Supporting information for:

Flavoplatins: Photoactivated platinum(IV) prodrugs bearing axial N-donors that trigger pyroptosis and reduce drug resistance

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Instruments and methods

Unless mentioned otherwise, all the chemicals were purchased from commercial suppliers and used without further purification. All the reactions were carried out under atmospheric pressure with protection from light by aluminum foil. ^{1}H, ^{13}C, and ^{195}Pt NMR spectra were recorded by using a Bruker AVANCE III 300 MHz spectrometer, a Bruker AVANCE III 400 MHz spectrometer, and a Bruker Ascend AVANCE III HD 600 MHz spectrometer at room temperature. Chemical shifts (δ) were reported in parts per million (ppm) and referenced as described below. ^{1}H and ^{13}C NMR spectra were referenced internally to residual solvent peaks, and deuterated dimethyl sulfoxide (DMSO-d_6) or deuterated water (D_2O) was used as the solvent. ^{195}Pt NMR spectra were referenced externally using K_2PtCl_4 in D_2O (δ = −1628 ppm vs Na_2PtCl_6). Electrospray ionization mass spectrometry (ESI-MS) was carried out on a Sciex X500R Q-TOF high-resolution mass spectrometer. A Shimadzu Prominence HPLC system equipped with a Phenomenex C18 column (5 μm, 110 Å, 250 x 4.60 mm, 1 mL/min flow) was applied to test the purity of the synthesized complexes, as well as analyze their solution behavior in HEPES buffer (pH 7.4). The UV-Vis detectors were set at 254 nm and 365 nm. A blue LED light (λ_{max} = 425 nm; power density at 400-450 nm: 1.0 mW/cm^2) and a green LED light (λ_{max} = 495 nm; power density at 450-550 nm: 0.9 mW/cm^2) are applied in experiments involving light irradiation (Figure S33). Unless mentioned otherwise, “blue light” refers to the light source at wavelengths of 400 to 450 nm; “green light” refers to the light source at wavelengths of 450 to 550 nm. A Perkin Elmer Optima 8000 ICP-OES spectrometer was used to determine the Pt concentration of the aquatic solution of the synthesized complexes. A PE Nexion 2000 ICP-MS spectrometer was used to determine the Pt concentration in cell lysates. A cyclic voltammogram was recorded on a CH 1750 A electrochemical analyzer. A NanoDrop 1000 Spectrophotometer was used to determine DNA content in solutions. A

FACSCalibur flow cytometer was used to analyze apoptotic cells. A Leica SPE Laser Confocal Scanning Microscope was used to image immunofluorescence. A Bio-Rad Chemidoc Touch Imaging System was used to image the immunoblots. Human ovarian carcinoma A2780 and cisplatin-resistant A2780cisR cells were cultured in RPMI1640 containing 10% FBS, 1% L-glutamine, and 100 units of penicillin/streptomycin at 37 °C with 5% CO_2. For A2780cisR cells, 1 μg/mL cisplatin was added to the complete medium to maintain the resistance. Unless otherwise mentioned, in cell-based assays, all the solutions or cell culture media for treatment contained 1% DMF.

Experimental sections

Synthesis of ligands flav-1 to flav-3. The synthetic methods of these flavonol derivatives were referred to references.[1,2] 93 mg (678 μmol, 1.2 eq.) of 3-hydroxy-4-acetylpyridine and 500 mg of NaOH were dissolved in 10 mL of methanol, stirred for 1 h at room temperature. To the mixture, 100 mg (565 μmol, 1.0 eq.) of 4-diethylaminobenzaldehyde was added, stirring at 70 ℃ overnight. 0.45 mL of concentrated nitric acid was added under stirring, followed by 0.15 mL of 50% H_2O_2 solution, and the mixture was then heated at 50 ℃ for 2 h. The reaction mixture was poured into 20 mL of water, neutralized with approximately 0.2 mL of concentrated nitric acid, and the orange solid was precipitated. The crude product was collected by centrifugation and purified by recrystallization with 5 mL of ethanol and 20 mL of water at 4℃.

$C_{18}H_{18}N_2O_3$ (**flav-1**): ^{1}H NMR (300 MHz, DMSO-*d_6*) δ 9.58 (s, 1H), 9.18 (s, 1H), 8.58 (d, *J* = 5.2 Hz, 1H), 8.15 (d, *J* = 9.2 Hz, 2H), 7.94 (d, *J* = 5.7 Hz, 1H), 6.83 (d, *J* = 9.3 Hz, 2H), 3.45 (q, *J* = 7.0 Hz, 4H), 1.15 (t, *J* = 7.0 Hz, 6H). ESI-MS (positive ion mode) cal. for $C_{18}H_{19}N_2O_3^+$ $[M+H]^+$: m/z 311.13902; found m/z 311.13709.

100 mg of **flav-1** and 0.1 mL (excess) of acetic anhydride were dissolved in 1 mL of DMF, stirred at room temperature overnight. The reaction mixture was poured into 10 mL of water and extracted with 10 mL of ethyl acetate twice. The organic phase was evaporated to collect the crude product of **flav-2**, after drying over anhydrous Na_2SO_4. The crude product was purified by silica column chromatography using ethyl acetate as eluent.

$C_{20}H_{20}N_2O_4$ (**flav-2**): ^{1}H NMR (300 MHz, DMSO-*d_6*) δ 9.23 (s, 1H), 8.66 (d, *J* = 5.4 Hz, 1H), 7.89 (d, *J* = 9.8 Hz, 3H), 6.86 (d, *J* = 8.9 Hz, 2H), 3.46 (d, *J* = 6.8 Hz, 4H), 2.39 (s, 3H), 1.16 (d, *J* = 6.8 Hz, 6H). ESI-MS (positive ion mode) cal. for $C_{20}H_{21}N_2O_4^+$ $[M+H]^+$: m/z 353.14958; found m/z 353.15004.

100 mg of **flav-1** and 83 μL (645 μmol, 2 eq.) of benzenesulfonyl chloride were dissolved in 5 mL of dichloromethane (DCM), in which 60 μL (645 μmol, 2 eq.) of triethylamine was added. After stirring overnight at room temperature, 10 mL of DCM was added to the reaction mixture, which was then washed with 10 mL of water twice. The organic phase was evaporated to collect the crude product of **flav-3**, after drying over anhydrous Na_2SO_4. The crude product was purified by silica column chromatography using ethyl acetate as eluent.

$C_{24}H_{22}N_2O_5S$ (**flav-3**): ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.20 (s, 1H), 8.67 (d, J = 5.6 Hz, 1H), 7.92 (d, J = 4.6 Hz, 1H), 7.80 (d, J = 7.9 Hz, 2H), 7.71 (d, J = 8.5 Hz, 2H), 7.65 (d, J = 7.2 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H), 6.60 (d, J = 8.9 Hz, 2H), 3.43 (d, J = 6.7 Hz, 4H), 1.15 (t, J = 6.8 Hz, 6H). ESI-MS (positive ion mode) cal. for $C_{24}H_{23}N_2O_5S^+$ $[M+H]^+$: m/z 451.13222; found m/z 451.12947.

Synthesis of flavoplatin 1a. 50 mg (107 μmol) of *cis, trans*-[$Pt(NH_3)_2$(CBDCA)(OH)Br] and 20 mg (118 μmol, 1.1 eq.) of silver nitrate were dissolved in 1 mL of DMF, stirred at room temperature overnight. The white precipitate was filtered off, then 50 mg (160 μmol, 1.5 eq.) of **flav-1** was added to the supernatant. The reaction mixture was stirred overnight at room temperature. After centrifugation, the supernatant was diluted with 5 mL of methanol, and the pure product was collected by a reverse-phase HPLC system.

cis, trans-[$Pt(NH_3)_2$(CBDCA)(OH)(**flav-1**)](NO_3) (flavoplatin **1a**): ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.42 (d, J = 13.3 Hz, 1H), 8.59 (s, 1H), 8.33 (s, 1H), 8.16 (d, J = 9.1 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.11 (s, 6H), 3.47 (d, J = 7.2 Hz, 4H), 2.58 (s, 2H), 2.26 (s, 1H), 2.14 (s, 1H), 1.76 (s, 2H), 1.16 (s, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 134.76, 131.39, 131.16, 129.66, 129.60, 128.30, 117.77, 111.07, 12.95. ^{195}Pt NMR (129 MHz, DMSO-d_6) δ 1143.76. ESI-MS (positive ion mode) cal. for $C_{24}H_{31}N_4O_8Pt^+$ $[M]^+$: m/z 698.17841; found m/z 698.17840.

Synthesis of flavoplatin 2a. 50 mg (107 μmol) of *cis, trans*-[$Pt(NH_3)_2$(CBDCA)(OH)Br] and 20 mg (118 μmol, 1.1 eq.) of silver nitrate were dissolved in 1 mL of DMF, stirred at room temperature overnight. The white precipitate was filtered off, then 57 mg (160 μmol, 1.5 eq.) of **flav-2** was added to the supernatant. The reaction mixture was stirred overnight at room temperature. After centrifugation, 5 mL of water was added to the supernatant, which was then washed three times with 10 mL of DCM. The crude product was collected by centrifugation of the aqueous phase and then purified using a reverse-phase HPLC system.

cis, trans-[$Pt(NH_3)_2$(CBDCA)(OH)(**flav-2**)](NO_3) (flavoplatin **2a**): ^{1}H NMR (300

MHz, DMSO-d_6) δ 9.53 (s, 1H), 8.69 (d, J = 8.0 Hz, 1H), 8.31 (d, J = 6.2 Hz, 1H), 7.91 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 9.6 Hz, 2H), 6.43 (s, 6H), 3.47 (s, 4H), 2.41 (s, 3H), 2.18 (s, 2H), 1.76 (s, 4H), 1.16 (s, 7H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 48.96, 44.26, 30.58, 29.48, 17.69, 12.91. ESI-MS (positive ion mode) cal. for $C_{24}H_{31}N_4O_8Pt^+$ $[M]^+$: m/z 740.18898; found m/z 740.18816.

Synthesis of flavoplatin 2b. 20 mg of crude flavoplatin **2a** was dissolved in 1 mL of DMF, to which 0.1 mL (excess) of acetic anhydride was added. The reaction mixture was stirred overnight at room temperature. After centrifugation, the supernatant was diluted with 5 mL of methanol, and the pure product was collected by a reverse-phase HPLC system.

cis, trans-[$Pt(NH_3)_2$(CBDCA)($OCOCH_3$)(**flav-2**)](NO_3) (flavoplatin **2b**): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.47 (s, 1H), 8.59 (d, J = 6.4 Hz, 1H), 8.30 (d, J = 6.3 Hz, 1H), 7.91 (d, J = 9.2 Hz, 2H), 7.10 (s, 6H), 6.91 (d, J = 9.3 Hz, 2H), 3.49 (d, J = 7.0 Hz, 4H), 2.49 (s, 2H), 2.42 (s, 3H), 2.29 – 2.23 (m, 2H), 2.02 (s, 3H), 1.84 – 1.78 (m, 2H), 1.17 (t, J = 7.0 Hz, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 176.82, 176.70, 160.92, 160.62, 151.03, 136.81, 134.95, 131.30, 129.66, 128.38, 128.13, 121.88, 112.83, 111.26, 106.05, 102.09, 55.89, 44.40, 40.512, 34.09, 29.82, 16.24, 12.94. ESI-MS (positive ion mode) cal. for $C_{28}H_{35}N_4O_{10}Pt^+$ $[M]^+$: m/z 782.19954; found m/z 782.19732.

Synthesis of flavoplatin 3a. 50 mg (107 μmol) of *cis, trans*-[$Pt(NH_3)_2$(CBDCA)(OH)Br] and 20 mg (118 μmol, 1.1 eq.) of silver nitrate were dissolved in 1 mL of DMF, stirred at room temperature overnight. The white precipitate was filtered off, then 72 mg (160 μmol, 1.5 eq.) of **flav-3** was added to the supernatant. The reaction mixture was stirred overnight at room temperature. After centrifugation, 5 mL of water was added to the supernatant, which was then washed three times with 10 mL of DCM. The crude product was collected by centrifugation of the aqueous phase and then purified using a reverse-phase HPLC system.

cis, trans-[$Pt(NH_3)_2$(CBDCA)(OH)(**flav-3**)](NO_3) (flavoplatin **3a**): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.44 (s, 1H), 8.63 (s, 1H), 8.24 (s, 1H), 7.75 (d, J = 7.7 Hz, 2H), 7.65 (d, J = 8.8 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.42 (s, 2H), 6.58 (s, 2H), 6.53 (d, J = 38.0 Hz, 6H), 3.38 (m, 4H), 2.54 – 2.50 (m, 2H), 2.15 (t, J = 7.8 Hz, 2H), 1.76 – 1.66 (m, 2H), 1.08 (t, J = 6.9 Hz, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 150.58, 150.41, 145.66, 142.68, 137.04, 134.76, 131.17, 129.61, 128.46, 128.30, 126.84, 125.95, 117.77, 113.60, 111.07, 60.88, 44.31, 40.90, 24.33, 12.95, 12.80. ^{195}Pt NMR (129 MHz, DMSO-d_6) δ 1140.29. ESI-MS (positive ion mode) cal. for $C_{30}H_{35}N_4O_{10}PtS^+$ $[M]^+$: m/z 838.17161; found m/z 838.16839.

Synthesis of flavoplatin 3b. 20 mg of crude complex flavoplatin **3a** was dissolved in 1 mL of DMF, to which 0.1 mL (excess) of acetic anhydride was added. The reaction mixture was stirred overnight at room temperature. After centrifugation, the supernatant was diluted with 5 mL of methanol, and the pure product was collected by a reverse-phase HPLC system.

cis, trans-[Pt(NH_3)$_2$(CBDCA)($OCOCH_3$)(**flav-3**)](NO_3) (flavoplatin **3b**): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.35 (s, 1H), 8.56 (d, J = 6.4 Hz, 1H), 8.35 (d, J = 6.3 Hz, 1H), 7.82 (d, J = 7.3 Hz, 2H), 7.74 (d, J = 9.2 Hz, 2H), 7.69 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.9 Hz, 2H), 6.83 – 6.55 (m, 6H), 3.46 (d, J = 7.0 Hz, 4H), 2.55 (s, 2H), 2.36 – 2.29 (m, 2H), 2.03 (s, 3H), 1.88 – 1.79 (m, 2H), 1.16 (t, J = 7.0 Hz, 6H).^{13}C NMR (151 MHz, DMSO-d_6) δ 176.79, 176.08, 161.07, 151.20, 146.16, 145.23, 144.92, 136.96, 136.87, 135.05, 132.54, 131.44, 129.74, 128.34, 122.21, 121.53, 112.62, 111.37. ESI-MS (positive ion mode) cal. for $C_{32}H_{37}N_4O_{11}PtS^+$ $[M]^+$: m/z 880.18218; found m/z 880.17722.

Synthesis of flavoplatin 3c. 50 mg (101 μmol) of *trans*-[Pt(DACH)(ox)(OH)Br] was dissolved in 0.5 mL of DMSO, and 19 mg (112 μmol, 1.1 eq.) of silver nitrate was dissolved in 1.5 mL of acetonitrile. The solutions were mixed up and stirred at room temperature overnight. The white precipitate was filtered off, then 72 mg (160 μmol, 1.5 eq.) of **flav-3** was added to the supernatant. The reaction mixture was stirred overnight at room temperature. After centrifugation, the supernatant was diluted with 5 mL of methanol, and the pure product was collected by a reverse-phase HPLC system.

trans-[Pt(DACH)(ox)(OH)(**flav-3**)](NO_3) (flavoplatin **3c**): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.54 (s, 1H), 8.79 (s, 1H), 8.35 (s, 1H), 8.28 (d, J = 7.7 Hz, 1H), 8.15 (d, J = 8.9 Hz, 1H), 7.84 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 8.9 Hz, 2H), 7.70 (s, 1H), 7.57 (s, 1H), 7.52 (t, J = 7.6 Hz, 2H), 6.94 (s, 1H), 6.65 (d, J = 9.0 Hz, 2H), 3.46 (s, 4H), 2.72 (d, J = 17.6 Hz, 2H), 2.05 (s, 2H), 1.54 (d, J = 36.3 Hz, 2H), 1.49 (s, 2H), 1.16 (s, 6H), 1.11 – 0.96 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 162.89, 151.08, 132.49, 131.92, 131.39, 129.71, 128.37, 111.27, 61.96, 61.07, 44.41, 12.94. ^{195}Pt NMR (129 MHz, DMSO-d_6) δ 833.87. ESI-MS (positive ion mode) cal. for $C_{32}H_{37}N_4O_{11}PtS^+$ $[M]^+$: m/z 864.18726; found m/z 864.18226.

Solubility Test. Excess amounts of flavoplatins **1a** to **3c** were respectively suspended in 1 mL of water (n = 3). The mixtures were treated in an ultrasonic bath for 30 min and cooled down to room temperature for 6 h. The supernatants were collected by filtration with a 0.22 μm membrane filter. After dilution, Pt content in the supernatants was determined by ICP-OES.

Hydrophilicity Test. The hydrophilicity of flavoplatins **1a** to **3c** was presented as the octanol/water partition coefficient (Log $P_{o/w}$), which was determined by a shake-flask method. 10 nmol of the Pt complexes were dissolved in 1 mL of PBS (n = 3). The solutions were mixed with 1 mL of octanol pre-saturated with PBS. The mixtures were protected from light by aluminum foil, shaken for 3 h at room temperature, and the two phases were separated by centrifugation. Platinum content in the two phases was determined by ICP-OES.

Hydrolysis test in HEPES buffer. 200 μM solutions of flavoplatins **1a** to **3c** were respectively prepared with 1 mL of 50 mM HEPES buffer (20% DMF, pH 7.4) and incubated in a 37 °C water bath. 20 μL of this solution was injected into a reverse-phase HPLC at time points: 0, 2, 4, 8, 12, 24 h; after 24 h, another 20 μL of this solution was injected into a reverse-phase LC-MS system to analyze the hydrolysis products. The HPLC program was set as follows: detection at 460 nm; 0% to 70% phase B (linear increase from 0 to 2 min), 70% to 80% phase B (from 2 to 12 min), 80% to 0% phase B (linear decrease from 12 to 14 min) and 0% phase B (from 14 to 15 min), then stopped at 15 min. Phase A: 94.9% water, 5% acetonitrile, 0.1% formic acid; Phase B: 5% water, 94.9% acetonitrile, 0.1% formic acid. Peak ratio (analyst/total peak area) was used to calculate the percentage remaining, and the value at the time point "0 h" was defined as 100%.

Reduction test. 200 μM solutions of flavoplatins **1a** to **3c** were respectively prepared with 1 mL of 50 mM HEPES buffer (20% DMF, pH 7.4) with 2 mM sodium ascorbate and incubated in a 37 °C water bath. 20 μL of this solution was injected into a reverse-phase HPLC at time points: 0, 2, 4, 8, 12, 24 h; after 24 h, another 20 μL of this solution was injected into a reverse-phase LC-MS system to analyze the hydrolysis products. HPLC program was set as follows: detection at 460 nm; 0% to 70% phase B (linear increase from 0 to 2 min), 70% to 80% phase B (from 2 to 12 min), 80% to 0% phase B (linear decrease from 12 to 14 min) and 0% phase B (from 14 to 15 min), then stopped at 15 min. Phase A: 94.9% water, 5% acetonitrile, 0.1% formic acid; Phase B: 5% water, 94.9% acetonitrile, 0.1% formic acid. Peak ratio (analyst/total peak area) was used to calculate the percentage remaining, and the value at the time point "0 h" was defined as 100%.

Photoactivation test by HPLC. 200 μM solutions of complexes flavoplatins **1a** to **3c** were respectively prepared with 1 mL of 50 mM HEPES buffer with 2 mM sodium ascorbate (20% DMF, pH 7.4) and irradiated by a green LED light at 37 °C. 20 μL of this solution was injected into a reverse-phase HPLC at time points: 0, 2, 10, 30, 60 min. The HPLC program was set as follows: detection at 460 nm; 0% to 70% phase B

(linear increase from 0 to 2 min), 70% to 80% phase B (from 2 to 12 min), 80% to 0% phase B (linear decrease from 12 to 14 min) and 0% phase B (from 14 to 15 min), then stopped at 15 min. Phase A: 94.9% water, 5% acetonitrile, 0.1% formic acid; Phase B: 5% water, 94.9% acetonitrile, 0.1% formic acid. Peak ratio (analyst/total peak area) was used to calculate the percentage remaining, and the value at the time point "0 min" was defined as 100%.

DFT calculations. Software: Gaussian 16 Revision A.03[3]

B3LYP/[SDD(Pt),6-31G*(others)] for geometry optimization (energy = E1, zero-point vibrational energy = ZPE)[4-10]

TD-B3LYP (SCRF, solvent=water)/def2-TZVP for energy calculation for the excited states of **flav-3** and flavoplatin **3a**[11]

Cellular Pt accumulation. A2780cisR cells were seeded into 6-well plates at a density of 200,000 cells per well and incubated for 48 h. Then cells were treated with 20 μM of carboplatin, oxaliplatin, and flavoplatins **1a**, **3a** to **3c** for 2 h. Afterward, the cells were washed with PBS twice and harvested by trypsinization. The cell suspensions were spun at 600 g for 3 min, and the cell pellets were washed with PBS three times. After counting, the cells were digested with concentrated nitric acid overnight. The cell lysates were diluted with milli-Q water to a final volume of 1 mL, and the Pt concentration was determined by ICP-MS.

Genomic DNA binding. A2780cisR cells were seeded into 6-well plates at a density of 100,000 cells per well and incubated for 48 h. Then cells were treated with 50 μM cisplatin, carboplatin, oxaliplatin, and flavoplatins **1a**, **3a** to **3c** for 2 h. The complexes-containing media were replaced with fresh phenol red-free RMPI1640 media. The flavoplatins-treated cells were irradiated by a green LED light for 1 h, while the control groups were kept in the dark, then incubated for another 21 h. Afterward, the cells were washed with PBS twice and harvested by trypsinization. The cell suspensions were spun at 600 g for 3 min, and the cell pellets were washed with PBS three times. The genomic DNA was extracted and purified by the GeneJET Genomic DNA Purification Kit (Thermo Fisher Scientific). The DNA content in the elution buffers was determined by a NanoDrop spectrophotometer, and the Pt concentration was determined by ICP-MS.

Immunofluorescence. A2780cisR cells were seeded in 8-well chamber slides at a density of 6,000 cells per well and incubated for 24 h. Then cells were treated for 2 h with compounds: 100 μM cisplatin; 50 μM flavoplatins **1a**, **3a** to **3c**. The complexes-containing media were replaced with fresh phenol red-free RMPI1640 media. The cells

were irradiated by a green LED light for 1 h, while the other groups were kept in the dark, then incubated for another 2 h. Afterward, the cells were washed with PBS and fixed with 4% paraformaldehyde at room temperature. The cells were permeabilized in PBS with 0.1% Triton X-100 (pH 7.4) for 30 min, then blocked in PBS-T (1x PBS with 0.1% Tween 20) with 4% BSA for 2 h. The cells were incubated with anti-γ-H2AX (phospho S139) antibody (1:250, ab81299, Abcam) in PBS-T with 4% BSA at 4 °C overnight. After washing with PBS-T three times, the cells were incubated with anti-rabbit IgG H&L (Alexa Fluor® 647) antibody (1:200, ab150077, Abcam) at r.t. for 1 h. The cells were washed with PBS-T three times, stained with 10 μg/mL DAPI solution, and imaged by a Laser Confocal Scanning Microscope (Ex 405 nm, Em 450-500 nm; Ex 635 nm, Em 655-700 nm).

Photocytotoxicity Test. A2780 and the corresponding Pt-resistant cells were seeded into 96-well plates at a density of 2,000 cells per well and incubated for 48 h. Then, the cells were treated with Pt complex-containing medium for 2 h. The complexes-containing media were replaced with fresh phenol red-free RMPI1640 media. The cells were irradiated by a blue LED or green LED light for 1 h, while the control groups were kept in the dark, then incubated for another 21 h. The medium was replaced by an FBS-free medium containing 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, 1 mg/mL), and the plates were further incubated for 1 h. The MTT-containing medium was then removed, and 100 μL per well of DMSO was added to dissolve the crystal. The IC_{50} value was calculated based on the absorbance at 570 and 730 nm, which was measured by a Biotek microplate reader, and presented as the average of results from three independent experiments (n = 3).

PI/Annexin V double staining assay. A2780cisR cells were seeded into 6-well plates at a density of 100,000 cells per well and incubated for 24 h. Then cells were treated for 2 h with the compounds: 200 μM cisplatin, carboplatin, and oxaliplatin; 50 μM flavoplatins **1a**, **3a** to **3c**. The flavoplatin-containing media were replaced with fresh phenol red-free RMPI1640 media. The cells were irradiated by a green LED light for 1 h, while the other groups were kept in the dark, then incubated for another 2 h. Afterward, the cells were washed with PBS twice and harvested by trypsinization, and the washing solutions were also collected. The cell suspensions were spun at 600 g for 3 min, and the cell pellets were washed twice with Annexin-binding buffer (10 mM HEPES, 140 mM NaCl, and 2.5 mM $CaCl_2$, pH = 7.4). Then the cells were double-stained with Annexin V-FITC and propidium iodide at r.t. for 15 min. The cell suspensions were then analyzed by a flow cytometer.

Cell cycle arrest. A2780cisR cells were seeded into 6-well plates at a density of

100,000 cells per well and incubated for 24 h. Then cells were treated for 2 h with the compounds: 200 μM cisplatin, carboplatin, and oxaliplatin; 50 μM flavoplatins **1a**, **3a** to **3c**. The flavoplatin-containing media were replaced with fresh phenol red-free RMPI1640 media. The cells were irradiated by a green LED light for 1 h, while the other groups were kept in the dark, then incubated for another 2 h. Afterward, the cells were washed with PBS twice and harvested by trypsinization. The cell suspensions were spun at 600 g for 3 min, and the cell pellets were washed again with PBS and fixed in 5 mL of 70% EtOH solution at 4 ℃ overnight. The cells were washed with PBS and suspended in 1 mL of PI solution (0.1% Triton X-100, 200 μg/mL RNase A, and 20 μg/mL PI in PBS, pH = 7.4) for staining at 37 ℃ for 15 min. The cell suspensions were then analyzed by a flow cytometer.

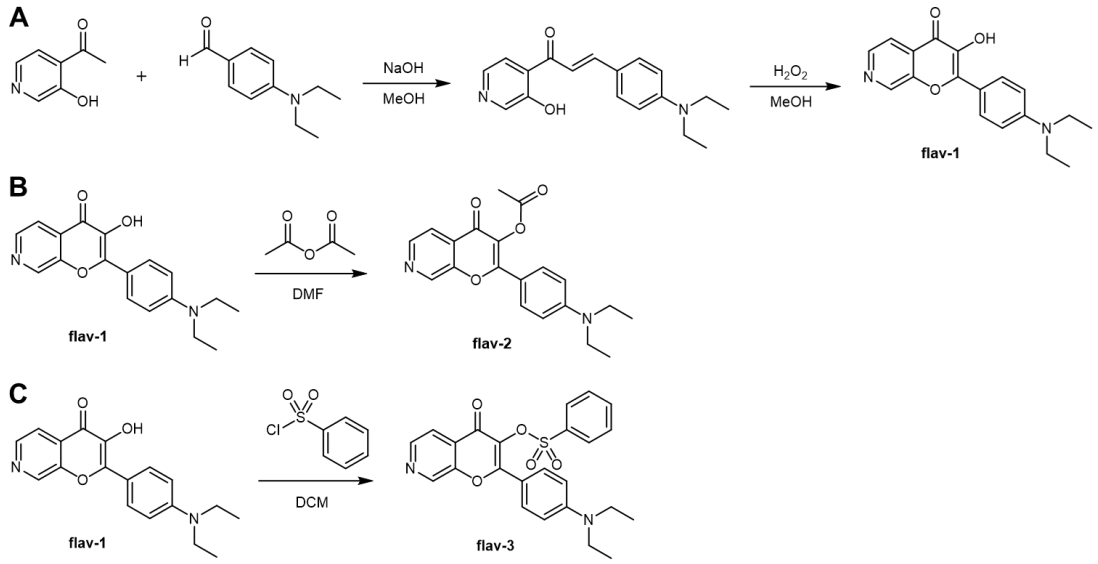
Cell morphology imaging. A2780cisR cells were seeded into 6-well plates at a density of 100,000 cells per well and incubated for 24 h. Then cells were treated for 2 h with 100 μM **flav-1** and **flav-3**; 50 μM flavoplatins **1a**, **3a** to **3c**. The complexes-containing media were replaced with fresh phenol red-free RMPI1640 media. The cells were irradiated by a green LED light for 1 h. The cell morphologies were imaged by an optical microscope.

ER tracking assay. A2780cisR cells were seeded in 8-well chamber slides at a density of 6,000 cells per well and incubated for 24 h. Then cells were treated for 2 h with 25 μM flavoplatins **1a**, **3a** to **3c**, as well as 25 μM **flav-3**. The complexes-containing media were removed, and the cells were washed with HBSS twice. The cells were then incubated with 1 μM ER-tracker green in HBSS for 30 min. Afterward, the cells were washed with phenol red-free RMPI1640 media twice and imaged by a Laser Confocal Scanning Microscope (Ex 405 nm, Em 570-630 nm and 625-675 nm; Ex 488 nm, Em 500-520 nm and 625-675 nm).

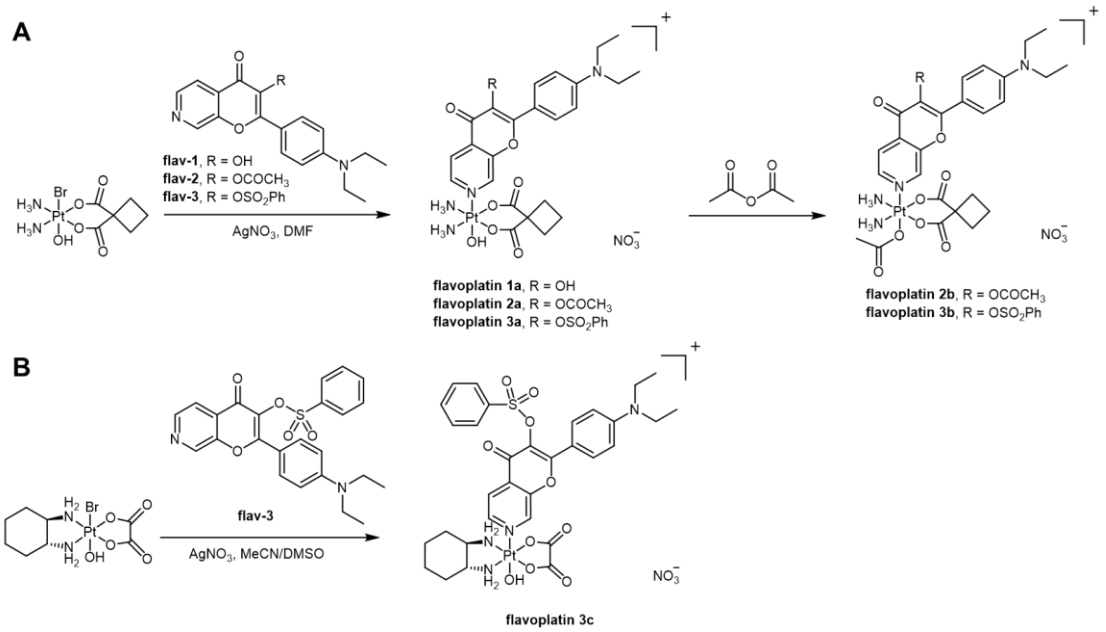
ROS assay. A2780cisR cells were seeded in 8-well chamber slides at a density of 6,000 cells per well and incubated for 24 h. The cells were incubated with 20 nM Cellular ROS Assay Kit (Deep red; ab186029) in PBS, at 37 ℃ for 30 min. After washing with PBS twice, the cells were treated for 2 h with 50 μM flavoplatins **1a**, **3a** to **3c**, as well as 5 mM H_2O_2 for 4 h, which was used as a positive control. Then, the flavoplatins-treated cells were irradiated by a green LED light for 30 min, while the untreated cells were kept in the dark. Afterward, the cells were washed with phenol red-free RMPI1640 media twice and imaged by a Laser Confocal Scanning Microscope (Ex 635 nm, Em 660-680 nm).

Western blotting. A549cisR cells were seeded into a 6-well plate at a density of 200,000 cells per well and incubated for 24 h. Then cells were treated with the

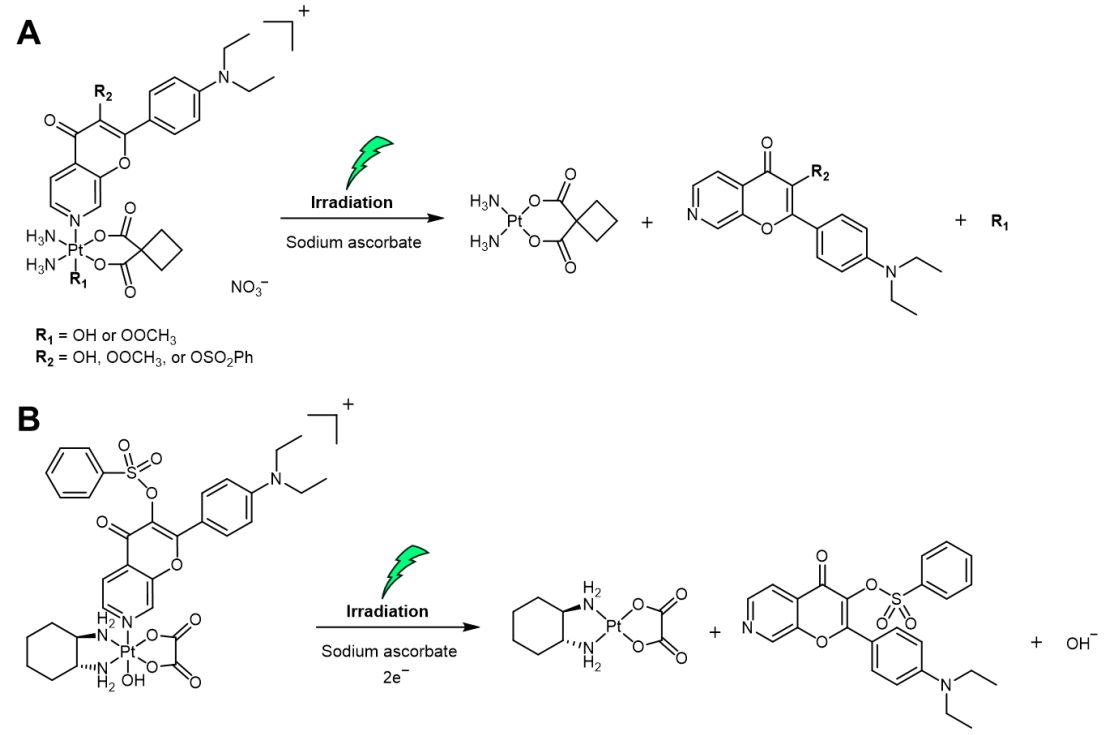
compounds: 200 μM cisplatin, doxorubicin (DOX), and 1 mM $MnCl_2$ for 4 h; 50 μM flavoplatins **3a** to **3c** and 100 μM **flav-3** for 2 h. The complexes-containing media were replaced with fresh phenol red-free RMPI1640 media, and the flavoplatin-treated cells were irradiated by a green LED light for 1 h. Afterward, the cells were washed with PBS twice and then scraped and lysed. The protein concentration in the cell lysates was determined by the BCA assay. The cell lysates were mixed with a loading buffer (Laemmli buffer recipe, 4% sodium dodecyl sulfate (SDS), 10% 2-mercaptoethanol, 20% glycerol, 0.004% bromophenol blue, and 0.125 M Tris-HCl, pH = 6.8). 20 μg of proteins from the samples were loaded and separated by SDS polyacrylamide gel electrophoresis at 110 V for 70 min, then proteins were transferred to the poly(vinylidene difluoride) membrane at 120 V for 70 min. The membrane was blocked in TBST (tris-buffered saline with 0.1% Tween 20) with 5% (w/v) nonfat milk powder at r.t. for 2 h. After washing with TBST three times, the membrane was incubated with primary antibodies (NLRP3 1:1000, ab283819; GSDMD 1:1000, ab210070; GSDMD-NT 1:1000, ab215203; GSDME-NT 1:1000, ab222408; β-actin 1:1000, #4967, CST; GAPDH 1:2500 #2118, CST; pro-caspase-1 1:1000, ab179515; active caspase-3 1:500, AC033, Beyotime) at 4 °C overnight. After washing with TBST three times, the membrane was incubated with anti-rabbit IgG (1:2000, #7074, CST) antibody at r.t. for 2 h. The membrane was then incubated with an enhanced chemiluminescence (Bio-Rad) solution for 5 min, and the blots were imaged by a Bio-Rad ChemiDoc Touch Imaging System. The intensity ratio of other blots/GAPDH was used for quantification; those values of the untreated group were defined as 100%.



Scheme S1. Synthesis of **flav-1**, **flav-2** and **flav-3**.



Scheme S2. (**A**) Synthesis of flavoplatins **1a**, **2a**, **2b**, **3a**, and **3b**. (**B**) Synthesis of flavoplatin **3c** (DMF = *N,N*-dimethylformamide; MeCN = acetonitrile; DMSO = dimethyl sulfoxide).



Scheme S3. Photoactivation process of flavoplatins **1a** to **3c** upon green light irradiation.

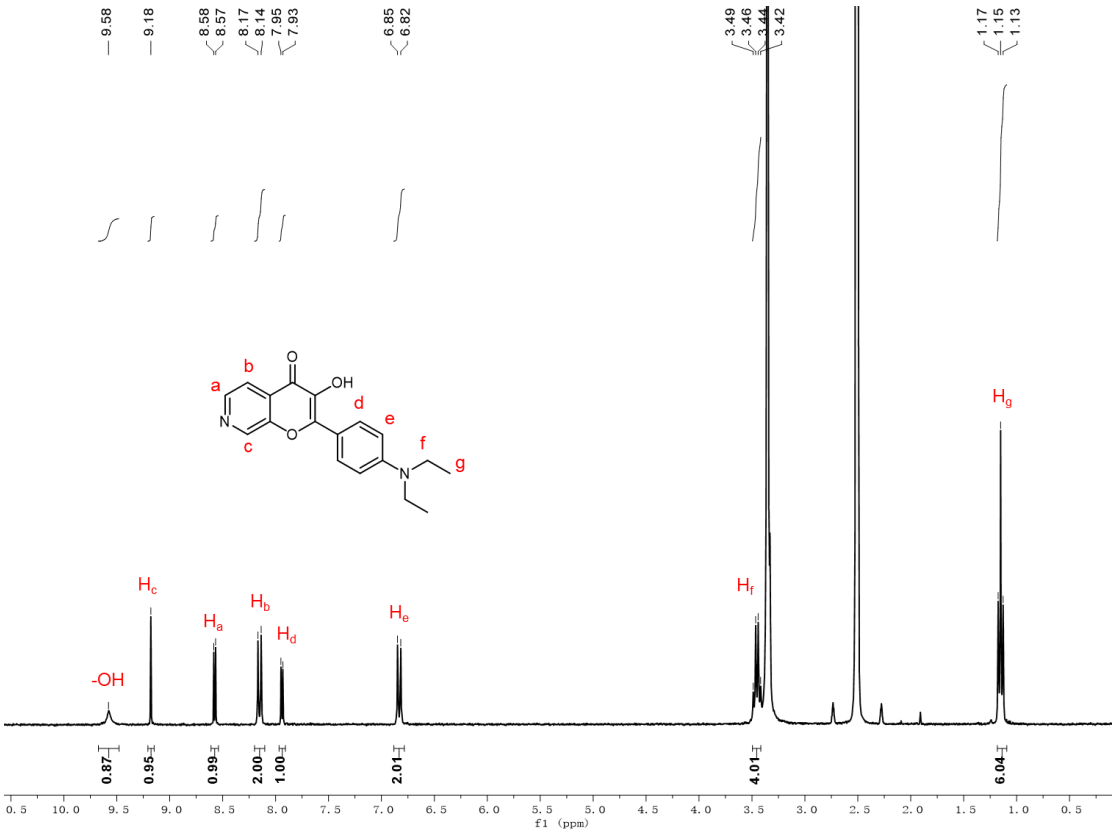


Figure S1. 300 MHz ^{1}H NMR spectrum of **flav-1** in DMSO-d_6.

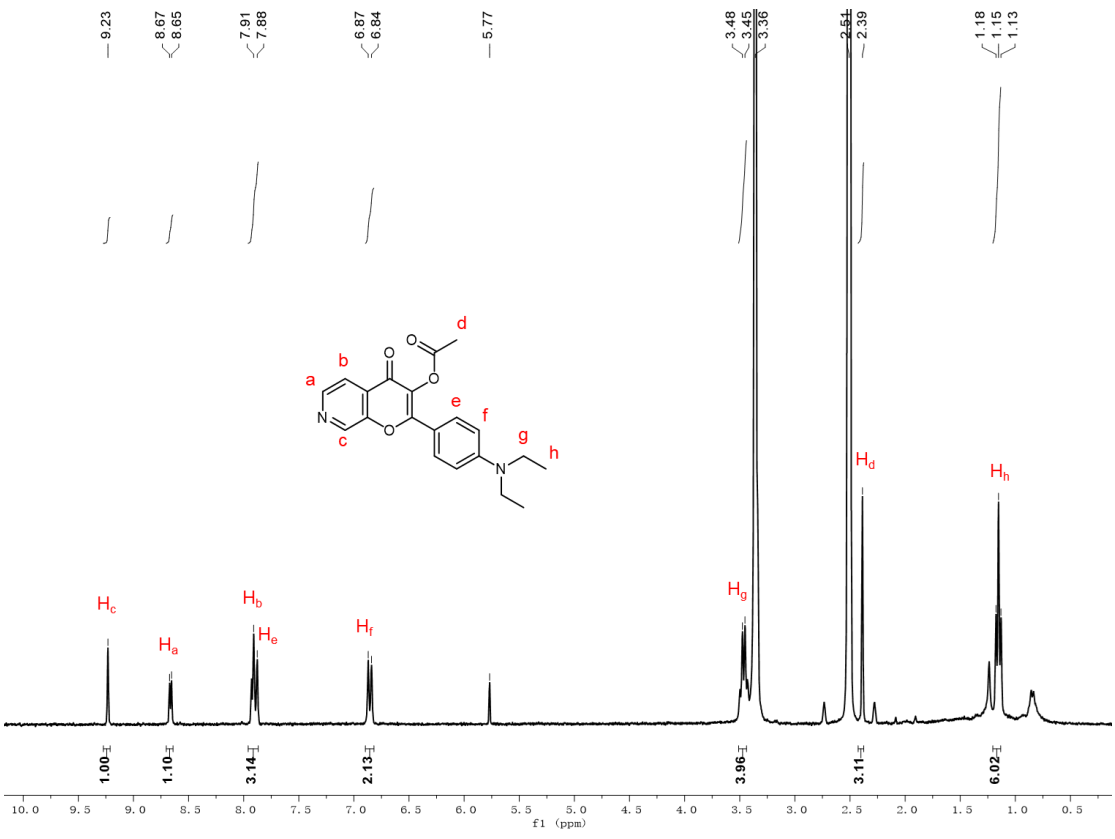


Figure S2. 300 MHz ^{1}H NMR spectrum of **flav-2** in DMSO-d_6.

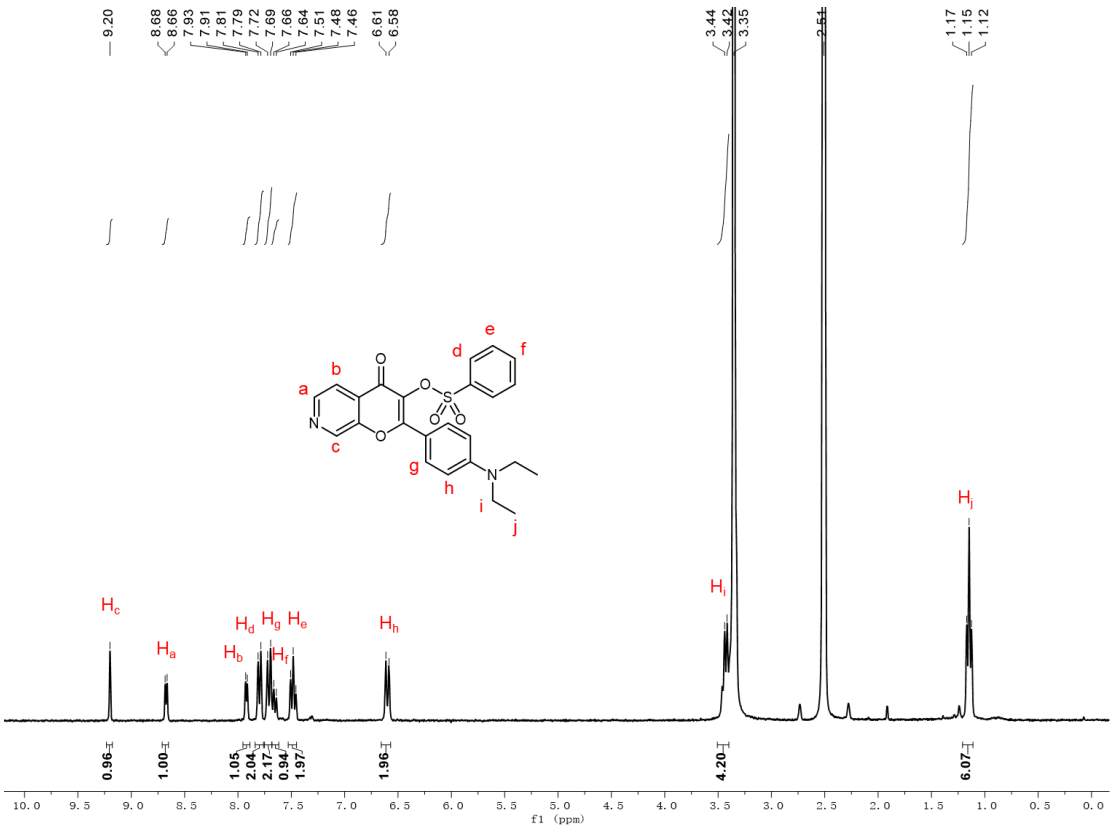


Figure S3. 300 MHz ^{1}H NMR spectrum of **flav-3** in DMSO-d_6.

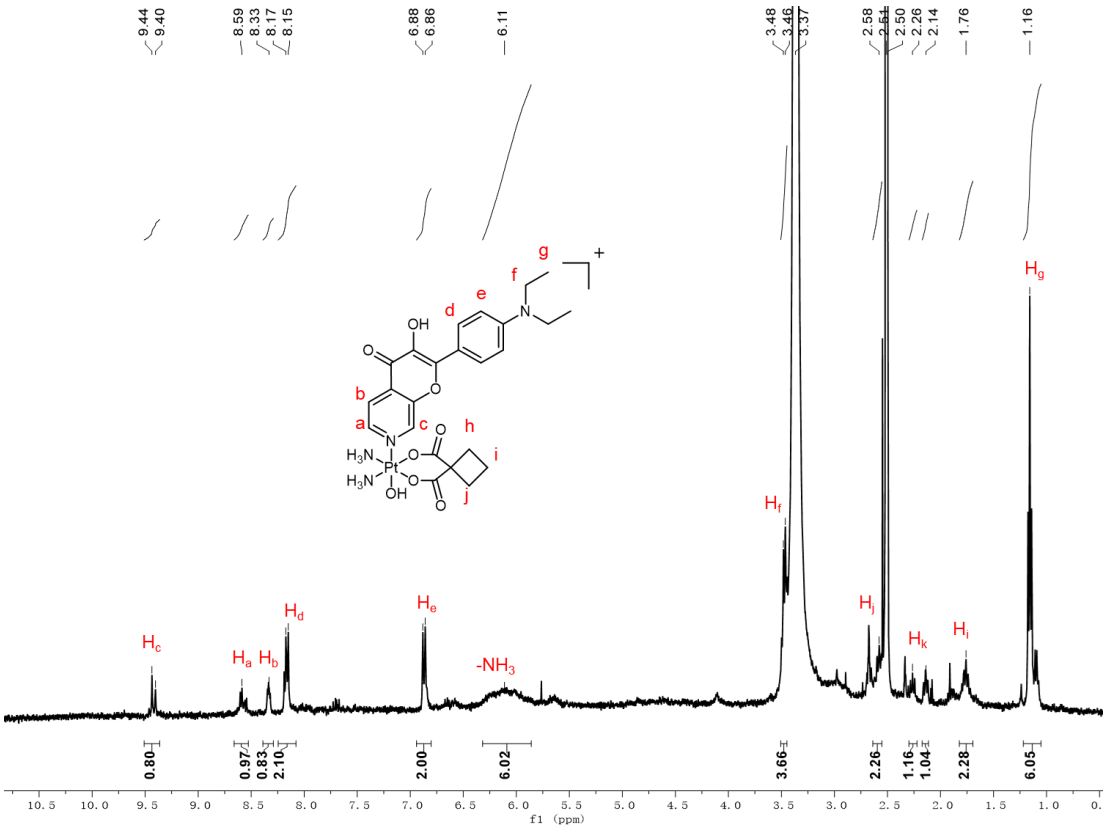


Figure S4. 400 MHz ^{1}H NMR spectrum of flavoplatin **1a** in DMSO-d_6.

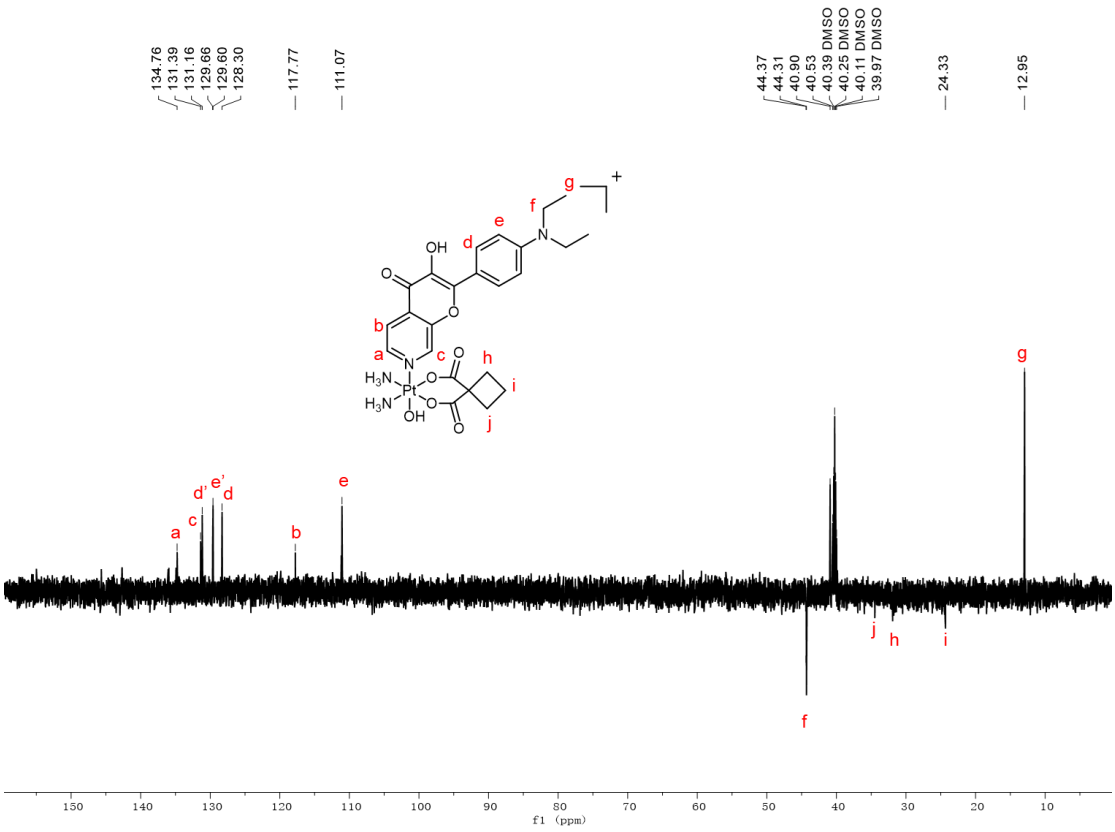


Figure S5. 151 MHz ^{13}C DEPT135 NMR spectrum of flavoplatin **1a** in DMSO-d_6.

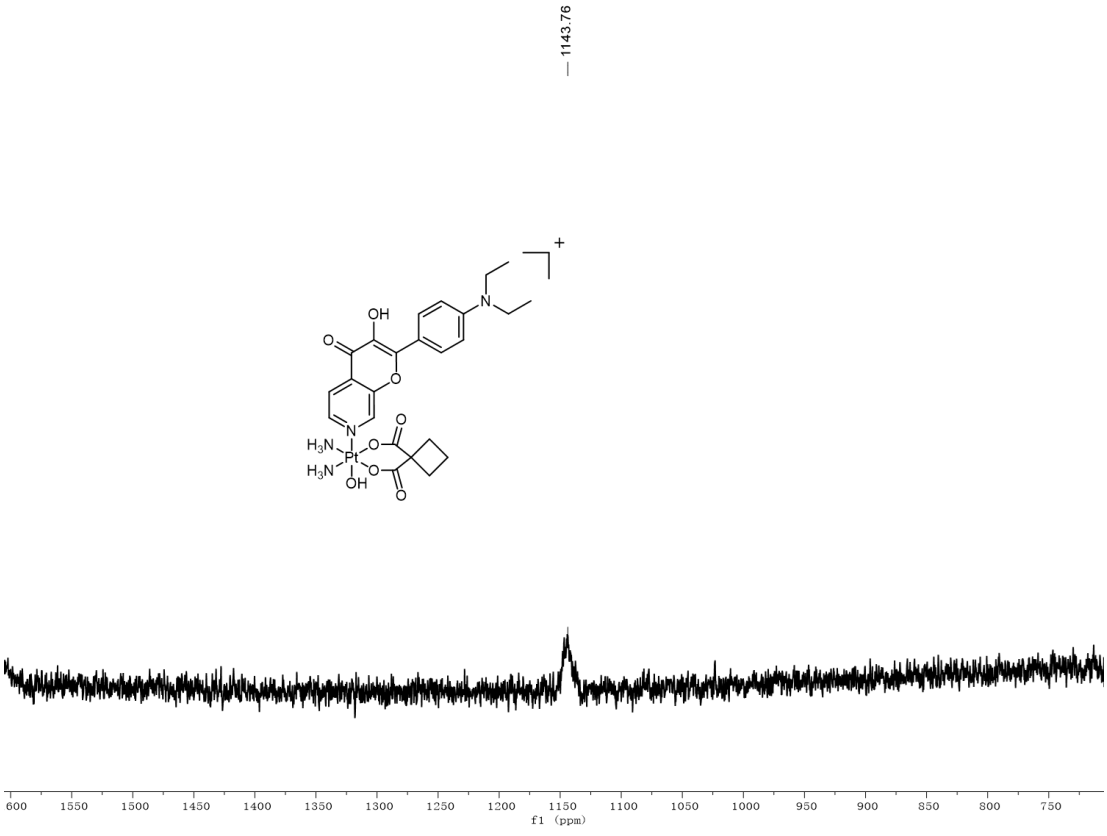


Figure S6. 129 MHz ^{195}Pt NMR spectrum of flavoplatin **1a** in DMSO-d_6.

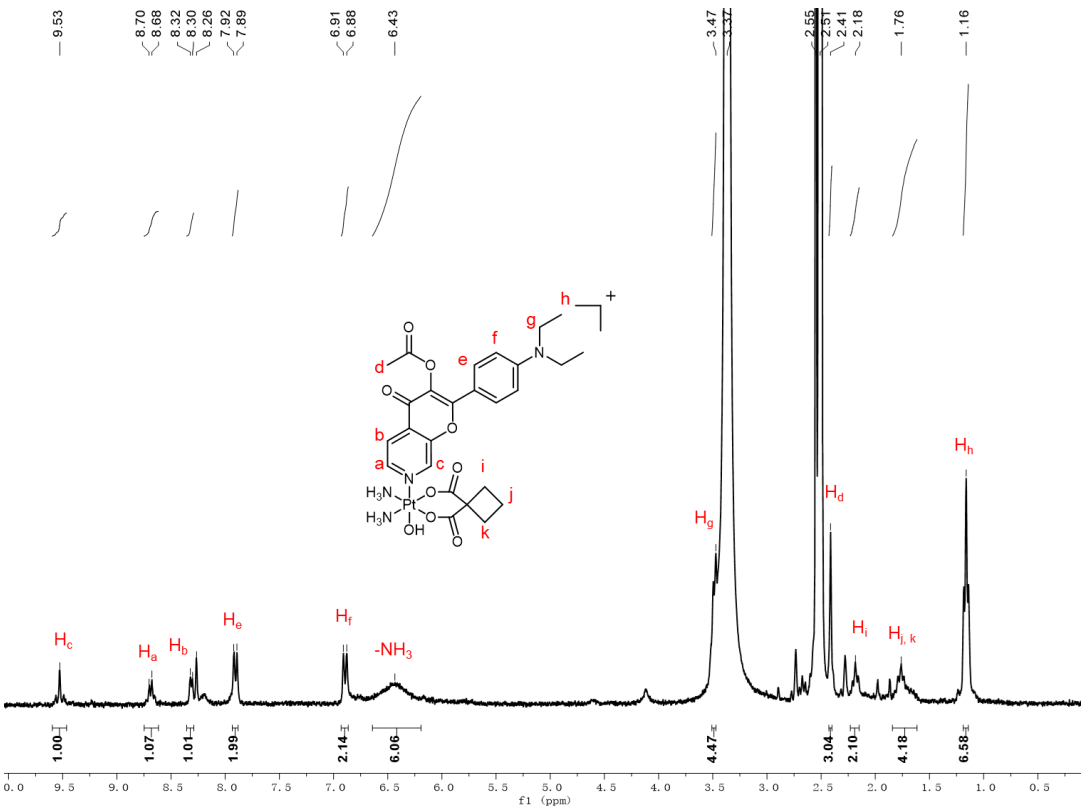


Figure S7. 400 MHz ^{1}H NMR spectrum of flavoplatin **2a** in DMSO-d_6.

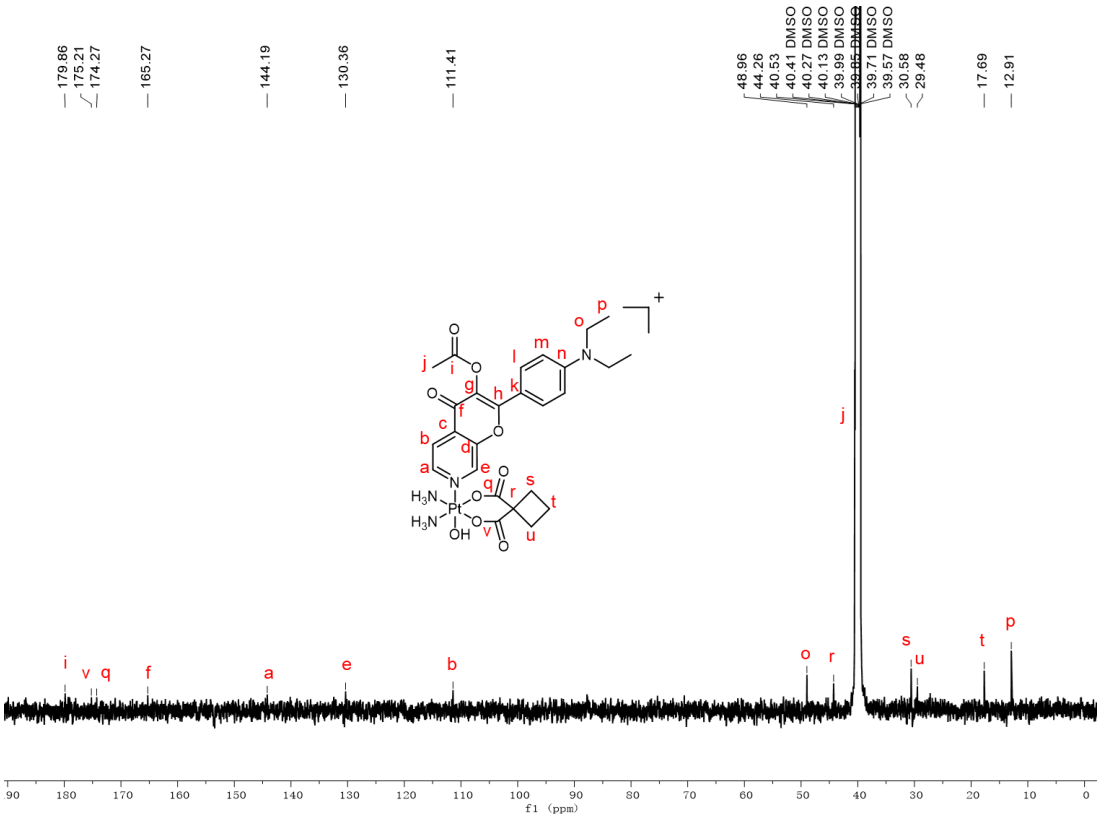


Figure S8. 151 MHz ^{13}C NMR spectrum of flavoplatin **2a** in DMSO-d_6.

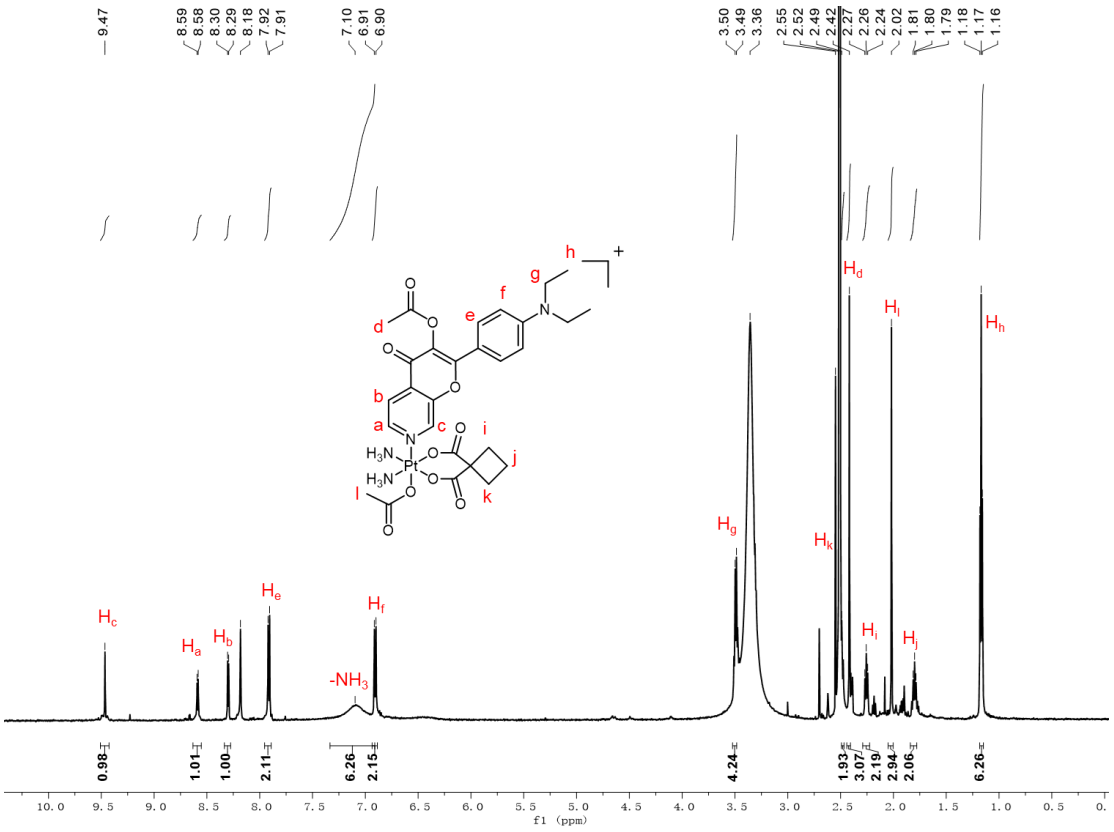


Figure S9. 600 MHz ^{1}H NMR spectrum of flavoplatin **2b** in DMSO-d_6.

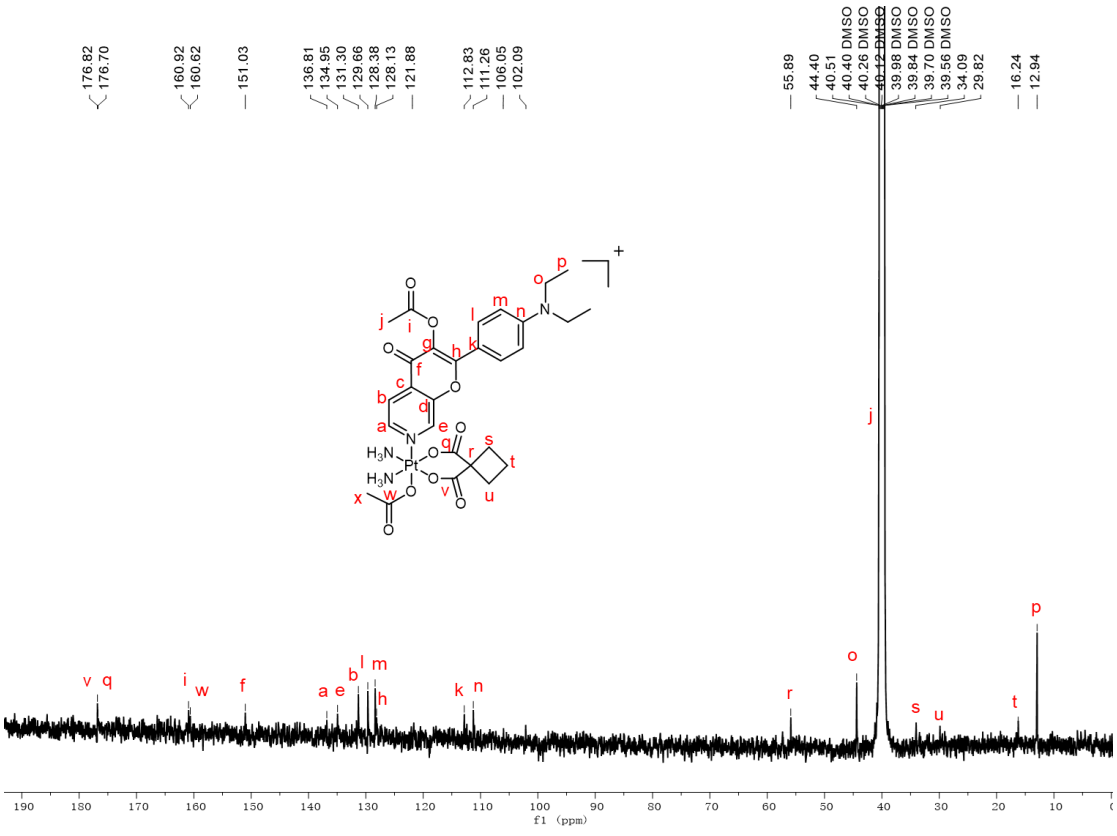


Figure S10. 151 MHz ^{13}C NMR spectrum of flavoplatin **2b** in DMSO-d_6.

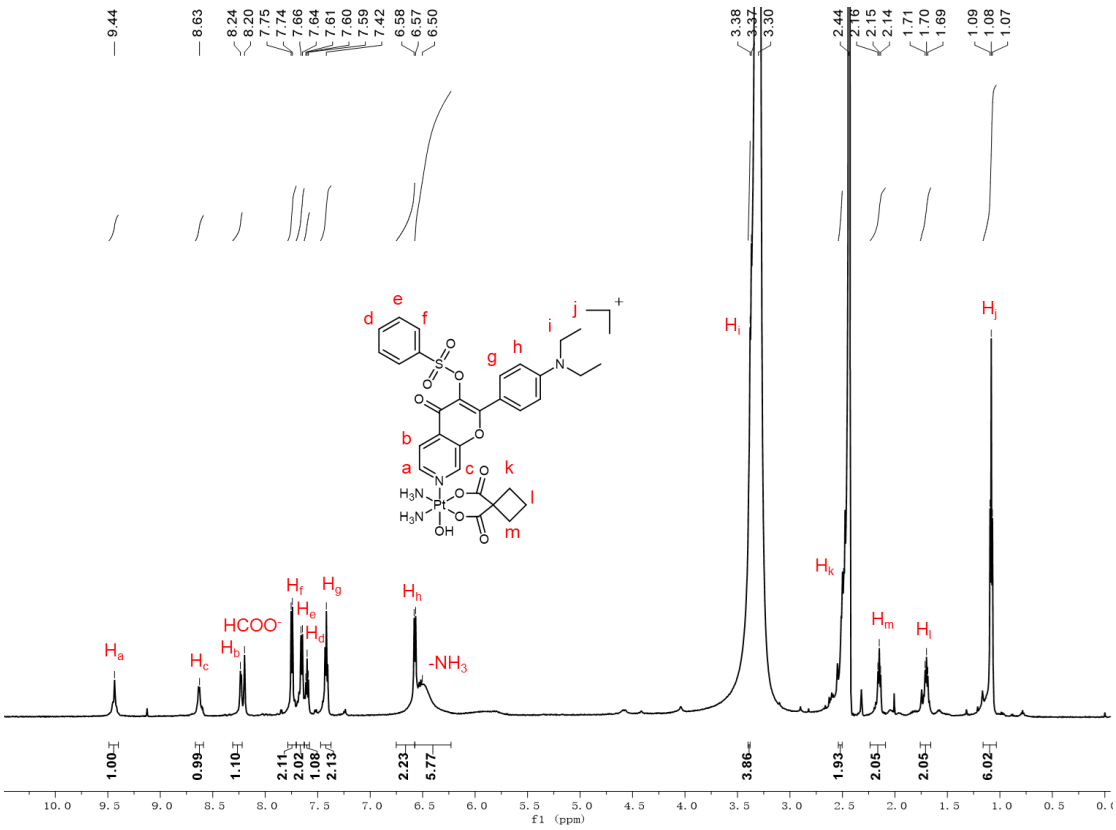


Figure S11. 600 MHz ^{1}H NMR spectrum of flavoplatin **3a** in DMSO-d_6.

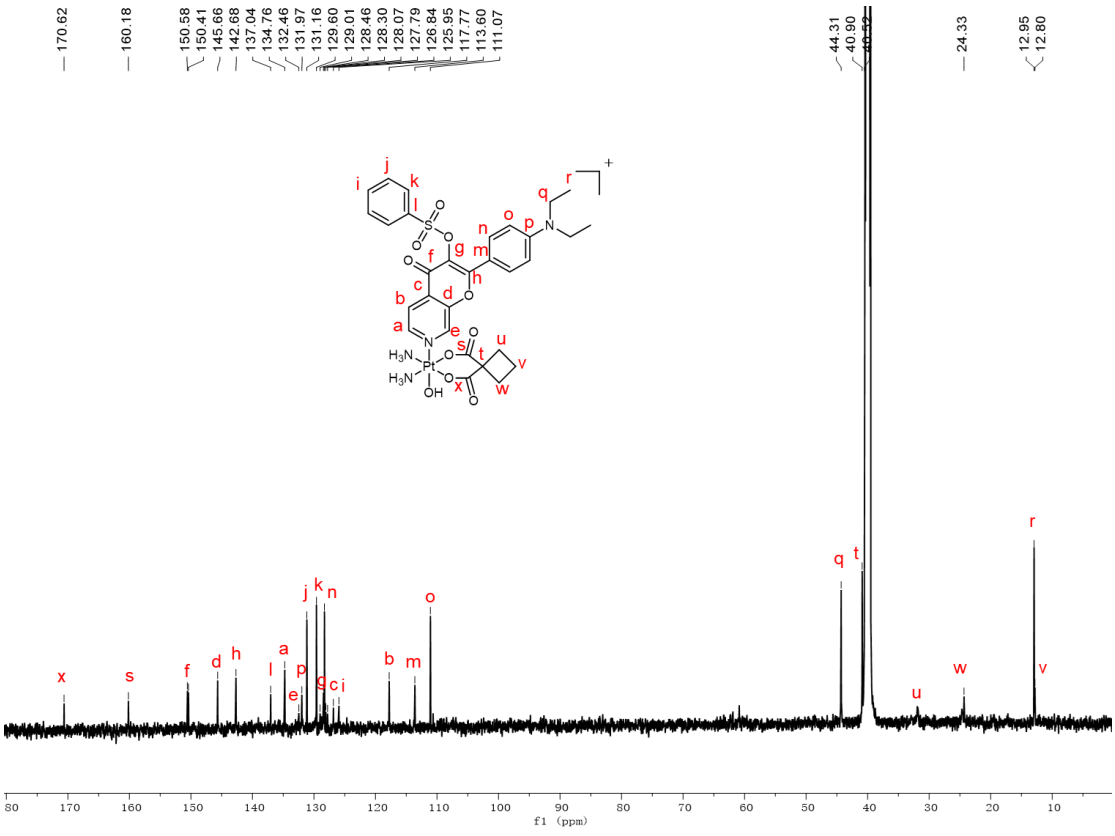


Figure S12. 151 MHz ^{13}C NMR spectrum of flavoplatin **3a** in DMSO-d_6.

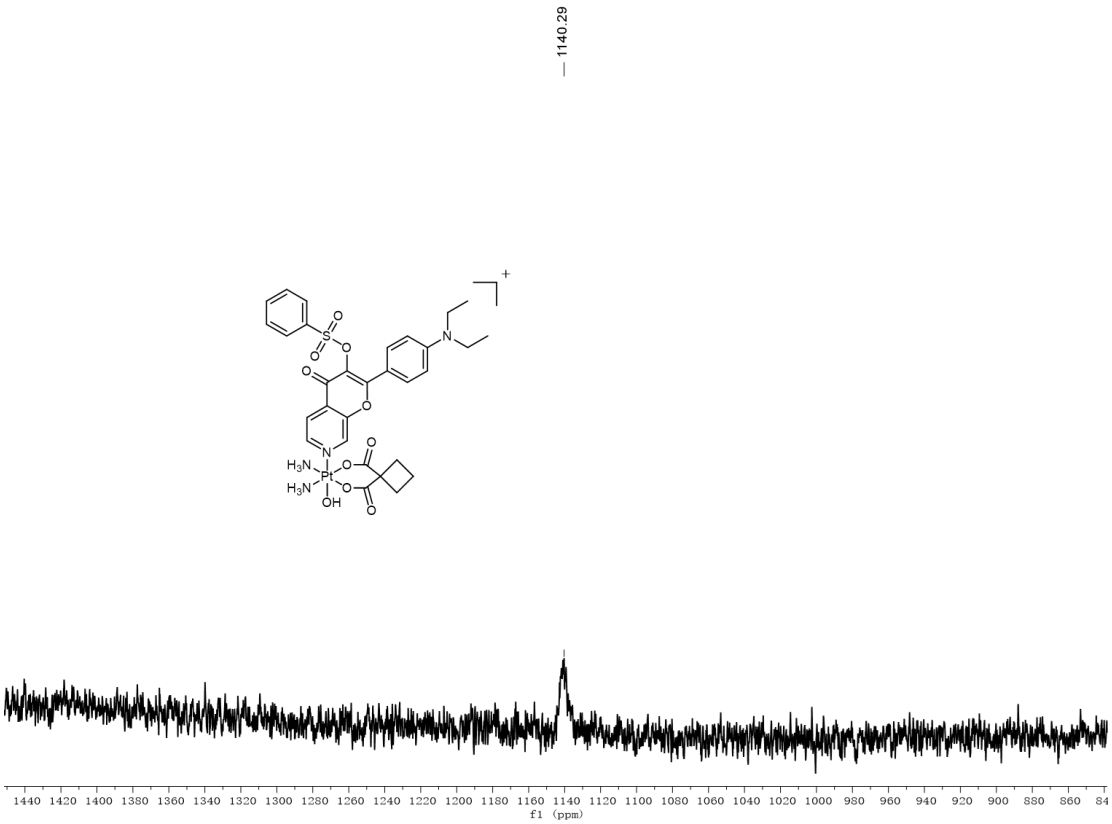


Figure S13. 129 MHz ^{195}Pt NMR spectrum of flavoplatin **3a** in DMSO-d_6.

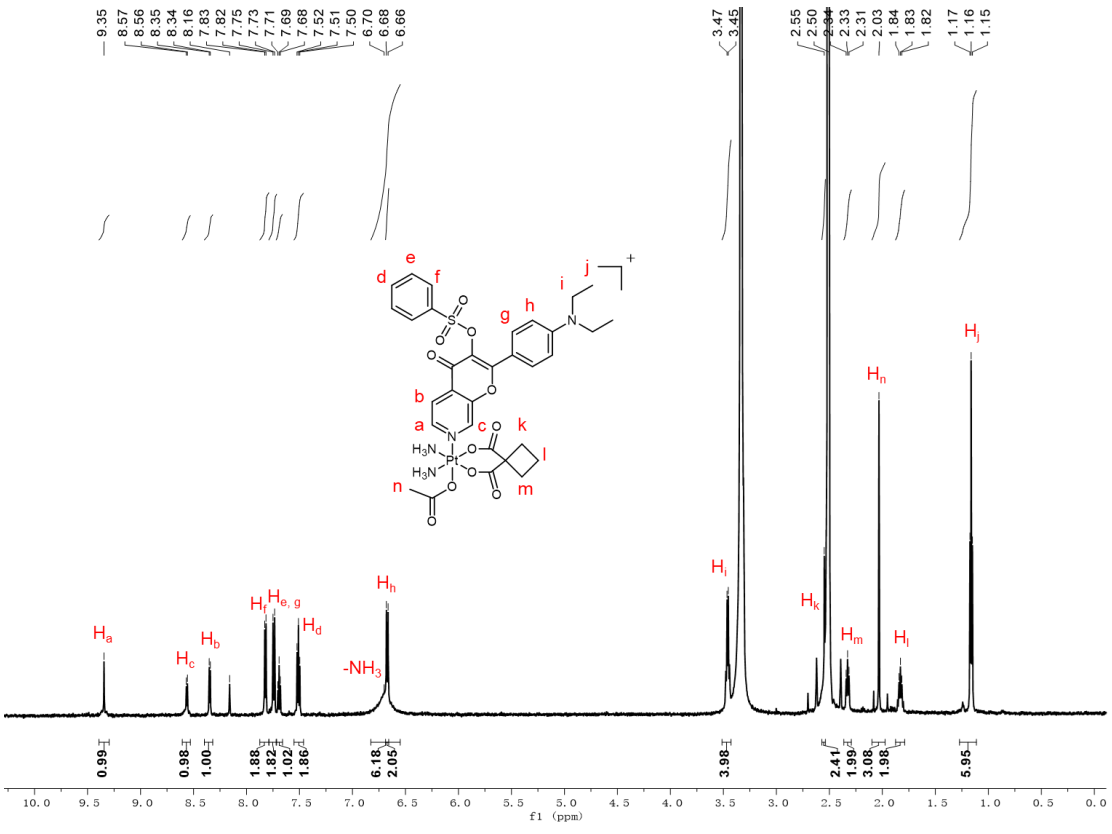


Figure S14. 600 MHz ^{1}H NMR spectrum of flavoplatin **3b** in DMSO-d_6.

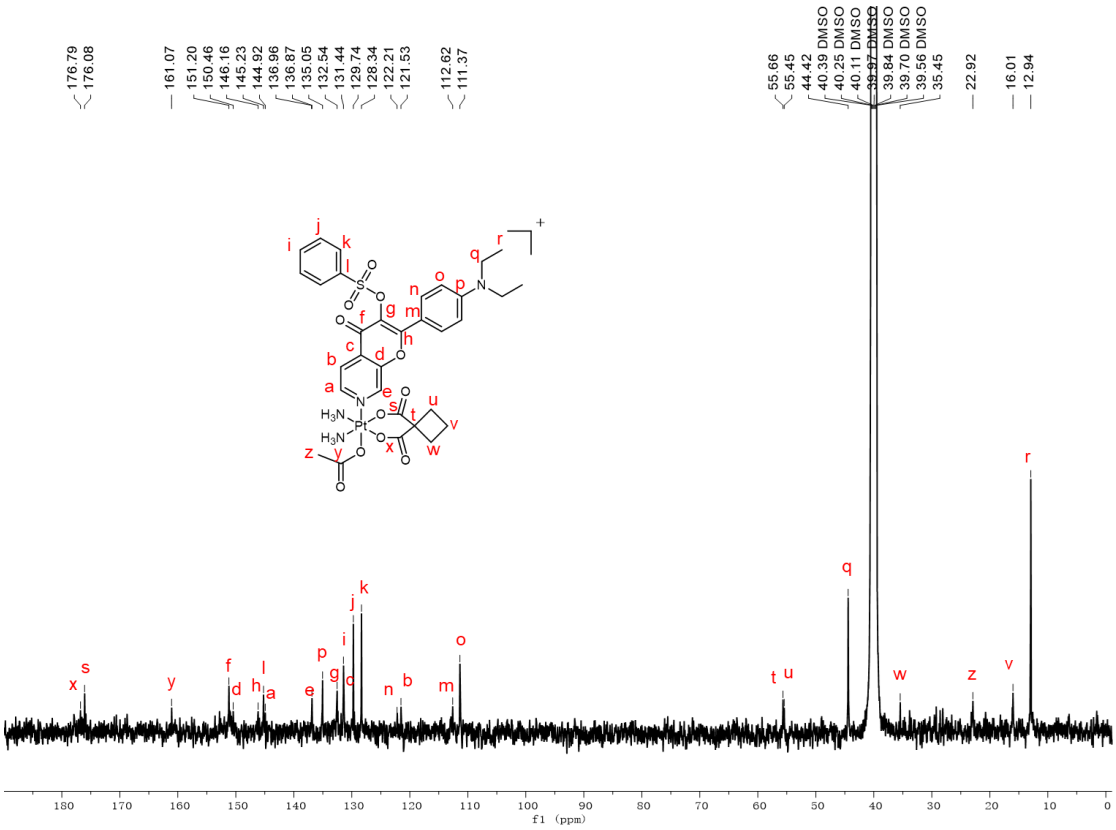


Figure S15. 151 MHz ^{13}C NMR spectrum of flavoplatin **3b** in DMSO-d_6.

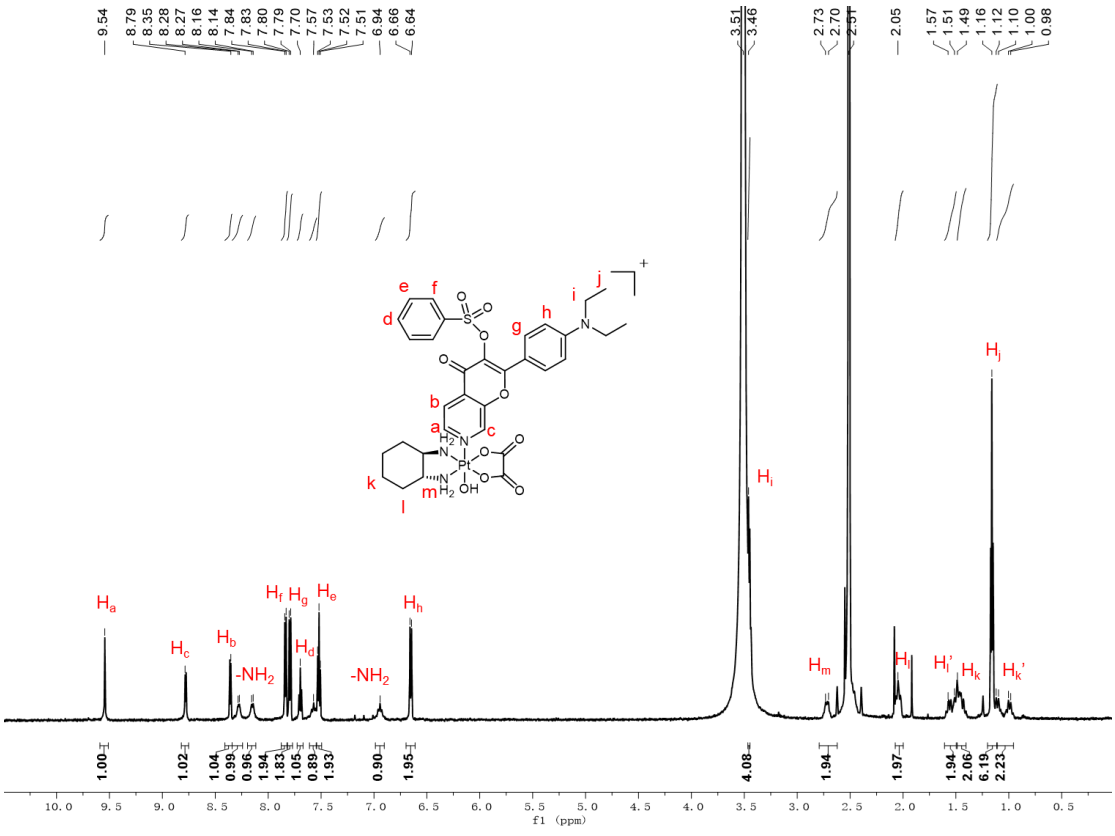


Figure S16. 600 MHz ^{1}H NMR spectrum of flavoplatin **3c** in DMSO-d_6.

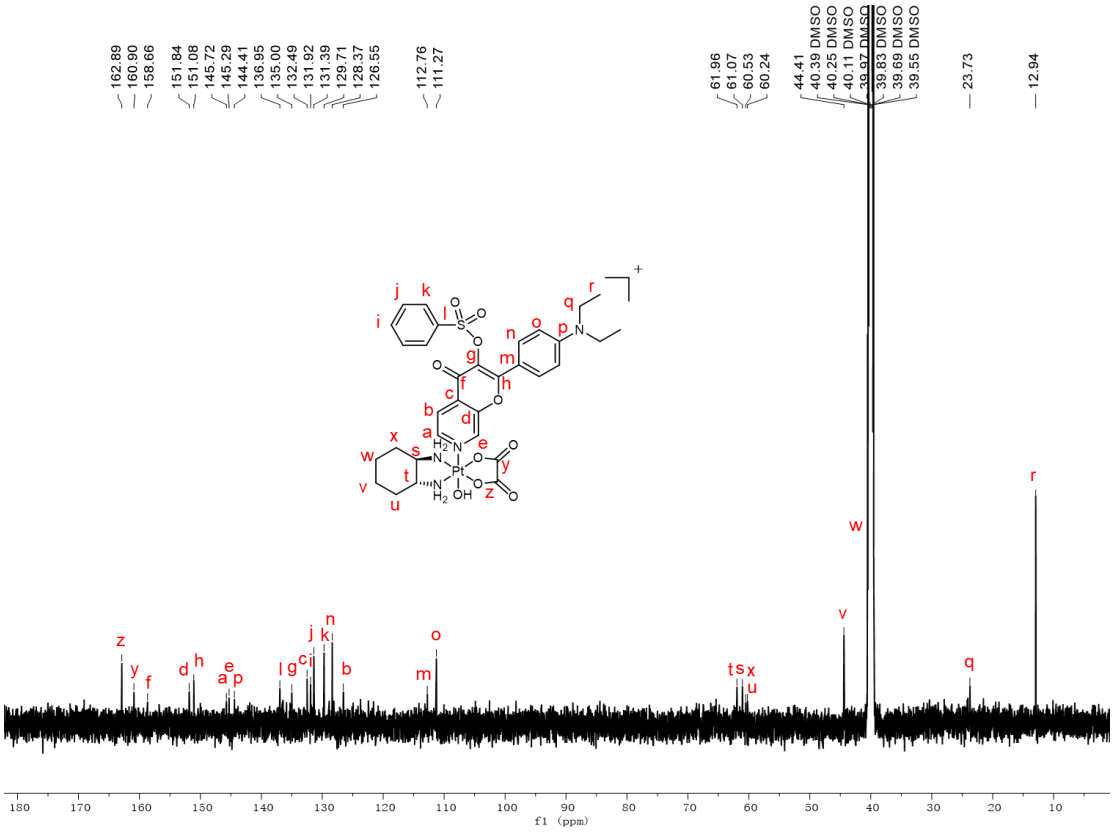


Figure S17. 151 MHz ^{13}C NMR spectrum of flavoplatin **3c** in DMSO-d_6.

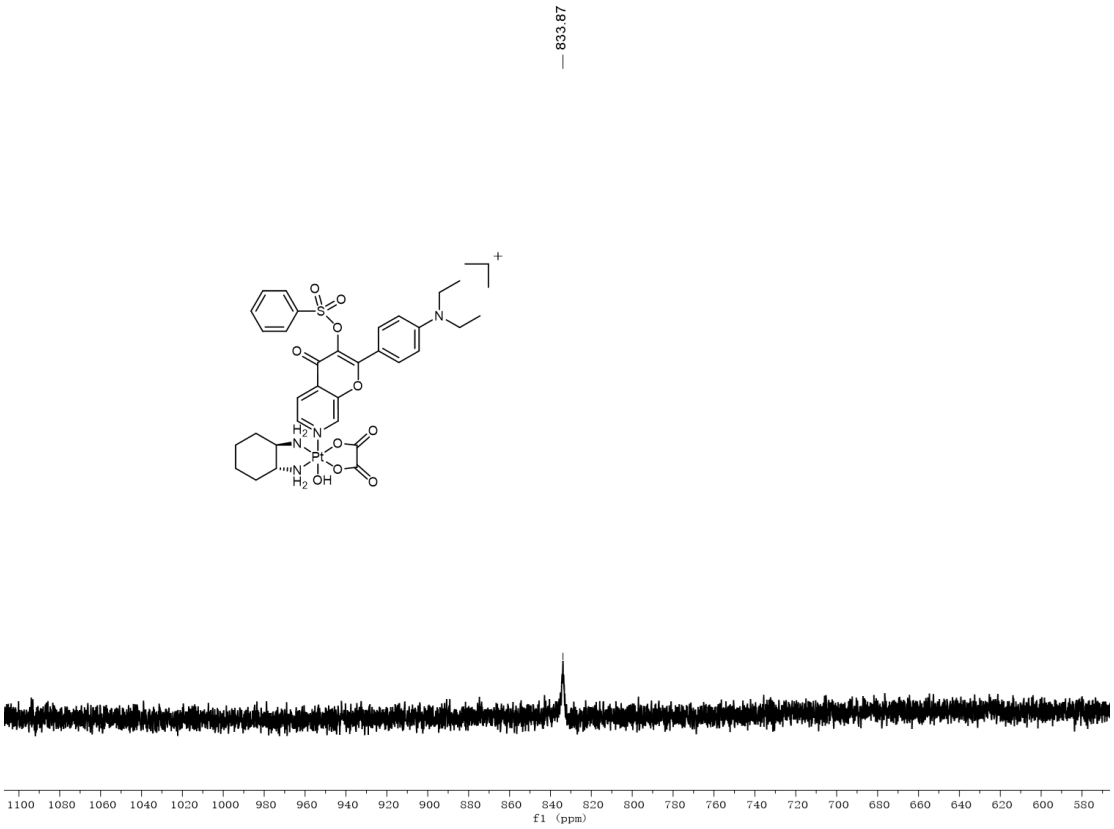


Figure S18. 129 MHz ^{195}Pt NMR spectrum of flavoplatin **3c** in DMSO-d_6.

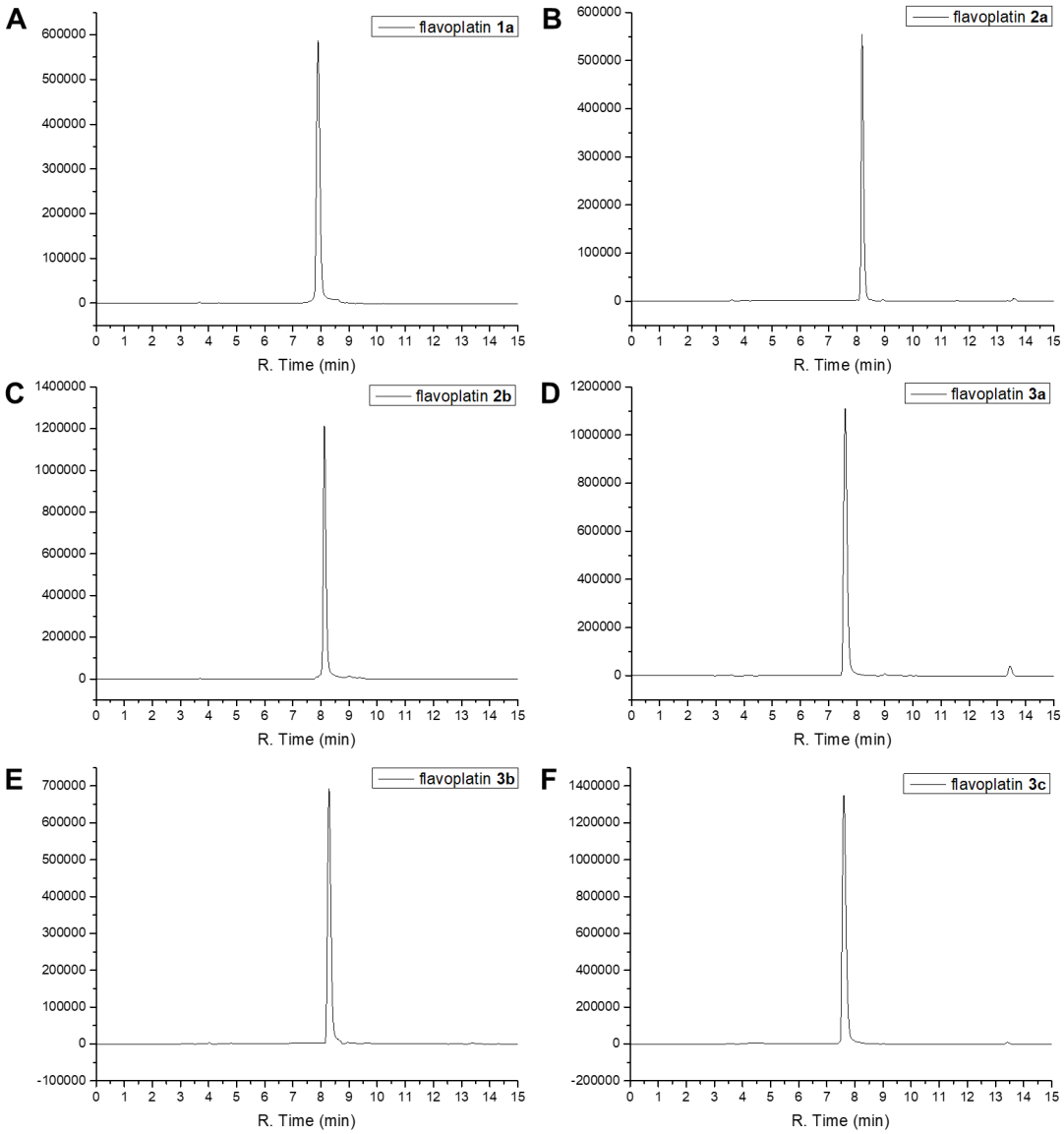


Figure S19. HPLC chromatograms of flavoplatins, detected at 480 nm. (**A**) flavoplatin **1a**, purity: 97%; (**B**) flavoplatin **2a**, purity: 98%; (**C**) flavoplatin **2b**, purity: 96%; (**D**) flavoplatin **3a**, purity: 95%; (**E**) flavoplatin **3b**, purity: 99%; (**F**) flavoplatin **3c**, purity: 98%. "R. Time" refers to the retention time of analysts.

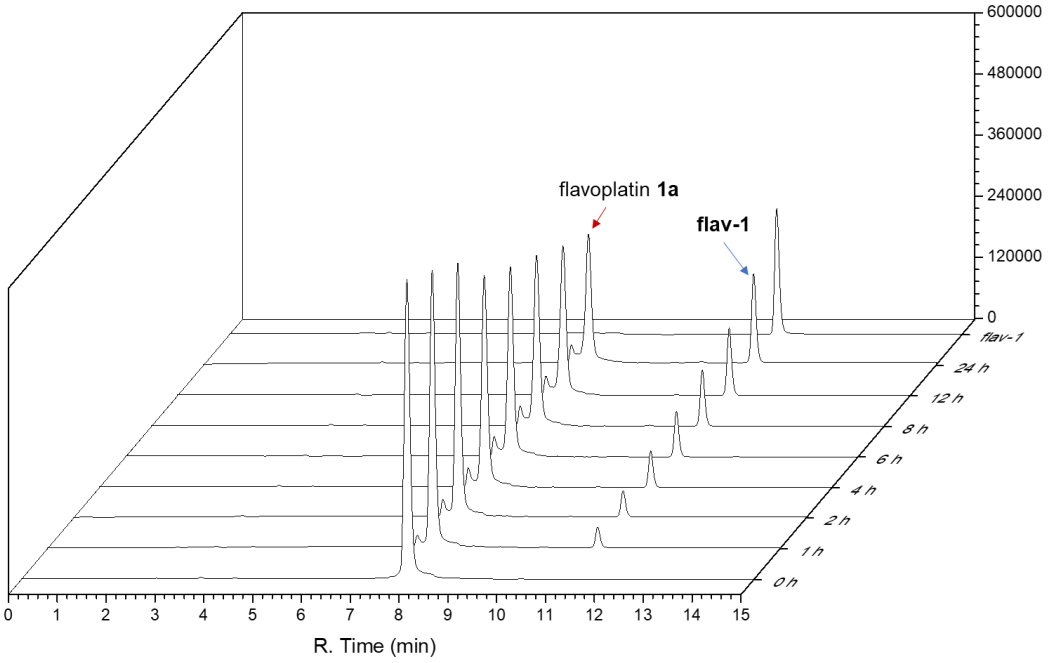


Figure S20. HPLC chromatograms of flavoplatin **1a** (200 μM) in 50 mM HEPES buffer (20% DMF, pH 7.4, 37 °C) from 0 to 24 h. "R. Time" refers to the retention time of analysts.

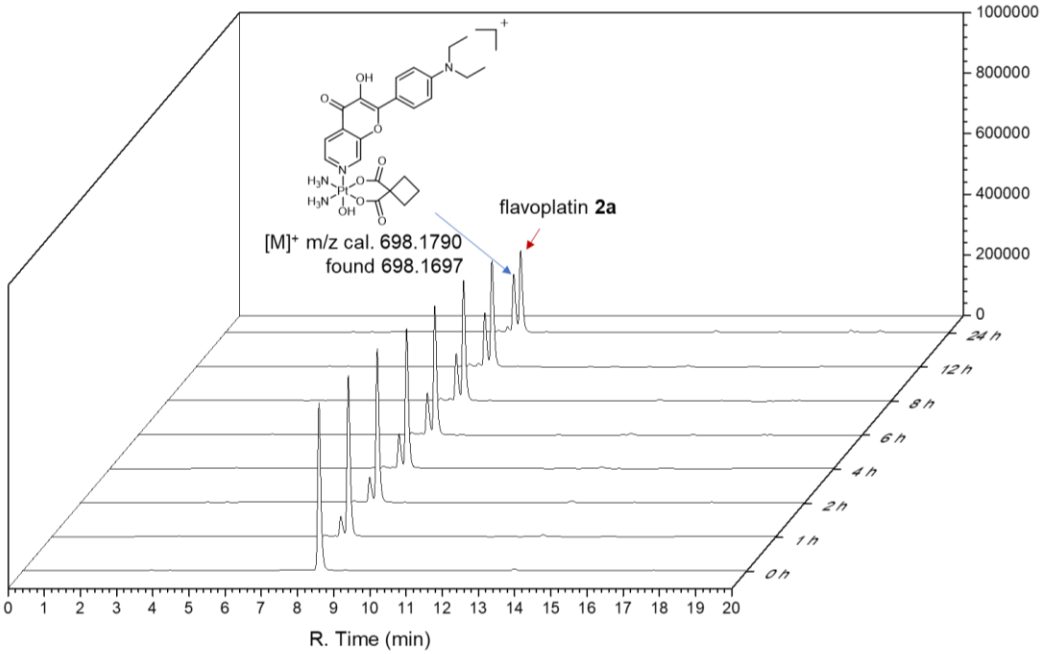


Figure S19. HPLC chromatograms of flavoplatin **2a** (200 μM) in 50 mM HEPES buffer (20% DMF, pH 7.4, 37 °C) from 0 to 24 h. "R. Time" refers to the retention time of analysts.

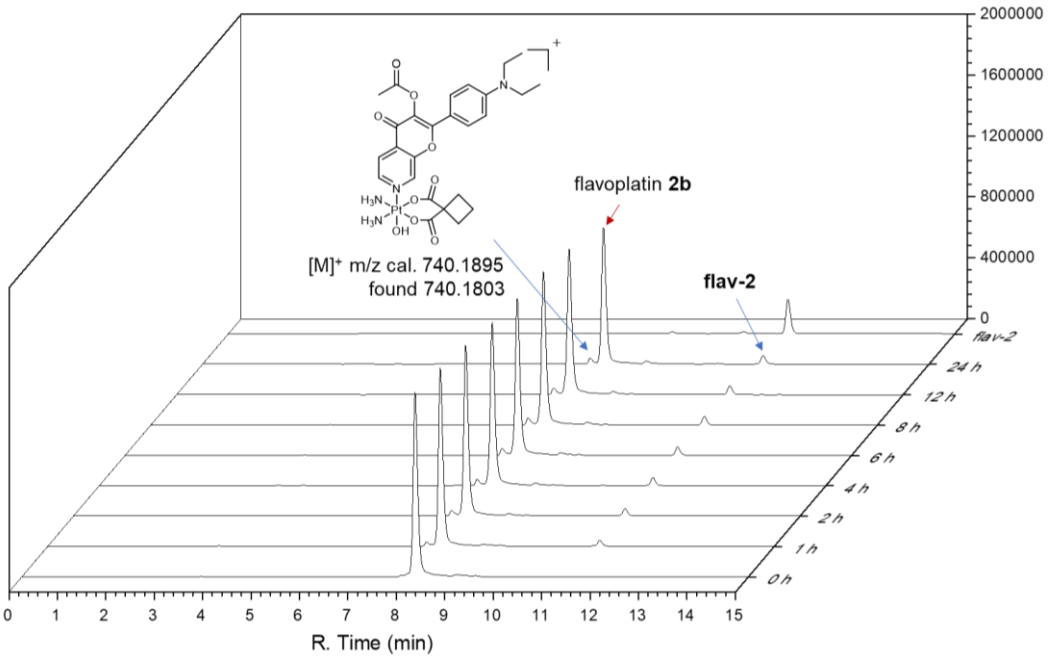


Figure S22. HPLC chromatograms of flavoplatin **2b** (200 μM) in 50 mM HEPES buffer (20% DMF, pH 7.4, 37 °C) from 0 to 24 h. "R. Time" refers to the retention time of analysts.

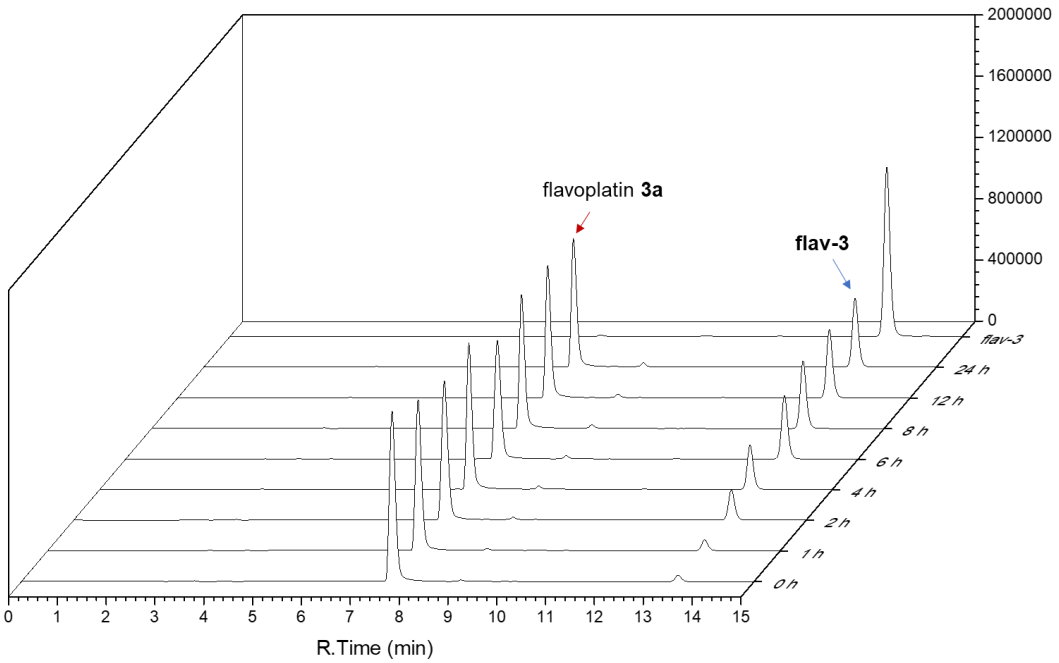


Figure S23. HPLC chromatograms of flavoplatin **3a** (200 μM) in 50 mM HEPES buffer (20% DMF, pH 7.4, 37 °C) from 0 to 24 h. "R. Time" refers to the retention time of analysts.

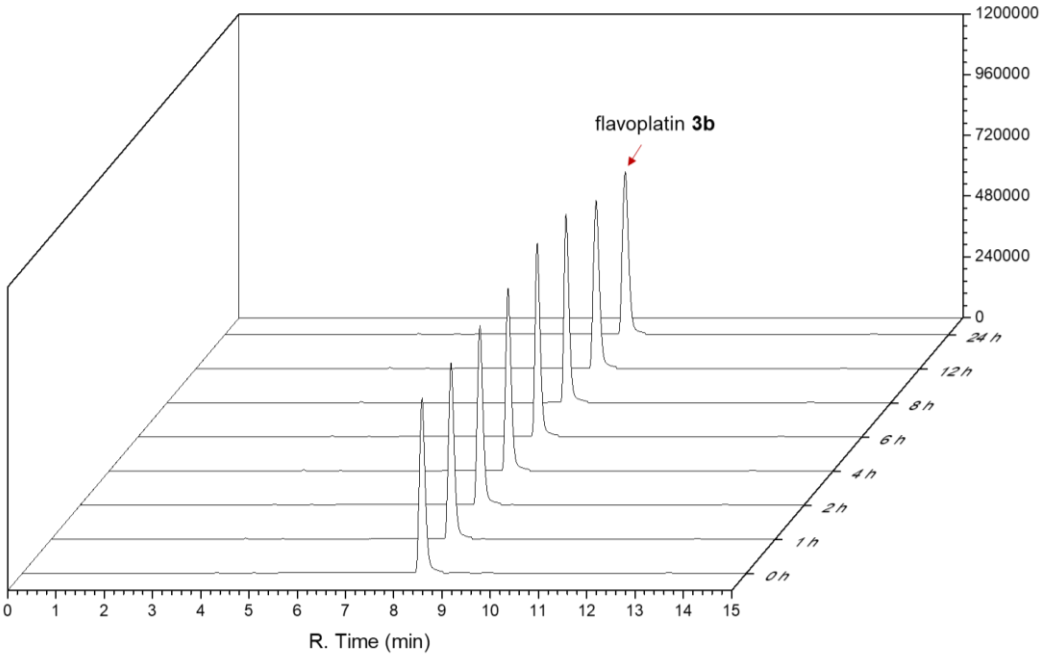


Figure S24. HPLC chromatograms of flavoplatin **3b** (200 μM) in 50 mM HEPES buffer (20% DMF, pH 7.4, 37 °C) from 0 to 24 h. "R. Time" refers to the retention time of analysts.

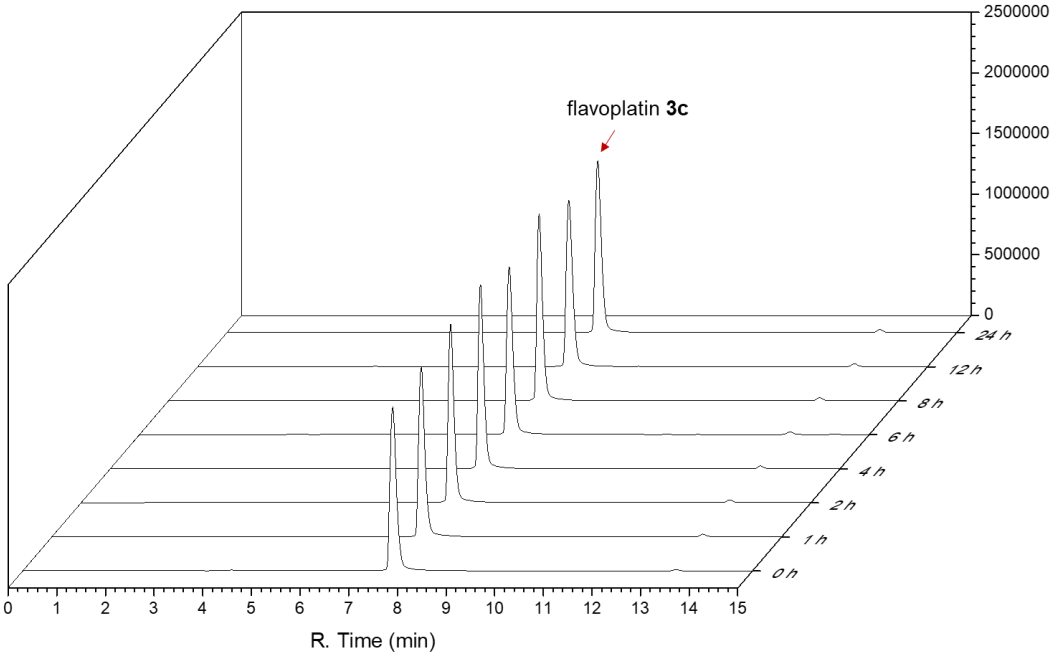


Figure S25. HPLC chromatograms of flavoplatin **3c** (200 μM) in 50 mM HEPES buffer (20% DMF, pH 7.4, 37 °C) from 0 to 24 h. "R. Time" refers to the retention time of analysts.

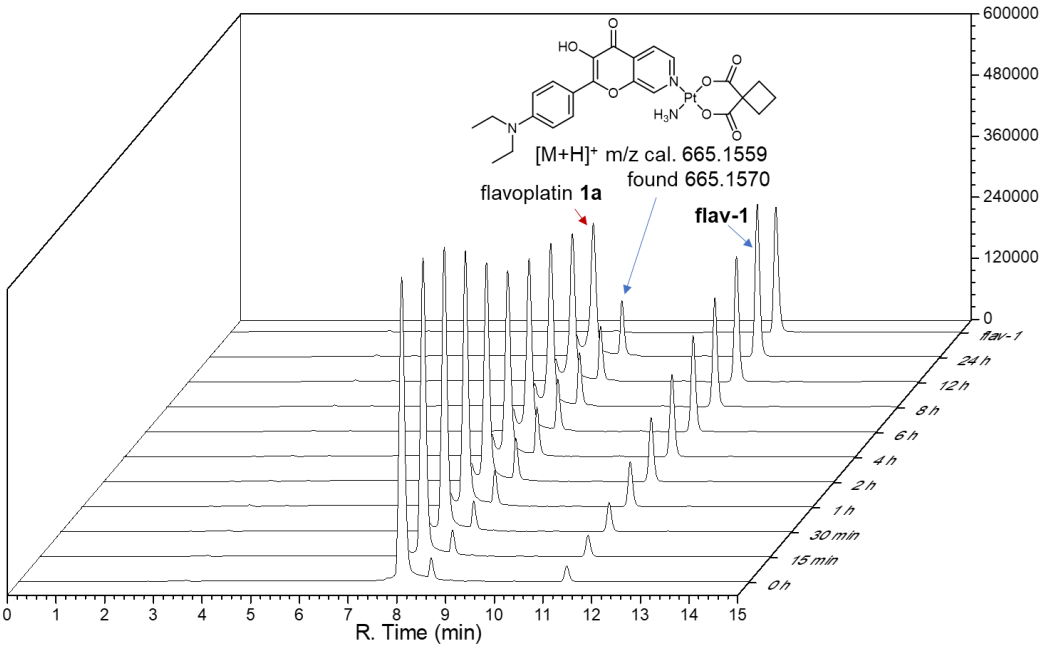


Figure S26. HPLC chromatograms of flavoplatin **1a** (200 μM) in 50 mM HEPES buffer with 2 mM sodium ascorbate (20% DMF, pH 7.4, 37 °C) from 0 to 24 h. "R. Time" refers to the retention time of analysts.

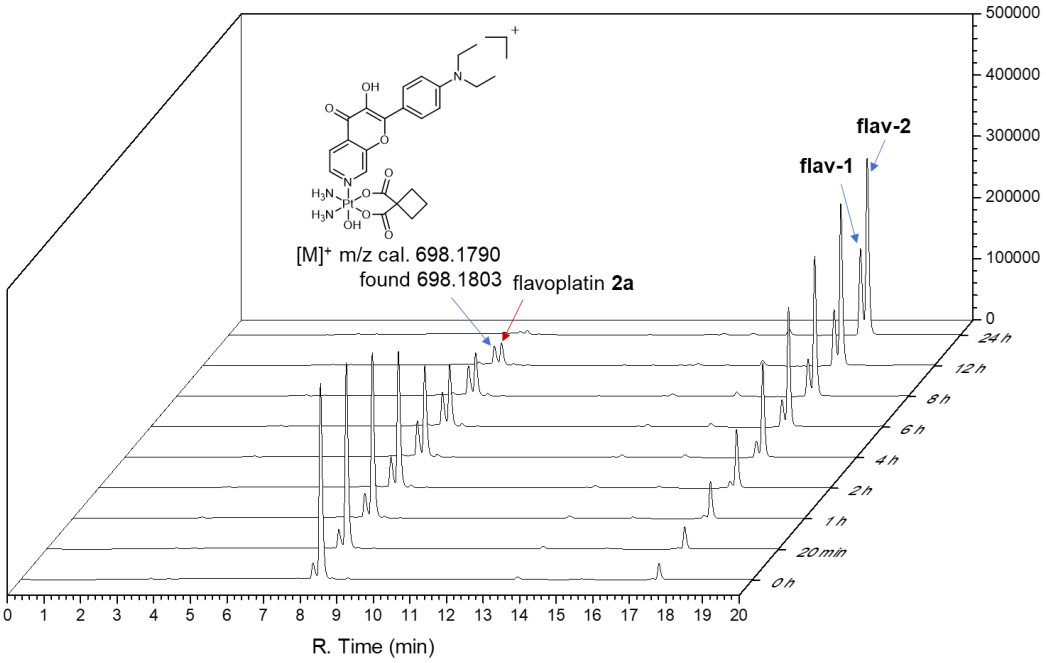


Figure S27. HPLC chromatograms of flavoplatin **2a** (200 μM) in 50 mM HEPES buffer with 2 mM sodium ascorbate (20% DMF, pH 7.4, 37 °C) from 0 to 24 h. "R. Time" refers to the retention time of analysts.

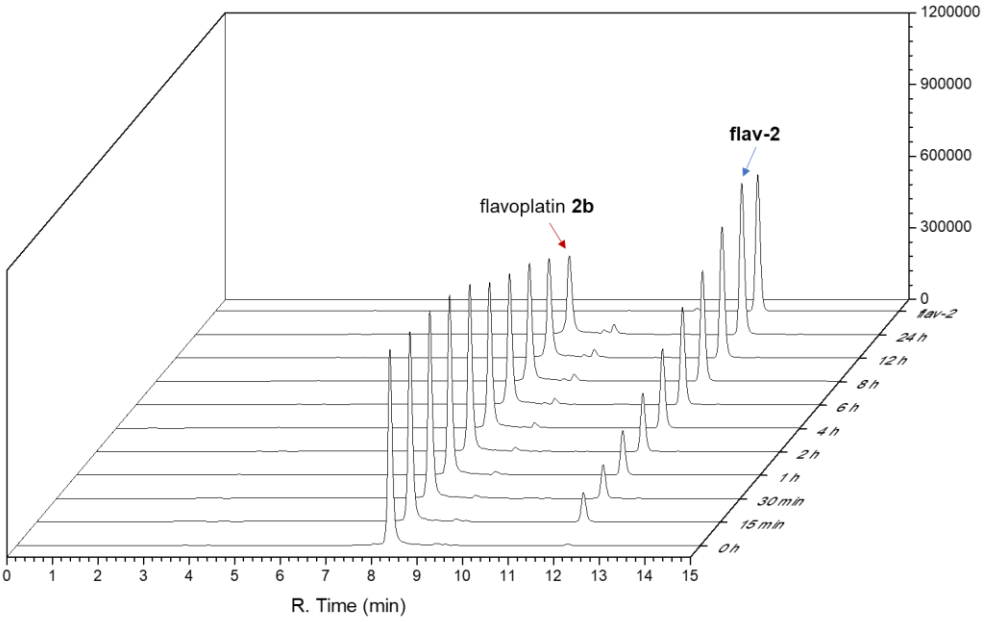


Figure S28. HPLC chromatograms of flavoplatin **2b** (200 μM) in 50 mM HEPES buffer with 2 mM sodium ascorbate (20% DMF, pH 7.4, 37 °C) from 0 to 24 h. "R. Time" refers to the retention time of analysts.

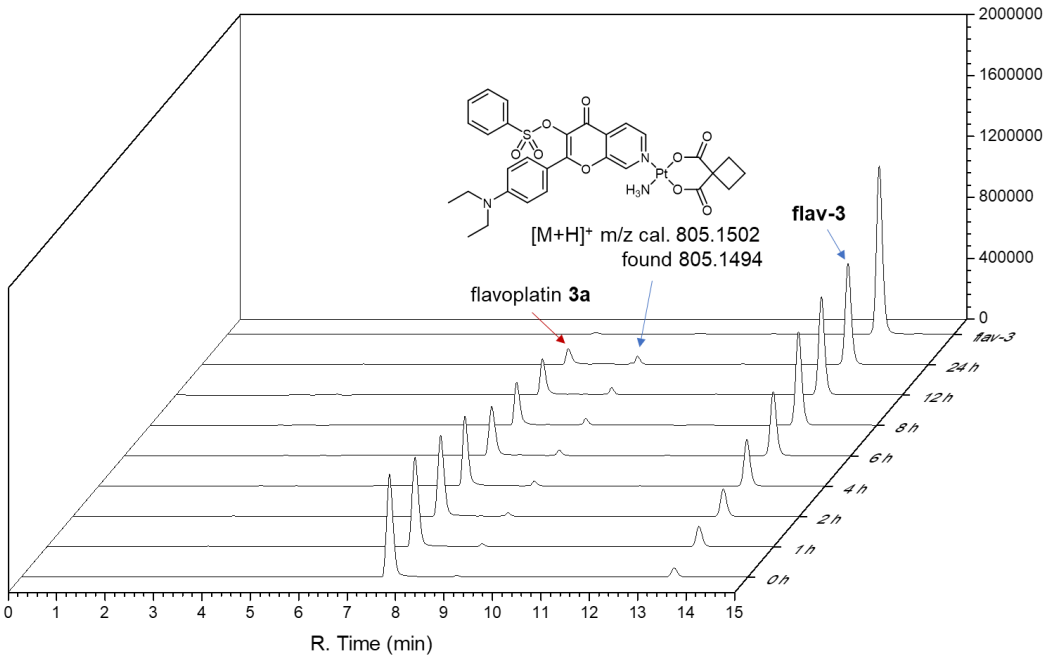


Figure S29. HPLC chromatograms of flavoplatin **3a** (200 μM) in 50 mM HEPES buffer with 2 mM sodium ascorbate (20% DMF, pH 7.4, 37 °C) from 0 to 24 h. "R. Time" refers to the retention time of analysts.

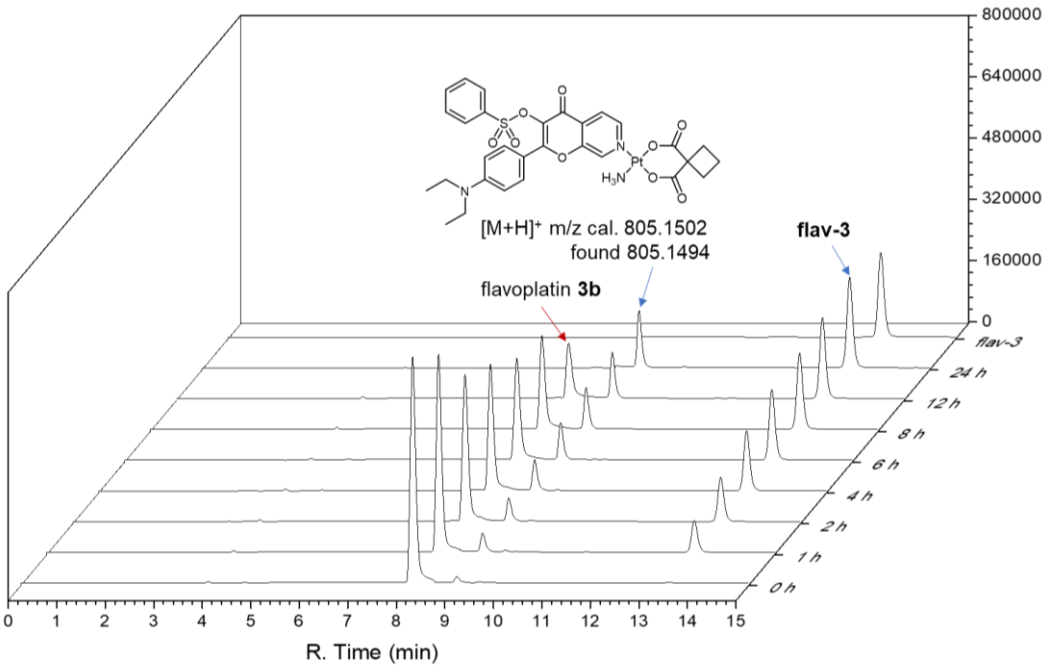


Figure S30. HPLC chromatograms of flavoplatin **3b** (200 μM) in 50 mM HEPES buffer with 2 mM sodium ascorbate (20% DMF, pH 7.4, 37 °C) from 0 to 24 h. "R. Time" refers to the retention time of analysts.

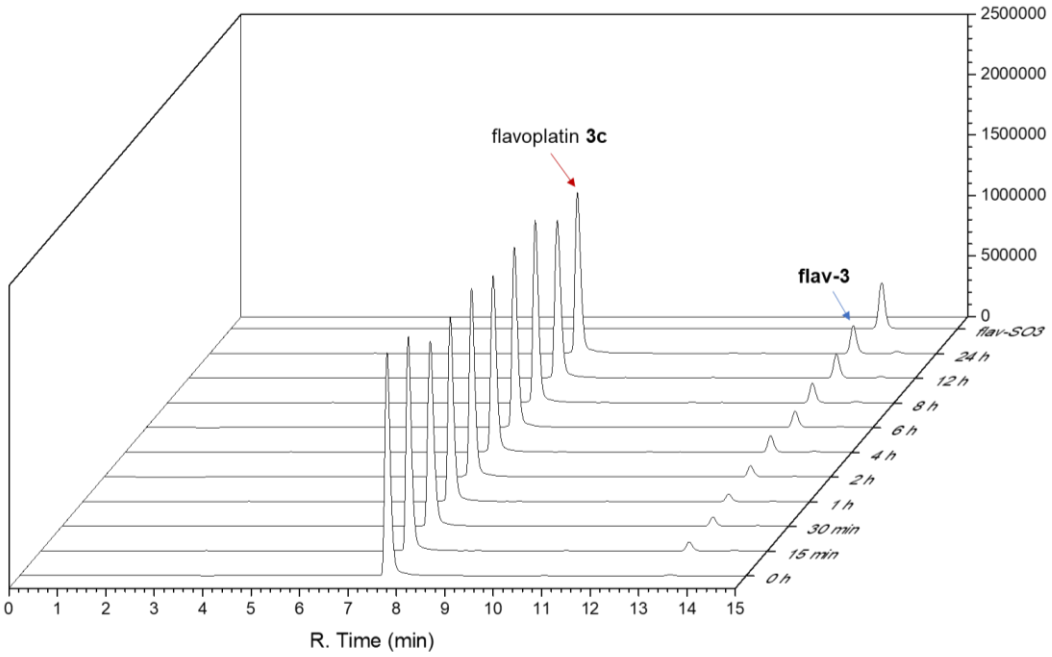
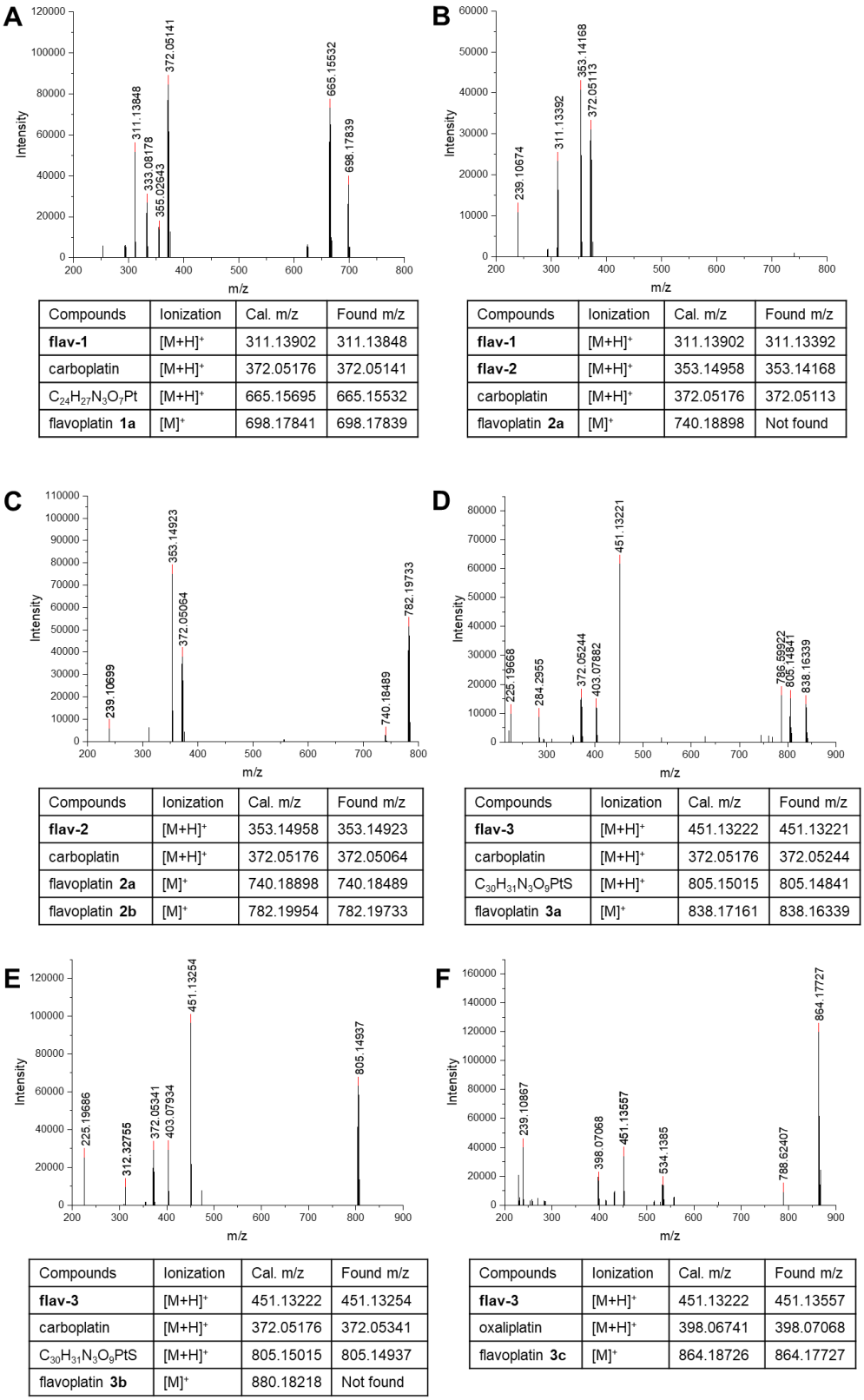


Figure S31. HPLC chromatograms of flavoplatin **3c** (200 μM) in 50 mM HEPES buffer with 2 mM sodium ascorbate (20% DMF, pH 7.4, 37 °C) from 0 to 24 h. "R. Time" refers to the retention time of analysts.



Compounds	Ionization	Cal. m/z	Found m/z
flav-1	$[M+H]^+$	311.13902	311.13848
carboplatin	$[M+H]^+$	372.05176	372.05141
$C_{24}H_{27}N_3O_7Pt$	$[M+H]^+$	665.15695	665.15532
flavoplatin **1a**	$[M]^+$	698.17841	698.17839

Compounds	Ionization	Cal. m/z	Found m/z
flav-1	$[M+H]^+$	311.13902	311.13392
flav-2	$[M+H]^+$	353.14958	353.14168
carboplatin	$[M+H]^+$	372.05176	372.05113
flavoplatin **2a**	$[M]^+$	740.18898	Not found

Compounds	Ionization	Cal. m/z	Found m/z
flav-2	$[M+H]^+$	353.14958	353.14923
carboplatin	$[M+H]^+$	372.05176	372.05064
flavoplatin **2a**	$[M]^+$	740.18898	740.18489
flavoplatin **2b**	$[M]^+$	782.19954	782.19733

Compounds	Ionization	Cal. m/z	Found m/z
flav-3	$[M+H]^+$	451.13222	451.13221
carboplatin	$[M+H]^+$	372.05176	372.05244
$C_{30}H_{31}N_3O_9PtS$	$[M+H]^+$	805.15015	805.14841
flavoplatin **3a**	$[M]^+$	838.17161	838.16339

Compounds	Ionization	Cal. m/z	Found m/z
flav-3	$[M+H]^+$	451.13222	451.13254
carboplatin	$[M+H]^+$	372.05176	372.05341
$C_{30}H_{31}N_3O_9PtS$	$[M+H]^+$	805.15015	805.14937
flavoplatin **3b**	$[M]^+$	880.18218	Not found

Compounds	Ionization	Cal. m/z	Found m/z
flav-3	$[M+H]^+$	451.13222	451.13557
oxaliplatin	$[M+H]^+$	398.06741	398.07068
flavoplatin **3c**	$[M]^+$	864.18726	864.17727

Figure S32. Mass spectra of (**A**) flavoplatin **1a**; (**B**) flavoplatin **2a**; (**C**) flavoplatin **2b**; (**D**) flavoplatin **3a**; (**E**) flavoplatin **3b**; and (**F**) flavoplatin **3c** in 50 mM HEPES buffer, which were incubated with 2 mM sodium ascorbate (20% DMF, pH 7.4, 37 ℃) for 24 h.

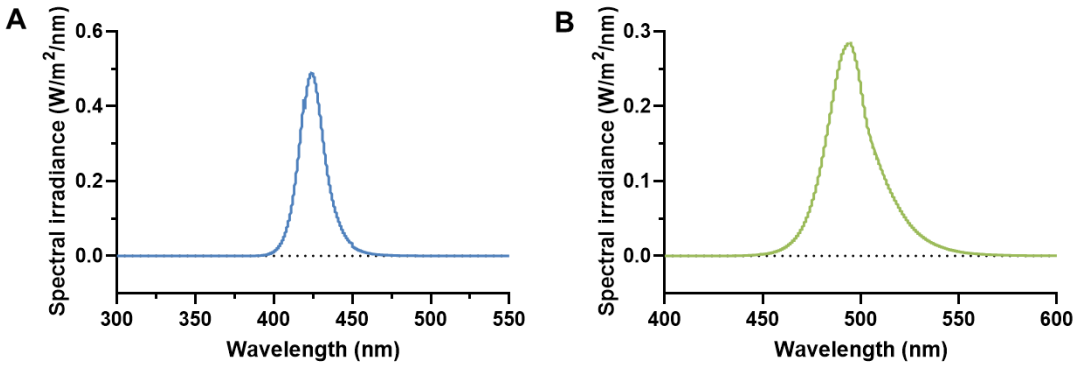


Figure S33. (A) Irradiation spectrum of the employed blue LED, power density = 1.0 mW/cm^2 (400 to 450 nm, λ_{max} = 425 nm). **(B)** Irradiation spectrum of the employed green LED, power density = 0.9 mW/cm^2 (450 to 550 nm, λ_{max} = 495 nm).

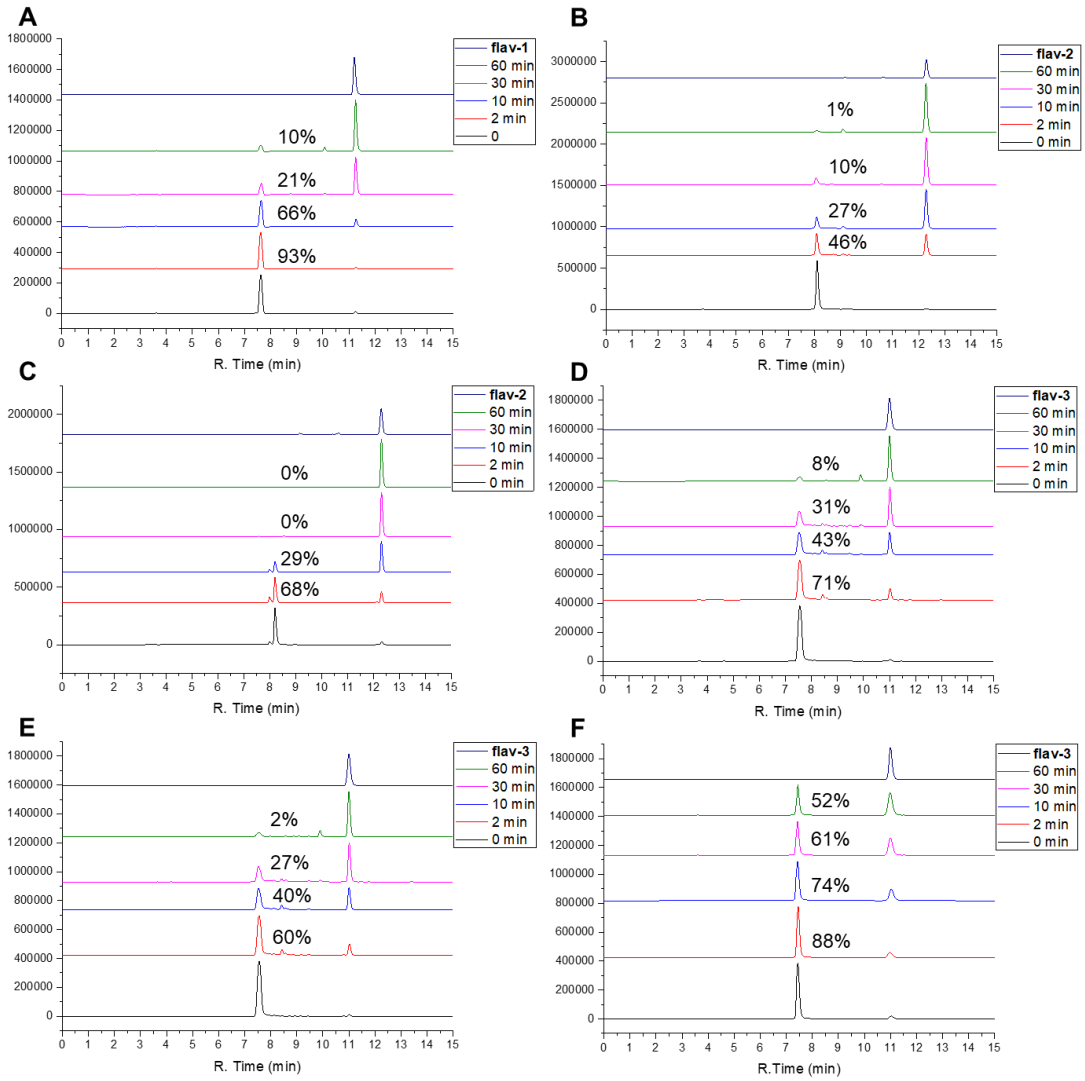


Figure S34. Photoactivation of (**A**) flavoplatin **1a**; (**B**) flavoplatin **2a**; (**C**) flavoplatin **2b**; (**D**) flavoplatin **3a**; (**E**) flavoplatin **3b**; (**F**) flavoplatin **3c**. The 200 μM solutions in 50 mM HEPES buffer containing 2 mM sodium ascorbate (pH 7.4, 20 % DMF) were irradiated by green light (495 nm, 0.9 mW/cm^2) from 0 to 60 min at 37 °C. HPLC chromatographs were detected at 460 nm. "R. Time" refers to the retention time of analysts.

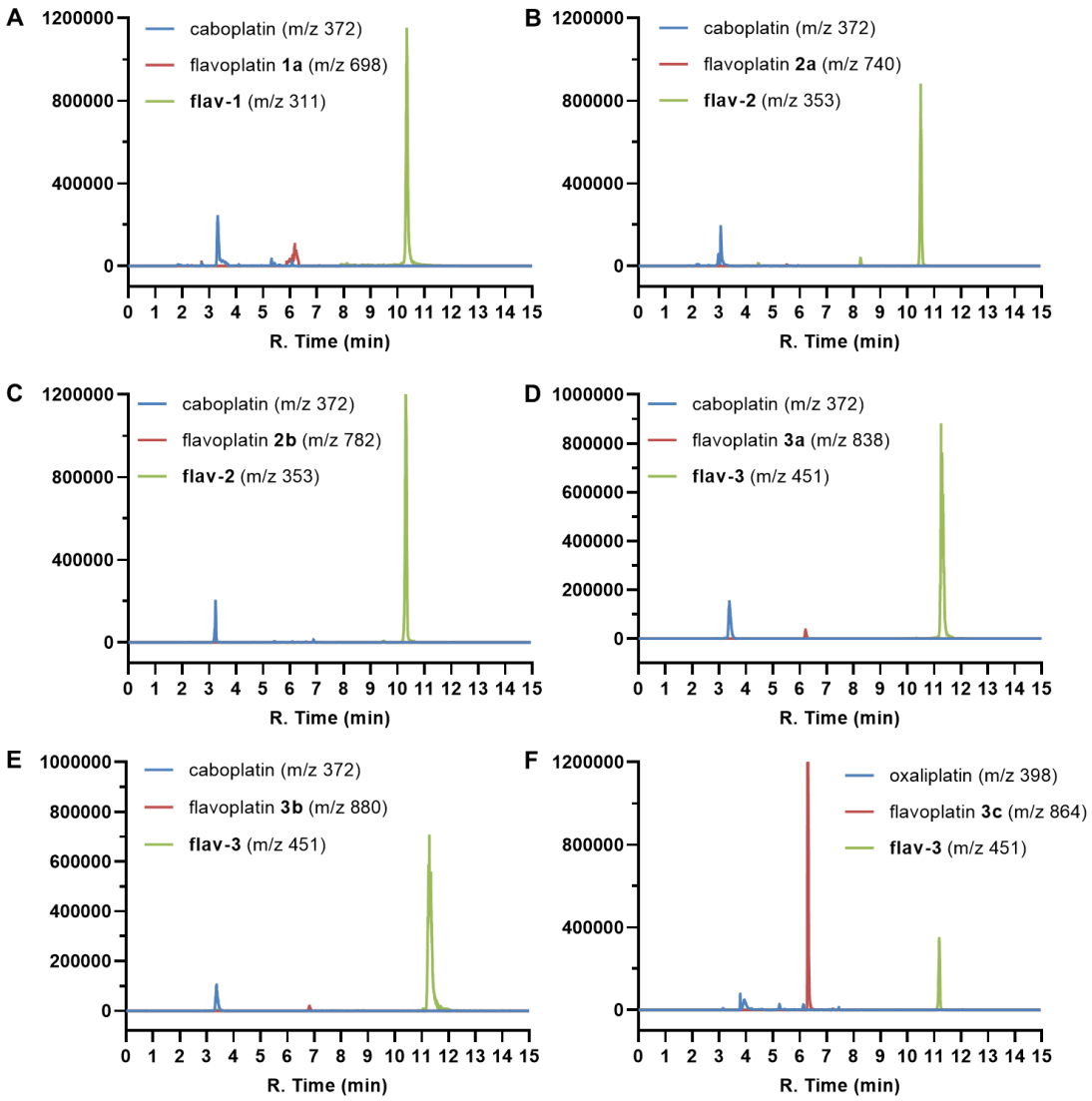


Figure S35. Extracted ion chromatographs (XIC) of (**A**) flavoplatin **1a**; (**B**) flavoplatin **2a**; (**C**) flavoplatin **2b**; (**D**) flavoplatin **3a**; (**E**) flavoplatin **3b**; (**F**) flavoplatin **3c**. The 200 μM solutions in 50 mM HEPES buffer containing 2 mM sodium ascorbate (pH 7.4, 20 % DMF) were irradiated by green light (495 nm, 0.9 mW/cm^2) for 60 min at 37 °C. The m/z values related to Pt(II) and Pt(IV) complexes or the ligands **flav-1** to **flav-3** were extracted for analysis: carboplatin (m/z 372.05±0.02), oxaliplatin (m/z 398.07±0.02), flavoplatin **1a** (m/z 698.18±0.02), flavoplatin **2a** (m/z 740.19±0.02), flavoplatin **2b** (m/z 782.19±0.02), flavoplatin **3a** (m/z 838.17±0.02), flavoplatin **3b** (m/z 880.18±0.02), flavoplatin **3c** (m/z 864.19±0.02), **flav-1** (m/z 311.14±0.02), **flav-2** (m/z 353.14±0.02), **flav-3** (m/z 451.13±0.02). "R. Time" refers to the retention time of analysts.

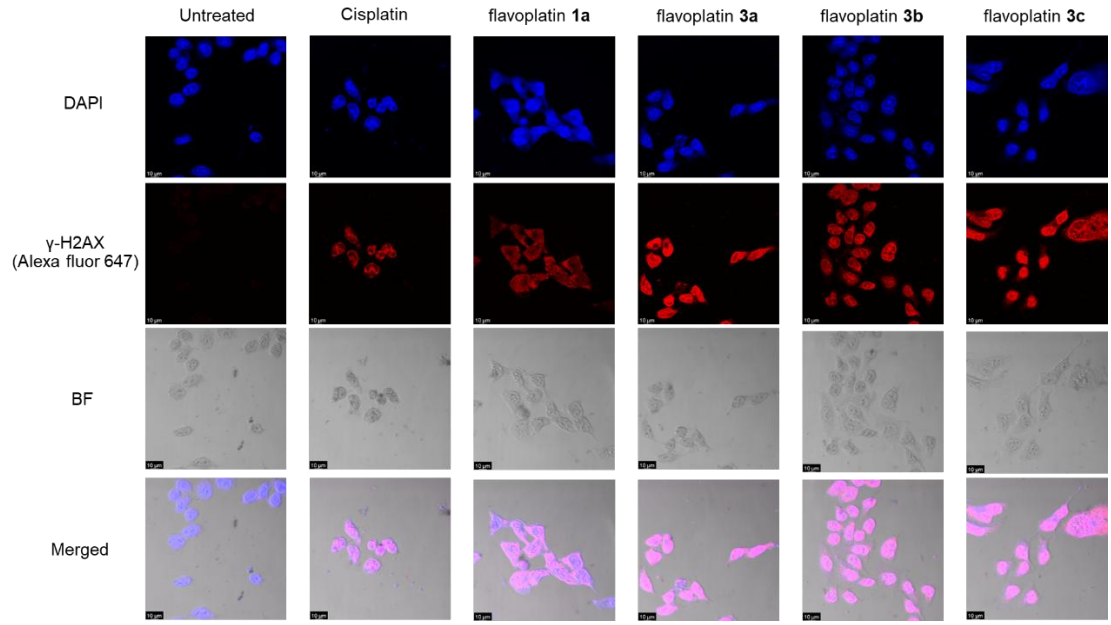


Figure S36. Immunofluorescence of γ-H2AX in A2780cisR cells, treated with 50 μM flavoplatins **1a**, **3a**, **3b**, and **3c** for 2 h**.** The flavoplatin-treated cells were irradiated by green light (495 nm, 0.9 mW/cm^2) for 1 h, while the untreated and cisplatin groups were kept in the dark. All groups were then incubated for another 2 h.

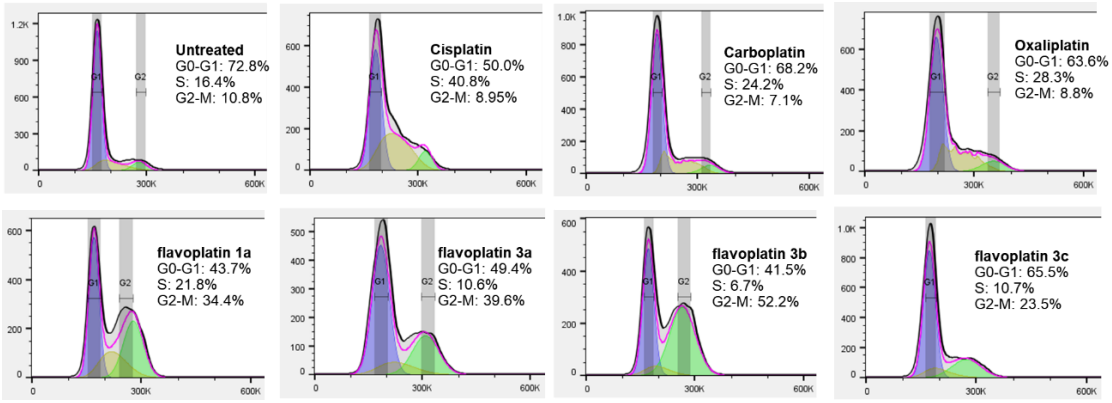


Figure S37. Cell cycle arrest of A2780cisR cells treated with 200 μM cisplatin, 200 μM carboplatin, and 200 μM oxaliplatin, as well as 50 μM flavoplatins **1a**, **3a**, **3b**, and **3c** for 2 h**.** The flavoplatin-treated cells were irradiated by green light (495 nm, 0.9 mW/cm^2) for 1 h, while other groups were kept in the dark. All groups were then incubated for another 2 h.

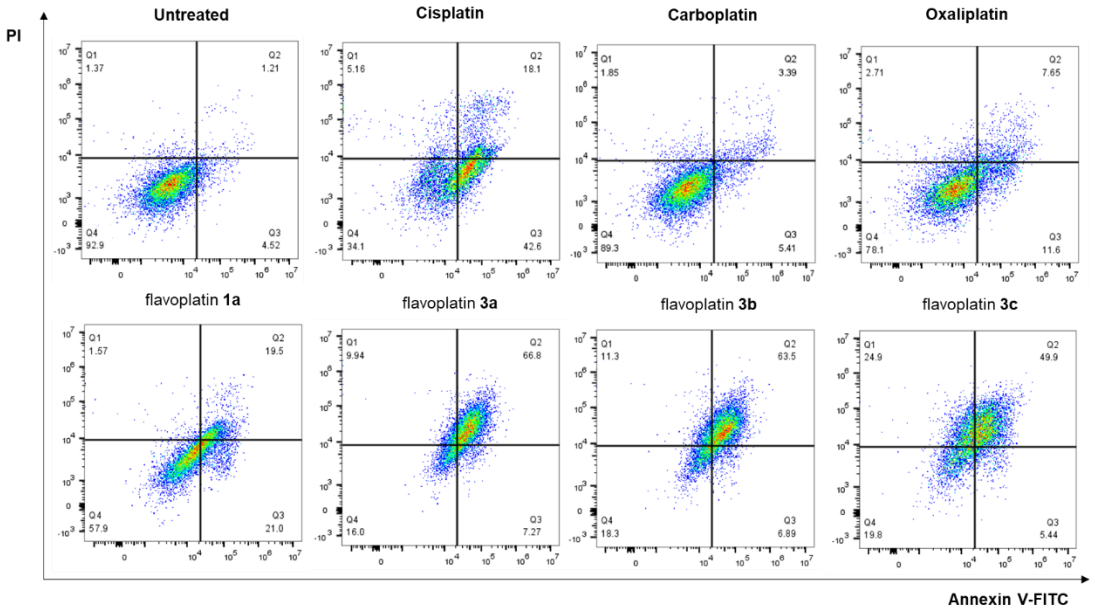


Figure S38. PI/Annexin V-FITC double staining of A2780cisR cells treated with 200 μM cisplatin, 200 μM carboplatin, and 200 μM oxaliplatin, as well as 50 μM flavoplatins **1a**, **3a**, **3b**, and **3c** for 2 h**.** The flavoplatin-treated cells were irradiated by green light (495 nm, 0.9 mW/cm^2) for 1 h, while other groups were kept in the dark. All groups were then incubated for another 2 h.

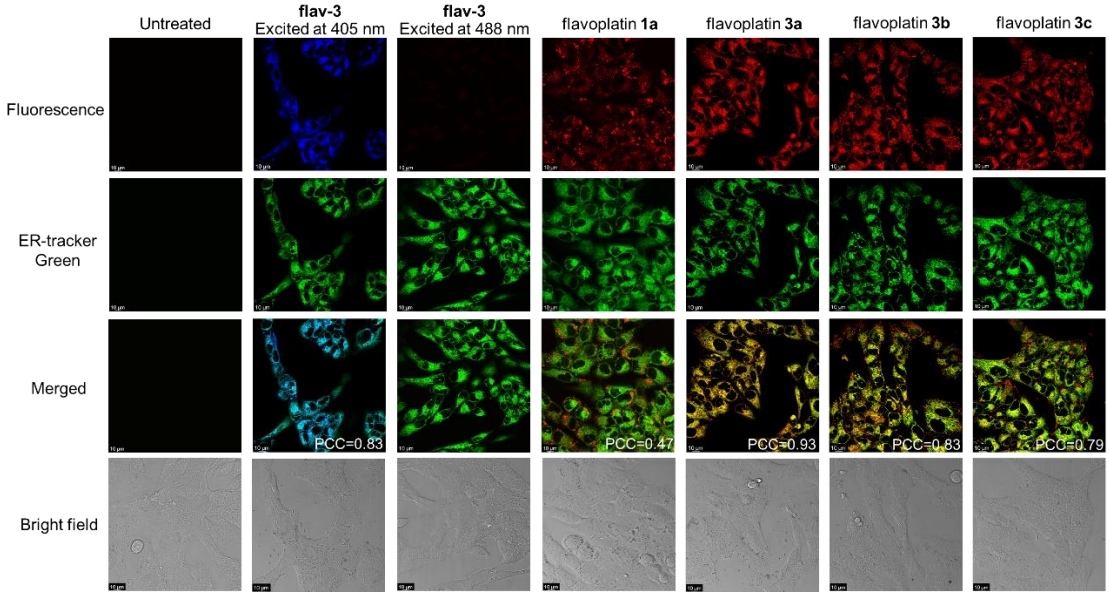


Figure S39. Co-localization of ER tracker green and flavoplatins in A2780cisR cells, treated with 25 μM **flav-3**, flavoplatins **1a**, **3a**, **3b**, and **3c** for 2 h**.** Cells were imaged by a Laser Confocal Scanning Microscope; Blue channel was excited at 405 nm, emission was recorded at 570 to 630 nm; Green channel was excited at 488 nm, emissions were recorded at 500 to 520 nm and 625 to 675 nm. Scale bar represents 10 μm.

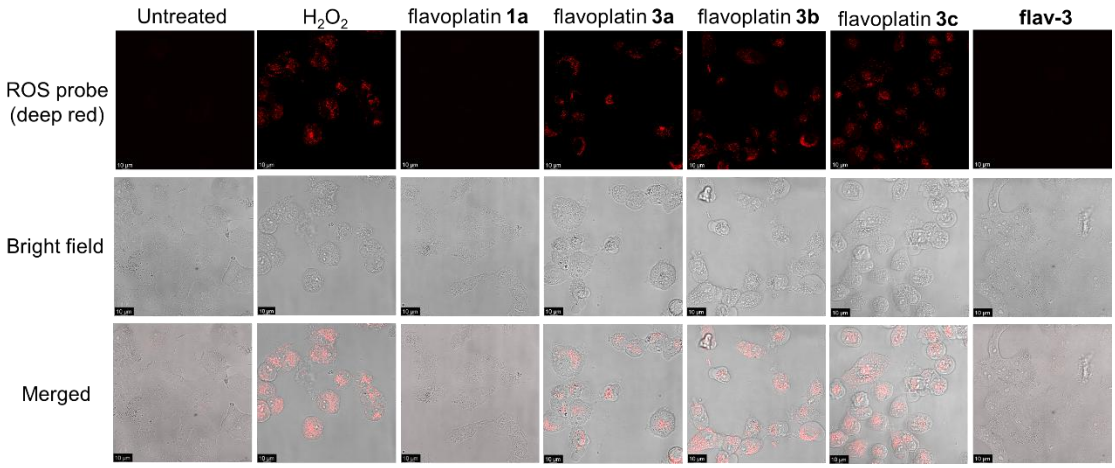


Figure S40. Fluorescence of a ROS probe (deep red) with the excitation at 635 nm, and emission was recorded at 660 to 680 nm. A2780cisR cells were treated with 50 μM **flav-3**, flavoplatins **1a**, **3a**, **3b**, and **3c** for 2 h, as well as 4 mM of H_2O_2 for 30 min. The flavoplatin-treated cells were irradiated by green light (495 nm, 0.9 mW/cm^2) for 30 min, while the untreated cells were kept in the dark. Scale bar represents 10 μm.

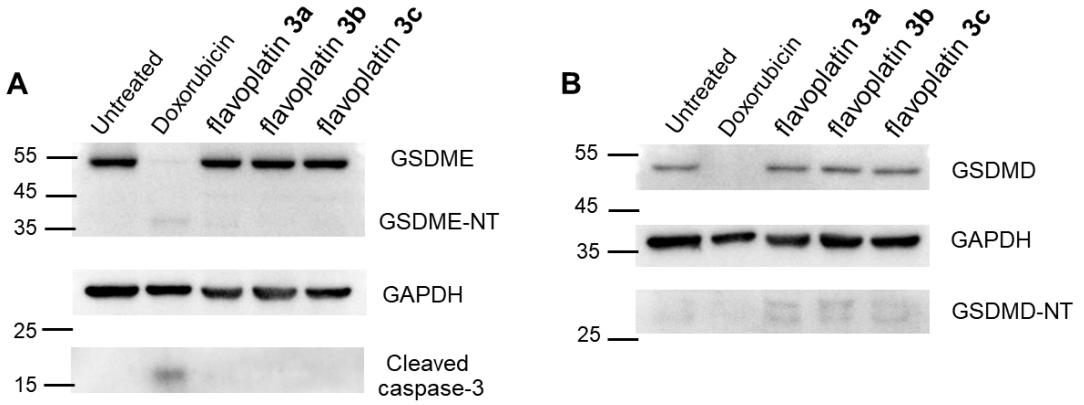


Figure S41. Western blot of (**A**) GAPDH, cleaved caspase-3, GSDME and its N-terminal fragment; (**B**) GAPDH, GSDMD and its N-terminal fragment. A2780cisR cells were treated with 50 μM flavoplatin **3a**, **3b**, and **3c** for 2 h**.** The flavoplatin-treated cells were irradiated by green light (495 nm, 0.9 mW/cm^2) for 1 h, while the untreated cells were kept in the dark. The cells treated with 200 μM doxorubicin for 4 h in the dark were included as the positive control.

Figure S42. Uncropped images that are shown in Figures 5F and 5G.

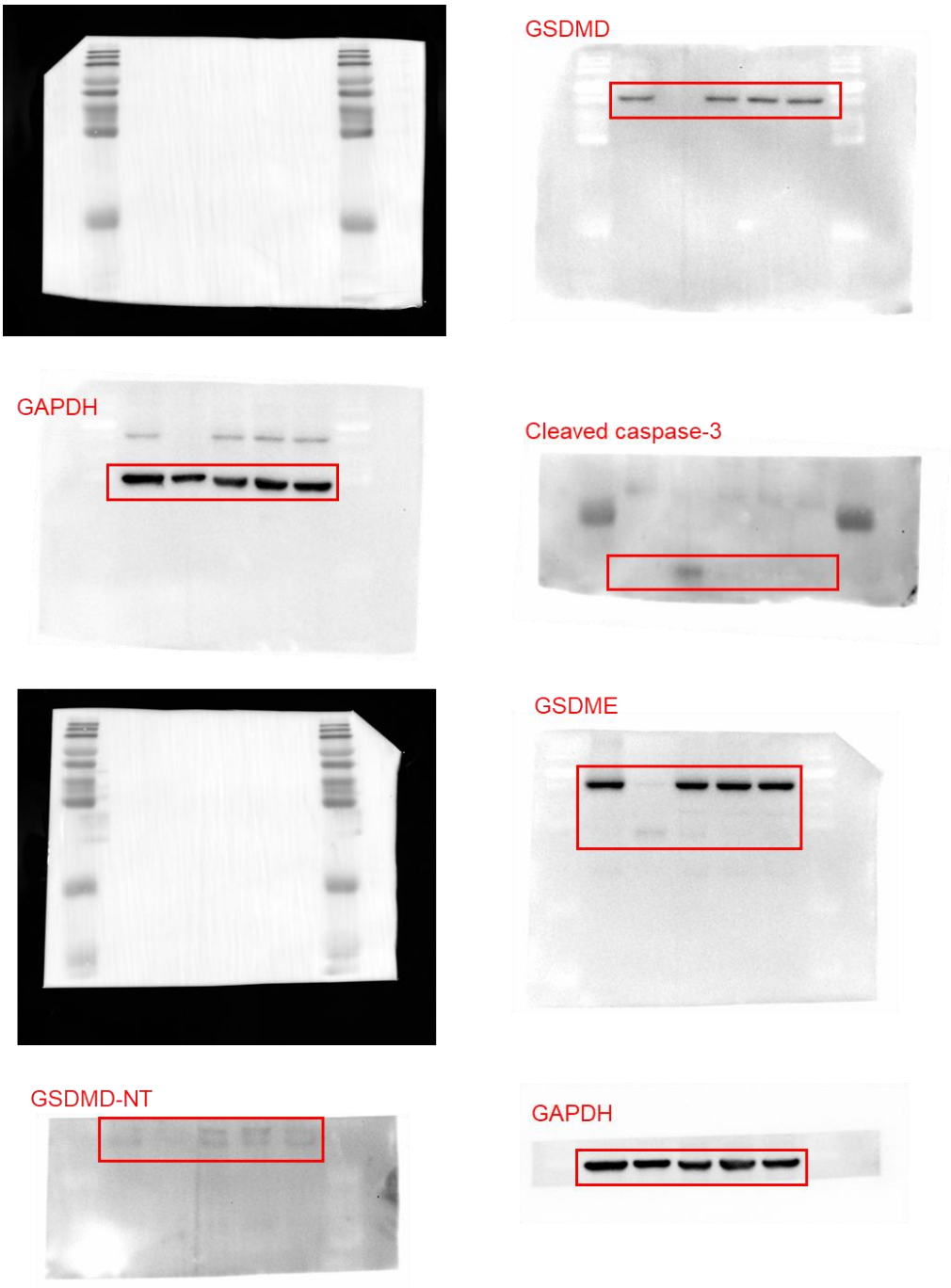


Figure S43. Uncropped images that are shown in Figure S41.

Table S1. Hydrolysis, reduction, water solubility, and hydrophilicity of flavoplatins.

Complexes	**Hydrolysis remaining**	**Reduction $t_{1/2}$ (remaining)**	**Solubility (mg/mL)**	**Log $P_{o/w}$**
flavoplatin **1a**	52%	15.4 h (44%)	0.87 ± 0.20	-1.03 ± 0.06
flavoplatin **2a**	51%	3.7 h (2%)	1.10 ± 0.11	-0.32 ± 0.08
flavoplatin **2b**	79%	>24 h (51%)	0.22 ± 0.02	-0.41 ± 0.04
flavoplatin **3a**	69%	4.2 h (15%)	0.95 ± 0.07	-0.91 ± 0.04
flavoplatin **3b**	95%	4.4 h (23%)	0.72 ± 0.02	-0.14 ± 0.01
flavoplatin **3c**	98%	>24 h (80%)	0.77 ± 0.01	-0.80 ± 0.03
Carboplatin			12.44 ± 0.50	-1.70 ± 0.23
Oxaliplatin			5.07 ± 0.15	-1.25 ± 0.02

Table S2. Excited states of **flav-3** and flavoplatin **3a** calculated at the TD-B3LYP (SCRF, solvent=water)/def2-TZVP level in a water solution. Oscillator strengths for the transitions from the ground state to triplet states are not determined.

flav-3				
Excitation	ΔE (eV)	λ (nm)	Osc. strength	Character
$S_0 \rightarrow T_1$	2.2215	558.12	-	
$S_0 \rightarrow S_1$	2.8715	431.78	0.5902	HOMO → LUMO
$S_0 \rightarrow T_2$	3.0768	402.96	-	
$S_0 \rightarrow T_3$	3.1601	392.34	-	
$S_0 \rightarrow T_4$	3.3980	364.87	-	
$S_0 \rightarrow S_2$	3.4761	356.67	0.1468	HOMO → LUMO+1
$S_0 \rightarrow T_5$	3.5996	344.44	-	
$S_0 \rightarrow T_6$	3.6329	341.28	-	
$S_0 \rightarrow T_7$	3.6640	338.38	-	
$S_0 \rightarrow T_8$	3.7129	333.93	-	
$S_0 \rightarrow S_3$	3.7374	331.74	0.0006	
$S_0 \rightarrow T_9$	3.7380	331.68	-	

$S_0 \rightarrow S_4$	3.8176	324.77	0.2259	HOMO → LUMO+2
$S_0 \rightarrow T_{10}$	3.8297	323.74	-	
$S_0 \rightarrow S_5$	4.0656	304.96	0.1450	HOMO-1 → LUMO
$S_0 \rightarrow S_6$	4.1921	295.76	0.0023	
$S_0 \rightarrow S_7$	4.3470	285.22	0.0013	
$S_0 \rightarrow S_8$	4.3891	282.48	0.0534	HOMO → LUMO+4
$S_0 \rightarrow S_9$	4.4347	279.58	0.0032	
$S_0 \rightarrow S_{10}$	4.5218	274.19	0.0654	HOMO → LUMO+5

flavoplatin 3a

Excitation	ΔE (eV)	λ (nm)	Osc. strength	Character
$S_0 \rightarrow T_1$	1.8295	677.71	-	
$S_0 \rightarrow S_1$	2.3279	532.61	0.3488	HOMO → LUMO
$S_0 \rightarrow T_2$	2.5354	489.02	-	
$S_0 \rightarrow T_3$	2.6057	475.82	-	
$S_0 \rightarrow S_2$	2.6076	475.57	0.0001	
$S_0 \rightarrow T_4$	2.8286	438.32	-	
$S_0 \rightarrow S_3$	2.8289	438.27	0.0150	
$S_0 \rightarrow T_5$	2.9147	425.37	-	
$S_0 \rightarrow S_4$	3.1183	397.61	0.5297	HOMO → LUMO+3
$S_0 \rightarrow T_6$	3.1936	388.23	-	
$S_0 \rightarrow T_7$	3.2112	386.10	-	
$S_0 \rightarrow T_8$	3.3193	373.52	-	
$S_0 \rightarrow T_9$	3.4608	358.25	-	
$S_0 \rightarrow S_5$	3.4991	354.33	0.0004	
$S_0 \rightarrow T_{10}$	3.5326	350.97	-	
$S_0 \rightarrow S_6$	3.6261	341.92	0.0349	HOMO → LUMO+4
$S_0 \rightarrow S_7$	3.6984	335.23	0.0001	
$S_0 \rightarrow S_8$	3.7261	332.75	0.0510	HOMO-1 → LUMO
$S_0 \rightarrow S_9$	3.7385	331.64	0.0010	
$S_0 \rightarrow S_{10}$	3.8591	321.28	0.0451	HOMO-2 → LUMO

Table S3. Molar extinction coefficient and photoreaction quantum yield of flavoplatins.

Complexes	Absorption wavelength (nm)	Molar extinction coefficient (M^{-1} cm^{-1})	Quantum yield[a]
flavoplatin **1a**	481	34624	0.0024
flavoplatin **2a**	486	51336	0.0030
flavoplatin **2b**	486	52888	0.0029
flavoplatin **3a**	484	53912	0.0028
flavoplatin **3b**	489	42116	0.0022
flavoplatin **3c**	478	36728	0.0026

[a]Quantum yield is defined as the number of molecules reacted/the number of photons absorbed during the photoactivation tests at 10 min.

Table S4. Cytotoxicity assays in A2780 and A2780cisR cells, which were treated with carboplatin, oxaliplatin, **flav-1**, **flav-3**, and flavoplatins **1a**, **3a**, **3b**, and **3c** for 2h, followed by blue light (425 nm, 1.0 mW/cm^2) or green light irradiation (495 nm, 0.9 mW/cm^2) for 1 h. The cells were incubated for another 21 h before the MTT assays, with the total treatment time being 24 h.

IC_{50} (μM) and PI[a]		A2780	FI[b]	A2780cisR	FI[b]	RF[c]
Cisplatin	Dark	63.8±19.1	-	417.1±73.8	-	6.5
	Blue	58.7±10.9	-	491.4±66.6	-	8.4
	Green	54.0±4.9	-	472.9±107.6	-	8.8
Carboplatin	Dark	>500	-	>500	-	**-**
	Blue	>500	-	>500	-	-
	Green	>500	-	>500	-	-
Oxaliplatin	Dark	72.9±10.0	-	>500	-	>6.8
	Blue	82.0±13.3	-	>500	-	>6.1
	Green	73.5±16.7	-	>500	-	>6.8
flav-1	Dark	>500	-	>500	-	-
	Blue	**42.6±4.3 (>11.7)**	**-**	**155.4±23.9 (>3.2)**	**-**	**3.6**
	Green	141.5±15.2 (>3.5)	-	346.4±14.6 (>1.4)	-	2.4
flav-2	Dark	>500	-	>500	-	-
	Blue	**92.4±40.9 (>5.4)**	**-**	**>500**	**-**	**>5.4**
	Green	265.3±50.0 (>1.9)	-	>500	-	>1.9
flav-3	Dark	> 500	-	> 500	-	-

	Blue	> 500	-	> 500	-	-
	Green	> 500	-	> 500	-	-
Carboplatin	Dark	353.8±47.7	>1.4	> 500	-	1.4
/flav-1 (1:1)	**Blue**	**153.1±4.0 (2.3)**	**>3.2**	**163.1±7.9 (>3.1)**	**>3.0**	**1.1**
	Green	229.8±62.5 (1.5)	>2.1	271.5±26.2 (>1.8)	>1.8	1.2
Carboplatin	Dark	>500	-	>500	-	-
/flav-2 (1:1)	**Blue**	**73.3±10.3 (>6.8)**	**-**	**>500**	**-**	**>6.8**
	Green	279.9±53.6 (>1.7)	-	>500	-	>1.7
Carboplatin	Dark	>500	-	>500	-	-
/flav-3 (1:1)	**Blue**	**80.2±20.5 (>3.9)**	**>6.2**	**80.1±41.4 (>3.9)**	**>6.2**	**1.0**
	Green	307.5±66.6 (>1.6)	>1.6	267.8±68.6 (>1.8)	>1.8	0.9
Oxaliplatin/	Dark	137.5±80.1	0.5	>500	-	>3.6
flav-3 (1:1)	**Blue**	**74.3±13.2 (1.8)**	**1.1**	**85.4±21.1 (>5.8)**	**>5.8**	**1.1**
	Green	103.5±25.5 (1.3)	0.7	112.0±6.8 (>4.4)	>4.4	1.1
flavoplatin	Dark	>100	-	>100	**-**	**-**
1a	Blue	79.4±10.7 (>1.2)	>6.3	>100	-	>1.2
	Green	**79.3±5.8 (>1.2)**	**>6.3**	**84.3±16.5 (>1.1)**	**>5.9**	**1.1**
flavoplatin	Dark	>100	-	>100	-	-
2a	Blue	>100	**-**	>100	**-**	**-**
	Green	>100	-	>100	-	-
flavoplatin	Dark	>100	-	>100	-	-
2b	Blue	>100	**-**	>100	**-**	**-**
	Green	>100	-	>100	-	-
flavoplatin	Dark	>100	-	>100	-	-
3a	Blue	20.7±2.8 (>4.8)	>24	23.5±4.6 (>4.2)	>21	1.1
	Green	**18.3±4.8 (>5.4)**	**>27**	**14.2±4.2 (>7.0)**	**>35**	**0.8**
flavoplatin	Dark	>100	-	>100	-	-
3b	Blue	25.8±5.0 (>3.8)	>19	19.6±0.6 (>5.1)	>25	0.8
	Green	**15.1±0.7 (>6.6)**	**>33**	**15.6±4.5 (>6.4)**	**>32**	**1.0**
flavoplatin	Dark	>100	<0.7	>100	-	-
3c	Blue	42.6±7.5 (>2.3)	1.9	46.3±6.6 (>2.1)	>10	1.1
	Green	**34.7±12.5 (>2.8)**	**2.1**	**29.8±12.7 (>3.3)**	**>16**	**0.9**

[a] Photo-index (PI) is defined as the IC_{50} of dark groups/the IC_{50} of irradiation groups. [b] Fold increase (FI) is defined as IC_{50} of carboplatin or oxaliplatin/IC_{50} of flavoplatins or the corresponding mixtures. [c] Resistance factor (RF) is defined as IC_{50} in A2780cisR/IC_{50} in A2780.

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