Research Article

Journal of Chemistry Letters
journal homepage: www.jchemlett.com
ISSN (online) 2717-1892 (print) 2821-0123

In-silico screening, molecular docking, pharmacokinetics studies and design of histone deacetylase inhibitors as anti-Alzheimer agents

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Alzheimer's disease
Design
drug-likeness
binding scores
multitarget-directed ligands

ABSTRACT

Alzheimer's Disease (AD) is a complex illness mechanism and an untreatable ailment that presently brings huge sorrow to patients and their relatives. Presently, the cure for this disease is zero. The existing drugs have several side effects. Therapeutic Chemistry, a vital field of research, has been working tirelessly to develop new treatments that can be effective in curing this disease. Design, molecular docking, and pharmacokinetic assessment (ADMET) methods are used to determine and confirm the sturdy configuration of the receptor pocket. 16 Histone Deacetylase inhibitors have been docked with the acetylcholinesterase target for protein-ligand interaction. Compound 2 was found to possess the highest binding scores of 19.758 kcal/mol. This was used as a template to design several HDAC derivatives, but seven of the designed compounds had higher binding scores and better interaction than the template; 1: -20.031 kcal/mol, 2:-20.583 kcal/mol, 3:-19.925 kcal/mol, 4:-21.639 kcal/mol, **5**:-21.950 kcal/mol, 6:-19.917 kcal/mol, and **7**:-23.289 kcal/mol. The pharmacokinetics evaluation of these designed compounds (ADMET) results showed good drug-likeness and oral bioavailability scores. Based on the binding affinity scores of the designed compounds against AD, the designed compounds have superior pharmacological characteristics and can be used as neuro-therapeutic candidates after rigorous in-silico investigation.

1. Introduction

Alzheimer's disease (AD) is a central nervous system problem involving environmental and genetic factors and is characterized by anomalous actions, a reduction in thinking ability, neuronal loss, confusion, difficulty in communicating, and an inability to reason well. It is one of the key public health challenges that is most problematic to treat, mostly due to the increasing elderly population in the universe today [1-2]. In the onset and progression of AD, some features have been implicated, like membrane structure and lipid production disruption, metal ion dyshomeostasis [3]. Recent research has proposed that some of these characteristics could be twined together with other facets (i.e., protein aggregation) of the illness [4]. As such, quick and immediate medicinal approaches need to be developed for the cure of this disease.Histone deacetylases (HDACs) are residues in histone and non-histone substrates with epigenetic receptor modulators that diacetylated lysine. They can be divided into four classes (class I, class IIa, class IIb, and class IV) [5-6]. An equilibrium between histone-acetylation and deacetylation in normal cells is achieved by the activities of HDACs and HATs, respectively [7]. Some diseases can emerge as a result of an imbalance in the activities of HDACs and HATs in normal cells [8]. For instance, a serious part in oncogenesis via the development of complexes with other proteins is being played by class 1 HDSCs. Also, in AD memory-related dysfunction, class 1 HDACs and HDAC6 are implicated [9-10]. Therefore, treatment of neurodegenerative disorders has been given attention because of the usage of HDACs as inhibitors [11]. In the cortex and hippocampus of AD patients, HDAC2 and HDAC6 are over-expressed. This was shown by research [12–13]. An indication of neurodegenerative diseases, including AD, is an accumulation deviation of insoluble hyperphosphorylated tau (ptau) [14]. Ptau aggregation can be promoted and prevented from being degraded by acetylation of tau at Lys280, leading to reduced cognitive ability [15]. Tau is caused by neurological disorders

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