

## Electronic Supplementary Information

### Interfering in apoptosis and DNA repair of cancer cells to conquer cisplatin resistance by platinum(IV) prodrugs

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#### Reagents and Instruments

All the reagents were of analytical grade and used as received without further purification. Cisplatin (CDDP) was purchased from Shandong Boyuan Pharmaceutical Co., Ltd. China. 3-Chloro-benzo[b]thiophene-2-carboxylic acid ( $L_1$ ) and 3-chloro-6-methyl benzo[b]thiophene-2-carboxylic acid ( $L_2$ ), O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU), triethylamine (TEA), and hydrogen peroxide ( $H_2O_2$ , 30%) were purchased from J&K Scientific. Water was deionized and ultrafiltered by a Milli-Q apparatus (Millipore Corporation, China). Annexin V conjugated with fluorescein isothiocyanate (Annexin V-FITC) and propidium iodide (PI) were purchased from KeyGen Biotech. Co. Ltd. (Nanjing, China). Ascorbic acid (AsA), Hoechst 33342, hematoxylin, eosin, and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) were obtained from Sigma-Aldrich. DNAzol reagent was purchased from ThermoFisher Scientific. The antibodies used for western blotting were purchased from Abcam. Mitochondria isolation kit was purchased from Beyotime Biotechnology (Jiangsu, China). *cis*-Diamminedichloro-*trans*-dihydroxyplatinum(IV) (oxoplatin) was prepared according to the literature procedure.<sup>1</sup>

The human ovarian carcinoma cell line Caov3 and breast carcinoma cell line MCF-7 were purchased from American Type Culture Collection (ATCC). The human lung carcinoma cell line A549, its CDDP-resistant counterpart A549/DDP, the human ovarian carcinoma cell line A2780, its CDDP-resistant counterpart A2780/DDP and the human normal liver cell line L-02 were got from Nanjing KeyGen Biotech Co., Ltd. Caov3, MCF-7 and L-02 cells were cultured in Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal bovine serum (FBS). A549 and A2780 cells were cultured in Roswell Park Memorial Institute (RPMI)-1640 containing 10% FBS. A549/DDP and A2780/DDP cells were cultured in RPMI-1640 medium containing 10% FBS and 1000 ng mL<sup>-1</sup> CDDP. FBS and all culture media were from Nanjing KeyGen Biotech Co., Ltd. Mice were purchased from the Model Animal Research Center of Nanjing University. The percentage of DMSO used in all the cell tests was less than 0.5%. All the control groups contain equal amount DMSO with the drug-treated groups.

<sup>1</sup>H-, <sup>13</sup>C-, and <sup>195</sup>Pt-NMR spectra were acquired on a Bruker DRX-400 spectrometer at 298 K. Elemental analysis (C, H and N) was performed using a CHN-

O-Rapid elemental analyzer. HPLC was carried out on a Beckman Coulter HPLC instrument equipped with a C18 reverse phase column. UV-visible absorption spectra were recorded on a PerkinElmer Lambda 35 spectrophotometer. The reduction potential was measured by cyclic voltammogram at room temperature on an electrochemical analyzer system (CHI630D). The data of MTT assay were determined using a Tecan Sunrise ELISA Reader at 570 nm. The content of Pt was determined on an inductively coupled plasma mass spectrometer (ICP-MS) using a standard Plasma-Quad II instrument (VG Elemental, Thermo OptekCorp.). Flow cytometric analysis was performed by using Cytomics FC500 Flow Cytometry (Beckman Coulter Ltd.). Western blotting was carried out on the Bio-Rad mini-PROTEAN tetra system and Bio-Rad Powerpack Universal. Images were captured using a Chemiscope 3400 mini (Clix science instrument co. Ltd). Fluorescence confocal imaging was carried out on a laser scanning confocal imaging system (Olympus TH4-200) consisting of ZEISS Laser Scanning Microscope (LSM 710) and a 20 mW-output 488 nm argon ion laser.

## Experimental Procedures

**Synthesis and Characterization of 1.** Oxoplatin (100 mg, 0.30 mmol) was stirred in dry DMF (10 mL) with L<sub>1</sub> (191 mg, 0.90 mmol), triethylamine (125  $\mu$ L, 0.90 mmol), and TBTU (290 mg, 0.90 mmol) at ambient temperature for 48 h. The obtained solution was concentrated by rotary evaporator to 5 mL, and then was added to a mixture of H<sub>2</sub>O and EtOH (20 mL, 1:1) to get a light-yellow precipitate. The precipitate was washed with methanol and diethyl ether twice, and dried under vacuum. Complex **1** was obtained as solid with a yield of 85%. <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  (ppm) 8.09–8.11 (m, 2H, H<sub>b</sub>), 7.92 (dd,  $J$  = 6.9, 1.8 Hz, 2H, H<sub>e</sub>), 7.55–7.62 (m, 4H, H<sub>c</sub>, H<sub>d</sub>), 6.73 (s, 6H). <sup>13</sup>C-NMR (100 MHz, DMSO-d<sub>6</sub>):  $\delta$  (ppm) 167.39, 138.17, 136.70, 129.25, 128.31, 126.11, 123.81, 123.35, 123.25. <sup>195</sup>Pt-NMR (69 MHz): 1227.05 ppm. Elemental analysis found (calcd) for C<sub>18</sub>H<sub>14</sub>Cl<sub>4</sub>N<sub>2</sub>O<sub>4</sub>PtS<sub>2</sub>: C, 29.51 (29.89); H, 2.06 (1.95); N, 3.82 (3.87).

**Synthesis and Characterization of 2.** Complex **2** was prepared following the same procedures as described for complex **1** except that L<sub>2</sub> (204 mg, 0.90 mmol) was used instead. Yield: 90%. <sup>1</sup>H-NMR (400 MHz, DMSO-d<sub>6</sub>):  $\delta$  (ppm) 7.87 (s, 2H, H<sub>b</sub>), 7.80 (d,  $J$  = 8.3 Hz, 2H, H<sub>e</sub>), 7.39 (dd,  $J$  = 8.3, 0.9 Hz, 2H, H<sub>d</sub>), 6.73 (s, 6H, H<sub>a</sub>), 2.48 (s, 6H, H<sub>c</sub>). <sup>13</sup>C-NMR (100 MHz, DMSO-d<sub>6</sub>):  $\delta$  (ppm) 167.51, 138.50, 138.43, 134.62, 127.95, 127.87, 123.23, 123.04, 21.73. <sup>195</sup>Pt-NMR (69 MHz): 1226.80 ppm. Elemental analysis found (calcd) for C<sub>20</sub>H<sub>18</sub>Cl<sub>4</sub>N<sub>2</sub>O<sub>4</sub>PtS<sub>2</sub>: C, 31.83 (31.97); H, 2.51 (2.41); N, 3.66 (3.73).

**Stability.** Complex **1** and **2** was dissolved in RIMI-1640 culture medium containing 10% FBS and 0.3% DMSO at 40  $\mu$ M, respectively, and kept at 37 °C for 24 h. UV-vis absorption spectra of the complexes were determined at 0 and 24 h after subtracting the baseline of the medium containing 10% FBS and 0.3% DMSO.

**Electrochemistry.** A cyclic voltammogram was measured in a three-electrode cell using a glassy carbon disc working electrode, a platinum auxiliary electrode, and

saturated calomel electrode as the reference electrode. The potential was corrected using a trace amount of ferrocene/ferrocenium as internal reference standard. CHI630D electrochemical workstation was used for the measurement at room temperature. Deaeration of the complex solutions (2 mM in DMF) was accomplished by passing a stream of nitrogen through the solution for 10 min.  $[\text{n-Bu}_4\text{N}][\text{PF}_6]$  (0.15 M) was used as a supporting electrolyte. The potential was measured at a scan rate of  $100\text{ mV s}^{-1}$ .

**Measurement of Partition Coefficient.** Shake-flask method was used to measure the partition coefficient for CDDP, **1** and **2**. Briefly, a mixture of an equal volume of n-octanol and phosphate buffer (10 mM, pH 7.4) was shaken on a mechanical shaker at room temperature for 24 h. Saturated solutions of the complexes in phosphate buffer (presaturated with n-octanol) were prepared in an ultrasonic bath followed by a filtration through a  $0.2\text{ }\mu\text{m}$  nylon filter. Equal volumes of the solution and n-octanol presaturated with phosphate buffer were mixed and the mixtures were shaken for 24 h at room temperature. Centrifugation was carried out at 2500 rpm for 30 min to separate the two phases. The aqueous layer was carefully separated and the Pt content in initial and final aqueous phases was analyzed by ICP-MS. The  $\log P_{\text{O/W}}$  was measured using the following equation:  $\log P_{\text{O/W}} = \log [(\text{Pt}_{\text{initial}} - \text{Pt}_{\text{final}})/\text{Pt}_{\text{final}}]$ .

**Reduction of the Complexes.** The lipophilicity of the two complexes is significantly higher than that of CDDP. Therefore, upon reduction, the hydrophobic compounds **1** and **2** ( $\log P = 0.6$  and  $0.84$ ) produce a hydrophilic  $\text{Pt}^{\text{II}}$  product, CDDP ( $\log P = -2.15$ ), which is scarcely extracted into octanol. Therefore, by measuring the Pt content in a water phase of the reduction mixture, the degree of reduction can be established. The reduction of complexes **1** and **2** by ascorbic acid was evaluated using this method. Complex **1** or **2** ( $4\text{ }\mu\text{M}$ ) was added to PBS (2 mL) containing 0.3% DMSO and ascorbic acid ( $40\text{ }\mu\text{M}$ ), and the resulting mixture was shaking on a shaker at  $37\text{ }^\circ\text{C}$  (600 rpm). At different time intervals (0, 6, 12, 24, 48 and 72 h),  $200\text{ }\mu\text{L}$  of the sample was drawn out from these tubes and added to a new microcentrifuge tube containing 0.6 mL of n-octanol. The sample was mixed on a vortexer for 10 min at R.T. and the two phases were separated by centrifugation at 2500 rpm for 20 min. The aqueous extract was determined by ICP-MS.

**Cytotoxicity.** Tumor cells were cultured over night after inoculation in RPMI-1640 or DMEM medium supplemented with 10% heat-inactivated FBS (v/v), 2 mM glutamine,  $100\text{ U mL}^{-1}$  penicillin, and  $100\text{ }\mu\text{g mL}^{-1}$  streptomycin. All cultures were maintained in an incubator in a highly humidified atmosphere of 95% air with 5%  $\text{CO}_2$  at  $37\text{ }^\circ\text{C}$ . The growth inhibition was measured by the MTT assay. Briefly, 4000 cells per well in culture medium ( $100\text{ }\mu\text{L}$ ) were planted in 96-well plates (Falcon, CA). The cells were treated in triplicate with different concentrations of complex at  $37\text{ }^\circ\text{C}$  for 72 h. Stock solution of CDDP was prepared in PBS, while those of complexes **1**, **2** and ligands  $\text{L}_1$ ,  $\text{L}_2$  were prepared in DMSO. The stock solutions were diluted in complete medium (DMSO  $< 0.5\%$ ). Aliquot MTT solution ( $20\text{ }\mu\text{L}$ ,  $5\text{ mg mL}^{-1}$ ) in PBS buffer (8 g NaCl, 0.2 g KCl, 1.44 g  $\text{Na}_2\text{HPO}_4$  and 0.24 g  $\text{KH}_2\text{PO}_4$  per liter, pH 7.40) was added to each

well and incubated for 4 h. The supernatant was removed and DMSO (150  $\mu$ L) was added to solubilize the MTT formazan. The amount of MTT formazan was determined using a Tecan Sunrise ELISA Reader at 570 nm after the plates were shaken for 30 min. The optical density (OD) was used to calculate the percentage of cell viability relative to the untreated control values. The background readings of MTT incubated in a cell-free medium were subtracted from each value before calculation. The IC<sub>50</sub> values of the complexes were obtained from the fitted inhibition curves at 72 h. The mean IC<sub>50</sub> was calculated using the data from three replicates.

**Cellular Uptake.** A549/DDP cells were seeded in a 6-well plate at a density of  $2 \times 10^5$  cells per well. After incubation for 24 h, the cells were treated with each complex for 12 h. The attached cells were harvested with trypsin and washed twice with PBS (4 °C). Cell pellets were collected by centrifugation and then were digested with nitric acid (100  $\mu$ L) for 2 h at 95 °C, followed by the addition of H<sub>2</sub>O<sub>2</sub> (50  $\mu$ L) at 95 °C for 1.5 h. Concentrated HCl (100  $\mu$ L) was added and kept at 95 °C until total volume was less than 50  $\mu$ L. Water was then added to dilute the solution to 1 mL and the final Pt content was determined by ICP-MS.

**DNA Platination.** A549/DDP cells were seeded in a 100 cm<sup>2</sup> cultural flask at a density of  $2 \times 10^7$  cells per flask. After incubation at 37 °C for 24 h, the cells were treated with each complex (1  $\mu$ M) for 36 h. The attached cells were washed twice with PBS (4 °C), harvested by trypsinization (0.5 mL) and washed with 1 mL of PBS. Cell pallets were lysed in DNAzol (1 mL genomic DNA isolation reagent, ThermoFisher Scientific) and the genomic DNA was extracted from lysate with pure ethanol (0.5 mL) by incubating the sample for 1–3 min at room temperature. The isolated DNA was washed with 75% ethanol and re-dissolved in NaOH (1 mL, 8 mM). The DNA concentration was determined using nanodrop spectrophotometer and the Pt content was quantified by ICP-MS.

**Cell Cycle Arrest.** A549/DDP cells were seeded in a 6-well plate at a density of  $2 \times 10^5$  cells per well and allowed to settle for 24 h. The medium was replaced with the fresh one containing CDDP, L<sub>1</sub>, L<sub>2</sub>, **1** and **2**, respectively. After incubation for 36 h, the cells were collected by trypsinization and washed with PBS, fixed in ice-cold ethanol (70%) for 12 h, pelleted by centrifugation, treated with RNaseA, stained with PI in PBS for 30 min and then analyzed by flow cytometry using a FACS.

**Western Blotting.** A549/DDP cells ( $10^7$ ) were treated with **1**, **2**, and CDDP (1  $\mu$ M), respectively, for 36 h. Total protein was extracted from A549/DDP cells using homogenizer with RIPA lysis buffer with protease and phosphatase inhibitor at 4 °C for 15 min. Protein concentrations were then measured using protein assay reagents, and equal amount of protein per lane was applied in SDS-PAGE and electrophoretically transferred onto a PVDF membrane. PVDF membranes were blocked at ambient temperature for 1 h in blocking buffer (5% skim milk/0.1% Tween-20/PBS). The primary antibodies in appropriate dilutions were incubated with the membranes at 4 °C overnight. The blots were washed with PBST (0.1% Tween-20/PBS) and incubated with peroxidase-conjugated secondary antibody in washing

buffer for 1 h. After washing with PBST, the blots were visualized by enhanced chemiluminescence kit from Millipore.

**Release of Cytochrome c.** A549/DDP cells ( $10^7$ ) were treated with **1**, **2**, and CDDP (1  $\mu$ M), respectively, for 36 h. Mitochondria and cytoplasm of cells were separated by the mitochondrion isolation kit. Cytoplasmic protein samples (80  $\mu$ g) were separated on SDS-polyacrylamide gel electrophoresis, with 5% and 15% polyacrylamide for concentration and isolation, respectively.  $\beta$ -Actin mouse monoclonal-antibody (1:5000), Cyt c rabbit monoclonal-antibody (1:1000), goat anti-mouse IgG H&L (HRP) and goat anti-rabbit IgG H&L (HRP, 1:5000) were used to perform the western blot assay.

**Flow Cytometric Analysis.** Cell death was analyzed by fluorescence-activated cell sorting (FACS) using Annexin V and propidium iodide (PI) staining assay. A549/DDP cells were seeded in a 6-well plate at a density of  $2 \times 10^5$  cells per well and allowed to settle for 24 h. The medium was replaced with the fresh one containing **1**, **2** and CDDP, respectively. After incubation for 72 h, the cells were washed twice with cold PBS, trypsinized and centrifuged (4000 g, 5 min). The supernatant was discarded and the cells were resuspended in binding buffer (500  $\mu$ L), stained with Annexin V and incubated in the dark for 45 min. The cells were treated with PI and analyzed by flow cytometry.

**Immunofluorescence Staining of RAD51.** A549/DDP cells were grown on coverslips in 6-well plates for 24 h before determination of the RAD51 level. For the immunofluorescence staining of RAD51, the cells were pre-treated with the complexes (1  $\mu$ M) for 36 h, respectively, then fixed with 4% formaldehyde, followed by treatment with 0.2% Triton X-100 in PBS for 5 min, and blocked with 5% bovine serum albumin in PBS containing 0.3% Triton X-100 for 30 min. Diluted (1:500) rabbit anti-Rad51 antibody was used. The specimens were incubated overnight at 4  $^{\circ}$ C. The cells were then washed thrice in PBS before incubating in the dark with a FITC-labeled secondary antibody for 60 min. After washing with PBS containing 0.3% Triton X-100 for 3 times, the cells were counterstained with Hoechst 33342 for 5 min. The coverslips were mounted to slides with an antifade solution. The slides were examined under a confocal microscope.

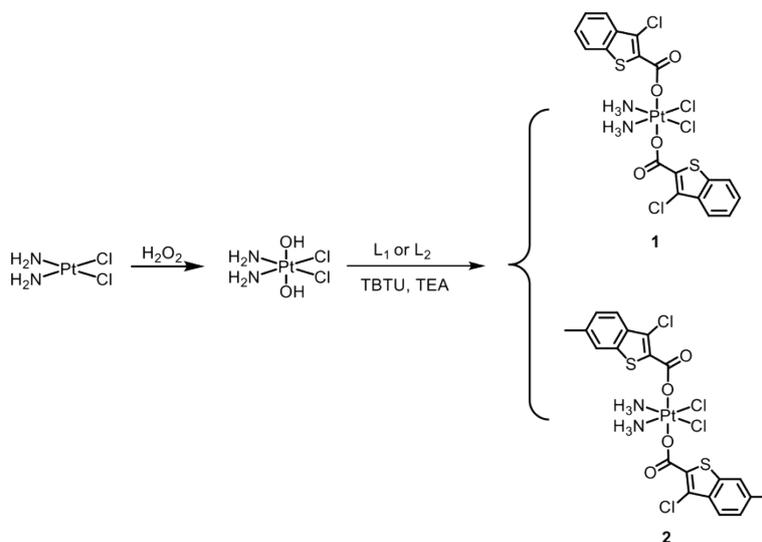
**Acute Toxicity.** Female mice were purchased and housed in polycarbonate cages at  $22 \pm 2$   $^{\circ}$ C and a 12 h light-darkness cycle with standard food and water available ad libitum. The cages were cleaned at regular interval. The use of mice for experimental purposes was approved by the Institutional Animal Care and Use Committee of Nanjing University. Complexes with different concentrations (5, 10, 20, 40 mg  $\text{kg}^{-1}$ ) were dissolved in PET (polyethylene glycol 400/ethanol/Tween-80, 6:3:1, v/v/v) with 2% DMSO and suspended in PBS. The mice were injected with identical PBS (200  $\mu$ L) or solvent control (PET : PBS = 2 : 8) (200  $\mu$ L) every two days. The experiment groups were injected intravenously with solutions of CDDP, **1**, and **2** in 200  $\mu$ L of PBS. The changes in body weight were recorded and the survival rate of the mice was

calculated over a period of 15 days. Finally, the LD<sub>50</sub> values of the compounds were calculated. All the experimental procedures on mice were performed in accordance with the Guidelines for Care and Use of Laboratory Animals of Nanjing University and experiments were approved by the Institutional Animal Care and Use Committee of Nanjing University.

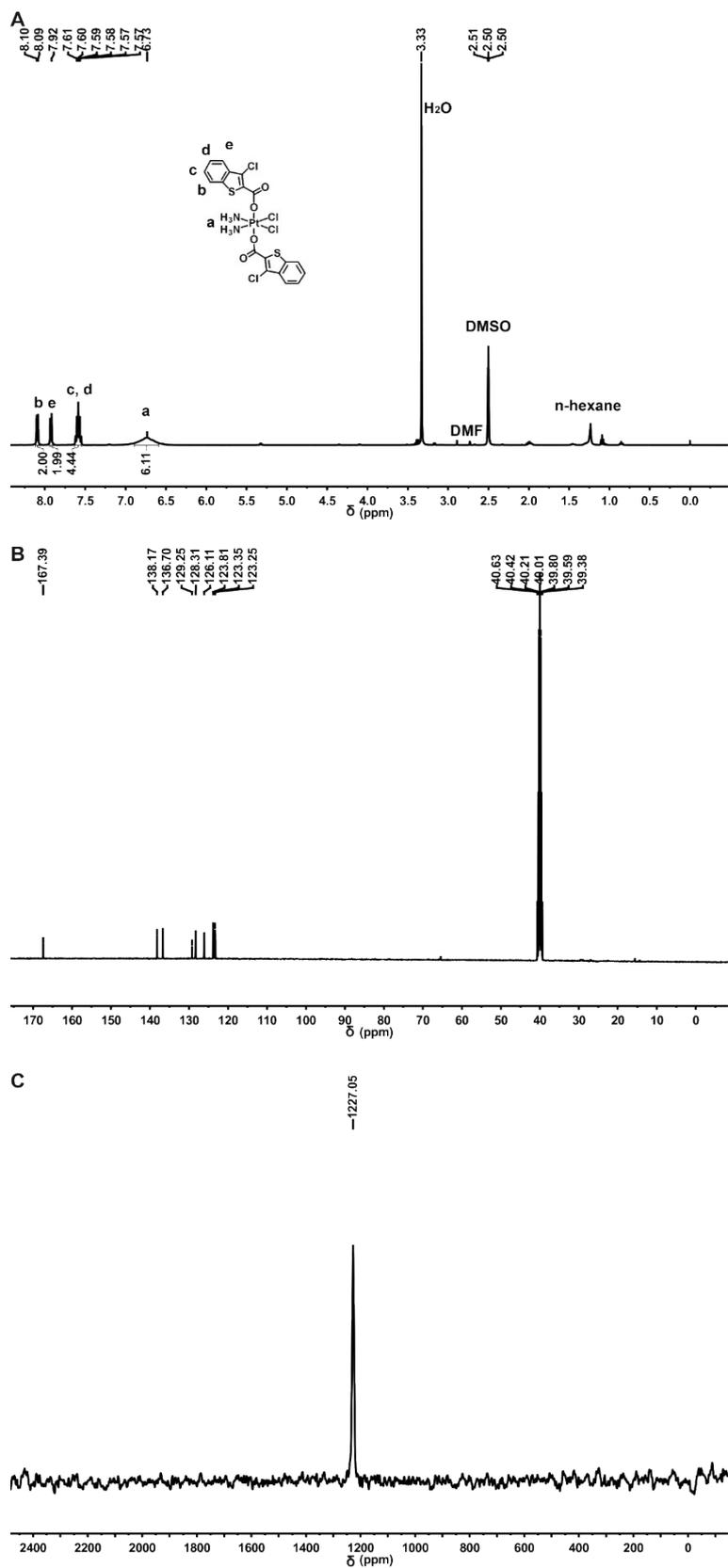
**H&E Staining.** Tissue samples were shown in histopathological examination using hematoxylin and eosin (H&E) staining. Mouse organs (heart, liver, spleen, lung and kidney) were collected in 4% paraformaldehyde for proper fixation and then embedded in paraffin using tissue embedding machine. Sections were prepared orderly by dewaxing, dehydration, and H&E staining. The tissue morphology was observed under fluorescence microscopy (Olympus BX41, Japan).

**In Vivo Antitumor Activity.** Lung cancer xenografts were set up using Balb/c nude mice (6-8 weeks old, female, n = 20). A549 cells (10<sup>6</sup>) were inoculated subcutaneously in the back of mice. The mice were randomized into four groups and were intravenously injected by vehicle, CDDP, **1**, and **2** every three day for 15 days, respectively. The volume of tumor was monitored by a vernier caliper and calculated according to the following formula: Volume = (width<sup>2</sup> × length)/2. The body weight of mice was measured at the same time.

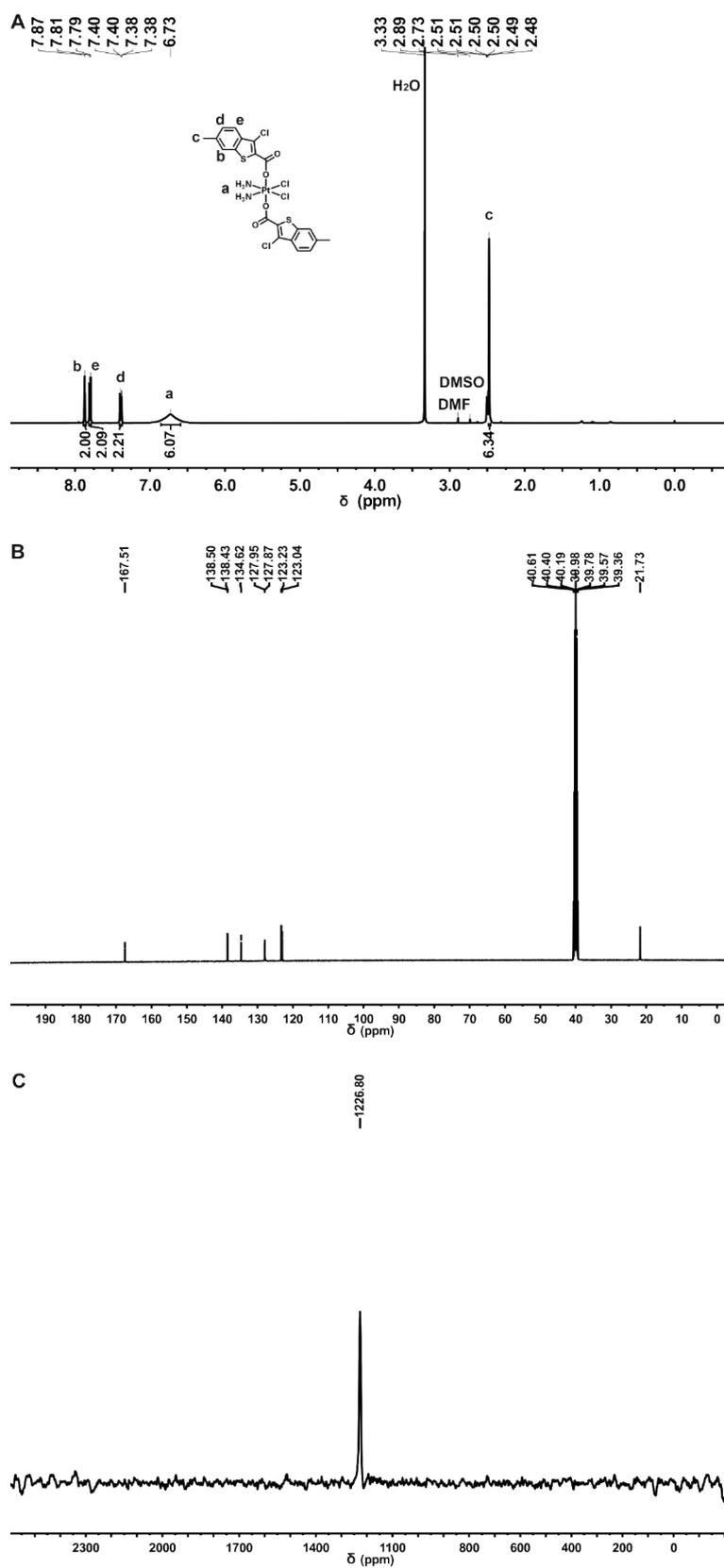
### Supplementary Figures and Tables



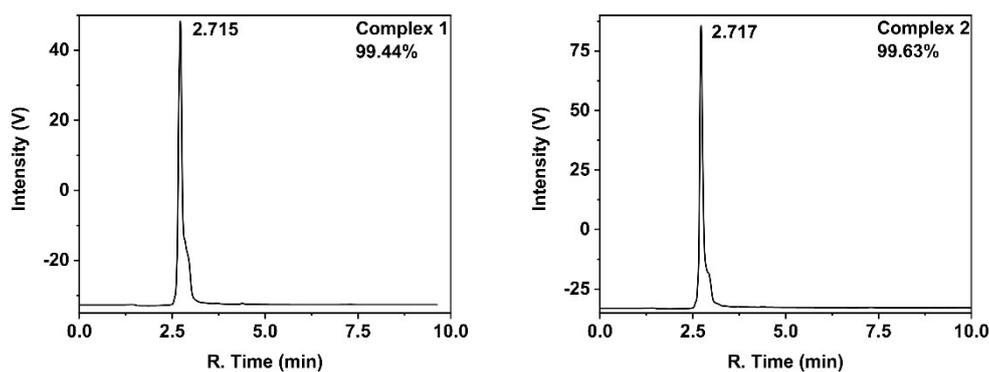
**Scheme S1.** Synthetic routes to **1** and **2**.



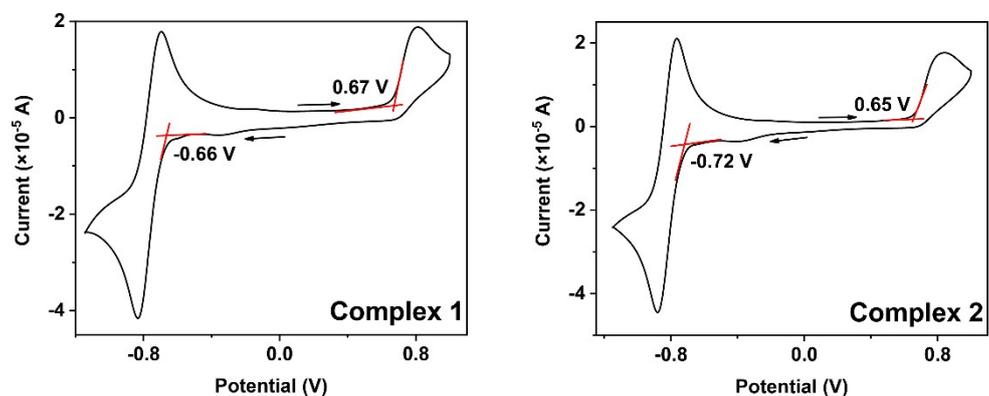
**Fig. S1**  $^1\text{H}$ -NMR (400 MHz,  $\text{DMSO-d}_6$ ) (A),  $^{13}\text{C}$ -NMR (100 MHz,  $\text{DMSO-d}_6$ ) (B), and  $^{195}\text{Pt}$ -NMR (69 MHz,  $\text{DMSO-d}_6$ ) (C) spectra of **1**.



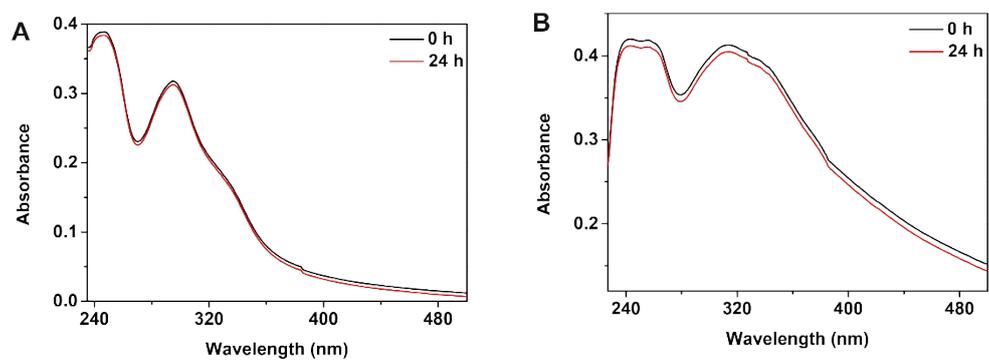
**Fig. S2**  $^1\text{H}$ -NMR (400 MHz, DMSO- $d_6$ ) (A),  $^{13}\text{C}$ -NMR (100 MHz, DMSO- $d_6$ ) (B), and  $^{195}\text{Pt}$ -NMR (69 MHz, DMSO- $d_6$ ) (C) spectra of **2**.



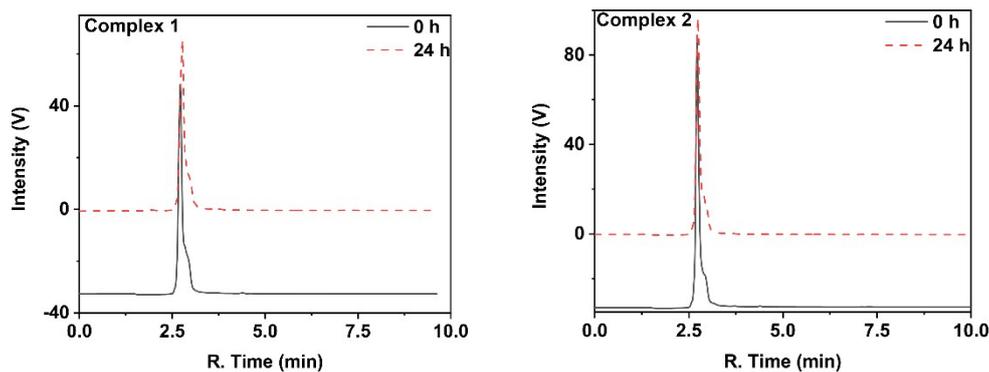
**Fig. S3** HPLC for **1** and **2** recorded at 254 nm on a Beckman Coulter HPLC instrument equipped with a C18 reverse phase column (eluent: CH<sub>3</sub>CN/H<sub>2</sub>O, 0.95).



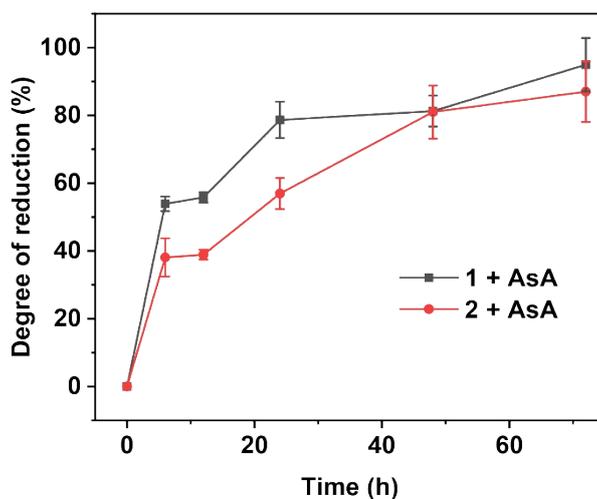
**Fig. S4** Cyclic voltammogram of **1** and **2** in DMF containing 0.1 M (n-Bu<sub>4</sub>N)PF<sub>6</sub> at a scan rate of 100 mV S<sup>-1</sup> using a glassy carbon as a working electrode.



**Fig. S5** UV-Vis spectra of **1** (A) and **2** (B) in RPMI-1640 cell culture media (containing 10% FBS) with 0.3% DMSO under physiological conditions (pH 7.4, 37 °C) at 0 and 24 h.



**Fig. S6** Stability of complexes **1** and **2** in PBS tested by HPLC at 37 °C.



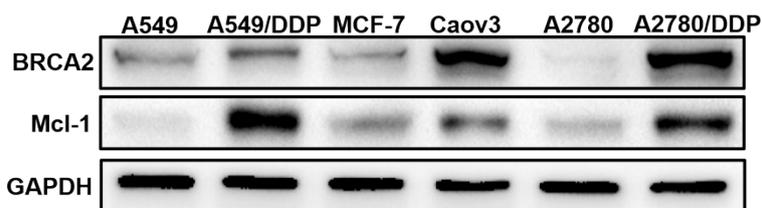
**Fig. S7** Reduction of **1** and **2** (4 μM) by AsA (40 μM) at 37 °C for different periods of time in PBS.

**Table S1.** Partition coefficient of **1**, **2**, and CDDP.

Compounds	<b>1</b>	<b>2</b>	CDDP
log <i>P</i>	0.60 ± 0.09	0.84 ± 0.04	-2.15 ± 0.30

**Table S2.** IC<sub>50</sub> (μM) of the compounds against different cells at 72 h.

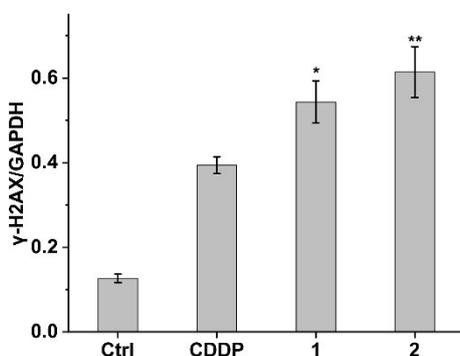
Complexes	Caov3	MCF-7	L-02
<b>1</b>	1.56 ± 0.11	1.03 ± 0.10	8.70 ± 1.61
<b>2</b>	0.85 ± 0.38	0.88 ± 0.19	10.85 ± 3.92
CDDP	25.28 ± 3.28	5.60 ± 0.73	14.95 ± 5.96
CDDP + 2L <sub>1</sub>	31.60 ± 1.12	7.20 ± 0.46	17.06 ± 1.12
CDDP + 2L <sub>2</sub>	33.72 ± 1.01	9.94 ± 1.77	16.88 ± 1.51
oxoplatin	> 50	> 50	> 50
L <sub>1</sub>	> 100	> 100	> 100
L <sub>2</sub>	> 100	> 100	> 100



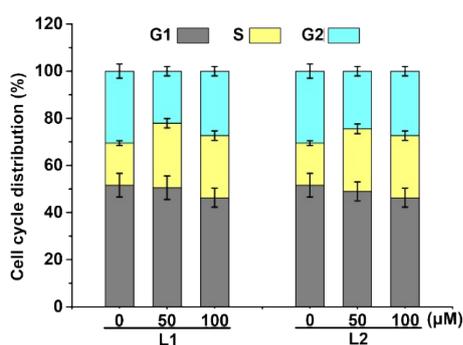
**Fig. S8** Expression of BRCA2 and Mcl-1 in different cancer cells.

**Table S3** Pt contents in A549/DDP cells after incubation with different concentration of Pt complexes for 36 h.

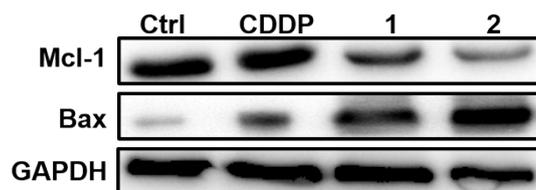
Complexes	CDDP			1			2		
Concentration	6 $\mu$ M	12 $\mu$ M	24 $\mu$ M	0.7 $\mu$ M	1.4 $\mu$ M	2.8 $\mu$ M	0.7 $\mu$ M	1.4 $\mu$ M	2.8 $\mu$ M
Pt contents (ng Pt/mg protein)	79.7 $\pm$ 3.2	102.3 $\pm$ 5.4	155.9 $\pm$ 8.2	74.5 $\pm$ 3.2	100.8 $\pm$ 4.5	139.4 $\pm$ 8.1	95.4 $\pm$ 4.7	195.3 $\pm$ 9.6	262.1 $\pm$ 15.9



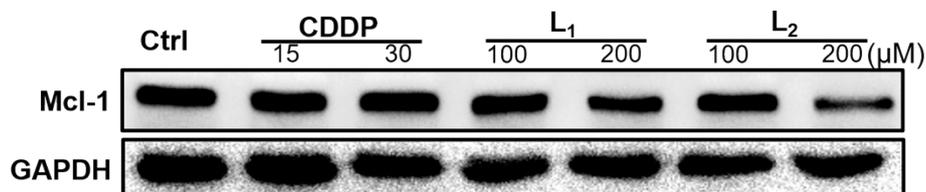
**Fig. S9** Relative expression levels of  $\gamma$ -H2AX to GAPDH in A549/DDP cells after incubation with the complexes (1  $\mu$ M) respectively for 36 h. \* $p$  < 0.05, \*\* $p$  < 0.01 (versus CDDP-treated group).



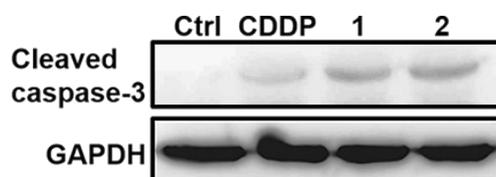
**Fig. S10** Cell cycle arrest of A549/DDP cells after incubation with L<sub>1</sub> and L<sub>2</sub>, respectively, for 36 h.



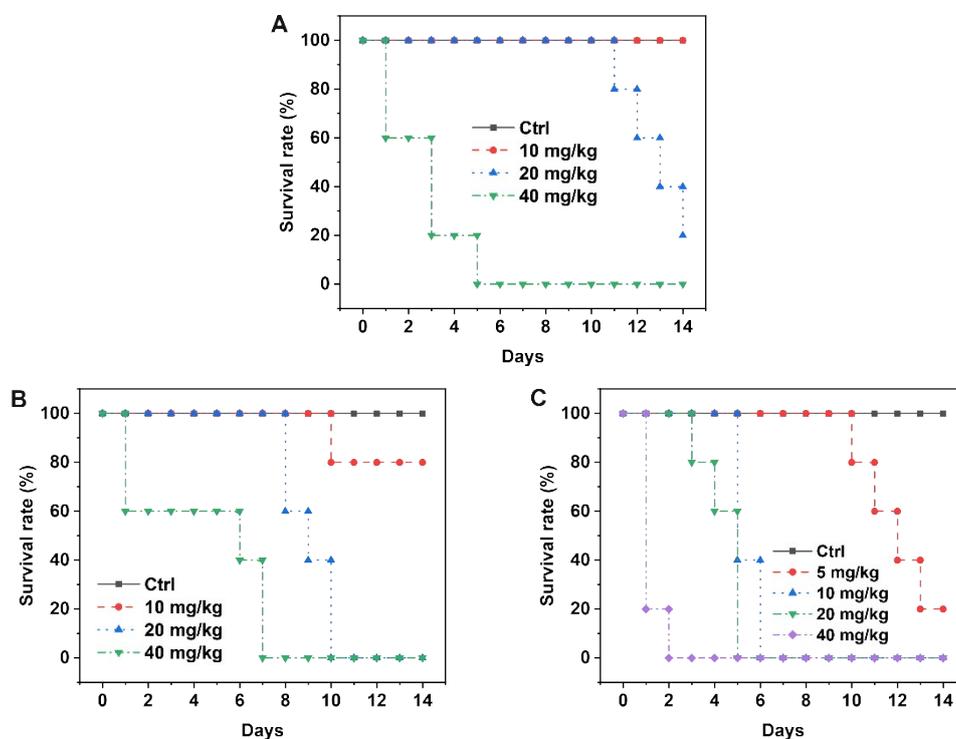
**Fig. S11** Expression of Mcl-1 and Bax in A549/DDP cells after treatment with 12  $\mu\text{M}$  of CDDP, 1.4  $\mu\text{M}$  of **1** and 0.7  $\mu\text{M}$  of **2** for 36 h.



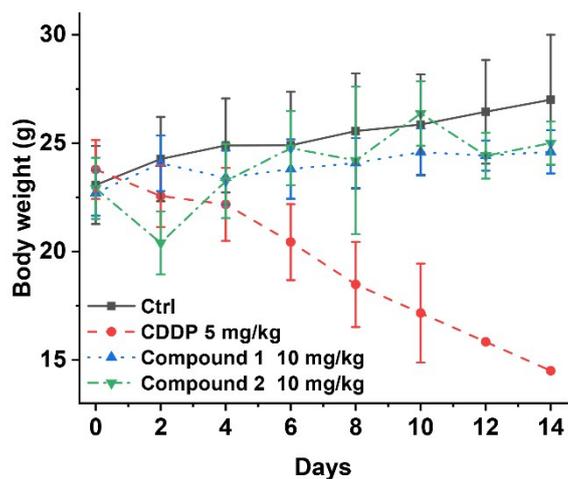
**Fig. S12** Expression of Mcl-1 in A549/DDP cells after treatment with CDDP, L<sub>1</sub> and L<sub>2</sub> for 36 h.



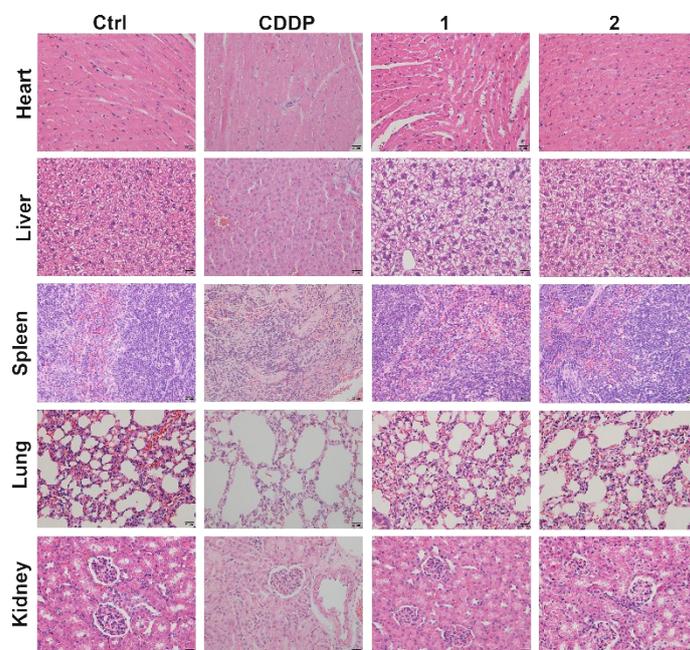
**Fig. S13** Expression of cleaved caspase-3 in A549/DDP cells after treatment with different complexes (1  $\mu\text{M}$ ) for 36 h.



**Fig. S14** Survival rate of mice treated intravenously with different doses of **1** (A), **2** (B), and CDDP (C), respectively, every two days.



**Fig. S15** Body weight of mice treated intravenously with CDDP, **1**, and **2**, respectively, every two days.



**Fig. S16** H&E-stained images of heart, liver, spleen, lung and kidney sections collected from mice after treatment with PBS, CDDP ( $5 \text{ mg kg}^{-1}$ ), **1** and **2** ( $10 \text{ mg kg}^{-1}$ ), respectively.



**Fig. S17** Images of A549 tumors after the intravenous treatment with CDDP ( $1.3 \text{ mg Pt kg}^{-1}$ ), **1**, and **2** ( $1.1 \text{ mg Pt kg}^{-1}$ ) for 15 d.

#### Reference

1. R. K. Pathak and S. Dhar, *Chem. Eur. J.*, 2016, **22**, 3029-3036.