New antimicrobial candidates - Quaternary ammonium compounds based on natural scaffold quinuclidine

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Quaternary Ammonium Compounds (QACs) are amphiphilic molecules of antimicrobial properties with applications in numerous industries. Recent studies show that environmental bacteria acquire resistance to QACs at an alarming pace, and that this resistance is mostly but not exclusively related to Qac efflux pump expression. Motivated by these findings, our research group has been mainly focused in developing new potent QACs derived from natural precursor(s). One such precursor that caught our attention is quinuclidine, a bicyclic part of alkaloids isolated from the bark of the Cinchona tree. In our two recent studies we have shown that quaternization of quinuclidine improves its bioactivity by several hundred folds (Previously published in: Odžak R et al. (2017), Open Chem. 15, 320-331 and Bazina L et al. (2019) Eur. J. Med. Chem. 163, 626-635). The most active identified candidate was QOH-C14. This compound, with the longest alkyl chain, exhibited the lowest MIC values across a selected panel of the bacteria, had good activity toward *Staphylococcus aureus* biofilms and had the lowest toxicity toward healthy human cell lines. Moreover, atomic force microscopy and flow cytometry indicated that QOH-C14 acts by disrupting the cell membrane provoking membrane disintegration and cell death. In addition, physicochemical characterization showed that derivatives with longer alkyl chains spontaneously form micelle and that their stability is also related to the number of carbon atoms in the chain (Previously published in: Bošković P et al. (2019) J. Surfact. Deterg. 23, 207-214). From these studies two main conclusions could be drown. First, quaternization of natural precursors could be a promising strategy in new QACs development. Second, alkyl chains are an important part of the structure whereby antimicrobial activity directly correlates with the number of carbon atoms in the chain.