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MEDICINAL CHEMISTRY RESEARCH



ORIGINAL RESEARCH

# Design, synthesis, characterization, and molecular modeling studies of novel oxadiazole derivatives of nipecotic acid as potential anticonvulsant and antidepressant agents

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**Abstract** A series of fifteen novel nipecotic acid 1,3,4-oxadiazole hybrids were synthesized with the intent to improve the lipophilicity of nipecotic acid and its penetration through the blood—brain barrier (BBB). The structures of the compounds were established by FT-IR, $^{1}$H-NMR, $^{13}$C-NMR, and elemental analysis. The effect of the synthesized compounds was assessed on motor coordination using the rotarod test in mice. Anticonvulsant activity was evaluated using the subcutaneous pentylenetetrazol (scPTZ) test in mice. Five compounds (**5d**, **5e**, **5g**, **5m**, and **5o**) exhibited significant protection against scPTZ-induced seizures. None of the compounds produced any disruption in motor coordination as observed in the rota-rod test, nor did they elevate the serum levels of biochemical markers related to hepatic and renal toxicity, affirming their relative safety. The derivatives also exhibited significant antidepressant activity, devoid of serotonergic augmentation as assessed using the despair swim test, 5-hydroxytryptophan (5-HTP)-induced head twitch test and learned helplessness test. In in silico docking studies on a homology model on target GABA transporter 1 (GAT1) protein and the most active compound **5e** helped to identify critical enzyme-ligand interactions leading to the inhibition of the GAT1 transporter.

**Keywords** Nipecotic acid · Homology modeling · Anticonvulsant · Antidepressant

## Introduction

Epilepsy is a neurological disorder attributed to hyper synchronous neuronal activity, which leads to the generation of seizures. Epidemiological studies estimate that more than 50 million people are affected with epilepsy worldwide with almost 90% of the affected population residing in developing countries (World Health Organization 2000). Antiepileptic drugs (AEDs) encompass a varied range of molecules acting mostly through: enhancement of γ-aminobutyric acid (GABA) mediated inhibitory neurotransmission, modulation of voltage-gated ion channels ($Na^{+}$, $Ca^{++}$), and reduction of excitatory, particularly glutamate-mediated, neurotransmission (Saravanan et al. 2012). Despite these therapeutic interventions, no complete cure for epileptic conditions exists. The available AEDs are known to suppress the seizure symptoms of epilepsy but are unable to affect the natural course of the epileptogenic process (Shorvon et al. 2015). Thus, the efficacies of many AEDs are marred by dose-related toxicities and diverse adverse drug reactions, including minimal brain impairment, megaloblastic anemia, and death from aplastic anemia

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