Supporting Information

Tetrazine-Norbornene *versus* Azide-Norbornene Ligation: Evaluating the Toolbox for Polymer-Polymer Coupling

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Content

1. Materials

Formic acid (*Sigma Aldrich*, LC-MS grade), acetonitrile (*VWR*, LC-MS grade), glacial acetic acid (AcOH, *VWR*, > 99.7%) and tetrahydrofuran (THF, *VWR International GmbH*, HPLC-grade) were used as recieved. Diethyl ether (Et_2O), ethyl acetate (EtOAc), dichlormethane (DCM), *n*-hexane and methanol (MeOH) from *Stockmeier Chemie GmbH* (technical grade) were distilled prior to use.

All chemicals were used as received, unless otherwise stated.

NMR solvents: $CDCl_3$ (D > 99%), DMF-d_7 (D > 99%), DMSO-d_6 (D > 99.8%) from *Deutero*. Mesitylen (*TCI*, > 97%) as an internal standard.

Tetrazine (Tz) synthesis: 4-Cyanobenzoic acid (*TCI*, > 98%), zinc triflate (*TCI ,* > 98%), hydrazine monohydrate (*Sigma-Aldrich*, 64-65% in H_2O, 98%), $NaNO_2$ (*Sigma-Aldrich*, > 97%), HCl (*Acros Organics*, 37%), Na_2SO_4 (*Grüssing GmbH*, 99%), silica gel (*Acros Organics*, 0.035-0.070 mm, 60 Å), RediSep Silver Silica Gel Disposable Flash Columns (*Teledyne ISCO*, 12 and 40 g).

Tetrazine NHS ester synthesis: EDCxHCl (*ABCR*, 98%), *N*-Hydroxysuccinimide (NHS, *TCI*, > 98%), DMAP (*Fluka*, > 98%), NaCl (*Grüssing GmbH*, 99%).

Azide (Az) synthesis: 4-Aminobencoic acid (*TCI*, > 99%), H_2SO_4 (*VWR International GmbH*, 95%), NaN_3 (*Sigma-Aldrich*, > 99%).

RAFT-agent synthesis: 4,4'-Azobis(4-cyanovaleric acid (*Sigma-Aldrich*, 97%), carbondisulfide (CS_2, *Acros Organics*, 99.9%), 1-dodecanethiol (*Sigma-Aldrich*, 98%), ethanol (EtOH, *VWR International GmbH*, absolute, 99.7%), 2-(hydroxymethyl)-5-norbornene (*TCI*, *endo*-/*exo*-mixture, > 98%), $MgSO_4$ (anhydrous, *Grüssing GmbH*, 99%), KOH (*Carl Roth*, > 85%), *p*-toluensulfonyl chloride (*Sigma-Aldrich*, 98%).

RAFT-polymerization: 1,4-Dioxane over molecular sieve (*Acros Organics*, dry, 99.5%), hexylamine (*Sigma-Aldrich*, 99%), styrene (*Fluka*, < 99%), *tert*-buthylacrylate (*Sigma-Aldrich*, 98%), 1,1'-azobis-(isobutyronitrile) (AIBN, *Sigma-Aldrich*, 98%; recrystallized twice from methanol prior to use).

$PEG_{3k/5k}$ syntheses: PyBOP (*Carl Roth*, > 98.5%), DIPEA (*Iris Biotech GmbH*, peptide grade), TFA (*Iris Biotech GmbH*, peptide grade), TES (*Sigma-Aldrich*, 99%).

2. Instrumentation and sample analysis procedures

Nuclear Magnetic Resonance spectroscopy (NMR): ^{1}H (500 MHz) and ^{13}C (125 MHz) spectra in $CDCl_3$ or benzene-d_6 were acquired from Bruker spectrometers (Advancd III – 500 MHz) and calibrated to residual solvent peaks (δ = 7.26 ppm and δ = 77.16 ppm for $CDCl_3$ and δ = 7.16 ppm and δ = 128.06 ppm for C_6D_6). Data were processed with the Topspin 4.0.3 (Bruker). The multiplicities were explained using the following abbreviations: s for singlet, d for doublet, t for triple, m for multiplet, bs for broad signal and dd for doublet of doublets.

^{1}H-NMR (400 MHz) spectra for kinetic studies in DMF-d^6 were acquired from Bruker spectrometers (Advancd III – 400 MHz).

DOSY-NMR (600 MHz) was carried out at 294 K on a Bruker DRX 600 MHz spectrometer equipped with an inverse 5mm BBI probe head.

THF Size Exclusion Chromatography (THF-SEC): SEC-measurements were carried out on an Eco-SEC-System at 35 °C with UV- and RI-detection (HLC-8320 GPC) from Tosoh (Griesheim, Germany). As solvent tetrahydrofuran (THF, HiPerSolv CHROMANORM® for HPLC) from VWR® Chemicals (Dresden, Germany) was used and SDV columns (1000 Å 5 µm, 100000 Å 5 µm and 1000000 Å 5 µm) from PSS (Mainz, Germany) were applied. The molar mass and dispersity values were calculated against polystyrene standards (*Agilent Technologies*: M_p = 580, 4730, 12980, 19920, 110 k g/mol; *MACHEREY-NAGEL GmbH & Co. KG:* 1060, 2950, 9200, 30.3 k, 66 k, 220 k, 514 k, 1950 k, 3040 k g/mol) and polyethylene glycol standards (*PSS Polmyer Standard Service GmbH*; M_p = 194, 430, 1030, 2130, 3450, 6530, 11.4 k, 25.3 k, 44 k g/mol).

DMAc Size Exclusion Chromatography (DMAc-SEC): Size exclusion chromatography measurements with dimethylacetamid (DMAc) were carried out on an Agilent HPLC system with UV- and RI-detection (1260 Infinity II GPC) from Agilent (Waldbronn, Germany) at 50 °C with a thermostated column compartment. The column set consisted of one pre-column PSS GRAM 10 µm and three PSS GRAM columns (30 Å 10 µm, 1000 Å 10 µm and 1000 Å 10 µm), which were applied from PSS (Mainz, Germany). DMAc was used containing 1 g/L LiBr at a flow rate of 1 mL/min and the molar mass and dispersity values were calculated against polystyrene standards (*Agilent Technologies*: M_p = 580, 4730, 12980, 19920,

110 k g/mol; *MACHEREY-NAGEL GmbH & Co. KG:* 1060, 2950, 9200, 30.3 k, 66 k, 220 k, 514 k, 1950 k, 3040 k g/mol).

Ultra-Performance Liquid Chromatography with Electron Spray Ionization Mass Spectrometry (UPLC-ESI-MS): UHPLC-ESI-MS was performed on an ACUIDITY-UPLC® H-Class CM Core System of Waters GmbH (Eschborn, Germany). Detection was done utilizing an ACUIDITY-UPLC® photo diode array (PDA)-detector (wavelength range 190-500 nm) and an ACUIDITY-UPLC® QDa mass detector with ESI-ionization. For analysis Waters software Empower TM 3 was used. Separation was conducted with ACUIDITY-UPLC® BEH C18 VanGuard^{TM} precolumn (110 Å, 1.7 µm, 5 × 21 mm ID) and an ACUIDITY-UPLC®BEH C18-column (110 Å, 1.7 µm, 5×21 mm ID) from Waters. As mobile phase, mixtures of solvent A (Milli-Q H_2O with 0.1% FA, v/v) and solvent B (acetonitrile with 0.1% FA, v/v) were used with 0.5 mL min^{-1} flow rates.

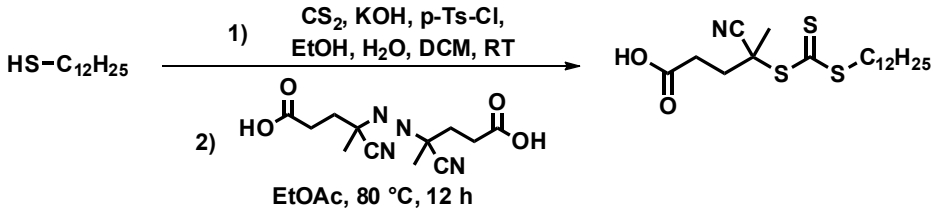
Ultraviolet-Visible spectroscopy (UV-Vis): UV-Vis spectroscopy was performed using a Shimadzu UV-2501- PC spectrometer (Shimadzu Corp., 604-8511 Kyoto, Japan) using quartz-cuvettes with 10 mm path. Data were collected with the UVProbe 2.62 (Shimadzu Corp., 604-8511 Kyoto, Japan).

Fourier-Transform Infrared spectroscopy (FT-IR): FT-IR-spectra were recorded on a Bruker Vertex 70v ATR-FT-IR-spectrometer (Bruker Optics GmbH, Ettlingen, Germany) with an evacuable optic in a range of 4000-400 cm^{-1}. Solid samples were measured under vacuum and room temperature and liquids were measured in air and at room temperature. The position of the IR-bands are recorded in cm^{-1} (ν) and the intensity of the bands are characterised as very strong (vs), strong (s), medium (m), weak (w) and very weak (vw).

Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF-MS): The coupling products were characterized by MALDI-TOF-MS performed on an Autoflex III Smartbeam system (Bruker Daltonik GmbH, Bremen) equipped with a Smartbeam laser (355 nm, 200 Hz working frequency). Detection of signals was performed with a Time-of-Flight detector and a voltage of 24 kV. Spectra were evaluated by using the software FlexControl 1.3. The samples were prepared with dithranol (*Sigma-Aldrich*, pharmaceutical secondary standard), *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene]malononitrile (DCTB, *Sigma-Aldrich*, > 99.0%) and silver trifluoaroacetate (AgTFA, *Alfa Aesar*, 98%)

3. Synthesis of precursors

3.1. Synthesis of 4-Cyano-4-[(dodecylsulfanylthiocarbonyl)sufanyl]pentanoic acid (CTA)



Scheme S1. Synthesis of the CTA-RAFT-agent.[1]

The synthesis of 4-Cyano-4-[(dodecylsulfanylthiocarbonyl)sufanyl]pentanoic acid (CTA) was performed according to the literature procedure.[1] Dodecanethiol (20.3 g, 100 mmol) was dissolved in 100 mL of a 10% ethanol aqueous solution. After solving KOH (6.7 g, 0.12 mol) in this solution, carbon disulfide (7.6 g, 101 mmol, 6.03 mL) was added dropwise over 30 min. After three hours stirring at room temperature the mixture was cooled in an ice bath and a solution of *p*-toluensulfonyl chloride (9.1 g, 50 mmol) in DCM (20 mL) was added slowly. The mixture was stirred overnight and afterwards extracted with DCM (30 mL) for three times. The combined organic phase was dried over $MgSO_4$, filtered and concentraded to yield bis(dodecylmercaptothiocarbonyl)disulfide (25.2 g, 45.4 mmol, 91%) as dark yellow oel. After solving this yellow oel in ethyl acetate (200 mL) 4,4'-azobis(4-cyanovaleric acid) (14 g, 49.8 mmol) were added and the mixture was stirred at 80 °C for 12 h. The product was purified by flash chromatographie on silica gel by elution with *n*-hexane/EtOAc (0% → 100% EtOAc) and CTA was obtained as yellow solid (18.6 g, 46.2 mmol, 51%).

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 3.33 (t, J^3(H,H) = 7.4 Hz, 2 H, S-CH_2), 2.69 (m, 2 H, CH_2), 2.51 (m, 1 H, CH_2), 2.39 (m, 1 H, CH_2), 1.88 (s, 3 H, CH_3), 1.69 (m, 2 H, CH_2), 1.43-1.21 (m, 18 H, CH_2), 0.88 (t, (t, J^3(H,H) = 7.1 Hz, 3 H, CH_3).

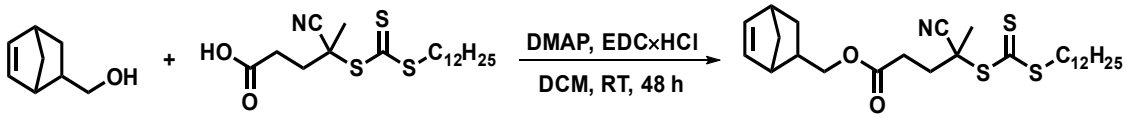
^{13}C-{^{1}H}-NMR (125 MHz, $CDCl_3$): δ [ppm] = 216.9, 172.2, 119.0, 46.3, 37.2, 33.6, 32.0. 29.8, 29.7, 29.6, 29.6, 29.5, 29.2, 29.1, 27.8, 25.0, 22.8, 14.3.

Elemental analysis:

calculated values for $C_{19}H_{33}NO_2S_3$: C: 56.54 %, H: 8.34 %, O: 7.93 %, N: 3.47 %, S: 23.83 %

found values for $C_{19}H_{33}NO_2S_3$: C: 56.45 %, H: 8.26 %, O: - , N: 3.36 %, S: 23.58 %

3.2. **Synthesis of Norbornene-CTA (Nb-CTA)**



Scheme S2. Synthesis of the Nb-CTA.[2]

The synthesis for Nb-CTA was realized following the procedure described in literature.[2] 4-Cyano-4-[[(dodecylthio)thiooxomethyl]-thio]-pentanoic acid (1 g, 2.5 mmol, 1 eq.) and DMAP (31 mg, 0.25 mmol) were added to a solution of 2-(hydroxymethyl)5-norbornene (354 mg, 2.75 mmol, 1.1 eq.) in 10 mL of dry dichloromethane (DCM). After cooling the reaction mixture in an ice bath for 10 min, EDCxHCl (480 mg, 2.5 mmol, 1.0 eq.) solved in 20 mL of dry DCM was added dropwise to this mixture. After 48 h of reaction time the raw product was purified by flash chromatographie (*n*-hexane: ethyl acetate; 0% → 20%). After removing the solvent under vacuum Nb-CTA (1.11 g, 2.2 mmol, 87%) was obtained as a yellow oil.

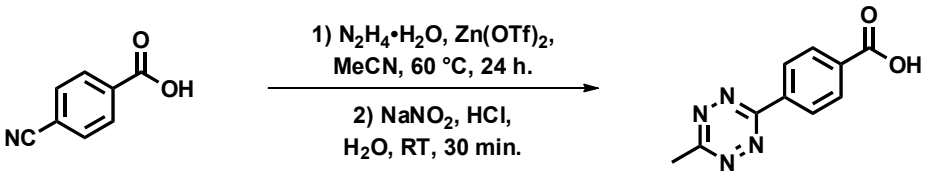
^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 6.16 (dd, 1 H, J^3 = 3.1 Hz, J^3 = 5.7 Hz, CH_{endo}), 6.09 (dq, 2 H, J^3 = 2.9 Hz, J^3 = 5.5 Hz =CH_{exo}), 5.93 (dd, 1 H, J^3 = 2.9 Hz, J^3 = 5.7 Hz, CH_{endo}), 4.17 (ddd, 1 H, J^4 = 0.9 Hz, J^3 = 6.5 Hz, J^3 = 10.9 Hz, O-$CH_{2/exo}$), 3.99 (td, 1 H, J^4 = 2.7 Hz, J^3 = 10.1 Hz, O-$CH_{2/exo}$), 3.88 (ddd, 1 H, J^4 = 1.5 Hz, J^3 = 6.7 Hz, J^3 = 10.7 Hz, O-$CH_{2/endo}$), 3.69 (td, 1 H, J^4 = 1.3 Hz, J^3 = 10.2 Hz, O-$CH_{2/endo}$), 3.32 (t, 2 H, J^3 = 7.4 Hz, S-CH_2), 2.87 (s, 1 H, CH_{endo}), 2.84 (s, 1 H, CH_{exo}), 2.82 (s, 1 H, CH_{endo}), 2.69 (s, 1 H, CH_{exo}), 2.63 (m, 2 H, CH_2), 2.53 (m, 1 H, CH_2), 2.38 (m, 2 H, CH_2, CH_{endo}), 1.88 (s, 3 H, CH_3), 1.84 (m, 1 H, CH_{endo}), 1.69 (m, 3 H, CH_2, CH_{exo}), 1.46 (dq, 1 H, $CH_{2/endo}$), 1.42-1.19 (m, 24 H, 9 CH_2, $CH_{2/endo}$, $CH_{2/exo}$, CH_{exo}), 1.16 (dt, 1 H, CH_{exo}), 0.87 (t, 3 H, J^3 = 6.9 Hz, CH_3), 0.56 (ddd, 1 H, J^4 = 2.0 Hz, J^3 = 11.7 Hz, J^3 = 4.6 Hz, CH_{endo}).

Elemental analysis:

calculated values for $C_{248}H_{491}NO_{116}S_3$: C: 63.61 %, H: 8.50 %, O: 6.28 %, N: 2.75 %, S: 18.87 %

found values for $C_{248}H_{491}NO_{116}S_3$: C: 63.54 %, H: 8.50 %, O: ---- , N: 2.85 %, S: 18.73 %

3.3. Synthesis of 4-(6-methyl-1,2,4,5-trazin-3-yl)-benzoic acid (Tz-COOH)



Scheme S3. Synthesis of 4-(6-methyl-1,2,4,5-trazin-3-yl)-benzoic acid (Tz-COOH).[3]

The tetrazine was synthesized following the procedure of Linden *et al.*.[3] 4-Cyanobezoic acid (200 mg, 1.36 mmol, 1.00 eq.), zinc triflate (247 mg, 0.68 mmol, 0.50 eq.), hydrazine monohydrate (64-65% in H_2O, 5.20 mL, 69.00 mmol, 50.60 eq.) and acetonitrile (0.70 mL, 13.60 mmol, 10.00 eq.) were mixed under argon atmosphere and stirred under reflux at 60 °C for 24 h. The orange suspension was cooled down to room temperature and $NaNO_2$ (1875 mg, 27.20 mmol, 20.00 eq.) dissolved in 5 mL of H_2O was added. Afterwards the suspension was acidified with 120 mL of HCl (1 M) to pH = 1. The now pink suspension was extracted three times with ethyl acetate. The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. After column chromatography with DCM/MeOH/AcOH (100:1:0.1, v/v/v) the tetrazine (222 mg, 1.03 mmol, 76%) was obtained as a pink solid.

^{1}H-NMR (500 MHz, DMSO-d6): δ [ppm] = 13.34 (s, 1 H, COOH), 8.58 (d, J^3 = 8.5 Hz, 2 H, 4-H, 8-H), 8.20 (d, J^3 = 8.5 Hz, 2 H, 5-H, 7-H), 3.02 (s, 3 H, H-11).

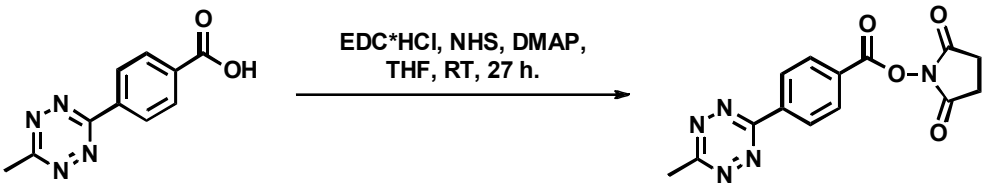
^{13}C-{^{1}H}-NMR (126 MHz, DMSO-d6): δ [ppm] = 167.4 (2-C), 166.7 (3-C), 162.8 (6-C), 135.7 (9-C), 134.0 (10-C), 130.2 (2C, 4-C, 6-C), 127.6 (2C, 5-C, 7-C), 20.9 (11-C).

FT-IR (ν(cm^{-1})): 3062 (m), 2921 (m), 2850 (m), 2665 (m), 2547 (m), 2362 (m), 1737 (m), 1676 (vs), 1575 (m), 1510 (m), 1398 (s), 1294 (s), 1118 (m), 1087 (m), 1012 (m), 931 (m), 873 (m), 808 (m), 767 (m), 694 (m), 632 (w), 559 (m).

ESI-MS: calcd. m/z = 217.07, $[M + H]^+$; found m/z = 217.24 $[M + H]^+$.

UV-Vis (DMF): λ_{max} = 538 nm.

3.4. **Synthesis of 2,5-dioxopyrrolidin-1-yl 4-(6-methyl-1,2,4,5-tetrazin-3-yl)benzoate**



Scheme S4. Synthesis 2,5-dioxopyrrolidin-1-yl 4-(6-methyl-1,2,4,5-tetrazin-3-yl)benzoate.[4]

The synthesis of the NHS ester was carried out according to the synthetic protocol of Yu *et al.*.[4] The tetrazine carboxylic acid (500 mg, 2.31 mmol, 1.00 eq.) was solved with EDCxHCl (537 mg, 2.80 mmol, 1.21 eq.), NHS (322 mg, 2.80 mmol, 1.21 eq.) and DMAP (11 mg, 0.09 mmol, 0.04 eq.) in THF (40 mL). The solution was then stirred at room temperature for 27 h. After this time, the mixture was diluted with H_2O (100 mL) and then extracted with EtOAc (8 x 100 mL). The organic phase was washed with NaCl solution (2 x 250 mL, saturated), before being dried over Na_2SO_4 and the solvent was removed in vacuo. The residue was purifed with column chromatography (DCM). The NHS ester (423 mg, 1.35 mmol, 58%) was obtained as a pink crystalline solid.

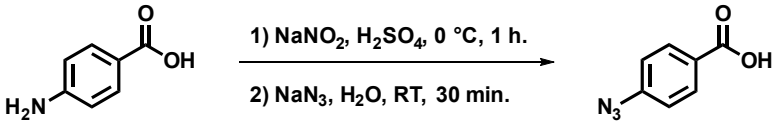
^{1}H-NMR (500 MHz, $CDCl_3$, 295.6 K): δ [ppm] = 2.95 (s, 4H, H-10), 3.15 (s, 3H, H-1), 8.37 (m, 2H, H-5), 8.76 (m, 2H, H-6).

^{13}C-NMR (126 MHz, $CDCl_3$, 295.4 K): δ [ppm] = 21.5 (C-1), 25.8 (C-10), 128.3 (C-5), 131.5 (C-6), 169.2 (C-9).

FT-IR (ν (cm^{-1})) = 3101 (w), 3074 (w), 2999 (w), 2947 (w), 2852 (w), 2360 (w), 1770 (m), 1737 (vs), 1404 (m), 1357 (m), 1232 (m), 1201 (m), 1068 (m), 989 (m), 894 (w), 838 (w), 810 (w), 754 (w), 690 (w), 648 (w), 603 (w), 563 (w), 495 (w).

ESI-MS: calcd. *m/z* = 314.08 [M+H]+; found *m/z* = 314.16 [M+H]+.

3.5. **Synthesis of 4-azidobenzoic acid (Az-COOH)**



Scheme 5. Synthesis of 4-azidobenzoic acid (Az-COOH).[5]

The synthesis was performed according to the literature.[5] To an ice-cooled solution of 4-aminobenzoic acid (0.50 g, 3.65 mmol, 1.00 eq.) in 4 mL of H_2SO_4 (3 M) was added $NaNO_2$ (0.30 g, 4.38 mmol, 1.20 eq.) dissolved in 1.5 mL of H_2O. After stirring the solution at 0 °C for 30 min NaN_3 (0.36 g, 4.38 mmol, 1.20 eq.) dissolved in 1.5 mL of H_2O was also added. After stirring the solution for an additional hour at room temperature it was extracted three times with ethyl acetate. The combined organic phases were washed with H_2O and saturated NaCl solution, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The product (396 mg, 3.65 mmol, quant.) was a pale yellowish solid.

^{1}H-NMR (500 MHz, DMSO-d6): δ [ppm] = 12.96 (s, 1H, COOH); 7.95 (d, J^3 = 8.7 Hz, 2H, 4-H, 8-H), 7.21 (d, J^3 = 8.42, 2 H, 5-H, 7-H).

^{13}C-{^{1}H}-NMR (126 MHz, DMSO-d6): δ [ppm] = 166.5 (2-C); 143.9 (6-C); 131.1 (4-C,8-C); 127.2 (3-C), 119.1 (5-C, 7-C)

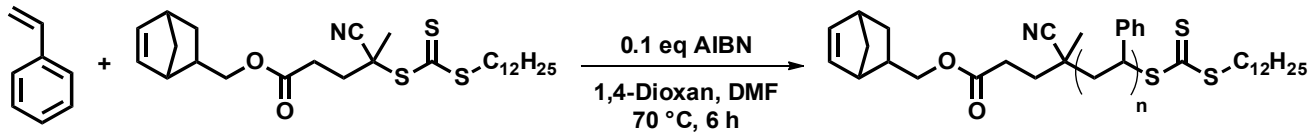
ESI-MS: calcd. m/z = 162.03 $[M - H]^-$; found m/z = 162.09 $[M - H]^-$.

FT-IR (ν(cm^{-1})): 3068 (w), 2979 (w), 2883 (w), 2817 (w), 2717 (w), 2671 (w), 2545 (w), 2543 (w), 2403 (w), 2275 (vw), 2104 (s), 1959 (vw), 1676 (vs), 1600 (vs), 1508 (w), 1425 (m), 1317 (m), 1282 (vs), 1178 (m), 1120 (m), 1033 (vw), 1012 (vw), 935 (w), 856 (m), 765 (m), 690 (w), 557 (w), 495 (w).

UV-Vis (EtOH): λ_{max} = 271 nm.

4. Synthesis of polymers

4.1. Synthesis of polystyrene-Norbornene ($PS_{1.5k}$-Nb)



Scheme 6. RAFT-Polymerization of Nb-CTA and styrene at 70 °C.

Styrene (6.34 g, 62.72 mmol, 80 eq.), AIBN (12.9 mg, 0.08 mmol, 0.1 eq.) and Nb-CTA (400 mg, 0.78 mmol, 1 eq.) were dissolved in 1,4-dioxane (7.2 mL) and DMF (240 µL, internal standard). After three freeze-pump-thaw degassing cycles of the reaction mixture the mixture was heated to 70 °C for 6 h. A sample was taken for the determination of the initial monomer ratio after one minute heating the reaction mixture to 70 °C. The conversion of the monomer was monitored by ^{1}H-NMR spectroscopy and the growth of the molecular weight was monitored by SEC measurements in THF. At regular intervals (0 h, 1 h, 2 h, 3 h, 4 h, 5 h, 6 h) aliquots were taken and 5 µL were dissolved in 1 mL THF for SEC analysis. The remaining aliquot was diluted in $CDCl_3$ (0.65 mL) for the ^{1}H-NMR measurements. After 6 h polymerization the PS-Nb was purified by precipitating it in cold methanol and dissolved in dichloromethane (2x). The precipitant was freeze-dried from 1,4-dioxane (30 mL) to obtain the PS-Nb (751 mg) as a yellow solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.43-6.29 (bs, 70 H, CH_{aro}), 6.20-5.87 (3 s, 2 H, $CH_{Norb\text{-}DB}$), 5.09-4.57 (bs, 1 H, O-$CH_{2/Nb}$), 4.20-3.57 (bs, 3 H, O-$CH_{2/Nb}$), 3.27 (m, 2 H, S-CH_2), 2.83 (m, 2 H, CH_{Nb}), 2.48-1.19 (bs, 73 H, CH, CH_2), 0.89 (t, J^3 = 6.8 Hz, 3 H, CH_3).

SEC (THF, PS standards): M_n = 1.7 kDa, PDI = 1.07.

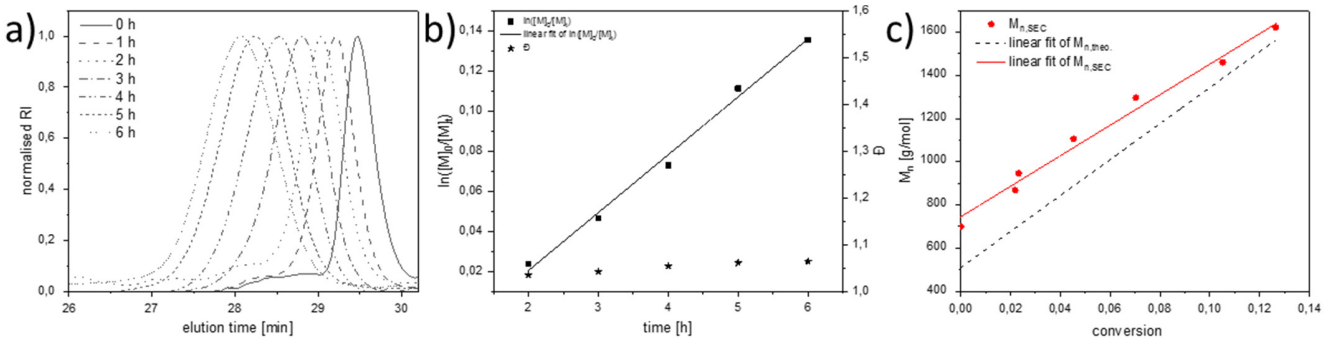


Figure S1. a) SEC traces (elution time) of PS RAFT-Nb polymerization at 70 °C, b) The kinetic plots of $\ln([M]_0/[M]_t)$ ($[M]_0$ = start monomer concentration, $[M]_t$ = monomer concentration after polymerization time) and dispersity Đ versus polymerization time, **c)** Number average molecular weight M_n versus conversion.

Aminolysis of PS-Nb

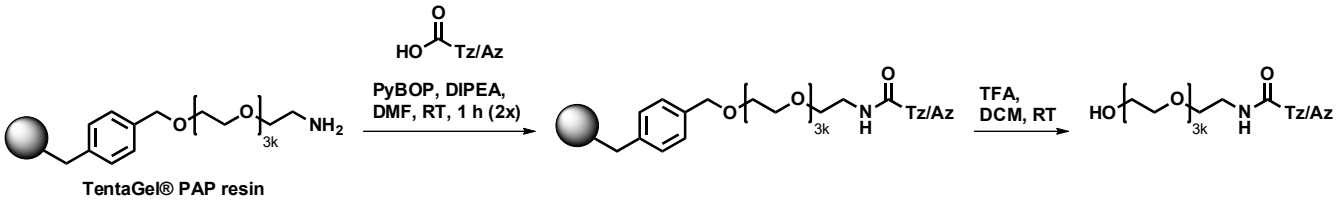
PS-Nb (498 mg) was dissolved in THF (5 mL) and *tert*-butylacrylate (460 µL, ≈ 10 eq.) was added. After four times freeze-pump-thaw degassing cycles of the reaction mixture degassed hexylamine (240 µL, ≈ 5.7 eq.) was added to mixture and stirred for 24 h. An UV-Vis-spectra in THF was measured to proof fully RAFT-aminolysis. The resulting polymer was purified by precipitating it in cold pentane (30 mL) and dissolved in dichloromethane (2x). The precipitant was freeze-dried from 1,4-dioxane (20 mL) to obtain the *tert*-buthylacrylat-PS-Nb (387 mg, 82 %) as a white solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.43-6.29 (bs, 70 H, CH_{aro}), 6.20-5.87 (3 s, 2 H, $CH_{Norb-DB}$), 5.09-4.57 (bs, 1 H, O-$CH_{2/Nb}$), 4.20-3.57 (bs, 3 H, O-$CH_{2/Nb}$), 3.27 (m, 2 H, S-CH_2), 2.83 (m, 2 H, CH_{Nb}), 2.48-1.19 (bs, 73 H, CH, CH_2), 0.89 (t, J^3 = 6.8 Hz, 3 H, CH_3).

SEC (THF, PS standards): M_n = 1.5 kDa, PDI = 1.08.

FT-IR (ν(cm^{-1})): 2925 (m), 1730 (m), 1600 (m), 1492 (m), 1452 (m), 1390 (vw), 1367 (w), 1328 (vw), 1301 (vw), 1251 (w), 1151 (m), 1029 (w), 757 (m), 698 (vs), 541 (w).

4.2. General procedure for PEG_{3k}-Tz/Az



Scheme 7. Resin functionalization and cleavage of the modified PEG-polymer.[6]

The PEGylated tetrazines and azides were synthesized with a modified procedure of the literature.[6] The PAP-resin (500 mg, 1.00 eq.) is swollen in 5 mL of DMF at room temperature for 15 min in a syringe reactor. After removing the solvent, a solution of the Tz-/Az-COOH (2.00 eq.), PyBOP (2.00 eq.) and DIPEA (3.00 eq.) dissolved in 5 mL of DMF is added to the resin and shaken for 1 h. This procedure is repeated, before the resin is washed three times each with DMF, DCM, DMF and Et_2O. After that the resin is dried in high vacuum for 1 h. After washing the resins with DCM five times, the PEG-Tz are cleaved off with a TFA solution (20% in DCM, 10 mL) for 1 h five times each, and the PEG-Az are cleaved off with a TFA solution (9.5 mL TFA, 0.45 mL TES, 0.05 mL H_2O) for 4 h each. The solutions are concentrated in a argon stream, before the polymers are precipitated two times in cold Et_2O, redissolved in a small amount of H_2O and lyophilized overnight.

4.2.1. PEG_{3k}-Tz

Tentagel PAP-resin (PEG_{3000}, loading: 0.25 mmol/g, 500 mg, 0.125 mmol, 1.00 eq.), Tz-COOH (54 mg, 0.25 mmol, 2.00 eq.), PyBOP (130 mg, 0.25 mmol, 2.00 eq.), DIPEA (70 µL, 0.375 mmol, 3.00 mmol);

The product (640 mg, 0.20 mmol, 80%) was obtained as a pinkish solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 8.65 (d, J^3 = 8.3 Hz, 2 H, CH_{Tz}), 8.06 (d, J^3 = 8.3 Hz, 2 H, CH_{Tz}), 4.46 (m, 2 H, CH_2-NH), 3.77 (m, 4 H, CH_2), 3.64 (bs, 488 H, CH_2), 3.49 (m, 4 H, CH_2), 3.43 (bs, 12 H, CH_2), 3.11 (s, 3 H, CH_{3_Tz}).
FT-IR (ν(cm^{-1})): 2883 (m), 1658 (vw), 1467 (w), 1406 (vw), 1359 (w), 1342 (m), 1278 (w), 1240 (w), 1147 (w), 1097 (vs), 1060 (m), 960 (m), 892 (vw), 840 (m), 530 (vw).
SEC (THF, PEG standards) = 3.2 kDa, PDI = 1.06.

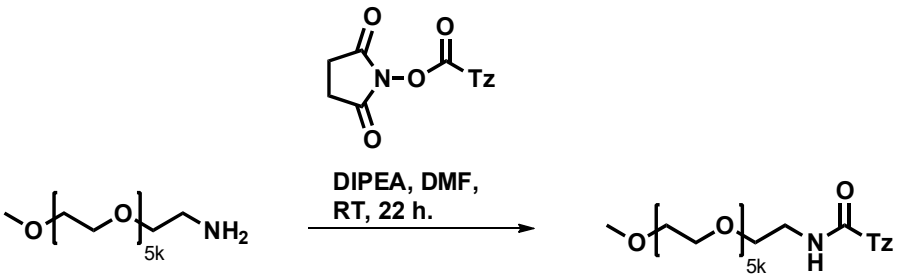
4.2.2. PEG_{3k}-Az

Tentagel PAP-resin (PEG_{3000}, loading: 0.25 mmol/g, 500 mg, 0.125 mmol, 1.00 eq.), Az-COOH (41 mg, 0.25 mmol, 2.00 eq.), PyBOP (130 mg, 0.25 mmol, 2.00 eq.), DIPEA (70 µL, 0.375 mmol, 3.00 mmol);

The product (661 mg, 0.21 mmol, 84%) was obtained as a pale yellow solid.

^{1}H-NMR (500 MHz, $CDCl_3$): δ [ppm] = 7.84 (d, J^3 = 8.7 Hz, 2 H, CH_{Az}), 7.06 (d, J^3 = 8.7 Hz, 2 H, CH_{Az}), 4.49 (m, 2 H, CH_2-NH), 3.78 (m, 4 H, CH_2), 3.63 (bs, 286 H, CH_2), 3.49 (m, 2 H, CH_2) 2.49 (bs, 5 H, CH_2).
FT-IR (ν(cm^{-1})): 2885 (s), 2115 (vw), 1465 (w), 1359 (w), 1340 (m), 1280 (m), 1240 (w), 1147 (m), 1101 (vs), 1060 (s), 954 (m), 842 (m), 501 (vw).
SEC (THF, PEG standards) = 3.3 kDa, PDI = 1.06.

4.3. **Synthesis of PEG_{5k}-Tz**



Scheme 8. PEG functionalization for PEG_{5k}-Tz.

The PEGylated tetrazine was synthesized following the literature.[4] The MeO-PEG_{5k}-NH_2 (200 mg,, 0.04 mmol, 1.00 eq.) is solved in 5 mL of DCM at room temperature and Tz NHS ester (26.7 mg, 0.20 mmol, 5.00 eq.) and DIPEA (17 µL, 0.10 mmol, 2.50 eq.) are added. The solution is shaken for 22 h, before the solvent is removed and the polymer precipitated five times in cold Et_2O, redissolved in a small amount of benzene and lyophilized overnight.

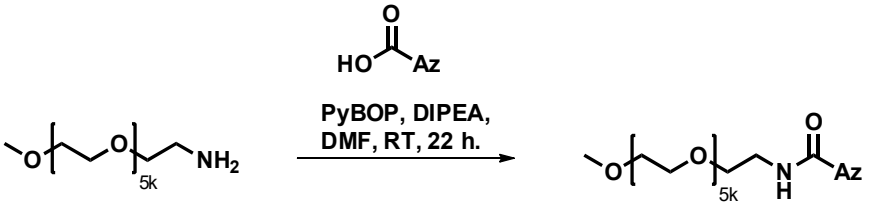
The product (156 mg, 0.03 mmol, 75%) was obtained as a pinkish solid.

^{1}H-NMR (500 MHz, DMSO-d6): δ [ppm] = 8.72 (t, J^3 = 5.6 Hz, 1 H, NH)), 8.48 (d, J^3 = 8.6 Hz, 2 H, CH_{Tz}), 8.04 (d, J^3 = 8.6 Hz, 2 H, CH_{Tz}), 3.58 (m, 2 H, CH_2), 3.44 (bs, 454 H, CH_2), 3.17 (s, 3 H, O-CH_3), 2.95 (s, 3 H, $CH_{3/Tz}$).

FT-IR (ν(cm^{-1})): 2883 (s), 1465 (w), 1359 (w), 1342 (m), 1280 (m), 1240 (w), 1147 (m), 1101 (vs), 1060 (m), 958 (m), 842 (m), 530 (vw).

SEC (THF, PEG standards) = 4.7 kDa, PDI = 1.05.

4.4. Synthesis of PEG_{5k}-Az



Scheme 9. PEG functionalization for PEG_{5k}-Az.

The PEGylated azide was adapted from the literature.[6] The MeOH-PEG_{5k}-NH_2 (200 mg, 0.04 mmol, 1.00 eq.) is solved in 5 mL of DCM at room temperature and Az-COOH (32.6 mg, 0.20 mmol, 5.00 eq.), PyBOP (104.1 mg, 0.20 mmol, 5.00 eq.) and DIPEA (47.6 µL, 0.28 mmol, 7.00 eq.) are added. The solution is shaken for 22 h, before the solvent is removed and the polymer precipitated five times in cold Et_2O, redissolved in a small amount of H_2O and lyophilized overnight.

The product (170 mg, 0.03 mmol, 78%) was obtained as a pale yellow solid.

^{1}H-NMR (500 MHz, DMSO-d6): δ [ppm] = 8.51 (t, J^3 = 5.7 Hz, 1 H, NH)), 7.89 (d, J^3 = 8.6 Hz, 2 H, CH_{Az}), 7.20 (d, J^3 = 8.6 Hz, 2 H, CH_{Az}), 3.51 (bs, 444 H, CH_2), 3.24 (s, 3 H, CH_3).

FT-IR (ν(cm^{-1})): 2883 (m), 1467 (w), 1359 (w), 1342 (m), 1278 (m), 1240 (w), 1147 (w), 1097 (vs), 1060 (m), 960 (m), 840 (m), 530 (vw).

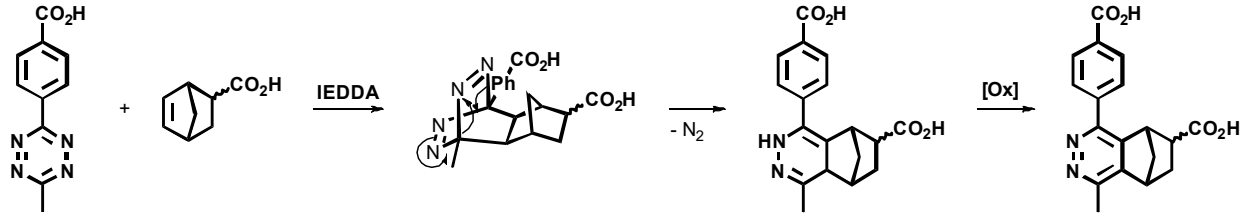
SEC (THF, PEG standards) = 4.8 kDa, PDI = 1.06.

5. Kinetics of Tetrazine/ Azide–Norbornene coupling

5.1. Small Molecules

5.1.1. Tz-Nb reaction

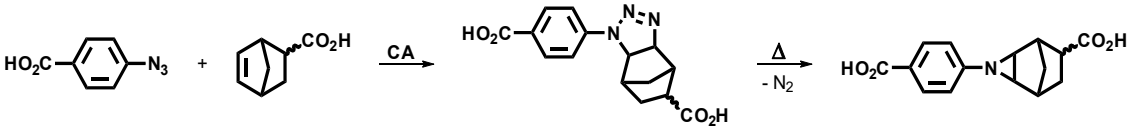
Tz-COOH (20 mg/mL) and Nb-COOH (ratio 1:1.6) were reacted in air at room temperature and 80 °C in DMF. The reaction rates were examined by means of UV-Vis-spectroscopy. For this purpose, 25 µL of the reaction solutions were taken at different times and diluted with 1 mL of DMF each. The samples taken were then transferred to a quartz glass cuvette and their absorptions at 538 nm were determined through UV-Vis-spectroscopy. By plotting the measured absorption against the reaction time, an exponential decrease in absorption was determined. The reactions were considered to be complete as soon as the absorption at the absorption maximum remained constant.



Scheme S10. IEDDA of Tz-COOH with *endo*- / *exo*-Nb-COOH.[7-9]

5.1.2. Az-Nb reaction

Az-COOH (30 mg/mL) and Nb-COOH (ratio 1:1.6) were reacted in air at room temperature and 80 °C in DMF-d^7 in NMR tubes. The reactions rates were examined by ^{1}H-NMR at different times. Within the reaction the signal of the phenylazid decreases and the aromatic signals of the products increase. The reactions were considered to be complete as soon as no Az-COOH signals could be viewed.



Scheme S11. Husigen-CA of Az-COOH with *endo*- / *exo*-Nb-COOH.[10,11]

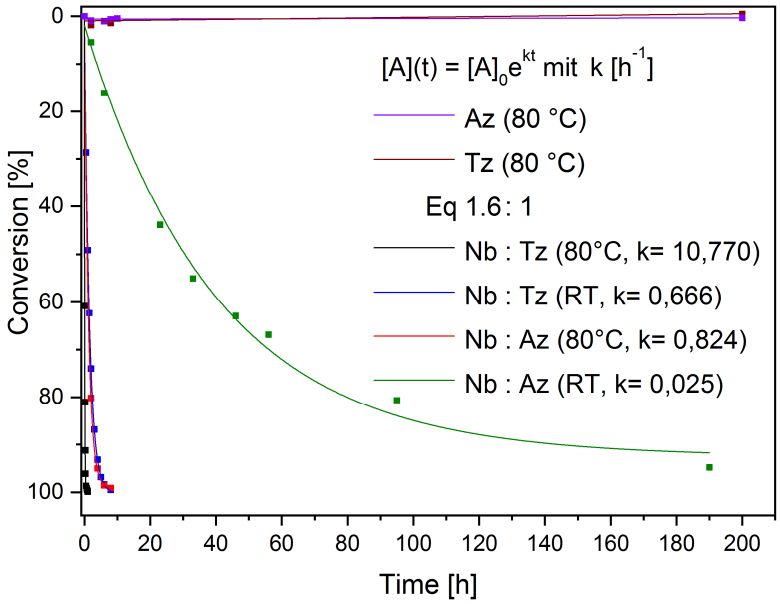
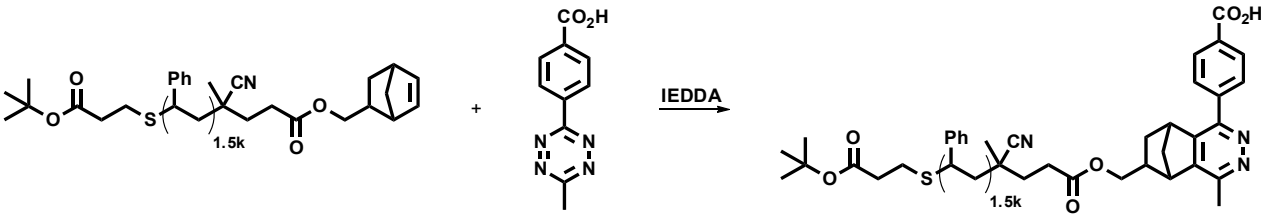


Figure 2. Kinetics monitored by UV-Vis spectroscopy (Tz) and ^{1}H-NMR (Az). [Conditions]: 1.6:1 ratio of Nb-COOH : Tz-/Az-COOH in DMF at room temperature and 80 °C.

5.2. Endpoint functionalization

5.2.1. $PS_{1.5k}$-Nb-Tz reaction

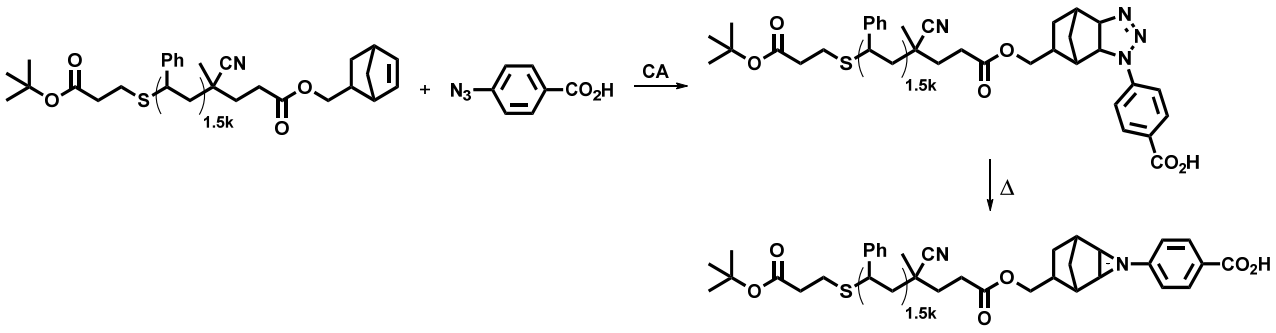
$PS_{1.5k}$-Nb and Tz-COOH (20 mg/mL, ratio 1:10/1) were reacted in air at 80 °C in DMF. The reaction rates were examined by means of UV-Vis-spectroscopy.



Scheme S12. IEDDA reaction of PS-Nb with Tz-COOH.

5.2.2. $PS_{1.5k}$-Nb-Az reaction

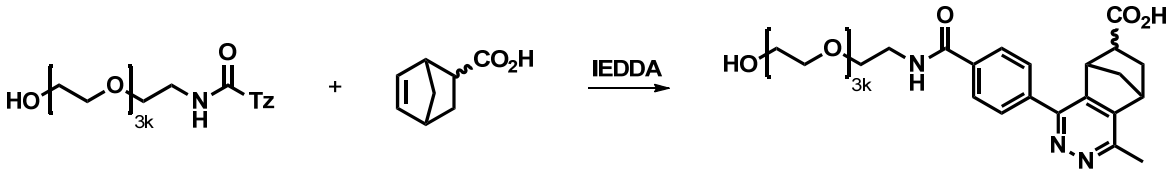
$PS_{1.5k}$-Nb and Az-COOH (30 mg/mL) ratio 1:10/1) were reacted in air at 80 °C in DMF-d^7 in NMR tubes. The reactions rates were examined by ^{1}H-NMR at different times.



Scheme S13. Husigen-CA of $PS_{1.5k}$-Nb with Az-COOH.

5.2.3. PEG$_{3k}$-Tz-Nb reaction

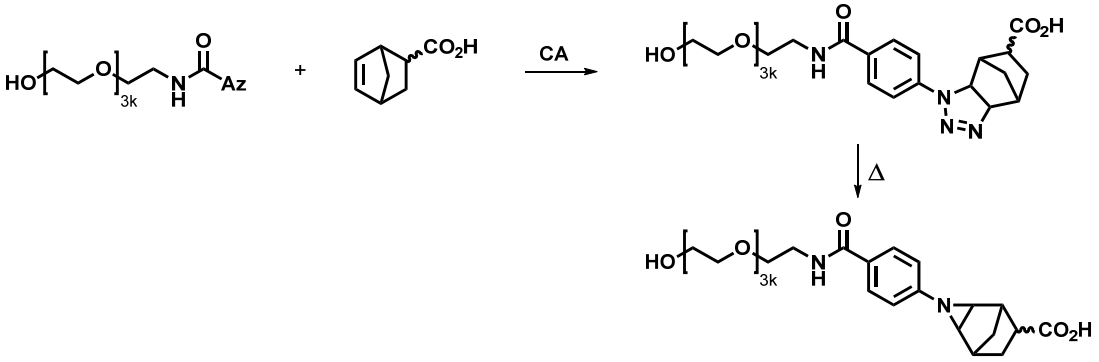
PEG_{3k}-Tz (20 mg/mL) and Nb-COOH (ratio 1:1) were reacted in air at 80 °C in DMF. The reaction rates were examined by means of UV-Vis-spectroscopy.



Scheme S14. IEDDA of PEG_{3k}-Tz with Nb-COOH.

5.2.4. PEG$_{3k}$-Az-Nb reaction

PEG_{3k}-Az (30 mg/mL) and Nb-COOH (ratio 1:1) were reacted in air at 80 °C in DMF-d^7 in NMR tubes. The reactions rates were examined by ^{1}H-NMR at different times.



Scheme S15. Huisgen-CA of PEG_{3k}-Az with Nb-COOH.

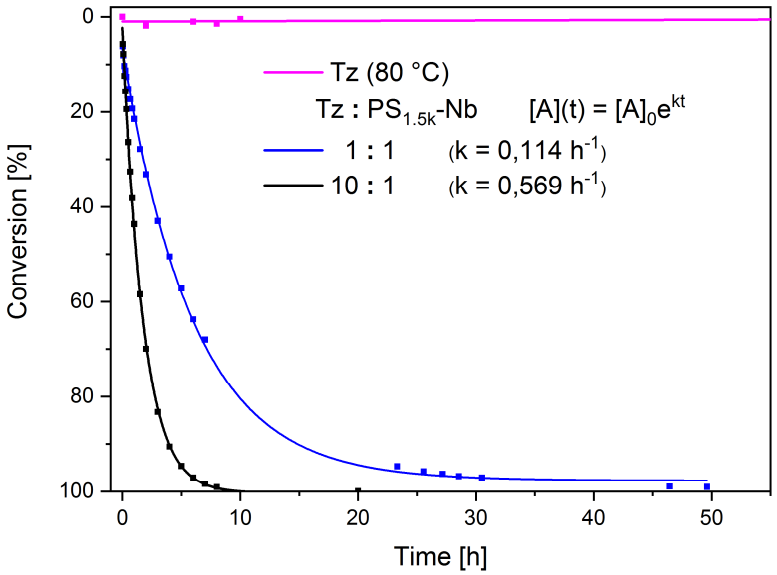


Figure S3. Kinetics of Tz-COOH with $PS_{1.5k}$-Nb with different molar ratios monitored by UV-Vis spectroscopy (1:1) and ^{1}H-NMR (1:10). [Conditions]: 1/10:1 ratio of Tz-COOH : Nb-$PS_{1.5k}$ in DMF at 80 °C.

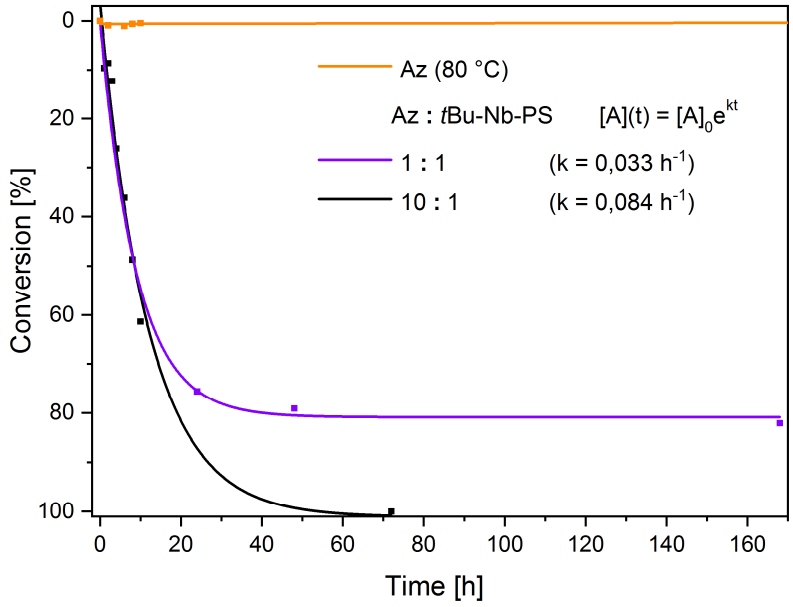
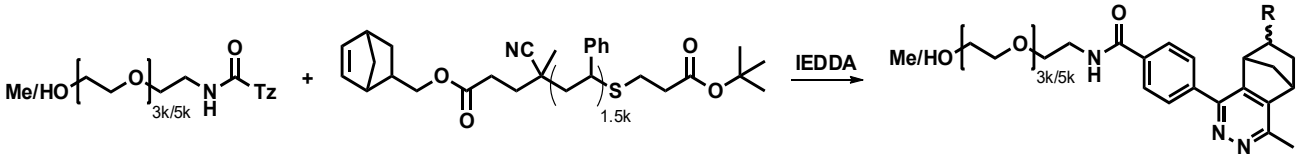


Figure S4. ^{1}H-NMR kinetics of Az-COOH with $PS_{1.5k}$-Nb with different molar ratios. [Conditions]: 1/10:1 ratio of Az-COOH : Nb-$PS_{1.5k}$ in DMF at 80 °C.

5.3. **Polymer-polymer ligation**

5.3.1. $PEG_{3k/5k}$-Tz-$PS_{1.5k}$-Nb reaction

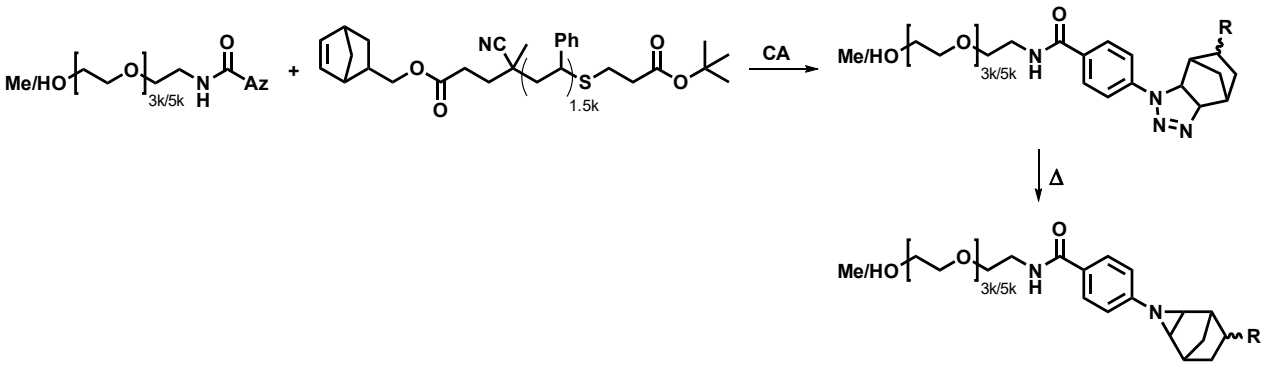
$PEG_{3k(OH)}$-Tz (20 mg/mL) and $PEG_{5k(OMe)}$-Tz (20 mg/mL) were reacted each with $PS_{1.5k}$-Nb (ratio 1:1) in air at 80 °C in DMF. The reaction rates were examined by means of UV-Vis-spectroscopy.
The reactions were also analysed with SEC. For this purpose, 25 µL of the reaction solutions were taken at different times and diluted with 475 µL of DMAz and 2.5 µL of LiBr solution was added.



Scheme S16. IEDDA of $PEG_{3k(OH)}$-Tz and $PEG_{5k(OMe)}$-Tz with $PS_{1.5k}$-Nb.

5.3.2. $PEG_{3k/5k}$-Az-$PS_{1.5k}$-Nb reaction

$PEG_{3k(OH)}$-Az (30 mg/mL) and $PEG_{5k(OMe)}$-Az (30 mg/mL) were reacted each with $PS_{1.5k}$-Nb (ratio 1:1) in air at 80 °C in DMF-d^7 in NMR tubes. The reactions rates were examined by ^{1}H-NMR at different times.
The reactions were also analysed with SEC. For this purpose, 25 µL of the reaction solutions were taken at different times and diluted with 475 µL of DMAz and 2.5 µL of LiBr solution was added.



Scheme S17. Huisgen-CA of $PEG_{3k(OH)}$-Az and $PEG_{5k(OMe)}$-Az with $PS_{1.5k}$-Nb.

5.4. Stability tests of the ligation reactants

5.4.1. Tz-COOH and PEG_{5k}-Tz

Solutions of Tz-COOH (20 mg/mL) and PEG_{5k}-Tz (20 mg/mL) were shaken in air at 80 °C in DMF. The change of the absorption maximum at 538 nm were examined by means of UV-Vis-spectroscopy at different times.

5.4.2. Az-COOH

A solution of Az-COOH (30 mg/mL) was shaken in air at 80 °C in DMF-d^7 in a NMR tube. Mesitylene was used as an internal standard. The change of the phenylazid signals against the mesitylene signals were examined by ^{1}H-NMR at different times.

5.4.3. PEG_{5k}-Az

A solution of PEG_{5k}-Az (30 mg/mL) was shaken in air at 80 °C in DMF-d_7 in a NMR tube. The change of the azide signals against the PEG signals were examined by ^{1}H-NMR at different times.

6. Characterization

6.1. NMR spectroscopy

6.1.1. Precusor molecules

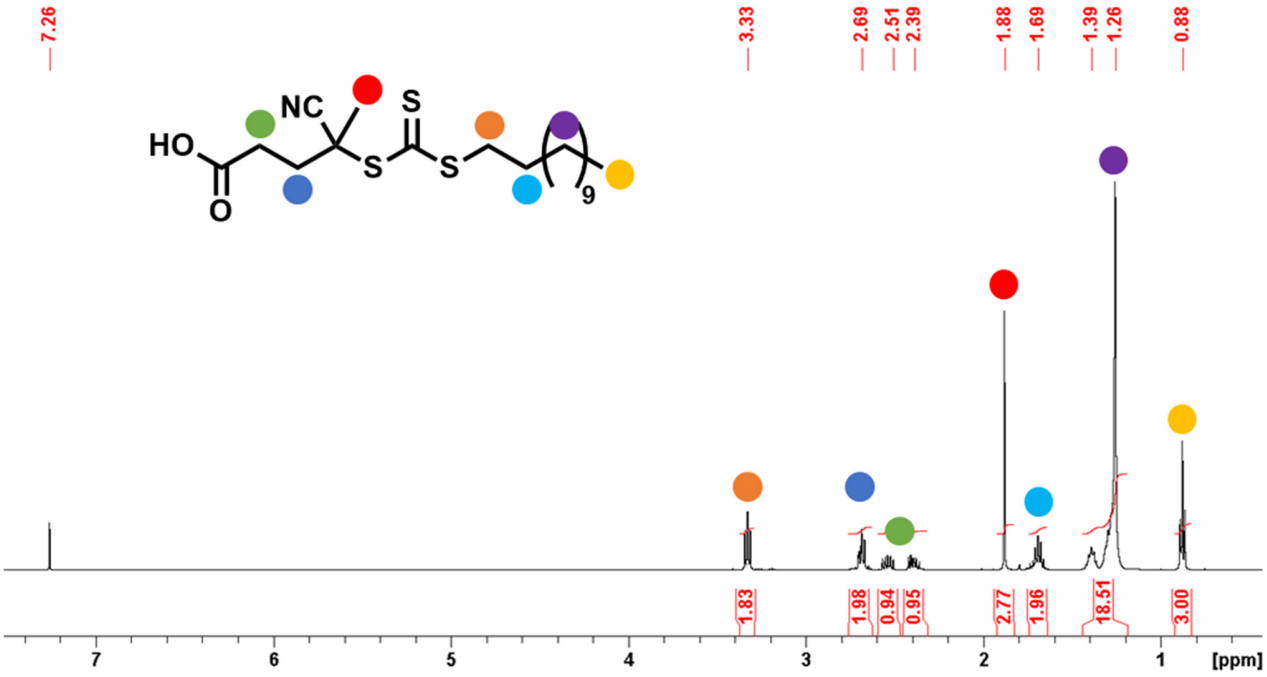


Figure S5. 500 MHz ^{1}H-NMR ($CDCl_3$) of CTA-RAFT-agent.

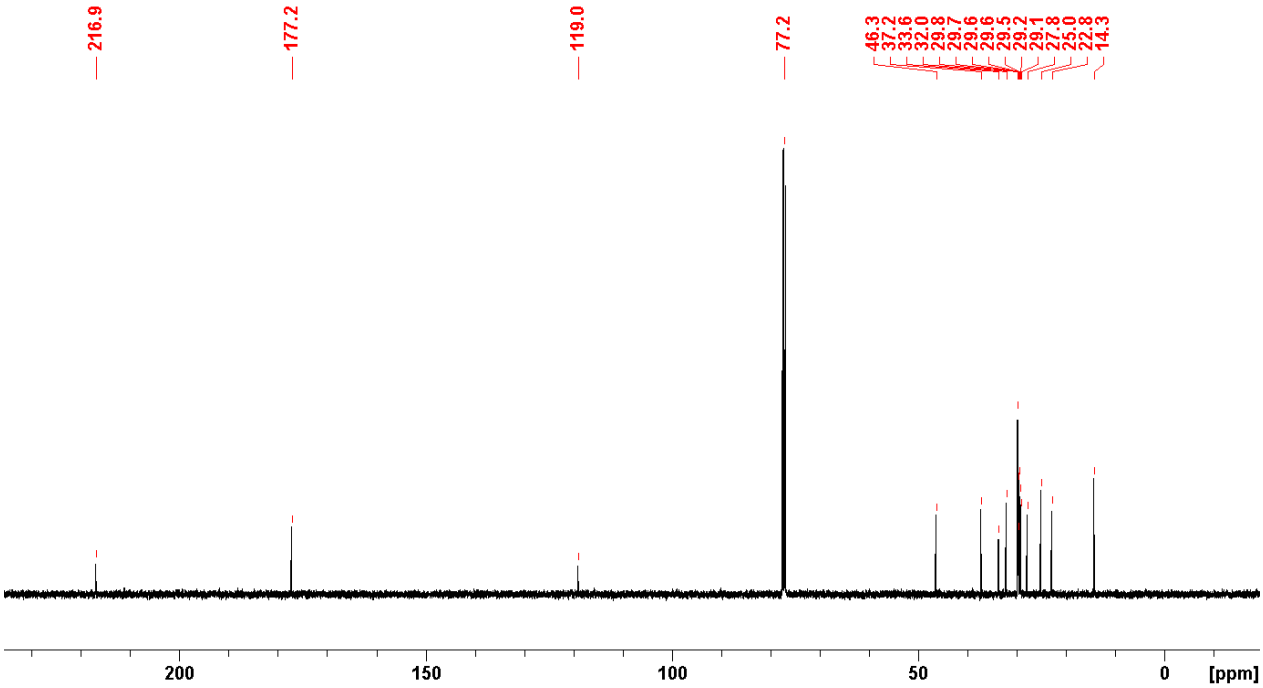


Figure S6. 125 MHz ^{13}C-NMR ($CDCl_3$) of CTA-RAFT-agent.

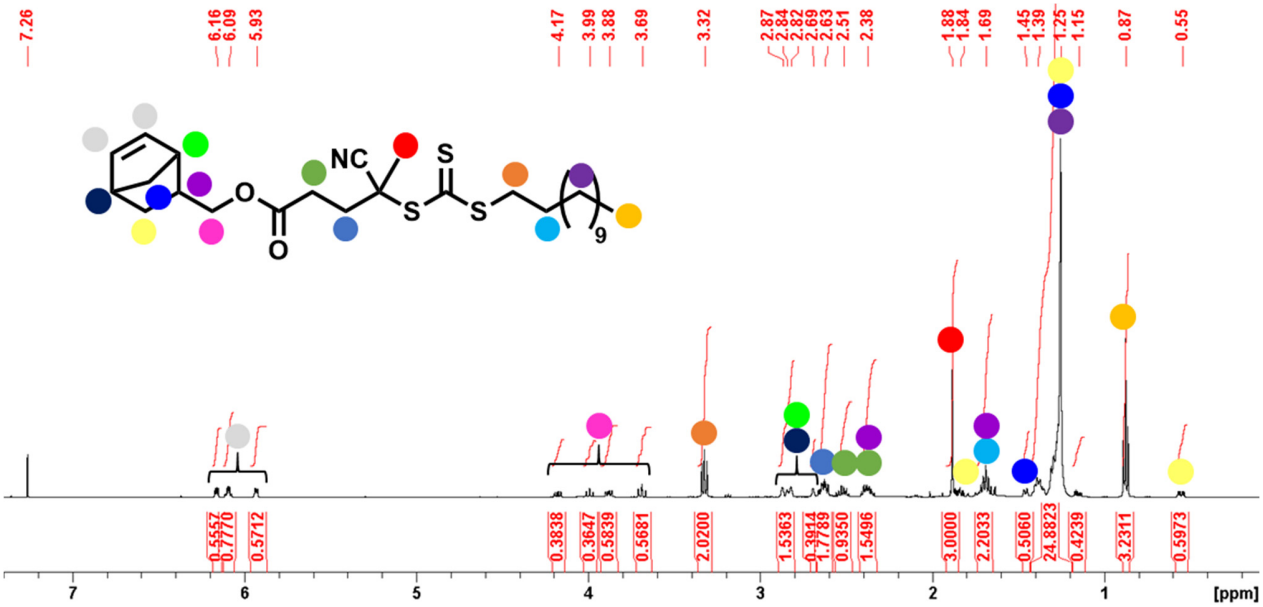


Figure S7. 500 MHz ^{1}H-NMR ($CDCl_3$) of Nb-CTA-RAFT-agent.

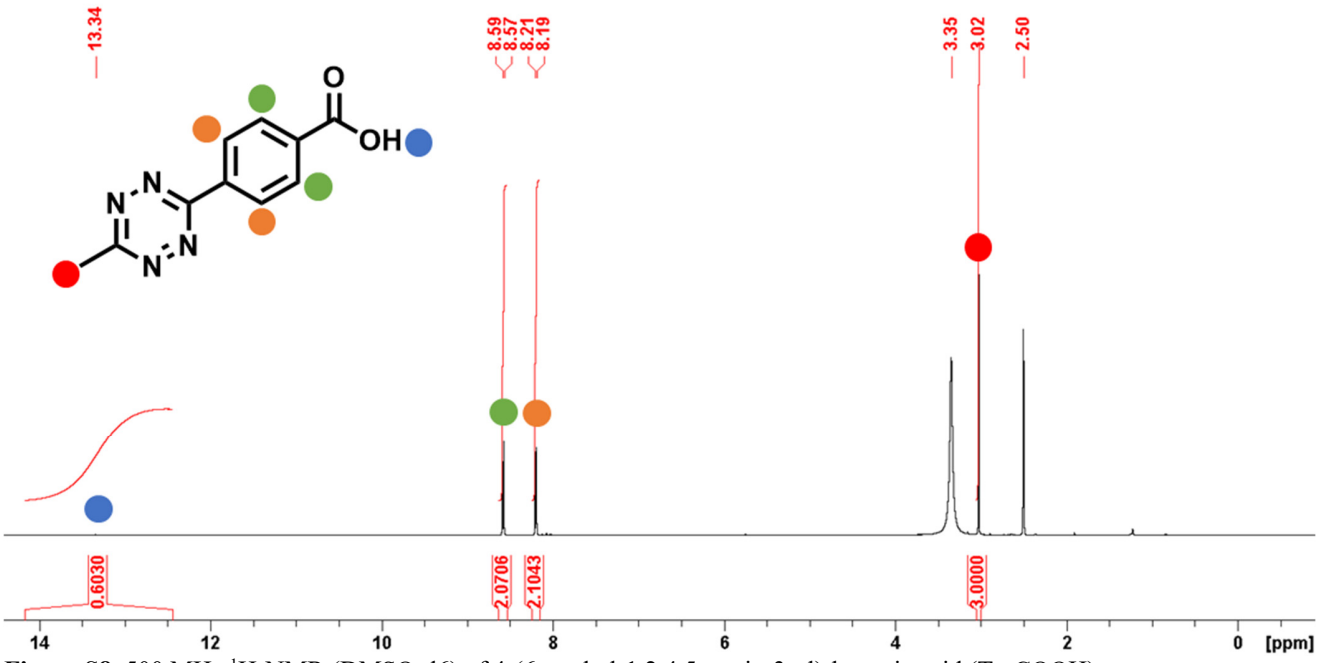


Figure S8. 500 MHz ^{1}H-NMR (DMSO-d6) of 4-(6-methyl-1,2,4,5-trazin-3-yl)-benzoic acid (Tz-COOH).

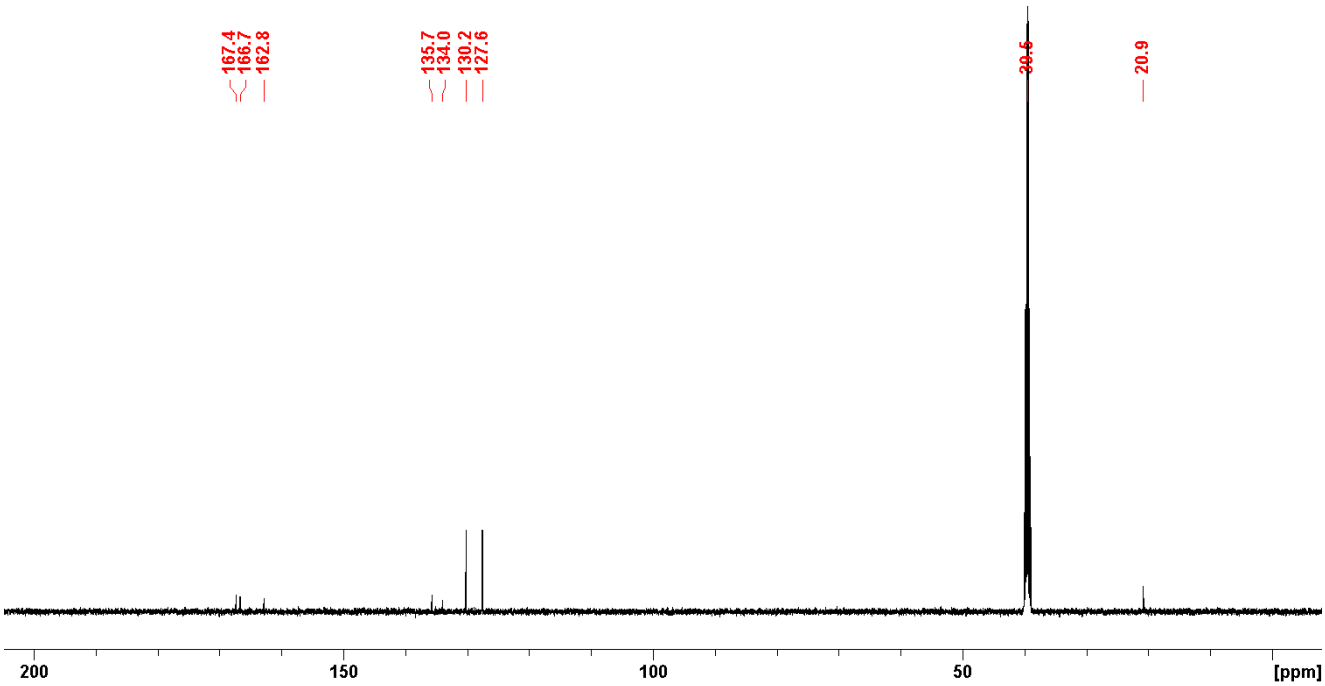


Figure S9. 125 MHz ^{13}C-NMR (DMSO-d6) of 4-(6-methyl-1,2,4,5-trazin-3-yl)-benzoic acid (Tz-COOH).

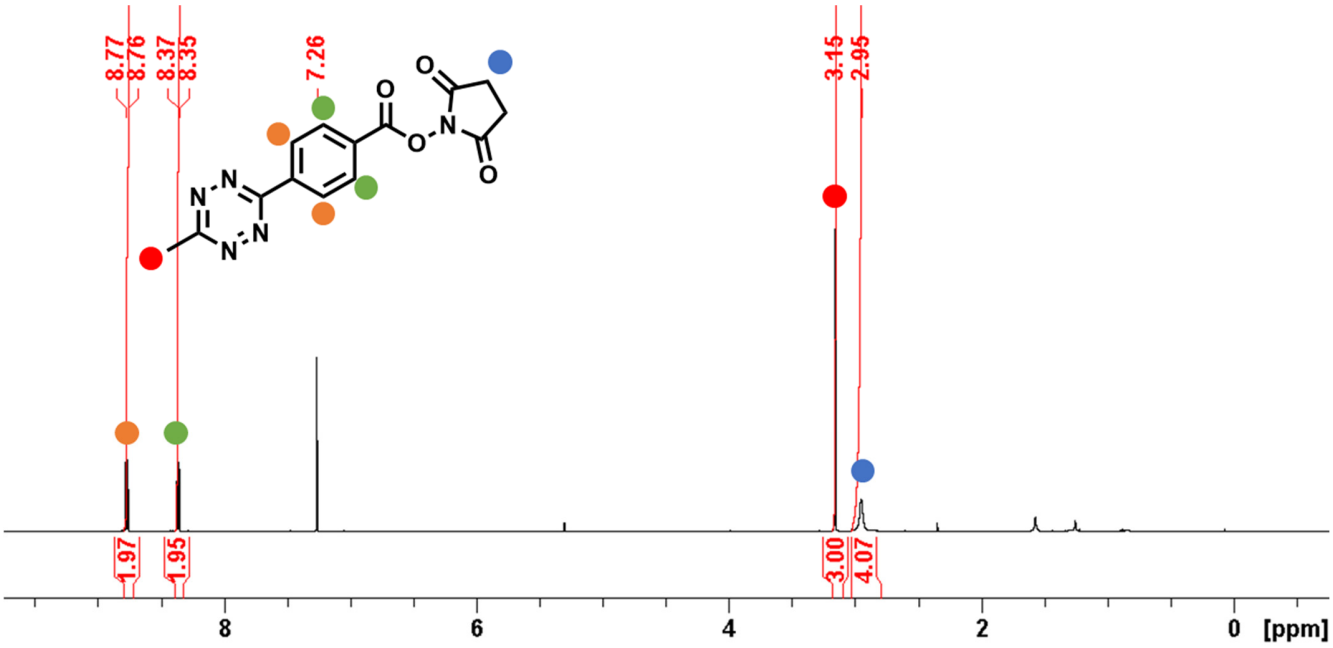


Figure S10. 500 MHz ^{1}H-NMR ($CDCl_3$) of 2,5-dioxopyrrolidin-1-yl 4-(6-methyl-1,2,4,5-tetrazin-3-yl)benzoate (Tz NHS ester).

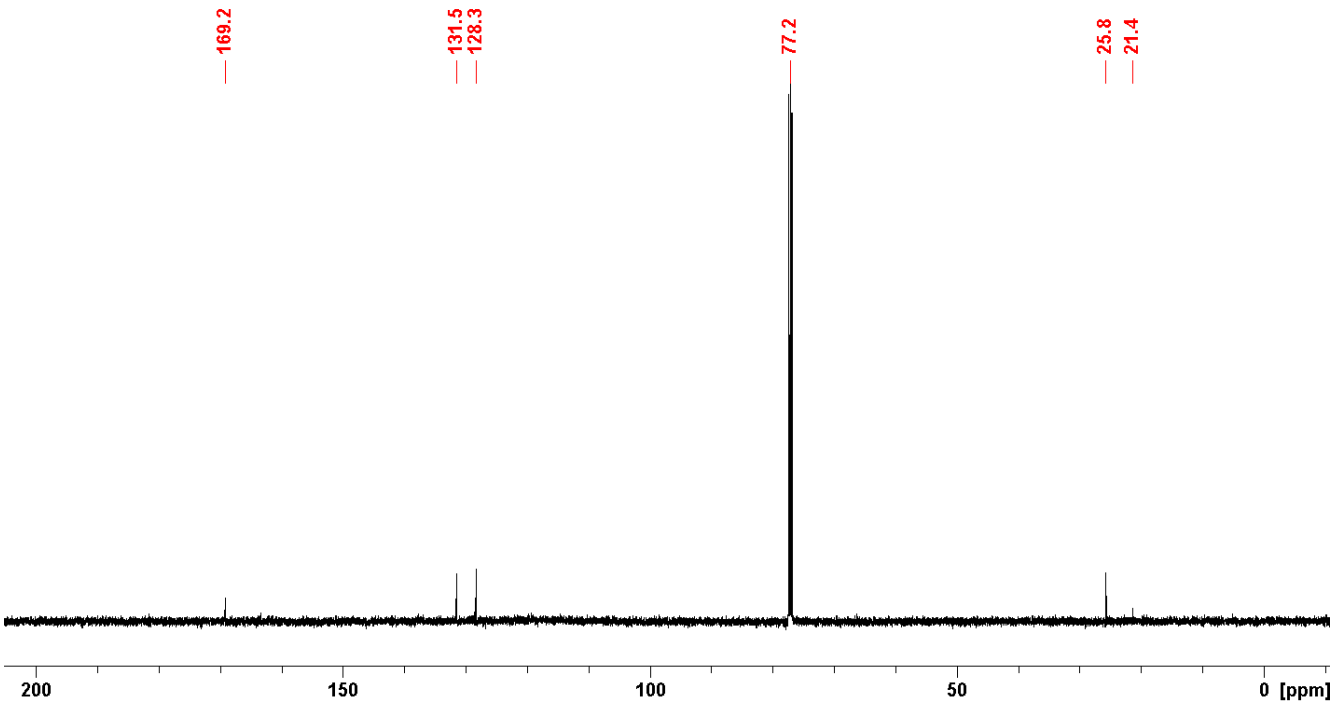


Figure S11. 125 MHz ^{13}C-NMR ($CDCl_3$) of 2,5-dioxopyrrolidin-1-yl 4-(6-methyl-1,2,4,5-tetrazin-3-yl)benzoate (Tz NHS ester).

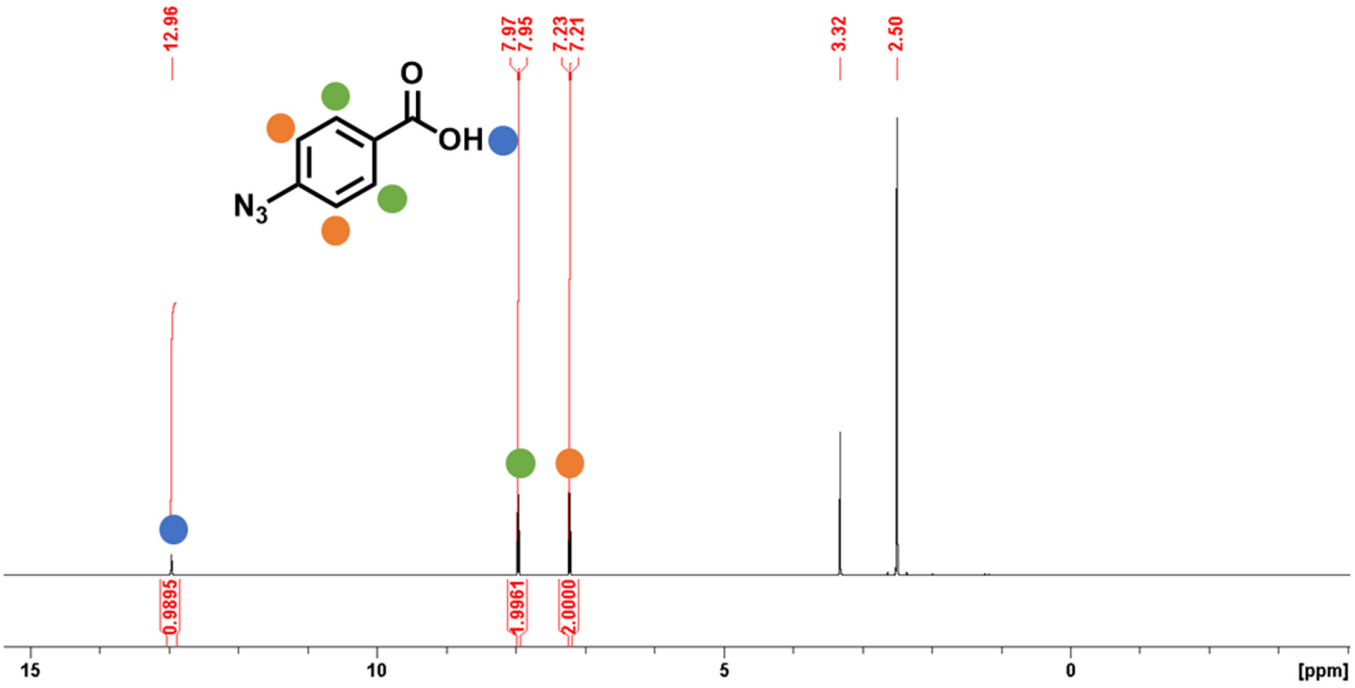


Figure S12. 500 MHz ^{1}H-NMR (DMSO-d6) of 4-azido-benzoic acid (Az-COOH).

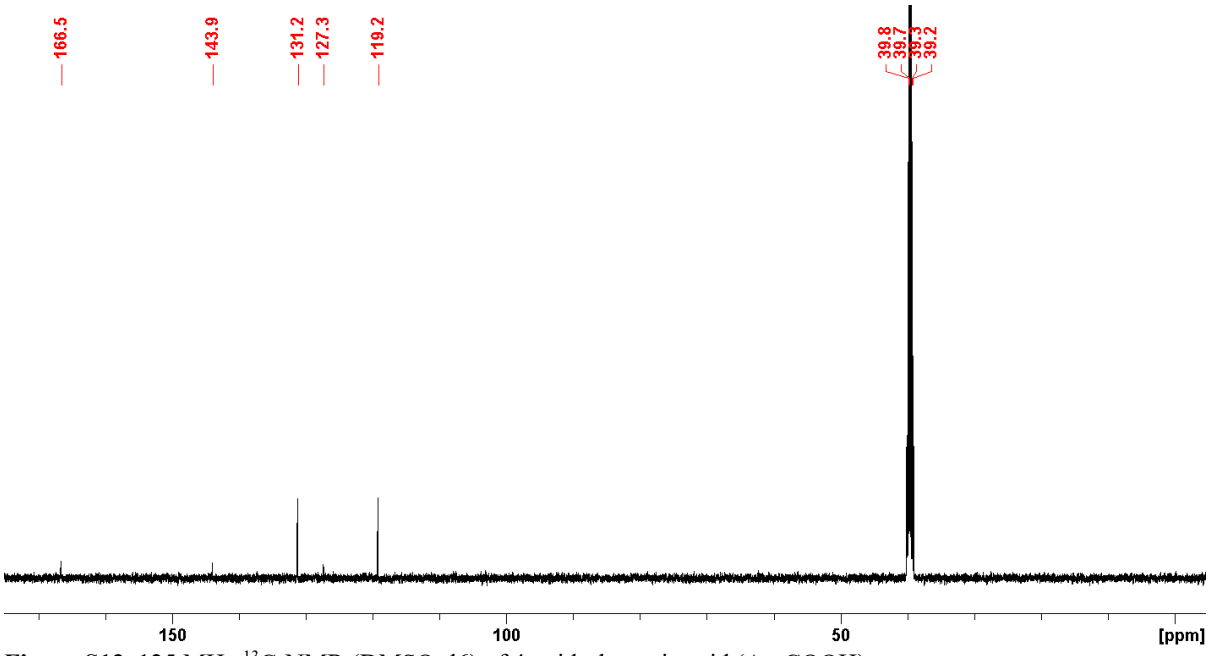


Figure S13. 125 MHz ^{13}C-NMR (DMSO-d6) of 4-azido-benzoic acid (Az-COOH).

6.1.2. *Polymers*

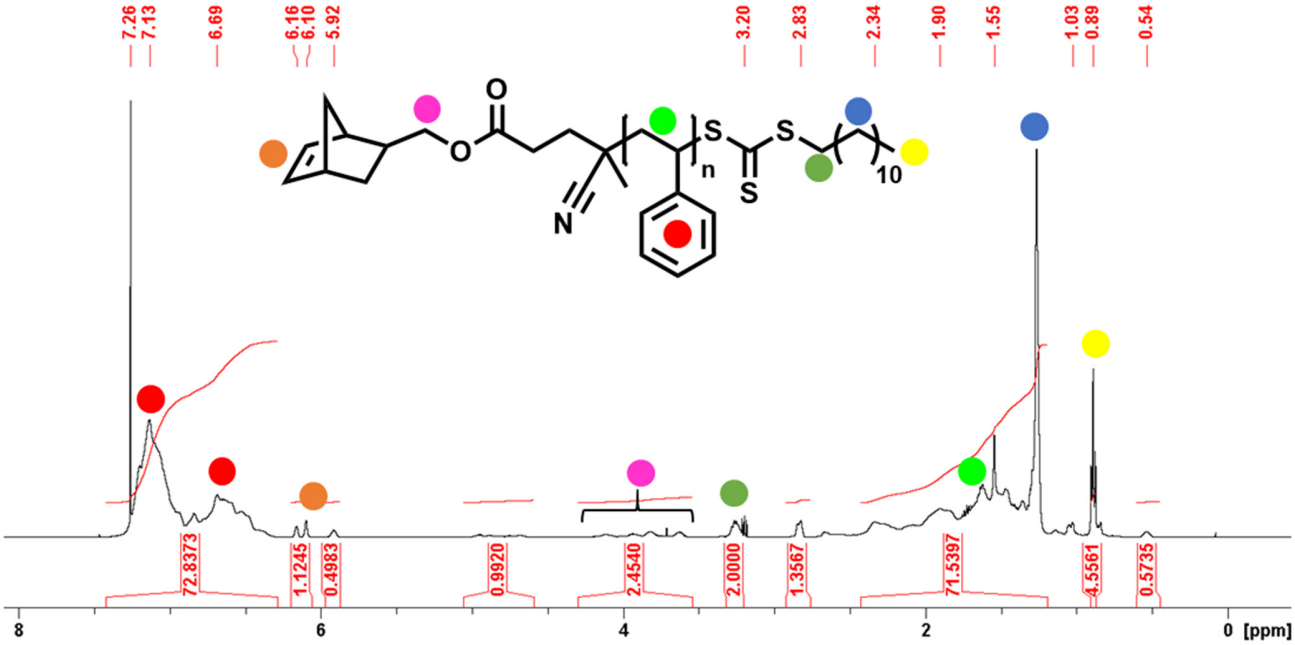


Figure S14. 500 MHz ^{1}H-NMR ($CDCl_3$) of $PS_{1.5k}$-Nb (M_w 1.9 kDa) prepared by RAFT.

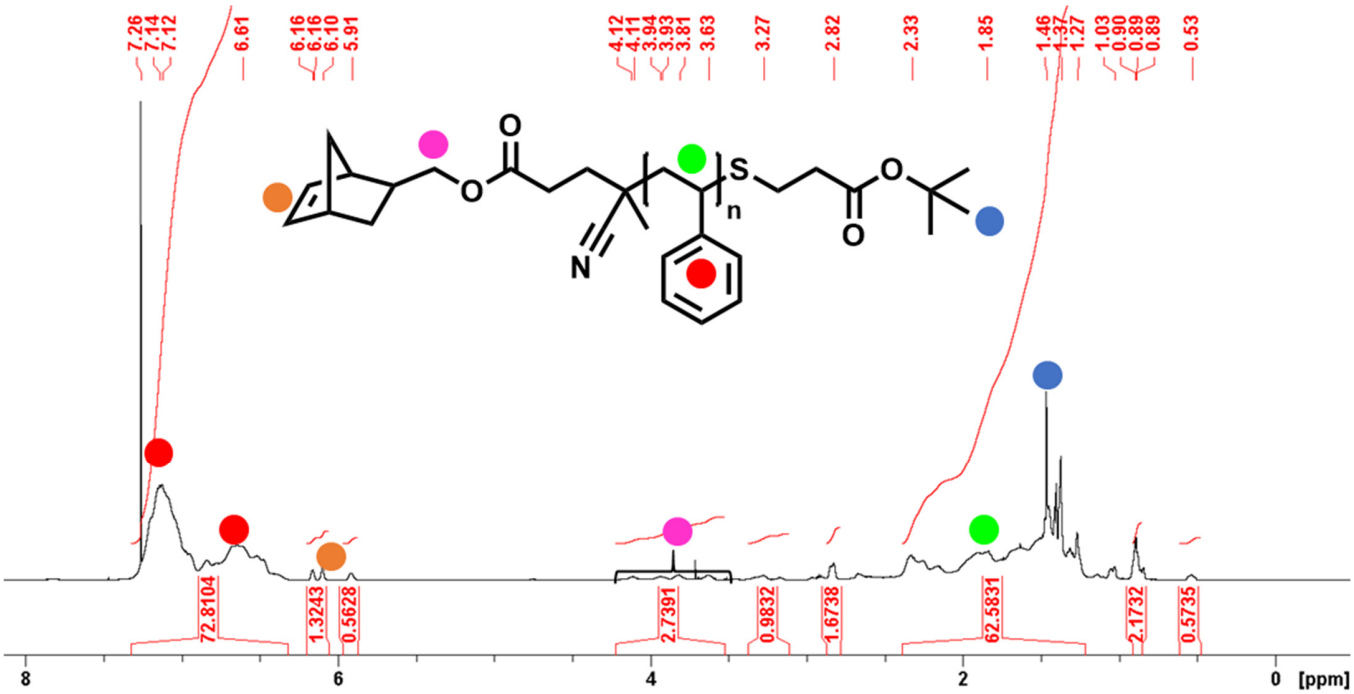


Figure S15. 500 MHz ^{1}H-NMR ($CDCl_3$) of $PS_{1.5k}$-Nb (M_w 1.8 kDa) after RAFT aminolysis.

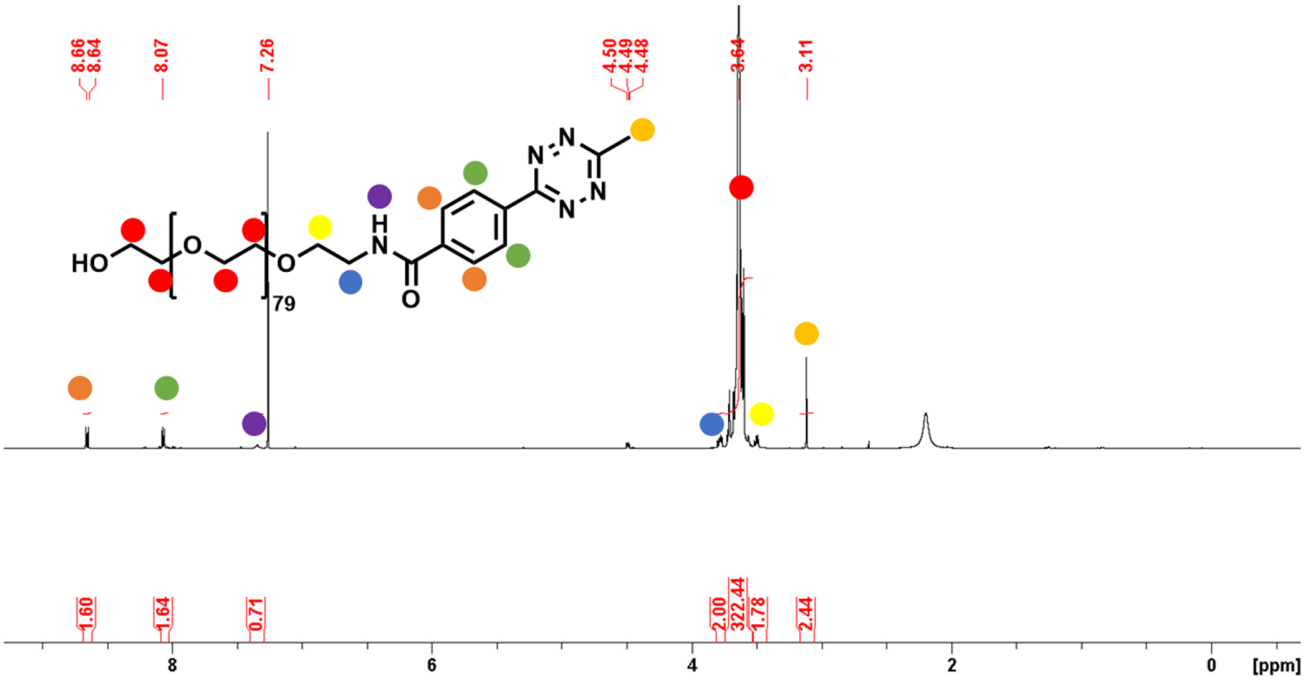


Figure S16. 500 MHz ^{1}H-NMR ($CDCl_3$) of PEG_{3k}-Tz.

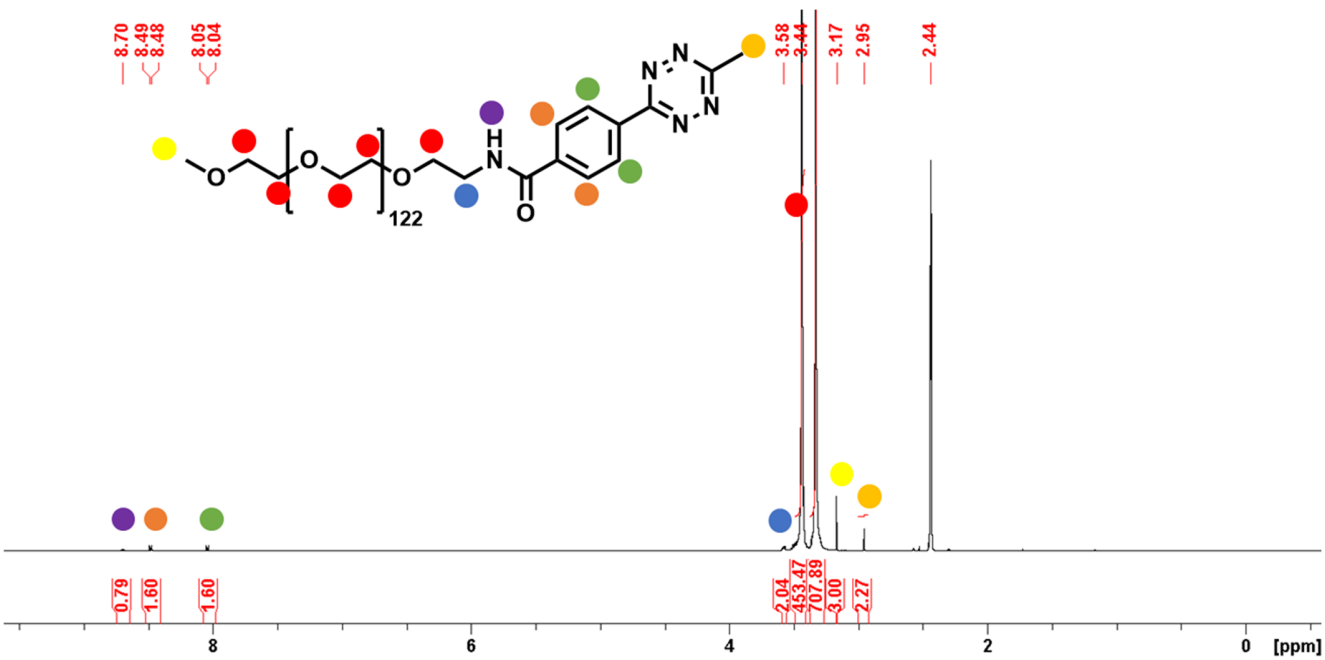


Figure S17. 500 MHz ^{1}H-NMR (DMSO-d6) of PEG_{5k}-Tz.

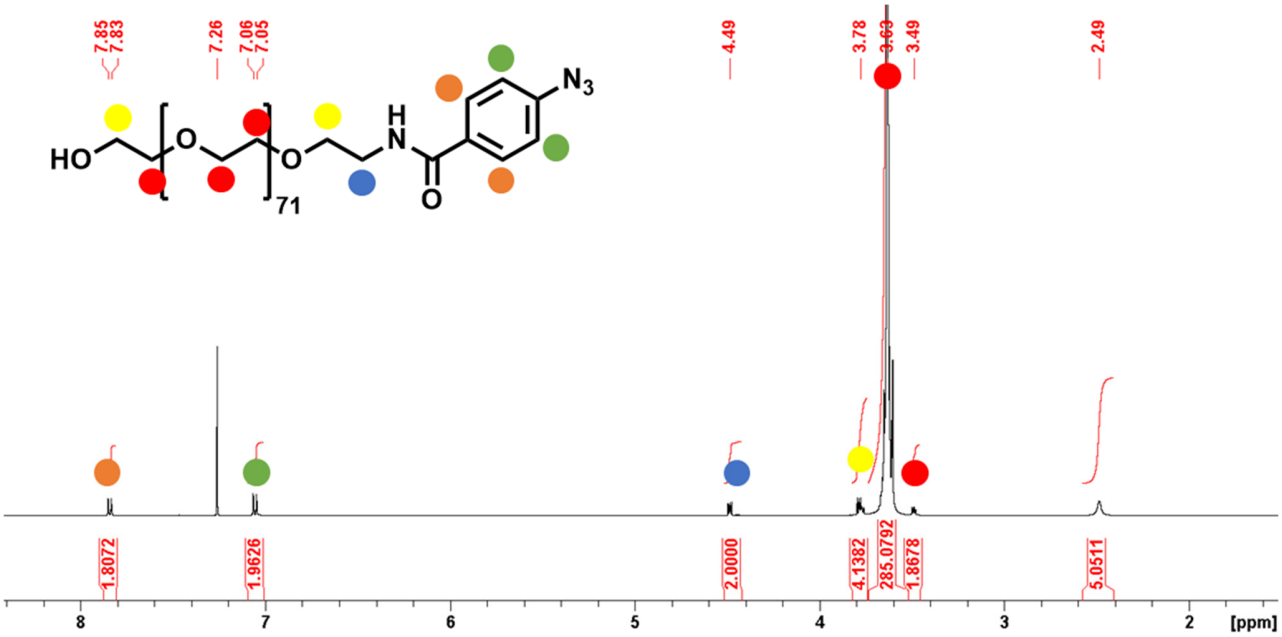


Figure S18. 500 MHz ^{1}H-NMR ($CDCl_3$) of PEG_{3k}-Az.

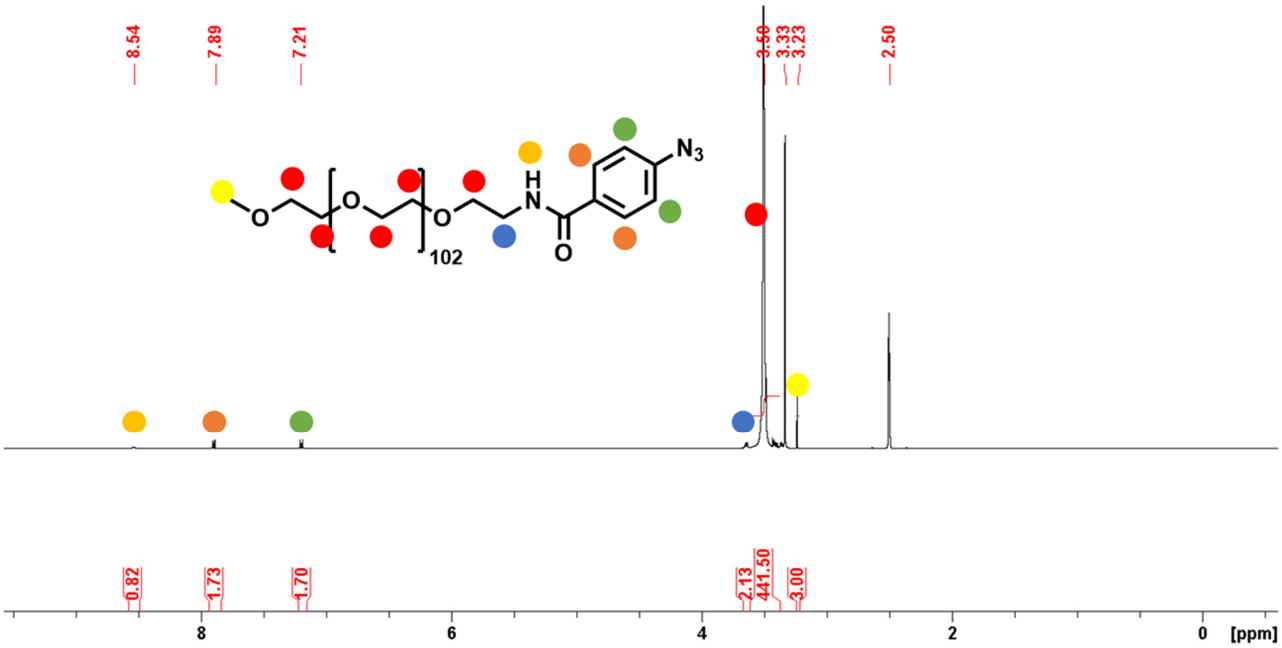


Figure S19. 500 MHz ^{1}H-NMR ($CDCl_3$) of PEG_{5k}-Az.

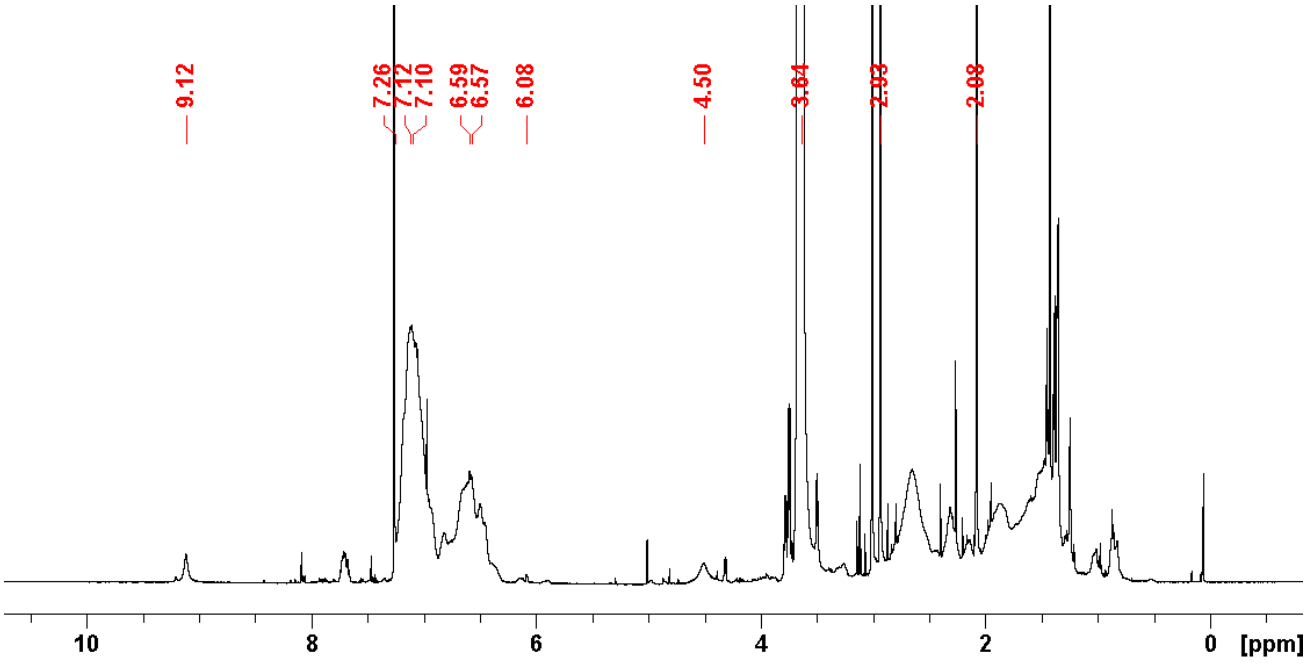


Figure 20. 500 MHz ^{1}H-NMR ($CDCl_3$) of the PEG_{3k}-Az and $PS_{1.5k}$-Nb coupling without precipitation.

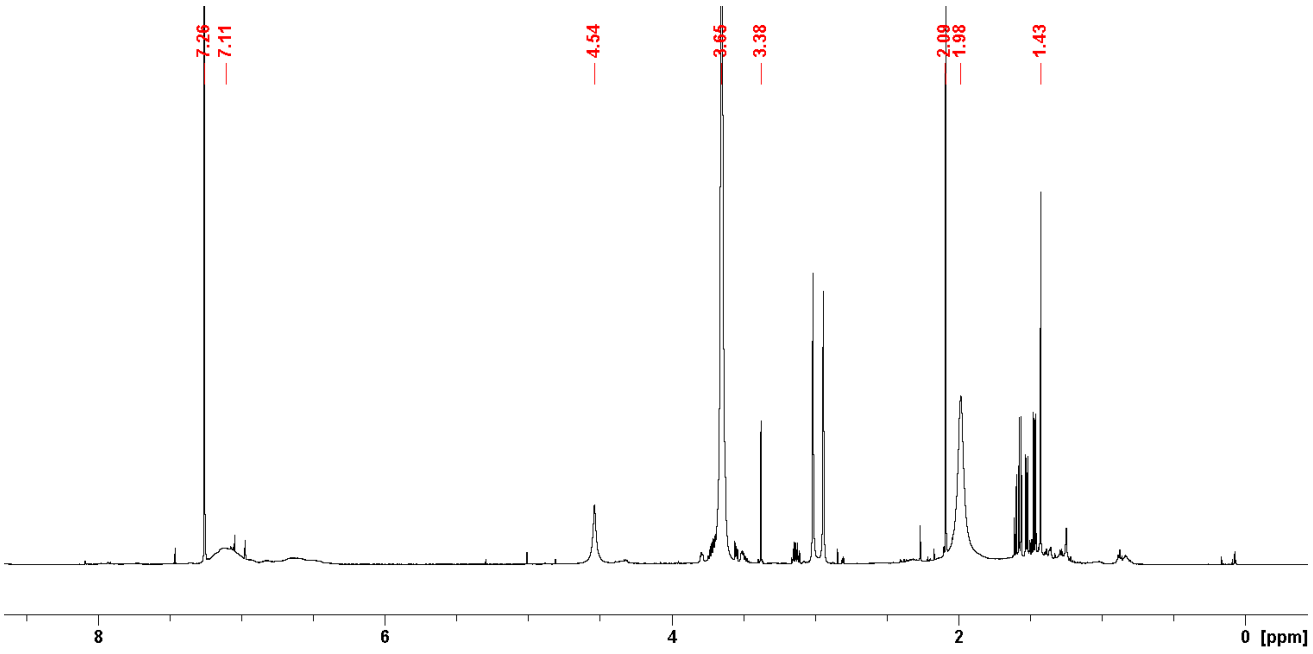


Figure S21. 500 MHz ^{1}H-NMR ($CDCl_3$) of the PEG_{5k}-Az and $PS_{1.5}$-Nb coupling without precipitation.

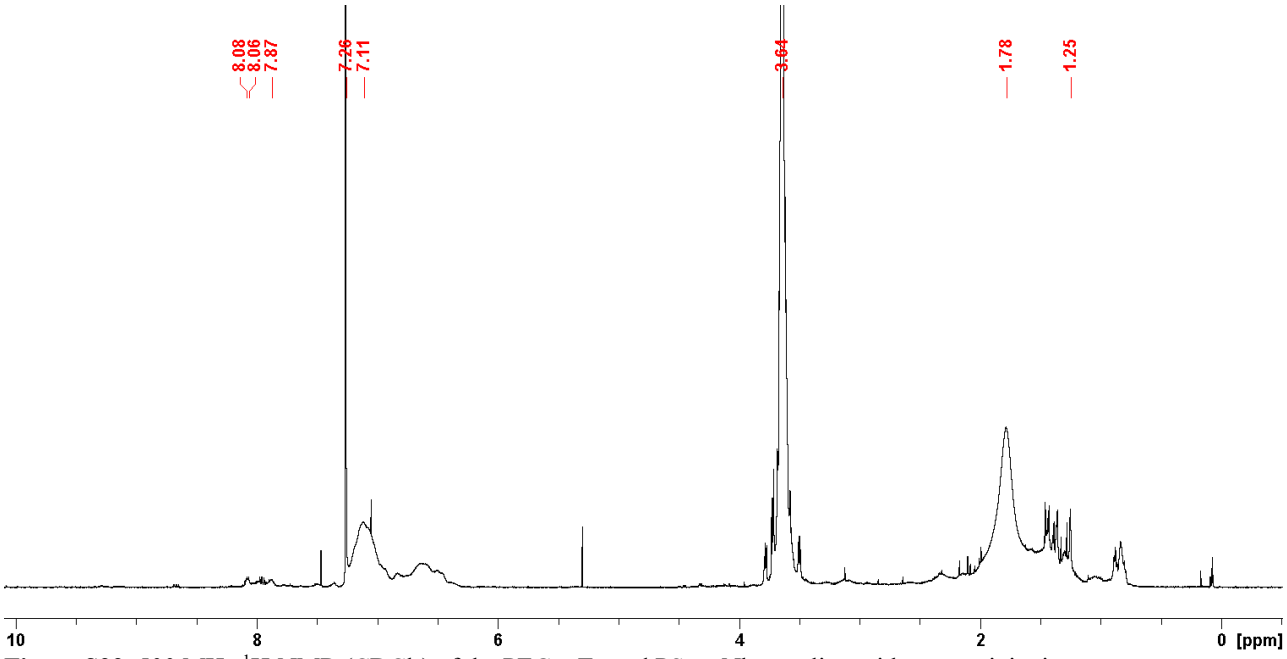


Figure S22. 500 MHz ^{1}H-NMR ($CDCl_3$) of the PEG_{3k}-Tz and $PS_{1.5k}$-Nb coupling without precipitation.

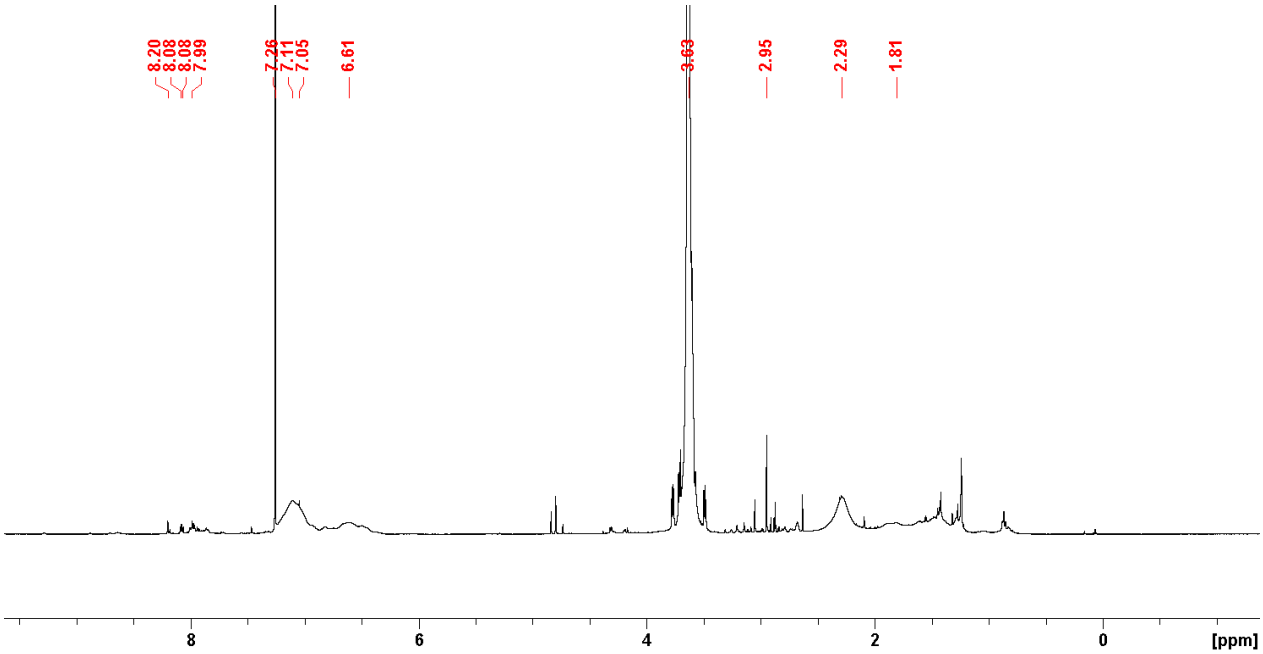


Figure S23: 500 MHz ^{1}H-NMR ($CDCl_3$) of the PEG_{5k}-Tz and $PS_{1.5k}$-Nb coupling without precipitation.

6.1.3. DOSY-NMR

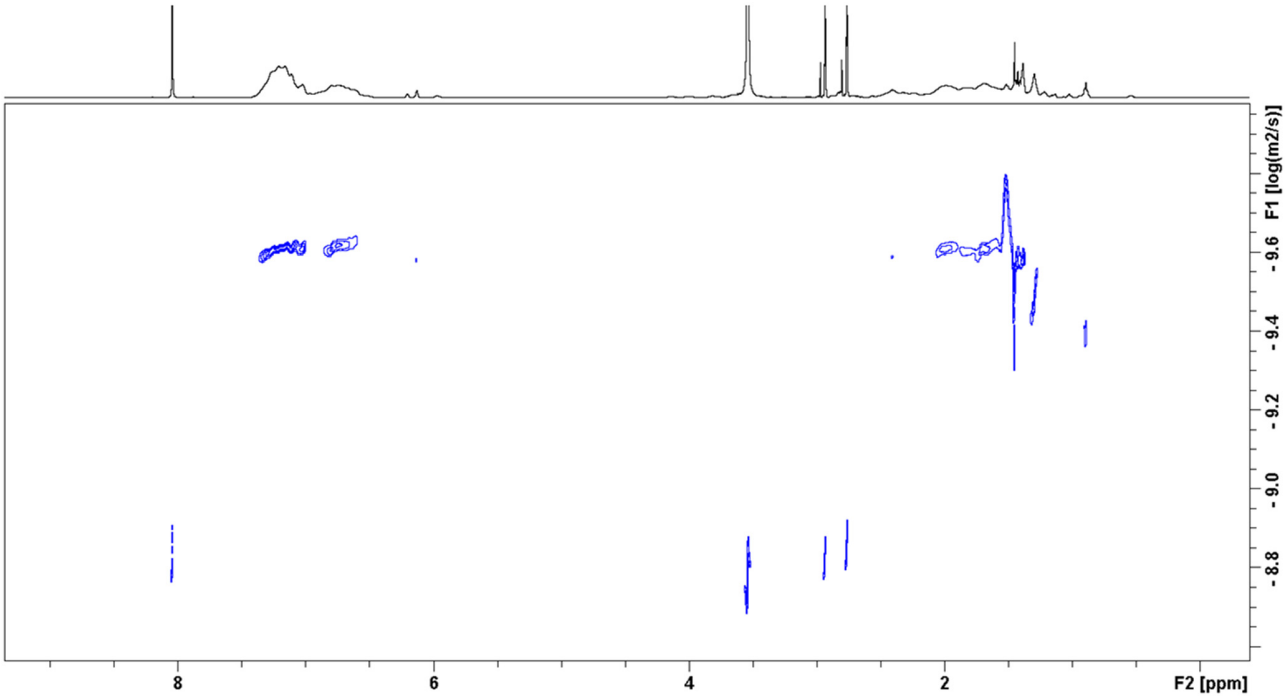


Figure S24. 600 MHz DOSY-NMR (DMF-d7) of $Nb_{1.5k}$-PS (M_n 1.6 kDa) after aminolysis.

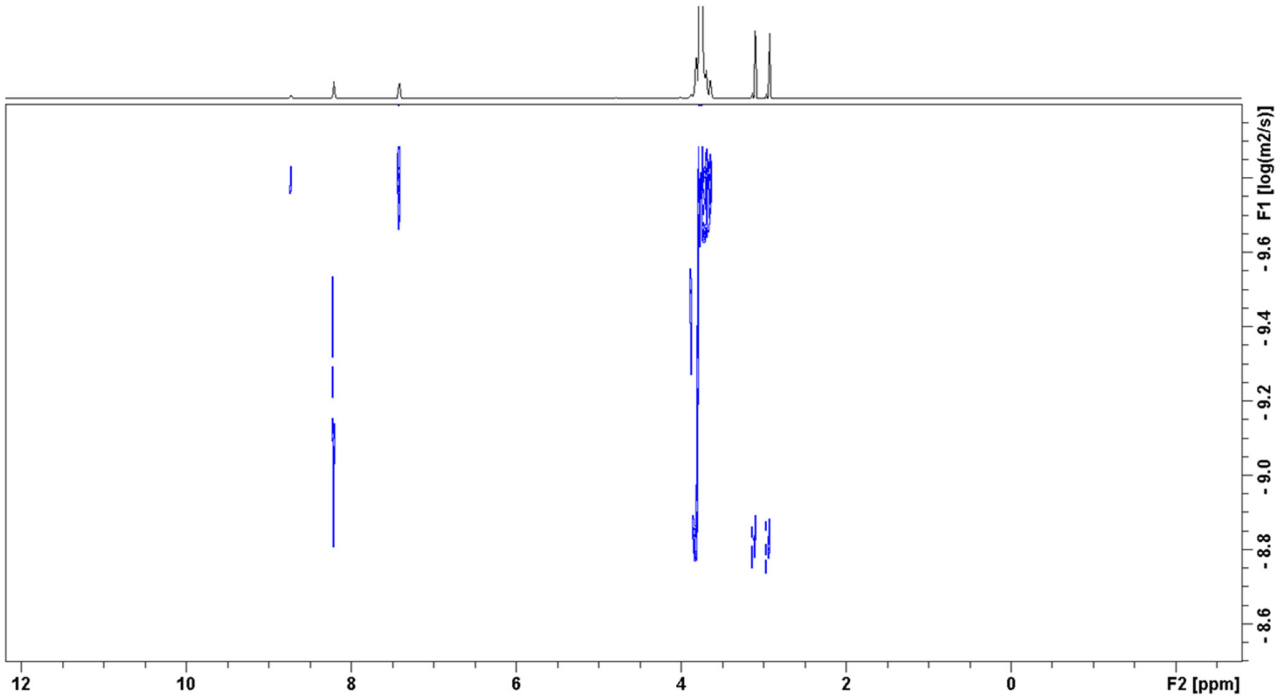


Figure S25. 600 MHz DOSY-NMR (DMF-d7) of PEG_{3k}-Az (M_n 3.3 kDa).

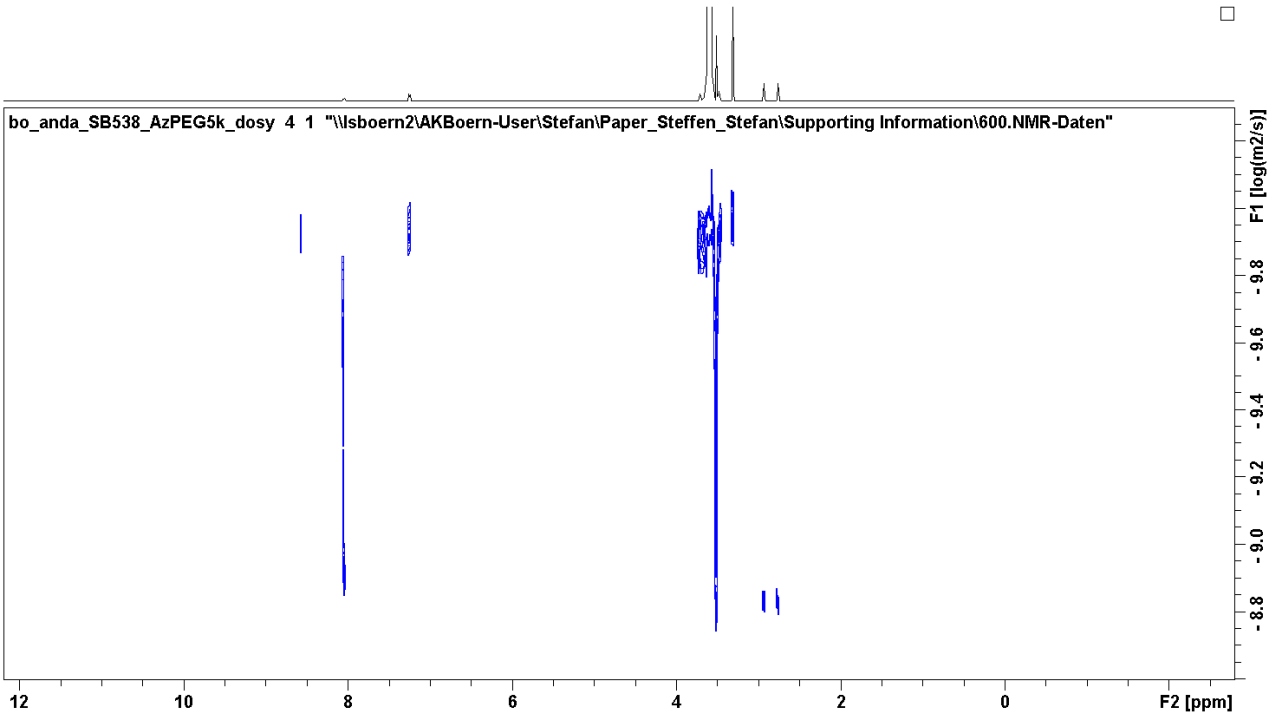


Figure S26. 600 MHz DOSY-NMR (DMF-d7) of PEG_{5k}-Az (M_n 4.6 kDa).

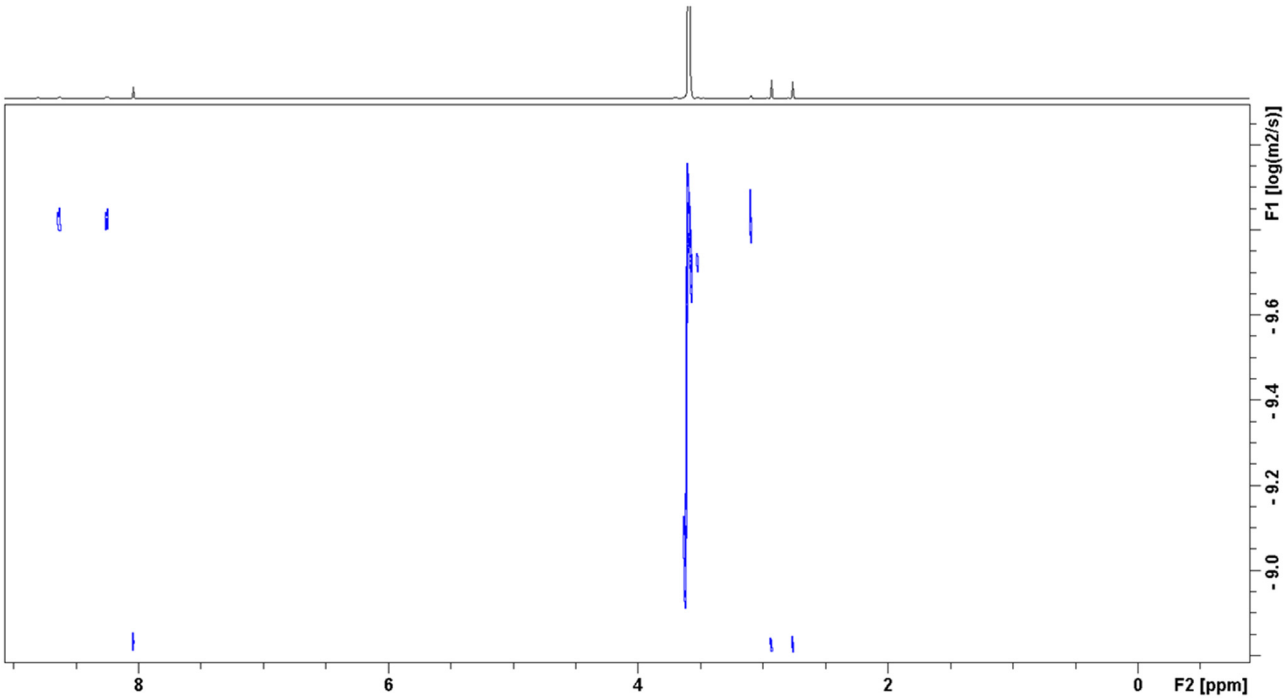


Figure S27. 600 MHz DOSY-NMR (DMF-d7) of PEG_{3k}-Tz (M_n 3.2 kDa).

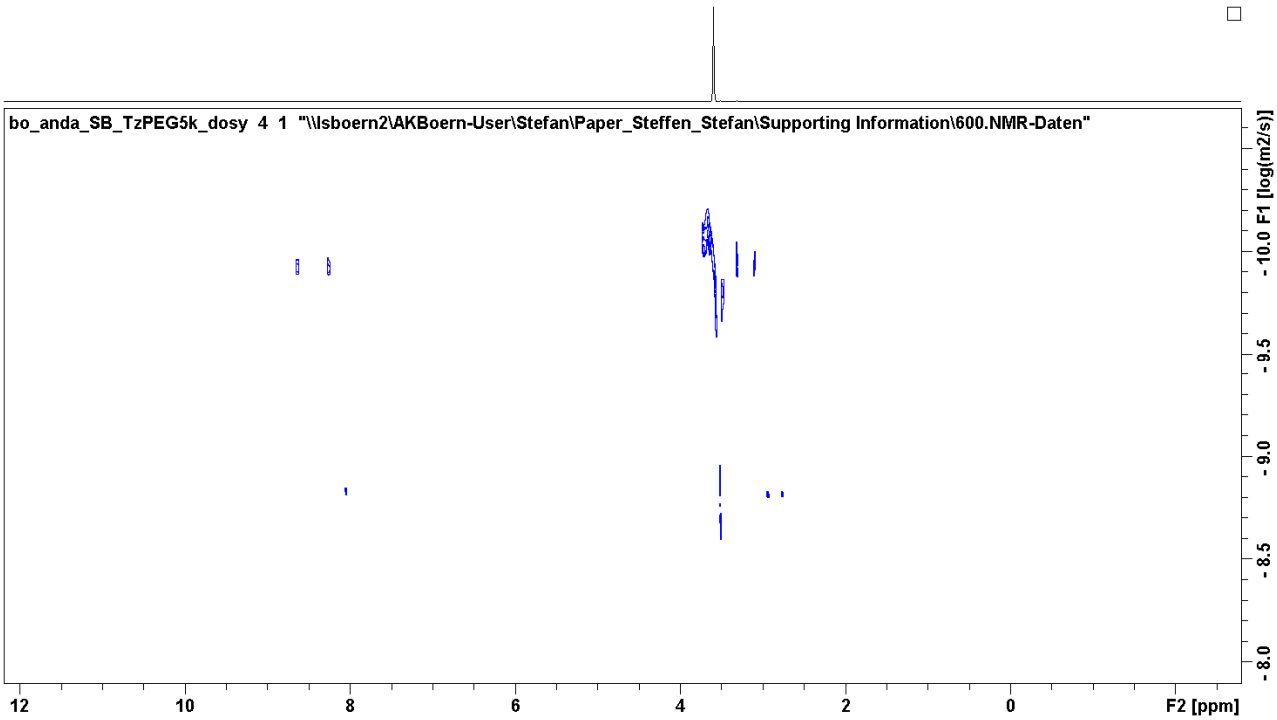


Figure S28. 600 MHz DOSY-NMR (DMF-d7) of PEG_{5k}-Tz (M_n 4.6 kDa).

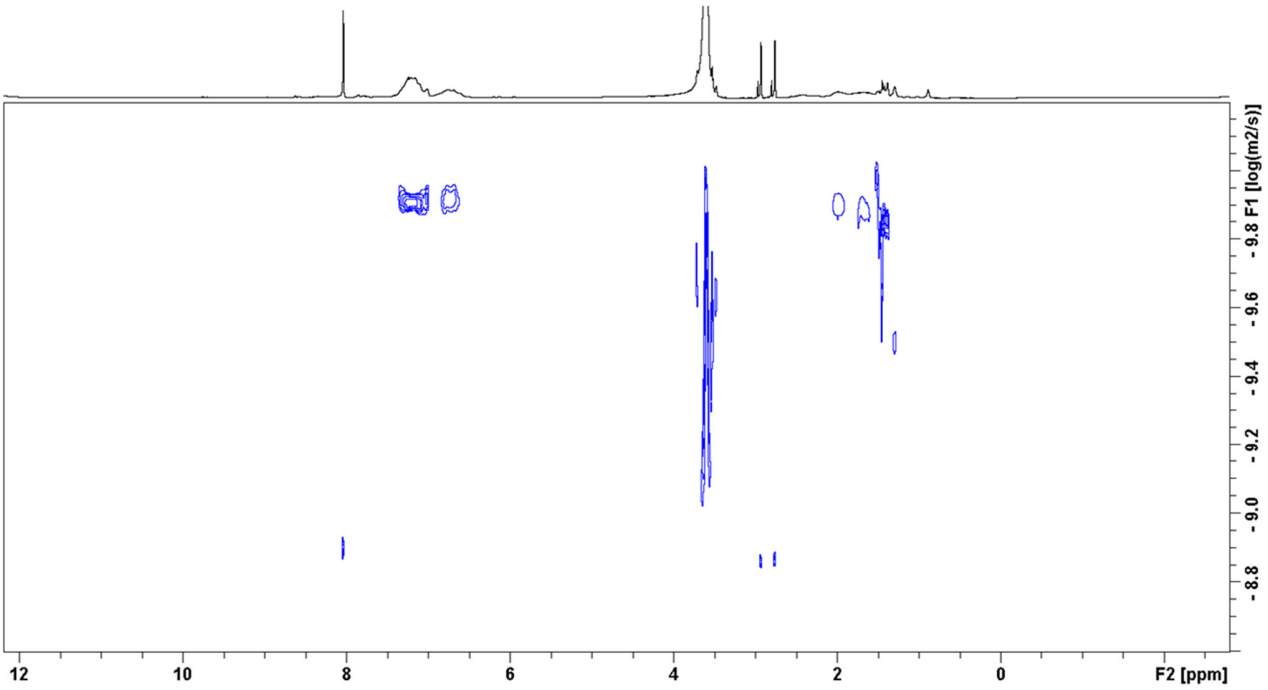


Figure S29. 600 MHz DOSY-NMR (DMF-d7) of the PEG_{3k}-Az $PS_{1.5k}$-Nb coupling.

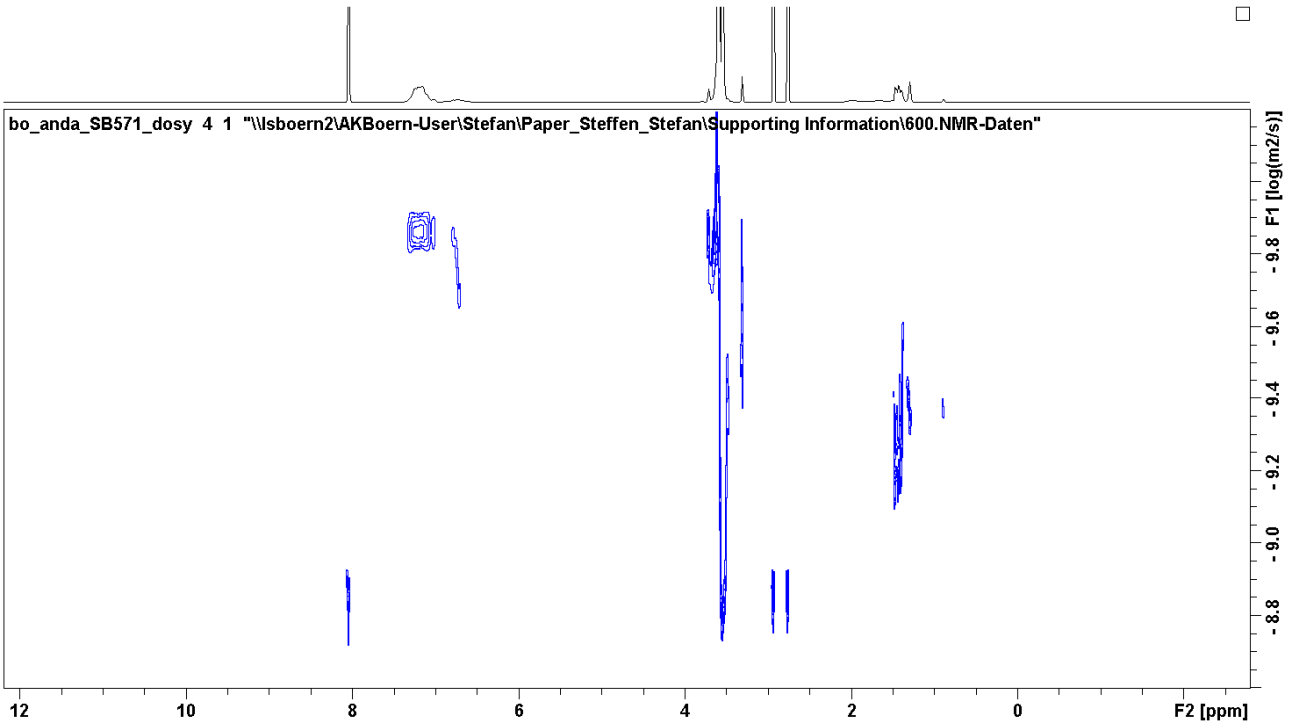


Figure S30. 600 MHz DOSY-NMR (DMF-d7) of the PEG_{5k}-Az $PS_{1.5k}$-Nb coupling.

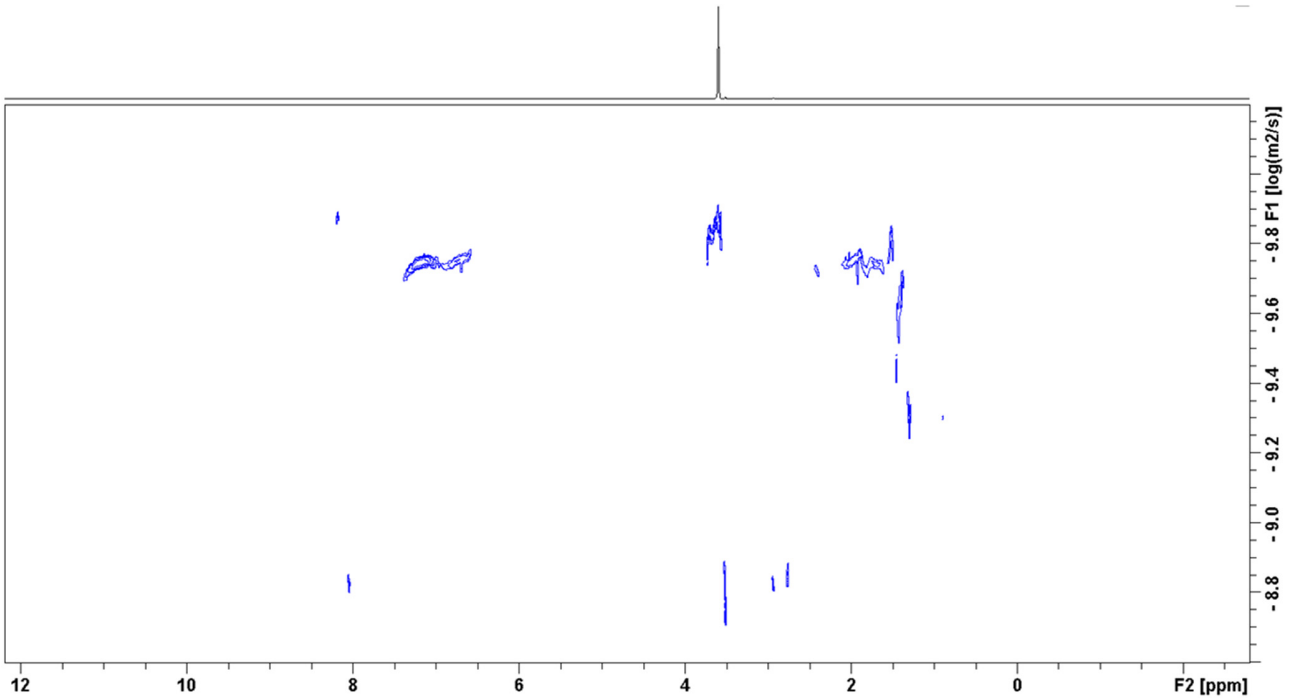


Figure S31. 600 MHz DOSY-NMR (DMF-d7) of the PEG_{3k}-Tz $PS_{1.5k}$-Nb coupling.

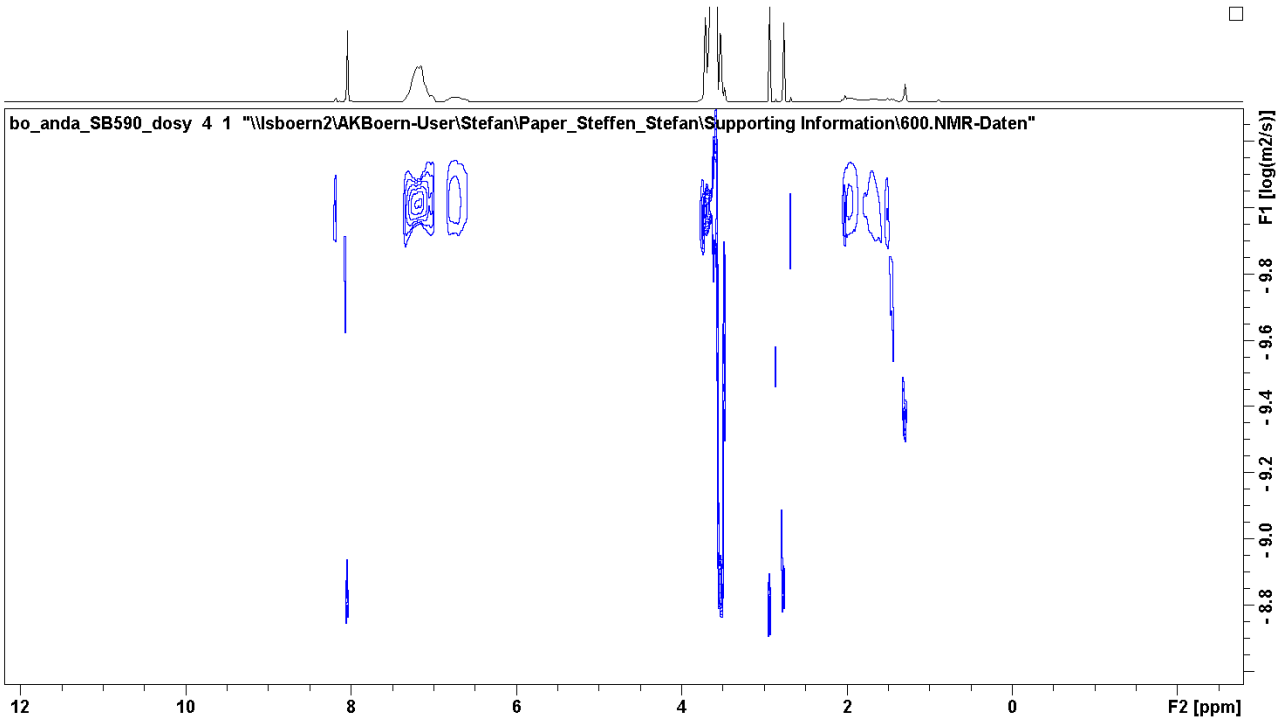


Figure S32. 600 MHz DOSY-NMR (DMF-d7) of the PEG_{5k}-Tz $PS_{1.5k}$-Nb coupling.

6.2. **Size exclusion chromatography (SEC)**

a) SEC-traces of the Tz-PEG$_{3k}$-Nb-PS-reaction in DMAc + LiBr

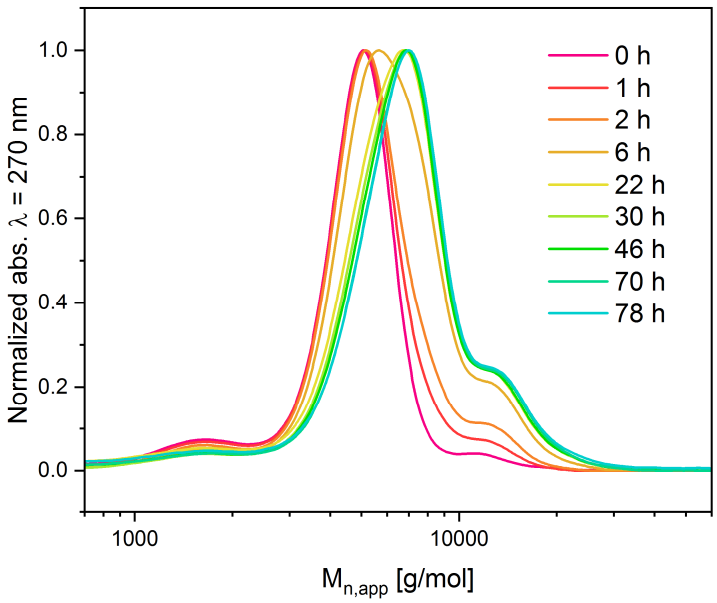


Figure S33. SEC-traced of the evolution of the PS-b-PEG conjugation showing the disappearance of the PS-signal and shift of the PEG-signal. [Conditions]: 1:1 ratio of PS$_{1.5k}$-Nb: PEG$_{3k}$-Tz in DMF at 80 °C, DMAc GPC, 50 °C, DMAc + LiBr.

b) SEC-traces of the Tz-PEG$_{5k}$-Nb-PS-reaction in DMAc + LiBr

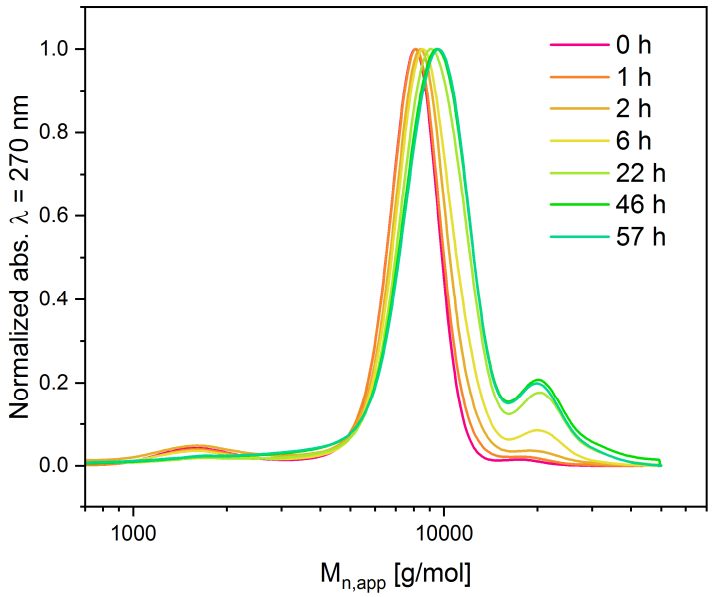


Figure S34. SEC-traced of the evolution of the PS-b-PEG conjugation showing the disappearance of the PS-signal and shift of the PEG-signal. [Conditions]: 1:1 ratio of PS$_{1.5k}$-Nb : PEG$_{5k}$-Tz in DMF at 80 °C, DMAc GPC, 50 °C, DMAc + LiBr.

c) SEC-traces of the Az-PEG$_{3k}$-Nb-PS-reaction in DMAc + LiBr

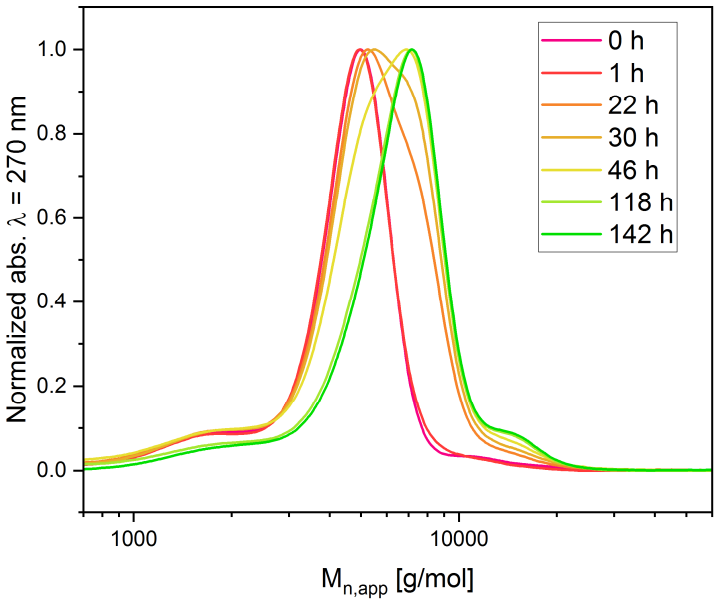


Figure S35. SEC-traced of the evolution of the PS-b-PEG conjugation showing the disappearance of the PS-signal and shift of the PEG-signal. [Conditions]: 1:1 ratio of PS$_{1.5k}$-Nb : PEG$_{3k}$-Az in DMF at 80 °C, DMAc GPC, 50 °C, DMAc + LiBr.

d) SEC-traces of the Az-PEG$_{5k}$-Nb-PS-reaction in DMAc + LiBr

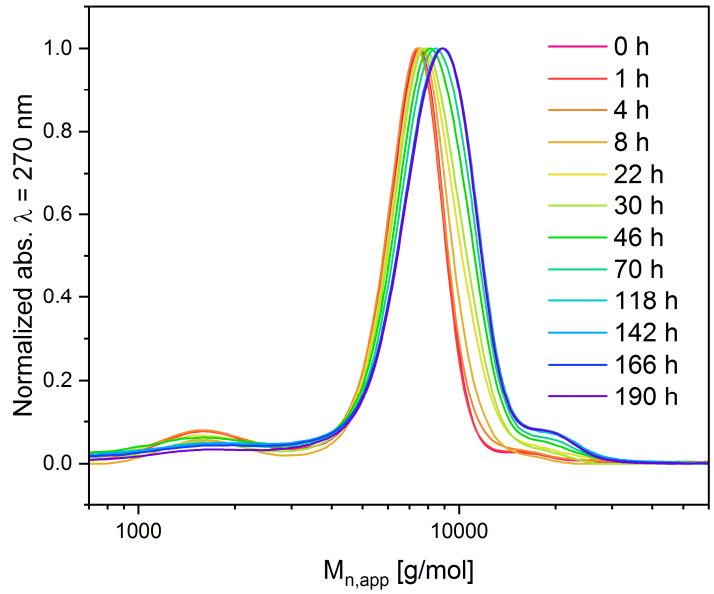


Figure S36. SEC-traced of the evolution of the PS-b-PEG conjugation showing the disappearance of the PS-signal and shift of the PEG-signal. [Conditions]: 1:1 ratio of PS$_{1.5k}$-Nb: PEG$_{5k}$-Az in DMF at 80 °C, DMAc GPC, 50 °C, DMAc + LiBr.

6.3. Matrix-Assisted Laser Desorption/Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF-MS)

a) MALDI-TOF-MS of the reaction products of $PS_{1.5k}$-Nb with Az-COOH

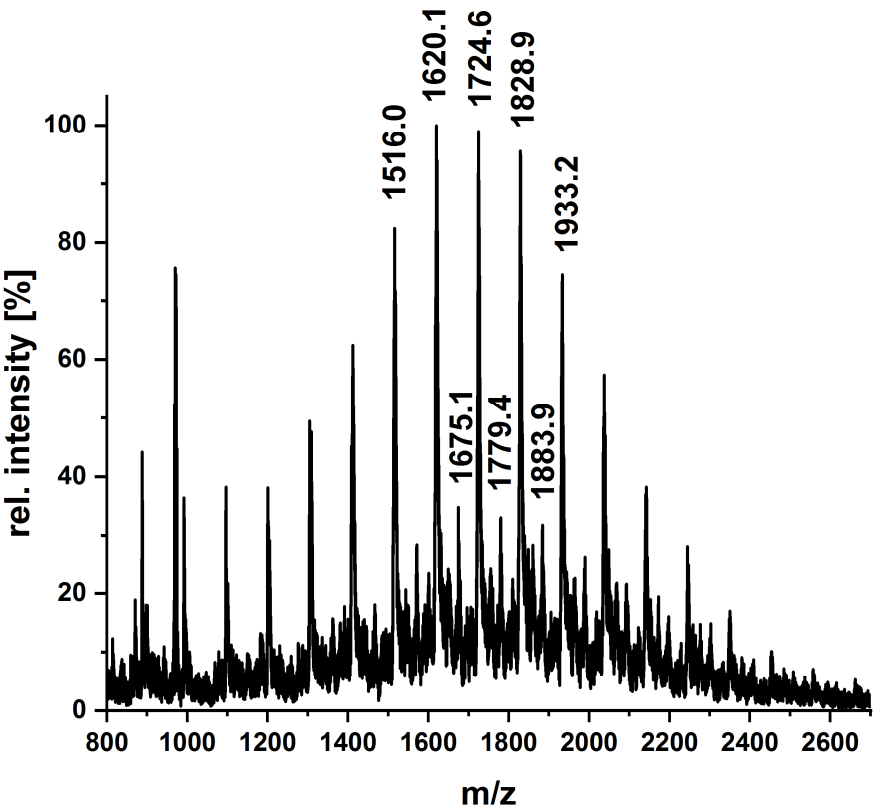


Figure S37. MALDI-TOF-MS of the coupling products of $PS_{1.5k}$-Nb (1.00 eq.) and Az-COOH (1.00 eq.). [conditions]: Matrix: Dithranol + AgTFA.

Triazoline product: DP (11)

Δm = 104.3 PS repeating unit

$M_{cal}[M+Na]^+$ = 1723.9 (m/z)

$M_{exp}[M+Na]^+$ = 1724.6 (m/z)

Aziridin product: DP (11)

Δm = 104.3 PS repeating unit

$M_{cal}[M+Ag]^+$ = 1780.8 (m/z)

$M_{exp}[M+Ag]^+$ = 1779.4 (m/z)

b) MALDI-TOF-MS of the reaction products of PEG_{3k}-Az with $PS_{1.5k}$-Nb

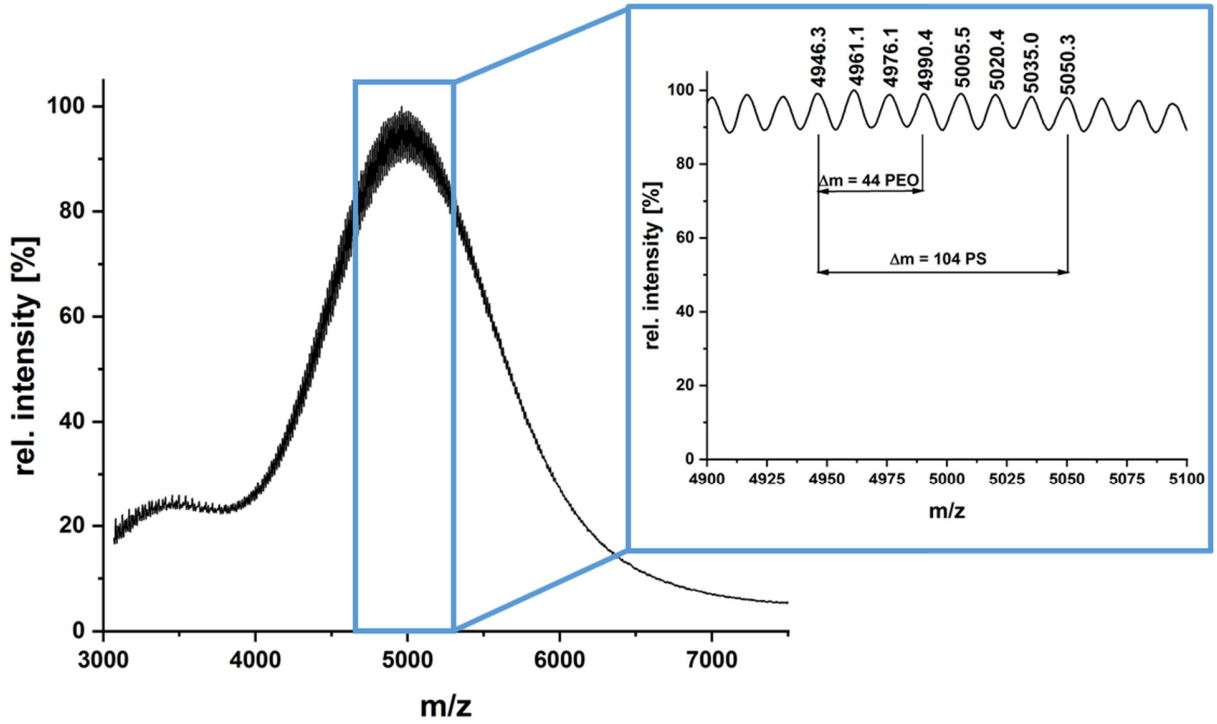


Figure S38. . MALDI-TOF-MS of the coupling product of PEG_{3k}-Az (1.00 eq.) and $PS_{1.5k}$-Nb (1.00 eq.). [conditions]: Matrix: DCTB + AgTFA.

Triazoline product: DP_{PS} (8), DP_{PEO} (78)

Δm = 104 PS repeating unit; Δm = 44 PEO repeating unit

$M_{cal}[M+Ag]^+ = 4945$ (m/z)

$M_{exp}[M+Ag]^+ = 4946$ (m/z)

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