

SUPPLEMENTARY MATERIALS

Bioactive Platinum(IV) Complexes Incorporating Halogenated Phenylacetates

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HPLC chromatograms of NHS esters

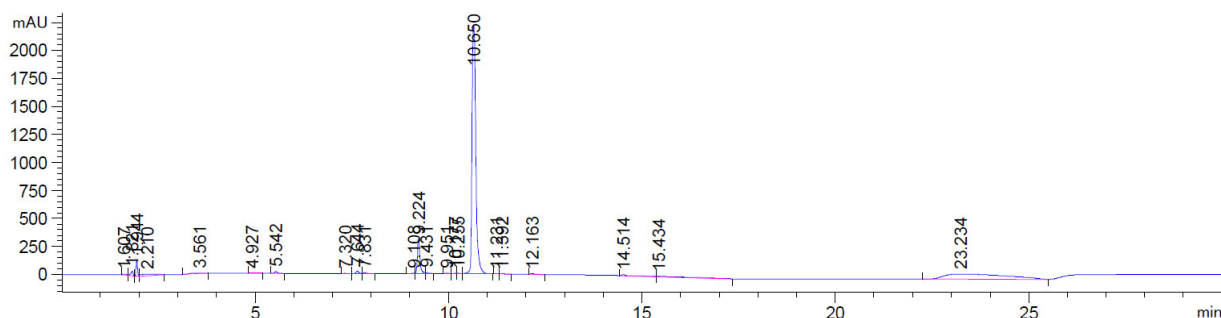


Figure S1: HPLC chromatogram of NHS-4-CPA within the collection wavelength of 254 nm obtained at 298 K, by an Agilent ZORBAX RX-C₁₈ column (100 × 4.6 mm, 3.5 μm pore size) using a 0 – 100% linear gradient over 15 min with a flow rate of 1 mL.min⁻¹.

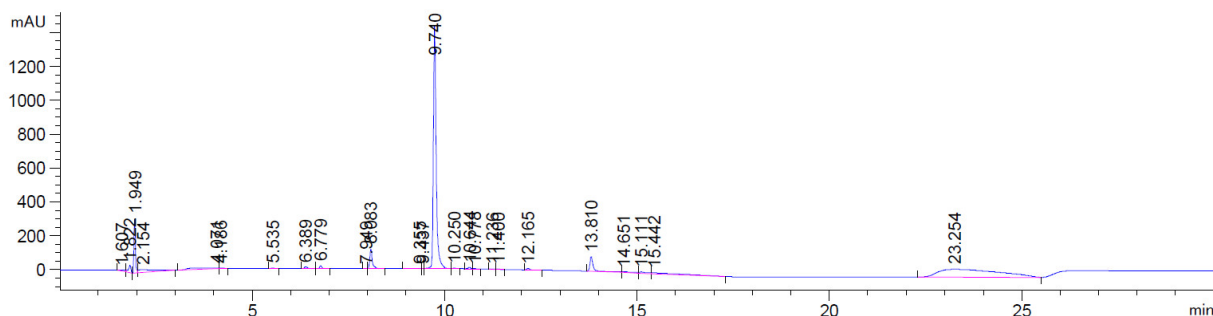


Figure S2: HPLC chromatogram of NHS-4-FPA within the collection wavelength of 254 nm obtained at 298 K, by an Agilent ZORBAX RX-C₁₈ column (100 × 4.6 mm, 3.5 μm pore size) using a 0 – 100% linear gradient over 15 min with a flow rate of 1 mL.min⁻¹.

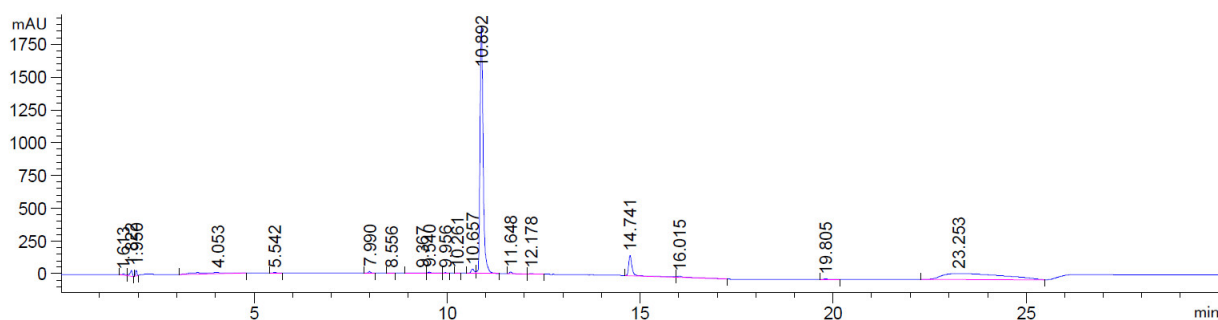


Figure S3: HPLC chromatogram of NHS-4-BPA within the collection wavelength of 254 nm obtained at 298 K, by an Agilent ZORBAX RX-C₁₈ column (100 × 4.6 mm, 3.5 μm pore size) using a 0 – 100% linear gradient over 15 min with a flow rate of 1 mL.min⁻¹.

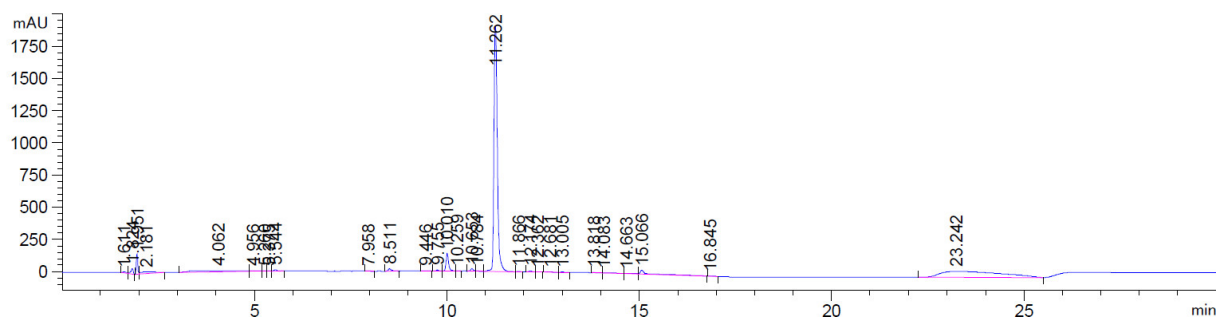


Figure S4: HPLC chromatogram of NHS-4-IPA within the collection wavelength of 254 nm obtained at 298 K, by an Agilent ZORBAX RX-C₁₈ column (100 × 4.6 mm, 3.5 μm pore size) using a 0 – 100% linear gradient over 15 min with a flow rate of 1 mL.min⁻¹.

¹H-NMR spectra of NHS esters

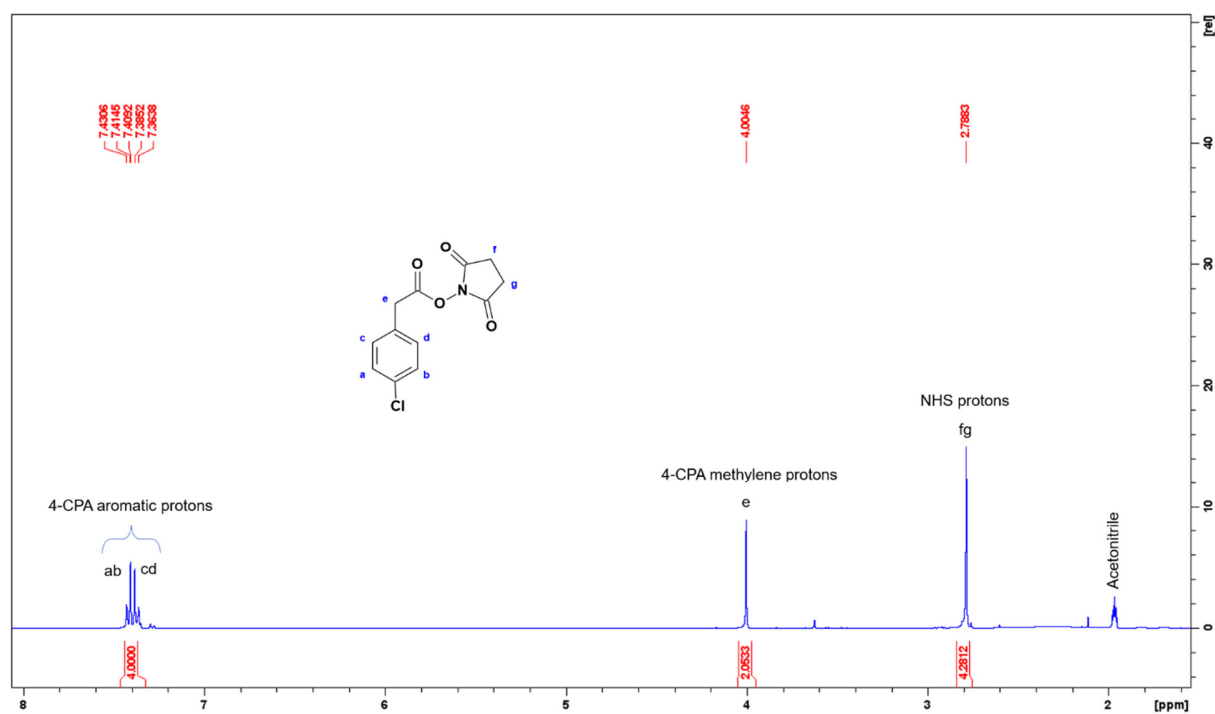


Figure S5: ¹H-NMR spectrum of NHS-4-CPA in CD₃CN obtained at 298 K. Inset: structure of NHS-4-CPA with proton labelling system.

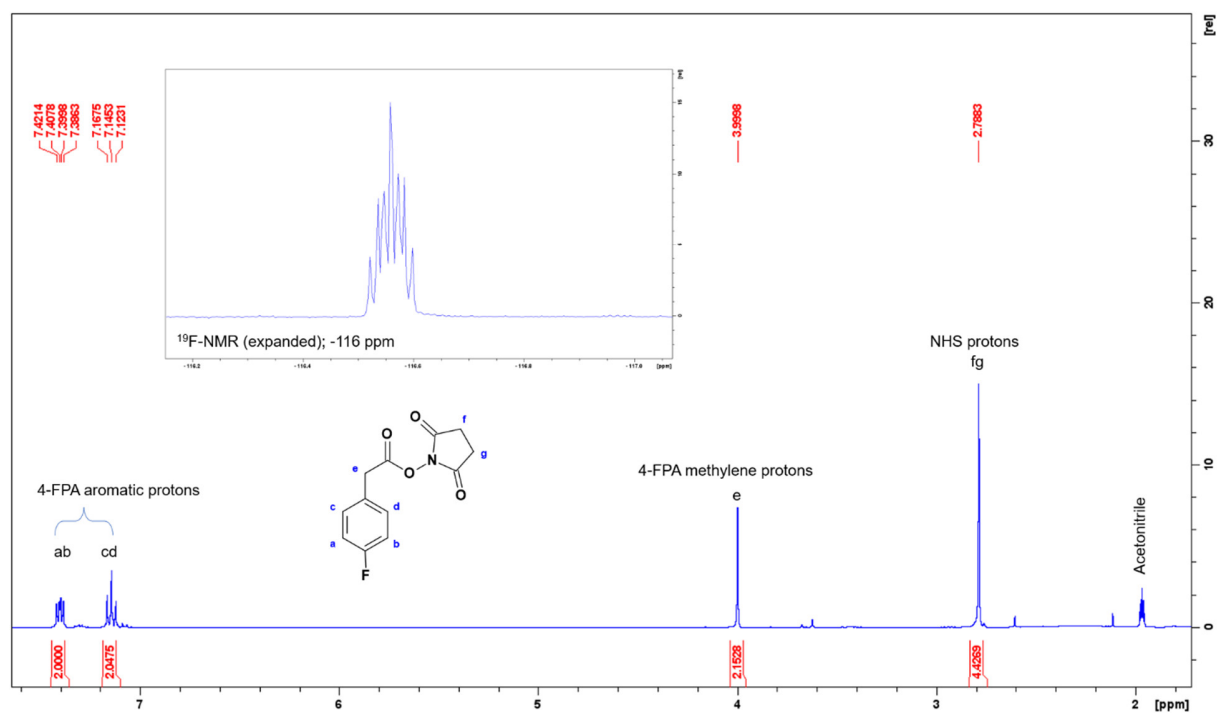


Figure S6: ^1H -NMR spectrum of NHS-4-FPA in CD_3CN obtained at 298 K. Inset: expanded ^{19}F -NMR and structure of NHS-4-FPA with proton labelling system.

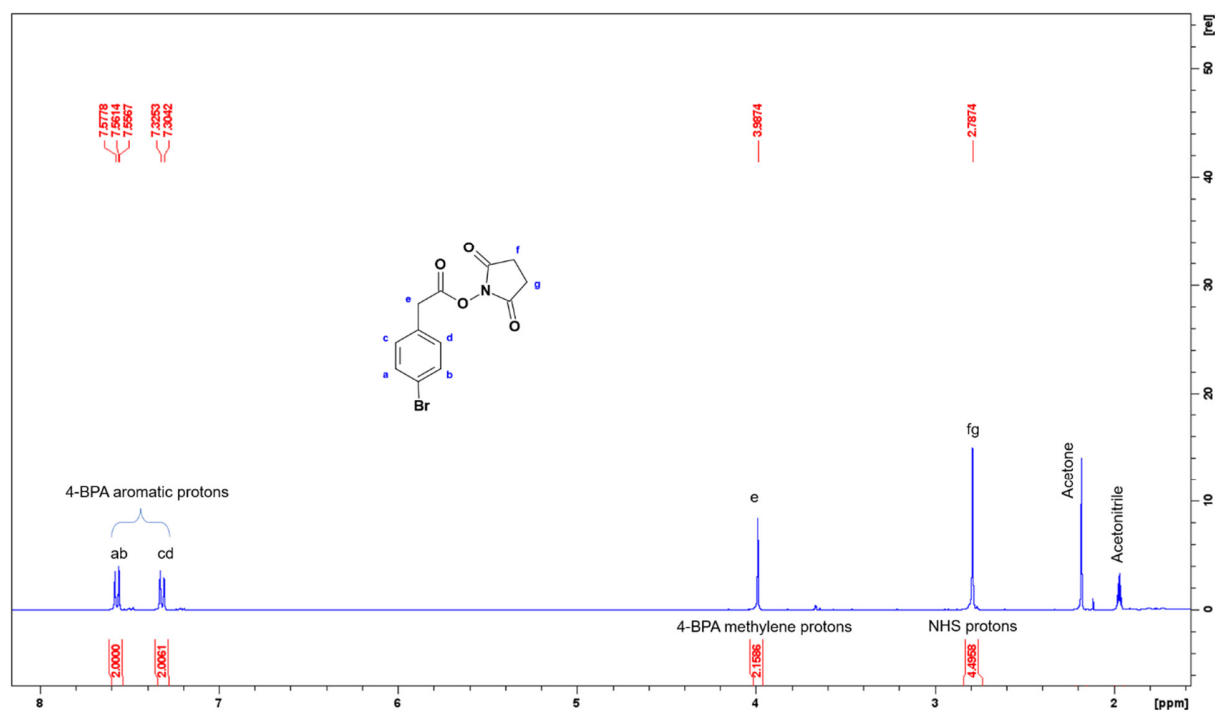


Figure S7: ^1H -NMR spectrum of NHS-4-BPA in CD_3CN obtained at 298 K. Inset: structure of NHS-4-BPA with proton labelling system.

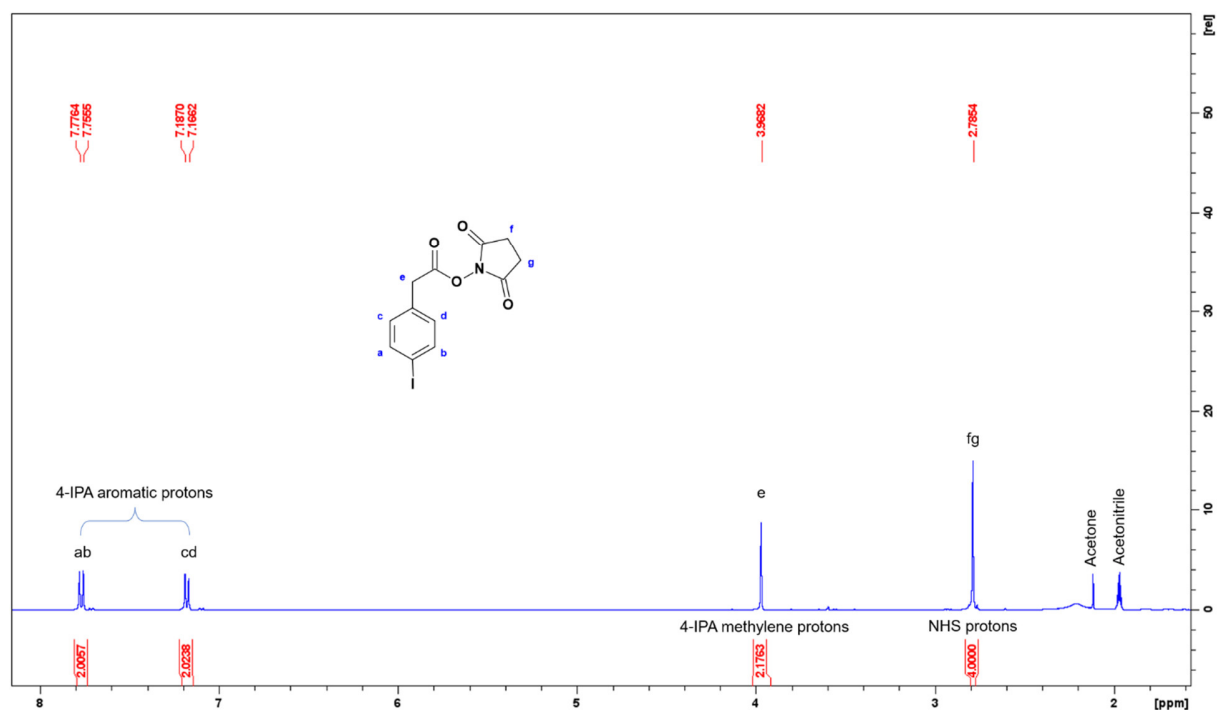


Figure S8: ^1H -NMR spectrum of NHS-4-IPA in CD_3CN obtained at 298 K. Inset: structure of NHS-4-IPA with proton labelling system.

ESI-MS spectra of NHS esters

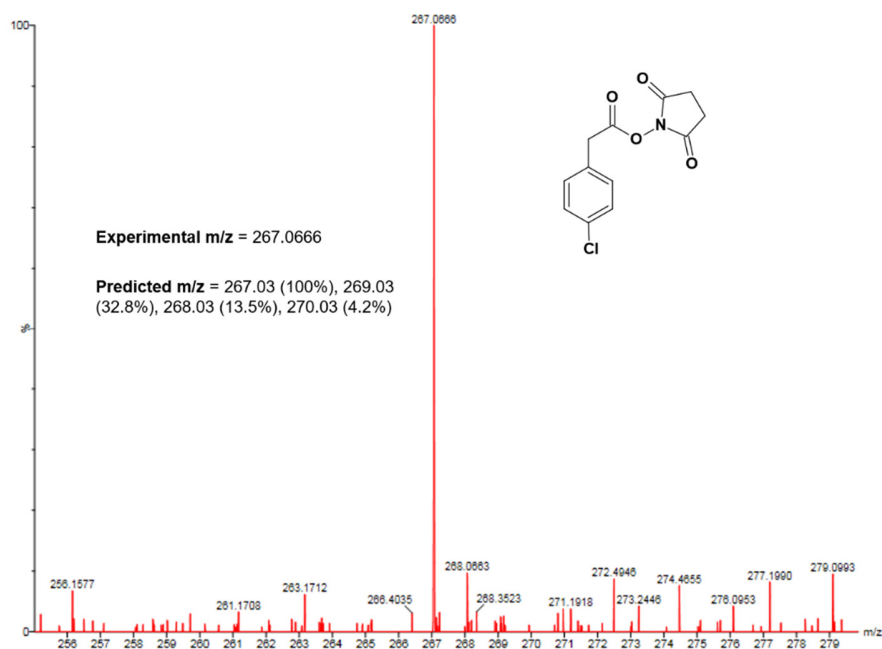


Figure S9: ESI-MS spectrum of NHS-4-CPA obtained at 298 K, using a Waters SYNAPT G2-Si quadrupole time-of-flight (QTOF) HDMS. Inset: structure of NHS-4-CPA.

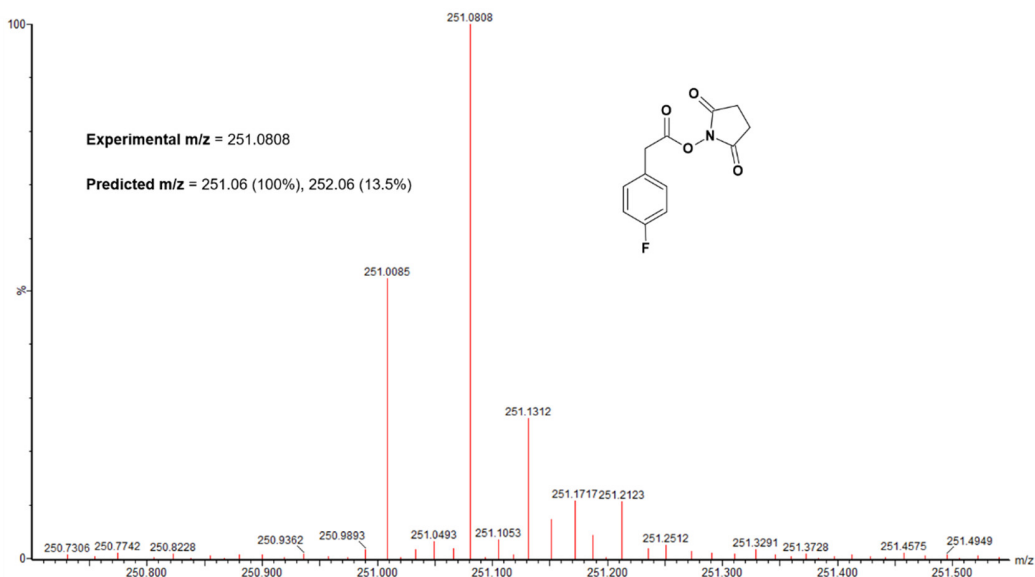


Figure S10: ESI-MS spectrum of NHS-4-FPA obtained at 298 K, using a Waters SYNAPT G2-Si quadrupole time-of-flight (QTOF) HDMS. Inset: structure of NHS-4-FPA.

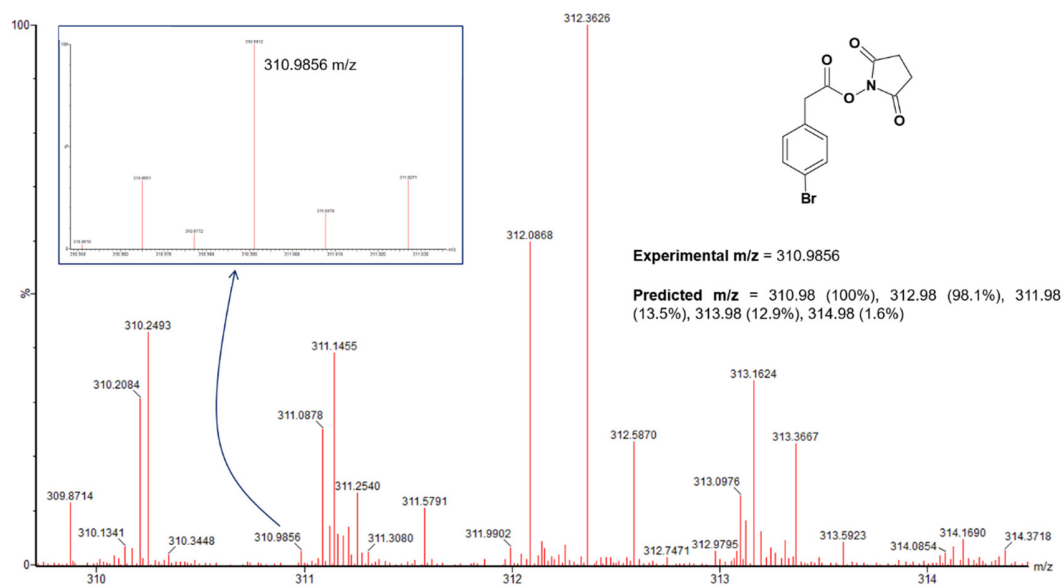


Figure S11: ESI-MS spectrum of NHS-4-BPA obtained at 298 K, using a Waters SYNAPT G2-Si quadrupole time-of-flight (QTOF) HDMS. Inset: structure of NHS-4-BPA.

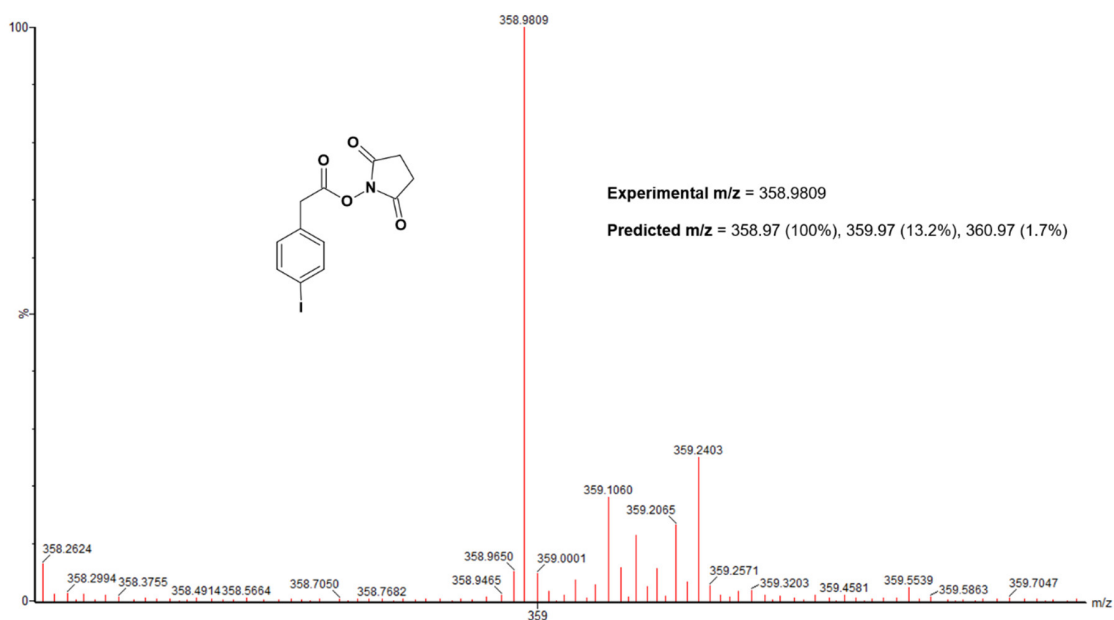


Figure S12: ESI-MS spectrum of NHS-4-IPA obtained at 298 K, using a Waters SYNAPT G2-Si quadrupole time-of-flight (QTOF) HDMS. Inset: structure of NHS-4-IPA.

HPLC chromatograms of platinum(IV) complexes, 1 – 8

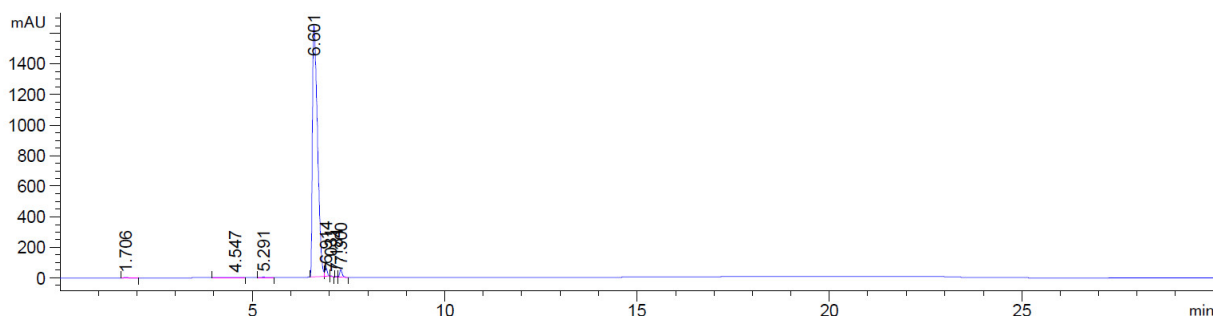


Figure S13: HPLC chromatogram of **1** within the collection wavelength of 254 nm obtained at 298 K, by a Phenomenex Onyx™ Monolithic C₁₈-reverse phase column (100 × 4.6 mm, 5 μm pore size) using a 0 – 100% linear gradient over 15 min with a flow rate of 1 mL.min⁻¹.

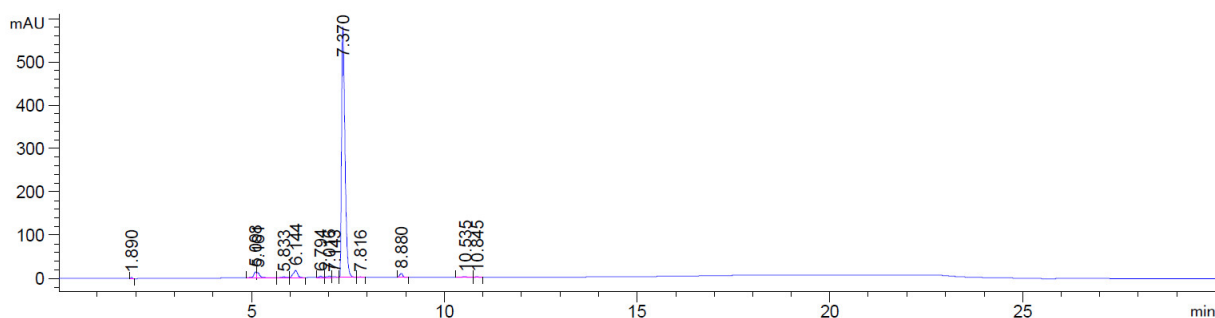


Figure S14: HPLC chromatogram of **2** within the collection wavelength of 254 nm obtained at 298 K, by a Phenomenex Onyx™ Monolithic C₁₈-reverse phase column (100 × 4.6 mm, 5 μm pore size) using a 0 – 100% linear gradient over 15 min with a flow rate of 1 mL.min⁻¹.

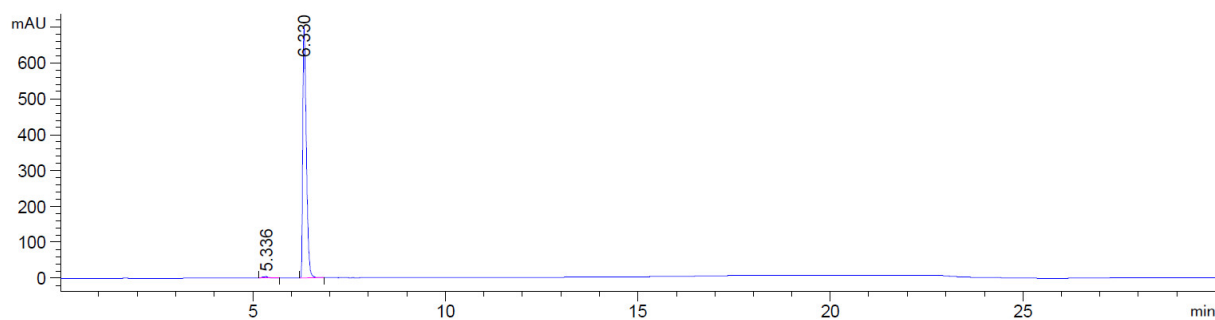


Figure S15: HPLC chromatogram of **3** within the collection wavelength of 254 nm obtained at 298 K, by a Phenomenex Onyx™ Monolithic C₁₈-reverse phase column (100 × 4.6 mm, 5 μm pore size) using a 0 – 100% linear gradient over 15 min with a flow rate of 1 mL.min⁻¹.

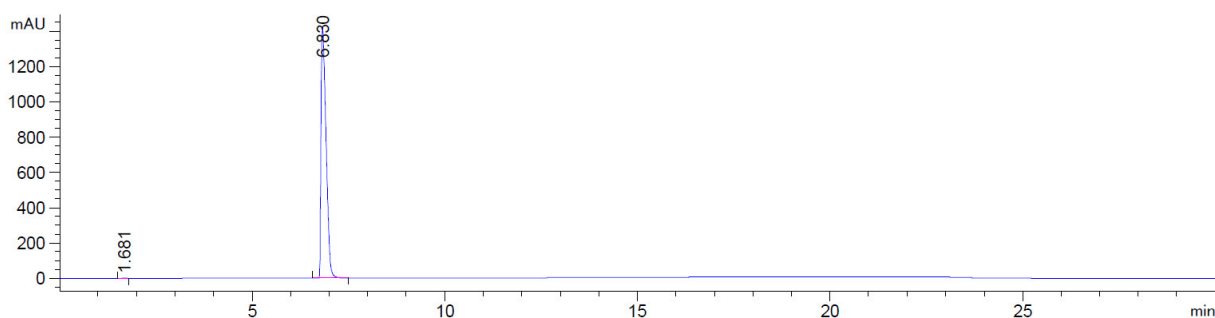


Figure S16: HPLC chromatogram of **4** within the collection wavelength of 254 nm obtained at 298 K, by a Phenomenex Onyx™ Monolithic C₁₈-reverse phase column (100 × 4.6 mm, 5 μm pore size) using a 0 – 100% linear gradient over 15 min with a flow rate of 1 mL.min⁻¹.

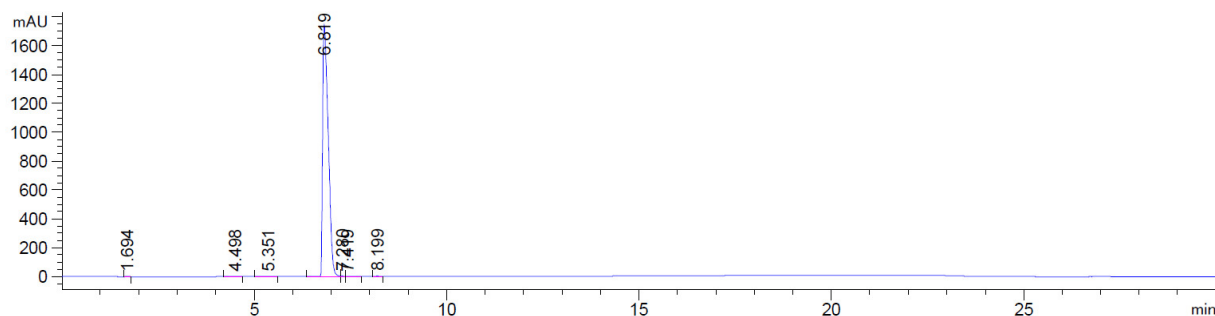


Figure S17: HPLC chromatogram of **5** within the collection wavelength of 254 nm obtained at 298 K, by a Phenomenx Onyx™ Monolithic C₁₈-reverse phase column (100 × 4.6 mm, 5 μm pore size) using a 0 – 100% linear gradient over 15 min with a flow rate of 1 mL.min⁻¹.

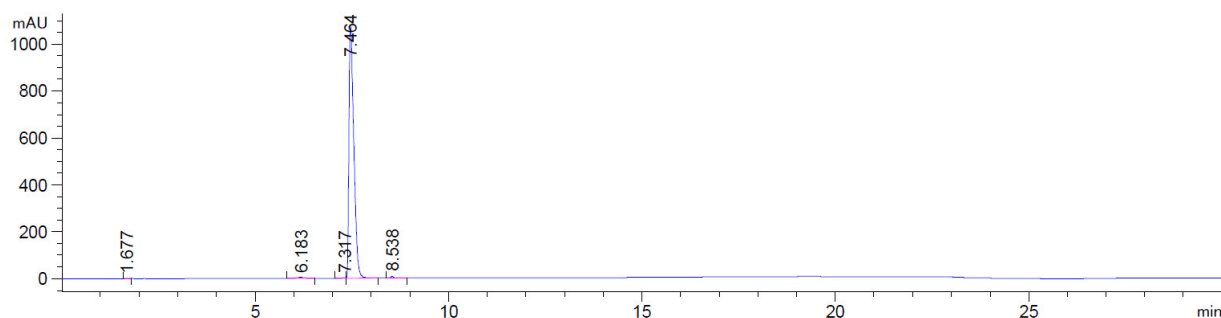


Figure S18: HPLC chromatogram of **6** within the collection wavelength of 254 nm obtained at 298 K, by a Phenomenx Onyx™ Monolithic C₁₈-reverse phase column (100 × 4.6 mm, 5 μm pore size) using a 0 – 100% linear gradient over 15 min with a flow rate of 1 mL.min⁻¹.

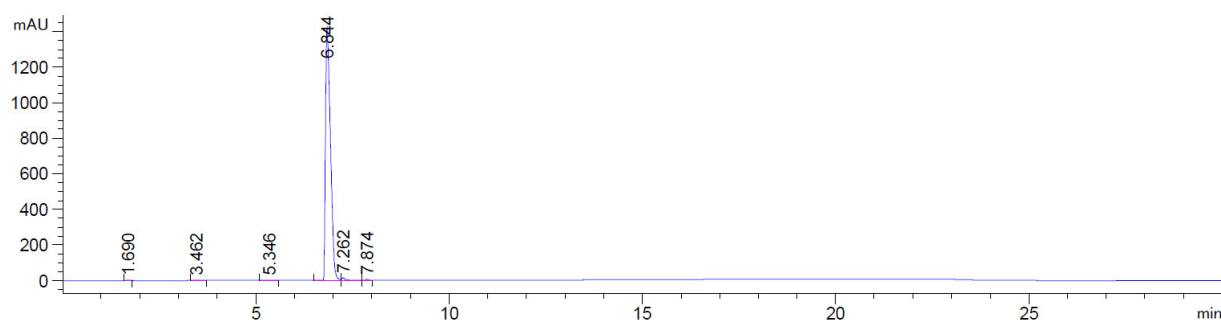


Figure S19: HPLC chromatogram of **7** within the collection wavelength of 254 nm obtained at 298 K, by a Phenomenx Onyx™ Monolithic C₁₈-reverse phase column (100 × 4.6 mm, 5 μm pore size) using a 0 – 100% linear gradient over 15 min with a flow rate of 1 mL.min⁻¹.

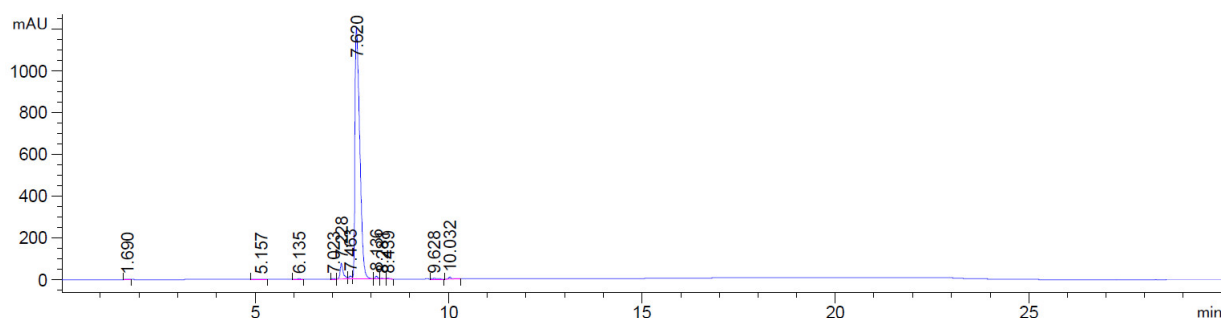


Figure S20: HPLC chromatogram of **8** within the collection wavelength of 254 nm obtained at 298 K, by a Phenomenx Onyx™ Monolithic C₁₈-reverse phase column (100 × 4.6 mm, 5 μm pore size) using a 0 – 100% linear gradient over 15 min with a flow rate of 1 mL.min⁻¹.

^1H -NMR, 2D-COSY and ^1H - ^{195}Pt -HMQC spectra of 1 – 8

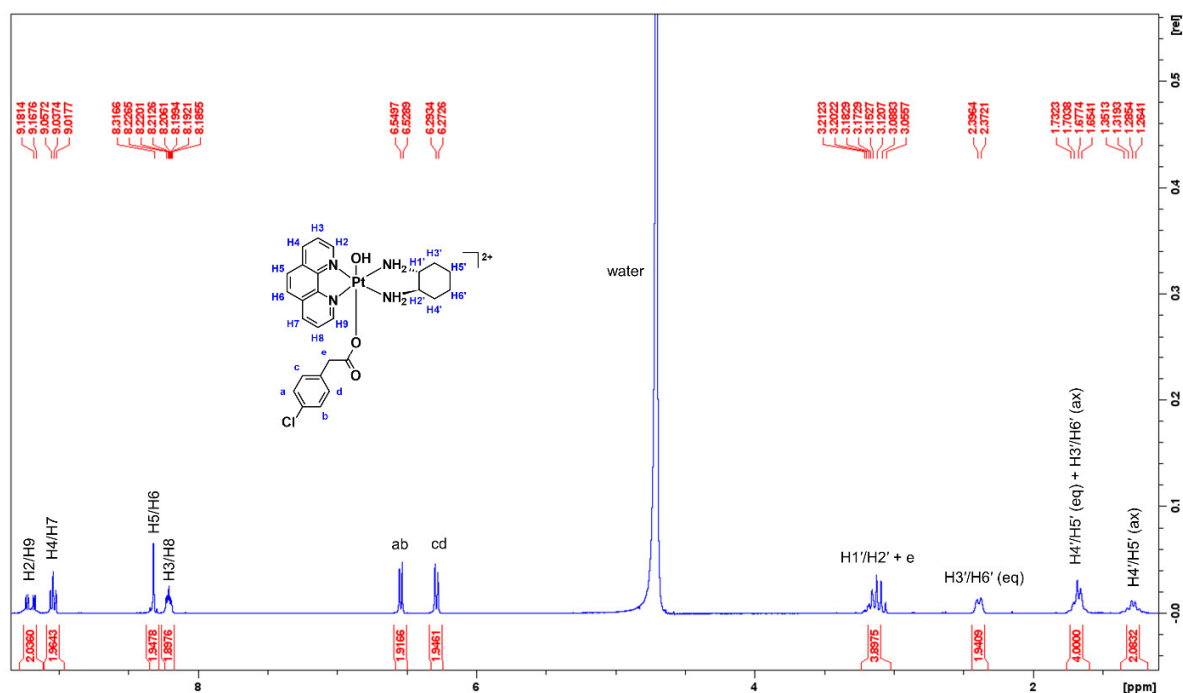


Figure S21: ^1H -NMR spectrum of **1** in D_2O obtained at 298 K Inset: structure of **1** with proton labelling system.

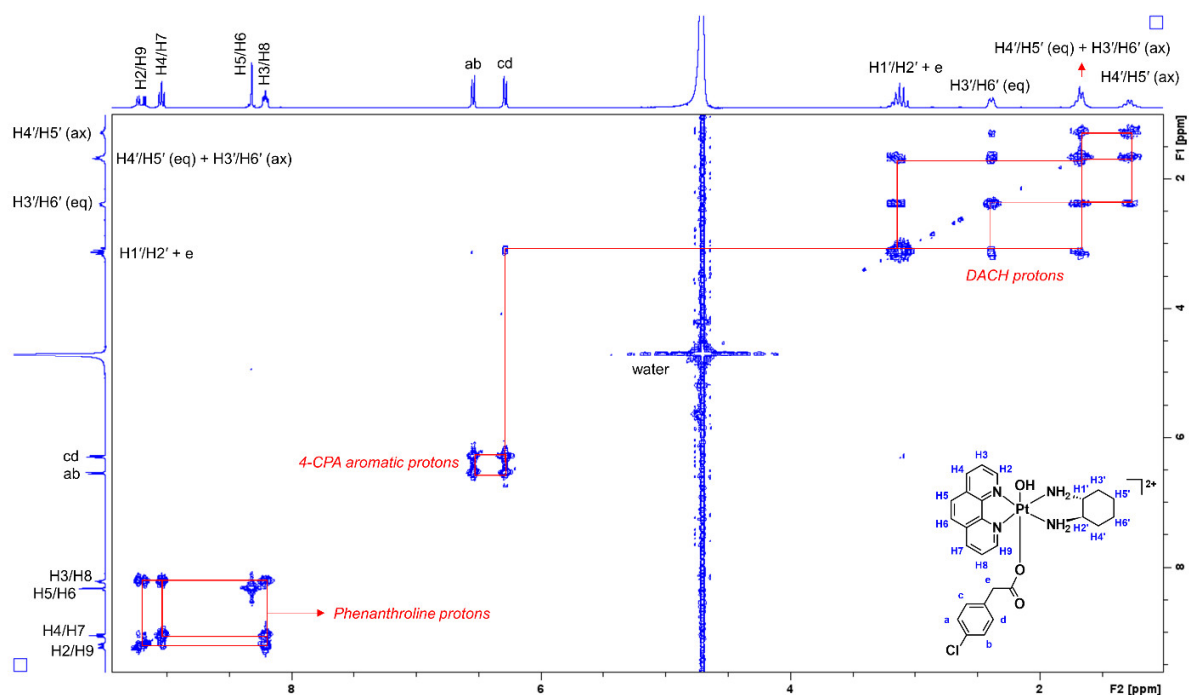


Figure S22: 2D-COSY spectrum of **1** in D₂O obtained at 298 K. Inset: structure of **1** with proton labelling system.

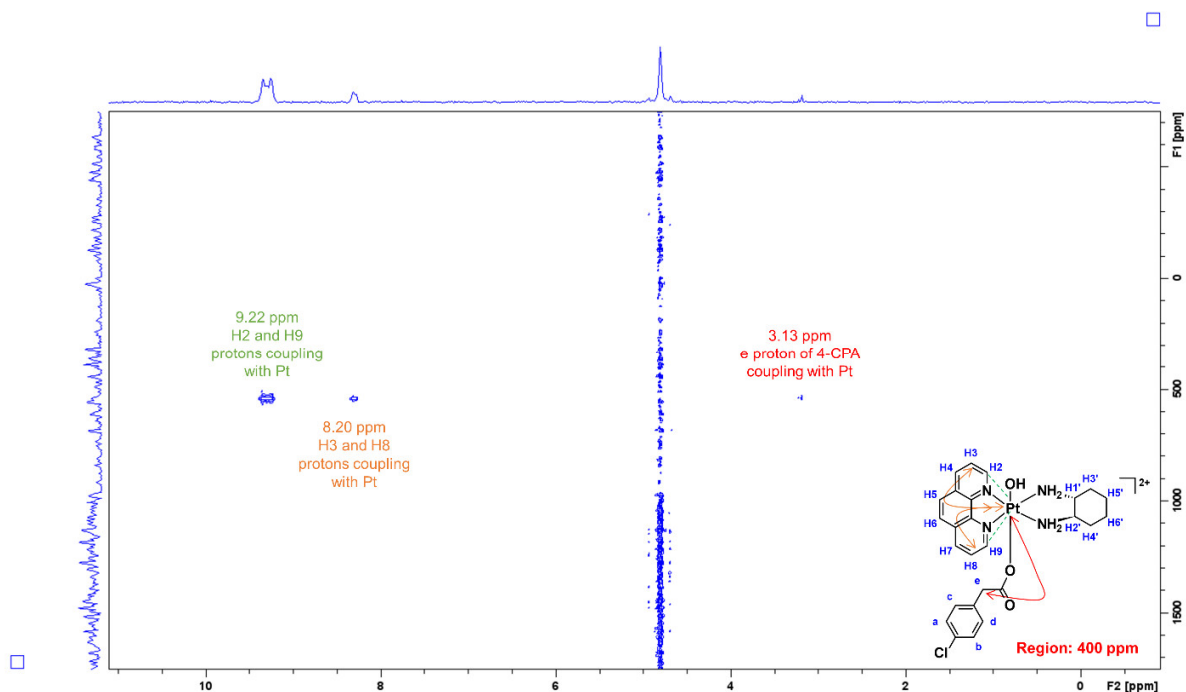


Figure S23: ^1H - ^{195}Pt -HMQC spectrum of **1** in D_2O obtained at 298 K. Region: 400 ppm. Inset: structure of **1** with proton labelling system and arrows that indicate coupling.

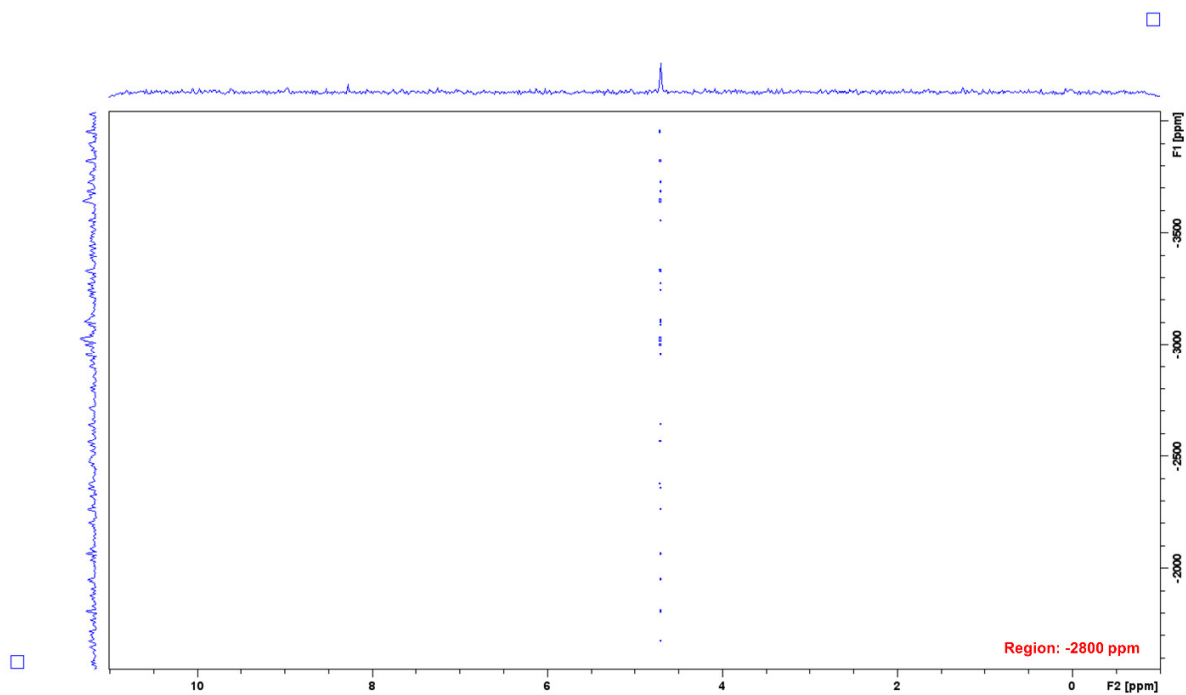


Figure S24: ^1H - ^{195}Pt -HMQC spectrum of **1** in D_2O obtained at 298 K. Region: -2800 ppm. Absence of platinum(II) resonance.

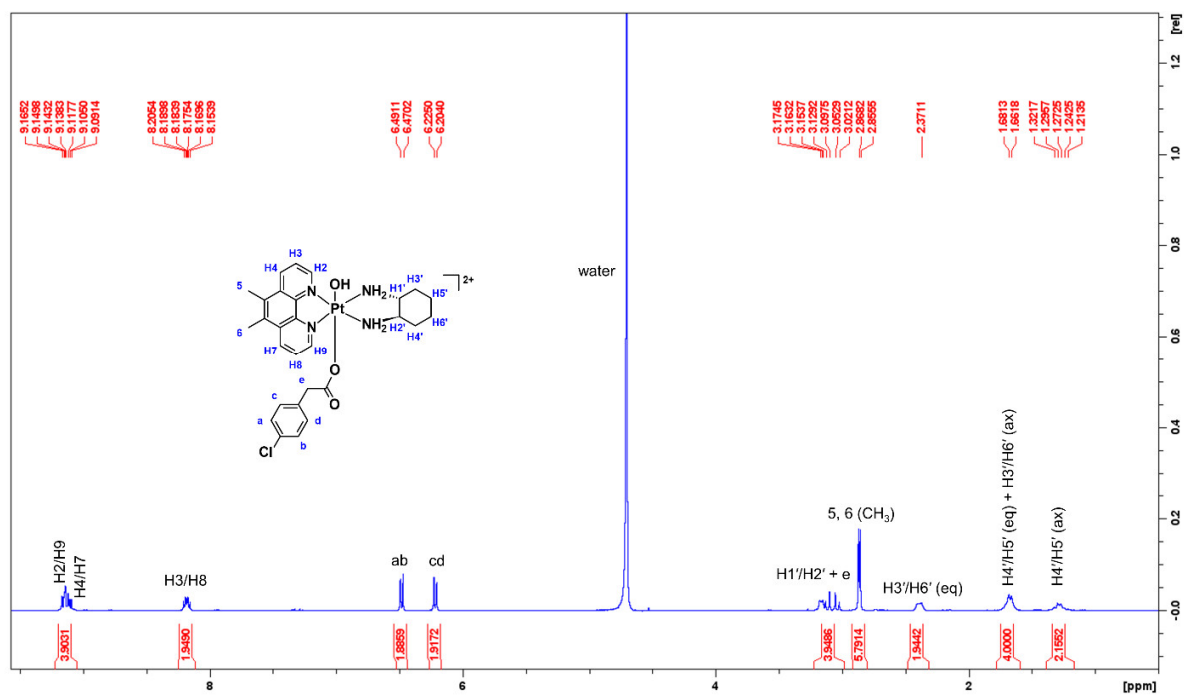


Figure S25: ^1H -NMR spectrum of **2** in D_2O obtained at 298 K Inset: structure of **2** with proton labelling system.

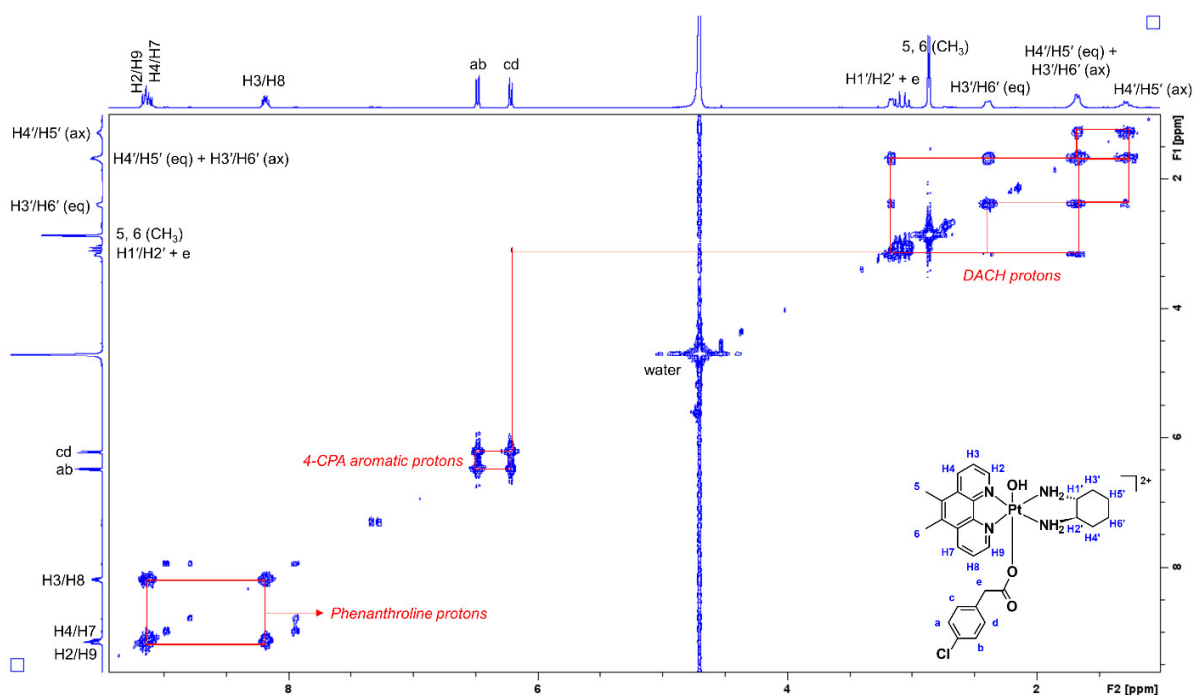


Figure S26: 2D-COSY spectrum of **2** in D₂O obtained at 298 K. Inset: structure of **2** with proton labelling system.

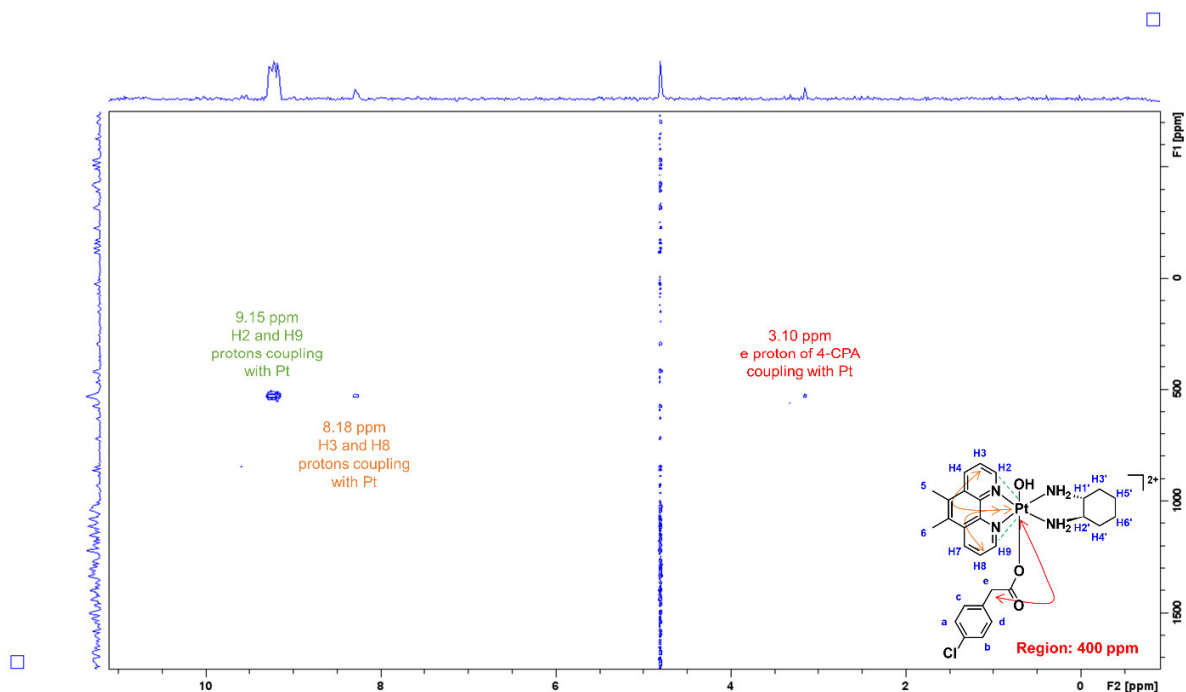


Figure S27: ^1H - ^{195}Pt -HMQC spectrum of **2** in D_2O obtained at 298 K. Region: 400 ppm. Inset: structure of **2** with proton labelling system and arrows that indicate coupling.

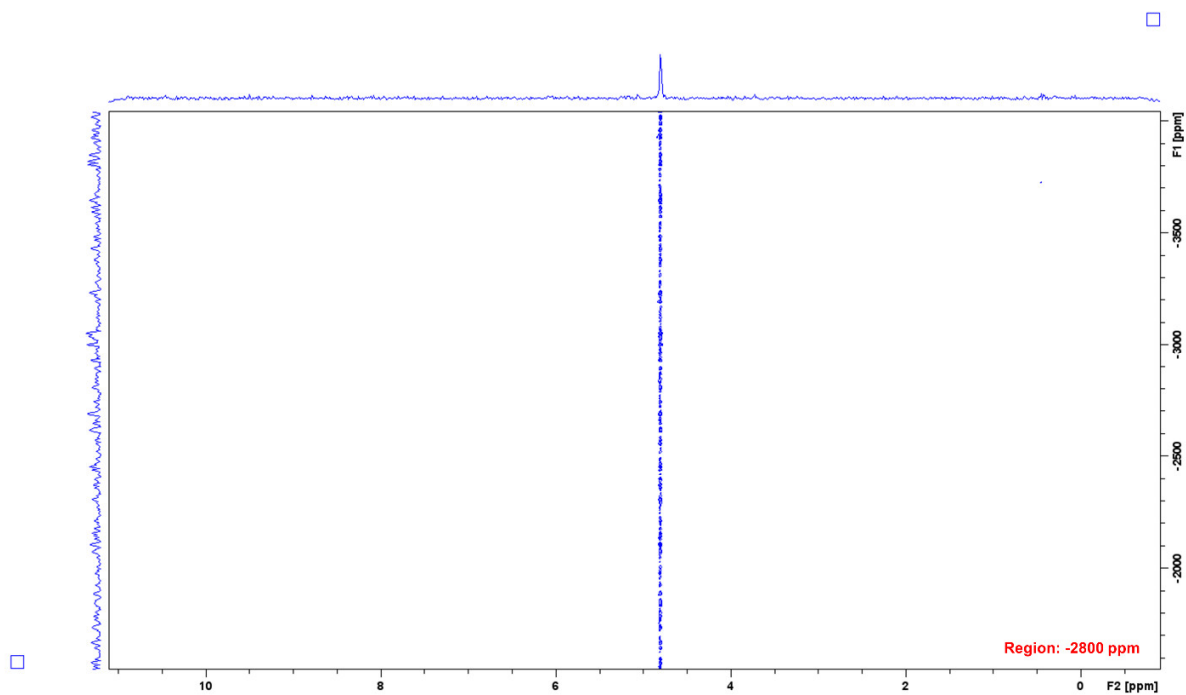


Figure S28: ^1H - ^{195}Pt -HMQC spectrum of **2** in D_2O obtained at 298 K. Region: -2800 ppm. Absence of platinum(II) resonance.

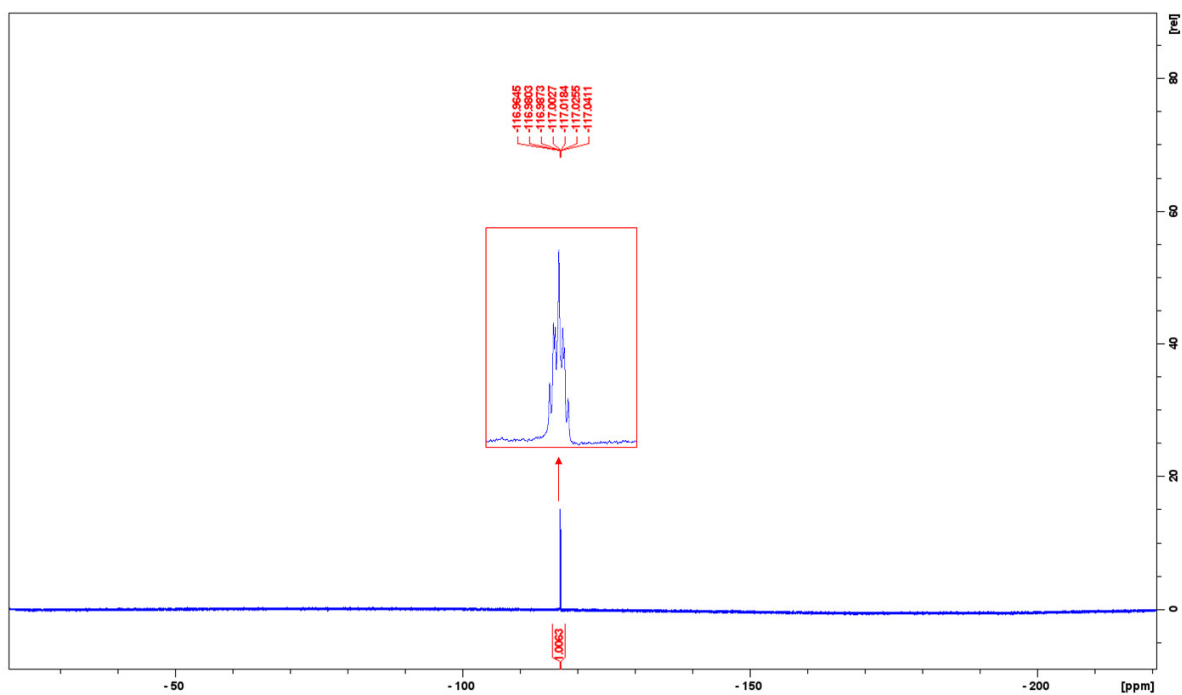


Figure S29: ^{19}F -NMR spectrum of **3** in D_2O obtained at 298 K.

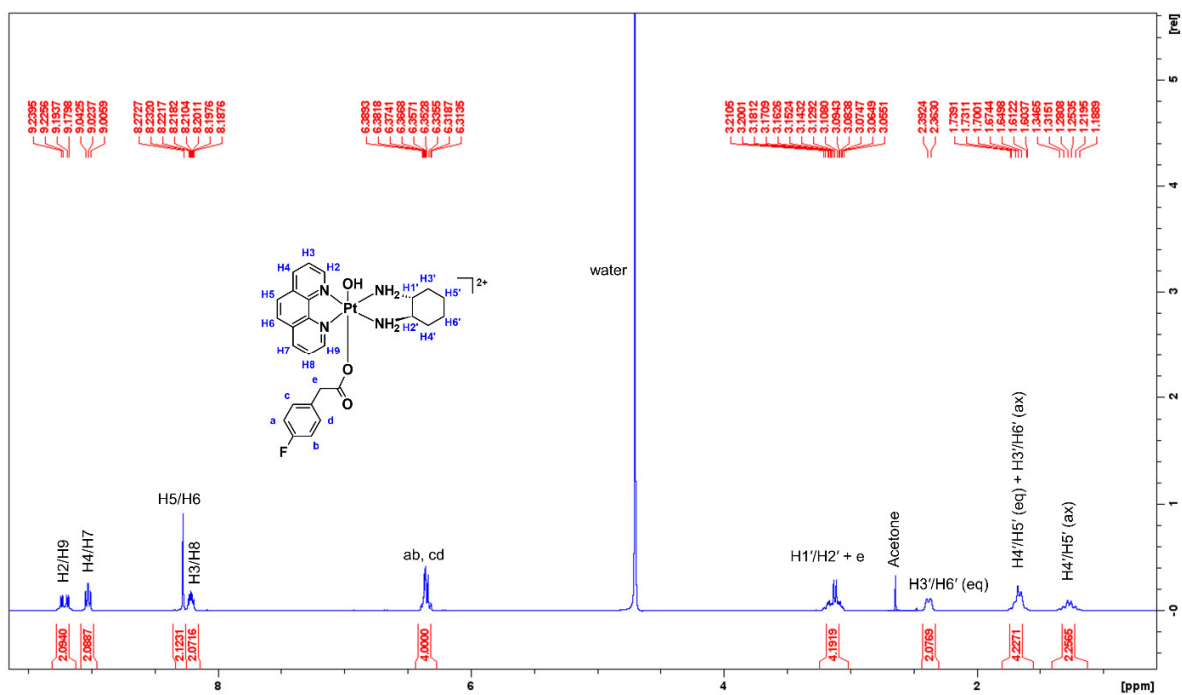


Figure S30: ^1H -NMR spectrum of **3** in D_2O obtained at 298 K Inset: structure of **3** with proton labelling system.

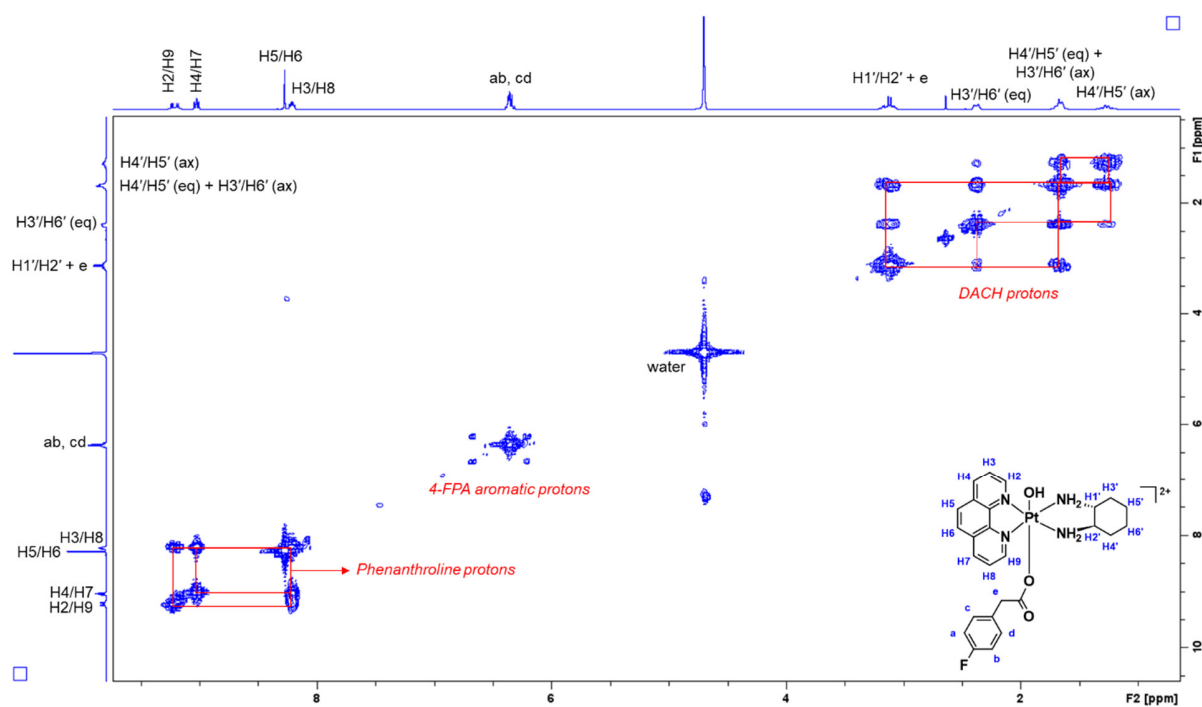


Figure S31: 2D-COSY spectrum of **3** in D₂O obtained at 298 K. Inset: structure of **3** with proton labelling system.

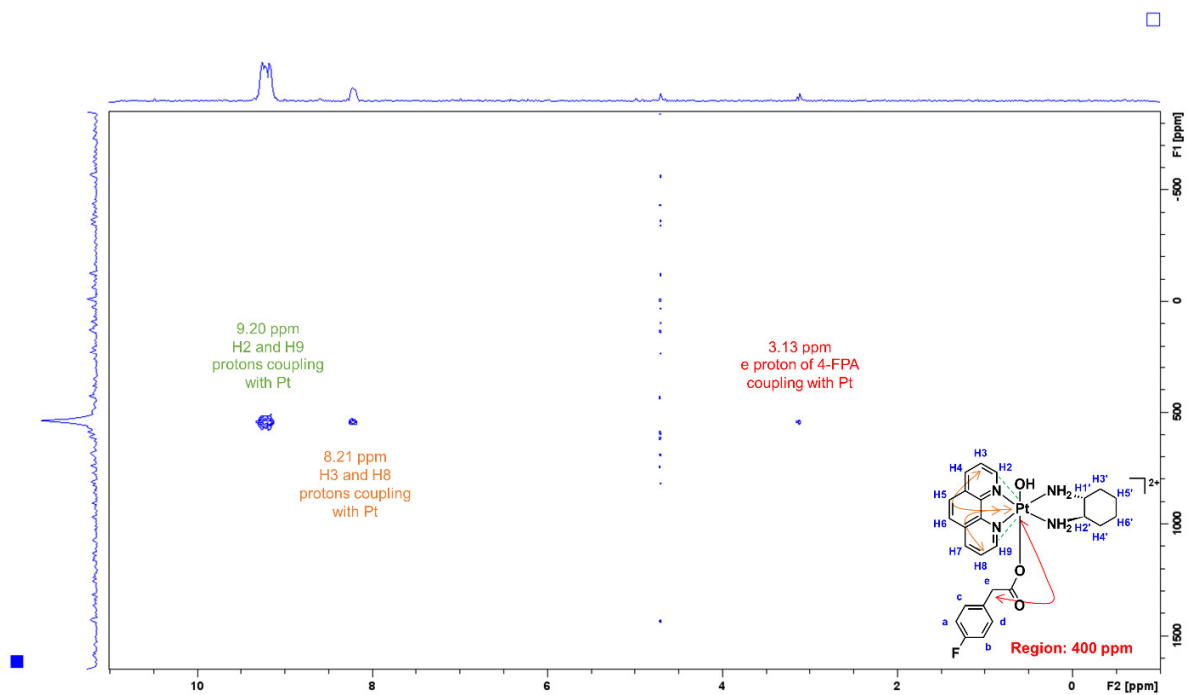


Figure S32: ^1H - ^{195}Pt -HMQC spectrum of **3** in D_2O obtained at 298 K. Region: 400 ppm. Inset: structure of **3** with proton labelling system and arrows that indicate coupling.

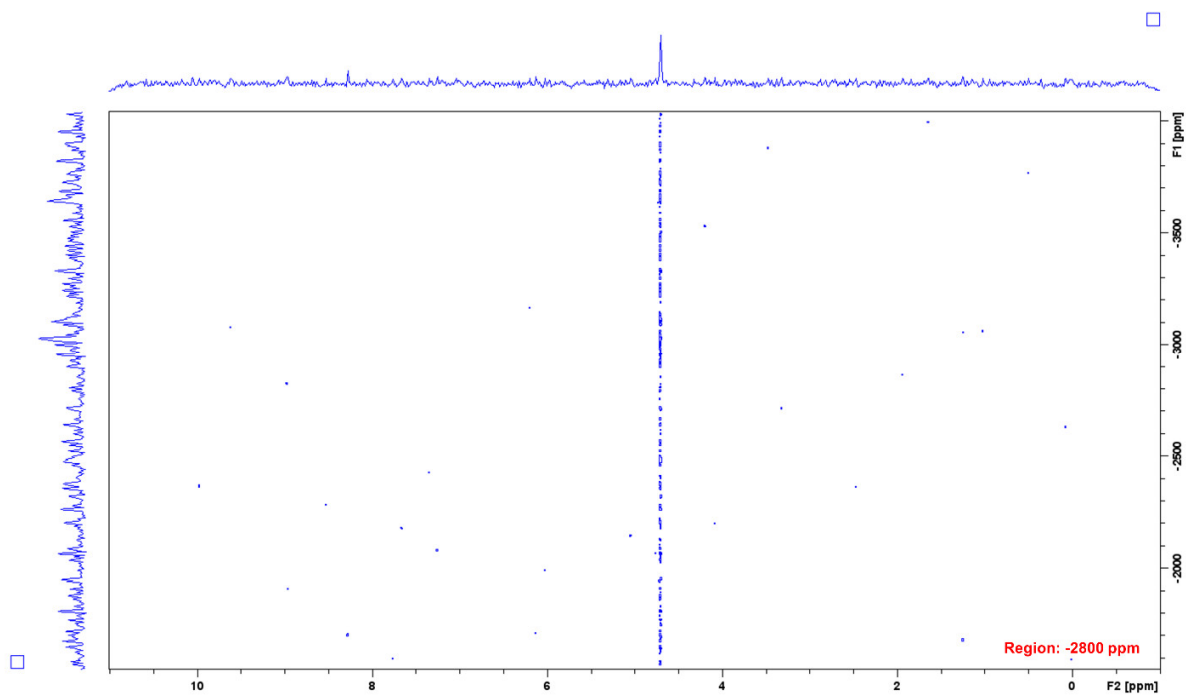


Figure S33: ^1H - ^{195}Pt -HMQC spectrum of **3** in D_2O obtained at 298 K. Region: -2800 ppm. Absence of platinum(II) resonance.

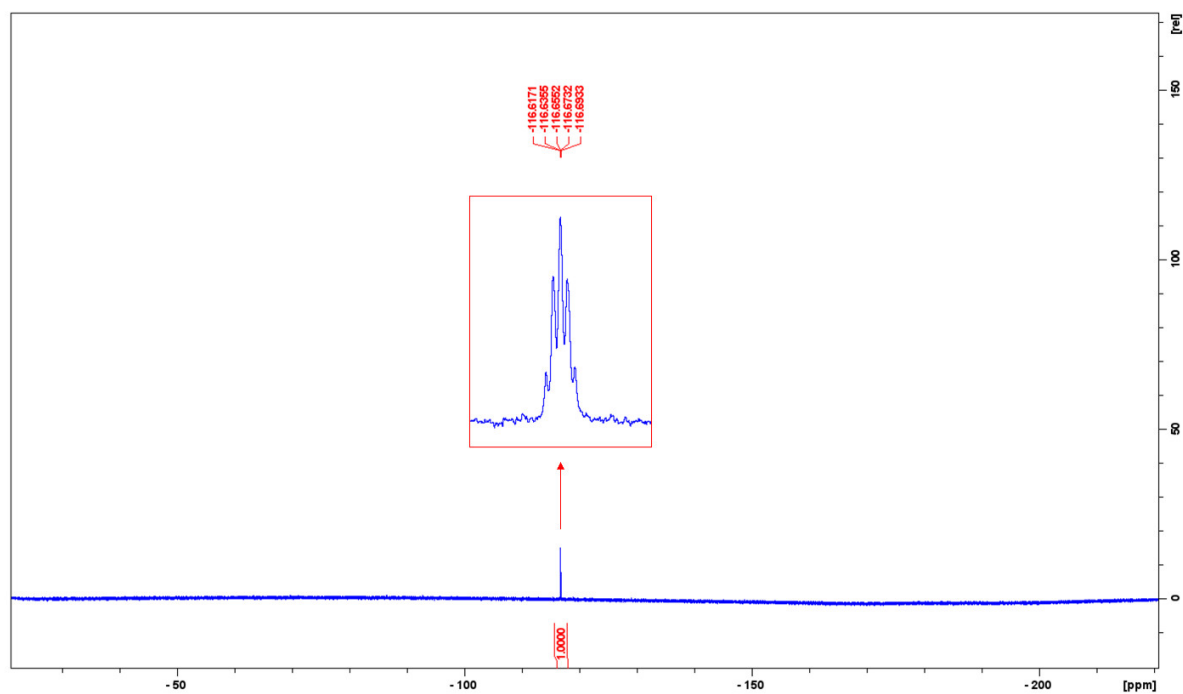


Figure S34: ^{19}F -NMR spectrum of **4** in D_2O obtained at 298 K.

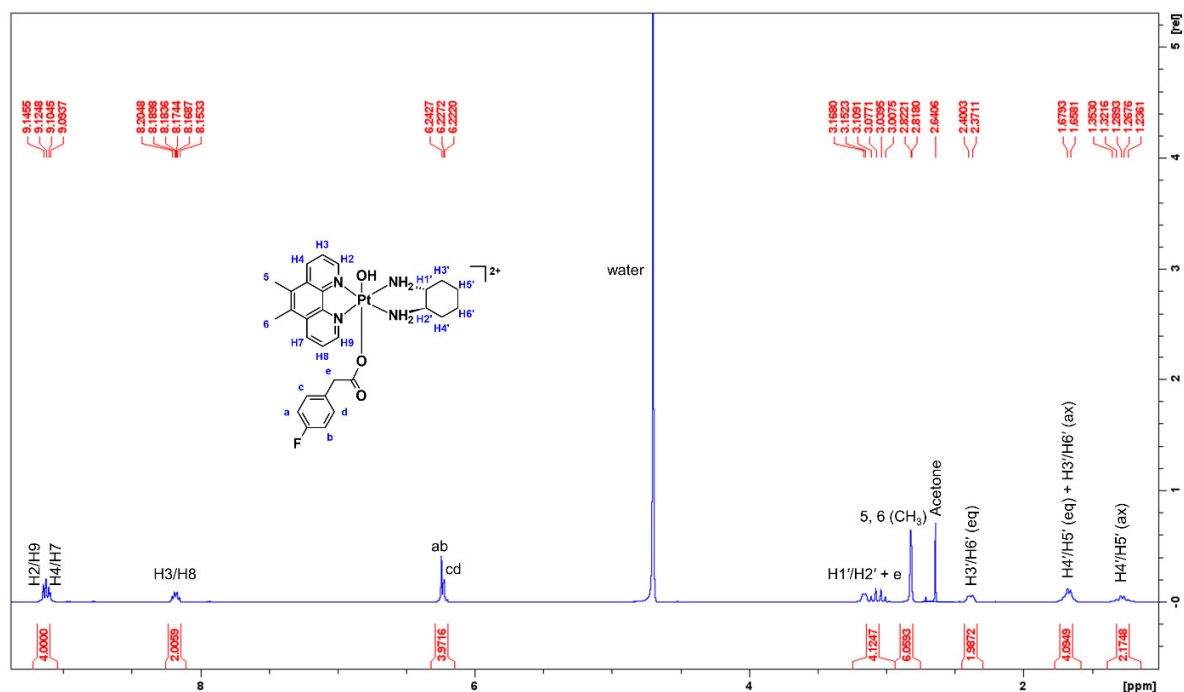


Figure S35: ¹H-NMR spectrum of **4** in D₂O obtained at 298 K Inset: structure of **4** with proton labelling system.

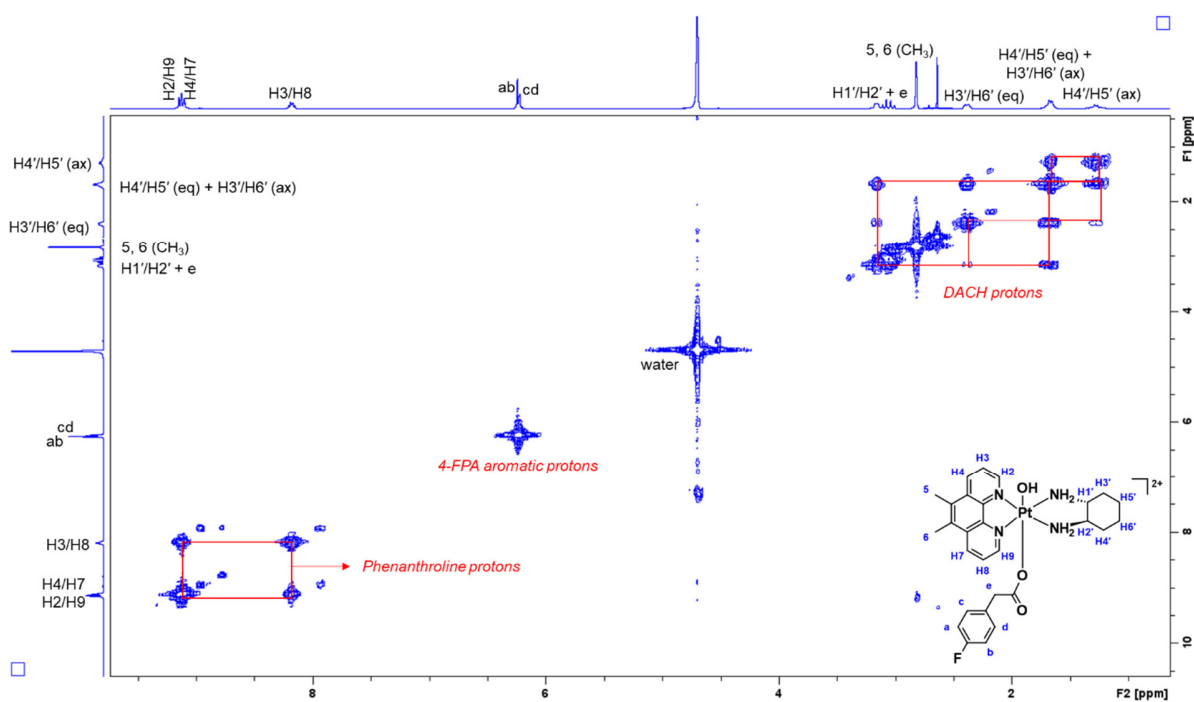


Figure S36: 2D-COSY spectrum of **4** in D₂O obtained at 298 K. Inset: structure of **4** with proton labelling system.

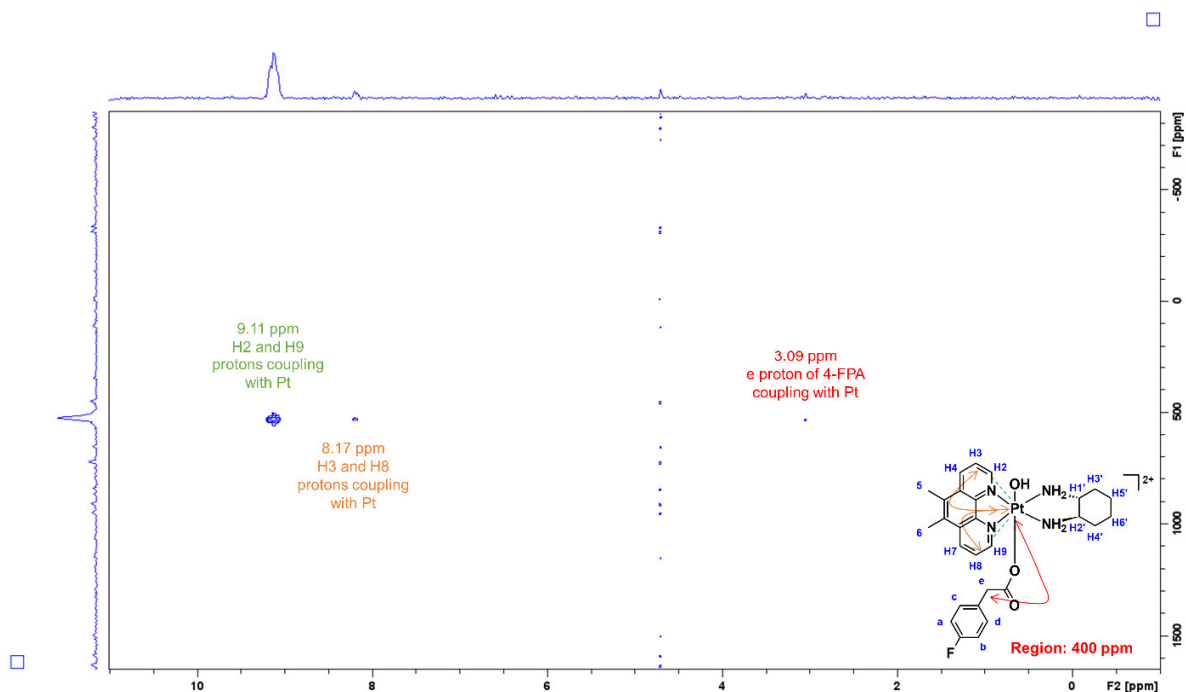


Figure S37: ^1H - ^{195}Pt -HMQC spectrum of **4** in D_2O obtained at 298 K. Region: 400 ppm. Inset: structure of **4** with proton labelling system and arrows that indicate coupling.

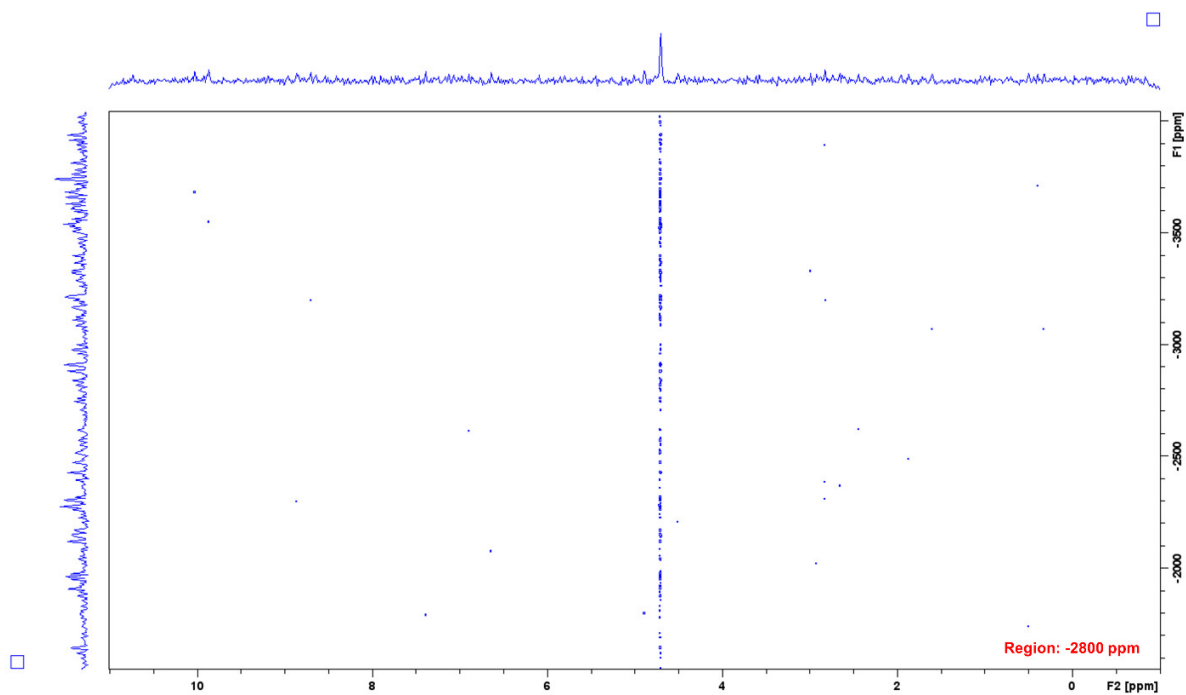


Figure S38: ^1H - ^{195}Pt -HMQC spectrum of **4** in D_2O obtained at 298 K. Region: -2800 ppm. Absence of platinum(II) resonance.

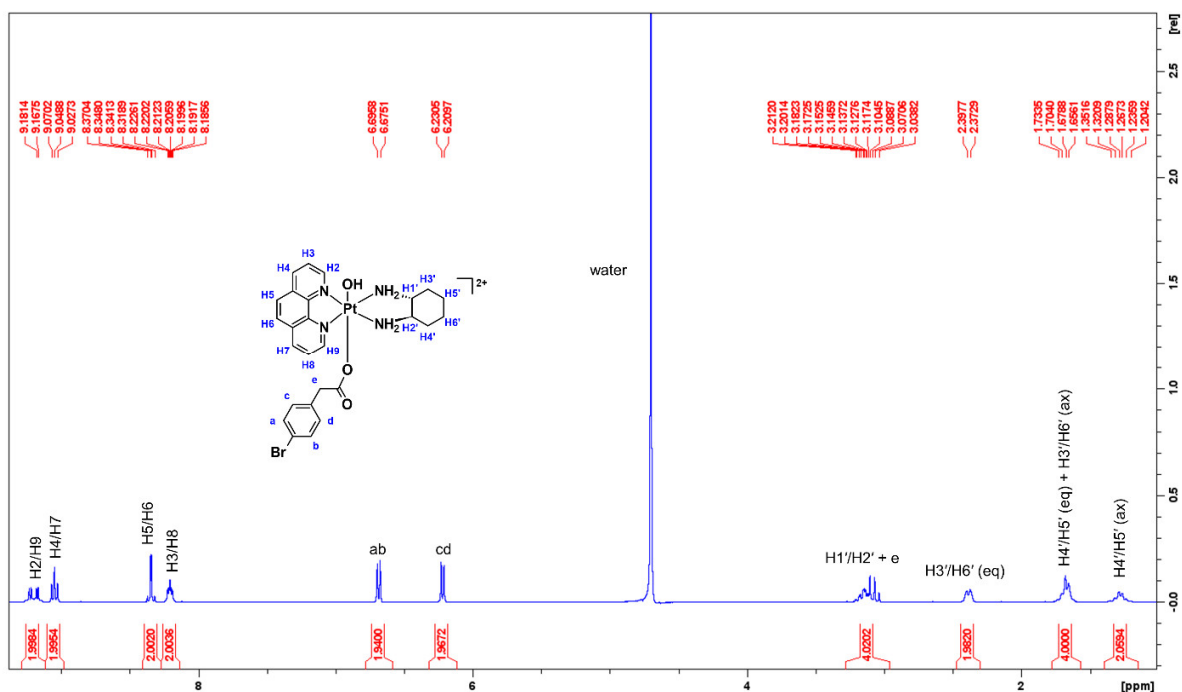


Figure S39: ^1H -NMR spectrum of **5** in D_2O obtained at 298 K Inset: structure of **5** with proton labelling system.

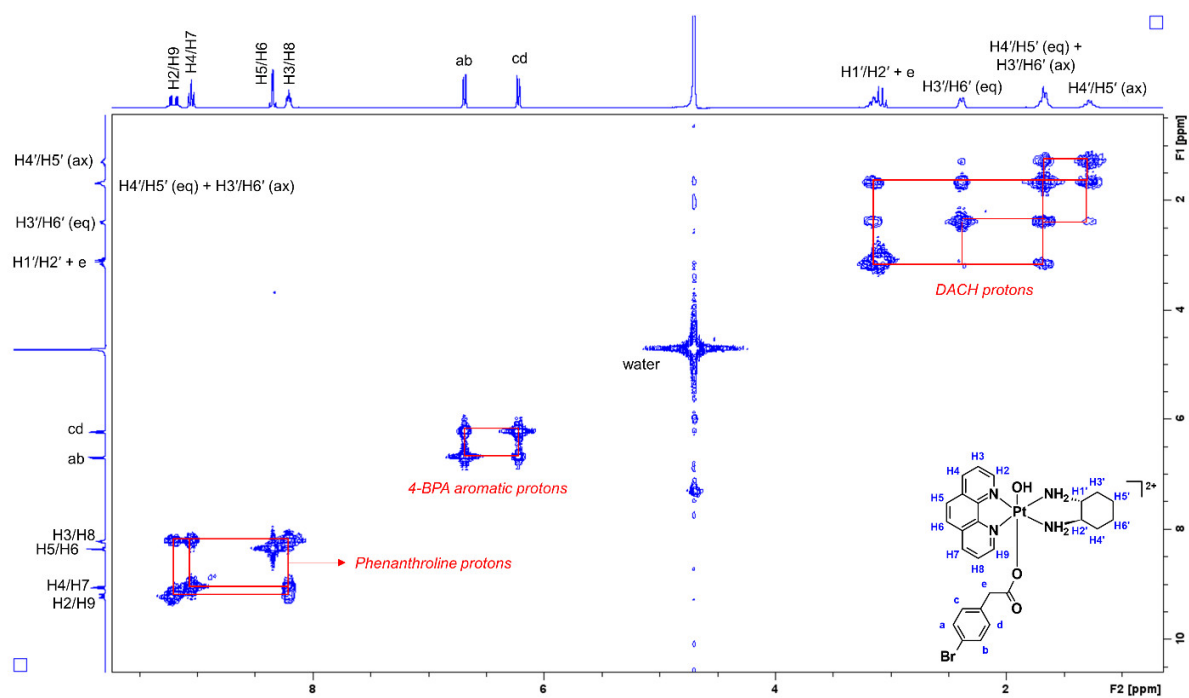


Figure S40: 2D-COSY spectrum of **5** in D₂O obtained at 298 K. Inset: structure of **5** with proton labelling system.

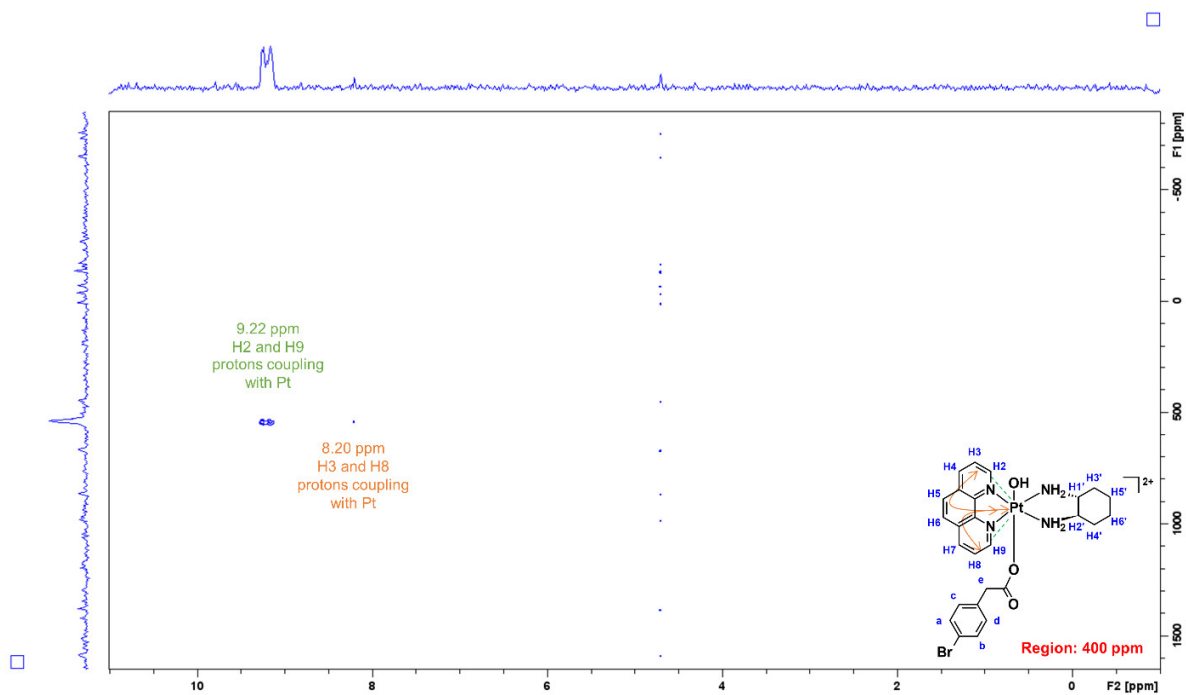


Figure S41: ^1H - ^{195}Pt -HMQC spectrum of **5** in D_2O obtained at 298 K. Region: 400 ppm. Inset: structure of **5** with proton labelling system and arrows that indicate coupling.

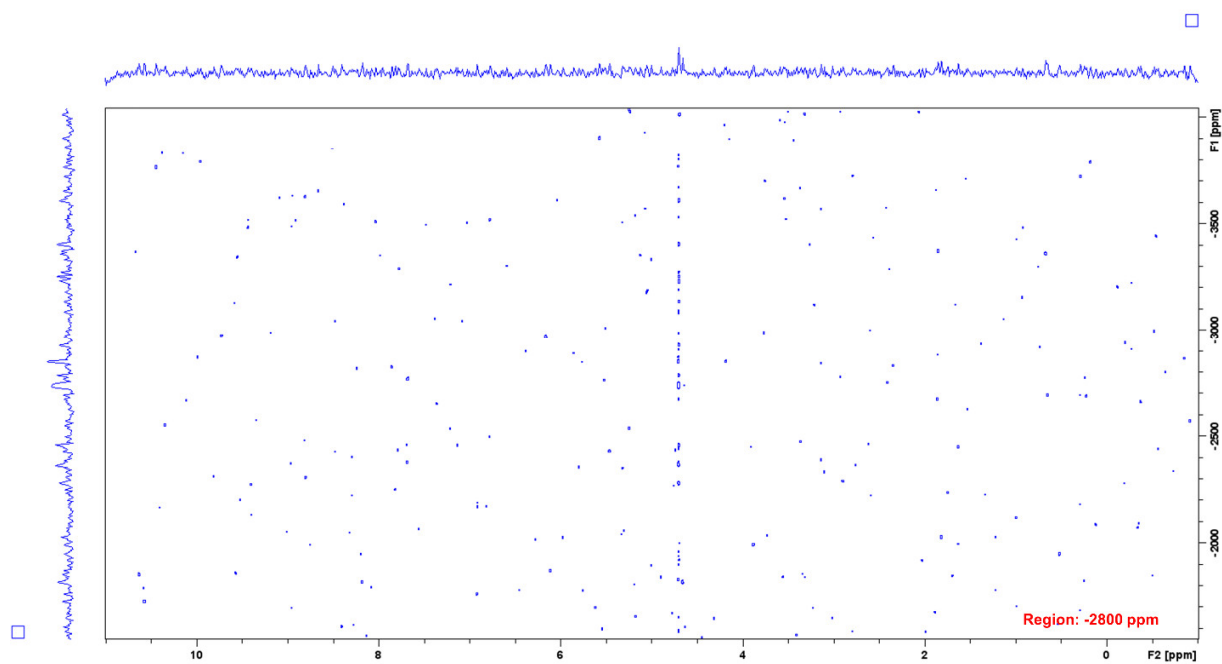


Figure S42: ^1H - ^{195}Pt -HMQC spectrum of **5** in D_2O obtained at 298 K. Region: -2800 ppm. Absence of platinum(II) resonance.

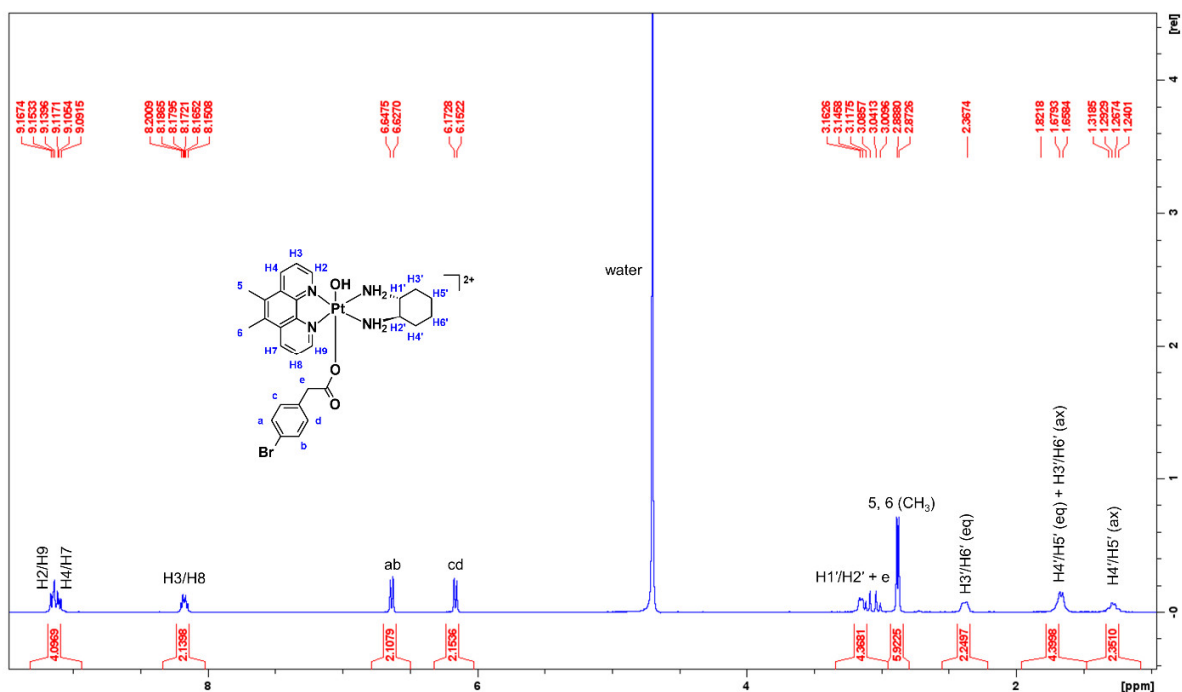


Figure S43: ^1H -NMR spectrum of **6** in D_2O obtained at 298 K Inset: structure of **6** with proton labelling system.

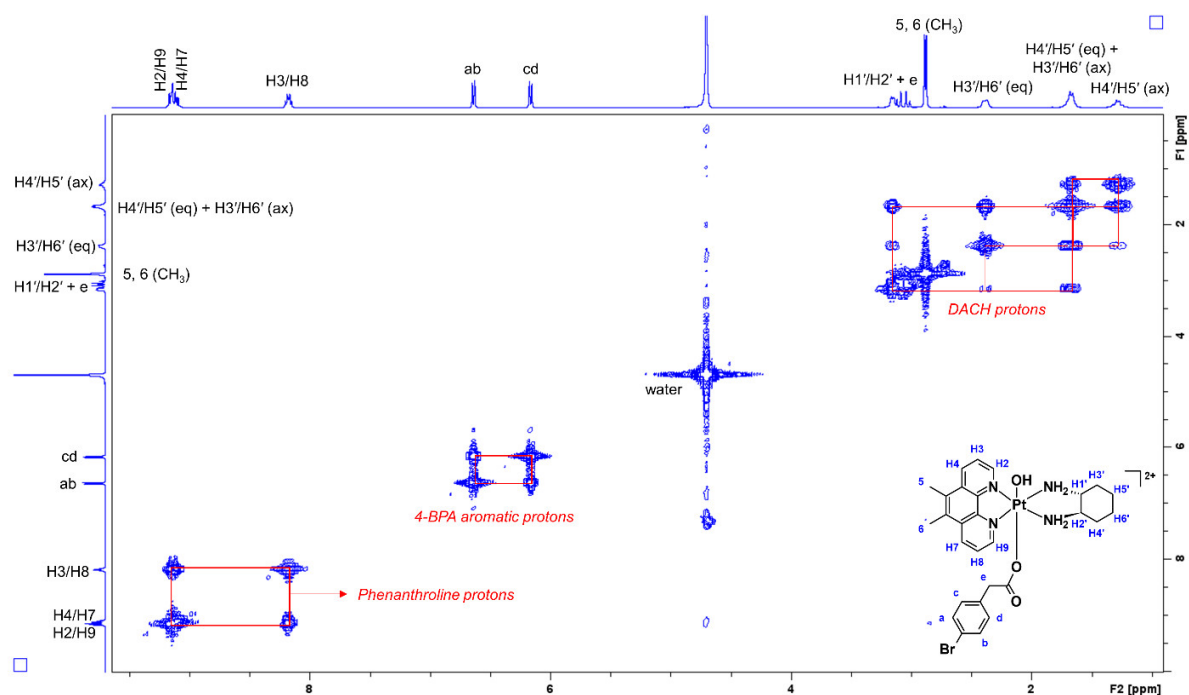


Figure S44: 2D-COSY spectrum of **6** in D₂O obtained at 298 K. Inset: structure of **6** with proton labelling system.

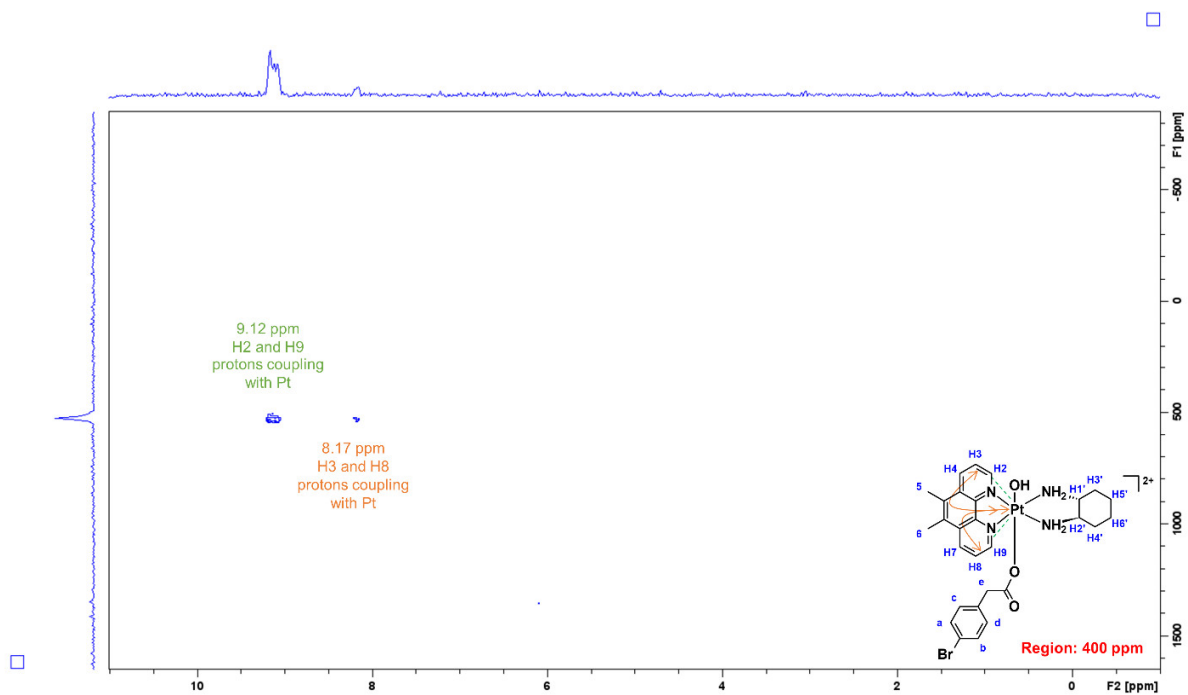


Figure S45: ^1H - ^{195}Pt -HMQC spectrum of **6** in D_2O obtained at 298 K. Region: 400 ppm. Inset: structure of **6** with proton labelling system and arrows that indicate coupling.

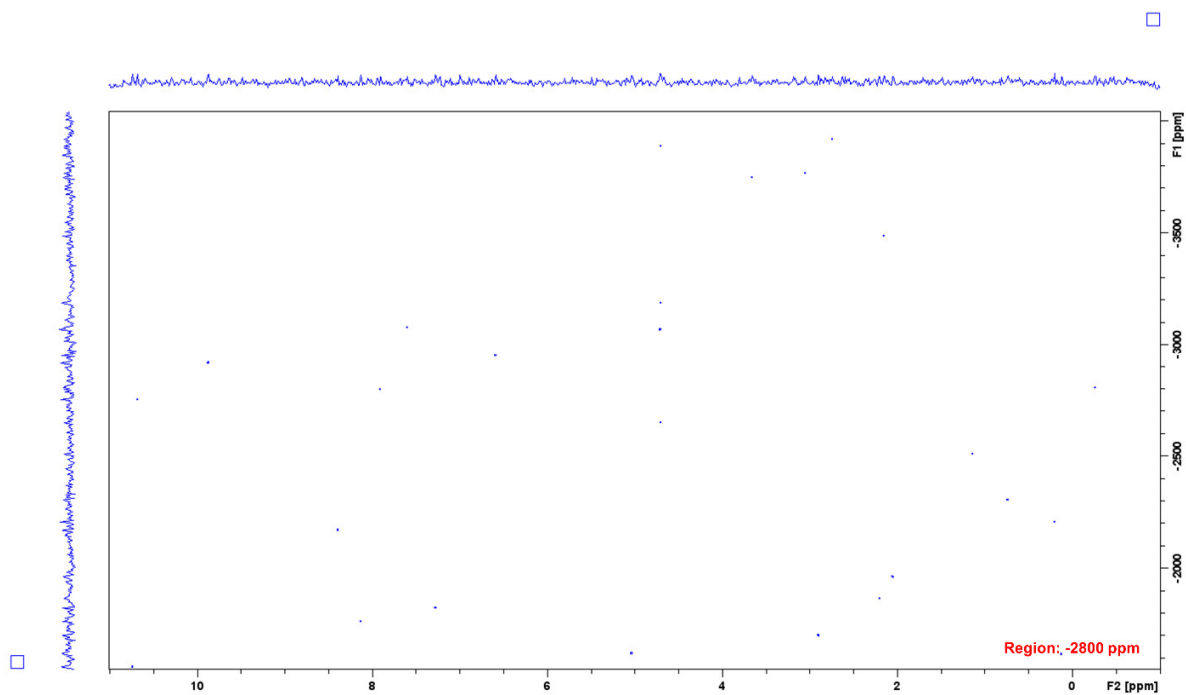


Figure S46: ^1H - ^{195}Pt -HMQC spectrum of **6** in D_2O obtained at 298 K. Region: -2800 ppm. Absence of platinum(II) resonance.

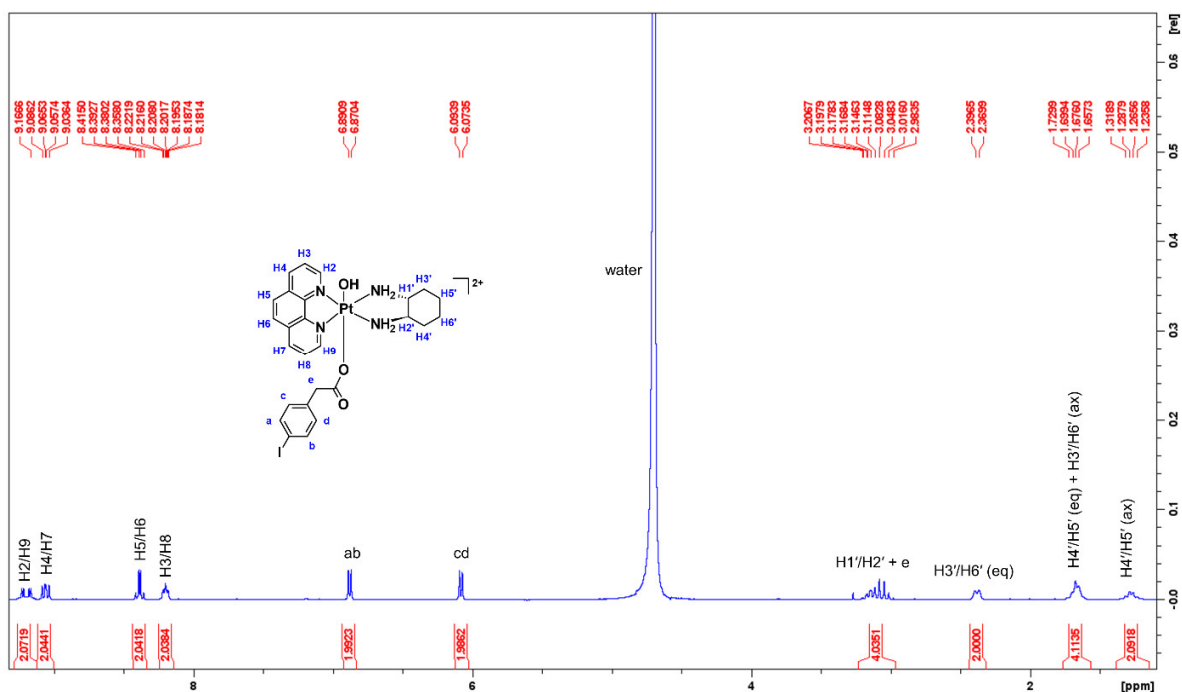


Figure S47: ^1H -NMR spectrum of **7** in D₂O obtained at 298 K Inset: structure of **7** with proton labelling system.

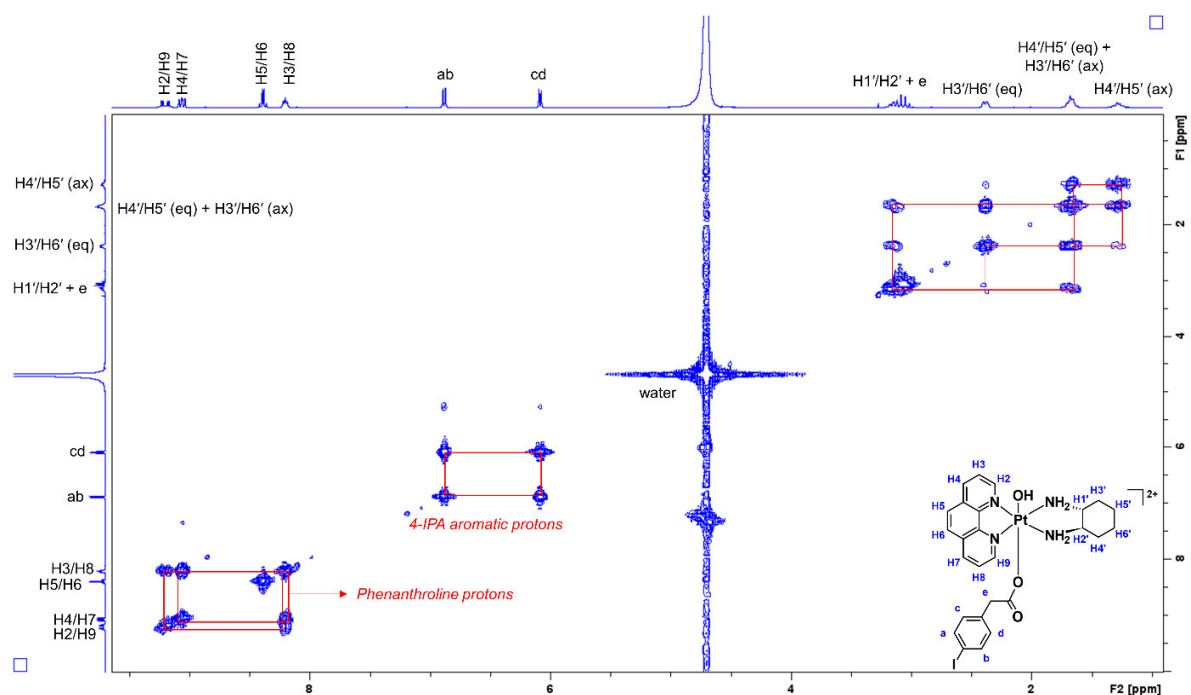


Figure S48: 2D-COSY spectrum of **7** in D₂O obtained at 298 K. Inset: structure of **7** with proton labelling system.

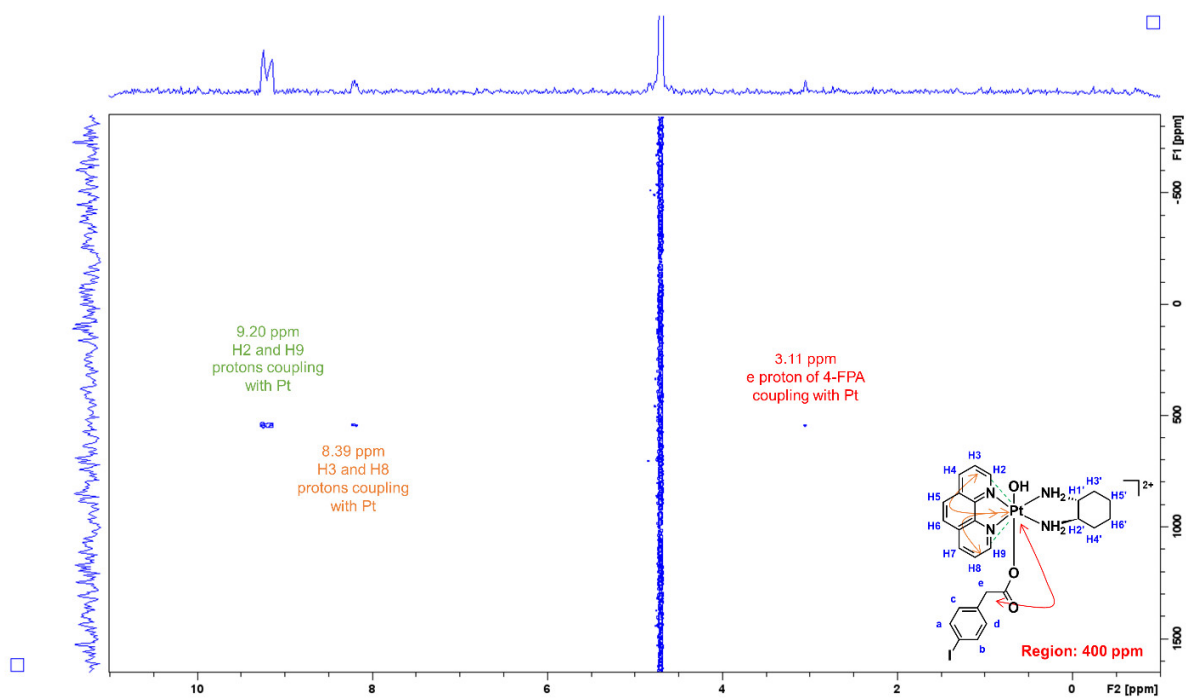


Figure S49: ^1H - ^{195}Pt -HMQC spectrum of **7** in D_2O obtained at 298 K. Region: 400 ppm. Inset: structure of **7** with proton labelling system and arrows that indicate coupling.

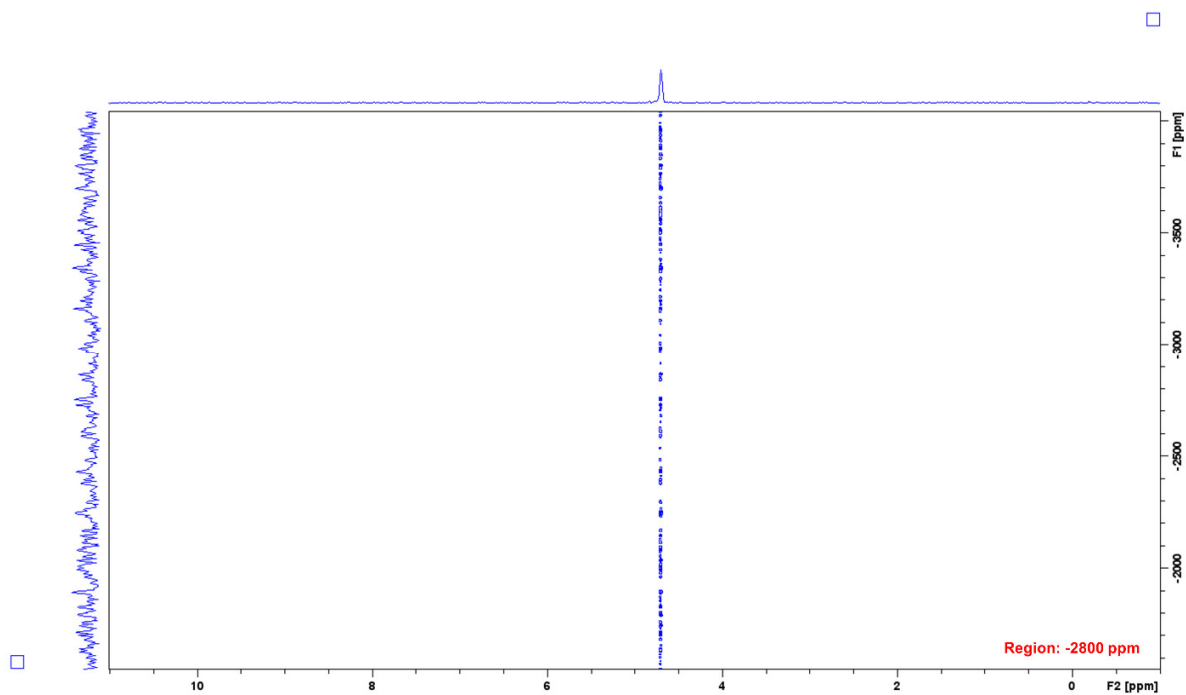


Figure S50: ^1H - ^{195}Pt -HMQC spectrum of **7** in D_2O obtained at 298 K. Region: -2800 ppm. Absence of platinum(II) resonance.

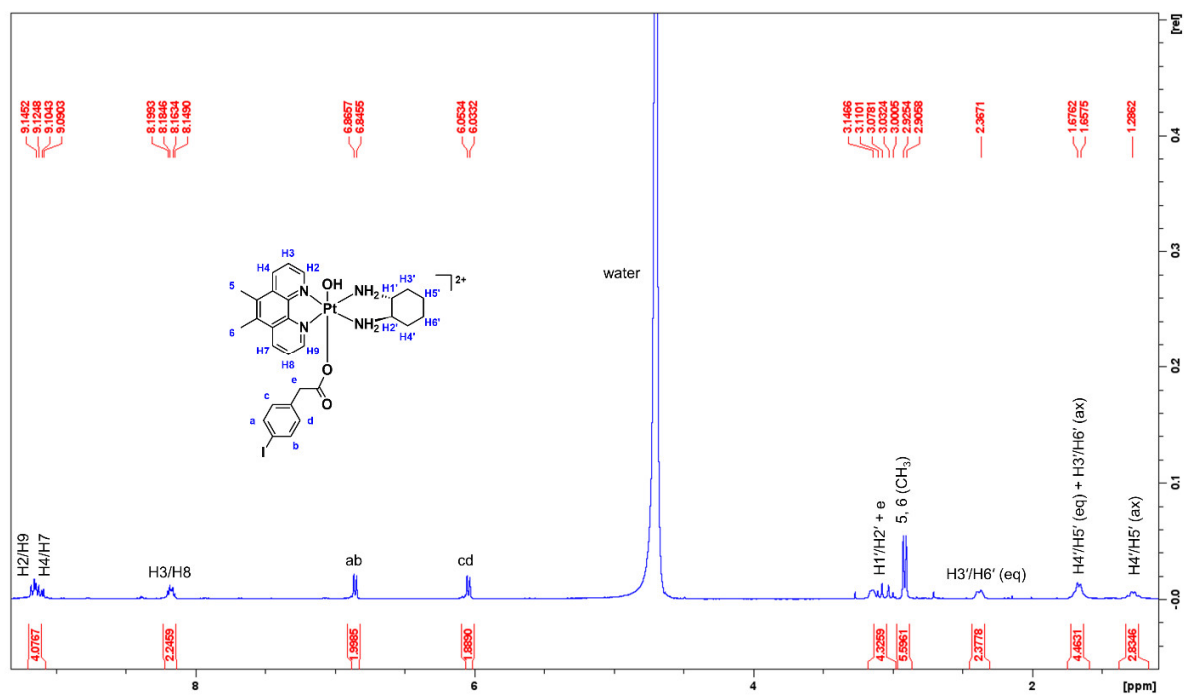
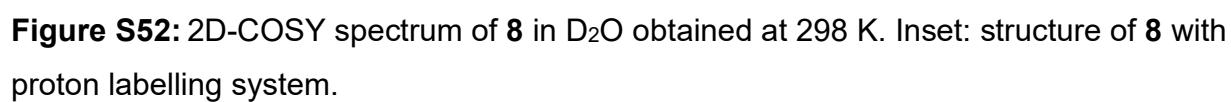


Figure S51: ¹H-NMR spectrum of **8** in D₂O obtained at 298 K Inset: structure of **8** with proton labelling system.



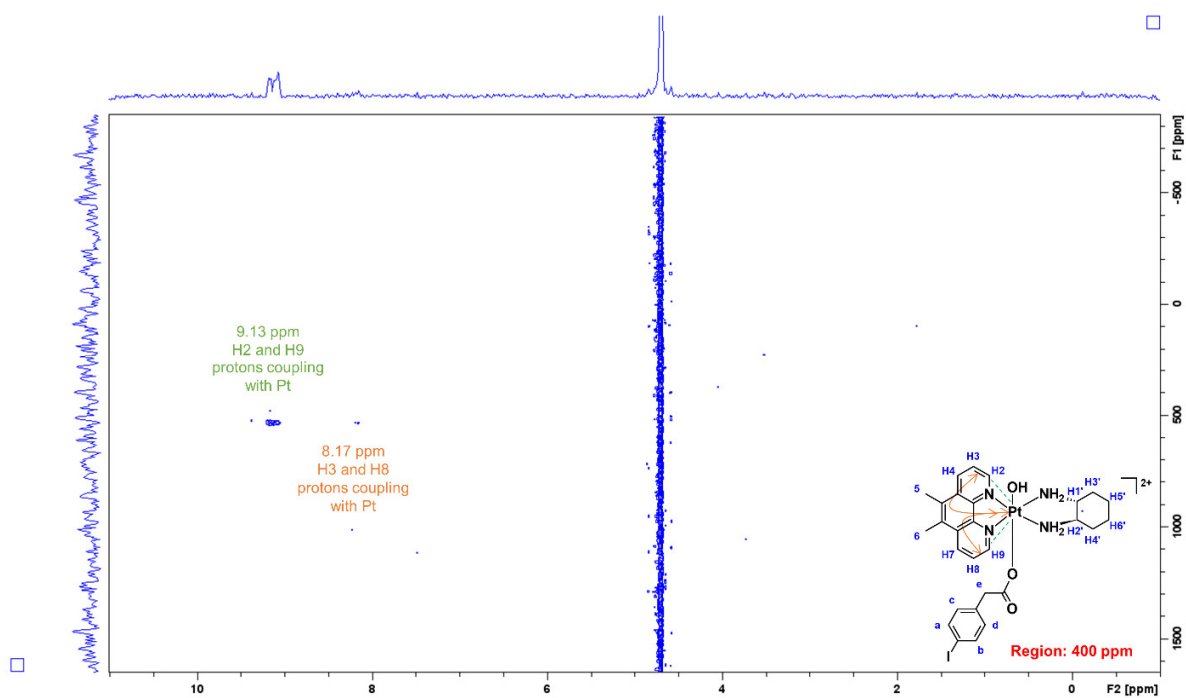


Figure S53: ^1H - ^{195}Pt -HMQC spectrum of **8** in D_2O obtained at 298 K. Region: 400 ppm. Inset: structure of **8** with proton labelling system and arrows that indicate coupling.

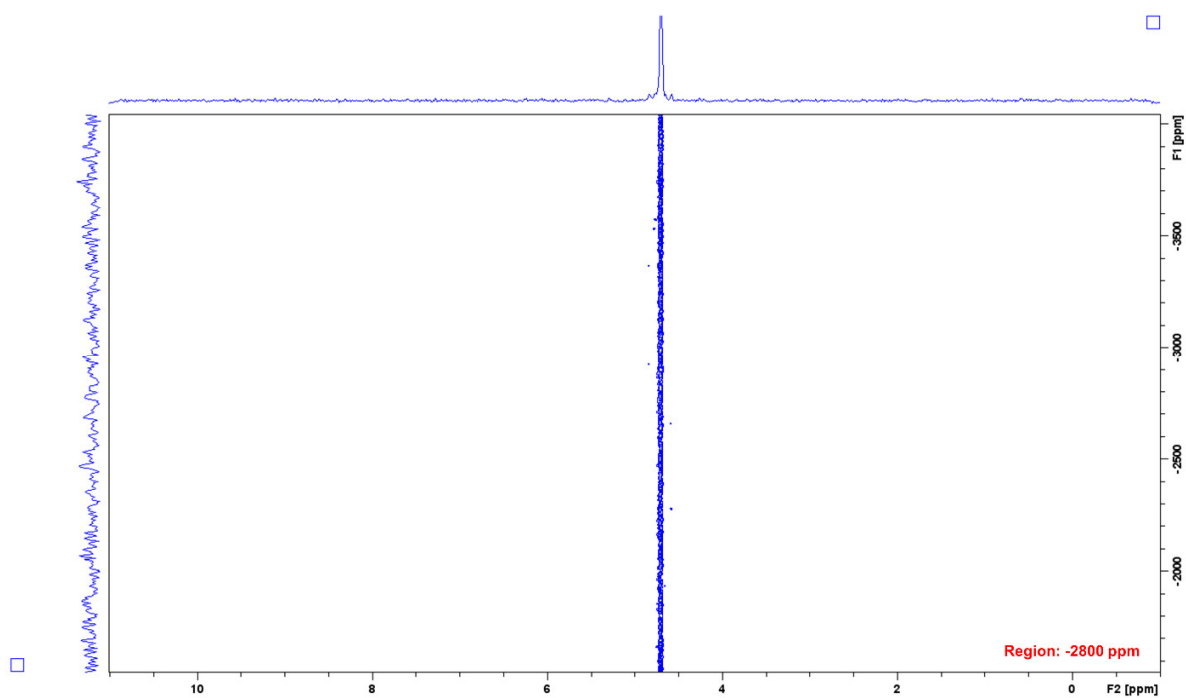


Figure S54: ^1H - ^{195}Pt -HMQC spectrum of **8** in D_2O obtained at 298 K. Region: -2800 ppm. Absence of platinum(II) resonance.

UV spectra of platinum(IV) complexes of 1 – 8

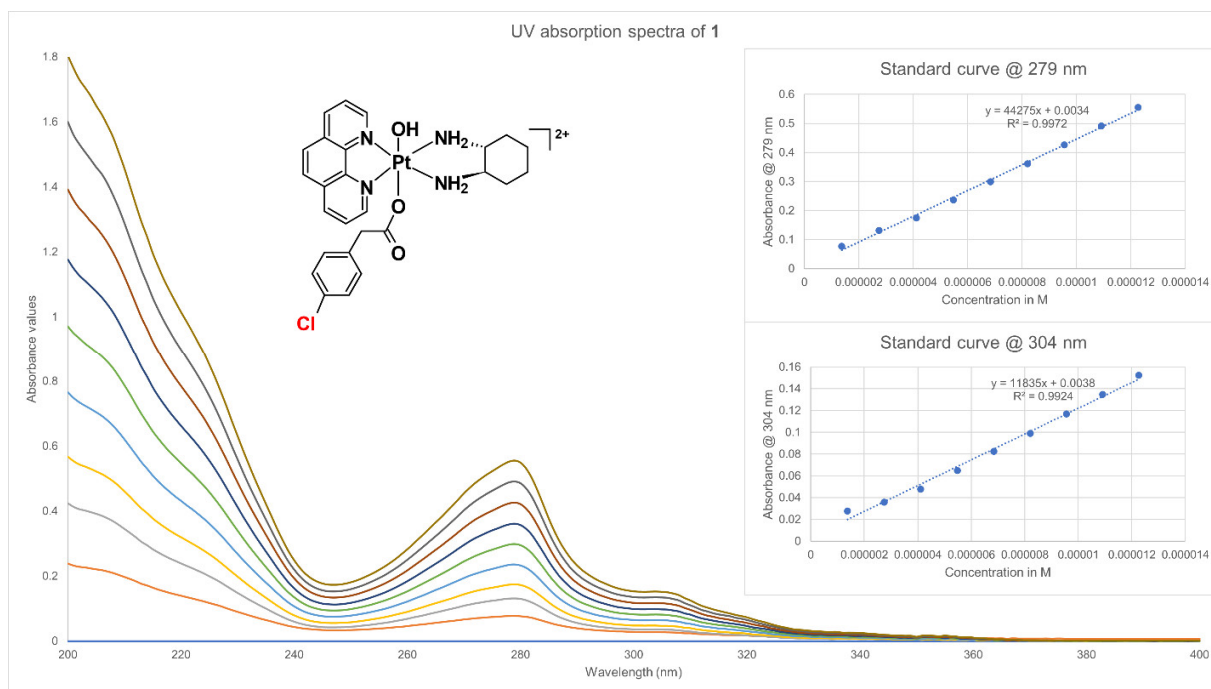


Figure S55: UV spectra of **1** obtained at 298 K. Inset: structure of **1** and generated plot curves within the wavelengths 279 and 304 nm.

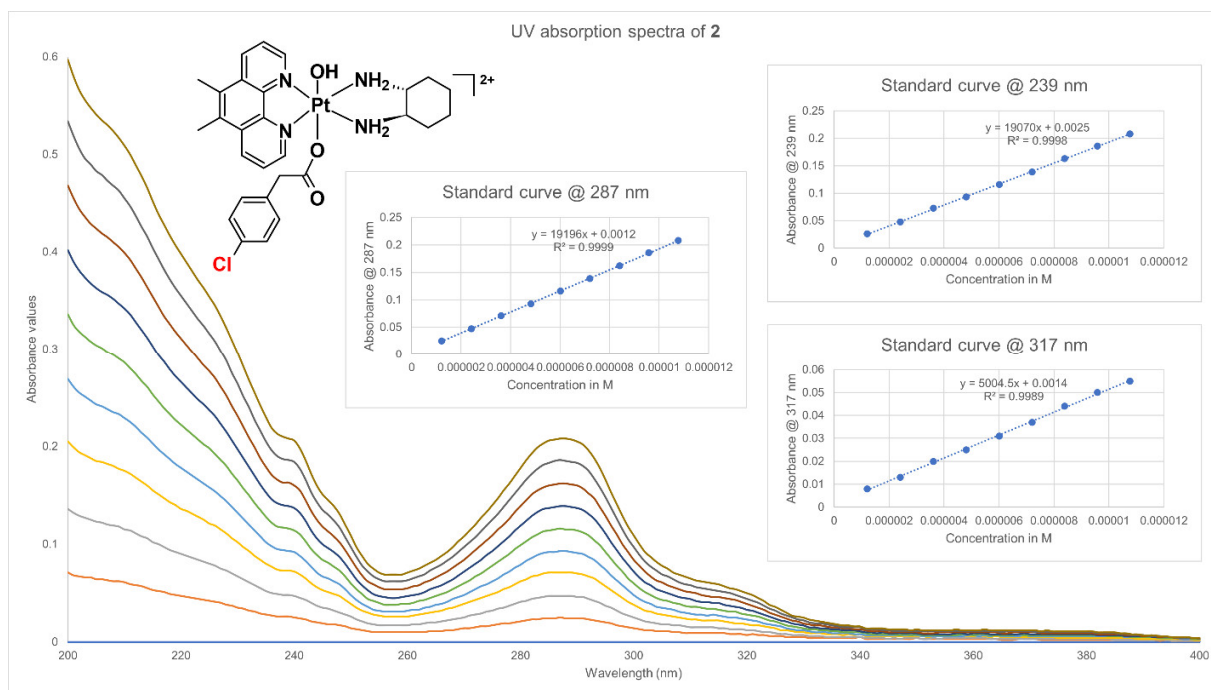


Figure S56: UV spectra of **2** obtained at 298 K. Inset: structure of **2** and generated plot curves within the wavelengths 239, 287 and 317 nm.

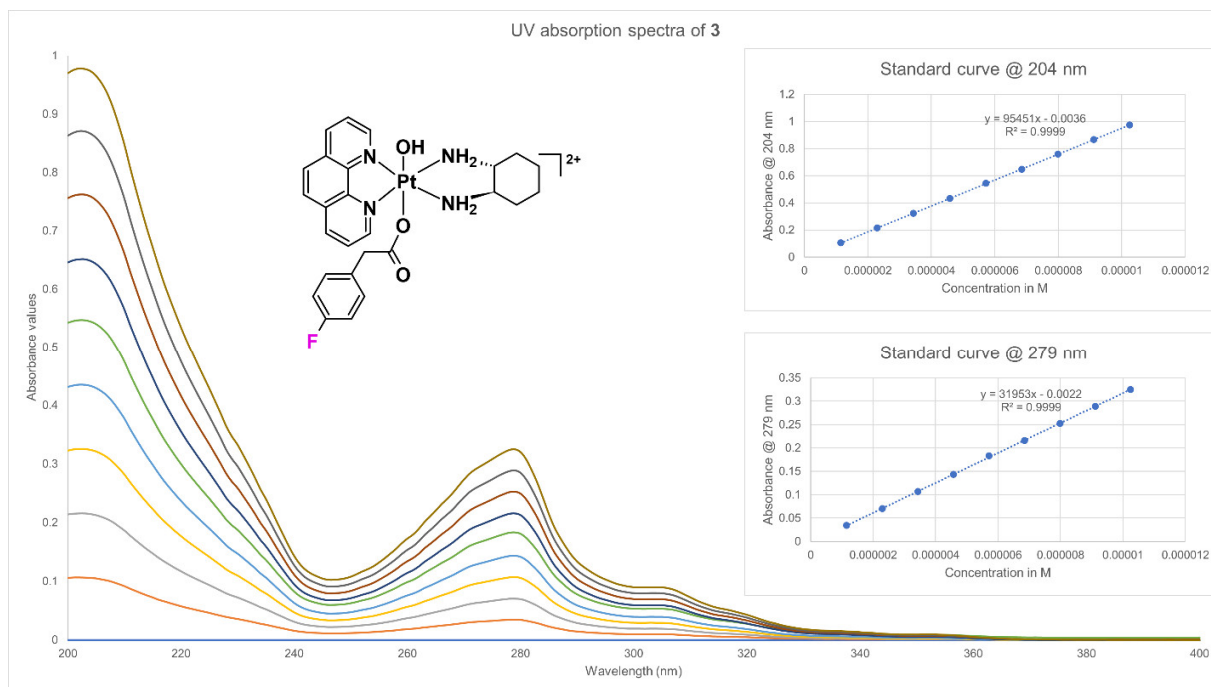


Figure S57: UV spectra of **3** at 298 K. Inset: structure of **3** and generated plot curves within the wavelengths 204 and 279 nm.

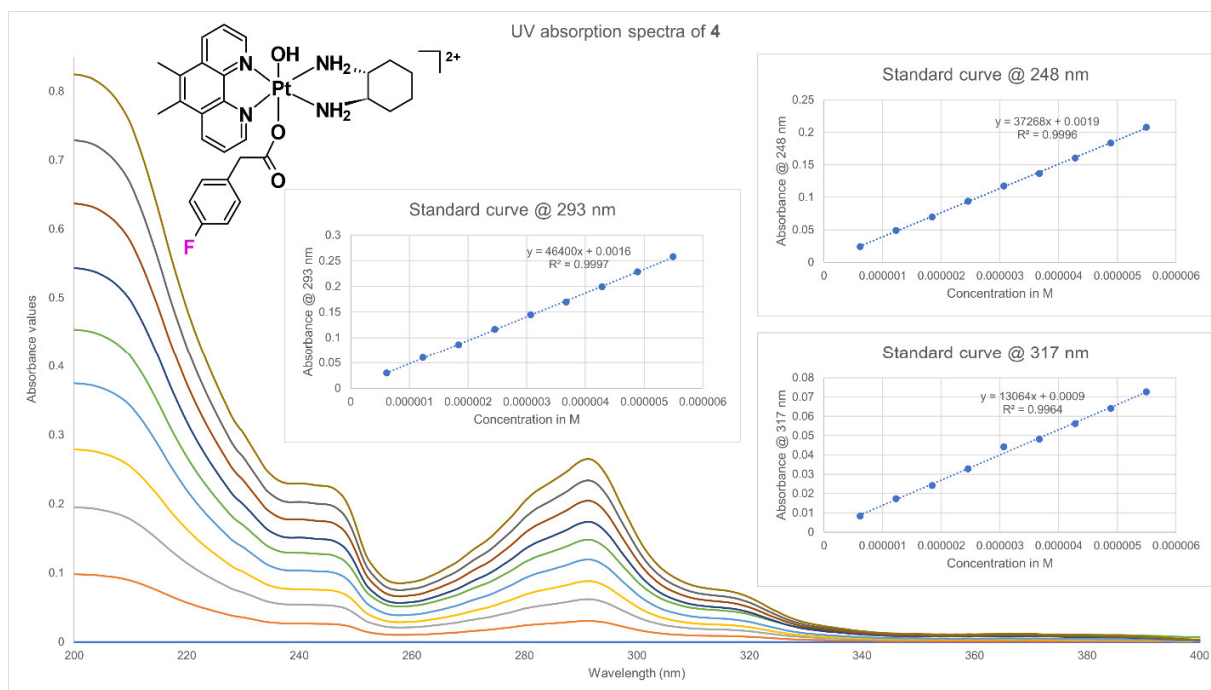


Figure S58: UV spectra of **4** obtained at 298 K. Inset: structure of **4** and generated plot curves within the wavelengths 248, 293 and 317 nm.

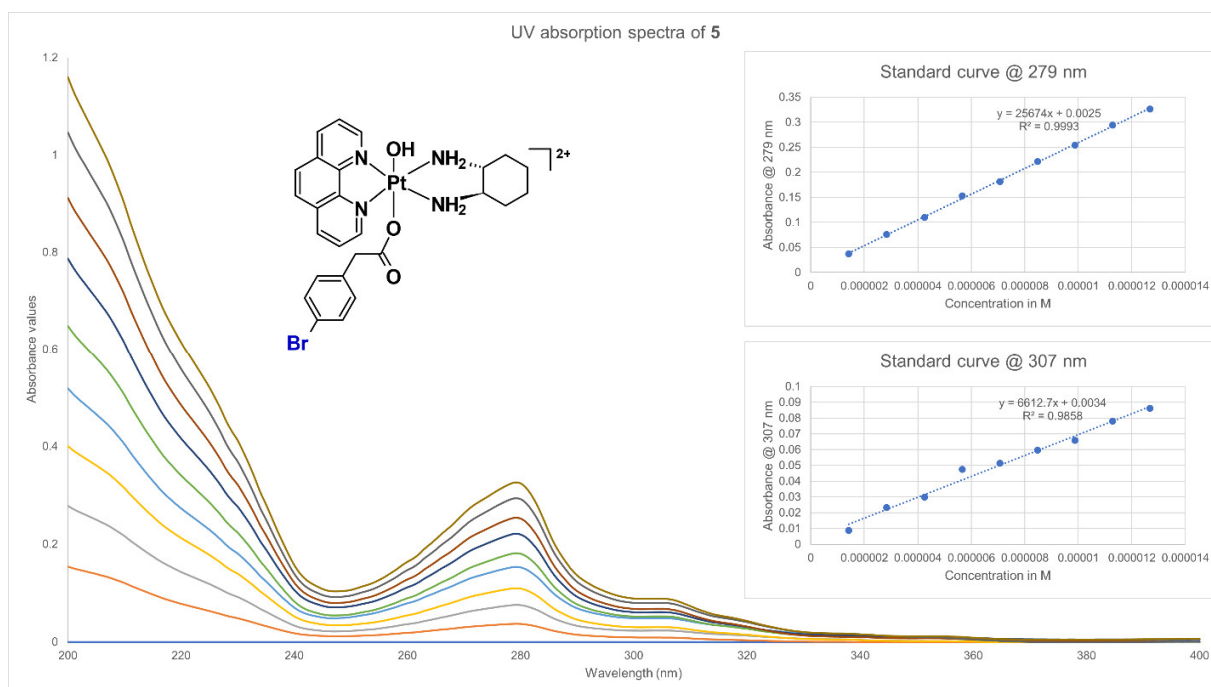


Figure S59: UV spectra of **5** obtained at 298 K. Inset: structure of **5** and generated plot curves within the wavelengths 279 and 307 nm.

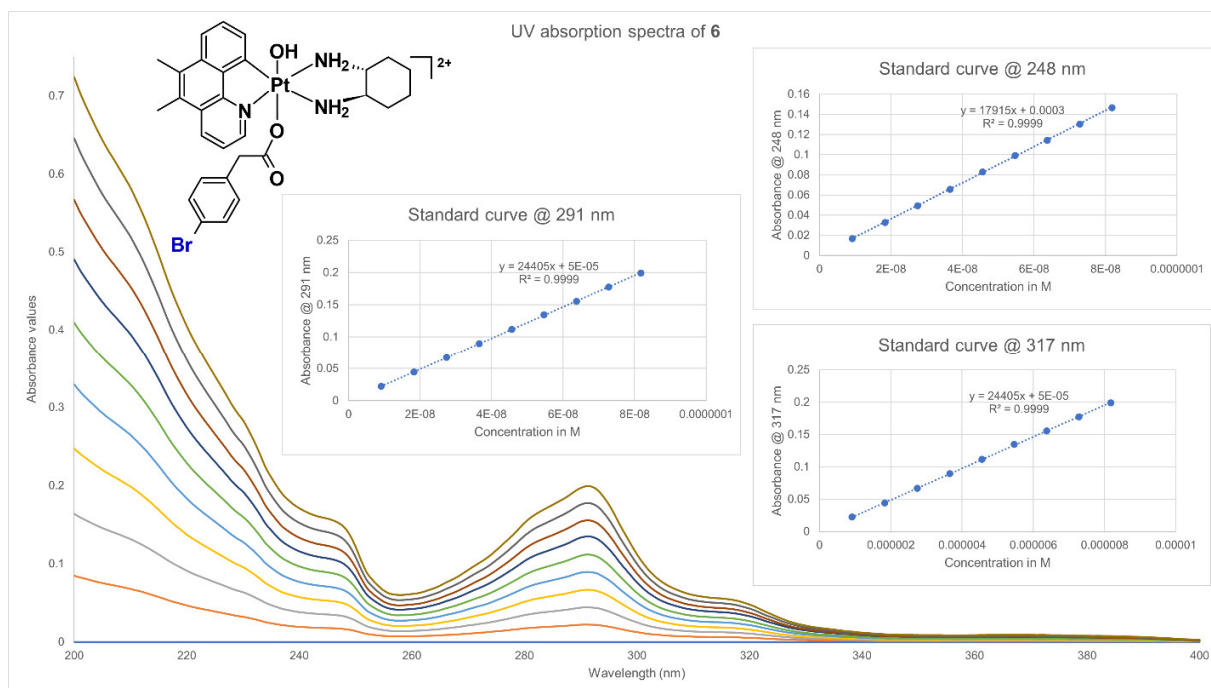


Figure S60: UV spectra of **6** obtained at 298 K. Inset: structure of **6** and generated plot curves within the wavelengths 248, 291 and 317 nm.

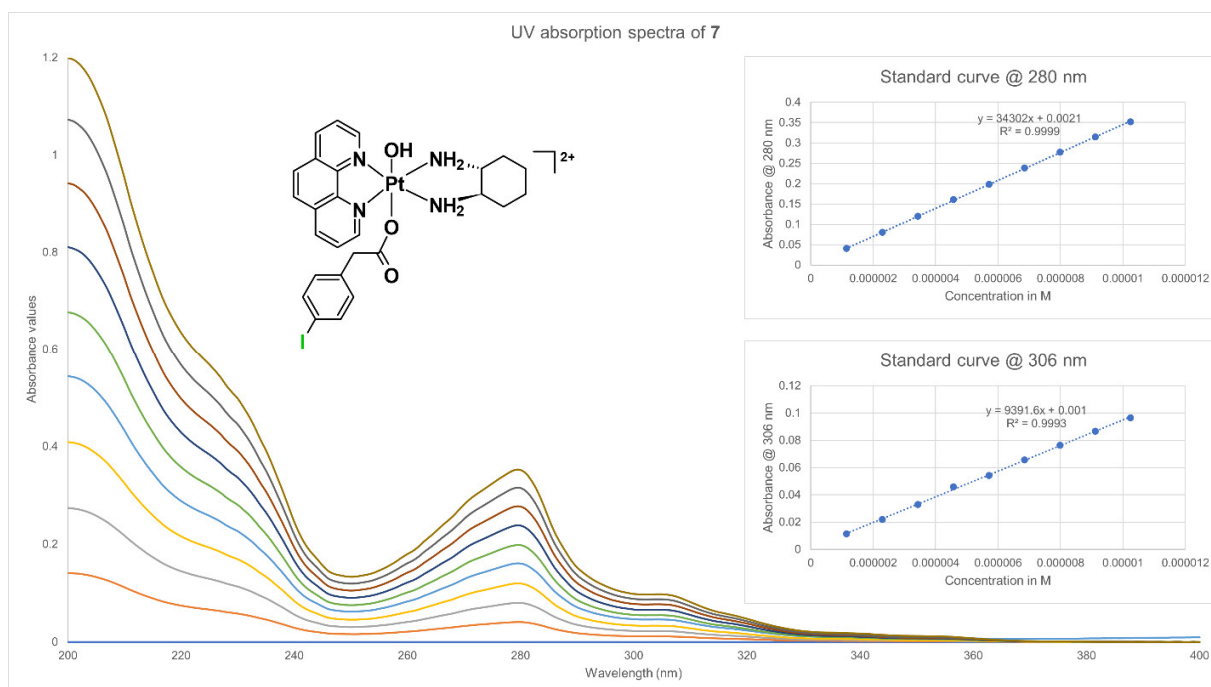


Figure S61: UV spectra of **7** obtained at 298 K. Inset: structure of **7** and generated plot curves within the wavelengths 280 and 306 nm.

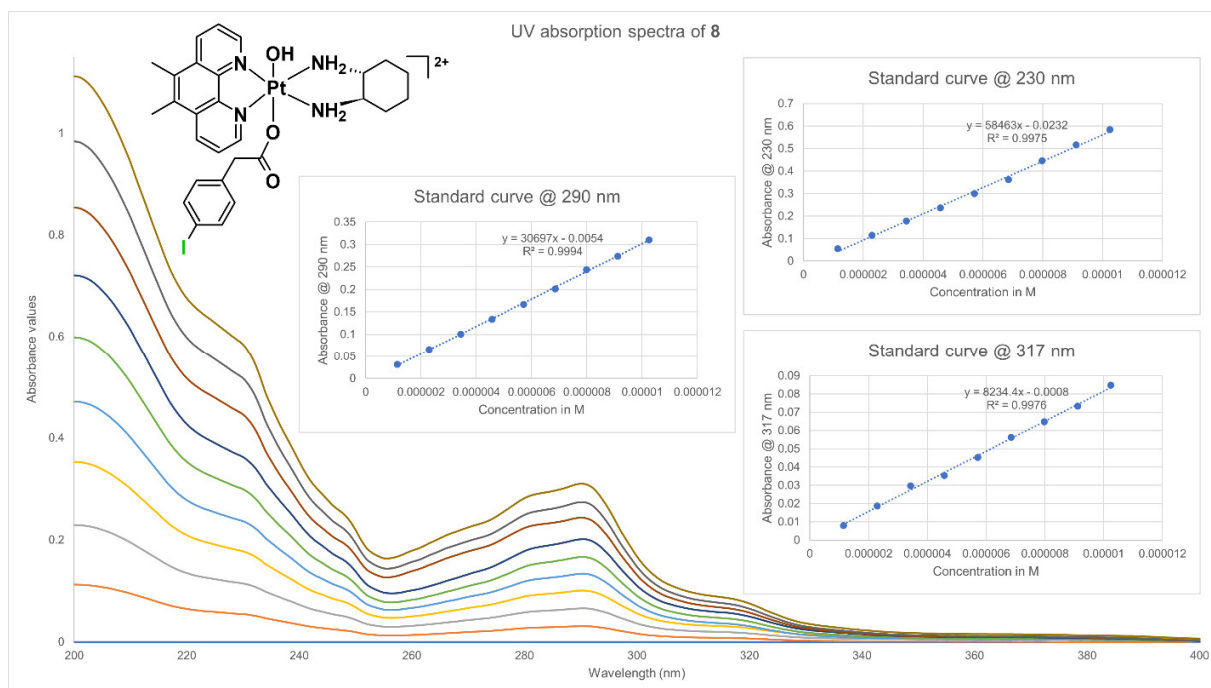


Figure S62: UV spectra of **8** obtained at 298 K. Inset: structure of **8** and generated plot curves within the wavelengths 230, 290 and 317 nm.

CD spectra of 1 – 8

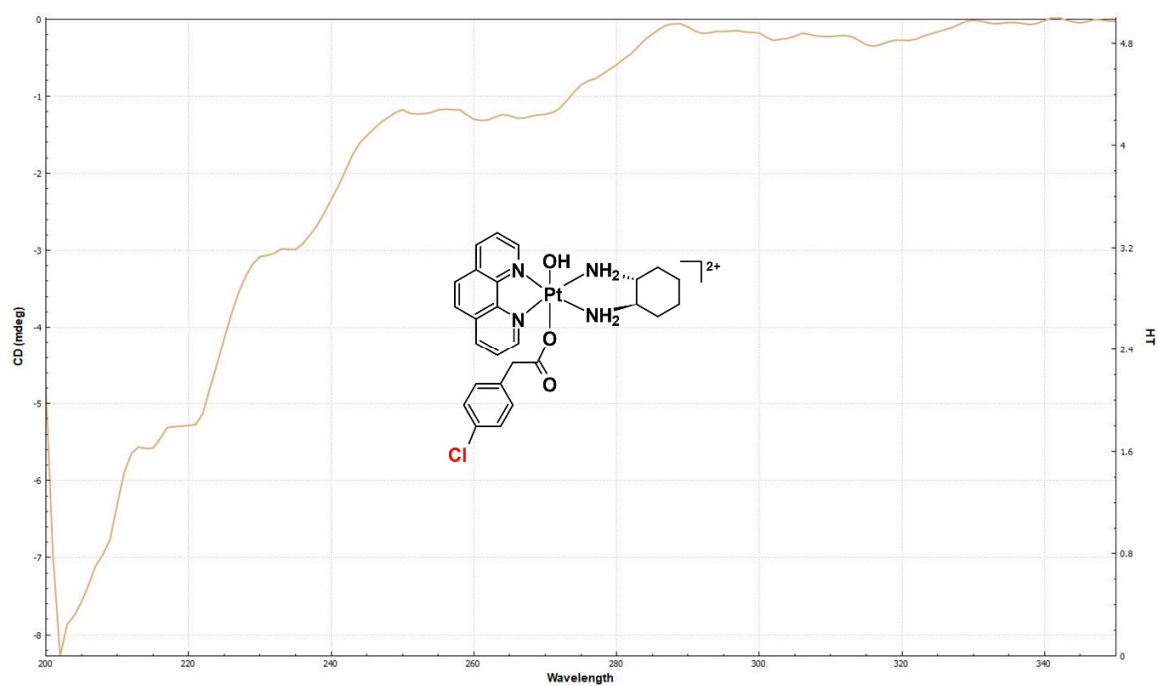


Figure S63: CD spectrum of **1** obtained at 298 K. Inset: structure of **1**.

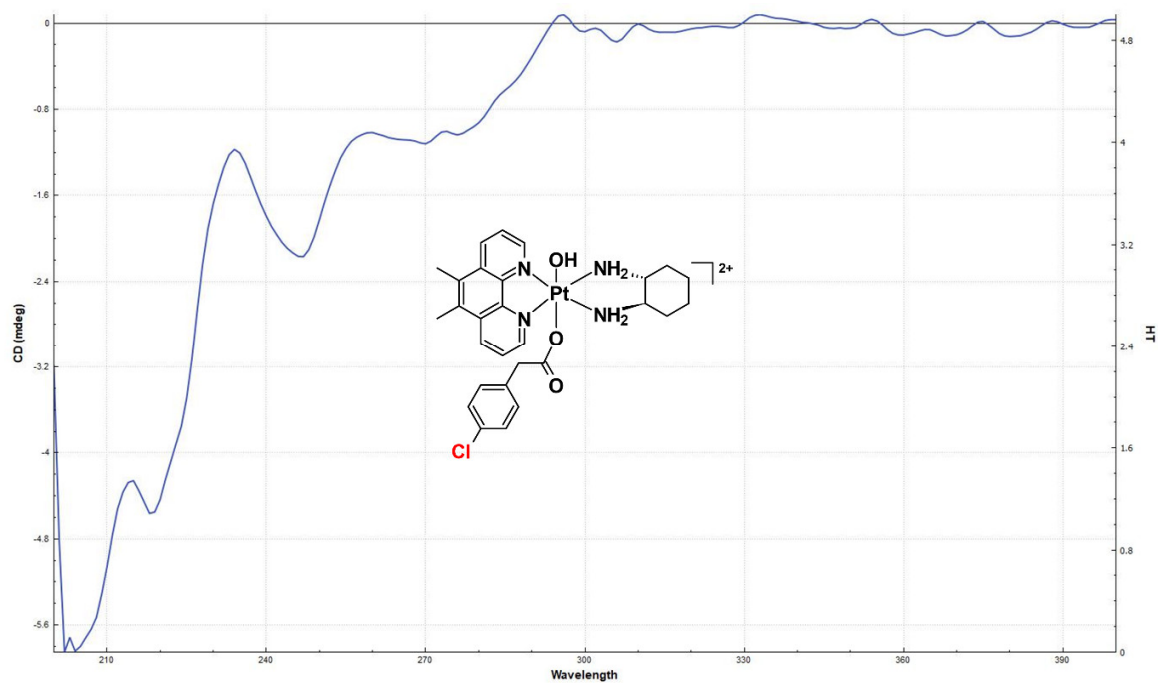


Figure S64: CD spectrum of **2** obtained at 298 K. Inset: structure of **2**.

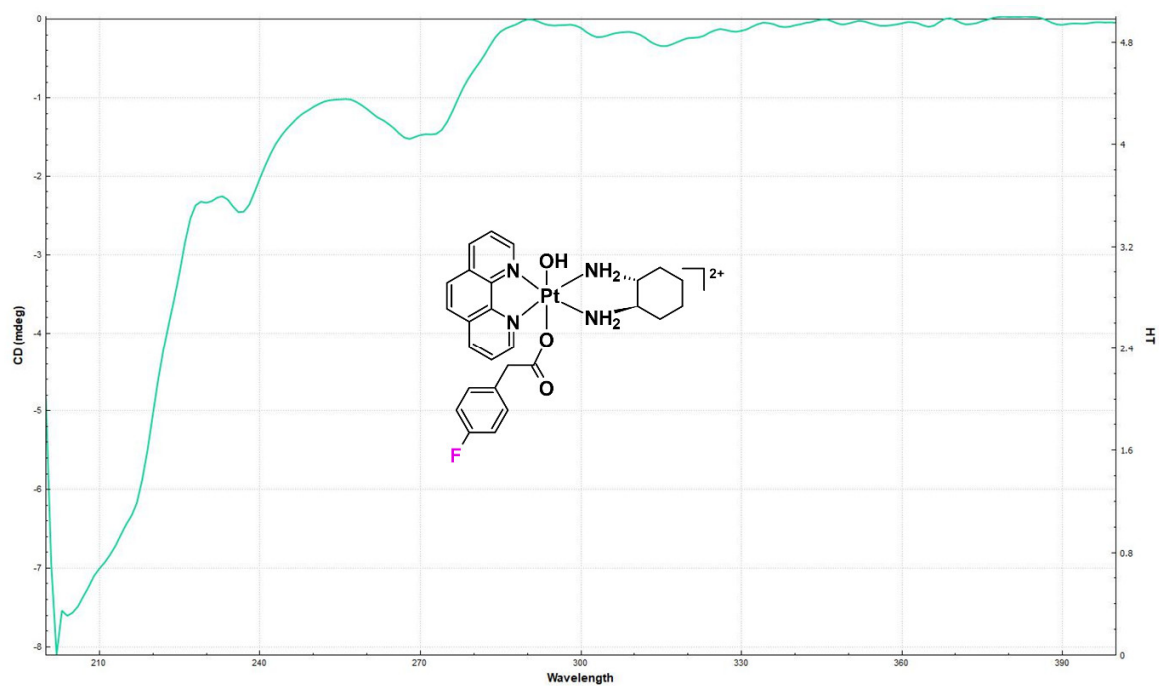


Figure S65: CD spectrum of **3** obtained at 298 K. Inset: structure of **3**.

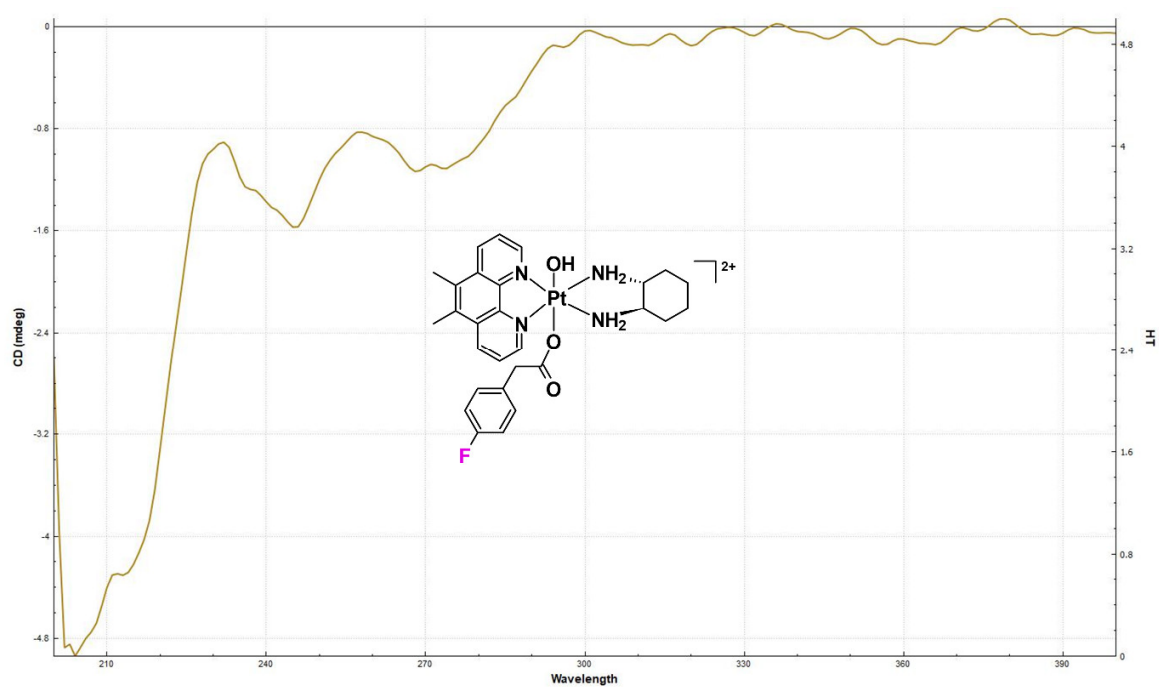


Figure S66: CD spectrum of **4** obtained at 298 K. Inset: structure of **4**.

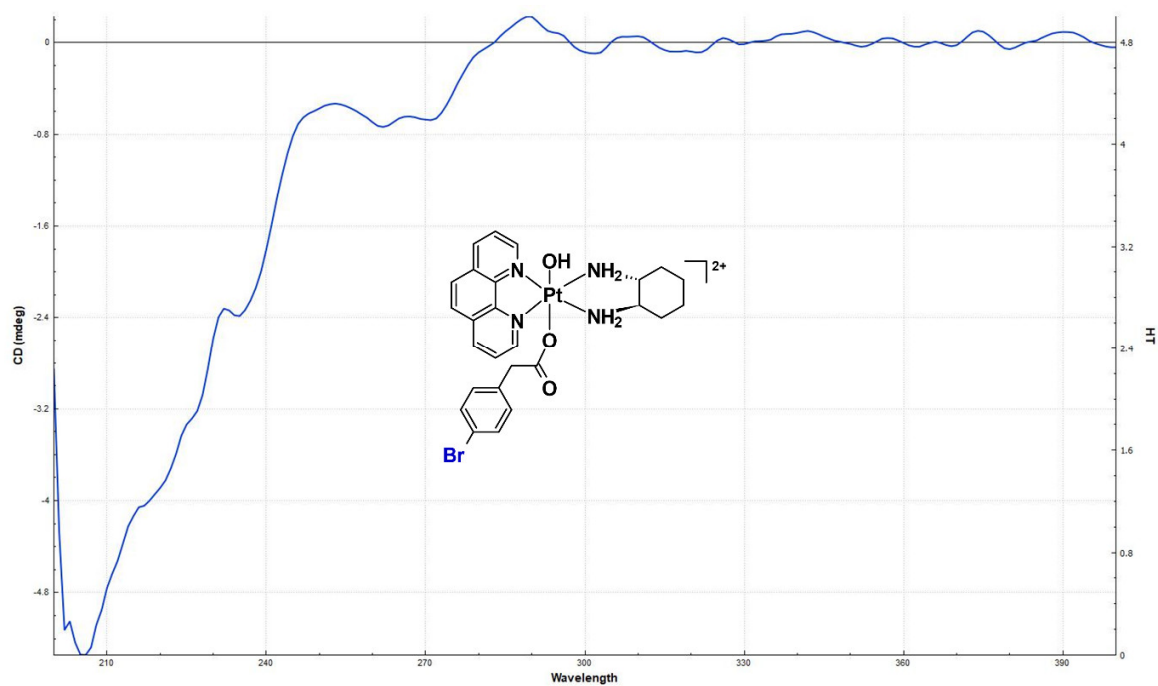


Figure S67: CD spectrum of **5** obtained at 298 K. Inset: structure of **5**.

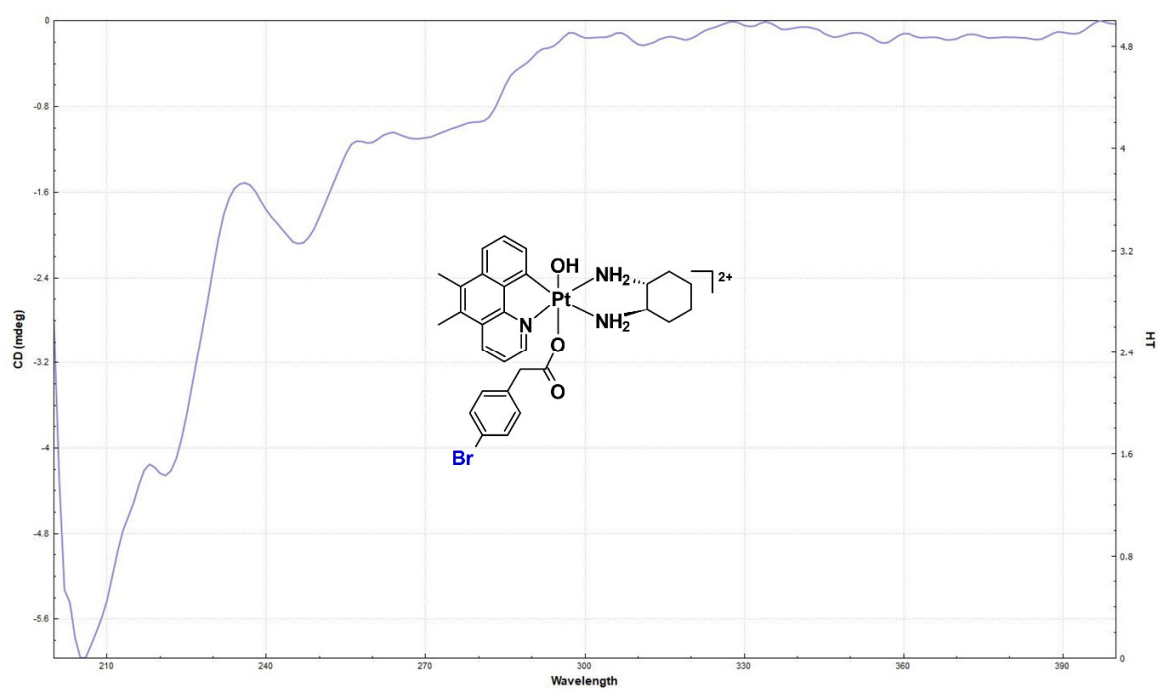


Figure S68: CD spectrum of **6** obtained at 298 K. Inset: structure of **6**.

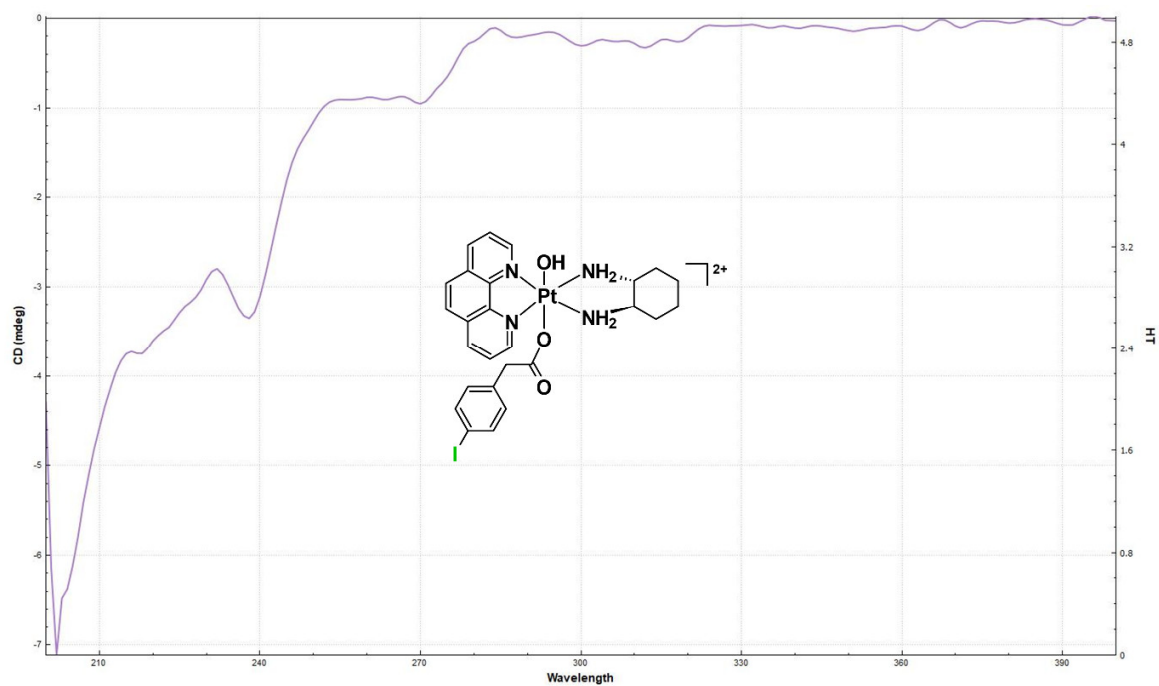


Figure S69: CD spectrum of **7** obtained at 298 K. Inset: structure of **7**.

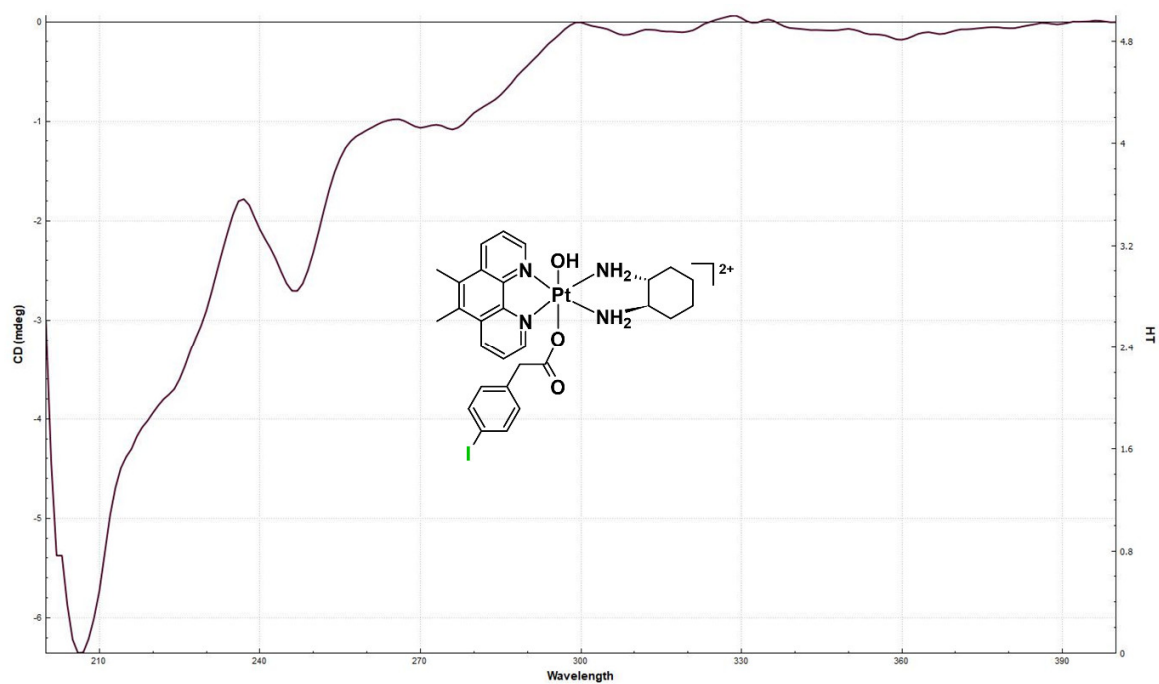


Figure S70: CD spectrum of **8** obtained at 298 K. Inset: structure of **8**.

ESI-MS spectra of 1 – 8

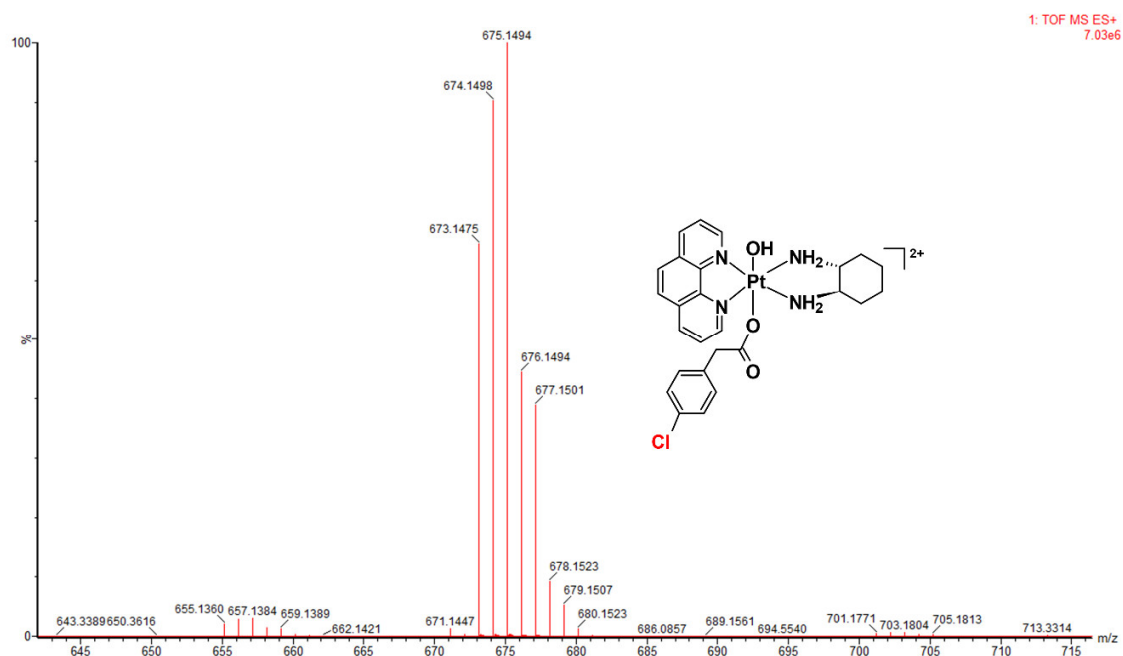


Figure S71: ESI-MS spectrum of **1** obtained at 298 K, using a Waters SYNAPT G2-Si quadrupole time-of-flight (QTOF) HDMS. Inset: structure of **1**.

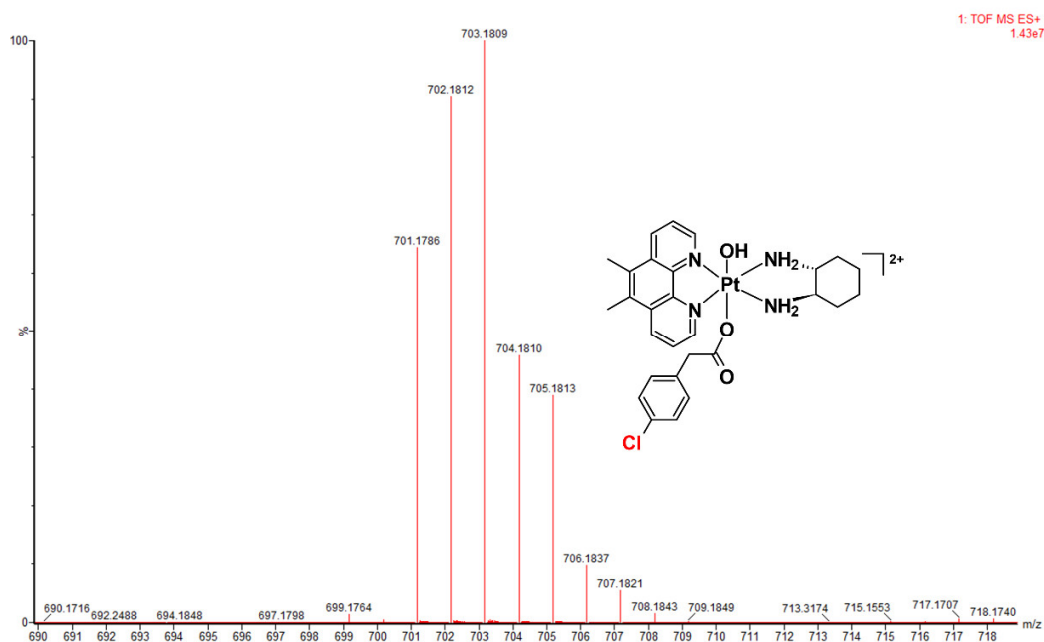


Figure S72: ESI-MS spectrum of **2** obtained at 298 K, using a Waters SYNAPT G2-Si quadrupole time-of-flight (QTOF) HDMS. Inset: structure of **2**.

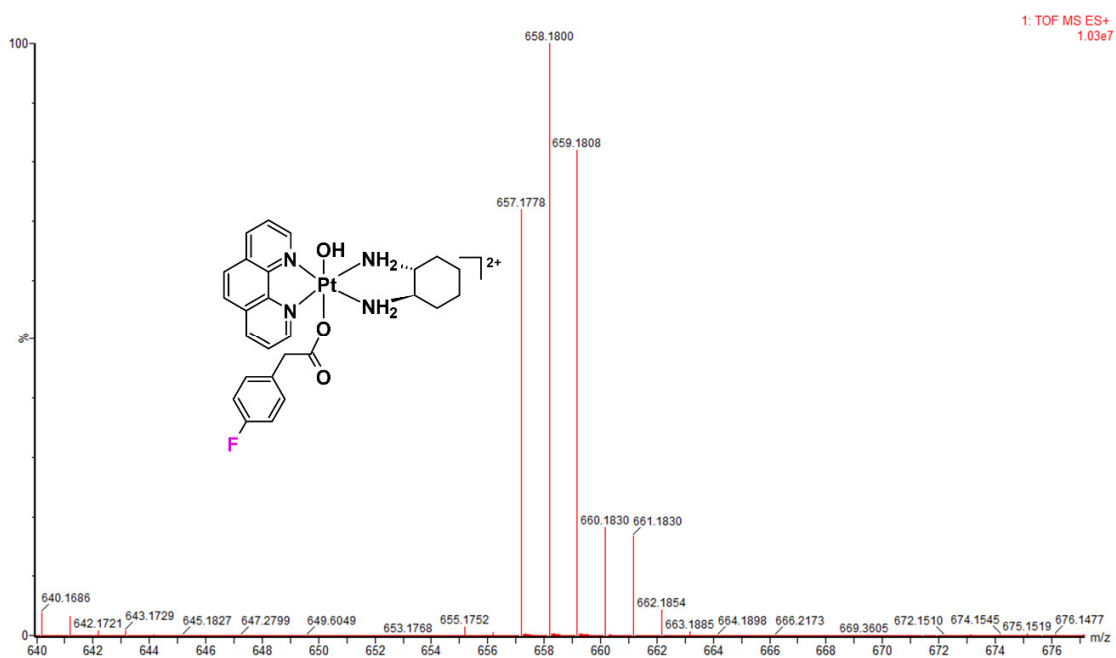


Figure S73: ESI-MS spectrum of **3** obtained at 298 K, using a Waters SYNAPT G2-Si quadrupole time-of-flight (QTOF) HDMS. Inset: structure of **3**.

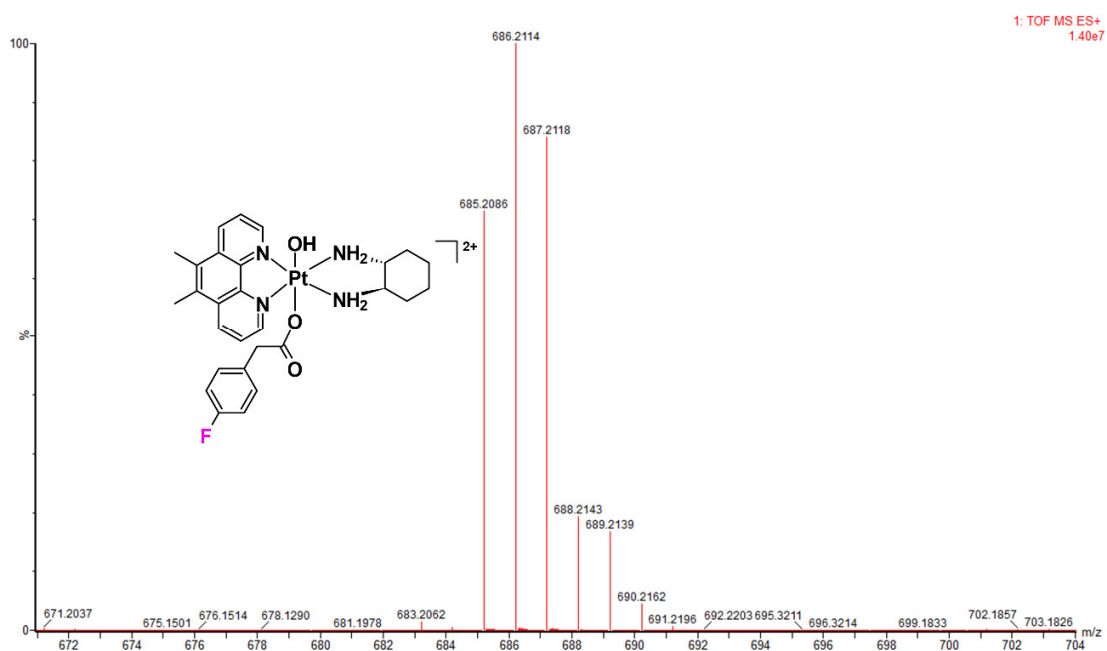


Figure S74: ESI-MS spectrum of **4** obtained at 298 K, using a Waters SYNAPT G2-Si quadrupole time-of-flight (QTOF) HDMS. Inset: structure of **4**.

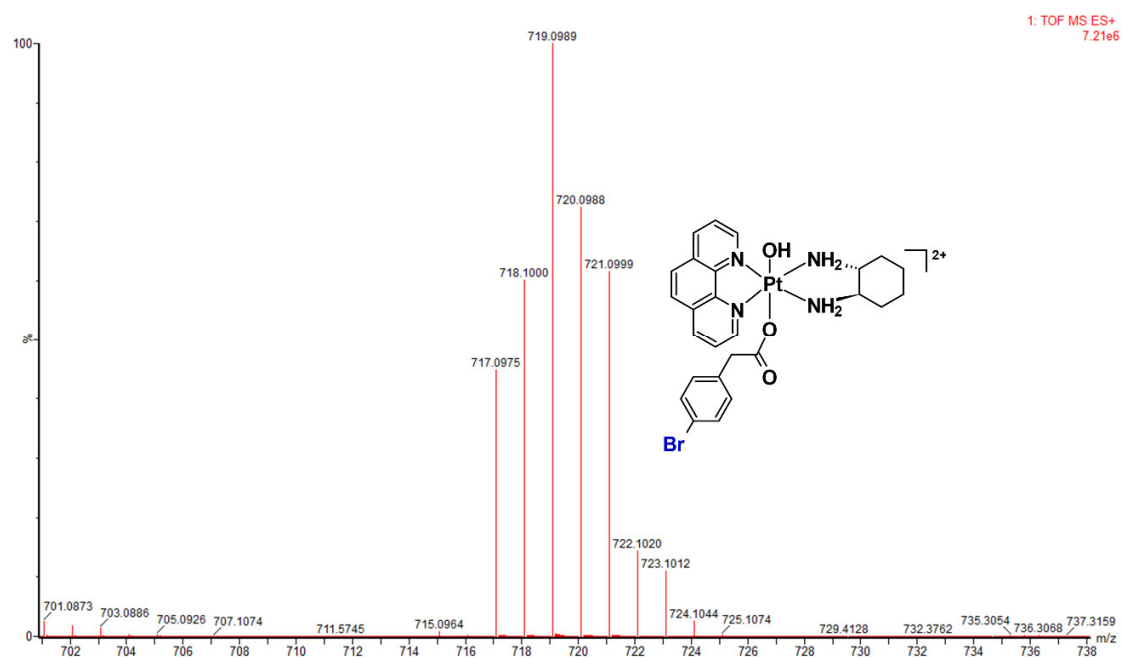


Figure S75: ESI-MS spectrum of **5** obtained at 298 K, using a Waters SYNAPT G2-Si quadrupole time-of-flight (QTOF) HDMS. Inset: structure of **5**.

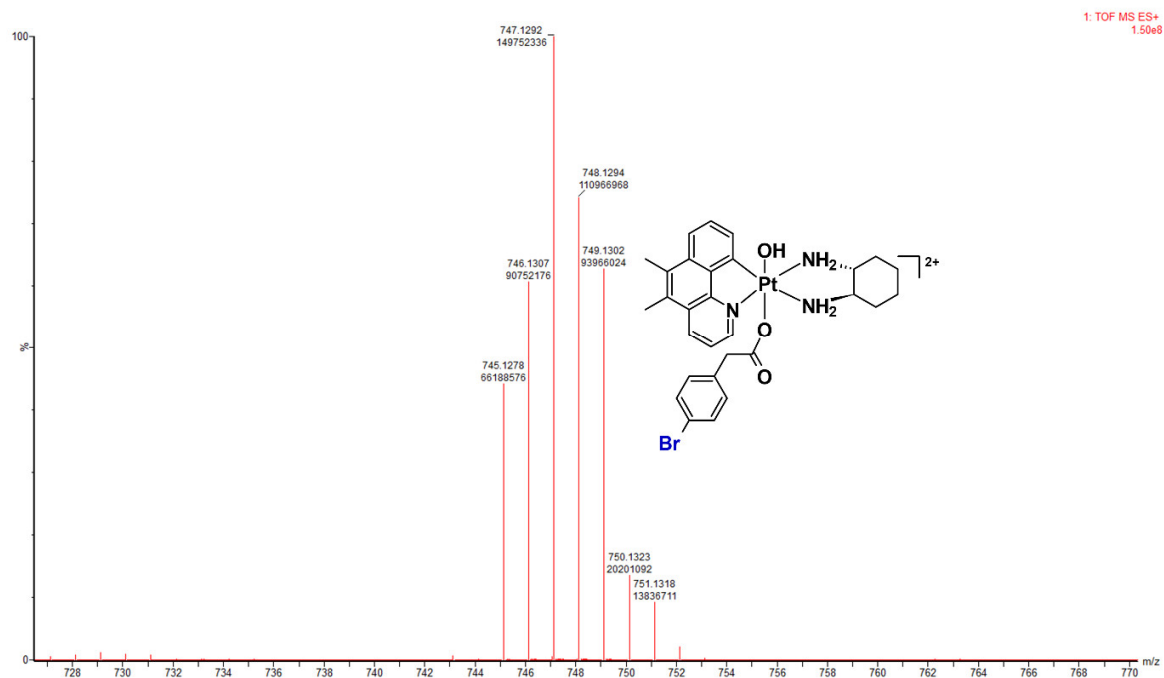


Figure S76: ESI-MS spectrum of **6** obtained at 298 K, using a Waters SYNAPT G2-Si quadrupole time-of-flight (QTOF) HDMS. Inset: structure of **6**.

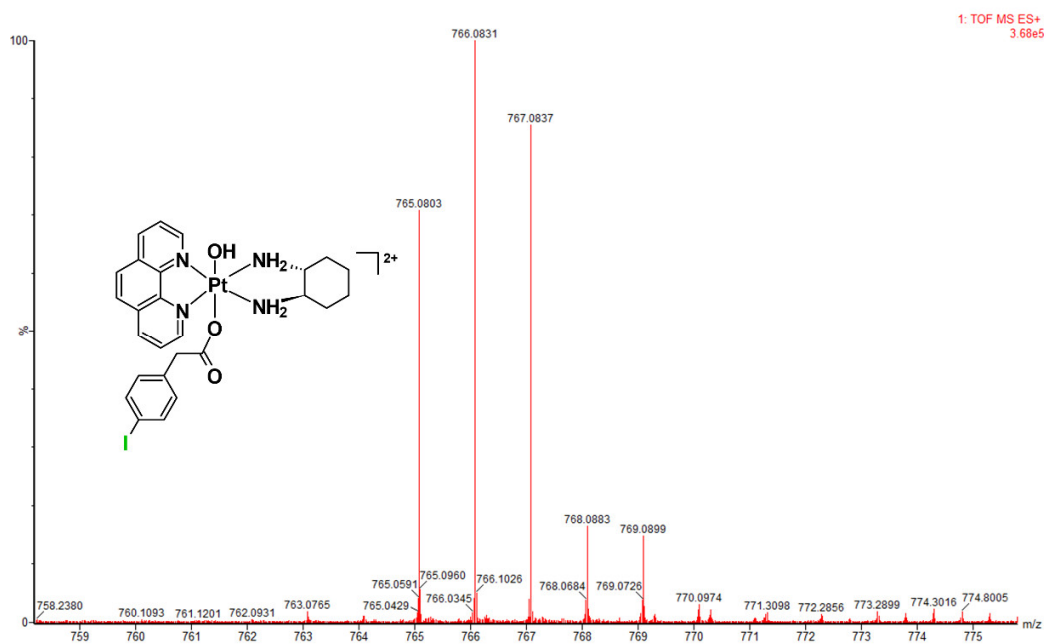


Figure S77: ESI-MS spectrum of **7** obtained at 298 K, using a Waters SYNAPT G2-Si quadrupole time-of-flight (QTOF) HDMS. Inset: structure of **7**.

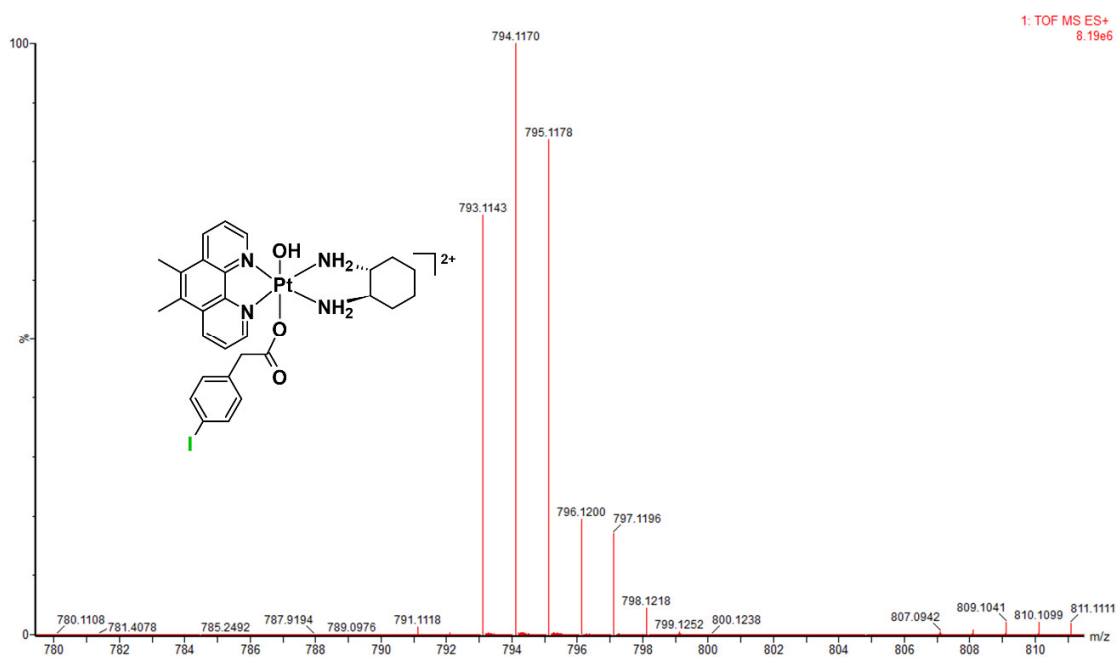


Figure S78: ESI-MS spectrum of **8** obtained at 298 K, using a Waters SYNAPT G2-Si quadrupole time-of-flight (QTOF) HDMS. Inset: structure of **8**.

Stability studies

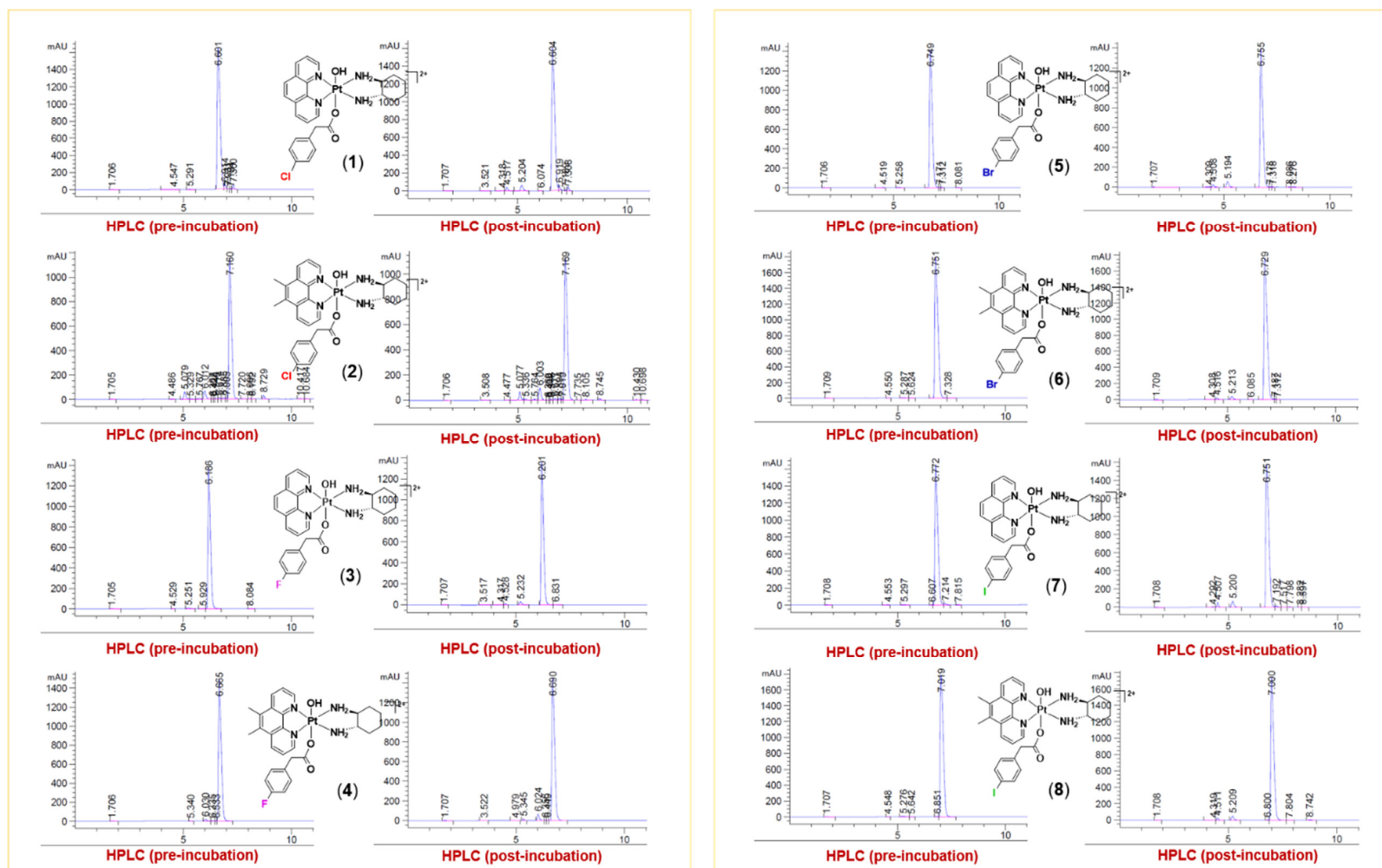


Figure S79: HPLC chromatograms of 1–8 in 10 mM PBS (~7.4 pH) PBS pre- and post-incubation (36 h) obtained at 298 K. Inset: structures of 1–8.

Lipophilicity measurements

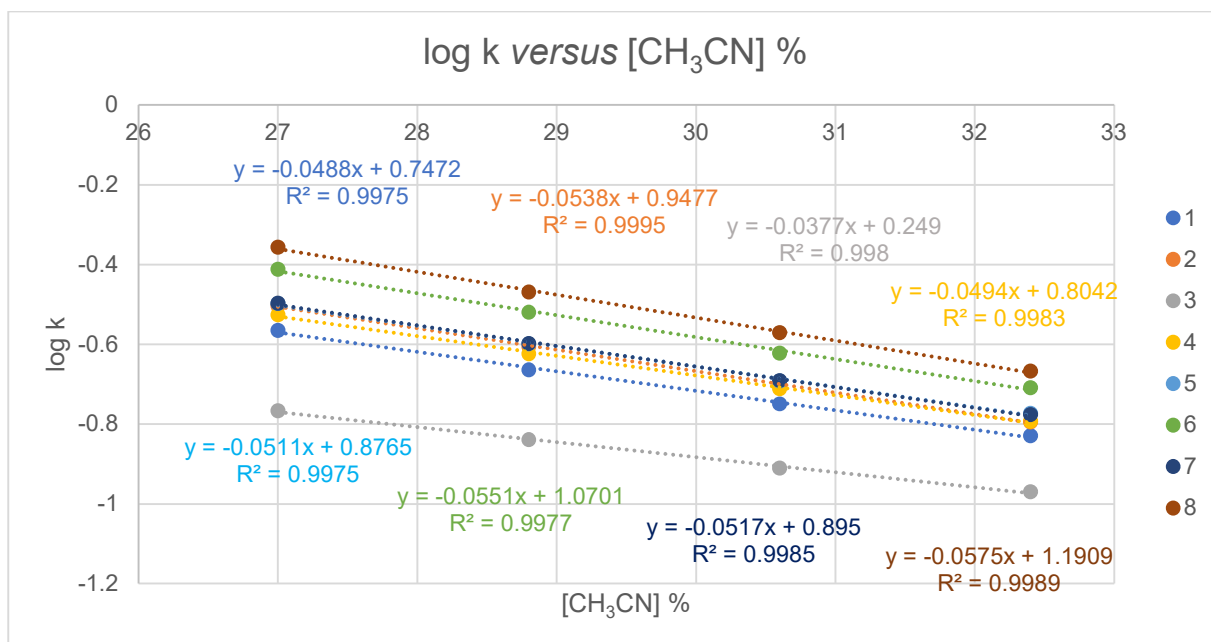


Figure S80: Generated plot curves of log k versus concentration of organic solvent, CH₃CN to determine the chromatographic lipophilicity index, log *k*_w of **1–8**.

Reduction reaction experiments

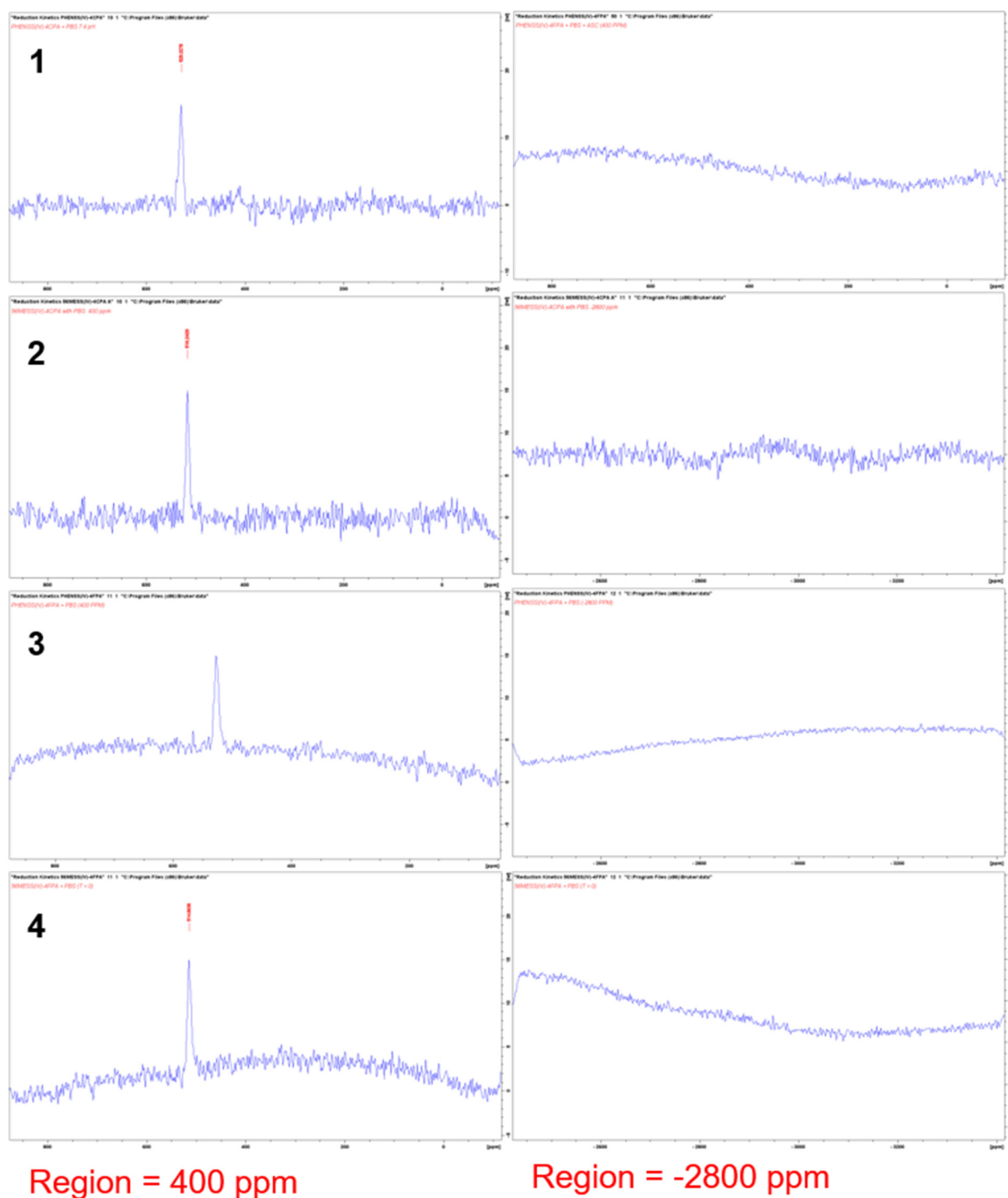


Figure S81: Preliminary 1D- ^{195}Pt -NMR spectra of **1**, **2**, **3** and **4** in 10 mM PBS (~7.4 pH) within the regions of -2800 and 400 ppm at 37 °C.

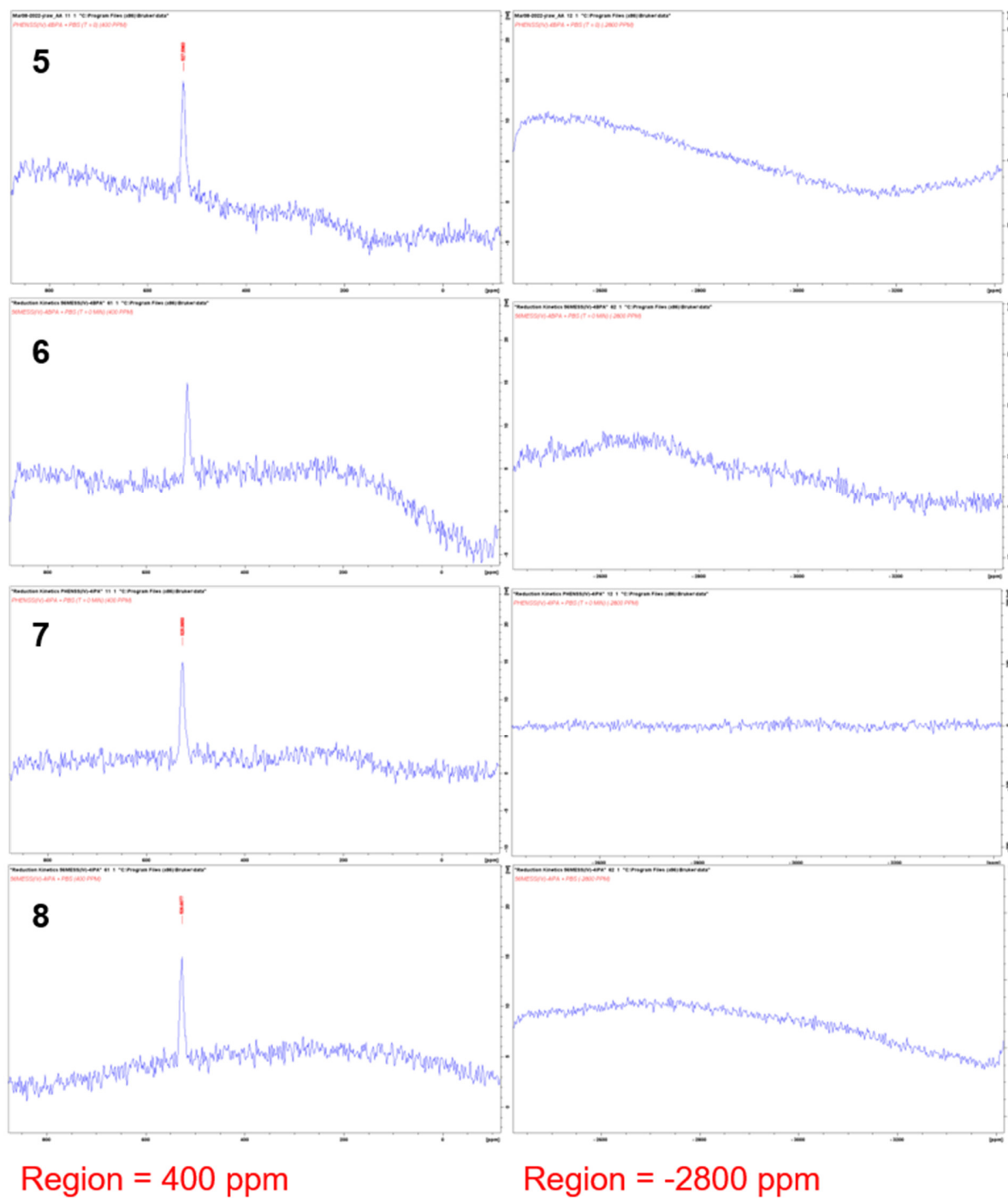


Figure S82: Preliminary 1D- ^{195}Pt -NMR spectra of **5**, **6**, **7** and **8** in 10 mM PBS (~7.4 pH) within the regions of -2800 and 400 ppm at 37 °C.

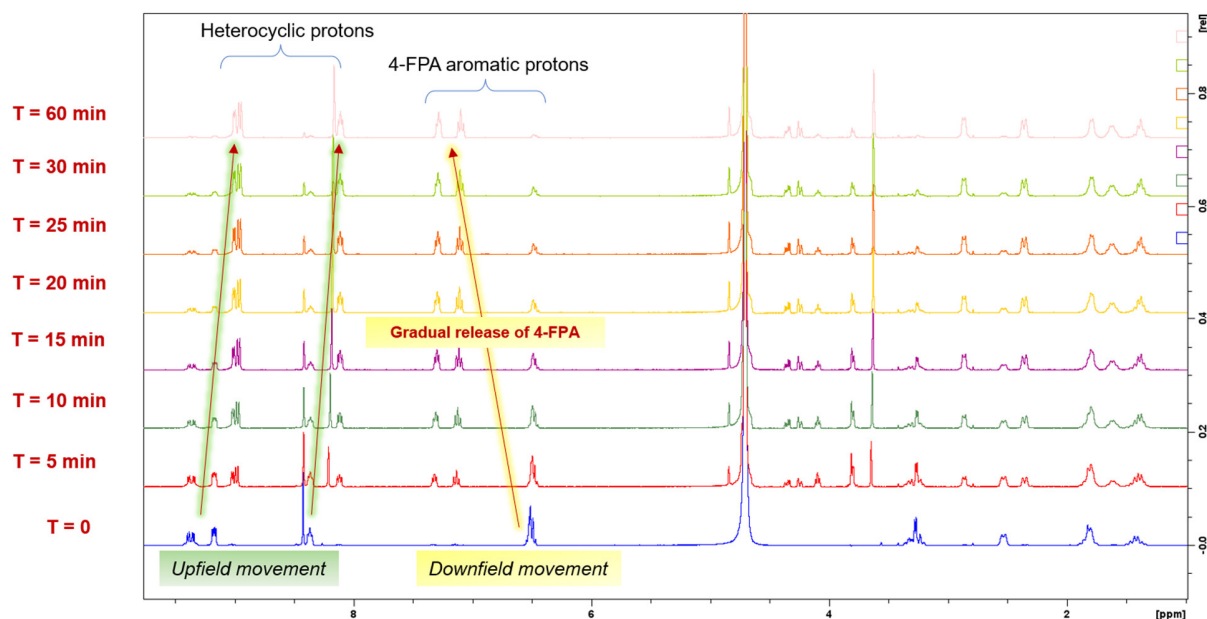


Figure S83: ^1H -NMR spectra of **3** with 10 mM PBS (~ 7.4 pH) and AsA in D_2O at 310.15 K, in different time intervals, highlighting the movement of resonances from the phenanthroline protons and the aromatic protons of the 4-FPA ligand as indicated by the red arrows. **T** represents time in min.

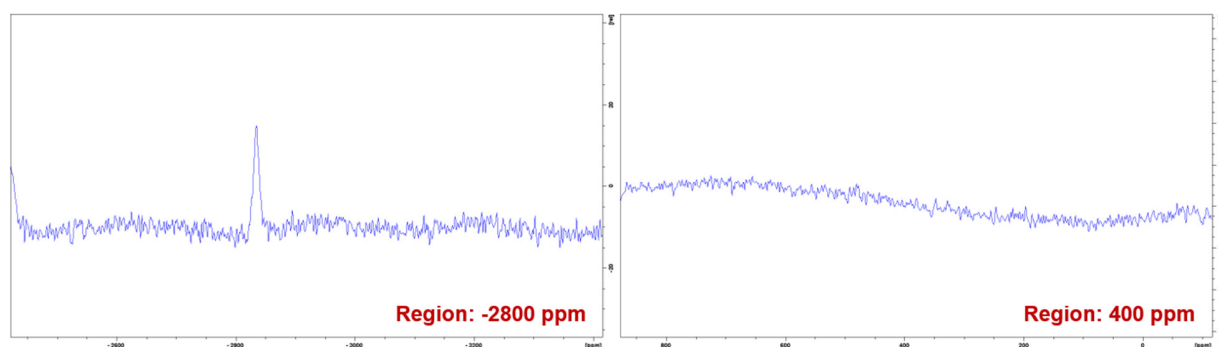


Figure S84: 1D- ^{195}Pt -NMR spectra of **3** with 10 mM PBS (~ 7.4 pH) and AsA in D_2O , within the regions of -2800 and 400 ppm at 310.15 K, highlighting its complete reduction after 1 h from the final ^1H -NMR experiment.

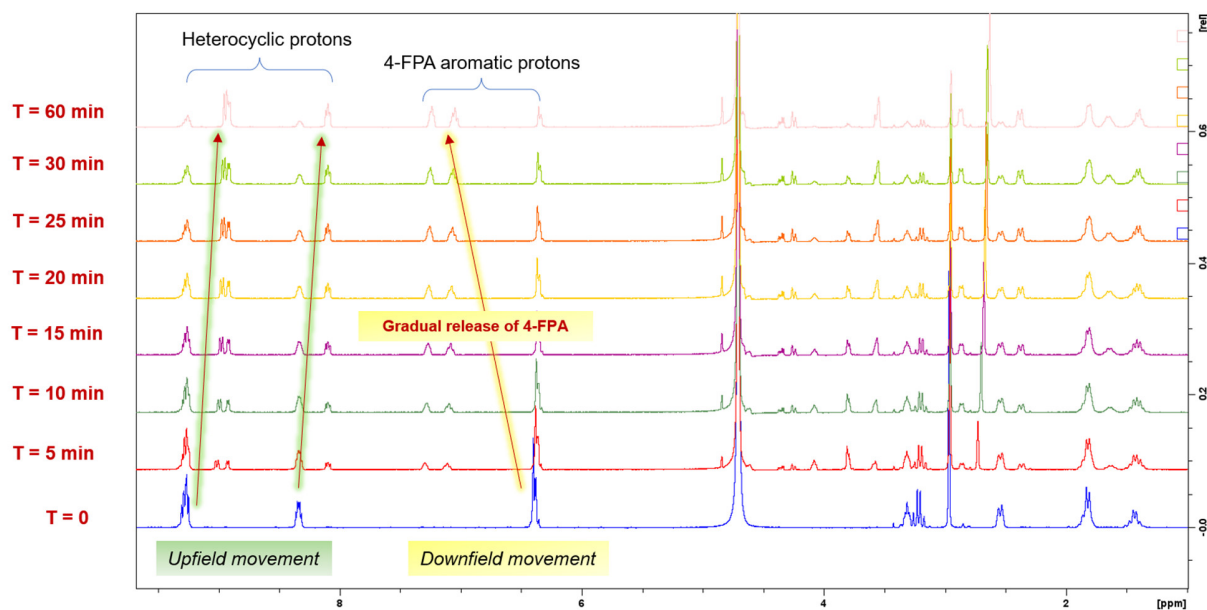


Figure S85: ^1H -NMR spectra of **4** with 10 mM PBS (~ 7.4 pH) and AsA in D_2O at 310.15 K, in different time intervals, highlighting the movement of resonances from the phenanthroline protons and the aromatic protons of the 4-FPA ligand as indicated by the red arrows. **T** represents time in min.

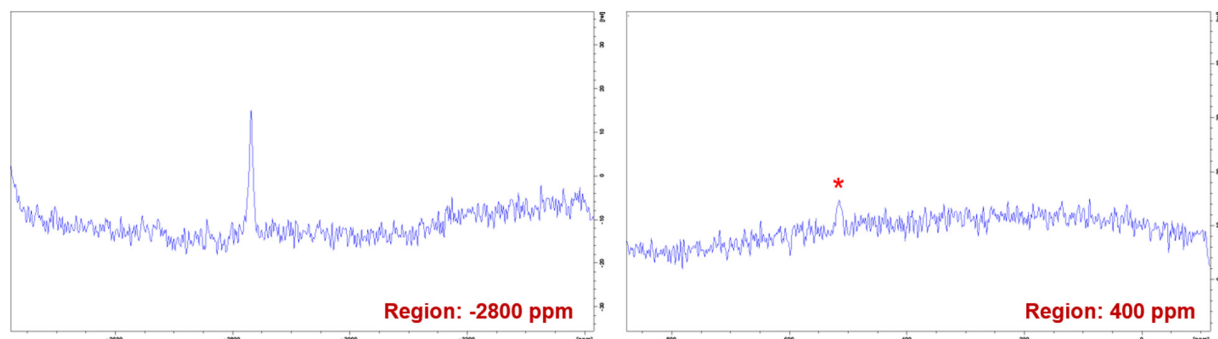


Figure S86: 1D- ^{195}Pt -NMR spectra of **4** with 10 mM PBS (~ 7.4 pH) and AsA in D_2O , within the regions of -2800 and 400 ppm at 310.15 K, highlighting its partial reduction after 1 h from the final ^1H -NMR experiment as indicated by *.

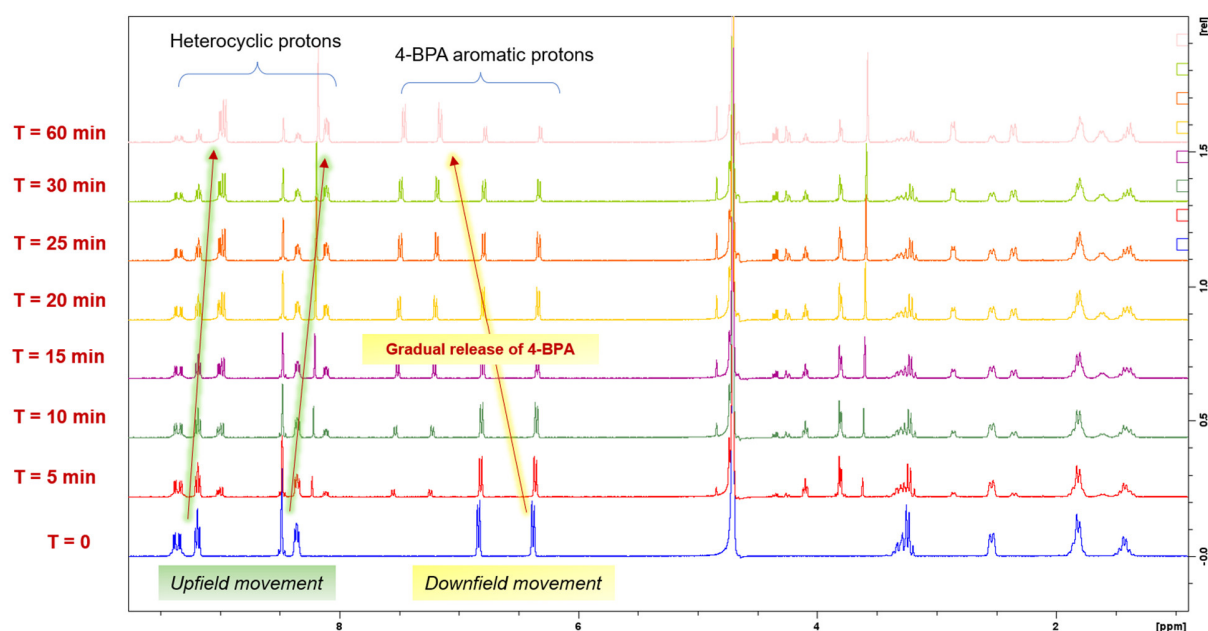


Figure S87: ^1H -NMR spectra of **5** with 10 mM PBS (~ 7.4 pH) and AsA in D_2O at 310.15 K, in different time intervals, highlighting the movement of resonances from the phenanthroline protons and the aromatic protons of the 4-FPA ligand as indicated by the red arrows. **T** represents time in min.

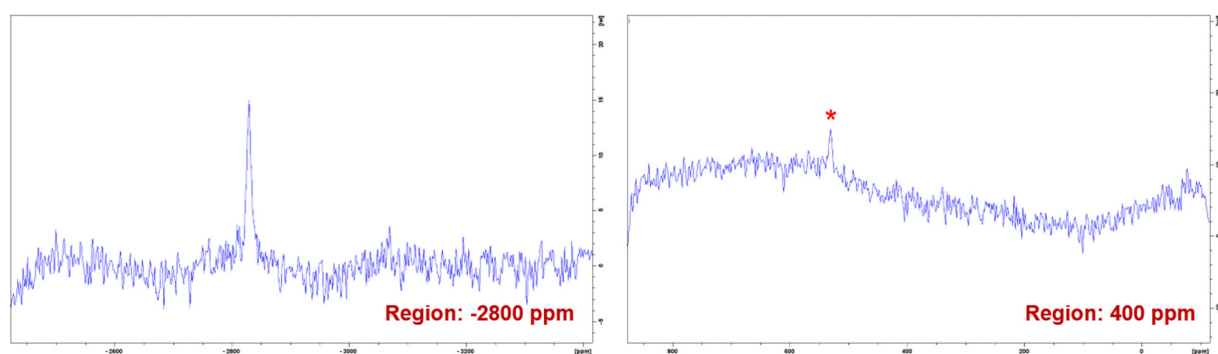


Figure S88: 1D- ^{195}Pt -NMR spectra of **5** with 10 mM PBS (~ 7.4 pH) and AsA in D_2O , within the regions of -2800 and 400 ppm at 310.15 K, highlighting its partial reduction after 1 h from the final ^1H -NMR experiment as indicated by *.

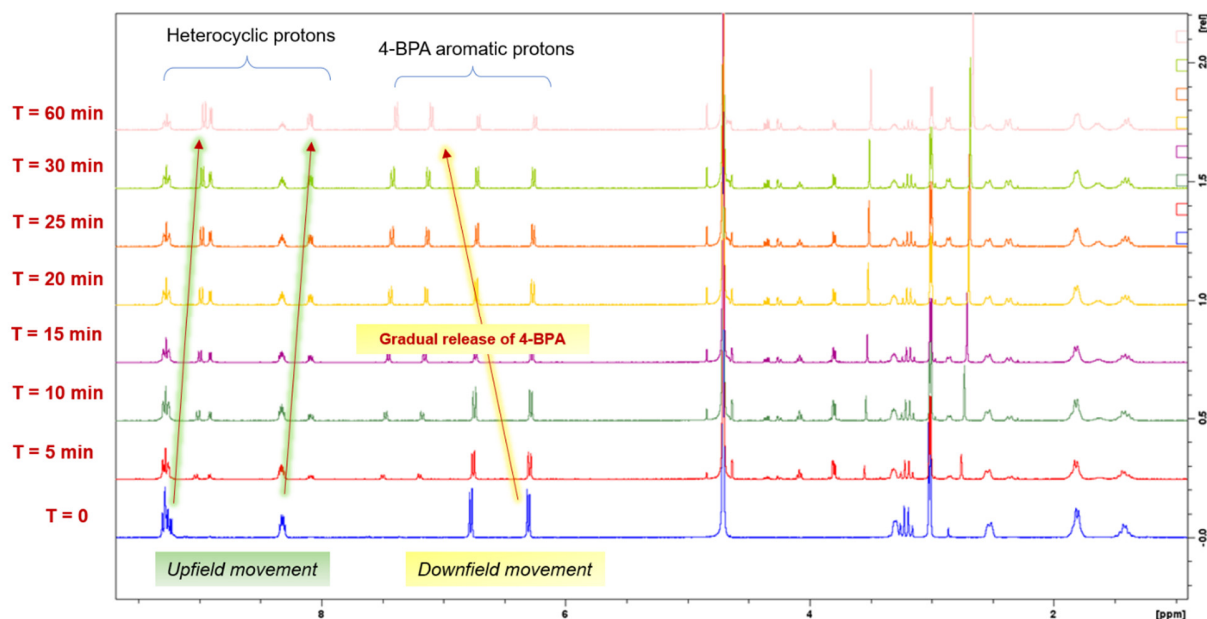


Figure S89: ^1H -NMR spectra of **6** with 10 mM PBS (~ 7.4 pH) and AsA in D_2O at 310.15 K, in different time intervals, highlighting the movement of resonances from the phenanthroline protons and the aromatic protons of the 4-FPA ligand as indicated by the red arrows. **T** represents time in min.

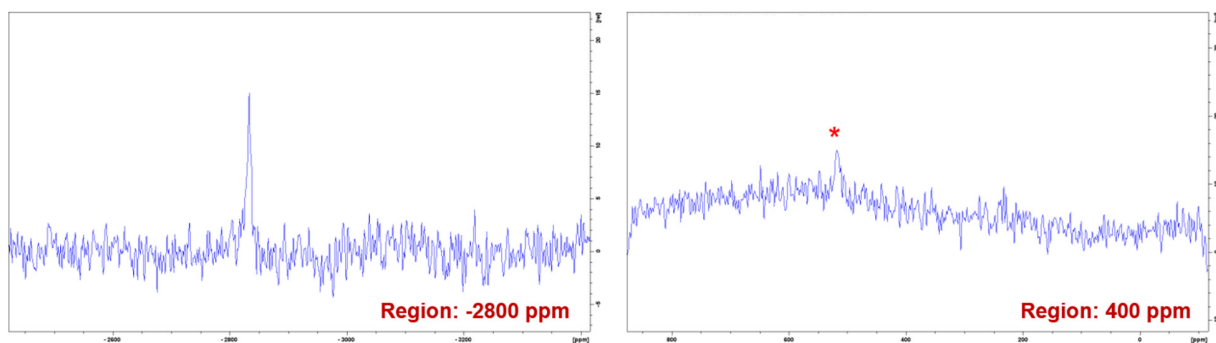


Figure S90: $1\text{D-}^{195}\text{Pt}$ -NMR spectra of **6** with 10 mM PBS (~ 7.4 pH) and AsA in D_2O , within the regions of -2800 and 400 ppm at 310.15 K, highlighting its partial reduction after 1 h from the final ^1H -NMR experiment as indicated by *.

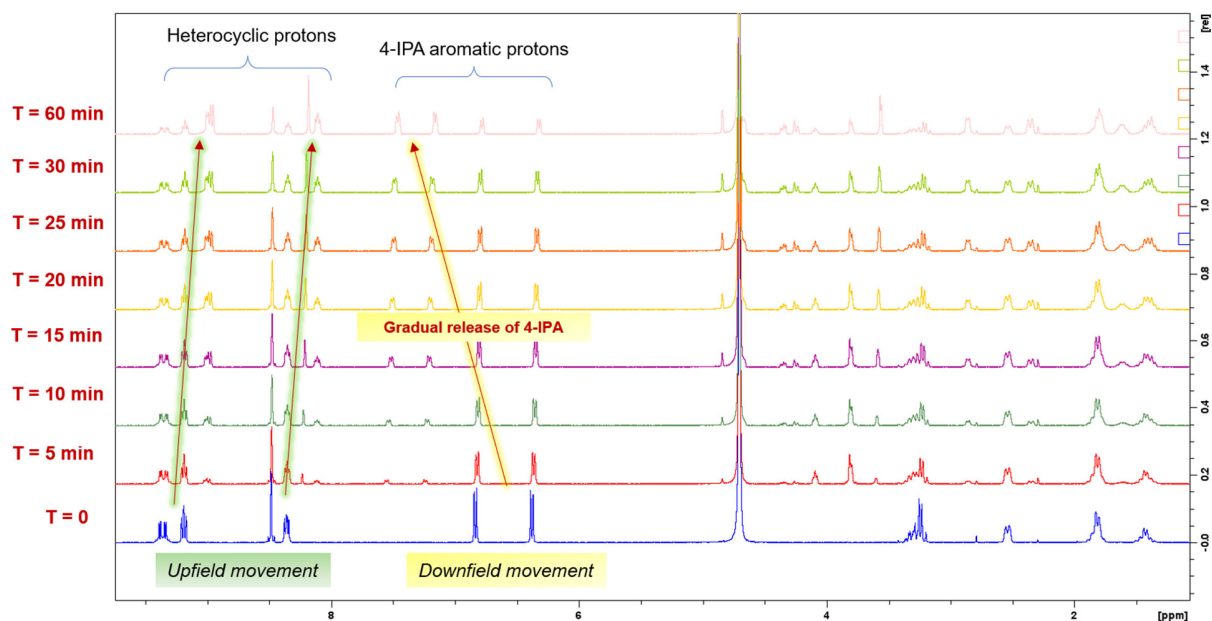


Figure S91: ^1H -NMR spectra of **7** with 10 mM PBS (~ 7.4 pH) and AsA in D_2O at 310.15 K, in different time intervals, highlighting the movement of resonances from the phenanthroline protons and the aromatic protons of the 4-FPA ligand as indicated by the red arrows. **T** represents time in min.

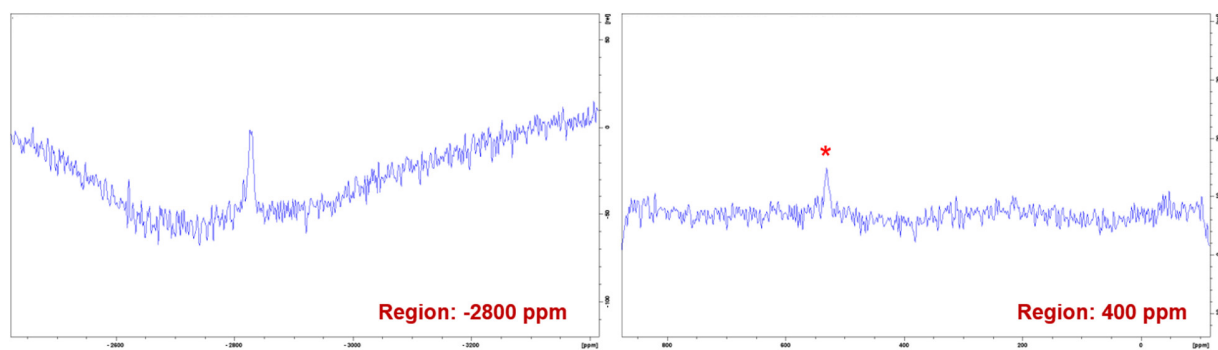


Figure S92: 1D- ^{195}Pt -NMR spectra of **7** with 10 mM PBS (~ 7.4 pH) and AsA in D_2O , within the regions of -2800 and 400 ppm at 310.15 K, highlighting its partial reduction after 1 h from the final ^1H -NMR experiment as indicated by *.

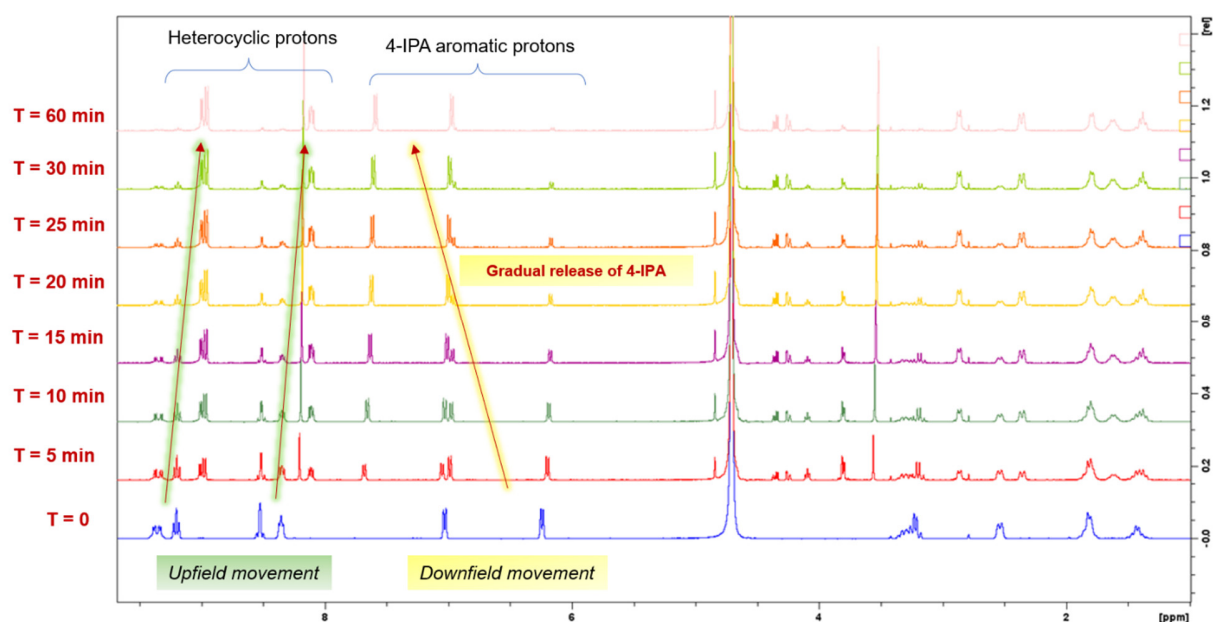


Figure S93: ^1H -NMR spectra of **8** with 10 mM PBS (~ 7.4 pH) and AsA in D_2O at 310.15 K, in different time intervals, highlighting the movement of resonances from the phenanthroline protons and the aromatic protons of the 4-FPA ligand as indicated by the red arrows. **T** represents time in min.

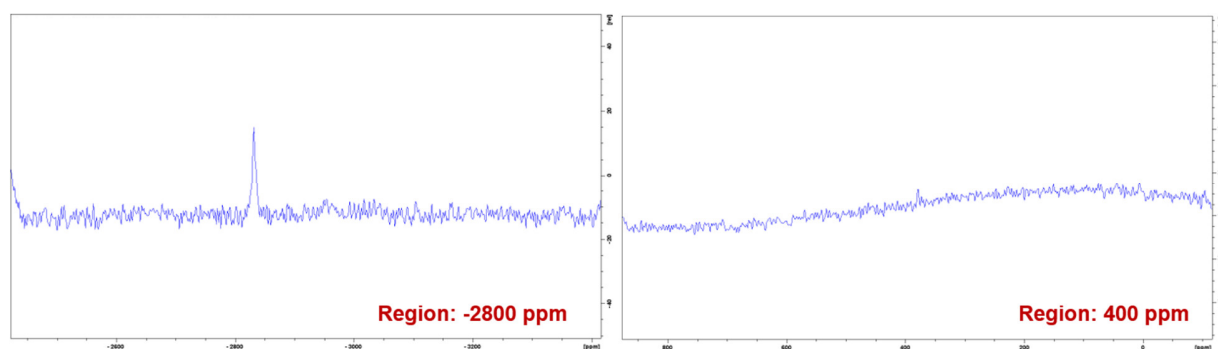


Figure S94: 1D- ^{195}Pt -NMR spectra of **8** with 10 mM PBS (~ 7.4 pH) and AsA in D_2O , within the regions of -2800 and 400 ppm at 310.15 K, highlighting its complete reduction after 1 h from the final ^1H -NMR experiment.

ROS experiments

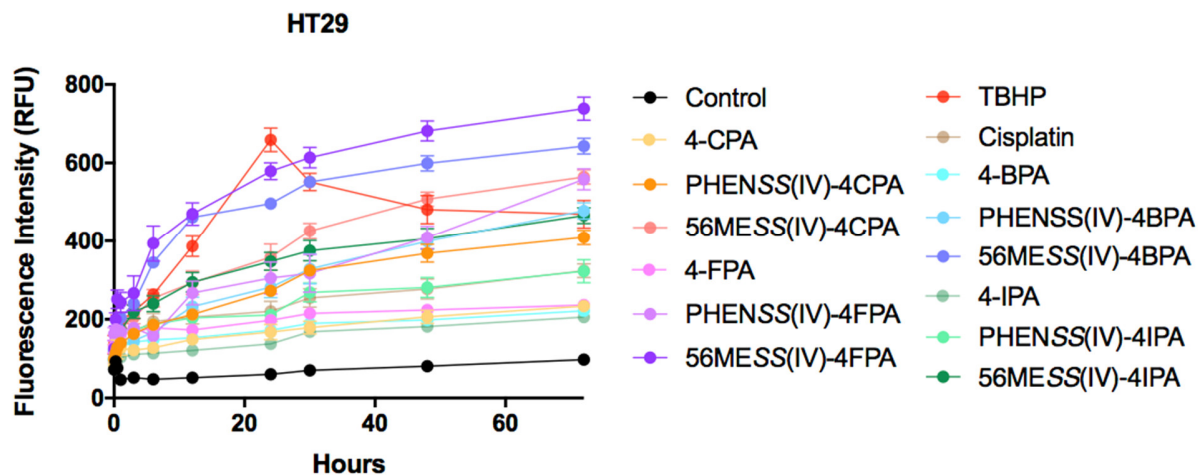


Figure S95: ROS production upon treatment with **1–8**, 4-CPA, 4-FPA, 4-BPA, 4-IPA and cisplatin in HT29 colon cells at 0, 0.25, 0.5, 1, 3, 6, 12, 24, 48 and 72 h. **PHENSS(IV)-4CPA** (1), **56MESS(IV)-4CPA** (2), **PHENSS(IV)-4FPA** (3), **56MESS(IV)-4FPA** (4), **PHENSS(IV)-4BPA** (5), **56MESS(IV)-4BPA** (6), **PHENSS(IV)-4IPA** (7), **56MESS(IV)-4IPA** (8). TBHP: t-butyl hydroperoxide. Data points denote mean \pm SEM. $n = 3$ from three independent experiments where samples were run in triplicates.