

Supporting Information

Design and Synthesis of dual Imageable Theranostic Platinum Prodrug for Efficient Cancer Therapy

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Experimental section:

Synthesis of 1:

In a round bottomed flask 1 g of cis-5-Norbornene-exo-2, 3-dicarboxylic anhydride (0.006 mol) and 0.55 g glycine (0.0072 mol) was dissolved in dry toluene. The flask was kept under nitrogen atmosphere and triethylamine was added to it. Then the reaction mixture was refluxed at 120 °C for 12 h. After completion of the reaction solvent was evaporated and the crude mass redissolved in DCM and washed with 2(N) HCl. The collected DCM layer was dried over anhydrous Na₂SO₄ and concentrated to get white solid mass as pure product. Yield: 1 g (80%, 0.0048 mol) ¹H NMR (DMSO-D₆, 500 MHz) δ (ppm): 13.1 (bs,1H), 6.32 (s, 2H), 4.065(s, 2H), 3.124 (s, 2H), 2.75 (s, 2H), 1.6 (m, 1H), 1.34(1H, m) (Figure S1).

Synthesis of 2:

2 g of 1, 3-Diamino-2-propanol (0.022 mol) was dissolved in THF-water mixture (1:1) and stirred in an ice bath. 10 g of boc anhydride (0.0466 mol) in THF was added to it in a drop-wise fashion. After complete addition the mixture was warmed to room temperature and stirred for overnight. After completion of the reaction the solvent was evaporated under reduced pressure. The basic residue was redissolved in water and washed with dichloromethane. Then the DCM layer was washed with brine solution, dried over anhydrous sodium sulphate and evaporated under reduced pressure to get white powder as pure product. Yield: 4.5 g (0.0165 mol, 75%) ¹H NMR (DMSO-D₆, 500 MHz) δ (ppm): 5.02 (s, 1H), 3.85 (m, 1H), 3.15-3.25 (4H, m), 1.37(s, 18H) (Figure S2). ¹³C NMR (CDCl₃, 500 MHz) δ (ppm):155.8, 80, 71.5, 43, 28; (Figure S3).

Synthesis of 2a:

1 g of **1** (0.0045 mol) was dissolved in dry DCM. To this 1 g of EDC. HCl (0.00675 mol) and catalytic amount of DMAP were added to it and the mixture was stirred for 1 h. Then 1.2 g of

2 (0.004 mol) was added to it and stirred for 24 h at room temperature. After completion of the reaction the precipitate was filtered off and diluted with DCM. Then the filtrate was washed with saturated sodium bicarbonate and brine solution. The filtrate was dried over anhydrous sodium sulphate and evaporated under reduced pressure to give white mass as product. Yield: 1.6 g, (0.0033 mol, 75%). **¹H NMR (DMSO-D₆, 500 MHz) δ (ppm):** 6.91(s, 2H), 6.32 (t, 2H), 4.74(m,1H), 4.19(2H, s), 3.124(2H, s), 3.05-2.8(4H, m), 2.75(2H, s), 1.37(18H, s), 1.2-1.3 (2H, m); **(Figure S4).** **¹³C NMR (DMSO-D₆, 500 MHz) δ (ppm):** 177.1, 155.9, 137.5, 77.6, 73.3, 68.9, 47.8, 44.5, 42.1, 28.3 **(Figure S5).** MS (ESI) calculated for C₂₄H₃₅N₃O₈ [M + H]⁺: 494.25 ; observed: 494.25 **(Figure S22).**

Synthesis of 3:

2 g of maleimide (0.02 mol) was dissolved in diethyl ether in a dry sealed tube and 3 ml of furan (0.04 mol) was added to it. The mixture was heated at 95 °C for 12 hours. After completion of the reaction the product was collected as white precipitate after washing with diethyl ether for several times. The product was dried for overnight under vacuum. Yield: 2.97g (0.018 mol, 90%). **¹H NMR (DMSO-D₆, 500 MHz):** δ (ppm): 6.5 (s, 2H), 5.2 (s, 2H), 2.9 (s, 2H), 11.1 (broad, 1H) **(Figure S6).** **¹³C NMR (DMSO-D₆, 500 MHz):** δ (ppm): 178, 136, 80, 48 **(Figure S7).**

Synthesis of 4:

A mixture of potassium carbonate 1.01 g (0.0073 mol) and 1 g of **1** (0.0049 mol) were dissolved in dry DMF in a two neck round bottomed flask equipped with magnetic stirrer. The reaction mixture was stirred for 1 hour at 50 °C and then it was degassed. 0.67 ml of propargyl bromide (0.00735 mol) was added in a drop wise fashion to that mixture and stirred for 24 hours at 50 °C. The crude product was collected from EtOAc layer and washed several

times with water. Column chromatography separation using EtOAc-Hexane as eluent produced the pure white product. Yield: 0.75 g (0.00369 mol, 75%). ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 6.5(s, 2H), 5.2(s, 2H), 4.2(d, 2H), 2.9(s, 2H), 2.2(s, 1H) (Figure S8). ¹³C NMR (CDCl₃, 500 MHz), δ (ppm): 175, 136, 81, 71, 47, 27, 76.5 (Figure S9).

Synthesis of 5:

Commercially purchased 1 g of glycine (0.013 mol) was dissolved in dioxane-water mixture (2:1). 550 mg of NaOH (0.01365 mol) was added to it and the mixture was stirred for 1 hour to get the clear solution. Then reaction mixture was cooled to 0 °C. Boc anhydride (0.0143 mol) was added drop wise to the reaction mixture over half an hour. The resulting reaction mixture was warmed to room temperature and stirred overnight. After completion of the reaction the solvent was evaporated under reduced pressure. The basic residue was redissolved in water and washed with ethyle acetate. Then the water layer was acidified using 1 (N) KHSO₄ solution to pH 2. Then the water layer washed again with ethyle acetate. The combined organic layer were dried over anhydride Na₂SO₄, filtered and concentrated under reduced pressure to afford colourless oil which slowly give colourless solid under high vacuum. Yield: 1.82 gm (0.0104 mol, 80%) ¹H NMR (DMSO-D₆, 500 MHz) δ (ppm): 12.4(s, 1H), 7.1(t, 1H), 3.6(d, 2H), 1.37(s, 9H) (Figure S12). ¹³C NMR (CDCl₃, 500 MHz) δ (ppm): 172, 156, 78, 42, 28 (Figure S13). ESI MS calculated for C₈H₇NO₃ [M+H]⁺, 166.04; observed, 166.09.

Synthesis of 6:

1 g of N-Boc glycine (0.0057 mol) was dissolved in THF and 1.29 g of DCC (0.0062 mol) was added to it and stirred vigorously at room temperature for half an hour. Then 7.8 g of PEO (0.0054 mol) and 0.069 g of DMAP (0.00057 mol) was added to it and the reaction

mixture stirred for overnight. After completion of the reaction acetone was added to it to precipitate the DCU. Then the reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue again re-dissolved in DCM and kept in 4° C for several hours. Then again filtered and precipitated in diethyl ether to get white sticky product. Yield: 6.4 g (0.0039 mol, 70%). ¹H NMR (DMSO-D₆, 500 MHz) δ (ppm): 7.2(t, 1H), 4.6(m, peg), 3.6(s, peg), 1.37(s, 9H) (Figure S14). ESI MS calculated for [M+H]⁺, 796.18; observed, 796.25.

Synthesis of 7:

1 g of exo-5-Norborne carboxylic acid (0.0072 mol) was dissolved in dry DCM. To this 1.65 g of DCC (0.0079 mol) and 0.088 g of DMAP (0.000724 mol) were added to it and the mixture was stirred for 1 hour. Then 11.1 g of **4** (0.00684 mol) was added to it and stirred for 24 hours at room temperature. After completion of the reaction the precipitate was filtered off. The filtrate was precipitated in cold hexane to get the white sticky product. Yield: 9.5 g, (0.00504 mol, 70%). ¹H NMR (CDCl₃, 500 MHz) δ (ppm): 6.1(m, 2H), 4.6(m, 4H), 3.6(m, peg), 2.9(1H, m), 3.03(1H, m), 2.2(1H, m), 1.9(1H, m), 1.5(1H, m), 1.44(9H, s) 1.2(1H, m) (Figure S15). ESI MS calculated for [M+H]⁺, 917.14, observed, 917.29.

Synthesis of 8:

1 g of **5** (0.000567 mol) was dissolved in DCM and TFA was added to it. The reaction mixture was stirred for 2 hours. After completion of the reaction the reaction mixture was concentrated under reduced pressure and re dissolved in DCM. Then it was washed with saturated NaHCO₃, followed by brine solution. The DCM layer was evaporated under reduced pressure and precipitated in cold hexane to get white sticky product. Yield: 850 mg (0.00051 mol, 90%) ¹H NMR (DMSO-D₆, 500 MHz) δ (ppm): 6.1(m, 2H), 4.1(4H, m),

3.6(s, broad), 2.98(1H, m), 2.9(1H, m), 2.1(1H, m), 1.8(1H, m), 1.2-1.3(2H, m) (**Figure S16**).

ESI MS calculated for $[M+H]^+$, 817.21 observed, 817.26.

Synthesis of 9:

In a round bottom flask 3 g of Cis-1,4-butanediol (0.034 mol), 7.2 g of succinic anhydride (0.071 mol), and 830 mg of DMAP (0.0068 mol) was dissolved in dry THF and the mixture was heated reflux for 12 h. After completion of the reaction the solvent was evaporated under reduced pressure. The pure product was obtained by crystallization from diethyl ether and acetone (15:5) mixture to give white crystalline **10** as pure product. Yield: 6.8 g (0.0238 mol, 70%). $^1\text{H NMR}$ ($\text{DMSO-}d_6$, 500 MHz) δ (ppm): 10.5-12.0 (bs, 2H), 5.75 (m, 2H), 4.7 (dd, 4H), 2.5-2.56 (m, 8H) (**Figure S18**). $^{13}\text{C NMR}$ (CDCl_3 , 500 MHz) δ (ppm): 173.6, 127.7, 59.5, 28.5 (**Figure S19**).

Synthesis of $\text{PtCl}_2(\text{DMSO})_2$:³⁵

500 mg (1.204 mmol) of Potassium tetra-chloroplatinate was dissolved in deionized water and 0.25 mL of DMSO was added to it and the resulting mixture was allowed to stand at room temperature till the formation of yellow crystal within 1 h. The crystal was washed several times with deionized water and dried under high vacuum. $^{195}\text{Pt NMR}$ ($\text{DMF}/\text{D}_2\text{O}$) = -3463.5 ppm (**Figure S27**).

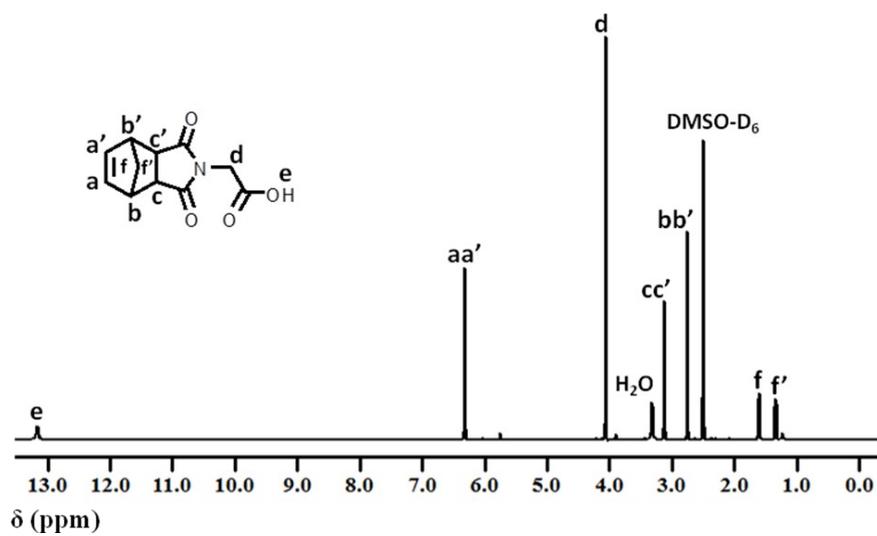


Figure S1: ^1H NMR spectrum of **1** in DMSO-D_6

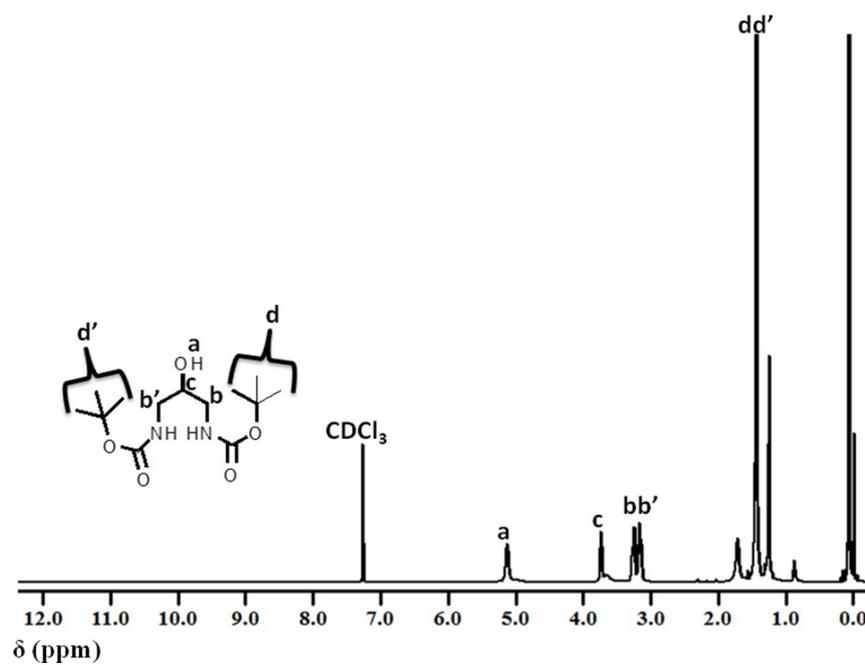


Figure S2: ^1H NMR spectrum of **2** in CDCl_3

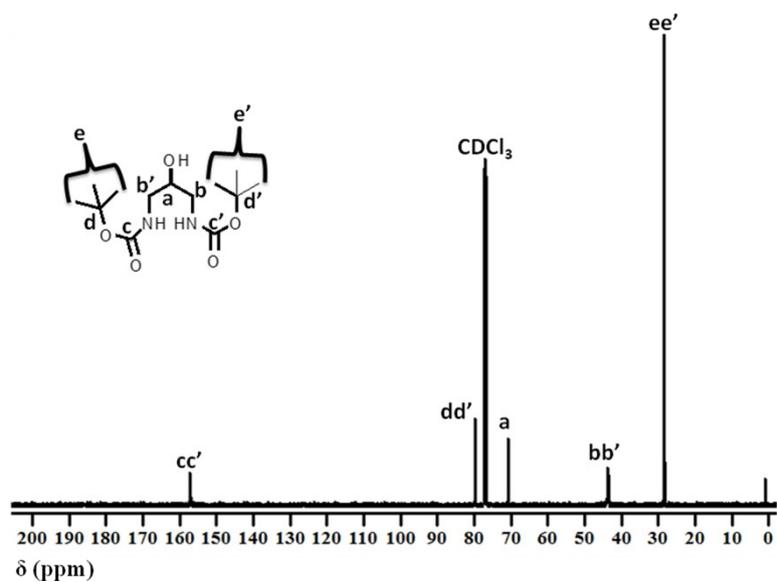


Figure S3: ^{13}C NMR spectrum of **2** in CDCl_3

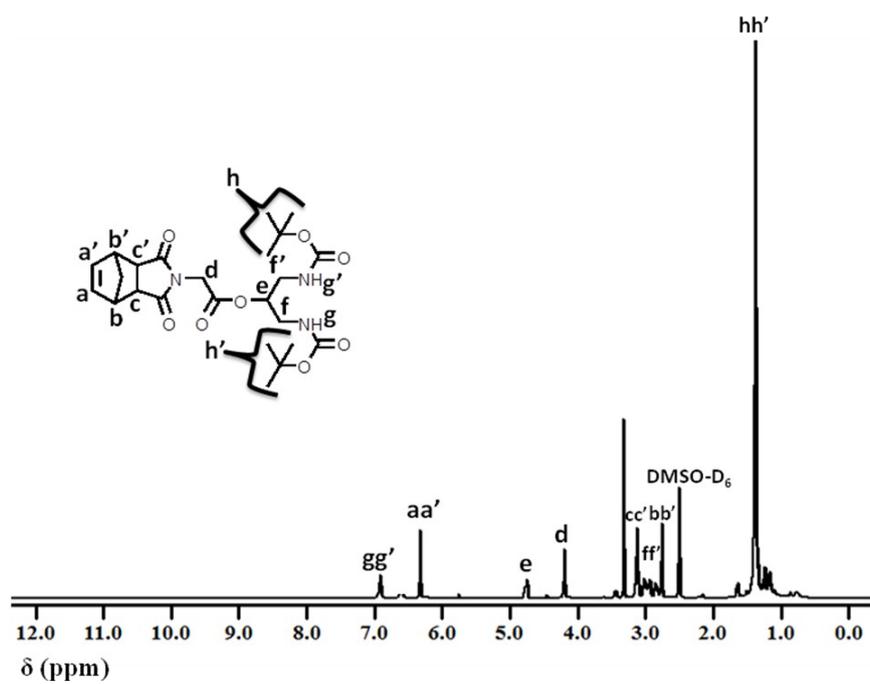


Figure S4: ^1H NMR spectrum of **2a** in DMSO-D_6

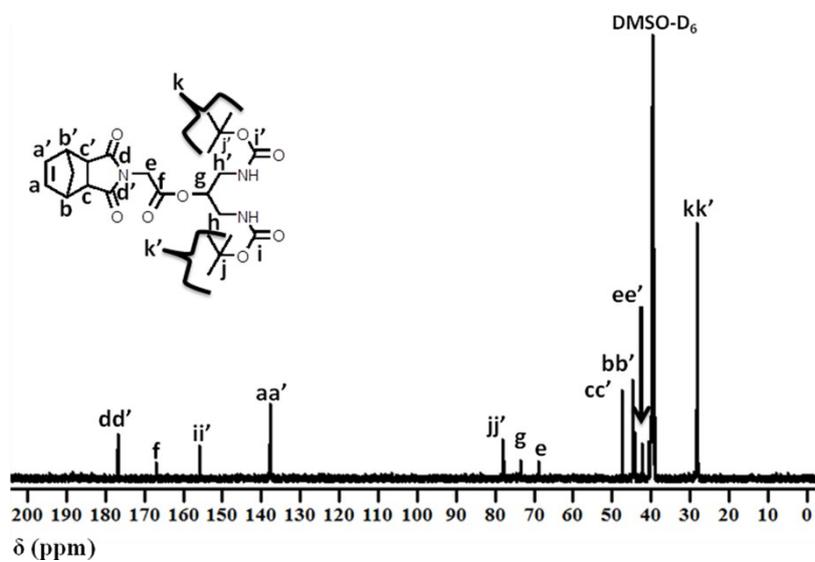


Figure S5: ^{13}C NMR spectrum of **2a** in DMSO-D_6

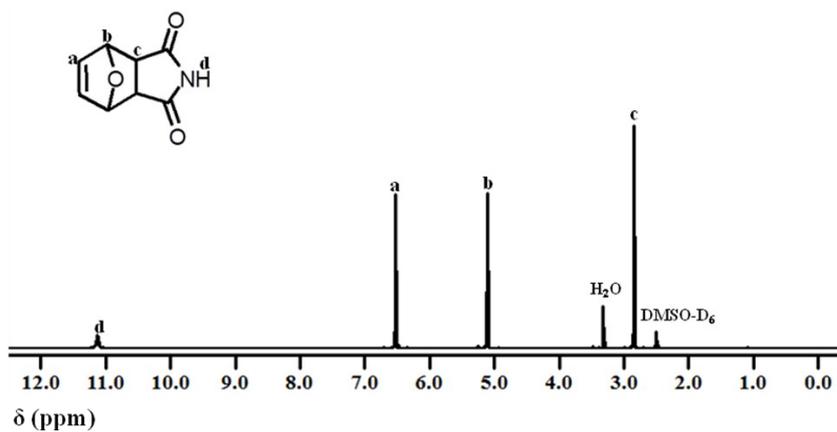


Figure S6: ^1H NMR spectrum of **3** in DMSO-D_6

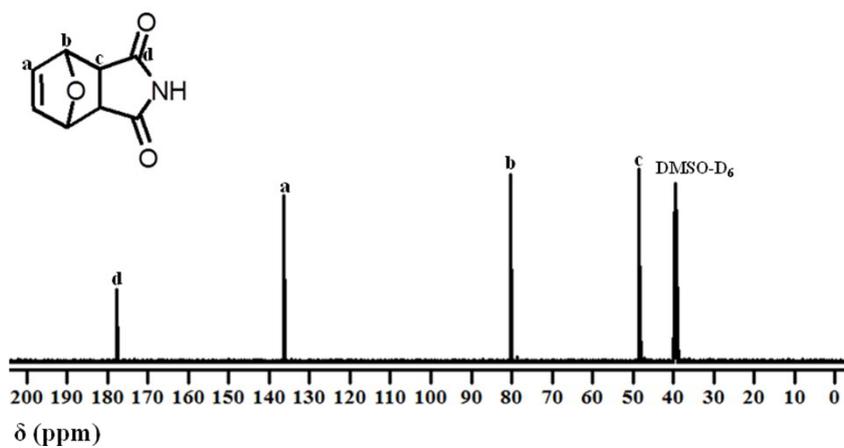


Figure S7: ^{13}C NMR spectrum of **3** in DMSO-D_6

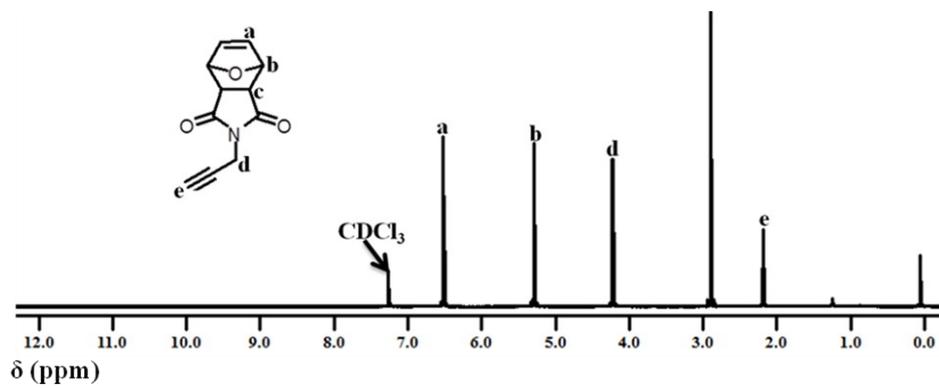


Figure S8: ^1H NMR spectrum of **4** in CDCl_3

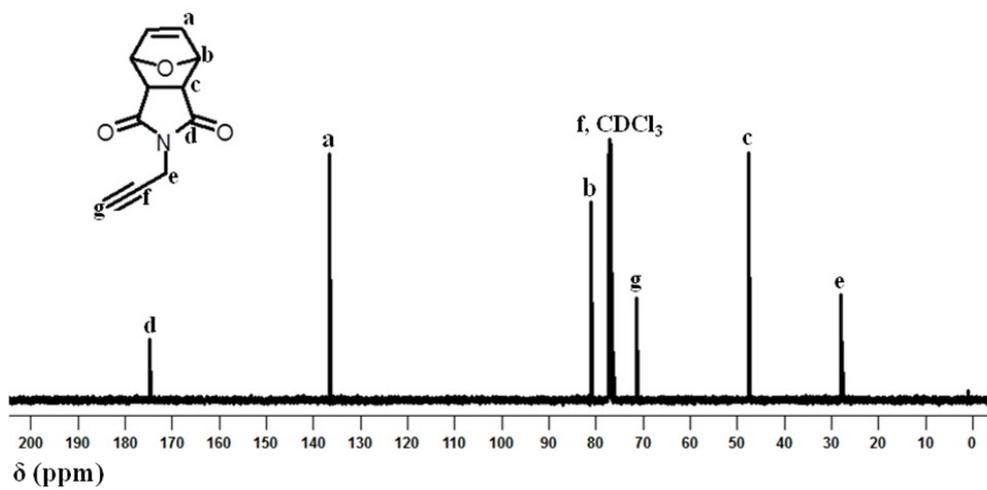


Figure S9: ^{13}C NMR spectrum of **4** in CDCl_3

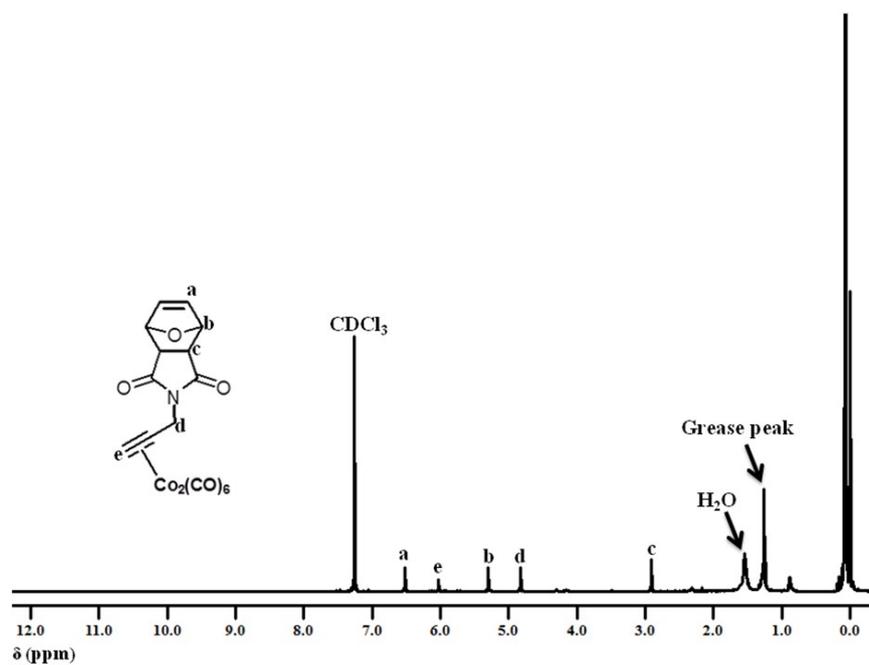


Figure S10: ^1H NMR spectrum of **4a** in CDCl_3

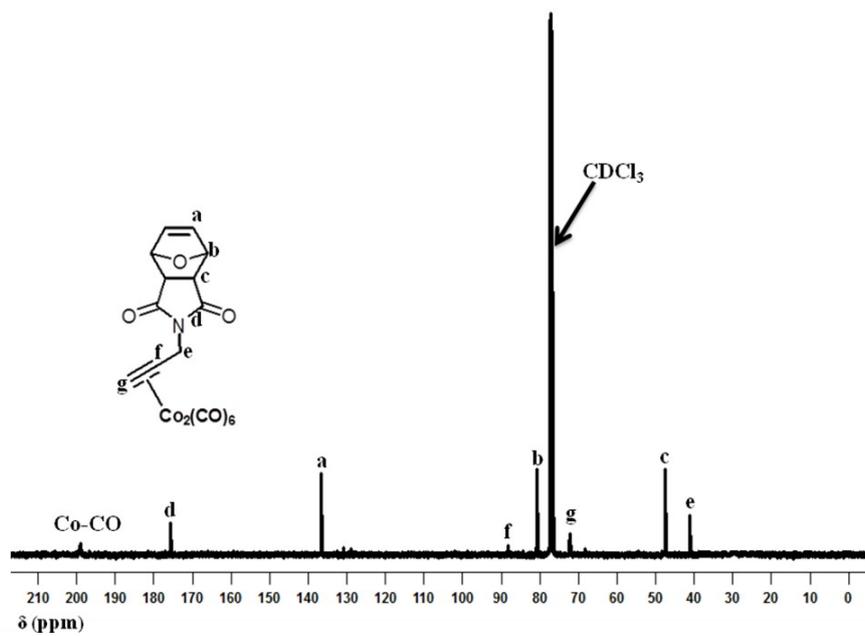


Figure S11: ^{13}C NMR spectrum of **4a** in CDCl_3

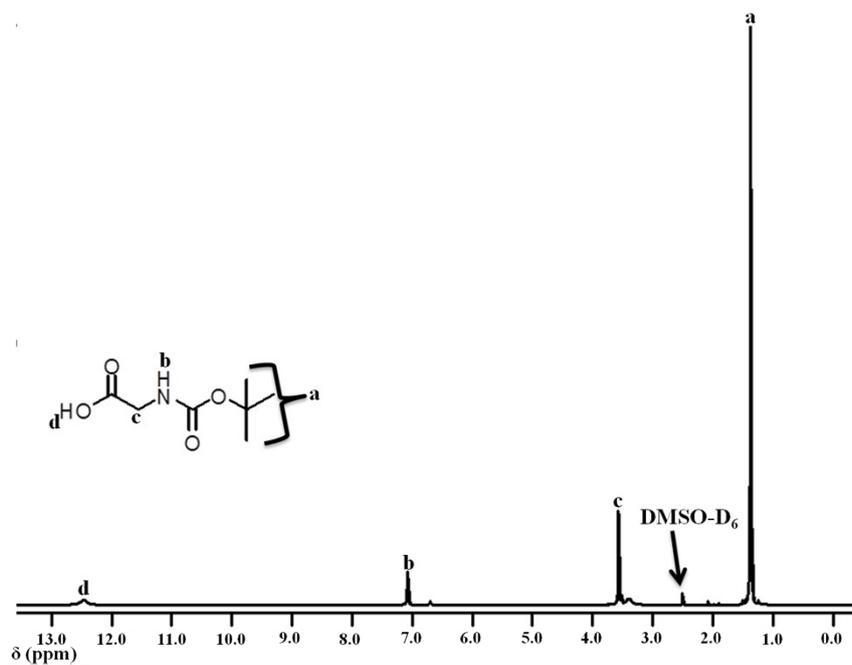


Figure S12: ^1H NMR spectrum of **5** in DMSO-D_6

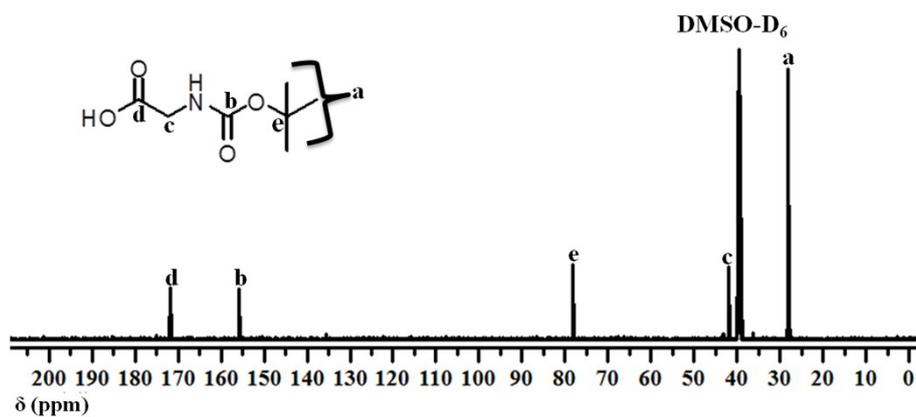


Figure S13: ^{13}C NMR spectrum of **5** in DMSO-D_6

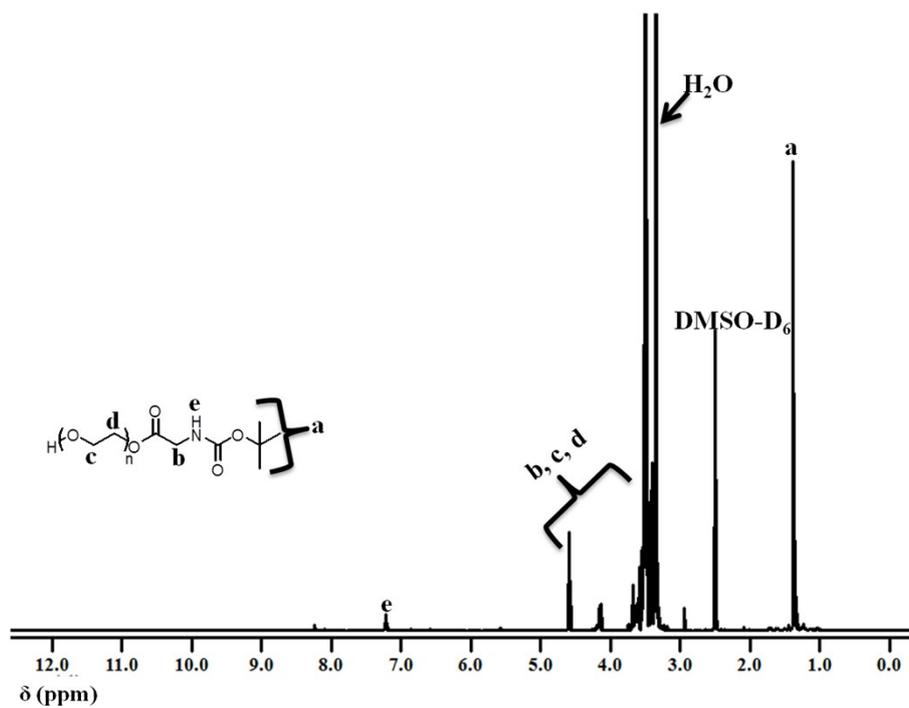


Figure S14: ^1H NMR spectrum of **6** in DMSO-D_6

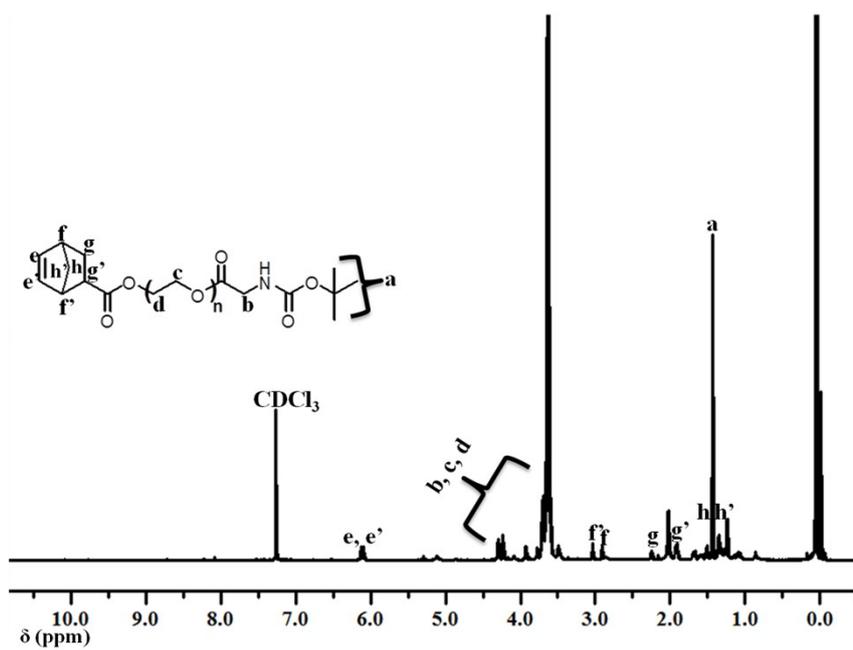


Figure S15: ^1H NMR spectrum of **7** in CDCl_3

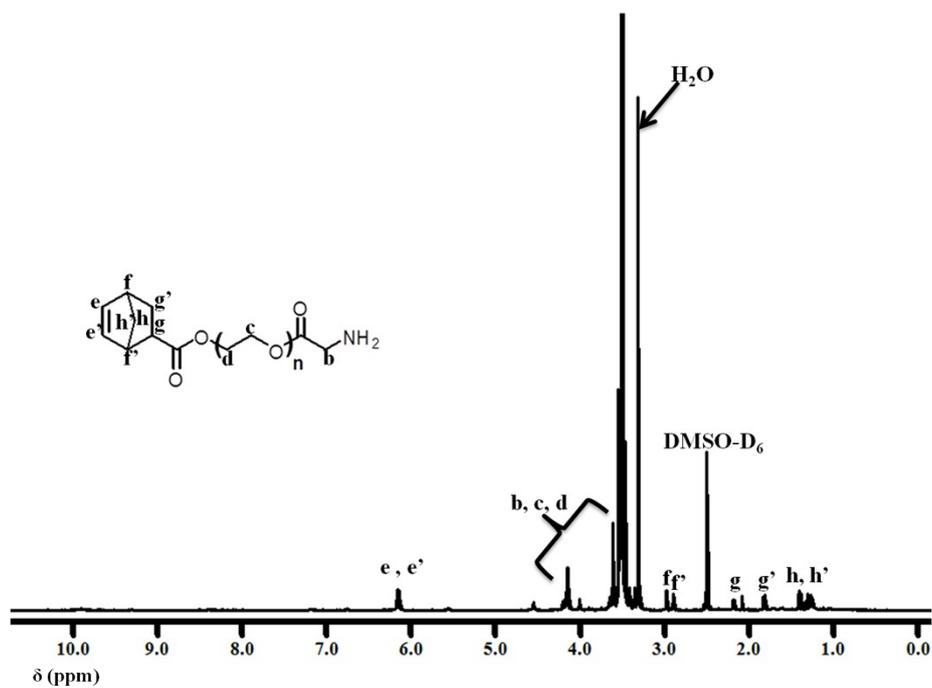


Figure S16: ^1H NMR spectrum of **8** in DMSO-D_6

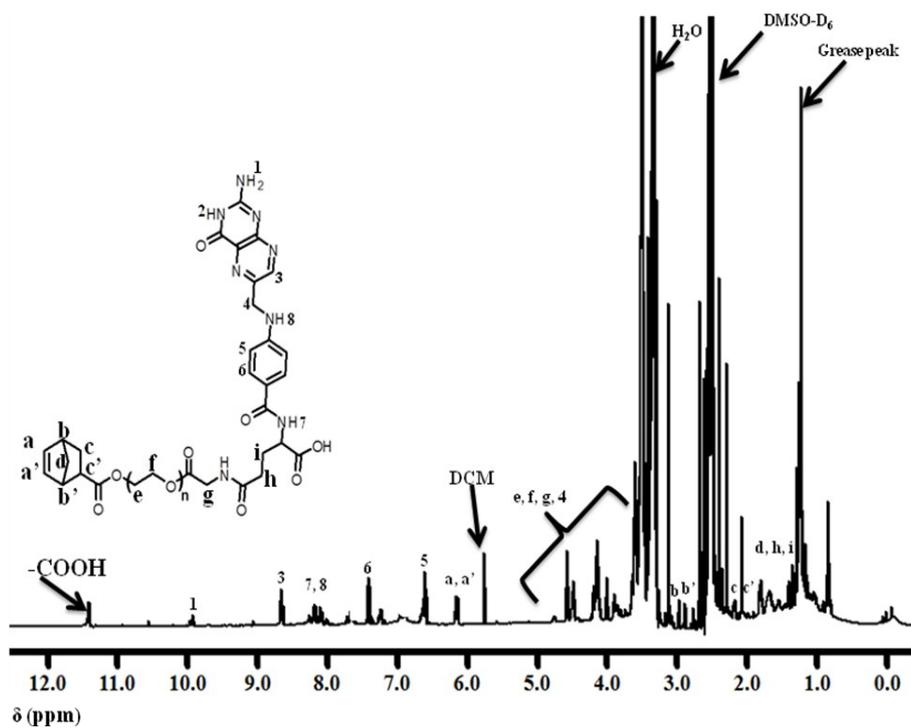


Figure S17: ^1H NMR spectrum of **8a** in DMSO-D_6

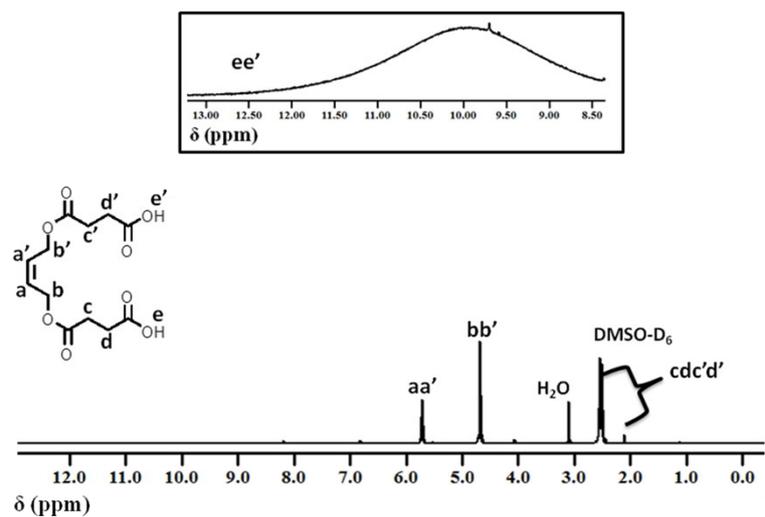


Figure S18: ^1H NMR spectrum of **9** in DMSO-D_6

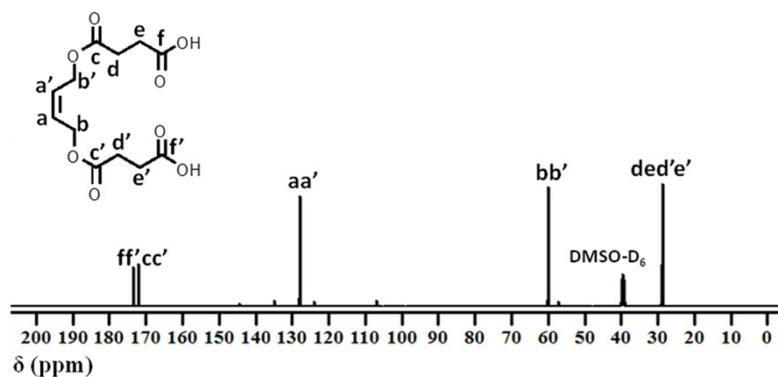


Figure S19: ^{13}C NMR spectrum of **9** in DMSO-D_6

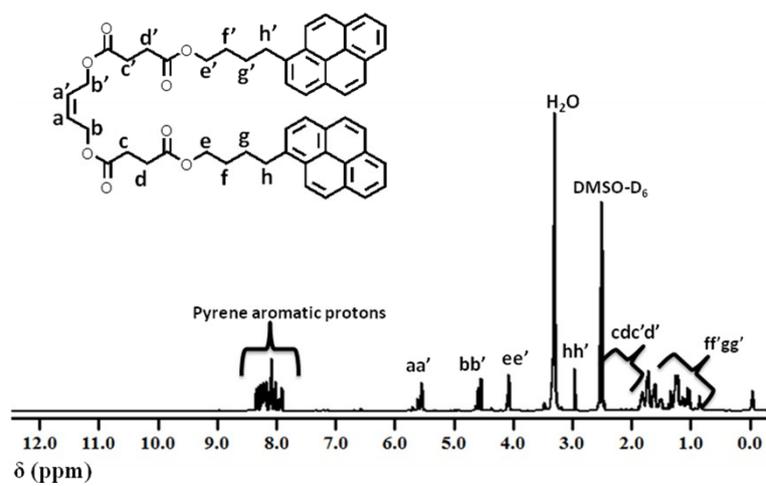


Figure S20: ^1H NMR spectrum of **9t** in DMSO-D_6

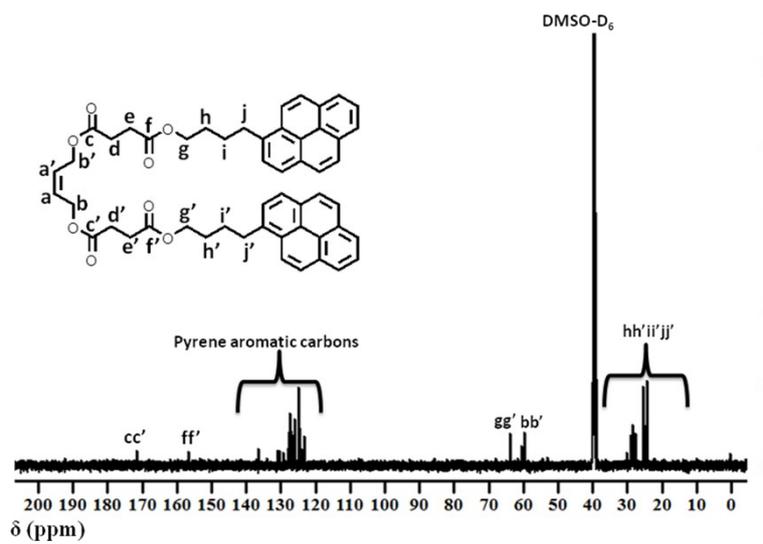


Figure S21: ^{13}C NMR spectrum of **9t** in DMSO-D_6

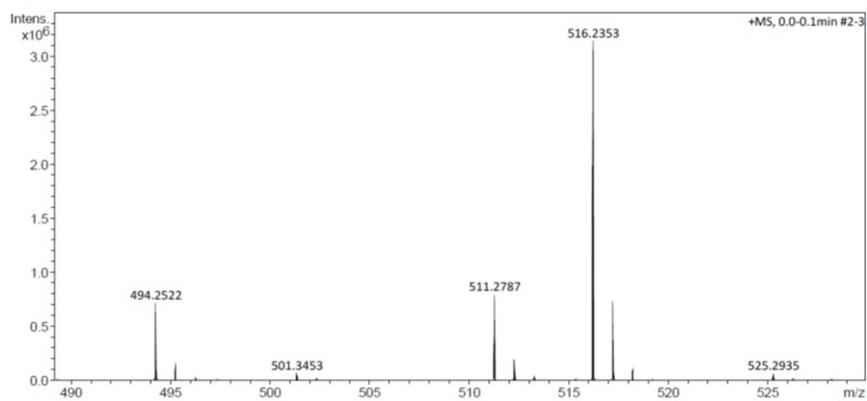


Figure S22: ESI-MS analysis of **2a**

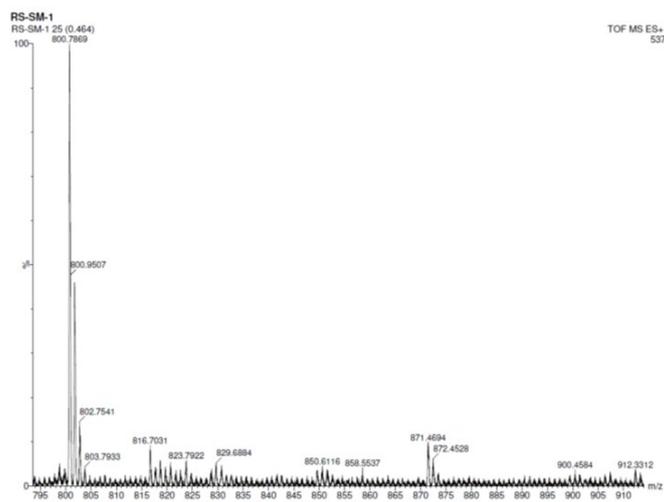


Figure S23: ESI-MS analysis of **9t**

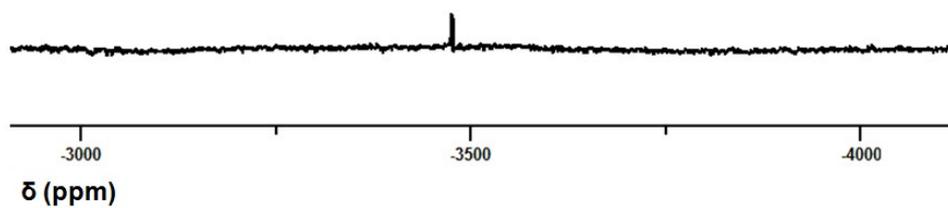


Figure S24: ^{195}Pt NMR of $[\text{PtCl}_2(\text{DMSO})_2]^{2-}$

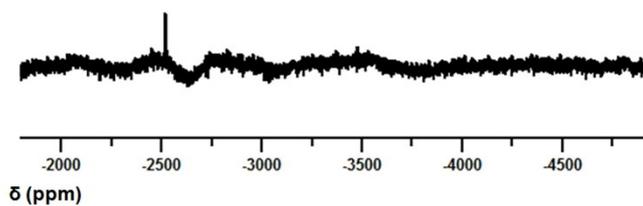


Figure S25: ^{195}Pt NMR of **Pnr-DapPt-Cbt-PgFl-endpy**

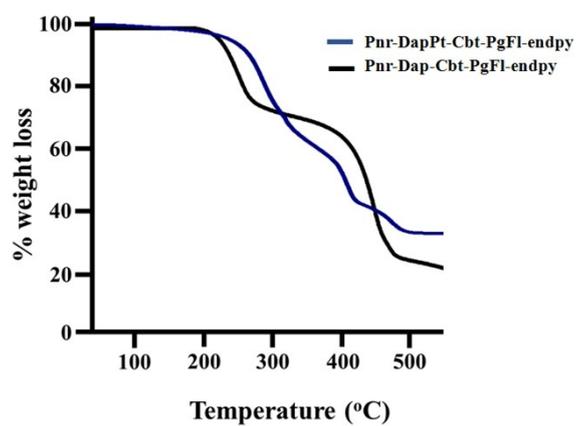


Figure S26: TGA analysis of **Pnr-Dap-Cbt-PgFl-endpy** and **Pnr-DapPt-Cbt-PgFl-endpy**