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# New Bis-thiazolium Analogues as Potential Antimalarial Agents: Design, Synthesis, and Biological Evaluation

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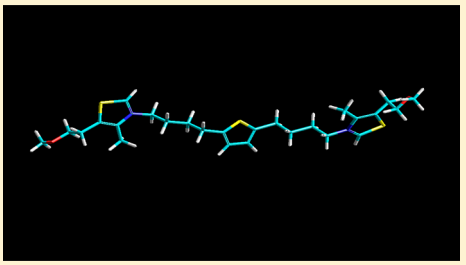
Supporting Information

**ABSTRACT:** Bis-thiazolium salts are able to inhibit phosphatidylcholine biosynthesis in *Plasmodium* and to block parasite proliferation in the low nanomolar range. However, due to their physicochemical properties (i.e., permanent cationic charges, the flexibility, and lipophilic character of the alkyl chain), the oral bioavailability of these compounds is low. New series of bis-thiazolium-based drugs have been designed to overcome this drawback. They feature linker rigidification via the introduction of aromatic rings and/or a decrease in the overall lipophilicity through the introduction of heteroatoms. On the basis of the structure−activity relationships, a few of the promising compounds (**9**, **10**, and **11**) were found to exhibit potent antimalarial in vitro and in vivo activities ($EC_{50}$ < 10 nM and $ED_{50}$ ip < 0.7 mg/kg).



## INTRODUCTION

Malaria is a widespread infectious disease in tropical and subtropical regions. The World Health Organization (WHO) estimates that half of the world population is at risk of malaria infection.[1] Moreover, *Plasmodium falciparum* parasites have become resistant to most marketed antimalarial drugs (chloroquine, mefloquine, quinine. and sulfadoxine/pyrimethamine), including artemisinin and its derivatives, even when used in combination therapies (ACTs).[2−4] As the emergence of multichemoresistance parasites could seriously undermine global malaria control, new chemotherapeutic approaches based on innovative mechanisms of action are needed.[5−9]

A decade ago, Vial et al. first described bis-quaternary ammonium salts as novel antimalarial chemotherapeutic agents.[10] Since then, bis-cationic choline analogues have been designed to inhibit the phospholipid metabolism.[11,12] These compounds have been shown to affect de novo plasmodial phosphatidylcholine biosynthesis in infected erythrocytes.[13,14] Further studies on structure−activity relationships, etc., led to the discovery of potent bis-thiazolium salts (**T3** and **T4**, Figure 1) displaying $IC_{50}$ values in the low nanomolar range.[15,16] **T3** was the first choline analogue to undergo phase 2 clinical trials, thus validating the chemotherapeutic approach.[11−16]

The presence of two permanent cationic charges and the flexibility and lipophilic character of the associated alkyl chain prevent intestinal barrier crossing, with each parameter lowering the oral bioavailability of these compounds. Several approaches have been developed because the cationic charge

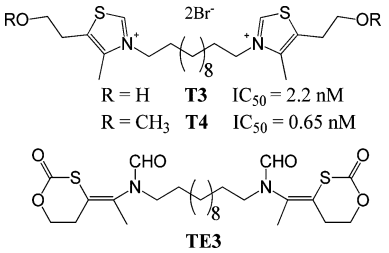



**Figure 1.** Structures of the lead compounds (**T3** and **T4**) and related prodrug (**TE3**).

may be hidden through the use of prodrugs.[11,16] These are neutral derivatives resulting from ring thiazolium opening and subsequent blocking of the thiol function through the formation of biolabile linkages. Structural variations in the prodrug moieties were designed to affect lipophilicity, water solubility, and enzymatic stabilities.[17,18] Some neutral prodrugs have exhibited potent in vitro antimalarial activity but still displayed limited oral bioavailability. The most relevant data was obtained with the cyclic thioester (**TE3**, Figure 1), which achieved 15% absolute oral bioavailability in rat.[19] Altogether, these results have shown that it is possible to temporarily hide the cationic charge and modulate release of the active bis-thiazolium drug. However, the oral drug-like properties of the

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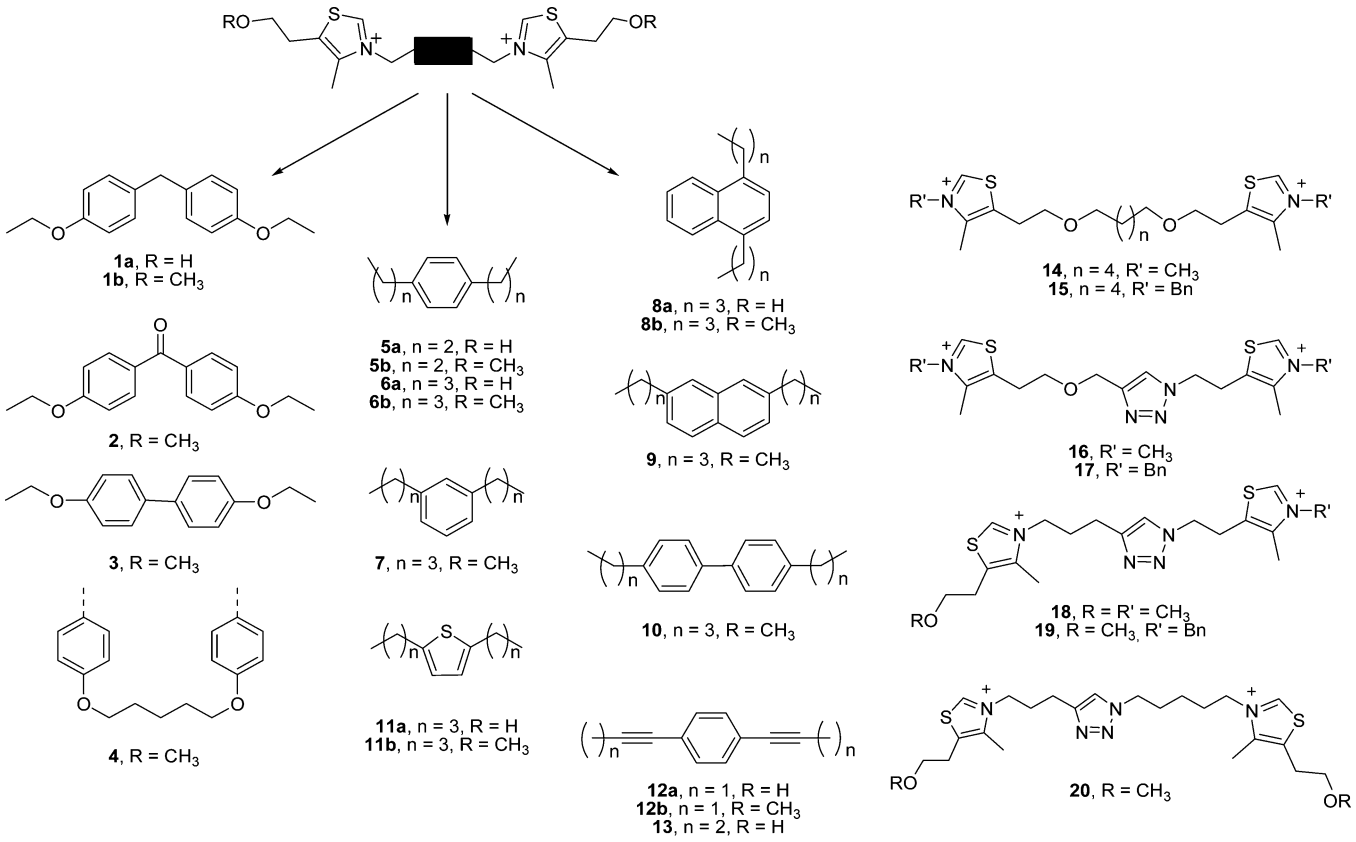
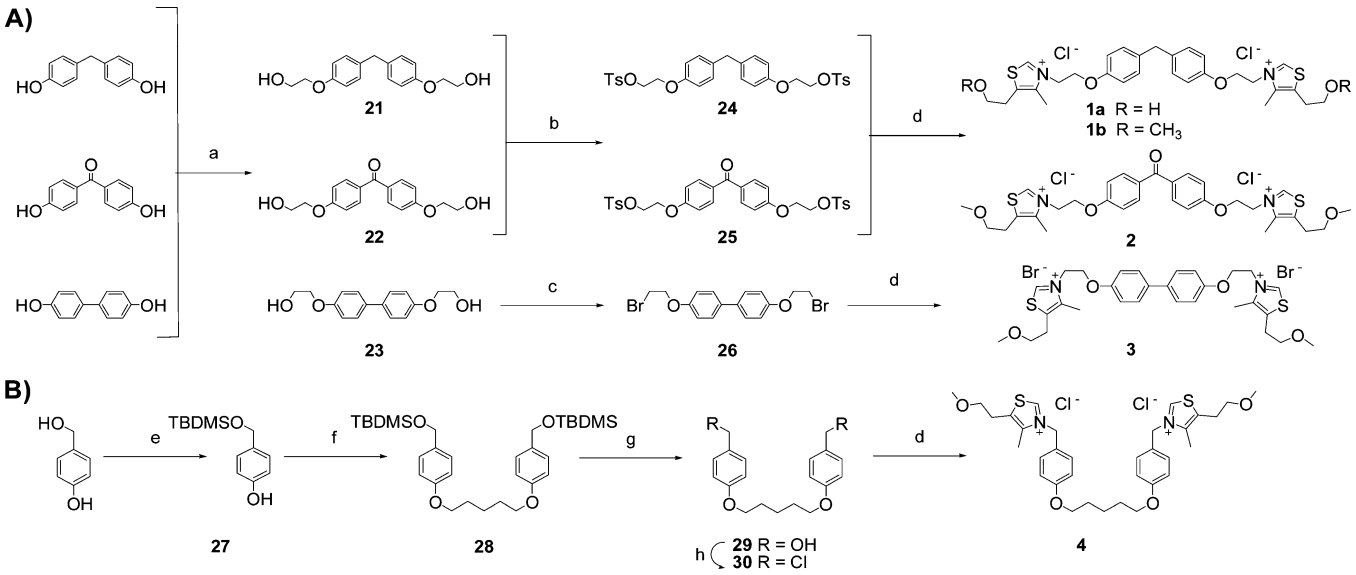



**Figure 2.** Targeted compounds.

**Scheme 1. Synthetic Pathways for Linkers Including a Phenoxy Moiety**[a]




[a]Reagents and conditions: (a) ethylene carbonate, $K_2CO_3$, DMF, 55−95%; (b) TsCl, $NEt_3$, DMAP, $CH_2Cl_2$, 59−95%; (c) $Br_2$, $P(Ph)_3$, $CH_2Cl_2$, 59%; (d) 4-Me-5-(2-hydroxyethyl)- or 4-Me-5-(2-methoxyethyl)thiazole, $CH_3CN$, MW, then Dowex Cl- for **1a,b** and **2**, 68−84%; (e) TBDMSCl, THF, 78%; (f) NaH, 1,5-dibromopentane, 76%; (g) $KHSO_4$, $THF/H_2O$, 77%; (h) $SOCl_2$, $CH_2Cl_2$, quantitative.

current prodrugs are limited by the physicochemical properties of the parent drugs, which include a lipophilic chain and a high degree of conformational freedom of the spacer that separates the two cationic heads.[20,21]

We recently showed that the presence of a phenyl moiety within the linker of bis-thiazolium derivatives did not substantially affect the antimalarial activity in cell experiments.[22] On the basis of these considerations, we explored further linker modifications to elucidate structural requirements to obtain a more rigid and less lipophilic chain while still having bioactive analogues. The present investigation involved the introduction of a variety of aryl moieties or heterocycles, such as thiophene or triazole, within the linker (Figure 2). In addition, we modified the lipophilic character of the spacer connected to the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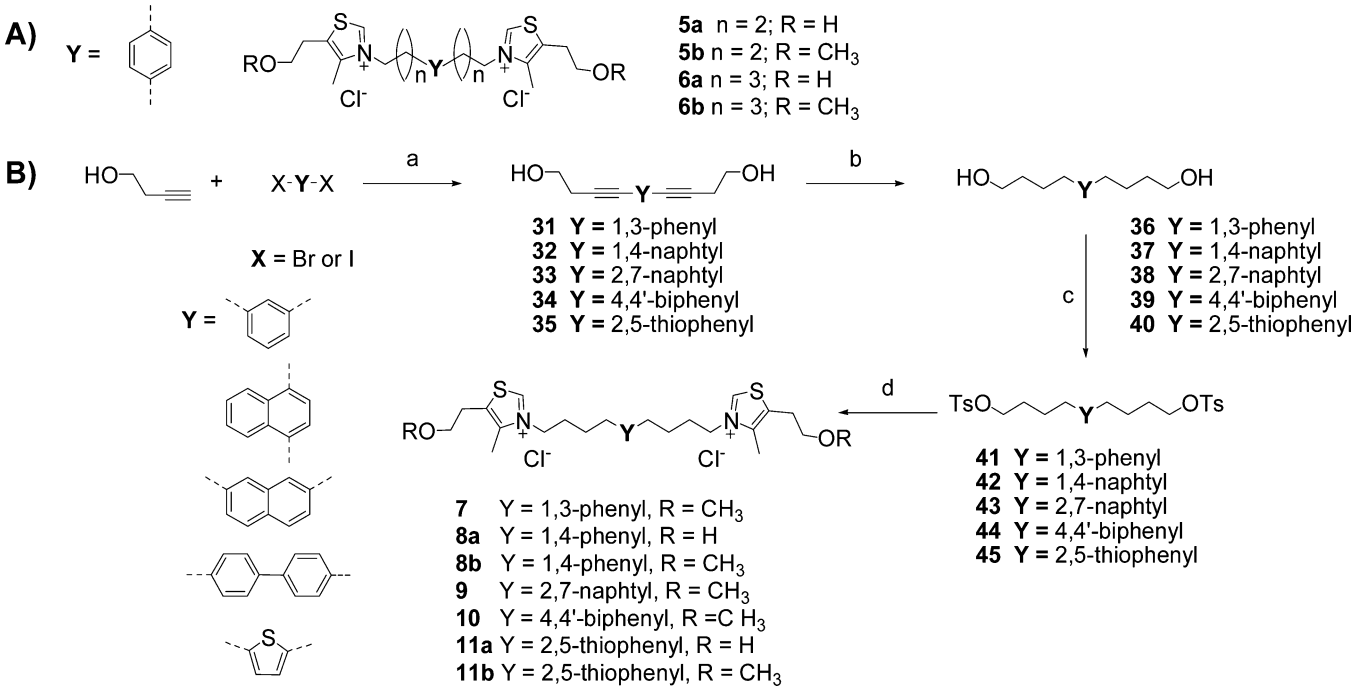
**Scheme 2. Synthetic Pathways for Linkers Including Benzenyl, Bis-phenyl, Naphthyl, and Thiophenyl Moieties**[a]




[a]Reagents and conditions: (a) $Pd[P(Ph)_3]_4$, CuI, $NEt_3$, $CH_2Cl_2$, 31−90%; (b) $H_2$, Pd/C, $CH_3OH$, 77−96%; (c) TsCl, $NEt_3$, DMAP, $CH_2Cl_2$, 51−96%; (d) 4-Me-5-(2-hydroxyethyl)- or 4-Me-5-(2-methoxyethyl)thiazole, $CH_3CN$, MW, then Dowex $Cl^-$, 39−60%.

thiazolium heads by incorporating various arrangements of oxymethylene motifs as well as acetylene units so as to further restrict the conformational flexibility and geometry. Thus, the in vitro antiplasmodial activity and in vivo antimalarial activity of the resulting compounds were studied in relation with the restriction of conformational flexibility, geometry, and polarity of the new compounds.

## RESULTS AND DISCUSSION

**1. Chemistry.** *1.1. Bis-phenoxy Moiety as Scaffold.* Bis-thiazolium salts **1a**, **1b**, **2**, and **3** were prepared in three steps from commercially available bis-phenols (Scheme 1A). Thus, bis-(4-hydroxyphenyl)methane, bis-(4-hydroxy-phenyl) methanone, and 4,4′-dihydroxybiphenyl were coupled to ethylene carbonate in the presence of $K_2CO_3$ to give rise to the diol derivatives **21**−**23** in 78, 56, and 95% yields, respectively.[23] Then treatment of the compounds **21** and **22** with *p*-toluenesulfonyl chloride (TsCl), in the presence of dimethylaminopyridine (DMAP), led to the intermediates **24** and **25**. A poorly soluble material was obtained when diol **23** was treated in the same conditions, making the following purification step very complex. Therefore, compound **23** was brominated, using bromine and triphenylphosphine, which gave rise to intermediate **26** in 59% yield. *N*-Alkylation of 4-methyl-5-(2-hydroxyethyl)thiazole or 4-methyl-5-(2-methoxyethyl)thiazole with tosyl or bromoalkyl intermediates **24**−**26** was then performed under microwave (MW) irradiation conditions to significantly decrease the reaction time. After purification by reverse-phase chromatography and ion-exchange (using a Dowex-$Cl^-$ resin) the corresponding hydrochloride salts **1a**, **1b**, and **2** were isolated in 82, 84, and 68% yields. The bromide salt **3** was obtained in 74% yield after reverse-phase chromatography.

Bis-thiazolium salt **4**, structurally related to pentamidine,[24,25] was prepared in five steps from 4-hydroxymethylphenol (Scheme 1B). First, the benzylic alcohol was selectively protected using *tert*-butyl-dimethylsilyl chloride (TBDMSCl), leading to the silylated compound **27** in 78% yield. Then the phenol was alkylated with 1,5-dibromopentane to give rise to the bis-phenoxy derivative **28** in 76% yield. Removal of the TBDMS protecting group was performed under mild acidic conditions, and the resulting primary alcohols were chlorinated using thionyl chloride ($SOCl_2$), leading to the intermediate **30** in 77% overall yield. Finally, the desired bis-thiazolium salt **4** was obtained under MW conditions as reported above.

*1.2. Benzenyl, Bis-phenyl, Naphthyl, and Thiophenyl Rings as Scaffold.* In this second series of bis-thiazolium salts, compounds **5a**,**b** and **6a**,**b** were synthesized (Scheme 2A) beforehand according to a previously published procedure.[22] In addition, new analogues **7**, **8a**, **8b**, **9**, **10**, **11a**, and **11b** were obtained from commercially available dihalogenated aromatic derivatives (Scheme 2B). First of all, diyne diols **31**−**35** were prepared from propargyl alcohol and 1,3-dibromobenzene or 1,4-dibromonaphthalene or 2,7-dibromonaphthalene or 4,4′-diiodobiphenyl and 2,5-dibromothiophene via double Pd(0)-mediated Sonogashira coupling.[26,27]

The resulting diynes were reduced under Pd/C-catalyzed hydrogenation to generate the corresponding alkyl diol derivatives **36**−**40**. Then the alcohols were activated using TsCl, giving rise to the corresponding intermediates **41**−**45**. Finally, the desired hydrochloride bis-thiazolium salts **7**, **8a**, **8b**, **9**, **10**, **11a**, and **11b** were isolated in moderate yields (37−60%) using the same procedure as described for compound **1a**.

*1.3. Diethynyl-Benzenyl as Scaffold.* The synthesis of bis-thiazolium salts **12a**, **12b**, and **13** was initiated with Sonogashira coupling of 1,4-diiodobenzene with 3-butyn-1-ol or 2-propyn-1-ol (Scheme 3).[28] The resulting diols **46** and **47** were converted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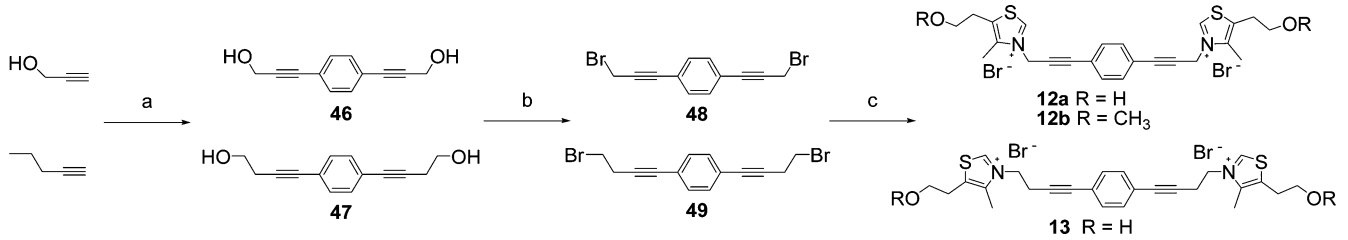
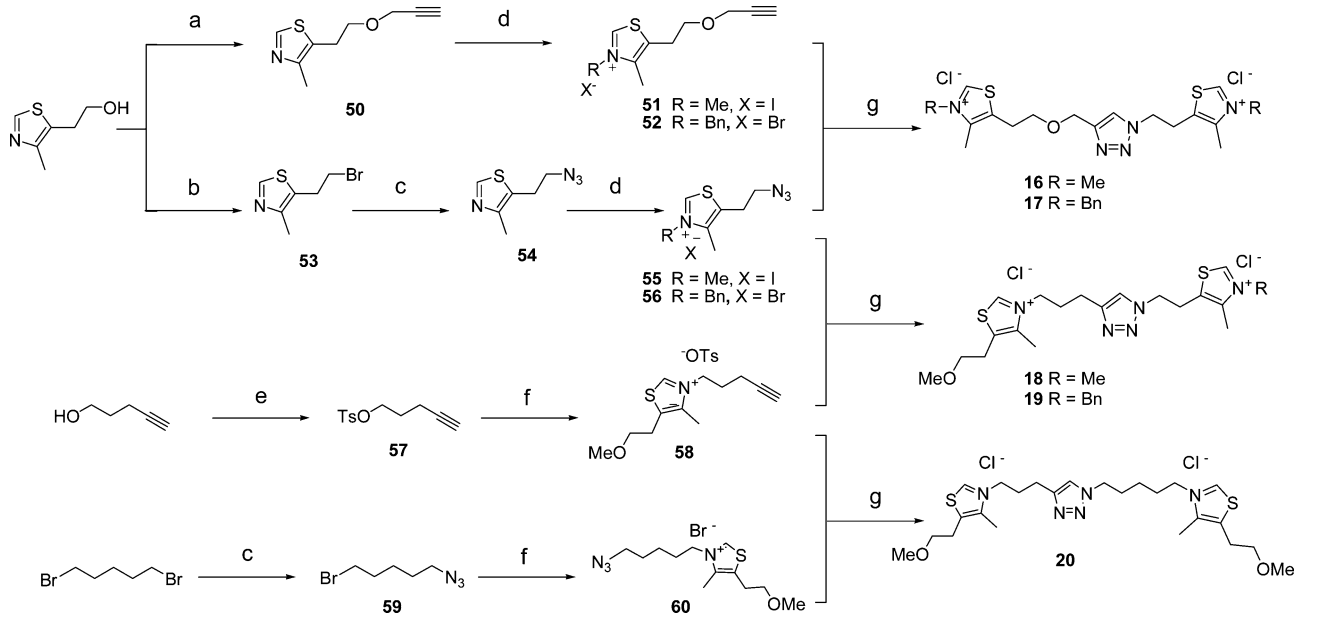
**Scheme 3. Synthetic Pathways for Linkers Including Diethynyl-Benzenyl Moiety**[a]




[a]Reagents and conditions: (a) 1,4-diodobenzene, $Pd[P(Ph)_3]_4$, CuI, $NEt_3$, $CH_2Cl_2$, 92%; (b) $Br_2$, $P(Ph)_3$, $CH_2Cl_2$, quantitative; (c) 4-Me-5-(2-hydroxyethyl)- or 4-Me-5-(2-methoxyethyl) thiazole, $CH_3CN$, MW, then Dowex $Cl^-$, 31−68%.

**Scheme 4. Synthetic Pathways for Linkers Including the 1,2,3-Triazole Moiety**[a]




[a]Reagents and conditions: (a) propargyl bromide, $CH_3CN$, 92%; (b) $PBr_3$, $CH_2Cl_2$, 98%; (c) $NaN_3$, DMF, 98% for **54** and 38% for **59**; (d) MeI or BnBr, $CH_3CN$, 75−98%; (e) TsCl, $NEt_3$, DMAP, $CH_2Cl_2$, 97%; (f) 4-Me-5-(2-methoxyethyl)thiazole, $CH_3CN$, 70−86%; (g) $CuSO_4{\cdot}5H_2O$−sodium ascorbate (2% and 10%, respectively), water/*t*BuOH (1/1, v/v), MW, then Dowex $Cl^-$, 32−56%.

to bromides **48** and **49** using bromine and triphenylphosphine. Finally, *N*-alkylation of the thiazolium ring was performed under MW activation as described above, leading to the desired bromide salts **12a**, **12b**, and **13** in moderate yields (31−68%).

*1.4. Triazole Ring as Scaffold.* Formation of the 1,2,3-triazole linkage (Figure 2, compounds **16**−**20**) was envisaged via Huisgen copper(I)-catalyzed 1,3-dipolar cycloaddition between thiazolium derivatives containing alkynyl- and azide functionalities, which were synthesized from 4-methyl-5-(2-hydroxyethyl)- or 4-methyl-5-(2-methoxyethyl)thiazole (Scheme 4).

Selective *O*-propargylation of 4-methyl-5-(2-hydroxyethyl)-thiazole was performed in the absence of a base, leading to terminal alkyne **50**, which in turn was converted to monothiazolium cations **51** and **52** by *N*-alkylation using methyl iodide or benzyl bromide in refluxing acetonitrile. Alkyne **58** was obtained by *N*-alkylation of thiazole using the tosylated intermediate **57**, which was prepared from commercially available 5-pentyn-1-ol.

Thiazolium-cationic azide counterparts **55** and **56** were generated from the common azide intermediate **54** by *N*-alkylation of the thiazole using methyl iodide or benzyl bromide as described for compounds **51** and **52**. Synthesis of azide **54** was performed by bromination of 4-methyl-5-(2-hydroxyethyl)-thiazole, followed by treatment of the resulting bromide **53** by $NaN_3$ in refluxing DMF. The last thiazolium-cationic azide, i.e., compound **60**, was isolated using the same procedure starting from bromoazidopentane **59**, which was obtained by monoazidation of 1,5-dibromopentane in the presence of $NaN_3$ in moderate yield (38%).[29]

Several reaction conditions for the copper(I) catalyzed azide−alcyne cycloaddition step were tested.[30] The selected ones require oxygen-free solvents, a fresh mixture of $CuSO_4{\cdot}5H_2O$/sodium ascorbate under MW irradiations.[31] The desired bis-thiazolium salts **16** and **17** were obtained from alkyne **51** and azide **55** and alkyne **52** and azide **56**, respectively. Using the same procedure, compounds **18** and **19** were prepared by coupling azides **55** or **56** with alkyne **58**, respectively. Finally, compound **20** was obtained from alkyne **58** and azide **60** in 32% yield.

As we hypothesized that the molecular properties may influence the biological effect and especially the oral bioavailability,[11,12,22] all bis-thiazolium derivatives were studied through molecular modeling (optimization of the geometry, intercationic distance), and a few parameters related to lipophilicity (clogP), number of H-bond donors and acceptors,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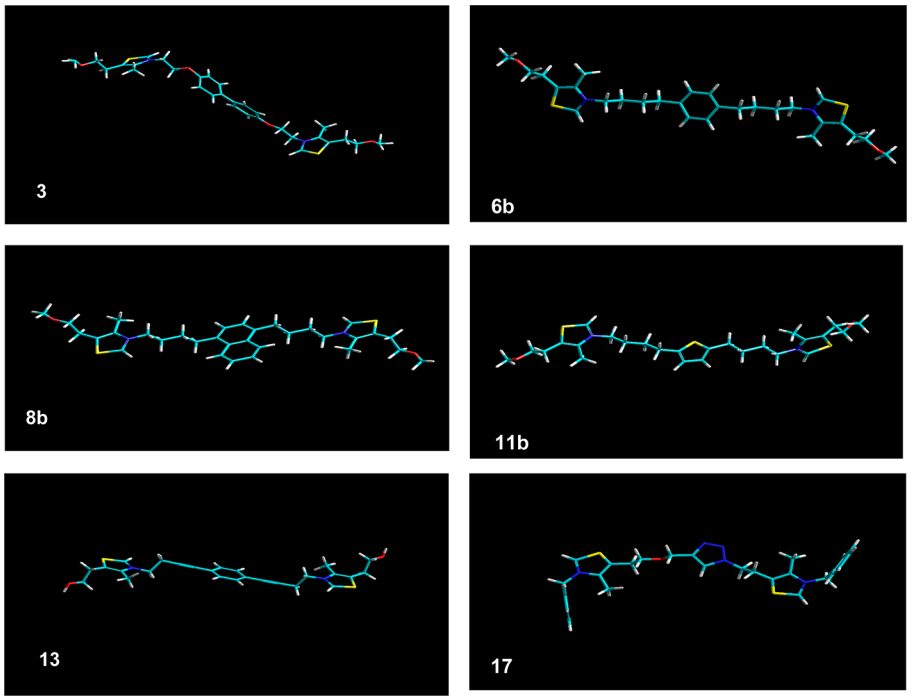


**Figure 3.** Molecular models of the selected compounds after optimization of their 3D geometry.

molecular flexibility (number of rotatable bonds, n rotb) were calculated. Selected data are reported in the following table in comparison to previously studied drugs such as **T3** and compounds **6a**, **6b**, **14**, and **15**. Optimization of the geometry revealed that most of the compounds had nearly the same profile, as illustrated in Figure 3, with the same "up and down" orientation of the thiazolium ring with regard to the rest of the molecule.

The average intercationic distance of 14.0−16.5 Å (16 compounds among 27) was in agreement with the previously reported pharmacophore.[6] However, for derivatives **12a** and **12b**, the triple bond on each side of the phenyl ring shortened the intercationic distance to 12−13 Å and fixed the rigid geometry with fewer than eight rotatable bonds (n rotb). This feature was also noted with compounds including a triazole ring, such as **16**, **17**, **18**, and **19**, that exhibited an n rotb ranging from 8 to 12.

The studied derivatives could be divided in two groups on the basis of the number of H-bonds. Most of the compounds had four H-bond acceptors (n ON), whereas derivatives including either two phenyl rings (**1a**, **1b**, **2**, **3**, and **4**) or a triazole moiety (**16**−**20**) had a higher n ON value of 6 or 7.

**2. Antimalarial Activity.** The newly synthesized series of bis-thiazolium derivatives were evaluated against *P. falciparum* in cell experiments and in vivo against *Plasmodium vinckei* in mice by intraperitoneal (ip) administration (Table 1).

*2.1. In Vitro Biological Evaluation.* The in vitro antiplasmodial activities were evaluated against the Nigerian *P. falciparum* strain in comparison to the clinical candidate, with compounds **6a**, **6b**, **14**, and **15** used as reference drugs. Eleven of the newly designed bis-thiazolium salts exhibited potent antimalarial activity in the low nanomolar range ($IC_{50}$ < 100 nM), with eight compounds having an $IC_{50}$ of below 20 nM.

Compounds **6b** and **7**, which have the same chain length but anchored at para and meta positions on the phenyl ring, exhibited similar activities with $IC_{50}$ of 8.3 and 9 nM, respectively. The ortho orientation was previously shown to decrease the antimalarial activity.[22] As for compounds **6b** and **7**, a similar effect was obtained with naphthyl moieties when chains of the same length were anchored at the 1,4 or the 2,7 positions; compounds **8a**, **8b**, and **9** exhibited similar activities. Interestingly, compound **8b** was 4-fold more active than compound **6b**, showing that the presence of $\pi$-systems in the center of the linker may be an important feature of the pharmacophore of these derivatives. In addition, compound **9** exerted a low toxic effect against the human Jurkat lymphoblast cell lines, with an $IC_{50}$ of 465 $\mu$M, i.e., in the same range as our **T3** reference compound ($IC_{50}$ 347 $\mu$M), clearly indicating selective toxicity against *Plasmodium*-infected erythrocytes. Consequently, the in vitro therapeutic indexes were ∼170000 and 150000 for compounds **9** and **T3**, respectively.

For compounds containing two phenyl rings (**1a**, **1b**, **2**, **3**, and **4**), the in vitro antiplasmodial activities markedly varied with respect to their relative positions. When the two aromatic rings were located at the center of the linker, therefore increasing its rigidity, the antimalarial activity was not affected (**1a**, **1b**, **3**, and **10** with $IC_{50}$ < 22 nM). On the other hand, insertion of an alkyl chain between the two phenyl groups (compound **4**) substantially decreased the antimalarial activity ($IC_{50}$ 313 nM). The presence of a hydrophobic aryl group in close proximity to the quaternary amine likely induced an unfavorable modification in the pharmacophore.

More strained compounds incorporating an aromatic ring conjugated to triple bonds exhibited lower antiplasmodial activity with $IC_{50}$ > 100 nM (compounds **12a**, **12b**, and **13**); the increase in linker rigidity (6 < n rotb < 8) and shortening of the intercationic distance to 12−13 Å for derivatives **12a** and **12b** led to a substantial loss of pharmacological activity ($IC_{50}$ > 400 nM).

Besides, the introduction of oxygen atoms to further decrease the lipophilicity of the corresponding prodrug did not improve


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**Table 1. Physicochemical Parameters of the Studied Compounds and Selected Data from in Vitro and in Vivo Antimalarial Evaluations**

| Compounds | n ON [a] | n OHNH [a] | n rotb [a] | Inter-cation distance [b] (Å) | $IC_{50}$ [c] (nM) *P. falciparum* | $ED_{50}$ [d] (mg/kg) *P. vinckei* |
|---|---|---|---|---|---|---|
| **T3** $(CH_2)_{10}$, R=H | **4** | **2** | **17** | **16.416** | **2.25** | **0.2** |
| **1a**, R=H | 6 | 2 | 14 | 14.969 | 22 | >>1 [e] |
| **1b**, R=$CH_3$ | 6 | 0 | 16 | 14.968 | 22.5 | >1 [e] |
| **2**, R=$CH_3$ | 7 | 0 | 16 | 15.091 | 80 | >>2 [f] |
| **3**, R=$CH_3$ | 6 | 0 | 15 | 16.575 | 18.5 | >>0.6 [e] |
| **4**, R=$CH_3$ | 6 | 0 | 18 | | 313 | >>0.4 [e] |
| **5a**, R=H, n=2 | **4** | **2** | **12** | **10.251** | 77.5 | >>0.5 [e] |
| **5b**, R= $CH_3$, n=2 | **4** | **0** | **14** | **10.243** | 36.5 | >>1 [e] |
| **6a**, R=H, n=3 | **4** | **2** | **14** | **15.126** | 20.5 | 1.2 [e] |
| **6b**, R= $CH_3$, n=3 | **4** | **0** | **16** | **15.127** | 9 | **0.13** [f] |
| **7**, R=$CH_3$, n=3 | 4 | 0 | 16 | 14.047 | 8.3 | >1 [e] |
| **11a**, R=H, n=3 | 4 | 2 | 14 | 14.464 | 16.5 | >>0.6 [e] |
| **11b**, R= $CH_3$, n=3 | 4 | 0 | 16 | 14.474 | 2.7 | **0.28** [e] |
| **8a**, R=H, n=3 | 4 | 2 | 14 | 15.157 | 6.7 | >0.6 [e] |
| **8b**, R= $CH_3$, n=3 | 4 | 0 | 16 | 15.157 | 2.1 | >>0.6 [e] |
| **9**, R= $CH_3$, n=3 | 4 | 0 | 16 | 16.042 | 6.3 | **0.5** [e] |
| **10**, R= $CH_3$, n=3 | 4 | 0 | 17 | 15.495 | 2.5 | **0.7** [e] |
| **12a**, R=H, n=1 | 4 | 2 | 6 | 12.652 | 1250 | Nd |
| **12b**, R= $CH_3$, n=1 | 4 | 0 | 8 | 12.859 | 420 | Nd |
| **13**, R=H, n=2 | 4 | 2 | 8 | 15.358 | 173 | Nd |
| **14**, R= $CH_3$, n=4 | **4** | **0** | **13** | | 120 | Nd |
| **15**, R= Bn, n=4 | **4** | **0** | **17** | | 15 | |


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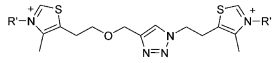
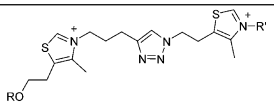
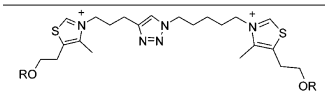
Table 1. continued

| Compounds | n ON [a] | n OHNH [a] | n rotb [a] | Inter-cation distance [b] (Å) | $IC_{50}$ [c] (nM) *P. falciparum* | $ED_{50}$ [d] (mg/kg) *P. vinckei* |
|---|---|---|---|---|---|---|
| **T3** $(CH_2)_{10}$, R=H | **4** | **2** | **17** | **16.416** | **2.25** | **0.2** |
|  **16**, R= $CH_3$ | 6 | 0 | 8 | 15.682 | 10000 | Nd |
| **17**, R= Bn | 6 | 0 | 12 | 15.670 | 640 | Nd |
|  **18**, R= $CH_3$ | 6 | 0 | 10 | 12.086 | 8200 | Nd |
| **19**, R= Bn | 6 | 0 | 12 | 12.089 | 7000 | Nd |
|  **20**, R= $CH_3$ | 7 | 0 | 16 | 12.237 | 1200 | Nd |

[a]Physicochemical parameters such as n ON (number of hydrogen bond acceptors), n OHNH (number of hydrogen bond donors), and n rotb (number of rotatable bonds) were calculated using the Mol Inspiration software program. [b]The intercationic distance was determined after modeling and optimization of the geometry of each compound using HyperChem software. [c]$IC_{50}$ values against *P. falciparum* in vitro are means of at least two independent experiments, with each being conducted in duplicate. [d]Antimalarial activities (efficient dose 50, $ED_{50}$) were determined against *P. vinckei* in mice after intraperitoneal (ip) administration of the compounds once daily for 4 days. $ED_{50}$ values were determined only when a decrease in parasitemia of at least 85% was observed during the experiment. When the decrease in parasitemia at the last dose was <10%, the $ED_{50}$ is indicated as "≫" at the highest dose. When the decrease in parasitemia at the last dose was between 10 and 50%, the $ED_{50}$ is indicated as ">" at the highest dose. [e]Treatment at higher doses was stopped due to the onset of initial clinical signs of toxicity. [f]No sign of clinical toxicity was observed after ip administration at the doses used. Nd: not determined.

the antimalarial activity; compound **3** was 7-fold less potent than derivative **10**.

Surprisingly, the compound including thiophene as heterocycle (**11b**, $IC_{50}$ = 2.7 nM) appeared to be as potent as our current clinical candidate, whereas the presence of the triazole ring dramatically decreased the antimalarial activity ($IC_{50}$ ≫ 640 nM). Note that in this last series several parameters may be considered as unfavorable, i.e., the number of hydrogen bond acceptors (n ON) was equal to or above 6, the number of rotatable bonds (n rotb) was lower or equal to 12 (except for derivative **20**), and the intercationic distance was lower than the average value of 14.0−16.5 Å. The toxicity of compound **11b** against Jurkat cells was moderate ($IC_{50}$ 63 $\mu$M).

*2.2. In Vivo Biological Evaluation.* Only compounds exhibiting potent in vitro antiplasmodial activity ($IC_{50}$ < 100 nM) were tested in vivo. In vivo antimalarial activities were evaluated against the *P. vinckei* strain (279BY) in female Swiss mice. The compounds were tested in infected mice by intraperitoneal (ip) or oral (po) administration once daily for four consecutive days (days 1−4 postinfection). The parasitemia levels were monitored in mice at day 5.

Most of the compounds containing bis-phenyl moieties (**1a**, **1b**, **2**, **3**, and **4**) exhibited significant antimalarial activity in vitro, but the parasitemia clearance was not achieved in vivo, so the $ED_{50}$ ip value could not be determined. For compounds including oxygen atoms within the linker, significant toxicity was observed in mice, thus overruling their use at higher doses. Their potential antimalarial activity could have been concealed by this toxic effect.

On the other hand, potent in vivo antimalarial activities were observed for compounds incorporating naphthyl (**9**), thiophenyl (**11b**), and biphenyl (**10**), with an $ED_{50}$ ip of 0.5, 0.28, and 0.7 mg/kg (Figure 4). These three compounds were able to clear antimalarial infections in mice at very low doses, comparable to that of the lead compound ($ED_{50}$ = 0.2 mg/kg). These four derivatives showed common features, such as an n ON = 4, n OHNH = 0, n rotb = 16 (17 for compound **10**), and an intercationic distance of 14.5−16.0 Å.

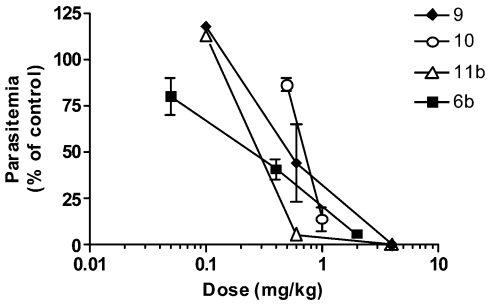



**Figure 4.** In vivo antimalarial activity of the best compounds (**6b**, **9**, **10**, and **11b**) in *P. vinkei*-infected mice. Mice were infected by intravenous injection of $10^7$ parasites, leading to parasitemia of 0.5−1% on day 1. The treatment consisted of a daily ip injection for 4 consecutive days. Results are the mean of three mice per dosage ± SEM.

## CONCLUSION

Our previous findings highlighting the presence of a phenyl ring in the middle of the lipophilic spacer of bisthiazolium salts resulted in the development of potent new drugs and may be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considered as a way to optimize the pharmacophore.[10,15] Thus, we explored new modifications with the aim of decreasing the molecular flexibility of the linker through the introduction of biphenyl or naphthyl rings as well as triple bonds. These modifications may help to optimize the bioavailability after oral administration of the corresponding neutral prodrugs. Compounds including a biaryl, naphthyl, or thiophenyl moiety were synthesized by coupling previously prepared halogenated or tosylated linkers under microwave irradiation. For derivatives containing a triazole ring, we developed an original approach involving the formation of a heteroaromatic ring in the last synthesis step through CuAAC coupling performed with cationic precursors.

The structure−activity relationships suggested that the presence of two aromatic groups was well tolerated, leading to bisthiazolium salts with valuable in vitro and in vivo activities. Compounds **9** and **10**, respectively, incorporating naphthyl and biphenyl moieties, were thus able to cure malarial infection in mice at very low doses (<1 mg/kg). We also assessed the introduction of heterocycles here and found that the presence of a thiophene ring in the center of the linker boosted the potency of compound **11b** after oral administration. Further synthesis and studies on the corresponding neutral precursors will be carried out to evaluate the impact of such linker modifications on the oral bioavailability.

## EXPERIMENTAL SECTION

**Chemistry.** *General Experimental Information.* All moisture-sensitive reactions were carried out under rigorous anhydrous conditions with argon atmosphere and using oven-dried glassware. Solvents were dried and distilled prior to use, and solids were dried over $P_2O_5$ under reduced pressure. $^1H$ NMR and $^{13}C$ NMR spectra were recorded at ambient temperature on a Bruker 300 Avance or DRX 400. Chemical shifts ($\delta$) are quoted in parts per million (ppm) referenced to the residual solvent peak, ($CDCl_3$ fixed at 7.26 and 77.16 ppm, DMSO-$d_6$ fixed at 2.50 and 39.52 ppm) relative to tetramethylsilane (TMS). Deuterium exchange and COSY experiments were performed in order to confirm proton assignments. Coupling constants, $J$, are reported in hertz. 2D $^1H-^{13}C$ heteronuclear COSY was recorded for the attribution of $^{13}C$ signals when needed. ESI mass and high resolution mass spectra were recorded in the positive or negative-ion mode on a Micromass Q-TOF. Thin-layer chromatography was performed on precoated aluminum sheets of Silica 60 F254 (Merck, Art. 5554), visualization of products being accomplished by UV absorbance and by charring with a phosphomolybdic acid solution (20 wt % in ethanol) and heating. Chromatography was performed on Merck Silica Gel 60 (230−400 mesh ASTM) or on Merck Lichroprep RP18 (25−40 $\mu$m) using an Isco purification system (Tris peristaltic pump, UA-6 UV detector, type 11 optical unit 254 nm). Analytical HPLC chromatograms were obtained using a Waters HPLC system (separation module 2695, 996 photodiode array detector 2996) and a Waters Symmetry Shield (50 mm × 4.6 mm, 3.5 $\mu$m) RP-18-column with a 1 mL/min flow rate. The elution solvents were water containing 0.1% (v/v) of TFA (solvent A) and acetonitrile containing 0.1% (v/v) TFA (solvent B). A linear gradient was performed from 100% of solvent A to 100% of solvent B in 7 or 15 min. All tested compounds were confirmed to have ≥95% purity, determined by HPLC. Molecular models and optimized geometry were obtained by performing energy minimization calculations with HyperChem software.

**Procedure A for Tosylation of Diol Intermediates, Compounds 24, 25, 41−45, and 57.** Anhydrous triethylamine (4 equiv), 4-(dimethylamino)pyridine (0.2 equiv), and toluene-4-sulfonyl chloride (2.8 equiv) were added to an ice-cooled solution of the appropriate alcohol derivative in anhydrous $CH_2Cl_2$ (0.1 M). The mixture was stirred at room temperature (2 to 16 h) and then diluted with $CH_2Cl_2$. The organic layer was washed successively with water and brine and finally dried over $MgSO_4$. The solvent was removed in vacuum, and the residue was purified by column chromatography ($CH_2Cl_2$/MeOH), affording the expected bis-tosylated derivative.

*((Methylene Bis(4,4′-phenylene))bis(oxy))bis(ethane-2,1-diyl)bis-(4-ethylbenzenesulfonate)* ***24***. According to procedure A, the title compound (1.07 g, 95%) was obtained, as a white solid, from compound **21**. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.81 (d, 4H, $J$ = 8.3), 7.33 (d, 4H, $J$ = 8.0), 7.03 (d, 4H, $J$ = 8.7), 6.70 (d, 4H, $J$ = 8.7), 4.34 (m, 4H), 4.11 (dd, 4H, $J$ = 4.0, 5.6), 3.83 (s, 2H), 2.44 (s, 6H). MS (ESI+): 597.3 $[M + H]^+$.

*((Carbonylbis(4,4′-phenylene))bis(oxy))bis(ethane-2,1-diyl)bis(4-ethylbenzenesulfonate)* ***25***. According to procedure A, the title compound (1.2 g, 59%) was obtained as a white solid from compound **22**. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.82 (d, 4H, $J$ = 8.3), 7.72 (d, 4H, $J$ = 8.8), 7.35 (d, 4H, $J$ = 8.0), 6.84 (d, 4H, $J$ = 8.8), 4.40 (dd, 4H, $J$ = 3.7, 5.6), 4.23 (dd, 4H, $J$ = 3.7, 5.6), 2.45 (s, 6H).

*1,3-Phenylenebis(butane-4,1-diyl)bis(4-methylbenzenesulfonate)* ***41***. According to procedure A, the title compound (3.78 g, 87%) was obtained, as a colorless oil, from compound **36**. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.78 (d, 4H, $J$ = 8.0), 7.33 (d, 4H, $J$ = 8.0), 7.15 (m, 1H), 6.90 (m, 3H), 4.02 (t, 4H, $J$ = 6.0), 2.52 (t, 4H, $J$ = 7.1), 2.43 (s, 6H), 1.65 (m, 8H). MS (ESI+): 531.2 $[M + H]^+$.

*Naphthalene-1,4-diylbis(butane-4,1-diyl)bis(4-methylbenzenesulfonate)* ***42***. According to procedure A, the title compound (2.16 g, 84%) was obtained, as a colorless oil, from compound **37**. $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.95 (dd, 2H, $J$ = 3.3, 6.5), 7.75 (d, 4H, $J$ = 8.3), 7.47 (dd, 2H, $J$ = 3.3, 6.5), 7.29 (d, 4H, $J$ = 8.0), 7.12 (s, 2H), 4.04 (m, 4H), 2.97 (m, 4H), 2.39 (s, 6H), 1.74 (m, 9H).

*Naphthalene-2,7-diylbis(butane-4,1-diyl)bis(4-methylbenzenesulfonate)* ***43***. According to procedure A, the title compound (0.90 g, 92%) was obtained, as a colorless oil, from compound **38**. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.77 (dd, 4H, $J$ = 1.6, 8.4), 7.70 (d, 2H, $J$ = 8.4), 7.46 (s, 2H), 7.30 (d, 4H, $J$ = 8.0), 7.20 (dd, 2H, $J$ = 1.6, 8.4), 4.05 (t, 4H, $J$ = 5.8), 2.72 (t, 4H, $J$ = 6.9), 2.42 (s, 6H), 1.72 (m, 8H). MS (ESI +): 581.2 $[M + H]^+$.

*[1,1′-Biphenyl]-4,4′-diylbis(butane-4,1-diyl)bis(4-methylbenzenesulfonate)* ***44***. According to procedure A, the title compound (0.63 g, 51%) was obtained, as a white solid, from compound **39**. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.79 (d, 4H, $J$ = 8.3), 7.47 (d, 4H, $J$ = 8.2), 7.33 (d, 4H, $J$ = 8.0), 7.17 (d, 4H, $J$ = 8.2), 4.05 (m, 4H), 2.60 (m, 4H), 2.44 (s, 6H), 1.70 (m, 9H). MS (ESI+): 607.4 $[M + H]^+$.

*Thiophene-2,5-diylbis(butane-4,1-diyl)bis(4-methylbenzenesulfonate)* ***45***. According to procedure A, the title compound (3.33 g, 96%) was obtained, as a yellow oil, from compound **40**. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.78 (d, 4H, $J$ = 8.5), 7.34 (d, 4H, $J$ = 8.5), 6.48 (s, 2H), 4.02 (t, 4H, $J$ = 6.0), 2.68 (t, 4H, $J$ = 7.0), 2.44 (s, 6H), 1.68 (m, 8H). MS (ESI+): 537.2 $[M + H]^+$.

*Pent-4-ynyl 4-Methylbenzenesulfonate* ***57***. According to procedure A, the title compound (8.56 g, 97%) was obtained, as an oil, from commercially available 5-penty-1-ol (3.0 g, 35.66 mmol). HPLC ($r_t$ = 10.05 min, purity 99%). $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.76 (d, 2H, $J$ = 8.1), 7.32 (d, 2H, $J$ = 8.1), 4.11 (t, 2H, $J$ = 6.1), 2.41 (s, 3H), 2.22 (td, 2H, $J$ = 6.9, 2.6), 1.90−1.76 (m, 3H). MS (ESI +): 239.1.

**Procedure B for Bromination of Diol Intermediates, Compounds 26, 48, and 49.** To an ice-cooled solution of triphenylphosphine (2.7 equiv) in anhydrous $CH_2Cl_2$ (8 mL/mmol), bromine was added (2.5 equiv). The mixture was stirred under nitrogen until the solution became colorless (ca. 15 min), and then the alcohol derivative was added. The reaction mixture was stirred for 1 h and then allowed to reach room temperature and stirred overnight. The crude material was filtered through a silica gel pad subsequently washed with $CH_2Cl_2$.

*4,4′-Bis(2-bromoethoxy)-1,1′-biphenyl* ***26***. According to procedure B, the residue was purified by column chromatography (petroleum ether/dichloromethane: 8/2) affording the expected compound (0.42 g, 59%) as a white solid from compound **23**. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.55 (d, 4H, $J$ = 8.8), 7.03 (d, 4H, $J$ = 8.8), 4.36 (t, 4H, $J$ = 5.4), 3.82 (t, 4H, $J$ = 5.4).

*1,4-Bis(3-bromoprop-1-yn-1-yl)benzene* ***48***. According to procedure B, the title compound (2.5 g, quantitative) was obtained, as a slightly yellow solid, from compound **46** (1.5 g, 8.06 mmol). The


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crude material was used in the next step after a simple filtration over silica gel. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.31 (s, 4H), 4.09 (s, 4H).

*1,4-Bis(4-bromobut-1-yn-1-yl)benzene* ***49***. According to procedure B, the title compound (0.8 g, quantitative) was obtained, as a white solid, from compound **47** (0.5 g, 1.07 mmol). The crude material was used in the next step after a simple filtration over silica gel. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.28 (s, 4H), 3.45 (t, 4H, $J$ = 7.3), 2.91 (t, 4H, $J$ = 7.2).

**Procedure C for Preparation of Bis-thiazolium Salts (Compounds 1a,b, 2−4, 7, 8a,b, 9, 10, 11a,b, 12a,b, and 13) and Derivatives 58 and 60.** To a solution of 4-methyl-5-(2-hydroxyethyl)thiazole or 4-methyl-5-(2-methoxyethyl)thiazole (3 equiv) in dry acetonitrile was added the appropriate dibromo or ditosyl intermediate. The reaction mixture was stirred at reflux for several hours to few days or submitted to MW irradiations (1−3.5 h, 120−150 °C, 400 W), then water was added and the mixture was extracted with $Et_2O$. The aqueous layer was concentrated under reduced pressure, and the crude was purified by RP-18 chromatography (gradient: $H_2O$ to MeOH). When needed, the tosylate counterions were exchanged to chloride by adding to the aqueous solution a Dowex resin (1 × 8−400, $Cl^-$ form). After 2 h to 5 days stirring, the resin was filtered off and the filtrate was concentrated and freeze-dried.

*3,3′-(((Methylenebis(4,4′-phenylene))bis(oxy))bis(ethane-2,1-diyl))bis(5-(2-hydroxy ethyl)-4-methylthiazol-3-ium) Chloride* ***1a***. According to procedure C, the title compound (422 mg, 82%) was obtained, as a white solid, from compound **24** (0.5 g, 0.84 mmol), 4-methyl-5-(2-hydroxyethyl)thiazole (0.36 g, 2.51 mmol), and acetonitrile (1 mL) after 3.5 h under MW irradiation at 120 °C. HPLC ($r_t$ = 5.67 min, purity 98%). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.21 (s, 2H), 7.09 (d, 4H, $J$ = 8.5), 6.83 (d, 4H, $J$ = 8.6), 4.92 (t, 4H, $J$ = 4.7), 4.38 (t, 4H, $J$ = 4.8), 3.78 (s, 2H), 3.62 (t, 4H, $J$ = 5.6), 3.03 (t, 4H, $J$ = 5.6), 2.53 (s, 6H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 157.7, 155.7, 141.9, 135.0, 134.6, 129.6, 114.5, 65.3, 59.6, 51.9, 39.2, 29.5, 11.5. HRMS (TOF-ESI+) calcd for $C_{29}H_{36}ClN_2O_4S_2^+$ [M − Cl]$^+$, 575.1805; found, 575.1808.

*3,3′-(((Methylenebis(4,4′-phenylene))bis(oxy))bis(ethane-2,1-diyl))bis(5-(2-ethoxyethyl)-4-methylthiazol-3-ium) Chloride* ***1b***. According to procedure C, the title compound (0.91 g, 84%) was obtained, as a white solid, from compound **24** (1.0 g, 1.67 mmol) and 4-methyl-5-(2-methoxyethyl)thiazole (0.79 g, 5.03 mmol) in acetonitrile (4 mL) after 2.5 h under MW irradiation at 150 °C. HPLC ($r_t$ = 6.33 min, purity 98%). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.27 (s, 2H), 7.09 (d, 4H, $J$ = 8.6), 6.83 (d, 4H, $J$ = 8.6), 4.93 (t, 4H, $J$ = 4.7), 4.38 (t, 4H, $J$ = 4.8), 3.78 (s, 2H), 3.55 (t, 4H, $J$ = 5.7), 3.28 (s, 6H), 3.14 (t, 4H, $J$ = 5.7), 2.53 (s, 6H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 158.3, 155.7, 142.2, 134.5, 129.6, 114.5, 70.3, 65.4, 60.0, 52.0, 39.2, 26.5, 11.5. HRMS (TOF-ESI+) calcd for $C_{31}H_{40}ClN_2O_4S_2^+$ [M − Cl]$^+$, 603.2118; found, 603.2109.

*3,3′-(((Carbonylbis(4,4′-phenylene))bis(oxy))bis(ethane-2,1-diyl))bis(5-(2-methoxyethyl)-4-methylthiazol-3-ium) Chloride* ***2***. According to procedure C, the title compound (730 mg, 68%) was obtained, as a yellow amorphous solid, from compound **25** (1.0 g, 1.63 mmol) and 4-methyl-5-(2-methoxyethyl)thiazole (0.77 g, 4.91 mmol) in acetonitrile (1.5 mL) after 1.5 h under MW irradiation at 150 °C. HPLC ($r_t$ = 6.02 min, purity 100%). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.39 (s, 2H), 7.67 (d, 4H, $J$ = 8.8), 7.09 (d, 4H, $J$ = 8.8), 5.03 (t, 4H, $J$ = 4.6), 4.57 (t, 4H, $J$ = 4.7), 3.56 (t, 4H, $J$ = 5.7), 3.29 (s, 6H), 3.16 (t, 4H, $J$ = 5.7), 2.57 (s, 6H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 193.1, 160,8, 158.4, 142.2, 134.6, 131.8, 130.6, 114.4, 70.3, 65.7, 58.0, 51.8, 26.6, 11.54. HRMS (TOF-ESI+) calcd for $C_{31}H_{38}ClN_2O_5S_2^+$ [M − Cl]$^+$, 617.1911; found, 617.1910.

*3,3′-(([1,1′-Biphenyl]-4,4′-diylbis(oxy))bis(ethane-2,1-diyl))bis(5-(2-methoxyethyl)-4-methyl thiazol-3-ium) Bromide* ***3***. According to procedure C, the title compound (0.25 g, 74%) was obtained, as a white solid, from compound **26** (0.19 g, 0.47 mmol) and 4-methyl-5-(2-methoxyethyl)thiazole (0.22 g, 1.42 mmol) in acetonitrile (10 mL) after 2 days refluxing. HPLC ($r_t$ = 6.26 min, purity 100%). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.13 (s, 2H), 7.54 (d, 4H, $J$ = 8.8), 6.98 (d, 4H, $J$ = 8.8), 4.94 (t, 4H, $J$ = 4.7), 4.46 (t, 4H, $J$ = 4.8), 3.56 (t, 4H, $J$ = 5.7), 3.29 (s, 6H), 3.16 (t, 4H, $J$ = 5.7), 2.56 (s, 6H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 157.9, 156.7, 142.2, 134.7, 132.9, 127.4, 115.1, 70.3, 65.3, 58.0, 52.1, 26.6, 11.5. HRMS (TOF-ESI+) calcd for $C_{30}H_{38}BrN_2O_4S_2^+$ [M − Br]$^+$, 633.1456; found, 633.1459.

*3,3′-(((Pentane-1,5-diylbis(oxy))bis(4,1-phenylene))bis(methylene))bis(5-(2-ethoxyethyl)-4-methylthiazol-3-ium) Chloride* ***4***. According to procedure C, the title compound (0.24 g, 45%) was obtained, as a white solid, from compound **30** (0.30 g, 0.85 mmol) and 4-methyl-5-(2-methoxyethyl)thiazole (0.73 g, 1.13 mmol) in acetonitrile (10 mL) after 1 h under MW irradiation at 120 °C. HPLC ($r_t$ = 7.16 min, purity 100%). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.13 (s, 2H), 7.32 (d, 4H, $J$ = 8.7), 7.00 (d, 4H, $J$ = 8.7), 5.69 (s, 4H), 3.99 (t, 4H, $J$ = 6.3), 3.55 (t, 4H, $J$ = 5.7), 3.29 (s, 6H), 3.12 (t, 4H, $J$ = 5.7), 2.39 (s, 6H), 1.77 (m, 4H), 1.56 (m, 2H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 159.1, 156.9, 141.8, 135.7, 130.1, 124.4, 115.0, 70.2, 67.5, 58.0, 55.5, 28.4, 26.5, 22.2, 11.5.

*3,3′-(1,3-Phenylenebis(butane-4,1-diyl))bis(5-(2-methoxyethyl)-4-methylthiazol-3-ium) Chloride* ***7***. According to procedure C, the title compound (0.64 g, 60%) was obtained, as a white solid, from compound **41** (1 g, 1.71 mmol) and 4-methyl-5-(2-methoxyethyl)-thiazole (0.81 g, 5.15 mmol) in acetonitrile (3.5 mL) after 2 h under MW irradiation at 140 °C. HPLC ($r_t$ = 6.05 min, purity 99%). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.28 (s, 2H), 7.20 (m, 1H), 7.04 (m, 3H), 4.54 (t, 4H, $J$ = 7.4), 3.57 (t, 4H, $J$ = 5.7), 3.30 (s, 6H), 3.14 (t, 4H, $J$ = 5.7), 2.61 (t, 4H, $J$ = 7.5), 2.46 (s, 6H), 1.81 (m, 4H), 1.61 (m, 4H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 156.7, 141.7, 141.6, 135.2, 128.4, 125.8, 70.3, 58.1, 52.6, 34.3, 28.5, 27.4, 26.6, 11.2. HRMS (TOF-ESI+) calcd for $C_{28}H_{42}ClN_2O_2S_2^+$ [M − Cl]$^+$, 537.2376; found, 537.2366.

*3,3′-(Naphthalene-1,4-diylbis(butane-4,1-diyl))bis(5-(2-hydroxyethyl)-4-methylthiazol-3-ium) Chloride* ***8a***. According to procedure C, the title compound (340 mg, 53%) was obtained, as a white solid, from compound **42** (0.62 g, 1.06 mmol) and 4-methyl-5-(2-hydroxyethyl)thiazole (0.45 g, 3.18 mmol) in acetonitrile (10 mL) after 4 days refluxing. HPLC ($r_t$ = 5.89 min, purity 100%). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.16 (s, 1H), 8.10 (dd, 1H, $J$ = 3.3, 6.5), 7.56 (dd, 1H, $J$ = 3.3, 6.5), 7.30 (s, 1H), 5.37 (t, 1H, $J$ = 5.1), 4.55 (t, 2H, $J$ = 7.3), 3.63 (q, 2H, $J$ = 5.4), 3.05 (m, 4H), 2.47 (s, 3H), 1.94 (s, 2H), 1.70 (s, 2H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 156.3, 141.5, 136.1, 135.6, 131.7, 125.7, 125.6, 124.5, 59.6, 52.6, 31.5, 29.5, 28.9, 26.9, 11.3. HRMS (TOF-ESI+) calcd for $C_{30}H_{40}ClN_2O_2S_2^+$ [M − Cl]$^+$, 559.2220; found, 559.2231.

*3,3′-(Naphthalene-1,4-diylbis(butane-4,1-diyl))bis(5-(2-methoxyethyl)-4-methylthiazol-3-ium) Chloride* ***8b***. According to procedure C, the title compound (364 mg, 55%) was obtained, as a white solid, from compound **42** (0.62 g, 1.05 mmol) and 4-methyl-5-(2-methoxyethyl)thiazole (0.49 g, 3.15 mmol) in acetonitrile (10 mL) after 4 days refluxing. HPLC ($r_t$ = 6.67 min, purity 100%). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.21 (s, 2H), 8.10 (dd, 2H, $J$ = 3.3, 6.5), 7.55 (dd, 2H, $J$ = 3.3, 6.5), 7.29 (s, 2H), 4.55 (t, 4H, $J$ = 7.4), 3.56 (t, 4H, $J$ = 5.7), 3.29 (s, 6H), 3.10 (dt, 8H, $J$ = 6.6, 15.2), 2.48 (s, 6H), 1.94 (m, 4H), 1.69 (m, 4H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 156.6, 141.7, 136.1, 135.2, 131.7, 125.7, 125.6, 124.5, 70.3, 58.0, 52.6, 31.5, 28.8, 26.92, 26.54, 11.20. HRMS (TOF-ESI+) calcd for $C_{32}H_{44}ClN_2O_2S_2^+$ [M − Cl]$^+$, 587.2533; found, 587.2539.

*3,3′-(Naphthalene-2,7-diylbis(butane-4,1-diyl))bis(5-(2-methoxyethyl)-4-methylthiazol-3-ium) Chloride* ***9***. According to procedure C, the title compound (0.20 g, 46%) was obtained, as a white solid, from compound **43** (0.41 g, 0.69 mmol) and 4-methyl-5-(2-methoxyethyl)thiazole (0.33 g, 2.09 mmol) in acetonitrile (1.5 mL) after 2 h under MW irradiation at 150 °C. HPLC ($r_t$ = 6.84 min, purity 100%). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.19 (s, 2H), 7.80 (d, 2H, $J$ = 8.4), 7.62 (s, 2H), 7.33 (d, 2H, $J$ = 9.9), 4.53 (t, 4H, $J$ = 7.3), 3.56 (t, 4H, $J$ = 5.7), 3.29 (s, 6H), 3.13 (t, 4H, $J$ = 5.7), 2.79 (t, 4H, $J$ = 7.4), 2.45 (s, 6H), 1.86 (m, 4H), 1.71 (m, 4H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 156.7, 141.6, 139.2, 135.1, 133.3, 130.2, 127.5, 126.5, 125.7, 70.2, 58.0, 52.7, 34.4, 28.4, 27.2, 26.5, 11.1. (HRMS (TOF-ESI +) calcd for $C_{32}H_{44}ClN_2O_2S_2^+$ [M − Cl]$^+$, 587.2533; found. 587.2534.

*3,3′-([1,1′-Biphenyl]-4,4′-diylbis(butane-4,1-diyl))bis(5-(2-methoxyethyl)-4-ethylthiazol-3-ium) Chloride* ***10***. According to proce-


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dure C, the title compound (0.13 g, 39%) was obtained, as a slightly yellow solid, from compound **44** (0.30 g, 0.50 mmol) and 4-methyl-5-(2-methoxyethyl)thiazole (0.23 g, 1.48 mmol) in acetonitrile (1 mL) after 2 h under MW irradiation at 150 °C. HPLC ($r_t$ = 7.57 min, purity 100%). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.17 (s, 2H), 7.56 (d, 4H, $J$ = 8.2), 7.28 (d, 4H, $J$ = 8.2), 4.53 (t, 4H, $J$ = 7.4), 3.56 (t, 4H, $J$ = 5.7), 3.30 (s, 6H), 3.14 (t, 4H, $J$ = 5.7), 2.67 (t, 4H, $J$ = 7.5), 2.46 (s, 6H), 1.84 (m, 4H), 1.65 (m, 4H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 156.6, 141.7, 140.6, 137.7, 135.2, 128.9, 126.4, 70.3, 58.0, 52.6, 33.9, 28.5, 27.3, 26.5, 11.2. HRMS (TOF-ESI+) calcd for $C_{34}H_{46}N_2O_2S_2^{2+}$ [M − 2Cl]$^{2+}$, 289.1500; found, 289.1478.

*3,3′-(Thiophene-2,5-diylbis(butane-4,1-diyl))bis(5-(2-hydroxyethyl)-4-methylthiazol-3-ium) Chloride* ***11a***. According to procedure C, the title compound (0.28 g, 50%) was obtained, as a slightly yellow solid, from compound **45** (0.55 g, 1.01 mmol) and 4-methyl-5-(2-hydroxyethyl) thiazole (0.44 g, 2.78 mmol) in acetonitrile (2 mL) after 3 h under MW irradiation at 140 °C. HPLC ($r_t$ = 5.06 min, purity 100%). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.23 (s, 2H), 6.65 (s, 2H), 4.54 (t, 4H, $J$ = 7.4), 3.63 (t, 4H, $J$ = 5.6), 3.03 (t, 4H, $J$ = 5.6), 2.78 (t, 4H, $J$ = 7.5), 2.46 (s, 6H), 1.85 (m, 4H), 1.61 (m, 4H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 156.4, 141.8, 141.4, 135.6, 124.2, 59.6, 52.3, 29.5, 28.6, 28.3, 27.6, 11.2. HRMS (TOF-ESI+) calcd for $C_{24}H_{36}ClN_2O_2S_3^+$ [M − Cl]$^+$, 515.1627; found, 515.1619.

*3,3′-(Thiophene-2,5-diylbis(butane-4,1-diyl))bis(5-(2-methoxyethyl)-4-methylthiazol-3-ium) Chloride* ***11b***. According to procedure C, the title compound (0.31 g, 57%) was obtained, as a slightly yellow solid, from compound **45** (0.50 g, 0.93 mmol) and 4-methyl-5-(2-methoxy-ethyl)thiazole (0.44 g, 2.78 mmol) in acetonitrile (2 mL) after 5 days under reflux. HPLC ($r_t$ = 5.96 min, purity 100%). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.21 (s, 2H), 6.65 (s, 2H), 4.52 (t, 4H, $J$ = 7.4), 3.56 (t, 4H, $J$ = 5.7), 3.30 (s, 6H), 3.14 (t, 4H, $J$ = 5.7), 2.77 (t, 4H, $J$ = 7.5), 2.46 (s, 6H), 1.83 (m, 4H), 1.62 (m, 4H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 156.6, 141.8, 141.7, 135.2, 124.2, 70.3, 58.0, 52.4, 28.7, 28.3, 27.7, 26.5, 11.2. HRMS (TOF-ESI+) calcd for $C_{26}H_{40}ClN_2O_2S_3^+$ [M − Cl]$^+$, 543.1940; found, 543.1934.

*3,3′-(1,4-Phenylenebis(prop-2-yne-3,1-diyl))bis(5-(2-hydroxyethyl)-4-methylthiazol-3-ium) Bromide* ***12a***. According to procedure C, the title compound (0.26 g, 68%) was obtained, as a white solid, from compound **48** (0.20 g, 0.64 mmol) and 4-methyl-5-(2-hydroxyethyl) thiazole (0.27 g, 1.90 mmol) in acetonitrile (1 mL) after 2 h under MW irradiation at 150 °C. HPLC ($r_t$ = 4.38 min, purity 100%). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.23 (s, 2H), 7.61 (s, 4H), 5.78 (s, 4H), 5.24 (t, 2H, $J$ = 4.9), 3.66 (dd, 4H, $J$ = 5.3, 10.5), 3.06 (t, 4H, $J$ = 5.5), 2.57 (s, 6H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 157.0, 141.5, 136.1, 132.1, 121.7, 87.3, 82.7, 59.6, 43.5, 29.4, 11.4. HRMS (TOF-ESI +) calcd for $C_{24}H_{26}BrN_2O_2S_2^+$ [M − Br]$^+$, 517.0619; found, 517.0605.

*3,3′-(1,4-Phenylenebis(prop-2-yne-3,1-diyl))bis(5-(2-methoxyethyl)-4-methylthiazol-3-ium) Bromide* ***12b***. According to procedure C, the title compound (0.28 g, 68%) was obtained, as a white solid, from compound **48** (0.20 g, 0.64 mmol) and 4-methyl-5-(2-methoxyethyl) thiazole (0.30 g, 1.90 mmol) in acetonitrile (6 mL) after 2 h under MW irradiation at 150 °C. HPLC ($r_t$ = 5.45 min, purity 100%). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.25 (s, 2H), 7.61 (s, 4H), 5.78 (s, 4H), 3.58 (t, 4H, $J$ = 5.7), 3.18 (t, 4H, $J$ = 5.7), 2.57 (s, 6H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 157.3, 141.7, 135.8, 132.1, 121.7, 87.3, 82.7, 70.2, 58.0, 43.6, 26.5, 11.3. HRMS (TOF-ESI+) calcd for $C_{26}H_{30}BrN_2O_2S_2^+$ [M − Br]$^+$, 545.0932; found, 545.0950.

*3,3′-(1,4-Phenylenebis(but-3-yne-4,1-diyl))bis(5-(2-hydroxyethyl)-4-methylthiazol-3-ium) Bromide* ***13***. According to procedure C, the title compound (0.15 g, 31%) was obtained, as a white solid, from compound **49** (0.20 g, 0.59 mmol) and 4-methyl-5-(2-hydroxyethyl)-thiazole (0.25 g, 1.76 mmol) in acetonitrile (1 mL) after 2 h under MW irradiation at 150 °C. HPLC ($r_t$ = 4.90 min, purity 100%). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.15 (s, 2H), 7.37 (s, 4H), 5.22 (t, 2H, $J$ = 4.9), 4.75 (t, 4H, $J$ = 6.4), 3.64 (q, 4H, $J$ = 5.4), 3.13 (t, 4H, $J$ = 6.4), 3.04 (t, 4H, $J$ = 5.6), 2.53 (s, 6H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 157.3, 141.6, 135.4, 131.6, 122.1, 87.4, 83.1, 59.6, 50.7, 29.5, 19.9, 11.2. HRMS (TOF-ESI+) calcd for $C_{26}H_{30}BrN_2O_2S_2^+$ [M − Br]$^+$, 545.0932; found, 545.0949.

*5-(2-Methoxyethyl)-4-methyl-3-(pent-4-ynyl)thiazol-3-ium 4-methylbenzenesulfonate* ***58***. According to procedure C, the title compound (5.75 g, 86%) was obtained, as a yellow oil, from compound **57** (4.04 g, 16.96 mmol) and 5-(2-methoxyethyl)-4-methylthiazole (4 g, 25.44 mmol) in acetonitrile (38 mL) after 4 days reflux. HPLC ($r_t$ = 4.04 min, purity 98%). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.10 (s, 1H), 7.51 (d, 2H, $J$ = 8.0), 7.11 (d, 2H, $J$ = 8.0), 4.52 (t, 2H, $J$ = 7.1), 3.61 (t, 2H, $J$ = 5.4), 3.52 (s, 3H), 3.12 (t, 2H, $J$ = 5.4), 2.92 (t, 1H, $J$ = 2.0), 2.48 (s, 3H), 2.2−2.41 (m, 5H), 1.92−2.06 (m, 2H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 155.4, 144.3, 140.4, 136.1, 133.6, 126.6, 124.0, 81.1, 70.8, 68.8, 56.6, 50.5, 26.2, 25.1, 19.3, 13.4, 9.7. MS (ESI+): 224.1.

*3-(5-Azidopentyl)-5-(2-methoxyethyl)-4-methylthiazol-3-ium Bromide* ***60***. According to procedure C, the title compound (1.4 g, 70%) was obtained, as a yellow oil, from compound **59** (1.07 g, 5.73 mmol) and 5-(2-methoxyethyl)-4-methylthiazole (1.35 g, 8.59 mmol) in acetonitrile (8 mL) at reflux for 4 days. HPLC ($r_t$ = 5.11 min, purity 100%). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.11 (s, 1H), 4.49 (t, 2H, $J$ = 5.8), 3.59 (t, 2H, $J$ = 5.7), 3.40−3.35 (m, 2H). 3.32 (s, 3H), 3.16 (t, 2H, $J$ = 5.7), 2.49 (s, 3H), 1.90−1.80 (m, 2H), 1.66−1.55 (m, 2H), 1.44−1.34 (m, 2H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 156.0, 141.2, 134.6, 69.7, 57.5, 52.0, 49.8, 27.8, 27.1, 26.0, 22.3, 10.7. MS (ESI+): 269.1.

**Procedure D for Sonogashira Coupling Reaction, Compounds 31−35, 46, and 47.** Appropriate commercially available diiodo- or dibromo-aryl starting material was dissolved in an anhydrous mixture of $CH_2Cl_2/Et_3N$ (v/v, 1/3, 10 mL/mmol) then CuI (0.02 equiv), 3-butyn-1-ol, or 2-propyn-1-ol (2.5 equiv) and tetrakis(triphenylphosphine)palladium (0.01 equiv) were added. The reaction mixture was refluxed overnight, in the dark, under nitrogen atmosphere, and the solvent was evaporated under reduced pressure. The residue was taken up in AcOEt and washed successively with a saturated ammonium chloride aqueous solution, water, and finally dried over $MgSO_4$. The solvent was removed in vacuum, and the residue was purified by column chromatography (petroleum ether/AcOEt: 1/1) to afford the expected bis-(but-3-yn-1-ol) or bis(prop-2-yn-1-ol) derivative.

*4,4′-(1,3-Phenylene)bis(but-3-yn-1-ol)* ***31***. According to procedure D, the title compound (2.88 g, 89%) was obtained, as a white solid, from 1,3-dibromobenzene (3 g, 10.5 mmol), CuI (0.12 g), 3-butyn-1-ol (2 mL), and tetrakis(triphenylphosphine)palladium (0.36 g). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.47 (s, 1H), 7.32 (m, 2H), 7.21 (m, 1H), 3.80 (t, 4H, $J$ = 6.3), 2.68 (t, 4H, $J$ = 6.3). MS (ESI+): 215.1 [M + H]$^+$.

*4,4′-(Naphthalene-1,4-diyl)bis(but-3-yn-1-ol)* ***32***. According to procedure D, the title compound (1.85 g, 67%) was obtained, as a white solid, from 1,4-dibromonaphthalene (3 g, 10.5 mmol), CuI (0.12 g), 3-butyn-1-ol (2 mL), and tetrakis(triphenylphosphine)palladium (0.36 g). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.31 (dd, 2H, $J$ = 3.3, 6.5), 7.61 (dd, 2H, $J$ = 3.3, 6.5), 7.55 (s, 2H), 3.90 (t, 4H, $J$ = 6.28), 2.84 (t, 4H, $J$ = 6.28), 1.93 (s, 2H). MS (ESI+): 265.2 [M + H]$^+$.

*4,4′-(Naphthalene-2,7-diyl)bis(but-3-yn-1-ol)* ***33***. According to procedure D, the title compound (1.29 g, 62%) was obtained, as a white solid, from 2,7-dibromonaphthalene (3 g, 10.5 mmol), CuI (0.12 g), 3-butyn-1-ol (2 mL), and tetrakis(triphenylphosphine)palladium (0.36 g). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.97 (s, 2H), 7.87 (d, 2H, $J$ = 8.5), 7.46 (dd, 2H, $J$ = 1.5, 8.5), 4.94 (t, 2H, $J$ = 5.6), 3.62 (dd, 4H, $J$ = 6.8, 12.4), 3.33 (s, 2H), 2.60 (t, 4H, $J$ = 6.8). MS (ESI+): 265.1 [M + H]$^+$.

*4,4′-([1,1′-Biphenyl]-4,4′-diyl)bis(but-3-yn-1-ol)* ***34***. According to procedure D, the title compound (0.88 g, 31%) was obtained, as a white solid, from 4,4′-diiodobiphenyl (3 g, 9.6 mmol), CuI (0.11 g), 3-butyn-1-ol (1.8 mL), and tetrakis(triphenylphosphine)palladium (0.33 g). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.68 (d, 4H, $J$ = 8.3), 7.47 (d, 4H, $J$ = 8.3), 4.94 (t, 2H, $J$ = 5.6), 3.59 (q, 4H, $J$ = 6.8), 2.57 (t, 4H, $J$ = 6.8). MS (ESI+): 291.2 [M + H]$^+$.

*4,4′-(Thiophene-2,5-diyl)bis(but-3-yn-1-ol)* ***35***. According to procedure D, the title compound (8.2 g, 90%) was obtained, as a slightly yellow solid, from 2,5-dibromothiophene (3 g, 9.6 mmol), CuI (0.11 g), 3-butyn-1-ol (1.8 mL), and tetrakis(triphenylphosphine)palladium


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(0.33 g). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 6.90 (s, 2H), 3.74 (t, 4H, $J$ = 5.9), 2.63 (t, 4H, $J$ = 6.2). MS (ESI+): 221.1 $[M + H]^+$.

*3,3′-(1,4-Phenylene)bis(prop-2-yn-1-ol)* ***46***. According to procedure D, the title compound (1.95 g, 92%) was obtained, as a white solid, from commercially available 1,4-diiodobenzene (5 g, 15.2 mmol) and 2-propyn-1-ol (2.9 mL, 37.9 mmol, 2.5 equiv). $^1$H NMR 300 MHz, $CDCl_3$): $\delta$ 7.38 (s, 4H), 4.50 (s, 4H), 1.6 (s, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 137.1, 127.6, 97.0, 88.3, 54.7.

*4,4′-(1,4-Phenylene)bis(but-3-yn-1-ol)* ***47***. According to procedure D, the title compound (5.99 g, 92%) was obtained, as a white solid, from 1,4-diiodobenzene (10 g, 30.3 mmol) and 3-butyn-1-ol (5.7 mL, 75.8 mmol, 2.5 equiv). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.33 (s, 4H), 3.81 (t, 4H, $J$ = 6.3), 2.69 (t, 4H, $J$ = 6.3), 1.81 (s, 2H). MS (ESI+): 215.2 $[M + H]^+$.

**Procedure E for Hydrogenation Reaction, Compounds 36–40.** The appropriate bis(but-3-yn-1-ol) or bis(prop-2-yn-1-ol) derivative was dissolved in methanol (12 mL/mmol), and palladium on activated charcoal (10% in weight) was added. The reaction mixture was stirred at room temperature under hydrogen atmosphere until a completed reaction was observed by TLC. The catalyst was removed by filtration through Celite and washed with methanol. The solvent was removed in vacuum, and the residue was purified by column chromatography ($CH_2Cl_2$/MeOH: 98/2).

*4,4′-(1,3-Phenylene)bis(butan-1-ol)* ***36***. According to procedure E, the title compound (1.99 g, 96%) was obtained, as a colorless oil, from compound **31**. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.18 (m, 1H), 6.99 (m, 3H), 3.62 (m, 4H), 2.61 (t, 4H, $J$ = 7.3), 1.67 (m, 8H). MS (ESI+): 223.2 $[M + H]^+$.

*4,4′-(Naphthalene-1,4-diyl)bis(butan-1-ol)* ***37***. According to procedure E, the title compound (0.48 g, 92%) was obtained, as a white solid, from compound **32**. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.05 (dd, 2H, $J$ = 3.3, 6.5), 7.48 (dd, 2H, $J$ = 3.3, 6.5), 7.21 (s, 2H), 3.63 (t, 4H, $J$ = 6.5), 3.43 (s, 2H), 3.05 (m, 4H), 1.79 (m, 4H), 1.66 (m, 4H). MS (EI+): 236.3 $[M + 2H_2O]^+$.

*4,4′-(Naphthalene-2,7-diyl)bis(butan-1-ol)* ***38***. According to procedure E, the title compound (0.52 g, 92%) was obtained, as a white solid, from compound **33**. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.76 (d, 2H, $J$ = 8.4), 7.58 (s, 2H), 7.30 (d, 2H, $J$ = 8.3), 3.68 (t, 4H, $J$ = 6.2), 2.82 (t, 4H, $J$ = 7.2), 2.08 (s, 2H), 1.73 (m, 8H). MS (ESI+): 273.2 $[M + H]^+$.

*4,4′-([1,1′-Biphenyl]-4,4′-diyl)bis(butan-1-ol)* ***39***. According to procedure E, the title compound (0.72 g, quantitative) was obtained, as a white solid, from compound **34**. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.54 (d, 4H, $J$ = 8.2), 7.25 (d, 4H, $J$ = 8.2), 4.40 (t, 2H, $J$ = 5.2), 3.41 (dd, 4H, $J$ = 6.4, 11.7), 2.60 (t, 4H, $J$ = 7.5), 1.61 (m, 4H), 1.45 (m, 4H). MS (ESI+): 299.3 $[M + H]^+$.

*4,4′-(Thiophene-2,5-diyl)bis(butan-1-ol)* ***40***. According to procedure E, the title compound (0.80 g, 77%) was obtained, as a slightly yellow oil, from compound **35**. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 6.55 (s, 2H), 3.61 (t, 4H, $J$ = 6.4), 2.76 (t, 4H, $J$ = 7.3), 2.27 (s, 2H), 1.68 (m, 8H). MS (ESI+): 229.1 $[M + H]^+$.

**Procedure F for *N*-Alkylation Reaction, Compounds 51, 52, 55, and 56.** The appropriate thiazolium derivative and methyl iodide or benzyl bromide (3 equiv) were dissolved in dry acetonitrile (0.6 M) and stirred under reflux overnight. Solvent was removed in vacuum, and the residue was diluted with water and then extracted with diethyl ether. The aqueous layer was concentrated and purified by RP18 column chromatography ($H_2O$/MeOH) to afford the expected *N*-methyl or *N*-benzyl thiazolium derivatives.

*3,4-Dimethyl-5-(2-(prop-2-yn-1-yloxy)ethyl)thiazol-3-ium Iodide* ***51***. According to procedure F, the title compound (1.8 g, 97%) was obtained, as a yellow solid, from compound **50** (1 g, 4.85 mmol) and methyl iodide (0.9 mL). HPLC ($r_t$ = 3.47 min, purity 100%). $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.98 (s, 1H), 4.21 (d, 2H, $J$ = 2.4), 4.08 (s, 3H), 3.67 (t, 2H, $J$ = 5.7), 3.49 (t, 1H, $J$ = 2.4), 3.18 (t, 2H, $J$ = 5.7), 2.44 (s, 3H). MS (ESI+): 196.1.

*3-Benzyl-4-methyl-5-(2-(prop-2-ynyloxy)ethyl)thiazol-3-ium Bromide* ***52***. According to procedure F, the title compound (2.1 g, 75%) was obtained, as a yellow solid, from compound **50** (1.44 g, 7.95 mmol) and benzyl bromide (2.9 mL). HPLC ($r_t$ = 5.48 min, purity 100%). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.27 (s, 1H), 7.49–7.32 (m, 5H), 5.86 (s, 2H), 4.21 (d, 2H, $J$ = 2.4), 3.68 (t, 2H, $J$ = 5.7), 3.50 (t, 1H, $J$ = 2.4), 3.40 (s, 3H), 3.18 (t, 2H, $J$ = 5.7), 2.37 (s, 3H). MS (ESI+): 272.1.

*5-(2-Azidoethyl)-3,4-dimethylthiazol-3-ium Iodide* ***55***. According to procedure F, the title compound (1.67 g, 98%) was obtained, as a yellow solid, from compound **54** (1.0 g, 5.95 mmol) and methyl iodide (1.1 mL). HPLC ($r_t$ = 2.86 min, purity 100%). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 8.54 (s, 1H), 4.08 (s, 3H), 3.43 (t, 2H, $J$ = 6.8), 2.96 (t, 2H, $J$ = 6.8), 2.35 (s, 3H). MS (ESI+): 183.1.

*5-(2-Azidoethyl)-3-benzyl-4-methylthiazol-3-ium Bromide* ***56***. According to procedure F, the title compound (2.04 g, 76%) was obtained, as a white solid, from compound **54** (1.76 g, 10.46 mmol) and benzyl bromide (3.8 mL). HPLC ($r_t$ = 5.47 min, purity 100%). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 11.23 (s, 1H), 7.36–7.28 (m, 5H), 6.03 (s, 2H), 3.63 (t, 2H, $J$ = 6.1), 3.08 (t, 2H, $J$ = 6.1), 2.42 (s, 3H). MS (ESI+): 259.1.

**Procedure G for Preparation of Azido Derivatives 54 and 59.** To a solution of the appropriate bromo intermediate in DMF (0.2 M) was added $NaN_3$ (2 equiv). After stirring overnight under reflux, the mixture was diluted with $CH_2Cl_2$, washed with water, and dried over $MgSO_4$. The solvent was concentrated under reduced pressure, and the residue was purified by column chromatography, affording the expected azido derivative.

*5-(2-Azidoethyl)-4-methylthiazole* ***54***. According to procedure G, the title compound (3.77 g, 98%) was obtained, as a yellow oil, from compound **53** (4.9 g, 23.77 mmol). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.54 (s, 1H), 3.43 (t, 2H, $J$ = 6.8), 2.96 (t, 2H, $J$ = 6.8), 2.35 (s, 3H). MS (ESI+): 168.1.

*1-Azido-5-bromopentane* ***59***. According to procedure G, the title compound (2.14 g, 38%) was obtained, as an oil, from commercially available 1,5-dibromopentane (5.1 g, 22.30 mmol). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 3.41 (t, 2H, $J$ = 6.7), 3.29 (t, 2H, $J$ = 6.6), 1.96–1.81 (m, 2H), 1.67–1.47 (m, 4H). MS: 112.1 $[M - Br]^+$

**Procedure H for Preparation of Bis-thiazolium Salts, Compounds 16–20.** To a mixture of oxygen free solvents $H_2O$/tBuOH (v/v, 1/1) were added under argon $CuSO_4{\cdot}5H_2O$ (0.2 equiv, 0.25 M) and sodium ascorbate (1.2 equiv), and the mixture was stirred for 15 min. To the resulted orange suspension were added alkyne (1 equiv) and azide (0.9 equiv), and the reaction mixture was submitted to MW irradiations (1h, 110 °C, 400 W). The solvent was removed in vacuum, and the residue was diluted with water and extracted three times with $CH_2Cl_2$. The aqueous layer was concentrated and purified by RP18 column chromatography ($H_2O$/MeOH). When needed, the counterions were exchanged to chloride by adding to the aqueous phase a Dowex resin (1 × 8–400, $Cl^-$ form). After 2 h to 5 days stirring, the resin was filtered off and the filtrate was concentrated and freeze-dried.

*5-(2-(4-((2-(3,4-Dimethylthiazol-3-ium-5-yl)ethoxy)methyl)-1H-1,2,3-triazol-1-yl)ethyl)-3,4-dimethylthiazol-3-ium Chloride* ***16***. According to procedure H, the title compound (0.16 g, 56%) was obtained, as a yellow oil, from compound **51** (0.15 g, 0.46 mmol) and compound **55** (0.22 g, 0.69 mmol). HPLC ($r_t$ = 2.97 min, purity 99%). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.5 (s, 1H), 9.99 (s, 1H), 8.22 (s, 1H), 4.66 (t, 2H, $J$ = 6.5), 4.58 (s, 2H), 4.10 (s, 3H), 4.06 (s, 3H), 3.67 (t, 2H, $J$ = 5.7), 3.56 (t, 2H, $J$ = 6.5), 3.17 (t, 2H, $J$ = 5.7), 2.44 (s, 3H), 2.28 (s, 3H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 156.7, 156.2, 143.2, 143.1, 141.9, 133.8, 132.1, 124.1, 67.53, 62.8, 48.7, 39.9, 26.3, 26.1, 10.9, 10.6. MS (ESI+): 414.1 $[M - Cl]^+$. HRMS (TOF-ESI+) calcd for $C_{17}H_{24}N_5OS_2^+$ $[M - 2Cl]^+$, 378.1429; found, 378.1422.

*3-Benzyl-5-(2-(4-((2-(3-benzyl-4-methylthiazol-3-ium-5-yl)-ethoxy)methyl)-1H-1,2,3-triazol-1-yl)ethyl)-4-methylthiazol-3-ium Bromide* ***17***. According to procedure H, the title compound (0.25 g, 52%) was obtained, as a yellow oil, from compound **52** (0.40 g, 1.14 mmol) and compound **56** (0.39 g, 1.14 mmol). HPLC ($r_t$ = 5.35 min, purity 99%). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.24 (s, 1H), 10.21 (s, 1H), 8.20 (s, 1H), 7.48–7.17 (m, 10H), 5.81 (d, 4H, $J$ = 7.0), 4.67 (t, 2H, $J$ = 6.3), 4.49 (s, 2H), 3.64 (t, 2H, $J$ = 5.6), 3.56 (t, 2H, $J$ = 6.3), 3.12 (t, 2H, $J$ = 5.5), 2.35 (s, 3H), 2.10 (s, 3H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 157.6, 156.9, 143.1, 142.7, 141.4, 135.2, 133.7, 132.5,


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128.7, 128.7, 128.4, 128.2, 127.5, 127.0, 124.0, 67.4, 62.8, 55.2, 48.7, 41.5, 26.4, 26.1, 11.1, 10.6. HRMS (ESI+): 610.1 $[M - Br]^+$. HRMS (TOF-ESI+) calcd for $C_{29}H_{33}BrN_5OS_2^+$ $[M - Cl]^+$, 610.1290; found, 610.1310.

*3-(3-(1-(2-(3,4-Dimethylthiazol-3-ium-5-yl)ethyl)-1H-1,2,3-triazol-4-yl)propyl)-5-(2-methoxyethyl)-4-methylthiazol-3-ium Chloride* ***18***. According to procedure H, the title compound (0.20 g, 43%) was obtained, as a yellow oil, from compound **55** (0.30 g, 0.96 mmol) and compound **58** (0.38 g, 0.96 mmol). HPLC ($r_t$ = 3.50 min, purity 100%). $^1$H NMR (300 MHz, DMSO-$d_6$: $\delta$ 10.03 (s, 1H), 9.97 (s, 1H), 8.01 (s, 1H), 4.57 (dt, 4H, $J$ = 14.9, 7.0), 4.06 (s, 3H), 3.61−3.48 (m, 4H), 3.30 (s, 3H), 3.14 (t, 2H, $J$ = 5.7), 2.71 (t, 2H, $J$ = 6.6), 2.47 (s, 3H), 2.29 (s, 3H), 2.15 (t, 2H, $J$ = 6.6). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 156.7, 156.0, 145.0, 143.1, 141.3, 134.6, 132.1, 122.3, 69.7, 57.5, 51.8, 48.6, 40.0, 28.0, 26.3, 26.1, 21.2, 10.9, 10.6. HRMS (TOF-ESI+) calcd for $C_{19}H_{29}ClN_5OS_2^+$ $[M - Cl]^+$, 442.1474; found, 442.1502.

*3-Benzyl-5-(2-(4-(3-(5-(2-methoxyethyl)-4-methylthiazol-3-ium-3-yl)propyl)-1H-1,2,3-triazol-1-yl)ethyl)-4-methylthiazol-3-ium Chloride* ***19***. According to procedure H, the title compound (0.11 g, 38%) was obtained, as a yellow oil, from compound **56** (0.39 g, 1.14 mmol) and compound **58** (0.45 g, 1.14 mmol). HPLC ($r_t$ = 4.51 min, purity 100%). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.21 (s, 1H), 10.14 (s, 1H), 7.96 (s, 1H), 7.49−7.37 (m, 3H), 7.22 (d, 2H, $J$ = 7.5), 5.79 (s, 2H), 4.62 (t, 2H, $J$ = 6.1), 4.52 (t, 2H, $J$ = 7.0), 3.64−3.49 (m, 4H), 3.31 (s, 3H), 3.14 (t, 2H, $J$ = 5.6), 2.63 (t, 2H, $J$ = 7.0), 2.46 (s, 3H), 2.17−2.03 (m, 5H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 158.0, 156.7, 145.4, 143.1, 141.7, 135.1, 134.2, 133.0, 129.1, 128.7, 127.5, 122.7, 70.2, 58.0, 55.7, 52.2, 49.1, 28.4, 26.9, 26.5, 21.6, 11.2, 11.0. HRMS (TOF-ESI+) calcd for $C_{25}H_{35}ClN_5OS_2^+$ $[M - Cl]^+$, 518.1814; found, 518.1815.

*5-(2-Methoxyethyl)-3-(3-(1-(5-(5-(2-methoxyethyl)-4-methylthiazol-3-ium-3-yl)pentyl)-1H-1,2,3-triazol-4-yl)propyl)-4-methylthiazol-3-ium Chloride* ***20***. According to procedure H, the title compound (0.12 mg, 32%) was obtained, as a yellow oil, from compound **58** (0.40 g, 1.00 mmol) and compound **60** (0.35 g, 1.0 mmol). HPLC (4.41 min, purity 97%). $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 10.31 (s, 1H), 10.28 (s, 1H), 8.04 (s, 1H), 4.58 (t, 2H, $J$ = 7.0), 4.49 (t, 2H, $J$ = 7.0), 4.34 (t, 2H, $J$ = 7.0), 4.34 (t, 2H, $J$ = 7.0), 3.57 (t, 4H, $J$ = 5.7), 3.30 (s, 3H), 3.31 (s, 3H), 3.14 (t, 4H, $J$ = 5.6), 2.72 (t, 2H, $J$ = 7.2), 2.49 (s, 6H), 2.24−2.11 (m, 2H), 1.91−1.79 (m, 2H), 1.35−1.20 (m, 2H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 156.9, 156.7, 145.1, 141.7, 135.1, 122.2, 70.2, 58.0, 52.4, 52.3, 48.8, 28.9, 28.4, 28.1, 26.5, 22.4, 21.8, 11.2, 11.1. HRMS (TOF-ESI+) calcd for $C_{24}H_{39}ClN_5O_2S_2^+$ $[M - Cl]^+$, 528.2196; found, 528.2234.

*2,2′-((Methylene Bis(4,4′-phenylene))bis(oxy))diethanol* ***21***. Bis-(4-hydroxyphenyl)methane (5 g, 24.90 mmol) was dissolved in DMF (25 mL). Potassium carbonate (0.69 g, 5.00 mmol, 0.2 equiv) and ethylene carbonate (4.84 g, 54.90 mmol, 2.2 equiv) were added, and the reaction mixture was refluxed overnight. Then, it was allowed to reach room temperature and water was added, and the resulting white precipitate was filtered and taken up with AcOEt. The organic layer was successively washed with water and brine and dried over $MgSO_4$. The solvent was removed in vacuum, and the residue was purified by column chromatography (cyclohexane/AcOEt 3:7), affording compound **21** (5.6 g, 78%) as a white solid. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.09 (d, 4H, $J$ = 8.6), 6.84 (d, 4H, $J$ = 8.6), 4.84 (t, 2H, $J$ = 5.5), 3.93 (t, 4H, $J$ = 5.0), 3.79 (s, 2H), 3.69 (dd, 4H, $J$ = 5.3, 10.3). MS (ESI−): 227.0 $[M - HOCH_2CH_2O^{\bullet}]$.

*Bis(4,4′-(2-Hydroxyethoxy)phenyl)methanone* ***22***. 4,4′-Dihydroxybenzophenone (4.0 g, 18.67 mmol) was dissolved in DMF (80 mL). Potassium carbonate (0.48 mg, 3.73 mmol, 0.2 equiv) and ethylene carbonate (3.62 g, 41.07 mmol, 2.2 equiv) were added and the mixture was refluxed overnight. The solvent was evaporated under reduced pressure and the residue was taken up in ethanol/water (v/v: 10/1) and refluxed for 1 h. The reaction mixture was allowed to reach room temperature and the precipitate was filtered, washed with water and dried over $MgSO_4$. Compound **22** (3.15 g, 56%, white solid) was used in the next step without further purification. $^1$H NMR (200 MHz, DMSO-$d_6$) $\delta$ 7.70 (d, 4H, $J$ = 8.7), 7.08 (d, 4H, $J$ = 8.7), 4.95 (s, 2H), 4.09 (t, 4H, $J$ = 4.7), 3.75 (m, 4H). MS (ESI+): 303.2 $[M + K]^+$.

*2,2′-([1,1′-Biphenyl]-4,4′-diylbis(oxy))diethanol* ***23***. 4,4′-Dihydroxybiphenyl (1.0 g, 5.37 mmol) was dissolved in DMF (6 mL). Potassium carbonate (0.37 g, 2.68 mmol, 2 equiv) and ethylene carbonate (1.18 g, 13.42 mmol, 2.5 equiv) were added, and the reaction mixture was refluxed overnight. Then it was allowed to reach room temperature, water was added, and the resulting white precipitate was filtered, washed with water, and dried over $MgSO_4$. Compound **23** (1.4 g, 95%, white solid) was used in the next step without further purification. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.53 (d, 4H, $J$ = 8.7), 6.99 (d, 4H, $J$ = 8.7), 4.94 (bs, 2H), 4.01 (t, 4H, $J$ = 5.0), 3.73 (t, 4H, $J$ = 5.0). MS (ESI+): 313.2 $[M + K]^+$.

*4-(((tert-Butyldimethylsilyl)oxy)methyl)phenol* ***27***. To an ice-bath cooled solution of 4-hydroxymethylphenol (11.89 g, 97.77 mmol) in DMF (90 mL) was added *tert*-butylchlorodimethylsilane (15.88 g, 164.36 mmol, 1.7 equiv). Then triethylamine was slowly added over 1 h period, and the reaction mixture was stirred for 3 h. The solvent was evaporated under reduced pressure, and the crude material was taken up in AcOEt and washed successively with water and brine and dried over $MgSO_4$. The solvent was removed in vacuum, and the residue was purified by column chromatography (petroleum ether/AcOEt 6:4), affording the expected compound **27** (18.16 g, 78%) as colorless oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.17 (d, 2H, $J$ = 4.6), 6.76 (d, 2H, $J$ = 4.8), 5.82 (s, 1H), 4.67 (s, 2H), 1.00 (s, 9H), 0.10 (s, 6H). MS (ESI−): 237.1 $[M - H]^-$.

*1,5-Bis(4-(((tert-butyldimethylsilyl)oxy)methyl)phenoxy)pentane* ***28***. Compound **27** (2.29 g, 9.50 mmol, 2.4 equiv) was dissolved in anhydrous DMF (10 mL), and potassium carbonate (1.5 g, 10.87 mmol, 2.5 equiv) was added. After 20 min stirring at room temperature, 1,5-dibromopentane (1.0 g, 4.35 mmol) was added and the reaction mixture was stirred for 18 h. The solvent was evaporated under reduced pressure, the residue was taken up in AcOEt, and the organic layer was washed with water and dried over $MgSO_4$. The solvent was removed in vacuum, and the residue was purified by column chromatography (petroleum ether/$Et_2O$ 98:2), affording the expected compound **28** (1.80 g, 76%) as a white solid. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.23 (d, 4H, $J$ = 8.7), 6.86 (d, 4H, $J$ = 8.6), 4.67 (s, 4H), 3.98 (t, 4H, $J$ = 6.4), 1.86 (m, 4H), 1.66 (m, 2H), 0.93 (s, 18H), 0.09 (s, 12H). MS (EI+): 412.4 $[M - OTBDMS - H]^+$.

*((Pentane-1,5-diylbis(oxy))bis(4,1-phenylene))dimethanol* ***29***. Compound **28** (1.16 g, 2.13 mmol) was diluted in 10 mL of a THF/water solution (v/v, 8/2), and $KHSO_4$ (0.29 g, 2.13 mmol, 1 equiv) was added. The reaction mixture was stirred for 2 h at 50 °C, and the solvent was evaporated under reduced pressure. The aqueous residue was taken up in AcOEt; the organic layer was washed with water and dried over $MgSO_4$. The solvent was removed in vacuum, and the residue was purified by column chromatography ($CH_2Cl_2$/$CH_3OH$ 95:5), affording the expected compound **29** (0.52 g, 77%) as a white solid. $^1$H NMR (300 MHz, DMSO-$d_6$): $\delta$ 7.20 (d, 4H, $J$ = 8.7), 6.87 (d, 4H, $J$ = 8.7), 5.04 (t, 2H, $J$ = 5.6), 4.40 (d, 4H, $J$ = 5.5), 3.96 (t, 4H, $J$ = 6.3), 1.76 (m, 4H), 1.54 (m, 2H). MS (ESI+): 299.2 $[M - OH]^+$, 339.2 $[M - Na]^+$.

*1,5-Bis(4-(chloromethyl)phenoxy)pentane* ***30***. To a solution of **29** (0.97 g, 3.04 mmol) in dry dichloromethane (20 mL) at 0 °C, thionyl chloride (0.89 mL, 12.2 mmol, 4 equiv) was added. After 30 min stirring, the reaction mixture was allowed to reach room temperature and stirred for an additional hour. The solvent and the excess of thionyl chloride were removed in vacuum to afford compound **30** (1.07 g, quantitative), which was used in the next step without further purification. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 7.34 (d, 4H, $J$ = 8.7), 6.92 (d, 4H, $J$ = 8.7), 4.71 (s, 4H), 3.99 (t, 4H, $J$ = 6.4), 1.77 (m, 4H), 1.58 (m, 2H).

*4-Methyl-5-(2-(prop-2-ynyloxy)ethyl)thiazole* ***50***. 4-Methyl-5-(2-hydroxyethyl)thiazole (2.0 g, 14 mmol) was added to a suspension of NaH (0.68 g, 16.80 mmol) in dry THF (40 mL) at 0 °C. After 30 min, propargyl bromide (3 mL, 28 mmol) was added dropwise. The reaction mixture was stirred overnight and diluted with $CH_2Cl_2$, and water was added. The aqueous layer was extracted twice with $CH_2Cl_2$, and the resulting organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure. The crude material was purified by silica gel column chromatography affording the expected compound


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**50** (2.51 g, 92%). HPLC ($r_t$ = 4.06 min, purity 100%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.51 (s, 1H), 4.10 (d,, 2H, $J$ = 2.4), 3.63 (t, 2H, $J$ = 6), 2.98 (t, 2H, $J$ = 6), 2.37 (t, 1H, $J$ = 3), 2.44 (s, 3H). MS (ESI+): 182.1 $[M + H]^+$. HRMS (TOF-ESI$^+$): calcd for $C_9H_{12}NOS$ $[M + H]^+$, 182.0640; found, 182.0637.

*5-(2-Bromoethyl)-4-methylthiazole* ***53***. To a solution of commercially available 2-(4-methylthiazol-5-yl) ethanol (4.0 g, 27.17 mmol) in dry $CH_2Cl_2$ (100 mL), at 0 °C, was added $PBr_3$ (38 mL, 40.76 mmol). After stirring overnight at reflux, the reaction mixture was cooled at 0 °C and the excess of $PBr_3$ was hydrolyzed with water. The mixture was basified to pH 10 using 2N NaOH aqueous solution and extracted with $CH_2Cl_2$. The resulting organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (Petroleum ether/EtOAc = 5/5), affording the expected compound **53** (5.8 g, 98%). $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ 8.60 (s, 1H), 3.51 (t, 2H, $J$ = 7.2), 3.31 (t, 2H, $J$ = 7.2), 2.41 (s, 3H). MS (ESI+): 206.9.

**Biology.** *In Vitro Antiplasmodial Activity.* Drug effects on in vitro *P. Falciparum* growth (Nigerian strain) were measured in microtiter plates according to a modified Desjardins test.[32,33] *P. falciparum* infected erythrocyte suspension (1.5% final hematocrit and 0.6% parasitemia) were grown in complete medium (Hepes-buffered RPMI 1640 + 10% AB human serum) with or without drug. The drugs were dissolved in DMSO and then further diluted in culture medium so that the final DMSO concentration never exceeded 0.25%. Parasites growth was assessed by measuring the incorporation of [$^3$H]hypoxanthine into nucleic acids after 48 h of contact with the drug, as previously described.[34] Results were expressed as $IC_{50}$, which is the drug concentration leading to 50% inhibition of parasite growth. The results are the means of two independent experiments performed in triplicate.

*In Vitro Toxicity against a Human Jurkat Lymphoblast Cell Line.* Human Jurkat lymphoblasts were incubated with studied derivatives for 24 h before adding [$^3$H]thymidine to determine cell viability. Values are means of two independent experiments conducted in duplicate, differing by less than 40%.

*In Vivo Antimalarial Activity.* Antimalarial activities were determined against the *Plasmodium Vinckei Petteri* (279BY) strain in female Swiss mice. Compounds were injected ip and orally in DMSO, or 0.9% NaCl, or a mixture of intralipid/DMSO (90/10). Parasitemia levels were monitored at day 5 after four days of treatment.[16] Results were expressed as efficient dose 50 ($ED_{50}$), which is the dose inhibiting by 50% parasitemia in mice. $ED_{50}$ value is determined only when a decrease of parasitemia of at least 85% is observed during the experiment.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Spectroscopic data ($^1$H NMR, HRMS, and HPLC chromatogram) for all final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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## ■ ABBREVIATIONS USED

ACTs, artemisinin-based combination therapy; DMAP, 4-(dimethylamino)pyridine; DMF, *N*,*N*-dimethylformamide; DMSO, dimethylsulfoxide; MW, microwave; TBDMS, *tert*-butyl-dimethylsilyl; Ts, *p*-toluenesulfonyl; WHO, World Health Organization

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