https://doi.org/10.48048/tis.2023.6008

In silico Pharmacological Evaluation of Tetrahydro-β-carboline Derivatives as Putative Inhibitors of Alpha-Synuclein and Dopa Decarboxylase for Parkinson's Disease

Tham Xuan Yao[1], Yusuf Oloruntoyin Ayipo[2,3,*] and Mohd Nizam Mordi[2]

[1]*Department of Biomedical Sciences, Universiti Putra Malaysia, Serdang Lama 43400, Malaysia*
[2]*Centre for Drug Research, Universiti Sains Malaysia, Pulau Pinang 11800, Malaysia*
[3]*Department of Chemistry and Industrial Chemistry, Kwara State University, Kwara 241103, Nigeria*

([*]Corresponding author's e-mail: yusuf.ayipo@kwasu.edu.ng)

Received: 18 September 2022, Revised: 22 October 2022, Accepted: 29 October 2022, Published: 28 August 2023

Abstract

Parkinson's disease (PD) is a neurological problem that results mostly in disability globally due to therapeutic challenges. Alpha-synuclein (ASN) and Dopa decarboxylase (DDC) are strongly implicated in the pathogenesis of PD including the aggregation of Lewy bodies and degeneration of dopamine-producing cells. These make them plausible drug targets commonly explored by researchers in the quest for potent inhibitors. However, up to this moment, no inhibitor of ASN has been approved for clinical application while only a handful is available for DDC, as such, searching for effective inhibitors of the dual targets remains essential. In this study, the in-house databases of tetrahydro-β-carboline and carbazole derivatives were virtually screened for putative ligands with multitarget inhibitory mechanisms against the ASN and DDC using molecular docking protocols. Relevant drugs such as phenylbutyrate, anle138b, levodopa, carbidopa and benserazide were used as references. The physicochemical, pharmacokinetics, pharmacodynamics and toxicological profiles of the selected ligands and references were also evaluated *in silico* using pkCSM. From the virtual screening, ligands 172, 082 and 013 interacted more strongly with ASN receptors with SP glide gscores of –9.154, –9.124 and –8.971 kcal/mol respectively as compared to phenylbutyrate and anle138b with SP glide gscores of –7.181 and –5.875 kcal/mol. They also showed higher binding affinities to DDC receptor by higher SP glide gscores of –6.758, –5.212 and –6.271 kcal/mol than levodopa, carbidopa and benserazide with values of –4.217, –4.502 and –4.18 kcal/mol respectively. Among the 3 ligands, ligand 172 satisfies Lipinski's Rules of 5 (RO5) and demonstrates ADMET parameters that favor a central nervous system (CNS) drug which was identified as potent inhibitors of ASN and DDC responsible for PD. The potential ligands with stronger inhibitory interactions and good ADMET profile are amenable for further experimental validation in the quest for potent inhibitors of ASN and DDC as anti-PD agents.

Keywords: Parkinson's disease, Alpha-synuclein, Dopa decarboxylase, Lewy bodies, Molecular docking, *In silico* ADMET, β-carboline alkaloids, Central nervous system

Introduction

PD is a progressive neurodegenerative disorder that is caused by the loss of dopamine-producing cells in the substantia nigra of the midbrain [1]. Common symptoms of PD include rigidity, resting tremors, bradykinesia, impaired motor coordination and instability in posture [2]. Among all the neurological disorders, PD has the fastest increase in prevalence with its high resultant in disability and deaths worldwide. It is being shown that in year 2016, 6.1 million people were reportedly affected by PD globally with 21.7 % increase in prevalence rate according to specified age groups within 26 years from year 1990 [3]. However, at present, no cure has been found for PD, though, there are a variety of drugs that can help to relieve the symptoms. ASN and DDC have attracted the attention of most researchers due to their relevance in PD pathogenesis. ASN is a major component of Lewy bodies that can be found aggregating in the substantia nigra of individuals with PD. The higher the levels of ASN protein, the more severe the pathology of Lewy bodies that are associated with the symptoms of PD [4]. The accumulation of Lewy bodies consequently leads to the damage of the dopamine cells [2], making the targeting of ASN for inhibition a plausible therapeutic pathway for maintaining dopamine levels and managing PD. Several