Synthesis, biological evaluation and structural analysis of novel peripherally active morphiceptin analogs.

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Rok wydania

2016

Czasopismo

Bioorganic and Medicinal Chemistry

Numer woluminu

24

Strony

1582-1588

DOI

10.1016/j.bmc.2016.02.034

Kolekcja

Naukowa

Język

Angielski

Typ publikacji

Artykuł

Streszczenie

Morphiceptin (Tyr-Pro-Phe-Pro-NH2), a tetrapeptide amide, is a selective ligand of the l-opioid receptor (MOR). This study reports the synthesis and biological evaluation of a series of novel morphiceptin analogs modified in positions 2 or/and 4 by introduction of 4,4-difluoroproline (F2Pro) in L or D configuration. Depending on the fluorinated amino acid configuration and its position in the sequence, new analogs behaved as selective full MOR agonists showing high, moderate, or relatively low potency. The most potent analog, Tyr-F2Pro-Phe-D-F2Pro-NH2, was also able to activate the j-opioid receptor (KOR), although with low potency. Docking studies and the comparison of results with the high resolution crystallographic structure of a MOR-agonist complex revealed possible structure–activity relationships of this compound family.

Słowa kluczowe

solid-phase peptide synthesis, binding studies, opioid receptors, hot-late test, gastrointestinal transit, molecular dynamics, docking

Adres publiczny

http://dx.doi.org/10.1016/j.bmc.2016.02.034

Strona internetowa wydawcy

http://www.elsevier.com