# Design and Biological Evaluation of New Platinum (II) Complexes Bearing ligands with DNA-targeting ability.

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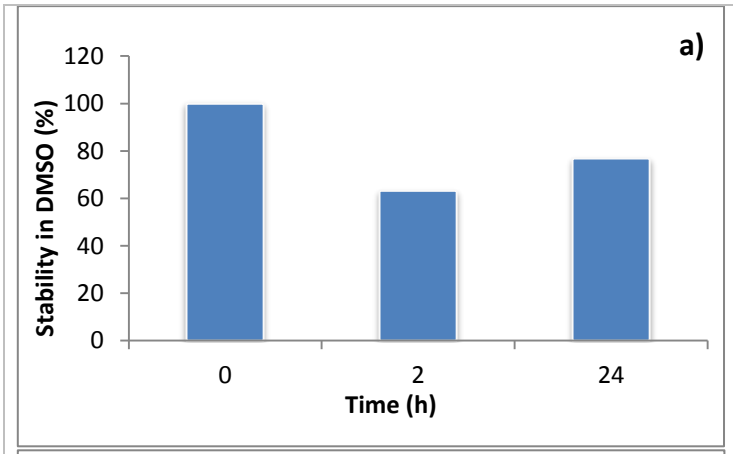
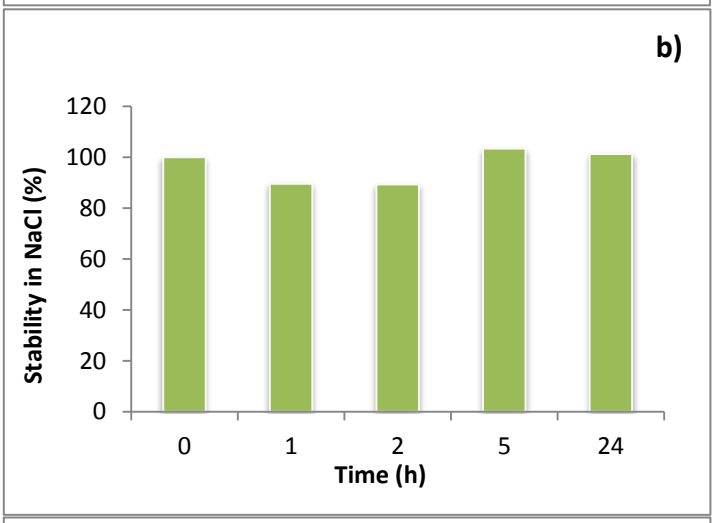
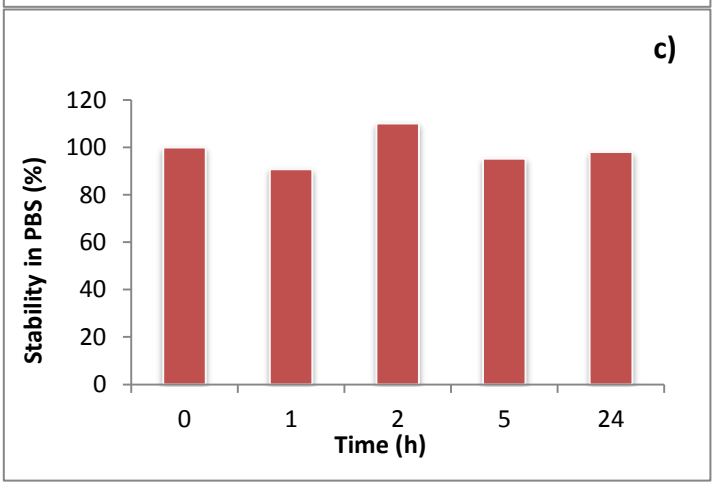
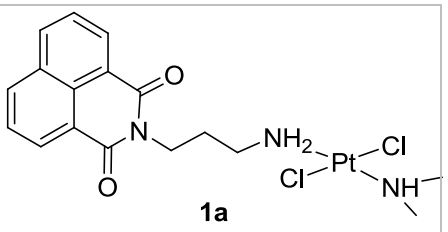
# STABILITY STUDIES




**1a**

**Figure S1**. Stability of **1a**, at different time points in a) DMSO, b) NaCl and c) PBS. Value is expressed as the amount of complex that remains intact using the initial amount (t = 0 h) as 100%

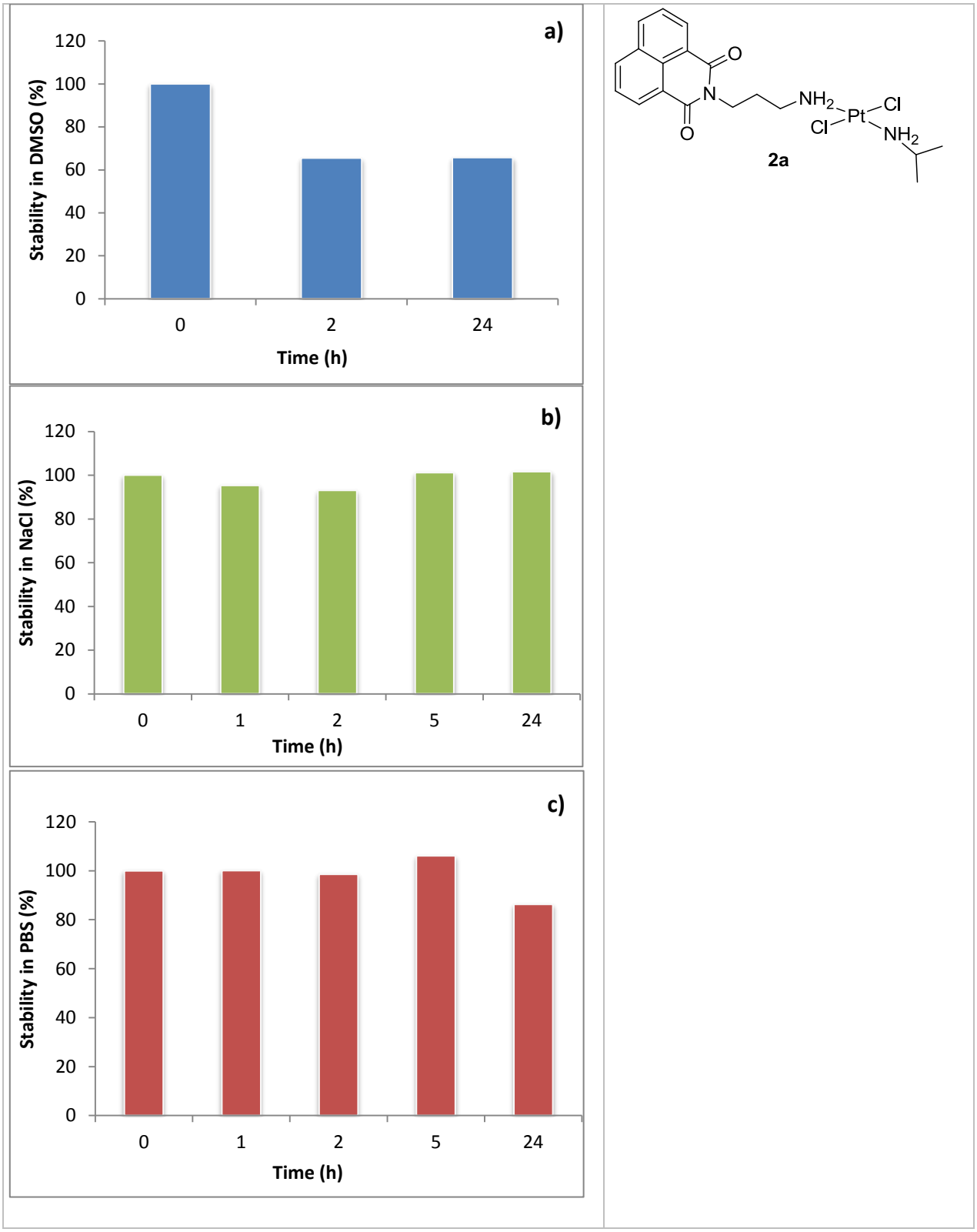



**Figure S2**. Stability of **2a**, at different time points in a) DMSO, b) NaCl and c) PBS. Value is expressed as the amount of complex that remains intact using the initial amount (t = 0 h) as 100%

# ABSORPTION AND EMISSION SPECTRA

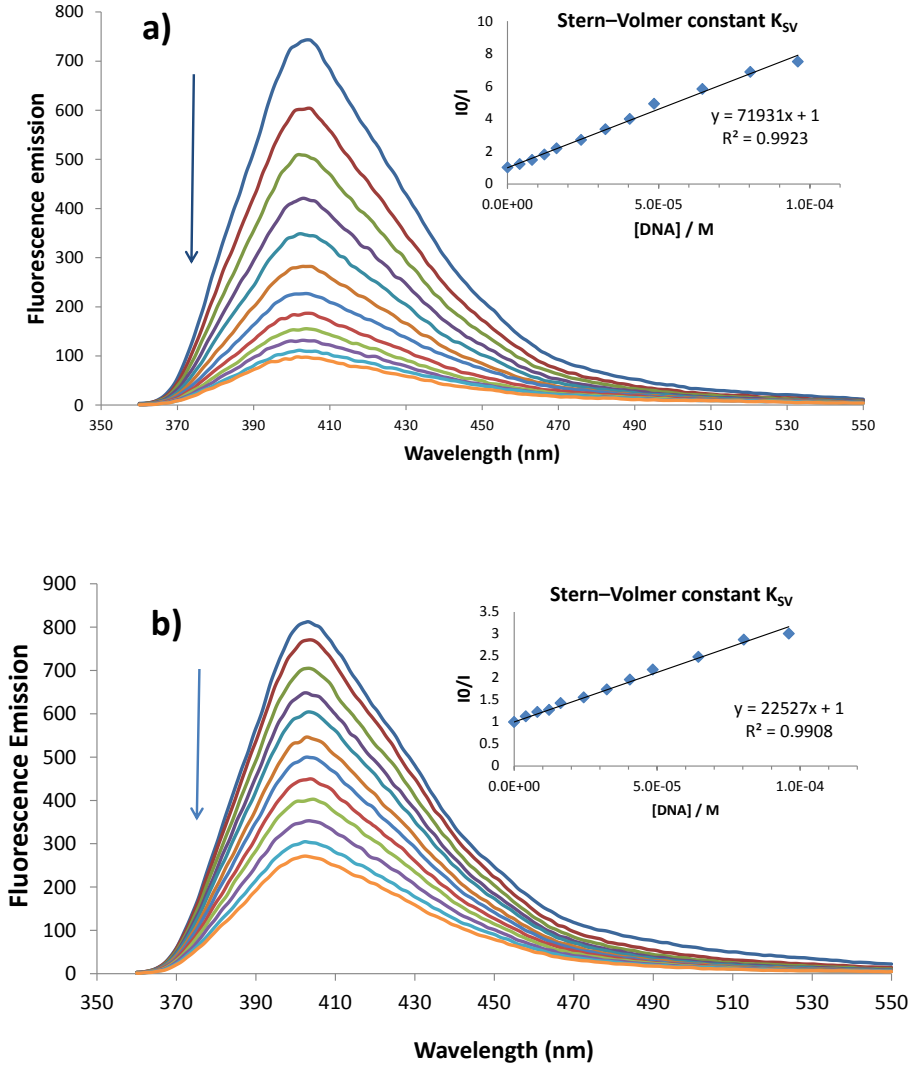



**Figure S3.** Fluorescence emission spectra of complex **1a** (a) and **2a** (b) (15 µM), in the presence of increasing concentrations of CT-DNA (0 to 100 µM) in PBS buffer (pH = 7.4). The arrows indicate the changes of the bands upon addition of CT-DNA. Inset representation of I0/I vs [DNA] to determine the value of Stern-Volmer constant. Excitation at 350 nm.

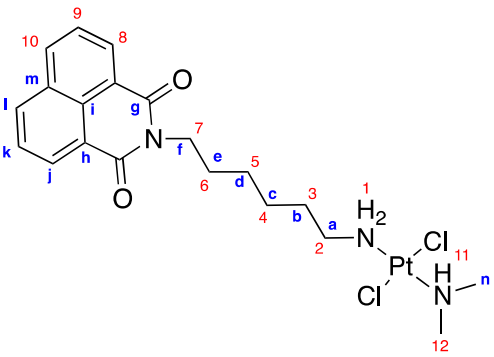
# EXPERIMENTAL PROCEDURES, CHARACTERIZATION AND 2D NMR SPECTRA

***N*-(3-Isonicotinamidopropyl)-1,8-naphthalimide (2c):** Isonicotinoyl chloride hydrochloride (0.50 g, 2.90 mmol), and triethyl amine (1.22 mL, 8.72 mmol) in 10 mL of dry DMF was stirred at room temperature and under argon atmosphere for 15 min. Then, ligand **1a** (1.11 g, 4.35 mmol) was added to the mixture and stirred at room temperature for 48 h. The reaction mixture was concentrated to dryness under reduced pressure. The solid was triturated with distilled water, filtered, washed thoroughly with cool distilled water, and vacuum-dried overnight at 40 °C in a drying oven to yield a pale orange solid (72%). MP: 152-155 ºC (decomposed). $^{1}$H NMR ($CD_3OD$, 300 MHz): δ 8.66 (dd, *J* = 4.5, 1.6 Hz, 2H, $H_1$), 8.50 (d, *J* = 7.3 Hz, 2H, $H_7$), 8.37 (d, *J* = 8.4 Hz, 2H, $H_9$), 7.80-7.73 (m, 4H, $H_2$ and $H_8$), 4.25 (t, *J* = 6.9 Hz, 2H, $H_6$), 3.49 (t, *J* = 6.8 Hz, 2H, $H_4$), 2.06 (pent, *J* = 6.9 Hz, 2H, $H_5$). $^{13}$C NMR ($CD_3OD$, 100 MHz): δ 167.6 (C, $C_d$), 165.7 (C, $C_h$), 150.9 (CH, $C_a$), 144.0 (C, $C_c$), 135.6 (CH, $C_n$), 133.1 (C, $C_o$), 132.2 (CH, $C_k$), 129.2 (C, $C_i$), 128.1 (CH, $C_m$), 123.6 (C, $C_j$), 122.8 (CH, $C_b$), 39.0 ($CH_2$, $C_g$), 38.9 ($CH_2$, $C_e$), 28.8 ($CH_2$, $C_f$). MS (EI) m/z: 360.1 $[M+H]^+$. Anal. Calcd for $C_{21}H_{17}N_3O_3$: C,70.18;H,4.77; N,11.69. Found: C, 69.68; H, 4.96; N, 11.30.

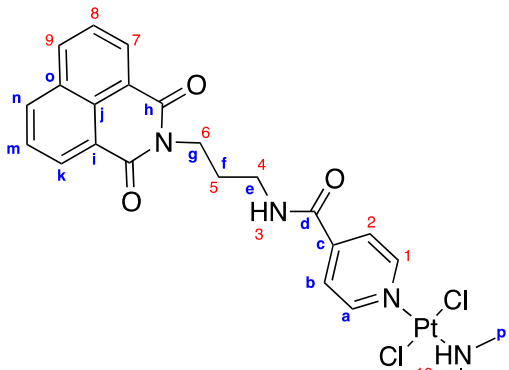
**General procedure for the synthesis of *trans*-platinum(II) complexes 3a-c.** To a solution of *cis*-$[PtCl_2(dma)_2]$ (0.20 g, 0.56 mmol,) in the minimum amount of water was added the corresponding ligand **1a-b** or, **2c** (2.25 mmol) and the mixture was stirred at 95 ºC for 16 h. After cooling, the mixture was filtrated and the yellow solution was refluxed with hydrogen chloride (11.20 mmol) at 95 ºC for 1 h (ligand **1a**) or 16 h (ligands **1b** and **2c**) to obtain a solid, which was filtered, washed with water and purified as indicated in each complex.

***trans*-[$PtCl_2$(1a)($NH(CH_3)_2$)] (3a)**: The pale yellow solid was dissolved in 20 mL of chloroform, filtered (0.2 μm filter) and precipitated using hexane to obtain a pale yellow solid, which was vacuum-dried for 48 h at 60 °C in a drying oven (31% yield). MP: 242-244 ºC (decomp.). $^{1}$H NMR (DMSO-$d_6$, 300 MHz): δ 8.52-8.42 (m, 4H, $H_5$ and $H_7$), 7.87 (t, *J* = 7.8 Hz, 2H, $H_6$), 5.10-4.98 (m, 1H, $H_8$), 4.47-4.35 (m, 2H, $H_1$), 4.10 (t, *J* = 6.3. Hz, 2H, $H_4$), 2.58-2.42 (m, 2H, $H_2$), 2.34 (d, *J* = 5.7 Hz, 6H, $H_9$), 2.15-2.03 (m, 2H, $H_3$). $^{13}$C NMR (DMSO-$d_6$, 75 MHz): δ 163.7 (C, $C_d$), 134.3 (CH, $C_h$), 131.2 (CH, $C_e$), 130.8 (CH, $C_f$), 127.4 (C, $C_j$), 127.2 (CH, $C_g$), 122.0 (CH, $C_i$), 42.9 ($CH_2$, $C_a$), 42.8 ($CH_3$, $C_k$), 37.0 ($CH_2$, $C_c$), 28.6 ($CH_2$, $C_b$). $^{195}$Pt NMR (DMSO-$d_6$, 64.5 MHz): δ - 2192. MS (MALDI) m/z: 530 $[M–Cl]^+$. Anal. Calcd for $C_{17}H_{21}Cl_2N_3O_2Pt$: C, 36.12; H, 3.74; N, 7.43. Found: C, 36.14; H, 3.84; N, 7.31.

***trans*-[PtCl$_2$(1b)(NH(CH$_3$)$_2$)]** (**3b**): The pale yellow solid was dissolved in 20 mL of chloroform, filtered (0.2 μm filter) and precipitated with hexane to obtain a pale yellow solid, which was vacuum-dried for 48 h at 60 °C in a drying oven (41% yield). MP: 169-171 ºC (decomp.). $^1$H NMR (CDCl$_3$, 300 MHz): δ 8.60 (d, *J* = 7.3 Hz, 2H, H$_8$), 8.20 (d, *J* = 8.3 Hz, 2H, H$_{10}$), 7.75 (t, *J* = 7.4 Hz, 2H, H$_9$), 4.17 (t, *J* = 7.3 Hz, 2H, H$_7$), 3.88-3.81 (bs, 1H, H$_{11}$), 3.38-3.17 (bs, 2H, H$_1$), 2.90-2.73 (m, 2H, H$_2$), 2.66 (d, *J* = 6.0 Hz, 6H, H$_{12}$), 1.81-1.60 (m, 4H, H$_3$ and H$_6$), 1.46-1.41 (m, 4H, H$_4$ and H$_5$). $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 164.4 (C, C$_g$), 134.0 (CH, C$_l$), 131.7 (C, C$_h$), 131.4 (CH, C$_j$), 128.3 (C, C$_i$), 127.1 (CH, C$_k$), 122.8 (C, C$_m$), 47.0 (CH$_2$, C$_a$), 43.6 (CH$_3$, C$_n$), 40.1 (CH$_2$, C$_f$), 31.2 (CH$_2$, C$_b$), 28.0 (CH$_2$, C$_e$), 26.6 (CH$_2$, C$_c$), 26.1 (CH$_2$, C$_d$). $^{195}$Pt NMR (CDCl$_3$, 64.5 MHz): δ - 2185. MS (ES$^+$) m/z: 608 [M]$^+$; 572 [M–Cl]$^+$. Anal. Calcd for C$_{20}$H$_{27}$Cl$_2$N$_3$O$_2$Pt: C, 39.55; H, 4.48; N, 6.92. Found: C, 39.54; H, 4.40; N, 6.68.



***trans*-[PtCl$_2$(2c)(NH(CH$_3$)$_2$)]** (**3c**): The pale yellow solid was resuspended in 20 mL of water and refluxed at 95 ºC for 2 h to obtain a pale yellow solid, which was vacuum-dried for 48 h at 60 °C in a drying oven (32% yield). MP: 230-232 ºC (decomp.).$^1$H NMR (CDCl$_3$, 300 MHz): δ 9.02 (d, *J* = 5.3 Hz, 2H, H$_1$), 8.67 (d, *J* = 7.3 Hz, 2H, H$_7$), 8.30 (d, *J* = 8.3 Hz, 2H, H$_9$), 7.99-7.91 (m, 1H, H$_3$), 7.88-7.79 (m, 4H, H$_8$ and H$_2$), 4.35 (t, *J* = 6.0 Hz, 2H, H$_6$), 4.26-4.21 (m, 1H, H$_{10}$), 3.42-3.48 (m, 2H, H$_4$), 2.78 (d, *J* = 6.0 Hz, 6H, H$_{11}$), 2.14-2.07 (m, 2H, H$_5$). $^{13}$C NMR (CDCl$_3$, 75 MHz): δ 165.1 (C, C$_h$), 163.2(C, C$_d$), 154.3(CH, C$_a$), 143.4(C, C$_c$), 134.8(CH, C$_n$), 132.0(CH, C$_k$), 131.8(C, C$_o$), 128.4(C, C$_i$), 127.3(CH, C$_m$), 122.9(CH, C$_b$), 122.2(C, C$_j$), 43.7(CH$_3$, C$_p$), 37.5(CH$_2$, C$_g$), 36.5(CH$_2$, C$_e$), 27.6(CH$_2$, C$_f$). $^{195}$Pt NMR (CDCl$_3$, 64.5 MHz): δ - 2046. MS (ES) m/z: 670 [M]$^+$; 635 [M–Cl]$^+$. Anal. Calcd for C$_{23}$H$_{24}$Cl$_2$N$_4$O$_3$Pt: C, 41.20; H, 3.61; N, 8.36. Found: C, 41.62; H, 3.71; N, 8.30.



**Synthesis of *trans*-platinum(IV) complex 4a:** To a solution of *cis*-[PtCl$_2$(dma)$_2$] (0.25 g, 0.70 mmol,) in water (10 mL) was added ligand **1a** (0.45 g, 1.76 mmol) and the mixture was stirred at 95 ºC for 16 h. After cooling, the mixture was filtrated and the pale yellow solution was refluxed with hydrogen chloride (11.20 mmol) at 95 ºC for 24 h. The resulting yellow solid was filtered, washed with water and purified by trituration with acetone/hexane (38% yield). MP: 230-232 ºC (decomp.).$^1$H NMR (acetone-d$_6$, 300 M

Hz): δ 8.61 (dd, *J* = 7.3, 1.0 Hz, 2H, $H_5$), 8.49 (dd, *J* = 8.3, 0.9 Hz, 2H, $H_7$), 7.92 (t, *J* = 7.4 Hz, 2H, $H_6$), 4.37 (t, *J* = 6.4 Hz, 2H, $H_4$), 3.17-3.07 (m, 2H, $H_2$), 2.74 (d, *J* = 5.8 Hz, 6H, $H_9$), 2.40 (quint, *J* = 6.7 Hz, 2H, $H_3$). $^{13}$C NMR (acetone-$d_6$, 100 MHz): δ 165.8 (C, $C_d$), 135.9 (CH, $C_i$), 133.5 (C, $C_j$), 132.7 (CH, $C_g$), 129.7 (C, $C_f$), 128.8 (CH, $C_h$), 124.3 (C, $C_e$), 46.5 ($CH_3$, $C_k$), 46.4 ($CH_2$, $C_a$), 38.4 ($CH_2$, $C_c$), 29.2 ($CH_2$, $C_b$). $^{195}$Pt NMR (acetone-$d_6$, 64.5 MHz): δ - 302. MS (MALDI) m/z: 600 [M–Cl]$^+$. Anal. Calcd for $C_{17}H_{21}Cl_4N_3O_2Pt$: C, 32.09; H, 3.33; N,6.60. Found: C, 32.43; H, 3.24; N, 6.32.

## [$^1$H $^{13}$C] 2D NMR SPECTRA

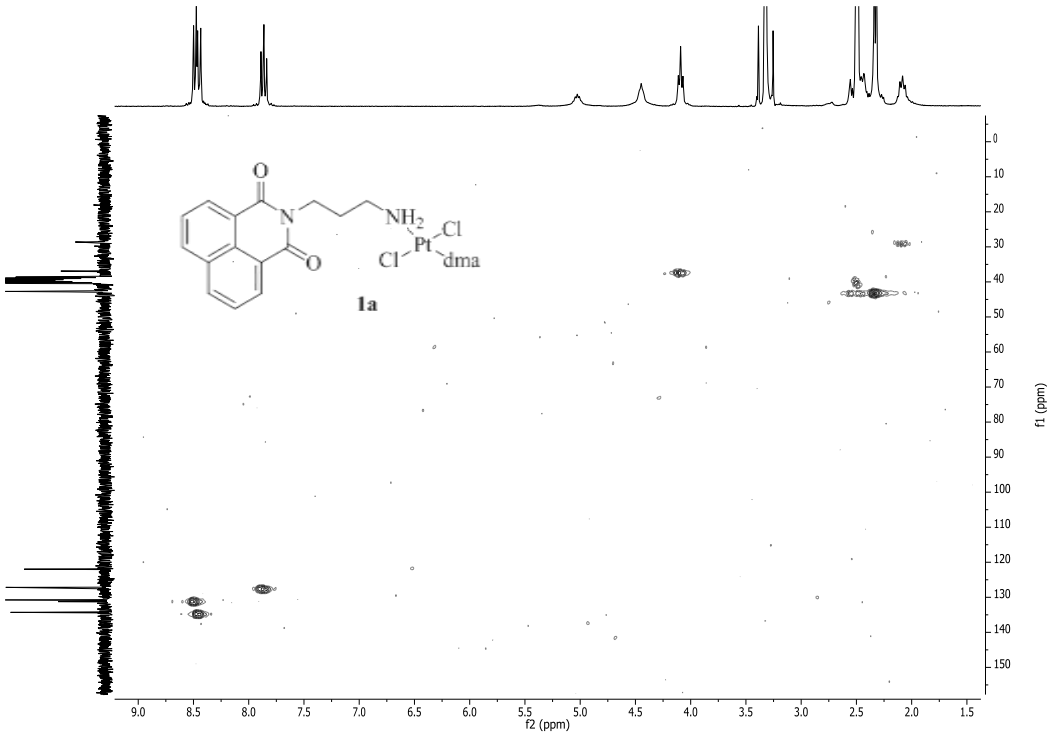



**Figure S4** . [$^1$H $^{13}$C] 2D NMR spectra of complex **1a**

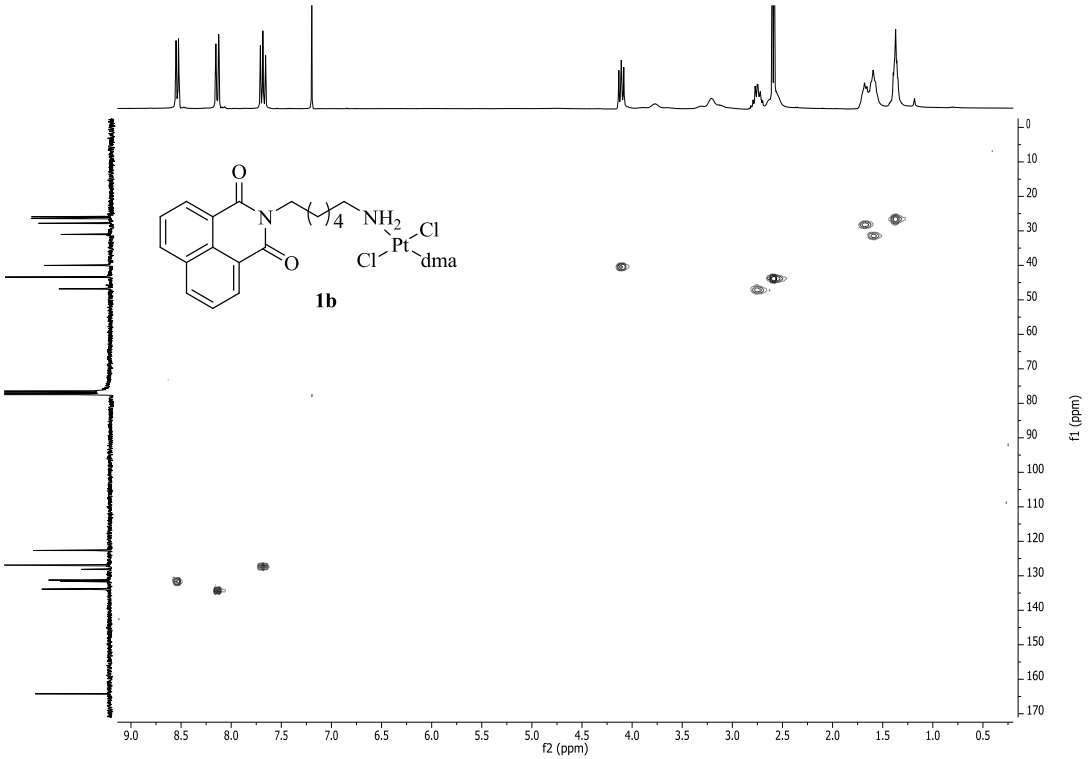



**Figure S5** . [$^{1}$H $^{13}$C] 2D NMR spectra of complex **1b**

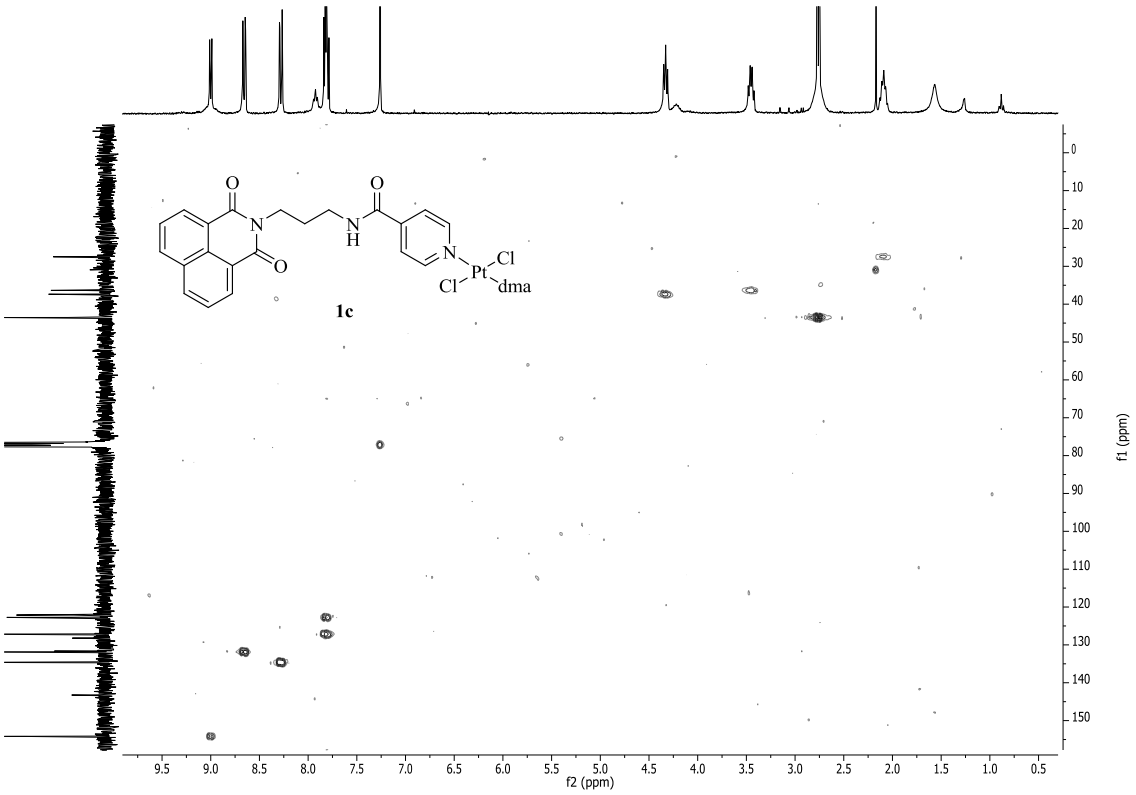



**Figure S6** . [$^{1}$H $^{13}$C] 2D NMR spectra of complex **1c**

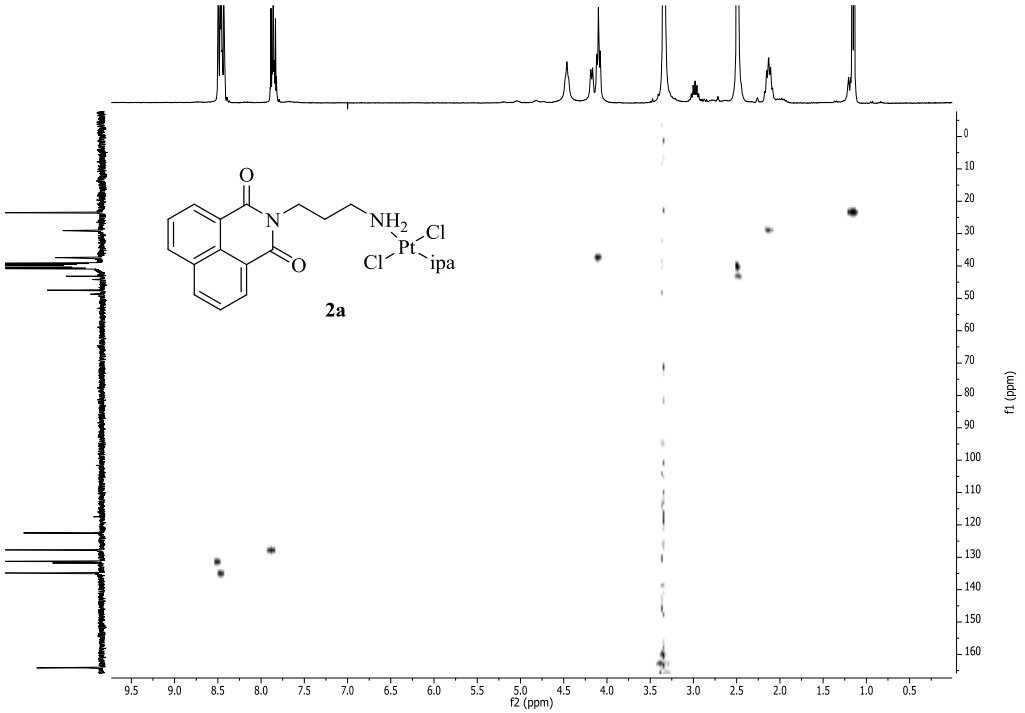



**Figure S7** . [$^{1}$H $^{13}$C] 2D NMR spectra of complex **2a**

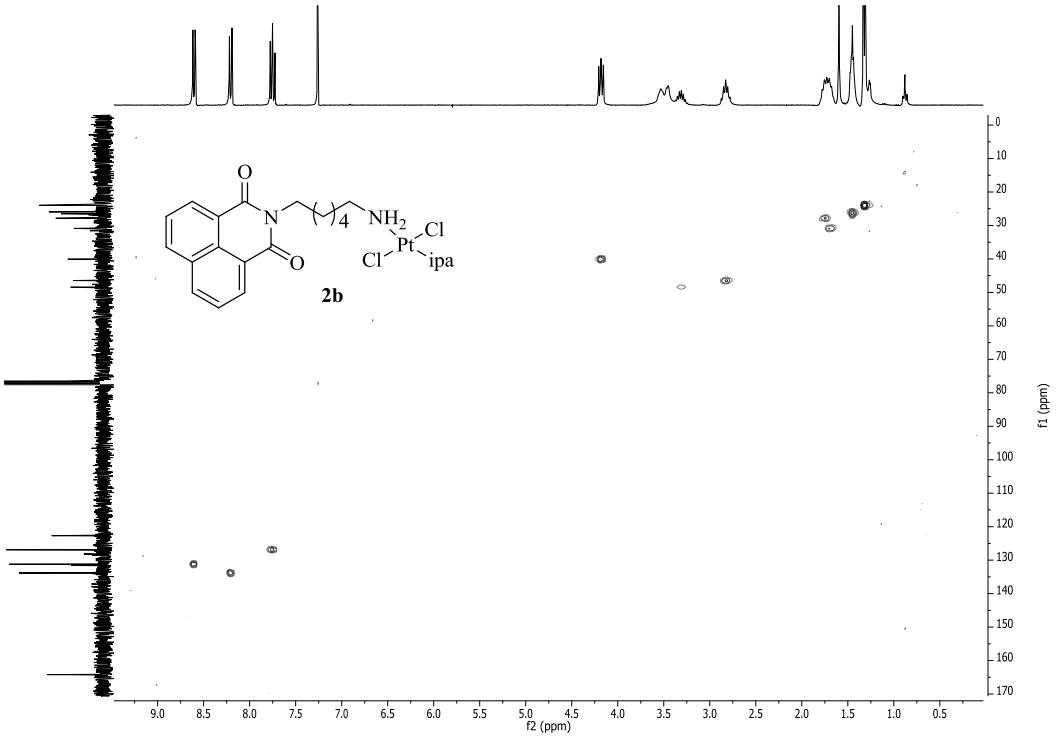



**Figure S8** . [$^{1}$H $^{13}$C] 2D NMR spectra of complex **2b**

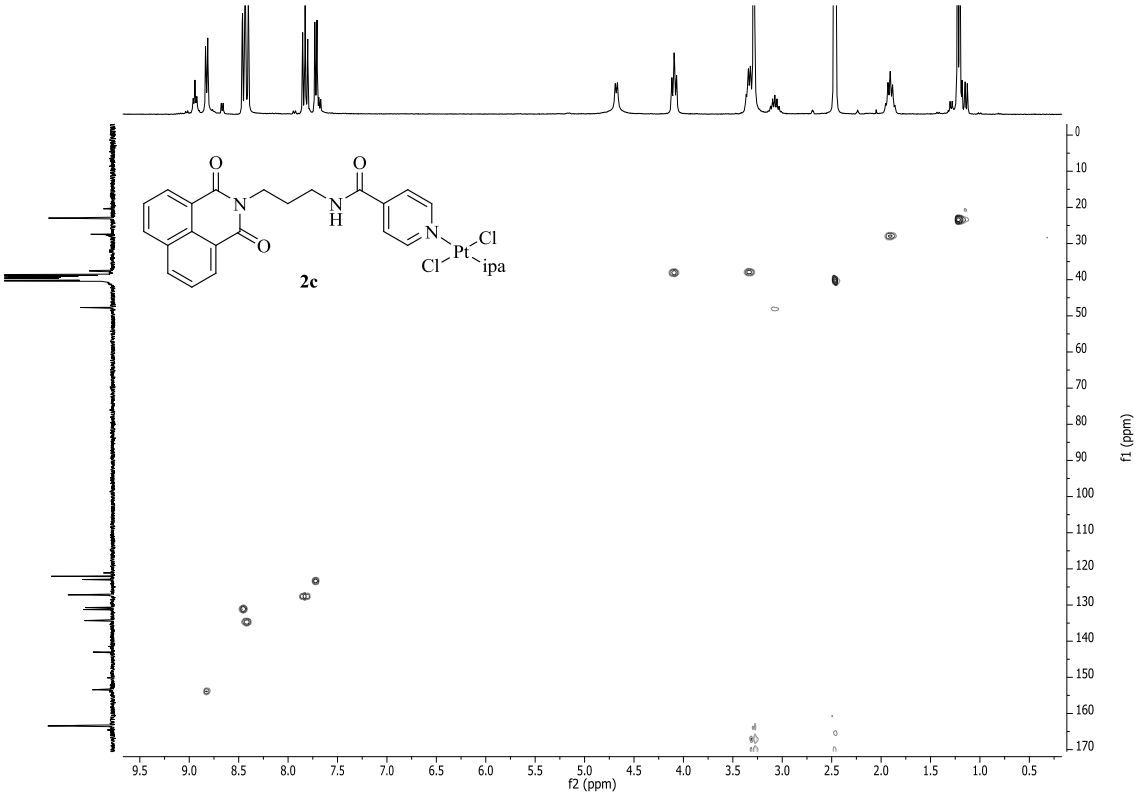



**Figure S9** . [$^{1}$H $^{13}$C] 2D NMR spectra of complex **2c**