Opioid drugs, such as morphine or oxycodone, induce strong analgesic effects through specific G protein coupled receptors, located on the surface of neuronal cells. Acting via mu (MOR) and kappa (KOR) opioid receptors, they reduce pain, but also cause side effects – euphoria and respiratory depression or dysphoria and aversion (mediated by MOR or KOR, respectively). Recent discoveries suggest that reduction of pain is mediated by G protein and that β-arrestin pathway is involved in side effects. These studies have opened up the possibility of searching for substances that selectively activate one of these proteins and associated signalling pathways. Such compounds have been called functionally selective agonists (biased agonists). In recent years, crystal structure of opioid receptors was discovered and models of these proteins were developed. In the present study we will use modern bioinformatics, that will allow for virtual viewing of existing and own created libraries of chemical compounds to search for substances that "fit" the sites of interaction with either G proteins or β- arrestin on opioid receptors. Next, the most selective substances will be synthesized and tested for their selectivity on cultured cells with specific opioid receptors. These studies will allow the selection of those compounds that bind to opioid receptors and selectively activate G protein or β-arrestin pathway. G protein biased agonists will be further tested in behavioral tests to determine their analgesic as well as euphoric and addictive (MOR agonists) or dysphoric (KOR agonists) effects. In the next stage, selected compounds will be tested to assess how they affect the release of neurotransmitters in the brain. **The overall goal of the study is to find new specific biased agonists of MOR and KOR, which will allow to uncover mechanisms of desired (analgesia) and undesired action of opioids and understand how does biased signaling produce distinct biological effects**. The project will aim to create tools for modelling, selection and synthesis of biased opioid compounds, and will allow to further study molecular and behavioral mechanisms of their action. The proposed research may have important implications for pain therapy in the future, because they may lead to the development of novel opioid analgesics without undesirable side effects. This is particularly interesting in the context of the growing epidemic of addiction to prescription opioids and desirable in the treatment of chronic pain.