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Supporting Information

Degradable Glycopolymers for saRNA Transfection

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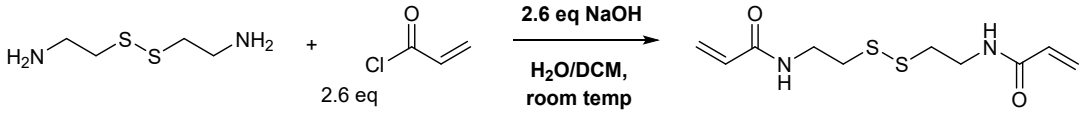
Synthesis of *N,N'*-bis(acryloyl)cystamine (BAC)



Scheme S1: General scheme for the synthesis of BAC monomer.

A solution of cystamine dihydrochloride (5.6 g, 24.9 mmol) and NaOH (4.6 g, 122 mmol) in water (50 mL) was added to a round bottom flask. Acryloyl chloride (5.3 mL, 65.2 mmol) was dissolved in DCM (20 mL) and added to the flask dropwise at 0 °C. The reaction was left stirring overnight at ambient temperature. Thereafter, the white precipitate was collected by filtration and recrystallised from hot ethyl acetate twice to obtain white crystals (5.21 g, 54%). δH: (400 MHz; DMSO) 2.81-2.84 (2H, t, -CH_2S, *J* = 6.8), 3.39-3.45 (4H, q, -CH_2), 4.77 (1H, s, -CHO), 5.58-5.61 (2H, dd, -CH=C, *J* = 17.2, 2,3), 6.05-6.26 (4H, m, -CH_2=C), 8.33 (2H, s, -NH); δC (100 MHz; DMSO) 37.1 (-CH_2S), 42.2 (-CH_2NH), 125.3 (-CH=CH_2), 131.2 (-CH_2=CH), 163.1 (-C=O).

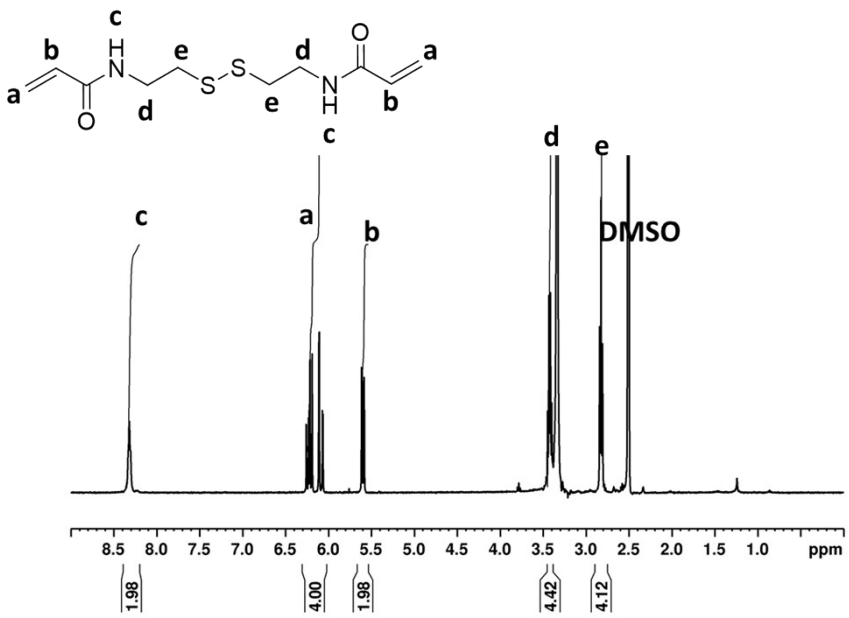


Figure S1: ^{1}H NMR spectrum of N,N′-bis(acryloyl)cystamine (BAC) in DMSO-d6.

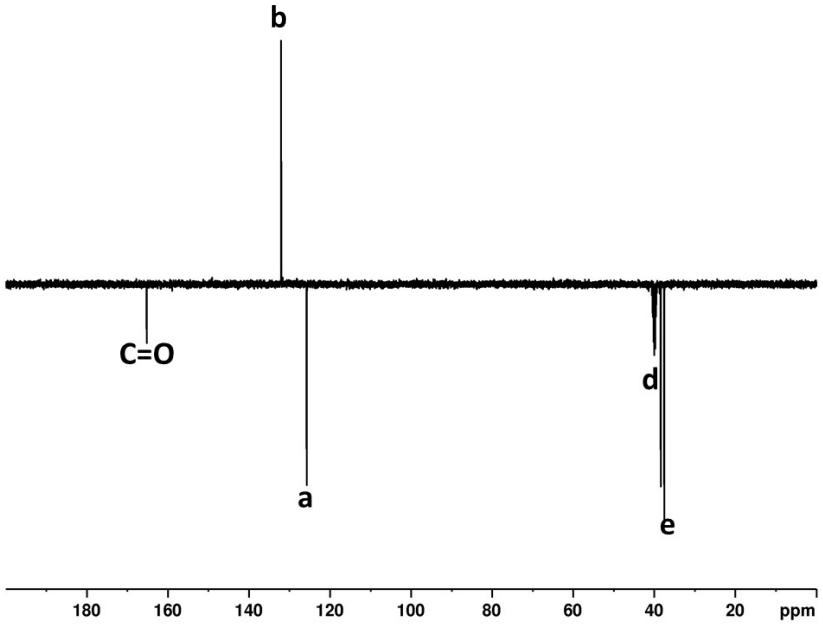
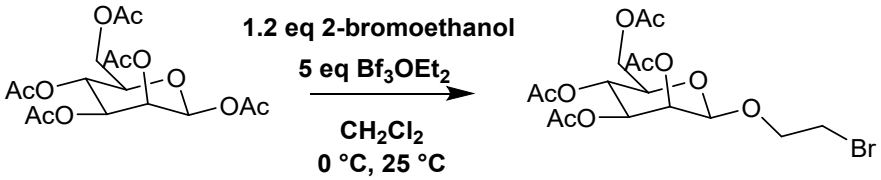


Figure S2: ^{13}C NMR spectrum of N,N′-bis(acryloyl)cystamine (BAC) $CDCl_3$.

Synthesis of bromo-substituted β-D-mannose



Scheme 2: General scheme for the synthesis of the bromo-substituted β-D-mannose.

Acetylated D-mannose (6.03 g, 15.5 mmol) was dissolved in DCM (200 mL) and added to a 500 mL round-bottom flask. 2-bromoethanol (2.13 mL, 30.0 mmol) was added to the flask whilst it was allowed to cool down in an ice bath. Subsequently, BF_3OEt (9.3 mL, 75.0 mmol) was added dropwise into the mixture which was allowed to stir overnight. Finally, the product was extracted using ice-cold water, an aqueous solution of sodium carbonate and distilled water. The extract was dried over $MgSO_4$ and the solvent removed to achieve a pale yellow solid (5.1 g, 73%). δH: (400 MHz; $CDCl_3$) 2.01-2.22 (12H, m, $-CH_3$), 3.49-3.56 (2H, t, $-CH_2Br$, J = 5.5), 3.86-4.03 (1H, m, $-CH_2OCH$), 4.12-4.17 (2H, m, $-CH_2O$), 4.25-4.42 (1H, m, $-CHCH_2$), 4.88 (1H, s, $-CHOCH_2$) 5.27-5.39 (3H, m, -CH); δC (100 MHz; $CDCl_3$) 20.9 ($-CH_3CO$), 29.4 ($-CH_2Br$), 62.5 ($-CH_2CO$), 65.7 ($-CH_2CH_2Br$), 68.6 ($-CH_2$), 68.8 ($-CH_2$), 76.9 ($-CH_2$), 97.9 (-CH), 170.3 (C=O).

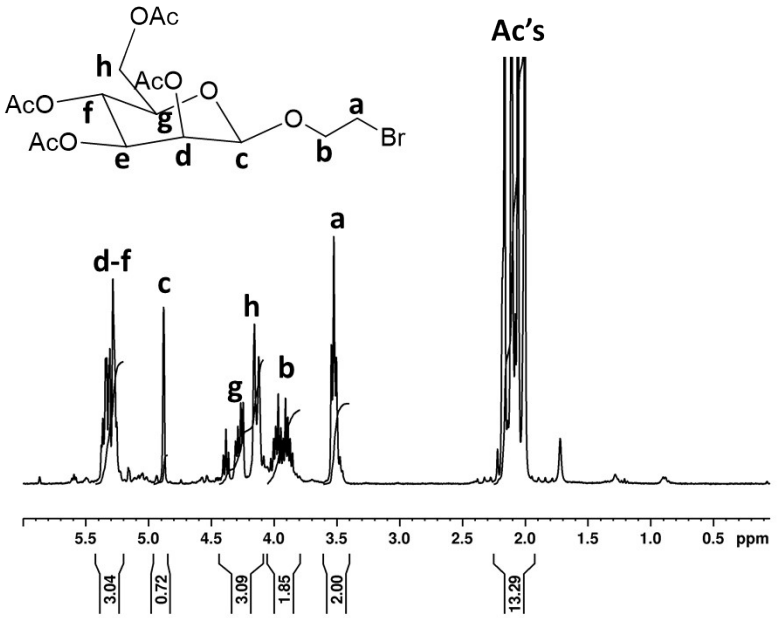
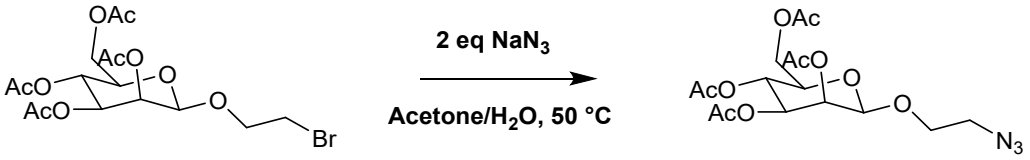


Figure S3: ^{1}H NMR spectrum of the bromo-substituted β-D-mannose in $CDCl_3$.

Synthesis of azido β-D-mannose



Scheme S3: General scheme for the synthesis of azido β-D-mannose from bromo β-D-mannose.

The bromo-substituted mannose was (5.0 g, 11.0 mmol) dissolved in acetone (30 mL) and added to a round-bottom flask. Meanwhile, NaN_3 (2.14 g, 33.0 mmol) was dissolved in distilled water (10 mL) and added dropwise to the reaction flask using a dropping funnel. The reaction was stirred overnight at ambient temperature. After removal of the acetone by evaporation, diethyl ether was added to the round-bottom flask. Thus, the product was purified by extraction with distilled water to remove any excess NaN_3. Finally, the diethyl ether was removed to collect a pale-yellow solid (3.4 g, 74%). δH: (400 MHz; $CDCl_3$) 1.91-2.17 (12H, m, -CH_3), 3.36-3.56 (2H, m, -CH_2N_3),

3.63-3.92 (1H, m, -CH_2OCH), 4.03-4.16 (2H, m, -CH_2O), 4.26-4.33 (1H, m, -$CHCH_2$), 4.87 (1H, s, -$CHOCH_2$) 5.25-5.40 (3H, m, -CH).

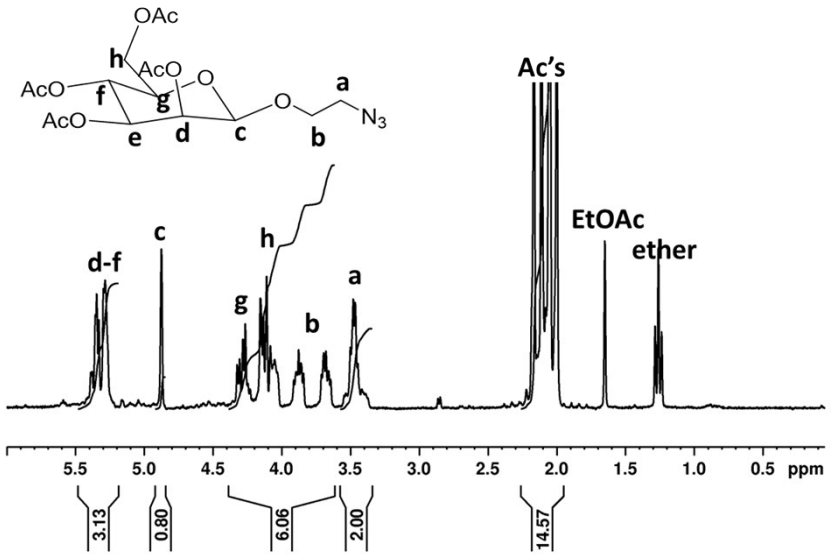
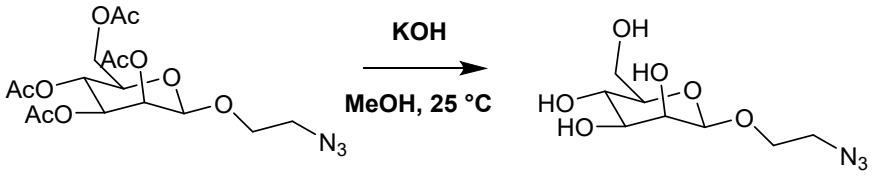


Figure S4: ^1H NMR spectrum of the acetylated azido-mannose in $CDCl_3$.

Deacetylation of azido β-D-mannose



Scheme S4: General scheme for the deprotection of acetylated azido β-D-mannose.

KOH (10 mol%) was added to a round-bottom flask containing azido-mannose (3.0 g, 7.2 mmol) in MeOH (30 mL). The reaction was stirred at room temperature overnight until the TLC showed complete deacetylation of the product. Thus, amberlite H^+ was washed with MeOH three times and then added to the round-bottom flask containing the deacetylated azido-mannose. The amberlite was filtered off after 15 minutes and the methanol was removed by evaporation to yield a white solid (1.5 g, 84%). δH: (400

MHz; D_2O) 3.44 (2H, m, -CH_2N_3), 3.57 (2H, m, -$CH_2CH_2N_3$), 3.61-3.90 (5H, m, -CH), 3.92 (2H, dd, -CH_2O), 4.84 (1H, s, -$CHOCH_2$).

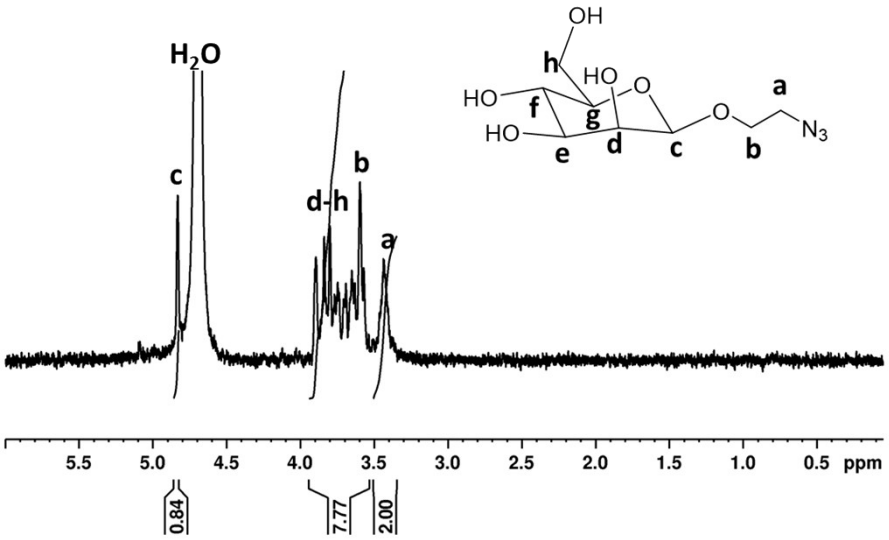
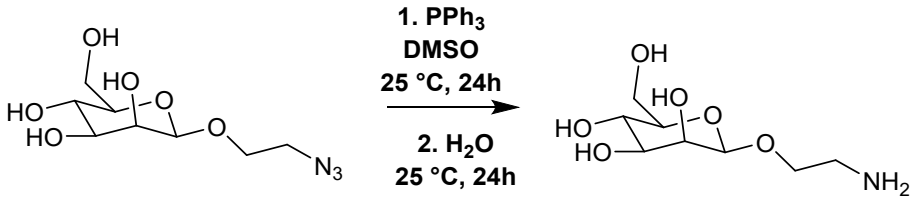


Figure S5: ^1H NMR spectrum of the deacetylated azido-mannose in D_2O.

Reduction of Azido β-D-mannose to β-D-mannosamine



Scheme S5: General scheme for the azide reduction to prepare β-D-mannosamine.

Azido-mannose (2.7 g, 11.0 mmol) was dissolved in DMSO and added to a round-bottom flask. Thus, triphenylphosphine (PPh_3) (5.6 g, 21.0 mmol) was added to a round-bottom flask containing the azido-mannose. The reaction mixture was allowed to stir at ambient temperature for 24 h. Thereafter, a small portion of water (1 mL) was added to the flask to quench the reaction and the mixture was stirred for a further 24 h. The final product was precipitated in cold ethanol and dried in a vacuum oven to

afford white crystals (2.3 g, 95%). δH: (400 MHz; D_2O) 2.87 (2H, m, -CH_2NH_2), 3.44 (2H, m, -$CH_2CH_2NH_2$), 3.57-3.89 (5H, m, -CH), 3.91 (2H, m, -CH_2O), 4.81 (1H, s, -$CHOCH_2$). δC (400 MHz; D_2O) 39.9 (-CH_2NH_2), 60.9 (-CH_2O), 66.8 (-$CH_2CH_2NH_2$), 67.6 (-CH), 70.0 (-CH), 70.4 (-CH), 72.6 (-CH_2), 99.8 (-$CHOCH_2$).

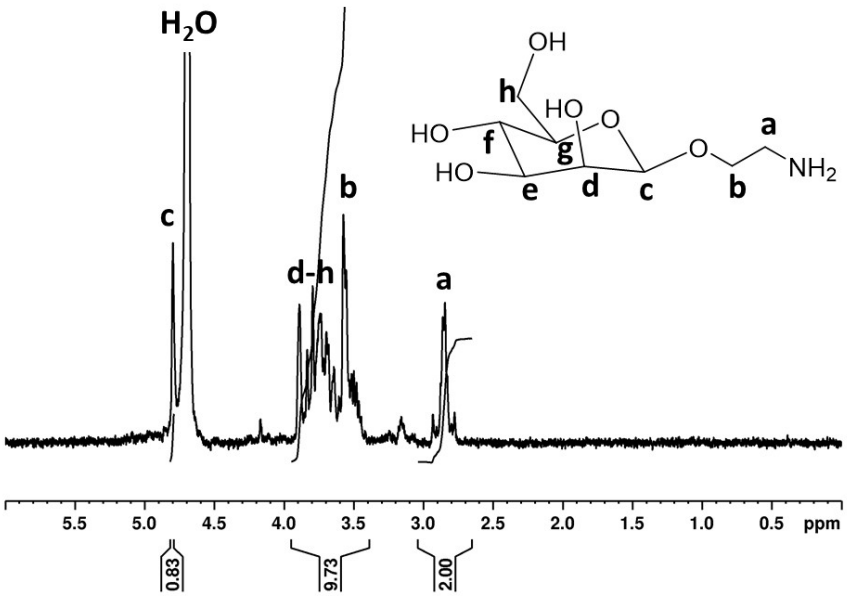


Figure S6: ^1H NMR spectrum of mannosamine in D_2O.

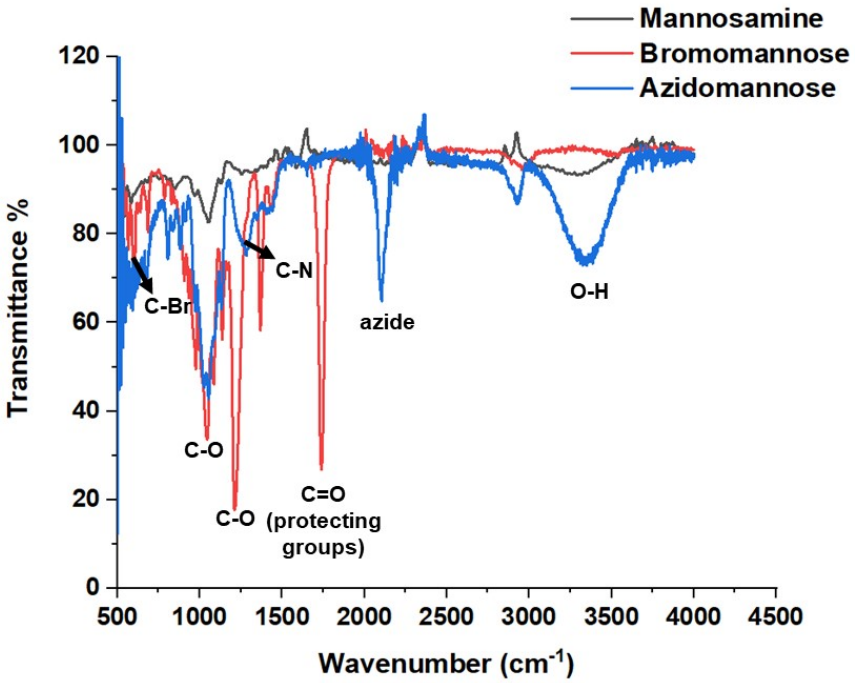


Figure S7: IR monitoring for the synthesis of mannosamine from bromo-mannose and azido-mannose.

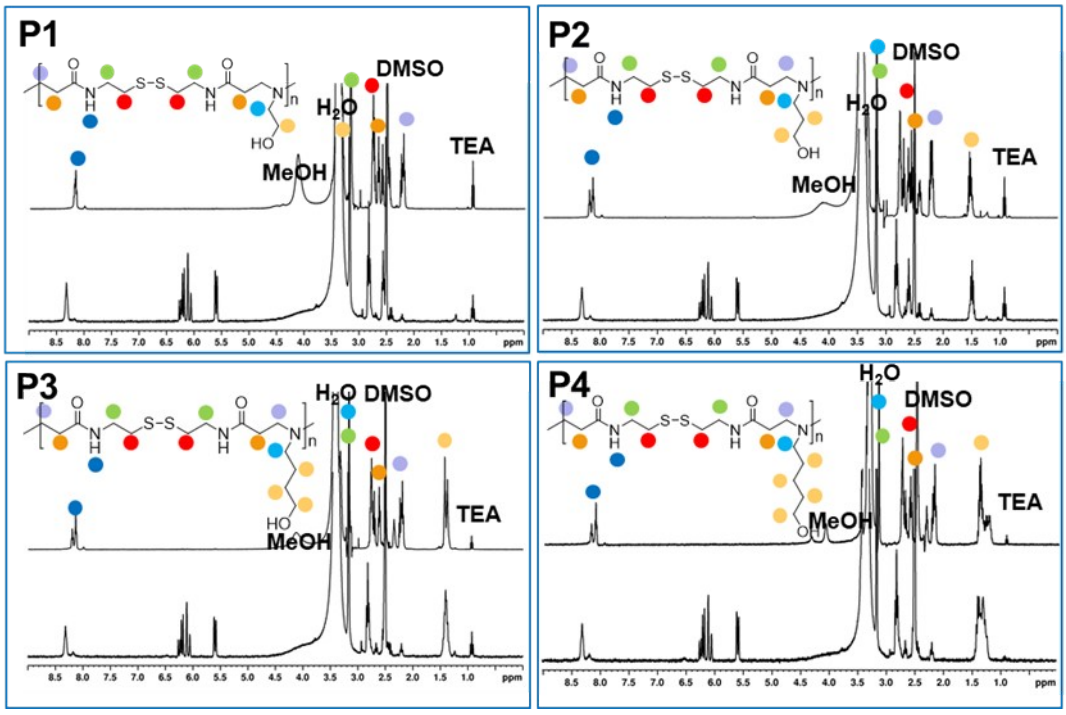


Figure S8: ^{1}H NMR spectra of **P1**-**P4**, showing t_0 (bottom spectrum in each frame) taken before the start of the reactions and t_f (top spectrum in each frame) taken at the end of the reactions. All spectra measured at 300 Mhz in DMSO-d_6.

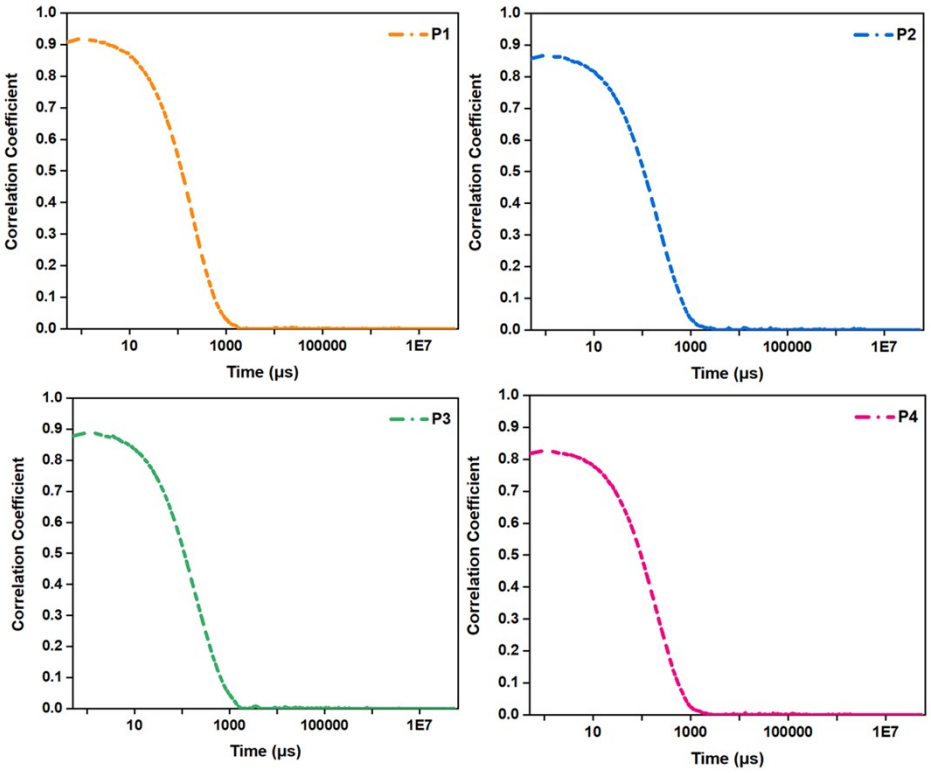


Figure S9: Correlation plots from the DLS measurements of the step growth polymers **P1-P4.**

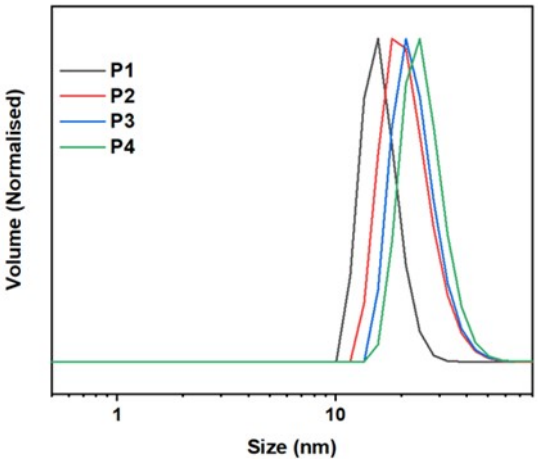


Figure S10: DLS traces of **P1-P4** in distilled water.

Table S1: Results obtained from the step-growth polymerisation of P2 using different reaction conditions. Highlighted are the variables changed in every reaction. [a] Values were from GPC measurements in DMF with 5 mM NH_4BF_4 using PMMA standards. [b] Conversion was determined by ^1H NMR spectroscopy from the integration of the vinyl peaks at 5.5-6.3 ppm and the methylene peaks at 1.2-1.5 ppm.

BAc:Amine ratio	Temperature °C	Solvent	Time (h)	$M_{n,GPC}$[a] (g mol $^{-1}$)	$M_{w,GPC}$[a] (g mol $^{-1}$)	Đ[a]	Conv.[b] %
1:1	45	MeOH/H_2O (2:1)	16	3900	5200	1.4	>99
1:1	45	MeOH/H_2O (1:1)	16	4000	5400	1.4	>99
1:1	45	MeOH	16	2800	3400	1.4	93
1:1	45	DMF	16	2100	2300	1.1	68
1:1	45	DMSO	16	1400	1900	1.3	55
1:1	80	MeOH/H_2O (2:1)	3	4000	5000	1.3	>99
1:1	80	MeOH/H_2O (1:1)	3	3800	5000	1.3	>99
1:1	80	MeOH	3	3000	3900	1.3	>99
1:1	80	DMF	16	2300	3200	1.4	91
1:1	80	DMSO	16	2800	3900	1.3	94
1:1	100	MeOH/H_2O (2:1)	2	4000	5100	1.4	>99
1:1	45	MeOH/H_2O (2:1)	24	4000	5200	1.3	>99
1:1	45	MeOH/H_2O (2:1)	96	4000	5300	1.3	>99
1.2:1	45	MeOH/H_2O (2:1)	16	5700	8800	1.5	90
1.2:1	45	MeOH/H_2O (2:1)	48	8000	9200	1.2	>99

Table S2: Kinetics values obtained from the SPR measurements of **P5** and **P6** with MBL and CLEC10A, respectively.

Lectin	Polymer	k_a (M^{-1} s^{-1})_	k_d (s^{-1})	K_A (M^{-1})	K_D (M)	RiU
MBL	**P5**	122	$6.79x10^{-5}$	$1.8x10^{6}$	$5.56x10^{-7}$	359
CLEC10A	**P6**	$3.05x10^{3}$	$1.51x10^{-3}$	$2.06x10^{6}$	$4.96x10^{-7}$	898