ARQII Publication
http://arqiipubl.com/ams
APPLICATIONS OF
MODELLING AND SIMULATION
eISSN 2600-8084
VOL 6, 2022, 122-133

Ligand-Based Pharmacophore Modelling Targeting α-Synuclein Misfolding for an Effective Treatment of Parkinson's Disease

Sani Yahaya Najib[1,2*], Yusuf Oloruntoyin Ayipo[1,3], Waleed Abdullah Ahmad Alananzeh[1] and Mohd Nizam Mordi[1]

[1]Centre for Drug Research, Universiti Sains Malaysia, USM 11800, Pulau Pinang, Malaysia
[2]Department of Pharmaceutical and Medicinal Chemistry, Bayero University Kano, PMB 3011, Kano, Nigeria
[3]Department of Chemistry, Kwara State University, Malete, PMB 1530, Ilorin, Nigeria

[*]Corresponding author: najibsani62@gmail.com

Submitted 30 September 2022, Revised 3 November 2022, Accepted 16 November 2022, Available online 4 December 2022.
Copyright © 2022 The Authors.

Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disease prominently observed in elderly population. Aggregation and misfolding of α-synuclein protein is strongly implicated as an underlying pathogenesis of the disease. PD is characterised by high amount of intracellular α-synuclein as the main constituents in Lewy bodies. However, PD drugs in clinical conditions elicit unpleasant side effects and develop resistance after long time application, making a search for better candidates imperative. This study is aimed at identifying potent inhibitors of α-synuclein from interbioscreen (IBS) database using ligand-based pharmacophore modelling, Glide standard precision docking, molecular dynamics, and pk-CSM pharmacokinetics parameters. Among the ten models generated, only one of the pharmacophore models was validated with Guner-Henry's goodness of hits (GH) scoring method and enrichment factor (EF) of 0.87 and 23.43 respectively, making it ideal for database screening. The pharmacophore model with features, HHHHHHDDDDA identified 100 hits from "877,337" IBS database natural compounds. The top hits, STOCK2S-85121, STOCK3S-13122, STOCK2S-57139, STOCK7S-07150, and STOCK4S-24924 demonstrated better docking scores of -4.789, -4.451, -4.413, -4.365 and -4.227 kcal/mol respectively, while the standard, Levodopa has docking score of -3.556 kcal/mol. The retrieved compounds have similar amino acid interactions with the standard compound (levodopa). The ligands are predicted to have good Blood Brain Barrier permeation, central nervous system penetrations and absorption, distribution, metabolism, elimination, and toxicity (ADMET) properties. Molecular dynamics for 50 ns further suggested that the highest docked compound (STOCK2S-85121) was stable into the binding pocket and displayed strong hydrogen bond interactions. Therefore, the compound is recommended for further evaluations as potential anti-PD agents.

Keywords: *In silico* ADMET; Ligand-based drug design; Natural products; Parkinson's disease; Pharmacophore model; α-synuclein inhibitors.

1. BACKGROUND

Brain is one of the vital organs in human system. Its functions deteriorate over time due to inevitable process of aging and accumulation of oxidative biomolecules, leading to neurodegenerative disease. Parkinson's disease (PD) is a chronic progressive neurodegenerative disease prominently observed in elderly population with characteristic movement disorders [1]. Globally, one out of every 100 people are affected by PD and yet limited effective curative options are available [2-4]. Specific course of PD is not fully understood and one of the most affected areas in the brain by PD is the substantia nigra, resulting to substantial loss of dopaminergic neurons and a concomitant decrease in dopamine levels within the striatum. Consequently, most prominent PD symptoms are manifested as impaired motor activity including muscle rigidity, and resting tremor [5]. The disease is characterized by intracellular inclusions known as Lewy bodies (LBs) and the main constituent of LBs is α-synuclein [6]. Aggregation of α-synuclein is one of the underlying molecular pathogeneses of PD. This is demonstrated when soluble α-synuclein monomers form oligomers to aggregated small protofibrils, and progressively to insoluble amyloid fibrils. These amyloid fibrils are neurotoxic, causing dopamine cells death. Therefore, this strongly supports the notion that α-synuclein is an essential target in the molecular pathogenesis of PD [2]. The α-synuclein protein is abundant in the brain, having short amino acid (AA) of 140 residues, and high concentration at presynaptic terminals as both soluble and membrane-associated fractions of the brain. The protein is estimated to account for as much as 1% of the total protein as a soluble cytosolic brain

This article is distributed under a Creative Commons Attribution 4.0 License that permits any use, reproduction and distribution of the work without further permission provided that the original work is properly cited.