Structural modifications often use bioisosterism that can play a key role in understanding the properties of drugs, i.e. interaction with the receptor, binding mechanism and its strength. Bioisosteres are substituents or groups which show similar physical, chemical and generally biological properties. The methods used to identify bioisosteric groups can be divided into two categories: knowledge-based and computer algorithms. Neither of these methods takes into account the role of solvation, that is, completely ignores the hydrophobic effect, which often dominates the free energy of binding between ligand and receptor. The project is based on the solid foundations of ligand design; however, it proposes a new approach to overcome one of the most difficult obstacles in medical chemistry, ie the prediction of Gibbs energy for ligand-receptor binding. Due to this fact, this project aims to verify, and then expand and improve the existing bioisostere base, considering the enthalpy effect (increase, decrease in the strength of non-covalent interactions) and the entropy effect (changes related to the release of water molecules from the binding pocket and the reduction of ligand and host conformational freedom). This goal will be achieved through a combination of experimental research: X-ray measurements and isothermal titration calorimetry and theoretical research: *ab-initio* calculations and molecular dynamics simulation on synthetic receptors, which will be used as a reference model for the definition of true bioisosteres. After segregation of bioisosteres into those whose binding strength is to a greater extent due to the enthalpy or entropy effect, physicochemical or electron density descriptors will be defined, which will be able to distinguish the tested bioisosteres. The proposed properties will then be used to search for new bioisosteres that will explore the chemical space more broadly.

Despite the revolution in drug design, the huge investments made in the last four decades, the number of drugs approved per year remains the same. Researchers also emphasize the fact that only 10% of "true" innovative drugs are involved. The focus should be on the quality of the proposed compounds for *in vitro* and *in vivo* experimental studies, not necessarily on their quantity. Many factors influence this result, on the one hand, the specificity of the pharmaceutical industry is important, but also the paradigm of the model of rigid recognition between molecules still prevails. The grant aims taking into account the system flexibility and the role of water, it is the only way to get a broader understanding of the principles that determine the molecular recognition. This will enable the creation of a new, improved bioisosteres database. This step is necessary for rational drug design, e.g. by improving widely used bioisosteres, understanding the chemical and biological similarity of molecules, as well as allowing the refinement of the force fields used to estimate the receptor-ligand binding energy.