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DEVELOPMENT OF HYBRID MOLECULES BASED ON 1,2,4 TRIAZOLE FOR COMBINED ANTICONVULSANT THERAPY

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ABSTRACT

The article is devoted to the systematization of modern data on the synthesis of derivatives of 1,2,4-triazole with potential anticonvulsant activity. The unique properties of 1,2,4-triazole as a universal heterocyclic platform that ensures stability, high bioavailability and pharmacological activity are considered. The strategies of molecular modeling of hybrid molecules based on triazole with various pharmacofores that show antiviral, antifungal, antitumor and immunomodulatory properties are analyzed. Particular attention was paid to the Piranian compounds [3,4-C] pyridine nucleus, which found high anticonvulsant, anxiolytic and antidepressant activity. Based on the analysis of literature over the last 10 years, the relationship between structural features, physicochemical characteristics and pharmacological effect has been established. The results create the basis for the development of new anti -epileptic drugs with high efficiency and safety, in particular through purposeful design of molecules.

KEYWORDS: derivatives of 1.2,4-triazole, anticonvulsant activity, epilepsy, treatment, molecular design, properties of compounds, «structure-act»

1. INTRODUCTION

Derivatives of 1,2,4-triazole occupy a special place in the development of modern science, because this structure has opened great prospects for the creation of new biologically active substances.[1] Domestic scientific schools have made a significant contribution to the study and practical use of these compounds, laying the basis for the emergence of unique Ukrainian drugs.[2,3] The achievements of Ukrainian scientists clearly demonstrate their scientific potential and the ability to create innovative solutions of world level. Examples are original medicines such as Trifusol-Neo and Vetmicoderm ™, which have expanded veterinary medicine, as well as a plant for Fortis Combi Plant, which has become a valuable tool in stimulating growth and development of crops. These developments are convincingly proved: Ukrainian scientists not only have high professionalism, but also form new areas of research, capable of competing with the leading world centers.[4] The scale of their work and skill in combination of fundamental knowledge with practical needs is the true heritage of national science.

A rather promising area of modern medical and pharmaceutical chemistry is molecular modeling of compounds based on 1,2,4 triazole in combination with different pharmacofores.[5] This approach opens wide opportunities for the creation of new biologically active substances with fundamentally new properties. 1,2,4-triazole is a universal heterocyclic platform, which is well known for its stability, ability to form hydrogen bonds, high bioavailability and various pharmacological

manifestations. That is why its use as a «nucleus» to construct hybrid molecules in combination with other pharmacoform fragments is logical and very productive.[6,7] Due to the flexibility of 1,2,4-triazole as a constructive element, this approach has already proven effective in the creation of antiviral, antifungal, antitumor, immunomodulatory and growing drugs. It is expected that a further purposeful combination of a triazole cycle with new pharmacophores will be the basis for the emergence of a whole generation of innovative molecules with high practical importance.[8,9]

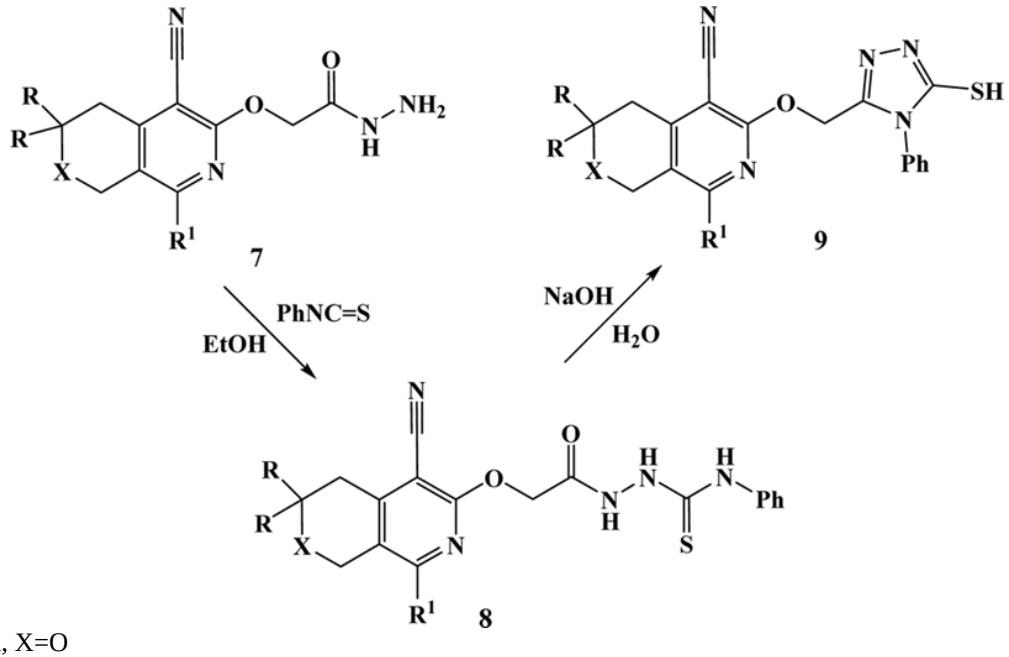
The purpose of the work is to systematize and generalize modern literature data on the synthesis of new derivatives of 1,2,4-triazole with potential anticonvulsant activity, analysis of physicochemical methods and pharmacological effect.

2. METHODS AND MATERIALS

To prepare the review article, a search and analysis of scientific publications devoted to the synthesis of new organic compounds, a fragment of molecules of which is 1.2,4-triazole, the study of their physicochemical characteristics and the study of anticonvulsant activity, was conducted. The literary search was carried out in PubMed, Scopus, Web of Science, Google School databases. The analysis includes articles published in reviewed journals over the last 10 years, as well as classical works of fundamental importance. A comparative analysis of literary data was performed in order to identify patterns between the structural features of the synthesized compounds, their physicochemical characteristics and the level of pharmacological activity.

3. RESULTS AND DISCUSSIONS

Particular attention was paid to compounds containing Pyrano [3,4-C] pyridic nucleus, since they found the highest biological activity.[10] Thus, the conducted studies allowed new hybrid compounds based on 1.2.4-triazole fragments that demonstrate significant anticonvulsant, anxiolytic and antidepressant activity (Fig. 1). The results create the basis for further research to evelop new drugs for the treatment of neurological and mental disorders.



R=H, R^1=Ph, X=O

Figure 1: Scheme of synthesis of some derivatives of 1,2,4-triazole.

Analysis of the relationship between structure and anticonvulsant activity by antagonism to pentilettetrazole showed that the presence of Pyano [3,4-C] pyridine, both in the pyperazin and on the three-nitrogen ring, is useful for anticonvulsant activity. Introduction 8- (Furan-2-Il) -6-Methox-3,3,3-Dimethyl-3,4-Dihydro-1H-Pirano [3,4-C] pyridine-5-carbonitril in a triazole ring and 1- (furan-2-y) -5,6,7,8-tetragidrozohinolin-4.[10] According to the authors[11], the molecular structure and bioactivity of anti -epileptic compounds is due to the space of distant hydrophobic domains (usually phenyl fragments), the presence of hydrogen bonds and lectronodonorn fragments (Fig.2)

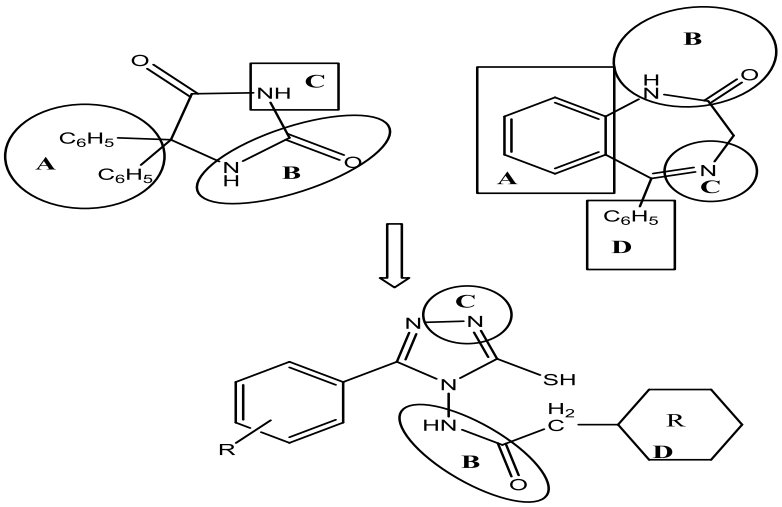
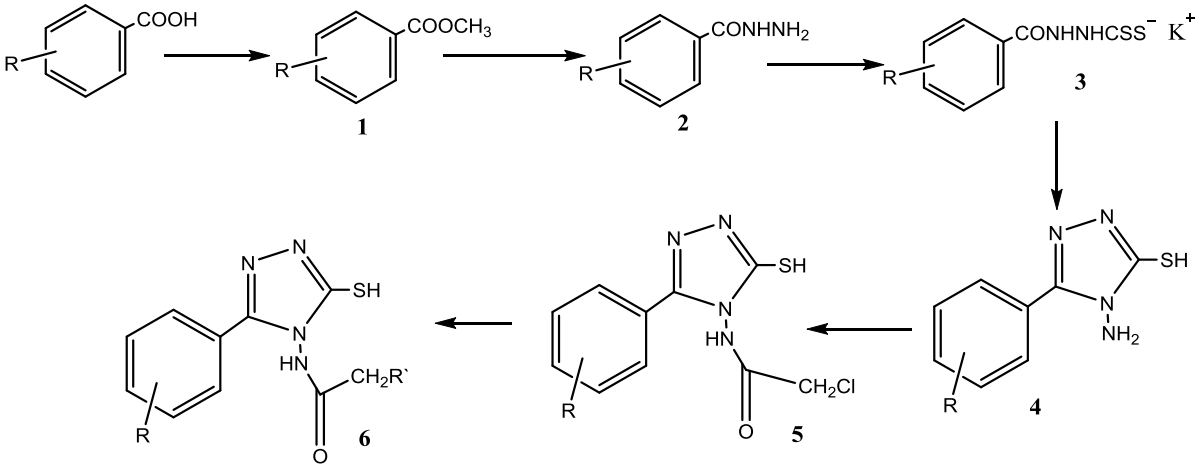


Figure 2: Structural features of the compound to ensure anticonvulsant activity: (a) hydrophobic aromatic area, (b) hydrogen-binding domain, (c) electrono-donor fragment and (D) a distant aromatic ring.

The authors for the synthesis of targeted compounds used a number of consecutive transformations according to the Figure 3. Further, the classical method synthesized the corresponding hydrazides (2), xentogenates (3), thiola (4). Thiols (4) were reacted with chloroacetyl chloride in toluene to give 5-aryl-4-(chloroacetylamino)-3-mercapto-1,2,4-triazole (5), which in the presence of various amines was converted into amino derivatives of 5-aryl-4-(chloroacetylamino)-3-mercapto-1,2,4-triazoles (6).



R=p-Cl, p-NO_2, m-NO_2, p-C_8H_{10}, o-OCH_3, p-OH, p-I, $CH_2C_6H_4OH$

R`=$(C_6H_5)_2N$-, $(C_2H_5)_2N$-,

Figure 3: Scheme of synthesis of some 1,2,4-triazole derivatives.

Scientists have proven that most of the synthesized compounds demonstrated anti-MES effects without any signs of neurological deficit.[11] All the tested compounds significantly reduced PTZ-induced seizures compared to the control group. Carbamazepine and phenytoin were used as positive controls for studying anticonvulsant activity. Adiphenylamine derivatives of 5-aryl-4-(chloroacetylamino) -3-mercapto-1,2,4-triazole and the piperidine derivative of 5-aryl-4-(chloroacetylamino) -3-mercapto-1,2,4-triazole demonstrated greater safety than phenytoin and carbamazepine in terms of neurotoxicity.[11] Literature sources confirm that various substitutions in the triazole ring contribute to the emergence of potent anticonvulsant activity without neurotoxicity.[12] The mentioned review is an attempt to compile registered potent triazole derivatives with significant anticonvulsant effects.[12] In recent years, in particular, 1,3,4-thiadiazoles and 1,2,4-triazoles have attracted attention in preclinical and clinical studies as important drug candidates due to their anticonvulsant properties.[13] The authors developed and synthesized a series of chiral 2,5-disubstituted-1,3,4-thiadiazoles and 4,5-disubstituted-1,2,4-triazole-3-thiones. (S)-(+)5-[1-(4-fluorobenzamido)-2-phenylethyl]-4-(4-fluorophenyl)-

2,4-dihydro -3H-1,2,4-triazole-3-thione and (S)-(+)-(5-[1-(4-fluorobenzamido)- 2-phenylethyl]-4-(4-methoxyphenyl) -2,4-dihydro-3H-1,2,4-triazole-3-thione were found to be the most promising candidates as anticonvulsant drugs, also demonstrating low neurotoxicity.[13]

Due to their structural characteristics, both 1,2,3- and 1,2,4-triazoles are able to accommodate a wide range of substituents (electrophiles and nucleophiles) around the core structures, paving the way for the construction of diverse new bioactive molecules.[14] Recently, considerable efforts have been made to involve triazole in the design of anticonvulsant agents, leading to the development of a large number of active compounds.[15] An original contribution regarding the synthesis of new (arylalkyl)azoles in the structure of N-[1-(4-chlorophenyl)-2-(1H-1,2,4-triazol-1-yl) ethylidene] hydroxylamine has been proposed by a team of authors.[16] For this series of compounds, anticonvulsant activity and pharmacokinetic properties were investigated. Another research group synthesized a series of new ester derivatives by reacting various acids with 1-phenyl/1-(4-chlorophenyl)-2-(1H-triazol-1-yl)ethanol and carried out in vivo screening for their anticonvulsant activity.[17] Pharmacological approaches to epilepsy treatment are primarily aimed at suppressing the initiation or spread of seizures rather than eliminating the underlying mechanisms of the disease. Some patients with epilepsy do not respond to current antiepileptic drugs, therefore the main goal of research in this field is the development of agents with higher anticonvulsant efficacy and lower toxicity compared to existing medications. It is known that experimentally induced seizures increase seizure susceptibility in genetically predisposed animals. At the same time, a significant number of chemicals used in industry have not yet undergone sufficient neurotoxicity testing due to the high cost and duration of such studies. Various in vitro models, including synaptic fractions, rat astrocyte cultures, and mouse spinal cord cultures, are widely used to assess neurotoxicity. In the present work, the synthesis results of 1,2,4-triazole derivatives are presented, and it has also been confirmed that all the studied compounds exhibit anticonvulsant activity.[18] The structures of some of the synthesized molecules are shown in Figure 4.

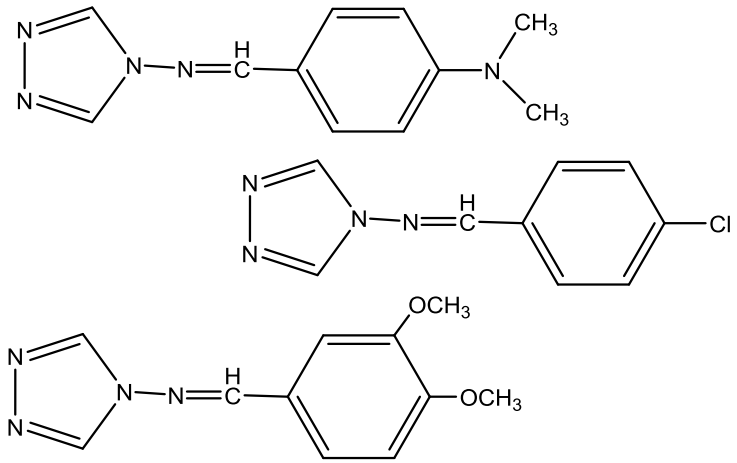
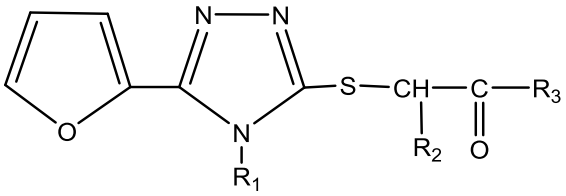


Figure 4: Structures of some 1,2,4-triazole derivatives.

The author substantiated the relevance of searching for new anticonvulsant agents due to the limited efficacy and side effects of existing drugs.[19] S-derivatives of 5-(furan-2-yl)-1,2,4-triazole-3-thiones were synthesized and investigated, and their anticonvulsant activity was evaluated in models of central nervous system stimulation. Theoretical computer analysis confirmed the potential of these compounds. The studies showed that two of them exhibited activity comparable to that of phenobarbital and mydocalm. A highly effective compound was identified—2-[5-(furan-2-yl)-4-phenyl-4H-1,2,4-triazol-3-ylthio]-1-(4-chlorophenyl)ethanone—whose anticonvulsant effect exceeded that of the reference drugs. For certain structures, structure–activity relationships were established, opening prospects for further pharmacological optimization.



R_1=H, C_6H_5, R_2=H, C_6H_5, R_3=C_6H_5, 4-ClC_6H_5, 4-OHC_6H_5

Figure 5: Structural formulas of some furan-containing 1,2,4-triazole derivatives.

The study showed that derivatives of 4-alkyl-5-substituted-1,2,4-triazole-3-thiones have significant potential as new antiepileptic agents.[20] The most promising were compounds with unbranched alkyl chains (butyl–hexyl), which demonstrated high anticonvulsant activity and the ability to interact with voltage-gated sodium channels. The combination of *in vivo*, in vitro, and *in silico* studies confirms the feasibility of further development of this group of compounds as candidates for the creation of effective antiepileptic drugs (Fig. 6).

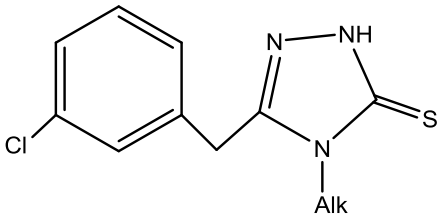


Figure 6: Structural formulas of some 1,2,4-triazole derivatives with anticonvulsant activity.

The results of scientific studies clearly indicate that new derivatives of 6-(R-phenyl)-thiazolo[3,2-b][1,2,4]triazole proved to be promising, with their activity investigated in maximal electroshock (MES) and pentylenetetrazole (PTZ) models.[21] Among the synthesized compounds, the most significant results were shown by: the 6-(4-fluorophenyl) derivative—selective activity in the MES test with a protection index of 1.9; and the 6-(4-propoxyphenyl) derivative—activity in both models, with a protection index of 1.7, exceeding that of carbamazepine. The obtained data suggest that these compounds may serve as a basis for the development of new antiepileptic drugs with an optimal balance of efficacy and safety.

The target compounds were synthesized according to the scheme shown in Fig. 7. 6-Phenylthiazolo[3,2-b][1,2,4]triazoles were obtained by heating 3-phenacylthio[1,2,4]triazoles in the presence of polyphosphoric acid. The intermediate compounds were readily obtained by the interaction of various phenacyl bromides with [1,2,4]triazole-3-thione in boiling ethanol.

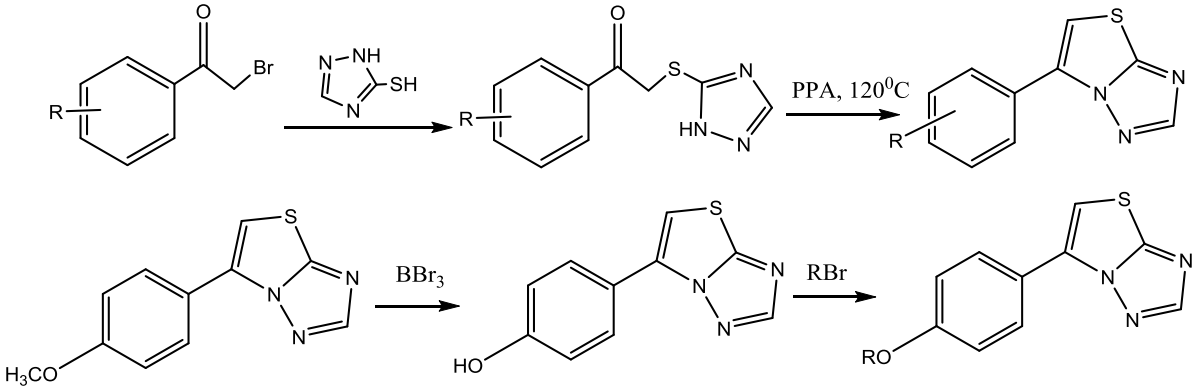


Figure 7: Scheme of the synthesis of new 1,2,4-triazole derivatives.

CONCLUSIONS

As a result of this work, contemporary literature data on strategies for the synthesis of new 1,2,4-triazole derivatives have been summarized, opening broad prospects for the creation of compounds with pronounced anticonvulsant activity. The main approaches to obtaining such molecules have been systematized, which makes it possible to reasonably select optimal synthetic pathways depending on the desired structural fragments. An important aspect is also the generalization of data on experimental approaches to the evaluation of anticonvulsant activity, which provide a foundation for determining the pharmacological potential of the studied molecules. Based on the conducted analysis, it was established that there is a close relationship between structural features, physicochemical properties, and manifestations of biological activity, knowledge of which enables the rational design of new 1,2,4-triazole derivatives with improved efficacy and safety.

Consent for publication: Not-applicable.

Authors' Contributions

This study is the result of joint research, and the contribution of each author is comparable to the others.

The roles of each author are as follows:

1. Borysenko N. M.: Conception, Design, Materials, Data Collection, data analysis, Literature Review and Writing.

2. Parchenko V. V.: Design, Supervision, Data, Processing, Data Analysis, Interpretation and Critical Review.

3. Bushueva I. V.: Conception, Design, Supervision, Writing and Critical Review.
4. Artemenko L. P.: Data Analysis.
5. Chmelova L. D.: Supervision, Writing.
6. Sukhovyi G. P.: Approval of the Article.

The final version of the manuscript was reviewed and approved by all co-authors.

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