Polymers with quadruple hydrogen-bonding end groups: controlling molecular weight using a small molecule photoswitch

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Supporting information

The spectrum obtained for DAN-PMMA **14** could be used to confirm the incorporation of DAN functionality *via* key proton environments (Figure S1). Due to the overlapping RAFT agent and polymer signals, it was not possible to calculate the exact quantity of DAN successfully incorporated into DAN-PMMA **14**. However, using the integrals of the DAN proton environments identified, an approximate M_n of 32,000 g mol^{-1} was calculated. This M_n was similar to that obtained by GPC, suggesting that incorporation of the DAN HBM was close to complete.

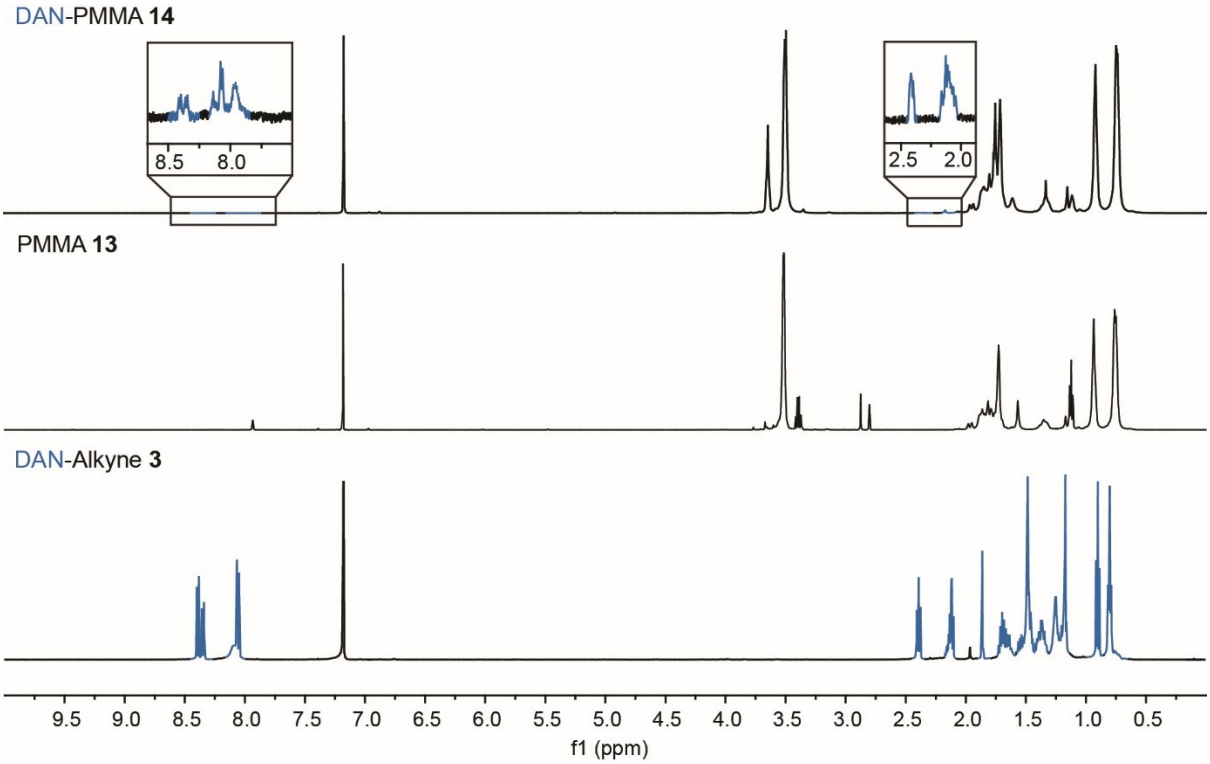


Figure S1. ^{1}H NMR spectra for DAN-Alkyne **3**, PMMA **13** and DAN-PMMA **14**. Insets show signals which indicate DAN HBM functionality has been incorporated into PMMA **14**.

Synthesis

General Considerations

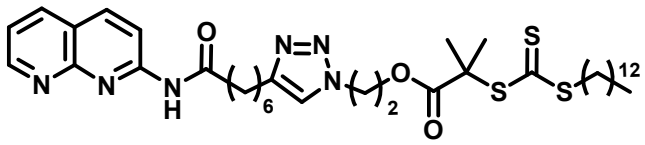
Solvents and reagents were purchased from Sigma Aldrich, Fluorochem or Fisher Scientific and used without further purification unless otherwise stated. Where anhydrous solvents or reagents were required, tetrahydrofuran was obtained from the in-house solvent purification system Innovative Inc. PureSolv®, anhydrous triethylamine was purchased from Fluorochem and anhydrous dimethylsulfoxide from Sigma Aldrich. All non-aqueous reactions were carried out in oven-dried glassware under a nitrogen atmosphere with magnetic stirrer bars, unless otherwise stated. All work-up and purification procedures were carried out using reagent-grade solvents under ambient atmosphere. Analytical thin layer chromatography was performed on Merck Kieselgel 60 F_{254} 0.25 mm pre-coated aluminium plates and visualised by UV quenching (λ_{max}=254 nm). Flash chromatography was carried out using Merck Kieselgel 60 silica gel. High-performance liquid chromatography (HPLC) was performed with an Agilent Technologies 1290 Infinity analytical preparative system equipped with a Kinetex EVO C18 reverse-phase column (φ 21.2 x 250 mm).

Infra-red (IR) spectra were obtained using a PerkinElmer Fourier transform IR spectrometer in which absorption maxima (ν_{max}) are expressed in wavenumbers (cm^{-1}). High-resolution mass spectrometry (HRMS) was performed using a Bruker maXis Impact QTOF mass spectrometer, with an electrospray ionisation (ESI) source. UV-Vis absorption spectra were recorded on an Agilent Technologies Cary Series UV-Vis spectrophotometer.

For NMR experiments anhydrous chloroform-*d* was purchased from Sigma Aldrich. All ^{1}H NMR spectra were acquired on Bruker AVANCE spectrometers, operating at 400 MHz or 500 MHz for ^{1}H, 100 MHz or 125 MHz for ^{13}C and 375 MHz for ^{19}F. NMR spectra were obtained at 298 K and referenced using residual solvent signals as internal standards unless stated otherwise. The spectrometers used for 1D experiments were either a two-channel Bruker AV3HD NMR spectrometer operating at 9.4 T (400 MHz ^{1}H) equipped with a 5 mm BBO probe or a two-channel Bruker AV-NEO NMR spectrometer operating at 11.7 T (500 MHz ^{1}H) equipped with a 5 mm DCH cryoprobe. DOSY spectra were obtained using a four-channel Bruker AV-NEO NMR spectrometer operating at 11.7 T (500 MHz ^{1}H) and equipped with 5mm TXI probe (δ = 0.002 s, Δ = 0.0999). Chemical shifts are expressed in parts per million (ppm) and the following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad).1D and 2D NMR spectra can be found appendices A and B respectively.

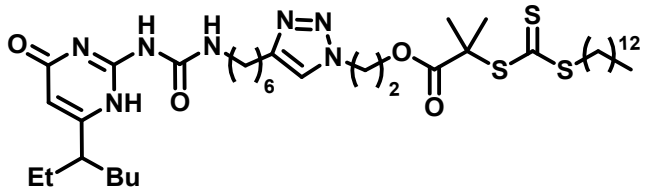
Compounds **1-3** were prepared as described previously.[1]

[1-[3-[2-[[(Dodecylthio)thioxomethyl]thio]-2-methyl-1-oxopropoxy]propyl]-1H-1,2,3-triazol-4-yl]-2- N-(1,8-naphthyridin-2-yl)oct-7-amide – 5



NAP alkyne **1** (0.37 g, 1.32 mmol, 1.0 eq.), 2- (dodecyl-thiocarbonothioylthio)-2-methylpropionic acid 3-azido-1-propanol ester **4** (1.1 mL, 2.63 mmol, 2.0 eq.) and tetrakis(acetonitrile)copper(I) hexafluorophosphate (0.05 g, 0.13 mmol, 0.1 eq.) were dissolved in anhydrous n,n-dimethylformamide (10 mL). N,N-diisopropylethylamine (0.52 mL, 2.99 mmol, 2.3 eq.) was added and the reaction stirred under nitrogen at 50 °C for 16 h. Upon cooling to room temperature, the reaction mixture was diluted with dichloromethane (50 mL), then washed with 5 % lithium chloride solution (3 x 50 mL), dried with sodium sulfate, filtered, and concentrated in vacuo. The title compound was isolated via column chromatography (SiO_2, dichloromethane: methanol (99:1 → 90:10)) to give the title compound **5** as a yellow solid (0.62 g, 0.85 mmol, 64 %). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 9.13 – 8.88 (m, 2H, 2 x Nap-*H*), 8.57 (d, 1H, *J* 8.9 Hz, Nap-*H*), 8.17 (m, 2H, Nap-*H* and NH), 7.41 (dd, 1H, *J* 8.0, 4.3 Hz, Nap-*H*), 7.29 (s, 1H, triazole-*H*), 4.36 (t, 2H, *J* 6.9 Hz, (triazole) N-CH_2), 4.11 (t, 2H, *J* 5.8 Hz, COO-CH_2), 3.27 (t, 2H, *J* 7.5 Hz, (triazole) C-CH_2), 2.71 (t, 2H, *J* 7.5 Hz, SSCS-CH_2), 2.49 (t, 2H, *J* 7.5 Hz, NHCC-CH_2), 2.24 (p, 2H, *J* 6.6 Hz, NCH$_2$CH_2CH$_2$O), 1.77 (p, 2H, *J* 7.5 Hz, SCH$_2$CH_2), 1.70 (s, 6H, SC(CH_3)$_2$), 1.66-1.63 (m, 4H, 2 x CH_2), 1.46 – 1.40 (m, 4H, 2 x CH_2), 1.38-1.33 (m, 2H, CH_2), 1.27-1.23 (m, 16 H, 8 x CH_2), 0.87 (t, 3H, *J* 6.9 Hz, CH_3); ^{13}C NMR (125 MHz, Chloroform-*d*) δ 222.1, 172.8, 172.6, 154.8, 153.82 (d, 2 x C), 148.2, 139.6, 136.6, 120.9 (d, 2 x C), 115.4 (d, 2 x C), 62.5, 56.0, 46.9, 37.8, 37.1, 31.9, 29.8 – 29.2 (m, 2 x C), 29.1, 29.0 – 28.4 (m, 10 x C), 27.9, 26.1 – 24.4 (m, 2 x C), 22.7, 14.1; ESI-HRMS *m/z* found 729.3671 [M + H]+ $C_{37}H_{57}N_6O_3S_3$ requires 729.3649; Rf 0.3 (9.5:0.5 dichloromethane: methanol); IR ν_{max} (solid state) = 3238.3, 3122.0, 2920.5, 2850.8, 2219.6, 1726.7 cm^{-1}.

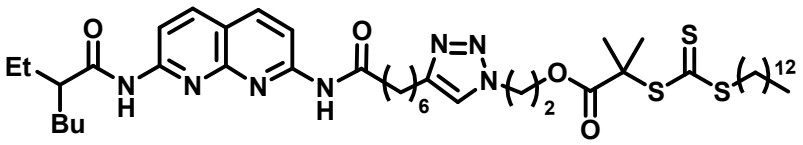
[1-[3-[2-[[(Dodecylthio)thioxomethyl]thio]-2-methyl-1-oxopropoxy]propyl]-1H-1,2,3-triazol-4-yl]-2-(oct-1-yl)-*N*-(4-(1-ethylpentyl)-1,6-dihydro-6-oxo-2-pyrimidinyl))urea – 6



UPy alkyne **2** (0.4 g, 1.18 mmol, 1 eq), 2- (dodecyl-thiocarbonothioylthio)-2-methylpropionic acid 3-azido-1-propanol ester **4** (1.0 mL, 2.37 mmol, 2 eq), tetrakis(acetonitrile) copper(I) hexafluorophosphate (0.05g, 0.12 mmol, 0.1 eq) and diisopropylethylamine (0.47 mL, 2.72

mmol, 2.3 eq) were dissolved in n,n-dimethylformamide (10 mL) under an inert gas atmosphere. The suspension was stirred for 16 h at 50 °C. The reaction mixture was diluted with dichloromethane (25 mL) and washed with 5% LiCl solution (3 x 25 mL), then dried with sodium sulfate, filtered and concentrated to give a yellow oil. The product was isolated *via* column chromatography (SiO_2, dichloromethane: methanol (99:1 → 95:5)) to afford title compound **6** as a brown oil (0.5 g, mmol, 52 %). ^{1}H NMR (500 MHz, chloroform-*d*) δ 13.25 (s, 1H, N*H*), 11.91 (s, 1H, N*H*), 10.18 (s, 1H, N*H*), 7.26 (s, 1H, triazole-*H*), 5.82 (s, 1H, Ar-*H*), 4.43 – 4.32 (m, 2H, (triazole) N-CH_2), 4.12 (t, 2H, J 5.8 Hz, COO-CH_2), 3.28 – 3.24 (m, 4H, (triazole) C-CH_2, NHCONH-CH_2), 2.70 – 2.69 (m, 2H, SSCS-CH_2), 2.32 – 2.29 (m, 1H, EtBu-*H*), 2.24 (t, 2H, *J* 6.3 Hz, $NCH_2CH_2CH_2O$), 1.70 (s, 6H, SC(CH_3)$_2$), 1.69 – 1.49 (m, 10H, 5 x CH_2), 1.44 - 1.41 (m, 4H, 2 x CH_2), 1.37-1.34 (m, 2H, CH_2), 1.31 – 1.20 (m, 20H, 10 x CH_2), 0.92 – 0.83 (m, 9H, 3 x CH_3); ^{13}C NMR (125 MHz, chloroform-*d*) δ 222.0, 173.2, 172.8, 156.7, 155.5, 154.9, 148.4, 121.0, 106.2, 62.5, 55.9, 46.85, 45.4, 40.1, 37.1, 32.9, 31.9, 30.0 – 29.2 (m, 3 x C), 29.2 – 28.3 (m, 10 x C), 27.9, 26.8, 26.6, 25.7, 25.4, 22.7, 22.5, 14.0 (d, 2 x C), 11.7; ESI-HRMS *m/z* found 808.4691 $[M + H]^+$ $C_{40}H_{70}N_7O_4S_3$ requires 808.4646; Rf 0.4 (9.5:0.5 dichloromethane: methanol); IR ν_{max} (solid state) = 3217.7, 2923.6, 2853.4, 2094.6, 1734.1 cm^{-1}.

[1-[3-[2-[[(Dodecylthio)thioxomethyl]thio]-2-methyl-1-oxopropoxy]propyl]-1H-1,2,3-triazol-4-yl]- 2-((n-((1,8-naphthyridin-2-yl)-2-ethylhexanamide)oct-8-amide – 7



DAN alkyne **3** (0.06 g, 0.14 mmol, 1.0 eq.), 2- (dodecyl-thiocarbonothioylthio) -2-methylpropionic acid 3-azido-1-propanol ester **4** (0.12 mL, 0.28 mmol, 2.0 eq.) and tetrakis(acetonitrile)copper(I) hexafluorophosphate (0.005 g, 0.014 mmol, 0.1 eq.) were dissolved in anhydrous n,n-dimethylformamide (10 mL). N,N-diisopropylethylamine (0.06 mL, 0.33 mmol, 2.3 eq.) was added and the reaction stirred under nitrogen at 50 °C for 16 h. Upon cooling to room temperature, the reaction mixture was diluted with dichloromethane (25 mL), then washed with 5 % lithium chloride solution (3 x 20 mL), dried with sodium sulfate, filtered, and concentrated in vacuo. The title compound was isolated *via* column chromatography (SiO_2, dichloromethane: methanol (95:5)) to give the title compound **7** as a yellow solid (0.07 g, 0.08 mmol, 58 %). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.75 (s, 1H, N*H*), 8.61 (s, 1H, N*H*), 8.40 – 8.34 (m, 2H, 2 x Nap-*H*), 8.12 – 8.00 (m, 2H, 2 x Nap-*H*), 7.23 (s, 1H, triazole-*H*), 4.31 (t, 2H, *J* 6.9 Hz, (triazole) N-CH_2), 4.05 (m, 2H, COO-CH_2), 3.20 (t, 2H, *J* 7.4 Hz, (triazole)C-CH_2), 2.62 (m, 2H, SSCS-CH_2), 2.36 (t, 2H, *J* 7.4 Hz, CONH-CH_2), 2.17 (m, 3H, EtBuC*H*,

$NCH_2CH_2CH_2O$), 1.63 (s, 6H, $SC(CH_3)_2$), 1.61 – 1.55 (m, 4H, 2 x CH_2), 1.34 – 1.26 (m, 6H, 3 x CH_2), 1.20 – 1.16 (m, 26H, 13 x CH_2), 0.86 (t, *J* 7.4 Hz, 3H, CH_3), 0.79 (dt, *J* 9.6, 6.7 Hz, 6H, 2 x CH_3); ^{13}C NMR (125 MHz, chloroform-*d*) δ 222.1, 175.8, 172.9, 171.2, 155.6, 154.1, 153.5, 148.3, 148.2, 139.2 (d, 2 x C), 121.3, 118.3, 113.8, 60.4, 50.7, 46.9, 37.7, 37.1, 32.4, 32.0, 31.6, 29.8-29.6 (d, 2 x C), 29.5-28.8 (m x 10 x C), 27.9, 26.0, 25.5-25.4 (d, 2 x C), 25.1, 22.7, 21.1, 14.3, 14.0, 12.0; ESI-HRMS *m/z* found 870.4840 $[M + H]^+$ $C_{45}H_{72}N_7O_4S_3$ requires 870.4802; Rf 0.3 (95:5 dichloromethane: methanol); IR v_{max} (solid state) = 3139.5, 2923.0, 2852.8, 2222.7, 1732.8 cm^{-1}.

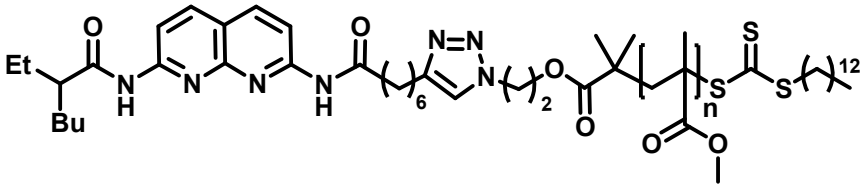
Polymerization of Methyl acrylate using functionalized RAFT agents (5-7)

Methyl acrylate (1.00 g, 1.00 mmol), AIBN (4.10 mg, 0.025 mmol), **5-7** (0.250 mmol) were dissolved in DMF (3.53 mL, 41.00 mmol). The flask was sealed and purged with nitrogen for 15 minutes while stirring before submerging in a pre-heated oil bath at 70°C. After 3h the reaction mixture was cooled and the reaction was quenched by exposure to air. The mixture was precipitated into methanol and isolated and dried by vacuum filtration yielding a yellow solid. Conversion was measured by ^{1}H NMR spectroscopy and M_n, M_w and *Đ* were measured by THF GPC.

Polymerization of Methyl methacrylate using an azide functional RAFT agent

Methyl methacrylate (1.00 g, 1.00 mmol), ACHN (6.11 mg, 0.025 mmol), **4** (0.250 mmol) were dissolved in DMF (3.53 mL, 41.00 mmol). The vial was sealed and purged with nitrogen for 15 minutes while stirring before being submerged in a pre-heated oil bath at 70°C. After 5h the reaction mixture was cooled and the reaction was quenched with air. The mixture was precipitated into methanol and isolated and dried by vacuum filtration yielding a yellow solid.

DAN-PMMA – 14



DAN alkyne **4** (0.01 g, 0.02 mmol, 1.0 eq.), azide-PMMA **13** (0.1 g, 0.02 mmol, 1.0 eq.) and tetrakis(acetonitrile)copper(I) hexafluorophosphate (0.7 mg, 0.002 mmol, 0.1 eq.) were

dissolved in anhydrous n,n-dimethylformamide (10 mL). N,N-diisopropylethylamine (8 µL, 0.05 mmol, 2.3 eq.) was added and the reaction stirred under nitrogen at 50 °C for 16 h. Upon cooling to room temperature, the reaction mixture was diluted with dichloromethane (25 mL), then washed with 5 % lithium chloride solution (3 x 20 mL), dried with sodium sulfate, filtered, and concentrated in vacuo. Size exclusion chromatography (Bio-Bead S-X1 Resin, chloroform) gave polymer **14** as a pale-yellow solid (0.1 g). ^{1}H NMR (500 MHz, chloroform-*d*) δ 8.42 – 8.30 (m, 2 x Nap-*H*), 8.15 – 8.07 (m, 2 x Nap-*H*), 3.53 (s, PMMA O-C*H*$_3$), 3.53 (s, PMMA O-C*H*$_3$), 1.80 – 1.74 (m, PMMA C*H*$_2$), 0.95 – 0.78 (m, PMMA C-C*H*$_3$). Additional signals cannot be distinguished due to masking from polymer signals; IR ν_{max} (solid state) = 2994.2, 2853.8, 1724.6, 1678.8 cm^{-1}.

Photoisomerisation Studies

For irradiation of foldamer samples, high-power LED system was used. Green 530 nm light was used for *E* to *Z* isomerisation and blue 405 nm light was used for *Z* to *E* isomerisation. Irradiation was carried out at room temperature, with stirring, for 10 minutes. Samples were stirred magnetically in a glass vial covered with foil. After irradiation samples were transferred to NMR tubes and immediately transferred to the NMR sample changer.

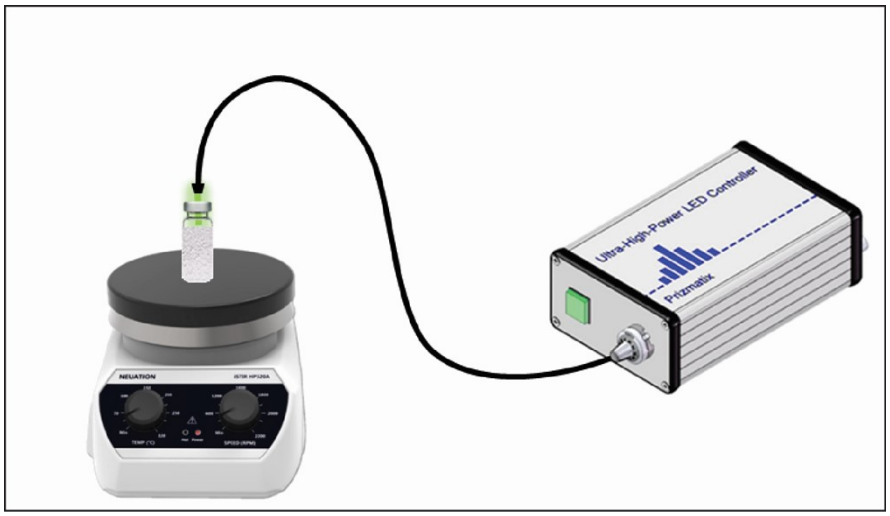


Figure S2. Representation of the equipment used for irradiation of samples.

DOSY NMR

DOSY spectra were obtained using a four-channel Bruker AV-NEO NMR spectrometer operating at 11.7 T (500 MHz ^{1}H) and equipped with 5mm TXI probe (δ = 0.002 s, Δ = 0.0999). Samples were prepared in Wilmad 500 MHz 5mm 528-PP-7 tubes using anhydrous deuterated chloroform purchased from Sigma Aldrich.

From the DOSY spectra obtained, reports were generated using the Bruker TopSpin Dynamics Centre software. Diffusion coefficient values were selected from the azobenzene proton peaks in the spectra. These peaks were selected as they showed clear evidence of switching after irradiation and were isolated from other proton environments in the spectra.

Molecular weights were estimated using the relationship $M_w = (D_{monomer}/D)^3$

The Stokes-Einstein equation [$D = (kT)/(6\pi\eta r)$] was used to determine volume changes on photoswitching using the viscosity of chloroform η = 0.536 mPa.s and T = 298K

DOSY Spectra

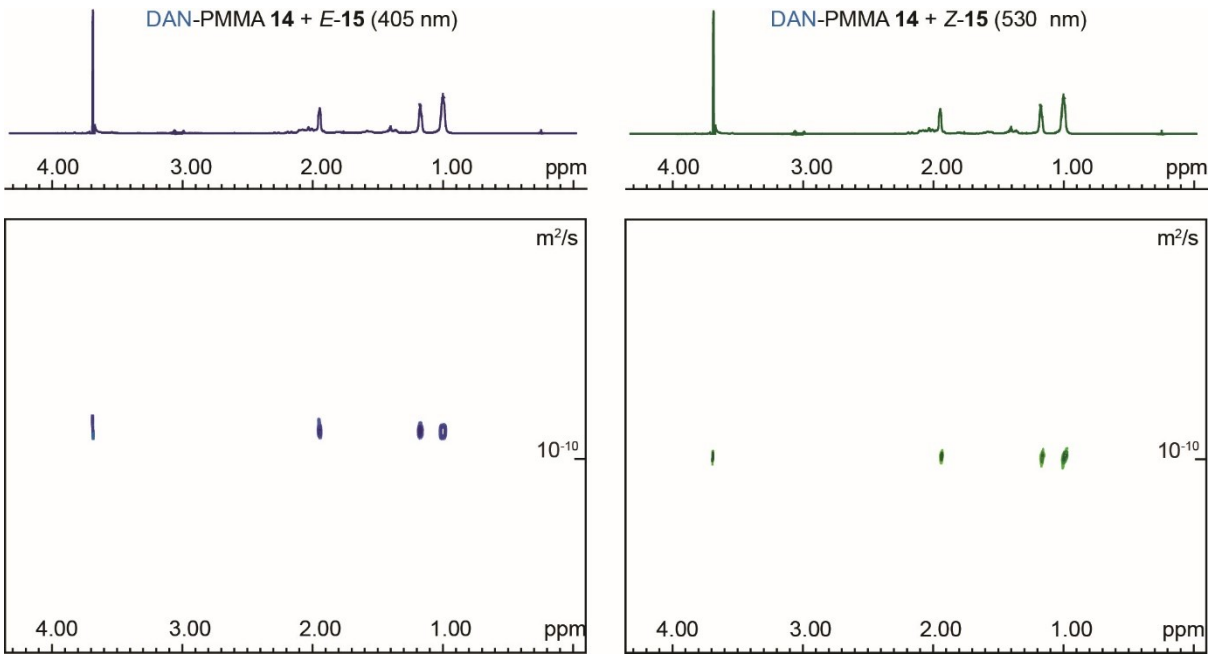


Figure S3. Expanded DOSY spectra shown in Figure 3

DOSY Data

DAN-PMMA 100 + UPy·UPy Foldamer III DOSY data

Cycle	*Wavelength (nm)*	*DAN-PMMA* 14 + 15	
		D (m^2/s)	Error (m^2/s)
1	530	1.21E-10	1.23E-12
2	405	9.45E-11	1.23E-12
3	530	1.29E-10	2.53E-12
4	405	9.63E-11	1.85E-12

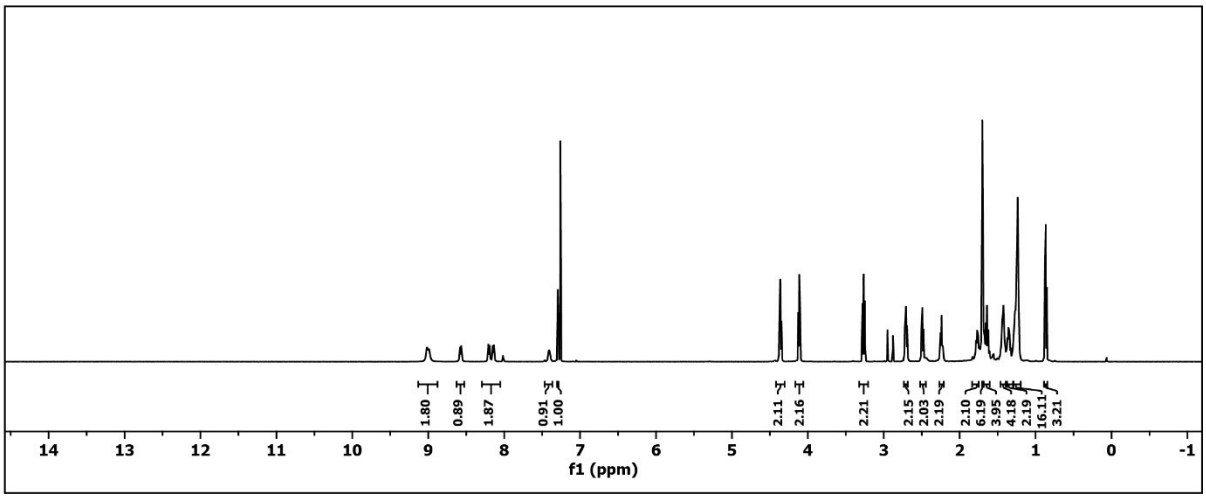
Table S1. Diffusion coefficients of DAN-PMMA **14** + **15** over 4 cycles of irradiation.

Cycle	*Wavelength (nm)*	*DAN-PMMA* 14 + 15	
		DP	Mw (g/mol^{-1})
1	530	1.00	31200.00
2	405	2.10	65496.08
3	530	0.83	25747.89
4	405	1.98	61891.62

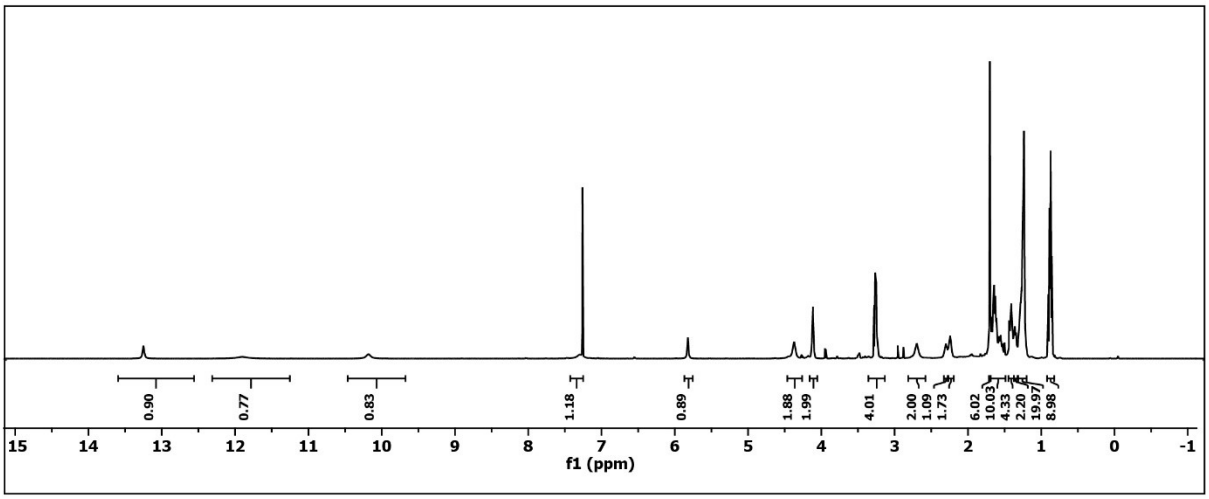
Table S2. Degrees of polymerisation and molecular weight of DAN-PMMA **14** + **15** over 4 cycles of irradiation.

^{1}H NMR Spectra

[1-[3-[2-[[(Dodecylthio)thioxomethyl]thio]-2-methyl-1-oxopropoxy]propyl]-1H-1,2,3-triazol-4-yl]-2- N-(1,8-naphthyridin-2-yl)oct-7-amide – 5



[1-[3-[2-[[(Dodecylthio)thioxomethyl]thio]-2-methyl-1-oxopropoxy]propyl]-1H-1,2,3-triazol-4-yl]-2-(oct-1-yl)-*N*-(4-(1-ethylpentyl)-1,6-dihydro-6-oxo-2-pyrimidinyl))urea – 6

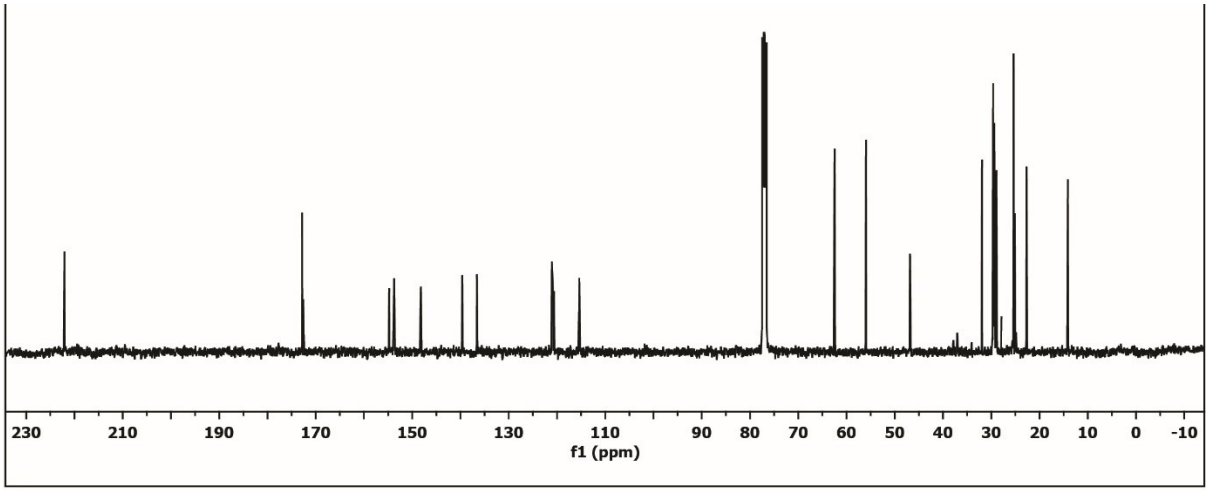


[1-[3-[2-[[(Dodecylthio)thioxomethyl]thio]-2-methyl-1-oxopropoxy]propyl]-1H-1,2,3-triazol-4-yl]- 2-((n-((1,8-naphthyridin-2-yl)-2-ethylhexanamide)oct-8-amide – 7

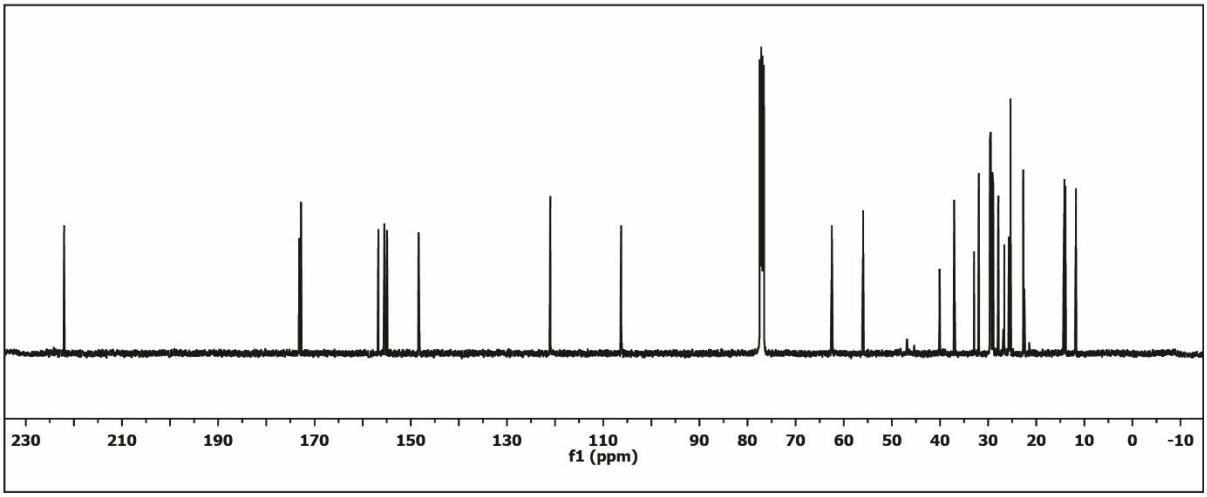
DAN-PMMA – 14

^{13}C NMR Spectra

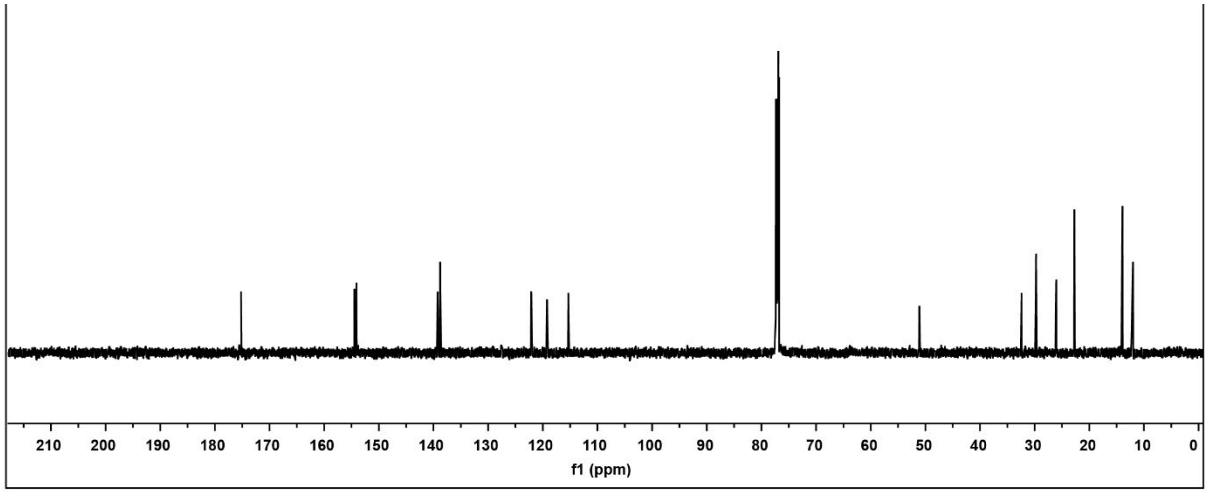
[1-[3-[2-[[(Dodecylthio)thioxomethyl]thio]-2-methyl-1-oxopropoxy]propyl]-1H-1,2,3-triazol-4-yl]-2- N-(1,8-naphthyridin-2-yl)oct-7-amide – 5



[1-[3-[2-[[(Dodecylthio)thioxomethyl]thio]-2-methyl-1-oxopropoxy]propyl]-1H-1,2,3-triazol-4-yl]-2-(oct-1-yl)-*N*-(4-(1-ethylpentyl)-1,6-dihydro-6-oxo-2-pyrimidinyl))urea – 6



[1-[3-[2-[[(Dodecylthio)thioxomethyl]thio]-2-methyl-1-oxopropoxy]propyl]-1H-1,2,3-triazol-4-yl]- 2-((n-((1,8-naphthyridin-2-yl)-2-ethylhexanamide)oct-8-amide – 7



References

1. E. M. Hilton, M. A. Jinks, A. D. Burnett, N. J. Warren and A. J. Wilson, *Chem. Eur. J.*, 2024, **30**, e202304033.