Supporting Information

Syntheses of previously reported compounds.

Preparation of transplatin, *trans*-[$PtCl_2(NH_3)_2$] (I)

The synthesis of transplatin was adapted from the method reported by Kauffman *et al*.[34] $K_2[PtCl_4]$ (1.81 g, 4.36 mmol) was dissolved in distilled water (60 mL) which was acidified with 5 drops of HCl (10 M). The solution was heated to 60 °C with stirring. Ammonium hydroxide (10 mL, 14 % v/v) was added to the mixture dropwise over 30 minutes. Over the course of the reaction the mixture changed from red to dull yellow/light brown in colour. Some formation of Magnus green salt resulted as a green precipitate, which was removed by filtration. Further heating of the supernatant yielded a pale-yellow coloured mixture. The volume was reduced to approximately 5 mL before HCl (150 mL, 6 M). The mixture was stirred until a yellow precipitate formed. The solid was collected by filtration and was washed with water and cold ethanol. Additional crops were obtained by adding HCl (40 mL, 6 M) to the filtrate and reducing the volume. Yield: 0.98 g, 3.28 mmol, 75%.

Preparation of *trans*-[$Pt(OAc)_2(NH_3)_2$] (IV)

The synthesis of *trans*-$[Pt(OAc)_2(NH_3)_2]$ was adapted from the methods reported by Ma *et al*.[21]

Transplatin (200 mg, 0.67 mmol) was suspended in distilled water (15 mL) and stirred at room temperature, silver acetate (217 mg, 1.3 mmol) was added and the mixture was stirred for a further 24- 48 hours. The reaction was monitored *in situ* periodically using ^{195}Pt NMR and the AgCl was removed by filtration. The solvent was removed under a stream of N_2(g). The crude solid was washed with methanol (2 mL) and diethyl ether (20 mL) and the colourless solid was collected by filtration. Yield: 176 mg, 0.51 mmol, 76%.

^{1}H NMR (400 MHz, D_2O, ppm): δ 3.83 (br, 4H, NH_3), 2.05 (s, 6H, CH_3). ^{195}Pt NMR (400 MHz, D_2O, ppm): δ -1444. Elemental analysis calculated for $C_4H_{12}N_2O_4Pt.H_2O$: C, 13.15; H, 3.86; N, 7.67. Found: C, 12.88; H, 3.64; N, 8.18.

Preparation of *trans*-[$PtCl_2(NH_3)(py)$] (V)

The synthesis of trans-[$PtCl_2(NH_3)(py)$] was adapted from the methods reported by Ma *et al*.[21] and Najajreh *et al*.[35]

cis-[$PtI_2(NH_3)_2$] (500 mg, 1.03 mmol) was suspended in distilled water (15 mL) and stirred at room temperature. Ag_2SO_4 (320 mg, 1.03 mmol) was added and the mixture was stirred for a further 24 hours in the absence of light. Insoluble silver iodide formed as a yellow precipitate and was removed by filtration. Pyridine (100 µL, 1.25 mmol) was added to the filtrate and the mixture was stirred for 24 hours. HCl (3 mL, 5 M) was added and the mixture was heated to reflux at 90 – 95 °C for 30 – 45 minutes, or until the colourless mixture changed to pale yellow. A pale-yellow precipitate formed upon cooling and was collected by filtration and washed with distilled water, followed by cold ethanol. Additional crops were obtained by refluxing the remaining filtrate in HCl. Combined yield: 273 mg, 0.75 mmol, 73%. ^{1}H NMR (500 MHz, DMSO-d_6, ppm): δ 9.31 (d, *J*=5.2 Hz, 2H, CH), 8.44 (t, *J*=7.7 Hz, 1H, CH), 7.91 (t, *J*= 7.4 Hz, 2H, CH), 4.2 (br, 3H, NH_3)). ^{13}C NMR (500 MHz, DMSO-d_6, ppm): δ 153.07 (CH), 138.27 (CH), 125.32 (CH). ^{195}Pt NMR (500 MHz, DMF, ppm): δ -2019. Elemental analysis calculated for $C_5H_8N_2Cl_2Pt$: C, 16.58; H, 2.23; N, 7.74. Found: C, 16.77; H, 2.24; N, 7.76.

Preparation of *trans, trans, trans*-[$PtCl_2(OH)_2(NH_3)_2$] (VII)

Transplatin (150 mg, 0.5 mmol) was suspended in distilled water (8 mL) and stirred at room temperature, hydrogen peroxide (1 mL, 30 %v/v) was added and the mixture was stirred for a further 24 hours. The solvent was removed under a stream of N_2(g). The crude solid was washed with methanol (1 mL) and diethyl ether (10 mL) and the pale-yellow solid was collected by filtration. Yield: 127 mg, 0.38 mmol, 76%. ^{195}Pt NMR (400 MHz, D_2O, ppm): δ 727.

Preparation of *trans, trans, trans*-[$PtCl_2(OAc)_2(NH_3)_2$] (VIII)

The synthesis of trans, trans, trans-[$PtCl_2(OAc)_2(NH_3)_2$] was adapted from the methods described by Giandomenico *et al*.[36] and Khokhar *et al*.[37]

trans, trans, trans-[$PtCl_2(OH)_2(NH_3)_2$] (75 mg, 0.22 mmol) was suspended in DMA (5 mL, anhydrous) and stirred at room temperature. Acetic anhydride (200 µL, 2.1 mmol) was added and the mixture was stirred for a further 24 to 72 hours. The progress of the reaction was periodically monitored by ^{195}Pt NMR spectroscopy. The solvent was removed under a stream of N_2(g). The crude solid was washed with methanol (2 mL) and diethyl ether (15 mL) and the pale-yellow solid was collected by filtration. Yield: 57 mg, 0.14 mmol, 62%. ^{1}H NMR (400 MHz, D_2O, ppm): δ 2.13 (s, 6H, CH_3). ^{195}Pt NMR (400 MHz, D2O, ppm): δ 1099.

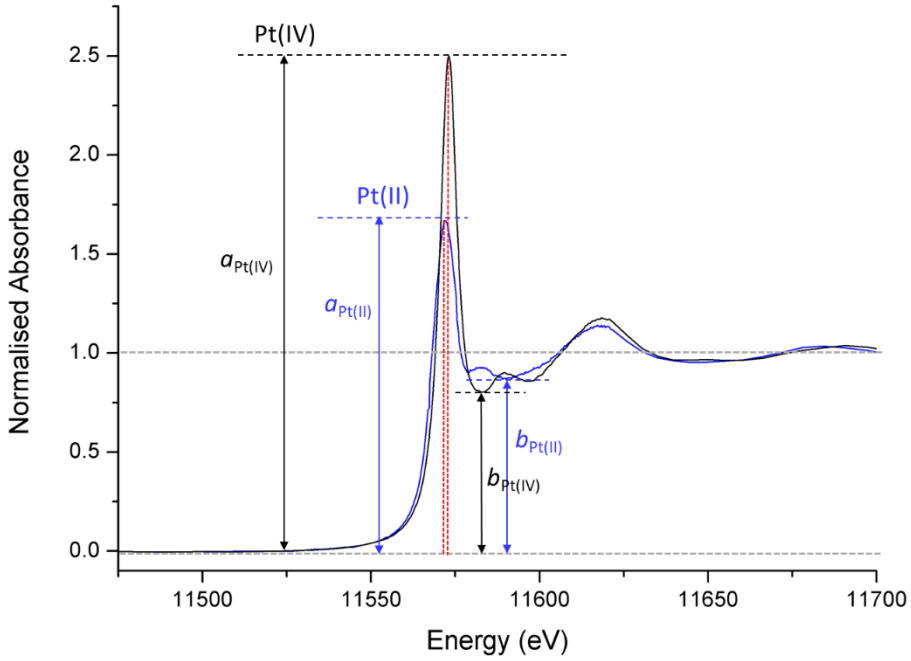


Figure S1. Normalised XANES spectra of Pt(II); (Blue), and Pt(IV); (black), corresponding to platinum complexes; *trans, trans, trans*-[$Pt(OAc)_4(NH_3)_2$](**XI**) and *trans*-[$Pt(OAc)_2(NH_3)_2$](**IV**). The "white line" peak at 11.569 eV Pt(II) 11.571 keV Pt(IV); (red), and the parameters *a* and *b* for the corresponding platinum(II) and platinum(IV) complexed used to calculate the peak height ratio, *a/b*.

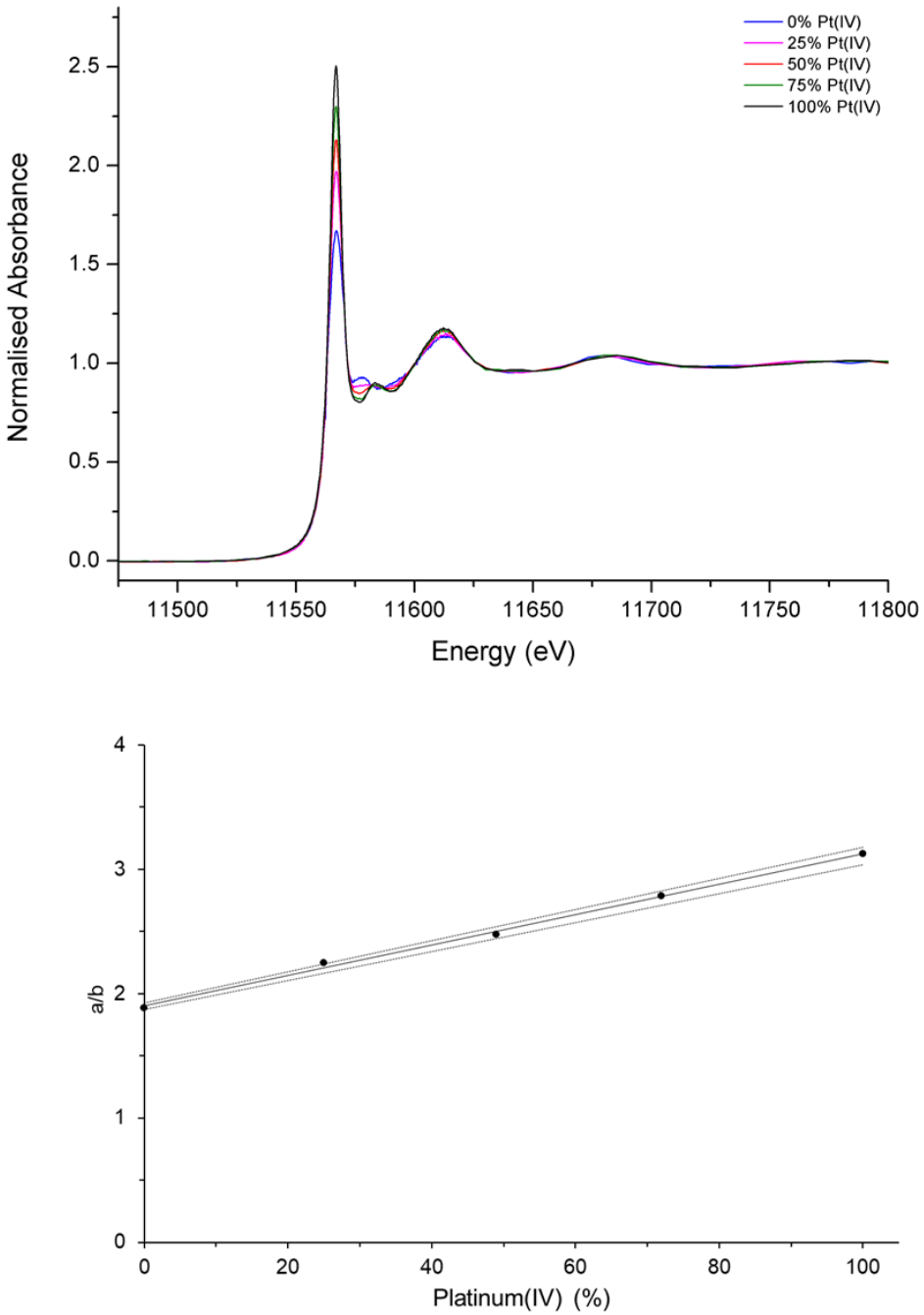


Figure S2. Normalised XANES spectra of *trans*-$[Pt(OAc)_2(NH_3)_2]$(**IV**), *trans, trans, trans*-$[Pt(OAc)_4(NH_3)_2$(**XI**) and 25:75; 50:50; 75:25 molar ratio mixtures (top) and linear fit of peak height ratios, *a/b*, derived from XANES spectra of *trans*-$[Pt(OAc)_2(NH_3)_2$ (**IV**), *trans, trans, trans*-$[Pt(OAc)_4(NH_3)_2$(**XI**) and 25:75; 50:50; 75:25 mixtures (R^2= 0.9960) (bottom).

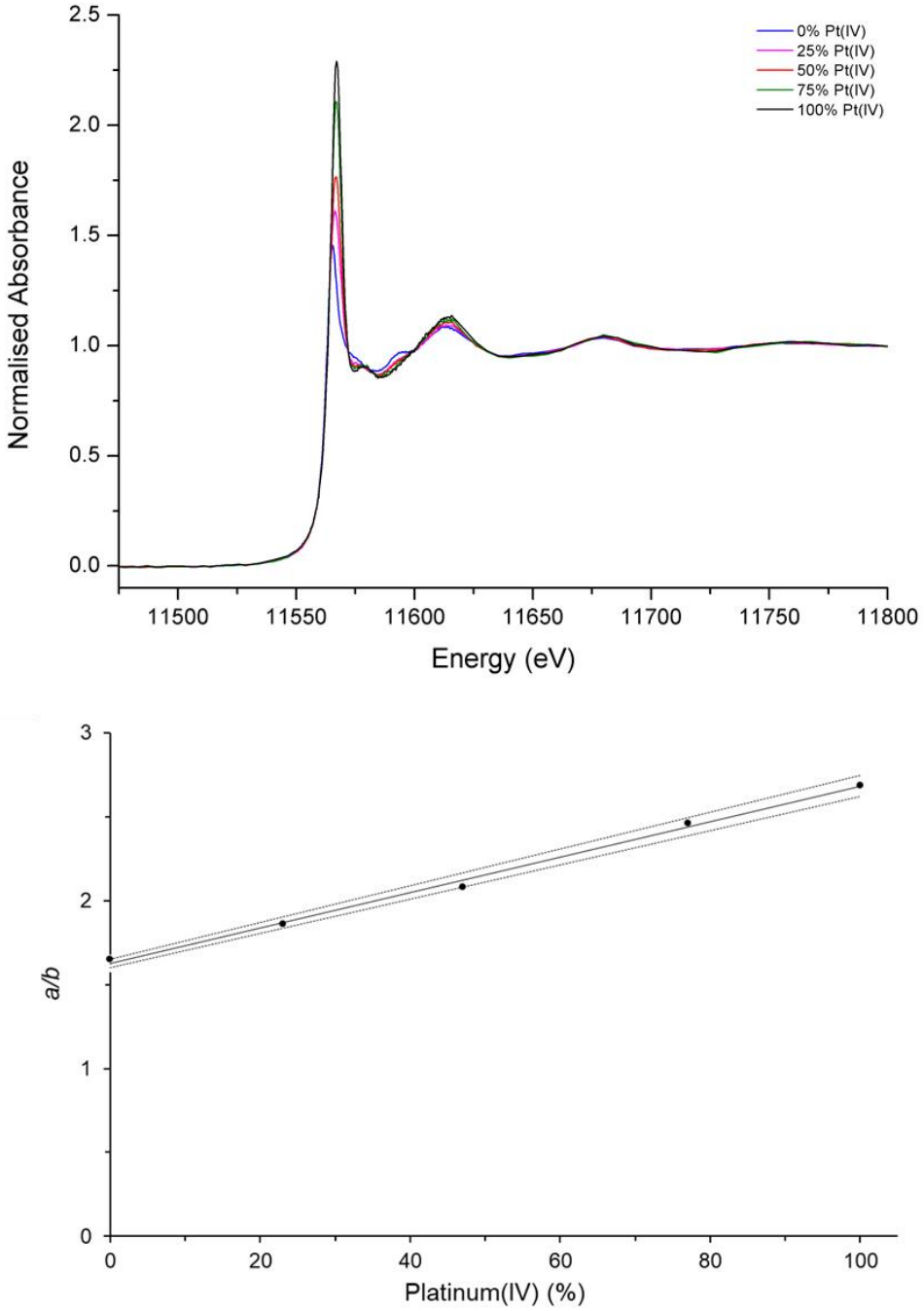


Figure S3. Figure Normalised XANES spectra of *trans*-$[PtCl_2(NH_3)_2]$(**I**), *trans, trans, trans*-$[PtCl_2(OAc)_2(NH_3)_2]$ (**VIII**) and 25:75; 50:50; 75:25 molar ratio mixtures (top) and linear fit of peak height ratios, *a/b*, derived from XANES spectra of *trans*-$[PtCl_2(NH_3)_2]$ (**I**), *trans, trans, trans*-$[PtCl_2(OAc)_2(NH_3)_2]$ (**VIII**) and 25:75; 50:50; 75:25 mixtures (R^2= 0.9885) (bottom).

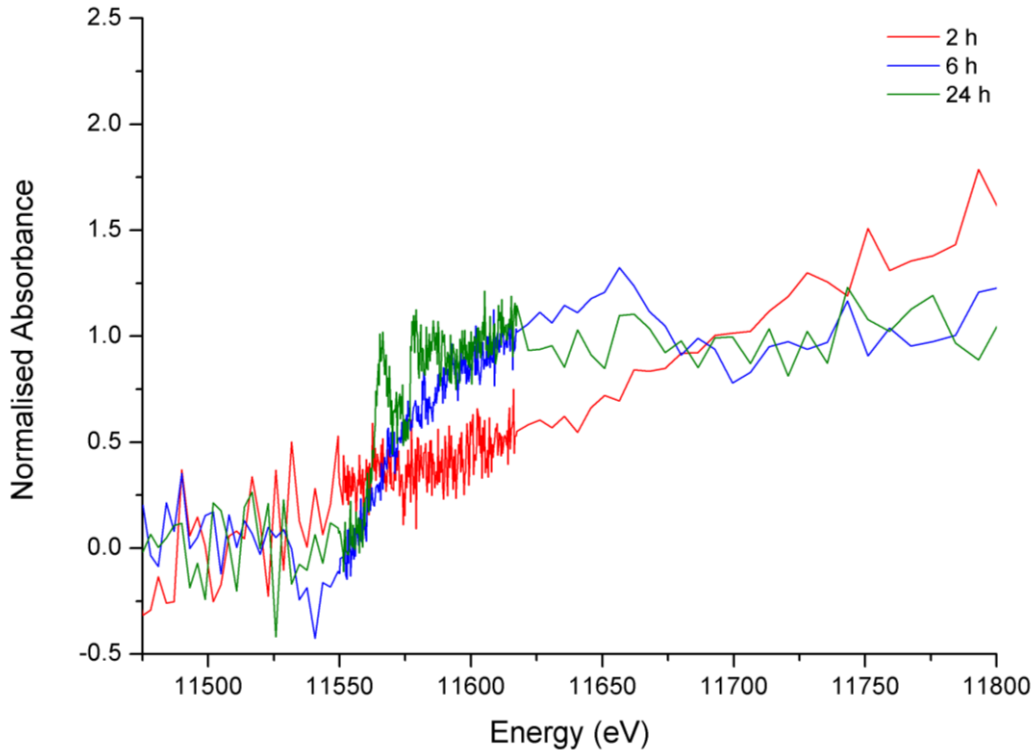


Figure S4. Normalised XANES spectra of DLD-1 human colorectal adenocarcinoma cells dosed with 50 μM of *trans, trans, trans*-[$Pt(OAc)_2(OH)_2(NH_3)_2$] (**X**) and incubated for 2 (red), 6 (blue), and 24 (green) hours.

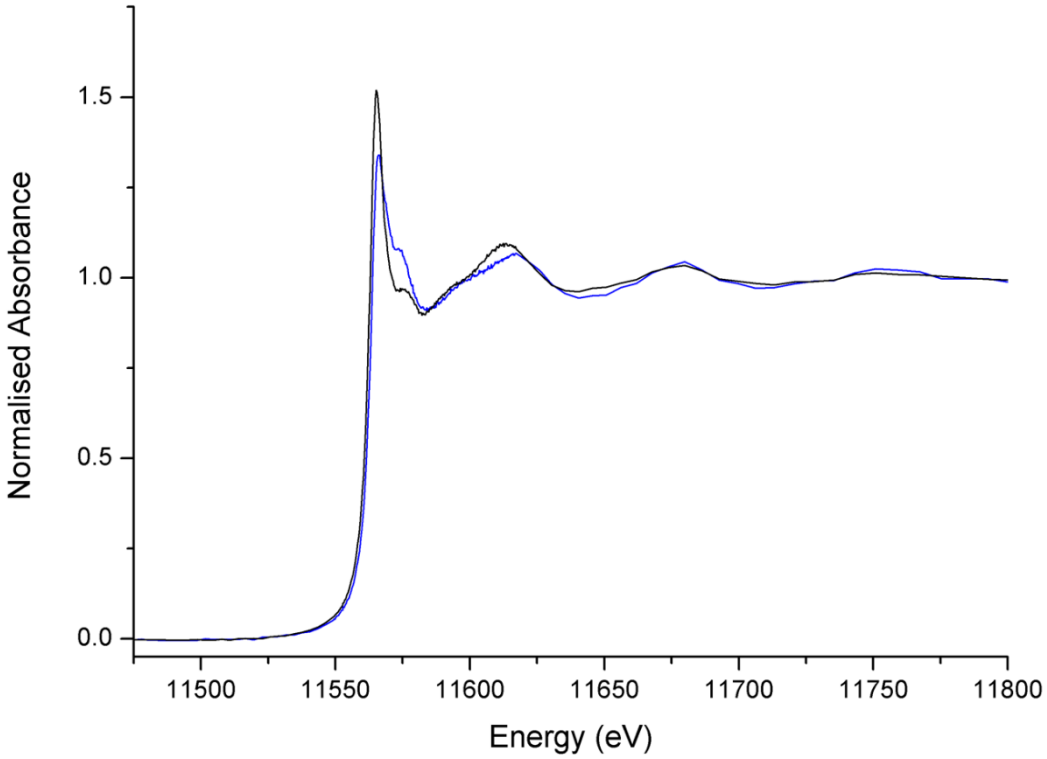


Figure S5. Normalised XANES spectra of cisplatin (*cis*-[$PtCl_2(NH_3)_2$]) (**II**) (black) and its cysteine bound analogue *cis*-[$Pt(cys)_2(NH_3)_2$] (blue).

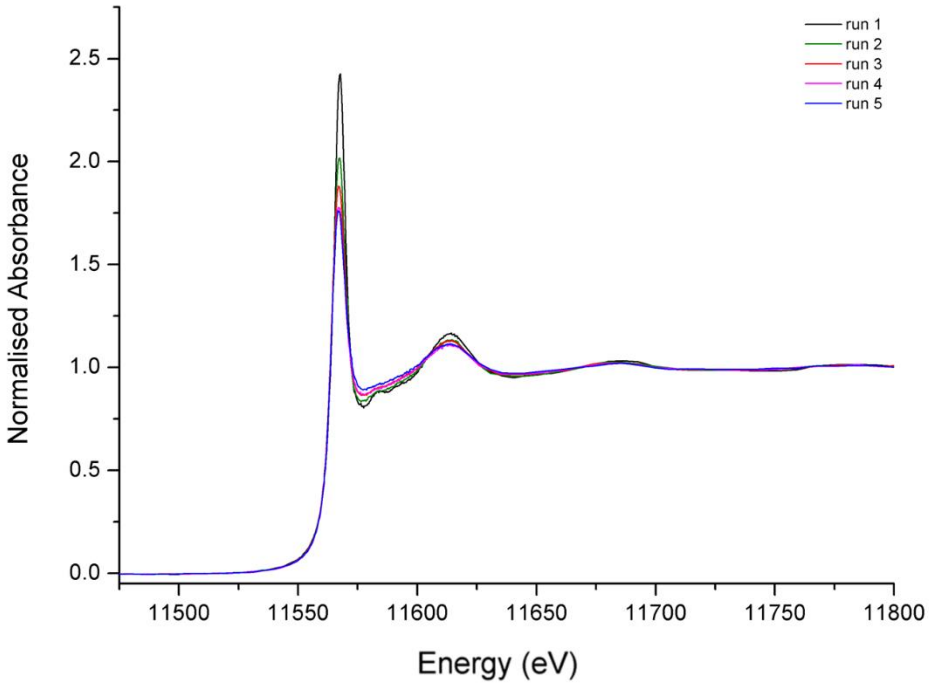


Figure S6. Radiation hardness testing of *trans*-[Pt(OAc)$_2$(ox)(en)] by repeated XANES scans of the same region of the solid sample. Repeated radiation exposure resulted in the significant degradation of the sample in subsequents.

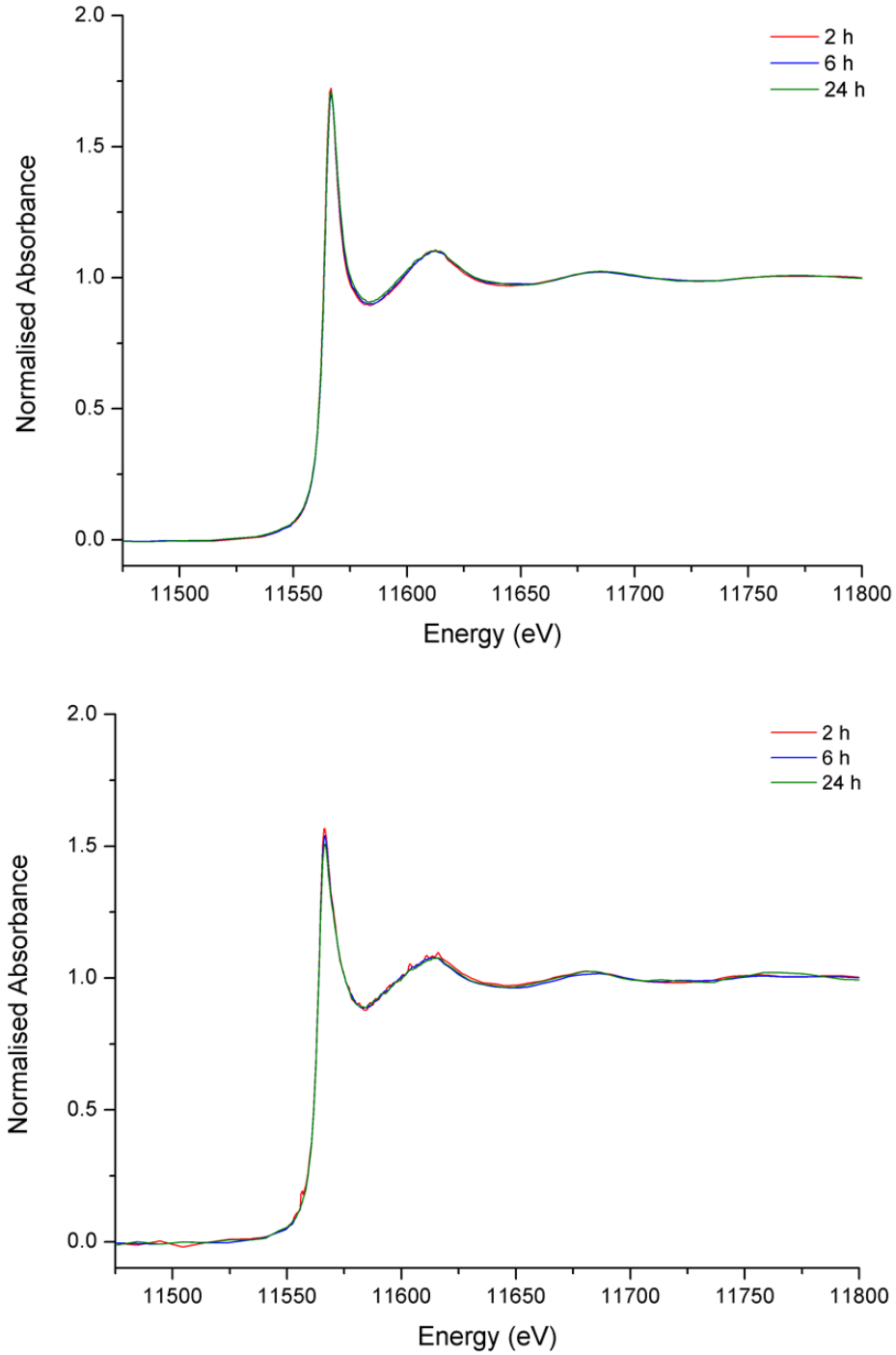


Figure S7. Normalised XANES spectra of human serum (top) and whole human blood (bottom) dosed with 50 μM of *trans, trans, trans*-$[PtCl_2(OH)_2(NH_3)_2]$ (**VII**) and incubated for 2 (red), 6 (blue), and 24 (green) hours

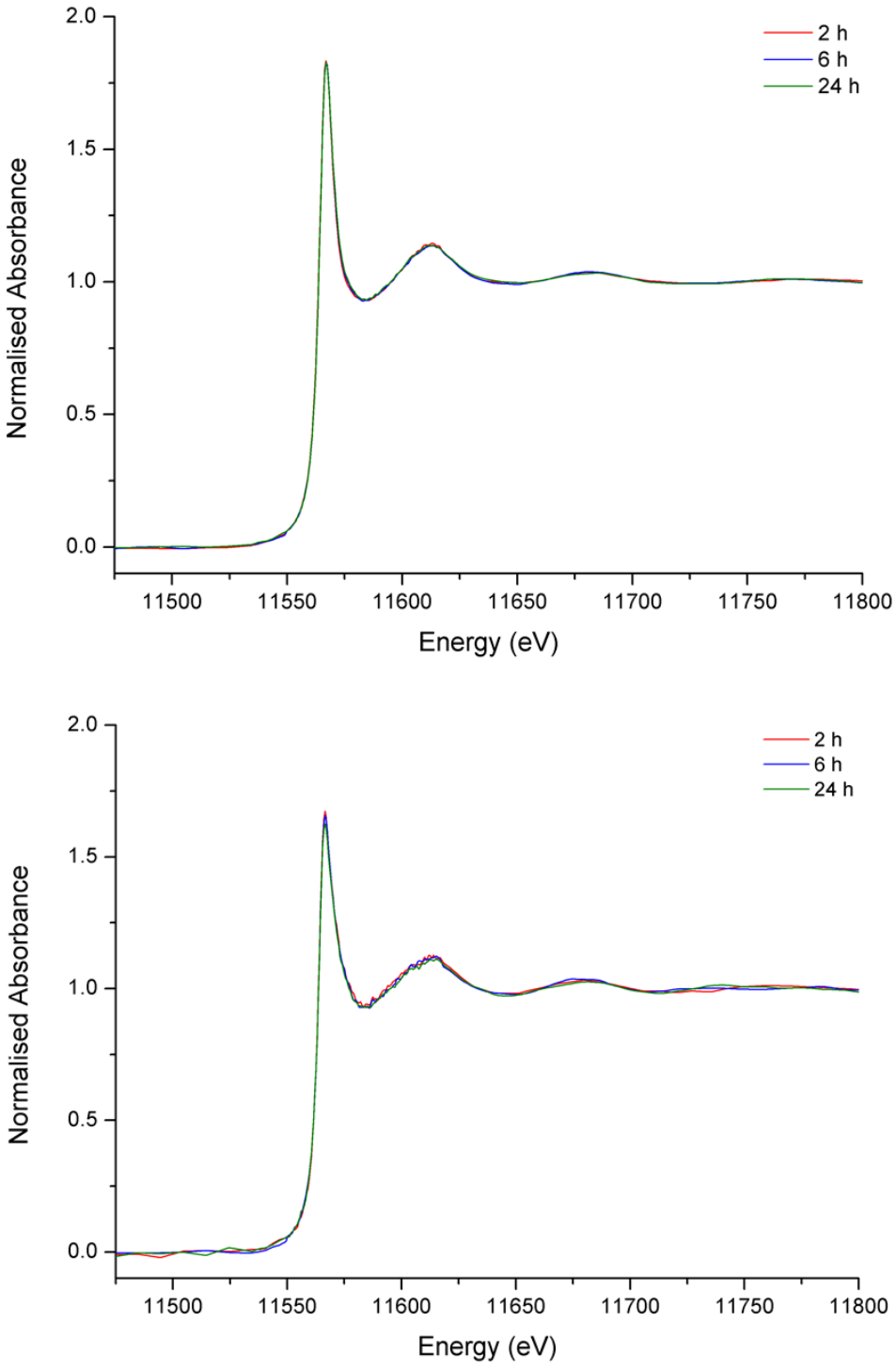


Figure S8. Normalised XANES spectra of human serum (top) and whole human blood (bottom) dosed with 50 μM of *trans, trans, trans*-$[PtCl_2(OAc)_2(NH_3)_2]$ (**VIII**) and incubated for 2 (red), 6 (blue), and 24 (green) hours

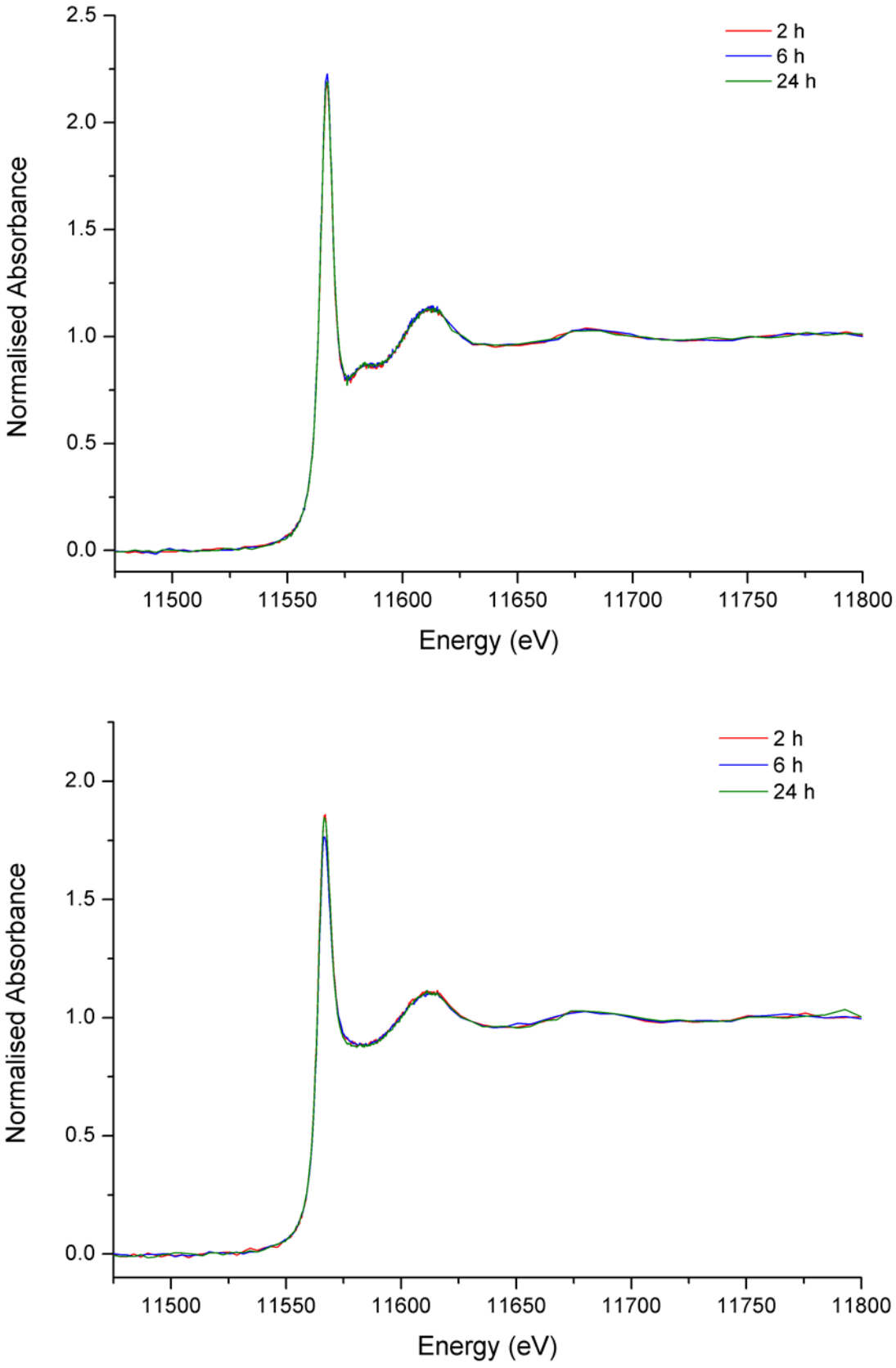


Figure S9. Normalised XANES spectra of human serum (top) and whole human blood (bottom) dosed with 50 μM of *trans, trans, trans*-$[Pt(OAc)_4(NH_3)_2]$ (**XI**) and incubated for 2 (red), 6 (blue), and 24 (green) hours.

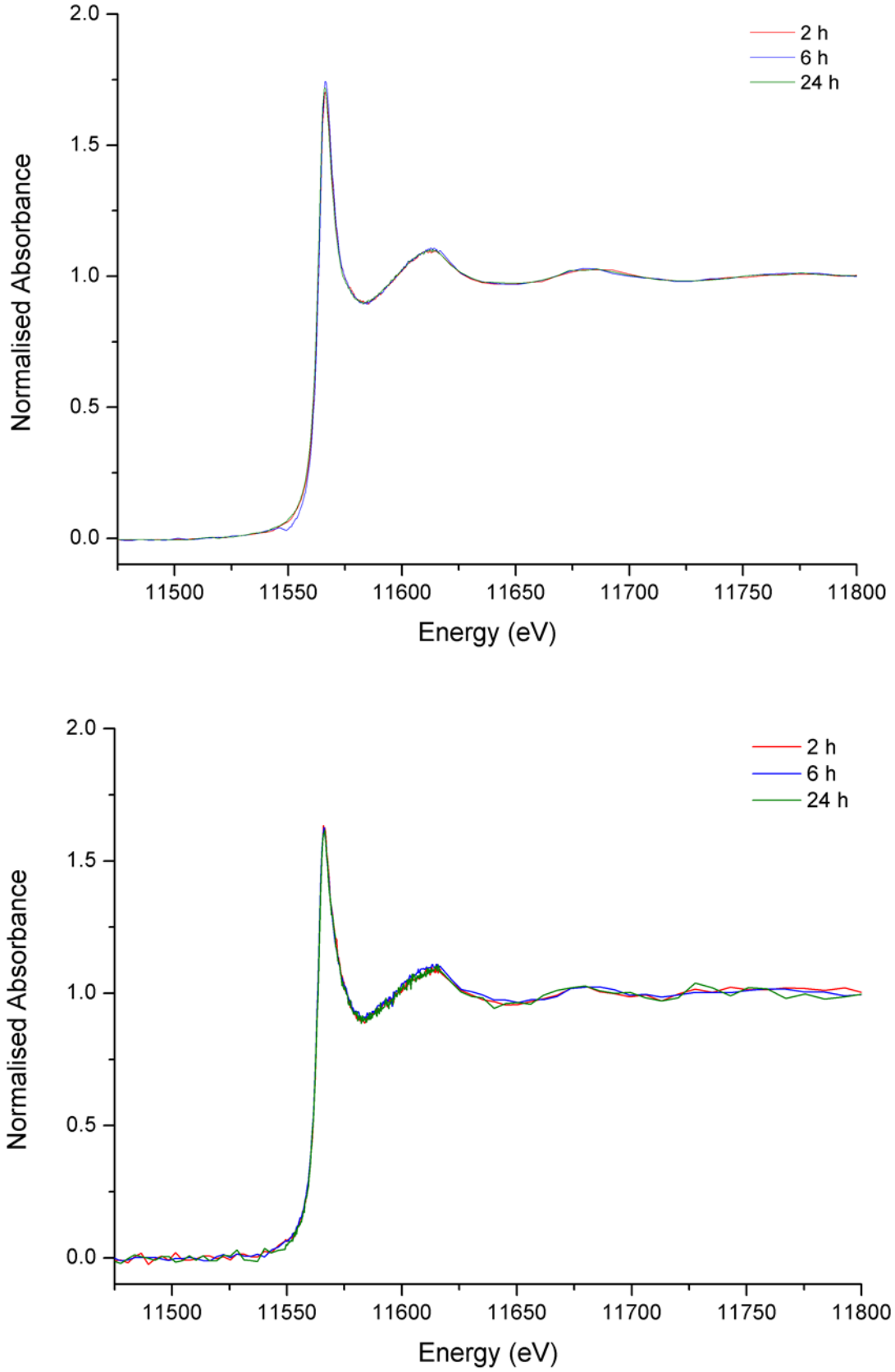


Figure S10. Normalised XANES spectra of human serum (top) and whole human blood (bottom) dosed with 50 μM of *transplatin* (**I**) and incubated for 2 (red), 6 (blue), and 24 (green) hours.

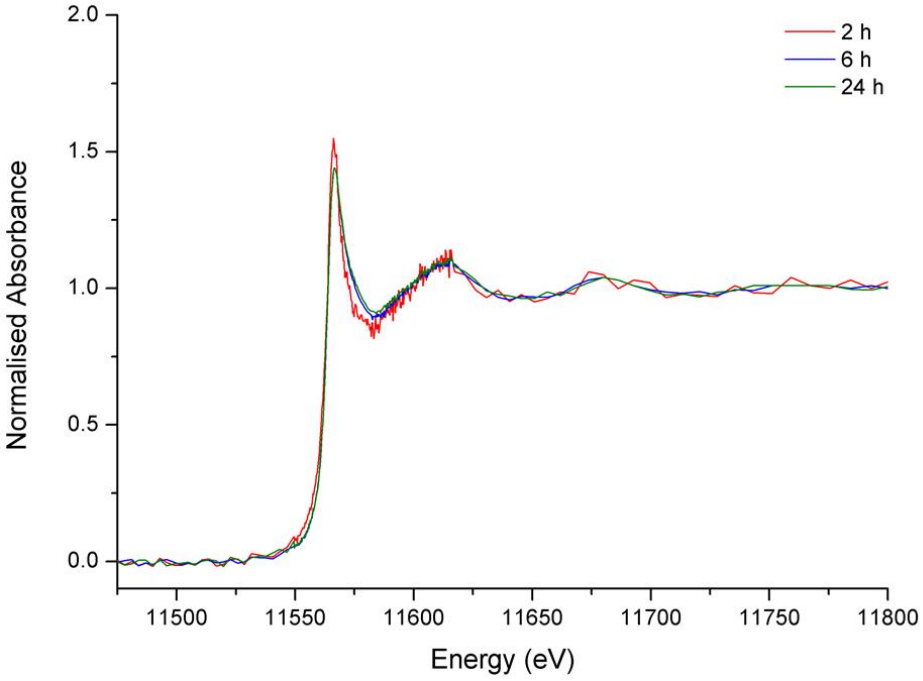


Figure S11. Normalised XANES spectra of DLD-1 human colorectal adenocarcinoma cells dosed with 50 μM of *trans, trans, trans*-$[PtCl_2(OH)_2(NH_3)_2]$ (**VII**) and incubated for 2 (red), 6 (blue), and 24 (green) hours.

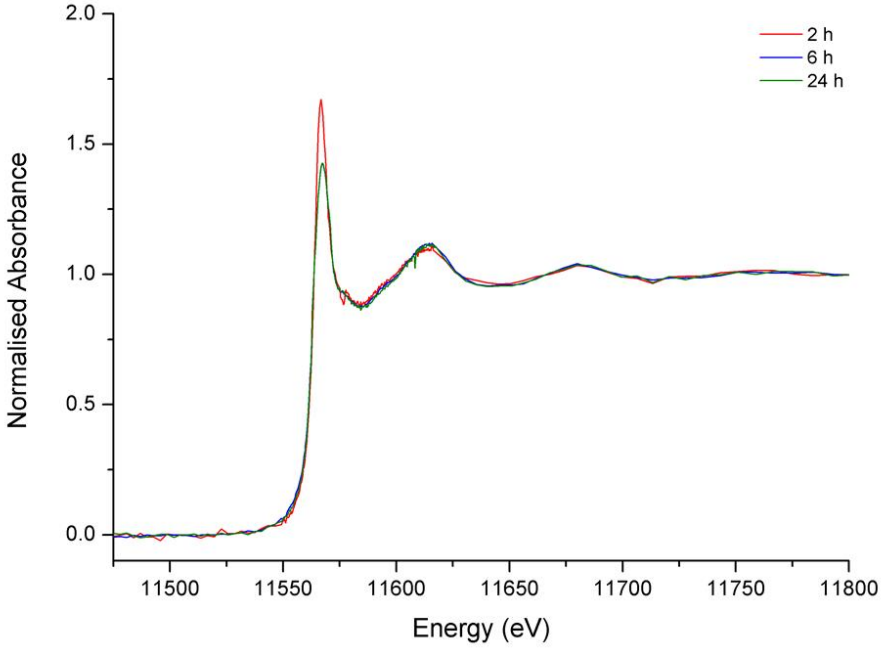


Figure S12. Normalised XANES spectra of DLD-1 human colorectal adenocarcinoma cells dosed with 50 μM of *trans, trans, trans*-$[PtCl_2(OAc)_2(NH_3)_2]$ (**VIII**) and incubated for 2 (red), 6 (blue), and 24 (green) hours.

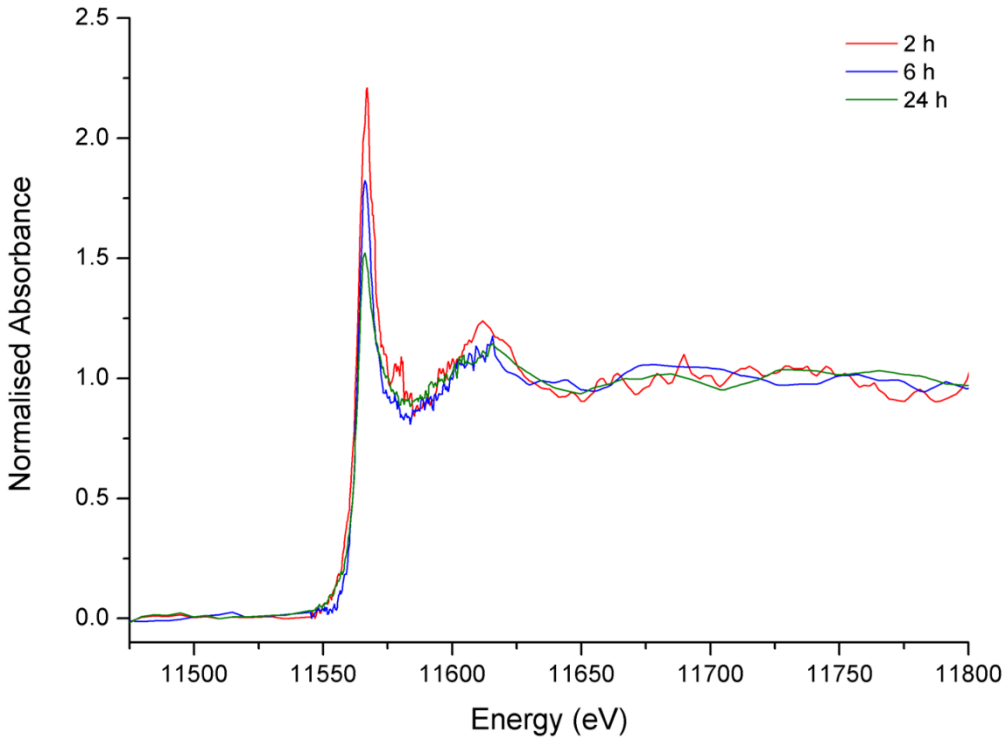


Figure S13. Normalised XANES spectra of DLD-1 human colorectal adenocarcinoma cells dosed with 50 μM of *trans, trans, trans*-$[Pt(OAc)_4(NH_3)_2]$ (**XI**) and incubated for 2 (red), 6 (blue), and 24 (green) hours.

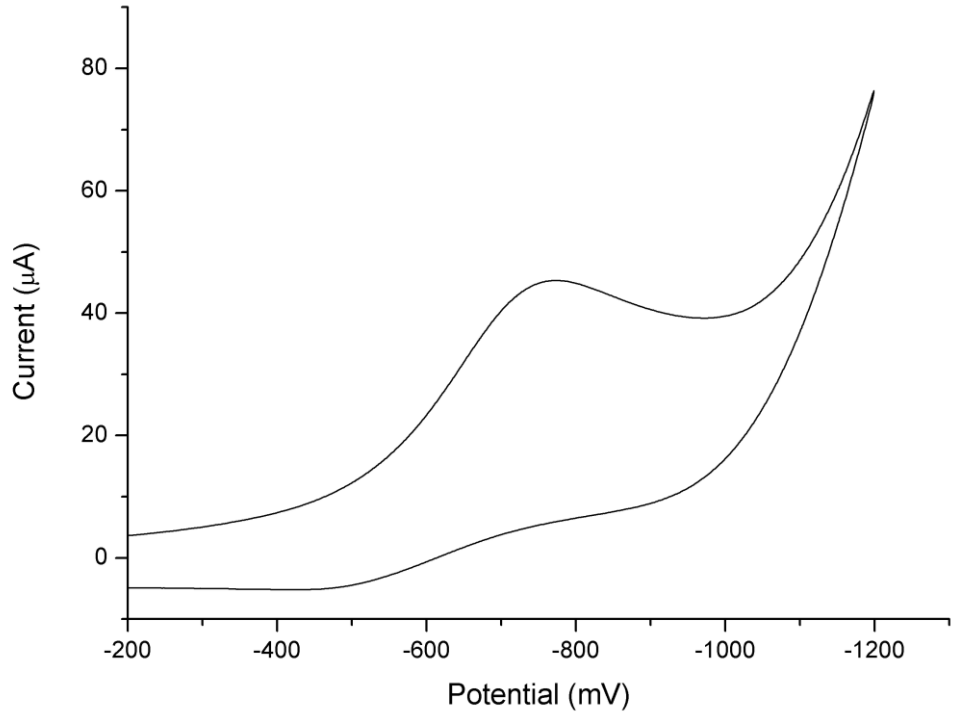


Figure S14. Cyclic voltammogram of complex *trans, trans, trans*-$[PtCl_2(OH)_2(NH_3)_2]$ (**VII**) in 0.1 M KCl at a scan rate of 100 mVs^{-1}, referenced to Ag/AgCl.

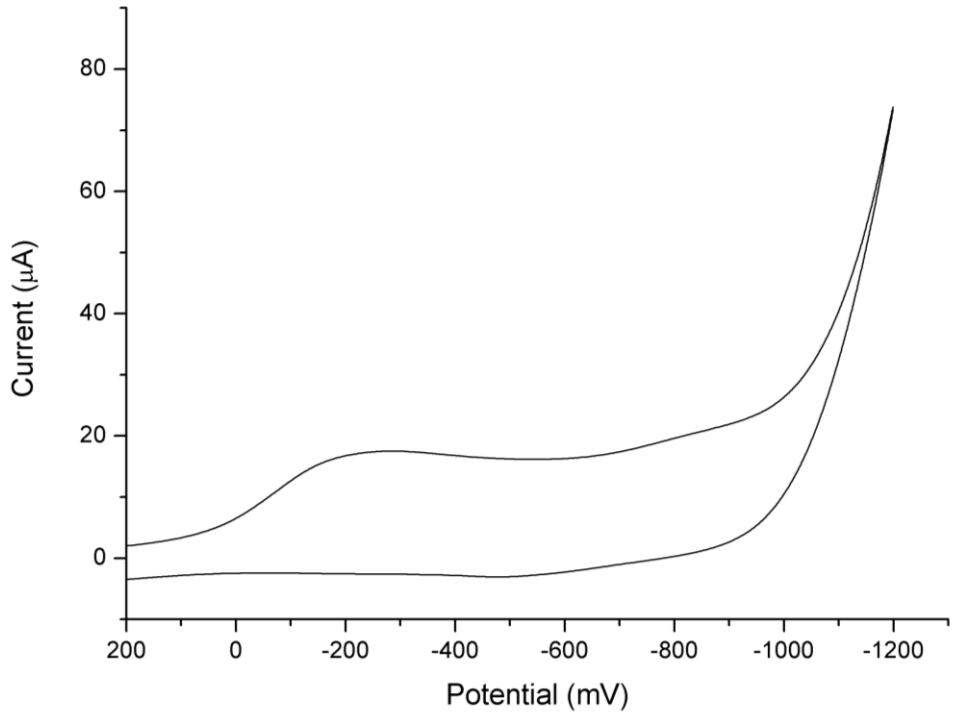


Figure S15. Cyclic voltammogram of complex *trans, trans, trans*-$[PtCl_2(OAc)_2(NH_3)_2]$ (**VIII**) in 0.1 M KCl at a scan rate of 100 mVs^{-1}, referenced to Ag/AgCl.

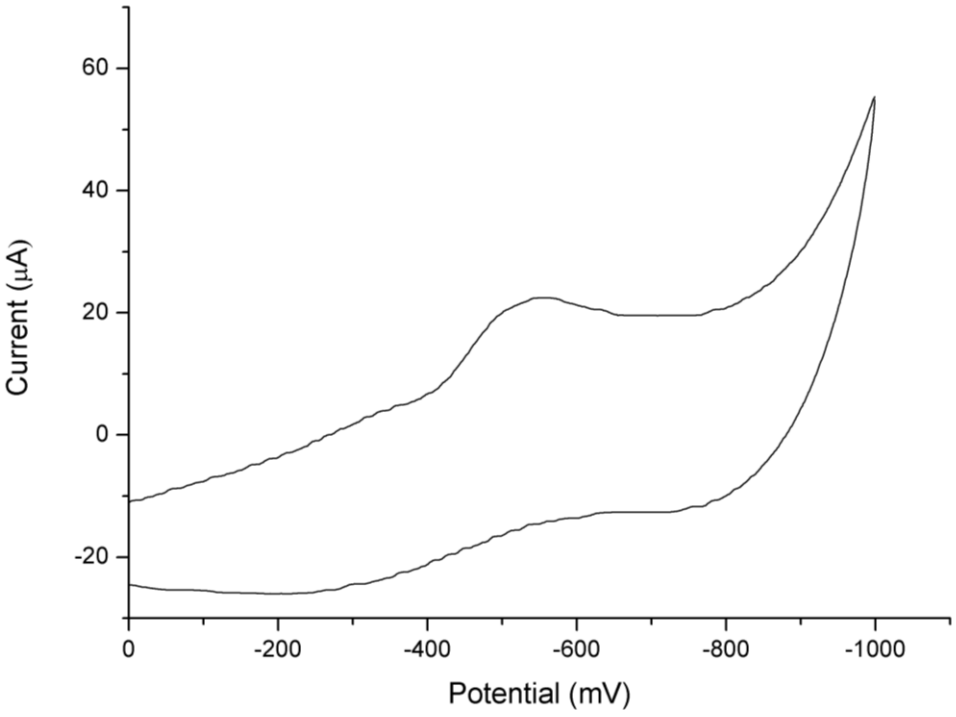


Figure S16. Cyclic voltammogram of complex *trans, trans, trans*-$[PtCl_2(OAc)_2(NH_3)_2]$ (**VIII**) in 0.1 M KCl at a scan rate of 100 mVs^{-1}, referenced to Ag/AgCl.

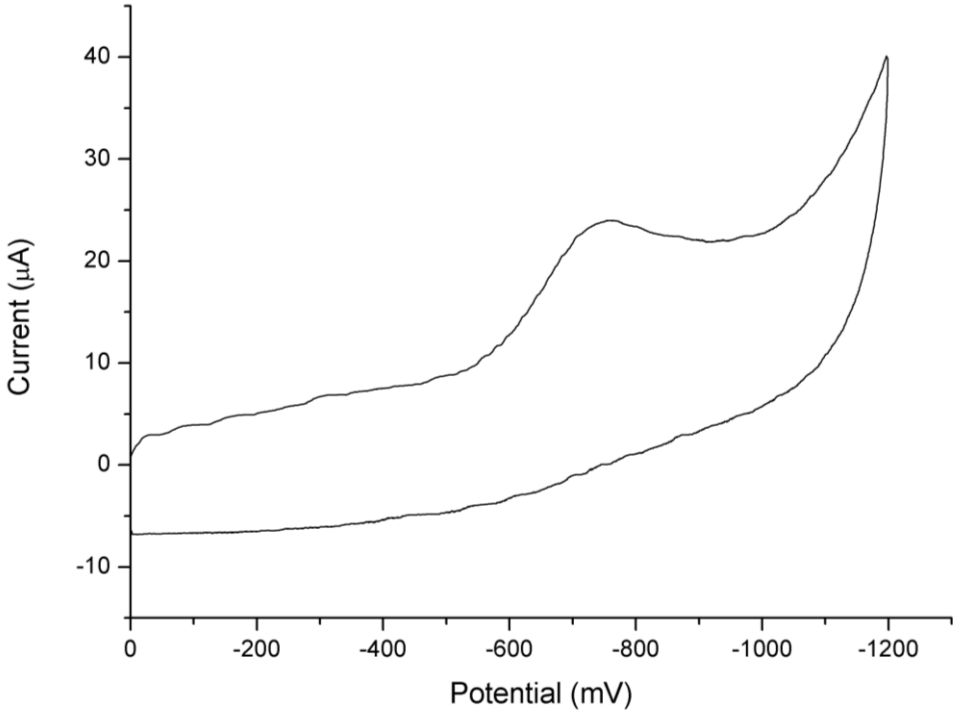


Figure S17. Cyclic voltammogram of complex *trans, trans, trans*-$[Pt(OAc)_4(NH_3)_2]$ (**XI**) in 0.1 M KCl at a scan rate of 100 mVs^{-1}, referenced to Ag/AgCl.

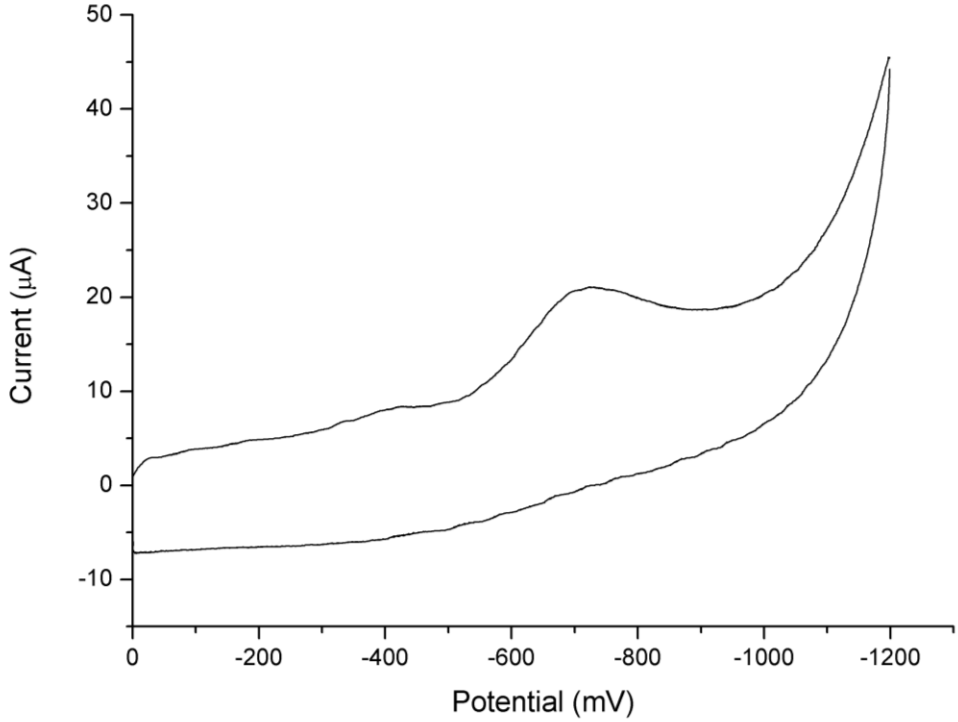


Figure S18. Cyclic voltammogram of complex *trans, trans, trans*-$[Pt(OAc)_2(OPr)_2(NH_3)_2]$ (**XII**) in 0.1 M KCl at a scan rate of 100 mVs^{-1}, referenced to Ag/AgCl.

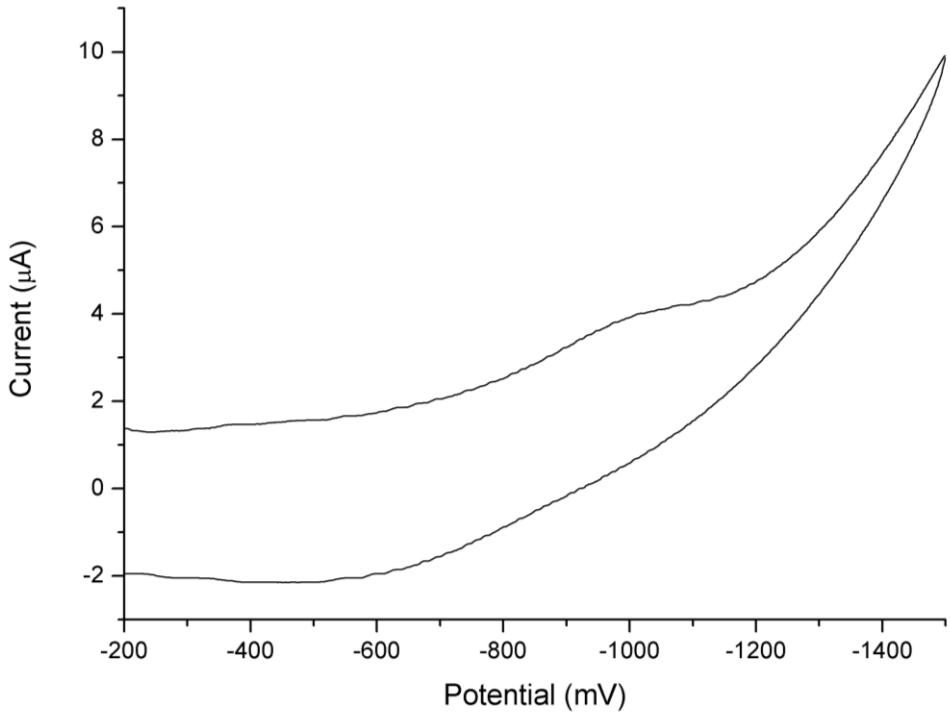


Figure S19. Cyclic voltammogram of complex *trans, trans, trans*-[$Pt(OAc)_3(OH)(NH_3)_2$] (**X**) in 0.1 M KCl at a scan rate of 100 mVs^{-1}, referenced to Ag/AgCl.

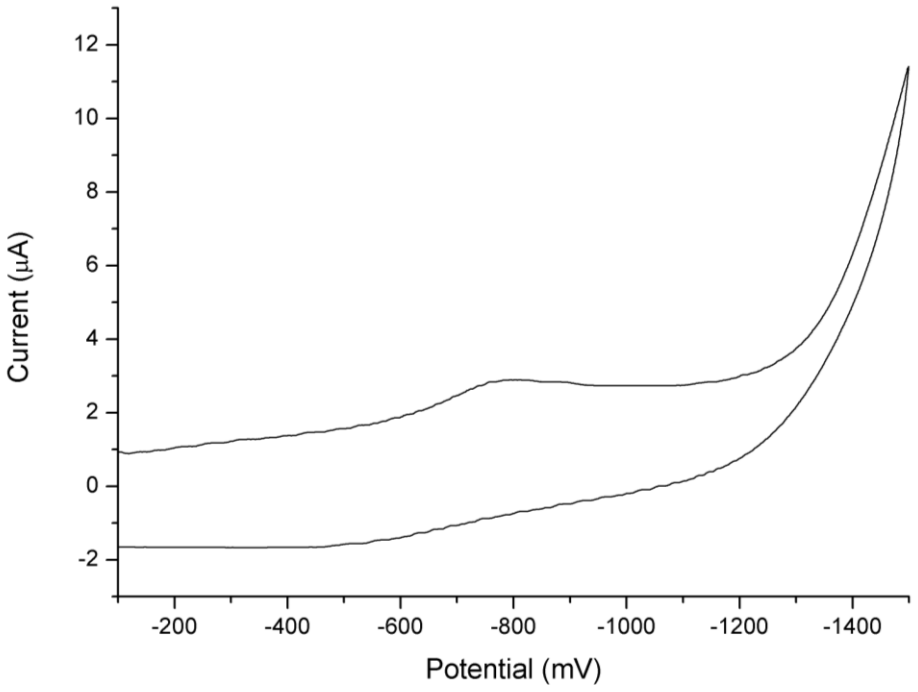


Figure S20. Cyclic voltammogram of complex *trans, trans, trans*-[$Pt(OAc)_4(NH_3)(py)$] (**XV**) in 0.1 M KCl at a scan rate of 100 mVs^{-1}, referenced to Ag/AgCl.

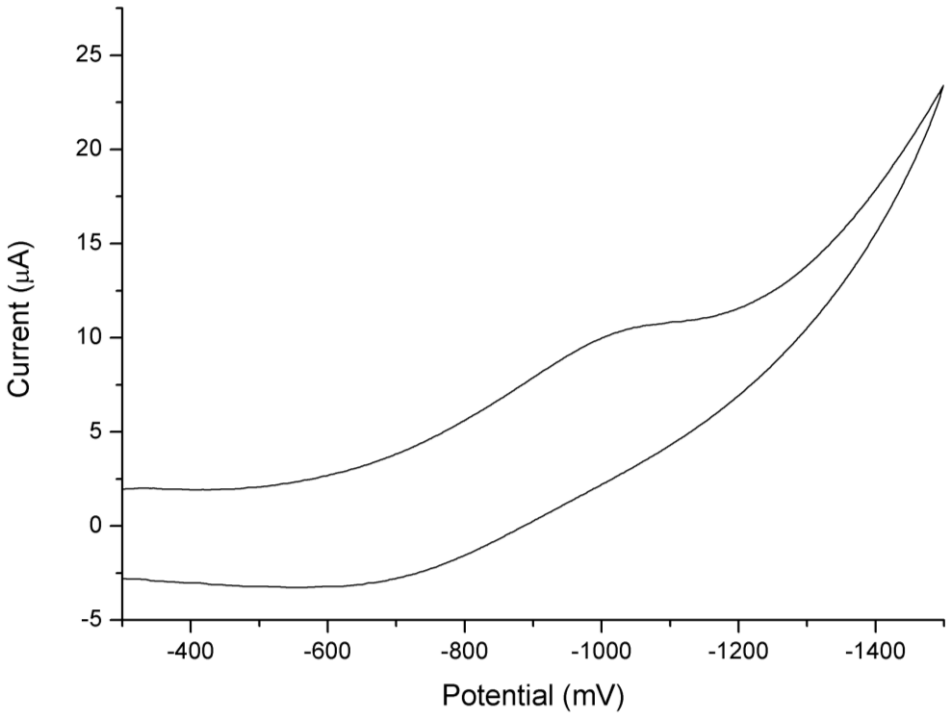


Figure S21. Cyclic voltammogram of complex *trans, trans, trans*-[Pt(OAc)$_3$(OH)(NH$_3$)(py)] (**XIV**) in 0.1 M KCl at a scan rate of 100 mVs^{-1}, referenced to Ag/AgCl.

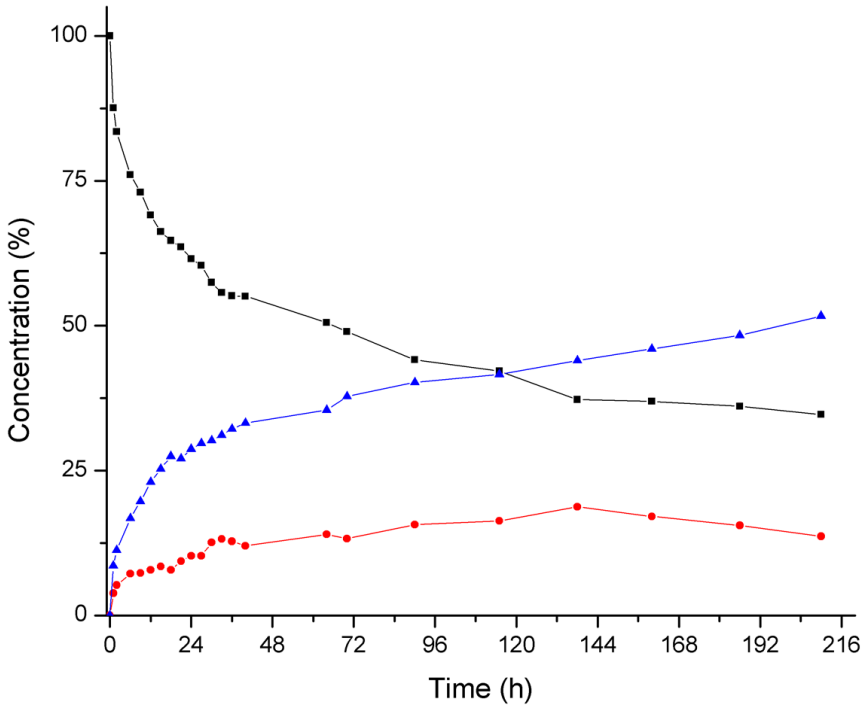


Figure S22. Relative concentrations of the complex *trans, trans, trans*-[Pt(OAc)$_4$(NH$_3$)$_2$] (**XI**) (■-filled black squares, solid black line) and its reduction products; *trans*-[Pt(OAc)$_2$(NH$_3$)$_2$], *trans*-[Pt(OAc)(OH$_2$)(NH$_3$)$_2$]$^+$/ *trans*-[Pt(OAc)(OH)(NH$_3$)$_2$] (●-filled red circles, solid red line) and uncoordinated OAc (▲-filled blue triangles, solid blue line), derived from ^{1}H NMR spectra of the reduction of complex (**XI**) by a ten-fold excess of ascorbate in phosphate buffer at 37°C.

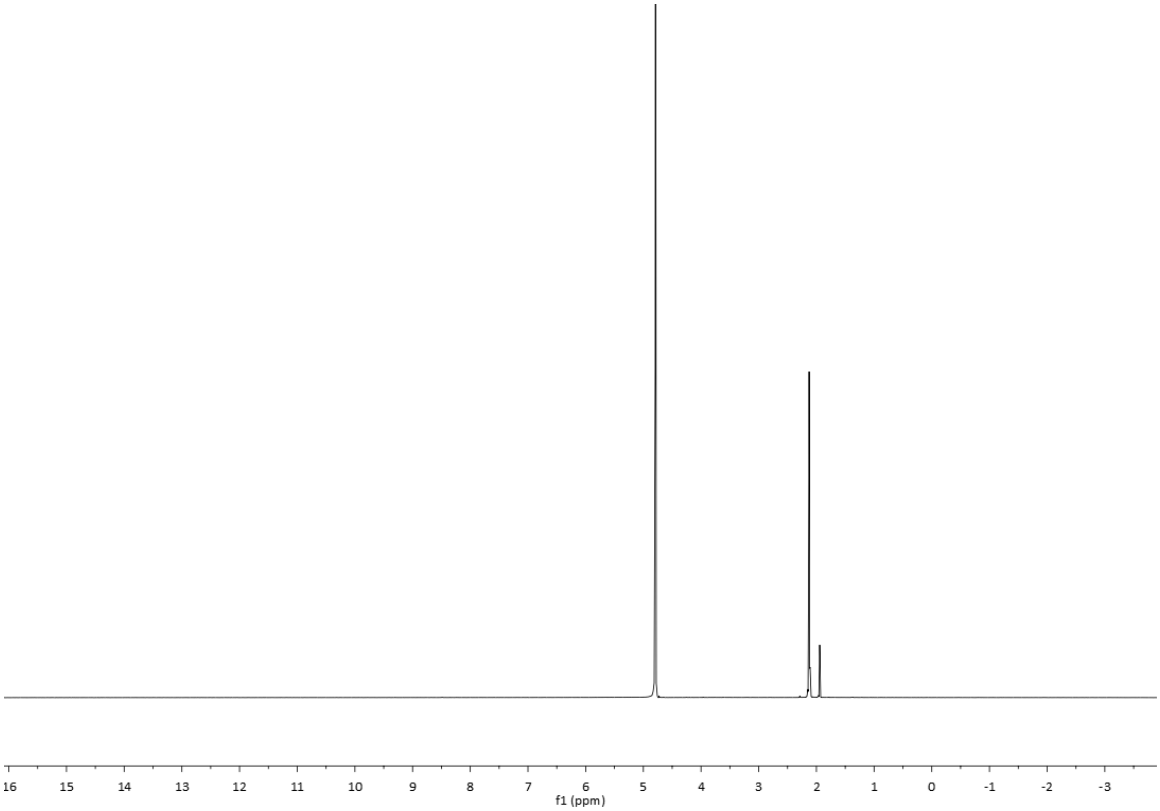


Figure S23. ^{1}H NMR spectrum of *trans, trans, trans* –[Pt(OAc)$_2$(OH)$_2$(NH$_3$)$_2$] (400 MHz, D$_2$O).

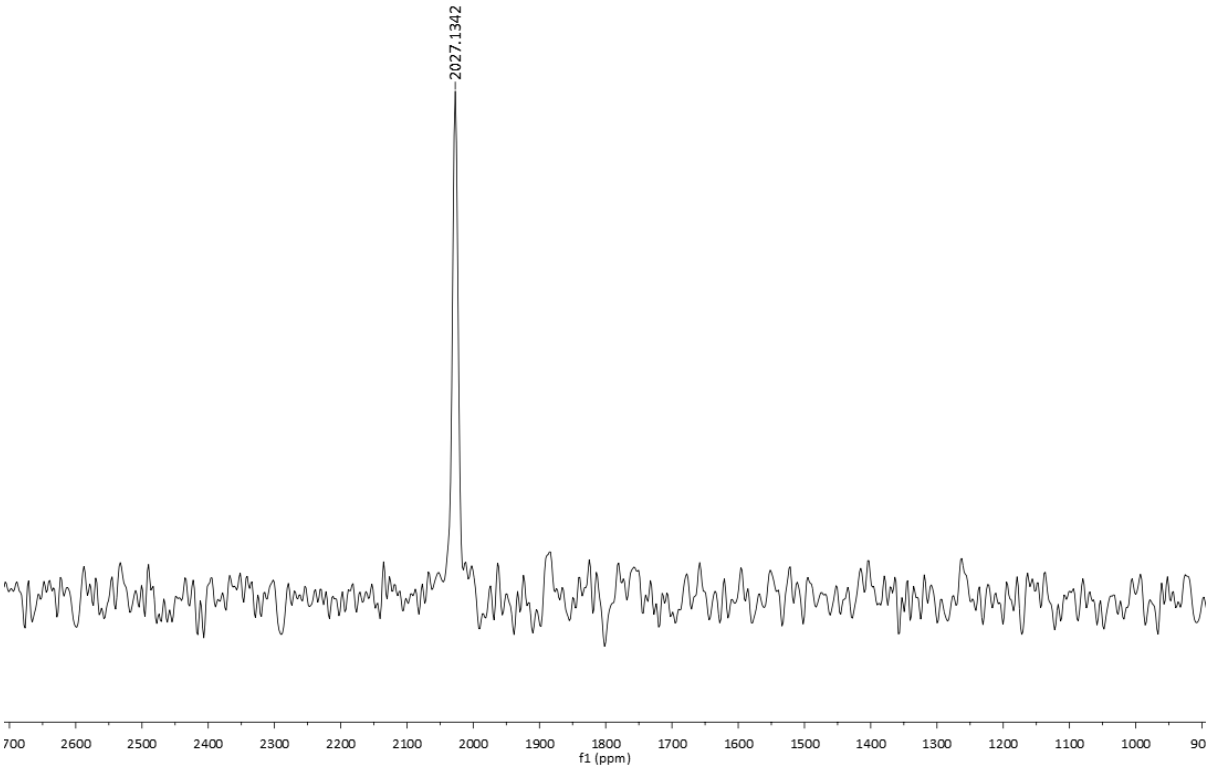


Figure S24. ^{195}Pt NMR spectrum of *trans, trans, trans* –[Pt(OAc)$_2$(OH)$_2$(NH$_3$)$_2$] (400 MHz, D$_2$O).

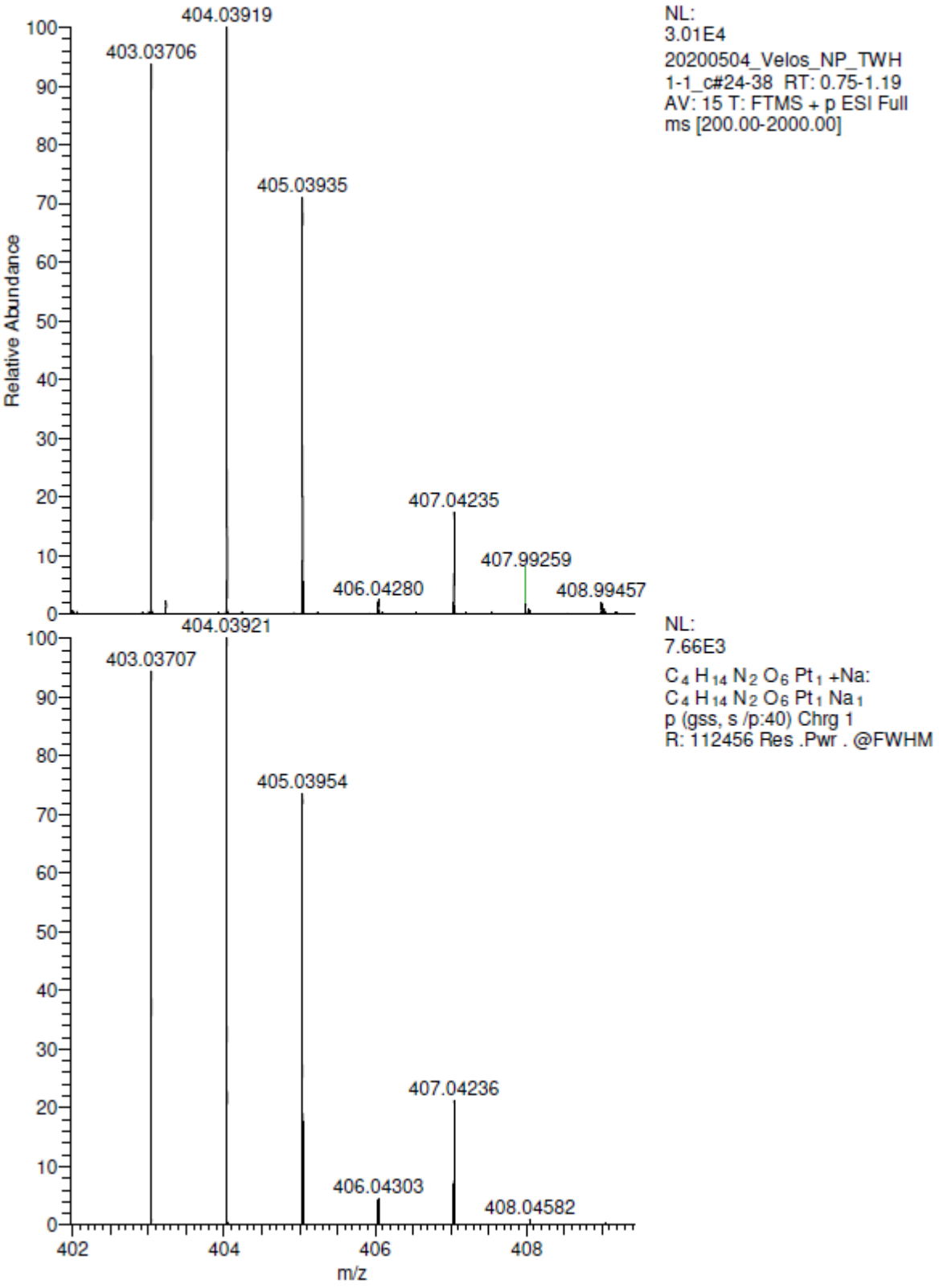
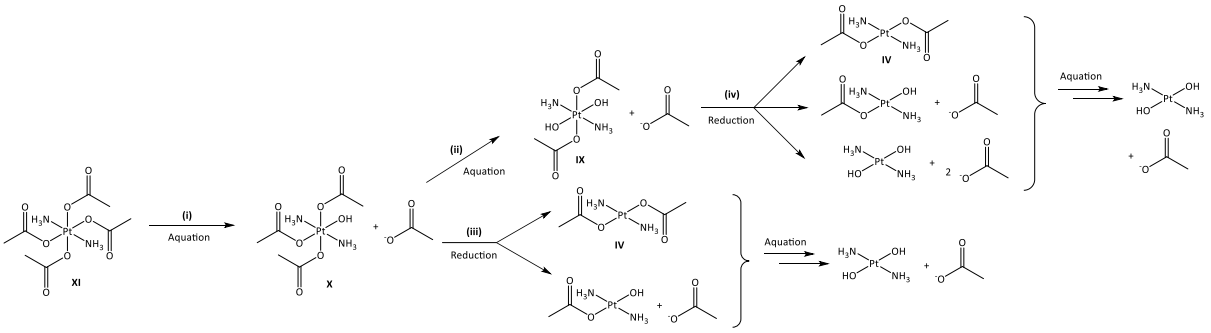


Figure S25. Observed and calculated high resolution mass spectrum for **IX** *trans, trans, trans*-$[Pt(OAc)_2(OH)_2(NH_3)_2]$ (**XI**)



Scheme S1. Proposed aquation and reduction pathways for complex **XI** where **(i)** the aquation of first acetate ligand gives complex **X** and one uncoordinated acetate, following which **(ii)** aquation of the second acetate ligand will give complex **IX** and another uncoordinated actate. Reduction of complexes **X** and **IX** via **(iii)** and **(iv)** respectively will give platinum(II) complexes which will subsequently undergo further aquation to produce further uncoordinated acetates.