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IN SILICO STUDY OF BIOLOGICAL ACTIVITY OF 2-[5-(FURAN-2-YL)-4-PHENYL-4N-1,2,4-TRIAZOL-3-YLTHIO]-1-(4-CHLOROPHENYLETHANONE)

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Introduction. *In modern conditions, where military conflicts are accompanied by significant psychological and physical stress on participants, the development of effective antiepileptic drugs has become one of the key challenges in medicine. This issue is particularly relevant due to the increasing number of cases of traumatic brain injuries, concussions, and other stress-related damages that can provoke convulsive states. In this context, derivatives of 1,2,4-triazole, which possess a broad spectrum of biological activity, including anticonvulsant effects, appear promising for the creation of new pharmaceutical agents capable of meeting the needs of military medicine.*

The purpose *of the study was to investigate the biological activity of 2-[5-(furan-2-yl)-4-phenyl-4H-1,2,4-triazol-3-ylthio]-1-(4-chlorophenyl)ethanone using computer-based predictive methods. This approach allows to determine the presence of new types of activity, which could expand scientific research pathways and establish a promising direction for further testing of this molecule.*

Materials and methods. *Molecular docking was performed using Autodock 4.2.6. For screening, the crystallographic structures of $GABA_A$ receptors –"4COF," "6D6T," and "6X3U" - obtained from the RCSB Protein Data Bank were used. Visualization of the results was conducted using Schrödinger Release 2018-1: Schrödinger, LLC, New York, NY, 2018. The grid parameters for binding were 30 Å × 30 Å × 30 Å, and the grid center coordinates were: 4COF (7 Å × 12 Å × 132 Å), 6D6T (119 Å × 181 Å × 126 Å), 6X3U (137 Å × 108 Å × 142 Å), which provided a sufficiently large space to encompass the receptor center. The ADME evaluation was performed using the free SwissADME tool, which is widely used in medicinal chemistry for analyzing pharmacokinetics, bioavailability, and interactions of small molecules with enzymes. This service considers six physicochemical characteristics: lipophilicity, size, polarity, solubility, flexibility and saturation. Each of these characteristics has its own physicochemical range, which is visualized as a pink zone on the radar plot. For a molecule to be considered drug-like, its radar profile must be entirely within this zone.*

Results. *The study of the interaction of the selected compound with $GABA_A$ receptors (4COF, 6D6T, 6X3U) demonstrated its ability to stably bind to the active sites of the receptors, as evidenced by binding energies ranging from –6.119 to –8.559 kcal/mol. The main interactions include hydrophobic contacts, hydrogen bonds, and electrostatic interactions, indicating the compound's potential to modulate receptor activity. The high binding energy values, particularly for the 6X3U structure, suggest the possibility of effectively influencing neuronal excitability, which is promising for the development of antiepileptic agents. The obtained results confirm that the selected compound has potential for further research as a candidate for the development of new pharmaceutical drugs.*

Conclusions. *The pharmacokinetic analysis demonstrated favourable bioavailability characteristics of the compound, including optimal lipophilicity, solubility, and molecular size, in accordance with the parameters typical for pharmaceutical drugs. This enhances the prospects for further investigation of the compound in experimental epilepsy models and for the development of new anticonvulsant drugs based on it. The use of computer modelling significantly accelerates the selection of promising compounds, reduces drug development costs, and contributes to the creation of more effective medications for military personnel in the future.*

Key words: *1,2,4-triazole derivatives, biological activity, activity prediction, in silico methods, pharmacophoric substituents, "structure-activity relationship".*

ДОСЛІДЖЕННЯ БІОЛОГІЧНОЇ АКТИВНОСТІ 2-[5-(ФУРАН-2-ІЛ)-4-ФЕНІЛ-4Н-1,2,4-ТРИАЗОЛ-3-ІЛТІО]-1-(4-ХЛОРФЕНІЛЕТАНОНУ) *IN SILICO* МЕТОДАМИ

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Вступ. *У сучасних умовах, коли військові конфлікти супроводжуються значним психологічним та фізичним навантаженням на учасників, розробка ефективних протиепілептичних препаратів стає однією з ключових задач медицини. Особливу актуальність ця проблема набуває у зв'язку зі зростанням кількості*

випадків травм головного мозку, контузій та інших стресових ушкоджень, які можуть спровокувати судомні стани. У цьому контексті похідні 1,2,4-триазолу, що володіють широким спектром біологічної активності, зокрема протисудомною дією, виглядають перспективними для створення нових лікарських засобів, здатних задовольнити потреби військової медицини.

***Метою** роботи стало дослідження біологічної активності 2-[5-(фуран-2-іл)-4-феніл-4H-1,2,4-триазол-3-ілтіо]-1-(4-хлорфенілетанону) за допомогою методів комп'ютерного прогнозу, що дозволить з'ясувати наявність нових видів активності, а це може розширити шляхи наукових досліджень і встановити перспективний напрям подальших випробувань для цієї молекули.*

Матеріали і методи. *Молекулярний докінг здійснювався за допомогою програми Autodock 4.2.6. Для скринінгу використовувалася кристалографічна структура GABAA-рецепторів «4COF», «6D6T», «6X3U», отриманих з RCSB The Protein Data Bank. Візуалізація результатів проводилася за допомогою Schrödinger Release 2018-1: Schrödinger, LLC, New York, NY, 2018. Параметри сітки для зв'язування становили 30 Å × 30 Å × 30 Å, а координати центру сітки були – 4COF (7 Å × 12 Å × 132 Å), 6D6T (119 Å × 181 Å × 126 Å), 6X3U (137 Å × 108 Å × 142 Å), що забезпечувало достатньо великий простір для охоплення центру рецептора. Оцінку ADME було здійснено за допомогою безкоштовного інструменту SwissADME, що широко використовується в медичній хімії для аналізу фармакокінетики, біодоступності та взаємодії малих молекул з ферментами. У цьому сервісі враховуються шість фізико-хімічних характеристик: ліпофільність, розмір, полярність, розчинність, гнучкість і насиченість. Кожна з цих характеристик має свій фізико-хімічний діапазон, який візуалізується рожевою зоною на діаграмі. Для того, щоб молекула вважалася подібною до лікарських засобів, її радіолокаційний профіль повинен повністю лежати в межах цієї зони.*

Результати. *Дослідження взаємодії обраної сполуки з $GABA_A$-рецепторами (4COF, 6D6T, 6X3U) показало її здатність стабільно зв'язуватися з активними центрами рецепторів, що підтверджується енергіями зв'язку від –6,119 до –8,559 ккал/моль. Основні взаємодії включають гідрофобні контакти, водневі зв'язки та електростатичні взаємодії, що свідчить про потенційну здатність сполуки модулювати активність рецепторів. Високі значення енергії зв'язку, особливо для структури 6X3U, вказують на можливість ефективного впливу на нейронну збудливість, що є перспективним для розробки протиепілептичних засобів. Отримані результати підтверджують, що обрана сполука має потенціал для подальших досліджень як кандидат для створення нових лікарських препаратів.*

Висновки. *Фармакокінетичний аналіз показав сприятливі характеристики біодоступності сполуки, що включають оптимальну ліпофільність, розчинність та молекулярний розмір, відповідно до параметрів, притаманних лікарським засобам. Це підвищує перспективність подальшого дослідження сполуки в експериментальних моделях епілепсії та розробки на її основі нових протисудомних препаратів. Використання комп'ютерного моделювання дозволяє значно прискорити відбір перспективних сполук, скоротити витрати на розробку лікарських засобів і створити більш ефективні препарати для військових у майбутньому.*

Ключові слова: *похідні 1,2,4-триазолу, біологічна активність, прогноз активності, in silico методи, фармакофорні замісники, взаємозв'язок «будова-дія».*

Introduction. In the context of military conflicts, where psychological stress and physical injuries are an inseparable part of reality, the need for effective antiepileptic (anticonvulsant) drugs becomes especially urgent. These pharmaceutical agents are critically important not only for the treatment of epilepsy but also for the prevention and control of seizures caused by traumatic brain injuries, concussions, and other stress-related factors encountered by military personnel. The specific nature of military service, which involves extreme physical and psychological stress, increases the risk of developing seizure conditions. Therefore, the development and implementation of new antiepileptic drugs – characterized by rapid action, minimal side effects, and ease of use in field conditions – is not only a scientific challenge but also a humanitarian issue. This problem requires the collaboration of researchers, pharmaceutical companies, and government agencies to ensure effective solutions. Given the urgent need for the development of effective antiepileptic drugs for military personnel, special attention is drawn to 1,2,4-triazole derivatives. These heterocyclic compounds are known for their broad biological activity, including anticonvulsant effects, making them promising candidates for the creation of new pharmaceutical agents. 1,2,4-Triazole derivatives have the ability to influence various neurochemical processes underlying the development of seizure conditions. They can modulate the activity of neurotransmitter systems such as the GABAergic, glutamatergic, and monoaminergic systems, which helps regulate neuronal excitability and prevent seizures. This opens up vast opportunities for the development of drugs with an optimal efficacy and safety profile, which is particularly crucial for military applications. Thus, the study of 1,2,4-triazole derivatives represents a promising direction in the development of new antiepileptic drugs for military personnel. Investigating their mechanisms of action, synthesizing new derivatives with enhanced properties, and conducting clinical trials will enable the creation of

effective and safe pharmaceutical agents that meet the demands of military medicine and pharmacy.

1,2,4-Triazoles are an important class of heterocyclic compounds, consisting of three nitrogen atoms and two carbon atoms in a five-membered ring [1]. Recent advancements in triazole chemistry highlight their exceptional value in pharmacy, agrochemistry, materials science, and biomedical research [2, 3]. Moreover, the toxicity of 1,2,4-triazole derivatives is minimal [4]. Triazoles play a key role in the development of new drugs due to their antibacterial, antiviral, antifungal, and antitumor properties [4, 5]. They are also used in the creation of new materials, such as corrosion inhibitors, polymers, and photovoltaic materials. Additionally, triazoles are widely applied as fungicides to protect agricultural crops from fungal infections. Popular fungicidal agents, such as tebuconazole and propiconazole, provide long-lasting protection and high efficacy.

Some 1,2,4-triazole derivatives are used in the development of biosensors and drug delivery systems. They facilitate the targeted delivery of pharmaceuticals to specific tissues or organs, minimizing side effects. The development of triazole-metal complexes has opened new possibilities in homogeneous and heterogeneous catalysis, which is crucial for environmentally friendly chemical production.

The use of *in silico* methods allows for the assessment of a compound's potential effects on targets associated with: anti-inflammatory properties, antibacterial activity, antioxidant effects (reducing oxidative stress in cells, which promotes faster wound healing) and neuroprotective action (the ability to interact with central nervous system receptors, which may be beneficial for managing stress disorders in military personnel).

Computer-based prediction is a crucial tool in the study of triazole properties, as it allows for the modelling of their molecular characteristics, interactions with other compounds, and the prediction of potential physicochemical properties [6, 7]. Using software tools such as Gaussian, AMBER, and CHARMM, the structure of triazole molecules can be modeled, their geometry optimized, and bond energies calculated. This enables the acquisition of more accurate data on molecular stability, reactivity, and potential reaction products. The application of quantum-chemical methods allows for the assessment of triazoles' potential as biologically active compounds, particularly their ability to interact with specific receptors or enzymes. This is achieved through calculations of interaction energies and molecular orbitals. To accomplish this, software programs for molecular docking (such as AutoDock) are often used, allowing researchers to predict how triazoles may bind to biological targets [8, 9].

Computational methods also play a crucial role in assessing the toxicity of triazoles. Using various models, such as QSAR (Quantitative Structure-Activity Relationship), it is possible to predict the potential toxic properties of compounds based on their molecular structure. This approach helps reduce both time and costs associated with experimental research [10]. Using molecular dynamics, the behavior of triazoles in different environments (e.g., aqueous solutions or organic solvents) can be modeled. This approach provides valuable insights into molecular stability, structural behavior in liquid media, and reaction mechanisms that may occur under specific conditions. Thus, computational prediction methods are an indispensable tool for studying the properties of triazoles. They significantly accelerate the discovery of new biologically active molecules, reduce experimental research costs, and contribute to the development of new technologies across various fields [11, 12].

A literature review confirms the high anticonvulsant activity of 2-[5-(furan-2-yl)-4-phenyl-4H-1,2,4-triazol-3-ylthio]-1-(4-chlorophenyl)ethanone [2]. In this regard, investigating the properties of this promising compound is scientifically relevant.

The purpose of this study is to investigate the biological activity of 2-[5-(furan-2-yl)-4-phenyl-4H-1,2,4-triazol-3-ylthio]-1-(4-chlorophenyl)ethanone using computational prediction methods. This approach will help determine the presence of new types of activity, which may expand research pathways and establish a promising direction for further testing of this molecule.

$GABA_A$-receptors are ligand-gated ion channels responsible for inhibitory neurotransmission in the brain. Under normal conditions, when GABA binds to the receptor, the chloride ion (Cl^-) channel opens, leading to neuron membrane hyperpolarization and the suppression of neuronal activity. This prevents excessive excitation and ensures a balance between inhibitory and excitatory signals. In pathological conditions that contribute to epileptic seizures, the function of $GABA_A$-receptors can be disrupted. One of the key mechanisms involves a decreased receptor sensitivity to GABA, which may result from mutations in receptor subunits (e.g., $GABRA_1$, $GABRB_3$) or alterations in allosteric regulation. As a result, inhibitory efficiency is reduced, leading to increased neuronal excitability and a higher risk of seizure development.

Another mechanism is associated with disruptions in the chloride ion gradient. For example, increased activity of the $Na^+/K^+/Cl^-$

cotransporter (NKCC1) or reduced activity of the K^+/Cl^- cotransporter (KCC2) can lead to chloride ion accumulation inside the cell. In this situation, the opening of $GABA_A$–receptors no longer induces the usual hyperpolarization. Instead, it can cause depolarization and neuronal excitation, which promotes seizure activity. Excessive activity of the GABA–transporter (GAT-1) promotes the rapid removal of GABA from the synaptic cleft, thereby reducing the duration of the inhibitory signal. As a result, even with a normal number of receptors, inhibition becomes less effective, leading to increased neuronal excitability and a higher risk of epileptic seizures.

Thus, the pro-epileptic effects of $GABA_A$-receptors can arise due to reduced sensitivity to GABA, alterations in the chloride gradient, or dysfunction in the GABA transport system (Figure 1). These mechanisms lead to a decrease in inhibitory influence within neuronal networks, increasing susceptibility to epileptic activity. The diagram in Figure 1 illustrates disruptions in chloride ion influx, abnormal transporter activity, and decreased receptor sensitivity, all of which contribute to neuronal hyperexcitability.

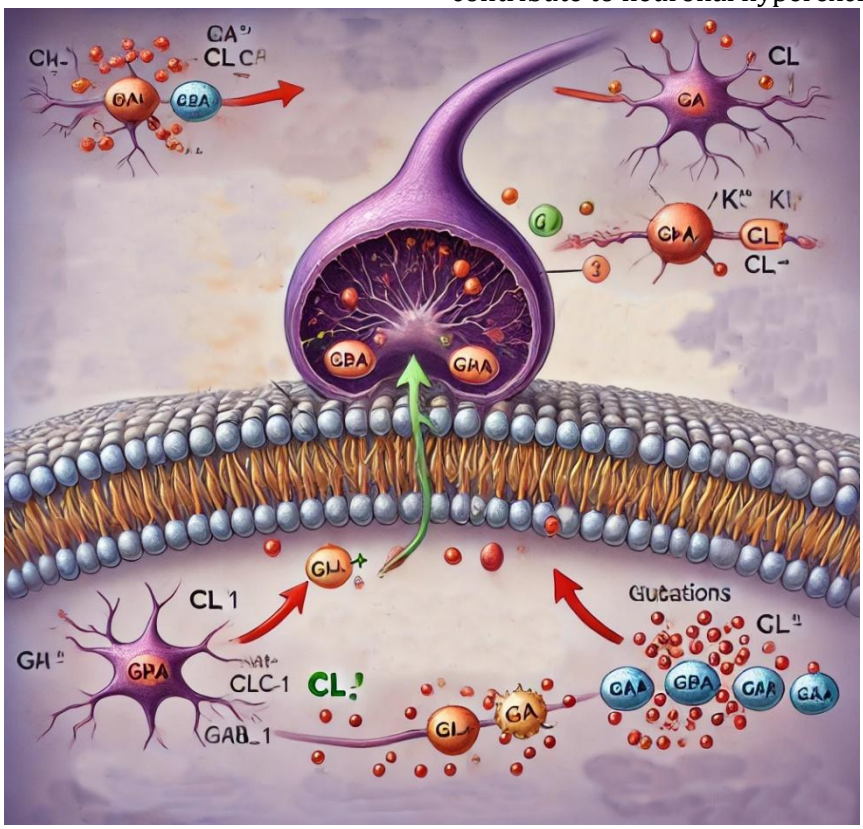

Figure 1. A diagram illustrating the pro-epileptic mechanism of $GABA_A$-receptors [created using artificial intelligence, OpenAI, February 27, 2025. Access mode: private interaction via the ChatGPT application]

Materials and Methods. *Molecular docking* was performed using AutoDock 4.2.6 [13]. For screening, the crystallographic structures of GABAA receptors– "4COF," "6D6T," and "6X3U" – were obtained from RCSB The Protein Data Bank [14–16]. Visualization of the results was conducted using Schrödinger Release 2018-1: Schrödinger, LLC, New York, NY, 2018. The grid parameters for binding were set to 30 Å × 30 Å × 30 Å, with the grid center coordinates as follows: 4COF (7 Å × 12 Å × 132 Å), 6D6T (119 Å × 181 Å × 126 Å), 6X3U (137 Å × 108 Å × 142 Å). These parameters provided a sufficiently large space to encompass the receptor's binding site.

Bioavailability. The ADME evaluation was conducted using the free SwissADME tool [17, 18], which is widely used in medicinal chemistry for analyzing pharmacokinetics, bioavailability, and interactions of small molecules with enzymes. This tool considers six physicochemical characteristics: lipophilicity, size, polarity, solubility, flexibility, saturation. Each of these properties has a specific physicochemical range, which is visualized as a pink zone on the radar chart. For a molecule to be classified as drug-like, its radar profile must fully fit within this zone.

Results and Discussion. $GABA_A$-receptors are the primary mediators of inhibitory neurotransmission in the central nervous system

(CNS). They belong to the family of ligand-gated ion channels and regulate the influx of chloride ions (Cl^-) into neurons, which promotes membrane hyperpolarization and reduces neuronal excitability. For this study, we selected three receptors from the Protein Data Bank (PDB): 4COF (crystal structure of the human gamma-aminobutyric acid receptor, homopentamer GABA(A)R-β3), 6D6T (a subtype of the human GABA-A receptor, conformation B), 6X3U (a subtype of the human GABA receptor). This comprehensive *in silico* study enables a deeper understanding of the anticonvulsant mechanism of the investigated compound.

The 4COF structure represents a homopentamer of β3-subunits of the human $GABA_A$–receptor with a resolution of 3 Å. This protein complex consists of five identical subunits, each containing extracellular, transmembrane, and intracellular domains. The extracellular domain houses the binding sites for GABA and other modulators, which can influence receptor sensitivity. This is where the primary activation of the receptor occurs following ligand interaction. The transmembrane domain consists of four α-helical segments (M1-M4), which form the ion channel. The M2 segment plays a key role in chloride ion (Cl^-) selectivity and the regulation of ion flow across the membrane. The intracellular domain interacts with regulatory proteins and participates in post-translational modifications, which can alter the functional activity of the receptor. The molecular docking results of the investigated compound with the crystallographic structure of 4COF (Crystal structure of a human gamma-aminobutyric acid receptor, the GABA(A)R-beta3 homopentamer) are presented in Table 1.

Table 1

Molecular docking results obtained using AutoDock 4.2.6

Binding Energy (kcal/mol)	Amino Acid Residues and Binding Interactions
–6,583	Hydrophobic: MET C:49, PHE C:105; polar: THR D:133, THR C:131, THR C:133, THR C:58, SER C:104; positively charged – LYS D:103, LYS D:102, LYS C:103; negatively charged – ASP D:56, ASP C:48

The compound interacts with a binding energy of –6.583 kcal/mol, indicating moderate affinity for the receptor.

The primary hydrophobic interactions involve MET C:49 and PHE C:105, facilitating the stable embedding of the molecule into the hydrophobic pocket of the protein. Polar residues such as THR D:133, THR C:131, THR C:133, THR C:58, and SER C:104 may form hydrogen bonds, further stabilizing the ligand within the binding site. Ionic interactions play a crucial role: positively charged residues (LYS D:103, LYS D:102, LYS C:103) and negatively charged residues (ASP D:56, ASP C:48). These electrostatic contacts may influence receptor conformational changes, affecting its functional state. Структура 6D6T має високу роздільну здатність (3,8 Å) і складається з п'яти субодиниць: двох α_1-, двох β_2- і однієї γ_2-субодиниці. The 6D6T structure has a high resolution (3.8 Å) and consists of five subunits: two α_1-, two β_2-, and one γ_2-subunit. This combination is the most common for $GABA_A$-receptors in the human brain and forms optimal binding sites for both GABA and allosteric modulators (including benzodiazepines).

The extracellular domains of the α_1- and β_2-subunits form two binding pockets for GABA, while the γ_2-subunit creates an additional binding site for benzodiazepines, which enhance the inhibitory effect of the receptor. The transmembrane domains, composed of α-helical segments (M1-M4), form the central ion channel, allowing Cl^- ions to flow in response to receptor activation. The activation process begins when two GABA molecules bind at the interface between the α_1- and β_2-subunits. This triggers conformational changes, which are transmitted from the extracellular domain to the transmembrane channel, leading to ion flux regulation. The opening of the ion channel allows Cl^- ions to enter the cell, leading to membrane hyperpolarization and a reduction in neuronal excitability. In the 6D6T structure, the mechanism of positive allosteric modulation is also clearly visible. Benzodiazepines bind to the γ2 subunit, enhancing the inhibitory effect of GABA by increasing both the probability and duration of the open state of the ion channel.

The molecular docking results of the compound on the crystallographic structure of 6D6T (Human GABA-A receptor alpha1-beta2-gamma2 subtype) are presented in Table 2.

The compound interacts with the $GABA_A$-receptor (6D6T, Human GABA-A receptor alpha1-beta2-gamma2 subtype) with a binding energy of –6.119 kcal/mol, indicating sufficient complex stability.

Table 2

Data and results of molecular docking obtained using the AutoDock 4.2.6 program

Binding Energy (kcal/mol)	Amino acid residues and non-binding interactions
–6,119	Hydrophobic: PRO E:127, VAL E:103, TRP E:123, VAL A:111, VAL A:109; polar: THR A:110, ASN A:85, SER E:100; ionized: positively charged – ARG E:129, LYS A:112

The primary interactions involve hydrophobic contacts with PRO E:127, VAL E:103, TRP E:123, VAL A:111, and VAL A:109, which contribute to the stabilization of the ligand within the hydrophobic environment of the binding pocket. Polar interactions with THR A:110, ASN A:85, and SER E:100 provide additional binding specificity through the formation of hydrogen bonds. Additionally, electrostatic interactions with the positively charged amino acid residues ARG E:129 and LYS A:112 may contribute to complex stabilization and influence conformational changes in the receptor. The interaction of this compound with the $GABA_A$-receptor may potentially modulate its activity, influencing neuronal excitability and contributing to the study of antiepileptic agents. The 6X3U structure, obtained using cryo-electron microscopy with high resolution (2.6 Å), represents the human $GABA_A$-receptor in complex with GABA and allopregnanolone, a neurosteroid positive modulator. This model provides deeper insights into the mechanisms of receptor activation, allosteric regulation, and potential therapeutic targets for epilepsy and other neurological disorders.

The $GABA_A$-receptor is a pentameric complex composed of two α_1-, two β_3-, and one γ_2-subunit. In the 6X3U structure, the binding sites for GABA can be clearly identified between the α1 and β3 subunits, as well as the allosteric modulation site for neurosteroids in the transmembrane domain. Extracellular domains form ligand-binding sites. Transmembrane segments (M1-M4) create the central pore, which regulates Cl^- ion flow. Upon GABA binding, conformational changes are transmitted from the extracellular domain to the transmembrane segments, leading to the opening of the ion channel.

The molecular docking results of the compound on the crystallographic structure of 6X3U (Human GABAA receptor alpha1-beta2-gamma2 subtype) are presented in Table 3.

Table 3

Data and results of molecular docking obtained using the AutoDock 4.2.6 program

Binding Energy (kcal/mol)	Amino acid residues and binding interactions
–8,559	Hydrophobic: PHE B:100, TYR B:160, ALA B:161, MET C:115, TYR C:62, VAL B:103, TYR B:210, ILE C:44, ALA C:45; polar: HID B:102, SER B:159, SER B:205; ionized: positively charged – LYS C:180; negatively charged – ASP C:43

The compound interacts with the $GABA_A$-receptor (6X3U, Human GABA-A receptor alpha1-beta2-gamma2 subtype) with a binding energy of –8.559 kcal/mol, indicating high affinity for the binding pocket. Primary hydrophobic interactions occur with PHE B:100, TYR B:160, ALA B:161, MET C:115, TYR C:62, VAL B:103, TYR B:210, ILE C:44, and ALA C:45, facilitating the stable embedding of the ligand into the receptor's hydrophobic environment. Polar contacts with HID B:102, SER B:159, and SER B:205 may provide additional stabilization through hydrogen bonds. Electrostatic interactions involve the positively charged LYS C:180 and negatively charged ASP C:43, which may contribute to the specific positioning of the compound in the active site. These interactions could influence the receptor's conformational dynamics, which is particularly relevant for its modulation, especially in the study of antiepileptic agents.

Figure 2 presents the interaction networks between GABAA receptors and the selected compound, displaying the amino acid residues and binding interactions.

Figure 3 presents the 3D visualization of the ligand-enzyme complex. The molecule exhibited zero RMSD values during the docking process.

The compound interacts with the $GABA_A$-receptor (6X3U, Human GABA-A receptor alpha1-beta2-gamma2 subtype) with a binding energy of –8.559 kcal/mol, indicating high affinity for the binding pocket.

Primary hydrophobic interactions occur with PHE B:100, TYR B:160, ALA B:161, MET C:115, TYR C:62, VAL B:103, TYR B:210, ILE C:44, and ALA C:45, facilitating the stable embedding of the ligand into the receptor's hydrophobic environment. Polar contacts with HID B:102, SER B:159, and SER B:205 may provide additional stabilization through hydrogen bonds.

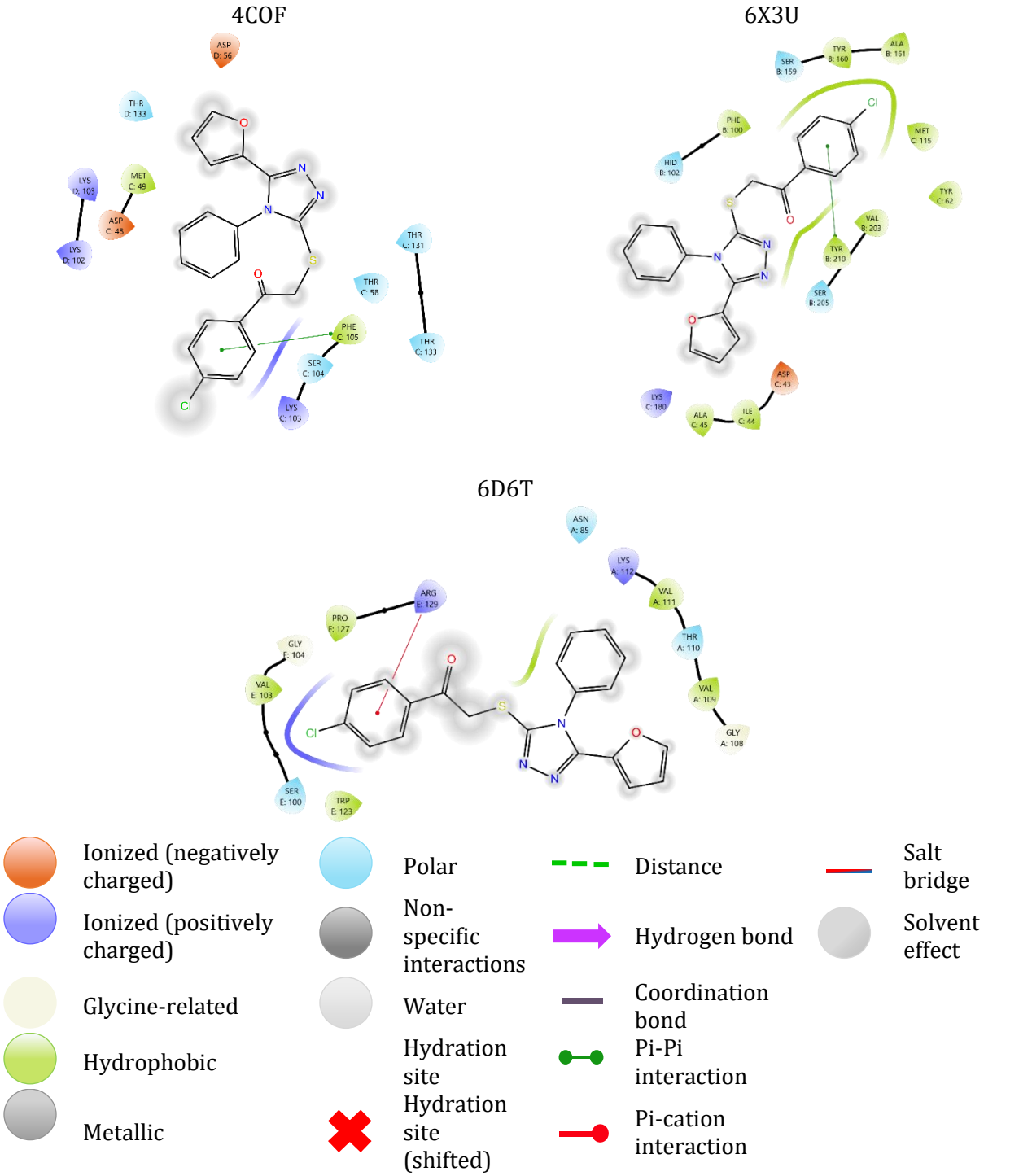

Figure 2. Interaction network between receptors and the selected compound. Negatively charged residues are shown in red, polar residues in blue, and hydrophobic residues in green [created using Schrödinger software]

Positively charged LYS C:180 and negatively charged ASP C:43 play a crucial role in electrostatic interactions, potentially contributing to the specific positioning of the compound in the active site. These interactions may influence the conformational dynamics of the receptor, which is significant for its modulation, particularly in the study of antiepileptic agents. Figure 3 illustrates the surface constructed around the active site of the enzyme: blue represents the hydrogen bond donor region, red represents the hydrogen bond acceptor region. As seen in the figure, the most active inhibitor, in its most probable docked conformation, is complementary to both the acceptor and donor hydrogen bond regions within the active site.

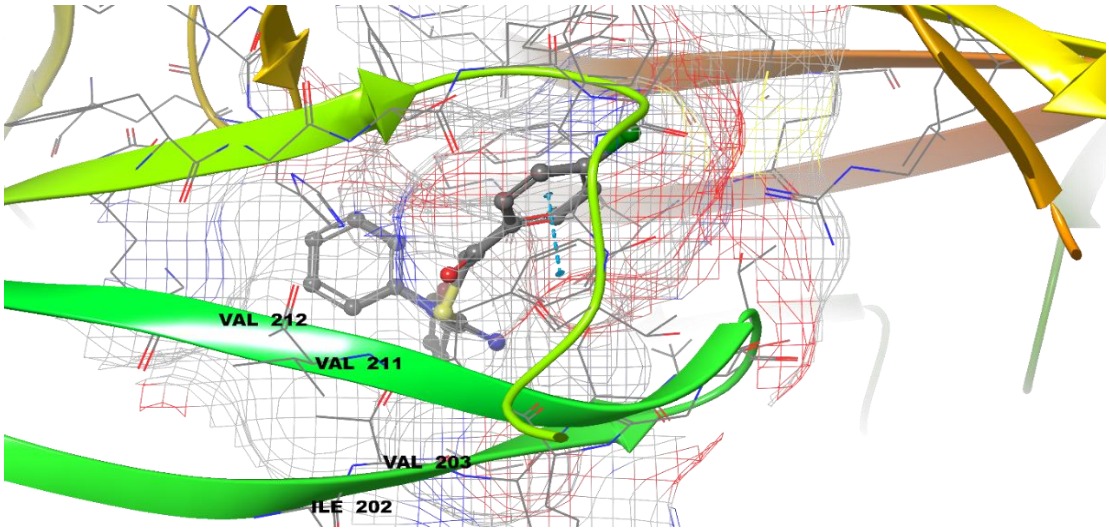

Figure 3. Interaction network between the 6X3U receptor (Human $GABA_A$ receptor alpha1-beta2-gamma2 subtype) and the selected compound in 3D coordinates [*created using Schrödinger Release 2018-1: Schrödinger, LLC, New York, NY, 2018*]

The key structural element of this interaction is the 1,2,4-triazole ring. The selected compound, due to its physical properties, as well as its pharmacokinetic and drug-likeness parameters, represents a promising candidate for the development of a new pharmaceutical substance (Figure 4).

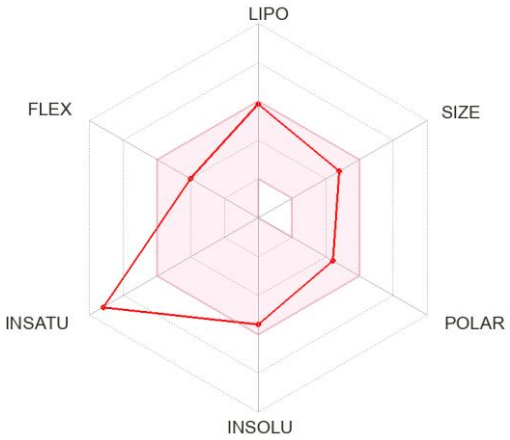

Figure 4. Bioavailability of the selected molecule in the SwissADME program, analyzed using various models, with data grouped according to different physicochemical properties (size, insolubility, lipophilicity, flexibility, unsaturation, and polarity)

The compound has a molecular mass of 395.86 g/mol and contains 27 heavy atoms, 22 of which are aromatic. The sp^3-hybridized carbon fraction is 0.05, indicating the predominantly aromatic nature of the molecule. The presence of six rotatable bonds suggests a certain degree of conformational flexibility. The molecule contains four hydrogen bond acceptors and no hydrogen bond donors, which may affect its interaction with target proteins and water solubility. The molar refractivity (105.51) suggests potential interactions with biological membranes. The topological polar surface area (TPSA) is 86.22 $Å^2$, indicating balanced permeability across cell membranes and potential interactions with transporters.

The calculated Log P values range from 3.38 to 5.16, with a consensus value of 4.21. This indicates pronounced lipophilicity, which may enhance membrane permeability but could also present challenges with water solubility. The compound exhibits high gastrointestinal absorption (GI absorption: High), which supports its effective uptake when administered orally. According to drug-likeness rules (Lipinski, Ghose, Veber, Egan, Muegge), the compound meets all criteria, making it a potential candidate for pharmaceutical application. The bioavailability score (0.55) suggests sufficient systemic action

potential after oral administration. The absence of structural "red flags" (PAINS and Brenk alerts) indicates a low likelihood of nonspecific or undesirable biological effects. The synthetic accessibility score (3.25) suggests relative ease of synthesis, an important factor for large-scale production feasibility.

The compound exhibits high lipophilicity, good gastrointestinal absorption, but poor water solubility, which may necessitate specialized drug formulations for effective delivery. Overall, the compound possesses promising properties for further research, but requires optimization to improve solubility.

Conclusions

1. The investigated compound exhibits moderate affinity for GABAA-receptors, as confirmed by molecular docking with three different receptor structures (4COF, 6D6T, and 6X3U). It was established that the interaction occurs through hydrophobic, polar, and ionic bonds with critical amino acid residues, which may contribute to the stabilization of the receptor in its active or modulated state.

2. The potential anticonvulsant mechanism of the compound involves modulating GABAA receptor activity by binding to functionally significant sites, which may enhance inhibitory neurotransmission and reduce neuronal hyperexcitability. This suggests that the compound could serve as a promising antiepileptic agent, acting through the mechanism of positive allosteric modulation of GABA-mediated signaling.

3. Pharmacokinetic analysis revealed favorable bioavailability characteristics of the compound, including optimal lipophilicity, solubility, and molecular size, aligning with parameters typical for pharmaceutical drugs. This enhances the prospects for further investigation of the compound in experimental epilepsy models and for the development of new anticonvulsant drugs based on it.

Future Research Prospects. Since military personnel frequently encounter infections, wounds, and inflammatory conditions, the investigated compound could serve as a basis for the development of new medications in the following areas: anti-inflammatory agents for wound and injury treatment, antibacterial drugs, particularly for combating antibiotic-resistant infections, neuroprotective agents for the recovery of the nervous system in cases of combat-related psychological disorders. The use of computational modeling significantly accelerates the selection of promising compounds, reduces drug development costs, and facilitates the creation of more effective medications for military applications in the future.

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