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An efficient synergistic cancer therapy by integrating cell cycle inhibitor and photosensitizer into polydopamine nanoparticles

- Supporting Information

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1.1. Synthesis of 4-(2,4,6-tris((dimethylamino)methyl)phenoxy)phthalonitrile

The compound 4-(2,4,6-tris((dimethylamino)methyl)phenoxy)phthalonitrile was synthesized according to the literature method with slight modification.[1] Briefly, 2, 4, 6-tris (*N, N'*-dimethylaminomethyl) phenol (2 g, 7.8 mmol) and K_2CO_3 (3.12 g, 22.6 mmol) were stirred in DMF (15 mL) for 1 h at room temperature (RT). To this mixture, a solution of 4-nitro-phthalonitrile (651.8 mg, 3.77 mmol) in DMF (15 mL) was added dropwise in 15 min at RT. The reaction mixture was then stirred for further 10 h until completion of the reaction, which was monitored by thin layer chromatography (TLC). The reaction mixture was filtered to remove the unreacted salt. The filtrate was added with water (30 mL), followed by concentrating under reduced pressure. Cold petroleum ether (15 mL at 3 ^oC) was added to the concentrate and stirred for 15 min to precipitate the product and wash out the impurities. The precipitates were collected and dried in vacuo to obtain 4-(2,4,6-tris((dimethylamino)methyl)phenoxy)phthalonitrile (750 mg, yield 50.8 %).

1.2. Synthesis of $ZnPc(TAP)_4$

$ZnPc(TAP)_4$ was synthesized by modifying the literature method as follows.[2, 3] 5 drops of 1, 8-diazabicyclo-[5.4.0]undec-7-ene (DBU) were stirred at a solution of compound 4-(2,4,6-tris((dimethylamino)methyl)phenoxy)phthalonitrile (500 mg, 1.28 mmol), and anhydrous zinc acetate (200 mg, 1.10 mmol) and n-pentanol (40 ml) were added. The reaction mixture was quickly heated up to 145 ^oC and refluxed for 8 h. At the end of reaction, the solvent was evaporated under reduced pressure and the residue was dissolved in THF (3 mL) followed by extraction of desired product by petroleum ether (30 mL). Next, the product was taken out of petroleum ether solution by washing with 0.25 M HCl aqueous solution (50 mL). Then, the solution was added with solid NaCl to become brine solution, followed by extraction with THF to remove the unreacted diiminoisoindoline impurities. Final, we used 0.25 M NaOH aqueous solution (50 mL) to precipitate the product. The precipitates were collected and dried in vacuo to obtain the $ZnPc(TAP)_4$ (100 mg, yield 19.2 %). ^{1}HNMR (DMSO-d_6), (δ: ppm): 7.70-7.52 (t, 12H, Pc-H), 7.31-7.25 (s, 8H, Ar-H), 3.67-3.45 (t, 24H, -CH_2), 2.44-2.20 (m, 72H, -CH_3).

1.3. Synthesis of $ZnPc(TAP)_4^{12+}$

Methylation of all amino moieties in compound $ZnPc(TAP)_4$ was carried out to synthesize compound $ZnPc(TAP)_4^{12+}$.[4] $ZnPc(TAP)_4$ (83 mg, 0.051 mmol) dissolved in DMF (50 mL) was reacted with CH_3I (43 µL, 0.6732 mmol) for 6 h at RT. The reaction mixture was concentrated to ~5 mL by removing the solvent under reduced pressure. The product was precipitated by addition of diethyl ether to the residue. The precipitates collected by centrifugation were dissolved in methanol. The insoluble impurities were filtered off and the filtrate was precipitated again by diethyl ether. The product was centrifuged and dried in vacuo to yield the $ZnPc(TAP)_4^{12+}$ (157 mg, yield 92 %). ^{1}HNMR (DMSO-d_6), (δ: ppm): 9.64-8.96 (m, 12H, Pc-H), 8.39-8.26 (s, 8H, Ar-H), 5.92-4.54 (d, 24H, -CH_2), 3.4-3.34 (s, 108H, -CH_3).

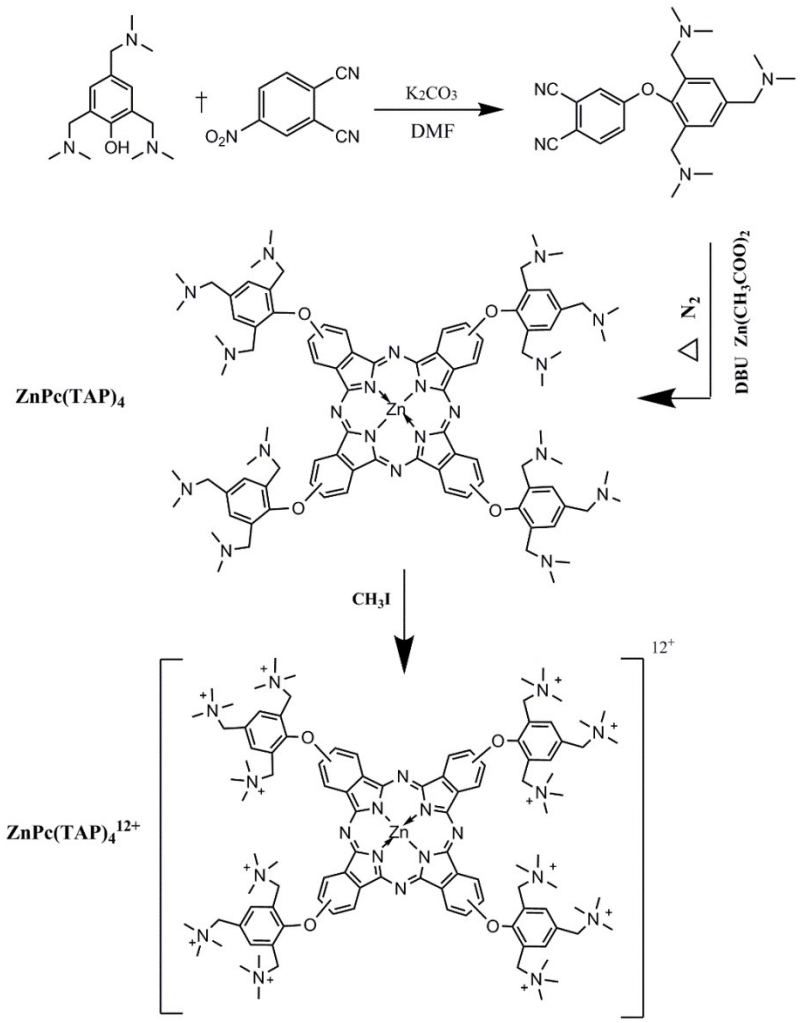

Figure S1. Synthesis of $ZnPc(TAP)_4^{12+}$. Briefly, 2, 4, 6-tris (N, N'-dimethylaminomethyl) phenol, 4-nitro-phthalonitrile and K_2CO_3 were stirred in DMF to yield the compound 4-(2,4,6-tris((dimethylamino)methyl)phenoxy)phthalonitrile, which were further processed to yield the $ZnPc(TAP)_4$. Methylation of all amino moieties in $ZnPc(TAP)_4$ was carried out to synthesize $ZnPc(TAP)_4^{12+}$.

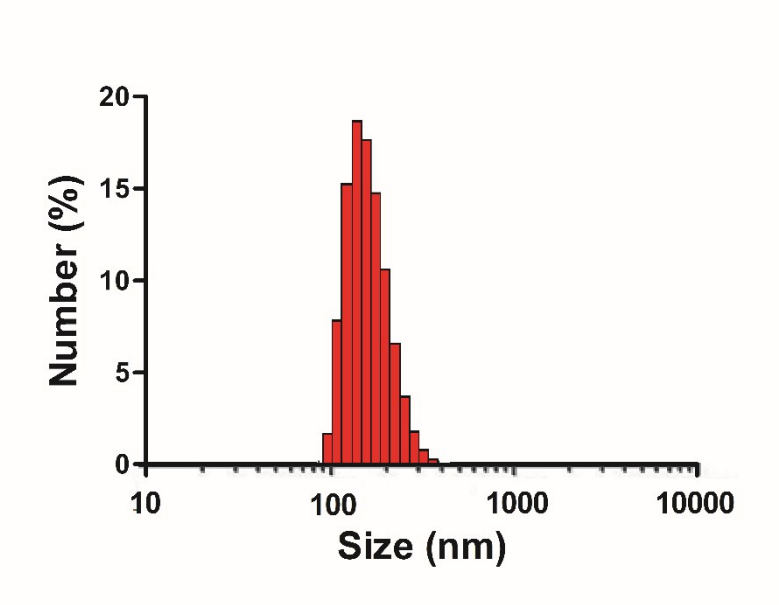

Figure S2. Size distributions of PDA nanoparticles in water measured with DLS.

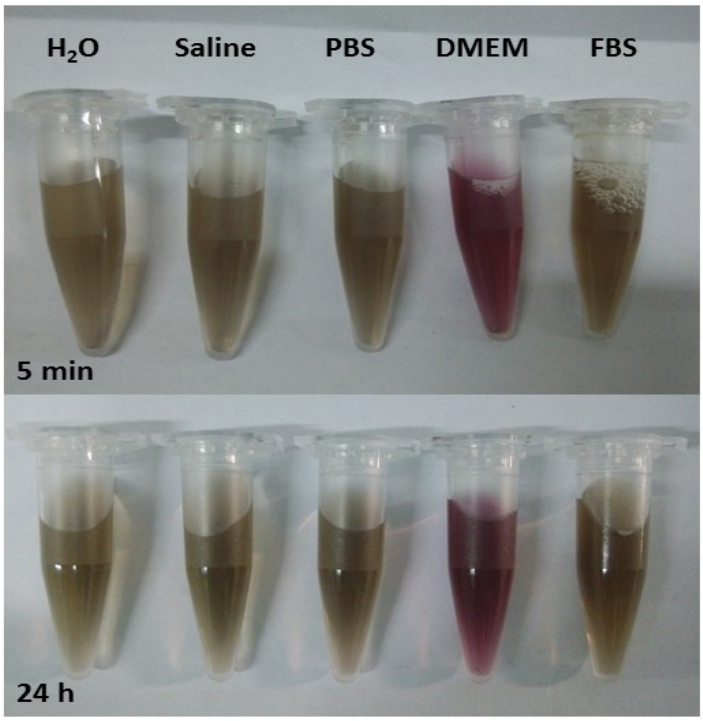

Figure S3. Photographs of PDA-NOC-ZnPc12^{+} nanoparticles in different solutions including water, saline, PBS, DMEM and FBS, which reveals the excellent dispersibility of PDA-NOC-ZnPc12^{+} nanoparticles.

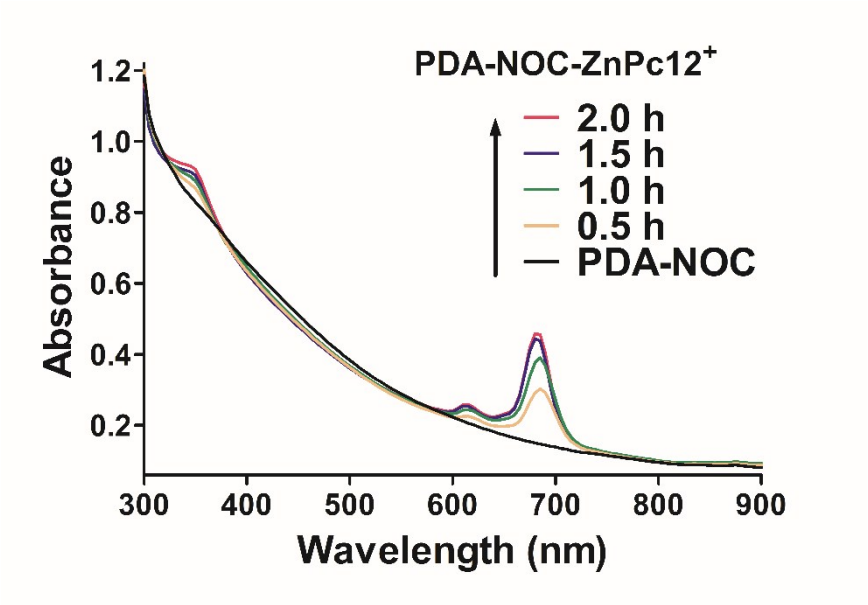

Figure S4. UV-Vis absorption spectrum of PDA-NOC and PDA-NOC-ZnPc12^{+} nanoparticles obtained at different incubation time.

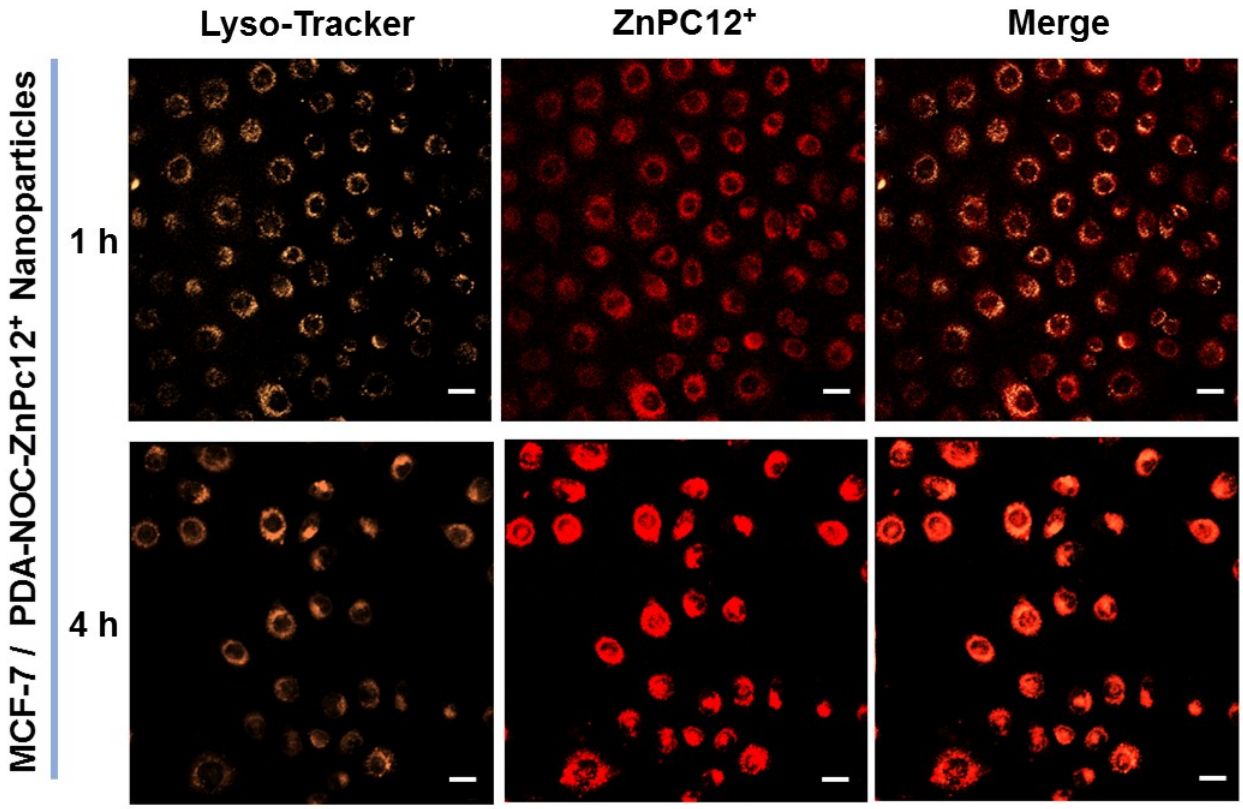

Figure S5. Cellular colocalization images of lysosomes (Lyso-Tracker) and PDA-NOC-ZnPc12^{+} nanoparticles at different incubation time (1, 4 h). Scale bar represents 20 μm.

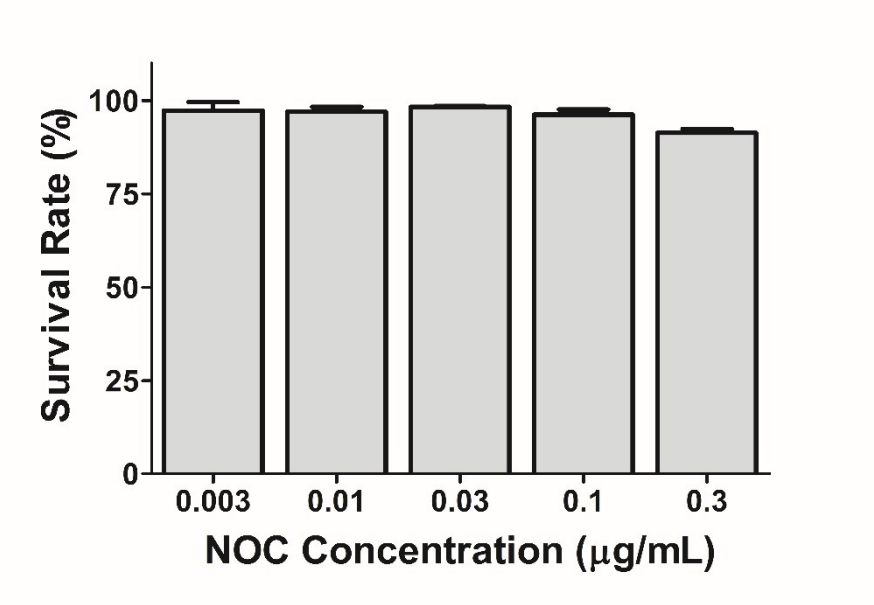

Figure S6. Relative viabilities of MCF-7 cells after being incubated with different concentrations of NOC.

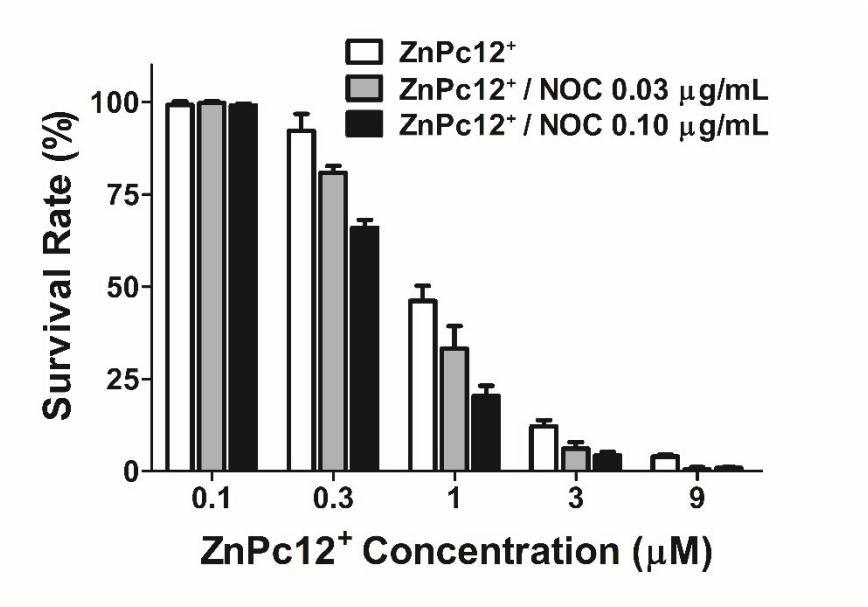

Figure S7. Relative viabilities of MCF-7 cells after being incubated with $ZnPc12^+$ (1 μM) and $ZnPc12^+$ + NOC (0.03 or 0.1 μg/mL).

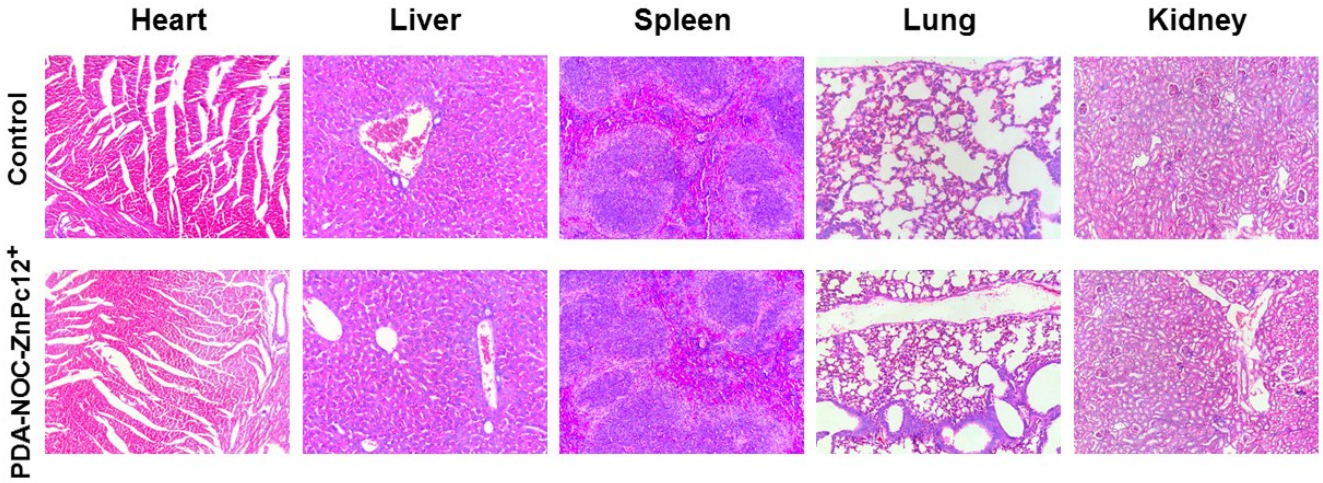

Figure S8. Representative H&E stained images of major organs from the mice of control and PDA-NOC-ZnPc12^{+} treated groups after experiments.

References

1. B. S. Sesalan, A. Koca and A. Gul, *Dyes. Pigments*, 2008, **79**, 259-264.
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