Electronic Supplementary Material (ESI) for ChemComm.

Real-time in-situ monitoring via europium emission of the photo-release of antitumor cisplatin from a Eu-Pt complex

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Supporting Information

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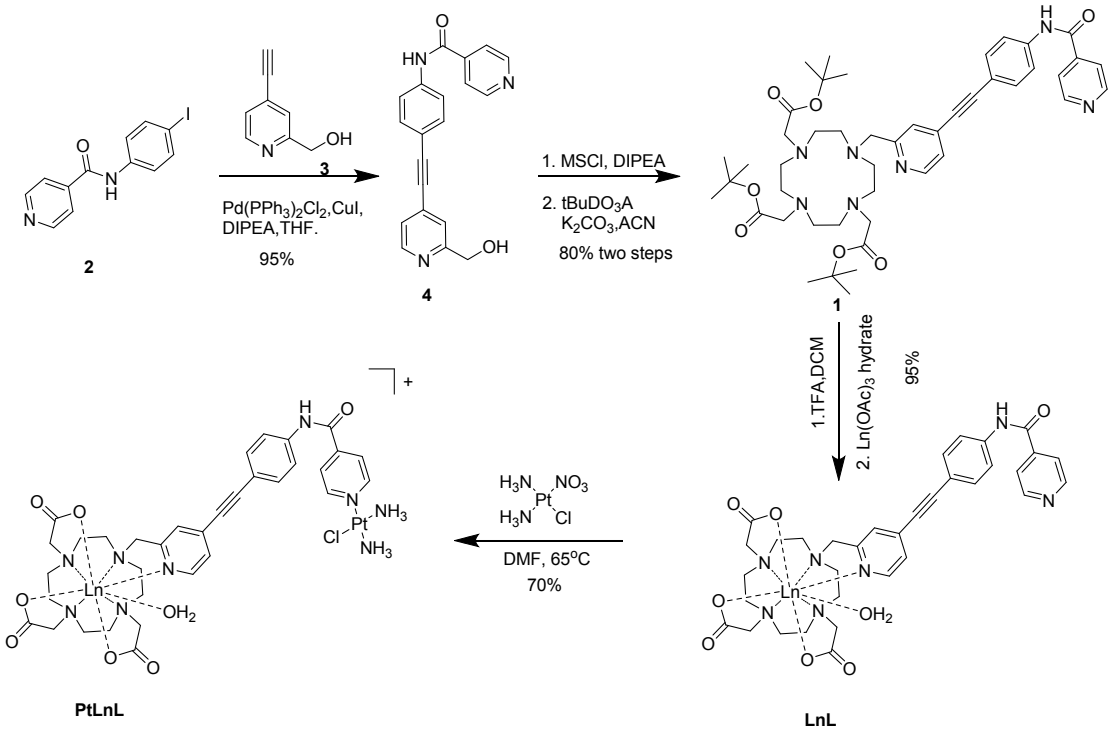
General Information about the compound synthesis.

Dried tetrahydrofuran (THF), dichloromethane (DCM), diisopropylamine (DIPA), acetonitrile (CH_3CN) and dimethylformamide (DMF) were dried over calcium hydride (CaH_2). All reactions were carried out with anhydrous solvents under nitrogen atmosphere, unless otherwise specified. All the reagents were obtained commercially with high quality and used without further purification. Reactions were monitored by thin-layer chromatography (TLC) on silica gel plates (0.25 mm, 60F-254) using UV light for visualization. Flash column chromatography was carried out on 200-300 mesh silica gel. ^1H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz (^1H: 400 MHz, ^{13}C: 100 MHz) spectrometer. The following abbreviations were used to depict the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, m = multiplet, br = broad. High resolution mass spectra were obtained using an ESI mass spectrometer.



Scheme S1. Synthetic scheme for **PtLnL** and **LnL** (**Ln** = **Eu** and **Gd**).

Synthesis of compound 2.

Isonicotinic acid (2.0 g, 16.2 mmol) was added into the solution of DMAP (5.9 g, 48.6 mmol) in dry DCM (200mL), followed by EDCI (4.6 g, 24.3mmol), after stirring about 10 min, 4-iodoaniline (3.9 g, 17.8 mmol) was added. The resulting solution was stirred for 12 h at rt under N_2 atmosphere. After that, the solvent was concentrated to 100 mL, white solids were collected as product compound **2** (1.2 g, ? mmol, 89%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.6 (s, 1H), 8.78 (d, *J* = 2 Hz, 2H), 7.84 (d, *J* = 2 Hz, 2H), 7.72 (d, *J* = 4 Hz, 2H), 7.62 (d, *J* = 4 Hz, 2H); ^{13}C NMR (DMSO-d_6, 100MHz) δ 164.1, 150.3, 141.7, 138.5, 137.4, 122.6, 121.6, 88.1.

Synthesis of compund 3.

Ethynyltrimethylsilane (2.7 ml, 20.74 mmol) was added into the solution of (4-bromopyridin-2-yl)methanol (3.0 g, 20.74 mmol), $Pd(PPh_3)_2Cl_2$ (112 mg, 0.16 mmol), CuI (60 mg, 0.32 mmol) and DIPEA (5 mL) in freshly distilled THF (50 mL), the resulting mixture was stirred at 45 ^{o}C for 6 h under N_2 atmosphere. Silica gel flash column chromatography (Hex/EA 2:1) of the concentrated residue gave a pale yellow oil. The oil-like compound was dissolved in MeOH, K_2CO_3 was added, and the resulting solution was stirred at rt for 1 h. The solid was filtered out and the filtrate was concentrated. Silica gel flash column chromatography (Hex/EA = 1:1) of the residue gave a white solid (2.20 g, 16.56 mmol, 80% in two steps) as the product. Melting point : 69–70^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.54 (d, *J* = 2 Hz, 1H), 7.37 (s, 1H), 7.28 (d, *J* = 2 Hz, 1H), 4.76 (s, 2H), 3.60 (br, 1H), 3.32 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 59.4, 148.3, 131.2, 124.8, 123.0, 82.2, 80.8, 63.9.

Synthesis of compund 4.

Compound **3** (0.23 g, 1.72 mmol) was added into the solution of compound **2** (0.84 g, 2.58 mmol), $Pd(PPh_3)_2Cl_2$ (36 mg, 0.052 mmol), CuI (20 mg, 0.104 mmol) and DIPEA (5 mL) in freshly distilled THF (50 mL), the resulting mixture was stirred at 45 ^{o}C for 6 h under N_2 gas. Silica gel flash column chromatography (DCM/MeOH 30:1) of the concentrated residue gave a pale yellow solid (0.54 g, 1.63 mmol, 95%) as the product. Melting point : 202–203^{o}C； ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.73 (s, 1H), 8.80 (dd, *J* = 4 Hz, 8 Hz, 2H), 8.52 (d, *J* = 2 Hz, 1H), 7.89 (d, *J* = 4 Hz, 2H), 7.86 (d, *J* = 2 Hz, 2H), 7.64 (d, *J* = 6 Hz, 2H), 7.54 (d, *J* = 2 Hz, 1H), 7.37 (dd, *J* = 4 Hz, 8 Hz 1H), 5.53 (t, *J* = 6 Hz, 1H), 4.58 (d, *J* = 4 Hz, 2H); ^{13}C NMR (DMSO-d_6, 100MHz): δ 164.4, 162.6, 150.3, 149.0, 141.7, 139.8, 132.5, 130.7, 123.2,121.6, 121.5, 120.3, 116.5, 93.4, 86.8, 64.0. HRMS *m/z* calcd. for $C_{20}H_{16}N_3O_2$ $[M+H]^+$ 330.1243, found 330.1239.

Synthesis of compund 1.

To a stirred solution of compound **4** (300 mg, 0.91 mmol) in anhydrous DCM (150 mL) DIPEA (1.59 mL, 9.11 mmol) and methanesulfonyl chloride (0.22 mL, 2.73 mmol) were added. The resulting mixture was stirred at rt for 3 hours. The resulting solution was then washed with saturated $NaHCO_3$ solution, saturated NH_4Cl solution and saturated NaCl solution. The organic layer was dried with anhydrous Na_2SO_4, concentrated to give a pale yellow solid which was directly used in the next step without further purification. The pale yellow solid was dissolved in dry MeCN (50 mL). Tri-*tert*-butyl 2,2',2''-(1,4,7,10-tetraazacyclododecane-1,4,7-triyl)triacetate (*t*BuDO$_3$A, 0.50 g, 0.61 mmol) and anhydrous K_2CO_3 (1.26 g, 9.1 mmol) were added. The resulting mixture was stirred at 50 ^oC for 12 hours under N_2 gas. The solids were filtered off, and the filtrate was concentrated. Silica gel flash column chromatography (CH_2Cl_2: MeOH = 20:1) of the residue gave a pale yellow solid (378 mg, 0.46 mmol, 75%) as the product. Melting point : 170–172^oC; ^1H NMR ($CDCl_3$, 400 MHz): δ 10.64 (s, 1H), 8.75 (d, J = 4 Hz, 2H), 8.22 (d, J = 4 Hz, 4H), 8.17 (d, J = 4 Hz, 2H), 7.48 (d, J = 6 Hz, 2H), 7.31 (s, 1H), 7.24 (d, J = 4 Hz, 1H), 3.17-2.15 (m, 32H), 1.50 (s, 27H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.4, 164.5, 158.3, 150.0, 148.5, 141.3, 140.1, 132.7, 132.1, 125.0, 123.8, 122.4, 121.3, 116.6, 95.5, 85.5, 82.0, 58.5, 56.1, 55.2, 54.2, 50.0, 42.5, 27.8, 27.7; HRMS *m/z* calcd. for $C_{46}H_{64}N_7O_7$ $[M+H]^+$ 826.4867, found 826.4860.

Synthesis of Complexes LnL (Ln = Eu and Gd).

To a solution of compound **1** (100 mg, 0.12 mmol) in DCM (2 mL), 2 mL of trifluoroacetic acid was added. The resulting solution was stirred for 24 hours at rt. The solvent was removed under vacuum, the residue was dissolved in 1 mL of methnol. The solution was added into 50 mL of cool ethyl ether. The yellow solid was collected and then dissolved in MeOH/H_2O (v:v = 1:1). Europium(III) nitrate pentahydrate (54 mg, 0.13 mmol) was then added. The resulting solution was maintained in a pH range 6.0-6.5 with NaOH solution (0.4 M) and stirred at rt for 24 hours. The solvents were removed under vacuum, the residue was dissolved in 1 mL of methanol and poured into diethyl ether (50 mL). The precipitate was filtered and washed with diethyl ether, dried under vacuum at rt. **EuL** was obtained as a white solid (94 mg, 0.11 mmol, yield = 95%). HRMS (+ESI) m/z calcd. for $C_{34}H_{37}EuN_7O_7$ $[M+H]^+$ 808.1967, found 808.1941, for $C_{34}H_{36}EuN_7NaO_7$ $[M+Na]^+$ 830.1786, found 830.1641. HPLC characterization: retention time = 11.92 min. (Table S1 and Figure S1)

GdL was obtained with a similar procedure showed above. **GdL** (95 mg, 0.11 mmol, yield = 95%). HRMS (+ESI) m/z calcd. for $C_{34}H_{37}GdN_7O_7$ $[M+H]^+$ 813.1995, found 813.2005, for $C_{34}H_{36}GdN_7NaO_7$ $[M+Na]^+$ 835.1815, found 835.1915. HPLC characterization: retention time = 11.78 min. (Table S1 and Figure S1)

Syntheisis of PtLnL (Ln = Eu, Gd)

cis-[$Pt(NH_3)_2Cl(DMF)$](NO_3) was prepared using the procedure described by Sadler et al.[S2] **EuL** or **GdL** in anhydrous DMF (1 mL) was added to the cis-[$Pt(NH_3)_2Cl(DMF)$](NO_3) solution and stirred at 65 °C in the dark for 16 hours. The solvent was removed under vacuum. The residue was dissolved in 3 mL of MeOH, followed with the filtration. The yellow unreacted cisplatin was filtered off. The filtrate was added into 50 mL of Et_2O, the precipitate formed was collected and re-dissolved in 3 mL of MeOH, which was then added into another 50 mL of Et_2O. The precipitate was collected and dried under vacuum at rt. The pale-yellow solid was afforded as the final product.

PtEuL 0.040 g, yield = 72%; HRMS (+ESI) m/z calcd. for $C_{34}H_{42}ClEuN_9O_7Pt$ [M-NO_3]$^+$ 1071.1756, found 1071.1743, for $C_{34}H_{43}ClEuN_9O_8Pt$ [M-NO_3-Cl+OH]$^+$ 1053.2095, found 1053.1546. HPLC characterization: retention time = 10.60 min. (Table S1 and Figure S1)

PtGdL 0.040 g, yield = 70%; HRMS (+ESI) m/z calcd. for $C_{34}H_{42}ClGdN_9O_7Pt$ [M-NO_3]$^+$ 1076.1784, found 1076.1821, for $C_{34}H_{43}ClGdN_9O_8Pt$ [M-NO_3-Cl+OH]$^+$ 1058.2123, found 1058.1654; HPLC characterization: retention time = 10.63 min. (Table S1 and Figure S1)

HPLC characterization of the complexes.

Table S1. Solvent gradient for HPLC

Time /min	0.05% TFA in water /%	0.05% TFA in CH_3CN /%
0	90	10
5	90	10
15	60	40
20	90	10

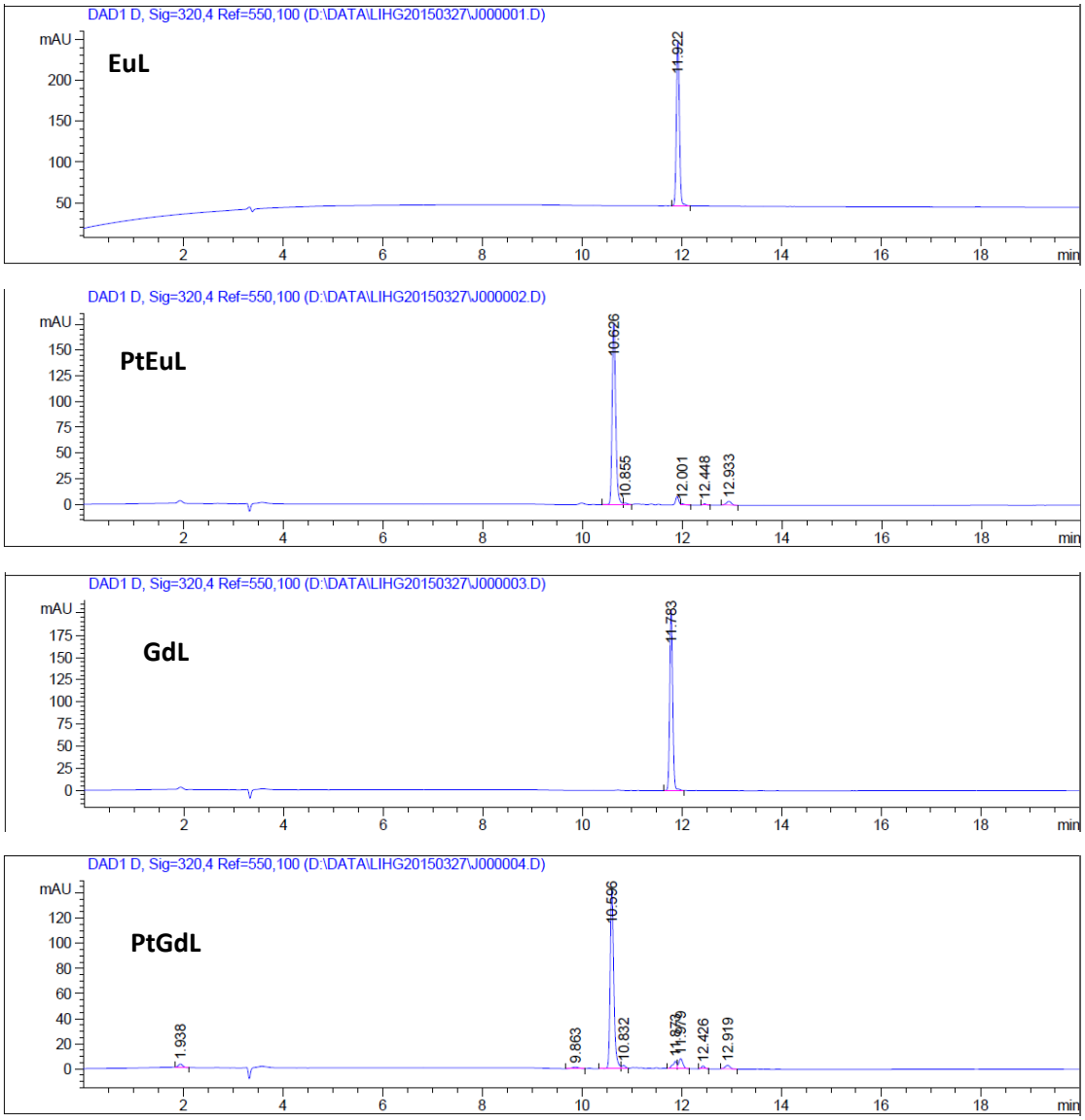


Fig. S1. HPLC chromatogram of the complexes. Elution conditions: column, Agilent ZORBAX SB-C18 (4.6 X 150 mm, particle size 5 μ); flow rate, 1.0 mL/min; gradient elution; detection wavelength, 320 nm. Retention time: **EuL**, 11.92 min; **PtEuL**, 10.60 min; **GdL**, 11.78 min; and **PtGdL**, 10.63 min.

HRMS characterization of the complexes LnL and PtLnL (Ln = Eu, Gd)

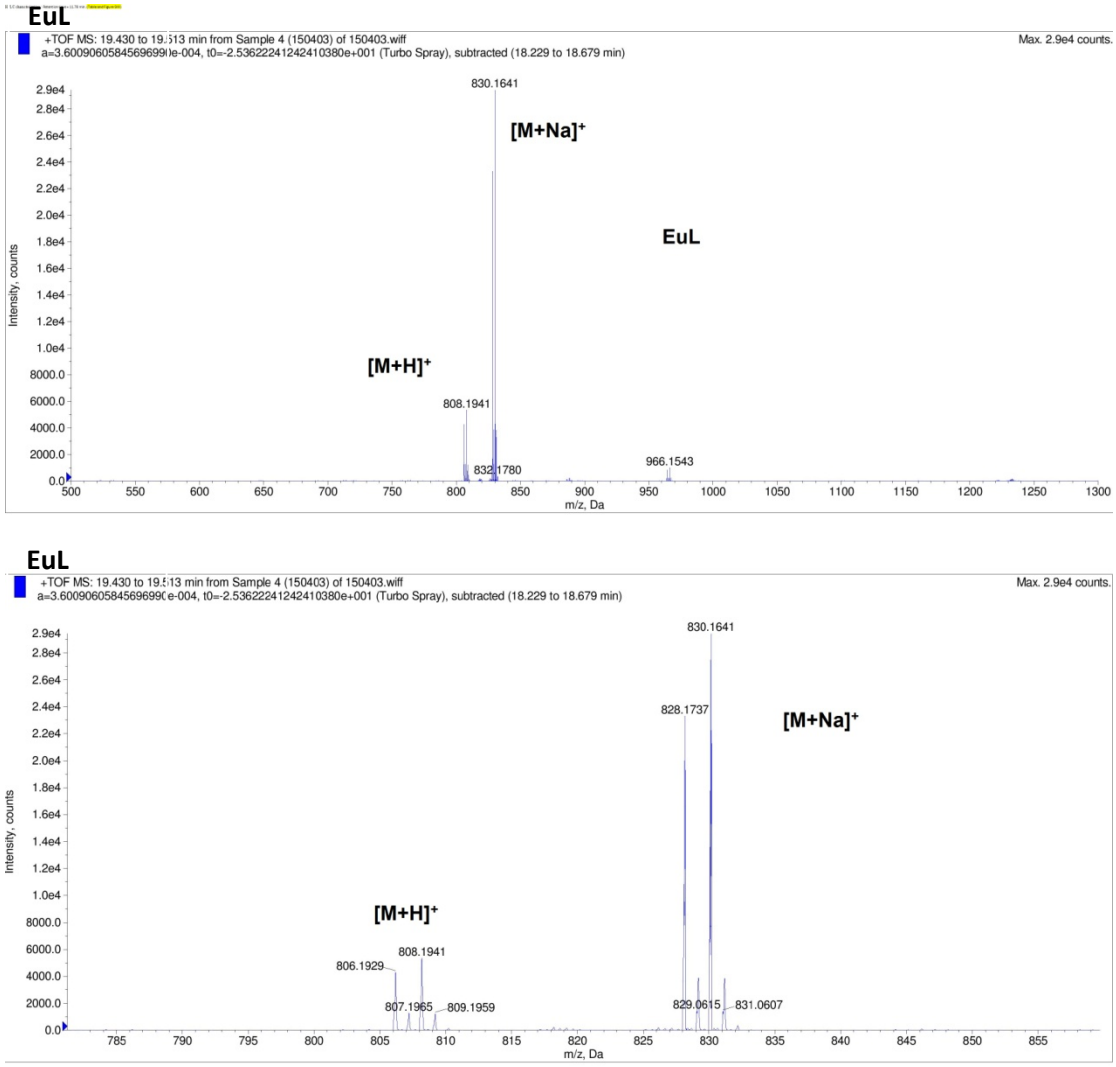
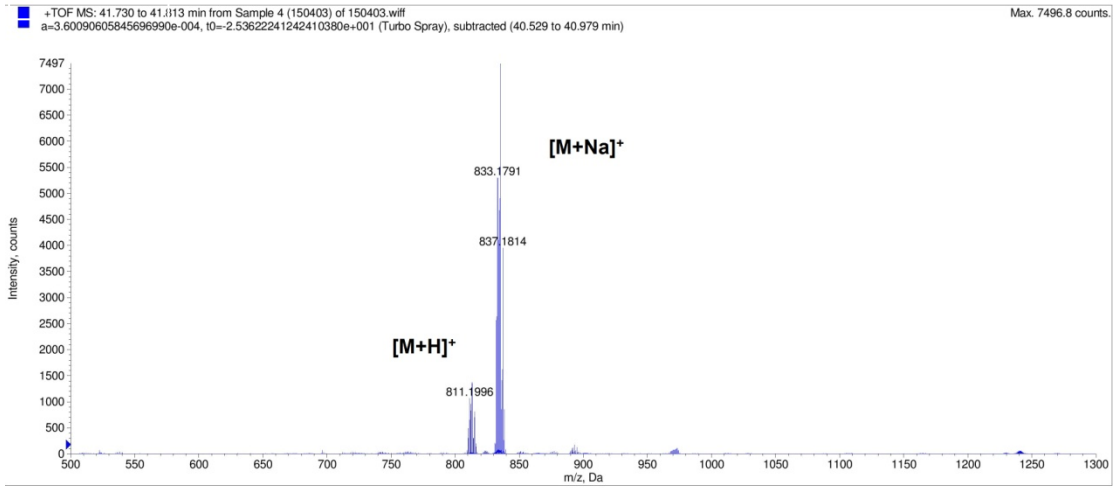


Fig. S2. HRMS spectra of **EuL.**

GdL



GdL

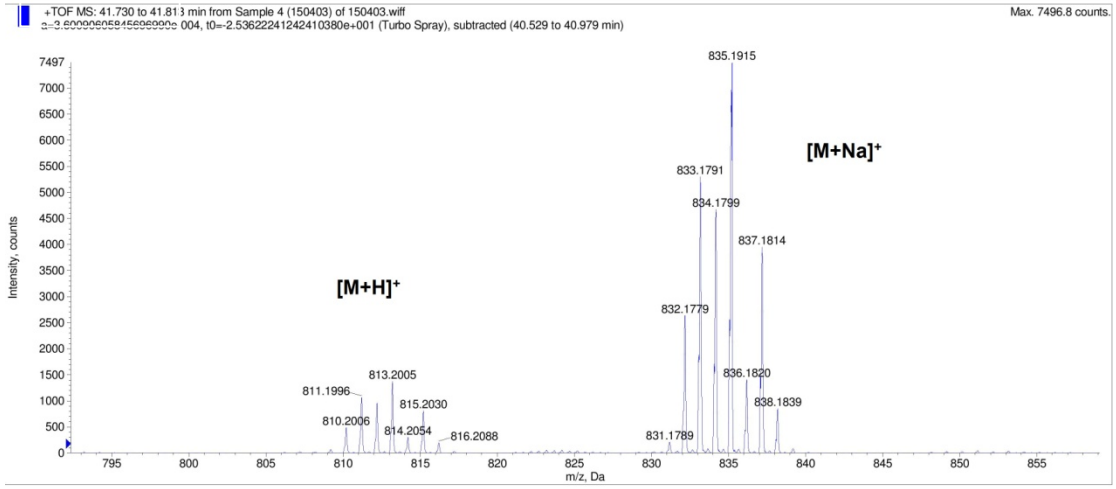
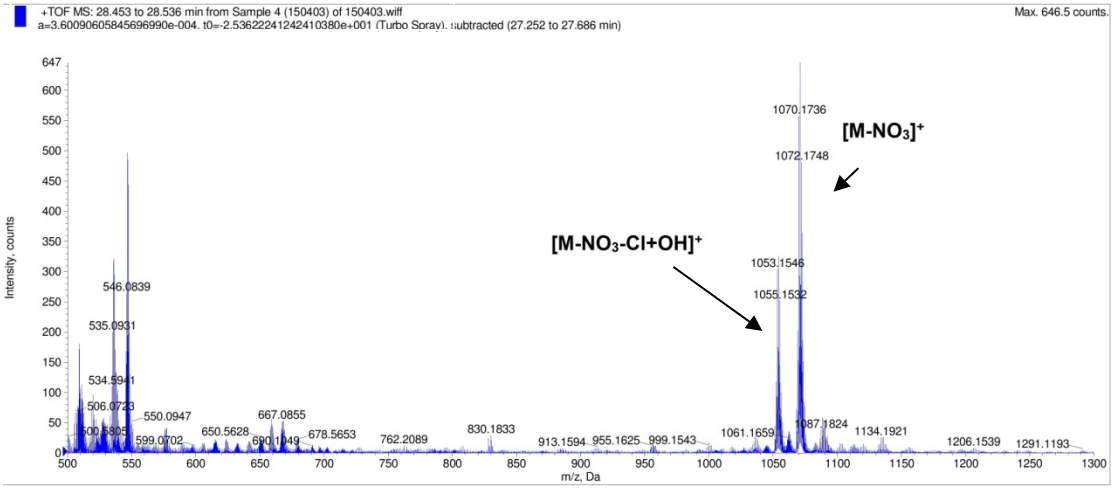


Fig. S3. HRMS spectra of **GdL.**

PtEuL



PtEuL

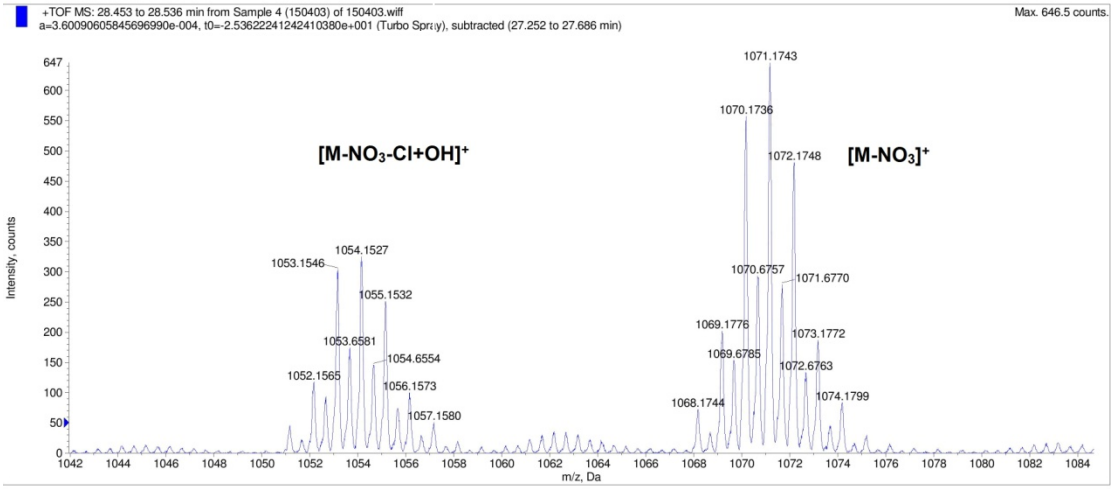
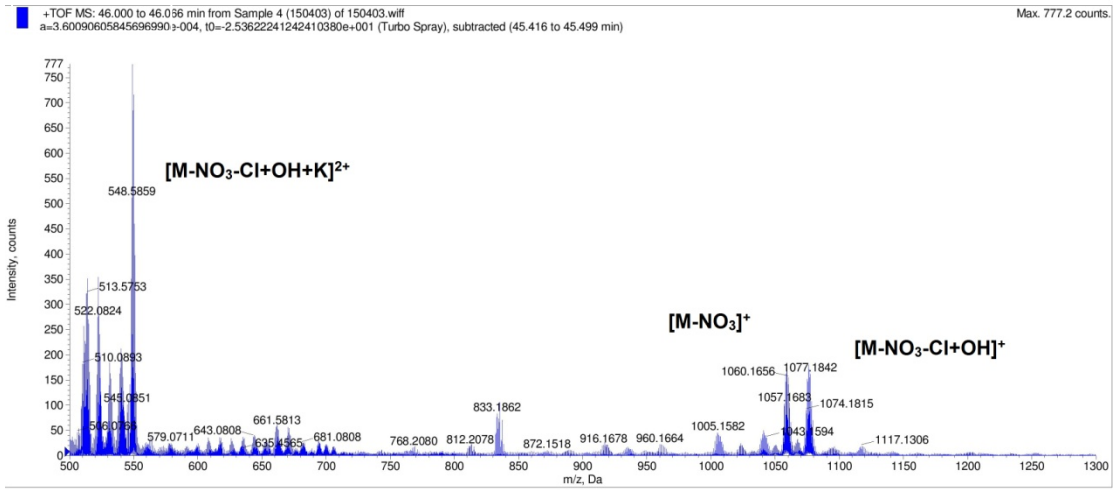


Fig. S4. HRMS spectra of **PtEuL.**

PtGdL



PtGdL

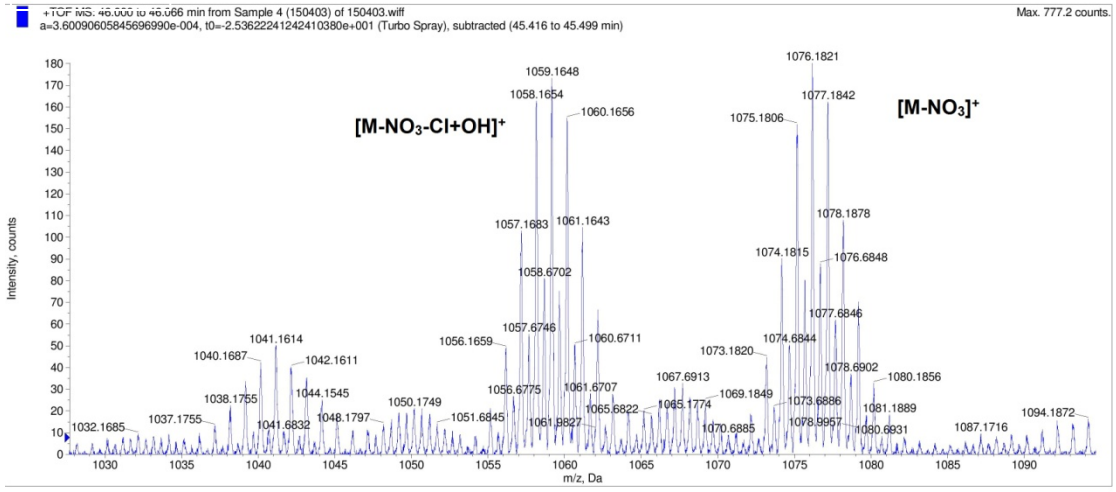


Fig. S5. HRMS spectra of **PtGdL.**

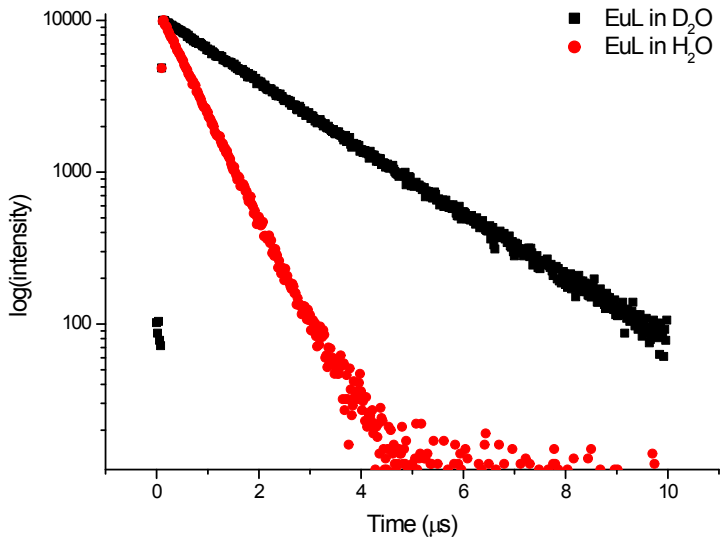


Fig. S6. Emission decay curves of **EuL** in H_2O and in D_2O. (λ_{em} = 615 nm. $^5D_0 \rightarrow {}^7F_2$. λ_{ex} = 325 nm)

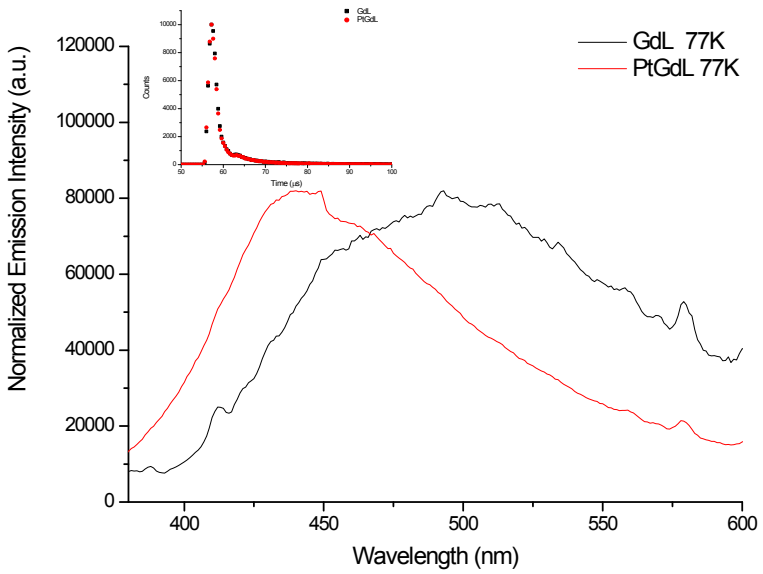


Fig. S7. Normalized emission spectra of **GdL** and **PtGdL** in H_2O/ glycerol (v:v = 1:1) at 77 K. Inset: phosphorescence decay of **GdL** and **PtGdL** in H_2O/ glycerol (v:v = 1:1), 77 K (λ_{em} = 490 nm and 445 nm for **GdL** and **PtGdL** respectively).

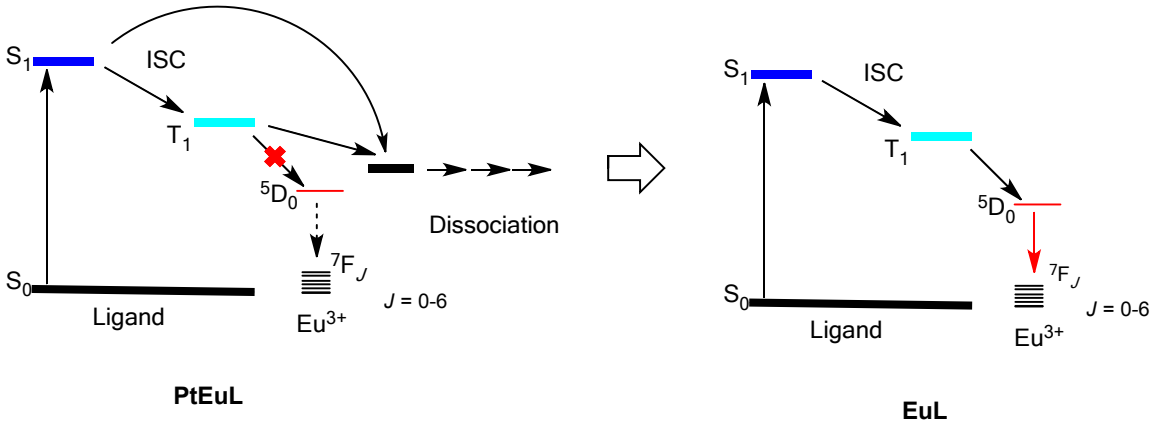


Fig. 8. Proposed energy transfer mechanisms of sensitized europium emission of **EuL** and photo-induced dissociation of **PtEuL**.

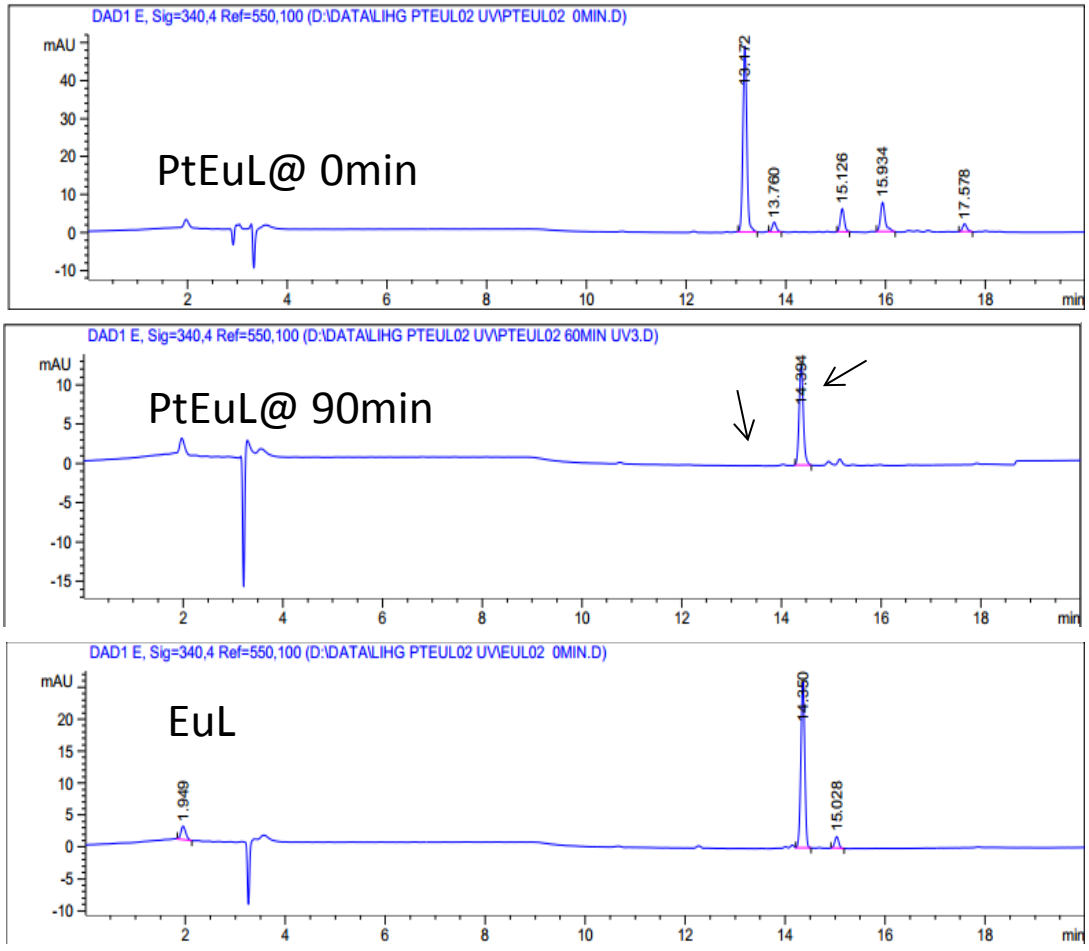


Fig. S9. HPLC analysis of **PtEuL** subjected to (a) 0 min and (b) 60 min of UVA irradiation. (c) The HPLC chromatogram of the synthesized **EuL** was obtained under the same experimental conditions as in Fig. 3a and Table S1. The retention time of the photoproduct from

PtEuL after 90 min of UVA irradiation was in close agreement with that of the **EuL** synthesized.

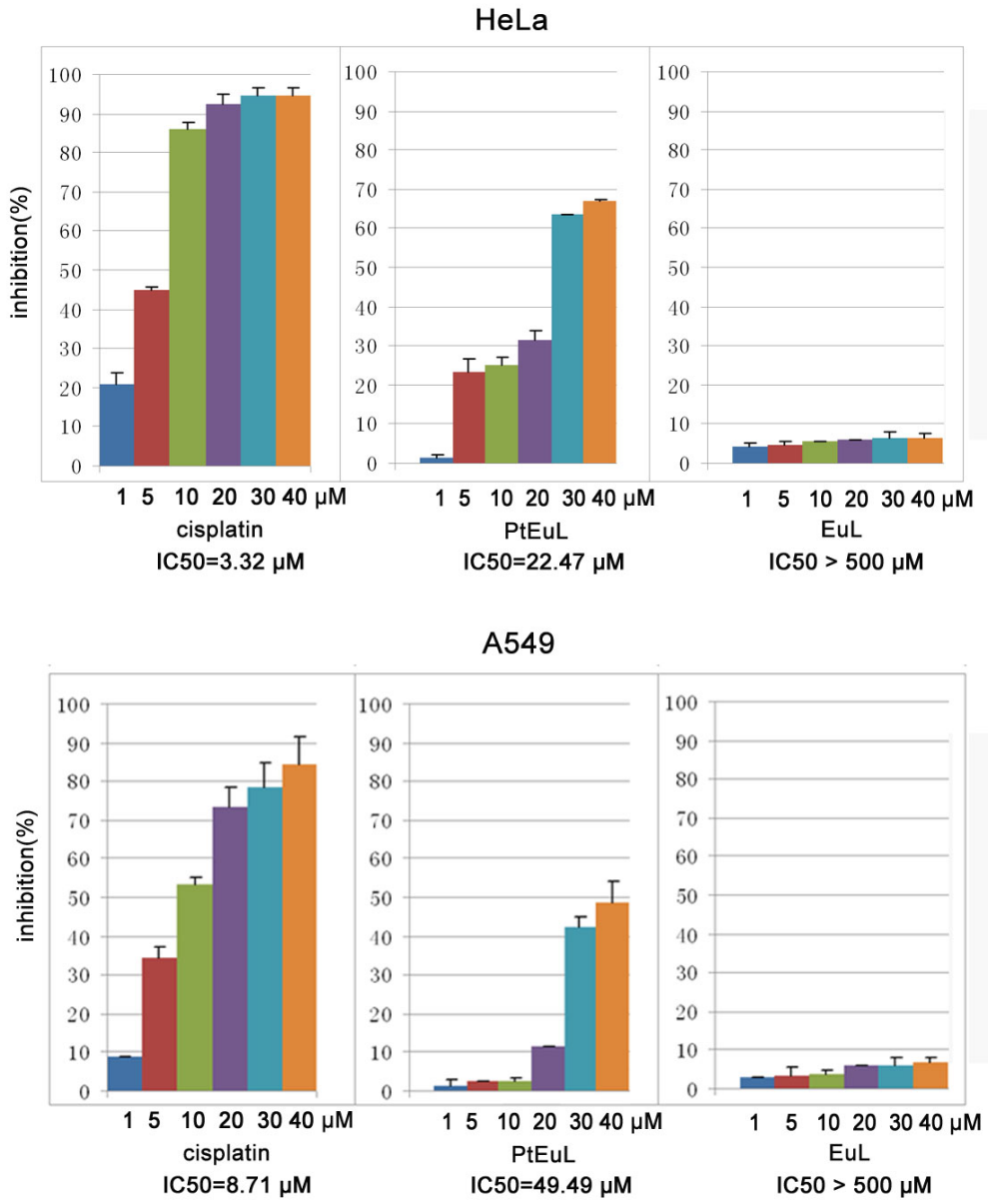


Fig. S10. Dark cytotoxicity of cisplatin, **EuL** and **PtEuL** on HeLa and A549 cells.

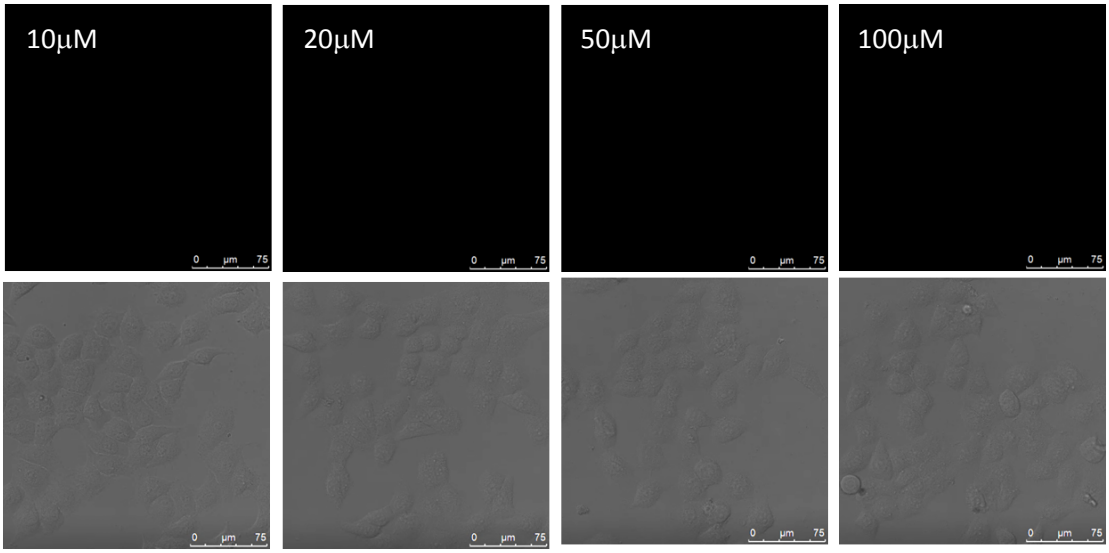


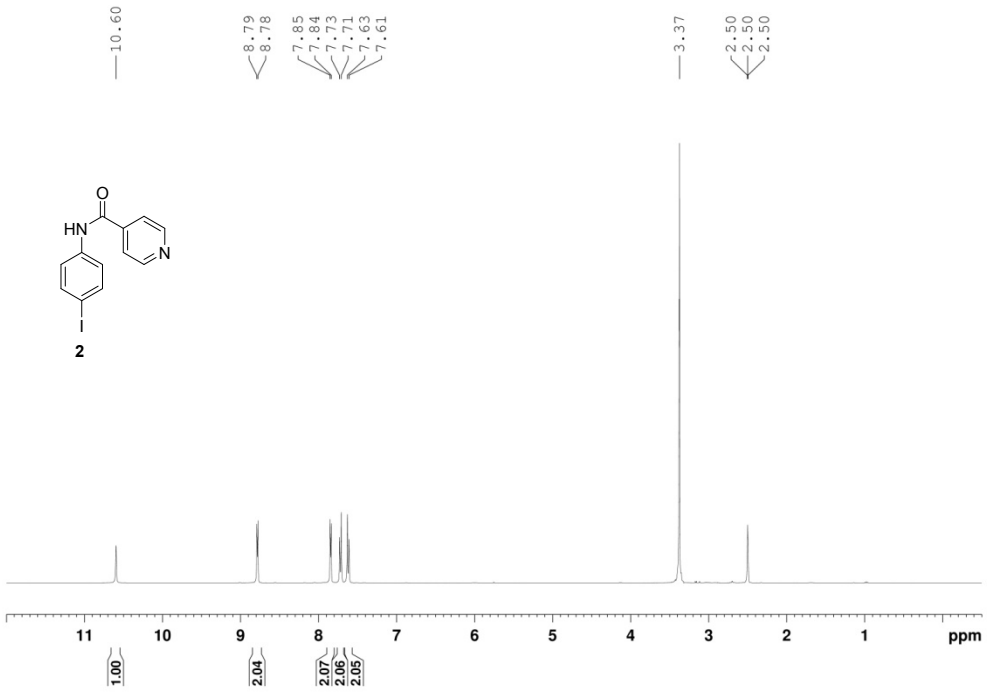
Fig. S11. The *in vitro* luminescent imaging (upper panel) of the HeLa cells after 24 hours of incubation with **EuL** (10, 20, 50 and 100 μM) after 20 min of 730 nm laser excitation (power = 500 mW). The experimental conditions were identical to those in Fig. 4. Images in the lower panel are bright field images. As evident from this figure, no red emission and no significant cell death can be observed even when the dose concentration of **EuL** was increased to 100 μM. Evidently, there was no significant uptake of **EuL** into HeLa cells even at 100 μM concentration.

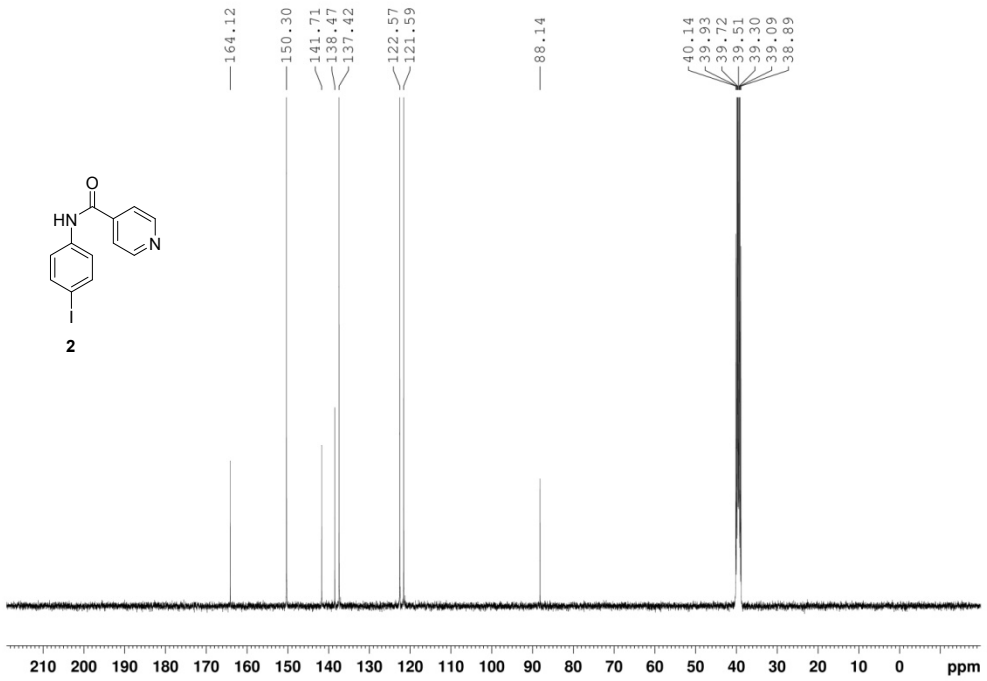
References

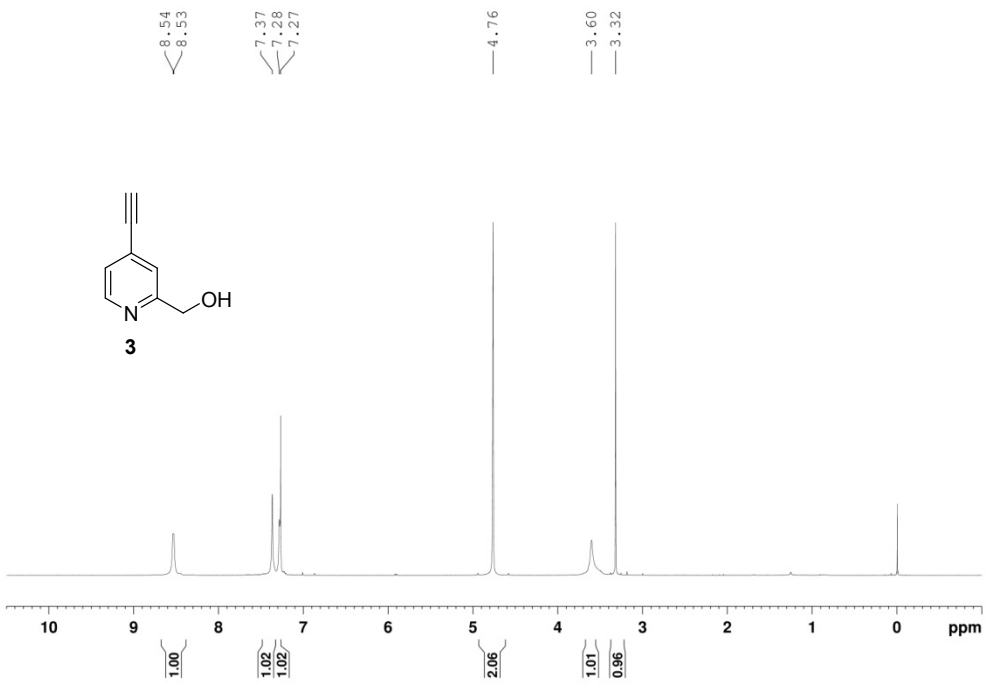
S1. Z. Zhu , S. Karasawa , and N. Koga, *Inorg. Chem.*, **2005**, *44*, 6004–6011.

S2. Z. Zhu, X. Wang, T. Li, S. Aime, P. J. Sadler, and Z. Guo, *Angew. Chem. Int. Ed.* **2014**, *53*, 13225 –13228.

NMR spectra of compounds 1-5



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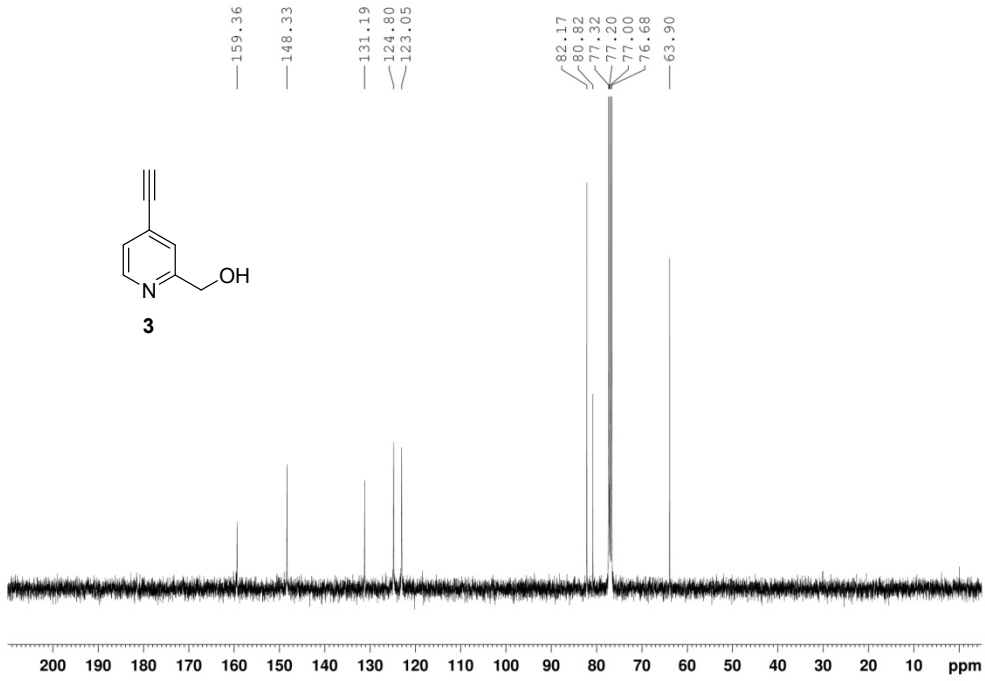
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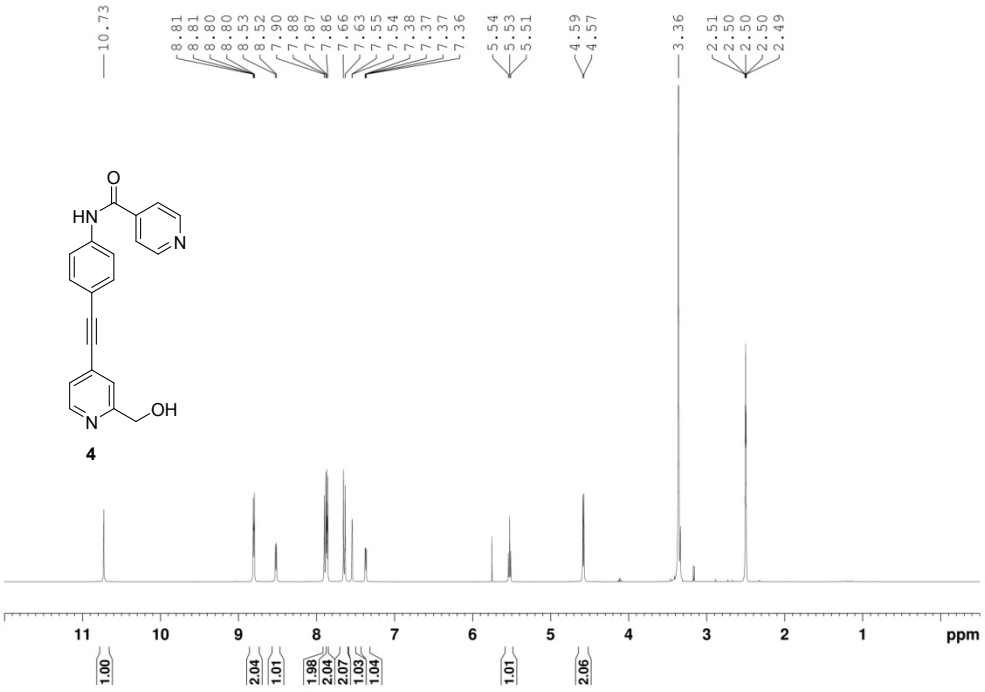
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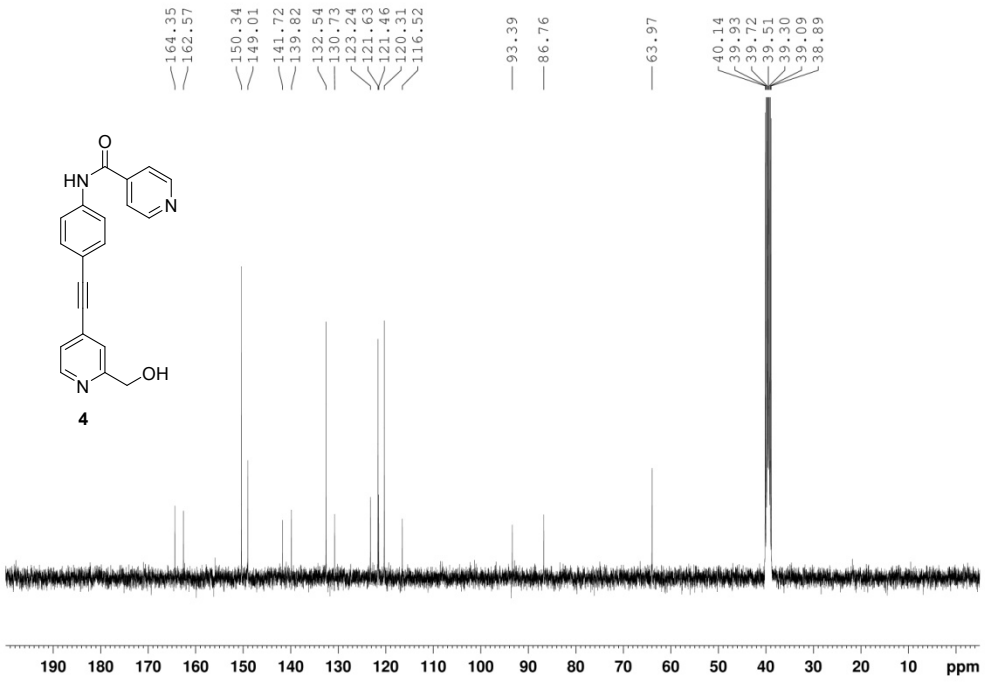
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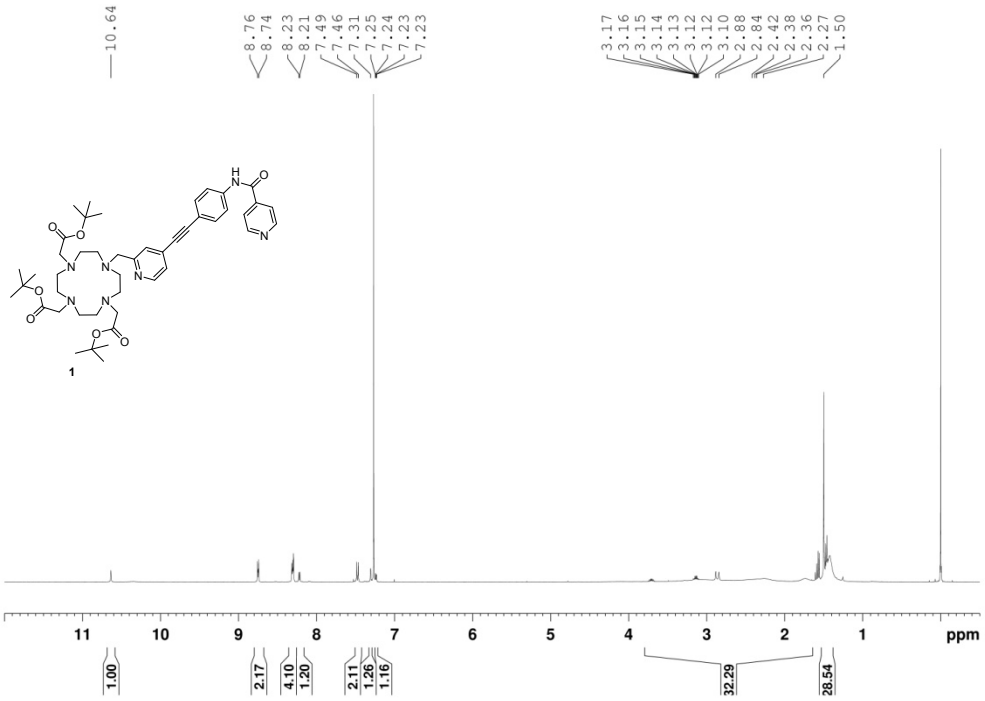
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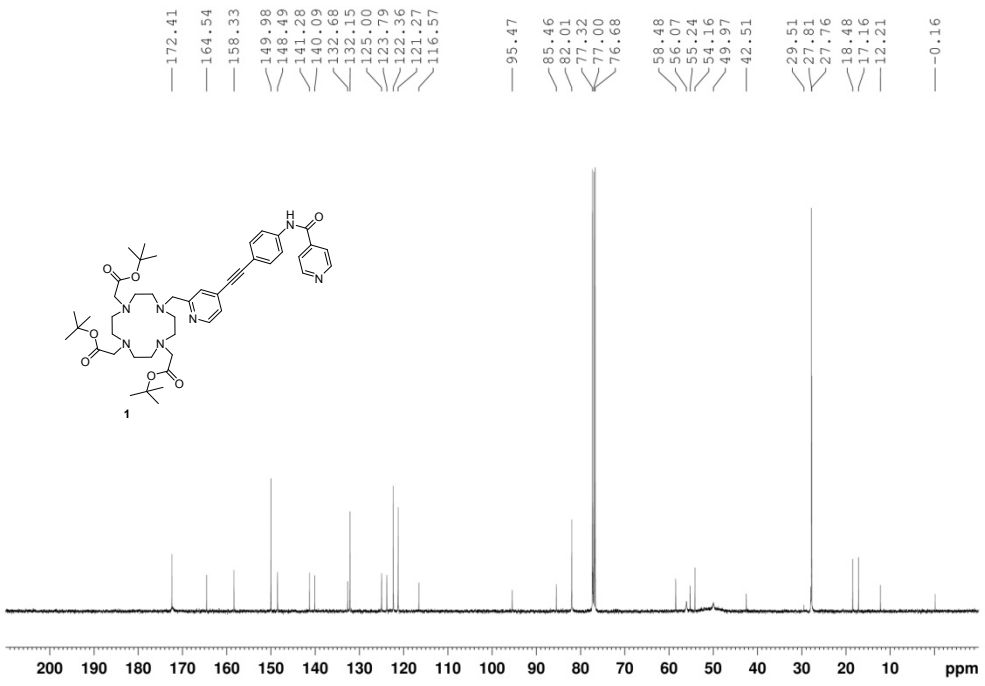
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