Electronic Supplementary Material (ESI) for Chemical Communications
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Supporting Information

Luminescent organoplatinum(II) complexes containing bis(N-heterocyclic carbene) ligands selectively target endoplasmic reticulum and induce potent photo-toxicity

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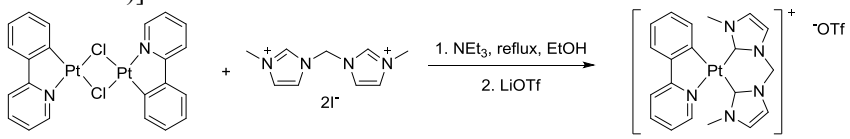
Materials and Methods

All starting materials were used as received from commercial sources. All the solvents were of analytical grade. $[Pt(C^N)(\mu\text{-}Cl)]_2$ (HC^N = 2-phenylpyridine, Hppy; benzo[*h*]quinolone, Hbzq; 2-(thiophen-2-yl)pyridine, Hthpy)[1] and $[bisIm]^{2+}I^-_2$ (bisIm = 1,1'-methylene-3,3'-dialkylbis(imidazolium))[2] were synthesized according to reported procedures. Gel mobility shift assay was performed according to a reported procedure. Fast Atom Bombardment (FAB) mass spectra were obtained on a Finnigan Mat 95 mass spectrometer. ^{1}H NMR spectra were obtained on DPX 400 M and 300 M Bruker FT-NMR spectrometers relative to the signal of tetramethylsilane. UV-vis spectra were recorded on a Perkin-Elmer Lambda 19 UV-vis spectrophotometer. Steady-state emission spectra were recorded on a SPEX 1681 Fluorolog-3 spectrophotometer. Elemental analysis was performed by the Institute of Chemistry at the Chinese Academy of Science, Beijing. For MTT and protein assays, the absorbance was quantified using Perkin Elmer Fusion Reader (Packard BioScience Company). Fluorescence images were examined in Axiovert 200 (Carl Zeiss) and in an Axio Vision Rel. 4.5 imaging system (Carl Zeiss).

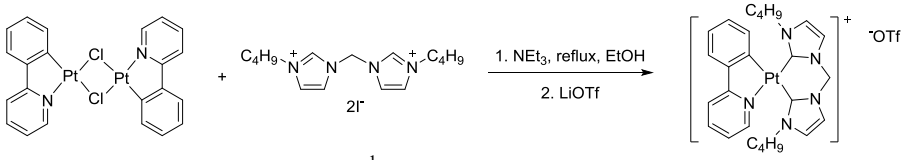
Experimental procedure and compound characterization[3]

1a $[Pt^{II}(ppy)(bisNHC^{2Me})]OTf$



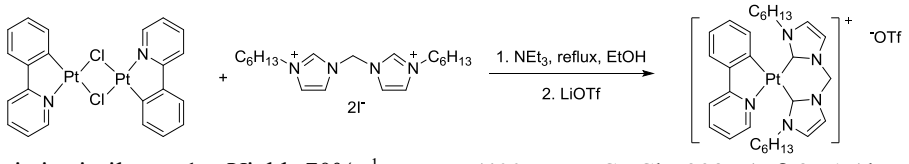
An ethanol solution (20 mL) of $[Pt(ppy)(\mu\text{-}Cl)]_2$ (60 mg, 0.078 mmol) was added with 67.4 mg of 1,1'-methylene-3,3'-dimethyllbis(imidazolium) diiodide (0.156 mmol) and Et_3N (1 mL). After refluxing the mixture for 12 h, excess of lithium triflate was added. The mixture was stirred for another 0.5 h and then evaporated. The residue was dissolved in water and extracted with CH_2Cl_2. The organic layer was evaporated to dryness. Purification of the product by column chromatography gave yellow-green solid. Yield: 80%. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 8.62 (d, 1 H, *J* = 4.7 Hz), 8.18 (d, 1 H, *J* = 1.9 Hz), 8.14 (d, 1 H, *J* = 2.0 Hz), 7.98 (m, 1 H), 7.88 (d, 1 H, *J* = 8.0 Hz), 7.68 (m, 1 H), 7.35 (m, 2 H), 7.30 (d, 1 H, *J* = 3.7 Hz), 7.24 (d, 1 H, *J* = 1.9 Hz), 7.17-7.20 (m, 2 H), 7.10 (d, 1 H, *J* = 2.0 Hz), 6.03 (d, 1 H, *J* = 12.8 Hz), 3.88 (s, 3 H), 3.77 (s, 3 H). MS-FAB(+): *m/z* 525.1 [M-OTf]. Elemental Analysis: calcd for $C_{21}H_{20}F_3N_5O_3PtS\bullet H_2O$: C, 36.42; H, 3.20; N, 10.11; found: C, 36.16; H, 3.23; N, 9.97.

1b $[Pt^{II}(ppy)(bisNHC^{2C4})]OTf$



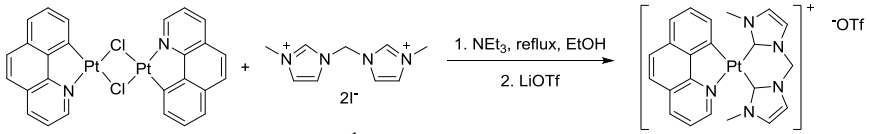
The synthesis is similar to **1a**. Yield: 75%. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 8.51 (d, 1 H, *J* = 4.9 Hz), 8.02 (d, 1 H, *J* = 2.0 Hz), 7.96-7.85 (m, 3 H), 7.68 (m, 1 H), 7.32 (m, 1 H), 7.21-7.19 (m, 3 H), 7.01 (d, 1 H, *J* = 2.0 Hz), 6.90 (m, 1 H), 6.76 (d, 1 H, *J* = 12.9 Hz), 6.10 (d, 1 H, *J* = 12.9 Hz), 4.34 (m, 1 H), 4.17 (m, 1 H), 4.05-3.93 (m, 2 H), 1.75-1.55 (m, 4 H), 1.40-0.94 (m, 4 H), 0.78 (m, 6 H). MS-FAB(+): *m/z* 609.2 [M-OTf]. Elemental Analysis: calcd for $C_{27}H_{32}F_3N_5O_3PtS\bullet 1.5H_2O$: C, 41.27; H, 4.49; N, 8.91; found: C, 41.01; H, 4.37; N, 9.22.

1c $[Pt^{II}(ppy)(bisNHC^{2C6})]OTf$



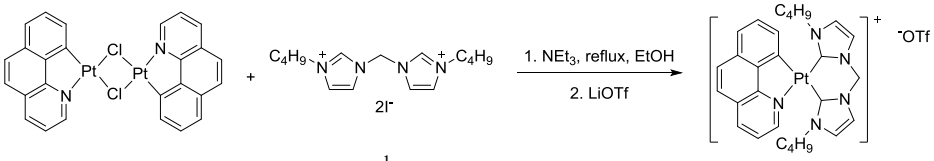
The synthesis is similar to **1a**. Yield: 70%. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 8.51 (d, *J* = 5.5 Hz, 1 H), 8.00 (m, 1 H), 7.98 – 7.94 (m, 1 H), 7.89 (m, 2 H), 7.68 (m, 1 H), 7.33 (m, 1 H), 7.21–7.16 (m, 3 H), 7.00 (d, *J* = 1.4 Hz, 1 H), 6.96 (d, *J* = 2.1 Hz, 1 H), 6.71 (d, *J* = 13.0 Hz, 1 H), 6.10 (d, *J* = 12.7 Hz, 1 H), 4.31 (m, 1 H), 4.08 (m, 1 H), 4.00–3.90 (m, 2 H), 1.72 – 1.63 (m, 4 H), 1.20 – 1.07 (m, 12 H), 0.78 (m, 6 H). MS-FAB(+): *m*/*z* 665.3 (M-OTf). Elemental Analysis: calcd for $C_{31}H_{40}F_3N_5O_3PtS•0.5H_2O$: C, 45.20; H, 5.02; N, 8.50; found: C, 45.24; H, 4.92; N, 8.51.

2a [Pt^{II}(bzq)(bisNHC^{2Me})]OTf



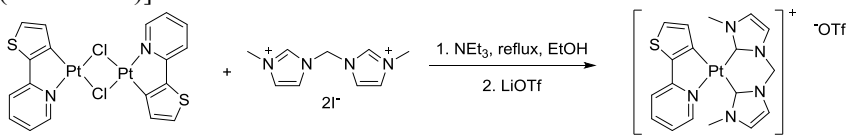
The synthesis is similar to **1a**. Yield: 72%. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 8.88 (d, 1 H, *J* = 5.3 Hz), 8.38 (d, 1 H, *J* = 8.1 Hz), 7.81-7.76 (m, 3 H), 7.65-7.52 (m, 5 H), 7.18 (d, 1 H, *J* = 1.9 Hz), 7.08 (d, 1 H, *J* = 2.1 Hz), 6.51 (d, 1 H, *J* = 13.0 Hz), 6.12 (d, 1 H, *J* = 13.0 Hz), 3.92 (s, 3 H), 3.86 (s, 3 H). MS-FAB(+): *m*/*z* 549.1 (M-OTf). Elemental Analysis: calcd for $C_{23}H_{20}F_3N_5O_3PtS•H_2O$: C, 38.55; H, 3.09; N, 9.77; found: C, 38.23; H, 3.00; N, 9.47.

2b [Pt^{II}(bzq)(bisNHC^{2C4})]OTf



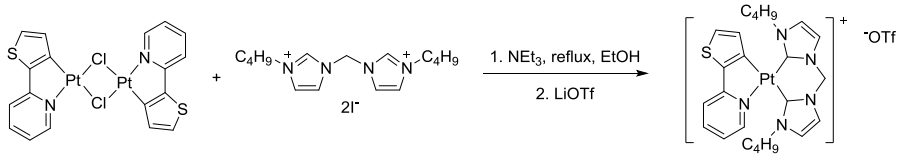
The synthesis is similar to **1a**. Yield: 74%. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 8.85 (d, 1 H, *J* = 5.3 Hz), 8.38 (d, 1 H, *J* = 8.1 Hz), 7.87 (d, 1 H, *J* = 1.9 Hz), 7.83 (m, 2 H), 7.67-7.55 (m, 5 H), 7.18 (d, 1 H, *J* = 2.0 Hz), 7.08 (d, 1 H, *J* = 2.1 Hz), 6.51 (d, 1 H, *J* = 13.0 Hz), 6.13 (d, 1 H, *J* = 12.9 Hz), 4.54 (m, 1 H), 4.35-4.12 (m, 2 H), 4.08 (m, 1 H), 1.72-1.60 (m, 4 H), 1.23-0.95 (m, 4 H), 0.78 (m, 6 H). MS-FAB(+): *m*/*z* 633.2 (M-OTf). Elemental Analysis: calcd for $C_{29}H_{32}F_3N_5O_3PtS•H_2O•CH_3CN$: C, 44.23; H, 4.43; N, 9.98; found: C, 44.13; H, 4.16; N, 10.01.

3a [Pt^{II}(thpy)(bisNHC^{2Me})]OTf



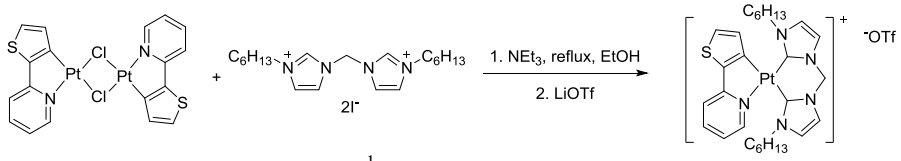
The synthesis is similar to **1a**. Yield: 68%. ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.51 (d, *J* = 5.5 Hz, 1H), 8.02 (t, *J* = 7.7 Hz, 1 H), 7.70-7.72 (m, 4 H), 7.48 (d, *J* = 13.5 Hz, 2 H), 7.22 (t, *J* = 6.5 Hz, 1 H), 7.01 (d, *J* = 4.6 Hz, 1 H), 6.20 (d, *J* = 13.3 Hz, 1 H), 6.12 (d, *J* = 13.2 Hz, 1 H), 3.78 (s, 3 H), 3.75 (s, 3 H). MS-FAB(+): *m*/*z* 531.0 (M-OTf). Elemental Analysis: calcd for $C_{19}H_{18}F_3N_5O_3PtS_2•2H_2O$: C, 31.85; H, 3.09; N, 9.77; found: C, 32.12; H, 2.89; N, 10.02.

3b [Pt^{II}(thpy)(bisNHC^{2C4})]OTf



The synthesis is similar to **1a**. Yield: 72%. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 8.33 (d, 1 H, *J* = 5.1 Hz), 7.85-7.78 (m, 3 H), 7.48 (d, 1 H, *J* = 7.9 Hz), 7.40 (d, 1 H, *J* = 4.7 Hz), 7.09 (d, 1 H, *J* = 2.0 Hz), 7.06 (m, 1 H), 7.01 (d, 1 H, *J* = 2.1 Hz), 6.93 (d, 1 H, *J* = 4.6 Hz), 6.58 (d, 1 H, *J* = 13.0 Hz), 5.99 (d, 1 H, *J* = 12.9 Hz), 4.45 (m, 1 H), 4.21-3.98 (m, 2 H), 3.96 (m, 1 H), 1.79-1.59 (m, 4 H), 1.26-0.95 (m, 4 H), 0.80 (m, 6 H). MS-FAB(+): *m/z* 615.2 (M-OTf). Elemental Analysis: calcd for $C_{25}H_{30}F_3N_5O_3PtS_2$•$3H_2O$: C, 36.67; H, 4.43; N, 8.55; found: C, 36.61; H, 4.12; N, 8.55.

3c [Pt^{II}(thpy)(bisNHC^{2C6})]OTf



The synthesis is similar to **1a**. Yield: 65%. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 8.34 (d, 1 H, *J* = 5.2 Hz), 7.89 (d, 1 H, *J* = 2.0 Hz), 7.82 (m, 2 H), 7.49 (d, 1 H, *J* = 7.9 Hz), 7.41 (d, 1 H, *J* = 4.6 Hz), 7.08 (d, 1 H, *J* = 2.0 Hz), 7.05 (m, 1 H), 7.01 (d, 1 H, *J* = 2.1 Hz), 6.94 (d, 1 H, *J* = 4.3 Hz), 6.72 (d, 1 H, *J* = 13.0 Hz), 6.00 (d, 1 H, *J* = 12.9 Hz), 4.37 (m, 1 H), 4.15 (m, 1 H), 4.09 (m, 1 H), 3.94 (m, 1 H), 1.68 (m, 4 H), 1.25-1.02 (m, 12 H), 0.79 (m, 6 H). MS-FAB(+): *m/z* 671.2 (M-OTf). Elemental Analysis for $C_{29}H_{38}F_3N_5O_3PtS_2$•$H_2O$: calcd for C, 41.52; H, 4.81; N, 8.35; found: C, 41.81; H, 4.82; N, 8.37.

Biological Study

Stability towards physiological thiols

UV-vis absorption experiment

1×PBS (containing 5% CH_3CN, v/v) was degassed with nitrogen for 5 min. Then GSH solid (final concentration 2 mM) and **1a** (final concentration 20 μM) were dissolved in the mixed solvent and the solution was bubbled with nitrogen for another 5 min. UV-vis absorption was detected at different time points.

^{1}H NMR experiment

The solution of D_2O (phosphate buffer, 10 mM, pH = 7.4, 10% d_6-DMSO, v/v) was degassed with nitrogen. Then **1a** and 2-fold GSH were added to the solution and the ^{1}H NMR spectra of the mixture were recorded on a Bruker 400 MHz spectrometer at different time points.

Photo-physical properties and application in protein binding and cell imaging

Absorption and emission

Solutions for photo-physical studies were degassed by using a high vacuum line in a two-compartment cell with five freeze-pump-thaw cycles. The emission quantum yield was measured with $[Ru(bpy)_3](PF_6)_2$ (Φ = 0.062) as reference. The emission lifetime measurements were performed on a Quanta Ray DCR-3 pulsed Nd:YAG laser system. Errors for λ values (±1 nm), τ (±10%), and Φ (±10%) are estimated.

Emission responses towards different analytes

The Pt(II) complexes were firstly dissolved in DMSO at room temperature to afford the probe stock solution (10 mM), and then the stock solution was added to 1×PBS : DMSO = 19:1 to a final concentration of 20 μM. The stock solutions of different analytes (BSA, ctDNA, Met, Lys, Asp, Ser, $CaCl_2$, $MgSO_4$, $NaHCO_3$) were prepared to a high concentration based on their solubility. Then aliquots of the stock solutions were added into the solutions of Pt(II) complexes. The resulting solution was shaken well. After 5 min, the emission spectra were recorded. The emission quantum yields and emission lifetimes of **1c** and **3c** upon binding with 0.5 equivalent of BSA were measured without degassing the solvent.

Absorption-titration experiment

Absorption titration experiment was performed according to a reported procedure.[4] The absorption spectra of a solution of **1c** in PBS (with 5% CH_3CN) was recorded and the solution was added with the aliquots of stock solution of ctDNA (10 mM) and the absorption spectra were recorded after equilibration for 1 min per aliquot until saturation point was almost reached. The binding constant was determined by applying the Scatchard equation:

$$[DNA]/\Delta\varepsilon_{ap} = [DNA]/\Delta\varepsilon + 1/(\Delta\varepsilon \times K_b),$$

where $\Delta\varepsilon_{ap} = |\varepsilon_A - \varepsilon_F|$ where $\varepsilon_A = A_{obs}/[complex]$, and $\Delta\varepsilon = |\varepsilon_B - \varepsilon_F|$ where ε_B and ε_F correspond to the extinction coefficients of the DNA-bound and -unbound complex, respectively. Plot of $[DNA]/\Delta\varepsilon_{ap}$ versus [DNA] gave a slop equalling to $1/\Delta\varepsilon$ and a y intercept equalling to $1/(\Delta\varepsilon \times K_b)$, and K was obtained from the ratio of the slop to the y-intercept.

Fluorescence quenching experiment

Fluorescence quenching experiment was followed with a reported procedure.[5] A solution of BSA (10 μM in PBS containing 5% CH_3CN) was excited at $\lambda = 280$ nm and the emission spectrum was recorded. Then the solution was added with the aliquots of stock solution of **1c** (10 mM) and the emission spectra were recorded at the same excitation wavelength after equilibration for 1 min per aliquot until saturation point was almost reached. The binding constant was determined by applying following equation

$$\log[(I_0 - I)/I] = \log K + n\log[Q]$$

where I_0 and I are the fluorescence intensity of BSA without and with **1c**, respectively; [Q] is **1c** concentration. Plot of $\log[(I_0 - I)/I]$ versus log[Q] gave the y-intercept equalling to log*K*, and the binding constant can be obtained accordingly.

Fluorescence microscopic examination

HeLa cells (2×10^5 cells) were seeded in a one chamber slide (Nalgene; Nunc) with culture medium (2 mL per well) and incubated at 37 °C in a humidified atmosphere of 5% CO_2/95% air for 24 h. After treating with **1c** or **3c** (5 μM) and ER-Tracker™ (1 μM) or Lysotracker® (100 nM) or Mitotracker® (50 nM) for 10 min, cells were directly exposed for fluorescent imaging without removing the old medium. Correlation analysis was done by using ImageJ following a reported procedure.[6]

Anticancer properties

Cell lines and growth inhibitory assay

The cell lines were maintained in cell culture media (minimum essential medium for HeLa, MCF-7, HepG2, MIHA; and dulbecco's modified eagle medium for SUNE1 and HONE1, Roswell Park Memorial Institute (RPMI) 1640 medium for HCC827 and H1975) supplemented with 10% fetal bovine serum, 100 U/mL penicillin, and 100 μg/mL streptomycin at 37 °C humidified atmosphere with 5% CO_2. Cell growth inhibitory effects of the platinum(II) complexes and cisplatin were determined by MTT cytotoxicity assay. Briefly, drug treated cells were incubated with MTT for 4 h at 37 °C in a humidified atmosphere of 5% CO_2 and were subsequently lysed in solubilizing solution. Cells were then maintained in a dark, humidified chamber overnight. The formation of formazan was measured by using a microtitre plate reader at 580 nm. Growth inhibition by a drug was evaluated by IC_{50} (concentration of a drug causing 50% inhibition of cell growth). Each growth inhibition experiment was repeated at least three times and results were expressed as means ± standard deviation (SD).

Lipophilicity determination

Lipophilicity was determined according to a modified procedure.[7] In general, 300 μL saturated *n*-octanol with sodium chloride was mixed with 300 μL aqueous solution with 0.9% NaCl (w/v), and then the mixture was added with each platinum complex (50 μM) and was further shaken for 1 h at 60 rpm on the shaker. Samples were centrifuged and 50 μL of each phase was added to 300 μL of 70% HNO_3. The sample was digested overnight and diluted to 50-200 fold with mini-Q water. The content

of the platinum complex in each phase was determined by inductively coupled plasma-mass spectrometry (ICP-MS). LogP was calculated as the logarithmic ratio of the concentrations of the platinum complex in the *n*-octanol and aqueous phases.

Cell transfection and fluorescence microscopic analysis

Cell transfection was performed according to a previously reported procedure.[8] HeLa cells (2×10^5) were cultured in MEM (without antibiotics) supplemented with 10% FBS in 35 mm glass-bottomed microwell dishes and incubated at 37 °C in a humidified atmosphere of 5% CO_2/95% air for 24 h. Then plasmid DNA of RFP-ER (0.4 μg/mL) and YFP-ER (0.4 μg/mL) were separately transfected into cells following Lipofectamine 2000 protocol. After incubation for another 24 h, the old medium was replaced with fresh MEM containing 5 μM of **1c**. The cells were then examined with the above mentioned fluorescence microscopic examination procedure.

Western-blot analysis

HeLa cells (1×10^6 cells) were seeded in 10 cm tissue-culture dishes with culture medium (10 mL per well) and incubated at 37 °C in a humidified atmosphere of 5% CO_2/95% air for 24 h, then treated with different concentrations of **1c** for different time. After washing with cold PBS for three times, cells were lysed in radio-immunoprecipitation assay (RIPA) buffer (500 μL, 1% Trition X-100, 10% deoxycholate, 50 mM Tris-HCl, *p*H 7.5, 150 mM NaCl, 0.1% SDS, 0.1 mm PMSF, 10 μg/mL leupeptin, 10 μg mL^{-1} aprotinin) at 0 °C. After centrifugation, the supernatants were collected. The cellular protein content was quantified by the DC Protein Assay (Bio-Rad). For detection, samples (15-45 μg/lane) were fractionated on a 12.5% SDS–PAGE in a Tris-Glycine running buffer and blotted on polyvinylidene fluoride (PVDF) membranes. The PVDF membranes were blocked overnight at room temperature in TBST containing 5% BSA powder. Afterwards, the blots were incubated at room temperature for an hour with the primary antibody, which was diluted in TBST containing 5% BSA powder. After washing with TBST three times, the membranes were then incubated with the respective secondary antibody for 2 h. Detection was performed by using the chemiluminescence procedure (ECL, Amersham).

Mitochondrial membrane depolarization assay

HeLa cells (2×10^5, 2 mL MEM) were seeded in 6-well plated and incubated at 37 °C in a humidified atmosphere of 5% CO_2/95% air for 24 h. Then the cells were treated with **1c** (5 or 10 μM) for 2 h. Afterwards, the media were removed and the cells were washed with PBS for 3 times. The cells were stained with JC-1 (5 μM) for another 20 min. After removing the old media and washing with PBS for 3 times, the cells in PBS were observed under fluorescence microscope. For positive control, carbonyl cyanide 3-chlorophenylhydrazone (CCCP, 50 μM) and JC-1 (5 μM) were co-incubated with HeLa cells for 20 min and examined with fluorescence microscope.

Determination of photo-toxicity

Photo-toxicity was determined according to a modified procedure.[9] Cells were seeded in a 96-well flat-bottomed microplate at 4×10^3 cells per well in 100 μL MEM containing 10% FBS and incubated for 24 h in a humidified atmosphere of 5% CO_2/95% air. Complexes **3a**, **3b** and **3c** were added to each well with serial dilution. The cells were incubated in the dark for 1 h to allow uptake of the complexes and then exposed to broadband visible light (2.8 mW/cm^2) for another 1 h. After further in the dark for 22 h, the cell viability was determined according to the above mentioned MTT assay.

Supporting figures and tables

Fig. S1 UV-vis absorption spectra of **1a** (20 μM) in PBS (containing 5% CH_3CN v/v, 2 mM GSH) at different time points.

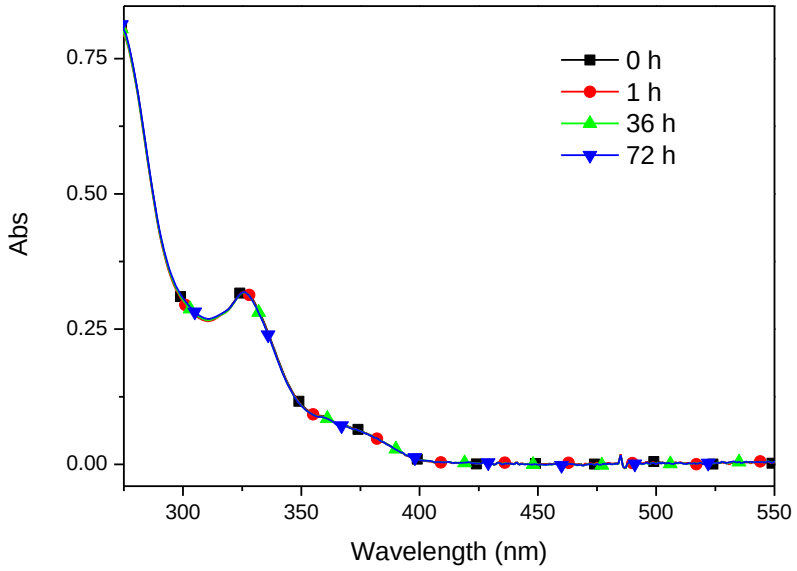


Fig. S2 ^{1}H NMR spectra of **1a** in D_2O (10 mM phosphate buffer, pH 7.4, 10% d_6-DMSO v/v) with 2 molar excess of GSH at different time points.

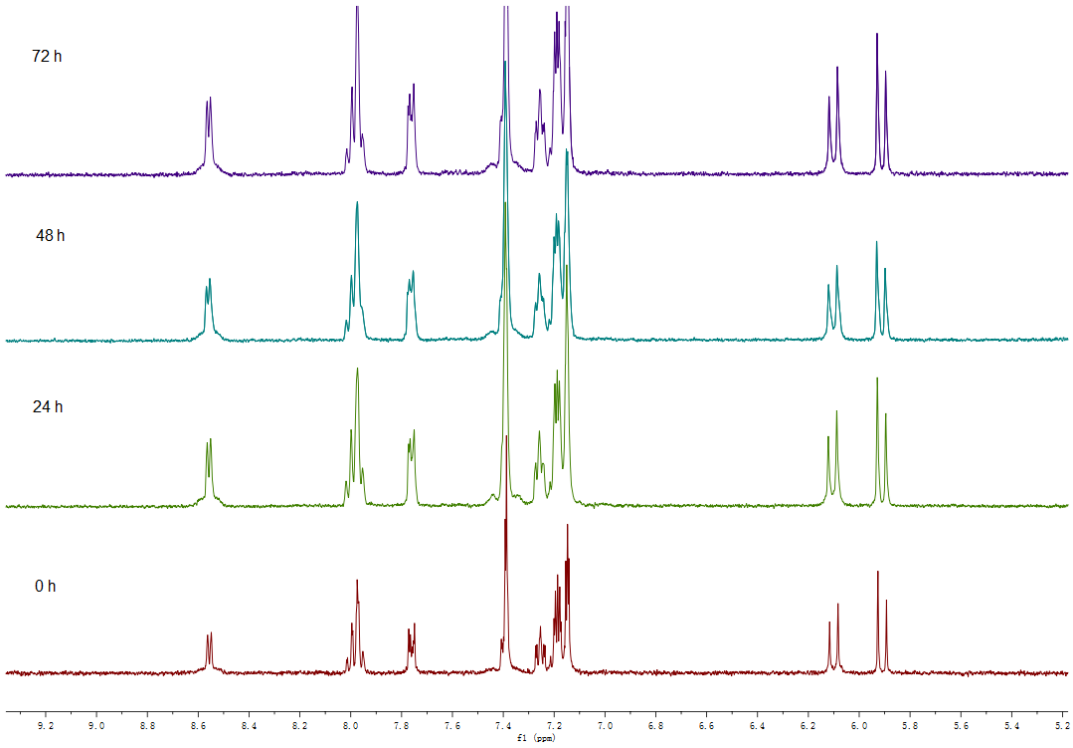


Fig. S3 Absorption and emission spectra of **1a**, **2a** and **3a** in degassed CH_2Cl_2.

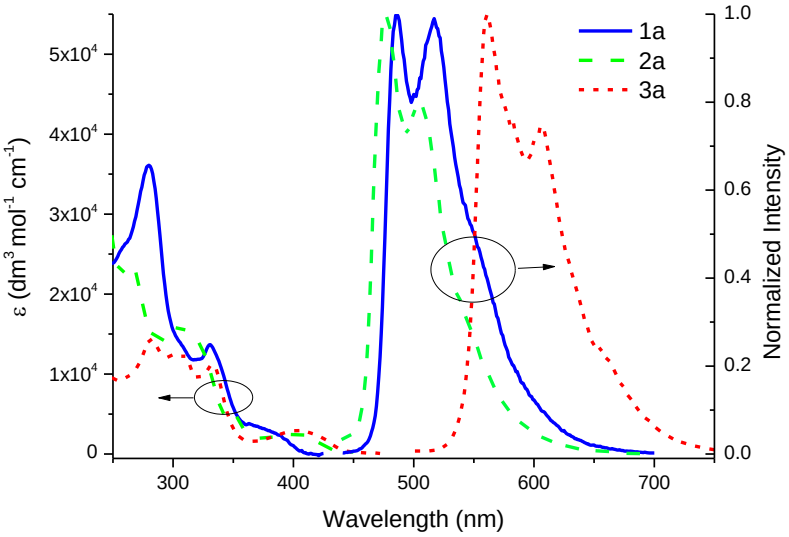


Table S1 Summary of emission data.

	λ_{max} (nm)*	quantum yield	τ (μs)
1a	486, 517	0.051	1.7
1b	486, 516	0.078	2.1
1c	485, 517	0.058	1.7
2a	477, 505	0.017	2.8
2b	476, 504	0.023	4.4
3a	562, 605	0.24	29.2
3b	561, 605	0.22	26.7
3c	560, 604	0.22	30.3

* **1a**-**1c** were excited at λ = 366 nm; **2a**-**2b** were excited at λ = 409 nm; **3a**-**3c** were excited at λ = 400 nm.

Fig. S4 Emission spectra of **1a** (a), **1c** (b), **3a** (c), **3c** (d) in PBS (containing 10% DMSO, v/v) before and after adding BSA. Insets: images of the platinum(II) complexes with/without BSA under UV irradiation. **1a** and **1c** were excited with λ = 370 nm; **3a** and **3c** were excited with λ = 394 nm. e) Peak emission intensity increasing ratios of **1c** (20 μM) towards different analytes. The concentration of BSA is 10 μM. The concentrations of other analytes are 1 mM.

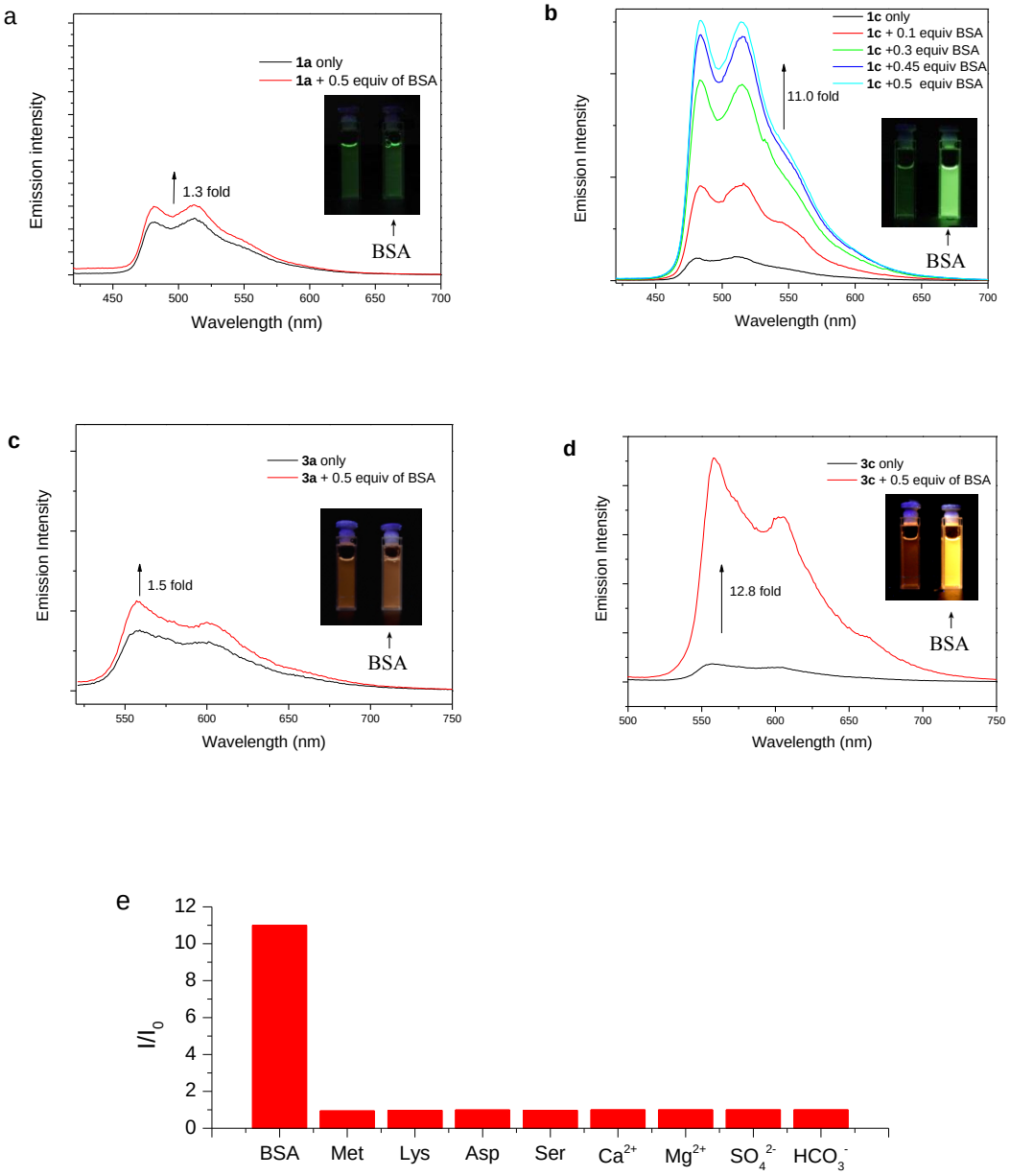


Fig. S5 a) Gel electrophoresis of 123 bp DNA ladder (50 μM base pairs) in 1.5% (w/v) agarose gel showing the mobility of the DNA in the absence (last lane, ve-), or the presence of **1c** (first lane) and ethidium bromide (EB, middle lane) in a 1:1 molar ratio. b) UV-vis spectral changes of **1c** in PBS (containing 5% CH_3CN, v/v) with increasing concentration of ctDNA at 292.8 K. Inset: plots of [ctDNA]/$\Delta\varepsilon_{ap}$ versus [ctDNA]. Absorbance was monitored at 326 nm.

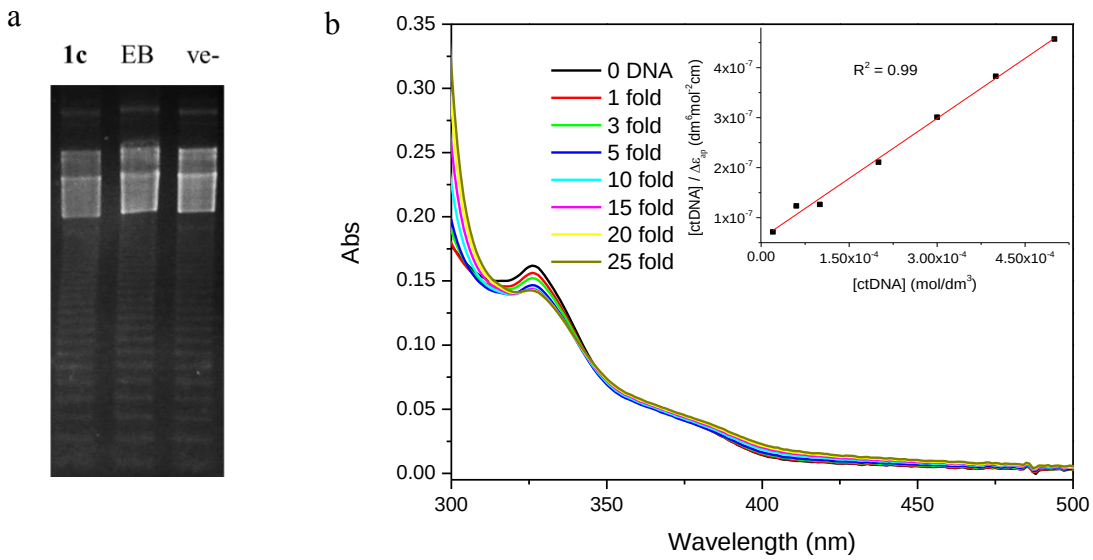


Fig. S6 Emission spectra of **1c** (20 μM, in PBS containing 5% CH_3CN, v/v) with increasing concentrations of ctDNA.

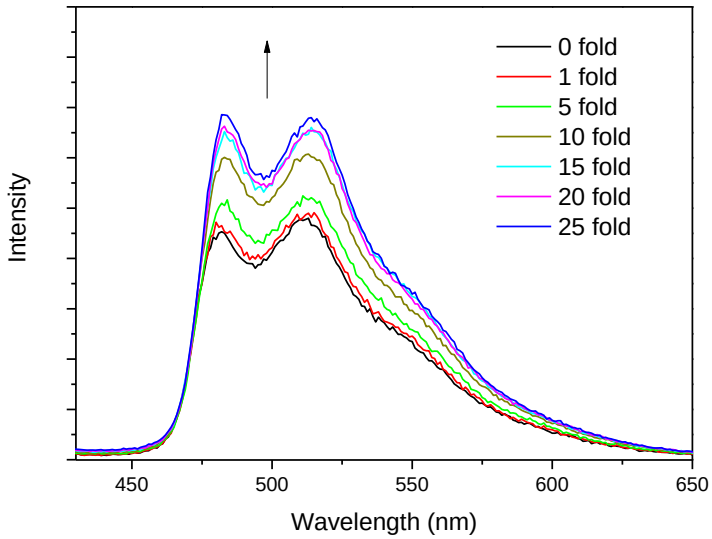


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Fig. S7 Emission spectral changes of BSA (10 μM, in PBS containing 5% CH_3CN, v/v) with increasing concentration of **1c**. The concentration of **1c** was varied from 0.0 to 30 μM. λ_{ex} = 280 nm.

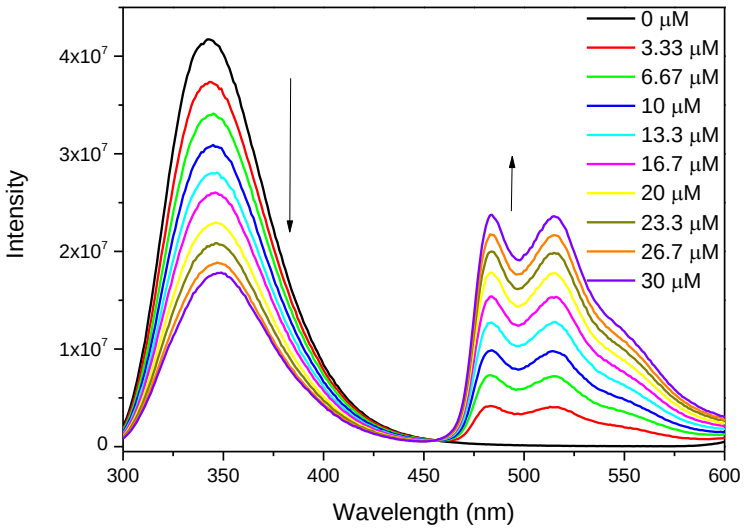

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Fig. S8 Fluorescence microscopic images of HeLa cells incubated with **1c** and ER-Tracker™, **1c** only, ER-Tracker™ only, or MEM only at different excitation wavelength.

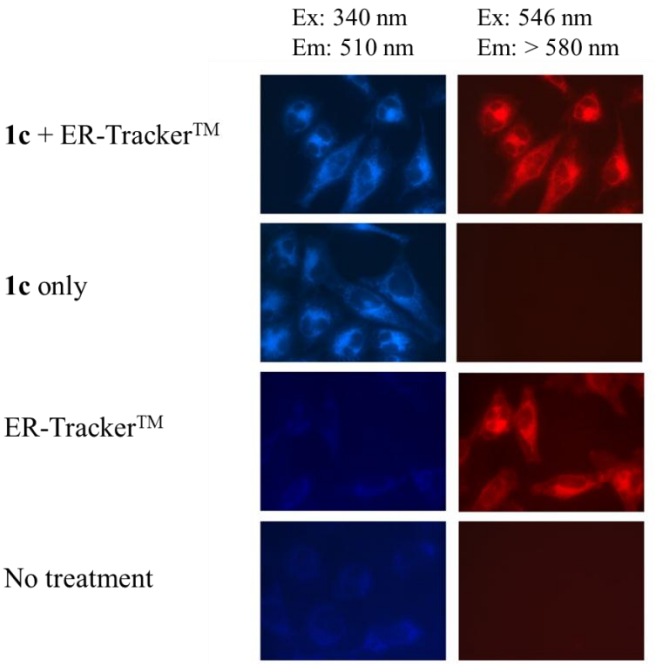

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Fig. S9 Fluorescence microscopic images of transfected HeLa cells after being treated with 5 μM of **1c** for 10 min. Top: images of **1c** treated HeLa cells with an ER-resident protein tagged yellow fluorescent protein (YFP-ER, top); bottom: images of **1c** treated HeLa cells with monomeric red fluorescent protein (mRFP, bottom). The respective excitation and emission condition are shown.

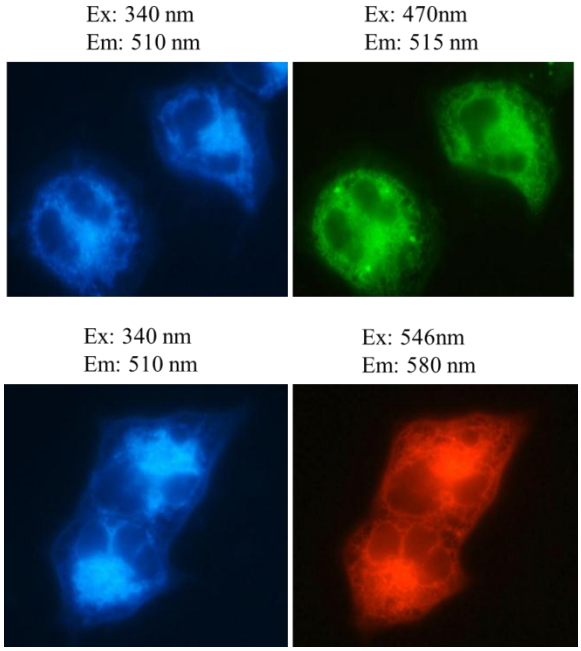

Fig. S10 Fluorescence microscopic images of HeLa cells incubated with **3c** and ER-Tracker™ (R = 0.90).

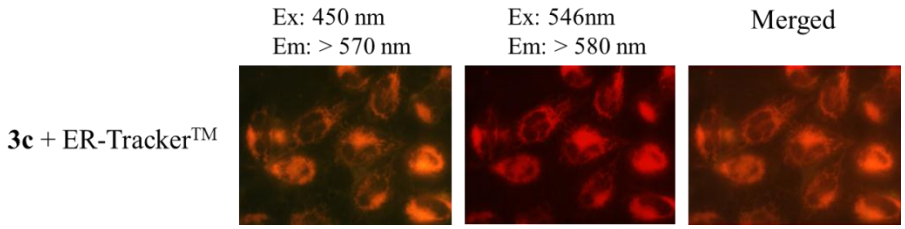

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Table S2 72 h cytotoxicity IC_{50} values (μM) of **1a**-**1c**, **2a**-**2b** and **3a**-**3c** in human carcinoma cell lines of HeLa, HONE1, SUNE1, MCF-7, HepG2, HCC827, H1975, and a non-tumorigenic liver cell of MIHA.

	HeLa	**HONE1**	**SUNE1**	**MCF-7**	**HepG2**	**HCC827**	**H1975**	**MIHA**
1a	3.79±1.05	2.55±0.35	3.07±0.99	52.2±5.4	42.6±3.4	12.0±1.72	5.58±1.34	4.09±1.57
1b	1.39±0.10	1.15±0.06	1.47±0.07	3.49±053	6.89±0.68	1.76±0.40	1.78±0.57	4.44±1.34
1c	0.68±0.30	0.52±0.05	0.62±0.04	0.66±0.03	1.59±0.14	0.72±0.11	0.45±0.11	0.81±0.12
2a	2.54±0.46	1.41±0.03	2.23±0.13	10.8±1.78	23.6±2.2	8.92±2.61	4.41±1.79	24.0±5.8
2b	0.91±0.10	0.83±0.20	1.35±0.09	1.52±0.10	2.50±0.33	1.11±0.15	0.64±0.02	1.35±0.05
3a	22.9±4.32	2.14±0.55	2.54±0.78	51.2±8.8	37.5±1.7	21.2±5.4	22.5±0.5	12.7±5.0
3b	2.14±0.56	1.14±0.05	1.74±0.56	2.91±0.07	3.32±0.25	2.50±0.51	1.76±0.85	2.06±0.22
3c	1.27±0.32	1.10±0.03	1.91±0.39	1.59±0.17	1.69±0.49	1.42±0.04	0.80±0.02	1.09±0.27
cisplatin	10.9±2.3	2.75±0.42	9.59±5.26	17.9±7.8	35.3±8.0	27.0±3.2	27.0±5.0	44.3±4.2

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Fig. S11 JC-1 staining of HeLa cells. Left: HeLa cell were treated with DMSO vehicle, **1c** (5 μM) and CCCP (carbonyl cyanide *m*-chlorophenyl hydrazine, a mitochondrial membrane potential disrupter, 50 μM) for 2 h, and then examined using fluorescence microscope with excitation at 470 nm. Right: JC1 fluorescence intensity ratio of I_{580nm}/I_{530nm} after treatment of HeLa cells with **1c**.

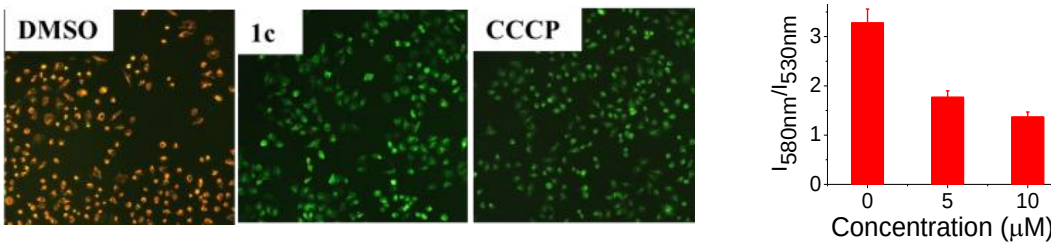

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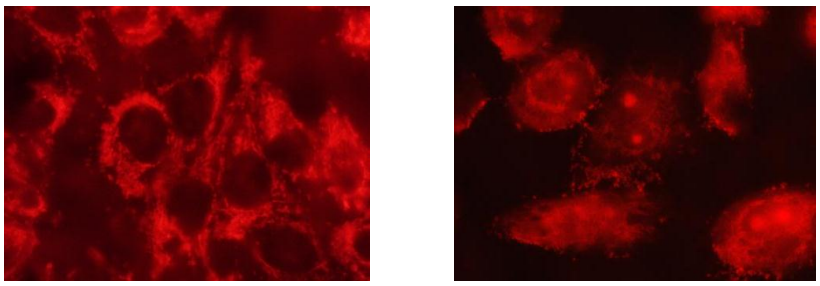
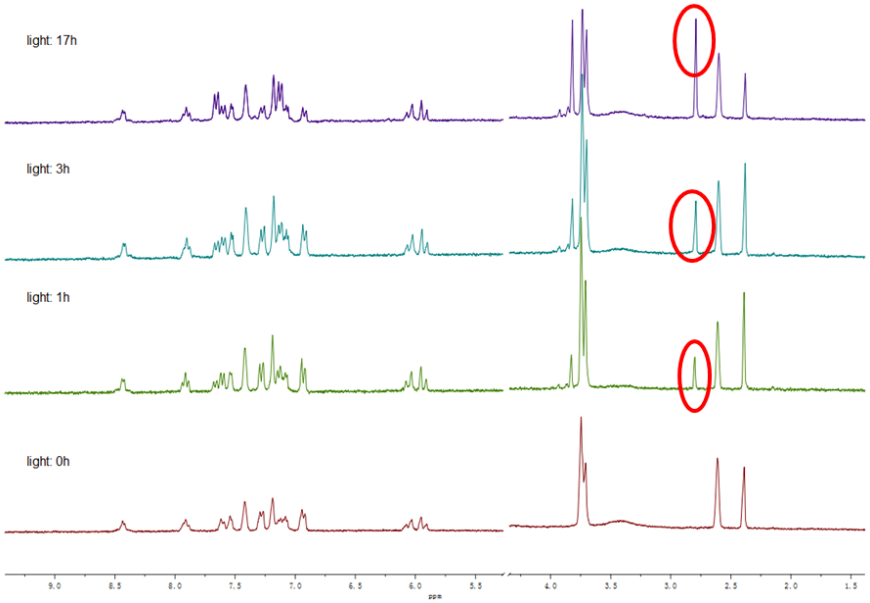
Fig. S12 Fluorescence microscopic images of HeLa cells treated without (left) or with (right) 5 μM **1c**. HeLa cells were stained with mitochondria specific Mitotracker®.



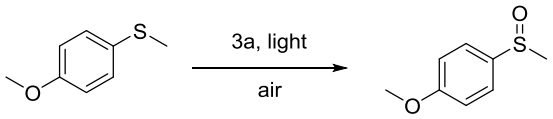
No treatment **1c**-treated

Fig. S13 a) ^{1}H NMR spectra of the mixture of **3a** and (4-methoxyphenyl)(methyl)sulfane in D_2O (pH 7.4, phosphate buffer, 10% d_6-DMSO) after exposing to 2.8 mW/cm^2 of visible light for different time. b) Proposed photo-oxidation reaction. c) ^{1}H NMR spectra of (4-methoxyphenyl)(methyl)sulfane in D_2O (pH 7.4, phosphate buffer, 10% d_6-DMSO) after exposing to 2.8 mW/cm^2 of visible light for different time.

a



b



c

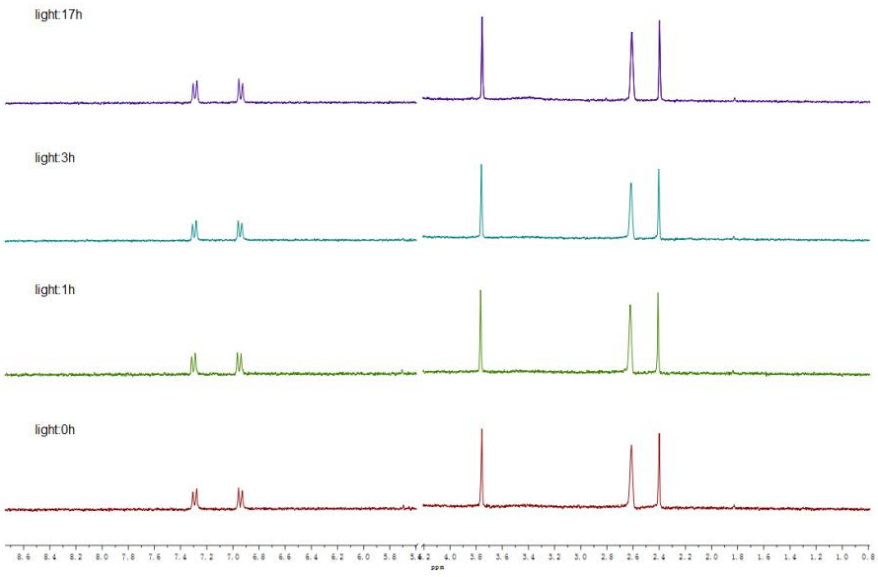


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Fig. S14 Emission spectra (a) and Uv-vis absorption spectra (b) of **3a** (20 μM, in PBS containing 5% CH_3CN, v/v) after exposing to visible light (λ > 400 nm, 2.8 mW/cm^2) for 24 h. λ_{ex} = 400 nm for emission spectra.

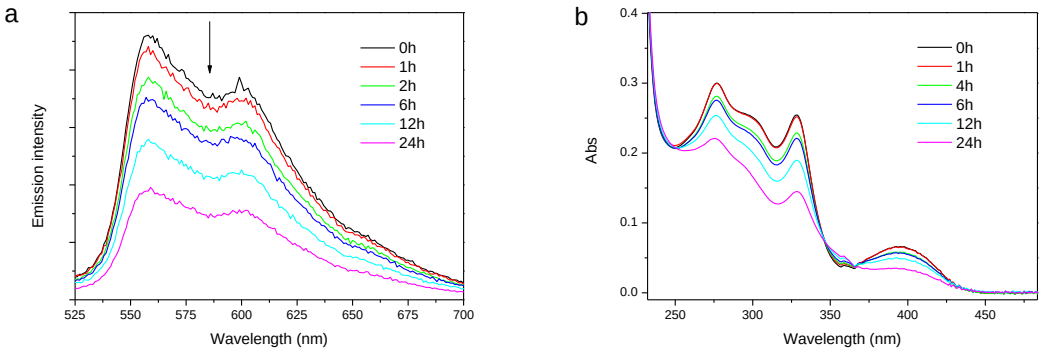

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Table S3 24 h cytotoxicity IC_{50} (μM) of **3a**–**3c** and cisplatin in human carcinoma cell lines of HeLa, MCF-7, HONE1, B16-F10, HepG2 and a non-tumorigenic liver cell of MIHA in the absence/presence of light.

	HeLa		**MCF-7**		**HONE1**		**B16-F10**		**HepG2**		**MIHA**	
	dark	light	dark	light	dark	light	dark	light	dark	light	dark	light
3a	59.6±5.4	2.11±0.70	152.6±23.9	7.25±0.99	54.0±10.0	1.63±0.84	59.4±12.1	5.63±0.45	>100	9.82±0.87	>100	31.3±4.0
3b	5.33±0.86	0.39±0.04	10.3±1.0	0.50±0.05	9.70±2.58	0.61±0.08	3.04±0.36	0.51±0.07	5.43±0.20	0.60±0.03	9.81±1.48	0.73±0.02
3c	2.92±0.02	0.29±0.03	5.52±0.16	0.40±0.01	4.45±0.73	0.41±0.15	2.18±0.54	0.39±0.03	3.99±0.14	0.47±0.05	5.15±0.47	0.62±0.04
cisplatin	31.8±2.1	37.7±3.8	123.1±11.8	122.2±17.1	39.9±8.41	55.5±24.7	100.1±11.7	92.4±12.4	>100	>100	>100	>100

Fig. S15 ^{1}H-^{1}H cosy NMR (500 MHz in MeOD, 298 K) spectrum of **1a**.

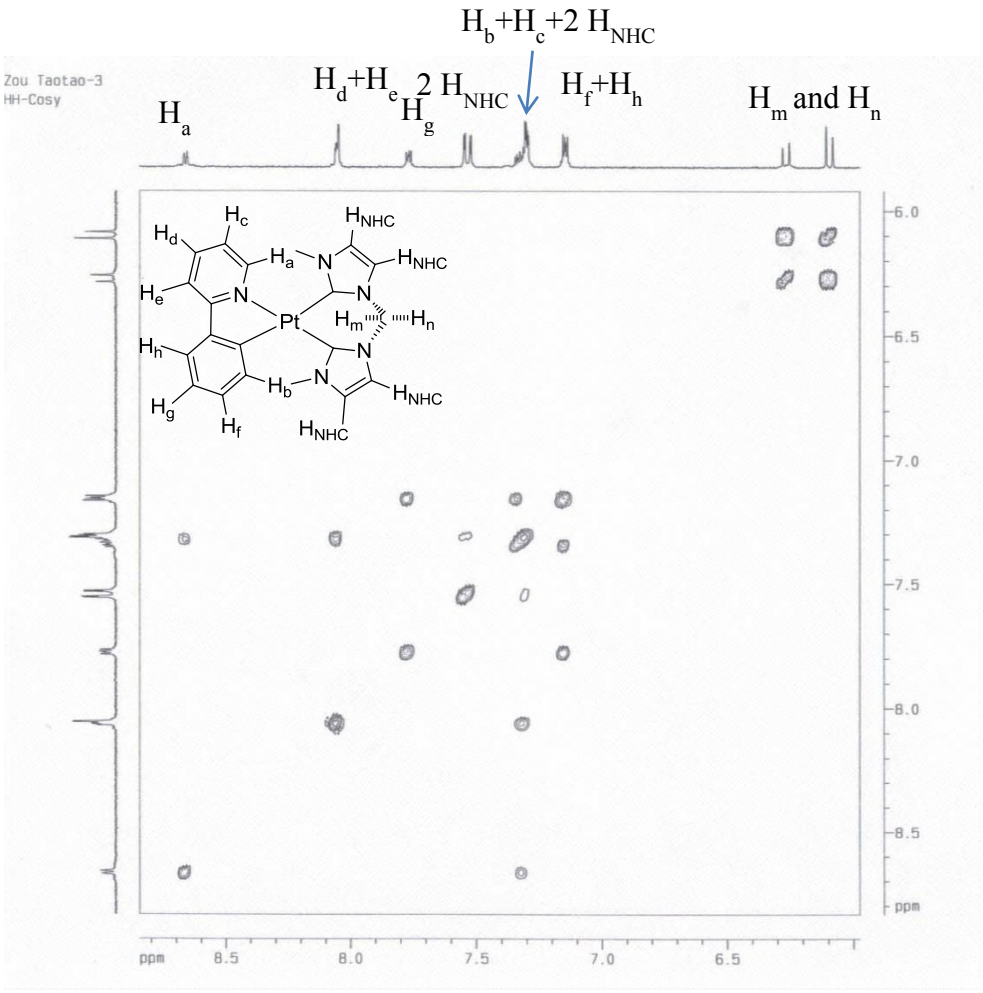
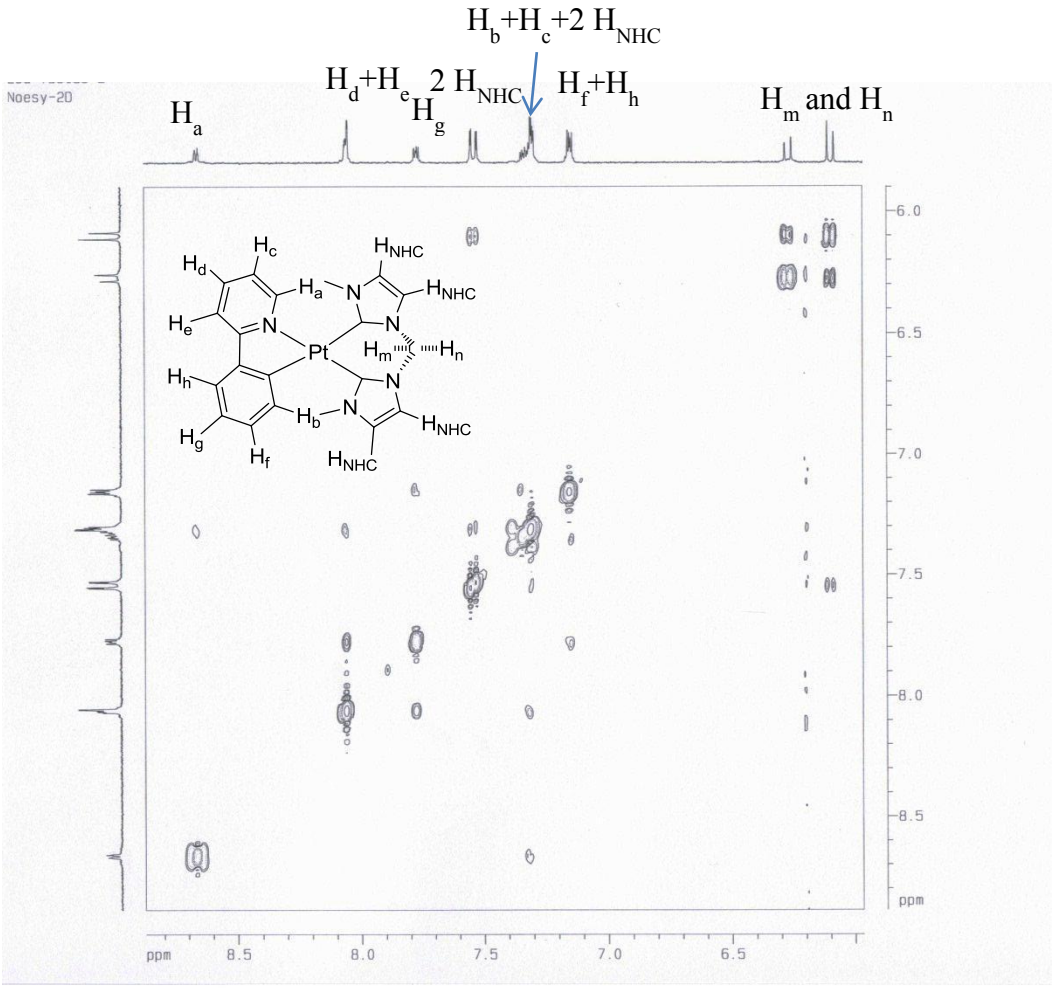


Fig. S16 ^{1}H-^{1}H noesy NMR (500 MHz in MeOD, 298 K) spectrum of **1a**.



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