[12]aneN₃-Modified Camptothecin and PEGylated AIEgens Co-assembly into Core-Shell Nanoparticles with ROS/NTR Dual-response for Enhanced Cancer Therapy

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Supporting Information

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I. Synthesis and Characterization

The synthesis of 1-a, 1-b and 1-c:

Synthesis of 1-a: The compound 1-a was prepared according to published procedure reported\(^1\).

Synthesis of 1-b: Compound 1-1 (6.00 g, 0.02 mol) and imidazole (1.36 g, 0.02 mol) were added to N, N-dimethylformamide under Ar atmosphere, then TBSCI (3.00 g, 0.02 mol) was added into mixture at 0 °C. The mixture was stirred for another 12 h at room temperature. The solution was washed with saturated brine, extracted with DCM and concentrated \textit{in vacuo}. The residue was purified by column chromatography (PE: EA = 5:1) to obtain white solid (3.2 g, 40%). \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 8.24 (d, \(J = 8.3\) Hz, 2H), 7.69 (d, \(J = 8.3\) Hz, 2H), 7.16 (s, 1H), 7.07 (s, 1H), 4.98 (s, 2H), 4.61 (s, 2H), 4.48 (s, 2H), 2.25 (s, 3H), 0.80 (s, 9H), \(-0.02\) (s, 6H). \(^1\)C NMR (101 MHz, DMSO-\(d_6\)) \(\delta\) 151.49, 147.52, 146.05, 135.38, 133.83, 133.54, 128.93, 128.66, 128.10, 124.09, 74.71, 60.48, 58.47, 26.29, 21.28, 18.50, \(-4.85\). ESI–MS: calcd. for C\(_{22}\)H\(_{31}\)NO\(_5\)Si 418.20 (M + H\(^+\)), found 418.20 (M + H\(^+\)).

Synthesis of 1-c: CPT (3.48 g, 0.01 mol) and triphosgene (1.00 g, 0035 mol) were added to anhydrous DCM under Ar atmosphere, then DIPEA (0.48 g, 0.04 mol) was added into the mixture. The mixture was stirred for another 2 h at 0 °C and compound 1-2 was added into the mixture. The solution was washed with 10% citric acid, the solvent was concentrated \textit{in vacuo}. The residue was purified by column chromatography (DCM: MeOH = 20:1) to obtain light yellow solid (6.4 g, 80%). \(^1\)H NMR (600 MHz, Chloroform-\(d\)) \(\delta\) 8.38 (s, 1H), 8.14 (d, \(J = 8.5\) Hz, 1H), 8.03 (d, \(J = 8.5\) Hz,
2H), 7.95 (d, J = 8.2 Hz, 1H), 7.84 (t, J = 8.4 Hz, 1H), 7.69 (t, J = 7.5 Hz, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.29 (s, 1H), 7.24 (s, 1H), 7.16 (s, 1H), 5.70 (d, J = 16.8 Hz, 1H), 5.40 (d, J = 17.1 Hz, 1H), 5.28 (d, J = 5.8 Hz, 2H), 5.17 (s, 2H), 4.97 (s, 2H), 4.67 (d, J = 6.1 Hz, 2H), 2.33 – 2.24 (m, 4H), 2.18 – 2.12 (m, 1H), 0.99 (t, J = 7.5 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H).

$^{13}$C NMR (151 MHz, Chloroform-d) δ 167.37, 157.31, 153.70, 152.56, 152.13, 148.63, 147.51, 146.30, 145.69, 144.55, 134.75, 134.29, 131.49, 130.98, 130.89, 130.64, 129.41, 128.55, 128.39, 128.31, 128.28, 128.09, 127.15, 123.60, 120.57, 96.15, 78.04, 77.34, 75.60, 67.20, 66.04, 60.46, 50.06, 32.08, 25.99, 20.96, 18.44, 7.69, -5.18. ESI–MS: calcd. for C_{43}H_{45}N_{3}O_{10}Si 792.29 (M + H$^+$), found 792.28 (M + H$^+$).

Synthesis of 1-4: Compound 1-3 (6.4 g, 0.08 mol) was dissolved in 50 mL EA/HCl. The mixture was stirred at 25 °C for 2 h, and the solvent was removed in vacuo. The residue was purified by recrystallization in MeOH to obtain yellow solid (4.3 g, 80%). $^1$H NMR (400 MHz, DMSO-d$_6$) δ 8.60 (s, 1H), 8.04 (t, J = 7.4 Hz, 2H), 7.98 (d, J = 8.4 Hz, 2H), 7.80 (t, J = 7.7 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.52 (d, J = 8.3 Hz, 2H), 7.21 (s, 1H), 7.06 (s, 1H), 6.99 (s, 1H), 5.71 (s, 1H), 5.52 – 5.42 (m, 2H), 5.19 – 5.05 (m, 4H), 4.87 (d, J = 9.8 Hz, 1H), 4.44 (d, J = 5.7 Hz, 2H), 2.19 – 2.06 (m, 5H), 0.86 (t, J = 7.3 Hz, 3H). $^{13}$C NMR (101 MHz, DMSO-d$_6$) δ 167.65, 156.95, 153.35, 152.44, 147.39, 146.59, 145.29, 145.06, 135.97, 134.10, 132.27, 131.02, 130.93, 130.14, 129.92, 129.26, 129.00, 128.50, 128.33, 127.71, 123.79, 119.77, 94.86, 78.40, 75.21, 67.02, 66.04, 58.35, 50.77, 30.94, 20.93, 8.04. ESI–MS: calcd. for C_{37}H_{31}N_{3}O_{10}678.21 (M + H$^+$), found 678.20 (M + H$^+$).

Synthesis of 1-5a: Compound 1-4 (0.44 g, 0.65 mmol), Boc-6-aminocaproic acid (0.15 g, 0.65 mmol) and 4-dimethylaminopyridine (33 mg, 0.27 mmol) were dissolved in 15 mL tetrahydrofuran under Ar atmosphere. After 30 min, 1-(3-(dimethylamino)propyl)-3-ethyl-carbodiimide (150 mg, 0.78 mmol) was added under 0 °C and stirred for another 4 h at 25 °C. The mixture was washed with saturated brine, extracted with dichloromethane, and the solvents were removed in vacuo. The residues were purified by column chromatography (DCM : MeOH = 10 : 1) to afford product as a yellow solid (0.46 g, 80%). $^1$H NMR (600 MHz, DMSO-d6) δ 8.62 (s, 1H), 8.10 – 8.03 (m, 2H), 8.01 (d, J = 8.7, 2H), 7.81 (t, J = 6.7 Hz, 1H), 7.68 (t, J = 7.6 Hz, 1H), 7.53 (d, J = 9.1 Hz, 2H), 7.18 (s, 1H), 7.15 (s, 1H), 6.98 (s, 1H), 6.70 (t, J = 5.8 Hz, 1H), 5.51 – 5.43 (m, 2H), 5.26 – 5.11 (m, 4H), 5.01 (s, 2H), 4.96 – 4.85 (m, 2H), 2.83 – 2.75 (m, 2H), 2.22 (t, J = 7.4 Hz, 2H), 2.18 – 2.06 (m, 5H),
1.47 – 1.37 (m, 2H), 1.31 (s, 9H), 1.29 – 1.23 (m, 2H), 1.15 – 1.09 (m, 2H), 0.86 (t, J = 7.4 Hz, 3H).

$^{13}$C NMR (151 MHz, DMSO-d$_6$) δ 173.18, 167.63, 162.86, 156.99, 156.12, 153.34, 153.31, 152.59, 148.39, 147.49, 146.78, 145.26, 144.74, 134.68, 132.15, 132.02, 131.50, 130.95, 130.18, 130.01, 129.44, 129.08, 128.87, 128.55, 128.49, 128.32, 123.87, 119.74, 94.68, 78.49, 77.83, 75.54, 67.03, 65.82, 61.19, 50.80, 36.32, 34.18, 33.86, 31.31, 30.95, 29.75, 29.63, 28.78, 28.26, 24.75, 24.61, 20.76, 8.03. ESI–MS: calcd. for C$_{48}$H$_{50}$N$_4$O$_{13}$ 891.34 (M + H$^+$), found 891.33 (M + H$^+$).

Synthesis of 1-5b: $^1$H NMR (400 MHz, DMSO-d$_6$) δ 8.64 (s, 1H), 8.12 – 8.04 (m, 2H), 8.01 (d, J = 8.7 Hz, 2H), 7.81 (t, J = 8.4 Hz, 1H), 7.69 (t, J = 7.6 Hz, 1H), 7.53 (d, J = 9.1 Hz, 2H), 7.19 (s, 1H), 7.15 (s, 1H), 6.98 (s, 1H), 6.70 (t, J = 5.8 Hz, 1H), 5.49 – 5.45 (m, 2H), 5.26 – 5.12 (m, 4H), 5.01 (s, 2H), 4.93 – 4.87 (m, 2H), 2.93 – 2.76 (m, 2H), 2.22 (t, J = 7.3 Hz, 2H), 2.18 – 2.07 (m, 5H), 1.43 – 1.35 (m, 2H), 1.32 – 1.25 (m, 10H), 1.15 – 1.07 (m, 8H), 0.86 (t, J = 7.3 Hz, 3H). $^{13}$C NMR (151 MHz, DMSO-d$_6$) δ 173.22, 167.63, 156.98, 156.11, 153.36, 152.59, 148.39, 147.48, 146.78, 145.26, 144.77, 134.66, 132.15, 131.54, 130.93, 130.18, 130.01, 129.44, 129.08, 128.84, 128.55, 128.51, 128.31, 123.85, 119.74, 94.68, 78.49, 77.79, 75.53, 67.03, 65.81, 61.24, 59.88, 50.80, 33.88, 30.95, 29.94, 29.16, 29.06, 28.87, 28.80, 26.71, 24.89, 20.75, 15.22, 8.03. ESI–MS: calcd. for C$_{51}$H$_{56}$N$_4$O$_{13}$ 933.39 (M + H$^+$), found 933.38 (M + H$^+$).

Synthesis of 1-5c: $^1$H NMR (600 MHz, DMSO-d$_6$) δ 8.64 (s, 1H), 8.09 – 8.02 (m, 2H), 8.01 (d, J = 8.7 Hz, 2H), 7.81 (t, J = 8.3 Hz, 1H), 7.68 (t, J = 7.5 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.19 (s, 1H), 7.15 (s, 1H), 6.98 (s, 1H), 6.70 (t, J = 5.8 Hz, 1H), 5.52 – 5.42 (m, 2H), 5.25 – 5.12 (m, 4H), 5.01 (s, 2H), 4.94 – 4.86 (m, 2H), 2.84 – 2.79 (m, 2H), 2.21 (t, J = 7.3 Hz, 2H), 2.16 – 2.08 (m, 5H), 1.42 – 1.35 (m, 2H), 1.31 (s, 10H), 1.18 – 1.09 (m, 14H), 0.86 (t, J = 7.4 Hz, 3H). $^{13}$C NMR (151 MHz, DMSO-d$_6$) δ 173.21, 167.62, 156.99, 156.11, 153.39, 153.34, 152.59, 148.38, 147.47, 146.77, 145.27, 144.77, 134.65, 132.14, 131.55, 130.93, 130.17, 130.00, 129.44, 129.08, 128.84, 128.55, 128.51, 128.31, 123.84, 119.74, 94.68, 78.49, 77.78, 75.53, 67.03, 65.80, 61.27, 50.80, 33.89, 30.95, 29.99, 29.49, 29.41, 29.38, 29.22, 28.92, 28.80, 26.78, 24.92, 20.75, 8.03. ESI–MS: calcd. for C$_{54}$H$_{59}$N$_4$O$_{13}$ 975.44 (M + H$^+$), found 975.44 (M + H$^+$).
The synthesis of 2: The compound 2 was prepared according to the published procedure\textsuperscript{2}.

The synthesis of 3:

Scheme S2 Schematic route for compound 3

Synthesis of 3-1: The compound 3-1 and 3-2 were prepared according to the published procedure\textsuperscript{3}.

Synthesis of 3-3:

Compound 3-2 (3.1 g, 0.005 mol), 5-formylthiophen-2-ylboronic pinacol ester (2.16 g, 0.006 mol), potassium carbonate (2.76 g, 0.02 mol) and [1,1'-Bis(diphenylphosphino)ferrocene]-dichloropalladium(II) (0.36 g, 0.5 mmol) were added to 1,4-dioxane/H\textsubscript{2}O (V/V = 4/1). The mixture was stirred at 75 °C for 4 h under Ar atmosphere. After the substrate was consumed, solvent was removed in a reduced vacuum to give a black solid. The crude product was purified by column chromatography (PE/EA = 10/1) to afford a yellow solid (1.92 g, 60%). \textsuperscript{1}H NMR (400 MHz, Chloroform-\textit{d}) \(\delta\) 9.85 (s, 1H), 7.69 (d, \(J = 3.9\) Hz, 1H), 7.41 (d, \(J = 8.2\) Hz, 2H), 7.33 (d, \(J = 3.9\) Hz, 1H), 7.15 – 6.98 (m, 7H), 6.96 – 6.86 (m, 4H), 6.69 – 6.52 (m, 4H), 3.86 (t, \(J = 6.6, 3.1\) Hz, 2H), 1.77 – 1.66 (m, 2H), 1.43 – 1.37 (m, 2H), 1.32 – 1.21 (m, 16H), 0.87 (t, \(J = 7.2\) Hz, 3H). \textsuperscript{13}C NMR (151 MHz, Chloroform-\textit{d}) \(\delta\) 182.78, 168.08, 156.68, 154.46, 146.01, 142.08, 141.24, 138.38, 137.51, 136.98, 132.71, 132.25, 131.48, 127.96, 126.46, 125.74, 123.82, 113.84, 82.38, 67.98, 65.75, 32.00, 29.70, 29.41, 28.55, 28.10, 26.14, 22.77, 14.20. ESI–MS: calcd. for C\textsubscript{43}H\textsubscript{46}O\textsubscript{3}S 643.32 (M + H\textsuperscript{+}), found 643.28 (M + H\textsuperscript{+}).
Synthesis of 3-4: Compound 3-3 (1.90 g, 0.3 mmol), tert-butyl bromoacetate (1.15 g, 0.6 mmol), and potassium carbonate (1.38 g, 0.01 mol) were added into N, N-dimethylformamide under Ar atmosphere. The mixture was stirred at 25 °C for 5 h. The insoluble solid was filtered and the solvent was removed in vacuo. The residues were purified by column chromatography (PE : EA = 10 : 1) to afford product as a pale yellow oil (2.3 g, 76%). ¹H NMR (400 MHz, Chloroform-d) δ 9.85 (s, 1H), 7.69 (d, J = 4.0 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 4.0 Hz, 1H), 7.11 – 6.98 (m, 7H), 6.97 – 6.88 (m, 4H), 6.69 – 6.56 (m, 4H), 4.43 (s, 2H), 3.86 (t, J = 6.6 Hz, 2H), 1.77 – 1.66 (m, 2H), 1.45 (s, 9H), 1.31 – 1.18 (m, 18H), 0.87 (t, J = 7.2 Hz, 3H). ¹³C NMR (151 MHz, Chloroform-d) δ 182.78, 168.08, 156.68, 154.46, 146.01, 142.08, 141.24, 138.38, 137.51, 136.98, 132.71, 132.25, 131.48, 127.96, 126.46, 125.74, 123.82, 113.84, 82.38, 67.98, 65.75, 32.00, 29.70, 29.41, 28.55, 28.10, 26.14, 22.77, 14.20. ESI–MS: calcd. for C₄₀H₅₆O₅S 757.39 (M + H⁺), found 757.35 (M + H⁺).

Synthesis of 3-5: At room temperature, compound 3-4 (1.68 g, 0.20 mmol) was dissolved in 30 mL of dry dichloromethane (DCM), and then 5 mL trifluoroacetic acid was slowly added dropwise under stirring for 30 min. When the reaction completes, fresh DCM was added to the solution, and then the organic solvent was removed in vacuo. The crude product was used directly in the next step without further purification.

Synthesis of 3-6: To a solution of compound 3-5 (1.40 g, 0.2 mmol) and Boc-glycine (0.32 g, 0.2 mmol) in 20 mL tetrahydrofuran, EDCI (0.38 g, 0.2 mmol) and DMAP (48 mg, 0.04 mmol) was added at 0 °C. The mixture was stirred for 4 h at room temperature. The mixture was diluted with 40 mL dichloromethane and washed with saturated brine. The solvent was removed in vacuo and purified by column chromatography (PE/EA = 5/1) to afford a yellow solid (1.22 g, 72%). ¹H NMR (400 MHz, Chloroform-d) δ 9.85 (s, 1H), 7.69 (d, J = 4.0 Hz, 1H), 7.40 (dd, J = 8.3, 3.5 Hz, 2H), 7.32 (d, J = 4.0 Hz, 1H), 7.13 – 7.07 (m, 3H), 7.06 – 6.98 (m, 4H), 6.97 – 6.87 (m, 4H), 6.70 – 6.56 (m, 4H), 4.57 (s, 2H), 4.25 – 4.18 (m, 2H), 3.86 (t, J = 6.6 Hz, 2H), 3.36 (t, J = 6.6 Hz, 2H), 1.77 – 1.66 (m, 2H), 1.43 (s, 9H), 1.31 – 1.22 (m, 18H), 0.87 (t, J = 7.2 Hz, 3H). ¹³C NMR (101 MHz, Chloroform-d) δ 182.81, 168.92, 168.86, 158.16, 158.03, 156.58, 156.45, 154.43, 154.35, 145.92,
Synthesis of 3-7: To a solution of compound 3-6 (1.26 g, 0.15 mmol), malononitrile (0.20 g, 0.3 mmol) in DCM, and one drop DIPEA was added at 0 ºC. The mixture was stirred for 0.5 h at room temperature. The mixture washed with saturated brine, then solvent was removed in vacuo and purified by column chromatography (PE/EA = 5/1) to afford a red oil (1.13 g, 85%). $^1$H NMR (400 MHz, Chloroform-d) δ 7.75 (s, 1H), 7.67 (d, $J = 4.1$ Hz, 1H), 7.44 – 7.39 (m, 2H), 7.36 (d, $J = 4.1$Hz, 1H), 7.14 – 7.09 (m, 3H), 7.08 – 7.00 (m, 4H), 6.98 – 6.87 (m, 4H), 6.68 – 6.59 (m, 4H), 4.58 (d, $J = 5.1$ Hz, 2H), 4.25 – 4.20 (m, 2H), 3.90 – 3.84 (m, 2H), 3.36 (t, $J = 5.8$ Hz, 3H), 1.75 – 1.69 (m, 2H), 1.43 (s, 9H), 1.33 – 1.20 (m, 18H), 0.87 (t, $J = 6.9$ Hz, 3H). $^{13}$C NMR (101 MHz, Chloroform-d) δ 168.90, 156.67, 150.58, 146.91, 143.66, 141.52, 140.11, 138.37, 137.27, 135.47, 133.99, 132.87, 132.68, 132.44, 131.47, 129.77, 128.04, 126.63, 126.02, 124.43, 114.38, 114.03, 113.92, 113.81, 113.71, 113.53, 79.86, 67.97, 65.28, 64.52, 39.62, 32.00, 29.70, 29.51, 29.41, 28.45, 26.14, 22.77, 14.21. ESI–MS: calcd. for C$_{52}$H$_{61}$NO$_7$S 844.42 (M + H$^+$), found 844.42 (M + H$^+$).

Synthesis of 3-8: At room temperature, compound 3-7 (0.89 g, 0.10 mmol) was dissolved in 30 mL HCl/EA. When the reaction completed, and then the organic solvent was removed in vacuo. The crude product was used directly in the next step without further purification.

Synthesis of 3: To a solution of compound 3-8 (0.83 g, 0.1 mmol) and 2, 2’-(propane-2, 2-diylbis (sulfanediyl)) diacetic acid (0.22 g, 0.1 mmol) in 20 mL DCM, HBTU (0.38 g, 0.1 mmol) and DIPEA (0.25 g, 0.2 mmol) was added at 0 ºC. The mixture was stirred for 4 h at room temperature. The mixture was diluted with 40 mL dichloromethane and washed with saturated brine. The solvent was removed in vacuo and purified by column chromatography (DCM: MeOH = 10/1) to afford a red solid (0.56 g, 58 %). $^1$H NMR (400 MHz, DMSO-d$_6$) δ 8.60 (s, 1H), 8.14 (t, $J = 5.8$ Hz, 3H),
7.88 (d, J = 4.2 Hz, 1H), 7.73 (d, J = 4.1 Hz, 1H), 7.57 (dd, J = 8.5, 1.9 Hz, 3H), 7.17 – 7.06 (m, 3H), 7.04 – 6.99 (m, 2H), 6.98 – 6.93 (m, 2H), 6.90 – 6.77 (m, 4H), 6.71 – 6.62 (m, 4H), 4.64 (s, 2H), 4.11 – 4.03 (m, 2H), 3.82 (t, J = 5.6 Hz, 2H), 3.33 (s, 2H), 3.23 – 3.17 (m, 4H), 1.64 – 1.56 (m, 2H), 1.48 (s, 3H), 1.47 (s, 3H), 1.28 – 1.14 (m, 18H), 0.81 (t, J = 6.9 Hz, 3H). \(^{13}\)C NMR (101 MHz, Chloroform-\(d\)) \(\delta\) 173.43, 169.75, 169.50, 169.45, 158.27, 158.11, 156.70, 156.61, 156.46, 156.29, 150.70, 150.58, 146.85, 143.63, 141.43, 140.27, 140.11, 138.48, 137.50, 135.44, 134.03, 133.99, 132.87, 132.66, 132.45, 132.40, 131.48, 131.44, 129.80, 128.05, 126.66, 126.03, 124.43, 114.37, 114.13, 113.95, 113.92, 113.74, 113.54, 68.03, 65.41, 63.98, 57.67, 39.14, 34.98, 32.73, 32.00, 30.20, 29.75, 29.72, 29.68, 29.66, 29.52, 29.43, 29.39, 26.15, 22.78, 14.22. ESI–MS: calcd. for C\(_{57}\)H\(_{63}\)N\(_3\)O\(_7\)S\(_3\) 998.39 (M + H\(^+\)), found 998.38 (M + H\(^+\)).
II. Supporting Figures and Tables

**Figure S1** The $^1$H NMR spectra of CNN1 (A) and TTP (B) in DMSO-$d_6$

**Figure S2** Proposed reaction pathway of NTR-catalyzed reduction and breakdown of CNN1
Figure S3 The $^1$H NMR spectra of TTP in DMSO (above) and 10% D$_2$O/DMSO-$d_6$ (below) after 24 h.

Figure S4 The Log concentrations of the CNN1 (A), CNN2 (B) and CNN3 (C) versus $I_{339}/I_{334}$ plot of pyrene in PBS buffer (pH = 7.4) at room temperature.
<table>
<thead>
<tr>
<th>Diameter (nm)</th>
<th>PDI</th>
</tr>
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<tr>
<td>CNN1</td>
<td>312.1 ± 5.6</td>
</tr>
<tr>
<td>CNN2</td>
<td>297.2 ± 7.6</td>
</tr>
<tr>
<td>CNN3</td>
<td>235.0 ± 9.2</td>
</tr>
</tbody>
</table>

**Table S1** DLS results of CNN1 ~ CNN3 nanoparticles in aqueous solution.

**Figure S5** TEM images of CNN1 (A), CNN2 (B) and CNN3 (C) nanoparticles.

**Figure S6** Fluorescence quenching curves of EB-bounded ctDNA by CNN1-D (A), CNN2-D (B) and CNN3-D (C) in 5mM Tris-HCl/50mM NaCl (pH 7.4, 25 °C). [EB] = 10 μM, [DNA] = 100 μM.
Figure S7 Linearly fitting functions deduced from the plots of emission intensity changes at 605 nm by quenching curves of EB-bounded ctDNA: **CNN1-D** (A), **CNN2-D** (B), **CNN3-D** (C).

Figure S8 The cell viability of **CNN1-D ~ CNN3-D** and CPT at 0.1–40 μM concentration in HUVEC cells.
**Figure S9** The cell viability of CNN1-D ~ CNN3-D and CPT at 0.1–40 μM concentration in HeLa cells.

**Figure S10** The fluorescence intensity of CNN2-D/pDNA and CNN2-DT/pDNA in 5mM Tris-HCl (pH 7.4, 25 °C, λex = 450 nm, λem = 645 nm).
Figure S11 The size of CNN2-DT/pTRAIL in aqueous solution for different time.

Figure S12 Agarose gel electrophoresis of naked pDNA and CNN2-DT/pDNA in 50% FBS at 37 °C at different indicated time.

Figure S13 The size of CNN2-D/pDNA in aqueous solution with 10% FBS for 24 h.
Figure S14 The calibration curve of CPT in DMSO/H$_2$O (V/V = 1/1). ($\lambda_{ex}$ = 365 nm, $\lambda_{em}$ = 450 nm, slit = 5 nm, 5 nm)

Figure S15 TEM image of CNN2-DT/pTRAIL treated with H$_2$O$_2$ and NTR after 2 h.

Figure S16 Cell apoptosis (early apoptosis, late apoptosis and total apoptosis) assay of HeLa cells was represented with different treatments.
Figure S17 (A) Western blot analysis of TRAIL protein expression with different treatments in HeLa cells using primary antibodies (anti-TRAIL 1:1000). (B) β-Actin was used as a control.

Figure S18 The mean fluorescence intensity (MFI) were detected by the treatment with different endocytosis inhibitors and at 4 °C by flow cytometry.
Figure S19 H&E-stained tissues excised from mice. Scale bar: 100 µm.
III. Spectra of Compounds

Figure S20 $^1$H NMR spectrum of compound 1-2 in DMSO-$d_6$ (400M Hz, 298 K)

Figure S21 $^{13}$C NMR spectrum of compound 1-2 in DMSO-$d_6$ (400M Hz, 298 K)
Figure S22 $^1$H NMR spectrum of compound 1-3 in DMSO-$d_6$ (600M Hz, 298 K)

Figure S23 $^{13}$C NMR spectrum of compound 1-3 in DMSO-$d_6$ (600M Hz, 298 K)
Figure S24 $^1$H NMR spectrum of compound 1-4 in DMSO-$d_6$ (400M Hz, 298 K).

Figure S25 $^{13}$C NMR spectrum of compound 1-4 in DMSO-$d_6$ (400M Hz, 298 K).
Figure S26 $^1$H NMR spectrum of compound 1-5a in DMSO-$d_6$ (600M Hz, 298 K)

Figure S27 $^{13}$C NMR spectrum of compound 1-5a in DMSO-$d_6$ (600M Hz, 298 K)
Figure S28 $^1$H NMR spectrum of compound 1-5b in DMSO-$d_6$ (400 MHz, 298 K)

Figure S29 $^{13}$C NMR spectrum of compound 1-5b in DMSO-$d_6$ (400 MHz, 298 K)
Figure S30 $^1$H NMR spectrum of compound 1-5c in DMSO-$d_6$ (600M Hz, 298 K)

Figure S31 $^{13}$C NMR spectrum of compound 1-5c in DMSO-$d_6$ (600M Hz, 298 K)
Figure S32 $^1$H NMR spectrum of compound CNN1 in DMSO-$d_6$ (600M Hz, 298 K)

Figure S33 $^{13}$C NMR spectrum of compound CNN1 in DMSO-$d_6$ (600M Hz, 298 K)
Figure S34 The ESI-HRMS spectrum of CNN1

Figure S35 $^1$H NMR spectrum of compound CNN2 in DMSO-$d_6$ (600M Hz, 298 K)
Figure S36 $^{13}$C NMR spectrum of compound CNN2 in DMSO-$d_6$ (600M Hz, 298 K)

Figure S37 The ESI-HRMS spectrum of CNN2
**Figure S38** $^1$H NMR spectrum of compound CNN3 in DMSO-$d_6$ (400M Hz, 298 K)

**Figure S39** $^{13}$C NMR spectrum of compound CNN3 in DMSO-$d_6$ (400M Hz, 298 K)
**Figure 40** The ESI-HRMS spectrum of CNN3

**Figure S41** $^1$H NMR spectrum of compound 3-3 in DMSO-$d_6$ (400M Hz, 298 K)
Figure S42 $^{13}$C NMR spectrum of compound 3-3 in DMSO-$d_6$ (400M Hz, 298 K)

Figure S43 $^1$H NMR spectrum of compound 3-4 in DMSO-$d_6$ (400M Hz, 298 K)
Figure S44 $^{13}$C NMR spectrum of compound 3-4 in DMSO-$d_6$ (400M Hz, 298 K)

Figure S45 $^1$H NMR spectrum of compound 3-5 in DMSO-$d_6$ (400M Hz, 298 K)
Figure S46 $^{13}$C NMR spectrum of compound 3-5 in DMSO-$d_6$ (400M Hz, 298 K)

Figure S47 $^1$H NMR spectrum of compound 3-6 in DMSO-$d_6$ (400M Hz, 298 K)
**Figure S48** $^{13}$C NMR spectrum of compound 3-6 in DMSO-$d_6$ (400M Hz, 298 K)

**Figure S49** $^1$H NMR spectrum of compound 3-7 in DMSO-$d_6$ (400M Hz, 298 K)
Figure S50 $^{13}$C NMR spectrum of compound 3-7 in DMSO-$d_6$ (400M Hz, 298 K)

Figure S51 $^1$H NMR spectrum of compound TTP in DMSO-$d_6$ (400M Hz, 298 K)
Figure S52 $^{13}$C NMR spectrum of compound TTP in DMSO-$d_6$ (400M Hz, 298 K)

Figure S53 MALDI-TOF spectrum of compound TTP
IV. Reference

