Endomorphin-2 analogs containing modified tyrosines: Biological and theoretical investigation of the influence on conformation and pharmacological profile.

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New analogs of the endogenous opioid agonist endomorphin-2 (EM-2, H-Tyr-Pro-Phe-Phe-NH_2) have been obtained by introducing modified tyrosines at the position 1 of the sequence. For all analogs, the *cis/trans* conformation ratio about the tyramine-Pro amide bond, lipophilicity, receptor affinities, and functional activities, have been determined. Among the novel derivatives, [Dmt(3′-Cl)]^{1}EM-2 (**4**) stood out for its subnanomolar μ-opioid receptor affinity and potent agonist activity, superior to that of the parent peptide EM-2. Hybrid quantum mechanics/molecular mechanics docking computations supported the *cis* tyramine-Pro bioactive conformation, and allowed us to analyze the contribution of the substituents of the “message” tyramine to binding, highlighting the role of halogen-bonding in the higher receptor affinity of peptide **4.**

Słowa kluczowe

Opioid peptides, Tyrosine analogs, Molecular docking, Halogen-bond

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