Elucidation of Enzyme-Substrate Interactions Using Molecular Modeling Approach: Case of Monoamine Oxidase B Inhibitors

KHERACHI Rania[1*], DAOUD Ismail[1,2], MELKEMI Nadjib[3], MESLI Fouzia[2]

[1]*University Mohamed kheider, Faculty of Sciences, Department of Chemistry- Biskra, 07000-Algeria*

[2] *Laboratory of Natural Substances and Bioactive (LASNABIO), University of Abou-Bakr Belkaid, 13000, Tlemcen, Algeria.*

[3] *Faculty of Sciences, LMCE Laboratory, Department of Chemistry, Group of Computational and Pharmaceutical Chemistry, University of Biskra, 07000, Biskra, Algeria*

Code CCP3

E-mail* : **rania.kherachi@univ-biskra.dz**

Introduction & Objectives: Parkinson's disease (PD) is the second most common neurodegenerative disorder, after Alzheimer's disease. It is characterized clinically by parkinsonism (resting tremor, bradykinesia, rigidity, and postural instability) [1] pathologically by the loss of neurons in the substantia nigra and else where in association with the presence of ubiquitinated protein deposits in the cytoplasm of neurons (Lewy bodies) [2].

The monoamine oxidases (MAO-A and MAO-B) are enzymes that are responsible for the metabolism of neurotransmitters, such as dopamine (DA) and adrenaline. Recent efforts toward the development of MAO inhibitors have focused on selective MAO-A or MAO-B inhibitors. Selective MAO-A inhibitors are effective in the treatment of depression and anxiety, where is the MAO-B inhibitors are useful for treatment Parkinson's disease [3].

Our aim is to explain the various forms of enzyme-ligand interactions and to analyze the stability of the complexes formed.

Methodology (Material and methods): In order to study the inhibition of the enzyme MAO-B (PDB:4a79) which involved in the PD, many molecular modeling methods are used such as: molecular docking and molecular dynamics using MOE software, as well as ADME prediction.

Results and Discussion: The molecular docking results show that the best two compounds L30 and L38 of (4-(benzyloxy)phenyl and biphenyl-4-yl derivatives) complexes which have the lowest score energy compared to other compounds, however to validate these results molecular dynamic calculation is carried out to confirm the stability of these complexes (MAO-B-L30 and MAO-B-L38), and the results show that both compounds L30 and L38 keep the same interactions type, which were appeared the hydrogen bond (H-acc) in the case the 4a79-L30 complex and Hydrophobic interaction (Pi-H) in the case the 4a79-L38 complex.

According to the literature, it seems that the two best candidates (compound L30 and compound L38) obtained from molecular docking/dynamic simulations, which have low energy scores also have low IC50 values given here: 0.110 and 0.305 µM respectively.

Conclusion: The combination between the two results of the two previous methods shows that the compounds L30 and L38 selected to be the best inhibitors of MAO-B, and that these two compounds fulfill the Lipinski, Veber, and Ega rules , also they are able to cross the BBB,. In addition, they may have the potential to be used in the development of new pharmacological agents for the treatment of patients with PD.

Keywords: Parkinson's disease, Molecular Docking, Molecular Dynamic, ADME,Interaction.

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