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A Short Review on Quaternary Ammonium Compounds (QACs): From Antibacterial Action to Next-Generation Design

Doris Crnčević, Renata Odžak, Matilda Šprung*

University of Split, Faculty of Science, Department of Chemistry, R. Boškovića 33, Split, Croatia

* Corresponding author's e-mail address: msprung@pmfst.hr

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Abstract: Quaternary ammonium compounds (QACs) are cationic surfactants used across various industries due to their physicochemical properties and biological activity. The most prominent characteristic of QACs is their profound antibacterial potential attributed to amphiphilic positively charged backbone which facilitates a strong membranolytic mode of action. However, concerns regarding bacterial resistance and environmental persistence have emerged due to their extensive use. Resistance mechanisms, including efflux pump activation and membrane modifications, threaten their long-term efficacy, while limited biodegradability leads to their accumulation in environmental settings. To mitigate these challenges, research is increasingly focused on developing next-generation QACs with enhanced biodegradability and lower toxicity. Structural modifications, such as the addition of the hydrolyzable functional groups and natural product-inspired derivatives, aim to balance antimicrobial efficacy with environmental sustainability. This review examines the structural diversity, mechanisms of action, and bacterial resistance development to QACs, alongside their ecological impact. Additionally, it highlights advances in sustainable QACs design, providing insight into future strategies for safer and more effective antimicrobial agents.

Keywords: quaternary ammonium compounds (QACs), antibacterial activity, mode of action, environmental concerns, bacterial resistance, next-generation QACs.

INTRODUCTION

QUATERNARY ammonium compounds (QACs), commonly referred to as "quats", comprise a diverse class of cationic surfactants extensively employed in household, agricultural, food and pharmaceutical industry.[1–3] Structurally, QACs consist of a permanently charged quaternary nitrogen atom most commonly substituted with hydrophobic alkyl or aryl groups, facilitating interactions with bacterial membranes. Since their early discovery, QACs have undergone continuous structural modifications to enhance their antibacterial properties. Key factors influencing their efficacy include the length and composition of alkyl chains, hydrophobicity, and molecular charge distribution, with bis- and poly-QACs containing two or more positively charged nitrogen atoms exhibiting superior antibacterial potential.[4] While initially considered solely as membrane-targeting agents, recent studies suggest that QACs may exert additional intracellular effects, influencing metabolic pathways and gene regulation.[5–7]

Despite their potent antibacterial properties, the drawback of commercial QACs is their persistency, causing negative impacts towards environment and human health.[8] Consequence of such property was particularly emphasized upon the widespread overuse of QAC-based disinfectants and antiseptics during the SARS-CoV-2 pandemic outbreak.[9–11] Extensive use of QAC-based products has led to the environmental accumulation of commercially available QACs (Figure 1), where sub-lethal concentrations promote intrinsic bacterial resistance mechanisms, ultimately reducing the efficacy of these compounds. In response, research efforts have shifted toward developing "soft" QACs designed for controlled degradation while retaining antimicrobial potency.[12–15]

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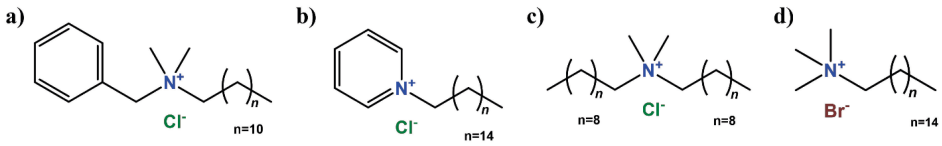

Figure 1. Chemical structures of most common commercially available quaternary ammonium compounds, QACs: (a) benzyldimethyldodecylammonium chloride (BAC), (b) cetylpyridinium chloride (CPC), (c) didecyldimethylammonium chloride (DDAC), and (d) cetyltrimethylammonium bromide (CTAB).

This review provides perspective on the structural attributes of QACs enabling their strong antibacterial activity, most commonly through membranolytic mode of action. Furthermore, it describes the challenges associated with bacterial resistance and environmental persistence, highlighting recent advances in next-generation QACs development. By addressing these concerns, future research could pave the way for the development of safer and more effective QAC derivatives with potentially targeted therapeutic effects.

History, Structural Features and Application of Quaternary Ammonium Compounds

Quaternary ammonium compounds (QACs) are a class of amphiphilic cationic surfactants used across a wide range of industries, mostly due to their potent antibacterial properties. Although the antibacterial activity of QACs was first reported in early 1916 it was not until the 1930s that their potential was fully recognized and further investigated.[21] Specifically, German bacteriologist Gerhard Domagk introduced benzyldimethyldodecylammonium chloride (BAC), demonstrating that the presence of a long aliphatic chain significantly enhances antimicrobial efficacy.[22] By the late 1940s, commercial derivatives of BAC, marketed under the name "*Zephirol*" became used in various hospital settings across the United States of America reinforcing its significance in infection control.[23,24] The success of BAC paved the way for the introduction of cetylpyridinium chloride (CPC) in 1939, a structurally similar QAC primarily used in oral healthcare products, particularly due to its targeted effect against *Streptococcus mutans*.[25,26]

Their chemical structure consists of a quaternized nitrogen atom permanently carrying a positive charge, typically paired with halide counterions. The synthesis of QACs follows an S_N2 nucleophilic substitution mechanism, in which a tertiary amine reacts with an alkyl or aryl halide, resulting in the formation of a stable quaternary ammonium salt. Based on the number of quaternized nitrogen atoms in their structure, QACs can be classified into mono-, bis-, and poly-QACs, with each category displaying distinct physicochemical and biological properties.

The correlation between QAC structure and antibacterial potency has been extensively studied. Research has shown that increasing the hydrophobicity of QACs enhances their ability to disrupt bacterial membranes.[27–29] One of the most notable example of this principle is didecyldimethylammonium chloride (DDAC), a QAC featuring two decyl chains attached to the quaternary nitrogen atom. The dual-chain structure resulting in an increased hydrophobicity enhances its interaction with bacterial membranes, leading to superior antimicrobial efficacy. As a result, DDAC has become a key ingredient in modern disinfectants, often surpassing BAC in effectiveness.[30,31] Accordingly, optimal chain lengths providing the greatest antibacterial activity against planktonic bacterial populations were found to be from ten to fourteen carbon atoms long.[32] On the other hand, for more complexed sessile biofilm architecture, additional hydrophobicity increase is needed, specifically from sixteen to eighteen carbon atoms.[33,34]

Due to their structure ensuring the physicochemical properties of cationic surfactants, QACs are often used as components of detergents and fabric softeners.[2,8,16] Their positively charged backbone also enables strong adsorption to negatively charged surfaces such as soil particles, which further extends their application, specifically in products such as herbicides and/or pesticides.[1,17,18] Considering their strong antibacterial potential, the most important application of this class of compounds is the household and pharmaceutical industry, therefore QACs are leading active ingredients of commercial disinfectants, antiseptics and hygiene products.[19,20]

Mechanisms of Antibacterial Action: Membrane Disruption and Beyond

The observed correlation between increased hydrophobicity and enhanced antibacterial activity led to the hypothesis that QACs primarily target bacterial membranes. This hypothesis was further supported by multiple studies showing that QACs exhibit greater activity against Gram-positive bacteria.[35–38] Specifically, Gram-negative bacteria possess an additional outer membrane as a protective barrier, limiting the membranolytic action of QACs.[39] Additionally, the higher enrichment of cell membrane with lipid content acts as another obstacle, with cephalin being the predominant lipid that binds cationic compounds and prevents their penetration through the membrane.[40,41] On

the other hand, Gram-positive bacteria lack an outer membrane but have a thick peptidoglycan layer that provides mechanical stability.[42] Furthermore, negatively charged teichoic acids embedded into the peptidoglycan matrix play a key role in membranolytic mode of action, providing the initial electrostatic interaction with the positively charged QAC backbone.[43–45]

Concept of QACs as membrane-disrupting agents was first proposed by Salton in 1968.[46] He described the disruption and disorganization of bacterial membrane as a stepwise mechanism – firstly, strong electrostatic interaction results in adsorption of QAC onto the membrane surface. Penetration of compound through the lipid bilayer causes initial membrane disorganization and eventually leads to the leakage of cytoplasmic contents. Ultimately, this disruption may trigger the activation of autolytic enzymes and cell lysis. Taking a step further, Salton also reported experimental evidence of the cellular contents released upon the treatment with cetyltrimethylammonium bromide, CTAB.[47] Furthermore, as a result of the membrane-targeting approach, substantial experimental data imply membrane depolarization due to the accumulation of net-positive charge at membrane surface upon treatment with QACs.[48–53] Molecular dynamics (MD) simulations also served as promising tool for correlation between structural features of QACs and membranolytic potency. Alkhalifa et al. utilized MD simulations to visualize proposed sequence of membrane integration for both mono- and poly- QACs.[45] On the other hand, Šprung's research group found that environmental friendly, "soft" QACs exhibit limited membrane penetration due to the predominantly irregular, "hook-like" conformations. Furthermore, these conformations primarily reside within a single layer in a realistic *Staphylococcus aureus* membrane model, suggesting the need for structural optimization to develop more potent derivatives.[54]

Although membrane disruption remains a well-established mechanism of QACs, their complete mode of action is still not fully described. Recent findings suggest that QACs may also interfere with intracellular targets, including inhibition of protein synthesis, interactions with DNA, and disruption of metabolic pathways.[7,54–56] These insights highlight the necessity of further research into the structure-activity relationships of QACs, which could pave the way for the design of new antimicrobial agents with enhanced efficacy and reduced resistance potential.

Challenges Associated with Environmental Accumulation of Quaternary Ammonium Compounds

TRIGGERS AND MECHANISMS OF BACTERIAL RESISTANCE TO QUATERNARY AMMONIUM COMPOUNDS

Specific structure of QACs in terms of their amphiphilic nature provides for their wide range of applications as common surfactants in both household and hygiene products, or as biocides in agricultural and food industry.[57] The usage of QAC-based products especially increased during the global outbreak of pandemic caused by the SARS-CoV-2 virus, implicating the necessity for exploration of environmental saturation with this class of compounds and further challenges associated with it.[58] Therefore, substantial literature data point out the presence of commercially available QAC analogues in wastewater effluents, surface waters and sediments, which is concerning given their persistent chemical stability.[57,59]

Inherent structural stability of commercial analogues which provides their bio and environmental accumulation, implicates the exposure of environmental bacterial strains to sub-inhibitory concentrations of those compounds. The subsequent adaptation of bacteria therefore triggers the activation of intrinsic resistance mechanisms, diminishing the effectiveness of commercial QACs. Bacterial resistance to QACs is primarily attributed to specific plasmid-borne *qac* genes, which can be horizontally transferred between bacteria, often alongside with antibiotic resistance genes.[38] Using DNA-intercalating dye ethidium bromide as a representative QAC, in 1969 Johnson and Dyke were the first to identify the location of genes promoting bacterial resistance to this class of compounds.[60] Until today, various *qac* genes have been described depending on the examined species (Table 1).[61] The greatest prevalence was found in Gram-positive bacteria, with high homology *qacA/qacB* and *qacC/qacD* as predominant across staphylococci species but was later also found in *Enterococcus faecalis*.[61–65] The *qacE* gene is most commonly found in Gram-negative bacteria, dominantly *Enterobacteriaceae*.[61,66,67]

Expression products of described genes are specific membrane proteins, known as efflux pumps, that mediate in bacterial resistance by expelling the compounds recognized as toxic across the cell membrane utilizing the energy of ATP hydrolysis.[61,68,69] Since *qacA* was identified as the predominant gene found across staphylococci species, including the methicillin resistant isolates, growing number of publications emerged describing the role of this specific gene and its expression product (Figure 2).[38]

Table 1. Distribution of *qac* genes found across particular bacterial species.

Gene	Bacterial species
qacA/qacB	staphylococci, enterococci
qacC/qacD	staphylococci
qacZ	enterococci
qacE	enterobacteriaceae, pseudomonadaceae
qacH	enterobacteriaceae

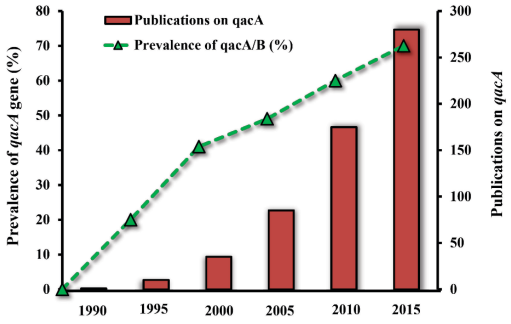

Figure 2. Graphical representation comparing the prevalence of *qacA* gene found across methicillin resistant *Staphylococcus aureus* isolates (primary axis, dashed green line) and the growing number of publications including the resistance mechanisms mediated by the transcription of *qacA* gene (secondary axis, red bars) from 1990 to 2015.[38]

Therefore, the most studied protein that mediates the bacterial resistance development to QACs is the 14-transmembrane domain QacA efflux pump. As a member of the major facilitator superfamily (MFS), QacA efflux pump mediates resistance for wide range of structurally diverse cationic, lipophilic compounds.[70–72] Its expression is under control of transcription repressor QacR composed of 188 amino acid residues.[73] In its native state, QacR is bound to inverted-repeat 1 (IR1) operator site sequence of DNA as pair of dimeric proteins, preventing the transcription of QacA.[74] Since active site of QacR is flexible enough to accommodate structurally diverse ligands, it is known as multidrug binding protein. Once the favorable ligand is bound to its active site, QacR dissociates from the operating sequence initiating the transcription and ultimately the expression of QacA efflux pump. While the exact mechanism of ligand binding is not yet fully understood, it is known that the active site of QacR contains four glutamic acid residues alongside several aromatic and polar amino acids, which contribute to its ability to recognize structurally diverse ligands.[75] Therefore, the negatively charged glutamic acid residues electrostatically interact with cationic compounds, facilitating the binding of QACs. Structural studies by Schumacher et al. have revealed six crystallized forms of QacR, each complexed with different QAC representatives, highlighting the flexibility extent of its binding pocket.[74–76] Notably, despite the structural similarity of various ligands, the binding site of QacR is capable of accommodating both mono- and bis-QACs, underscoring its role in multi-drug recognition and resistance.

Despite resistance to QACs primarily implies the expression of Qac efflux pumps, emerging evidence highlights cell membrane modifications as an alternative mechanism. Adaptations in fatty acid and protein composition have been reported in *Pseudomonas aeruginosa* and *Listeria monocytogenes* following exposure to commercial QAC analogues.[77–79] Additionally, resistance can involve changes in surface charge, specifically *Pseudomonas fluorescens* reduces its negative membrane charge to diminish electrostatic interactions with cationic agents, thereby lowering their membranolytic effect.[80]

TOXICITY RISKS OF COMMON QUATERNARY AMMONIUM COMPOUNDS

Other than promoting bacterial resistance mechanisms, another concern is the potential toxicity of QACs against organisms in aquatic ecosystems. This is primarily attributed to the inefficient QACs removal mediated by wastewater treatment plants (WWTPs).[59,81,82] Given the high stability exemplified by nine months half-life of benzalkonium chloride (BAC), potential hazards towards aquatic organisms have raised concerns, especially upon the global pandemic implicating higher use of QAC-based products.[80,83] While QACs retain biocidal properties in aquatic settings, their acute toxicity to marine organisms appears limited, likely due to strong surface adsorption.[84–86] However, species-specific variations in toxicity have been reported, particularly as QAC concentrations continue to rise. Studies show susceptibility of green algae to QACs, with toxicity increasing in correlation with alkyl chain length.[87–89] The toxic effects of QACs also extend to higher aquatic organisms, particularly fish, although toxicity levels vary between species.[8,90,91]

Beyond environmental risks, QACs pose potential health hazards to humans, especially through chronic exposure. While acute toxicity is uncommon, prolonged contact with QAC-based household and hygiene products has been linked to respiratory issues, such as asthma, particularly among healthcare workers.[92–95] Accordingly, concerns over long-term exposure intensified following the SARS-CoV-2 pandemic, with studies detecting QAC residues in human blood and breast milk.[96,97] Nevertheless, severity of chronic exposure was highlighted through the study of Kirkpatrick et al. suggesting that prolonged exposure to common QACs, such as alkyldimethylbenzylammonium chloride (ADBAC) and didecyldimethylammonium chloride (DDAC), may impair reproductive health, as demonstrated in both *in vitro* and *in vivo* models.[98]

To mitigate their environmental and health impact, minimization of QAC-related risks, through improvement of commercial formulations and development of safer, biodegradable alternatives, is an essential step.

Next-Generation Quaternary Ammonium Compounds: Balancing Efficacy and Biodegradability

The main synthetic objective of next-generation QACs is to retain potent antibacterial activity while enhancing

biodegradability and reducing the likelihood of resistance development.

One common approach in this direction involves modification of QAC scaffolds available on the market to potentially circumvent intrinsic bacterial resistance mechanisms. For this purpose, the backbone of two most common QACs, benzalkonium chloride (BAC) and cetylpyridinium chloride (CPC) were used as starting points.[99–102] Structural modifications, such as incorporation of pyridine moieties or introduction of multicationic centers, have yielded derivatives with improved antibacterial potency, including enhanced efficacy against methicillin-resistant *Staphylococcus aureus* (MRSA). Additionally, rational design strategies based on structure-activity relationships have facilitated the development of QACs with optimized alkyl chain lengths and functional groups to balance efficacy, selectivity, and environmental safety.

Beyond synthetic modifications of traditional commercial analogues, natural product-inspired QACs have emerged as promising alternatives. In this manner, multiple research groups have explored various precursors such as alkaloids quinine and nicotine, piperazine, and even bicyclic cores of 1,4-diazabicyclo[2.2.2]octane (DABCO), 1-azabicyclo[2.2.2]octane (quinuclidine) to synthesize new QAC derivatives (Figure 3).[37,103–105] These naturally inspired QACs have demonstrated significantly improved antimicrobial activity compared to their non-quaternized precursor structures, with minimum inhibitory concentrations (MICs) often in the low micromolar range against both Gram-positive and Gram-negative pathogens. Notably, quinuclidine- and DABCO-based QACs have shown potent activity against methicillin-resistant *Staphylococcus aureus* (MRSA), in some cases surpassing the efficacy of commercial QACs.[37,105] In addition to their antimicrobial potency, many of these derivatives displayed reduced cytotoxicity toward mammalian cells compared to traditional QACs, suggesting a more favorable safety profile. Given the lower cytotoxicity and economic aspect of synthetic procedure, such examples highlight the potential of natural products as precursors in next-generation QAC development. Taken together, such findings emphasize the potential of natural product guided synthesis in the development of next-generation QACs. However, a more detailed investigation of structure activity relationships is essential to potentially elucidate the structural features driving antibacterial potency and ensure further rational design.

Aiming to reduce environmental accumulation, another promising strategy involves the synthesis of environmental-friendly "soft" QACs, designed with potential to undergo controlled decomposition into non-toxic products unable to trigger resistance mechanisms.[15,45,105,106] This is achieved through the introduction of hydrolyzable functionalities such as ester or amide groups into the QAC backbone which could potentially allow for degradation under physiological or environmental conditions (Figure 4). Although the incorporation of such functionalities suggests environmental sustainability, differences in antibacterial potential of obtained compounds were observed, pointing out the necessity of structure-activity relationship investigation.

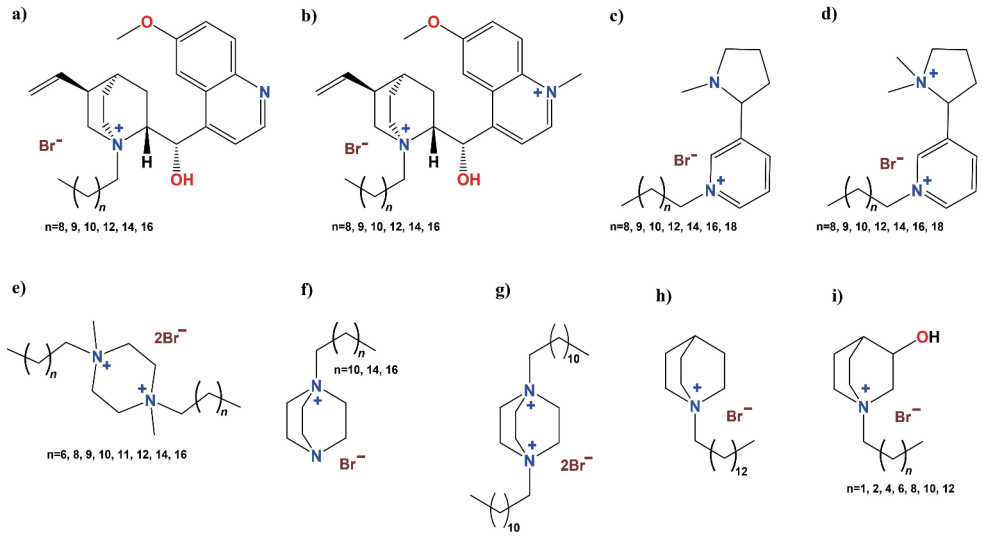

Figure 3. Chemical structures of quaternary ammonium compounds (QACs) derived from naturally occurring precursors: (a) and (b) QACs derived from quinine, (c) and (d) QACs derived from nicotine, (e) piperazine-based QACs, (f) and (g) QACs derived from 1,4-diazabicyclo[2.2. 2]octane, DABCO, (h) QACs derived from 1-azabicyclo[2.2.2]octane, quinuclidine, and (i) QACs derived from 1-azabicyclo[2.2.2]octan-3-ol, quinuclidine-3-ol.

Specifically, Alkhalifa et al. investigated the membranolytic properties of alkyl-based QACs in contrast to "soft" ester-containing variants.[45] Both experimental and computational analyses consistently demonstrated that alkyl derivatives displayed superior antibacterial effects. The authors attributed the reduced efficacy of "soft" QACs to the chemical instability of incorporated ester functional group, leading to the uncontrolled degradation and, consequently, diminished antimicrobial potency. Further exploration of hydrolysis-prone functional groups led to the identification of the amide bond as a more sustainable alternative. The spontaneous degradation behavior was inspected by Allen et al., whose findings indicated the stability of amide- analogues for more than 16 hours across a broad pH conditions.[15] Supporting this, Kontos et al. identified amide-functionalized QACs derived from piperazine and 2,2-diazabicyclo[2.2.2]octane (DABCO) as highly effective antibacterial agents, as evidenced by low micromolar minimum inhibitory concentrations (MICs) often exceeding commercial QACs.[105] At the same time, amide bond containing compounds are potentially favorable protease substrates which implies the potential of such compounds for controlled decomposition into non-toxic products.[106]

On the other hand, it was further shown that the introduction of polar functional group affects antibacterial potential, possibly by hindering the initial electrostatic interaction with bacterial membrane.[54,107] Understanding how the increased polarity correlates with antibacterial efficacy and mode of action is particularly important, as most studies on QAC structure-activity relationships have been focused on the rigidity of precursor scaffolds rather than the impact of backbone functionalization.[105,108] Future research should focus on further exploration of natural precursors and optimization of the hydrophilic: hydrophobic ratio to maximize antimicrobial efficacy while ensuring environmental sustainability of the compounds.

In addition to natural product-inspired and "soft" analogues, the design and synthesis of hybrid QACs have emerged as a promising approach to enhance the pharmacological and physicochemical properties of traditional analogues. These hybrid compounds are typically created by linking QAC moieties to established pharmacophores, aiming to improve membrane permeability, increase target selectivity, and reduce the likelihood of resistance development. Recent studies have demonstrated that hybrid QACs can exert both antibacterial and anti-biofilm effects while addressing the limitations in absorption, distribution, metabolism, and excretion (ADME) commonly associated with permanently charged compounds.[109,110]

By integrating synthetic innovations, natural product scaffolds, and environmentally sustainable design, next-generation QACs hold the potential to address the challenges of antimicrobial resistance and environmental impact while maintaining their essential disinfectant properties.

CONCLUSIONS

For over a century, quaternary ammonium compounds (QACs) remained indispensable antimicrobial agents widely used in various industries. However, their persistent environmental accumulation and the rise of bacterial resistance necessitate innovative solutions to ensure their sustainable use. Structural modifications, including the

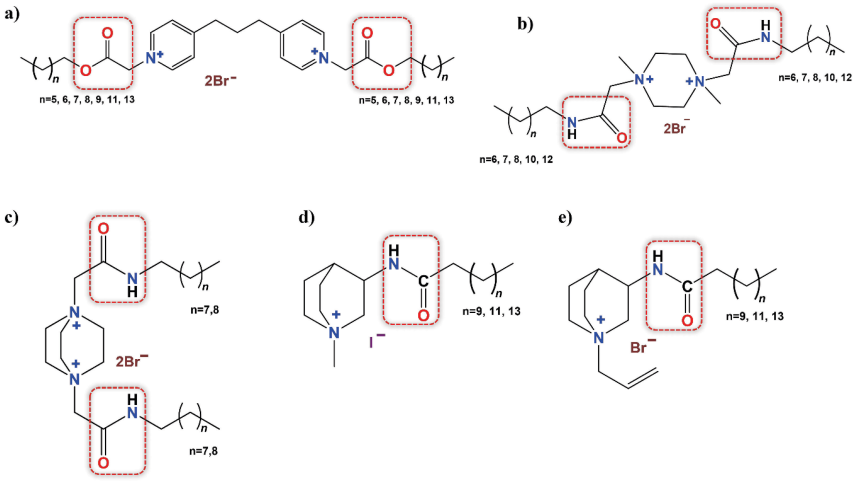

Figure 4. Examples of "soft" quaternary ammonium compounds (QACs): (a) ester- containing bispyridinium derivatives, (b), amide- containing piperazine derivatives, (c), amide-containing 1,4-diazabicyclo[2.2.2]octane, DABCO, derivatives (d) and (e) "soft" analogues of 3-amidoquinuclidine. Hydrolyzable ester- and amide- functional groups are represented in red dashed rectangular shape.

incorporation of hydrolysable functional groups and the development of multicationic and natural product-inspired derivatives, offer promising strategies for enhancing QAC efficacy while reducing ecological and health risks.

The synthesis of next-generation QACs, particularly those prone to controlled degradation to non-toxic products through introduction of hydrolyzable functionalities, represents a significant advancement in mitigating environmental persistence. Additionally, the exploration of alternative backbone precursor structures through natural product guided synthesis provides a promising avenue for expanding the antimicrobial potency of naturally occurring compounds.

To ensure these innovations lead to practical, long-term solutions, future research should focus on fine-tuning the balance between efficacy and safety. This includes refining structure-activity relationships, mapping degradation pathways, and assessing the broader ecological effects of QACs. With continued innovation and a multidisciplinary approach, next-generation QACs can be optimized to remain effectiveness against resistant bacteria while reducing their impact on the environment paving the way for a more sustainable future in antimicrobial development.

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