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ORIGINAL ARTICLE

N-substituted tetrahydro-beta-carboline as mu-opioid receptors ligands: in silico study; molecular docking, ADMET and molecular dynamics approach

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Abstract

Manipulating intracellular signals by interaction with transmembranal G-protein-coupled receptors (GPCRs) is the way of action of more than 30% of available medicines. Designing molecules against GPCRs is most challenging due to their flexible binding orthosteric and allosteric pockets, a property that lead to different mode and extent of activation of intracellular mediators. Here, in the current study we aimed to design N-substituted tetrahydro-beta-carbolines (THβC's) targeting Mu Opioid Receptors (MORs). We performed ligand docking study for reference and designed compounds against active and inactive states of MOR, as well as the active state bound to intracellular mediator of Gi. The reference compounds include 40 known agonists and antagonists, while the designed compounds include 25,227 N-substituted THβC analogues. Out of the designed compounds, 15 compounds were comparatively having better extra precision (XP) Gscore and were analyzed for absorption, distribution, metabolism, and excretion-toxicity (ADMET) properties, drug-likness, and molecular dynamic (MD) simulation. The results showed that N-substituted tetrahydro-beta-carbolines with and without C6-methoxy group substitutions (THBC/6MTHBC) analogues of A1/B1 and A9/B9 have relatively acceptable affinity and within pocket-stability toward MOR compared to the reference compounds of morphine (agonist) and naloxone (antagonist). Moreover, the designed analogues interact with key residue within the binding pocket of Asp 147 that is reported to be involved in receptor activation. In conclusion, the designed THBC analogues represent a good starting point for designing opioid receptor ligands other than morphinan scaffold, that have good synthetic accessibility which promotes feasible structural manipulation to tailor pharmacological effects with minimal side effects.

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