Supplementary Information for:

Improving the anticancer activity of platinum(IV) prodrugs using a dual-targeting strategy with dichloroacetate axial ligand

Fengfan Liu[a], Xiaomei Dong[a], Qiwen Shi[a], Jianli Chen[b], Weike Su[a,b]*

[a] *National Engineering Research Center for Process Development of Active Pharmaceutical Ingredients, Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, Zhejiang University of Technology, Hangzhou, P. R. China.*

[b] *College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou, P. R. China.*

Content

1. NMR spectra of complexes 1a-2b

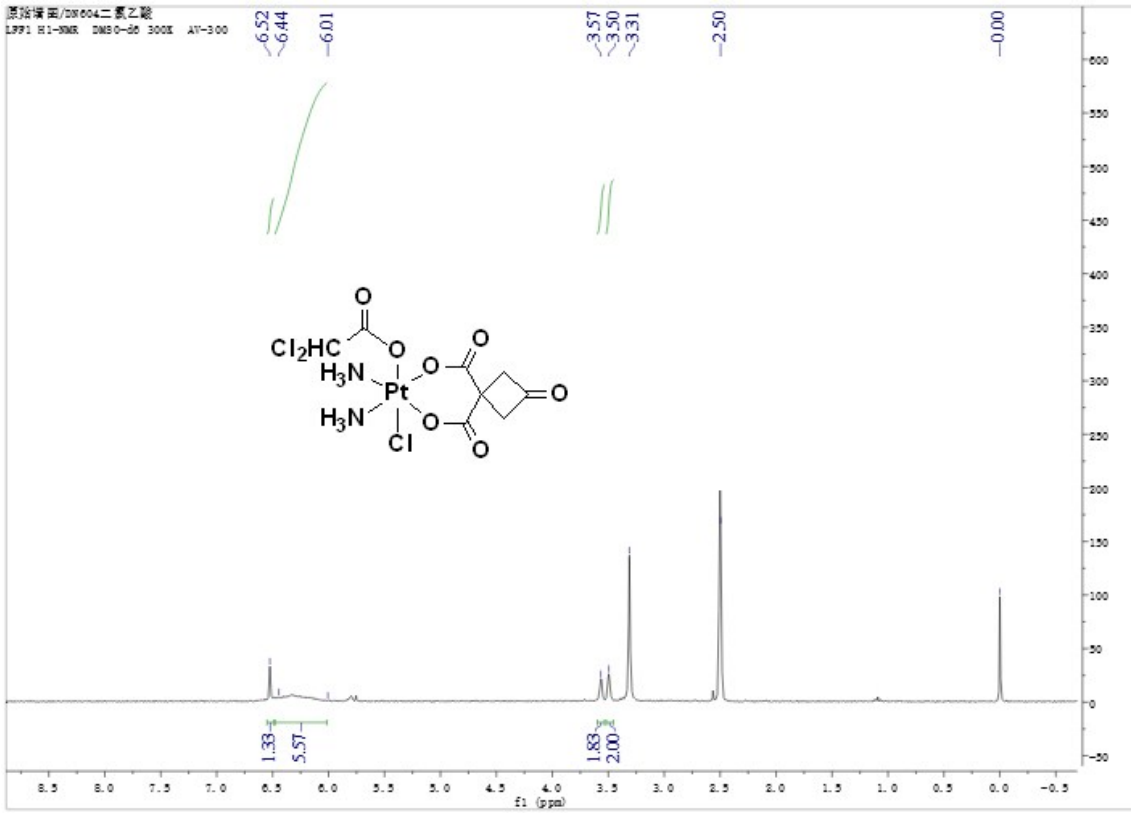

Fig. S1.[1]H NMR (DMSO) spectrum of complex 1a

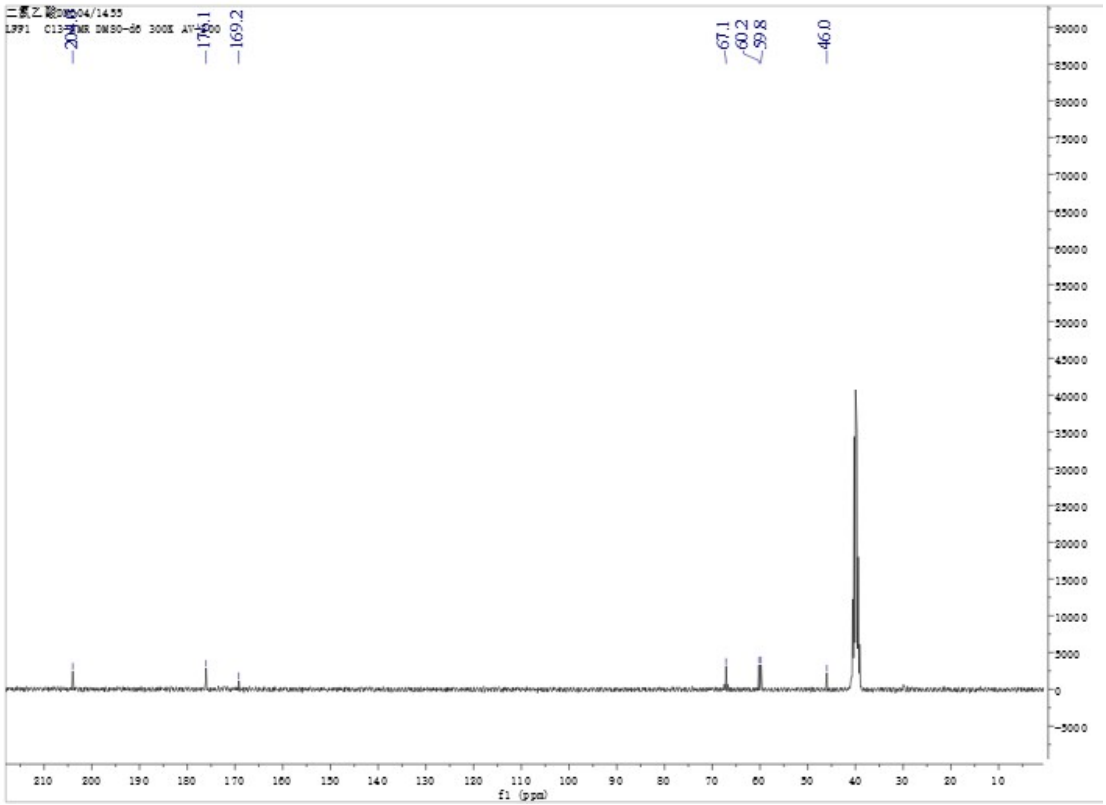

Fig. S2.[13]C NMR (DMSO) spectrum of complex 1a

Acquisition Parameter

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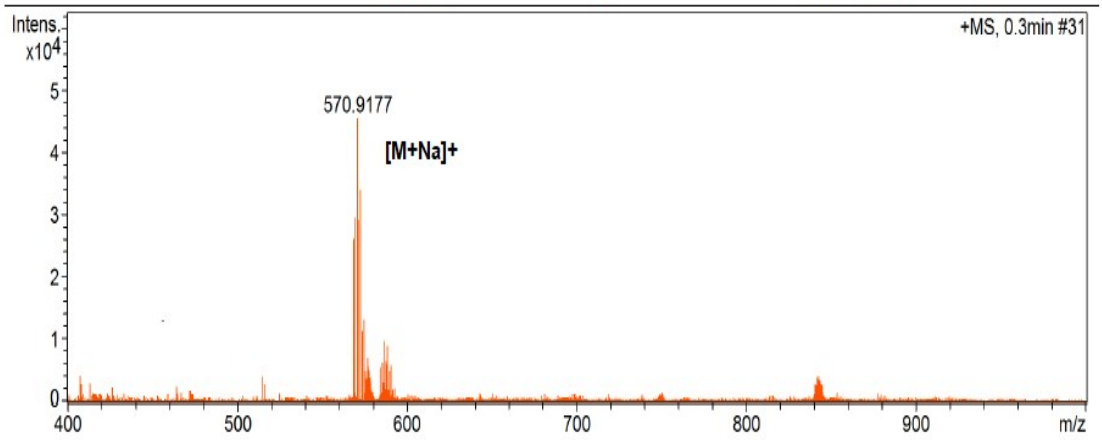
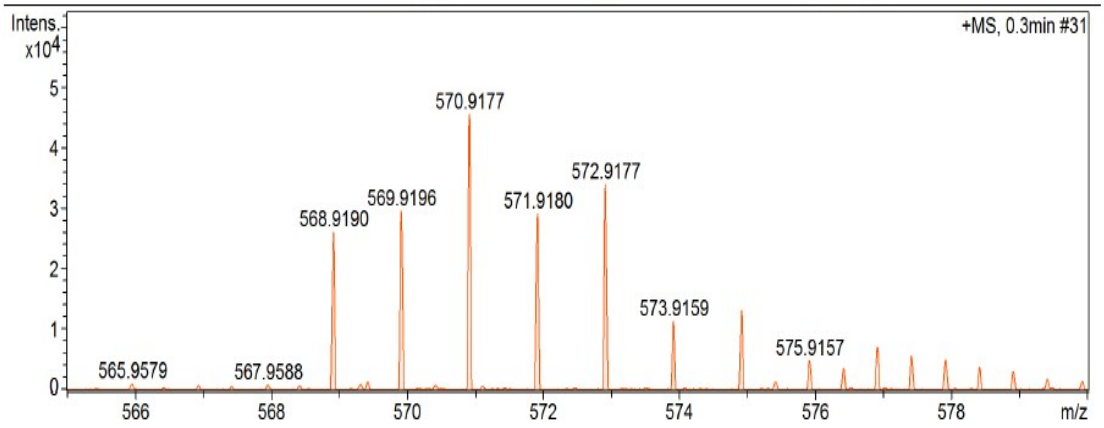


Meas. m/z	Ion Formula	Sum Formula	m/z	err [ppm]
569.9196	C8H11Cl3N2NaO7Pt	C8H11Cl3N2O7Pt	569.9172	-4.0

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	3.0 l/min
Scan End	1200 m/z	Set Charging Voltage	2000 V	Set Divert Valve	Waste
		Set Corona	0 nA	Set APCI Heater	0 °C



Meas. m/z	Ion Formula	Sum Formula	m/z	err [ppm]
569.9196	C8H11Cl3N2NaO7Pt	C8H11Cl3N2O7Pt	569.9172	-4.0

Fig. S3. HR-MS (ESI) spectrum of complex 1a

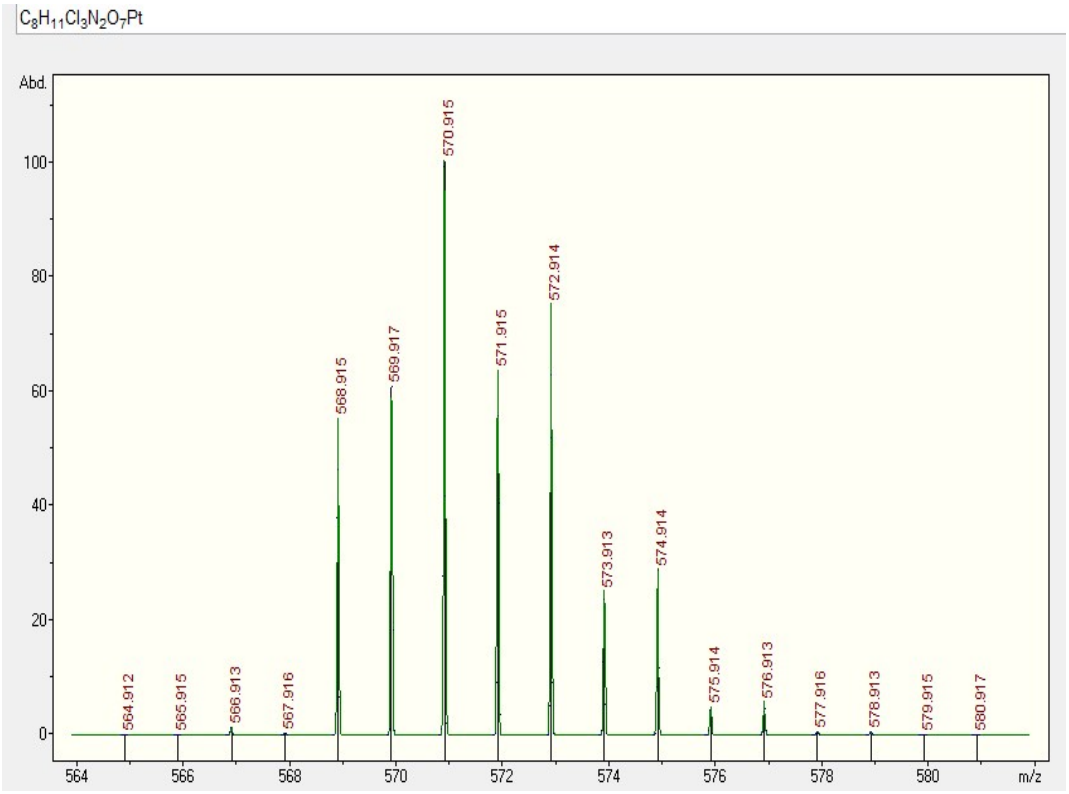


Fig. S4. The simulation of HR-MS (ESI) spectrum of complex 1a

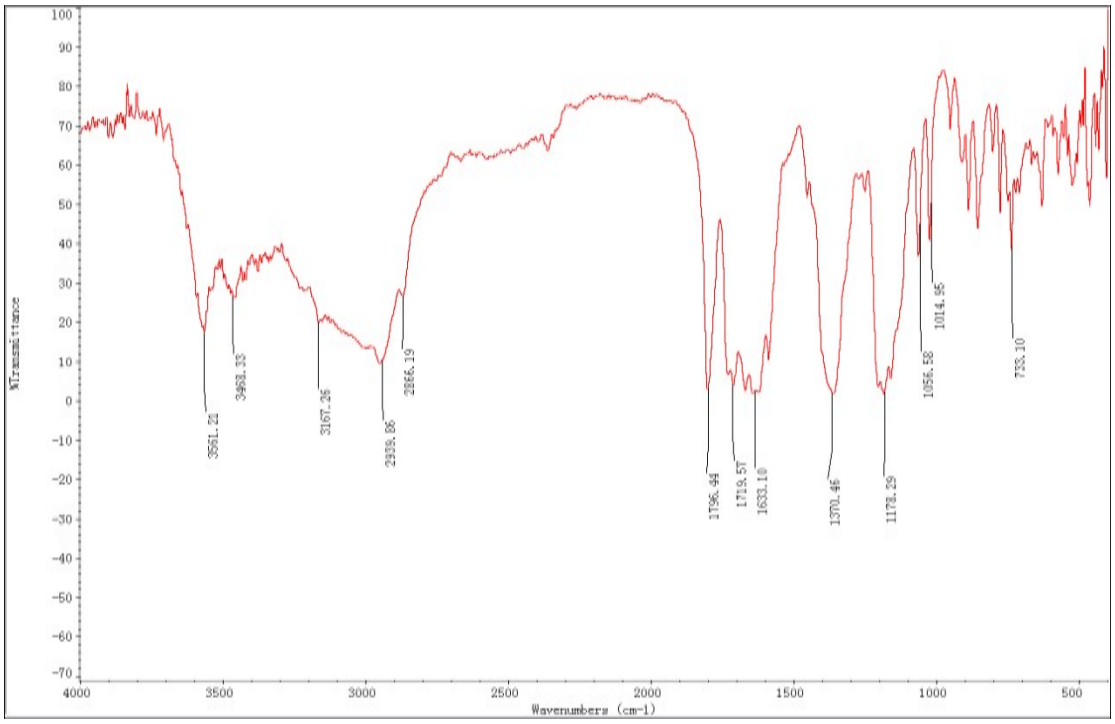


Fig. S5. IR spectrum of complex 1a

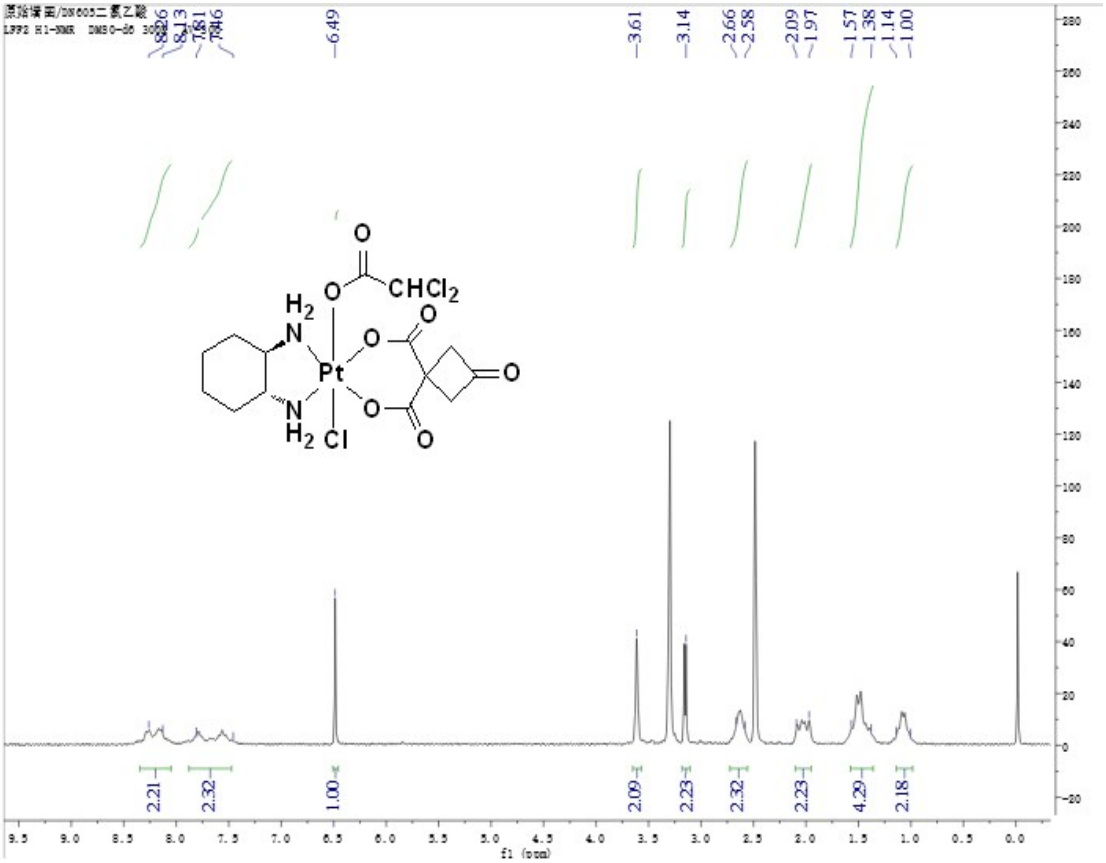


Fig. S6. ^{1}H NMR (DMSO) spectrum of complex 1b

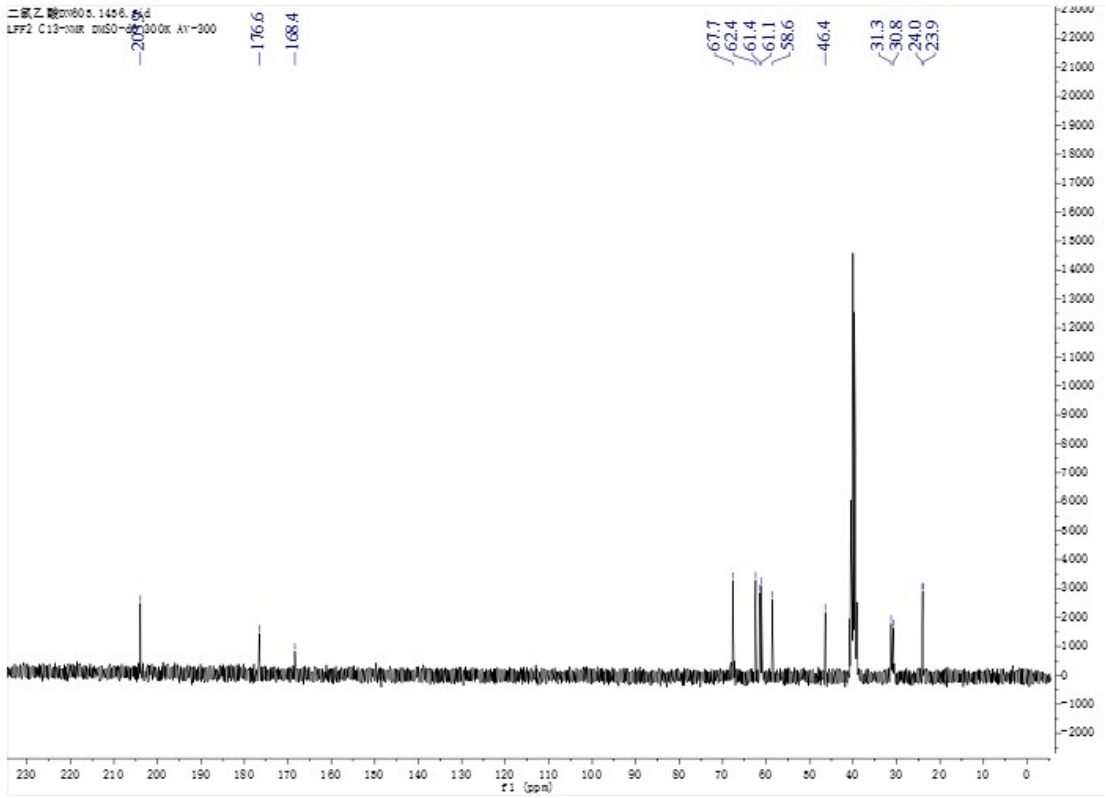


Fig. S7. ^{13}C NMR (DMSO) spectrum of complex 1b

Acquisition Parameter

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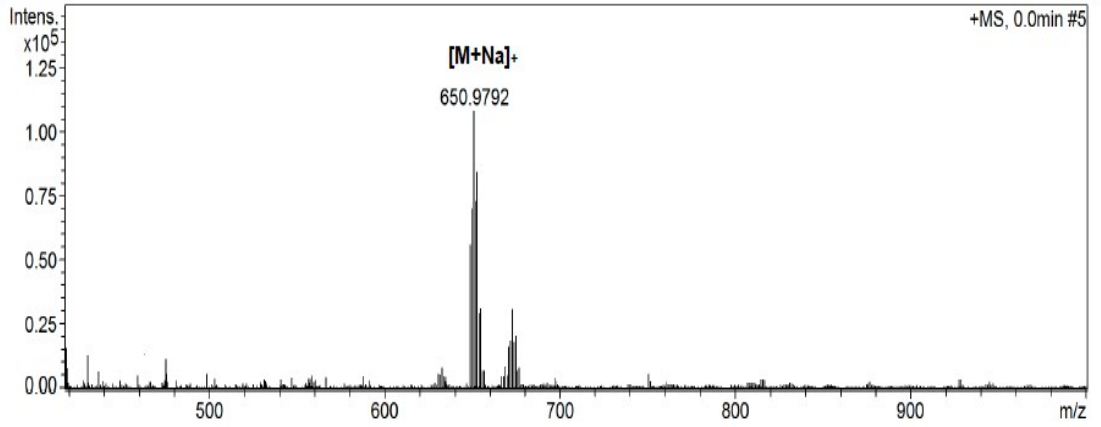
Scan End	1200 m/z	Set Charging Voltage	2000 V	Set Divert Valve	Waste
		Set Corona	0 nA	Set APCI Heater	0 °C



Meas. m/z	Ion Formula	Sum Formula	m/z	err [ppm]
649.9818	C14H19Cl3N2NaO7Pt	C14H19Cl3N2O7Pt	649.9798	-2.9

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
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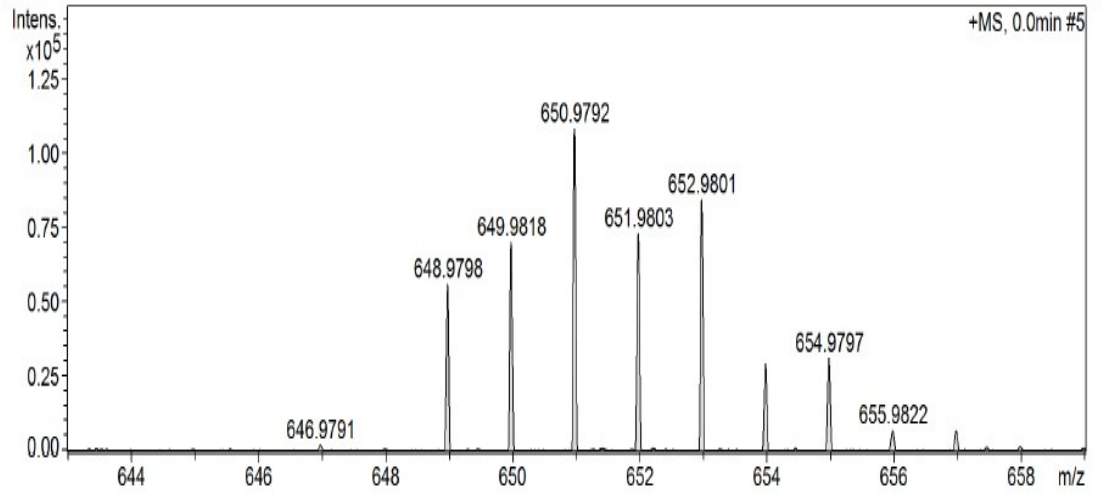
Scan End	1200 m/z	Set Charging Voltage	2000 V	Set Divert Valve	Waste
		Set Corona	0 nA	Set APCI Heater	0 °C



Meas. m/z	Ion Formula	Sum Formula	m/z	err [ppm]
649.9818	C14H19Cl3N2NaO7Pt	C14H19Cl3N2O7Pt	649.9798	-2.9

Fig. S8. HR-MS (ESI) spectrum of complex 1b

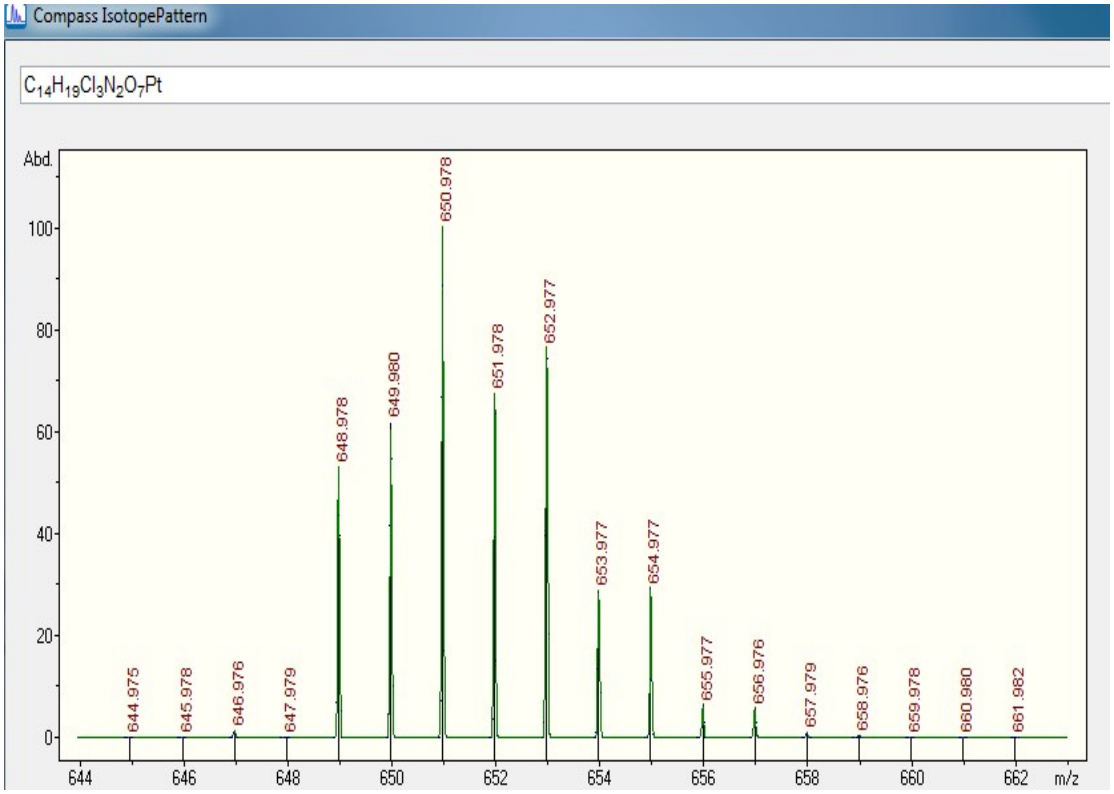


Fig. S9. The simulation of HR-MS (ESI) spectrum of complex 1b

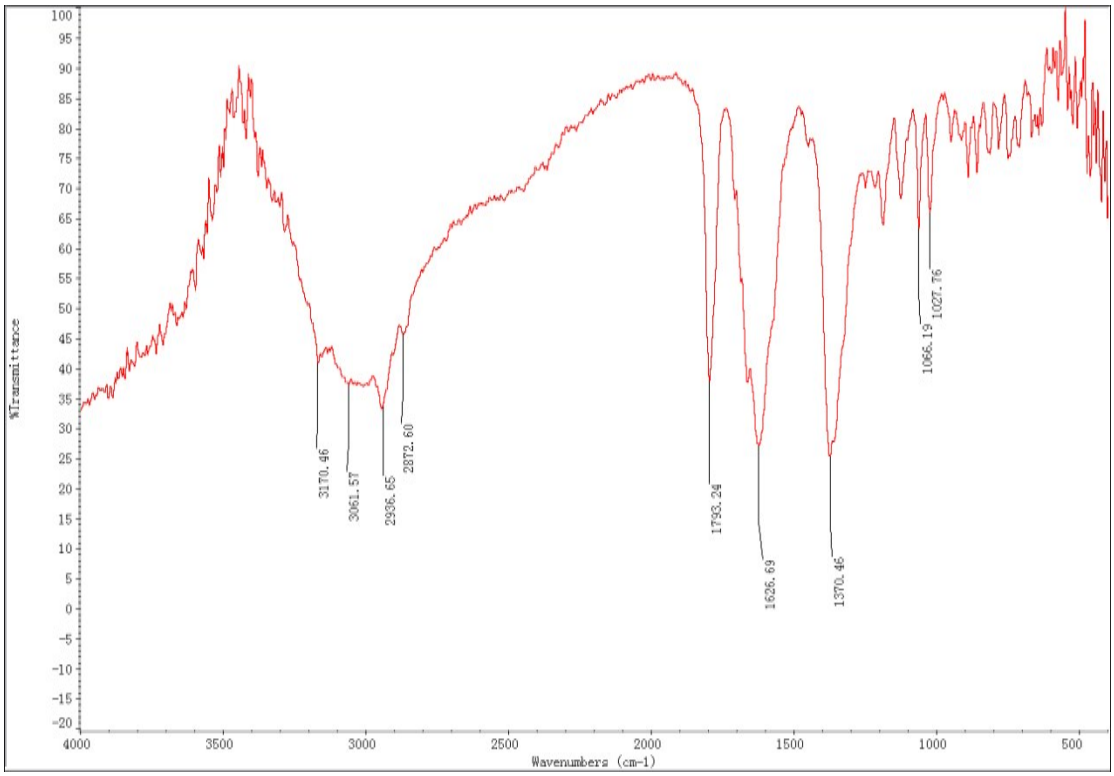


Fig. S10. IR spectrum of complex 1b

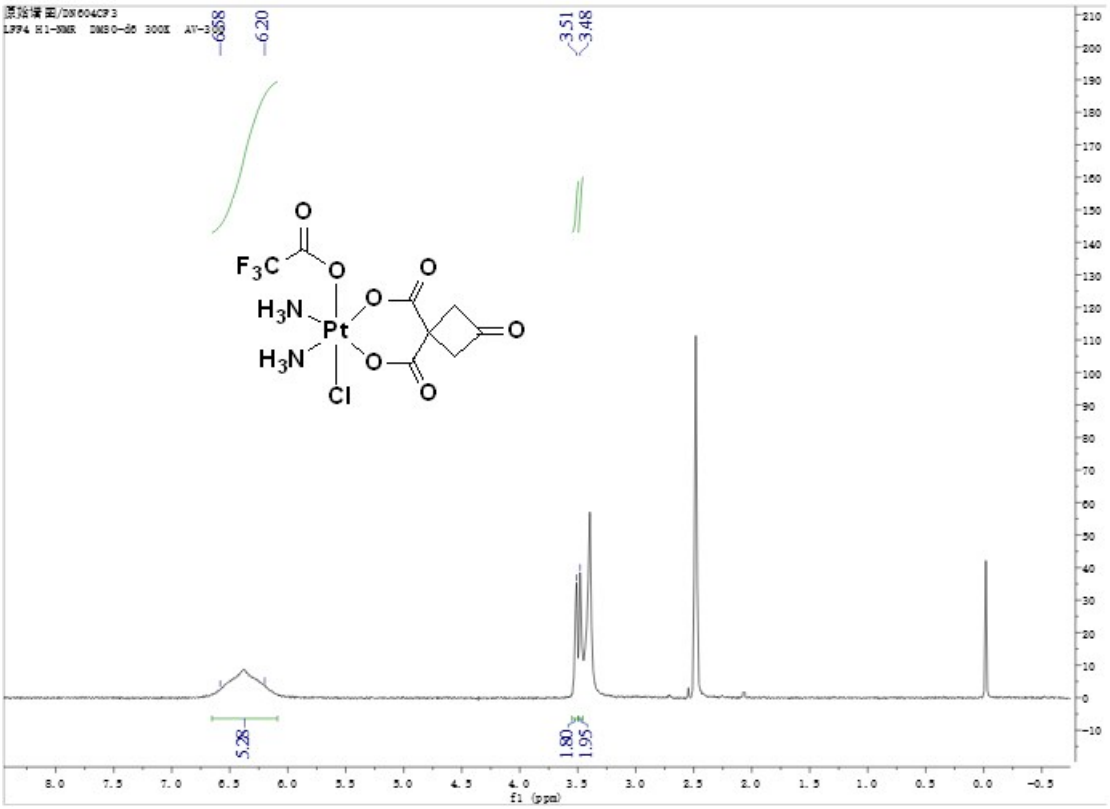


Fig. S11. ^{1}H NMR (DMSO) spectrum of complex 2a

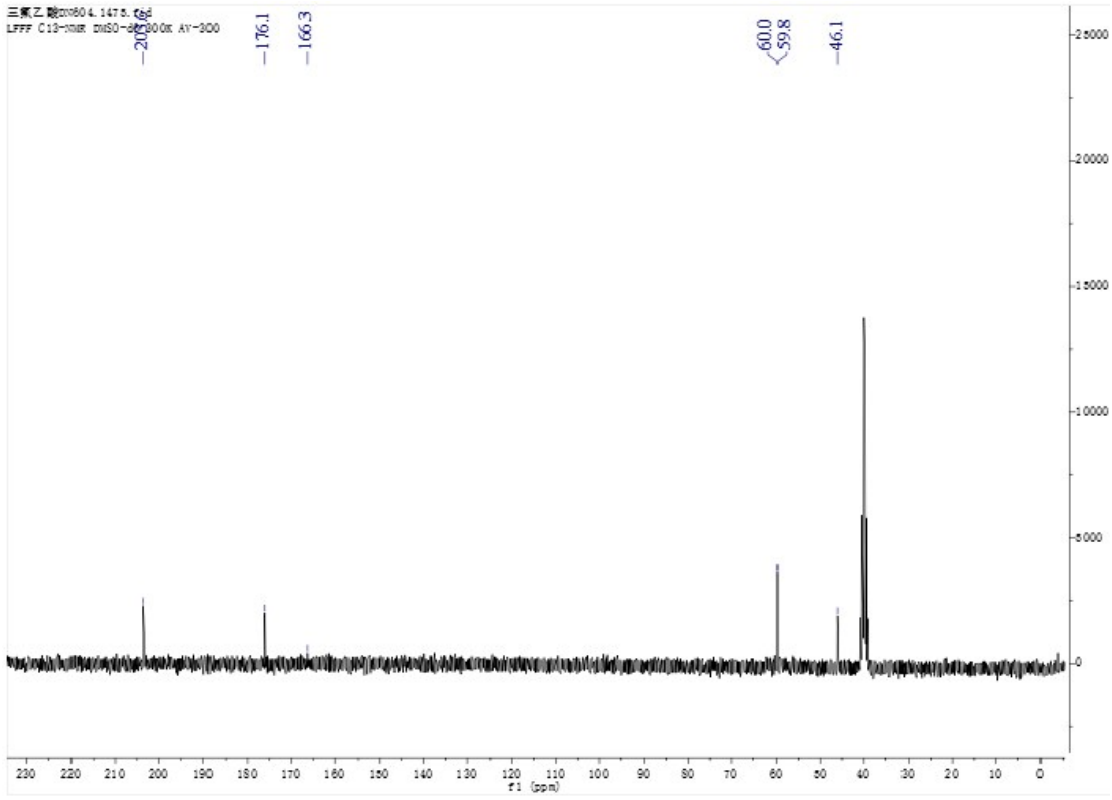


Fig. S12.^{13}C NMR (DMSO) spectrum of complex 2a

Acquisition Parameter

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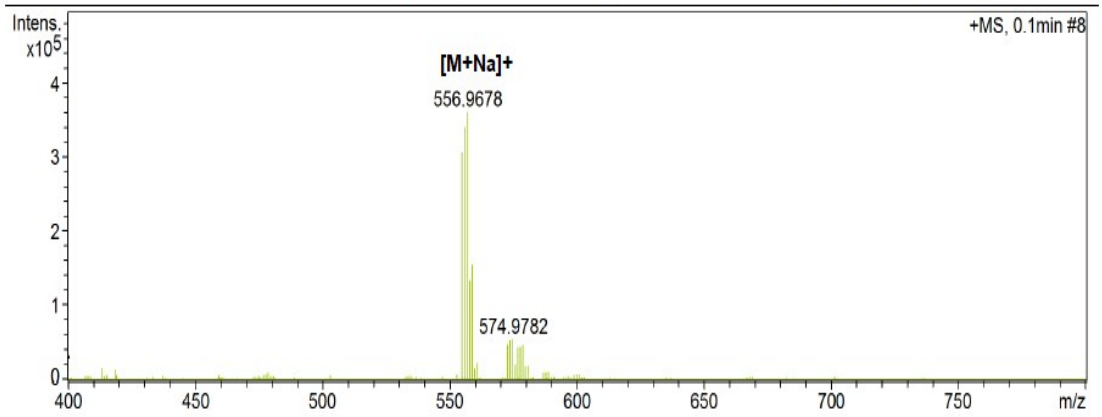
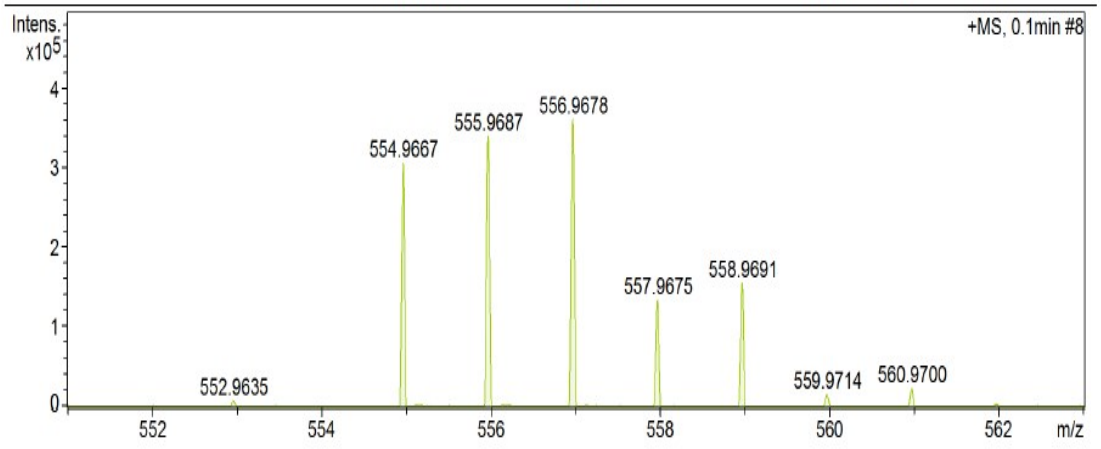
Scan End	1200 m/z	Set Charging Voltage	2000 V	Set Divert Valve	Waste
		Set Corona	0 nA	Set APCI Heater	0 °C



Meas. m/z	Ion Formula	Sum Formula	m/z	err [ppm]
555.9687	C8H10ClF3N2NaO7Pt	C8H10ClF3N2O7Pt	555.9669	-3.2

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	3.0 l/min
Scan End	1200 m/z	Set Charging Voltage	2000 V	Set Divert Valve	Waste
		Set Corona	0 nA	Set APCI Heater	0 °C



Meas. m/z	Ion Formula	Sum Formula	m/z	err [ppm]
555.9687	C8H10ClF3N2NaO7Pt	C8H10ClF3N2O7Pt	555.9669	-3.2

Fig. S13. HR-MS (ESI) spectrum of complex 2a

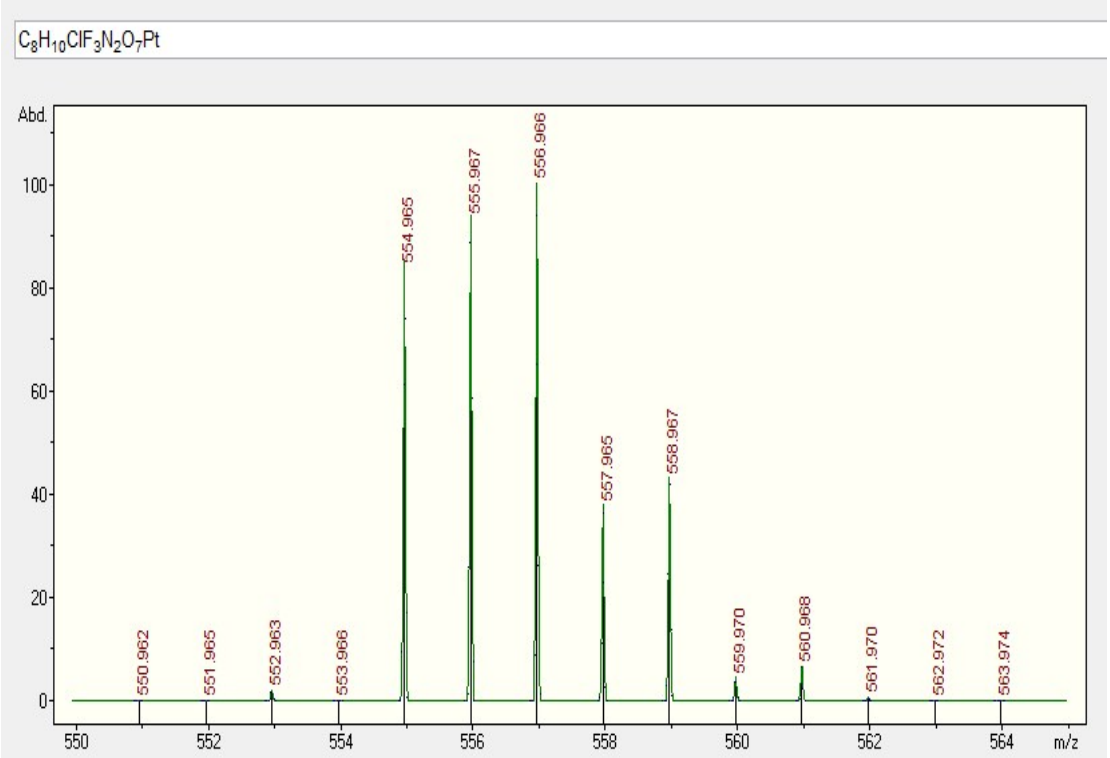


Fig. S14. The simulation of HR-MS (ESI) spectrum of complex 2a

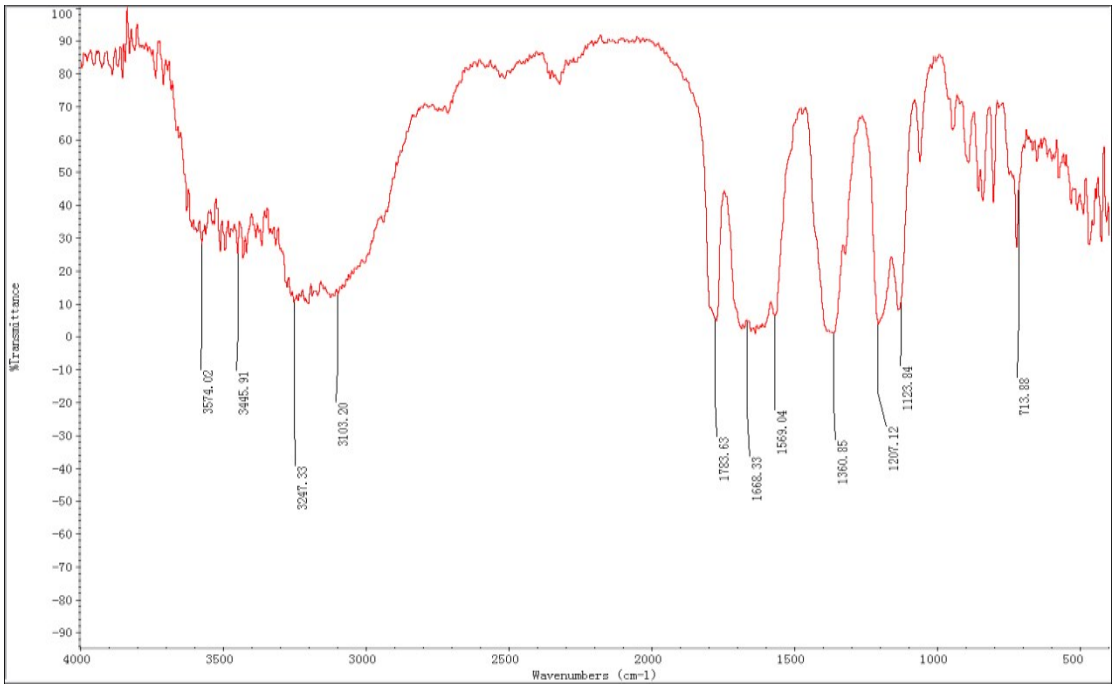


Fig. S15. IR spectrum of complex 2a

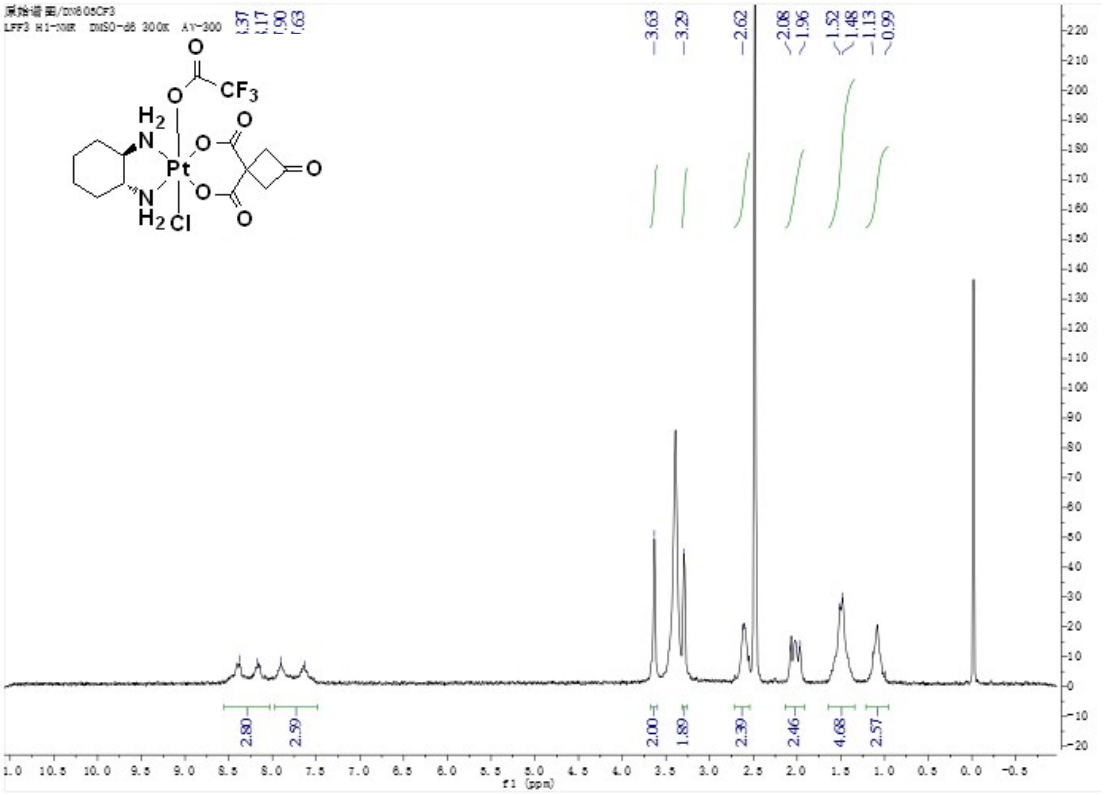


Fig. S16.^{1}H NMR (DMSO) spectrum of complex 2b

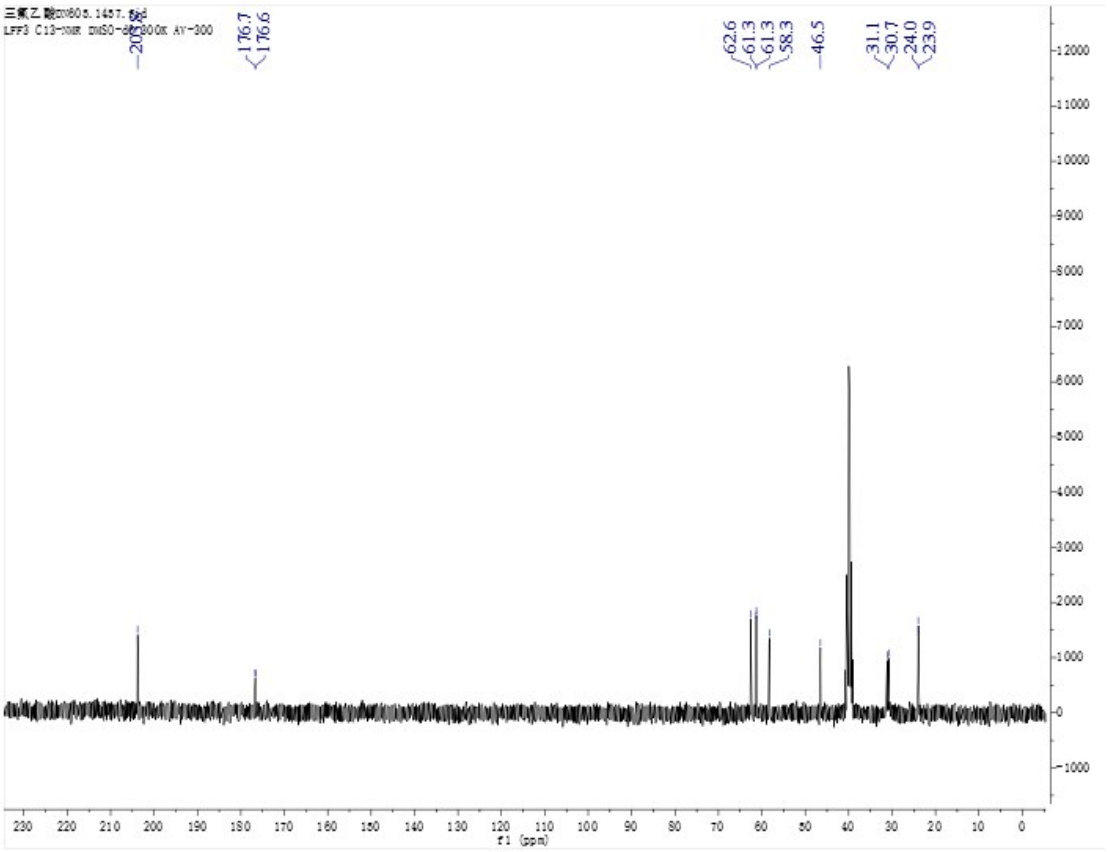


Fig. S17.^{13}C NMR (DMSO) spectrum of complex 2b

Acquisition Parameter

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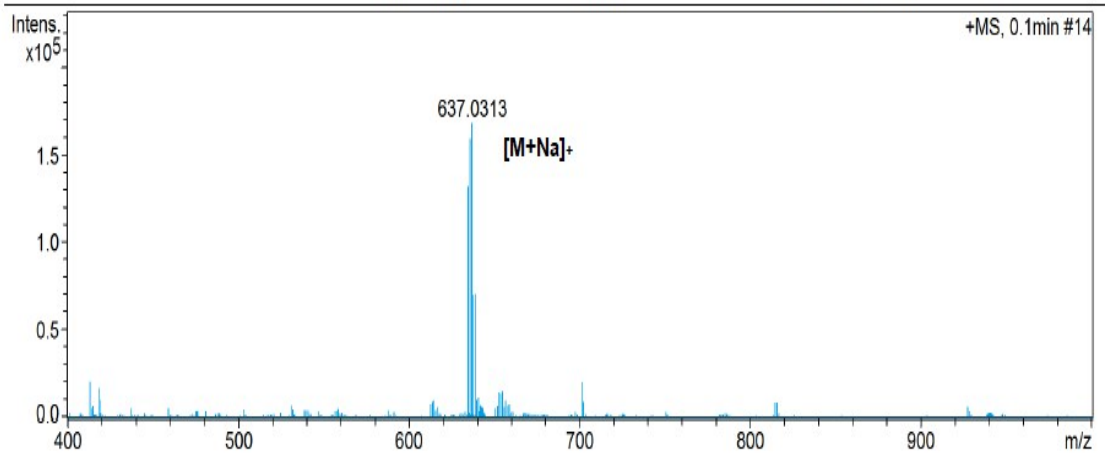
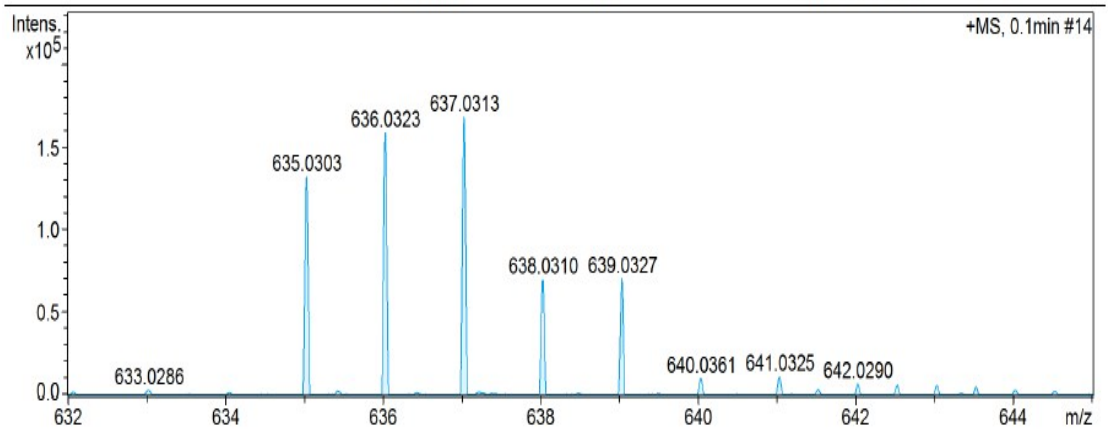
Scan End	1200 m/z	Set Charging Voltage	2000 V	Set Divert Valve	Waste
		Set Corona	0 nA	Set APCI Heater	0 °C



Meas. m/z	Ion Formula	Sum Formula	m/z	err [ppm]
636.0323	C14H18ClF3N2NaO7Pt	C14H18ClF3N2O7Pt	636.0295	-4.2

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.4 Bar
Focus	Not active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	3.0 l/min
Scan End	1200 m/z	Set Charging Voltage	2000 V	Set Divert Valve	Waste
		Set Corona	0 nA	Set APCI Heater	0 °C



Meas. m/z	Ion Formula	Sum Formula	m/z	err [ppm]
636.0323	C14H18ClF3N2NaO7Pt	C14H18ClF3N2O7Pt	636.0295	-4.2

Fig. S18. HR-MS (ESI) spectrum of complex 2b

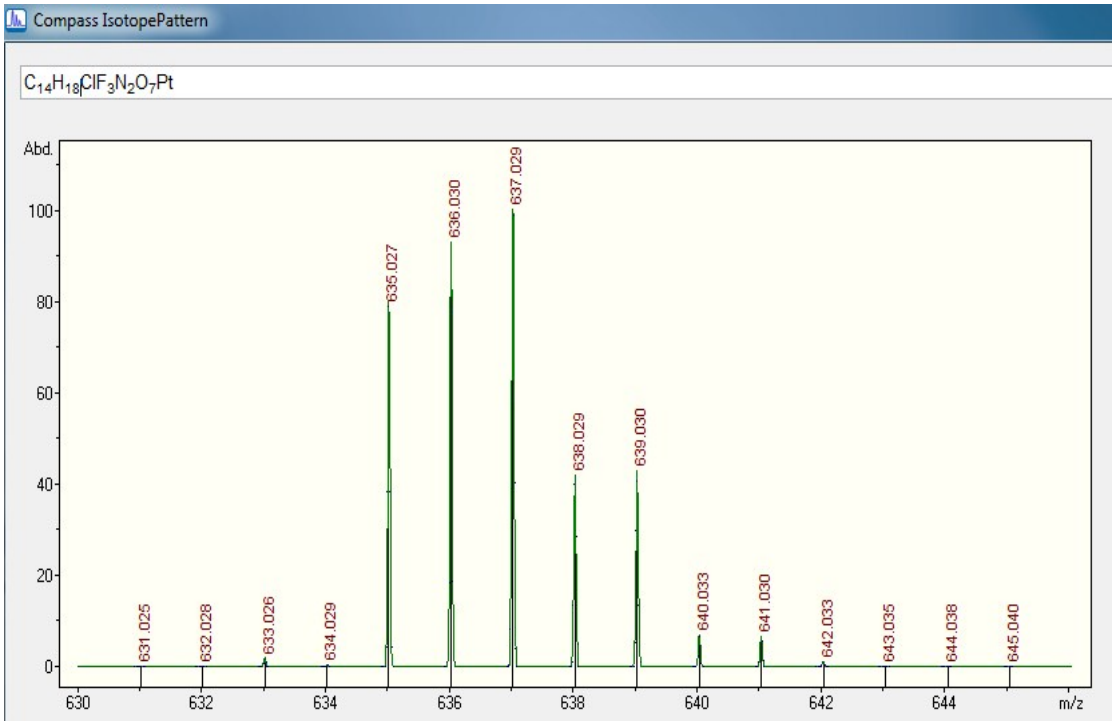


Fig. S19. The simulation of HR-MS (ESI) spectrum of complex 2b

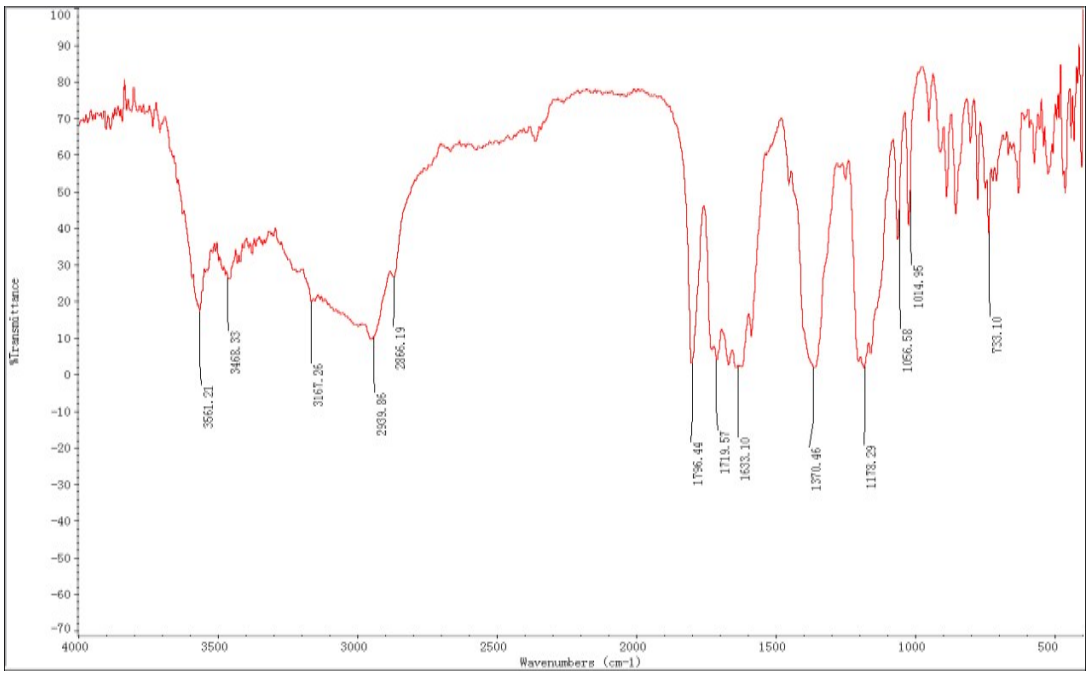


Fig. S20. IR spectrum of complex 2b

2. The stability of complexes 1a-2b in MeOH/PBS buffer

(a) ^{1}H-NMR (400 MHz) spectra of complex **1a** in deuterated aqueous, phosphate buffered solution

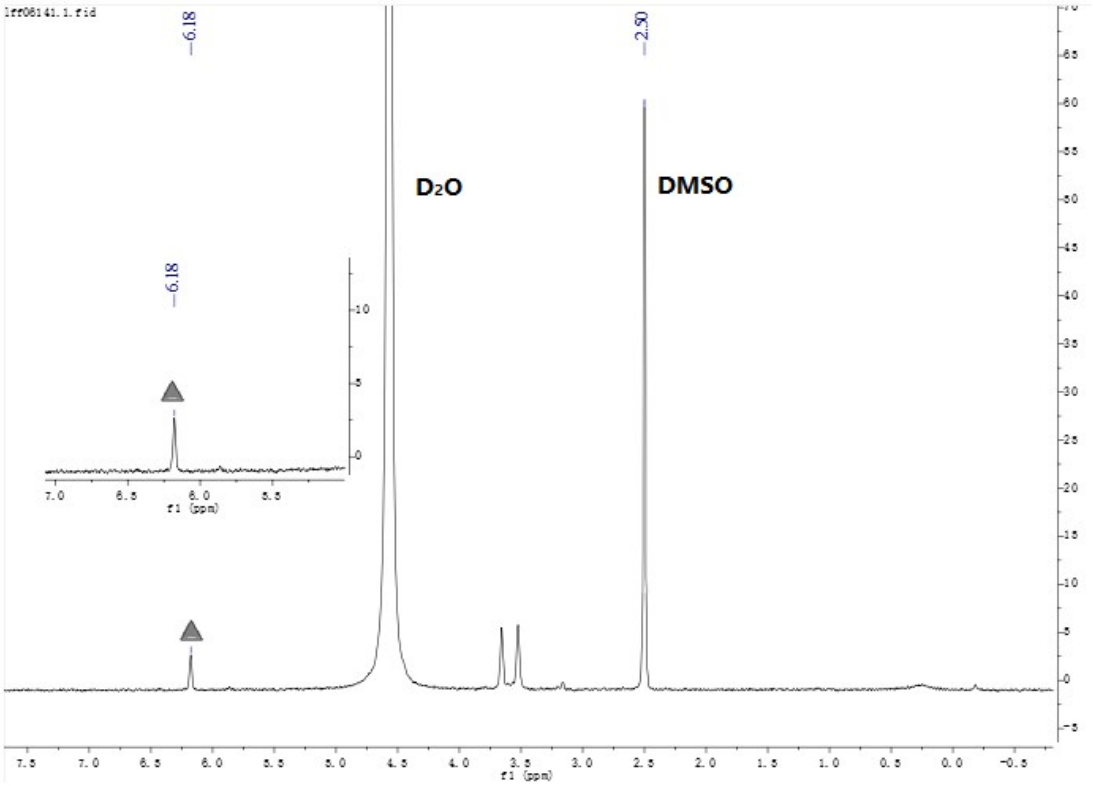


Fig.21. [1]H NMR spectra of complex **1a** treated with PBS (7.87 mM, pH 7.4; at 37°C) at 0 min (DMSO-*d*6/D_2O, 10/90, v/v). ▲ indicates the peak of coordinated DCA in complex **1a**.

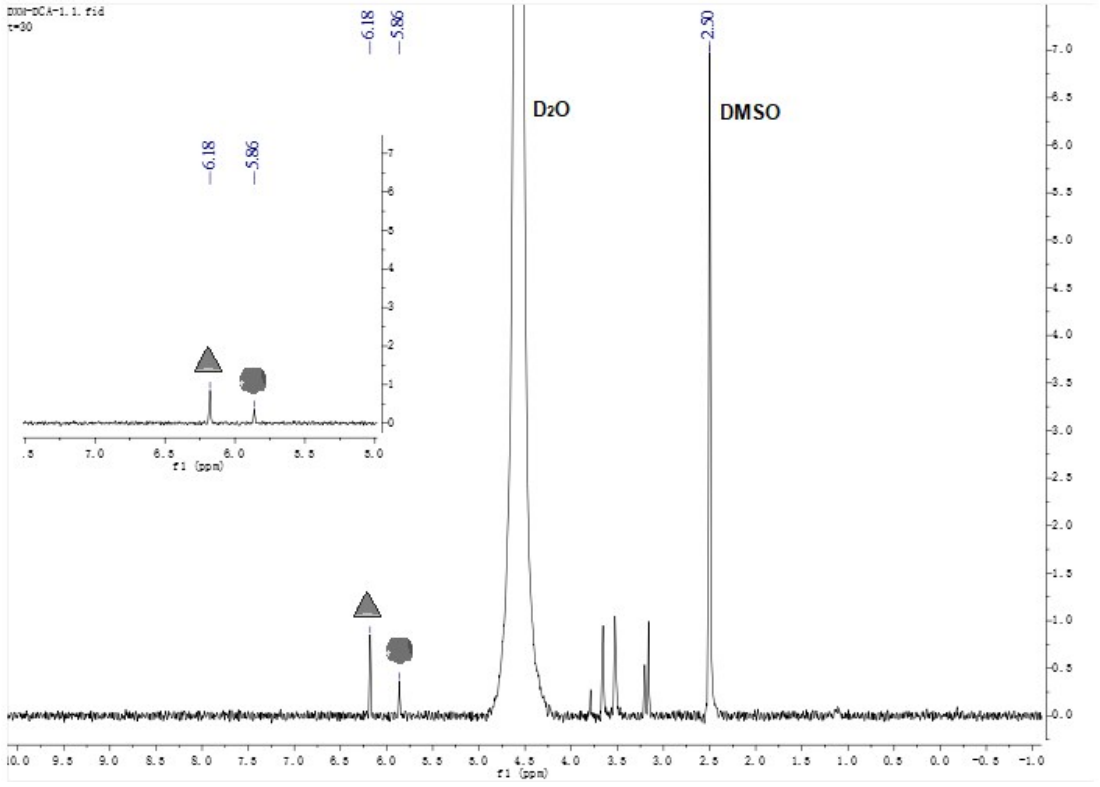


Fig.22. [1]H NMR spectra of complex **1a** treated with PBS (7.87 mM, pH 7.4; at 37°C) at 50 mins (DMSO-*d*6/D_2O, 10/90, v/v). ▲ indicates the peak of coordinated DCA in complex **1a**. ● indicates the peak of free DCA.

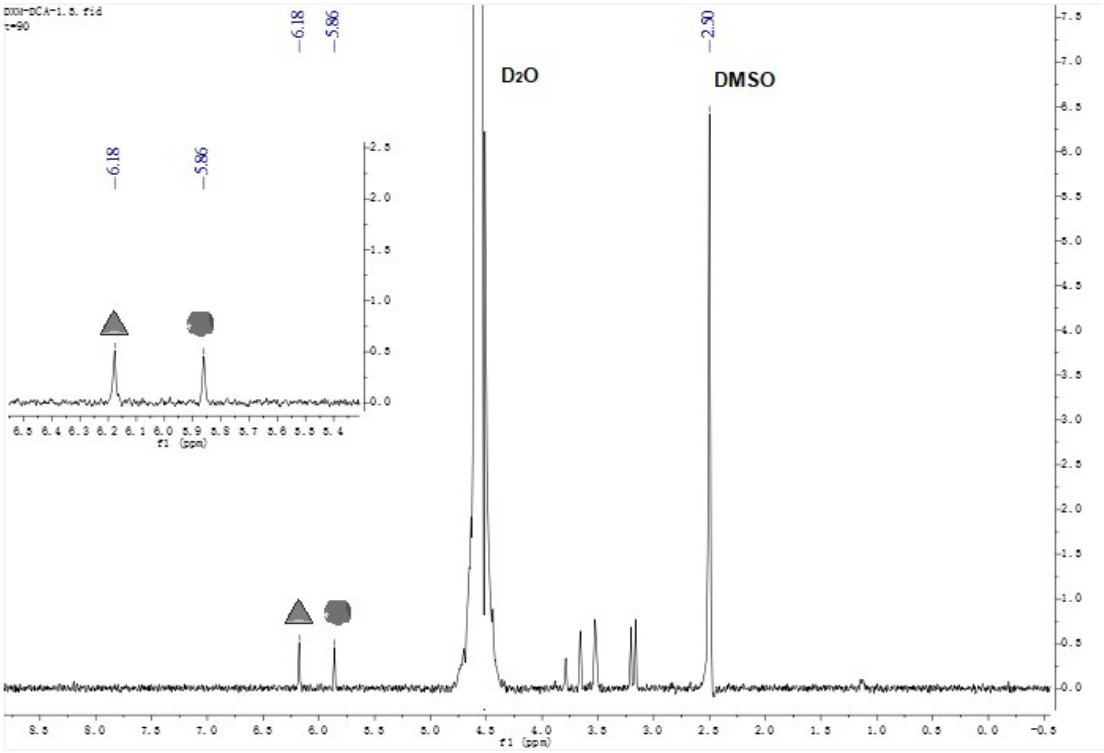


Fig.23. ^{1}H NMR spectra of complex **1a** treated with PBS (7.87 mM, pH 7.4; at 37°C) at 100 mins (DMSO-*d*6/D_2O, 10/90, v/v). ▲ indicates the peak of coordinated DCA in complex **1a**. ● indicates the peak of free DCA.

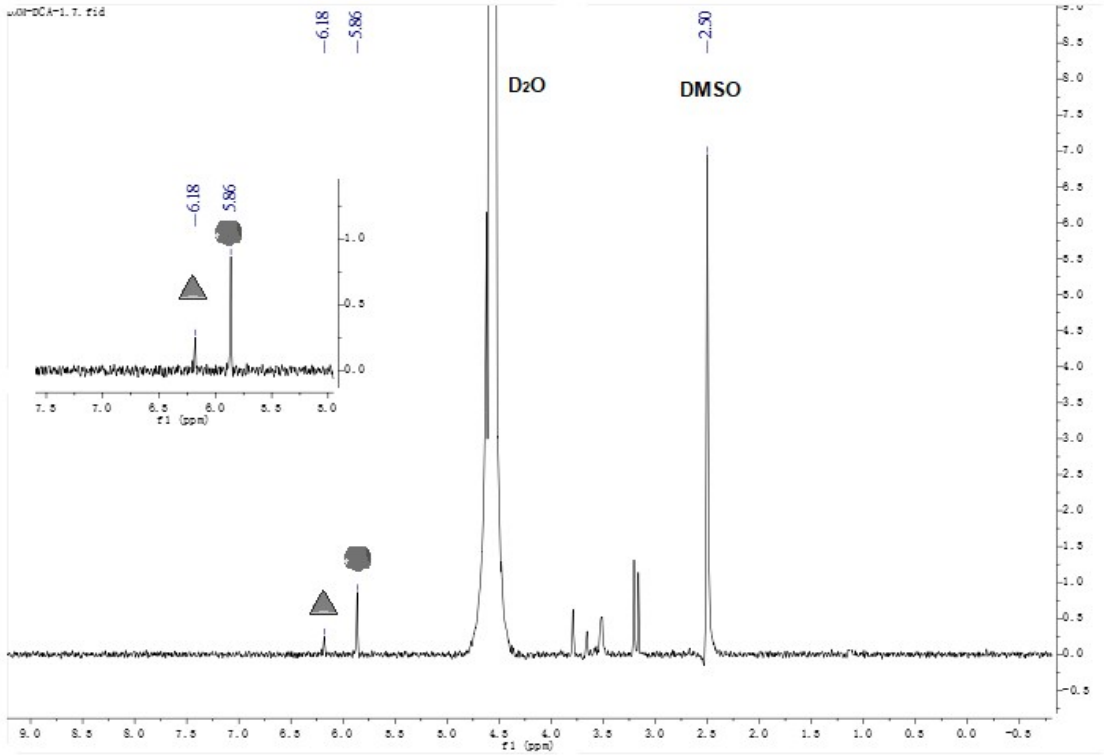


Fig.24. ^{1}H NMR spectra of complex **1a** treated with PBS (7.87 mM, pH 7.4; at 37°C) at 150 mins (DMSO-*d*6/D_2O, 10/90, v/v). ▲ indicates the peak of coordinated DCA in complex **1a**. ● indicates the peak of free DCA.

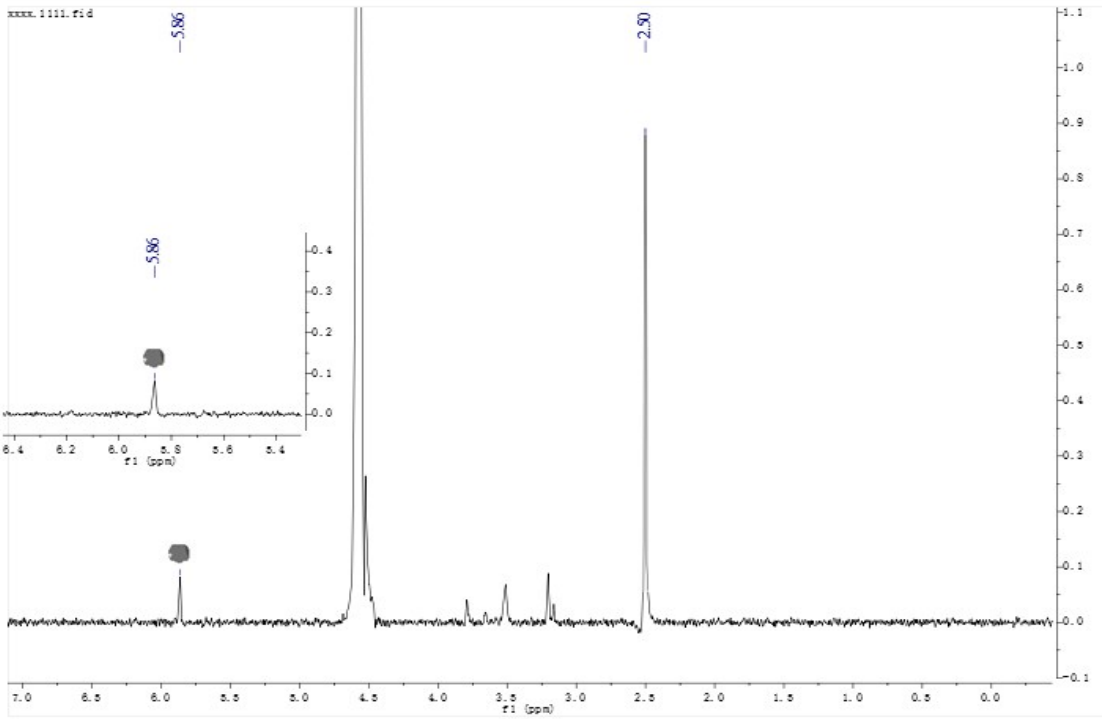


Fig.25. ^{1}H NMR spectra of complex **1a** treated with PBS (7.87 mM, pH 7.4; at 37^{o}C) at 200 mins (DMSO-*d*6/D_2O, 10/90, v/v). ▲ indicates the peak of coordinated DCA in complex **1a**. ● indicates the peak of free DCA.

(b) ^{1}H-NMR(400 MHz, 1H) spectra of complex **1b** in deuterated aqueous, phosphate buffered solution

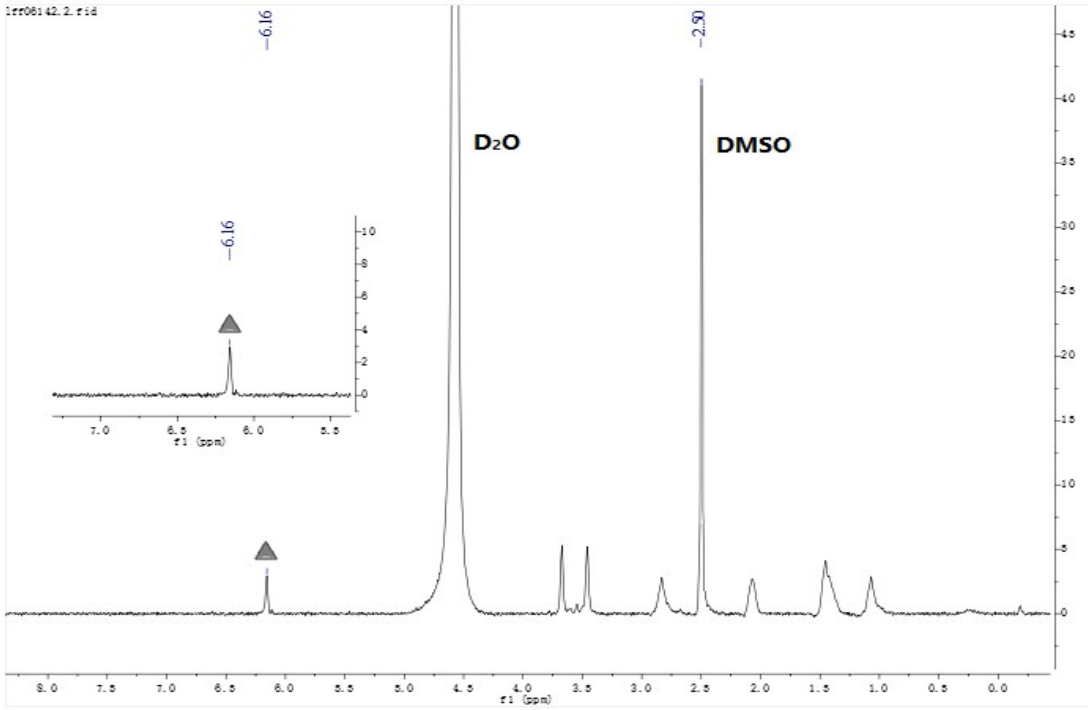


Fig.26. ^{1}H NMR spectra of complex **1b** treated with PBS (7.87 mM, pH 7.4; at 37^{o}C) at 0 min (DMSO-*d*6/D_2O, 10/90, v/v). ▲ indicates the peak of coordinated DCA in complex **1b**.

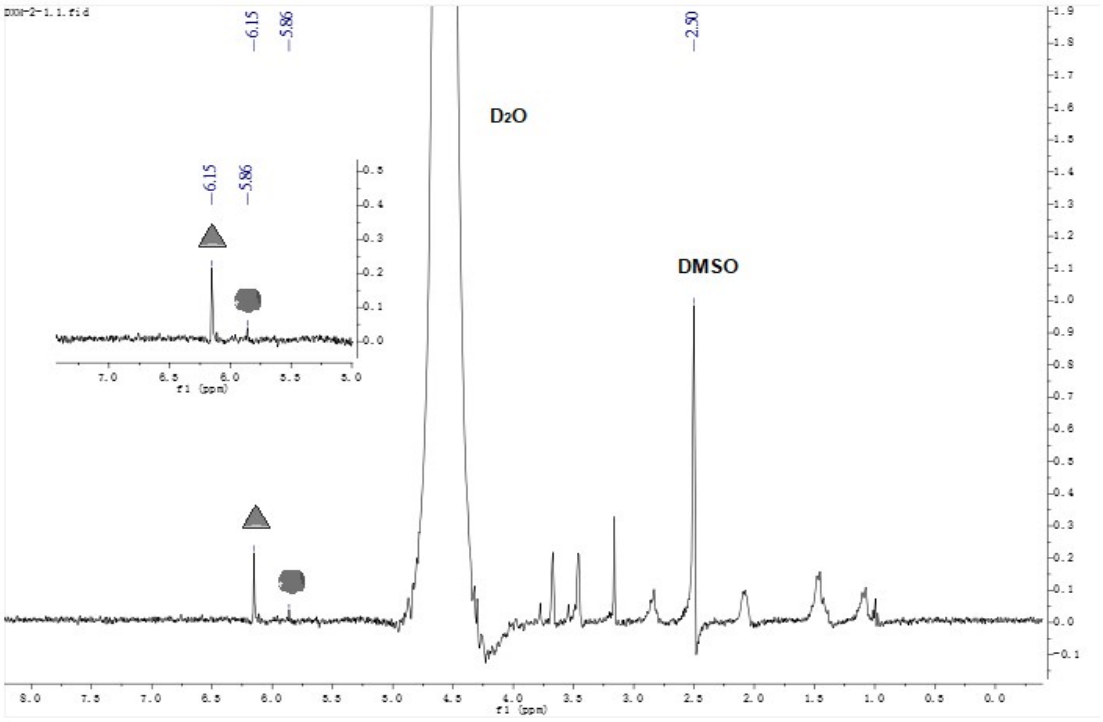


Fig.27. ^{1}H NMR spectra of complex **1b** treated with PBS (7.87 mM, pH 7.4; at 37^{o}C) at 30 mins (DMSO-*d*6/D_2O, 10/90, v/v). ▲ indicates the peak of coordinated DCA in complex **1b**. ● indicates the peak of free DCA.

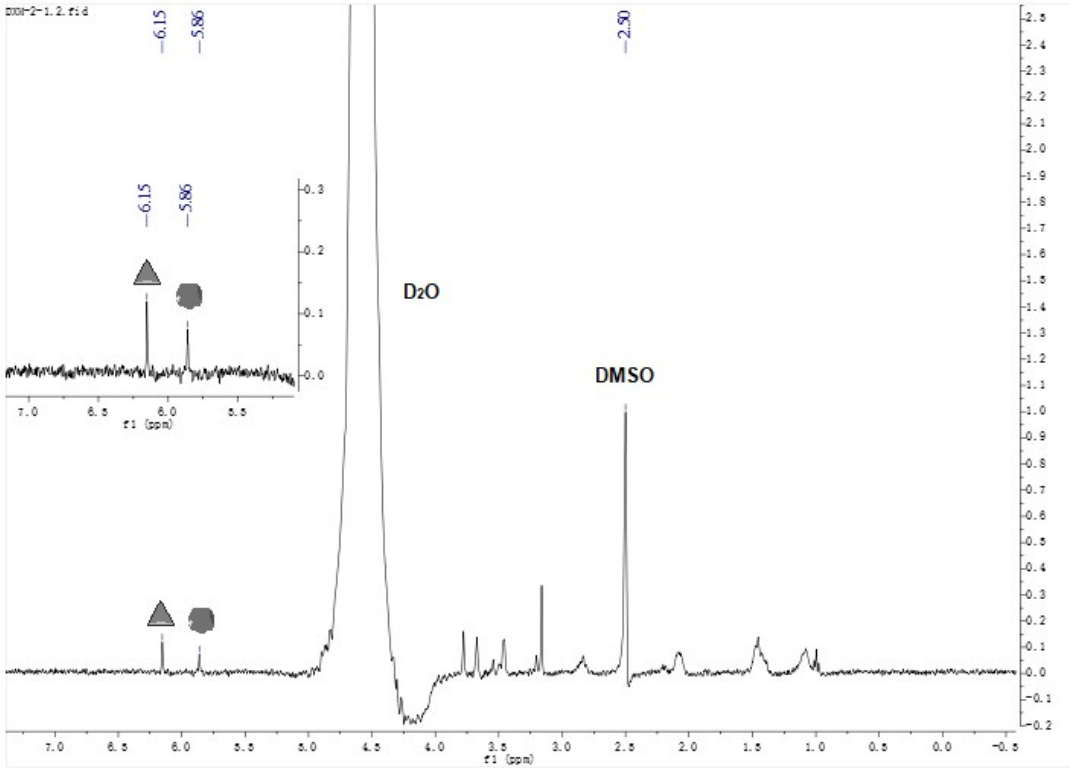


Fig.28. ^{1}H NMR spectra of complex **1b** treated with PBS (7.87 mM, pH 7.4; at 37^{o}C) at 60 mins (DMSO-*d*6/D_2O, 10/90, v/v). ▲ indicates the peak of coordinated DCA in complex **1b**. ● indicates the peak of free DCA.

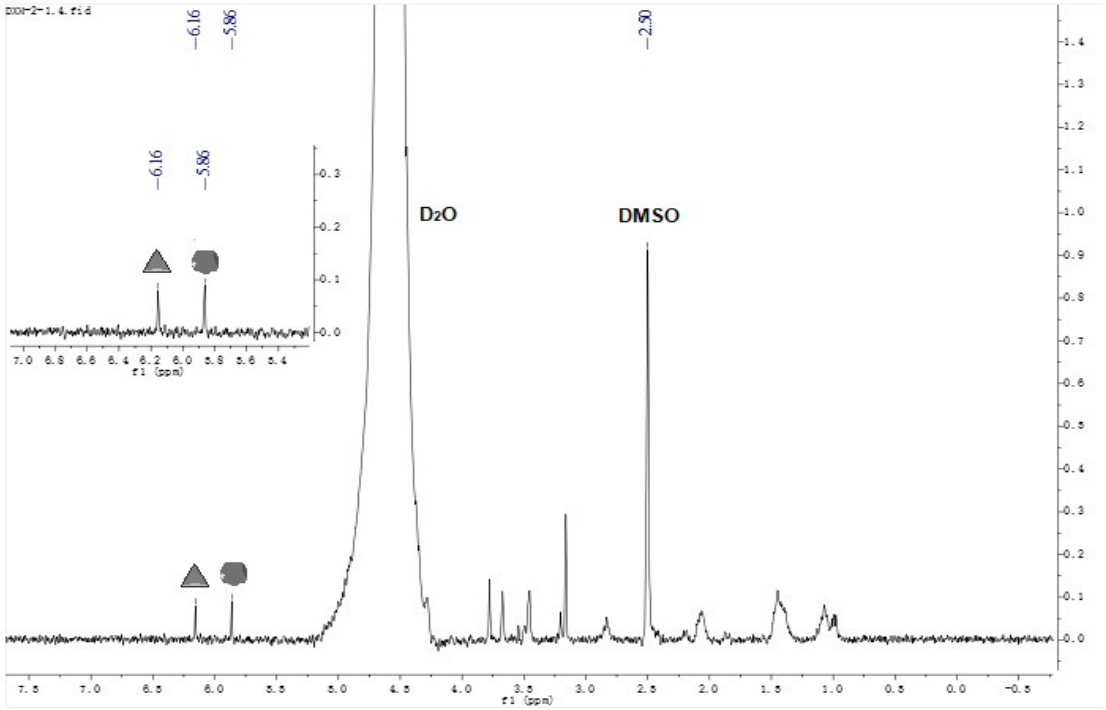


Fig.29. ^{1}H NMR spectra of complex **1b** treated with PBS (7.87 mM, pH 7.4; at 37^{o}C) at 120 mins (DMSO-*d*6/D_2O, 10/90, v/v). ▲indicates the peak of coordinated DCA in complex **1b**. ● indicates the peak of free DCA.

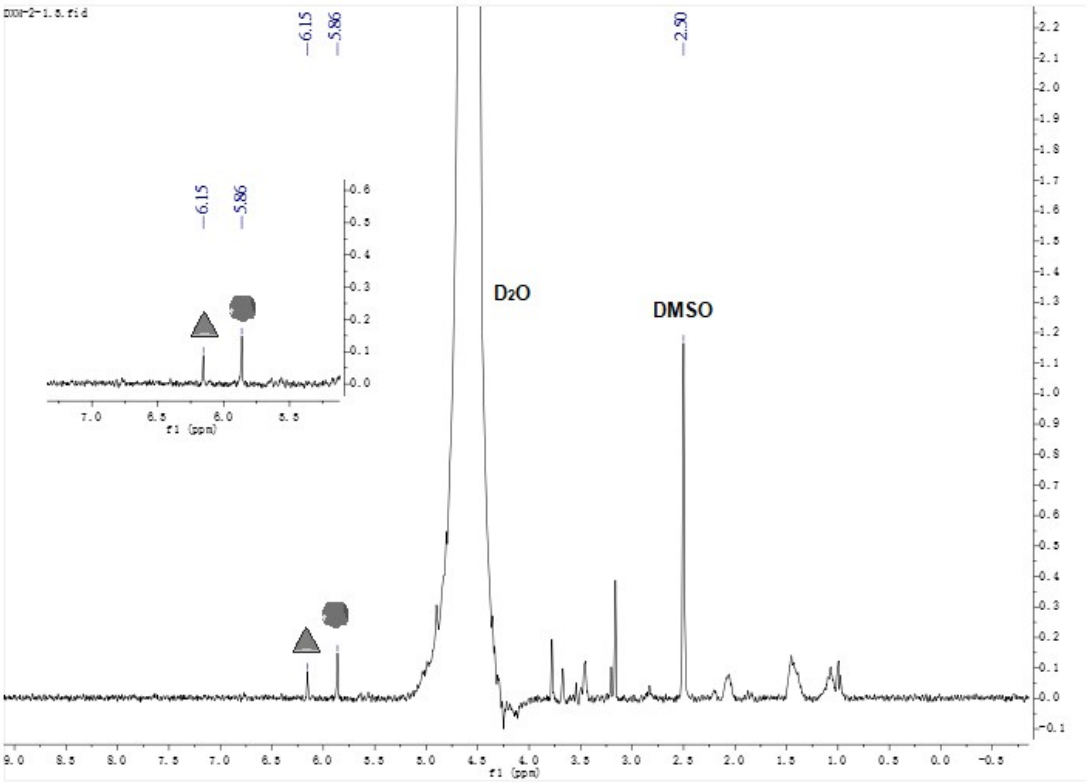


Fig.30. ^{1}H NMR spectra of complex **1b** treated with PBS (7.87 mM, pH 7.4; at 37^{o}C) at 180 mins (DMSO-*d*6/D_2O, 10/90, v/v). ▲indicates the peak of coordinated DCA in complex **1b**. ● indicates the peak of free DCA.

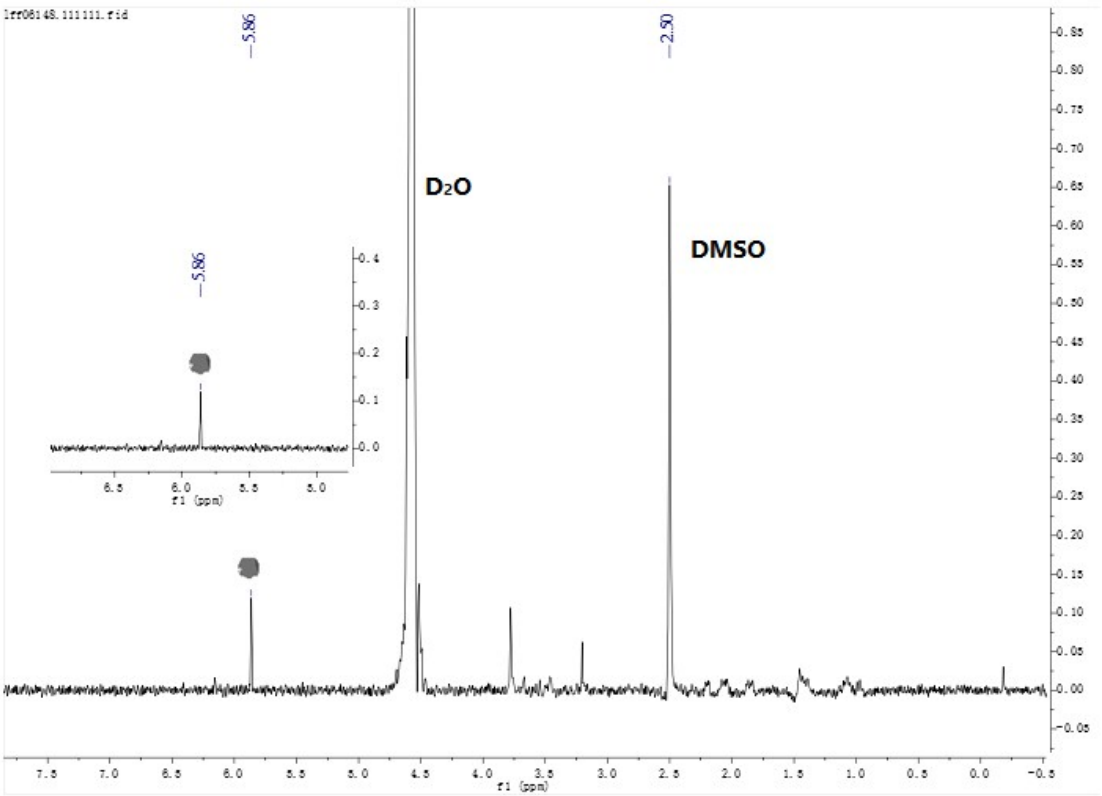


Fig.31. ^{1}H NMR spectra of complex **1b** treated with PBS (7.87 mM, pH 7.4; at 37°C) at 250 mins (DMSO-*d*6/D_2O, 10/90, v/v). ● indicates the peak of free DCA.

(c) HPLC spectra of complex **1a** and **1b** in phosphate buffered solution

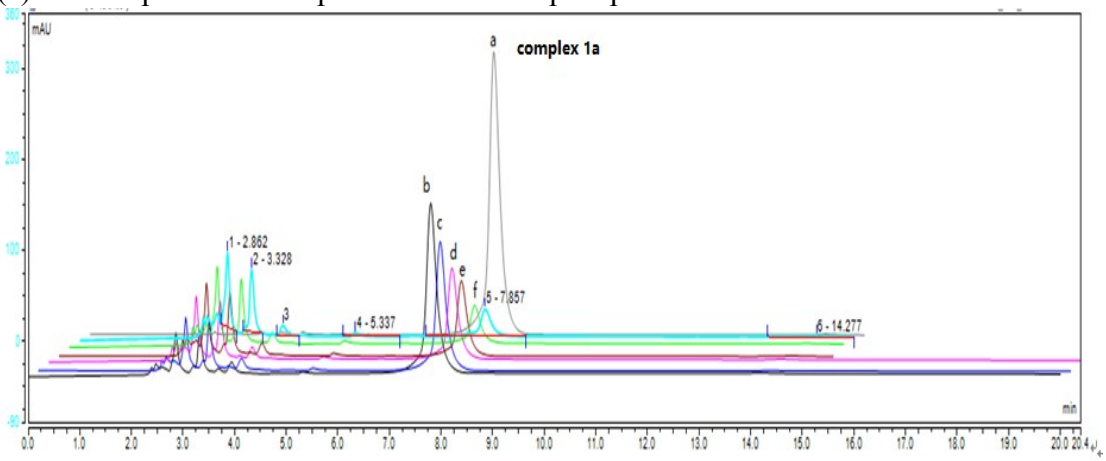


Fig. S32. Complex **1a** in PBS (PBS 7.87 mM, pH 7.4; at 37°C): (a) 0 min; (b) 50 min; (c) 80 min; (d) 100 min; (e) 150min; (f) 180min (250×4.6 mm ODS; 226 nm; MeCN : H_2O = 25:75 (v/v); 1.0 mL/min)

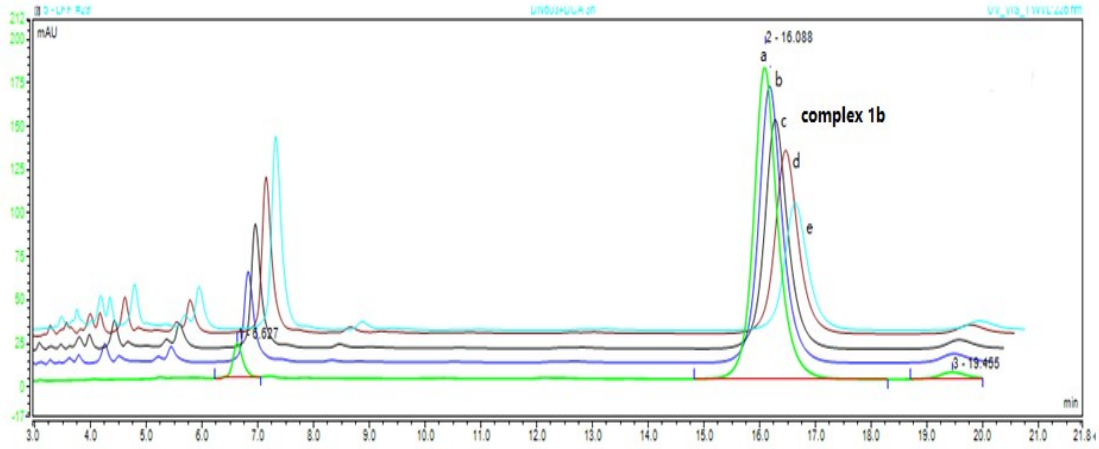


Fig. S33. Complex **1b** in PBS (PBS 7.87 mM, pH 7.4; at 37°C): (a) 0 min; (b) 15 min; (c) 30 min; (d) 60 min; (e) 150min (250×4.6 mm ODS; 226 nm; MeCN : H_2O = 25:75 (v/v); 1.0 mL/min)

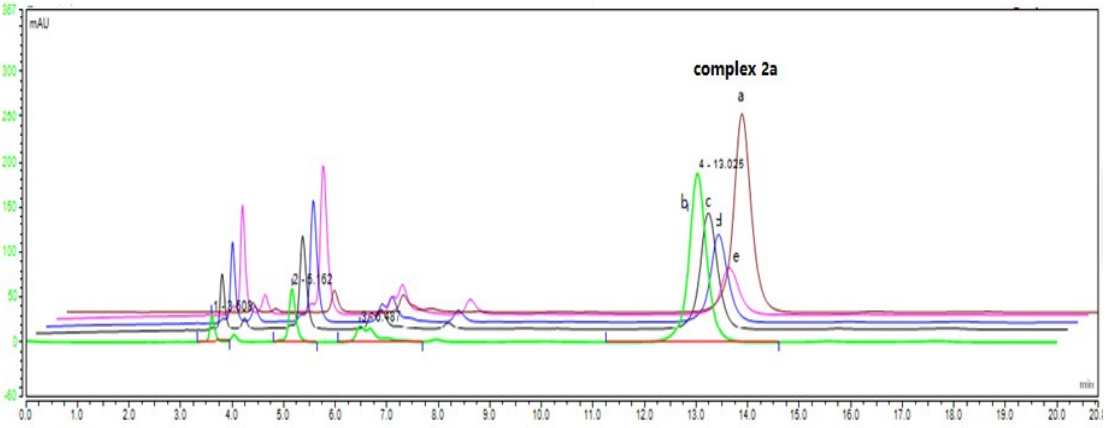


Fig. S34. Complex **2a** in PBS (PBS 7.87 mM, pH 7.4; at 37°C): (a) 0 min; (b)30min; (c)60 min; (d)90 min; (e)150min (250×4.6 mm ODS; 226 nm; MeCN : H_2O = 25:75 (v/v); 1.0 mL/min)

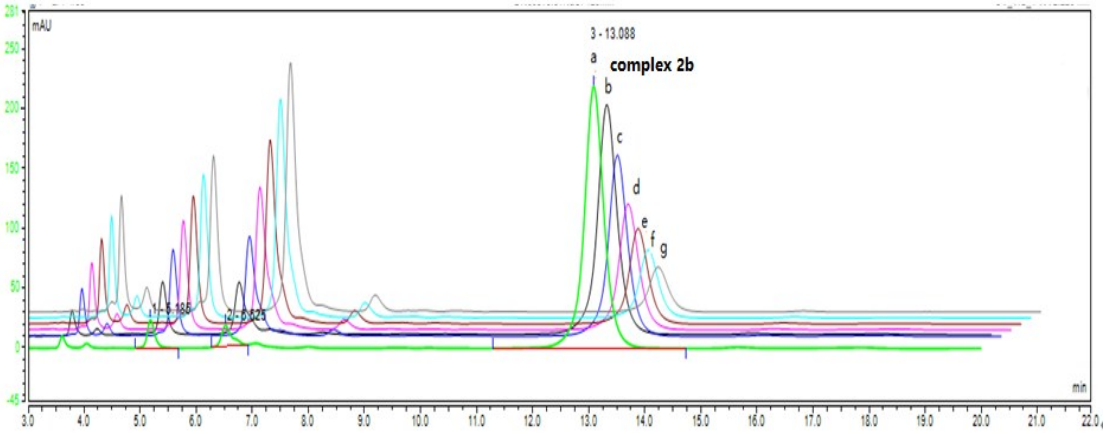


Fig. S35. Complex **2b** in PBS(PBS 7.87 mM, pH 7.4; at 37°C): (a) 0 min; (b)30min; (c)45 min; (d)60 min; (e)85min; (f)100min; (g)130min (250×4.6 mm ODS; 226 nm; MeCN : H_2O = 25:75 (v/v); 1.0 mL/min)

4. The stability of complexes 1a-2b in MeOH

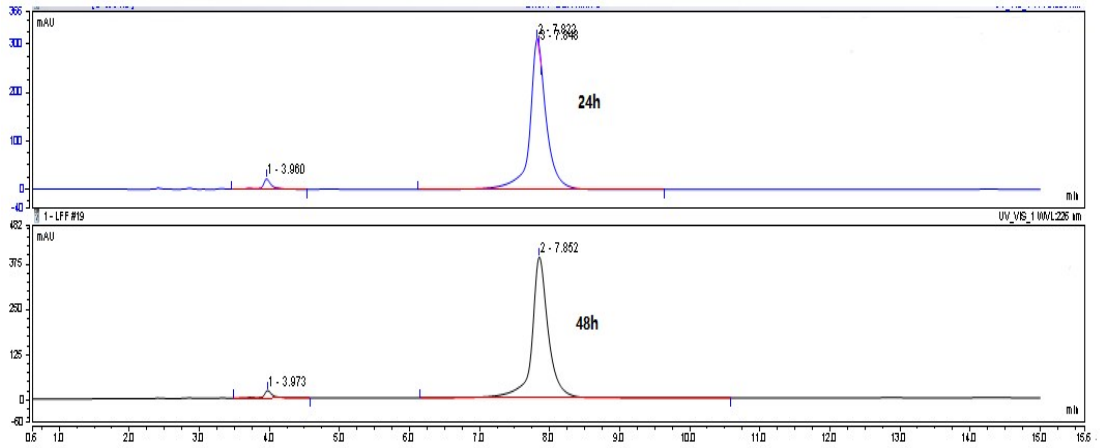


Fig.36. The stability of complexes **1a** in MeOH (0-48h); (250×4.6 mm ODS; 226 nm; MeCN : H_2O = 25:75 (v/v); 1.0 mL/min)

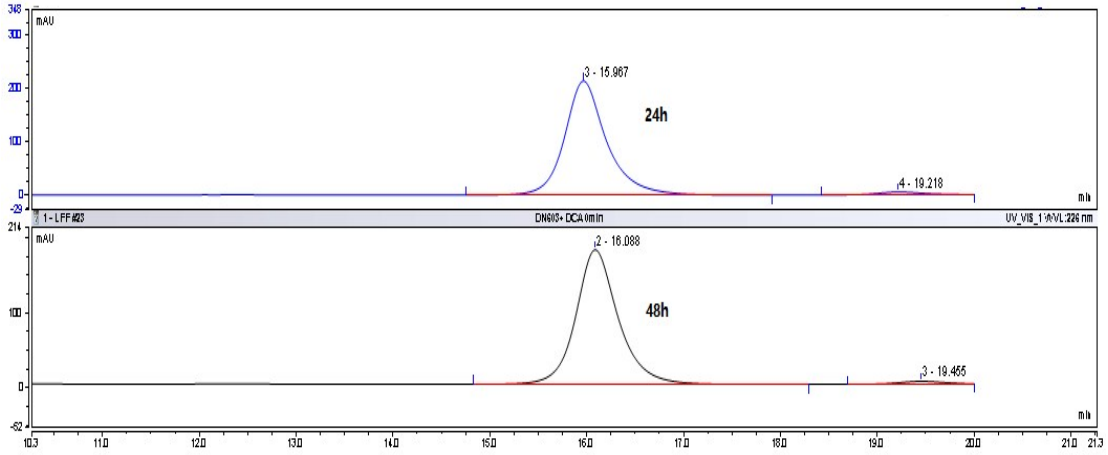


Fig.37. The stability of complexes **1b** in MeOH (0-48h); (250×4.6 mm ODS; 226 nm; MeCN : H_2O = 25:75 (v/v); 1.0 mL/min)

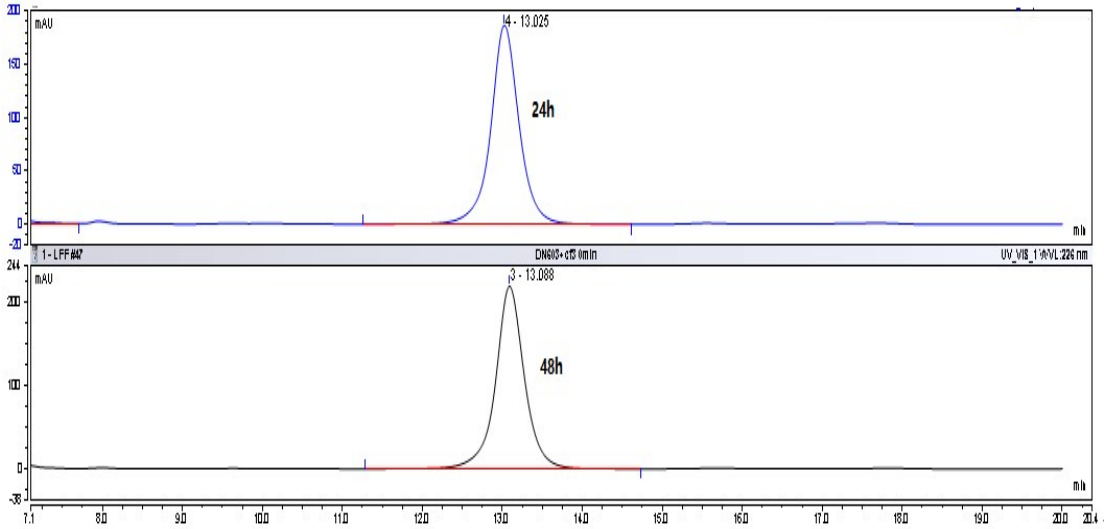


Fig.38. The stability of complexes **2a** in MeOH (0-48h); (250×4.6 mm ODS; 226 nm; MeCN : H_2O = 25:75 (v/v); 1.0 mL/min)

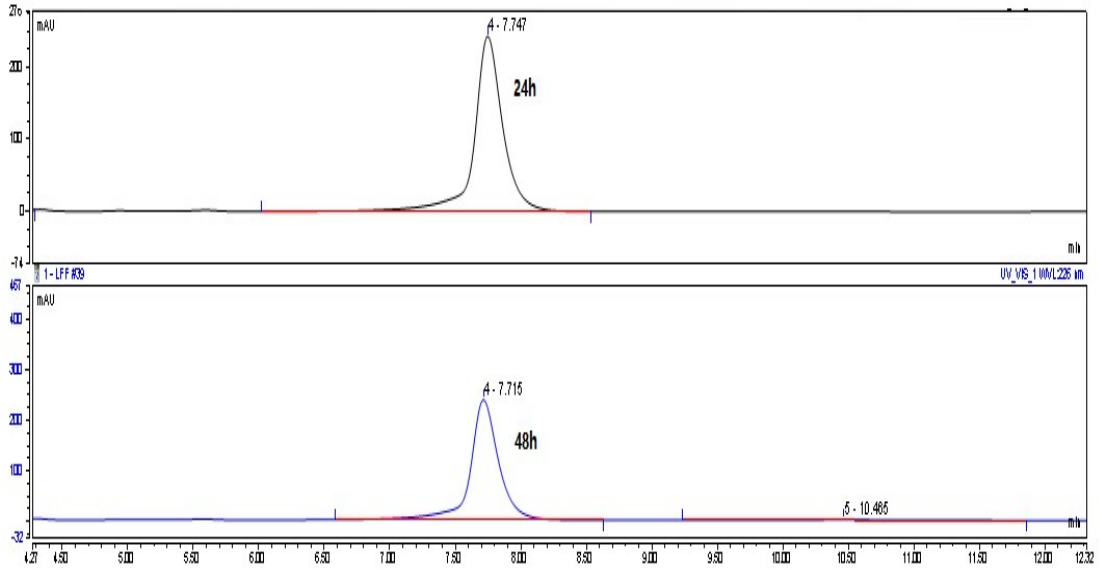


Fig.39. The stability of complexes **2b** in MeOH (0-48h); (250×4.6 mm ODS; 226 nm; MeCN : H_2O = 25:75 (v/v); 1.0 mL/min)

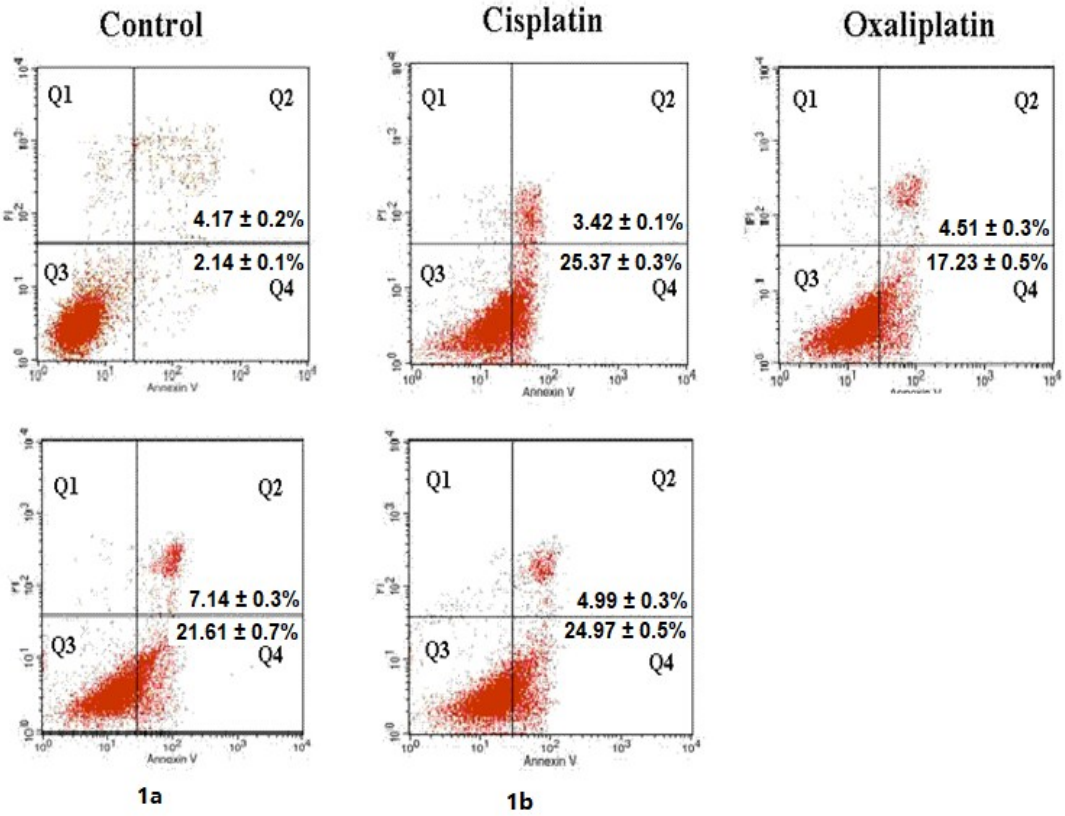


Fig.40. Flow cytometric analysis of the distribution of HepG-2 cells treated with 50 μM of cisplatin, oxaliplatin, complex **1a** and **1b** for 24 hours (DMF final concentration < 0.4%). Cells were stained with 5 mL of Annexin V-FITC and incubated in the dark at 25 °C for 10 mins. The fluorescence was measured by using a flow cytometer. The results were expressed as the percentage of normal and apoptotic cells at various stages by FCSExpress software.

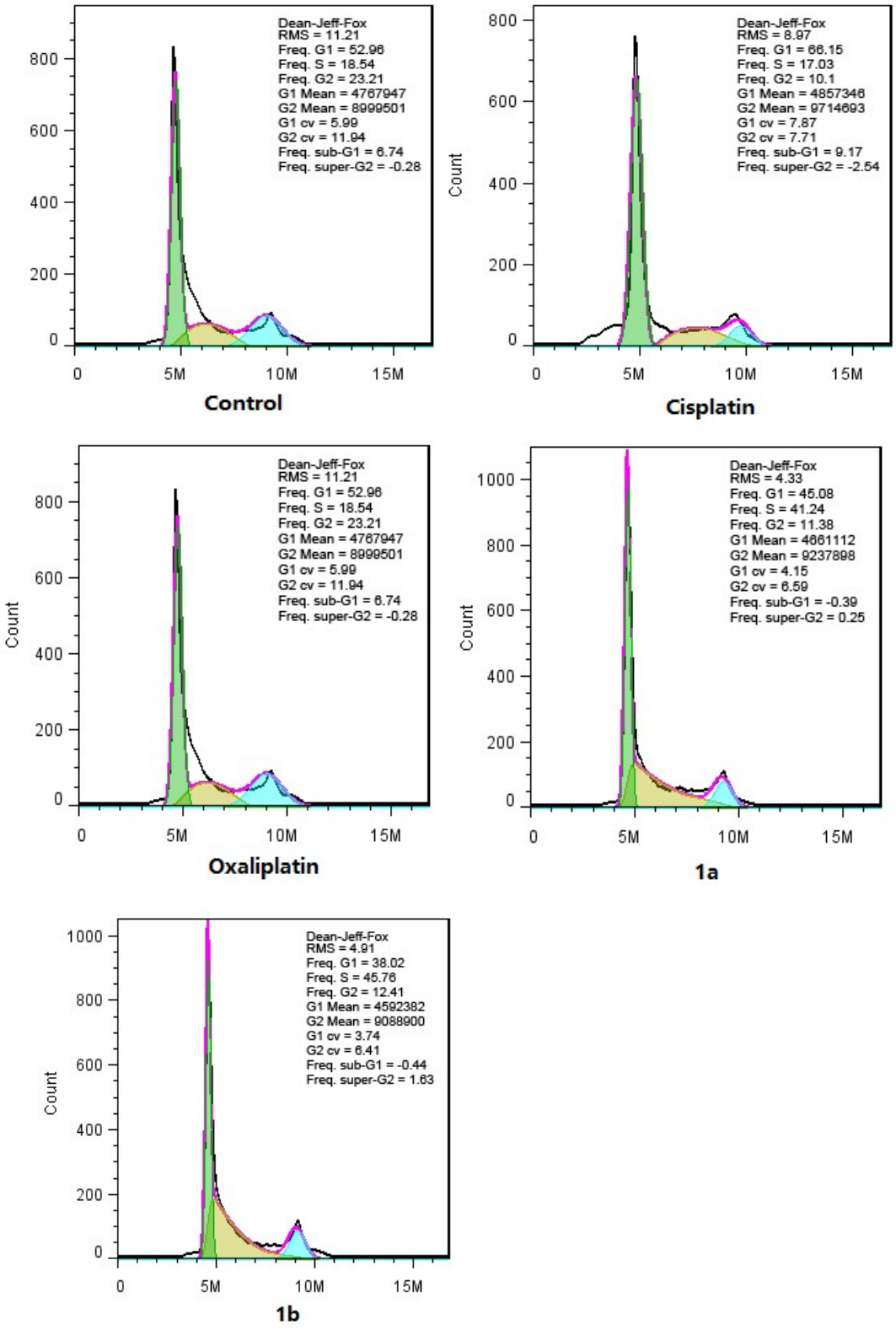


Fig.41. Cell cycle distribution of HepG-2 cells cultured in the presence of 30 μM of cisplatin, oxaliplatin, complex **1a** and **1b** (DMF final concentration < 0.4%). The cells were seeded in 6-well plates for 12 hours, and then the cells were treated with cisplatin, oxaliplatin, complex **1a** and **1b**. After 12 hours of treatment, cells were harvested with trypsin and washed twice with PBS.