

# Synthesis and anticancer activity of two highly water-soluble and ionic Pt(IV) complexes as prodrugs for Pt(II) anticancer drugs

Anli Gao (✉ [gaoanli@126.com](mailto:gaoanli@126.com))

Kunming Institute of Precious Metals <https://orcid.org/0000-0002-4718-3081>

Yaxi Wu

Kunming Medical University

Jing Jiang

Kunming Institute of Precious Metals

Hongyu Gong

Kunming Medical University

Juan Yu

Kunming Institute of Precious Metals

Caihong Yang

Kunming Medical University

Weiping Liu

Kunming Institute of Precious Metals

Chen Qing

Kunming Medical University

---

## Research Article

**Keywords:** Pt(IV) prodrug, Mesylate, Synthesis, Anticancer activity

**Posted Date:** September 2nd, 2021

**DOI:** <https://doi.org/10.21203/rs.3.rs-839613/v1>

**License:** © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

---

**Version of Record:** A version of this preprint was published at RSC Medicinal Chemistry on January 1st, 2022. See the published version at <https://doi.org/10.1039/D2MD00004K>.

## Abstract

Two new Pt(IV) complexes featuring mesylate as outer sphere anions, *cis,trans,cis*-[PtCl<sub>2</sub>(OH<sub>2</sub>)<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>](CH<sub>3</sub>SO<sub>3</sub>)<sub>2</sub> (**SPt-1**) and *cis,trans,cis*-[PtCl<sub>2</sub>(OH<sub>2</sub>)<sub>2</sub>((1*R*,2*R*-DACH))](CH<sub>3</sub>SO<sub>3</sub>)<sub>2</sub> (**SPt-2**) were synthesized, and characterized by elemental analysis, <sup>1</sup>H- and <sup>13</sup>C-NMR, IR, and ESI-MS. Both complexes have excellent water-solubility and high molar conductivity as well as good water-stability. They exhibit an irreversible two-electron reduction event with the peak potentials (E<sub>p</sub>) for the processes being - 0.39 V and - 0.64 V for **SPt-1** and 0.09 V and - 0.52 V for **SPt-2**. The biological tests reveal that **SPt-2** possesses high *in vitro* anticancer activity against three human cancer cell lines and its overall anticancer activity is slightly greater than that of oxaliplatin, whereas **SPt-1** is less active than cisplatin. Moreover, the antitumor efficacy of **SPt-2** on human colon carcinoma HCT-116 xenografts in nude mice is also greater than that of oxaliplatin, suggesting **SPt-2** deserves further evaluation as a prodrug for oxaliplatin.

## Introduction

In today's world, malignant tumors have become one of the most prevalent and serious diseases, and rank first in human disease-related lethality. Chemotherapy is a central component in the fight against malignant tumors, and is based on different classes of anticancer drugs. Among them, platinum-based drugs represent an important class characterized by killing cancer cells primarily through cross-linking DNA and inhibiting transcription [1, 2]. Platinum-based drugs now available for clinical options include cisplatin, carboplatin, oxaliplatin, nedaplatin, heptaplatin lobaplatin and miriplatin hydrate, and they have been successfully used in the treatment of solid tumors [3–5]. However, like other chemotherapy agents, the clinical applications of platinum-based drugs are largely restricted by side-effects as well as drug resistance [6–8]. As a result, the need for the development of new strategies to overcome these drawbacks is highlighted.

One of the strategies involves providing Pt(IV) complexes as prodrugs for Pt(II) anticancer drugs. Platinum(IV) complexes are almost always six-coordinated with octahedron geometries, the saturated, kinetically much more inert coordination sphere is less susceptible to ligand substitution reactions than four-coordinate platinum(II) centers, thus minimizing undesired side reactions with biomolecules prior to DNA binding [9]. In addition, the two extra axial ligands of low-spin d<sub>6</sub> platinum(IV) centers provide a means to endow and fine-tune desired biological properties such as lipophilicity, redox stability, cancer-cell targeting, orthogonal or complementary bioactivity, and improved cellular uptake [10–15]. However, although platinum(IV) complexes can platinate DNA in their oxidized form, the formation of cytotoxic lesions by ligand substitution occurs on the scale of weeks [16], therefore, reduction of the platinum(IV) center to homologous platinum(II), accompanied by the loss of two axial ligands, is thought to be essential for these agents to exert anticancer activity [17]. So far, four Pt(IV) complexes, including iproplatin, satraplatin, tetraplatin and LA-12 (Fig. 1), have undergone clinical trials, However, the outcomes of clinical trials are unsatisfactory as expected, none of these compounds has been approved for clinical application, because they can't exhibit overall effectiveness that surpassed that of their prototype Pt(II) anticancer drugs or have severe neurotoxicity, etc. [18–21].

Herein, we present two new Pt(IV) complexes, **SPt-1** and **SPt-2**, as shown in Fig. 2. They belong to ionic complexes with high molar conductivity featuring with two axial aqua ligands in the inner coordination sphere and two mesylate ions in the outer coordination sphere. Both complexes have good water-solubility and water-stability compared with other Pt(II) and Pt(IV) anticancer complexes, Moreover, **SPt-2** seems to be more active against colorectal cancer than its corresponding Pt(II) drug, oxaliplatin.

## Experimental

All reactions were carried out under normal atmospheric conditions. Reagents are commercially available and were used as received without additional drying or purification. The compounds *cis,trans,cis*-[PtCl<sub>2</sub>(OH)<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>] and *cis,trans,cis*-

[PtCl<sub>2</sub>(OH)<sub>2</sub>((1*R*,2*R*-DACH))] were synthesized using *cis*-[PtCl<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>] and *cis*-[PtCl<sub>2</sub>((1*R*,2*R*-DACH))] as the starting material, respectively [22,23], and *cis*-[PtCl<sub>2</sub>((1*R*,2*R*-DACH))] was synthesized as described in the literature[23].

Composition analyses for C, H, and N were performed with using a Carlo-Erba Instrument, whereas platinum content was determined according to the method in USP24. Electrospray ionization mass spectrometry (ESI-MS) measurements were acquired on a Agilent G6230 Spectrometry in the ESI<sup>+</sup> mode. FT-IR spectra were recorded in the 4,000–400 cm<sup>-1</sup> region on a BRUKER Tensor-27 spectrometer with KBr pellets. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded in deuterated oxide (D<sub>2</sub>O) on a Bruker AVANCE III 500 MHz spectrometer at 20°C. All NMR chemical shifts (δ) were reported in parts per million (ppm). <sup>1</sup>H and <sup>13</sup>C NMR spectra were referenced internally to residual solvent peaks and chemical shifts are expressed relative to TMS.

Cyclic voltammograms were obtained by using a BAS100 potentiostat at room temperature. A three electrode system was used consisting of a glassy carbon electrode as the working electrode, a Pt wire as the auxiliary electrode, and Ag/AgCl electrode as the reference electrode. Samples were prepared as 1 mM solutions in water with 0.05 mM Na<sub>2</sub>SO<sub>4</sub> as the supporting electrolyte. Reported values were peak potentials of the irreversible reduction event at a scan rate of 100 mV/s. Both constant pressure and initial pressure were 0.9 V.

## Synthesis

### *cis,trans,cis*-[Pt(IV)Cl<sub>2</sub>(OH)<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>](CH<sub>3</sub>SO<sub>3</sub>)<sub>2</sub> (SPT-1)

Methanesulfonic acid (2.93 g, 30.5 mmol) was mixed with *cis,trans,cis*-[PtCl<sub>2</sub>(OH)<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>] (5.12 g, 15.3 mmol) in 40 mL H<sub>2</sub>O with stirring at 60 °C for 8 h. The resulting solution became clarified, and then was concentrated under reduced pressure to obtain yellow product. The desired product was collected, washed successively with ethanol and diethyl ether, and dried in vacuo. Yield: 4.5 g (56%). <sup>1</sup>H NMR (D<sub>2</sub>O,500MHz): δ 2.73(s, 6H, 2CH<sub>3</sub>SO<sub>3</sub>),4.79(s, solvent). <sup>13</sup>C NMR (D<sub>2</sub>O,500MHz): δ 38.42 (s, 2C, 2CH<sub>3</sub>SO<sub>3</sub>). IR (KBr, cm<sup>-1</sup>): 3428(v, ν<sub>H2O</sub>), 3190, 3061(m, ν<sub>N-H</sub>), 2852(w, ν<sub>CH3</sub>), 2794 (w, δ<sub>CH3</sub>), 1415, 1396(m, δ<sub>C-H</sub>), 1208 (vs, ν<sub>as</sub>(SO<sub>2</sub>)), 1170 (vs, ν<sub>a</sub>(SO<sub>2</sub>)), 781(m, ν<sub>C-S</sub>), 591(s, ν<sub>Pt-N</sub>), 546(s, ν<sub>Pt-O</sub>), 509 (s, ν<sub>Pt-Cl</sub>). ESI-MS (positive ion mode): 333 m/z [M]<sup>2+</sup>. Anal. Calcd. for C<sub>2</sub>H<sub>16</sub>N<sub>2</sub>Cl<sub>2</sub>O<sub>8</sub>S<sub>2</sub>Pt: C, 4.56; H, 3.04; N,5.32; Pt, 37.07. Found: C, 4.58; H, 3.00; N, 5.34; Pt, 36.78.

### *cis,trans,cis*-[Pt(IV)Cl<sub>2</sub>(OH)<sub>2</sub>(1*R*,2*R*-DACH)](CH<sub>3</sub>SO<sub>3</sub>)<sub>2</sub> (SPT-2)

*Cis,trans,cis*-[PtCl<sub>2</sub>(OH)<sub>2</sub>(1*R*,2*R*-DACH)] (4.1 g, 10 mmol) was suspended in water(70 mL) and then methanesulfonic acid (1.88 g, 19.6 mmol) was added. The mixture was stirred for 8 h at 60°C, resulting in the formation of a homogenous solution. The solution was rotary evaporated, leaving yellowish-brown product. The desired product was obtained by filtration, washed successively with ethanol and diethyl ether, and finally dried under vacuum. Yield: 5.76 g (96%). <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O): δ 4.79(s, solvent), 3.02(d, 2H, N-CH), 2.77(s, 6H, 2CH<sub>3</sub>SO<sub>3</sub>), 2.21 (d, 2H, CH<sub>2</sub>), 1.56 (d, 4H, CH<sub>2</sub>), 1.19 (t, 2H, CH<sub>2</sub>). <sup>13</sup>C NMR (100 MHz, D<sub>2</sub>O): δ 62.48(s, 2C, N-CH), 39.29 (s, 2C, 2CH<sub>3</sub>SO<sub>3</sub>), 30.43(s, 2C, CH<sub>2</sub>), 23.21(s, 2C, CH<sub>2</sub>). IR (KBr, cm<sup>-1</sup>): 3503, 3444(m, ν<sub>N-H</sub>), 2968 (m, ν<sub>CH3</sub>), 2865 (m, δ<sub>CH3</sub>), 1218 (vs, ν<sub>as</sub>(SO<sub>2</sub>)), 1160 (vs, ν<sub>a</sub>(SO<sub>2</sub>)), 780(m, ν<sub>S-O</sub>), 554(s, ν<sub>Pt-N</sub>), 536(s, ν<sub>Pt-O</sub>),446 (s, ν<sub>Pt-Cl</sub>). ESI-MS (positive ion mode): 420 m/z [M]<sup>2+</sup>. Anal. Calcd. for C<sub>8</sub>H<sub>24</sub>N<sub>2</sub>Cl<sub>2</sub>O<sub>8</sub>S<sub>2</sub>Pt: C, 15.81; H, 4.04; N, 4.60; Pt, 32.19. Found: C, 15.84; H, 3.96; N,4.62; Pt, 32.18.

## Investigation of water-stability

10 mg of **SPT-1** or **SPT-2** was added to an NMR tube and dissolved by 1 ml D<sub>2</sub>O. The tube was kept in the dark at 25 °C, and <sup>1</sup>H NMR was measured at different time points.

## Cell culture

All human cancer cell lines HCT-116, A549, MKN-1 were purchased from the Cell Bank of the Shanghai Institute for Life Sciences, Chinese Academy of Sciences (Shanghai, China), and were grown in DMEM or RPMI-1640 medium (Hyclone, USA) containing 10% fetal bovine serum. Both media were supplemented with 100 U/ml of penicillin and 100 µg/ml of streptomycin. Cells were maintained at 37°C in a humidified incubator with an atmosphere of 5% CO<sub>2</sub> for 24 h, and then seeded at a density of 5×10<sup>4</sup> cells per well in 96-well microplates.

## MTT assay

*In vitro* cytotoxic activity was determined by colorimetric MTT [3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide] assay. A 100 µL of cell suspension was seeded in 96-well cell culture plates and allowed to adhere overnight. The tested complexes were dissolved in 5% glucose solution just before the incubation with cancer cells, and diluted in culture media at the indicated concentrations. The cells were incubated with drugs for 72 h, and then a 20 µL of CellTiter 96® Aqueous One Solution Reagent (Promega, Madison, USA) was added and the cells were further incubated at 37 °C for 1–2 h. Cell viability was measured by reading the absorbance at the wavelength of 490 nm. Concentrations of 50% inhibition of growth (IC<sub>50</sub>) were calculated on the basis of the relative survival curve.

## *In vivo* tests

Four- to five-week-old female BALB/c-nude mice were purchased from Beijing Weitonglihua Experimental Animal Technology Co., Ltd. and were kept in a pathogen-free environment. Animal experiments were conducted by following a well-established and recognized methods. Every procedure with animals was done in a laminar airflow cabinet. 5×10<sup>6</sup> HCT-116 cells with 0.2ml per mice were implanted subcutaneously into the right axillary region of BALB/c mice. When tumor volumes reached 100-300 mm<sup>3</sup>, the mice were randomly assigned to control and treatment groups and the administration of drug or compound tested was started. Animals were given i.p. every other day (on day 0 to day 25) with SPT-2 (1.25µM/kg, 2.5µM/kg and 5µM/kg dissolved in 5% glucose) or oxaliplatin (2.5µM/kg and 5µM/kg in 5% glucose). Animals in the control group received the same amount of 5% glucose solution. Tumor size was assessed regularly by vernier caliper measurement and tumor volume was expressed as (length × width<sup>2</sup>)/2. The relative tumor growth rate (T/C, %) was used as an indicator to evaluate the *in vivo* antitumor activity. Mice body weight was determined at baseline before the drug administration and recorded regularly during the experiment which was terminated on day 25.

All animal experiments were conducted in accordance with the Institutional Animal Care and Use Committee Guidelines of Kunming Medical University.

## Results And Discussion

The synthesis of the platinum(IV) mesylate complexes was accomplished by treating *cis,trans,cis*-[PtCl<sub>2</sub>(OH)<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>] or *cis,trans,cis*-[Pt(IV)(1*R*,2*R*-DACH)(OH)<sub>2</sub>Cl<sub>2</sub>] with methylsulfonic acid in water. Because two dihydroxy intermediates are largely insoluble in water, the progress of the reaction can be monitored visually by observing the conversion of the reaction mixture from suspension to homogenous solution. After the dihydroxy intermediate was dissolved in methylsulfonic acid, the solution was rotary evaporated to precipitate the desired product.

The chemical structures were well confirmed by elemental analysis and spectroscopic (Supplementary Fig. S1–S8), which were in accordance with the expected structures (Fig. 2). The compositions were in good agreement with the calculated values based on the molecular formula. A peaks of relative intensity developed at m/z 333 and 420 were corresponding to [M]<sup>2+</sup> of **SPT-1** and **SPT-2** respectively. The characteristic absorption bands arising from NH<sub>3</sub> groups of **SPT-1** were apparent at 3190 and 3061 cm<sup>-1</sup>, whereas NH<sub>2</sub> groups of **SPT-2** were at 3503 and 3444 cm<sup>-1</sup>. The ν<sub>as</sub>(SO<sub>2</sub>) and ν<sub>s</sub>(SO<sub>2</sub>) value of **SPT-**

**1** were 1208 and 1170  $\text{cm}^{-1}$  compared with that of **SPt-2** at 1218 and 1160  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR was consistent with the protons of **SPt-1** and **SPt-2** both in terms of chemical shifts and integration. All the  $^{13}\text{C}$  NMR signals could be assigned to the corresponding carbon atoms in the complex molecule. The chemical shift of carbon was nearly equal to that of  $\text{CH}_3\text{SO}_3\text{Na}$ , indicating that  $\text{CH}_3\text{SO}_3^-$  did not bind to platinum center in the coordination way.

The solubility of **SPt-1** in water was 14 mg/ml and that of **SPt-2** was 50 mg/ml, much larger than that of the corresponding platinum(II) complexes. The water-stability was judged by the changes in  $^1\text{H}$  NMR of these compounds in  $\text{D}_2\text{O}$  (10 mg/mL) with time. As seen from Fig. 3 and Fig. 4, there were no apparent changes of  $^1\text{H}$  signals of **SPt-1** and **SPt-2** in  $\text{D}_2\text{O}$  within 48 h at 20°C, implying that they have sufficient water stability as drug candidates. The molar conductivity of **SPt-1** and **SPt-2** in water were determined to be 297.2 and 288.71  $\Omega^{-1}\text{cm}^2\text{mol}^{-1}$ , respectively, at room temperature, similar to that of  $\text{Ca}(\text{CH}_3\text{SO}_3)_2$ , suggesting that they were ionic compounds, consistent with the proposed structures.

### Cyclic voltammetry

The biological activity of platinum(IV) complexes was regulated by their redox chemistry. In most cases, unlike their platinum(II) progeny, platinum(IV) complexes did not bind directly to DNA or other biological nucleophiles. The redox potential of platinum(IV) complexes was therefore considered to be an important factor in their efficacy as antitumor agents. As illustrated in Fig. 5, the complexes exhibited an irreversible two-electron reduction event in the potential window of +1.0 to -1.0 V vs. Ag/AgCl. The peak potentials ( $E_p$ ) were found to be -0.39 and -0.64 V for **SPt-1**, and 0.09 and -0.52 V for **SPt-2**, implying that both Pt(IV) complexes could be readily reduced to platinum(II) in the hypoxia environment of cancerous cells.

### *In vitro* cytotoxic activity

The cytotoxicity of **SPt-1**, **SPt-2** along with their corresponding platinum(II) compounds, cisplatin and oxaliplatin, was tested by the means of MTT assay against three human cancer cell lines: colon carcinoma (HCT-116), non-small-cell lung carcinoma (A549) and gastric carcinoma (MKN-1) cells. The  $\text{IC}_{50}$  values, defined as the concentrations corresponding to 50% growth inhibition, were presented in Table 1. **SPt-1** and **SPt-2** showed significantly inhibiting effect against the growth of the three cancer cell lines in a good time-effect relationship manner. The overall anticancer activity of **SPt-2** was greater than that of oxaliplatin, whereas **SPt-1** was inferior to cisplatin. In particular, **SPt-2** exhibited the highest cytotoxicity against HCT-116 cancer cells, which was distinctly higher than oxaliplatin, a first-line chemotherapeutic agent for metastatic colorectal cancer.

**Table 1** Cytotoxicity of **SPt-1** and **SPt-2** against three human cancer cell lines.

Compounds	Exposure / h	IC <sub>50</sub> (μM) Mean±SD (n=3)		
		HTC-116	A549	MKN-1
<b>SPt-1</b>	48	46.62±13.09	45.85±2.42	26.30±9.34
	72	35.29±7.86	38.52±8.17	30.41±-
<b>Cisplatin</b>	48	14.47±4.79	29.47±2.69	15.67±7.12
	72	12.48±3.16	22.51±0.93	13.14±8.72
<b>SPt-2</b>	48	7.28±1.91	40.8±4.88	33.8±5.23
	72	3.61±1.27	34.2±2.02	17.1±2.18
<b>Oxaliplatin</b>	48	39.8±6.63	52.1±6.36	48.9±10.6
	72	30.1±12.0	44.8±7.40	28.2±11.4

### *In vivo* antitumor activity

The *in vivo* antitumor activity of **SPt-2** and oxaliplatin was compared on HCT-116 xenograft in nude mice. As seen from Table 2, at the dose of 1.25 μM kg<sup>-1</sup>, 2.5 μM kg<sup>-1</sup>, and 5 μM kg<sup>-1</sup>, T/C after the treatment with **SPt-2** was 53% (*p* < 0.01), 40% (*p* < 0.01) and 31% (*p* < 0.001), respectively, which implied it could significantly inhibit the growth of tumor in a dose-dependent manner, while obvious inhibition effect of oxaliplatin on the growth of tumor wasn't manifested until the dose was up to 5 μM/kg and then T/C was 44%. In the meantime, the apparent change in mice body weights during the treatment of **SPt-2** did not occur at low and medium doses. As a consequence, the curative effect of **SPt-2** on HCT-116 xenograft in nude mice was superior to oxaliplatin at the same dose.

**Table 2** The curative effect of **SPt-2** and oxaliplatin on xenograft in nude mice HCT-116

Compounds	Dosage	Administration Route	Number of animals		Body weight of mice (g)		Tumor volume (mm <sup>3</sup> )		T/C (%)
			d <sub>0</sub>	d <sub>25</sub>	d <sub>0</sub>	d <sub>25</sub>	d <sub>0</sub>	d <sub>25</sub>	
Control Group	5% G.S		6	6	20.8±0.85	20.8±0.85	343±76.5	2879±826	100
Oxaliplatin	2.5 μM/kg	i.p.	6	6	21.1±1.33	16.6±1.24	378±135	2340±977	54
	5 μM/kg		6	6	21.2±1.33	16.6±1.24	396±84.7	1808±681**	44
<b>SPt-2</b>	1.25 μM/kg		6	6	21.1±1.22	16.8±1.84	353±86.5	1715±603**	53
	2.5 μM/kg		6	6	21.3±0.90	16.4±0.68	353±117	1574±684**	40
	5 μM/kg		6	6	20.7±1.30	13.9±1.24**	363±111	1030±297***	31

## Conclusions

In this paper, we present two new water-soluble and stable platinum(IV) prodrugs featuring the ionic-type complexes. They exhibit an irreversible two-electron reduction event and can be reduced to active platinum(II) species. Both platinum(IV) prodrugs show cytotoxicity against the proliferation of three human cancer cell lines, especially **SPt-2**, whose *in vitro*

cytotoxicity and *in vivo* antitumor efficacy were stronger than those of oxaliplatin, a first-line chemotherapeutic agent for colorectal cancer, suggesting **SPT-2** deserves further evaluation as a prodrug for oxaliplatin in the treatment of colorectal cancer.

## Declarations

## Acknowledgement

This work was supported by the Applied Basic Research Foundation of Yunnan Province (Grant No. 202001AT070090, 202102AA310026).

## References

1. Harper BW, Krause-Heuer AM, Grant MP, Manohar M, Garbutcheon-Singh KB, Aldrich-Wright JR (2010) Chem Eur J 16:7064
2. Kelland L (2007) Nat Rev Cancer 7:573
3. Zutphen SV, Reedijk J (2005) Coord Chem Rev 249:2845
4. Kostova I (2006) Recent Pat. Anticancer Drug Discov 1:1
5. Wilson JJ, Lippard SJ (2014) Chem Rev 114:4470
6. Wang X, Guo Z (2013) Chem Soc Rev 42:202
7. Muhammad N, Guo Z (2014) Curr Opin Chem Biol 19:144
8. Min Y, Mao C, Chen S, Ma G, Wang J, Liu Y (2012) Angew Chem Int Ed 51:6742
9. Johnstone TC, Suntharalingam K, Lippard SJ (2016) Chem Rev 116:3436
10. Lee VEY, Lim ZC, Chew SL, Ang WH (2021) Inorg Chem 60:1823
11. Lee VEY, Chin CF, Ang WH (2019) Dalton Trans 48:7388
12. Ferrari B, Roda E, Priori EC, Luca FD, Facoetti A, Ravera M, Brandalise F, Locatelli CA, Rossi P, Bottone MG (2021) Org Res 15:1
13. Lee VEY, Lim ZC, Ang WH (2021) S. I. Chew. Inorg Chem 60:1823
14. Shi H, Imberti C, Huang H, Hands-Portman I, Sadler PJ (2020) Chem Commun 56:2320
15. Kenny RG, Marmion CJ (2019) Chem Rev 119:1058
16. Dolman. RC, Deacon GB, Hambley TW (2002) J Inorg Biochem 88:260
17. Ravera M, Gabano E, Zanellato I, Rangone B, Perin E, Ferrari B, Bottone MG, Osella D (2021) Dalton Trans 50:3161
18. O'Rourke TJ, Weiss GR, New P, Burris HA, Rodriguez G, Eckhardt J, Hardy J, Kuhn JG, Fields S, Clark GM, D. D.von Hoff, Anti-Cancer Drugs, **5**, 520 (1994)
19. Clavel M, Monfardini S, Gundersen S, Kaye S, Siegenthaler P, Renard J, van Glabbeke M, Pinedo HM, Eur. J. Cancer Clin Oncol. 24, 1345 (1988)
20. Sternberg CN, Whelan P, Hetherington J, Paluchowska B, Th. PH, Slee J, Vekemans K, Van Erps P, Theodore C, Koriakine O, Oliver T, Lebwohl D, Debois M, Zurlo A, Collette L (2005) Oncology 68:2
21. Bouchal P, Jarkovsky J, Hrazdilova K, Dvorakova M, Struharova I, Hernychova L, Damborsky J, Sova P, Vojtesek B (2011) Proteome Sci 9:68
22. Brandon RJ, Dabrowiak JC (1984) J Med Chem 27:861
23. Rocca JD, Huxford RC, Comstock-Duggan E, Lin W (2011) Angew Chem Ind Ed 50:10330

# Figures

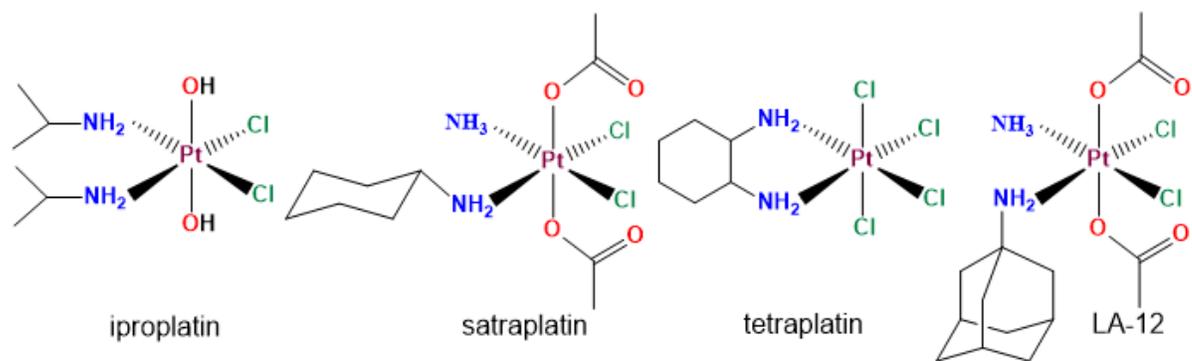


Figure 1

Chemical structures of platinum(IV) agents that have undergone clinical trials

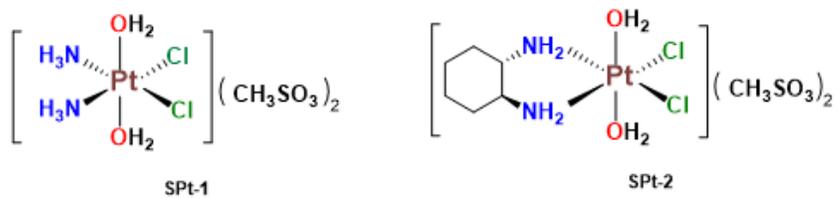
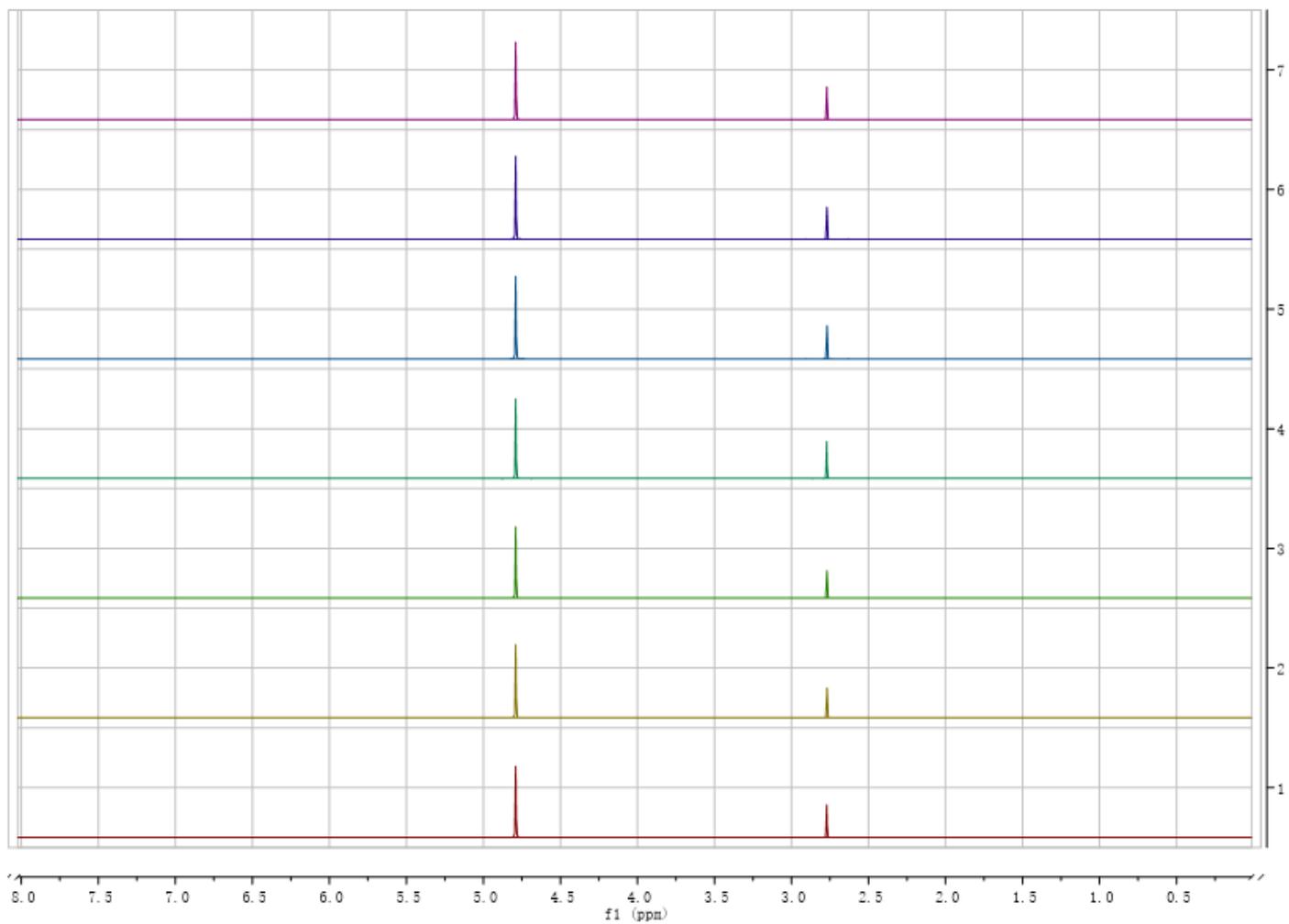


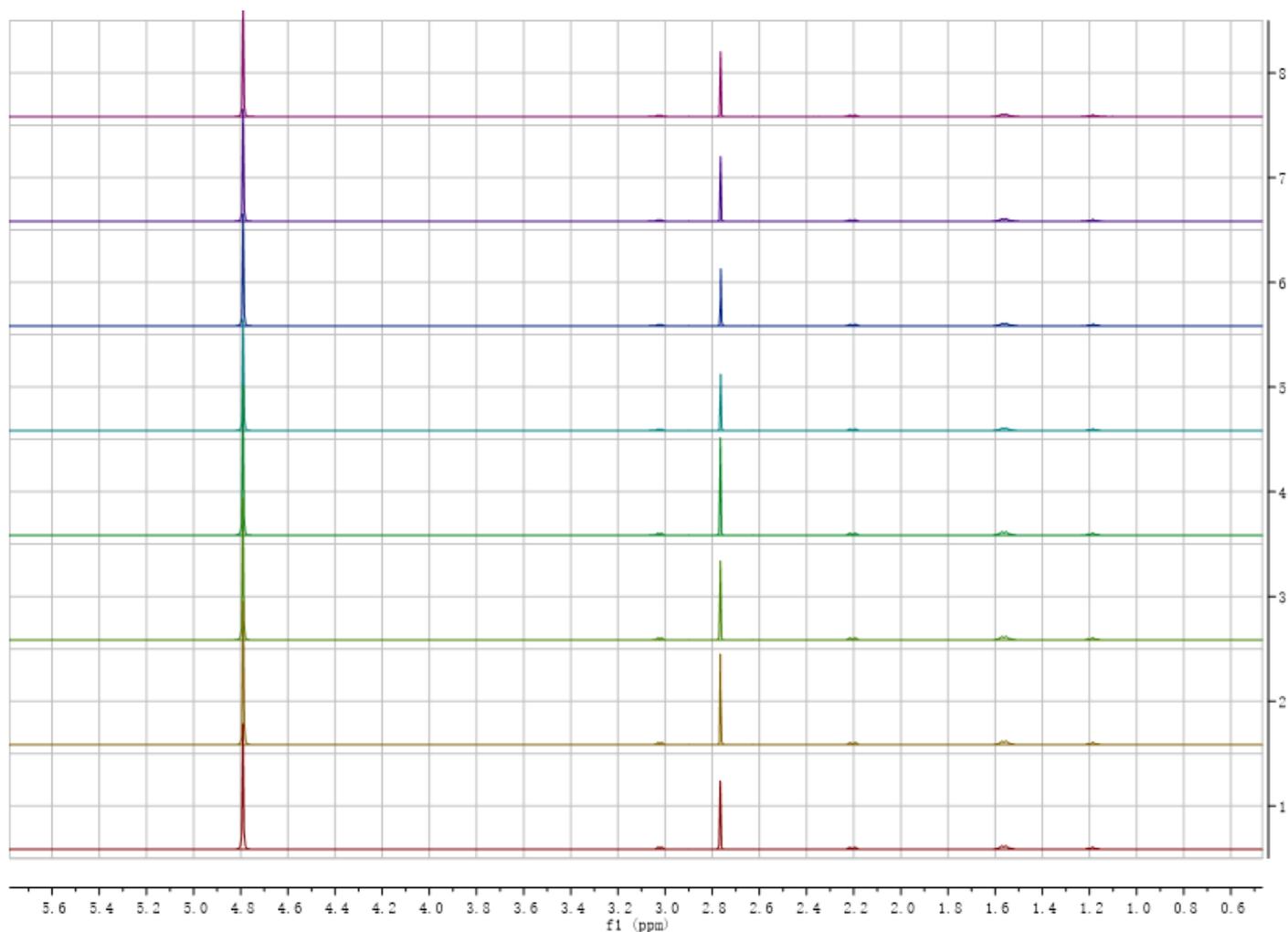
Figure 2

The chemical structures of SPt-1 and SPt-2.



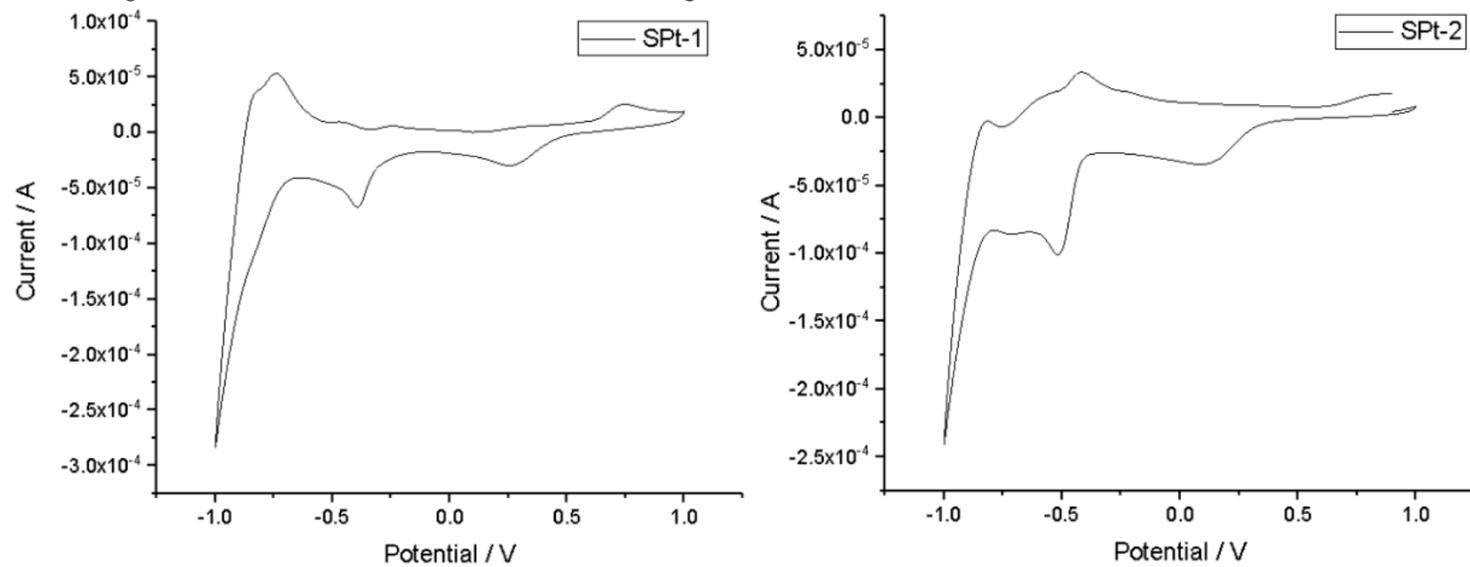
**Figure 3**

The change in <sup>1</sup>H NMR of SPT-1 in D<sub>2</sub>O with the standing time



**Figure 4**

The change in 1H NMR of SPT-2 in D2O with the standing time



**Figure 5**

Cyclic voltammogram for SPT-1 and SPT-2 measured in aqueous solution.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supportingfiles.docx](#)