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RESEARCH ARTICLE

Small Heterocyclic Molecules as Possible $Na_v1.6$ Inhibitors: In Silico Screening and Preliminary Evaluation

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ABSTRACT

Epilepsy is a clinical condition that impairs mental and physical abilities. Although a number of effective drugs for the treatment of epilepsy are present in the market, they are associated with one or more adverse effects. This calls for the need for some new anti-epileptic agents with a safe drug profile. The study, therefore, focused on designing and synthesizing a novel series of Schiff bases of 2-amino-benzimidazole, **A (1–8)**. The synthesized compounds were characterized by physico-chemical parameters, and their structures were confirmed by spectral techniques and elemental analysis. The compounds were tested for their in vivo anti-epileptic potential using maximal electroshock and pentylenetetrazole-induced seizure models. The compounds **A5, A6,** and **A7** were the most promising from the series in both the test models, with percentage inhibition of seizures in the range 62% to 79%, compared to 80% and 82% by the positive control, phenytoin. The molecular docking study was carried out using AutoDock software, and the data were in accordance with the in vivo experimental results. The compounds were also subjected to an in silico ADMET study. The study proposes benzimidazole as a promising scaffold for the development of more such novel anti-epileptic agents, with a good drug profile.

1 | Introduction

In spite of the various programs launched globally by the World Health Organization, the International Bureau for Epilepsy, and the International League Against Epilepsy to bring the disease out of the shadows and to improve care and reduce the disease's impact, there has been large number of cases pertaining to the disease. The WHO reports about 50 million people worldwide to be affected by epilepsy [1, 2]. Anti-epileptic drugs, also called AEDs, have been known to act through various molecular mechanisms, including glutamate-mediated excitatory neurotransmission, voltage-gated ion channels (Na^+ and Ca^{2+}), and GABA-mediated inhibitory neurotransmission. Gamma-amino-butyric acid (GABA) is an inhibitory neurotransmitter that lowers the excitability of neurons in brain cells. GABA-AT, an aminotransferase enzyme, breaks it down. This leads to an increase in the excitability of neurons. When the GABA-AT enzyme is inhibited, the effect is reversed [3, 4]. However, the AEDs available in the market may produce severe side effects, including naupathia, headache, and ataxia [5, 6]. Although they are capable of providing symptomatic relief but may not completely address epileptogenesis. In recent years, drug resistant epilepsy has become a major problem among patients on AEDs [7].

Numerous biological activities are found to be associated with the heterocyclic ring systems. Benzimidazole, also referred to as 1,3-benzodiazole or 1*H*-benzimidazole, has an imidazole ring fused to a benzene ring and possesses nitrogen atoms at positions 1 and 3 [8]. Studies have reported benzimidazole to display activities, such as anticancer [9, 10], antimalarial [11], antimicrobial [12], antileishmanial [13], antitubercular [14], antiviral [15, 16],