Supporting information for

Synthesis of Photodegradable Macromers for Conjugation and Release of Bioactive Molecules

Donald R. Griffin, Jessica L. Schlosser, Sandra F. Lam, Thi H. Nguyen, Heather D. Maynard, and Andrea M. Kasko*

Materials. Acryloyl chloride (AC) (Alfa Aesar, 96%), methacryloyl chloride (Acros, 97%), triethylamine (TEA) (Fisher Scientific, 99%), ammonium persulfate (AP) (J.T. Baker, 98%), tetramethylethylenediamine (TEMED) (EMD, 99%), biotin (Fisher Bioreagents, >99%) *N,N*-dimthylformamide (DMF) (ACS grade, VWR International) dimethylsulfoxide (DMSO) (EMD, 99.9%), tetrahydrofuran (THF) (Fisher Scientific, 99.9%), chloroform (Fisher Scientific, 99.9%), dichloromethane (DCM) (Fisher Scientific, 99.9%), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide-HCl (EDC) (CreoSalus), *N,N'*-Dicyclohexylcarbodiimide (DCC) (Acros, 99%), 4-dimethyl-aminopyridine (DMAP) (Acros Organics, 99%), *p*-nitrophenylacetate (Alfa Aesar, 98+%), ammonium hydroxide (EMD, 30% aq.), bismuth trichloride (Alfa Aesar, 98%), succinic anhydride (Acros Organics, 99%), *N*-hydroxysuccinimide (Alfa Aesar, 98%), di-*tert*-butyl-dicarbonate (AK Scientific), fluorescein-NHS (Pierce), *p*-toluene sulfonyl chloride (Acros Organics, 99%), poly(ethylene glycol) methacrylate (M_n = 526) (PEG 526MA) (Aldrich Chemistry), phosphorous pentachloride (Alfa Aesar, 98%), phosphorous tribromide (Strem Chemicals), potassium hydroxide (Fisher Scientific), and potassium fluoride (J.T. Baker, 99.8%). AC was distilled under vacuum into an airfree flask and stored under N_2 at -20^{o}C in the absence of light. TEA was distilled under N_2 and stored over KOH pellets. DCM was distilled under N_2 and stored under N_2 in a dry, airfree flask. THF was distilled from CaH_2 and stored under Ar in a dry, airfree flask. All other chemicals were used as received. 2-(Pyridin-2-yldisulfanyl)ethanol[1], 4-(4-(1-hydroxyethyl)-2-methoxy-5-nitrophenoxy)butanoic acid, 4-(4-(1-acryloyloxyethyl)-2-methoxy-5-nitrophenoxy)butanoic acid and poly(ethylene glycol) diacrylate were synthesized as previously reported.[2]

Techniques

All reactions were performed under an N_2 atmosphere using a Schlenk line unless noted otherwise. ^{1}H NMR spectra (δ ppm) were recorded on a Bruker Biospin Ultrashield 300MHz NMR Spectrometer.

Synthesis

Tos-PEG526-methacrylate: PEG 526MA (5.00 g, 9.51 mmol) and *p*-toluene sulfonyl chloride (1.99 g, 10.5 mmol) were dissolved in DCM (9.5 mL) and cooled to 0°C. To this mixture potassium hydroxide (4.27 g, 76.1 mmol) was slowly added and stirred for 3 hours. To collect the reaction, DCM (9.5 mL) and cold water (19 mL) were added while stirring followed by removal of the organic layer. The organic layer was then washed with water (3 x eq. vol.), dried with $MgSO_4$, and concentrated to dryness via rotary evaporation to yield 5.19 g (85%) as a viscous pale yellow liquid. ^{1}H NMR ($CDCl_3$): δ= 7.78 (d, 2-H[1], Ar-**H**), δ= 7.36 (d, 2-H[1], Ar-**H**), δ= 6.18, 5.58 (s, s, OC(O)C(CH_3)C**H$_2$**), δ= 4.30 (t, ROC**H$_2$**$CH_2(OCH_2CH_2)_{11}$), δ= 4.15 (t, C**H$_2$**OC(O)C(CH_3)CH_2), δ= 3.55-3.78 (m, 40-H[1]), δ= 2.45 (s, Ar-C**H$_3$**), δ= 1.95 (s, OC(O)C(C**H$_3$**)CH_2).

PEG526-methacrylate-4-(4-(1-hydroxyethyl)-2-methoxy-5-nitrophenoxy)butanoate: 4-(4-(1-Hydroxyethyl)-2-methoxy-5-nitrophenoxy)butanoic acid (3.00 g, 10.0 mmol) was dissolved in a solution of DMF (30 mL) and potassium fluoride (1.16 g, 20.0 mmol), and stirred for 10 minutes at room temperature[3]. To this mixture tos-PEG526-methacrylate (4.52 g, 7.01 mmol) in DMF (5.0 mL) was added and the solution was stirred for an additional 48 hours at 50°C. The reaction was diluted with DCM (50 mL), washed with water (3 x eq. vol.), and dried with $MgSO_4$. The solution was treated with activated carbon, passed through a basic alumina plug with DCM as the eluent, and concentrated to dryness via rotary evaporation to yield 3.41 g (52%) as a viscous, pale yellow liquid. ^{1}H NMR (*d_6*-Acetone): δ= 7.57 (s, Ar-**H** *ortho* to Ar-NO_2), δ=7.48 (s, Ar-**H** *met*a to Ar-NO_2), δ=5.46 (m, Ar-C**H**(CH_3)OH), δ=6.08, 5.62 (s, s, OC(O)C(CH_3)C**H$_2$**), δ=4.53 (d, Ar-CH(CH_3)O**H**), δ=4.25 (t, C**H$_2$**OC(O)C(CH_3)CH_2), δ=4.20 (t, Ar-OCH_2CH_2C**H$_2$**CO_2CH_2), δ=4.15 (t, Ar-OC**H$_2$**$CH_2CH_2CO_2CH_2$), δ=3.98 (s, Ar-OC**H$_3$**),δ=3.70 (t, C**H$_2$**CH_2OC(O)C(CH_3)CH_2), δ=3.65 (t, Ar-$OCH_2CH_2CH_2CO_2CH_2$C**H$_2$**O), δ=3.55-3.60 (m, (OC**H$_2$**C**H$_2$**)$_9CH_2CH_2$OC(O)C(CH_3)CH_2), δ=2.58 (t, Ar-OCH_2CH_2C**H$_2$**CO_2CH_2), δ=2.15 (m, Ar-OCH_2C**H$_2$**$CH_2CO_2CH_2$), δ=1.92 (s, OC(O)C(C**H$_3$**)CH_2), δ=1.48 (d, Ar-CH(C**H$_3$**)OH).

PEG526-methacrylate-4-(1-(4-(3-carboxypropoxy)-5-methoxy-2-nitrophenoxy)ethoxy-4-butanoate: PEG526-methacrylate-4-(4-(1-hydroxyethyl)-2-methoxy-5-nitrophenoxy)butanoate (0.50 g, 0.62 mmol), succinic anhydride (0.124 g, 1.24 mmol), and DMAP (0.0076 g, 0.062 mmol) were dissolved in DMF (3 mL) and heated to 40 °C overnight. The solution was diluted with DCM (30 mL), washed with water (3 x eq. vol.), dried with $MgSO_4$, passed through a silica plug using DCM as the eluent and concentrated to dryness via rotary evaporation to yield 0.47 g (84%) as a viscous, pale yellow liquid. ^{1}H NMR (d_6-DMSO): δ= 7.52 (s, Ar-**H** *ortho* to Ar-NO_2), δ=7.12 (s, Ar-**H** *meta* to Ar-NO_2), δ=6.25 (m, Ar-C**H**(CH_3)OC(O)$CH_2CH_2CO_2$H), δ=6.00, 5.65 (s, s, OC(O)C(CH_3)C**H$_2$**), δ=4.15 (t, C**H$_2$**OC(O)C(CH_3)CH_2), δ=4.10 (t, Ar-OCH_2CH_2C**H$_2$**CO_2CH_2), δ=4.05 (t, Ar-OC**H$_2$**$CH_2CH_2CO_2CH_2$), δ=3.85 (s, Ar-OC**H$_3$**),δ=3.62 (t, C**H$_2$**CH_2OC(O)C(CH_3)CH_2), δ=3.55 (t, Ar-$OCH_2CH_2CH_2CO_2CH_2$C**H$_2$**O), δ=3.40-3.50 (m, (C**H$_2$**C**H$_2$**O)$_9$$CH_2CH_2$OC(O)C($CH_3$)$CH_2$), δ=2.60 (m, Ar-CH($CH_3$)OC(O)$CH_2$C**H$_2$**$CO_2$H), δ=2.50 (m, Ar-CH($CH_3$)OC(O)C**H$_2$**$CH_2CO_2$H), δ=2.45 (t, Ar-$OCH_2CH_2$C**H$_2$**$CO_2CH_2$), δ=1.95 (m, Ar-$OCH_2$C**H$_2$**$CH_2CO_2CH_2$), δ=1.82 (s, OC(O)C(C**H$_3$**)CH_2), δ=1.55 (m, Ar-CH(C**H$_3$**)OC(O)$CH_2CH_2CO_2$H).

PEG526-methacrylate-4-(2-methoxy-5-nitro-4-(1-(4-oxo-4-(2-(pyridin-2-yldisulfanyl)ethoxy)butanoyl)oxy))butanoate: PEG526-methacrylate-4-(1-(4-(3-carboxypropoxy)-5-methoxy-2-nitrophenoxy)ethoxy-4-butanoate (0.10 g, 0.11 mmol), 2-(pyridin-2-yldisulfanyl)ethanol (0.0196 g, 0.105 mmol), EDC (0.0264 g, 0.138 mmol), and DMAP (0.002 g, 0.0165 mmol) were dissolved in DCM (5 mL) and stirred overnight. The reaction was purified via gradient column chromatography (DCM:EtOAc) and the product was concentrated to dryness via rotary evaporation to yield 0.023 g (20%) as a viscous, pale yellow liquid. ^{1}H NMR (d_6-DMSO): δ=8.42, 7.82, 7.72, 7.25 (d, d, t, t, Ar-CH(CH_3)OC(O)$CH_2CH_2CO_2CH_2CH_2SS(C_5NH_4)$), δ= 7.52 (s, Ar-**H** *ortho* to Ar-NO_2), δ=7.12 (s, Ar-**H** *meta* to Ar-NO_2), δ=6.25 (m, Ar-C**H**(CH_3)OC(O)), δ=6.00, 5.65 (s, s, OC(O)C(CH_3)C**H$_2$**), δ=4.20 (t, CO_2C**H$_2$**$CH_2SS(C_5NH_4)$), δ=4.15 (t, C**H$_2$**OC(O)C(CH_3)CH_2), δ=4.10 (t, Ar-

$OCH_2CH_2C\mathbf{H_2}CO_2CH_2$), δ=4.05 (t, Ar-$OC\mathbf{H_2}CH_2CH_2CO_2CH_2$), δ=3.85 (s, Ar-$OC\mathbf{H_3}$), δ=3.62 (t, $C\mathbf{H_2}CH_2OC(O)C(CH_3)CH_2$), δ=3.55 (t, Ar-$OCH_2CH_2CH_2CO_2CH_2C\mathbf{H_2}O$), δ=3.40-3.50 (m, $(C\mathbf{H_2}C\mathbf{H_2}O)_9CH_2CH_2OC(O)C(CH_3)CH_2$), δ=2.62, 2.55 (t, t, Ar-$CH(CH_3)OC(O)C\mathbf{H_2}C\mathbf{H_2}CO_2$), δ=2.45 (t, Ar-$OCH_2CH_2C\mathbf{H_2}CO_2CH_2$), δ=1.95 (m, Ar-$OCH_2C\mathbf{H_2}CH_2CO_2CH_2$), δ=1.82 (s, $OC(O)C(C\mathbf{H_3})CH_2$), δ=1.55 (m, Ar-$CH(C\mathbf{H_3})OC(O)CH_2CH_2CO_2$.

4-(4-(1-Aminoethyl)-2-methoxy-5-nitrophenoxy)butanoic acid: 4-(4-(1-Hydroxyethyl)-2-methoxy-5-nitrophenoxy)butanoic acid (3.40 g, 11.4 mmol) was reacted with phosphorous tribromide (3.25 mL, 34.2 mmol) in DCM (34 mL), stirred at RT, and monitored by TLC (3:2 EtOAc:DCM; R_f = 0.8) until completion. The solution was then washed with water (3 x eq. vol.), dried with $MgSO_4$, and concentrated to dryness via rotary evaporation to yield a yellow solid (3.30 g, 9.11 mmol). The solid was immediately dissolved in THF (16.5 mL) and added to aqueous ammonium hydroxide (122 mL) at room temperature. The mixture was stirred overnight, followed by removal of ammonia from solution under reduced pressure. The solution was acidified with HCl and washed with ethyl acetate (3 x eq. vol.) to remove 4-(4-(1-hydroxyethyl)-2-methoxy-5-nitrophenoxy)butanoic acid from solution. The product was then concentrated to dryness via rotary evaporation and recrystallized with MeOH to yield 1.70 g (63%) as a pale yellow solid. ^{1}H NMR (d_6-DMSO): δ=8.63 (d, Ar-$CH(CH_3)N\mathbf{H_2}$), δ= 7.57 (s, Ar-**H** *ortho* to Ar-NO_2), δ=7.52 (s, Ar-**H** *meta* to Ar-NO_2), δ=4.92 (m, Ar-$C\mathbf{H}(CH_3)NH_2$), δ=4.12 (t, Ar-$OC\mathbf{H_2}CH_2CH_2CO_2H$), δ=3.95 (s, Ar-$OC\mathbf{H_3}$), δ=2.45 (t, Ar-$OCH_2CH_2C\mathbf{H_2}CO_2H$), δ=1.98(s, Ar-$OCH_2C\mathbf{H_2}CH_2CO_2H$), δ=1.58 (d, Ar-$CH(C\mathbf{H_3})NH_2$).

4-(4-(1-(Boc-amino)ethyl)-2-methoxy-5-nitrophenoxy)butanoic acid: 4-(4-(1-Aminoethyl)-2-methoxy-5-nitrophenoxy)butanoic acid (1.20 g, 4.01 mmol) was dissolved in a mixture of THF (4 mL) and water (4 mL) before cooling to 0°C. To this mixture, di-*tert*-butyl-dicarbonate (1.05 g, 4.83 mmol) and sodium bicarbonate (1.01 g, 12.0 mmol) were added and allowed to stir overnight. The solution was then acidified with citric acid, resulting in a pale yellow precipitate, which was recrystallized from MeOH to

yield pale yellow crystals (0.96 g, 60%).[1]H NMR (*d_6*-DMSO): δ=7.60 (d, Ar-CH(CH_3)N**H**C(O)OC(CH_3)$_3$), δ= 7.48 (s, Ar-**H** *ortho* to Ar-NO_2), δ=7.21 (s, Ar-**H** *meta* to Ar-NO_2), δ=5.13 (m, Ar-C**H**(CH_3)NHC(O)OC(CH_3)$_3$), δ=4.12 (t, Ar-OC**H$_2$**$CH_2CH_2CO_2H$), δ=3.90 (s, Ar-OC**H$_3$**), δ=2.40 (t, Ar-OCH_2CH_2C**H$_2$**CO_2H), δ=1.95(s, Ar-OCH_2C**H$_2$**CH_2CO_2H), δ=1.35 (d, Ar-CH(CH_3)N**H**C(O)OC(CH_3)$_3$), δ=1.32 (s, 9H, Ar-CH(CH_3)NHC(O)OC(C**H$_3$**)$_3$).

PEG526-methacrylate-4-(4-(1-(boc-amino)ethyl)-2-methoxy-5-nitrophenoxy)butanoate: 4-(4-(1-(Boc-amino)ethyl)-2-methoxy-5-nitrophenoxy)butanoic acid (0.385 g, 0.966 mmol), PEG 526MA (0.339 g, 0.644 mmol), EDC (0.241 g, 1.26 mmol), and DMAP (0.0118 g, 0.0966 mmol) were added to DCM (5 mL) and stirred overnight at RT. The mixture was then diluted with DCM (25 mL), washed with water (3 x eq. vol.), dried with $MgSO_4$, and passed through basic alumina with DCM as the eluent. The product was concentrated to dryness via rotary evaporation to yield 0.484 g (83%) as a viscous, pale yellow liquid. [1]H NMR ($CDCl_3$): δ= 7.55 (s, Ar-C(CH3)N**H**C(O)OC(C**H$_3$**)$_3$), δ= 7.26 (s, Ar-**H** *ortho* to Ar-NO_2), δ=6.92 (s, Ar-**H** *meta* to Ar-NO_2), δ=6.11, 5.58 (s, s, OC(O)C(CH_3)C**H$_2$**), δ=5.32 (m, Ar-C**H**(CH_3)NHBoc), δ=4.30 (t, C**H$_2$**OC(O)C(CH_3)CH_2), δ=4.26 (t, Ar-OCH_2CH_2C**H$_2$**CO_2CH_2), δ=4.10 (t, Ar-OC**H$_2$**$CH_2CH_2CO_2CH_2$), δ=3.92 (s, Ar-OC**H$_3$**), δ=3.72 (t, C**H$_2$**CH_2OC(O)C(CH_3)CH_2), δ=3.68 (t, Ar-$OCH_2CH_2CH_2CO_2CH_2C$**H$_2$**O), δ=3.60-3.65 (m, (C**H$_2$**C**H$_2$**O)$_9$$CH_2CH_2$OC(O)C($CH_3$)$CH_2$), δ=2.58 (t, Ar-$OCH_2CH_2C$**H$_2$**$CO_2CH_2$), δ=2.18 (m, Ar-$OCH_2C$**H$_2$**$CH_2CO_2CH_2$), δ=1.92 (s, OC(O)C(C**H$_3$**)CH_2), δ=1.48 (m, Ar-CH(C**H$_3$**)NHC(O)OC(C**H$_3$**)$_3$), δ=1.2-1.45 (m, 9H, Ar-CH(CH_3)NHC(O)OC(C**H$_3$**)$_3$).

PEG526-methacrylate-4-(4-(1-aminoethyl)-2-methoxy-5-nitrophenoxy)butanoate: PEG526-methacrylate-4-(4-(1-(boc-amino)ethyl)-2-methoxy-5-nitrophenoxy)butanoate (0.05 g, 0.055 mmol) was dissolved in acetonitrile/water (50:1) (1 mL), bismuth trichloride (0.0035 g, 0.011 mmol) was added, and the reaction stirred at 55°C for 1 hour. An additional amount of bismuth trichloride (0.0035 g, 0.011 mmol) was added and the reaction was stirred for an additional 1 hour. The mixture was cooled to RT, sodium bicarbonate (0.05 g, 0.59 mmol) was added, and the reaction mixture was filtered through

celite.[4] The product was concentrated to dryness via rotary evaporation to yield 0.0359 g (81%) as a viscous, pale yellow liquid. ^{1}H NMR (d_6-DMSO): δ=8.62 (d, Ar-CH(CH_3)N**H$_2$**), δ= 7.56 (s, Ar-**H** *ort*ho to Ar-NO_2), δ=7.50 (s, Ar-**H** *met*a to Ar-NO_2), δ=6.00, 5.65 (s, s, OC(O)C(CH_3)C**H$_2$**), δ=4.90 (m, Ar-C**H**(CH_3)NH_2), δ=4.15 (t, C**H$_2$**OC(O)C(CH_3)CH_2), δ=4.10 (t, Ar-OCH_2CH_2C**H$_2$**CO_2CH_2), δ=4.05 (t, Ar-OC**H$_2$**$CH_2CH_2CO_2CH_2$), δ=3.85 (s, Ar-OC**H$_3$**),δ=3.62 (t, C**H$_2$**CH_2OC(O)C(CH_3)CH_2), δ=3.55 (t, Ar-O$CH_2CH_2CH_2CO_2CH_2$C**H$_2$**O), δ=3.40-3.50 (m, (C**H$_2$**C**H$_2$**O)$_9$$CH_2CH_2$OC(O)C($CH_3$)$CH_2$), δ=2.45 (t, Ar-O$CH_2CH_2$C**H$_2$**$CO_2CH_2$), δ=1.95 (m, Ar-O$CH_2$C**H$_2$**$CH_2CO_2CH_2$), δ=1.82 (s, OC(O)C(C**H$_3$**)CH_2), δ=1.56 (d, Ar-CH(C**H$_3$**)NH_2).

PEG526-methacrylate-4-(4-(1-acryloyloxyethyl)-2-methoxy-5-nitrophenoxy)butanoate: 4-(4-(1-Acryloyloxyethyl)-2-methoxy-5-nitrophenoxy)butanoic acid (1.50 g, 4.25 mmol), PEG 526MA (1.49 g, 2.83 mmol), EDC (1.05 g, 5.52 mmol), and DMAP (0.052 g, 0.43 mmol) were dissolved in DCM (20 mL) and stirred overnight at RT. The mixture was diluted with DCM (80 mL), washed with water (3 x eq. vol.) and saturated aqueous sodium bicarbonate (3 x eq. vol.), dried with $MgSO_4$, concentrated via rotary evaporation, and passed through a plug of basic alumina with DCM as the eluent. The product was concentrated to dryness via rotary evaporation to yield 1.82 g (75%) as a viscous, pale yellow liquid. ^{1}H NMR (d_6-DMSO): δ= 7.52 (s, Ar-**H** *ort*ho to Ar-NO_2), δ=7.12 (s, Ar-**H** *met*a to Ar-NO_2), δ=6.35, 5.95 (d, d, Ar-OCH(CH_3)CHC**H$_2$**), δ=6.25 (m, Ar-C**H**(CH_3)$OCHCH_2$), δ=6.20 (m, Ar-OCHC**H**CH_2), δ=6.00, 5.65 (s, s, OC(O)C(CH_3)C**H$_2$**), δ=4.15 (t, C**H$_2$**OC(O)C(CH_3)CH_2), δ=4.10 (t, Ar-OCH_2CH_2C**H$_2$**CO_2CH_2), δ=4.05 (t, Ar-OC**H$_2$**$CH_2CH_2CO_2CH_2$), δ=3.85 (s, Ar-OC**H$_3$**),δ=3.62 (t, C**H$_2$**CH_2OC(O)C(CH_3)CH_2), δ=3.55 (t, Ar-O$CH_2CH_2CH_2CO_2CH_2$C**H$_2$**O), δ=3.40-3.50 (m, (C**H$_2$**C**H$_2$**O)$_9$$CH_2CH_2$OC(O)C($CH_3$)$CH_2$), δ=2.45 (t, Ar-O$CH_2CH_2$C**H$_2$**$CO_2CH_2$), δ=1.95 (m, Ar-O$CH_2$C**H$_2$**$CH_2CO_2CH_2$), δ=1.82 (s, OC(O)C(C**H$_3$**)CH_2), δ=1.55 (m, Ar-OCH(C**H$_3$**)$CHCH_2$).

PEG526-methacrylate-4-(4-(1-((4-((2,5-dioxopyrrolidin-1-yl)oxy)-4-oxabutanoyl)oxy)ethyl)-2-methoxy-5-nitrophenoxybutanoate: PEG526-methacrylate-4-(1-(4-(3-carboxypropoxy)-5-methoxy-2-

nitrophenoxy)ethoxy-4-butanoate (0.20 g, 0.22 mmol), N-hydroxysuccinimide (0.031 g, 0.265 mmol), and EDC (0.053 g, 0.276 mmol) were dissolved in DCM (4 mL) and stirred overnight. The reaction was diluted with DCM (20 mL), washed with water (3 x eq. vol.), dried with $MgSO_4$, and concentrated to dryness via rotary evaporation to yield 0.15 g (69%) as a viscous, pale yellow liquid. ^{1}H NMR (*d_6*-DMSO): δ= 7.52 (s, Ar-**H** *ortho* to Ar-NO_2), δ=7.12 (s, Ar-**H** *meta* to Ar-NO_2), δ=6.25 (m, Ar-C**H**(CH_3)OC(O)$CH_2CH_2CO_2$NHS), δ=6.00, 5.65 (s, s, OC(O)C(CH_3)C**H_2**), δ=4.15 (t, C**H_2**OC(O)C(CH_3)CH_2), δ=4.10 (t, Ar-OCH_2CH_2C**H_2**CO_2CH_2), δ=4.05 (t, Ar-OC**H_2**$CH_2CH_2CO_2CH_2$), δ=3.85 (s, Ar-OC**H_3**),δ=3.62 (t, C**H_2**CH_2OC(O)C(CH_3)CH_2), δ=3.55 (t, Ar-$OCH_2CH_2CH_2CO_2CH_2C$**H_2**O), δ=3.40-3.50 (m, (C**H_2**C**H_2**O)$_9CH_2CH_2$OC(O)C(CH_3)CH_2), δ=2.80 (s, Ar-CH(CH_3)OC(O)C**H_2**C**H_2**CO_2NHS), δ=2.95, 2.75 (t, t, Ar-CH(CH_3)OC(O)$CH_2CH_2CO_2$**NHS**), δ=2.45 (t, Ar-OCH_2CH_2C**H_2**CO_2CH_2), δ=1.95 (m, Ar-OCH_2C**H_2**$CH_2CO_2CH_2$), δ=1.82 (s, OC(O)C(C**H_3**)CH_2), δ=1.55 (m, Ar-CH(C**H_3**)OC(O)$CH_2CH_2CO_2$NHS).

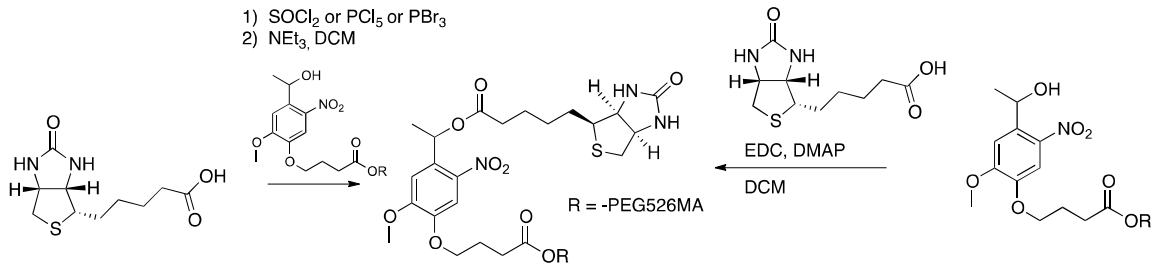
2-(Pyridin-2-yldisulfanyl)ethyl succinate: 2-(pyridin-2-yldisulfanyl)ethanol (0.33 g, 1.76 mmol), succinic anhydride (0.22 g, 2.20 mmol), and DMAP (0.021 g, 0.18 mmol) were dissolved in THF (5mL) and stirred at room temperature until the reaction was complete according to TLC (R_f= 0, 9:1 DCM:EtOAc) and ^{1}H NMR. The solution was concentrated to dryness via rotary evaporation. The crude product was dissolved in DCM, washed with DI water (3× eq vol.), dried over $MgSO_4$, and concentrated to dryness via rotary evaporation to yield 0.257 g (51%) as a viscous yellow liquid. ^{1}H NMR ($CDCl_3$): δ= 8.25 ^{1}H NMR ($CDCl_3$): δ= 8.25 (d, Pyr-**H**), δ= 7.63 (d, Pyr-**H**), δ= 7.36 (t, Pyr-**H**), δ= 7.18 (t, Pyr-**H**), δ= 4.21 (t, Pyr-SS-C**H_2**CH_2OC(O)C(CH_2)CH_2COOH)), δ= 2.84 (t, Pyr-SS-CH_2C**H_2**OC(O)CH_2CH_2COOH), δ= 2.84, 2.73 (t, t, RCH_2CH_2OC(O)C**H_2**C**H_2**COOH).

4-(2-methoxy-5-nitro-4-(1-(4-oxo-4-(2-(pyridin-2-yldisulfanyl)ethoxy)butanamido)ethyl)phenoxy)butanoic acid: 2-(Pyridin-2-yldisulfanyl)ethyl succinate (110 mg, 0.38 mmol), EDC (80 mg, 0.42 mmol), dimethylaminopyridine (4.6 mg, 0.038 mmol) and N-

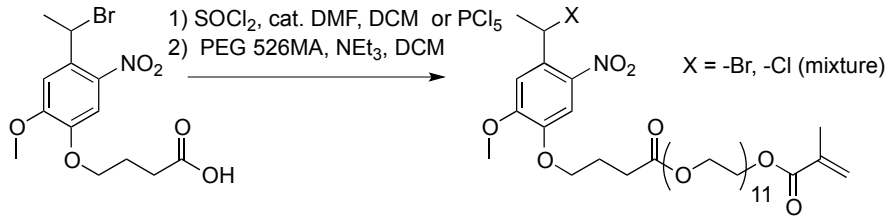
hydroxysuccinimide (47 mg, 0.40 mmol) were dissolved in DCM (3 mL) and the formation of 2,5-dioxopyrrolidin-1-yl 2-(pyridin-2-yldisulfanyl)ethyl succinate was followed by TLC until determined complete by disappearance of 2-(pyridin-2-yldisulfanyl)ethyl succinate. The solution was then washed with water (3 x eq. vol.), dried with magnesium sulfate and dried under vacuum. The resultant crude product (120 mg, 0.31 mmol, 82%) was immediately dissolved (to avoid NHS hydrolysis) in DCM (1 mL) and added dropwise to (4-(4-(1-aminoethyl)-2-methoxy-5-nitrophenoxy)butanoic acid (138 mg, 0.46 mmol) and triethylamine (0.13 mL, 0.92 mmol) dissolved in DCM (3 mL) and reacted overnight. The reaction was observed by TLC for disappearance of NHS-ester. The solution was washed with water (3 x eq. vol.). The solution was dried with magnesium sulfate and dried under vacuum. The resultant crude product was purified via column chromatography (eluent: 2:3 DCM/EtOAc; Product R_f = 0.38) to yield 130 mg (0.22 mmol, 72%) as a yellow viscous liquid.

PEG 10,000 dimethacrylate/PEG 10,000 methacrylate 4-(2-methoxy-5-nitro-4-(1-(4-oxo-4-(2-(pyridin-2-yldisulfanyl)ethoxy)butanamido)ethyl)phenoxy)butanoate: 4-(2-methoxy-5-nitro-4-(1-(4-oxo-4-(2-(pyridin-2-yldisulfanyl)ethoxy)butanamido)ethyl)phenoxy)butanoic acid (0.063 g, 0.11 mmol), PEG 10,000 (9.94 g, 0.99 mmol), DCC (0.041 g, 0.22 mmol), and DMAP (0.0026 g, 0.022 mmol) were dissolved in DCM (25 mL) and reacted overnight. The solution was rotovapped to dryness under vacuum, dissolved in water, filtered to remove urea, and lyophilized. The reaction yielded 7.75 g of mixed product, ^{1}H NMR indicated the presence of the photodegradable group, but the signal was too weak to quantify. The material was reacted without further purification. The PEG 10,000/ PEG 10,000 methacrylate 4-(2-methoxy-5-nitro-4-(1-(4-oxo-4-(2-(pyridin-2-yldisulfanyl)ethoxy)butanamido)ethyl)phenoxy)butanoate mixture (5.52 grams) was reacted with methacryloyl chloride (0.27 g, 2.7 mmol) with triethylamine (0.46 mL, 3.3 mmol) in DCM (25 mL). The reaction was checked for complete methacrylation of the PEG by ^{1}H NMR. The crude product was dried under vacuum and dissolved in water. The solution was dialyzed to remove impurities and

lyophilized. To test for the amount of PEG 10,000 methacrylate 4-(2-methoxy-5-nitro-4-(1-(4-oxo-4-(2-(pyridin-2-yldisulfanyl)ethoxy)butanamido)ethyl)phenoxy)butanoate present in the mixture, the product (0.1 g) was dissolved in water (5 mL) and monitored for 2-pyridinethione release when combined with a solution of GSH (5mM). The result indicated 4% of the PEG in solution was comprised of PEG 10,000 methacrylate 4-(2-methoxy-5-nitro-4-(1-(4-oxo-4-(2-(pyridin-2-yldisulfanyl)ethoxy)butanamido)ethyl)phenoxy)butanoate, with the rest being PEG 10,000 dimethacrylate.



Scheme S1. Synthesis of PEG526-methacrylate-4-(4-(1-biotinylethyl)-2-methoxy-5-nitrophenoxy)butanoate



Scheme S2. Synthesis of PEG526-methacrylate-4-(4-(1-bromoethyl)-2-methoxy-5-nitrophenoxy)butanoate

REFERENCES

(1) Murthy, N.; Campbell, J.; Fausto, N.; Hoffman, A. S.; Stayton, P. S. *Bioconjugate Chem* 2003, *14*, 412.
(2) Griffin, D. R.; Patterson, J.; Kasko, A. M. *Biotechnology and Bioengineering* 2010, *107*, 1012.
(3) Burakowska, E.; Zimmerman, S. C.; Haag, R. *Small* 2009, *5*, 2199.
(4) Navath, R. S.; Pabbisetty, K. B.; Hu, L. Q. *Tetrahedron Lett* 2006, *47*, 389.