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# 1,3,4-Oxadiazole as a Privileged Scaffold for Anticonvulsant Activity: Design, Syntheses and ADMET Studies

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**Abstract**—The compounds with an –N=C–O– linkage have been widely used in the drug development. In the 1,3,4-oxadiazole ring, substitutions made at position 2 and position 5 make the molecule behave as an anchor for lipophilic groups. The present study focuses on the synthesis of a novel series of 2,5-disubstituted 1,3,4-oxadiazoles using a two-step reaction. The first step involves the synthesis of acid hydrazides from substituted methyl esters, followed by reaction with aromatic carboxylic acids using $POCl_3$ as the cyclizing agent to form the title compounds. All the synthesized compounds were characterized using physicochemical and spectral methods. The compounds were tested for anti-convulsant potential using maximal electroshock seizure and Isoniazid-induced seizure models. The 2-(4-bromophenyl)-5-(2,3-dichlorophenyl)-1,3,4-oxadiazole was found to be the best in the series, with percentage inhibition of 61 and 75% in the MES and the INH models, respectively. Molecular docking study was also carried against the GABA-selective protein, PDB ID 6HUP. The binding energy was predicted in the range of –6.59 to –7.91 kcal/mol. The partition coefficient for the compounds was found to be coordinated with the in vivo experimental results and with the molecular docking prediction data. The in silico ADMET data suggested the compounds to be safe anti-convulsant agents. Thus, 1,3,4-oxadiazole may be a promising pharmacophore for designing effective and safe anticonvulsant agents.

**Keywords:** 1,3,4-oxadiazole, in vivo anticonvulsant activity, maximal electroshock seizure model, isoniazid-induced model, in silico molecular docking, ADMET predictions

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## INTRODUCTION

According to the key facts released by the WHO in the year 2024, around fifty million of the world population experiences epilepsy, which makes it one of the most common neurological conditions [1]. Despite numerous anticonvulsant drugs [2, 3], the associated adverse effects such as vertigo [4], ataxia [5], headache [6], hirsutism [7], hepatotoxicity [8], gastrointestinal [9], alopecia [10] and cardiovascular [11] gravely limit their effectiveness. The examples include, pregabalin [12], stiripentol [13], zonisamide [14], tiagabine [15], lamotrigine [16], levetiracetam [17, 18], and topiramate [19]. Therefore, development of potentially safer and effective antiepileptic drugs remains a challenge [20].

The heterocyclic nucleus has always played a vital role in chemical and life sciences. In particular, the five-membered heterocyclic systems have been found to exhibit a range of biological functions [21], one of which is the 1,3,4-oxadiazole [22]. The potential pharmacological actions of 1,3,4-oxadiazole may be

**Scheme 1.**