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Original Research Article

Design of Novel Drugs (P3TZ, H2P3TZ, M2P3TZ, H4P3TZ and M4P3TZ) Based on Zonisamide for Autism Treatment by Binding to Potassium Voltage-gated Channel Subfamily D Member 2 (Kv4.2)

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ABSTRACT

The present research article relates to the discovery of the novel drugs based on Zonisamide to treatment of autism disease. In first step, the electronic properties, reactivity and stability of the said compound are discussed. To attain these properties, the said molecular structure is optimized using B3LYP/6-311++G(d,p) level of theory at room temperature. The frontier molecular orbitals (FMOs) energies are used to calculate the global reactivity indices. Based on these indices, Zonisamide is a high stable compound and has low reactivity. In the next step, the optimized molecular structure of Zonisamide is docked into the potassium voltage-gated channel subfamily D member 2 (Kv4.2) and ligand-receptor interactions are analyzed. After that, the novel molecular structures based on Zonisamide backbone are designed and optimized. Designing the novel drugs are done using changes the backbone of Zonisamide and various functional groups. The interactions of the optimized molecular structures with the said potassium

channel are analyzed using docking study.Based on these studies, ten molecules showed better ligand-receptor binding than Zonisamide. Finally, the physicochemical properties of the title compounds are analyzed. The compounds P3TZ, H2P3TZ, M2P3TZ, H4P3TZ and M4P3TZ are our novel drugs to treatment of autism disease based on the molecular docking and physicochemical properties.

Keywords: *Autism; Drug design; Molecular docking; Molecular simulation; potassium channel; Zonisamide.*

Introduction

Autism spectrum disorders (ASDs) are complex and prevalent neurodevelopmental disorders predominantly diagnosed through observation of a wide variety of atypical behavior, expressed by impairments in socialization, communication, thinking, interests, activities and cognitive skills as well as restricted and repetitive behavior. Autism is considered a heterogeneous condition with both medical and psychiatric comorbidities [1, 2]. Medical comorbidities include gastrointestinal disorders, neuro-inflammation, immune system disorders, vitamin deficiencies, sleep disorders and epilepsy while psychiatric comorbidities include attention-deficit hyperactivity disorder, social anxiety disorder, depression, bipolar disorder and intellectual disability [3]. The risk of premature mortality in ASD patients has been observed to be noticeably higher in comparison with the general population [5-8]. Moreover, this condition imposes a financial burden on families, society and health systems [9, 10]. Several interventions and treatments have been considered for the management of ASD, mostly focusing on ameliorating comorbidities and enhancing the quality of life in patient afflicted with this disorder. The precise mechanism of ASD pathogenesis is not yet fully understood and has been associated with both genetic and non-genetic factors [11-16]. Recent genetic analyses have uncovered important evidence pertaining to the role of potassium channels in etiology of ASD. The A-type voltage-gated potassium channel Kv4.2 is encoded by KCND2. Mutations of the Kv4.2 channel gene have been associated with ASD onset [17]. Furthermore, Kv4.2 mRNA