Supporting Information

Suppression of Lysosome Metabolism-Meditated GARP/TGF-β1 Complexes Specifically Depletes Treg Cells to Inhibit Breast Cancer Metastasis

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Contents

Experimental Procedures

Reagents and instruments

All reagents were used as received without further purification. Cisplatin and oxaliplatin were purchased from Yurui Chemical Co. Ltd. (Shanghai, China). All other chemicals were obtained from commercial suppliers, such as Alfa Aesar, Aldrich, J&K, and GL Biochem Ltd. and were of analytical grade. If necessary, the reactions were conducted in dry solvents and under an argon atmosphere. 1H NMR and 13C NMR spectra were recorded on a Bruker AVANCE AV300 (300 MHz). High-resolution mass spectra (HRMS) were obtained on an IonSpec QFT mass spectrometer with ESI ionization. 3-(4,5-dimethylthiazol-2-yl)-2,5–diphenyl tetrazolium bromide (MTT), ascorbic acid (AsA), 5'-GMP (purity ≥ 98.0%), DMEM and RPMI 1640 medium containing 10% foetal bovine serum were purchased from GL Biochem Ltd. A Genomic DNA mini preparation kit from Beyotime (China) was used for cellular drug uptake and DNA platination experiments and the organelle extraction kit was purchased from Beijing Solarbio Science & Technology Co., Ltd. Phosphate-buffered saline (PBS) contained 137 mM NaCl, 2.7 mM KCl, 10 mM Na2HPO4 and 2 mM KH2PO4. Foetal bovine serum (FBS), 0.25% trypsin/EDTA solution, and penicillin-streptomycin solution were purchased from Invitrogen (Grand Island, NY, USA). A549cisR cells were maintained with 2 μg/mL cisplatin. HPLC analyses were performed on a Waters E2695-2998 system equipped with a Venusil MP C18 column (150 × 4.6 mm, 5 μm). HPLC profiles were recorded with a UV detector at 273 nm and a fluorescence detector at an excitation wavelength of 275 nm and an emission wavelength of 545 nm at room temperature. The mobile phase consisted of MeOH and H_2O and was used at a flow rate of 0.5 mL/min (20 μL injection volume). Reactions involved in the preparation of platinum compounds were conducted in the dark. Platinum levels were examined by inductively coupled plasma mass spectrometry (ICP-MS, PE Elan 6100 DRC or PE Nexion 2000).

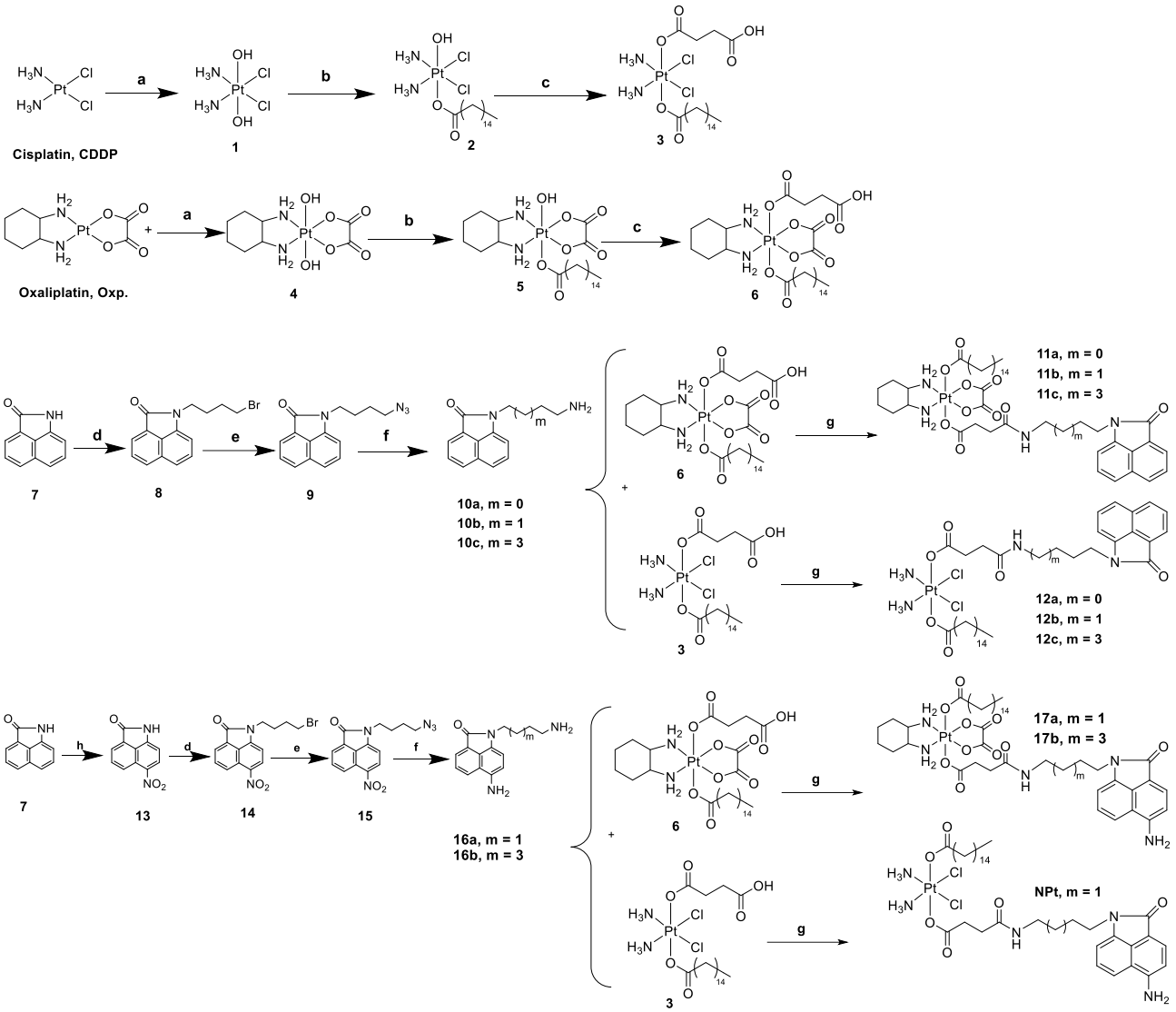
Method for purification of target compounds. The purities of all target compounds were determined by HPLC. The HPLC analyses were performed on a Waters E2695-2998 instrument equipped with a Venusil MP C18 column (150×4.6 mm, 5 μm). The purity of the platinum complexes (**11a-11c**, **12a-12c, 17a-17b** and NPt) was confirmed to be ≥95% by analytical HPLC. The method and purities result of target compounds were as follows (Table S1 and Table S2). The final concentration of their compounds in cell samples was also checked as the method for purity determination of target compounds by RP-HPLC at room temperature in dark.

Table S1. Method for purification of target compounds.

Time (min)	A (water)	B (methanol)
0	90%	10%
5	90%	10%
35	0%	100%
45	0%	100%

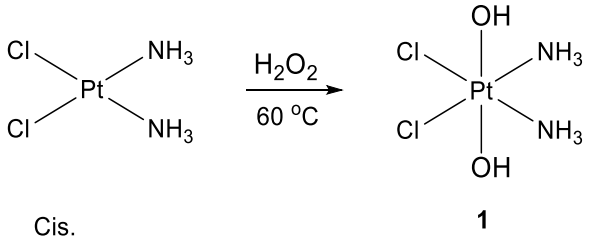
Table S2. Purities results of target compounds.

Compounds	R.T.	Purity (%)	Compounds	R.T.	Purity (%)
11a	6.80	95.79	**12c**	6.50	95.49
11b	6.60	96.83	**17a**	6.49	95.73
11c	6.59	96.69	**17b**	6.48	95.00
12a	6.40	95.14	NPt	6.39	95.16
12b	6.40	95.14			



Scheme S1. Chemical structures and synthetic route of 11a-11c, 12a-12c, 17a-17b and NPt in yield of 25%-30%. Reagents and conditions: (a) H_2O_2, 60℃. **(b)** DMSO, R.T. **(c)** succinic anhydride, DMSO. **(d)** 1,4-butylbromide, K_2CO_3, CH_3CN, reflux, 6h. **(e)** NaN_3, DMF 70°C, overnight. **(f)** Pd/C, H_2, MeOH, room temperature, overnight. **(g)** HATU, DIPEA room temperature, 24 h. **(h)** HNO_3, HAc, 55°C, 3 h.

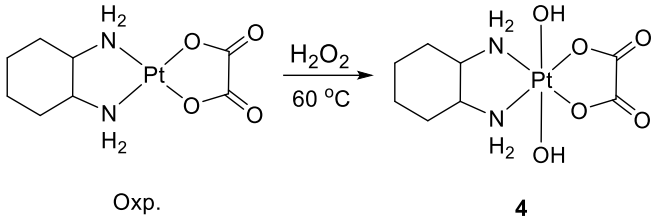
General Procedure for the Synthesis of Compound 1.



Scheme S2. Chemical structures and synthetic route of **1.**

The key step involved the preparation of oxoplatin **1** which was reacted successively in water (12 mL) with cisplatin (0.2 g) and H_2O_2 (20 mL) at 60 °C for 4 h with yield of 70% as our previous reported[1].

General Procedure for the Synthesis of Compound 4.

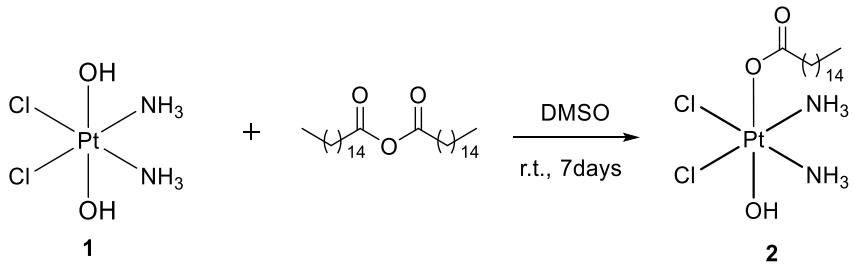


Oxp. **4**

Scheme S3. Chemical structures and synthetic route of **4**.

The key step involved the preparation of oxoplatin **4** which was reacted successively in water (12 mL) with oxaliplatin (0.2 g) and H_2O_2 (20 mL) at 60 °C for 4 h with the yield of 75% as our previous reported[1].

General Procedure for the Synthesis of Compound 2.

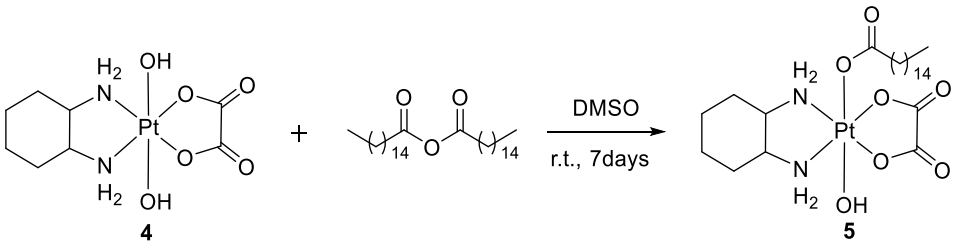


1 **2**

Scheme S4. Chemical structures and synthetic route of **2**.

In our case, we used cis, cis, trans-[$PtCl_2(NH_3)_2$ (palmitate)] (**1**) as the precursor for the synthesis of the conjugates. **2** was prepared from oxoplatin **1** (1 equiv.) and Palmitic anhydride (4 equiv.) in anhydrous DMSO at r.t. for 7 days. DMSO was removed under vacuum to afford a yellow oil. And then the oil was washed with dichloromethane and diethylether and dried in a vacuum. The target complex **2** was obtained as a pale-yellow solid after purification by recrystallization with the yield of 89% as our previous reported[1].

General Procedure for the Synthesis of Compound 5.

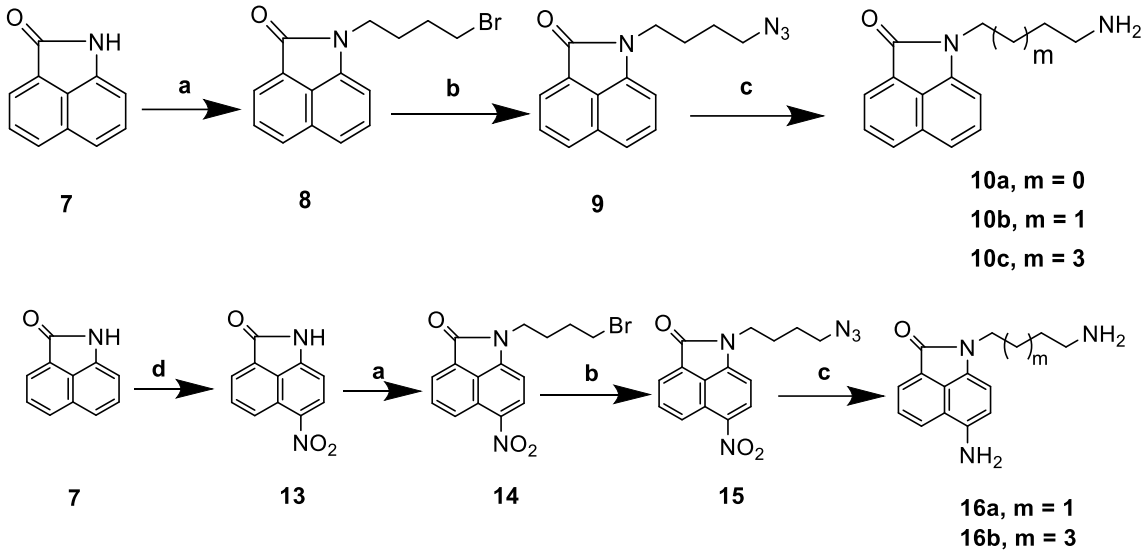


4 **5**

Scheme S5. Chemical structures and synthetic route of **5**.

In our case, we used **4** as the precursor for the synthesis of the conjugates. **5** was prepared from oxoplatin 4 (1 equiv.) and Palmitic anhydride (4 equiv.) in anhydrous DMSO at r.t. for 7 days. DMSO was removed under vacuum to afford a yellow oil. And then the oil was washed with dichloromethane and diethylether and dried in a vacuum. The target complex **5** was obtained as a pale-yellow solid after purification by recrystallization with the yield of 90% as our previous reported[1].

General Procedure for the Synthesis of Compound 10a-10c and 16a-16b.



Scheme S6. Chemical structures and synthetic route of naphthalimide intermediate 10a-10c and 16a-16b in yield of 55%-70%. Reagents and conditions: (a) 1,4-butylbromide, K_2CO_3, CH_3CN, reflux, 6h. **(b)** NaN_3, DMF 70°C, overnight. **(c)** Pd/C, H_2, MeOH, room temperature, overnight. **(d)** HNO_3, HAc, 55°C, 3 h.

Known intermediate **10a-10c** and **16a-16b** were prepared by a conventional method using concentrated nitric acid in glacial acetic acid [2]. To a solution of **7** (1 mmol) and K_2CO_3 in EtOH (10 mL) was added a solution containing alkane (1 mmol) in EtOH (5 mL) at 0 °C. Then the mixture was heated to 85 °C for 5 h. After monitoring by TLC, the reaction mixture was cooled to room temperature and concentrated under vacuum to give an oily residue. After extraction and purification by column chromatography with dichloromethane/methanol (100:1 −100:3, v/v) as elution solvent, **10a-10c** and **16a-16b** were obtained in yield of 60-70%.

Synthesis of Compound 8

1.8g of 1,8-naphthalenolactam was dissolved in acetonitrile, and 2 times the eq. of 1,3-dibromopropane, 1,4-dibromobutane, 1,6-dibromohexane was added to the reaction bottle , and then 3 times the equivalent of K_2CO_3 and an appropriate amount of KI were added to the reaction solution, the reaction was refluxed overnight at 90 ° C, and the acetonitrile was evaporated to dryness. The residue was chromatographed on silica gel to afford the desired product (83%) as a yellow oil.

Synthesis of compound 9

3.76 g of compound **8** was dissolved in a small amount of DMF. 4 eq. of sodium azide were carefully dissolved in DMF, and the reaction mixture was stirred overnight at 70°C, DMF was removed the next day. The residue was chromatographed on silica gel (PE/EA 10:1) to afford the desired product (74%) as an orange yellow oil.

Synthesis of Compounds 10a-10c

Compound **9**: palladium carbon was added into the reaction bottle according to the ratio of 10:1, and sealed with a rubber stopper. The reaction mixture was stirred under hydrogen for three days. The palladium carbon in the reaction was filtered out by Buchner funnel.The residue was chromatographed on silica gel (PE/EA 10:1) to afford the desired product 10a, 10b, and 10c (74%) as red oil. **10a,** ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.95 (dd, *J* = 12.7, 7.5 Hz, 2H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.49 – 7.37 (m, 2H), 6.90 (d, *J* = 6.8 Hz, 1H), 3.98 (t, *J* = 6.6 Hz, 1H), 2.82 (d, *J* = 20.7 Hz, 2H), 1.94 (t, *J* = 6.6 Hz, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 168.32, 139.12, 130.86, 129.04, 128.64, 128.52, 126.40, 125.06, 124.31, 120.38, 105.22, 38.67, 37.33, 29.72. ESI-MS m/z: 226$[M+H]^+$.(yield:87%)

10b, ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.98 (dd, *J* = 12.7, 7.5 Hz, 1H), 7.65 (dd, *J* = 8.1, 7.0 Hz, 1H), 7.54 – 7.36 (m, 1H), 6.91

(d, *J* = 6.8 Hz, 1H), 3.92 (t, *J* = 7.0 Hz, 2H), 2.82 (t, *J* = 7.1 Hz, 2H), 1.98 – 1.73 (m, 2H), 1.64 (d, *J* = 7.8 Hz, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 167.66, 138.80, 130.31, 128.58, 128.15, 128.02, 126.07, 123.78, 119.81, 104.67, 40.77, 39.45, 29.09, 25.65.ESI-MS m/z: 240.75$[M+H]^+$. (yield:80%)

10c, ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.05 (d, *J* = 7.0 Hz, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.69 (dd, *J* = 8.1, 7.0 Hz, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.46 (d, *J* = 6.8 Hz, 1H), 6.90 (d, *J* = 6.8 Hz, 1H), 3.91 (t, *J* = 7.2 Hz, 2H), 2.69 (t, *J* = 6.6 Hz, 2H), 1.79 (t, *J* = 6.9 Hz, 4H), 1.60 – 0.97 (m, 4H).^{13}C NMR (75 MHz, $CDCl_3$) δ 168.09, 139.52, 130.74, 129.11, 128.64, 128.50, 126.73, 125.13, 124.22, 120.19, 105.03, 41.79, 40.16, 32.96, 28.73, 26.71, 26.48. ESI-MS m/z: 268.86[M+H]+. (yield:85%)

Synthesis of Compound 13

16.9 g of 1,8-naphtholactam were dissolved in glacial acetic acid. Under ice-bath conditions, 20 mL of concentrated nitric acid was slowly added dropwise to the reaction solution, and the reaction mixture was stirred at 55°C for 3 h, and the reaction solution was poured into ice water while hot to precipitate a yellow solid and filtered with a Buchner funnel. The orange-yellow solid was washed several times with water until the filtrate was weakly acidic in 82% yield.

Synthesis of Compounds 14, 15, 16

The synthesis of compounds **14**, **15**, and **16** is the same as that of compounds **8**, **9,** and **10**, and the final reaction is to obtain intermediates **16a, 16b.**

16a, ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.05 (d, *J* = 7.0 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.66 (dd, *J* = 8.2, 7.0 Hz, 1H), 6.71 (d, *J* = 7.5 Hz, 1H), 6.61 (d, *J* = 7.5 Hz, 1H), 4.13 (s, 2H), 3.90 (t, *J* = 7.1 Hz, 2H), 2.72 (t, *J* = 7.0 Hz, 2H), 1.87 – 1.71 (m, 2H), 1.61 – 1.46 (m, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 167.11, 137.99, 130.87, 126.92, 125.04, 124.85, 123.90, 109.17, 106.13, 41.43, 39.58, 30.65, 25.80. ESI-MS m/z: 255.81$[M+H]^+$. (yield:72%)

16b, ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.03 (dd, *J* = 18.2, 7.7 Hz, 2H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.05 – 6.17 (m, 2H), 3.87 (t, *J* = 7.2 Hz, 2H), 2.64 (t, *J* = 6.3 Hz, 2H), 1.97 – 1.52 (m, 4H), 1.38 (s, 4H).^{13}C NMR (75 MHz,) δ 167.52, 138.38, 138.36, 131.44, 127.36, 125.24, 124.32, 121.45, 109.72, 109.64, 106.54, 42.04, 40.13, 33.60, 28.81, 26.76, 26.52. ESI-MS m/z: 283.93$[M+H]^+$. (yield:70%)

General Procedure for the Synthesis of Compound 11a-11c, 12a-12c, 17a-17b and NPt.

Synthetic route of 11a.

0.35 g of compound **6** was dissolved in 10 mL of anhydrous DMF and stirring was started under N2. 1.25eq. of **10a** was dissolved in DMF and placed in a 4mL EP tube. 0.45g HATU was dissolved in as little DMF as possible and then injected into the reaction vial with a needle and stirred at room temperature for 15min. The pre-dissolved **10a** and DIPEA were added into the reaction vial and stirred at room temperature for 24h. The residue was chromatographed on silica gel(DCM/MeOH 20:1) to afford the desired product **11a** (54%) as a yellow-green solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.01 (s, 2H), 7.70 (dt, *J* = 5.9, 3.1 Hz, 2H), 7.52 (dd, *J* = 5.6, 3.4 Hz, 2H), 3.98 (s, 2H), 3.69 (d, *J* = 4.0 Hz, 2H), 3.29 – 3.02 (m, 2H), 2.65 (m, 6H), 1.99 (s, 2H), 1.50 (s, 3H), 1.48 (s, 3H), 1.44 (s, 2H), 1.41 (s, 2H), 1.24 (s, 28H), 0.87 (d, *J* = 5.0 Hz, 3H). ^{13}C NMR (75 MHz, DMSO) δ 180.32, 172.28, 171.45, 167.10, 134.72, 129.44, 128.56, 127.70, 126.33, 124.60, 124.35, 122.20, 119.34, 41.61, 31.73, 31.54, 30.06, 29.31, 29.04, 28.96, 28.62, 28.45, 26.33, 25.60, 22.66, 22.34, 14.19. ESI-MS: (negative ion mode): m/z$[M-H]^-$： calcd:976.4039, obsd: 976.4042. Elemental Analysis for $C_{39}H_{56}N_4O_{10}Pt$ C 50.05%, H 6.03%, N 5.99%; Found C 50.10%, H 6.08%, N 6.04%.

Synthetic route of 11b.

0.35 g of compound **6** was dissolved in 10 mL of anhydrous DMF and stirring was started under N2. 1.25eq. of **10b** was dissolved in DMF and placed in a 4mL EP tube. 0.45g HATU was dissolved in as little DMF as possible and then injected into the reaction vial with a needle and stirred at room temperature for 15min. The pre-dissolved **10b** and DIPEA were added into the reaction vial and stirred at room temperature for 24h. The residue was chromatographed on silica gel(DCM/MeOH 20:1) to afford the desired

product **11b** (74%) as a yellow-green solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.51 (d, *J* = 4.5 Hz, 1H), 8.21 (d, *J* = 8.5 Hz, 1H), 7.95 (t, *J* = 7.7 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 7.44(m, 1H), 6.93 (d, *J* = 6.8 Hz, 1H), 3.88 (s, 1H), 3.71 (m, 1H), 3.16 (dq, *J* = 14.9, 7.4, 6.8 Hz, 4H), 2.61 – 2.07 (m, 6H), 1.44 (dd, *J* = 21.6, 6.9 Hz, 14H), 1.21 (d, *J* = 7.7 Hz,28H), 0.84 (t, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.23, 182.13, 173.20, 168.29, 139.09, 134.90, 130.95, 129.05, 128.69, 128.61, 126.44, 124.96, 120.45, 54.17, 42.38, 39.90, 39.11, 31.92, 29.72, 29.69, 29.66, 29.57, 29.37, 29.20, 26.49, 26.24, 25.73, 22.69, 14.12. ESI-MS: (negative ion mode): m/z[M-H]$^-$：calcd: 990.4196, obsd: 990.4207. Elemental Analysis for $C_{40}H_{58}N_4O_{10}Pt$ C 50.57%, H 6.15%, N 5.90%; Found C 50.60%, H 6.18%, N 5.94%.

Synthetic route of 11c.

0.35 g of compound **6** was dissolved in 10 mL of anhydrous DMF and stirring was started under N2. 1.25eq. of **10c** was dissolved in DMF and placed in a 4mL EP tube. 0.45g HATU was dissolved in as little DMF as possible and then injected into the reaction vial with a needle and stirred at room temperature for 15min. The pre-dissolved **10c** and DIPEA were added into the reaction vial and stirred at room temperature for 24h. The residue was chromatographed on silica gel(DCM/MeOH 20:1) to afford the desired product **11c** (57%) as a yellow-green solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 7.99 (dd, *J* = 11.8, 7.8 Hz, 2H), 7.67 (t, *J* = 7.6 Hz,1H), 7.47 (dd, *J* = 16.9, 7.8 Hz, 2H), 6.89 (t, *J* = 6.7 Hz, 1H), 3.87 (t, *J* = 7.1 Hz, 2H), 3.22 – 2.97 (m, 2H), 2.70 – 2.31 (m, 4H), 2.20 (t, *J* = 7.6 Hz,2H), 1.75 – 1.44 (m, 12H), 1.62 – 1.29 (m, 5H), 1.15 (s, 30H), 0.85 (s, 3H). ^{13}C NMR (75 MHz, CDCl3) δ 184.23, 182.10, 172.94, 168.23, 139.28, 130.92, 129.10, 128.68, 128.60, 126.57, 125.03, 124.31, 120.39, 105.41, 40.05, 31.94, 29.75, 29.73, 29.69, 29.61, 29.44, 29.38, 29.25, 29.12, 28.61, 26.35, 25.75, 24.02, 22.71, 14.14. ESI-MS: (negative ion mode): m/z[M-H]$^-$：calcd:1018.4509, obsd: 1018.4508. Elemental Analysis for $C_{42}H_{62}N_4O_{10}Pt$ C 51.58%, H 6.39%, N 5.73%; Found C 51.60%, H 6.48%, N 5.94%.

Synthetic route of 12a.

0.35 g of compound **3** was dissolved in 10 mL of anhydrous DMF and stirring was started under N2. 1.25eq. of **10a** was dissolved in DMF and placed in a 4mL EP tube. 0.45g HATU was dissolved in as little DMF as possible and then injected into the reaction vial with a needle and stirred at room temperature for 15min. The pre-dissolved **10a** and DIPEA were added into the reaction vial and stirred at room temperature for 24h. The residue was chromatographed on silica gel(DCM/MeOH 20:1) to afford the desired product **12a** (69%) as a yellow-green solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.37 – 7.80 (m, 2H), 7.82 – 7.55 (m, 1H), 7.57 – 7.39 (m, 2H), 6.99 (d, *J* = 6.7 Hz, 1H), 3.98 (s, 2H), 3.23 (s, 2H), 3.07 – 2.83 (m, 2H), 2.36 (s, 2H), 2.20 (s, 2H), 1.95 (s, 2H), 1.47 (dd, *J* = 20.8, 7.3 Hz, 8H), 1.24 (s, 24H), 0.87 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, CDCl3) δ 175.42, 172.90, 167.80, 138.61, 132.43, 131.29, 130.92, 128.80, 128.63, 126.06, 124.65, 120.90, 47.48, 42.17, 40.63, 38.73, 37.31, 37.11, 36.28, 31.94, 30.95, 30.37, 28.94, 28.01, 24.85, 23.75, 23.00, 22.71, 14.08.ESI-MS: (negative ion mode): m/z[M-H]$^-$：calcd:879.2982, obsd: 879.2992. Elemental Analysis for C39H56N4O10Pt C 50.05%, H 6.03%, N 5.99%; Found C 50.10%, H 6.08%, N 6.04%.

Synthetic route of 12b.

0.35 g of compound **3** was dissolved in 10 mL of anhydrous DMF and stirring was started under N2. 1.25eq. of **10b** was dissolved in DMF and placed in a 4mL EP tube. 0.45g HATU was dissolved in as little DMF as possible and then injected into the reaction vial with a needle and stirred at room temperature for 15min. The pre-dissolved **10b** and DIPEA were added into the reaction vial and stirred at room temperature for 24h. The residue was chromatographed on silica gel(DCM/MeOH 20:1) to afford the desired product **12b** (68%) as a yellow-green solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.53 (s, 1H), 8.19 (d, *J* = 8.3 Hz, 1H), 7.97 (m, 1H), 7.66 (m, 1H), 7.45 (dd, *J* = 9.5, 5.7 Hz, 1H), 6.91 (d, *J* = 6.4 Hz, 1H), 3.67 (m, 2H), 3.12 (d, *J* = 7.4 Hz, 4H), 2.56 (s, 4H), 1.55 – 1.21 (m, 36H), 0.88 (m, 3H). ^{13}C NMR (75 MHz, DMSO) δ 181.32, 180.46, 171.63, 167.41, 139.36, 131.52, 129.44, 129.14, 126.37, 124.66, 124.50, 120.50, 106.25, 36.13, 31.89, 31.77, 31.34, 29.54, 29.19, 27.03, 26.15, 25.94, 22.58, 14.44. ESI-MS: (negative ion mode): m/z[M-H]$^-$：calcd:893.3139, obsd: 893.3148. Elemental Analysis for $C_{40}H_{58}N_4O_{10}Pt$ C 50.57%, H 6.15%, N 5.90%; Found C 50.60%, H 6.18%, N 5.94%.

Synthetic route of 12c.

0.35 g of compound **3** was dissolved in 10 mL of anhydrous DMF and stirring was started under N2. 1.25eq. of **10c** was dissolved in DMF and placed in a 4mL EP tube. 0.45g HATU was dissolved in as little DMF as possible and then injected into the reaction vial with a needle and stirred at room temperature for 15min. The pre-dissolved **10c** and DIPEA were added into the reaction vial and stirred at room temperature for 24h. The residue was chromatographed on silica gel(DCM/MeOH 20:1) to afford the desired product **12c** (70%) as a yellow-green solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.58 (s, 1H), 8.15 – 7.87 (m, 1H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.43 (dd, *J* = 14.7, 7.0 Hz, 1H), 6.88 (d, *J* = 6.3 Hz, 1H), 6.35 (s, 1H), 3.63 (dd, *J* = 11.6, 6.0 Hz, 2H), 3.37 – 2.92 (m, 2H), 2.51 (s, 3H), 2.25 (s, 3H), 1.46 (d, *J* = 7.2 Hz, 4H), 1.38 (d, *J* = 6.7 Hz, 6H), 1.18 (s, 30H), 0.81 (s, 3H). ^{13}C NMR (75 MHz, CDCl3) δ177.24, 173.52, 168.31, 130.94, 129.05, 128.69, 126.52, 124.98, 124.45, 124.30, 120.43, 105.56, 42.39, 40.01, 37.11, 35.97, 31.95, 29.75, 29.72, 29.68, 29.64, 29.51, 29.39, 29.34, 26.16, 24.88, 22.72, 14.17. ESI-MS: (negative ion mode): m/z[M-H]$^{-}$: calcd:921.3453, obsd: 921.3439. Elemental Analysis for $C_{42}H_{62}N_4O_{10}Pt$ C 51.58%, H 6.39%, N 5.73%; Found C 51.60%, H 6.48%, N 5.94%.

Synthetic route of 17a.

0.35 g of compound **6** was dissolved in 10 mL of anhydrous DMF and stirring was started under N2. 1.25eq. of **16a** was dissolved in DMF and placed in a 4mL EP tube. 0.45g HATU was dissolved in as little DMF as possible and then injected into the reaction vial with a needle and stirred at room temperature for 15min. The pre-dissolved **16a** and DIPEA were added into the reaction vial and stirred at room temperature for 24h. The residue was chromatographed on silica gel(DCM/MeOH 20:1) to afford the desired product **17a** (55%) as a yellow-green solid. ^{1}H NMR (300 MHz, Chloroform-*d*) δ 8.45 (s, 1H), 8.15 (s, 1H), 7.88 (d, *J* = 50.8 Hz, 1H), 7.16 (s, 1H), 6.61 (s, 1H), 5.08 (s, 2H), 3.83 – 3.46 (s, 2H), 3.12 (s, 2H), 2.70 – 1.92 (d, 6H), 1.52 – 1.34 (d, 10H), 1.23 (s, 28H), 0.86 (s, 3H). ^{13}C NMR (75 MHz, CDCl3) δ 173.32, 167.53, 139.59, 134.73, 126.26, 124.64, 120.17, 42.25, 31.92, 29.73, 29.67, 29.60, 29.37, 29.24, 25.77, 22.69, 14.12. Elemental Analysis for $C_{31}H_{48}Cl_2N_4O_6Pt$ C 44.39%, H 5.77%, N 6.68%; Found C 44.42%, H 5.83%, N 6.73%.

Synthetic route of 17b.

0.35 g of compound **6** was dissolved in 10 mL of anhydrous DMF and stirring was started under N2. 1.25eq. of **10b** was dissolved in DMF and placed in a 4mL EP tube. 0.45g HATU was dissolved in as little DMF as possible and then injected into the reaction vial with a needle and stirred at room temperature for 15min. The pre-dissolved **10b** and DIPEA were added into the reaction vial and stirred at room temperature for 24h. The residue was chromatographed on silica gel(DCM/MeOH 20:1) to afford the desired product **17b** (59%) as a yellow-green solid. ^{1}H NMR (300 MHz, DMSO-*d*6) δ 8.73 (s, 2H), 8.53 (s, 1H), 7.50 (s, 2H), 3.87 (s, 2H), 3.62 (d, *J* = 145.9 Hz, 4H), 2.51 (s, 2H), 2.32 – 1.58 (m, 4H), 1.21 (s, 36H), 0.84 (s, 3H). ^{13}C NMR (75 MHz, CDCl3) δ 173.20, 173.07, 172.37, 171.03, 167.93, 167.89, 138.95, 130.46, 130.00, 129.88, 126.07, 125.86, 125.73, 125.62, 125.25, 123.92, 121.16, 42.29, 41.99, 40.03, 39.95, 39.82, 35.35, 29.66, 29.63, 29.51, 29.48, 29.33, 26.00, 25.78, 25.53, 25.41, 25.34, 25.25, 25.21, 22.66, 14.10. ESI-MS: (negative ion mode): m/z[M-H]$^{-}$: calcd:1033.4618, obsd: 1033.4626. Elemental Analysis for $C_{31}H_{48}Cl_2N_4O_6Pt$ C 44.39%, H 5.77%, N 6.68%; Found C 44.42%, H 5.83%, N 6.73%.

Synthetic route of NPt.

0.35 g of compound **3** was dissolved in 10 mL of anhydrous DMF and stirring was started under N2. 1.25eq. of **16a** was dissolved in DMF and placed in a 4mL EP tube. 0.45g HATU was dissolved in as little DMF as possible and then injected into the reaction vial with a needle and stirred at room temperature for 15min. The pre-dissolved **16a** and DIPEA were added into the reaction vial and stirred at room temperature for 24h. The residue was chromatographed on silica gel(DCM/MeOH 20:1) to afford the desired product **NPt** (84%) as a yellow-green solid. ^{1}H NMR (300 MHz, Methanol-d_4) δ 8.39 (dd, *J* = 8.5, 1.3 Hz, 1H), 8.29 (d, *J* = 8.2 Hz, 1H), 8.03 (d, *J* = 7.0 Hz, 1H), 7.70 (dd, *J* = 8.1, 6.8 Hz, 1H), 7.49 (dd, *J* = 8.5, 4.4 Hz, 1H), 3.73 (p, *J* = 6.7 Hz, 2H), 3.23 (d, *J* = 7.4

Hz, 2H), 2.58 (d, *J* = 6.7 Hz, 2H), 2.38 (dt, *J* = 15.2, 7.1 Hz, 4H), 1.41 – 1.34 (m, 12H), 1.33 – 1.23 (m, 24H), 0.90 (d, *J* = 2.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.89, 184.98, 177.92, 171.95, 138.89, 133.41, 132.24, 130.76, 130.71, 128.02, 125.51, 124.52, 112.39, 46.39, 39.66, 35.25, 33.29, 33.06, 33.01, 32.91, 32.82, 30.34, 29.95, 29.62, 26.31, 15.79. ESI-MS :(negative ion mode):m/z[M-H]$^-$：calcd:908.3248, obsd: 908.3226. (yield:84%) Elemental Analysis for $C_{31}H_{48}Cl_2N_4O_6Pt$ C 44.39%, H 5.77%, N 6.68%; Found C 44.42%, H 5.83%, N 6.73%.

Results and Discussion

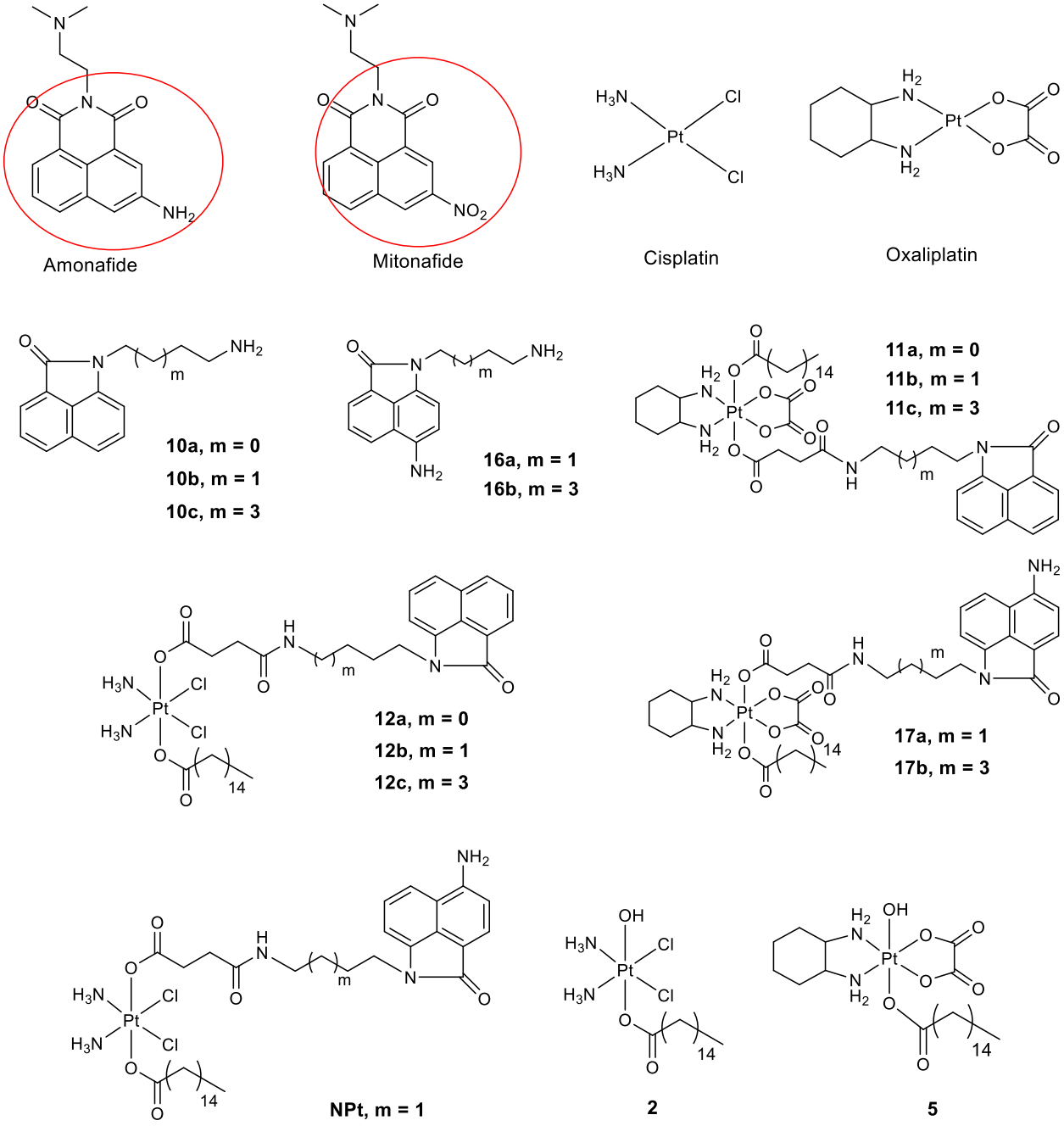
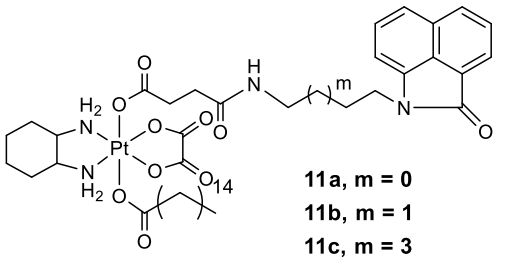


Fig. S1. Chemical structures of amonafide, mitonafide, cisplatin and oxaliplatin in clinic, key intermediates **10a-10c** and **16a-16b**, naphthalamide-platinum conjugates **11a-11c**, **12a-12c**, **17a-17b**, NPt, and platinum drugs **2, 5** without naphthalamide modified.

Table S3. IC_{50} values (concentrations of 50% inhibition of cell proliferation) (micromolar) of **11a-11c**, **12a-12c, 17a-17b** and NPt, the positive control cisplatin and oxaliplatin. The cell viability was determined by MTT assays[a].



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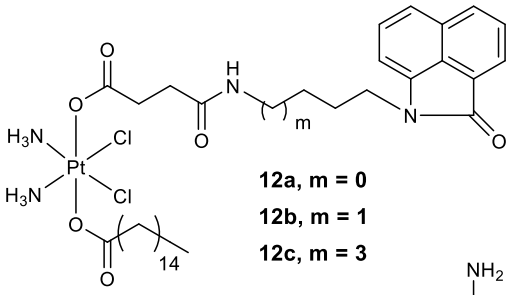
11b, m = 1
11c, m = 3



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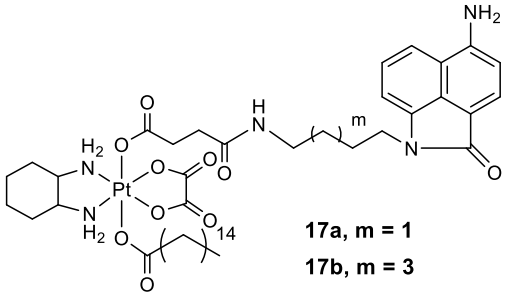
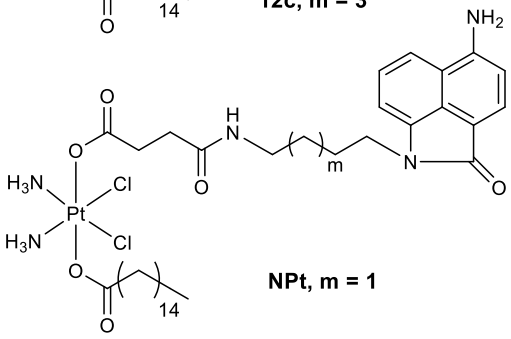


17a, m = 1
17b, m = 3



NPt, m = 1

	MCF-7	MDA-MB-231	HCT-116	HT-29	HepG2	Huh-7	A549	A549CisR	RF
11a	1.39±0.12	2.58±0.37	19.60±1.26	9.98±0.87	7.03±0.58	3.98±0.31	21.56±2.2	53.26±2.8	2.47
12a	1.57±0.12	1.48±0.13	9.57±0.89	9.81±0.75	3.23±0.16	10.84±0.94	33.22±2.7	33.09±2.51	0.99
17a	1.68±0.15	1.51±0.12	5.56±0.47	5.99±0.30	4.11±0.38	7.62±0.69	13.43±0.92	30.01±2.76	2.23
NPt	1.28±0.10	0.94±0.08	5.03±0.47	4.91±0.25	2.87±0.19	2.46±0.18	8.71±0.85	22.70±1.57	2.61
11b	1.37±0.11	1.26±0.09	29.86±2.4	11.71±0.95	2.77±0.15	11.16±0.98	27.69±1.89	>100	/
12b	4.58±0.32	4.66±0.38	12.86±0.11	17.04±1.23	14.31±1.28	19.56±1.78	24.50±2.25	24.37±2.06	0.99
17b	3.67±0.28	12.93±0.94	9.09±0.78	13.59±0.94	10.27±0.91	23.27±1.83	16.82±1.32	67.09±4.31	3.98
11c	1.29±0.78	1.9±0.18	2.76±0.17	24.42±1.20	2.65±0.22	5.55±0.48	28.45±1.25	15.34±1.13	0.54
12c	3.25±0.29	1.29±0.09	34.04±1.87	38.21±2.34	2.57±0.15	17.42±1.38	26.23±2.43	31.91±2.97	1.22
Cis.	13.26±1.16	16.95±1.41	10.72±0.95	29.84±1.87	11.37±0.87	10.04±0.91	8.15±0.78	46.80±3.72	5.74
Oxp.	17.24±1.56	20.04±1.75	7.55±0.68	13.56±0.75	10.73±1.02	9.92±0.87	9.98±0.69	43.05±3.52	4.31
FI[b](NPt)	10.36	18.03	2.13	6.07	5.10	0.90	0.94	2.06	
FI[c](NPt)	13.47	21.32	1.50	2.76	4.81	0.89	1.15	1.90	

[a] An average of three measurements.

[b] FI (fold increase) is defined as IC_{50}(cisplatin)/IC_{50}(NPt), introduced to contrast the antitumor effects with the positive drugs.

[c] FI (fold increase) is defined as IC_{50}(oxaliplatin)/IC_{50}(NPt).

Table S4. IC_{50} values (concentrations of 50% inhibition of cell proliferation) (micromolar) of naphthalimide intermediates **10a-10c** and **16a-16b**, the positive control amonafide, cisplatin and oxaliplatin. The cell viability was determined by MTT assays[a].

	HepG-2	Huh-7	MDA-MB-231	MCF-7	A549cisR	A549	RF[b]
10a	>30	>30	>30	>30	>30	>30	>30
10b	>30	>30	>30	>30	>30	>30	>30
10c	>30	4.14±0.40	>30	>30	>30	>30	>30
16a	>30	>30	>30	>30	11.5±1.05	>30	ND
16b	>30	>30	>30	>30	>30	>30	>30
amonafide	9.38±0.35	8.52±0.47	10.23±1.13	15.93 ±0.55	9.56±0.89	23.46 ±2.35	0.41
Cis.	8.90±0.78	15.02±1.50	32.48±1.49	9.60±0.60	42.89±1.89	10.20±0.89	4.01
Oxp.	19.98±1.89	16.17±1.59	17.72±0.89	11.62±0.78	38.97±3.23	10.00±1.23	3.9

[a] An average of three measurements. ND = Not determined.

[b] The RF (resistance factor) is defined as the IC_{50} value in A549cisR cells/IC_{50} value in A549 cells.

Table S5. IC_{50} values (μM) of NPt, cisplatin and oxaliplatin in cancer cells and matched normal cells. Cells were treated for 48 h, and the cell viability was determined by MTT assays[a]

	Huh-7	HL-7702	SI[b]
NPt	2.46±0.13	9.47±0.49	3.85
Cisplatin	10.04±1.26	5.60±0.20	0.56
Oxaliplatin	9.92±1.88	6.77±0.78	0.68

[a] An average of three measurements.

[b] SI (selectivity index) is defined as IC_{50} in HL-7702/IC_{50} in Huh-7.

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Table S6. Percent survival in life extension rate of BALB/c mice (n = 10) in the anti-tumor model.

	NPt ligand	Oxp. (2.95 mgPt/kg)	Cis. (3.90 mgPt/kg)	NPt (1.07mgPt/kg)	NPt (2.15 mg Pt/kg)
Percent survival	5.30%	16.30%	19.70%	35.20%	41.50%

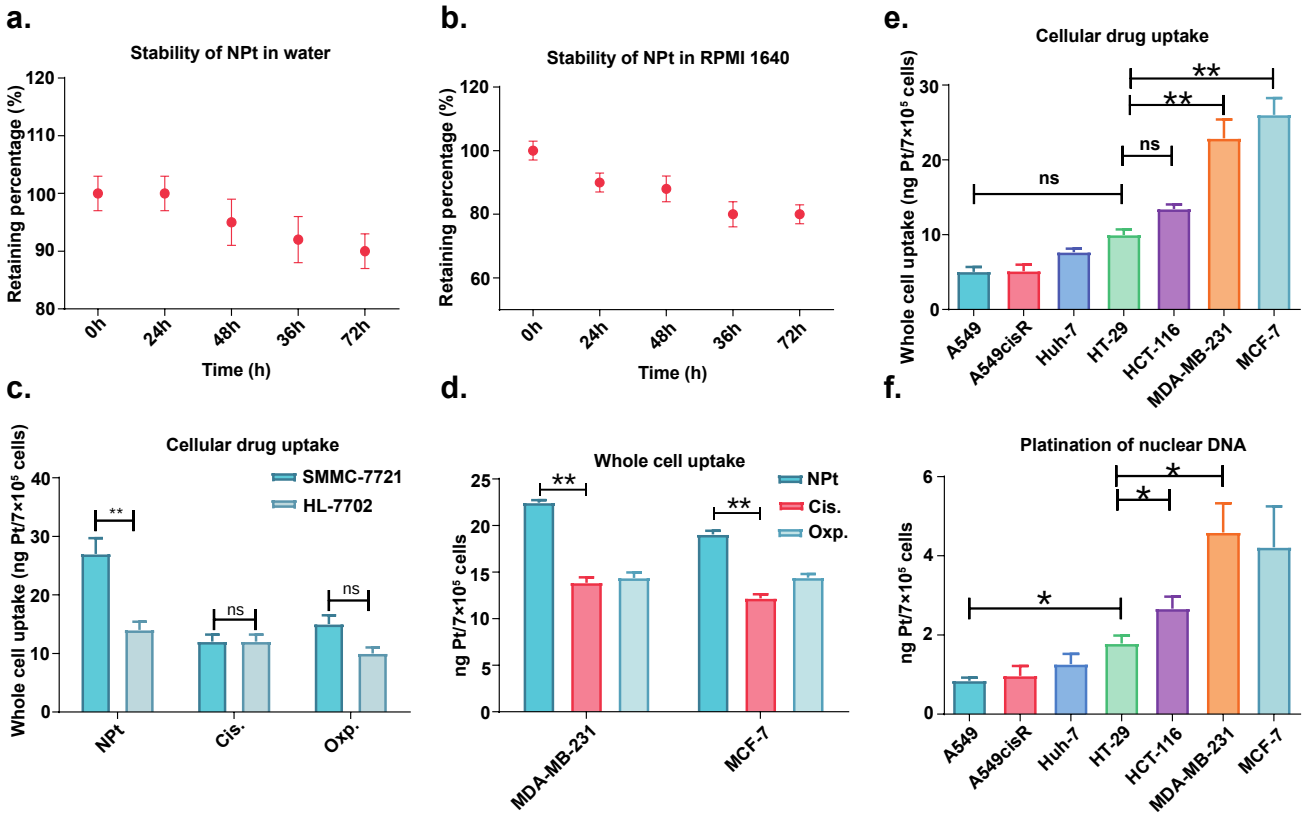

Fig. S2. **Determination of stability of NPt in darkness by RP-HPLC and platinum uptake by ICP-MS. (a)** Stability of compounds NPt in water. **(b)** Stability of compounds NPt in RPMI-1640. **(c)** Cellular uptake and distribution in cancer cells and matched normal cells with 10 μM of tested complexes. **(d)** Cellular uptake in MDA-MB-231 and MCF-7 cells with 10 μM of NPt, cisplatin, and oxaliplatin. Cellular drug uptake **(e)** and DNA platination **(f)** of NPt in lung carcinoma cell A549 and A549cisR, hepatoma carcinoma cell Huh-7, colorectal cancer HCT-116 and HT-29, breast cancer cell MDA-MB-231 and MCF-7. *, P< 0.05; **, P< 0.01; ***, P< 0.001.

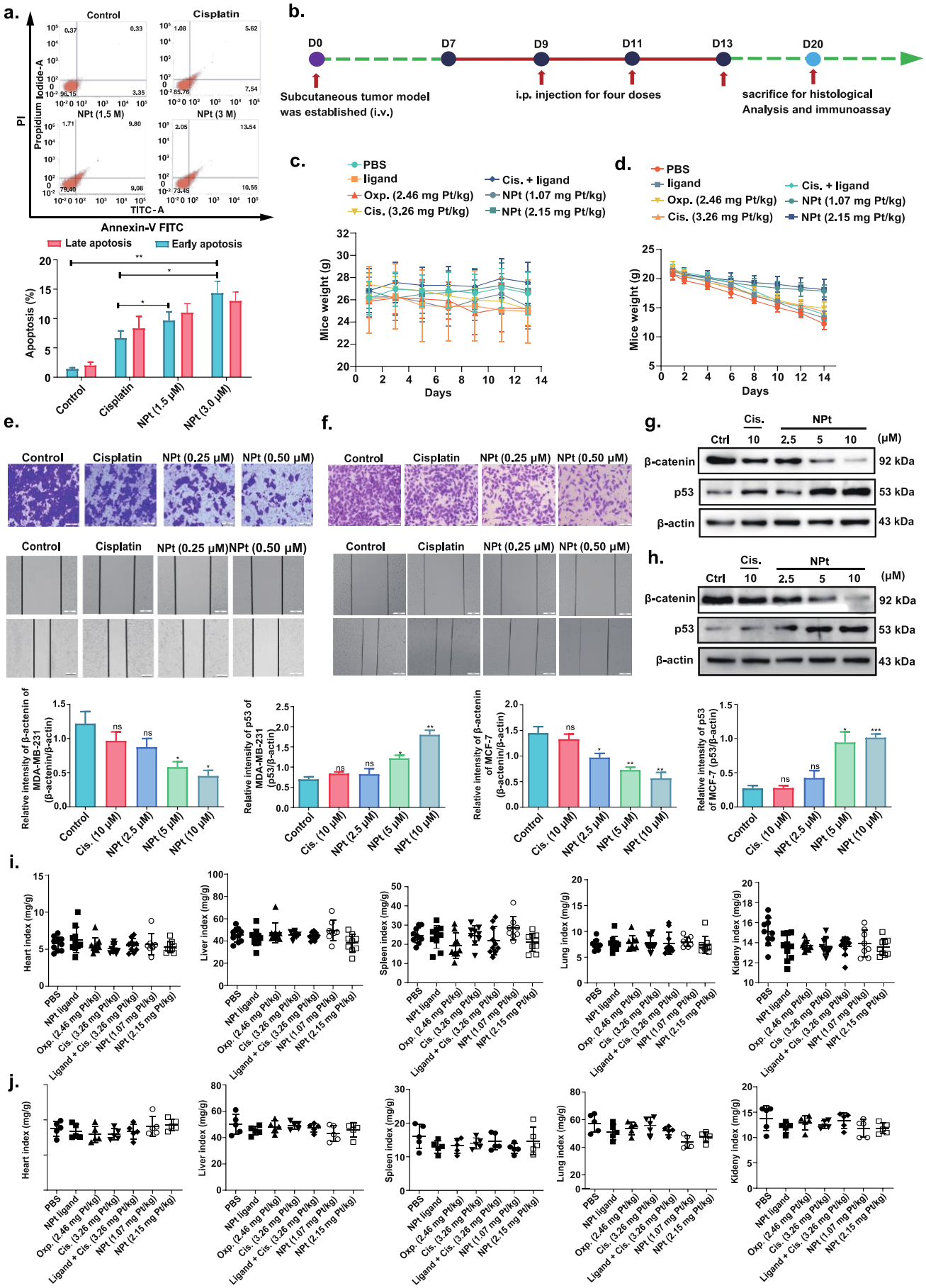
a.
Control
Cisplatin
NPt (1.5 M)
NPt (3 M)
PI
Propidium Iodide-A
TITC-A
Annexin-V FITC
Late apotosis
Early apotosis
Apoptosis (%)
Control
Cisplatin
NPt (1.5 μM)
NPt (3.0 μM)
b.
D0
D7
D9
D11
D13
D20
Subcutaneous tumor model was established (i.v.)
i.p. injection for four doses
sacrifice for histological Analysis and immunoassay
c.
PBS
ligand
Oxp. (2.46 mg Pt/kg)
Cis. (3.26 mg Pt/kg)
Cis. + ligand
NPt (1.07 mg Pt/kg)
NPt (2.15 mg Pt/kg)
Mice weight (g)
Days
d.
PBS
ligand
Oxp. (2.46 mg Pt/kg)
Cis. (3.26 mg Pt/kg)
Cis. + ligand
NPt (1.07 mg Pt/kg)
NPt (2.15 mg Pt/kg)
Mice weight (g)
Days
e.
Control
Cisplatin
NPt (0.25 μM)
NPt (0.50 μM)
f.
Control
Cisplatin
NPt (0.25 μM)
NPt (0.50 μM)
g.
Cis.
NPt
Ctrl
10
2.5
5
10
(μM)
β-catenin
p53
β-actin
92 kDa
53 kDa
43 kDa
h.
Cis.
NPt
Ctrl
10
2.5
5
10
(μM)
β-catenin
p53
β-actin
92 kDa
53 kDa
43 kDa
Relative intensity of β-actenin of MDA-MB-231 (β-actenin/β-actin)
Relative intensity of p53 of MDA-MB-231 (p53/β-actin)
Relative intensity of β-actenin of MCF-7 (β-actenin/β-actin)
Relative intensity of p53 of MCF-7 (p53/β-actin)
Control
Cis. (10 μM)
NPt (2.5 μM)
NPt (5 μM)
NPt (10 μM)
i.
Heart index (mg/g)
Liver index (mg/g)
Spleen index (mg/g)
Lung index (mg/g)
Kideny index (mg/g)
PBS
NPt ligand
Oxp. (2.46 mg Pt/kg)
Cis. (3.26 mg Pt/kg)
Ligand + Cis. (3.26 mg Pt/kg)
NPt (1.07 mg Pt/kg)
NPt (2.15 mg Pt/kg)
j.
Heart index (mg/g)
Liver index (mg/g)
Spleen index (mg/g)
Lung index (mg/g)
Kideny index (mg/g)
PBS
NPt ligand
Oxp. (2.46 mg Pt/kg)
Cis. (3.26 mg Pt/kg)
Ligand + Cis. (3.26 mg Pt/kg)
NPt (1.07 mg Pt/kg)
NPt (2.15 mg Pt/kg)

Fig. S3. NPt inhibits breast cancer cell growth, migration and invasion *in vitro* and *in vivo*. (a) Flow cytometry scatter plots showed the percentage of apoptotic in MDA-MB-231 cells treated without or with NPt 1.5 μM, 3 μM and cisplatin 3 μM. **(b)** Schematic diagram of in vivo tumor migration inhibition experiment. 4T1 cells were first injected into Balb/c mice (i.v.), and treated with NPt ligand, oxaliplatin, cisplatin, cisplatin+ligand, NPt (1.07 mg Pt/kg), NPt (2.15 mg Pt/kg) four times after 7 days, and the experiment was over, the complete lung tissues were then fixed in paraformaldehyde. **(c)** Body weight of the mice during treatment in anti-tumor model *in vivo*. **(d)** Body weight of the mice during treatment in anti-migration model *in vivo*. Compound cisplatin and NPt inhibited the migration of MDA-MB-231 **(e)** and MCF-7 **(f)** cells after treatment for 24 h by transwell and wound healing assays. The protein expression of migration gene β-catenin and apoptosis gene p53 was analyzed using western blot in MDA-MB-231 **(g)** cells and MCF-7 **(h)** cells. Organ weight indexes (heart, liver, spleen, lung, and kidney) after treatment with PBS, NPt ligand, cisplatin, oxaliplatin, cisplatin + NPt ligand, NPt for anti-tumor **(i)** and anti-metastasis **(j)** models in vivo. Statistical significance was calculated via two-sided unpaired t-test. Data are given as means ± SD (n = 3).*, P < 0. 05 **, P < 0.01 ***, P < 0.001.

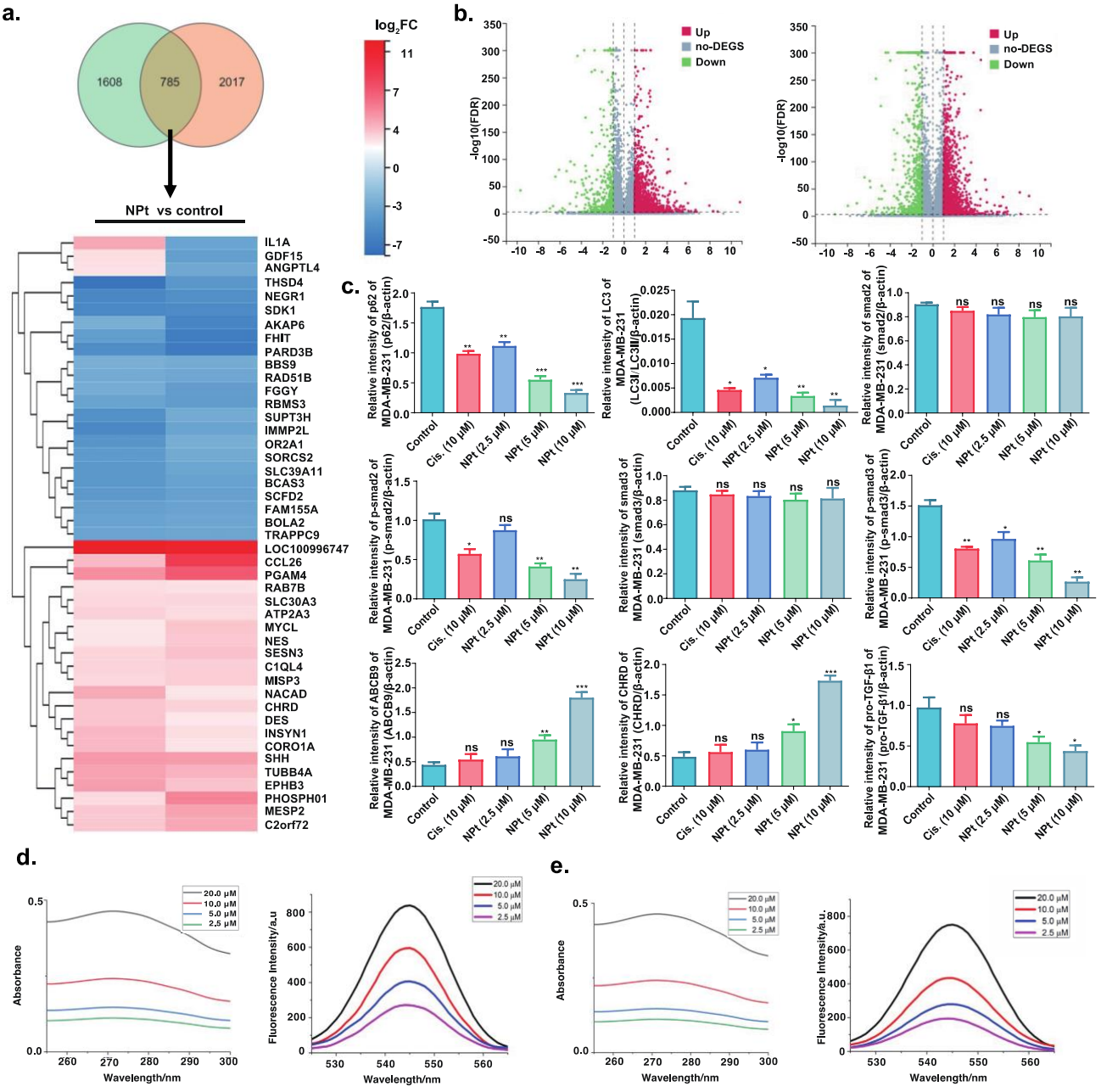

Fig. S4. (a) RNA-Seq was performed after MDA-MB-231 and MCF-7 cells were treated with trizol, and 45 genes that were

significantly changed in both MDA-MB-231 and MCF-7 cells were screened out by significant difference. **(b)** Two MA plots, depicting the log-fold changes with significant DEGs marked in color. Cells were treated with NPt (10 μM) for 24 h in both MDA-MB-231 and MCF-7 breast cancer cells. **(c)** Protein expression statistics of the p62/CHRD/Smad2/3 signaling pathway associated with ABCB9-mediated TGF-β activation using Western blot analysis in MDA-MB-231 cells. Changes in the absorption and emission spectra of NPt in H_2O **(d)** and PBS **(e)**. P values were obtained by two-tailed unpaired t-test. *, P < 0.05 **, P < 0.01 ***, P < 0.001.

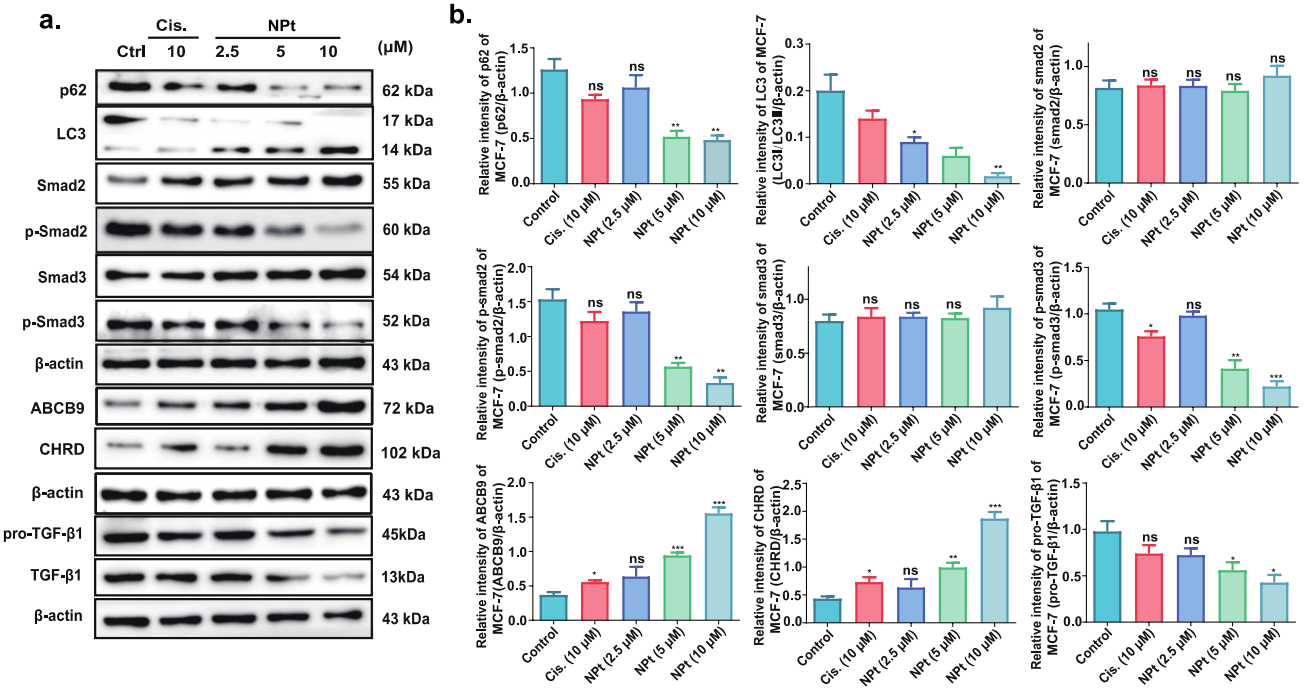

Fig. S5. (a–b) Western blot analysis of protein expression associated with ABCB9-mediated TGF-β activation through the p62/CHRD/Smad2/3 signaling pathway in MCF-7 cells and the corresponding statistics. P values were obtained by two-tailed unpaired t-test. *, P < 0.05 **, P < 0.01 ***, P < 0.001.

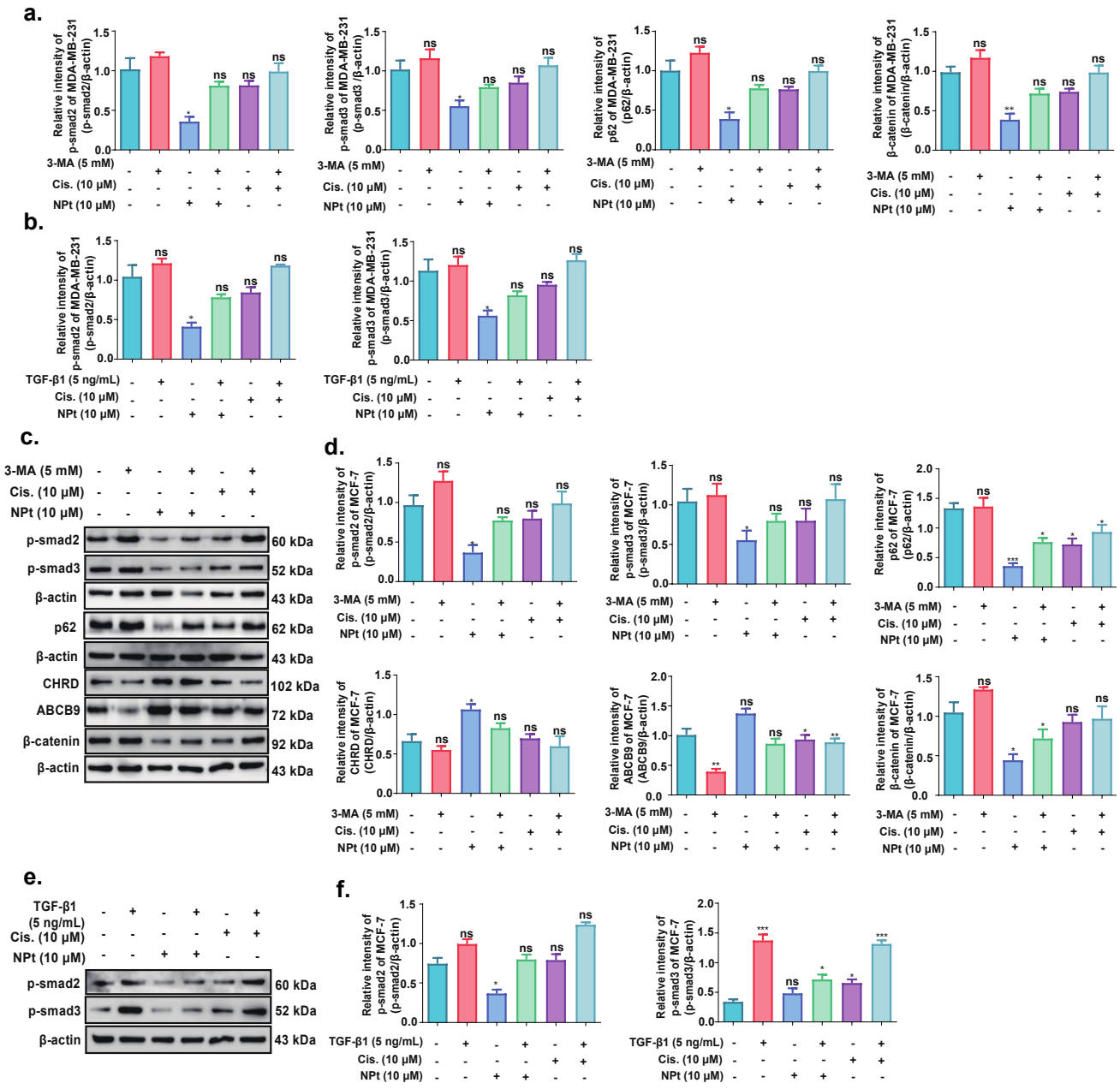

Fig. S6. **(a)** TGF-β activation mediated by p62/CHRD/Smad2/3 signaling pathway and ABCB9 in the presence or absence of 3-MA (5 mM, 2 hr) in MDA-MB-231 was analyzed by western blot statistical graph of related protein expression. **(b)** Whole cell lysates from MDA-MB-231 cells treated with cisplatin or NPt (10 μM) in the presence or absence of TGF-β1 (5 ng/mL) for the western blot of p-Smad2/3 analytical charts. **(c-d)** The expression of proteins related to ABCB9-meditated TGF-β activation through p62/CHRD/Smad2/3 signaling pathway was analyzed using western blotting in the presence or absence of 3-MA (5 mM, 2 h) in MCF-7 cells. **(e-f)** In the presence or absence of TGF-β1 (5 ng/mL), whole cell lysates from MCF-7 cells were treated with cisplatin or NPt (10 μM), and western blot analysis was performed on p-Smad2/3. P values were obtained by two-tailed unpaired t-test. *P< 0.05, **P < 0.01; ***P < 0.001.

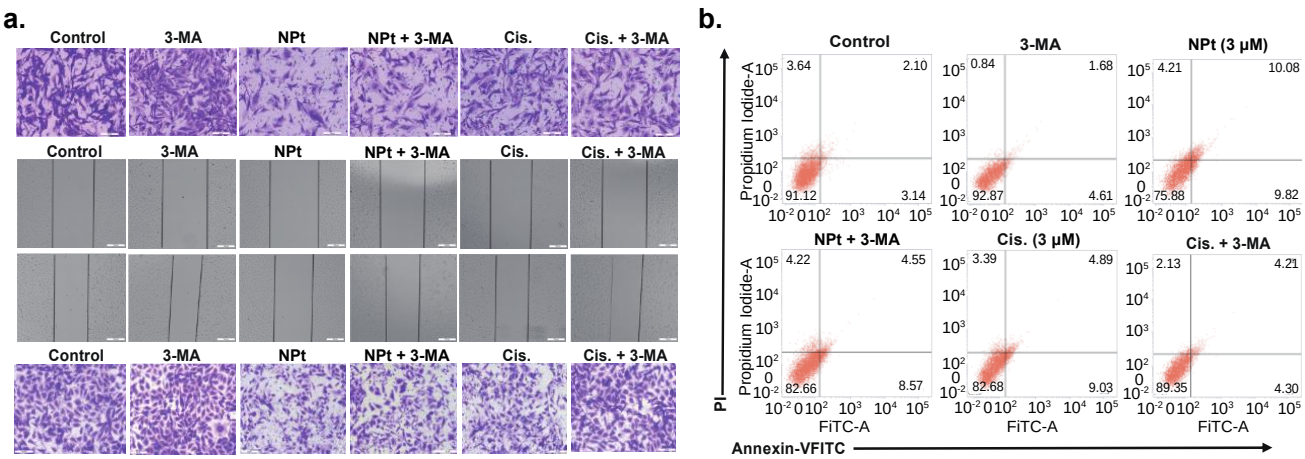

Fig. S7. **(a)** In the presence or absence of 3-MA (5μM, 2 hours), the transwell assays and wound-healing assay of MDA-MB-231 cells in the presence of NPt or Cis. after 24 h. In the presence or absence of 3-MA (5μM, 2 hours), the transwell assays of MCF-7 cells in the presence of NPt or Cis. after 24 h. **(b)** Flow cytometry scatter plots showed the percentage of apoptotic in MDA-MB-231 cells with cisplatin or NPt in the presence or absence of 3-MA (5μM, 24 hours). *, P < 0. 05 **, P < 0.01.

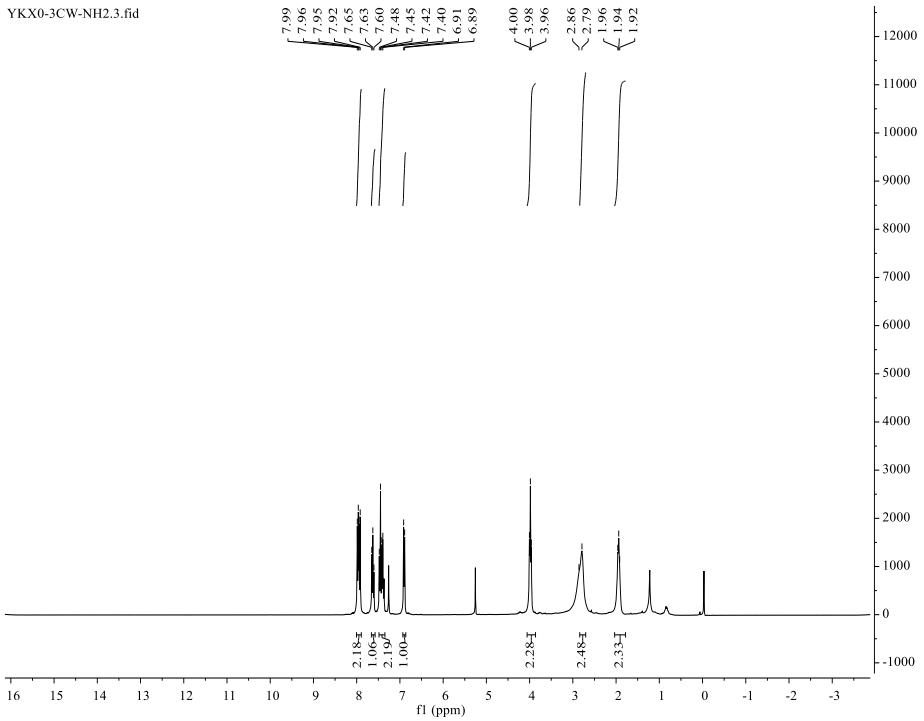

Fig. S8. [1]HNMR spectrum of compound **10a**.

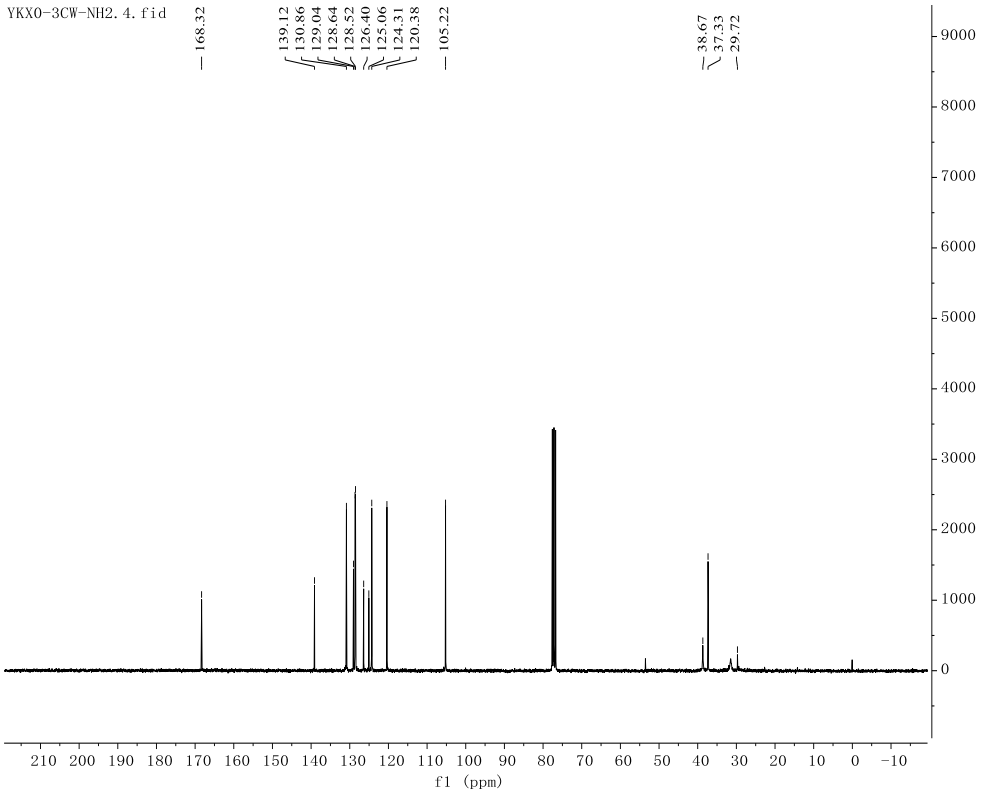

Fig. S9.[13]CNMR spectrum of compound **10a.**

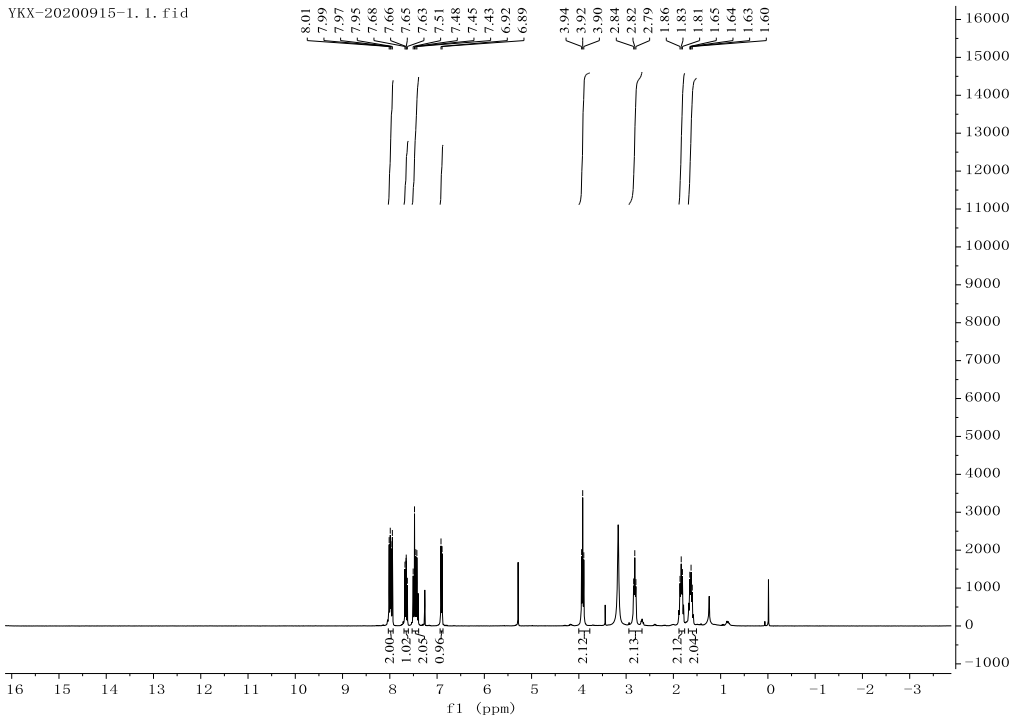

Fig. S10. [1]HNMR spectrum of compound**10b**.

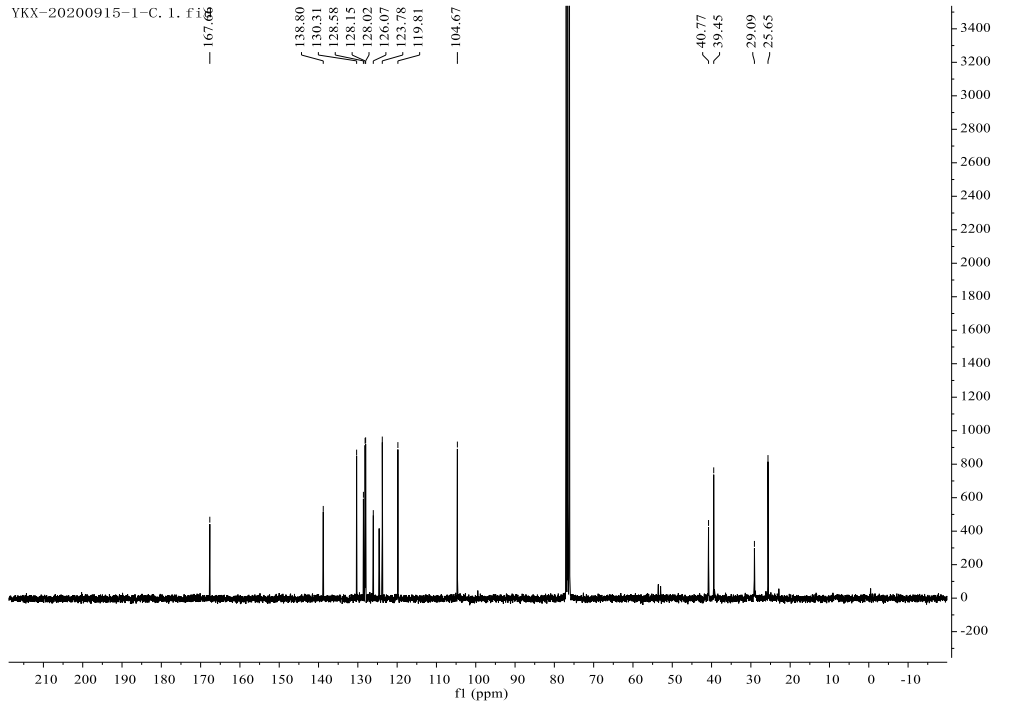

Fig. S11.[13]CNMR spectrum of compound **10b.**

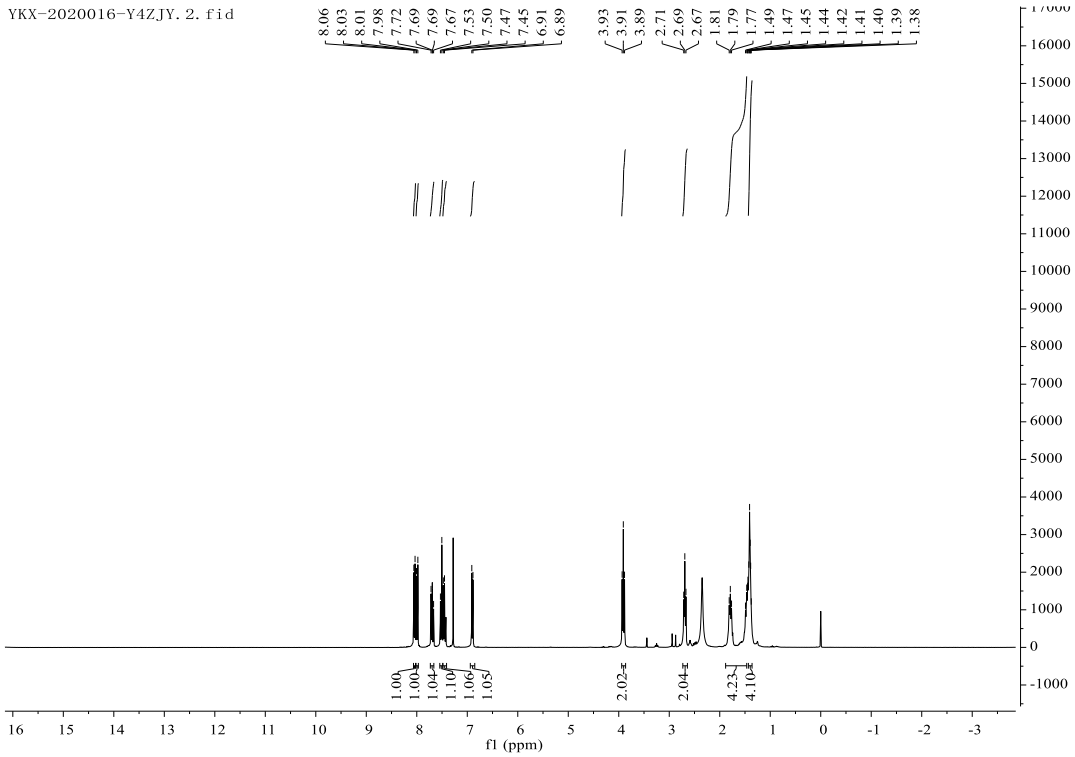

Fig. S12.[1]HNMR spectrum of compound **10c.**

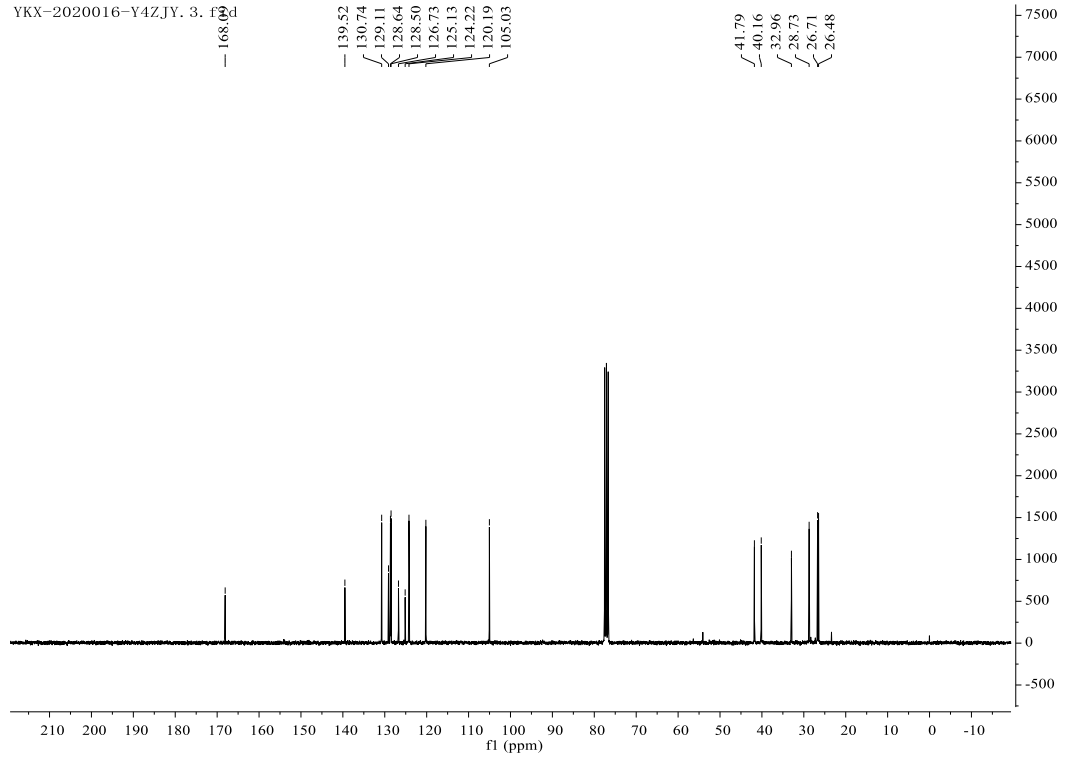

Fig. S13. [13]CNMR spectrum of compound **10c.**

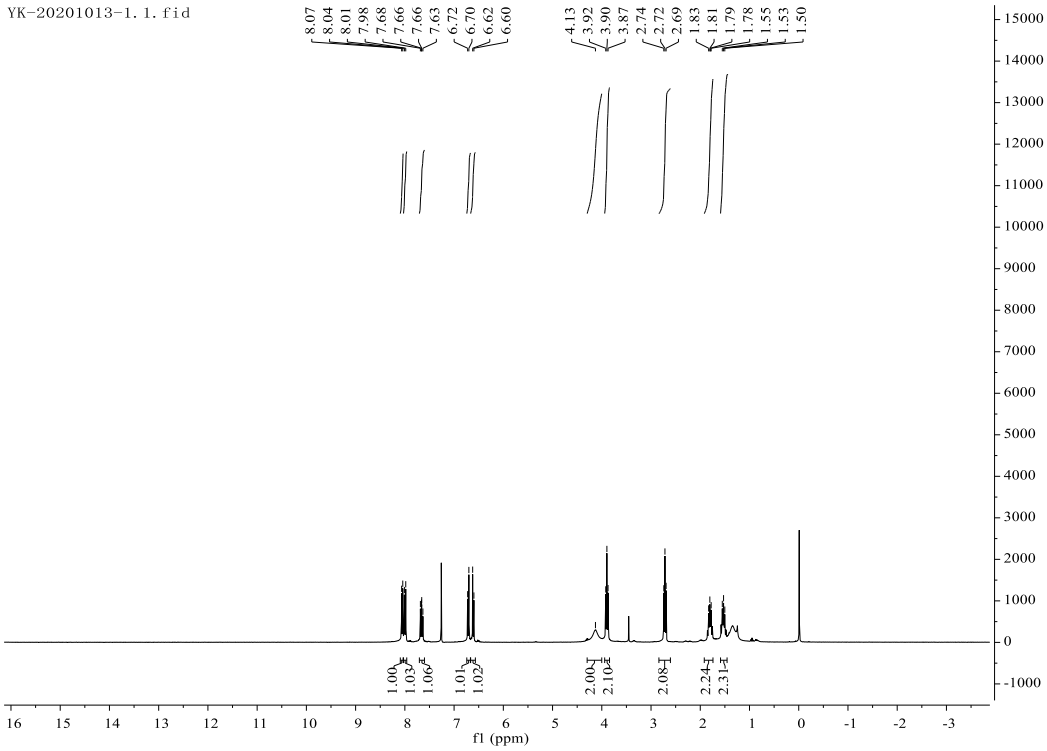

Fig. S14.[1]HNMR spectrum of compound **16a.**

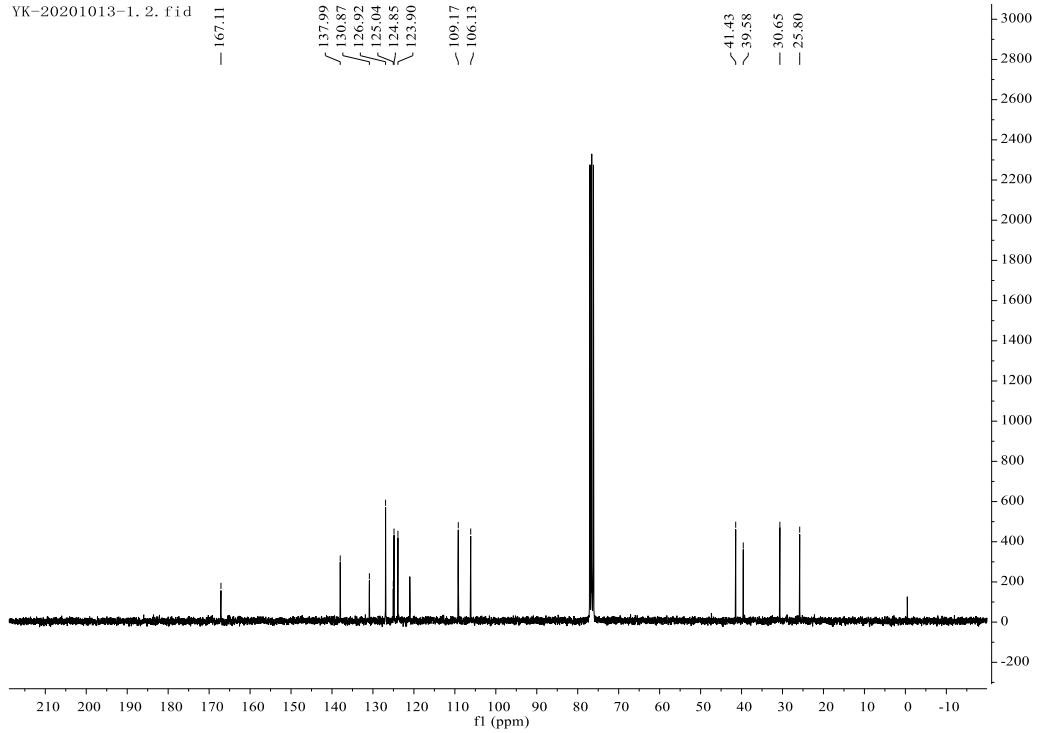

Fig. S15.[13]CNMR spectrum of compound **16a.**

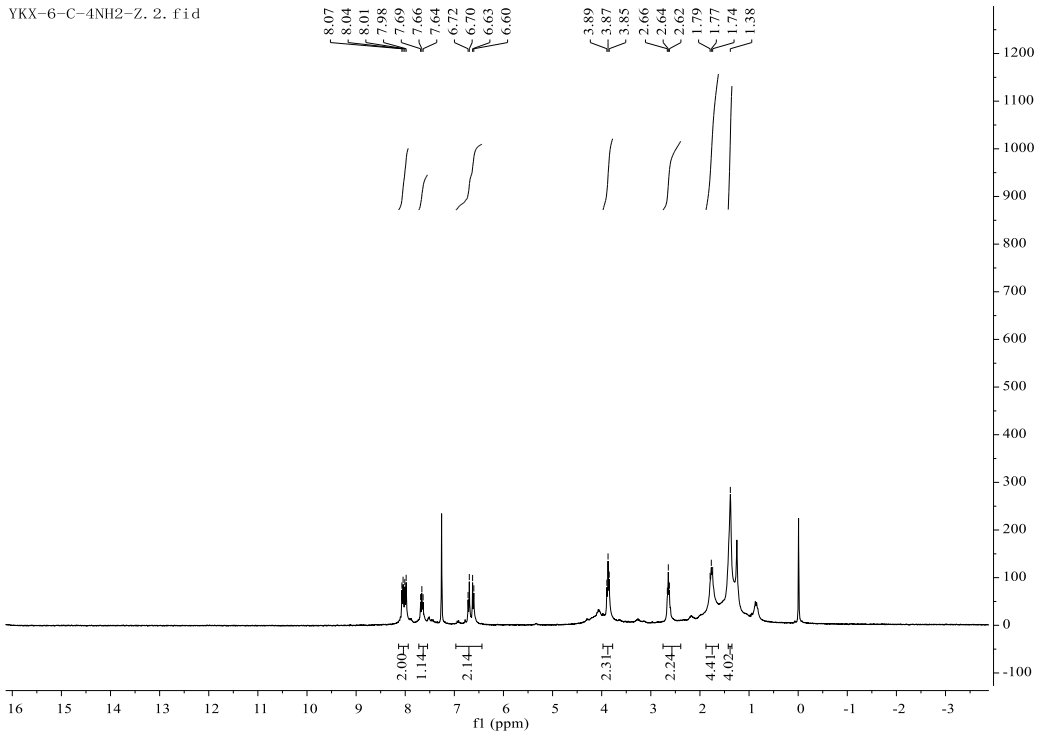

Fig. S16.[1]HNMR spectrum of compound **16b.**

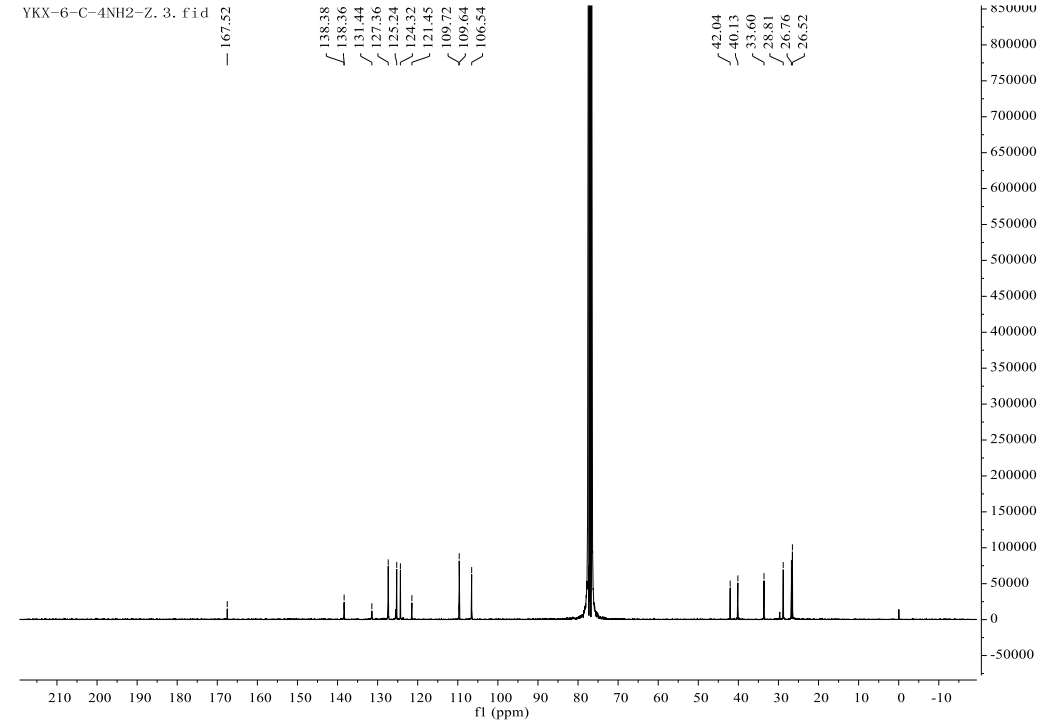

Fig. S17. [13]CNMR spectrum of compound **16b.**

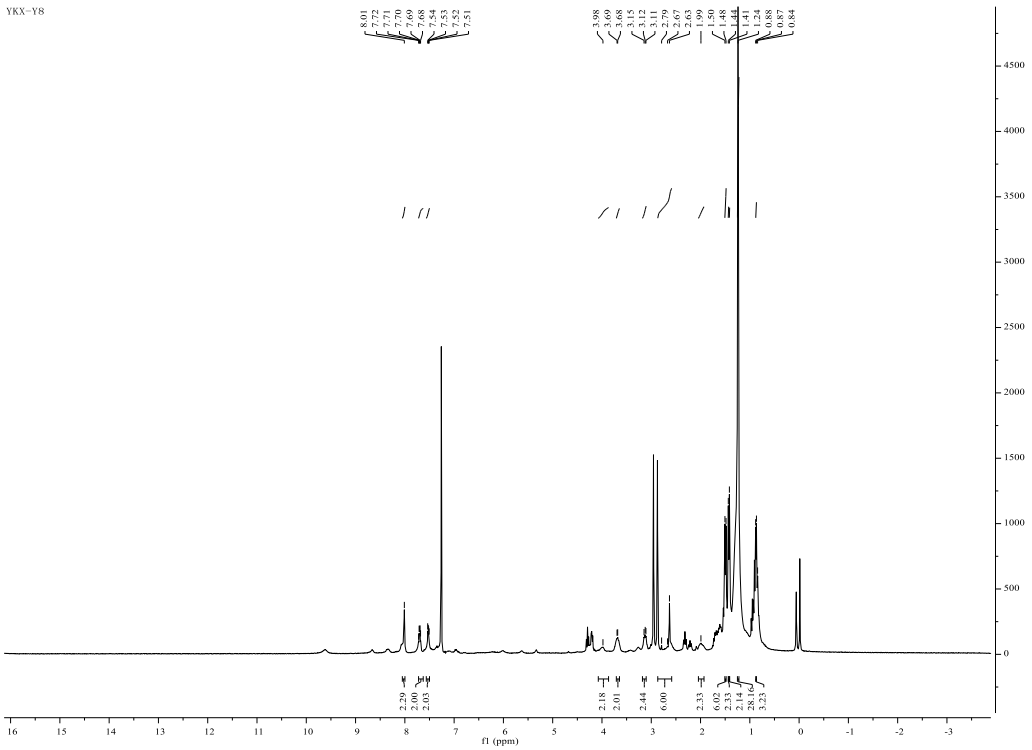

Fig. S18. [1]HNMR spectrum of compound **11a.**

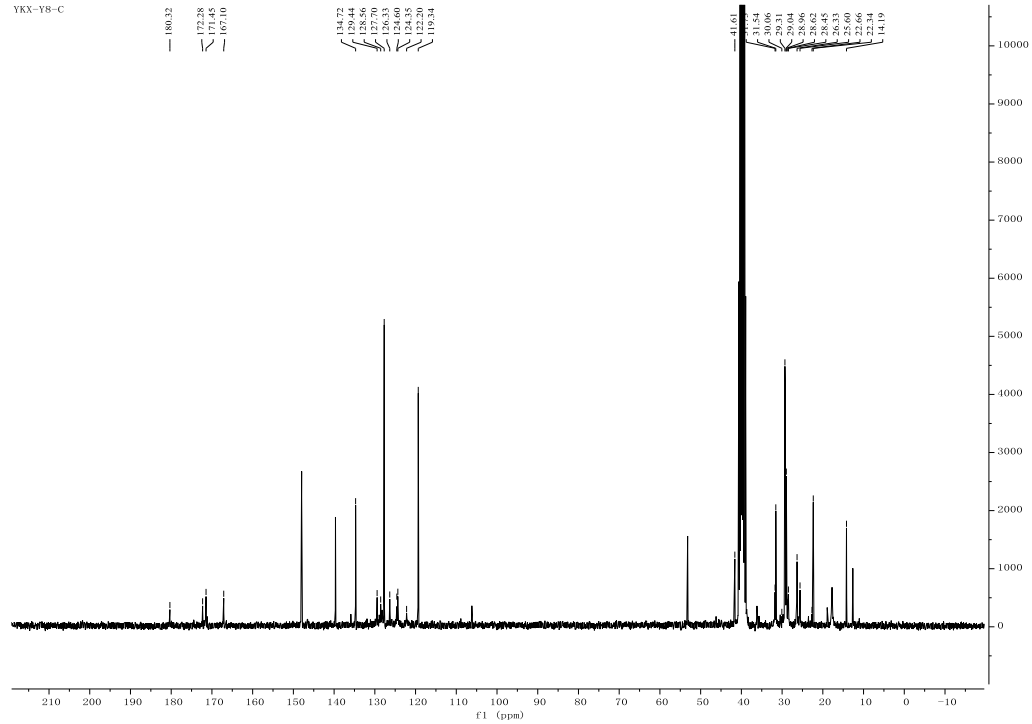

Fig. S19.[13]CNMR spectrum of compound **11a.**

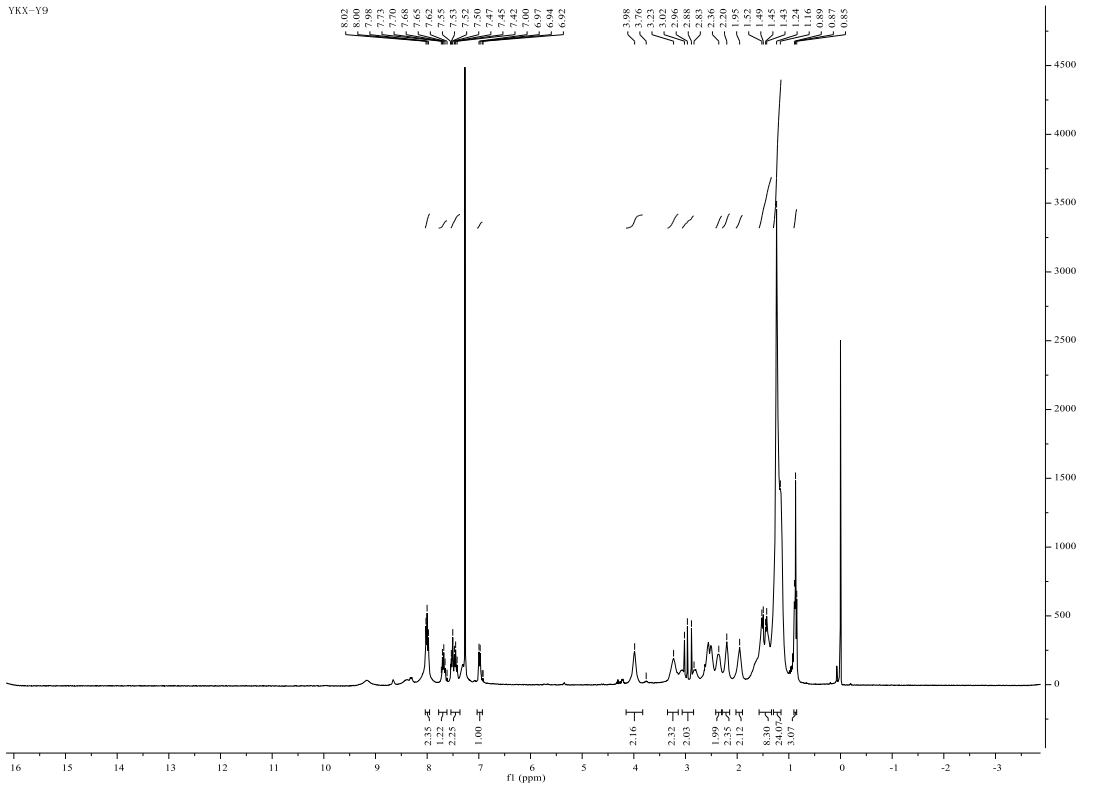

Fig. S20.[1]HNMR spectrum of compound **12a.**

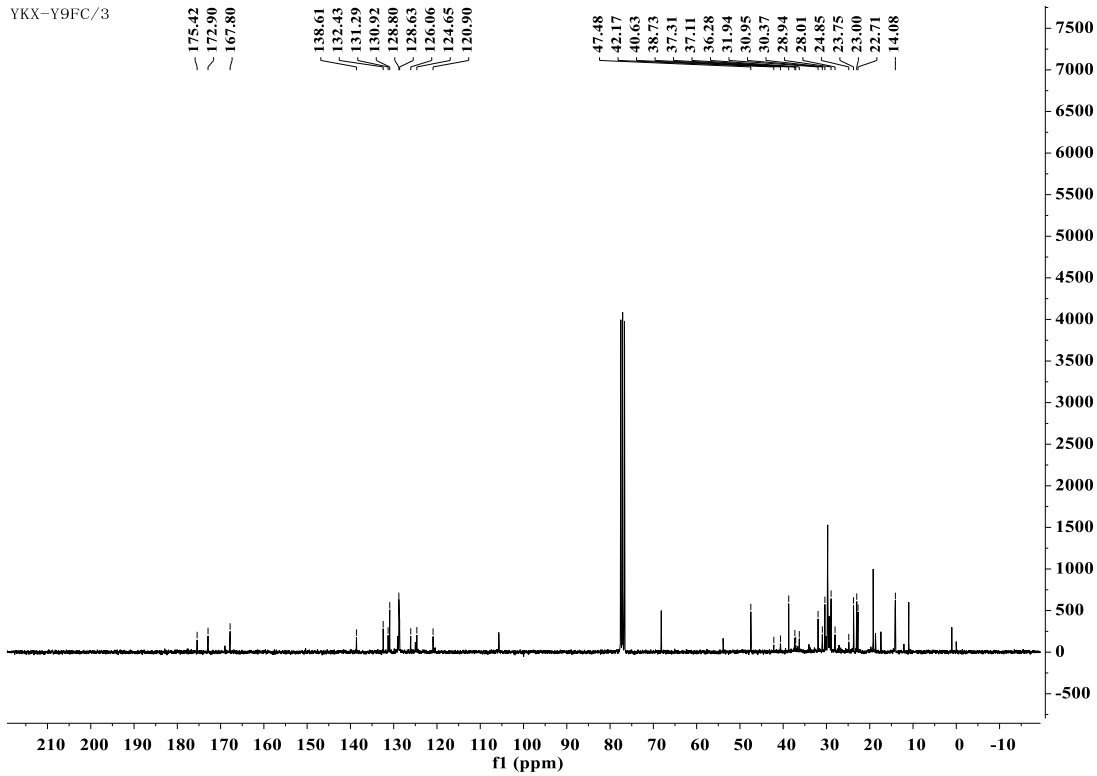

Fig. S21.[13]CNMR spectrum of compound **12a.**

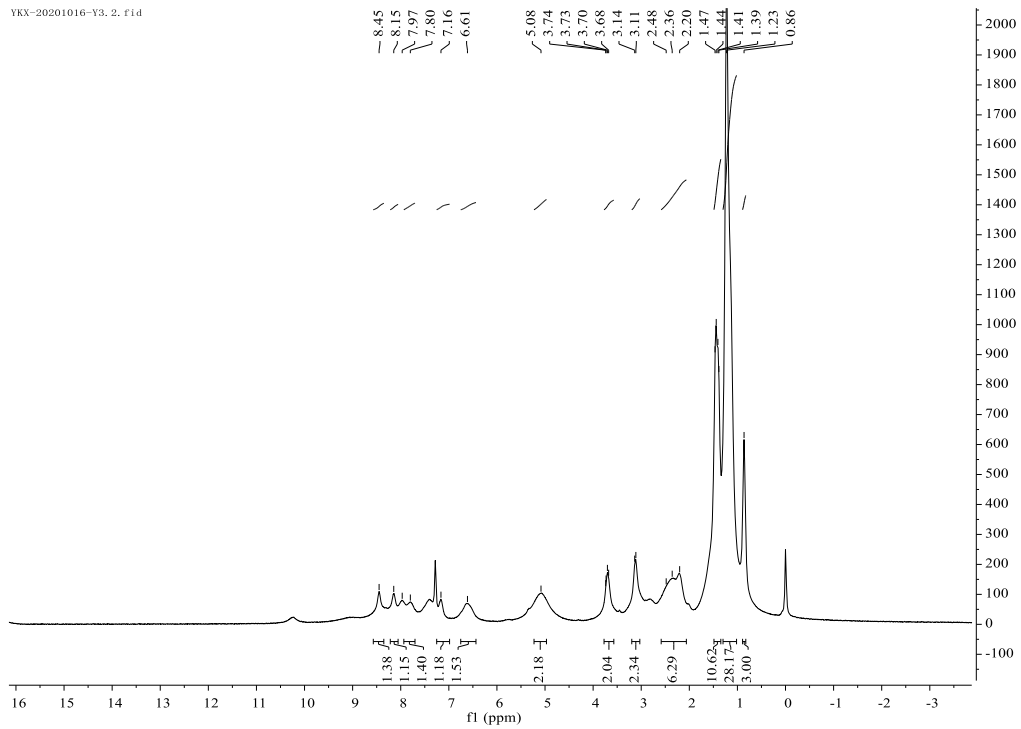

Fig. S22. [1]HNMR spectrum of compound **17a.**

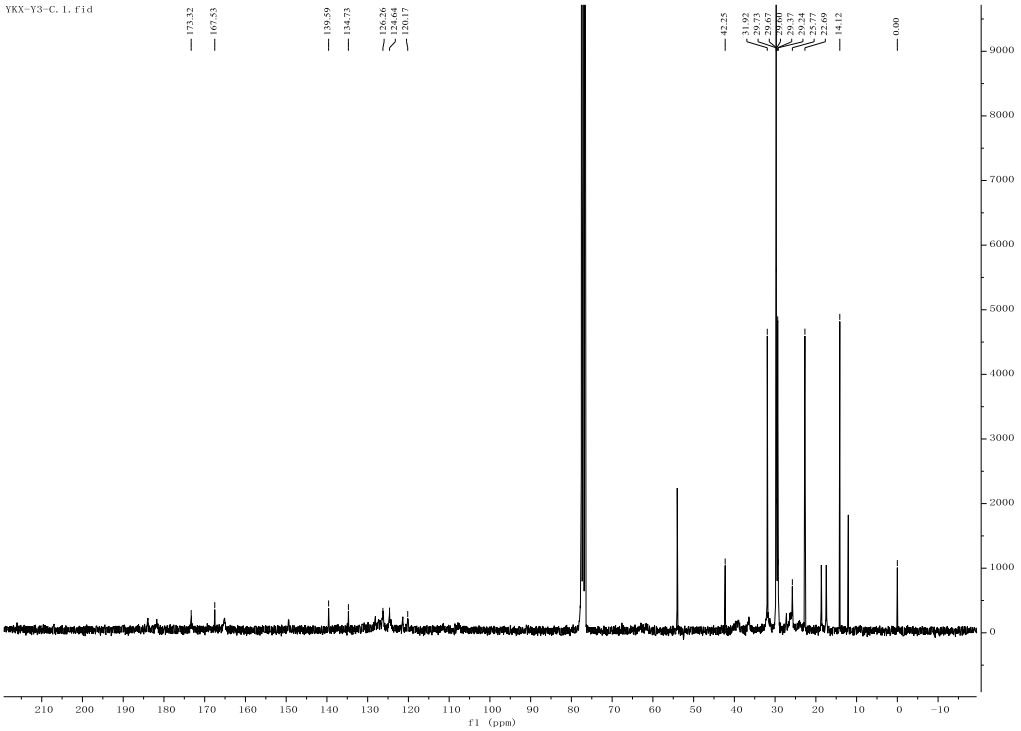

Fig. S23.[13]CNMR spectrum of compound **17a.**

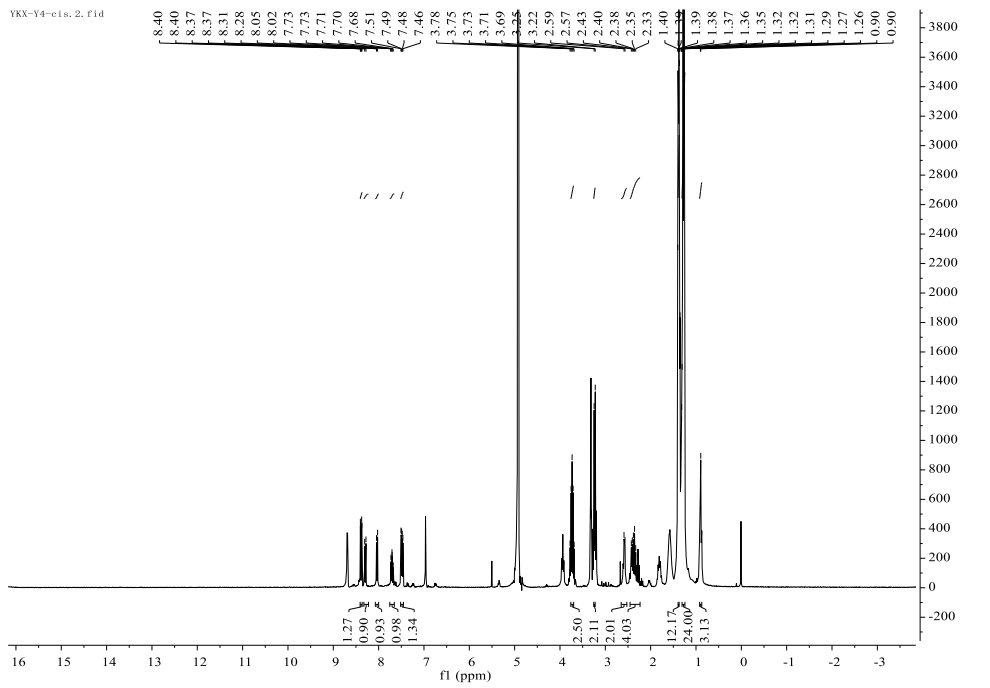

Fig. S24.[1]HNMR spectrum of compound **NPt.**

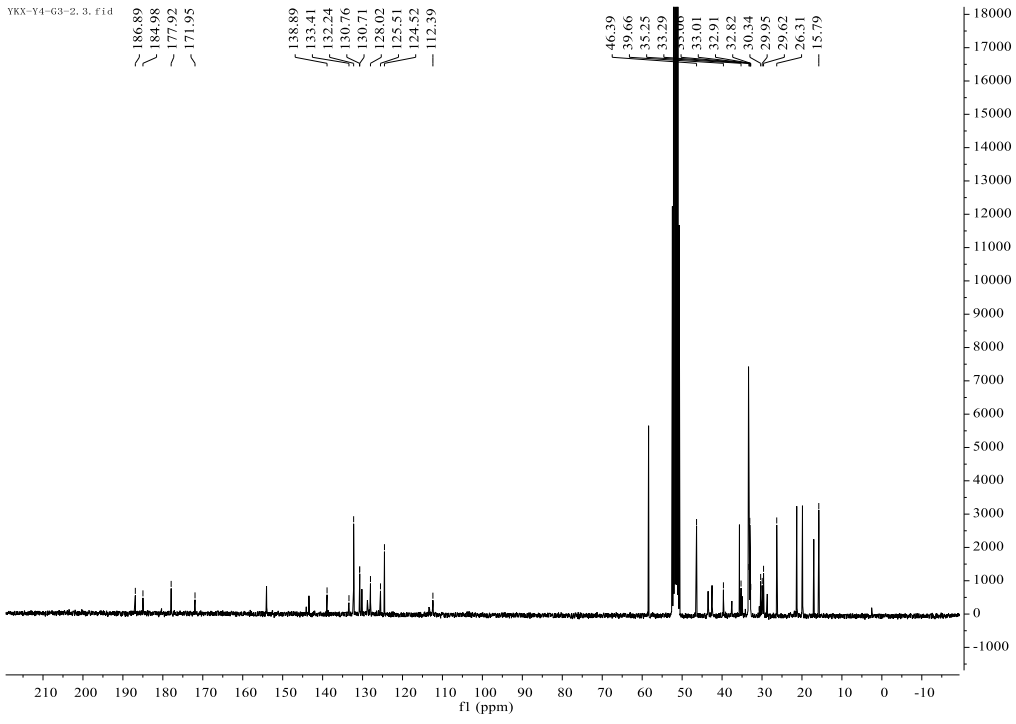

Fig. S25.[13]CNMR spectrum of compound **NPt.**

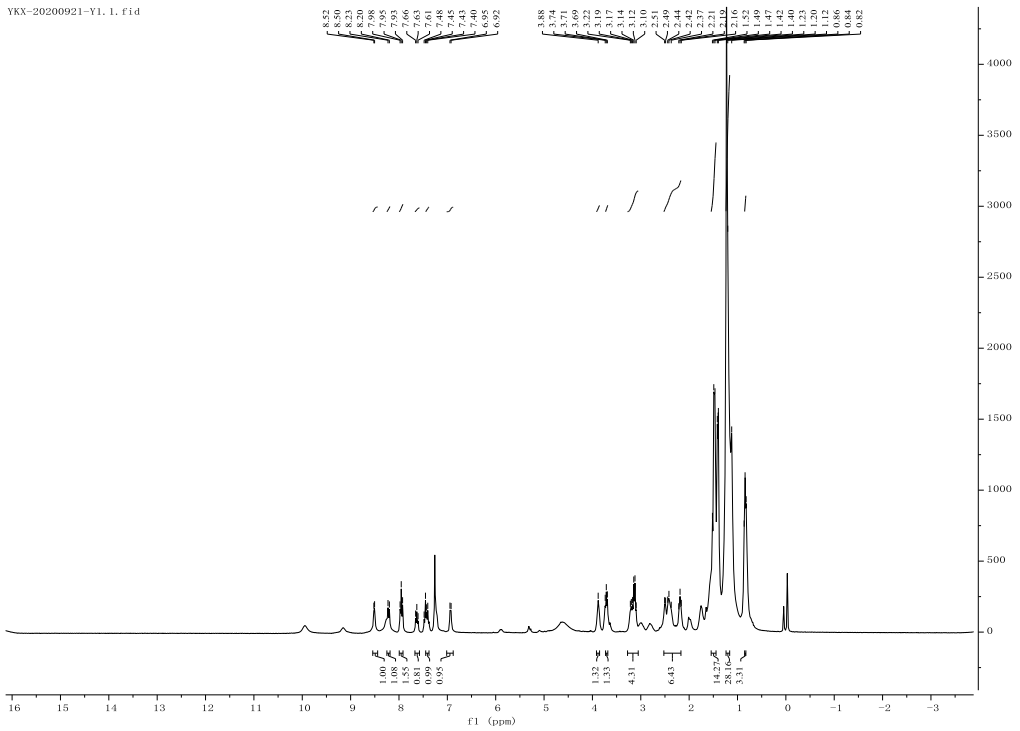

Fig. S26. [1]HNMR spectrum of compound **11b.**

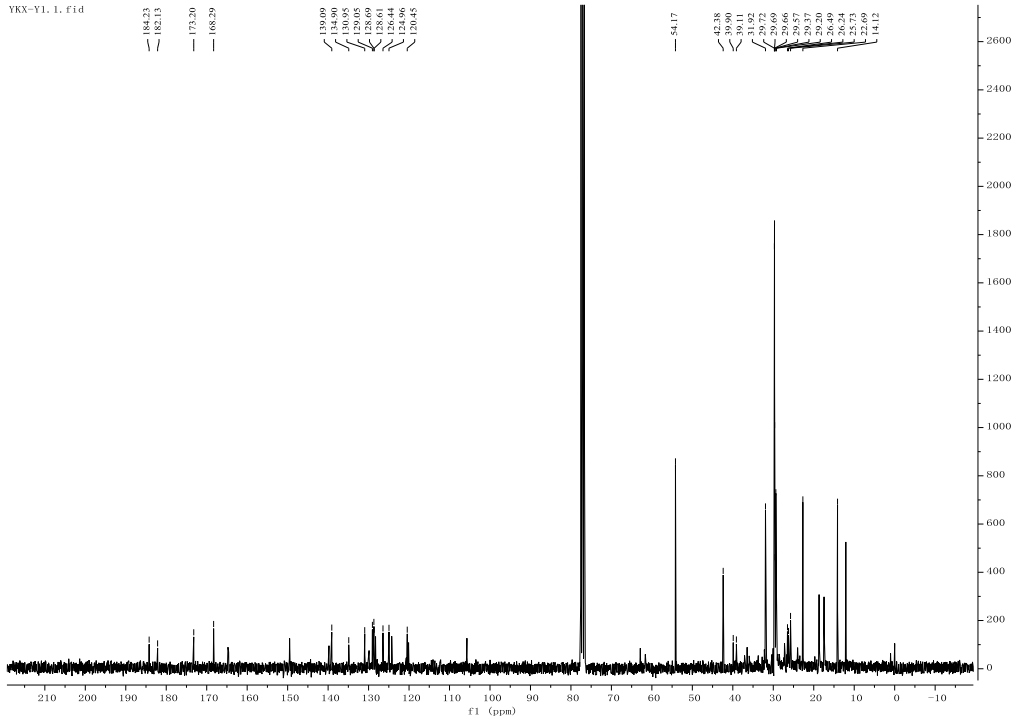

Fig. S27. [13]CNMR spectrum of compound **11b.**

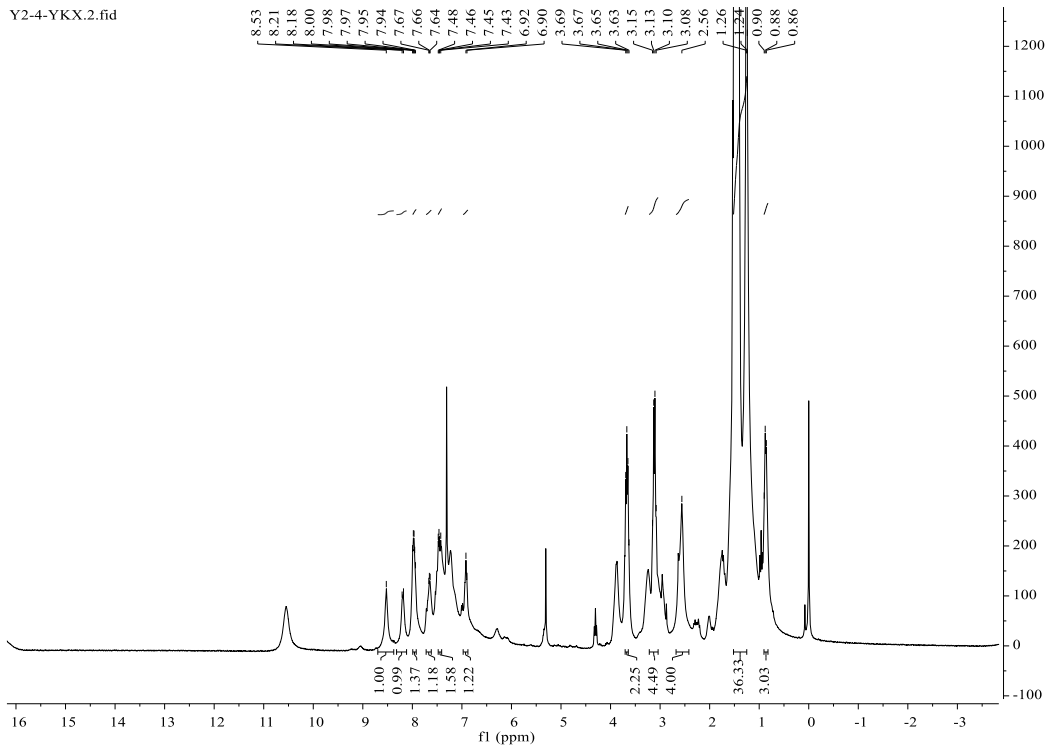

Fig. S28. [1]HNMR spectrum of compound **12b.**

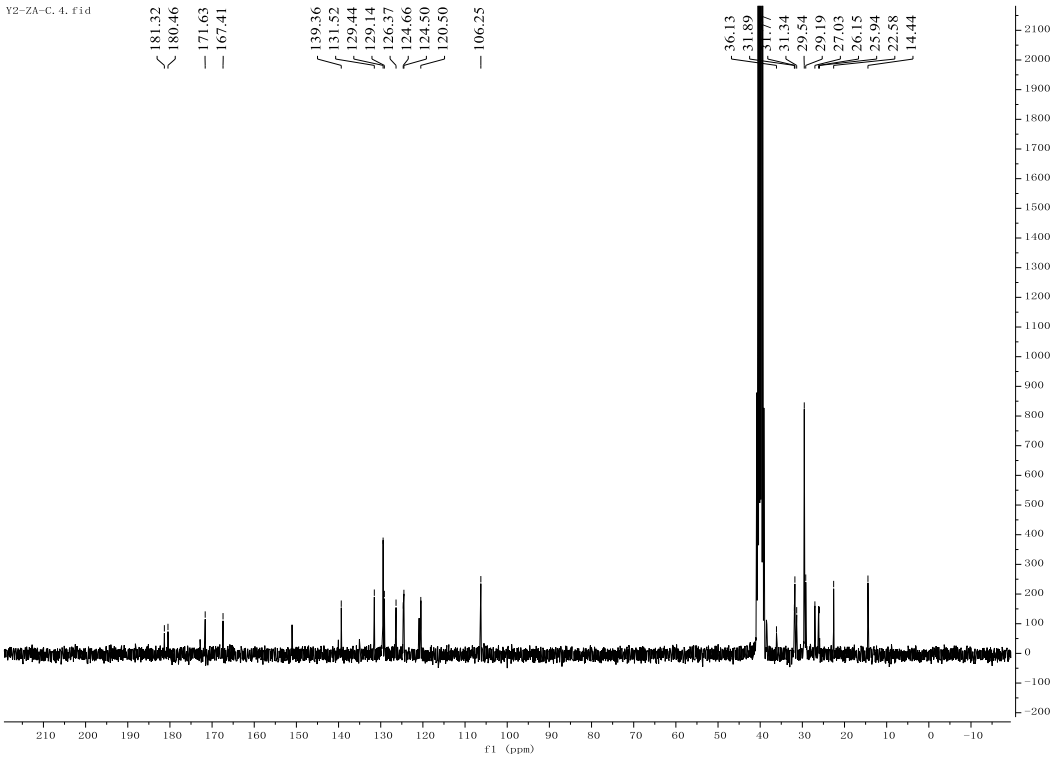

Fig. S29.[13]CNMR spectrum of compound **12b.**

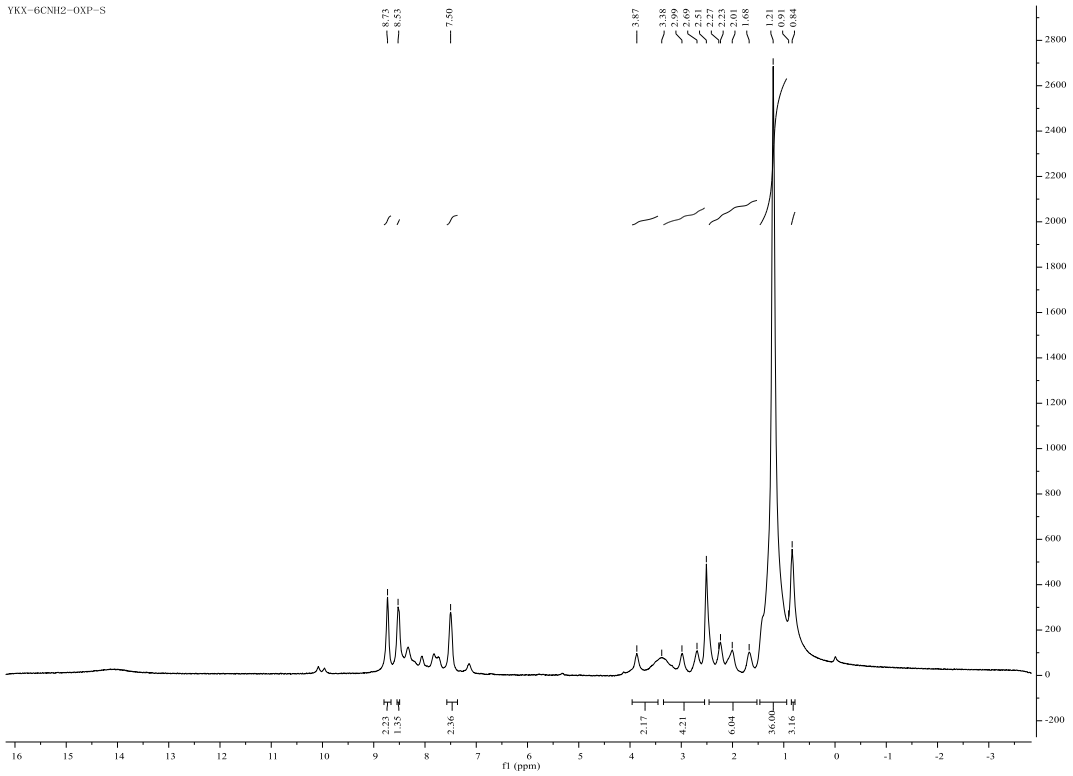

Fig. S30.[1]HNMR spectrum of compound **17b.**

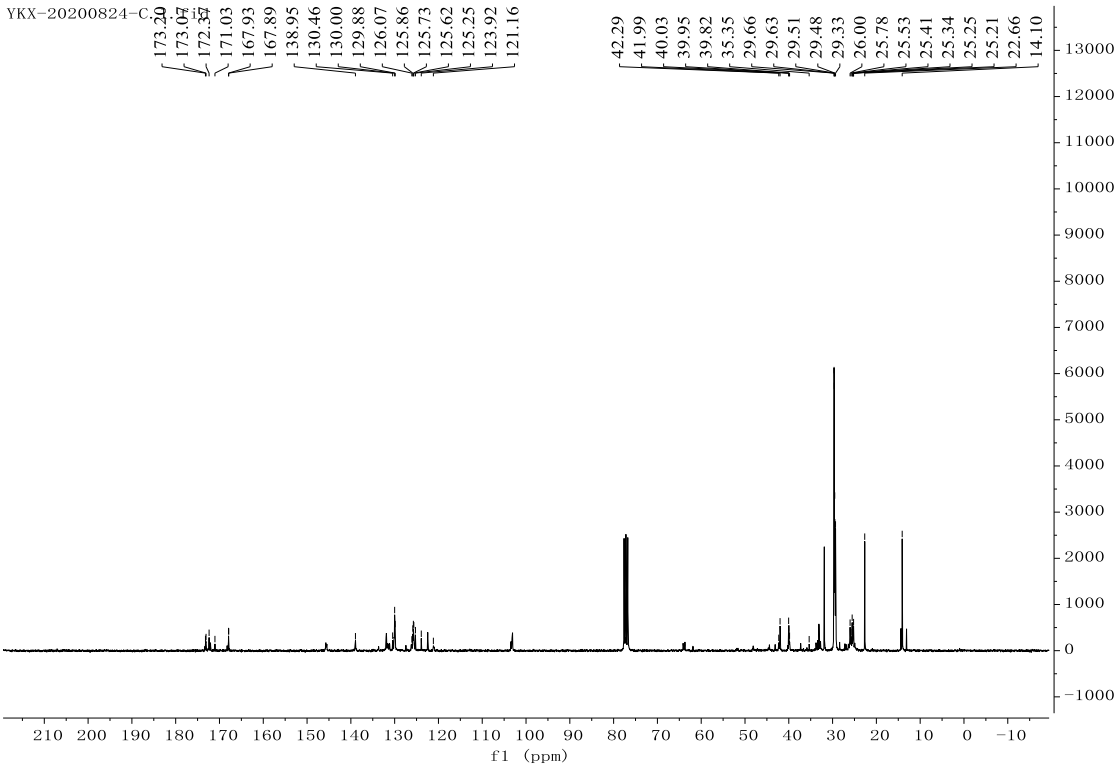

Fig. S31. [13]CNMR spectrum of compound **17b.**

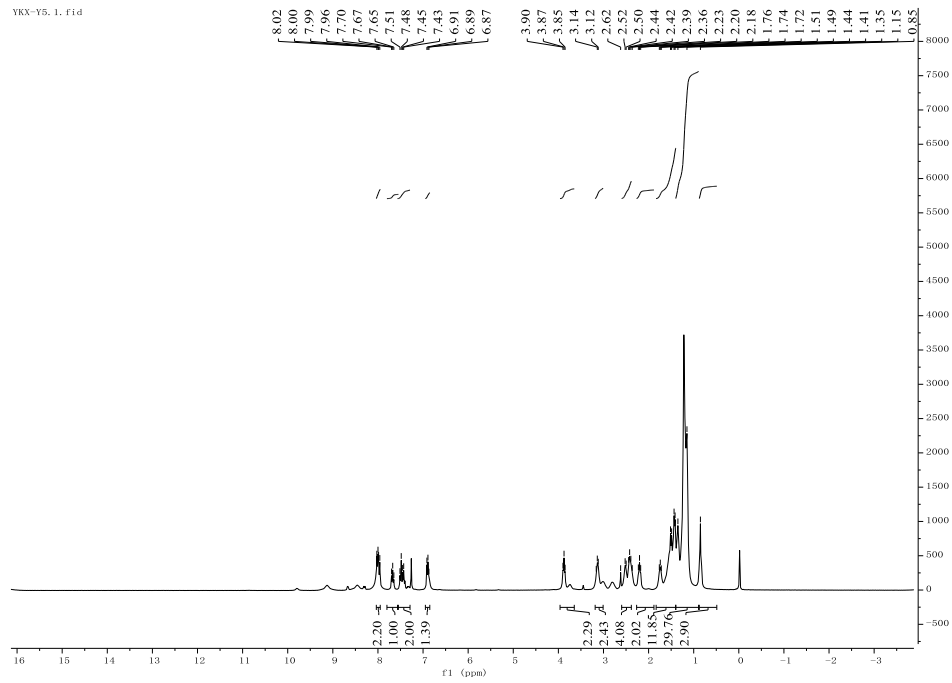

Fig. S32. [1]HNMR spectrum of compound **11c.**

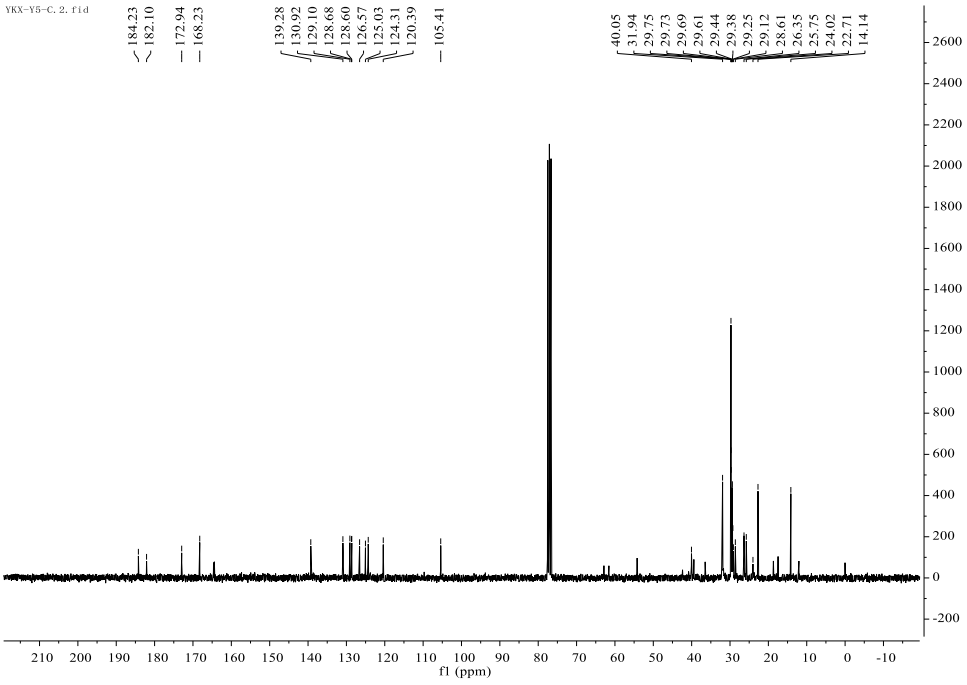

Fig. S33. [13]CNMR spectrum of compound **11c.**

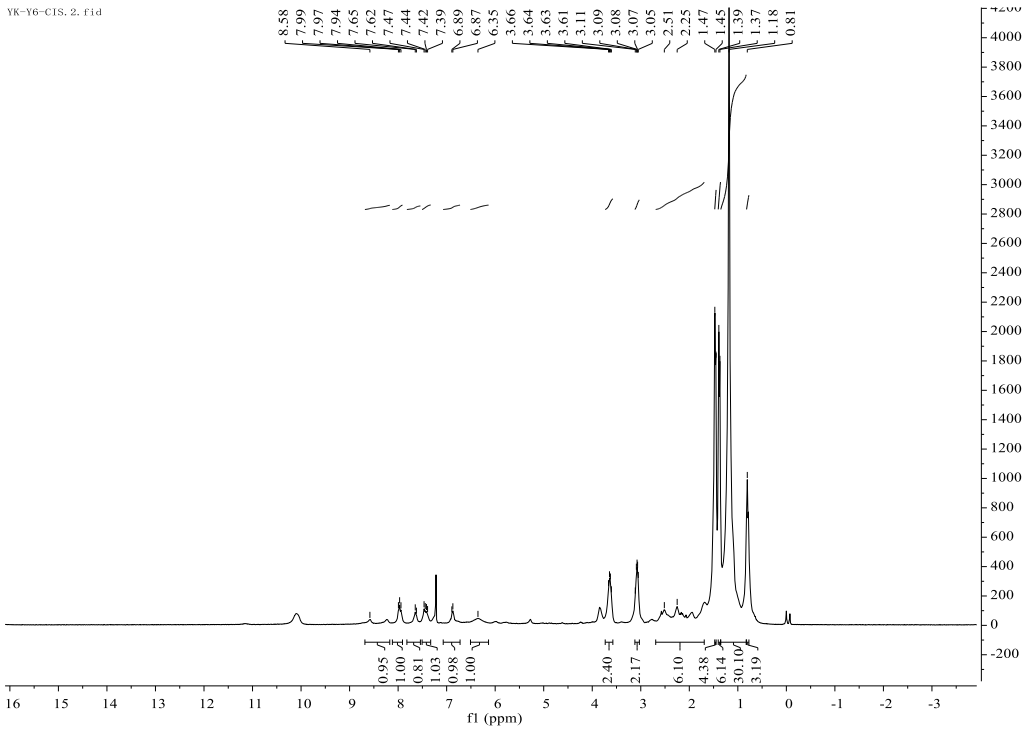

Fig. S34. [1]HNMR spectrum of compound **12c.**

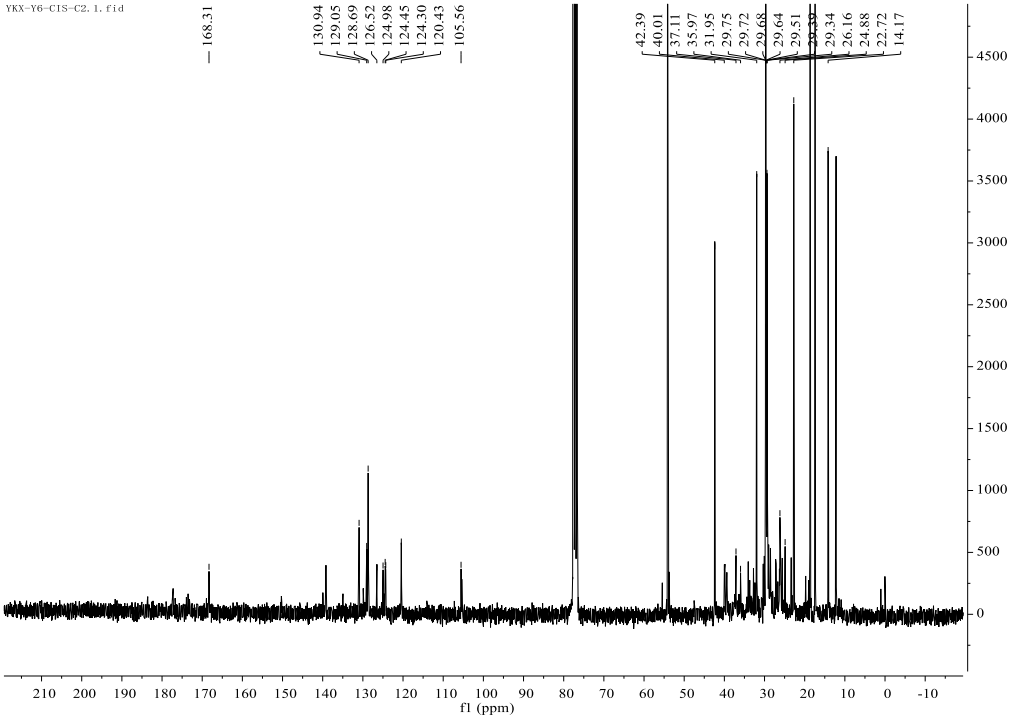

Fig. S35. [13]CNMR spectrum of compound **12c.**

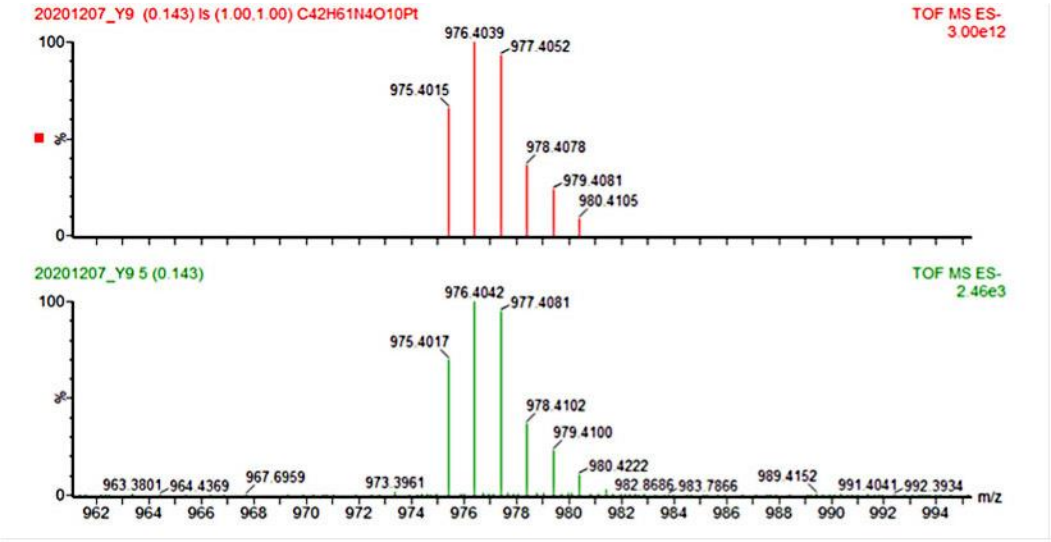

Fig. S36. ESI mass spectrum of compound **11a.**

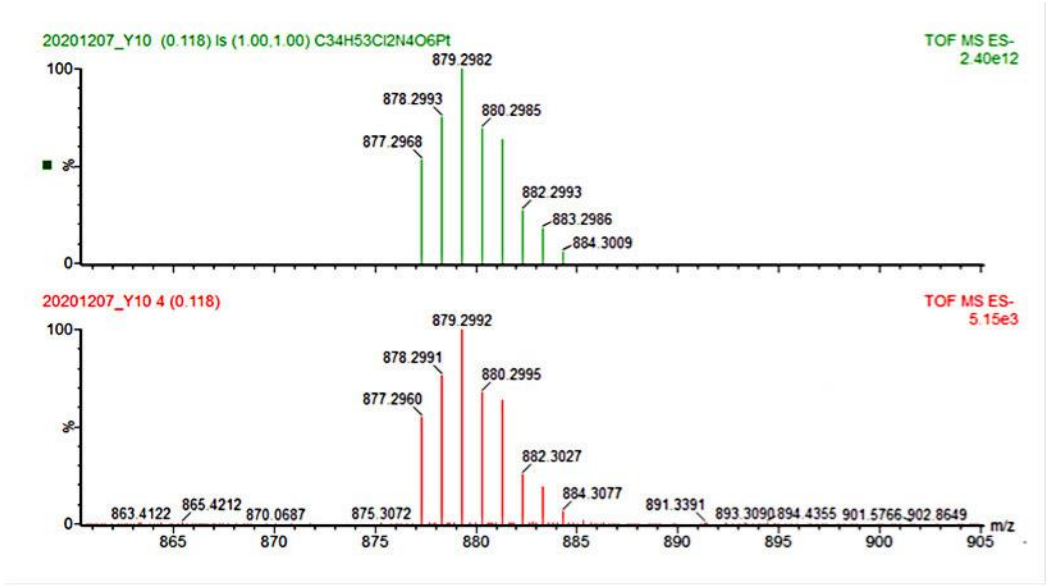

Fig. S37. ESI mass spectrum of compound **12a.**

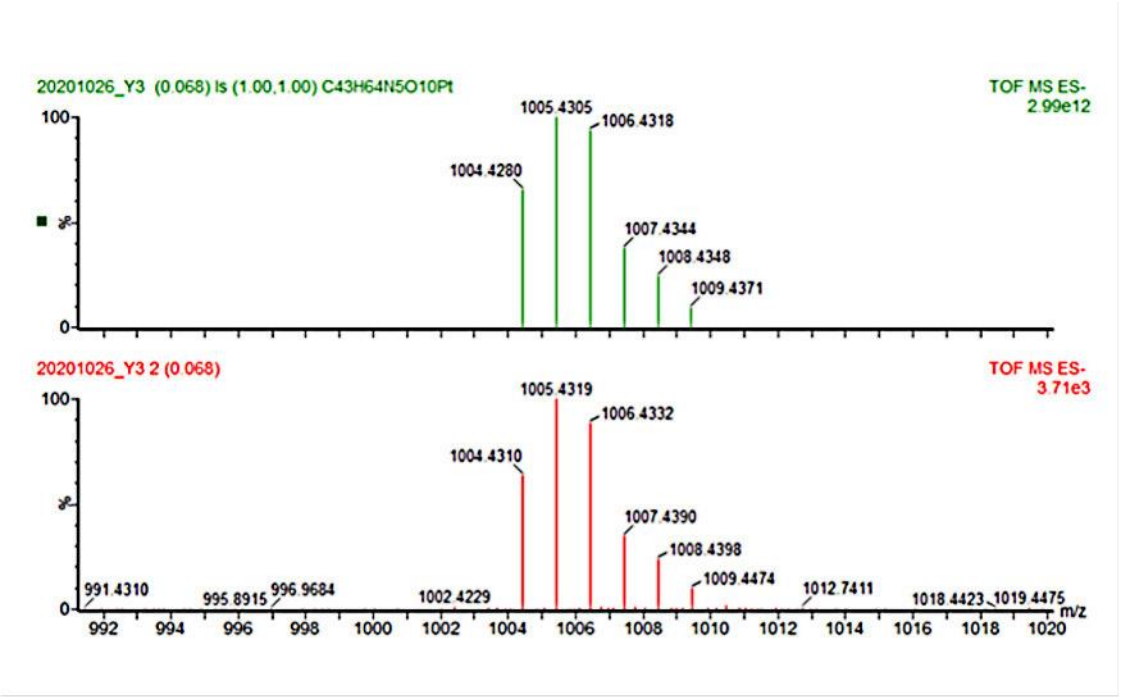

Fig. S38. ESI mass spectrum of compound **17a.**

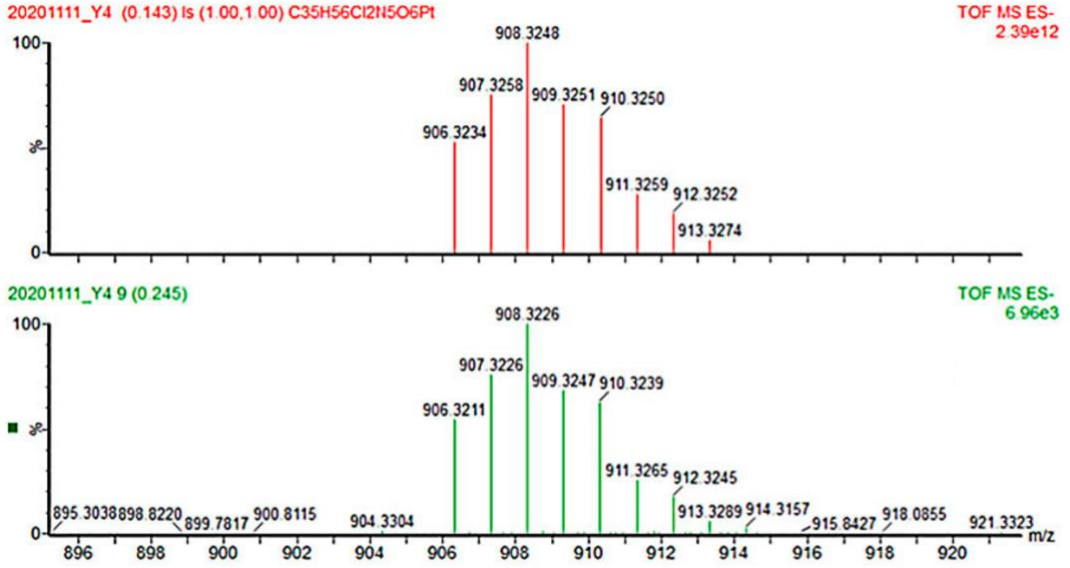

Fig. S39. ESI mass spectrum of compound **NPt.**

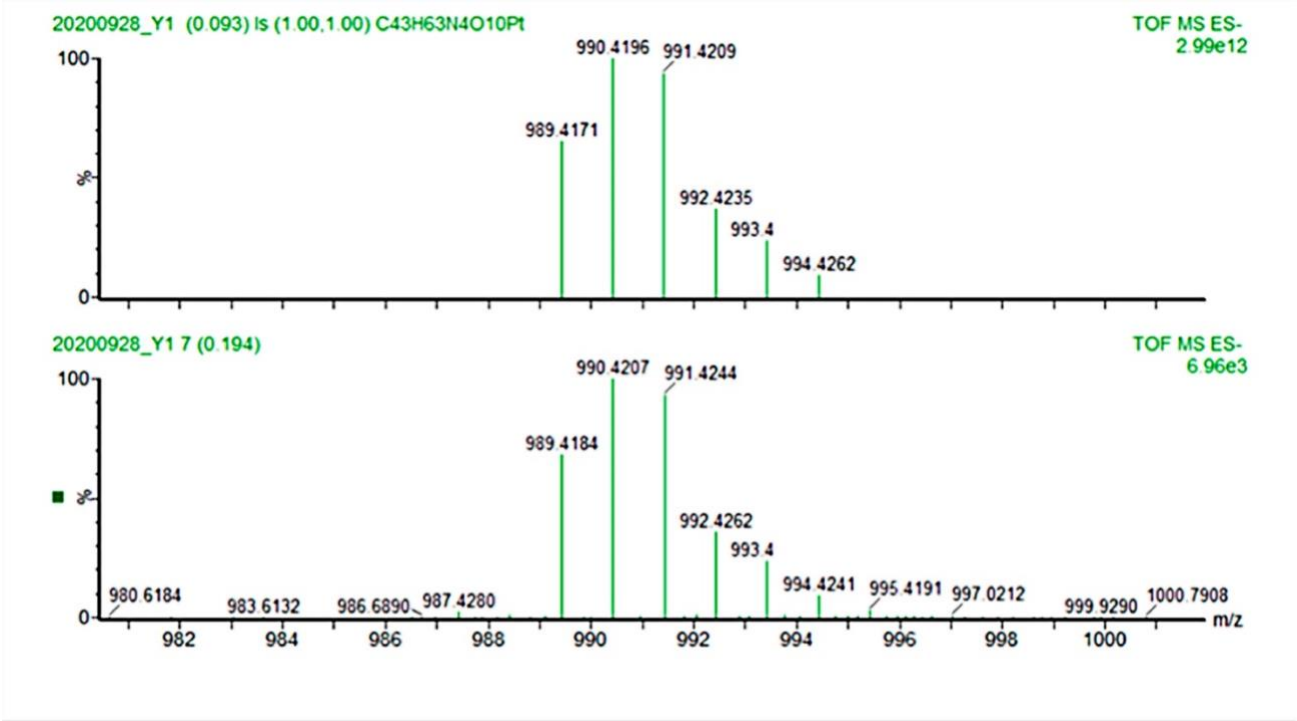

Fig. S40. ESI mass spectrum of compound **11b.**

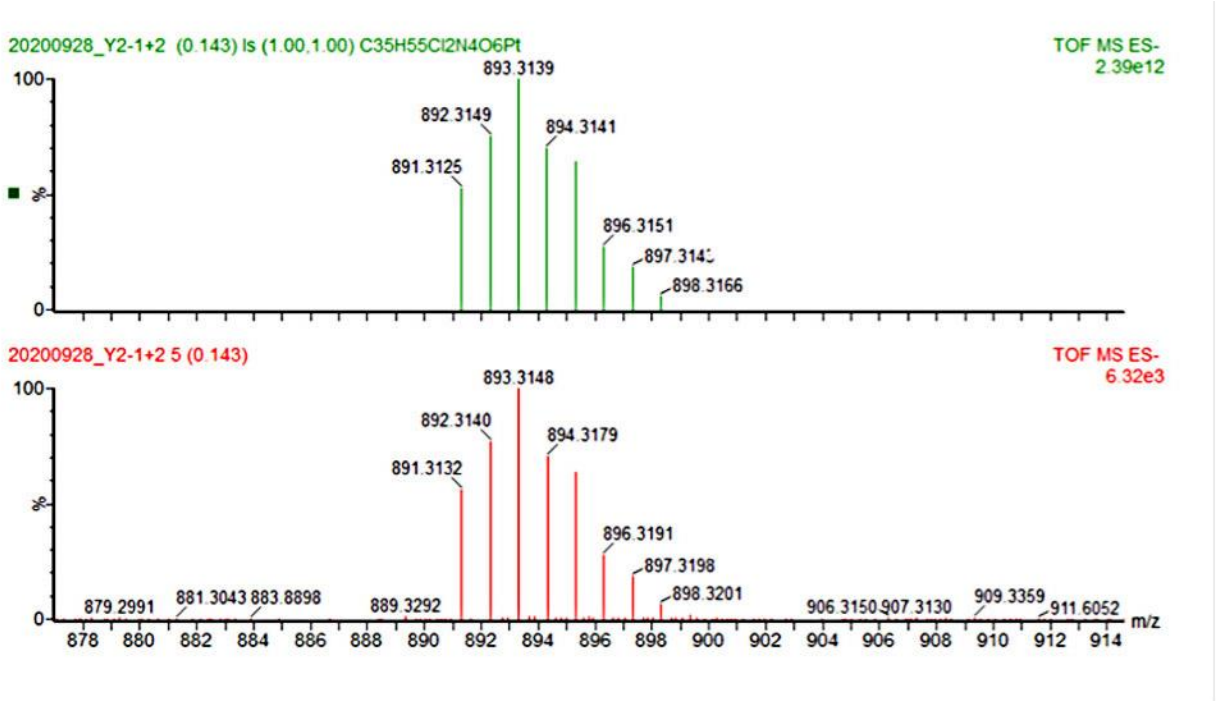

Fig. S41. ESI mass spectrum of compound **12b.**

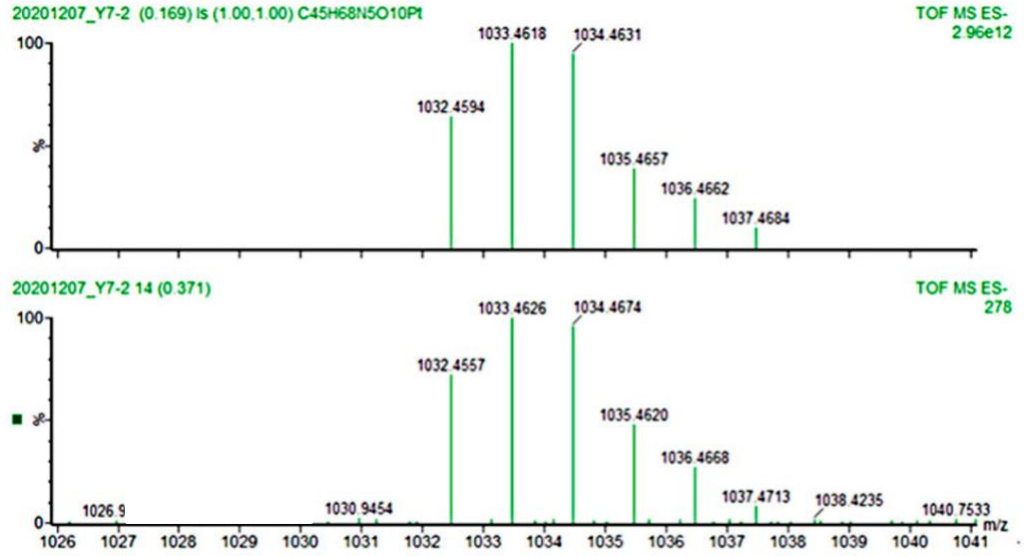

Fig. S42. ESI mass spectrum of compound **17b.**

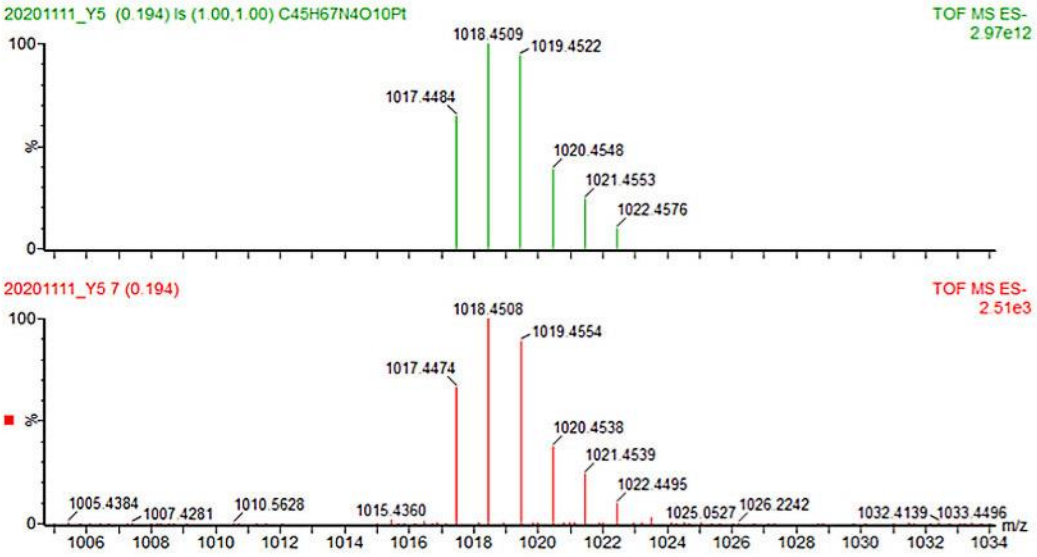

Fig. S43. ESI mass spectrum of compound **11c.**

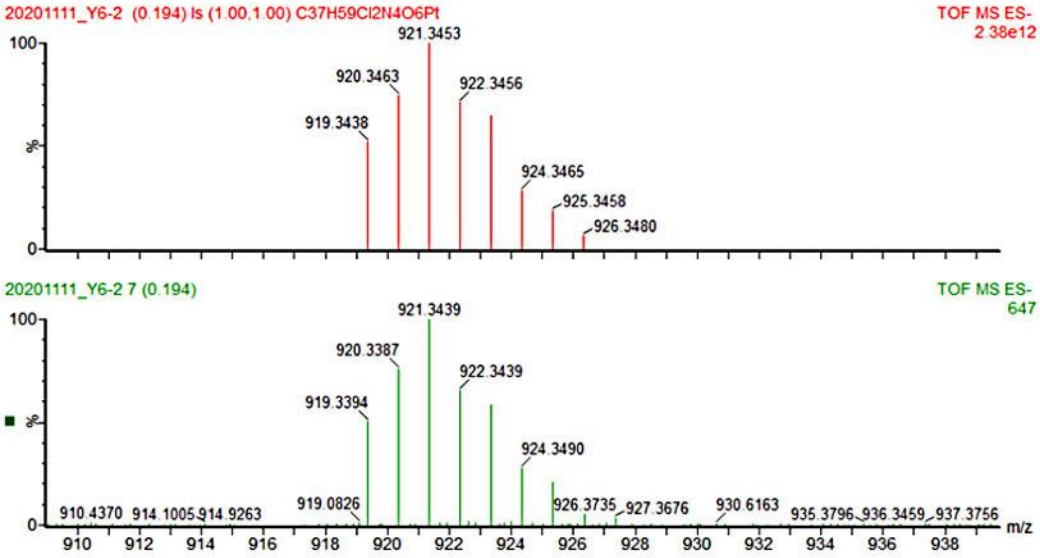

Fig. S44. ESI mass spectrum of compound **12c.**

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