Chronic pain management is one of the most important clinical problems which causes the disability and distress of more than 20% of population. Pain reduces the quality of life of those people, but also decreases their productivity and the need for long-term treatment generates an immerse financial cost for the society. Unfortunately, the problem of chronic pain often remains unresolved by currently available treatments and is one of the main challenges of modern science.

One of the most clinically effective analgesics is morphine, an opioid drug of alkaloid structure. However, its clinical use is limited by the development of severe adverse effects such as respiratory depression and constipation and also by tolerance, dependence and addiction. The strong antinocieptive effect, but also side effects of morphine are the result of activation of opioid receptors, which are localized in the central nervous system (CNS) and also in many peripheral tissues. Opioid receptors (mu, delta and kappa) are members of the G protein-coupled receptor (GPCR) family and are involved in mediating the effects of opioids, most importantly regulation of pain. GPCRs transduce signals through coupling to G proteins. Further inhibition of receptor-G interactions is an effect of β-arrestin recruitment. More recently, it has been discovered that β-arrestin is also an independent signal transducer and therefore GPCRs may activate distinct biochemical pathways depending on the recruitment of either G proteins or β-arrestins. Interestingly, some GPCR ligands may act as biased agonists that after binding to a single receptor are able to activate, with different efficacy, G protein over β-arrestin or *vice versa*.

Among the three types of opioid receptors, the mu receptor was identified as the one essential for the pain-relieving effects. They are targeted by endogenous opioid peptides and opioid drugs of alkaloid structure, such as morphine, which is one of the most clinically effective analgesics. However, the analgesic activity of morphine is accompanied by serious side effects such as sedation, respiratory depression, constipation, tolerance, and the potential for abuse. It was hypothesized that analgesic effect of morphine is associated with promotion of G protein signaling while development of side effects is β-arrestin-dependent.

Therefore, mu opioid receptor agonists biased to either G protein or β-arrestin may be used to segregate physiological responses downstream of the receptor and may represent a new strategy for the development of more effective and safer drugs.

In 1997 two endogenous mu opioid receptor peptide ligands, endomorphin-1 (EM-1) and endomorphin-2 (EM-2), were discovered. Similarly to morphine, these peptides activate both, G protein and β-arrestin pathways and evoke strong antinociceptive effect after central administration (directly to the brain) in laboratory animals. Unfortunately, their use as drugs is hampered by their short half-life in biological fluids. However, opioid peptides were thought to be an alternative for morphine-based drugs, as they have high potency, exquisite selectivity and low toxicity and produced less side effects than morphine. Therefore, numerous chemical modifications have been proposed to increase stability and bioavailability of opioid peptides, such as incorporation of D-amino acids, unnatural amino acids, pseudo-peptide bonds or by cyclization.

Finding of mu-selective endomorphin analogs ligands that exhibit either G protein or β-arrestin pathway selectivity would allow to understand the involvement of those different pathways in pain recognition and would be a step forward to development of more effective and better tolerated analgesic drugs.

The goal of this project is to synthesize a small library of mu-selective opioid peptide analogs and characterization of pharmacological properties of compounds: opioid receptor affinities; functional assay to determine the agonist activities for opioid receptors; enzymatic degradation studies; estimation of bioavailability of compounds by determination of their lipophilicity and ability to permeable the artificial membrane; assessment of toxicity and pharmacological characterization of compounds toward possible selective activation of G protein or β-arrestin pathway.