The aim of the proposed project is to investigate the role of the so called “halogen bonds” in the interaction of chemical compounds (namely – ligands) used in the therapy of depression.

The target (which can be comprised of e.g. a receptor protein or an enzyme) of most of nowadays used antidepressants is the serotonin transporter (SERT) present in a human nervous system. Its role is to regulate the transmission of signals in the nervous system through eliminating serotonin one of the key neurotransmitters in the brain, from synaptic cleft. Serotonin transfers neural signals by stimulating specific molecules called serotonin receptors. After completing its task it should be quickly eliminated to avoid overstimulation of neurons, which is done by serotonin transporter. Numerous research have proved that serotonin neurotransmission is responsible for several functions like sleep, mood, sex or memory. Since the discovery of the first antidepressant drugs in the 50’s of the XX century, it has been implicated that abnormalities in the signal transduction mediated by serotonin are responsible for mood disorders like depression. Because of that, most antidepressant drugs act by a direct stimulation of the serotonin receptors or by modulation of serotonin level. Most of the clinically relevant substances belong to the latter and are comprised of monoaminooxidase inhibitors (MAOI) and serotonin transporter inhibitors (SRI). MAOIs act by inhibiting serotonin decomposition and SRIs act by blocking SERT, both cause the increase of serotonin level in the brain. SERT inhibitors, in particular selective serotonin reuptake inhibitors (SSRI, e.g. fluoxetine – Prozac, sertraline – Zoloft), has gained so far the greatest approval and are presently most widely used for the treatment of depression. In spite of their success they exhibit many side effects including: insomnia, nausea, sexual dysfunction, dangerous interaction with many popular drugs (e.g. Aspirin) and increased risk of suicide. Additionally, it was revealed that they exhibit limited potency together with long delay between beginning of treatment and appearance of therapeutic effects. To avoid this, an augmentation therapy is implemented with the use of drugs that directly interact with serotonergic receptors. Unfortunately, this can lead to possible dangerous cumulative side effects and interactions between drugs. This is why the search for new, better substances is still in progress. Much hope is given to **polypharmacological substances** that act on several selected targets and exhibit lower incidence of side effects. Unfortunately, mechanisms that govern the multitarget activity of drugs are still far from understanding. To be able to effectively search for new therapeutics they need to be further investigated.

The aim of this project is to investigate the role of halogen bonds in binding of ligands to SERT. The fact that five out six FDA approved SSRIs possess halogens in their structure suggests important role of halogen bonds in interaction between ligand and SERT, which was confirmed by scrupulous research.

The research will be comprised, *inter alia*, of the synthesis of FDA approved SSRI derivatives, that will be substituted with heavier halogens (chlorine, bromine, iodine). Only sparse examples of such derivatives can be found in scientific literature and there is still too few of them to make a conclusion. The obtained SSRI derivatives, after evaluating their SERT activity, will be thoroughly analysed with the use of modern hybrid molecular modelling techniques that implement both quantum mechanics and molecular dynamics. This scientific method should propose explanation for the role of halogen bonds in SERT-ligand interactions and provide a model that will be valuable in the future design of novel therapeutics. In the next step, a series of compounds will be obtained in an attempt to create a polypharmacological substance exhibiting simultaneous activity at SERT and 5-HT_6/5-HT_7 receptors, which were recently recognized as promising targets for new antidepressant drugs. **Up to date no research team has reported a synthesis of a compound that simultaneously acts on these targets**.