Electronic Supplementary Information

ctc-[Pt(NH_3)$_2$(Cinnamate)(Valproate)Cl_2] **is a highly potent and low-toxic triple action anticancer prodrug**

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Reagents and Instruments

All chemicals were obtained from commercial sources and used without further purification unless otherwise noted. Cisplatin (CDDP) was purchased from Shandong Boyuan Pharmaceutical Co., Ltd. (Shandong, China). H_2O_2 (30 wt % in H_2O), cinnamic acid, aspirin, valproic acid, dichloroacetic acid and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC·HCl) were purchased from Shanghai Aladdin Biochemical Technology Co., Ltd. (Shanghai, China). DMEM medium, RPMI1640 medium, methyl thiazolyl tetrazolium (MTT) and trypsin were purchased from Shanghai Yuanpei Biotechnology Co., Ltd. (Shanghai, China). Animal tissue/cell genomic DNA extraction Kit was purchased from G-clone Biotechnology Co., Ltd (Beijing, China). Histone deacetylase, matrix metalloproteinase-2 and -9 (MMP-2 and -9) ELISA kit was purchased from Abmart Medical Technology Co., Ltd. (Shanghai, China).

^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 with a Bruker 600 or 400 MHz spectrometer. HPLC analysis was performed as on an Shimadzu LC-20AD system equipped with a Welch Ultimate AQ-C18 column (4.60 × 250 mm, 5 μm). Elemental analyses for C, H and N were obtained on a Vario cube elemental analyzer

(Elementary). Electrospray ionization mass spectrometry (ESI-HRMS) was recorded on LCMS-IT-TOF. Platinum levels were examined by inductively coupled plasma mass spectrometer (ICP-MS, Agilent 7700s). All animal experiments were conducted in accordance with the protocol approved by the Animal Nursing and Use Committee of Chongqing Medical University.

Experimental Procedures

General synthesis procedure of anhydride. Various anhydrides were synthesized according to the previously reported procedure.[1] The free acid was dissolved in CH_2Cl_2 resulting in a final concentration (50 mM) in the presence of 0.6 times amount of EDC·HCl under stirring overnight at room temperature. The mixture was washed three times with citric acid, $NaHCO_3$ and NaCl solution at (10 mg/mL), respectively. The organic phase was dried over anhydrous sodium sulfate, and then evaporated to dryness under reduced pressure to obtained the anhydrides.

Synthesis of oxoplatin. Oxoplatin was synthesized according to the previously reported method.[2,3] H_2O_2 was added drop wise to a round bottom flask containing CDDP (1.0000 g, 3.33 mmol). The mixture was heated to 75 °C, and the reaction was continued with stirring in the dark for 5 h. The bright yellow solution obtained was then kept at 4 °C to afford yellow crystals. The crystals were recovered by filtration, washed with cold water, ethanol and ether, and dried in vacuum. Melting Point: 294-297°C. Yield: 85.3% (0.9470 g, 2.84 mmol).

Synthesis of Asp-Pt(IV)-OH. Synthetic procedure for Asp-Pt(IV)-OH was refined from a reported procedure.[4,5] A mixture of oxoplatin (0.5000 g, 1.50 mmol) and aspirin

anhydride (1.0270 g, 3.00 mmol) was added to 50 mL dimethysulfoxide (DMSO) with continuously stirring at room temperature for 24 h to obtain a clear yellow solution. After remove of unreacted oxoplatin, the filtrate was lyophilized and precipitated with diethyl ether. The resultants were washed with acetone and diethyl ether to yield a pale yellow solid, and then was dried in vacuum. Yield: 60.7% (0.4487 g, 0.91 mmol).

According the procedure for Asp-Pt(IV)-OH, valproic anhydride (0.4868 g, 1.80 mmol) was used to synthesize Val-Pt(IV)-OH. Yield: 61.3% (0.4231 g, 0.92 mmol).

Synthesis of Cin-Pt(IV)-OH. The synthesis of Cin-Pt(IV)-OH was based on the procedure for Asp-Pt(IV)-OH except cinnamic anhydride (0.6257 g, 2.25 mmol) was used. Yield: 58.0% (0.4023 g, 0.87 mmol). ^{1}H NMR (DMSO-d_6): δ (ppm) 7.71 (t, 1H, Ar-CH=), 7.38 (m, 5H, Ar-H), 6.50 (t, 1H, -COOCH=), 6.00 (m, 6H, NH_3), 2.10 (s, 1H, OH). ^{13}C NMR (DMSO-d_6): δ (ppm) 174.48, 140.70, 135.31, 129.86, 129.35, 128.11, 123.73. ESI-HRMS m/z calcd for $C_9H_{14}N_2O_3Cl_2Pt$: $[M-H]^-$ 461.9957, found 461.9963. Elemental analysis calcd (%) for $C_9H_{14}N_2O_3Cl_2Pt$: C, 23.29; H, 3.07; N, 6.03. found: C, 22.95; H, 3.69; N, 5.52. The purity was determined by HPLC (>95%).

Synthesis of Cin-Pt(IV)-Cin. A mixture of oxoplatin (0.2000 g, 0.67 mmol) and cinnamic anhydride (0.8342 g, 3.00 mmol) in 20 mL N,N-Dimethylformamide (DMF) was stirred for 48 h at 50 °C to obtain a clear yellow solution. The solution was filtered and vacuum concentration get yellow viscous solid, which was washed with diethyl ether and dichloromethane several times and dried under vacuum to obtain a pale-yellow powder. Yied: 25.4% (0.1024 g, 0.17 mmol). ^{1}H NMR (DMSO-d_6): δ (ppm) 7.63 (t, 2H, Ar-CH=), 7.45 (m, 10H, Ar-H), 6.53 (t, 2H, -COOCH=), 6.71 (m, 6H,

NH_3). ^{13}C NMR (DMSO-d_6): δ (ppm) 174.25, 141.63, 134.96, 130.18, 129.40, 128.30, 121.69. ESI-HRMS m/z calcd for $C_{18}H_{20}N_2O_4Cl_2Pt$: $[M-H]^-$ 592.0377, found 592.0363. Elemental analysis calcd (%) for $C_{18}H_{20}N_2O_4Cl_2Pt$: C, 36.38; H, 3.39; N, 4.71. found: C, 37.43; H, 3.69; N, 4.67. The purity was determined by HPLC (>95%).

Synthesis of Cin-Pt(IV)-Asp. A mixture of Asp-Pt(IV)-OH (0.2000 g, 0.40 mmol) and cinnamic anhydride (0.5602 g, 2.01 mmol) in 20 mL DMF was stirred for 24 h at 50 °C to get a clear yellow solution. The solution was filtered and vacuum concentration get yellow viscous solid, which was washed with diethyl ether and dichloromethane several times and dried under vacuum to obtain a pale-yellow powder. Yield: 35.0 % (0.0863 mg, 0.14 mmol). ^1H NMR (DMSO-d_6): δ (ppm) 7.0-8.0 (m, 11H, Ar-H and Ar-CH=), 6.63 (m, 6H, NH_3), 6.50 (t, 1H, -COOCH=), 2.25 (s, 3H, $-CH_3$). ^{13}C NMR (DMSO-d_6): δ (ppm) 174.26, 172.19, 169.65, 149.76, 141.73, 134.94, 132.74, 132.49, 130.21, 129.41, 128.31, 126.86, 125.87, 124.17, 121.52, 21.52. ESI-HRMS m/z calcd for $C_{18}H_{20}N_2O_6Cl_2Pt$: $[M-H]^-$ 624.0275, found 624.0276. Elemental analysis calcd (%) for $C_{18}H_{20}N_2O_6Cl_2Pt$: C, 34.52; H, 3.22; N, 4.47. found: C, 34.69; H, 3.67; N, 4.40. The purity was determined by HPLC (>95%).

Synthesis of Cin-Pt(IV)-Val. Synthesis was based on the procedure for Cin-Pt(IV)-Asp except Val-Pt(IV)-OH (0.2000 g, 0.44 mmol) and cinnamic anhydride (0.6061 g, 2.18 mmol) was used at room temperature. Yield: 29.5% (0.0736 g, 0.13 mmol). ^1H NMR (DMSO-d_6): δ (ppm) 7.63 (t, 1H, Ar-CH=), 7.38 (m, 5H, Ar-H), 6.81 (t, 1H, -COOCH=), 6.62 (m, 6H, NH_3), 2.25 (m, 1H ,-CH-), 1.49 (m, 4H, $-CH_2-$), 1.25 (m, 4H, $-CH_2$-Me), 0.78 (m, 6H, $-CH_3$). ^{13}C NMR (DMSO-d_6): δ (ppm) 184.58, 174.14, 149.10,

141.48, 134.99, 134.03, 130.12, 129.53, 129.47, 129.37, 128.27, 121.76, 46.91, 35.19, 20.51, 14.65. ESI-HRMS m/z calcd for $C_{17}H_{28}N_2O_4Cl_2Pt$: $[M-H]^-$ 588.1003, found 588.0999. Elemental analysis calcd (%) for $C_{17}H_{28}N_2O_4Cl_2Pt$: C, 34.58; H, 4.78; N, 4.74. found: C, 34.73; H, 4.76; N, 4.39. The purity was determined by HPLC (>95%).

Synthesis of Cin-Pt(IV)-Dic. A mixture of Cin-Pt(IV)-OH (0.2000 g, 0.42 mmol) and dichloroacetic anhydride (1.0130 g, 4.22 mmol) in 20 mL dichloromethane was stirred at room temperature for 24 h and then centrifuged. The residue was collected, washed with ether, and dried in vacuo to give a yellow precipitate. Yield: 83.3% (0.1983 g, 0.35 mmol). ^{1}H NMR (DMSO-d_6): δ (ppm) 7.71 (t, 1H, Ar-CH=), 7.38 (m, 5H, Ar-H), 6.63 (m, 6H, NH_3), 6.58 (t, 1H, -COOCH=), 6.50 (s, 1H, -$COOCHCl_2$). ^{13}C NMR (DMSO-d_6): δ (ppm) 174.10, 171.02, 141.89, 134.85, 130.26, 129.40, 128.34, 120.99, 66.23. ESI-HRMS m/z calcd for $C_{11}H_{14}N_2O_4C_{l4}Pt$: $[M-H]^-$ 571.9283, found 571.9274. Elemental analysis calcd (%) for $C_{11}H_{14}N_2O_4C_{l4}Pt$: C, 22.97; H, 2.45; N, 4.87. found: C, 23.41; H, 2.64; N, 4.84. The purity was determined by HPLC (>95%).

Reduction by Ascorbate and Glutathione. The experimental conditions for reduction were referred to the previous reported.[6] Cin-Pt(IV)-Val (1 mM), Cin-Pt(IV)-Val (1 mM) + AsA (10 mM) and Cin-Pt(IV)-Val (1 mM) + GSH (10 mM) were dissolved in acetonitrile : water (60 : 40) and incubated for 0, 2, 8, and 24 h at 37 °C, respectively. HPLC profiles were recorded by UV detector at 258 nm and acetonitrile: water (60: 40, 0.1% acetic acid) as mobile phase.

Stability analysis. Complex Cin-Pt(Ⅳ)-Val was incubated in a PBS/ACN (60:40, v:v) and Cell Culture Medium/ACN (60:40, v/v) at 37 °C and then checked by HPLC under

experimental conditions identical to those used in the reduction experiments, respectively.

Cells and the tested samples. All cell lines including human lung carcinoma A549, breast carcinoma MCF-7, hepatocellular carcinoma HepG2 and bladder carcinoma 5637, mice breast carcinoma 4T1 were obtained from the Cell Bank of the Chinese Academy of Sciences (Shanghai, China), mice bladder carcinoma MB49 was obtained from the Shanghai Huiying Biotechnology Co., Ltd (Shanghai, China). A549, HepG-2 and MCF-7 Cells were cultured in DMEM medium containing 10 % FBS, while 5637, 4T1 and MB49 Cells in 1640 medium, at 37 °C in a humidified atmosphere of 5% CO_2.

Pt(IV) complexes were dissolved in DMSO to stock solutions of 1 mg/mL just before the experiment, and a calculated amount of drug solution was added to the cell growth medium to a final solvent concentration were less than 1‰, which had no discernible effect on cell killing. CDDP was dissolved just before the experiment in a 0.9% NaCl solution. They were stored at -20 °C in dark.

Cyclic Voltammetry. The conditions of cyclic voltammetry were referred to previous reports.[6] The electrochemical measurements were performed on three-electrode cell using an Autolab PGSTAT 302 electrochemical workstation (Metrohm Ltd, Switzerland). The working electrode was a platinum disk, the counter electrode was a platinum wire and the reference electrode was saturate calomel electrode. Cin-Pt(IV)-Val (0.1 mM) solutions were prepared in 5% DMF-phosphate buffered saline (PBS) at pH 7.4 and pH 6.4 with 0.1 M KCl. The cyclic voltammogram was recorded at 25 °C and the scan rate was 100 mV s^{-1}.

Antiproliferative activity. MTT assay (tetrazolium salt reduction method) was used to detect the inhibition of cell growth. Briefly, the cultured cells with better vitality were seeded in 96-well plates at a density of 3000-8000 cells per well and incubated at 37°C in a 5% CO_2 atmosphere. After 24 h, the culture medium was replaced with 200 μL of freshly culture medium containing drugs at different concentrations and incubated for another 48 h, then the medium in each well was replaced with 100μL fresh culture medium. After that, 20 μL of MTT (5mg mL^{-1}) solution was added to each well for another 4 h. Finally, the medium was removed and DMSO (150 μL) was added. The absorbance was measured at 570 nm using a Bio-Rad 680 microplate reader. The IC_{50} values were calculated using Statistical Product and Service Solutions (SPSS 17.0) software, which were based on three parallel experiments.

Cell Migration Assay. The wound healing experiment was carried out by the scratch method to evaluate the migration ability of tumor cells. Briefly, MB49 cells were seeded into 6-well plates at a density of 5×10^5 cells/well. After 24 h, a sterilized 200 μL pipette tip was used to generate a wound across the cells. PBS was slowly added into the wells to remove the detached cells. Then the cells were treated with varied complexes at the indicated concentrations for 24 h. Cells migrating into the wounded area were observed at different time points (0 and 24 h), and the images were captured and processed with Motic Images Advanced 3.2. Each experiment was performed at least three times.

Cellular uptake and DNA platination. The MB49 cells were cultured in a 6-well plate at a density of 5×10^5 cells mL^{-1}. After the cells reached about 80 % confluence, 5 μM

of CDDP and Pt(IV) complex were added, respectively, and then incubated for 12 h. After that, cells were collected and washed three times with ice-cold PBS. The harvested cells were counted, concentrated and then digested by nitric acid. The Pt level in cells were checked by the ICP-MS. Animal tissue/cell genomic DNA extraction Kit (G-clone) was used for the isolation of DNA in MB49 cells and used an ultra-micro spectrophotometer to measure DNA concentration (Thermo Nanodrop One), Pt concentration in cellular DNA in MB49 cells digested by nitric acid was also measured by ICP-MS.

Apoptosis Analysis by Annexin V-FITC/PI staining. MB49 cells (5×10^5 cells per well) were seeded in 6-well plates at 37 °C for 24 h to attach. Then, the cells were exposed to complexes at 3 μM. After 24 h, the cells were washed with PBS and digested with trypsase (no EDTA), and collected into 1.5 mL tubes. The staining procedures were performed according to the Annexin V-FITC/PI Apoptosis Detection Kit (Elabscience) instruction. The apoptosis was detected by Flow cytometry (BD FACS Verse).

Cell Cycle Arrest Assay. MB49 cells with good vitality were transferred into 6-well plates at 5×10^5 per well. After attachment, the cells were treated with CDDP and Pt(IV) complexes at 3 μM and maintained with the proper culture medium in 5% CO_2 at 37 °C. 24 h later, cells were collected, fixed and permeabilized with ice-cold 70 % ethanol at 20 °C for 48 h. Then cells were centrifuged at 2000 rpm for 5 min. The samples were resuspended by 250 μL PBS, added 2.5 μL RNase A, and incubated for 30 min at 37 °C. Then 12.5 μL propidium iodide (1 mg mL^{-1}) was added to stain for 30

min. Cell cycle arrest assay was performed on a flow cytometer (CytoFLEX), and the results were processed by CytExpert 2.3 soft.

Histone Deacetylase Assay. The inhibition of HDAC was measured in MB49 cells by using Human histone deacetylase ELISA kit. MB49 cells with good vitality were transferred into 6-well plates at 5×10^5 per well, after the cells reached about 80 % confluence, 1 μM of CDDP and Cin-Pt(IV)-Val were added, respectively, and then incubated for 24 h. After that, the culture medium was withdrawn and centrifuged at 2000 rpm for 3 min, obtaining the supernatant of culture medium. The remaining cells were digested with trypsase, centrifuged at 2000 rpm for 3 min and washed with ice-cold PBS three times. The cells were counted and broken. The supernatant of culture medium and cells as the tested samples, were processed according to the manufacturer's instruction processed as reported by the manufacturer instructions. The inhibition of the HDAC induced by the tested complexes was detected by measuring the absorbance of each well at 450 nm, using a Rayto RT-6100 microplate reader. Similarly, MMP-2 and -9 activity inhibition were also determined using MMP-2 and -9 ELISA kit. Each experiment was performed at least three times. The inhibition rate was calculated according to the following formula.

$$\text{Inhibition rate} = \left(1 - \text{Tested}_{\text{group}}/\text{Control}_{\text{group}}\right) \times 100\%$$

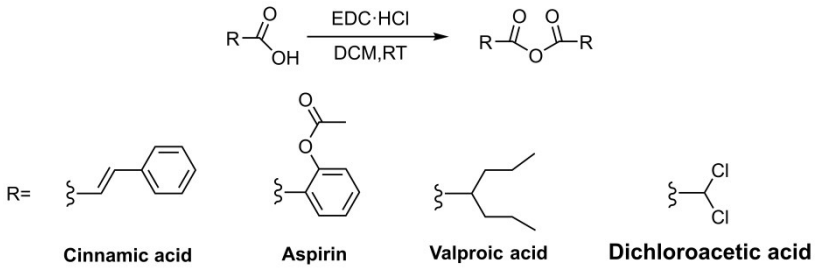
In vivo anti-tumor activity. Six-week-old female BALB/c mice (15-16 g weight) were purchased from Chongqing Medical University (Chongqing, China). All animal experiments were conducted in accordance with the protocol approved by the Animal Nursing and Use Committee of Chongqing Medical University. The 4T1 single-cell

suspension in PBS (5×10^6 cell/0.1 mL/mouse) was injected subcutaneously into the buttock of the mouse. When the tumor grew to a size of 50-100 mm^3, the mice were numbered and randomly divided into 5 groups: (1) PBS; (2) CDDP (2.5 mg/kg Pt); (3) Cin-Pt(IV)-Val (2.5 mg/kg Pt); (4) CDDP (5 mg/kg Pt); (5) Cin-Pt(IV)-Val (5 mg/kg Pt), and administered intravenously with the above formulations once every 3 days for 4 times. The tumor volumes were measured every other two days: tumor volume (mm^3) = 0.5 × length × $width^2$. After 12 days, all the animals were sacrificed, the tumors and major organs (heart, liver, spleen, lung and kidney) were collected for tissue damage determination. The content of Pt in main tissues was evaluated by ICP-MS. The tumor growth inhibition rate was calculated by the formula:

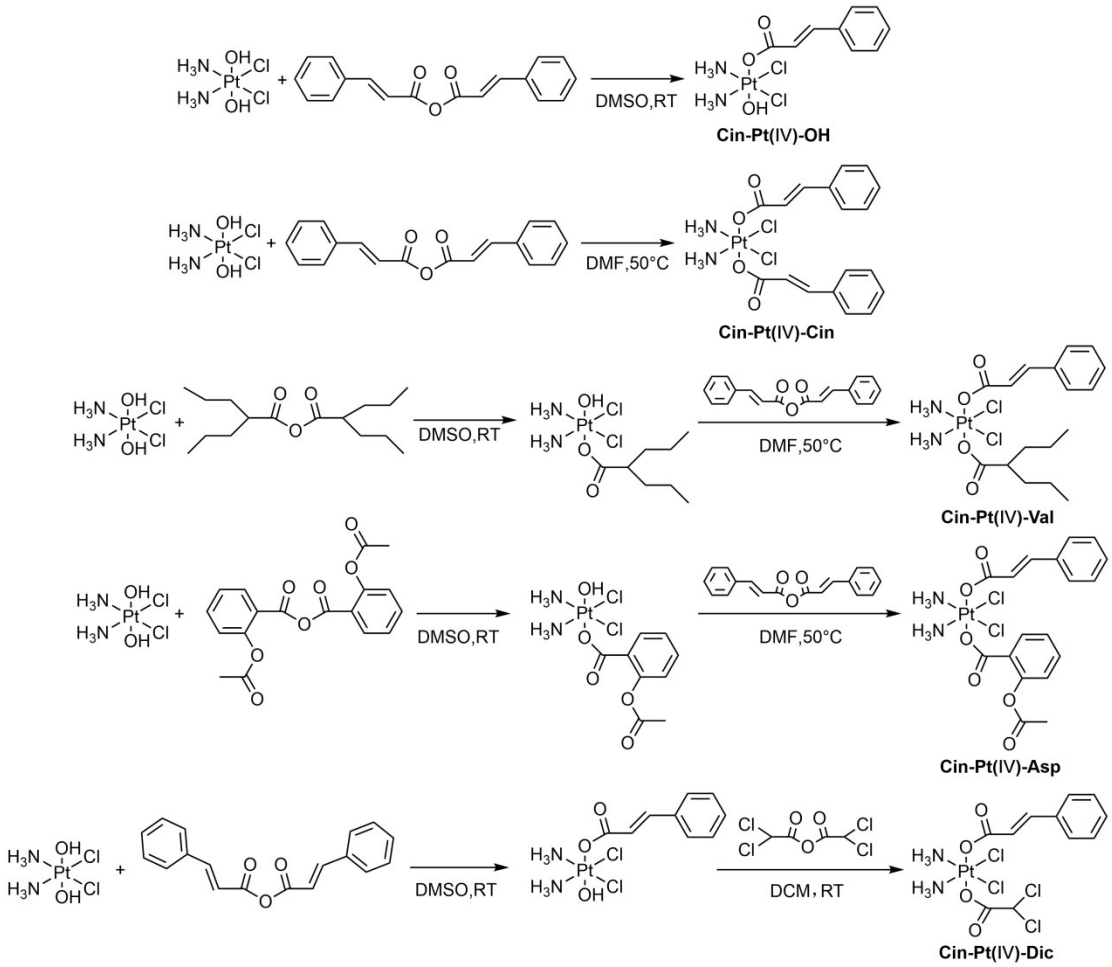
$$\text{Inhibition rate} = \left[1 - \left(\text{Treated}_{\text{last}} - \text{Treated}_{\text{first}}\right)/\left(\text{Control}_{\text{last}} - \text{Control}_{\text{first}}\right)\right] \times 100\%$$

It should be noted that $\text{Treated}_{\text{first}}$ or $\text{Control}_{\text{first}}$ are tumor volumes at the time of the first measurement, and $\text{Treated}_{\text{last}}$ or $\text{Control}_{\text{last}}$ are tumor volumes at the time of the last measurement.

Supplementary Figures and Tables



Scheme S1. General synthesis procedure of anhydride.



Scheme S2. Synthetic routes to Pt(Ⅳ) complexes.

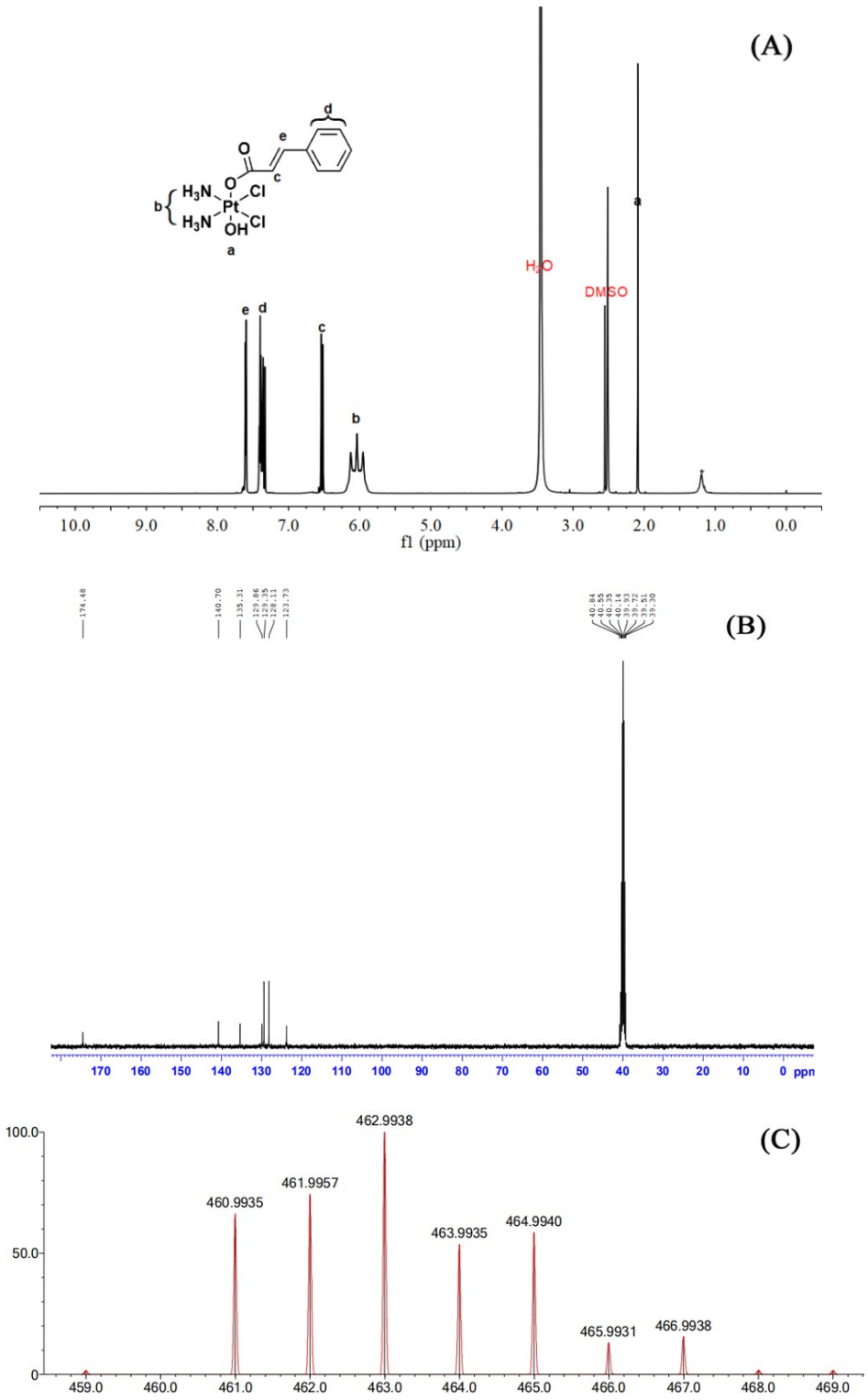


Fig. S1 ^{1}H NMR (600 MHz, DMSO-d_6) (A), ^{13}C NMR (400 MHz, DMSO-d_6) (B), and HRMS $[M-H]^-$ (C) spectra of Cin-Pt(Ⅳ)-OH.

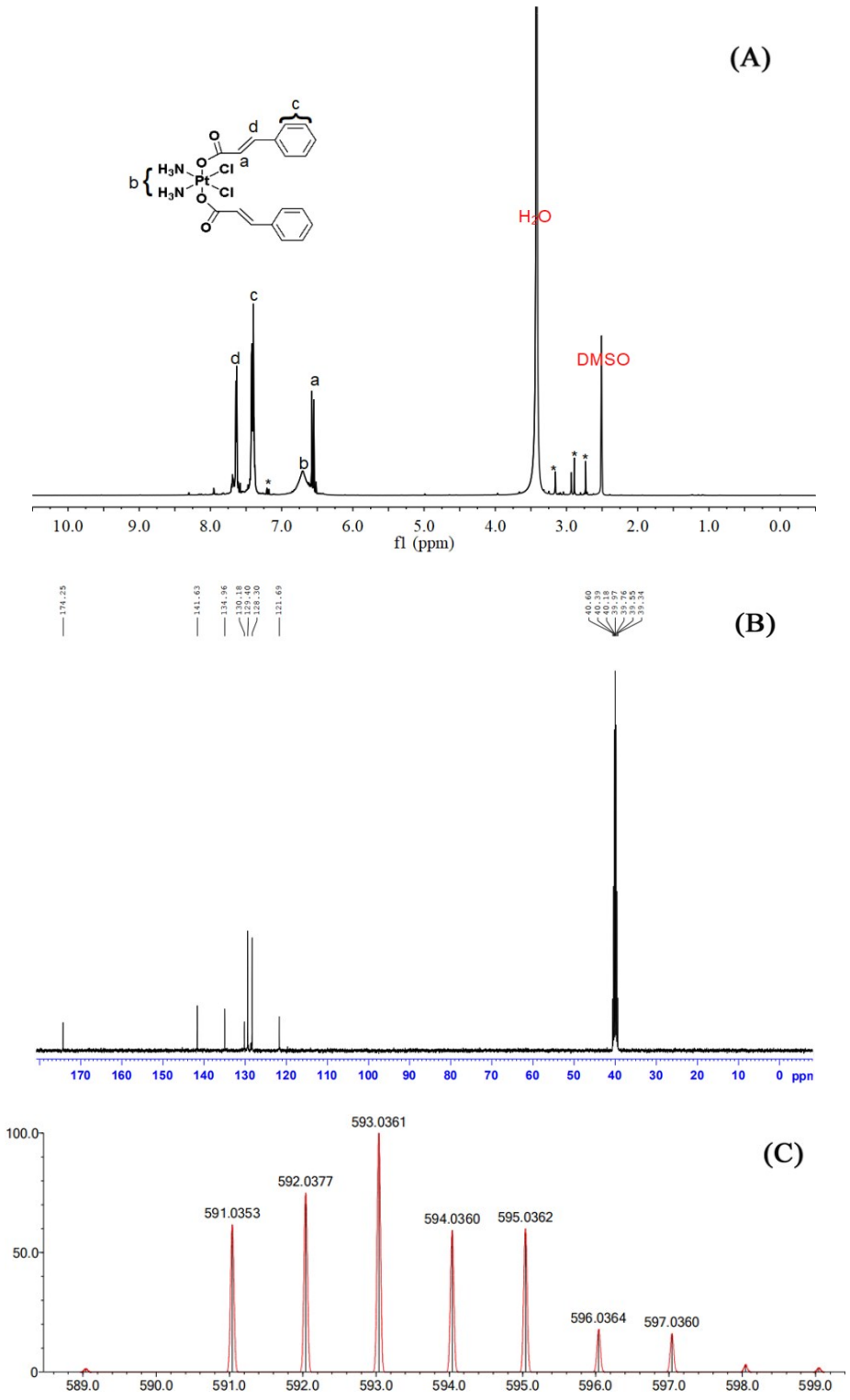


Fig. S2 ^{1}H NMR (600 MHz, DMSO-d_6) (A), ^{13}C NMR (400 MHz, DMSO-d_6) (B), and HRMS $[M-H]^-$ (C) spectra of Cin-Pt(Ⅳ)-Cin.

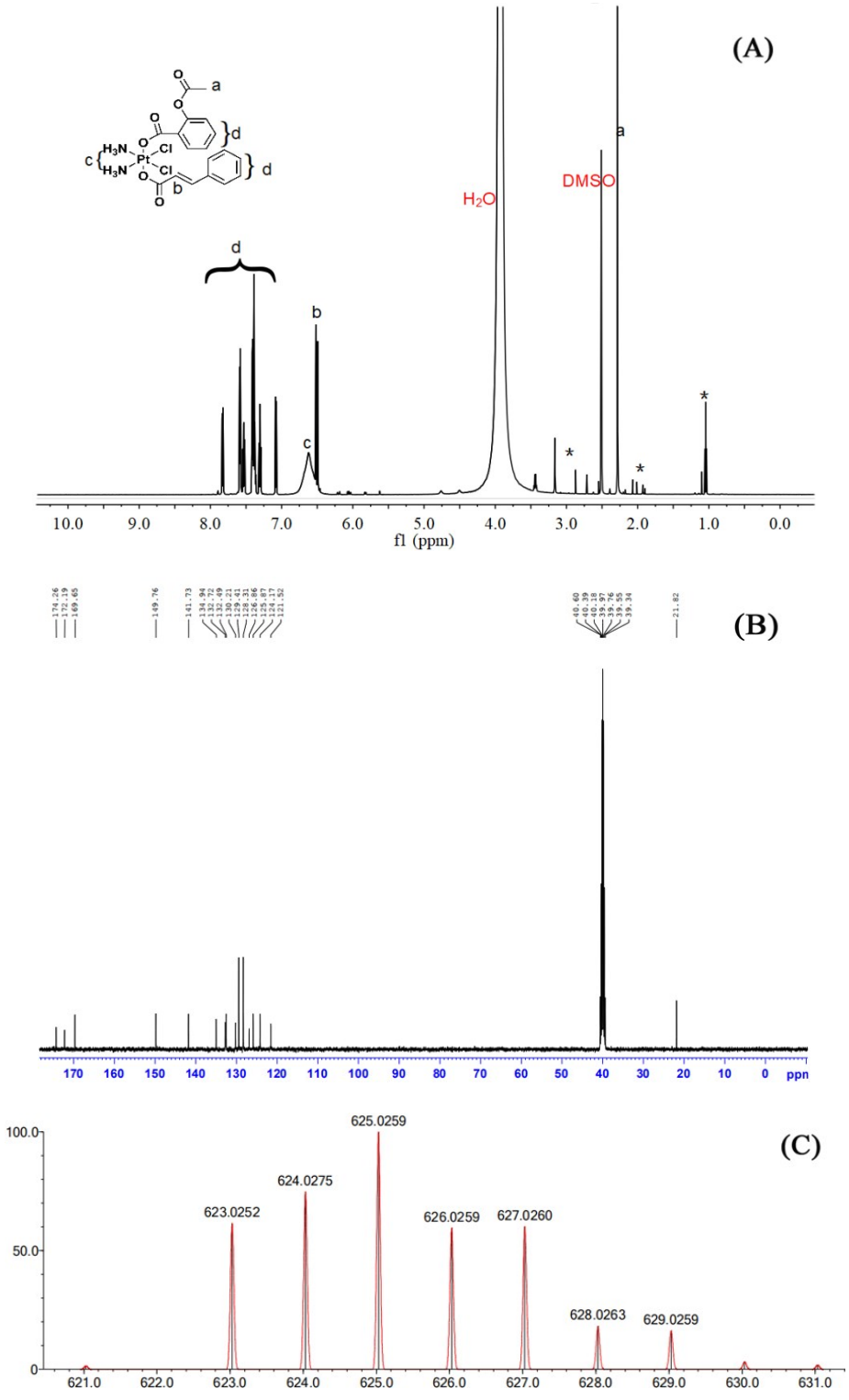


Fig. S3 ^{1}H NMR (600 MHz, DMSO-d_6) (A), ^{13}C NMR (400 MHz, DMSO-d_6) (B), and HRMS $[M-H]^-$ (C) spectra of Cin-Pt(Ⅳ)-Asp.

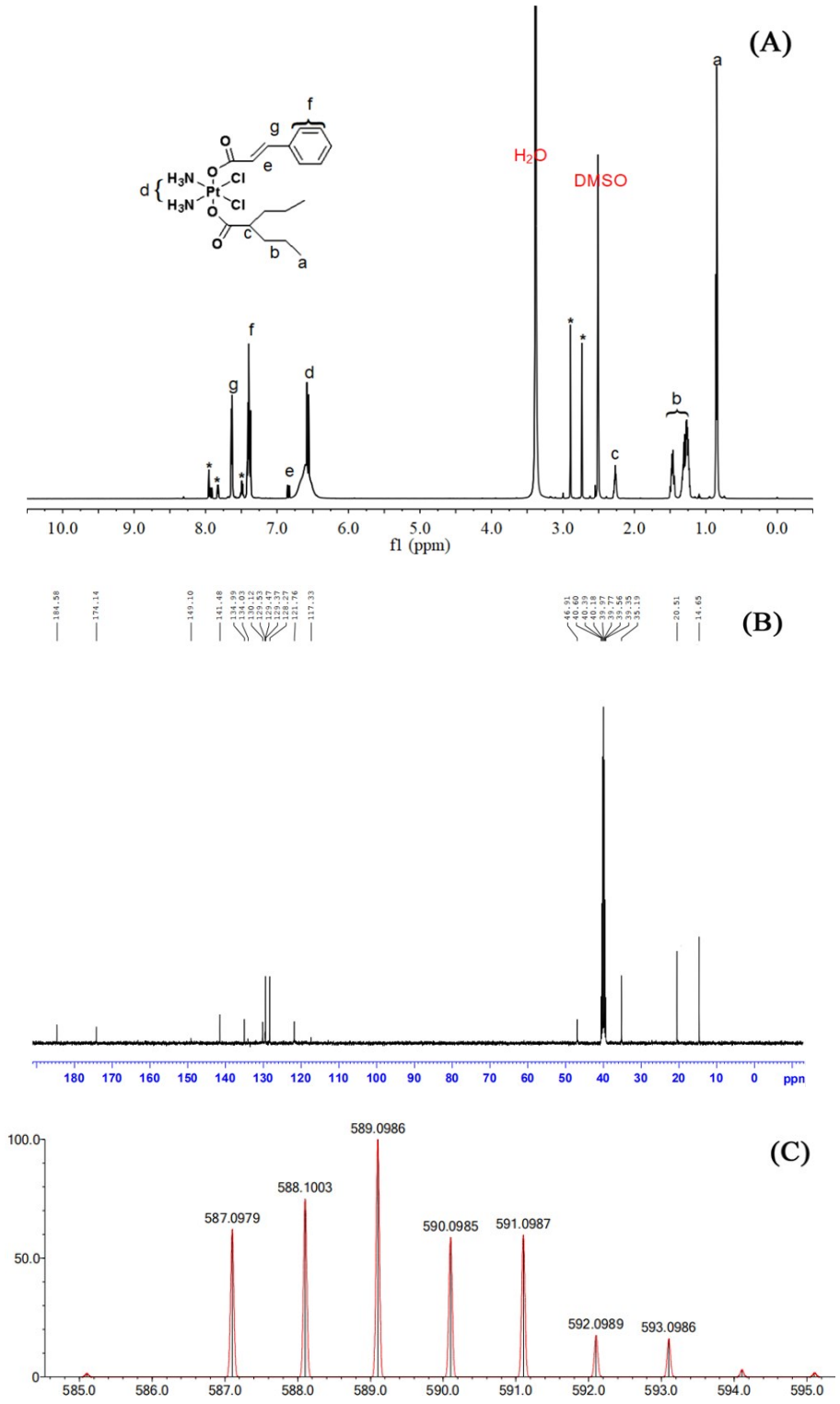


Fig. S4 ^{1}H NMR (600 MHz, DMSO-d_6) (A), ^{13}C NMR (400 MHz, DMSO-d_6) (B), and HRMS $[M-H]^-$ (C) spectra of Cin-Pt(Ⅳ)-Val.

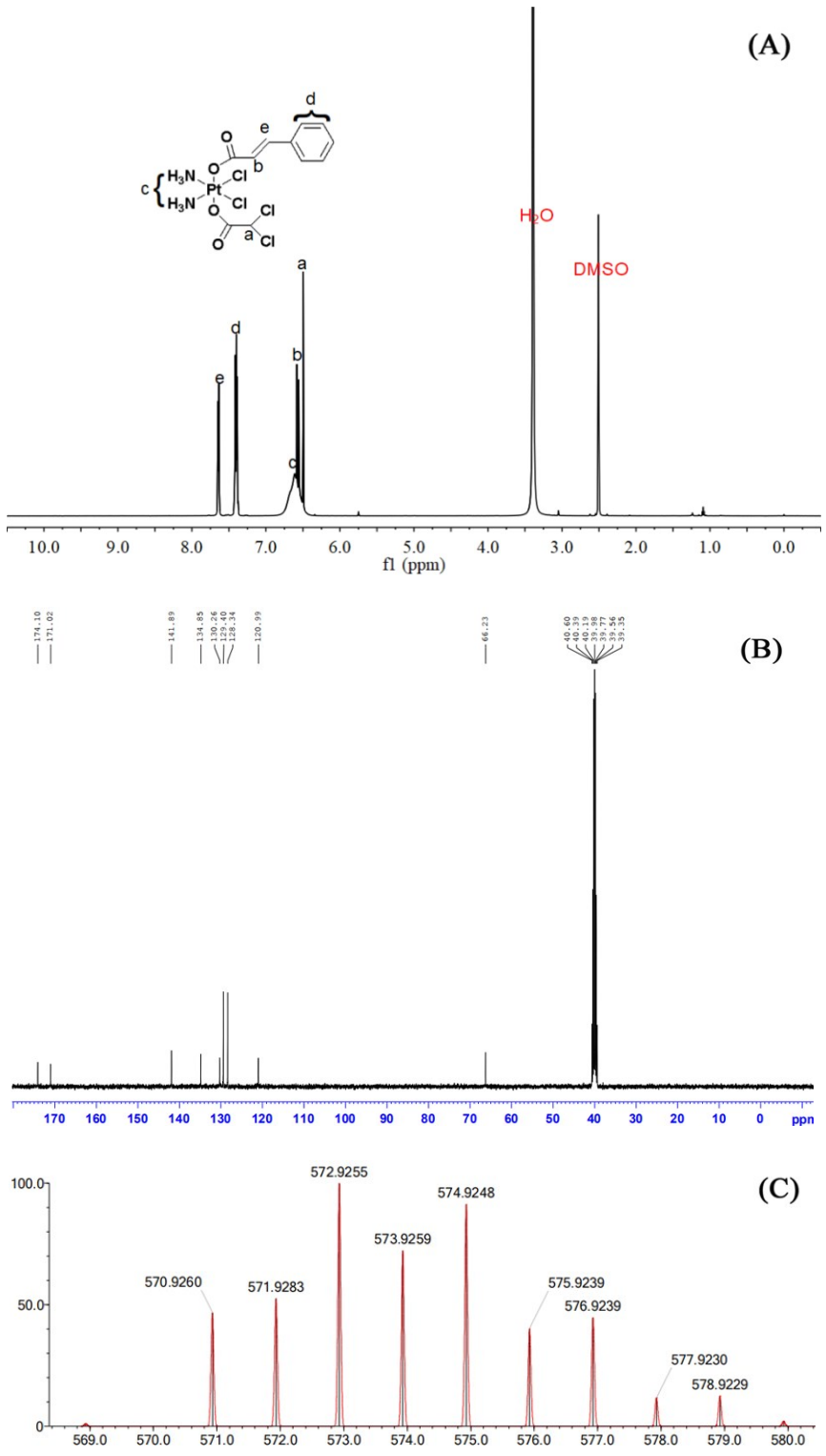


Fig. S5. ^{1}H NMR (600 MHz, DMSO-d_6) (A), ^{13}C NMR (400 MHz, DMSO-d_6) (B), and HRMS $[M-H]^-$ (C) spectra of Cin-Pt(Ⅳ)-Dic.

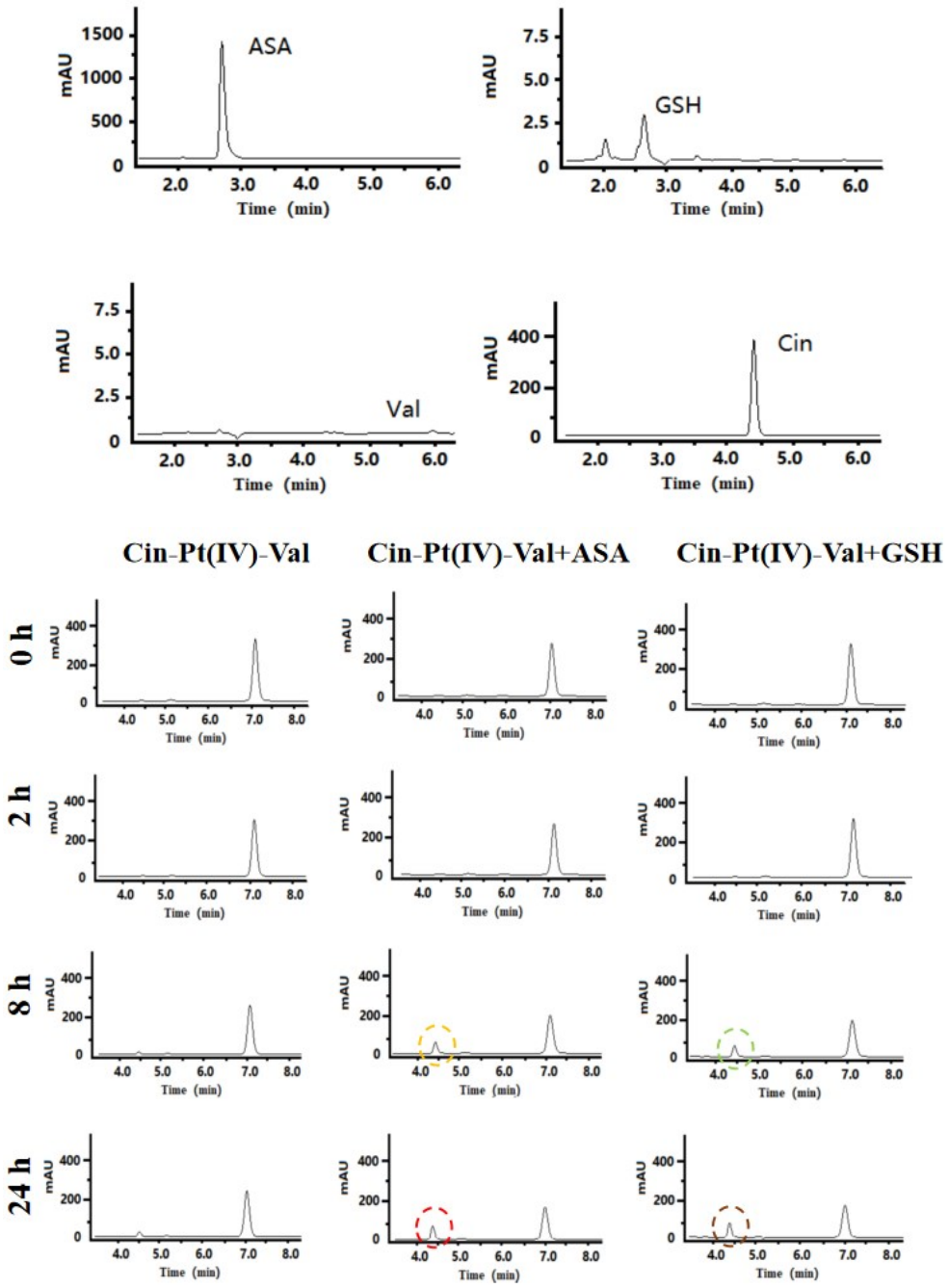


Fig. S6 HPLC analysis of the reduction ability of Cin-Pt(IV)-Val complex. Pt(IV) complex was incubated at 10 mM AsA or GSH for 0, 2, 8 and 24 h at 37 °C, respectively. HPLC profiles were recorded by UV detector at 258 nm and a 60:40 acetonitrile: water with 0.1% acetic acid as mobile phase.

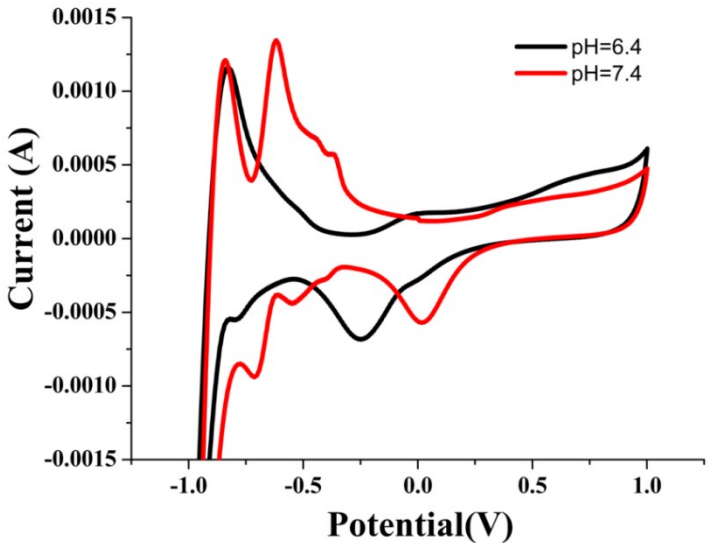


Fig. S7 Cyclic voltammograms of Cin-Pt(IV)-Val complex in phosphate buffer-0.1 M KCl with the scan rate of 100 mv/s at pH6.4 and pH7.4.

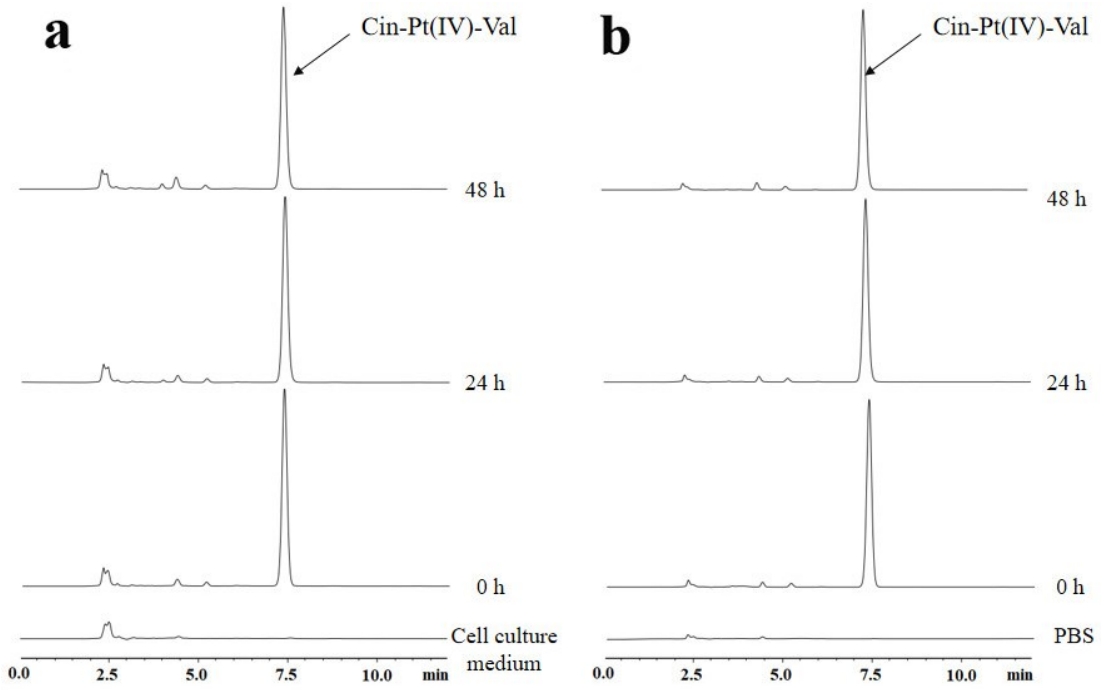


Fig. S8 Stability analysis of of Cin-Pt(IV)-Val in cell culture medium (1640 containing 10% FBS) (a) and in PBS (pH7.4) (b).

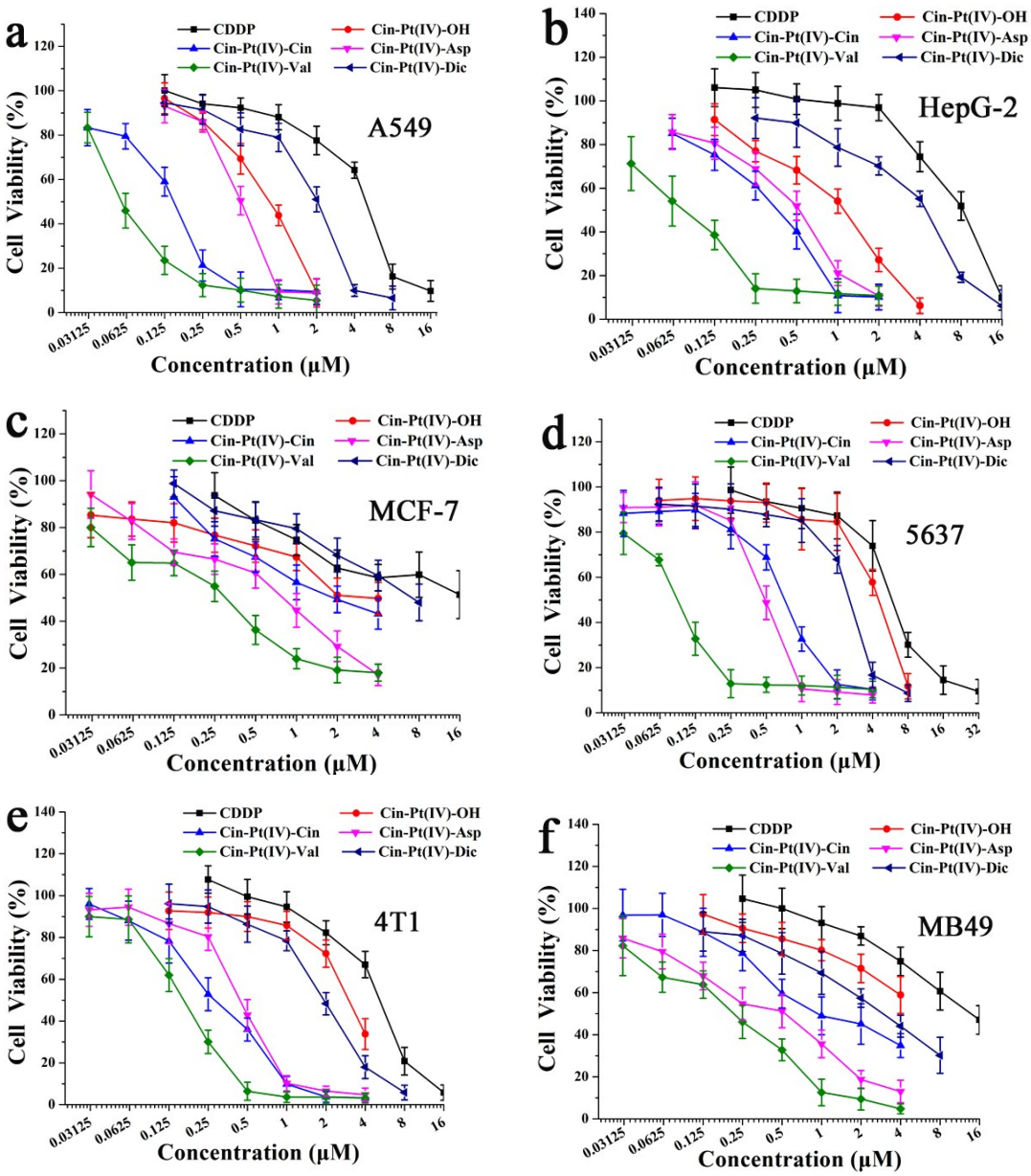


Fig. S9 Cytotoxicity assay of CDDP, Cin-Pt(IV)-OH. Cin-Pt(IV)-Cin. Cin-Pt(IV)-Asp. Cin-Pt(IV)-Val and Cin-Pt(IV)-Dic. (a) A549 cells, (b) HepG-2 cells, (c) MCF-7 cells (d) 5637 cells, (e) 4T1 cells, (f) MB49.

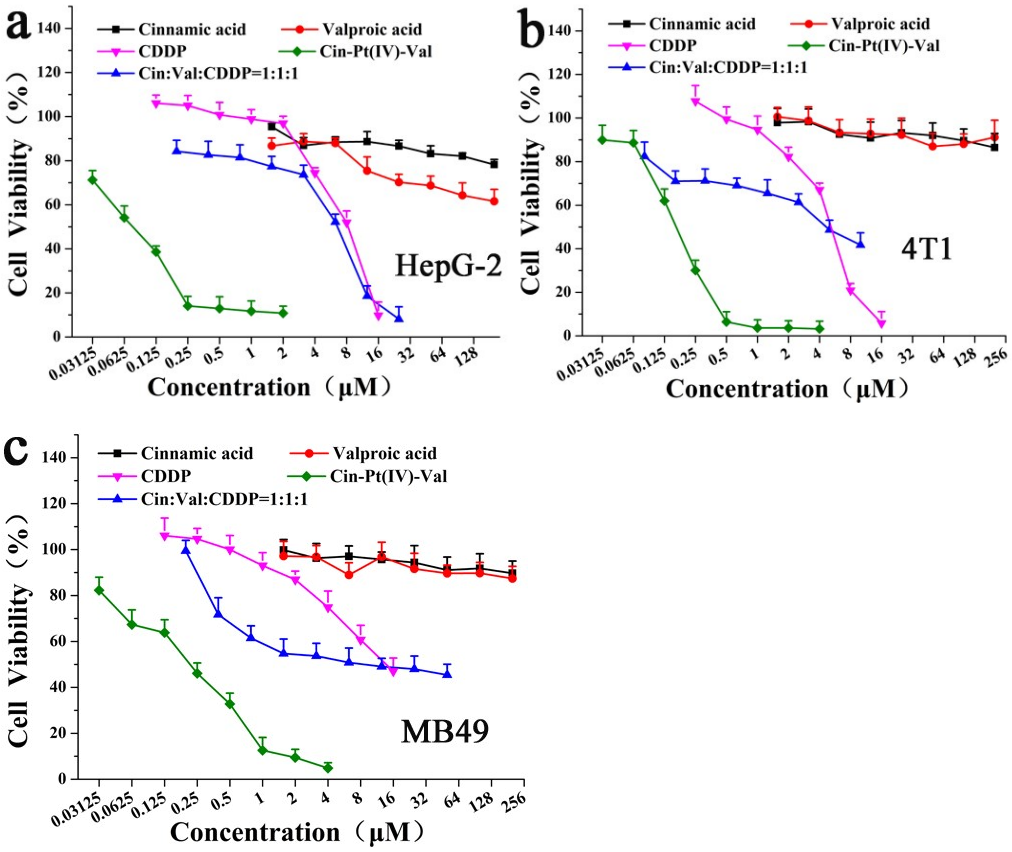


Fig. S10 Cytotoxicity assay of all three representing free constituents, the physical mixtures of CDDP, Cin and Val in 1:1:1 molar ratios, and complex Cin-Pt(IV)-Val. (a), HepG-2 cells, (b), 4T1 cells, and (c), MB49 cells.

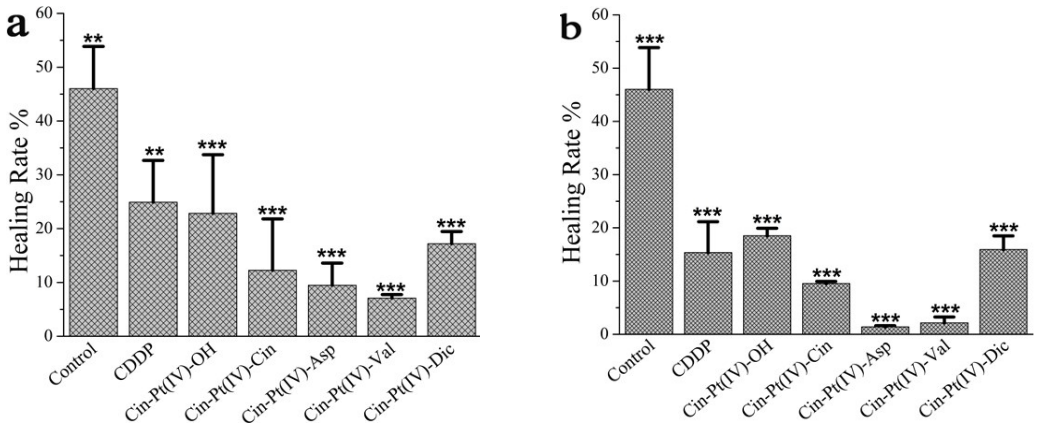


Fig. S11 Statistical analysis of cell migration under (a) 2.5μM and (b) 5μM complexes treatment. ***P < 0.001, **P < 0.01, compared with control group.

Table S1. The predicted Log P values using MolinsPiration software.

Pt complexes	predicted value	ligands	predicted value
CDDP	-2.83		
Oxoplatin	-3.30	-	-
Cin-Pt(IV)-OH	-0.79	-	-
Cin-Pt(IV)-Dic	0.55	Dic	0.74
Cin-Pt(IV)-Asp	0.88	Asp	1.43
Cin-Pt(IV)-Cin	1.71	Cin	1.91
Cin-Pt(IV)-Val	2.61	Val	2.80

Table S2. Cellular platinum accumulation, DNA platination in MB49 Cells.

	cellular uptake (ng Pt/10^6 cells)	DNA platination (pg Pt/ng DNA)
CDDP	14.39±4.45	14.35±2.41
Cin-Pt(IV)-OH	16.05±3.36	295.67±53.81
Cin-Pt(IV)-Dic	71.47±18.15	172.53±47.00
Cin-Pt(IV)-Asp	239.78±25.91	700.50±38.27
Cin-Pt(IV)-Cin	353.93±12.48	324.25±22.84
Cin-Pt(IV)-Val	369.63±15.39	751.27±36.05

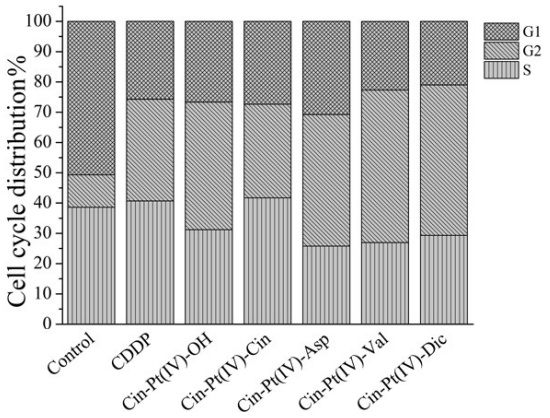


Fig. S12 Statistical analysis of cell cycle distribution of MB49 cells.

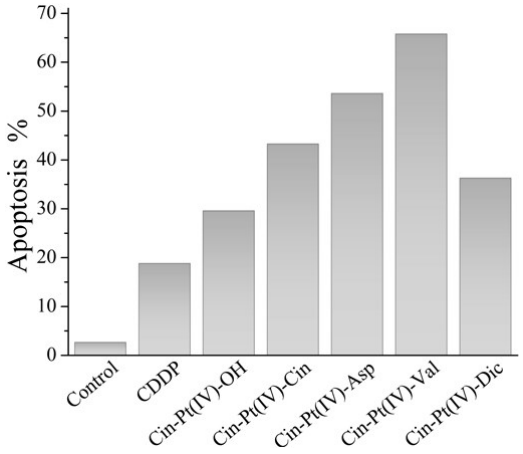


Fig. S13 Statistical analysis results of apoptosis in MB49 cells.

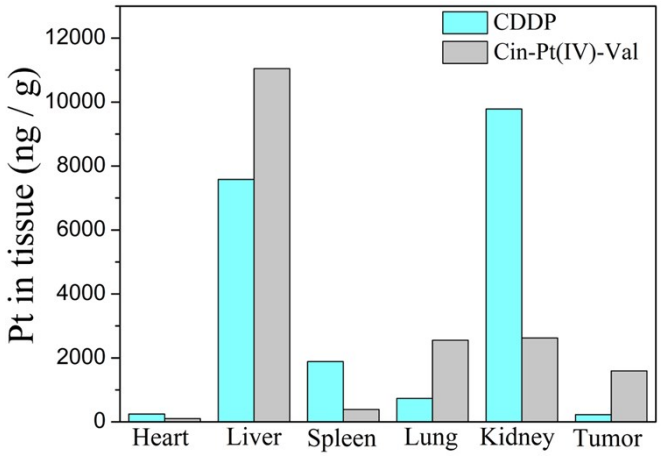


Fig. S14 Biodistribution of Cin-Pt(IV)-Val and CDDP at 5mg/Kg Pt in 4T1 bearing mice assessed by ICP-MS.

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