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Novel boronium salt exhibits substantial antibacterial activity when compared to a commercial quaternary ammonium disinfectant

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ABSTRACT

Commercial disinfectants are routinely used to decontaminate surfaces where microbes are expected and unwelcome. Several disinfectants contain quaternary ammonium salts, or "quats", all being derived from ammonium. Quaternary alkyl dimethyl benzyl ammonium chloride or bromide disinfectants are widely available. These compounds are effective in reducing or eliminating bacteria on contaminated nonporous surfaces. A unique benzyl derived boronium salt with strong detergent action has been developed. It demonstrated 4-8X greater antibacterial activity against 3 different bacteria when compared to an equal concentration of a commercial quant disinfectant solution containing alkyl dimethyl benzyl ammonium chloride and alkyl dimethyl ethylbenzyl ammonium chloride. Antibacterial effectiveness of each agent was determined by the minimum inhibitory concentration (MIC) method.

Disinfectants are routinely used to decontaminate fomite (inanimate) surfaces that are likely to harbor infectious microbes. This includes working surfaces found in several areas of medical facilities.[1] Environmental contamination of surfaces occurs in areas used for food preparation, treatment rooms, patient rooms, operating suites, and even visitor waiting areas. Several types of commercially available disinfectants are available for decontaminating these surfaces. However, they can vary widely in their ability to reduce or eliminate different microorganism types such as bacteria, mycobacteria, fungi, and viruses. Additionally, some disinfectant agents require extended contact time with the surface to be fully effective.[2] There is the further concern about their suitability for use on different fomite materials. For example, the use of corrosive hypochlorite-based disinfectants on dark colored surfaces or medical equipment may be contraindicated.[3]

The presence of a microbial biofilm on fomite surfaces present an additional problem for disinfectant use. Biofilm-associated microbes produce a slippery extracellular matrix (ECM) composed of polymeric substances like polysaccharides, proteins, and lipids. Here, the microbes can remain hidden inside a biomass away from superficially applied disinfectants. This enables their resistance and/or tolerance to disinfectant agents that is not similarly seen when these same microbes are challenged by the same disinfectants in their planktonic (free-living) form. Biofilms have been described as demonstrating "remarkable resilience" to antimicrobials of either chemical, physical, or biological origins.[4] Biofilms are also refractory to antibiotics. Worldwide, they remain a major cause of chronic and recurrent infections by clinically important pathogens such as *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*.[5] Additionally, moderate to heavy soiling of non-biofilm contaminated surface with organic matter presents a similar issue in effectively disinfecting them. Precleaning of soiled surfaces is usually recommended before applying a disinfectant.[6] Consequently, a disinfectant agent exhibiting both strong detergent (penetrance) action of either soiled or biofilm surfaces and enhanced biocidal activity would be useful in meeting these cleaning challenges.

Quaternary ammonium compounds (QACs) are cationic surfactants where the replacement of ammonium hydrogens with alkyl or aryl groups (*i.e.* benzyl group) creates a strong base and its salt. QACs gained attention in 1935 when Domagk first described their antibacterial properties.[7] QACs antibacterial activity was initially gauged against the gold-standard phenol-coefficient test. A test that often gave varied results making it difficult to interpret. Cationic surfactants are basically soaps, in which the hydrophilic portion contains a positively-charged

Abbreviations: CFU, Colony Forming Unit; K-B, Kirby-Bauer; MBC, Minimum Bactericidal Concentration; M-H, Mueller-Hinton; MIC, Minimum Inhibitory Concentration; QAC, Quaternary ammonium compound; SBA, 5% Sheep Blood Agar; SLS, Sodium Lauryl Sulfate.

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ammonium cation. An alkyl chain of various lengths comprises the hydrophobic portion. The expression of hydrophobic-hydrophilic portions enhances both their surface activity and ability to readily form liposomes. This twofold arrangement allows for interaction of these cationic surfactants with the cell membrane phospholipids of microorganisms.[8] QACs membrane active properties contribute to their antimicrobial activity, which appears to be at least partially due to their ability to disrupt microorganism lipid membranes.[9]

However, the widespread use of QACs has resulted in the development of microbial resistance.[10] Novel QACs have been developed to circumvent this problem. This would include gemini quaternary ammonium salts, which possess dual hydrophilic-hydrophobic portions. Gemini surfactants with hydrophobic chains of 10 and 12 carbons were shown to produce the greatest biological activity against tested microorganisms.[8] However, the use of QAC wipes made of cotton or containing large amounts of cellulose may reduce their antimicrobial effectiveness.[11]

Anionic surfactants are valued for their large ability to reduce surface tension and foaming action. They are often used for cleaning and pharmaceutical purposes.[12] Increasing attention has been given to amino acid-based surfactants. One reason is easy cleavage of the ester or an amide bond linking the naturally occurring polar head-group to the hydrophobic tail. The ester-linked variety are very susceptible to alkaline hydrolysis, which allows for generating a biocide with short-lived action.[13] Anionic surfactants have shown antiviral activity. For example, anionic sodium lauryl sulfate (SLS) has shown solubilization of viral envelopes along with denaturation of proteins associated with the envelope and/or protective capsid.[14]

The current study reports on the synthesis and antimicrobial activity testing of a unique boronium ion with an attached 16-carbon alkyl chain an overall neutral charge. It demonstrates strong solubilizing characteristics. Boronium ions of the present type are long known to be materials of exceptional stability towards water, air, and acidic or basic conditions.[15] A derived benzylated form of the same boronium ion was shown to be very effective in inhibiting growth and killing of three types of bacteria when compared to a commercial QAC disinfectant.

Microbe characteristics and testing

Tested bacteria included *Escherichia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 29213), and *Pseudomonas aeruginosa* (ATCC 27853); (See Table 1). Stock bacterial cultures were maintained by periodic passage on nutrient agar containing 5% sheep blood (SBA); (Remel, Lenexa, KS) and incubated at 37 °C under ambient conditions (no CO_2). To ensure logarithmic growth, a single well isolated colony of each test organism was transferred to a fresh SBA plate and incubated 18–24 h before each assay.

Antimicrobial sensitivity testing (AST) had been previously performed on all 3 test bacteria using a Phoenix 50 instrument (Becton, Dickinson and Co., Franklin Lakes, NJ). AST results indicated that the *E. coli* strain used in this study was sensitive to all antimicrobials used in the gram-negative rod (GNR) panel as was the *S. aureus* strain to gram-positive cocci (GPC) panel, with the exception of penicillin G where *S. aureus* was resistant. However, the *P. aeruginosa* strain was resistant to 9 of 19 antimicrobials (47%) used in the GNR panel.

Table 1
Characteristics of tested bacteria.

Characteristic	Bacterium		
	Escherichia coli	*Pseudomonas aeruginosa*	*Staphylococcus aureus*
Gram stain reaction	Negative	Negative	Positive
Morphology	Rod-shaped (bacillus)	Rod-shaped (bacillus)	Spherical (coccus)
Metabolism	Facultative anaerobe	Obligate aerobe	Facultative anaerobe

Two to three colonies of a single bacterial type were transferred to 3 ml Muller-Hinton (M−H) broth (Remel, Lenexa, KS) in a glass screw top tube and adjusted to match a 0.5% McFarland turbidity standard using a DEN-1 McFarland Densiotometer (Grant-Bio, Beaver Falls, PA). This reading results in a suspension of approximately 1.0×10^8 colony forming units (CFU)/mL^{-1}. An additional 1:100 dilution of the adjusted sample was made in M−H broth to yield approximately 1.0×10^6 colony forming units (CFU)/mL^{-1}.

BDD BacDown detergent disinfectant (Decon Labs, King of Prussia, PA) was used as a positive control.[16] BacDown is a QAC containing a mixture of *n*-alkyl dimethyl benzyl ammonium chlorides (2.25%) and *n*-alkyl dimethyl ethylbenzyl ammonium chlorides (2.25%). All tested boronium salt compounds were adjusted to a similar 4.5% (45,000 μg/mL) starting concentration. Dimethyldodecylamine was used as a negative control. Two-fold serial dilutions were prepared as described by Balows (Balows, 1991) in deionized water from the stock 4.5% agents. These included a positive control (BDD BacDown), a negative control (Dimethyldodecylamine), or boronium variant.

Two boronium salts were tested with each bacterium. The first one (**A**) being called a base ion (see Fig. 1). The second one (**B**) having the base ion structure but a terminal methyl group being replaced by a benzyl group. One hundred microliters of each test sample dilution or control dilution were then distributed to separate well of a 96-well untreated microtiter plate (see Fig. 2).

An additional 100 μL aliquot of the 1:00 dilution inoculum (~1.0×10^6 CFU/mL^{-1}) containing a test bacterium was added to each dilution well. This resulted in a 1:2 dilution of bacterial numbers being knocked down to approximately 5.0×10^5 CFU/mL^{-1}. Final concentrations of each agent in test wells ranged from 22.5 mg/mL down to 0.02 mg/mL.

Growth control wells containing 200 μL of the M−H broth without bacteria were added to detect broth contamination. The plate was covered with a fitted lid and sides wrapped with Parafilm® to prevent sample desiccation. The plate was transferred to incubator for 18–24 h @ 37 °C under ambient conditions with constant rotation at 100 RPM using a MaxQ 4450 shaking incubator (Thermo Fisher Scientific, Waltham, MA).

To enumerate bacteria, 4 ten-fold serial dilutions were prepared of the adjusted inoculum in 0.9% sterile saline. A 100 μL aliquot of each dilution was transferred to a separate SBA plate and spread using a sterile cell spreader (Thermo-Fisher, Waltham, MS). Plates were incubated overnight at 37 °C under ambient conditions. After 24-hours, plates were inspected for growth and colony counted. CFU/mL^{-1} were determined by counting the number of colonies on a plate demonstrating between 10 and 100 colonies. This number was multiplied by the reciprocal of the dilution indicated on the counted plate and multiplied by 10 to account for the 100 μL (0.1 ml) sample size.

Untreated 6 mm Whatman™ antibiotic assay discs (GE Healthcare, Fairfield, CT) were prepared for disc diffusion testing as follows. Twenty microliters of the 1:8 (2.81 mg/mL) dilution and 1:128 dilution (0.17 mg/mL) of each agent was transferred to a separate filter disc. Paper discs were dried under a laminar flow hood for 30 min. Dried discs were marked with contents using a pencil and stored at 4–8 °C until use. On the day of testing, bacterial inoculums of ~1.0×10^6 CFU/mL^{-1} were prepared as previously described. An additional 1:2 dilution was made of the adjusted inoculum to yield approximately 5.0×10^5 CFU/mL^{-1}. Plate counts were performed as previously described. A bacterial lawn was created on a 15 × 150 mm M−H agar plate (Remel, Lenexa, KS) as follows. A sterile cotton tipped swab was inserted in the inoculum liquid. Excess fluid was eliminated by wring the swab against the tube before removing. The M−H agar plate was placed on a free-spinning rotating disc device and spun rapidly. The wetted swab was applied to the center of the agar plate and moved to the periphery while the plate was still rotating. This process created a confluent uniform lawn of bacteria. Paper discs containing either controls, test agents, or commercially

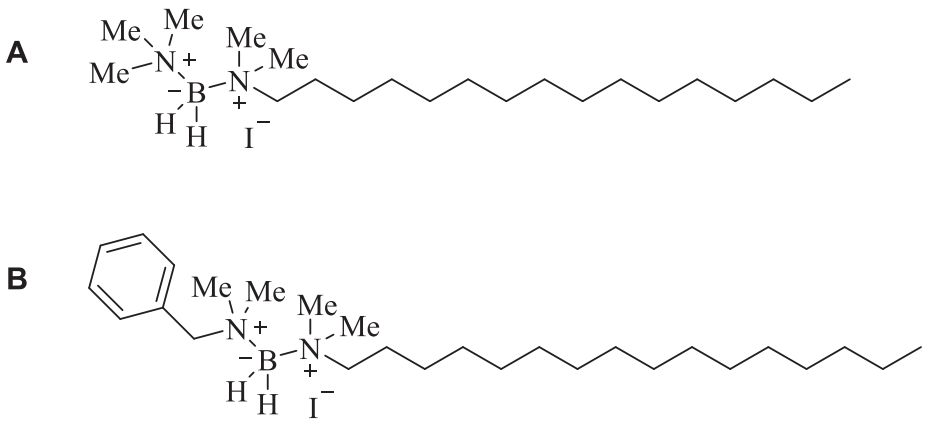

Fig. 1. Structure of base boronium salt (A) along with benzyl derived form (B).

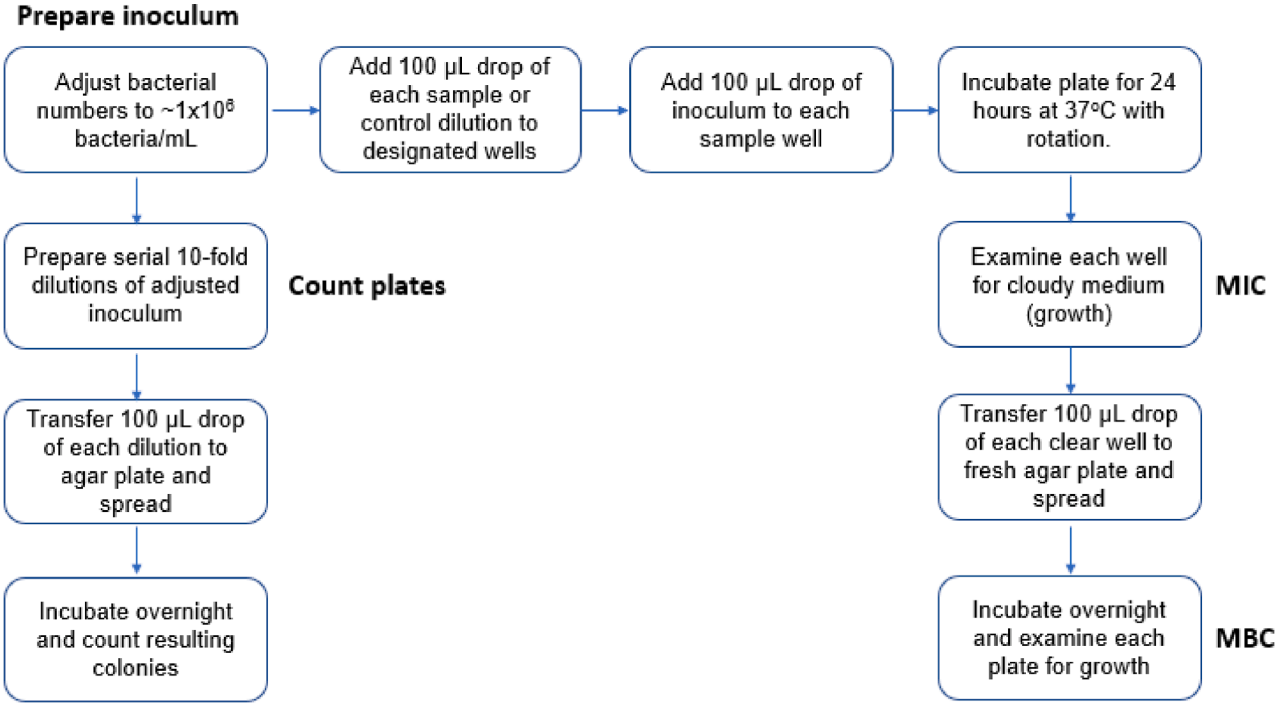

Fig. 2. Schematic diagram of minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) testing procedure.

prepared antibiotics (BD BBL, Franklin Lakes, NJ) were added to the plate, which was incubated for 24 h @ 37C. Resulting zone of inhibition (ZOI) seen around each disk was measured in millimeters using a digital caliper (World Precision Instrument, Sarasota, FL).

After 24 h, the 96-well microplate was removed from the incubator and each well examined for the presence or absence of cloudiness. Presence of cloudiness (turbidity) in a well indicated bacterial growth whereas a clear well indicated growth inhibition by the contained agent. A mirrored plate reader with 3X magnification was used to examine each well for cloudiness (Bel-Art™ SP Scienceware™, Wayne, NJ). The lowest concentration of each agent demonstrating a clear well (no turbidity) was designated as the minimum inhibitory concentration (MIC). A 100 µL of sample from each clear well including determined MIC well was transferred to a fresh SBA plate labeled with the corresponding dilution, spread over the plate surface, and incubated for 18–24 h. Each spread plate was examined for growth. The first concentration demonstrating zero colonies was designated as the minimum bactericidal concentration (MBC).

Synthesis of boronium compounds

Commercial reagents were obtained from Aldrich Chemical and Oakwood Chemicals and used without further purification. ^{1}H and ^{13}C NMR was recorded on a 500 MHz JEOL spectrometer using $CDCl_3$ as a solvent at room temperature. All chemical shifts for ^{1}H and ^{13}C NMR were reported downfield using tetramethylsilane (TMS, at d ¼ 0.00 ppm).

The benzyl derived boronium ion was synthesized in two steps (See Fig. 3). First, benzyl dimethylammonium iodoborane **4** was synthesized. Second, the resulting compound was reacted with hexadecyldimethylamine to produce the final benzyl-modified boronium ion. The initial synthesis step was accomplished using a 100 ml round-bottom flask containing a magnetic stirring bar and borane-THF complex **2** solution in THF (1.0 equiv, 20 mmol) where *N*,*N*-dimethylbenzylamine (1.0 equiv, 20 mmol) was added in a dropwise manner and stirred overnight at room temperature under nitrogen. At reaction completion, the solvent was removed under reduced pressure to furnish benzyl dimethylammonium borane **3** as a white solid. This product was transferred into

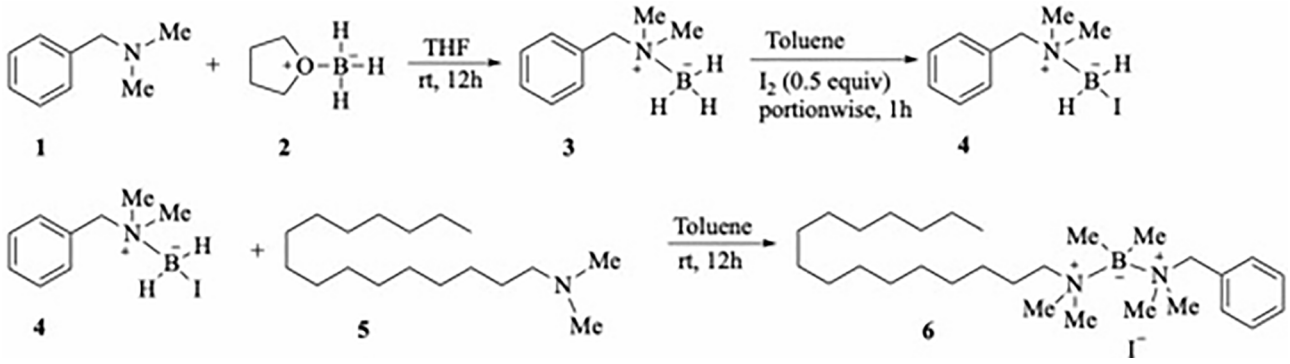

Fig. 3. Synthesis steps involved in producing a benzyl derived boronium ion and subsequent addition of a N,N-dimethylhexadecylamine. Corresponding step numbers (e.g., 4) are mentioned in the synthesis description given in the above paragraph

a 200 ml round-bottom flask containing a stirring bar and dissolved in 100 ml of toluene. Iodine (0.5 equiv) was added portion wise for 30 min and left to stir for an hour until a clear solution was achieved. In the final step, hexadecyldimethylamine (1.0 equiv) was added and stirred overnight at room temperature to result hexadecyldimethyl[(*dimethylbenzylamino*)*boranyl*]azanium iodide as a white solid.

Hexadecyldimethylimino)boranyl]trimethylazanium iodide **9** was synthesized using the procedure outlined in 2.2.2. In a 200 ml round-bottom flask equipped with a magnetic stirring bar, the borane trimethylamine complex (1.0 equiv) was dissolved in 100 ml of toluene. Iodine (0.5 equiv) was added portion wise within 30 min and left it to stir for an hour until clear solution was achieved. Then, hexadecyldimethylamine (1.0 equiv) was added and stirred overnight at room temperature to result [(hexadecyldimethylimino)boranyl]trimethylazanium iodide **9** as a white solid (See Fig. 4).

Study limitations include that only three bacterial species were tested. However, these same bacteria appear to be routinely used to assess broad spectrum antibacterial activity of disinfectants. Further testing against other types of microbes such as fungi and viruses may also be warranted. For example, *Aspergillus fumigatus* mold and *Candida albicans* yeast will be used to determine the boronium ion's effectiveness against fungus. Additionally, the bacteria *Serratia marcescens,* another gram-negative rod, will be similarly tested. *S. marcescens* was selected because of (1) its close phylogenetic relationship to *E. coli* and (2) increased resistance to 6/18 (33%) of the antibiotics included in the GNR antibiotic sensitivity panel. A potential limitation for use as a surface disinfectant is that the benzyl derived boronium salt has not been tested for any inherent toxicity. However, the extremely low concentrations required to kill the tested bacteria (see Table 3) suggests that toxicity may not be an issue. Additionally, protective gloves are usually worn when using QAC surface disinfectants. This same precaution would be advisable in applying a boronium based disinfectant.

Inhibition of microbe growth

Bacterial counts indicated that comparable numbers of each test bacteria were separately distributed to each M−H agar plate (*E. coli* at 3.3×10^6 CFU/mL^{-1}, *P. aeruginosa* at 2.0×10^6 CFU/mL^{-1}, *S. aureus* at 2.8×10^6 CFU/mL^{-1}). Nonetheless, the results of disk diffusion testing were considered inconclusive. Neither *E. coli* nor *P. aeruginosa* demonstrated a measurable ZOI at either 1:8 (2,810 μg/mL) or 1:128 (170 μg/mL) dilutions. The BacDown QAC demonstrated a ZOI of 9.9 mm and 0 mm at the 1:128 dilution for *S. aureus* while benzyl derived boronium salt demonstrated a 14.8 mm ZOI at 1:8 dilution and 7.6 mm ZOI at 1:128 dilution. The control antibiotics Aztreonam (30 μg) Cefoxitin (30 μg) both demonstrated ZOIs consistent with published results for each tested bacterium.[17]

The small Kirby-Bauer ZOI results suggest that neither the BacDown QAC nor benzyl derived boronium salt readily diffused away from the 6 mm paper disc into the adjacent agar medium under the tested conditions. The hydrophobic nature of the boronium ion alkyl chain may have prevented its movement from the disc into the predominantly aqueous surrounding agar medium (~93% H_2O). The larger ZOIs for the benzyl derived boronium salt appears to offer some support the lower MIC results for *S. aureus*, when compared to *E. coli* and *P. aeruginosa*.

Direct plate counts indicated that bacterial numbers used in the MIC/MBC assays ranged from a low of 3.5×10^5 CFU/mL^{-1} for *E. coli* to a high of 1.0×10^6 CFU/mL^{-1} for *S. aureus* (see Table 2). Contamination checks of both the sterile saline and M−H broth were negative for growth.

All negative control dilution wells containing only the alkyl amine appeared with visible growth (cloudiness). The same negative result (growth) was seen for the base boronium ion without added benzyl group. It should be noted that the first three dilution wells of the boronium salt were difficult to determine growth since they appeared somewhat turbid. This was attributed to the nature of the compound,

Table 2
Initial and final count of each tested bacterium.

Bacterium	Total count	Sample well count (1:2)
E. coli	0.7×10^6 CFU/mL	3.5×10^5 CFU/mL
S. aureus	2.1×10^6 CFU/mL	10.0×10^5 CFU/mL
P. aeruginosa	1.4×10^6 CFU/mL	7.0×10^5 CFU/mL

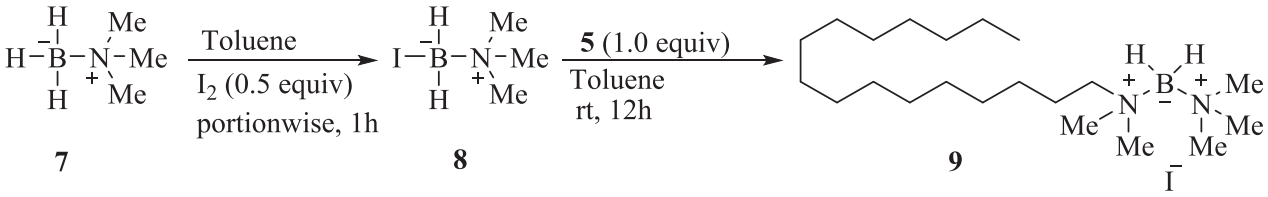

Fig. 4. Synthesis steps involved in producing the base boronium ion. Corresponding step numbers (e.g., 9) are mentioned in the synthesis description given in the above paragraph.

which appears cloudy until diluted. In contrast, several dilutions of the positive control (BacDown) and the benzyl derived boronium salt demonstrated clear wells indicating growth suppression (see Table 3).

MICs varied for each tested bacterium. The greatest inhibitory effects of both the BacDown QAC (80 μg/mL) and benzyl derived boronium salt (20 μg/mL) was seen with *S. aureus*. The least was seen with BacDown QAC (1410 μg/mL) and benzyl derived boronium salt (170 μg/mL) for *P. aeruginosa*, as demonstrated by the larger MIC values. The MIC results for *E. coli* were in between these values with BacDown at 170 μg/mL and benzyl derived boronium salt at 40 μg/mL. It should be noted that the *S. aureus* inoculum size was nearly 3 times greater than that of *E. coli* and nearly 1.5 times greater than *P. aeruginosa*.

Hemolysis was seen on the MBC plates at the point of drop application the higher concentrations of the boronium ion with and without benzyl group. The amount of hemolysis diminished with each successive plate, which contained a lower ion concentration. Here, complete or beta hemolysis was seen on the first and second plates with higher ion concentrations while alpha or partial hemolysis was seen on the third plate. Subsequent plates demonstrated either little alpha hemolysis or no hemolysis. Similar hemolysis was not readily apparent with BDD BacDown sample plates.

Overall, the MIC values demonstrated that the inhibitory action of the benzylated boronium ion was more effective at inhibiting the growth of all tested bacteria than an equal concentration of the BacDown QAC disinfectant (see Table 4). Of the three tested bacteria, *S. aureus* was seen to be most susceptible to the effects of both the benzylated boronium ion and BacDown QAC. However, *P. aeruginosa* exhibited the largest difference between the effects of the benzylated boronium ion and BacDown QAC. The 8X greater effectiveness of modified boronium salt vs. BacDown QAC, as demonstrated by MIC result, is a noteworthy finding since *P. aeruginosa* was the most antibiotic resistant bacterium tested.

Corresponding MBC results also demonstrates substantial bactericidal activity of the benzylated boronium ion when compared to the BacDown QAC. *E. coli* demonstrated a similar difference in inhibition by either benzylated boronium ion or BacDown QAC as did *S. aureus*. Although *E. coli* required a higher concentration of either agent to achieve this same effect.

The apparent hemolysis seen on the SBA plates used for MBC determinations of the benzylated boronium ion is noteworthy. It demonstrates that this ionic compound and perhaps the base boronium ion are capable of disrupting plasma membranes of intact red blood cells (RBCs) suspended in agar medium. The reason for this disruption is unknown but may be at least partially related to the ionic compound's amphiphilic character. It may have simply inserted itself in between the adjacent phospholipids of these nonviable cell membranes. If true, it did so in sufficient numbers great enough to result in the noted hemolysis. What is equally unknown is how, or if, this same boronium compound affects the activity of living bacteria cell membranes.

It is suspected that the same amphiphilic property that allowed disruption of RBC membranes also allows the ionic compound to interact with viable bacterial cell plasma membranes. The mechanism of this interaction is unknown. What is known is that the base boronium ion was unable to kill the tested bacteria while the benzylated form demonstrated great capability to do so. This result suggests that living bacteria, unlike nonviable RBCs, are able to repair any membrane disruption caused by the boronium compound. It also suggests that all 3 tested bacteria were susceptible to the attached benzyl group rather than the presence of the base ionic compound.

Table 4
Effectiveness of benzylated boronium salt versus BacDown detergent against either *S. aureus*, *P. aeruginosa* or *E. coli* bacteria.

Condition	*S. aureus* MIC (μg/mL)	*P. aeruginosa* MIC (μg/mL)	*E. coli* MIC (μg/mL)
BacDown QAC disinfectant	80	1410	170
Boronium w/ benzyl group	20	170	40
BBG effectiveness vs. BacDown	4X	8X	4X

BBG = Boronium w/ benzyl group.

It is suggested that the benzylated boronium ion with attached 16-carbon alkyl chain was able to further access the intracellular cytosolic compartment. This process may have involved the use of a flippase enzyme, which have been demonstrated in prokaryote cells.[18] Phospholipid flippases transport 16–18 carbon fatty acid chain through the membrane hydrophobic region. They are used by polar phospholipids to enter cell cytoplasm.[19]

It is entirely possible that living bacterial cells are equipped to deal with the presence of the base boronium ion by either degrading it or removing it from the cell by some mechanism (e.g., efflux). This does not appear to be the case for the benzylated boronium ion. Here, an accumulation of this molecule inside the cell may have severely disturbed cellular metabolic pathways leading to cell death. This concept is purely speculative but would help explain the difference in antibacterial activity seen between the base boronium ion and the benzyl derived variant.

In conclusion, further evaluation of the benzylated boronium ion is required to determine the suitability for use as a surface disinfectant. These would include establishing its toxicity profile, biodegradable properties, and a time-to-kill study. The latter study determines the required application time of a disinfectant that is needed to eliminate 90% of the bacterial population.[20] Additional testing is also suggested against other microbes such as fungi to establish its full range of antimicrobial activity. Even so, preliminary results demonstrating the benzylated boronium ion's ability to kill all 3 bacteria at concentrations considerably lower than that of the BacDown QAC is very promising. The demonstrated ability of the benzylated boronium ion to disrupt nonviable red blood cell membranes likewise suggests a potential usefulness as an alternative disinfectant to anionic SLS or cationic QAC in eliminating enveloped viruses such as COVID-19. The considerable solubilizing activity of the boronium ion on these cell membranes supports this type of investigation.

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Declaration of Competing Interest

The authors declare that they have no known competing financial

Table 3
Comparison of antibacterial efficacy of tested compounds against either *S. aureus* (10×10^5 CFU/mL), *P. aeruginosa* (7.0×10^5 CFU/mL) or *E. coli* (3.5×10^5 CFU/mL).

Condition	*S. aureus*		*P. aeruginosa*		*E. coli*	
	MIC (μg/mL)	MBC (μg/mL)	MIC (μg/mL)	MBC (μg/mL)	MIC (μg/mL)	MBC (μg/mL)
Pos. control (BacDown)	80	80	1,410	1,410	170	350
Neg. control (alkyl amine)	>22,500	N/A	>22,500	N/A	>22,500	N/A
Boronium w/ benzyl group	20	40	170	170	40	40
Boronium w/o benzyl group	>22,500	N/A	>22,500	N/A	>22,500	N/A

interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bmcl.2021.127808.

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