Abstract

The doctoral thesis presents the synthesis of a series of 19 new cyclic analogs of selected opioid peptides: Leu-enkephalin, Met-enkephalin, endomorphin-2, morphiceptin and dermorphin. The created modifications consist in the formation of a biaryl bridge in the *meta* or *para* position of the tyrosine and/or phenylalanine aromatic rings. Cyclization with formation of the biaryl bridge was performed with the use of the solid supported Suzuki-Miyaura reaction on a peptide with halogenated and boron derivatives of tyrosine and/or phenylalanine.

The work demonstrates for the first time the modification of peptides with Suzuki-Miyaura reaction of peptides with a *tert*-butyl protected tyrosine residue. Moreover a new method of synthesis of iodinated tyrosine residues: Fmoc-Tyr(3-I,tBu)-OMe and Boc-Tyr(3-I,tBu)-OMe using silver salts in the presence of base is presented.

The doctoral thesis presents the results of conformational analysis of new cyclic opioid peptide analogs with a biphenyl bridge using circular dichroism and NMR. CD allows only to compare the conformations of individual peptides, while NMR analysis together with calculations with the XPLOR program provides detailed information about their conformations. Cyclic opioid peptides with a biaryl moiety assume a type IV β-bend conformation in solution, without the participation of stabilizing hydrogen bonds. In addition, NMR analysis showed a significant distortion of the geometry (pyramidality) of the aromatic carbon atoms forming the biaryl linkage. Studies indicate a smaller conformational freedom of peptides in which the carbon atom in the *para* position of the aromatic ring of phenylalanine participates in the formation of the biaryl linkage.

In addition, the impact of such modifications on fragmentation using tandem mass spectrometry and proteolytic stability against chymotrypsin was analyzed. The results of the analyzes confirm the influence of the size of the ring and the configuration of the biaryl linkage on the restriction of conformational freedom.

The conducted studies on the biological activity of selected new cyclic opioid peptides indicate a low affinity for the μ-opioid receptor. In order to understand the low affinity of the cyclic opioid peptide analogs for the MOR, molecular docking studies were performed for the cyclic Met-enkephalin analog. Molecular docking results show that biaryl opioid peptide analogs do not mimic the bioactive conformation of the parent peptides.