Electronic Supplementary Material (ESI) for Metallomics.

Supporting Information

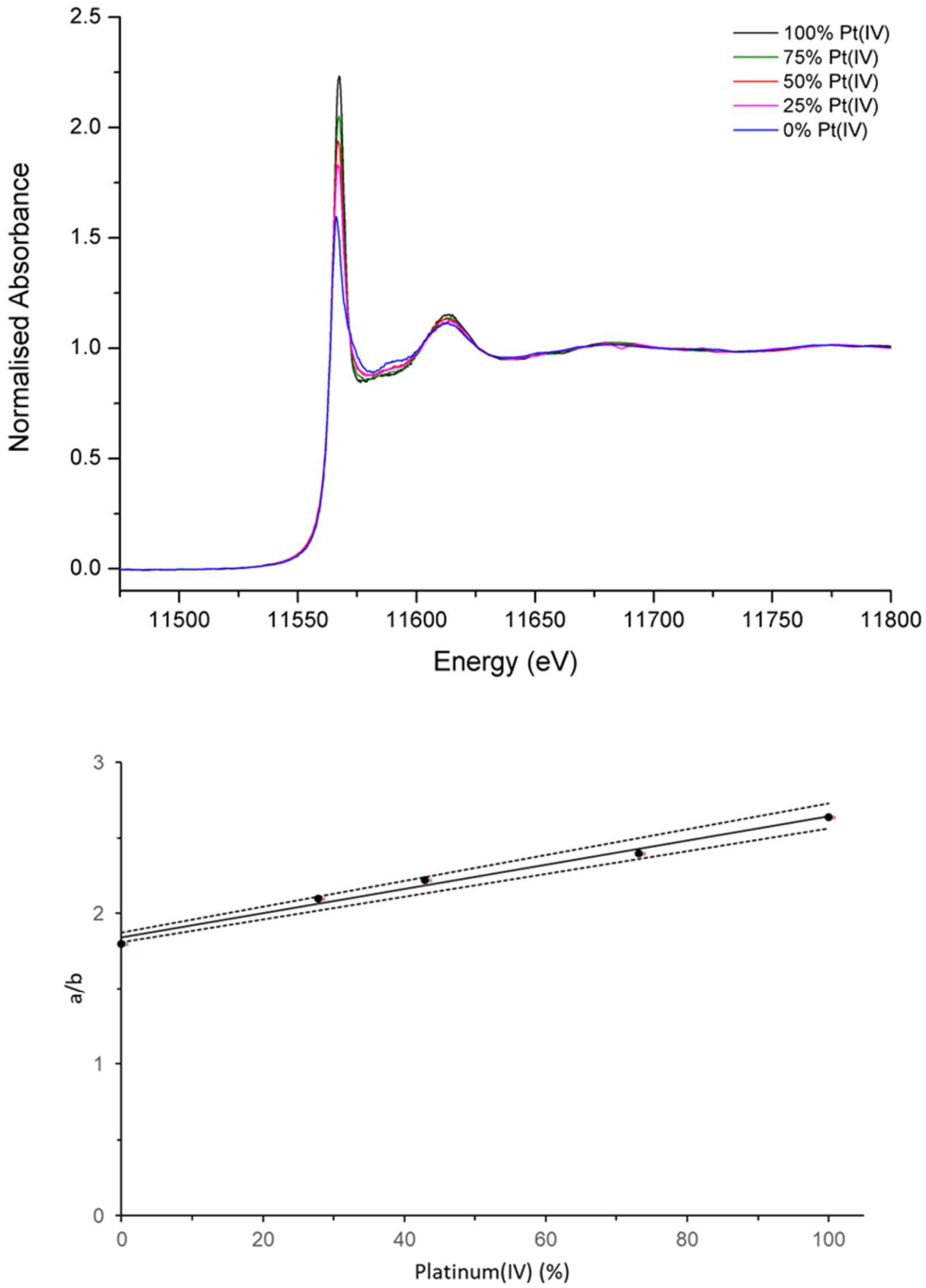

Figure S1. Normalised XANES spectra of $[Pt(en)_2]$(**X**), *trans*-$[Pt(OAc)_2(en)_2]$(**I**) and 25:75; 50:50; 75:25 molar ratio mixtures (top) and linear fit of peak height ratios, *a/b*, derived from XANES spectra of $[Pt(en)_2]$(**X**), *trans*-$[Pt(OAc)_2(en)_2]$(**I**) and 25:75; 50:50; 75:25 mixtures (R^2= 0.9876) (bottom). Uncertainty of the linear fit (dashed) was derived from the standard deviations of the gradient and intercept of the linear regression.

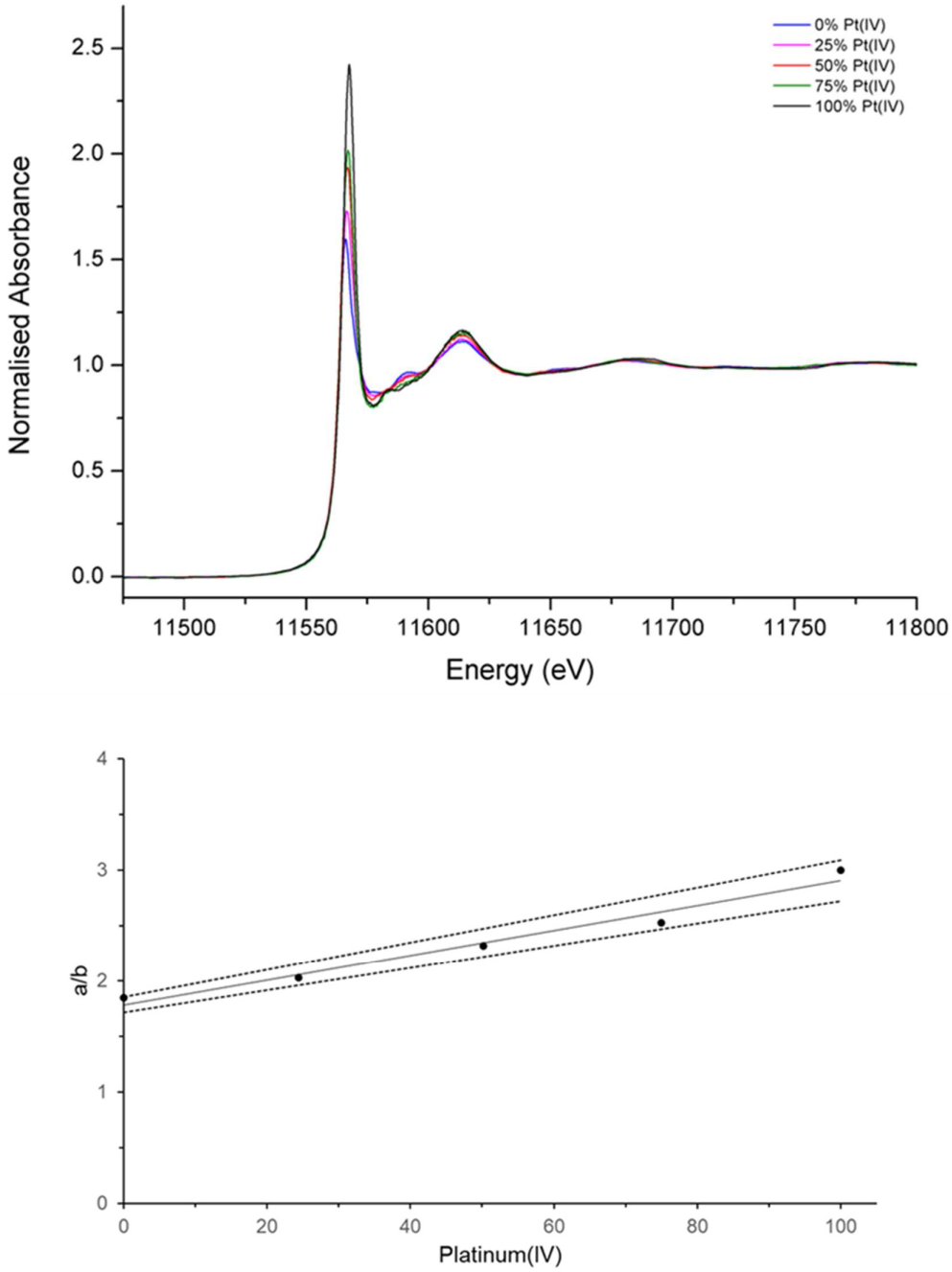

Figure S2. Normalised XANES spectra of [Pt(ox)(en)](**XI**), *trans*-[Pt(OAc)$_2$(ox)(en)](**IV**) and 25:75; 50:50; 75:25 molar ratio mixtures (top) and linear fit of peak height ratios, *a/b*, derived from XANES spectra of [Pt(ox)(en)](**XI**), *trans*-[Pt(OAc)$_2$(ox)(en)](**IV**) and 25:75; 50:50; 75:25 mixtures (R^2= 0.9692) (bottom). Uncertainty of the linear fit (dashed) was derived from the standard deviations of the gradient and intercept of the linear regression.

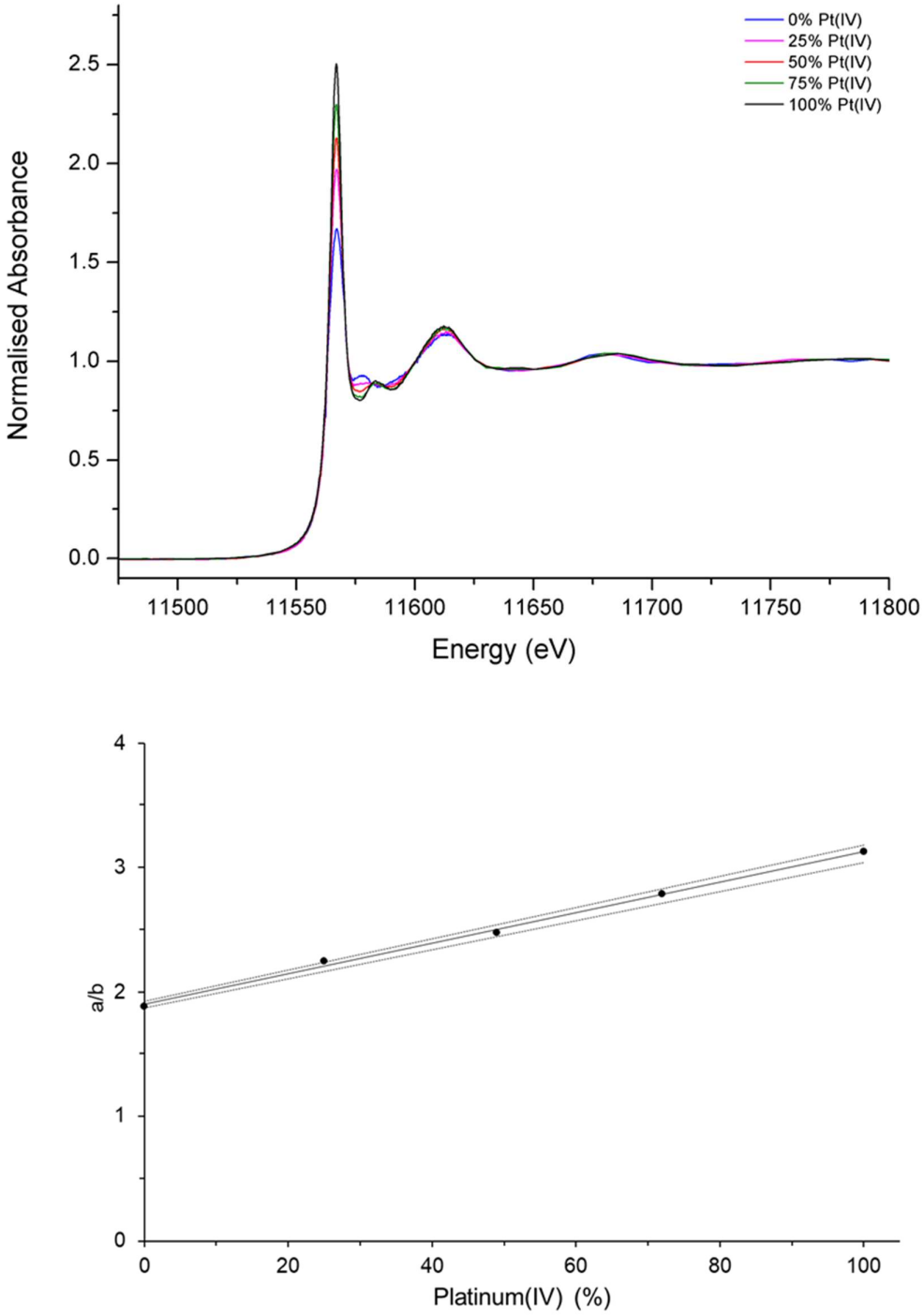

Figure S3. Normalised XANES spectra of *trans*-$[Pt(OAc)_2(NH_3)_2]$(**XII**), *trans, trans, trans*-$[Pt(OAc)_4(NH_3)_2$(**VII**) and 25:75; 50:50; 75:25 molar ratio mixtures (top) and linear fit of peak height ratios, *a/b*, derived from XANES spectra of *trans*-$[Pt(OAc)_2(NH_3)_2$ (**XII**), *trans, trans, trans*-$[Pt(OAc)_4(NH_3)_2$(**VII**) and 25:75; 50:50; 75:25 mixtures (R^2= 0.9960) (bottom). Uncertainty of the linear fit (dashed) was derived from the standard deviations of the gradient and intercept of the linear regression.

Table S1. Cytotoxicity values for platinum(IV) complexes in DLD-1 cells. Cytotoxicity is expressed as IC_{50} (μM) following a 72 hour incubation period. Average IC_{50} values are reported from at least three independent experiments.

Complex	Net charge	Coordination sphere	IC_{50}
			DLD-1
trans-$[Pt(OAc)_2(en)_2]^{2+}$ (**I**)	2^+	$Pt^{IV}N_4O_2$	>200
trans-$[Pt(OAc)(OSuc)(en)_2]^+$ (**II**)	1^+	$Pt^{IV}N_4O_2$	>200
trans-$[Pt(OSuc)_2(en)_2]$ (**III**)	0	$Pt^{IV}N_4O_2$	>200
trans-$[Pt(OAc)_2(ox)(en)]$ (**IV**)	0	$Pt^{IV}N_2O_4$	>200
trans-$[Pt(OAc)(OSuc)(ox)(en)]^-$ (**V**)	1^-	$Pt^{IV}N_2O_4$	>200
trans-$[Pt(OSuc)_2(ox)(en)]^{2-}$ (**VI**)	2^-	$Pt^{IV}N_2O_4$	>200
trans, trans, trans-$[Pt(OAc)_4(NH_3)_2]$ (**VII**)	0	$Pt^{IV}N_2O_4$	>200
trans, trans, trans-$[Pt(OSuc)(OAc)_3(NH_3)_2]^-$ (**VIII**)	1^-	$Pt^{IV}N_2O_4$	>200
trans, trans, trans-$[Pt(OSuc)_2(OAc)_2(NH_3)_2]^{2-}$ (**IX**)	2^-	$Pt^{IV}N_2O_4$	>200

Table S2. Peak height ratio (*a/b*) calculated from XANES spectra of human blood serum and whole blood dosed with 50 µM of platinum(IV) complexes after 2, 6, and 24 hour incubation at 37 °C. Values represent averages of three independent samples with standard error values reported.

Complex	Oxidation state	Charge	Human serum			Whole blood		
			2 h	6 h	24 h	2 h	6 h	24 h
trans-$[Pt(OAc)_2(en)_2]^{2+}$ (**I**)	Pt(IV)	2+	2.59 ± 0.05	2.52 ± 0.04	2.50 ±0.04	2.27 ± 0.04	2.31 ± 0.05	2.23 ± 0.06
trans-$[Pt(OAc)(Osuc)(en)_2]^{+}$ (**II**)	Pt(IV)	1+	2.39 ± 0.04	2.44 ± 0.05	2.39 ± 0.04	2.27 ± 0.04	2.25 ± 0.08	2.22 ± 0.05
trans-$[Pt(OSuc)_2(en)_2]$ (**III**)	Pt(IV)	0	2.37 ± 0.04	2.39 ± 0.04	2.41 ± 0.04	2.32 ± 0.04	2.27 ± 0.04	2.22 ± 0.04
trans-$[Pt(OAc)_2(ox)(en)]$ (**IV**)	Pt(IV)	0	2.75 ± 0.08	2.75 ± 0.06	2.73 ± 0.08	1.99 ± 0.08	2.03 ± 0.09	2.03 ± 0.08
trans-$[Pt(OAc)(Osuc)(ox)(en)]^{-}$ (**V**)	Pt(IV)	1-	2.73 ± 0.08	2.68 ± 0.06	2.60 ± 0.06	2.02 ± 0.07	1.98 ± 0.06	1.99 ± 0.06
trans-$[Pt(OSuc)_2(ox)(en)]^{2-}$ (**VI**)	Pt(IV)	2-	2.73 ± 0.06	2.71 ± 0.06	2.60 ± 0.06	2.43 ± 0.06	2.24 ± 0.06	2.25 ± 0.06
trans, trans, trans-$[Pt(OAc)_4(NH_3)_2]$ (**VII**)	Pt(IV)	0	2.77 ± 0.06	2.78 ± 0.07	2.69 ± 0.06	2.10 ± 0.06	1.99 ± 0.06	2.11 ± 0.06
trans, trans, trans- $[Pt(OAc)_3(OSuc)(NH_3)_2]^{-}$ (**VIII**)	Pt(IV)	1-	2.75 ± 0.06	2.70 ± 0.06	2.63 ± 0.06	2.40 ± 0.08	2.36 ± 0.06	2.40 ± 0.06
trans, trans, trans- $[Pt(OAc)_2(OSuc)_2(NH_3)_2]^{2-}$ (**IX**)	Pt(IV)	2-	2.66 ± 0.07	2.62 ± 0.06	2.65 ± 0.06	2.35 ± 0.08	2.28 ± 0.06	2.37 ± 0.06

Table S3. Fraction of reduction in whole blood attributed to human serum and red blood cells after 2, 6, and 24 hours incubation. Ratios of the total reduction attributed to serum and red blood cells for the reduction of platinum(IV) complexes in whole blood (Table S4). Percentages are calculated as ratios were calculated using equations (6) and (7). Standard errors represent interpolated errors derived from Table 3.

Complex	Oxidation state	Charge	Serum (%)			Red blood cells (%)		
			2 h	6 h	24 h	2 h	6 h	24 h
trans-$[Pt(OAc)_2(en)_2]^{2+}$ (**I**)	Pt(IV)	2+	7.3 ± 8	19.6 ± 8	19.9 ± 10	92.7 ± 8	80.0 ± 8	80.1 ± 9
trans-$[Pt(OAc)(Osuc)(en)_2]^{+}$ (**II**)	Pt(IV)	1+	37.5 ± 8	29.4 ± 12	33.4 ± 8	62.5 ± 7	70.6 ± 11	66.6 ± 8
trans-$[Pt(OSuc)_2(en)_2]$ (**III**)	Pt(IV)	0	47.1 ± 8	37.1 ± 8	30.1 ± 8	52.9 ± 7	62.9 ± 7	69.9 ± 7
trans-$[Pt(OAc)_2(ox)(en)]$ (**IV**)	Pt(IV)	0	8.6 ± 10	12.7 ± 9	10.7 ± 10	91.4 ± 9	87.3 ± 8	89.3 ± 10
trans-$[Pt(OAc)(Osuc)(ox)(en)]^{-}$ (**V**)	Pt(IV)	1-	10.1 ± 9	12.7 ± 8	18.1 ± 8	89.9 ± 8	87.3 ± 7	82.8 ± 7
trans-$[Pt(OSuc)_2(ox)(en)]^{2-}$ (**VI**)	Pt(IV)	2-	18.8 ± 8	18.4 ± 8	25.0 ± 8	81.2 ± 7	81.6 ± 7	75.0 ± 7
trans, trans, trans-$[Pt(OAc)_4(NH_3)_2]$ (**VII**)	Pt(IV)	0	17.9 ± 8	15.9 ± 8	22.9 ± 8	82.1 ± 7	84.1 ± 8	77.1 ± 7
trans, trans, trans- $[Pt(OAc)_3(OSuc)(NH_3)_2]^{-}$ (**VIII**)	Pt(IV)	1-	28.8 ± 9	30.7 ± 8	38.0 ± 10	71.2 ± 9	69.3 ± 7	62.0 ± 9
trans, trans, trans- $[Pt(OAc)_2(OSuc)_2(NH_3)_2]^{2-}$ (**IX**)	Pt(IV)	2-	33.9 ± 9	33.2 ± 8	35.1 ± 8	66.1 ± 9	66.8 ± 7	64.9 ± 7

Radiation Damage

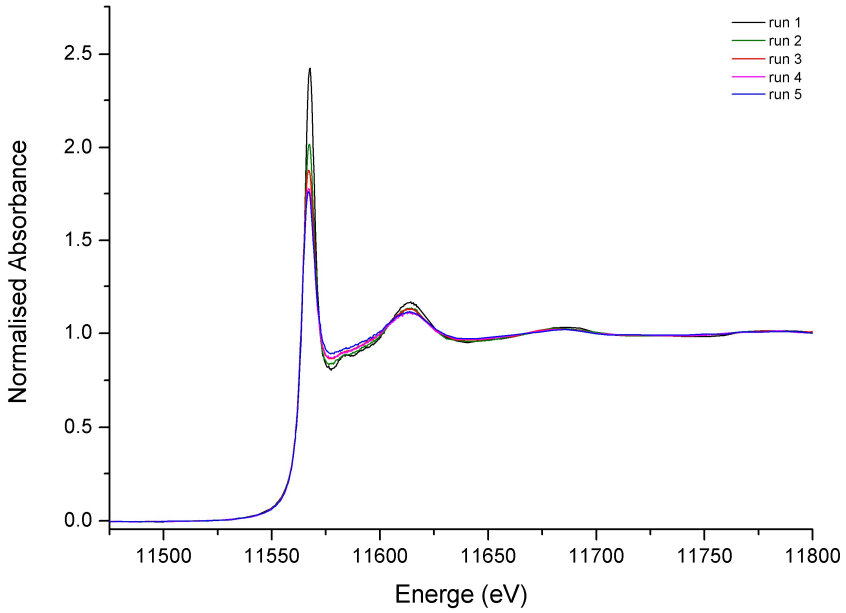

Figure S4. Radiation hardness testing of the solid standard *trans*-[Pt(OAc)$_2$(ox)(en)] (**IV**) by repeated XANES scans of the same region of the solid sample. Repeated radiation exposure resulted in the significant degradation of the sample in subsequent scans.

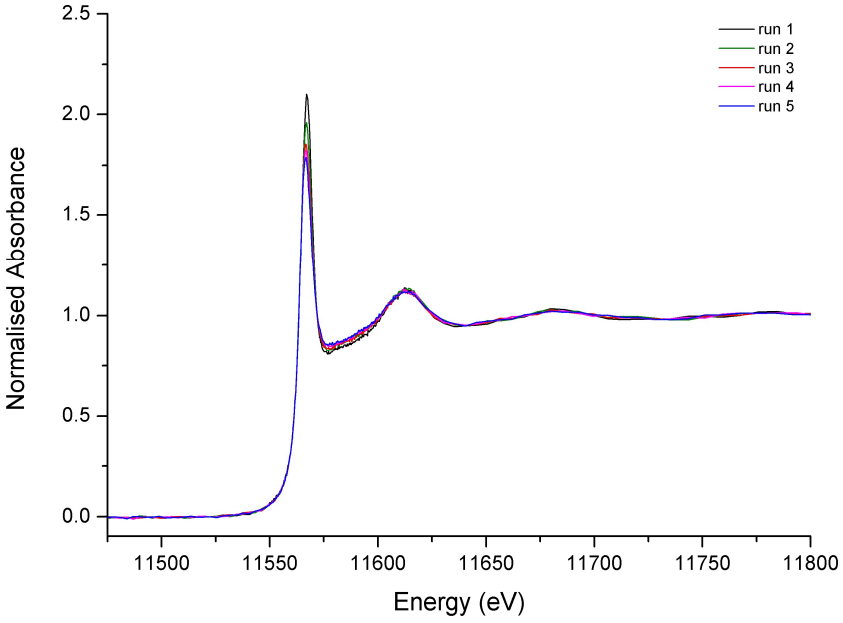

Figure S5. Radiation hardness testing of the solid biological sample containing human serum dosed with *trans*-[Pt(OSuc)$_2$(ox)(en)]$^{2-}$ (**III**) (50 µM) after 2 hours of incubation at 37 °C by repeated XANES scans of the same region of the solid sample. Repeated radiation exposure resulted in the significant degradation of the sample in subsequent scans.

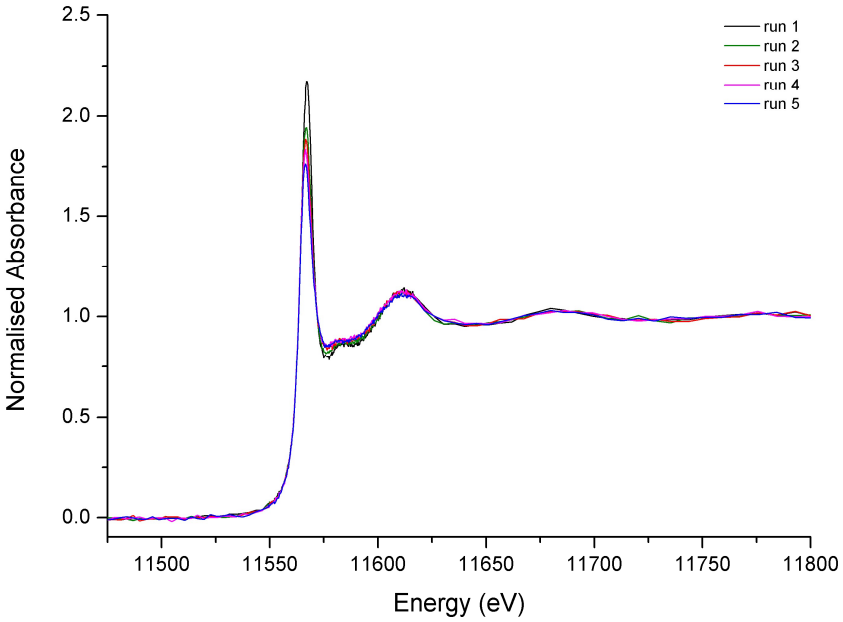

Figure S6. Radiation hardness testing of the solid biological sample containing human serum dosed with *trans*-$[Pt(OAc)_4(NH_3)_2]^{2-}$ (**VII**) (50 µM) after 2 hours of incubation at 37 °C by repeated XANES scans of the same region of the solid sample. Repeated radiation exposure resulted in the significant degradation of the sample in subsequent scans.

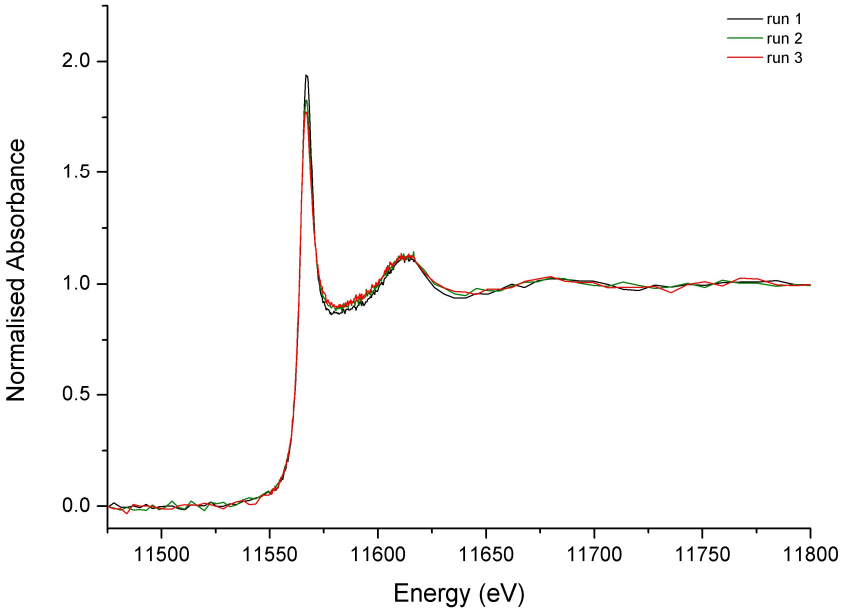

Figure S7. Radiation hardness testing of the solid biological sample containing whole blood dosed with *trans*-$[Pt(OAc)_2(en)_2]^{2+}$ (**I**) (50 µM) after 2 hours of incubation at 37 °C by repeated XANES scans of the same region of the solid sample. Repeated radiation exposure resulted in the significant degradation of the sample in subsequent scans.

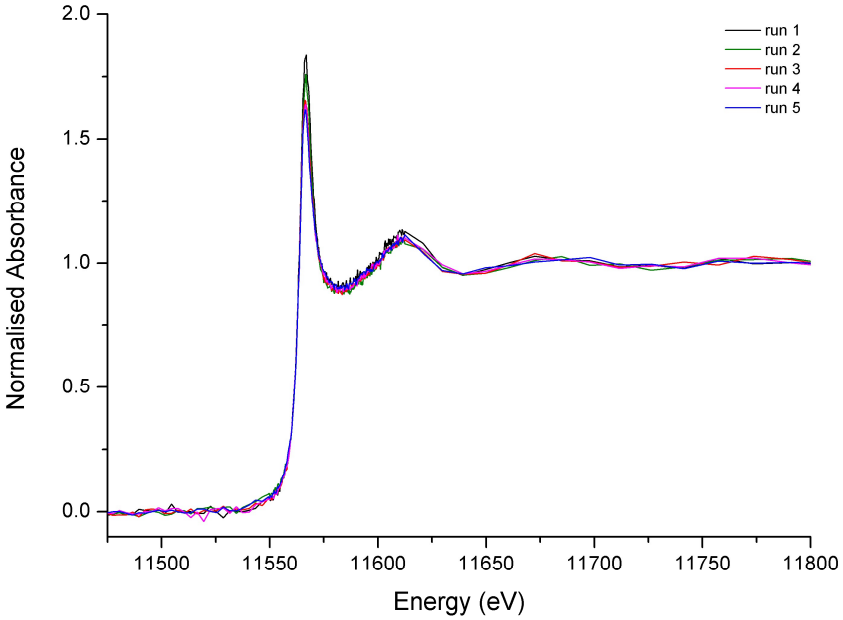

Figure S8. Radiation hardness testing of the solid biological sample containing whole blood dosed with *trans*-$[Pt(OAc)_2(en)_2]^{2+}$ (**I**) (50 µM) after 2 hours of incubation at 37 °C by repeated XANES scans of the same region of the solid sample. Repeated radiation exposure resulted in the significant degradation of the sample in subsequent scans.

XANES spectra for biological samples

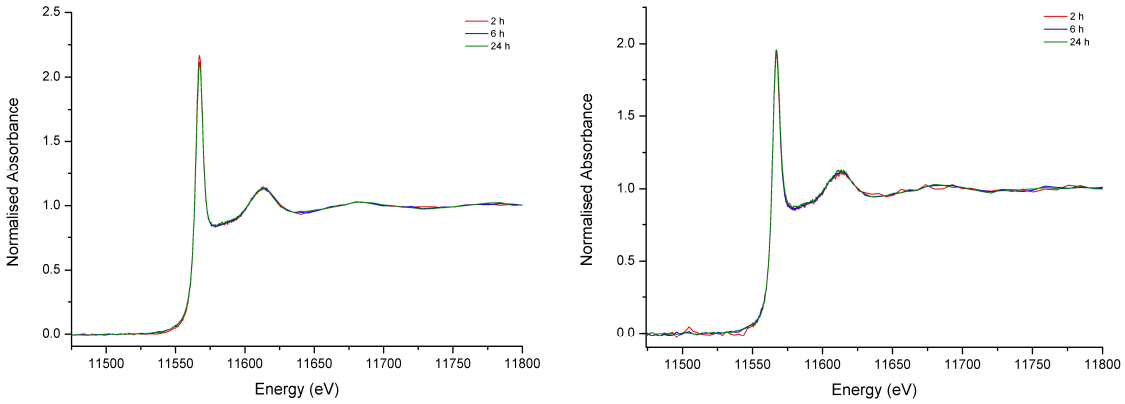

Figure S9. XANES spectra of solid biological samples containing; (a) human serum (left) and (b) whole blood (right) dosed with *trans*-$[Pt(OAc)_2(en)_2]^{2+}$ (**I**) (50 µM) after 2, 6, and 24 hours incubation at 37 °C.

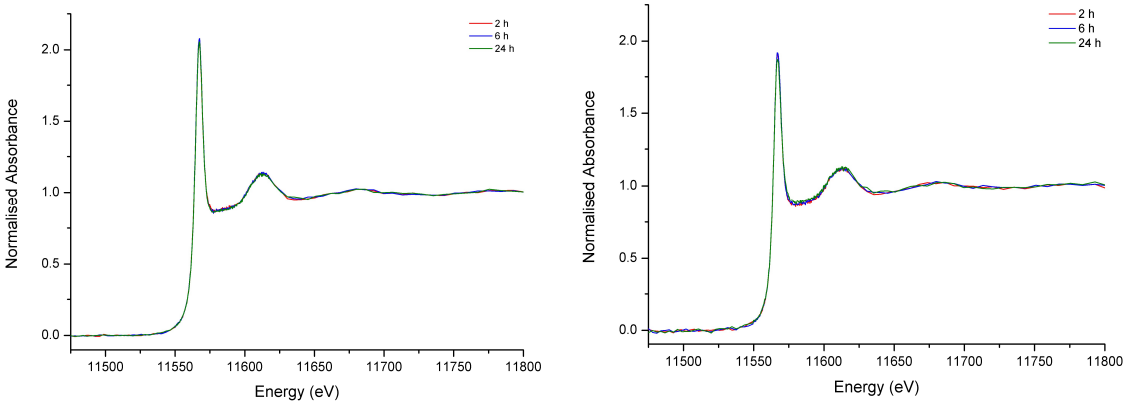

Figure S10. XANES spectra of solid biological samples containing; (a) human serum (left) and (b) whole blood (right) dosed with *trans*-$[Pt(OAc)(Osuc)(en)_2]^{+}$ (**II**) (50 µM) after 2, 6, and 24 hours incubation at 37 °C.

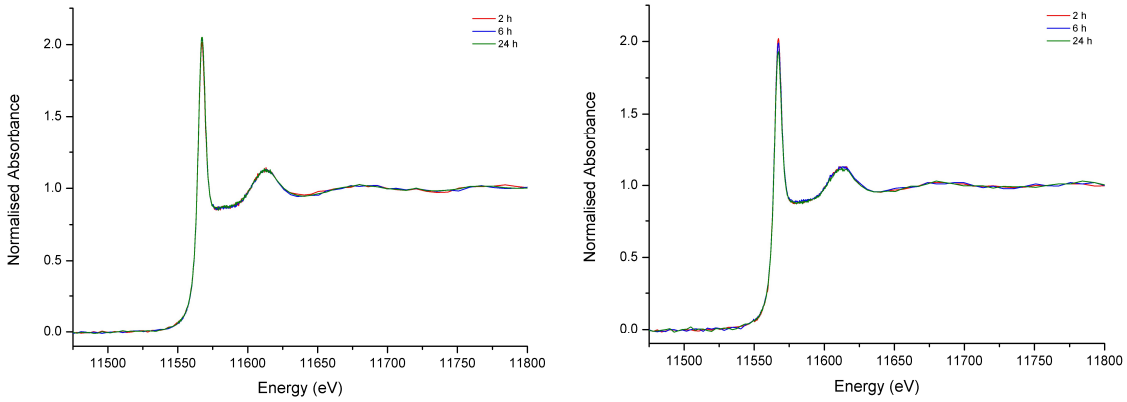

Figure S11. XANES spectra of solid biological samples containing; (a) human serum (left) and (b) whole blood (right) dosed with *trans*-$[Pt(Osuc)_2(en)_2]^+$ (**III**) (50 µM) after 2, 6, and 24 hours incubation at 37 °C.

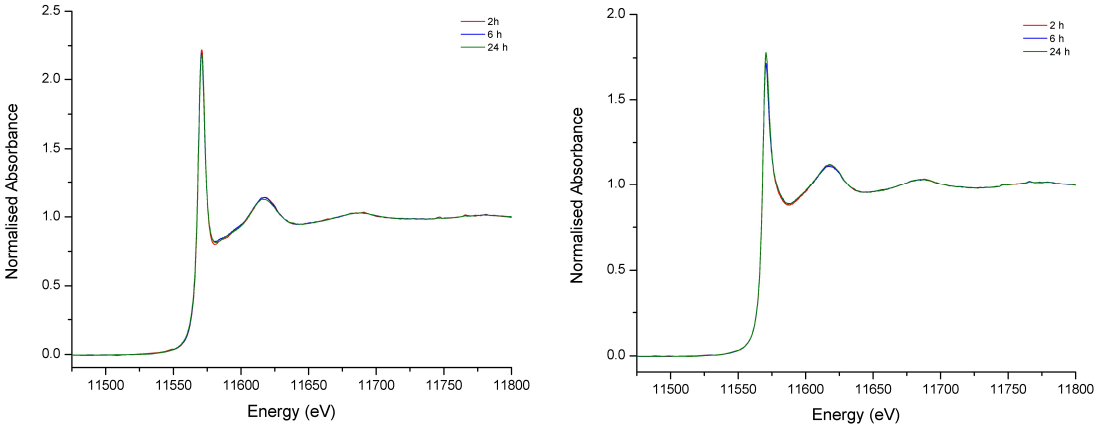

Figure S12. XANES spectra of solid biological samples containing; (a) human serum (left) and (b) whole blood (right) dosed with *trans*-$[Pt(OAc)_2(ox)(en)_2]$ (**IV**) (50 µM) after 2, 6, and 24 hours incubation at 37 °C.

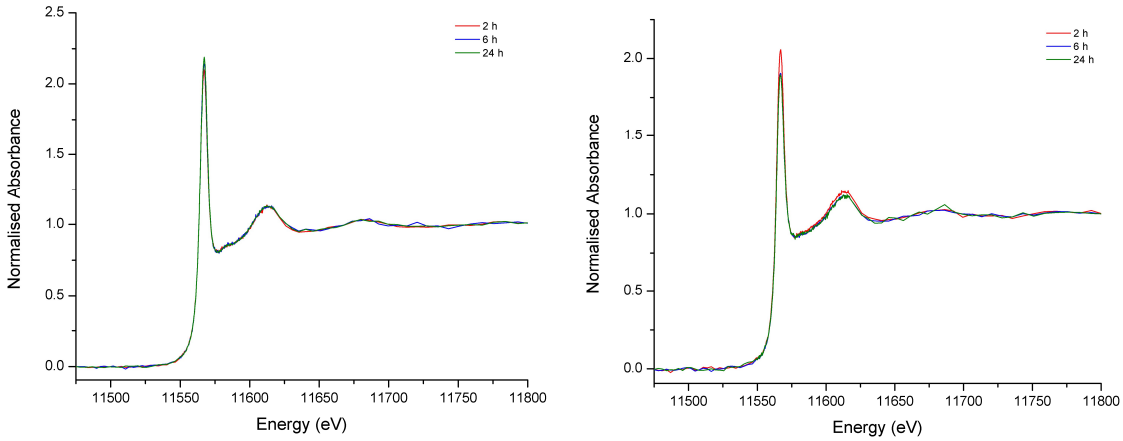

Figure S13. XANES spectra of solid biological samples containing; (a) human serum (left) and (b) whole blood (right) dosed with *trans*-$[Pt(OAc)(OSuc)(ox)(en)_2]^-$ (**V**) (50 µM) after 2, 6, and 24 hours incubation at 37 °C.

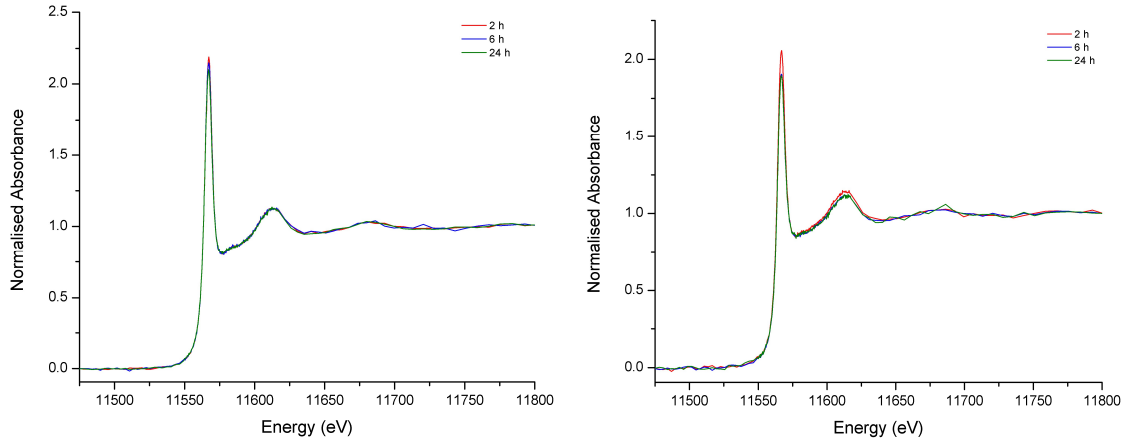

Figure S14. XANES spectra of solid biological samples containing; (a) human serum (left) and (b) whole blood (right) dosed with *trans*-$[Pt(OSuc)_2(ox)(en)_2]^-$ (**VI**) (50 µM) after 2, 6, and 24 hours incubation at 37 °C.

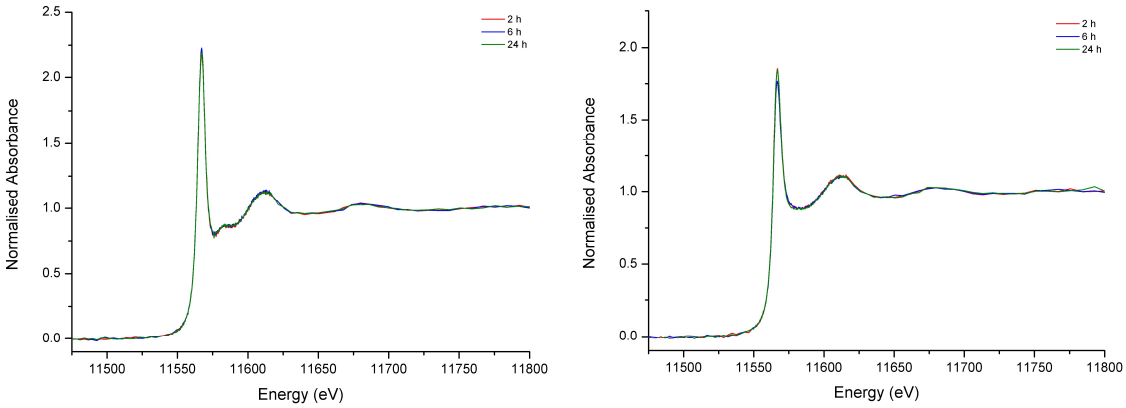

Figure S15. XANES spectra of solid biological samples containing; (a) human serum (left) and (b) whole blood (right) dosed with *trans, trans, trans*-$[Pt(OAc)_4(NH_3)_2]$ (**VII**) (50 µM) after 2, 6, and 24 hours incubation at 37 °C.

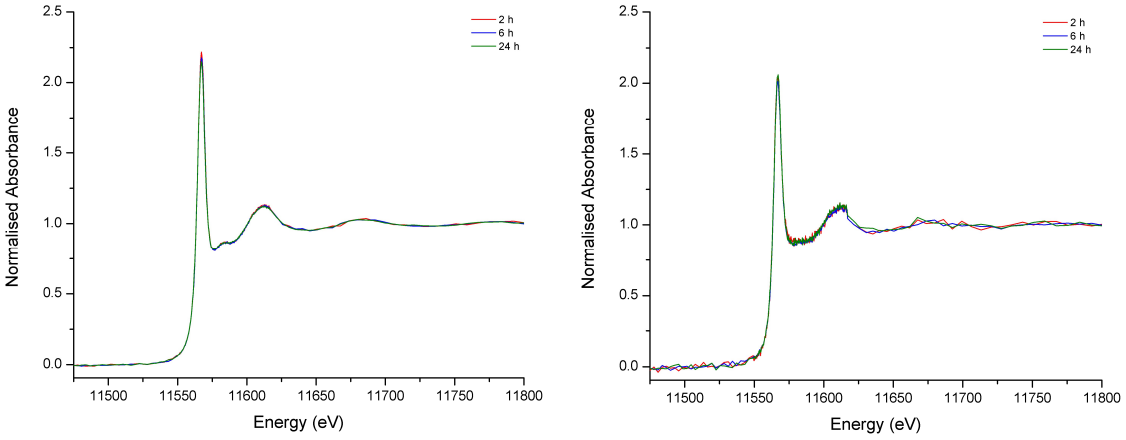

Figure S16. XANES spectra of solid biological samples containing; (a) human serum (left) and (b) whole blood (right) dosed with *trans, trans, trans*-$[Pt(OAc)_3(OSuc)(NH_3)_2]^-$ (**VIII**) (50 µM) after 2, 6, and 24 hours incubation at 37 °C.

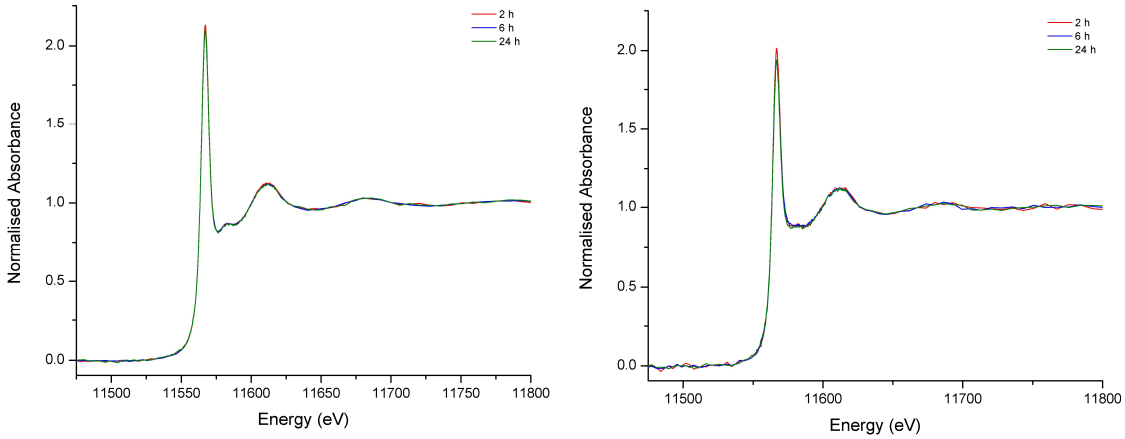

Figure S17. XANES spectra of solid biological samples containing; (a) human serum (left) and (b) whole blood (right) dosed with *trans, trans, trans*-$[Pt(OAc)_2(OSuc)_2(NH_3)_2]^{2-}$ (**IX**) (50 µM) after 2, 6, and 24 hours incubation at 37 °C.

Blood serum partition study

Table S4. Platinum concentrations in whole blood and serum partition samples dosed with platinum complexes (50 μM) after 2, 6, and 24 hours incubation at 37 °C. Values represent experimental averages from three independent experiments with standard errors reported.

Complex	Oxidation state	Charge	RBC			HS		
			2 h	6 h	24 h	2 h	6 h	24 h
trans-$[Pt(OAc)_2(en)_2]^{2+}$ (**I**)	Pt(IV)	2^+	75.5 ± 12.5	125.6 ± 15.5	165.4 ± 5.7	423.0 ± 11.3	335.7 ± 16.2	340.8 ± 18.5
trans-$[Pt(OAc)(Osuc)(en)_2]^+$ (**II**)	Pt(IV)	1^+	80.3 ± 8.8	63.1 ± 1.1	97.6 ± 11.5	272.2 ± 13.8	253.0 ± 7.4	271.5 ± 5.8
trans-$[Pt(OSuc)_2(en)_2]$ (**III**)	Pt(IV)	0	68.7 ± 12.3	82.0 ± 9.9	140.1 ± 15.3	384.0 ± 18.5	345.7 ± 14.8	296.1 ± 17.8
trans-$[Pt(OAc)_2(ox)(en)]$ (**IV**)	Pt(IV)	0	97.0 ± 7.3	75.5 ± 9.5	135.8 ± 9.0	379.8 ± 20.3	304.5 ± 6.5	345.9 ± 18.8
trans-$[Pt(OAc)(Osuc)(ox)(en)]^-$ (**V**)	Pt(IV)	1^-	75.3 ± 4.3	72.5 ± 4.7	84.1 ± 11.8	232.9 ± 5.4	244.4 ± 4.2	262.7 ± 16.4
trans-$[Pt(OSuc)_2(ox)(en)]^{2-}$ (**VI**)	Pt(IV)	2^-	99.8 ± 16.2	84.6 ± 7.3	138.5 ± 1.9	345.1 ± 18.3	335.3 ± 21.7	389.3 ± 20.8
trans, trans, trans-$[Pt(OAc)_4(NH_3)_2]$ (**VII**)	Pt(IV)	0	238.2 ± 2.5	170.4 ± 3.4	236.3 ± 7.5	282.3 ± 14.0	267.2 ± 2.0	292.9 ± 24.7
trans, trans, trans- $[Pt(OAc)_3(OSuc)(NH_3)_2]^-$ (**VIII**)	Pt(IV)	1^-	175.3 ± 13.1	110.1 ± 1.9	187.8 ± 7.3	403.4 ± 11.8	371.5 ± 14.8	294.2 ± 4.7
trans, trans, trans- $[Pt(OAc)_2(OSuc)_2(NH_3)_2]^{2-}$ (**IX**)	Pt(IV)	2^-	129.6 ± 6.3	99.0 ± 11.7	108.1 ± 10.5	357.7 ± 17.7	363.8 ± 14.8	264.5 ± 4.2
cis, trans-$[PtCl_2(OH)_2(en)]$	Pt(IV)	0	86.4 ± 8.5	115.9 ± 19.2	127.9 ± 12.1	386.7 ± 14.3	316.7 ± 20.4	354.4 ± 20.1
cis, trans-$[PtCl_2(OAc)_2(en)]$	Pt(IV)	0	83.1 ± 8.9	156.6 ± 9.2	188.8 ± 18.6	318.9 ± 32.8	287.2 ± 6.8	246.8 ± 12.6
trans-$[Pt(OH)_2(ox)(en)]$	Pt(IV)	0	51.2 ± 4.0	78.4 ± 8.2	108.5 ± 6.3	247.7 ± 5.9	238.4 ± 3.1	258.1 ± 8.4
Cisplatin	Pt(II)	0	99.9 ± 6.3	121.4 ± 18.8	164.8 ± 6.6	244.8 ± 7.0	274.2 ± 10.5	297.3 ± 10.5
[Pt(ox)(en)]	Pt(II)	0	117.3 ± 10.4	140.5 ± 14.1	123.8 ± 17.6	330.8 ± 9.3	337.1 ± 3.25	350.3 ± 16.7
cis-$[PtCl_2(en)]$	Pt(II)	0	126.8 ± 17.8	138.0 ± 11.1	149.7 ± 24.9	331.1 ± 25.9	370.2 ± 14.9	324.6 ± 17.3
trans-$[Pt(OAc)_2(NH_3)_2]$	Pt(II)	0	109.7 ± 8.4	190.3 ± 18.2	243.2 ± 16.1	270.0 ± 4.1	250.6 ± 11.9	250.4 ± 6.7
Control	-	-	-5.3 ± 0.5	-	-	-6.5 ± 0.6	-	-