Multi-specific Niflumic Acid Platinum(IV) Complexes Displaying Potent Antitumor Activities by Improving Immunity and Suppressing Angiogenesis besides Causing DNA Damage

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‡ These author contributed equally to this work.

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1. Supplementary figures for organ index

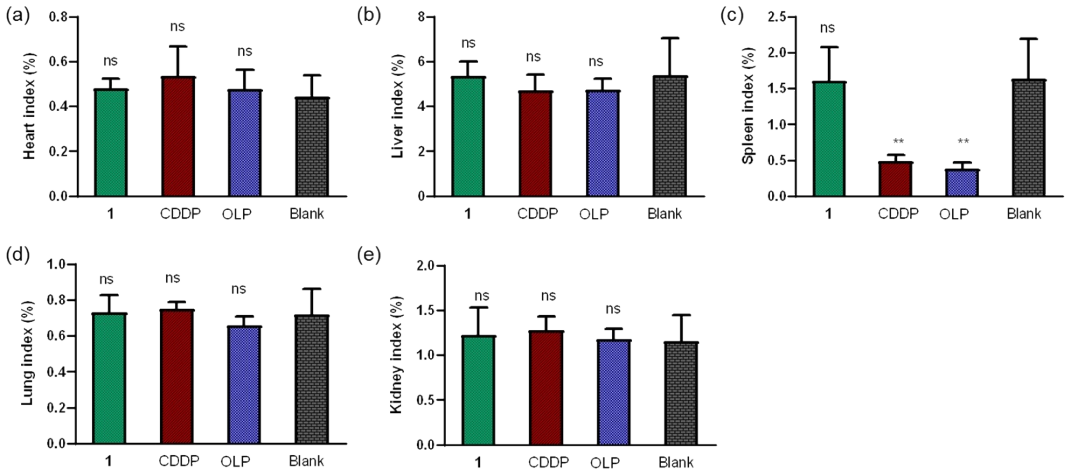


Figure S1. The organ index of BALB/c mice from compound **1**, CDDP and OLP treated groups in comparison with blank group (n = 5). (a) Heart. (b) Liver. (c) Spleen. (d) Lung. (e) Kidney. Organ index = weight of organ/body weight × 100%. Unpaired t-tests were applied for statistic tests. $^{**}P < 0.01$, *ns*: no significant difference compared with control group.

2. Supplementary figures for wound healing assay

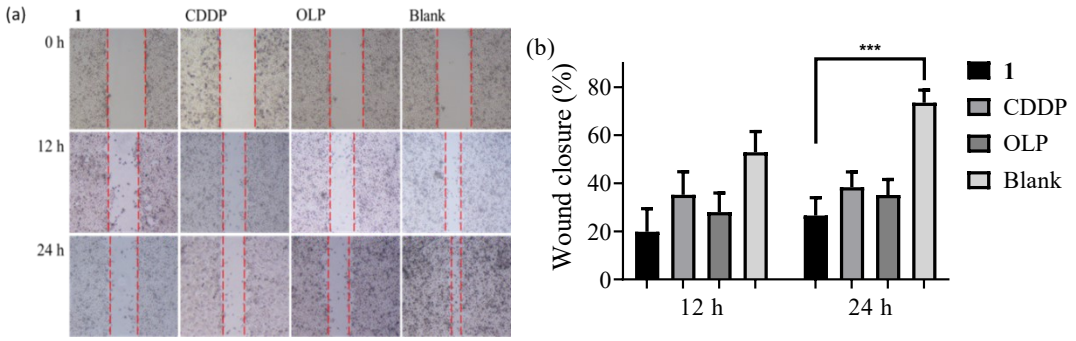


Figure S2. Migration inhibition properties of complex **1**, CDDP, and OLP at 10 μM to 4T1 cells *in vitro*. The extent of wound healing was observed at 0, 12, and 24 h. Results were determined based on three parallel experiments. Unpaired t-tests were applied for statistic tests. (a) Representative images. (b) Analysis of wound closure. $^{***}P < 0.001$.

3. Supporting information for compound Log$P_{o/w}$

Table S1. Log$P_{o/w}$ values of the platinum complexes **1**, CDDP and OLP.

Compound	Log$P_{o/w}$
1	1.96±0.24
CDDP	-2.30[S1]
OLP	-1.54[S1]

4. Supplementary figures for DNA damage

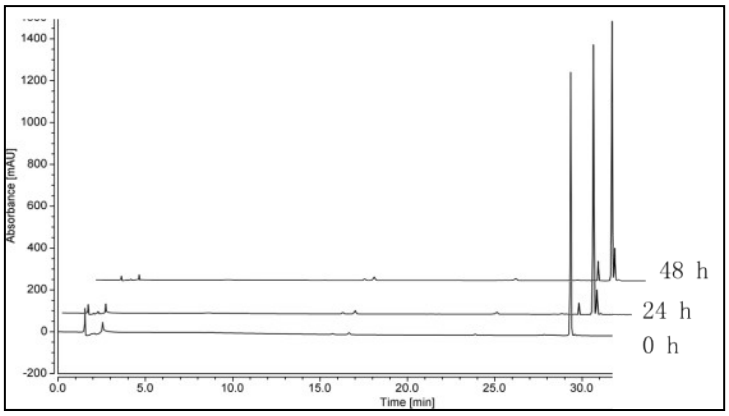


Figure S3. Stability of complex **1** in RPMI1640 in 48 h.

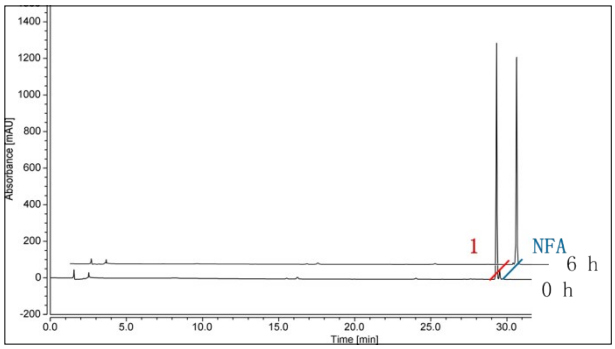


Figure S4. Reduction of complex **1** in RPMI1640 in the presence of AsA (1 mM).

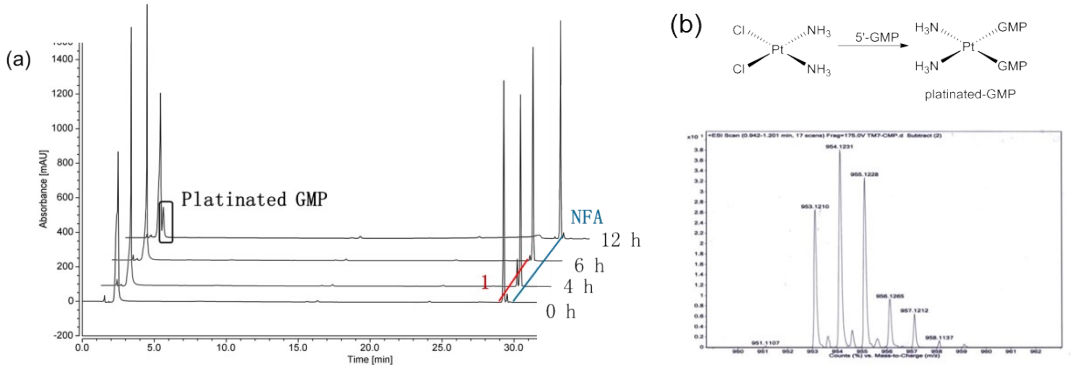


Figure S5. DNA damage properties of complex **1** in RPMI1640 in the presence of AsA (1 mM) and GMP (3 mM). (a) Spectra at different time. (b) HRMS of platinated-GMP peak.[S2]

5. Supplementary information for synthetic procedure

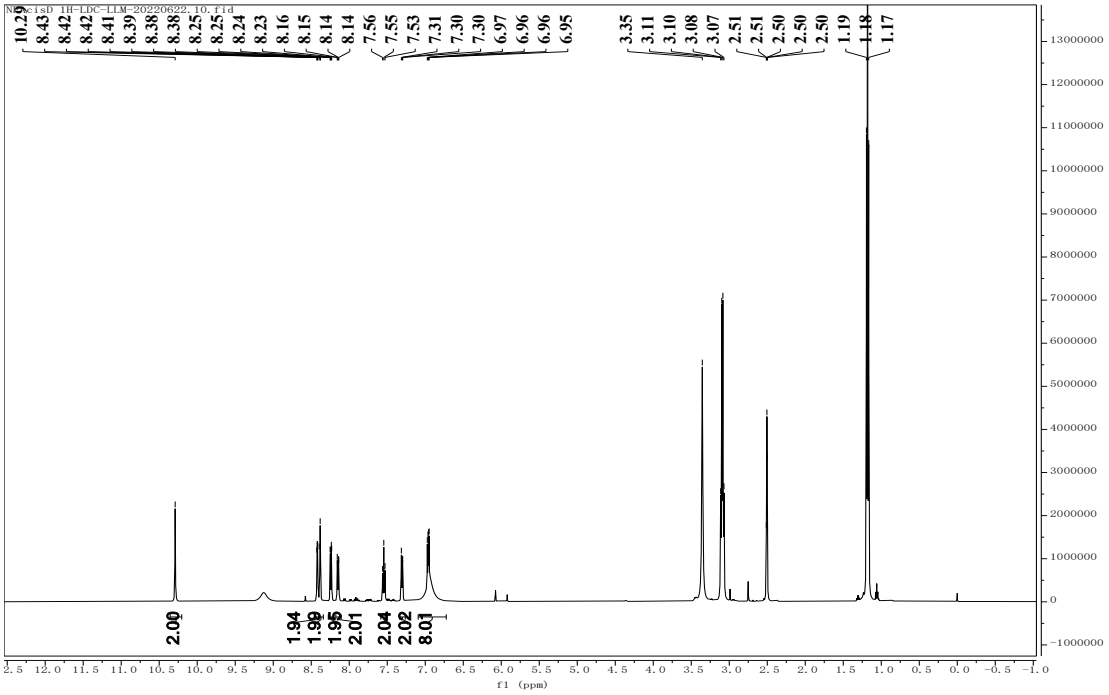
5.1 Preparation of oxoplatin **O1**[S3-S5]

Cisplatin (1.0 g, 3.3 mmol) was suspended in distilled water 30 mL and stirred at room temperature. Then H_2O_2 (30%) 50 mL was added drop wise, then the suspension was stirred at 60 °C for 4 h. Then the resultant mixture was recrystallized at 4 °C. The crude product **B1** was obtained as yellow solid after filtration. The further recrystallization in water afford pure compound **O1** as yellow crystals (0.71 g, 65%).

5.2 Preparation of oxoplatin **O2**[S2-S4]

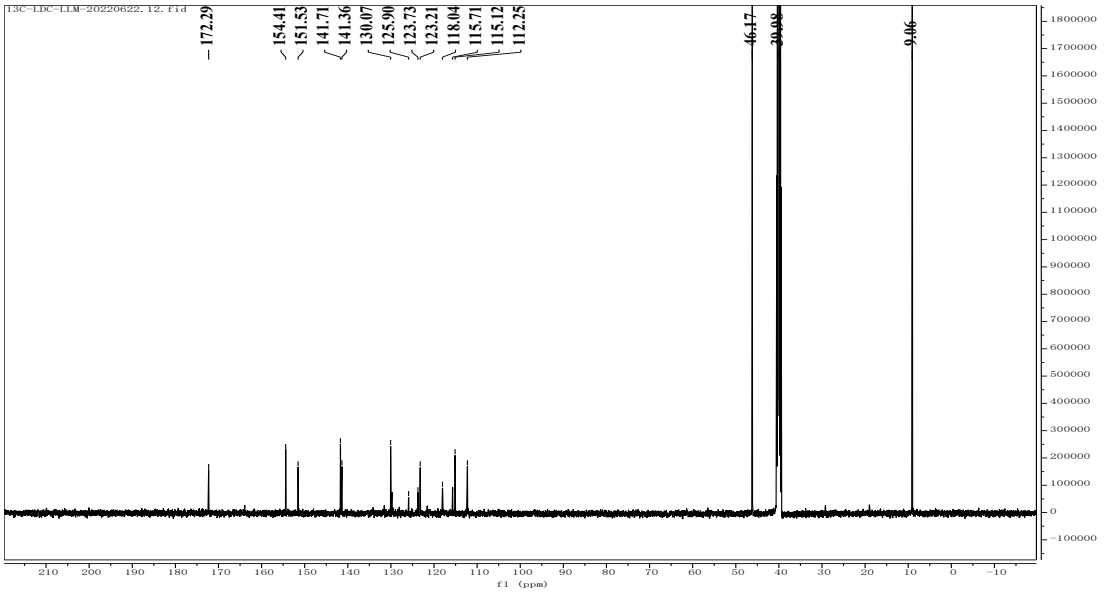
A suspension of oxaliplatin (1.0 g, 2.5 mmol) in distilled water 30 mL was stirred at room temperature. Then H_2O_2 (30%) 50 mL was added drop wise. The mixture was kept stirring for 4 h at 60 °C. Then the resultant mixture was recrystallized at 4 °C. Crude product as yellow solid was obtained after filtration. Then recrystallization in water afforded pure oxoplatin as white needles (0.67 g, 63%).

6. NMR, ESI-MS, HRMS and HPLC spectra



* Peaks at 1.18 (t) and 3.09 (q) are ascribed to Et_2O.

Figure S6. ^{1}H NMR spectrum for complex **1** in DMSO-d_6.



* Peaks at 9.1 and 46.2 are ascribed to Et_2O.

Figure S7. $^{13}C\{^{1}H\}$ NMR spectrum for complex **1** in DMSO-d_6.

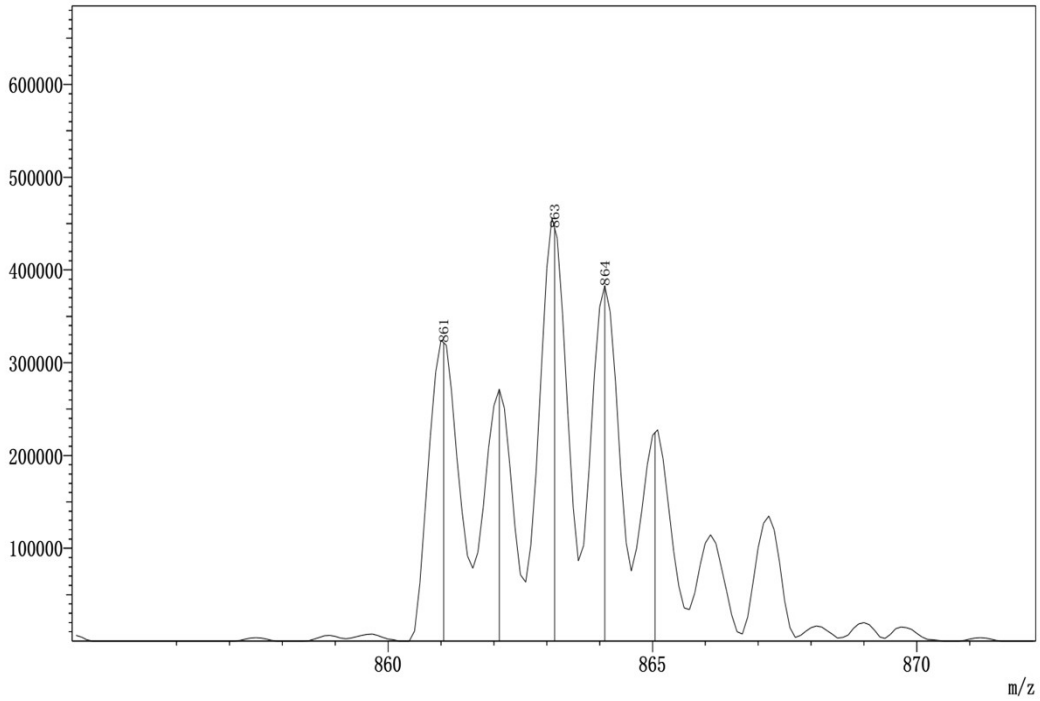


Figure S8. MS spectrum for complex **1**.

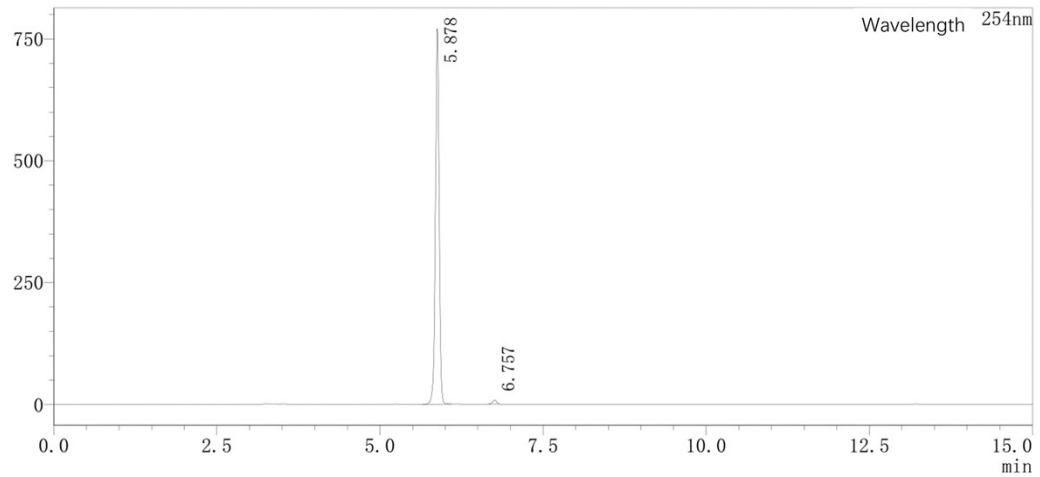


Figure S9. HPLC spectrum for complex **1**.

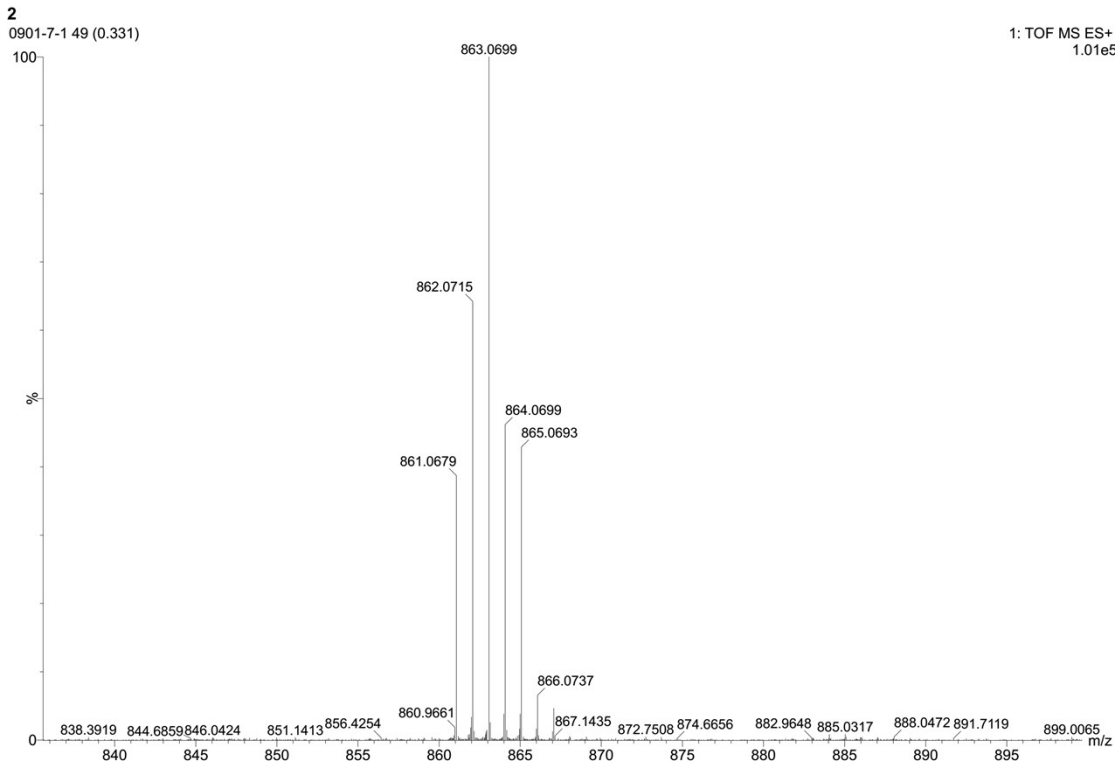


Figure S10. HRMS spectrum for complex **1**.

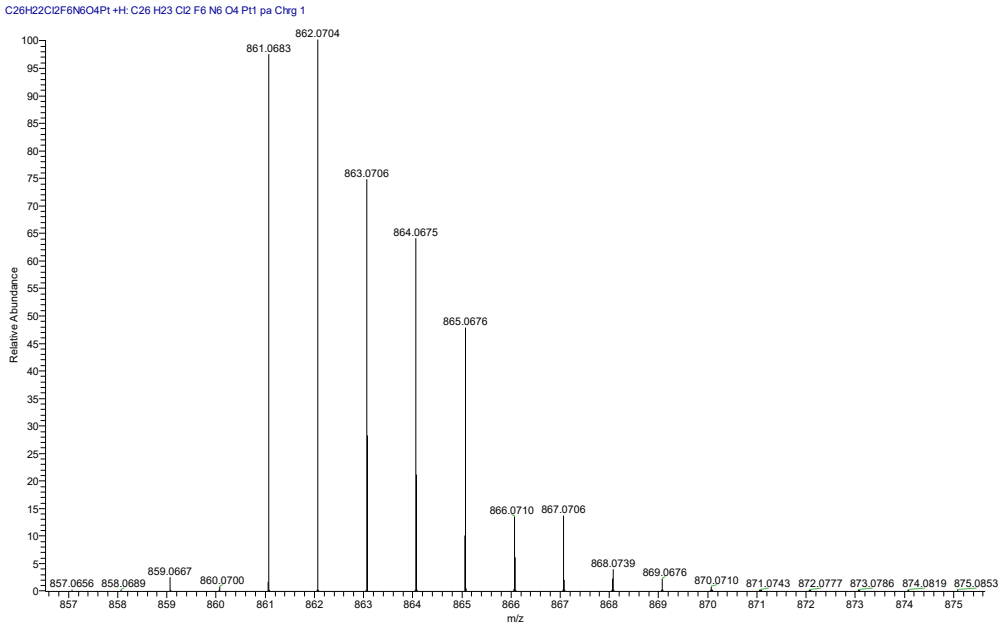


Figure S11. Theoretical isotopic patterns of HRMS for compounds **1**.

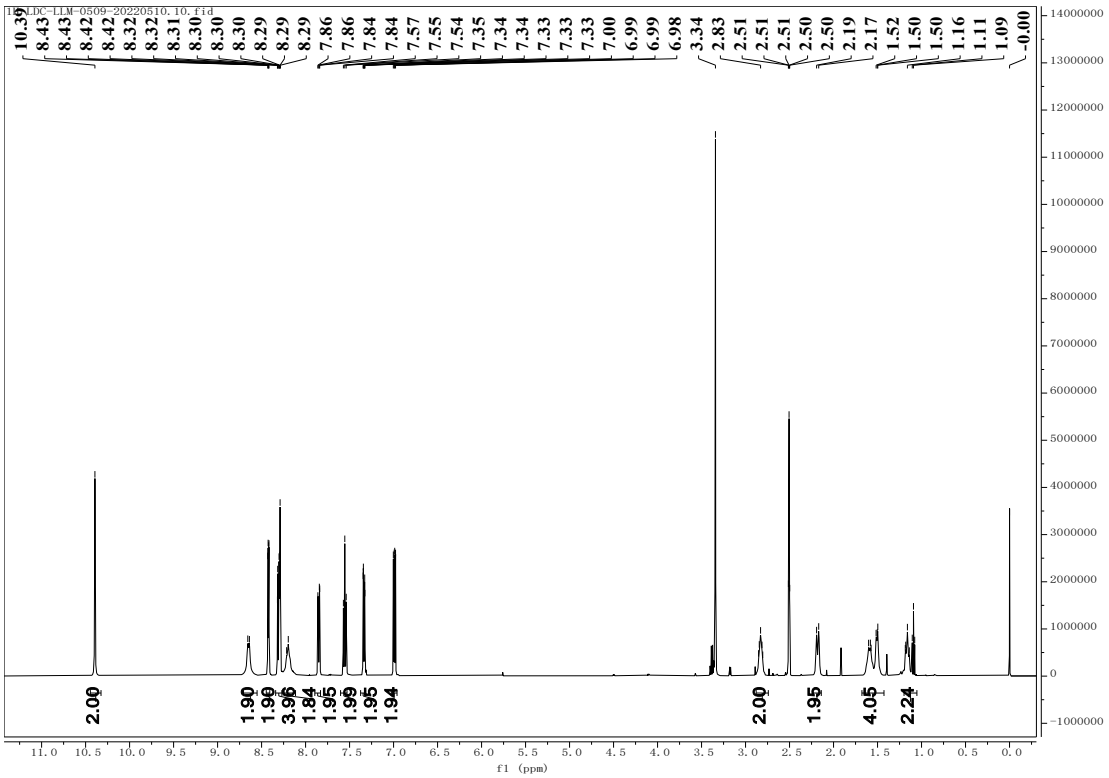


Figure S12. ^{1}H NMR spectrum for complex **2** in DMSO-d_6.

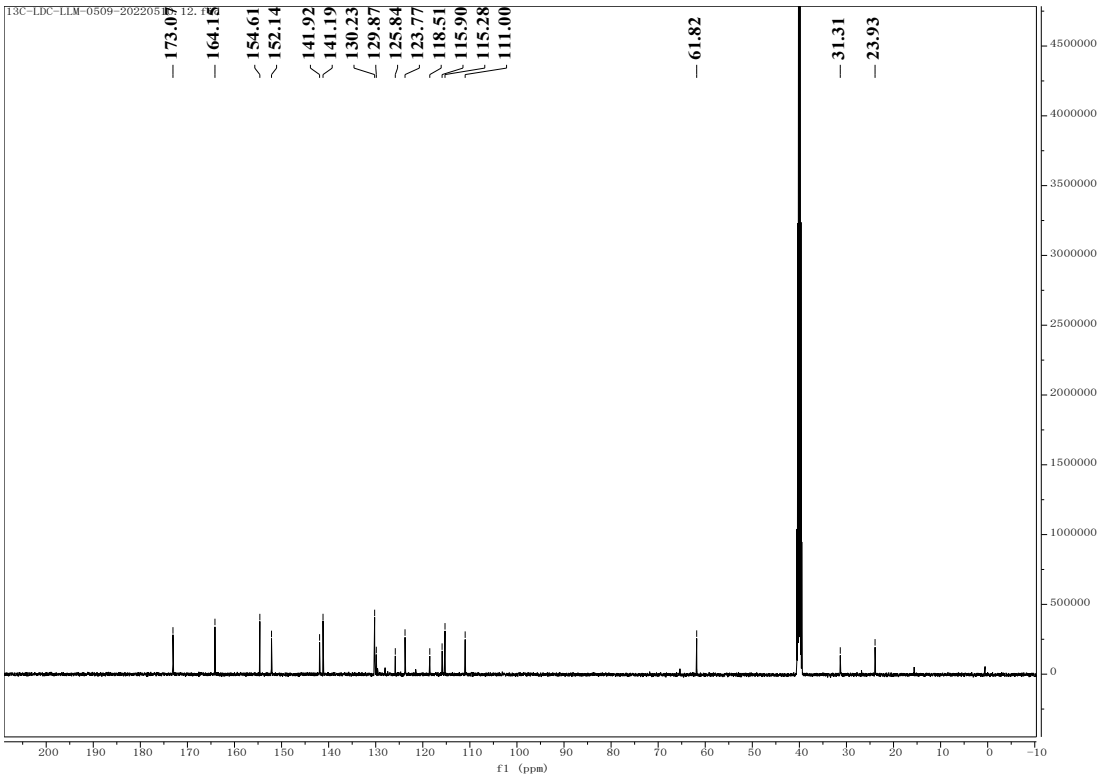


Figure S13. ^{13}C{^{1}H} NMR spectrum for complex **2** in DMSO-d_6.

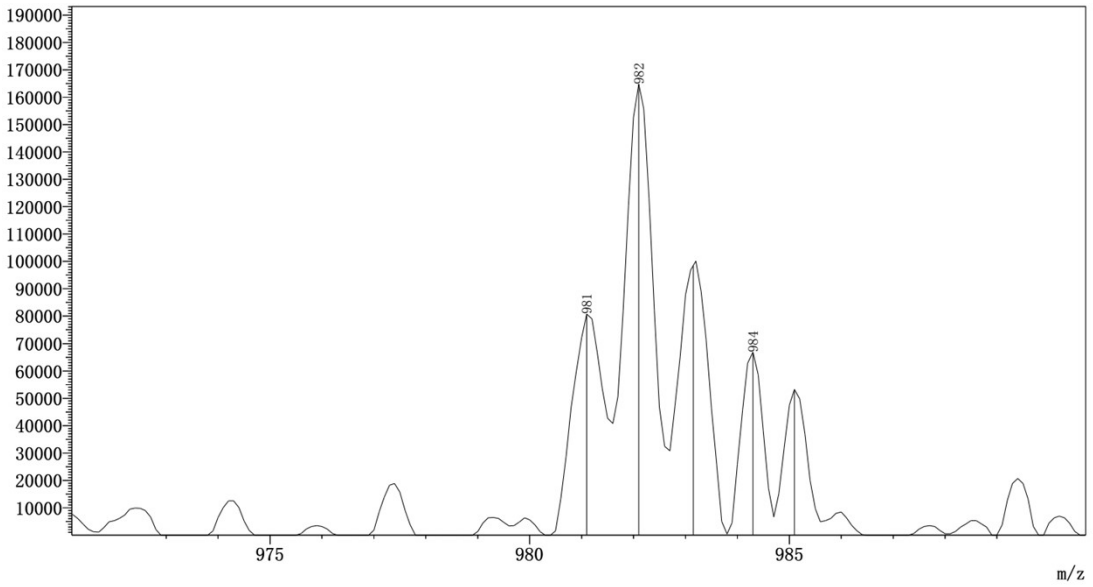


Figure S14. MS spectrum for complex **2**.

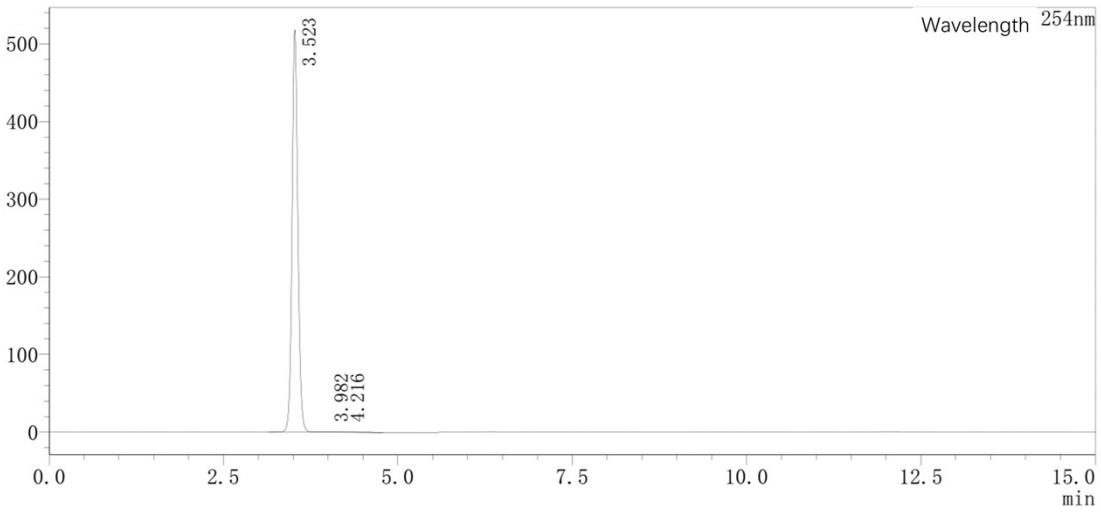


Figure S15. HPLC spectrum for complex **2**.

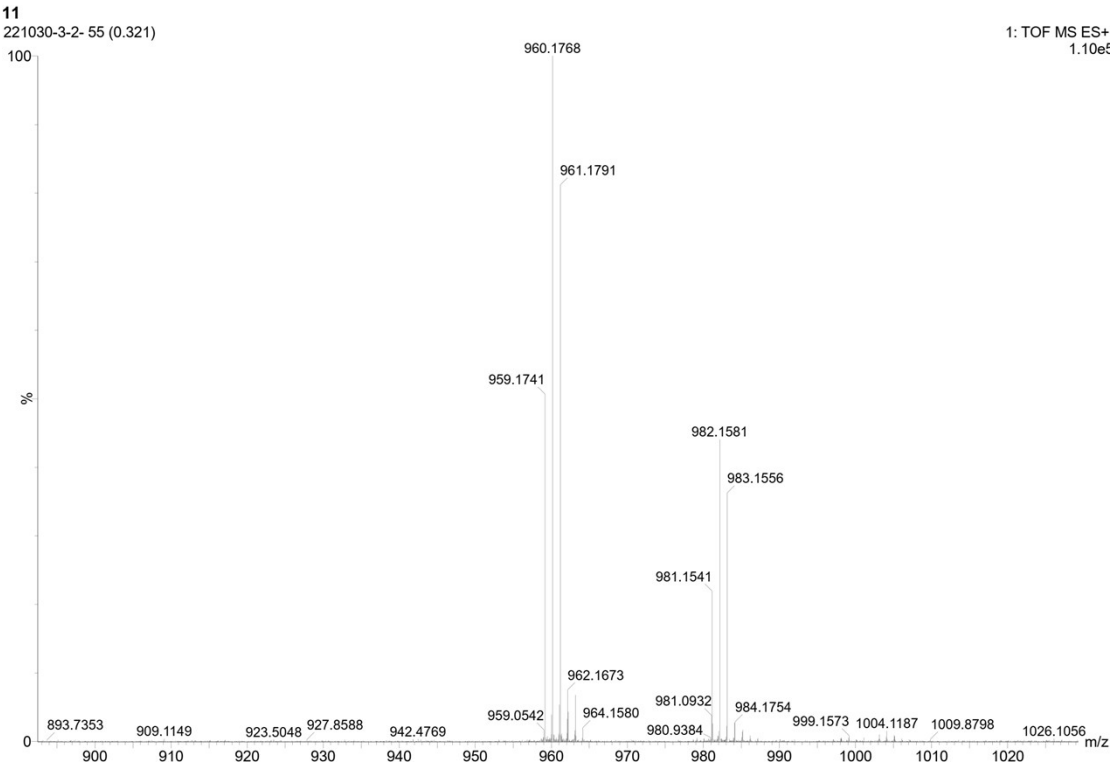


Figure S16. HRMS spectrum for complex **2**.

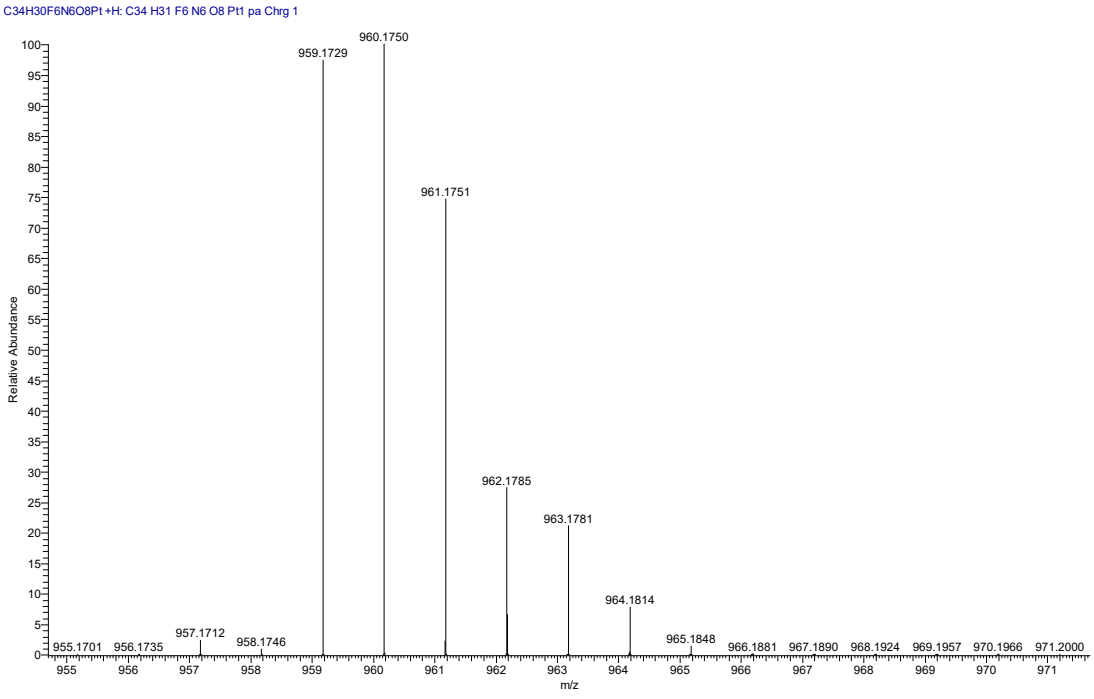


Figure S17. Theoretical isotopic patterns of HRMS for compounds **2**.

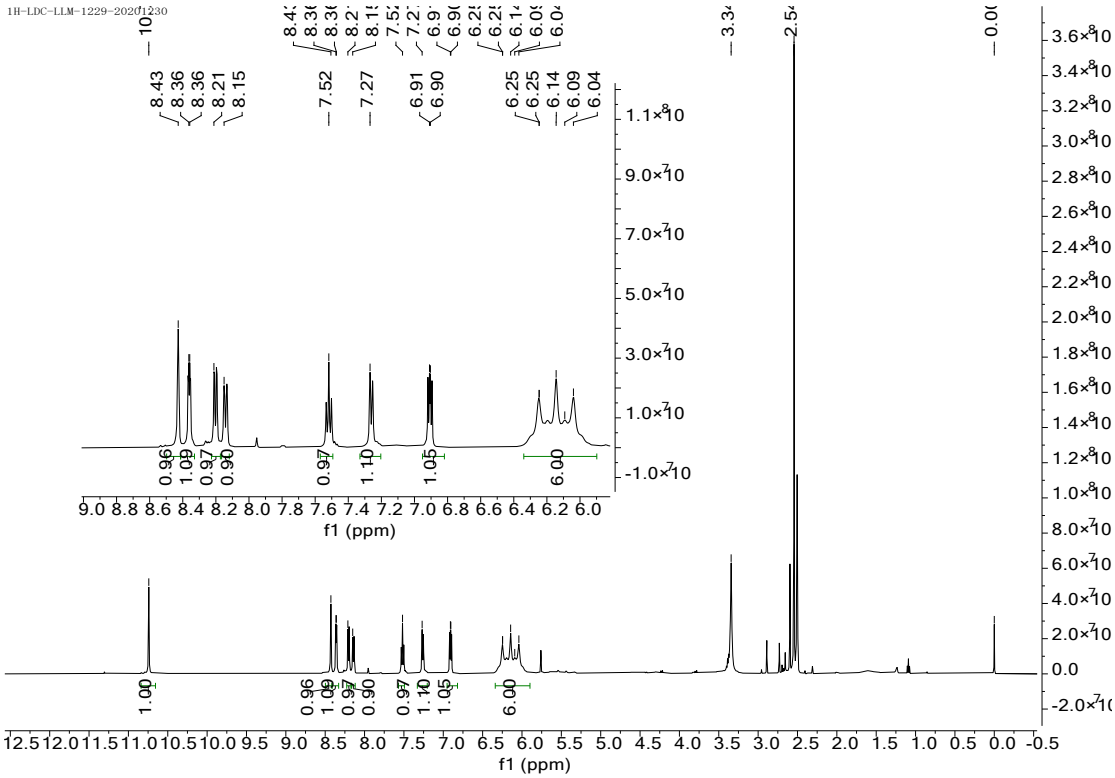


Figure S18. ^{1}H NMR spectrum for complex **3** in DMSO-d_6.

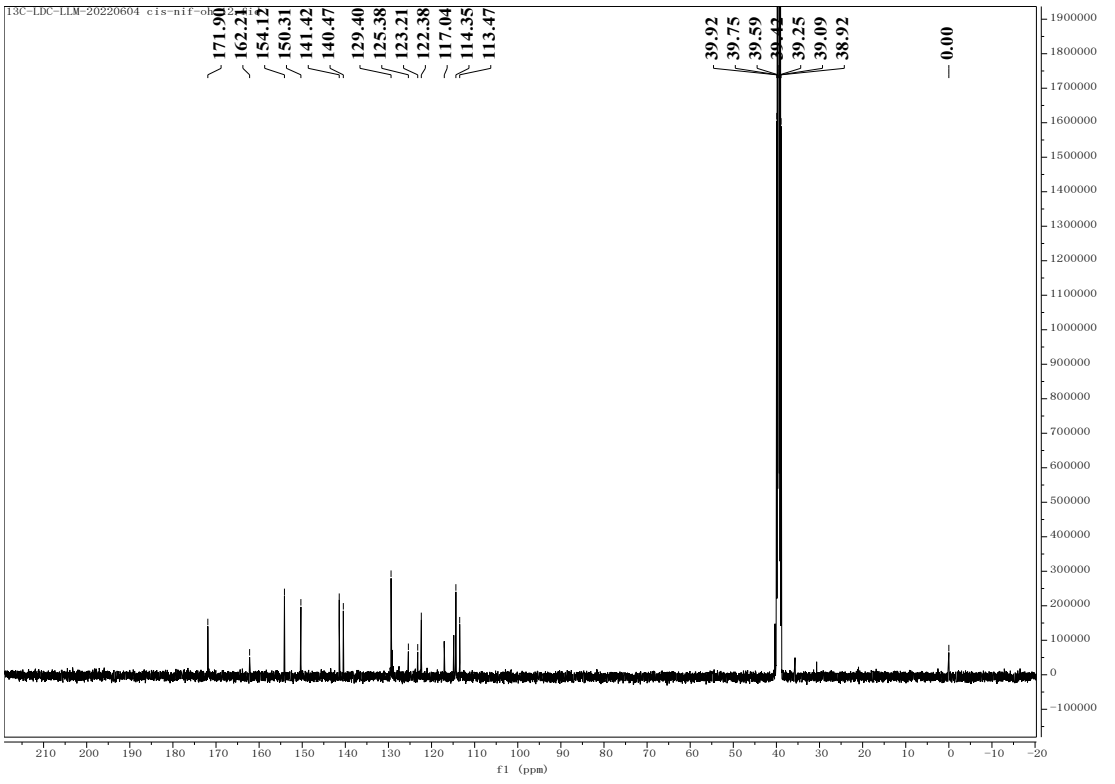


Figure S19. ^{13}C{^{1}H} NMR spectrum for complex **3** in DMSO-d_6.

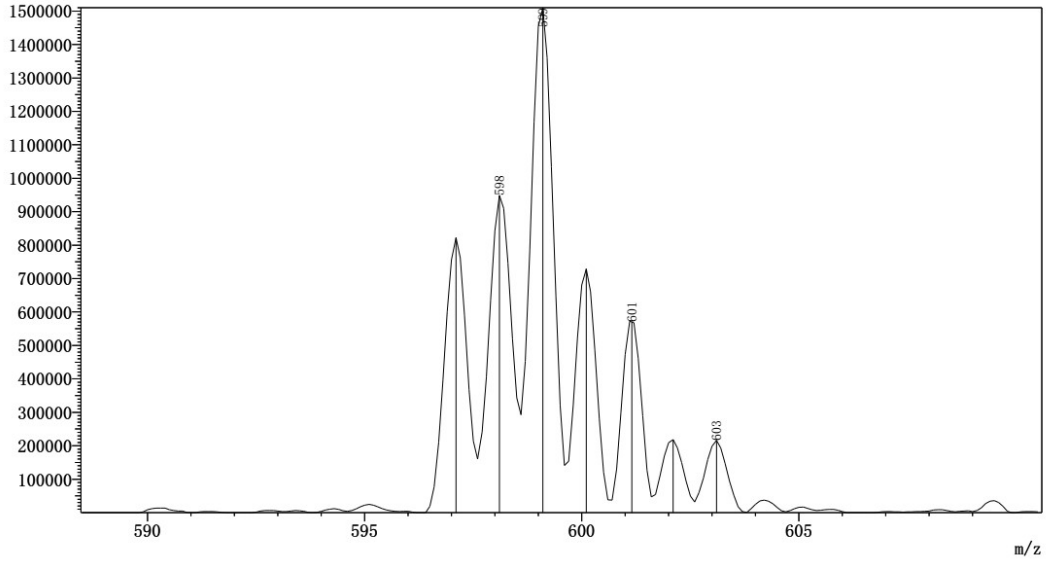


Figure S20. MS spectrum for complex **3**.

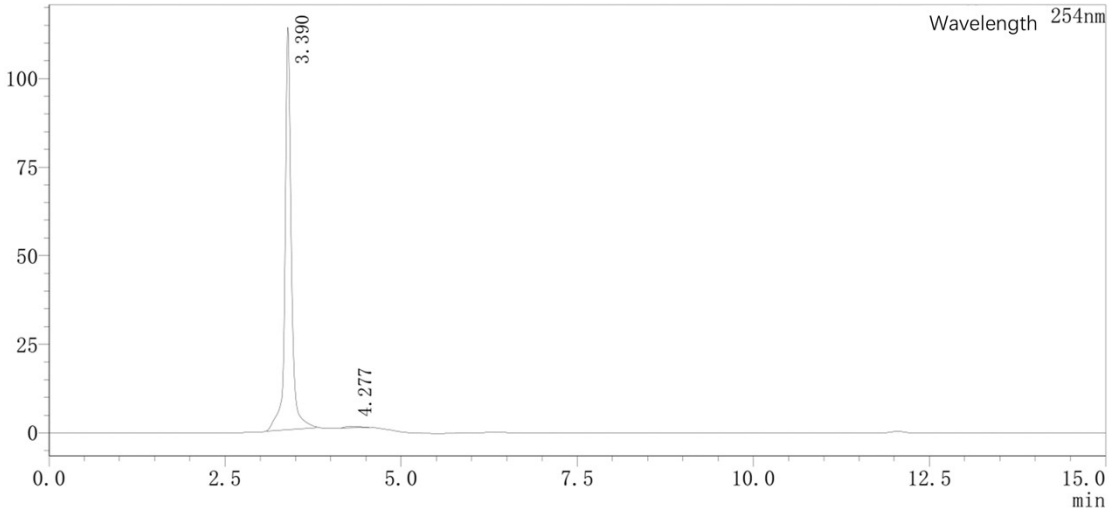


Figure S21. HPLC spectrum for complex **3**.

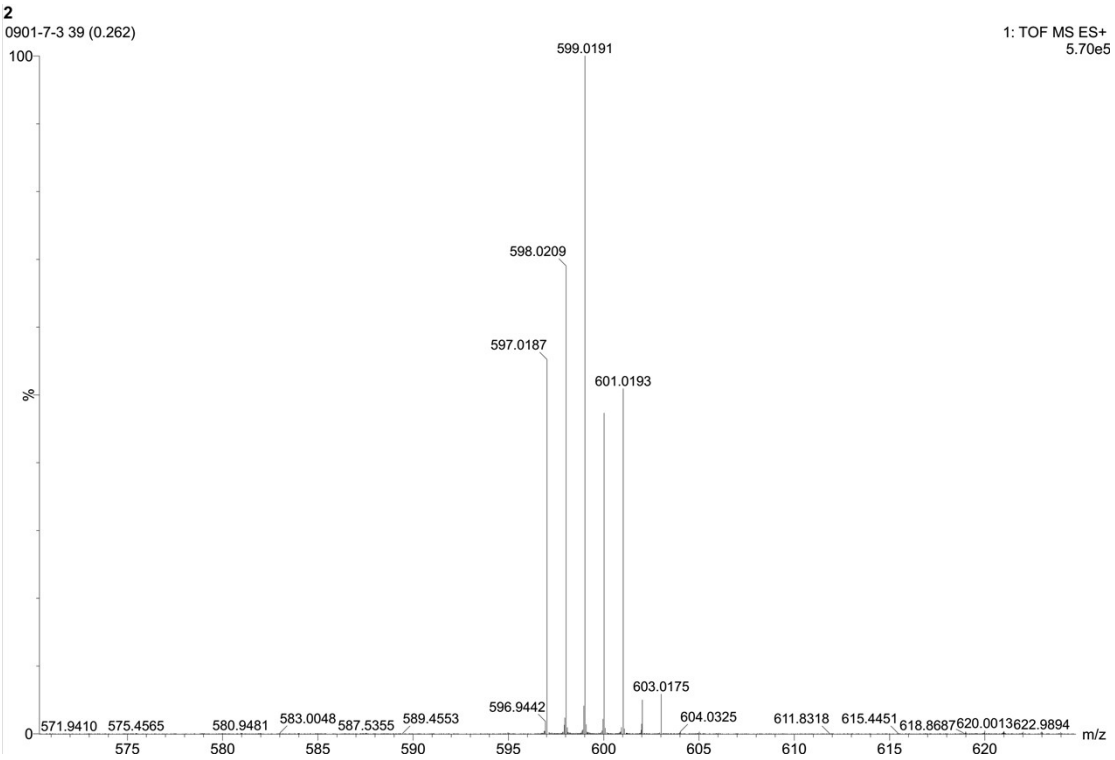


Figure S22. HRMS spectrum for complex **3**.

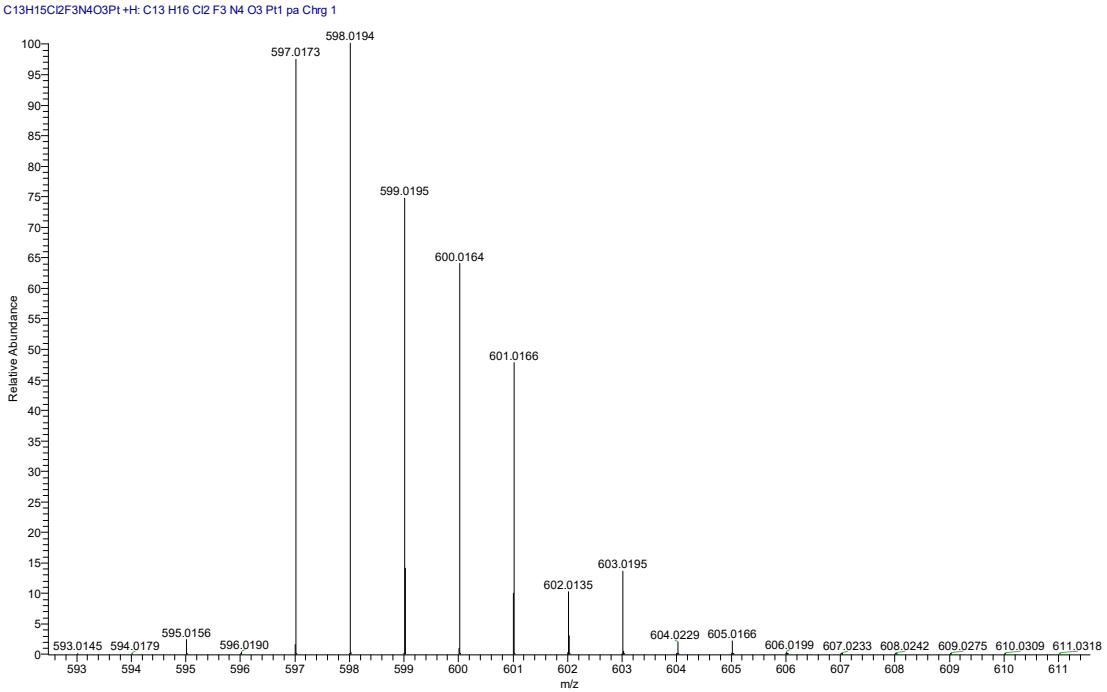


Figure S23. Theoretical isotopic patterns of HRMS for compounds **3**.

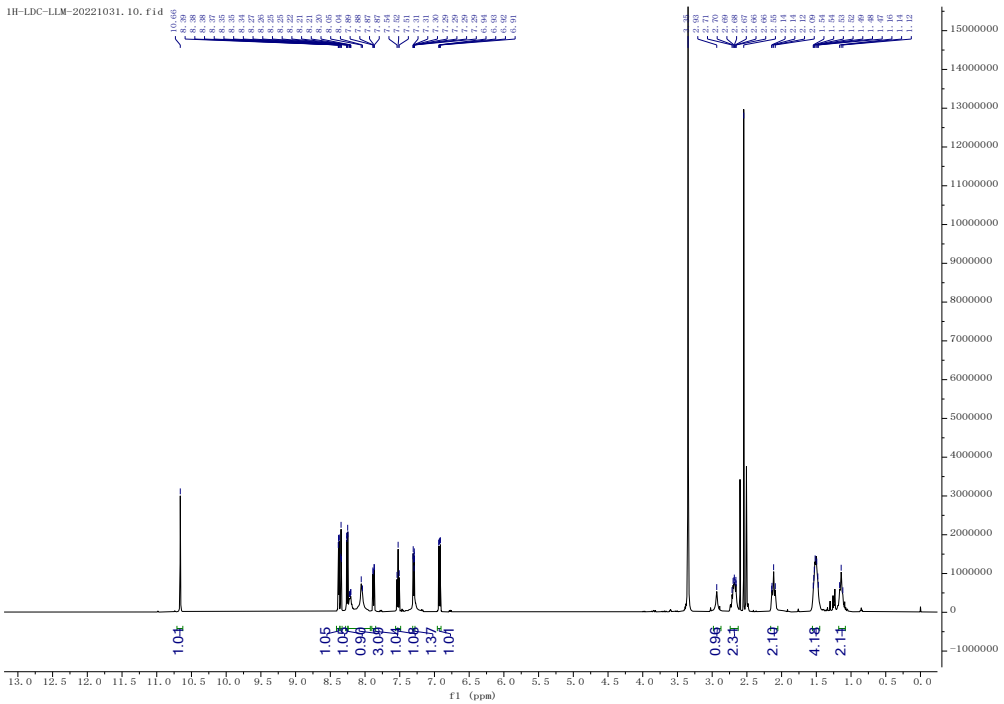


Figure S24. ^{1}H NMR spectrum for complex **4** in DMSO-d_6.

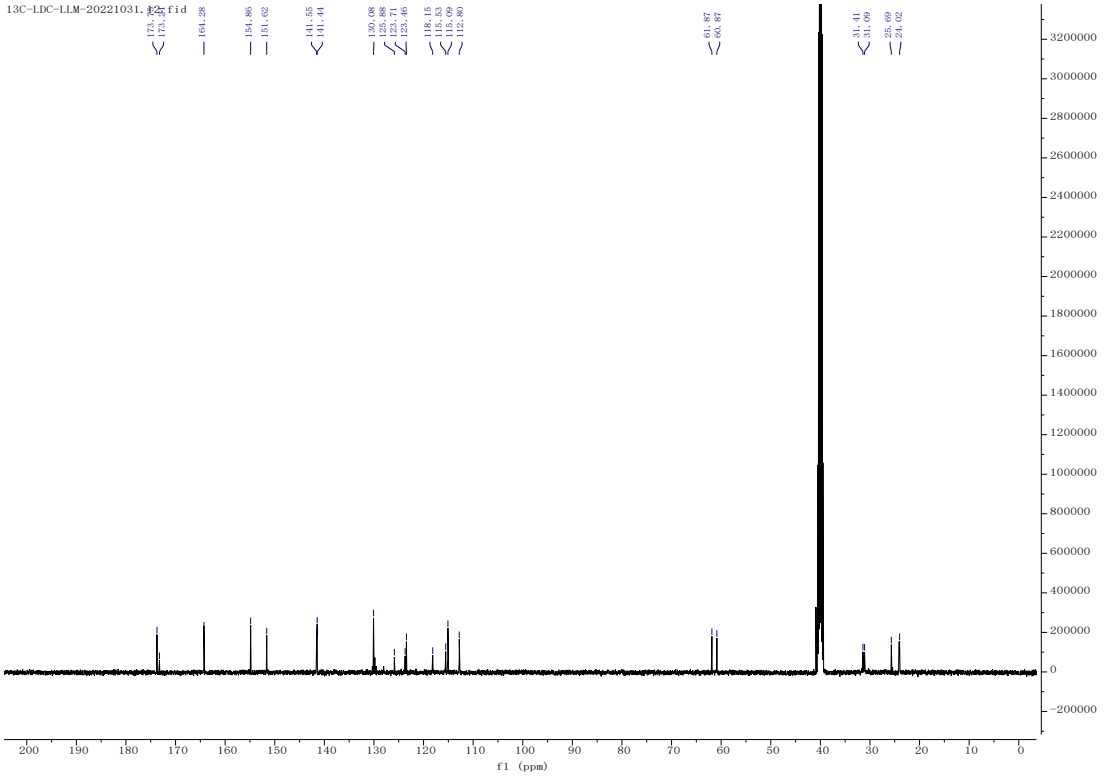


Figure S25. ^{13}C{^{1}H} NMR spectrum for complex **4** in DMSO-d_6.

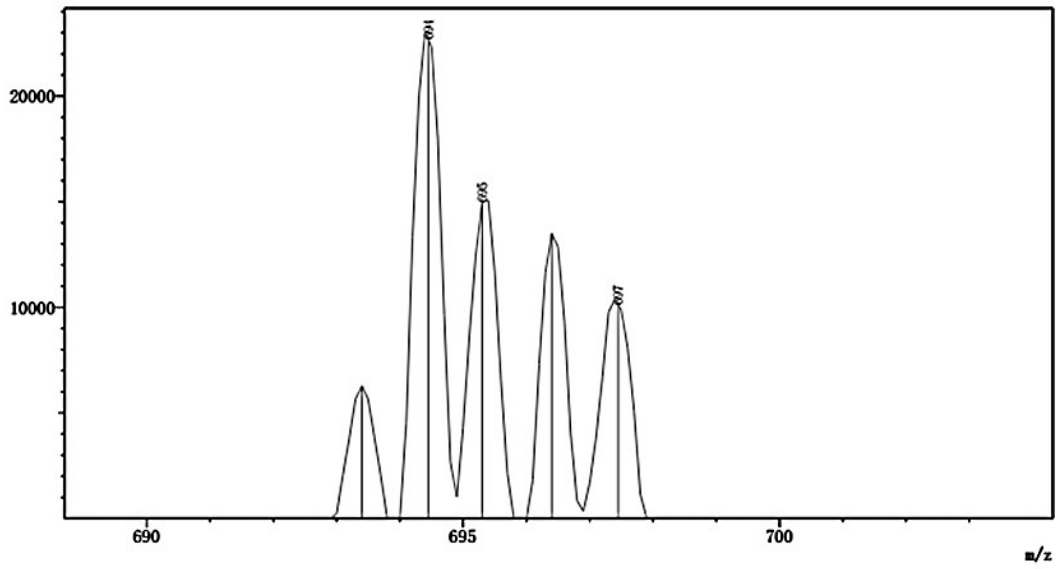


Figure S26. MS spectrum for complex **4**.

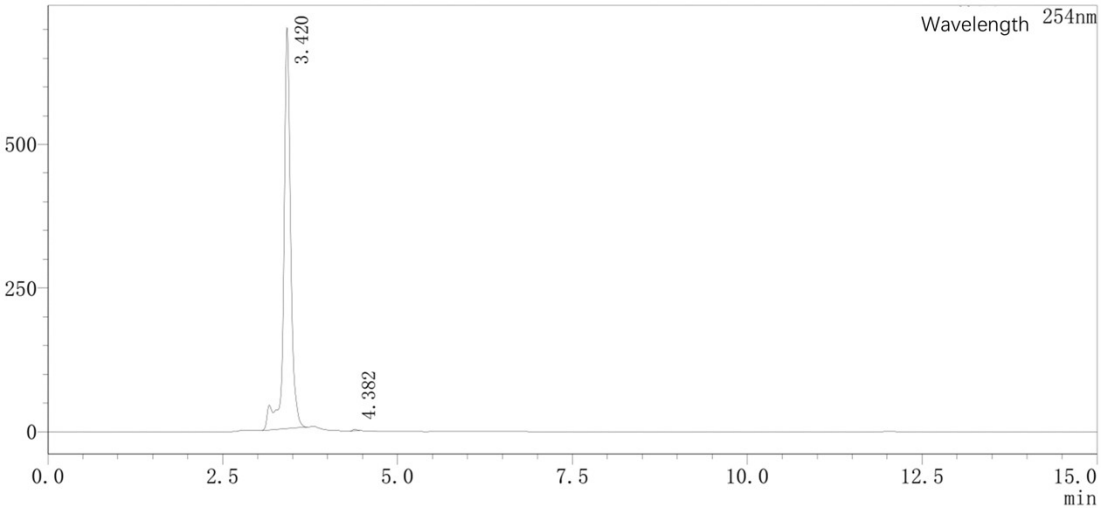


Figure S27. HPLC spectrum for complex **4**.

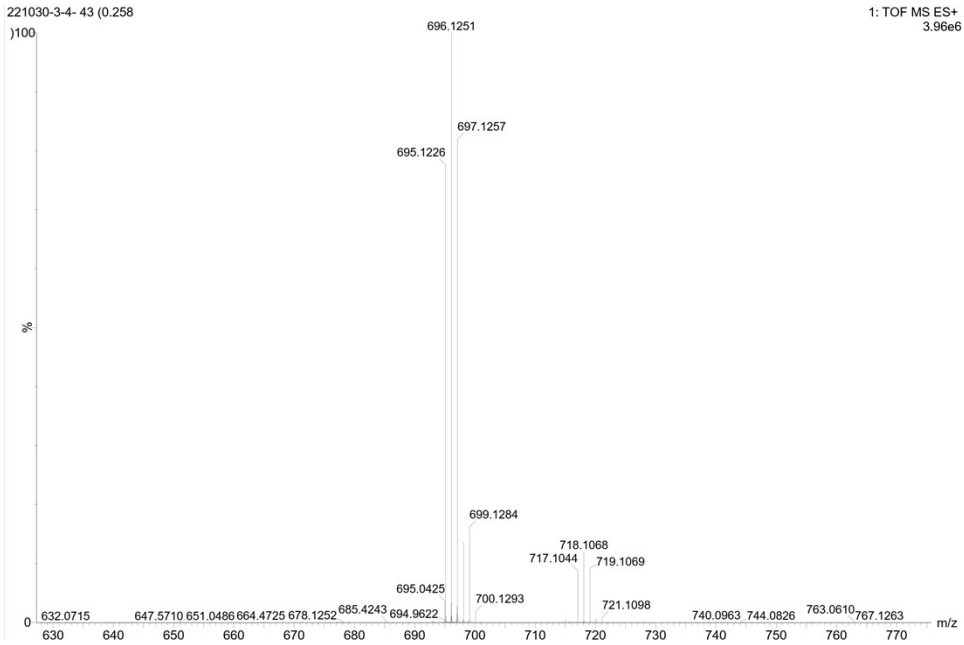


Figure S28. HRMS spectrum for complex **4**.

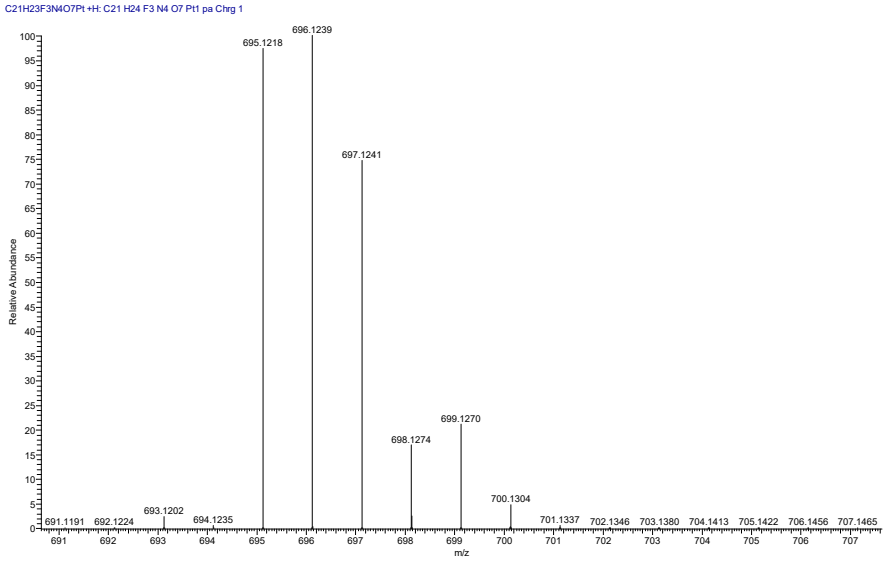


Figure S29. Theoretical isotopic patterns of HRMS for compounds **4**.

Reference

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synthesis and biological evaluation of a novel series of glycosylated platinum(IV) complexes as antitumor agents. *Dalton Trans.* **2016**, *45*, 10366–10374.

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