Urease is an amidohydrolase involved in the degradation of urea to ammonia and carbamate, and then to carbon dioxide. The scientific developments on urease predestinate the enzyme to hold a special position among milestones of biochemistry. In 1926 it was the first ever enzyme crystallized and identified as a protein (Nobel Prize for James Sumner, 1946) and then demonstrated as nickel-dependent. Urease is also characteristic by an exceptional rate of hydrolysis enhancement (10^{14}-fold). The functions of the hydrolase involve participation in global nitrogen circulation as it is present in plants, fungi and bacteria, such as *Proteus mirabilis*, *Klebsiella aerogenes* and *Helicobacter pylori*. This occurrence determines its significance to humans, in particular in public health context. The activity of bacterial ureases is related with colonization by microorganisms of the urinary and gastrointestinal tracts, and persistent infections. Accordingly, *H. pylori* is the main etiological agent of peptic ulcers in the stomach by producing the alkaline environment which facilitates the colonization of the mucosal lining (Nobel Prize for Barry Marshall, 2005).

Inhibition of ureolytic activity of microorganisms is an attractive approach to intelligent antimicrobial therapies based on specific interactions with the enzymatic target at a molecular level. Thus, tremendous effort are dedicated to develop the agents that affect the urease activity in order to control urease-dependent bacterial and fungal infections. Our research group is well-experienced in computer-aided design, chemical syntheses, kinetic characteristics and structure-activity analysis of such inhibitors. Organophosphorus compounds (phosphonic and phosphinic acid), mimicking the substrate in the transition state of the enzymatic process, have been the most intensively studied. They were found highly active towards ureases from *Sporosarcina pasteurii*, *P. mirabilis* and *H. pylori*, avoiding hydrolytical lability of phosphoramidates, the canonical phosphorus-based transition state analog inhibitors. Recently, a remarkable level of inhibition has been also achieved by cysteine-reactive compounds that target the thiol group of Cys322 residue forming a movable flap of the enzyme active site.

Following these developments we wish to envisage within the current project a concept of urease inhibition by dually acting compounds, constructed to combine the reactivity toward the SH of the cysteine with potent nickel-binding properties. An extensive set of new structures is planned to be obtained, their affinity to model and pathogenic ureases measured and the mode of action confirmed. Importantly, selected virulent bacterial and fungal strains will be targeted in whole-cell experiments. The results are expected to bring high-affinity compounds that will be validated as potent and selective agents targeted against *Helicobacter* infections and cryptococcosis.