FACING THE SUPERBUG CHALLENGE WITH INNOVATIVE APPROACHES

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The ability of antibiotics to cure bacterial infections is at serious risk due to the emergence and worldwide spread of superbugs (multi-drug resistant bacteria). A lack of innovation and investment for almost 50 years has led to significant efforts currently being devoted to find alternative and innovative therapies to face this challenge. Of particular concern is the increasing incidence in healthcare-associated systems, since in these cases the weak immune systems of patients facilitate the pathogenicity of bacteria. Resistance to antibiotics is reaching such dangerous levels that the World Health Organization (WHO) estimates that by 2050 around 10 million people could die every year as a result of this problem, and deaths from antibiotic resistance will exceed those caused by cancer. Therefore, there is a great interest in the search not only for more effective anti-infective drugs but also to develop novel chemical entities with new mechanisms of action.

Our research group is exploring the potential of unexploited essential targets for bacterial viability, which are involved in the aromatic amino acids biosynthesis, as well as in the development of novel scaffolds that target them. Our efforts are also focused in disabling bacterial pathogenicity (capacity to cause infection), which is an attractive choice that is increasingly being explored. In particular, we have developed irreversible compounds capable of modulating their reactivity when complementarity with the specific target takes place. These are rationally designed inhibitors bearing "latent electrophiles", which are functional groups that become activated toward covalent bond formation upon binding to a specific protein or enzyme but they are silent to non-specific targets. The mechanism of action of the target compounds have been studied by a combined multidisciplinary approach combining Molecular Dynamics and QM/MM simulation studies, protein X-ray crystallography and biochemical studies. In this talk, examples of both approaches will be presented.

References

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