Electronic Supplementary Information

Synthesis and Modification of Polymers by Thiol-Phenylsulfone Substitution Reaction

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Contents

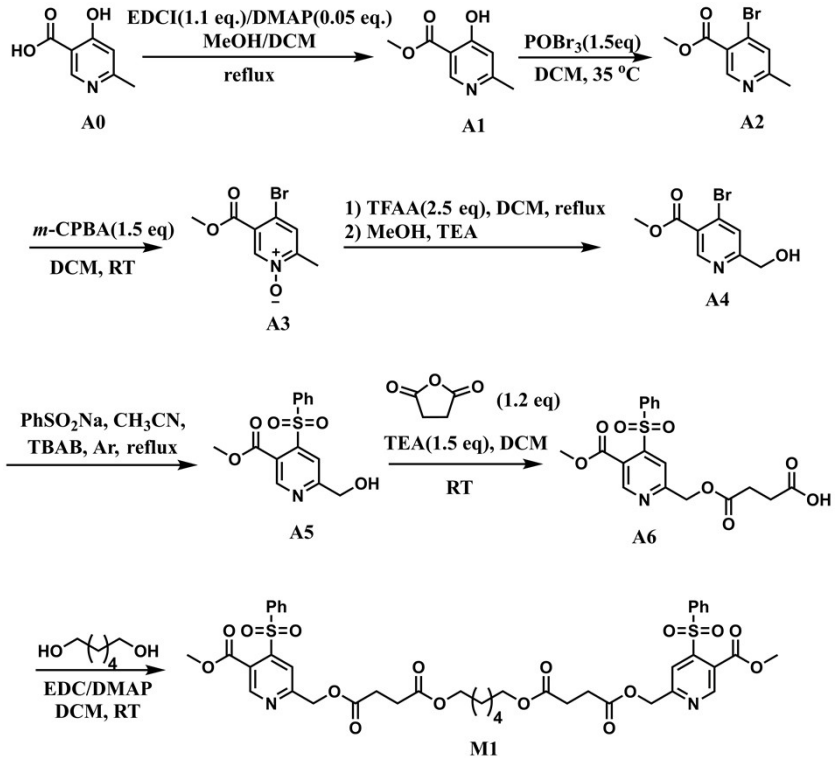
EXPERIMENTAL SECTION

1. Materials. 4-Hydroxy-6-methylnicotinic acid (98%) and 1-ethyl-3-(3-dimethylpropylamine) carbodiimide hydrochloride (EDCI, 99%) were purchased from Shanghai Bidepharm Co. 4-Dimethylaminopyridine (DMAP, 99%), sodium benzenesulfinate (98%), tetrabutylammonium bromide (TBAB, 98%), succinic anhydride (99%), 1,6-hexanediol (98%), 2,2'-dithiodipyridine (99%), and 1-pyrenebutanoic acid (98%) were purchased from Tianjin Heowns Co. Phosphoryl tribromide (99%) was purchased from Beijing Inno-Chem Co. 3-Chloroperoxybenzoic acid (*m*-CPBA, 85wt%) was purchased from Meryer (Shanghai) Co. Trifluoroacetic anhydride (TFAA, 99%) was purchased from Panjin Infinity Scientific Co. mPEG-OH with a number-average molecular weight of 2 K was purchased from Alfa Aesar Co. Dithiothreitol (DTT, 99%) was purchased from Sigma-Aldrich Co. 4,4'-Thiodibenzenethiol (98%) was purchased from Shanghai Macklin Co. CH_2Cl_2, MeOH, CH_3CN and Et_3N (TEA) were purchased from Tianjin Bohua Co.

2. Characterization.

NMR spectra of all the polymers and the compounds were collected on a Bruker Avance III 400 M nuclear magnetic resonance spectrometer, using $CDCl_3$ DMSO-d_6 or D_2O as the solvents. High resolution mass spectrometry (HRMS) measurements were conducted on an Agilent 6520 Q-TOF LC/MS equipped with an electrospray interface. MALDI-TOF MS was conducted on AutoflexIII LRF200-CID system (Bruker Daltonics). The size-exclusion chromatography (SEC) elution curves of the polymers generated by thiol-phenylsulfone reactions were collected on a SEC equipped with a Hitachi L-2130 HPLC pump, a Hitachi L-2350 column operated at 50 °C, a Hitachi L-2490 refractive index detector and a Viscotek 270 Dual Detector. DMF was used as the eluent at a flow rate of 1.0 mL/min, and PMMA (poly(methyl methacrylate)) standards were used for calibration. Steady state fluorescence spectra were recorded on a Shimadzu RF-5301PC fluorescence spectrophotometer. The excitation and emission slits were both set at 5 nm. The excitation wavelength of the emission spectra was set at 343 nm. Differential scanning calorimetry (DSC) measurements were performed on a Mettler Toledo DSC1 STAR^e system at a heating rate of 10 °C/min.

3. Synthesis of O'[1],O[1]-(hexane-1,6-diyl) 4,4'-bis((5-(methoxycarbonyl)-4-(phenylsulfonyl)pyridin-2-yl)methyl) di(butanedioate) (M1). The synthesis of M1 is shown in **Scheme S1**. After six-step reactions, 4-((5-(methoxycarbonyl)-4-(phenylsulfonyl)pyridin-2-yl)methoxy)-4-oxobutanoic acid (**A6**) was synthesized. **M1** was synthesized by esterification between **A6** and 1,4-butanediol.



Scheme S1. Synthetic routes for the synthesis of O'[1],O[1]-(hexane-1,6-diyl) 4,4'-bis((5-(methoxycarbonyl)-4-(phenylsulfonyl)pyridin-2-yl)methyl) di(butanedioate) (M1).

3.1 Synthesis of methyl 4-hydroxy-6-methylnicotinate (A1). To a solution of 4-hydroxy-6-methylnicotinic acid (30.6 g, 200 mmol) in DCM (250 mL) and MeOH (250 mL) mixture, were added EDCI (42.2 g, 220 mmol) and DMAP (1.222 g, 10.00 mmol) at room temperature. The solution was stirred under reflux condition. After the completely disappearance of 4-hydroxy-6-methylnicotinic acid as monitored by thin-layer chromatography (TLC), the mixture was concentrated on a rotary evaporator. The residue was purified by silica gel column chromatography with elution (DCM/MeOH = 20:1 by volume) to give the product **A1** (29.5 g, yield: 88%).

^{1}H NMR (400 MHz, Deuterium Oxide) δ 8.15 (s, 1H), 6.16 (s, 1H), 4.80 (s, 1H), 3.70

(s, 3H), 2.16 (s, 3H). ^{13}C NMR (101 MHz, D_2O) δ 177.62, 166.19, 150.20, 143.84, 118.60, 114.80, 51.97, 17.79. ^{1}H NMR, ^{13}C NMR and HRMS spectra of A1 are shown in **Figure S1**.

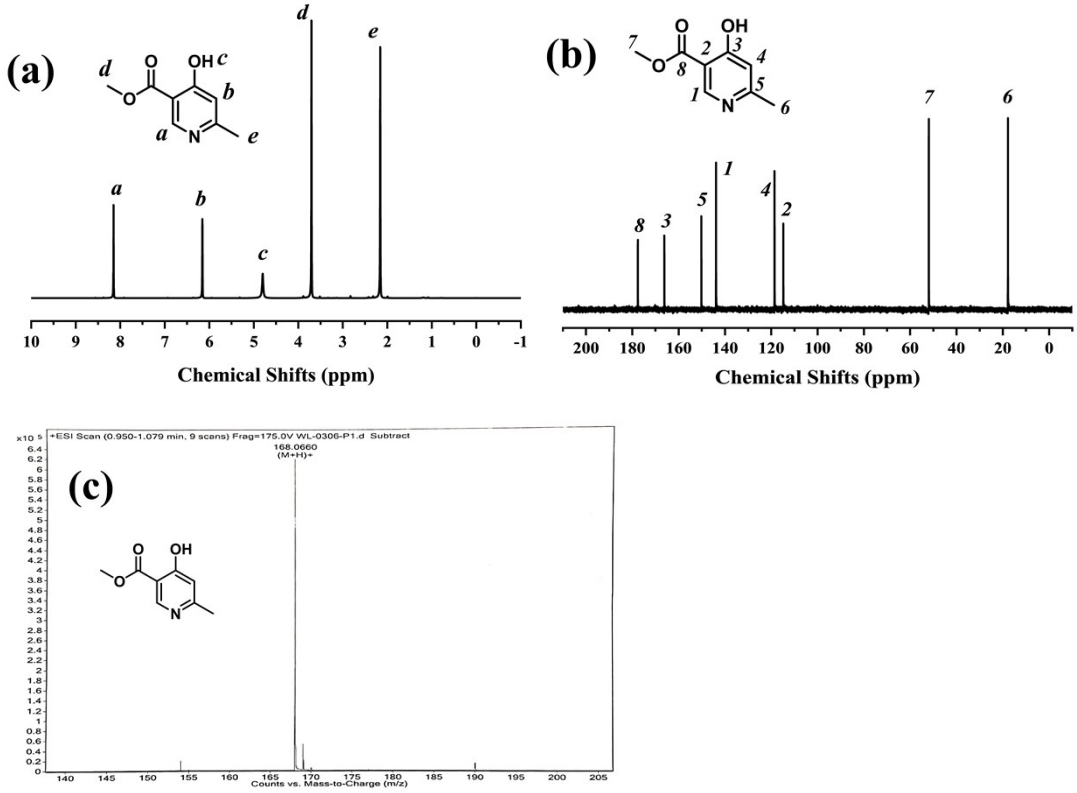


Figure S1. (a) ^{1}H NMR, (b) ^{13}C NMR and (c) HRMS spectra of methyl 4-hydroxy-6-methylnicotinate (A1).

3.2 Synthesis of methyl 4-bromo-6-methylnicotinate (A2). To the DCM (150 mL) solution of A1 (25.1 g, 150 mmol) was added $POBr_3$ (64.5 g, 225 mmol) in five portions at 0 ˚C。The solution was stirred at 35 ˚C until the completely disappearance of A1 (monitored by TLC). The reaction mixture was concentrated on a rotary evaporator and then cooled to 0 ˚C. Ethanol and saturated $NaHCO_3$ aqueous solution were successively added into the mixture dropwise until no gas was released. The mixture was washed with brine for three times (80 mL×3). The combined organic layers were dried over $MgSO_4$ and concentrated on a rotary evaporator. The crude product was purified by silica gel column chromatography with elution (PE/EA = 4:1 by volume) yielding yellow solids A2 (28.4 g, yield: 82%).

^{1}H NMR (400 MHz, Chloroform-d) δ 8.79 (s, 1H), 7.40 (s, 1H), 3.85 (s, 3H), 2.47 (s,

3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.62, 162.43, 151.43, 132.95, 128.65, 124.61, 52.46, 24.00. ^{1}H NMR, ^{13}C NMR and HRMS spectra of A2 are shown in **Figure S2**.

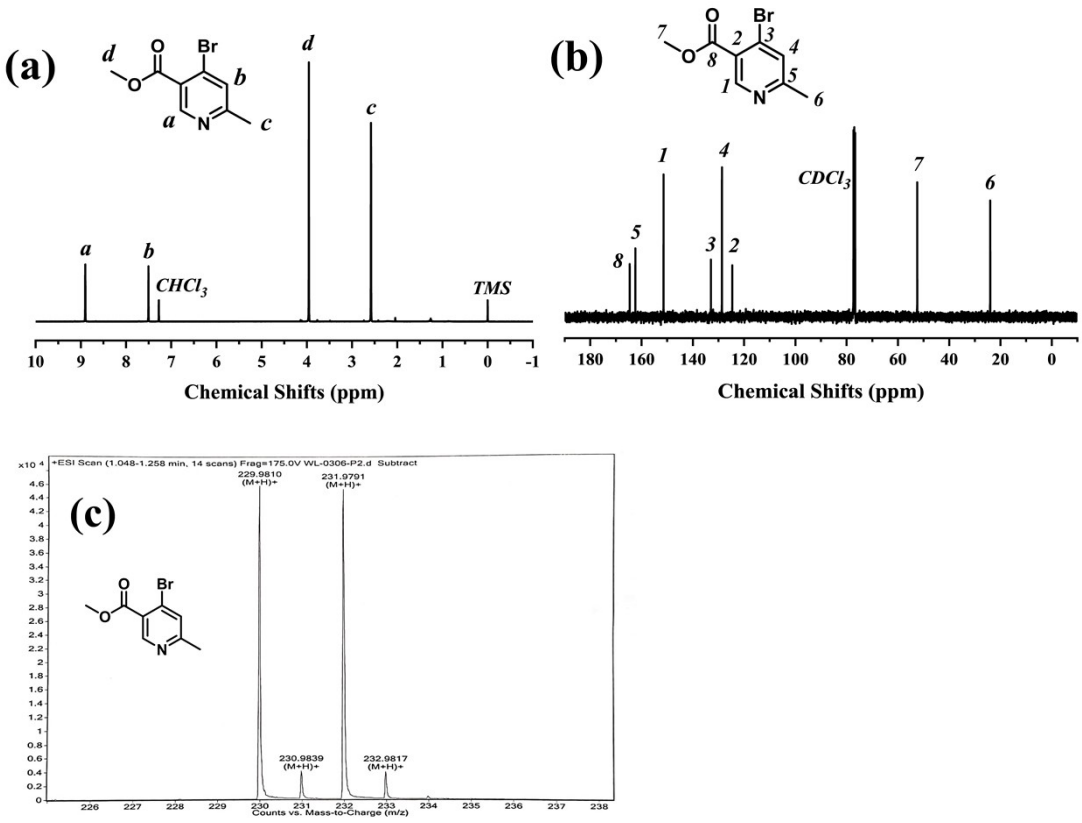


Figure S2. (a) ^{1}H NMR, (b) ^{13}C NMR and (c) HRMS spectra of methyl 4-bromo-6-methylnicotinate (A2).

3.3 Synthesis of 4-bromo-5-(methoxycarbonyl)-2-methylpyridine 1-oxide (A3). A2 (27.6 g, 120 mmol) and DCM (120 mL) were sequentially added into 500 mL round-bottom-flask and the solution was stirred at room temperature for 10 min; and then *m*-CPBA (85wt%, 36.5 g, 180 mmol) was added into the solution in five portions at 0 ˚C. The solution was stirred vigorously at room temperature until the completion of the reaction as evidenced by TLC. After removal of *m*-chlorobenzoic acid through kieselguhr column, the solution was washed with saturated aqueous solution of $NaHCO_3$ twice (80 mL×2) and brine (80 mL). The combined organic layer was dried over $MgSO_4$ and concentrated on a rotary evaporator. The residue was purified by silica gel column chromatography with elution (EA) yielding yellow solids A3 (26.6 g,

yield: 90%).

^{1}H NMR (400 MHz, Chloroform-d) δ 8.70 (s, 1H), 7.61 (s, 1H), 3.97 (s, 3H), 2.54 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.20, 152.56, 141.17, 131.40, 127.35, 117.87, 52.96, 17.39. ^{1}H NMR, ^{13}C NMR and HRMS spectra of A3 are shown in **Figure S3**.

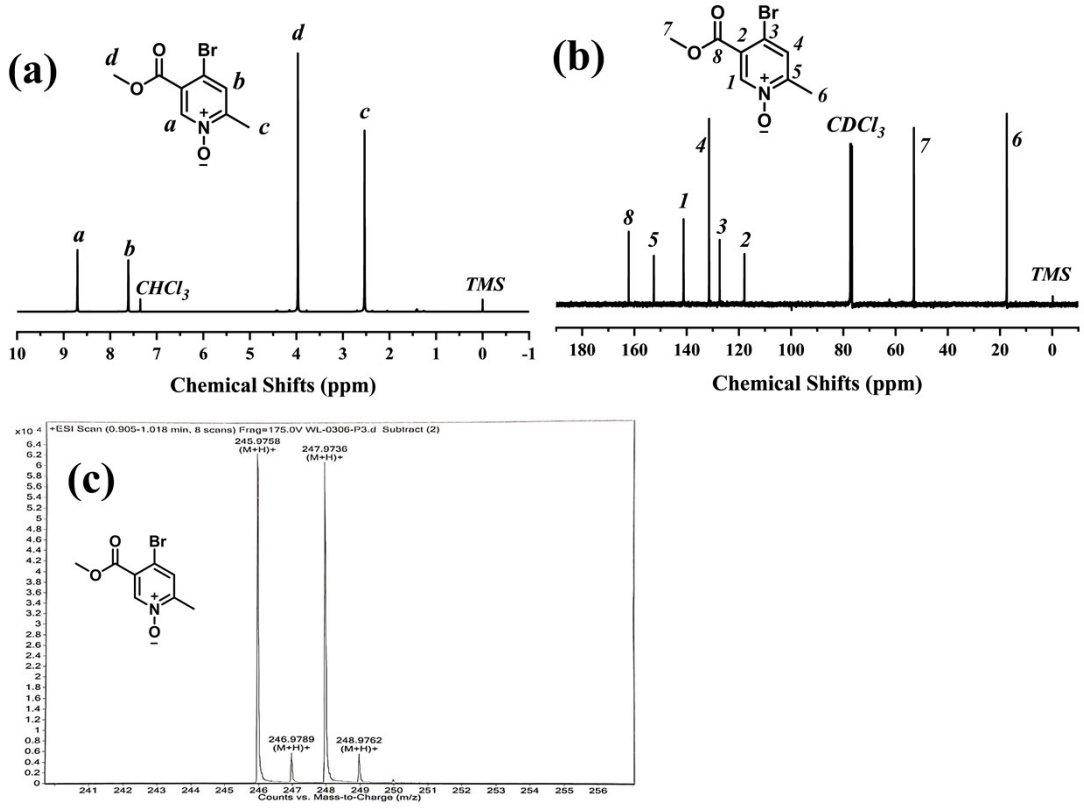


Figure S3. (a) ^{1}H NMR, (b) ^{13}C NMR and (c) HRMS spectra of 4-bromo-5-(methoxycarbonyl)-2-methylpyridine 1-oxide (A3).

3.4 Synthesis of methyl 4-bromo-6-(hydroxymethyl)nicotinate (A4). A3 (24.6 g, 100 mmol) was dissolved in DCM (160 mL) at room temperature. A solution of trifluoroacetic anhydride (35.2 mL, 250 mmol) in DCM (20 mL) was added dropwise into the solution at 0 ˚C. The solution was stirred under reflux condition. After the completion of the reaction as monitored by TLC, the solution was concentrated on a rotary evaporator. The residue was dissolved in MeOH (200 mL), into which Et_3N was added dropwise until the solution is neutral, and the solution was stirred for 4 h at room temperature. MeOH, methyl trifluoroacetate, trifluoroacetic acid and Et_3N were all removed by rotary evaporation. The residue was dissolved in DCM (100 mL) and washed with brine for three times (80 mL×3). Organic phase was dried over $MgSO_4$

and concentrated on a rotary evaporator. The residue was purified by silica gel column chromatography with elution (PE/EA=1:1 by volume) yielding yellow solids A4 (13.3g, yield: 54%).

^{1}H NMR (400 MHz, Chloroform-d) δ 8.91 (s, 1H), 7.71 (s, 1H), 4.80 (s, 2H), 3.97 (s, 3H), 3.83 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.47, 163.60, 151.00, 133.76, 126.19, 126.03, 63.81, 52.68. ^{1}H NMR, ^{13}C NMR and HRMS spectra of A4 are shown in **Figure S4**.

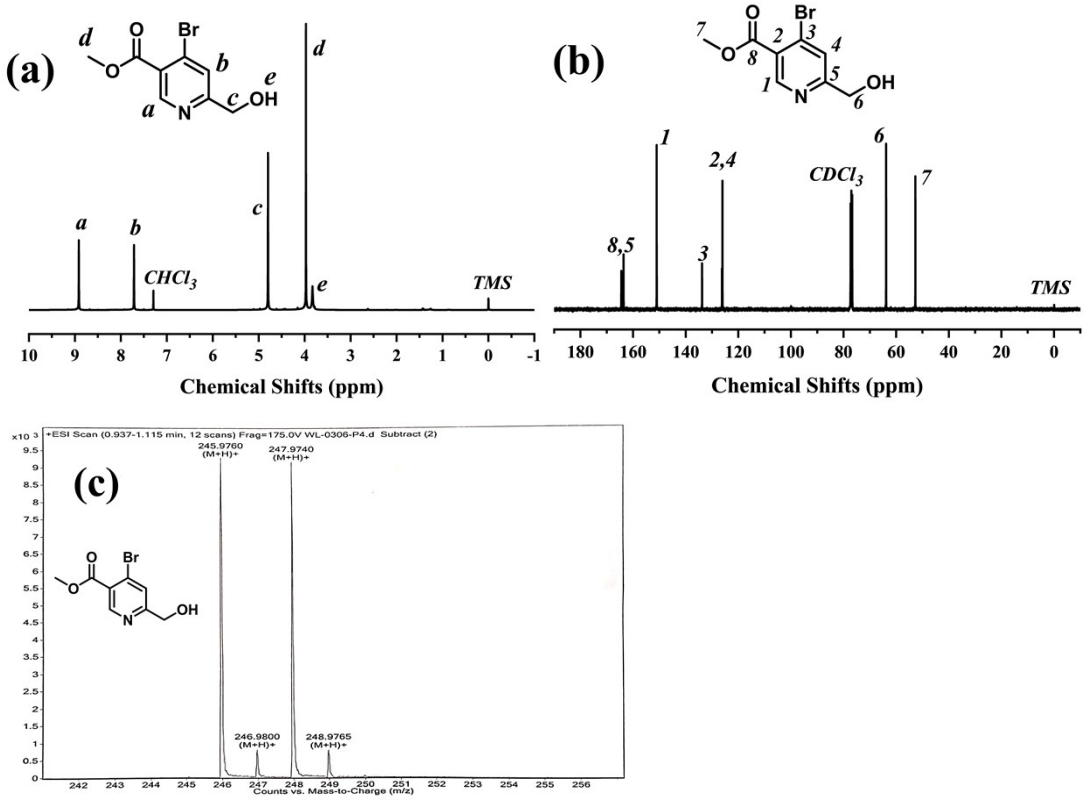


Figure S4. (a) ^{1}H NMR, (b) ^{13}C NMR and (c) HRMS spectra of methyl 4-bromo-6-(hydroxymethyl)nicotinate (A4).

3.5 Synthesis of methyl 6-(hydroxymethyl)-4-(phenylsulfonyl)nicotinate (A5). Under Ar atmosphere, A4 (12.3 g, 50.0 mmol), sodium benzenesulfinate (20.5 g, 125 mmol) and tetrabutylammonium bromide (1.61 g, 5.00 mmol) were sequentially dissolved in CH_3CN (100 mL), and the solution was refluxed for about 18 h. After the completion of the reaction as evidenced by TLC, the solution was filtered through kieselguhr column to remove $PhSO_2Na$, and concentrated on a rotary evaporator. The residue

was purified by silica gel column chromatography with elution (PE/EA=1:1 by volume) yielding yellow solids A5 (12.4 g, yield: 81%).

^{1}H NMR (400 MHz, Chloroform-d) δ 8.82 (d, J = 1.9 Hz, 1H), 8.11 (d, J = 1.9 Hz, 1H), 7.99 (dd, J = 7.7, 1.9 Hz, 2H), 7.68 – 7.61 (m, 1H), 7.56 (td, J = 7.8, 1.9 Hz, 2H), 4.90 (d, J = 2.0 Hz, 2H), 3.95 (d, J = 1.9 Hz, 3H), 3.85 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.28, 164.74, 149.55, 148.15, 139.43, 134.02, 129.08, 128.23, 124.85, 119.39, 64.33, 53.22. ^{1}H NMR, ^{13}C NMR and HRMS spectra of A5 are shown in Figure S5.

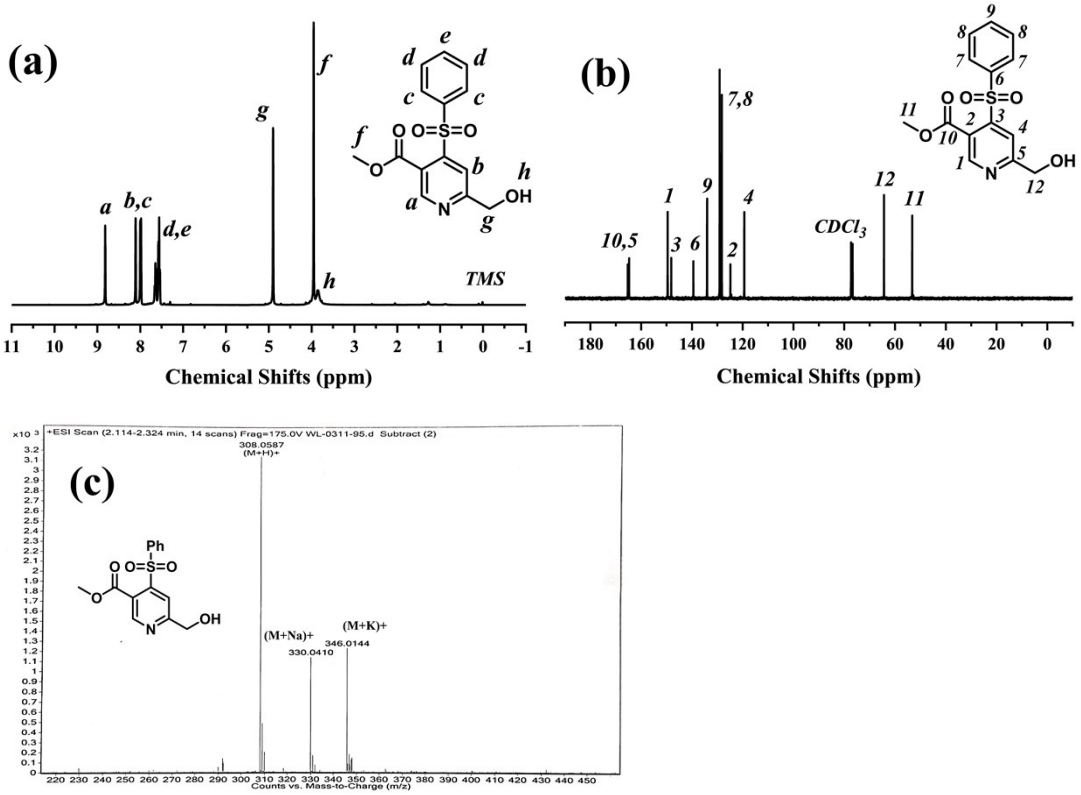


Figure S5. (a) ^{1}H NMR, (b) ^{13}C NMR and (c) HRMS spectra of methyl 6-(hydroxymethyl)-4-(phenylsulfonyl)nicotinate (A5).

3.6 Synthesis of 4-((5-(methoxycarbonyl)-4-(phenylsulfonyl)pyridin-2-yl)methoxy)-4-oxobutanoic acid (A6). A5 (3.00 g, 9.76 mmol) and Et_3N (2.0 mL) was dissolved in DCM (30 mL), and succinic anhydride (1.172 g, 11.71 mmol) was added dropwise into the solution. The solution was stirred until the completion of the reaction as evidenced by TLC. The solution was concentrated on a rotary evaporator. The residue was dissolved in saturated aqueous solution of $NaHCO_3$, and the mixture was stirred

for 1 h. Aqueous solution of HCl (1 N) was added dropwise into the solution until pH=4, and the solution was stirred at room temperature for 30 min. White solids precipitated in the solution was filtered, and the filter cake was flushed with distilled water and petroleum ether successively, and dried under vacuum condition for 12h. White solids A6 were obtained without further purification (3.8 g, yield: 96%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.35 (s, 1H), 8.97 (s, 1H), 8.27 – 7.99 (m, 3H), 7.77 (dt, J = 33.8, 7.3 Hz, 3H), 5.37 (s, 2H), 3.91 (s, 3H), 2.71 (t, J = 6.4 Hz, 2H), 2.58 (t, J = 6.5 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 173.37, 171.94, 165.13, 160.54, 149.76, 146.86, 139.02, 134.65, 129.67, 128.11, 125.05, 120.17, 65.43, 53.25, 28.63. ^{1}H NMR, ^{13}C NMR and HRMS spectrum of A6 are shown in **Figure S6**.

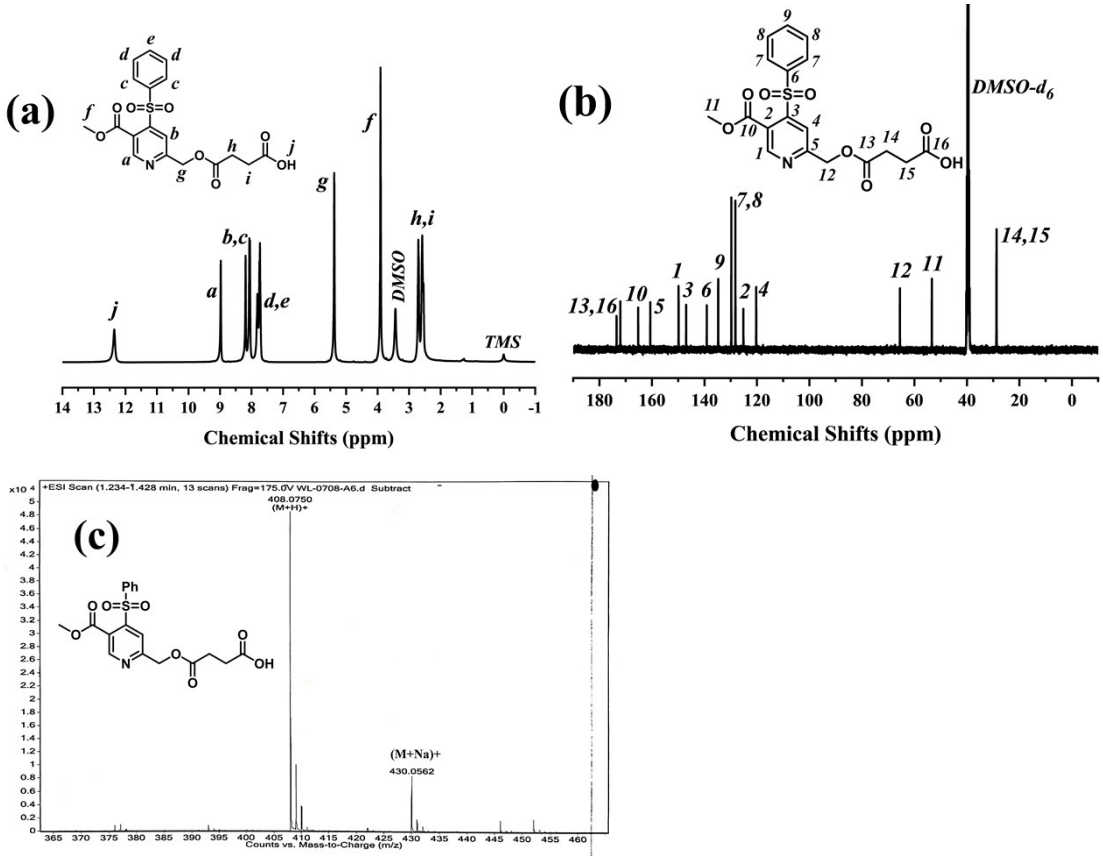


Figure S6. (a) ^{1}H NMR, (b) ^{13}C NMR and (c) HRMS spectra of 4-((5-(methoxycarbonyl)-4-(phenylsulfonyl)pyridin-2-yl)methoxy)-4-oxobutanoic acid (A6).

3.7 Synthesis of M1. EDCI (5.26 g, 12.9 mmol), DMAP (52.5 mg, 0.430 mmol), and 1,6-hexanediol (406.5 mg, 3.440 mmol) were added successively into the DCM

solution of A6 (3.5 g, 8.6 mmol). The solution was stirred until the completion of the reaction as evidenced by TLC. The solution was washed with brine for three times (30 mL×3). The organic phase was dried over $MgSO_4$ and concentrated on a rotary evaporator. The residue was purified by silica gel column chromatography with elution (PE/EA=1:3 by volume) yielding yellow solids M1 (2.68 g, yield: 87%).

^{1}H NMR (400 MHz, Chloroform-d) δ 8.84 (s, 2H), 8.07 – 7.99 (m, 6H), 7.70 – 7.62 (m, 2H), 7.57 (t, J = 7.6 Hz, 4H), 5.35 (s, 4H), 4.11 (t, J = 6.7 Hz, 4H), 3.95 (s, 6H), 2.79 (dd, J = 7.9, 5.9 Hz, 4H), 2.70 (dd, J = 7.4, 5.5 Hz, 4H), 1.63 (t, J = 6.7 Hz, 4H), 1.41 – 1.31 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.09, 171.71, 165.20, 160.19, 150.05, 148.36, 139.57, 134.05, 129.11, 128.41, 125.48, 120.01, 65.83, 64.75, 53.28, 28.92, 28.90, 28.36, 25.43. ^{1}H NMR, ^{13}C NMR and HRMS spectra of M1 are shown in **Figure S7**.

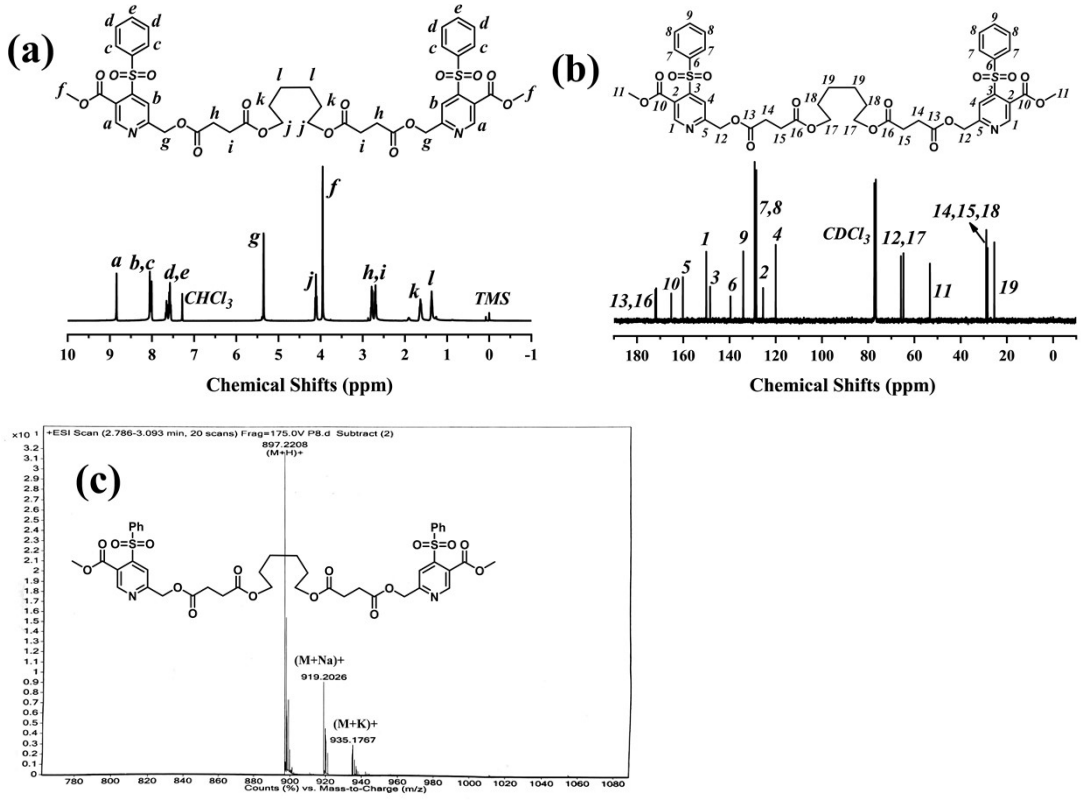


Figure S7. (a) ^{1}H NMR, (b) ^{13}C NMR and (c) HRMS spectra of M1.

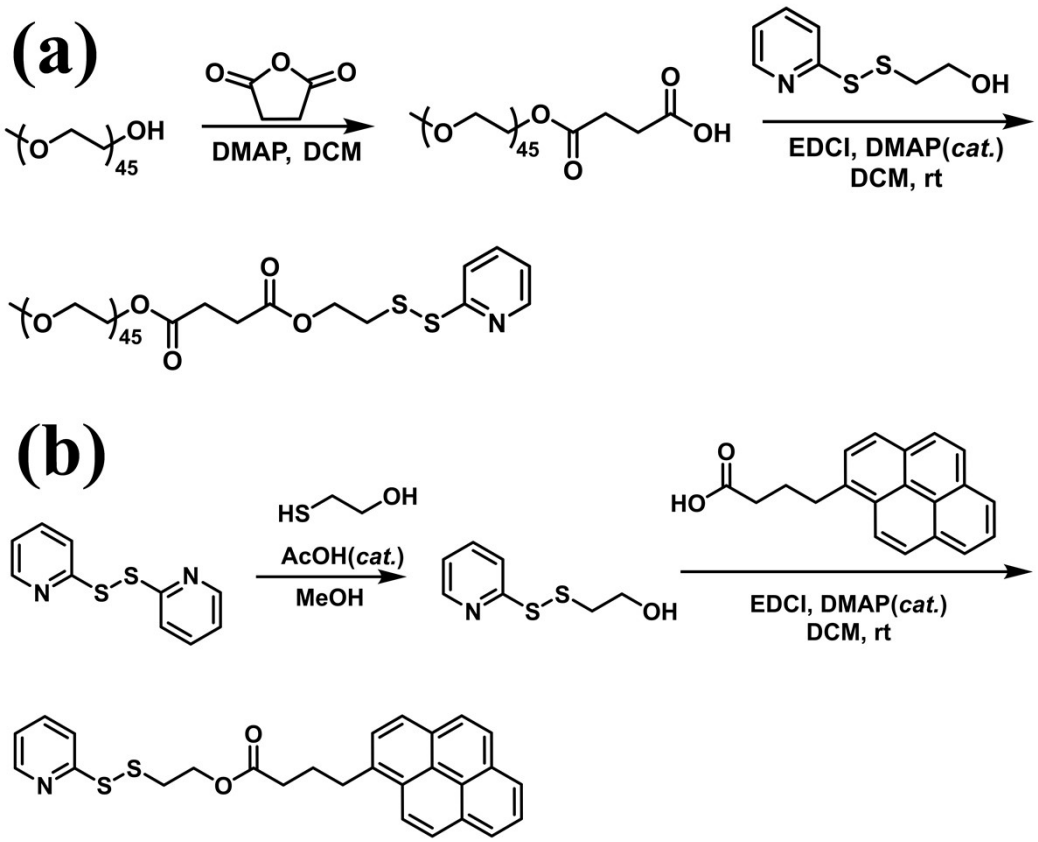
4. Polymerization of M1. A typical polymerization process is described as follows. M1 (134.5 mg，0.1500 mmol) was dissolved in dry DMF (0.5 mL), and TEA (83.4

μL) was added into the solution. After three freeze-pump-thaw cycles, dithiothreitol (DTT, 23.1 mg, 0.150 mmol) or 4,4'-thiolbisbenzenethiol (TBT, 37.56 mg, 0.150 mmol) was added into solution under argon atmosphere. After two freeze-pump-thaw cycles, the solutions were stirred at 50 ˚C. After the reactions, P1 and P2 polymers were prepared. SEC was used to determine the apparent molecular weights of the polymers produced at different times and ^{1}H NMR was employed to analyze the chemical structures of the polymers.

P1 polymer: ^{1}H NMR (400 MHz, Chloroform-d) δ 8.93 (d, J = 5.3 Hz, 2H), 7.35 (d, J = 4.2 Hz, 2H), 5.24 (d, J = 4.1 Hz, 4H), 4.05 (m, J = 12.9, 4.9 Hz, 6H), 3.90 (d, J = 3.8 Hz, 6H), 3.27 (qd, J = 13.5, 6.1 Hz, 4H), 2.80 – 2.62 (m, 8H), 1.68 – 1.48 (m, 4H), 1.40 – 1.22 (m, 4H).

P2 polymer: ^{1}H NMR (400 MHz, Chloroform-d) δ 8.95 (s, 2H), 7.53 – 7.40 (m, 8H), 6.56 (s, 2H), 5.06 – 4.94 (m, 4H), 4.12 – 3.83 (m, 10H), 2.48 (dq, J = 10.3, 5.7 Hz, 8H), 1.51 (dq, J = 11.8, 6.6 Hz, 4H), 1.31 – 1.20 (m, 4H).

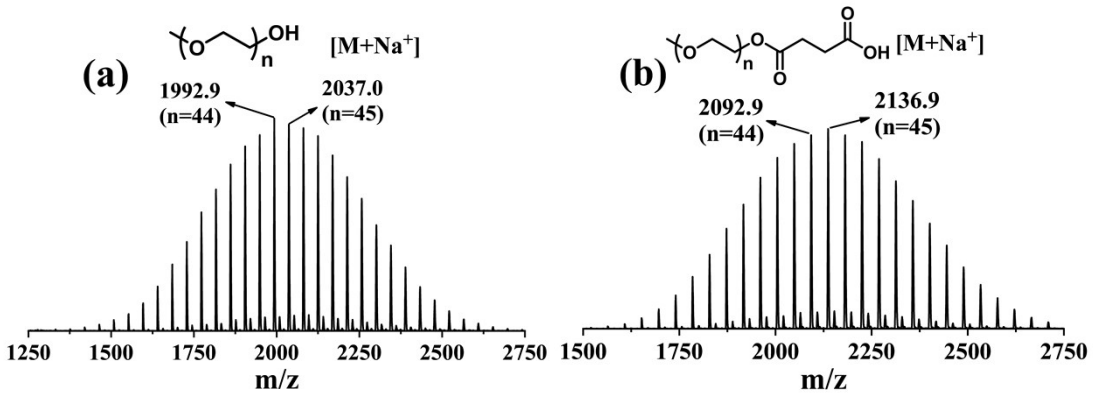
5. Synthesis of pyridyl disulfide-terminated poly(ethylene glycol) monomethyl ether (mPEG-SS-py) and 2-(pyridin-2-yldisulfanyl)ethyl 4-(pyren-1-yl)butanoate (pyrene-SS-py). The synthetic routes for mPEG-SS-py and pyrene-SS-py are illustrated in **Scheme S2**. Poly(ethylene glycol) monomethyl ether (mPEG-OH) was reacted with succinic anhydride and carboxylic acid terminated PEG (mPEG-COOH) was synthesized. An esterification reaction between mPEG-COOH and 2-(pyridin-2-yldisulfaneyl)ethan-1-ol leads to the synthesis of mPEG-SS-py (**Scheme S2a**). The details are described as follows.



Scheme S2. Synthetic routes for the synthesis of (a) 2-(pyridin-2-yldisulfanyl)ethyl 4-(pyren-1-yl)butanoate (pyrene-SS-py) and (b) pyridyl disulfide-terminated poly(ethylene glycol) monomethyl ether (mPEG-SS-py).

mPEG-OH (4.0 g, 2.0 mmol), succinic anhydride (300 mg, 3.00 mmol) and DMAP (24.4 mg, 0.200 mmol) were dissolved in dry DCM (40 mL). The solution was stirred at room temperature for 10 h, and concentrated on a rotary evaporator. The residue was dissolved in distilled water (40 mL). After stirring for 10 min, the aqueous solution was washed with EA for three times (30 mL×3). NaCl was added into the aqueous solution and a saturated solution was obtained. The aqueous solution was washed with DCM for three times (40 mL×3). The organic phase was dried over $MgSO_4$, and concentrated on a rotary evaporator. The crude product was precipitated in glacial diethyl ether (50 mL). After centrifugation (8000 rpm, 5 min), the targeted polymer, succinic anhydride-modified PEG (mPEG-COOH), was dried under reduced pressure (3.3 g, yield: 82.5%).

mPEG-COOH (3.0 g, 1.5 mmol), 2-(pyridine-2-yldisulfanyl)ethanol (843.7 mg, 4.500 mmol), DMAP (9.2 mg, 0.075 mmol) and EDCI (431.3 mg, 2.250 mmol) were successively dissolved in DCM (30 mL). The solution was stirred at room temperature for 10 h, and concentrated on a rotary evaporator. The residue was dissolved in 40 mL of water under stirring. The aqueous polymer solution was washed with EA for three times (30 mL×3). NaCl was added to the aqueous solution until it was saturated. The solution was washed with DCM for three times (40 mL×3). The organic phase was dried over $MgSO_4$ and concentrated on a rotary evaporator. The crude product was precipitated in 50 mL of glacial diethyl ether. After centrifugation (8000 rpm, 5 min), the targeted polymer mPEG-SS-py was collected (2.8 g, yield: 87%). MALDI-TOF results of mPEG-OH, mPEG-COOH and mPEG-SS-py are shown in **Figure S8**, which confirm the synthesis of mPEG-COOH and mPEG-SS-py. mPEG-OH: ^{1}H NMR (400 MHz, Chloroform-d) δ 3.81 – 3.44 (m, ~176H), 3.36 (s, 3H). mPEG-COOH: ^{1}H NMR (400 MHz, Chloroform-d) δ 4.31 – 4.21 (m, 2H), 3.82 – 3.45 (m, ~174H), 3.37 (s, 3H), 2.73 – 2.56 (m, 4H). mPEG-SS-py: ^{1}H NMR (400 MHz, Chloroform-d) δ 8.46 (d, J = 4.7 Hz, 0.80H), 7.75 – 7.59 (m, 1.60H), 7.11 (ddd, J = 6.7, 4.9, 1.8 Hz, 0.80H), 4.33 (t, J = 6.4 Hz, 2H), 4.25 – 4.20 (m, 2H), 3.80 – 3.43 (m, ~174H), 3.52 (dd, J = 5.8, 3.6 Hz, 2H), 3.35 (s, 3H), 3.03 (t, J = 6.4 Hz, 2H), 2.66 – 2.57 (m, 4H).



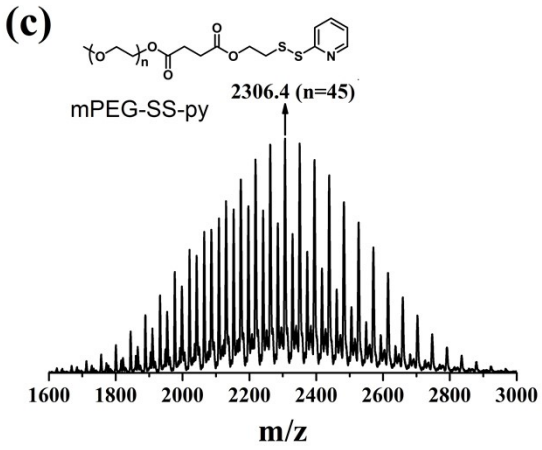


Figure S8. Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectra of (a) mPEG-OH, (b) mPEG-COOH and (c) mPEG-SS-py.

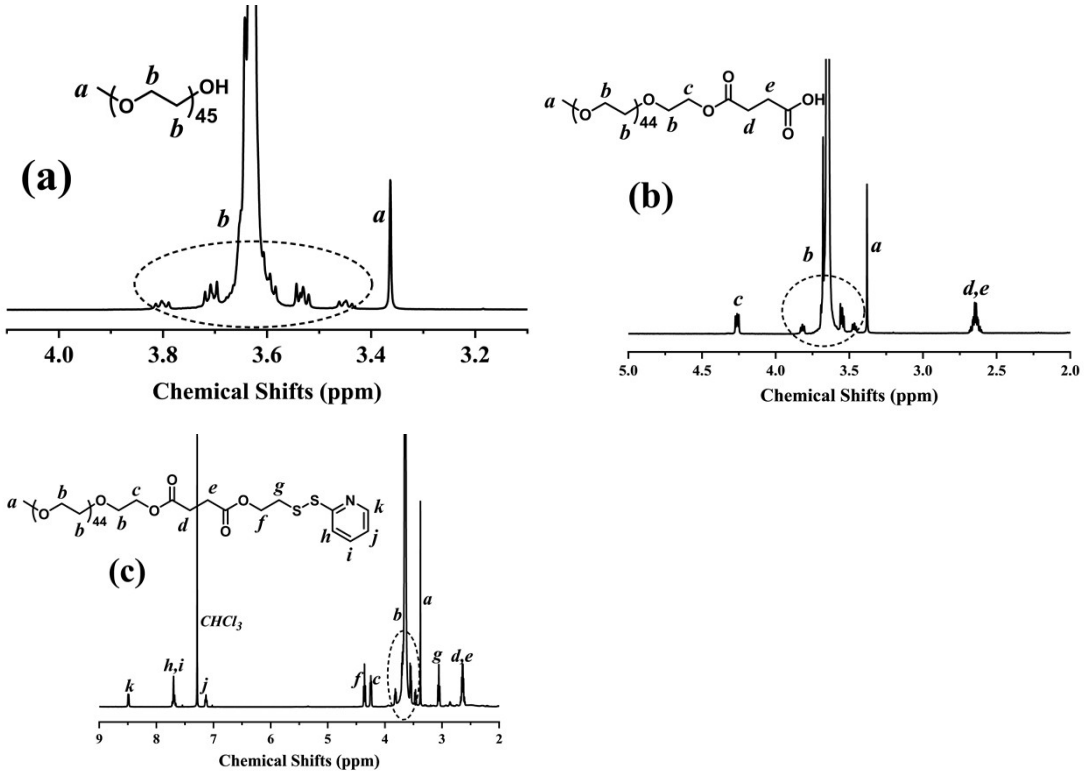
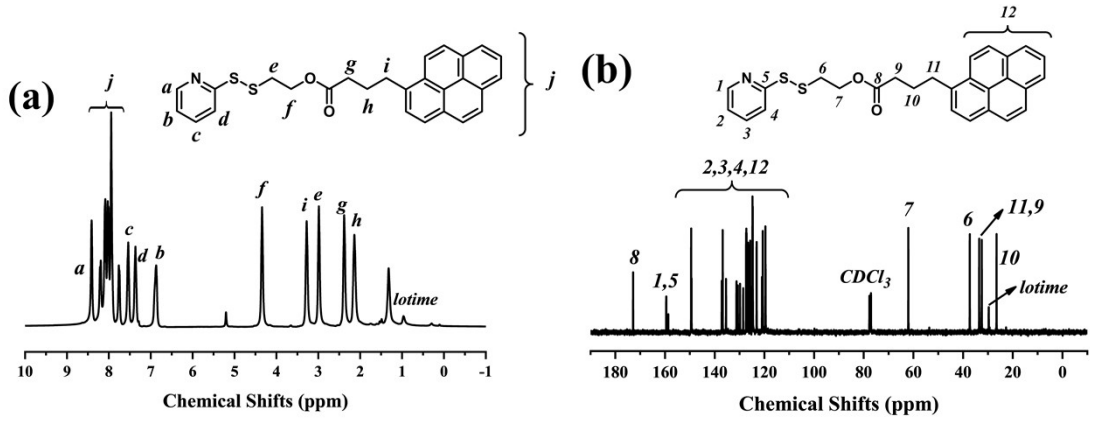


Figure S9. ^{1}H NMR spectra of (a) mPEG-OH, (b) mPEG-COOH, and (c) mPEG-SS-py.

As shown in **Scheme 2b**, pyrene-SS-py was synthesized by esterification between 1-pyrenebutanoic acid and hydroxylethylmercaptopyridine. 1-Pyrenebutanoic acid

(500 mg, 1.73 mmol), hydroxylethylmercaptopyridine (486.9 mg, 2.600 mmol), DMAP(10.5 mg, 0.0860 mmol) and EDCI (500 mg, 2.61mmol) were successively added into DCM (10 mL). The solution was stirred at room temperature under dark condition for 6 h. After the reaction, the solution was diluted with of DCM (30 mL) and washed with brine for three times (20 mL×3). The organic phase was concentrated on a rotary evaporator, and the residue was purified by silica gel column chromatography with elution (PE/EA=3:1 by volume), affording the target compound pyrene-SS-py (4.41g, yield: 79%).

^{1}H NMR (400 MHz, Chloroform-d) δ 8.48 – 8.33 (m, 1H), 8.20 (d, J = 9.3 Hz, 1H), 8.16 – 7.82 (m, 7H), 7.75 (d, J = 7.8 Hz, 1H), 7.54 (t, J = 7.0 Hz, 1H), 7.36 (t, J = 7.8 Hz, 1H), 6.89 (dt, J = 13.1, 5.9 Hz, 1H), 4.33 (d, J = 6.6 Hz, 2H), 3.28 (t, J = 7.7 Hz, 2H), 2.98 (d, J = 6.7 Hz, 2H), 2.37 (d, J = 7.6 Hz, 2H), 2.22 – 2.03 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.46, 159.11, 158.30, 149.08, 148.94, 136.75, 136.38, 135.05, 130.84, 130.32, 129.40, 128.15, 126.96, 126.85, 126.75, 126.17, 125.33, 124.49, 124.41, 124.31, 124.27, 122.73, 120.55, 120.25, 119.19, 119.12, 61.64, 36.91, 33.12, 32.09, 29.29, 26.13. ^{1}H NMR, ^{13}C NMR and HRMS spectra of pyrene-SS-py are shown in Figure S9.



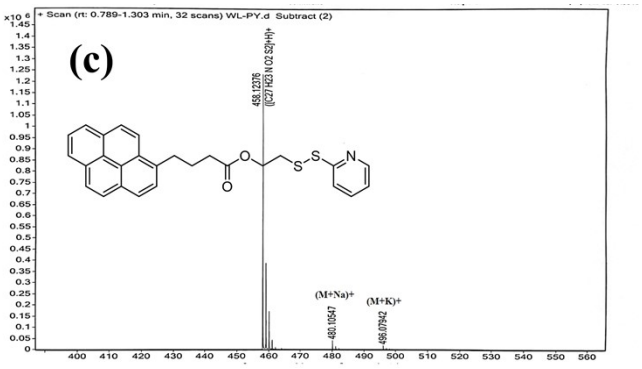
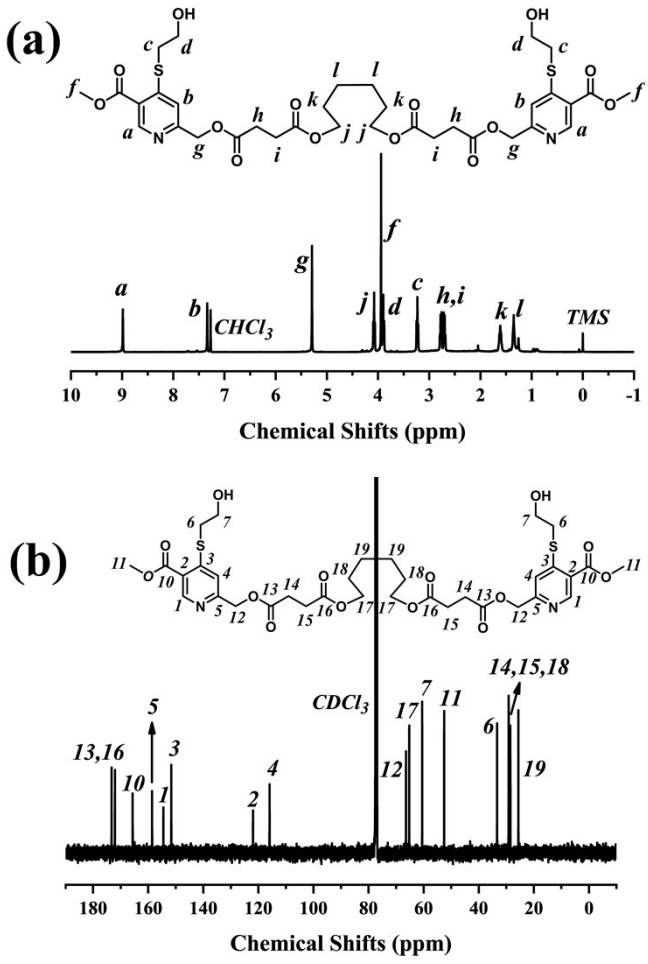


Figure S10. (a) ^{1}H NMR, (b) ^{13}C NMR and (c) HRMS spectra of 2-(pyridin-2-yldisulfanyl)ethyl 4-(pyren-1-yl)butanoate (pyrene-SS-py).



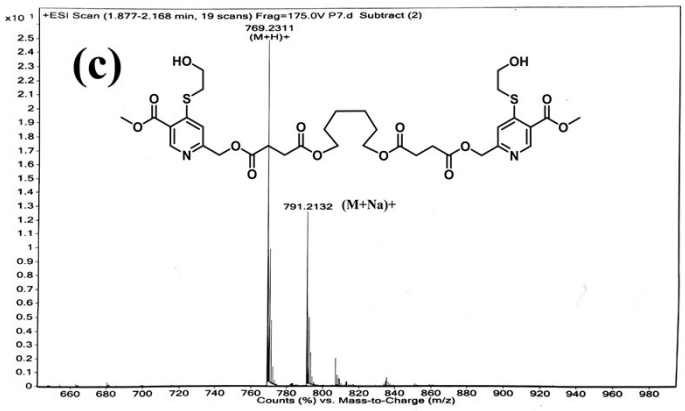


Figure S11. (a) ^{1}H NMR, (b) ^{13}C NMR and (c) HRMS spectra of the reaction product of M1 and 2-mercapto-ethanol.

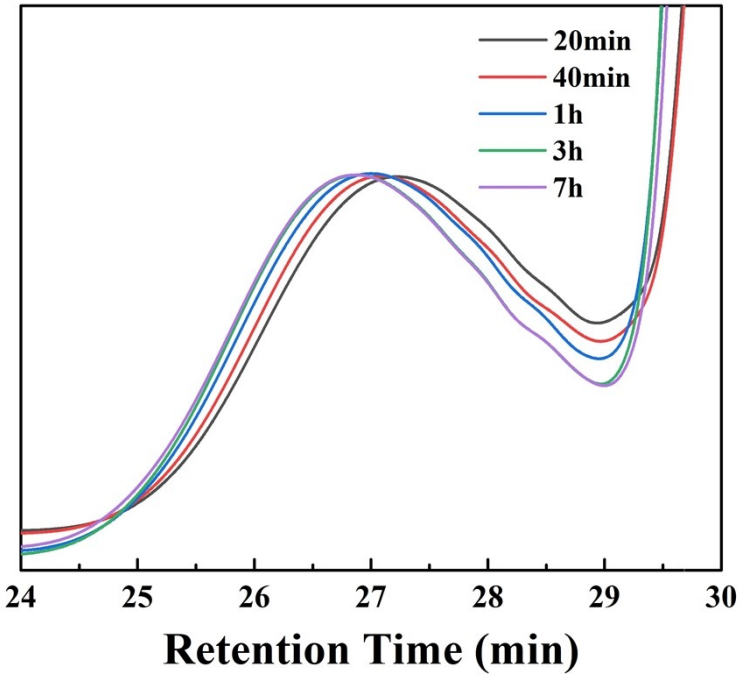


Figure S12. SEC curves of P2 obtained at different polymerization times.

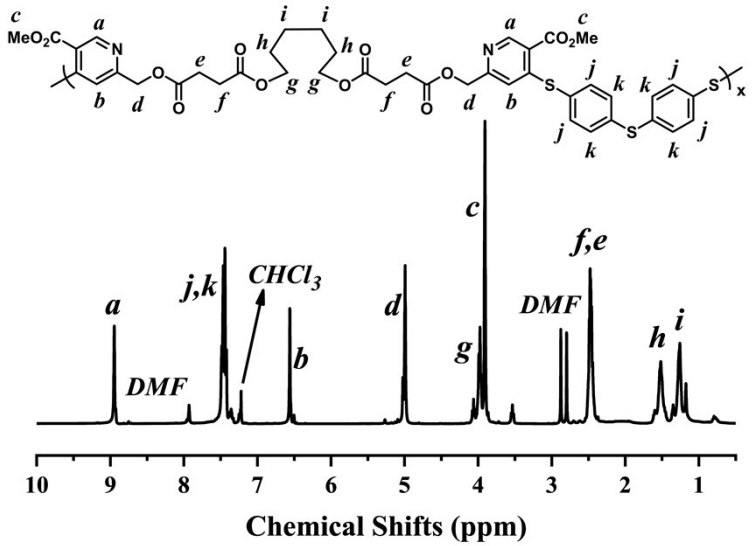


Figure S13. ^{1}H NMR spectrum of P2.

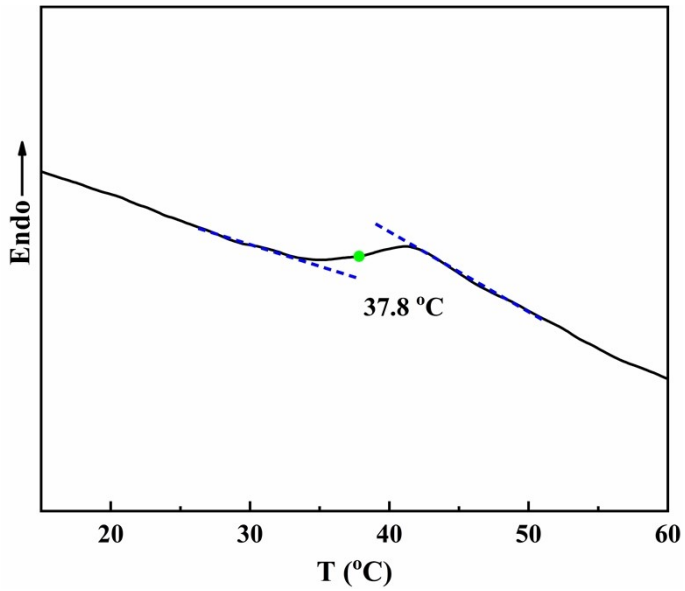


Figure S14. DSC curves of P2 collected after 3h of polymerization.