Fluorine is the most electronegative element found in nature, which in comparison to the other halogens (Cl, Br or I) induces quite different properties in organic molecules – it increases the acidity of carboxylic and hydroxyl groups and decreases basicity of amines, and strongly influences bioavailability, lipophilicity and metabolic stability. Recently, the fluorination of chemical molecules has become the commonly used modification in the development of new drugs. Since the approval by the Food and Drug Administration (FDA) of the first drug containing fluorine substituent ($–CF_3$ in halothane – 1950), more than 200 drugs containing fluorine atom(s) have been launched on the pharmaceutical market (and now more than 400 compounds are in the clinical trials). In recent years, the number of fluorinated drugs has increased to about 30% of all newly approved drugs and according to the latest statistics, drugs containing fluorine atom are among the most recommended and, at the same time, the most profitable in the US pharmaceutical market. Moreover, in agrochemicals, they represented 3% in 1970 and about 50% of the market today. Surprisingly fluorine, as the most electronegative element, is a weak acceptor of hydrogen bonds and in contrast to other elements in its group, it cannot create halogen bonds in organic molecules.

Despite the importance of fluorine in medical chemistry, it is still not fully explained how this element affects both physicochemical properties of compounds, and changes of their biological activity (substitution with fluorine may cause both a decrease, but also several hundred-fold increase in a biological activity of a given leading structure). Quite often the search for new fluorinated derivatives takes place through trial and error, because the available software for rational drug design, does not have adequate information to predict changes caused by the substitution of hydrogen or other functional groups by fluorine at various places in the molecule. However, based on intensive preliminary studies on model systems performed at the Department of Medicinal Chemistry, we have gained knowledge about the effect of fluorine on the formation of hydrogen bonds through neighboring functional groups. This multidisciplinary project aims to clarify the role of fluorine in the formation of hydrogen bonds and its effects on biological activity and selectivity of drugs.

The main goal of this project is to propose a new *in silico* algorithm, which will allow determining the role of fluorine to improve a pharmacodynamic property of bioactive compounds on an example of five well-known, selected drugs (like risperidone and paracetamol). The results obtained from high-performance quantum chemical calculations (molecular modeling, molecular docking, molecular dynamics) will be considered in the rational design of new, more active fluorinated derivatives of the mentioned drugs. The second goal of this project is to determine the role of fluorine during the formation of an intermolecular hydrogen bond (HB) in biological systems because there is no clearly how fluorine act as an acceptor of HB and what is the contribution to the stabilization energy of such interactions in biomolecular systems.

The obtained results can be used in further research not only by our team but also by other groups of researchers working with the rational design of new drugs. At the same time, the results can facilitate the rational use of fluorine to steer the pharmacodynamic properties of existing drugs or new ligands, i.e. by controlling intermolecular interactions formed by fluorine or neighboring functional groups. Additionally, the obtained knowledge and algorithms may become the basis for obtaining a new or improving the existing software for a computer-aided drug design – which will lead to minimizing the time and number of possible modifications of the lead structure to obtain the optimal molecular structure of a given drug.