Supporting Information

Synthesis of Cyclic Graft Polymeric Prodrugs with Heterogeneous Grafts of Hydrophilic OEG and Reducibly Conjugated CPT for Controlled Release

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Materials

Oligo(ethylene glycol) monomethyl ether methacrylate (OEGMA, M_n = 300 g/mol, 4~5 pendent EO units, Sigma-Aldrich) and 2-hydroxyethyl methacrylate (HEMA, 99%, Sigma-Aldrich) were purified by passing through a basic Al_2O_3 column to remove the inhibitor. *N, N, N', N'', N''*-pentamethyldiethylenetriamine (PMDETA, 99%, Aladdin), 2,2′-bipyridyl (bpy, 98.0%, Sigma-Aldrich), copper(I) bromide (CuBr, 99.999%, Sigma-Aldrich), copper(II) bromide ($CuBr_2$, 99%, Aladdin), 2-bromoisobutyryl bromide (iBuBr, 98%, Sigma-Aldrich), triphosgene (98%, J&K), 4-dimethylaminopyridine (DMAP, 99%, J&K), *N, N'*-dicyclohexylcarbodiimide (DCC, 99%, J&K), 4-Pentynoic acid (95%, J&K), 2-hydroxyethyl disulfide (Sigma-Aldrich), sodium azide (NaN_3, Sanyou, Shanghai), ethyl 2-bromoisobutyrate (99%, Sigma-Aldrich), glutathione (GSH, Aladdin), camptothecin (CPT, 99.9 %, Chengdu Tianyuan Natural Product Co., Ltd), 2-propanol (IPA, 99.0%, Kelong, Chengdu, China), Anisole (99.0%, Kelong, Chengdu, China) and pyridine (99.5%, XLHG, Guangdong, China) were used as received. Propargyl alcohol, ethyl acetate, n-hexane, dichloromethane (DCM), *N, N*′-dimethylformamide (DMF), 1,4-dioxane, anhydrous ethyl ether, dimethyl sulfoxide (DMSO) and tetrahydrofuran (THF) were purchased from Tianjin Chemical Reagent Factory (China) and futher purified according to the standard protocols. Minimum essential medium, Ham's F-12 K (Kaighn's) medium, penicillin/streptomycin and trypsin were purchased from Thermofisher and used as received. Hela cells were obtained from the Cell Bank of the Chinese Academy of Sciences (Shanghai, China) and cultured in RPMI 1640 media containing 10% FBS at

37 °C in a humidified atmosphere with 5% CO_2. 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H tetrazolium (MTS) was purchased from Promega.

Measurements

^{1}H NMR spectra were recorded on a JNM-ECS 400 MHz spectrometer (JEOL, Tokyo, Japan) operated in the Fourier transform mode using $CDCl_3$ or DMSO-d_6 as the solvent and tetramethylsilane (TMS) as the internal reference. The size-exclusion chromatography and multi-angle laser light scattering (SEC-MALLS) analyses were used to determine the molecular weight (M_w) and molecular weight distribution ($Đ = M_w/M_n$) of the prepared polymers. SEC was carried out using HPLC-grade DMF containing 0.1 wt % LiBr at 60 °C as the eluent at a flow rate of 1 mL/min. Tosoh TSK-GEL R-3000 and R-4000 columns (Tosoh Bioscience, Montgomeryville, PA, USA) were connected in series to a Agilent 1260 series (Agilent Technologies, Santa Clara, CA, USA), an interferometric refractometer (Optilab-rEX, Wyatt Technology, anta Barbara, CA, USA) and a MALLS device (DAWN EOS, Wyatt Technology, Santa Barbara, CA,USA). The MALLS detector was operated at a laser wavelength of 690.0 nm. The FT-IR spectroscopic measurements were conducted on a NEXUS 670 FT-IR spectrometer (Nicolet, WI, USA) and solid samples were pressed into potassium bromide (KBr) pellet prior to the measurements. Dynamic light scattering (DLS) was performed on a Zetasizer (Nano ZS, Malvern, Worcestershire, UK) at a fixed detection angle of 173^o. TEM images were recorded on a JNM-2010 instrument

operating at an acceleration voltage of 200 keV. The specimens for TEM observation were prepared by placing a drop of micelle solution onto a carbon-coated copper grid. After deposition, excess solution was removed using a strip of filter paper. The sample was further stained using phosphotungstic acid (1% w/w) and dried in air prior to visualization. UV-vis absorbance was measured at room temperature by UV-1780 UV-vis spectrophotometer (Shimadzu Corporation, Japan). Fluorescence spectra were recorded on a LS55 luminescence spectrometer (Perkin-Elmer, Waltham, MA, USA).

Synthesis of *l*-P(OEGMA)-Br macroinitiator

l-P(OEGMA)-Br was synthesized by ATRP of OEGMA using propargyl 2-bromoisobutyrate[1] as an initiator. Typically, propargyl 2-bromoisobutyrate (32.81 mg, 0.16 mmol), OEGMA (4.80 g, 16 mmol), bpy (51 mg, 0.32 mmol), and anisole (16 mL) were loaded in a Schlenk tube (50 mL) with a magnetic stirring bar. After three freeze-pump-thaw cycles, CuBr (22.95 mg, 0.16 mmol) was introduced under the protection of nitrogen flow. After another three freeze–pump–thaw cycles, the reaction mixture was sealed and placed in an oil bath thermostated at 60 °C to start the polymerization. After 1.5 h, the reaction tube was dipped in liquid nitrogen to stop the polymerization and diluted using THF. The reaction mixture was passed through a neutral alumina column to remove the copper catalyst. After removing the solvents by a rotary evaporator, the residues were dissolved in THF and precipitated into an excess of *n*-hexane to remove residual monomers. The above dissolution-precipitation cycle was repeated three times. The final product was dried in a vacuum oven until

constant weight (1.8 g, yield: 37.3%, $M_{w,\ GPC}$ = 17.2 kDa, $Đ$ = 1.1). The actual degree of polymerization (DP) of *l*-P(OEGMA)-*Br* was determined to be 38 based on ^{1}H NMR analysis of the monomer conversion. Thus, the polymer was denoted as *l*-P(OEGMA)$_{38}$-*Br*.

Synthesis of *l*-P(OEGMA)-*b*-P(HEMA)-Br

l-P(OEGMA)-*b*-P(HEMA)-Br block polymer was prepared by ATRP using *l*-P(OEGMA)$_{38}$-Br as a macroinitiator. In a 25 mL Schlenk flask, *l*-P(OEGMA)$_{38}$-Br (277.5 mg, 23.91 μmol), HEMA (248.95 mg, 1.91 mmol), bpy (7.62 mg, 47.82 μmol), and $CuBr_2$ (1.08 mg, 4.78 μmol) were dissolved in a 9:1 % w/w IPA/water mixture to obtain a 0.5 M HEMA solution. After three freeze-pump-thaw cycles, CuBr (2.74 mg, 19.13 μmol) was added under the protection of nitrogen flow. After another three freeze-pump-thaw cycles, the flask was sealed and placed in an oil bath thermostated at 50 °C to start the polymerization. After 30 min, the reaction tube was dipped in liquid nitrogen to stop the polymerization. The reaction mixture was transferred directly to a dialysis tube (MWCO, 3.5 kDa) and dialyzed against distilled water for 36 h. The purified *l*-P(OEGMA)-*b*-P(HEMA)-Br was harvested by freeze-drying (294 mg, yield: 55.8%, $M_{w,\ GPC}$ = 19.1 kDa, $Đ$ = 1.1). The actual DP of P(HEMA) block was determined to be 9 by ^{1}H NMR analysis in DMSO-d_6. Thus, the diblock copolymer was denoted as *l*-P(OEGMA)$_{38}$-*b*-P(HEMA)$_9$-Br.

Synthesis of *l*-P(OEGMA)-*b*-P(HEMA)-N_3

To a 10 mL round-bottomed flask, *l*-P(OEGMA)$_{38}$-*b*-P(HEMA)$_9$-Br (284 mg, 22.2 μmol), DMF (3 mL), and NaN_3 (28.9 mg, 444 μmol) were added, and the reaction mixture was allowed to stir at 45 °C for 48 h. After purification by extensive dialysis to remove residual sodium salts for 36 h, the purified product, *l*-P(OEGMA)$_{38}$-*b*-P(HEMA)$_9$-N_3, was obtained by freeze-drying (273 mg, yield: 96%, $M_{w,\ GPC}$ = 19.0 kDa, $Đ$ = 1.1).

Synthesis of *c*-P(OEGMA)-*b*-P(HEMA)

In a typical procedure, a 1000-mL three-neck flask charged with DMF (450 mL) was thoroughly deoxygenated by bubbling with nitrogen for 1 h. PMDETA (983 μL, 4.66 mmol) and CuBr (669 mg, 4.66 mmol) were then charged into the flask under the protection of nitrogen flow. A solution of *l*-P(OEGMA)$_{38}$-*b*-P(HEMA)$_9$-N_3 (270 mg, 21.2 μmol) in degassed DMF (10 mL) was added to the copper catalyst solution via a syringe pump at the rate of 0.42 mL/h. The reaction was carried out at 100 °C in a nitrogen atmosphere for 24 h. At the end of the polymer solution addition, the mixture was allowed to proceed for another 24 h. After the mixture was cooled to room temperature, DMF was removed under reduced pressure, and the concentrated residue was transferred directly to a dialysis tube (MWCO, 3.5 kDa) and dialyzed against distilled water to remove the copper catalyst. After the removal of insoluble material by filtration, the remaining solution was collected and further dialyzed against distilled water for another 36 h. The resulting diblock copolymer-based cyclic template, *c*-P(OEGMA)$_{38}$-*b*-P(HEMA)$_9$, was harvested by freeze-drying (226 mg,

yield: 84%, $M_{w,\,GPC}$ = 17.9 kDa, $Đ$ = 1.2).

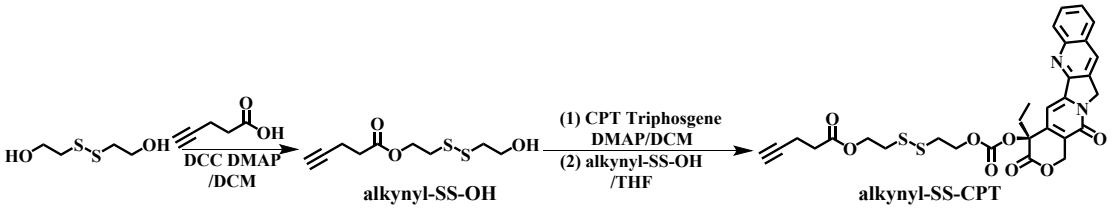
Synthesis of *c*-P(OEGMA)-*b*-P(HEMA-Br)

In a 10 mL round-bottomed flask, *c*-P(OEGMA)$_{38}$-*b*-P(HEMA)$_9$ (210 mg, 148.4 μmol -OH) was added and dissolved in 5 mL anhydrous pyridine. After cooling to 0 °C in an ice-water bath, iBuBr (146.7 μL, 1.19 mmol) was quickly injected into the rapidly stirring solution. The solution was stirred for 1 h at 0 °C, and then at room temperature for 24 h. The reaction mixture was transferred directly to a dialysis tube (MWCO, 3.5 kDa) and dialyzed against distilled water for 36 h. The purified *c*-P(OEGMA)$_{38}$-*b*-P(HEMA-Br)$_9$ was harvested by freeze-drying (216 mg, yield: 93%, $M_{w,\,GPC}$ = 28.2 kDa, $Đ$ = 1.2).

Synthesis of *c*-P(OEGMA)-*b*-P(HEMA-N_3) (*cg*-N_3)

A 10 mL round-bottom flask was charged with *c*-P(OEGMA)$_{38}$-*b*-P(HEMA-Br)$_9$ (210 mg, 134 μmol-Br), DMF (5 mL), and NaN_3 (174 mg, 2.68 mmol). The reaction mixture was allowed to stir at 45 °C for 48 h. After purification by extensive dialysis to remove residual sodium salts for 36 h, The purified product *c*-P(OEGMA)$_{38}$-*b*-P(HEMA-N_3)$_9$ was harvested by freeze-drying (197 mg, yield: 94%, $M_{w,\,GPC}$ = 25.0 kDa, $Đ$ = 1.2).

Synthesis of alkynyl-SS-CPT



Scheme S1. Synthesis of reducible CPT prodrug with a disulfide-linked alkynyl terminus (alkynyl-SS-CPT).

Alkynyl-SS-CPT was synthesized according to previous literature reports with slight modifications (see Scheme S1).[2] Firstly, 2-((2-hydroxyethyl)disulfanyl)ethyl pent-4-ynoate (alkynyl-SS-OH) was first synthesized by monoesterfication between 2-hydroxyethyl disulfide and 4-Pentynoic acid. Briefly, 2-hydroxyethyl disulfide (6 g, 38.9 mmol), DCC (4.85 g, 23.3 mmol), DMAP (240 mg, 1.9 mmol), and dry DCM (50 mL) were charged into a 100 mL round-bottom flask, which was cooled to 0 °C in an ice bath. 4-Pentynoic acid (2 g, 19.4 mmol) in 9 mL of dry DCM was later added dropwise over a period of 30 min under vigorous magnetic stirring. After the addition, the reaction mixture was allowed to stir for 30 min in an ice bath and further stirred overnight at room temperature. After filtration and evaporation of all the solvents, the residues were purified by column chromatography on silica gel (ethyl acetate : hexane = 1:4, v/v) to yield the product as a colorless liquid (3.63 g, yield: 80%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm, Figure S6): δ 4.39 (t, 2H), 3.88 (q, 2H), 2.94 (t, 2H), 2.89 (t, 2H), 2.03 (t, 1H), 2.62−2.55 (m, 2H), 2.55−2.48 (m, 2H), 1.98 (t, 1H).

And then, CPT (2.45 g, 7.03 mmol) and DMAP (2.58 g, 21.10 mmol) were suspended in dry DCM (50 mL) under nitrogen atmosphere. Triphosgene (0.697 g, 2.34 mmol) was added and the mixture was stirred for 30 min at room temperature. Alkynyl-SS-

OH (1.81 g, 7.75 mmol, in 15 mL dry THF) was added dropwise via a constant pressure funnel over a period of 30 min. The reaction mixture was stirred overnight during which a yellow precipitate was formed. After the solvent was removed by rotary evaporation, the crude product was purified by column chromatography using ethyl acetate as eluent to give alkynyl-SS-CPT as a pale solid powder (4 g, yield: 36%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm, Figure S7): δ 8.38 (s, 1H), 8.20 (d, 1H), 7.92 (d, 1H), 7.82 (m, 1H), 7.65 (t, 1H), 7.31 (s, 1H), 5.50 (d, 2H), 5.27 (s, 2H), 4.34 (m, 2H), 4.28 (t, 2H), 2.92 (t, 2H), 2.87 (t, 2H), 2.55−2.40 (m, 4H), 2.26 (dq, 1H), 2.15 (dq, 1H), 1.95 (t, 1H), 0.99 (t, 3H).

Synthesis of *cg*-P(OEGMA)-*b*-P(HEMA-SS-CPT) (*cg*-prodrug)

c-P(OEGMA)$_{38}$-*b*-P(HEMA-N_3)$_9$ (80 mg, 52.3 μmol-N_3), alkynyl-SS-CPT (33.4 mg, 55 μmol), bpy (16.68 mg, 104.7 μmol), and 1,4-dioxane (2.617 mL) were charged into a 25 mL Schlenk flask equipped with a magnetic stirring bar. The mixture was degassed by three freeze−pump−thaw cycles, and then CuBr (7.51 mg, 52.3 μmol) was introduced under nitrogen. After another three freeze-pump-thaw cycles, the flask was sealed and placed in an oil bath thermostated at 60 °C. After stirring for 12 h, the reaction flask was quenched into liquid N_2, opened and exposed to air, and diluted with 5 mL THF. The mixture was then passed through neutral alumina column using THF as the eluent to remove copper catalysts. After removal of all the solvents on a rotary evaporator, the residues were dissolved in THF and precipitated into an excess of cold diethyl ether three times. The obtained solids were further purified by dialysis

(MWCO, 3.5 kDa) against deionized water for 36 h, and then harvested by freeze-drying (76 mg, yield: 68%, $M_{w,\,GPC}$ = 42.6 kDa, $Đ$ = 1.1).

Synthesis of *bg*-P(OEGMA)-*b*-P(HEMA-SS-CPT) (*bg*-prodrug)

The analogues of *bg*-prodrug was prepared following identical procedures to the aforementioned synthesis of *cg*-prodrug (Scheme S2) except using ethyl 2-azidoisobutyrate[3] (EAB) end-capped *l*-P(OEGMA)$_{38}$-*b*-P(HEMA)$_9$-Br for the drug conjugation in the last step. Briefly, ethyl 2-bromoisobutyrate (1.0 g, 5.1 mmol), NaN_3 (1.0 g, 15.3 mmol), and DMF (4 mL) were charged into a 25 mL of round-bottom flask, which was stirred at 50 °C for 24 h. Deionized water (50 mL) was added to the mixture. The aqueous solution was extracted with ethyl acetate (3 × 30 mL). The organic layers were merged, washed with water (2 × 50 mL) and brine (3 × 50 mL), dried over Na_2SO_4, filtered, and evaporated. The EAB was obtained as a pale-yellow liquid (0.55 g, yield: 68%). ^{1}H NMR (400 MHz, $CDCl_3$, ppm, Figure S8): δ 4.23 (q, 2H), 1.46 (s, 6H), 1.31 (t, 3H).

Subsequently, *l*-P(OEGMA)$_{38}$-*b*-P(HEMA)$_9$-Br (315 mg, 24.66 μmol), EAB (116.2 mg, 0.74 mmol), bpy (7.86 mg, 49.3 μmol), and DMF (2.467 mL) were charged into a 25 mL Schlenk flask equipped with a magnetic stirring bar. The mixture was degassed by three freeze−pump−thaw cycles, and then CuBr (3.54 mg, 24.6 μmol) was introduced under nitrogen. After another three freeze-pump-thaw cycles, the flask was sealed and placed in an oil bath thermostated at 60 °C. After stirring for 24 h, the reaction flask was quenched into liquid N_2, opened and exposed to air. The reaction

mixture was transferred directly to a dialysis tube (MWCO, 3.5 kDa) and dialyzed against distilled water for 36 h. The purified product *l*-EAB-P(OEGMA)$_{38}$-*b*-P(HEMA)$_9$-Br was harvested by freeze-drying (287 mg, yield: 90%, $M_{w,\ GPC}$ = 21.3 kDa, $Đ$ = 1.2).

Micelle preparation

The *cg* and *bg*-prodrug-based micelles were prepared via nanoprecipitation by dropping the polymer solution prepared in DMSO into water followed by extensive dialysis against deionized water to remove any organic solvent. Taking micelles of *cg*-prodrugs as an example, *cg*-prodrug (2.0 mg) was first dissolved in 1.0 mL DMSO, and then dropwise added to 9 mL of distilled water under vigorous stirring. The mixture solution was further stirred for another 2 h, followed by dialysis (MWCO, 3.5 kDa) against deionized water.

Determination of critical micelle concentration (CMC)

CMCs of *cg* and *bg*-prodrug-based micelles were measured using pyrene as a fluorescence probe. 0.8 mL of pyrene solution (3×10^{-6} M in acetone) was added to containers, and the acetone was allowed to evaporate. Then 4 mL aqueous polymer solutions at different concentrations were subsequently added to the containers containing the pyrene residue and the combined solutions of pyrene and copolymers were equilibrated at room temperature in dark for 24 h prior to measurements. The final concentration of pyrene was 6×10^{-7} M in water. Excitation was carried out at 339

nm, and emission spectra were recorded ranging from 350 to 500 nm. Both excitation and emission bandwidths were 1.5 nm. From the pyrene emission spectra, the intensities (peak height) of $I_{373\ nm}$ were recorded. The CMC value was determined from the intersection of the tangent to the curve at the inflection with the horizontal tangent to the curve through the points at low concentration.

***In vitro* drug release study**

The *cg* and *bg*-prodrug-based micelles were first dispersed in PBS (pH 7.4, 150 mM) at the concentration of 0.2 mg/ml. 1 mL of the solution was loaded in a dialysis tube with a MWCO of 3.5 kDa, and then immersed in a tube containing 25 mL of different buffer solutions as the release media. The tubes were kept in a horizontal laboratory shaker thermos-stated at a constant temperature of 37 °C and a stirring speed of 120 rpm. At predetermined time intervals, 3 mL of release medium was taken out and replenished with equal volume of fresh medium. The drug concentration was determined by measuring CPT absorbance at 369 nm. The concentration of released CPT from each micelle formulation was calculated based on the standard curves.[2] The experiment was performed in quadruplicate for each sample.

Fluorescence imaging

HeLa cells were seeded in 6-well plates at a plating density of 1.5×10^5 cells per well in 1 mL of complete growth medium and incubated in a 37 °C, 5% CO_2 environment for 24 h. Solutions of free CPT, *cg* and *bg*-prodrug-based micelles were prepared in

complete growth medium at 25 μg/mL equivalent CPT concentration. After incubation for 4 h at 37 °C, cells were rinsed with PBS (3 ×1 mL), and the endo/lysosomes were stained with lysotracker green. Coverslips were mounted onto glass slides and imaged using an Echo-Labs Revolve fluorescence microscope.

Evaluation of cellular uptake by flow cytometry

HeLa cells were seeded in 24-well plates at a plating density of 1.5×10^5 cells per well in 1.0 mL of complete growth medium and incubated for 24 h at 37 °C in 5% CO_2 environment. Next, fresh MEM containing different samples was added to replace the original medium, and the cells without drug treatment were set as a control. The CPT concentration for free CPT, micelles based on *bg* and *cg*-prodrugs in MEM was set at 25 μg/mL. After incubation for 4 h, the sample solutions were aspirated, and the cells were rinsed twice with PBS. The cells were then harvested by incubation with 200μL of Trypsin-EDTA, followed by resuspension with 1 mL of complete growth medium. Subsequently, the cells were transferred to 1.5 mL of microcentrifuge tubes and pelleted at 300g for 5 min at 4 °C. The supernatant was aspirated, and the cell pellets were resuspended in 500 μL of PBS. The cells were analyzed for uptake of fluorescent samples using a BD LSRFortessa flow cytometer with an excitation wavelength of 365 nm. A minimum of 10,000 cells were analyzed for each sample with the fluorescence intensity.

***In vitro* cytotoxicity study**

In vitro cytotoxicity of *cg*-N_3, *bg*-N_3, *cg* and *bg*-prodrugs-based micelles was evaluated by the MTS cell viability assay. HeLa cells were seeded in 96-well plates at a plating density of 1×10^4 cells per well in 100 μL of complete growth medium and incubated in a 37 °C, 5% CO_2 environment for 24 h. Samples were prepared in serial dilutions in sterilized water and then diluted in 10-fold in MEM medium. The cells were rinsed once with PBS and were further incubated with 80 μL of the sample solutions with different polymer or CPT concentrations at 37 °C for 72 h. Cells were later rinsed with PBS and replaced with complete growth medium. After addition of 20 μL of MTS reagent to each well, cells were incubated for 3 h at 37 °C. The absorbance of each well was measured at 490 nm on a Tecan Safire2 plate reader (Männerdorf, Switzerland). Cell viability for each treatment condition was determined by normalizing to the cells only signal.

References

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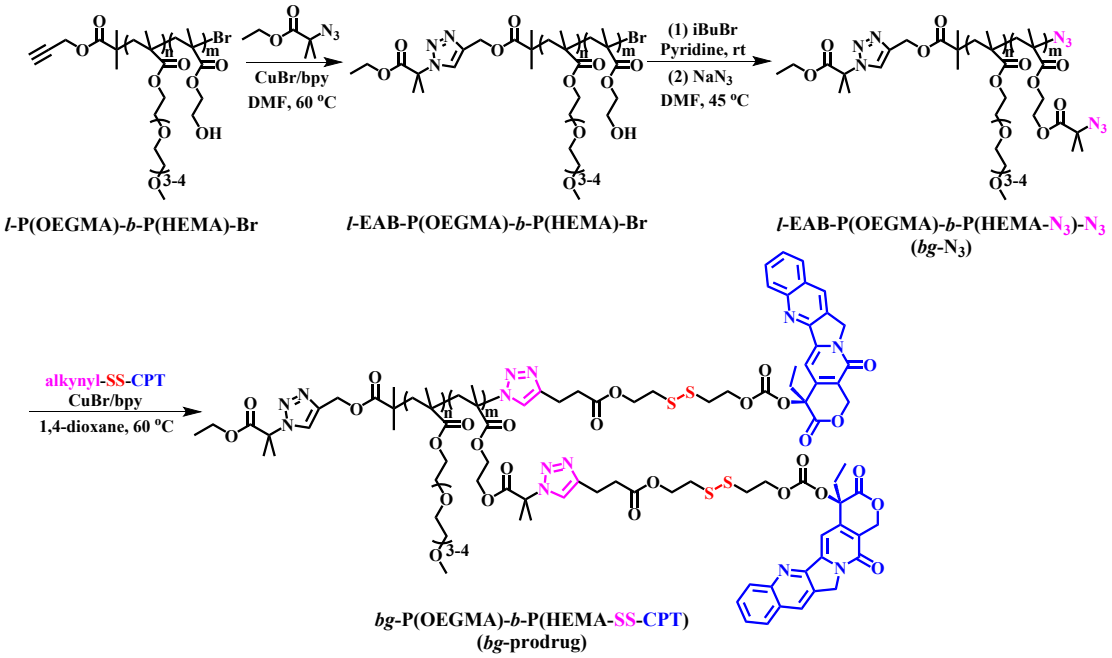
2. L. Zheng, Y. Wang, X. Zhang, L. Ma, B. Wang, X. Ji and H. Wei, *Bioconjugate Chem.*, 2018, **29**, 190-202.
3. C. G. Wang and A. Goto, *J. Am. Chem. Soc.*, 2017, **139**, 10551-10560.



Scheme S2. Synthesis of *bg*-prodrug.

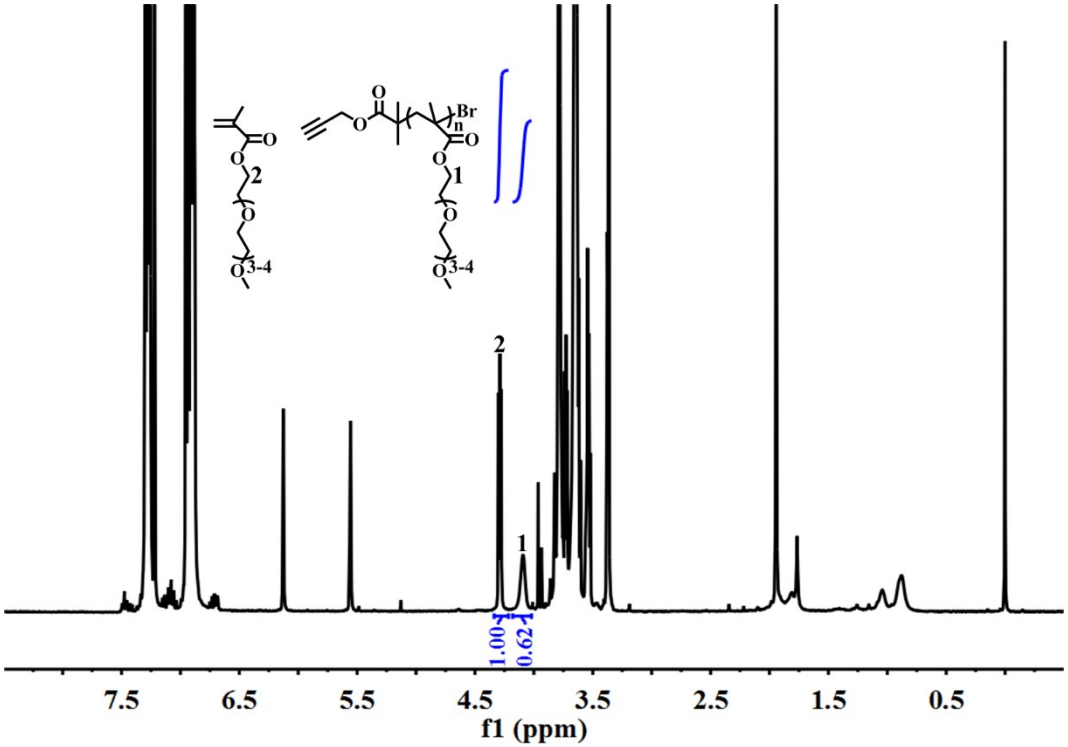
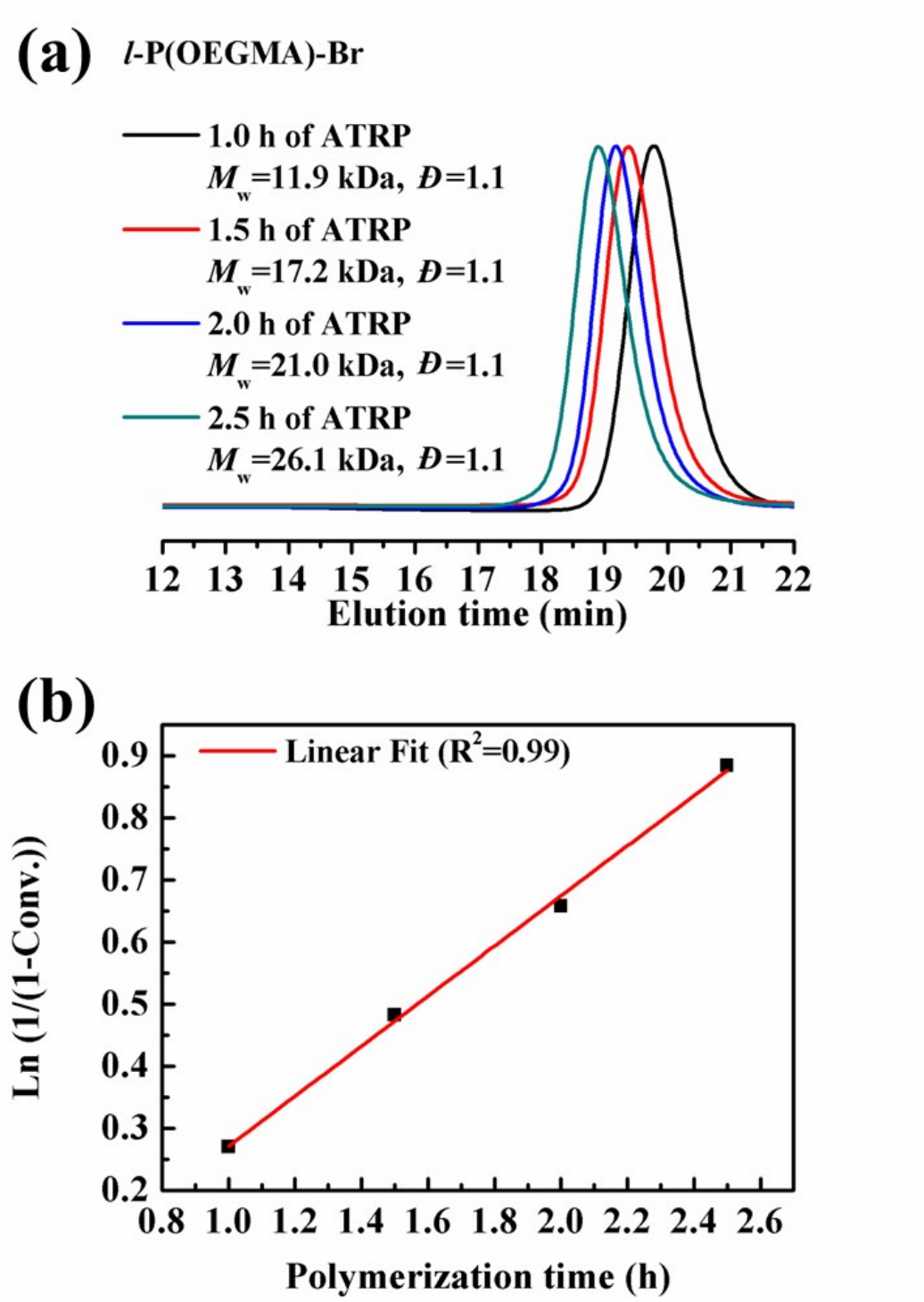


Figure S1. ^{1}H NMR spectrum of unpurified P(OEGMA) in $CDCl_3$.


(a)
l-P(OEGMA)-Br
1.0 h of ATRP
Mw=11.9 kDa, Đ=1.1
1.5 h of ATRP
Mw=17.2 kDa, Đ=1.1
2.0 h of ATRP
Mw=21.0 kDa, Đ=1.1
2.5 h of ATRP
Mw=26.1 kDa, Đ=1.1
12 13 14 15 16 17 18 19 20 21 22
Elution time (min)
(b)
Linear Fit (R2=0.99)
Ln (1/(1-Conv.))
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.8 1.0 1.2 1.4 1.6 1.8 2.0 2.2 2.4 2.6
Polymerization time (h)

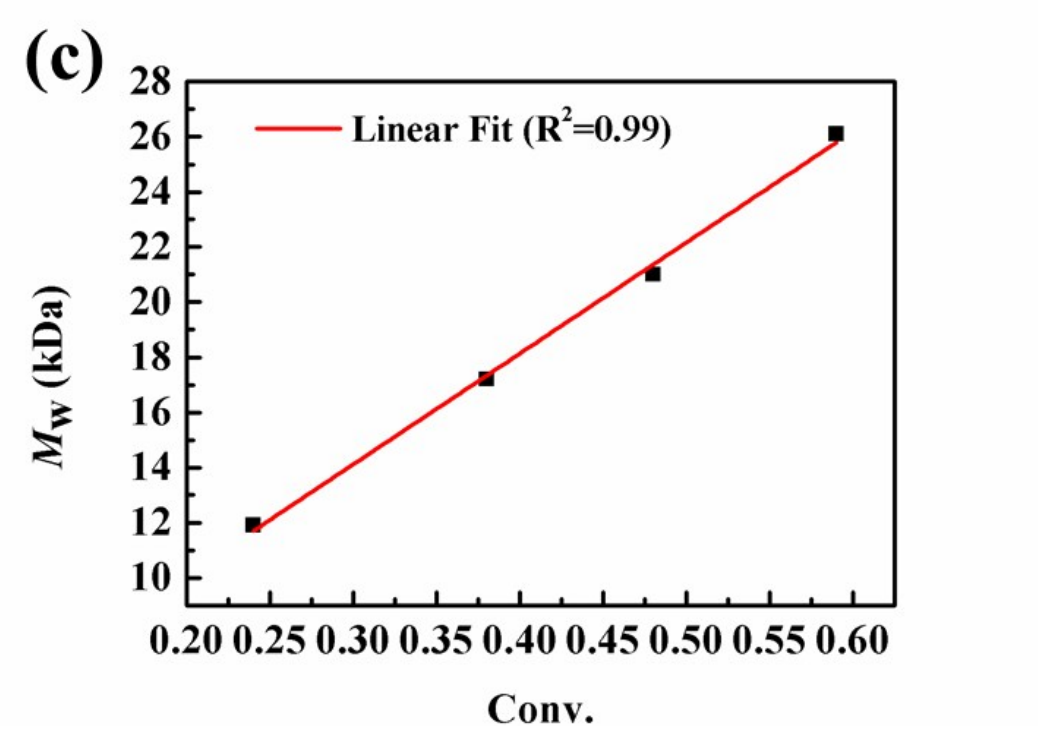
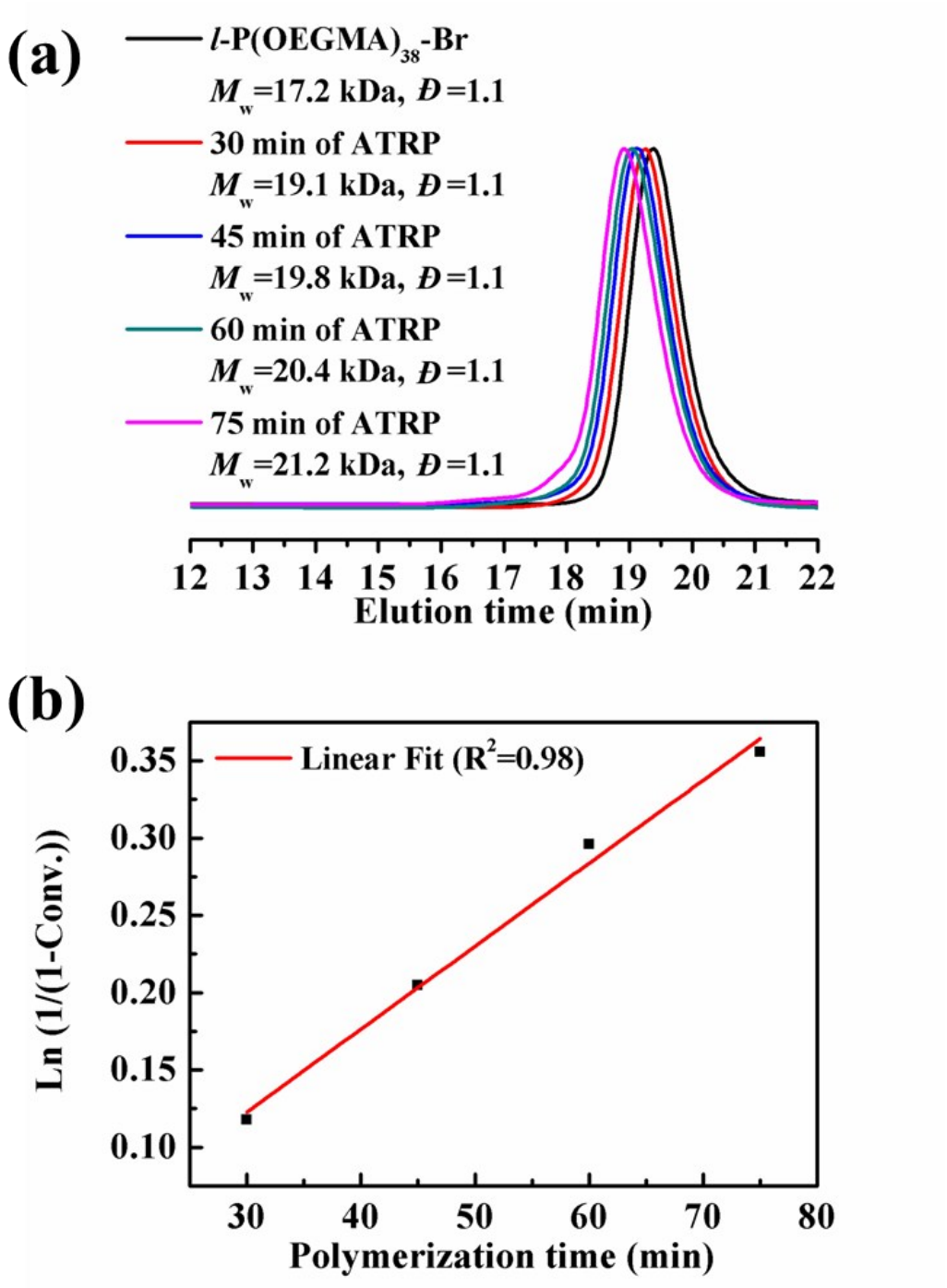


Figure S2. ATRP kinetics study for the synthesis of *l*-P(OEGMA)-Br. (a) SEC elution traces of ATRP-synthesized *l*-P(OEGMA)-Br at various polymerization times; (b) pseudo-first order kinetics; and (c) plots of M_w with conversion.


(a)
l-P(OEGMA)38-Br
Mw=17.2 kDa, Đ=1.1
30 min of ATRP
Mw=19.1 kDa, Đ=1.1
45 min of ATRP
Mw=19.8 kDa, Đ=1.1
60 min of ATRP
Mw=20.4 kDa, Đ=1.1
75 min of ATRP
Mw=21.2 kDa, Đ=1.1
12 13 14 15 16 17 18 19 20 21 22
Elution time (min)
(b)
Linear Fit (R2=0.98)
0.35
0.30
0.25
0.20
0.15
0.10
Ln (1/(1-Conv.))
30 40 50 60 70 80
Polymerization time (min)

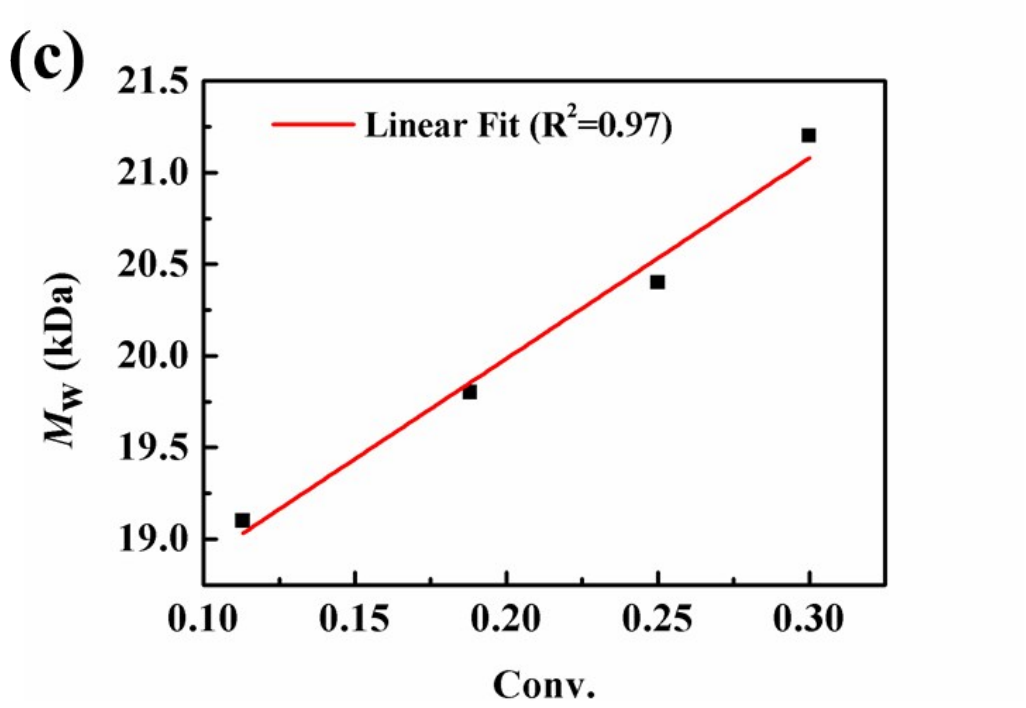


Figure S3. ATRP kinetics study for the synthesis of *l*-P(OEGMA)-*b*-P(HEMA)-Br. (a) SEC elution traces of ATRP-synthesized *l*-P(OEGMA)-*b*-P(HEMA)-Br at various polymerization times; (b) pseudo-first order kinetics; and (c) plots of M_w with conversion.

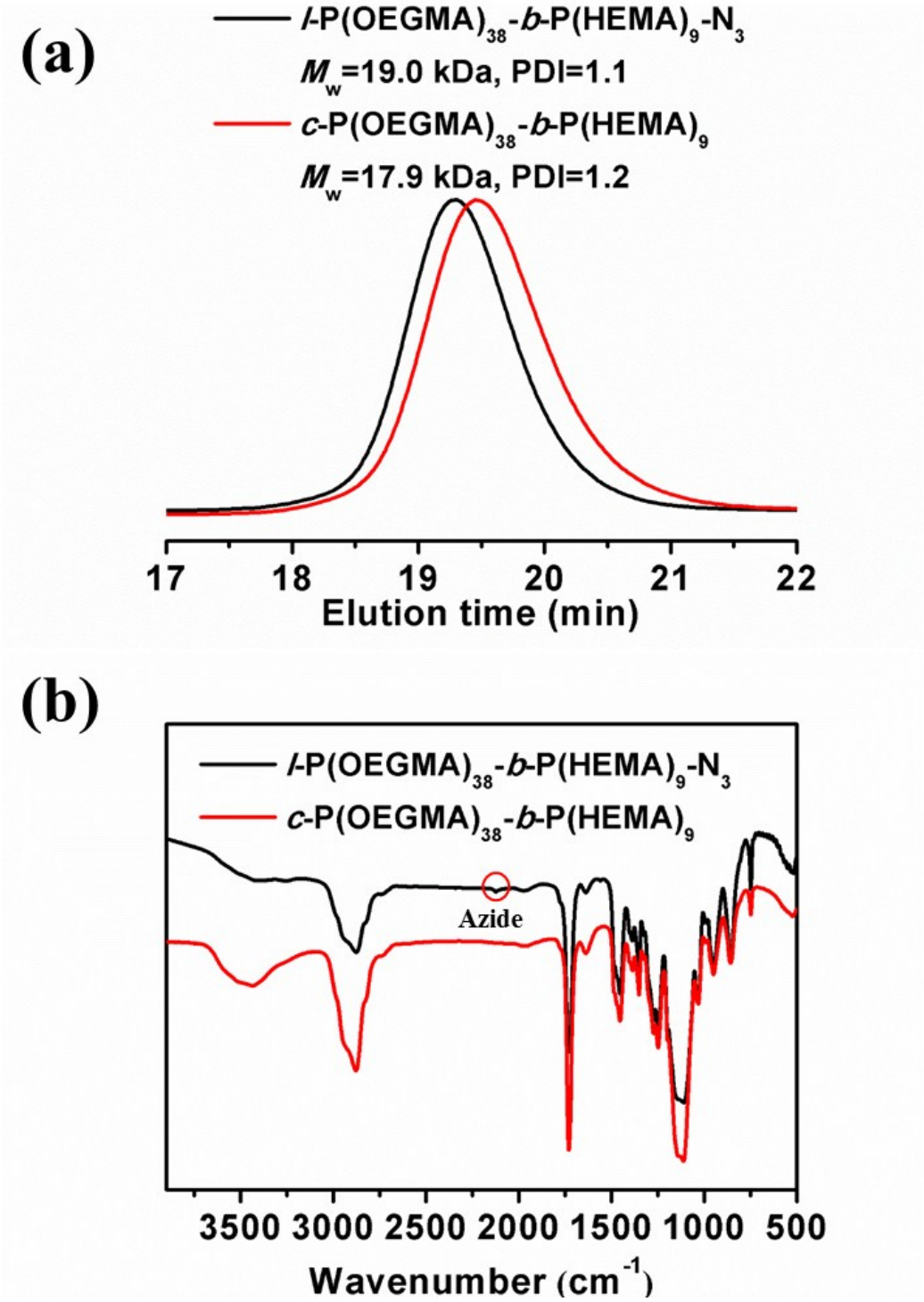


Figure S4. (a) SEC elution traces and (b) FT-IR spectra of *c*-P(OEGMA)$_{38}$-*b*-P(HEMA)$_9$ and *l*-P(OEGMA)$_{38}$-*b*-P(HEMA)$_9$-N$_3$.

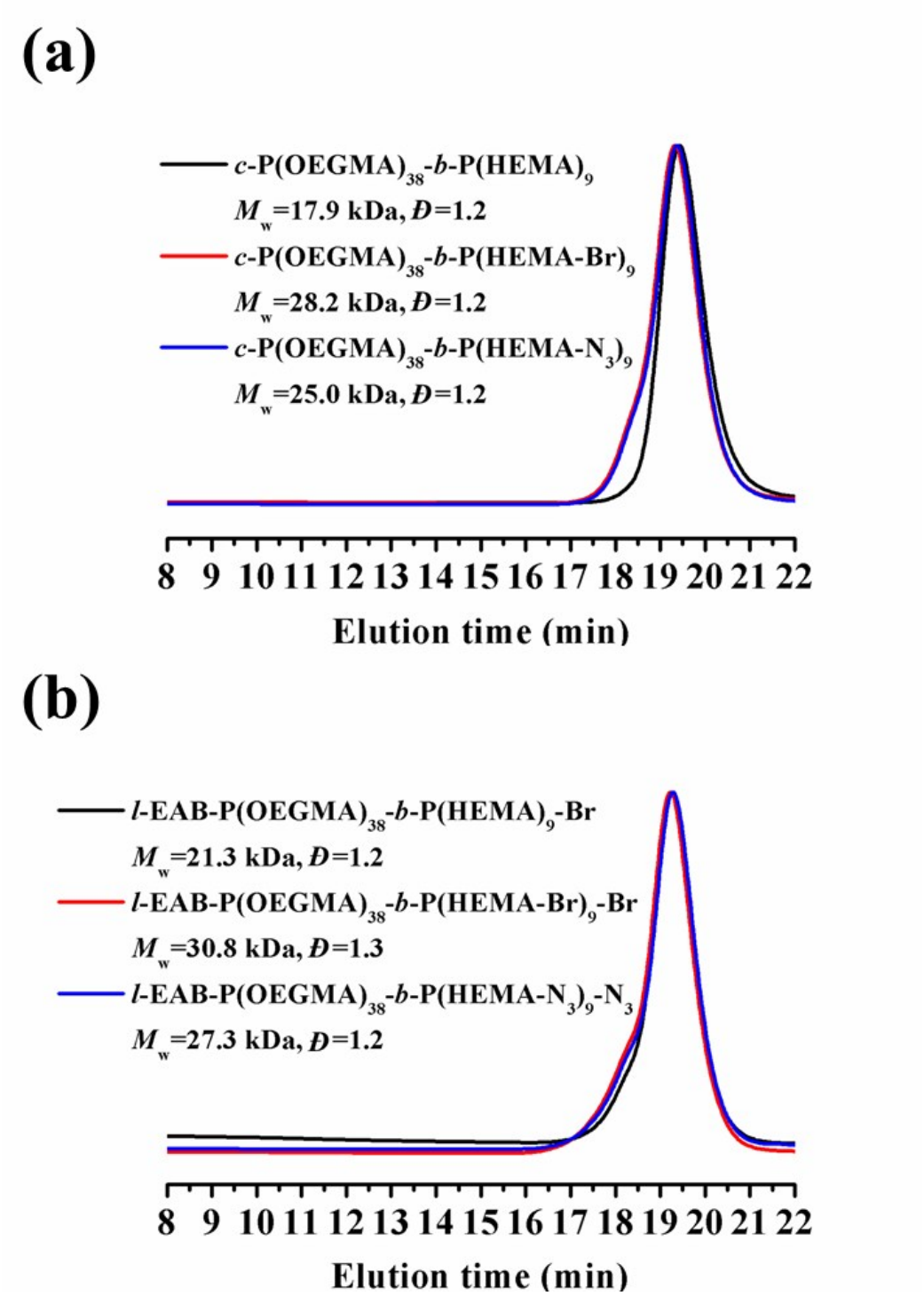


Figure S5. SEC elution traces of (a) *c*-P(OEGMA)$_{38}$-*b*-P(HEMA)$_9$, *c*-P(OEGMA)$_{38}$-*b*-P(HEMA-Br)$_9$, and *c*-P(OEGMA)$_{38}$-*b*-P(HEMA-N$_3$)$_9$; (b) *l*-EAB-P(OEGMA)$_{38}$-*b*-P(HEMA)$_9$-Br, *l*-EAB-P(OEGMA)$_{38}$-*b*-P(HEMA-Br)$_9$-Br, and *l*-EAB-P(OEGMA)$_{38}$-*b*-P(HEMA-N$_3$)$_9$-N$_3$.

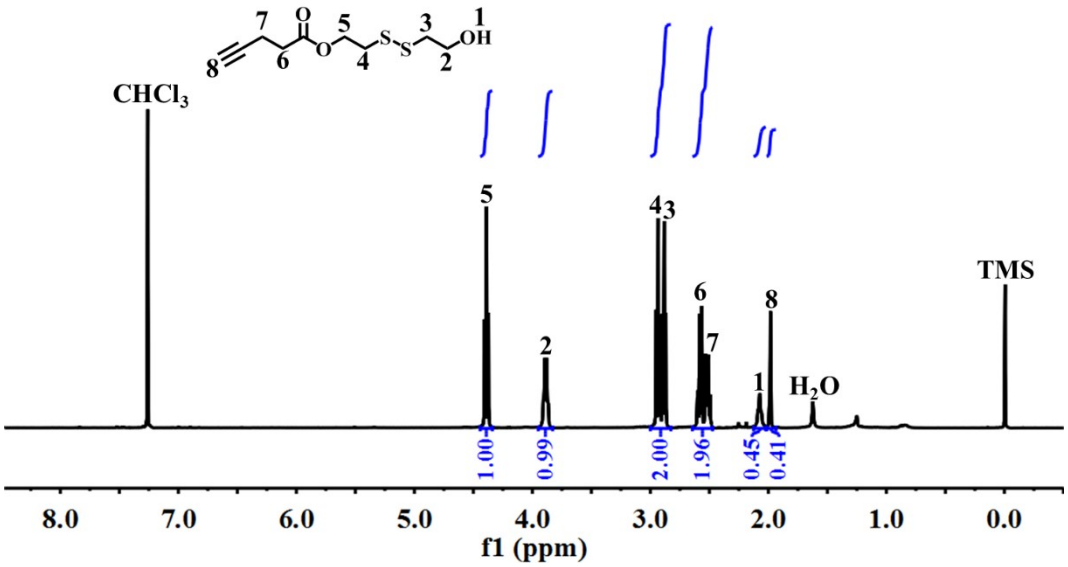


Figure S6. ^{1}H NMR spectrum of alkynyl-SS-OH in $CDCl_3$.

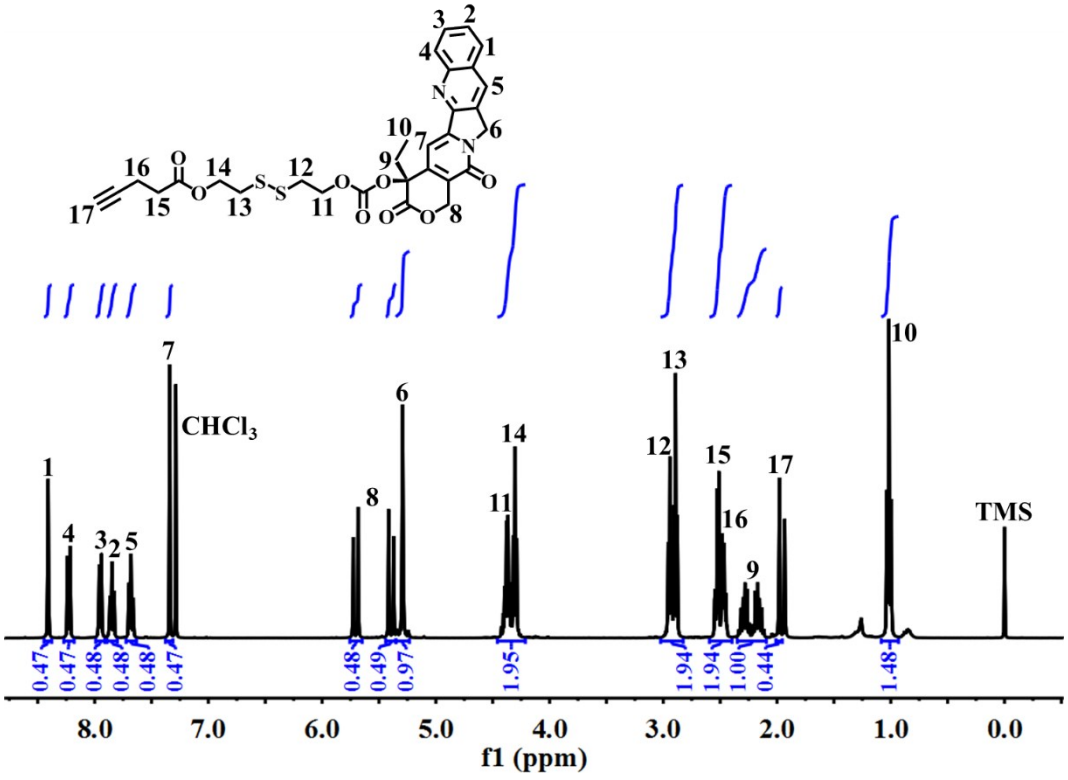


Figure S7. ^{1}H NMR spectrum of alkynyl-SS-CPT in $CDCl_3$.

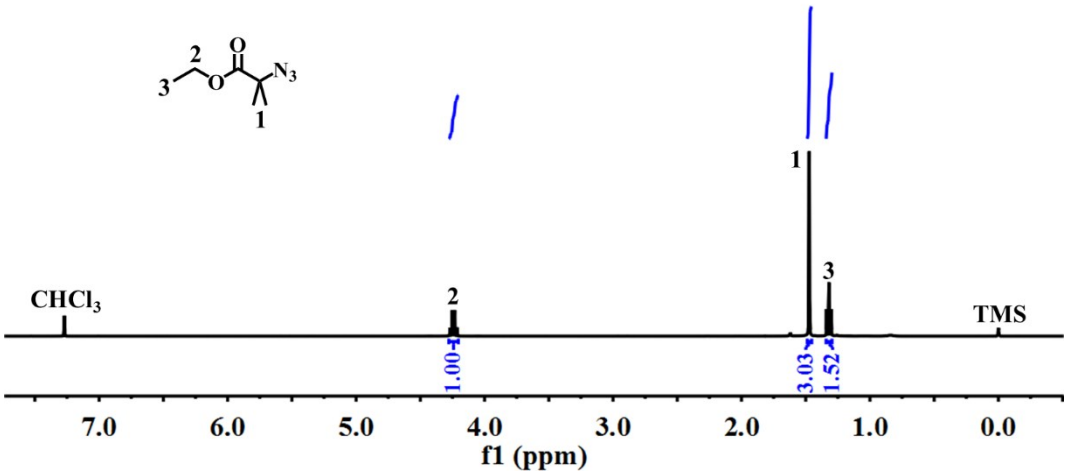


Figure S8. ^{1}H NMR spectrum of EAB in $CDCl_3$.

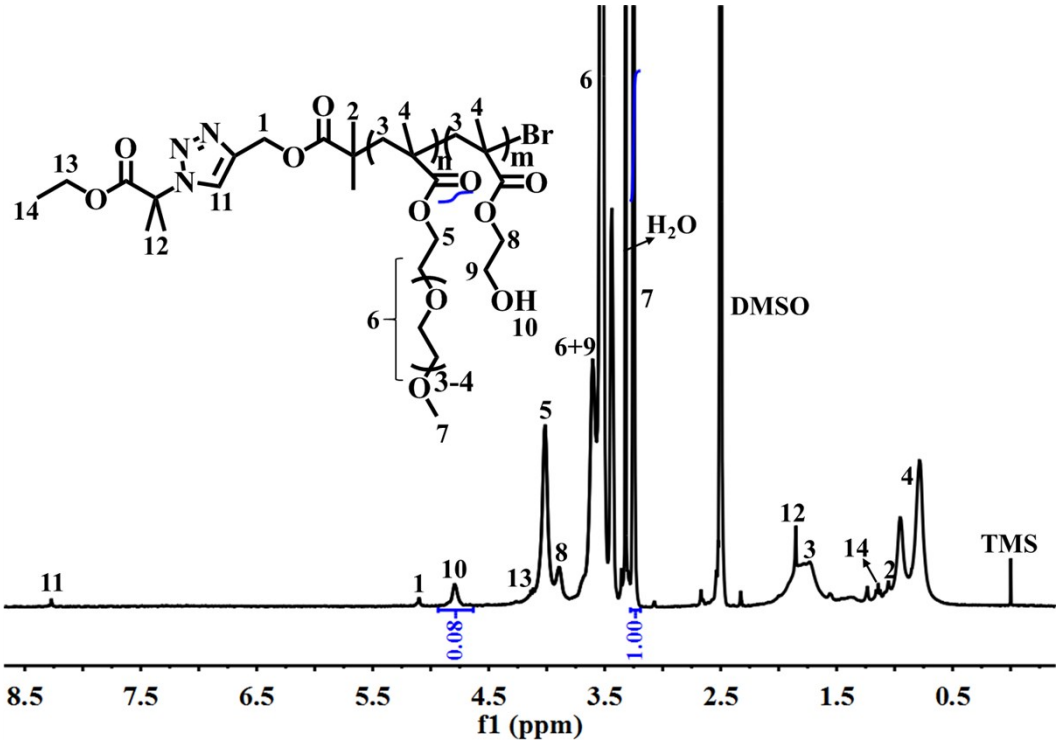


Figure S9. ^{1}H NMR spectrum of *l*-EAB-P(OEGMA)$_{38}$-*b*-P(HEMA)$_9$-Br in DMSO-d_6.

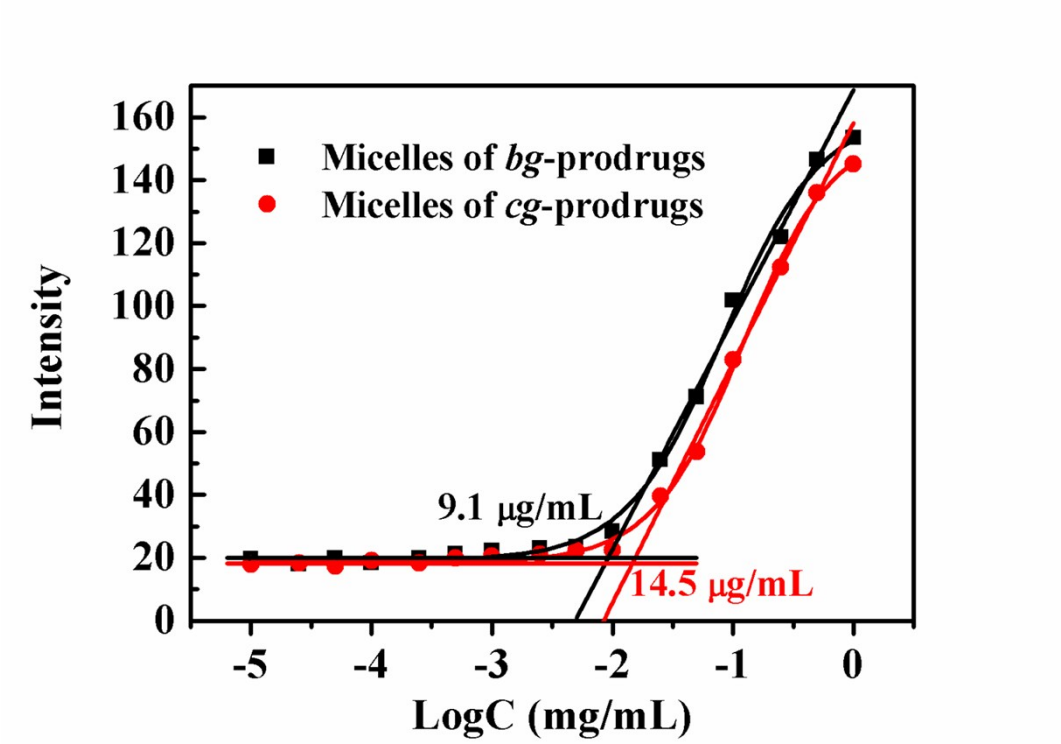


Figure S10. The intensity of $I_{373\ nm}$ in the emission spectra as a function of the logarithm of the concentrations of *cg* and *bg*-prodrugs.

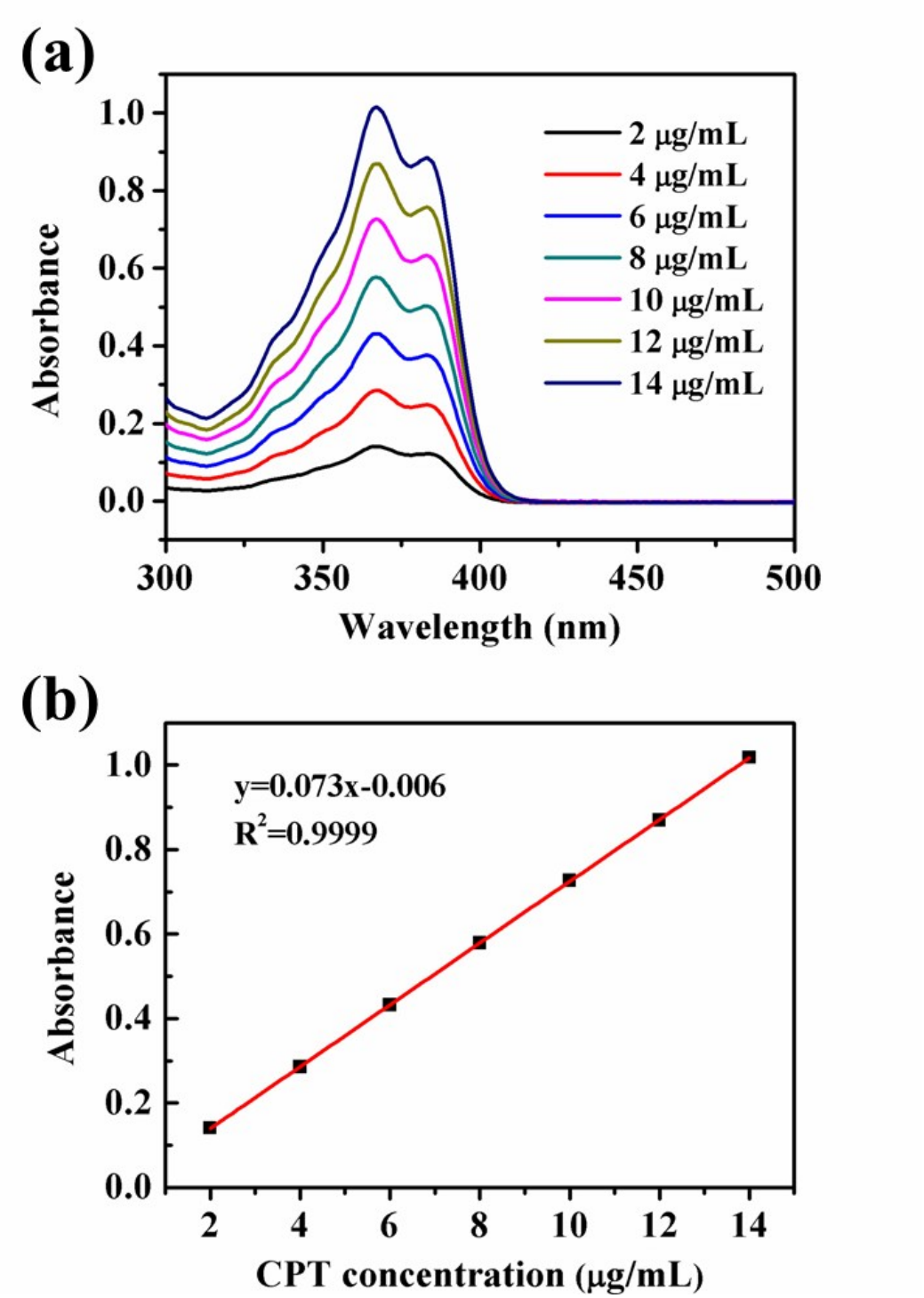


Figure S11. (a) UV-vis spectra of CPT in DMSO at different concentrations and (b) The absorbance of CPT as a function of the concentration (μg/mL) at a wavelength of 367 nm.

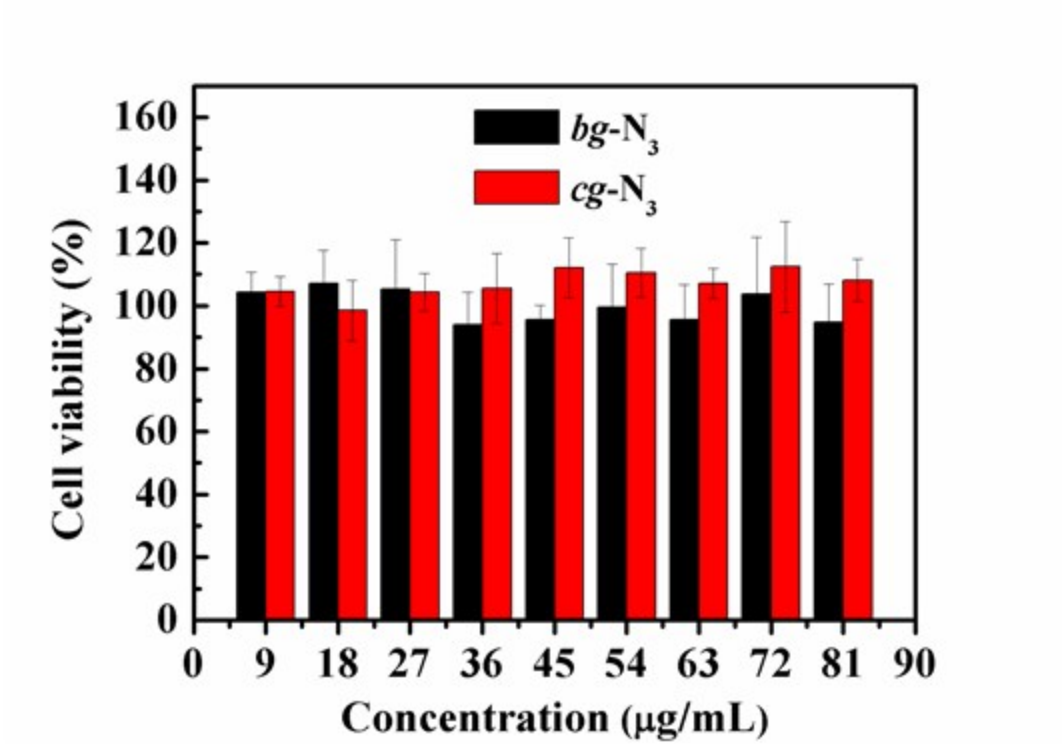


Figure S12. *In vitro* viability of HeLa cells treated with *cg*-N_3 and *bg*-N_3 at various polymer concentrations for 72 h of incubation.