Supporting Information For

Mercapto-Responsive Polymeric Nano-carrier Capable to Release Sulfur Dioxide

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Materials

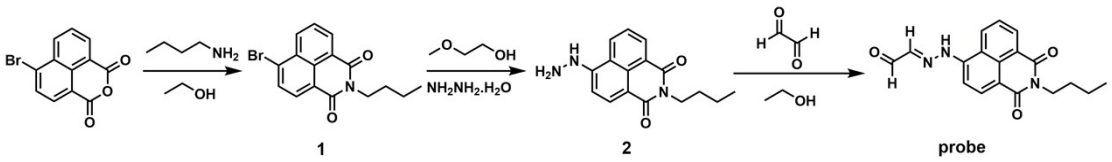
4-Bromo-1,8-naphthalic anhydride (Bidepharm, 96.0%), 2,4-dinitrobenzene-sulfonyl chloride (Alfa Aesar, 98.0%), *N*,*N*-dimethylformamide (DMF, J&K, 99.8%), 4-(benzenecarbonothioylsulfanyl)-4-cyanopentanoic acid (Bidepharm, 98.0%), 2-hydroxyethyl acetate (TCI, 60.0%), 1,3-dicyclohexylcarbodiimide (Bidepharm, 98.0%), poly(ethylene glycol) monomethyl ether (PEG-OH, M_n = 2000 g/mol, Aldrich, 99.0%), 2-hydroxyethyl methacrylate (HEMA, TCI, 95.0%), *L*-cysteine (Cys, Acros, 99.0%), butan-1-amine (Macklin, 99.5%), hydrazine hydrate (Adamas, 80.0%), glyoxal solution (Aladdin, 40% wt in H_2O), 7-ethyl-10-hydroxycamptothecin (SN-38, Bidepharm, 98.0%) and triethylamine (Et_3N, Aldrich, 99.5%) were used as received. 2,2'-Azobisisobutyronitrile (AIBN, Aladdin, 99.0%) was recrystallized from anhydrous ethanol. Dichloromethane (CH_2Cl_2, J&K, 99.9%) and 1,4-dioxane (Aladdin, 99.0%) was distilled over Na under N_2 prior to use. Other reagents not specially mentioned were purchased from Aladdin and used as received without further purification.

Instrumentation

All ^1H and ^{13}C NMR analyses were performed on a JEOL resonance ECZ 400S (400 MHz) in $CDCl_3$ and DMSO-d_6, tetramethylsilicone was used as internal standard. Electrospray ionization mass spectrometry (ESI-MS) and high resolution mass spectrometry (HR-MS) were performed by an Agilent LC/MSD SL system and a Thermo Fisher Scientific LTQ FT Ultra system. Gel permeation chromatography

(GPC) system is equipped with a Waters 1515 Isocratic HPLC pump, a Waters 2410 refractive index detector, a Waters 2487 dual λ absorbance detector and a set of Waters Styragel columns (HR3 (500-30,000), HR4 (5,000-600,000) and HR5 (50,000- 4000,000), 7.8×300 mm, particle size: 5 μm). GPC measurements were carried out at 35°C using THF as the eluent with a flow rate of 1.0 mL/min. The system was calibrated with linear polystyrene standards. Fluorescence spectra were measured at room temperature on a Hitachi F-2700 fluorescence spectrophotometer with a bandwidth of 10/10 nm. Transmission electron microscopy (TEM) images were obtained by a JEOL JEM-2100 instrument operated at 80 kV. Dynamic light scattering (DLS) measurements were performed at room temperature (23°C) on a Malvern Nano-ZS90 Zetasizer at a scattering angle of 173°.

Synthesis of probe



Scheme S1. Synthetic route for probe.

4-Bromo-1,8-naphthalic anhydride (10.00 g, 36.0 mmol), butan-1-amine (2.61 g, 36.0 mmol) and ethanol (200 mL) were added to a three-neck flask equipped with a magnetic stirrer under N_2. The reaction mixture was stirred at 78℃ for 4 h and then cooled to room temperature. The crude product was concentrated and purified by silica column chromatography (eluent: *n*-hexane/ethyl acetate, v/v = 10/1) to give 6-bromo-2-butyl- 1H-benzo[de]isoquinoline-1,3(2H)-dione **1** (1.76 g, 15% yield) as a

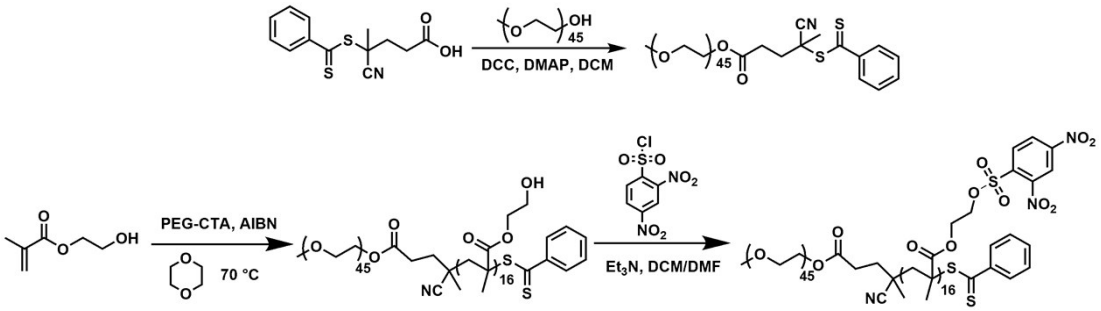
white powder. ^{1}H NMR ($CDCl_3$): δ (ppm): 8.65 (d, 1H, Ar*H*), 8.56 (d, 1H, Ar*H*), 8.41 (d, 1H, Ar*H*), 8.04 (d, 1H, Ar*H*), 7.85 (t, 1H, Ar*H*), 4.17 (t, 2H, $NCH_2CH_2CH_2CH_3$), 1.71 (m, 2H, $NCH_2CH_2CH_2CH_3$), 1.45 (m, 2H, $NCH_2CH_2CH_2CH_3$), 0.98 (t, 3H, $NCH_2CH_2CH_2CH_3$). ^{13}C NMR (DMSO-d_6): δ (ppm): 162.60, 132.50, 131.49, 131.29, 130.88, 129.70, 129.04, 128.73, 128.18, 122.67, 121.90, 38.48, 29.56, 19.82, 13.73. ESI-MS: *m/z* Calcd for $C_{16}H_{14}BrNO_2$ ($[M]^+$): 331.0208, found: 331.0217.

1 (1.50 g, 4.5 mmol) and 2-methoxyethanol (15.0 mL) were added to a three-neck flask equipped with a magnetic stirrer under N_2. The mixture was stirred at 120℃ in order to obtain a cleared lysate. Hydrazine hydrate (1.5 mL) was added dropwise and the reaction mixture was stirred at 120℃ for 4 h. The mixture was cooled to room temperature, concentrated and precipitated into ethanol to give 2-butyl-6-hydrazinyl-1H-benzo[de]isoquinoline-1,3(2H)-dione **2** (1.14 g, 89% yield) as an orange powder. ^{1}H NMR (DMSO-d_6): δ (ppm): 9.12 (s, 1H, NH_2NH), 8.61 (d, 1H, Ar*H*), 8.40 (d, 1H, Ar*H*), 8.27 (d, 1H, Ar*H*), 7.63 (t, 1H, Ar*H*), 7.24 (d, 1H, Ar*H*), 4.67 (s, 2H, NH_2NH), 3.99 (t, 2H, $NCH_2CH_2CH_2CH_3$), 1.57 (m, 2H, $NCH_2CH_2CH_2CH_3$), 1.32 (m, 2H, $NCH_2CH_2CH_2CH_3$), 0.90 (t, 3H, $NCH_2CH_2CH_2CH_3$). ^{13}C NMR (DMSO-d_6): δ (ppm): 163.45, 162.60, 152.70, 133.70, 130.26, 128.99, 127.90, 123.80, 121.21, 118.00, 107.02, 103.54, 38.71, 29.66, 19.53, 13.27. ESI-MS: *m/z* Calcd for $C_{16}H_{18}N_3O_2$ ($[M+H]^+$): 284.1394, found: 284.1390.

2 (0.20 g, 0.7 mmol), ethanol (14.0 mL) and glyoxal solution (1.3 mL) were added to a three-neck flask equipped with a magnetic stirrer under N_2. The mixture was stirred at room temperature for 5 h followed by concentration and purification through

silica column chromatography (eluent: *n*-hexane/ethyl acetate, v/v = 2/1) to give the probe (0.15 g, 66% yield) as an orange powder. ^{1}H NMR (DMSO-d_6): δ (ppm): 12.16 (s, 1H, N*H*NCHCHO), 9.59 (d, 1H, C*H*O), 8.66 (d, 1H, Ar*H*), 8.44 (d, 1H, Ar*H*), 8.35 (d, 1H, Ar*H*), 7.79-7.84 (m, 2H, Ar*H*, NHNC*H*CHO), 7.71 (d, 1H, Ar*H*), 3.96 (t, 2H, NCH_2CH$_2$CH$_2$CH$_3$), 1.58 (m, 2H, NCH$_2$CH_2CH$_2$CH$_3$), 1.32 (m, 2H, NCH$_2$CH$_2$CH_2CH$_3$), 0.90 (t, 3H, NCH$_2$CH$_2$CH$_2$CH_3). ^{13}C NMR (DMSO-d_6): δ (ppm): 190.72, 162.44, 143.32, 140.44, 132.06, 130.38, 128.23, 127.29, 125.61, 121.74, 119.12, 114.10, 109.07, 38.46, 29.14, 19.30, 13.32. ESI-MS: *m/z* Calcd for $C_{18}H_{18}N_3O_3$ ([M+H]$^+$): 324.1343, found: 324.1338.

Synthesis of PEG$_{45}$-*b*-PDNPSEMA$_{16}$



Scheme S2. Synthesis of PEG$_{45}$-*b*-PDNPSEMA$_{16}$ diblock copolymer.

Dry CH_2Cl_2 (250 mL), PEG-OH (17.90 g, 9.0 mmol), 4-dimethylaminopyridine (0.22 g, 1.8 mmol) and 4-(benzenecarbonothioylsulfanyl)-4-cyanopentanoic acid (5.00 g, 17.9 mmol) were added to a three-neck flask equipped with a magnetic stirrer under N_2. After the mixture was stirred at 0℃ for 15 min, a CH_2Cl_2 solution of 1,3-dicyclohexylcarbodiimide (3.69 g, 17.9 mmol) was added dropwise. The mixture was slowly warmed to room temperature and stirred overnight. The solid was filtered

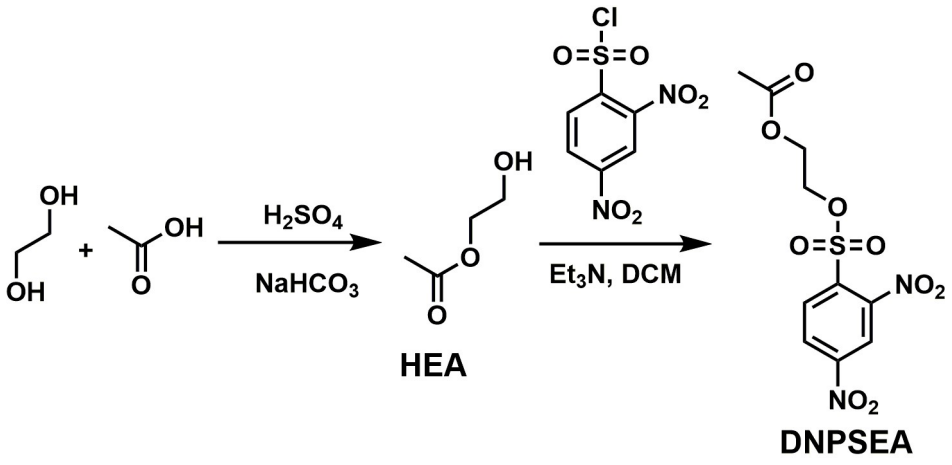
followed by washing with CH_2Cl_2 until the filtrate was colorless. The filtrate was concentrated followed by precipitation in cold diethyl ether. After repeated purification by dissolution in CH_2Cl_2 and precipitation in cold diethyl ether, PEG-CTA was obtained after drying *in vacuo* overnight as a pink powder. GPC: M_n = 3,400 g/mol, M_w/M_n = 1.03. ^{1}H NMR (DMSO-d_6): δ (ppm): 7.91 (2H, Ar*H*), 7.69 (1H, Ar*H*), 7.50 (2H, Ar*H*), 4.14 (2H, $CO_2CH_2CH_2O$), 3.66 (2H, $CO_2CH_2CH_2O$), 3.49 (176H, $(OCH_2CH_2)_{44}$), 3.21 (3H, OCH_3), 2.62 (2H, $O_2CCH_2CH_2C$), 2.32 (2H, $O_2CCH_2CH_2C$), 1.90 (3H, CCH_3).

AIBN (37.80 mg, 0.2 mmol) and PEG-CTA (1.74 g, 0.8 mmol) were added into a 100 mL Schlenk flask (flame-dried under vacuum prior to use) under N_2. HEMA (2.00 g, 15.4 mmol) and dry 1,4-dioxane (8.0 mL) were added via a gastight syringe, respectively. After three cycles of freezing-pumping-thawing, the flask was stirred at 70℃ for 3.5 h under N_2. The polymerization was terminated by placing the flask into liquid N_2. The reaction mixture was precipitated in cold diethyl ether. After repeated purification by dissolution in CH_2Cl_2 and precipitation in cold diethyl ether, PEG_{45}-*b*-$PHEMA_{16}$ was obtained after drying *in vacuo* overnight as a light pink powder. GPC: M_n = 3,900 g/mol, M_w/M_n =1.12. ^{1}H NMR (DMSO-d_6): δ (ppm): 7.82 (2H, Ar*H*), 7.63 (1H, Ar*H*), 7.46 (2H, Ar*H*), 4.81 (16H, O*H*), 4.13 (2H, $CO_2CH_2CH_2O$), 3.88 (32H, $(CO_2CH_2CH_2OH)_{16}$), 3.67 (2H, $CO_2CH_2CH_2O$), 3.58 (32H, $(CO_2CH_2CH_2OH)_{16}$), 3.50 (176H, $(OCH_2CH_2)_{44}$), 3.24 (3H, OCH_3), 2.66 (2H, $O_2CCH_2CH_2C$), 2.32 (2H, $O_2CCH_2CH_2C$), 1.68-2.05 (35H, $(CCH_2)_{16}$, $CCNCH_3$), 0.75-0.95 (48H, $(CCH_3)_{16}$).

PEG_{45}-*b*-$PHEMA_{16}$ (0.67 g, 0.2 mmol), CH_2Cl_2/DMF (36 mL, v:v = 5/1) and Et_3N

(0.62 g, 6.1 mmol) were added to a three-neck flask equipped with a magnetic stirrer under N_2 at 0℃. A CH_2Cl_2 solution of 2,4-dinitrobenzenesulfonyl chloride (1.66 g, 6.2 mmol) was added into the flask slowly at 0℃. The mixture was slowly warmed to room temperature and stirred for 22 h under N_2. The reaction mixture was precipitated in cold diethyl ether four times to give PEG_{45}-*b*-$PDNPSEMA_{16}$ as a brown solid. GPC: M_n = 5,000 g/mol, M_w/M_n =1.09. ^{1}H NMR (DMSO-d_6): δ (ppm): 8.06-8.54 (48H, Ar*H*), 7.46-7.82 (5H, Ar*H*), 3.82-4.15 (68H, $(CO_2CH_2CH_2O)_{16}$, $CO_2CH_2CH_2OCH_2$), 3.50 (176H, $(OCH_2CH_2)_{44}$), 3.23 (3H, OCH_3), 2.65 (2H, $O_2CCH_2CH_2C$), 2.32 (2H, $O_2CCH_2CH_2C$), 1.68-2.05 (35H, $(CCH_2)_{16}$, $CCNCH_3$), 0.79-0.97 (48H, $(CCH_3)_{16}$).

Synthesis of 2-(2,4-dinitrophenylsulfonyloxy)ethyl acetate



Scheme S3. Synthetic route for DNPSEA.

Ethylene glycol (18.61 g, 0.3 mol), acetic acid (6.00 g, 99.9 mmol) and concentrated sulfuric acid (0.112 mL, 98%) were added to a three-neck flask equipped with a magnetic stirrer under N_2. After the solution was stirred at room temperature for 24 h, saturated sodium bicarbonate solution (17.0 mL) was added into the mixture and stirred overnight. The mixture was concentrated and purified by silica column

chromatography (eluent: CH_2Cl_2/methanol, v/v = 30/1) to give 2-hydroxyethyl acetate (HEA, 6.09 g, 59%) as a colorless liquid. ^{1}H NMR (DMSO-d_6): δ (ppm): 4.76 (t, 1H, O*H*), 3.99 (t, 2H, $CO_2CH_2CH_2OH$), 3.54 (q, 2H, $CO_2CH_2CH_2OH$), 1.99 (s, 3H, O_2CCH_3). ^{13}C NMR (DMSO-d_6): δ (ppm): 170.76, 65.87, 59.17, 21.04. EI-MS: *m/z* Calcd for $C_4H_9O_3$ ($[M+H]^+$): 105.0546, found: 105.0549.

HEA (0.50 g, 4.8 mmol), CH_2Cl_2 (25.0 mL) and Et_3N (0.73 g, 7.2 mmol) were added to a three-neck flask equipped with a magnetic stirrer under N_2 at 0℃. A CH_2Cl_2 solution of 2,4-dinitrobenzenesulfonyl chloride (1.92 g, 7.2 mmol) was added into the flask slowly at 0℃. After the mixture was stirred for 3 h under N_2 at 0℃, 1 M hydrochloric acid (50.0 mL) and CH_2Cl_2 (50.0 mL) were added dropwise at 0℃. After decanting, the organic phase was washed with cold hydrochloric acid (50.0 mL) three times, and then with water (150.0 mL) twice. After the crude product was dried with anhydrous $MgSO_4$, the mixture was concentrated and purified by silica column chromatography (eluent: *n*-hexane/ethyl acetate, v/v = 4/1) to give 2-(2,4-dinitrophenyl sulfonyloxy)ethyl acetate (DNPSEA, 0.45 g, 28% yield) as a yellow liquid. ^{1}H NMR (DMSO-d_6): δ (ppm): 8.88 (d, 1H, Ar*H*), 8.80 (dd, 1H, Ar*H*), 8.35 (d, 1H, Ar*H*), 4.00-4.31 (m, 4H, $CO_2CH_2CH_2$), 1.98 (s, 3H, O_2CCH_3). ^{13}C NMR (DMSO-d_6): δ (ppm): 170.41, 149.94, 147.05, 146.00, 129.67, 127.62, 120.86, 66.51, 62.77, 20.81. DART-MS: *m/z* Calcd for $C_{10}H_{14}N_3O_9S$ ($[M+NH_4]^+$): 352.0445, found: 352.0440.

Detection of DNPSEA with different stimuli

Acetate buffer (0.1 M, pH = 5.0) solutions of 3-mercaptoisobutyric, Cys, Gly, GSH, Hcy, arginine, glucose and Thr (0.31 mL, 1.94 mM) were charged into a sample bottle, respectively, followed by adding a DMSO solution of DNPSEA (1.23 mL, 0.49 mM). All the samples were placed in a shaker and an acetate buffer (940 μL) was added after 2 h. After further incubation for another 15 min, a DMSO solution of probe (20 μL, 1 mM) was added into the mixture. The fluorescence intensity (λ_{ex} = 427 nm, slit: 10/10 nm) of all the samples were recorded after 8 min.

Eight aliquots of DMSO-d_6 solution of DNPSEA (0.6 mL, 25 mg/mL) were charged into a NMR tube, respectively, followed by adding excess of different stimuli (3-mercaptoisobutyric acid, Cys, Gly, GSH, Hcy, arginine, glucose and Thr). ^{1}H NMR spectra were recorded after 6 h.

Mercapto-triggered SO_2 release of PEG_{45}-*b*-$PDNPSEMA_{16}$ by fluorescent spectrometry

An acetate buffer (0.1 M, pH 5.0) solution of Cys (312.5 μL, 0.01 M) was charged into a sample bottle followed by adding a DMSO solution of PEG_{45}-*b*-$PDNPSEMA_{16}$ (1.23 mL, 0.09 mM). After 2 h, an acetate buffer (937.5 μL) and a DMSO solution of probe (20.0 μL, 1 mM) were added. The fluorescence intensity (λ_{ex} = 427 nm, slit: 10/10 nm) of the solution was recorded after 35 min.

Mercapto-responsiveness of PEG_{45}-*b*-$PDNPSEMA_{16}$ monitored by ^{1}H NMR and

GPC

A THF solution of PEG_{45}-*b*-$PDNPSEMA_{16}$ (0.8 mL) was added into an acetate buffer (0.2 mL), followed by adding excess Cys and Hcy, respectively. After the mixtures were placed in a shaker (150 rpm, 37°C) for 24 h. GPC and ^1H NMR measurements were carried out after lyophilization.

DLS and TEM detection of PEG_{45}-*b*-$PDNPSEMA_{16}$ micelles with different stimuli

A PEG_{45}-*b*-$PDNPSEMA_{16}$ micellar solution (5.0 mL) was transferred into a dialysis bag (MW_{cutoff} = 3.5 KDa), followed by immersing into solutions of different stimulus-species (100 mL, 0.02 M) in a shaker (100 rpm, 37°C). After 46 h, micellar solution in dialysis bag was transferred to a sample bottle for further DLS and TEM measurements. For TEM, 10 μL of micellar solution was placed on a Formvar and carbon-coated copper grid for 1 min and then a filter paper touched the edge of drop to absorb most of liquid on the grid. The grid was allowed to dry *in vacuo*.

Preparation of PEG_{45}-*b*-$PDNPSEMA_{16}$ micellar solution encapsulated with SN-38

To prepare PEG_{45}-*b*-$PDNPSEMA_{16}$ micellar solution, PEG_{45}-*b*-$PDNPSEMA_{16}$ (43 mg) was dissolved in THF (22 mL), followed by adding water (22 mL) dropwise. The mixture was stirred overnight and dialyzed against water for 24 h to remove THF.

To prepare PEG_{45}-*b*-$PDNPSEMA_{16}$ micelles encapsulated with SN-38, a DMF

solution of SN-38 (350 μL, 10 mg/mL) and a THF solution of PEG_{45}-*b*-$PDNPSEMA_{16}$ (22 mL, 2 mg/mL) were added dropwise into water (22 mL) under stirring. After the mixture was stirred for 24 h at room temperature, the mixture was dialyzed by a dialysis tube (MW_{cutoff} = 3.5 KDa) in PBS buffer (0.2 M, pH = 7.26) for three days to remove DMF and THF. Next, 5 mL of dialysate and 2 mL of micellar solution were frozen-dry, followed by dissolving in DMSO (2 mL). 20 μL of micellar solution was further diluted with DMSO (1.98 mL) for fluorescence measurement.

Release of SN-38 from PEG_{45}-*b*-$PDNPSEMA_{16}$ micelles with different stimuli

A PEG_{45}-*b*-$PDNPSEMA_{16}$ micellar solution (3.0 mL) loaded with SN-38 was transferred into a dialysis bag (MW_{cutoff} = 3.5 KDa). The dialysis bag with same volume (3.0 mL) of micellar solution was dialyzed against aqueous solutions of Cys (0.01 M), Hcy (0.01 M) and GSH (0.01 M) at 37°C, respectively. After 23 h, 3.0 mL of release medium was taken out. All the solutions were lyophilized and dissolved in DMSO (2.0 mL). Fluorescence spectra were then recorded to measure the amount of released SN-38.

Release of SN-38 from PEG_{45}-*b*-$PDNPSEMA_{16}$ micelles with different concentration of Cys

A PEG_{45}-*b*-$PDNPSEMA_{16}$ micellar solution (5.0 mL) loaded with SN-38 was transferred into a dialysis bag (MW_{cutoff} = 3.5 KDa). The dialysis bag with same volume (5.0 mL) of micellar solution was dialyzed against aqueous solutions of Cys

(0.007 and 0.021 M) at 37°C, respectively. After 45.5 h, 5.0 mL of release medium was taken out, and then the solution were lyophilized and dissolved in DMSO (3.0 mL). The amount of released SN-38 was determined by fluorescence spectroscopy based on the standard curve shown in Figure S13B.

SUPPORTING FIGURES

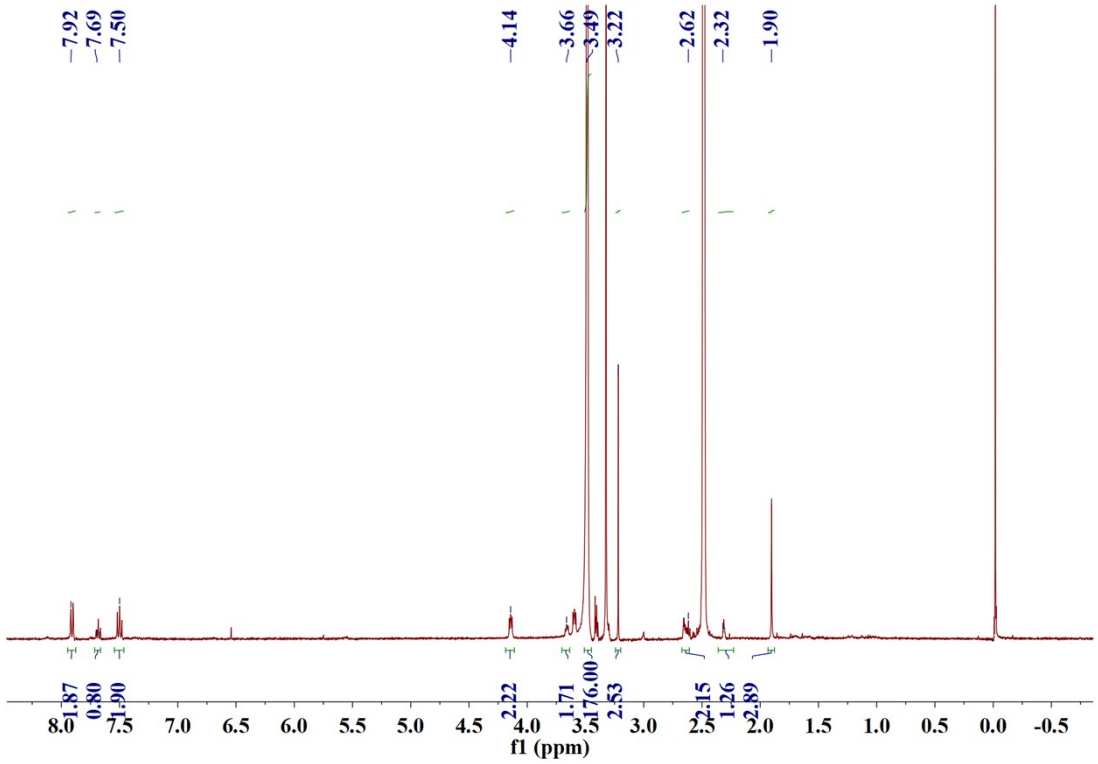


Figure S1. ^{1}H NMR spectrum of PEG-CTA in DMSO-d_6.

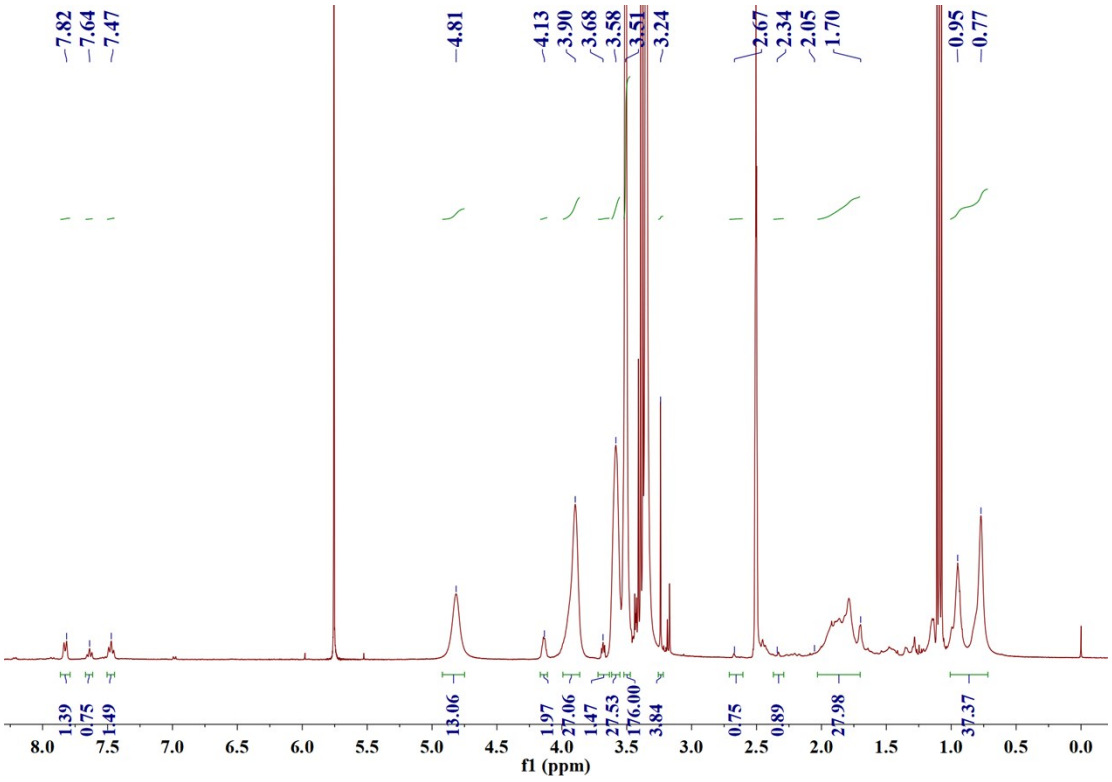


Figure S2. ^{1}H NMR spectrum of PEG_{45}-*b*-$PHEMA_{16}$ in DMSO-d_6.

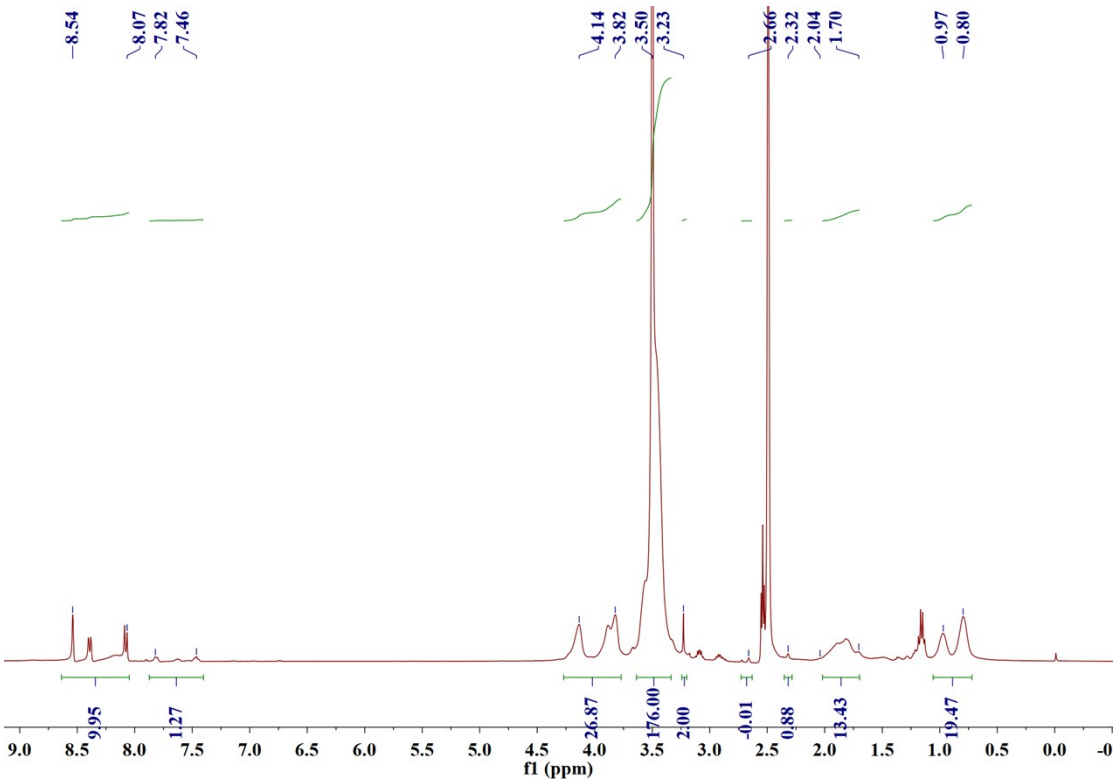


Figure S3. ^{1}H NMR spectrum of PEG_{45}-*b*-$PDNPSEMA_{16}$ in DMSO-d_6.

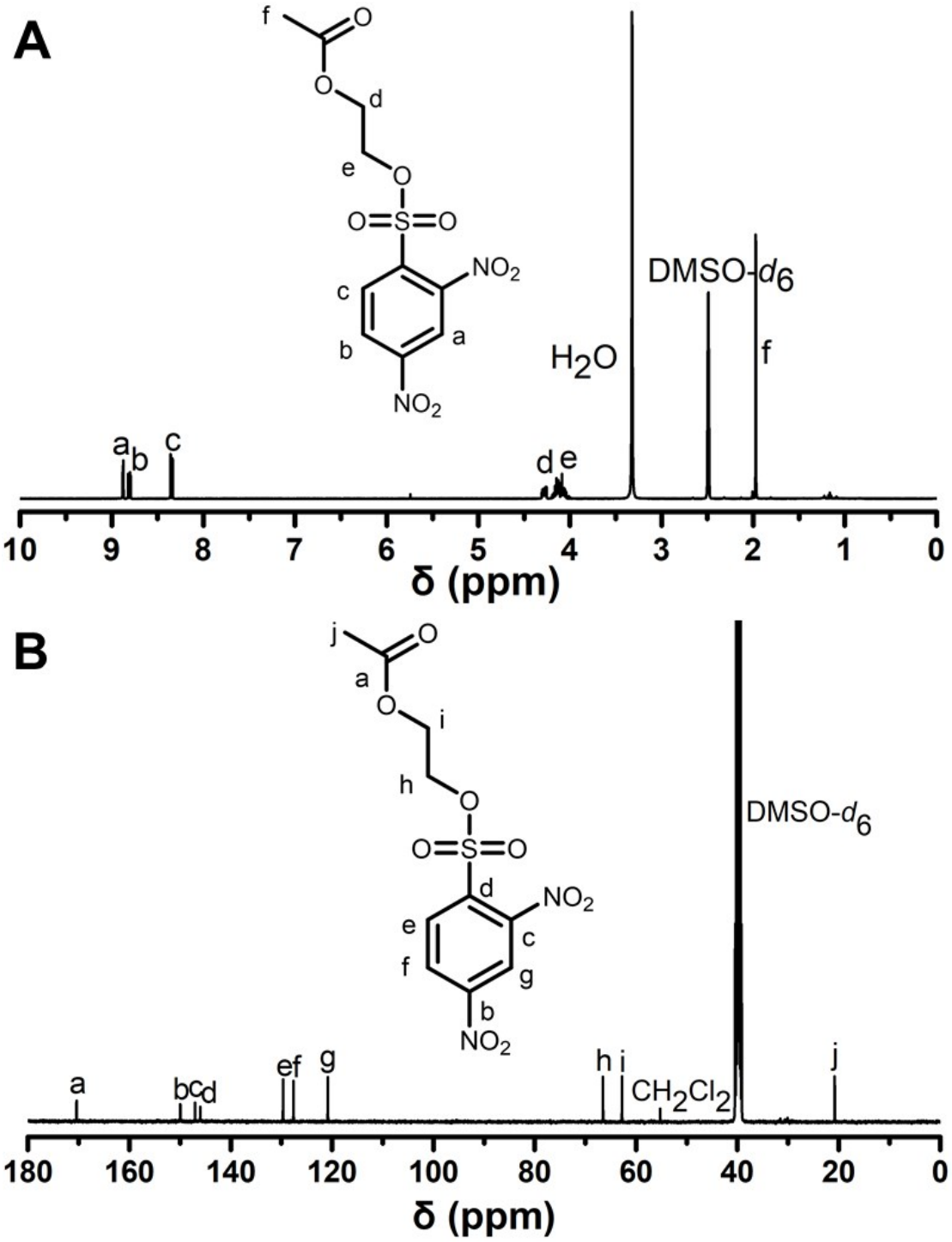


Figure S4. ^{1}H (A) and ^{13}C (B) NMR spectra of DNPSEA in DMSO-d_6.

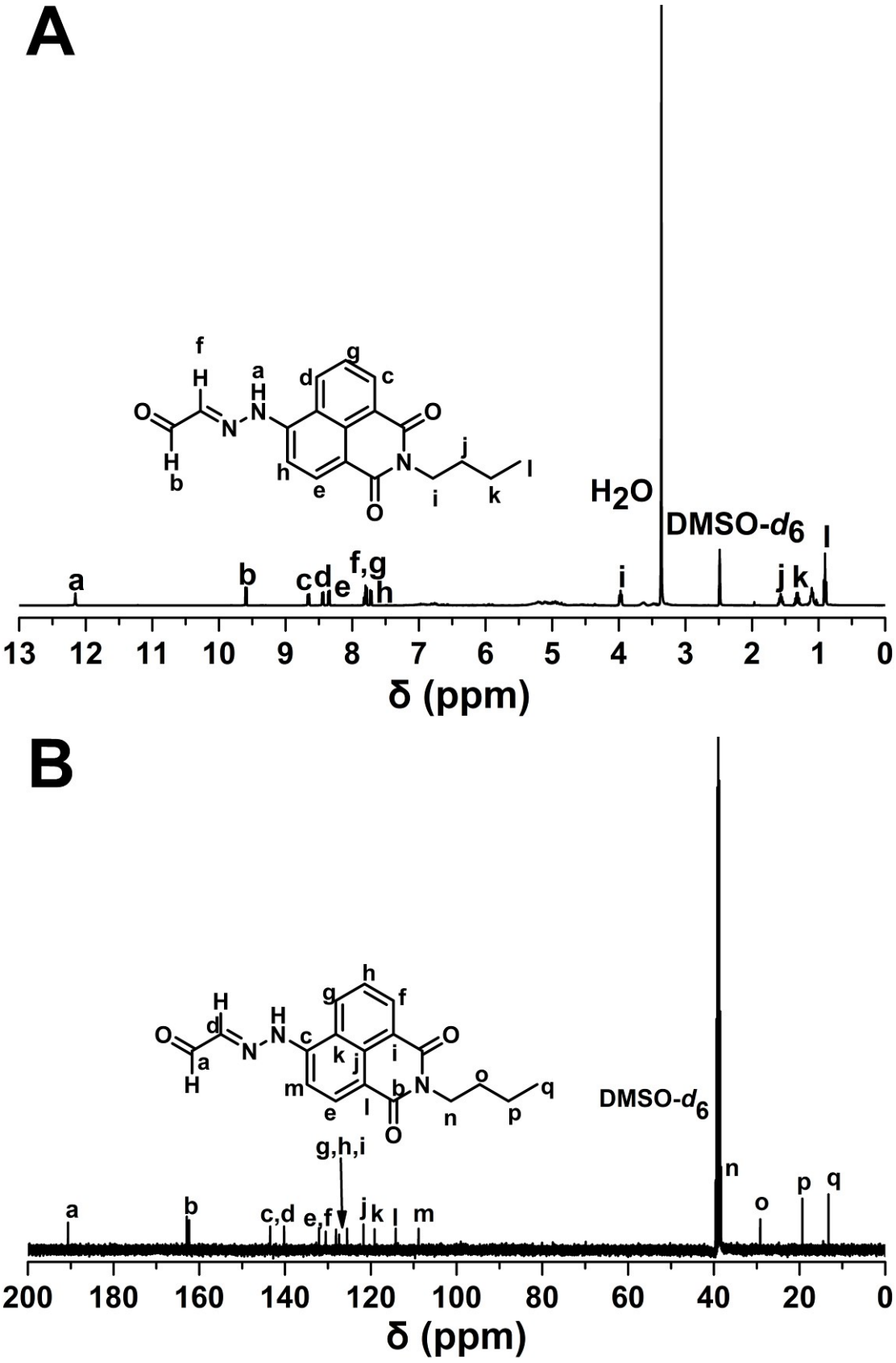


Figure S5. ^{1}H (A) and ^{13}C (B) NMR spectra of probe in DMSO-d_6.

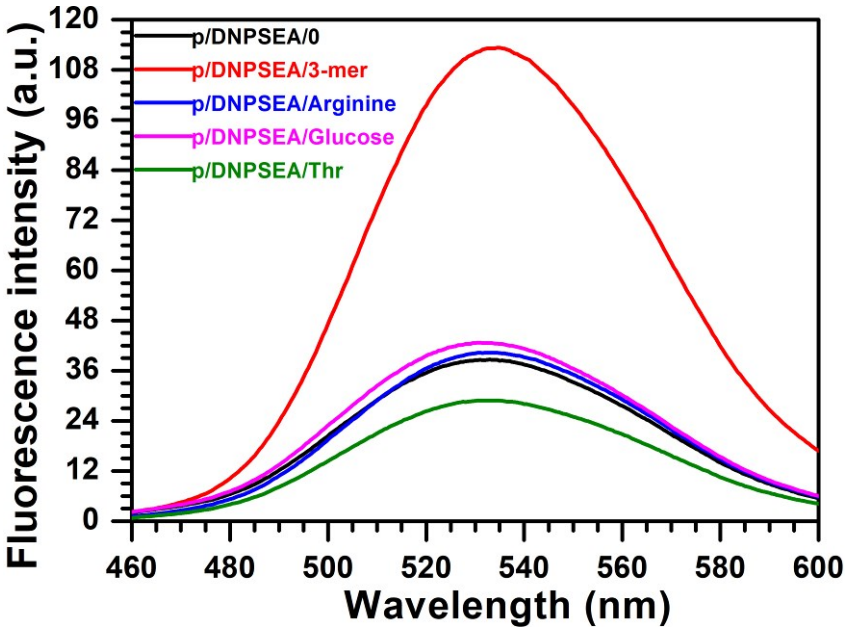


Figure S6. Fluorescence spectra (λ_{ex} = 427 nm, slit: 10/10 nm) of aqueous solution of probe (8 μM in DMSO/acetate buffer (0.1 M, pH = 5.0, $V_{DMSO}/V_{acetate\ buffer}$ = 1:1)) and 2-(2,4-dinitrophenyl sulfonyloxy)ethyl acetate (240 μM) with 3-mercaptoisobutyric acid, arginine, glucose and Thr (240 μM), respectively.

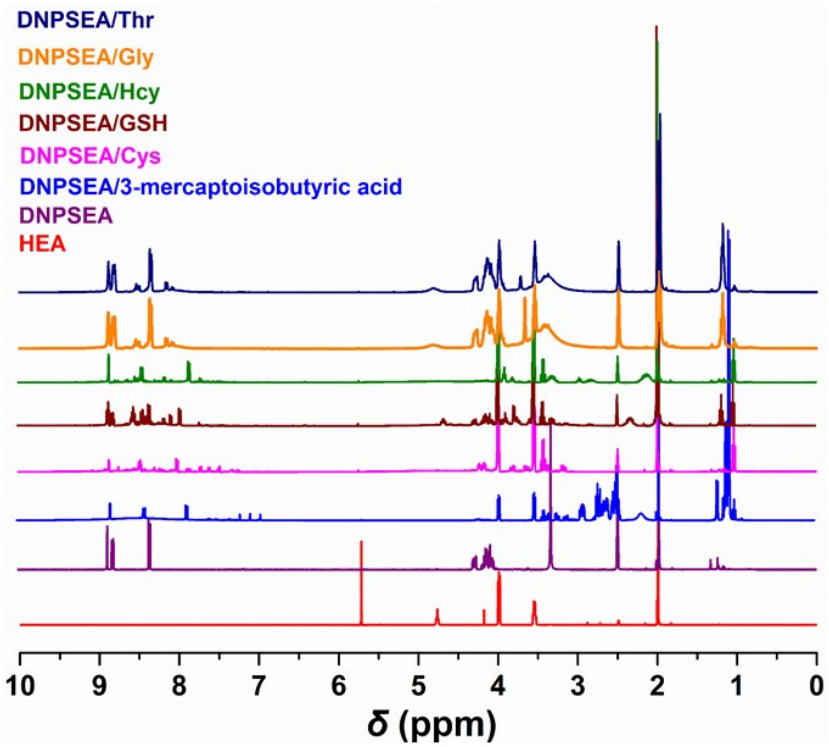


Figure S7. ^{1}H NMR spectra of DNPSEA, HEA and DNPSEA after the treatment with 3-mercaptoisobutyric acid, Cys, GSH, Hcy, Gly and Thr in DMSO-d_6.

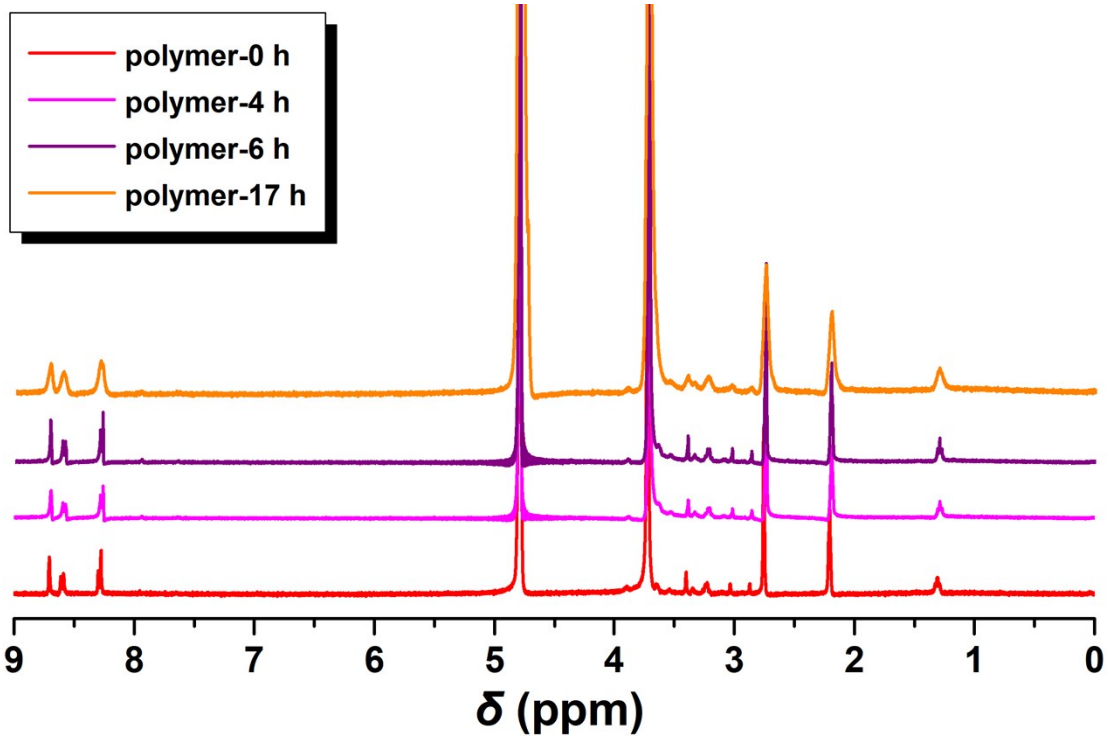


Figure S8. ^{1}H NMR spectra of PEG_{45}-*b*-$PDNPSEMA_{16}$ upon the incubation for different time intervals in $D_2O/(CD_3)_2CO$ ($V_{D2O}/V_{(CD3)2CO}$ = 5:1).

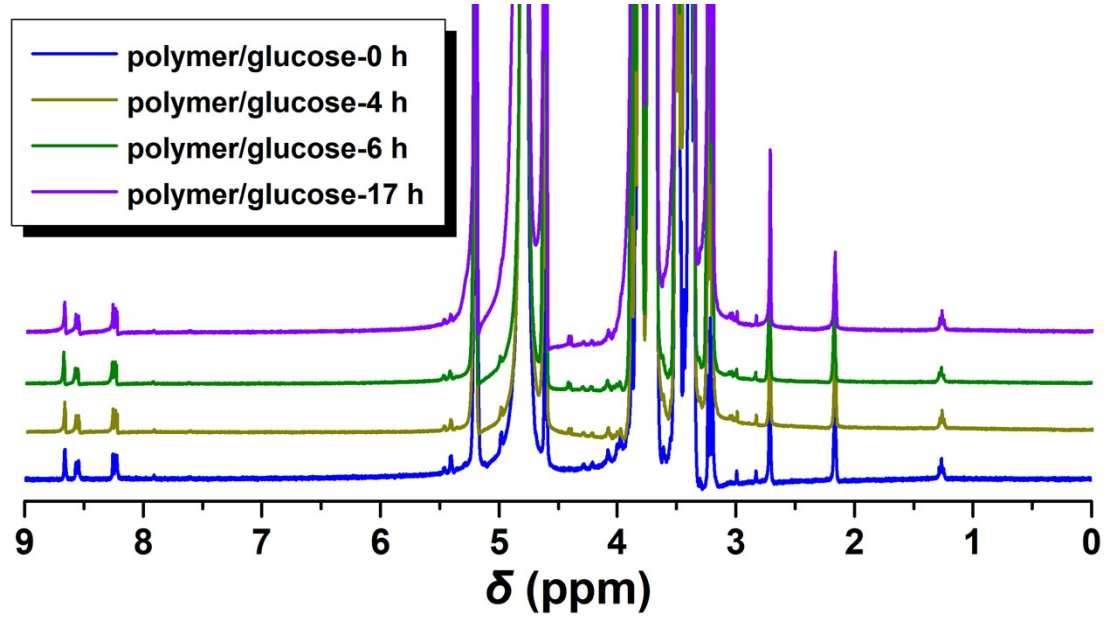


Figure S9. ^{1}H NMR spectra of PEG_{45}-*b*-$PDNPSEMA_{16}$ after the treatment with glucose for different time intervals in $D_2O/(CD_3)_2CO$ ($V_{D2O}/V_{(CD3)2CO}$ = 5:1).

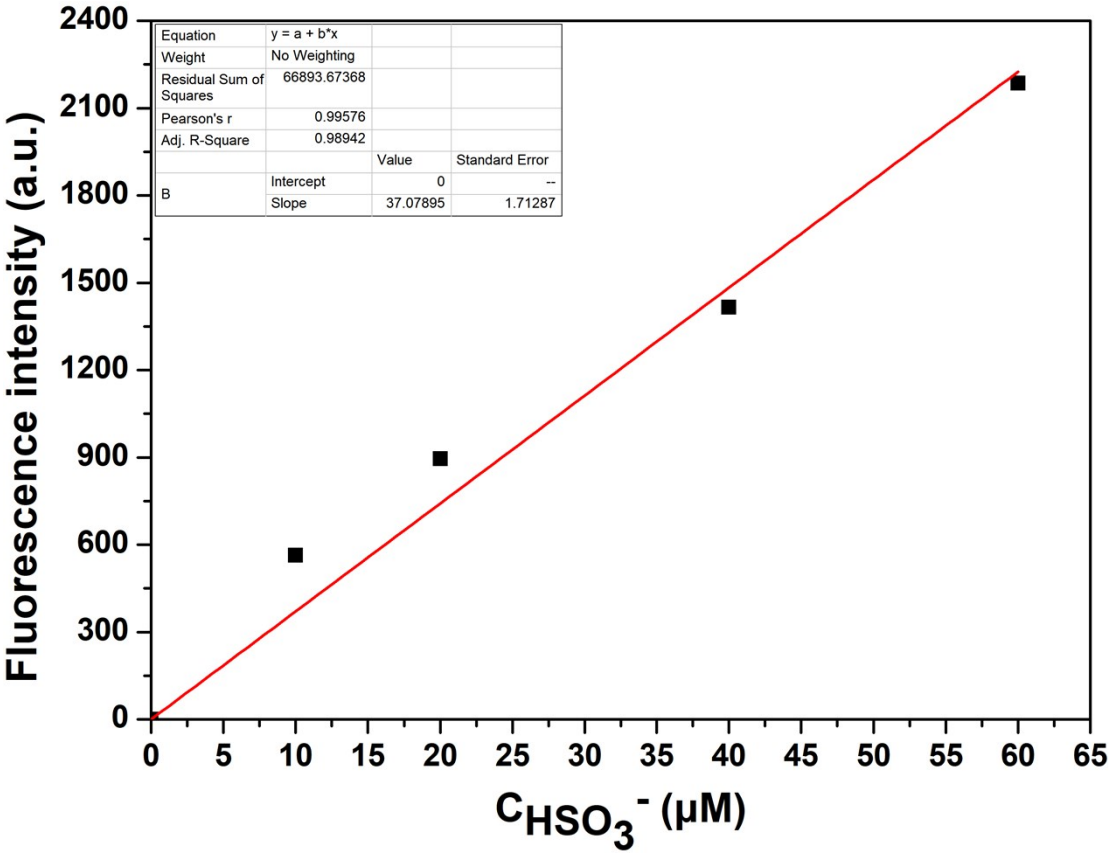


Figure S10. Fluorescence intensity (λex = 427 nm, slit: 10/10 nm) of aqueous solution of probe (8 μM in DMSO/acetate buffer (0.1 M, pH = 5.0, $V_{DMSO}/V_{acetate\ buffer}$ = 1:1)) as a function of the concentration of HSO_3^- at 535 nm.

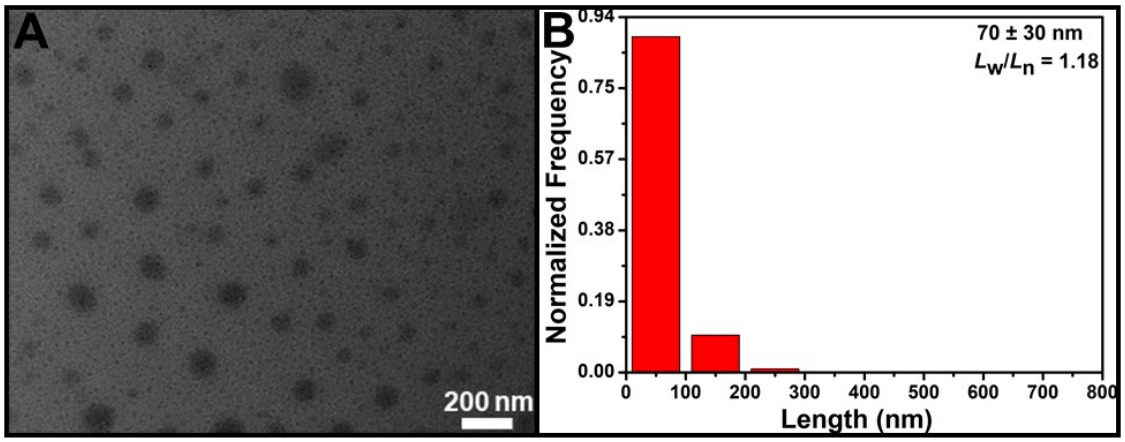


Figure S11. TEM image (A) and control diameter distribution histogram (B) of PEG_{45}-*b*-$PDNPSEMA_{16}$ after the treatment with GSH.

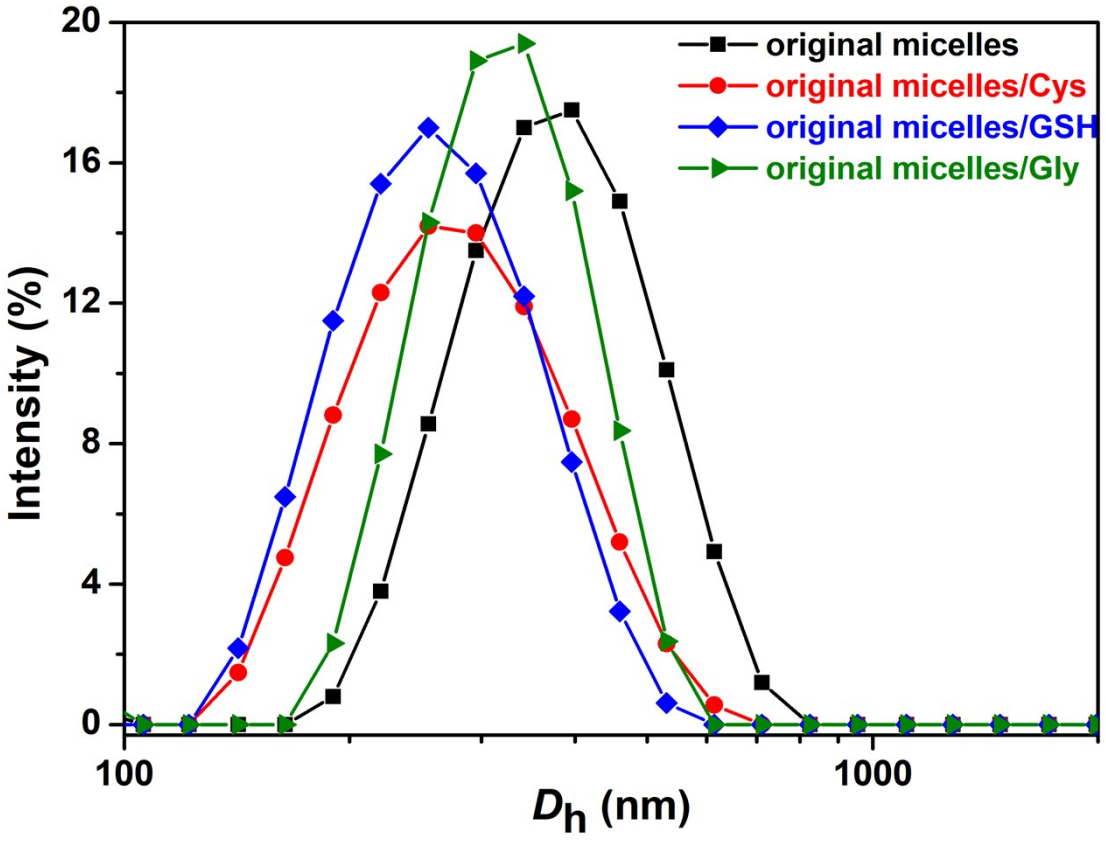


Figure S12. Hydrodynamic diameter distributions of pristine micellar solution of PEG_{45}-*b*-$PDNPSEMA_{16}$ and micellar solutions after the treatment with Cys, GSH and Gly.

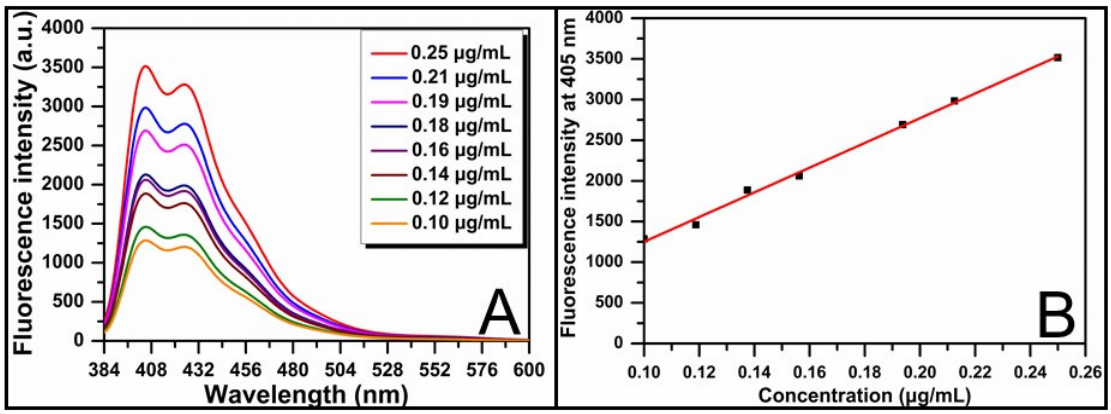


Figure S13. (A) Fluorescence spectra (λ_{ex} = 365 nm) of SN-38 in DMSO at different concentrations and (B) fluorescence intensity of SN-38 in DMSO at 405 nm as a function of the concentration of SN-38.