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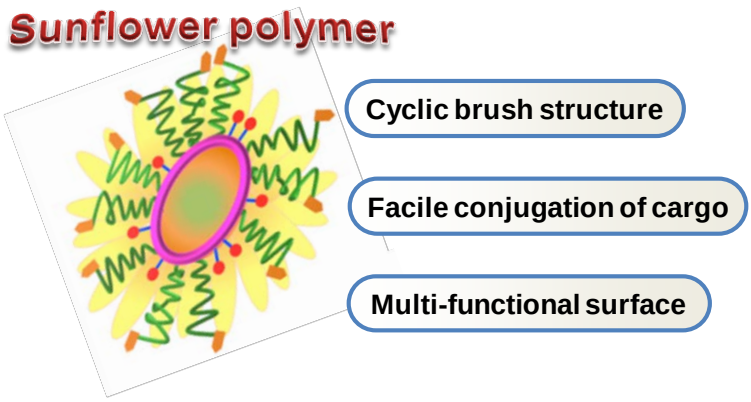

Supporting Information

of

ATRP Synthesis of Sunflower Polymers using Cyclic Multimacroinitiator

Hua Wei,[1,‡,#] Christine E. Wang,[1,‡] Nicholas Tan,[1] Andrew J. Boydston,[2] and Suzie H. Pun[1,*]

[1] Department of Bioengineering and Molecular Engineering & Sciences Institute and

[2] Department of Chemistry, University of Washington, Seattle, Washington 98195, United States

‡ These authors contributed equally.

Present address: Department of Chemistry, Lanzhou University, Lanzhou, 730000, China

* Corresponding author: spun@uw.edu

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1. Experimental Methods

Materials

All materials were purchased from Sigma-Aldrich unless otherwise noted.

Synthesis of ethyl glycinate methacrylamide (EGMA) monomer

Ethyl glycinate hydrochloride (10.15 g, 0.072 mol) was dissolved in 100 mL of dry dichloromethane (DCM). Anhydrous TEA (20 mL, 0.144 mol) was then added at room temperature, and the solution was cooled to 0°C in an ice bath. Methacryloyl chloride (7.251 mL, 0.072 mol) was added dropwise via a syringe pump to the cooled ethyl glycinate solution over 2 h. After completion of this addition, the reaction mixture was warmed up to room temperature and was stirred for another 2 h. After the reaction, the solution was filtered to remove the by-product triethylamine hydrochloride precipitate. Subsequently, the solvent was removed by rotary evaporation, and the crude product was purified by column chromatography with an ethyl acetate/hexane mixture (1/2, v/v, R_f = 0.2-0.3 on silica). The product was isolated by evaporation of the solvents and further dried in a vacuum oven to form a colorless oily residue. Yield: 78% (9.55 g). ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.19 (t, 3H), 4.10 (m, 2H), 3.81 (d, 2H), 8.40 (s, 1H), 1.87 (s, 3H), 5.40 (s, 1H), 5.71 (s, 1H).

Synthesis of linear P(HEMA-*st*-EGMA) precursors (Alkyne-P(HEMA-*st*-EGMA)-N_3)

The linear precursor with Br terminus was prepared by ATRP of 2-hydroxyethyl methacrylate (HEMA) and EGMA in a 2-propanol (IPA)/*N*,*N*-dimethylformamide (DMF) mixed solution, using propargyl 2-bromoisobutyrate[1] as the initiator and *N*,*N*,*N*′,*N*′′,*N*′′-pentamethyldiethylenetriamine **(**PMDETA)/Cu(I)Br as the catalyst. Typically, a 10 mL round-bottom flask was charged with propargyl 2-bromoisobutyrate (0.041 g, 0.2 mmol), HEMA (1.30 g, 10 mmol), EGMA (0.57 g, 3.33 mmol) to obtain a HEMA and initiator molar ratio ([HEMA]/[Initiator]) of 50. The above mixture was dissolved in a 9:1 % w/w IPA/DMF mixture to obtain a 50% w/w HEMA solution. The flask was degassed using a stream of dry nitrogen gas to remove any trace of oxygen in the system. CuBr catalyst and PMDETA (relative molar ratios of initiator: CuBr: PMDETA = 1:1:1) were then added quickly under a nitrogen flow. Finally, the reaction mixture was sealed, followed by immersing the flask into an oil bath preheated to 65°C to start the polymerization. The reaction mixture turned green and became viscous as the

reaction progressed. After 16 h, the reaction mixture was quenched by exposing to air. The reaction mixture was diluted with 2 mL of methanol and then subjected directly to dialysis against distilled water to remove the copper catalyst. The product was harvested by freeze-drying. Yield: 70~80%. ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.61-1.04 (m, -CC**H**$_3$, HEMA; -CC**H**$_3$, EGMA), 1.17 (m, -CH$_2$C**H**$_3$, EGMA), 1.60-2.00 (b, -CC**H**$_2$-, HEMA; -CC**H**$_2$-, EGMA), 3.58 (s, -C**H**$_2$OH, HEMA), 3.90 (s, -COOC**H**$_2$-, HEMA; -NHC**H**$_2$COO-, EGMA), 4.05 (m, -COOC**H**$_2$-, EGMA), 4.81 (s, -CH$_2$O**H**, HEMA).

A non-clickable linear analogue was synthesized following the same reaction conditions except using ethyl 2-bromoisobutyrate (EBB) as the initiator. ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.61-1.04 (m, -CC**H**$_3$, HEMA; -CC**H**$_3$, EGMA), 1.17 (m, -CH$_2$C**H**$_3$, EGMA), 1.60-2.00 (b, -CC**H**$_2$-, HEMA; -CC**H**$_2$-, EGMA), 3.58 (s, -C**H**$_2$OH, HEMA), 3.90 (s, -COOC**H**$_2$-, HEMA; -NHC**H**$_2$COO-, EGMA), 4.05 (m, -COOC**H**$_2$-, EGMA), 4.81 (s, -CH$_2$O**H**, HEMA).

Afterward, the linear precursor with azide terminus was obtained as follows. Alkyne-P(HEMA-*st*-EGMA)-Br (1.0 g) and NaN_3 in a 20-fold molar excess were dissolved in a 1/4 v/v % water/DMF mixed solvent (10 mL) in a round-bottom flask equipped with a magnetic stirrer. The flask was sealed with a rubber septum and was stirred at 45°C for 48 h. After purification by extensive dialysis to remove residual sodium salts, the linear precursor, alkyne-P(HEMA-*st*-EGMA)-N_3, was obtained by freeze-drying. Yield: 90% (0.9 g). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.61-1.04 (m, -CC**H**$_3$, HEMA; -CC**H**$_3$, EGMA), 1.17 (m, -CH$_2$C**H**$_3$, EGMA), 1.60-2.00 (b, -CC**H**$_2$-, HEMA; -CC**H**$_2$-, EGMA), 3.58 (s, -C**H**$_2$OH, HEMA), 3.90 (s, -COOC**H**$_2$-, HEMA; -NHC**H**$_2$COO-, EGMA), 4.05 (m, -COOC**H**$_2$-, EGMA), 4.81 (s, -CH$_2$O**H**, HEMA).

The bromo-terminus of the non-clickable linear copolymer was also converted to an azide group following the same methods.

Synthesis of cyclic P(HEMA-*st*-EGMA) copolymer by intra-chain click cyclization

In a typical procedure, 750 mL of DMF was placed in a 1000 mL three-neck flask and degassed by bubbling dry nitrogen gas for 1 h. 20-fold molar equivalents of PMDETA and CuBr were then charged into the flask under the protection of nitrogen flow. A solution of alkyne-P(HEMA-*st*-EGMA)-N_3 linear precursor (0.5 g) in degassed DMF (10 mL) was added to the copper catalyst solution via a syringe pump at the rate of 0.007 mL/min. 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 concen-

trated residue was transferred directly to a dialysis tube (MWCO: 3.5 kDa, Fisher Scientific) and dialyzed against distilled water to remove the copper catalyst. The resulting cyclic polymer, cyclic P(HEMA-*st*-EGMA), was harvested by freeze-drying. Yield: 80% (0.4 g). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.61-1.04 (m, -CC**H**$_3$, HEMA; -CC**H**$_3$, EGMA), 1.17 (m, -CH$_2$C**H**$_3$, EGMA), 1.60-2.00 (b, -CC**H**$_2$-, HEMA; -CC**H**$_2$-, EGMA), 3.58 (s, -C**H**$_2$OH, HEMA), 3.90 (s, -COOC**H**$_2$-, HEMA; -NHC**H**$_2$COO-, EGMA), 4.05 (m, -COOC**H**$_2$-, EGMA), 4.81 (s, -CH$_2$O**H**, HEMA).

Preparation of cyclic poly(2-(2-bromoisobutyrnyloxy)ethyl methacrylate-*st*-EGMA) (P((HEMA-iBuBr)-*st*-EGMA)) macroinitiator

Cyclic poly(2-(2-bromoisobutyrnyloxy)ethyl methacrylate-*st*-EGMA) (P((HEMA-iBuBr)-*st*-EGMA)) macroinitiator was prepared by esterification of cyclic P(HEMA-*st*-EGMA). Cyclic P(HEMA-*st*-EGMA) (0.2 g, 1.07 mmol of HEMA units) was dissolved in 10 mL of dry DMF, and then anhydrous TEA (581 μL, 4.17 mmol) was added at room temperature. The solution was cooled to 0°C in an ice bath. 2-bromoisobutyryl bromide (404 μL, 3.2 mmol) was added dropwise via a syringe pump to the cooled polymer solution over 30 min. After completion of this addition, the solution was further stirred at 0°C for 1 h and at room temperature for 48 h. After the reaction, the reaction mixture was poured into distilled water to precipitate the product. The product was separated by centrifugation and further purified twice by redissolving/reprecipitating with DMF/water, and finally dried in a vacuum oven for 24 h, yielding a light yellow powdery product. Yield: 58% (0.21 g). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.61-1.04 (m, -CC**H**$_3$, HEMA; -CC**H**$_3$, EGMA), 1.17 (m, -CH$_2$C**H**$_3$, EGMA), 1.90 (s, COC(C**H**$_3$)$_2$Br), 1.70-2.00 (b, -CC**H**$_2$-, HEMA; -CC**H**$_2$-, EGMA), 3.70 (s, -NHC**H**$_2$COO-, EGMA), 3.90 (m, -COOC**H**$_2$-, EGMA), 4.10-4.50 (b, -COO**H**$_2$C**H**$_2$OCO, HEMA).

Linear multimacroinitiator for the preparation of comb-like polymer was prepared following the same procedures except using non-clickable linear copolymer, P(HEMA-*st*-EGMA)-N$_3$.

Preparation of sunflower polymer, P((HEMA-*sunflower*-oligo(ethylene glycol) monomethyl ether methacrylate-*st*-EGMA) (P((HEMA-*sf*-OEGMA)-*st*-EGMA))

A panel of sunflower polymers, P((HEMA-*sf*-OEGMA)-*st*-EGMA), with OEGMA radiating rays was prepared by ATRP using cyclic P((HEMA-iBuBr)-*st*-EGMA) macroinitiator. Cyclic P((HEMA-iBuBr)-*st*-EGMA) macroinitiator (0.05 g, 0.149 mmol of initiator sites), and OEGMA (M_n=300 g/mol, 4.46 g, 14.9 mmol) were dissolved in a 1:2 v/v % anisole/DMF mixed solution (30 mL). The solution was split in equal volumes into five 10 mL round-bottom flasks. After putting in a stir bar

and sealing with a rubber septum, each solution was thoroughly degassed by nitrogen bubbling for 10 min. Meanwhile, a catalyst stock solution of $CuBr_2$ (3.3 mg, 14.9 μmol) and 2,2'-bipyridine (51.2 mg, 327.8 μmol) was made in DMF (500 μL). The solution was bubbled with nitrogen to deoxygenate the mixture. Solid CuBr (21 mg, 149 μmol) was added to the copper stock solution under nitrogen atmosphere and sonicated to promote dissolution. The resultant copper catalyst stock solution (100 μL) was added quickly to each cyclic initiator-monomer mixture under a nitrogen blanket. Finally, the reaction mixtures were sealed, followed by immersing the flasks into an oil bath preheated to 60°C to start the polymerization. The reactions were subsequently quenched by exposing flasks to air at predetermined time intervals. Each reaction mixture was poured into ethyl ether to precipitate the product. The product was separated by centrifugation and further purified by extensive dialysis against distilled water to remove the copper catalyst. The resulting sunflower polymer was harvested by freeze-drying. The conversion of polymerization and molecular weight of each sunflower polymer were determined by ^{1}H NMR and GPC analyses. ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.61-1.04 (m, -CC**H**$_3$, OEGMA), 1.60-2.00 (b, -CC**H**$_2$-, OEGMA), 3.30 (s, -CH_2CH_2OC**H**$_3$, OEGMA), 3.60 (m, -OCH_2C**H**$_2$O-, OEGMA), 4.00 (s, -COOC**H**$_2CH_2O$-, OEGMA).

Comb-like polymer was prepared following the same polymerization condition except using the linear multimacroinitiator.

Preparation of folate-conjugated sunflower polymer (FA-sunflower polymer) by click coupling

Similar to the synthesis of alkyne-P(HEMA-*st*-EGMA)-N_3 linear precursor, sunflower polymer with an azide terminus on each OEGMA radiating ray was prepared by reacting the resultant sunflower polymer with NaN_3 in a 20-fold molar excess in a 1/4 v/v % water/DMF mixed solvent. The reaction was carried out at 45°C for 48 h. After the reaction, the product was purified by extensive dialysis to remove residual sodium salts, and harvested by freeze-drying. ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.61-1.04 (m, -CC**H**$_3$, OEGMA), 1.60-2.00 (b, -CC**H**$_2$-, OEGMA), 3.30 (s, -CH_2CH_2OC**H**$_3$, OEGMA), 3.60 (m, -OCH_2C**H**$_2$O-, OEGMA), 4.00 (s, -COOC**H**$_2CH_2O$-, OEGMA).

To a round-bottom flask containing thoroughly degassed DMF solution (10 mL) of azide-terminated sunflower polymer (210 mg, 97 μmol of azide terminus) and alkyne-functionalized folate[2] (0.05 g, 106 μmol), PMDETA (20.3 μL, 97 μmol), and CuBr (14 mg, 97 μmol) were added quickly under a nitrogen flow. The reaction mixture was stirred at room temperature for 24 h. After the reaction, the mixture was poured into ethyl ether to precipitate the product and to remove the unreacted propargyl folate. The product was separated by centrifugation and further purified by dialysis against distilled water to re-

move the copper catalyst. The resulting FA-sunflower polymer was isolated by freeze-drying. Yield: 86% (220 mg). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.61-1.04 (m, -CC**H**$_3$, OEGMA), 1.60-2.00 (b, -CC**H**$_2$-, OEGMA), 3.30 (s, -CH_2CH_2OC**H**$_3$, OEGMA), 3.60 (m, -OCH_2C**H**$_2$O-, OEGMA), 4.00 (s, -$COOC$**H**$_2CH_2O$-, OEGMA), 6.50-9.00 (m, folate).

Folate-conjugated comb-like polymer was prepared following the same reaction conditions.

The amount of folate conjugated to each polymer was determined by absorbance at 360 nm based on a standard curve obtained from solutions of free folic acid. Each polymer (sunflower and comb) contains approximately 25-28 folate groups, a conjugation efficiency of 61-69% based on the theoretical polymer composition of 41 HEMA groups available for polymerization of petals and subsequent folate conjugation.

Preparation of P((HEMA-*sf*-OEGMA-folate)-*st*-(GMA-hydrazide))

A 50 mL falcon tube equipped with a magnetic stirrer was charged with FA-sunflower polymer (220 mg, 32.3 μmol of EGMA units), hydrazine hydrate (18 μL, 370 μmol), and anhydrous methanol (6 mL). The reaction was performed at room temperature for 10 h. After the reaction, the resultant polymer precursor, P((HEMA-*sf*-OEGMA-folate)-*st*-(GMA-hydrazide)), was purified by extensive dialysis against distilled water and collected by freeze-drying. Yield: 82% (180 mg). The content of hydrazide was determined to be 85% (29.2 μmol) by modified TNBSA assays[3,4].

Preparation of P((HEMA-*sf*-OEGMA-folate)-*st*-(GMA-fluorescein))

A 50 mL falcon tube equipped with a magnetic stirrer was charged with the polymer precursor P((HEMA-*sf*-OEGMA-folate)-*st*-(GMA-hydrazide)) (90.0 mg, 14.6 μmol of hydrazide), NHS-Fluorescein (PI-46410, Thermo Scientific, MW = 473.4 g/mol, 13.8 mg, 29.2 μmol), and anhydrous methanol (4 mL). The tube was sealed, and the reaction was allowed to proceed in the dark at room temperature for 48 h. The resultant fluorescein-labeled sunflower polymer, P((HEMA-*sf*-OEGMA-folate)-*st*-(GMA-fluorescein)), was purified by extensive dialysis against distilled water (4L) for 24 h and collected by freeze-drying. Yield: 75.1% (67.6 mg). ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.61-1.04 (m, -CC**H**$_3$, OEGMA), 1.60-2.00 (b, -CC**H**$_2$-, OEGMA), 3.30 (s, -CH_2CH_2OC**H**$_3$, OEGMA), 3.60 (m, -OCH_2C**H**$_2$O-, OEGMA), 4.00 (s, -$COOC$**H**$_2CH_2O$-, OEGMA), 6.50-9.00 (m, overlap of folate and fluorescein).

Folate-comb polymer-fluorescein was prepared following the same reaction conditions.

The amount of fluorescein conjugated to each polymer was determined by NMR. Assuming an average DP of 7 per p(OEGMA) petal (based on 7.1% conversion, Figure 2), each polymer contains approximately 6-8 fluorescein molecules, a conjugation efficiency of 59-78% based on the theoretical polymer composition of 12 EGMA groups and 85% conversion of EGMA to hydrazide groups for fluorescein incorporation.

Characterization of polymers

^{1}H NMR spectra were recorded on a Bruker AV 500 nuclear magnetic resonance (NMR) instrument using DMSO-d_6, $CDCl_3$, and D_2O as the solvents. Fourier transform infrared (FT-IR) spectra were recorded on a Bruker Vector 33 FT-IR spectrometer. Samples were pressed into potassium bromide (KBr) pellets for measurements. Gel permeation chromatography (GPC) was used to determine molecular weight and polydispersity (M_w/M_n, PDI) of polymer samples prepared. SEC Tosoh TSK-GEL R-3000 and R-4000 columns (Tosoh Bioscience, Montgomeryville, PA) were connected in series to a Agilent 1200 series (Agilent Technologies, Santa Clara, CA), refractometer Optilab-rEX and triple-angle static light scattering detector miniDAWN TREOS (Wyatt Technology, Santa Barbara, CA). HPLC-grade DMF containing 0.1 wt% LiBr at 60°C was used as the mobile phase at a flow rate of 1 mL/min. Absolute molecular weight averages and dn/dc were calculated using ASTRA software (Wyatt). Average dimensions of sunflower polymers in an aqueous phase were measured by dynamic light scattering (DLS) with a ZetaPALS (Brookhaven Instruments Corp.) at a detection angle of 90°. The measurements were performed in triplicate. The aqueous solution was passed through a 0.22 μm pore-sized syringe filter before measurements.

Cell culture

KB cells (ATCC CCL-17) and A549 cells (ATCC CCL-185) were maintained in folate-free RPMI 1640 (Life Technologies) and F-12K media, respectively. Media was supplemented with 10% fetal bovine serum and 1% penicillin/streptomycin. Cells were cultured as a monolayer in a 37°C, 5% CO_2 environment. Medium was replaced every 2-3 days. Cells were passaged at ~70-80% confluence by incubation with Trypsin-EDTA, followed by resuspension in complete growth medium.

Uptake and competition study by flow cytometry

Cells were seeded in 24-well plates at a density of 40,000 cells per well in 1 mL of complete growth medium and incubated in a 37°C, 5% CO_2 environment for 24 h. Cells were rinsed once with PBS and incubated in 1 mL of supplemented folate-free RPMI 1640 medium +/- 2 mM folate competition for 1 h at room temperature. Polymer samples at varying concentrations were prepared in serial dilutions in water and then diluted 10-fold in supplemented folate-free RPMI 1640 medium +/- 2 mM folate. The media was aspirated from each well, and cells were incubated with 200 µL of polymer solution for 20 min at 37°C. After incubation, the polymer solutions were aspirated, and the cells were rinsed twice with PBS/1% BSA. Cells were then harvested by incubation with 200 µL of Trypsin-EDTA, followed by resuspension with 1 mL of complete growth medium. Cells were transferred to 1.5 mL microcentrifuge tubes and pelleted at 300 *g* for 5 min at 4°C. The supernatant was aspirated, and the cell pellets were resuspended in 200 µL of PBS/1% BSA containing 2 µg/mL propidium iodide (PI) as a marker for cell viability. Cells were analyzed for uptake of fluorescent polymer using a MACSQuant Analyzer flow cytometer (Miltenyi).

Cell viability study

The cytotoxicities of various polymers were evaluated *in vitro* using the MTS assay. The cells were seeded in 96-well plates at a density of 2500 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 water and then diluted 10-fold in Opti-MEM medium (Invitrogen). The cells were rinsed once with PBS and incubated with 40 µL of the sample solutions with different polymer concentrations at 37°C for 4 h. Cells were then rinsed with PBS and the medium was replaced with 100 µL of culture medium. At 48 h, 20 µL of 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS, Promega) reagent was added to each well. Cells were then incubated at 37°C, 5% CO2 for 3 h. The absorbance of each well was measured at 490 nm on a Tecan Safire 2 plate reader (Männerdorf, Switzerland). Cell viability (%) for each concentration was normalized to the concentration = 0 (cells only) signal.

2. Calculation of P(HEMA-*st*-EGMA) Composition and Discussion

In the ^{1}H NMR spectrum of EGMA (**Figure S2a**), the resonance signals at chemical shift of 5.39 and 5.71 ppm (methylene protons of methacrylamide moieties) and 4.08 ppm (methylene protons next to the ester bond of ethyl glycinate moieties) have an intensity ratio of 2.27/2.31, very close to 1/1, indicating equivalent coupling of ethyl glycinate and methacryloyl chloride.

The ^{1}H NMR spectrum of P(HEMA$_x$-*st*-EGMA$_y$) (Figure S2b) was analyzed and used to determine the polymer composition according to the reported data[4]. The real composition of the statistical copolymer (molar ratio of HEMA and EGMA, x/y) was determined based on the integral ratios of the characteristic signals at 3.90 ppm ("c"+"i", an overlap of -COOC***H***$_2$CH$_2$OH in HEMA unit and -CONHC***H***$_2$COO- in EGMA unit) and 4.07 ppm ("j", -COOC***H***$_2$CH$_3$ in EGMA unit) as follows,

$(2x+2y) / 2y = 27.13/6.30,$

Thus, x/y (HEMA/EGMA molar ratio) was calculated to be 3.3/1. The integration area of the characteristic signal at 3.58 ppm ("d", -COOCH$_2$C***H***$_2$OH in HEMA unit) should be smaller than that of the peak at 3.90 ppm; however, the presence of an unassigned small peak at 3.60 ppm contributed significantly to the main resonance signal at 3.58 ppm as a shoulder, resulting in a larger integration area for signal "d". Hence, the polymer composition was not calculated using this signal. Similar phenomenon was observed in the reference[4] as well.

ATRP kinetics study of HEMA and EGMA (Figure S1b) showed that polymerization for 16 h resulted in a decently high conversion of monomers (~ 82%), affording polymer of DP ~41, close to the target value of 50. We therefore believe the smaller molecular weight determined by GPC (Figure 1a) does not reveal the actual molecular weight of the polymer. Because GPC results are dependent on the GPC apparatus used, such as the type of column, eluent, and polymer standard, GPC analysis of the same sample using various apparatus can provide different results. To confirm this point, the same polymer was subjected to molecular weight analysis on another GPC set-up equipped with a Waters 1515 pump and a Waters 2414 differential refractive index detector, and using poly(methyl methacrylate) (PMMA) calibration standards. The results (Figure S1a) showed a M_n of 10.1 kDa, and a PDI of 1.25. Such difference indicates it is probably inaccurate to determine the polymer structure based on the GPC data. Instead, the DP of polymer was calculated based on the kinetics data. Taken together with the HEMA/EGMA molar ratio (3.3/1) obtained from ^{1}H NMR study, the DPs of HEMA and EGMA units

were calculated to be 41 and 12 respectively. The resulting copolymer was denoted P($HEMA_{41}$-*st*-$EGMA_{12}$).

The linear precursor P($HEMA_{41}$-*st*-$EGMA_{12}$)-N_3 and cyclic P($HEMA_{41}$-*st*-$EGMA_{12}$) copolymers show quite similar ^{1}H NMR spectra (Figure S3) to P($HEMA_{41}$-*st*-$EGMA_{12}$)-Br (Figure S2b) with unaltered HEMA/EGMA molar ratio, demonstrating that terminal azidonation of linear polymer and "intra-chain" click cyclization of linear precursor did not affect the composition of the parent statistical copolymer. Similar ^{1}H NMR results were recorded for sunflower polymer with bromo- (Figure S6a) and azide (Figure S4b) petal termini as well.

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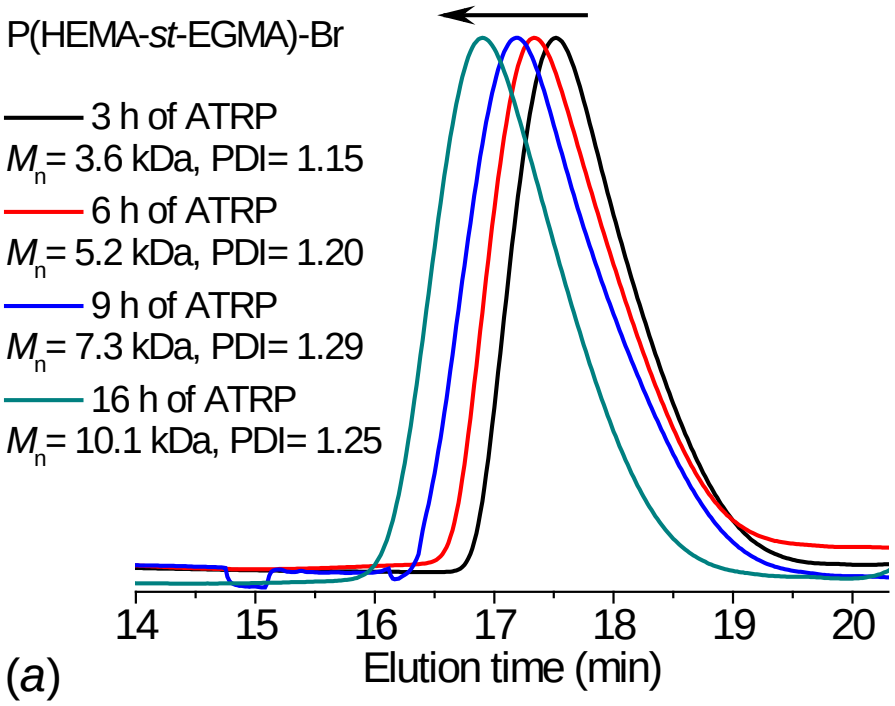
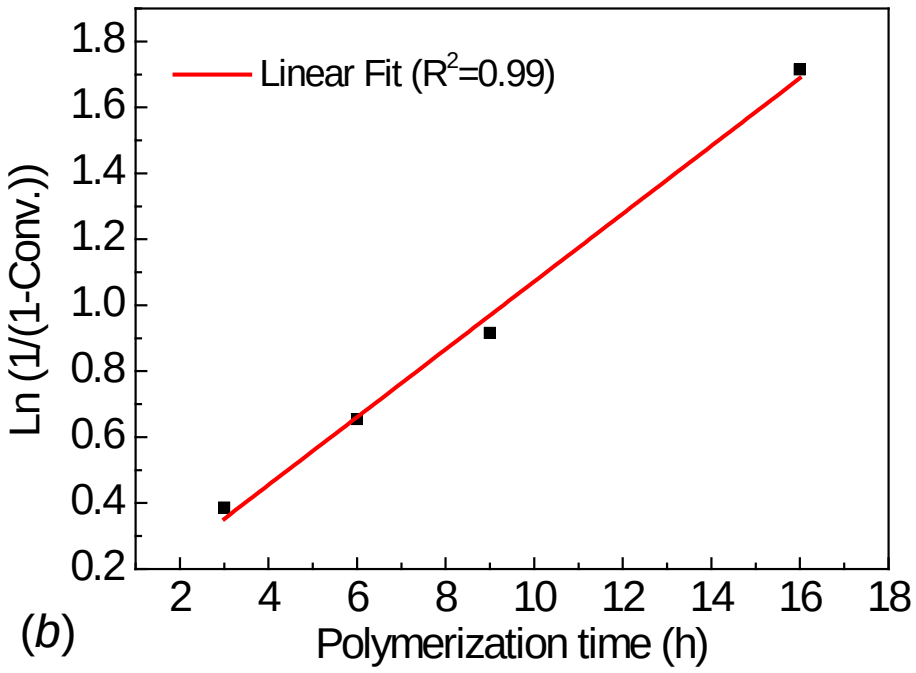
3. Figures S1-S10





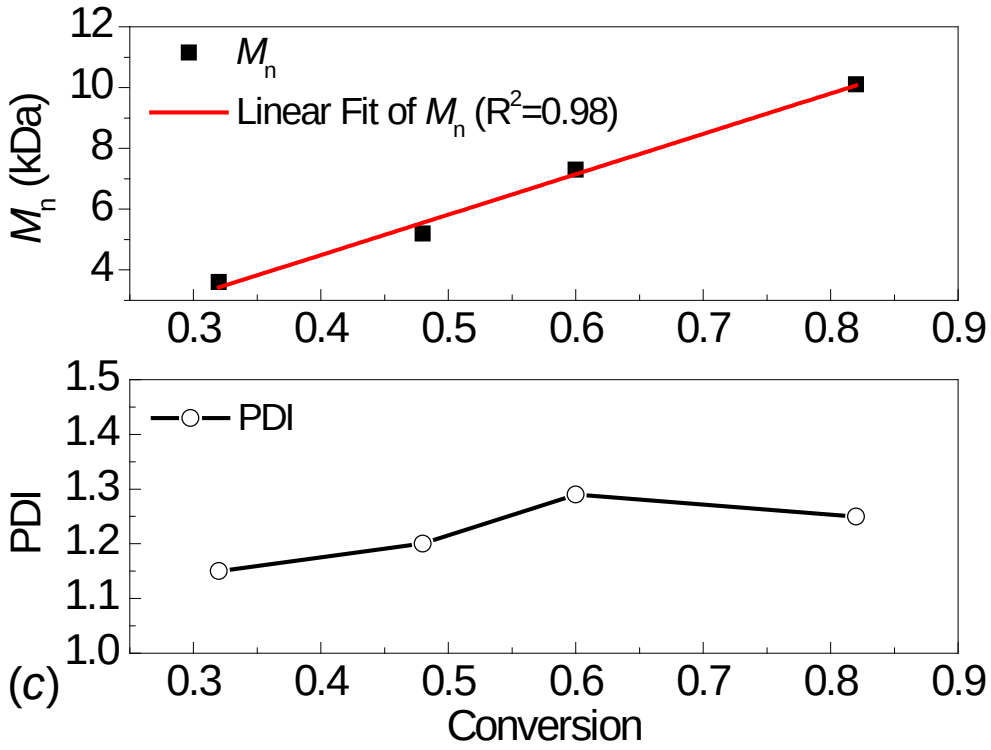


Figure S1. ATRP kinetics study for the synthesis of P(HEMA-*st*-EGMA). (a) GPC elution traces of ATRP-synthesized P(HEMA-*st*-EGMA) at various polymerization times; (b) pseudo-first order kinetics; and (c) plots of M_n and PDI with conversion.

The molecular weights and molecular weight distributions were determined by gel permeation chromatography (GPC) equipped with a Waters 1515 pump and a Waters 2414 differential refractive index detector. It used a series of three linear Styragel columns HT2, HT4, and HT5 at an oven temperature of 60°C. DMF was used as the eluent at a flow rate of 1.0 mL/min. PMMA standards were employed for the GPC calibration.

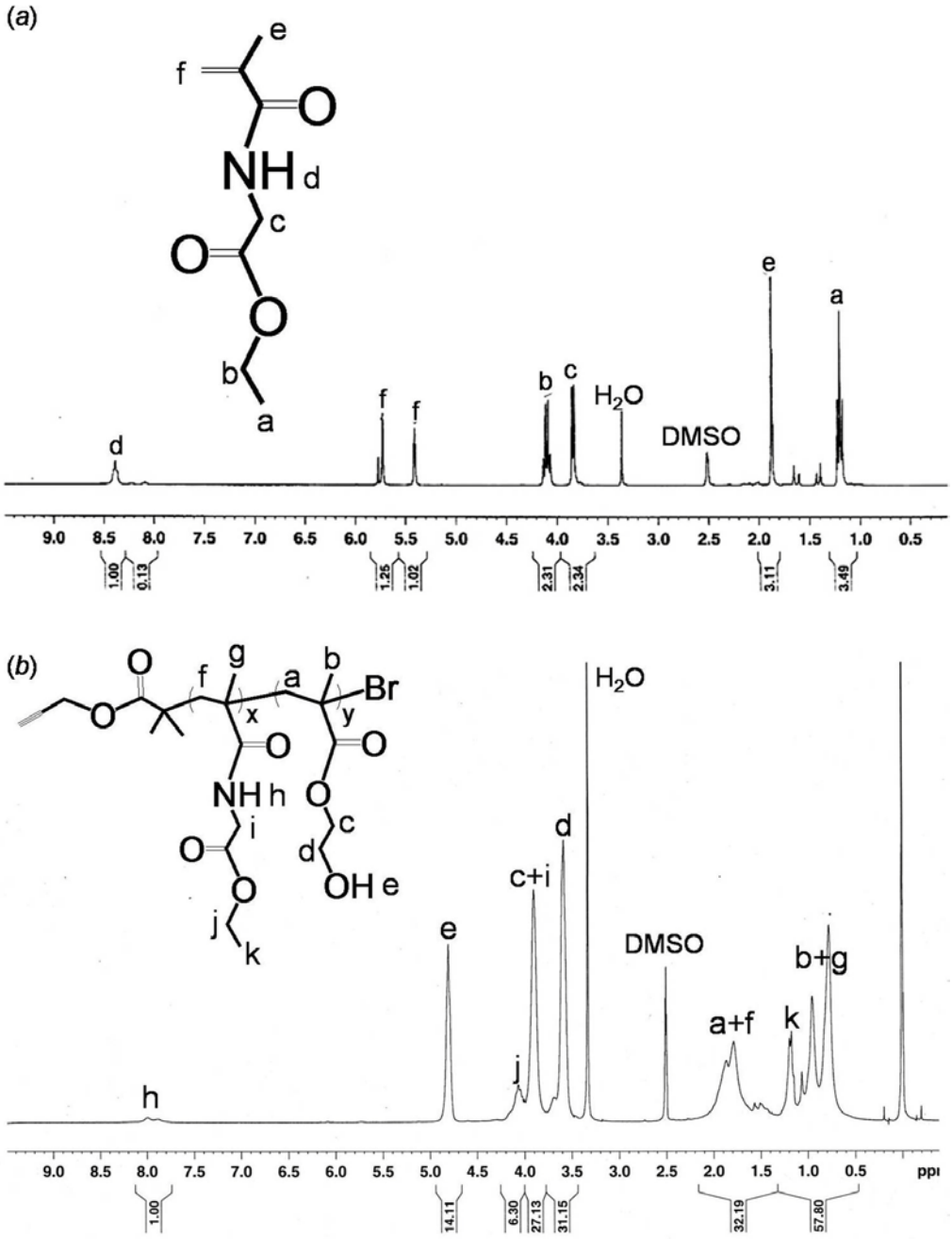


Figure S2. ^{1}H NMR spectra of (a) EGMA monomer, and P(HEMA-*st*-EGMA)-Br copolymer.

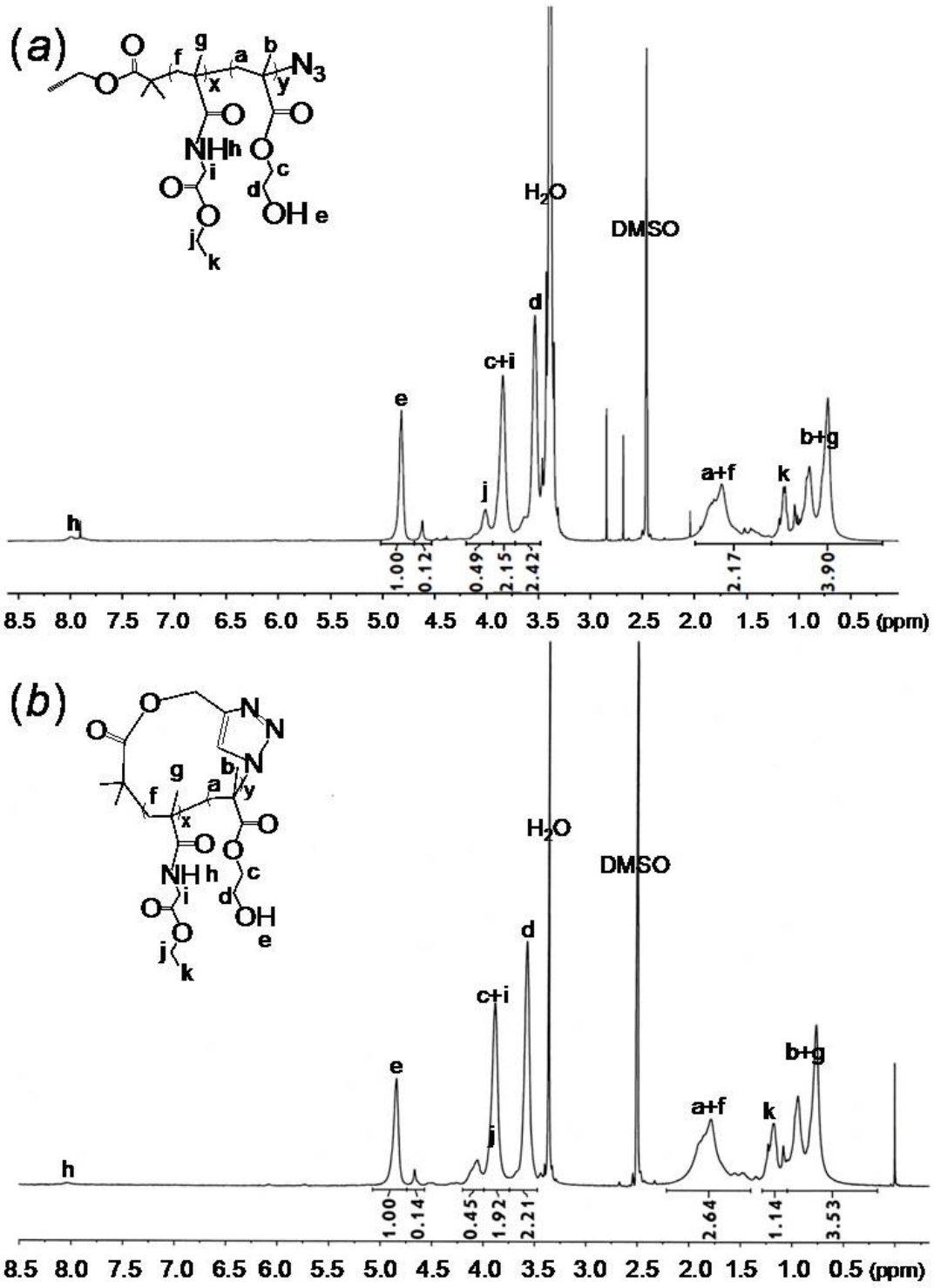


Figure S3. ^{1}H NMR spectra of (a) linear precursor P(HEMA-*st*-EGMA)-N_3 and (b) cyclic P(HEMA-*st*-EGMA).

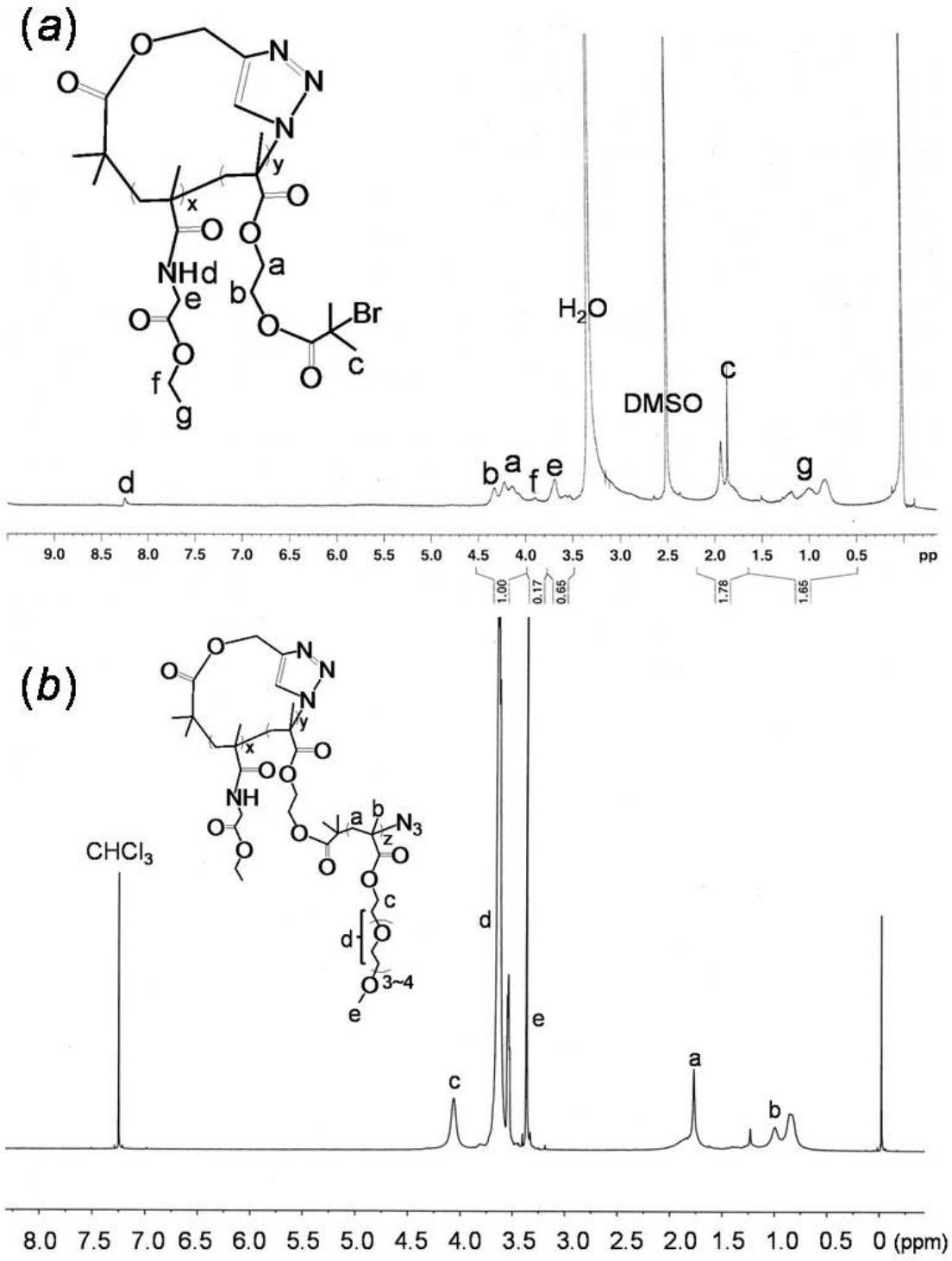


Figure S4. ^{1}H NMR spectra of (a) cyclic multimacroinitiator and (b) sunflower polymer with azide-terminated P(OEGMA) petals.

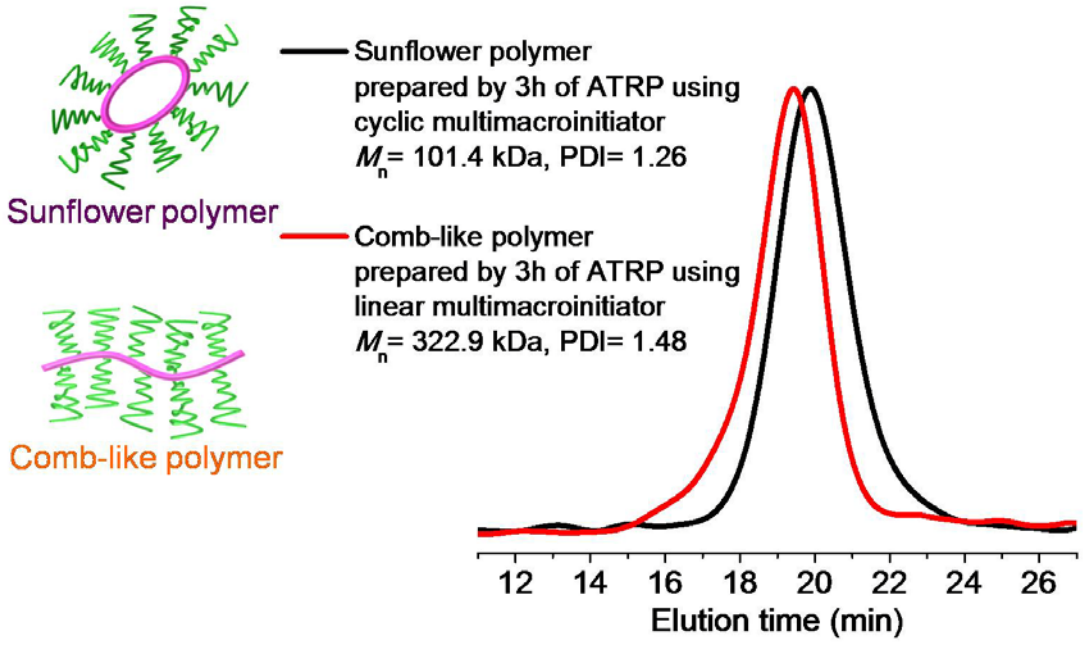


Figure S5. GPC elution traces of sunflower polymer and comb-like polymer prepared with the same polymerization time using cyclic and linear multimacroinitiators.

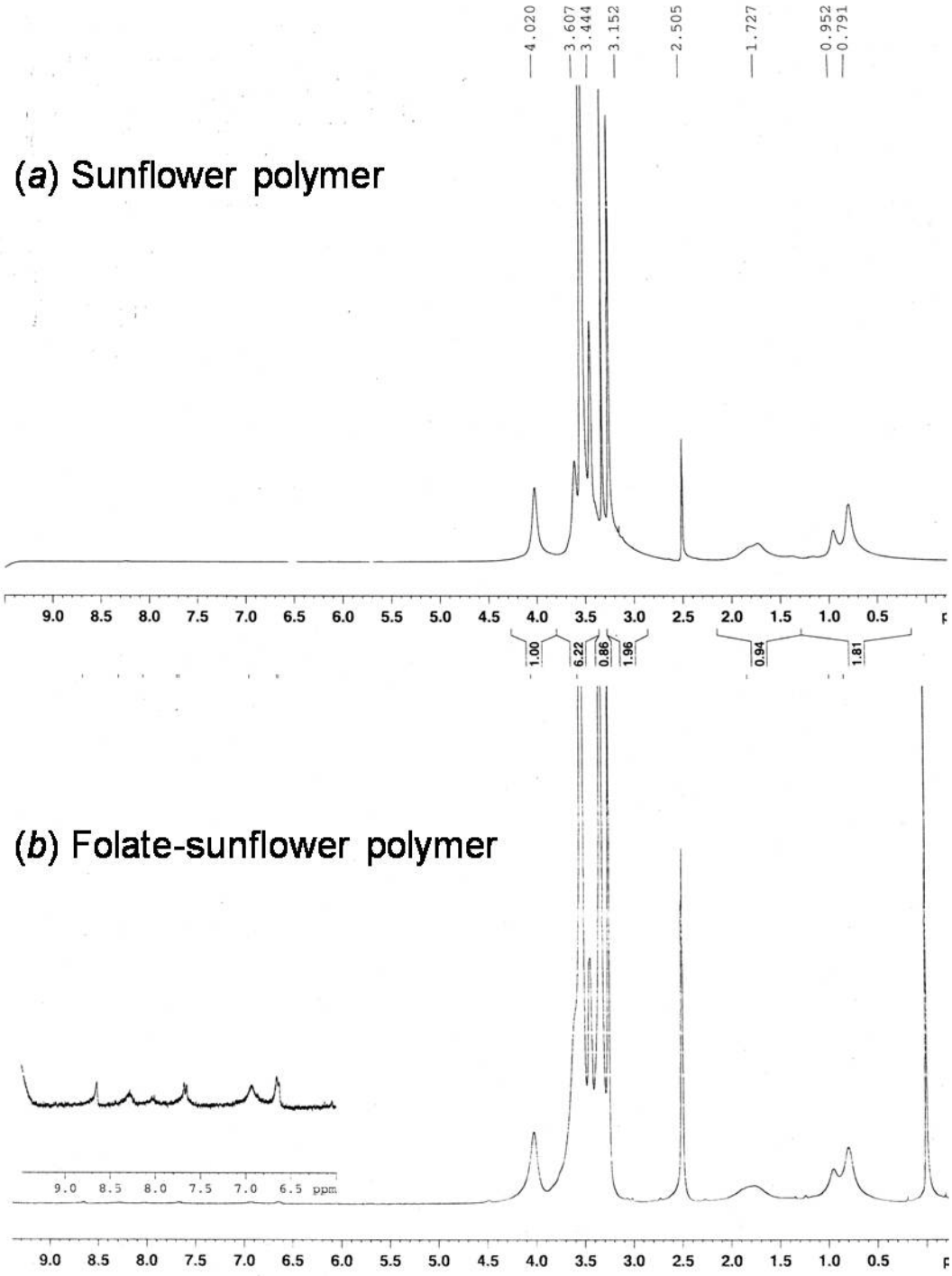


Figure S6. ^{1}H NMR spectra of (a) sunflower polymer and

(b) folate-sunflower polymer.

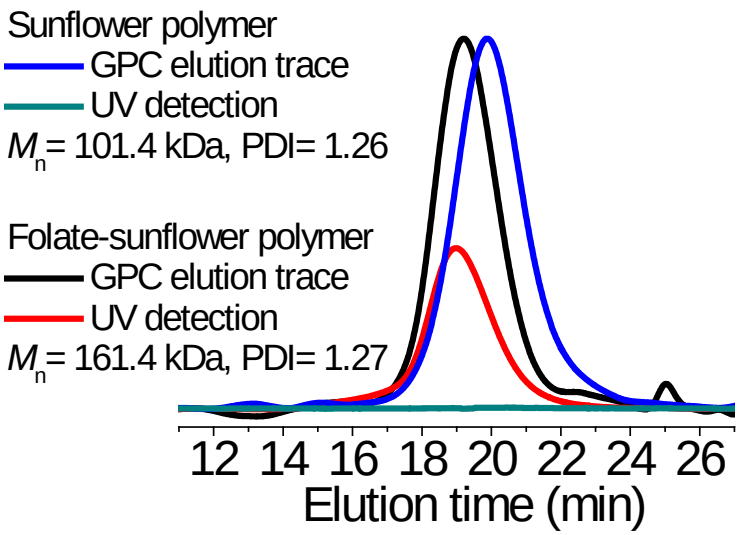


Figure S7. GPC elution traces and UV-detected signals of sunflower polymer and folate-conjugated sunflower polymer.

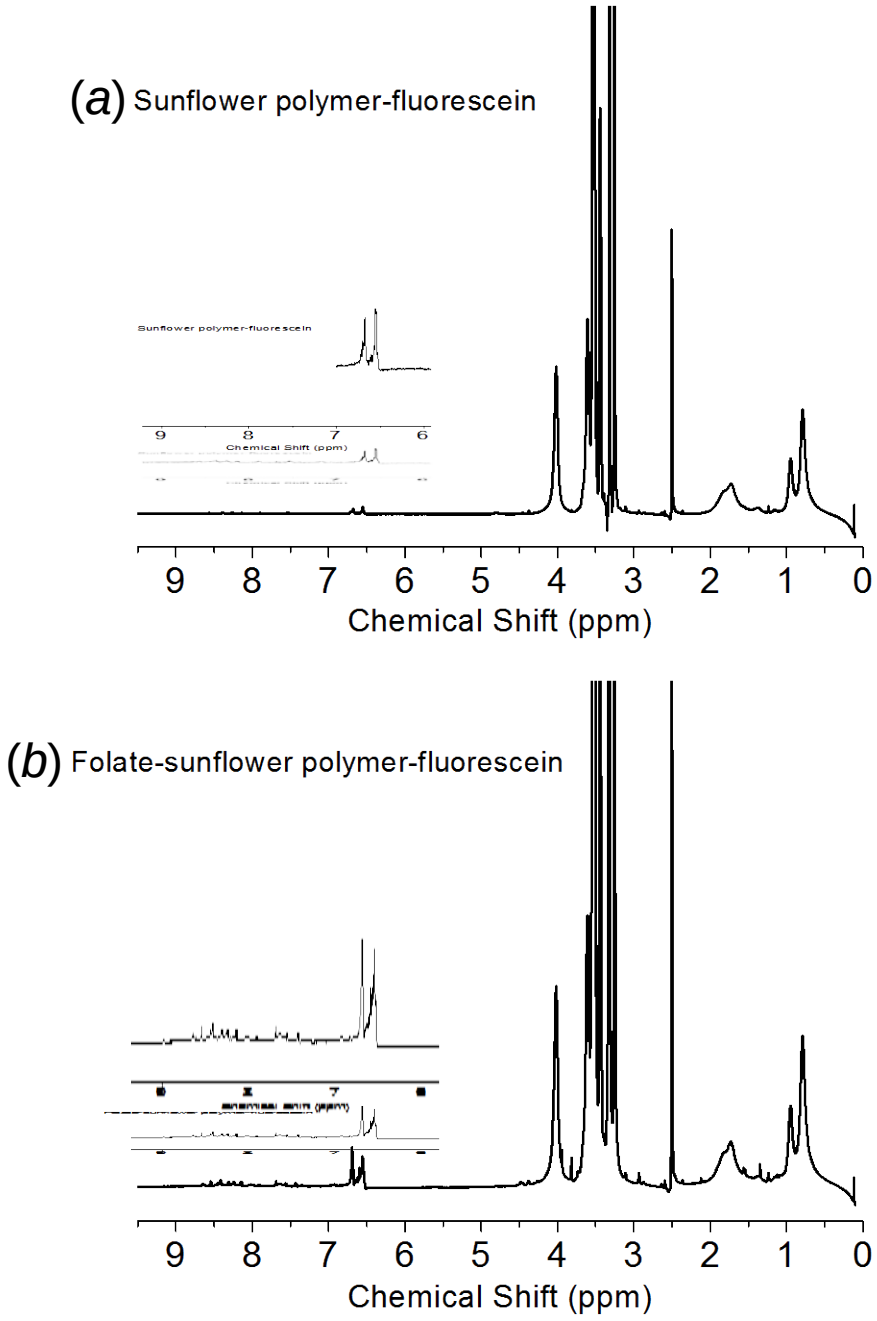


Figure S8. ^{1}H NMR spectra of (a) sunflower polymer-fluorescein and (b) folate-sunflower polymer-fluorescein.

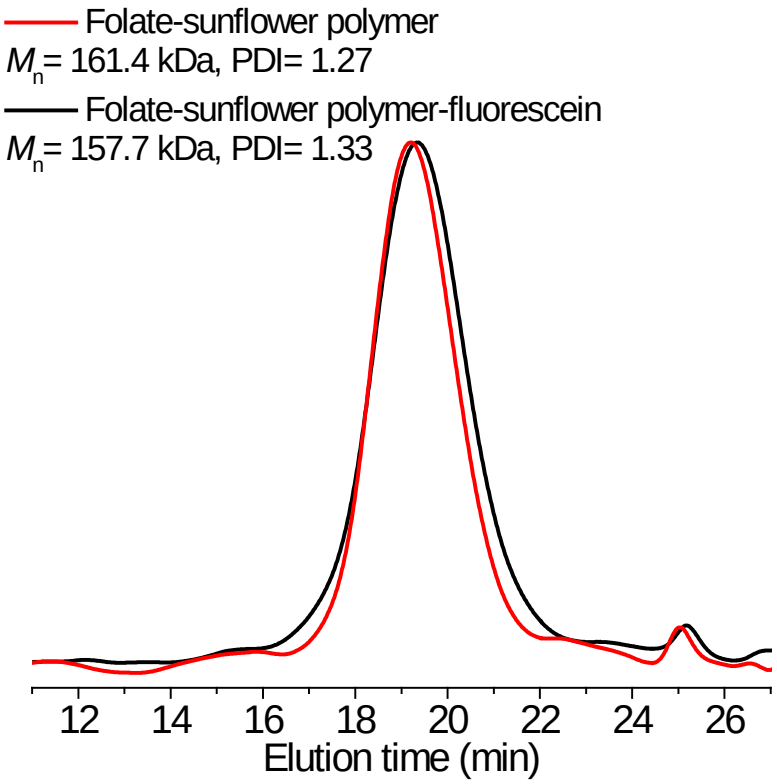


Figure S9. GPC elution trace of folate-sunflower polymer and folate-sunflower polymer-fluorescein.

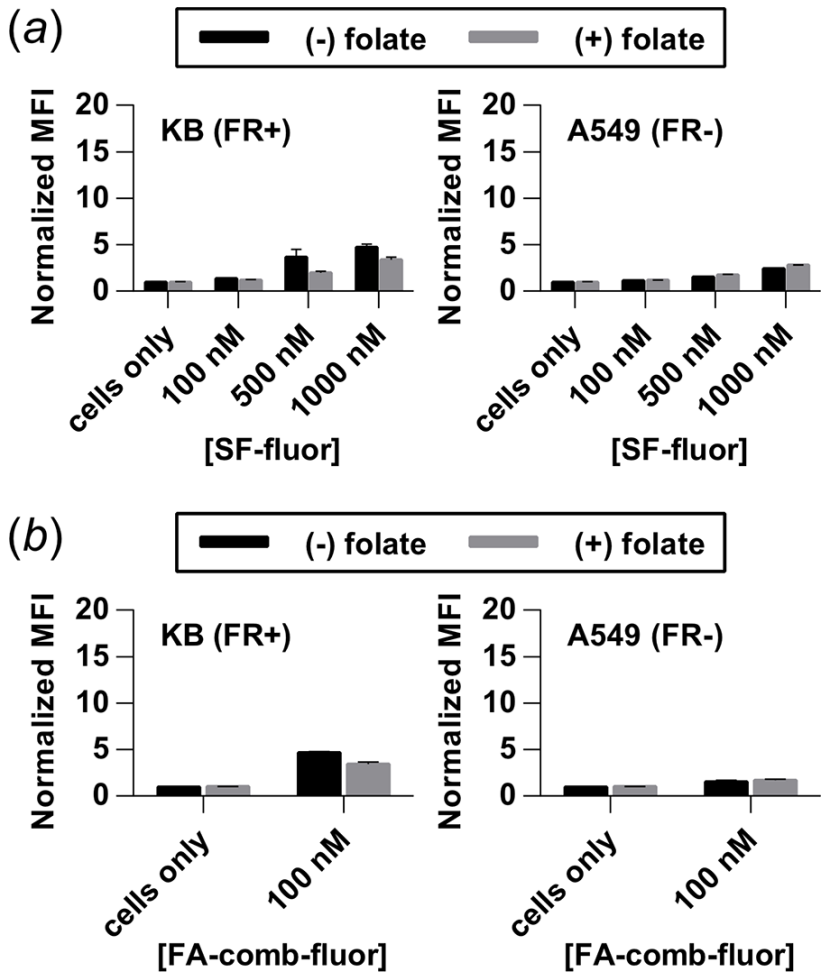


Figure S10. Uptake of (a) untargeted SF-fluor and (b) FA-comb-fluor polymers in FR+ KB cells and FR- A549 cells in the absence (black bars) and presence (gray bars) of 2 mM competing free folate.