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Synthesis and Antibacterial Evaluation of Bis-thiazolium, Bis-imidazolium, and Bis-triazolium Derivatives

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Given the worldwide spread of bacterial drug resistance, there is an urgent need to develop new compounds that exhibit potent antibacterial activity and that are unimpaired by this phenomenon. Quaternary ammonium compounds have been used for many years as disinfectants, but recent advances have shown that polycationic derivatives exhibit much stronger activity and are less prone to bacterial resistance than commonly used monocationic compounds. In this sense, we prepared three series of new bis-cationic compounds: bis-thiazoliums, bis-imidazoliums, and bis-1,2,4-triazoliums. If some compounds of the first series showed fair antibacterial activity, most of those belonging to the two other series were highly potent, with minimum inhibitory concentrations close to 1 $\mu g\,mL^{-1}$. Some of them also exhibited low toxicity toward eukaryotic MRC-5 lung fibroblasts, and we showed that this toxicity is clearly correlated with clog*P*. Finally, four selected compounds were found to exhibit a clear bactericidal effect.

The World Health Organization recently published a list[1] of 12 bacteria whose capacity for resistance against antibiotics is so high that they constitute a real threat to human health; this highlights that the time to act is now. A recent review chaired by Jim O'Neill[2] also listed major recommendations to fight antimicrobial resistance. These include improving hygiene, minimizing the unnecessary use of antibiotics, improving global surveillance of drug resistance, and implementing better incentives to promote investment for new drugs. Developing new chemical entities is thus urgently required. Quaternary ammonium compounds (QACs) were first discovered by Domagk in 1935[3] and were used for many years as skin disinfectants. Mono-ammonium compounds such as benzalkonium chloride or cetylpyridinium chloride were followed by bis-ammonium compounds such as dequalinium chloride and chlorhexidine. Recent advances in this area indeed showed that bis- or polycationic compounds exhibit much stronger activity than monocationic compounds. They also suggest that some derivatives of this class could be used for other purposes than simple topical administration.[4–6] In particular, polycationic compounds are less prone to induce bacterial resistance than the classical monocationic compounds, which are still in commercial use.[7,8] Furthermore, one general drawback of this class of compounds comes from the low selectivity toward eukaryotic cells. Thus, some efforts have been made to correlate the structural features of QACs and both their antibacterial activity and eukaryotic toxicity.[9,10] In addition, other recent efforts led to the design of powerful molecules that show very low toxicity toward mammalian cells.[11] Besides, QACs may exhibit antimalarial activity, and some bis-cationic derivatives proved to be very potent both in vitro and in vivo.[12] Later, analogous compounds were prepared, in which the cationic charges were harbored by thiazolium moieties.[4,13] The latter compounds were found to be as potent as their classical ammonium counterparts, but were much less toxic on a rodent model. We wondered whether these positively charged heterocycles could also exhibit attractive antibacterial activity. However, some mono-thiazolium compounds showed low potency on reference bacterial strains,[14] but we envisioned that dimeric analogues could be much more active. Thus, we prepared numerous derivatives and tested them against reference bacterial strains. The most active compound was selected for toxicity evaluation on eukaryotic MRC-5 cells. Moreover, we intended to extend this study to related five-membered heterocycles such as imidazole derivatives. Some bis-imidazolium compounds were already prepared by others[15,16] and showed interesting, yet moderate, antibacterial activity. We envisioned replacing some alkyl moieties with aromatic groups to determine their influence on both antibacterial activity and toxicity versus eukaryotic cells. Finally, 1,2,4-triazole analogues were also prepared, as in the context of antifungal therapy, they have led to more active compounds,[17] and interesting antibacterial activities have recently been reported.[18] All these compounds were tested against reference bacterial strains and also against clinical isolates harboring various and different mechanisms of resistance toward antibiotics. Furthermore, the cytotoxicity on eukaryotic cells was determined for each compound.

Bis-thiazolium derivatives were easily prepared as previously described[13] (Scheme 1) by N-alkylation of 4-methyl-5-(2-hydroxyethyl)thiazole with various α,ω-diiodoalkanes, the latter being prepared from commercial α,ω-dibromoalkanes.[13] In contrast to this previous study, each even and odd linkers from $n=4$ to $n=12$ were prepared. As activity increased with n,

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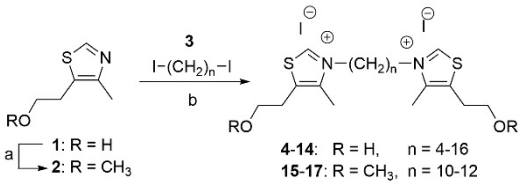


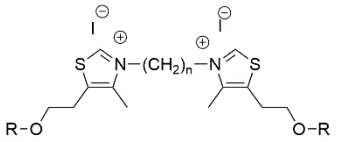
Scheme 1. Synthesis of bis-thiazolium compounds. a) NaH/THF, CH_3I; b) CH_3CN, reflux, 72 h.

1,14-dibromotetradecane and 1,16-dibromohexadecane were prepared according to a reported procedure.[19] Conversion into the diiodo counterparts allowed the preparation of longer analogues. Besides, *O*-methylation[13] prior to dimerization afforded three more compounds.

The minimum inhibitory concentrations (MICs) were evaluated against four reference strains: two Gram-positive bacteria (*Staphylococcus aureus* and *Enterococcus faecalis*) and two Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) (Table 1).

As a result, short-linker compounds exhibited no activity, which overall increased with the linker length. Surprisingly, compound **11** ($n=11$) showed no potency, whereas **10** ($n=10$) and **12** ($n=12$) were active against *E. coli* and *S. aureus* strains.

Table 1. Minimum inhibitory concentration values of prepared bis-thiazoliums.



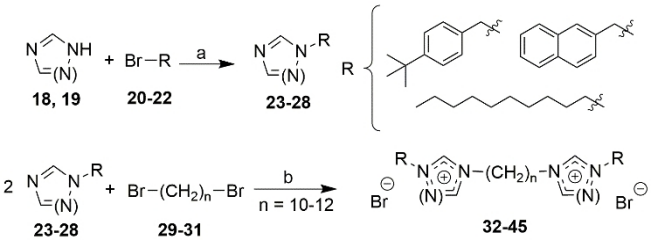
R = H: **4-14**
R = CH_3: **15-17**

Compd	*n*	MIC [μg mL^{-1}][a]			
		S.a.	*E.f.*	*E.c.*	*P.a.*
Chx[b]		1	2	0.5	8
4	4	>256	>256	>256	>256
5	5	>256	>256	>256	>256
6	6	128	128	128	>256
7	7	>256	>256	>256	>256
8	8	>256	>256	>256	>256
9	9	>256	>256	>256	>256
10	10	64	128	64	128
11	11	256	>256	>256	>256
12	12	**16**	>256	**16**	>256
13	14	32	256	256	256
14	16	**16**	64	128	256
15	10	>256	>256	>256	>256
16	11	256	>256	256	>256
17	12	64	>256	128	>256

[a] All MIC data were acquired by compilation of the highest value of at least two independent trials. Twofold serial dilutions of the compounds were prepared from a stock solution at 1024 μg mL^{-1}. Each condition was repeated in eight wells. See the Supporting Information for further details. Organisms used in this study: *S.a.* (*Staphylococcus aureus* ATCC 29213), *E.f.* (*Enterococcus faecalis* ATCC 29212), *E.c.* (*Escherichia coli* ATCC 25922), *P.a.* (*Pseudomonas aeruginosa* ATCC 27853). [b] Reference compound: chlorhexidine.

Compound **12** was the most active compound of this series, with MICs reaching 16 μg mL^{-1} against these strains. No activity was observed against *E. faecalis and P. aeruginosa.* Increasing the linker length did not bring significantly better activities. Compound **14** ($n=16$), however, showed better MIC than **12** against *E. faecalis* (64 vs. 256 μg mL^{-1}), but it was less potent against *E. coli* (128 vs. 16 μg mL^{-1}). Thus, we selected the lower-molecular-weight compound **12** for further consideration. In vitro cytotoxicity (IC_{50}) on eukaryotic lung fibroblasts (MRC-5 cells, ATCC CCL-171) was determined for this molecule and was equal to 256 μg mL^{-1}, leading to a selectivity index ($SI = IC_{50}/MIC$) of **16** toward the sensitive strains. Surprisingly, compounds **15**–**17**, O-methylated analogues of compounds **10**–**12**, were much less active than their counterparts.

With these considerations in mind, we intended to prepare bis-imidazolium and bis-1,2,4-triazolium analogues. Prior to dimerization, we first alkylated the heterocycles with various agents. In addition to a simple alkyl (i.e., decyl) chain, we also introduced aromatic substituents such as 4-*tert*-butylbenzyl or 2-methylnaphtalenyl moieties. This was achieved by using commercially available alkyl bromides under basic conditions (Scheme 2). To avoid any trace of over-alkylation, the heterocycles were introduced in excess relative to the alkylating agents (3:1 ratio). The desired compounds were obtained in 41–74%

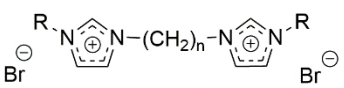


Scheme 2. Synthesis of bis-imidazolium and bis-1,2,4-triazolium compounds. a) K_2CO_3, DMF, Δ; b) CH_3CN, Δ.

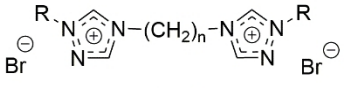
yields after column chromatography. Under the conditions used (DMF, K_2CO_3, 80 °C), a highly regioselective 1-alkylation was observed in the case of the 1,2,4-triazole compounds **26**–**28**. This was easily determined by ^{1}H NMR spectroscopy, which showed unsymmetrical patterns. Only traces of the other regioisomer were observed in the case of compound **28** and they were easily removed by chromatography (see Supporting Information). Dimerization with α,ω-dibromoalkanes afforded the desired bis-imidazolium or bis-1,2,4-triazolium compounds in excellent (75–98%) yields after crystallization (Scheme 2). The above-mentioned results led us to choose here linkers with $n=10$–12 methylene units.

The MICs of the resulting 14 compounds were evaluated against the same four reference strains, but also against four clinical isolates harboring various resistance mechanisms (Table 2). Unfortunately, compound **41** was too highly lipophilic to be soluble under the conditions used, and thus its antibacterial activity could not be evaluated. Globally, all the prepared bis-imidazolium and bis-1,2,4-triazolium compounds showed strong to very strong activities toward most of the

Table 2. Minimum inhibitory concentration and IC_{50} values of prepared bis-imidazolium and bis-triazolium compounds.



32-38



39-45

Compd	*n*	clog*P*	R[c]	MIC [μg mL^{-1}][a]								IC_{50} [μg mL^{-1}][e]
				S.a.	MRSA	*E.f.*	VRE	*E.c.*	ESBLE	*P.a.*	PAR	
Chx[b]				1	1	2	2	**0.5**	1	8	16	22.3
32	10	2.68	4-*t*bb	1	1	1	2	1	2	16	64	15.2
33	11	3.08	4-*t*bb	**0.5**	**0.5**	1	1	1	1	16	16	9.6
34	12	3.48	4-*t*bb	**0.25**	**0.5**	**0.5**	**0.5**	**0.5**	1	4	8	6.6
35	10	1.43	2-mn	1	**0.5**	**0.5**	4	1	4	64	128	25.2
36	11	1.83	2-mn	1	1	1	1	1	1	32	64	13.3
37	12	2.23	2-mn	**0.5**	**0.5**	**0.5**	**0.5**	1	1	16	16	3.9
38	10	3.05	decyl	**0.5**	**0.5**	1	**0.5**	1	1	2	2	1.7
39	10	3.35	4-*t*bb	1	1	2	4	1	4	16	32	9.8
40	11	3.74	4-*t*bb	**0.5**	**0.5**	**0.5**	2	1	2	16	16	8.4
41	12	4.14	4-*t*bb	n.d.[d]	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
42	10	2.1	2-mn	1	1	2	2	1	2	64	64	37.6
43	11	2.49	2-mn	**0.5**	**0.5**	2	2	2	4	16	32	20.7
44	12	2.89	2-mn	1	1	1	1	1	1	8	16	8.5
45	10	3.71	decyl	**0.5**	**0.5**	**0.5**	**0.5**	**0.5**	1	2	2	1.8

[a] All MIC data were acquired by compilation of the highest value of at least two independent trials. Twofold serial dilutions of the compounds were prepared from a stock solution at 1024 μg mL^{-1}. Each condition was repeated in eight wells. See the Supporting Information for further details. Organisms used in this study: *S.a.* (*Staphylococcus aureus* ATCC 29213), MRSA (methicillin-resistant *Staphylococcus aureus*, *mecA*), *E.f.* (*Enterococcus faecalis* ATCC 29212), VRE (vancomycin-resistant *Enterococcus faecalis*, *vanA*), *E.c.* (*Escherichia coli* ATCC 25922), ESBLE (extended-spectrum β-lactamase-producing *Escherichia coli*), *P.a.* (*Pseudomonas aeruginosa* ATCC 27853), PAR (*Pseudomonas aeruginosa* resistant, efflux pump). [b] Reference compound: chlorhexidine. [c] 4-*t*bb = 4-*tert*-butylbenzyl; 2-mn = 2-methylnaphthalenyl. [d] Not determined (insoluble compound). [e] IC_{50} values were determined on MRC-5 cells according to published procedures.[20,21]

tested strains, with MICs around 1 μg mL^{-1}. Besides, both strains of *P. aeruginosa* appeared to be less sensitive; however, some compounds exhibited low to very low MICs. Such strong activity of our compounds against Gram-negative bacteria is rare in this class of antibacterials and has to be highlighted. The majority of these compounds proved to be as active as the reference compound (chlorhexidine), and a few were found to be more active. This is even more evident when taking into account the lower molecular weight of chlorhexidine (see the Supporting Information for MICs in μM units). In addition, for most of the compounds and for each bacterial species, there is almost no difference in activity toward the reference strain compared with the resistant clinical isolate. This is highly important considering the need for treatments devoted to drug-resistant bacteria. There is no clear difference in antimicrobial activity between the bis-imidazolium and bis-1,2,4-triazolium series. In either case, the positive charge is spread over the heterocyclic structure, as in QACs bearing a pyridinium structure.[9] Considering compounds with the same linker length, derivatives bearing a 4-*tert*-butylbenzyl moiety are slightly more active than those with a 2-methylnaphthalenyl group (for example, compare **33** with **36**, **34** with **37**, and **40** with **43**). Nevertheless, it is clear that independent of these two substituents, a longer linker is associated with higher potency. For the compounds bearing a decyl substituent (compounds **38** and **45**), only one linker ($n = 10$) was envisioned; remarkably, these compounds were found to be the most active, especially against both strains of *P. aeruginosa*.

To evaluate the potential safety of our compounds, they were tested against MRC-5 eukaryotic lung fibroblasts, and the results are listed as IC_{50} values (Table 2). The obtained values are very different from each other. Clearly, compounds **38** and **45**, which showed the strongest antibacterial activity, also exhibited the highest toxicity toward these eukaryotic cells. Compounds with aromatic substituents are less toxic than those bearing an alkyl (decyl) group. A longer linker increases the toxicity, and for the same linker length, 2-methylnaphtalenyl derivatives are less toxic than 4-*tert*-butylbenzyl compounds. No clear difference in toxicity was observed between imidazolium and 1,2,4-triazolium compounds, as 4-*tert*-butylbenzyl bis-imidazoliums are less toxic than their 1,2,4-bis-triazolium counterparts (for example, compare **32** with **39**), but 2-methylnaphtalenyl bis-imidazoliums are more toxic than their 1,2,4-bis-triazolium counterparts (compare **35** with **42**). The latter are the least toxic derivatives of the series, with compound **42** exhibiting an IC_{50} value of 37.6 μg mL^{-1}. To confirm the low toxicity of this compound, it was further evaluated in a red blood cell lysis test. At roughly its IC_{50} value (i.e., 40.0 μg mL^{-1}), no significant lysis was observed (see Supporting Information), confirming the high potential of this compound.

To rationalize the above results, we intended to search for a possible link between the antibacterial activities and eukaryotic toxicities on the one hand, and the lipophilicities of the molecules on the other. For this purpose, we used calculated log*P* (clog*P*) as reported in Table 2. As mentioned above, the more lipophilic 4-*tert*-butylbenzyl moiety is associated with slightly

higher activity than the less lipophilic 2-methylnaphthalenyl derivatives. In addition, the better activity observed with the compounds with longer linkers may be attributed to their higher lipophilicity. Finally, the two compounds exhibiting the highest activities—compounds **38** and **45**—are highly lipophilic, but not the most so. In addition, as reported above, no clear difference in activity was observed between the bis-imidazolium and bis-1,2,4-triazolium series, even though the former is less lipophilic than the latter. To clarify these facts and with the aim of linking them with the eukaryotic toxicities, we generated some plots (Figure 1) showing the relationships between IC_{50} and clog*P*, and between SI ($SI = IC_{50}/MIC$) and clog*P* for three bacterial strains. In the case of compounds bearing the less lipophilic 2-methylnaphthalenyl moiety, there is a clear linear correlation between IC_{50} and clog*P* in the bis-imidazolium series (compounds **35**, **36**, and **37**) and also in the bis-1,2,4-triazolium series (compounds **42**, **43**, and **44**). In both cases, the slope is negative, as less lipophilic compounds (i.e., with shorter linkers) show higher IC_{50} values. In contrast, for these six compounds and for the same linker length, each bis-1,2,4-triazolium analogue is more lipophilic and shows a higher IC_{50} value than its bis-imidazolium counterpart, with compound **42** being the least toxic. Besides, considering compounds bearing the more lipophilic 4-*tert*-butylbenzyl moiety, all the compounds are more toxic than their 2-methylnaphthalenyl counterpart. Once again, a linear correlation is observed between IC_{50} and clog*P* in the bis-imidazolium series, but with a lower (negative) slope than previously, and only two bis-1,2,4-triazolium compounds could be tested.

In contrast with the previously evoked 2-methylnaphthalenyl series, 4-*tert*-butylbenzyl bis-imidazolium derivatives are less toxic than their bis-1,2,4-triazolium counterparts. Finally, both compounds harboring a linear alkyl chain as substituent (compounds **38** and **45**) are highly lipophilic and exhibit high toxicity. To study the potential therapeutic interest of our molecules, the selectivity indexes (SI) toward three bacterial strains were evaluated (Figure 1). Concerning *E. coli*, as most of the MIC values are equal to 1, SI values reflect the IC_{50} values, except for compounds **34** (MIC = 0.5) and **43** (MIC = 2), with compound **42** showing the best SI of 37.6. Concerning *S. aureus*, it is interesting to take a closer look at bis-imidazolium compounds. The one bearing a 2-methylnaphthalenyl moiety shows the usual negative slope: a lower clog*P* correlates with a higher SI. In contrast, the compounds bearing a 4-*tert*-butylbenzyl moiety show a positive slope: a higher clog*P* correlates with a higher SI. As a result, compounds **34** (4-*t*bb, $n = 12$) and **35** (2-mn, $n = 10$) exhibit nearly the same SI (26.4 vs. 25.2, respectively). This reflects the very low MIC of **34**. A similar tendency is observed for 1,2,4-bis-triazolium bearing a 4-*tert*-butylbenzyl moiety. For those bearing a 2-methylnaphthalenyl substituent, the MIC value (0.5) of **43** compensates for its relatively low IC_{50} (20.7), yielding an interesting SI of 41.4, to be compared with the SI of the least toxic compound **42** (37.6). Concerning *E. faecalis*, most of the compounds show low SI, except compound **35**, which is a bis-imidazolium compound bearing a 2-methylnaphthalenyl substituent. With a MIC of 0.5 and an IC_{50} value of 25.2, it combines high activity with relatively low toxicity toward our eukaryotic cell model; thus its SI reaches 50.4, which is the best of the series.

Based on these data, we decided to further characterize the antibacterial properties of some compounds. The bis-imidazolium and bis-1,2,4-triazolium derivatives showing the best anti-

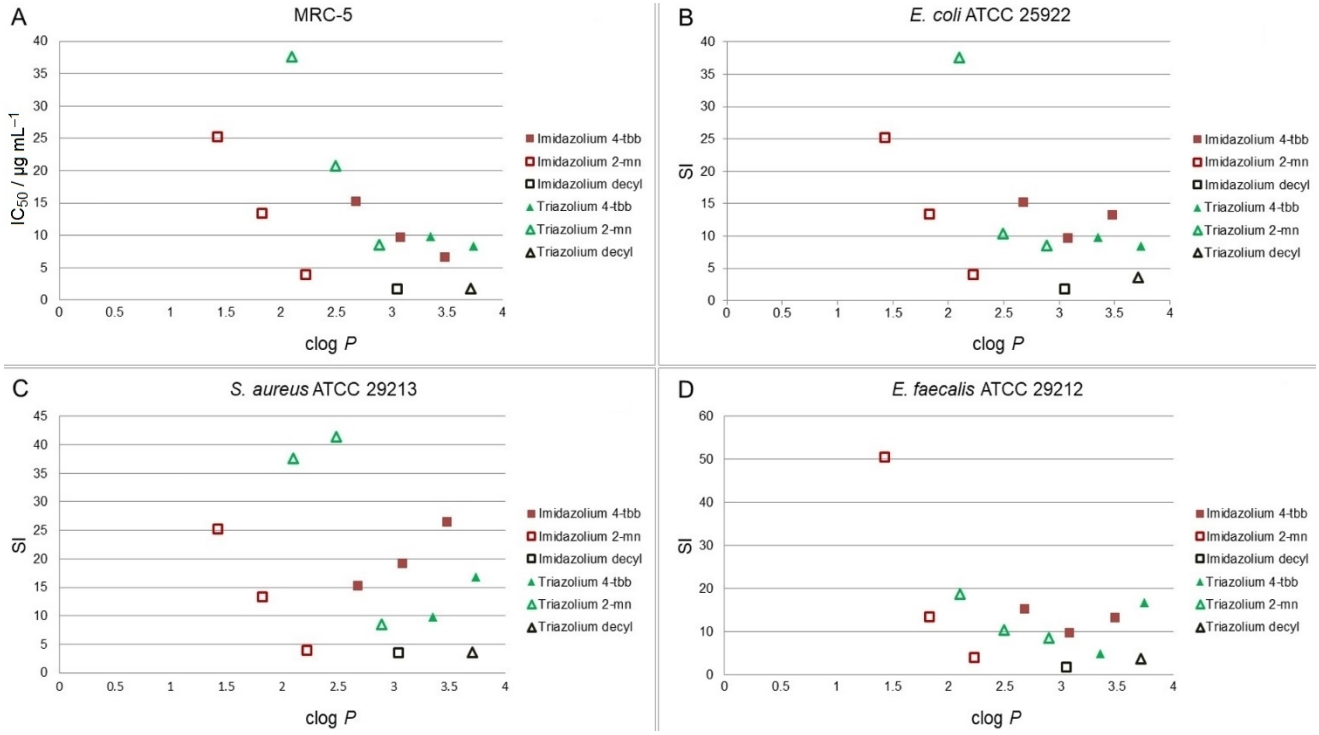


Figure 1. A) Toxicity of the various molecules on MRC-5 strains as a function of clog*P*. B–D) Selectivity indexes (SI) of the various molecules toward *E. coli* (B), *S. aureus* (C), and *E. faecalis* (D) as a function of clog*P*.

microbial activities, lowest cytotoxicities, or interesting SI were selected. Thus, we evaluated the bactericidal activity of compounds **35**, **42**, **43**, and **45** on two reference bacterial strains, *E. coli* (Gram-negative) and *S. aureus* (Gram-positive). The bactericidal activity was defined as a $\geq$3-log-unit decrease in the initial inoculum with treatment compared with untreated control, for a compound concentration not greater than 4×MIC, after 24 h of incubation at 35 °C.[22] In the case of compounds **43** and **45**, analysis of the minimal bactericidal concentration (MBC) showed clear bactericidal activity on both tested bacterial strains, with $>3\log$ decrease in the initial inoculum, after 24 h of incubation (Table 3). In that instance, the MBC was attained independently of the compound concentration used in the assay, 1×MIC and 4×MIC. Regarding compound **35** at 1× MIC, we observed a killing effect for *E. coli* (starting inoculum

Table 3. Reduction of initial bacterial inoculum after 24 h of incubation with the test compound at 35 °C.

Compd	*S. aureus* ATCC 29213		*E. coli* ATCC 25922	
	1×MIC	4×MIC	1×MIC	4×MIC
35	$>$**3 log$_{10}$**	$>$**3 log$_{10}$**	$<3\log_{10}$	$>$**3 log$_{10}$**
42	$<3\log_{10}$	$<3\log_{10}$	$>$**3 log$_{10}$**	$>$**3 log$_{10}$**
43	$>$**3 log$_{10}$**	$>$**3 log$_{10}$**	$>$**3 log$_{10}$**	$>$**3 log$_{10}$**
45	$>$**3 log$_{10}$**	$>$**3 log$_{10}$**	$>$**3 log$_{10}$**	$>$**3 log$_{10}$**

of $4.2\times10^5\pm0.2\times10^5$ CFU mL^{-1}, breakpoint at 420 CFU mL^{-1}, mean of 770 CFU mL^{-1} obtained), although the bactericidal breakpoint is not reached. Nevertheless, the bactericidal breakpoint for *E. coli* is reached at 4×MIC ($<$10 CFU mL^{-1}), while for *S. aureus*, both tested concentrations proved bactericidal. Similarly, for compound **42**, at 4×MIC the bactericidal breakpoint for *S. aureus* was not reached, but a killing effect was also obtained (starting inoculum of $6.7\times10^5\pm0.5\times10^5$ CFU mL^{-1}, breakpoint at 670 CFU mL^{-1}, mean of 1600 CFU mL^{-1} obtained). On the opposite, the impact of the compound on *E. coli* led to $>3\log$ reduction of the initial inoculum. As compound **42** was particularly interesting in terms of SI, we went further and made a preliminary evaluation of the reduction of initial inoculum of *E. coli*. At the MIC, the inoculum reduction was superior to 5 log, which emphasizes the high activity of this molecule.

In this study, we addressed the issue of the increase in antibiotic-resistant bacteria by designing new antibacterial compounds designed to maintain their activity toward clinically occurring drug-resistant bacteria. With this aim, we prepared numerous bis-cationic compounds, among which bis-imidazolium and bis-1,2,4-triazolium derivatives appeared to show high antibacterial activity against two Gram-positive (*S. aureus* and *E. faecalis*) and two Gram-negative (*E. coli* and *P. aeruginosa*) reference bacterial strains. For most of these compounds, the MICs were around 1 μg mL^{-1}, except against *P. aeruginosa*. All these compounds were at least as potent as chlorhexidine, a molecule commonly used as a disinfectant. Notably, the antibacterial activity was maintained against resistant clinical isolates. Furthermore, four selected compounds exhibited low-dose bactericidal activity toward two representative bacterial strains. Interestingly, some of our compounds showed low toxicity toward eukaryotic MRC-5 lung fibroblasts. In addition, we could demonstrate very interesting linear relationships between eukaryotic cytotoxicity and clog*P* of our compounds, and between selectivity index and clog*P*. This study opens new perspectives in the design of new bis-cationic features with high antibacterial potency while maintaining low eukaryotic toxicity.

Experimental Section

Full experimental details are provided in the Supporting Information.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: 1,2,4-triazolium · antibacterial agents · clog*P* · cytotoxicity · imidazolium

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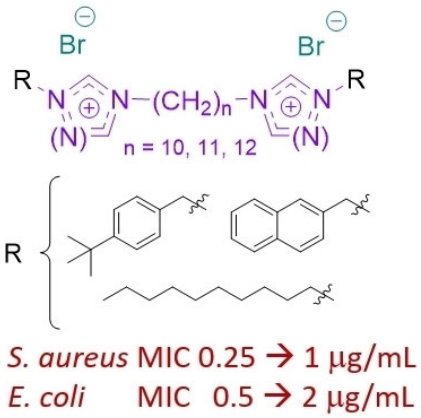
COMMUNICATIONS

Highly potent antibacterials: New bis-cationic compounds were prepared, among which bis-imidazolium and bis-1,2,4-triazolium compounds were found to exhibit low to very low MICs toward a panel of bacterial strains. These activities were also observed toward resistant clinical isolates. Some derivatives displayed low toxicity toward a model of eukaryotic cells. Very interesting correlations were found between these activities and the lipophilicity of the compounds.



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Synthesis and Antibacterial Evaluation of Bis-thiazolium, Bis-imidazolium, and Bis-triazolium Derivatives