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Building a Better Quaternary Ammonium Compound (QAC): Branched Tetracationic Antiseptic Amphiphiles

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Bacteria contaminate surfaces in a wide variety of environments, causing severe problems across a number of industries. In a continuation of our campaign to develop novel antibacterial quaternary ammonium compounds (QACs) as useful antiseptics, we have identified a starting material bearing four tertiary amines, enabling the rapid synthesis of several tris- and tetracationic QACs. Herein we report the synthesis and biological activity of a series of 24 multiQACs deemed the "superT" family, and an investigation of the role of cationic charge in antimicrobial and anti-biofilm activity, as well as toxicity. This class represents the most potent series of QACs reported to date against methicillin-resistant *Staphylococcus aureus* (MRSA), with minimum inhibitory concentrations (MICs) and minimum biofilm eradication concentrations (MBECs) as low as 0.25 and 25 μM, respectively. Based on the significant cell-surface-charge differences between bacterial and eukaryotic cells, in certain cases we observed excellent efficacy-to-toxicity profiles, exceeding a 100-fold differential. This work further elucidates the chemical underpinnings of disinfectant efficacy versus toxicity based on cationic charge.

Cationic amphiphiles, and quaternary ammonium compounds (QACs) in particular, have represented a mainstay of antiseptics since 1915, when Jacobs presented a series of three papers describing the derivatization of hexamethylenetetramine with a variety of amide- and ester-containing alkyl halides (e.g. **1**, Figure 1).[1] This was followed two decades later with the report by Domagk of a structure that would become synonymous with QACs: benzalkonium chloride (BAC, **2**).[2] Further commercialized advances in antiseptic QAC technology included the addition of an ethyl group to the benzyl substituent (**3**), the modification of the alkyl chain of BAC to include ethers and aromatic groups (e.g., benzethonium chloride, **4**), the use of bis-alkyl QACs such as didecyl dimethyl ammonium chloride (DDAC, **5**), and the incorporation of pyridinium residues as in cetyl pyridinium chloride (CPC, **6**). The mixing of these components has often been exploited to prepare improved formulations. Polymeric applications,[3] including polyguanidinium examples (e.g., **7** and **8**), have also been developed.

To diversify the structures of QACs, many academic groups have investigated modifications of QAC architectures, often coming back to the theme of multicationic systems.[4] For example, as early as the 1980s, biscationic structures were being evaluated for antimicrobial activity; notable advances include symmetric derivatives of tetramethyl ethylenediamine,[5,6] asymmetric derivatives,[7] and structures with longer alkyl linkers between ammonium centers.[8,9] The explicit role of charge has also been explored, with reports ranging from mono- to bis- to trisQACs all derivatized from various cores containing one hydrophobic chain.[10,11] Still others have focused on the design of "soft" amphiphiles, which incorporate hydrolyzable bonds that may decrease toxicity due to their ability to be readily metabolized.[12–14] Such QACs typically display equipotent activity to their non-hydrolyzable counterparts, while degrading after a few hours to a few days. Our laboratories have likewise endeavored to advance our QAC capacities, investigating a variety of bis- and multiQAC structures;[15–20] a review of our efforts has recently been reported.[21] Common themes have emerged—optimal alkyl chain lengths are generally ~12 carbons, and the incorporation of at least two ammonium cations generally leads to an increase in antimicrobial activity, as well as significant biofilm eradication capability. MultiQACs also show the promise to address bacterial resistance; whereas bacteria bearing genes for key efflux pumps show increased tolerance toward many commercially available QACs, resistant bacteria are seemingly thwarted in most cases by multicationic systems.[22] Thus we have adopted a scaffold-hopping approach to the installation of multiple cationic residues in a variety of rapidly assembled multiQAC systems.

Previous studies of bacterial susceptibility to QACs suggested that the presence of efflux pumps is a strong protective factor, even stronger perhaps than the presence of a second bacterial membrane as in Gram-negative strains.[20] QACs that do not trigger bacterial resistance, namely *qac*-encoded efflux pumps, are thus more efficacious. We hypothesized that an extended cationic surface (wherein charges were spread over a larger surface area) would greatly decrease diffusion into bacterial cells, thus minimizing resistance and promoting efficacy. Furthermore, we postulated that these scaffolds might also have increased selectivity against prokaryotic cells based on their phospholipid composition in comparison with their eukaryotic counterparts. Our research group previously used a T-shaped tetraamine starting material, tris(2-dimethylaminoethyl)amine (T-0,0,0, Figure 2), which, upon quaternization, provided a modest dispersal of cationic centers. After evaluating

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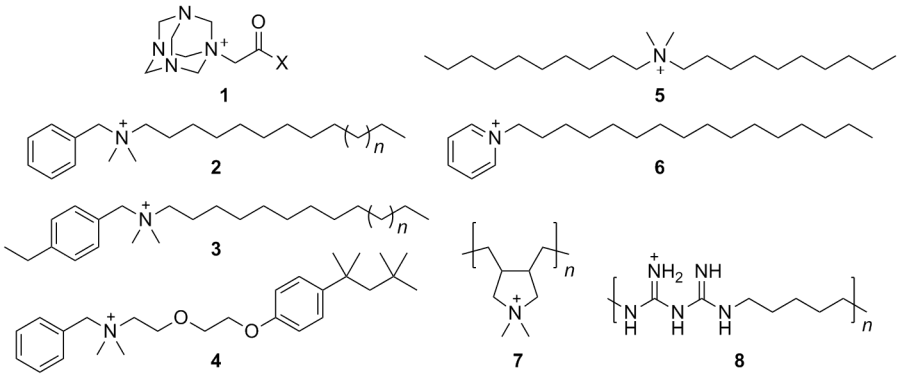


Figure 1. The history of quaternary ammonium compound antiseptics: a selection of commercialized QACs.

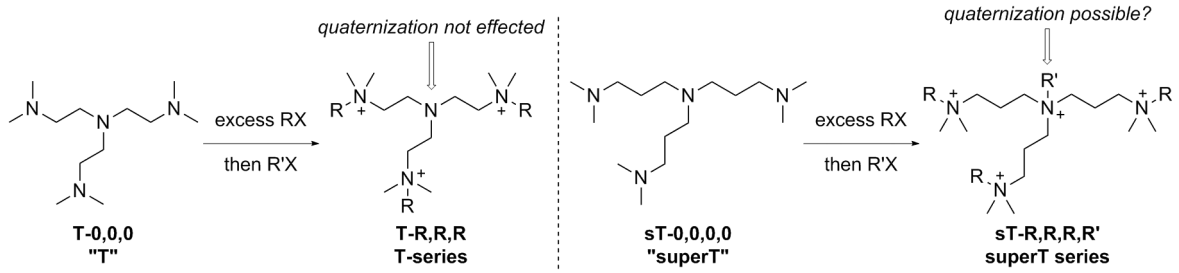
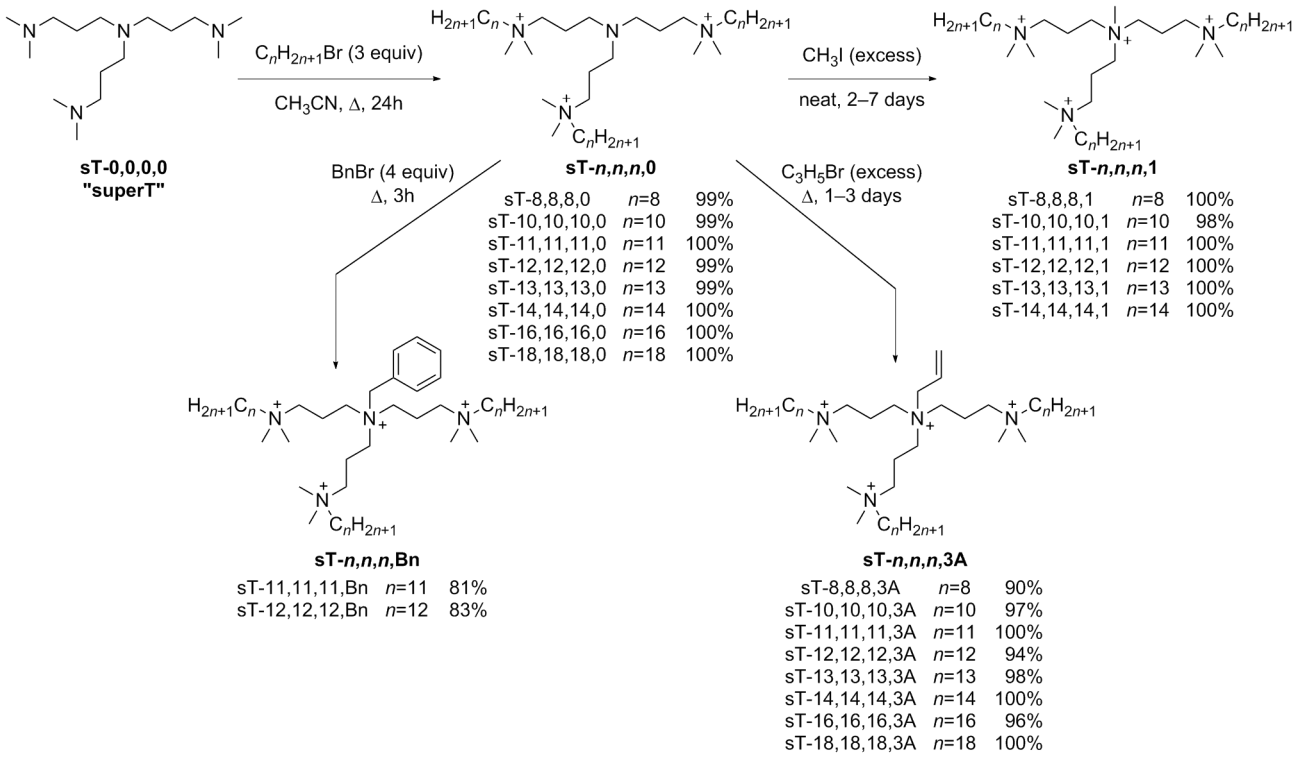


Figure 2. Comparison of previously prepared trisQAC T-series derived from T-0,0,0, and tetraQAC superT series derived from sT-0,0,0,0.

the antimicrobial activity of the triscationic derivatives, we found MIC values approaching 1 μM against a range of bacteria. However, we saw little ability to derivatize the central nitrogen, for steric and electronic reasons. Fortunately, another readily available tetraamine starting material, *N*,*N*-bis[3-(dimethylamino)propyl]-*N*′,*N*′-dimethylpropane-1,3-diamine, referred to as "superT", was identified. We thought that this increased linker distance between tertiary amines would engender nucleophilicity to the central nitrogen, even when all terminal amines were quaternized.

Additionally, we conjectured that the distancing of the cations might lead to an improved antimicrobial activity to toxicity of eukaryotic cells profile (as measured by $Lysis_{20}$ values for red blood cells). Such a comparison has been used for QACs for over half a century and is a standard measure of therapeutic index.[23] Previous work in determining selectivity of antimicrobial activity over toxicity to eukaryotic cells has largely been focused on amphiphilic antimicrobial peptides (AMPs), biological analogues of QACs.[24–26] Such work has established that greater cationic nature tends to confer selectivity for bacterial cell surfaces, as these tend to be more negatively charged than eukaryotic cells and are comprised of different components. Prokaryotic cell walls possess a plethora of anionic molecules, namely lipopolysaccharides in Gram-negative bacteria and lipoteichoic acids in Gram-positive bacteria. Prokaryotic cell membranes likewise contain a high proportion of acidic phospholipids, such as phosphatidylglycerol and cardiolipin. In contrast, eukaryotic cells are mainly comprised of zwitterionic phosphatidylcholine and sphingomyelin, with a much smaller proportion of negatively charged components. It has been shown that when presented with bacterial and eukaryotic cells in the same environment, fluorescently labeled AMPs preferably collect on the surface of bacterial cells, further adding to this proposal.[24] With this in mind, along with the newly identified superT scaffold, we sought to examine the relationship of efficacy to toxicity with the superT QAC series. Herein, we report the preparation of 24 amphiphiles based on this superT motif, and the biological evaluation of their antimicrobial activity (as MIC), their biofilm disruption capacity (as MBEC), as well as their toxicity (as $Lysis_{20}$).

Twenty-four multiQACs were prepared from sT-0,0,0,0; numbers in this abbreviation indicate the number of carbons of appended alkyl chains, if any. Selective alkylation of the terminal tertiary amines was readily achieved. Thus, alkylation with the corresponding alkyl bromide (3 equiv, $C_nH_{2n+1}Br$) furnished the sT-*n*,*n*,*n*,0 series in high yield. Whereas a fourth equivalent of a long-chained alkyl halide was not successfully incorporated, the resulting scaffold could subsequently be exposed to neat methyl iodide for 2–7 days to provide fully quaternized tetraQACs, dubbed sT-*n*,*n*,*n*,1, in high yields; methylation of the 16- and 18-carbon analogues was unsuccessful due to poor solubility. The alkylated superT series was also exposed to excess allyl bromide at reflux for 1–3 days, resulting in high yields of the sT-*n*,*n*,*n*,3A series. Finally, exposure to four equivalents of benzyl bromide at reflux for 3 h provided a pair of superT compounds abbreviated as sT-*n*,*n*,*n*,Bn. Moderate yields of the sT-*n*,*n*,*n*,Bn series were observed. The reaction schemes for all superT compounds are illustrated in Scheme 1; complete ex-



sT-n,n,n,0		
sT-8,8,8,0	n=8	99%
sT-10,10,10,0	n=10	99%
sT-11,11,11,0	n=11	100%
sT-12,12,12,0	n=12	99%
sT-13,13,13,0	n=13	99%
sT-14,14,14,0	n=14	100%
sT-16,16,16,0	n=16	100%
sT-18,18,18,0	n=18	100%

sT-n,n,n,1		
sT-8,8,8,1	n=8	100%
sT-10,10,10,1	n=10	98%
sT-11,11,11,1	n=11	100%
sT-12,12,12,1	n=12	100%
sT-13,13,13,1	n=13	100%
sT-14,14,14,1	n=14	100%

sT-n,n,n,Bn		
sT-11,11,11,Bn	n=11	81%
sT-12,12,12,Bn	n=12	83%

sT-n,n,n,3A		
sT-8,8,8,3A	n=8	90%
sT-10,10,10,3A	n=10	97%
sT-11,11,11,3A	n=11	100%
sT-12,12,12,3A	n=12	94%
sT-13,13,13,3A	n=13	98%
sT-14,14,14,3A	n=14	100%
sT-16,16,16,3A	n=16	96%
sT-18,18,18,3A	n=18	100%

Scheme 1. Synthesis of the superT series of QACs.

perimental details and characterization are presented in the Supporting Information.

Bioactivity of these 24 amphiphiles was assessed against a standard panel of bacteria: *Staphylococcus aureus* SH1000 (SA), *Enterococcus faecalis* OG1RF (EF), *Escherichia coli* MC4100 (EC), and *Pseudomonas aeruginosa* PAO1 (PA), as well as against two strains of methicillin-resistant SA [community-acquired methicillin-resistant SA (CA-MRSA, USA300-0114), hospital-acquired methicillin-resistant SA (HA-MRSA, ATCC 33591)]. These data are presented in Table 1, wherein multiQACs are grouped according to alkyl chain length; comparison was made to the previously prepared triscationic T-compounds. $Lysis_{20}$ values represent toxicity, and are measured as the concentration of compound that lyses 20% or less of red blood cells (RBC). Anti-biofilm activity against SA and CA-MRSA is reported as minimum biofilm eradication concentrations (MBEC), which represents the concentration yielding complete eradication of a pre-established biofilm.

The antimicrobial activity of these superT analogues represent the strongest of the >300 antiseptic compounds we have prepared and investigated to date. Nine different compounds out of this set of 24 displayed an average MIC value of <1 μM against the six-bacteria panel. MIC values generally correlated to chain length; superT compounds with alkyl chain lengths of 10–12 carbons were generally optimal. We have seen this preference for ~11 carbon chains when there are three or more alkyl chains present; dodecyl chains tend to be optimal in bisQAC systems.

A direct comparison of the activity of the sT-*n*,*n*,*n*,0 compounds to the similarly triscationic T-*n*,*n*,*n* compounds shows a modest improvement in activity in this less clustered system. The addition of a fourth quaternary ammonium center yielding tetraQACs, a major motive in moving to this system, seems to provide no further improvements to antimicrobial activity. It is possible that this is a reflection of the basicity of the central nitrogen when unsubstituted; it may end up being protonated under neutral conditions anyway, so the final substitution may not effect a major change. This is in agreement with earlier work published by Clardy, Losick, and Kolter, where they observed that the protonation of polyamine derivatives directly contributed to their biological activity.[27]

To our delight, we saw no significant difference in activity between SA and *qac*-bearing CA-MRSA in the entire superT series. However, disparity between the MIC values against SA as compared with HA-MRSA was evident for the first time in our hands, observed in select shorter-chained (8 carbons) and longer chained (16–18 carbon) amphiphiles; this difference was most apparent for sT-8,8,8,1 and sT-18,18,18,3A. This two-stage susceptibility to QAC resistance has been observed in another series of compounds we have prepared, based on polyaromatic dye systems and CA-MRSA,[20] and is likely due to differences in membrane permeability of these varying length hydrophobic chains. The bioactivity of the shorter- and longer-chained superT compounds against HA-MRSA matched that against EF, another Gram-positive organism, so we are hesitant to ascribe this to a true resistance event.

In a preliminary toxicity assessment, we analyzed $Lysis_{20}$ values. While many of our potent compounds displayed RBC lysis at low concentrations, a therapeutic window was present. For example, the potent tetraQACs sT-11,11,11,1 and sT-

Table 1. Biological activity of superT compounds.

Compound	Antibacterial activity (MIC [μM])[a]						$Lysis_{20}$[b]	MBEC [μM][c]	
	SA	EF	EC	PA	CA-MRSA	HA-MRSA		SA	CA-MRSA
BAC	8	8	32	63	32	8	63	>200	>200
sT-0,0,0	>500	>500	>500	500	>500	>500	250	>200	>200
T-8,8,8	2	16	16	63	8	16	125	NT	NT
sT-8,8,8,0	4	32	32	125	2	32	125	>200	>200
sT-8,8,8,1	0.5	16	4	250	1	16	125	200	200
sT-8,8,8,3A	1	16	4	125	1	8	125	200	>200
T-10,10,10	1	1	1	2	1	0.5	8	NT	NT
sT-10,10,10,0	0.5	0.5	1	2	0.5	0.5	8	50	25
sT-10,10,10,1	0.5	0.5	0.5	2	0.5	0.5	8	75	50
sT-10,10,10,3A	0.5	0.5	0.5	1	0.25	0.5	8	100	25
T-11,11,11	0.5	1	1	2	1	0.5	8	NT	NT
sT-11,11,11,0	0.5	0.5	0.5	1	0.5	0.5	4	100	50
sT-11,11,11,1	0.5	0.25	0.25	1	0.5	0.5	4	>200	50
sT-11,11,11,3A	0.5	0.5	0.5	1	0.5	1	4	>200	50
sT-11,11,11,Bn	0.5	0.5	0.5	1	0.5	0.5	4	>200	25
T-12,12,12	1	1	2	8	2	1	8	NT	NT
sT-12,12,12,0	0.5	1	1	4	0.5	1	4	200	200
sT-12,12,12,1	1	1	1	4	0.5	2	16	>200	>200
sT-12,12,12,3A	1	0.5	0.5	2	1	0.5	4	>200	100
sT-12,12,12,Bn	1	0.5	0.5	2	0.5	0.5	4	>200	100
sT-13,13,13,0	1	1	1	8	0.5	1	4	>200	>200
sT-13,13,13,1	2	1	1	4	0.5	1	4	>200	>200
sT-13,13,13,3A	2	1	1	4	1	1	2	>200	≥200
T-14,14,14	4	4	16	63	32	2	8	NT	NT
sT-14,14,14,0	1	2	4	16	0.5	2	4	>200	≥200
sT-14,14,14,1	4	2	4	32	2	2	4	>200	>200
sT-14,14,14,3A	2	2	4	32	2	2	2	>200	>200
sT-16,16,16,0	8	16	16	32	4	16	4	>200	>200
sT-16,16,16,3A	4	8	16	63	4	16	4	>200	>200
sT-18,18,18,0	8	16	32	63	4	32	8	>200	>200
sT-18,18,18,3A	2	32	32	125	2	16	4	>200	>200

[a] Minimum inhibitory concentrations against *Staphylococcus aureus* (SA), *Enterococcus faecalis* (EF), *Escherichia coli* (EC), *Pseudomonas aeruginosa* (PA), community-acquired methicillin-resistant *S. aureus* (CA-MRSA), and hospital-acquired methicillin-resistant *S. aureus* (HA-MRSA) are based on the majority of three independent replicates. [b] $Lysis_{20}$ values represent the compound concentration at which 20% or less of red blood cells are lysed. [c] MBEC is the compound concentration that completely eradicates a pre-established biofilm based on six replicates; NT: not tested.

12,12,12,1 showed MIC values 4–32-fold less than the observed $Lysis_{20}$. In the shorter series (e.g., sT-8,8,8,1 and sT-8,8,8,3A), the therapeutic index was 125 when comparing the MIC against CA-MRSA to the observed $Lysis_{20}$. It is interesting to note that this toxicity decrease went hand-in-hand with a decrease in efficacy against PA. Based on previous work with AMPs, we hypothesized that increasing charge state may lead to decreased toxicity. The +1 increase in charge, however, did not appear to be the case as lysis values for each set of analogous tris- and tetraQACs did not differ significantly.

In measuring the MBEC values, there seems to be a benefit to having somewhat shorter chains, specifically decyl derivatives; sT-10,10,10,0 is the top QAC tested in regards to biofilm eradication, with an MBEC of 50 μM against SA and 25 μM against MRSA. This is in itself a puzzling observation that was observed repeatedly in the superT series, as MRSA is more susceptible to biofilm inhibition than its SA counterpart. We have noted—as have others—that many MRSA strains tend to grow weaker biofilms (that is, with less extracellular matrix) than SA in the absence of triggering antibiotics.[28] Based on this observation and our previous studies that as tris- and tetraQACs do not appear to induce resistance in MRSA, one possible explanation is that there are lower levels of extracellular DNA production in the MRSA biofilms, leading to stronger interaction between QACs and extracellular DNA in the SA biofilm matrix. This claim, while supported by the data, warrants further investigation. Nonetheless, no appreciable differences in anti-biofilm activity were found in the comparison of tris- to tetraQACs,

lending credence to previous claims that increased cationic nature does not necessarily confer the ability to disrupt biofilms.[29]

In summary, we have prepared a set of multiQACs which use a different disposition of charges as well as increased overall charge in attempt to improve antimicrobial activity and minimize toxicity. Whereas highly potent (sub-micromolar) activity was observed for top compounds, additional cationic charge was not the key factor involved in conferring antimicrobial activity. We again reason that judicious choice of scaffold can lead to optimized activity and therapeutic index, including this case which worked to optimize the spacing of cationic charges. Finally, we have observed an unexpected result wherein ostensibly resistant biofilms (CA-MRSA) showed greater susceptibility to eradication by select QACs as compared with a non-resistant bacterial analogue; we intend to further investigate this anomaly.

Conflict of interest

W.M.W. and K.P.C.M. are equity shareholders in NovaLyse BioSolutions.

Acknowledgements

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Keywords: bacterial biofilms · disinfectants · methicillin-resistant *Staphylococcus aureus* (MRSA) · quaternary ammonium compounds

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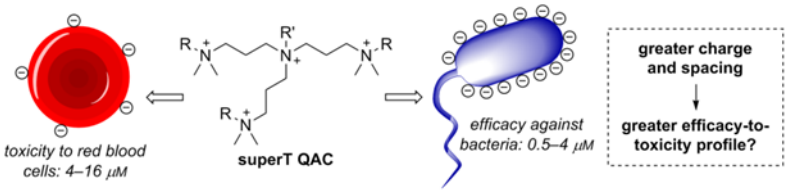
Building a Better Quaternary Ammonium Compound (QAC): Branched Tetracationic Antiseptic Amphiphiles



"SuperT" QACs: Disinfectants must have two key features: potent activity against a variety of microorganisms, and minimal toxicity to eukaryotic cells. How do we design nonspecific antibacterial agents that kill bacteria, yet are safe enough to use in households, hospitals, and industry? This work examines the role of charge and spacing in developing novel antiseptics with desirable efficacy to toxicity profiles.