Supporting Information Available

Bioconjugation of Supramolecular Metallacages to Integrin Ligands for Targeted Delivery of Cisplatin

Jiaying Han,[a],† Andreas F. B. Räder,[b],† Florian Reichart,[b],† Brech Aikman,[c] Margot N. Wenzel,[c] Benjamin Woods,[c] Michael Weinmüller,[b] Beatrice S. Ludwig,[b] Stefan Stürup,[d] Geny M. M. Groothuis,[a] Hjalmar P. Permentier,[a] Rainer Bischoff,[a] Horst Kessler,[b]* Peter Horvatovich,[a]* and Angela Casini[c]*

† Authors contributed equally to the work.

[a] *Groningen Research Institute of Pharmacy, University of Groningen, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands.*

[b] *Institute for Advanced Study and Center of Integrated Protein Science München (CIPSM), TU München, Department Chemie, Lichtenbergstr. 4, 85747 Garching, Germany.*

[c] *School of Chemistry, Cardiff University, Main Building, Park Place, CF10 3AT Cardiff, United Kingdom.*

[d] *Dept. of Pharmacy, University of Copenhagen, Universitetsparken 2, 2100 Copenhagen, Denmark.*

Corresponding authors' emails:

casinia@cardiff.ac.uk; p.l.horvatovich@rug.nl; kessler@tum.de

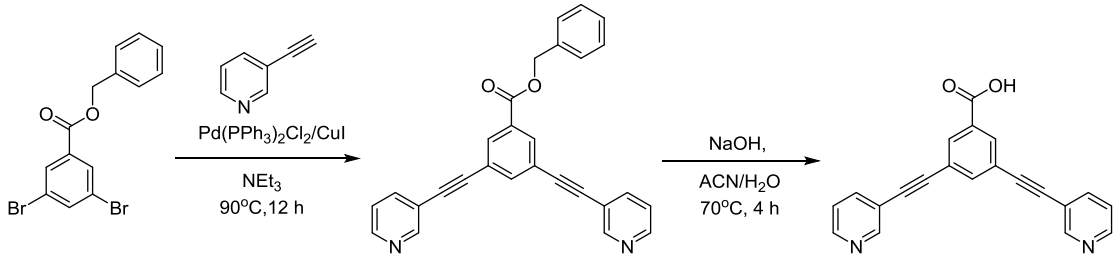
1. General remarks

Chemicals. All reagents, solvents and resins were obtained from commercial suppliers and used without further purification, unless otherwise stated.

Chromatography. Semi-preparative reversed phase HPLC was performed on a *Waters* instrument: *Waters 2545* (Binary Gradient Module), *Waters SFO* (System Fluidics Organizer), *Waters 2996* (Photodiode Array Detector), *Waters 2767* (Sample Manager) equipped with a C18-column (Reprosil 100 C18, 5 µm, 150 x 30 mm, *Dr. Maisch*). Suitable linear gradients (40 mL/min) of H_2O (0.1%*v/v* trifluoroacetic acid (TFA), buffer A) and acetonitrile (0.1%*v/v* TFA, buffer B) were applied for the purification of all compounds. Analytical HPLC-HESI-MS (*heated electrospray ionization mass spectrometry*) was performed on an *UltiMate 3000 UHPLC focused* chromatographic system (*Dionex*) connected to a *LCQ Fleet mass spectrometer* (*Thermo Scientific*) equipped with a C18 column (Accucore C18, 80 Å, 2.6 µm, 50 x 2.1 mm, *Thermo Scientific*). Linear gradients (0.9 mL/min, 5 min) of water (0.1% formic acid) and acetonitrile (0.1% formic acid) were used for analytical purpose. Further, analytical ESI-MS spectra of the metal-ligand **L** were recorded on a Walter Synapt G2SI QTOF. High resolution mass (HRMS) was measured on a LTQ Orbitrap XL *(Thermo Scientific)*.

NMR. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a 500 MHz DMX (Bruker), a 500 MHz cryo AV (Bruker), on a 400 MHz AV spectrometer (Bruker) and on a 400 MHz Ultrashield spectrometer (*Bruker*), respectively, at 298 K. DOSY-NMR was measured on a 400 MHz Ultrashield spectrometer (*Bruker*) at 298 K. Chemical shifts are given in *parts per million* (ppm). Abbreviations for NMR multiplicities are: singlet (s), doublet (d), triplet (t), multiplet (m). Coupling constants *J* are given in Hz. Following solvents were used as internal standards: DMSO-d_6: 2.50 ppm (^{1}H-NMR) and 39.52 ppm (^{13}C-NMR); $CDCl_3$: 7.26 ppm (^{1}H-NMR) and 77.16 ppm (^{13}C-NMR).[1]

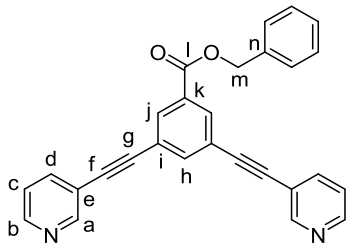
2. Synthesis and analysis of ligand L0



SI-1 **L0**

Scheme S1. Synthesis of ligand **L0** *via* Sonogashira cross-coupling.

- **Benzyl 3,5-bis(pyridin-3-ylethynyl)benzoate (SI-1)**



Chemical Formula: $C_{28}H_{18}N_2O_2$
Exact Mass: 414,13683
Molecular Weight: 414,46400

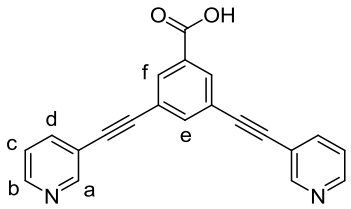
A mixture of benzyl 3,5-dibromobenzoate (370 mg, 1.00 mmol, 1.00 eq.), 3-ethynylpyridine (309 mg, 3.00 mmol, 3.00 eq.), [$Pd(PPh_3)_2Cl_2$] (68.1 mg, 0.10 mmol, 0.10 eq.), and CuI (18.5 mg, 0.10 mmol, 0.10 eq.), was suspended in distilled triethylamine (15 mL) and stirred under a nitrogen atmosphere at 90°C. After 24 h, the reaction mixture was diluted with ethylacetate (50 mL) and filtered over glass-fritted funnel (por. 3). The solvent was removed under vacuum and the crude residue further purified by column chromatography on silica gel (Ethylacetate:Methanol = 100:5, R_f = 0.57) to give the product **SI-1** as an off white solid (311 mg, 0.75 mmol, 75%).

^{1}H-NMR (400 MHz, DMSO-d_6): δ [ppm] = 8.80 (d, *J* = 1.4 Hz, 2H, H_a), 8.61 (dd, *J* = 1.6, 5.0 Hz, 2H, H_b), 8.12 (d, *J* = 1.6 Hz, 2H, H_f) 8.06 (t, *J* = 1.6, 1H H_e) 8.02 (dt, *J* = 1.8, 8.0 Hz, 2H, H_d) 7.64-7.35 (m, 7H, phenyl, H_c), 5.39 (s, 2H, H_g).

^{13}C{^{1}H}-NMR (101 MHz, DMSO-d_6): δ [ppm] = 164.5 (C_l), 152.3 (C_a), 149.9 (C_b), 139.3 (C_h), 138.7 (C_d), 136.1 (C_k), 132.5 (C_j), 131.9 (C_{phenyl}), 131.4 (C_n) 129.2 (C_{phenyl}), 129.1 (C_{phenyl}), 128.8 (C_{phenyl}), 128.7 (C_{phenyl}), 124.1 (C_c), 123.3 (C_i), 119.2 (C_e), 90.5 (C_f/C_g), 88.6 (C_f/C_g), 67.4 (C_m).

HRMS (ESI) calcd. for $C_{28}H_{19}N_2O_2$ $[M+H]^+$: *m/z* = 415.1447; found: 415.1448; δ = 0.2 ppm.

- **3,5-bis(pyridin-3-ylethynyl)benzoic acid (L0)**



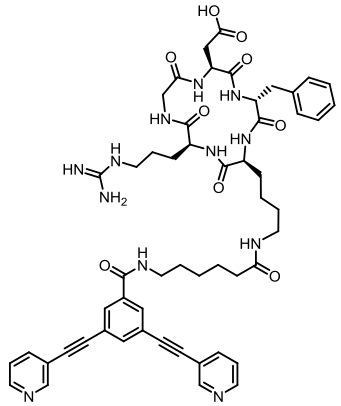
Chemical Formula: $C_{21}H_{12}N_2O_2$
Exact Mass: 324,08988
Molecular Weight: 324,33900

Benzyl 3,5-bis(pyridin-3-ylethynyl)benzoate (**SI-1**) (415 mg, 1.00 mmol, 1.00 eq.) was dissolved in acetonitrile (5 mL). To the yellow solution, deionised water (2 mL) was added and the solution was heated to 70°C before sodium hydroxide (100 mg, 2.50 mmol, 2.50 eq.), was added. The resulting orange solution was stirred at 70°C for 4 h. 1 M HCl was added to acidify the solution (~pH 6). The resulting yellow precipitate was collected by filtration, washed with diethyl ether and re-suspended in methanol. The solvent was removed under vacuum to give the product **L0** as a white powder (301 mg, 0.93 mmol, 93%) (Overall yield 66% [2]).

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 8.82 (dd, *J* = 0.89, 2.2 Hz, 2H, H_a), 8.63 (dd, *J* = 1.7, 4.8 Hz, 2H, H_b), 8.12 (d, *J* = 1.6, 2H, H_f), 8.08-8.01 (m, 3H, H_e, H_d), 7.50 (ddd, *J* = 0.90, 4.9, 8.2 Hz, 2H, H_c).
^{13}C{^{1}H}-NMR (101 MHz, DMSO-d_6): δ = 166.2(C_l), 152.3(C_a), 150.0(C_b), 139.3(C_h), 138.1(C_d/C_k), 132.8(C_j), 124.2(C_c), 123.5(C_i), 119.3(C_e), 90.7(C_f/C_g), 88.3(C_f/C_g).
HRMS (ESI) calcd for $C_{21}H_{13}N_2O_2$ $[M+H]^+$: *m/z* = 324.0899; found: 324.0901; δ = 0.6 ppm.

3. <u>Synthesis and Analysis of ligands L1-L4</u>

- ***cyclo*(RGDfK((3,5-bis(pyridin-3-ylethynyl)benzoyl)Ahx)) (L1)**



Chemical Formula: $C_{54}H_{62}N_{12}O_9$
Exact Mass: 1022,47627
Molecular Weight: 1023,16500

The carboxylic acid **L0** (8.37 mg, 25.8 µmol, 1.00 eq.) and the free amine **1** (18.5 mg, 25.8 µmol, 1.00 eq.) were converted according to the above-mentioned procedure. The final bioconjugated metal ligand **L1** was isolated after purification *via* preparative RP-HPLC (20-35% buffer B, 10 min, Waters) and lyophilization as a white solid (9.0 mg, 8.78 µmol, 34%).

^{1}H-NMR (500 MHz, DMSO-d_6): δ = 12.25 (bs, 1H), 8.81 (d, *J* = 2.0 Hz, 2H), 8.71 (t, *J* = 5.6 Hz, 1H), 8.64 (dd, *J* = 4.8, 1.7 Hz, 2H), 8.41 (dd, *J* = 7.5, 4.4 Hz, 1H), 8.15 – 7.98 (m, 7H), 7.96 (t, *J* = 1.6 Hz, 1H), 7.76 (t, *J* = 5.6 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.45 (t, *J* = 5.9 Hz, 1H), 7.29 – 7.21 (m, 2H), 7.20 – 7.14 (m, 1H), 7.17 – 7.11 (m, 2H), 4.63 (td, *J* = 8.5, 5.9 Hz, 1H), 4.44 (dd, *J* = 7.5 Hz, 1H), 4.18 – 4.10 (m, 1H), 4.04 (dd, *J* = 15.0, 7.6 Hz, 1H), 3.95 – 3.86 (m, 1H), 3.32 – 3.21

(m, 3H), 3.09 (*virt.* p, *J* = 6.6 Hz, 2H), 2.99 – 2.87 (m, 3H), 2.81 (dd, *J* = 13.4, 6.0 Hz, 1H), 2.70 (dd, *J* = 16.2, 8.6 Hz, 1H), 2.42 – 2.35 (m, 1H), 2.07 (t, *J* = 7.5 Hz, 2H), 1.74 – 1.65 (m, 1H), 1.60 – 1.45 (m, 6H), 1.44 – 1.20 (m, 7H), 1.01 (*virt.* p, *J* = 7.8 Hz, 2H).

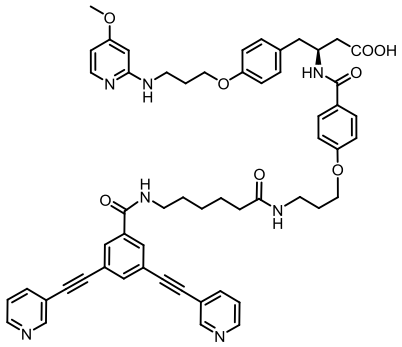
$^{13}C\{^{1}H\}$-NMR (126 MHz, DMSO-d_6): δ = 172.1, 172.0, 171.7, 171.2, 170.7, 170.0, 169.6, 164.1, 158.2, 157.9, 156.5, 151.7, 149.5, 138.8, 137.2, 136.2, 135.8, 130.5, 129.1, 128.2, 126.3, 123.8, 122.7, 118.9, 90.6, 87.6, 54.6, 54.9, 51.9, 48.9, 43.2, 40.3, 39.0 (HSQC), 38.2, 37.4, 35.4, 35.0, 30.9, 28.8, 28.6, 28.5, 26.2, 25.3, 25.1, 22.8.

RP-HPLC (5-95% B, 5 min): t_R = 2.92 min.

MS (HESI): *m/z* = 512.63 $[M+2H]^{2+}$, 1023.27 $[M+H]^{+}$.

HRMS (ESI) calcd. for $C_{54}H_{64}N_{12}O_9^{+}$ $[M+H]^{+}$: *m/z* = 1023.48410; found: 1023.48354; δ = 0.5 ppm.

- **(*S*)-3-(4-(3-(6-(3,5-bis(pyridin-3-ylethynyl)benzamido)hexanamido)propoxy)benzamido)-4-(4-(3-((4-methoxypyridin-2-yl)amino)propoxy)phenyl)butanoic acid (L2)**



Chemical Formula: $C_{56}H_{57}N_7O_8$
Exact Mass: 955,42686
Molecular Weight: 956,11300

The carboxylic acid **L0** (2.75 mg, 8.46 µmol, 1.00 eq.) and the free amine **2** (5.50 mg, 8.46 µmol, 1.00 eq.) were converted according to the above-mentioned procedure. The final bioconjugated metal ligand **L2** was isolated after purification *via* preparative RP-HPLC (20-45% buffer B, 10 min, Waters) and lyophilization as a white solid (6.5 mg, 6.80 µmol, 80%).

^{1}H-NMR (500 MHz, DMSO-d_6): δ = 12.65 (s, 1H), 8.81 (d, *J* = 2.1 Hz, 2H), 8.70 (t, *J* = 5.5 Hz, 1H), 8.63 (dd, *J* = 4.8, 1.7 Hz, 2H), 8.15 (d, *J* = 8.3 Hz, 1H), 8.10 (d, *J* = 1.6 Hz, 2H), 8.02 (dt, *J* = 8.0, 1.9 Hz, 2H), 7.95 (t, *J* = 1.6 Hz, 1H), 7.86 (t, *J* = 5.6 Hz, 1H), 7.79 (d, *J* = 7.2 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 2H), 7.50 (dd, *J* = 7.9, 4.9 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 6.50 (dd, *J* = 7.3, 2.5 Hz, 1H), 6.35 (d, *J* = 2.5 Hz, 1H), 4.41 (h, *J* = 7.3 Hz, 1H), 4.00 (td, *J* = 6.0, 3.1 Hz, 4H), 3.87 (s, 3H), 3.44 (q, *J* = 6.5 Hz, 2H), 3.27 (q, *J* = 6.7 Hz, 2H), 3.18 (q, *J* = 6.5 Hz, 2H), 2.79 (dd, *J* = 13.6, 8.0 Hz, 1H), 2.72 (dd, *J* = 13.6, 5.9 Hz, 1H), 2.49 (s, 1H), 2.40 (dd, *J* = 15.4, 6.2 Hz, 1H), 2.07 (t, *J* = 7.4 Hz, 2H), 2.00 (p, *J* = 6.4 Hz, 2H), 1.83 (p, *J* = 6.6 Hz, 2H), 1.53 (pd, *J* = 7.3, 3.1 Hz, 4H), 1.29 (tt, *J* = 9.8, 6.0 Hz, 2H).

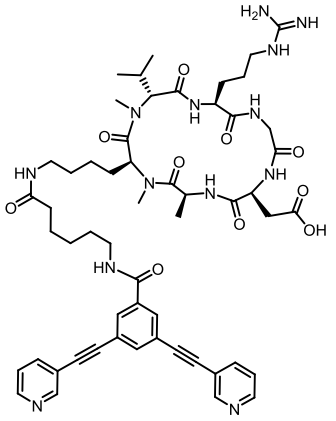
$^{13}C\{^{1}H\}$-NMR (126 MHz, DMSO-d_6): δ = 172.6, 172.1, 165.1, 164.1, 160.8, 156.8, 154.5, 151.7, 149.4, 138.9, 135.8, 131.0, 130.5, 130.1, 129.0, 126.8, 123.8, 122.7, 118.9, 114.1, 113.8, 104.0 (HSQC), 90.6, 87.5, 65.4, 64.5, 56.6, 48.4, 39.5 (HSQC), 39.1 (HSQC), 28.9 (HSCQ), 38.8, 35.4, 35.4, 28.9, 28.7, 27.8, 26.2, 25.1.

RP-HPLC (5-95%, 5 min): t_R = 3.38 min.

MS (HESI): *m/z* = 479.04 $[M+2H]^{2+}$, 956.27 $[M+H]^{+}$.

HRMS (ESI) calcd. for $C_{56}H_{58}N_7O_8^{+}$ $[M+H]^{+}$: *m/z* = 956.43469; found: 956.43355; δ = 1.2 ppm.

- ***cyclo*(RGDA*L*v)((3,5-bis(pyridin-3-ylethynyl)benzoyl)Ahx)) (L3)**



Chemical Formula: $C_{55}H_{71}N_{13}O_{10}$
Exact Mass: 1073,54469
Molecular Weight: 1074,25400

The carboxylic acid **L0** (8.45 mg, 26.0 µmol, 1.00 eq.) and the free amine **3** (20.0 mg, 26.0 µmol, 1.00 eq.) were converted according to the above-mentioned procedure. The final bioconjugated metal ligand **L3** was isolated after purification *via* preparative RP-HPLC (20-35% buffer B, 10 min, Waters) and lyophilization as a white solid (8.0 mg, 7.45 µmol, 59%).

^{1}H-NMR (500 MHz, DMSO-d_6): δ = 8.88 – 8.78 (m, 3H), 8.70 (t, *J* = 5.6 Hz, 1H), 8.67 – 8.59 (m, 3H), 8.09 (d, *J* = 1.5 Hz, 2H), 8.04 (dt, *J* = 8.0, 1.9 Hz, 2H), 7.96 (t, *J* = 1.6 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.74 (t, *J* = 5.6 Hz, 1H), 7.55-7.48 (m, *J* = 7.9, 4.9, 0.9 Hz, 2H), 7.46 (t, *J* = 5.9 Hz, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 4.76 – 4.65 (m, 2H), 4.58 (q, *J* = 7.6, 6.1 Hz, 1H), 4.47 (q, *J* = 7.1 Hz, 1H), 4.35 (t, *J* = 7.0 Hz, 1H), 3.75 (dd, *J* = 15.0, 5.3 Hz, 1H), 3.40 (dd, *J* = 15.0, 6.0 Hz, 1H), 3.27 (q, *J* = 6.7 Hz, 2H), 3.16 – 3.04 (m, 2H), 3.03 – 2.98 (m, 1H), 3.01 (s, 3H), 2.88 – 2.79 (m, 1H), 2.77 (s, 3H), 2.18 – 2.08 (m, 1H), 2.05 (t, *J* = 7.4 Hz, 2H), 1.80 – 1.58 (m, 3H), 1.58 – 1.45 (m, 5H), 1.45 – 1.34 (m, 4H), 1.34 – 1.22 (m, 5H), 1.19 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.70 (d, *J* = 6.7 Hz, 3H).

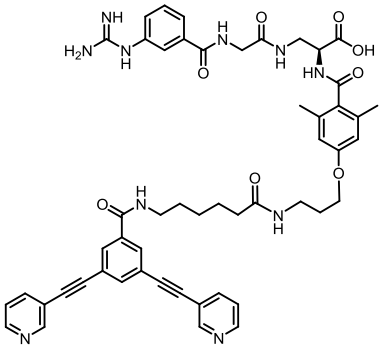
^{13}C{^{1}H}-NMR (126 MHz, DMSO-d_6): δ = 172.1, 172.0, 171.9, 171.8, 171.6, 169.7, 169.3, 168.8, 164.1, 156.5, 151.7, 149.4, 138.9, 136.2, 135.8, 130.5, 123.8, 122.6, 118.9, 117.4, 115.0, 90.6, 87.5, 60.7, 57.4, 51.0, 49.1, 45.9, 43.1, 40.3, 38.1, 35.4, 34.6, 32.9, 30.0, 29.1, 28.7, 26.2, 25.7, 25.1, 24.9, 23.7, 20.3, 18.4, 16.5.

RP-HPLC (5-95%, 5 min): t_R = 2.68 min.

MS (HESI): *m/z* = 538.14 $[M+2H]^{2+}$, 1074.39 $[M+H]^{+}$.

HRMS (ESI) calcd. for $C_{55}H_{72}N_{13}O_{10}^{+}$ $[M+H]^{+}$: *m/z* = 1074.55196; found: 1074.55619; δ = -3.9 ppm.

- **(S)-2-(4-(3-(6-(3,5-bis(pyridin-3-ylethynyl)benzamido)hexanamido)propoxy)-2,6-dimethylbenzamido)-3-(2-(3-guanidinobenzamido)acetamido)propanoic acid (L4)**



Chemical Formula: $C_{52}H_{54}N_{10}O_8$
Exact Mass: 946,41261
Molecular Weight: 947,06600

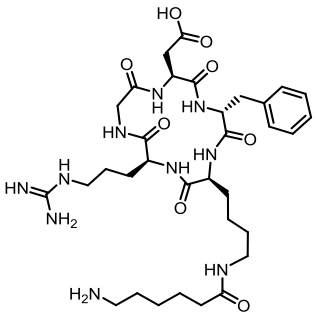
The carboxylic acid **L0** (7.59 mg, 23.4 µmol, 1.00 eq.) and the free amine **4** (15.0 mg, 23.4 µmol, 1.00 eq.) were converted according to the above mentioned procedure. The final bioconjugated metal ligand **L4** was isolated after purification *via* preparative RP-HPLC (20-35% buffer B, 10 min, Waters) and lyophilization as a white solid (8.04 mg, 8.49 µmol, 54%).

^{1}H-NMR (500 MHz, DMSO-d_6): δ = 12.74 (s, 1H), 9.80 (s, 1H), 8.84 – 8.79 (m, 2H), 8.78 (t, *J* = 6.0 Hz, 1H), 8.70 (t, *J* = 5.6 Hz, 1H), 8.64 (d, *J* = 4.0 Hz, 2H), 8.35 (d, *J* = 7.7 Hz, 1H), 8.10 (d, *J* = 1.6 Hz, 2H), 8.04 (t, *J* = 1.9 Hz, 1H), 8.04 – 7.99 (m, 2H), 7.96 (t, *J* = 1.6 Hz, 1H), 7.85 (t, *J* = 5.7 Hz, 1H), 7.77 (d, *J* = 7.9 Hz, 1H), 7.72 (t, *J* = 1.9 Hz, 1H), 7.56 – 7.47 (m, 6H), 7.42 – 7.36 (m, 1H), 6.57 (s, 2H), 4.51 (td, *J* = 7.8, 5.2 Hz, 1H), 3.96 – 3.87 (m, 3H), 3.82 (dd, *J* = 16.3, 5.8 Hz, 1H), 3.61 – 3.52 (m, 1H), 3.45 – 3.31 (m, 1H), 3.31 – 3.23 (m, 2H), 3.16 (q, *J* = 6.6 Hz, 2H), 2.20 (s, 6H), 2.08 (t, *J* = 7.4 Hz, 2H), 1.79 (p, *J* = 6.7 Hz, 2H), 1.59 – 1.48 (m, 4H), 1.35 – 1.26 (m, 2H).
^{13}C{^{1}H}-NMR (126 MHz, DMSO-d_6): δ = 172.1, 171.8, 169.3, 169.2, 165.6, 164.1, 158.2, 158.1, 158.0, 155.7, 151.7, 149.4, 138.8, 136.2, 135.8, 135.6, 135.4, 130.7, 130.5, 129.8, 127.4, 125.2, 123.8, 123.5, 122.7, 118.9, 112.9, 90.6, 87.5, 65.1, 52.0, 42.5, 35.5, 35.4, 29.0, 28.7, 26.2, 25.1, 19.2.
RP-HPLC (5-95%, 5 min): t_R = 2.80 min.
MS (HESI): *m/z* = 474.51 $[M+2H]^{2+}$, 947.22 $[M+H]^+$.
HRMS (ESI) calcd. for $C_{52}H_{55}N_{10}O_8^+$ $[M+H]^+$: *m/z* = 947.41989; found: 947.41991; δ = 0.02 ppm.

4. Synthesis and Analysis of Ligands 1-4

*Synthesis of **1***

- ***cyclo*(RGDfK(Ahx)) (1)**



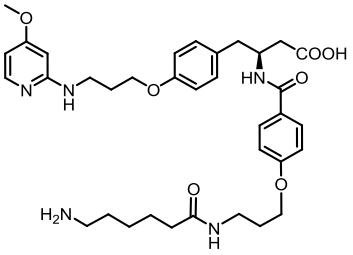
Chemical Formula: $C_{33}H_{52}N_{10}O_8$
Exact Mass: 716,39696
Molecular Weight: 716,84100

The linear peptide was synthesized according GP1 – GP3 on solid support starting with Fmoc-Gly-OH following standard Fmoc-strategy. After cleavage according GP4 and cyclisation according GP5 the Cbz-group of lysine was cleaved according GP6. Coupling of Boc-Ahx-OH according GP7 followed by a general deprotection according GP8. The final compound **1** was isolated after purification *via* preparative RP-HPLC (05-40% buffer B, 10 min, Waters) and lyophilization as a white solid.

RP-HPLC (5-95%, 5 min): t_R = 1.38 min.
MS (HESI): *m/z* = 359.49 $[M+2H]^{2+}$, 717.43 $[M+H]^+$.
HRMS (ESI) calc. for $C_{33}H_{53}N_{10}O_8^+$ $[M+H]^+$: *m/z* = 717.40478; found: 717.40424, δ = 0.8 ppm.
The *spectral data correspond to those given in the literature.*[3]

*Synthesis of **2***

- **(*S*)-3-(4-(3-(6-aminohexanamido)propoxy)benzamido)-4-(4-(3-((4-methoxypyridin-2-yl)amino)propoxy)phenyl)butanoic acid (2)**



Chemical Formula: $C_{35}H_{47}N_5O_7$
Exact Mass: 649,34755
Molecular Weight: 649,78900

The unprotected ligand was synthesized on solid support according to the literature.[4] The crude product was purified *via* preparative HPLC (05-60% buffer B, 10 min, Waters) and after lyophilization isolated as a white TFA-salt.

^{1}H-NMR (500 MHz, DMSO-d_6): δ = 12.83 (bs, 1H), 12.16 (bs, 1H), 8.33 (bs, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 7.89 (t, *J* = 5.6 Hz, 1H), 7.81 (d, *J* = 7.2 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 2H), 7.67 (s, 3H), 7.13 (d, *J* = 8.6 Hz, 2H), 6.96 (d, *J* = 8.9 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.48 (dd, *J* = 7.2, 2.4 Hz, 1H), 6.34 (d, *J* = 2.5 Hz, 1H), 4.46 – 4.35 (m, 1H), 4.02 (virt. q, *J* = 6.1 Hz, 4H), 3.87 (s, 3H), 3.44 (q, *J* = 6.5 Hz, 2H), 3.19 (q, *J* = 6.6 Hz, 2H), 2.85 – 2.68 (m, 4H), 2.53 – 2.51 (m, 1H), 2.40 (dd, *J* = 15.4, 6.1 Hz, 1H),

2.07 (t, *J* = 7.4 Hz, 2H), 2.00 (p, *J* = 6.5 Hz, 2H), 1.85 (p, *J* = 6.6 Hz, 2H), 1.50 (h, *J* = 8.0 Hz, 4H), 1.32 – 1.20 (m, 2H).

$^{13}C\{^{1}H\}$-NMR (126 MHz, DMSO-d_6): δ = 172.6, 171.9, 165.1, 160.8, 156.8, 130.9, 130.1, 129.0, 126.8, 114.2, 113.8, 103.8 (HSQC), 91.4 (HSQC), 65.5, 64.6, 56.5, 48.4, 38.7, 35.5, 35.1, 28.9, 27.9, 26.9, 25.6, 24.8.

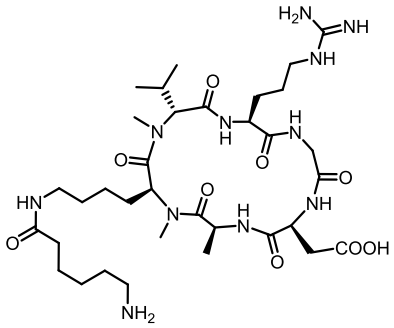
RP-HPLC (5-95%, 5 min): t_R = 1.98 min.

MS (HESI): *m/z* = 325.94 $[M+2H]^{2+}$, 650.32 $[M+H]^{+}$.

HRMS (ESI) calc. for $C_{35}H_{48}N_5O_7^+$ $[M+H]^+$: *m/z* = 650.35483; found: 650.35528, δ = -0.7 ppm.

*Synthesis of **3***

- **(S)-3-(4-(3-(6-aminohexanamido)propoxy)benzamido)-4-(4-(3-((4-methoxypyridin-2-yl)amino)propoxy)phenyl)butanoic acid (3)**



The linear peptide was synthesized according GP1 – GP3 and GP9 on solid support starting with Fmoc-Gly-OH following standard Fmoc-strategy. After cleavage according GP4 and cyclisation according GP5 the Dde-group of lysine was cleaved according GP10. Coupling of Boc-Ahx-OH according GP7 followed by a general deprotection according GP8. The final compound **3** was isolated after purification *via* preparative RP-HPLC (10-60% buffer B, 10 min, Waters) and lyophilization as a white solid.

^{1}H-NMR (500 MHz, DMSO-d_6): δ = 12.28 (s, 1H), 8.83 (t, *J* = 5.7 Hz, 1H), 8.64 (d, *J* = 8.6 Hz, 1H), 7.83 – 7.72 (m, 2H), 7.63 (s, 4H), 7.49 (t, *J* = 5.9 Hz, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 4.73 – 4.64 (m, 2H), 4.58 (td, *J* = 7.8, 6.1 Hz, 1H), 4.47 (q, *J* = 7.1 Hz, 1H), 4.38 (dd, *J* = 7.9, 6.3 Hz, 1H), 3.75 (dd, *J* = 15.1, 5.3 Hz, 1H), 3.41 (dd, *J* = 15.0, 6.0 Hz, 1H), 3.08 (dt, *J* = 12.5, 6.7 Hz, 2H), 3.01 (s, 3H), 3.05 – 2.98 (m, 2H), 2.88 – 2.80 (m, 1H), 2.78 (s, 3H), 2.77 – 2.71 (m, 2H), 2.49 – 2.44 (m, 1H), 2.20 – 2.08 (m, 1H), 2.04 (t, *J* = 7.4 Hz, 3H), 1.76 – 1.66 (m, 2H), 1.66 – 1.57 (m, 1H), 1.57 – 1.44 (m, 4H), 1.44 – 1.33 (m, 3H), 1.33 – 1.22 (m, 5H), 1.20 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.71 (d, *J* = 6.8 Hz, 3H).

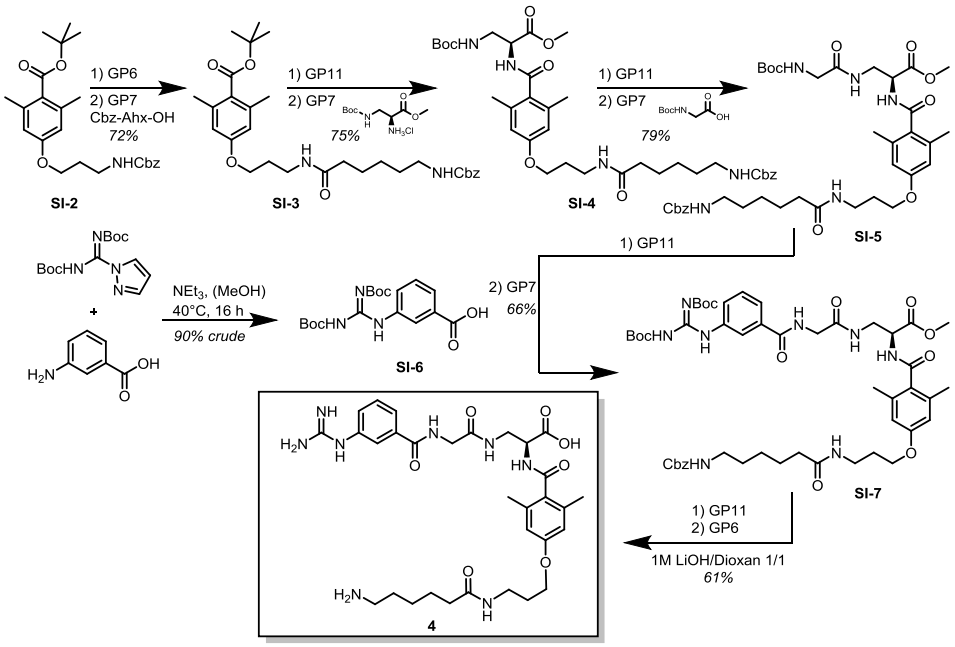
$^{13}C\{^{1}H\}$-NMR (126 MHz, DMSO-d_6): δ = 172.12, 172.05, 171.73, 171.69, 171.6, 169.7, 169.3, 168.7, 156.6, 60.7, 57.3, 51.0, 49.1, 45.9, 43.1/43.0, 40.3, 38.7, 38.1, 35.1, 34.6, 32.8, 30.3, 30.0, 29.1, 27.6, 26.9, 25.7, 25.5, 24.9, 24.8, 23.7, 20.3, 18.4, 16.5.

RP-HPLC (5-95%, 5 min): t_R = 1.98 min.

MS (HESI): *m/z* = 325.94 $[M+2H]^{2+}$, 650.32 $[M+H]^{+}$.

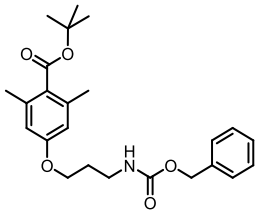
HRMS (ESI) calc. for $C_{34}H_{62}N_{11}O_9^+$ $[M+H]^+$: *m/z* = 768.47320; found: 768.47140; δ = -0.7 ppm.

*Synthesis of **4***



Scheme S2. Preparation of peptide **4** as solution synthesis.

- ***tert*-butyl-4-(3-(((benzyloxy)carbonyl)amino)propoxy)-2,6-dimethylbenzoate (SI-2)**



Chemical Formula: $C_{24}H_{31}NO_5$
Exact Mass: 413,22022
Molecular Weight: 413,51400

Compound **SI-2** was prepared as described in the literature[5] and isolated as a white solid (5.29 g, 12.8 mmol, 81%) after flash chromatography [SiO_2, 900 mL, CyHex/EtOAc = 3/1 → 2/1].

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.39 – 7.28 (m, 5H), 6.52 (s, 2H), 5.10 (s, 2H), 4.98 (s, 1H), 4.00 (t, *J* = 5.9 Hz, 2H), 3.39 (q, *J* = 6.4 Hz, 2H), 2.31 (s, 6H), 1.98 (p, *J* = 6.2 Hz, 2H), 1.58 (s, 9H).

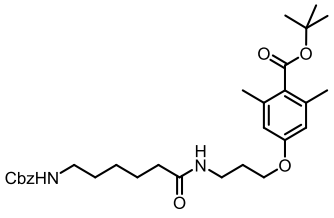
^{13}C{^{1}H}-NMR (101 MHz, $CDCl_3$): δ = 169.3, 158.8, 156.6, 136.9, 128.7, 128.5, 128.2, 113.7, 81.5, 66.8, 65.8, 38.7, 29.5, 28.4, 20.2.

RP-HPLC (5-95%, 7 min): t_R = 4.13

MS (HESI): *m/z* = 413.76 $[M+H]^+$, 430.97 $[M+NH_4]^+$, 436.12 $[M+Na]^+$, 826.61 $[2M+H]^+$.

The spectral data correspond to those given in the literature.[5]

- ***tert*-butyl-4-(3-(6-(((benzyloxy)carbonyl)amino)hexanamido)propoxy)-2,6-dimethylbenzoate (SI-3)**



Chemical Formula: $C_{30}H_{42}N_2O_6$
Exact Mass: 526,30429
Molecular Weight: 526,67400

Compound **SI-2** (1.00 g, 2.42 mmol1.00 eq.) was converted according to the GP6 and GP7 with Cbz-Ahx-OH (770 mg, 2.90 mmol, 1.20 eq.) to the Cbz-protected Amin **SI-3**. After removal of the solvent *in vacuo* the crude product was purified *via* preparative RP-HPLC (30-80% buffer B, 10 min, Waters) and after lyophilization **SI-3** was obtained as a white solid (0.91 g, 1.74 mmol, 72% over 2 steps).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.26 (s, 5H), 6.44 (d, *J* = 0.8 Hz, 2H), 5.94 (d, *J* = 6.1 Hz, 1H), 5.00 (s, 2H), 4.87 – 4.71 (m, 1H), 3.91 (t, *J* = 5.8 Hz, 2H), 3.35 (q, *J* = 6.3 Hz, 2H), 3.08 (q, *J* = 6.7 Hz, 2H), 2.23 (t, *J* = 0.6 Hz, 6H), 2.17 – 2.02 (m, 2H), 1.89 (p, *J* = 6.2 Hz, 2H), 1.61 – 1.48 (m, 2H), 1.50 (s, 9H), 1.48 – 1.33 (m, 2H), 1.25 (qd, *J* = 7.3, 6.5, 4.1 Hz, 2H).

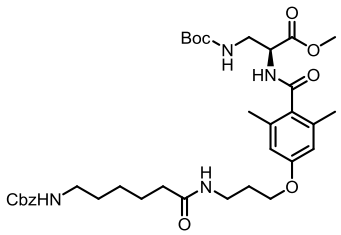
^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$): δ = 173.5, 169.3, 158.7, 156.6, 136.9, 136.7, 128.6, 128.6, 128.2, 128.2, 113.6, 81.6, 66.7, 66.2, 40.9, 37.5, 36.6, 29.8, 29.0, 28.4, 26.3, 25.3, 20.1.

RP-HPLC (5-95%, 5 min): t_R = 3.88 min.

MS (HESI): *m/z* = 526.91 $[M+H]^+$, 1052.98 $[2M+H]^+$.

HRMS (ESI) calc. for $C_{30}H_{43}N_2O_6^+$ $[M+H]^+$: 527.31211; found: 527.31147; δ = 1.2 ppm.

- **methyl-(S)-2-(4-(3-(6-(((benzyloxy)carbonyl)amino)hexanamido)propoxy)-2,6-dimethylbenzamido)-3-((*tert*-butoxycarbonyl)amino)propanoate (SI-4)**



Chemical Formula: $C_{35}H_{50}N_4O_9$
Exact Mass: 670,35778
Molecular Weight: 670,80400

The *tert*-butyl protected carboxylic acid **SI-3** (914 mg, 1.74 mmol, 1.05 eq.) was dissolved in CH_2Cl_2 (3 mL) and TFA (12 mL) was added at room temperature. After stirring for 30 min, the reaction mixture was processed according to GP8. The crude carboxylic acid was coupled according to GP7 with methyl-(*S*)-2-amino-3-((*tert*-butoxycarbonyl)amino)propanoate hydrochloride (421 mg, 1.65 mmol, 1.00 eq.). After removal of the solvent *in vacuo* the crude reaction mixture was purified *via* RP-HPLC (30-80% buffer B, 10 min, Waters) and after lyophilization the product **SI-4** was obtained as a white solid (832 mg, 1.23 mmol, 75% over 2 steps).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.26 (s, 5H), 6.99 – 6.84 (m, 1H), 6.44 (s, 2H), 6.10 (t, *J* = 5.7 Hz, 1H), 5.03 (d, *J* = 7.2 Hz, 1H), 4.99 (s, 2H), 4.87 (d, *J* = 6.1 Hz, 1H), 4.69 (q, *J* = 5.9 Hz, 1H), 3.91 (t, *J* = 5.8 Hz, 2H), 3.71 (s, 3H), 3.52 (t, *J* = 5.8 Hz, 2H), 3.34 (q, *J* = 6.3 Hz, 2H), 3.04 (q, *J* = 6.7 Hz, 2H), 2.22 (s, 6H), 2.14 – 2.05 (m, 2H), 1.89 (p, *J* = 6.2 Hz, 2H), 1.53 (p, *J* = 7.6 Hz, 2H), 1.38 (q, *J* = 7.5 Hz, 2H), 1.32 (s, 9H), 1.28 – 1.19 (m, 2H).

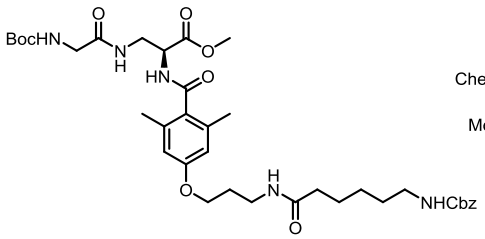
^{13}C{^{1}H}-NMR (126 MHz, $CDCl_3$): δ 173.9, 170.9, 170.8, 158.8, 156.7, 136.7, 136.6, 129.9, 128.6, 128.2, 128.2, 113.5, 80.3, 69.6, 66.7, 66.2, 53.8, 52.8, 42.2, 40.8, 37.6, 36.5, 29.6, 28.8, 28.4, 26.3, 25.3, 19.6.

RP-HPLC (5-95%, 8 min): t_R = 6.05 min.

MS (HESI): *m/z* = 671.24 $[M+H]^+$, 1340.57 $[2M+H]^+$.

HRMS (ESI) calc. for $C_{35}H_{51}N_4O_9^+$ $[M+H]^+$: *m/z* = 671.36560; found: 671.36482; δ = 1.2 ppm.

- **methyl-(*S*)-2-(4-(3-(6-(((benzyloxy)carbonyl)amino)hexanamido)propoxy)-2,6-dimethylbenzamido)-3-(2-((*tert*-butoxycarbonyl)amino)acetamido)propanoate (SI-5)**



Chemical Formula: $C_{37}H_{53}N_5O_{10}$
Exact Mass: 727,37924
Molecular Weight: 727,85600

The Boc-protected amine **SI-4** (130 mg, 194 µmol, 1.00 eq.) was converted according to GP8 for 30 min and GP7 for 1 h with Boc-Gly-OH (40.7 mg, 233 µmol, 1.20 eq.). After removal of the solvent *in vacuo* the crude product was purified by RP-HPLC (20-60% buffer B, 10 min, Waters) and after lyophilization the product **SI-5** was obtained as a white solid (112 mg, 154 µmol, 79% over 2 steps).

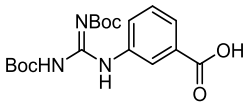
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.43 – 7.28 (m, 5H), 6.99 (d, *J* = 7.6 Hz, 1H), 6.86 (t, *J* = 5.8 Hz, 1H), 6.52 (s, 2H), 6.09 (s, 1H), 5.12 (t, *J* = 5.6 Hz, 1H), 5.07 (s, 2H), 4.95 (s, 1H), 4.86 (t, *J* = 6.2 Hz, 1H), 4.00 (t, *J* = 5.7 Hz, 2H), 3.84 – 3.80 (m, 1H), 3.79 (s, 3H), 3.76 – 3.68 (m, 2H), 3.71 – 3.67 (m, 1H), 3.45 (*virt.* q, *J* = 6.2 Hz, 2H), 3.17 – 3.03 (m, 2H), 2.29 (s, 6H), 2.20 (t, *J* = 7.5 Hz, 2H), 1.98 (p, *J* = 6.1 Hz, 2H), 1.67 – 1.56 (m, 2H), 1.52 – 1.44 (m, 2H), 1.41 (s, 9H), 1.41 – 1.26 (m, 2H).

RP-HPLC (5-95%, 5 min): t_R = 3.04 min

MS (HESI): *m/z* = 728.22 $[M+H]^+$, 1454.75 $[2M+H]^+$.

HRMS (ESI) calc. for $C_{37}H_{54}N_5O_{10}^+$ $[M+H]^+$: *m/z* = 728.38707; found: 728.38644; δ = 0.9 ppm.

- **3-(2,3-bis(*tert*-butoxycarbonyl)guanidino)benzoic acid (SI-6)**



Chemical Formula: $C_{18}H_{25}N_3O_6$
Exact Mass: 379,17434
Molecular Weight: 379,41300

According to the literature,[6] *N*,*N´*-bis(*tert*-butoxycarbonyl)-1*H*-pyrazole-1-carboxamidine (5.19 g, 16.7 mmol, 1.00 eq.) and 3-aminiobenzoic acid (2.40 g, 17.5 mmol, 1.05 eq.) were suspended in MeOH (67mL, 0.25 M) and triethylamine (6.96 mL, 5.06 g, 50.0 mmol, 3.00 eq.) was added. The mixture was heated at 40°C for 16 h and after reaction control, cooled down to room temperature. The solvent was removed *in vacuo* and after addition of ethyl acetate (150 mL) the crude product mixture was washed with $HCl_{aq.}$ (150 mL, 1 M) and brine (150 mL). The organic phase was dried over Na_2SO_4, filtrated and the solvent removed *in vacuo*. The product **SI-6** was isolated as a white solid (5.67 g, 14.9 mmol, 90%) and used for further reactions without additional purification.

^{1}H-NMR (500 MHz, DMSO-d_6): δ = 12.85 (bs, 1H), 11.35 (bs, 1H), 10.11 (bs, 1H), 8.00 (s, 1H), 7.87 – 7.75 (m, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.48 (t, *J* = 7.9 Hz, 1H), 1.45 (s, 18H).

^{13}C{^{1}H}-NMR (126 MHz, DMSO-d_6): δ = 166.9, 158.5, 153.7, 151.1, 148.4, 131.4, 129.0, 127.2, 125.6, 123.5, 81.9, 79.0, 27.8.

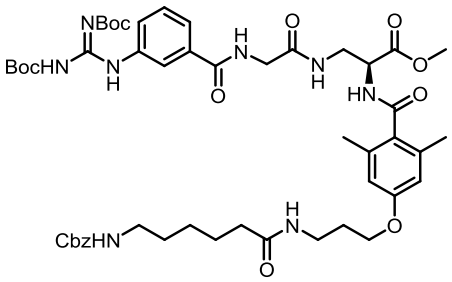
RP-HPLC (5-95%, 5 min): t_R = 3.77 min.

MS (HESI): *m/z* = 379.85 $[M+H]^+$, 780.81 $[2M+H]^+$.

HRMS (ESI) calcd. for $C_{18}H_{26}N_3O_6^+$ $[M+H]^+$: *m/z* = 380.18216; found: 380.18155; δ = 0.9 ppm.

The *spectral data correspond to those given in the literature.*[6]

- **Methyl (*S*)-2-(4-(3-(6-(((benzyloxy)carbonyl)amino)hexanamido)propoxy)-2,6-dimethyl benzamido)-3-(2-(3-(2,3-bis(*tert*-butoxycarbonyl)guanidino)benzamido)acetamido) propanoate (SI-7)**



Chemical Formula: $C_{50}H_{68}N_8O_{13}$
Exact Mass: 988,49058
Molecular Weight: 989,13700

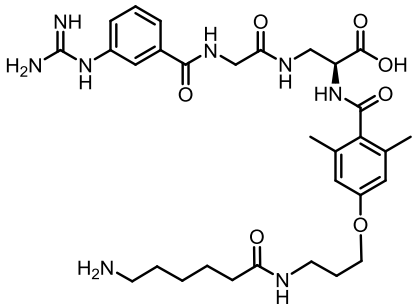
Compound **SI-5** (480 mg, 659 µmol, 1.00 eq.) was Boc-deprotected according to GP11 and the crude product used as the amine for further coupling with compound **SI-6** (300 mg, 791 µmol, 1.20 eq.) according to GP7. After removal of the solvent *in vacuo* the crude product was purified *via* RP-HPLC (20-80% buffer B, 10 min, Waters) and after lyophilization the product **SI-7** was obtained as a white solid (428 mg, 435 µmol, 66% over 2 steps).

RP-HPLC (5-95%, 5 min): t_R = 3.93 min.

MS (HESI): *m/z* = 495.24 $[M+2H]^{2+}$, 989.23 $[M+H]^+$.

HRMS (ESI) calc. for $C_{50}H_{69}N_8O_{13}^+$ $[M+H]^+$: *m/z* = 989.49786; found: 989.49738; δ = 0.5 ppm.

- **(*S*)-2-(4-(3-(6-aminohexanamido)propoxy)-2,6-dimethylbenzamido)-3-(2-(3-guanidinobenzamido)acetamido)propanoic acid (4)**



Chemical Formula: $C_{31}H_{44}N_8O_7$
Exact Mass: 640,33330
Molecular Weight: 640,74200

Compound **SI-7** (214 mg, 216 µmol, 1.00 eq.) was deprotected according to GP8 and GP6. The isolated crude product was further treated with a mixture of dioxane and aqueous solution of LiOH (1 M, 1:1, 3 mL each). After full consumption of the starting material, the solution was neutralized with an aqueous solution of HCl (1 M) and the solvents removed in vacuo. The crude product was purified *via* semi-preparative RP-HPLC (05-50% buffer B, 10 min, Waters) and compound **4** (85 mg, 132 µmol, 61% over 3 steps) was isolated as a white solid after lyophilization.

^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.07 (s, 1H), 8.81 (virt. t, *J* = 5.9 Hz, 1H), 8.36 (d, *J* = 7.7 Hz, 1H), 8.03 (virt. t, *J* = 5.9 Hz, 1H), 7.88 (virt. t, *J* = 5.6 Hz, 1H), 7.77 (virt. dt, *J* = 7.9, 1.3 Hz, 1H), 7.76 – 7.58 (m, 7H), 7.54 (virt. t, *J* = 7.9 Hz, 1H), 7.39 (ddd, *J* = 7.9, 2.2, 1.0 Hz, 1H), 6.58 (s, 2H), 4.56 – 4.44 (m, 1H), 3.99 – 3.86 (m, 3H), 3.82 (dd, *J* = 16.3, 5.8 Hz, 1H), 3.62 – 3.35 (m, 2H), 3.24 – 3.09 (m, 2H), 2.83 – 2.68 (m, 2H), 2.21 (s, 6H), 2.06 (virt. t, *J* = 7.4 Hz, 2H), 1.87 – 1.72 (m, 2H), 1.57 – 1.42 (m, 4H), 1.33 – 1.19 (m, 2H).

$^{13}C\{^1H\}$-NMR (126 MHz, DMSO-d_6): δ = 172.0, 171.8, 169.4, 169.3, 165.8, 158.5 (q, *J* = 32.3 Hz, TFA), 158.1, 155.9, 136.0, 135.7, 135.5, 130.8, 129.8, 127.4, 125.2, 123.4, 116.9 (q, *J* = 297.9 Hz, TFA), 113.0, 65.2, 52.1, 42.6, 39.6, 38.8, 35.5, 35.2, 29.0, 26.9, 25.6, 24.8, 19.2.

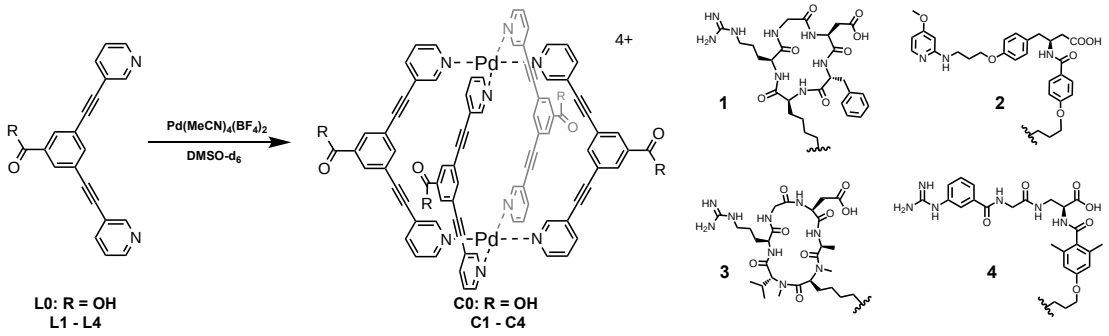
RP-HPLC (5-95%, 5 min): t_R = 1.18 min.

MS (HESI): *m/z* = 321.33 $[M+2H]^{2+}$, 641.18 $[M+H]^+$.

HRMS (ESI) calc. for $C_{31}H_{45}N_8O_7^+$ $[M+H]^+$: *m/z* = 641.34057; found: 641.34046; δ = 0.2 ppm.

The *spectral data correspond to those given in the literature.*[4]

5. Cage formation and analysis (C0, C1-C4)



Scheme S3. Synthesis of cage **C0, C1-C4** *via* metal-mediated self-assembly.

*Analysis of cage **C0***

^1H NMR (400 MHz, DMSO-d_6): δ [ppm] = 9.60 (s, 2H, H_a), 9.40 (d, *J* = 5.8 Hz, 2H, H_b), 8.35 (d, *J* = 8.8 Hz, 2H, H_d), 8.20 (s, 2H, H_f) 8.15 (s, 1H, H_e), 7.85 (dd, *J* = 6.1, 8.2 Hz, 2H, H_c).

$^{13}C\{^1H\}$ NMR (400 MHz, DMSO-d_6): δ [ppm] = 165.9, 153.2, 151.3, 143.6, 137.9, 134.0, 133.1, 127.9, 122.9, 122.6, 93.3, 86.5.

$^{11}B\{^1H\}$ NMR (128 MHz, DMSO-d_6): δ [ppm] = -1.18.

$^{19}F\{^1H\}$ NMR (376 *MHz,* DMSO-d_6*):* δ [ppm] = *-147.8.*

HRMS (ESI) calcd. for $C_{84}H_{44}N_8O_8Pd_2$ $[M\text{-}4(BF_4)]^{4+}$: *m/z* = 377.5426; found: 377.5406; δ = 5.3 ppm).

6. Integrin binding studies

αvβ3

(1) 1.0 µg/mL human vitronectin; Merck Millipore.

(2) 2.0 µg/mL, human αvβ3-integrin, R&D.

(3) 2.0 µg/mL, mouse anti-human CD51/61, BD Biosciences.

(4) 2.0 µg/mL, anti-mouse IgG-POD, Sigma-Aldrich.

αvβ5

(1) 5.0 µg/mL; human vitronectin, Merck Millipore.

(2) 3.0 µg/mL, human αvβ5-integrin, R&D.

(3) 1:500 dilution, anti-αv mouse anti-human MAB1978, Merck Millipore.
(4) 2.0 µg/mL, anti-mouse IgG-POD, Sigma-Aldrich.

αvβ6
(1) 0.4 µg/mL; LAP (TGF-β), R&D.
(2) 0.5 µg/mL, human αvβ6-integrin, R&D.
(3) 1:500 dilution, anti-αv mouse anti-human MAB1978, Merck Millipore.
(4) 2.0 µg/mL, anti-mouse IgG-POD, Sigma-Aldrich.

α5β1
(1) 0.5 µg/mL; human fibronectin, Sigma-Aldrich.
(2) 2.0 µg/mL, human α5β1-integrin, R&D.
(3) 1.0 µg/mL, mouse anti-human CD49e, BD Biosciences.
(4) 2.0 µ g/mL, anti-mouse IgG-POD, Sigma-Aldrich.

7. NMR Spectroscopy

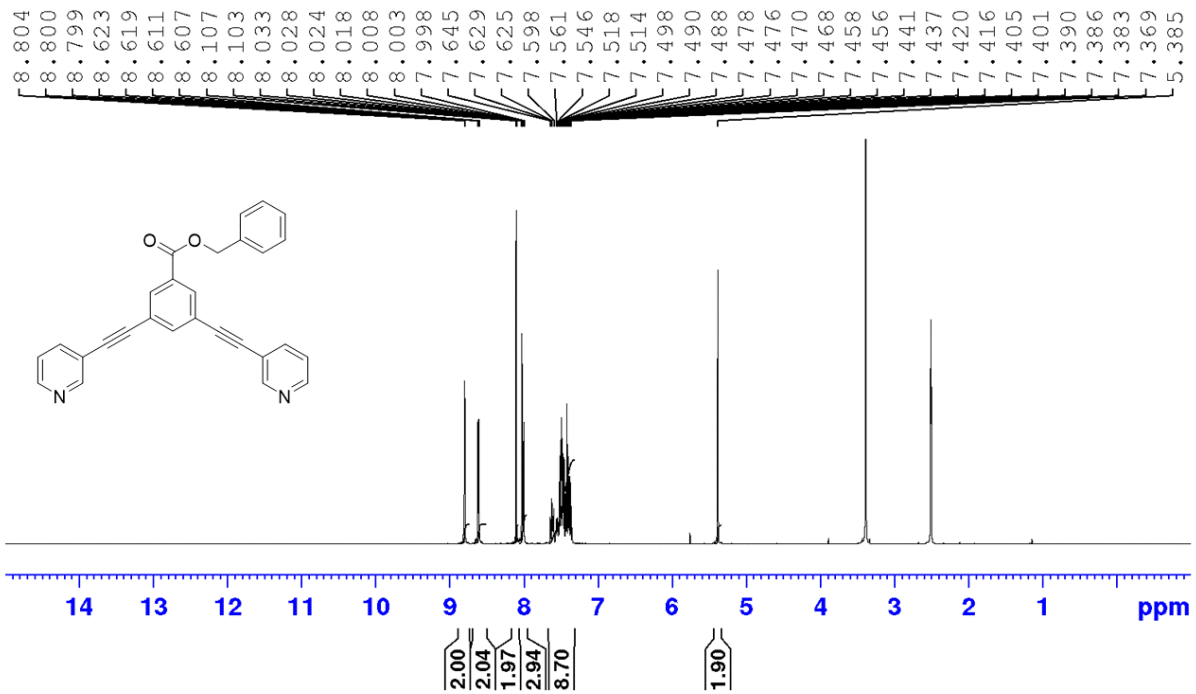


Figure S1. ^{1}H NMR (400 MHz, DMSO-d_6, 298K) of Benzyl 3,5-bis(pyridin-3-ylethynyl)benzoate **SI-1**.

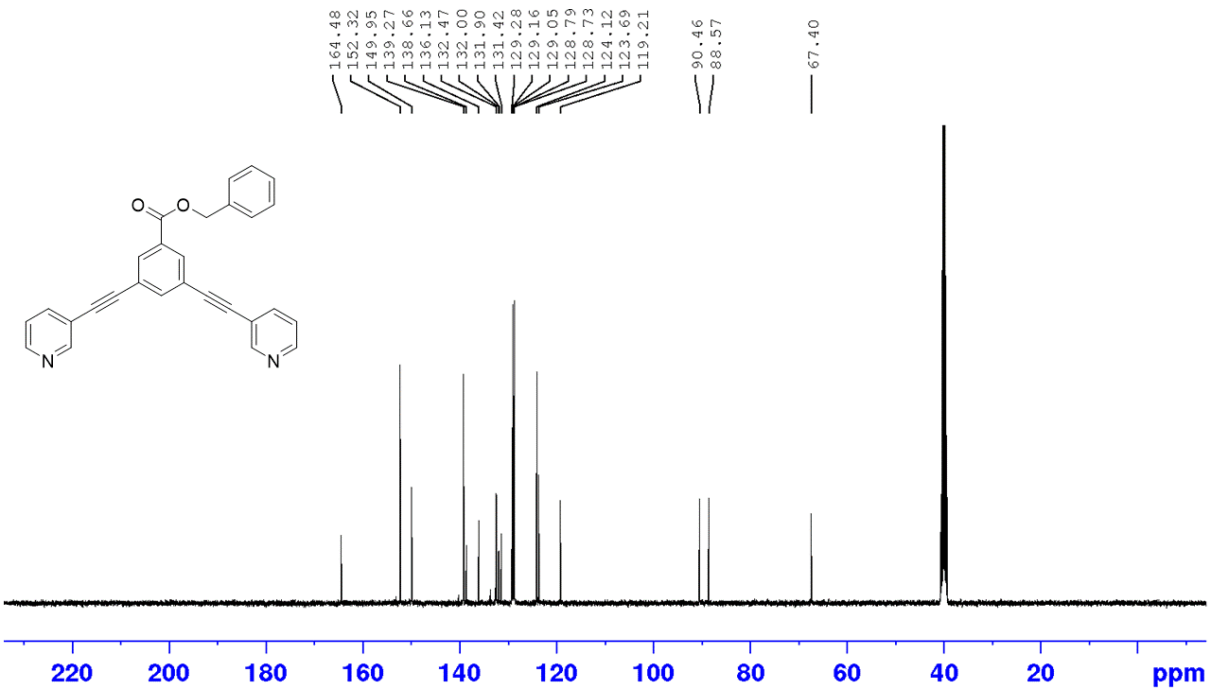


Figure S2. $^{13}C\{^{1}H\}$ NMR (400 MHz, DMSO-d_6, 298K) of Benzyl 3,5-bis(pyridin-3-ylethynyl)benzoate **SI-1**.

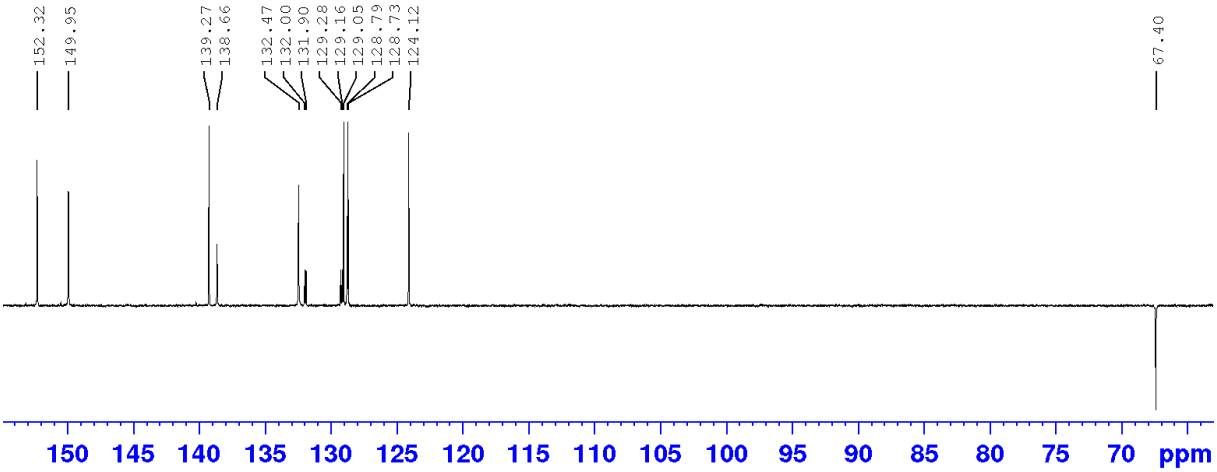


Figure S3. DEPT135-^{13}C NMR (400 MHz, DMSO-d_6, 298K) of Benzyl 3,5-bis(pyridin-3-ylethynyl)benzoate **SI-1**.

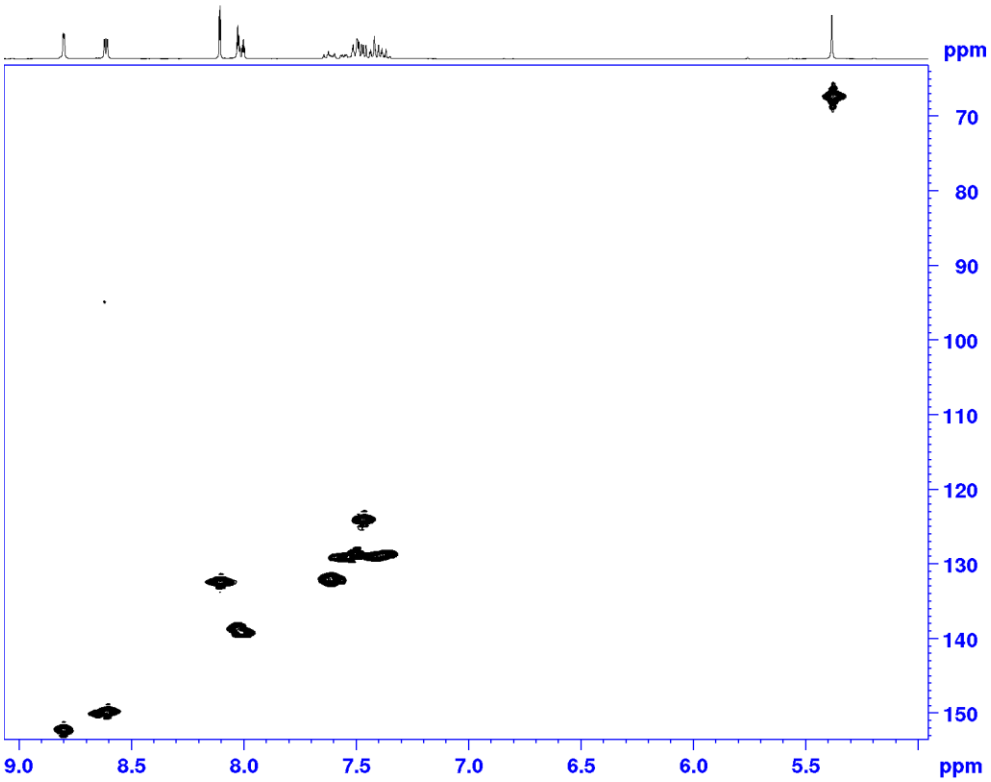


Figure S4. HSQC NMR (400 MHz, DMSO-d_6, 298K) of Benzyl 3,5-bis(pyridin-3-ylethynyl)benzoate **SI-1**.

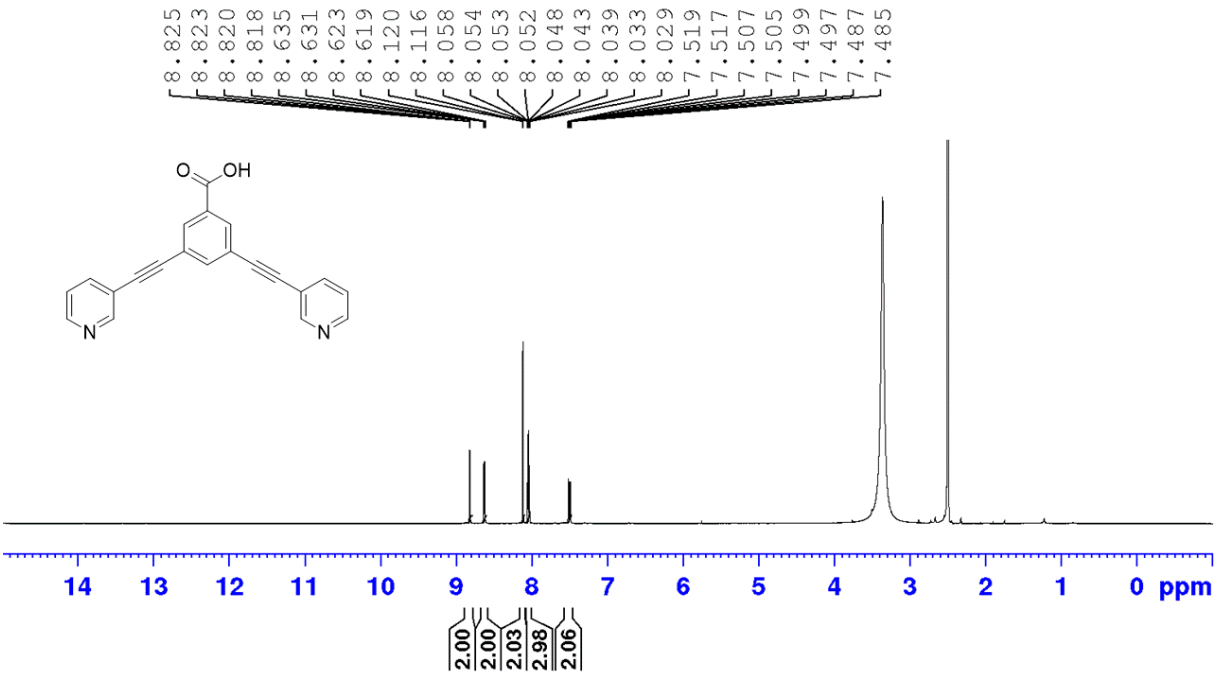


Figure S5. ^{1}H NMR (400 MHz, DMSO-d_6, 298K) of ligand **L0**.

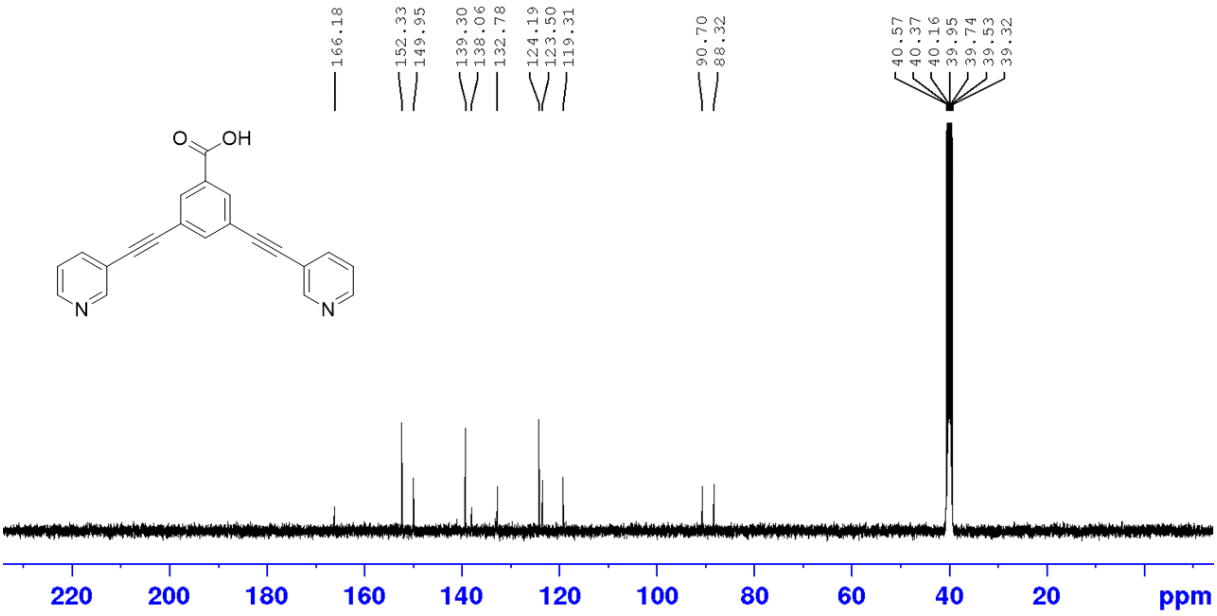


Figure S6. $^{13}C\{^{1}H\}$ NMR (400 MHz, DMSO-d_6, 298K) of ligand **L0**.

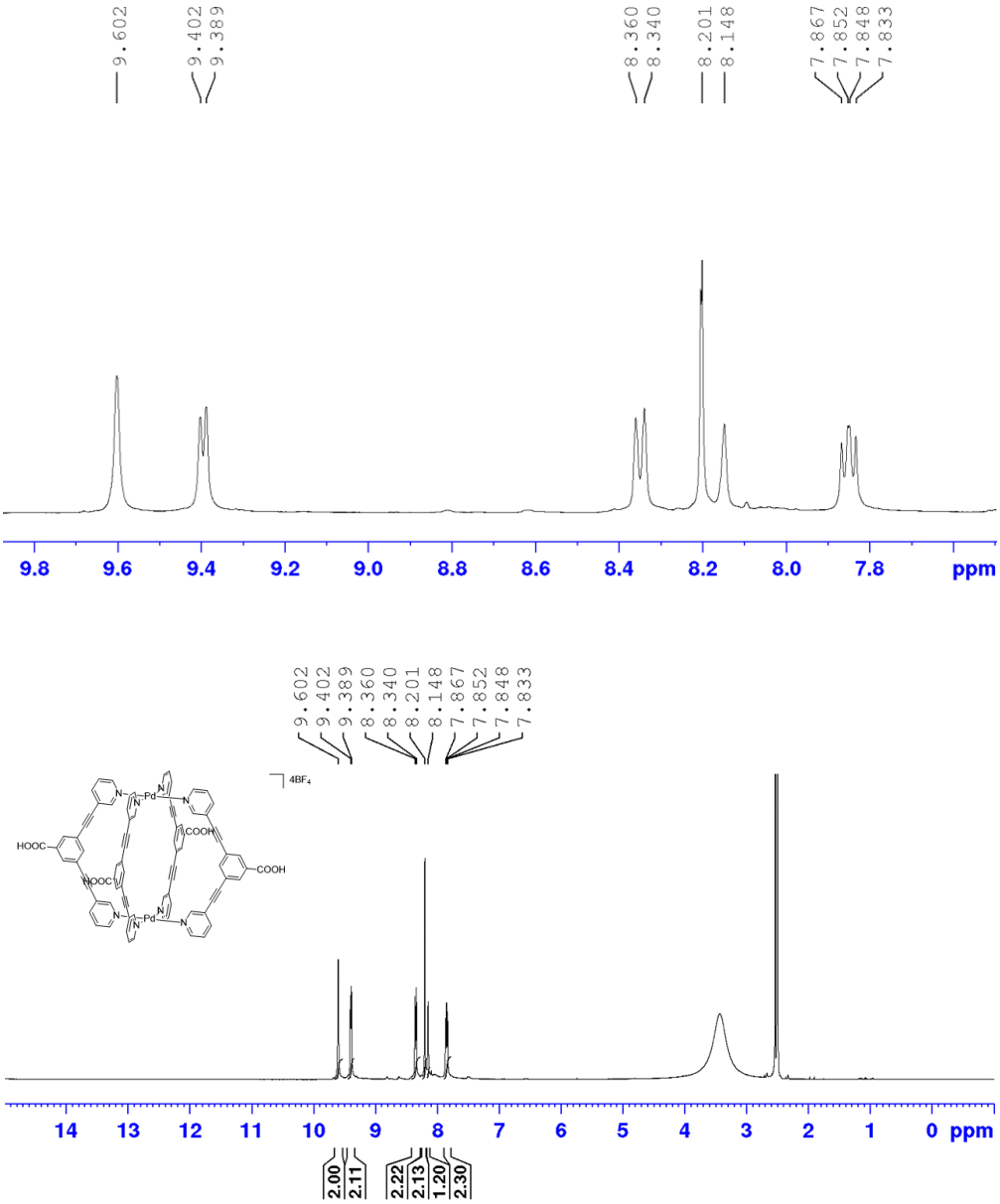


Figure S7. ^{1}H NMR (400 MHz, DMSO-d_6, 298K) of cage **C0** (bottom) and related zoom (top).

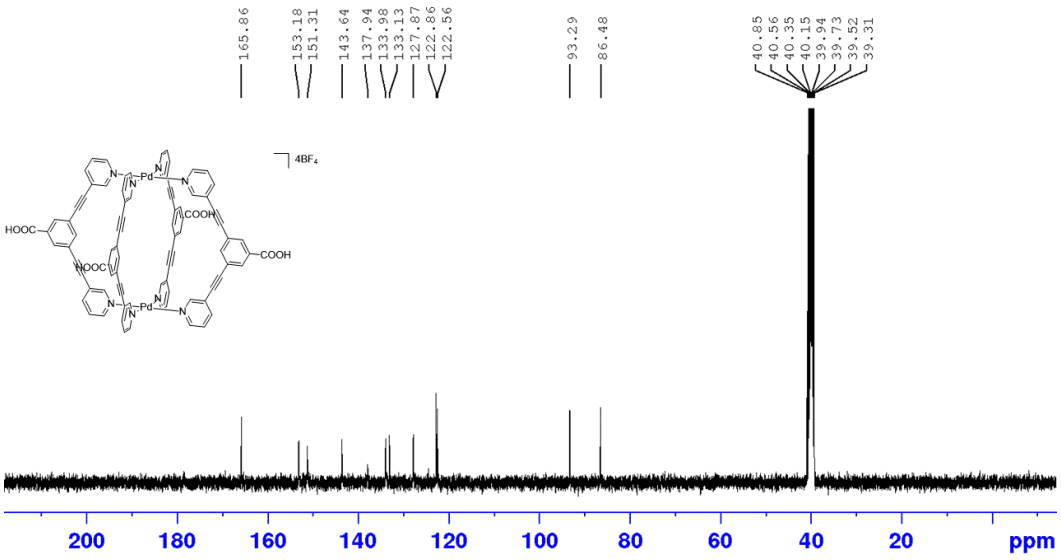


Figure S8. $^{13}C\{^{1}H\}$ NMR (400 MHz, DMSO-d_6, 298K) of cage **C0**.

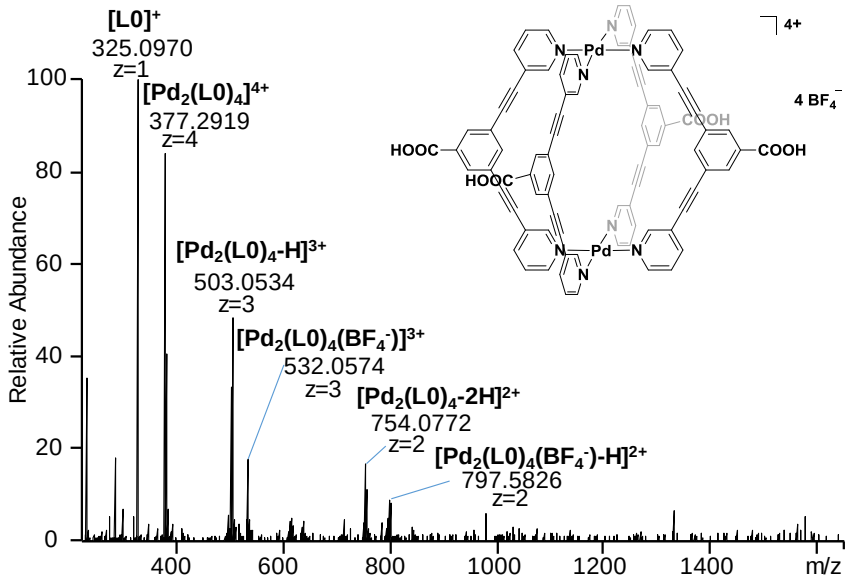


Figure S9. High-resolution MS spectrum of cage **C0** in H_2O with 0.1% Formic Acid.

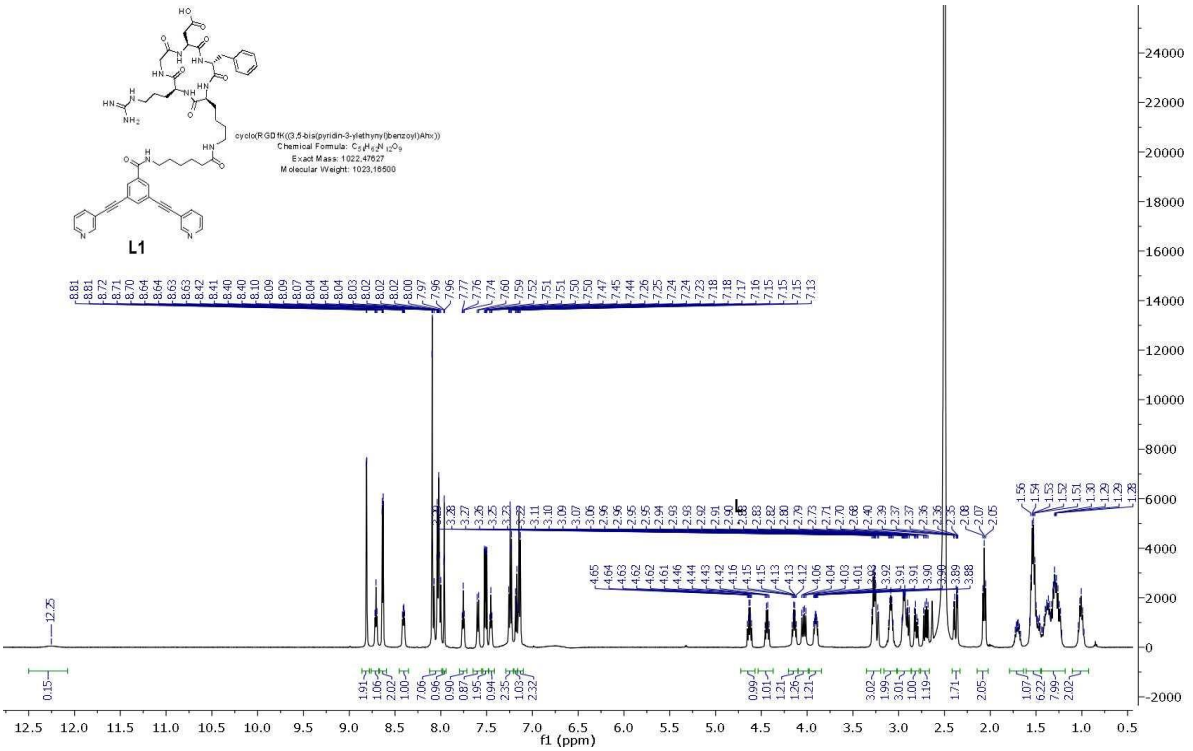


Figure S10. ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of ligand **L1**.

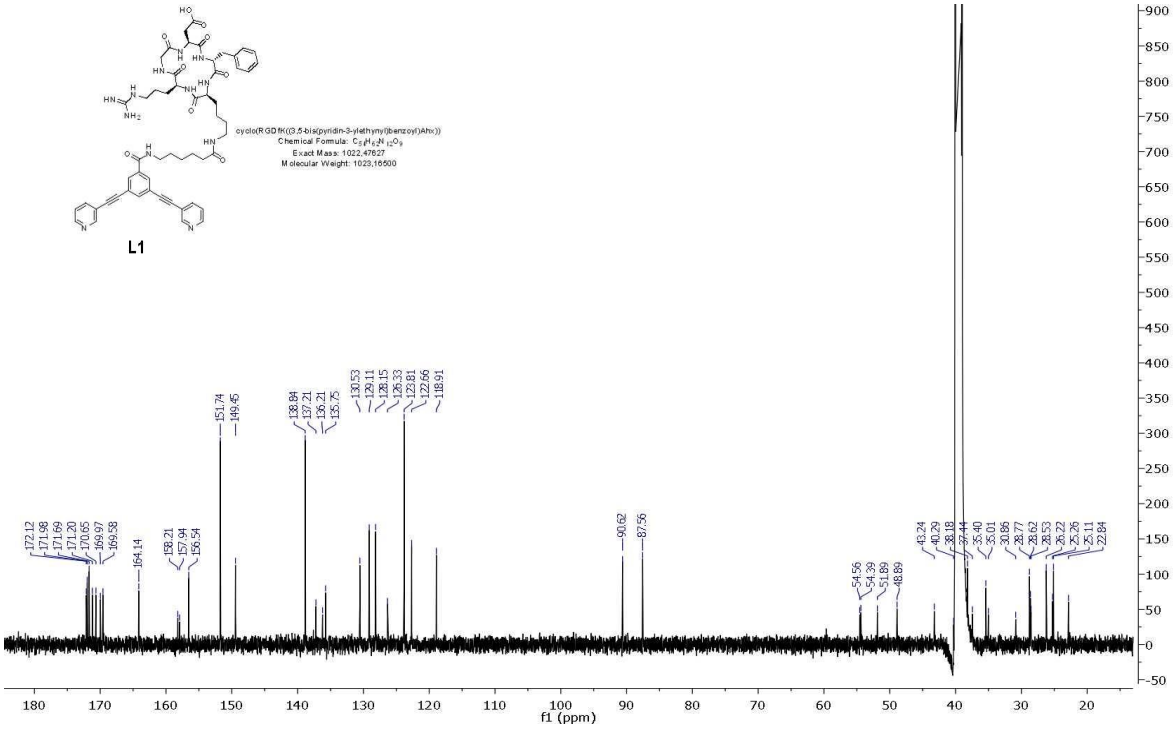


Figure S11. $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6) spectrum of ligand **L1**.

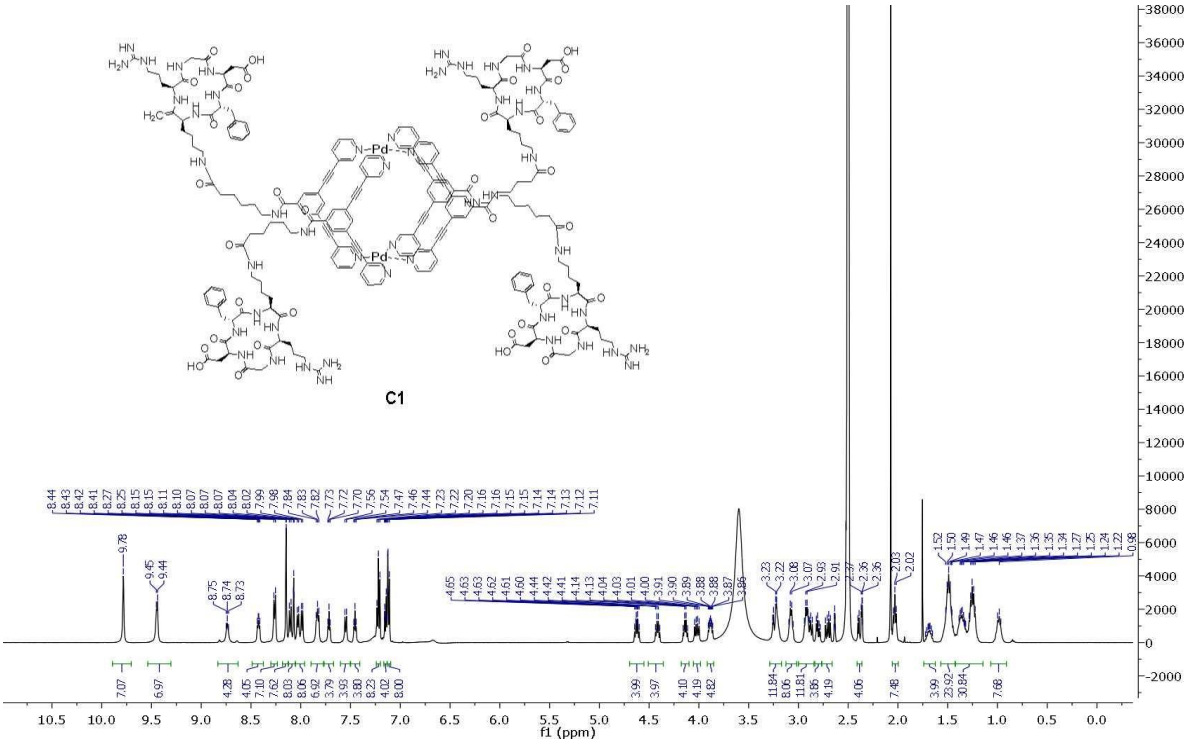


Figure S12. ^{1}H NMR (400 MHz, DMSO-d_6) spectrum of cage **C1**.

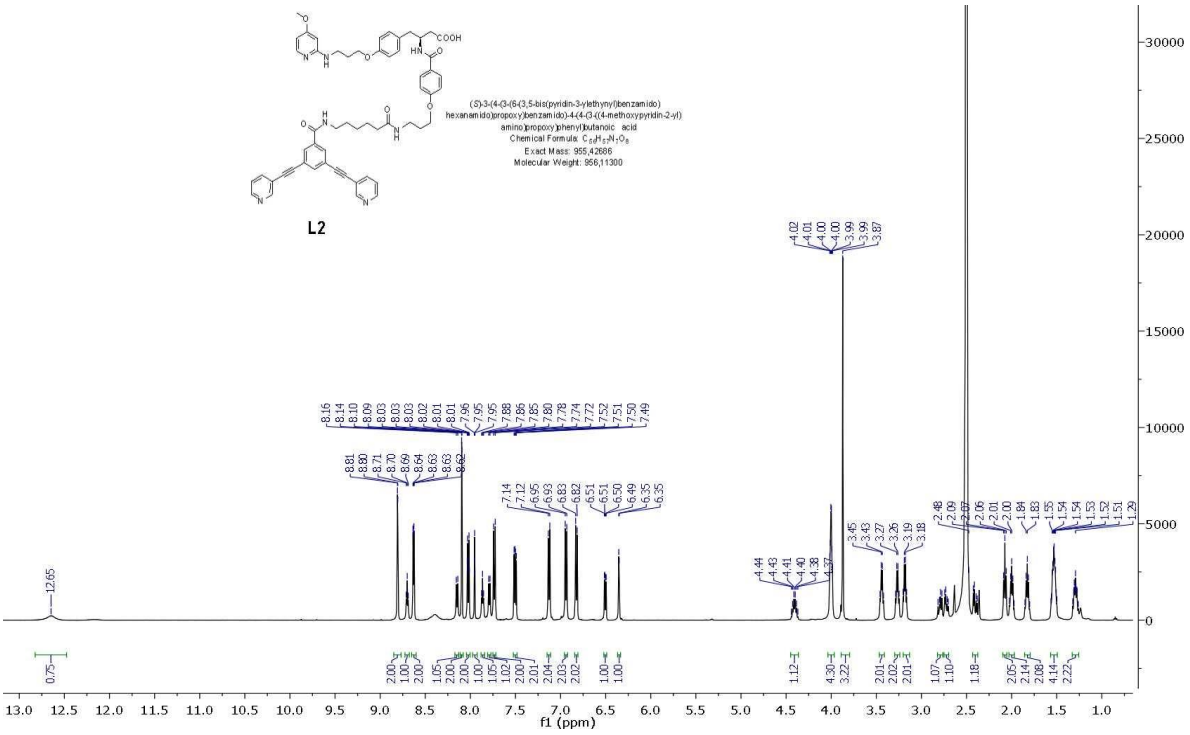


Figure S13. ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of ligand **L2**.

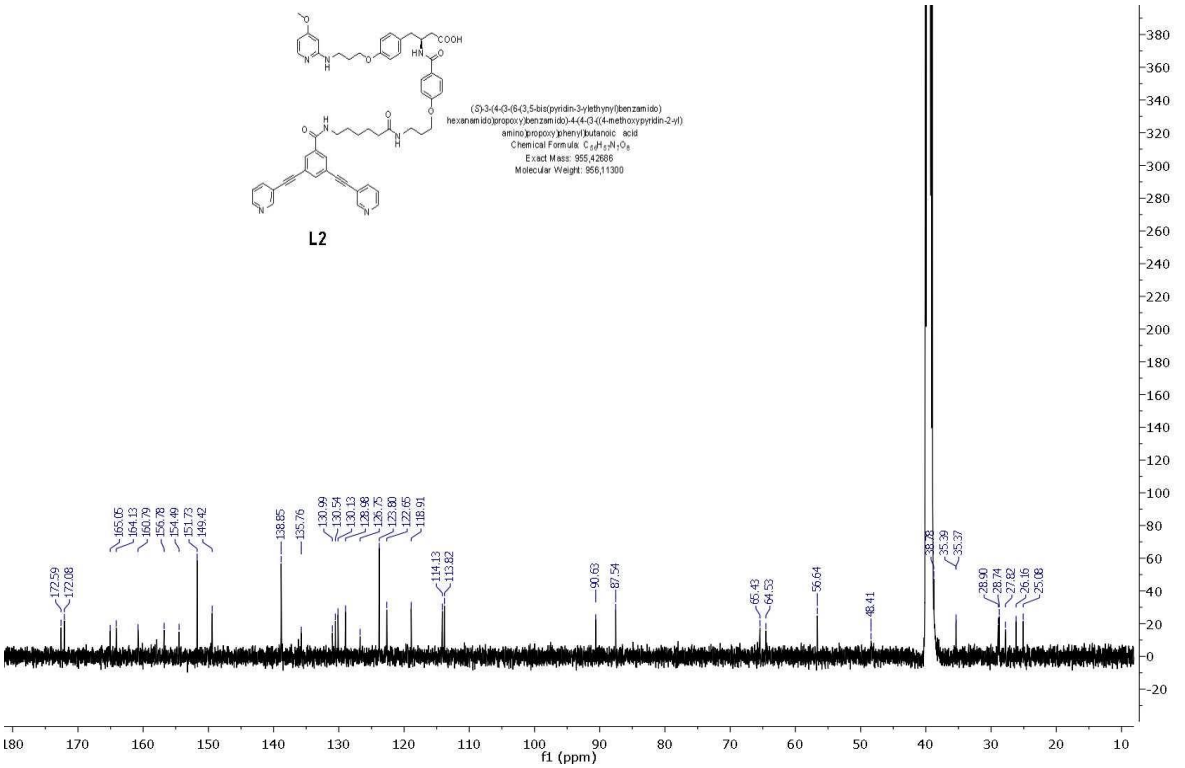


Figure S14. $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6) spectrum of ligand **L2**.

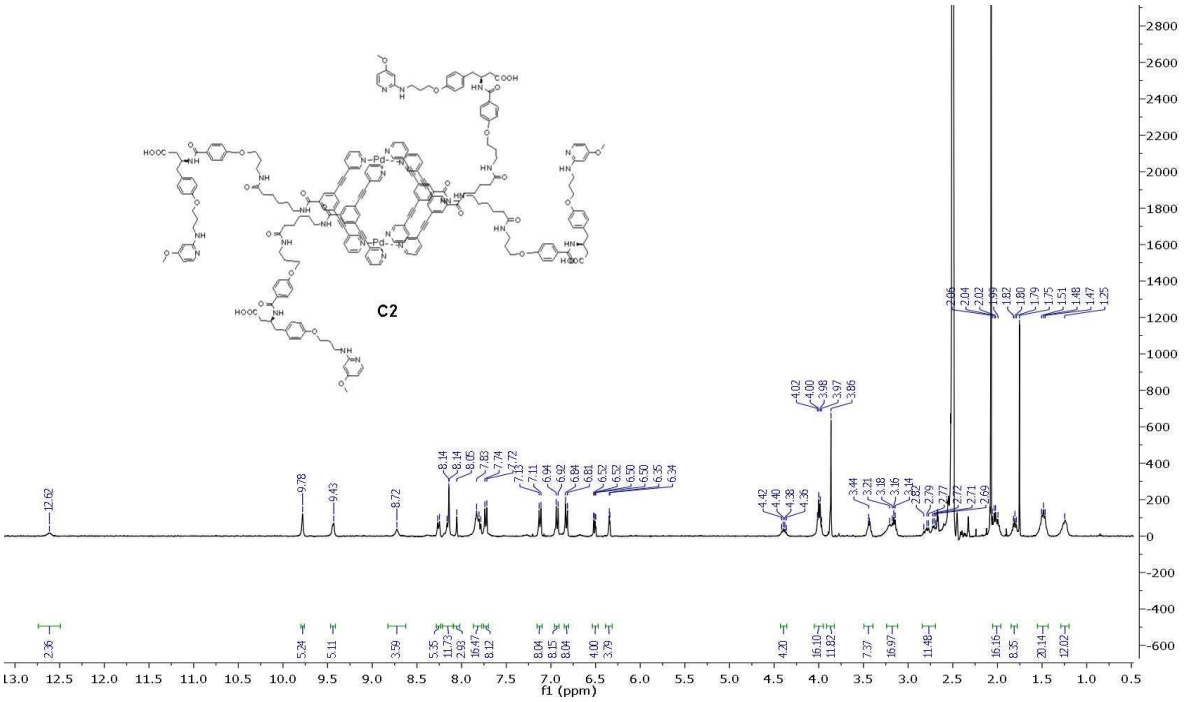


Figure S15. ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of cage **C2**.

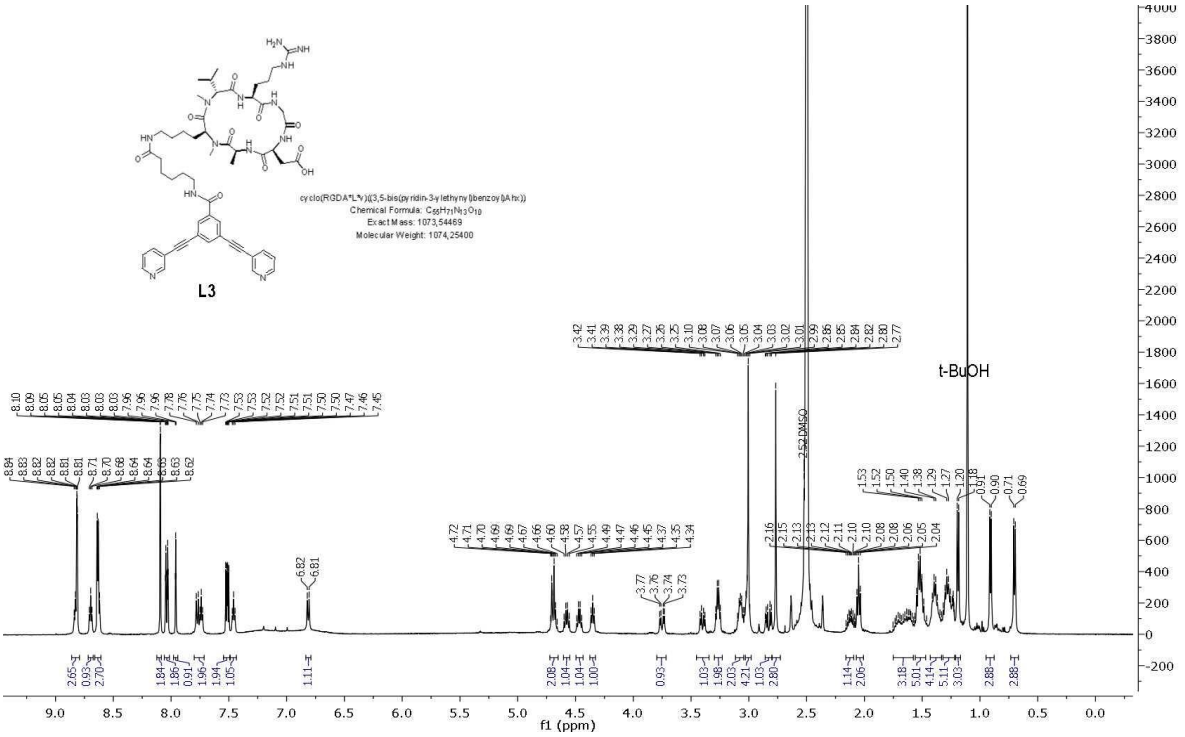


Figure S16. ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of ligand **L3**.

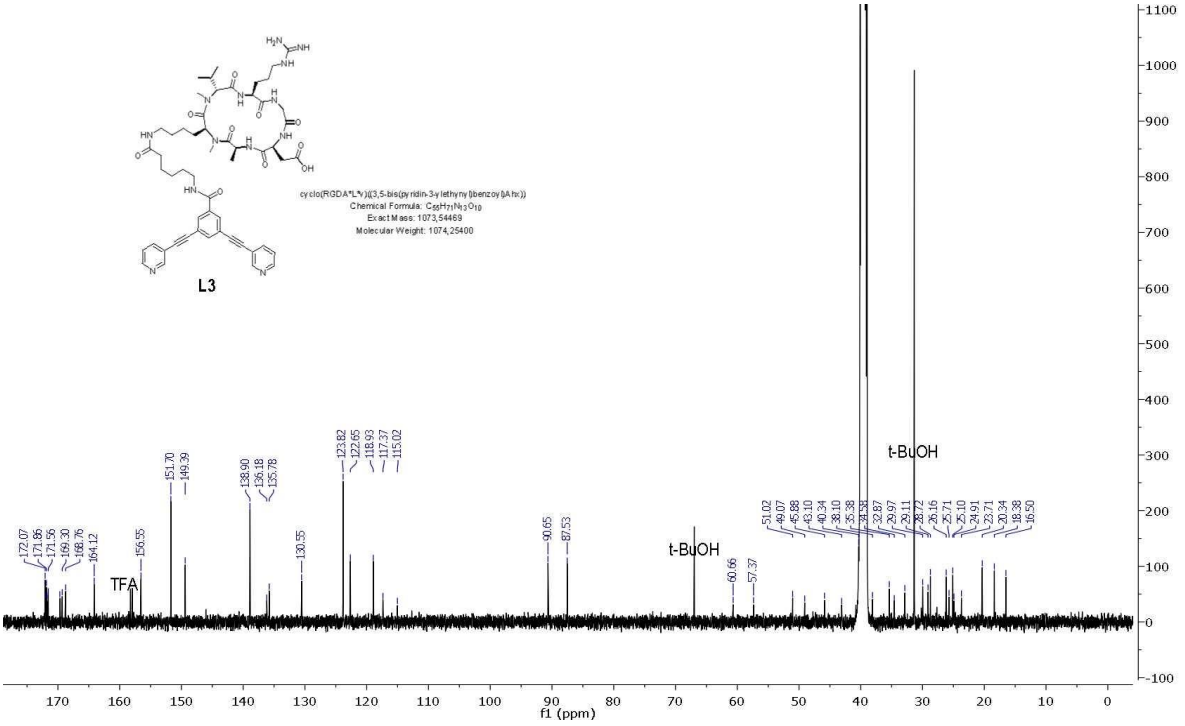


Figure S17. $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6) spectrum of ligand **L3**.

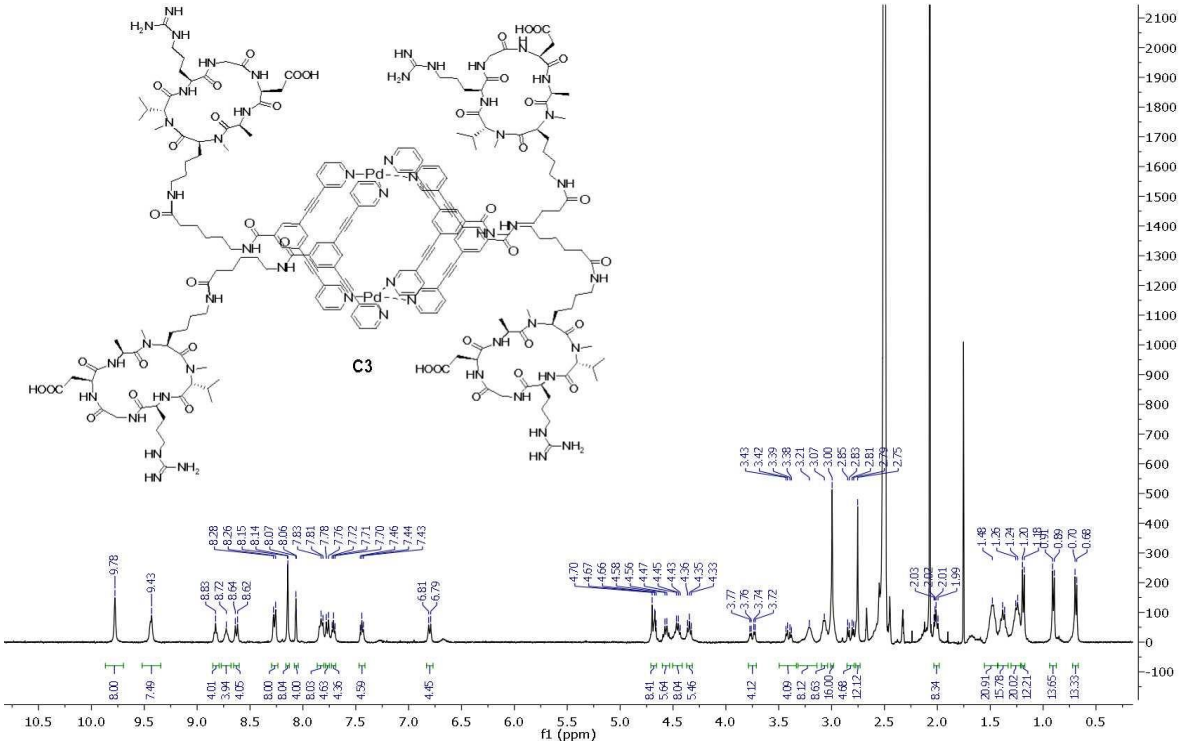


Figure S18. ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of cage **C3**.

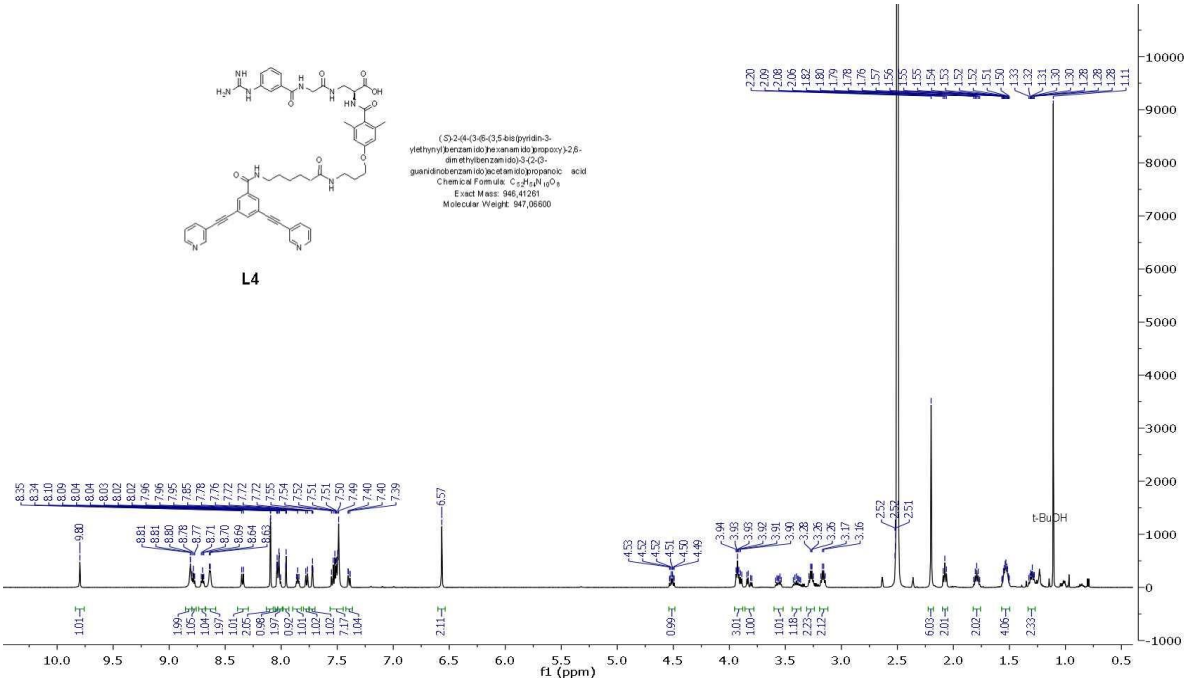


Figure S19. ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of ligand **L4**.

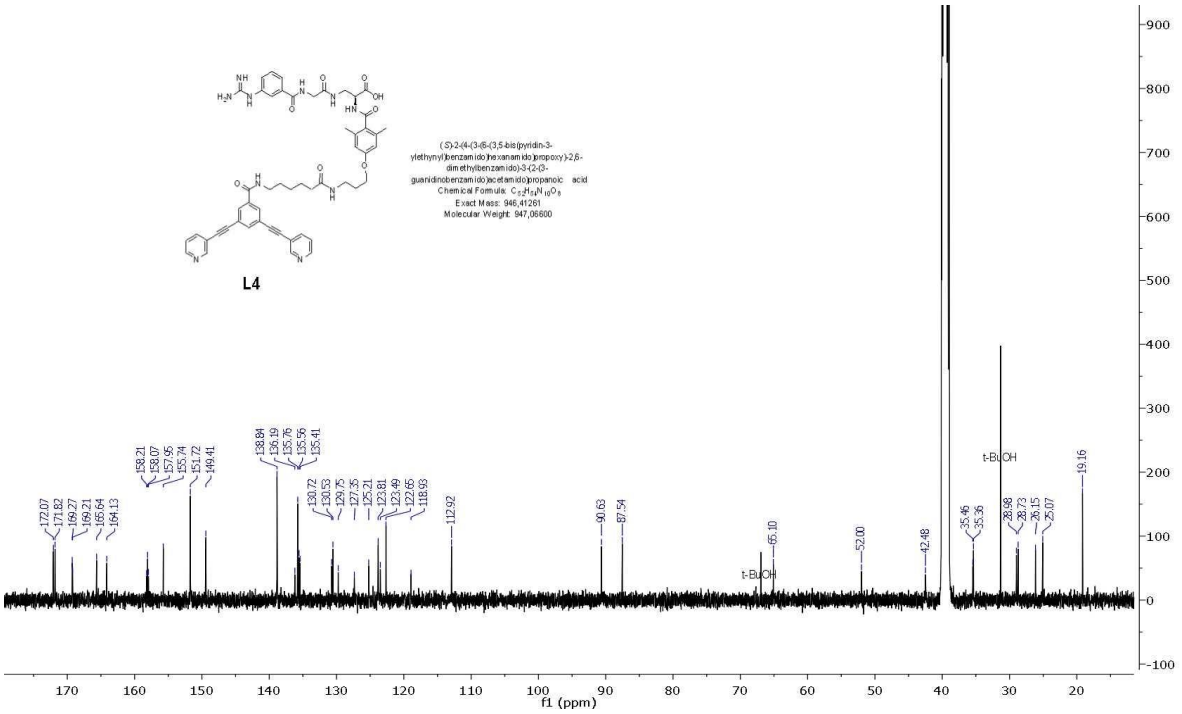


Figure S20. $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-d_6) spectrum of ligand **L4**.

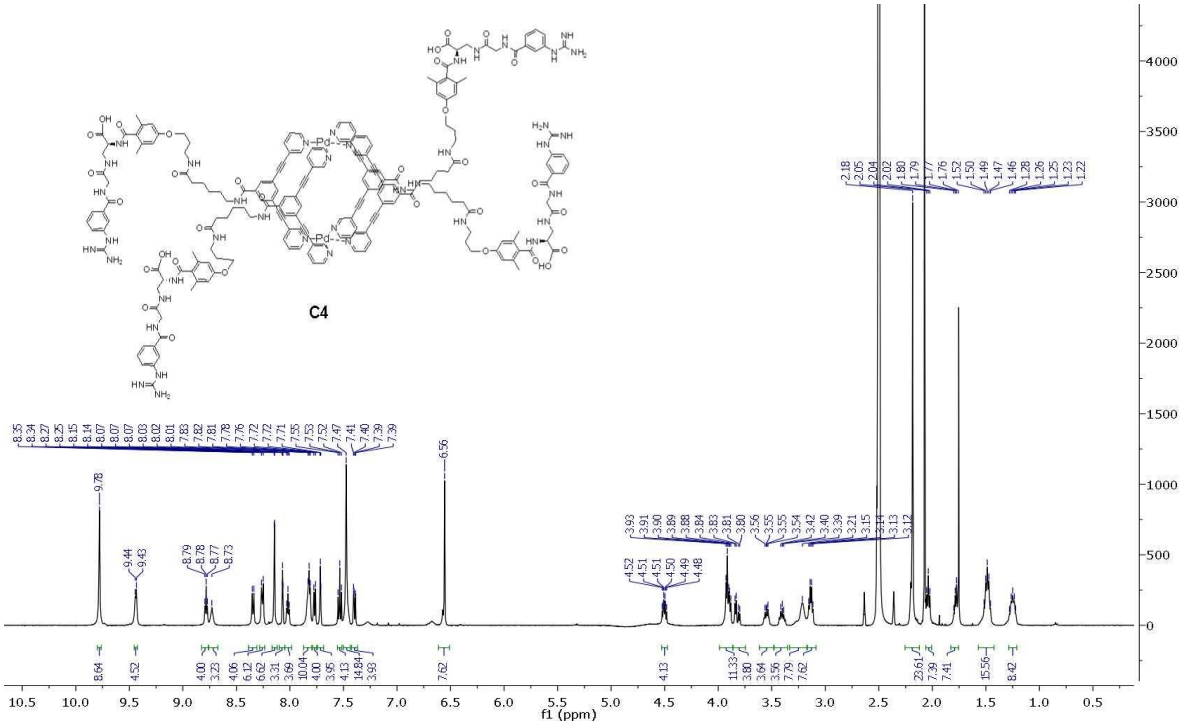


Figure S21. ^{1}H NMR (500 MHz, DMSO-d_6) spectrum of cage **C4**.

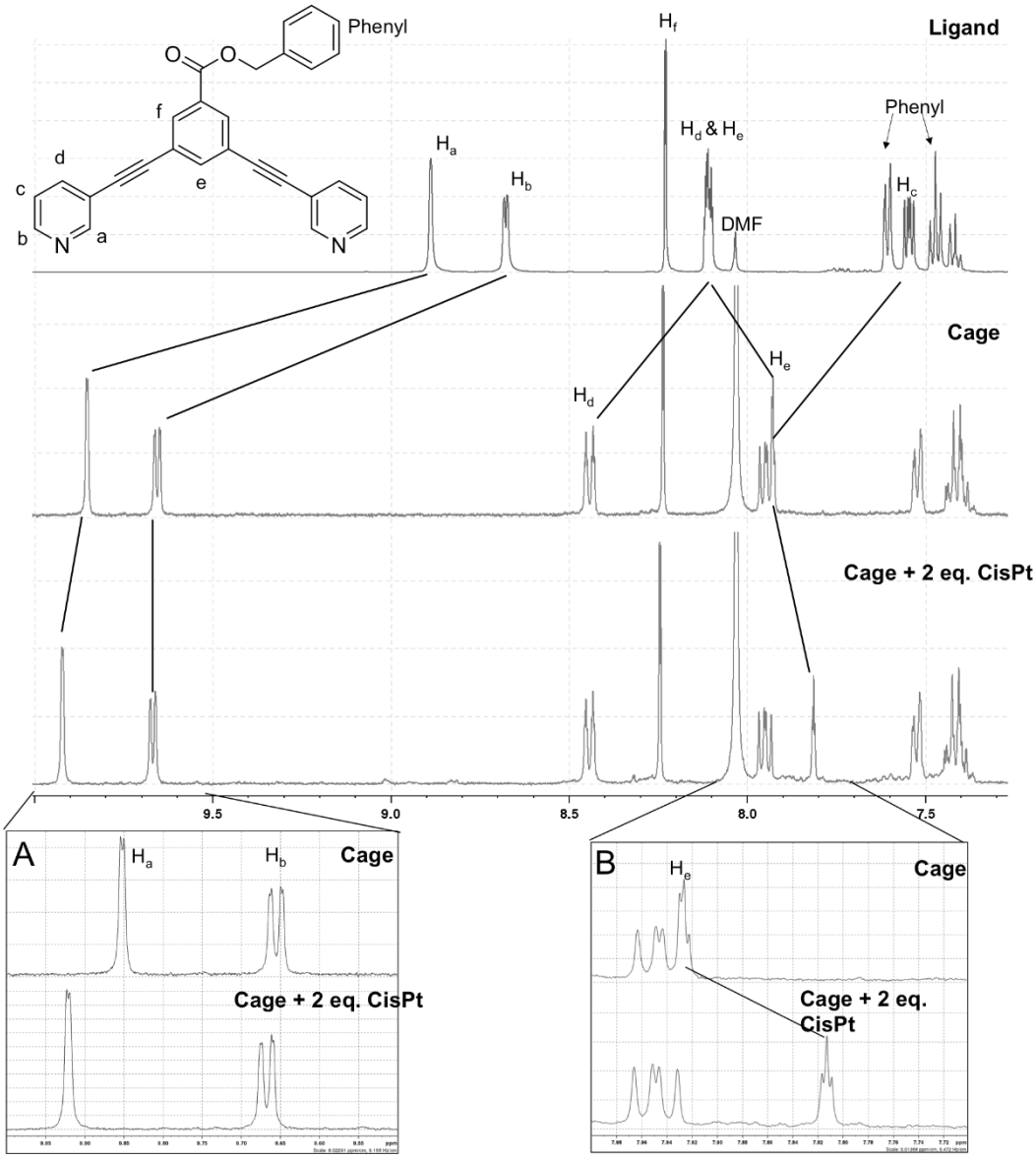


Figure S22. Stacked aromatic region ^{1}H NMR (DMF-d_7) showing: Top: Free ligand. Middle: Pd_2L_4 metallacage formation. Bottom: Pd_2L_4 metallacage encapsulating two equivalents of cisplatin. Box A: Magnified region showing the downfield shift of peaks H_a and H_b upon cisplatin encapsulation. Box B: Peak upfield shift of peak H_e.

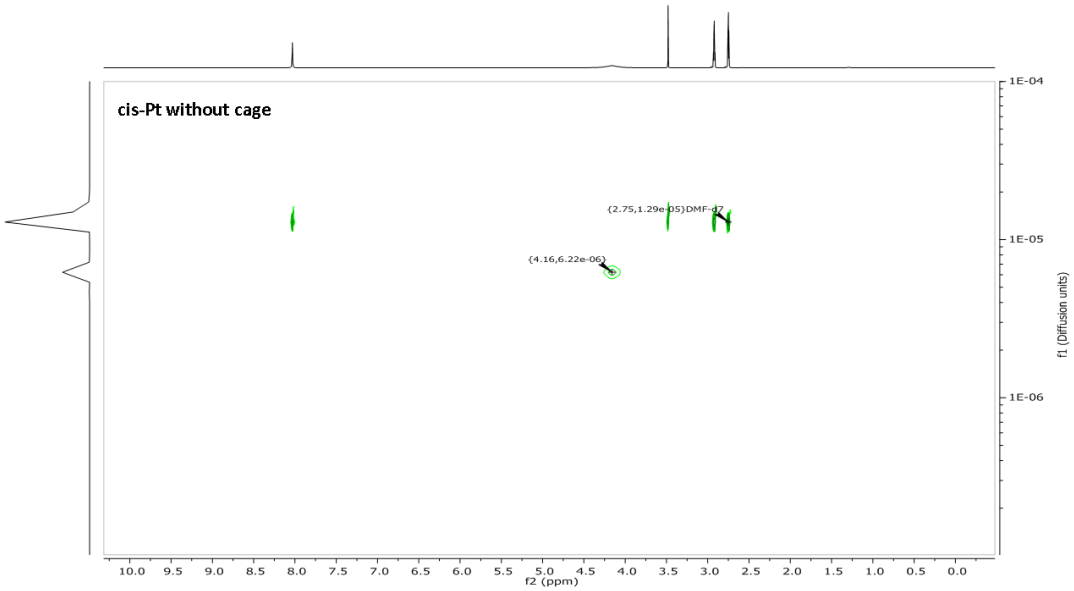


Figure S23. ^{1}H-DOSY-NMR of Cisplatin in DMF-d_7.

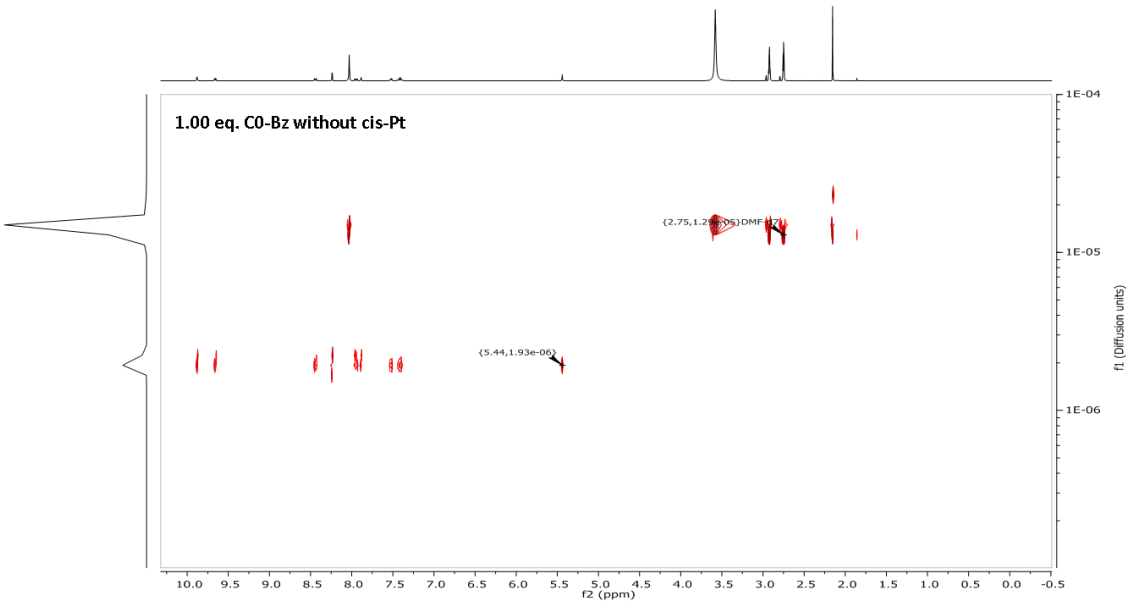


Figure S24. ^{1}H-DOSY-NMR of **C0-Bz** in DMF-d_7.

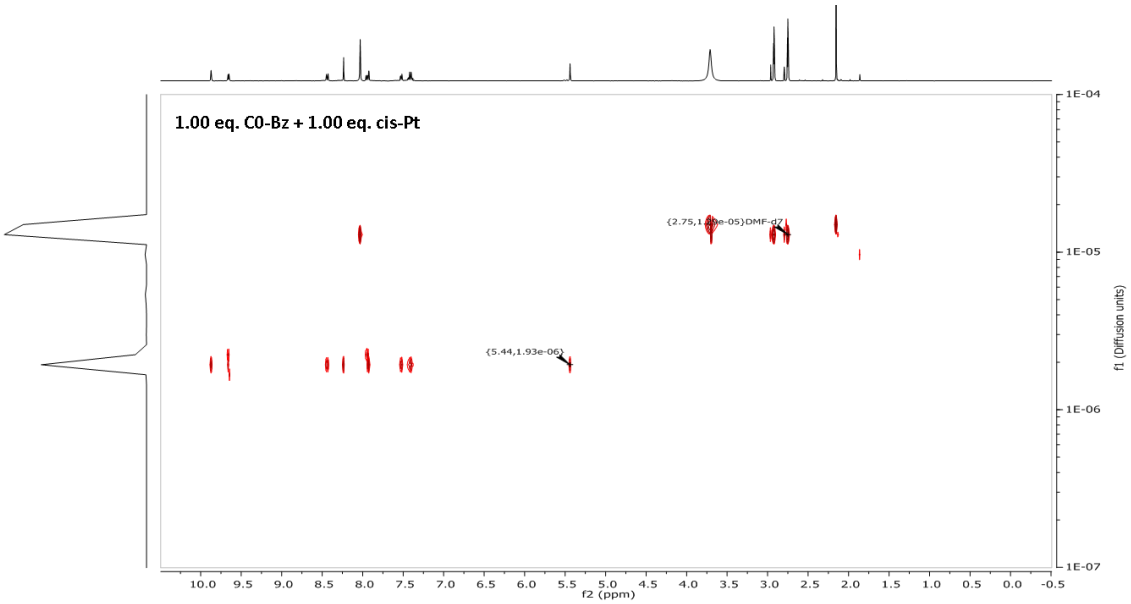


Figure S25. ^{1}H-DOSY-NMR of 1.00 eq. **C0-Bz** and 1.00 eq. Cisplatin in DMF-d_7.

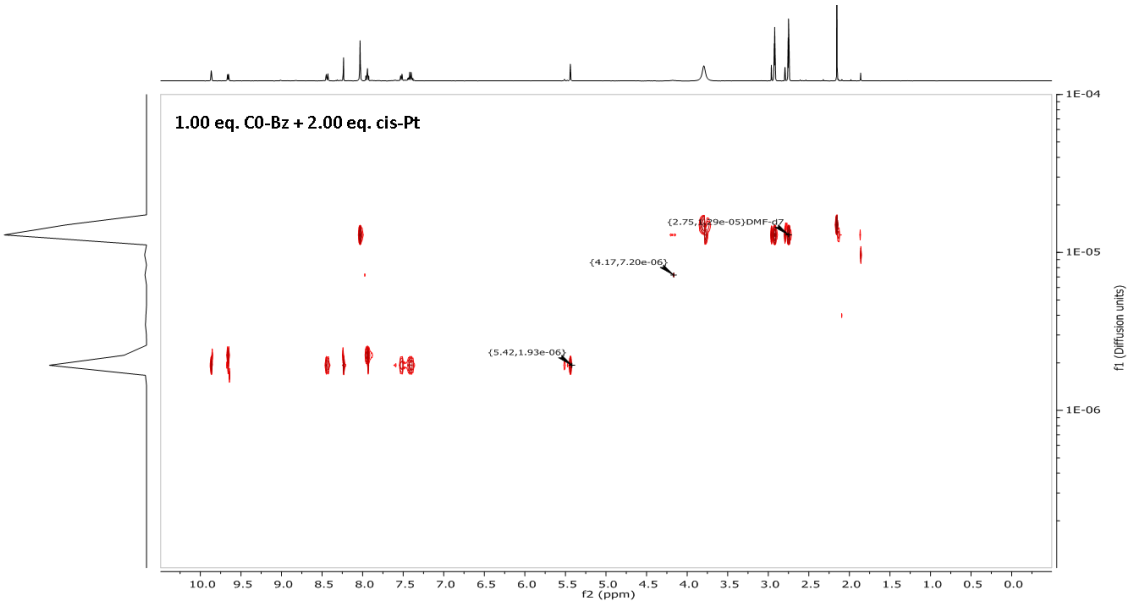


Figure S26. ^{1}H-DOSY-NMR of 1.00 eq. **C0-Bz** and 2.00 eq. cisplatin in DMF-d_7.

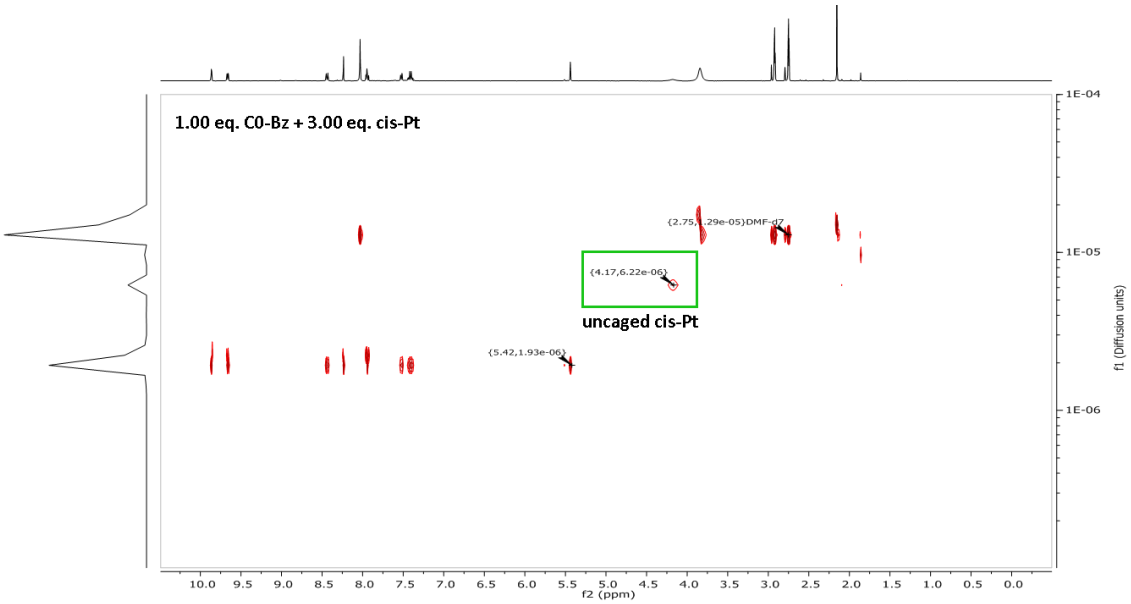


Figure S27. ^{1}H-DOSY-NMR of 1.00 eq. **C0-Bz** and 3.00 eq. cisplatin in DMF-d_7.

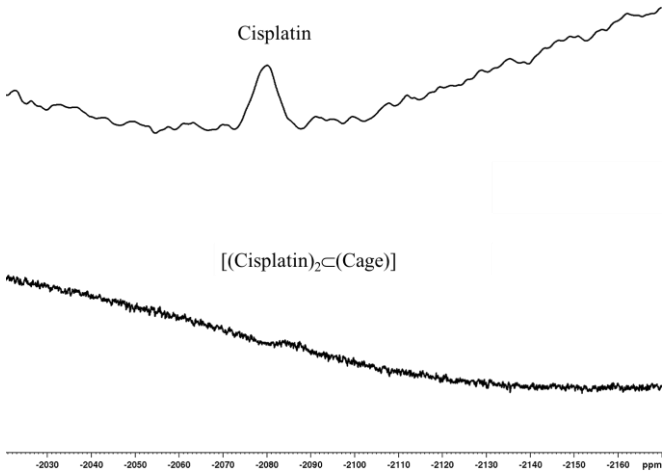


Figure S28. ^{195}NMR of (top) cisplatin and (bottom) 1.00 eq. **C0-Bz** and 2.00 eq. cisplatin in DMF-d_7.

8. References

1 H. E. Gottlieb, V. Kotlyar, A. Nudelman, *J. Org. Chem.* **1997**, *62*, 7512-7515.

2 A. Schmidt, M. Hollering, M. Drees, A. Casini, F. E. Kuhn, *Dalton Trans.* **2016**, *45*, 8556-8565.

3 M. Kantlehner, D. Finsinger, J. Meyer, P. Schaffner, A. Jonczyk, B. Diefenbach, B. Nies, H. Kessler, *Angew. Chem. Int. Ed.* **1999**, *38*, 560-562; *Angew. Chem*. **1999**, *111*, 587-590.

4 S. Neubauer, F. Rechenmacher, A. J. Beer, F. Curnis, K. Pohle, C. D'Alessandria, H.-J. Wester, U. Reuning, A. Corti, M. Schwaiger, H. Kessler, *Angew. Chem. Int. Ed.* **2013**, *52*, 11656-11659; *Angew. Chem*. **2013**, *125*, 11870-11873.

5 F. Rechenmacher, S. Neubauer, J. Polleux, C. Mas-Moruno, M. De Simone, E. A. Cavalcanti-Adam, J. P. Spatz, R. Fässler, H. Kessler, *Angew. Chem. Int. Ed.* **2013**, *52*, 1572-1575; *Angew. Chem*. **2013**, *125*, 1612-1616.

6 A. G. Riches, T. Cablewski, V. Glattauer, H. Thissen, L. Meagher, *Tetrahedron* **2012**, *68*, 9448-9455.