MOLECULAR MODELING OF BUTYRYLCHOLINESTERASE INHIBITORS AS POTENTIAL DRUGS AGAINST ALZHEIMER'S DISEASE

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INTRODUCTION

Alzheimer disease (AD) is the neurogenerative disease most common in the world. According to the World Health Organization (WHO) data, until 2050, it will affect 152 million people. Loss of memory, observed as a principal symptom of AD, is caused mainly by the decrease in the concentration of the acetylcholine (ACh) neurotransmitter. This reduction may be due to the increased activity of the cholinesterase enzymes, i.e., acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), since both isoforms are capable of hydrolyzing acetylcholine. However, as the disease progresses, AChE activity decreases, while BChE activity increases, indicating the importance of BChE inhibitors.

OBJECTIVE

Our study aims to find new potential BChE inhibitors, capable of minimizing the symptoms resulting from the deficit of the Ach neurotransmitter in patients with advanced AD, by molecular modeling for drug design, using computational chemistry programs as a virtual approach.

Ligands: Structure Construction, Optimization & Conformational Analysis
Spartan'14
(https://www.wavefun.com/)

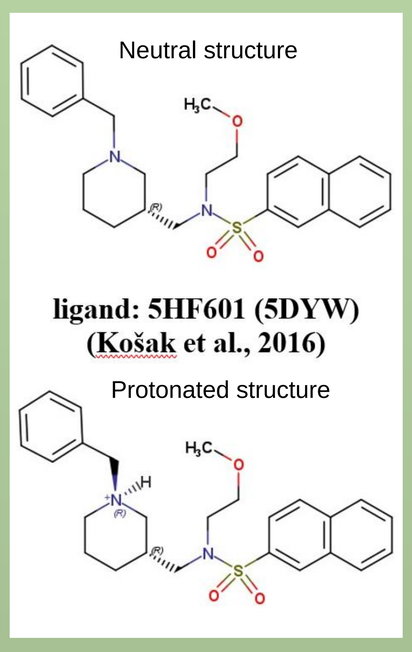
Selection of 90 ligands
(Košak et al., 2016 & Košak et al., 2018)

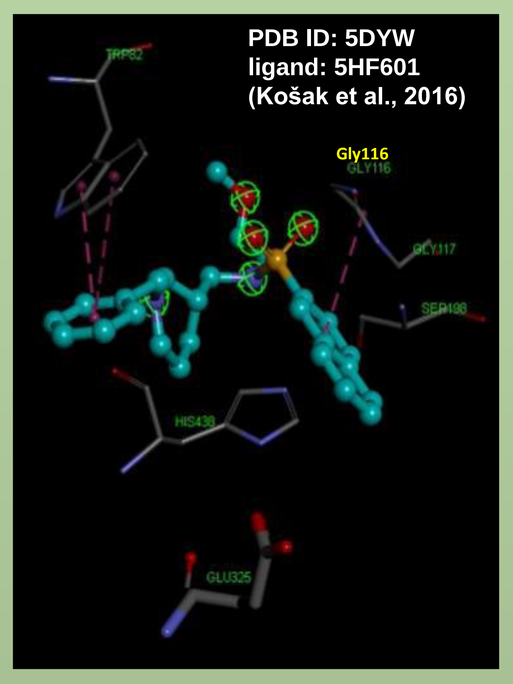
Molecular Docking
DockThor
(https://dockthor.lncc.br/v2/)

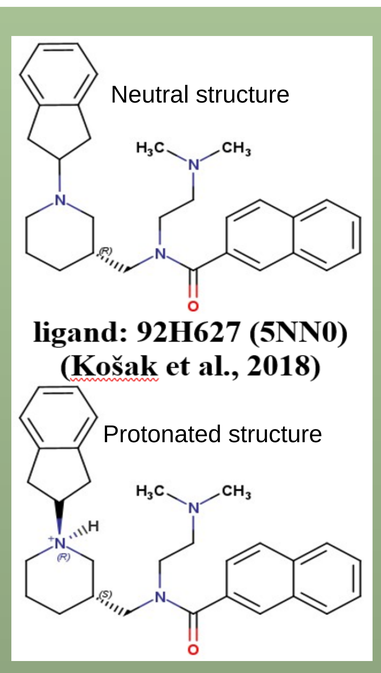
Selection of alpha-Carbon of Gly116 residue
Discovery Studio Visualizer
(https://discover.3ds.com/)

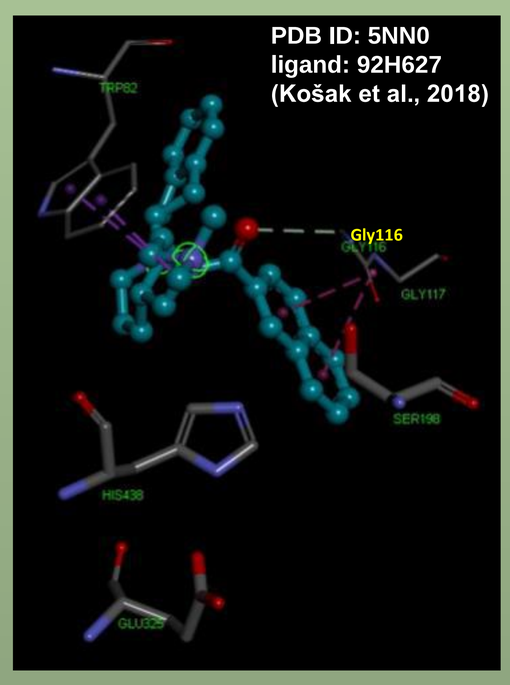
METHODOS

We used two 3D structures of human BChE complexes with potent inhibitors, resolved by X-ray diffraction and available in the Protein Data Bank, under the PDB IDs: 5DYW (Košak et al., 2016) and 5NN0 (Košak et al., 2018). These inhibitors have a piperidine heterocycle showing absolute (*R*) configuration at C3 of the piperidine ring, whose amino group is protonated, according to Košak et al. (2016, 2018). The construction of the 3D structures of the inhibitors (ligand **5HF601** on ligand-protein 5DYW complex and ligand **92H627** on the 5NN0 complex) was carried out in the Spartan'14 software, followed by geometry optimization and conformational analysis (systematic and random), using the MMFF94 force field. The molecular docking/redocking steps were performed on the DockThor server (https://dockthor.lncc.br/v2/), where the alpha-Carbon atoms from Gly116 (chain A) at the active site, was chosen as the center of the 20x20x20 Å box.



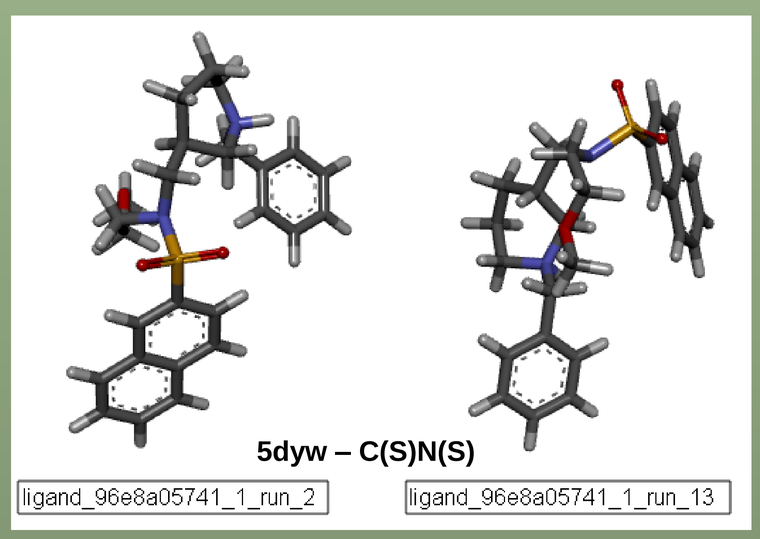


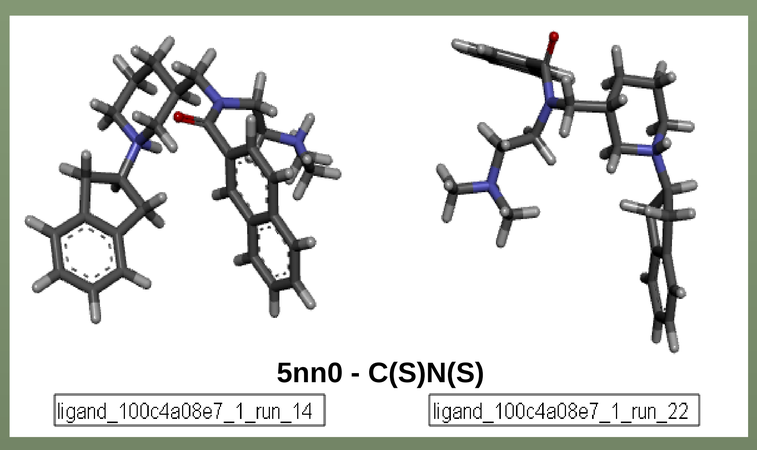




RESULTS

Preliminarily results shows that, for both ligands, the solutions (poses) with the best scores are those structures where the absolute configurations of both, C3 and N (pyridine protonated) are (*S*). In the case of C3, according Košak et al. (2016, 2018), the configuration is (*R*), while the configuration of the protonated pyridine nitrogen atom is not described, probably due the possibility of both configurations coexist in equilibrium.





CONCLUSION

Therefore, our study suggest the re-evaluation of the configuration of these stereogenic centers on the structure of these inhibitors. As a perspective, we will study the binding modes of other inhibitors of these series.

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ACKNOWLEDGMENTS

UFRJ – UNIRIO - CNPq - FAPERJ - CAPES