Supporting Information

Light-Responsive Polymersomes with Charge-Switch for Targeted Drug Delivery

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**Experimental section**

**Materials.**

All chemical reagents were purchased from commercial sources, such as Sigma Aldrich, J&K or TCI, and were used without further purification. Dry dichloromethane (DCM) was distilled from calcium hydride; triethylamine (TEA) was redistilled and stored over KOH pellets prior to use. Azodiisobutyronitrile (AIBN), a free radical initiator, was recrystallized by ethanol before use. Deionized water was used to prepare all aqueous systems. The buffer used in all the experiments is 0.01 M PBS buffer (pH = 7.2). CCK-8 kit (Japan Tongren Institute of Chemistry) was purchased from Shanghai Biyuntian Biotechnology Co. Ltd. Cell culture medium Dulbecco’s modified eagle medium supplemented with 10 % (V/V) inactivated FBS and 1 % (V/V) antibiotic/antimycotic solution (DMEM) was purchased from Sigma Company.

**Characterizations.**

Proton and carbon magnetic resonance spectra ($^1$H, $^{13}$C NMR) were recorded on a Bruker Avance 400 MHz spectrometer. Chemical shifts were reported in parts per million (ppm) downfield from the Me$_4$Si resonance which was used as the internal standard when recording $^1$H NMR spectra. Mass spectra were recorded on a Micromass GCTTM and a Micromass LCTTM. Absorption spectra were recorded on a Shimadzu UV-2550 UV-Vis spectrometer. The reversed-phase HPLC was monitored on an Agilent 1200 Series using BetaBasic-18 column. Confocal luminescence imaging was performed with an A1R Nikon confocal microscope with 10 × or 4 × objective lens. Malvern Zetasizer Nano ZSP was used for the determination of diameters and zeta potential of prepared polymersomes. All data were averaged over three measurements. TEM measurements were conducted on a JEM 1400 Transmission Electron Microscopy. Samples for TEM observations were prepared by placing 5 μL vesicular dispersion on copper grids and drying without any staining procedures.
Gel permeation chromatography (GPC) equipped with Waters 1515 pump was used to determine the molecular weight of polymers. The eluent was THF at a flow rate of 1.0 mL min\(^{-1}\). A series of low polydispersity polystyrene standards were employed for calibration.

**Synthesis of compounds.**

**Compound 1:** A solution of 3,4-dihydroxyacetophenone (5 g, 32.9 mmol), 1-bromododecane (32.8 g, 131.6 mmol), sodium iodide (4.9 g, 32.9 mmol) and potassium carbonate (22.7 g, 164.5 mmol) in acetonitrile (ACN 200 mL) was refluxed for 12 h. Then the mixture was cooled to room temperature and the precipitate was filtered. After removing the solvent under vacuum, colorless solid appeared. Then the crude product was dissolved with ethyl acetate (EA, 200 mL) and followed by washing with brine (3×100 mL). After drying with anhydrous Na\(_2\)SO\(_4\), filtering and concentrating, the residue was purified by silica gel flash column chromatograph (PE/DCM = 2:1) to afford compound 1 as a white solid (14.03 g, 87.3 % yield). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.61-7.44 (m, 2H), 6.86 (d, \(J = 8.3\) Hz, 1H), 4.05 (dd, \(J = 11.9, 6.6\) Hz, 4H), 2.55 (s, 3H), 1.91-1.73 (m, 4H), 1.52-1.42 (m, 4H), 1.41-1.15 (m, 32H), 0.88 (t, \(J = 6.8\) Hz, 6H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) (ppm): 196.79, 153.36, 148.73, 130.17, 122.96, 112.22, 111.40, 69.14, 31.72, 29.32, 25.91, 22.50, 14.03. MS (ESI): \(m/z\): Calcd. for C\(_{32}\)H\(_{56}\)O\(_3\) [M+H]\(^+\): 489.4. Found: 489.1.

**Compound 2:** To a solution of conc. HNO\(_3\) (10 mL) in an ice-bath was added acetic anhydride (10 mL) dropwise. The mixture was stirred for 30 min. Then the compound 1 (7 g, 14.3 mmol) was finely ground and added slowly. The reaction was stirred for another 30 min and then poured into ice-water (1 L). The precipitate was filtered out, dissolved with DCM and followed by washing with brine (3×100 mL). The combined organic layers were dried over anhydrous Na\(_2\)SO\(_4\), filtered and concentrated. The residue was purified by silica gel flash column chromatography (PE/DCM = 2:1) to afford the product as a pale yellow solid compound 2 (5.03 g, 65.8 % yield). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.58 (s,
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm): 7.54 (s, 1H), 7.25 (s, 1H), 5.53 (q, J = 6.3 Hz, 1H), 4.10 (tt, J = 8.3, 4.2 Hz, 2H), 4.06-3.99 (m, 2H), 1.92-1.77 (m, 4H), 1.47-1.41 (m, 4H), 1.39-1.17 (m, 32H), 0.88 (t, J = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm): 153.93, 147.39, 139.94, 136.47, 109.47, 76.91, 31.77, 29.55, 29.25, 28.85, 25.83, 24.03, 22.59, 14.01. MS (ESI): m/z Calcd. for C$_{32}$H$_{57}$NaO$_5$ [M+Na]$^+$: 558.4. Found: 558.4.

**Compound 3:** To a solution of compound 2 (5 g, 9.37 mmol) in methanol (200 mL) and DCM (50 mL) was added NaBH$_4$ (1.42 g, 37.49 mmol). The reaction mixture was stirred at room temperature for 1 h and acidified with 1 N HCl to pH = 6. The volume of the reaction mixture was then reduced to 15 mL under vacuum. The reaction mixture was diluted with brine (100 mL) followed by extraction with DCM (3×100 mL). The obtained organic layers were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated. The residue was purified by silica gel flash column chromatography (PE/DCM = 1:2) to afford the product as a pale yellow solid compound 3 (4.6 g, 92 % yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.54 (s, 1H), 7.25 (s, 1H), 5.53 (q, J = 6.3 Hz, 1H), 4.10 (tt, J = 8.3, 4.2 Hz, 2H), 4.06-3.99 (m, 2H), 1.92-1.77 (m, 4H), 1.47-1.41 (m, 4H), 1.39-1.17 (m, 32H), 0.88 (t, J = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm): 153.93, 147.39, 139.94, 136.47, 109.47, 76.91, 31.77, 29.55, 29.25, 28.85, 25.83, 24.03, 22.59, 14.01. MS (ESI): m/z: Calcd. for C$_{32}$H$_{57}$NaO$_5$ [M+Na]$^+$: 558.4. Found: 558.4.

**Compound 4:** To a solution of compound 3 (3 g, 5.6 mmol) and triethylamine (1.42 mL, 14 mmol) in DCM (200 mL) at 0 °C was added bromoacetyl bromide (2.26 g, 11.2 mmol) in DCM (20 mL) dropwise. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was washed with brine (3×100 mL) and followed by drying over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuum. The crude product was purified by silica gel flash column chromatography (PE/DCM=1:1) to afford the product as a pale yellow solid compound 4 (3.06 g, 83.3 % yield). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.59 (s, 1H), 7.06 (s, 1H), 6.54 (q, J = 6.4 Hz, 1H), 4.16 - 4.07 (m, 2H), 4.04 (t, J = 6.6 Hz, 2H), 3.90 (d, J = 11.8 Hz, 1H), 3.80 (d, J = 11.8 Hz, 1H), 1.92-1.77 (m, 4H), 1.47-1.41 (m, 4H), 1.39-1.17 (m, 32H), 0.88 (t, J = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm): 153.93, 147.39, 139.94, 136.47, 109.47, 76.91, 31.77, 29.55, 29.25, 28.85, 25.83, 24.03, 22.59, 14.01. MS (ESI): m/z: Calcd. for C$_{32}$H$_{57}$NaO$_5$ [M+Na]$^+$: 558.4. Found: 558.4.
1.65 (d, J = 6.4 Hz, 3H), 1.46 (dd, J = 14.0, 8.6 Hz, 4H), 1.41-1.16 (m, 32H),
0.88 (t, J = 6.8 Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ (ppm): 165.62, 153.85,
147.9, 139.27, 131.92, 109.17, 70.3, 69.36, 31.76, 29.37, 25.81, 22.58, 21.88,
18.43, 13.99. MS (ESI): m/z: Calcd. for C$_{34}$H$_{58}$BrNNaO$_6$ [M+Na]$^+$: 678.3. Found:
678.3.

![Figure S1. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of Compound 1.](image-url)
Figure S2. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of Compound 2.

Figure S3. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of Compound 3.
Figure S4. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of Compound 4.
Figure S5. a) $^1$H NMR spectrum (400 MHz, DMSO) of Compound C$_{12}$NB. b) HRMS (ESI) spectrum recorded for Compound C$_{12}$NB.
Figure S6. HRMS (ESI) spectrum recorded for Compound 5.