New piperidine derivatives. Studies *in silico* on α7 nicotinic acetylcholine receptors (nAChRs)

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ABSTRACT

A series of new derivatives of piperidine (**1a** and **2a**) were designed, synthesized and chemically characterized. Additionally, electrophysiological recordings of the I_{Ch} (Ch-induced current) in interneurons from the hippocampal indicated that the compound **2a** inhibited the I_{Ch} more strongly than the corresponding compound **1a**, **2a** showing the most potent antagonistic effect on α7-containing nAChRs. The molecular docking studies and molecular dynamics simulations give us new insights about these findings. In this regard, the compound **2a** forms cation-π interactions with the aromatic cage (residues **Y89**, **W143 Y185**, **Y192** of the principal (+)-side and **W53** of the complementary (-)-side) of the α7 nAChR, important for ligand affinity to the α7 nAChR[1]. In further, the aliphatic chain of **2a** presents van der Waals interactions with **L106** and **Q115** of the complementary (-)-side. These interactions were conserved during almost all molecular dynamics simulation time (20 ns) preventing both conformational changes of the receptor and its activation, which may account for the slow recovery of the I_{Ch} inhibition observed in electrophysiological assays. Regarding with the non-methylated compound **1a** the piperidine nitrogen of the compound is protonated at physiological pH, producing a hydrogen bond that forms a solvation network with the water molecules in the binding cavity of the α7 nAChR (see **Figure 1**). As in the case of **2a** during the molecular dynamics simulation, the aliphatic chain of **1a** maintains van der Waals interactions with **Q115**, helping to stabilize the ligand in the cavity. These interactions may allow activation of the receptor diminishing the antagonism activity.

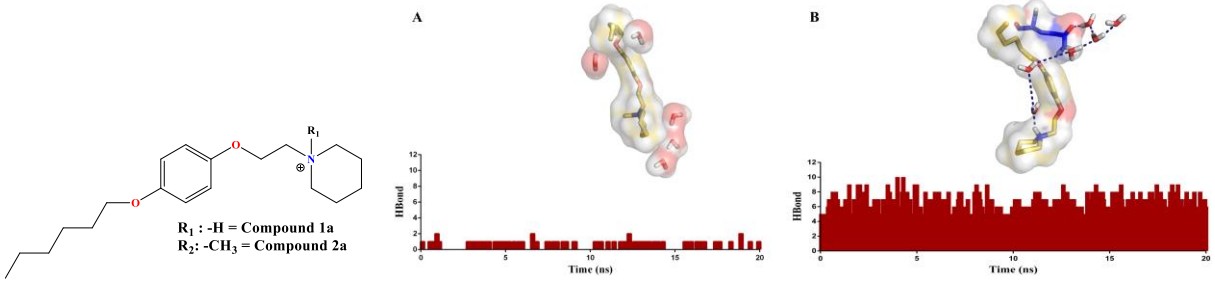

Figure 1. Histogram of hydrogen bonds during the molecular dynamic simulation for **1a** (A) and **2a** (B). In B a network of hydrogen bonds was represented in dashed line.

References

1- Olsen JA, Balle T, Gajhede M, Ahring PK, Kastrup JS (2014). PLOS ONE 9(3):1-8