Supporting Information

Hydrazone- and Imine-Containing $[PdPtL_4]^{4+}$ Cages: a Comparative Study of the Stability and Host-Guest Chemistry

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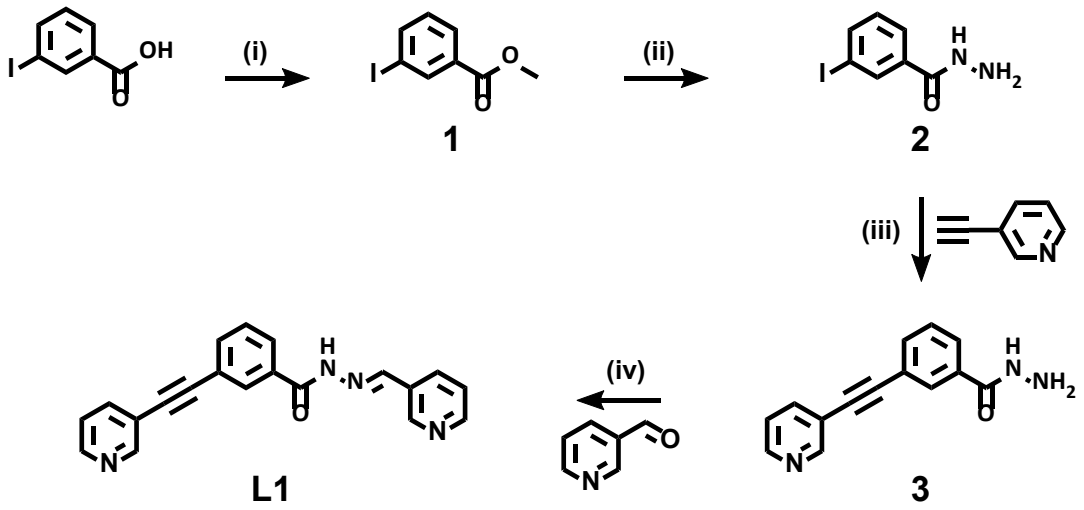
1 Experimental Procedures

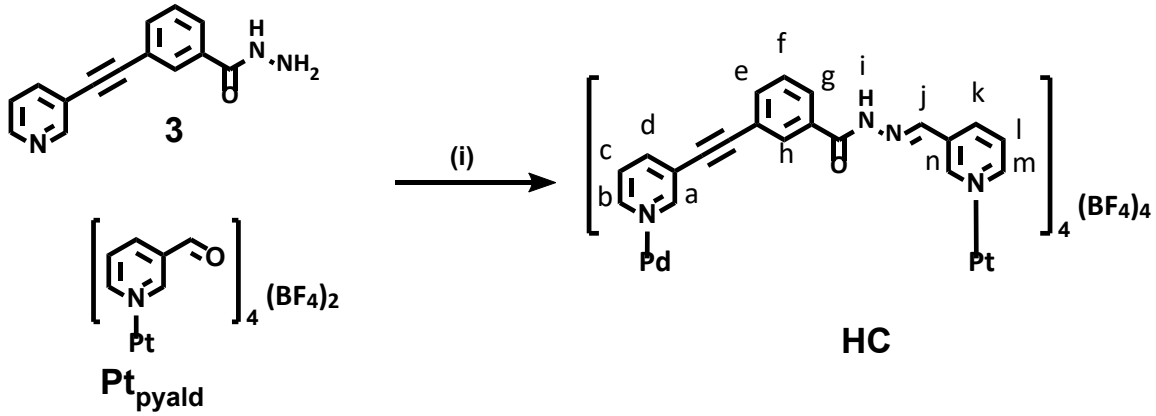
1.1 General

All reagents were purchased from commercial sources and used without further purification. $[Pd(DMAP_4)_2](BF_4)_2$,[1] 1-methyl-3-iodobenzoate,[2] $[Pt(3\text{-pyridylcarboxyaldehyde})_4](BF_4)_2$ ($\mathbf{Pt_{pyald}}$),[3] **4**,[3] and the imine-based Pd(II)/Pt(II) cage (**IC**)[3] were synthesized using previously established methods. The solvents used were of laboratory reagent grade unless specified otherwise. Petroleum ether refers to the fraction of petrol boiling in the range of 40–60 °C. Abbreviations for solvents and reagents include acetonitrile (CH_3CN), dichloromethane (DCM), dimethylformamide (DMF), dimethylsulfoxide (DMSO), ethylenediaminetetraacetate (EDTA), methanol (MeOH), ethanol (EtOH), tetrahydrofuran (THF), and triethylamine (TEA). A 0.1 M ammonium hydroxide/ethylenediaminetetraacetic acid (NH_4OH/EDTA) solution was made by mixing 30 g EDTA in 900 mL water and 100 mL NH_4OH. ^1H and $^{13}C\{^1H\}$ NMR spectra were collected using either 400 MHz Varian/Agilent 400-MR or Varian 500 MHz AR spectrometers. Chemical shifts (δ) are reported in parts per million (ppm) and referenced to residual solvent peaks ($CDCl_3$: ^1H δ, 7.26 ppm, ^{13}C δ, 77.16 ppm; CD_3CN: ^1H δ, 1.94 ppm, ^{13}C δ, 1.32 & 118.26 ppm; d_6-DMSO: ^1H δ, 2.50 ppm, ^{13}C δ, 39.52 ppm). Coupling constants (*J*) are reported in Hertz (Hz). Standard abbreviations indicating multiplicities were used as follows: m = multiplet, t = triplet, tt = triplet of triplets, d = doublet, dd = doublet of doublets, and s = singlet. ^1H DOSY NMR spectra were obtained using a Bruker Advance 400 MHz NMR spectrometer and processed on MestReNova 14.2.2 using the peak fit method. ESI-mass spectra (ESIMS) were collected using either a Bruker microTOF-Q spectrometer or a Shimadzu LCMS-9030 spectrometer. ESIMS data of metal complexes were obtained using either pseudo coldspray or coldspray conditions (nebulizer and heating gasses cooled to room temperature or -10 °C, respectively). Microanalyses were conducted at the Campbell Microanalytical Laboratory at the University of Otago.

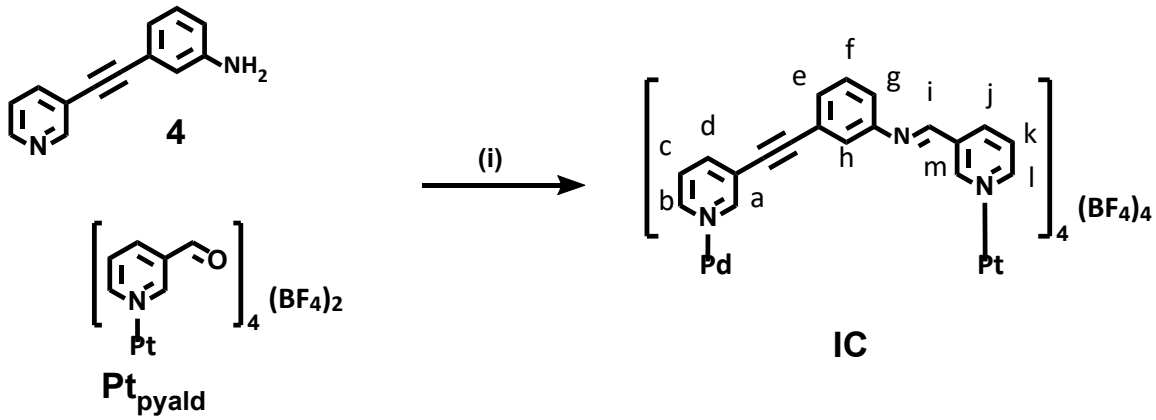
1.2 Synthetic Schemes



Scheme S1 Synthesis of **L1** (i) H_2SO_4, MeOH, 65 °C, 20 h, (ii) hydrazine monohydrate, EtOH, reflux, 20 h, (iii) CuI, $[Pd(PPh_3)_2Cl_2]$, TEA, THF, 65 °C, 14 h, (iv) EtOH, RT, 14 h.



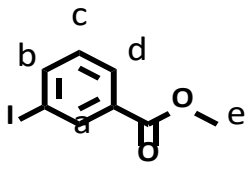
Scheme S2 Synthesis of **HC** (i) $[Pd(CH_3CN)_4](BF_4)_2$, DMSO, RT, 14 h.



Scheme S3 Synthesis of **IC** (i) $[Pd(CH_3CN)_4](BF_4)_2$, DMSO, RT, 1 h.[3]

1.3 Experimental

1.3.1 Synthesis of 1[2]



3-Iodobenzoic acid (0.946 g, 3.82 mmol) and H_2SO_4 (0.212 mL, 3.82 mmol) were dissolved in MeOH (20 mL, 0.494 mol) and refluxed for 20 h. MeOH was removed under vacuum and the crude material was dissolved in sat. $NaHCO_{3(aq)}$ (100 mL). The product was extracted with DCM (3 × 20 mL) and the combined organic extracts were washed with water (20 mL) and brine (20 mL) and dried over Na_2SO_4. The solvent was removed under vacuum to give a colourless solid (Yield: 0.91 g, 91%). ^{1}H NMR (400 MHz, CD_3CN) δ 8.34 (t, *J* = 1.7 Hz, 1H, H_a), 7.99 (tt, *J* = 7.9, 1.4 Hz, 2H, $H_{b,d}$), 7.28 (t, *J* = 7.8 Hz, 1H, H_c), 3.88 (s, 2H, H_e).

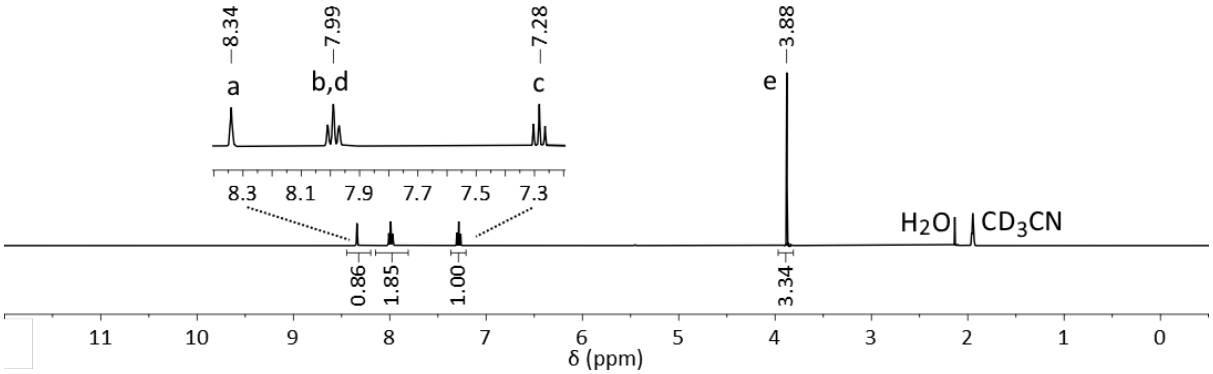
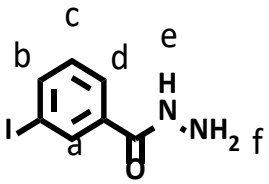


Figure S1 ^{1}H NMR spectrum (400 MHz, CD_3CN, 298 K) of **1**.

1.3.2 Synthesis of 2[2]



1 (0.500 g, 1.91 mmol) and hydrazine monohydrate (2.00 mL, 41.2 mmol) were dissolved in EtOH and refluxed for 20 h. EtOH was removed under vacuum and the crude material was dissolved in DCM (10 mL). Water (25 mL) was added and the product was extracted with DCM (3 × 15 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum to give a colourless solid (Yield: 0.390 g, 85%). ^{1}H NMR (400 MHz, 298 K, d_6-DMSO) δ 9.85 (s, 1H, H_e), 8.15 (t, J = 1.7 Hz, 1H, H_a), 7.93 – 7.71 (m, 2H, $H_{b,d}$), 7.26 (t, J = 7.8 Hz, 1H, H_c), 4.52 (s, 2H, H_f). ^{13}C NMR (100 MHz, 298 K, d_6-DMSO) δ = 163.8, 140.5, 135.5, 135.3, 131.5, 126.3, 93.5. ESIMS: (MeOH) m/z = 262.9655 [**M** + H]$^+$ (calc. for $C_7H_8IN_2O$, 262.9676), 284.9474 [**M** + Na]$^+$ (calc. for $C_7H_7IN_2ONa$, 284.9495).

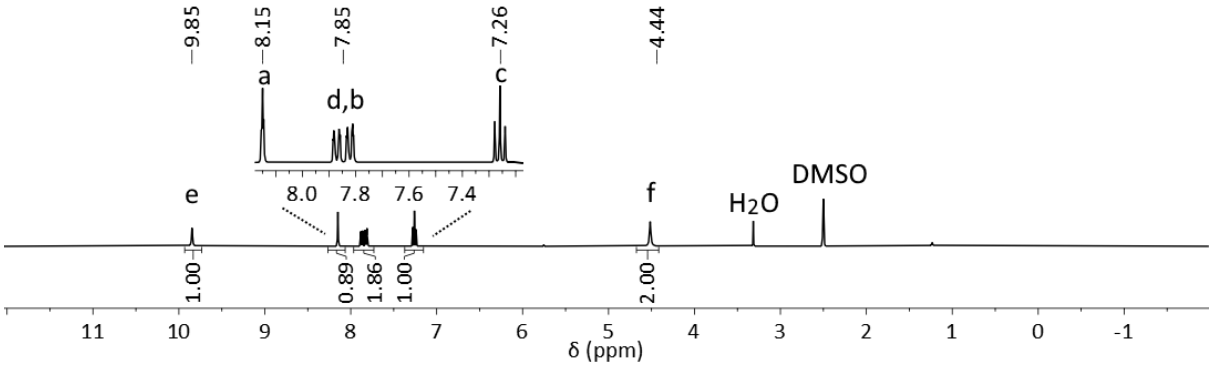


Figure S2 ^{1}H NMR spectrum (400 MHz, d_6-DMSO, 298 K) of **2**.

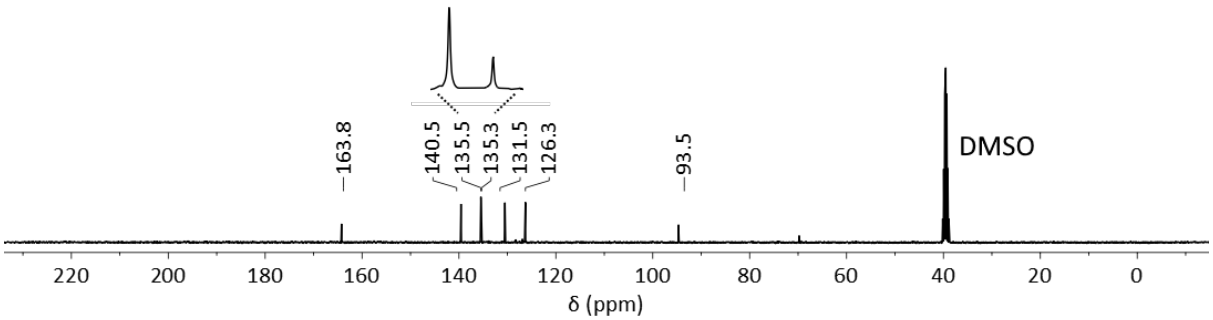
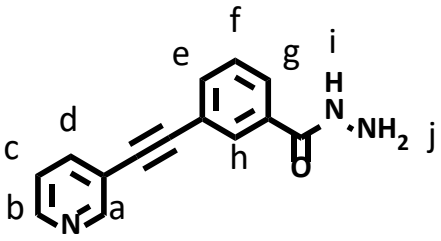


Figure S3 ^{13}C{^{1}H} NMR spectrum (100 MHz, 298 K, d_6-DMSO) of **2**.

1.3.3 Synthesis of 3



3-Ethynylpyridine (0.213 g, 2.06 mmol) and **2** (0.450 g, 1.72 mmol) were added to a degassed solution of TEA:THF (1:1 v/v, 4 mL) in a sealed tube under $Ar_{(g)}$. Copper(I) iodide (0.030 g, 0.017 mmol) and dichloridobis(triphenylphosphine)palladium(II) (0.036 g, 0.052 mmol) were added and the solution was heated at 65 ℃ for 14 h. The solvents were removed under vacuum. The reaction mixture was dissolved in DCM (100 mL) and washed with EDTA/NH_4OH (0.10 M, 200 mL), water (200 mL) and brine (200 mL) and dried over Na_2SO_4. The solvent was removed under vacuum to give the crude product as a brown oil. The crude oil was purified by column chromatography (deactivated silica (1:19 TEA:DCM), 1:0 – 0:1 DCM/CH_3CN) yielding an off-white solid (Yield: 0.191 g, 47%). ^{1}H NMR (400 MHz, 298 K, *d*$_6$-DMSO) δ 9.90 (s, 1H, H_i), 8.79 (s, 1H, H_a), 8.59 (s, 1H, H_b), 8.05 – 7.97 (m, 2H, $H_{c,h}$), 7.87 (d, *J* = 7.1 Hz, 1H, H_g), 7.72 (d, *J* = 7.1 Hz, 1H, H_e), 7.59 – 7.43 (m, 2H, $H_{f,d}$), 4.57 (s, 2H, H_j). ^{13}C NMR (100 MHz, 298 K, *d*$_6$-DMSO) δ 164.8, 151.7, 149.2, 148.8, 138.6, 133.8, 130.0, 129.0, 127.7, 123.7, 121.8, 119.2, 91.6, 86.7. Anal. Calc. for $C_{14}H_{11}N_3O$ C, 69.81; H, 4.77; N, 17.45%. Found C, 70.05; H, 5.11; N, 17.10%. ESIMS: (MeOH) *m/z* = 238.0968 [**M** + H]$^+$ (calc. for $C_{14}H_{12}N_3O$, 238.0975), 260.0788 [**M** + Na]$^+$ (calc. for $C_{14}H_{11}N_3ONa$, 260.0784).

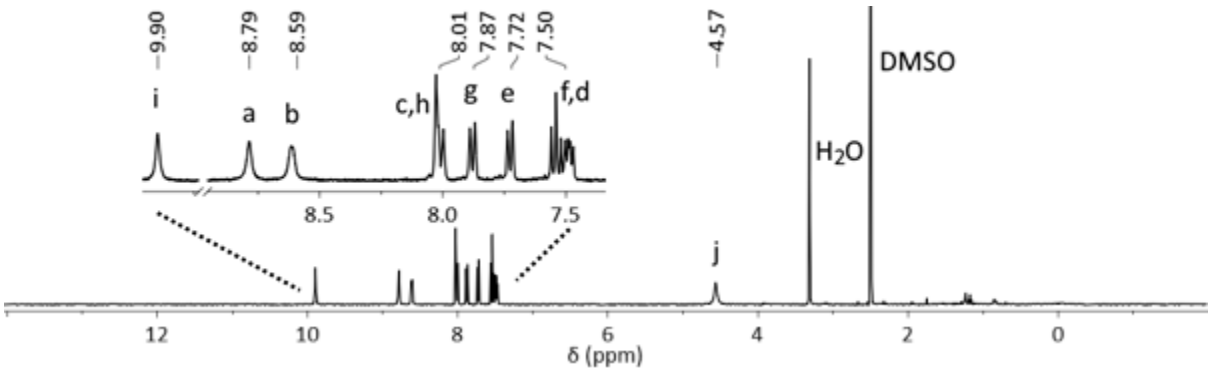


Figure S4 ^{1}H NMR spectrum (400 MHz, *d*$_6$-DMSO, 298 K) of **3**.

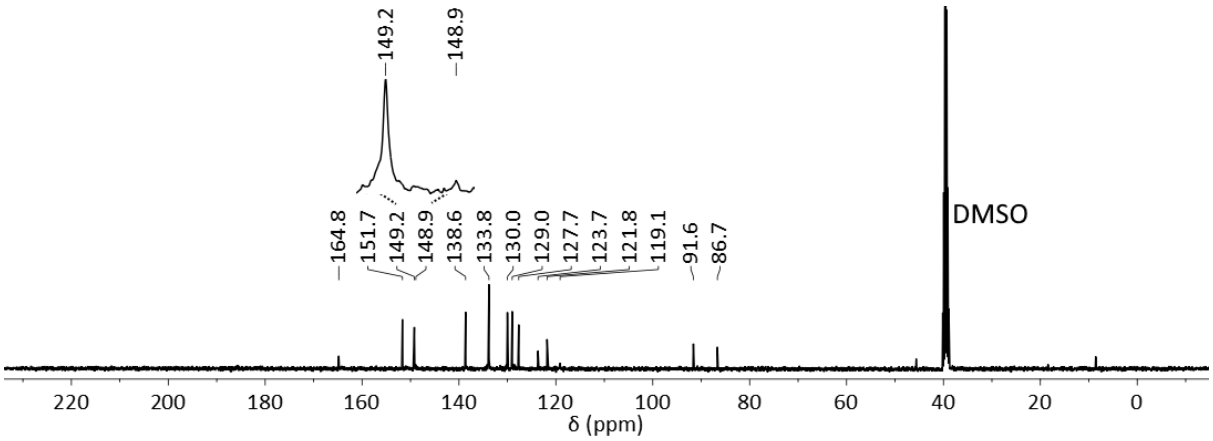
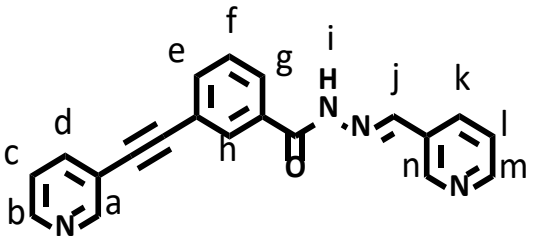


Figure S5 $^{13}C\{^{1}H\}$ NMR spectrum (100 MHz, 298 K, d_6-DMSO) of **3**.

1.3.4 Synthesis of L1



3 (0.050 g, 0.21 mmol) and 3-pyridylcarboxaldehyde (0.034 g, 0.32 mmol) were added to EtOH (5 mL) and stirred at RT for 14 h. The solvent was removed under vacuum and the crude material was dissolved in DCM and centrifuged. The supernatant was collected and dried under vacuum to give the pure product as a colourless solid (Yield: 0.046 g, 66%). ^{1}H NMR (500 MHz, 298 K, d_6-DMSO) δ 12.14 (s, 1H, H_i), 8.84 (s, 1H, H_n), 8.80 (s, 1H, H_a), 8.68 (m, 2H, $H_{b,m}$), 8.52 (s, 1H, H_j), 8.15 (m, 2H, $H_{h,k}$), 8.00 (m, 2H, $H_{d,g}$), 7.80 (d, J = 7.7 Hz, 1H, H_e), 7.64 (t, J = 7.8 Hz, 1H, H_f), 7.49 (m, 2H, $H_{c,l}$). ^{13}C NMR (125 MHz, 298 K, d_6-DMSO) δ 162.2, 151.7, 151.6, 149.3, 148.7, 145.4, 138.7, 134.6, 133.8, 133.2, 130.4, 130.2, 129.3, 128.6, 124.1, 123.7, 121.1, 119.1, 91.8, 86.9. Anal. calc. for $C_{20}H_{14}N_4O{\cdot}0.2H_2O$ C 72.80, H 4.40, N 16.98%. Found C 72.48, H 4.43, N 17.21%. ESIMS (CH_3CN) *m/z* = 327.1223 [**M**+ H]$^+$ (calc. for $C_{20}H_{15}N_4O$, 327.1240), 349.1042 [**M** + Na]$^+$: (calc. for $C_{20}H_{14}N_4ONa$, 349.1060).

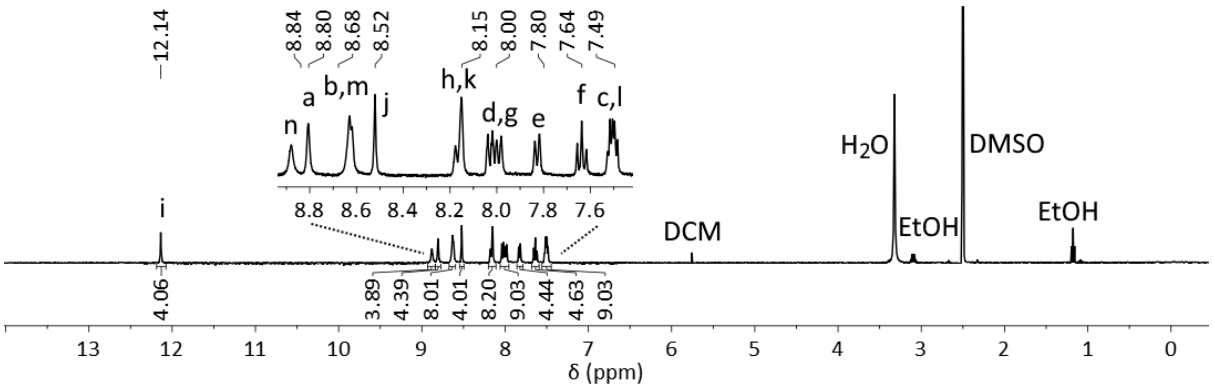


Figure S6 ^{1}H NMR spectrum (400 MHz, d_6-DMSO, 298 K) of **L1**.

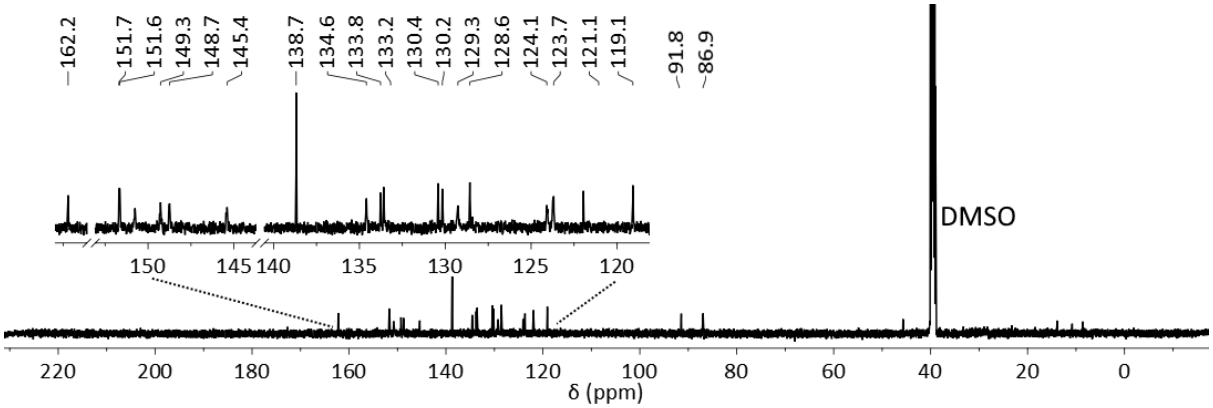
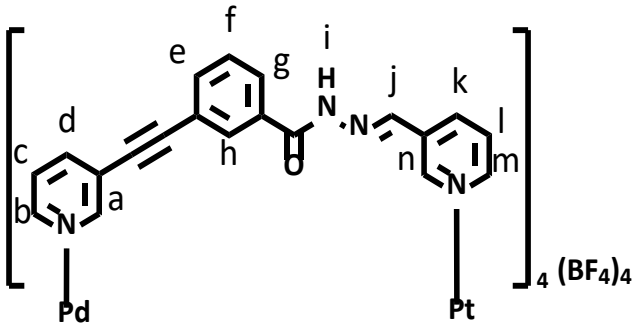


Figure S7 $^{13}C\{^{1}H\}$ NMR spectrum (125 MHz, 298 K, d_6-DMSO) of **L1**.

1.3.5 Synthesis of HC



3 (0.051 g, 0.215 mmol), $\mathbf{Pt_{pyald}}$ (0.043 g, 0.054 mmol), and $[Pd(CH_3CN)_4](BF_4)_2$ (0.024 g, 0.054 mmol) were combined in DMSO (1.5 mL) and stirred at RT for 14 h. The product was precipitated using ethyl acetate (15 mL) and washed with DCM (4 mL) and collected as an off-white solid (0.090 g, 99%). ^{1}H NMR (400 MHz, 298 K, d_6-DMSO) δ 12.42 (s, 4H, H_i), 10.02 (s, 4H, H_n), 9.64 (s, 4H, H_a), 9.42 (dd, J = 13.3, 5.8 Hz, 8H, $H_{b,m}$), 8.46 (d, J = 17.2 Hz, 8H, $H_{h,j}$), 8.30 – 8.20 (m, 8H, $H_{d,k}$), 8.14 (d, J = 7.9 Hz, 4H, H_g), 7.89 – 7.76 (m, 12H, $H_{c,e,l}$), 7.65 (t, J = 7.7 Hz, 4H, H_f). ^{1}H NMR (400 MHz, 298 K, CD_3CN) δ 10.77 (s, 4H, H_i), 9.89 (s, 4H, H_n), 9.48 (s, 4H, H_a), 9.09 (dd, J = 16.9, 5.8 Hz, 8H, $H_{b,m}$), 8.55 (s, 4H, H_j), 8.34 (s, 4H, H_h), 8.10 – 8.00 (m, 8H, $H_{d,k}$), 7.97 (d, J = 7.9 Hz, 4H, H_g), 7.78 (d, J = 7.6 Hz, 1H, H_e), 7.69 – 7.54 (m, 12H, $H_{c,f,l}$). ^{13}C NMR (125 MHz, 298 K, d_6-DMSO) δ 161.5, 153.4, 151.8, 150.3, 148.5, 143.8, 142.4, 140.8, 134.6, 134.0, 133.3, 132.8, 132.8, 129.4, 127.6, 127.2, 122.3, 121.6, 94.0, 85.3. Anal. Calc. for $C_{80}H_{56}N_{16}O_4PtPdB_4F_{16}$·2DCM: C, 46.37; H, 2.85; N, 10.55, Found C, 46.59; H, 3.11; N, 10.89%. ESIMS: (MeOH) m/z = 401.5834 $[\mathbf{M} - 4BF_4]^{4+}$ (calc. for $C_{80}H_{56}N_{16}O_4PtPd$ 401.5839), 547.1015 $[\mathbf{M} - 4BF_4 + Cl]^{3+}$ (calc. for $C_{80}H_{56}N_{16}O_4PtPdCl$ 547.1014), 564.4460 $[\mathbf{M} - 3BF_4]^{3+}$ (calc. for $C_{80}H_{56}N_{16}O_4PtPdBF_4$, 564.4466), 864.1548 $[\mathbf{M} - 3BF_4 + Cl]^{2+}$ (calc. for $C_{80}H_{56}N_{16}O_4PtPdBF_4Cl$ 564.1542), 889.6712 $[\mathbf{M} - 2BF_4]^{2+}$ (calc. for $C_{80}H_{56}N_{16}O_4PtPdB_2F_8$, 889.6720).

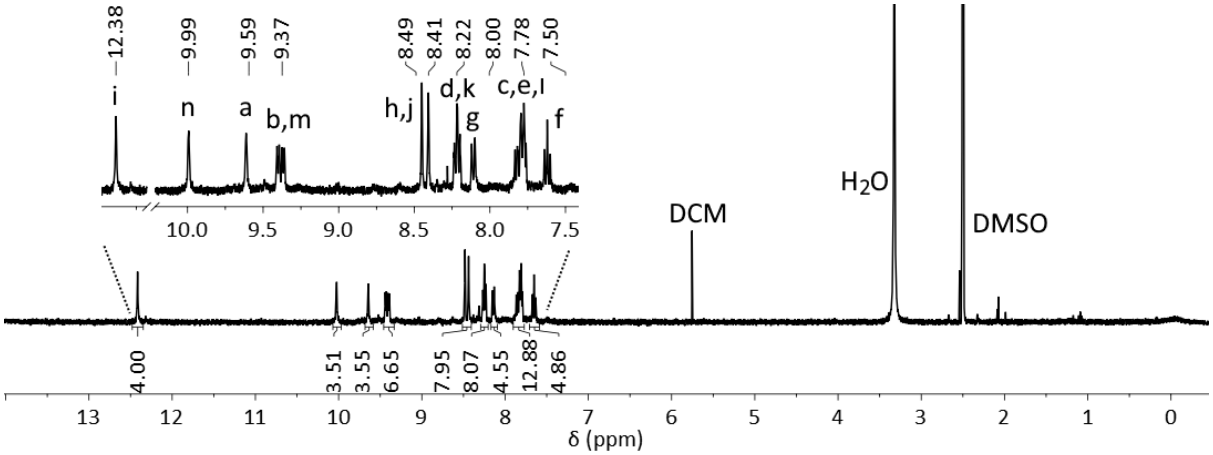


Figure S8 ^{1}H NMR spectrum (400 MHz, d_6-DMSO, 298 K) of **HC**.

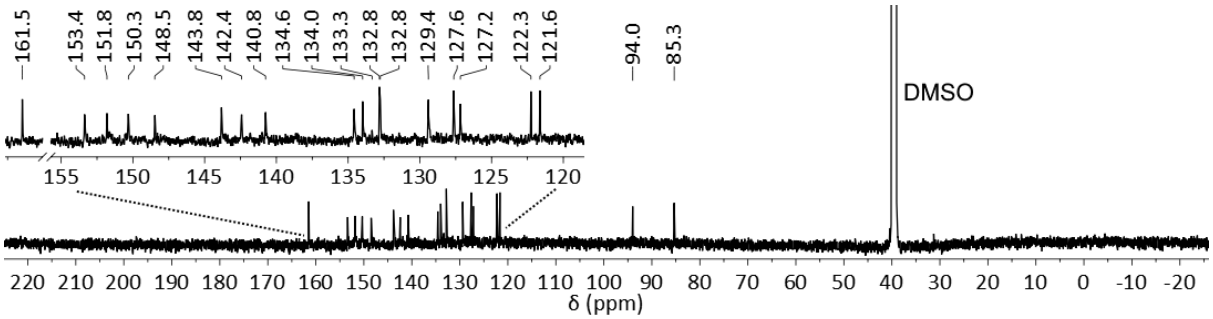


Figure S9 ^{13}C{^{1}H} NMR spectrum (125 MHz, 298 K, d_6-DMSO) of **HC**.

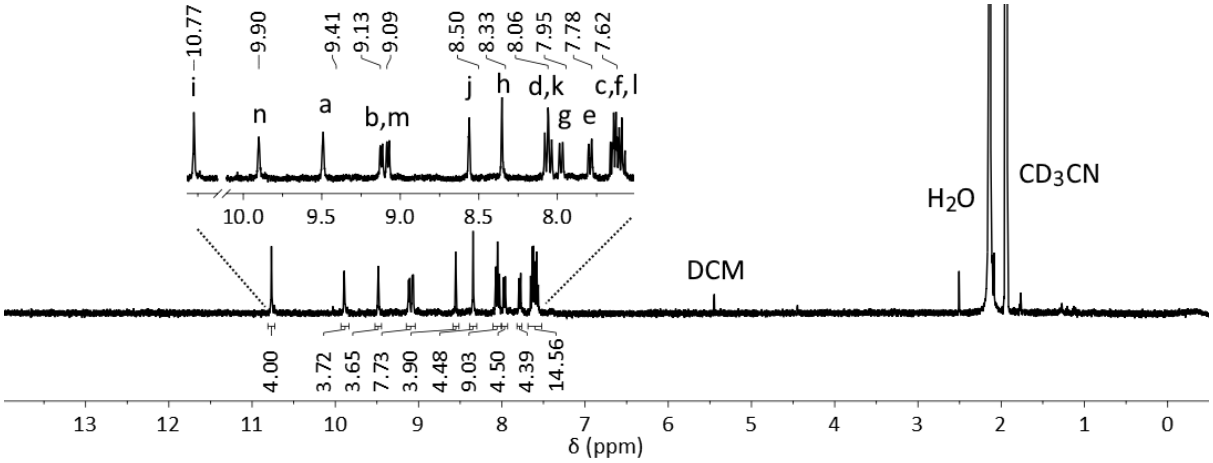


Figure S10 ^{1}H NMR spectrum (400 MHz, CD_3CN, 298 K) of **HC**.

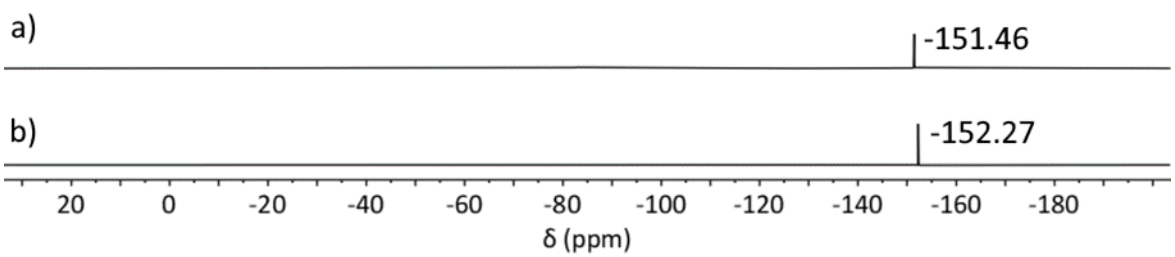


Figure S11 ^{19}F NMR spectra (CD_3CN, 298 K, 376 MHz) of a) $NaBF_4$ and b) **HC**.

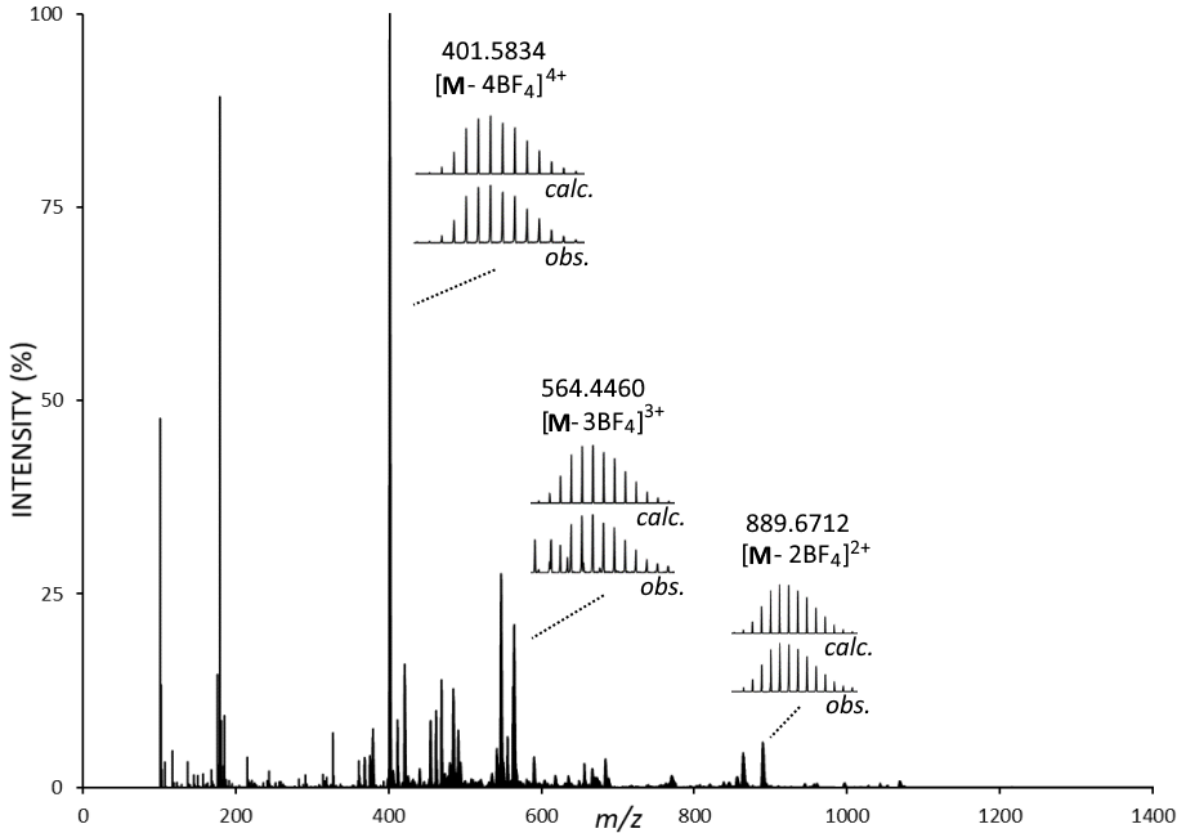


Figure S12 ESIMS spectrum (CH_3CN) of **HC**.

1.3.6 ^{1}H DOSY NMR data

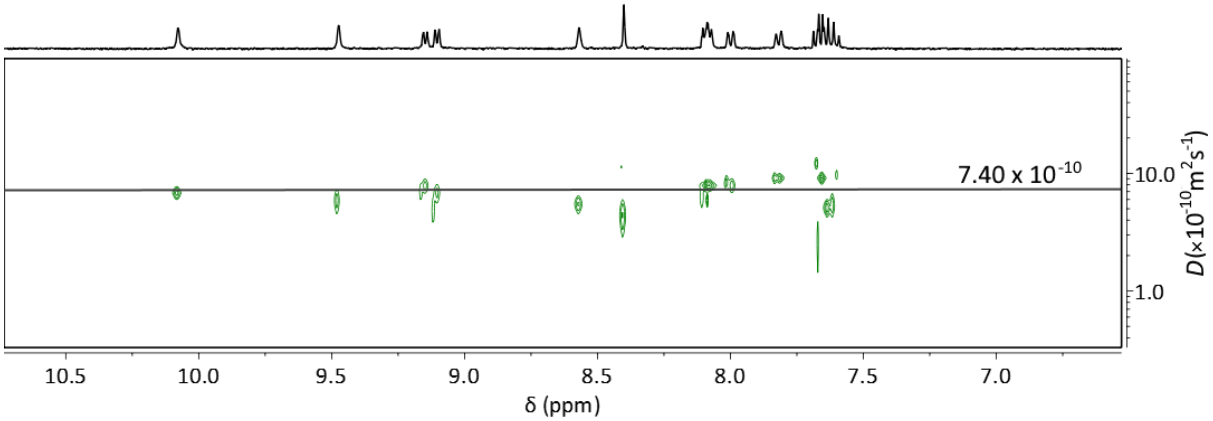


Figure S13 Partial ^{1}H NMR and corresponding DOSY NMR spectra for **HC** (400 MHz, CD_3CN, 298 K).

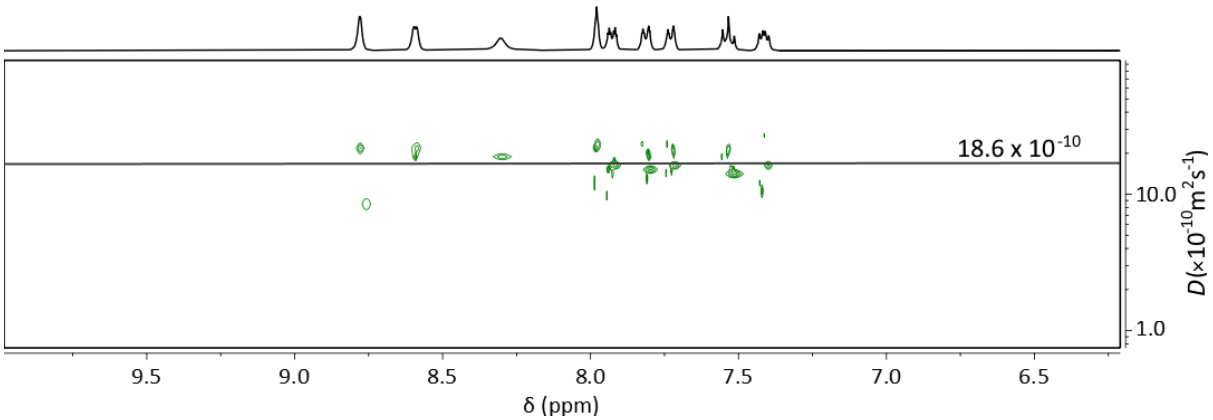


Figure S14 Partial ^{1}H NMR and corresponding DOSY NMR spectra for **3** (400 MHz, CD_3CN, 298 K).

Table S1 Diffusion coefficients as obtained via ^{1}H DOSY NMR experiments (400 MHz, CD_3CN, 298 K).

Species	Molecular Weight (g mol^{-1})	Diffusion Coefficient (× 10^{-10} m^2 s^{-1})
3	237.26	18.6
HC	1954.15	7.40
IC[4]	2966.67	5.55
Pt$_{pyald}$[4]	797.13	8.10

1.4 Cage Opening and Closing

The transformation of **HC** into the $[Pt(\mathbf{L1})_4]^{2+}$ complex was conducted by titrating a stock solution of DMAP (0.168 M) in d_6-DMSO into a solution of **HC** (1.60 μM, 0.500 mL d_6-DMSO) in 1 eq. increments. After each addition of DMAP, a ^{1}H NMR spectrum of the resulting mixture was obtained. ESIMS (CH_3CN): *m/z* = 297.1191 $[Pd(DMAP)_4]^{2+}$ (calc. for $C_{28}H_{40}N_8Pd$, 297.1205); 750.2140 $[Pt(\mathbf{L1})_4]^{2+}$ (calc. for $C_{80}H_{56}N_{16}O_4Pt$ 750.2164). To close the cage, TsOH (5 eq.) was added to the resulting mixture as a solid. The solution was left at RT for 1.5 h and a ^{1}H NMR spectrum was obtained.

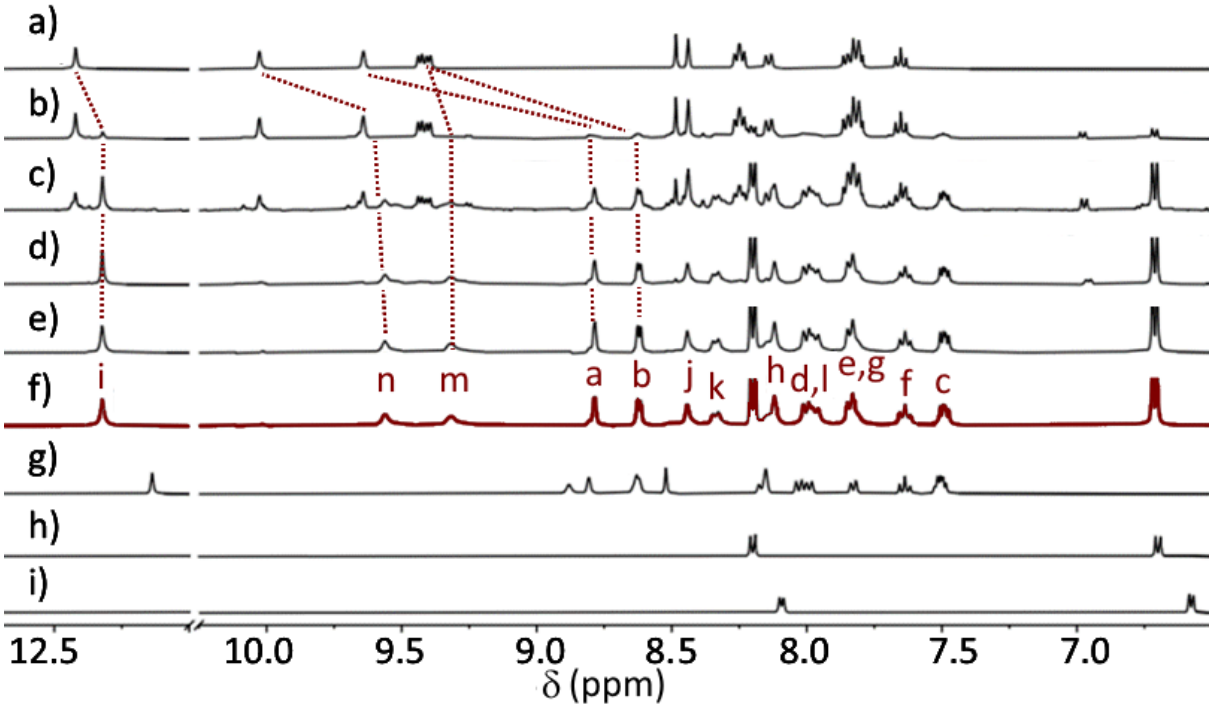


Figure S15 Stacked partial ^{1}H NMR spectra (d_6-DMSO, 298 K, 400 MHz) for the titration of DMAP into **HC**; a) **HC**, b) + 1 eq., c) + 2 eq. DMAP, d) + 3 eq. DMAP, e) + 4 eq. DMAP, f) + 5 eq. DMAP, g) **L1**, h) $[Pd(DMAP)_4](BF_4)_2$, i) DMAP.

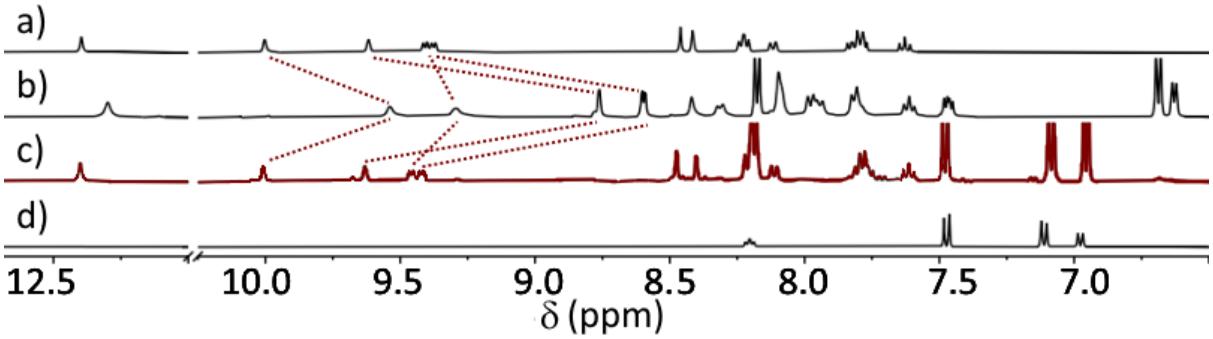


Figure S16 Stacked partial ^{1}H NMR spectra (d_6-DMSO, 298 K, 400 MHz) of a) **HC**, b) **HC** + 5 eq. DMAP, c) **HC** + 5 eq. DMAP + 4 eq. TsOH, d) DMAP + TsOH.

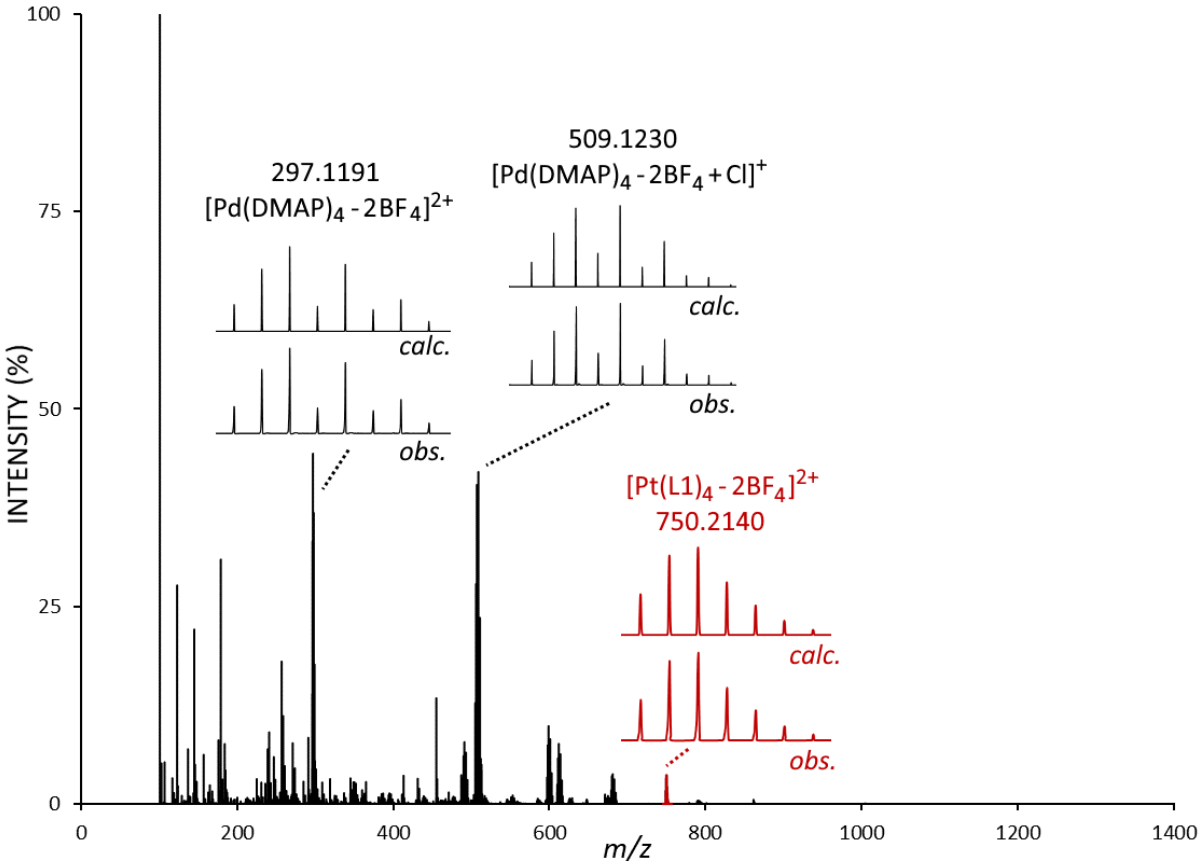
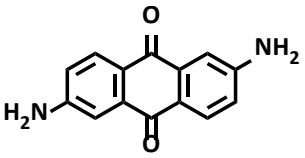


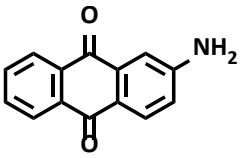
Figure S17 ESIMS spectrum of **HC** + 4 eq. DMAP in CH_3CN.

1.5 **Host-Guest Chemistry**

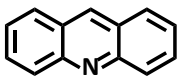
1,4-benzoquinone (**BQ**)



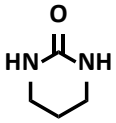
2,6-diaminoanthraquinone (**DAQ**)



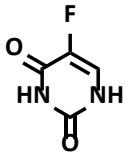
2-aminoanthraquinone



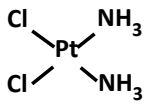
acridine



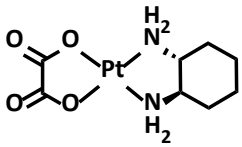
tetrahydro-2-pyrimidione



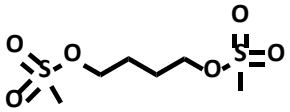
5-fluorouracil (**5-FU**)



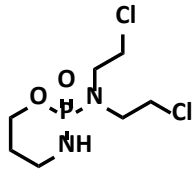
cisplatin (**CP**)



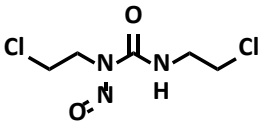
oxaliplatin (**Oxpt**)



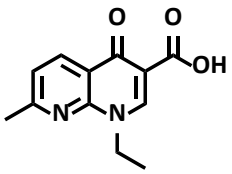
busulfan



cyclophosphamide



carmustine



nalidixic acid

Figure S18 Guest molecules screened for their binding within **HC** and **IC**.

1.5.1 Guest Screening

Binding studies of the potential guest molecules shown in Figure S18 within **IC** and **HC** were conducted at a 1:2 host to guest ratio in CD_3CN and d_6-DMSO. **IC** or **HC** (0.5 µmol, 1.0 mM) were dissolved in CD_3CN or d_6-DMSO (500 µL) in an NMR tube. To the solution of the host cage, the guest was added as a solid (1.0 µmol) and a ^{1}H NMR spectrum (400 MHz, 298 K) of the resulting host-guest mixture was obtained. The spectrum of the mixture was compared to that of the host and the guest to examine if there were peak shifts suggestive of guest binding.

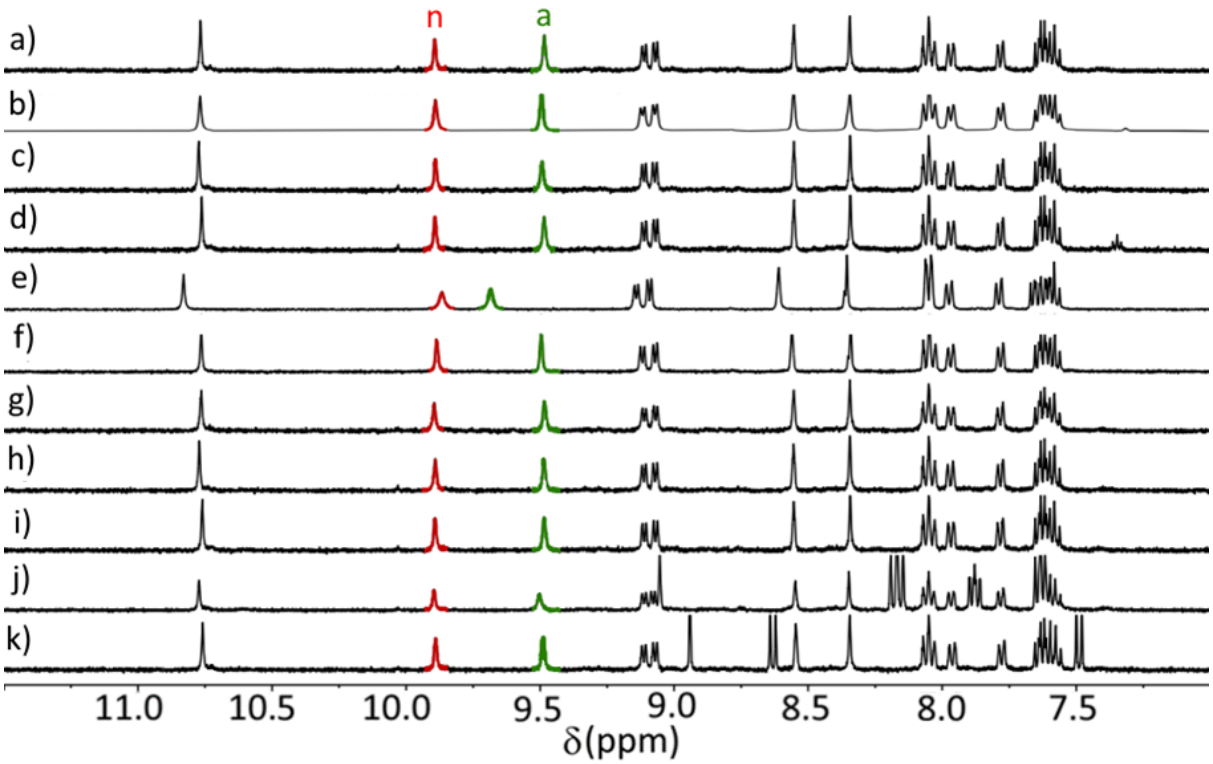


Figure S19 Stacked partial ^{1}H NMR spectra (CD_3CN, 298 K, 400 MHz) of a) **HC** with added b) 2,6-diaminoanthraquinone, c) tetrahydro-2-pyrimidinone, d) 5-fluorouracil, e) cisplatin, f) oxaliplatin, g) busulfan, h) cyclophosphamide, i) carmustine, j) acridine, k) nalidixic acid.

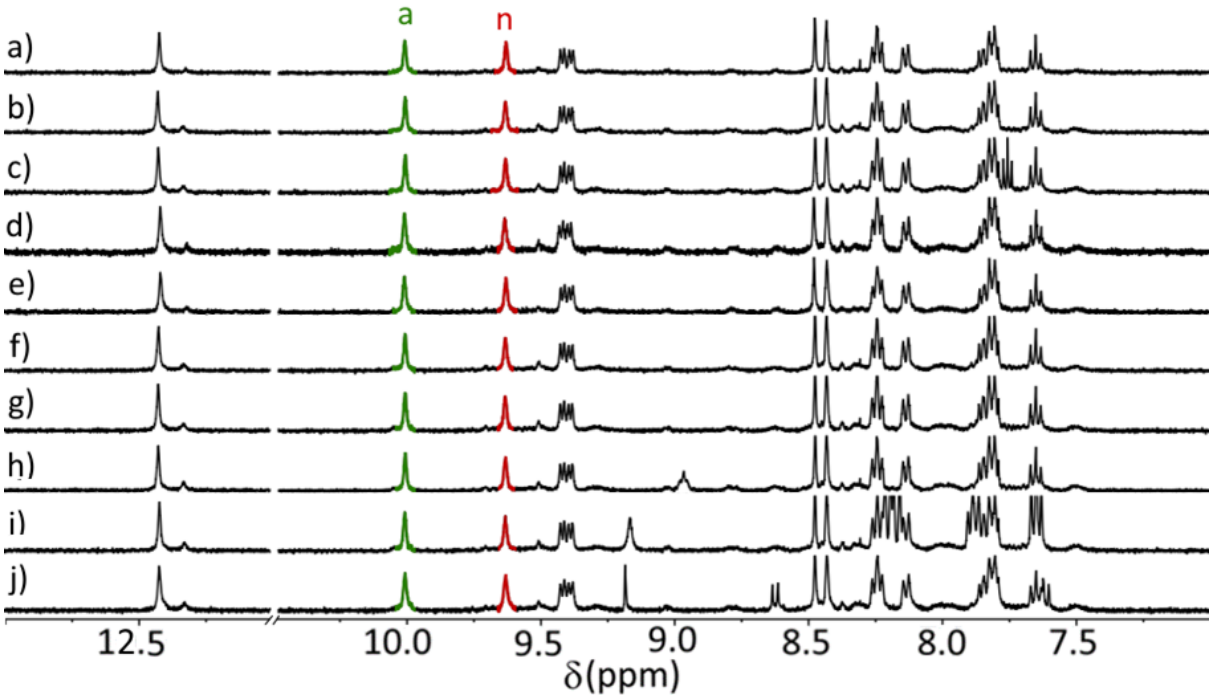


Figure S20 Stacked partial ^{1}H NMR spectra (d_6-DMSO, 298 K, 400 MHz) of a) **HC** with added b) tetrahydro-2-pyrimidinone, c) 5-fluorouracil, d) cisplatin, e) oxaliplatin, f) cyclophosphamide, g) busulfan, h) carmustine, i) acridine, j) nalidixic acid.

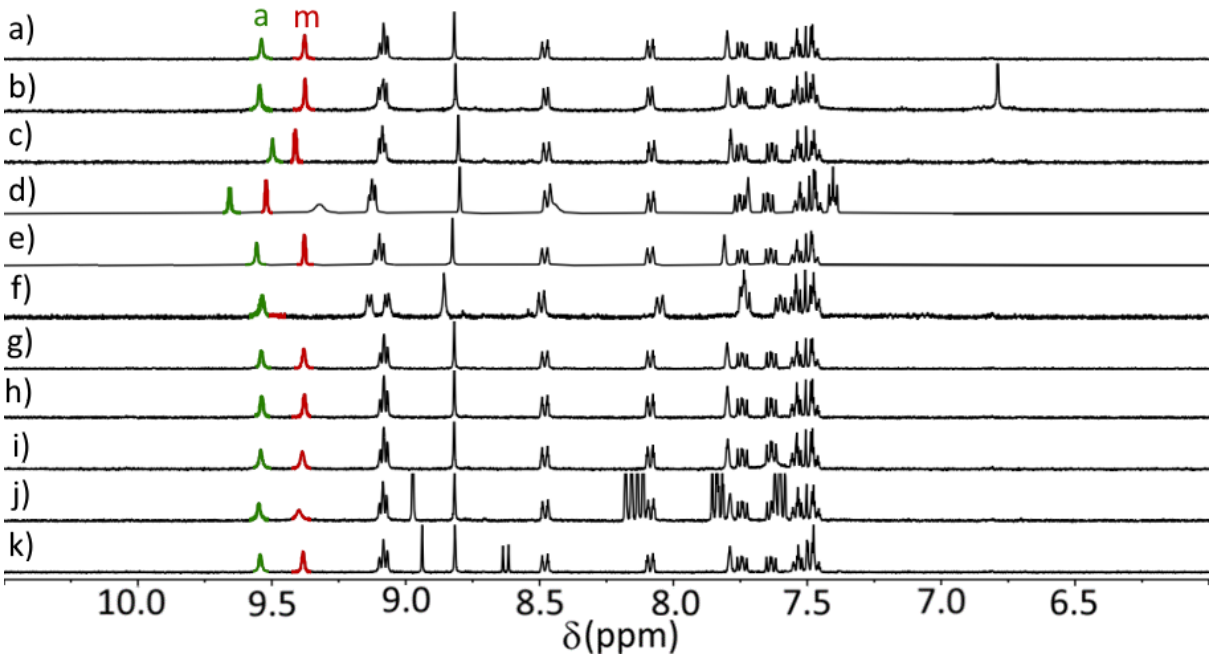


Figure S21 Stacked partial ^{1}H NMR spectra (CD_3CN, 298 K, 400 MHz) of a) **IC** with added b) 1,4-benzoquinone, c) tetrahydro-2-pyrimidinone, d) 5-fluorouracil, e) cisplatin, f) oxaliplatin, g) busulfan, h) cyclophosphamide, i) carmustine, j) acridine, k) nalidixic acid.

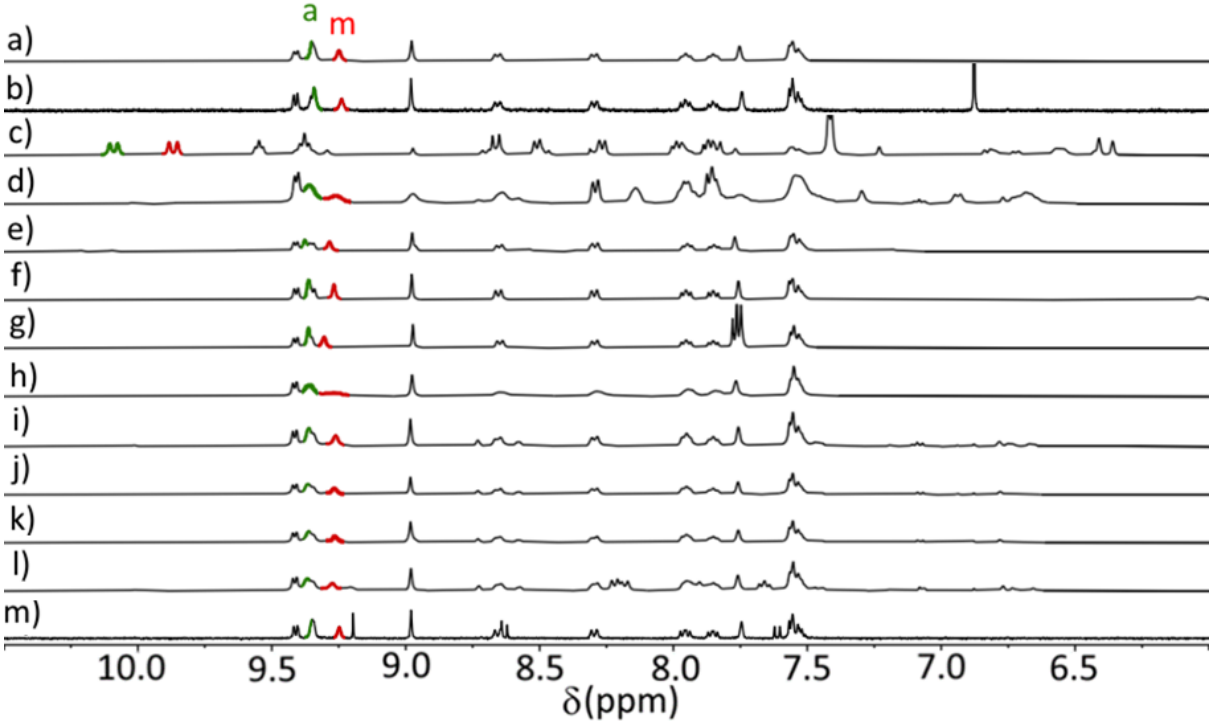


Figure S22 Stacked partial ^{1}H NMR spectra (d_6-DMSO, 298 K, 400 MHz) of a) **IC** with added b) 1,4-benzoquinone, c) 2,6-diaminoanthraquinone, d) 2-aminoanthraquinone, e) tetrahydro-2-pyrimidinone, f) 5-fluorouracil, g) cisplatin, h) oxaliplatin, i) busulfan, j) cyclophosphamide, k) carmustine, l) acridine, m) nalidixic acid.

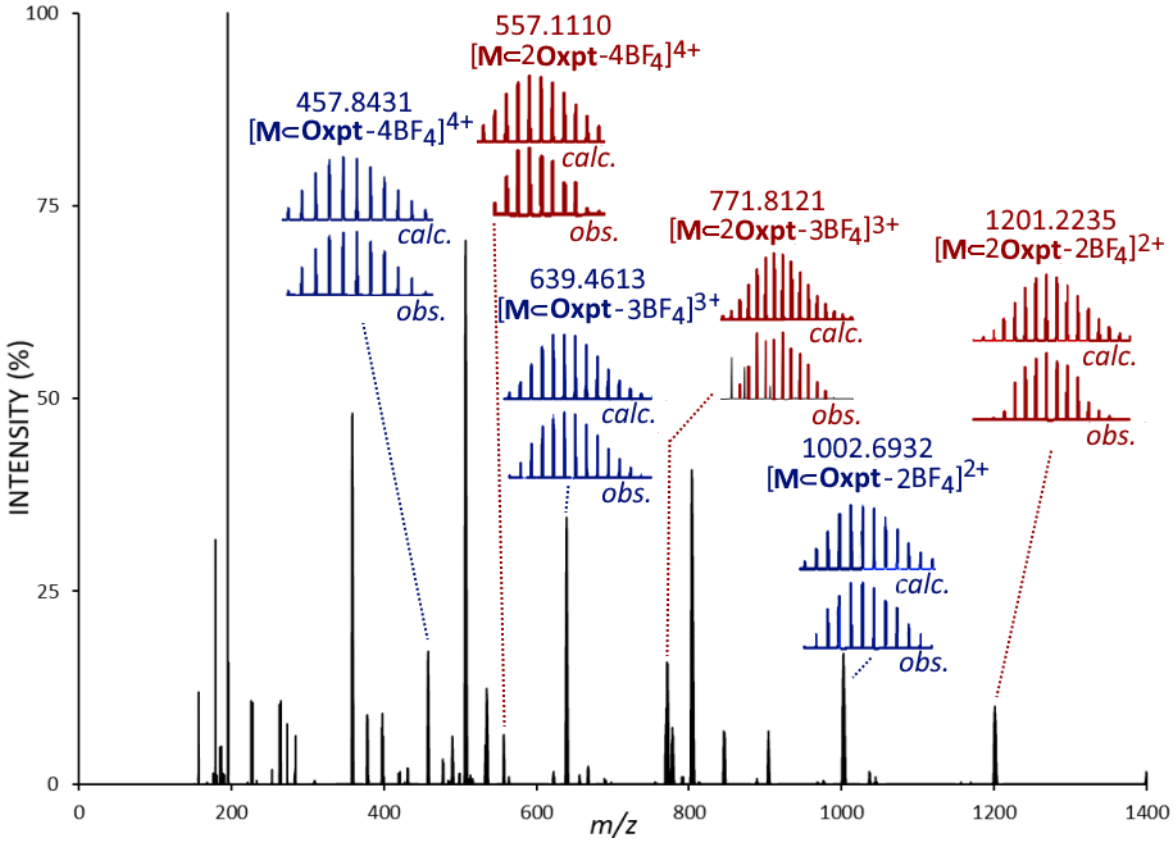


Figure S23 ESIMS spectrum (CH_3CN) of 1:2 **IC:**oxaliplatin (**Oxpt**) mixture.

2 Molecular Modelling

All MMFF models were obtained using SPARTAN 16®. The structures were energy-minimised to give the optimised models.

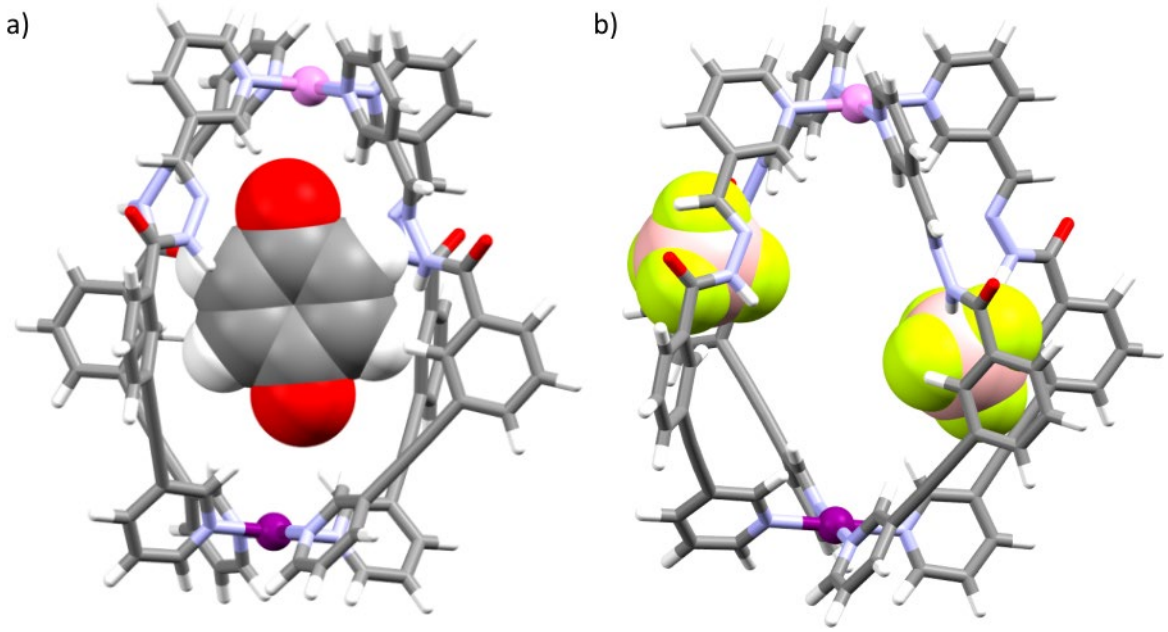


Figure S24 Energy-minimised Spartan'16® models of a) [**HC⊂BQ**] (O_{BQ} – α-C = 3.68 – 5.04 Å) and b) [**HC**⊂$(BF_4)_2$]

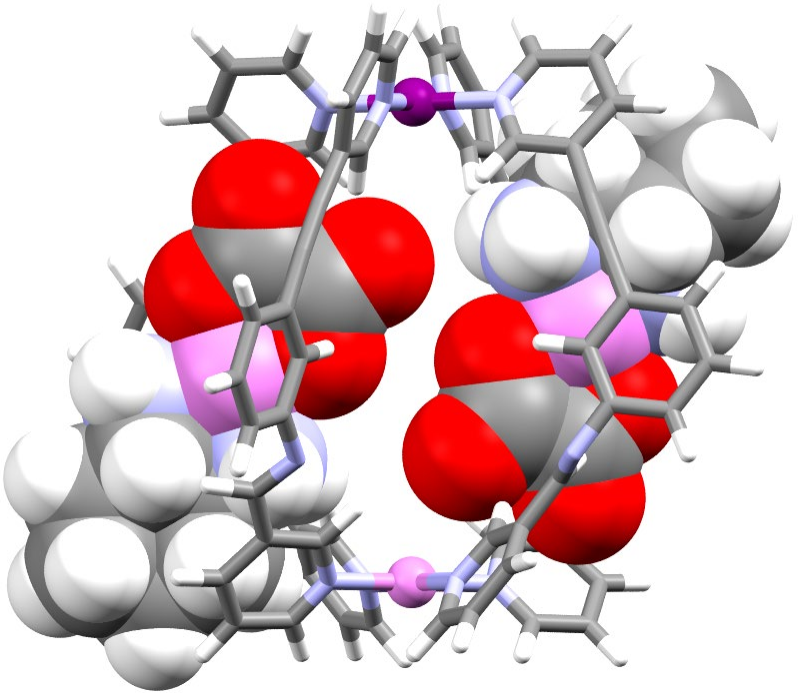


Figure S25 Spartan'16® model of two oxaliplatin (**Oxpt**) molecules docked within **IC**.

2.1.1 ^{1}H NMR stability study of host-guest mixtures

The stability of the **IC** and **HC** cages in the presence of the guest molecules cisplatin, oxaliplatin and 5-fluorouracil were monitored using ^{1}H NMR spectroscopy over 72 h. **IC** or **HC** (0.5 µmol, 1.0 mM) were dissolved in d_6-DMSO (500 µL). To the solution, the guest was added as a solid (1.0 µmol) to give a 1:2 host-guest ratio and ^{1}H NMR spectra were collected at a range of different time points up to 72 hours.

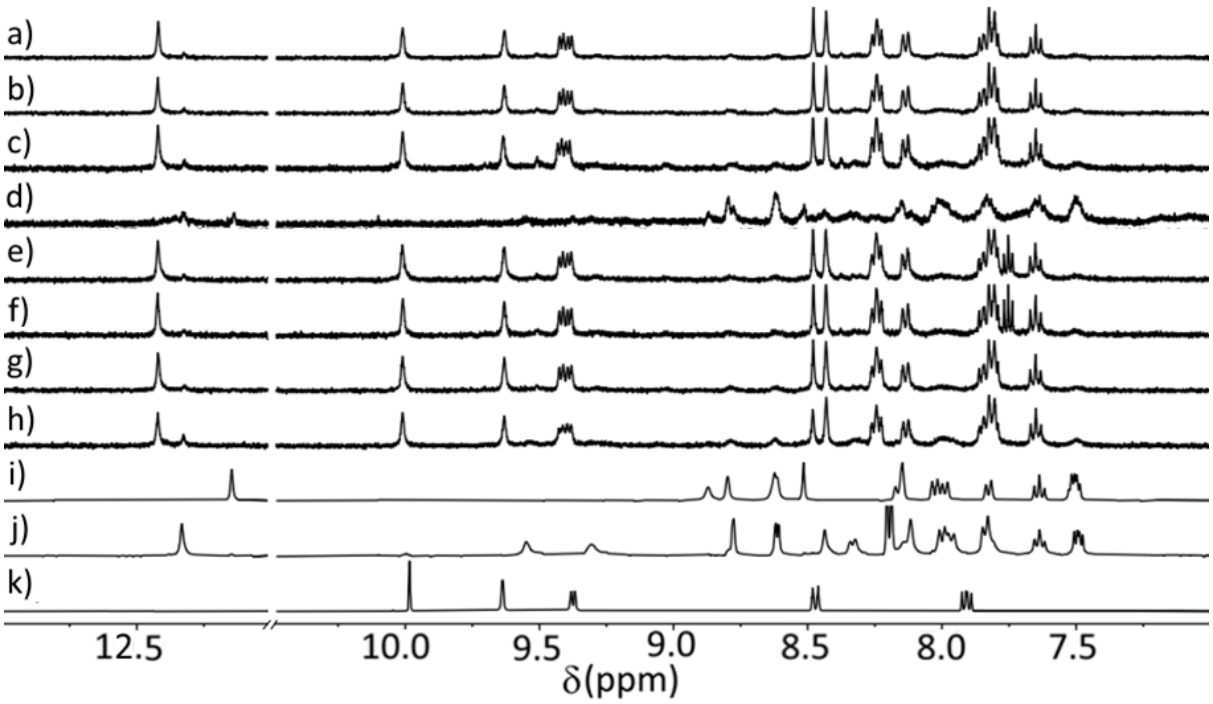


Figure S26 Stacked partial ^{1}H NMR spectra (d_6-DMSO, 298 K, 400 MHz) of a) **HC** at 0 h, b) **HC** after 72 h, c) **HC** + cisplatin at 0 h, d) **HC** + cisplatin at 72 h, e) **HC** + 5-fluorouracil at 0 h, f) **HC** + 5-fluorouracil at 72 h, g) **HC** + oxaliplatin at 0 h, h) **HC** + oxaliplatin at 72 h, i) **L1**, **j**) **3**, k) $\mathbf{Pt_{pyald}}$.

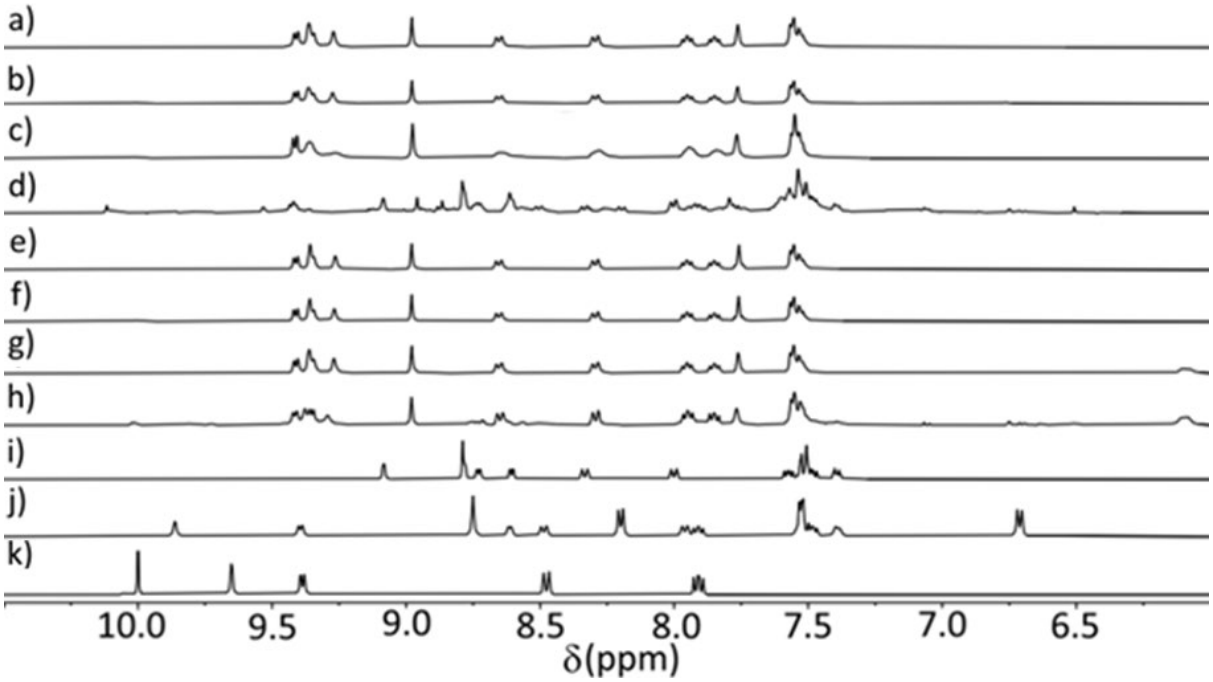


Figure S27 Stacked partial ^{1}H NMR spectra (d_6-DMSO, 298 K, 400 MHz) of a) **IC** at 0 h, b) **IC** after 72 h, c) [**IC** + cisplatin at 0 h, d) **IC** + cisplatin at 72 h, e) $\mathbf{IC}_4$ + 5-fluorouracil at 0 h, f) **IC** + 5-fluorouracil at 72 h, g) **IC** + oxaliplatin at 0 h, h) **IC** + oxaliplatin at 72 h, i) ligand, j) **4**, k) $\mathbf{Pt_{pyald}}$.

3 Aqueous Stability

Initially, the stability of **IC** and **HC** (0.52 µmol) in the presence of water was investigated in a 1:19 D_2O/d_6-DMSO (600 µL) solvent mixture and monitored using ^1H NMR (d_6-DMSO, 298 K, 500 MHz or 400 MHz) spectroscopy over 72 h. A second water stability study of **IC** or **HC** (0.52 µmol) in a 1:1 D_2O/d_6-DMSO solvent mixture was conducted and monitored using ^1H NMR (d_6-DMSO, 298 K, 500 MHz or 400 MHz) spectroscopy over 3 h.

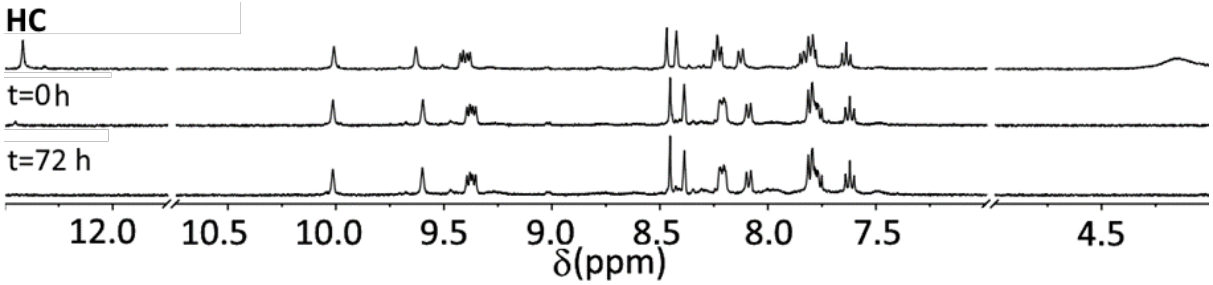


Figure S28 Stacked partial ^1H NMR spectra (referenced to d_6-DMSO, 298 K, 400 MHz) for a decomposition study of **HC** in 1:19 v/v D_2O/ d_6-DMSO over 72 hours. A deuterium exchange was observed for H_i after the addition of D_2O.

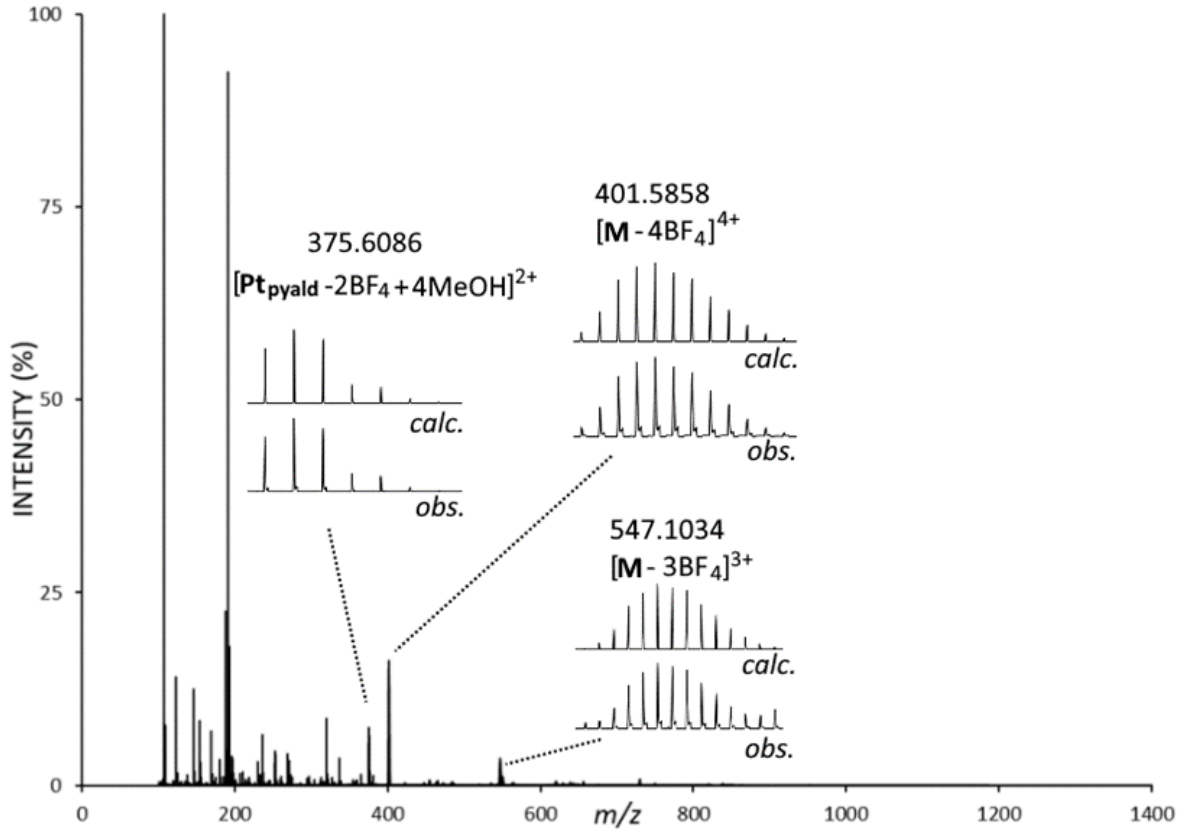


Figure S29 ESIMS spectrum (CH_3OH) of the decomposition product of **HC** in 1:19 v/v H_2O/DMSO after 72 hours.

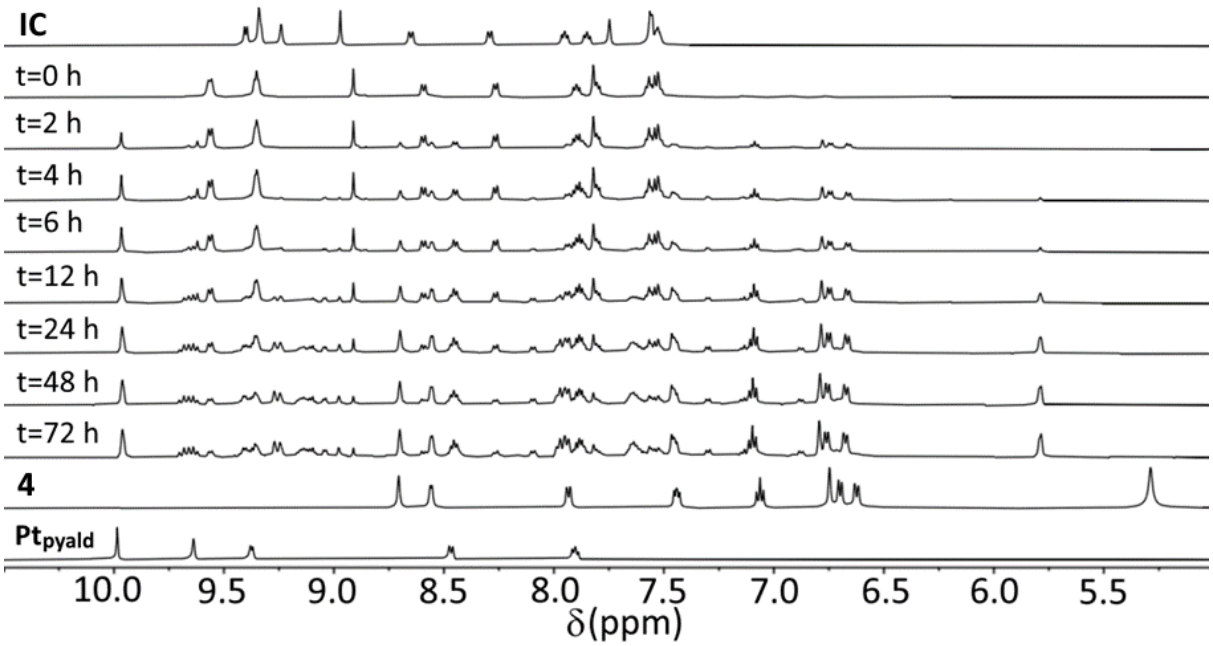


Figure S30 Stacked partial ^{1}H NMR spectra (referenced to d_6-DMSO, 298 K, 500 MHz) for a decomposition study of **IC** in 1:19 v/v D_2O/d_6-DMSO over 72 hours.

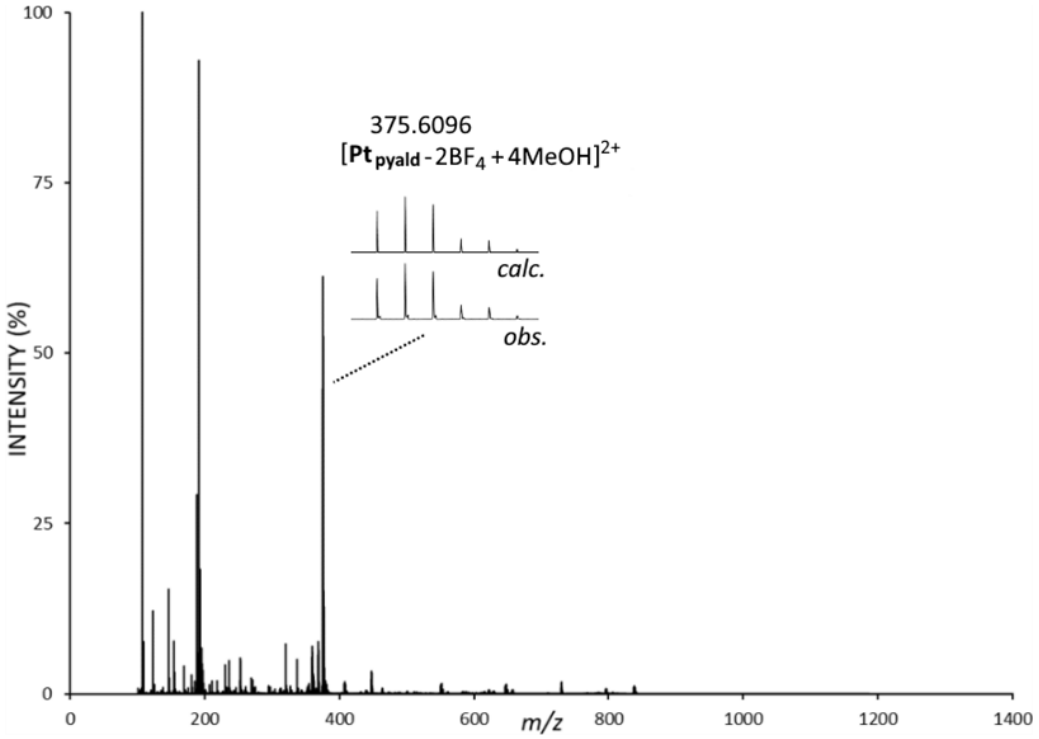


Figure S31 ESIMS spectrum (CH_3OH) of the decomposition product of **IC** in 1:19 v/v H_2O/DMSO after 72 hours.

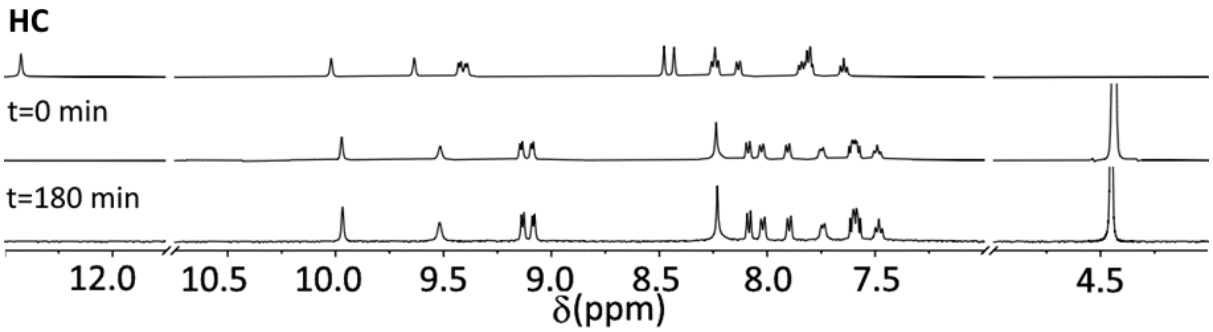


Figure S32 Stacked partial ^{1}H NMR spectra (d_6-DMSO, 298 K, 500 MHz) for a decomposition study of **HC** in 1:1 v/v D_2O/d_6-DMSO.

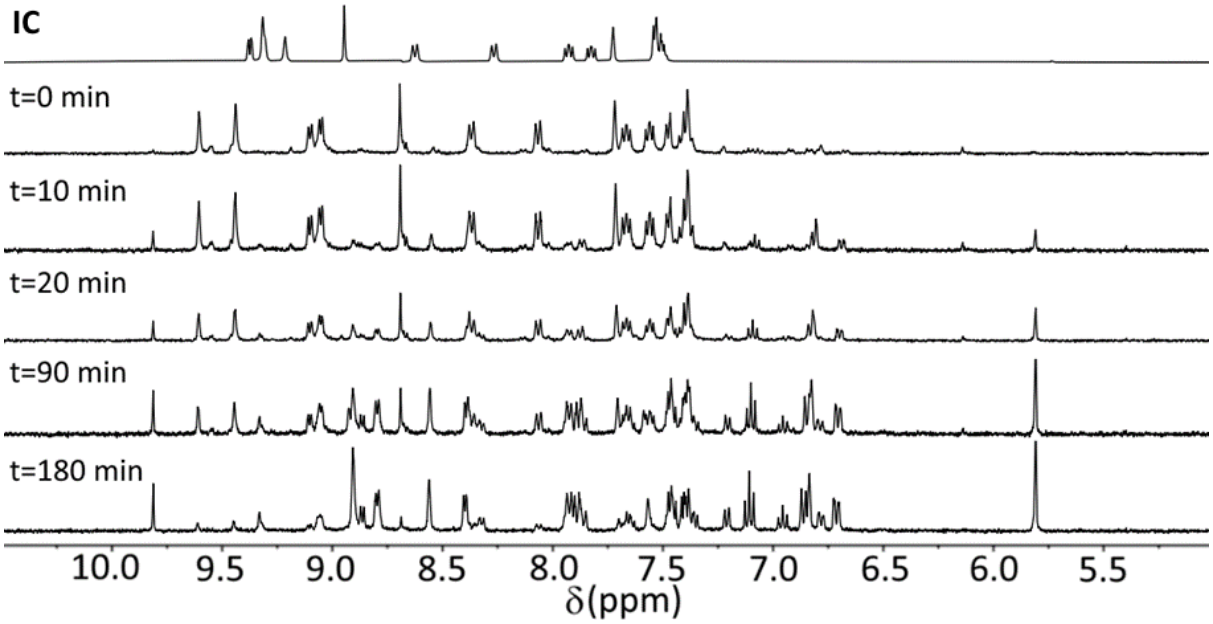


Figure S33 Stacked partial ^{1}H NMR spectra (d_6-DMSO, 298 K, 400 MHz) for a decomposition study of **IC** in 1:1 v/v D_2O/d_6-DMSO.

4 Antiproliferative Activity

Sulforhodamine B Assay.

HCT116, SW480 and NCI-H460 cells were supplied by ATCC, and SiHa cells were supplied by Dr. David Cowan, Ontario Cancer Institute, Canada. The cells were grown in α-MEM (Life Technologies) supplemented with 5% fetal calf serum (Moregate Biotech) at 37 °C in a humidified incubator with 5% CO_2. The cells were seeded at 750 (HCT116, NCI-H460), 4000 (SiHa) and 5000 (SW480) cells/well in 96-well plates and left to settle for 24 h. Due to the limited solubility of the cages and host-guest mixtures in water, samples were prepared by dissolution in DMSO followed by dilution with biological media (1:100 DMSO/biological media). Compounds were added to the plates in a series of 3-fold dilutions for 72 h before the assay was terminated by addition of 10% trichloroacetic acid (Merck Millipore) at 4 °C for 1 h. Cells were stained with 0.4% sulforhodamine B (Sigma-Aldrich) in 1% acetic acid for 30 min in the dark at room temperature and then washed with 1% acetic acid to remove unbound dye. The stain was dissolved in unbuffered tris base (10 mM; Serva) for 30 min on a plate shaker in the dark and quantitated using a BioTek EL808 microplate reader at an absorbance of 490 nm with a reference wavelength of 450 nm to determine the percentage of cell-growth inhibition by determining the

absorbance of each sample relative to a negative (no inhibitor) and a no-growth control (day 0). IC_{50} values were calculated with SigmaPlot 12.5 (Systat Software Inc.) using a three-parameter logistic sigmoidal dose−response curve between the calculated growth inhibition and the compound concentration. The presented IC_{50} values are the mean of at least 3 independent experiments, where 10 concentrations were tested in duplicate for each compound.

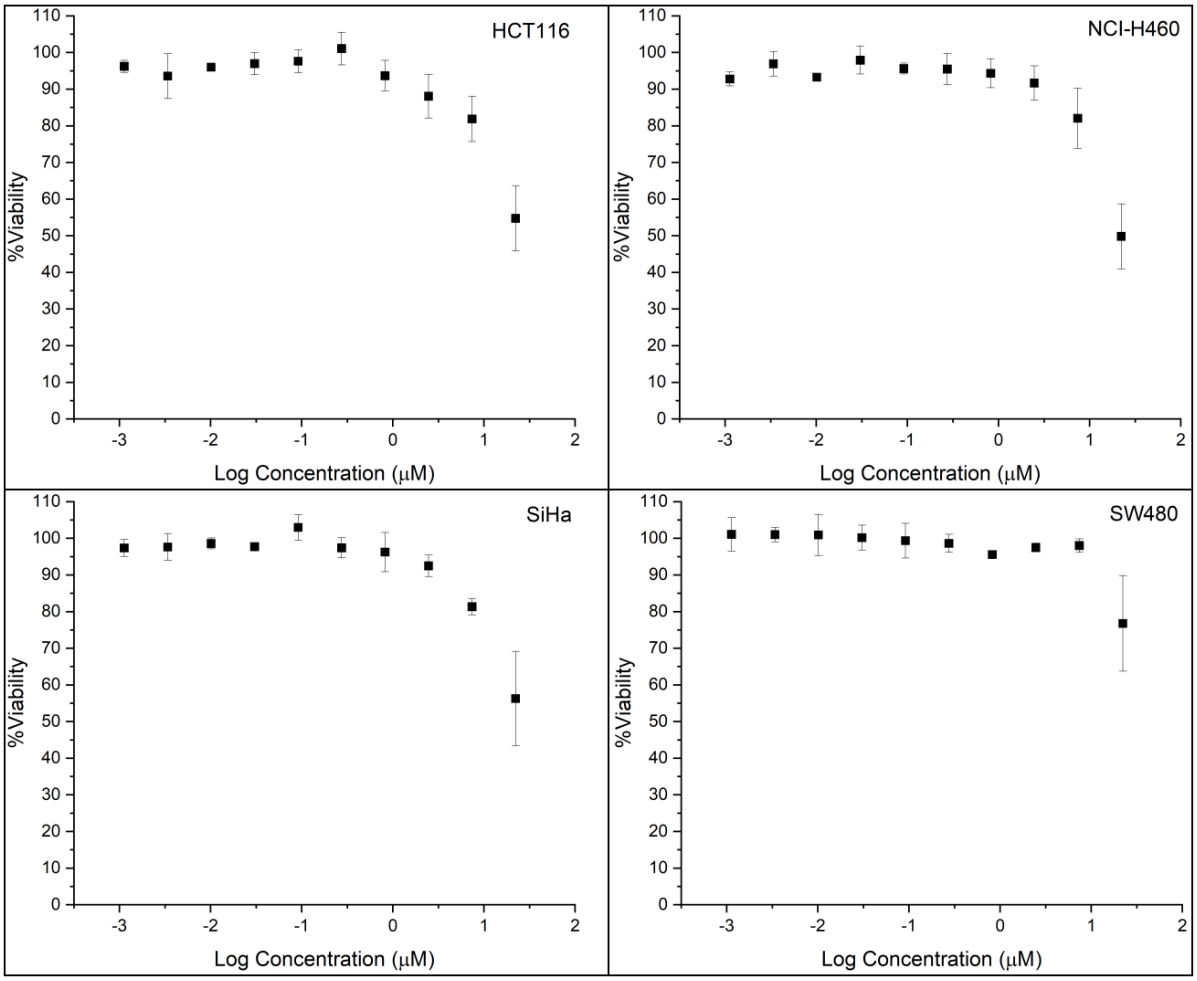


Figure S34 Representative plots showing the % viability of cells against log concentration of **IC** (μM) for the cell lines HCT116 (top left), NCI-H460 (top right), SiHa (bottom left) and SW480 (bottom right)

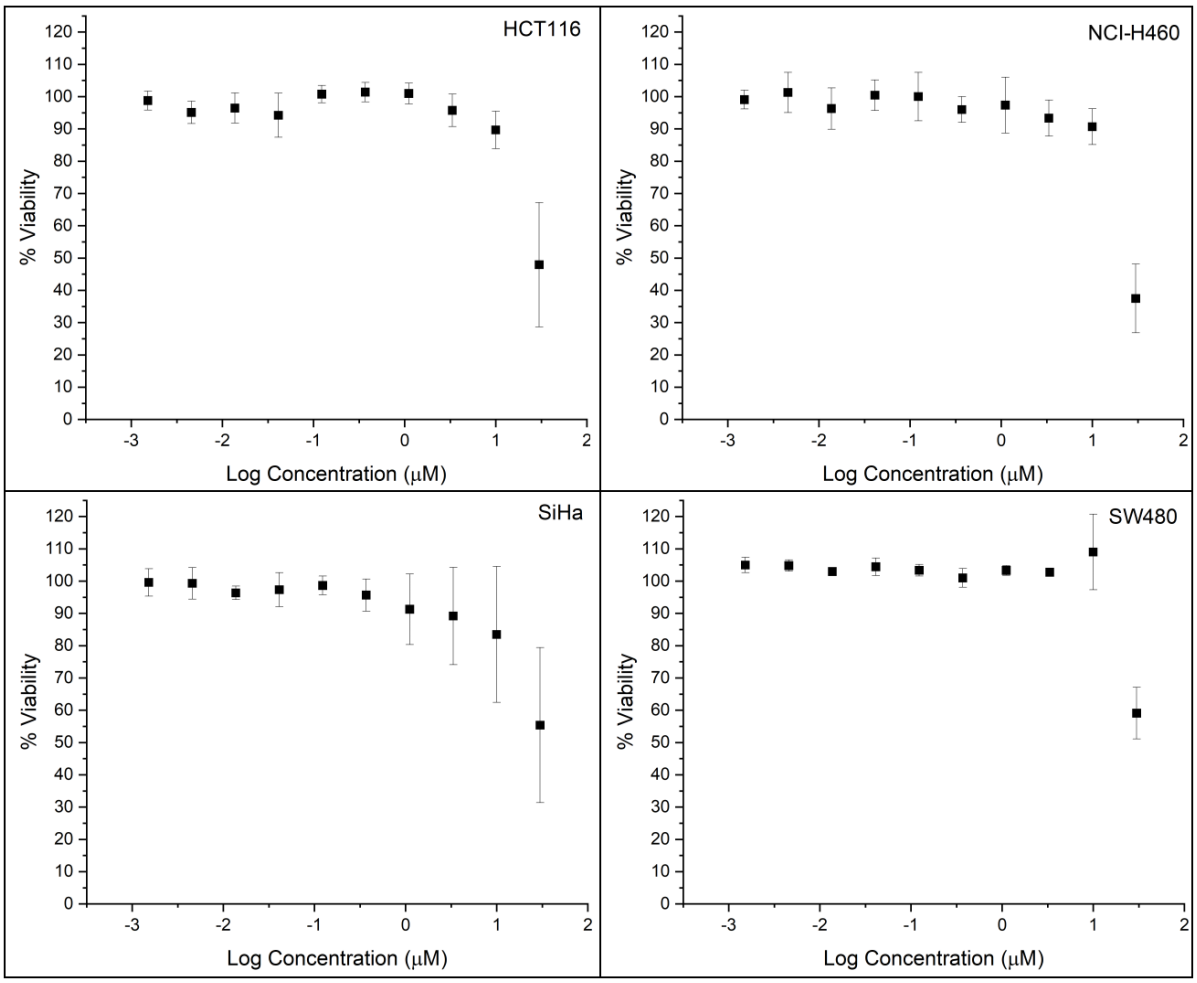


Figure S35 Representative plots showing the % viability of cells against log concentration of **HC** (μM) for the cell lines HCT116 (top left), NCI-H460 (top right), SiHa (bottom left) and SW480 (bottom right)

5 References

1. J. E. M. Lewis, E. L. Gavey, S. A. Cameron and J. D. Crowley, *Chem. Sci.*, 2012, **3**, 778-784.
2. D. J. Kahl, K. M. Hutchings, E. M. Lisabeth, A. J. Haak, J. R. Leipprandt, T. Dexheimer, D. Khanna, P.-S. Tsou, P. L. Campbell, D. A. Fox, B. Wen, D. Sun, M. Bailie, R. R. Neubig and S. D. Larsen, *J. Med. Chem.*, 2019, **62**, 4350-4369.
3. L. S. Lisboa, J. A. Findlay, L. J. Wright, C. G. Hartinger and J. D. Crowley, *Angew. Chem., Int. Ed.*, 2020, **59**, 11101 –11107.
4. L. S. Lisboa, D. Preston, C. J. McAdam, L. J. Wright, C. G. Hartinger and J. D. Crowley, *Angew. Chem. Int. Ed.*, 2022, **61**, e202201700.