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Research paper

Design, synthesis, antibacterial activity and toxicity of novel quaternary ammonium compounds based on pyridoxine and fatty acids

Sergey V. Sapozhnikov [1], Alina E. Sabirova [1], Nikita V. Shtyrlin [1], Anastasia Y. Druk, Mariya N. Agafonova, Milana N. Chirkova, Renata R. Kazakova, Denis Y. Grishaev, Tatyana V. Nikishova, Elena S. Krylova, Elena V. Nikitina, Airat R. Kayumov, Yurii G. Shtyrlin*

Kazan (Volga Region) Federal University, Kremlyovskaya St. 18, Kazan, 420008, Russian Federation

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ABSTRACT

A diverse series of 43 novel "soft antimicrobials" based on quaternary ammonium pyridoxine derivatives which include six-membered acetals and ketals of pyridoxine bound via cleavable linker moieties (amide, ester) with a fragment of fatty carboxylic acid was designed. Nine compounds exhibited *in vitro* promising antibacterial activity against Gram-positive and Gram-negative bacterial strains with MIC values comparable with reference antiseptics miramistin, benzalkonium chloride and chlorohexidine. On various clinical isolates, the lead compounds **6i** and **12a** exhibited antibacterial activity comparable with that of benzalkonium chloride while higher than that of miramistin. Moreover, **6i** and **12a** were able to kill bacteria embedded into the matrix of mono- and dual species biofilms. The treatment of bacterial cells by either **6i** and **12a** lead to fast depolarization of the membrane suggesting that the membrane is an apparent molecular target of compounds. **6i** and **12a** were non mutagenic neither in SOS-chromotest nor in Ames test and non-toxic *in vivo* at acute oral (LD_{50} > 2000 mg/kg) and cutaneous administration (LD_{50} > 2500 mg/kg) on mice. Taken together, our data allow suggesting described active compounds as promising starting point for the new antibacterial agents development.

1. Introduction

The bacterial resistance to antimicrobials is one of serious challenges of healthcare worldwide. The multicenter monitoring notices the continuous spread of bacterial strains resistant to many external factors, and pathogenic bacteria quickly become resistant to existing commercially available antibiotics and antiseptics [1,2]. A similar increase is observed for both nosocomial hospital infections arising due to the direct spread of bacteria from patient to patient and for community-acquired infections [3,4].

Since the 1930s, quaternary ammonium compounds (QACs) are widely used as antiseptics and disinfectants [5]. A number of QACs such as the benzalkonium chloride [5], dequalinium chloride [6], cetylpyridinium chloride [7] have been widely used for a variety of clinical purposes (e.g., preoperative disinfection of intact skin, application to mucous membranes, disinfection of noncritical surfaces etc.). According to literature [7], the general mechanism of the antibacterial activity of QACs is the damage of the cytoplasmic and outer membrane lipid bilayers via 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. Because of universal basic architecture of cellular membranes, these properties of QACs have disadvantage such as high toxicity [8]. Moreover, many classical representatives of these compounds has a long half-life in environment, increasing the frequency of bacterial resistance developing to QACs [9,10]. One of possible ways to solve this problem could be the strategy of soft drugs, i.e. substances that are readily degraded into nontoxic and biologically inactive products both *in vivo* and in the environment. The inclusion of a metabolically sensitive fragment into the structure of designed products allows predicting the main metabolic

* Corresponding author.
E-mail address: yurii.shtyrlin@kpfu.ru (Y.G. Shtyrlin).
[1] Authors contributed equally to this manuscript.

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