Electronic Supplementary Material (ESI) for ChemComm.

Electrodrugs: An electrochemical prodrug activation strategy

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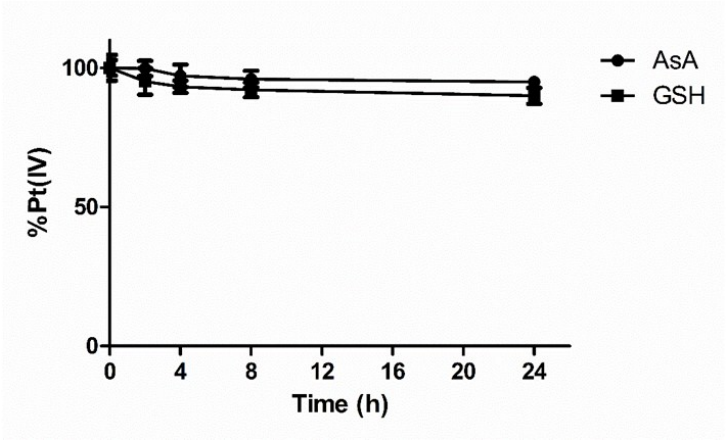


Figure S1. Ascorbic acid (AsA) and glutathione (GSH) reduction of **1** as analysed by HPLC. A solution of **1** (100 μM) in PBS at 37 °C was treated with AsA or GSH to give final concentrations of 1 mM of each reductant.

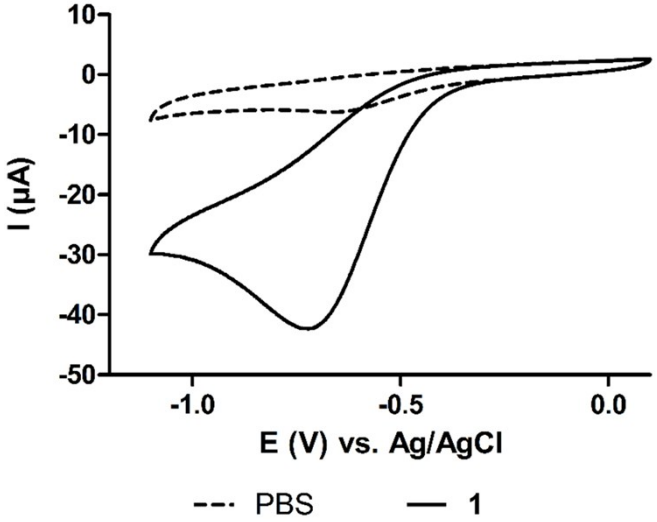


Figure S2. Cyclic voltammograms of PBS alone (dashed line) and a solution of prodrug **1** (2 mM) in PBS. A glassy carbon electrode was used as the working electrode, with potentials shown relative to the Ag/AgCl reference electrode employed.

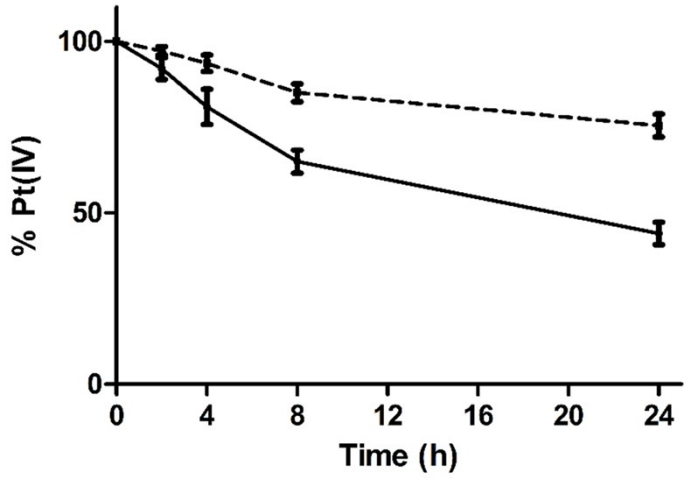


Figure S3. Electroactivation of **1** (100 μM) with the mediator (50 μM) in PBS (solid line) and without mediator (dashed line), as measured by HPLC. A reduction potential of -0.4 V was applied to a glassy carbon electrode vs. the Ag/AgCl reference electrode over 24 h, with samples taken at time-points for analysis.

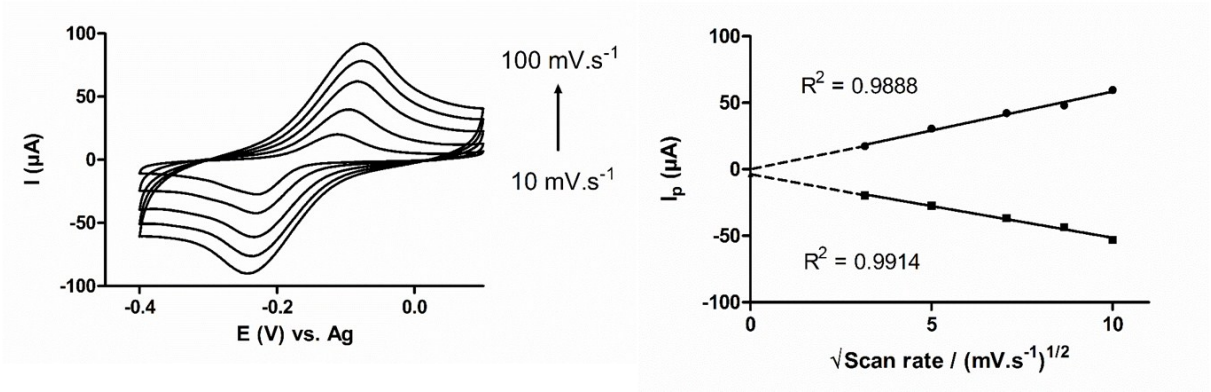


Figure S4. Cyclic voltammograms from the modified screen-printed carbon electrode recorded at scan rates of 10, 25, 50, 75 and 100 mV/s in PBS and the corresponding linear plots of the peak currents of the anodic and cathodic processes against the square root of the scan rate, which shows that this reversible process is diffusion-limited. Potentials are relative to the Ag pseudo-reference employed, which by comparison with the Ru(II)/Ru(III) redox peaks in Fig. 1 has a stable potential of –0.035V with respect to the Ag/AgCl reference electrode in this and subsequent experiments.

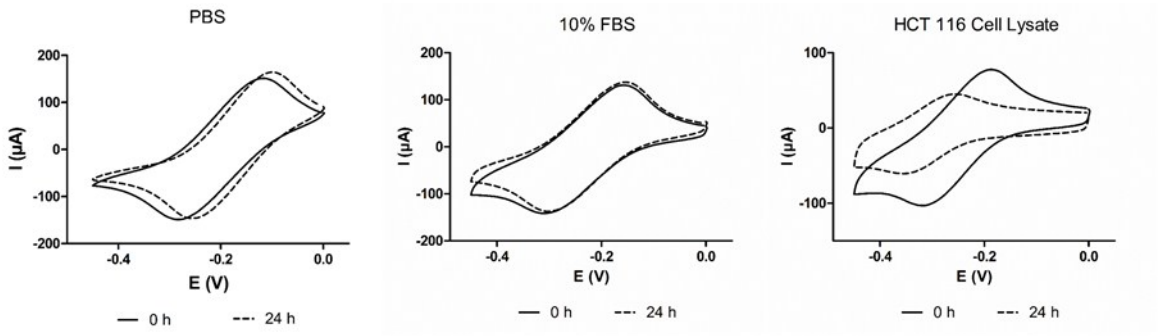


Figure S5. Cyclic voltammograms recorded for a modified screen-printed electrode in: (a) PBS, (b) FBS and (c) cell lysate over 24 h. Potentials are relative to the Ag pseudo-reference."

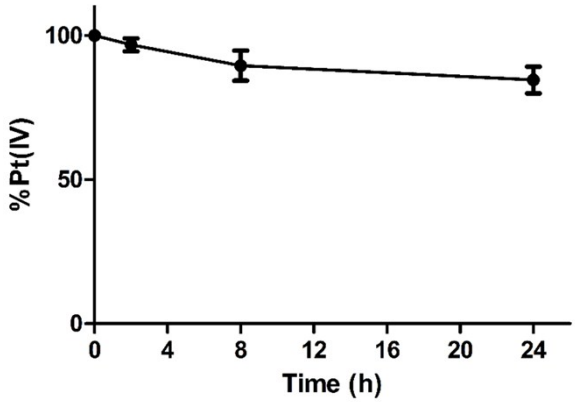


Figure S6. Stability of **1** (100 µM) in 10% FBS at 37 °C as measured by HPLC.

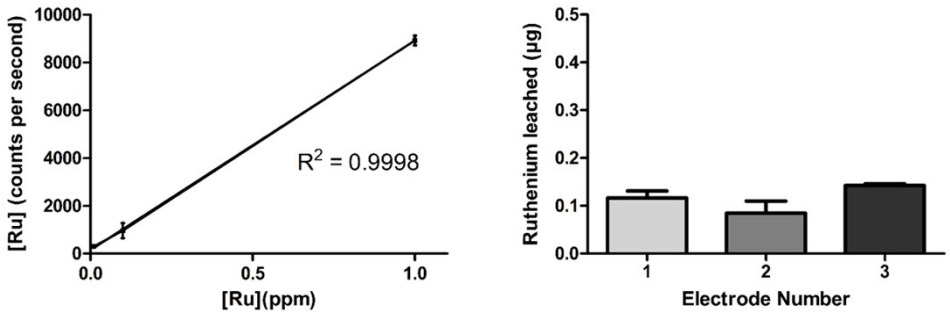


Figure S7. ICP-OES Calibration and quantification of mediator leaching from the electrode; (a) Calibration curve of standard Ru concentrations detected at 350 nm with ICP-OES using $RuCl_3$ (n = 3); (b) Quantification of Ru content in solution after application of -0.4 V with the modified electrodes (n = 3) for 24 h. After 24 h of continuous application of a reduction potential of -0.4 V in 0.1 M KCl, 115 ± 14 ng of Ru (10% of total Ru content) was found to have leached out of the modified electrode device into solution (n = 3).

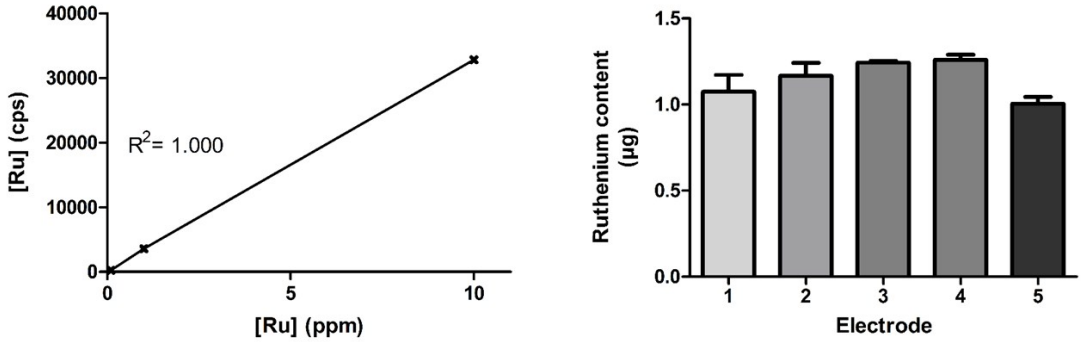


Figure S8. Calibration curve and quantification of total Ru content in modified electrodes (n = 5) as analysed by ICP-OES; (a) Calibration curve of standard ruthenium concentrations detected at 349.9 nm with ICP-OES using $RuCl_3$ (n = 3); (b) The Ru content of modified electrodes was analysed by digesting the polymer layer in aq. HNO_3 (10%, 1 mL). This was further diluted to 2% HNO_3 before analysis. The total Ru content retained within each modified electrode was found to contain approximately 1.08 ± 0.02 µg of mediator (n = 5).

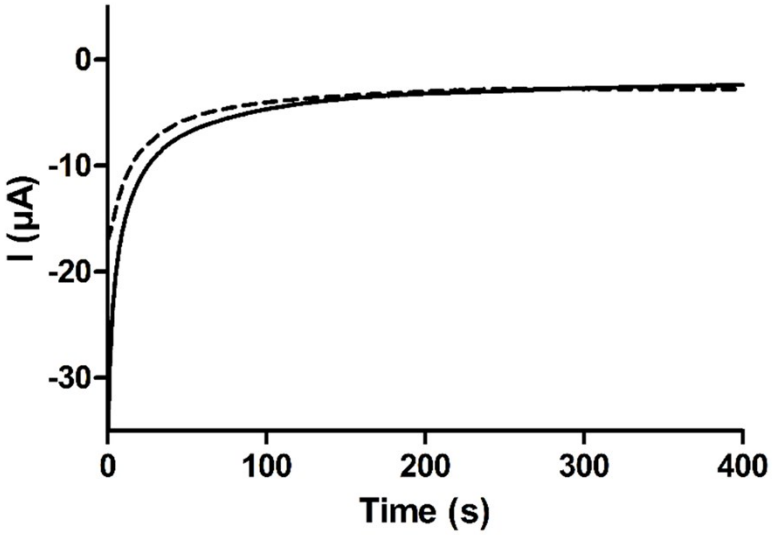


Figure S9. Amperometric quantification of redox-active mediator retained within modified electrodes. A potential of -0.4 V was applied to a modified electrode (solid line) and a blank SPCE (dashed line) and the difference in total charge over 400 s was used to quantify the redox-active mediator. The total Ru content retained within each modified electrode was quantified by ICP-OES (see above), with each found to contain approximately 1.08 ± 0.02 µg of mediator. The redox-active content of mediator was found to be 0.84 µg or around 78% of the total content.

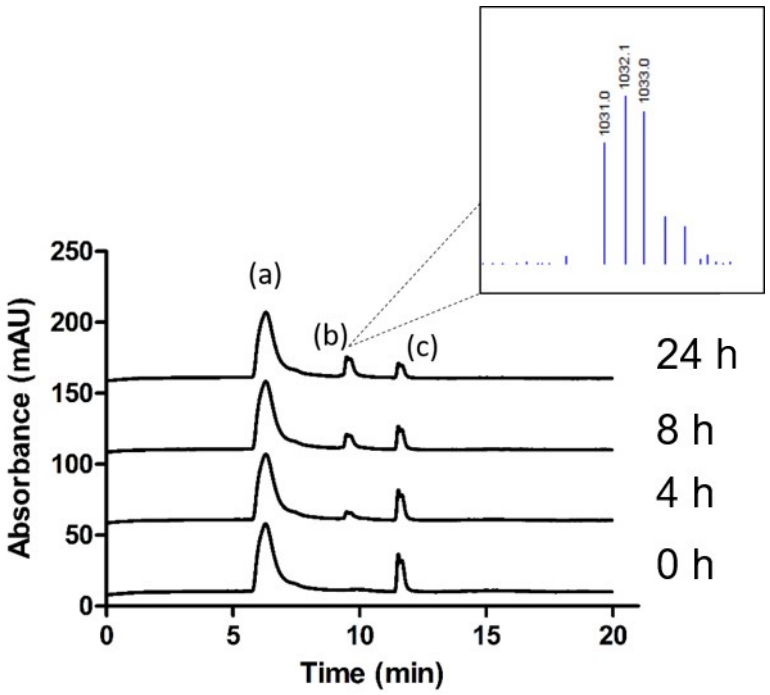


Figure S10. HPLC trace showing: (a) GMP, (b) Pt(II)-GMP_2, (c) **1**. Inset: Analysis of peak (b) by LC-MS confirmed that DACH-Pt-GMP_2 was formed.

HPLC analysis was performed on an Agilent Technologies 1100 modular HPLC system equipped with a Phenomenex Eclipse® 5 µm XDB-C18 column (150 x 10 mm, 5 µm) with a flow rate of 2.0 mL/min. Elution was with ACN and H_2O, with a gradient of 5 to 40% over 15 min then 40 to 95% over another 5 min with an initial isocratic period of 2 min and a final isocratic period of 2 min. Detection was at 254 nm. Peak (b) was collected and confirmed to be the *bis*-adduct of oxaliplatin with GMP by LC-MS (inset).

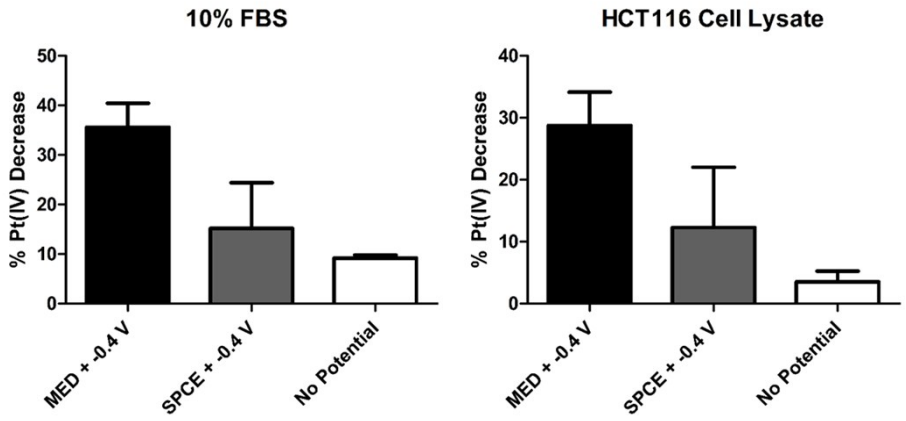


Figure S11. Electrochemical reduction of prodrug **1** by the modified electrode upon the application of a reduction potential of -0.4 V in 10% FBS and HCT 116 cell lysate via HPLC monitoring.

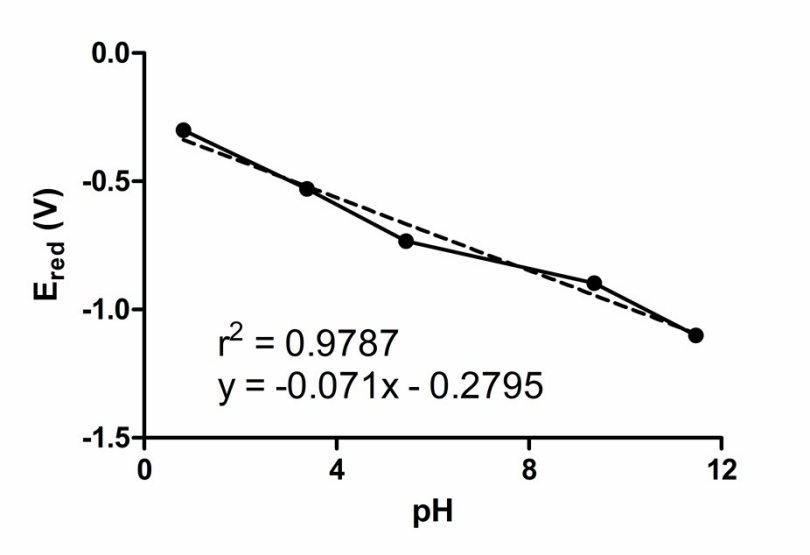


Figure S12. Relationship between pH of solution and the peak reduction potential of **1** (2 mM) in PBS. CV analysis was carried out with a glassy carbon electrode with potentials relative to the Ag/AgCl reference electrode. This plot confirms that a mediated reduction of **1** will take place for pH values above 2, value which is not going to be reached during the electroreduction of **1** at the concentration range used in the biological setting employed, as shown in Table S2. This pH dependency is thought to be due to a mechanism of reduction of **1** that comprises both direct and oxygen-mediated reduction, as previously reported (1).

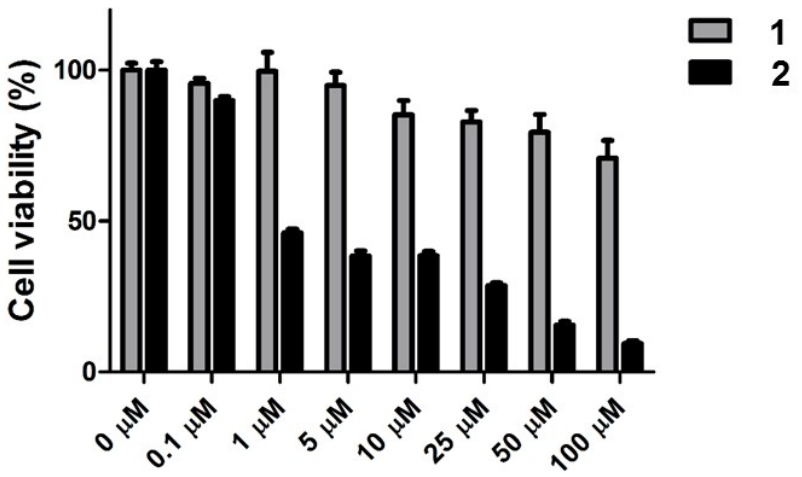


Figure S13. Cell viability of HCT 116 cells treated with **1** and **2**. Cells were incubated with 0 μM to 100 μM of **1** or **2** for 72 h after which cell viability was measured (MTT assay, n = 3).

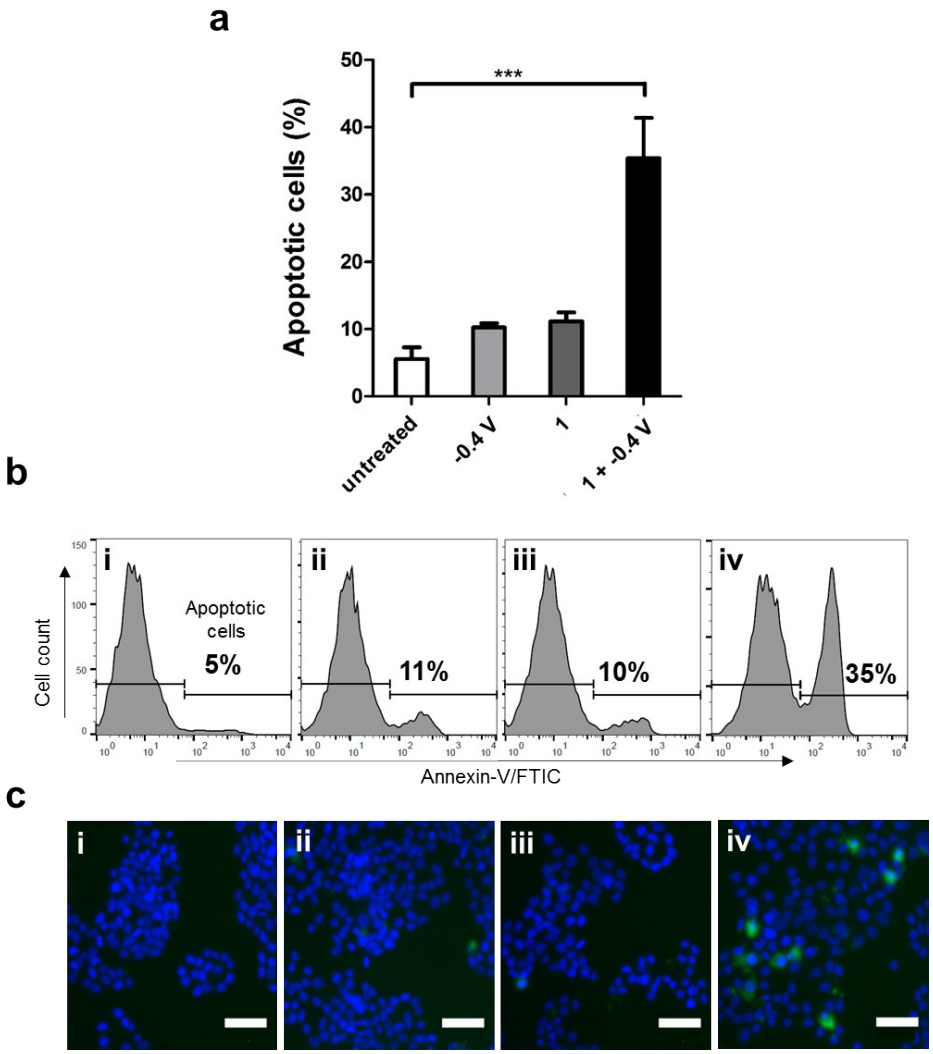


Figure S14. Apoptotic effect of electrochemical activation of **1**.

(a) HCT 116 cells were incubated with **1** (50 μM) and treated with -0.4 V for 1 h. Cells were incubated for 24 h and stained with Annexin-V/FITC, followed by flow cytometry analysis (n=3). The data represents the mean ± S.D. *** P<0.001 by one-way ANOVA with Dunnett post-test, compared with the untreated control group; (b) Flow cytometry of cells incubated as above: (i) untreated cells, (ii) cells treated with **1** (50 μM), (iii) cells with -0.4 V applied, and (iv) cells treated with **1** (50 μM) and -0.4 V applied; (c) HCT 116 cells were incubated with **1** (50 μM) and -0.4 V was applied for 1 h, after which the cells were incubated for 24 h and stained with Annexin-V/FITC and Hoechst 33452 (nuclei stain) and imaged by fluorescence microscopy: (i) untreated cells (cell nuclei are shown in blue), (ii) cells treated with **1** (50 μM), (iii) cells treated with -0.4 V, and (iv) cells treated with **1** (50 μM) and -0.4 V (Annexin-V/FITC is shown in green). Scale bar = 100 μM.

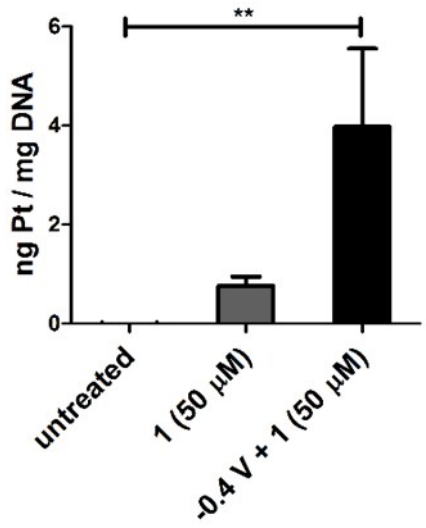


Figure S15. Pt quantification of DNA in HCT 116 cells. Cells were incubated with **1** (50 μM) and treated with a reduction potential of -0.4 V for 1 h. Cells were then incubated for 4 h, harvested and DNA isolated (Qiagen DNeasy blood and tissue kit). The Pt content of the DNA was determined by ICP-MS (n = 3). The data represent the mean ± S.D. ** P<0.001 by one-way ANOVA with Dunnett post-test, compared with the untreated control group.

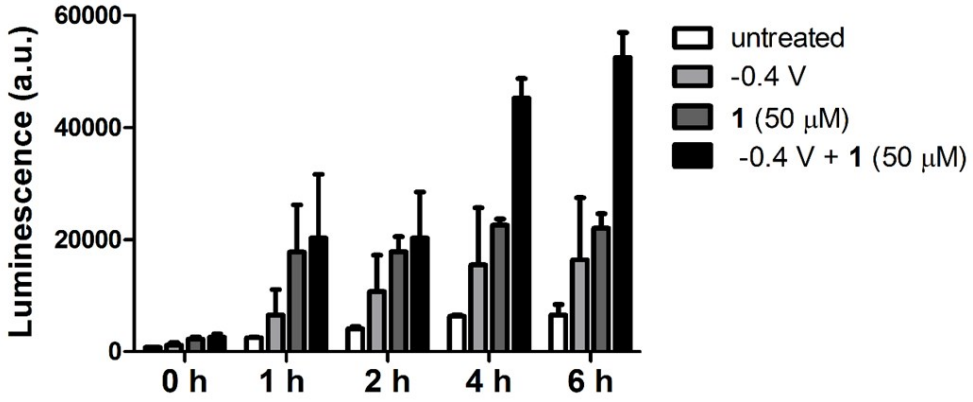


Figure S16. Real-time monitoring of onset of apoptosis by electro-activation of **1** in cell spheroids. HCT 116 spheroids were incubated with **1** (50 μM) and treated with a reduction potential of -0.4 V for 1 h. Cells were incubated with RealTime-Glo™ Annexin V Apoptosis assay (according to the manufacturer's instructions) and luminescence increase monitored at different time points. The data represents the mean ± S.D.

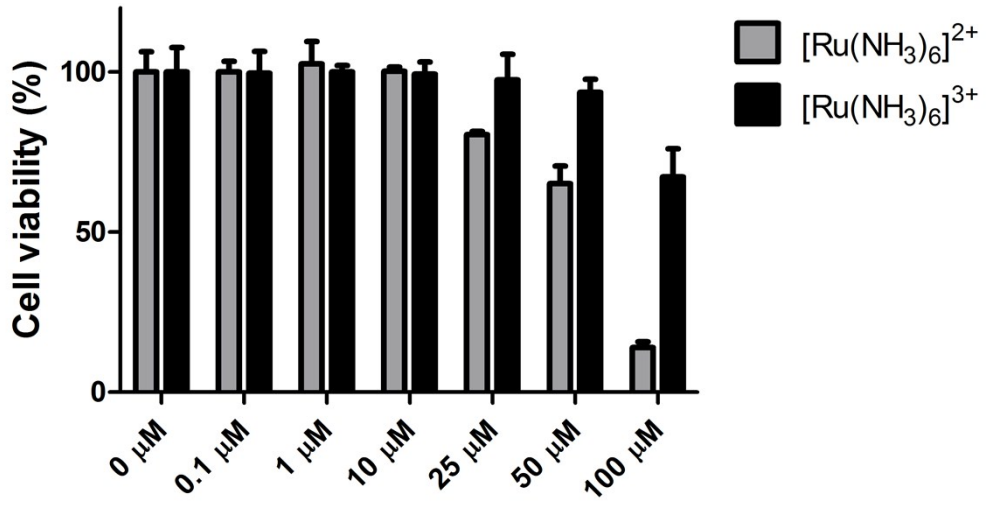


Figure S17. Cell viability of HCT 116 cells treated with $[Ru(NH_3)_6]Cl_3$ and $[Ru(NH_3)_6]Cl_2$. Cells were incubated with 0 µM to 100 µM $[Ru(NH_3)_6]Cl_3$ and $[Ru(NH_3)_6]Cl_2$ for 72 h (MTT assay, n = 3) to verify that any Ru potentially leached from the device would not have any effect on cell viability. Both $[Ru(NH_3)_6]Cl_3$ and $[Ru(NH_3)_6]Cl_2$ were investigated in cell culture assays, showing no effect on cell viability up to 25 µM. The total maximum leaching per device was 1.08 µg (equivalent to 10 µM) if all of the mediator dissociated from the Nafion layer completely. Cells after incubation with **1** and applying -0.4 V displayed a Ru content of 0.2 ng / 10^6 cells (equivalent to 0.02% of total Ru content per device), as analysed by ICP-MS.

S2. Experimental

S2.1 General Materials and Methods

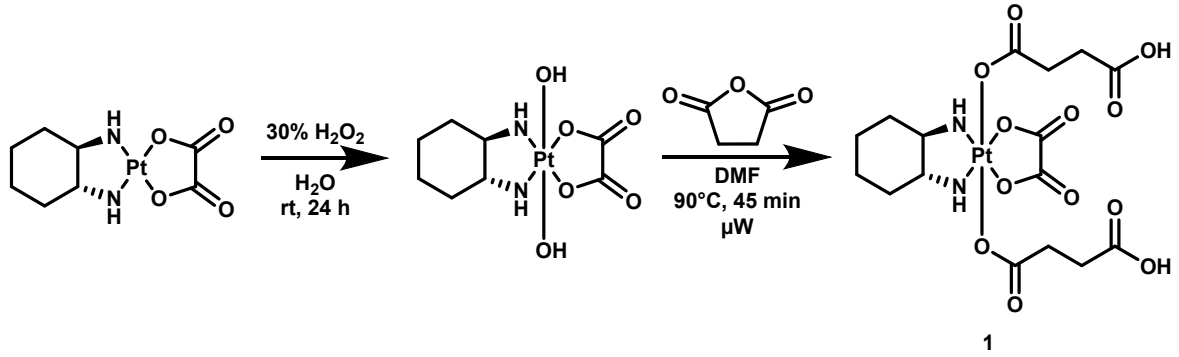
Chemicals and solvents for synthesis, unless otherwise stated, were purchased from Sigma-Aldrich and used without further purification. Oxaliplatin was purchased from Carbosynth Ltd. $[Ru(NH_3)_6]Cl_3$ and $[Ru(NH_3)_6]Cl_2$ were purchased from Fisher Scientific. Dulbecco's Phosphate Buffered Saline (1×, [KCl] = 2.7 mM, [NaCl] = 138 mM, $[KH_2PO_4]$ = 1.47 mM, [Na2HPO4] = 8.16 mM) was used throughout. ^1H and ^{13}C spectra were recorded on a Bruker AVA-500 (at 500 and 125 MHz, respectively) at 298 K in the solvents indicated (resonances are in ppm). ^{195}Pt spectra were recorded on a Bruker PRO-500 at 107 Hz with external standard of K_2PtCl_4 in D_2O. For reaction monitoring, a Bruker 600 MHz NMR spectrometer was used with water presaturation. pH measurements were recorded with a Mettler-Toledo FiveGo F2, which was calibrated with a three-point calibration before use.

Low Resolution Mass Spectra (LRMS) were obtained using an Agilent LCMS 1100 ChemStation with a G1946B quadrupole mass detector. High Resolution Mass Spectra (HRMS) were performed on a Bruker 3.0 T Apex II spectrometer. Analytical RP-HPLC was performed using an Agilent 1100 Chemstation equipped with a Zorbax Eclipse C18 reverse phase column (4.6 mm × 100 mm, 3.5 µm) eluting with a gradient of 5-95% of water/formic acid (0.1%) to MeCN/formic acid (0.1%) over 10 min

with a flow rate of 1 mL/min, and compounds were detected by an ELS detector and a multiwavelength detector. For monitoring Pt(IV) conversion, an Agilent 1100 Chemstation was used equipped with a Zorbax Eclipse C18 reverse phase column (9.4 mm × 250 mm, 3.5 µm) eluting with a gradient of 5-40% MeCN/formic acid (0.1%) in water/formic acid (0.1%) over 15 min then to 95% over a further 5 min with a flow rate of 2 mL/min, and compounds were detected at 254 nm. ICP-OES were obtained on a Perkin Elmer Optima 5300 DV ICP-OES suitable for the trace analysis of metals between 0.0002–1000 ppm. Microwave reactions were carried out in a Biotage Initiator in sealed 2-5 mL sealed microwave vials, with microwave heating ramping over 40 seconds to the desired temperature. Flow cytometry analysis was carried out on a Becton Dickinson (BD) FACSAriaTM and analysed using FlowJo.

S2.2 Synthesis of *c,c,t*-Pt(DACH)(Ox)(Suc)$_2$ (1)

The compound was synthesised using an adaptation of the procedure of Sessler *et* al. (1)



Scheme S1. Synthetic route for **1**.

Oxaliplatin (1 g, 2.52 mmol) was suspended in water (12 mL) and 30% H_2O_2 (3 mL) was added and the reaction left for 24 h at room temperature (reaction completion was determined by monitoring by LC-MS). The reaction mixture was then heated to 50 °C for 3 h. The reaction mixture was then cooled and left at 4 °C overnight to facilitate precipitation of the product. The mother liquor was decanted and the precipitate washed with cold water and dried at 40 °C in a vacuum oven for 12 h.

The intermediate *c,c,t*-Pt(DACH)(Ox)(OH)$_2$ (100 mg, 0.23 mmol) was suspended in DMF (5 mL) in a microwave vial, to which a 5-fold molar excess of succinic anhydride was added. The mixture was heated at 90 °C with microwave heating for 45 min. Following completion of the reaction, the solvent was removed *in vacuo* and the residue re-dissolved in methanol and the solution filtered. The filtrate was then added dropwise to a Falcon tube of rapidly stirred diethyl ether (20 mL). The precipitate was isolated via centrifugation and dried in a vacuum oven at 40 °C for 12 h to afford compound **1**. Yield: 102 mg (70%). ^{1}H NMR (600 MHZ, D_2O) δ 1.20 (m, 2H), 1.46-1.63 (m, 2 × 2H), 2.23 (m, 2H), 2.46 (m, 4H), 2.57 (m, 4H), 2.82 (m, 2H). ^{1}H NMR (600 MHZ, DMSO-d6) δ 1.16 (m, 2H), 1.39 (m, 2H), 1.50 (m, 2H), 2.11 (m, 2H), 2.40 (m, 4H), 2.52 (m, 4H, overlapping with DMSO solvent peak), 2.59 (m, 2H), 8.15 (s, 2H), 8.36 (s, 2H) 12.10 (br, 2H). ^{13}C NMR (150 MHz, DMSO-d6) δ 24.0, 30.1, 31.0, 31.4, 61.3, 163.8, 174.1, 180.1. ^{195}Pt NMR (108 MHz, DMSO-d6) δ 1617. HRMS (+): *m/z* $[M+H]^+$ calcd: 632.105 found: 632.105, $[M+Na^+]$ calcd: 654.087 found: 654.087.

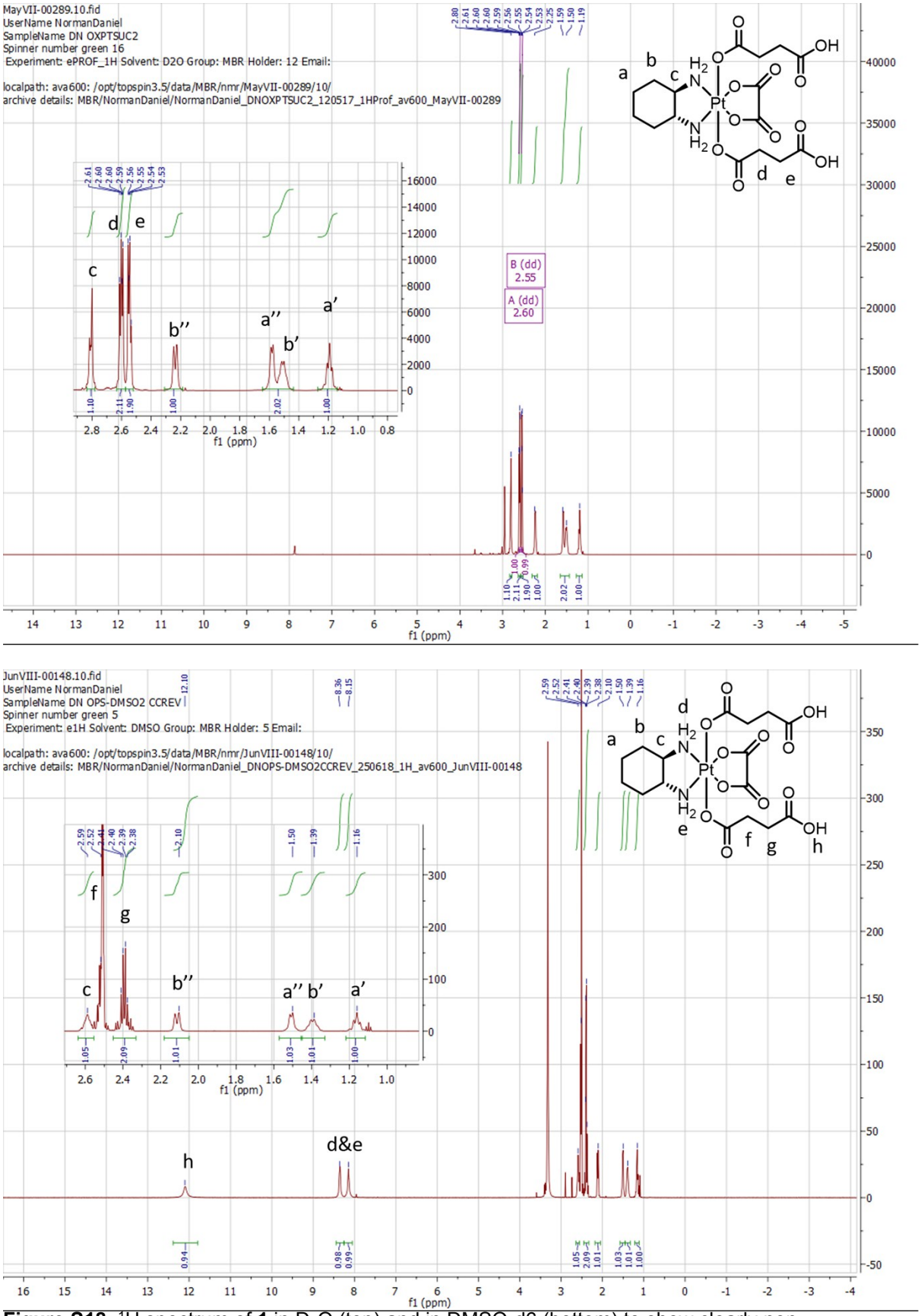


Figure S18. ^{1}H spectrum of **1** in D_2O (top) and in DMSO-d6 (bottom) to show clearly non-exchangeable and exchangeable protons, respectively.

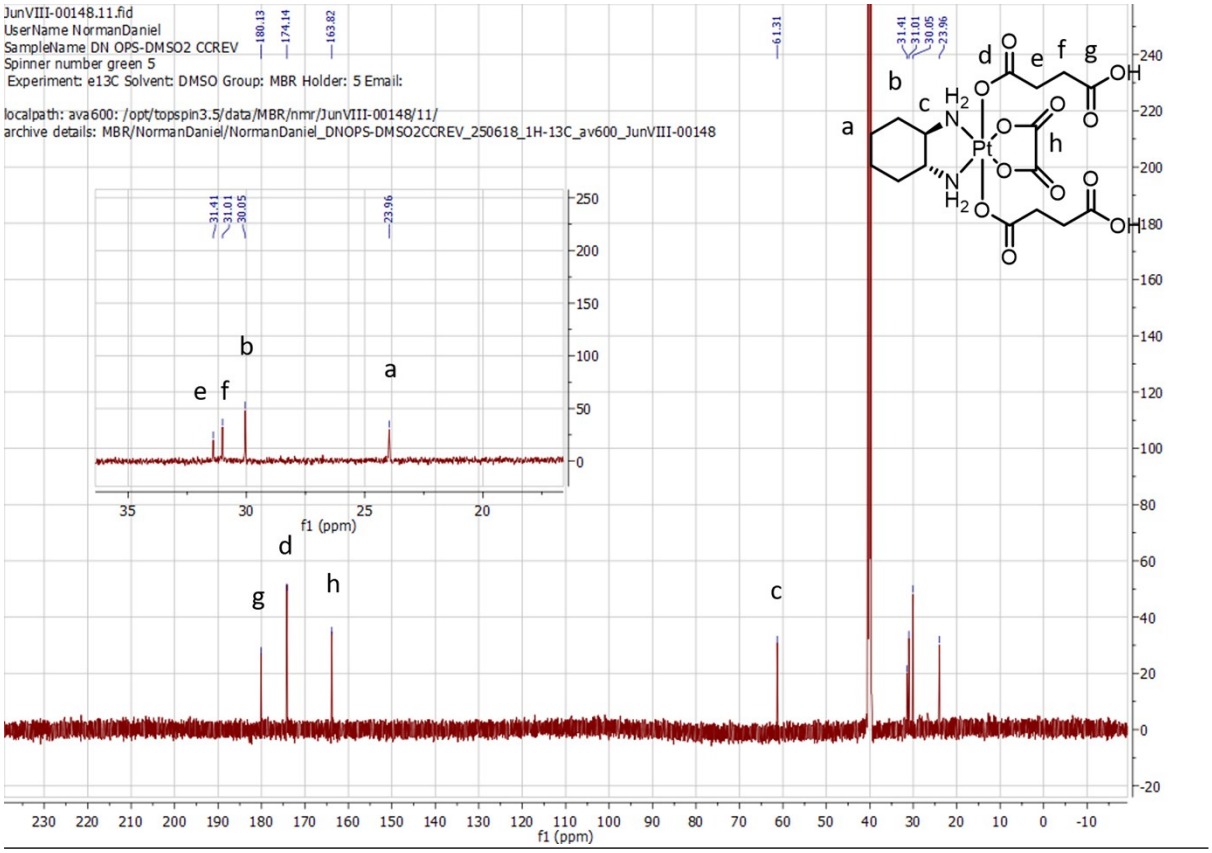


Figure S19. ^{13}C spectrum of **1** in DMSO-d6 (150 MHz).

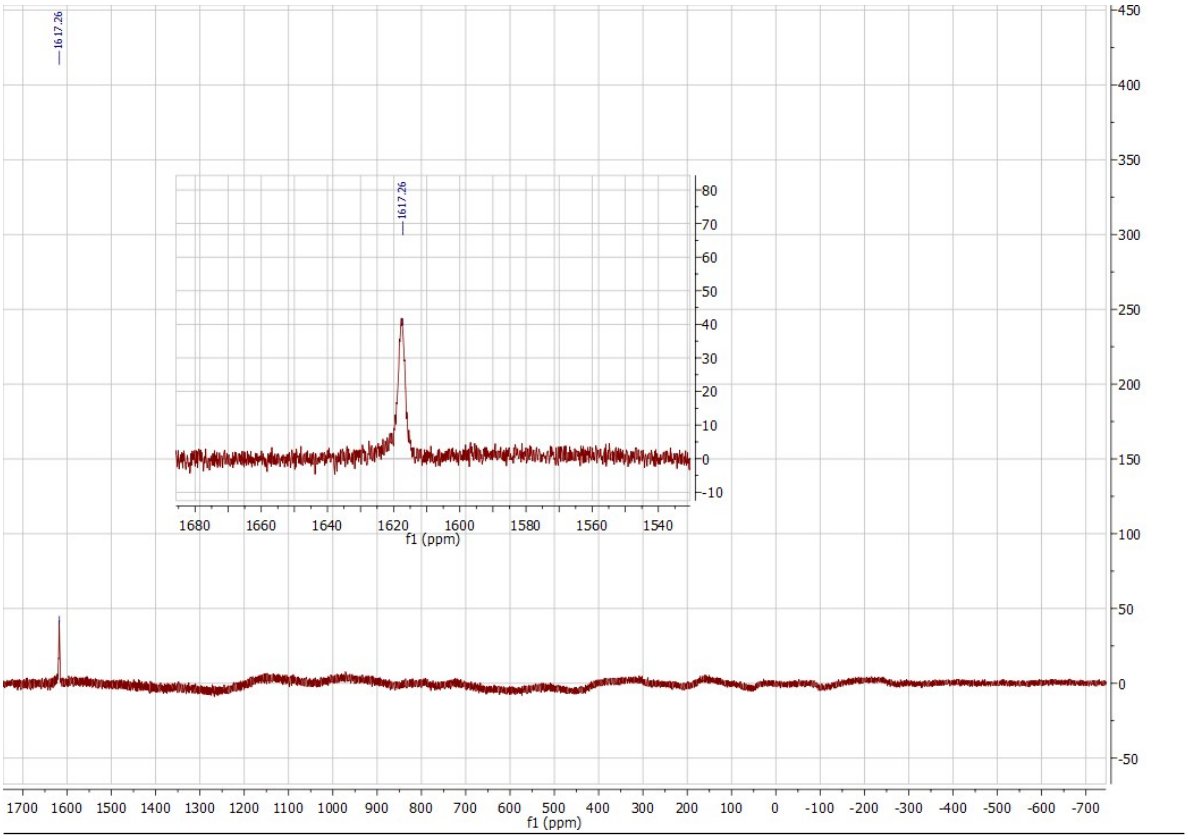


Figure S20. ^{195}Pt spectrum of **1** in DMSO-d6 (108 MHz).

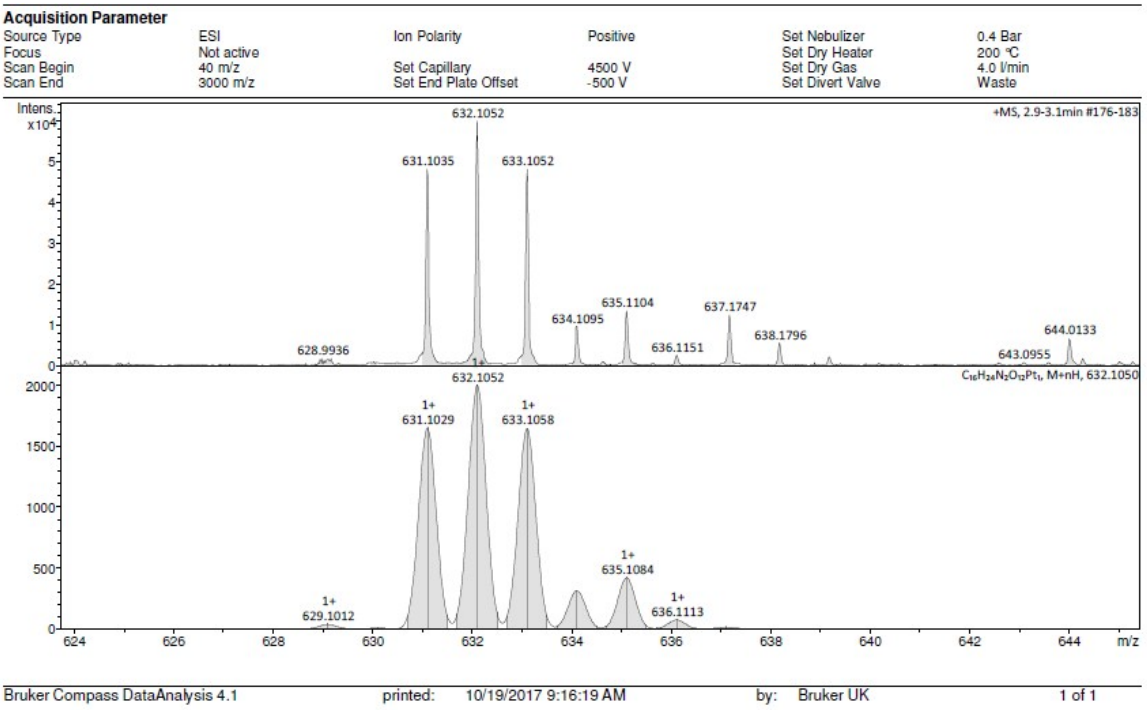


Figure S21. HRMS spectrum of **1** in H_2O

S2.3 Reduction of 1 by biological reductants

Reduced glutathione (1.54 mg, 5 μmol) or ascorbic acid (0.88 mg, 5 μmol) were added to a solution of **1** (100 μM) in PBS (prepared in D_2O (0.5 mL), pH 7.4) to give a 100-fold molar excess of reductant. These solutions were incubated at 37 °C for 24 h in the absence of light and the reaction monitored by HPLC.

S2.4 Electrochemical measurements

Electrochemical measurements were performed using a conventional three-electrode electrochemical cell driven by a computer-controlled AutoLab PGstat-30 potentiostat running the GPES 4.9 software (EcoChemie, The Netherlands) or a Dropsens Multipotentiostat running the Dropview software. Carbon ink screen printed electrodes, SPCEs, (C110, Dropsens, Spain) were used for conversion studies and a 1.6 mm diameter glassy carbon electrode, GCE (BASi) was used as a working electrode for electrochemical characterisation along with a platinum wire and a Ag│AgCl│KCl (3 M) (Bioanalytical Systems, Inc., USA), as counter and reference electrodes, respectively. SPCEs were composed of a carbon ink working and counter electrode with a silver pseudo-reference. The potential of the Ag|AgCl|KCl (3M) against Standard Hydrogen Electrode (SHE) is + 0.210 V. The electrodes were washed with deionised water and ethanol prior to use. The GCE was polished with a 0.05 μm alumina slurry and thoroughly washed with deionised water prior to use.

S2.5 Preparation of Modified Electrode Devices (MED).

Nafion® perfluorinated resin solution (3 µL, 5% in a mixture of lower aliphatic alcohols and water) was drop casted onto clean carbon ink screen-printed electrodes (SPCE) and air-dried at room temperature for 1 h. Once dried, the Nafion®-coated electrodes were dipped into a solution of $[Ru(NH_3)_6]Cl_3$ (3 mM) in deionised water for 2 h and transferred to a vial containing water and allowed to age overnight. Before use, the electrodes were washed with water and the redox properties of the Nafion®-bound mediator were analysed by cyclic voltammetry.

S2.6 Quantification of total Ru content in modified electrodes by ICP-OES analysis

Carbon ink with Nafion®-bound Ru was removed from a modified electrode in 1 mL of aqueous HNO_3 (10%) in Eppendorf tubes. Resulting mixtures were sonicated and vortexed intermittently for 10 min before centrifugation at 7000 rpm for 5 min. The supernatant was decanted and further diluted to 2% aqueous HNO_3. The Ru content was then analysed by ICP-OES with calibration against Ru standard solutions.

S2.7 Quantification of redox-active Ru in modified electrodes by coulometric analysis

Redox-active Ru content was analysed by integration of total charge difference between modified electrodes and Nafion®-coated SPCEs (i.e. without any Ru mediator) after applying -0.4 V for 400 s (n = 4). Faraday's law was applied to quantify the mass (w) of Ru related to the charge (Q):

$$w = \frac{(MW.Q)}{(n.F)}$$

where MW is molecular weight, n is number of electrons involved in redox process and F is Faraday's constant.

S2.8 Cell culture and MCTS culture

HCT 116 cells were cultured in Dulbecco's modified Eagle medium (DMEM) supplemented with 10% fetal bovine serum (FBS), *L*-glutamine (4 mM) and antibiotics (penicillin and streptomycin, 100 units/mL). Cell culture was performed in a 5% CO_2 atmosphere at 37 °C in a SteriCult 200 (Hucoa-Erloss) incubator. The day before the assays, the cells were washed with PBS, detached with trypsin/EDTA (0.25% trypsin, 1 mM EDTA), counted, and diluted with DMEM to the appropriate concentration.

Spheroids were generated by the hanging drop method. A cell suspension drop (20 µL, 1000 cells per drop) in DMEM was dispensed onto the lid of a petri dish (90 mm), inverted and incubated under standard conditions (DMEM was added to the dish to avoid evaporation). The spheroids were incubated for 7 days with the addition of fresh DMEM (5 µL) to the drops every 2 days. The size of the spheroids was monitored by inverted microscopy. For the treatment with **1** the spheroids were transferred to a 24 well-plate coated with 1% agarose (containing 350 µL DMEM).

S2.9 Preparation of cell lysate

HCT 116 cells (3 million) were washed with PBS, detached with Trypsin/EDTA, harvested with water (2 mL) and lysed by subsequent sonication for 30 min. The lysate was centrifuged for 10 min at 13,000 rpm and the supernatant collected and used as a cell lysate in the *in vitro* studies.

S2.10 Cell viability studies

HCT 116 cells grown in a 96-well plate (5,000 cells/well) were incubated with a solution of **1** or **2** at the desired concentrations and the cells incubated for 3 d. The media was then replaced with 100 µL of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) solution (1 mg/mL) in PBS and the cells incubated for 3 h at 37 °C. After incubation, the resulting formazan crystals were dissolved by adding 100 µL of MTT solubilisation solution (10% Triton-X 100 in 0.1 N HCl in isopropanol). The absorbance was measured at a wavelength of 570 nm (BioTek HT Synergy multi-mode reader using the Gen5 microplate and imaging software 2.0.) and the results compared to untreated cells.

S2.11 Electrochemical mediated prodrug activation in cell culture.

HCT 116 cells grown in a 24-well plate (15,000 cells/well) were incubated with a solution of **1** (50 µM) in a total volume of 1.7 mL. The SPCEs were added to the wells treated with **1** or with DMEM (as a control). A potential of -0.4 V was applied for 1 h, after which the SPCEs were removed and the cells incubated at 37 °C for 3 days. The media was then replaced with 350 µL of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) solution (1 mg/mL) in PBS and the cells incubated for 3 h at 37 °C. After incubation, the resulting formazan crystals were dissolved by adding 350 µL of MTT solubilisation solution (10% Triton-X 100 in 0.1 N HCl in isopropanol). The absorbance was measured at a wavelength of 570 nm (BioTek HT Synergy multi-mode reader using the Gen5 microplate and imaging software 2.0.) and the results compared to untreated cells.

For analysis of cell apoptosis, cells were treated as above and incubated for 24 h at 37 °C. After incubation, fluorescein-conjugated Annexin-V (Annexin V-FITC) binding assay was performed. Labelling of cells with Annexin-V-FITC conjugate was performed using an Apoptosis Detection Kit (eBiosciences, San Diego, CA) according to manufacturer's instructions with Annexin V-FITC and binding buffer included as controls. Flow cytometry (Becton Dickinson (BD) FACScan) was performed with excitation at 488 nm. FITC fluorescence was measured at 515–545 nm. Cell debris was excluded from analysis by appropriate forward light scatter threshold setting. For fluorescence imaging, cells were washed with PBS after Annexin-V/FITC incubation, stained with Hoechst 33342 for 10 min and imaged with a Zeiss Axio Vert inverted fluorescence microscope. Microscope lasers settings were: excitation laser lines at 405 nm and 488 nm with emission filters of 385–470 nm for Hoechst 33342 (nuclei stain) and 505–530 nm for Annexin-V/FITC.

S2.12 ICP-MS of cell content

HCT 116 cells were grown in a 6 well-plate until confluent and then treated with **1** (50 µM) and -0.4 V was applied for 1 h. The cells were incubated at 37 °C for 24 h and the media removed, the cells washed with PBS (3×), detached with trypsin, and counted (haemocytometer). The cells were

centrifuged at 7000 rpm for 5 min after which the cell pellet was suspended in aqueous HNO_3 (5%), sonicated for 1 h and analysed by ICP-MS with calibration against Pt standard solutions, to give the final results as ng of Pt / 10^6 cells (see Table S3). To determine the amount of leached Ru from the modified electrode, the cell pellet was analysed by ICP-MS with calibration against Ru standard solution, to give 0.20 ± 0.05 ng Ru / 10^6 cells (see Table S1).

For quantification of platinated DNA, the cell pellet obtained by centrifugation (see above) was resuspended in PBS (200 µL) and subjected to DNA isolation and purification using a Qiagen DNeasy blood and tissue kit. The DNA concentration was analysed by nanodrop spectroscopy of 2 µL of DNA solution (average of three measurements). The samples were prepared by suspending the DNA solution in aqueous HNO_3 (5%) and analysed by ICP-MS to give the final results as ng of Pt / mg of DNA (Table S4).

Table S1. Ruthenium concentration in HCT 116 cells (sample volume = 1.5 mL).

Sample	Concentration (µg/L)	Cells (×10^6)	ng Ru / million cells
(1) 1 (50 µM) + -0.4 V	0.151	1.61	0.14
(2) 1 (50 µM) + -0.4 V	0.208	1.36	0.23
(3) 1 (50 µM) + -0.4 V	0.204	1.24	0.24

Table S2. pH monitored throughout the electroactivation process of **1** (50 µM) in PBS with a modified electrode. The slight change in pH throughout the reduction process may be through reactions unrelated to the reduction of **1**, such as the reduction of oxygen which consumes protons to afford water. Data is mean of triplicate experiments with standard deviation as error.

Time	PBS + 1
pH before addition of **1**	6.99 ± 0.01
pH after addition of **1**	6.91 ± 0.04
After 2 h conversion	6.93 ± 0.05
After 4 h conversion	6.99 ± 0.02
After 8 h conversion	7.14 ± 0.06
After 24 h conversion	7.41 ± 0.06

Table S3. Platinum concentration in HCT 116 cells (sample volume = 4 mL).

Sample	Concentration (µg/L)	Cells ($\times 10^6$)	ng Pt / million cells
(1) 1 (50 µM)	4.24	1.64	10.33
(2) 1 (50 µM)	3.68	1.67	8.82
(3) 1 (50 µM)	4.53	1.81	10.03
(4) 1 (50 µM) + -0.4 V	29.67	1.61	73.71
(5) 1 (50 µM) + -0.4 V	30.27	1.36	89.03
(6) 1 (50 µM) + -0.4 V	30.48	1.24	98.32

Table S4. Platinum concentration in DNA of HCT 116 cells (sample volume = 1.2 mL).

Sample	Concentration (µg/L)	DNA (µg)	ng Pt / mg DNA
(1) 1 (50 µM)	0.056	108.0	0.62
(2) 1 (50 µM)	0.093	114.6	0.97
(3) 1 (50 µM)	0.078	137.1	0.68
(4) 1 (50 µM) + -0.4 V	0.361	80.5	5.39
(5) 1 (50 µM) + -0.4 V	0.258	72.6	4.26
(6) 1 (50 µM) + -0.4 V	0.265	140.0	2.27

S3. References

1. Thiabaud G, McCall R, He G, Arambula J.F., Siddik Z.H., Sessler J.L. Activation of Platinum(IV) Prodrugs By Motexafin Gadolinium as a Redox Mediator. Angewandte Chemie International Edition. 2016;55(41):12626-31.