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Three novel candidates as mu opioid receptor antagonists: an in silico study

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Abstract

Background and Objective: Morphine overdose is a lethal condition that is reversible by administration of mu opioid antagonists like naloxone. This treatment can be associated with side effects like opioid toxicity recurrence. We aimed to design novel chemical compounds as potential mu opioid receptor (MOR) antagonists.

Materials and Methods: We used Chemdraw, Hyperchem and Autodock Tools softwares to design, optimize and dock these compounds to the receptor. We designed 11 chemical compounds that 3 of them were successfully docked. None of these 3 compounds were found in Google scholar, Google search engine and other databases. Exclusion criteria included unsolved non-integral charge, half electron approximation in geometry with minimum energy, non-bonded atoms and optimization errors.

Results: The obtained results of the molecular docking simulation using the mu opioid receptor (PDB code: 4DKL) showed lowest binding energies (LBEs) and estimated Inhibition constants (KIs). Three novel compounds including a 8-Carboxamidocyclazocine analogue (LBE= -8.99 kcal/mol, Ki=256.85 nM) and two triazole derivatives (LBE= -9.21 kcal/mol, Ki=178.45 nM and LBE= -8.66 kcal/mol, Ki=445.88 nM) were suitably fitted in the active site of MOR in comparison with the main ligand (LBE=-10.13 kcal/mol, Ki=37.78 nM) in MOR. In parallel, LBEs and KIs of 3 novel compounds and standard antagonist naloxone (LBE=-8.21 kcal/mol, Ki=960.18 nM) in temperature of 298.15 K were compared.

Conclusion: All of three novel compounds had better potential antagonist properties than standard antagonist naloxone. The best antagonist candidate among them was 7-amino-3-(cyclopropylmethyl)-6,11-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methanobenzo[d]azocine-8 carboxamide. We suggest further studies to evaluate these potential antidotes in morphine overdose.

Biography

Meisam Fadaei-Kenarsary is Senior PhD by Research Candidate; He is working on molecular, electrophysiological, cognitive and behavioral aspects of morphine dependence in Kerman Neuroscience Research Center. His interests are drug design and neurobiotechnology.

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Volume 8 | Issue 5 | 03