Electronic Supporting Information Materials

Oxoplatin Complexed with Rhein and Ferulic Acid Ligands as Platinum(IV) Prodrugs with High Anti-tumor Activity

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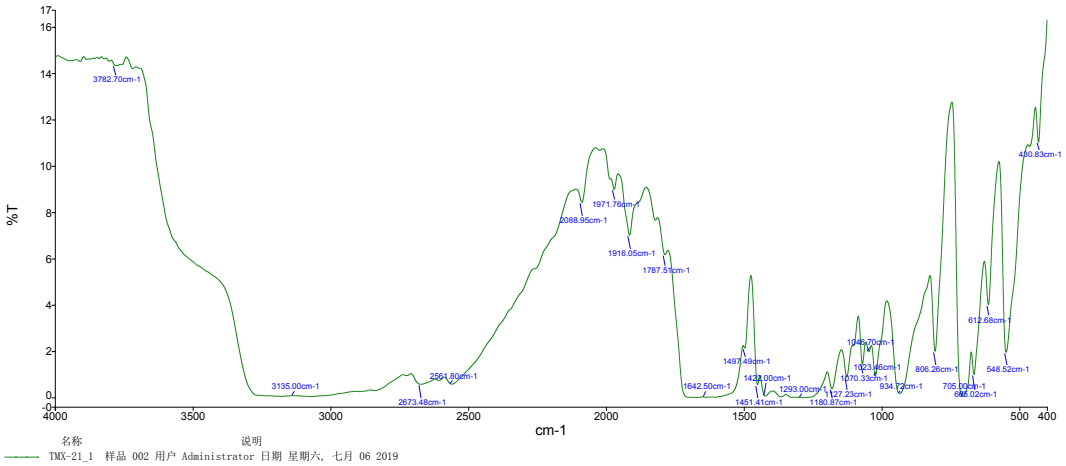

Figure S1. IR (KBr) spectra of **Pt-1.**

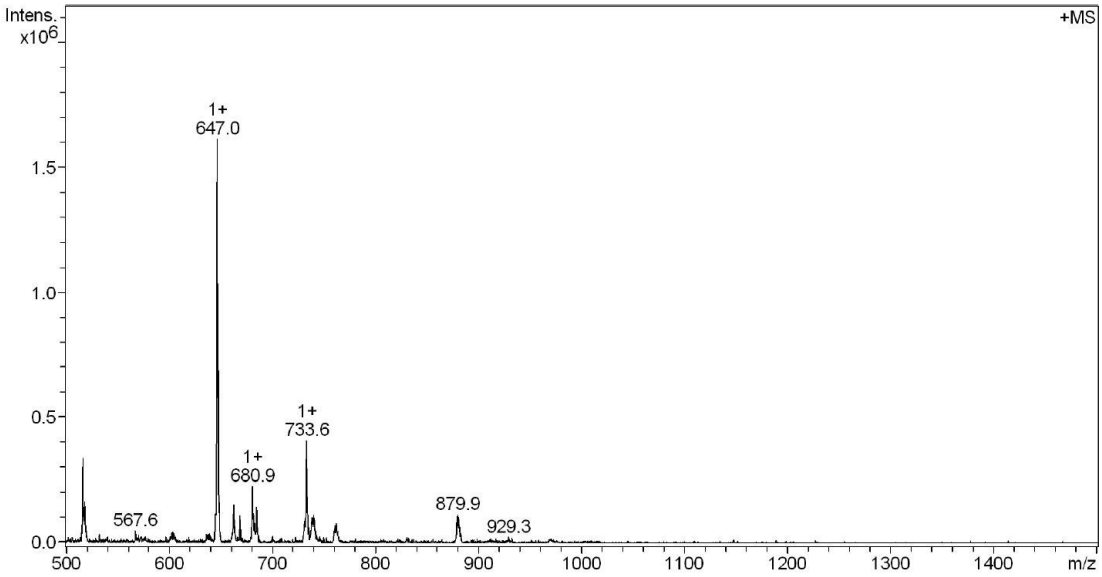

Figure S2. The mass spectra of **Pt-1** in Tris-HCl buffer solution (containing 5% DMSO) for 0 h.

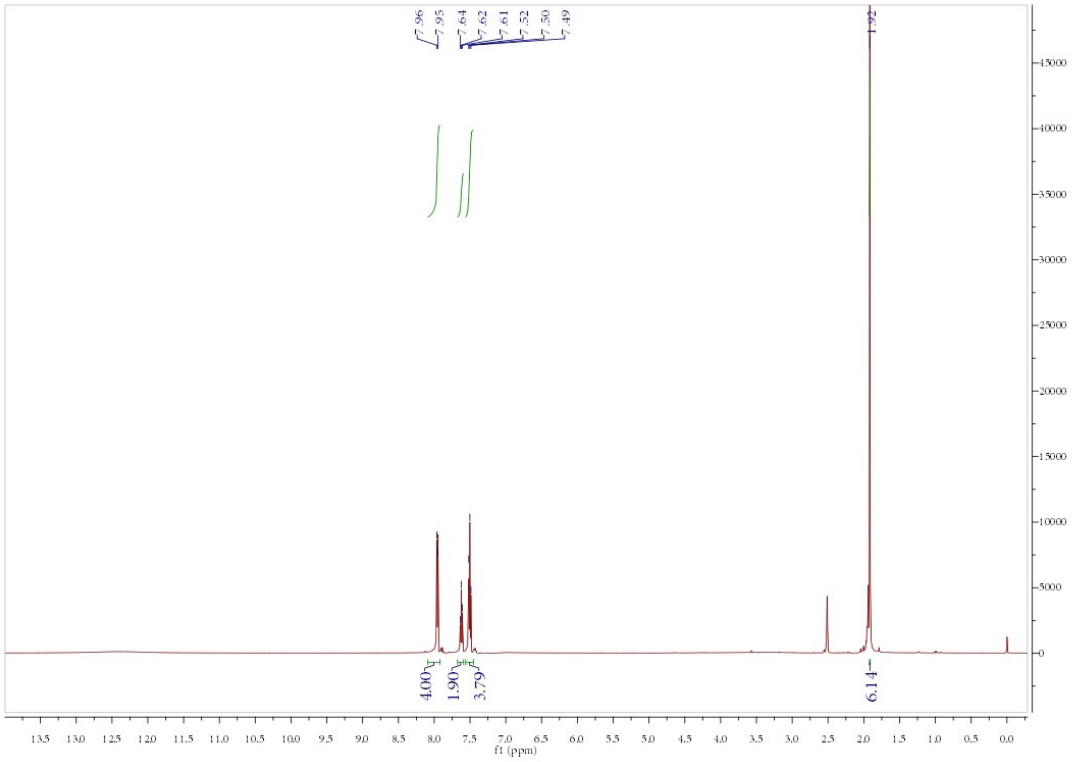

Figure S3. ^{1}H NMR (500MHz, DMSO-d_6) for **Pt-1**.

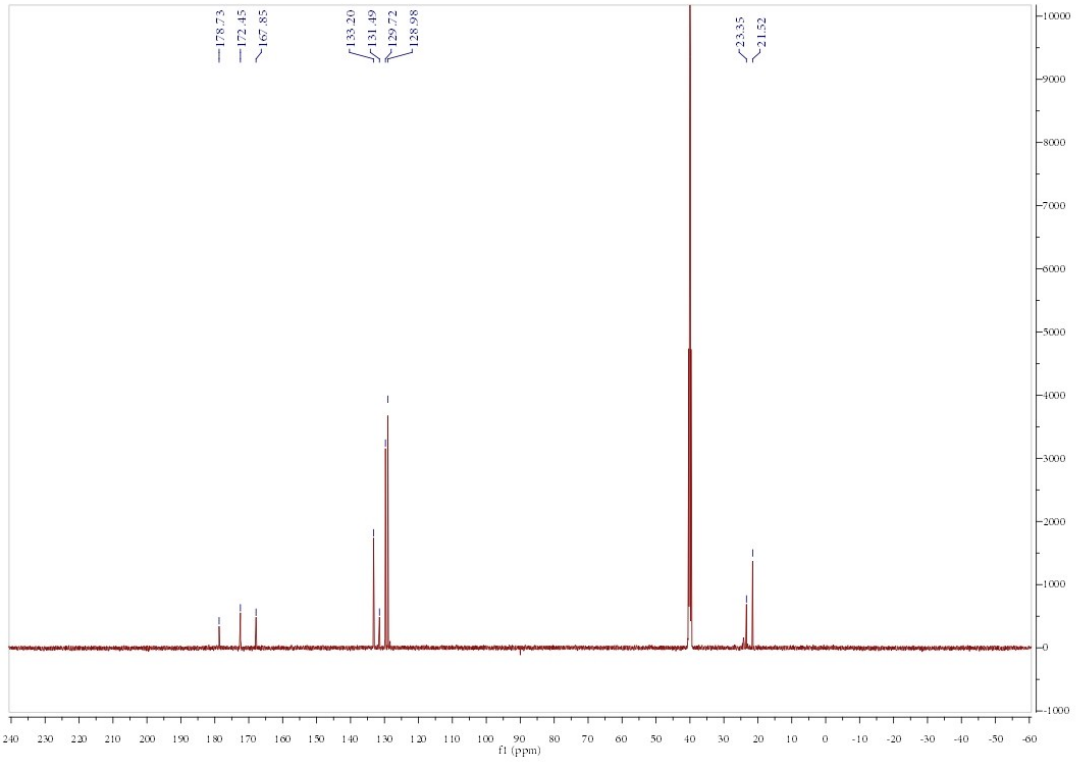

Figure S4. ^{13}C NMR (126MHz, DMSO-d_6) for **Pt-1**.

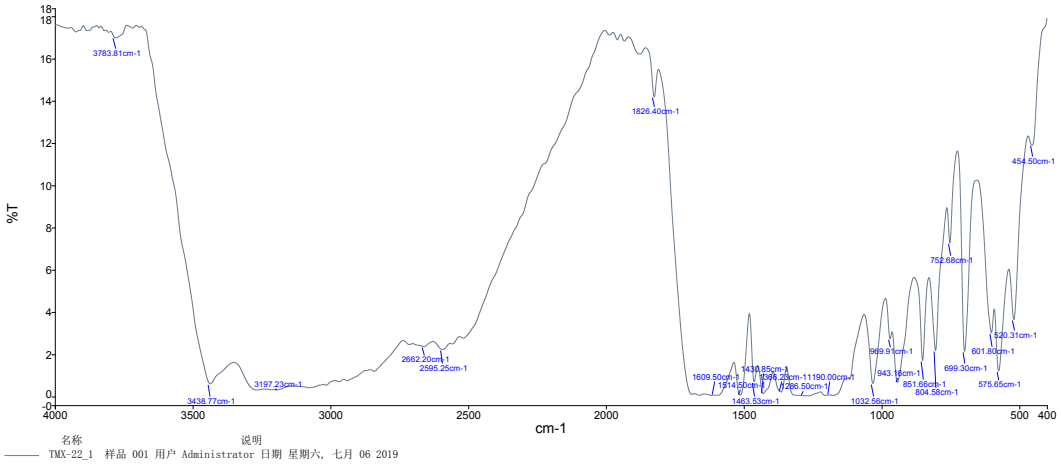

Figure S5. IR (KBr) spectra of **Pt-2.**

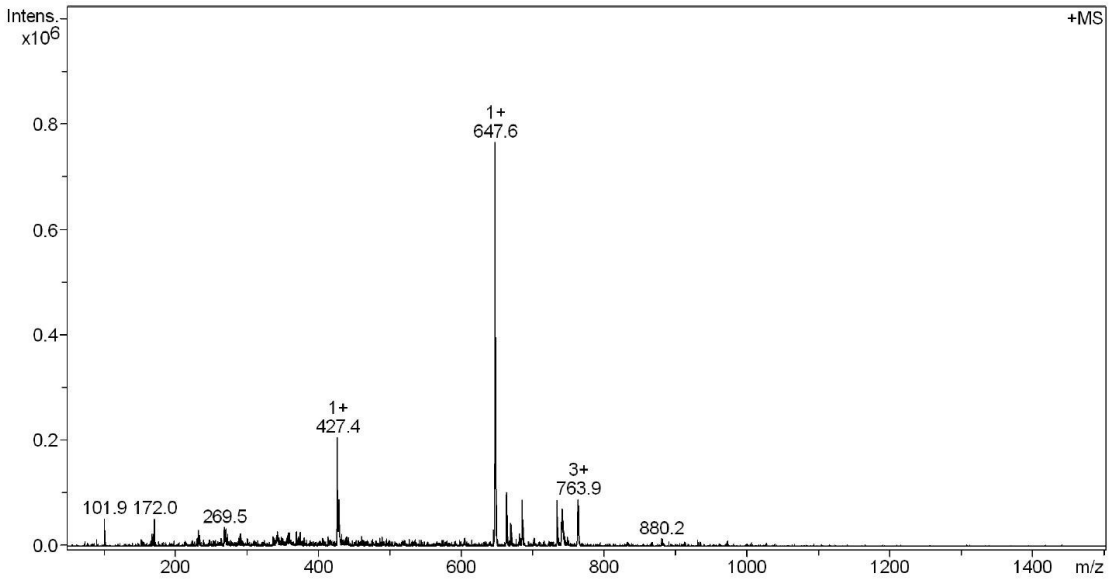

Figure S6. The mass spectra of **Pt-2** in Tris-HCl buffer solution (containing 5% DMSO) for 0 h.

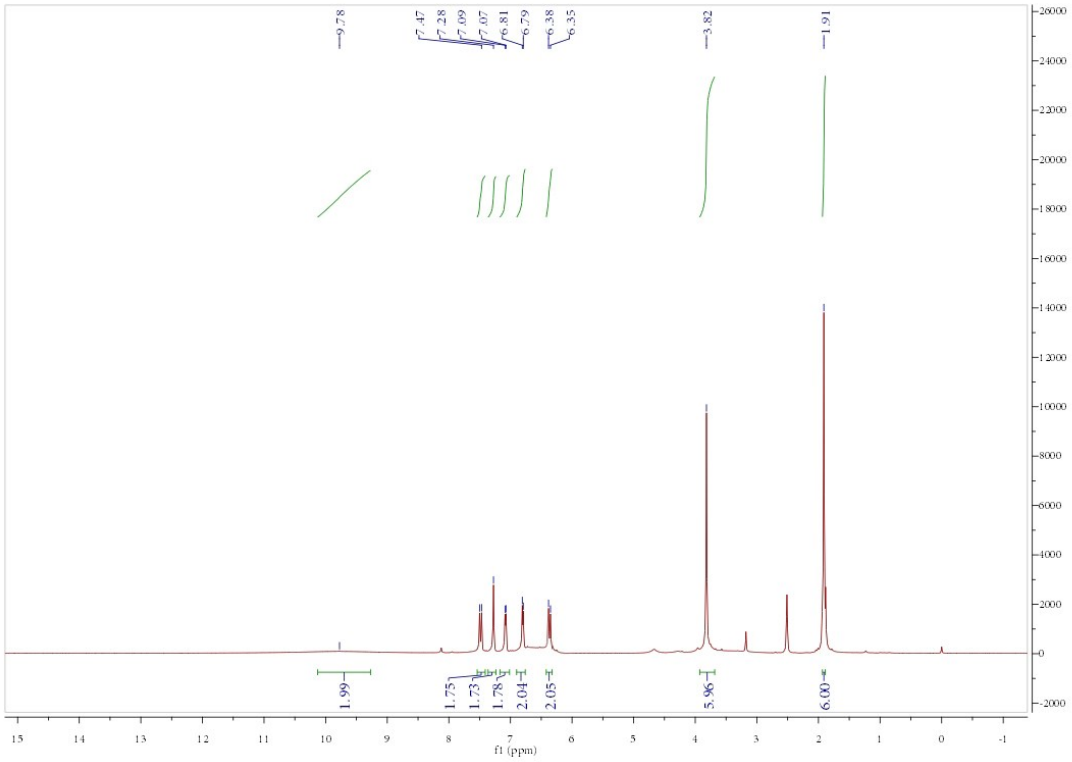

Figure S7. ^{1}H NMR (500MHz, DMSO-d_6) for **Pt-2**.

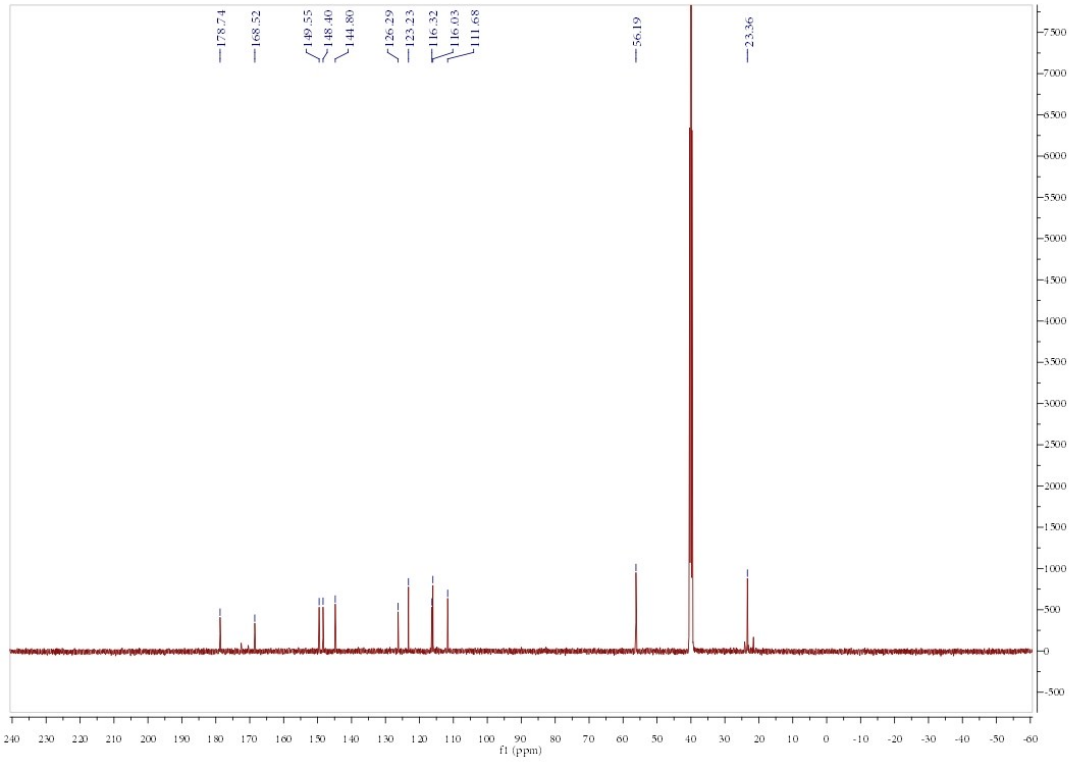

Figure S8. ^{13}C NMR (126MHz, DMSO-d_6) for **Pt-2**.

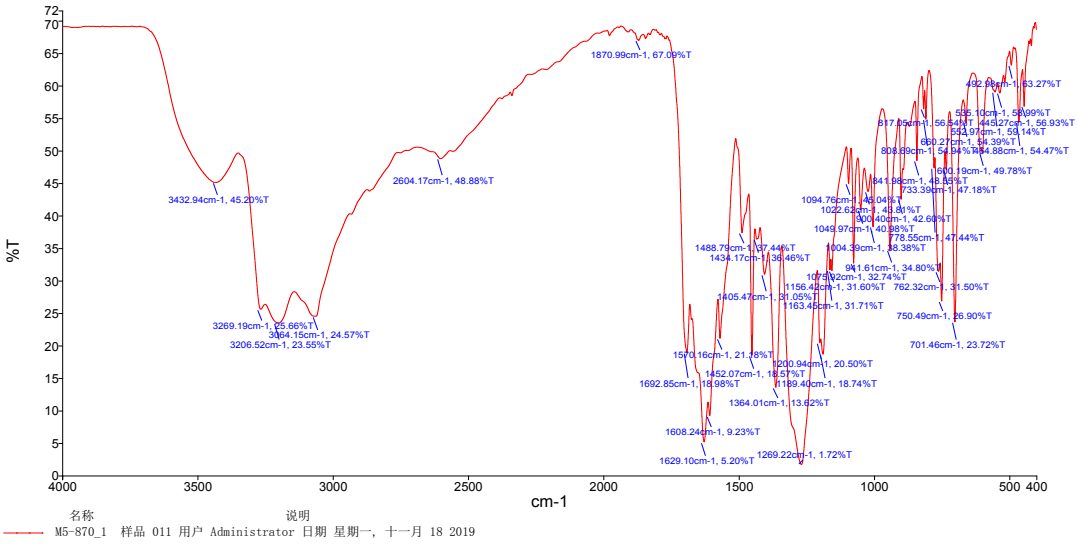

Figure S9. IR (KBr) spectra of **Pt-3.**

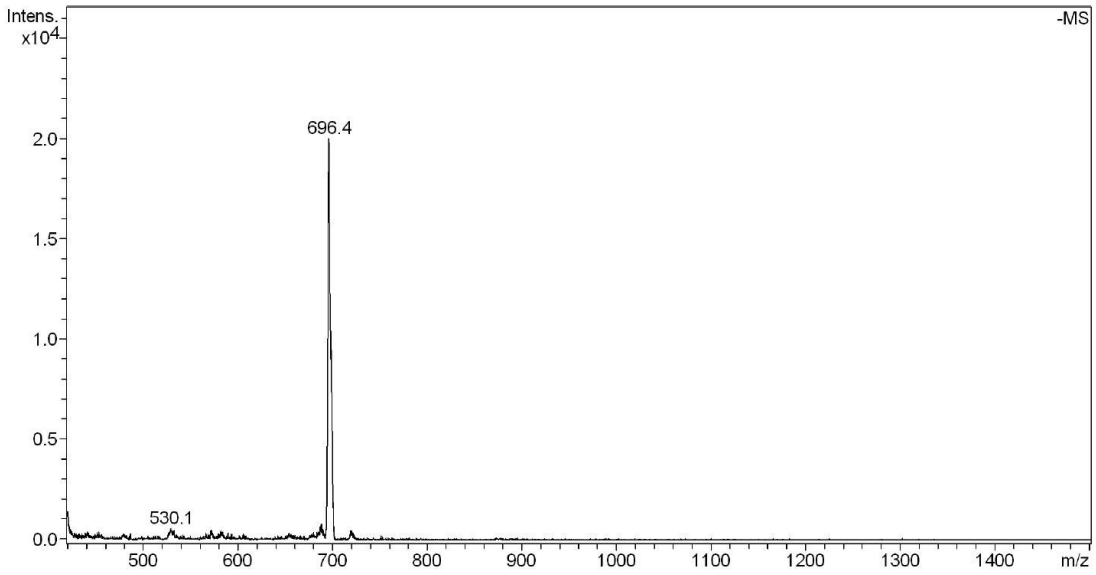

Figure S10. The mass spectra of **Pt-3** in Tris-HCl buffer solution (containing 5% DMSO) for 0 h.

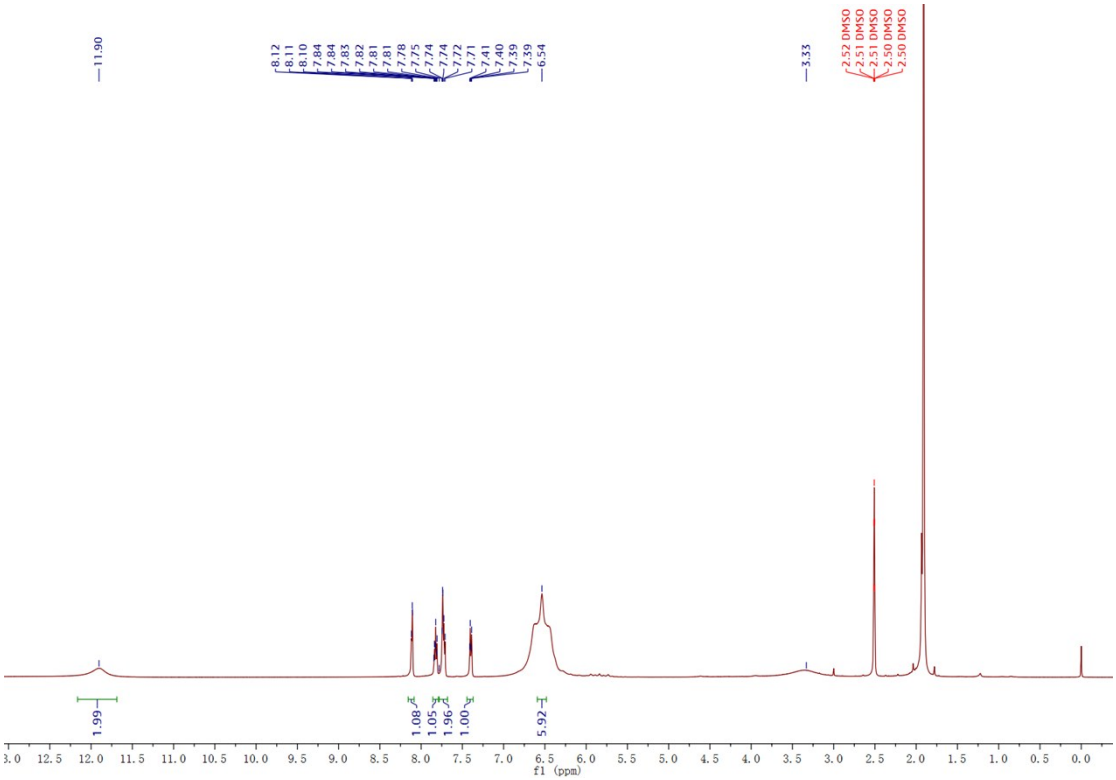

Figure S11. ^{1}H NMR (500MHz, DMSO-d_6) for **Pt-3**.

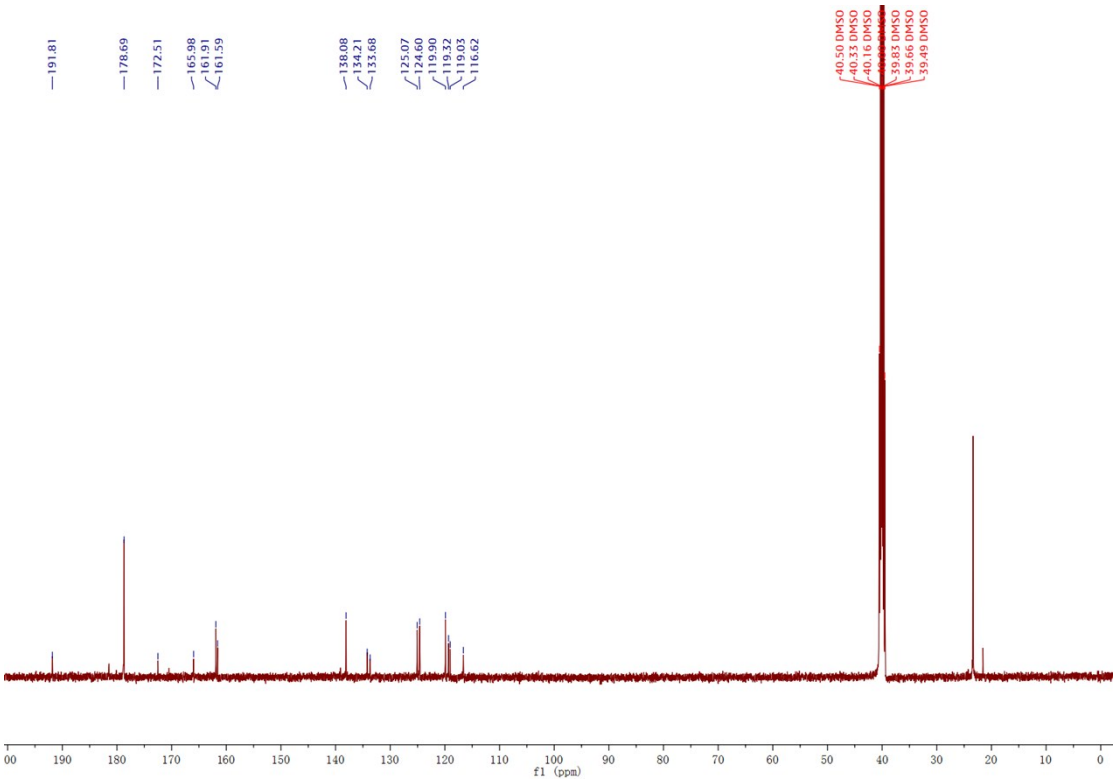

Figure S12. ^{13}C NMR (126MHz, DMSO-d_6) for **Pt-3**.

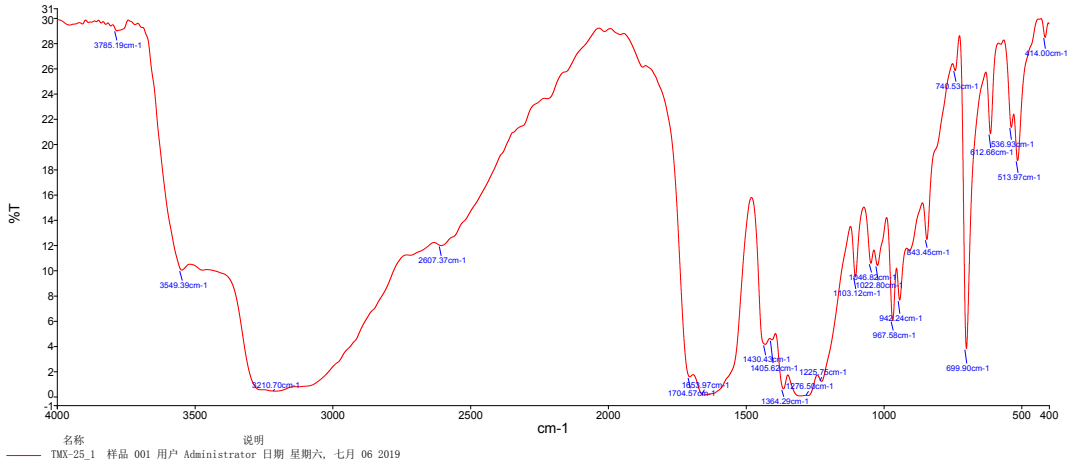

Figure S13. IR (KBr) spectra of **Pt-4.**

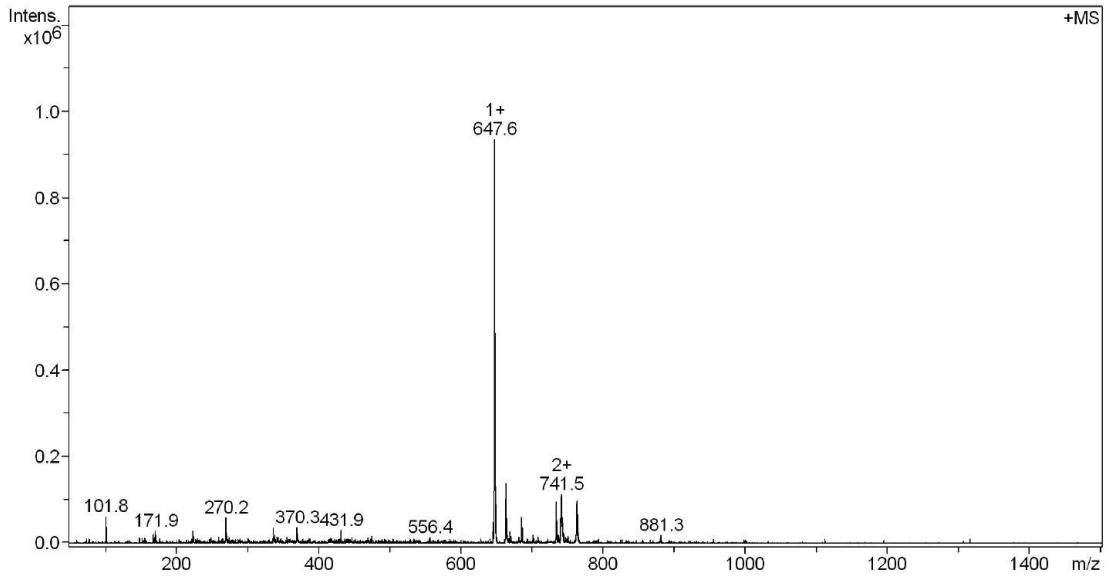

Figure S14. The mass spectra of **Pt-4** in Tris-HCl buffer solution (containing 5% DMSO) for 0 h.

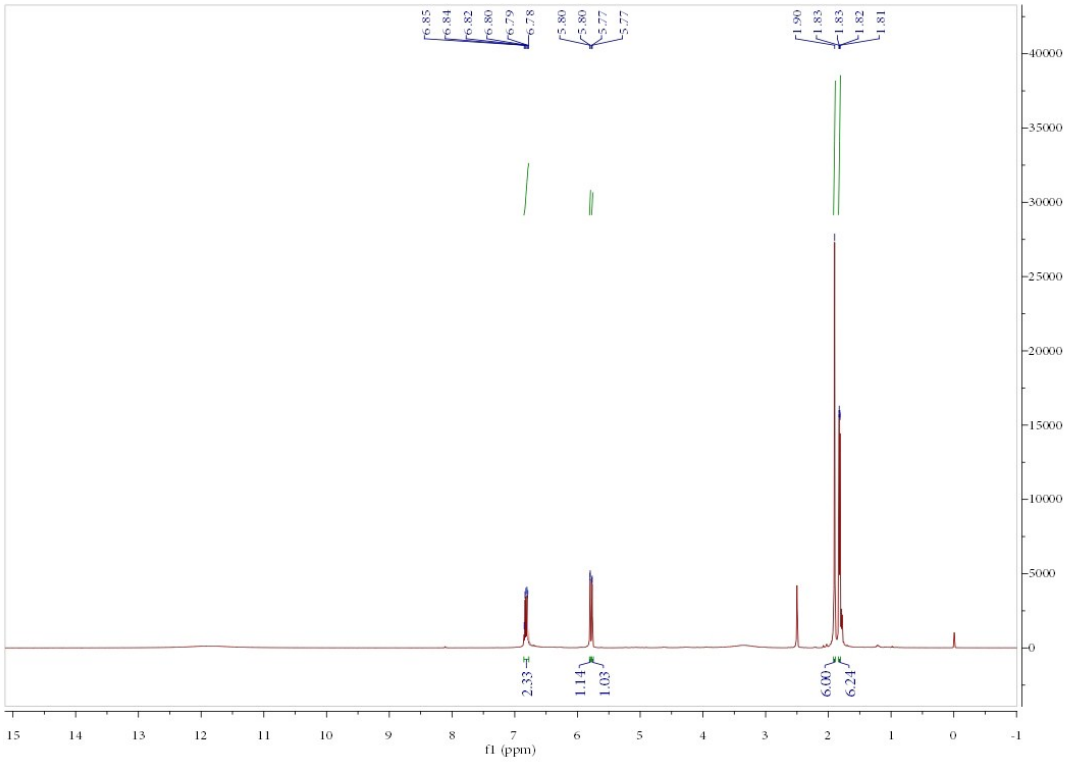

Figure S15. ^{1}H NMR (500MHz, DMSO-d_6) for **Pt-4**.

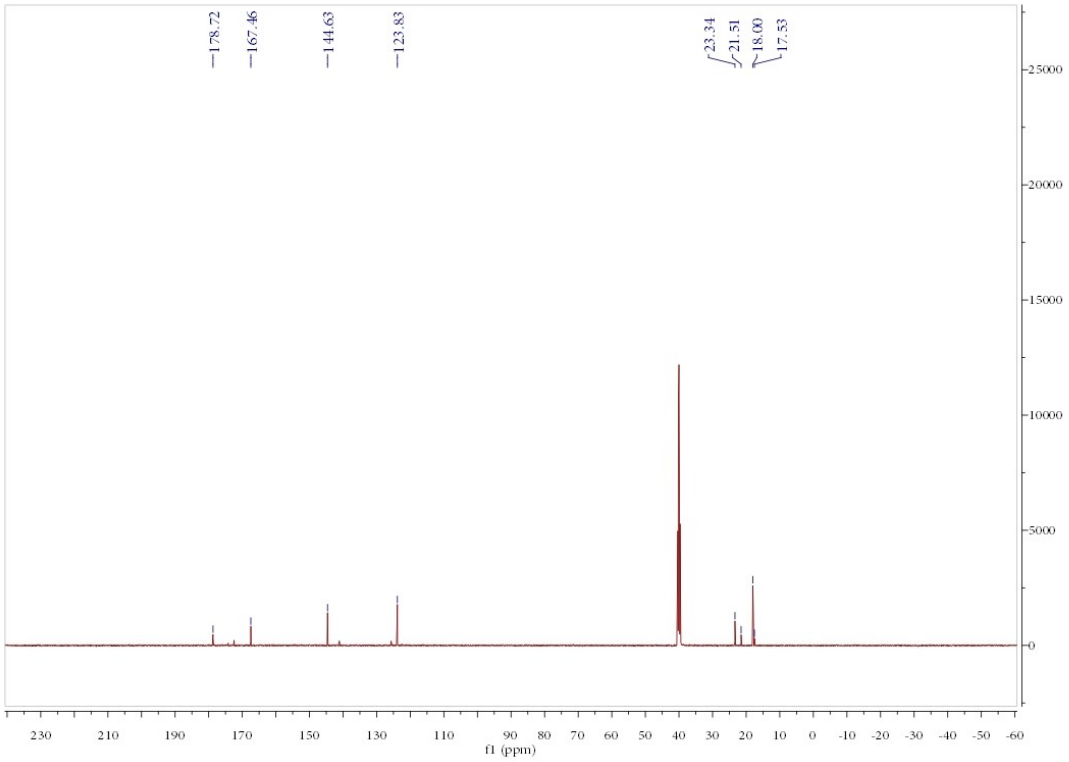

Figure S16. ^{13}C NMR (126MHz, DMSO-d_6) for **Pt-4**.

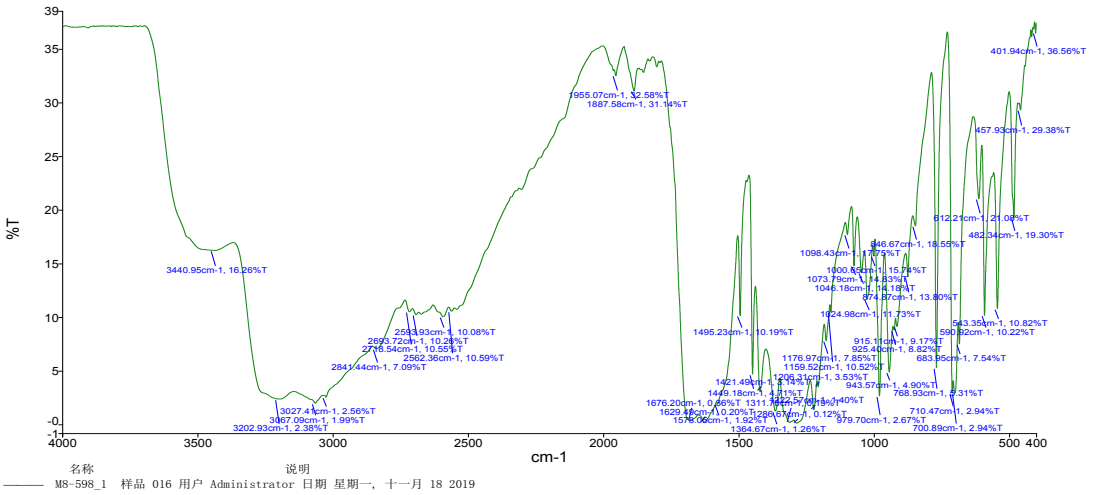

Figure S17. IR (KBr) spectra of **Pt-5.**

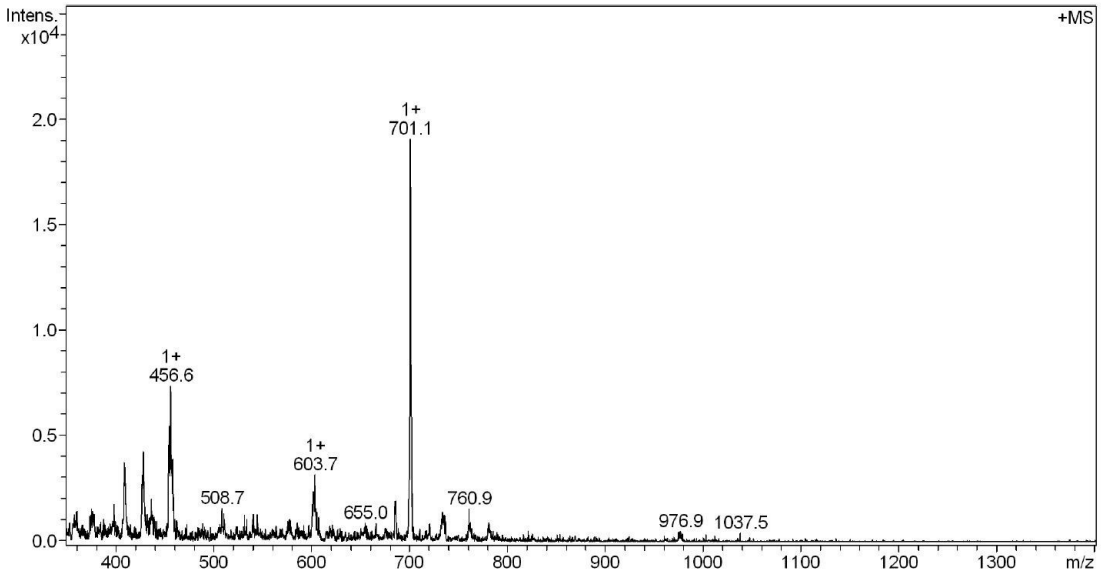

Figure S18. The mass spectra of **Pt-5** in Tris-HCl buffer solution (containing 5% DMSO) for 0 h.

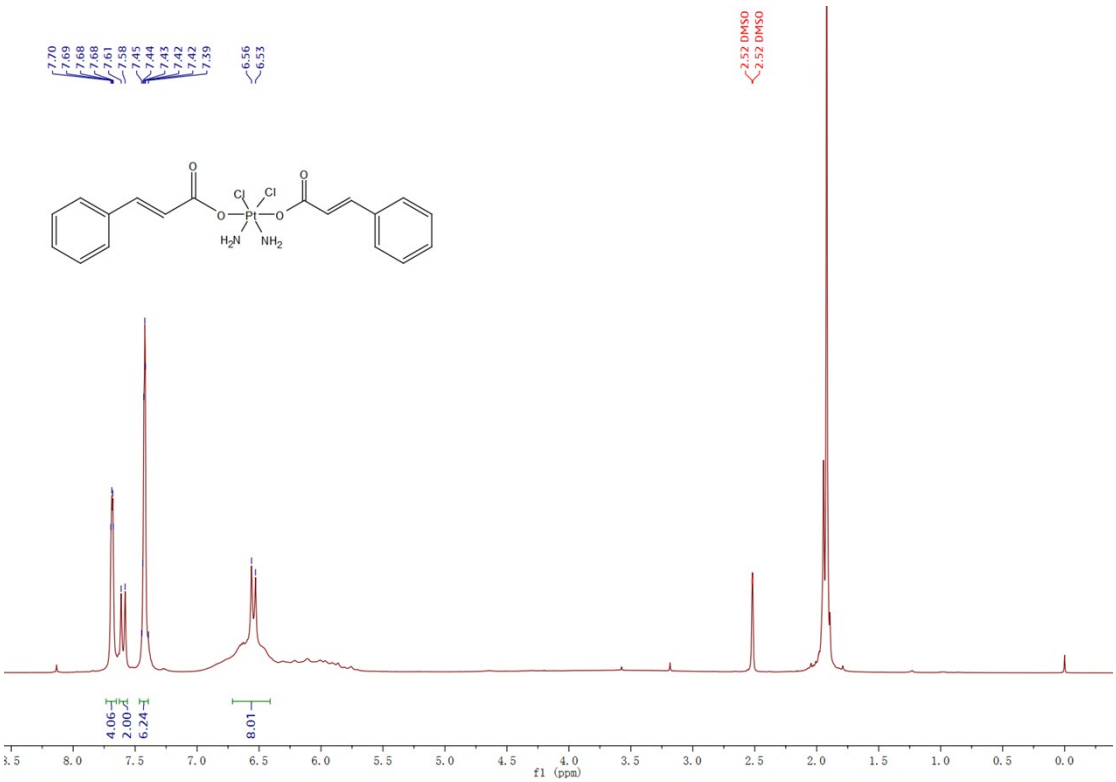

Figure S19. ^{1}H NMR (500MHz, DMSO-d_6) for **Pt-5**.

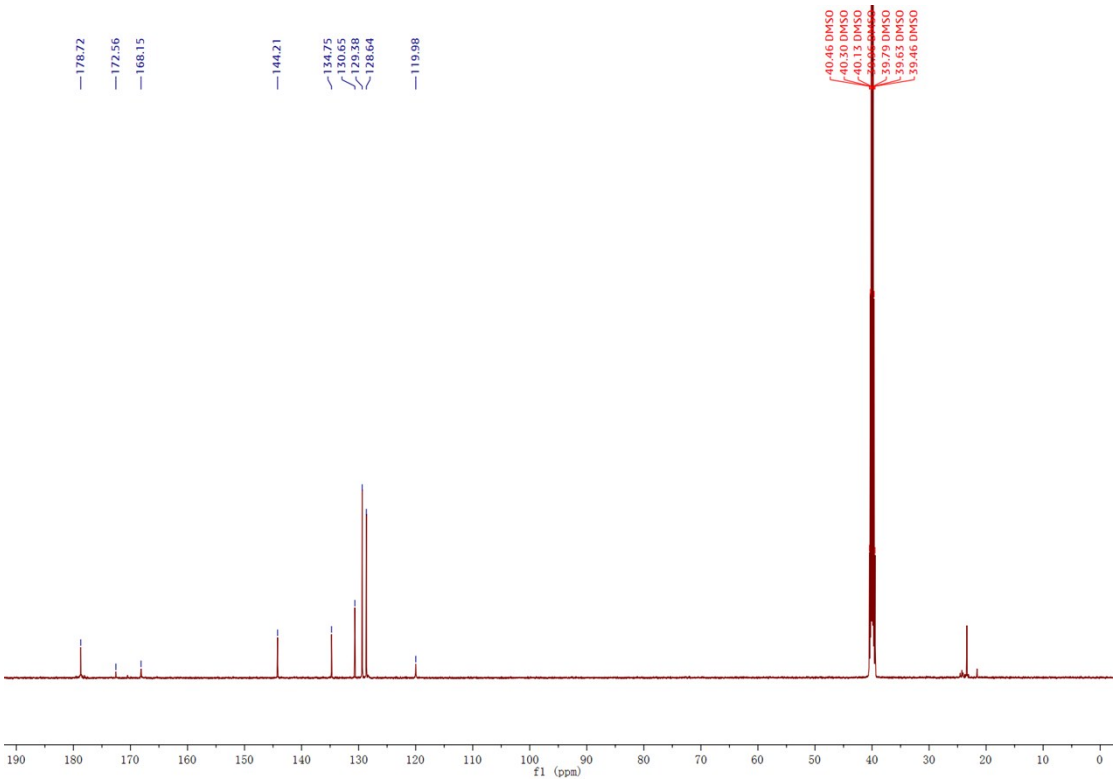

Figure S20. ^{13}C NMR (126MHz, DMSO-d_6) for **Pt-5**.

Table S1. The tumor volume in treated and non-treated mice from the date of surgery to the study end point in the A549/DDP xenograft model.

Group	Tumor Volume (mm^3)		T/C (%)
	(start)	(end)	
control group	79.91±0.82	1208.31±24.82	-
cisplatin (2.0 mg/kg per 2 days)	79.90±0.30	803.10±15.40	66.46[a]
Pt-2 (2.0 mg/kg per 2 days)	80.00±0.20	864.00±50.00	71.43[a]
Pt-3 (2.0 mg/kg per 2 days)	79.70±0.60	386.40±31.90	32.06[a]

[a] mean $p<0.05$, *p vs* vehicle control

Table S2. Average body weight in treated and non-treated mice from the date of surgery to the study end point in the A549/DDP xenogfart model.

Group	Body Weight (g)		RBW (%)
	(start)	(end)	(end)
control group	19.40±0.34	21.43±0.26	110.48 [a]
cisplatin (2.0 mg/kg per 2 days)	19.20±0.30	21.00±0.10	109.66 [a]
Pt-2 (2.0 mg/kg per 2 days)	19.70±0.10	21.20±0.30	107.80 [a]
Pt-3 (2.0 mg/kg per 2 days)	19.50±0.30	21.00±0.20	107.71 [a]

[a] mean $p<0.05$, *p vs* control.

Table S3. In vivo anticancer activity of complexes (2.0 mg/kg per 2 days) toward A549/DDP tumor xenograft.

Group	average tumor weight(mean ± SD g)	inhibition of tumor growth(%)
control group	1.626±0.029	-
cisplatin (2.0 mg/kg per 2 days)	1.222±0.028	33.05 [a]
Pt-2 (2.0 mg/kg per 2 days)	1.269±0.044	28.12 [a]
Pt-3 (2.0 mg/kg per 2 days)	0.971±0.010	67.45 [a]

[a] mean $p<0.05$, *p vs* control.

Anti-cancer activity toward A549/DDP tumor xenograft *in vivo*

A549/DDP cells were harvested and injected subcutaneously into the right flank of nude mice with 5.0×10^6 cells in 200 μL of serum-free medium. When the xenograft tumor growth to the volume about 1000 mm^3, the mice were killed and the tumor tissue were cut into about 1.5 mm^3 small pieces, and then transplanted into the right flank of female nude mice, When tumors reach a volume of 80-190 mm^3 on all mice, the mice were randomized into vehicle control and treatment groups (n=6/group), received the following treatments: (a) control, 5.0% v/v DMSO/saline vehicle, (b) **Pt-2** at dose 2.0 mg/kg every two day (5.0% v/v DMSO/saline), (c) **Pt-3** at dose 2.0 mg/kg every two day (5.0% v/v DMSO/saline), (d) cisplatin at dose 2.0 mg/kg every two day (5.0% v/v DMSO/saline). The tumor volumes were determined every three days by measuring length (*l*) and width (*w*) and calculating volume, tumor volume and inhibition of tumor growth were calculated using formulas 1−3:

Tumor volume: $V = (w^2\times l)/2$ (1)

The tumor relative increment rate: $T/C\ (\%) = T_{RTV}/C_{RTV}\times100\%$ (2)

inhibition of tumor growth: $IR(\%) = (W_c - W_t)/W_c\times100\%$ (3)

Where w and l mean the shorter and the longer diameter of the tumor respectively; T_{RTV} and C_{RTV} was the RTV of treated group and control group respectively. (RTV: relative tumor volume, $RTV= V_t /V_0$); W_t and W_c mean the average tumor weight of complex-treated and vehicle controlled group respectively.

Statistical Analysis

The experiments have been repeated from three to five times, and the results obtained are presented as means ± standard deviation (SD). Significant changes were assesses by using Student's *t* test for unpaired data, and p values of <0.05 were

considered significant.

Abbreviations

MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; TGI, tumor growth inhibition; PI, propidium iodide; MMP, mitochondrial membrane potential; IR, tumor growth inhibition rate.