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Review article

The importance of triazole scaffold in the development of anticonvulsant agents

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ABSTRACT

Epilepsy is one of the most important neurological disorders with high prevalence worldwide. Many epileptic patients are not completely treated with available drugs and need multiple therapies. Also, many antiepileptic drugs have shown unwanted side effects and drug interactions. Therefore there are continuing interests to find new anticonvulsant drugs. Triazole ring has been found in the structure of many compounds with diverse biological effects. Due to the success of several triazole-containing drugs that entered the pharmaceutical market as CNS-active drugs, this class of heterocyclic compounds has great importance for discovery and development of new anticonvulsant drugs. In this article, we have tried to summarize the latest efforts which have been made in the design and development of triazole-derived anticonvulsant agents.

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1. Introduction

Epilepsy is a central nervous system (CNS) disorder characterized by rapid and excessive electrical neuronal discharges [1]. The imbalance of excitatory and inhibitory processes within neurons of the brain leads to uncontrolled convulsions and lack of consciousness [2]. The main strategy for epilepsy treatment is pharmacotherapy with antiepileptic or anticonvulsant drugs [3]. In general, the antiepileptic drugs act through several ways: (i) restriction of excitatory processes by blocking excitatory amino acid receptors and/or voltage activated sodium channels, (ii) enhancement of inhibitory processes by potentiating the activity of the γ-aminobutyric acid (GABA) as brain's inhibitory neurotransmitter, and (iii) stabilization of thalamic neurons through inhibition of T-type calcium channels [4].

Based on the epidemiological studies, at least 50 million people worldwide suffer from epilepsy while in less than 70% of the patients seizures are completely controlled by using available antiepileptic drugs [5]. In some cases monotherapy is not sufficient and poly-therapy with multiple drugs is required for successful treatment [6]. Also, many epileptic patients suffer from side effects of anticonvulsant agents due to the long-term medication [7]. In recent years, investigations are continued to discover new anticonvulsant drugs and several new drugs such as felbamate, gabapentin, lacosamide, eslicarbazepine acetate, lamotrigine, oxcarbazepine, pregabaline, levetiracetam, retigabine, stiripentol, rufinamide, tiagabine, zonisamide, vigabatrine and topiramate entered to the market [8,9]. However, due to the low efficiency, drug resistance and toxicity of existing drugs, new attempts in this area are still necessary [10].

The search for new anticonvulsant drugs has traditionally been focused on compounds that suppress seizures in a symptomatic fashion. Several animal models including maximum electroshock (MES), pentylenetetrazole (PTZ), thiosemicarbazide (TSZ), isoniazid (INH), 3-mercaptopropionic acid (3MPA) and strychnine (STR)-induced seizures methods were widely used in the preclinical discovery and development of novel anticonvulsant agents [11–13]. However, the MES and PTZ-induced seizures tests are the most widely used animal models of epilepsy to characterize the anticonvulsant activity [14].

1,2,4-Triazole is a five member heterocycle with two carbons and three nitrogen atoms and molecular formula $C_2H_3N_3$. This compound is a basic aromatic heterocycle with two different tautomeric forms (Fig. 1) [15]. It should be noted that three different tautomers **A**, **B** and **C** (N1–H, N2–H, and N4–H, respectively) are possible for the substituted 1,2,4-triazoles (Fig. 2) [16,17].

A literature survey revealed that triazole derivatives possess variety of biological properties including antimicrobial [18], antifungal [19–21], antileishmanial [22], antiviral [23], antitubercular [24], anticancer [25,26], antioxidant [27], anticholinesterase [28], anti-inflammatory [29,30], antidepressant, antianxiety and anticonvulsant activities [31]. In particular, many well-known CNS active drugs such as loreclezole (**1**), rizatriptan (**2**), estazolam (**3**), alprazolam (**4**), etizolam (**5**), triazolam (**6**), rilmazafone (**7**), nefazodone (**8**) and trazodone (**9**) are triazole derivatives (Fig. 3).

Due to the importance of triazole scaffold in the discovery and development of CNS active drugs, we intended to review triazole derivatives which have been recently synthesized and had notable anticonvulsant activity. These derivatives have been classified into the following structural categories: *N*-(arylalkyl)triazoles, *N*-aryltriazoles, 3,5-disubstituted-4*H*-1,2,4-triazoles, triazolones and triazole thiones, and fused-triazoles.

2. *N*-(Arylalkyl)triazoles

N-(Arylalkyl)azoles are a distinct class of anticonvulsant agents exemplified by imidazole analogs nafimidone (**10**) and denzimol (**11**, Fig. 4) [32,33]. It seems that these compounds with lipophilic aryl ring linked by an alkylene bridge to nitrogen of azole could be better penetrating to the blood–brain barrier. Based on the structure-activity relationship studies, the presence of oxygen functional group (such as carbonyl, carbamoyl, ethylene dioxy, methoxy, acyloxy, and hydroxy substituents) on the alkylene bridge can improve their anticonvulsant potencies [34,35]. The 1,2,4-triazole analog loreclezole (**1**, Fig. 4) is a representative anticonvulsant with broad-spectrum activity [36,37]. In the loreclezole structure, the lipophilic 2,4-dichlorophenyl moiety is connected to the triazole ring via a two carbons linker containing electronegative chlorine atom. In vivo studies have been suggested that loreclezole acts on the neuromodulatory site within the $GABA_A$ receptor complex, which is unlikely to be a benzodiazepine receptor [36]. Indeed, loreclezole is a positive modulator of $GABA_A$ receptor with selectivity for $\beta2/\beta3$-over $\beta1$-subunit [37,38].

A series of (arylalkyl)azoles namely [1-(2-naphthyl)-2-(1,2,4-triazol-1-yl)ethanone oximes **12** and oxime ethers **13** (Fig. 4) were designed and synthesized by Karakurt et al. as nafimidone analogs. The synthesized compounds were evaluated by MES and PTZ tests in mice and rats. Based on the anticonvulsant and neurotoxicity screening data, compounds with small alkyl groups such as methyl, ethyl, propyl and allyl showed better activity in the

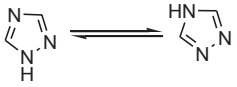

Fig. 1. Tautomeric forms of triazole.

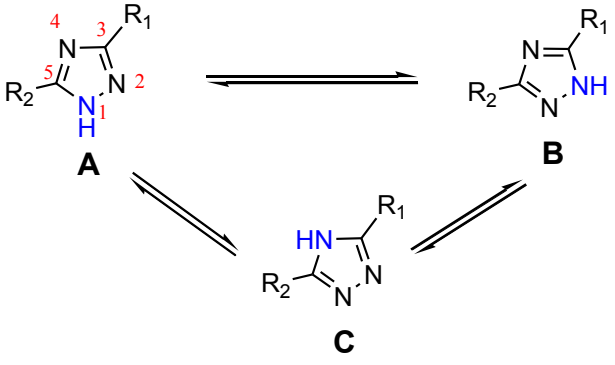

Fig. 2. Tautomerism in substituted 1,2,4-triazoles.