The effect of photo-isomerization on the enzymatic hydrolysis of polymeric micelles bearing photo-responsive azobenzene groups at their cores

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Supplementary Information

Instrumentation and Materials:

Instrumentation:

HPLC: All measurements were recorded on a Waters Alliance e2695 separations module equipped with a Waters 2998 photodiode array detector. All solvents were purchased from Bio-Lab Chemicals and were used as received. All solvents are HPLC grade. **^{1}H and ^{13}C NMR:** spectra were recorded on Bruker Avance I and Avance III 400MHz spectrometers as indicated. Chemical shifts are reported in ppm and referenced to the solvent. The molecular weights of the PEG-dendron hybrids were determined by comparison of the areas of the peaks corresponding to the PEG block (3.63 ppm) and the protons peaks of the dendrons. **GPC:** All measurements were recorded on Viscotek GPCmax by Malvern using refractive index detector and PEG standards (purchased from Sigma-Aldrich) were used for calibration. **Infrared spectra:** All measurements were recorded on a Bruker Tensor 27 equipped with a platinum ATR diamond. **Fluorescence spectra:** All measurements were recorded on an Agilent Technologies Cary Eclipse Fluorescence Spectrometer using quartz cuvettes. **CMC:** All measurements were recorded on a TECAN Infinite M200Pro device. **MALDI-TOF MS:** Analysis was conducted on a Bruker AutoFlex MALDI-TOF MS (Germany). DHB matrix was used. **High resolution MS:** Analysis was conducted on Autospec HRMS (EI) Micromass (UK) or Synapt High Definition MS (ESI), Waters Inc. (USA). **Isotope abundance analysis:** Analysis was conducted by GC-MS with Cold EI (Aviv Analytical model 5975-SMB). Cold EI is electron ionization of vibrationally cold molecules in supersonic molecular beams, which enhances the molecular ions.[1] The molecular ion was

analyzed for its elemental formula via by the Aviv Analytical TAMI Molecule Identifier software that combines possible improved quadrupole MS mass accuracy with isotope abundance analysis.[2] **DLS:** All measurements were recorded on a Corduan technology VASCO$^{\gamma}$ – particle size analyzer. **TEM:** Images were taken by a Philips Tecnai F20 TEM at 200kV.

Materials:

Poly (Ethylene Glycol) methyl ether (5kDa), 2-mercaptoethanol (98%), 2,2-dimethoxy-2-phenylacetophenone (DMPA, 99%), Porcine liver esterase (PLE), Allyl bromide (99%), Propargyl bromide (80% in toluene), 4-nitrophenol (99.5%), N,N'-dicyclohexylcarbodiimide (DCC, 99%), 4-phenylazophenol (98%), Ethylbromoacetate (98%) and Sephadex® LH20 were purchased from Sigma-Aldrich. Anhydrous $NaSO_4$ (granular, 10-60mesh) was purchased from Macron. Anhydrous K_2CO_3 (99%) was purchased from Alfa Aesar. Potassium hydroxide and DIPEA were purchased from Merck. Silica Gel 60Å, 0.040-0.063mm, NaOH and all solvents were purchased from Bio-Lab and were used as received. Deuterated solvents for NMR were purchased from Cambridge Isotope Laboratories (CIL), Inc.

Synthesis

Synthesis of branching units:

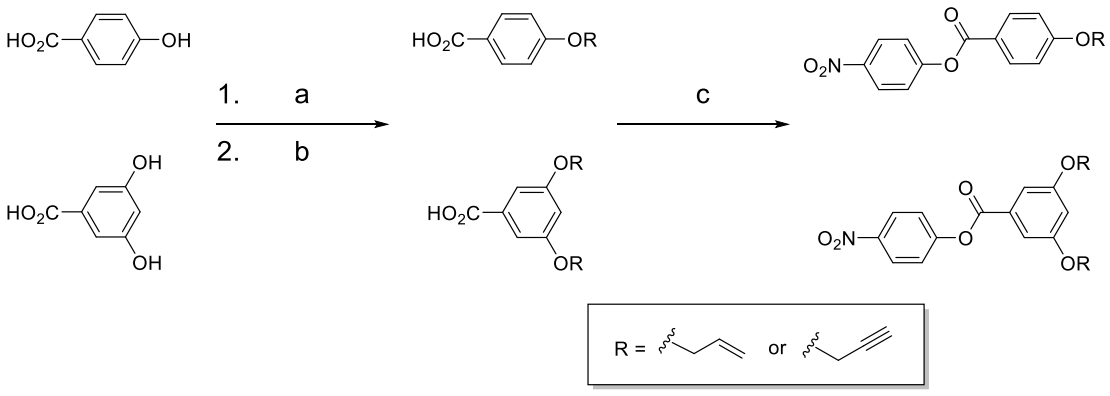

Figure S1: General conditions for preparation of branching units. a) Allyl or propargyl bromide, anhydrous K_2CO_3, DMF, 60°C, 3h. b) NaOH, dioxane:H_2O 80:20v/v, 60°C, 15min. c) 4-nitrophenol, DMAP, DCC, THF, 0°C=>RT, 4h.

General procedure for allylation/propargylation:

4-hydroxy or 3,5 dihydroxy benzoic acid was dissolved in DMF (25mL per 1.5g) and crushed anhydrous K_2CO_3 (2eq + 2eq per phenol) was added to form a suspension. Allyl bromide or propargyl bromide (2eq + 2eq per phenol) was added and the flask was heated to 60°C for 3

hours. Flask was allowed to cool to RT and then the reaction mixture was filtered through celite. The celite was washed three times with toluene and all organic solvents were removed in vacuum. The obtained oily residue was redissolved with dioxane:H_2O 80:20v/v (50mL per 1.5g), NaOH 4N (2eq) was added and the flask was heated to 60°C for 15 minutes. Then, pH was neutralized with HCl 1N, organic solvents were removed in vacuum, and the residue was transferred into a separation funnel using EtOAc (150mL per 1.5g). This organic phase was washed with HCl 1N (2x100mL) and brine (2x100mL), dried over $NaSO_4$, filtered and evaporated to dryness. Further purification was obtained by passing the product through a silica column with hexane:EtOAc 50:50v/v +1%AcOH as eluent.

General procedure for esterification with 4-nitrophenol:

Followed by the allylation/propargylation step, the desired benzoic acid, 4-nitrophenol (1.1eq) and DMAP (0.1eq) were dissolved in THF (20mL per 1g). The flask was cooled to 0°C and DCC (1.1eq) was added. Reaction was stirred for 4 hours and allowed to reach ambient temperature. Reaction mixture was filtered through celite and the celite was washed with DCM. Organic solvents were removed in vacuum to afford a yellowish crude mixture. The product, a white fluffy solid, was purified using a silica column with 100% DCM as eluent.

Synthesis of 4-nitrophenyl 4-(allyloxy) benzoate:

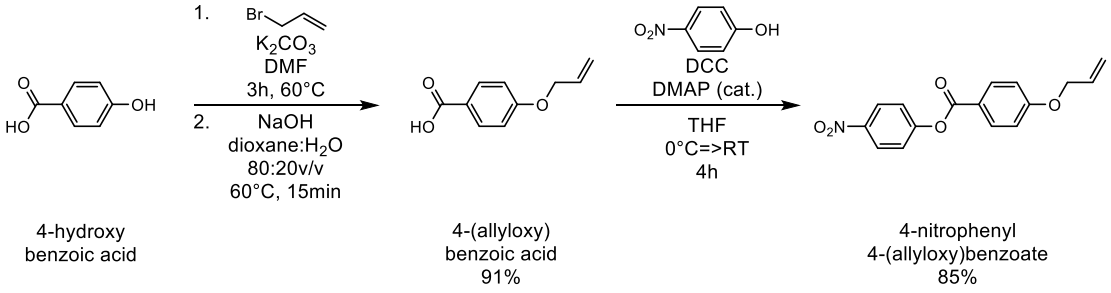

Figure S2: Preparation of 4-nitrophenyl 4-(allyloxy) benzoate.

4-(allyloxy) benzoic acid: 4-hydroxy benzoic acid (1.38g, 10mmol), anhydrous K_2CO_3 (5.53g, 40mmol, 4eq) and allyl bromide (3.5mL, 40mmol, 4eq) were reacted in DMF (25mL), and then treated with NaOH 4N (5mL, 20mmol, 2eq) in dioxane:H_2O 80:20v/v (50mL) according to the general procedure. The product was obtained as an off-white solid in 91% yield (1.62g) and its characterizations correlated with previous data.[3]

^{1}H-NMR (DMSO-d6): δ 7.88 (d, *J* = 9.0Hz, 2H, arom H), 7.03 (d, *J* = 9.0Hz, 2H, arom H), 6.00-6.09 (m, 1H, vinylic H), 5.40 (dq, *J* = 17.3Hz, 1.7Hz, 1H, *E* vinylic H), 5.28 (dq, *J* = 10.6Hz, 1.5Hz, 1H, *Z* vinylic H), 4.64 (dt, *J* = 5.2Hz, 1.5Hz, 2H, allylic H); ^{13}C-NMR (DMSO-d6): δ 166.9, 161.7, 133.2,

131.3, 123.1, 117.8, 114.4, 68.4; FT-IR (ATR), ν(cm^{-1}): 1692, 1677, 1666, 1427, 1413, 1320, 1303, 1291, 1249, 1173, 1128, 1106, 1018, 999, 949, 928, 849, 769.

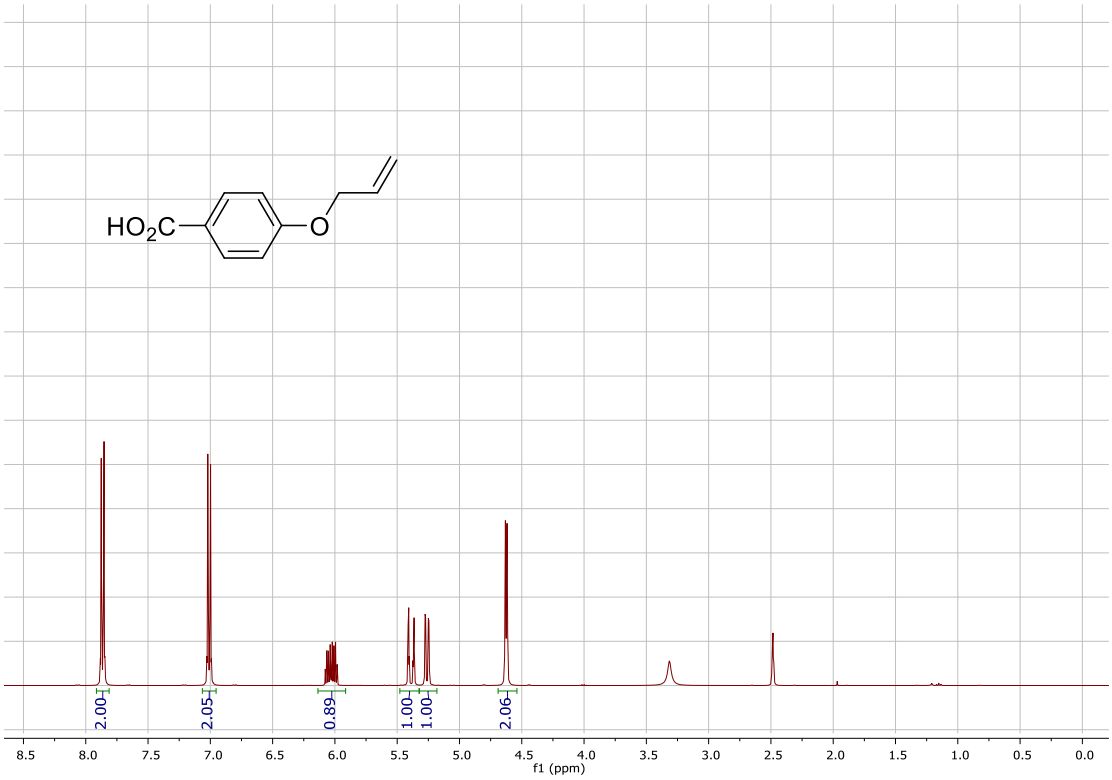

Figure S3: ^{1}*H-NMR of 4-(allyloxy) benzoic acid in DMSO-d6.*

4-nitrophenyl 4-(allyloxy) benzoate: 4-(allyloxy) benzoic acid (0.54g, 3mmol), 4-nitrophenol (0.46g, 3.3mmol, 1.1eq), DMAP (37mg, 0.3mmol, 0.1eq) and DCC (0.68g, 3.3mmol, 1.1eq) were reacted in THF (10mL) according to the general procedure. The product was obtained as a fluffy white solid in 85% yield (0.76g).

^{1}H-NMR ($CDCl_3$): δ 8.31 (d, *J* = 9.2Hz, 2H, arom H), 8.14 (d, *J* = 9.0Hz, 2H, arom H), 7.40 (d, *J* = 9.2Hz, arom H), 7.02 (d, *J* = 9.0Hz, 2H, arom H), 6.02-6.12 (m, 1H, allylic H), 5.45 (dq, *J* = 17.3Hz, 1.5Hz, 1H, *E* vinylic H), 5.35 (dq, *J* = 10.5Hz, 1.3Hz, 1H, *Z* vinylic H), 4.65 (dt, *J* = 5.3Hz, 1.5Hz, 2H, allylic H); ^{13}C-NMR ($CDCl_3$): δ; 164.0, 163.5, 156.1, 145.4, 132.7, 132.4, 125.4, 122.8, 121.0, 118.5, 114.9, 69.2; FT-IR (ATR), ν(cm^{-1}): 1742, 1730, 1607, 1592, 1520, 1513, 1351, 1265, 1220, 1171, 1109, 1059, 1023, 1007, 936, 876, 865, 844, 817, 757, 745; High resolution MS (EI, positive mode, 70eV): calculated mass: 299.0794, found: 299.0800. The molecular ion was analyzed for its elemental formula ($C_{16}H_{13}NO_5$) and the correct elemental formula was provided and rated as number one in a list of possible elemental formula.

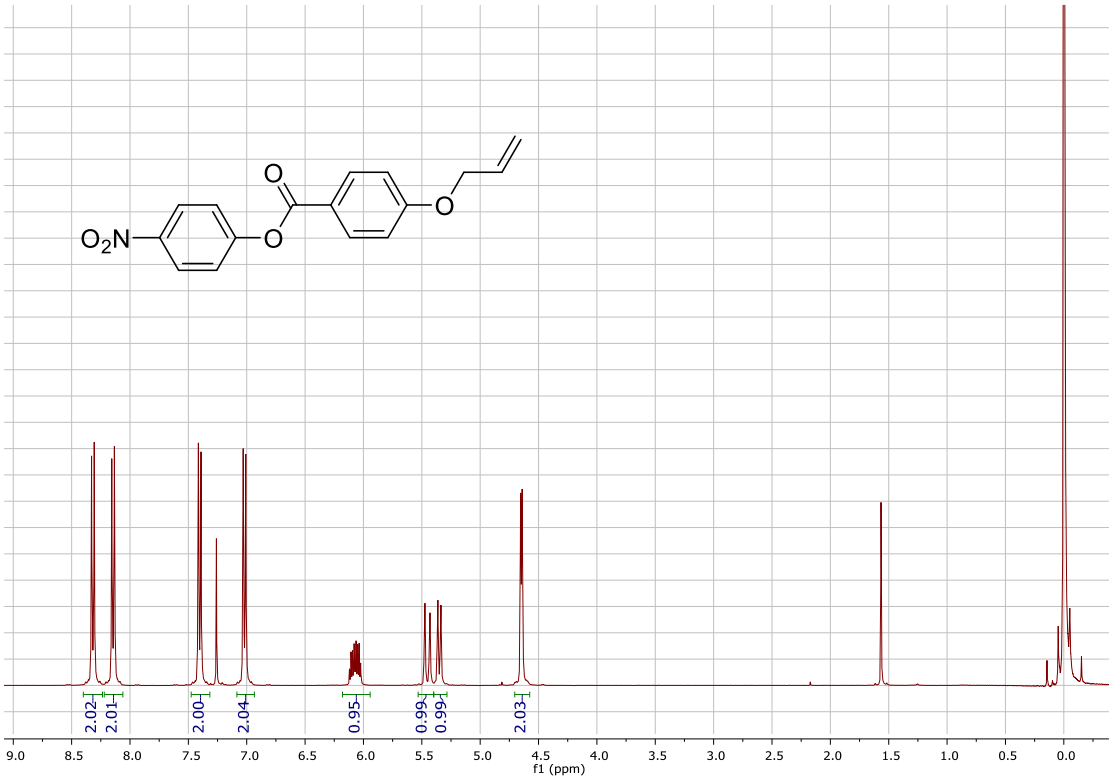

Figure S4: *^{1}H-NMR spectrum of 4-nitrophenyl 4-(allyloxy)benzoate in $CDCl_3$.*

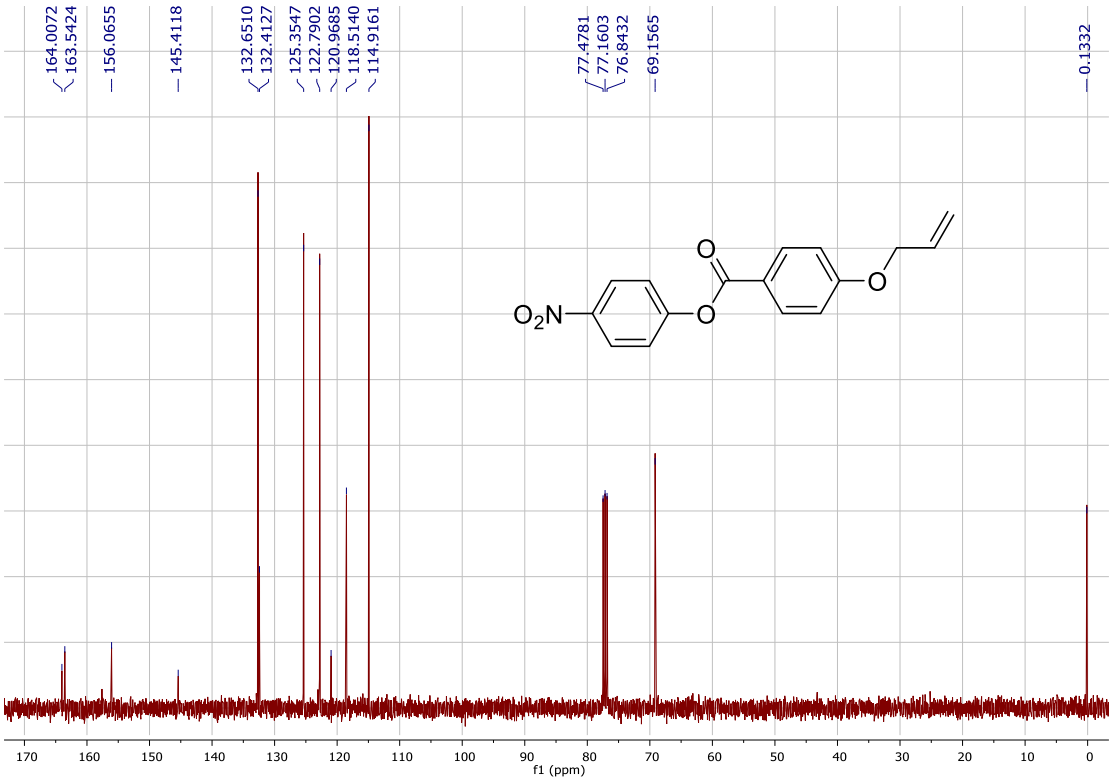

Figure S5: *^{13}C-NMR spectrum of 4-nitrophenyl 4-(allyloxy)benzoate in $CDCl_3$.*

Synthesis of 4-nitrophenyl 3,5-bis(allyloxy) benzoate:

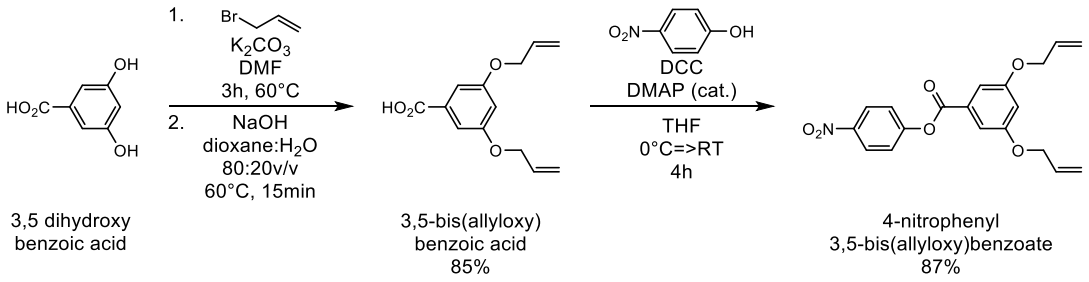

Figure S6: Preparation of 4-nitrophenyl 3,5-bis(allyloxy)benzoate.

3,5-bis(allyloxy) benzoic acid: 3,5 dihydroxy benzoic acid (1.54g, 10mmol), anhydrous K_2CO_3 (8.3g, 60mmol, 6eq) and allyl bromide (5.2ml, 60mmol, 6eq) were reacted in DMF (25mL), and then treated with NaOH 4N (5mL, 20mmol, 2eq) in dioxane:H_2O 80:20v/v (50mL) according to the general procedure. The product was obtained as an off-white solid in 85% yield (2.0g) and its characterizations correlated with previous reports.[3]

^{1}H-NMR (DMSO-d6): δ 7.07 (d, *J* = 2.3Hz, 2H, arom H), 6.78 (t, *J* = 2.3Hz, 1H, arom H), 5.98-6.08 (m, 2H, vinylic H), 5.39 (d, *J* = 17.3Hz, 2H, *E* vinylic H), 5.26 (d, *J* = 10.5Hz, 2H, *Z* vinylic H), 4.60 (d, *J* = 5.0Hz, 4H, allylic H); ^{13}C-NMR (DMSO-d6): δ 167.0, 159.3, 133.5, 132.9, 117.6, 107.8, 106.2, 68.5; FT-IR (ATR), ν(cm^{-1}): 1688, 1597, 1462, 1445, 1420, 1309, 1272, 1255, 1152, 1050, 1028, 1001, 987, 929, 880, 857, 766, 733.

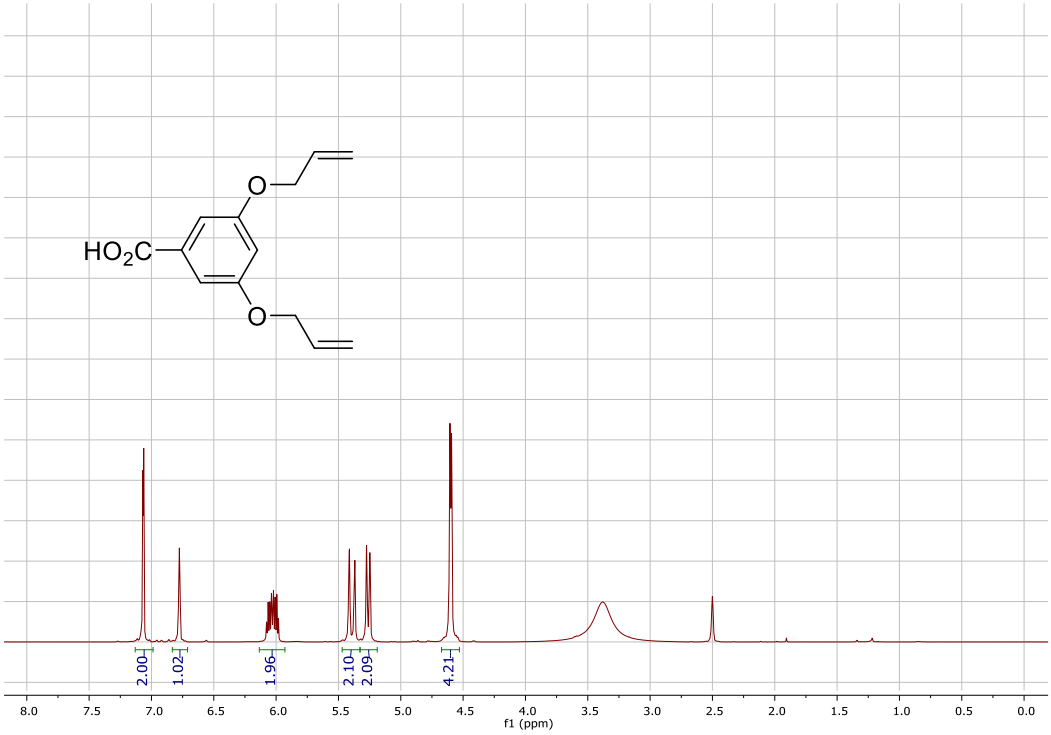

Figure S7: ^{1}H-NMR spectrum of 3,5-bis(allyloxy)benzoic acid in DMSO-d6.

4-nitrophenyl 3,5-bis(allyloxy)benzoate: 3,5-bis(allyloxy) benzoic acid (0.47g, 2mmol), 4-nitrophenol (0.31g, 2.2mmol, 1.1eq), DMAP (24mg, 0.2mmol, 0.1eq) and DCC (0.45g, 2.2mmol, 1.1eq) were reacted in THF (10mL) as described in the general procedure. The product was obtained as a fluffy white solid in 87% yield (0.62g).

^{1}H-NMR ($CDCl_3$): δ 8.33 (d, *J* = 9.1Hz, 2H, arom H), 7.41 (d, *J* = 9.1Hz, 2H, arom H), 7.34 (d, *J* = 2.4Hz, 2H, arom H), 6.79 (t, *J* = 2.4Hz, 1H, arom H), 6.01-6.11 (m, 2H, vinylic H), 5.44 (dq, *J* = 17.3Hz, 1.5Hz, 2H, *E* vinylic H), 5.33 (dq, *J* = 10.5Hz, 1.3Hz, 2H, *Z* vinylic H), 4.59 (dt, *J* = 5.3Hz, 1.5Hz, 4H, allylic H); ^{13}C-NMR ($CDCl_3$): δ 164.1, 160.0, 155.8, 145.6, 132.7, 130.4, 125.4, 122.7, 118.3, 109.0, 108.3, 69.3; FT-IR (ATR), ν(cm^{-1}): 1738, 1593, 1522, 1492, 1453, 1444, 1423, 1347, 1297, 1210, 1174, 1150, 1115, 1094, 1051, 1022, 998, 943, 872, 859, 784, 752, 738. High resolution MS (ESI, positive mode): calculated mass (+Na): 378.0954, found: 378.0953.

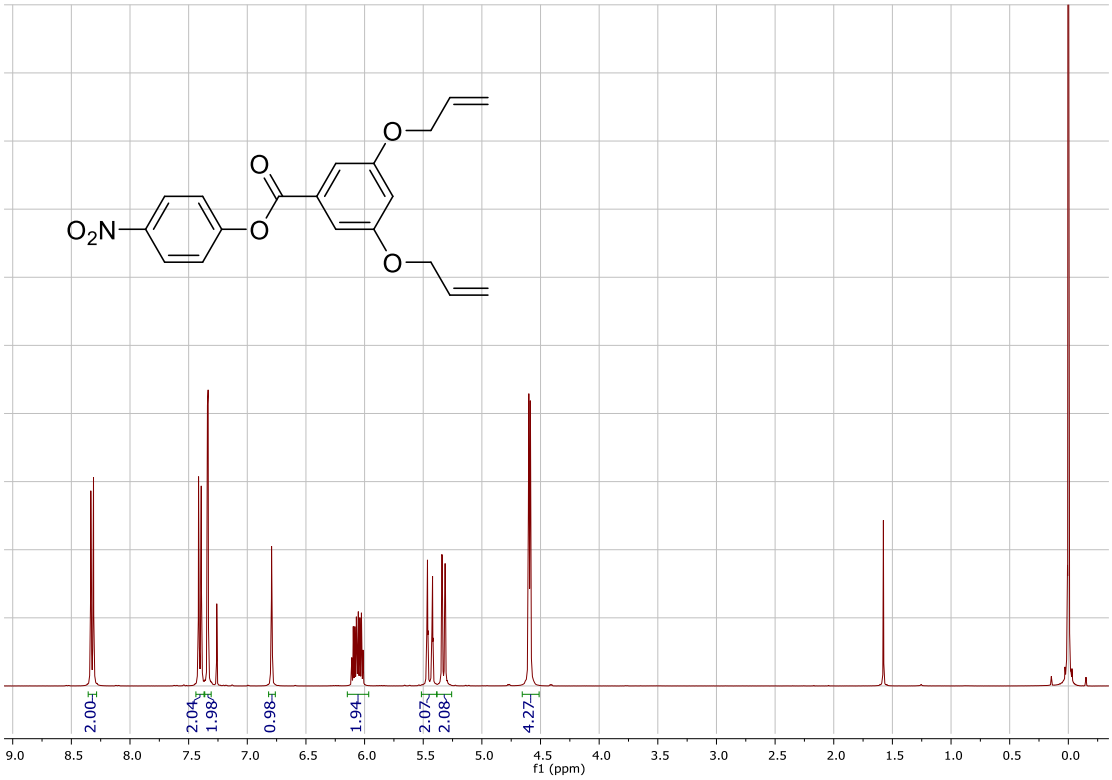

Figure S8: ^{1}H-NMR spectrum of 4-nitrophenyl 3,5-bis(allyloxy)benzoate in $CDCl_3$.

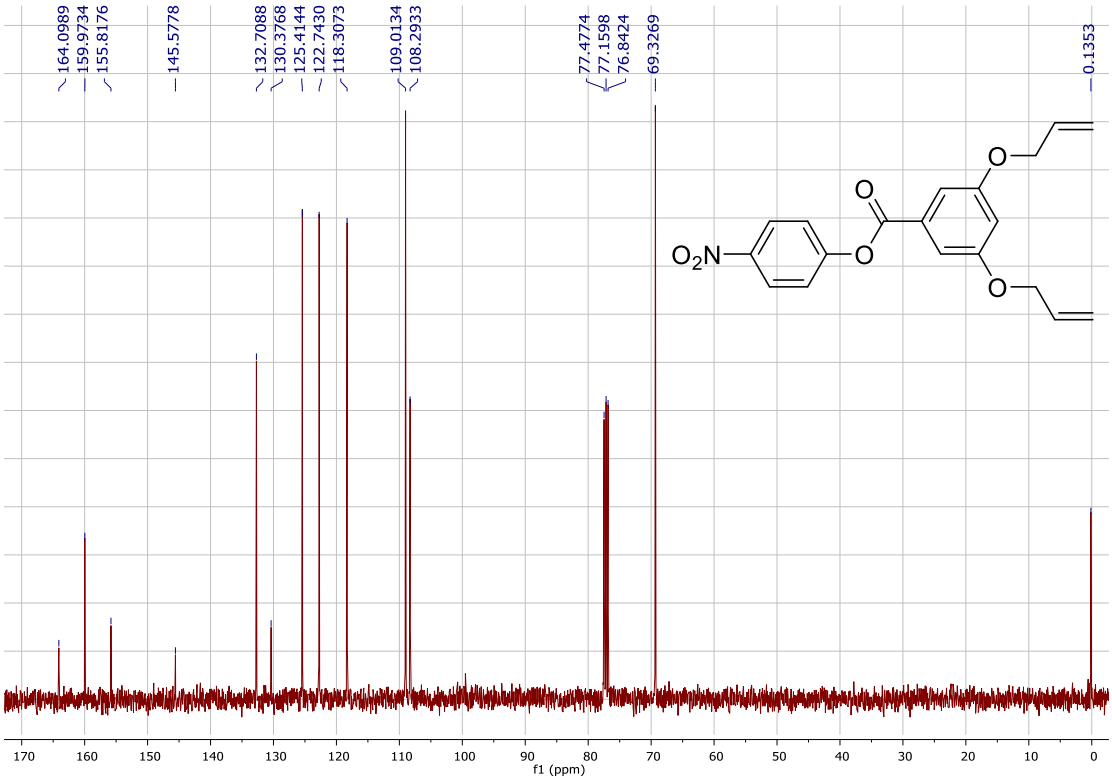

Figure S9: ^{13}C-NMR spectrum of 4-nitrophenyl 3,5-bis(allyloxy)benzoate in $CDCl_3$

Synthesis of 4-nitrophenyl 3,5-bis(propargyloxy) benzoate:

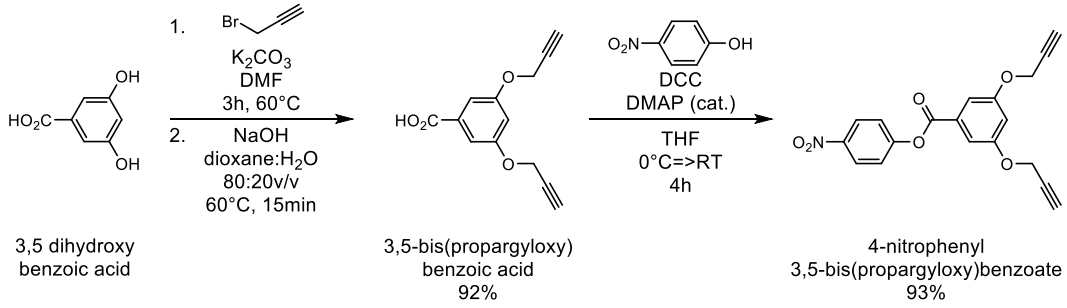

Figure S10: Preparation of 4-nitrophenyl 3,5-bis(propargyloxy)benzoate.

3,5-bis(propargyloxy) benzoic acid: 3,5 dihydroxy benzoic acid (1.54g, 10mmol), anhydrous K_2CO_3 (8.3g, 60mmol, 6eq) and 80% propargyl bromide in toluene (6.4mL, 60mmol, 6eq) were reacted in DMF (25mL), and then treated with NaOH 4N (5mL, 20mmol, 2eq) in dioxane:H_2O 80:20v/v (50mL) according to the general procedure. The product was obtained as an off-white solid in 92% yield (2.1g).

^{1}H,^{13}C-NMR and FT-IR were identical to previous reports.[4]

4-nitrophenyl 3,5-bis(propargyloxy)benzoate: 3,5-bis(propargyloxy)benzoic acid (0.69g, 3mmol), 4-nitrophenol (0.46g, 3.3mmol,1.1eq), DMAP (37mg, 0.3mmol, 0.1eq) and DCC (0.52g,

3.3mmol, 1.1eq) were reacted in THF (15mL) as described in the general procedure. The product was obtained as a fluffy white solid in 93% yield (0.98g).

^{1}H, ^{13}C-NMR and FT-IR were identical to previous reports.[4]

Synthesis of azo-acid:

The azo acid was prepared according to a previous report in the literature.[5] The two synthetic steps were joined into a one pot reaction and slight modifications were made in the workup stage.

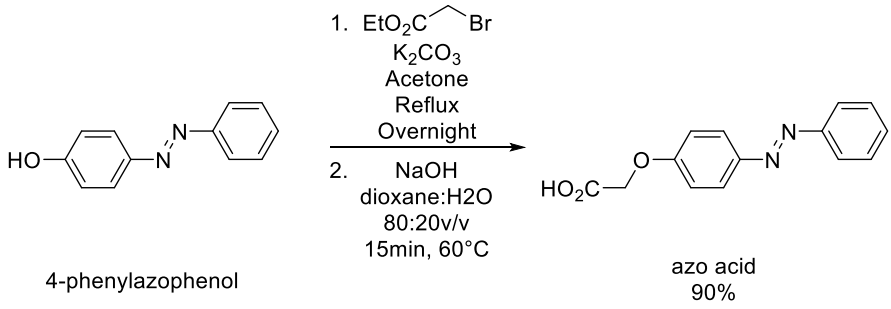

Figure S11: Preparation of azo-acid from 4-phenylazophenol.

Azo acid: 4-phenylazophenol (1.98g, 10mmol) and anhydrous K_2CO_3 (2.1g, 15mmol, 1.5eq) were dissolved in acetone (40mL) to form a suspension. Ethylbromoacetate (1.7mL, 15mmol, 1.5eq) was added and the flask was refluxed overnight. Reaction mixture was filtered through celite and the celite was washed with DCM. Organic solvents were evaporated to dryness and the orange crude mixture was redissolved with dioxane:H_2O 80:20v/v (50mL). NaOH 4N (5mL, 20mmol, 2eq) was added and the flask was heated to 60°C for 15 minutes. Then, the pH was neutralized with HCl 1N and organic solvents were removed in vacuum. The obtained residue was transferred into a separation funnel with EtOAc (150mL) and this organic phase was washed with HCl 1N (2x100mL) and brine (2x100mL), dried over $NaSO_4$, filtered and evaporated to dryness. The product was further purified using a silica column with EtOAc+1%AcOH as eluent. The product was obtained as an orange solid in 90% yield (2.3g).

^{1}H-NMR (DMSO-d6): δ 7.89 (d, *J* = 9.0Hz, 2H, arom H), 7.85 (dd, *J* = 8.3Hz, 1.2Hz, 2H, arom H), 7.50-7.60 (m, 3H, arom H), 7.12 (d, *J* = 9.0Hz, 2H, arom H), 4.82 (s, 2H, HO_2C-C**H_2**-O-); ^{13}C-NMR (DMSO-d6): δ 169.8, 160.5, 152.0, 146.4, 130.9, 129.4, 124.4, 122.3, 115.1, 64.7; FT-IR (ATR), ν(cm^{-1}): 1707, 1604, 1583, 1498, 1428, 1411, 1373, 1342, 1322, 1300, 1272, 1231, 1153, 1143, 1099, 1060, 961, 919, 835, 815, 801.

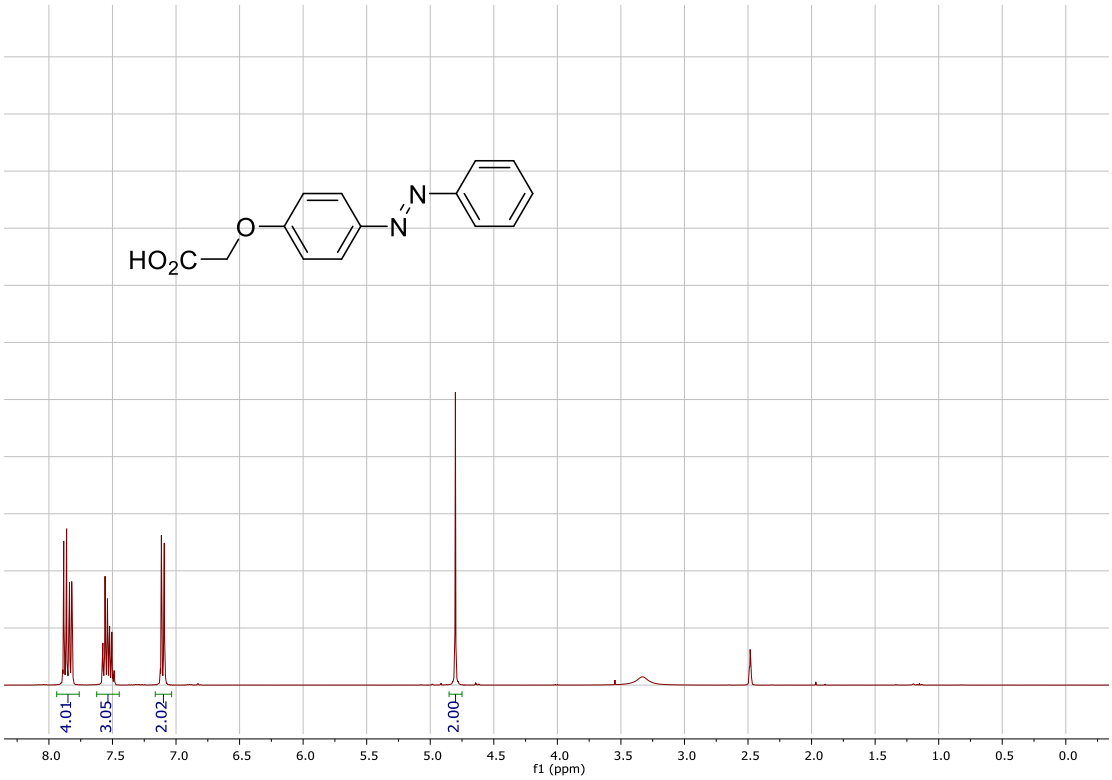

Figure S12: ^{1}H-NMR spectrum of azo-acid in DMSO-d6.

Synthesis of 5kDa mPEG building blocks:

Synthesis of $mPEG_{5kDa}$-NH_2 from $mPEG_{5kDa}$-OH:

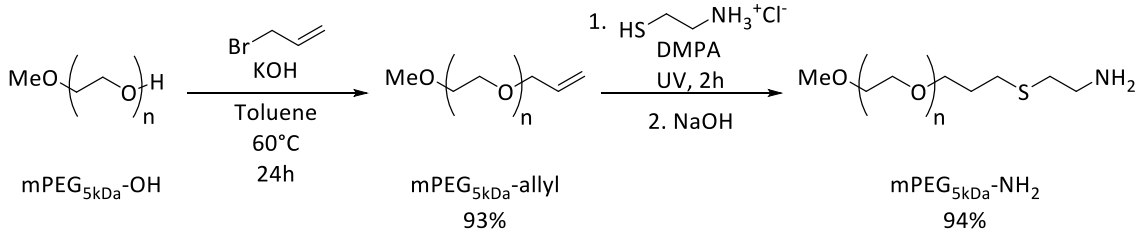

Figure S13: Preparation of methoxy amino PEG.

$mPEG_{5kDa}$-allyl: methoxy poly(ethylene glycol) (M_n=5kDa, 5.00g, 1mmol) and KOH (1.68g, 30mmol, 30eq) were added to toluene (50mL). Flask was intensively refluxed using a Dean Stark water separation apparatus for 1 hour and then allowed to reach 60°C with constant stirring (at that point the KOH precipitated but the PEG remained soluble). Allyl bromide (2.6mL, 30mmol, 30eq) was added and the reaction was allowed to stir for 24 hours. The reaction was filtered hot through celite and the celite was washed with DCM (3x25mL). Organic solvents were evaporated to dryness, the obtained oily residue was redissolved with DCM (25mL), and the product was precipitated by the drop-wise addition of ether:hexane 1:1v/v

(250mL). The solid was filtered, washed with ether (3x25mL) and hexane (3x25mL), and then dried under high vacuum. Product was obtained as a white solid in 93% yield (4.7g).

^{1}H,^{13}C-NMR and FT-IR were identical to previous reports.[4]

$mPEG_{5kDa}$-NH_2: $mPEG_{5kDa}$-allyl (2.52g, 0.5mmol), cystamine hydrochloride (1.14g, 10mmol, 20eq) and DMPA (26mg, 0.1mmol, 0.2eq) were dissolved in MeOH (12mL). The pinkish clear solution was purged with N_2 for 15 minutes and then stirred under UV light for 2 hours. Next, the solution was diluted into a mixture of Brine:NaOH 4N 3:1v/v (200mL) and mixed for 10 minutes. Then, this aqueous phase was extracted with DCM (3x100mL) and the combined organic phases were filtered through celite. The celite was washed with DCM and then the DCM was evaporated to dryness. The oily residue was redissolved with DCM (15mL) and the PEG was precipitated by the drop-wise addition of ether:hexane 1:1v/v (150mL). The white solid was filtered, washed with ether (3x20mL) and hexane (3x20mL), and then dried under high vacuum. The product was obtained as a white solid in 94% yield (2.41g).

^{1}H,^{13}C-NMR and FT-IR were identical to previous reports.[2]

Synthesis of PEG-dendron hybrids:

General procedures for preparation of hybrids:

General procedure for conjugation of $mPEG_{5kDa}$-NH_2 and branching units:

$mPEG_{5kDa}$-NH_2 was dissolved in DCM:DMF 1:1v/v (1mL per 100mg PEG). DIPEA (9eq) and the 4-nitrophenol active ester of the branching unit (3eq) were added, and the reaction was allowed to stir overnight. Then, the yellowish reaction mixture was loaded as-is on a MeOH-based LH20 (Sephadex®) size exclusion column. Fractions that contained the product (identified by UV light and/or coloring with I_2) were unified and the MeOH was evaporated to dryness. In order to facilitate the solidification of the product, the oily residue was redissolved in DCM (2mL per 100mg PEG) and hexane (10mL per 100mg PEG) was added. Organic solvents were evaporated to dryness and the white solid was dried under high vacuum.

General procedure for thiol-ene/yne with 2-mercaptoethanol:

The PEG reactant and DMPA (1mol% with respect to the thiol) were dissolved in 2-mercaptoethanol (20eq per double bond or 40eq per triple bond) + MeOH (0.5mL per 100mg PEG). The solution was purged with N_2 for 15 minutes and then stirred under UV light for 2 hours. The product was isolated and purified as described in the general procedure for conjugation of $mPEG_{5kDa}$-NH_2 with the branching units.

General procedure for esterification of mono/di/tetra hydroxy PEG with azo acid:

The PEG reactant was dissolved in DCM:DMF 90:10v/v (2mL per 100mg PEG). Azo acid (5eq per OH) and DMAP (1eq per OH) were added, the flask was cooled to 0°C, and DCC (5eq per OH) was added. Reaction was stirred overnight and allowed to reach ambient temperature. Then, the PEG product was precipitated by the drop-wise addition of ether (50mL per 100mg PEG). The orange solid was filtered off and washed with ether (3x10mL) and hexane (3x10mL). Next, the solid was redissolved with DCM and loaded on a silica column. The silica was washed with 100% MeOH and equilibrated back to 100% EtOAc prior to loading. The column was flushed with EtOAc+1% AcOH, 100% DCM, DCM:MeOH 95:5v/v, DCM:MeOH 90:10v/v and finally with DCM:MeOH 80:20v/v. Fractions that contained the product were unified and evaporated to dryness. In order to facilitate the solidification of the product, the product was redissolved with DCM (2mL per 100mg PEG) and hexane (10mL per 100mg PEG) was added. Organic solvents were evaporated to dryness and the orange solid was dried under high vacuum.

Synthesis of $mPEG_{5kDa}$-dend-$(azo)_1$ (hybrid 1)

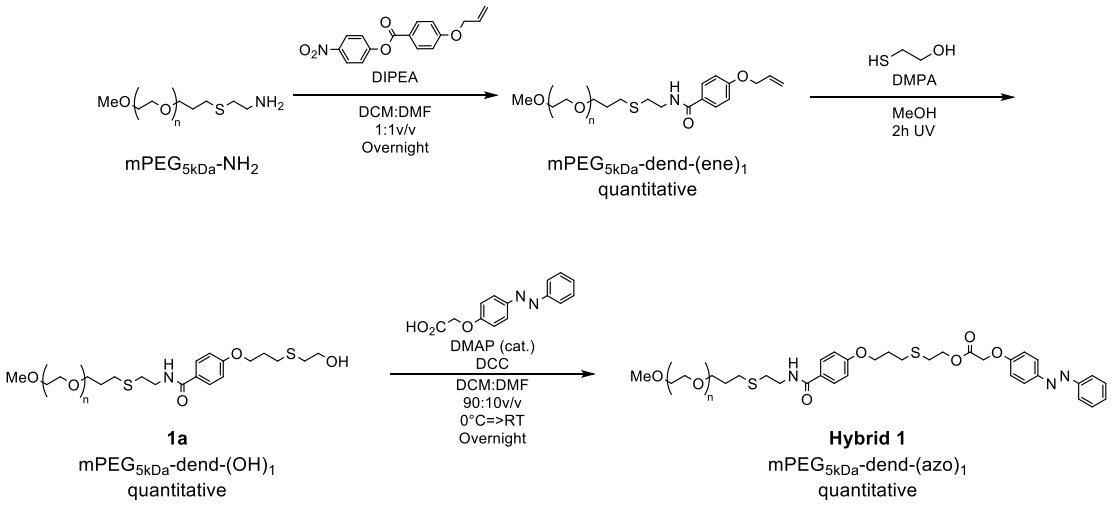

Figure S14: Preparation of $mPEG_{5kDa}$-dend-$(azo)_1$.

$mPEG_{5kDa}$-dend-$(ene)_1$: $mPEG_{5kDa}$-NH_2 (200mg, 0.039mmol), 4-nitrophenyl 4-(allyloxy)benzoate (35mg, 0.117mmol, 3eq) and DIPEA (60µL, 0.351mmol, 9eq) were reacted in DCM:DMF 1:1v/v (2mL) according to the general procedure. The product was obtained as a white solid in quantitative yield (206mg).

^{1}H-NMR ($CDCl_3$): δ 7.73 (d, *J* = 8.8Hz, 2H, arom H), 6.91 (d, *J* = 8.8Hz, 2H, arom H), 6.69 (t, *J* = 4.9Hz, 1H, -NH-CO-), 5.97-6.07 (m, 1H, vinylic H), 5.39 (dd, *J* = 17.3Hz, 1.6Hz, 1H, *E* vinylic H), 5.28 (dd, *J* = 10.5Hz, 1.4Hz, 1H, *Z* vinylic H), 4.55 (dt, *J* = 5.2Hz, 1.4Hz, 2H, allylic H), 3.42-3.80 (m, 521H, PEG backbone), 3.35 (s, 3H, -O-CH_3), 2.74 (t, *J* = 6.5Hz, 2H, -CH_2-S-), 2.62 (t, *J* = 7.2Hz, 2H, -

CH_2-S-), 1.86 (qui, *J* = 6.7Hz, 2H, -O-CH_2-C***H*****$_2$**-CH_2-S-); ^{13}C-NMR ($CDCl_3$): δ 167.0, 161.3, 132.8, 128.9, 127.0, 118.1, 114.6, 72.1, 70.9, 70.7, 70.3, 69.6, 59.1, 38.8, 32.0, 29.8, 28.4; FT-IR, ν(cm^{-1}): 2880, 1467, 1360, 1341, 1280, 1241, 1147, 1099, 1060, 959, 947, 842; GPC (DMF + 25mM NH_4Ac): M_n = 5.3kDa, PDI = 1.03.

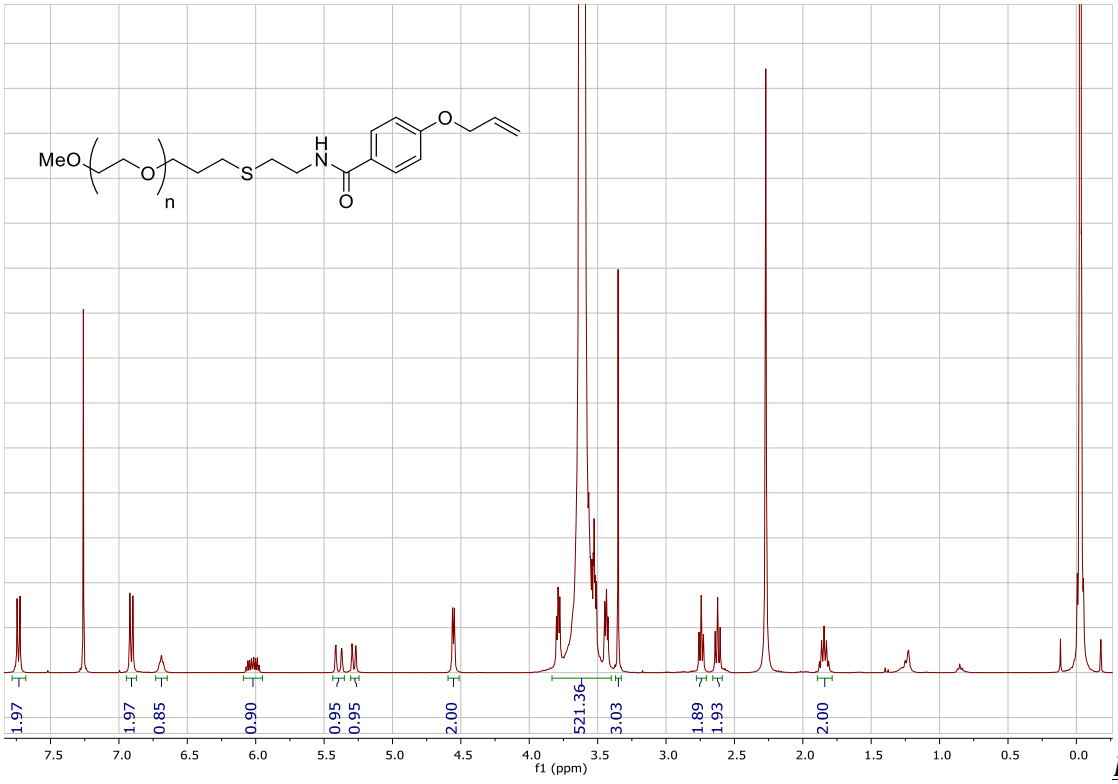

Figure S15: ^{1}H-NMR spectrum of mPEG$_{5kDa}$-dend-(ene)$_1$ in $CDCl_3$.

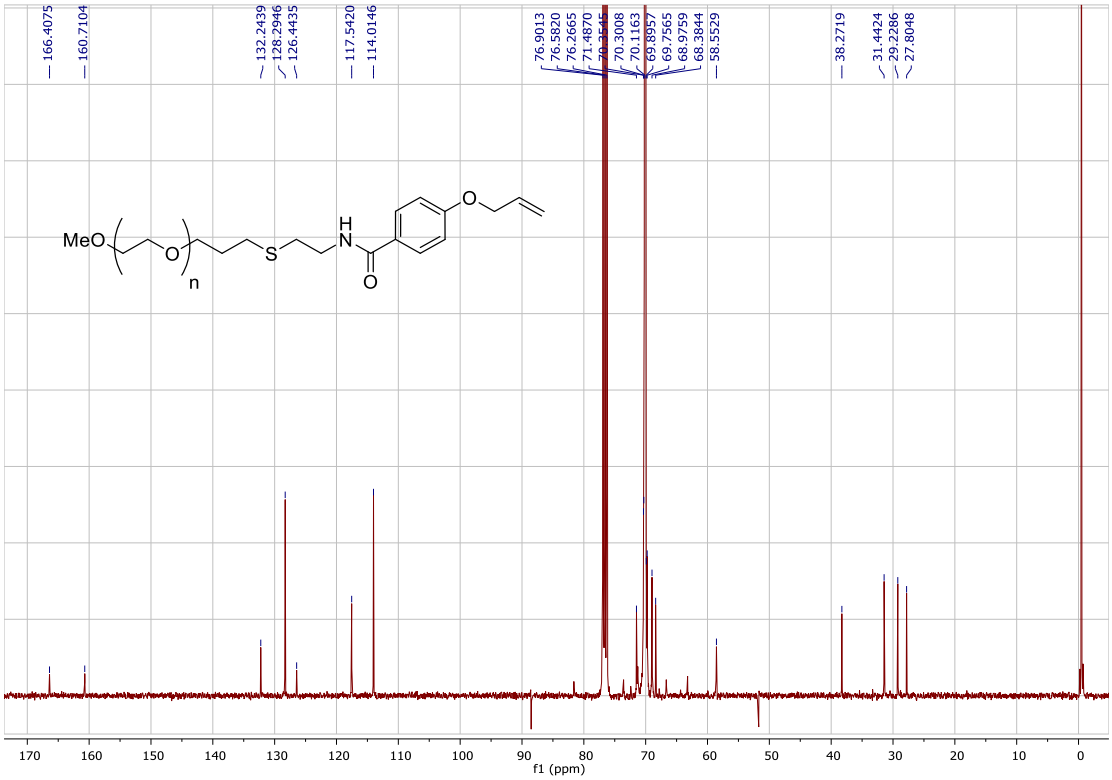

Figure S16: ^{13}C-NMR spectrum of mPEG$_{5kDa}$-dend-(ene)$_1$ in CDCl$_3$.

mPEG$_{5kDa}$-dend-(OH)$_1$: mPEG$_{5kDa}$-dend-(ene)$_1$ (153mg, 0.033mmol), 2-mercaptoethanol (50µL, 0.66mmol, 20eq) and DMPA (1.7mg, 6.6µmol, 0.2eq) were reacted in MeOH (0.77mL) according to the general procedure. The product was obtained as a white solid in quantitative yield (158mg).

^{1}H-NMR (CDCl$_3$): δ 7.74 (d, *J* = 8.8Hz, 2H, arom H), 6.90 (d, *J* = 8.8Hz, 2H, arom H), 6.66 (t, *J* = 5.7Hz, 1H, -NH-CO-), 4.09 (t, *J* = 6.0Hz, 2H, -O-CH$_2$-), 3.43-3.81 (m, 549H, PEG backbone), 3.36 (s, 3H, -O-CH$_3$), 2.70-2.77 (m, 6H, -CH$_2$-S-), 2.63 (t, *J* = 7.2Hz, 2H, -CH$_2$-S-), 2.07 (qui, *J* = 6.6Hz, 2H, -O-CH$_2$-C***H$_2$***-CH$_2$-S-), 1.85 (qui, *J* = 6.7Hz, 2H, -O-CH$_2$-C***H$_2$***-CH$_2$-S-); ^{13}C-NMR (CDCl$_3$): δ 166.9, 161.4, 128.9, 126.2, 114.2, 72.0, 70.6, 70.2, 69.4, 66.2, 60.5, 59.1, 38.8, 35.2, 31.8, 29.7, 29.3, 28.3, 28.2; FT-IR, ν(cm^{-1}): 2884, 1760, 1598, 1501, 1466, 1454, 1360, 1341, 1279, 1239, 1188, 1146, 1100, 1060, 959, 949, 841; GPC (DMF + 25mM NH$_4$Ac): M$_n$ = 5.4kDa, PDI = 1.05.

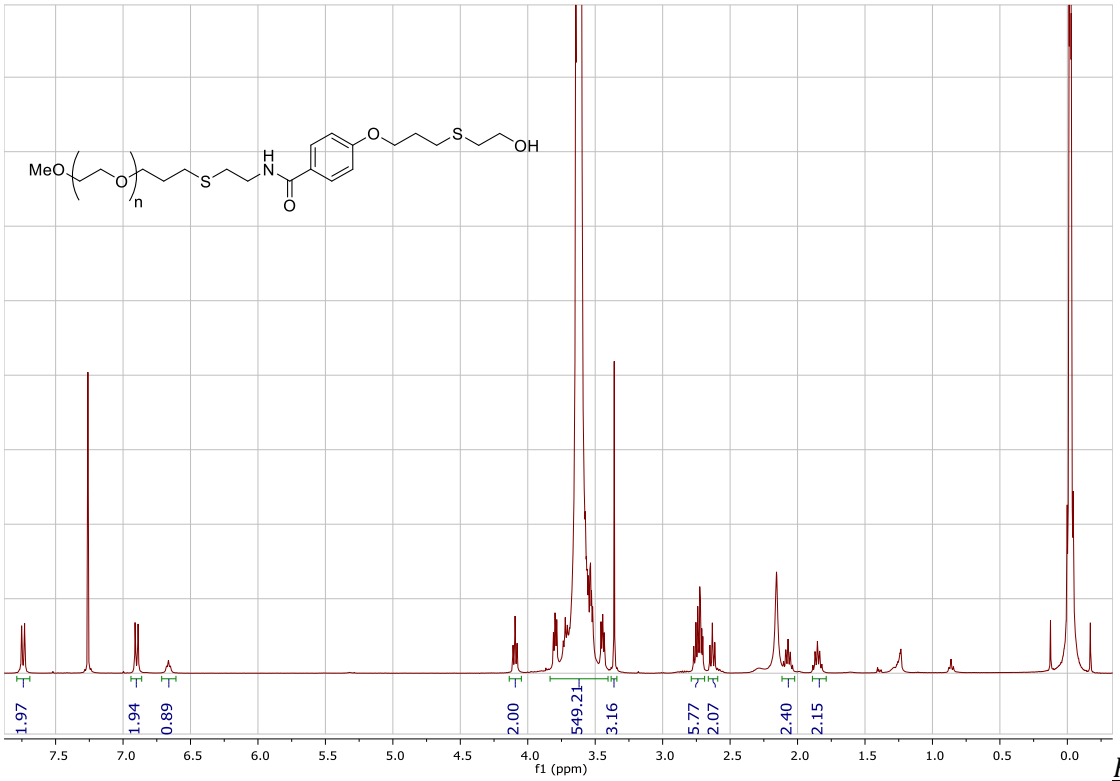

Figure S17: *^{1}H-NMR spectrum of mPEG$_{5kDa}$-dend-(OH)$_1$ in CDCl$_3$.*

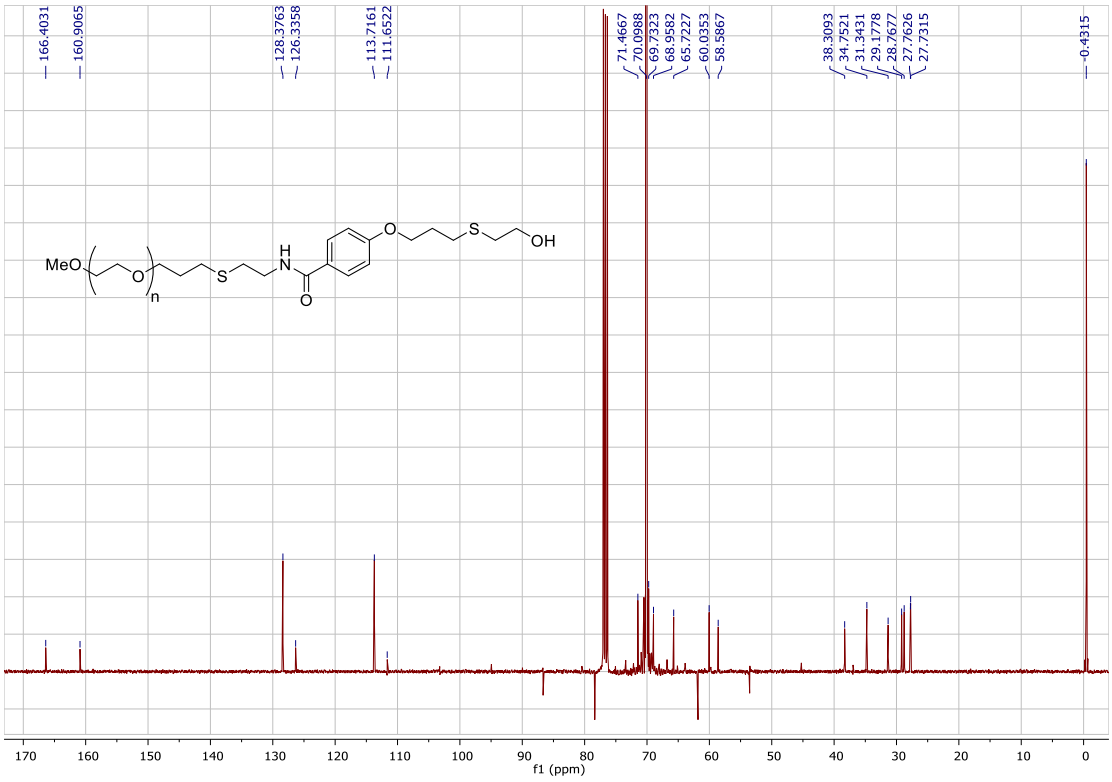

Figure S18: *^{13}C-NMR spectrum of mPEG$_{5kDa}$-dend-(OH)$_1$ in CDCl3.*

mPEG$_{5kDa}$-dend-(azo)$_1$: mPEG$_{5kDa}$-dend-(OH)$_1$ (100mg, 0.019mmol), azo acid (24mg, 0.095mmol, 5eq), DMAP (2.3mg, 0.019mmol, 1eq) and DCC (20mg, 0.095mmol, 5eq) were

reacted in DCM:DMF 90:10v/v (2mL) according to the general procedure. The product was obtained as an orange solid in quantitative yield (104mg).

^{1}H-NMR ($CDCl_3$): δ 7.89 (d, *J* = 8.9Hz, 2H, arom H), 7.85 (dd, *J* = 8.3Hz, 1.6Hz, 2H, arom H), 7.72 (d, *J* = 8.8Hz, 2H, arom H), 7.39-7.52 (m, 3H, arom H), 7.00 (d, *J* = 8.9Hz, 2H, arom H), 6.88 (d, *J* = 8.8Hz, 2H, arom H), 6.65 (t, *J* = 5.7Hz, 1H, -NH-CO-), 4.71+4.59 (s, 2H, trans+cis –O-CO-C***H₂***-O-azo), 4.37 (t, *J* = 6.8Hz, 2H, -CH_2-O-CO-), 4.06 (t, *J* = 6.0Hz, 2H, Ar-O-CH_2-), 3.43-3.81 (m, 543H, PEG backbone), 3.35 (s, 3H, -O-CH_3), 2.68-2.83 (m, 6H, -CH_2-S-), 2.62 (t, *J* = 7.2Hz, 2H, -CH_2-S-), 2.05 (qui, *J* = 6.5Hz, 2H, -S-CH_2-C***H₂***-CH_2-O-), 1.84 (qui, *J* = 6.7Hz, 2H, -S-CH_2-C***H₂***-CH_2-O-). ^{13}C-NMR ($CDCl_3$): δ 168.4, 166.9, 161.4, 160.0, 152.7, 147.7, 130.7, 129.1, 128.9, 126.9, 124.8, 122.7, 114.9, 114.2, 72.0, 71.0, 70.6, 70.3, 69.5, 65.4, 64.1, 62.3, 59.1, 38.8, 31.9, 30.5, 29.7, 29.2, 28.8, 28.3; FT-IR, ν(cm^{-1}): 2882, 1757, 1591, 1470, 1362, 1342, 1281, 1243, 1146, 1099, 1061, 960, 949, 843; GPC (DMF + 25mM NH_4Ac): M_n = 5.5kDa, PDI = 1.05; MALDI TOF-MS: molecular ion centered at 5.6kDa, expected M_n = 5.6kDa.

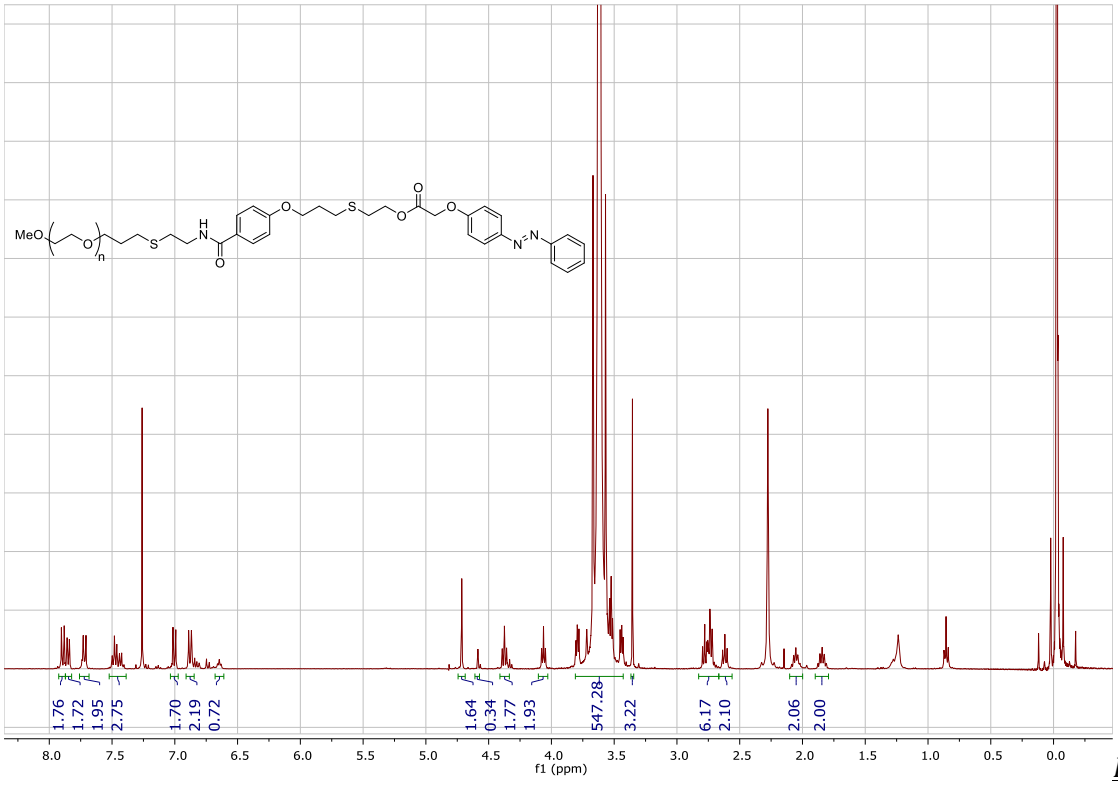

Figure S19: ^{1}H-NMR spectrum of mPEG$_{5kDa}$-dend-(azo)$_1$ in $CDCl_3$.

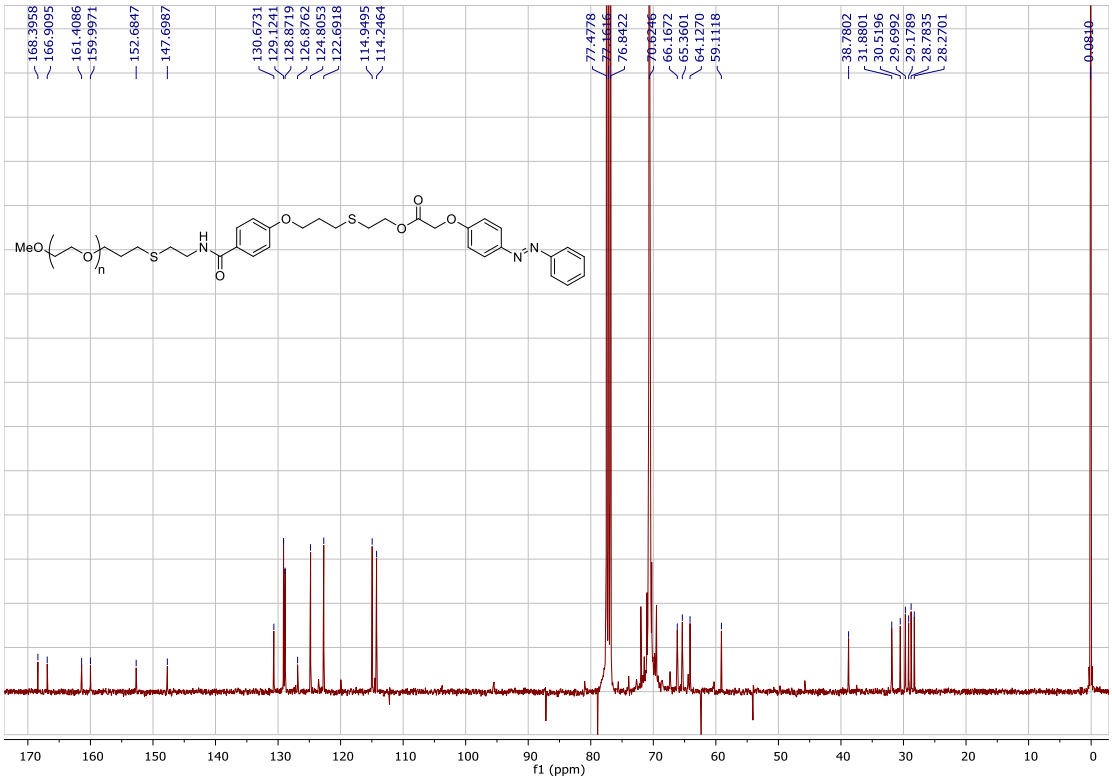

Figure S20: ^{13}C-NMR spectrum of mPEG$_{5kDa}$-dend-(azo)$_1$ in CDCl$_3$.

Synthesis of mPEG$_{5kDa}$-dend-(azo)$_2$ (hybrid 2)

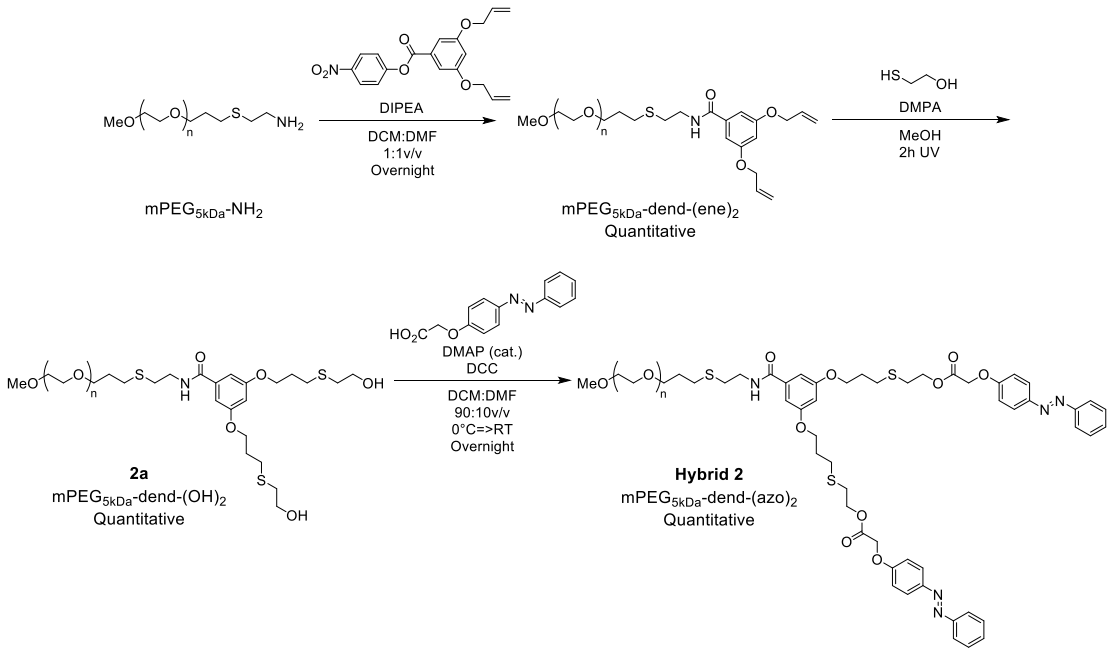

Figure S21: Preparation of mPEG$_{5kDa}$-dend-(azo)$_2$.

mPEG$_{5kDa}$-dend-(ene)$_2$: mPEG$_{5kDa}$-NH$_2$ (205mg, 0.04mmol), 4-nitrophenyl 3,5-bis(allyloxy)benzoate (43mg, 0.12mmol, 3eq) and DIPEA (63µL, 0.36mmol, 9eq) were reacted

in DCM:DMF 1:1v/v (mL) according to the general procedure. The product was obtained as a white solid in quantitative yield (216mg).

^{1}H-NMR ($CDCl_3$): δ 6.91 (d, *J* = 2.2Hz, 2H, arom H), 6.71 (t, *J* = 5.3Hz, 1H, -NH-CO-), 6.57 (t, *J* = 2.2Hz, 1H, arom H), 5.96-6.05 (m, 2H, vinylic H), 5.38 (dd, *J* = 17.2Hz, 1.4Hz, 2H, *E* vinylic H), 5.26 (dd, *J* = 10.5Hz, 1.3Hz, 2H, *Z* vinylic H), 4.52 (dt, *J* = 5.3Hz, 1.4Hz, 4H, allylic H), 3.42-3.79 (m, 546H, PEG backbone), 3.34 (s, 3H, -O-CH_3), 2.73 (t, *J* = 6.5Hz, 2H, -CH_2-S-), 2.61 (t, *J* = 7.2Hz, 2H, -CH_2-S-), 1.84 (qui, *J* = 6.7Hz, 2H, -O-CH_2-C***H*****$_2$**-CH_2-S-); ^{13}C-NMR ($CDCl_3$): δ 167.1, 159.8, 136.7, 132.9, 118.0, 106.0, 105.1, 72.0, 70.6, 70.3, 69.5, 69.1, 59.1, 38.9, 31.8, 29.7, 28.3; FT-IR, ν(cm^{-1}): 2882, 1559, 1541, 1523, 1510, 1467, 1458, 1361, 1341, 1281, 1241, 1147, 1097, 1060, 958, 947, 842; GPC (DMF + 25mM NH_4Ac): M_n = 5.2kDa, PDI = 1.04.

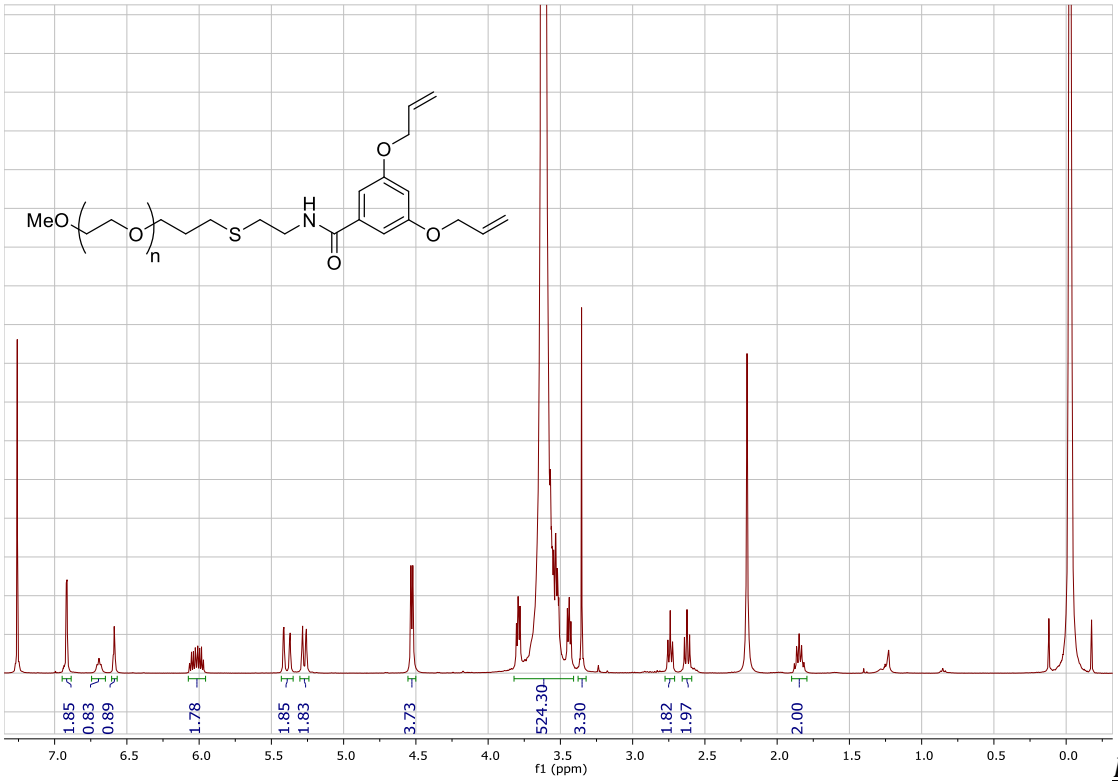

Figure S22: ^{1}H-NMR spectrum of mPEG$_{5kDa}$-dend-(ene)$_2$ in $CDCl_3$.

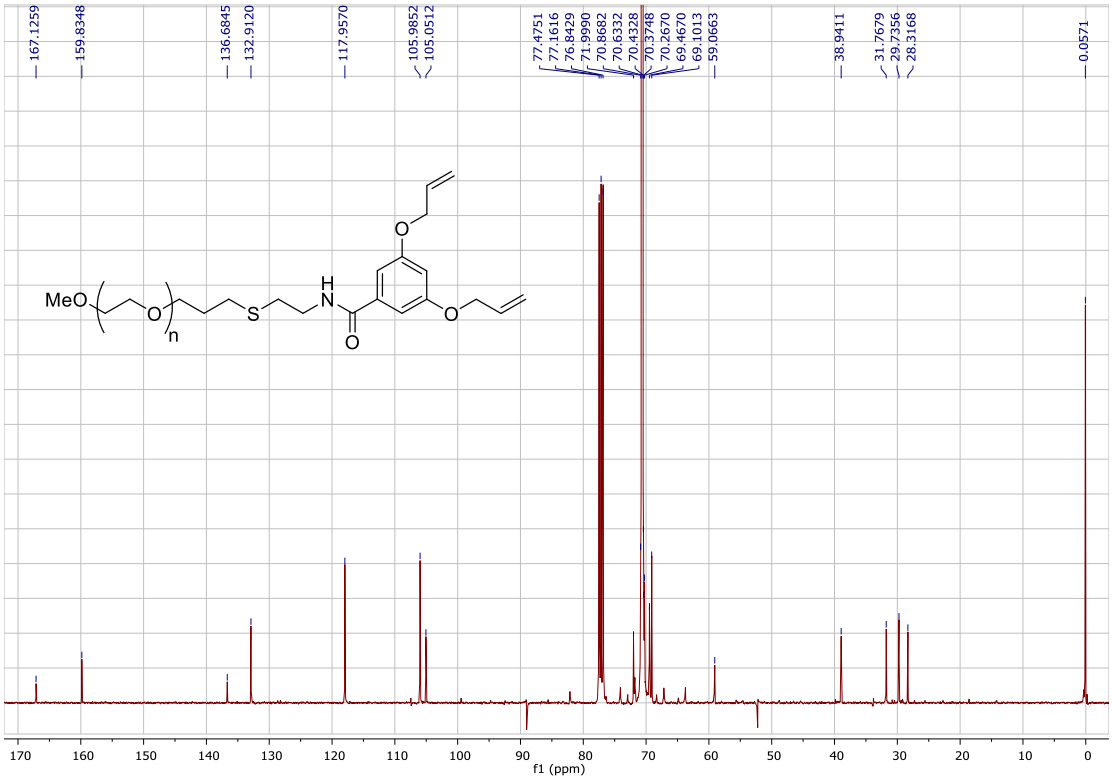

Figure S23: ^{13}C-NMR spectrum of mPEG$_{5kDa}$-dend-(ene)$_2$ in CDCl$_3$.

mPEG$_{5kDa}$-dend-(OH)$_2$: mPEG$_{5kDa}$-dend-(ene)$_2$ (170mg, 0.031mmol), 2-mercaptoethanol (87µL, 1.24mmol, 40eq) and DMPA (7.6mg, 0.062mmol, 2eq) were reacted in MeOH (0.85mL) according to the general procedure. The product was obtained as a white solid in quantitative yield (173mg).

^{1}H-NMR (CDCl$_3$): δ 6.90 (d, *J* = 2.2Hz, 2H, arom H), 6.78 (t, *J* = 5.6Hz, 1H, -NH-CO-, 6.54 (t, *J* = 2.2Hz, 1H, arom H), 4.07 (t, *J* = 6.0Hz, 4H, Ar-O-CH$_2$-), 3.42-3.80 (m, 550H, PEG backbone), 3.35 (s, 3H, -O-CH$_3$), 2.68-2.75 (m, 10H, -CH$_2$-S-), 2.62 (t, *J* = 7.2Hz, 2H, -CH$_2$-S-), 2.49 (m, 2H, -OH), 2.03 (qui, *J* = 6.5Hz, 4H, -O-CH$_2$-C***H$_2$***-CH$_2$-S-), 1.84 (qui, *J* = 6.7Hz, 2H, -O-CH$_2$-CH$_2$-CH$_2$-S-); ^{13}C-NMR (CDCl$_3$): δ 167.2, 160.1, 136.8, 105.8, 104.7, 72.0, 70.6, 70.3, 69.5, 66.5, 60.7, 59.1, 39.0, 35.3, 31.8, 29.7, 29.4, 28.4, 28.3; FT-IR, ν(cm^{-1}): 2884, 1759, 1600, 1586, 1501, 1468, 1451, 1444, 1359, 1342, 1279, 1239, 1189, 1146, 1099, 1060, 960, 948, 841; GPC (DMF + 25mM NH$_4$Ac): M$_n$ = 5.4kDa, PDI = 1.06.

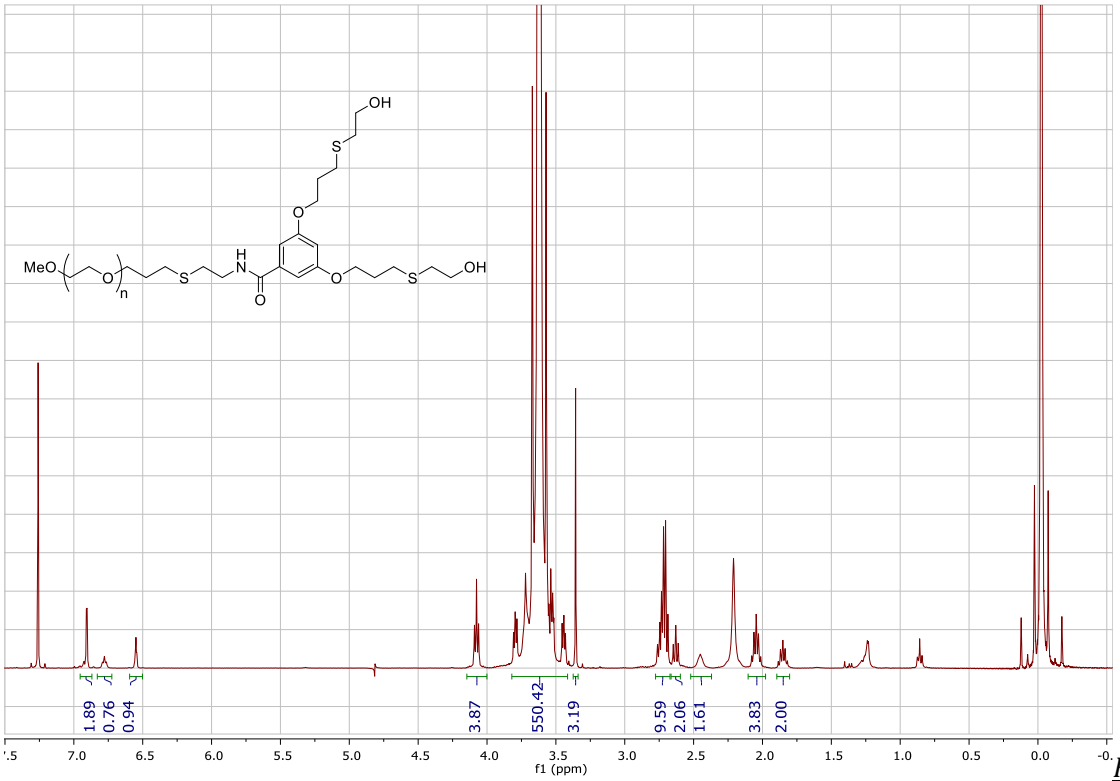

Figure S24: ^{1}H-NMR spectrum of mPEG$_{5kDa}$-dend-(OH)$_2$ in CDCl$_3$.

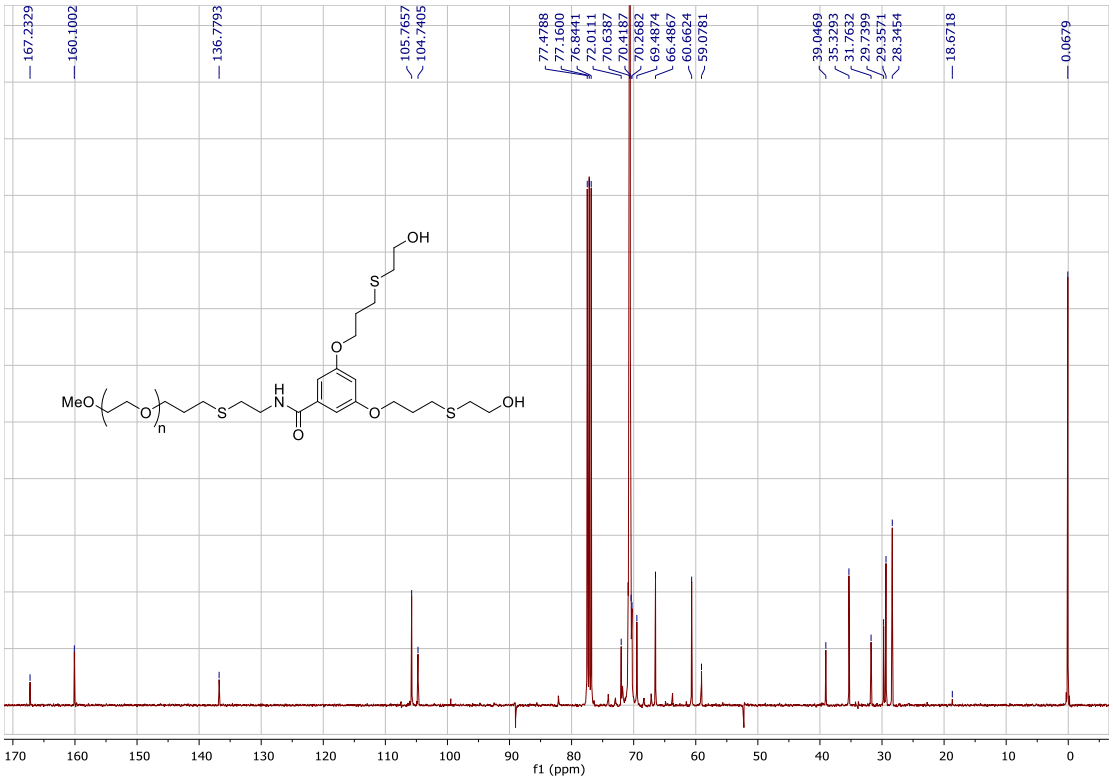

Figure S25: ^{13}C-NMR spectrum of mPEG$_{5kDa}$-dend-(OH)$_2$ in CDCl$_3$.

mPEG$_{5kDa}$-dend-(azo)$_2$: mPEG$_{5kDa}$-dend-(OH)$_2$ (100mg, 0.018mmol), azo acid (46mg, 0.18mmol, 10eq), DMPA (4.4mg, 0.036mmol, 2eq) and DCC (37mg, 0.18mmol, 10eq) were reacted in

DCM:DMF 90:10v/v (2mL) according to the general procedure. The product was obtained as an orange solid in quantitative yield (108mg).

^{1}H-NMR ($CDCl_3$): δ 7.87 (d, *J* = 9.0Hz, 4H, arom H), 7.84 (dd, *J* = 8.3Hz, 1.5Hz, 4H, arom H), 7.38-7.51 (m, 3H, arom H), 6.98 (d, *J* = 9.1Hz, 4H, arom H), 6.87 (d, *J* = 2.2Hz, 2H, arom H), 6.73-6.75 (m, 1H, -NH-CO-), 6.52 (t, *J* = 2.2Hz, 1H, arom H), 4.70+4.57 (s, 4H, trans+cis –O-CO-CH_2-O-azo), 4.36 (t, *J* = 6.8Hz, 4H, -CH_2-O-CO-), 4.02 (t, *J* = 5.9Hz, 4H, Ar-O-CH_2-), 3.42-3.80 (m, 510H, PEG backbone), 3.35 (s, 3H, -O-CH_3), 2.66-2.80 (m, 10H, -CH_2-S-), 2.60 (t, *J* = 7.2Hz, 2H, -CH_2-S-), 2.01 (qui, *J* = 6.5Hz, 4H, -O-CH_2-C***H*****$_2$**-CH_2-S-), 1.83 (qui, *J* = 6.7Hz, 2H, -O-CH_2-C***H*****$_2$**-CH_2-S-); ^{13}C-NMR ($CDCl_3$): δ 168.4, 167.2, 160.1, 160.0, 152.8, 147.8, 136.8, 130.7, 129.1, 124.8, 122.7, 115.0, 105.8, 104.6, 72.0, 70.7, 70.3, 69.6, 66.4, 65.4, 64.2, 59.1, 39.1, 31.8, 30.6, 29.8, 29.3, 28.8, 28.4; FT-IR, ν(cm^{-1}): 2884, 1757, 1599, 1467, 1359, 1342, 1278, 1240, 1148, 1099, 1061, 959, 948, 841; GPC (DMF + 25mM NH_4Ac): M_n = 5.6kDa, PDI = 1.05; MALDI TOF-MS: molecular ion centered at 6.0kDa, expected M_n = 6.0kDa.

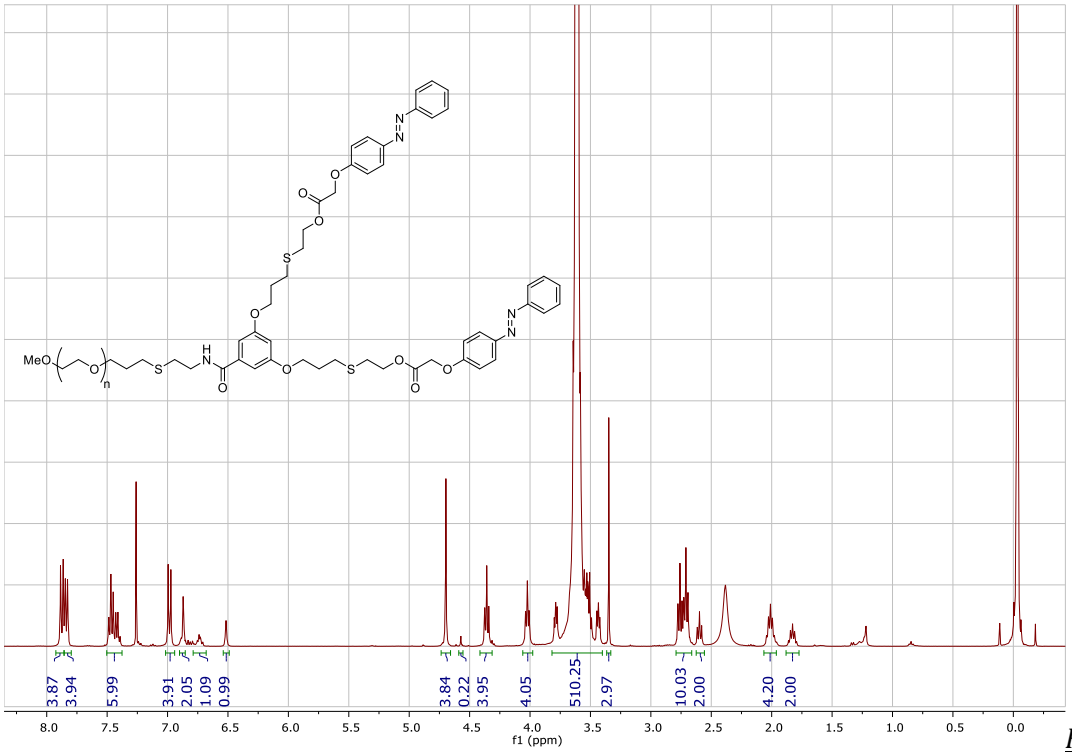

Figure S26: ^{1}H-NMR spectrum of mPEG$_{5kDa}$-dend-(azo)$_2$ in $CDCl_3$.

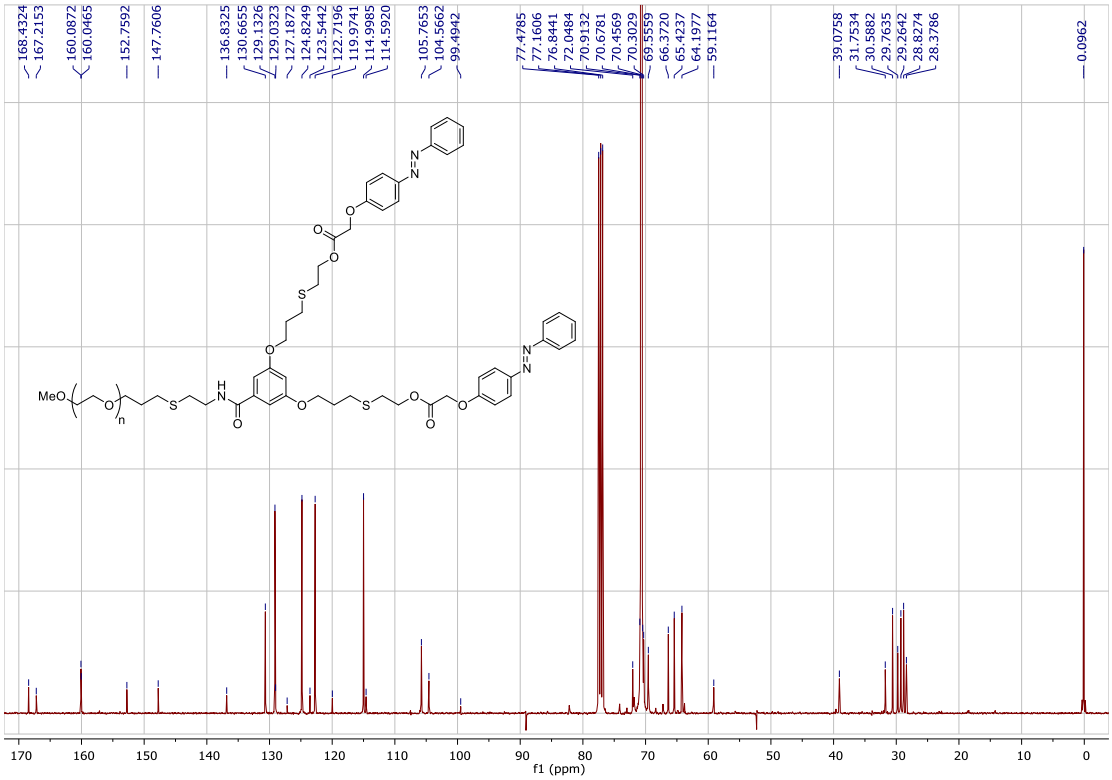

Figure S27: ^{13}C-NMR spectrum of mPEG$_{5kDa}$-dend-(azo)$_2$ in CDCl$_3$.

Synthesis of mPEG$_{5kDa}$-dend-(azo)$_4$ (hybrid 3)

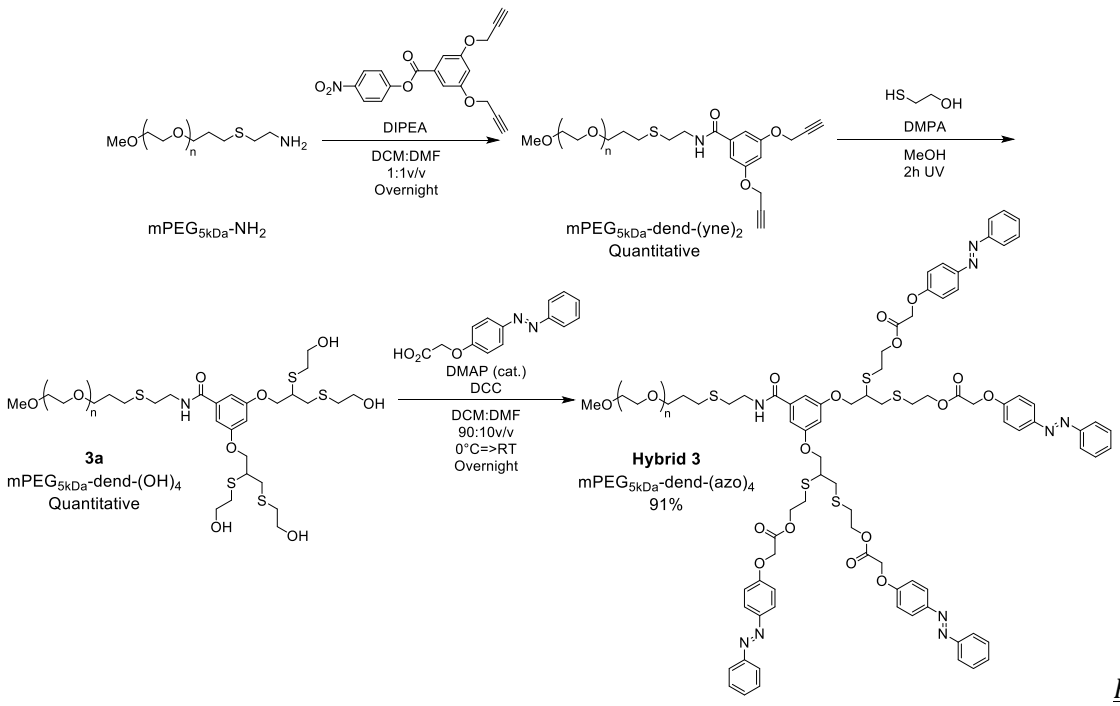

Figure S28: Preparation of mPEG$_{5kDa}$-dend-(azo)$_4$.

mPEG$_{5kDa}$-dend-(yne)$_2$: mPEG$_{5kDa}$-NH$_2$ (256mg, 0.05mmol), 4-nitrophenyl 3,5-bis(propargyloxy)benzoate (53mg, 0.15mmol, 3eq) and DIPEA (78µL, 0.45mmol, 9eq) were

reacted in DCM:DMF 1:1v/v (2.5mL) according to the general procedure. The product was obtained as a white solid in quantitative yield (262mg).

^{1}H,^{13}C-NMR and FT-IR were found to correlate with previous reports.[4]

GPC (DMF+25mM NH_4Ac): M_n = 5.2kDa, PDI = 1.03.

mPEG$_{5kDa}$-dend-(OH)$_4$: mPEG$_{5kDa}$-dend-(yne)$_2$ (160mg, 0.03mmol), 2-mercaptoethanol (170µL, 2.4mmol, 80eq) and DMPA (6mg, 0.024mmol, 0.8eq) were reacted in MeOH (0.8mL) according to the general procedure. The product was obtained as a white solid in quantitative yield (165mg).

^{1}H,^{13}C-NMR and FT-IR were found to correlate with previous reports.[6]

GPC (DMF+25mM NH_4Ac): M_n = 5.5kDa, PDI = 1.03.

mPEG$_{5kDa}$-dend-(azo)$_4$: mPEG$_{5kDa}$-dend-(OH)$_4$ (113mg, 0.02mmol), azo acid (103mg, 0.4mmol, 20eq), DMPA (10mg, 0.08mmol, 4eq) and DCC (83mg, 0.4mmol, 20eq) were reacted in DCM:DMF 90:10v/v (2mL) according to the general procedure. The product was obtained as an orange solid in 91% yield (120mg).

^{1}H-NMR ($CDCl_3$): δ 7.79-7.94 (m, 16H, arom H), 7.39-7.52 (m, 12H, arom H), 6.92-7.04 (m, 10H, arom H), 6.54-6.61 (m, 1H, arom H), 4.61-4.74 + 4.46-4.53 (m, 8H, trans+cis –O-CO-CH_2-O-azo), 4.24-4.29 (m, 8H, -S-CH_2-C***H*****$_2$**-O-CO-), 3.82-4.08 (m, 4H, -Ar-O-CH_2-), 3.82-3.44 (m, 549H, PEG backbone), 3.37 (s, 3H, -O-CH_3), 3.19 (qui, *J* = 6.5Hz, 2H, -CH-S-), 2.66-3.02 (m, 14H, -CH_2-S-), 2.59 (t, *J* = 7.2Hz, 2H, -CH_2-S-), 1.83 (qui, *J* = 6.6Hz, 2H, -O-CH_2-CH_2-CH_2-S-); ^{13}C-NMR ($CDCl_3$): δ 168.5, 168.4, 166.8, 160.0, 159.5, 152.7, 147.7, 137.0, 130.7, 129.1, 124.8, 122.7, 115.0, 106.3, 104.6, 72.0, 70.6, 70.2, 69.9, 69.6, 65.4, 64.4, 64.0, 59.1, 45.6, 39.5, 34.9, 31.6, 31.5, 30.4, 29.7, 28.4; FT-IR, ν(cm^{-1}): 2883, 1758, 1599, 1500, 1466, 1455, 1360, 1341, 1301, 1279, 1240, 1188, 1146, 1100, 1060, 960, 949, 841; GPC (DMF + 25mM NH_4Ac): M_n = 6.0kDa, PDI = 1.03; MALDI TOF-MS: molecular ion centered at 6.6kDa, expected M_n = 6.6kDa.

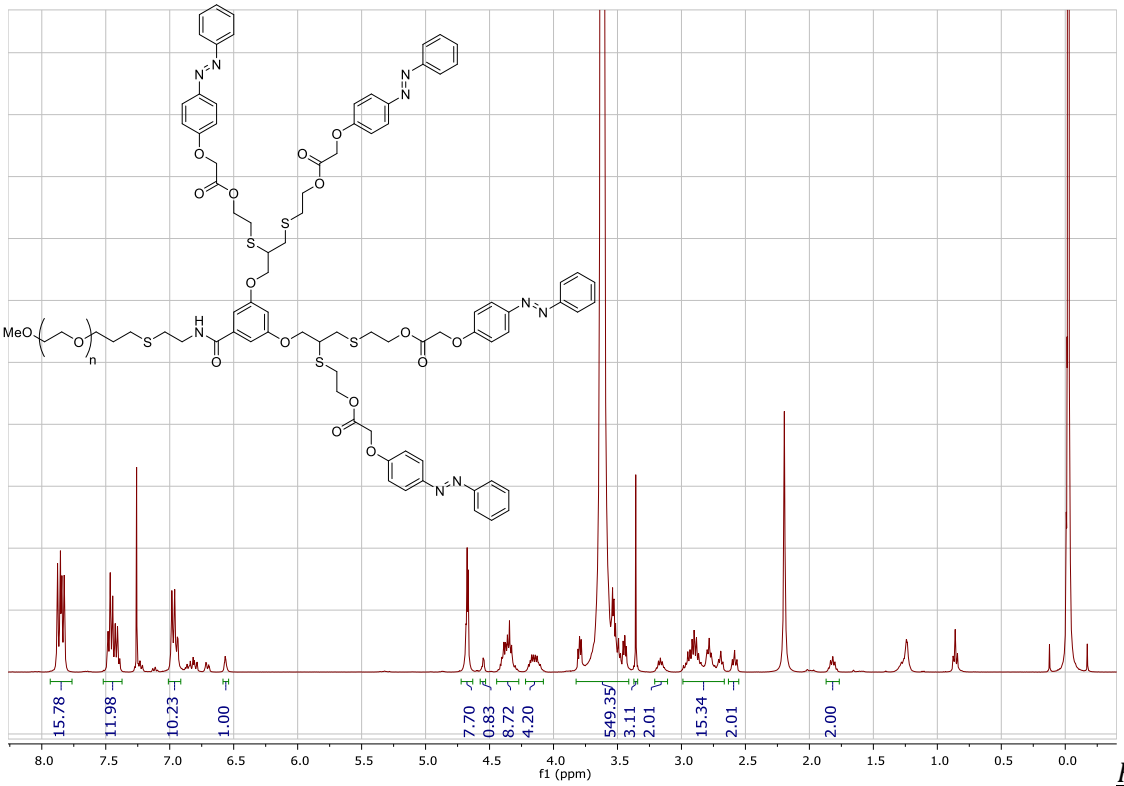

Figure S29: ^{1}H-NMR spectrum of mPEG$_{5kDa}$-dend-(azo)$_4$ in CDCl$_3$.

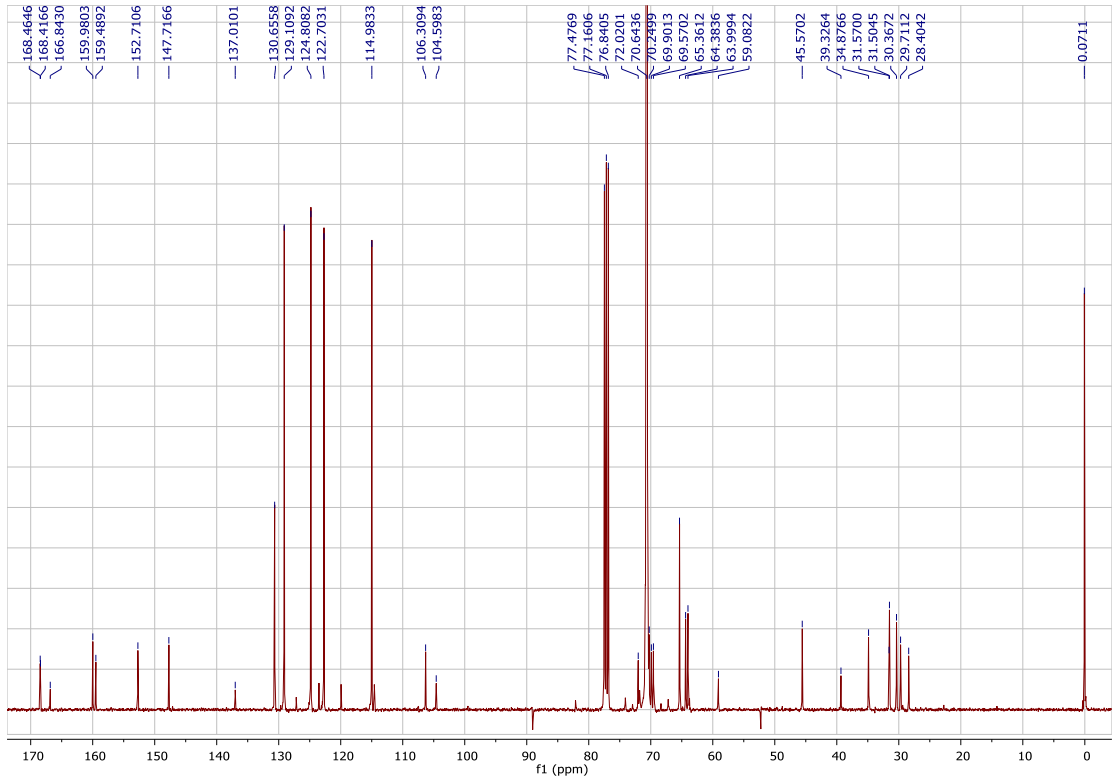

Figure S30: ^{13}C-NMR spectrum of mPEG$_{5kDa}$-dend-(azo)$_4$ in CDCl$_3$.

Characterization of PEG-dendron hybrids

Gel permeation chromatography (GPC)

Instrument method:

Instrument: Malvern Viscotek GPCmax

Columns: 2xPSS GRAM 1000Å + PSS GRAM 30Å

Columns temperature: 50°C

Flow rate: 0.5mL/min

Injection time: 90min

Injection volume: 50µL from a 10mg/ml sample

Diluent + mobile phase: DMF + 25mM NH_4Ac

Needle wash: DMF

Detector: Viscotek VE3580 RI detector

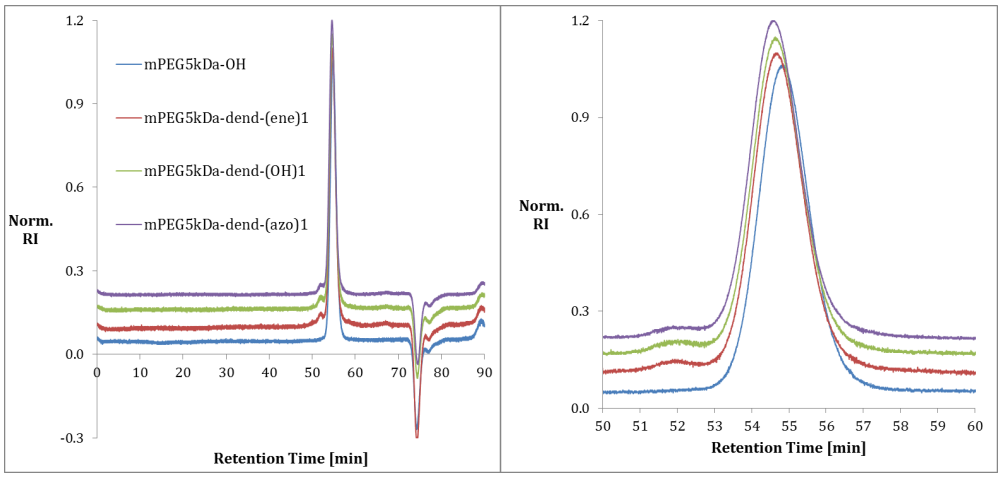

Figure S31: GPC overlay of commercial 5kDa methoxy PEG (blue), $mPEG_{5kDa}$-dend-$(ene)_1$ (red), $mPEG_{5kDa}$-dend-$(OH)_1$ and $mPEG_{5kDa}$-dend-$(azo)_1$ (hybrid 1, purple).

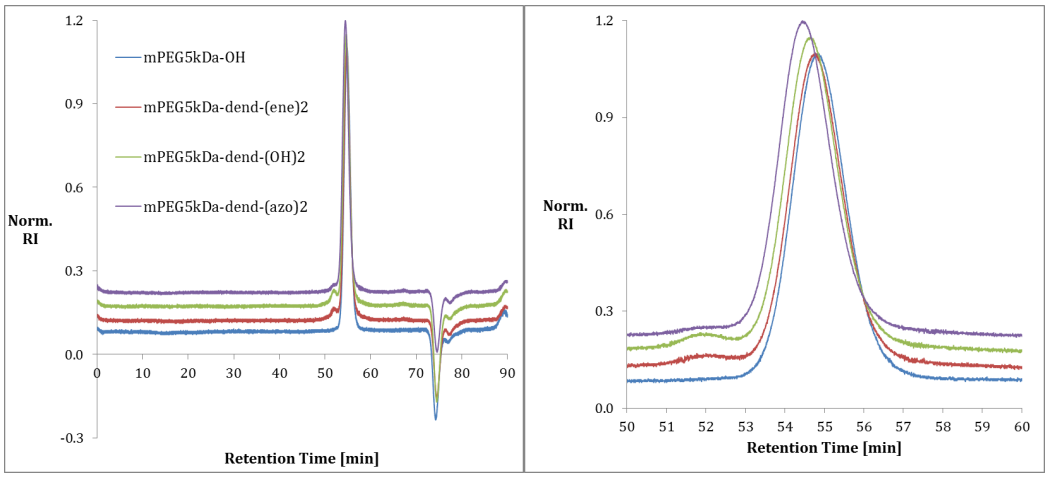

Figure S32: GPC overlay of commercial 5kDa methoxy PEG (blue), $mPEG_{5kDa}$-dend-$(ene)_2$ (red), $mPEG_{5kDa}$-dend-$(OH)_2$ and $mPEG_{5kDa}$-dend-$(azo)_2$ (hybrid 2, purple).

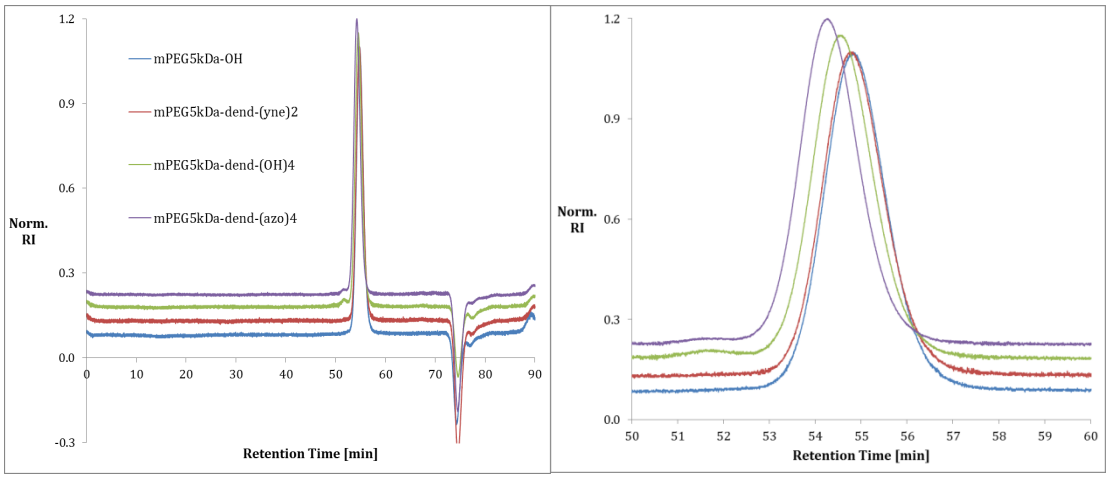

Figure S33: GPC overlay of commercial 5kDa methoxy PEG (blue), $mPEG_{5kDa}$-dend-$(yne)_2$ (red), $mPEG_{5kDa}$-dend-$(OH)_4$ and $mPEG_{5kDa}$-dend-$(azo)_4$ (hybrid 3, purple).

Critical micelles' concentration (CMC)

General procedure of measurement:

Preparation of diluent:

Nile Red stock solution (0.88mg/ml in ethanol) was diluted into a phosphate buffer (100mM, pH 7.4) to afford a final concentration of 1.25µM.

Preparation and measurement of samples:

The PEG-dendron hybrid was directly dissolved in the diluent to give a final concentration of 500µM. Solution was sonicated for 15 minutes and vortexed vigorously until the hybrid was

completely dissolved. This solution was consecutively diluted by a factor of 1.5 with the diluent to afford a series of 24 samples. 150µL of each sample was loaded onto a 96 well plate and a fluorescence emission scan was performed for each well. In order to determine the hybrid's CMC – the maximum emission of Nile Red (at about 630nm) was plotted as a function of the hybrid's concentration.

Instrument method:

Instrument: TECAN Infinite M200Pro

Excitation: 550nm

Emission intensity scan: 580-800nm

Step: 2nm

Number of flashes: 15

Gain: 100

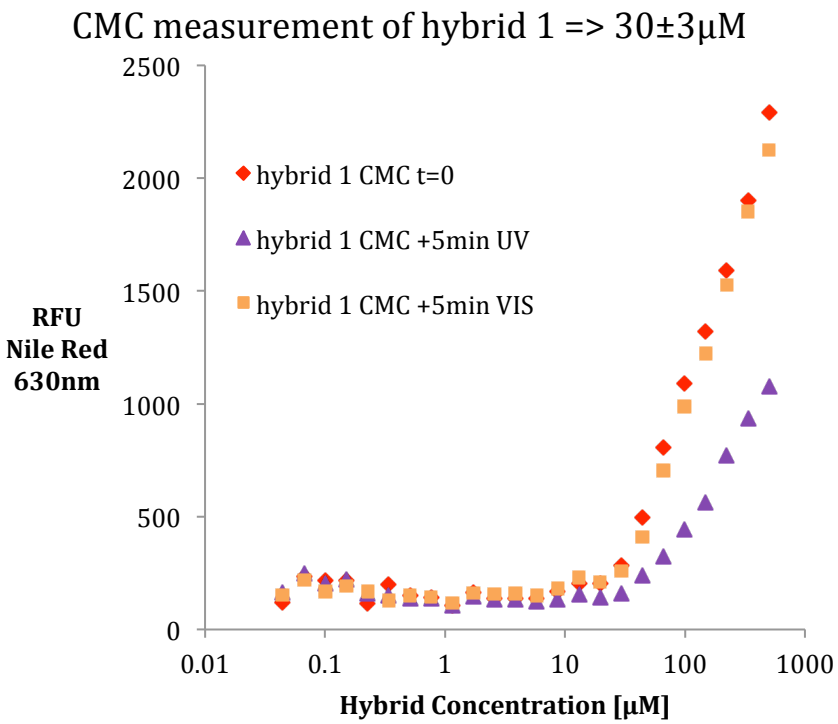

Figure S34: CMC measurement of hybrid 1 using Nile Red method (red). Emission was measured again after exposing the plate to UV light for 5 minutes (purple) and to VIS light for 5 minutes (orange).

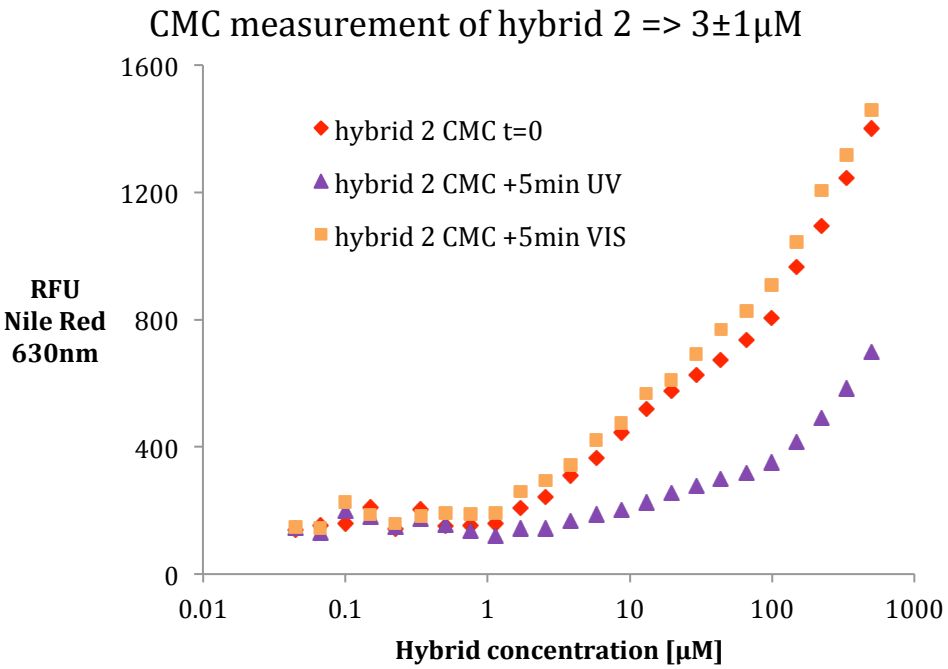

Figure S35: CMC measurement of hybrid 2 using Nile Red method (red). Emission was measured again after exposing the plate to UV light for 5 minutes (purple) and to VIS light for 5 minutes (orange).

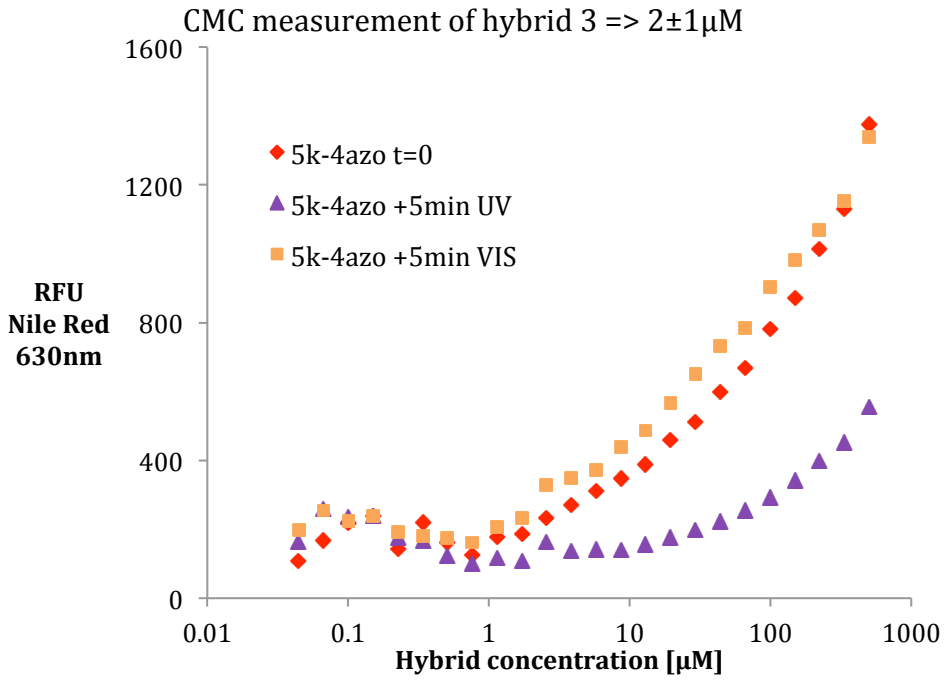

Figure S36: CMC measurement of hybrid 3 using Nile Red method (red). Emission was measured again after exposing the plate to UV light for 5 minutes (purple) and to VIS light for 5 minutes (orange).

^{1}H-NMR in D_2O

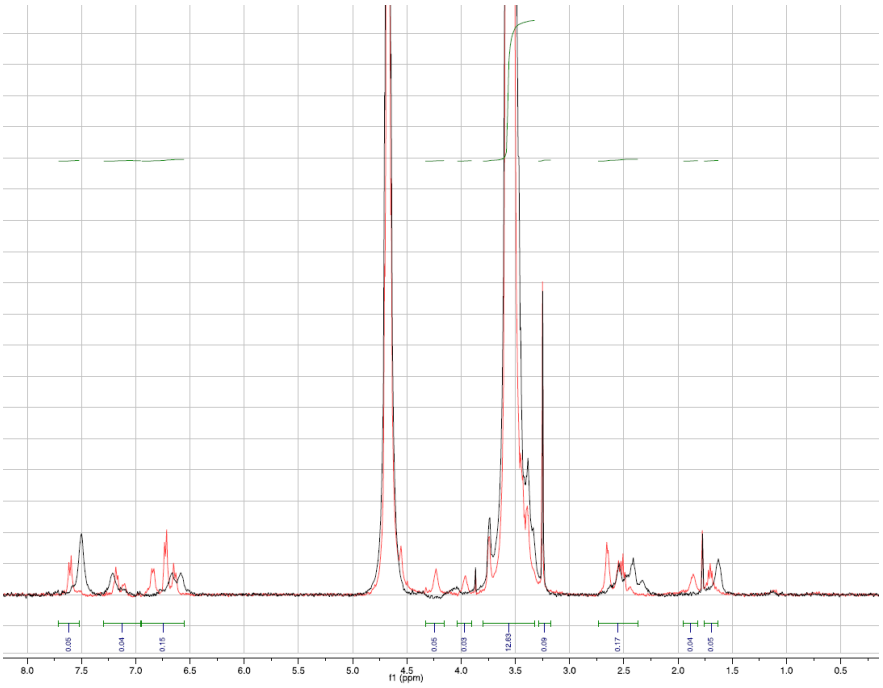

Figure S37: *^{1}H-NMR in D_2O of hybrid 1 (320µM) at t=0 (black) and after UV (red).*

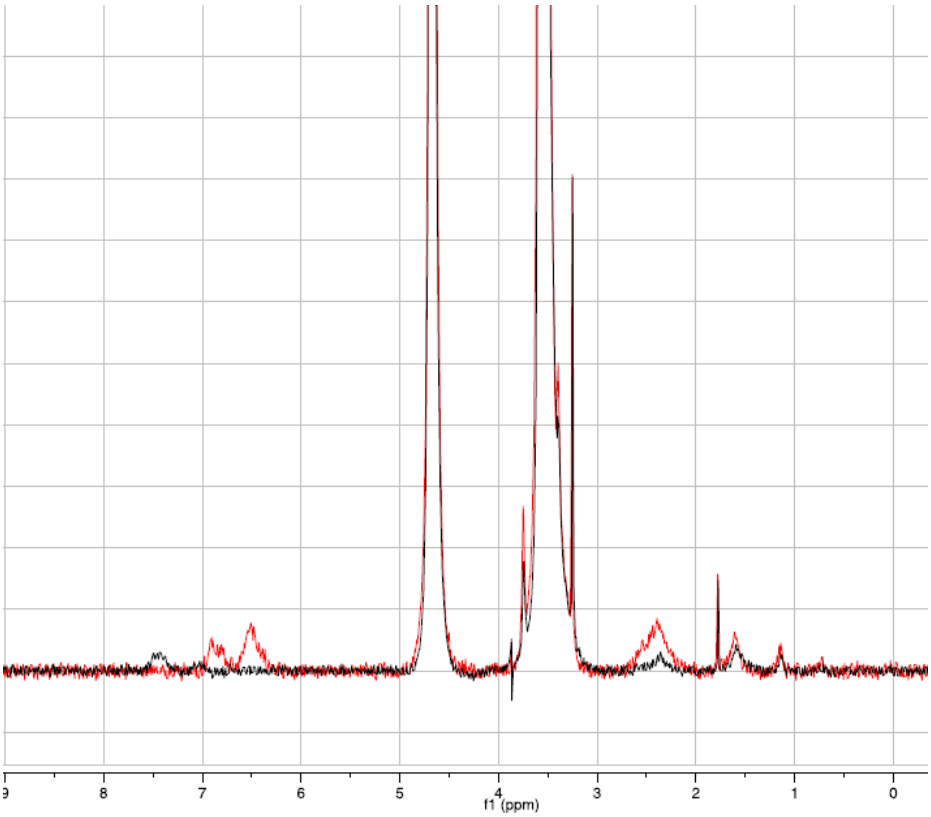

Figure S38: *^{1}H-NMR in D_2O of hybrid 2 (160µM) at t=0 (black) and after UV (red).*

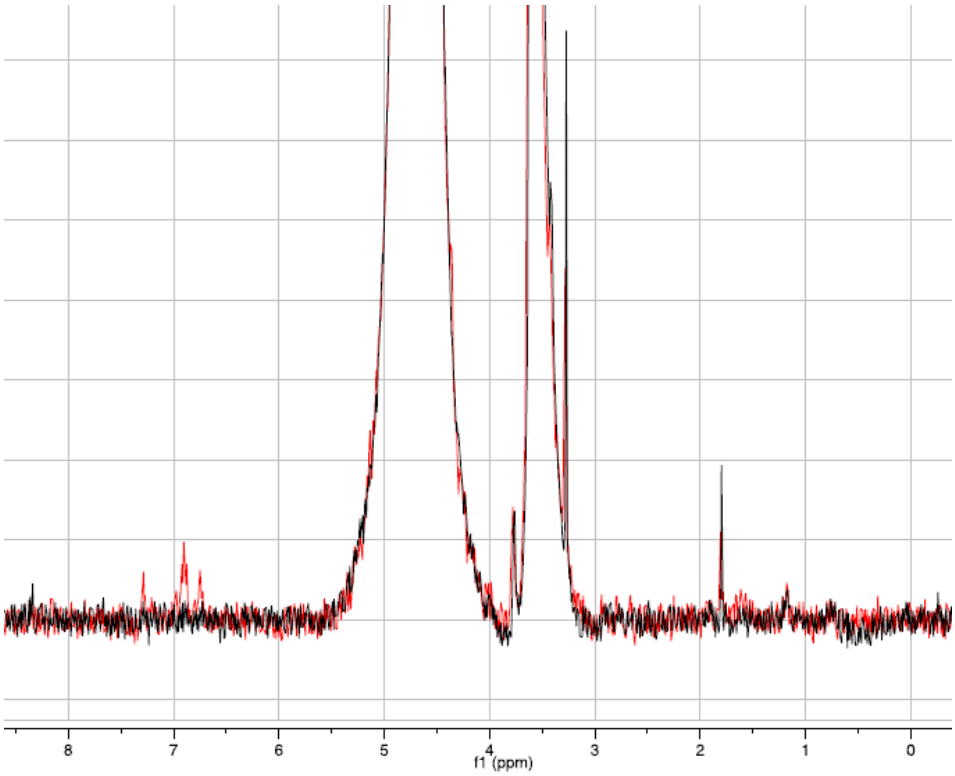

Figure S39: *^{1}H-NMR in D_2O of hybrid 3 (320µM) at t=0 (black) and after UV (red).*

Dynamic light scattering

Instrument method:

Instrument: Corduan technology VASCO$^\gamma$ – particle size analyzer

Time interval: 15µsec

Number of channels: 200

DTC position: down

Laser power: 50%

Cell temperature: 37°C

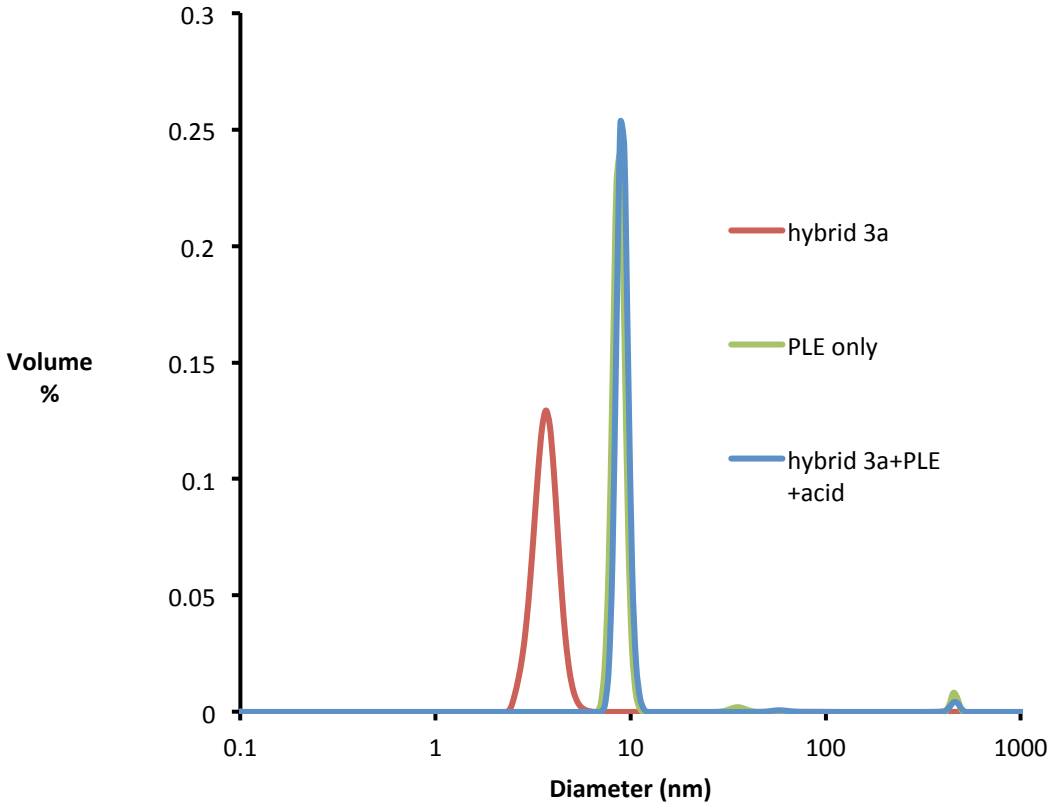

Figure S40: DLS measurements of 80µM hybrid 3a (red), 50U/ml PLE enzyme (green) and mixture of 80µM hybrid 3a + 50U/ml PLE enzyme + 320µM azo acid (blue).

Fluorescence measurements

Instrument: Agilent Technologies Cary Eclipse Fluorescence Spectrometer

Excitation: 550nm

Emission scan: 580-800nm

Scan rate: 600nm/min

Averaging time: 0.1sec

PMT detector voltage: 600V

Sample preparation:

Hybrids 1-3 were dissolved in phosphate buffer (100mM, pH 7.4) to give a final concentration of 320, 160 and 80μM, respectively. Nile Red (0.88mg/ml in ethanol) was added to give a final concentration of 1.25μM. Solution was sonicated for 15 minutes and then vortexed thoroughly. Solution was transferred to a quartz cuvette and the emission intensity of Nile Red was measured at t=0. Cuvette was exposed to UV light for 45 seconds intervals, after each the emission was measured again. The same procedure was performed for irradiation with visible light.

HPLC measurements

Instrument: Waters Alliance e2695

Column: Aeris WIDEPORE, C4, 3.6μm, 150x4.6mm

Column temperature: 30°C

Sample temperature: 37°C

Solution A: 0.1% $HClO_4$:ACN 95:5v/v

Solution B: 0.1% $HClO_4$:ACN 5:95v/v

Solution C: THF

Flow rate: 1mL/min

Gradient program for 30 minutes injection:

Time [minutes]	Sol. A [%]	Sol. B [%]	Sol. C [%]
0.0	95	0	5
1.0	95	0	5
20.0	0	95	5
23.0	0	95	5
23.1	95	0	5
30.0	95	0	5

Gradient program for 15 minutes injection:

Time [minutes]	Sol. A [%]	Sol. B [%]	Sol. C [%]
0.0	95	0	5
1.0	95	0	5
8.0	0	95	5
9.0	0	95	5
9.1	95	0	5
15.0	95	0	5

Injection volume: 30µL

Seal wash: H_2O:MeOH 90:10v/v

Needle wash: MeOH

Detector: Waters 2998 photodiode array detector

Sampling rate: 2 points/sec

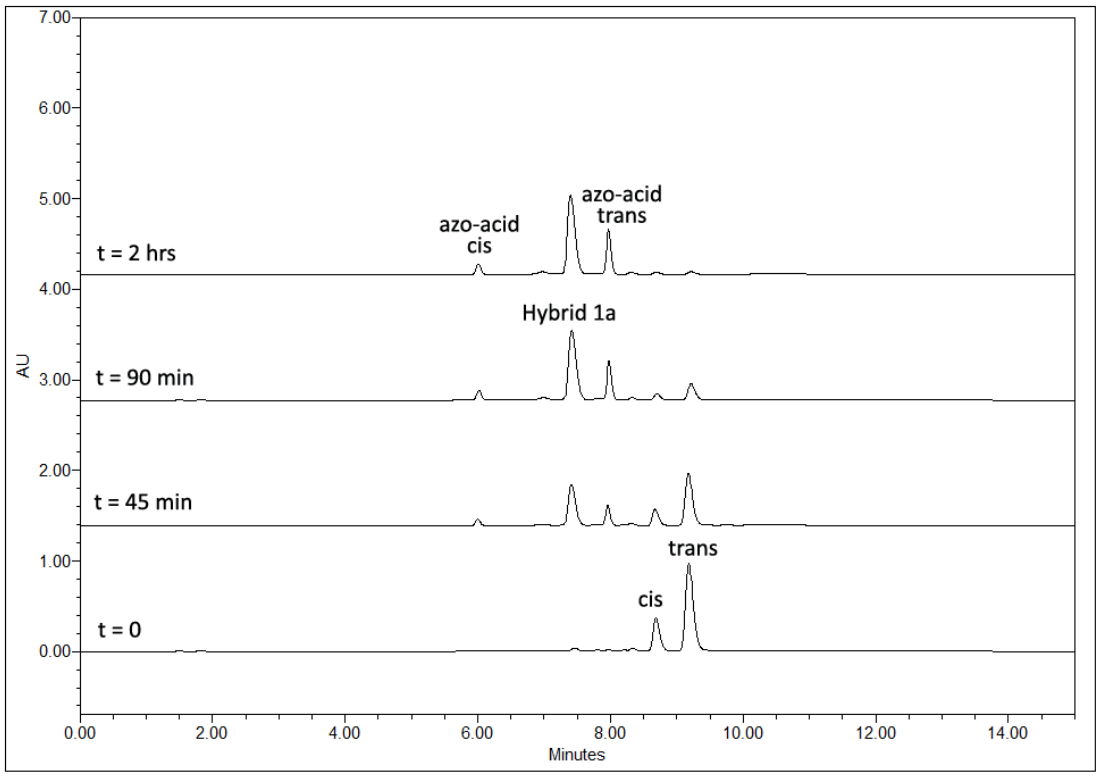

Figure S41: HPLC overlay of mPEG$_{5kDa}$-dend-(azo)$_1$ (320μM) with PLE (50mU/ml).

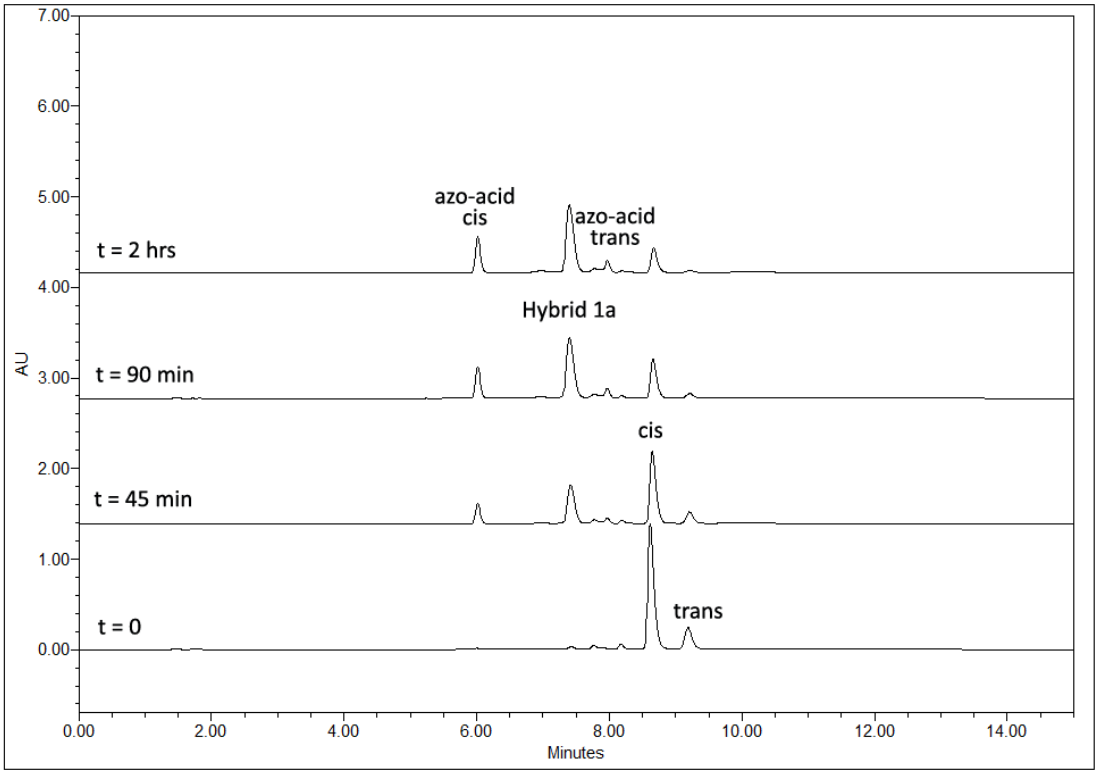

Figure S42: HPLC overlay of mPEG$_{5kDa}$-dend-(azo)$_1$ (320μM) after UV irradiation with PLE (50mU/ml).

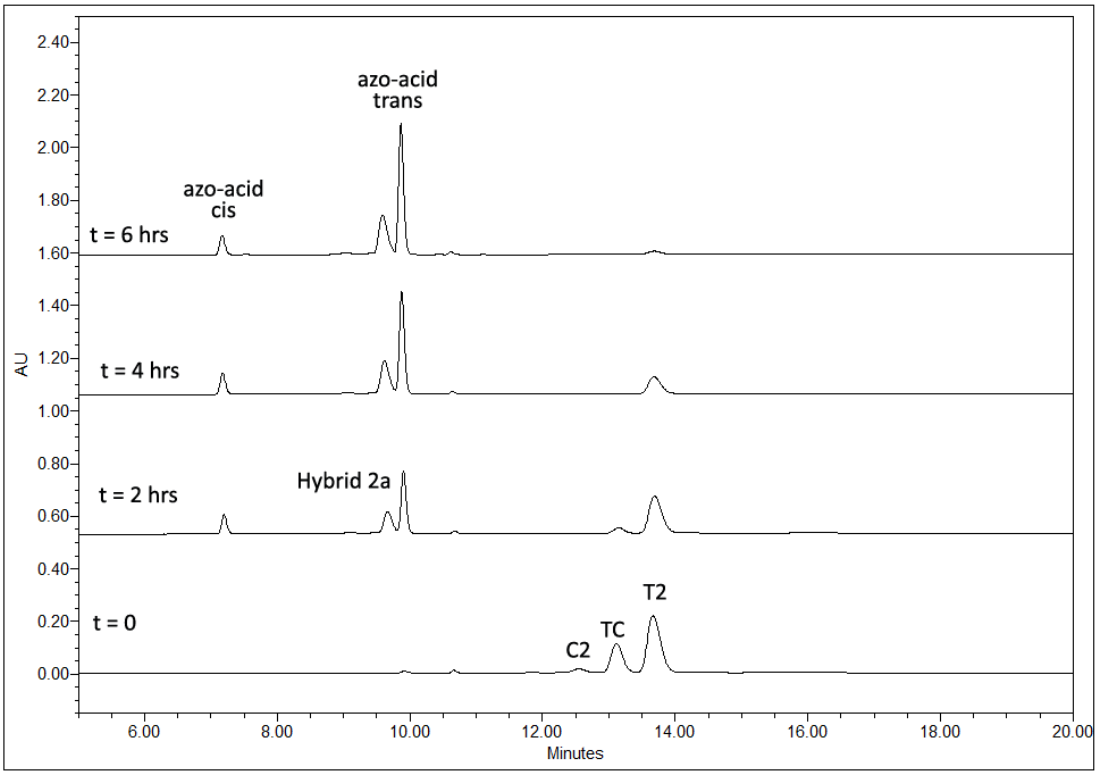

Figure S43: HPLC overlay of mPEG$_{5kDa}$-dend-(azo)$_2$ (160μM) with PLE (0.5U/ml).

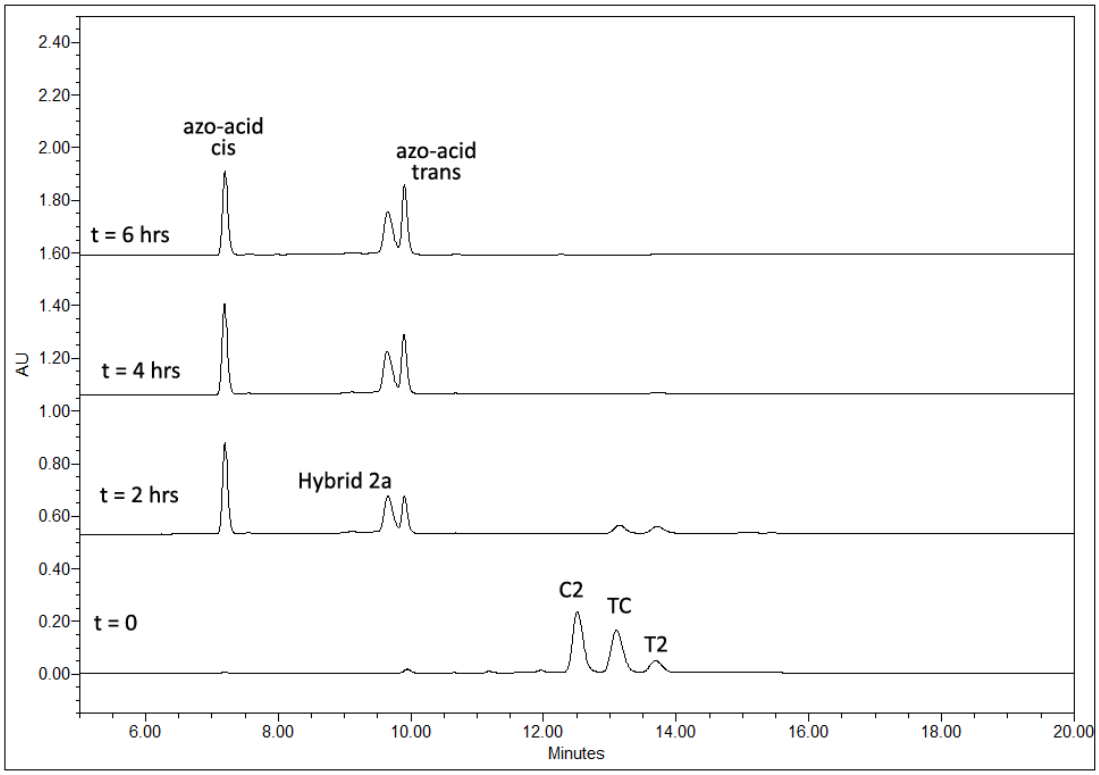

Figure S44: HPLC overlay of mPEG$_{5kDa}$-dend-(azo)$_2$ (160μM) after UV irradiation with PLE (0.5U/ml).

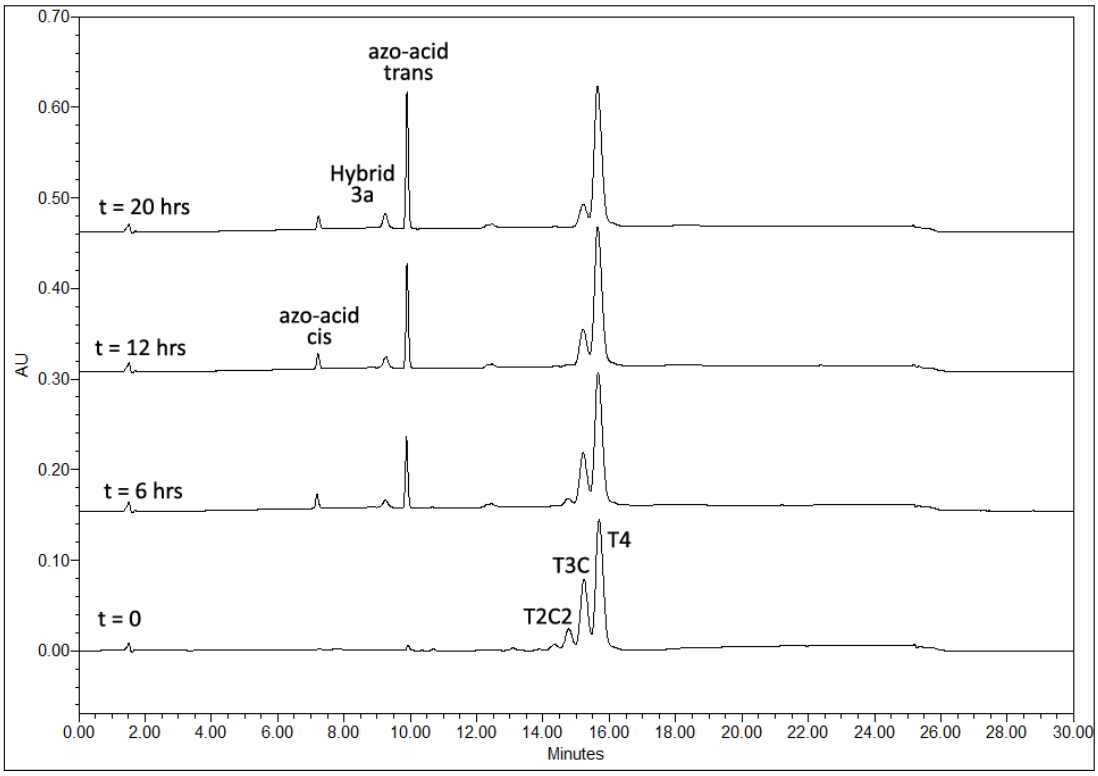

Figure S45: HPLC overlay of mPEG$_{5kDa}$-dend-(azo)$_4$ (80μM) with PLE (50U/ml)

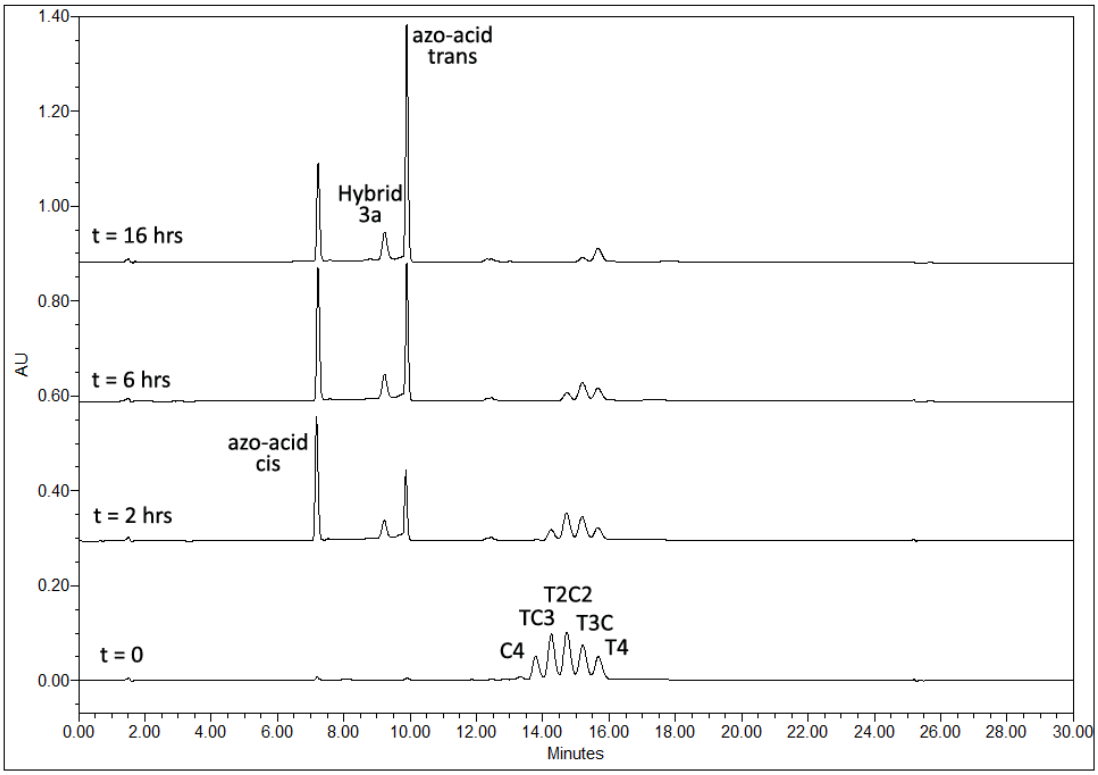

Figure S46: HPLC overlay of mPEG$_{5kDa}$-dend-(azo)$_4$ (80μM) with PLE (50U/ml).

TEM imaging:

Sample preparation:

Hybrids 1, 2 and 3 were dissolved in phosphate buffer (pH 7.4) to afford a final concentration of 320, 160 and 80μM, respectively. 10 μL of each solution were dropped cast onto carbon copper grids (In the case of the cis containing hybrids, the droplets were further irradiated by UV lamp on the grid to ensure the photoisomerization of the hybrids). The excessive solvent of the droplet was wiped away using a solvent-absorbing filter paper after 1 minute and the sample grids were left to dry in air at room-temperature for 1 hour. Then, grids were inspected in transmission electron microscope (TEM), operated at 200kV (Philips Tecnai F20).

References:

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