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One-pot synthesis of monodisperse dual-functionalized polyethylene glycols through macrocyclic sulfates†

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Dual-functionalization of monodisperse oligoethylene glycols, especially hetero-functionalization, provides a series of highly valuable intermediates for life and materials sciences. However, the existing methods for the preparation of these compounds suffer excessive protecting and activating group manipulation as well as tedious purification. Here, a one-pot dual-substitution strategy with macrocyclic sulfates of polyethylene glycols as the key intermediates was developed for the convenient and scalable preparation of a series of homo-functionalized and hetero-functionalized oligoethylene glycols in just 1 step. A high synthetic efficacy was achieved by avoiding the protecting and activating group manipulation and the intermediate purification.

Introduction

As the "gold standard" polymers in life and materials sciences, polyethylene glycols (PEGs) have been extensively used to improve solubility and stability, reduce immunogenicity and dosing frequency, and prolong blood circulation.[1] For example, the high biocompatibility and "stealthy" effect of PEGs make them ideal modifiers and linkers for drugs. Since 1991, the US FDA has approved 14 PEG-containing drugs, including the blockbuster drug Pegasys®. PEGylation, conjugation of PEGs of certain molecular weights and functional groups with biomacromolecules or nanomaterials, has become one of the most successful strategies in biopharmaceutics development. Therefore, properly functionalized PEGs with high purity are of great importance in many fields.

During PEGylation, PEGs are usually pre-modified into dual-functionalized forms $X(CH_2CH_2O)_{n-1}CH_2CH_2Y$; X, Y = OH, CH_2CO_2H, SH, NH_2, N_3, *etc.*), especially into hetero-functionalized forms (X ≠ Y). However, it is very challenging to prepare highly pure dual-functionalized PEGs because there are two major difficulties in their synthesis. First, as polymers of ethylene oxide, the heterogeneity in regular PEGs and their derivatives is inevitable, which leads to difficulties in PEGylation, purification, characterization, clinical application, and drug regulatory approval.[2] Therefore, although the synthesis of Monodisperse PEGs (M-PEGs) is challenging,[3] it is highly beneficial to replace regular PEGs with M-PEGs for achieving the optimal physicochemical properties, drug efficacy and safety, *etc.*[4] Second, dual-functionalization of PEGs, especially hetero-functionalization of PEGs, suffers the tedious protecting and activating group manipulation, which dramatically prolongs their synthetic route, degrades the synthetic efficacy, and complicates the purification process.[3] In addition, for hetero-functionalization of PEGs, a necessary mono-functionalization step is very challenging because there is no steric or electronic effect to assist the mono-functionalization of linear PEGs and it is very tedious to purify the resulting mono-, dual- and non-functionalized PEG mixture. For these reasons, dual-functionalized PEGs, especially the monodisperse ones, are very expensive. Thus, novel strategies for the convenient and efficient synthesis of highly pure dual-functionalized PEGs are highly valuable.

Recently, a macrocyclic sulfate-based strategy for the highly efficient synthesis of monodisperse PEGs (M-PEGs) and their derivatives was developed by this group (Scheme 1).[5] In this strategy, selective nucleophilic ring opening of the M-PEG macrocyclic sulfates conveniently provided a series of mono-functionalized M-PEGs in just one step without protecting or activating group manipulation. To transform these mono-functionalized PEGs into hetero-functionalized PEGs for biomedical application, additional activating and substituting steps are required.[6] Herein, we expanded the macrocyclic sulfate-based strategy to one-pot dual-functionalization of oligoethylene glycols (Scheme 1). In organic synthesis, cyclic sulfates are usually employed as highly active precursors for

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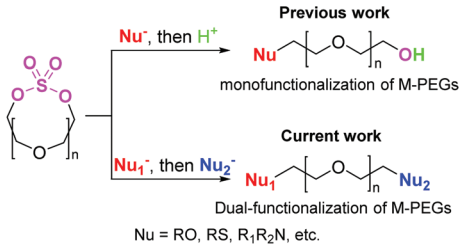


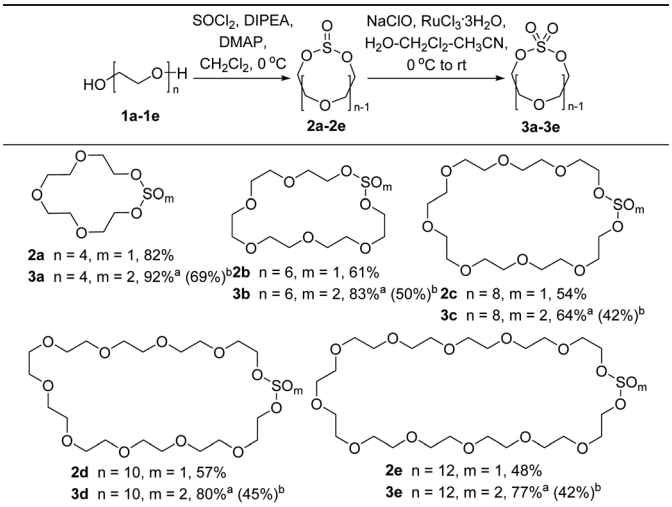
Scheme 1 Previous and current work on the functionalization of M-PEGs.

the preparation of α-substituted alcohols through the nucleophilic ring-opening reaction, during which the sulfate salt intermediates prevent further nucleophilic substitution and selectively provide the mono-substituted products after acidic hydrolysis.[7] However, in some cases, traces of dual-substituted products were isolated by us during the ring-opening reaction of M-PEG macrocyclic sulfates. Therefore, we envision that the M-PEG sulfate salt intermediates could be activated for further nucleophilic substitution and provide the dual-functionalized M-PEGs in just 1 step. In this way, dual-functionalized M-PEGs could be conveniently prepared with minimum reaction steps.

Results and discussion

With these ideas in mind, the M-PEG macrocyclic sulfates were prepared as the starting materials for dual-functionalized M-PEGs. Our previous method involves the oxidation of M-PEG macrocyclic sulfites to the corresponding macrocyclic sulfates with expensive reagents such as $NaIO_4$ and $RuCl_3{\cdot}H_2O$. To reduce the cost of the M-PEG macrocyclic sulfates, many oxidation systems were explored on tetraethylene glycol macrocyclic sulfite **2a**. However, due to the low stability of macrocyclic sulfite **2a** and high reactivity of macrocyclic sulfate **3a**, many widely used oxidation systems failed to provide macrocyclic sulfate **3a**, including H_2O_2, H_2O_2–$RuCl_3{\cdot}3H_2O$, CrO_3, CrO_3–H_2SO_4, K_2FeO_4, *t*BuOOH, *m*CPBA, $K_2Cr_2O_7$, $KBrO_3$, and trichloroiso-cyanuric acid. Fortunately, macrocyclic sulfate **3a** was isolated in a 30% yield when $KMnO_4$ in the presence of H_2SO_4 was employed in the reaction. Further, macrocyclic sulfate **3a** was obtained in high yield when NaOCl and $RuCl_3{\cdot}3H_2O$ were used in the reaction. After a series of reaction condition optimization, 4.0 equiv. of NaOCl and 0.005 equiv. of $RuCl_3{\cdot}3H_2O$ in a solvent mixture of CH_2Cl_2–CH_3CN–H_2O (1 : 1 : 2) at 0 °C to room temperature were identified as the preferred oxidation reaction conditions (Table S1†). Compared to our previous method, this method is made more environmentally friendly by replacing the severe environmental pollutant CCl_4 with CH_2Cl_2 and much less expensive by replacing expensive $NaIO_4$ with inexpensive NaOCl. Under the reaction conditions, a series of macrocyclic sulfites **2a–2e**, which were prepared with our previous method,[5] were oxidized to the corresponding macrocyclic sulfates **3a–e** in good yields (Table 1). Macrocyclic sulfates **3a–e** were also prepared through one-pot macrocyclization and oxidation from M-PEGs **1a–1e** with good yields. It is noteworthy that the yields are comparable to those of our previous method. Finally, a 51-gram scale preparation of macrocyclic sulfate **3a** was carried out with an 88% yield under the reaction conditions.

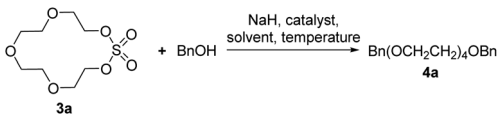
Table 1 Preparation of macrocyclic sulfates **3a–3e**



[a] Yields of oxidation reactions with **2a–2e** as the starting materials. [b] Yields of one-pot macrocyclization and oxidation reactions with **1a–1e** as the starting materials.

The homo-functionalization of M-PEGs was first explored with tetraethylene glycol macrocyclic sulfate **3a** and benzyl alcohol (Table 2). When 4.0 equiv. of benzyl alcohol were treated with 4.0 equiv. of NaH followed by 1.0 equiv. of macrocyclic sulfate **3a** in THF at 25 °C or 60 °C, no dual-benzylated tetraethylene glycol **4a** but mono-benzylated one was isolated. Then, the one-pot dual-functionalization reaction was split into two stages. First, under our previous nucleophilic ring opening conditions, macrocyclic sulfate **3a** was treated with 1.1 equiv. of benzyl alcohol in the presence of 2.0 equiv. of NaH at 25 °C to provide the sulfate salt intermediate. Second, the reaction mixture containing the sulfate salt intermediate was treated with additional 2.9 equiv. of benzyl alcohol and 2.0 equiv. of NaH and the resulting mixture was stirred at 60 °C for 12 hours. To our delight, dual-benzylated tetraethylene glycol **4a** was isolated in a 40% yield (entry 1). It was found that when all 4.0 equiv. of NaH were added to the first portion of benzyl alcohol, dual-benzylated M-PEGs **4a** was isolated with the same yield, which simplified the reaction procedures (entry 1). Further optimization of the reaction conditions showed that phase transfer catalysts could promote the reaction, which is probably due to the formation of charged sulfate salt intermediates (entries 2–6). Among the phase transfer catalysts tested, tetrabutylammonium hydrogen sulfate ($TBAHSO_4$) effectively catalyzed the reaction with a 66% yield of **4a** (entry 6). After a screening of the amount of $TBAHSO_4$, 0.1 equiv. of $TBAHSO_4$ was identified as the appropriate amount of catalyst loading. Solvent played an important role in the reaction (entries 7–10). Toluene was chosen as the best

Table 2 Optimization of the reaction conditions



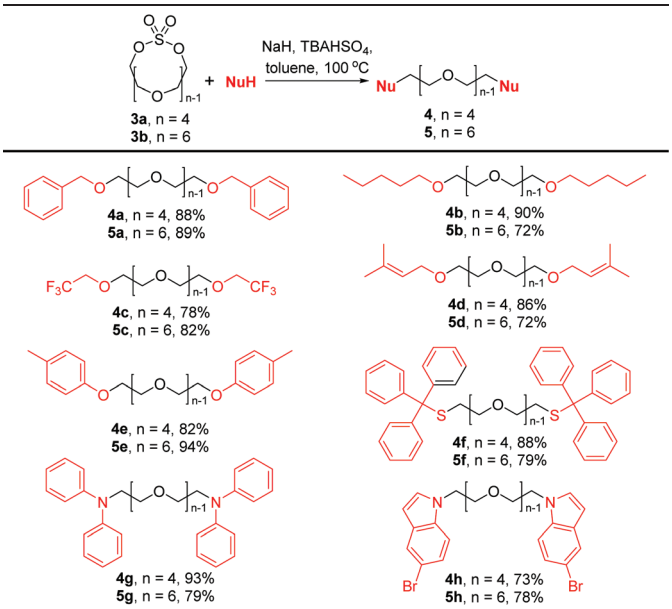
Entry	NaH (equiv.)	BnOH[a] (equiv.)	Catalyst	Solvent	Temp. (°C)	Yield (%)
1[b]	2.0 + 2.0	1.1 + 2.9	—	THF	0–60	40
2	4.0	1.1 + 2.9	TBAC	THF	0–60	50
3	4.0	1.1 + 2.9	TBAB	THF	0–60	63
4	4.0	1.1 + 2.9	TBAI	THF	0–60	58
5	4.0	1.1 + 2.9	18-C-6	THF	0–60	60
6[c]	4.0	1.1 + 2.9	$TBAHSO_4$	THF	60	66
7	4.0	1.1 + 2.9	$TBAHSO_4$	DMF	60	5
8	4.0	1.1 + 2.9	$TBAHSO_4$	CH_3CN	60	6
9	4.0	1.1 + 2.9	$TBAHSO_4$	Dioxane	60	7
10	4.0	1.1 + 2.9	$TBAHSO_4$	Toluene	60	82
11	4.0	1.1 + 2.9	$TBAHSO_4$	Toluene	20	17
12	4.0	1.1 + 2.9	$TBAHSO_4$	Toluene	40	41
13	4.0	1.1 + 2.9	$TBAHSO_4$	Toluene	80	86
14[d]	4.0	1.1 + 2.9	$TBAHSO_4$	Toluene	100	88
15	2.0	1.1 + 2.9	$TBAHSO_4$	Toluene	100	29
16	3.0	1.1 + 2.9	$TBAHSO_4$	Toluene	100	63
17	5.0	1.1 + 2.9	$TBAHSO_4$	Toluene	100	59
18	4.0	1.1 + 1.9	$TBAHSO_4$	Toluene	100	79
19	4.0	1.1 + 3.9	$TBAHSO_4$	Toluene	100	72
20	4.0	4.0	$TBAHSO_4$	Toluene	100	63

[a] BnOH was added in two portions as indicated. [b] When NaH was added in one portion, the yield was 40%. [c] When 0.05 equiv. and 0.2 equiv. of $TBAHSO_4$ were added to the reaction mixture, the yields were 63% and 48%, respectively. [d] When 4 mL and 6 mL toluene were used as the solvent, the yields were 75% and 67%, respectively.

solvent for the following investigation. Other solvents were found to be less effective for this reaction. 1,4-Dioxane and acetonitrile couldn't dissolve the intermediates well and DMF resulted in side reactions. The yield was further improved by elevating the reaction temperature (entries 11–14). Diluting the concentration of the macrocyclic sulfate **3a** lowered the yield of **4a**. It was also found that benzyl alcohol with 1.1 equiv. of benzyl alcohol in the presence of 4.0 equiv. of NaH for the first nucleophilic substitution and 2.9 equiv. of benzyl alcohol for the second one were essential for the reaction (entries 15–19). When benzyl alcohol was added in one portion, the yield of **3a** was much lower. Finally, the reaction was carried out on an 8 mmol scale and dual-functionalized M-PEGs **4a** was obtained in an 84% yield.

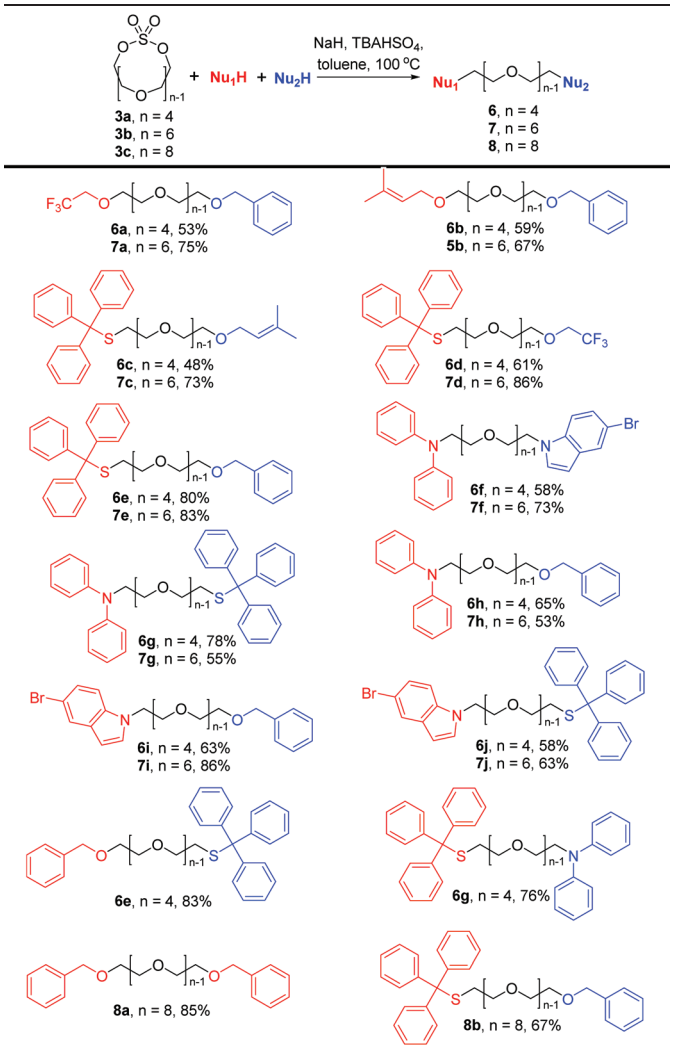
Under the optimized reaction conditions, the scope of the dual-nucleophilic substitution on macrocyclic sulfates **3a** and **3b** with the same nucleophile was first investigated (Table 3). Through this reaction, a series of homo-functionalized M-PEGs were prepared with high efficacy. First, alcohols, including benzyl, alkyl, fluorinated, and allyl alcohols, in the presence of NaH were good nucleophiles and M-PEG di-ethers were obtained with good yields (**4a–4d**, **5a–5d**). Second, phenol ethers **4e** and **5e** were obtained with high efficacy when the macrocyclic sulfates **3a** and **3b** were treated with 4-methylphenol, respectively. Third, thio-ethers **4f** and **5f** were conveniently prepared with this method, which could be further transformed into dithiolated M-PEGs under mild conditions. Fourth, nucleophilic nitrogen atoms were able to dual-substitute the macrocyclic sulfates and provide M-PEG-containing amines **4g**, **5g** and indoles **4h**, **5h** with high yields.

Table 3 Dual-nucleophilic substitution on macrocyclic sulfates **3a** and **3b** with one nucleophile



Encouraged by these results, we investigated the dual-nucleophilic substitution on macrocyclic sulfates with two

Table 4 Dual-nucleophilic substitution on macrocyclic sulfates **3a** and **3b** with two nucleophiles



different nucleophiles to provide hetero-functionalized M-PEGs (Table 4). Hetero-functionalized M-PEGs are the most used forms in PEGylation and bioconjugation. Compared to homo-functionalized M-PEGs, hetero-functionalized M-PEGs are more valuable and their synthesis is more challenging. Under the optimized reaction conditions, 1.1 equiv. of the first nucleophile, 1,1,1-trifuoroethanol, was treated with 4.0 equiv. of NaH followed by macrocyclic sulfate **3a** at 25 °C. After completion of the nucleophilic ring opening reaction, 2.9 equiv. of the second nucleophile, benzyl alcohol, were added to the reaction mixture and the resulting mixture was stirred at 100 °C overnight. Fortunately, the hetero-functionalized product **6a** was isolated in a 53% yield. The scope the hetero-functionalization reaction was then investigated on macrocyclic sulfates **3a** and **3b**. A series of O-, S-, N-containing nucleophiles could react effectively with macrocyclic sulfates **3a** and **3b** either in the first nucleophile substitution or in the second nucleophilic substitution to provide a variety of hetero-functionalized M-PEGs **6a–6j** and **7a–7j** in good yields. It was found that the order of adding the nucleophile had little effect on the yield of the product (**6e** and **6g** were synthesized in 2 different orders). The dual-nucleophilic substitution reaction was expanded to the macrocyclic sulfate of octaethylene glycol **3c**. Both homo-functionalized product **8a** and hetero-functionalized product **8b** were obtained in good yields.

Conclusions

In this work, we developed a one-pot dual-nucleophilic substitution method for the preparation of both homo-functionalized and hetero-functionalized M-PEGs. Compared to the existing methods, the macrocyclic sulfate-based method is highly efficient and scalable which avoids the tedious protecting and activating group manipulation. To facilitate the method, a low cost and environmentally friendly process for macrocyclic sulfates was also developed. Although cyclic sulfates are extensively used in organic synthesis, their application is limited to the mono-nucleophilic substitution providing α-substituted alcohols. As far as we know, this is the first example of dual-nucleophilic substitution providing dual-functionalized products. Besides broadening the application of cyclic sulfates, this study also provides quick access to a series of highly valuable homo- and hetero-functionalized M-PEGs which suffer limited availability due to their synthetic difficulties. This process may promote the availability of functionalized M-PEGs and therefore the wide applications of M-PEGs in biomedicine and beyond.

Experimental section

General

^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer. ^{1}H NMR spectra were referenced to tetramethylsilane (s, 0.00 ppm) using $CDCl_3$ as a solvent. ^{13}C NMR spectra were referenced to solvent carbons (77.16 ppm for $CDCl_3$). ^{19}F NMR spectra were referenced to 2% perfluorobenzene (s, −164.90 ppm) in $CDCl_3$. The splitting patterns for ^{1}H NMR spectra were denoted as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. High resolution mass spectra were recorded on a 4.7 Tesla FT-MS using Electron Spray Ionization (ESI). Unless otherwise noted, solvents and reagents were purchased from commercial suppliers and used as received. Flash chromatography was performed on silica gel (200–300 mesh) with EtOAc/petroleum ether (PE, 60–90 °C). Macrocyclic sulfites **2a–2e** were prepared according to reported procedures.[5a]

General procedure for the preparation of macrocyclic sulfates 3a–3e (using the synthesis of 3a as an example)

Under an atmosphere of Ar, $SOCl_2$ (95.2 mg, 0.8 mmol, in 2.0 mL of CH_2Cl_2) was added over 0.5 h to a stirring solution of tetraethylene glycol **1a** (77.7 mg, 0.4 mmol), DIPEA (248.1 mg, 1.9 mmol) and DMAP (2.5 mg, 20.0 μmol) in

CH_2Cl_2 (8 mL) at 0 °C. After the addition, the mixture was stirred at 0 °C for 1 h and quenched with cold brine (8 mL). The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (20 mL, twice). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated to give 78.7 mg of macrocyclic sulfites **2a** as a brown oil in 82% yield. Macrocyclic sulfite **2a** (78.7 mg, 0.3 mmol) was dissolved in a mixture of CH_3CN (1.6 mL), CH_2Cl_2 (1.6 mL) and water (2.5 mL) at 0 °C. NaOCl (0.8 mL, 1.3 mmol, available chlorine 10%) and $RuCl_3{\cdot}3H_2O$ (0.5 mg, 1.7 μmol) were sequentially added to the reaction mixture and the resulting mixture was stirred at 0 °C for 1 h. The organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (20 mL, twice). The combined organic layer was dried over anhydrous Na_2SO_4, filtered through a pad of Celite, concentrated under vacuum, and purified by flash chromatography on silica gel with EtOAc/PE (1/1) as the eluent to give the macrocyclic sulfate **3a** as a white wax (77.3 mg, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49 (t, J = 5.0 Hz, 4H), 3.88–3.82 (m, 4H), 3.73–3.62 (m, 8H).

Macrocyclic sulfate 3b was prepared from hexaethylene glycol **1b** by following the general procedure for the preparation of macrocyclic sulfate **3a** as a clear oil (68.8 mg, 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50–4.43 (m, 4H), 3.87–3.81 (m, 4H), 3.70–3.64 (m, 16H).

Macrocyclic sulfate 3c was prepared from octaethylene glycol **1c** by following the general procedure for the preparation of macrocyclic sulfate **3a** as a clear oil (72.6 mg, 42% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.48–4.42 (m, 4H), 3.83–3.78 (m, 4H), 3.70–3.64 (m, 24H).

Macrocyclic sulfate 3d was prepared from decaethylene glycol **1d** by following the general procedure for the preparation of macrocyclic sulfate **3a** as a clear oil (93.7 mg, 45% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.51–4.38 (m, 4H), 3.83–3.78 (m, 4H), 3.68–3.64 (m, 32H).

Macrocyclic sulfate 3e was prepared from dodecaethylene glycol **1e** by following the general procedure for the preparation of macrocyclic sulfate **3a** as a clear oil (102.2 mg, 42% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.47–4.37 (m, 4H), 3.82–3.76 (m, 4H), 3.72–3.57 (m, 40H).

General procedure for the preparation of homo-substituted M-PEGs 4a–4h and 5a–5h (using the synthesis of 4a as an example)

A stirring suspension of NaH (64.0 mg, 60% in mineral oil, 1.6 mmol) in anhydrous toluene (0.5 mL) was cooled to 0 °C and a solution of benzyl alcohol (47.5 mg, 0.4 mmol) in anhydrous toluene (0.5 mL) was added slowly. After 30 min, a solution of macrocyclic sulfate **3a** (102.4 mg, 0.4 mmol) in anhydrous toluene (0.5 mL) was slowly added. The reaction mixture was stirred for 4 h at room temperature. Then a solution of benzyl alcohol (125.3 mg, 1.2 mmol) and $TBAHSO_4$ (13.6 mg, 40.0 μmol) in anhydrous toluene (1.0 mL) was added at room temperature. The reaction mixture was stirred for 12 h at 100 °C and the reaction was quenched with water. After the removal of solvent under vacuum, the residue was dissolved in EtOAc (20 mL) and washed with water (5 mL, three times). The organic layer was concentrated under vacuum and purified by flash chromatography on silica gel with EtOAc/PE (1/1) as the eluent to give **4a** as a clear oil (131.7 mg, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.29 (m, 8H), 7.29–7.23 (m, 2H), 4.55 (s, 4H), 3.85–3.45 (m, 16H).

6,9,12,15,18-Pentaoxatricosane 4b was prepared from 1-pentanol by following the general procedure for the preparation of homo-substituted M-PEGs **4a** as a clear oil (120.3 mg, 90% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71–3.62 (m, 12H), 3.58 (m, 4H), 3.45 (t, J = 6.8 Hz, 4H), 1.64–1.52 (m, 4H), 1.37–1.26 (m, 8H), 0.89 (t, J = 6.9 Hz, 6H).

1,1,1,17,17,17-Hexafluoro-3,6,9,12,15-pentaoxaheptadecane 4c was prepared from 2,2,2-trifluoroethanol by following the general procedure for the preparation of homo-substituted M-PEGs **4a** as a clear oil (111.7 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (q, J = 8.8 Hz, 4H), 3.82–3.77 (m, 4H), 3.70–3.64 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.1 (q, J = 279.6 Hz), 72.0, 70.8, 70.7, 70.8, 68.8 (q, J = 33.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.33. HRMS (ESI) calcd for $C_{12}H_{20}F_6KO_5^+$ ($[M + K]^+$) 397.0847, found 397.0845.

2,20-Dimethyl-5,8,11,14,17-pentaoxahenicosa-2,19-diene 4d was prepared from isopentenyl alcohol by following the general procedure for the preparation of homo-substituted M-PEGs **4a** as a clear oil (113.6 mg, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.43–5.28 (m, 2H), 4.00 (d, J = 6.4 Hz, 4H), 3.62–3.67 (m, 12H), 3.60–3.56 (m, 4H), 1.74 (s, 6H), 1.67 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 121.1, 70.7, 70.5, 69.1, 67.6, 25.8, 18.0. HRMS (ESI) calcd for $C_{18}H_{34}NaO_5^+$ ($[M + Na]^+$) 353.2298, found 353.2294.

4,4′-((((Oxybis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl))bis(oxy))bis(methylbenzene) 4e was prepared from *p*-cresol by following the general procedure for the preparation of homo-substituted M-PEGs **4a** as a clear oil (122.1 mg, 82% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, J = 8.2 Hz, 4H), 6.81 (d, J = 8.3 Hz, 4H), 4.09 (t, J = 4.8 Hz, 4H), 3.84 (t, J = 4.8 Hz, 4H), 3.79–3.61 (m, 8H), 2.28 (s, 6H).

1,1,1,15,15,15-Hexaphenyl-5,8,11-trioxa-2,14-dithiapentadecane 4f was prepared from triphenylmethyl mercaptan by following the general procedure for the preparation of homo-substituted M-PEGs **4a** as a yellow oil (250.0 mg, 88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.39 (m, 12H), 7.23–7.26 (m, 12H), 7.19–7.14 (m, 6H), 3.49–3.52 (m, 4H), 3.38–3.42 (m, 4H), 3.27 (t, J = 6.9 Hz, 4H), 2.42 (t, J = 6.9 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 129.7, 128.0, 126.8, 70.6, 70.2, 69.7, 66.7, 31.7. HRMS (ESI) calcd for $C_{46}H_{46}KO_3S_2^+$ ($[M + K]^+$) 749.2520, found 749.2513.

***N*,*N*′-(((Oxybis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl))bis(*N*-phenylaniline) 4g** was prepared from diphenylamine by following the general procedure for the preparation of homo-substituted M-PEGs **4a** as a cyaneous oil (184.6 mg, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.21 (m, 8H), 7.06–6.98 (m, 8H), 6.92 (t, J = 7.1 Hz, 4H), 3.93 (t, J = 7.7 Hz, 4H), 3.67 (t, J = 7.8 Hz, 4H), 3.57–3.59 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 129.4, 121.4, 121.0, 70.8, 70.8, 68.2, 51.6. HRMS (ESI) calcd for $C_{32}H_{36}N_2NaO_3^+$ ($[M + Na]^+$) 519.2618, found 519.2615.

1,1′-(((Oxybis(ethane-2,1-diyl))bis(oxy))bis(ethane-2,1-diyl))-bis(5-bromo-1*H*-indole) 4h was prepared from 5-bromine indole by following the general procedure for the preparation of homo-substituted M-PEGs **4a** as a brown oil (160.0 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 2H), 7.21 (d, J = 8.7 Hz, 2H)., 7.15 (d, J = 8.7 Hz, 2H), 7.10 (d, J = 3.0 Hz, 2H), 6.36 (d, J = 2.8 Hz, 2H), 4.15 (t, J = 5.4 Hz, 4H), 3.66 (t, J = 5.4 Hz, 4H), 3.43–3.31 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 129.7, 128.0, 126.7, 70.6, 70.6, 70.5, 70.2, 69.7, 66.7, 31.7. HRMS (ESI) calcd for $C_{24}H_{26}Br_2KN_2O_3^+$ ([M + K]$^+$) 586.9942, found 586.9938.

1,21-Diphenyl-2,5,8,11,14,17,20-heptaoxahenicosane 5a was prepared from benzyl alcohol by following the general procedure for the preparation of homo-substituted M-PEGs **4a** as a clear oil (164.6 mg, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.29 (m, 8H), 7.29–7.26 (m, 2H), 4.57 (s, 4H), 3.69–3.61 (m, 24H).

6,9,12,15,18,21,24-Heptaoxanonacosane 5b was prepared from 1-pentano by following the general procedure for the preparation of homo-substituted M-PEGs **4a** as a clear oil (121.6 mg, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77–3.52 (m, 24H), 3.45 (t, J = 6.8 Hz, 4H), 1.64–1.55 (m, 4H), 1.35–1.27 (m, 8H), 0.89 (t, J = 6.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.7, 70.7, 70.7, 70.7, 70.2, 29.4, 28.4, 22.7, 14.2. HRMS (ESI) calcd for $C_{22}H_{46}NaO_7^+$ ([M + Na]$^+$) 445.3136, found 445.3130.

1,1,1,23,23,23-Hexafluoro-3,6,9,12,15,18,21-heptaoxatrico-sane 5c was prepared from 2,2,2-trifluoroethanol by following the general procedure for the preparation of homo-substituted M-PEGs **4a** as a clear oil (146.3 mg, 82% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (q, J = 8.8 Hz, 4H), 3.82–3.77 (m, 4H), 3.72–3.62 (m, 20H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.1 (q, J = 279.6 Hz), 72.0, 70.8, 70.7, 70.7, 70.6, 68.83 (q, J = 33.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.49. HRMS (ESI) calcd for $C_{16}H_{28}F_6NaO_7^+$ ([M + Na]$^+$) 469.1631, found 469.1630.

2,26-Dimethyl-5,8,11,14,17,20,23-heptaoxaheptacosa-2,25-diene 5d was prepared from isopentenyl alcohol by following the general procedure for the preparation of homo-substituted M-PEGs **4a** as a clear oil (120.5 mg, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.38–5.33 (m, 2H), 4.01 (d, J = 6.9 Hz, 4H), 3.68–3.64 (m, 20H), 3.61–3.56 (m, 4H), 1.76–1.72 (m, 6H), 1.67 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0, 121.2, 70.8, 70.7, 69.3, 67.8, 25.9, 18.2. HRMS (ESI) calcd for $C_{22}H_{42}NaO_7^+$ ([M + Na]$^+$) 441.2823, found 441.2818.

1,17-Bis(*p*-tolyloxy)-3,6,9,12,15-pentaoxaheptadecane 5e was prepared from *p*-cresol by following the general procedure for the preparation of homo-substituted M-PEGs **4a** as a clear oil (173.8 mg, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, J = 8.4 Hz, 4H), 6.81 (d, J = 8.5 Hz, 4H), 4.12–4.06 (m, 4H), 3.86–3.81 (m, 4H), 3.74–3.70 (m, 4H), 3.69–3.62 (m, 12H), 2.27 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 130.1, 130.0, 114.5, 70.9, 70.7, 70.6, 69.9, 67.5, 20.6. HRMS (ESI) calcd for $C_{26}H_{38}NaO_7^+$ ([M + Na]$^+$) 485.2510, found 485.2506.

1,1,1,21,21,21-Hexaphenyl-5,8,11,14,17-pentaoxa-2,20-dithia-henicosane 5f was prepared from triphenylmethyl mercaptan by following the general procedure for the preparation of homo-substituted M-PEGs **4a** as a yellow oil (252.3 mg, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.39 (m, 12H), 7.30–7.25 (m, 12H), 7.23–7.17 (m, 6H), 3.63–3.53 (m, 12H), 3.48–3.42 (m, 4H), 3.27 (t, J = 6.9 Hz, 4H), 2.42 (t, J = 6.9 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 129.7, 128.0, 126.7, 70.6, 70.6, 70.5, 70.2, 69.7, 66.7, 31.7. HRMS (ESI) calcd for $C_{50}H_{54}NaO_5S_2^+$ ([M + Na]$^+$) 821.3305, found 821.3298.

***N*^{1},*N*^{1},*N*^{17},*N*^{17}-Tetraphenyl-3,6,9,12,15-pentaoxaheptadecane-1,17-diamine 5g** was prepared from diphenylamine by following the general procedure for the preparation of homo-substituted M-PEGs **4a** as a cyaneous oil (184.6 mg, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27–7.22 (m, 8H), 7.05–6.99 (m, 8H), 6.93 (t, J = 7.1 Hz, 4H), 3.93 (t, J = 6.5 Hz, 4H), 3.67 (t, J = 6.5 Hz, 4H), 3.63–3.57 (m, 16H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 129.4, 121.4, 121.0, 70.8, 70.7, 70.7, 68.2, 51.6. HRMS (ESI) calcd for $C_{36}H_{44}N_2NaO_5^+$ ([M + Na]$^+$) 607.3142, found 607.3138.

1,17-Bis(5-bromo-1*H*-indol-1-yl)-3,6,9,12,15-pentaoxahepta-decane 5h was prepared from 5-bromine indole by following the general procedure for the preparation of homo-substituted M-PEGs **4a** as a brown oil (198.2 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 2H), 7.26–7.20 (m, 4H), 7.16 (d, J = 3.1 Hz, 2H), 6.40 (d, J = 3.1 Hz, 2H), 4.24 (t, J = 5.5 Hz, 4H), 3.75 (t, J = 5.5 Hz, 4H), 3.56–3.49 (m, 16H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.9, 130.3, 129.8, 124.3, 123.4, 112.7, 111.0, 100.9, 70.8, 70.6, 70.6, 70.6, 70.2, 46.5. HRMS (ESI) calcd for $C_{28}H_{34}Br_2KN_2O_5^+$ ([M + K]$^+$) 675.0466, found 675.0469.

General procedure for the preparation of hetero-substituted M-PEGs M-PEGs 6a–6j and 7a–7j (using the synthesis of 6a as an example)

A suspension of NaH (64.0 mg, 60% in mineral oil, 1.6 mmol) in anhydrous toluene (0.5 mL) was cooled to 0 °C and a solution of trifluoroethanol (44.0 mg, 0.4 mmol) in anhydrous toluene (0.5 mL) was added slowly at 0 °C. After 30 min of stirring at 0 °C, a solution of macrocyclic sulfate **3a** (102.4 mg, 0.4 mmol) in anhydrous toluene (0.5 mL) was added slowly. The reaction mixture was stirred for 4 h at room temperature. Then a solution of benzyl alcohol (125.3 mg, 1.2 mmol) and $TBAHSO_4$ (13.6 mg, 40.0 μmol) in anhydrous toluene (1.0 mL) was added at room temperature. The reaction mixture was stirred for 12 h at 100 °C and the reaction was quenched with water. After the removal of solvent under vacuum, the residue was dissolved in EtOAc (20 mL) and washed with water (5 mL, three times). The organic layer was concentrated under vacuum and purified by flash chromatography on silica gel with EtOAc/PE (1/1) as the eluent to give **6a** as a clear oil (77.6 mg, 53% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (m, 4H), 7.30–7.25 (m, 1H), 4.56 (s, 2H), 3.89 (q, J = 8.8 Hz, 2H), 3.79–3.74 (m, 2H), 3.70–3.61 (m, 14H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 128.4, 127.71 (d, J = 15.2 Hz), 124.1 (q, J = 279.6 Hz), 73.3, 71.9, 70.7, 70.7, 70.6, 69.5, 68.8 (q, J = 33.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.40. HRMS (ESI) calcd for $C_{17}H_{25}F_3NaO_5^+$ ([M + Na]$^+$) 389.1546, found 389.1540.

17-Methyl-1-phenyl-2,5,8,11,14-pentaoxaoctadec-16-ene 6b was prepared from isopentenyl alcohol and benzyl alcohol by

following the general procedure for the preparation of hetero-substituted M-PEGs **6a** as a clear oil (83.1 mg, 59% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.30 (m, 4H), 7.29–7.26 (m, 1H), 5.35 (t, J = 6.9 Hz, 1H), 4.57 (s, 2H), 4.00 (d, J = 6.9 Hz, 2H), 3.69–3.56 (m, 16H), 1.74 (s, 3H), 1.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 137.0, 128.5, 127.9, 127.7, 121.2, 73.4, 70.8, 70.8, 70.7, 69.5, 69.3, 67.8, 25.9, 18.2. HRMS (ESI) calcd for $C_{20}H_{32}NaO_5^+$ ($[M + Na]^+$) 375.2141, found 375.2136.

17-Methyl-1,1,1-triphenyl-5,8,11,14-tetraoxa-2-thiaoctadec-16-ene 6c was prepared from triphenylmethyl mercaptan and isopentenyl alcohol by following the general procedure for the preparation of hetero-substituted M-PEGs **6a** as a yellow clear oil (99.9 mg, 48% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.38 (m, 6H), 7.29–7.25 (m, 6H), 7.23–7.18 (m, 3H), 5.34 (t, J = 6.3 Hz, 1H), 3.99 (d, J = 6.8 Hz, 2H), 3.65–3.60 (m, 6H), 3.59–3.53 (m, 4H), 3.47–3.42 (m, 2H), 3.29 (t, J = 6.9 Hz, 2H), 2.43 (t, J = 6.9 Hz, 2H), 1.73 (s, 3H), 1.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 137.0, 129.7, 128.0, 126.7, 121.2, 70.8, 70.7, 70.7, 70.5, 70.2, 69.7, 69.3, 67.7, 66.7, 31.7, 25.9, 18.2. HRMS (ESI) calcd for $C_{32}H_{40}NaO_4S^+$ ($[M + Na]^+$) 543.2540, found 543.2535.

16,16,16-Trifluoro-1,1,1-triphenyl-5,8,11,14-tetraoxa-2-thiahexadecane 6d was prepared from triphenylmethyl mercaptan and 2,2,2-trifluoroethanol by following the general procedure for the preparation of hetero-substituted M-PEGs **6a** as a yellow oil (130.3 mg, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.39 (m, 6H), 7.30–7.24 (m, 6H), 7.22–7.17 (m, 3H), 3.88 (q, J = 8.8 Hz, 2H), 3.78–3.73 (m, 2H), 3.67–3.61 (m, 6H), 3.59–3.54 (m, 2H), 3.47–3.42 (m, 2H), 3.30 (t, J = 6.9 Hz, 2H), 2.43 (t, J = 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 129.7, 128.0, 126.8, 124.1 (q, J = 279.6 Hz), 72.0, 70.8, 70.7, 70.7, 70.6 70.2, 69.7, 68.8 (q, J = 33.9 Hz), 66.7, 31.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.31. HRMS (ESI) calcd for $C_{29}H_{33}F_3NaO_4S^+$ ($[M + Na]^+$) 557.1944, found 557.1939.

1,15,15,15-Tetraphenyl-2,5,8,11-tetraoxa-14-thiapentadecane 6e was prepared from triphenyl-methyl mercaptan and benzyl alcohol by following the general procedure for the preparation of hetero-substituted M-PEGs **6a** as a yellow oil (173.5 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.39 (m, 6H), 70.37–70.31 (m, 4H), 7.30–7.24 (m, 7H), 7.23–7.17 (m, 3H), 4.55 (s, 2H), 3.68–3.55 (m, 10H), 3.47–3.42 (m, 2H), 3.33–3.27 (m, 2H), 2.42 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 138.4, 129.7, 128.5, 128.0, 127.9, 127.7, 126.8, 73.4, 70.7, 70.6, 70.3, 69.7, 69.5, 66.7, 31.7. HRMS (ESI) calcd for $C_{34}H_{38}NaO_4S^+$ ($[M + Na]^+$) 565.2383, found 565.2377.

***N*-(2-(2-(2-(2-(5-Bromo-1*H*-indol-1-yl)ethoxy)ethoxy)ethoxy)ethyl)-*N*-phenylaniline 6f** was prepared from diphenylamine and 5-bromine indole by following the general procedure for the preparation of hetero-substituted M-PEGs **6a** as a brown oil (121.1 mg, 58% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.27–7.21 (m, 6H), 7.15 (d, J = 3.1 Hz, 1H), 7.02 (d, J = 8.1 Hz, 4H), 6.93 (t, J = 7.3 Hz, 2H), 6.39 (d, J = 3.0 Hz, 1H), 4.23 (t, J = 5.5 Hz, 2H), 3.92 (t, J = 6.5 Hz, 2H), 3.75 (t, J = 5.5 Hz, 2H), 3.66 (t, J = 6.5 Hz, 2H), 3.54–3.47 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 134.9, 130.4, 129.8, 129.4, 124.3, 123.4, 121.4, 121.1, 112.7, 111.0, 100.9, 70.9, 70.8, 70.8, 70.2, 68.3, 51.7, 46.6. HRMS (ESI) calcd for $C_{28}H_{31}BrN_2NaO_3^+$ ($[M + Na]^+$) 545.1410, found 545.1406.

***N*,*N*,1,1,1-Pentaphenyl-5,8,11-trioxa-2-thiatridecan-13-amine 6g** was prepared from diphenylamine and triphenylmethyl mercaptan by following the general procedure for the preparation of hetero-substituted M-PEGs **6a** as a cyaneous oil (188.2 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 7.8 Hz, 6H), 7.28–7.19 (m, 13H), 7.01 (dd, J = 8.6, 1.0 Hz, 4H), 6.92 (dd, J = 10.5, 4.2 Hz, 2H), 3.92 (t, J = 6.5 Hz, 2H), 3.66 (t, J = 6.5 Hz, 2H), 3.57–3.51 (m, 6H), 3.43–3.41 (m, 2H), 3.30–3.26 (m, 2H), 2.42 (t, J = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 144.9, 129.7, 129.4, 128.0, 126.8, 121.4, 121.0, 70.8, 70.7, 70.6, 70.3, 69.7, 68.2, 66.7, 51.6, 31.7. HRMS (ESI) calcd for $C_{39}H_{41}NNaO_3S^+$ ($[M + Na]^+$) 626.2699, found 626.2693.

***N*,*N*,1-Triphenyl-2,5,8,11-tetraoxatridecan-13-amine 6h** was prepared from diphenylamine and benzyl alcohol by following the general procedure for the preparation of hetero-substituted M-PEGs **6a** as a brown oil (113.2 mg, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.22 (m, 9H), 7.05–7.00 (m, 4H), 6.93 (t, J = 7.3 Hz, 2H), 4.55 (s, 2H), 3.93 (t, J = 6.5 Hz, 2H), 3.71–3.58 (m, 14H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 138.4, 129.4, 128.5, 127.8, 127.7, 121.4, 121.0, 73.3, 70.8, 70.8, 70.7, 69.5, 68.2, 51.6. HRMS (ESI) calcd for $C_{27}H_{33}NNaO_4^+$ ($[M + Na]^+$) 458.2302, found 458.2296.

5-Bromo-1-(1-phenyl-2,5,8,11-tetraoxatridecan-13-yl)-1*H*-indole 6i was prepared from 5-bromine indole and benzyl alcohol by following the general procedure for the preparation of hetero-substituted M-PEGs **6a** as a brown oil (116.2 mg, 63% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 1.5 Hz, 1H), 7.35–7.23 (m, 7H), 7.17 (d, J = 3.1 Hz, 1H), 6.40 (d, J = 3.1 Hz, 1H), 4.55 (s, 2H), 4.25 (t, J = 5.5 Hz, 2H), 3.77 (t, J = 5.5 Hz, 2H), 3.65–3.51 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 129.8, 128.5, 127.8, 124.3, 123.4, 111.0, 100.9, 73.4, 70.9, 70.4, 70.2, 69.5, 46.6. HRMS (ESI) calcd for $C_{23}H_{28}BrNNaO_4^+$ ($[M + Na]^+$) 484.1094, found 484.1090.

5-Bromo-1-(1,1,1-triphenyl-5,8,11-trioxa-2-thiatridecan-13-yl)-1*H*-indole 6j was prepared from 5-bromine indole and triphenylmethyl mercaptan by following the general procedure for the preparation of hetero-substituted M-PEGs **6a** as a brown oil (146.1 mg, 58% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.47–7.39 (m, 6H), 7.29–7.15 (m, 12H), 6.37 (d, J = 2.9 Hz, 1H), 4.20 (t, J = 5.5 Hz, 2H), 3.73 (t, J = 5.5 Hz, 2H), 3.51–3.25 (m, 10H), 2.41 (t, J = 5.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 134.9, 130.3, 130.2, 129.7, 128.0, 126.7, 124.2, 123.3, 112.7, 111.0, 100.9, 70.8, 70.6, 70.5, 70.2, 70.2, 69.6, 66.7, 46.5, 31.7. HRMS (ESI) calcd for $C_{35}H_{36}BrNNaO_3S^+$ ($[M + Na]^+$) 652.1491, found 652.1489.

22,22,22-Trifluoro-1-phenyl-2,5,8,11,14,17,20-heptaoxa-docosane 7a was prepared from 2,2,2-trifluoroethanol and benzyl alcohol by following the general procedure for the preparation of hetero-substituted M-PEGs **6a** as a clear oil (136.3 mg, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32(m, 4H), 7.30–7.26 (m, 1H), 4.57 (s, 2H), 3.91 (d, J = 8.8 Hz, 2H), 3.80–3.77 (m, 2H), 3.67–3.63 (m, 22H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 128.4, 127.8, 127.7, 124.1 (q, J = 279.6 Hz), 73.3, 72.0, 70.7, 70.7, 70.6, 69.5, 68.8 (q, J = 33.9 Hz). ^{19}F NMR

(376 MHz, $CDCl_3$) δ −77.48. HRMS (ESI) calcd for $C_{21}H_{33}F_3NaO_7^+$ ($[M + Na]^+$) 477.2070, found 477.2063.

23-Methyl-1-phenyl-2,5,8,11,14,17,20-heptaoxatetracos-22-ene 7b was prepared from isopentenyl alcohol and benzyl alcohol by following the general procedure for the preparation of hetero-substituted M-PEGs **6a** as a clear oil (118.0 mg, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47–7.19 (m, 5H), 5.35 (t, J = 6.3 Hz, 1H), 4.56 (s, 2H), 4.00 (d, J = 6.9 Hz, 2H), 3.70–3.55 (m, 24H), 1.74 (s, 3H), 1.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 136.7, 128.2, 127.6, 127.5, 121.0, 73.1, 70.6, 70.5, 70.5, 70.4, 69.3, 69.0, 67.5, 25.7, 17.9. HRMS (ESI) calcd for $C_{24}H_{40}KO_7^+$ ($[M + K]^+$) 479.2406, found 479.2400.

23-Methyl-1,1,1-triphenyl-5,8,11,14,17,20-hexaoxa-2-thiatetracos-22-ene 7c was prepared from triphenylmethyl mercaptan and isopentenyl alcohol by following the general procedure for the preparation of hetero-substituted M-PEGs **6a** as a yellow oil (177.6 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.39 (m, 6H), 7.27 (t, J = 7.5 Hz, 6H), 7.20 (t, J = 7.2 Hz, 3H), 5.43–5.26 (m, 1H), 4.00 (d, J = 6.9 Hz, 2H), 3.65–3.55 (m, 18H), 3.46–3.42 (m, 2H), 3.29 (t, J = 7.0 Hz, 2H), 2.43 (t, J = 7.0 Hz, 2H), 1.74 (s, 3H), 1.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 136.9, 129.7, 127.9, 126.7, 121.2, 70.7, 70.6, 70.5, 70.2, 69.6, 69.2, 67.7, 66.6, 31.7, 25.9, 18.1. HRMS (ESI) calcd for $C_{36}H_{48}NaO_6S^+$ ($[M + Na]^+$) 631.3064, found 631.3060.

22,22,22-Trifluoro-1,1,1-triphenyl-5,8,11,14,17,20-hexaoxa-2-thiadocosane 7d was prepared from triphenylmethyl mercaptan and 2,2,2-trifluoroethanol by following the general procedure for the preparation of hetero-substituted M-PEGs **6a** as a yellow oil (214.1 mg, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.38 (m, 6H), 7.30–7.25 (m, 6H), 7.23–7.17 (m, 3H), 3.90 (q, J = 8.8 Hz, 2H), 3.79–3.76 (m, 2H), 3.67–3.59 (m, 14H), 3.58–3.54 (m, 2H), 3.47–3.42 (m, 2H), 3.29 (t, J = 6.9 Hz, 2H), 2.43 (t, J = 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 129.7, 127.9, 126.7, 124.1 (q, J = 279.6 Hz), 72.0, 70.7, 70.7, 70.6, 70.6, 70.5, 70.2, 69.6, 68.8 (q, J = 33.9 Hz), 66.6, 31.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ −77.44. HRMS (ESI) calcd for $C_{33}H_{41}F_3NaO_6S^+$ ($[M + Na]^+$) 645.2468, found 645.2465.

1,21,21,21-Tetraphenyl-2,5,8,11,14,17-hexaoxa-20-thiahenicosane 7e was prepared from triphenylmethyl mercaptan and benzyl alcohol by following the general procedure for the preparation of hetero-substituted M-PEGs **6a** as a yellow oil (209.3 mg, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.36 (m, 6H), 7.35–7.30 (m, 4H), 7.30–7.24 (m, 7H), 7.23–7.17 (m, 3H), 4.56 (s, 2H), 3.68–3.60 (m, 16H), 3.55 (d, J = 3.5 Hz, 2H), 3.44 (s, 2H), 3.29 (t, J = 6.8 Hz, 2H), 2.43 (t, J = 6.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 138.3, 129.7, 128.4, 127.9, 127.8, 127.7, 126.7, 73.3, 70.7, 70.6, 70.5, 70.2, 69.6, 69.5, 66.6, 31.7. HRMS (ESI) calcd for $C_{38}H_{46}NaO_6S^+$ ($[M + Na]^+$) 653.2907, found 653.2901.

17-(5-Bromo-1*H*-indol-1-yl)-*N*,*N*-diphenyl-3,6,9,12,15-pentaoxaheptadecan-1-amine 7f was prepared from diphenylamine and 5-bromine indole by following the general procedure for the preparation of hetero-substituted M-PEGs **6a** as a brown oil (178.2 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 1.4 Hz, 1H), 7.27–7.21 (m, 6H), 7.16 (d, J = 3.1 Hz, 1H), 7.06–6.99 (m, 4H), 6.93 (t, J = 7.3 Hz, 2H), 6.40 (d, J = 3.0 Hz, 1H), 4.25 (t, J = 5.5 Hz, 2H), 3.93 (t, J = 6.5 Hz, 2H), 3.76 (t, J = 5.5 Hz, 2H), 3.67 (t, J = 6.5 Hz, 2H), 3.62–3.49 (m, 16H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 134.9, 130.3, 129.8, 129.4, 124.3, 123.4, 121.4, 121.0, 112.7, 111.0, 100.9, 70.9, 70.8, 70.7, 70.7, 70.7, 70.6, 70.2, 68.2, 51.6, 46.6. HRMS (ESI) calcd for $C_{32}H_{39}BrN_2NaO_5^+$ ($[M + Na]^+$) 633.1935, found 633.1930.

***N*,*N*,1,1,1-Pentaphenyl-5,8,11,14,17-pentaoxa-2-thianona-decan-19-amine 7g** was prepared from diphenylamine and triphenylmethyl mercaptan by following the general procedure for the preparation of hetero-substituted M-PEGs **6a** as a cyaneous oil (152.1 mg, 55% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.38 (m, 6H), 7.28–7.16 (m, 14H), 7.00–7.04 (m, 3H), 6.94–6.89 (m, 2H), 3.93 (t, J = 6.5 Hz, 2H), 3.68 (d, J = 6.5 Hz, 2H), 3.61–3.54 (m, 14H), 3.45–3.40 (m, 2H), 3.28 (t, J = 6.9 Hz, 2H), 2.42 (t, J = 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 144.9, 129.7, 129.3, 127.9, 126.7, 121.3, 121.0, 70.7, 70.7, 70.6, 70.6, 70.5, 70.2, 69.6, 68.2, 66.6, 51.6, 31.7. HRMS (ESI) calcd for $C_{43}H_{49}NNaO_5S^+$ ($[M + Na]^+$) 714.3224, found 714.3219.

***N*,*N*,1-Triphenyl-2,5,8,11,14,17-hexaoxanonadecan-19-amine 7h** was prepared from diphenylamine and benzyl alcohol by following the general procedure for the preparation of hetero-substituted M-PEGs **6a** as a brown oil (110.9 mg, 53% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.30 (m, 4H), 7.29–7.21 (m, 5H), 7.08–6.97 (m, 4H), 6.93 (t, J = 7.1 Hz, 2H), 4.56 (s, 2H), 3.93 (t, J = 6.5 Hz, 2H), 3.73–3.53 (m, 22H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 138.3, 129.3, 128.4, 127.8, 127.7, 121.4, 121.0, 73.3, 70.8, 70.7, 70.7, 70.6, 69.5, 68.2, 51.6. HRMS (ESI) calcd for $C_{31}H_{41}NNaO_6^+$ ($[M + Na]^+$) 546.2826, found 546.2822.

5-Bromo-1-(1-phenyl-2,5,8,11,14,17-hexaoxanonadecan-19-yl)-1*H*-indole 7i was prepared from 5-bromine indole and benzyl alcohol by following the general procedure for the preparation of hetero-substituted M-PEGs **6a** as a brown oil (188.9 mg, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 1.1 Hz, 1H), 7.35–7.23 (m, 7H), 7.17 (d, J = 3.1 Hz, 1H), 6.41 (d, J = 3.0 Hz, 1H), 4.56 (s, 2H), 4.26 (t, J = 5.5 Hz, 2H), 3.77 (t, J = 5.5 Hz, 2H), 3.68–3.61 (m, 12H), 3.58–3.50 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 134.9, 130.3, 129.8, 128.4, 127.8, 127.7, 124.2, 123.3, 112.7, 111.0, 100.9, 73.3, 70.8, 70.7, 70.6, 70.6, 70.6, 70.2, 69.5, 46.5. HRMS (ESI) calcd for $C_{27}H_{36}BrNNaO_6^+$ ($[M + Na]^+$) 572.1618, found 572.1614.

5-Bromo-1-(1,1,1-triphenyl-5,8,11,14,17-pentaoxa-2-thianonadecan-19-yl)-1H-indole 7j was prepared from 5-bromine indole and triphenylmethyl mercaptan by following the general procedure for the preparation of hetero-substituted M-PEGs **6a** as a brown oil (180.7 mg, 63% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 1.3 Hz, 1H), 7.43–7.38 (m, 6H), 7.30–7.18 (m, 12H), 6.41 (d, J = 3.1 Hz, 1H), 4.26 (t, J = 5.5 Hz, 2H), 3.77 (t, J = 5.5 Hz, 2H), 3.60–3.50 (m, 14H), 3.45–3.42 (m, 2H), 3.29 (t, J = 6.9 Hz, 2H), 2.42 (t, J = 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 134.9, 130.3, 129.8, 129.7, 128.0, 126.7, 124.3, 123.4, 112.7, 111.0, 70.8, 70.7, 70.6, 70.6, 70.5, 70.2, 69.7, 66.7, 46.6, 31.7. HRMS (ESI) calcd for $C_{39}H_{44}BrNNaO_5S^+$ ($[M + Na]^+$) 740.2016, found 740.2012.

1,27-Diphenyl-2,5,8,11,14,17,20,23,26-nonaoxaheptacosane 8a was prepared from benzyl alcohol by following the general pro-

cedure for the preparation of homo-substituted M-PEGs **4a** as a clear oil (187.5 mg, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.29 (m, 8H), 7.29–7.25 (m, 2H), 4.56 (s, 4H), 3.70–3.59 (m, 32H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 128.4, 127.8, 127.7, 73.3, 70.7, 70.7, 70.6, 69.5. HRMS (ESI) calcd for $C_{30}H_{46}NaO_9^+$ ($[M + Na]^+$) 573.3034, found 573.3036.

1,27,27,27-Tetraphenyl-2,5,8,11,14,17,20,23-octaoxa-26-thiaheptacosane 8b was prepared from benzyl alcohol and triphenylmethyl mercaptan by following the general procedure for the preparation of hetero-substituted M-PEGs **6a** as a brown oil (192.3 mg, 67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 7.5 Hz, 6H), 7.36–7.30 (m, 4H), 7.29–7.24 (m, 7H), 7.22–7.17 (m, 3H), 4.56 (s, 2H), 3.68–3.59 (m, 24H), 3.57–3.53 (m, 2H), 3.46–3.42 (m, 2H), 3.29 (t, J = 7.0 Hz, 2H), 2.42 (t, J = 6.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.9, 138.4, 129.7, 128.4, 128.0, 127.8, 127.7, 126.7, 73.3, 70.7, 70.7, 70.6, 70.5, 70.2, 69.7, 69.5, 66.7, 31.7. HRMS (ESI) calcd for $C_{42}H_{54}NaO_8S^+$ ($[M + Na]^+$) 741.3432, found 741.3448.

Conflicts of interest

The authors declare no conflicts of interest.

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