Electronic Supplementary Material (ESI) for Polymer Chemistry.

Mild and Efficient Synthesis of ω,ω-Heterodifunctionalized Polymers and Polymer Bioconjugates

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Materials

Monomethyl ether poly(ethylene glycol) (mPEG, 2000 g/mol, Sigma Aldrich, *trans*-2-[3-(4-tert-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB, Santa Cruz Biotechnology, ≥99%), anthralin (AK Scientific, 98%), trifluoroacetic acid (TFA, Fisher Scientific, 97%), sodium trifluoroacetate (NaTFA, Aldrich, 98%), and Pierce avidin agarose (Thermo Scientific) were used as received. All other reagents were purchased from VWR International and used as received. mPEG-amine was synthesized according to the procedure outline below. Oct-7-ene-amine,[1] the azide derivative of coumarin 1,[2] and 2-mercaptoethylbiotin[3] were synthesized according to previous reports. All solvents were purchased from Fisher Scientific and used as received. DMF was purified using a Glass Contour solvent system (Glass Contour, Inc., now Pure Process Technology), degassed in 20 L drums, and passed through two columns of molecular sieves under an argon atmosphere. Thin Layer Chromatography (TLC) was performed using aluminum-backed silica gel plates. The plates were developed using UV light and ninhydrin staining. Flash column chromatography was performed using SiO_2-60 230-400 mesh silica gel.

Characterization

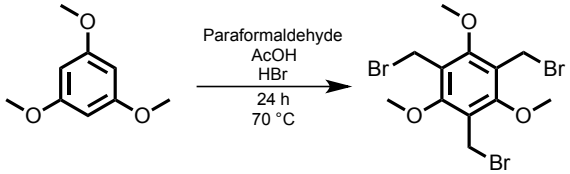
^{1}H NMR spectroscopy was conducted on an Inova 500 MHz, 2 RF channel instrument at 25 °C. Chloroform-*d* (Cambridge Isotopes Laboratories, Inc., 99.8%) solvent was used as received.

Matrix assisted laser desorption/ionization time-of-flight (MALDI-TOF/TOF) was performed on a Bruker Microflex LRF MALDI TOF (Billerica, MA) mass spectrometer in reflectron, positive ion mode using an N_2 on-axis laser. Spectra were collected in flexControl (Bruker Daltronics Inc., Billerica, MA) and analyzed using flexAnalysis (Bruker Daltronics Inc., Billerica, MA) and Polymerix Version 3 software (Sierra Analytics, Modesto, CA). Analysis of mPEG-amine was performed by mixing dithranol matrix (20.0 mg/mL in DCM) and polymer solution (2.0 mg/mL in DCM with 2 drops trifluoroacetic acid) at a v:v ratio of 5:2 matrix:polymer and 3 μL were spotted on a stainless steel Bruker MSP 96 target polished steel BC plate and air dried. Analysis of mPEG-BTF conjugates was performed by mixing solutions of DCTB matrix (10.0 mg/mL in THF) and polymer (2.00 mg/mL in THF) at a v:v ratio of 5:2 matrix:polymer and 2.00 μL were spotted, then dried under N_2, on a stainless steel AB Sciex Plate. Subsequently, 1.00 μL of a NaTFA solution (1.00 mg/mL in THF) was spotted on top of the polymer-matrix spot and dried under N_2.

Size exclusion chromatography (SEC) was performed in *N,N*-dimethylacetamide (DMAc) with 50 mM LiCl at 50 °C and a flow rate of 1.0 mL min^{-1} (Agilent isocratic pump, degasser, and autosampler, colums: Plgel 5 μm guard + two ViscoGel I-series G3078 mixed bed columns: molecular weight range 0-20 × 10^3 and 1-100 × 10^4 g mol^{-1}). Detection consisted of a Wyatt Optilab T-rEX refractive index detector operating at 658 nm and a Wyatt miniDAWN Treos light scattering detector operating at 659 nm. Absolute molecular weights and polydispersities were calculated using the Wyatt ASTRA software and 100% mass recovery methods.

Methods

Synthesis of Benzotrifuranone (BTF)



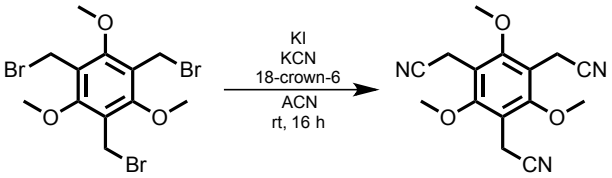
1,3,5-Tris(bromomethyl)-2,4,6-trimethoxybenzene. To a 350 mL sealed pressure vessel was added 1,3,5-trimethoxybenzene (15 g, 89 mmol), paraformaldehyde (10 g, 33 mmol), and glacial acetic acid (35 mL). The solution was allowed to stir for one hour at room temperature. HBr (33% in AcOH, 75 mL) was added to the flask and the solution was stirred for 3 hours at 70 °C. The resulting orange solution was cooled to room temperature and allowed to stir for 16 hours. The reaction mixture was poured into water (700 mL), and CH_2Cl_2 was added until all solids were dissolved. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. All

organics were combined and washed successively with saturated $NaHCO_3$, brine, and water. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a brown oil. The oil was purified via column chromatography (2:1 hexanes:CH_2Cl_2) to yield 1,3,5-tris(bromomethyl)-2,4,6-trimethoxybenzene as a white solid (12 g, 29%).

^{1}H NMR ($CDCl_3$) δ 4.15 (s, 9H), 4.63 (s, 6H).

^{13}C NMR ($CDCl_3$) δ 22.6, 62.8, 123.4, 160.2.

HRMS (DART) calculated for $C_{12}H_{15}O_3Br_3$ $[M + NH_4]^+$ 463.8889, found 463.8903.

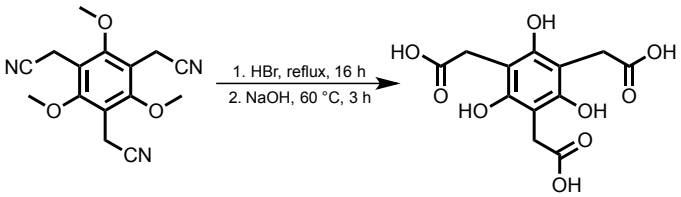


2,2′,2-(2,4,6-Trimethoxybenzene-1,3,5-triyl)triacetonitrile. Presented here is a modified and improved synthetic procedure to the one we originally published in 2005.[4] To a solution of 1,3,5-tris(bromomethyl)-2,4,6-trimethoxybenzene (17 g, 37 mmol) in acetonitrile (250 mL) and water (33 mL) was added KI (0.37 g, 1.5 mmol), KCN (12 g, 12 mmol) and 18-crown-6 (2.5 g, 6.2 mmol). The resulting solution was allowed to stir overnight at room temperature. The solution was poured into ice water (700 mL) and suction filtered as soon as the ice melted. The filtered solid was dried under reduced pressure to afford 2,2′,2-(2,4,6-trimethoxybenzene-1,3,5-triyl)triacetonitrile as a white solid (11 g, 100%).

^{1}H NMR ($CDCl_3$) δ 3.72 (s, 6H), 4.02 (s, 9H).

^{13}C NMR ($CDCl_3$) δ 13.0, 62.9, 116.2, 117.7, 158.6.

HRMS (DART) calculated for $C_{15}H_{15}N_3O_3$ $[M+NH_4]^+$ 303.1452, found 303.1462.

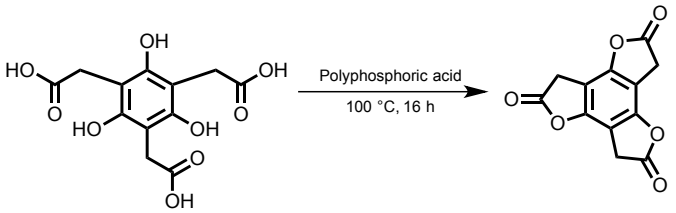


2,2′,2-(2,4,6-Trimethoxybenzene-1,3,5-triyl)triacetic acid. Presented here is an updated synthetic procedure to the ones we originally published in 2005[4] and 2009.[5] A solution of 2,2',2''-(2,4,6-trimethoxybenzene-1,3,5-triyl)triacetonitrile (8.5 g, 28 mmol) in HBr (48%, 95 mL) was heated to reflux overnight. The solution was cooled to room temperature at which a precipitate formed. Water (200 mL) was added to the flask and the mixture was extracted with ethyl acetate. The organic layers were combined, dried over $MgSO_4$, and concentrated under reduced pressure. The solid was then hydrolyzed with NaOH (22 g NaOH in 100 mL water) at 60 °C for 3 hours. The resultant solution was cooled on an ice bath, acidified with concentrated HCl, and extracted with ethyl acetate. The organics were combined, dried over $MgSO_4$, and concentrated under reduced pressure yielding 2,2′,2-(2,4,6-trihydroxybenzene-1,3,5-triyl)triacetic acid (8.8 g, 95%).

^{1}H NMR (DMSO-d6) δ 3.46 (s, 6H), 8.23 (s, 3H), 11.95 (s, 3H).

^{13}C NMR (DMSO-d6) δ 29.7, 103.0, 153.0, 173.5.

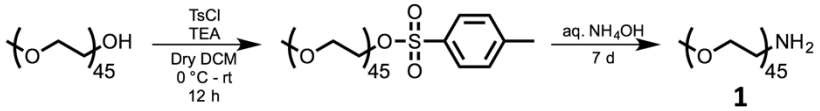
HRMS (ESI) calculated for $C_{12}H_{12}O_9$ $[M=Na]^+$ 323.0374, found 323.0380.



Benzo[1,2-*b*:3,4-*b*′:5,6-*b*]trifuranone (BTF). Presented here is an updated synthetic procedure to the one we originally published in 2009.[5] A solution of 2,2′,2-(2,4,6-trihydroxybenzene-1,3,5-triyl)triacetic acid (4.4 g, 15 mmol) and polyphosphoric acid (PPA, 50 g) were heated to 110 °C overnight. The solution was cooled to 0 °C and 800 mL ice water was added with stirring. The aqueous solution was extracted with CH_2Cl_2 (emulsion). The

organics were combined, washed with water, brine, and dried over Na_2SO_4. The solution was filtered and then clarified with activated carbon. The solution was concentrated under reduced pressure to yield BTF (1.1 g, 30%). The solid was purified by column chromatography (98% CH_2Cl_2/acetone) and obtained was a light tan product.
^{1}H NMR ($CDCl_3$) δ 3.80 (s, 6H).
^{13}C NMR ($CDCl_3$) δ 30.3, 101.4, 150.3, 171.9.
HRMS (GC-CI-MS) calculated for $C_{12}H_6O_6$ $[M+H]^+$ 247.0243, found 247.0243.

Synthesis of mPEG-amine (1)

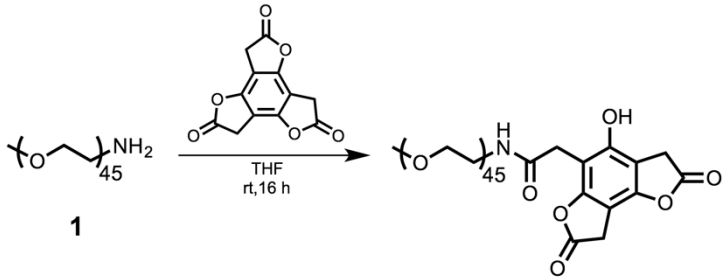


1

The synthesis was adapted from a previous report.[6] First, mPEG (50 g, 25 mmol) was dissolved in toluene (300 mL) and dried during the azeotropic distillation of approximately 150 mL toluene. The flask was backfilled with N_2, cooled to 0 °C, and TEA (13 g, 13 mmol) was added. Subsequently, *p*-toluene sulfonyl chloride (24 g, 130 mmol) was dissolved in dry DCM and cannulated into the cooled flask. The reaction was held at 0 °C for 2 h then allowed to warm to room temperature and stir overnight. The salts were filtered off, the solution concentrated, and the polymer precipitated 2× into cold diethyl ether yielding 49 g of mPEG-TS. The amination was performed in two batches. One of the batches proceeded as follows: mPEG-TS (20 g, 10 mmol) was dissolved in 30% ammonium hydroxide solution (300 mL) in a plastic Nalgene bottle, wrapped in Parafilm, and left to stir for 7 days. The reaction was opened and placed in the back of the hood to allow the ammonia to evaporate over 7 days. The pH was then adjusted to 13 using 1.0 M NaOH and the aqueous solution was washed 4× with DCM. The organic layers were combined, concentrated, and the polymer precipitated 2× into cold diethyl ether yielding the PEG-amine product **1** (38.8 g total yield across both batches).

Synthesis of mPEG-BTF conjugates

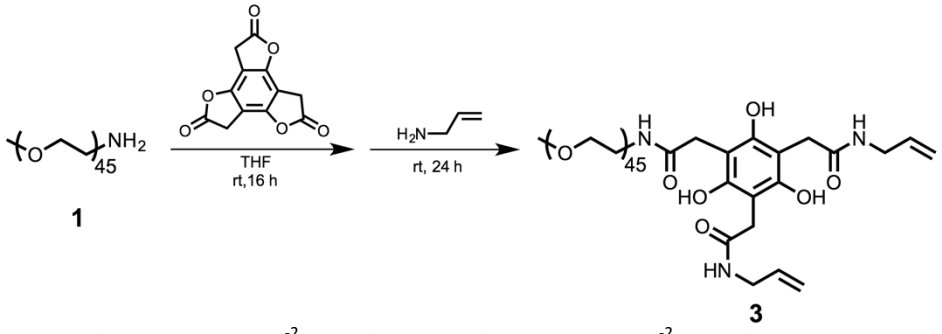
mPEG-amine conjugation to BTF



1 **2**

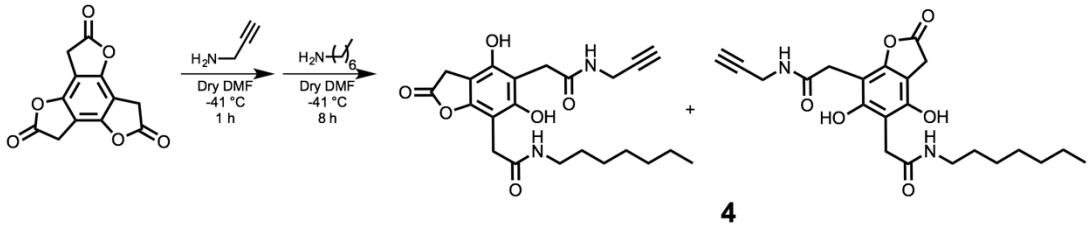
1 (40 mg, 2.0×10^{-2} mmol) and BTF (6.2 mg, 2.5×10^{-2} mmol) were dissolved in THF (1.6 mL) and left to stir at room temperature for 16 h. The polymer was then precipitated from cold diethyl ether yielding the functionalized mPEG **2**.

One-pot mPEG-amine conjugation to BTF followed by diallyl-amine addition conjugate



1 3

mPEG-amine (100 mg, 5.0×10^{-2} mmol) and BTF (15 mg, 6.3×10^{-2} mmol) were dissolved in THF (2.0 mL) and left to stir at room temperature for 16 h. Subsequently, allyl amine (13 mg, 0.23 mmol) was added and the reaction left to stir for an additional 24 h. The polymer was then precipitated from cold diethyl ether yielding the functionalized mPEG **3**.



4

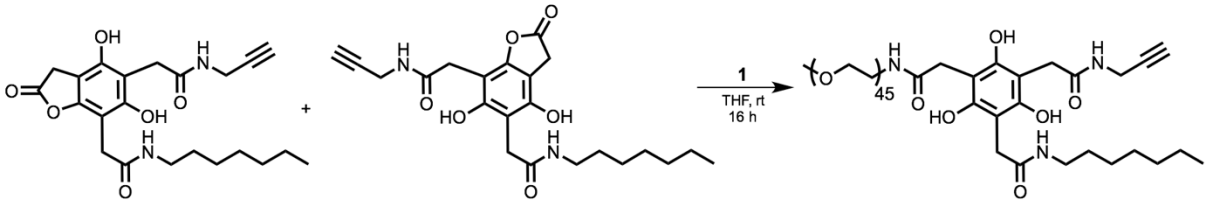
2-(4,6-Dihydroxy-2-oxo-5-(2-oxo-2-(prop-2-yn-1-ylamino)ethyl)-2,3-dihydrobenzofuran-7-yl)-*N*-heptylacetamide (4). To a solution of BTF (50 mg, 0.20 mmol) in dry DMF (2.0 mL) cooled to -41 °C was added propargylamine (11 mg, 0.20 mmol, 0.40 mL of 0.50 M solution in DMF). The reaction stirred for 1 h and then heptylamine (23 mg, 0.20 mmol, 0.81 mL of 0.25 M solution in DMF) was added. The resulting reaction mixture stirred at -41 °C for 8 h and was then poured in to EtOAc (75 mL). The organic solution was washed with water (5 × 25 mL) and water (1 × 25 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (40:60 EtOAc:Hex) to yield product **4** (0.42 g, 49%) as a mixture of regioisomers (43% and 57%).

^{1}H NMR (DMSO-d_6) δ 0.85 (t, 6H, J = 6.9 Hz), 1.24 (s, 6H), 1.40 (m, 4H), 3.04 (dq, 4H J = 5.5 Hz), 3.09 (t, 1H, J = 2.6 Hz), 3.11 (t, 1H, J = 2.5 Hz), 3.43 (s, 2H), 3.46 (s, 4H), 3.50 (s, 2H), 3.70 (s, 4H), 3.86 (ddd, 4H, J = 2.52 and 5.31 Hz), 8.26 (t, 1H, J = 5.5 Hz), 8.37 (t, 1H, J = 5.5 Hz), 8.50 (t, 1H, J = 5.5 Hz), 8.63 (t, 1H, J = 5.4 Hz), 9.71 (s, 1H), 9.92 (s, 1H), 10.7 (s, 1H) 10.9 (s, 1H).

^{13}C NMR (DMSO-d_6) δ 13.9, 22.0, 26.3, 28.1, 28.2, 28.3, 28.4, 28.7, 28.8, 30.4, 30.7, 30.8, 31.2, 31.2, 31.3, 31.6, 3.1.7, 39.0, 73.0, 73.2, 80.8, 81.1, 98.1, 98.5, 100.5, 100.7, 106.4, 106.6, 150.5, 150.7, 151.7, 152.1, 155.4, 155.5, 170.8, 171.4, 171.9, 172.6, 172.6, 174.6.

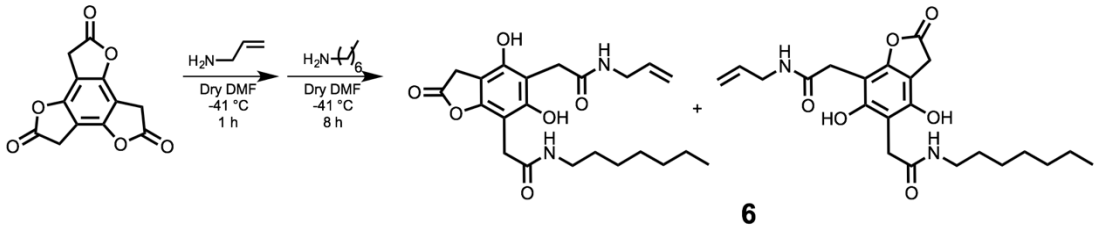
HRMS (ESI) calculated for $C_{22}H_{28}N_2O_6$ $[M+H]^+$ 417.2020, found 417.2039.

*mPEG-amine conjugation to BTF conjugate **4***



4 5

1 (37 mg, 1.8×10^{-2} mmol) and BTF conjugate **4** (9.5 mg, 2.3×10^{-2} mmol) were dissolved in THF (0.73 mL) and left to stir at room temperature for 16 h. The polymer was then precipitated from cold diethyl ether yielding the functionalized mPEG **5**.



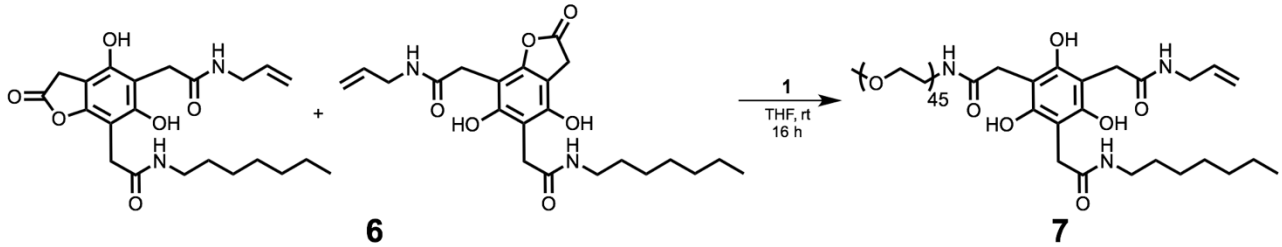
6

***N*-Allyl-2-(5-(2-(heptylamino)-2-oxoethyl)-4,6-dihydroxy-2-oxo-2,3-dihydrobenzofuran-7-yl)acetamide (6).** To a solution of BTF (40 mg, 0.16 mmol) in dry DMF (2.0 mL) cooled to -41 °C was added allylamine (9.1 mg, 0.16 mmol, 0.33 mL of 0.5 M solution in DMF). The resulting solution was allowed to stir for 1 h before the addition of heptylamine (18 mg, 0.16 mmol, 0.65 mL of 0.25 M solution in DMF). The solution then stirred for an additional 6 h at -41 °C before being poured in to EtOAc (75 mL). The organic solution was washed with water (5 × 25 mL) and brine (1 × 25 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (1:1 EtOAc:Hex) to yield product **6** (0.38 g, 56%) as a mixture of regioisomers (43% and 57%).

^{1}H NMR (DMSO-d_6) δ 0.85 (t, 6H, J = 6.5 Hz), 1.19 – 1.30 (m, 16H), 1.34 – 1.45 (m, 4H), 3.04 (dq, 4H J = 5.9 Hz), 3.45 (s, 2H), 3.46 (s, 2H), 3.49 (s, 2H), 3.50 (s, 2H), 3.65 – 3.73 (m, 8H), 5.01 – 5.08 (m, 2H), 5.09 – 5.12 (m, 1H), 5.15 – 5.18 (m, 1H), 5.70 – 5.85 (m, 2H), 8.20 (dt, 2H J = 5.0 Hz), 8.45 (dt, 2H, J = 5.0 Hz), 9.87 (s, 1H), 9.98 (s, 1H), 10.9 (s, 1H), 11.0 (s, 1H).

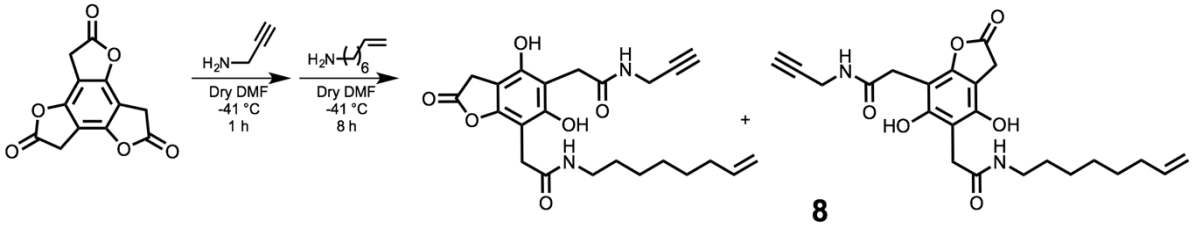
^{13}C NMR (DMSO-d_6) δ 13.9, 22.1, 26.3, 28.3, 28.4, 28.7, 28.8, 30.7, 30.8, 31.0, 31.2, 31.2, 31.3, 31.6, 31.7, 38.9, 39.0, 41.1, 41.2, 98.3, 98.5, 100.6, 100.7, 106.5, 106.7, 115.2, 115.4, 134.8, 134.9, 150.6, 150.7, 151.7, 151.9, 155.4, 155.5, 171.2, 171.7, 171.9, 172.4, 174.6, 174.6. HRMS (ESI) calculated for $C_{22}H_{30}N_2O_6$ $[M+H]^+$ 419.2177, found 419.2177.

*mPEG-amine conjugation to BTF conjugate **6***



6 **7**

1 (20 mg, 1.0 × 10^{-2} mmol) and BTF conjugate **6** (5.0 mg, 1.2 × 10^{-2} mmol) were dissolved in THF (0.20 mL) and left to stir at room temperature for 16 h. The polymer was then precipitated from cold diethyl ether yielding the functionalized mPEG **7**.



8

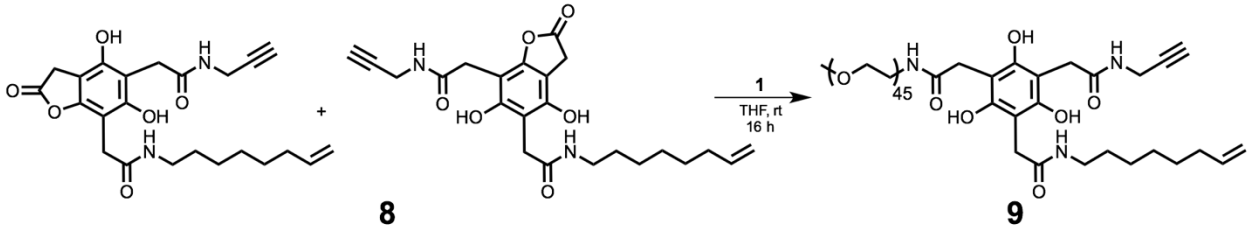
2-(4,6-Dihydroxy-2-oxo-7-(2-oxo-2-(prop-2-yn-1-ylamino)ethyl)-2,3-dihydrobenzofuran-5-yl)-*N*-(oct-7-en-1-yl)acetamide (8). To a solution of BTF (50 mg, 0.20 mmol) in dry DMF (2.0 mL) at -41 °C was added propargylamine (11 mg, 0.20 mmol, 0.40 mL of 0.50 M solution in DMF). The resulting solution was allowed to stir for 1.5 h before the addition of oct-7-en-1-amine (25 mg, 0.20 mmol, 0.81 mL of 0.25 M in DMF) was added and the solution stirred for 8 h at -41 °C. The reaction mixture was then poured in to EtOAc (75 mL). The organic solution was washed with water (5 × 25 mL) and brine (1 × 25 mL), dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography (1:1 EtOAc:Hex) to yield product **8** (29 mg, 34%) as a pair of inseparable regioisomers (34% and 66%).

^{1}H NMR (DMSO-d_6) δ 1.25–1.42 (m, 16H), 2.00 (q, 4H, J = 6.7 Hz), 3.04 (dq, 4H J = 5.6 Hz), 3.09 (t, 1H, J = 2.5 Hz), 3.11 (t, 1H, J = 2.4 Hz), 3.43 (s, 4H), 3.46 (s, 2H), 3.49 (s, 2H), 3.70 (s, 4H), 3.86 (ddd, 4H, J = 2.49 and 5.30 Hz), 4.91–5.02 (m, 4H), 5.72 – 5.85 (m, 2H), 8.26 (t, 1H, J = 5.3 Hz), 8.37 (t, 1H, J = 5.5 Hz), 8.50 (t, 1H, J = 5.5 Hz), 8.63 (t, 1H, J = 5.5 Hz), 9.71 (s, 1H), 9.92 (s, 1H), 10.7 (s, 1H), 10.9 (s, 1H).

^{13}C NMR (DMSO-d_6) δ 26.2, 28.2, 28.2, 28.6, 28.7, 30.4, 30.7, 30.9, 31.3, 31.7, 31.7, 33.1, 38.9, 38.9, 72.9, 73.2, 80.8, 81.1, 98.1, 98.5, 100.5, 100.7, 106.4, 106.6, 114.6, 138.8, 150.4, 150.7, 151.7, 152.1, 155.4, 155.5, 170.8, 171.5, 171.8, 172.6, 174.5, 174.6.

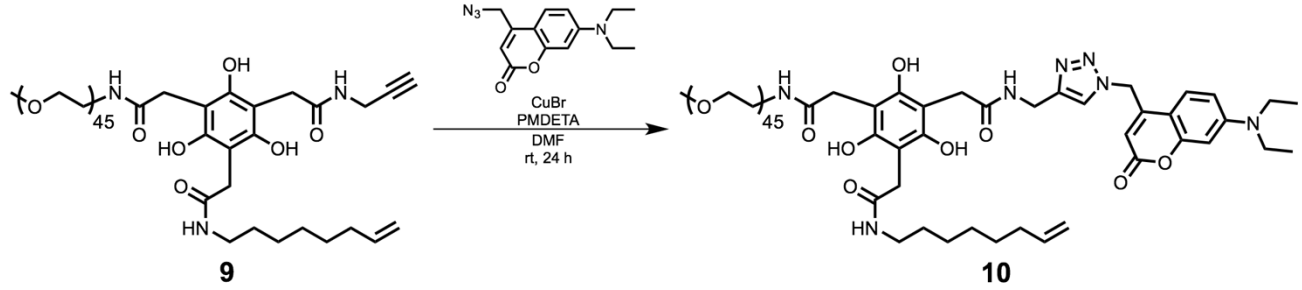
HRMS (ESI) calculated for $C_{23}H_{28}N_2O_6$ $[M+H]^+$ 429.2020, found 429.2033.

*mPEG-amine conjugation to BTF conjugate **8***



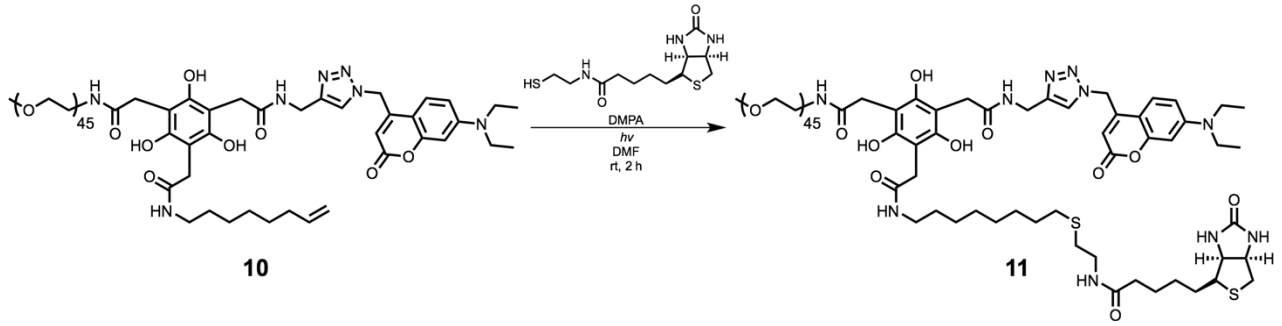
1 (35 mg, 1.8 × 10^{-2} mmol) and BTF conjugate **8** (9.4 mg, 2.2 × 10^{-2} mmol) were dissolved in THF (0.70 mL) and left to stir at room temperature for 16 h. The polymer was then precipitated from cold diethyl ether yielding the functionalized mPEG **9**.

*Copper-mediated azide-alkyne cycloaddition of mPEG-BTF conjugate **9** and azido coumarin*



mPEG-BTF conjugate **9** (50 mg, 2.1 × 10^{-2} mmol), azido coumarin (6.2 mg, 2.3 × 10^{-2} mmol), and *N ,N ,N′ ,N′′, N′′*-pentamethyldiethylene triamine (2.6 mg, 1.5 × 10^{-2} mmol) were dissolved in DMF (0.75 mL) in a Schlenk flask and the solution was purged with argon for 20 min. The reaction was placed in liquid N_2 and Cu(I)Br (1.5 mg, 1.0 × 10^{-2} mmol) was added on top the frozen solution. The head-space was purged with argon for an additional 20 min, the solution thawed, and the reaction set to stir for 24 h at room temperature. The reaction was quenched by exposure to air, filtered through neutral alumina, and polymer **10** was precipitated from cold diethyl ether.

*Thiol-ene of polymer **10** with 2-mercaptoethylbiotin*



10 (30 mg, 1.1 × 10^{-2} mmol), 2-mercaptoethylbiotin (17 mg, 5.5 × 10^{-2} mmol), and 2,2-dimethoxy-2-phenylacetophenone (14 mg, × 10^{-2} mmol) were dissolved in DMF (0.50 mL) in a Schlenk flask, wrapped in foil, and purged with argon for 20 min. The flask was then placed under UV irradiation for 2 h. The reaction was quenched

by exposure to air and polymer **11** was purified via dialysis against DI water (1000 MCWO tubing) and lyophilization.

Avidin conjugations

*Purification of **11** using avidin agarose gel beads*

11 (1.5 mg, 0.5 mL of a 3.0 mg/mL PBS solution) was added to a suspension of avidin agarose gel beads (0.50 mL) in a centrifuge tube. The mixture was agitated for 2 h at room temperature. Subsequently, the solution was centrifuged, the supernatant was removed, PBS was added (0.50 mL), and the solution was agitated for 1 h at room temperature. This cycle was repeated 5× until the supernatant appeared colorless, while the gel retained a light yellow coloration. The avidin-agarose gel beads were added to a biotin solution in PBS (1.0 mL, ca. 1.00×10^{-2} M) and stirred for 48 h at room temperature. Isolation of the polymer was conducted via 4 cycles of centrifugation, supernatant collection, and addition of PBS. The collected supernatant was combined, dialyzed against DI water (1000 MWCO tubing), and lyophilized yielding the polymer product **11**.

Polymer conjugation to Avidin

Biotin-containing polymer conjugate **11** (1.5 mg, 4.97×10^{-4} mmol) and avidin (0.60 mg, 9.95×10^{-6} mmol) were dissolved in PBS (1.2 mL) and stirred at room temperature for 16 h. Sodium dodecyl sulfate-polyacrylamide gel electrophoresis was performed using aliquots taken directly from this solution.

Spectra and Additional Figures

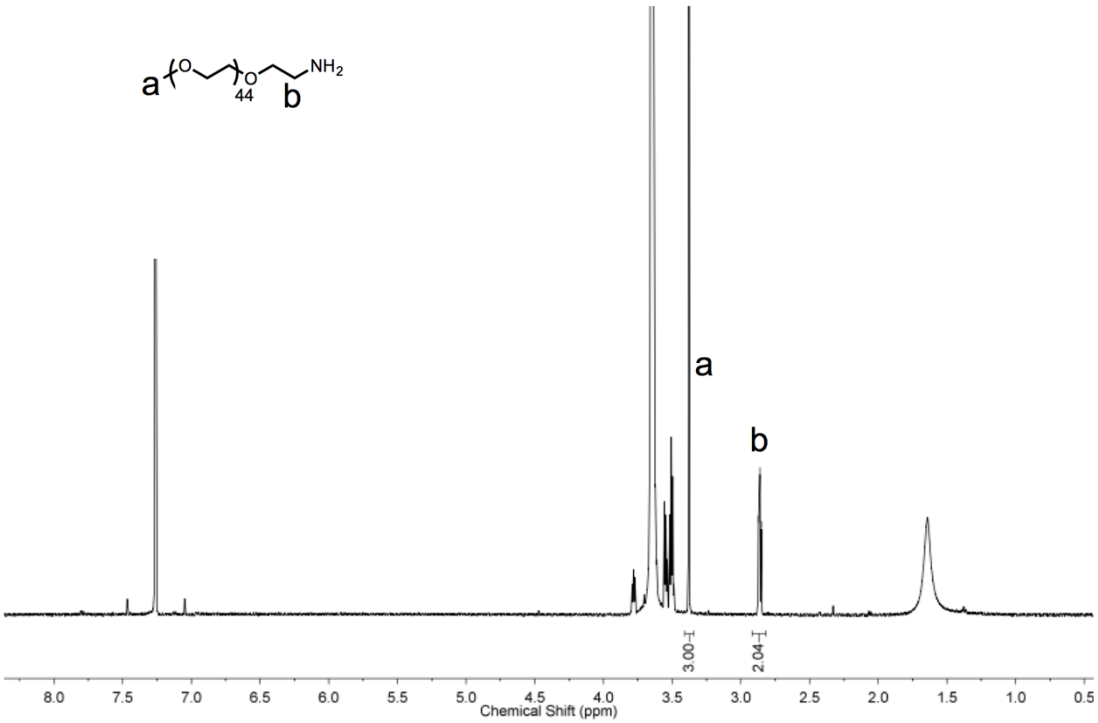


Figure S1. ^{1}H NMR spectrum of compound 1.

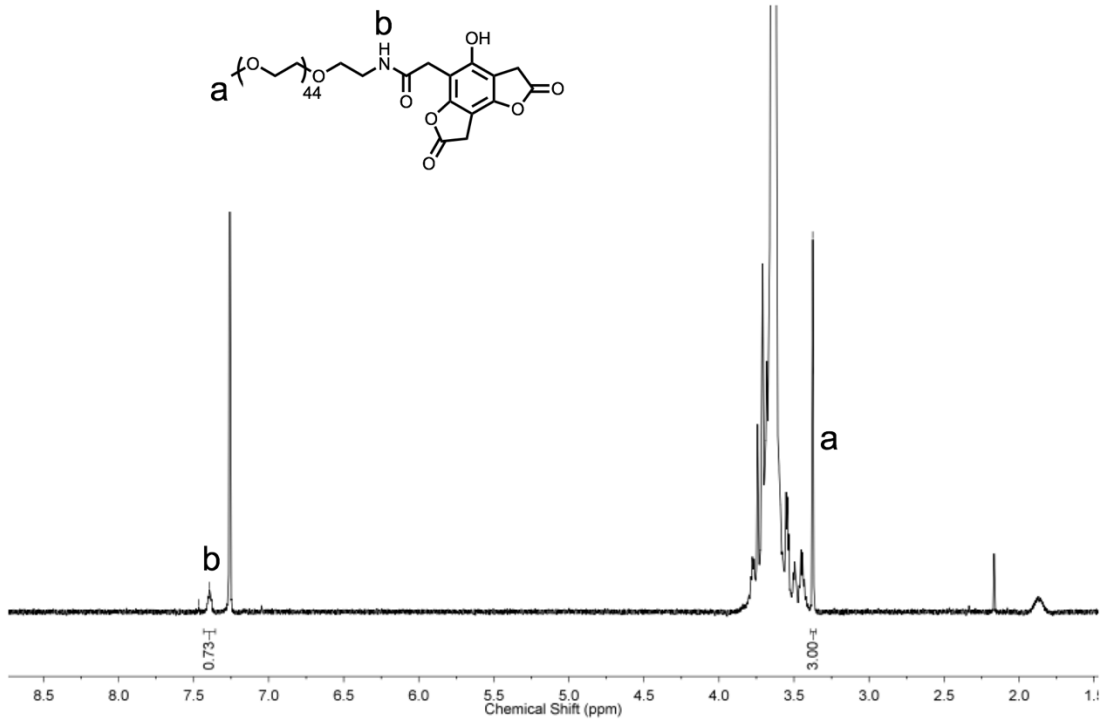


Figure S2. ^{1}H NMR spectrum of compound 2.

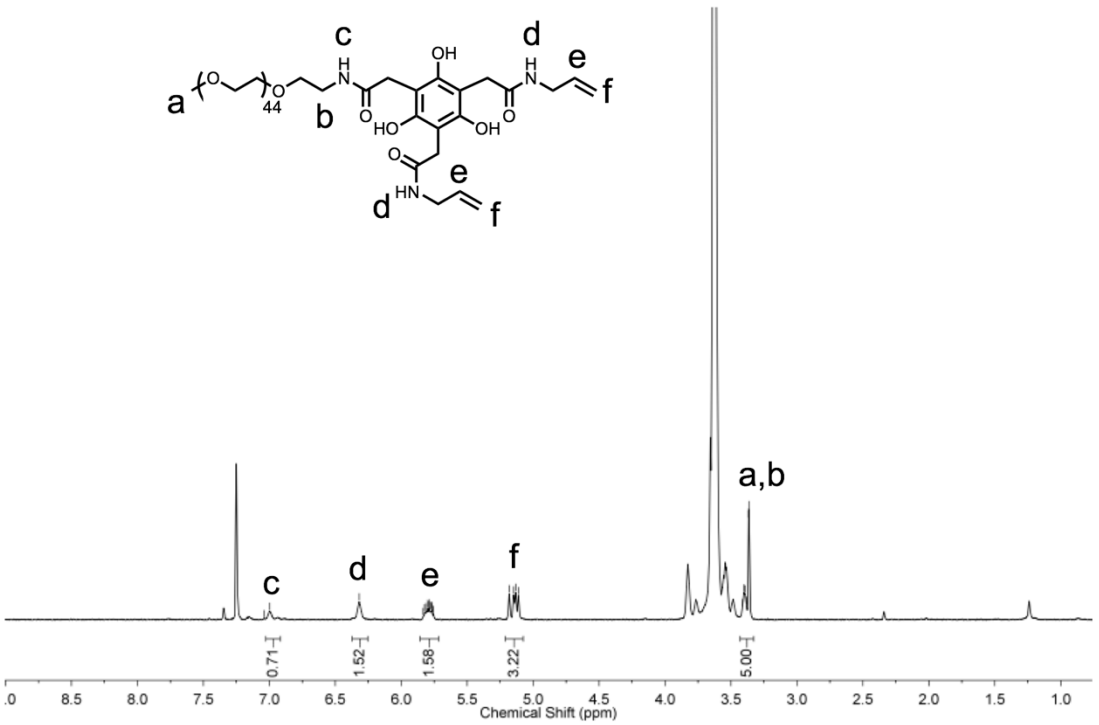


Figure S3. ^{1}H NMR spectrum of compound 3.

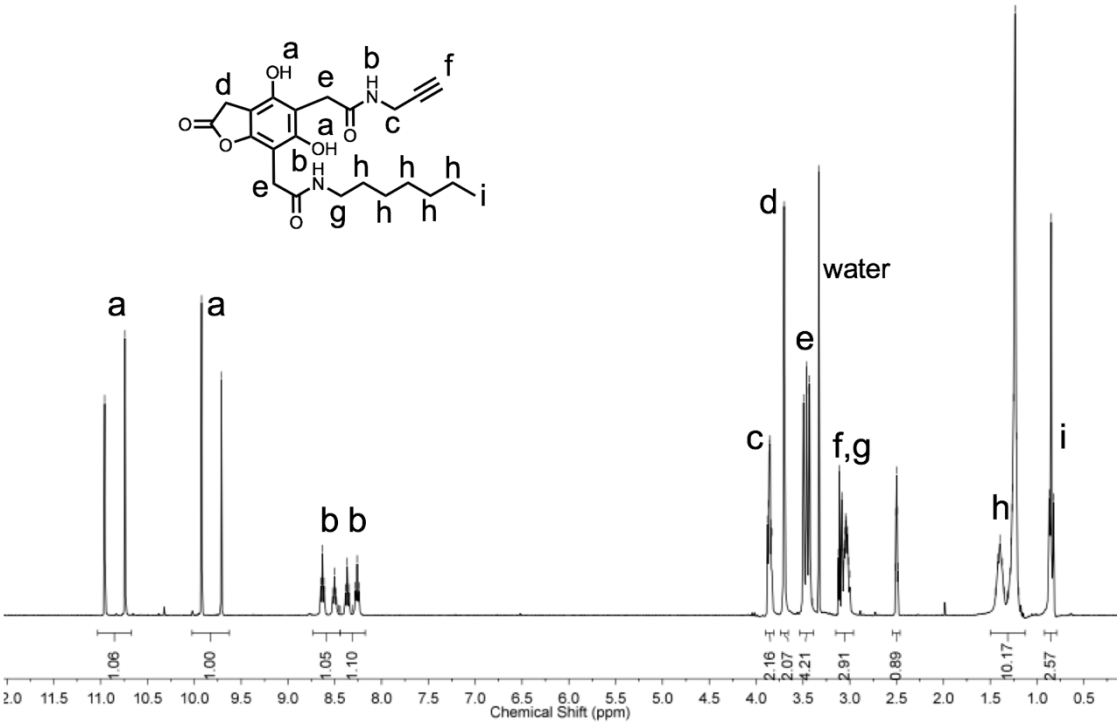


Figure S4. ^{1}H NMR spectrum of compound 4.

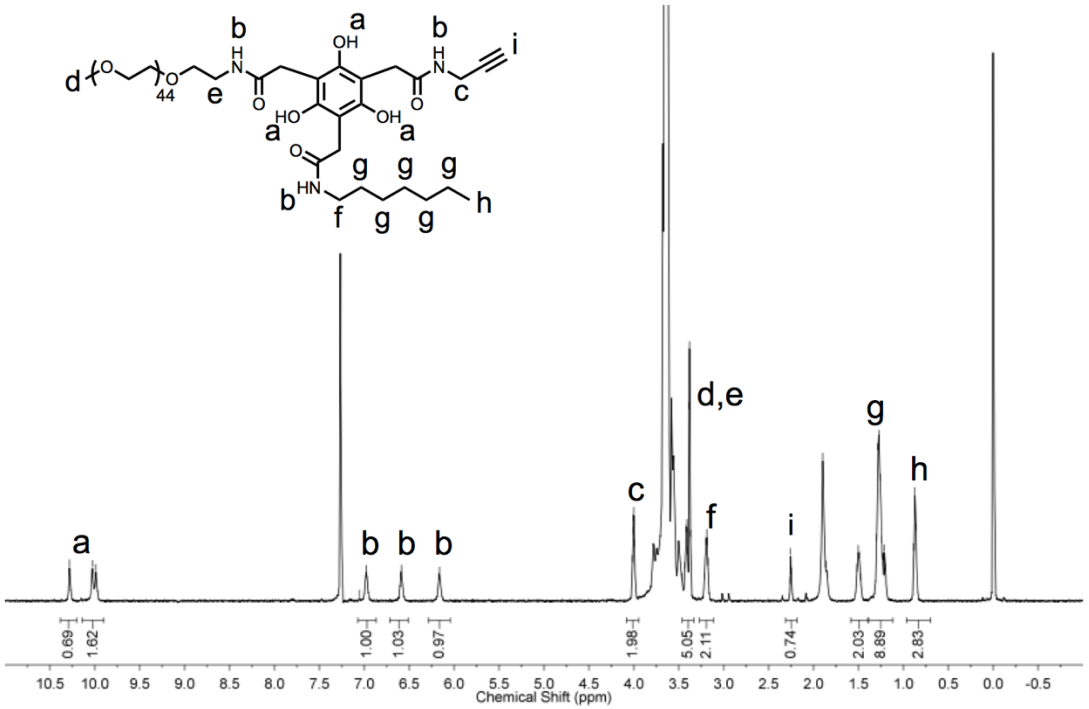


Figure S5. ^{1}H NMR spectrum of compound 5.

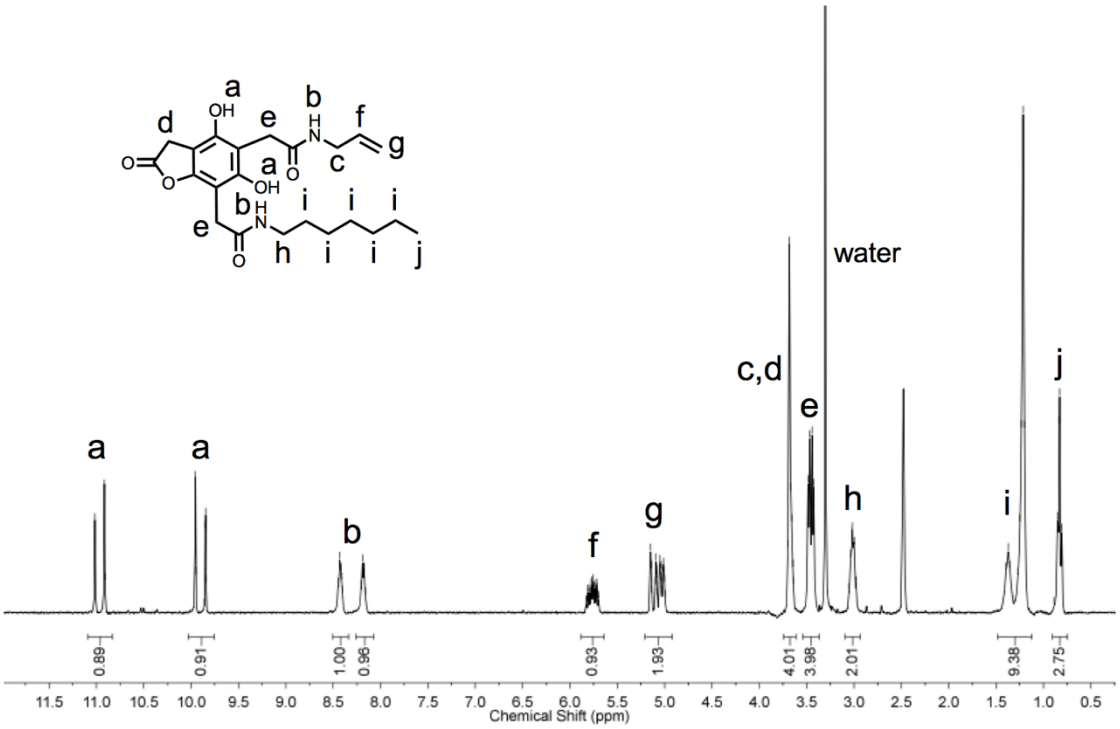


Figure S6. ^{1}H NMR spectrum of compound 6.

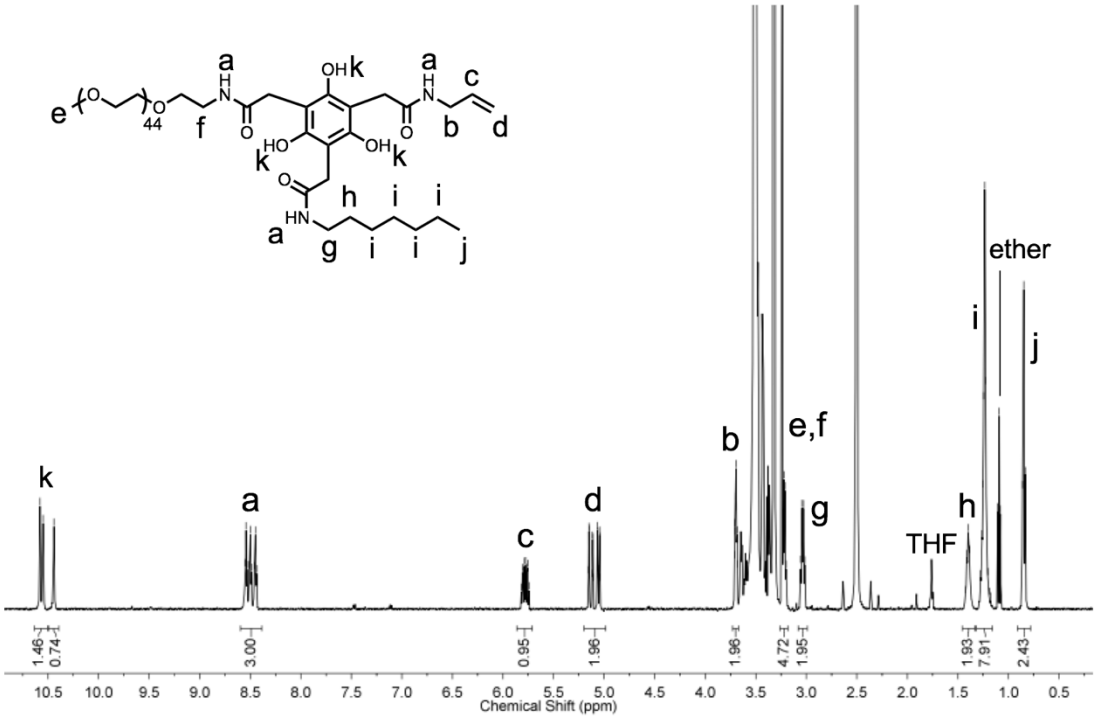


Figure S7. ^{1}H NMR spectrum of compound 7.

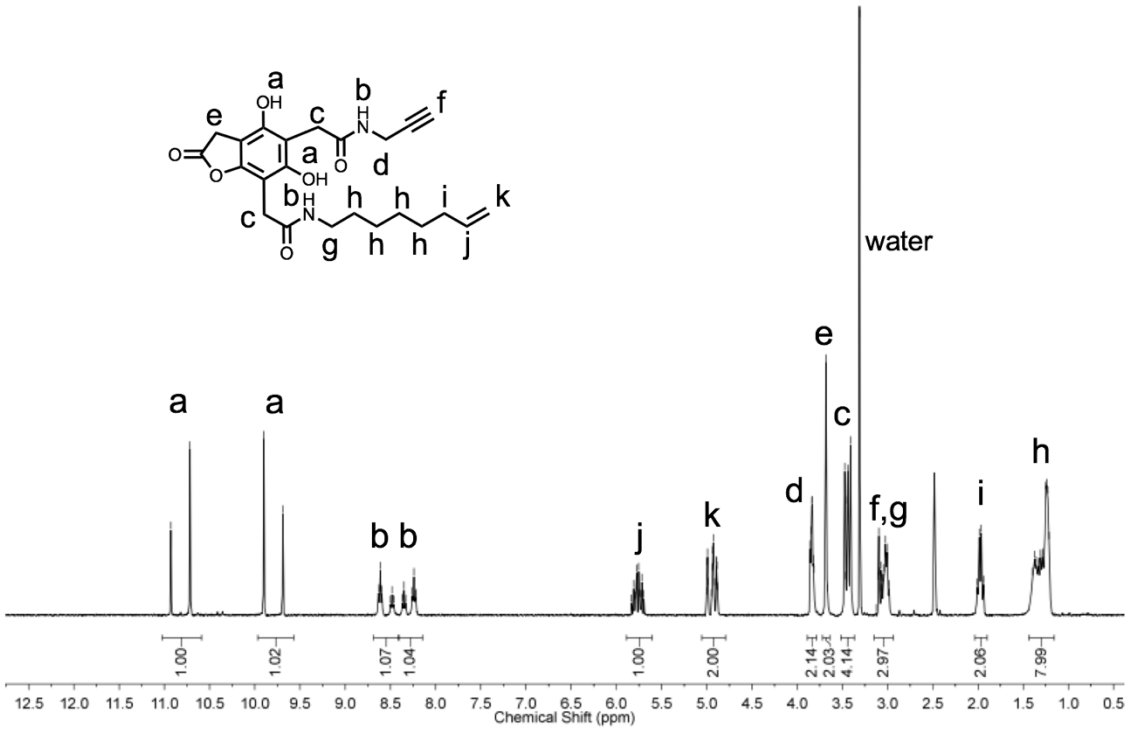


Figure S8. ^{1}H NMR spectrum of compound 8.

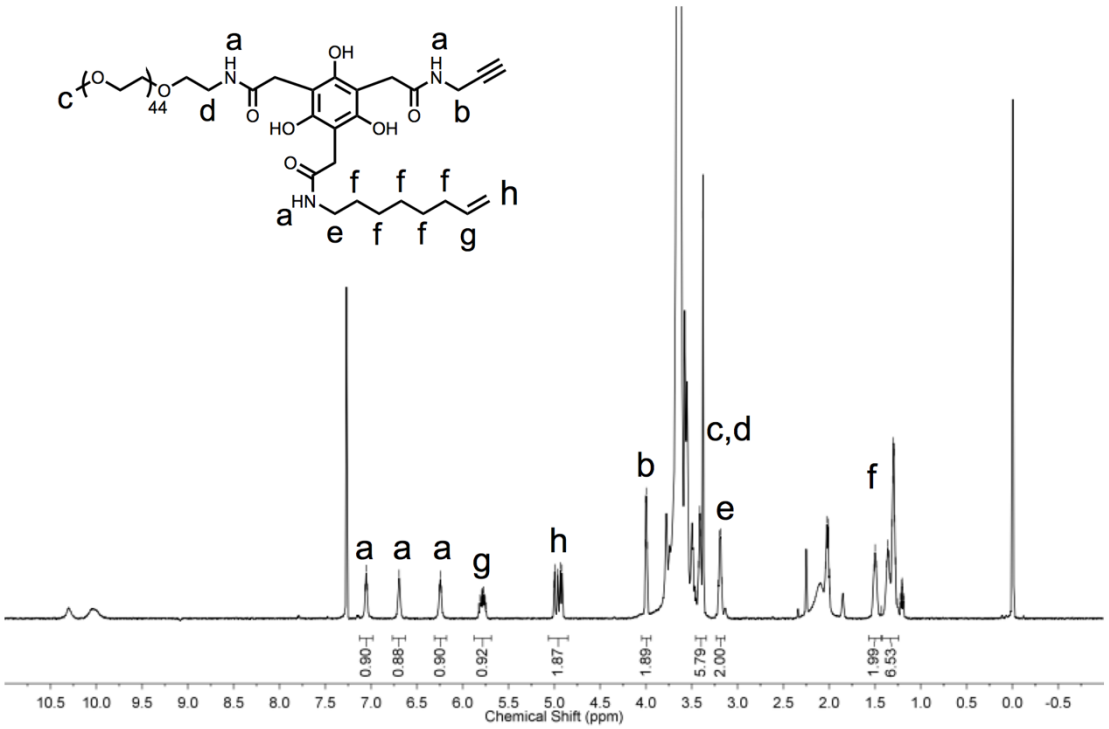


Figure S9. ^{1}H NMR spectrum of compound 9.

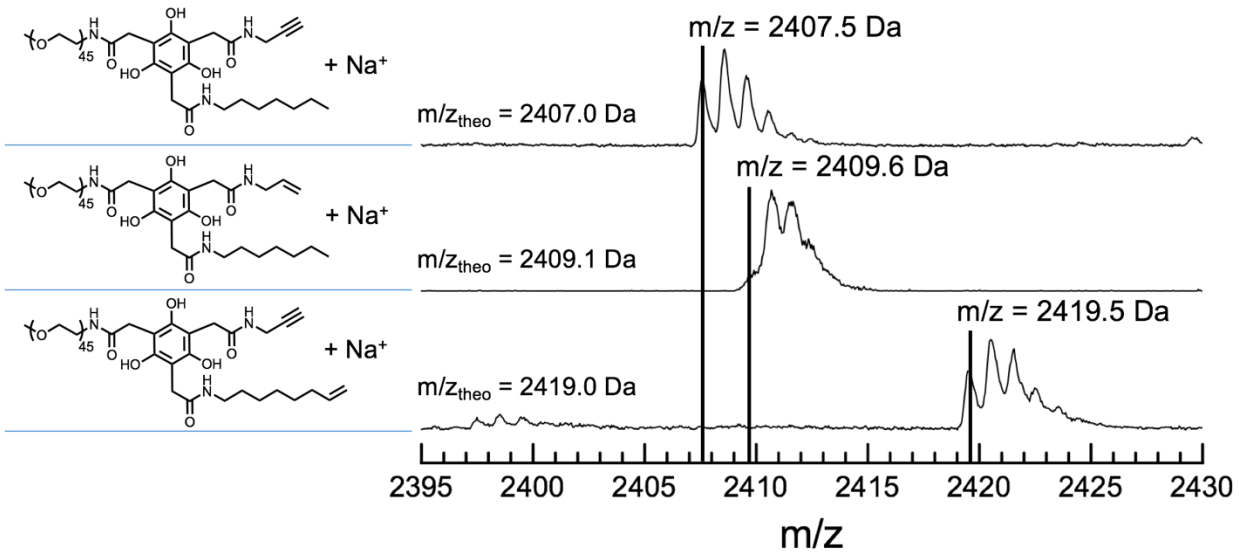


Figure S10. Matrix-assisted laser desorption-ionization time-of-flight mass spectrum of compounds 5, 7, and 9 confirming quantitative end-group functionalization.

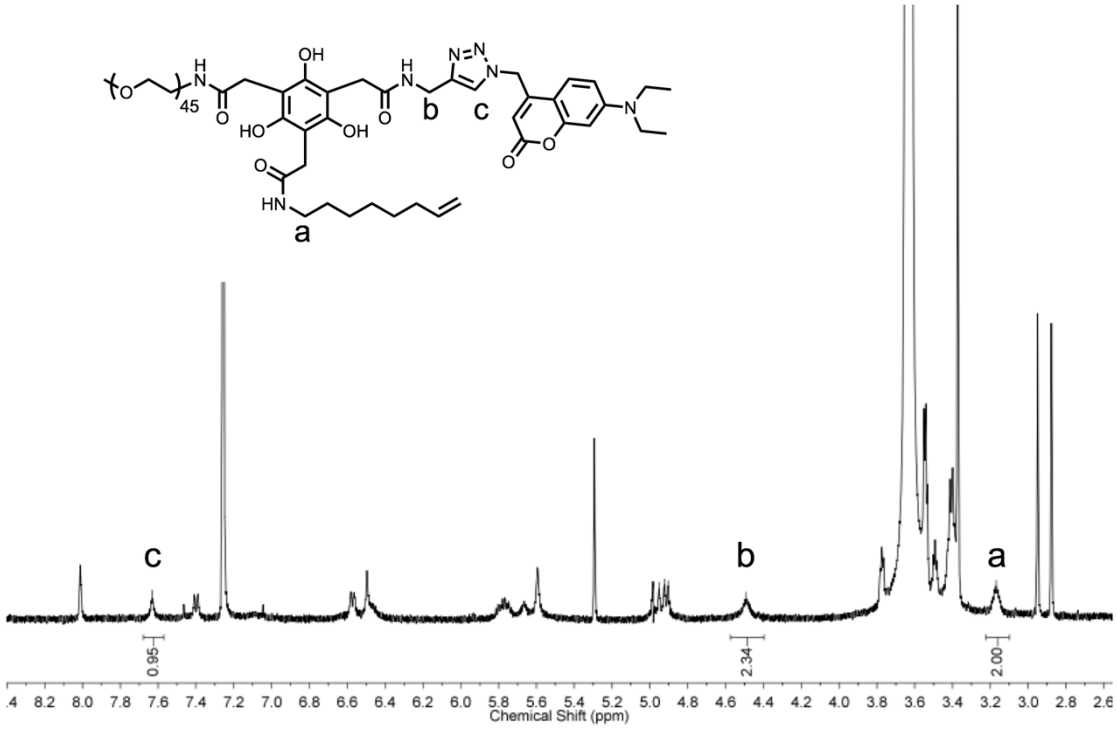


Figure S11. ^{1}H NMR spectrum of compound 10.

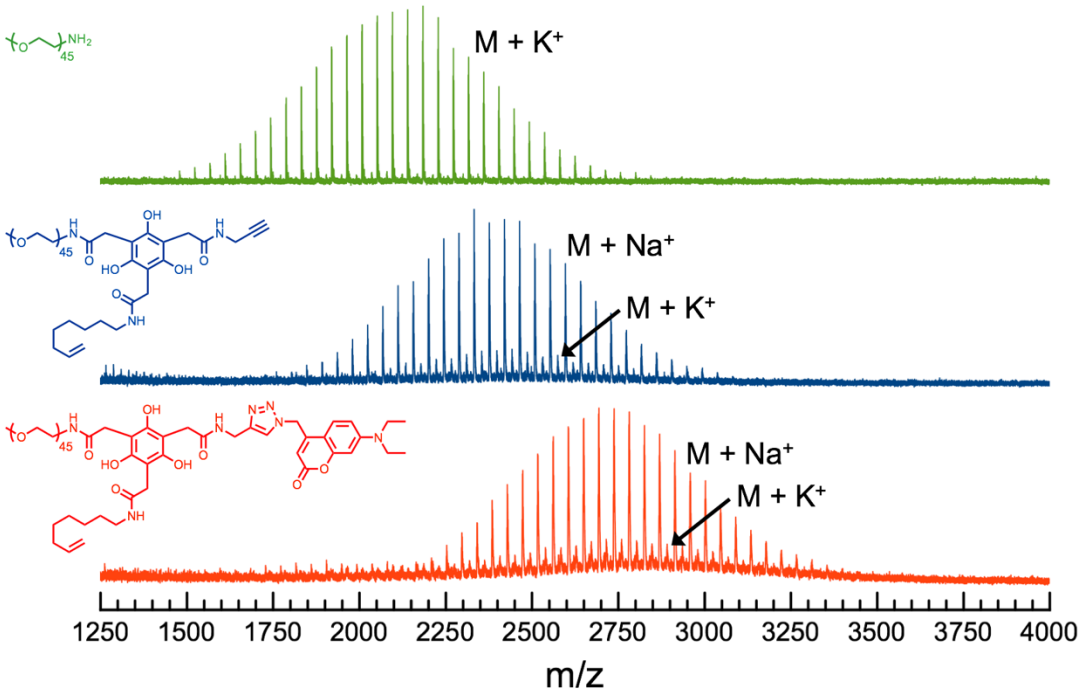


Figure S12. Matrix-assisted laser desorption-ionization time-of-flight mass spectrum of compounds 1, 9, and 10, confirming the presence of the dye-containing ω,ω-heterodifunctionalized adduct.

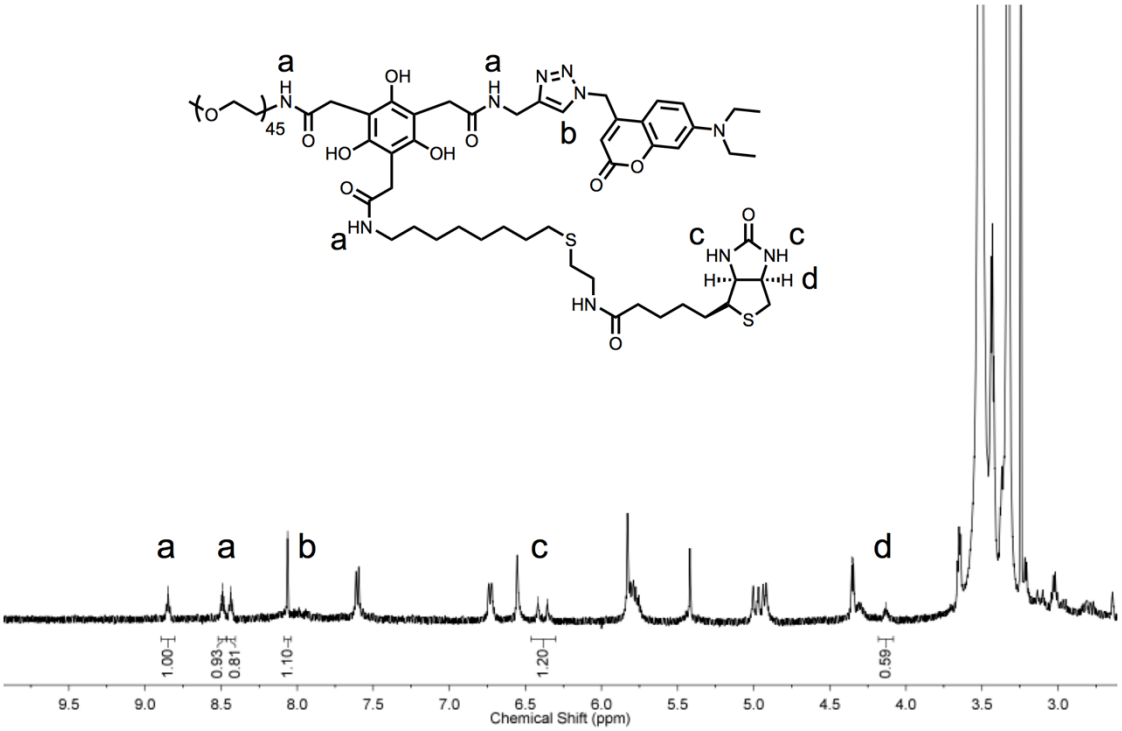


Figure S13. ^{1}H NMR spectrum of compound 11.

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