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Design, synthesis and molecular docking studies of 5,6-difluoro-1*H*-benzo[*d*]imidazole derivatives as effective binders to $GABA_A$ receptor with potent anticonvulsant activity

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ABSTRACT

In the search for more effective and safer antiepileptic drugs, a series of 5,6-difluoro-1*H*-benzo[*d*]imidazole derivatives (4a-e) were designed and synthesized. Elemental analysis, ^{1}H NMR, ^{13}C NMR and mass spectroscopic techniques were used to confirm the structure and purity of the resultant compounds. Maximum electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ) screenings were used in mice for preliminary anticonvulsant screening. In each of the animals used for anticonvulsant assessment, two compounds, 4d and 4e, demonstrated positive anticonvulsant activity with 100% protection. The most active congeners, compounds 4d and 4e, were quantified to be 2.68 and 3.26 folds, respectively, more potent than the reference medication, carbamazepine, in the MES model. The rotarod technique was used to test all the substances for acute neurotoxicity to detect motor impairment, and all the substances passed the test. Additionally, the in vitro binding studies revealed that compounds 4d and 4e had the most affinity for binding to the $GABA_A$ receptor, with IC_{50} values of 0.74 and 0.18 μM, respectively. Additionally, the GABA concentration in rat brains was examined. The findings indicated that both compounds 4d and 4e may have influenced the GABA system by raising GABA concentration in rat brains. The $GABA_A$ receptor and drug binding modes were examined using molecular docking. Compounds 4d and 4e demonstrated substantial interactions with residues at the $GABA_A$ receptor's benzodiazepine binding site. According to Lipinski's rule of five, all the compounds show promise as potential oral medication candidates. Thus, the current study has offered suitable epilepsy research subjects for further study.

1. Introduction

Epileptic seizures, which are frequent and unpredictable disruptions of regular brain activity, are the main feature of the brain condition epilepsy. On how to define the terms "seizure" and "epilepsy," there is little consensus [1]. Epilepsy can have a variety of origins, including genetic, structural-metabolic, and, frequently, still-unknown factors [2]. Worldwide, there are thought to be 50 million epileptics, 30% of whom are unresponsive to medications [3]. Additionally, epileptic patients have a very high risk of seizure, trauma, hospitalization, and mortality, all of which have a highly detrimental influence on the patient's physical, mental, and social health [4]. More than 20 third-generation anti-epileptic drugs (AEDs) with reasonable advances have been available since the 1980s and are used to treat a variety of seizure types. Although various novel AED classes have been developed, there is still a long way to go before epilepsy may be completely treated [5]. Additionally, these AEDs have significant adverse effects such as neurotoxicity, anemia, hepatic failure, etc., and are ineffective against the 30% of patients with refractory epilepsy [6]. Therefore, there is a pressing need in a clinic for the development of more efficient AEDs,

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