of 7.

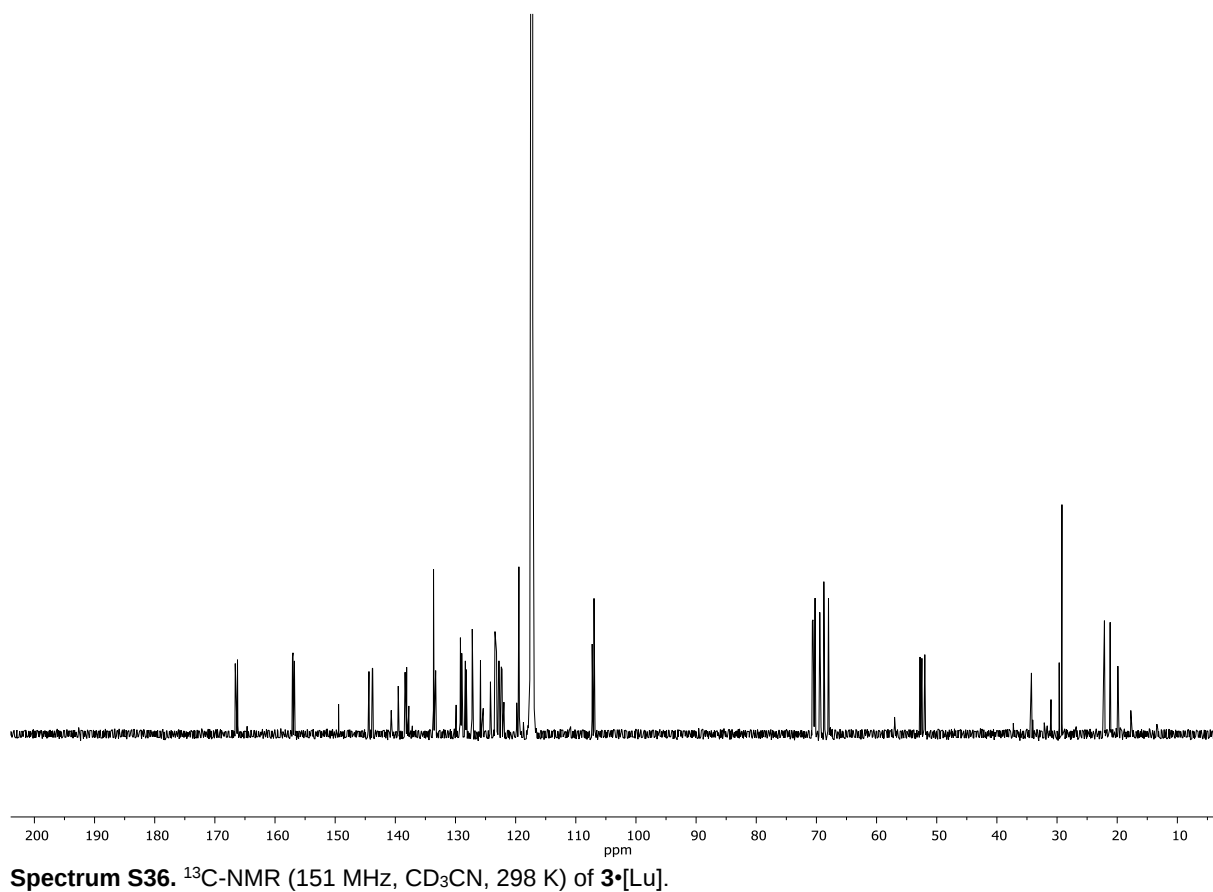
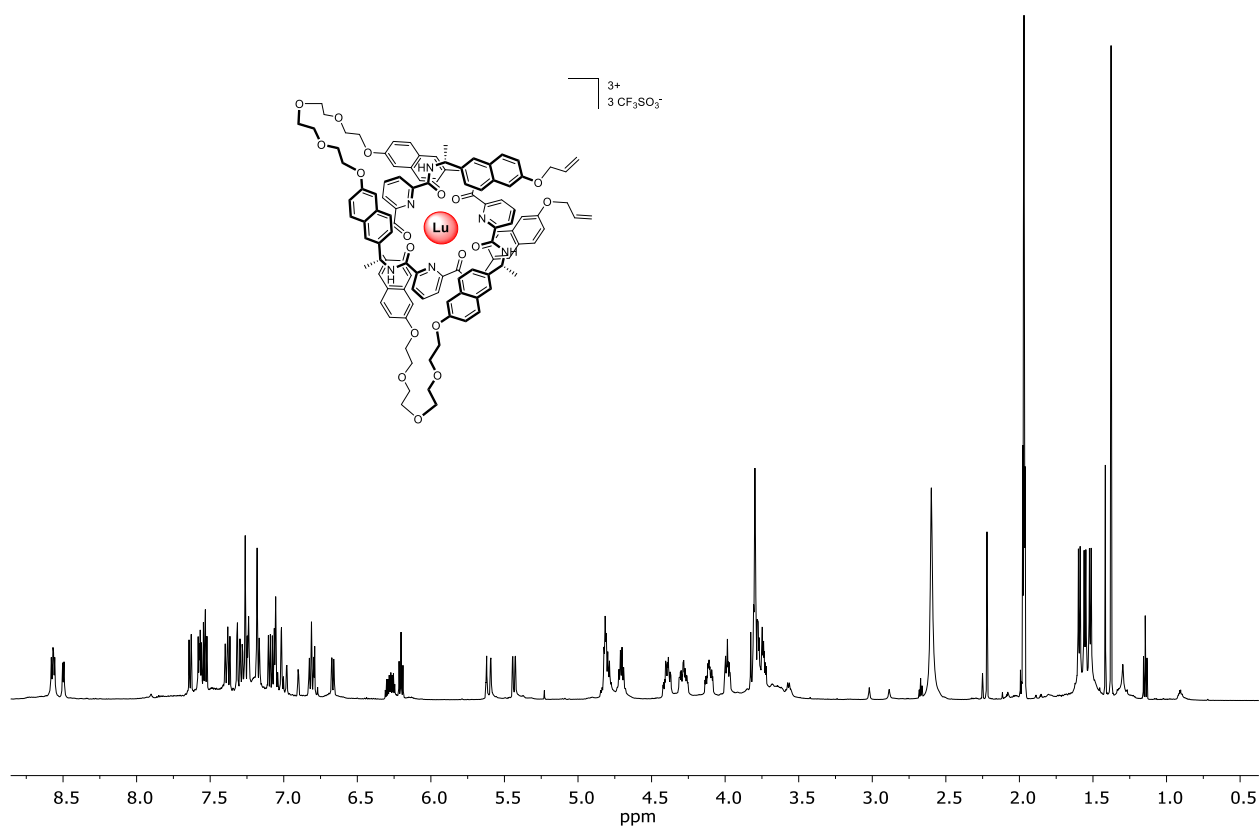


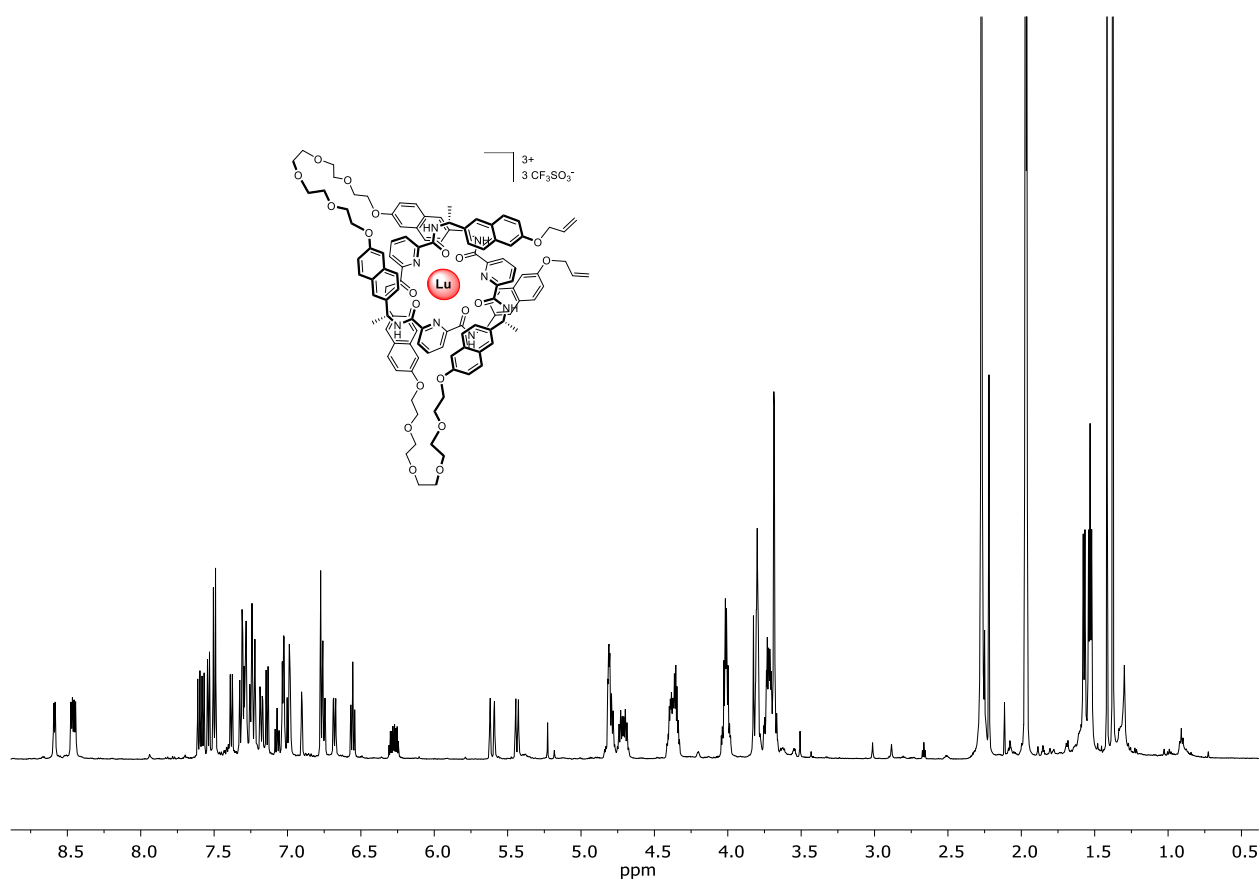
Spectrum S31. ^1H -NMR (500 MHz, $\text{DMSO}-d_6$, 298 K) of **8**.



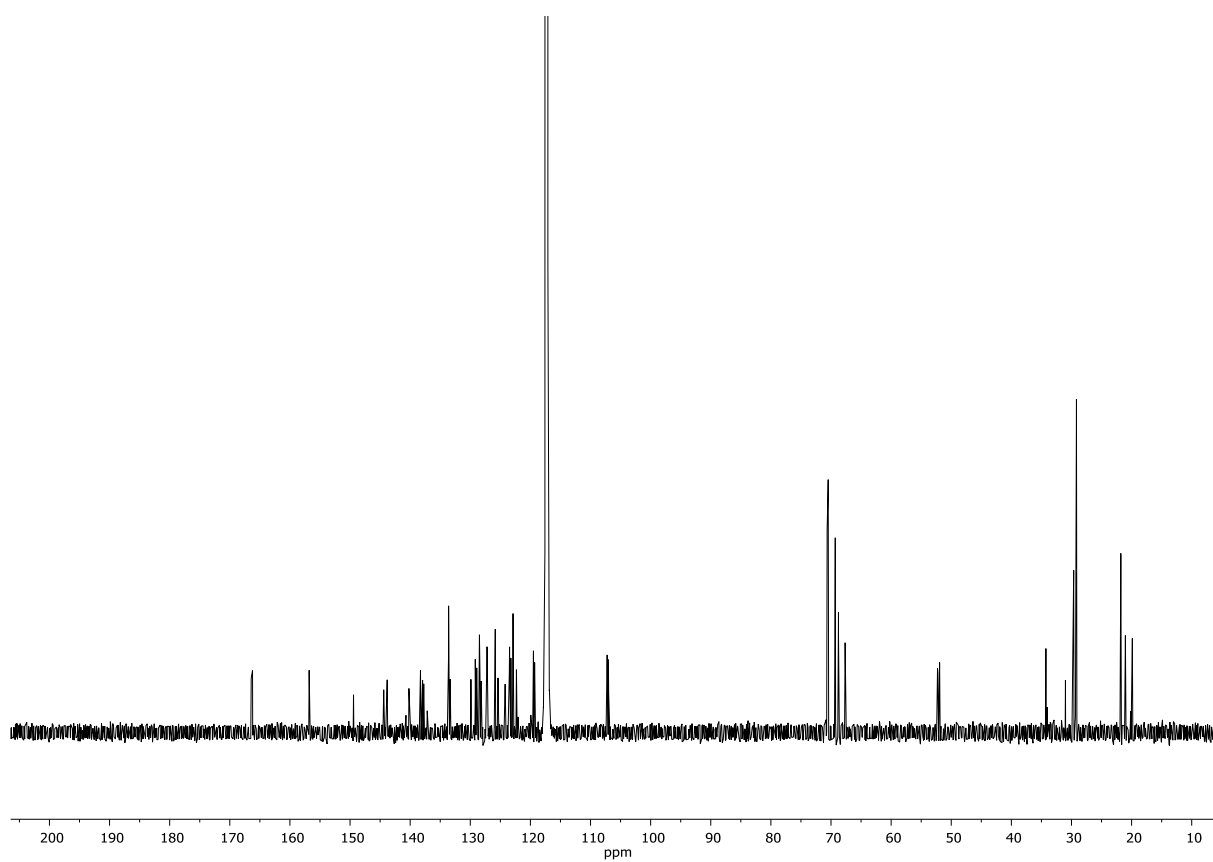
Spectrum S32. ^{13}C -NMR (125 MHz, $\text{DMSO}-d_6$, 298 K) of **8**.



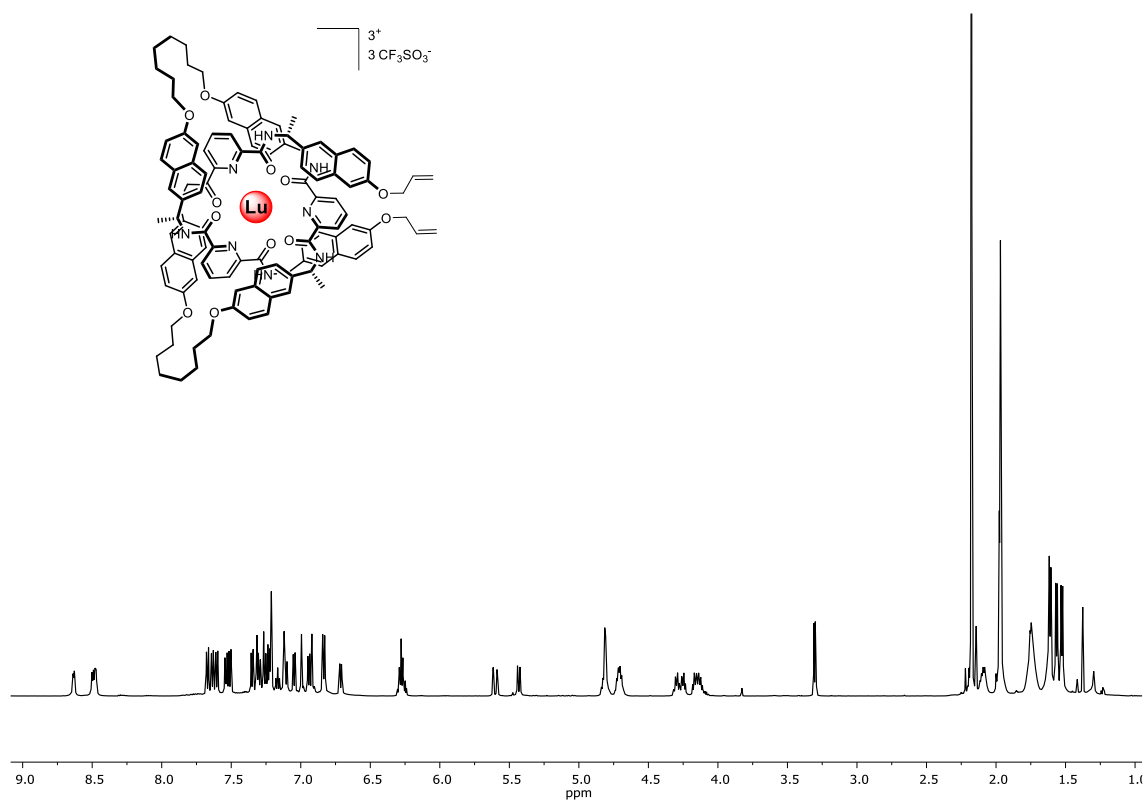




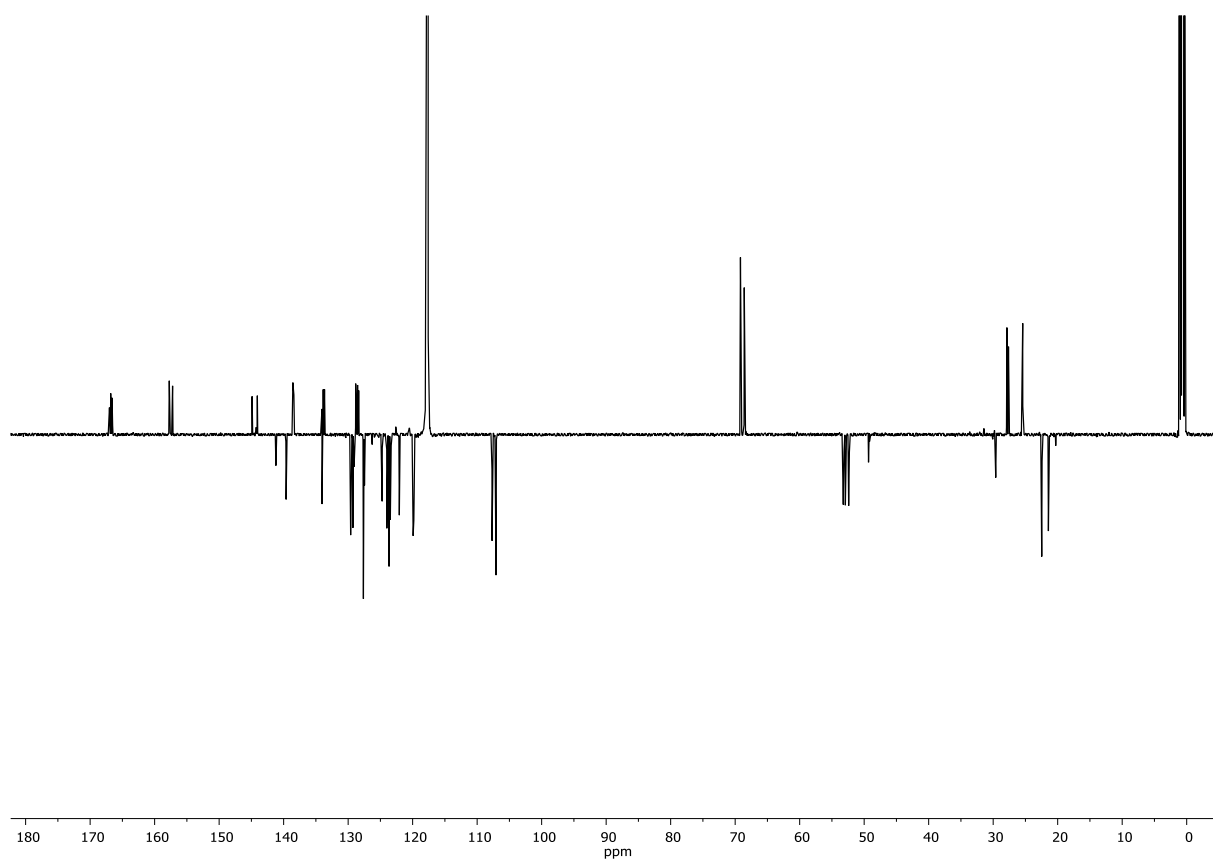
Spectrum S37. $^1\text{H-NMR}$ (600 MHz, CD_3CN , 298 K) of $4\bullet[\text{Lu}]$.



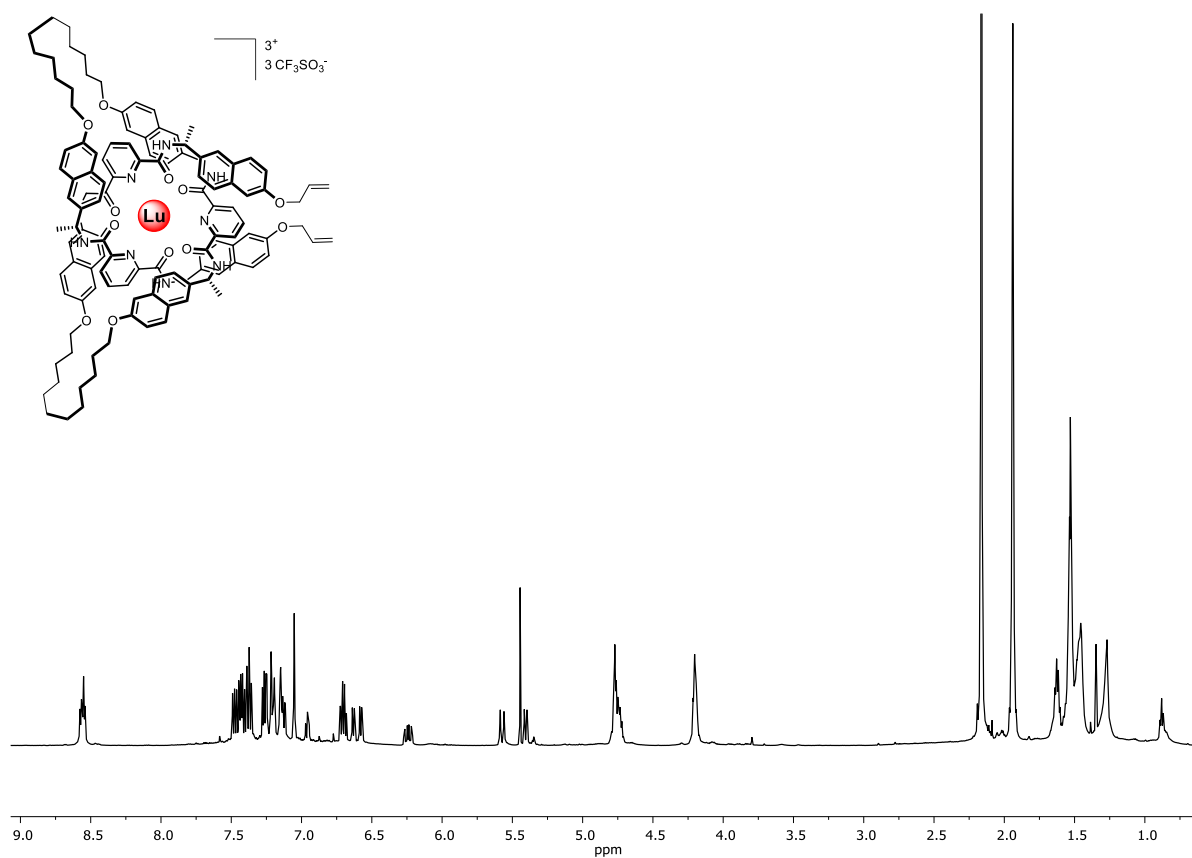
Spectrum S38. $^{13}\text{C-NMR}$ (151 MHz, CD_3CN , 298 K) of $4\bullet[\text{Lu}]$.



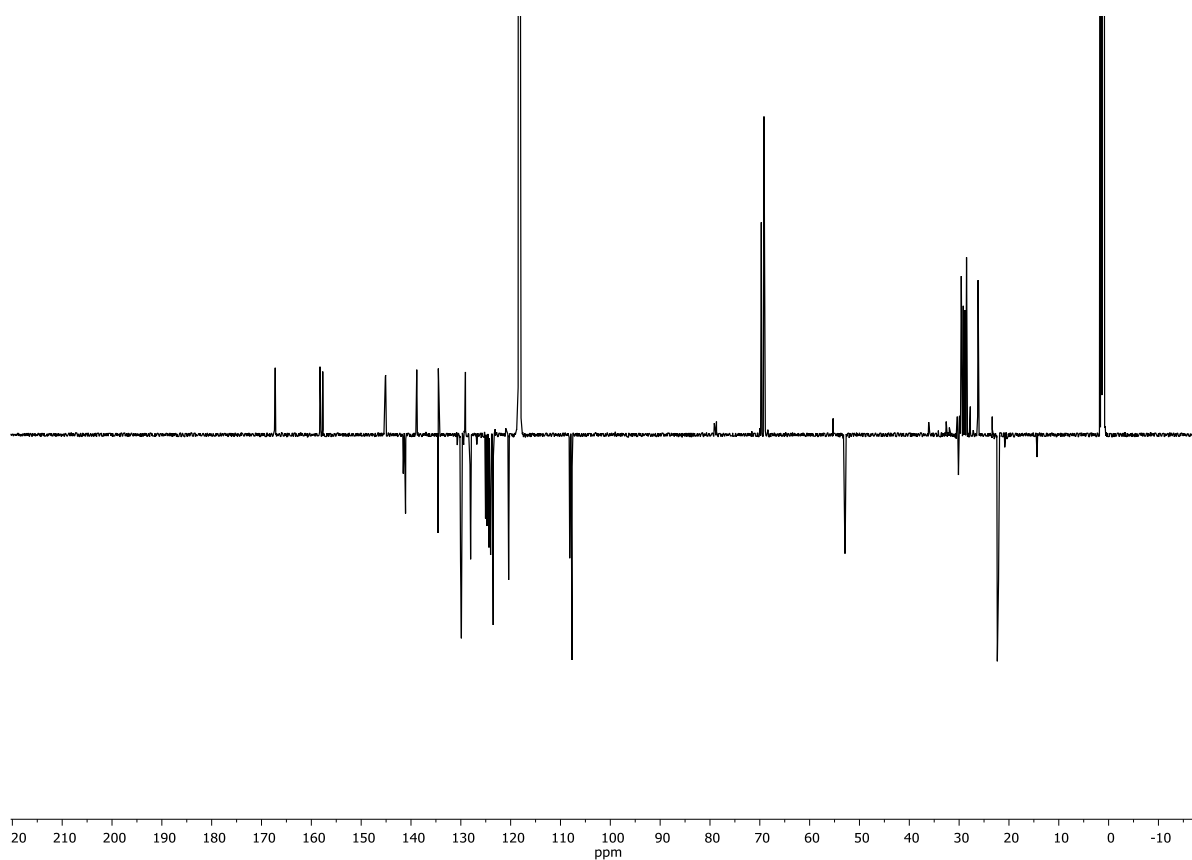
Spectrum S39. ¹H-NMR (600 MHz, CD₃CN, 298 K) of **5**•[Lu].



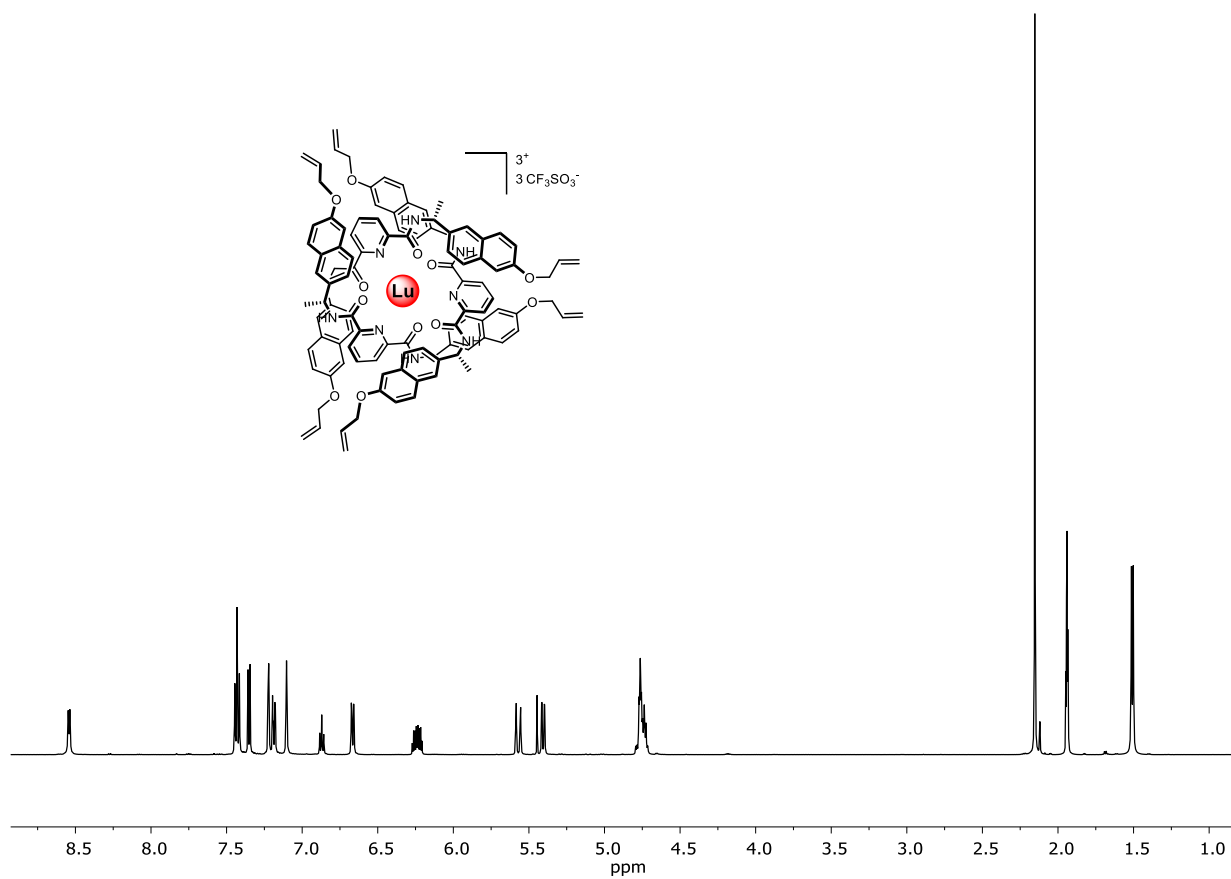
Spectrum S40. ¹³C DEPT-NMR (151 MHz, CD₃CN, 298 K) of **5**•[Lu].



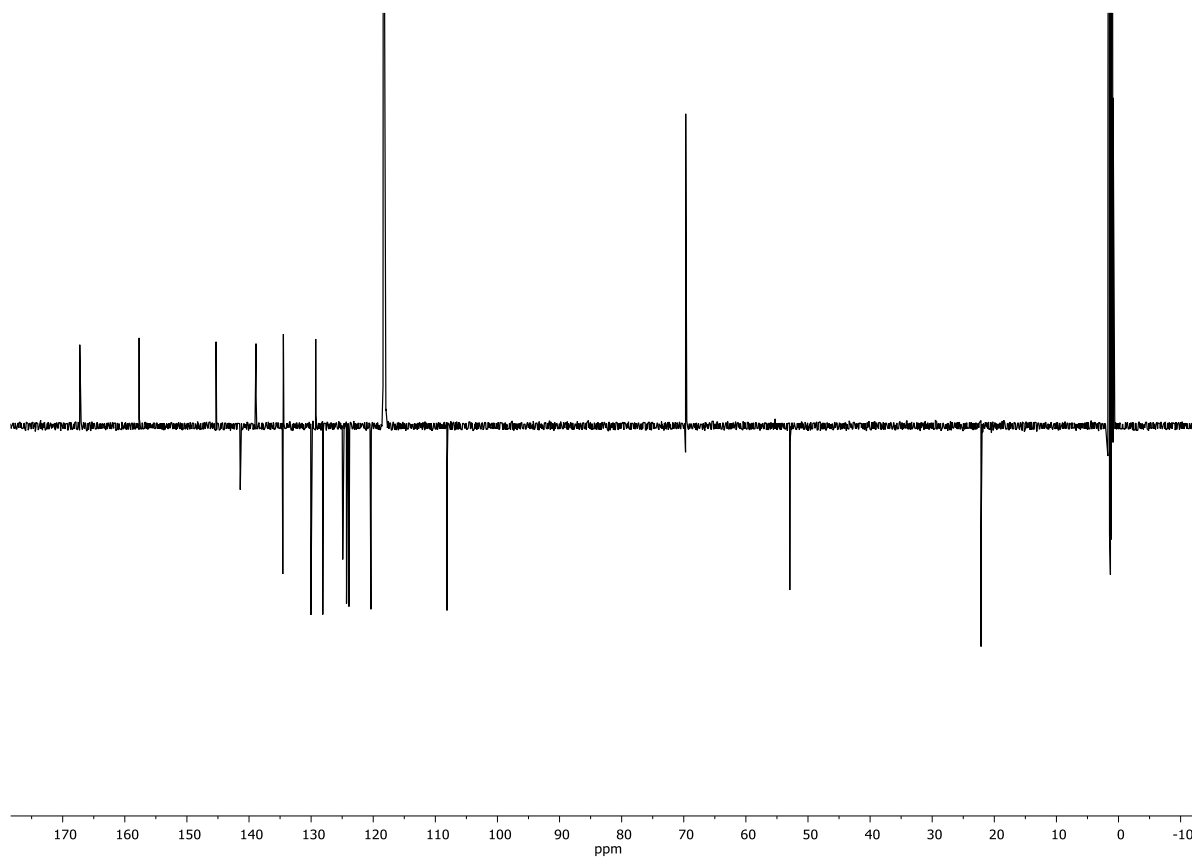
Spectrum S41. ¹H-NMR (600 MHz, CD₃CN, 298 K) of **6•[Lu]**.



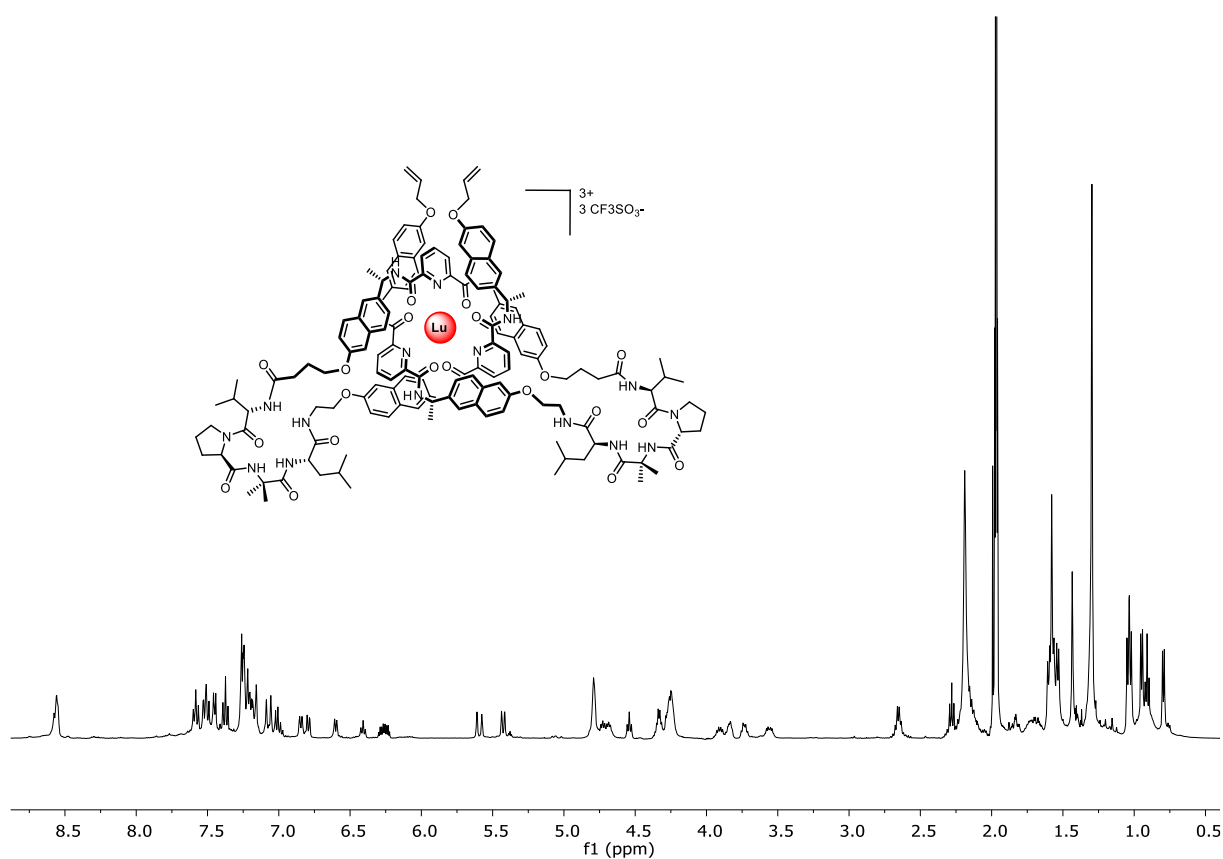
Spectrum S42. ¹³C DEPT-NMR (151 MHz, CD₃CN, 298 K) of **6•[Lu]**.



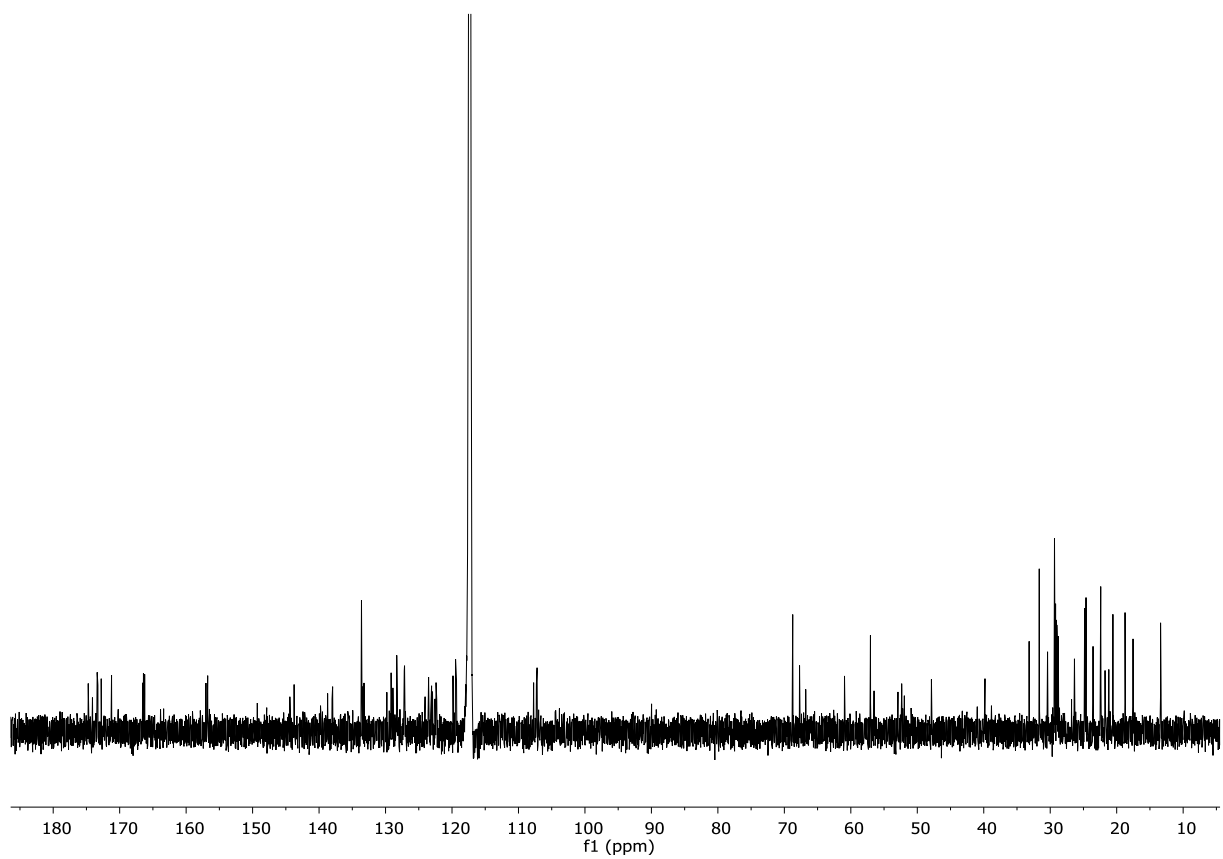
Spectrum S43. ^1H -NMR (600 MHz, CD_3CN , 298 K) of $7_3\bullet[\text{Lu}]$.



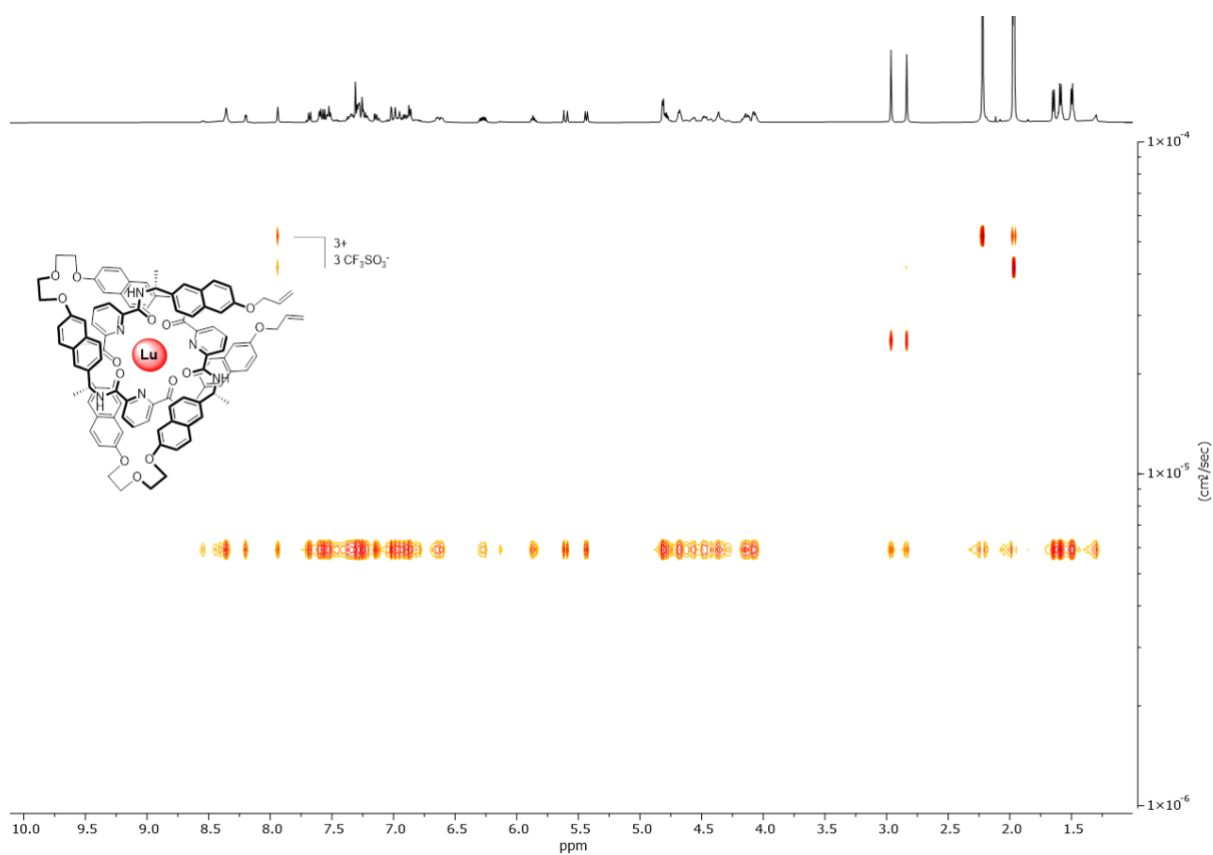
Spectrum S44. ^{13}C DEPT-NMR (151 MHz, CD_3CN , 298 K) of $7_3\bullet[\text{Lu}]$.



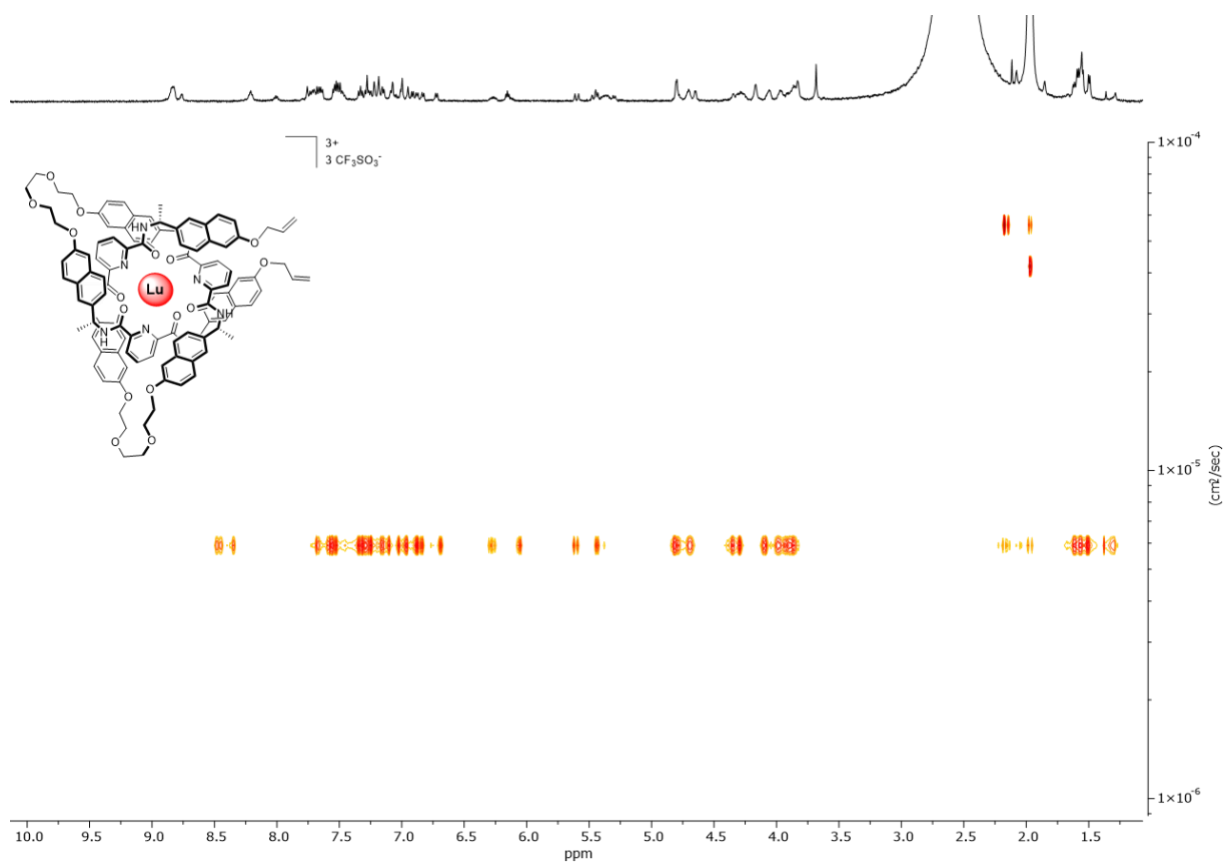
Spectrum S45. ^1H -NMR (500 MHz, CD_3CN , 298 K) of **8•[Lu]**.



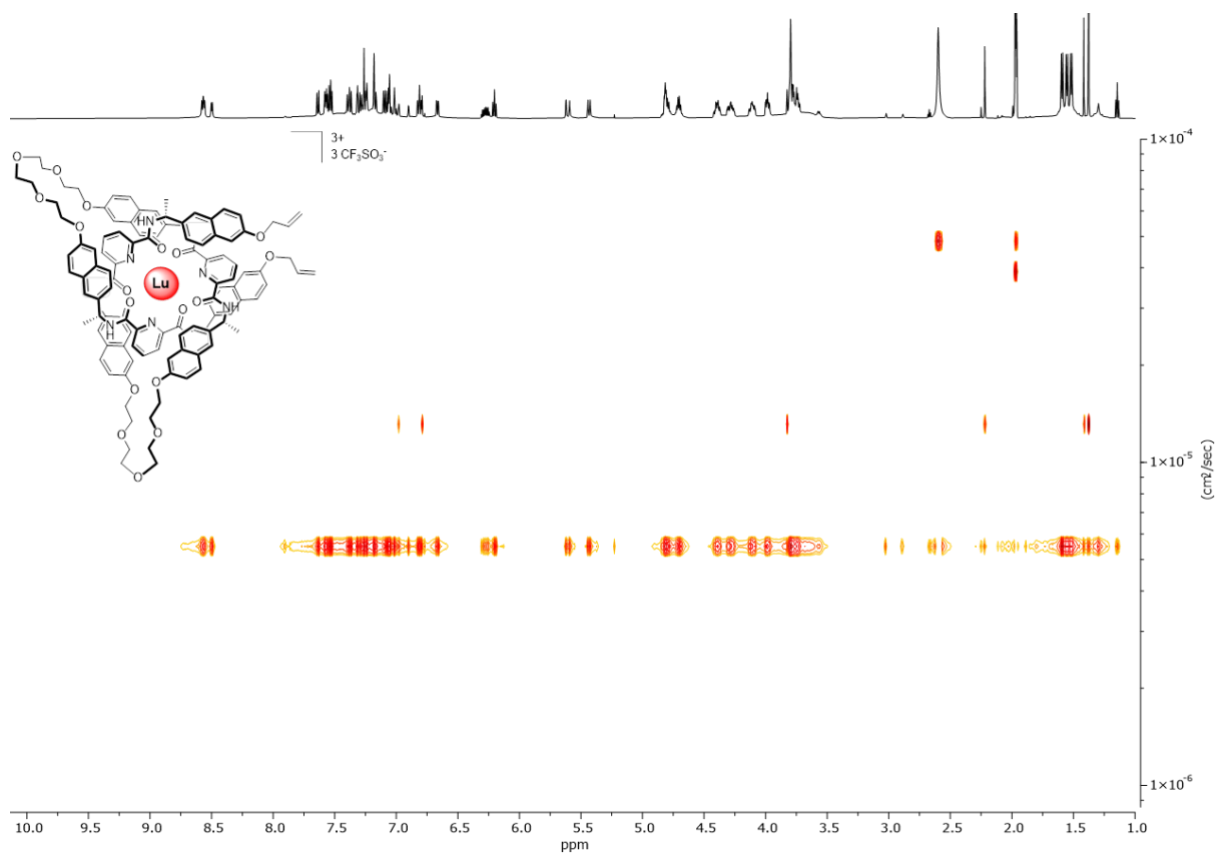
Spectrum S46. ^{13}C -NMR (125 MHz, CD_3CN , 298 K) of **8•[Lu]**.



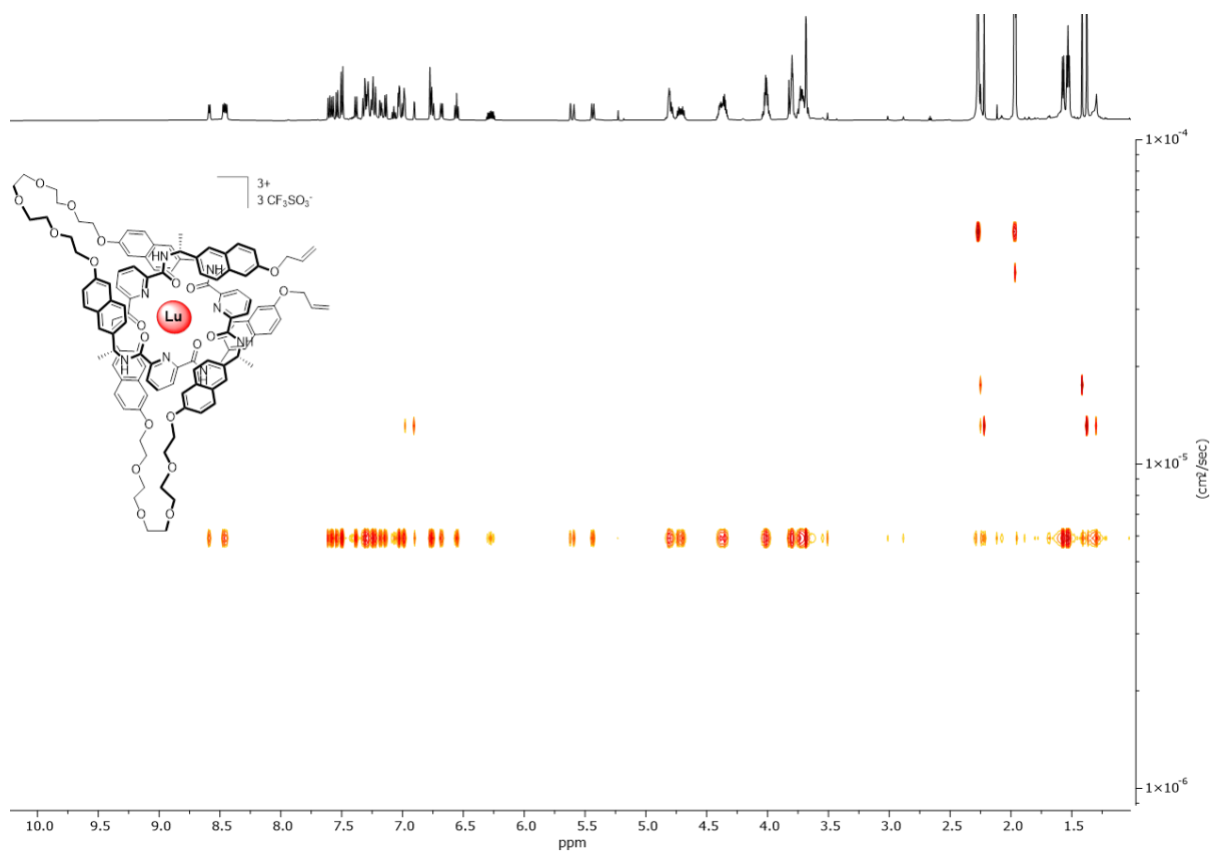
Spectrum S47. DOSY NMR (600 MHz, 298 K, MeCN-*d*₃) of **1•[Lu]**.



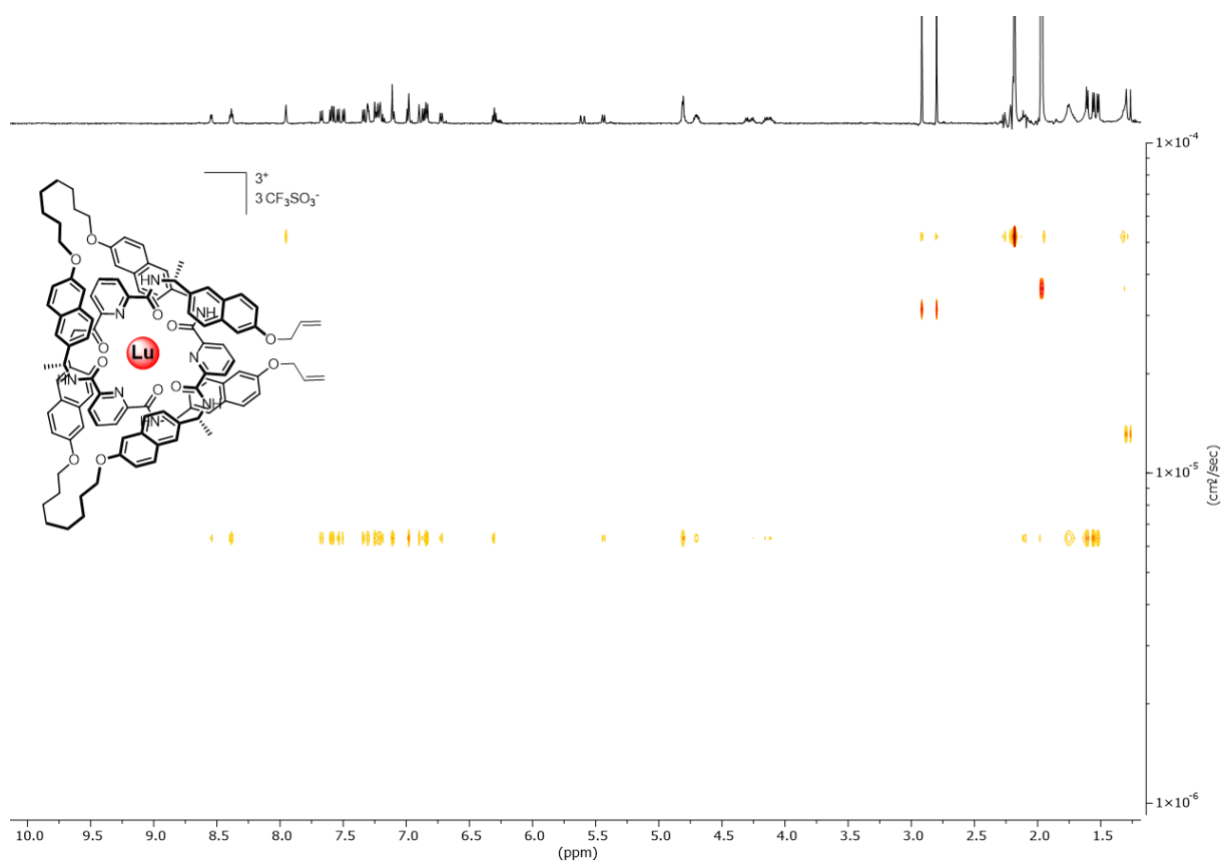
Spectrum S48. DOSY NMR (600 MHz, 298 K, MeCN-*d*₃) of **2•[Lu]**.



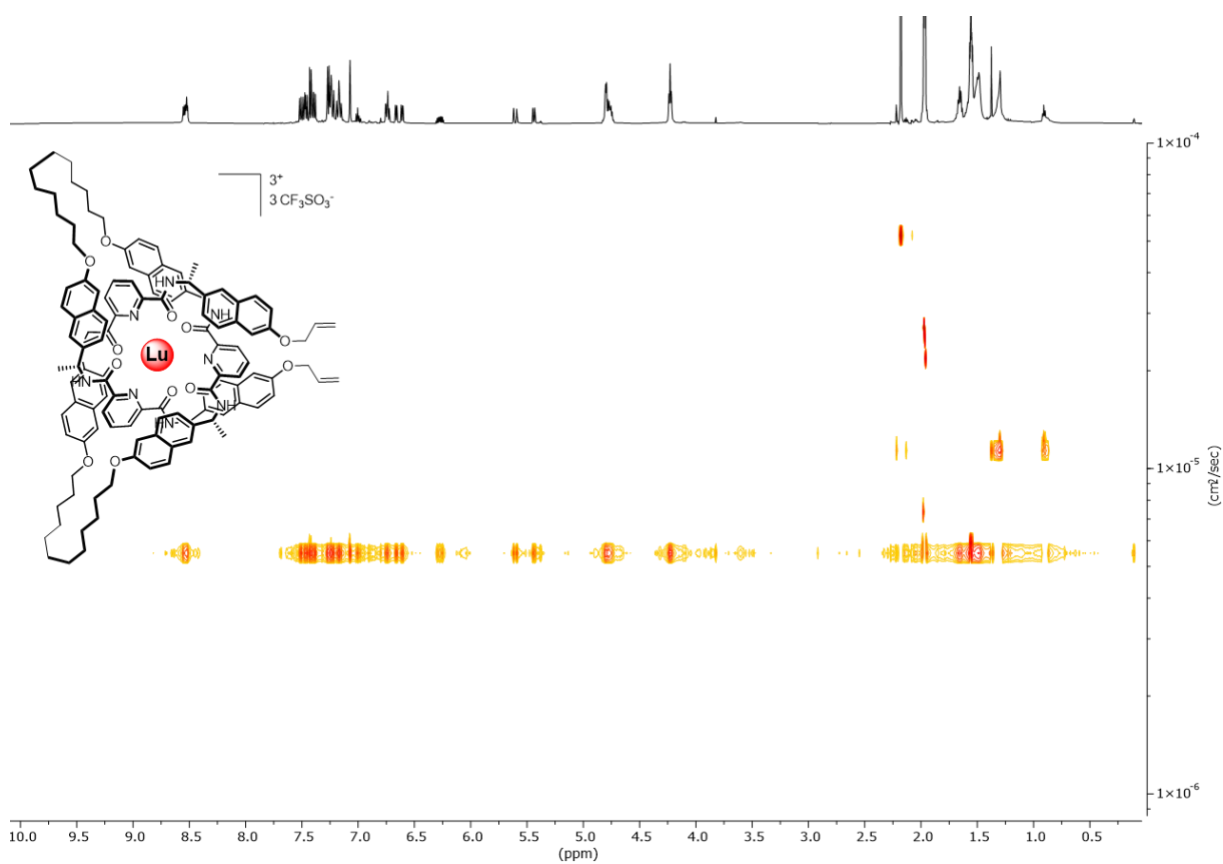
Spectrum S49. DOSY NMR (600 MHz, 298 K, $\text{MeCN-}d_3$) of $3\bullet[\text{Lu}]$.



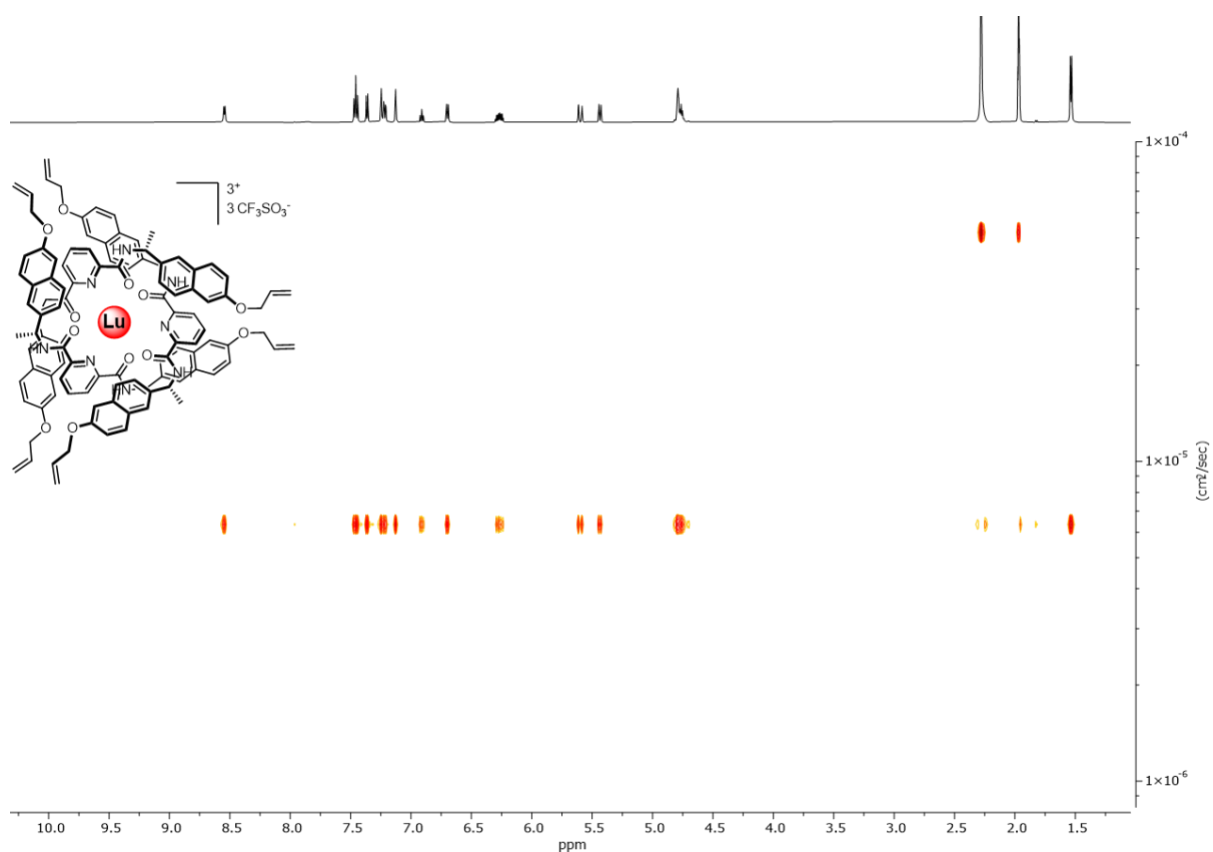
Spectrum S50. DOSY NMR (600 MHz, 298 K, $\text{MeCN-}d_3$) of $4\bullet[\text{Lu}]$.



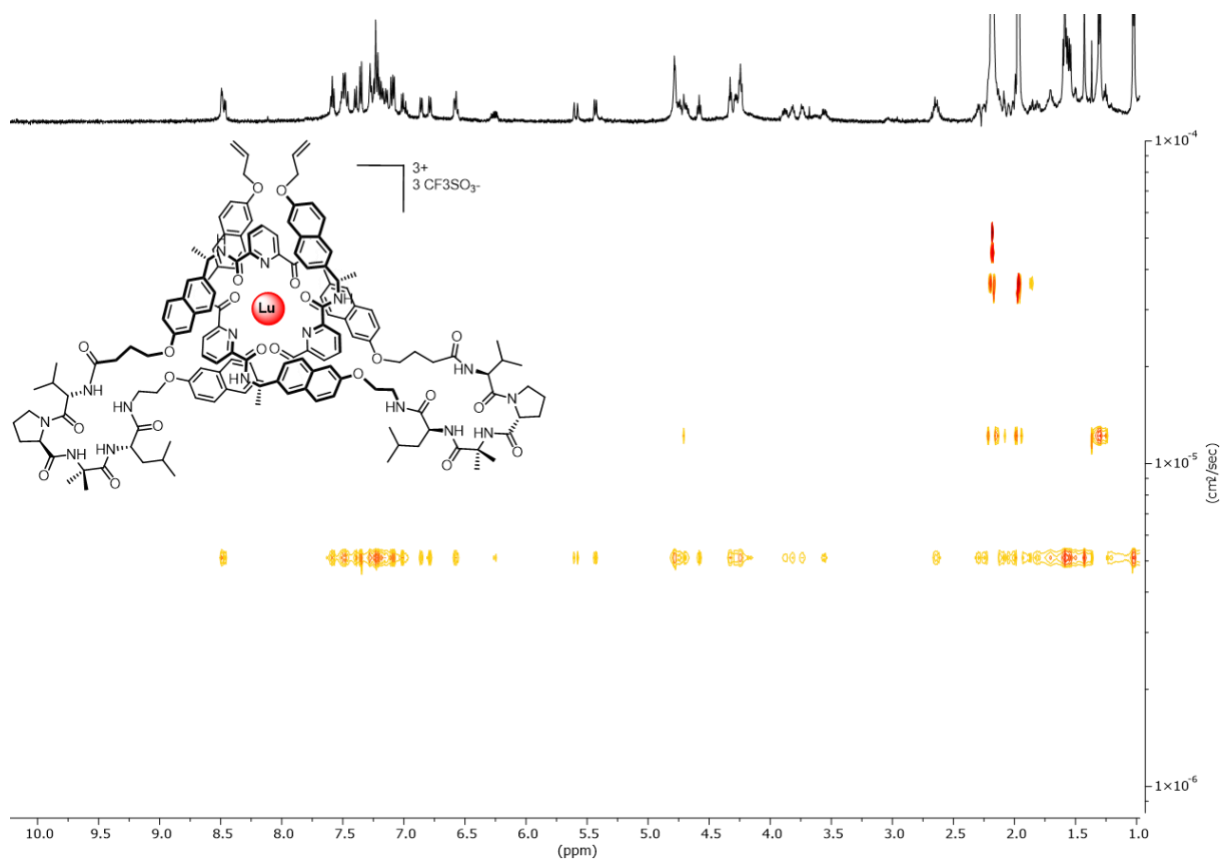
Spectrum S51. DOSY NMR (600 MHz, 298 K, $\text{MeCN-}d_3$) of **5•[Lu]**.



Spectrum S52. DOSY NMR (600 MHz, 298 K, $\text{MeCN-}d_3$) of **6•[Lu]**.



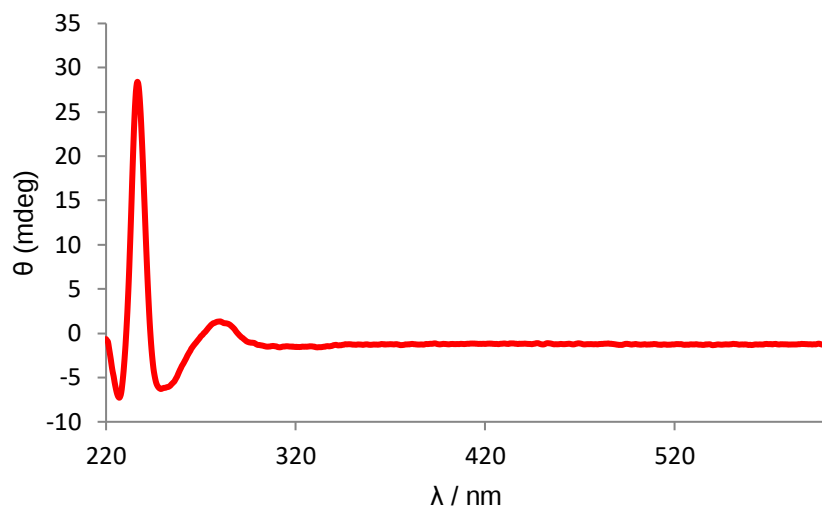
Spectrum S53. DOSY NMR (600 MHz, 298 K, $\text{MeCN}-d_3$) of $73^{\bullet}[\text{Lu}]$.



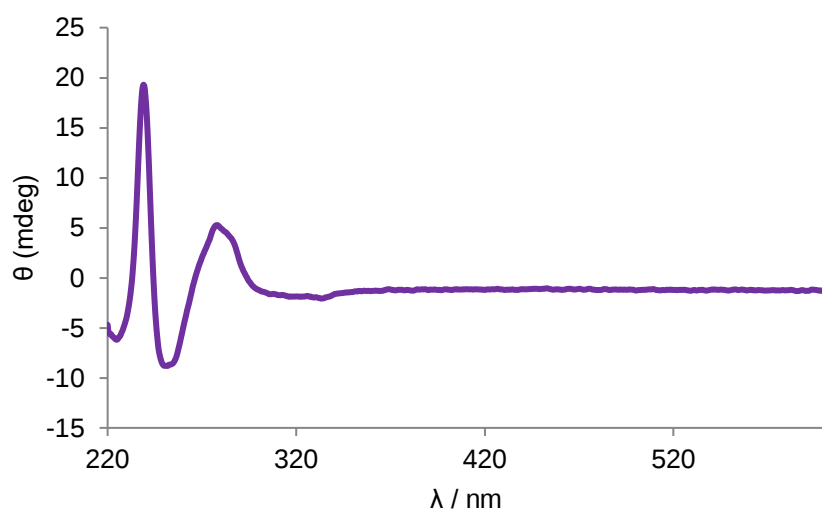
Spectrum S54. DOSY NMR (600 MHz, 298 K, $\text{MeCN}-d_3$) of $8^{\bullet}[\text{Lu}]$.

S7. CIRCULAR DICHROISM AND ABSORPTION SPECTRA

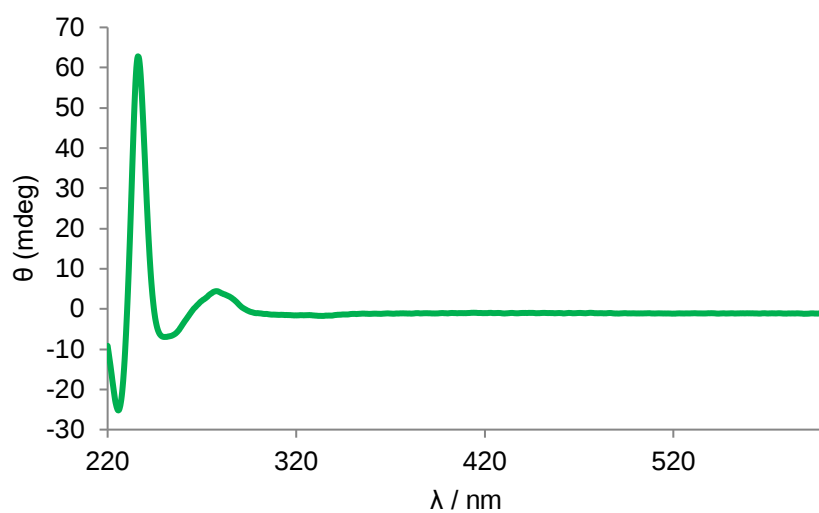
S7.1 CD spectroscopy



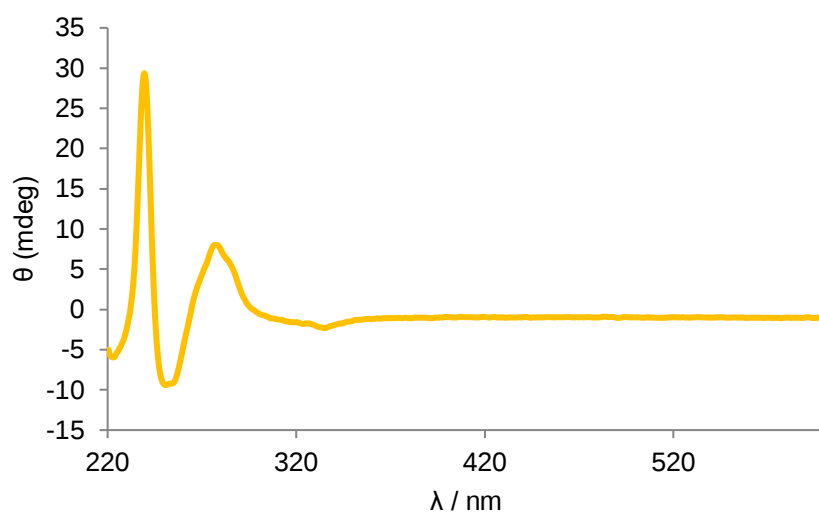
Spectrum S55. CD of knot **1•[Lu]** (0.1 mM, MeCN).



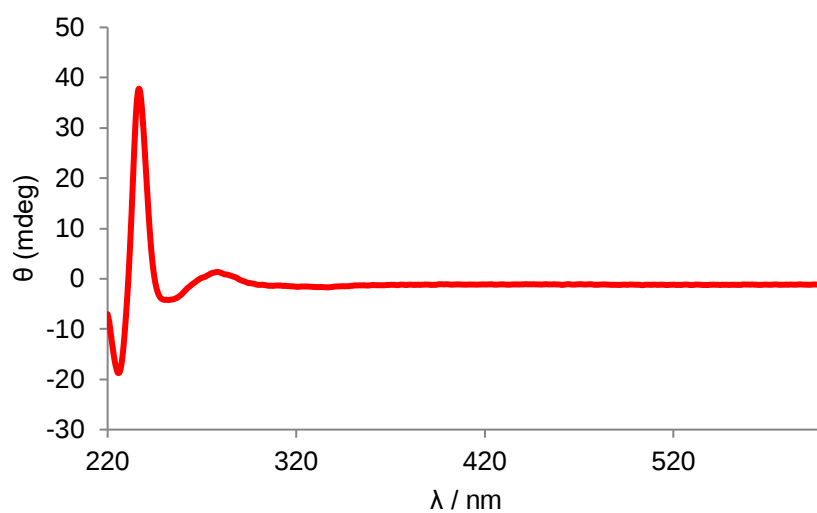
Spectrum S56. CD of knot **2•[Lu]** (0.1 mM, MeCN).



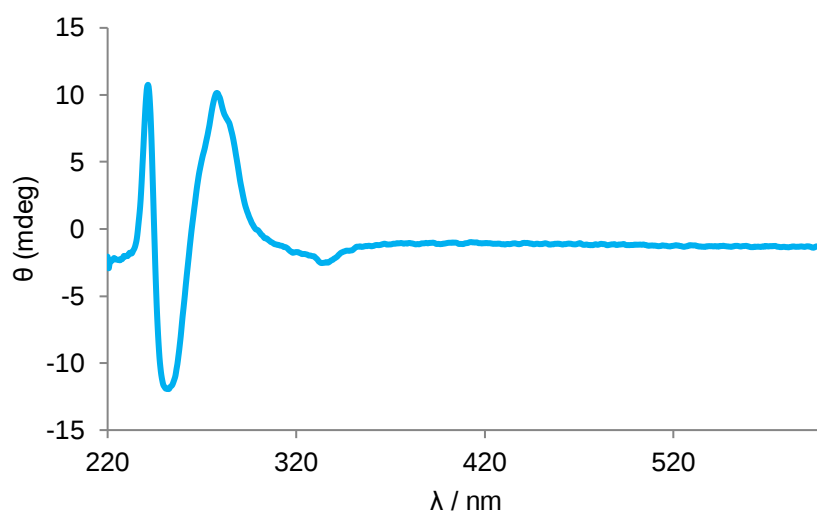
Spectrum S57. CD of knot **3•**[Lu] (0.1 mM, MeCN).



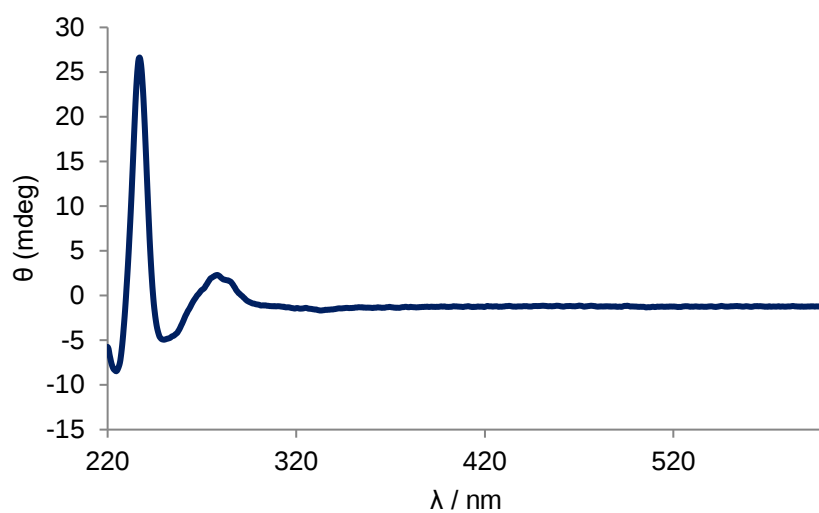
Spectrum S58. CD of knot **4•**[Lu] (0.1 mM, MeCN).



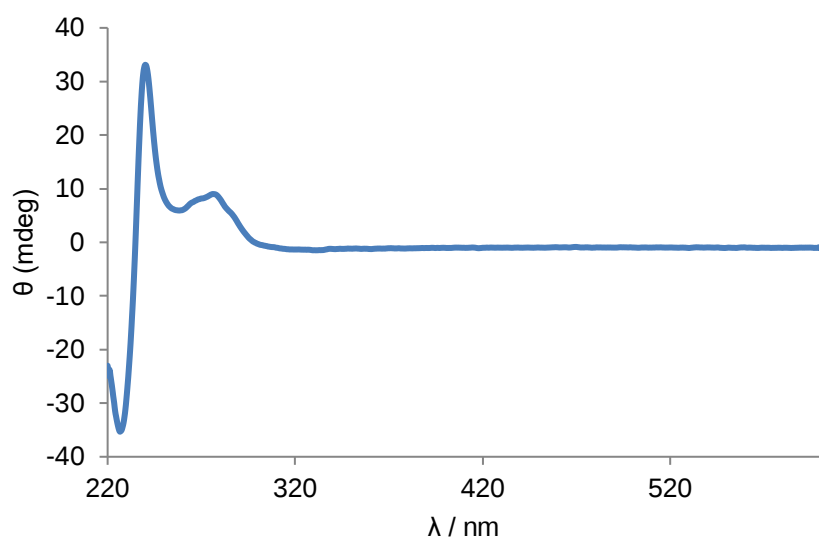
Spectrum S59. CD of knot **5•**[Lu] (0.1 mM, MeCN).



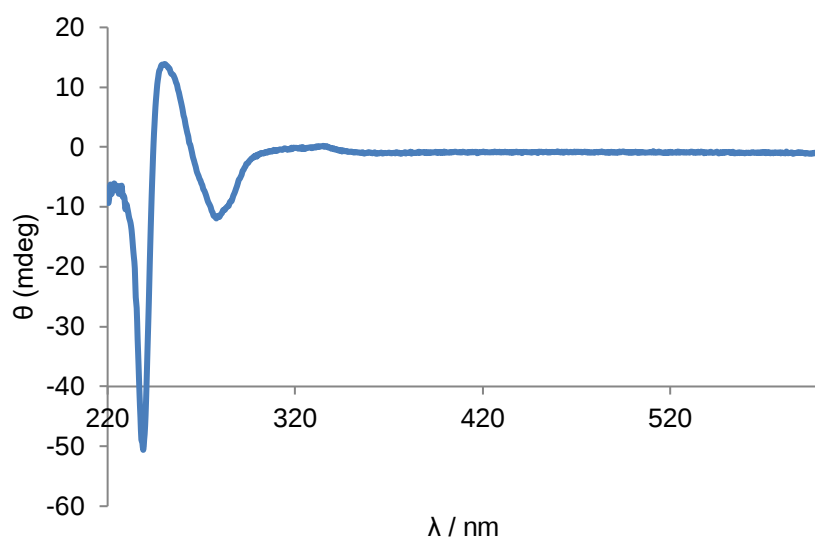
Spectrum S60. CD of knot **6•**[Lu] (0.1 mM, MeCN).



Spectrum S61. CD of circular helicate **73**•[Lu] (0.1 mM, MeCN).

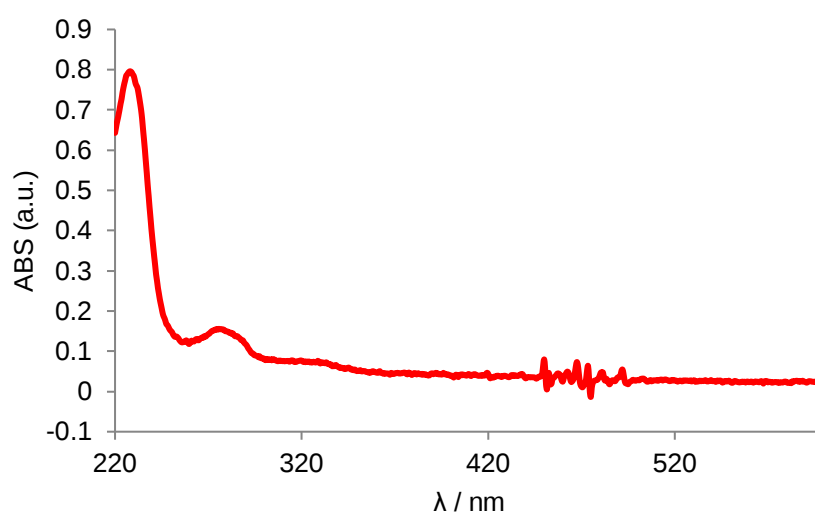


Spectrum S62. CD of metallopeptide ligand **8** (0.025 mM, CH₂Cl₂).

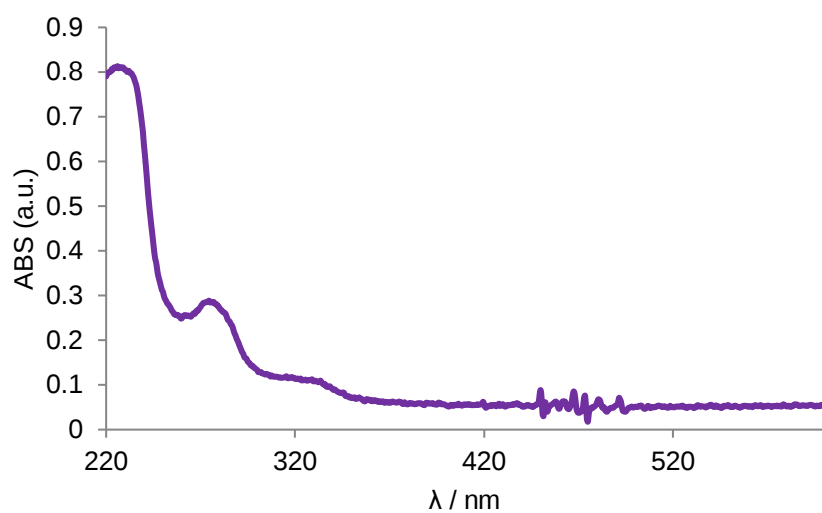


Spectrum S63. CD of metalloprotein knot **8**•[Lu] (0.1 mM, MeCN).

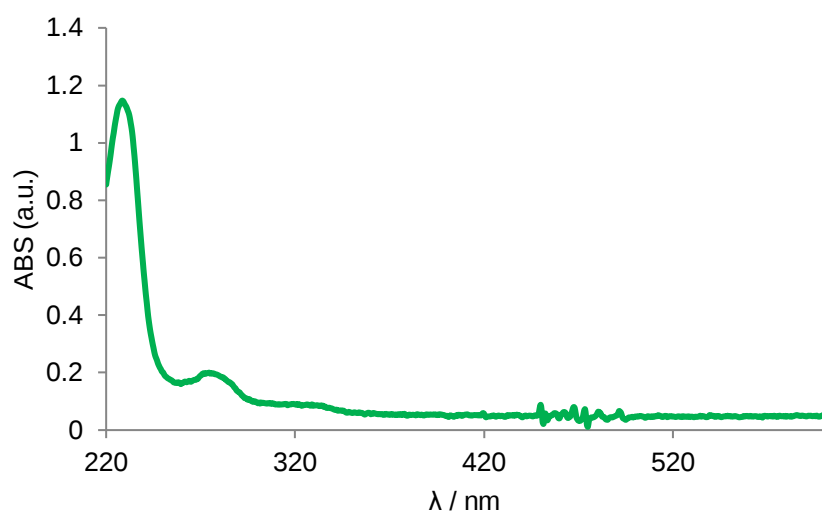
S7.2 UV/Vis spectroscopy



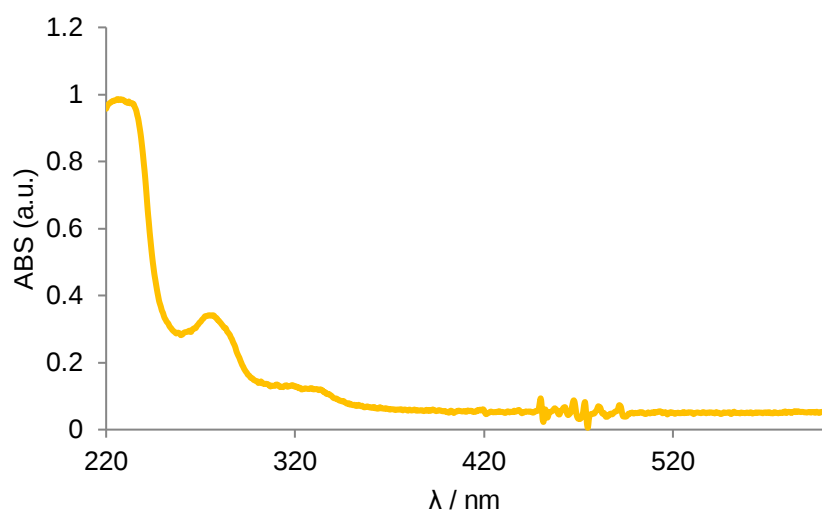
Spectrum S64. UV/Vis of knot **1**•[Lu](MeCN).



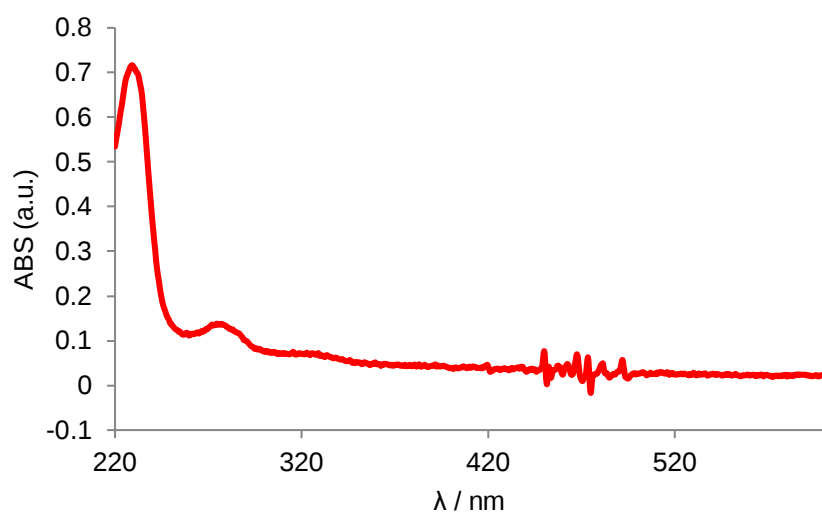
Spectrum S65. UV-Vis of knot **2•[Lu]** (MeCN).



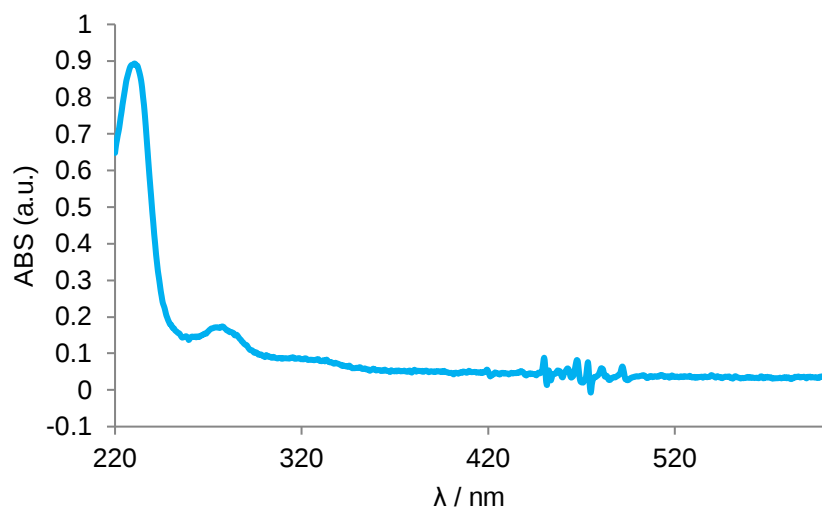
Spectrum S66. UV-Vis of knot **3•[Lu]** (MeCN).



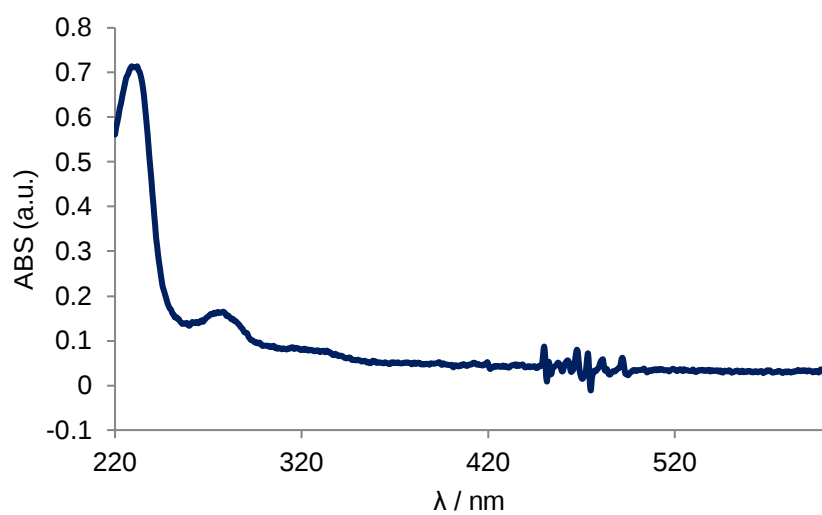
Spectrum S67. UV-Vis of knot 4•[Lu] (MeCN).



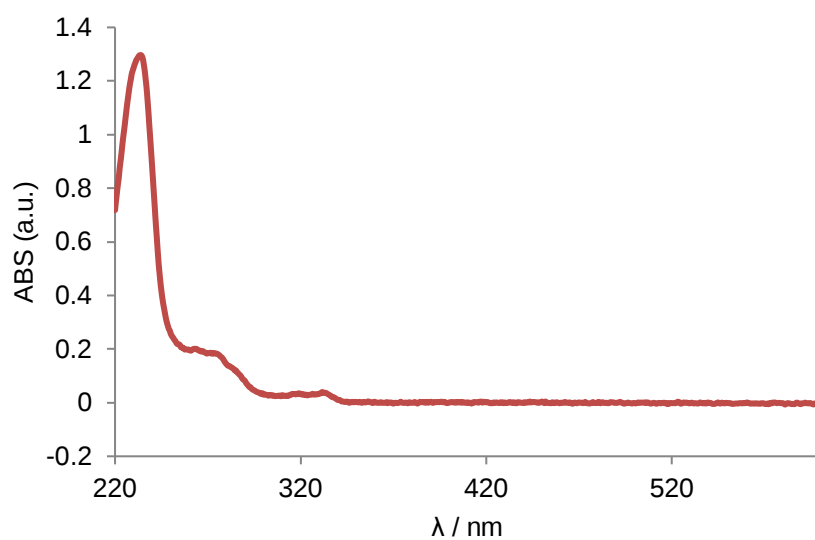
Spectrum S68. UV-Vis of knot 5•[Lu] (MeCN).



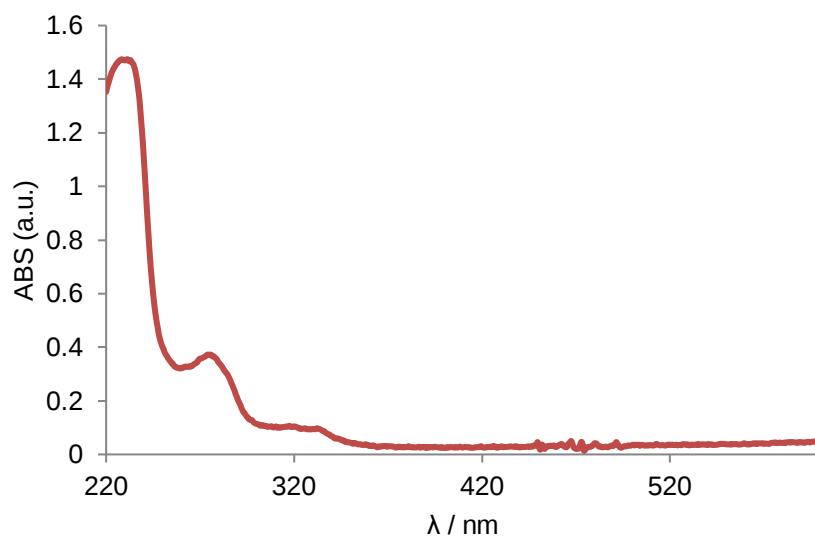
Spectrum S69. UV-Vis of knot **6•[Lu]** (MeCN).



Spectrum S70. UV-Vis of circular helicate **73•[Lu]** (MeCN).



Spectrum S71. UV-Vis of metallopeptide ligand **8** (CH_2Cl_2).



Spectrum S72. UV-Vis of metallopeptide knot **8•[Lu]** (MeCN).

S8. CRYSTALLOGRAPHY

Data Collection. X-Ray data for compound Λ -4•[Lu] were collected at a temperature of 100 K using a synchrotron radiation at single crystal X-ray diffraction beamline I19 in Diamond light Source,⁹ equipped with a Pilatus 2M detector and an Oxford Cryosystems Cobra nitrogen flow gas system. Data was measured using GDA suite of programs.

Crystal structure determinations and refinements. X-Ray data were processed and reduced using CrysAlisPro suite of programmes. Absorption correction was performed using empirical methods (SCALE3 ABSPACK) based upon symmetry-equivalent reflections combined with measurements at different azimuthal angles.¹⁰ The crystal structures were solved and refined against all F^2 values using the SHELX and Olex 2 suite of programmes.¹¹ All atoms except hydrogens were refined anisotropically. Hydrogen atoms were placed in the calculated positions. Naphthalene and the aliphatic groups were found and modelled over two positions. The C-C and C-O 1,2 and 1,3 distances in the aliphatic chains were restrained using distance restrains (SHELX; DFIX and SADI). The atomic displacement parameters (adp) of the ligands were restrained using rigid body restrains (SHELX RIGU and SIMU commands). The triflate anions were constrained to have the ideal structure. The adps were also restrained using rigid body restrains (SIMU and RIGU commands).

Compound Λ -4•[Lu] present medium size voids filled with a lot of scattered electron density. The solvent mask protocol inside Olex 2 software was used to account for the void electron density corresponding to the disordered solvent of the intermolecular space in the crystal structure. 45 electrons were accounted in a volume of 286 Å³. The electron count is compatible with 2 molecules of acetonitrile per void. The calculated flack parameter 0.050(5) shows that the absolute configuration of crystal structure Λ -4•[Lu] was correctly assigned.

CCDC 1997561 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

Table S1. Crystallographic information for Λ -4•[Lu]

Identification code	Λ -4•[Lu]
Empirical formula	$C_{123.64}H_{127.46}F_9LuN_{9.82}O_{29}S_3$
Formula weight	2657.11
Temperature/K	100(2)
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a/Å	13.2976(2)
b/Å	25.7772(2)
c/Å	38.6074(7)
$\alpha/^\circ$	90
$\beta/^\circ$	90
$\gamma/^\circ$	90
Volume/Å ³	13233.6(3)
Z	4
$\rho_{\text{calc}}/\text{cm}^3$	1.334
μ/mm^{-1}	0.802
F(000)	5480.0
Crystal size/mm ³	0.12 × 0.09 × 0.08
Radiation	Synchrotron ($\lambda = 0.6889$)
2 Θ range for data collection/ $^\circ$	3.062 to 51.006
Index ranges	$-16 \leq h \leq 16, -32 \leq k \leq 32, -48 \leq l \leq 48$
Reflections collected	175761
Independent reflections	27068 [$R_{\text{int}} = 0.0932, R_{\text{sigma}} = 0.0658$]
Data/restraints/parameters	27068/2940/1957
Goodness-of-fit on F^2	1.015
Final R indexes [$ I \geq 2\sigma(I)$]	$R_1 = 0.0780, wR_2 = 0.2195$
Final R indexes [all data]	$R_1 = 0.1254, wR_2 = 0.2503$
Largest diff. peak/hole / e Å ⁻³	1.20/-0.66
Flack parameter	0.050(5)

S9. BCR CALCULATION

Backbone-to-crossing (BCR) ratios provide a measure of the tightness of a given knot. BCRs can also be used for open entanglements such as the overhand knots in this study (as is commonly done for knots in biology).^[12] However, in such a case it is important to define what is the core part of the entanglement. For proteins, this is generally defined per amino acid – the moment when an amino acid is removed so that the minimized projection of the protein knot is no longer entangled is the minimum entanglement degree. For this study, we used a precise atomic definition and defined the peripheral naphthol oxygens as the endpoints of the entangled region, see Figure S11 for full numbering of an example ligand. This definition generated the approximate BCR values represented in Table S2 below.

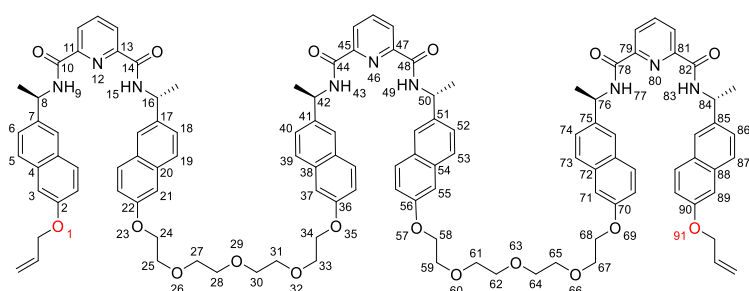


Figure S11. Example definition of numbering of ligand **3** to calculate BCR ratios.

Table S2. Backbone-to-crossing-ratios of the ligands used in this study

Compound	Backbone n	BCR for 3₁ knot
1	79	26
2	85	28
3	91	30
4	97	32
5	85	28
6	93	31
8	107	37

S10. REFERENCES

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APPENDIX. XYZ COORDINATES FOR 8•[Lu]

Lu	-0.129700	-2.223400	-1.380400
O	-0.783100	-0.559400	0.101500
O	-2.314900	-2.078400	-2.134900
O	1.842200	-1.092100	-1.006800
O	0.720500	-2.893400	0.813200
O	-0.509700	-4.338800	-2.185500
O	0.455900	-2.096900	-3.632900
N	-0.474800	-0.017500	-2.422700
N	1.883200	-3.618600	-1.565100
C	-1.462100	-3.535300	1.431100
C	-0.592800	1.339500	-4.379000
H	-0.473600	1.463600	-5.457600
N	0.035100	-6.471900	-2.672500
H	0.770800	-7.168200	-2.756400
C	-0.863100	0.644300	-0.205800
C	0.346500	-5.240600	-2.286500
C	2.705000	-1.731900	-5.985700
O	8.915500	-3.688800	-0.140500
N	0.375400	-1.187900	-5.700300
H	0.115400	-0.386400	-6.268000
C	-3.324900	-2.320000	-1.440500
C	-0.345400	0.117800	-3.744500
C	4.063600	-2.979900	2.564300
H	3.863800	-2.027500	3.056100
C	4.153500	-5.145200	-1.828500
N	-4.553100	-2.028500	-1.863600
H	-5.373500	-2.194000	-1.272500
C	-3.743100	-3.465600	2.177500
H	-4.493100	-3.573900	2.963300
C	0.172700	-1.140700	-4.384200
C	-1.002300	2.421300	-3.596300
H	-1.227200	3.381200	-4.061800
N	-1.826600	-3.122600	0.213000
N	3.946400	-1.042800	-0.203500
H	4.760800	-1.581700	0.081900
C	-3.112200	-2.877700	-0.060800
N	0.546900	-4.079100	2.739200
H	-0.076100	-4.630500	3.322300
C	2.904800	-5.696200	-2.118100
H	2.828700	-6.727200	-2.467600
C	-4.108400	-3.008600	0.911200
H	-5.141300	-2.735300	0.695500
C	-4.526900	0.705100	-1.353300
H	-4.664800	-0.028300	-0.559800
C	4.601300	-5.438100	1.362000
H	4.810000	-6.402400	0.890200
C	4.245900	-3.821400	-1.385600
H	5.219900	-3.381200	-1.179600
C	-2.521100	-6.813800	-0.984300
H	-1.712000	-7.397900	-0.533700
C	3.552600	-2.505600	-5.220600
H	3.246500	-3.507000	-4.902800
C	-0.841300	1.014000	-1.661100

C	3.805200	0.318200	0.348100
C	-4.252400	2.605300	-3.396900
C	7.494600	-2.320300	1.234600
H	8.253400	-1.534600	1.198300
C	7.763300	-3.558100	0.586300
C	1.288300	-2.184300	-6.302600
H	1.094200	-3.135600	-5.788900
C	-6.152100	-1.482700	-3.632000
H	-6.363000	-0.801600	-4.471200
H	-6.217800	-2.522400	-3.997500
H	-6.916700	-1.347700	-2.854200
C	-2.401600	-3.743400	2.446900
H	-2.100000	-4.060500	3.446500
O	-3.296300	6.583400	-2.472700
C	-0.461400	2.575200	2.899600
H	0.471700	3.035700	2.524500
H	-1.297000	3.287100	2.778800
H	-0.338200	2.376200	3.976100
C	-1.290500	-6.823700	-3.214400
H	-1.402200	-6.265300	-4.158800
C	6.299500	-2.129100	1.895900
H	6.103100	-1.168200	2.379800
C	-1.127500	2.263800	-2.213600
H	-1.452800	3.104000	-1.603900
C	-4.730500	-5.738800	-0.761500
C	-4.347600	2.029400	-1.019900
H	-4.366200	2.363500	0.019200
C	-3.765300	-6.884000	1.179000
H	-2.944700	-7.443900	1.638400
C	1.775200	-4.882200	-1.971500
C	-4.171700	3.007800	-2.026600
C	0.031100	-3.514200	1.639400
C	3.086000	-3.954400	2.559600
C	3.068800	-3.087600	-1.254200
C	-4.764700	-1.196000	-3.051900
H	-4.002600	-1.488200	-3.788300
N	-0.911900	1.590700	0.730500
H	-0.967900	2.566900	0.457700
C	2.930700	-1.661600	-0.803800
C	-4.556700	0.280500	-2.706200
C	3.371000	-5.206800	1.948500
H	2.608800	-5.992200	1.943100
C	1.823400	-3.672700	3.357700
H	1.770100	-2.578000	3.485100
C	-4.889100	-6.585200	1.914200
H	-4.986600	-6.899800	2.956200
C	-4.616400	-5.324300	-2.116100
H	-5.427700	-4.742000	-2.563900
C	10.122500	-3.993700	0.574200
H	10.441400	-5.010100	0.281500
H	9.923100	-3.996000	1.660400
C	6.842100	-2.221600	-3.448700
H	7.515600	-2.838500	-2.848800
C	-3.500500	-5.647300	-2.859300
H	-3.424000	-5.307600	-3.896700

C	-4.437800	1.231700	-3.706500
H	-4.476900	0.933300	-4.759500
C	1.911800	-4.310400	4.748800
H	2.805900	-3.930000	5.268000
H	1.024400	-4.052000	5.354500
H	1.991300	-5.409600	4.674500
C	5.325600	-3.169700	1.947700
C	-2.440800	-6.414000	-2.306000
C	-0.763700	1.270900	2.156600
H	0.105300	0.597800	2.239600
O	-7.017000	-5.626800	2.167700
C	5.608700	-4.429400	1.325800
C	4.808900	-2.002200	-4.783200
C	-5.964000	-5.850500	1.334300
C	-3.648100	-6.482200	-0.184000
C	6.849700	-4.595300	0.646600
H	7.077100	-5.536700	0.139300
C	-3.863300	4.354200	-1.685000
H	-3.786200	4.605900	-0.627500
C	5.180900	-0.656600	-5.109400
C	-3.814400	4.914200	-4.050900
H	-3.672600	5.683200	-4.815000
C	-3.664900	5.291400	-2.681600
C	-5.877400	-5.424000	0.020200
H	-6.660200	-4.822900	-0.442900
O	8.238400	-0.250500	-3.146600
C	6.357600	-0.103700	-4.546100
H	6.631500	0.932900	-4.758000
C	7.154500	-0.853700	-3.695000
C	4.319800	0.096700	-5.958800
H	4.618200	1.106500	-6.253800
C	3.013400	0.308800	1.657400
H	3.577900	-0.230500	2.430200
H	2.871600	1.334700	2.020600
H	2.033800	-0.175600	1.521600
C	-4.097600	3.611900	-4.394500
H	-4.180300	3.330800	-5.449100
C	3.122600	-0.429300	-6.386800
H	2.466400	0.179400	-7.016800
C	5.699600	-2.772900	-3.990400
H	5.469300	-3.825600	-3.818100
C	11.242500	-3.023200	0.236100
H	11.310500	-2.891600	-0.853400
H	12.190100	-3.483400	0.578400
O	-7.856500	-1.164300	4.667300
C	8.648500	-0.610800	-1.820800
H	9.655900	-1.046800	-1.876300
H	7.964900	-1.367400	-1.402800
C	1.002300	-2.344100	-7.792100
H	1.691300	-3.092600	-8.216100
H	-0.033600	-2.688600	-7.955200
H	1.152600	-1.395400	-8.337900
C	-8.126200	-4.861800	1.713300
H	-8.990900	-5.210600	2.296900
H	-8.334900	-5.063800	0.649500

C	-1.298400	-8.320900	-3.529700
H	-2.261400	-8.598400	-3.988400
H	-0.490600	-8.577200	-4.238200
H	-1.165700	-8.915500	-2.608900
C	-7.884000	-3.359800	1.949600
H	-8.087700	-3.098100	2.998500
C	-5.429700	-1.067200	4.626600
H	-5.338900	-1.547900	5.602700
C	-6.675000	-0.852900	4.058700
C	-6.781900	-0.232800	2.782900
H	-7.772900	-0.060400	2.356300
C	-5.653500	0.203400	2.125500
H	-5.774300	0.739700	1.186200
C	-4.366800	0.060000	2.713100
C	-4.252000	-0.608000	3.973700
C	-2.955200	-0.740300	4.548300
H	-2.848900	-1.278500	5.494300
C	-1.849700	-0.184400	3.937300
H	-0.864600	-0.288300	4.404800
C	-1.974800	0.541900	2.720200
C	-3.209600	0.623100	2.117200
H	-3.318800	1.167800	1.184500
C	7.251000	1.215000	-0.788400
H	6.600700	0.454700	-0.320100
C	8.648200	0.634700	-0.951100
H	9.046000	0.360400	0.036600
H	9.333800	1.383700	-1.379800
C	-7.584900	0.460900	6.513500
H	-7.855100	0.574200	7.578200
H	-6.487400	0.555800	6.461500
C	-7.982200	-0.953900	6.082800
H	-7.388400	-1.700400	6.639300
H	-9.046500	-1.146000	6.287600
C	-8.246600	1.577000	5.670100
H	-8.537000	1.175100	4.685700
C	3.275900	1.269700	-0.718700
H	1.964700	2.354800	0.593700
C	2.357900	2.251800	-0.412400
C	3.318600	2.051400	-3.034300
C	1.919000	3.190200	-1.378600
C	3.761400	1.184500	-2.058300
C	2.386600	3.087400	-2.727800
C	1.037600	4.250700	-1.041400
H	4.476200	0.401800	-2.330300
H	2.255200	3.937900	-4.730100
H	3.684500	1.948200	-4.058400
C	0.604900	5.153300	-1.990000
H	0.712600	4.367500	-0.002600
H	-0.052700	5.968200	-1.689700
C	1.034000	5.023600	-3.340300
C	1.918600	4.011900	-3.692900
H	4.831600	0.622100	0.606400
O	0.617800	5.850800	-4.335400
C	-0.256600	6.932400	-4.037200
H	-0.652600	7.260600	-5.014400

H	-1.130600	6.580300	-3.459300
C	-2.892400	6.997000	-1.163800
H	-2.343700	7.938200	-1.341000
H	-2.182700	6.262500	-0.739000
C	-4.037600	7.240800	-0.220600
H	-4.844100	7.878600	-0.607300
C	-4.081300	6.761600	1.026700
H	-4.909800	6.990900	1.707000
H	-3.296400	6.100800	1.413700
C	0.409300	8.089600	-3.342100
H	-0.279100	8.892800	-3.045500
C	1.717700	8.199900	-3.089200
H	2.124600	9.082100	-2.581000
H	2.428500	7.415700	-3.376900
O	-7.096800	-2.170500	-0.477700
C	-8.251400	-2.001500	-0.066600
N	-8.695800	-2.514800	1.096500
H	-9.643000	-2.302800	1.393400
C	-9.302800	-1.248800	-0.889100
H	-10.143400	-0.977600	-0.237200
C	-9.796300	-2.128500	-2.057700
H	-8.932000	-2.360600	-2.706300
N	-8.789300	0.005800	-1.399900
H	-8.123900	-0.031200	-2.160900
C	-9.247800	1.210600	-0.969100
O	-10.020400	1.327100	-0.026600
C	-8.880200	2.432200	-1.857700
C	-7.823100	2.138800	-2.931500
H	-8.167700	1.381000	-3.656600
H	-6.880700	1.806400	-2.471100
H	-7.614700	3.062700	-3.495700
C	-10.197300	2.894700	-2.505800
H	-10.605100	2.098700	-3.151200
H	-10.018500	3.787700	-3.130600
H	-10.937900	3.139400	-1.727600
N	-8.401400	3.518800	-1.002400
H	-8.657100	4.459100	-1.280600
C	-7.502400	3.330200	-0.010700
O	-7.121600	2.214800	0.321700
C	-10.503700	-3.439800	-1.677700
H	-9.811600	-4.048500	-1.063700
C	-6.949800	4.598600	0.678800
N	-6.728700	4.328600	2.098400
C	-7.909300	4.715700	2.892500
C	-8.840000	5.406700	1.878800
C	-7.898200	5.804200	0.737400
H	-8.388300	3.834900	3.342900
H	-7.613800	5.394600	3.708300
H	-9.376600	6.259000	2.323700
H	-9.590100	4.689200	1.503000
H	-8.418400	6.034700	-0.204900
C	-5.536100	3.882500	2.568100
O	-4.572000	3.671900	1.832400
H	-5.988300	4.829800	0.197100
C	-5.457100	3.646200	4.095300

H	-5.804400	4.556500	4.610100
C	-4.015600	3.353100	4.568600
H	-3.563900	2.653900	3.847500
C	-3.998600	2.698500	5.954800
H	-4.545600	3.311900	6.693300
H	-2.957800	2.579400	6.304900
H	-4.460600	1.698100	5.932300
C	-3.199600	4.650000	4.565300
H	-3.613900	5.371900	5.294700
H	-3.202900	5.125000	3.570200
H	-2.149700	4.452300	4.845900
N	-6.418800	2.620100	4.459200
H	-6.429400	1.764800	3.909400
C	-7.317900	2.766600	5.470200
O	-7.370000	3.776300	6.169600
H	-10.485200	-1.505200	-2.656800
C	-10.821700	-4.242000	-2.947000
H	-11.297200	-5.206200	-2.692200
H	-9.908700	-4.454800	-3.533000
H	-11.519800	-3.681900	-3.597300
C	-11.780600	-3.193600	-0.860200
H	-11.577400	-2.703100	0.108600
H	-12.298500	-4.144700	-0.641800
H	-12.480500	-2.546800	-1.421900
O	11.736200	-0.531000	-1.000300
C	11.457900	-0.569800	0.194300
N	11.095900	-1.707600	0.841500
H	11.101500	-1.658100	1.864500
C	11.577800	0.679000	1.110500
H	12.428900	0.419500	1.765600
C	11.908400	1.963000	0.342300
H	11.000200	2.591100	0.266600
N	10.443600	0.884300	2.015500
H	9.758300	1.609700	1.791300
C	10.394900	0.286600	3.221900
O	11.179500	-0.611400	3.546100
C	9.352300	0.777100	4.243000
C	10.145000	1.307600	5.455700
H	9.443300	1.629400	6.244300
H	10.799400	0.518000	5.852500
H	10.774800	2.168400	5.165900
C	8.489300	-0.418300	4.675300
H	7.963100	-0.871200	3.825700
H	7.742700	-0.091200	5.418400
H	9.143800	-1.175000	5.133900
N	8.552400	1.908900	3.754000
H	8.888000	2.811100	4.078000
C	7.268600	1.911000	3.296400
O	6.701000	0.958400	2.781100
C	13.055900	2.776900	0.968600
H	13.959300	2.136000	0.939000
C	6.556700	3.254800	3.577700
N	5.165000	3.227600	3.155600
C	4.278100	2.793200	4.251000
C	5.213300	2.610900	5.453500

C	6.416700	3.488100	5.099900
H	3.519400	3.574200	4.422400
H	3.748500	1.868600	3.976800
H	4.730700	2.904800	6.398700
H	5.530600	1.557100	5.547600
H	7.324200	3.234900	5.668000
H	6.184500	4.553500	5.270000
C	4.611200	3.708600	2.020100
O	3.386000	3.722900	1.880800
H	7.118100	4.062400	3.088700
C	5.543700	4.194900	0.884000
H	6.466600	4.622300	1.298200
C	4.837600	5.250300	0.010200
H	3.914800	4.780900	-0.372900
C	5.704400	5.669900	-1.181800
H	6.624100	6.181400	-0.841200
H	5.142000	6.370800	-1.825100
H	6.004300	4.809600	-1.804100
C	4.437900	6.472900	0.847300
H	5.330000	6.955800	1.290600
H	3.747000	6.197700	1.659700
H	3.929800	7.221100	0.213200
N	5.946400	3.036600	0.095100
H	5.222600	2.627500	-0.492500
C	7.179100	2.465900	0.077600
O	8.139100	2.898700	0.717000
H	12.181000	1.682500	-0.686800
C	13.343800	4.024700	0.127100
H	12.452100	4.679200	0.082000
H	13.618000	3.751500	-0.908600
H	14.174600	4.613200	0.557600
C	12.787400	3.146500	2.434200
H	13.613200	3.757100	2.841700
H	12.690500	2.253100	3.075700
H	11.854300	3.734400	2.530100
H	6.808000	1.438400	-1.774800
H	-9.159200	1.947300	6.160800
H	-6.832600	-3.123100	1.743600
H	-7.304800	6.693900	1.008300
H	5.057700	-5.744700	-1.954600