Combined structure-based drug design approaches and ADME analysis for the study of novel antiparkinsonian agents.

Merzaka METTAI[1*], Ismail DAOUD[1,3], Nadjib MELKEMI[2], Fouzia MESLI[3]

[1]*University Mohamed kheider, Faculty of Sciences, Department of Chemistry- Biskra, 07000-Algeria*
[2]*Faculty of Sciences, LMCE Laboratory, Department of Chemistry, Group of Computational and Pharmaceutical Chemistry, University of Biskra, 07000, Biskra, Algeria*
[3] *Laboratory of Natural Substances and Bioactive (LASNABIO), University of Abou-Bakr Belkaid, 13000, Tlemcen, Algeria.*

Code CCP1

E-mail*: Merzaka.metai@univ-biskra.dz

Introduction & Objectives: Parkinson's disease (PD) is a major age-related chronic disease[1,2], known as the second most common neurodegenerative disorder in the elderly [3], caused by the loss of dopaminergic neurons in the substantia nigra par compacta (SNpc), which leads to the dopamine (DA) depletion. Among the symptoms, it is characterized by motor symptoms (resting tremor and rigidity…..), and nonmotor symptoms (coherent defacement and disorganization,…..) [4]. Monoamine oxidase B is an interesting target in PD. It has been shown that inhibition of this enzyme increases the level of dopamine in the brain by preventing its degradation especially in the early stages of the disease [3]. In the present work, we perform a structure-based drug design study coupled with ADME analysis in the order to reduce the metabolic depletion of dopamine through studying the interacts of new classes of thirty-seven molecules [5,6] with the MAO-B which involved in the Parkinson disease (PD).

Methodology (Material and methods): A molecular docking study was performed to explain interactions and affinities between the active site residues of MOA-B (PDB: 6RKB) and a new class derivatives of 4-(benzyloxy) phenyl and biphenyl-4-yl followed by molecular dynamics simulation to study the variation of potential energy (U) as a function of time in order to confirms the stability of the Enzyme-ligand complexes. Also a calculation of ADME properties that allowed us to check the druglikeness properties of the best ligands obtained during the molecular modeling simulation was done.

Results and Discussion: Molecular docking study shows that the three complexes (6RKB-C34, 6RKB-C35-, and 6RKB-C36) present a high negative score energy: -7.809 (kcal/mol), -7.812 (kcal/mol), -8.098 (kcal/mol) respectively with the following RMSD values: 0.519 (Å), 1.203 (Å), 1.033 (Å). Moreover a molecular dynamics simulation confirms that these three complexes keep the same types of interactions. in addition, the ADME properties analysis proves that ligands: C34, C35 and C36 accomplish the Lipinski, Ghose, Veber and Egan rules, which means that they have an oral bioavailability and a high level of gastrointestinal absorption.

Conclusion: From the results obtained through the three proposed methods (Molecular docking, molecular dynamics and ADME prediction), we concluded that compound C36 can be approved as the best inhibitor to fight Parkinson's disease or delay its progression.

Keywords: Parkinson's disease, 4-(benzyloxy) phenyl and biphenyl-4-yl derivatives, Molecular docking, molecular dynamics, ADME prediction.

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