

Synthesis of mixed opioid affinity cyclic endomorphin-2 analogues with fluorinated phenylalanines.

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Streszczenie

As part of our continuing studies on the structure–activity relationships of cyclic pentapeptides based on the structure of endomorphin-2 (EM-2), we report here the synthesis and biological activities of a new series of analogues of a general sequence Tyr/Dmt-c[d-Lys-Phe-Phe-Asp]NH₂ (where Dmt = 2',6'-dimethyltyrosine), incorporating fluorinated amino acids: 4-fluorophenylalanine (4-F-Phe), 2,4-difluorophenylalanine (2,4-F-Phe), or 4-trifluoromethylphenylalanine (4-CF₃-Phe) instead of the Phe residue in position 3 or 4. Depending on the fluorinated amino acid residue and its position in the sequence, analogues were mixed, high affinity MOP/KOP receptor agonists, MOP/DOP/KOP agonists, or selective KOP agonists. The *in vitro* potencies and efficacies of all novel analogues were assessed in calcium mobilization assay. The most potent analogues, Dmt-c[d-Lys-Phe-4-F-Phe-Asp]NH₂ and Dmt-c[d-Lys-Phe-2,4-F-Phe-Asp]NH₂, were tested *in vivo* in the mouse hot-plate test. They produced strong antinociceptive effect not only after intracerebroventricular but also after intraperitoneal injection, indicating that they were able to cross the blood–brain barrier.

Słowa kluczowe

Opioid receptor affinity, calcium mobilization assay, antinociceptive activity, blood–brain barrier

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