ABSTRACT

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Doctoral Degree Program	Pharmaceutical Chemistry
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Title of Doctoral Thesis	Hybridization approach in the discovery of new antiinvasive drugs

The worldwide increasing development of drug-resistant infectious diseases together with the increasing number of patients diagnosed with various types of cancer constitute fundamental challenges in the field of medicinal chemistry and thus create the need for the continuous development of new effective molecules.

In the theoretical part, the presented dissertation deals with the hybridization of molecules as a tool in the discovery of new drugs, it categorizes hybrid compounds according to their composition into several groups and gives examples of successful hybrids, both registered and experimental ones. Furthermore, it focuses on organic boron compounds, more specifficaly boronic acids, defines their properties, and discusses the possibilities of their use in the field of pharmaceutical chemistry with the introduction of preclinically and clinically important molecules. The following practical part is a commentary on summarizing the chemical procedures, and biological and computational methods used in the experimental part of the work. Furthermore, the published works are commented on. They are in most cases based on the concept of hybrid compounds, and their antimycobacterial, antibacterial, and antiproliferative effects are presented, with special emphasis is placed on defining their structure-activity relationships. Part of the annotated publications then shows the possibilities of using the unique physicochemical properties of boron when designing new compounds. The most active compounds achieved MIC values = 2.6–21.59 μM against Mycobacterium tuberculosis H37Rv. Perspective candidates were tested on clinical isolates of resistant strains of Mycobacterium tuberculosis and in some cases in vivo on mouse models of tuberculosis. Interestingly, the prepared boronic acid derivatives showed higher inhibition of proliferation of the studied prostate cancer cell line (IC50 = 19.2–27.8 μM) than the bicalutamide standard and represent a potential innovation in the category of experimental non-steroidal antiandrogens due to their structure. The obtained results bring valuable insight into the category of anti-invasive drugs.