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RESEARCH ARTICLE

Potent Small Molecules Inhibitors Discovery through Ligand-based Modelling For Effective Treatment Of Parkinson's Disease

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Abstract: ***Background*:** Parkinson's disease (PD) is a chronic neurodegenerative disease affecting mostly aged people. The disease's symptoms develop gradually over time and include tremors, bradykinesia, rigidity, and postural instability. Current treatment options for PD are only symptom-targeted. Prolyl oligopeptidase (POP) is a serine protease enzymes implicated in PD pathogenesis *via* an increase in the aggregation of α-synuclein protein in the brain.

***Aim*:** This study aims to identify potent anti-PD ligands with inhibitory potential against POP

***Method*:** Ligand-based pharmacophore modeling, Glide extra precision (XP) docking, and post-simulation analysis methods were used.

***Result*:** The adopted ligand-based (LB) modeling generated pharmacophoric features, including 1 hydrophobic group, 1 positive ionizable group, 2 aromatic rings, and 2 hydrogen bond acceptors. A total of 23 hits with a Gunner-Henry score of 0.7 and an enrichment factor of 30.24 were obtained as validation protocols, making it an ideal model. The LB model retrieved 177 hit compounds from the 69,543 natural screening ligands available in the Interbioscreen database. Interestingly, ligands 1, 2, 3, 4, and 5 orderly demonstrated higher binding affinities with Glide XP docking of -9.0, -8.8, -8.7, -8.7, -8.7 kcal/mol compared to reference drugs, GSK552 and ZPP with -8.2, and -6.8 kcal/mol respectively. Similarly, their MM/GBSA values were recorded as -54.4, -51.3, -58.4, -49.3, - 33.5, & -32.5 kJ/mol respectively. Further, MD analysis indicated that ligands had higher favorable binding and stability to the receptor.

***Conclusion*:** Overall, the study paves the way for developing potential anti-PD therapeutics. The ligands are recommended as adjuvant/single candidate as anti-PD candidates upon further experiment.

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1. INTRODUCTION

Serine protease enzymes (S9) are a diverse family of enzymes with numerous physiological functions in the body. The notable families of enzymes include dipeptidyl peptidase IV (DPP-IV) and oligopeptidase B. These enzymes play an important role in glucose uptake, regulation, and degradation of incretins, especially glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) [1, 2]. One of the most important members of the serine protease enzyme is prolyl oligopeptidase (POP), a highly expressed enzyme in the brain, implicated in many pharmacological conditions, including enhancement of oligomer aggregation in PD pathogenesis and inactivation of oxytocin in the uterus [3]. The POP is a systolic serine peptidase enzyme and a member of the S9 family of protease enzymes that cleaves peptide bonds at the carboxyl end of proline molecule having size smaller than 3kDa, similar to the fibroblast activation protein alpha (FAP). The localization of POP across tissues and cell layers in the brain makes it an enzyme of concern in neurological diseases [4]. Both POP and FAP remain in plasma circulation and are involved in neurological and inflammatory pathological processes in the brain [1, 5, 6]. POP is involved in neurodegeneration, and increase in aggregation of α-synuclein, which is the major constituent Lewi's body (LBs). The LBs is the major pathological indication of Parkinson's disease (PD). Therefore, POP is an important target for treatment of PD [7].

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