World Journal of Pharmaceutical Science and Research
www.wjpsronline.com
Research Article
ISSN: 2583-6579
SJIF Impact Factor: 5.111
Year - 2025
Volume: 4; Issue: 1
Page: 712-722

DERIVATIVES OF 1,2,4-TRIAZOLE AS NEW CANDIDATES FOR THE TREATMENT OF EPILEPTIC DISORDERS

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Article Received: 05 January 2025 | | ***Article Revised: 26 January 2025*** | | ***Article Accepted: 17 February 2025***

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DOI: https://doi.org/10.5281/zenodo.14939484

How to cite this Article: Borysenko N. M., Hubenko I. Ya., Parchenko V. V., Bushueva I. V., Demchenko A. V., Sukhovyi G. P. (2025). DERIVATIVES OF 1,2,4-TRIAZOLE AS NEW CANDIDATES FOR THE TREATMENT OF EPILEPTIC DISORDERS. World Journal of Pharmaceutical Science and Research, 4(1), 712-722. https://doi.org/10.5281/zenodo.14939484

ABSTRACT

Epilepsy is one of the most common neurological disorders. The use of antiepileptic drugs to control seizures is a crucial aspect of epilepsy treatment and other seizure-associated conditions. However, it presents several challenges related to effectiveness, side effects, and individualized treatment adaptation. In some cases, the disease may become resistant to specific anticonvulsant drugs, meaning that seizures persist despite medication use. This necessitates a shift in treatment approaches and the search for alternative therapies. Derivatives of 1,2,4-triazole are widely utilized in pharmaceutical practice as active substances in effective synthetic drugs. Many of these compounds exhibit relatively low toxicity, making them attractive for clinical application. Some of them can act through multiple mechanisms simultaneously, allowing for the effective treatment of various types of seizures. Conducting research aimed at evaluating the mechanisms of action of triazole derivatives, their impact on neuronal activity, as well as studying their toxicity and pharmacokinetic characteristics, is particularly relevant at this stage. Considering that epilepsy is one of the most widespread neurological diseases worldwide - with approximately 50 million people affected, accounting for 1% of the global population, according to the World Health Organization - the scientific interest in this issue is well justified.

KEYWORDS: 1,2,4-triazoles, anticonvulsant agents, mechanisms of anticonvulsant activity, epilepsy therapy, computer prediction, in vivo studies, organic molecules, physicochemical properties.

INTRODUCTION

Epilepsy is one of the most common neurological disorders. Many individuals continue to experience seizures despite medical and surgical treatment, highlighting the urgent need for the development of new antiepileptic (anticonvulsant) drugs. The use of antiepileptic drugs to control seizures is a crucial aspect of epilepsy treatment and other conditions associated with seizures. However, this approach presents several challenges related to efficacy, side effects, and the individualized adaptation of therapy.

Anticonvulsant drugs do not always have the same effect on all patients. There is no universal solution, as what works for one person may prove ineffective for another. Depending on the type of seizures, overall health condition, and other factors, a physician may need to make several attempts to identify the most suitable drug and dosage. This process can take a considerable amount of time, during which the patient may continue to experience recurrent seizures..

Anticonvulsant drugs can have serious side effects, including drowsiness, dizziness, impaired coordination, memory problems, depression, and behavioral changes. In some cases, they may lead to dependence or other psychiatric disorders, complicating treatment. Additionally, these drugs can interact with other medications taken by the patient, particularly if they suffer from chronic conditions requiring additional pharmaceutical treatments. Such interactions may reduce treatment efficacy or increase the risk of adverse effects.

Regular monitoring of drug levels in the bloodstream is essential to ensure effectiveness and prevent toxicity. This requirement places an additional burden on both patients and healthcare providers, as continuous health monitoring is necessary to adjust treatment when needed.

In some cases, the disease may develop resistance to specific anticonvulsant drugs, meaning that seizures persist despite medication use. This necessitates a shift in treatment strategies and the exploration of alternative therapies.

Derivatives of 1,2,4-triazole are widely used in pharmaceutical practice as active substances in effective synthetic drugs.[1,2] Additionally, they represent a class of organic compounds that have attracted scientific interest due to their potential in the treatment of various neurological disorders, particularly as anticonvulsant agents.[3] This interest is driven by their ability to interact with specific neurotransmitters and receptors in the central nervous system, helping to reduce the frequency and severity of seizures.[4]

Many of these compounds exhibit relatively low toxicity, making them attractive for clinical application. Some of them can act through multiple mechanisms simultaneously, enabling the effective treatment of different types of seizures.[5]

Thus, the **aim** of this study is to investigate the anticonvulsant properties of 1,2,4-triazole derivatives and assess their efficacy as potential drugs for the treatment of epilepsy and other seizure disorders. Specifically, the research focuses on evaluating the mechanisms of action of triazole derivatives, their impact on neuronal activity, as well as studying their toxicity and pharmacokinetic characteristics to determine their prospects for clinical application.

MATERIALS AND METHODS

Docking modeling was used to determine the interaction mechanism of the studied compounds with the binding cavity of the human voltage-gated sodium channel (VGSC). The selected compounds were also evaluated using an ADME-

Tox testing panel, which included parallel artificial membrane permeability analysis (PAMPA), single-cell gel electrophoresis (SCGE), and cytotoxicity assessment in HepG2 cells.

The obtained results demonstrated that unbranched alkyl chains ranging from butyl to hexyl, attached to the 1,2,4-triazole core, are crucial for both anticonvulsant activity and strong interaction with VGSCs. A combination of in vivo, *in vitro*, and in silico studies highlights that 4-alkyl-5-substituted-1,2,4-triazole-3-thiones are promising agents in the development of new anticonvulsant drugs.

In the following study, oxime and oxime ether derivatives of [1-(2-naphthyl)-2-(1,2,4-triazol-1-yl)ethanone] were synthesized as potential anticonvulsant and antimicrobial compounds.[2] The oxime was synthesized via the reaction of ketone with hydroxylamine hydrochloride. O-alkylation of the oxime with various alkyl halides yielded oxime ether derivatives.

The anticonvulsant activity of the compounds was evaluated using the maximal electroshock (MES) test and the subcutaneous pentylenetetrazol (PTZ) test in mice and rats, following the procedures of the Anticonvulsant Screening Program of the U.S. National Institutes of Health. Neurotoxicity was assessed using the rotarod test in mice and the positional sense and grip strength tests in rats. A series of 3- and 5-aryl-1,2,4-oxadiazole derivatives was synthesized and tested for anticonvulsant activity in various seizure models.[3] These compounds exhibited significant activity in both PTZ and MES seizure models. Neurotoxicity (rotarod test) was observed at ED_{50} of 335 mg/kg.

Researchers identified several compounds that acted as selective GABA-potentiating agents without interaction with the benzodiazepine binding site. A series of 1-alkoxy-4-(1H-1,2,4-triazol-1-yl)phthalazine derivatives was synthesized using 2,3-dihydrophthalazine-1,4-dione as the starting material.[4]

The structures of the compounds were characterized using elemental analysis, IR, NMR (^{1}H-NMR), and PMR spectroscopy. The anticonvulsant activity of the compounds was assessed using the MES test after intraperitoneal injection in mice. Among the synthesized compounds, the most active one demonstrated: The most active one demonstrated: ED_{50} = 28.9 mg/kg; TD_{50} = 173.6 mg/kg; Protective Index (PI) = 6.0.

RESULTS AND DISCUSSION

The treatment of epilepsy remains a complex challenge, as nearly 30% of patients suffer from pharmacoresistant forms of the disease. Therefore, there is an urgent need to identify new candidate antiepileptic drugs.

This study demonstrated that 4-alkyl-5-substituted-1,2,4-triazole-3-thione derivatives exhibit strong anticonvulsant activity in the maximal electroshock (MES) seizure model.[1] The authors investigated the influence of chemical structure on the anticonvulsant activity of 1,2,4-triazole-3-thione-based molecules and their binding interactions with voltage-gated sodium channels (VGSCs) and GABA receptors.

The next study focused on the synthesis of two series of compounds: 8-alkoxy-5-(4H-1,2,4-triazol-4-yl)quinolines and 8-alkoxy-5-(2H-1,2,4-triazol-3-one-4-yl)quinolines.[5] The anticonvulsant activity of these compounds was evaluated using the maximal electroshock seizure (MES) test and the rotarod test.

Among the synthesized compounds, 8-oxy-5-(4H-1,2,4-triazol-4-yl)quinoline was identified as the most active, with: ED_{50} = 8.80 mg/kg; TD_{50} = 176.03 mg/kg;

Protective Index (PI) = 20.0. This compound demonstrated lower neurotoxicity than all other synthesized compounds and was significantly less neurotoxic than the reference drug carbamazepine.

Furthermore, its effectiveness against seizures induced by pentylenetetrazol (PTZ), 3-mercaptopropionic acid, and bicuculline suggests a broad spectrum of activity. Its mechanisms of action, likely involving inhibition of voltage-gated ion channels and modulation of GABAergic activity, may contribute to its anticonvulsant effects.

Additionally, a series of new purine derivatives containing triazole and other heterocyclic substituents was synthesized and preliminarily evaluated for anticonvulsant activity and neurotoxicity using the MES test, subcutaneous PTZ (scPTZ) test, and rotarod neurotoxicity test (TOX).[6]

Among the tested compounds, 9-decyl-6-(1H-1,2,4-triazol-1-yl)-9H-purine emerged as the most potent, with: Average effective dose (ED_{50}) = 23.4 mg/kg; High protective index; (PI) > 25.6 after intraperitoneal injection in mice. This compound also exhibited significant oral activity against MES-induced seizures in mice, with: ED_{50} = 39.4 mg/kg; PI > 31.6.

These results indicate that the compound demonstrates superior anticonvulsant activity and safety compared to commercially available drugs carbamazepine and valproate in MES, scPTZ, and TOX models.

Also of interest is the work devoted to the design and synthesis of new substituted 5-alkoxythieno[2,3-e][1,2,4]triazolo[4,3-c]pyrimidine derivatives derived from 3-amino-2-thiophenecarboxylic acid methyl ester.[7] The final compounds were tested for anticonvulsant activity in vivo using the maximal electroshock (MES) and subcutaneous pentylenetetrazole (scPTZ) tests. Neurotoxicity (NT) was tested using the rotarod test. Analysis of the relationship between structure and anticonvulsant activity showed that the most effective structural compound is a substituted phenol, especially when it is substituted with one chloro-, fluoro- or trifluoromethyl group (in the meta position), or two chlorine atoms. These molecules had high activity according to the MES and scPTZ models. Two series of 1-alkyl-4-(4H-1,2,4-triazol-4-yl)piperidines and 1-alkyl-4-(2H-1,2,4-triazol-3-one-4-yl)piperidines were synthesized and their anticonvulsant and antibacterial activities were evaluated.[8]

Significant interest is also drawn to a study focused on the design and synthesis of novel substituted derivatives of 5-alkoxythieno[2,3-e][1,2,4]triazolo[4,3-c]pyrimidine, obtained from the methyl ester of 3-amino-2-thiophenecarboxylic acid.[7] The final compounds were evaluated for in vivo anticonvulsant activity using the maximal electroshock (MES) test and the subcutaneous pentylenetetrazol (scPTZ) test. Neurotoxicity (NT) was assessed using the rotarod test. Structure-activity relationship (SAR) analysis demonstrated that the most effective structural compound was a substituted phenol, particularly when substituted with a single chloro-, fluoro-, or trifluoromethyl group (in the meta-position) or with two chlorine atoms. These molecules exhibited high activity in both the MES and scPTZ models.

Additionally, two series of compounds—1-alkyl-4-(4H-1,2,4-triazol-4-yl)piperidines and 1-alkyl-4-(2H-1,2,4-triazol-3-one-4-yl)piperidines - were synthesized and evaluated for anticonvulsant and antibacterial activity.[8]

Pharmacological tests showed that three of the synthesized compounds exhibit 100% protection at a dose of 100 mg/kg. 4-(1-Octylpiperidin-4-yl)-2,4-dihydro-3H-1,2,4-triazol-3-one was found to be the most active compound in this study, with ED_{50} of 65.4 mg/kg and TD_{50} of 241.2 mg/kg, corresponding to a PI of 3.6. The authors designed, synthesized, and tested a series of 1-substituted 6-(4H-1,2,4-triazol-4-yl)-3,4-dihydroquinolin-2(1H)-ones for antidepressant and anticonvulsant activity.[9] In the maximal electroshock seizure test, the compounds demonstrated a moderate level of anticonvulsant activity, providing 100% protection at a dose of 100 mg/kg. None of the synthesized compounds showed neurotoxicity in the rotarod test at a dose of 100 mg/kg. Among the synthesized compounds, 3-heptyloxy-4-(4-(hexyloxy)-phenyl)-4H-1,2,4-triazole was the most active anticonvulsant compound.[10]

In the anti-MES test, it showed an average effective dose (ED_{50}) of 37.3 mg/kg, an average toxic dose (TD_{50}) of 422.5 mg/kg, and a protective index (PI) of 11.3, which is significantly higher than that of the reference drug carbamazepine (PI = 6.4). In addition to demonstrating anti-MES effectiveness, the compound was also found to be effective against seizures induced by pentylenetetrazol, 3-mercaptopropionic acid, and bicuculline, suggesting that GABA-mediated mechanisms may be involved in its anticonvulsant activity, such as: Enhancement of GABAergic neurotransmission or activity; GABA receptor activation; Inhibition of GABA-T.

Another research group developed and synthesized a series of 2-substituted-6-(4H-1,2,4-triazol-4-yl)benzo[d]oxazoles.[11] Their anticonvulsant activity was evaluated using the maximal electroshock seizure (MES) model and subcutaneous pentylenetetrazol (scPTZ) model in mice. All compounds exhibited anti-MES activity to varying degrees, and some proved to be the most promising, with ED_{50} values of 31.7 mg/kg and 12.7 mg/kg, respectively.

Based on the hybridization of (arylalkyl)triazoles and aroylhydrazones, a series of phenacyltriazole hydrazones was developed as new anticonvulsant agents.[12] The target compounds were easily synthesized from the corresponding phenacyltriazoles and aryl acid hydrazides and were characterized using IR, NMR, and mass spectrometry. Evaluation of the anticonvulsant activity of the synthesized compounds in vivo using the MES and PTZ tests showed that they were more effective in the MES model than in the PTZ test.

All compounds showed 33-100% protection against MES-induced seizures at a dose of 100 mg/kg. However, the isonicotinic acid hydrazide derivative showed the best activity profile in both models. Molecular docking studies of the compound with different targets (NMDA, AMPA, GABA_A, and sodium channels) suggested that the compound acts predominantly through GABA_A receptors. In silico molecular property prediction showed that all compounds have favorable oral bioavailability and blood-brain barrier (BBB) permeability.

Histamine H_3 receptor (H_3R) antagonists are emerging as a promising therapeutic approach for epilepsy treatment. This study designed and synthesized novel non-imidazole H_3R antagonists by hybridizing the H_3R pharmacophore (an aliphatic amine with a propyloxy chain) with a 1,2,4-triazole fragment.[13]

Most antagonists obtained in this study exhibited moderate to strong activity in a luciferase screening assay using a cAMP-response element (CRE). At the same time, compounds with higher H_3R-antagonistic activity provided seizure protection in the maximal electroshock (MES) model in mice. Moreover, MES-induced seizure protection was completely abolished when mice were simultaneously treated with RAMH, a CNS-penetrating H_3R agonist.

Another study synthesized a series of 3,6-substituted-1,2,4-triazolo-1,3,4-thiadiazole derivatives and evaluated their anticonvulsant activity and neurotoxicity.[14] The structures of the synthesized compounds were confirmed through elemental analysis and spectral data. These compounds exhibited potent anticonvulsant activity, comparable to standard drugs phenytoin and carbamazepine.

A series of 6-alkoxy-[1,2,4]triazolo[4,3-b]pyridazine derivatives was also synthesized.[15] In the anti-MES test, the compounds demonstrated: ED_{50} = 17.3 mg/kg; TD_{50} = 380.3 mg/kg; Protective Index (PI) = 22.0. This PI value was significantly superior to that of the reference drugs. In a subsequent test, one compound had an average hypnotic dose (HD_{50}) of 746.6 mg/kg, demonstrating a substantially better safety margin compared to reference drugs.

The presented study describes the synthesis and anticonvulsant activity of 7-(substituted-phenyl)-6,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidin-5(4H)-ones and their derivatives.[16] Most of the synthesized compounds exhibited potent anticonvulsant activity in the maximal electroshock seizure (MES) test.

The most promising compound demonstrated significant anticonvulsant activity in the MES test, with: ED_{50} = 19.7 mg/kg. Additionally, it exhibited a wide safety margin, with a protective index (PI) significantly higher than that of standard drugs. Furthermore, the compound's effectiveness against seizures induced by pentylenetetrazol, isoniazid, thiosemicarbazide, 3-mercaptopropionic acid, and bicuculline in chemically induced seizure tests suggests that it exhibits a broad spectrum of activity across multiple models.

This finding indicates that the compound likely operates through multiple mechanisms of action, including: Inhibition of voltage-gated ion channels; Modulation of GABAergic activity. A series of 6-phenyl-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine derivatives was developed, considering the broad biological activity of 1,2,4-triazoles and their heterocyclic derivatives.[17] Pharmacological results demonstrated that most compounds exhibited a certain degree of anticonvulsant activity. Among them, 6-(4-chlorophenyl)-7H-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazine was identified as the most promising compound, with: ED_{50} = 40.9 mg/kg; Protective Index (PI) = 6.5.

Epilepsy is the most common neurological disease, affecting about 1% of the world's population. There is an urgent need to develop new antiepileptic drugs with higher efficacy and lower toxicity. In this work, a series of new 6-(substituted-phenyl)thiazolo[3,2-b][1,2,4]triazole derivatives were synthesized and their anticonvulsant activity was tested using maximal electroshock (MES) and subcutaneous pentylenetetrazole (PTZ), which are the most common seizure models for early identification of anticonvulsant drug candidates.[18] Their neurotoxicity was determined using the rotarod test. Among these compounds, 6-(4-fluorophenyl)thiazolo[3,2-b][1,2,4]triazole demonstrated selective protection against MES-judgment with an ED50 value of 49.1 mg/kg and a TD50 value of 94.1 mg/kg, providing the compound with a protective index (PI = TD50/ED50) of 1.9 in the MES test.

Epilepsy is the most common neurological disorder, affecting approximately 1% of the global population. Currently, there is an urgent need to develop new antiepileptic drugs with higher efficacy and lower toxicity levels. In this study, a series of novel 6-(substituted-phenyl)thiazolo[3,2-b][1,2,4]triazole derivatives was synthesized and tested for anticonvulsant activity using the maximal electroshock seizure (MES) test and the subcutaneous pentylenetetrazol (PTZ) test, which are the most commonly used seizure models for the early identification of potential anticonvulsant drug candidates.[18] Neurotoxicity was assessed using the rotarod test. Among these compounds, 6-(4-

fluorophenyl)thiazolo[3,2-b][1,2,4]triazole demonstrated selective protection against MES-induced seizures, with: ED_{50} = 49.1 mg/kg; TD_{50} = 94.1 mg/kg; Protective Index (PI = TD_{50} / ED_{50}) = 1.9 in the MES test.

The triazole structure has attracted significant interest due to its broad spectrum of biological activity, including antitumor, anti-inflammatory, antimicrobial, antiviral, and anticonvulsant effects. As part of the presented research, several novel 7-substituted 5-phenyl-[1,2,4]triazolo[1,5-a]pyrimidines were synthesized by incorporating a triazole fragment into the pyrimidine ring.[19] Their anticonvulsant activity was evaluated using the maximal electroshock seizure (MES) test. Carbamazepine and valproate were used as positive control drugs for anticonvulsant activity (ED_{50} = 11.8 mg/kg and 272 mg/kg, respectively). Among the tested compounds, 7-(heptyloxy)-5-phenyl-[1,2,4]triazolo-[1,5-a]pyrimidine exhibited potent anticonvulsant activity, with: ED_{50} = 84.9 mg/kg. This activity was weaker than that of carbamazepine but superior to valproate.

Another study synthesized a new series of 7-substituted [1,2,4]triazolo[4,3-f]pyrimidine derivatives as potential anticonvulsant agents.[20] Their anticonvulsant activity was evaluated using the maximal electroshock seizure (MES) test, while neurotoxicity was assessed using the rotarod neurotoxicity test. Pharmacological results demonstrated that 7-(4-chlorophenoxy)-[1,2,4]triazolo[4,3-f]pyrimidine was among the most active agents, with: ED_{50} = 34.7 mg/kg; TD_{50} = 262.9 mg/kg; Protective Index (PI = TD_{50} / ED_{50}) = 7.6. Additionally, the authors synthesized a series of novel 5-alkoxy-[1,2,4]triazolo[4,3-a]pyridine derivatives and evaluated their anticonvulsant activity and neurotoxicity using the MES test and rotarod test, respectively.[21]

The most promising compounds, 5-(4-chlorophenoxy)-[1,2,4]triazolo[4,3-a]pyridine and 5-(4-bromophenoxy)-[1,2,4]triazolo[4,3-a]pyridine, exhibited: Average effective doses (ED_{50}) of 13.2 mg/kg and 15.8 mg/kg and Protective index (PI) values of 4.8 and 6.9, respectively. Additionally, 2,5-disubstituted [1,2,4]triazolo[1,5-a]pyrimidin-7(4H)-ones and eight novel 2,5-disubstituted [1,2,4]triazolo[1,5-a]pyrimidine amino derivatives based on the new marine natural product esramycin were identified as promising anticonvulsant agents.[22] Their antiepileptic activity was evaluated using the 4-aminopyridine (4-AP)-induced hyperexcitability model in primary cultured neocortical neurons. Five compounds containing the [1,2,4]triazolo[1,5-a]pyrimidin-7(4H)-one core exhibited significant antiepileptic activity. A preliminary structure-activity relationship (SAR) analysis suggested that the pyrimidin-7(4H)-one moiety is an essential “active core” for antiepileptic activity.

In the search for more effective and safer antiepileptic drugs, a series of 2,5-disubstituted [1,2,4]triazolo[1,5-a]pyrimidin-7(4H)-one derivatives was designed and synthesized.[23] For *in vitro* phenotypic screening, spontaneous Ca^{2+} oscillations in cortical neurons were used. The maximal electroshock seizure (MES) test and pentylenetetrazol (PTZ) test were employed to assess anticonvulsant activity, while the rotarod test was used to evaluate neurotoxicity. The active compounds in the *in vitro* model were particularly effective in the pentylenetetrazol (PTZ) model, but not in the maximal electroshock (MES) model. More importantly, they exhibited lower neurotoxicity compared to well-known anticonvulsant drugs. Additionally, 4-methyltetrazolo[1,5-a]quinoxaline was synthesized via azide cyclocondensation of 2-chloro-3-methylquinoxaline.[24] The reaction with aromatic aldehydes yielded 4-styryltetrazolo[1,5-a]quinoxalines. Ring closure was achieved through the reaction of orthoesters with trifluoroacetic acid, forming 4-methyl-1-(substituted)[1,2,4]triazolo[4,3-a]quinoxalines. Some of the synthesized compounds were tested in vivo for anticonvulsant activity. However, only a few demonstrated promising results. Additionally, a series of 5-substituted-[1,2,4]triazolo[4,3-a]quinazolines was synthesized.[25] The anticonvulsant effects and neurotoxicity of

these compounds were evaluated using the maximal electroshock seizure (MES) test and the rotarod test following intraperitoneal administration in mice.[25]

Pharmacological studies revealed that 5-pentyloxy-[1,2,4]triazolo[4,3-a]quinazoline was the most potent compound, with: ED_{50} = 19.7 mg/kg; Protective Index (PI = TD_{50} / ED_{50}) = 6.2. To elucidate the possible mechanism of anticonvulsant activity, the compound was tested in several chemically induced seizure models. The results demonstrated its effectiveness against seizures induced by pentylenetetrazol, isoniazid, 3-mercaptopropionic acid, and thiosemicarbazide. These findings suggest that the anticonvulsant effects of this series of compounds may be mediated through: Enhancement of γ-aminobutyric acid (GABA)ergic neurotransmission; Activation of glutamate decarboxylase (GAD); Inhibition of α-oxoglutarate aminotransferase (GABA-T) in the brain.

Among the studied 4-R-[1,2,4]triazolo[4,3-a]quinazolin-5(4H)-ones, several compounds demonstrated a wide safety margin, with protective index (PI) values significantly higher than those of currently used drugs.[26] Some compounds exhibited significant oral activity against MES-induced seizures in mice, with: ED_{50} = 88.02 mg/kg; ED_{50} = 94.6 mg/kg. Additionally, a series of novel purines containing triazole and other heterocyclic substituents was synthesized and evaluated for preliminary anticonvulsant activity and neurotoxicity using the maximal electroshock seizure (MES) test, subcutaneous pentylenetetrazol (scPTZ) test, and rotarod neurotoxicity test (TOX).[27]

Among the studied compounds, 9-decyl-6-(1H-1,2,4-triazol-1-yl)-9H-purine was identified as the most potent, with: ED_{50} = 23.4 mg/kg; High protective index (PI > 25.6) after intraperitoneal administration in mice. To identify new compounds with higher anticonvulsant activity and lower neurotoxicity, a new series of 6-substituted pyrido[3,2-d]pyridazine derivatives was synthesized using furo[3,4-b]pyridine-5,7-dione as the starting material.[28] Experimental results revealed that N-m-chlorophenyl-[1,2,4]triazolo[4,3-b]pyrido[3,2-d]pyridazin-6-amine was the most potent anticonvulsant, with: ED_{50} = 13.6 mg/kg; Protective Index (PI = TD_{50} / ED_{50}) = 7.2 in the MES test. Additionally, N-m-chlorophenyl-[1,2,4]tetrazolo[5,1-b]pyrido[3,2-d]pyridazin-6-amine exhibited significant anticonvulsant activity in the MES test, with: PI = 13.4. This compound was found to be safer than the commercially available drug carbamazepine.

The authors also investigated the anticonvulsant activity of the synthesized compounds using maximal electroshock seizure (MES) models and chemically induced seizure models.[29] 5-Hexyl-[1,2,4]triazolo[4,3-a]quinoxalin-4(5H)-one was found to be safer than carbamazepine in the MES test following intravenous administration. It also provided protection against chemically induced seizures.

Two series of 8-alkoxy-4,5-dihydrobenzo[b][1,2,4]triazolo[4,3-d][1,4]thiazepine derivatives were synthesized and evaluated for anticonvulsant activity using the maximal electroshock seizure (MES) test.[30] All obtained compounds exhibited significant efficacy. Among them, the most promising compound demonstrated: ED_{50} = 26.3 mg/kg; Protective Index (PI) = 12.6. The compound's effectiveness against seizures induced by pentylenetetrazol, 3-mercaptopropionic acid, and bicuculline suggests the involvement of two potential mechanisms of action in its anticonvulsant activity: Inhibition of voltage-gated ion channels; Modulation of GABAergic activity.

CONCLUSIONS

1,2,4-Triazole derivatives exhibit great potential as anticonvulsant agents, particularly for patients with drug-resistant epilepsy. However, their clinical application requires further research to confirm their efficacy and safety, as well as to achieve a better understanding of their mechanisms of action. In this study, we conducted a systematic analysis of recent literature sources regarding the anticonvulsant properties of 1,2,4-triazole derivatives. Special attention was given to the various mechanisms of action, the efficacy of these compounds, and the structure-activity relationship (SAR) between their chemical structure and pharmacological effects.

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