Covalent inhibition of bacterial urease by bifunctional catechol-based phosphonates and phosphinates

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Urease activity has been identified as a primary factor in the colonization and development of persistent infections of several microbial species. The priority pathogen list indicated by the World Health Organization for the research and development of new antibiotics includes urease-dependent antibiotic-resistant bacteria, several of which are involved in bacterial infections of the respiratory apparatus, and it is remarkable that half of patients who died of the recent COVID-19 epidemics in Wuhan (China) became co-infected with bacteria in the lungs and also required antibiotics.[1]
In this study, a new class of bifunctional inhibitors of bacterial ureases, important molecular targets for antimicrobial therapies, was developed. The structures of the inhibitors consist of a combination of a phosphonate or (2-carboxyethyl)phosphinate functionality with a catechol-based fragment, both of which are located on the short propionate scaffold. The β-substituting phosphorus-based moieties were dedicated to complexation of the catalytic nickel ions, while catechol was used to provide simultaneous covalent bonding with the thiol group of Cys322.

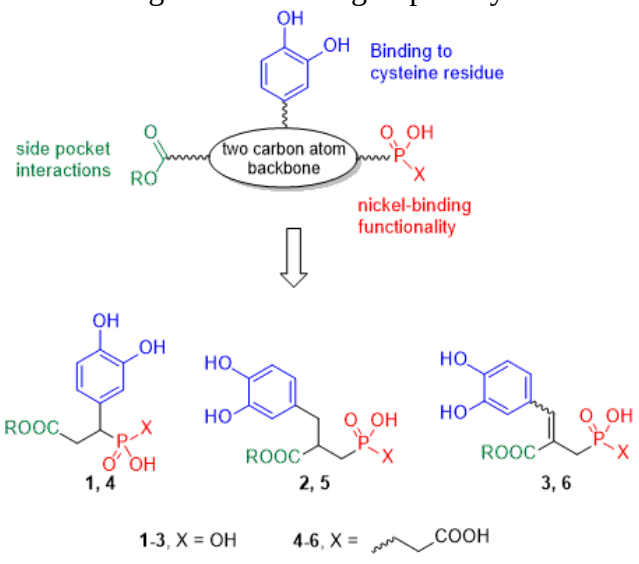

Fig. 1: Bifunctional inhibitors synthesized

References:

1. L. Mazzei, F. Musiani, S. Ciurli, *Journal of Biological Inorganic Chemistry*, **2020**, https://doi.org/10.1007/s00775-020-01808-w