The need to control pain is as old as mankind but reaching this goal is still elusive. Probably the oldest drug ever known to man was opium, sticky exudate from the poppy plant which was used for pain relief and other medical purposes in China over two thousand years ago and in Mesopotamia even before that. At the beginning of the XIX century, crude extract derived from poppies, containing a complex mixture of alkaloids, was separated by Friedrich Serturner and morphine, the principle alkaloid of opium and the one responsible for its analgesic activity, was identified. Morphine in the pure form was far more effective in controlling pain than opium and is still used today for the treatment of acute and chronic pain, such as cancer or post-operative pain, despite the serious side-effects, such as physical dependence, tolerance, respiratory depression, constipation, which accompany its administration.

Morphine produces its clinical effects by interaction with three types of opioid receptors, designated MOR, DOR and KOR but mostly by activation of the MOR.

The discovery of opioid receptors in the 70ties of the last century was promptly followed by the identification of their endogenous ligands: enkephalins, dynorphins and endorphins. It took almost 20 years to find in the brain two tetrapeptides, which, on the basis of their exceptional affinity and selectivity for the MOR, were considered the endogenous ligands of this receptor. These two peptides were designated endomorphin-1 and endomorphin-2, respectively, and these names were chosen to stress the similarity to morphine in terms of analgesic activity.

Even though morphine and endomorphins act at the same opioid receptor, the latter are thought to inhibit pain without some of the undesired side-effects of morphine.

The initial hopes that the discovery of endomorphins will quickly result in the development of effective drugs for the treatment of pain, devoid of the side-effects of morphine were soon followed by the realization of problems with the exogenous administration of peptides. The use of endomorphins as analgesics is of little therapeutic value because these peptides are quickly degraded by digestive enzymes and have a very limited ability to reach the brain. These unfavorable pharmacological properties have hindered the development of endomorphins for clinical use. To overcome the limited access of exogenously administered endomorphins to the brain and to search for analogs with minimal side-effects, numerous chemical modifications of their structure have been proposed

The aim of the project is the search for novel peptide analogs based on endomorphin structure which would be stable against proteolytic enzymes and could reach the brain after peripheral administration.

A novel approach proposed in this project is the synthesis of hybrid analogs that incorporate active fragments of two compounds. Such hybrid analogs may have lower propensity to induce dependence. Chemically, such hybrids will be made of a cyclic part responsible for analgesic effect and linear part decreasing side effects.