

A facile strategy for the high yielding, quantitative conversion of polyglycol end-groups to amines

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1. Synthesis of α,ω -diamino PEG_{1.5k} via the Staudinger reaction

The reduction of α,ω -diazido PEG_{1.5k} to α,ω -diamino PEG_{1.5k} via the Staudinger reaction was conducted according to published literature procedures [1, 2] with modification. α,ω -Diazido PEG_{1.5k} (1.00 g, 667 μ mol) and PPh₃ (1.40 g, 5.33 mmol, 4 equiv. per azide group) were dissolved in a 1:3 v/v ultrapure water:THF solution (8 mL) and stirred at 25 °C for 24 h. The reaction mixture was filtered with a sintered funnel under vacuum and the filtrate was concentrated *in vacuo* to remove the THF. 1 M HCl was added to the residue to adjust the pH to 1 and the resulting precipitate was filtered off using a sintered funnel under vacuum. The aqueous filtrate was then extracted with diethyl ether (3 \times 10 mL), and the pH was adjusted to 13 using 1 M NaOH prior to extraction with DCM (3 \times 5 mL). The combined DCM extracts were concentrated *in vacuo* to ~ 3 mL in volume and then precipitated into cold (0 °C) diethyl ether (40 mL) with stirring. The precipitated polymer was collected via centrifugation (6000 rpm, 3 min), redissolved in DCM (3 mL) and precipitated into cold (0 °C) diethyl ether (40 mL) with stirring; this step was repeated twice. The precipitated polymer was collected via centrifugation (5000 rpm, 3 min) and dried under high vacuum (0.1 mbar) to afford the product (0.59 g) contaminated with PPh₃ and PPh₃O.

2. Supporting Figures

a. FTIR spectra of α -methoxy PEG_{5k} derivatives

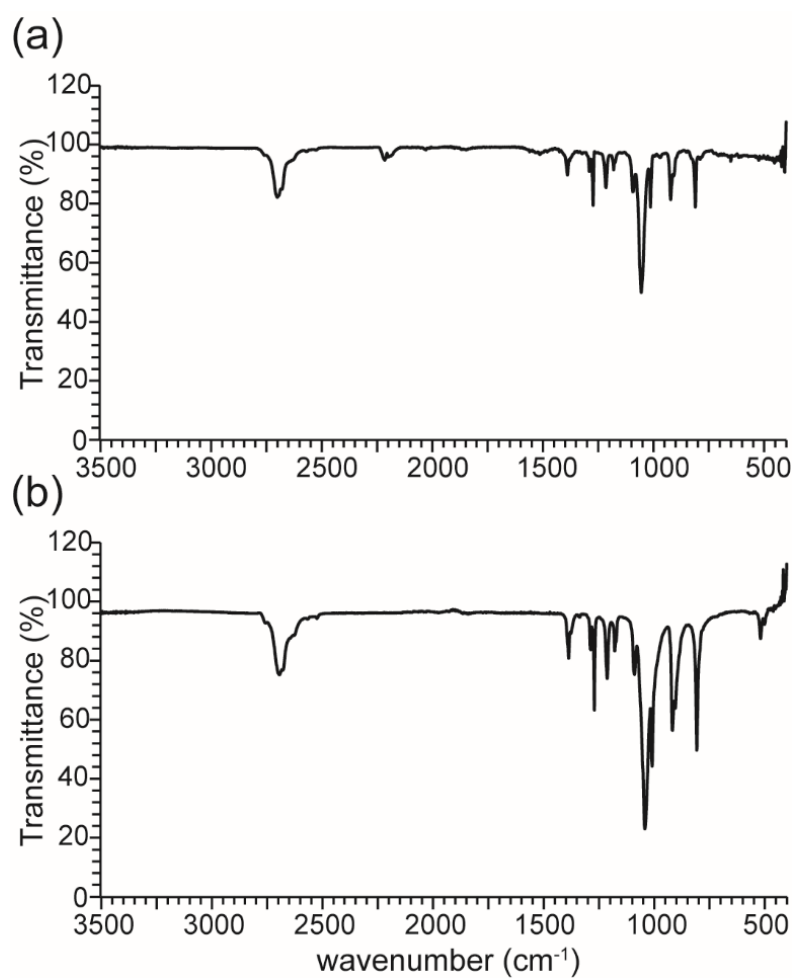


Figure S1. FTIR spectra of (a) α -methoxy- ω -hydroxy and (b) α -methoxy- ω -amino PEG_{5k}

b. NMR spectra of amino-terminated PEG_{1.5k} prepared via the Staudinger reaction

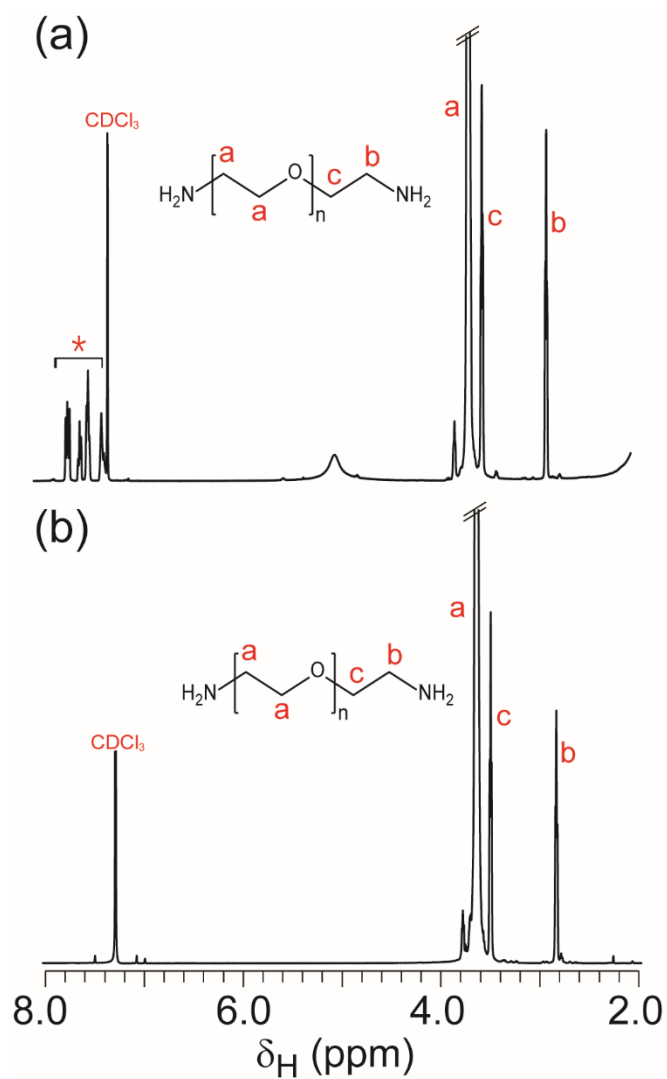


Figure S2. ¹H NMR spectra (500 MHz, 23 °C, CDCl₃) of α,ω-diamine PEG_{1.5k} prepared from α,ω-diazido PEG_{1.5k} via (a) the Staudinger reaction (* indicates Ph₃P and Ph₃PO impurities present after purification) and (b) Zn / NH₄Cl reduction.

c. GPC chromatograms of α -methoxy PEG_{5k} derivatives

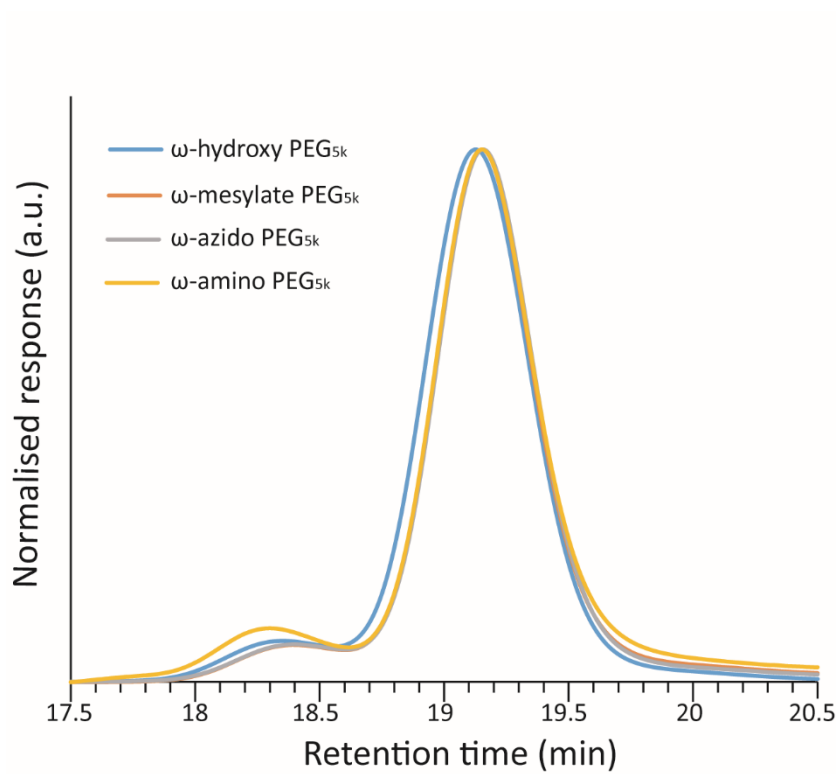


Figure S3. GPC chromatograms of the α -methoxy- ω -hydroxy, α -methoxy- ω -mesylate, α -methoxy- ω -azido and α -methoxy- ω -amino PEG_{5k} derivatives recorded using THF as the mobile phase.

d. NMR spectra showing the conversion of hydroxy- to amino-terminated polyglycols

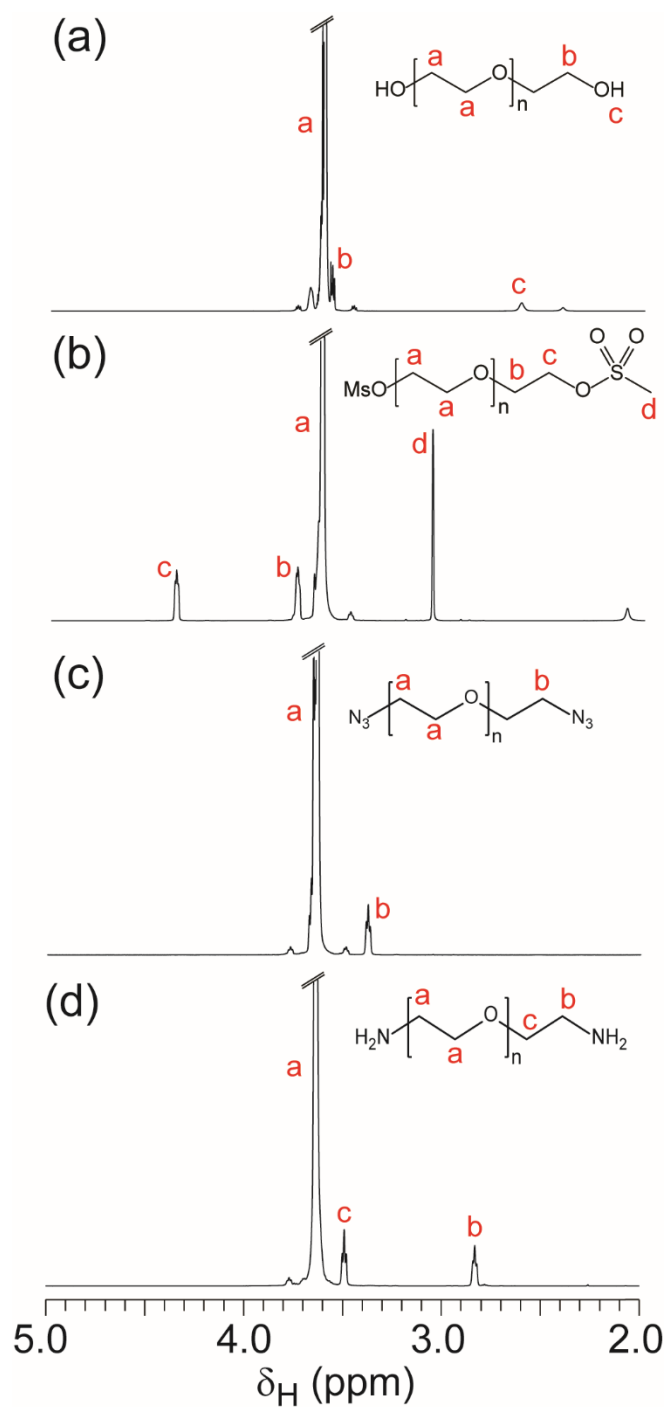


Figure S4. ^1H NMR spectra (500 MHz, 23 °C, CDCl_3) showing the conversion of the (a) α,ω -dihydroxy $\text{PEG}_{1.5k}$ to its (b) α,ω -dimesylate, (c) α,ω -diazido and (d) α,ω -diamino $\text{PEG}_{1.5k}$ derivatives.

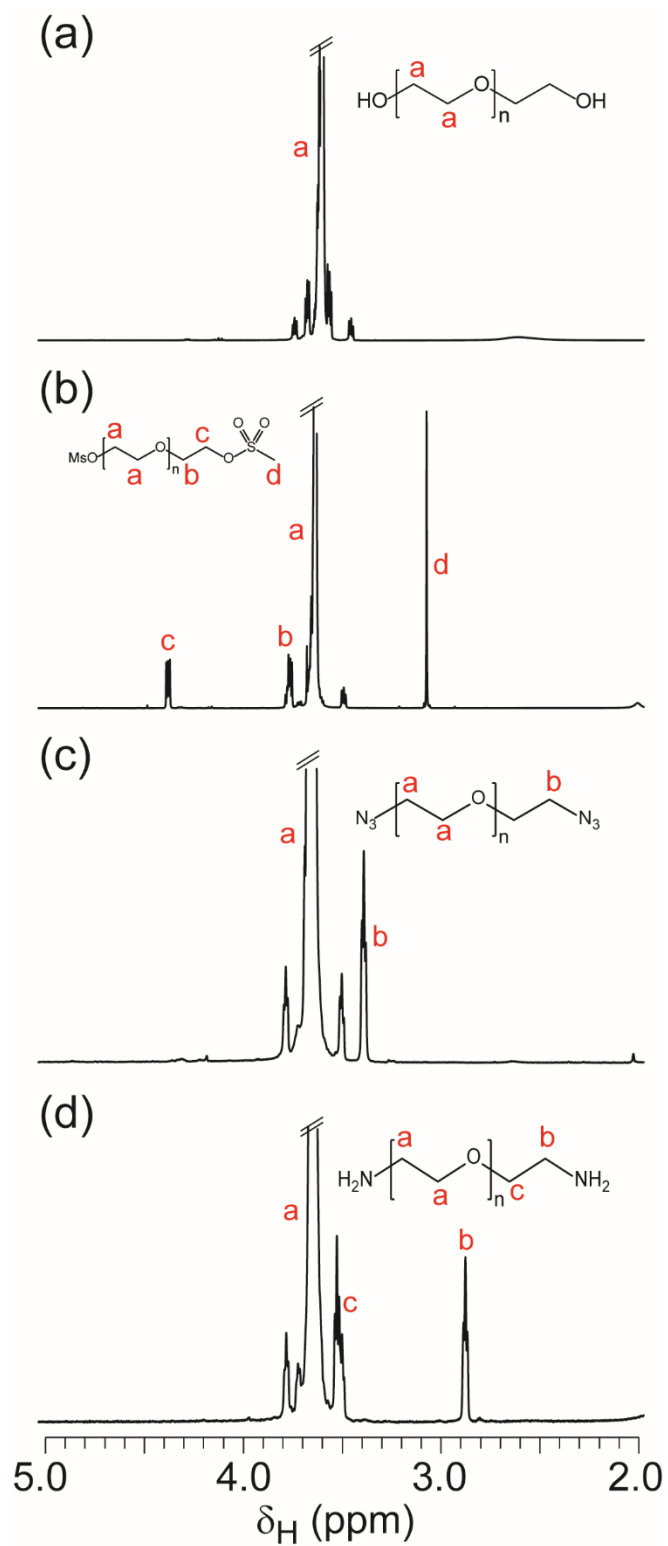


Figure S5. ^1H NMR spectra (500 MHz, 23 °C, CDCl_3) showing the conversion of the (a) α,ω -dihydroxy PEG_{4k} to its (b) α,ω -dimesylate, (c) α,ω -diazido and (d) α,ω -diamino PEG_{4k} derivatives.

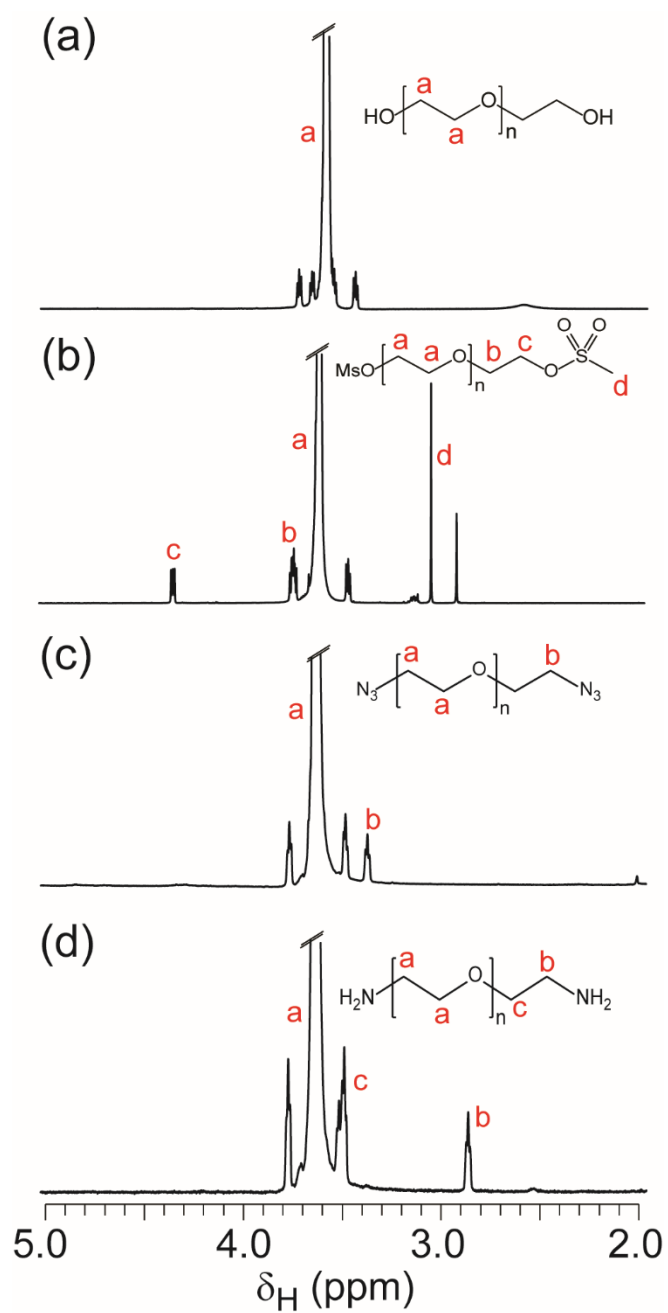


Figure S6. ^1H NMR spectra (500 MHz, 23 °C, CDCl_3) showing the conversion of the (a) α,ω -dihydroxy PEG_{10k} to its (b) α,ω -dimesylate, (c) α,ω -diazido and (d) α,ω -diamino PEG_{10k} derivatives.

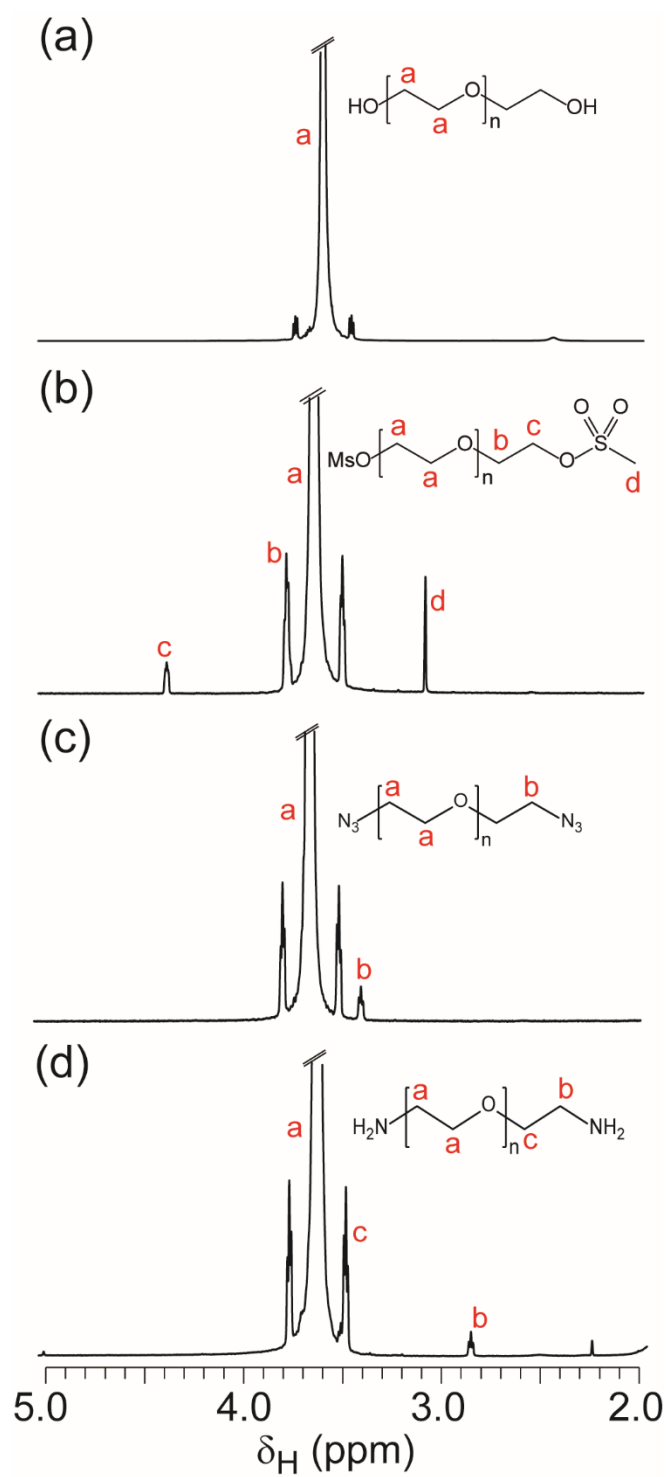


Figure S7. ^1H NMR spectra (500 MHz, 23 $^\circ\text{C}$, CDCl_3) showing the conversion of the (a) α,ω -dihydroxy PEG_{35k} to its (b) α,ω -dimesylate, (c) α,ω -diazido and (d) α,ω -diamino PEG_{35k} derivatives.

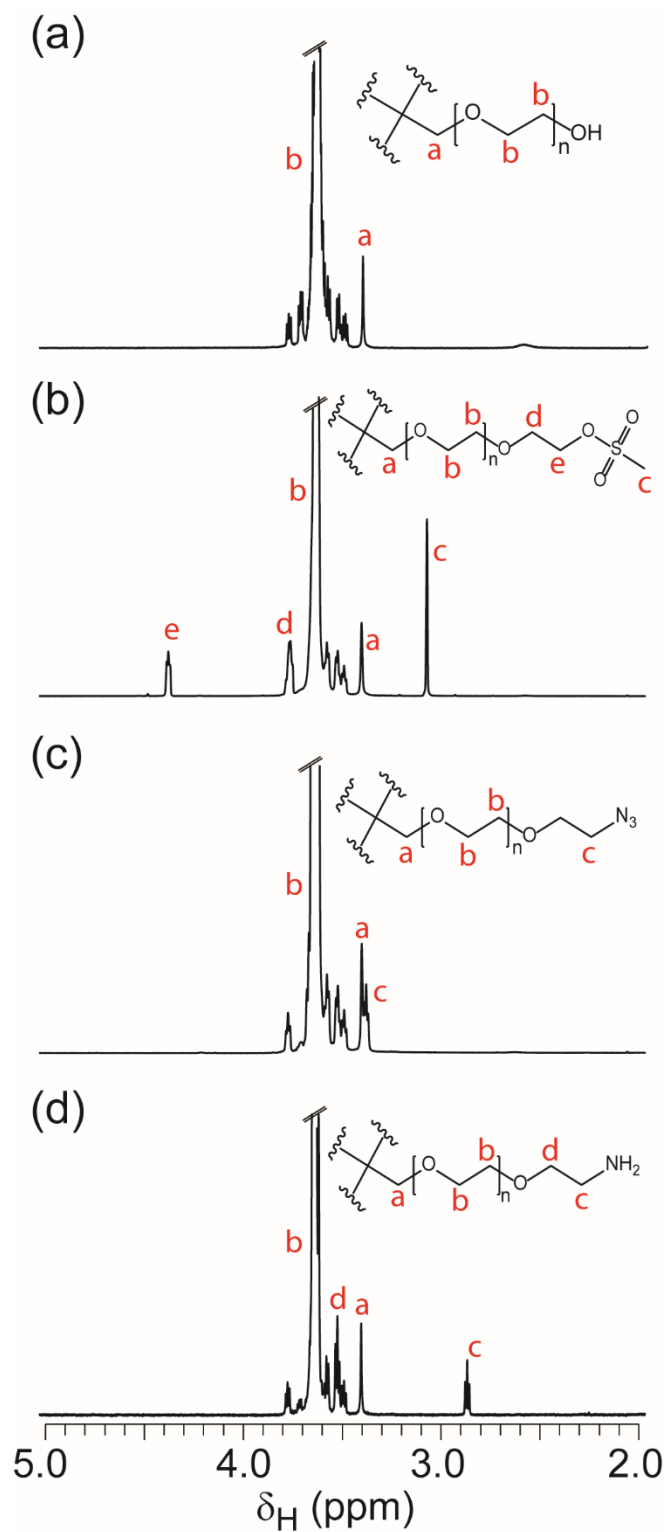


Figure S8. ^1H NMR spectra (500 MHz, 23 °C, CDCl_3) showing the conversion of the (a) 4-armed tetrahydroxy PEG_{10k} to its (b) mesylate-, (c) azido-, and (d) amino-terminated derivatives.

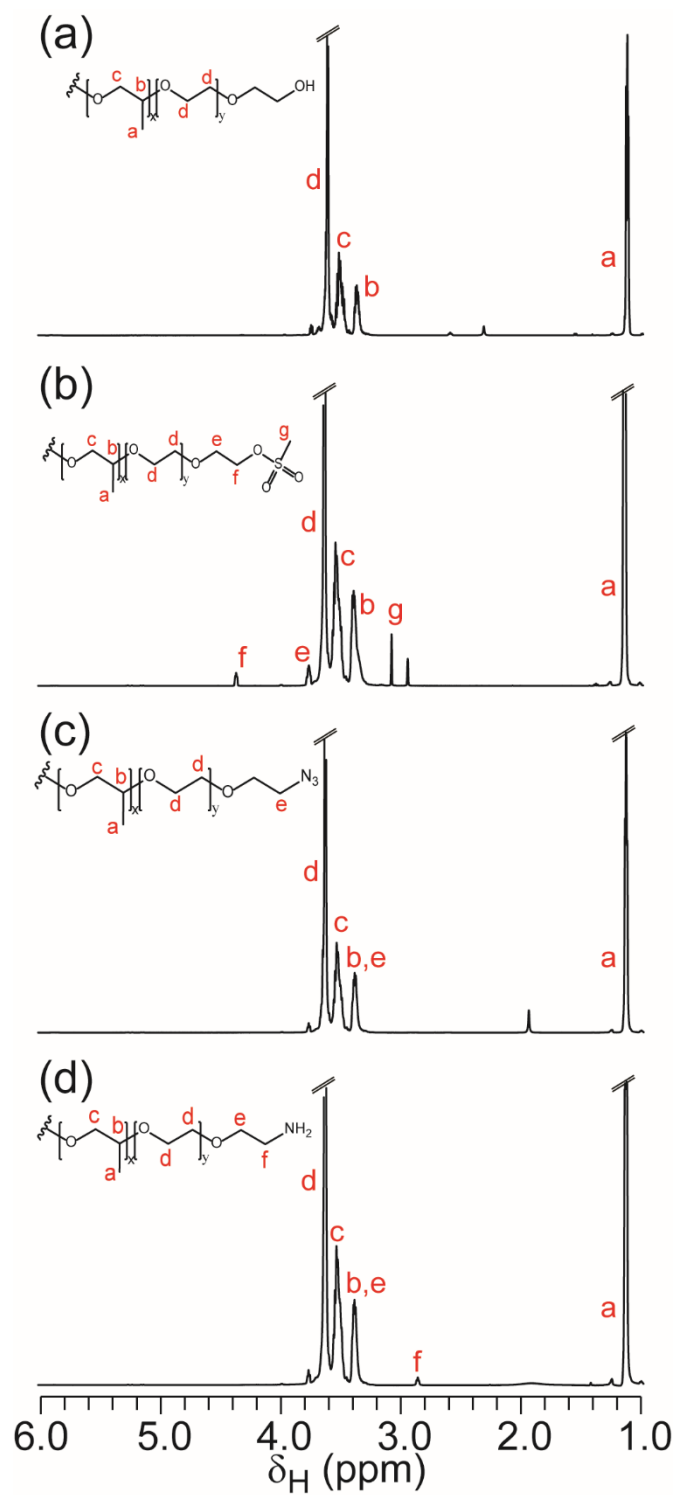


Figure S9. ^1H NMR spectra (500 MHz, 23 °C, CDCl_3) showing the conversion of (a) Pluronic® F-127 (α,ω -dihydroxy PEG-PPG-PEG triblock copolymer, $M_n \sim 12600$) to its (b) α,ω -dimesylate, (c) α,ω -diazido and (d) α,ω -diamino derivatives.

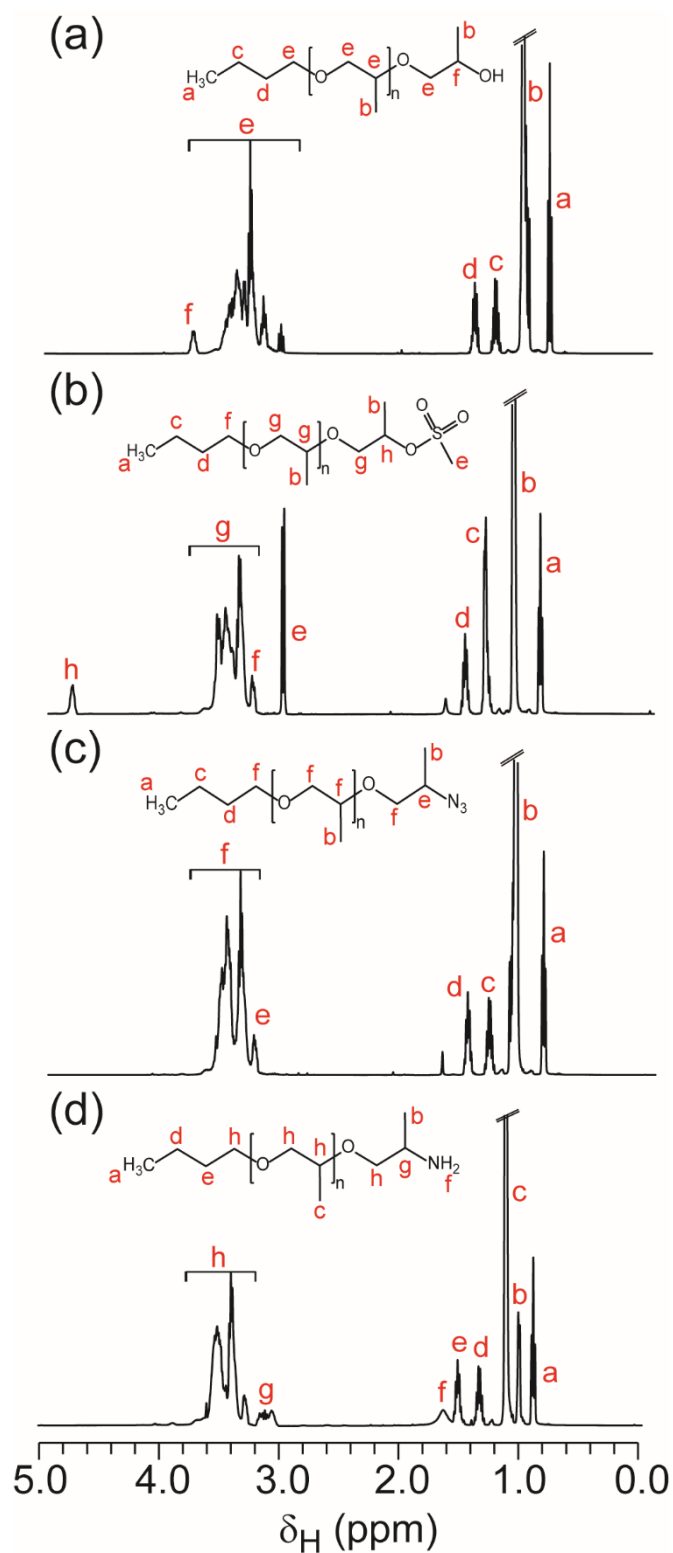


Figure S10. ^1H NMR spectra (500 MHz, 23 °C, CDCl_3) showing the conversion of (a) α -butyl- ω -hydroxy PPG to its (b) α -butyl- ω -mesylate, (c) α -butyl- ω -azido and (d) α -butyl- ω -amino PPG derivatives.

e. MALDI-ToF mass spectra showing the conversion of hydroxy- to amino-terminated polyglycols

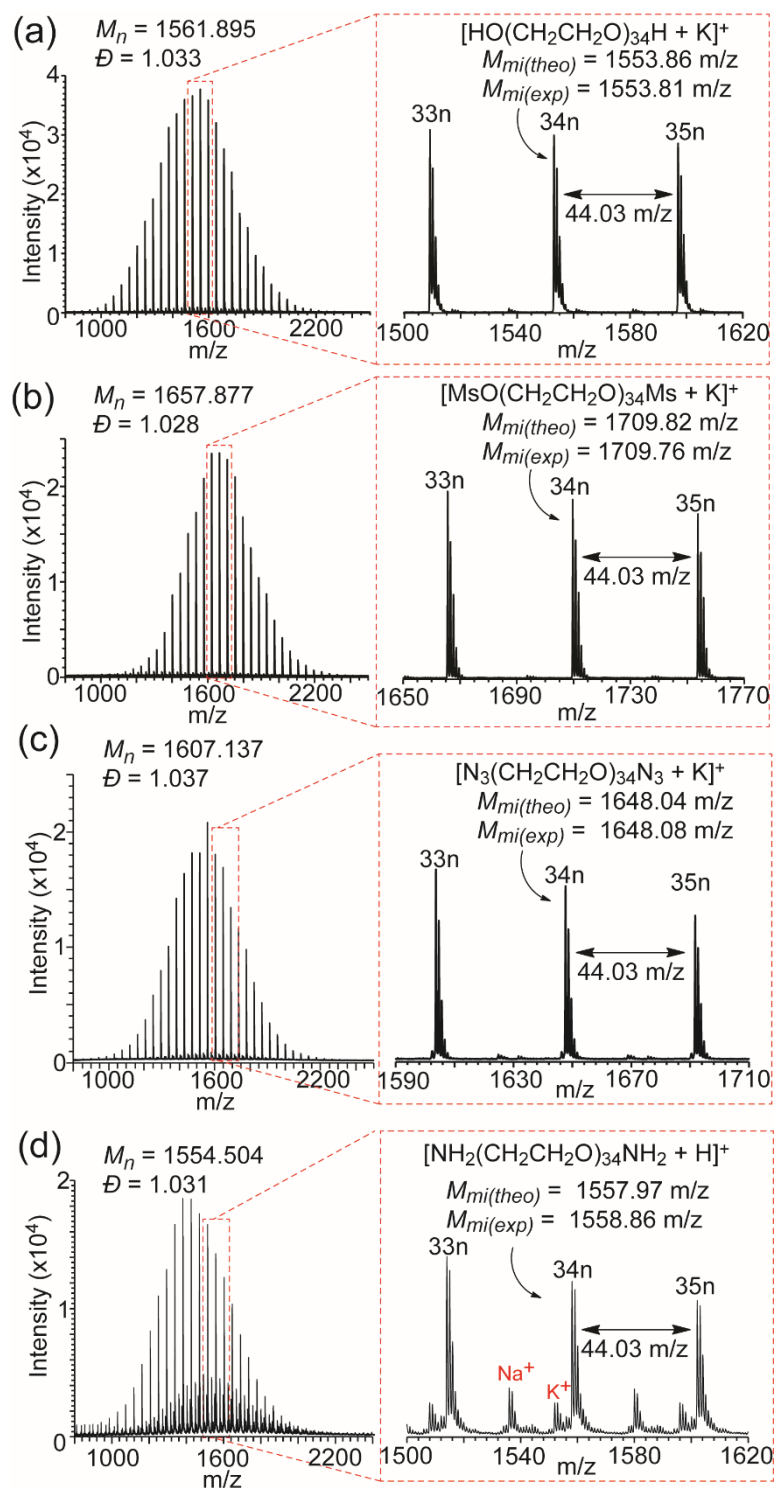


Figure S111. MALDI-ToF mass spectra showing the conversion of the (a) α,ω -dihydroxy PEG_{1.5k} to its (b) α,ω -dimesylate, (c) α,ω -diazido and (d) α,ω -diamine PEG_{1.5k} derivatives: expansions show 33-35 repeat unit region of the spectra with the theoretical ($M_{mi(\text{theo})}$) and experimentally determined ($M_{mi(\text{exp})}$) monoisotopic mass values for the potassium or proton adducts of polymers with $n = 34$.

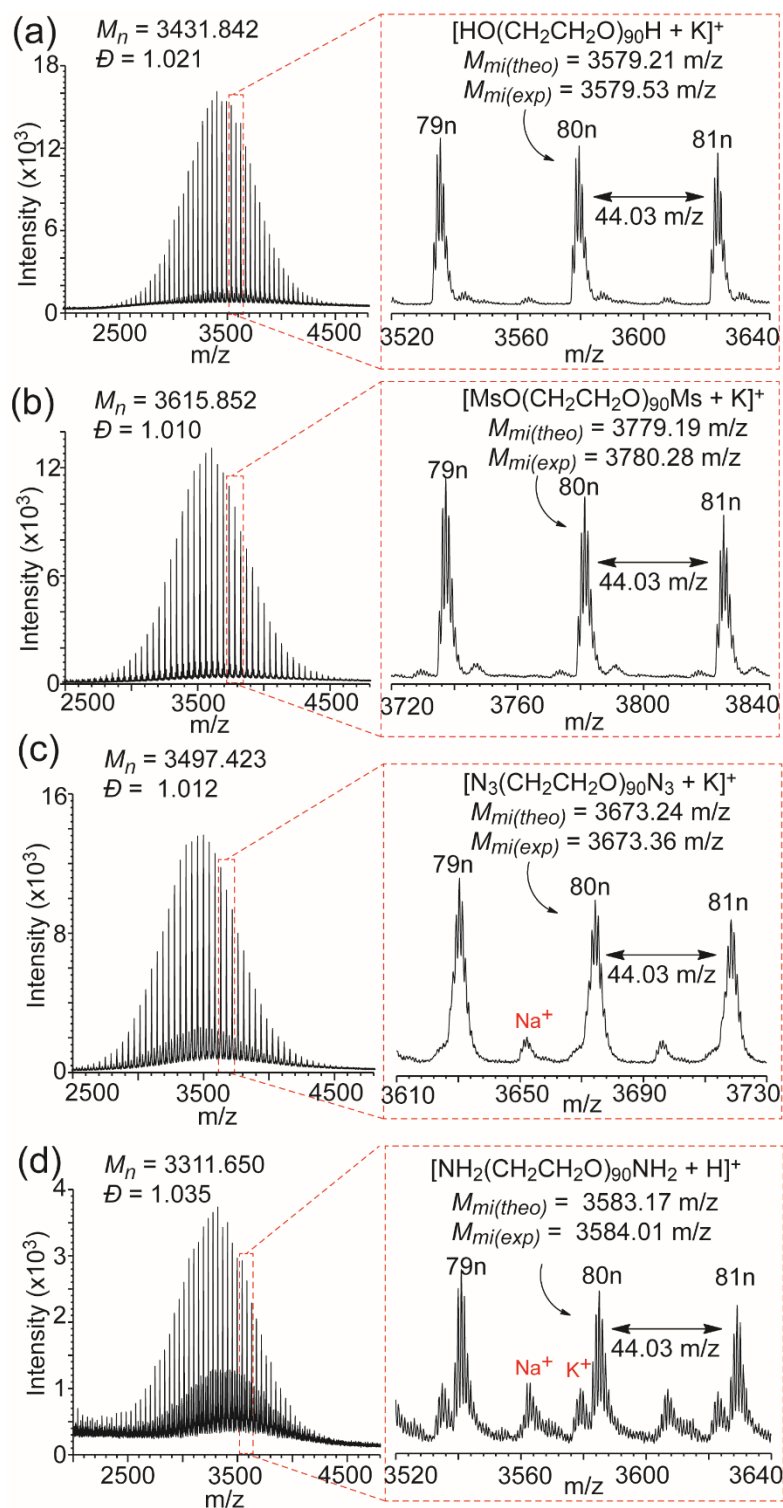


Figure S12. MALDI-ToF mass spectra showing the conversion of the (a) α,ω -dihydroxy PEG_{4k} to its (b) α,ω -dimesylate, (c) α,ω -diazido and (d) α,ω -diamine PEG_{4k} derivatives: expansions show 79-81 repeat unit region of the spectra with the theoretical ($M_{mi(theo)}$) and experimentally determined ($M_{mi(exp)}$) monoisotopic mass values for the potassium or proton adducts of polymers with $n = 80$.

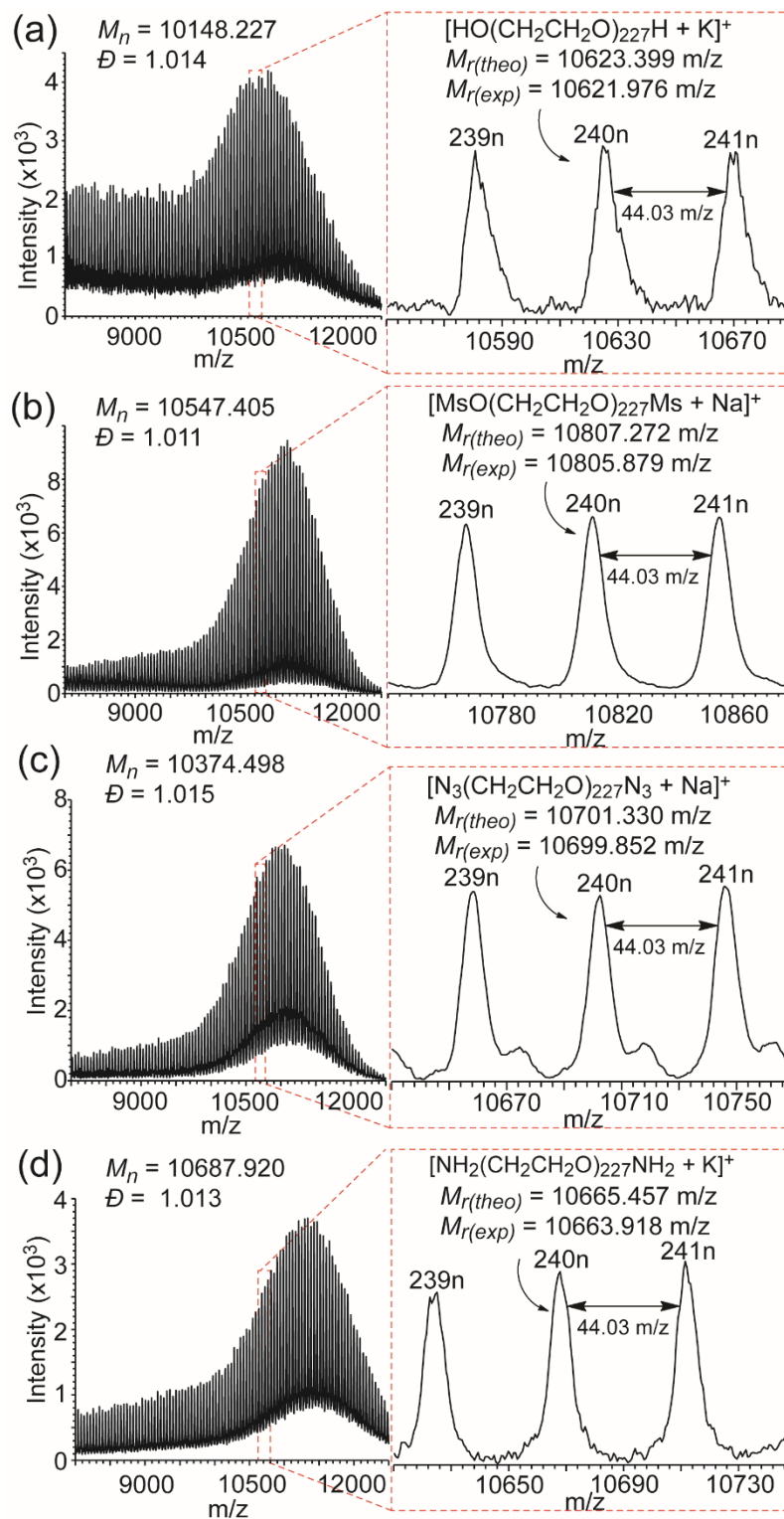


Figure S13. MALDI-ToF mass spectra showing the conversion of the (a) α,ω -dihydroxy PEG_{10k} to its (b) α,ω -dimesylate, (c) α,ω -diazido and (d) α,ω -diamine PEG_{10k} derivatives: expansions show 239-241 repeat unit region of the spectra with the theoretical ($M_{r(theo)}$) and experimentally determined ($M_{r(exp)}$) average molecular mass values for polymers with $n = 240$.

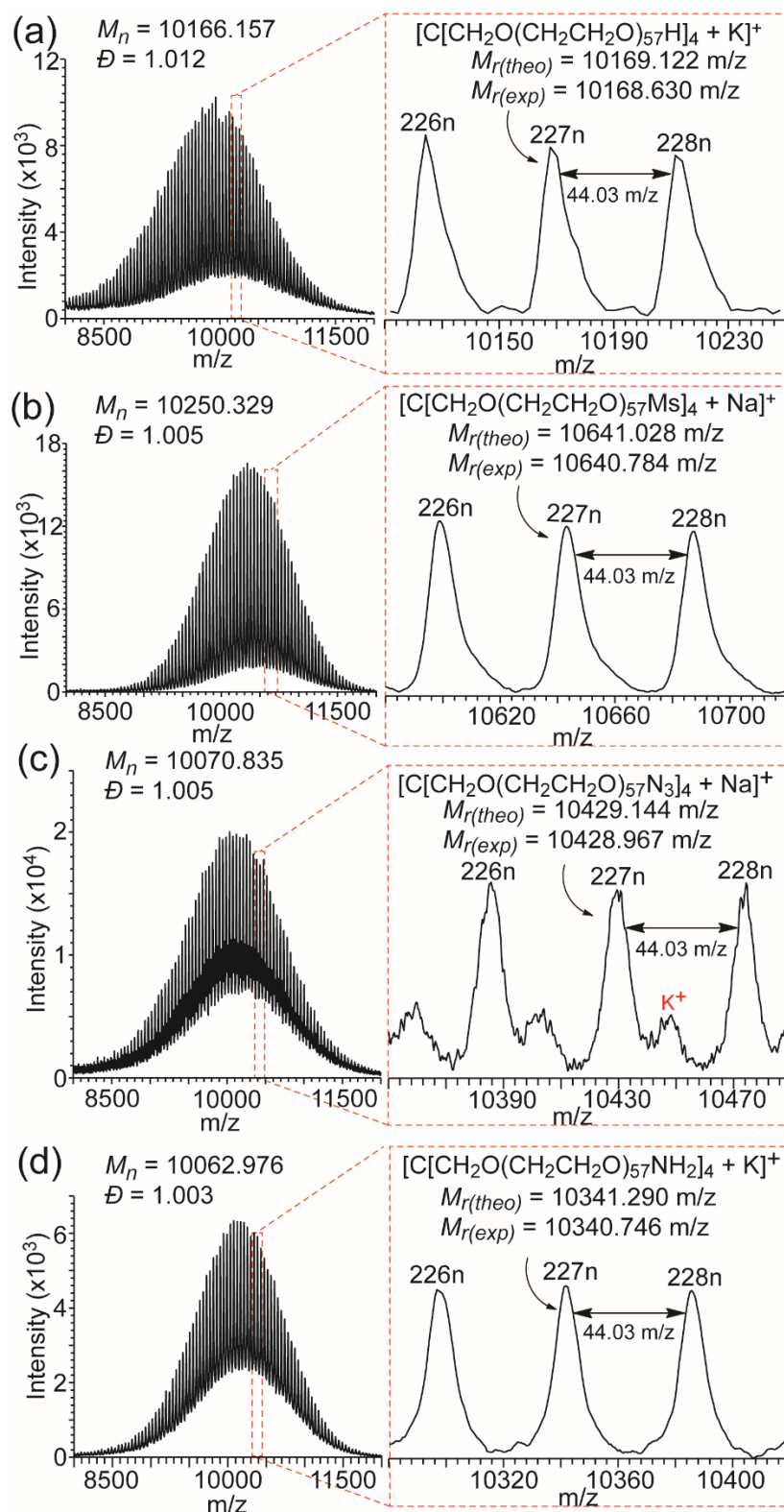


Figure S14. MALDI-ToF mass spectra showing the conversion of the (a) 4-armed tetrahydroxy PEG_{10k} to its (b) mesylate-, (c) azido-, and (d) amino-terminated derivatives: expansions show 226-228 repeat unit region of the spectra with the theoretical ($M_{r(theo)}$) and experimentally determined ($M_{r(exp)}$) average molecular mass values for polymers with $n = 227$.

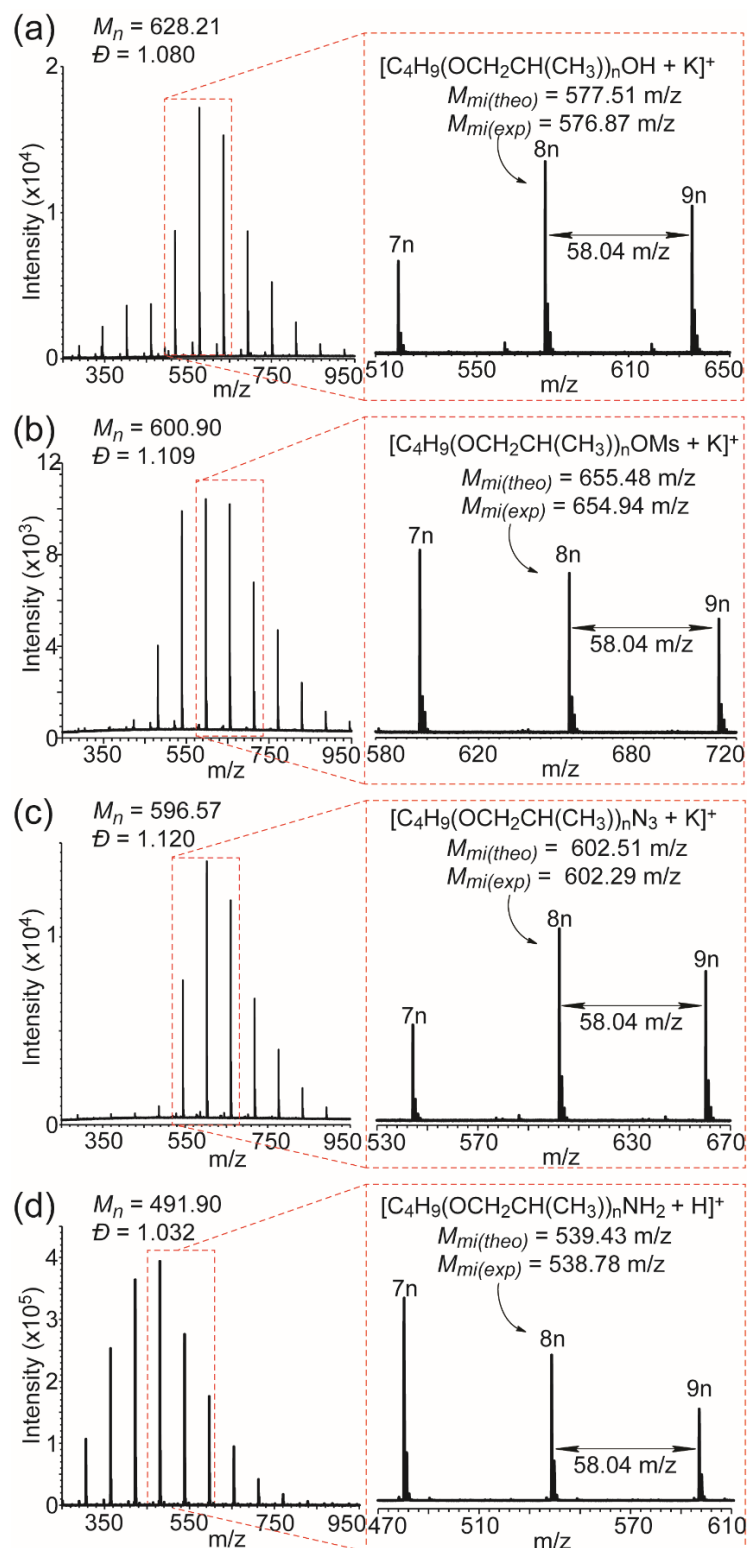


Figure S15. MALDI-ToF mass spectra showing the conversion of (a) α -butyl- ω -hydroxy PPG to its (b) α -butyl- ω -mesylate, (c) α -butyl- ω -azido and (d) α -butyl- ω -amino PPG derivatives: expansions show 7-9 repeat unit region of the spectra with the theoretical ($M_{mi(theo)}$) and experimentally determined ($M_{mi(exp)}$) monoisotopic mass values for the potassium or proton adducts of polymers with $n = 8$.

f. GPC chromatograms showing the conversion of hydroxy- to amino- terminated polyglycols

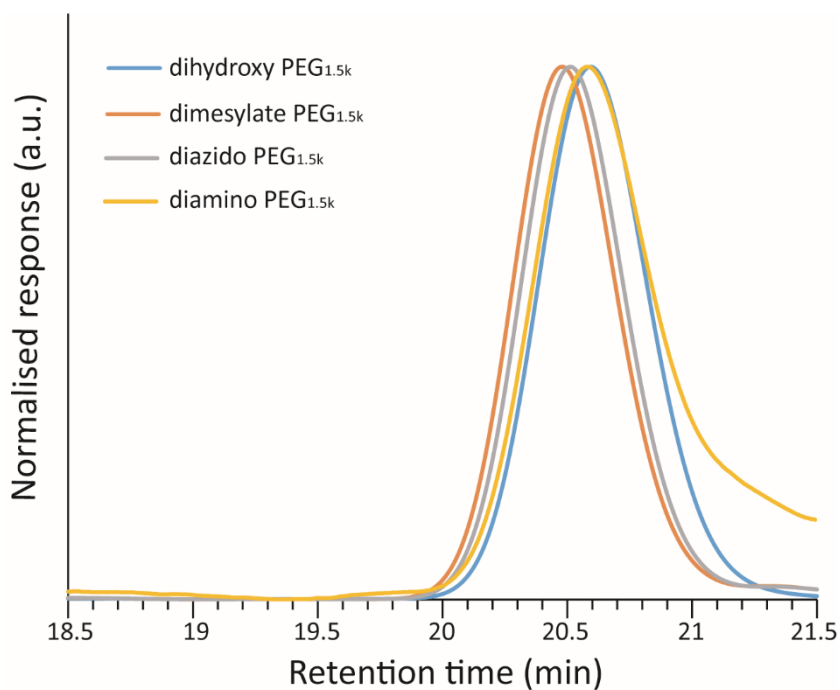


Figure S16. GPC chromatograms showing the conversion of the α,ω -dihydroxy PEG_{1.5k} to its α,ω -dimesylate, α,ω -diazido and α,ω -diamino PEG_{1.5k} derivatives recorded using THF as the mobile phase.

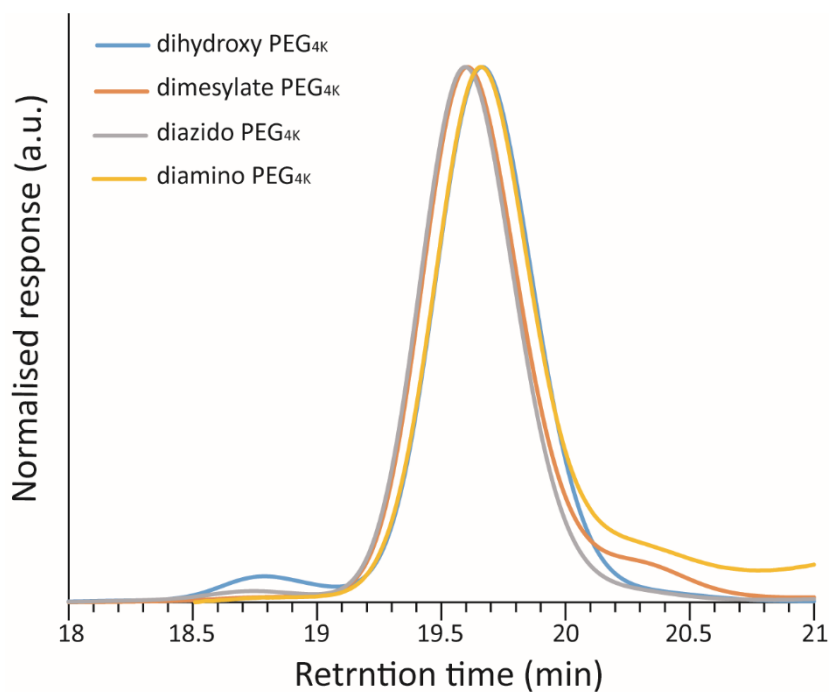


Figure S17. GPC chromatograms showing the conversion of the α,ω -dihydroxy PEG_{4k} to its α,ω -dimesylate, α,ω -diazido and α,ω -diamino PEG_{4k} derivatives recorded using THF as the mobile phase.

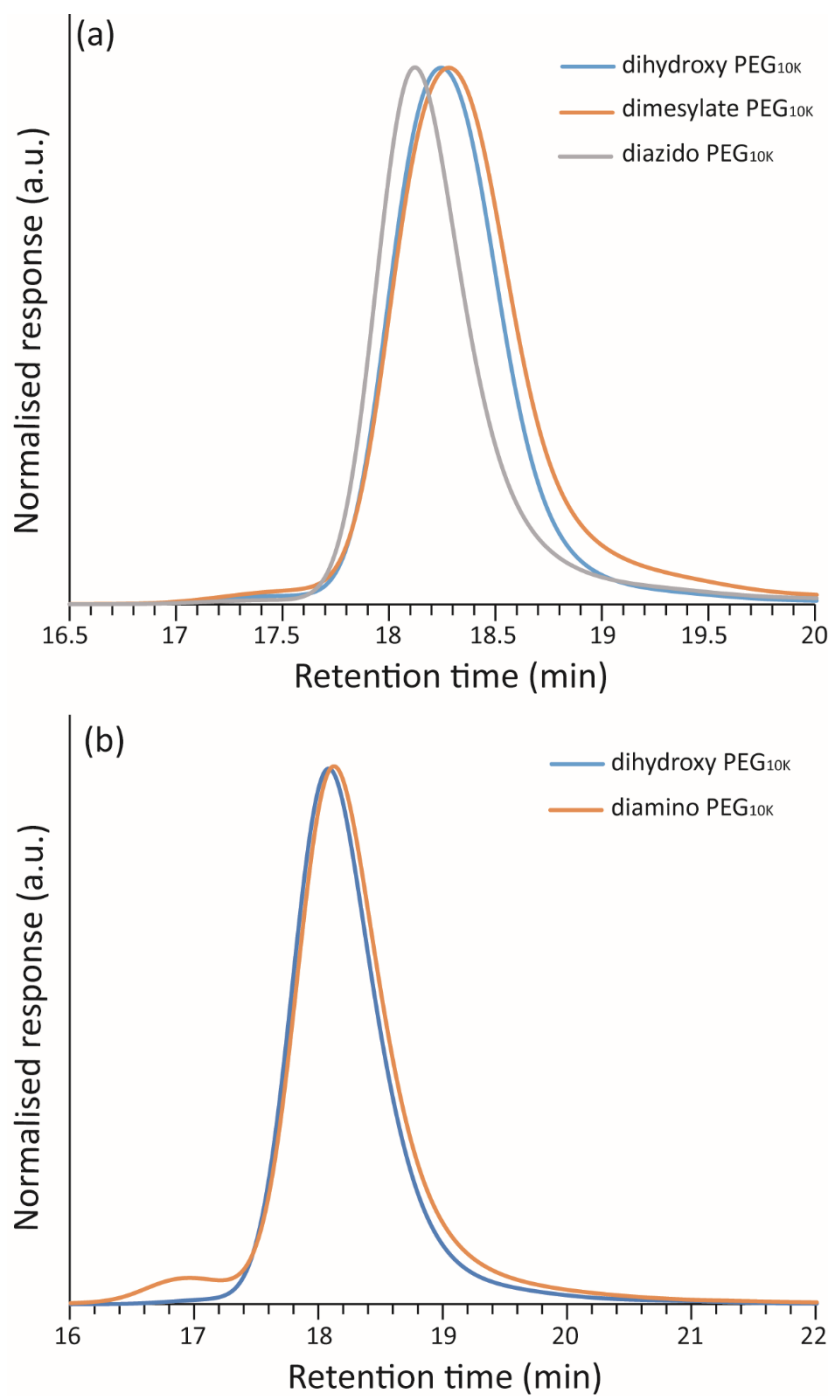


Figure S18. GPC chromatograms showing the conversion of the α,ω -dihydroxy PEG_{10K} to its α,ω -dimesylate, α,ω -diazido and α,ω -diamino PEG_{10K} derivatives recorded using (a) THF or (b) 1:1 v/v MeOH:water (due to the poor solubility and aggregation of the α,ω -diamino PEG_{10K} derivative in THF) as the mobile phase.

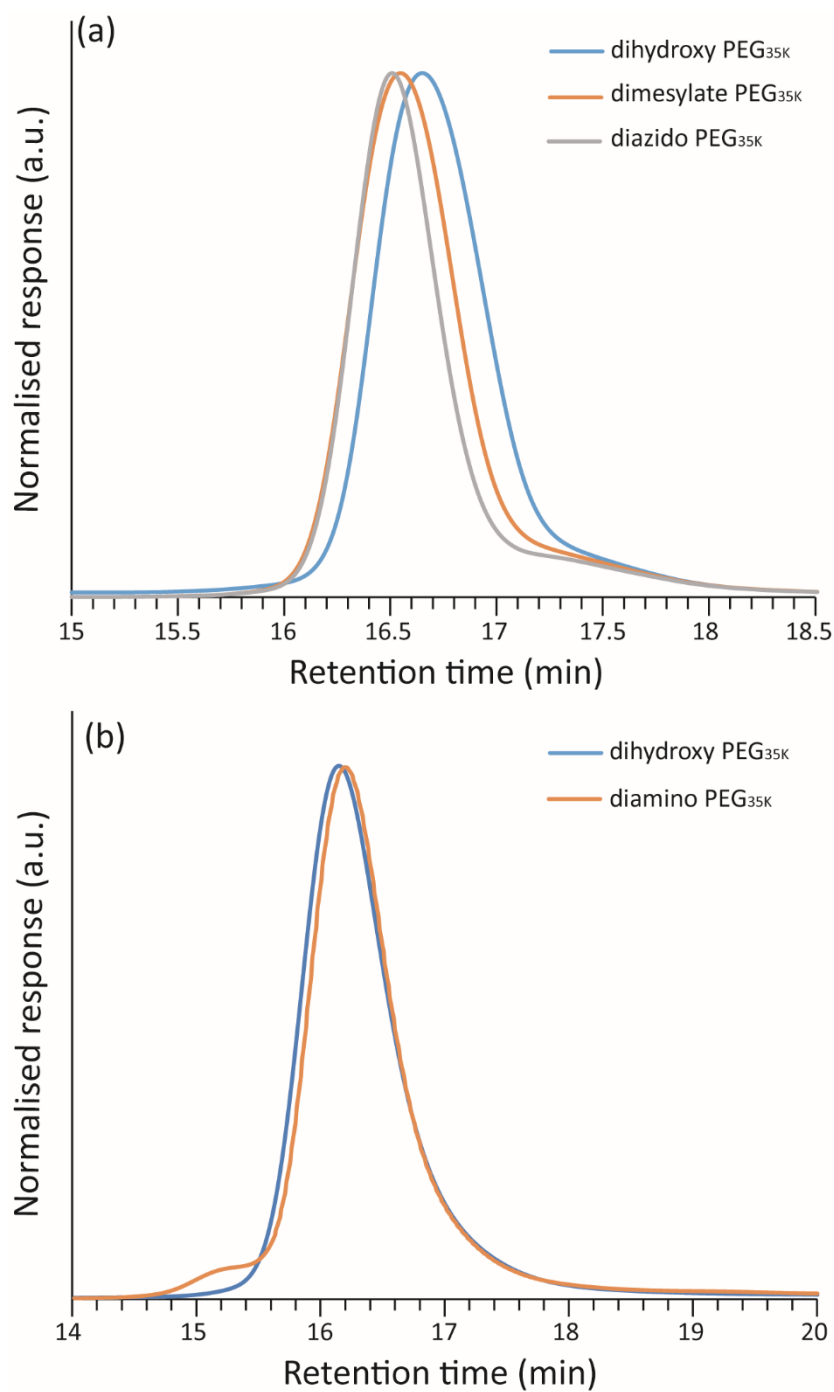


Figure S19. GPC chromatograms showing the conversion of the α,ω -dihydroxy PEG_{35k} to its α,ω -dimesylate, α,ω -diazido and α,ω -diamine PEG_{35k} derivatives recorded using (a) THF or (b) 1:1 v/v MeOH:water (due to the poor solubility and aggregation of the α,ω -diamino PEG_{10k} derivative in THF) as the mobile phase.

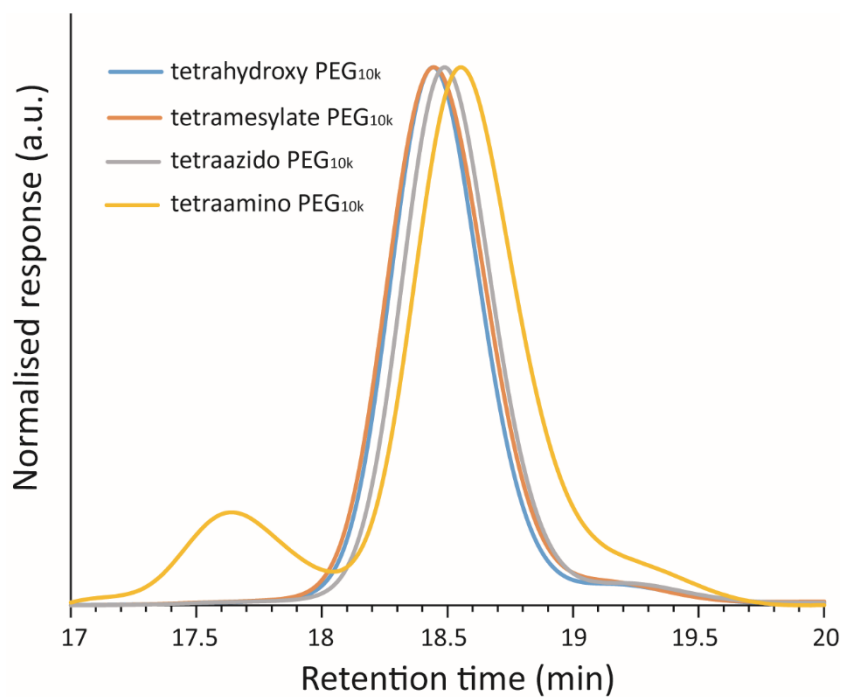


Figure S20. GPC chromatograms showing the conversion of the 4-armed tetrahydroxy PEG_{10k} to its mesylate-, azido- and amino-terminated derivatives recorded using THF as the mobile phase.

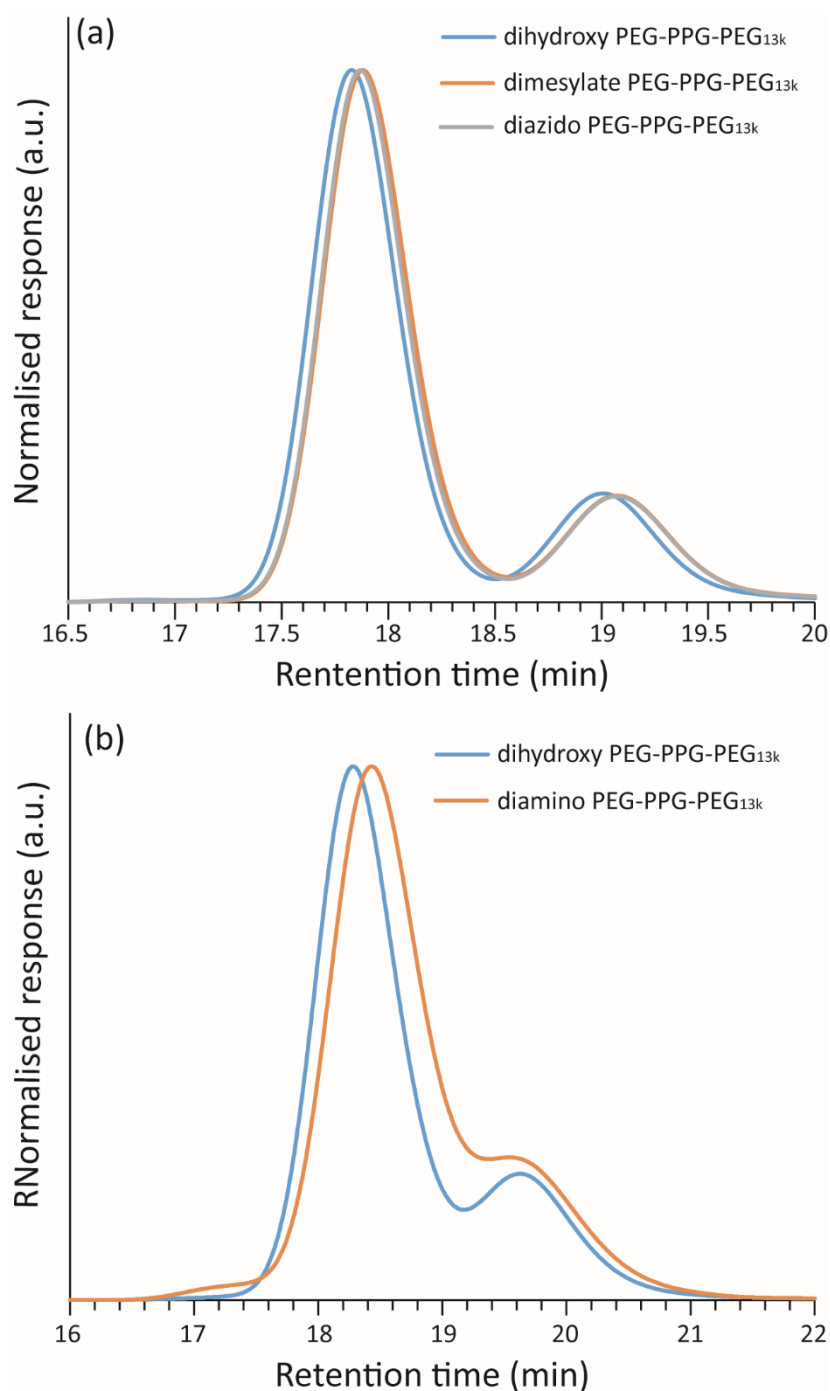


Figure S21. GPC chromatograms showing the conversion of the α,ω -dihydroxy PEG-PPG-PEG (Pluronic® F-127) to its α,ω -dimesylate, α,ω -diazido and α,ω -diamine PEG-PPG-PEG derivatives recorded using **(a)** THF or **(b)** 1:1 v/v MeOH:water (due to the poor solubility and aggregation of the α,ω -diamino PEG_{10k} derivative in THF) as the mobile phase.

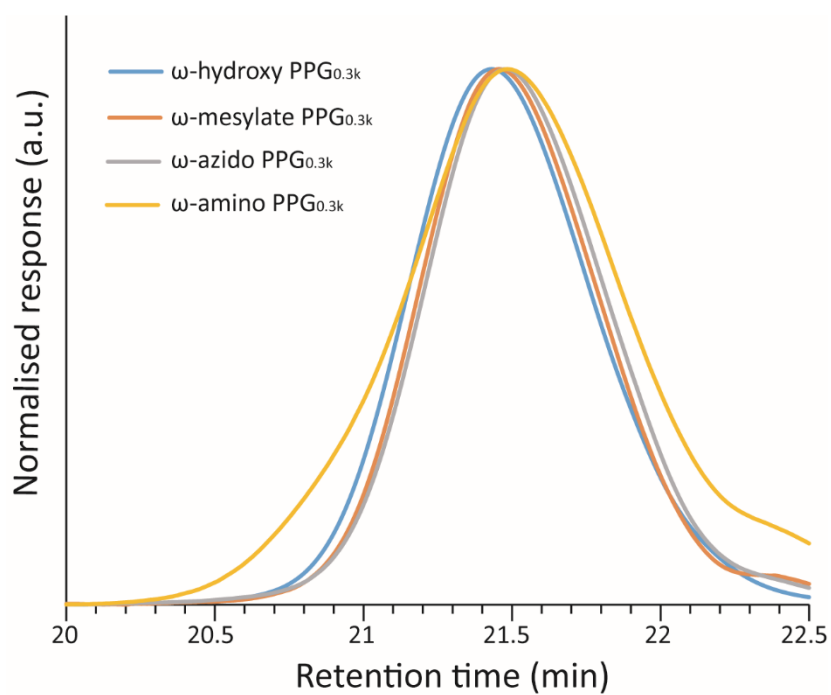


Figure S22. GPC chromatogram showing the conversion of the α -butyl- ω -hydroxy PPG_{0.3k} to its α -butyl- ω -mesylate, α -butyl- ω -azido and α -butyl- ω -amino PEG_{0.3k} derivatives recorded using THF as the mobile phase.

g. Figures for sequential reagent addition synthesis

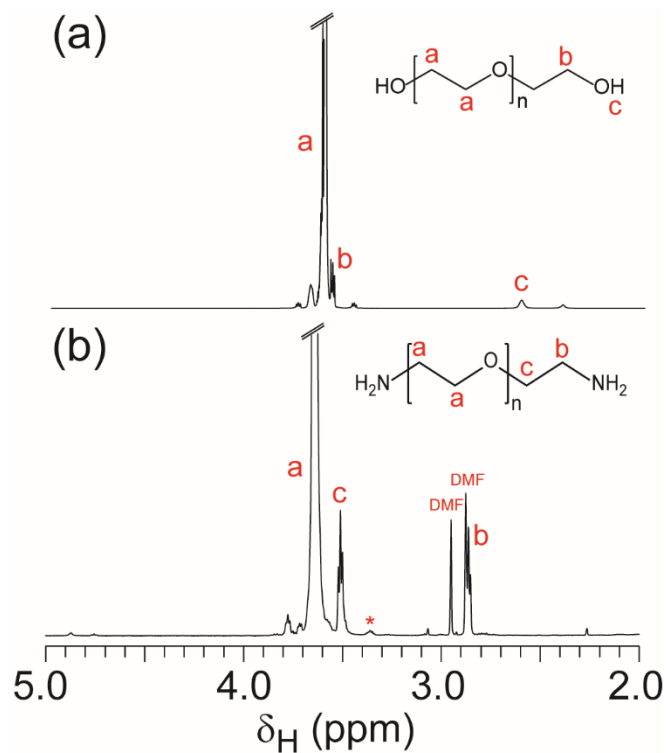


Figure S23. ^1H NMR spectra (500 MHz, 23 °C, CDCl_3) of (a) α,ω -dihydroxy $\text{PEG}_{1.5\text{k}}$ and (b) the α,ω -diamine $\text{PEG}_{1.5\text{k}}$ derivative prepared using sequential reagent addition without intermediate purification and isolation steps (* indicates the remaining unreacted azido end-group).

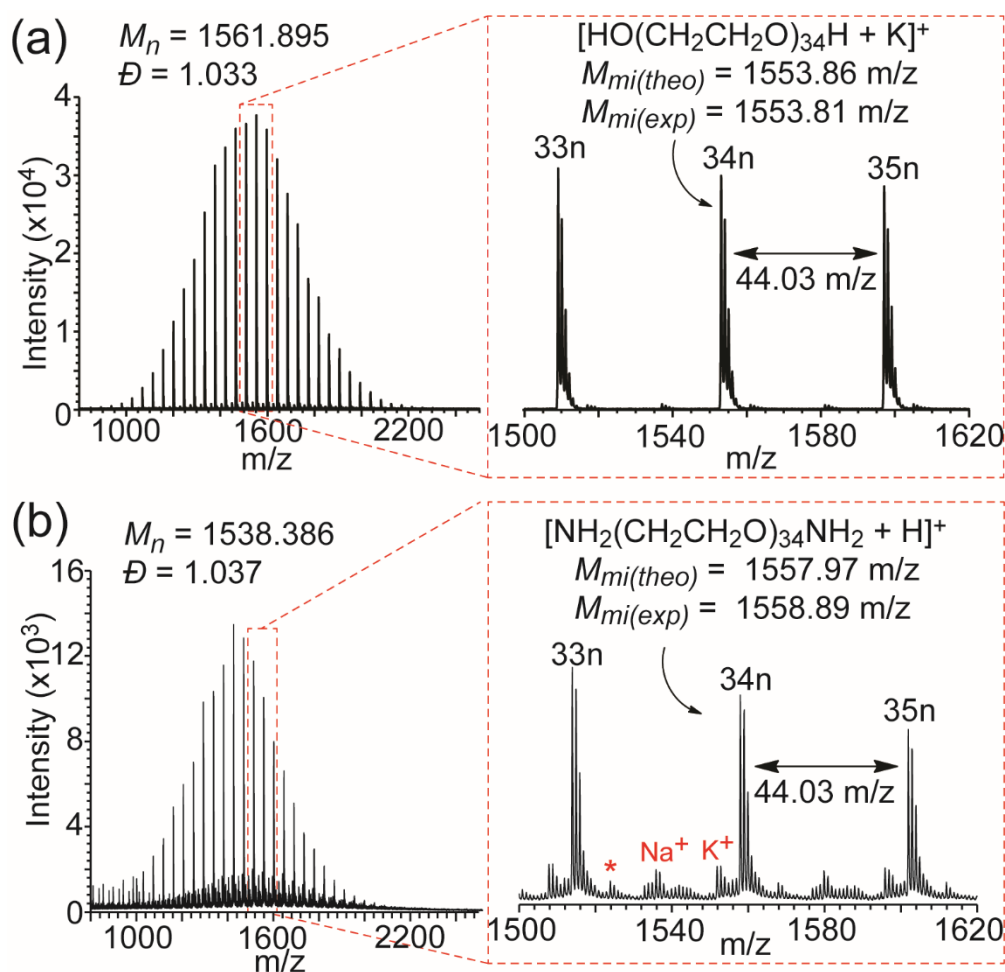


Figure S24. MALDI-ToF mass spectra of **(a)** α,ω -dihydroxy PEG_{1.5k} and **(b)** the α,ω -diamine PEG_{1.5k} derivative prepared using sequential reagent addition without intermediate purification and isolation steps (* indicates the presence of the $\text{N}_3\text{-PEG-NH}_2$ series as the proton adduct): expansions show 33-35 repeat unit region of the spectra with the theoretical ($M_{mi(\text{theo})}$) and experimentally determined ($M_{mi(\text{exp})}$) monoisotopic mass values for the potassium or proton adducts of polymers with $n = 34$.

3. Supporting Table

Table S1. Molecular weight characteristics of the polyglycols determined *via* ^1H NMR spectroscopy, MALDI-ToF MS and GPC.

Polymer	End-group	^1H NMR ^a	M_n (kDa)		\bar{D}	
			MALDI-ToF MS ^b	GPC ^c	MALDI-ToF MS ^b	GPC ^c
MeOPEG_{5.0k}	hydroxyl	5.2	5.4	5.4	1.01	1.09
	mesylate	5.2	5.4	5.2	1.01	1.03
	azido	5.2	5.4	5.2	1.01	1.10
	amino	5.2	5.7	5.2	1.02	1.11
PEG_{1.5k}	hydroxyl	d	1.6	1.3	1.03	1.05
	mesylate	1.4	1.7	1.5	1.03	1.06
	azido	1.5	1.6	1.4	1.04	1.09
	amino	1.4	1.6	1.3	1.03	1.06
PEG_{4.0k}	hydroxyl	d	3.4	3.3	1.02	1.07
	mesylate	3.3	3.6	3.3	1.01	1.06
	azido	3.2	3.5	3.4	1.01	1.07
	amino	3.3	3.3	3.1	1.04	1.07
PEG_{10k}	hydroxyl	d	10.2	11.0 (10.9)	1.01	1.08 (1.08)
	mesylate	9.9	10.5	10.4	1.01	1.10
	azido	9.7	10.4	11.9	1.02	1.07
	amino	9.7	10.7	(10.6)	1.01	(1.12)
PEG_{35k}	hydroxyl	d	e	33.0 (31.5)	e	1.11 (1.14)
	mesylate	31.7	e	34.5	e	1.11
	azido	31.1	e	36.9	e	1.10
	amino	31.0	e	(31.1)	e	(1.17)
4-Armed	hydroxyl	10.6	10.2	9.5	1.01	1.05
PEG_{10k}	mesylate	10.3	10.3	9.6	1.01	1.05
	azido	10.2	10.1	9.5	1.01	1.02
	amino	10.1	10.1	9.5	1.00	1.11
Pluronic[®]	hydroxyl	d	e	12.3 (11.9)	e	1.22 (1.24)
F-127	mesylate	12.8	e	11.5	e	1.24
	azido	12.7	e	11.7	e	1.24
	amino	12.6	e	(11.6)	e	(1.28)
<i>n</i>BuOPPG_{0.3k}	hydroxyl	0.5	0.6	0.6	1.08	1.10
	mesylate	0.6	0.6	0.6	1.11	1.08
	azido	0.6	0.5	0.5	1.12	1.10

amino	0.5	0.5	0.5	1.03	1.17
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^a Number-average molecular weight determined from ¹H NMR spectroscopy by comparing the integration of the end-group proton resonances to the repeating unit proton resonances. ^b Number-average molecular weight determined from MALDI ToF MS for the major adduct series, using Polymerix software (Sierra Analytics). ^c Number-average molecular weight determined from GPC versus a conventional column calibration with PEG standards using THF as the mobile phase; values in brackets were determined using 1:1 v/v MeOH:water as the mobile phase. ^d Number-average molecular weight could not be determined from ¹H NMR as the characteristic resonances for the terminal methylene protons adjacent to the hydroxyl groups were not resolved to provide reference for calculation. ^e Number-average molecular weight could not be determined as average mass peaks for the polymer were not resolved.

Reference

1. Zeng, R., Luo, Z., Zhou, D., Cao, F., Wang, Y., A novel PEG coating immobilized onto capillary through polydopamine coating for separation of proteins in CE. *Electrophoresis*, **2010**, 31, 3334-3341.
2. Zhou, C., Truong, V.X., Qu, Y., Lithgow, T., Fu, G., Forsythe, J.S., Antibacterial poly (ethylene glycol) hydrogels from combined epoxy - amine and thiol - ene click reaction. *J. Polym. Sci. Part A: Polym. Chem.*, **2016**, 54, 656-667.