Water soluble, cyclometalated Pt(II)-Ln(III) conjugates towards novel bimodal imaging agents

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Electronic Supplementary Information

Synthesis



Scheme S1. Step-wise synthesis of the heterometallic Pt-Ln targets.

All reactions were performed with the use of vacuum line and Schlenk techniques. Reagents were commercial grade and were used without further purification. ¹H NMR spectra were recorded on a Bruker Avance dpx 400 or 250 MHz spectrometer and Bruker AvanceIII-400 spectrometer, ¹³C{¹H} NMR spectra on a Joel Eclipse 300 MHz or Bruker Avance dpx 500 MHz spectrometer and ¹⁹⁵Pt NMR spectra on Bruker Avance dpx 500 MHz spectrometer, and were recorded in CDCl₃, D₂O, CD₃CN or d⁶-DMSO solutions. ¹H, ¹³C 1 H} and ¹⁹⁵Pt NMR chemical shifts (δ) were determined relative to internal tetramethylsilane, Si(CH₃)₄ and are given in ppm. Low-resolution mass spectra were obtained by the staff at Cardiff University. High-resolution mass spectra were carried out by the staff at Cardiff University and the EPSRC National Mass Spectrometry Service at Swansea University, UK. All photophysical data was obtained on a JobinYvon-Horiba Fluorolog-3 spectrometer fitted with a JY TBX picosecond photodetection module and a Hamamatsu R5509-73 detector (cooled to -80 °C using a C9940 housing) was used for near-IR luminescence measurements. For the near-IR lifetimes the pulsed laser source was a Continuum Minilite Nd:YAG configured for 355 nm output. Emission spectra were uncorrected and excitation spectra were instrument corrected. The pulsed source was a Nano-LED configured for 295, 372 or 459 nm output operating at 500 kHz or 1 MHz. Luminescence lifetime profiles were obtained using the JobinYvon-Horiba FluoroHub single photon counting module and the data fits yielded the lifetime values using the provided DAS6 deconvolution software. IR spectra were recorded on an ATR equipped Shimadzu IRAffinity-1 spectrophotometer. UV-vis data were recorded as solutions on a Perkin Elmer Lamda20 spectrophotometer.

DFT studies

Non-relativistic calculations were performed on the Gaussian 09 program.¹ Geometry optimisations were carried out without constraints using the B3LYP functional.² The Stuttgart-Dresden basis set was used for the Pt centres,³ and was invoked with pseudo-potentials for the core electrons, with a 6-31G(d) basis set⁴ for all remaining atoms. TD-DFT studies were performed using the same functional, but with 6-31+G(d,p) on all non-metal atoms, and also included a simulated MeCN environment using the polarized continuum model (PCM) approach.⁵ For prediction of absorption spectra, the geometry used to calculate orbital and other properties was used without modification. For the prediction of emission energies, however, the triplet state was allowed to relax to its optimal geometry using unrestricted B3LYP in the gas phase, prior to solvated TD-DFT.

Confocal microscopy

Cells tested were MCF-7 human breast adenocarcinoma cell line and *Schizosaccharomyces pombe* (fission yeast).

MCF-7: Cells were detached from culture flask using trypsin-EDTA, re-suspended in DMEM medium and concentrated by centrifugation. Cells were re-suspended 7 ml fresh DMEM medium, aliquoted into 1 ml volumes in Eppendorfs and incubated at 37°C (under 5% CO₂ and 95% air) with 20µl of each compound (final concentration was 100 µg/ml for test compounds) for 30 min. Cells were washed in PBS (pH 7.2) and re-suspended in 100 µl HMEM for imaging.

S. pombe: 1 ml overnight cell suspension incubated initially with 20 μ l of each compound separately (final concentration was 100 μ g/ml). These were incubated at room temperature for 30 min. Cells were then washed 2x in PBS (pH 7.2) to remove medium and background fluorescence signal, and re-suspended in 1 ml PBS for imaging.

Cell preparations were viewed by epifluorescence and transmitted light (Nomarski differential interference contrast optics) using a Leica TCS SP2 AOBS confocal laser microscope (Leica, Germany) using ×63 or ×100 objectives. Imaging parameters were λ_{ex} 405 nm diode laser and λ_{em} 580-640 nm which corresponds to the ³MLCT emission energy of the Pt(II) lumophore.

Synthesis of pq-1: Following a general procedure ⁶ but using 2-phenyl-4quinolinecarboxylic acid (0.521 g, 2.095 mmol) and 2-(2-aminoethoxy)ethanol (0.200 g, 1.905 mmol). Yield = 0.416 g, (65%). ¹H NMR (400 MHz, CDCl₃): δ_{H} 8.10 (1H, d, ³*J*_{HH} = 8.8 Hz, Ar), 8.06 – 8.03 (3H, m, Ar), 7.76 (1H, s, Ar), 7.69 – 7.66 (1H, m, Ar), 7.50 – 7.43 (4H, m, Ar), 7.14 (1H, br. t, ³*J*_{HH} = 4.4 Hz, N*H*), 3.71 – 3.64 (6H, m, C*H*₂), 3.56 – 3.50 (2H, m, C*H*₂), 2.77 (1H, br. S, O*H*) ppm. ¹³C{¹H} NMR (75.6 MHz, CDCl₃): δ_{C} 167.7 (<u>C</u>O), 156.6 (Ar), 148.2 (Ar), 143.0 (Ar), 138.4 (Ar), 130.9 (Ar), 130.3 (Ar), 129.9 (Ar), 129.6 (Ar), 128.9 (Ar), 127.5 (Ar), 127.3 (Ar), 125.1 (Ar), 123.4 (Ar), 72.4 (<u>C</u>H₂), 69.6 (<u>C</u>H₂), 61.7 (<u>C</u>H₂), 39.9 (<u>C</u>H₂) ppm. MS(ES) found *m*/*z* = 359.14 for [M + H]⁺. UV-vis (CHCl₃): λ_{max} (ε / dm³ mol⁻¹ cm⁻¹) 261 (30500), 329 (69900) nm. IR (thin film): v_{max} 3404, 3273, 1643, 1546 cm⁻¹.

Synthesis of pq-2: Following a general procedure⁶ but using 2-phenyl-4quinolinecarboxylic acid chloride (0.200 g, 0.748 mmol) and diethylene glycol monomethyl ether (0.135 g, 1.121 mmol). Yield = 0.252 g, (96%). ¹H NMR (400 MHz, CDCl₃): δ_{H} 8.75 (1H, dd, ³*J*_{HH} = 8.4 Hz, ⁴*J*_{HH} = 1.2 Hz, Ar), 8.42 (1H, s, Ar), 8.24 – 8.19 (3H, m, Ar), 7.80 – 7.75 (1H, m, Ar), 7.65 – 7.61 (1H, m, Ar), 7.57 – 7.48 (3H, m, Ar), 4.68 – 4.60 (2H, m, *CH*₂), 3.98 – 3.93 (2H, m, *CH*₂), 3.76 – 3.71 (2H, m, *CH*₂), 3.62 – 3.57 (2H, m, *CH*₂), 3.39 (3H, s, Me) ppm. ¹³C{¹H} NMR (125.8 MHz, CDCl₃): δ_{C} 166.5 (<u>C</u>O), 156.8 (Ar), 149.3 (Ar), 138.8 (Ar), 135.9 (Ar), 130.3 (Ar), 129.9 (Ar), 129.7 (Ar), 128.9 (Ar), 128.8 (Ar), 127.8 (Ar), 127.6 (Ar), 127.5 (Ar), 125.5 (Ar), 124.0 (Ar), 120.4 (Ar), 72.0 (<u>CH</u>₂), 70.7 (<u>CH</u>₂), 69.1 (<u>CH</u>₂), 64.8 (<u>CH</u>₂), 59.1 (<u>CH</u>₃) ppm. HR-MS: calcd. for $[C_{24}H_{40}N_7O_7]^+$ 538.2984, found *m/z* = 538.2974; and cald. 560.2803 for $[NaC_{24}H_{39}N_7O_7]^+$, found *m/z* = 560.2792. UV-vis (CHCl₃): λ_{max} (ϵ / dm³ mol⁻¹ cm⁻¹) 265 (29900), 339 (7680) nm. IR (thin film): v_{max} 3061, 2876, 1723, 1591, 1549, 1495, 1447, 1343, 1246, 1231, 1194, 1107, 1020, 770, 692 cm⁻¹.

Synthesis of [Pt(pq-2)CI]₂: Based on a modified literature methodology⁷ using potassium tetrachloroplatinate(II) (0.100 g, 0.241 mmol) and **pq-2** (0.064 g, 0.182 mmol). A solution of potassium tetrachloroplatinate(II) (1.0 eq.) in water (2 mL) was added to a stirring solution of **pq-2** (1.0 eq.) in 2-ethoxyethanol (6 mL) under dinitrogen and heated to 80 °C for 16 h in a foil-wrapped flask. Brine (10 mL) was added to the cooled solution and the resultant precipitate was collected on a sinter and washed with water (2 × 10 mL) and dried. The isolated solid was used without purification. Yield = 0.062 g, (59%).

Synthesis of [Pt(pq-2)(DMSO)CI]: Adapted from a literature methodology⁸ using [Pt(pq-2)Cl]₂ (0.062 g, 0.053 mmol). Crude [Pt(pq-2)(µ-Cl)]₂ was dissolved in a minimum volume of DMSO before being precipitated with brine (10 mL), filtered on a sinter and washed with water (2 \times 20 mL) and dried. The dark brown compound was purified by dissolving in a minimum volume of dichloromethane and precipitating dark brown impurities by slow addition of diethyl ether. The filtrate was then dried and triturated with diethyl ether until the sticky oil formed a bright orange precipitate. Yield = 0.049 g, (70%). ¹H NMR (400 MHz, CDCl₃): δ_{H} 9.06 (1H, d, ³J_{HH} = 8.8 Hz, Ar), 8.58 (1H, dd, ³J_{HH} = 8.8 Hz, ⁴J_{HH} = 1.2 Hz, Ar), 8.37 – 8.34 (1H, m, Ar), 8.32 (1H, s, Ar), 7.78 – 7.73 (1H, m, Ar), 7.71 – 7.69 (1H, m, Ar), 7.65 – 7.61 (1H, m, Ar), 7.29 – 7.26 (2H, m, Ar), 4.70 – 4.67 (2H, m, CH₂), 3.95 – 3.92 $(2H, m, CH_2)$, 3.76 – 3.74 $(2H, m, CH_2)$, 3.67 $(6H, s \text{ with satellites } {}^{3}J_{HPt} = 21.2 \text{ Hz}$, 2 × Me from coordinated DMSO), 3.62 – 3.60 (2H, m, CH₂), 3.41 (3H, s, Me) ppm. ¹³C $\{^{1}H\}$ NMR (125.8 MHz, CDCl₃): δ_C 166.5 (CO), 165.2 (Ar), 147.6 (Ar), 145.6 (Ar), 143.0 (Ar), 139.7 (Ar), 133.8 (Ar), 130.8 (Ar), 129.7 (Ar), 128.5 (Ar), 128.3 (Ar), 126.0 (Ar), 125.4 (Ar), 125.2 (Ar), 124.9 (Ar), 117.7 (Ar), 72.0 (CH₂), 70.7 (CH₂), 68.9 (CH₂), 65.3 (CH₂), 59.1 (CH₃), 46.2 ((CH₃)₂SO) ppm. ¹⁹⁵Pt (107.5 MHz, CDCl₃): δ_{Pt} -3665 ppm. MS(ES) found m/z = 586.08 for $[M - SO(CH_3)_2 - CI + CH_3CN]^+$ and 627.10 for $[M - SO(CH_3)_2 - CI + 2CH_3CN]^+$. HR-MS: calcd. 626.1550 for $[C_{25}H_{26}N_3O_4^{194}Pt]^+$, found m/z = 626.1567. UV-vis (CHCl₃): λ_{max} (ϵ / dm³ mol⁻¹ cm⁻¹) 253, (12500), 291 (8790), 362 (4130), 424 (1410) nm. IR (thin film): v_{max} 2876, 1728, 1597, 1580, 1545, 1454, 1379, 1294, 1275, 1250, 1198, 1138, 1022, 766, 731 cm⁻¹.

Synthesis of P2: 4-pyridinecarboxaldehyde (0.083 g, 0.779 mmol) was added to a stirring solution of P1 (0.476 g, 0.779 mmol) in 1,2-dichloroethane (8 mL) and was stirred under dintrogen. After 16 h, Na(OAc)₃BH (0.500 g, excess) was added and the reaction was left stirring for 16 h. NaHCO₃ (sat. soln., 10 mL) was added and the product was extracted with dichloromethane (20 mL). The organic phase was washed with water (2 x 20 mL) and brine (20 mL) before being dried over MgSO₄, filtered and dried *in vacuo*. Yield = 0.505 g, (92%). ¹H NMR (400 MHz, CDCl₃): δ_{H} 8.99 (1H, br, NH), 8.47 (2H, d, ³J_{HH} = 6.0 Hz, Ar), 7.46 (2H, d, ${}^{3}J_{HH}$ = 6.0 Hz, Ar), 4.69 (2H, br. s, CH₂), 3.92 (2H, br. s, CH₂), 3.67 - 1.87 (28H, br. m, CH₂), 1.39 – 1.36 (27H, m, *tert*-Bu) ppm. ¹³C{¹H} NMR (125.8 MHz, CDCl₃): δ_C 171.3 (CO), 171.1 (CO), 148.7 (Ar), 145.6 (Ar), 123.1 (Ar), 81.1 (C(CH₃)), 81.0 (C(CH₃)), 55.1 (CH₂), 54.8 (CH₂), 54.7 (CH₂), 50.3 (CH₂), 46.8 (CH₂), 37.1 (CH₂), 27.2 $(C(CH_3))$, 27.0 $(C(CH_3))$ ppm. MS(ES) found m/z = 728.45 for $[M + Na]^+$. Trifluoroacetic acid (3 mL, excess) was then added to a stirring solution of the tert-butyl protected precursor (0.505 g, 0.717 mmol) in dichloromethane (3 mL). The reaction was stirred for 48 h before the solvent was removed in vacuo. The residue was dissolved in a minimal volume of acetonitrile and added, dropwise, to a vigorously stirred vessel of ice-cold diethyl ether (20 mL). The resultant precipitate was filtered under dinitrogen to yield P2 as a white solid. Yield = 0.350 g, (91%). ¹H NMR (500 MHz, D₂O): $\delta_{\rm H}$ 8.87 (2H, d, ³J_{HH} = 7.0 Hz, Ar), 8.21 (2H, br. m, Ar), 4.70 (2H, s, CH_2), 3.97 – 2.88 (28H, br. m, CH_2) ppm. ¹³C{¹H} NMR (125.8 MHz, D₂O): δ_C 162.2 (CO), 161.9 (CO), 150.8 (Ar), 141.1 (Ar), 126.7 (Ar), 65.1 (CH₂), 54.2 (CH₂), 50.2 (br, CH₂), 48.4 (br CH₂), 47.3 (br CH₂), 34.6 (CH₂) ppm. HR-MS: calcd. 501.2900 for $[C_{35}H_{37}N_2O]^+$, found m/z = 501.2889.

Synthesis of [Gd-py]: Gadolinium(III) triflate (0.112 g, 0.186 mmol) and **P2** (0.100 g, 0.186 mmol) were dissolved in methanol (10 mL) and heated to 50 °C for 24 h under dinitrogen. The solution was cooled and diethyl ether (20 mL) was added. The precipitate was filtered under dinitrogen to yield an off-white solid. Yield = 0.112 g, (87%). HR-MS: calcd. 687.1947 for $[C_{24}H_{37}^{152}GdN_7O_7]^+$, found m/z = 687.1941. UV-vis (CHCl₃): λ_{max} (ϵ / dm³ mol⁻¹ cm⁻¹) 201 (7240), 256 (1840) nm. IR (thin film): v_{max} 3397, 1582, 1402, 1244, 1225, 1165, 1082, 1026, 635 cm⁻¹.

Synthesis of [Yb-py]: Ytterbium(III) triflate (0.115 g, 0.186 mmol) and **P2** (0.100 g, 0.186 mmol) were dissolved in methanol (10 mL) and heated to 50 °C for 24 h under dinitrogen. The solution was cooled and diethyl ether (20 mL) was added. The precipitate was filtered

under dinitrogen to yield an off-white solid. Yield = 0.121 g, (92%). ¹H NMR (400 MHz, D₂O): δ_{H} +133.44, +125.59, +120.46, +119.57, +33.43, +26.95, +23.45, +22.16, +21.00, +18.62, +16.42, +13.35, +8.97, +3.18, -1.77, -2.38, -24.53, -27.53, -31.67, -42.19, -45.47, -57.61, -58.91, -74.55, -76.88. HR-MS: calcd. 705.2102 for $[C_{24}H_{37}N_7O_7^{170}Yb]^+$, found *m/z* = 705.2110. UV-vis (CHCl₃): λ_{max} (ϵ / dm³ mol⁻¹ cm⁻¹) 201 (7800), 256 (1430) nm. IR (thin film): v_{max} 3408, 1601, 1410, 1258, 1167, 1084, 1026, 800, 640 cm⁻¹.

Synthesis of [Pt-Gd]: [Pt(**pq-2**)(DMSO)Cl] (0.052 g, 0.079 mmol) and **Gd-py** (0.050 g, 0.072 mmol) were dissolved in acetone and heated to 40 °C for 48 h under dinitrogen. The solvent was removed *in vacuo* and the solid dissolved in minimal acetonitrile and precipitated with diethyl ether. The solid was filtered and washed with dichloromethane to yield a bright orange solid. Yield = 0.062 g, (68%). HR-MS: calcd. 1233.2922 for $[C_{45}H_{56}N_8O_{11}^{155}Gd^{194}Pt]^+$, found *m/z* = 1233.2953. UV-vis (CHCl₃): λ_{max} (ϵ / dm³ mol⁻¹ cm⁻¹) 203 (25000), 246 (13300), 285 (9320), 364 (4450) nm. IR (thin film): v_{max} 3433, 1732, 1591, 1456, 1404, 1246, 1167, 1084, 1028, 941, 903, 841, 762, 723, 637 cm⁻¹.

Synthesis of [Pt-Yb]: [Pt(**pq-2**)(DMSO)Cl] (0.051 g, 0.078 mmol) and **Yb-py** (0.050 g, 0.071 mmol) were dissolved in acetone and heated to 40 °C for 48 h under dinitrogen. The solvent was removed *in vacuo* and the solid dissolved in minimal acetonitrile and precipitated with diethyl ether. The solid was filtered and washed with dichloromethane to yield a bright orange solid. Yield = 0.072 g, (79%). HR-MS: calcd. 1249.3059 for $[C_{45}H_{56}N_8O_{11}^{171}Yb^{194}Pt]^+$, found *m/z* = 1249.3076. UV-vis (CHCl₃): λ_{max} (ϵ / dm³ mol⁻¹ cm⁻¹) 203 (26300), 248 (14100), 284 (9920), 364 (4640) nm. IR (thin film): v_{max} 3408, 1730, 1595, 1458, 1400, 1389, 1248, 1165, 1084, 1028, 943, 909, 843, 762, 727, 638 cm⁻¹.



Figure S1. ¹H NMR spectra of Yb-py recorded in D₂O (400 MHz).



Figure S2. Comparison of the observed (bottom) and theoretical (top) isotopic distribution for the $[M-CI]^+$ ion of **Pt-Gd**.



Figure S3. Calculated orbital representations for [PtCl(epqc)(DMSO)] (top, I-to-r: HOMO, LUMO) and [PtCl(epqc)(py)] (bottom, I-to-r: HOMO-1, HOMO, LUMO).

X-ray diffraction

A suitable crystal was selected and measured following a standard method⁹ on a *Rigaku AFC12* goniometer equipped with an enhanced sensitivity (HG) *Saturn724*+ detector mounted at the window of a *FR-E*+ *SuperBright* molybdenum rotating anode generator with HF *Varimax* optics (100µm focus) at 100K. Cell determination, data collection, reduction, cell refinement and absorption correction carried out using *CrystalClear-SM Expert* 3.1b27.¹⁰ Structures solved using *SUPERFLIP*¹¹ and refined using *SHELXL*-2013.¹²

Crystal data for [PtCl(pq-2)(DMSO)] : $C_{23}H_{26}CINO_5PtS$, M = 659.05, dark orange blade, a = 9.5830(7), b = 9.8654(7), c = 14.2517(10) Å, $\alpha = 104.643(5)^{\circ}$, $\beta = 95.718(3)^{\circ}$, $\gamma = 114.866(4)^{\circ}$, V = 1149.74(15) Å³, Triclinic, space group *P-1*, Z = 2, $\mu = 6.345$ mm⁻¹, reflections collected = 15635, independent reflections = 5262, R_{int} = 0.0403, *R*1 = 0.0237, $wR2 = 0.0.619 [F^2 > 2\sigma(F^2)]$, *R*1 = 0.0245, wR2 = 0.0623 (all data).

Table S1. Selected bond lengths (Å) and angles (deg).

Bond lengths (Å)		Bond angles (deg)	
Pt(1)-C(1)	2.003(3)	C(1)-Pt(1)-N(1) 80.66(10)	
Pt(1)-Cl(1)	2.4135(7)	C(1)-Pt(1)-S(31) 98.67(8)	
Pt(1)-N(1)	2.078(2)	N(1)-Pt(1)-S(31) 172.42(7)	
Pt(1)-S(31)	2.2141(8)	C(1)-Pt(1)-Cl(1) 161.82(9)	
		N(1)-Pt(1)-Cl(1) 94.79(7)	
		S(31)-Pt(1)-Cl(1) 88.10(3)	
		1	

[PtCl(pq-2)(DMSO)]

Table S2. Calculated d-orbital contributions to the frontier orbitals.

Compound	HOMO-2	HOMO-1	НОМО	LUMO
[PtCl(epqc)(DMSO)]	11.54%	16.38%	23.29%	0.32%
[Pt(epqc)(py)Cl]	7.10%	11.25%	26.48%	1.00%

% Pt 5*d*-orbital character



Figure S4. ¹H NMRD for 1mM **Gd-py** and **Pt-Gd** recorded in water at 25 °C and 37 °C (pH 6.5-6.7).



Figure S5. Confocal fluorescence microscopy images of *S. pombe* using **Pt-Gd** (λ_{ex} 405 nm and λ_{em} 580-640 nm) showing fluorescence, transmitted and superimposed images.



Figure S6. Confocal fluorescence microscopy images of *S. pombe* using **Pt-Gd** (λ_{ex} 405 nm and λ_{em} 580-640 nm) showing fluorescence, transmitted and superimposed images.

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