Supplementary Materials

Synthesis of aminoalkynes 6a–d (Scheme S1)

Scheme S1. Synthesis of aminoalkynes 6a–d.

a. i. NaH, DMF, 0 °C; ii. propargyl bromide, rt, o/n; b. TsCl, KOH, DMF, 0 °C to rt, o/n; c. NaN₃, DMF, TBAI, 120 °C, o/n; d. i) PS-PPh₃, THF, o/n; ii) H₂O, rt, o/n, yields over 4 steps: 6a = 27%, 6b = 31%, 6c = 28%, 6d = 46%

General Procedure A: Propargylation of polyethylene glycol

Sodium hydride (1.5 eq.) was added under a nitrogen atmosphere to a cooled (0 °C) solution of polyethylene glycol 9 (1 eq.) in anhydrous DMF followed by a solution of propargyl bromide in toluene (80% wt, 3 eq.). The reaction mixture was stirred at room temperature for 2 days. It was then concentrated in vacuo to give an oil, which was purified by column chromatography (hexane/EtOAc).

2-(2-(Prop-2-yn-1-yloxy)ethoxy)ethanol S1a General procedure A was followed using diethylene glycol 9a (3.0 mL, 0.030 mol) to yield S1a as a light amber oil (3.0 g, 0.019 mol, 65%). ¹H-NMR (300 MHz, CDCl₃) δ 2.38–2.51 (m, 1H), 3.55–3.81 (m, 10H), 4.20–4.22 (m, 2H). ¹H-NMR data were in accordance with the literature [1].

2-(2-(2-(Prop-2-yn-1-yloxy)ethoxy)ethoxy)ethanol S1b. General procedure A was followed using triethylene glycol 9b (5.0 mL, 0.040 mol) to yield S1b (4.1 g, 0.023 mol, 58%) as a light amber oil. ¹H-NMR (300 MHz, CDCl₃) δ 2.40 - 2.44 (m, 1H), 3.56–3.79 (m, 12H), 4.21 (t, J = 2.2 Hz, 2H). ¹H-NMR data were in accordance with the literature [2].

3,6,9,12-Tetraoxapentadec-14-yn-1-ol S1c. General procedure A was followed using tetraethylene glycol 9c (2.0 mL, 0.010 mol) to yield S1c as a light amber oil (1.4 g, 5.12 mmol, 51%). ¹H-NMR (300 MHz, CDCl₃) δ 2.43 (t, J = 2.4 Hz, 1H), 3.56–3.77 (m, 16H), 4.21 (d, J = 2.3 Hz, 2H). ¹H-NMR data were in accordance with the literature [3].

3,6,9,12,15-Tetraoxaoctadec-14-yn-1-ol S1d. General procedure A was followed using pentaethylene glycol 9d (3.0 mL, 0.010 mol) to yield S1d as a yellow oil (2.4 g, 6.12 mmol, 61%). ¹H-NMR (400 MHz, CDCl₃) δ 2.42 (t, J = 2.4 Hz, 1H), 3.56–3.78 (m, 20H), 4.20 (d, J = 2.4 Hz, 2H). ¹H-NMR data were in accordance with the literature. ¹H-NMR data were in accordance with the literature [4].

General Procedure B: Tosylation of compounds S1a–d

Freshly ground potassium hydroxide (2 eq.) was added to a cooled (0 °C) solution of S1 in anhydrous DCM under a nitrogen atmosphere. The mixture was then stirred at this temperature for an
hour before the slow addition of \( p\)-toluene sulfonylchloride (1.1 eq.). The reaction mixture was then stirred at room temperature overnight before being concentrated in \textit{vacuo} to give a beige oily solid. The crude product was then taken up in EtOAc (25 mL) and the resulting suspension stirred at room temperature for 30 minutes. The insoluble solid was removed by filtration and the filtrate concentrated in \textit{vacuo} to afford \( S2 \).

2-(2-(2-(Prop-2-yn-1-yloxy)ethoxy)ethoxy)ethanol \( S2a \). General procedure B was followed using 2-(2-(prop-2-yn-1-yloxy)ethoxy)ethanol \( S1a \) (2.8 g, 0.02 mol) to give \( S2a \) as an amber oil (4.5 g, 0.018 mol, 89%). \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \( \delta \) 2.42–2.45 (m, 4H), 3.55–3.76 (m, 6H), 4.10–4.25 (m, 4H), 7.29–7.39 (m, 2H), 7.79–7.81 (m, 2H). \(^1\)H-NMR data were in accordance with the literature [1].

2-(2-(Prop-2-yn-1-yloxy)ethoxy)ethyl 4-methylbenzenesulfonate \( S2b \). General procedure B was followed using 2-(2-(2-(prop-2-yn-1-yloxy)ethoxy)ethoxy)ethanol \( S1b \) (3.3 g, 0.020 mol) to give \( S2b \) as an amber oil (3.1 g, 0.019 mol, 95%). \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \( \delta \) 2.43–2.45 (m, 4H), 3.56–3.75 (m, 10H), 4.11–4.24 (m, 4H), 7.31–7.38 (m, 2H), 7.74–7.86 (m, 2H). \(^1\)H-NMR data were in accordance with the literature [2].

3,6,9,12-Tetraoxapentadec-14-yn-1-yl 4-methylbenzenesulfonate \( S2c \). General procedure B was followed using 3,6,9,12-tetraoxapentadec-14-yn-1-ol \( S1c \) (1.4 g, 5.94 mmol) to give \( S2c \) as an amber oil (2.9 g, 5.40 mmol, 91%). \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \( \delta \) 2.42–2.44 (m, 4H), 3.54–3.75 (m, 14H), 4.08–4.26 (m, 4H), 7.30–7.40 (m, 2H), 7.74–7.86 (m, 2H). \(^1\)H-NMR data were in accordance with the literature [5].

3,6,9,12,15-Pentaoxaoctadec-17-yn-1-yl 4-methylbenzenesulfonate \( S2d \). General procedure B was followed using 3,6,9,12,15-pentaoxaoctadec-17-yn-1-ol \( S1d \) (1.8 g, 6.69 mmol) to give \( S2d \) as an amber oil (2.5 g, 5.75 mmol, 86%). \(^1\)H-NMR (300 MHz, CDCl\(_3\)) \( \delta \) 2.42–2.45 (m, 4H), 3.55–3.79 (m, 18H), 4.05–4.24 (m, 4H), 7.28–7.39 (m, 2H), 7.74–7.85 (m, 2H). \(^1\)H-NMR data were in accordance with the literature [6].

General Procedure C: Synthesis of Azide \( S3 \)

\texttt{Caution: The following procedures should be performed with care given the explosive nature of azide-containing compounds.}

\texttt{\textit{tert}-Butyl ammonium iodide (10 mol\%) was added to solution of the \( S2 \) in anhydrous DMF (50 mL) under a nitrogen atmosphere followed by sodium azide (1.1 eq.). The reaction mixture was then heated at 45 °C for 20 hours before being concentrated in \textit{vacuo} to give a colourless oily solid. The residue obtained was triturated with Et\(_2\)O and the insoluble salt removed by filtration. The filtrate was then concentrated in \textit{vacuo} to give a colourless oil, which was taken up in toluene. The mixture obtained was once again concentrated in \textit{vacuo} to give \( S3 \).}

3-(2-(2-Azidoethoxy)ethoxy)prop-1-yn \( S3a \). General procedure C was followed using 2-(2-(2-(prop-2-yn-1-yloxy)ethoxy)ethoxy)ethanol \( S2a \) (5.3 g, 0.020 mol) to give \( S3a \) as an amber oil (1.6 g, 0.011 mol,
55%). \(^1\)H-NMR (300 MHz, CDCl\(_3\)) δ 2.42–2.45 (m, 1H), 3.35–3.47 (m, 2H), 3.61–3.80 (m, 6H), 4.21–4.24 (m, 2H). \(^1\)H-NMR data were in accordance with the literature [7].

3-((2-(2-Azidoethoxy)ethoxy)ethoxy)prop-1-yne S3b. General procedure C was followed using 2-((prop-2-yn-1-yloxy)ethoxy)ethyl 4-methylbenzenesulfonate S2b (5.5 g, 0.020 mol) to afford S3b as an amber oil (2.1 g, 0.012 mol, 61%). \(^1\)H-NMR (300 MHz, CDCl\(_3\)) δ 2.41 -2.43 (m, 1H), 3.34–3.47 (m, 2H), 3.59–3.80 (m, 10H), 4.21–4.23 (m, 2H). \(^1\)H-NMR data were in accordance with the literature [2].

1-Azido-3,6,9,12-tetraoxapentadec-14-yn-1-yl 4-methylbenzenesulfonate S2c (2.0 g, 8.61 mmol) to give S3c as a light yellow oil (1.5 g, 5.85 mmol, 68%). \(^1\)H-NMR (300 MHz, CDCl\(_3\)) δ 2.42 -2.44 (m, 1H), 2.80–3.01 (m, 3H), 3.42–3.78 (m, 7H), 4.20 (d, \(J = 2.4\) Hz, 2H). \(^1\)H-NMR data were in accordance with the literature [7].

1-Azido-3,6,9,12,15-pentaoxoctadec-17-yne S3d. General procedure C was followed using 3,6,9,12,15-pentaoxoctadec-17-yn-1-yl 4-methylbenzenesulfonate S2d (2.4 g, 5.69 mmol) to give S3d as a yellow oil (1.5 g, 5.18 mmol, 91%). \(^1\)H-NMR (300 MHz, CDCl\(_3\)) δ 2.42 (t, \(J = 2.2\) Hz, 1H), 2.80–2.91 (m, 1H), 3.32–3.79 (m, 14H), 4.20 (d, \(J = 2.3\) Hz, 2H). \(^1\)H-NMR data were in accordance with the literature [7].

**General Procedure D: Staudinger reduction of Azides**

Polymer-supported triphenylphosphine (1.15 eq.) was added to a solution of the azido alkyne S3 in anhydrous THF. The reaction mixture was then stirred at room temperature for 48 days. H\(_2\)O (1 mL) was then added to the flask and the resulting mixture stirred at room temperature for a further 48 hours. The reaction mixture was filtered through Celite and the insoluble solid collected washed with EtOAc (25 mL). The filtrate obtained was concentrated in vacuo to afford aminoalkyne 6.

2-(2-(2-azidoethoxy)ethoxy)prop-1-yne S3a (1.5 g, 9.22 mmol) to obtain 6a as an amber oil (1.1 g, 7.93 mmol, 86%). \(^1\)H-NMR (300 MHz, CDCl\(_3\)) δ 2.41-2.44 (m, 1H), 2.80–3.01 (m, 3H), 3.42–3.78 (m, 7H), 4.20 (d, \(J = 2.4\) Hz, 2H). \(^1\)H-NMR data were in accordance with the literature [8].

3,6,9,12-Tetraoxapentadec-14-yn-1-amine 6c. General procedure D was followed using 1-azido-3,6,9,12-tetraoxapentadec-14-yn-1-yl 4-methylbenzenesulfonate S3c (1.4 g, 5.60 mmol) to obtain 6c as an amber oil (1.2 g, 4.98 mmol, 89%). \(^1\)H-NMR (300 MHz, CDCl\(_3\)) δ 1.19–1.22 (m, 1H), 2.42 (q, \(J = 2.2\) Hz, 1H), 2.80–2.91 (m, 1H), 3.32–3.79 (m, 14H), 4.20 (d, \(J = 2.4\) Hz, 2H). \(^1\)H-NMR data were in accordance with the literature [7].
3,6,9,12,15-Pentaoxaoctadec-17-yn-1-amine 6d. General procedure D was followed using 1-azido-3,6,9,12,15-pentaoxaoctadec-17-yn-1-amine S3d (1.5 g, 4.98 mmol) to obtain 6d as an amber oil (1.2 g, 4.38 mmol, 88%). $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 1.80–1.88 (m, 1H), 2.41–2.44 (m, 1H), 2.81–2.90 (m, 1H), 3.44–3.79 (m, 18H), 4.19 (d, $J$ = 2.4 Hz, 2H). $^1$H-NMR data were in accordance with the literature [7].

Synthesis of aminoazide

Scheme S2. Synthesis of aminoazide 7.

General Procedure E: Di-tosylation of polyethylene glycol

$p$-Toluene sulfonyl chloride (2 eq.) was added at 0 °C to a solution of the polyethylene glycol 9 in anhydrous DCM. Freshly ground potassium hydroxide (8 eq.) was carefully added in small portion to keep the temperature of the reaction mixture below 5 °C. After complete addition of the base, the reaction was stirred at 0 °C for 3 hours. The mixture was then poured onto ice/water. The 2 layers were separated and the aqueous one extracted with DCM (3 × 25 mL). The combined organic extracts were washed with H$_2$O (2 × 50 mL), dried over MgSO$_4$, filtered and concentrated in vacuo to give S4.

Oxybis(ethane-2,1-diyl) bis(4-methylbenzenesulfonate) S4a. General procedure E was followed using diethylene glycol 9a (10 mL, 0.10 mol) to give S4a as a colourless oil (25 g, 0.090 mol, 90%). $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 2.44 (s, 6H), 3.57–3.64 (m, 4H), 4.05–4.12 (m, 4H), 7.30–7.39 (m, 4H), 7.73–7.83 (m, 4H). $^1$H-NMR data were in accordance with the literature [9].

(Ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl) bis(4-methylbenzenesulfonate) S4b. General procedure E was followed using triethylene glycol 9b (15 mL, 0.11 mol) to give S4b as a colourless oil (41 g, 0.090 mol, 82%). $^1$H-NMR (400 MHz, CDCl$_3$) $\delta$ 2.43 (s, 6H), 3.51 (s, 4H), 3.60–3.67 (m, 4H), 4.08–4.18 (m, 4H), 7.29–7.37 (m, 4H), 7.73–7.82 (m, 4H). $^1$H-NMR data were in accordance with the literature [9].

((Oxybis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl)bis(4-methylbenzenesulfonate) S4c. General procedure E was followed using tetraethylene glycol 9c (15 mL, 0.11 mol) to give S4c as a yellow oil (42 g, 0.088 mol, 98%). $^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 2.42 (s, 6H), 3.47–3.72 (m, 12H), 4.08–4.18 (m, 4H), 7.27–7.38 (m, 4H), 7.71–7.82 (m, 4H). $^1$H-NMR data were in accordance with the literature [9].

3,6,9,12-Tetraoxatetradecane-1,14-diy bis(4-methylbenzenesulfonate) S4d. General procedure E was followed using pentaethylene glycol 9d (15 mL, 0.070 mol) to give S4d as light yellow oil (35 g,
0.064 mol, 92%). $^1$H-NMR (300 MHz, CDCl$_3$) δ 2.44 (s, 6H), 3.53–3.75 (m, 18H), 4.05–4.20 (m, 4H), 7.29–7.39 (m, 4H), 7.74–7.85 (m, 4H). $^1$H-NMR data were in accordance with the literature [9].

General Procedure F: Synthesis of diazide

*Caution:* The following procedures should be performed with care given the explosive nature of azide-containing compounds.

*tert*-Butyl ammonium iodide (10 mol%) was added to solution of the ditosylated ethylene glycol S4 in anhydrous DMF (50 mL) under a nitrogen atmosphere followed by sodium azide (4 eq.). The reaction mixture was then heated at 80 °C for 20 hours before being concentrated in vacuo to give a colourless oily solid. The residue obtained was triturated with Et$_2$O and the insoluble salt removed by filtration. The filtrate was then concentrated in vacuo to give a colourless oil, which was taken up in toluene. The mixture obtained was once again concentrated in vacuo to give S5.

1-Azido-2-(2-azidoethoxy)ethane S5a. General procedure F was followed using oxybis(ethane-2,1-diyl) bis(4-methylbenzenesulfonate) S4a (15 g, 0.060 mol) to give S5a as a light yellow oil (6.7 g, 0.045 mol, 75%). $^1$H-NMR (300 MHz, CDCl$_3$) δ 3.41 (t, $J$ = 5.0 Hz, 4H), 3.68 (dd, $J$ = 5.5, 4.5 Hz, 4H). $^1$H-NMR data were in accordance with the literature [9].

1,2-bis(2-Azidoethoxy)ethane S5b. General procedure F was followed using (ethane-1,2-diylbis(oxy))bis(ethane-2,1-diyl) bis(4-methylbenzenesulfonate) S4b (25 g, 0.050 mol) to give S5b as a light amber oil (8.3 g, 0.035 mol, 70%). $^1$H-NMR (300 MHz, CDCl$_3$) δ 3.39 (t, $J$ = 5.0 Hz, 4H), 3.58–3.83 (m, 8H). $^1$H-NMR data were in accordance with the literature [9].

1-Azido-2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethane S5c. General procedure F was followed using ((oxybis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl)bis(4-methylbenzenesulfonate) S4c (25 g, 0.050 mol) to give S5c as a light yellow oil (12 g, 0.049 mol, 98%). $^1$H-NMR (300 MHz, CDCl$_3$) δ 3.33–3.46 (m, 4H), 3.61–3.78 (m, 12H). $^1$H-NMR data were in accordance with the literature [9].

1,14-Diazido-3,6,9,12-tetraoxatetradecane S5d. General procedure F was followed using 3,6,9,12-tetraoxatetradecane-1,14-diyl bis(4-methylbenzenesulfonate) S4d (25 g, 0.040 mol) to give S5d as a light amber oil (12 g, 0.036 mol, 90%). $^1$H-NMR (300 MHz, CDCl$_3$) δ 3.39 (dd, $J$ = 5.6, 4.6 Hz, 4H), 3.61–3.75 (m, 16H). $^1$H-NMR data were in accordance with the literature [9].

General Procedure G: Mono-Staudinger reduction of Azides

A solution of triphenylphosphine in Et$_2$O was added dropwise over 30 minutes to a solution of the diazido compound S5 in a mixture of Et$_2$O/THF/HCl 1N (5/1/5) at room temperature. The reaction mixture was then vigorously stirred at this temperature overnight. The 2 layers were then separated and the aqueous one extracted with DCM (3 × 15 mL). The aqueous layer was then basified by the addition of sodium hydroxide pellets to pH 14. The resulting solution was then extracted with DCM (4 × 25 mL) and the combined organic extracts dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to give the aminoazide 7.
2-(2-Azidoethoxy)ethanamine 7a. General procedure G was followed using 1-azido-2-(2-azidoethoxy)ethane S5a (8.0 g, 0.050 mol) to give 7a as a light yellow oil (3.9 g, 0.029 mol, 59%). 1H-NMR (400 MHz, CDCl3) δ 2.88 (t, $J = 5.1$ Hz, 2H), 3.35–3.42 (m, 2H), 3.49–3.58 (m, 2H), 3.60–3.72 (m, 2H). 1H-NMR data were in accordance with the literature [10].

2-(2-(2-Azidoethoxy)ethoxy)ethanamine 7b. General procedure G was followed using 1,2-bis(2-azidoethoxy)ethane S5b (10 g, 0.040 mol) to give 7b as a light yellow oil (4.9 g, 0.024 mol, 61%) 1H-NMR (400 MHz, CDCl3) δ 2.82–2.91 (m, 2H), 3.34–3.42 (m, 2H), 3.51 (td, $J = 5.2$, 1.0 Hz, 2H), 3.57–3.71 (m, 6H). 1H-NMR data were in accordance with the literature [11].

2-(2-(2-(2-Azidoethoxy)ethoxy)ethoxy)ethanamine 7c. General procedure G was followed using 1-azido-2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethane S5c (10 g, 0.040 mol) to give 7c as a light yellow oil (5.8 g, 0.026 mol, 65%). 1H-NMR (400 MHz, CDCl3) δ 2.80 (td, $J = 5.2$, 1.7 Hz, 2H), 3.28–3.36 (m, 2H), 3.45 (m, 2H), 3.51–3.65 (m, 10H). 1H-NMR data were in accordance with the literature [12].

14-Azido-3,6,9,12-tetraoxatetradecan-1-amine 7d. General procedure G was followed using 1,14-diazido-3,6,9,12-tetraoxatetradecane S5d (10 g, 0.030 mol) to give 7d as a colourless oil (5.2 g, 0.017 mol, 57%). 1H-NMR (400 MHz, CDCl3) δ 2.83–2.91 (m, 2H), 3.35–3.43 (m, 2H), 3.52 (td, $J = 5.3$, 1.2 Hz, 2H), 3.63–3.68 (m, 14H). 1H-NMR data were in accordance with the literature [13].

Sample Availability: Samples of the compounds 6a–d and 7a–d are available from the authors.
$^1$H-NMR Spectrum of tBu-MTX-Cmpd2.2

tBu-MTX-Cmpd2.2 (DMSO, 500 MHz)
$^{13}$C-NMR Spectrum of $t$Bu-MTX-Cmpd2.2

tBu-MTX-Cmpd2.2 (DMSO, 126 MHz)
Partial 2D HSQC Spectrum of ′Bu-MTX-Cmpd2.2 (δH/δC: 5.90–8.90/102 - 165)
2D HMBC Spectrum of tBu-MTX-Cmpd2.2

tBu-MTX-Cmpd2.2 (DMSO, 500 MHz)
\textsuperscript{1}H-NMR Spectrum of MTX-Cmpd2.2
$^{13}$C-NMR Spectrum of MTX-Cmpd2.2

MTX-Cmpd2.2 (DMSO, 126 MHz)
2D HMBC Spectrum of MTX-Cmpd2.2

MIX-Cmpd2.2 (DMSO, 500 MHz)
References


