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The Impact of Efflux Pump Inhibitor on the Activity of Benzosiloxaboroles and Benzoxadiboroles against Gram-Negative Rods

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Abstract : 1,3-dihydro-1-hydroxy-2,1-benzoxaborole and its derivatives are a particularly interesting group of synthetic agents and were successfully employed in supramolecular chemistry medicine. The first important compounds, 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole and 5-chloro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole were identified as potent antifungal agents. In contrast, (S)-3-(aminomethyl)-7-(3-hydroxypropoxy)-1-hydroxy-1,3-dihydro-2,1-benzoxaborole hydrochloride is in the second phase of clinical trials as a drug for the treatment of Gram-negative bacterial infections of the Enterobacteriaceae family and Pseudomonas aeruginosa. Equally important and difficult task is to search for compounds active against Gram-negative bacilli, which have multi-drug-resistance efflux pumps actively removing many of the antibiotics from bacterial cells. We have examined whether halogen-substituted benzoxaborole-based derivatives and their analogues possess antibacterial activity and are substrates for multi-drug-resistance efflux pumps. The antibacterial activity of 1,3-dihydro-3-hydroxy-1,1-dimethyl-1,2,3-benzosiloxaborole and 10 halogen-substituted its derivatives, as well as 1,2-phenylenediboronic acid and 3 synthesised fluoro-substituted its analogs, were evaluated. The activity against the reference strains of Gram-positive (n=5) and Gram-negative bacteria (n=10) was screened by the disc-diffusion test (0.4 mg of tested compounds was applied onto paper disc). The minimal inhibitory concentration values and the minimal bactericidal concentration values were estimated according to The Clinical and Laboratory Standards Institute and The European Committee on Antimicrobial Susceptibility Testing recommendations. During the minimal inhibitory concentration values determination with or without phenylalanine-arginine beta-naphthylamide (50 mg/L) efflux pump inhibitor, the concentrations of tested compounds ranged 0.39-400 mg/L in the broth medium supplemented with 1 mM magnesium sulfate. Generally, the studied benzosiloxaboroles and benzoxadiboroles showed a higher activity against Gram-positive cocci than against Gram-negative rods. Moreover, benzosiloxaboroles have the higher activity than benzoxadiboroles compounds. In this study, we demonstrated that substitution (mono-, di- or tetra-) of 1,3-dihydro-3-hydroxy-1,1-dimethyl-1,2,3-benzosiloxaborole with halogen groups resulted in an increase in antimicrobial activity as compared to the parent substance. Interestingly, the 6,7-dichloro-substituted parent substance was found to be the most potent against Gram-positive cocci: Staphylococcus sp. (minimal inhibitory concentration 6.25 mg/L) and Enterococcus sp. (minimal inhibitory concentration 25 mg/L). On the other hand, mono- and dichloro-substituted compounds were the most actively removed by efflux pumps present in Gram-negative bacteria mainly from Enterobacteriaceae family. In the presence of efflux pump inhibitor the minimal inhibitory concentration values of chloro-substituted benzosiloxaboroles decreased from 400 mg/L to 3.12 mg/L. Of note, the highest increase in bacterial susceptibility to tested compounds in the presence of phenylalanine-arginine beta-naphthylamide was observed for 6-chloro-, 6,7-dichloro- and 6,7-difluoro-substituted benzosiloxaboroles. In the case of Escherichia coli, Enterobacter cloacae and P. aeruginosa strains at least a 32-fold decrease in the minimal inhibitory concentration values of these agents were observed. These data demonstrate structure-activity relationships of the tested derivatives and highlight the need for further search for benzoxaboroles and related compounds with significant antimicrobial properties. Moreover, the influence of phenylalanine-arginine beta-naphthylamide on the susceptibility of Gram-negative rods to studied benzosiloxaboroles indicate that some tested agents are substrates for efflux pumps in Gram-negative rods.

Keywords : antibacterial activity, benzosiloxaboroles, efflux pumps, phenylalanine-arginine beta-naphthylamide
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