Bis(benzosiloxaboroles) as a new class of potential antibiotics - a perspective solution to growing problem of antimicrobial resistance

Organoboron compounds, *i.e.* organic compounds containing at least one direct boron-carbon bond, are well recognizable mainly by their vast utility in modern organic synthesis and broadly understood material chemistry. In recent years they also became widely exploited in medicinal chemistry as attractive antimicrobial, anti-cancer or anti-inflammatory agents. Their great potential in this field is connected with the unique physicochemical properties of the boron atom, which may be responsible for specific interactions with biomolecules. Thanks to these properties, organoboron compounds can address a broad spectrum of biological targets, often using new, previously unknown mechanisms of action. The leading role in this field belongs to the boracyclic compounds, especially benzoxaboroles. Benzoxaboroles are organic compounds that consist of a benzene ring fused with a five-membered boracyclic ring featuring a B–O–C linkage. Thanks to intensive efforts made by scientists in the last two decades, two of these compounds – Tavaborole and Crisaborole – have already been successfully marketed as drugs for the treatment of onychomycosis and atopic dermatitis, respectively. Other benzoxaboroles, *e.g.*, targeted at treating severe gram-negative bacteria infections, are at various stages of clinical trials. A few years ago, we turned our attention to silicon congeners of benzoxaboroles – benzosiloxaboroles. They constitute an attractive alternative to the former compounds due to slightly different properties and synthesis. Our initial studies showed that some functionalized benzosiloxaboroles demonstrate promising antifungal and antibacterial activity, whereas other derivatives exhibit inhibitory activity towards enzymes responsible for drug resistance in bacteria.

Very recently, we have found that specific diboronic systems, such as biphenyl-based bis(benzosiloxaboroles), display strong antibacterial activity. These results indicate that the presence of two siloxaborole rings within the structure of one molecule enhances the antimicrobial potency, which can be explained by synergistic effects. Inspired by this discovery, we found it reasonable to check whether the type of the linkage of two benzosiloxaborole subunits may impact the activity. Thus, we designed a series of novel synthesizable bis(benzosiloxaboroles) with various functional groups as linkers. Principally, the project is aimed at the synthesis of these compounds, followed by basic structural and physicochemical characterization. Obtained derivatives will be subjected to antimicrobial activity studies on the extensive collection of bacteria and yeast strains, including multidrug-resistant clinical strains. Additionally, theoretical studies utilizing state-of-the-art bioinformatic methods will be undertaken in order to check the affinity of novel compounds towards putative molecular targets. Upon obtaining the first target compounds, both antimicrobial and molecular modelling studies will be conducted along with the synthetic part of the project. Regular evaluation of antimicrobial potential will allow to analyze the structure-activity relationship (SAR) and, consequently, to design and synthesize more potent derivatives.

We firmly believe that designed bis(benzosiloxaboroles) would become an attractive novel class of antimicrobials. At this point, it should be stressed that providing basic research targeted at developing new antibiotics is highly prioritised. According to WHO, antimicrobial resistance (AMR) is among the TOP10 contemporary threats to humanity. Hence, immediate multisectoral action involving both academia and industry is strongly desirable.