Supplementary information

Experimental Details

General

^{1}H NMR, ^{13}C NMR and ^{195}Pt NMR spectra were recorded on either a Bruker Avance 400 MHz Ultrashield NMR spectrometer or a Bruker Avance 500 MHz NMR spectrometer. Mass spectral data were obtained on a Bruker Daltonics Esquire 3000 spectrometer by Mrs. L. Haigh (Imperial College London). 2-hydroxy-4-(2-(piperidin-1-yl)ethoxy)benzaldehyde and $PhICl_2$ were prepared following a previously reported synthetic procedure.[1,2]

For DNA binding studies, compounds **1** and **2** were dissolved in DMSO to yield 1 mM stock solutions. All solutions were stored at -20 ºC and defrosted and diluted immediately before use. They were then further diluted to the appropriate concentrations, using suitable buffer.

Oligonucleotide Solutions

The oligonucleotides HTelo DNA (5'- AGG-GTT-AGG-GTT-AGG-GTT-AGG-G -3'), *c-Myc* DNA (5'-TGA-GGG-TGG-GTA-GGG-TGG-GTA-A-3'), and ds26 DNA (5`-CAA-TCG-GAT-CGA-ATT-CGA-TCC-GAT-TG-3`) were purchased from Eurogentec. Each oligonucleotide was dissolved in Milli Q water to yield a 1 mM stock solution. The corresponding solution was then diluted using 10 mM lithium cacodylate buffer (pH 7.4) in the appropriated KCl concentration (10 mM for HTelo-K, 1 mM for *c-Myc* and 100 mM for ds26) or NaCl concentration (100 mM for HTelo-Na). Prior to use, the HTelo DNA and ds26 DNA were annealed by heating the solutions to 95 ºC for 5 min, and then cooling to room temperature overnight. *c-Myc* DNA was annealed by heating the solution to 95 ºC for 5 min, followed by cooling in an ice bath.

Synthesis of 1. A mixture of 2-hydroxy-4-(2-(piperidin-1-yl)ethoxy)benzaldehyde (0.350 g, 1.4 mmol) and *o*-phenylenediamine (0.076 g, 0.7 mmol) were dissolved in methanol to obtain a yellow solution which was heated to 60 °C for 4 h under a nitrogen atmosphere. Subsequently, the solvent was removed under reduced pressure and DMSO (2 mL) was added to the crude solid. The reaction mixture was stirred for 5 minutes after which time NaOAc (0.114 g, 1.4 mmol) was added. This was followed by addition of a solution of K_2PtCl_4 (0.247 g, 0.9 mmol) in DMSO (3 mL). Upon addition, the solution changed in colour from yellow to orange and after a few more minutes to dark red. The reaction mixture was heated at 50 °C for 15 h under nitrogen atmosphere after which time it was leave to cool down and upon addition of methanol and diethyl ether, a dark orange solid precipitated. The resulting solid was recrystallized using a MeOH:Et_2O mixture to afford **1** as an orange/red solid. Yield: 17% (0.091 g). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.26 (s, 2H, H-3), 8.31 (dd, *J* = 6.4, 3.5 Hz, 2H, H-2), 7.69 (d, *J* = 9.0 Hz, 1H, H-5), 7.34 (dd, *J* = 6.4, 3.4 Hz, 2H, H-1), 6.55 (s, H-6), 6.42 (dd, *J* = 9.0, 2.4 Hz, 2H, H-4), 4.12 (t, *J* = 5.8 Hz, 4H, H-8), 2.64 (t, *J* = 5.8 Hz, 4H, H-7), 2.46 (m, 8H, H-9), 1.47 (p, *J* = 5.7 Hz, 8H, H-10), 1.46 – 1.31 (m, 4H, H-11). ^{13}C NMR (101 MHz, DMSO-d_6): δ 171.9, 166.4, 149.7, 144.4, 136.8, 127.1, 116.6, 116.4, 108.1, 102.7, 54.2, 25.4, 21.1. ^{195}Pt NMR (86 MHz, DMSO-d_6) δ: -1759 ppm. ESI-MS calcd. for $C_{34}H_{40}N_4O_4Pt$: 763.8 a.m.u.; found: 764.8 a.m.u. Elemental Analysis calculated for $C_{34}H_{40}N_4O_4Pt{\cdot}HCl{\cdot}H_2O$: C, 49.91; H, 5.30; N, 6.85; found C, 50.27; H, 5.04; N, 6.82.

Synthesis of 2. $PhICl_2$ (0.044 g, 0.16 mmol) was added to a solution of **1** (0.100 g, 0.15 mmol) in DMF (~5 mL). The solution was stirred for 48 hours at 40 ºC. Diethyl ether (100 mL) was added to the reaction mixture resulting in the precipitation of a yellow solid. The yellow precipitate was collected by vacuum filtration, washed with diethyl ether and dried under vacuum. The resulting yellow solid was dissolved in DMSO and a saturated aqueous solution

of $NaPF_6$ was added to precipitate the desired product as a PF_6 salt. Yield: 82% (0.139 g). ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.28 (s, 2H, H-12), 9.40 (s, 2H, H-3, $^3J_{Pt-H}$ = 48Hz), 8.61 (dd, *J* = 6.3, 3.2 Hz, 2H, H-2), 7.96 (d, *J* = 9.0 Hz, 2H, H-5), 7.49 (dd, *J* = 6.3, 3.2 Hz, 2H, H-1), 6.79 (s, 2H, H-6), 6.62 (dd, *J* = 9.0, 2.4 Hz, 2H, H4), 4.65 (t, *J* = 5.1 Hz, 3H, H-8), 3.50 (t, *J* = 8.3 Hz, 6H, H-9), 3.02 (dt, *J* = 12.9, 9.8 Hz, 4H, H-7), 1.79 (td, *J* = 37.8, 33.7, 13.2 Hz, 8H,H-10), 1.39 (dd, *J* = 14.6, 10.9 Hz, 2H, H-11). ^{13}C NMR (101 MHz, DMSO-d_6) δ 206.5, 166.2, 165.8, 162.3, 154.4, 141.1, 138.6, 128.8, 117.8, 114.6, 109.3, 102.1, 62.8, 54. 8, 52.4, 35.8, 30.8, 30.7, 22.3, 21.2. ^{195}Pt NMR (86 MHz, DMSO-d_6) δ: + 507 ppm. ^{31}P NMR (161 MHz, DMSO- d_6): δ P -144.21 (sept, 1P, PF_6). ESI-MS calcd. for $C_{34}H_{40}N_4O_4Pt$: 834.7 a.m.u., found: 833.7 a.m.u. Elemental Analysis calcd for $C_{34}H_{40}Cl_2F_{12}N_4O_4P_2Pt \cdot 2H_2O$: C, 35.18; H, 3.82; N, 4.83; found C, 35.30; H, 3.93; N, 4.80.

Synthesis of 3. Compound **3** was prepared using the same protocol than compound **2** but using a 5-fold excess of oxidant. The amounts used of each reagent were: $PhICl_2$ (206 mg, 0.75 mmol) and **1** (100 mg, 0.150 mmol) in DMF (~5 mL). Yield: 71% (0.134 g). ^{1}H NMR (400 MHz, DMSO- d_6): δ 10.99 (s, 2H), 9.79 (s, 2H, $^3J_{Pt-H}$ = 56Hz), 8.68 (dd, *J* = 6.5, 3.5 Hz, 2H), 8.34 (s, 2H), 7.65 (dd, *J* = 7.1, 3.5 Hz, 2H), 4.63 (t, *J* = 5.2 Hz, 4H), 3.58 (q, *J* = 5.1 Hz, 8H), 3.14 – 3.00 (m, 4H), 1.84 (tq, *J* = 8.7, 4.6, 4.1 Hz, 8H), 1.70 (dd, *J* = 10.2, 6.7 Hz, 2H), 1.42 (td, *J* = 13.4, 12.2, 6.7 Hz, 2H). ^{13}C NMR (101 MHz, DMSO- d_6) δ: 162.3, 158.3, 157.6, 156.9, 141.2, 135.2, 130.6, 118.5, 117.5, 116.6, 68.2, 55.3, 52.5, 52.5, 35.8, 30.8, 22.3, 21.2, 21.2. ^{195}Pt NMR (86 MHz, DMSO- d_6) δ: + 453 ppm. Elemental Analysis calcd for $C_{34}H_{36}Cl_6F_{12}N_4O_4P_2Pt \cdot 3H_2O$: C, 31.02; H, 3.22; N, 4.26 found C, 30.75; H, 2.98; N, 4.32.

CD spectroscopy

For each experiment, 10 μM oligonucleotides were annealed in the appropriate buffer (see oligonucleotide preparation section). CD spectra were recorded on a JASCO J-810 spectrophotometer using a 1 mm path-length quartz cuvette. CD measurements were performed at 20 °C over a range of 220–320 nm, using a response time of 1 s, 1 nm step, and 0.5 nm bandwidth. The recorded spectra represent an average of three normalized scans (molar ellipticity is quoted in $deg \cdot cm^2 \cdot mol^{-1}$), and the spectrum of the corresponding buffer was subtracted from that of the sample. In melting experiments, the oligonucleotides were heated from a baseline temperature of 25 ºC to 95 ºC, at the rate of 1 ºC per minute, and spectra were recorded at intervals of 5 ºC. Melting curves were obtained by plotting normalized molar ellipticity recorded at 280 or 265 nm for ds26 and *c-Myc* respectively.

Emission spectroscopy

The emission spectra were obtained using a Varian Cary Eclipse spectrometer. For fluorescent binding measurement of the complexes with HTelo, *c-Myc* and ds26-DNA, 2 μM of the complex was titrated with concentrated solutions of DNA in 10 mM lithium cacodylate buffer (pH 7.4) with 100 mM KCl. Fluorescent spectra were recorded 2 minutes after each addition of concentrated DNA solution, in order to allow complete stabilization of the complex and oligonucleotide until fluorescence saturation was reached. A 1 cm path-length quartz cuvette was used to carry out the measurements. All spectrometric titrations were performed at least three times to ensure the reproducibility. The data were analysed according to the independent-site model[3] by nonlinear fitting to equation 1.

Equation 1:

$$\frac{I - I_o}{I_{Sat} - I_0} = \frac{\mathrm{A} + \mathrm{B} + \mathrm{nx} - \sqrt{(A + B + nx)^2 - 4\mathrm{Bnx}}}{2B}$$

where I = fluorescence intensity, I_0 = initial fluorescence intensity, I_{Sat} = fluorescence intensity upon saturation, A = 1/K_a, B = [Complex], n = number of independent binding sites and x = [DNA]. The parameters were found via the Levenberg−Marquardt fitting routine in Origin 8.5 software, whereas n was varied to obtain a better fit. We determined the number of binding sites as follows (based on the best fitting with chi-square higher than 98%): 2 binding sites for HTelo-K, 0.5 binding sites for HTelo-Na, 1 binding site for c-Myc and 3 binding sites for ds26.

Cyclic Voltammetry

Cyclic voltammetry was performed with a Reference 600 potentiostat (Gamry Instruments, USA) by using a conventional three-electrode glass cell. Glassy Carbon (GC, 6 mm diameter, CH Instruments, Inc), Pt coil and Ag/AgCl(sat) electrodes were employed as working, counter and reference electrodes, respectively. 0.1 M tetrabutylammonium hexafluorophosphate ($TBAPF_6$, Sigma–Aldrich, ≥99.0%) in DMF was employed as electrolyte. Prior to use, the surface of the GC electrode was polished with 1 µm, 0.3 µm, 0.1 µm and 0.05 µm alumina powder, and rinsed with ultrapure water. The GC was then cycled in 0.5 M H_2SO_4 between -0.3 to 1.2 V (vs Ag/AgCl(sat)), in order to remove remaining contaminants. The Pt coil was cleaned by H_2 annealing for ~5 min, quenched in the water and then transferred to the electrochemical cell. The cyclic voltammograms (CVs) were recorded at room temperature (24 °C) in an Argon atmosphere. The electrolyte was degassed with Argon for 10 min prior the measurements and Ar atmosphere above the solution was maintained throughout the

measurements. CVs of GC in the blank electrolyte were recorded prior to the addition of compound **2** and **3**, showing no peak in the potential window of interest, cf. fig. S17.

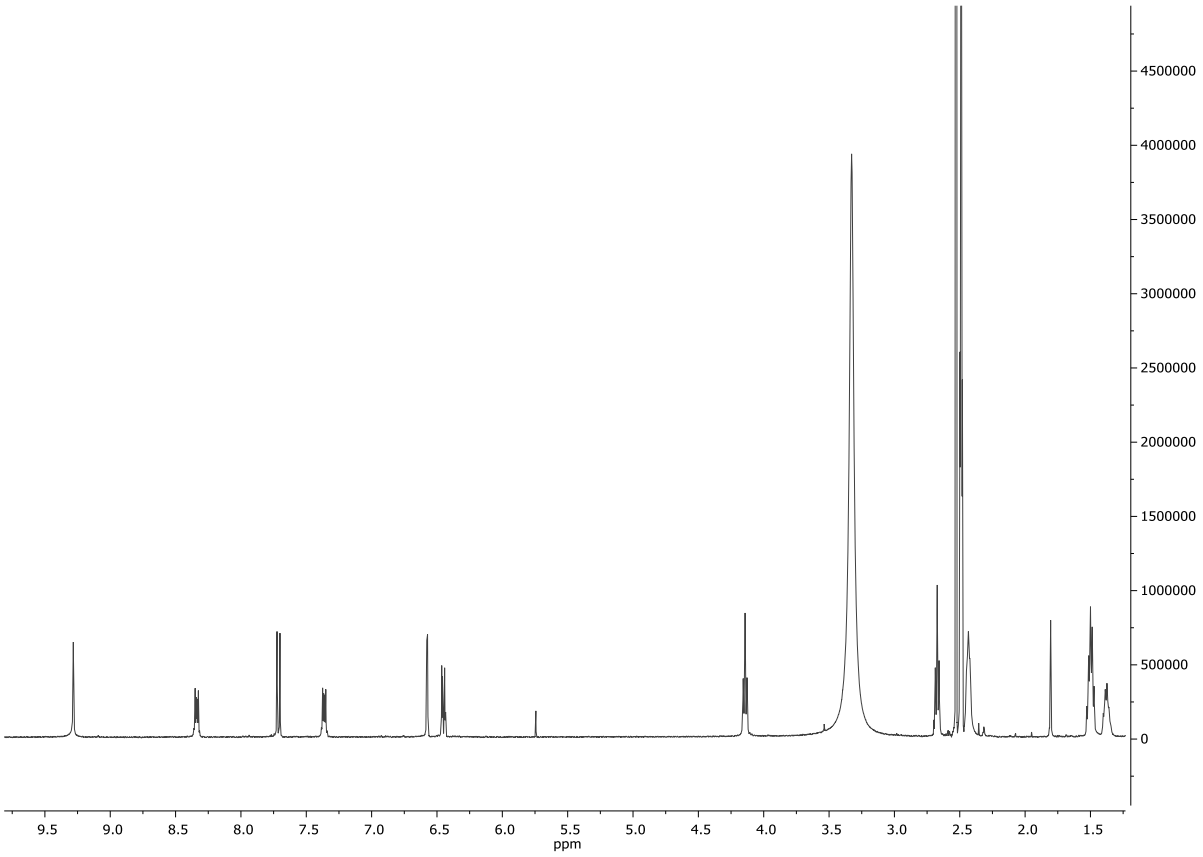

Figure S1 – ^{1}H NMR spectrum for compound **1** in DMSO-d_6.

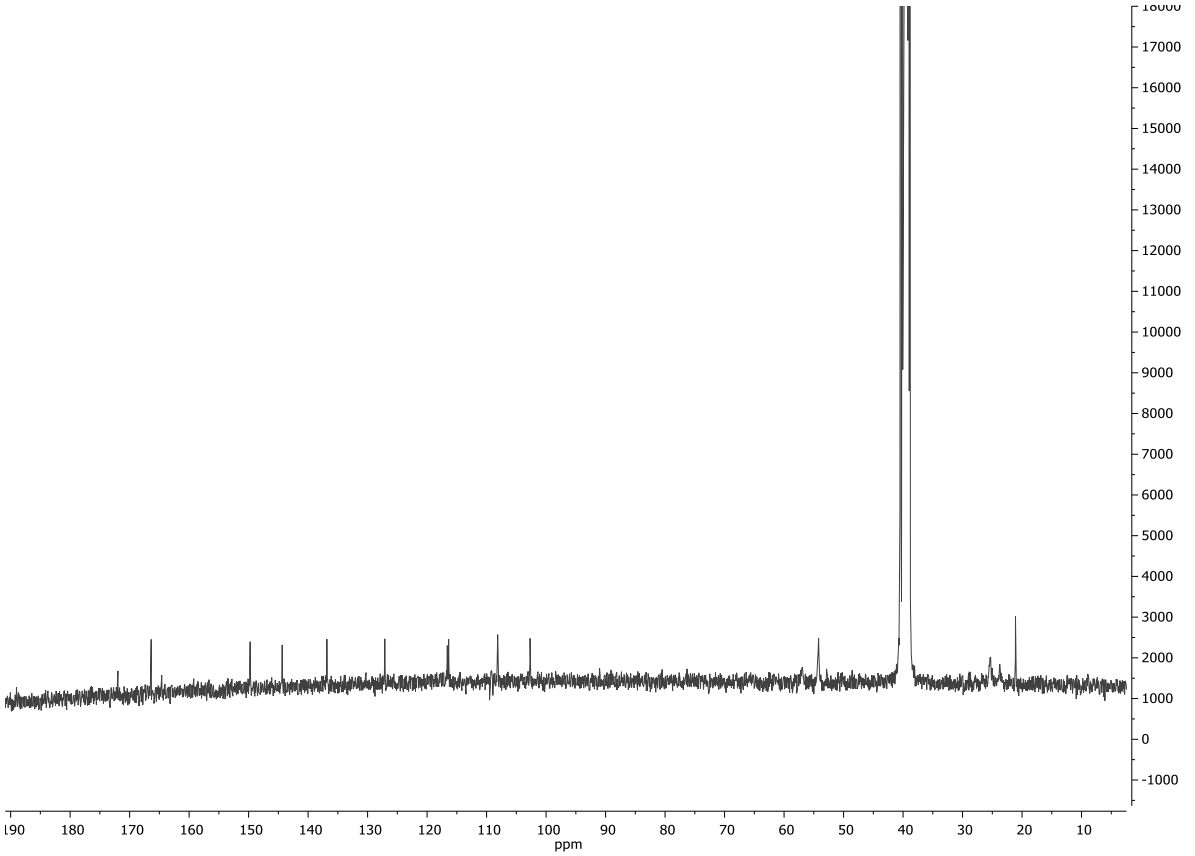

Figure S2 – ^{13}C NMR spectrum for compound **1** in DMSO-d_6.

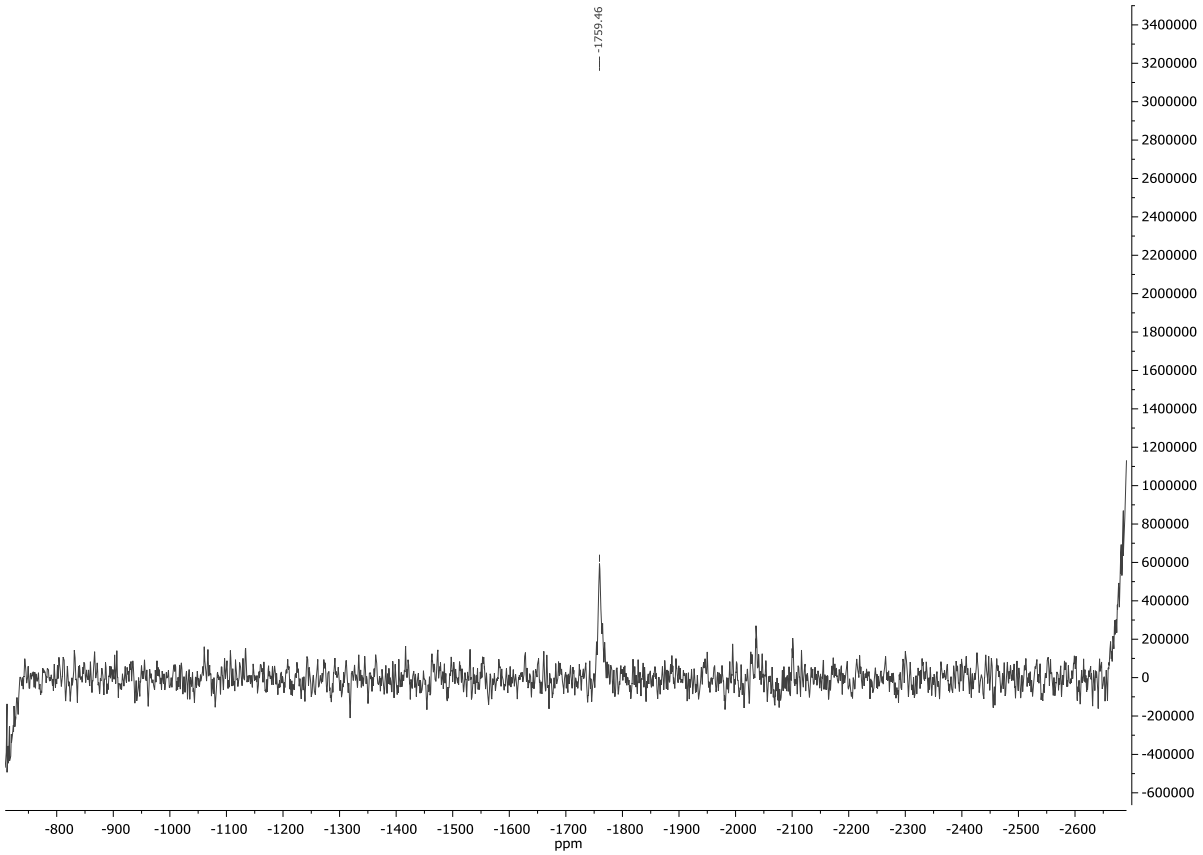

Figure S3 – ^{195}Pt NMR spectrum for compound **1** in DMSO-d_6.

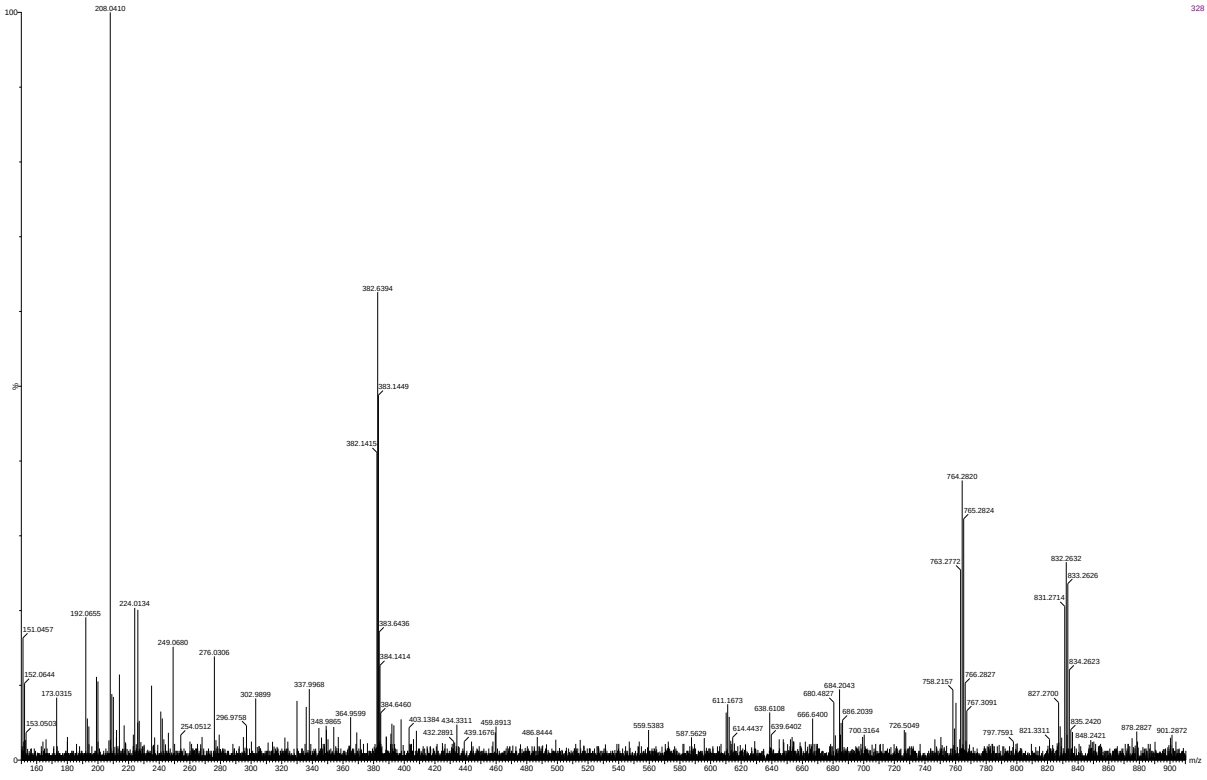

Figure S4 – ESI(+) mass spectrum for compound **1**

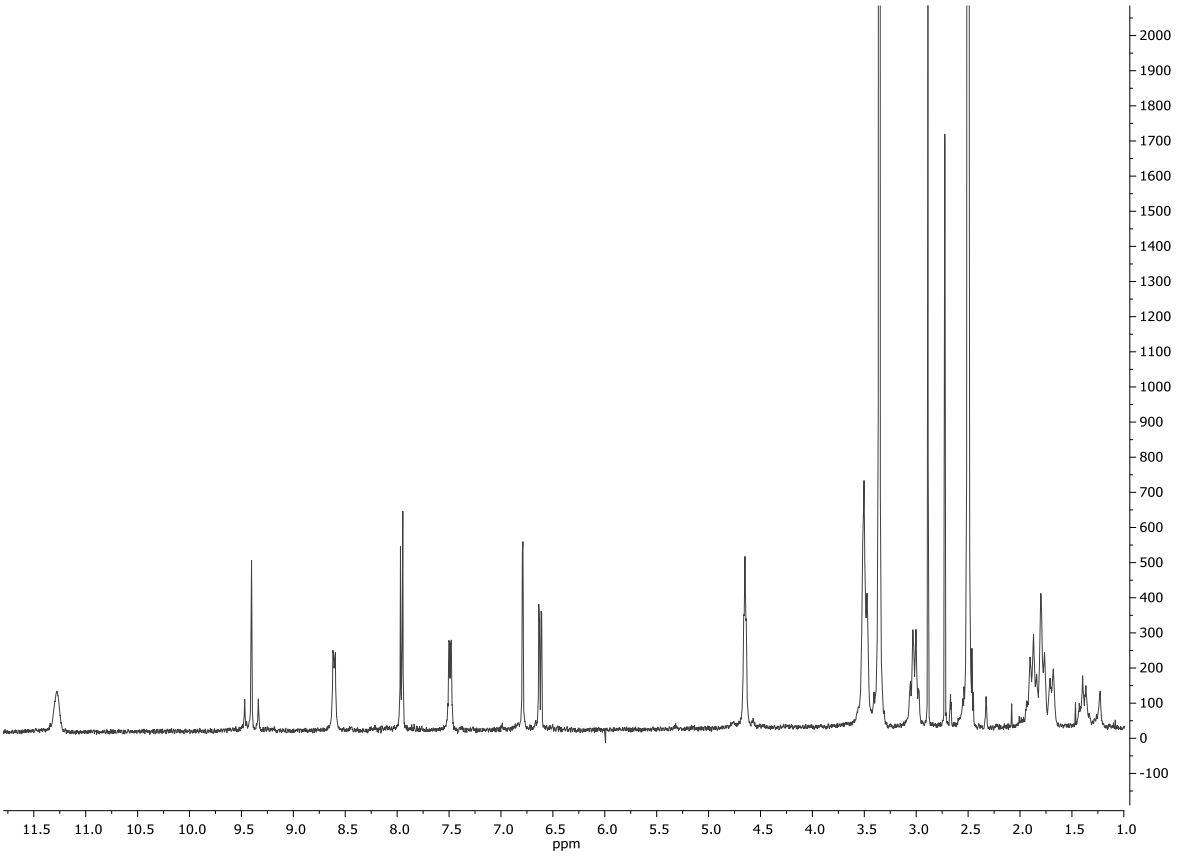

Figure S5 – ^{1}H NMR spectrum for compound **2** in DMSO-d_6.

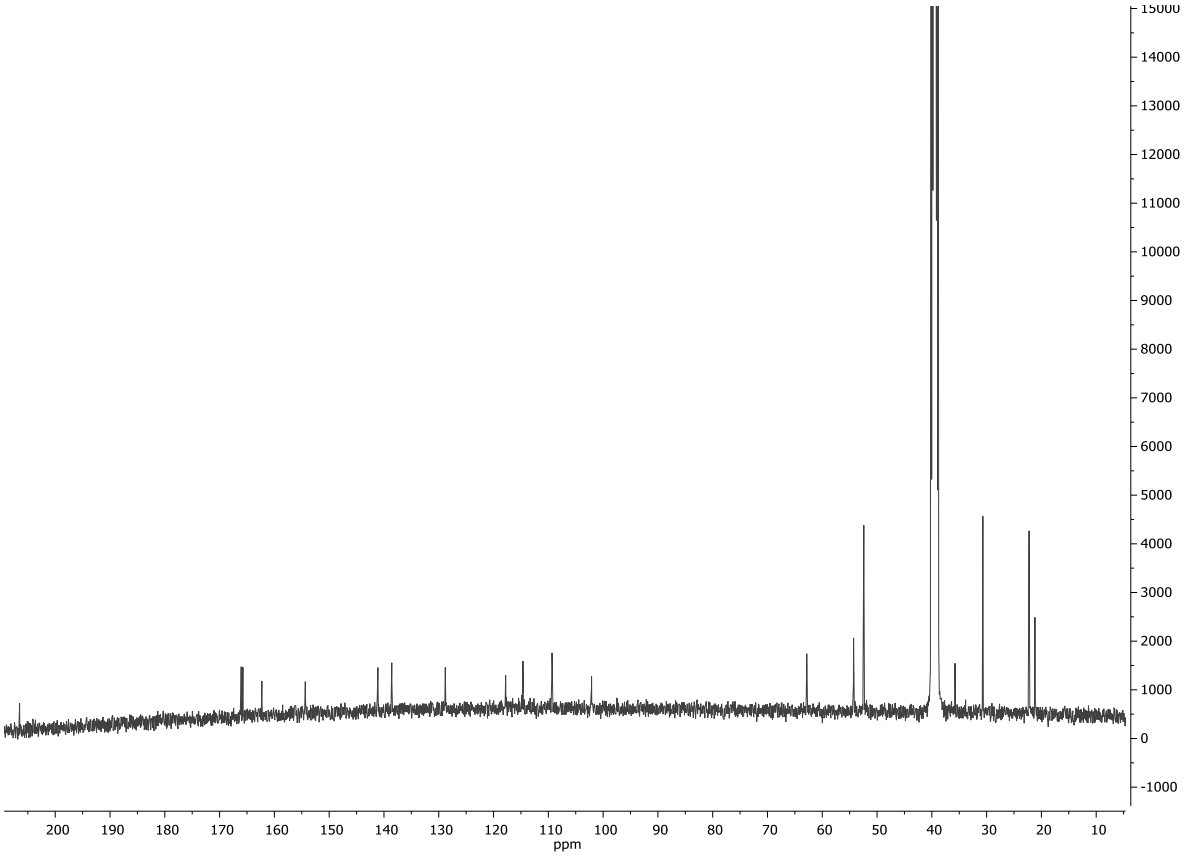

Figure S6 – ^{13}C NMR spectrum for compound **2** in DMSO-d_6.

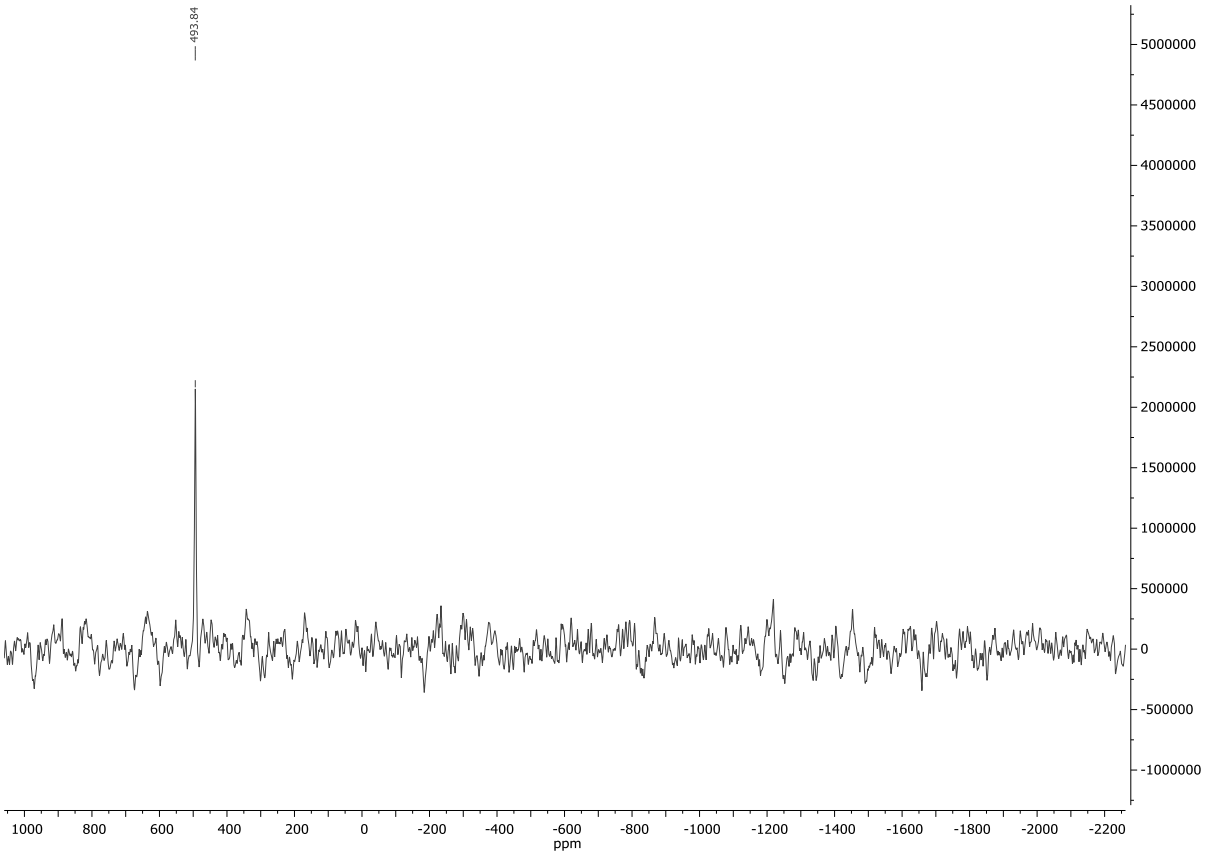

Figure S7 – ^{195}Pt NMR spectrum for compound **2** in DMSO-d_6.

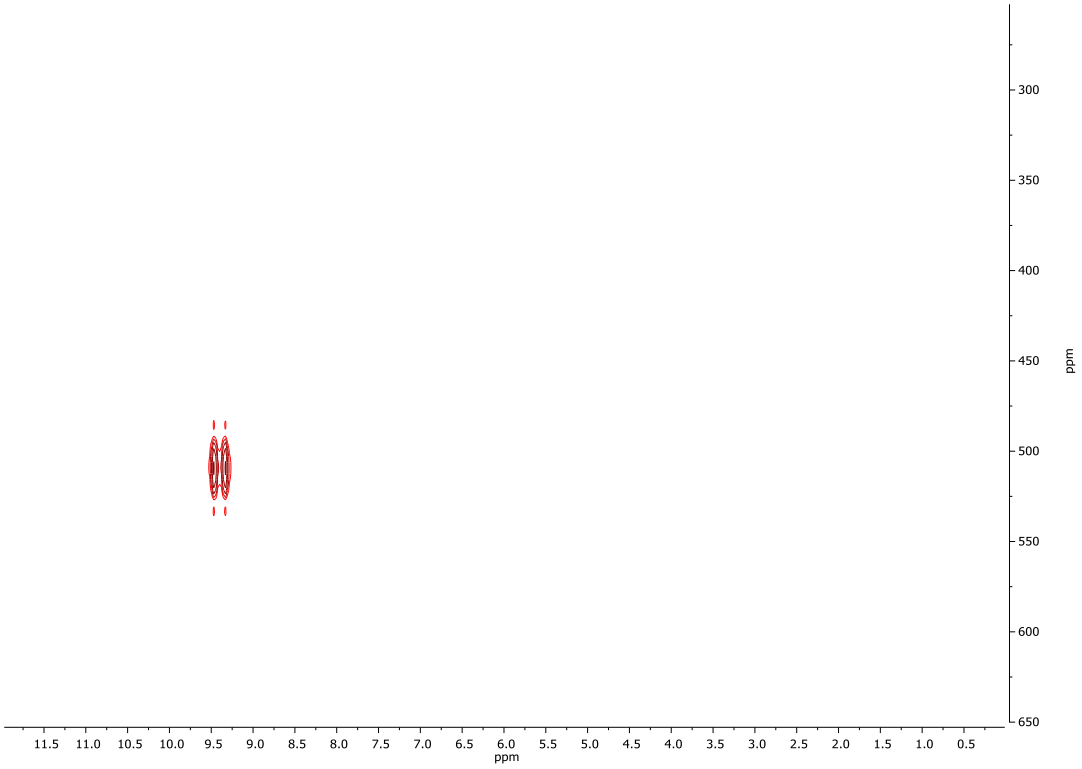

Figure S8 – 2D ^{1}H-^{195}Pt NMR spectrum for compound **2** in DMSO-d_6.

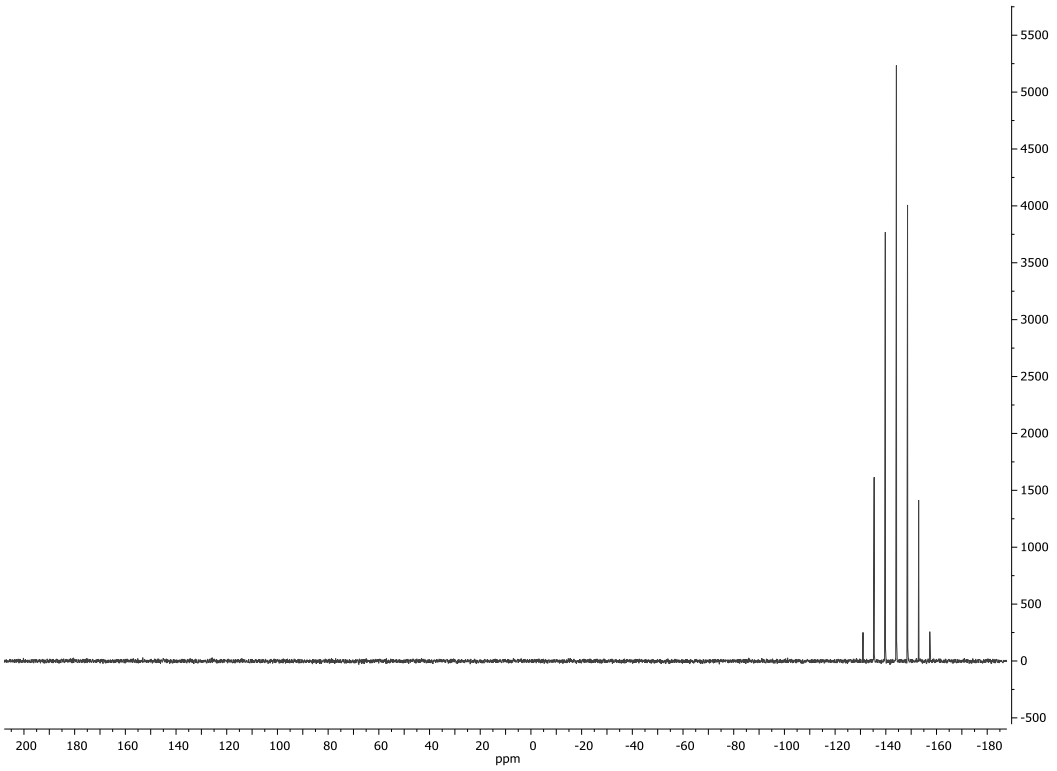

Figure S9 – ^{31}P NMR spectrum for compound **2** in DMSO-d_6.

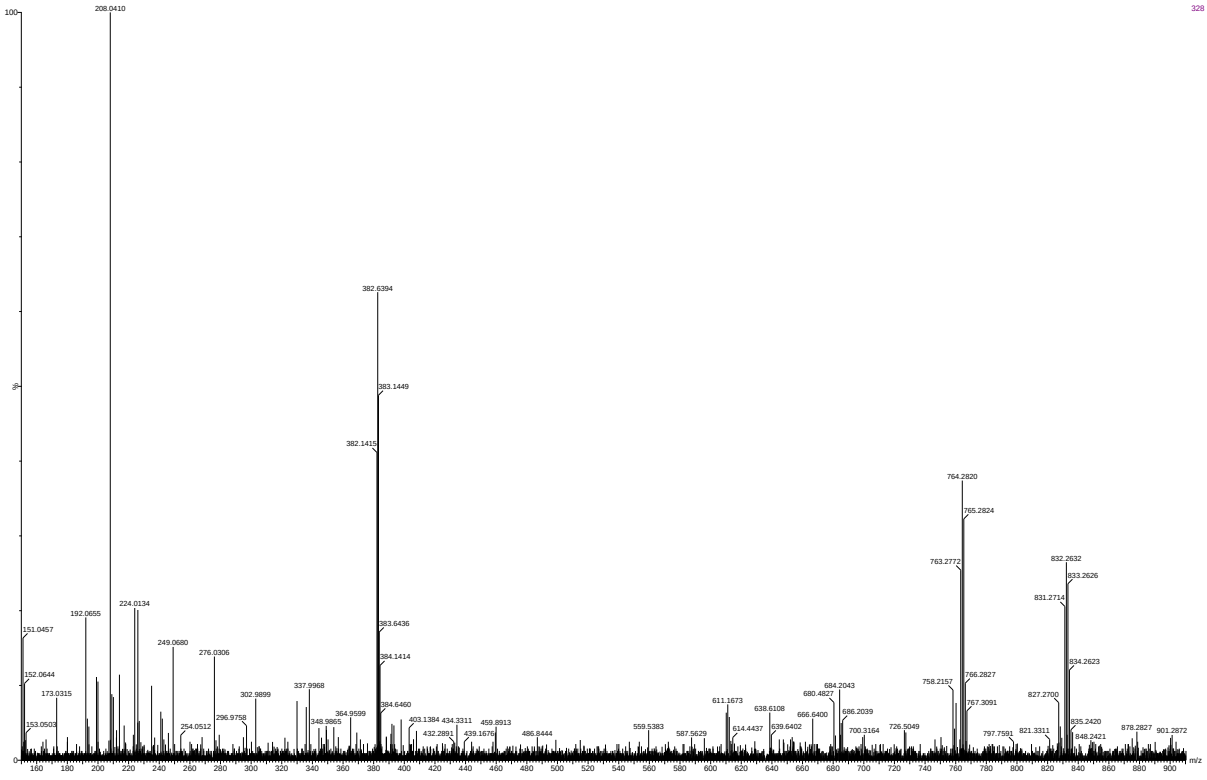

Figure S10 – ESI(+) mass spectrum for compound **2**

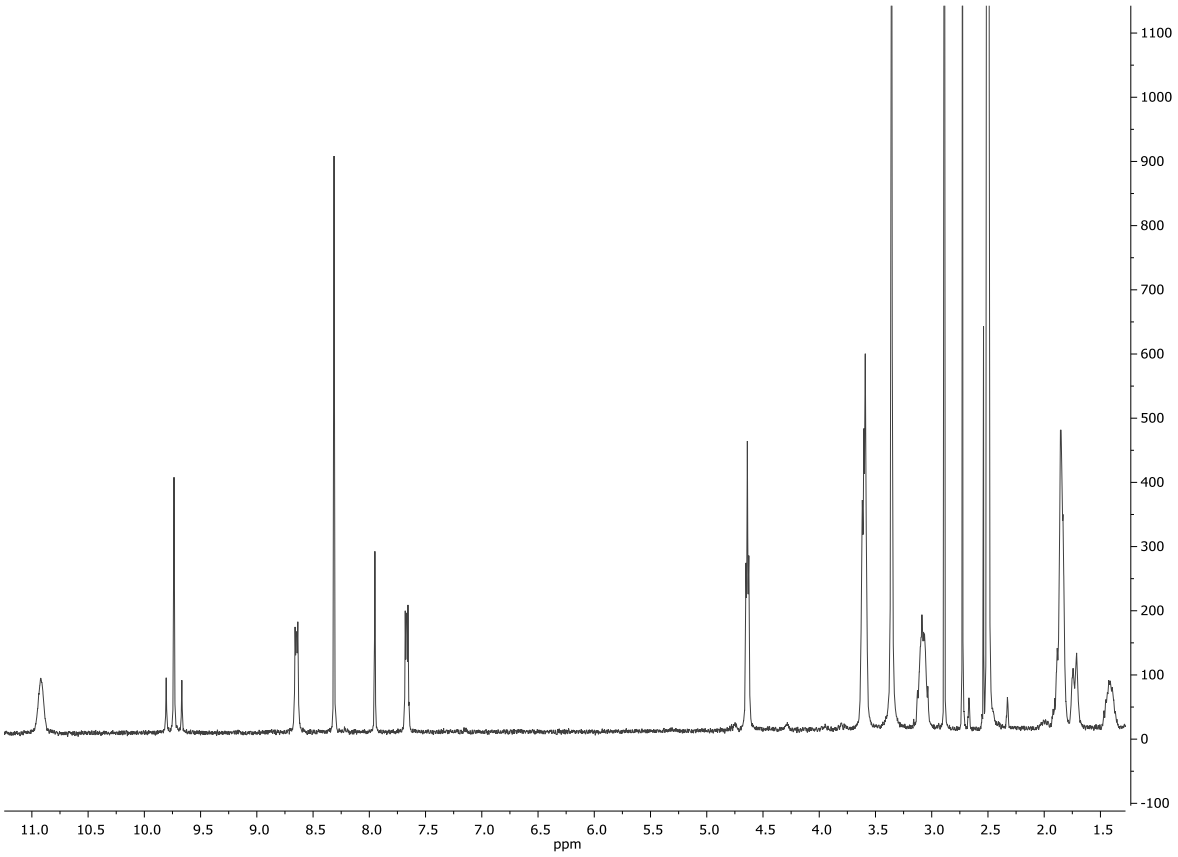

Figure S11 – ^{1}H NMR spectrum for compound **3** in DMSO-d_6.

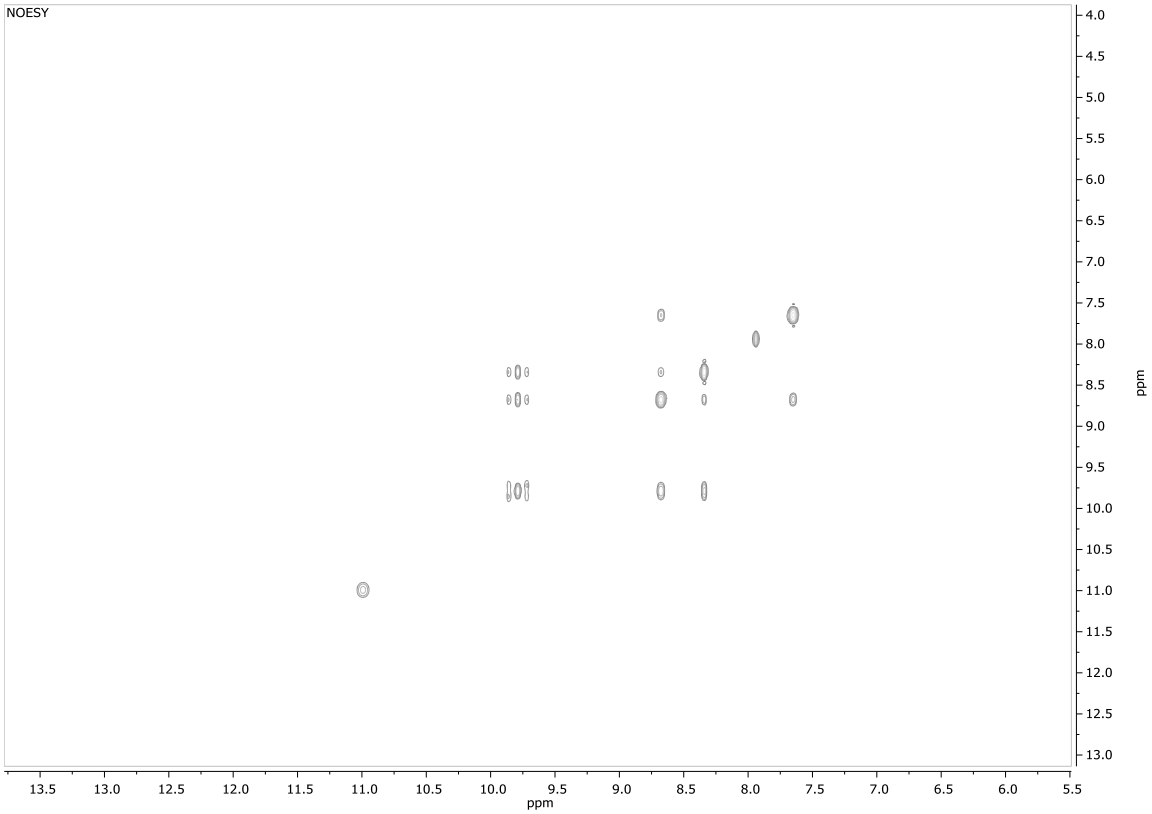

Figure S12 – NOESY ^{1}H–^{1}H 2D NMR spectrum of compound **3** in DMSO-d_6.

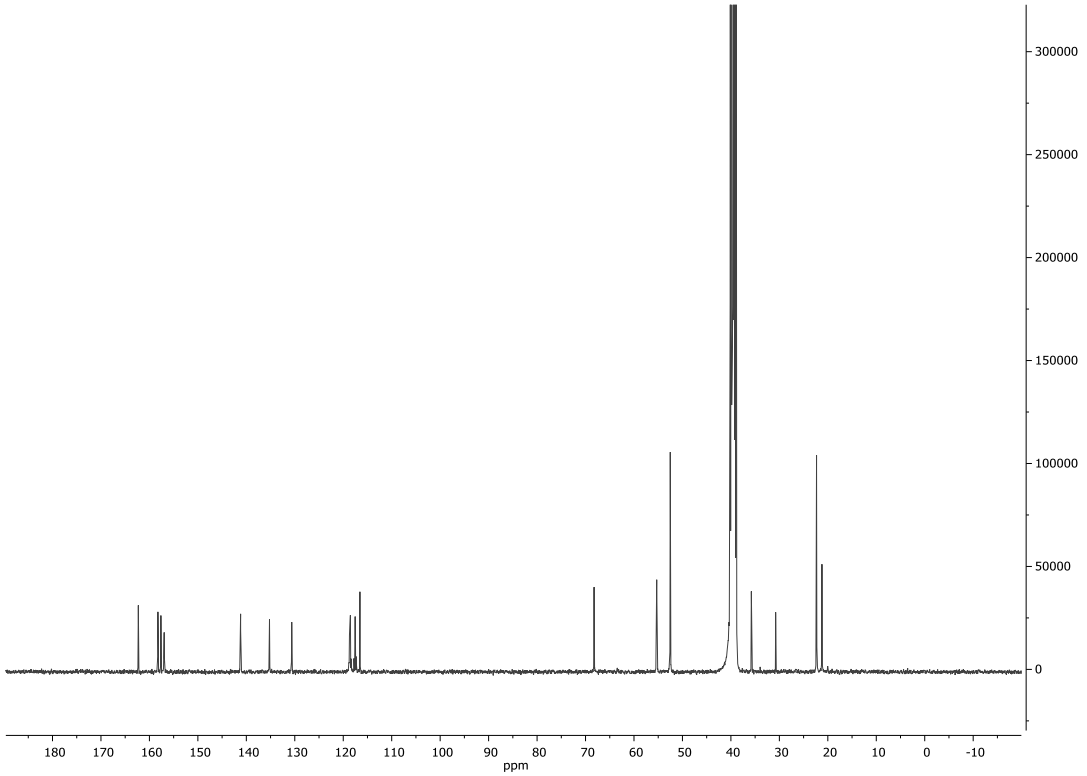

Figure S13 – ^{13}C NMR spectrum for compound **3** in DMSO-d_6.

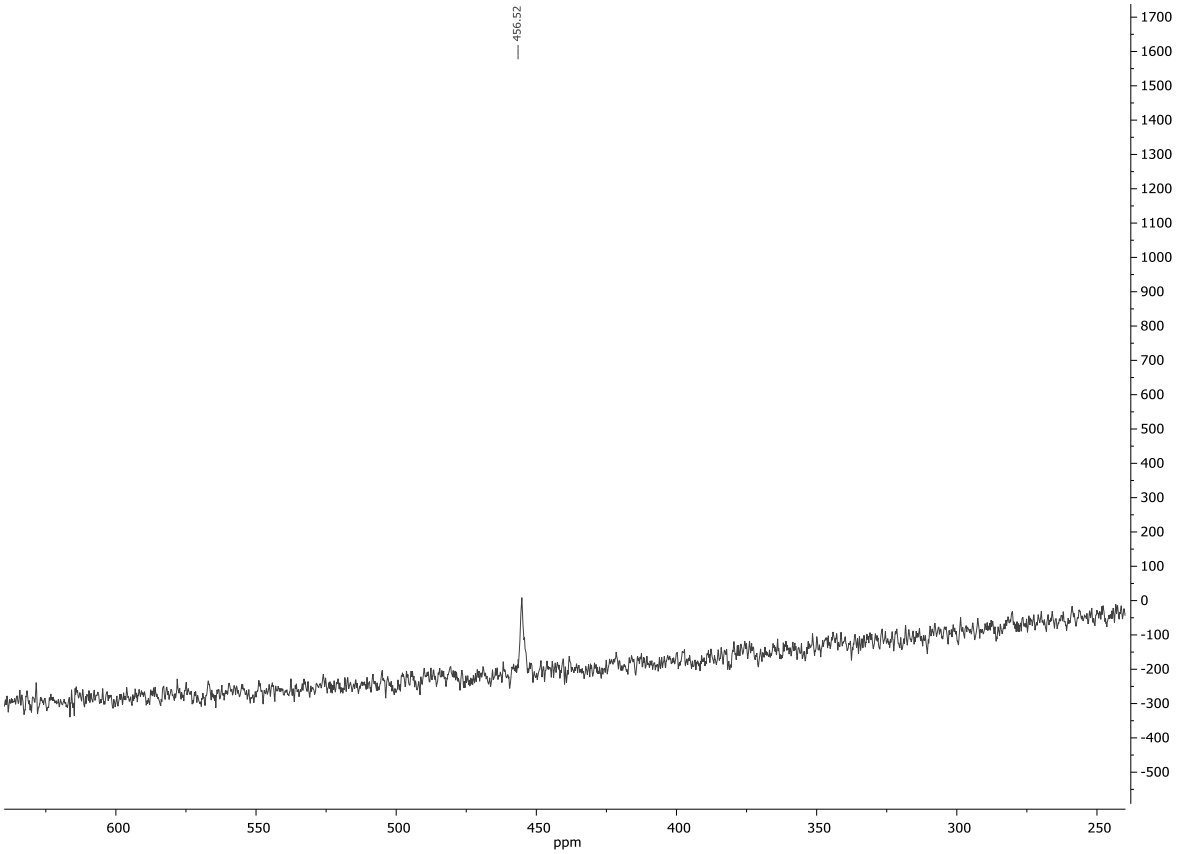

Figure S14 – ^{195}Pt NMR spectrum for compound **3** in DMSO-d_6.

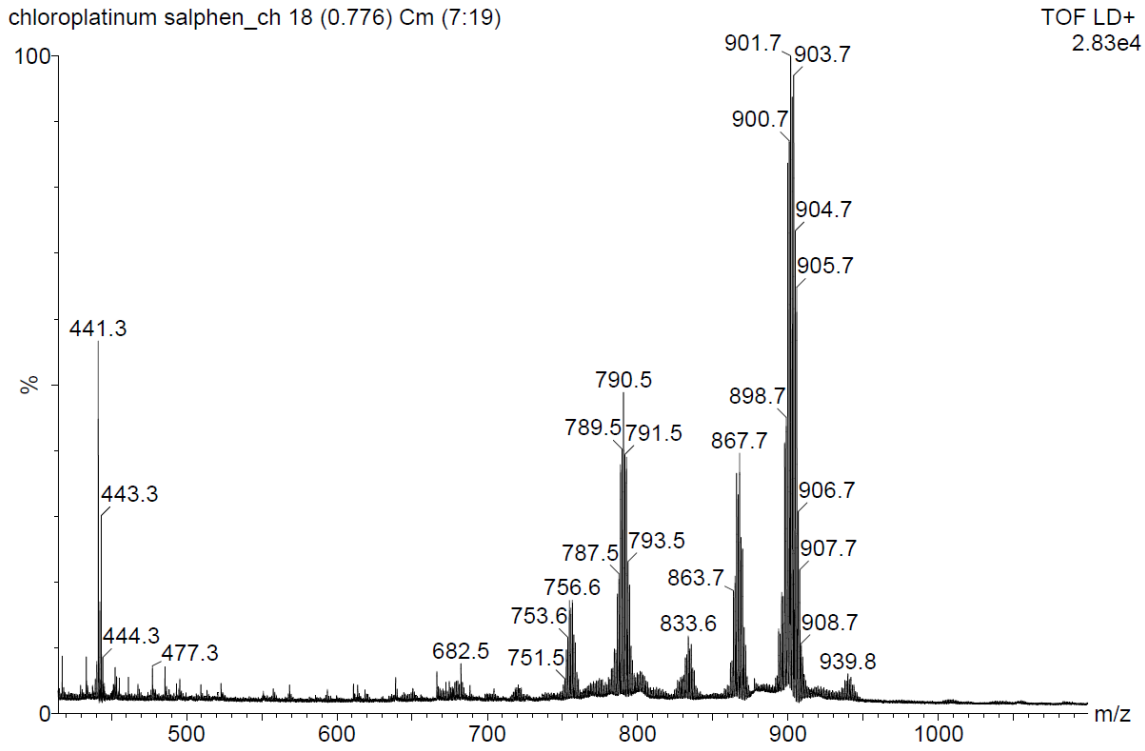

Figure S15 – ESI(+) mass spectrum for compound **3.**

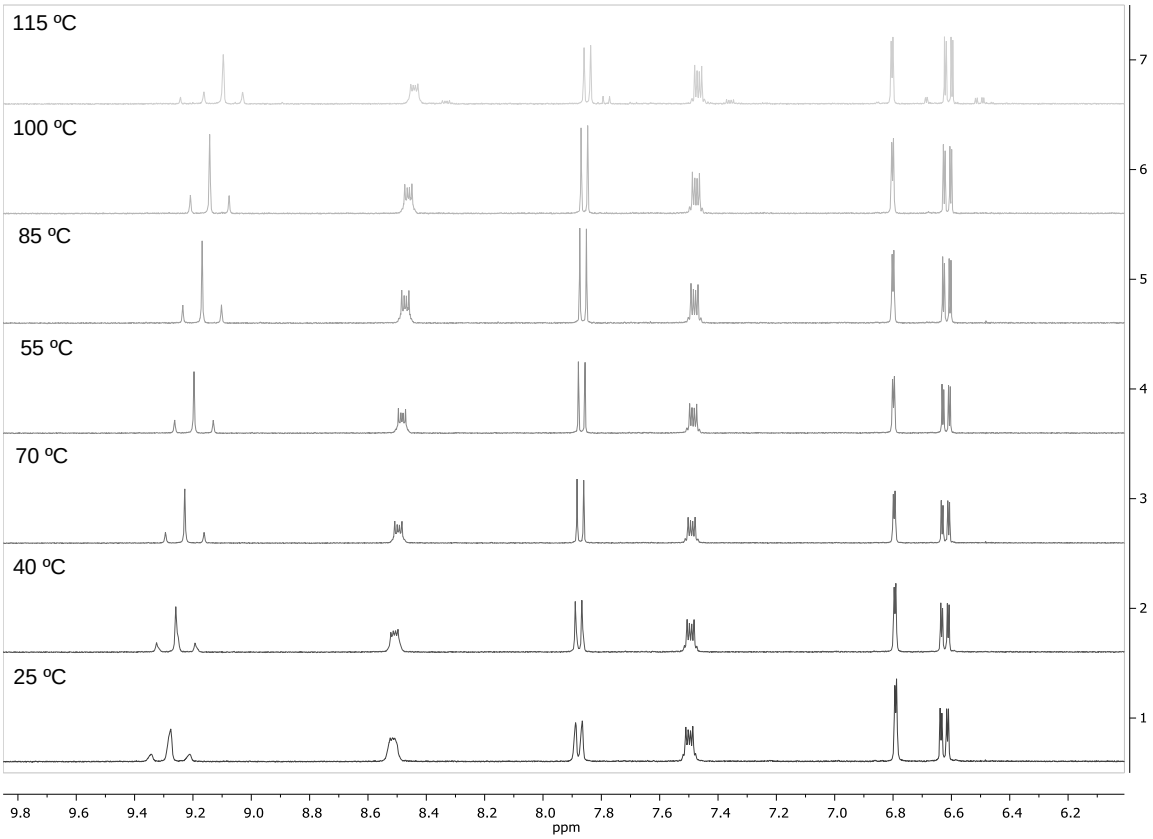

Figure S16 – Variable temperature ^{1}H NMR spectra (aromatic region) for compound **2** (DMSO-d_6).

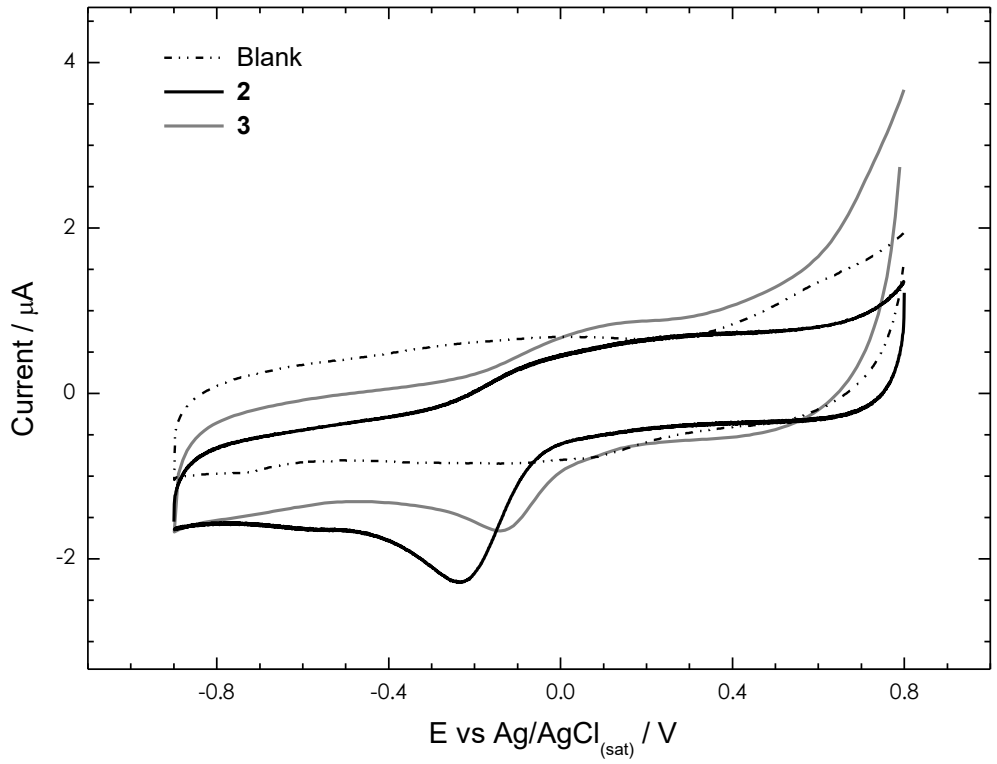

Figure S17 – Cyclic voltammograms for compounds **2** and **3** in DMF. Parameters: 0.1 Vs^{-1} scan rate, 0.1 M $TBAPF_6$ in DMF supporting electrolyte, analyte concentration: 0.2 mM. CV of the GC working electrode in the same conditions is shown in grey.

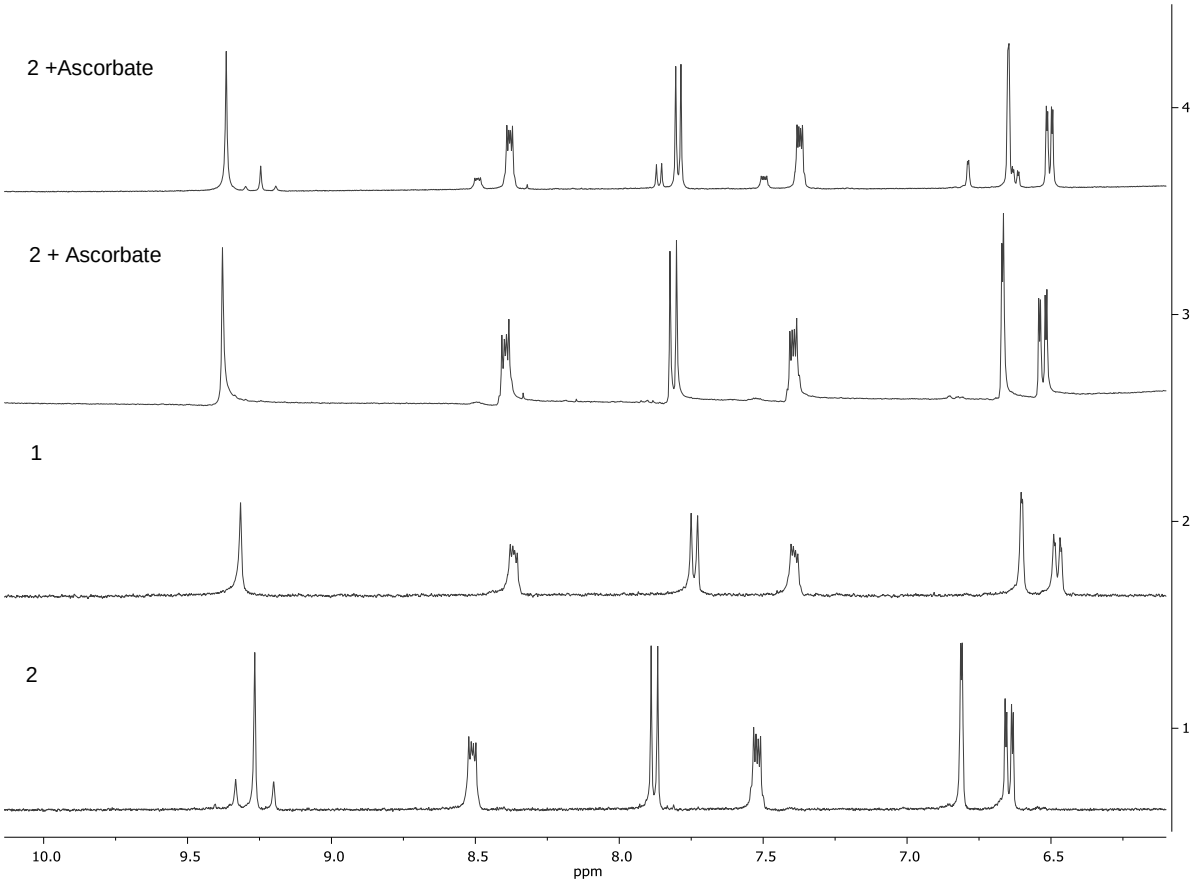

Figure S18 – ^{1}H NMR spectra obtained for ascorbate + **2** after 12 h, ascorbate + **2** after 24 h incubation at 37 °C, **1** and **2** in DMSO-d_6.

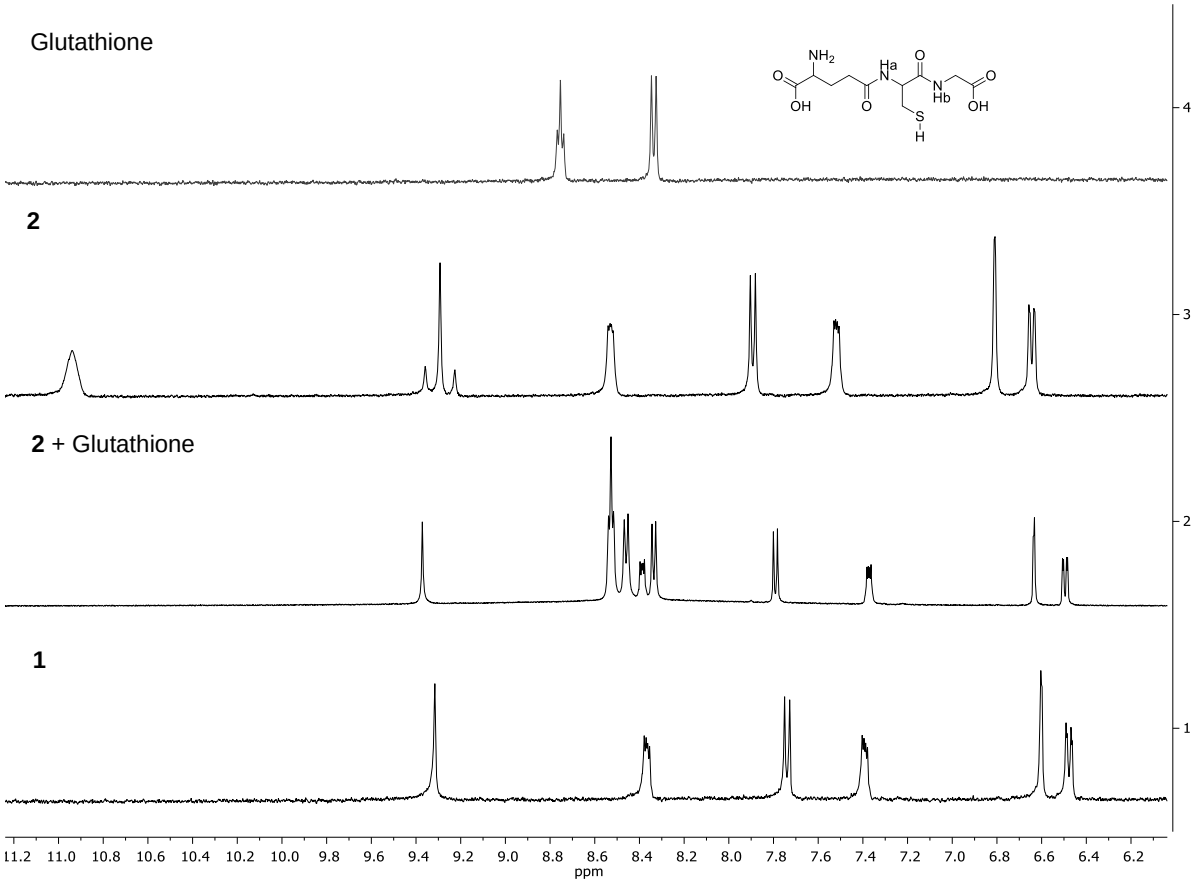

Figure S19 – ^{1}H NMR spectrum obtained for glutathione, **2**, **2**+glutathione after 24 h incubation at 37 °C and **1** in DMSO-d_6.

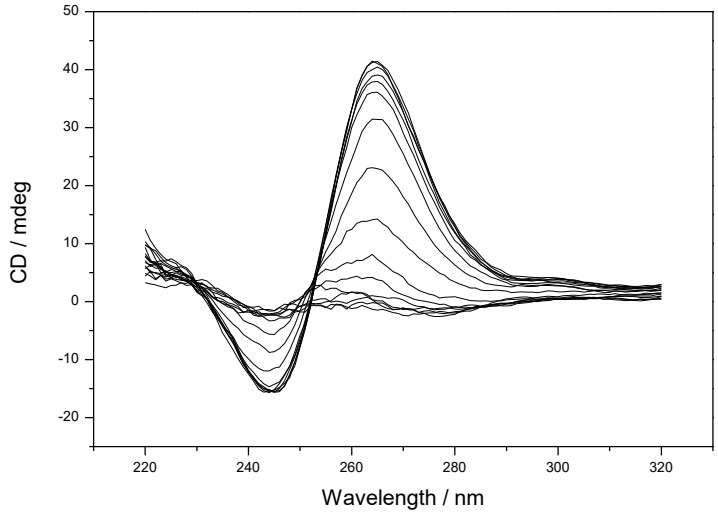

Figure S20 - CD melting spectra of *c-Myc* quadruplex DNA (5 µM) in potassium cacodylate buffer (10 mM LiCac, 1 mM KCl, 99 mM LiCl, pH = 7.3).

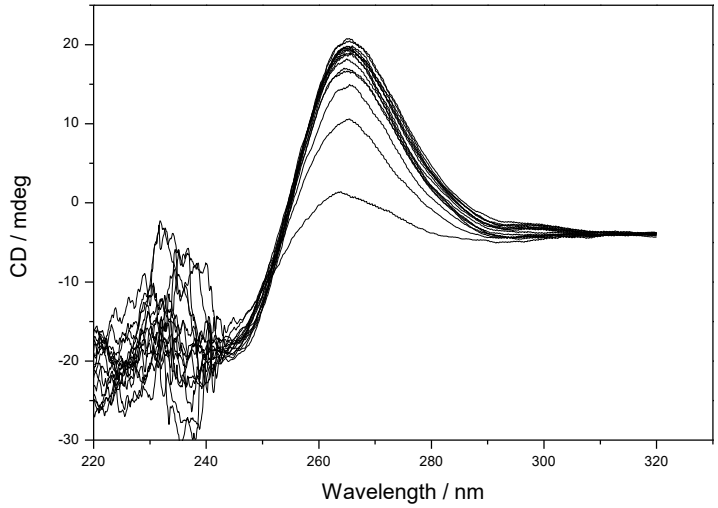

Figure S.21 - CD melting spectra of *c-Myc* DNA (5 µM) + complex **1** (25 µM) in potassium cacodylate buffer (10 mM LiCac, 1 mM KCl, 99 mM LiCl, pH = 7.3).

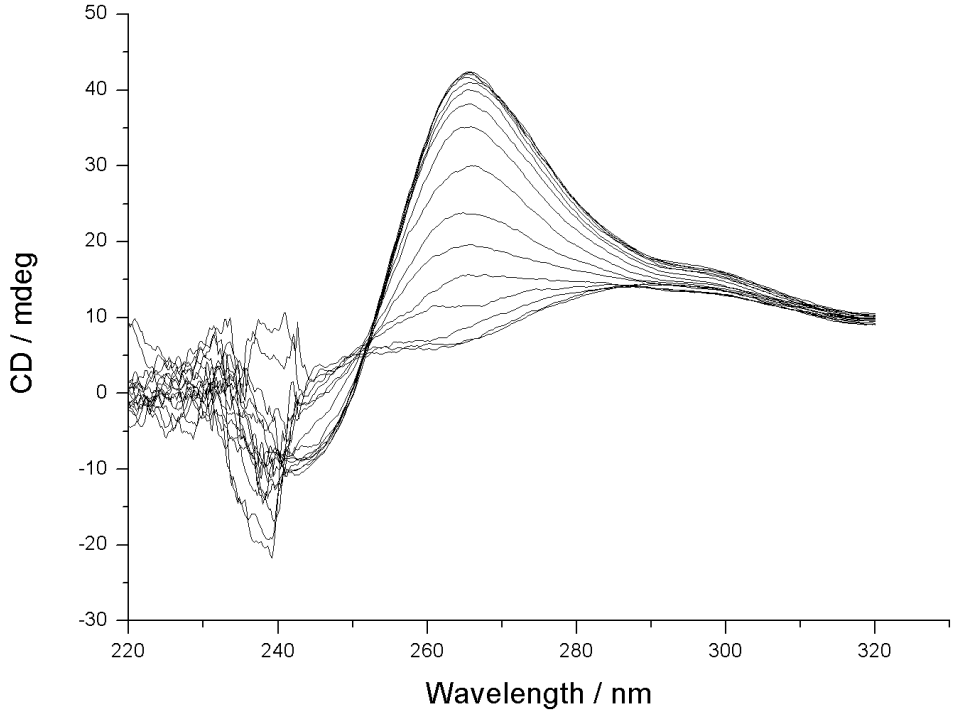

Figure S22 -. CD melting spectra of *c-Myc* DNA (5 µM) + complex **2** (25 µM) in potassium cacodylate buffer (10 mM LiCac, 1 mM KCl, 99 mM LiCl, pH = 7.3).

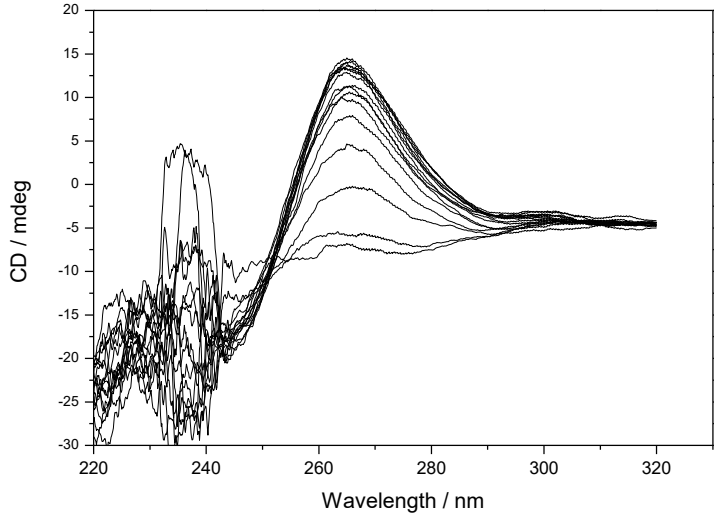

Figure S23 - CD melting spectra of *c-Myc* DNA (5 µM) + complex **2** (25 µM) + glutathione (250 µM) in potassium cacodylate buffer (10 mM LiCac, 1 mM KCl, 99 mM LiCl, pH = 7.3).

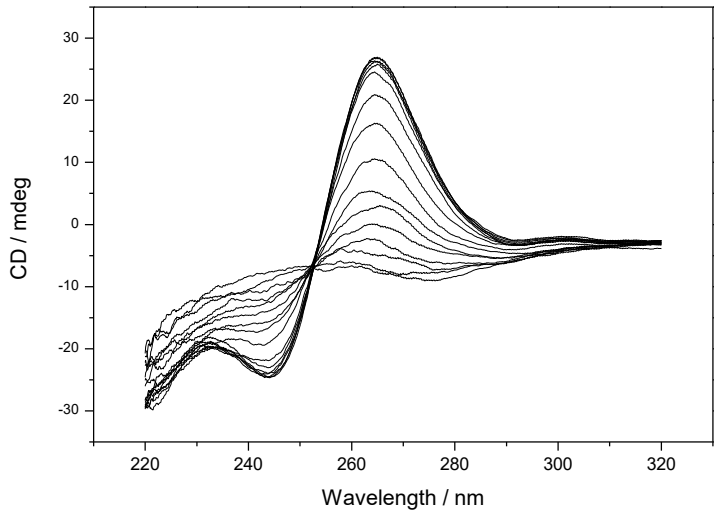

Figure S24 - CD melting spectra of *c-Myc* DNA (5 µM) + glutathione (250 µM) in potassium cacodylate buffer (10 mM LiCac, 1 mM KCl, 99 mM LiCl, pH = 7.3).

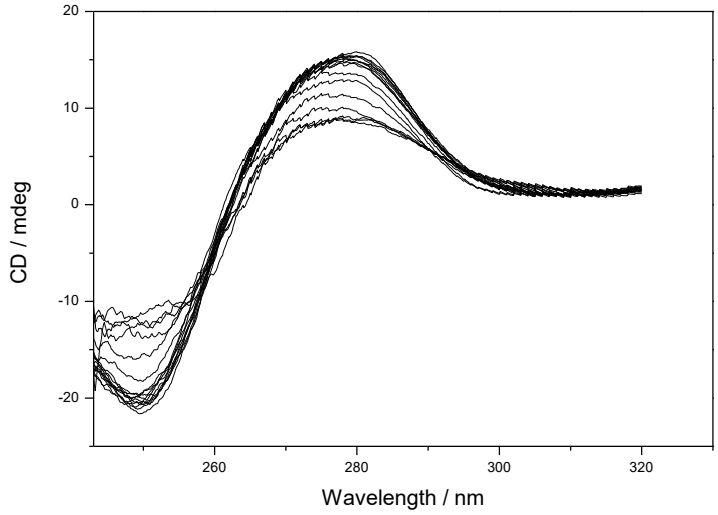

Figure S25 - CD melting spectra of ds26 duplex DNA (5 µM) in potassium cacodylate buffer (10 mM LiCac, 100 mM KCl, pH = 7.3).

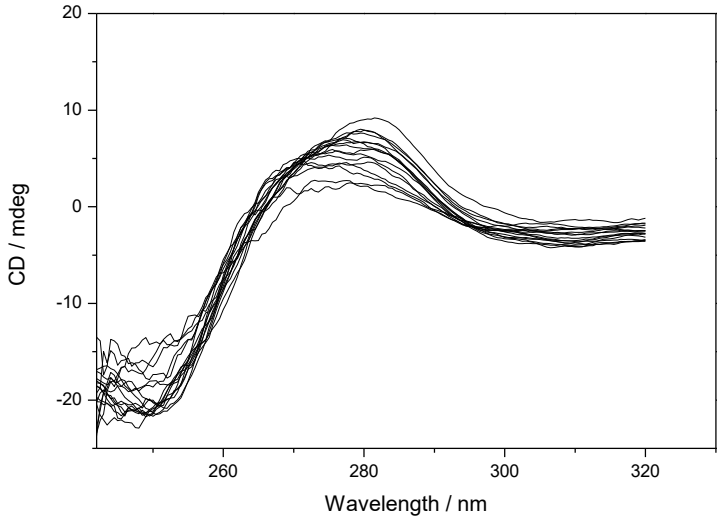

Figure S26 - CD melting spectra of ds26 duplex DNA (5 µM) + complex **1** (25 µM) in potassium cacodylate buffer (10 mM LiCac, 1 mM KCl, 99 mM LiCl, pH = 7.3).

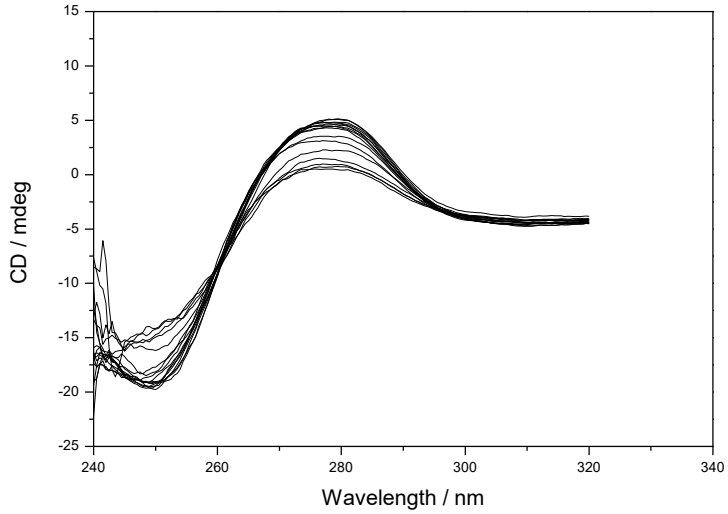

Figure S26 - CD melting spectra of ds26 duplex DNA (5 µM) + complex **2** (25 µM) in potassium cacodylate buffer (10 mM LiCac, 100 mM KCl, pH = 7.3).

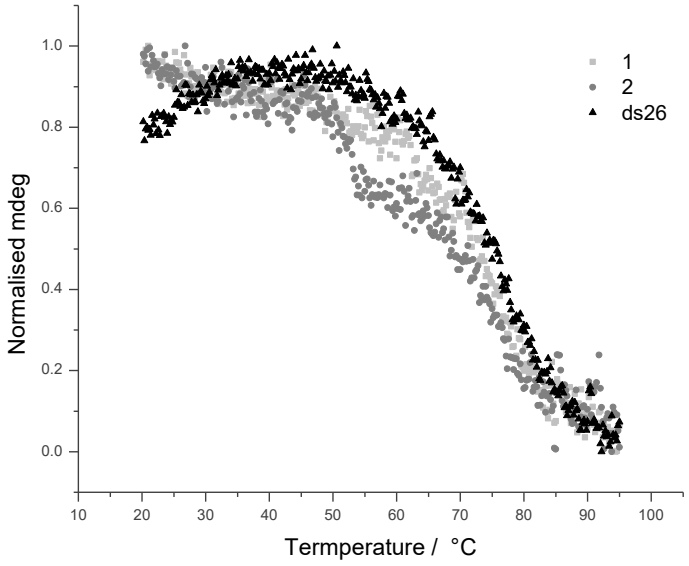

Figure S27. CD melting curve of compound ds26 duplex DNA in the presence of **1** and **2** in potassium cacodylate buffer *(*10 mM LiCac, 100 mM KCl, pH = 7.3).

References

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