Pharmacological profile and molecular modeling of cyclic opioid analogues incorporating various phenylalanine derivatives.

Autorzy

Anna Adamska-Bartłomiejczyk

Piotr F. J. Lipiński

Justyna Piekielna-Ciesielska

Alicja Kluczyk

Anna Janecka

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Streszczenie

Peptide-based agonists of the μ opioid receptor (μOR) are promising therapeutic candidates for pain relief with reduced side effects compared to morphine. A deep understanding of μOR–ligand interactions is necessary for future design of peptide-based opioid analgesics. To explore the requirements of the μOR binding pocket, eight new analogues of our cyclic peptide Tyr-c[d-Lys−Phe−Phe−Asp]NH_2 displaying high μOR affinity were synthesized, in which Phe in either the third or fourth position was replaced by various derivatives of this amino acid (β^3-Phe, homoPhe, β^3-homoPhe and PhGly). The aim of this research was to examine the structural effects of such modifications on the bioactivity, and both experimental and theoretical methods were used. The binding of the cyclic analogues to all three OR types (μ, δ, κ) was assessed by radioligand competitive binding assay, and their functional activity was determined in a calcium mobilization assay. In order to provide structural hypotheses explaining the obtained experimental affinities, the complexes of the cyclic peptides with μOR were subjected to molecular modeling.

Słowa kluczowe

binding, cyclic peptides, molecular modeling, opioid receptors, structure-activity relationships

Adres publiczny

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