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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

New quaternary ammonium pyridoxine derivatives: synthesis and antibacterial activity

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Abstract A diverse library of 34 new quaternary mono-ammonium and bis-ammonium pyridoxine derivatives was synthesized, and their antibacterial activity against several clinically relevant bacterial strains was evaluated in vitro. Several mono-ammonium compounds demonstrated high antibacterial activity against methicillin-resistant *Staphylococcus* strains with minimum inhibitory concentrations in the range of 0.5–8 μg/mL, which exceeded activity of miramistin and was comparable to that of benzalkonium chloride. SOS-chromotest in *Salmonella typhimurium* showed the lack of DNA-damage activity for all active compounds. A clear correlation has been observed between the lipophilicity of the obtained compounds and their activity against the studied Gram-positive bacterial strains. Cytotoxicity studies on HEK-293 cells demonstrated that some of the active compounds were less toxic than the reference drugs. Antibacterial activity studies in the presence of $CaCl_2$ suggested that the cell wall damage associated with the removal of Ca^{2+} ions from the bacterial membrane is one of the possible mechanisms of antibacterial activity. The obtained results make the described active compounds a promising starting point for the development of new antibacterial therapies.

Keywords Quaternary ammonium salts · Pyridoxine · Antibacterial activity · Cytotoxicity · Genotoxicity · Cell wall damaging agents

Introduction

Growing antibiotic resistance has become a major health problem in recent decades and has encouraged many researchers to search for novel antibacterial drugs. In particular, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci and multidrug-resistant *Pseudomonas aeruginosa* are associated with increased rates of illness and death (Nordmann et al. 2007).

Since the 1930s, quaternary ammonium compounds (QACs) are widely used for the control of bacterial growth in clinical and industrial environments. Broad-spectrum antimicrobial and antifungal activity (Krátký and Vinšová 2013; Oblak et al. 2013; Massi et al. 2003; Ohkura et al. 2003) and surfactant properties have made QACs such as benzalkonium chloride (Domagk 1935), fluomizin (Tischer et al. 2012), miramistin and cetylpyridinium chloride (Fromm-Dornieden et al. 2015) the favored hygienic adjuncts in disinfectant cleansing formulations, and they have also been increasingly deployed in therapy of patients with local pyoinflammatory processes.

According to literature data (Tischer et al. 2012), QACs generally act by disrupting the cytoplasmic and outer membrane lipid bilayers through association of the positively charged quaternary nitrogen with the anionic head groups of acidic phospholipids and interaction of the lipophilic tail with the hydrophobic membrane core. As a result, QACs form mixed-micelle aggregates with hydrophobic membrane components that solubilize membrane and lyse the cells. Bacterial cell lethality occurs through generalized and progressive

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