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Synthesis and Evaluation of Bis-Thiazolium Salts as Potential Antimalarial Drugs

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An innovative therapeutic approach based on the use of dicationic derivatives was previously designed to inhibit the biosynthesis of phosphatidylcholine in *Plasmodium* spp. Among these, bis-thiazolium salts were shown to block proliferation of the malaria parasite at concentrations in the low nanomolar range. However, due to unsuitable molecular properties such as the presence of the two polar heads and flexibility in the linker, these compounds have low oral bioavailability. To characterize the structural requirements of the linker that lead to more rigid analogues with fewer rotatable bonds but which retain antimalarial activity, a new series of compounds incorporating an aryl moiety and eventually oxygen atoms were prepared, and their biological activity was evaluated. Structure–activity relationships suggest that the optimal linker construct is an aromatic group with two *n*-butyl chains branched at the *para* position; two new leads (compounds **39** and **40**) were selected for further development.

Introduction

Malaria is one of the most prevalent diseases throughout the tropical and subtropical regions of the world. Approximately 40% of the world's population is at risk of malaria, which causes 300 million acute illnesses every year in developing countries. Malaria is caused by protozoan parasites of the *Plasmodium* genus. *P. falciparum* is the dominant species and is responsible for nearly one million deaths annually.[1] Owing to the absence of vaccine and of a widely accessible vector control strategy, the most efficient way to control malaria remains chemotherapy.[2,3] The resistance of *P. falciparum* to most antimalarial drugs is a major obstacle to the eradication of this disease. This is also of considerable concern, in light of a recent report on decreased sensitivity to artemisinin drugs in Southeast Asia.[4] Thus, new chemotherapeutic approaches based on innovative mechanisms of action are needed.

During the last decade, an original approach that targets the particular lipid characteristics of the parasite has been developed.[5–7] During its intra-erythrocytic development, the parasite requires a considerable quantity of phospholipids synthesized from various precursors such as serine, ethanolamine, choline, and fatty acids that are scavenged from the human host. With the most abundant lipid in erythrocytes being phosphatidylcholine (PC), its content increases sixfold after infection.[8–10] Therefore, PC biosynthesis has been viewed as an ideal target for the development of new antimalarials.[11] The essential role of PC for parasite survival has been demonstrated through the use of choline analogues, rationally designed and optimized for their ability to inhibit PC biosynthesis in *Plasmodium*.

In this context, three generations of compounds were synthesized and evaluated for their biological and pharmacological activities. The first derivatives were bis-ammonium salts incorporating a long alkyl chain ($\geq$12 methylene units).[5,6,12] The lead compound **G25** [1,16-hexadecamethylene-bis(*N*-methylpyrrolidinium) dibromide] efficiently inhibits drug-resistant malaria in vitro, with IC_{50} values of 0.6–1.2 nM,[13] and eliminates *Plasmodium* infection without recrudescence in rodent[14] and primate[15] models at very low doses. To overcome the low oral absorption of these permanently charged derivatives, bioisosteric analogues such as bis-amidines and bis-thiazolium salts were envisaged. Among the bis-thiazolium salts, **T3** and **T4** (Figure 1) exhibited promising activities with in vitro IC_{50} values

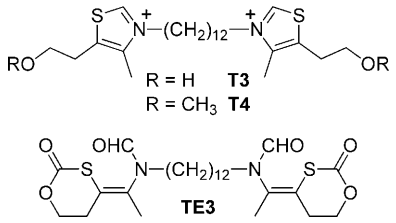

Figure 1. T3 and **T4**, lead compounds of the third generation, and the neutral prodrug **TE3**.

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of 2.2 and 0.65 nM against *P. falciparum*, and in vivo ED_{90} values of 0.2 and 0.14 mg kg^{-1} in mice infected by *P. vinckei* (intraperitoneal administration). Thus, **T3**/SAR97276 was selected as a clinical candidate and is currently in development by Sanofi–Aventis (ongoing phase II clinical trials) for the treatment of severe malaria by the parenteral route.

As observed for the first-generation compounds, the bis-thiazolium salts exhibited low oral bioavailability (< 5%). However, such derivatives could be administered as neutral precursors, which are expected to revert back in vivo (after enzymatic conversion) to the parent drugs. Thus, a few prodrug approaches were developed on the basis of **T3**, and proof-of-principle demonstrations were carried out in murine models.[16] These compounds also led to a complete cure of *P. cynomolgi* infection, attesting to their suitable pharmacokinetic properties.[16] For example, the absolute oral bioavailability of the cyclic thioester prodrug **TE3** (Figure 1) reached 15% in rats.[17] Unfortunately, this remains too weak to envisage further clinical development. Examination of some molecular parameters[18–20] (such as molecular weight, flexibility as determined by the number of rotatable bounds, and lipophilicity) of the prodrugs of **T3** revealed that they are unsuitable for oral administration. To modulate molecular flexibility, a parameter common to both the drug and its corresponding prodrug, we envisaged a new series of **T3** analogues in which the linker (dodecyl chain) is rigidified through the introduction of an aromatic moiety (Figure 2). The synthesis and antimalarial activities of such compounds are described below.

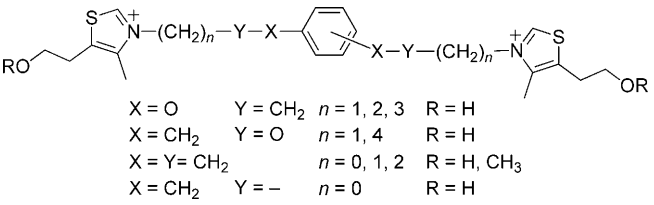
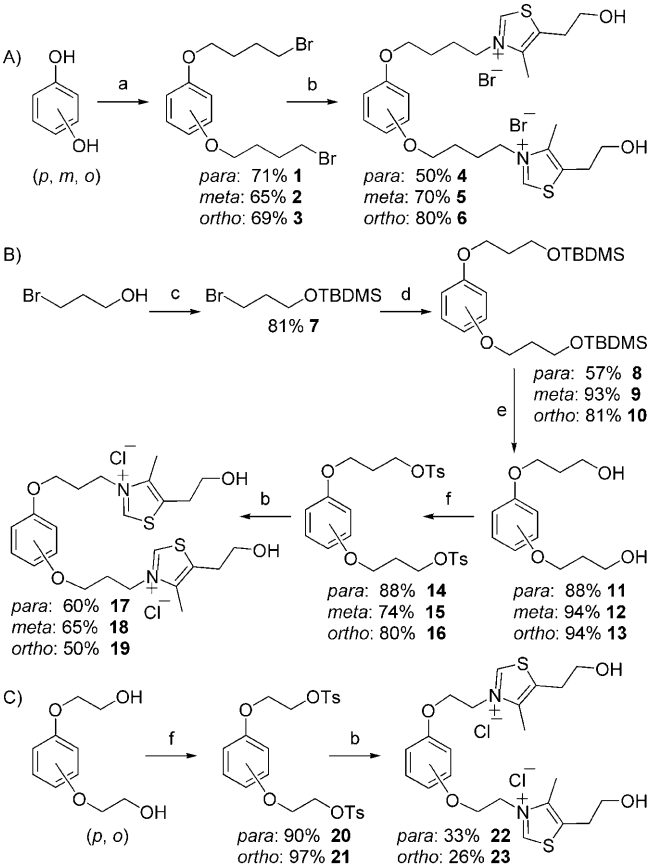


Figure 2. General structures of targeted derivatives.



Scheme 1. Reagents and conditions: a) 1,4-dibromobutane, 4 N NaOH, H_2O, Bu_4NHSO_4 or K_2CO_3, DMF, RT, 14 h; b) 4-methyl-5-(2-hydroxyethyl)thiazole, CH_3CN, MW (400 W), 100 °C, 5 h; c) TBDMSCl, imidazole, DMF; d) hydroquinone or resorcinol or catechol, K_2CO_3, DMF, 100 °C, 48 h; e) HCl (1.25 M in MeOH); f) TsCl, pyridine, CH_2Cl_2.

Results and Discussion

Chemistry

3,3′-{4,4′-[Phenylenebis(oxy)]bis(butane-4,1-diyl)}bis-thiazolium salts

Bis-thiazolium salts **4**, **5**, and **6** were prepared in two steps from commercially available hydroquinone, resorcinol, and catechol, respectively (Scheme 1 A). The 1,4- and 1,3-benzenediols were coupled to 1,4-dibromobutane (in excess) in the presence of tetra(*n*-butyl)ammonium hydrogen sulfate (Bu_4NHSO_4) in a concentrated aqueous solution of sodium hydroxide, whereas 1,2-benzenediol was reacted with potassium carbonate in *N*,*N*-dimethylformamide (DMF). The corresponding bromoalkyl linkers **1**, **2**, and **3** were obtained in 71, 65, and 69% yields, respectively. Alkylation of the nitrogen atom of 4-methyl-5-(2-hydroxyethyl)thiazole with the bromoalkyl linker was then performed in CH_3CN by microwave (MW) irradiation to significantly decrease reaction time; this afforded the thiazolium bromide salts **4**, **5**, and **6**. The conversion rate was quantitative, but several purification steps were required to isolate the target compounds with suitable purity for biological testing (> 98% as determined by NMR and HPLC); consequently, the final yields ranged between 50 and 80%.

3,3′-{3,3′-[Phenylenebis(oxy)]bis(propane-3,1-diyl)}bis-thiazolium salts

Bis-thiazolium salts **17**, **18**, and **19** were obtained in four steps from the same starting materials as above (Scheme 1 B). In contrast to the synthetic pathway used for derivatives **4**–**6**, the 1,3-bis(3-bromopropoxy)benzene intermediates could not be isolated with acceptable yields owing to a side reaction (elimination) that afforded the mono- and bis-allyloxybenzene derivatives. Thus, synthesis of 3,3′-[phenylenebis(oxy)]dipropan-1-ols **11**, **12**, and **13** was performed using the following steps: 1) alkylation of hydroquinone, resorcinol, and catechol with 3-bromopropoxy-*tert*-butyldimethylsilane **7** in the presence of potas-

sium carbonate in DMF at 100 °C (compounds **8**, **9**, and **10** were obtained in 41, 58, and 80% yields, respectively); 2) TBDMS removal under acidic conditions. Finally, toluenesulfonylation lead to the intermediates **14**, **15**, and **16** (in 88, 74, and 80% respective overall yields), and the desired bis-thiazolium salts were obtained using the same procedure as described above. The crude material was percolated through an ion-exchange resin (Dowex Cl^- form) before purification to afford the corresponding chloride salts **17**, **18**, and **19**.

2,2′-[Phenylenebis(oxy)]bis(ethane-2,1-diyl)bis-thiazolium salts

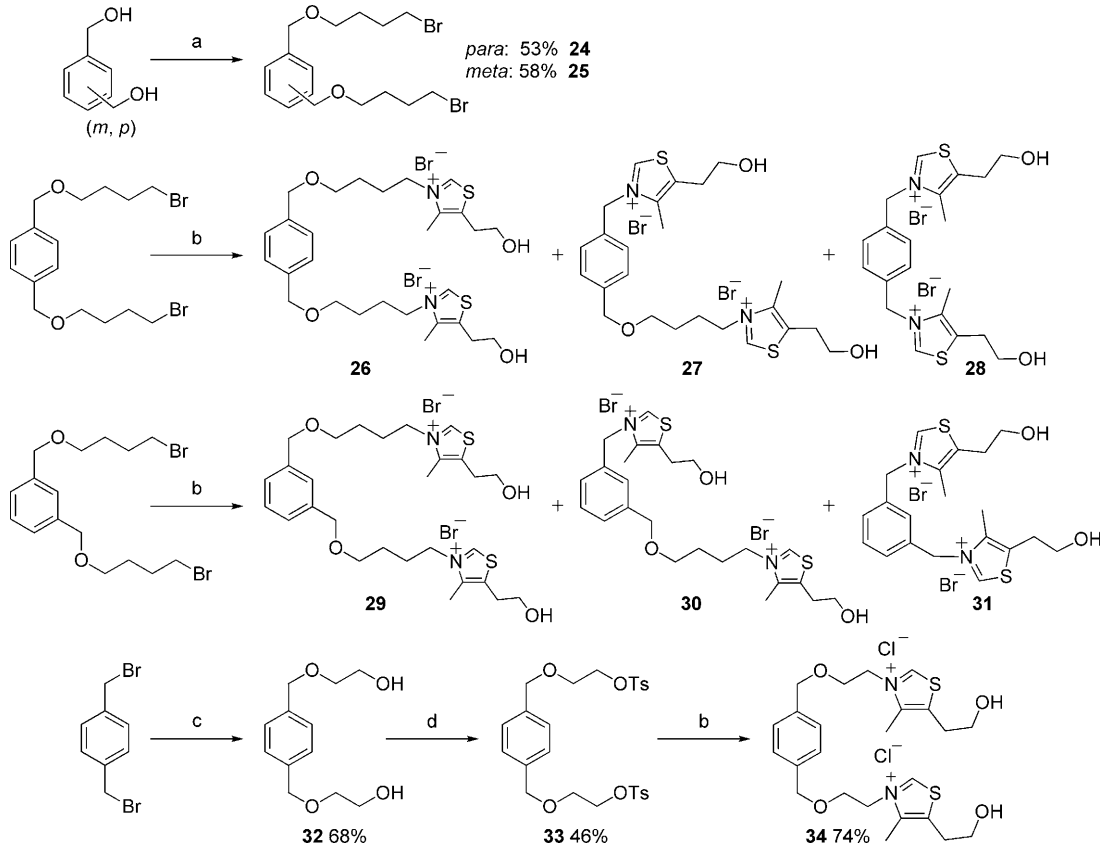
Compounds **22** and **23** were prepared in two steps (30 and 25% respective overall yields) from commercially available alcohols 1,4- and 1,2-bis(2-hydroxyethoxy)benzene using the same procedure as for compounds **17** and **19** (Scheme 1C).

3,3′-{4,4′-[Phenylenebis(methylene)]bis(oxy)bis(butane-4,1-diyl)}bis-thiazolium salts

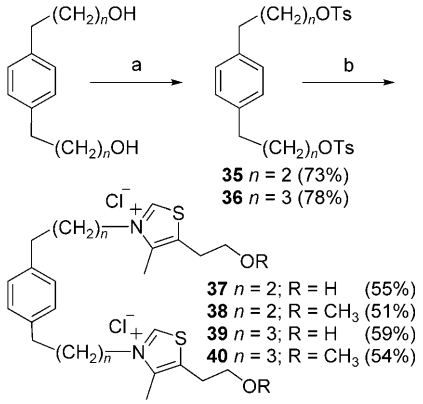
Attempts to obtain derivatives **26** and **29** from 1,4- and 1,2-benzenedimethanols were somewhat puzzling (Scheme 2). Briefly, excess 1,4-dibromobutane was first reacted with the diols in the presence of Bu_4NHSO_4 in an aqueous solution of concentrated sodium hydroxide; this afforded bis[(4-bromobutoxy)methyl]benzenes **24** and **25** in 53 and 58% yields, respectively. Treatment of these dibromo intermediates with 4-methyl-5-(2-hydroxyethyl)thiazole lead us to isolate **29** in low yield as well as various dicationic derivatives **27**, **28**, **30**, and **31**, which resulted from the loss of one or both *n*-butoxy chains. Despite modification of the reaction conditions (temperature, MW or thermal heating, and the nature of the leaving group: iodo, trifluoromethanesulfonate, toluenesulfonate), these by-products were still observed. Nevertheless, each compound was isolated from the reaction mixture by using RP-18 liquid chromatography.

3,3′-[3,3′-(1,4-Phenylene)bis(propane-3,1-diyl)]bis-thiazolium and 3,3′-[4,4′-(1,4-phenylene)bis(butane-4,1-diyl)]bis-thiazolium salts

Compounds **37**–**40** were synthesized in two steps using the same route as described for derivatives **22** and **23**. The starting materials 3,3′-(1,4-phenylene)dipropan-1-ol and 4,4′-(1,4-phenylene)dibutan-1-ol were prepared beforehand according to published procedures.[7] Thus, corresponding bis-thiazolium salts **37**, **38**, **39**, and **40** were isolated in 51–59% yields (Scheme 3).



Scheme 2. Reagents and conditions: a) 1,4-dibromobutane, 4 N NaOH, H_2O, Bu_4NHSO_4, RT, 48 h; b) 4-methyl-5-(2-hydroxyethyl)thiazole, CH_3CN, MW (400 W), 150 °C, 1 h; c) ethylene glycol, NaH, THF; d) TsCl, NEt_3, CH_2Cl_2.



Scheme 3. Reagents and conditions: a) TsCl, pyridine, CH_2Cl_2; b) 4-methyl-5-(2-hydroxyethyl)thiazole or 4-methyl-5-(2-methoxyethyl)thiazole, CH_3CN, MW (400 W), 100 °C, 5 h.

Antimalarial activity

In vitro biological evaluation

All **T3** analogues incorporating phenyl, benzyl moieties, and eventually oxygen atoms in place of the original dodecyl chain between the two cationic head groups were evaluated in cell culture experiments (Table 1). The in vitro antimalarial activities were monitored by adding the compounds to a *P. falciparum*-infected erythrocyte suspension for a complete 48 h parasite cycle before assessing the parasite viability. First, the influence of linker length including one aromatic ring and pending chains from one to six methylene units in length was studied. As expected, lengthening of the linker led to increased antimalarial activity. For compounds **4**, **17**, **22**, and **28**, the arms in the *para* position were 5, 4, 3, and 1 methylene units long, respectively, and the activity ranged from 66 nM (compound **4**) to 800 nM (compound **28**). Likewise, compound **39** (20.5 nM) is 3.7-fold more active than **37** (77.5 nM), which has a shorter linker by two methylene units. A similar effect was observed when the two chains were branched in the *meta* (compounds **5**, **18**, **23**, and **29**) or *ortho* (compounds **6**, **19**, and **31**) positions. For compounds with the same chain length but anchored at different positions on the aromatic ring, the *para* and *meta* compounds exhibited similar activity, whereas the *ortho* orientation led to a decrease in activity. Thus, compounds **4** and **5** were 1.6-fold more potent than **6** (110 nM), with IC_{50} values of 66 and 61 nM, respectively. This finding may be associated with the overall geometry of the molecule, with more strained compounds having lower affinity for the pharmacological target. Furthermore, the presence of oxygen atoms was detrimental to in vitro activity; compounds **17** (215 nM) and **34** (905 nM) were far less potent than **39**. Likewise, compound **22** was 15-fold less active than **37**. Asymmetric compounds **27** and **30**, the linkers of which are one methylene group shorter than those of compound **17**, exhibited similar activity.

Table 1. Selected data from in vitro and in vivo antimalarial evaluations.

Compd	IC_{50} [nM][a]	ED_{50} i.p.[b]		ED_{90} p.o.[b]	
		[mg kg^{-1}]	[μmol kg^{-1}]	[mg kg^{-1}]	[μmol kg^{-1}]
T3	2.25	0.2[c]	0.28	25	35
4	66	> 1[d]	1.5	60	90
5	61	> 5[c]	7.5	> 90	135
6	110	> 5[c]	7.5	> 90	135
17	215	ND		ND	
18	180	> 1[d]	1.7	> 90	152
19	425	> 5[c]	8.4	> 90	152
29	31.5	> 5[c]	7.2	> 90	130
30	170	> 1[d]	1.6	> 90	145
37	77.5	> 0.5[d]	0.97	> 120	232
38	36.5	> 1[d]	1.8	ND	
39	20.5	2.2[c]	4.0	53	97
40	9	0.13[c]	0.23	12	21

[a] *P. falciparum*: data represent the mean of at least two independent experiments carried out in duplicate. [b] *P. vinckei* antimalarial activities (effective dose, ED_{50} or ED_{90} values) were determined after intraperitoneal (i.p.) or oral (p.o.) administration of the compounds to infected mice once daily for four days; ND = not determined. [c] No sign of clinical toxicity was observed after i.p. or p.o. administration at the doses used. [d] Treatment at higher doses was stopped due to the appearance of initial clinical signs of toxicity.

In vivo biological evaluation

Among the thiazolium salts studied in vitro, 13 derivatives were also evaluated in vivo against *P. vinckei* in mice (Table 1). All the compounds containing oxygen atoms within the linker showed significant clinical toxicity in mice which prevents their use at higher doses; such toxicity may therefore conceal their antimalarial activities. We observed a favorable pharmacological profile (i.p. $ED_{50} < 5$ mg kg^{-1} and p.o. $ED_{90} < 50$ mg kg^{-1}) for compounds **39** and **40**, which are also the derivatives that exhibit the best in vitro activity. Both compounds, which have a phenyl group and two *n*-butyl chains branched at the *para* position, were as potent as the lead compound **T3** and were able to clear the malarial infection in mice at very low doses with respective ED_{50} values of 2.2 and 0.13 mg kg^{-1} after i.p. administration and ED_{90} values of 53 and 12 mg kg^{-1} after p.o. administration.

Conclusions

In addition to the physicochemical parameters described by Lipinski et al.,[18] other properties[19,20] have been related to oral bioavailability. Among them, decreased molecular flexibility (which may be related to the number of rotatable bonds) has been reported as an important predictor for good oral bioavailability, independent of molecular weight.[20] Thus, a new series of bis-thiazolium salts were envisaged to optimize the molecular properties of the corresponding parent drug **T3**, and we initially focused on the study of analogues containing an aromatic ring. These derivatives were efficiently prepared from dibromo or ditoluenesulfonyl linker intermediates using microwave irradiation and were evaluated in vitro and in vivo for their antimalarial properties. The structure–activity relationships suggest that the optimal linker construct is an aromatic moiety branched with two *n*-butyl chains at the *para* position. Two promising compounds, **39** and **40**, incorporating modified

linkers were identified and were able to cure malarial infection at very low doses in mice. Synthesis of the corresponding neutral precursors is currently in progress, and will allow evaluation, at the prodrug level, of the influence of decreased molecular flexibility on oral bioavailability.

Experimental Section

General procedure A for the preparation of bis(4-bromobutoxy)methylbenzene and bromobutoxybenzene compounds 1–3

Benzenedimethanol or benzenediol and Bu_4NHSO_4 (0.2 equiv) were dissolved in aqueous 4 N NaOH (5 equiv), and 1,4-dibromobutane (10 equiv) was added. The mixture was stirred for 48 h at 80 °C. The aqueous layer was extracted with $CHCl_3$. The organic layer was washed twice with H_2O and dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by column chromatography (cyclohexane/EtOAc 9.5:0.5→9:1) to afford bis[(4-bromobutoxy)methyl]benzene or bromobutoxybenzene as a white powder.

1,4-bis(4-bromobutoxy)benzene (1). According to procedure A, the title compound (2.5 g, 71 %) was obtained from hydroquinone (1.02 g, 9.08 mmol), NaOH (1.82 g, 46.3 mmol), 1,4-dibromobutane (10.7 mL, 90.8 mmol), Bu_4NHSO_4 (0.61 mg, 1.85 mmol), and H_2O (11 mL); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.75–2.10 (m, 8H, $4CH_2$), 3.41 (t, J = 6.5 Hz, 4H, CH_2Br), 3.88 (t, J = 6 Hz, 4H, CH_2OPh), 6.74 ppm (s, 4H, CH_{ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.9 (CH_2CH_2OPh), 28.0 (CH_2CH_2Br), 33.4 (CH_2Br), 67.5 (CH_2OPh), 115.4 (CH_{ar}), 153.1 ppm (Cq_{ar}); HPLC (conditions A): 3.01 min; MS (FAB+, NBA): 378 $[M+H]^+$.

General procedure B for the preparation of bis-thiazolium salts 4–6, 17–19, 22, 23, 27–31, and 37–40

In a sealed 5 mL pressure vial, the appropriate dibromo or ditoluenesulfonyl linker was added to a solution of 4-methyl-5-(2-hydroxyethyl)thiazole (3 equiv) in CH_3CN. After MW irradiation (400 W), H_2O was added, and the mixture was extracted with Et_2O. The aqueous layer was concentrated under reduced pressure. When required, the toluenesulfonate counter-ions were exchanged with chloride by adding to the aqueous phase a Dowex resin (1×8–400, Cl^- form). After stirring for 1 h, the resin was filtered off, and the filtrate was evaporated to dryness. The residue was dissolved in a minimal amount of *i*PrOH, and the product was precipitated from Et_2O.

3,3′-{4,4′-[1,4-phenylenebis(oxy)]bis(butane-4,1-diyl)}bis[5-(2-hydroxyethyl)-4-methylthiazol-3-ium] bromide (4). According to procedure B, the title compound was obtained from 1,4-bis(4-bromobutoxy)benzene **1** (420 mg, 1.10 mmol), 4-methyl-5-(2-hydroxyethyl)thiazole (0.53 mL, 4.42 mmol), and CH_3CN (0.44 mL) after 5.5 h under MW irradiation at 100 °C. The compound was purified by precipitation and then RP-18 chromatography (gradient: H_2O→H_2O/MeOH 9:1) to afford a yellow hygroscopic powder (491 mg, 67 %); ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 1.70–2.05 (m, 8H, $4CH_2$), 2.48 (s, 6H, CH_3), 3.03 (t, J = 5.4 Hz, 4H, $2CH_2CH_2OH$), 3.65 (q, J = 5.3 Hz, 4H, $2CH_2CH_2OH$), 3.95 (t, J = 6.0 Hz, 4H, $2CH_2OPh$), 4.55 (t, J = 7.4 Hz, 4H, $2CH_2N^+$), 5.21 (t, J = 5 Hz, 2H, 2OH), 6.86 (s, 4H, CH_{ar}), 10.09 ppm (s, 2H, $CH_{thiazole}$); ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 11.2 ($2CH_3$), 25.4, 25.8 ($2CH_2$), 29.4 ($2CH_2CH_2OH$), 52.4 ($2CH_2N^+$), 59.6 ($2CH_2OH$), 67.1 ($2CH_2OPh$), 115.3 ($4CH_{ar}$), 135.5 ($2C_qS$), 141.5 ($2C_qN^+$), 152.5 ($2C_{qar}$), 156.2 ppm ($2CH_{thiazole}$); HPLC (conditions B): 4.88 min; MS (ESI+): 253.2 $[(M-2Br)/2]^{2+}$, 585.3 $[M-Br]^+$, 619.3 $[M-2Br+TFA]^+$; HRMS (TOF-ESI+) calcd for $C_{26}H_{38}BrN_2O_4S_2$ $[M-Br]^+$: 585.1456, found: 585.1447.

3-Bromopropoxy-*tert*-butyldimethylsilane (7). The title compound was prepared, according to the procedure described by Choi et al.,[21] from 3-bromopropan-1-ol (1.1 g, 7.19 mmol), *tert*-butyldimethylsilyl chloride (1.19 g, 7.19 mmol), imidazole (539 mg, 7.19 mmol), and DMF (6 mL); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0 (s, 6H, $2CH_3$), 0.83 (s, 9H, $3CH_3$), 1.96 (q, J = 6.1 and 4.2 Hz, 2H, CH_2), 3.45 (t, J = 6.4 Hz, CH_2Br), 3.66 ppm (t, J = 4 Hz, CH_2O); ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.4 ($2SiCH_3$), 18.0 (Cq), 26.1 (Si*t*Bu), 30.6 (CH_2Br), 35.4 (CH_2), 60.4 ppm (CH_2O).

General procedure C for the preparation of bis[3-(tert-butyldimethylsilyloxy)propoxy]benzenes 8–10

Benzenediol and K_2CO_3 (2.5 equiv) were suspended in anhydrous DMF (2.2 mL mmol^{-1}), and the mixture was stirred at room temperature. After 30 min, a solution of 3-bromopropoxy-*tert*-butyldimethylsilane **7** (2.5 equiv) in DMF (0.2 mL mmol^{-1}) was added dropwise, and the reaction mixture was heated at 100 °C for 48 h. The solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc and washed successively with H_2O, brine, and finally dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by column chromatography (PE/Et_2O 9.6:0.4) to afford the expected bis[3-(*tert*-butyldimethylsilyloxy)propoxy]benzene as a colorless liquid.

1,4-bis[3-(*tert*-butyldimethylsilyloxy)propoxy]benzene (8). According to procedure C, the title compound (0.818 g, 41 %) was obtained from hydroquinone (0.348 g, 3.15 mmol), K_2CO_3 (1.04 g, 7.84 mmol), and 3-bromopropoxy-*tert*-butyldimethylsilane **7** (2 g, 7.84 mmol); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0 (s, 6H, $2CH_3$), 0.84 (s, 9H, $3CH_3$), 1.91 (quintet, J = 6.13 Hz, 4H, CH_2), 3.75 (t, J = 6.05 Hz, 4H, CH_2OSi), 3.96 (t, J = 6.23 Hz, 4H, CH_2OPh), 6.78 ppm (s, 4H, CH_{ar}); ^{13}C NMR (75 MHz, $CDCl_3$): −5.4 ($4CH_3$), 18.3 ($2C_qSi$), 25.9 ($6CH_3$), 32.5 ($2CH_2$), 59.6 ($2CH_2OSi$), 65.1 ($2CH_2OPh$), 115.3 ($2CH_{ar}$), 153.1 ppm ($2C_{qar}$); HPLC (conditions B): 17.03 min; MS (ESI+): 455.1 $[M+H]^+$.

General procedure D for the preparation of 3,3′-[1,4-phenylenebis(oxy)]dipropan-1-ols 11–13

A methanolic solution of HCl (1.25 M, 0.35 mL mmol^{-1}) was added to an ice-cold solution of bis[3-(*tert*-butyldimethylsilyloxy)propoxy]-benzene in anhydrous MeOH (2 mL mmol^{-1}). The mixture was stirred for 1 h at room temperature, and then the solvent was evaporated under reduced pressure. The residue was dissolved in EtOAc and washed successively with H_2O, brine, and finally dried over Na_2SO_4. The solvent was removed in vacuo to afford the expected 3,3′-[1,4-phenylenebis(oxy)]dipropan-1-ol as a white powder. The compound was used directly without further purification.

3,3′-[1,4-phenylenebis(oxy)]dipropan-1-ol (11). According to procedure D, the title compound (0.269 g, 88 %) was obtained from 1,4-bis[3-(*tert*-butyldimethylsilyloxy)propoxy]benzene **8** (0.763 g, 1.19 mmol), MeOH (3 mL), and a methanolic solution of HCl (0.5 mL); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.85 (quintet, J = 4H, CH_2), 3.55 (q, 4H, CH_2OH), 3.98 (t, J = Hz, 4H, CH_2OPh), 4.55 (t, J = Hz, 2H, OH), 6.85 ppm (s, 4H, CH_{ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.44 (CH_2), 62.6 (CH_2OH), 70.1 (CH_2OPh), 120.4 (CH), 157.8 ppm (Cq_{ar}); HPLC (conditions A): 1.58 min; MS (ESI+): 227.2 $[M+H]^+$.

General procedure E for the preparation of 3,3′-[phenylenebis-(oxy)]bis(propane-3,1-diyl)bis(4-methylbenzenesulfonates) 14–16, 20, 21, 33, 35, and 36

Anhydrous pyridine or Et_3N (4–6 equiv) and toluene-4-sulfonyl chloride (3 equiv) were added to an ice-cold solution of 3,3′-[phenylenebis(oxy)]dipropan-1-ol in anhydrous CH_2Cl_2 (4 mL mmol^{-1}). In a few cases 4-(dimethylamino)pyridine (0.2 equiv) was also added. The mixture was stirred for 16 h at room temperature and then diluted with CH_2Cl_2. The organic layer was washed successively with H_2O, brine, and finally dried over Na_2SO_4. The solvent was removed in vacuo, and the residue was purified by column chromatography (cyclohexane/EtOAc 8:2) to afford the expected 3,3′-[phenylenebis(oxy)]bis(propane-3,1-diyl)bis(4-methylbenzenesulfonate).

3,3′-[1,4-phenylenebis(oxy)]bis(propane-3,1-diyl)bis(4-methylbenzenesulfonate) (14). According to procedure E, the title compound (626.1 mg, 88%) was obtained as a white powder from 3,3′-[1,4-phenylenebis(oxy)]dipropan-1-ol **11** (300 mg, 1.32 mmol), toluene-4-sulfonyl chloride (708 mg, 3.71 mmol), Et_3N (0.74 mL, 5.3 mmol), and CH_2Cl_2 (8 mL); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.11$ (quintet, $J = 5.9$ Hz, 4H, $2CH_2$), 2.42 (s, 6H, $2CH_3$), 3.92 (t, $J = 5.9$ Hz, 4H, CH_2OTs), 4.26 (t, $J = 6.0$ Hz, 4H, $2CH_2OPh$), 6.69 (s, 4H, CH_{ar}), 7.28 (d, $J = 8.0$ Hz, 2H, CH_{arTos}), 7.78 ppm (d, $J = 8.3$ Hz, 1H, CH_{arTos}); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.6$ (CH_3), 29.0 (CH_2), 63.7 (CH_2OTs), 67.1 (CH_2OPh), 115.3 ($2CH_{ar}$), 127.8 (CH_{arTos}), 129.8 (CH_{arTos}), 132.9 (Cq-Me), 144.8 (Cq-SO_2), 152.8 ppm (Cq-O); HPLC (conditions B): 2.84 min; MS (ESI+): 363.1 $[M-TsO]^+$, 535.1 $[M+H]^+$.

5-(2-hydroxyethyl)-3-[3-(4-{3-[5-(2-hydroxyethyl)thiaz-ol-3-ium-3-yl]propoxy}phenoxy)propyl]-4-methylthiaz-ol-3-ium chloride (17). According to procedure B, the title compound was obtained from 1,3-bis(4-bromobutoxy)benzene **2** (500 mg, 1.31 mmol), 4-methyl-5-(2-hydroxyethyl)thiazole (0.47 mL, 3.95 mmol), and CH_3CN (0.5 mL) after 5.5 h under MW irradiation at 100 °C. The compound was isolated by precipitation to afford a yellow hygroscopic powder (586 mg, 66%); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.28$ (m, 4H, $2CH_2$), 2.48 (s, 6H, CH_3), 3.04 (t, $J = 5.6$ Hz, 4H, $2CH_2CH_2OH$), 3.65 (q, $J = 5.3$ Hz, 4H, $2CH_2CH_2OH$), 4.02 (t, $J = 5.6$ Hz, 4H, $2CH_2OPh$), 4.66 (t, $J = 6.9$ Hz, 4H, $2CH_2N^+$), 5.33 (t, $J = 5.0$ Hz, 2H, 2OH), 6.81 (s, 4H, CH_{ar}), 10.14 ppm (s, 2H, $CH_{thiazole}$); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 11.2$ ($2CH_3$), 28.5 ($2CH_2$), 29.4 ($2CH_2CH_2OH$), 50.5 ($2CH_2N^+$), 59.6 ($2CH_2OH$), 65.0 ($2CH_2OPh$), 115.2 ($4CH_{ar}$), 135.3 ($2C_qS$), 141.6 ($2C_qN^+$), 152.2 ($2C_{qar}$) 156.7 ppm ($2CH_{thiazole}$); HPLC (conditions B): 6.07 min; MS (ESI+): 239.1 $[(M-2Cl)/2]^{2+}$, 591.2 $[M-2Cl+TFA]^+$; HRMS (TOF-ESI+) calcd for $C_{24}H_{34}BrN_2O_4S_2^+$ $[M-Br]^+$: 513.1649, found: 513.1657.

2,2′-[1,4-phenylenebis(oxy)]bis(ethane-2,1-diyl)bis(4-methylbenzenesulfonate) (20). According to procedure E, the title compound (5.57 mg, 72%) was obtained as a white powder from 1,4-bis(2-hydroxyethoxy)benzene (3 g, 15.13 mmol), toluene-4-sulfonyl chloride (8.63 g, 45.4 mmol), pyridine (7.3 mL, 90.8 mmol), and CH_2Cl_2 (45 mL) and after purification by column chromatography (CH_2Cl_2/PE 8:2→CH_2Cl_2/MeOH 9.8:0.2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.03$ (quintet, $J = 5.9$ Hz, 4H, $2CH_2$), 2.31 (s, 6H, $2CH_3$), 3.85 (t, $J = 5.8$ Hz, 4H, CH_2OTs), 4.16 (t, $J = 6.0$ Hz, 4H, $2CH_2OPh$), 6.14 (t, $J = 2.3$ Hz, 1H, CH_{ar}), 6.29 (dd, $J = 2.3$ and 8.2 Hz, 2H, CH_{ar}), 7.04 (t, $J = 8.2$ Hz, 1H, CH_{ar}), 7.19 (d, $J = 8.0$ Hz, 2H, CH_{arTos}), 7.68 ppm (d, $J = 8.3$ Hz, 1H, CH_{arTos}); ^{13}C NMR (75 MHz, $CDCl_3$): 22.6 (CH_3), 66.2 (CH_2OTs), 68.2 (CH_2OPh), 115.7 (CH_{ar}), 128.0 (CH_{arTos}), 129.8 ($2CH_{arTos}$), 132.9 (Cq-Me), 144.9 (Cq-SO_2), 152.7 ppm (Cq-O); HPLC (conditions A): 2.78 min; MS (ESI+): 335.2 $[M-TsO]^+$, 507.2 $[M+H]^+$.

3,3′-{2,2′-[1,4-phenylenebis(oxy)]bis(ethane-2,1-diyl)}bis[5-(2-hydroxyethyl)-4-methylthiazol-3-ium] chloride (22). According to procedure B, the title compound was obtained from intermediate **21** (500 mg, 0.99 mmol), 4-methyl-5-(2-hydroxyethyl)thiazole (0.355 mL, 2.96 mmol), and CH_3CN (0.8 mL) after 1 h under MW irradiation at 150 °C. After ion-exchange chromatography, the compound was isolated by precipitation to afford a yellow hygroscopic powder (310 mg, 60%); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.53$ (s, 6H, $2CH_3$), 3.04 (t, $J = 5.5$ Hz, 4H, $2CH_2CH_2OH$), 3.63 (q, $J = 5.4$ Hz, 4H, $2CH_2CH_2OH$), 4.36 (t, $J = 4.7$ Hz, 4H, $2CH_2OPh$), 4.90 (t, $J = 4.7$ Hz, 4H, $2CH_2N^+$), 5.39 (t, $J = 5.0$ Hz, 2H, OH), 6.87 (s, 4H, CH_{ar}), 10.17 ppm (s, 2H, $CH_{thiazole}$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.5$ ($2CH_3$), 29.4 ($2CH_2CH_2OH$), 51.9 ($2CH_2N^+$), 59.5 ($2CH_2CH_2OH$), 65.8 ($2CH_2OPh$), 115.6 ($4CH_{ar}$), 135.0 ($2C_qS$), 141.8 ($2C_qN^+$), 152.0 ($2C_{qar}$), 157.7 ppm ($2CH_{thiazole}$); HPLC (conditions B): 3.90 min; MS (ESI+): 225.1 $[(M-2Cl)/2]^{2+}$, 485.2 $[M-Cl]^+$; HRMS (TOF-ESI+) calcd for $C_{22}H_{30}ClN_2O_4S_2^+$ $[M-Cl]^+$: 485.1336, found: 485.1326.

1,4-bis[(4-bromobutoxy)methyl]benzene (24). According to procedure A, the title compound was obtained as a white powder (3.1 g, 53%) from 1,4-benzenedimethanol (2 g, 14.47 mmol), NaOH (2.88 g, 72.3 mmol), 1,4-dibromobutane (17 mL, 144.7 mmol), Bu_4NHSO_4 (0.98 g), and H_2O (18 mL); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta =$ 1.60–2.00 (m, 8H, $4CH_2$), 3.30–3.5 (m, 8H, CH_2Br), 4.42 (s, 4H, $PhCH_2O$), 7.22 ppm (m, 4H, CH_{ar}); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 26.9 (CH_2CH_2OPh), 28.3 (CH_2CH_2Br), 33.8 (CH_2Br), 69.2 (CH_2OPh), 72.7 ($PhCH_2O$), 127.7 (CH_{ar}), 137.8 ppm (Cq_{ar}); HPLC (conditions A): 2.28 min; MS (ESI+): 406.7 $[M+H]^+$.

3,3′-{4,4′-[1,3-phenylenebis(methylene)]bis(oxy)bis(butane-4,1-diyl)}bis[5-(2-hydroxyethyl)-4-methylthiazol-3-ium] bromide (29), 5-(2-hydroxyethyl)-3-[3-({4-[5-(2-hydroxyethyl)-4-methylthiazol-3-ium-3-yl]butoxy}methyl)benzyl]-4-methylthiazol-3-ium bromide (30), and 3,3′-[1,3-phenylenebis(methylene)]bis[5-(2-hydroxyethyl)-4-methylthiazol-3-ium] bromide (31). According to procedure B, the title compounds were obtained from 1,3-bis[(4-bromobutoxy)methyl]benzene **25** (500 mg, 1.23 mmol), 4-methyl-5-(2-hydroxyethyl)thiazole (0.442 mL, 3.68 mmol), and CH_3CN (1.2 mL) after 1 h under MW irradiation at 150 °C. The crude was purified by RP-18 chromatography (gradient: H_2O→H_2O/MeOH 8:2) to afford compounds **29** (110 mg, 13%) and **30** (156 mg, 20%) as yellow hygroscopic powders, and **31** as a white solid (39 mg, 6%). Compound **29**: ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 1.62$ (m, 4H, $2CH_2$), 1.87 (m, 4H, $2CH_2$), 2.49 (s, 6H, $2CH_3$), 3.05 (t, $J = 5.5$ Hz,, 4H, $2CH_2CH_2OH$), 3.49 (t, $J = 6.2$ Hz, 4H, $2CH_2O$), 3.64 (q, $J = 5.3$ Hz, 4H, $2CH_2CH_2OH$), 4.46 (s, 4H, $2PhCH_2O$), 4.51 (t, $J = 7.5$ Hz, 4H, $2CH_2N^+$), 5.20 (t, $J = 5.0$ Hz, 2H, OH), 7.15–7.45 (m, 4H, CH_{ar}), 10.12 ppm (s, 2H, $CH_{thiazole}$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.2$ ($2CH_3$), 25.8, 26.0 ($2CH_2$), 29.5 ($2CH_2CH_2OH$), 52.5 (CH_2N^+), 59.6 ($2CH_2CH_2OH$), 68.9 ($2CH_2O$), 71.8 ($PhCH_2O$), 126.6, 128.2 ($4CH_{ar}$), 135.4 ($2C_qS$), 139.6 (Cq_{ar}), 141.5 ($2C_qN^+$), 156.2 ppm ($2CH_{thiazole}$); HPLC (conditions B): 5.01 min; MS (ESI+): 267.2 $[(M-2Br)/2]^{2+}$, 615.3 $[M-Br]^+$, 647.4 $[M-2Br+TFA]^+$; HRMS (TOF-ESI+) calcd for $C_{28}H_{42}BrN_2O_4S_2^+$ $[M-Br^-]^+$: 613.1769, found: 613.1746. Compound **30**: ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 1.62$ (m, 2H, CH_2), 1.89 (m, 2H, CH_2), 2.39 (s, 3H, CH_3), 2.49 (s, 3H, CH_3), 3.03 (m, 4H, $2CH_2CH_2OH$), 3.30–3.80 (m, 6H, CH_2O and $2CH_2CH_2OH$), 4.50 (m, 4H, CH_2N^+ and CH_2OPh), 5.87 (s, 2H, $PhCH_2N^+$), 7.10–760 (m, 4H, CH_{ar}), 10.15 (s, 1H, $CH_{thiazole}$) 10.24 ppm (s, 1H, $CH_{thiazole}$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.3$, 11.6 ($2CH_3$), 25.7, 26.0 ($2CH_2$), 29.4 ($2CH_2CH_2OH$), 52.5 (CH_2N^+), 55.6 ($PhCH_2N^+$), 59.6 ($2CH_2CH_2OH$), 68.9 (CH_2O), 71.4 ($PhCH_2O$), 126.9, 127.0, 127.9, 129.2 ($4CH_{ar}$), 133.0 (Cq_{ar}), 135.4, 136.2 ($2C_qS$), 139.6 (Cq_{ar}), 141.5, 141.6 ($2C_qN^+$), 156.2, 157.0 ppm ($2CH_{thiazole}$); HPLC (conditions B): 4.22 min; MS (ESI+):

231.2 [(*M*−2Br)/2]$^{2+}$, 543.3 [*M*−Br]$^{+}$, 575.3 [*M*−2Br+TFA]$^{+}$; HRMS (TOF-ESI+) calcd for $C_{24}H_{34}BrN_2O_3S_2^{+}$ [*M*−Br]$^{+}$: 541.1194, found: 541.1216. Compound **31**: ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.35 (s, 6H, 2CH$_3$), 3.05 (t, *J* = 5.5 Hz, 4H, 2*CH*$_2$CH$_2$OH), 3.66 (t, *J* = 5.5 Hz, 4H, 2CH$_2$*CH*$_2$OH), 5.88 (s, 4H, 2PhCH$_2$N^{+}), 7.40 (m, 3H, 4CH$_{ar}$), 7.56 (t, *J* = 7.6 Hz, 1H, CH$_{ar}$), 10.24 ppm (s, 2H, CH$_{thiazole}$); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 11.6 (2CH$_3$), 29.4 (2*CH*$_2$CH$_2$OH), 55.3 (PhCH$_2$N^{+}), 59.6 (2CH$_2$*CH*$_2$OH), 127.5, 128.3, 130.1 (4CH$_{ar}$), 134.1 (Cq$_{ar}$), 136.2 (2C$_q$S), 141.6 (2C$_q$N^{+}), 157.2 ppm (2CH$_{thiazole}$); HPLC (conditions B): 3.27 min; MS (ESI+): 195.1 [(*M*−2Br)/2]$^{2+}$, 469.2 [*M*−Br]$^{+}$; HRMS (TOF-ESI+) calcd for $C_{20}H_{26}BrN_2O_2S_2^{+}$ [*M*−Br]$^{+}$: 469.0619, found: 469.0618.

2,2′-[1,4-phenylenebis(methylene)]bis(oxy)diethanol (32). Ethylene glycol (2.78 mL, 45.46 mmol) dissolved beforehand in anhydrous THF (10 mL) was added dropwise to a solution of NaH (666 mg, 16.6 mmol) in anhydrous THF (10 mL). After stirring for 30 min, 1,4-bis(bromomethyl)benzene (2 g, 7.58 mmol) was added, and the mixture was held at reflux overnight. The solvent was removed in vacuo, and the residue was purified by column chromatography (PE/EtOAc 3:7→1:9) to afford the expected compound **32** as a colorless oil (1.16 g, 68%); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 3.50 (m, 4H, 2CH$_2$OH), 3.70 (m, 4H, 2CH$_2$), 4.53 (s, 4H, 2CH$_2$Ph), 7.32 ppm (s, 4H, CH$_{ar}$); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 61.8 (2CH$_2$OH), 71.4 (2CH$_2$O), 73.0 (2CH$_2$Ph), 127.8 (4CH$_{ar}$), 137.5 ppm (2Cq$_{ar}$); HPLC (conditions B): 4.71 min; MS (ESI+): 227.1 [*M*+H]$^{+}$.

2,2′-[1,4-phenylenebis(methylene)]bis(oxy)bis(ethane-2,1-diyl)-bis(4-methylbenzenesulfonate) (33). According to procedure E, the title compound was obtained as a white powder (770 mg, 46%) from **32** (0.7 g, 3.09 mmol), toluene-4-sulfonyl chloride (1.78 g, 9.28 mmol), pyridine (1.49 mL, 18.56 mmol), and CH$_2$Cl$_2$ (10 mL); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.35 (s, 6H, 3.50) 3.57 (m, 4H, 2CH$_2$), 4.11 (m, 4H, 2CH$_2$), 4.39 (s, 4H, 2CH$_2$Ph), 7.14 (s, 4H, CH$_{ar}$), 7.23 (d, *J* = 8.0 Hz, 2H, CH$_{arTos}$), 7.71 ppm (d, *J* = 8.3 Hz, 1H, CH$_{arTos}$); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.1 (2CH$_3$), 67.5 (2CH$_2$OTs), 69.3 (2CH$_2$O), 72.9 (2CH$_2$Ph), 127.3 (CH$_{ar}$), 128.0 (CH$_{arTos}$), 129.8 (2CH$_{arTos}$), 133.0 (Cq-Me), 137.2 (Cq-CH$_2$O), 144.9 ppm (Cq-SO$_2$); HPLC (conditions B): 11.97 min; MS (ESI+): 535.3 [*M*+H]$^{+}$.

3,3′-{2,2′-[1,4-phenylenebis(methylene)]bis(oxy)bis(ethane-2,1-diyl)}bis[5-(2-hydroxyethyl)-4-methylthiaz-ol-3-ium] chloride (34). According to procedure B, the title compound was obtained from **33** (357 mg, 0.667 mmol), 4-methyl-5-(2-hydroxyethyl)thiazole (0.24 mL, 2.0 mmol), and CH$_3$CN (0.5 mL) after 1 h under MW irradiation at 150 °C. After ion-exchange chromatography, the compound was purified by precipitation and then RP-18 chromatography (gradient: H$_2$O→H$_2$O/MeOH 8.5:1.5) to afford a white powder (273 mg, 74%); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.46 (s, 6H, 2CH$_3$), 3.04 (t, *J* = 5.6 Hz, 4H, 2*CH*$_2$CH$_2$OH), 3.64 (m, 4H, 2CH$_2$*CH*$_2$OH), 3.85 (t, 4H, *J* = 4.8 Hz, 2CH$_2$O), 4.50 (s, 4H, 2PhCH$_2$O), 4.76 (t, *J* = 4.8 Hz, 4H, 2CH$_2$N^{+}), 5.47 (m, 2H, OH), 7.17 (s, 4H, CH$_{ar}$), 10.14 ppm (s, 2H, CH$_{thiazole}$); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 16.2 (2CH$_3$), 34.2 (2*CH*$_2$CH$_2$OH), 57.1 (CH$_2$N^{+}), 64.3 (2CH$_2$*CH*$_2$OH), 71.6 (2CH$_2$O), 76.3 (PhCH$_2$O), 132.1 (4CH$_{ar}$), 139.7 (2C$_q$S), 141.8 (Cq$_{ar}$), 146.5 (2C$_q$N^{+}), 162.0 ppm (2CH$_{thiazole}$); HPLC (conditions B): 4.23 min; MS (ESI+): 239.1 [(*M*−2Cl)/2]$^{2+}$, 513.3 [*M*−Cl]$^{+}$, 591.3 [*M*−2Cl+TFA]$^{+}$; HRMS (TOF-ESI+) calcd for $C_{24}H_{34}ClN_2O_4S_2^{+}$ [*M*−Cl]$^{+}$: 513.1649, found: 513.1625.

3,3′-(1,4-phenylene)bis(propane-3,1-diyl)bis(4-methylbenzene sulfonate) (35). According to procedure E, the title compound was obtained as a white powder (3.79 mg, 73%) from 3,3′-(1,4-phenylene)dipropan-1-ol (2 g, 10.29 mmol), toluene-4-sulfonyl chloride (5.9 g, 30.88 mmol), pyridine (4.97 mL, 61.76 mmol) and CH$_2$Cl$_2$ (40 mL); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.85 (m, 4H, 2CH$_2$), 2.39 (s, 6H, 2CH$_3$), 2.53 (t, *J* = 7.6 Hz, 4H, CH$_2$OTs), 3.95 (t, *J* = 6.2 Hz, 4H, 2CH$_2$Ph), 6.88 (s, 4H, CH$_{ar}$), 7.26 (d, *J* = 8.0 Hz, 2H, CH$_{arTos}$), 7.72 ppm (d, *J* = 8.3 Hz, 1H, CH$_{arTos}$); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 21.6 (CH$_3$), 30.5 (CH$_2$), 31.0 (CH$_2$OTs), 69.6 (CH$_2$Ph), 127.9 (CH$_{ar}$), 128.5 (CH$_{arTos}$), 129.8 (CH$_{arTos}$), 133.1 (Cq-Me), 138.2 (Cq$_{ar}$) 144.7 ppm (Cq-SO$_2$); HPLC (conditions A): 2.82 min; MS (ESI+): 331.2 [*M*−TsO]$^{+}$, 503.3 [*M*+H]$^{+}$.

4,4′-(1,4-phenylene)bis(butane-4,1-diyl)bis(4-methylbenzene sulfonate) (36). According to procedure E, the title compound (4.73 mg, 78%) was obtained as a white powder from 4,4′-(1,4-phenylene)dibutan-1-ol (2.62 g, 11.8 mmol), toluene-4-sulfonyl chloride (6.75 g, 35.40 mmol), 4-(dimethylamino)pyridine (144 mg, 1.18 mmol), pyridine (5.7 mL, 70.8 mmol), and CH$_2$Cl$_2$ (30 mL); ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.50–1.90 (m, 8H, 4CH$_2$), 2.35–2.70 (s, 10H, 2CH$_2$OTs, 2CH$_3$), 4.07 (t, *J* = 6 Hz, 4H, 2CH$_2$Ph), 7.02 (s, 4H, CH$_{ar}$), 7.38 (d, *J* = 8 Hz, 2H, CH$_{arTos}$), 7.82 ppm (d, *J* = 8 Hz, 1H, CH$_{arTos}$); ^{13}C NMR (75 MHz, CDCl$_3$): δ = 21.6 (CH$_3$), 27.1 (CH$_2$), 28.3 (CH$_2$), 34.6 (CH$_2$OTs), 70.4 (CH$_2$Ph), 127.9 (CH$_{ar}$), 128.7 (CH$_{arTos}$), 130.2 (CH$_{arTos}$), 133.1 (Cq-Me), 139.1 (Cq$_{ar}$) 144.7 ppm (Cq-SO$_2$); HPLC (conditions A): 13.57 min; MS (ESI+): 531.3 [*M*+H]$^{+}$.

3,3′-[3,3′-(1,4-phenylene)bis(propane-3,1-diyl)]bis[5-(2-hydroxyethyl)-4-methylthiazol-3-ium] chloride (37). According to procedure B, the title compound was obtained from 3,3′-(1,4-phenylene)-bis(propane-3,1-diyl)bis(4-methylbenzenesulfonate) **32** (1 g, 1.99 mmol), 4-methyl-5-(2-hydroxyethyl)thiazole (0.715 mL, 5.97 mmol), and CH$_3$CN (0.8 mL) after 1 h under MW irradiation at 150 °C. After ion-exchange chromatography, the compound was purified by precipitation to afford a yellow hygroscopic powder (573 mg, 51%); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.05–2.3 (m, 4H, 2CH$_2$), 2.45 (s, 6H, CH$_3$), 2.65 (t, *J* = 7.7 Hz, 4H, 2CH$_2$Ph), 3.02 (t, *J* = 5.5 Hz, 4H, 2*CH*$_2$CH$_2$OH), 3.61 (t, *J* = 5.5 Hz, 4H, 2CH$_2$*CH*$_2$OH), 4.51 (t, *J* = 7.4 Hz, 4H, 2CH$_2$N^{+}), 7.17 (s, 4H, CH$_{ar}$), 10.2 ppm (s, 2H, CH$_{thiazole}$); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 11.2 (2CH$_3$), 29.4 (2*CH*$_2$CH$_2$OH), 30.2 (2CH$_2$), 31.1 (2CH$_2$Ph), 52.4 (2CH$_2$N^{+}), 59.5 (2CH$_2$OH), 128.2 (4CH$_{ar}$), 135.3 (2C$_q$S), 138.0 (2C$_{qar}$), 141.4 (2C$_q$N^{+}), 156.1 ppm (2CH$_{thiazole}$); HPLC (conditions B): 4.35 min; MS (ESI+): 223.2 [(*M*−2Cl)/2]$^{2+}$, 481.3 [*M*−Cl]$^{+}$, 559.3 [*M*−2Cl+TFA]$^{+}$; HRMS (TOF-ESI+) calcd for $C_{24}H_{34}ClN_2O_2S_2^{+}$ [*M*−Cl]$^{+}$: 481.1750, found: 481.1768.

3,3′-[4,4′-(1,4-phenylene)bis(butane-4,1-diyl)]bis[5-(2-hydroxyethyl)-4-methylthiazol-3-ium] chloride (38). According to procedure B, the title compound was obtained from 4,4′-(1,4-phenylene)-bis(butane-4,1-diyl)bis(4-methylbenzenesulfonate) **34** (1.5 g, 2.98 mmol), 5-(2-hydroxyethyl)-4-methylthiazole (1.4 mg, 8.95 mmol), and CH$_3$CN (5.5 mL) after 1.5 h under MW irradiation at 150 °C. After ion-exchange chromatography, the compound was purified by precipitation and then RP-18 chromatography (gradient: H$_2$O→H$_2$O/MeOH 8.5:1.5) to afford a white powder (827 mg, 51%); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.05–2.25 (m, 4H, 2CH$_2$), 2.45 (s, 6H, CH$_3$), 2.65 (t, *J* = 7.7 Hz, 4H, 2CH$_2$Ph), 3.13 (t, *J* = 5.7 Hz, 4H, 2*CH*$_2$CH$_2$OH), 3.30 (s, 6H, OCH$_3$), 3.56 (t, *J* = 5.7 Hz, 4H, 2CH$_2$*CH*$_2$OH), 4.53 (t, *J* = 7.4 Hz, 4H, 2CH$_2$N^{+}), 7.17 (s, 4H, CH$_{ar}$), 10.3 ppm (s, 2H, CH$_{thiazole}$); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 11.2 (2CH$_3$), 26.5 (2*CH*$_2$CH$_2$OH), 30.2 (2CH$_2$), 31.2 (2CH$_2$Ph), 52.4 (2CH$_2$N^{+}), 58.0 (2OCH$_3$), 70.2 (2CH$_2$OH), 128.2 (4CH$_{ar}$), 134.9 (2C$_q$S), 138.0 (2C$_{qar}$), 141.6 (2C$_q$N^{+}), 156.8 ppm (2CH$_{thiazole}$); HPLC (conditions B): 4.98 min; HRMS (TOF-ESI+) calcd for $C_{26}H_{38}ClN_2O_2S_2^{+}$ [*M*−Cl]$^{+}$: 509.2063, found: 509.2052.

5-(2-hydroxyethyl)-3-[4-(4-{4-[5-(2-hydroxyethyl)thiaz-ol-3-ium-3-yl]butyl}phenyl)butyl]-4-methylthiazol-3-ium chloride (39). Ac-

cording to procedure B, the title compound was obtained from 4,4′-(1,4-phenylene)bis(butane-4,1-diyl)bis(4-methylbenzenesulfonate) **34** (0.517 g, 0.975 mmol), 4-methyl-5-(2-hydroxyethyl)thiazole (0.350 mL, 2.82 mmol), and CH_3CN (1 mL) after 1 h under MW irradiation at 150 °C. After ion-exchange chromatography, the compound was purified by precipitation and then RP-18 chromatography (gradient: $H_2O \rightarrow H_2O$/MeOH 8.5:1.5) to afford a white powder (315.3 mg, 59%); ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 1.5$–2.0 (m, 8H, 4CH_2), 2.45 (s, 6H, CH_3), 2.59 (t, $J = 7.5$ Hz, 4H, 2CH_2Ph), 3.03 (t, $J = 5.5$ Hz, 4H, 2CH_2CH_2OH), 3.63 (q, $J = 5.4$ Hz, 4H, 2CH_2CH_2OH), 4.52 (t, $J = 7.2$ Hz, 4H, 2CH_2N^+), 5.41 (t, $J = 5.1$ Hz, 2H, 2OH), 7.12 (m, 4H, CH_{ar}), 10.21 ppm (s, 2H, $CH_{thiazole}$); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 11.2$ (2CH_3), 27.4 (2CH_2), 28.4 (2CH_2) 29.5 (2CH_2CH_2OH), 33.9 (2CH_2Ph), 52.4 (2CH_2N^+), 59.6 (2CH_2OH), 128.2 (4CH_{ar}), 135.5 (2C_qS), 138.9 (2C_{qar}), 141.6 (2C_qN^+), 156.3 ppm (2$CH_{thiazole}$); HPLC (conditions B): 5.18 min; MS (ESI+): 237.2 $[(M-2Cl)/2]^{2+}$, 509.3 $[M-Cl]^+$; HRMS (TOF-ESI+) calcd for $C_{26}H_{38}ClN_2O_2S_2^+$ $[M-Cl]^+$: 509.2063, found: 509.2056.

3,3′-[4,4′-(1,4-phenylene)bis(butane-4,1-diyl)]bis[5-(2-methoxyethyl)-4-methylthiazol-3-ium] chloride (40). According to procedure B, the title compound was obtained from 4,4′-(1,4-phenylene)bis(butane-4,1-diyl)bis(4-methylbenzenesulfonate) **34** (500 mg, 9.42 mmol), 5-(2-methoxyethyl)-4-methylthiazole (0.444 mL, 2.82 mmol), and CH_3CN (1 mL) after 1 h under MW irradiation at 150 °C. After ion-exchange chromatography, the compound was purified by precipitation and then RP-18 chromatography (gradient: $H_2O \rightarrow H_2O$/MeOH 8.5:1.5) to afford a white powder (573 mg, 51%); ^{1}H NMR (300 MHz, [D$_6$]DMSO): $\delta = 1.45$–2.00 (m, 8H, 4CH_2), 2.46 (s, 6H, CH_3), 2.59 (t, $J = 7.6$ Hz, 4H, 2CH_2Ph), 3.14 (t, $J = 5.6$ Hz, 4H, 2CH_2CH_2OMe), 3.30 (s, 6H, OCH_3), 3.57 (t, $J = 5.6$ Hz, 4H, 2CH_2CH_2OMe), 4.53 (t, $J = 7.3$ Hz, 4H, 2CH_2N^+), 7.12 (m, 4H, CH_{ar}), 10.25 ppm (s, 2H, $CH_{thiazole}$); ^{13}C NMR (75 MHz, [D$_6$]DMSO): $\delta = 11.1$ (2CH_3), 26.5 (2CH_2), 27.3 (2CH_2CH_2OMe), 28.4, (2CH_2), 33.9 (2CH_2Ph), 52.5 (2CH_2N^+), 58.0 (2OCH_3), 70.2 (2CH_2CH_2OMe), 128.2 (4CH_{ar}), 135.1 (2C_qS), 138.9 (2C_{qar}), 141.6 (2C_qN^+), 156.6 ppm (2$CH_{thiazole}$); HPLC (conditions B): 6.07 min; HRMS (TOF-ESI+) calcd for $C_{28}H_{42}ClN_2O_2S_2^+$ $[M-Cl]^+$: 537.2376, found: 537.2394.

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