Structural and functional computational analysis of nicotine analogs as potential neuroprotective compounds in Parkinson disease

Becerra G.P.

Rojas-Rodríguez F.

Ramírez D.

Loaiza A.E.

Tobar-Tosse F.

Mejía S.M.

González J.

As the mechanism of interaction between nicotinic receptors with nicotine analogs is not yet fully understood, information at molecular level obtained from computational calculations is needed. In this sense, this work is a computational study of eight nicotine analogs, all with pyrrolidine ring modifications over a nicotine-based backbone optimized with B3LYP-D3/aug-cc-pVDZ. A molecular characterization was performed focusing on geometrical parameters such as pseudo-rotation angles, atomic charges, HOMO and LUMO orbitals, reactivity indexes and intermolecular interactions. Three analogs, A2 (3-(1,3-dimethyl-4,5-dihydro-1h-pirazole-5-yl) pyridine), A3 (3-(3-methyl-4,5-dihydro-1H-pyrazol-5-yl)-pyridine) and A8 (5-methyl-3-(pyridine-3-yl)-4,5-dihydroisoxazole), were filtered suggesting putative neuroprotective activity taking into account different reactivity values, such as their lowest hardness: 2.37 eV (A8), 2.43 eV (A2) and 2.56 eV (A3), compared to the highest hardness value found: 2.71 eV for A5 (3-((2S,4R)-4-(fluoromethyl)-1-methylpyrrolidine-2-il) pyridine), similar to the value of nicotine (2.70 eV). Additionally, molecular docking of all 8 nicotine analogs with the ? 7 nicotinic acetylcholine receptor (? 7 nAChR) was performed. High values of interaction between the receptor and the three nicotine analogs were obtained: A3 (-7.1 kcal/mol), A2 (-6.9 kcal/mol) and A8 (-6.8 kcal/mol); whereas the affinity energy of nicotine was -6.4 kcal/mol. Leu116 and Trp145 are key residues in the binding site of ? 7 nAChR interacting with nicotine analogs. Therefore, based upon these results,

possible application of these nicotine analogs as neuroprotective compounds and potential implication at the design of novel Parkinson's treatments is evidenced.

DFT calculations

Molecular Orbitals

Natural Bond Orbitals

Neurodegenerative Diseases

Nicotine analogs

Geometry

Hardness

Pyridine

Computational analysis

Computational calculations

Computational studies

Intermolecular interactions

Molecular characterization

Neuroprotective activity

Nicotinic acetylcholine receptors

Reactivity indices

Nicotine