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Synthesis and antibacterial activity of novel phosphonium salts on the basis of pyridoxine

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ABSTRACT

A series of 13 phosphonium salts on the basis of pyridoxine derivatives were synthesized and their antibacterial activity against clinically relevant strains was tested in vitro. All compounds were almost inactive against gram-negative bacteria and exhibited structure-dependent activity against gram-positive bacteria. A crucial role of ketal protection group in phosphonium salts for their antibacterial properties was demonstrated. Among synthesized compounds 5,6-bis[triphenylphosphonio(methyl)]-2,2,8-trimethyl-4*H*-[1,3]dioxino[4,5-*c*]pyridine dichloride (compound **20**) was found to be the most effective towards *Staphylococcus aureus* and *Staphylococcus epidermidis* strains (MIC 5 μg/ml). The mechanism of antibacterial activity of this compound probably involves cell penetration and interaction with genomic and plasmid DNA.

1. Introduction

Organophosphorus compounds have been extensively utilized in organic synthesis. Among them quaternary phosphonium salts are of special interest due to their use in material sciences[1–10] and medicinal chemistry.[11–17] In particular, these compounds have been applied as intracellular antioxidants,[11–13] anticholinesterase inhibitors,[14] tumor imaging agents[15,16] and chemotherapeutic agents.[17]

Antimicrobial properties of some quaternary phosphonium salts have been reported. Phosphonium salts grafted on styrene–divinylbenzene copolymers were shown to exhibit antibacterial activity against *Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*.[18] Triphenylphosphonium-modified PPO (polyphenylene oxide) polymer also found to have antimicrobial activity on *Staphylococcus epidermidis* and *Escherichia coli*.[19] Taladriz et al., recently demonstrated antitrypanosomal activity of benzyltriphenylphosphonium salts against *Trypanosoma brucei*.[20] Benzophenone-derived bisphosphonium salts exhibited lethal activity towards human protozoan parasite *Leishmania*.[21] Kanazawa et al.,[22] synthesized di- and trimethyl-substituted phosphonium salts with long alkyl chaines (C_{10}–C_{18}) with bacteriostatic action against 11 widespread pathogens including methicillin-resistant *S. aureus* (MRSA). Organ-clay minerals intercalated by tetradecyl tributyl phosphonium bromide (TDTB)[23] as well as tetradecyl triphenyl phosphonium bromide (TTP) functionalized few-layered graphite (FG)[24] exerted long-term antimicrobial activity against *E. coli* and *S. aureus*.

Chemical modification of biologically active compounds of natural origin is one of the most efficient approaches in drug development. Among them, vitamin B_6 (pyridoxine) is of particular interest as a starting compound as it participates in over a hundred enzymatic reactions involved in biosynthesis, metabolism, and regulatory functions in living organisms.[25–29]

In our study, we describe the synthesis of novel derivatives of quaternary phosphonium salts on the basis of pyridoxine and its 6-hydroxymethyl derivatives. We reveal the effect of quantity and location of phosphonium fragments in pyridoxine molecule on the antibacterial activity of synthesized substances as well as the probable mechanism of action.

2. Results and discussion

2.1. Chemistry

The synthesis of the target compounds was based on the nucleophilic substitution of chlorine derivatives of pyridoxine with triphenylphosphine resulting in the corresponding phosphonium salts (Schemes 1–7).

Various known synthetic approaches were used for the synthesis of different chlorine derivatives of pyridoxine, such as: introduction of ketal or acetate protection to the hydroxyl groups for selective functionalization of pyridoxine and its derivatives, the

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