ABSTRACT

Urease is an enzyme found in many organisms and plays a key role in the global nitrogen cycle. Nevertheless, its uncontrolled activity is an undesirable phenomenon from the point of view of agriculture or health care. Many pathogenic bacteria, such as *Helicobacter pylori*, *Proteus mirabilis* and *Staphylococcus aureus*, use this protein as a virulence factor. Urease inhibitors weakening the virulence of microorganisms, used in combination with antibiotics, may help reduce resistance to available drugs. The aim of the doctoral thesis was to develop new classes of bacterial urease inhibitors containing groups capable of forming both covalent bonds and non-covalent interactions in the catalytic center. It is assumed that such compounds will work more effectively and with greater specificity.

The literature part of the dissertation summarizes basic information about the subject of research, focusing on the types of urease inhibitors, their mechanisms of action and synthesis methods. As part of my own research, several types of structures (55 individual chemical compounds) with a hybrid mode of action, combining functional elements with different mechanisms of inhibitory antiureolytic activity, were planned and synthesized. These were phosphonic or phosphine groups dedicated to coordinating nickel ions, as well as fragments of catechol or 1,2-benzisoselenazol-3(2*H*)-one, which are reactive towards thiols. This required planning individual synthetic paths leading to complex target molecules, additionally showing complementarity to the active center of the protein. The obtained organophosphate and/or organoselenium compounds were a subject to biological activity tests against purified urease from the bacteria *Sporosarcina pasteurii* and ureolysis demonstrated by *H. pylori* cells. Extremely effective inhibitors of the model enzyme were identified: catechol derivatives showed inhibition constants in the micromolar range, but 1,2-benzisoselenazol-3(2*H*)-one derivatives showed inhibition constants in the nanomolar range. Moreover, in each group, exceptionally active antiureolytic compounds were found in *in vitro* tests against pathogenic bacteria. Cytotoxicity tests against mammalian cells were performed for the most effective inhibitors, showing a negligible or low impact on their viability. As a part of the doctoral thesis, a number of derivatives with desirable properties were obtained in the context of possible use in combined antimicrobial therapies.

Marta Grabarek