Bioorg. Med. Chem. 29 (2021) 115905

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Thiacalixarene based quaternary ammonium salts as promising antibacterial agents

P.L. Padnya [a], O.S. Terenteva [a], A.A. Akhmedov [a], A.G. Iksanova [b], N.V. Shtyrlin [b], E.V. Nikitina [b], E.S. Krylova [b], Yu. G. Shtyrlin [b], I.I. Stoikov [a,*]

[a] A.M. Butlerov Chemical Institute, Kazan Federal University, 420008 Kazan, Russian Federation
[b] Scientific and Educational Center of Pharmaceutics, Kazan Federal University, 420008 Kazan, Russian Federation

ARTICLE INFO

Keywords:
Quaternary ammonium salts
Thiacalixarene
Antibacterial activity
Gram-positive bacteria
Antibiotic resistance

ABSTRACT

The search for new antibacterial and antiseptic drugs is an urgent problem due to the resistance of microorganisms to existing drugs. In this work, for the first time, the design of antibacterial and bactericidal agents based on quaternary ammonium compounds on thiacalixarene macrocyclic platform was proposed and implemented. A series of tetrasubstituted quaternary ammonium salts with different nature and length of the substituent ($-N^+(CH_3)_2R$, R = CH_2Ph, C_nH_{2n+1}, n = 1, 4, 8, 10) based on *p-tert*-butylthiacalix[4]arene in *cone* and *1,3-alternate* conformations was obtained with excellent yields. The obtained compounds have a high antibacterial effect against Gram-positive (*S. aureus, S. epidermidis, B. subtilis*) bacteria comparable with commercial antiseptics chlorhexidine, miramistin and benzalkonium chloride. It was found that quaternary ammonium derivatives of thiacalix[4]arene in *1,3-alternate* conformation more effectively inhibit the growth of the tested bacterial strains in comparison with compounds in *cone* conformation. Cytotoxicity studies on human skin fibroblast (HSF) cells demonstrated that all compounds were less toxic compared to reference drugs. The different type of interaction of the studied compounds with model DPPC lipid membranes explains different antibacterial activity and cytotoxicity of compounds. The compounds in *cone* conformation are adsorbed on the DPPC vesicles membrane surface, while the incorporation of lipophilic alkyl fragments of macrocycles in *1,3-alternate* conformation into the membrane leads to "clumping" of DPPC vesicles. It was shown the saving of antibacterial activity of thiacalixarene derivatives in *1,3-alternate* conformation on Gram-positive clinical strains. The obtained results allow viewing the described thiacalixarene based quaternary ammonium compounds as promising molecules in the development of the new antibacterial agents.

1. Introduction

Infectious diseases take 3-4th place in the ranking of causes of death according to WHO.[1] Collectively, infectious diseases accounted for an estimated 4.3 million deaths in 2016. The use of antibiotics and antiseptics is a mandatory WHO recommendation for the comprehensive prevention and treatment of serious diseases such as Ebola, Avian influenza, Coronavirus, in the fight against the diseases spread.

Increasing resistance to existing drugs leads humanity to search for new, more effective drugs with a safety profile. The medical chemistry of macrocyclic compounds has been actively developing in recent years.[2] Due to their large size, structure and the possibility of simple modification by receptor fragments, macrocyclic compounds can interact with biological targets through spatially distributed interactions, thereby increasing both the efficiency and selectivity of binding. Over the past decades, macrocyclic compounds such as cyclodextrins,[3,4] cucurbiturils,[5] porphyrins,[6] macrocyclic peptides,[7] calixarenes,[8,9] pillararenes[10,11] have been used in drug discovery and design, as a part of biosensors, for bioimaging, targeted drug delivery and other biomedical applications.[12,13] The development of drugs based on macrocycles is possible due to their unique physicochemical properties, such as spatial preliminary organization, the presence of a hydrophobic cavity and hydrophilic substituents, low pharmacologically active concentrations and toxicity, antiallergenicity, etc.[14]

Calixarenes are one of the most studied classes of macrocyclic compounds. The use of calixarenes as drugs or targeted delivery systems is limited by their low water solubility.[15] The introduction of polar and/or charged fragments into the macrocycles structure increases their

* Corresponding author at: Kazan Federal University, A.M. Butlerov Chemistry Institute, 18 Kremlevskaya, 420008 Kazan, Russian Federation.
E-mail address: ivan.stoikov@mail.ru (I.I. Stoikov).

https://doi.org/10.1016/j.bmc.2020.115905
Received 2 November 2020; Received in revised form 26 November 2020; Accepted 26 November 2020
Available online 4 December 2020