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FULL PAPER

Synthesis, characterization, and antitumor activity of novel tumor-targeted platinum(IV) complexes

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Four tumor-targeted platinum(IV) complexes with ammonia and cyclohexylamine as the carrier groups and biotin as the axial group were designed, synthesized, and characterized. *In vitro* evaluation of the antitumor activity of complexes C1–C4 against lung cancer cells (A549), liver cancer cells (SMMC-7721), breast cancer cells (MCF-7), and colon cancer cells (SW480) was carried out. Complex C3 had the best cellular activity. Compared with cisplatin, complex C3 showed good anticancer activity against A549 cell line,complex C3 (6.34±0.44) is 3 times more cytotoxic than cisplatin (19.40±0.71),and against MCF-7 cell line complex C3 (4.22±0.11) is 5.4 times more cytotoxic than cisplatin (22.96±0.58), and against SW480 cell line complex C3 (6.65±0.60) is 3.4 times more cytotoxic than cisplatin (23.15±0.22). (Table 1) Axial chloride increased the redox power of complex C3 to increase the intercellular accumulation and the introduction of mixed amine had the ability to overcome cisplatin resistance. Complex C3 works best on MCF-7, then SW480, A549, and SMMC-7721. Thus, complex C3 is targeted by the axial introduction of biotin.

KEYWORDS
oral, platinum(IV), tumor targeted

1 | INTRODUCTION

Classical platinum(II) anticancer agents are chemotherapeutic drugs that are widely used in the clinic against a range of cancers.[1] However, as classical platinum(II) antitumor drugs are used as a carrier group with symmetrical diamine or amino, they can be damaged in the gastrointestinal tract, and therefore cannot be taken orally, only injected. They also cause severe side effects and cross resistance.[2,3] The side effects and cross-resistance are the main obstacles which limit the application and effectiveness of these drugs. The side effects of cisplatin (Figure 1), such as nephrotoxicity, neurotoxicity, ototoxicity, and spitting, limit its efficacy. The main clinical manifestation of carboplatin (Figure 1) limitations is that bone marrow depression limits its dosage range.[4,5] Oxaliplatin (Figure 1) is limited in dosage range due to side effects such as neurotoxicity, hematology, gastrointestinal toxicity, neutropenia, nausea, and vomiting.[6] Therefore, the development of platinum-based complexes with good anticancer activity, fewer side effects, and low drug resistance is the focus of anticancer drug research.

In the search for platinum drugs with low toxicity and favorable pharmacological profiles, platinum(IV) complexes emerge as promising candidates for overcoming the shortcomings of platinum(II) drugs.[7] The oral properties of platinum(IV) drugs break the current situation that platinum(II) drugs can only be injected.[8,9] Platinum(IV) complexes are stable and undamaged in the gastrointestinal environment. They can be absorbed into the blood system and then reduced to active platinum(II), so they can be taken orally. Importantly, they contain

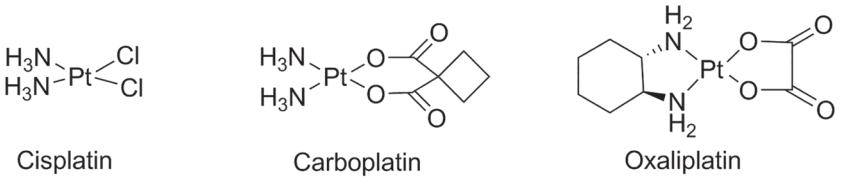


FIGURE 1 Structures of cisplatin, carboplatin, and oxaliplatin

two axial ligands, which can be used to influence the reduction kinetics, lipophilicity, cellular accumulation, and activity of the platinum species.[10,11] It has been reported that chloride increases the reduction power of platinum(IV), leading to its preferential combination with glutathione and reduction to platinum(II).[6,12,13] The most prominent platinum(IV) drug is satraplatin, which has been investigated in advanced phase III clinical trials.[14] The asymmetric amino and cyclohexylamine ligands of satraplatin have unique and excellent antitumor activity. Due to the different structure–activity relationship between the asymmetric carrier groups and the symmetrical amine ligands of classical platinum drugs, the mechanism of action of the two groups is different.[15] Satraplatin is reduced to divalent platinum by intracellular antioxidants after entering the cell and acts directly on DNA to form an adduct with it. The adduct does not bind to high mobility group protein 1, identifies DNA damage caused by cisplatin, and prevents DNA replication by inhibiting some DNA polymerase transfer, making it possible to overcome cross-resistance.[16] In addition, the satraplatin-induced adduct is not recognized by DNA mismatch repair protein, solving the problem of classical platinum drug resistance.

The non-selectivity distribution of platinum drugs in normal and cancer cells can lead to severe systemic toxicity, reducing the accumulation of drugs in tumor cells and increasing drug resistance. In addition, platinum drugs interact with plasma and tissue proteins, which could lead to inactivation of platinum-based drugs. An efficient way to solve these problems is to increase the targeting of platinum drugs to cancer cells.[17] Biotin, also known as vitamin H, is a necessary nutrient to maintain human natural growth, development and normal functional health.[18] Vitamin H is widely used in drug delivery for tumor targeting because of its high demand for the rapid growth of tumors, which leads to overexpression of biotin-specific receptors on the surface of cancer cells.[19] Biotin-induced platinum-toxic complexes have high cytotoxicity to breast cancer cells, but low toxicity to breast epithelial cells. In the treatment of breast cancer, the mono-biotinylated platinum(IV) complexes

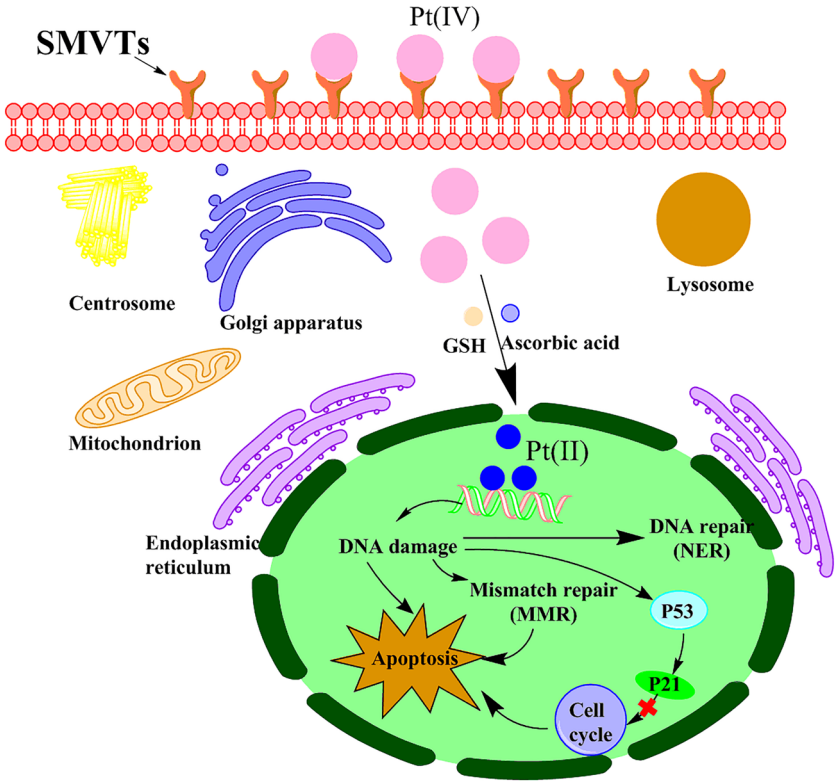


FIGURE 2 Mechanism of action of platinum(IV)

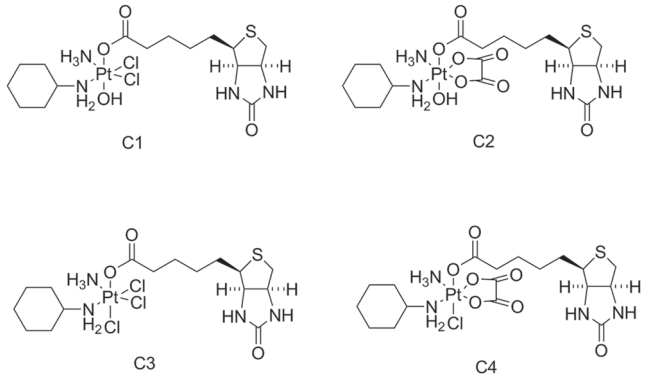


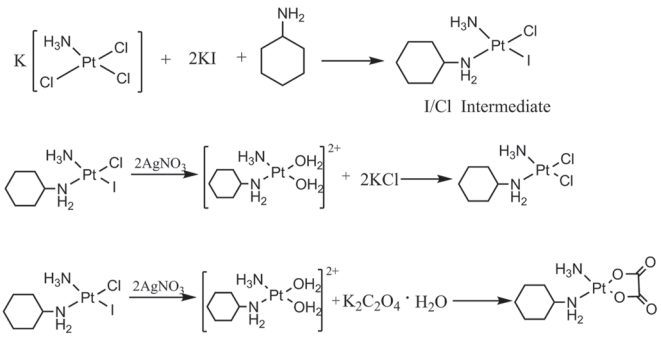
FIGURE 3 Platinum(IV) complexes C1–C4, with ammonia and cyclohexylamine as the carrier groups and biotin as the axial group

are more targeted than the di-biotinylated complexes.[20,21] Moreover, sodium-dependent multi-vitamin transporters also promote biotin uptake, leading to overexpression of cancer cell lines and the potential advantages of chloride in increasing reduction power, which significantly enhance the bioactivity of platinum complexes (Figure 2).

We therefore synthesized novel tumor-targeted platinum(IV) complexes C1–C4 (Figure 3), with ammonia and cyclohexylamine as the carrier groups and biotin as the axial group, with the advantages of satraplatin and targeted drug therapy.

2 | RESULTS AND DISCUSSION

We prepared the Iodine/Chloride (I/CI) intermediate by reaction of potassium trichloroplatinate with KI and cyclohexylamine in a water bath, followed by filtration and drying. The I/Cl intermediate hydrolyzed with silver nitrate to form a hydrolysate and reacted with KI to form Dichloro, ammonia and cyclohexylamine platinum (Pt (II)L1). The I/Cl intermediate also hydrolyzed with silver nitrate to form a hydrolysate and reacted with $K_2C_2O_4{\cdot}H_2O$ to form oxalate, ammonia and cyclohexylamine platinum (PT(II)L2) (Scheme 1).

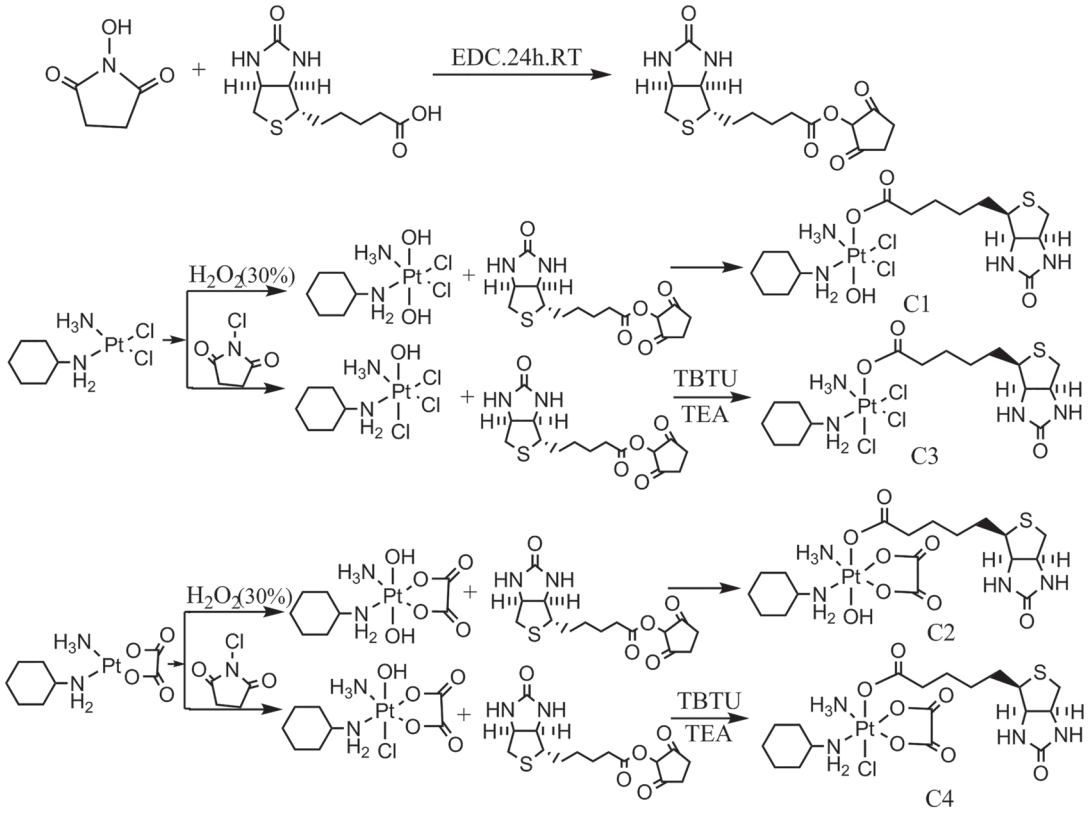


SCHEME 1 Synthesis of I/Cl intermediate, Pt (II)L1, and Pt (II)L2

When preparing the targeted platinum complexes, we first prepared the biotin-NHS ester. Pt(II)L1 was oxidized with H_2O_2 (30%) and *N*-chlorosuccinimide to form platinum(IV) precursors, which further reacted with biotin-NHS ester to form complexes C1 and C3. Pt(II)L2 was also oxidized with H_2O_2 (30%) and *N*-chlorosuccinimide to form platinum(IV) precursors, which further reacted with biotin-NHS ester to form complexes C2 and C4 (Scheme 2).

Pt(II)L1, Pt(II)L2, and the targeted platinum(IV) complexes were characterized by IR, ^{1}H NMR, ^{13}C NMR and ESI-MS spectra. The ^{1}H NMR, ^{13}C NMR and HR-MS of all products have provided as a supporting information. In the IR spectra, amino group participation in binding with Pt(IV) was confirmed by the examination of the νNH_2 and δNH_2 frequencies, which were shifted to lower frequencies compared with the free amino group due to Pt(IV)–NH_2 coordination. The binding of the axial hydroxyl of Pt(IV) with the carboxylic acid of the biotin-NHS ester was confirmed by the examination of Pt–O absorptions shifting from near 959 cm^{-1} to bands near 934–869 cm^{-1}. The complexes showed $[M - H]^-$, $[M + H]^+$, $[M + Na]^+$ or $[M + K]^+$ corresponding to their formula weights and relative fragment peaks in their ESI mass spectra. The ^{1}H NMR spectral of all prepared complexes in Figure 3 were consistent with their corresponding protons in both chemical shift and number of protons.

The *in vitro* cytotoxicity of platinum complexes C1–C4 against human lung cancer cells (A549), liver cancer cells (SMMC-7721), breast cancer cells (MCF-7), and colon cancer cells (SW480) was measured by 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. The maximum inhibitory concentrations (IC_{50}) of platinum complexes C1–C4 at 48 hr are shown in Table 1. Cisplatin and satraplatin were selected as positive controls to compare the cytotoxic activity of the targeting platinum(IV) complexes C1–C4, which took biotin as the active target group of the tumor. It can be seen from Table 1 that complexes C2 and C4 have weak cytotoxicity to the four kinds of cancer cells, while complex C1 only shows certain biological activity to specific colon cancer cells (28.37 ± 0.98). The antitumor activity of C1 is close to that of cisplatin in the SW480 cell line. Compared with cisplatin, complex C3 with chloride in the axial direction showed good anticancer activity against A549 cell line,complex C3 (6.34±0.44) is 3 times more cytotoxic than cisplatin (19.40±0.71), and against MCF-7 cell line complex C3 (4.22±0.11) is 5.4 times more cytotoxic than cisplatin (22.96±0.58), and against SW480



SCHEME 2 Synthesis of complexes C1–C4

TABLE 1 *In vitro* cytotoxicity against four selected human tumor cell lines of complexes C1 to C4

	IC_{50} (μM)[a]			
Complex	**A549[b]**	**SMMC-7721[c]**	**MCF-7[d]**	**SW480[e]**
C1	>40	>40	>40	28.37 ± 0.98
C2	>40	>40	>40	>40
C3	6.34 ± 0.44	19.45 ± 0.50	4.22 ± 0.11	6.65 ± 0.60
C4	>40	>40	>40	>40
Satraplatin	12.01 ± 0.30	16.00 ± 0.34	3.81 ± 0.23	7.15 ± 0.31
Cisplatin	19.40 ± 0.71	14.91 ± 0.36	22.96 ± 0.58	23.15 ± 0.22

[a]All IC_{50} values (drug concentration giving 50% survival) calculated based on at least three separated experiments.
[b]Human nonsmall-cell lung cancer cell.
[c]Human liver cell.
[d]Human breast carcinoma cell.
[e]Human colon cancer cell.

cell line complex C3 (6.65±0.60) is 3.4 times more cytotoxic than cisplatin (23.15±0.22). (Table 1) Compared with satraplatin, the antitumor activity of complex C3 against A549 and SW480 was also improved, while the cytotoxic activity against SMMC-7721 and MCF-7 was comparable. The cell activity of C3 is significantly better than that of other complexes, which may reduce the redox potential and increase the reduction power due to the presence of chloride on the axis, increasing the accumulation of C3 in cells and giving it better anticancer activity than cisplatin and satraplatin in specific cell lines. Of the four cancer cell lines, C3 works best on MCF-7, then SW480, A549, and SMMC-7721. The active tumor targeting function of biotin also plays a role, showing the best cytotoxic activity against MCF-7, which is consistent with the original intention of our design.

3 | CONCLUSIONS

In summary, we designed and synthesized novel platinum(IV) complexes with ammonia and cyclohexylamine as carrier groups and targeted biotin as the axial group, and evaluated their antitumor activity. Complexes C2 and C4 showed weak antitumor activity against the four cell lines. Complex C1 only showed antitumor activity against the SW480 cell line which is similar to cisplatin. Lemma et al[22] concluded that reduction attack of ascorbate on the chloride ligands that forms a bridged transition state in which a concerted two-electron transfer from ascorbate to platinum(IV) leads to the release of two chlorides.[13] Choi et al concluded that the reduction rates and reduction potentials increased in the following order of axial ligand substitution: OH < Cl.[23] Moreover, it was found by MTT assay that a faster reduction rate exhibit higher cytotoxicity. Complex C3 showed good antitumor activity against A549 and SW480 cell lines that was better than satraplatin. Compared with cisplatin, complex C3 showed good anticancer activity against A549 cell line, complex C3(6.34±0.44) is 3 times more cytotoxic than cisplatin(19.40±0.71),and against MCF-7 cell line complex C3(4.22±0.11) is 5.4 times more cytotoxic than cisplatin(22.96±0.58),and against SW480 cell line complex C3(6.65±0.60) is 3.4 times more cytotoxic than cisplatin(23.15±0.22). (Table 1) The cytotoxic order of complex C3 among the four cell lines was MCF-7, A549, SW480, and SMMC-7721. Complex C3 has particularly prominent antitumor activity in MCF-7 compared to other cell lines. Thus, biotin enacts complex C3 to target breast cancer cells.

4 | MATERIALS AND METHODS

4.1 | Synthesis of complex [Pt(II)L1]

I/Cl intermediate (10 mmol) was dissolved in about 300 ml of purified water, bathed at 50°C, and stirred evenly. $AgNO_3$ (10 mmol) was dissolved in 30 ml of purified water. The separation funnel was slowly added into I/Cl intermediate aqueous solution and the reaction was kept in the dark for 3 hr. After the reaction was finished, the AgI and AgCl precipitates were removed by filtration and the pale yellow liquid was collected and water bathed at 50°C to continue stirring. KCl (10 mmol) was dissolved in purified water and slowly added to the reaction system, which was then kept in the dark for 3 hr. After the reaction, cool it in the refrigerator to below 10°C. Then, G4 sand core funnel filtration, filter cake purification water run-wash two to three times, ethanol run-wash once or twice, and dried in an oven at 60°C. Data for [Pt(II)L1]: yield 51.23%, light yellow solid. IR (ν, cm^{-1}): ν(NH) broad 3240, 3194 cm^{-1}, ν_s(CH), ν_{as}(CH) 2922, 2859 cm^{-1}, δ(NH) 1453 cm^{-1}, ν(C–C) 1299 cm^{-1}, ν(Pt–Cl) 783 cm^{-1}, ν(Pt–N) 534 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6) δ: 4.84–4.71 (m, 3H), 4.00 (s, 1H), 2.28–2.16 (m, 2H), 1.73–1.53 (m, 4H), 1.28–0.99 (m, 6H). high resolution mass spectrum (HR-MS) (m/z): $[C_6H_{16}Cl_2N_2Pt + Na]^+$ = 404.0222. ^{13}C NMR (151 MHz, DMSO) δ: 54.84, 54.51, 40.11, 39.99, 39.85, 39.72, 39.58, 39.44, 39.30, 39.16, 33.58, 33.49, 25.27, 25.01, 24.94, 24.65, 24.57.

4.2 | Synthesis of complex [Pt(II)L2]

I/Cl intermediate (10 mmol) was dissolved in about 300 ml of purified water, bathed at 50°C, and stirred evenly. $AgNO_3$ (10 mmol) was dissolved in 30 ml of purified water. The separation funnel was slowly added into I/Cl intermediate aqueous solution and the reaction was kept in the dark for 3 hr. After the reaction was finished, the AgI and AgCl precipitates were removed by filtration, the pale yellow liquid was collected and water bathed at 50°C with continuous stirring. $K_2C_2O_4{\cdot}H_2O$ (10 mmol) was dissolved in purified water and slowly added to the reaction system, and the reaction was kept in the dark for 3 hr. After the reaction, cool it in the refrigerator to below 10°C.Then, G4 sand core funnel filtration, filter cake purification water run-wash two to three times, ethanol run-wash once or twice, and dried in an oven at 60°C. Data for [Pt(II)L2]: yield 65.18%, grey solid. IR (ν, cm^{-1}): ν(NH) br 3267, 3116 cm^{-1}, ν_s(CH), ν_{as}(CH) 2936, 2854 cm^{-1}, δ(NH) 1448 cm^{-1}, ν(C–O) 1696, 1586 cm^{-1}, ν(C–C) 1248 cm^{-1}, ν(Pt–O) 807 cm^{-1}, ν(Pt–N) 633 cm^{-1}. ^{1}H NMR (600 MHz, DMSO) δ: 5.12–5.13 (d, 2H), 4.28 (s, 3H), 2.20–2.17 (m, 2H), 1.69–1.65 (m, 2H), 1.56–1.52 (m, 1H), 1.22–1.03 (m, 6H). HR-MS (m/z): $[C_8H_{16}N_2O_4Pt + H]^+$ = 400.0831. ^{13}C NMR (151 MHz, DMSO) δ: 166.47, 166.34, 54.69, 39.97, 39.83, 39.69, 39.55, 39.42, 39.28, 39.14, 33.26, 25.22, 24.41.

4.3 | Synthesis of complexes C1 and C2

Pt(II)L1 (10 mmol) and Pt(II)L2 (10 mmol), for complexes C1 and C2 respectively, were dissolved in about 250 mL of purified water, bathed at 50°C, and stirred evenly. H_2O_2 (30%; 15 mL) was slowly added to the aqueous solution of Pt(II)L1 or Pt(II)L2. The reactions were conducted in the dark for 5 hr. After the reactions were finished, a light green (C1) or yellow (C2) solid was obtained through filtration. Dried after washing with pure water and ethanol. The filtrate was

collected, evaporated, and concentrated to 50–60 ml then cooled in a refrigerator. After solid precipitation, filtered, washed by purified water and ethanol and dried to solids. Combine the solids twice, get the intermediates. The intermediate products (10 mmol) were dissolved in 20 ml of N,N-dimethylformamide (DMF) in a water bath at 60°C and evenly stirred. Biotin-NHS ester (10 mmol) was added and the reactions were kept in the dark for 24 hr. After the reactions were finished, G4 sand core funnels were used to filter and collect the clarified yellow liquid. The filtrate was reversed osmosis by methanol and ether, and the yellow solids were precipitated by G3 sand-core funnel filtration and methanol:ethyl ether = 1:1 rinsing two to three times, vacuum drying at 50°C, and complexes C1 and C2 were obtained. Data for C1: yield 43.02%, yellow solid. IR (ν, cm^{-1}): ν(NH) br 3378, 3220 cm^{-1}, ν_s(CH), ν_{as}(CH) 2930, 2855 cm^{-1}, δ(NH) 1453 cm^{-1}, ν(C–O) 1685, 1622 cm^{-1}, ν(C–C) 1265 cm^{-1}, ν(Pt–O) 891 cm^{-1}, ν(Pt–Cl) 675 cm^{-1}, ν(Pt–N) 579 cm^{-1}. ^{1}H NMR (600 MHz, DMSO) δ: 6.71–6.60 (s, 1H), 6.52–6.34 (s, 2H), 5.23–6.04 (m, 3H), 4.36–4.30 (m, 1H), 4.18–4.10 (s, 1H), 3.15–3.02 (m, 1H), 2.85–2.78 (m, 1H), 2.70–2.61 (s, 1H), 2.58–2.54 (m, 2H), 1.25–1.95 (m, 4H), 1.74–0.95 (m, 14H). HR-MS (m/z): $[C_{16}H_{32}Cl_2N_4O_4PtS + H]^+$ = 642.1242. ^{13}C NMR (151 MHz, DMSO) δ: 181.70, 162.78, 61.11, 59.24, 55.57, 55.54, 53.95, 40.48, 39.98, 39.92, 39.84, 39.71, 39.57, 39.43, 39.29, 39.15, 36.81, 32.45, 31.96, 28.38, 28.19, 25.69, 25.03, 24.74, 24.65. Data for C2: yield 42.00%, yellow solid. IR (ν, cm^{-1}): ν(NH) br 3246, 3071 cm^{-1}, ν_s(CH), ν_{as}(CH) 2933, 2853 cm^{-1}, δ(NH) 1443 cm^{-1}, ν(C–O)1697, 1615 cm^{-1}, ν(C–C) 1254 cm^{-1}, ν(Pt–O) 934 cm^{-1}, ν(Pt–Cl) 745 cm^{-1}, ν(Pt–N) 534 cm^{-1}. ^{1}H NMR (600 MHz, DMSO) δ: 7.22–6.97 (s, 1H), 6.48–6.29 (m, 2H), 6.22–5.96 (m, 3H), 4.33–4.24 (s, 1H), 4.16–4.03 (s, 1H), 3.09–3.02 (m, 1H), 2.83–2.77 (m, 1H), 2.72–2.64 (s, 1H), 2.57–2.54 (m, 1H), 2.20–1.98 (m, 4H), 1.70–1.05 (m, 16H). HR-MS (m/z): $[C_{16}H_{32}Cl_3N_4O_3PtS + H]^+$ = 660.0903. ^{13}C NMR (151 MHz, DMSO) δ: 181.03, 164.37, 164.01, 162.79, 61.12, 61.09, 59.23, 55.59, 55.53, 53.97, 40.46, 40.09, 39.97, 39.91, 39.83, 39.69, 39.56, 39.42, 39.28, 39.14, 36.17, 36.14, 31.89, 31.35, 31.33, 28.35, 28.31, 28.19, 28.15, 25.65, 24.97, 24.51, 24.42.

4.4 | Synthesis of complexes C3 and C4

Pt(II)L1 (10 mmol) and Pt(II)L2 (10 mmol), for complexes C3 and C4 respectively, were dissolved in about 200 mL of purified water, bathed at room temperature, and stirred evenly. *N*-chlorosuccinimide (10 mmol) was added to the reactions and reacted overnight. After the reaction, the yellow solids were obtained by evaporation and concentration, washed by ethanol and ethyl ether, and vacuum dried at 60°C. The intermediates (10 mmol), O-(Benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate (TBTU) (15 mmol), and triethylamine (10 mmol) were dissolved in 15 ml dimethyl sulfoxide (DMSO) and the mixture was evenly stirred in a water bath at 40°C. Biotin-NHS ester (10 mmol) was added and the reactions were kept in the dark for the night. After the reactions were finished, CH_2Cl_2 was added to the reaction solutions, mixed evenly, and poured into the separating funnels. Purified water was added and extracted two to three times to remove the condensation agent in the reaction solution. The organic phase was collected and the water was removed with $MgSO_4$, then the CH_2Cl_2 was evaporated and concentrated. The products obtained were gray and oily. Methanol dissolved, and then added ether, got solid precipitations. G3 sand core funnels filter, solids used methanol: ether =1:1 wash two to three times, and vacuum dried at 60°C. Data for C3: yield: 43.04%, gray solid. IR (ν, cm^{-1}): ν(NH) br 3389, 3224 cm^{-1}, ν_s(CH), ν_{as}(CH) 2932, 2856 cm^{-1}, δ(NH) 1454 cm^{-1}, ν(C–O) 1711, 1682 cm^{-1}, ν(C–C) 1264 cm^{-1}, ν(Pt–O) 897 cm^{-1}, ν(Pt–N) 578 cm^{-1}. ^{1}H NMR (600 MHz, DMSO) δ: 6.48–6.34 (s, 2H), 4.35–4.29 (m, 1H), 4.22–4.10 (m, 1H), 3.15–3.04 (m, 1H), 2.92–2.90 (s, 1H), 2.85–2.81 (m, 1H), 2.77–2.66 (d, 2H), 2.62–2.54 (d, 1H), 2.32–2.13 (m, 4H), 1.66–1.07 (m, 17H). HR-MS (m/z): $[C_{18}H_{31}N_4O_8PtS + H]^+$ = 660.1655. ^{13}C NMR (101 MHz, DMSO) δ: 174.42, 162.72, 127.25, 124.45, 119.07, 109.64, 61.05, 59.18, 55.38, 40.11, 39.90, 39.69, 39.48, 39.28, 39.07, 38.86, 33.48, 28.10, 28.02, 24.52. Data for C4: yield 43.68%, gray solid. IR (ν, cm^{-1}): ν(NH) br 3425, 3250 cm^{-1}, ν_s(CH), ν_{as}(CH) 2933, 2859 cm^{-1}, δ(NH) 1464 cm^{-1}, ν(C–O) 1693, 1557 cm^{-1}, ν(C–C) 1263 cm^{-1}, ν(Pt–O) 869 cm^{-1}, ν(Pt–Cl) 743 cm^{-1}, ν(Pt–N): 668 cm^{-1}. ^{1}H NMR (600 MHz, DMSO) δ: 6.78–6.55 (s, 1H), 6.42–6.13 (d, 2H), 4.36–4.24 (t, 1H), 4.13–4.07 (m, 1H), 3.09–3.01 (s, 1H), 2.85–2.77 (m, 2H), 2.76–2.66 (s, 1H), 2.60–2.54 (d, 1H), 2.38–2.09 (m, 4H), 2.05–1.94 (d, 1H), 1.72–1.06 (m, 17H). HR-MS (m/z): $[C_{18}H_{31}ClN_4O_7PtS + H]^+$ = 678.1340. ^{13}C NMR (151 MHz, DMSO) δ: 170.78, 162.78, 65.41, 61.49, 59.61, 55.43, 40.36, 40.22, 40.08, 39.94, 39.81, 39.67, 39.53, 36.26, 32.50, 31.23, 25.91, 25.69, 25.29, 24.83, 24.79.

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