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Abstract of the PhD thesis tittled

Synthesis of cyclic endomorphin-2 analogs with potential antinociceptive activity

Treatment of severe and chronic pain has been one of the main problems of humanity since ancient times. Isolated from opium morphine is still one of the most effective painkillers. Morphine acts through opioid receptors: MOP, DOP and KOP which are present in the central nervous system (CNS), but also in many peripheral tissues. Unfortunately administration of morphine, especially chronic, causes tolerance, dependence and other serious side effects, including, constipation, respiratory depression or hypotension.

The strongest antinociceptive effect is associated with activation of MOP receptors. The endogenous ligands of MOP receptor, endomorphine-1 (EM-1) and endomorphine-2 (EM-2), are present mainly in the CNS and show similar to morphine affinity for this receptor producing strong antinociceptive effect after central administration. However due to their peptide structure, endomorphins have short half-lives in biological fluids and are unable to cross the blood-brain barrier after peripheral administration which limits their use in pain therapy.

The aim of the thesis was the synthesis and characterization of pharmacological properties of new cyclic EM-2 analogs.

As part of my dissertation I studied the cyclization reaction carried out both, on resin and in solution, through an amide bond or disulphide bridge between side chains of suitable amino acids. Cyclization allowed me to obtain compounds stable against enzymatic degradation and also with increased lipophilicity which is one of the decisive factors influencing the penetration of peptides through biological barriers.

Two of the obtained analogs which showed mixed affinity for opioid receptors, produced stronger than EM-2 antinociceptive responses after central administration. These peptides were also active after peripheral administration which indicated that they were able to cross the blood-brain barrier.

Therefore, cyclization can be considered an important step forward in the design and synthesis of non-peptide mimetics which can be viewed as a new generation of peptide-based drugs.