https://doi.org/10.36290/csf.2025.024

ADME Profile Calculation and Drug Similarity Study of New 1,2,4-Triazole Derivatives Containing 2-Bromo-5-Methoxyphenyl Radical

Mykola Skoryi[1], Roman Shcherbyna[1], Sergii Kulish[1], Volodymyr Salionov[2], Oleksandra Cherchesova[3]
[1]Department of Toxicological and Inorganic Chemistry, Faculty of Pharmacy, Zaporizhzhia Medical and Pharmaceutical University, Zaporizhzhya, Ukraine
[2]Department of Biological Chemistry, Faculty of Pharmacy, Zaporizhzhia Medical and Pharmaceutical University, Zaporizhzhya, Ukraine
[3]Professional Medical and Pharmaceutical College of PJSC „Higher Education Institution" MAUP, Kyiv, Ukraine

Introduction: Evaluating ADME (absorption, distribution, metabolism, excretion) profiles is critical in drug development to ensure bioavailability, efficacy, and safety. 1,2,4-Triazole derivatives, particularly those with a 2-bromo-5-methoxyphenyl radical, are promising due to their broad biological activities, yet their pharmacokinetic properties are insufficiently studied. The objective of this study was to predict the ADME characteristics and drug-likeness of these compounds to identify candidates with optimal pharmacokinetic potential for therapeutic applications.
Objectives: This study aimed to assess the ADME profiles of new 1,2,4-triazole derivatives incorporating a 2-bromo-5-methoxyphenyl fragment using in silico methods and evaluate their compliance with drug-likeness criteria, such as Lipinski's Rule of 5, for potential pharmaceutical development.
Methods: A series of 28 derivatives, including 5-(2-bromo-5-methoxyphenyl)-4-R-1,2,4-triazole-3-thiols (3a–3d), thioacetic acids (4a–4d), and esters (5a–5t), were analyzed via the Molinspiration Property Calculator. Key parameters assessed were lipophilicity (miLogP), polar surface area (TPSA), molecular weight (MW), hydrogen bond donors (nOHNH) and acceptors (nON), rotatable bonds (nrotb), and Lipinski rule violations (nviolations).
Results: Thiol derivatives (3a–3d) showed moderate lipophilicity (miLogP 3.02-3.33) and TPSA (39.95–50.81 Å^2), suggesting good permeability. Thioacetic acids (4a–4d) had higher TPSA (77.25–88.11 Å^2) and lower miLogP (2.46–3.81), indicating enhanced solubility but reduced permeability. Esters (5a–5t) varied widely in lipophilicity (miLogP 3.08–5.86), with three compounds (5l, 5p, 5t) exceeding Lipinski's miLogP limit (> 5). Most compounds complied with Lipinski's Rule, with MW ranging from 286.15–476.40 g/mol and nrotb from 2–10.
Conclusion: Structural modifications significantly influenced ADME profiles, with thiols and thioacetic acids showing favorable drug-like properties. High-lipophilicity esters may require optimization. These findings support the potential of these triazole derivatives as drug candidates, warranting further pharmacological studies.

Key words: 1,2,4-triazole, ADME, in silico, drug-likeness, pharmacokinetics, 2-bromo-5-methoxyphenyl.

Výpočet ADME profilu a studie podobnosti s léčivy u nových derivátů 1,2,4-triazolu obsahujících radikál 2-brom-5-methoxyfenyl

Úvod: Hodnocení ADME (absorpcí, distribuce, metabolismu a exkrece) je zásadní součástí vývoje léčiv, protože zajišťuje biologickou dostupnost, účinnost a bezpečnost. Deriváty 1,2,4-triazolu, zejména ty obsahující radikál 2-brom-5-methoxyfenyl, jsou perspektivní díky své široké biologické aktivitě, avšak jejich farmakokinetické vlastnosti jsou dosud nedostatečně prozkoumány. Cílem této studie bylo predikovat ADME charakteristiky a podobnost s léčivy u těchto sloučenin, a identifikovat tak kandidáty s optimálním farmakokinetickým potenciálem pro terapeutické využití.

Roman Shcherbyna
Department of Toxicological and Inorganic Chemistry, Faculty of Pharmacy, Zaporizhzhia Medical and Pharmaceutical University, Zaporizhzhya, Ukraine
rscherbyna@gmail.com

Cit. zkr: Čes. slov. Farm. 2025;74(3):E1-E5
Článek přijat redakcí: 9. 6. 2025
Článek přijat po recenzích: 1. 8. 2025

Cíle: Tato studie si kladla za cíl zhodnotit ADME profily nových derivátů 1,2,4-triazolu obsahujících fragment 2-brom-5-methoxyfenyl pomocí in silico metod a posoudit jejich soulad s kritérii „drug-likeness", jako je např. Lipinského pravidlo pěti, s ohledem na jejich možné farmaceutické využití.
Metodika: Byla analyzována série 28 derivátů, včetně 5-(2-brom-5-methoxyfenyl)-4-R-1,2,4-triazol-3-thiolů (3a–3d), thiooctových kyselin (4a–4d) a esterů (5a–5t), pomocí nástroje Molinspiration Property Calculator. Hodnocené parametry zahrnovaly lipofilicitu (miLogP), polární povrchovou plochu (TPSA), molekulovou hmotnost (MW), počet donorů (nOHNH) a akceptorů (nON) vodíkových vazeb, počet rotovatelných vazeb (nrotb) a porušení Lipinského pravidla (nviolations).
Výsledky: Thiolové deriváty (3a–3d) vykazovaly střední lipofilicitu (miLogP 3,02–3,33) a TPSA (39,95–50,81 Å^2), což naznačuje dobrou propustnost. Thiooctové kyseliny (4a–4d) měly vyšší TPSA (77,25–88,11 Å^2) a nižší miLogP (2,46–3,81), což ukazuje na lepší rozpustnost, ale nižší propustnost. Estery (5a–5t) vykazovaly široké rozpětí hodnot lipofility (miLogP 3,08–5,86), přičemž tři sloučeniny (5l, 5p, 5t) překročily limit Lipinského pravidla pro miLogP (>5). Většina sloučenin byla v souladu s Lipinského pravidlem, s molekulovou hmotností v rozmezí 286,15–476,40 g/mol a počtem rotovatelných vazeb 2–10.
Závěr: Strukturní modifikace měly výrazný vliv na ADME profily, přičemž thioly a thiooctové kyseliny vykazovaly příznivé vlastnosti podobné léčivům. Estery s vysokou lipofilitou mohou vyžadovat optimalizaci. Výsledky podporují potenciál těchto derivátů triazolu jako kandidátů pro vývoj léčiv a odůvodňují další farmakologické studie.

Klíčová slova: 1,2,4-triazol, ADME, in silico, podobnost s léčivy, farmakokinetika, 2-brom-5-methoxyfenyl.

Introduction

The development of new pharmaceuticals is a complex and multi-stage process, wherein the evaluation of pharmacokinetic properties of molecules plays a pivotal role. A critical aspect of this process is the analysis of ADME parameters (absorption, distribution, metabolism, and excretion), which determine the bioavailability, efficacy, and safety of potential drug compounds (1, 2). Studies indicate that a significant proportion of drug candidates are rejected at late stages due to unfavorable pharmacokinetic characteristics. Consequently, the consideration of ADME profiles during the preclinical phase is an essential prerequisite for the successful development of novel therapeutics (3).

The assessment of ADME parameters is conducted using experimental (in vitro and in vivo) and computational (in silico) methods (4). In vitro studies enable the investigation of permeability across biological membranes, metabolic stability, and potential interactions with hepatic enzymes. In vivo models provide a comprehensive evaluation of a compound's behavior in the organism but are costly and resource-intensive. In contrast, in silico approaches, such as molecular docking and quantitative structure-activity relationship (QSAR) modeling, facilitate the rapid identification of promising molecules and the prediction of their pharmacokinetic profiles prior to laboratory experimentation (5,6).

The contemporary approach to drug development involves the integration of these methods, optimizing the selection of bioactive compounds, reducing time and resource expenditures, and enhancing the likelihood of successfully introducing a new drug. Thus, ADME profile analysis constitutes a key step in the creation of effective and safe pharmaceuticals (7).

Heterocyclic compounds, particularly 1,2,4-triazoles, garner significant attention in modern medicinal chemistry due to their structural versatility and broad spectrum of biological activities (8, 9). Incorporating a triazole moiety into the structure of bioactive molecules can substantially enhance their pharmacokinetic properties, including solubility, metabolic stability, and bioavailability (10, 11).

The pharmacological value of 1,2,4-triazoles stems from their ability to interact with diverse biological targets (12, 13). These compounds can serve as hydrogen bond donors and acceptors and engage in various non-covalent interactions, rendering them promising candidates for drug development (14, 15). To date, numerous biological effects of triazole derivatives have been documented, with the most extensively studied being antimicrobial, anti-inflammatory, antitumor, antifungal, and antioxidant activities (8, 9, 12, 13, 14, 16,17).

One of the most significant properties of 1,2,4-triazoles is their capacity to inhibit enzymatic systems, which is leveraged in the design of antitumor agents, protease inhibitors, and enzymes associated with metabolic disorders (18). For instance, certain triazole compounds exhibit activity against tyrosine kinases, making them promising for the treatment of oncological diseases (19).

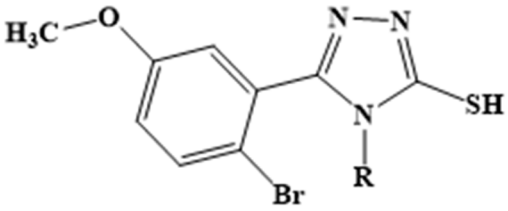
Furthermore, 1,2,4-triazoles have found applications in the development of antimicrobial agents. Their mechanism of action is often linked to the inhibition of bacterial cell wall biosynthesis or interference with nucleic acid synthesis, rendering them effective against resistant microbial strains (18). A notable direction is the development of antifungal triazoles, which block enzymes essential for ergosterol synthesis – a critical component of fungal membranes (20).

Additional interest arises from the neuroprotective activity of triazole derivatives. Some compounds within this class demonstrate the ability to modulate neurotransmitter systems, opening prospects for their use in neurodegenerative disorders such as Alzheimer's and Parkinson's diseases (21, 22).

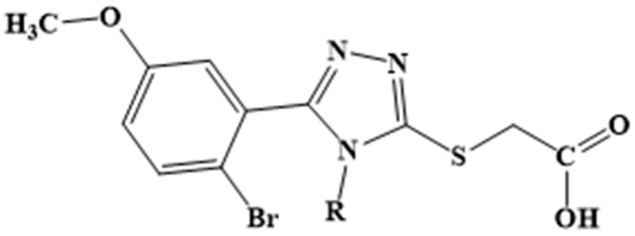
Thus, 1,2,4-triazoles represent promising scaffolds for the development of novel pharmaceuticals that combine high biological activity with favorable pharmacokinetic profiles. Further research in this field will contribute to the creation of effective and safe drugs for the treatment of a wide range of pathologies.

The aim of this study is to conduct in silico investigations of 5-(2-bromo-5-methoxyphenyl)-4-R-1,2,4-triazole-3-thiol derivatives to evaluate their ADME parameters – namely absorption, distribution, metabolism, and excretion – to determine the bioavailability, efficacy, and safety of these potential drug compounds.

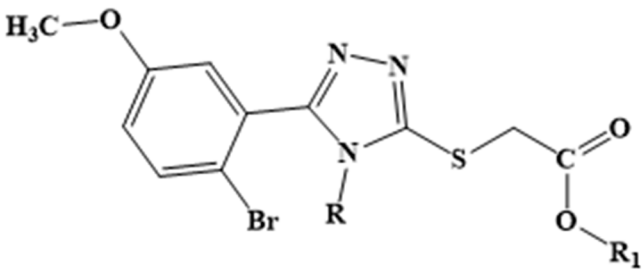
Fig. 1. *Chemical structural of derivatives of 5-(2-bromo-5-methoxyphenyl)-4-R – 1,2,4-triazole-3-thiols (3a-3d), 2-((5-(2-bromo-5-methoxyphenyl)-4-R--1,2,4-triazol-3-yl)thio)acetic acids (4a-4c) and ethers 2-((5-(2-bromo-5-methoxyphenyl)-4-R-4H-1,2,4-triazol-3-yl)thio)acetic acids (5a-5t)*



3a R=H, 3b R=CH_3, 3c R=C_2H_5, 3d R= C_6H_5



4a R=H, 4b R=CH_3, 4c R=C_2H_5, 4d R= C_6H_5



5a R=H, R_1=CH_3, 5b R=CH_3, R_1=CH_3, 5c R=C_2H_5, R_1=CH_3, 5d R=C_6H_5, R_1=CH_3,
5e R=H, R_1=C_2H_5, 5f R=CH_3, R_1=C_2H_5, 5g R=C_2H_5, R_1=C_2H_5, 5h R=C_6H_5, R_1=C_2H_5,
5i R=H, R_1=C_3H_7-n, 5j R=CH_3, R_1=C_3H_7-n, 5k R=C_2H_5, R_1=C_3H_7-n, 5l R=C_6H_5, R_1=C_3H_7-n,
5m R=H, R_1=C_3H_7-i, 5n R=CH_3, R_1=C_3H_7-i, 5o R=C_2H_5, R_1=C_3H_7-i, 5p R=C_6H_5, R_1=C_3H_7-i,
5q R=H, R_1=C_4H_9-n, 5r R=CH_3, R_1=C_4H_9-n, 5s R=C_2H_5, R_1=C_4H_9-n, 5t R=C_6H_5, R_1=C_4H_9-n.

Materials and methods

Objects of Study

The subjects of this research were newly synthesized derivatives, namely 5-(2-bromo-5-methoxyphenyl)-4-R-1,2,4-triazole-3-thiols, 2-((5-(2-bromo-5-methoxyphenyl)-4-R-1,2,4-triazol-3-yl)thio)acetic acids, and esters of 2-((5-(2-bromo-5-methoxyphenyl)-4-R-4H-1,2,4-triazol-3-yl) thio)acetic acids (3a–5t). These compounds were previously synthesized and assessed for potential toxicity, as reported earlier (Fig. 1) (23, 24).

Prediction of Drug-Likeness of 1,2,4-Triazole Derivatives

To evaluate the drug-likeness and pharmacokinetic properties of 1,2,4-triazole derivatives, the online tool Molinspiration Property Calculator (https://www.molinspiration.com/cgi/properties) was employed. Molinspiration is a robust tool for analyzing chemical and pharmacokinetic characteristics, making it valuable in the early stages of drug development. Its primary advantage lies in its ability to rapidly predict the drug-likeness of 1,2,4-triazole derivatives based on their chemical structures. The tool facilitates assessment of compliance with Lipinski's Rule of 5, a key criterion for oral bioavailability. Additionally, Molinspiration analyzes lipophilicity, topological polar surface area (TPSA), and potential deviations from pharmacokinetic constraints, aiding in the selection of promising drug candidates (25).

Another significant benefit is its intuitive web interface, which enables the upload and analysis of molecular structures without requiring complex configurations. Furthermore, the service provides the capability to assess the potential biological profile of compounds based on their structure, assisting in the identification of promising candidates for subsequent in vitro and in vivo testing. The structural formulas of the investigated compounds were obtained in SMILES (Simplified Molecular Input Line Entry System) format and inputted into the Molinspiration Property Calculator to analyze the following physicochemical parameters:

miLogP (Partition Coefficient Logarithm, LogP): The LogP parameter characterizes the hydrophilicity or lipophilicity of a molecule, determining its distribution between aqueous and lipid phases. High LogP values (>5) indicate excessive lipophilicity, which may reduce water solubility and adversely affect intestinal absorption and tissue distribution. Conversely, very low LogP values (<0) suggest high hydrophilicity, potentially limiting penetration through cellular membranes. Optimal LogP values for orally bioavailable drugs typically range from 0 to 5.

TPSA (Topological Polar Surface Area): TPSA represents the total surface area of a molecule associated with hydrophilic atoms capable of forming hydrogen bonds. Elevated TPSA values (>140 $Å^2$) indicate significant hydrophilicity, which may restrict permeability across the blood-brain barrier and cellular membranes. Optimal TPSA values for effective intestinal absorption are generally below 90 $Å^2$.

n atoms (Number of Atoms): This parameter encompasses all atoms in a molecule, excluding hydrogen atoms. It serves as a general indicator of molecular size, which influences bioavailability and phar-

macokinetics. Excessively large molecules may encounter difficulties in permeating biological membranes.

MW (Molecular Weight): Molecular weight (MW) is a critical parameter in pharmacokinetic analysis. High MW values (> 500 Da) may suggest poor membrane permeability, thereby limiting bioavailability. Drug-like molecules typically exhibit MW values within the range of 200–500 Da.

nON (Number of Hydrogen Bond Acceptors): This includes the count of oxygen and nitrogen atoms capable of accepting hydrogen bonds. Optimal values for this parameter do not exceed 10, in accordance with Lipinski's Rule of 5.

nOHNH (Number of Hydrogen Bond Donors): This encompasses atoms capable of donating hydrogen bonds (e. g., – OH or – NH groups). An excessive number of hydrogen bond donors (> 5) reduces a molecule's membrane permeability.

nviolations (Number of Lipinski's Rule of 5 Violations): This metric indicates the number of Lipinski's Rule criteria violated by a molecule. A higher number of violations correlates with a lower probability of favorable absorption and bioavailability.

nrotb (Number of Rotatable Bonds): The nrotb parameter quantifies the number of bonds that can freely rotate, affecting molecular flexibility. An excessive number of rotatable bonds (>10) may impede membrane penetration.

Volume (Molecular Volume): Molecular volume defines the spatial characteristics of a molecule and influences its ability to permeate biological barriers. Large molecules (> 500 Å^3) often exhibit poor permeability (26).

Following the calculation of these parameters, an analysis was conducted to identify potentially drug-like molecules. Compounds fully compliant with the Rule of 5 (Ro5) criteria were deemed promising for further investigation, while those with a single violation were considered suitable for additional optimization. Molecules exhibiting two or more violations were regarded as less promising for oral drug development but could be viable for alternative formulations, such as parenteral or topical applications. Thus, the use of the Molinspiration Property Calculator enabled a preliminary screening of compounds with potentially favorable ADME characteristics for subsequent pharmacological testing.

Results

Within the scope of this study, a detailed analysis of the physicochemical properties of a series of 5-(2-bromo-5-methoxyphenyl)-4H-1,2,-4-triazole-3-thiol derivatives was conducted. These compounds were categorized into three groups: compounds 3a–3d, 4–4d, and 5a–5t. The findings are presented in a table encompassing the following parameters: partition coefficient (miLogP), topological polar surface area (TPSA), total number of atoms (n atoms), molecular weight (MW), number of hydrogen bond acceptors (nON), number of hydrogen bond donors (nOHNH), number of Lipinski's Rule violations (nviolations), number of rotatable bonds (nrotb), and molecular volume (volume). These metrics enable the evaluation of the structural and functional characteristics of each compound.

The first group (3a–3d) exhibits moderate lipophilicity, with miLogP values ranging from 3.02 for compound 3a (5-(2-bromo-5-methoxyphenyl)-4H-1,2,4-triazole-3-thiol) to 3.33 for compounds 3c (4-ethyl substituent) and 3d (4-phenyl substituent). The TPSA for compound 3a is 50.81 Å^2, the highest in this group, decreasing to 39.95 Å^2 for compounds 3b, 3c, and 3d, likely due to the substitution of a hydrogen atom with alkyl or phenyl groups. Molecular weight increases progressively from 286.15 g/mol (3a) to 314.21 g/mol (3c and 3d), reflecting the addition of atoms to the structure. The number of atoms varies from 15 (3a) to 17 (3c, 3d), with molecular volume rising from 193.22 Å^3 (3a) to 221.16 Å^3 (3c, 3d). The number of rotatable bonds increases from 2 (3a, 3b) to 3 (3c, 3d), indicating enhanced conformational flexibility.

The second group (4a – 4d), comprising derivatives with a thioacetic acid moiety, displays lower miLogP values compared to the 3a–3d group, ranging from 2.46 (4a) to 3.81 (4d). This may be attributed to the presence of a carboxyl group, which increases molecular polarity. TPSA values are notably higher, at 88.11 Å^2 for 4a and 77.25 Å^2 for 4b–4d, suggesting a greater capacity for hydrogen bonding. The number of hydrogen bond acceptors (nON) is consistently 6 across this group, while the number of donors (nOHNH) varies from 2 (4a) to 1 (4b–4d). Molecular weight rises from 344.19 g/mol (4a) to 420.29 g/mol (4d), correlating with an increase in atom count (19 to 25) and molecular volume (237.49 Å^3 to 309.28 Å^3). The number of rotatable bonds is higher (5–6) than in the previous group, reflecting the incorporation of a flexible thioacetic fragment.

The third group (5a–5t) consists of thioacetic acid esters with varying alkyl groups (methyl, ethyl, propyl, isopropyl, butyl). The miLogP values span a wide range, from 3.08 (5a) to 5.86 (5t), indicating a significant influence of alkyl chain length and type on lipophilicity. For instance, within the subgroup sharing the same triazole core (5a, 5e, 5i, 5m, 5q), miLogP increases from 3.08 (methyl ester) to 4.52 (butyl ester). TPSA ranges from 66.26 Å^2 (compounds with alkyl-substituted triazoles) to 77.11 Å^2 (compounds with unsubstituted triazoles). The number of atoms rises from 20 (5a) to 29 (5t), with molecular weight increasing from 358.22 g/mol (5a) to 476.40 g/mol (5t). The number of rotatable bonds escalates from 6 (5a–5b) to 10 (5s–5t), corresponding to the elongation of the ester chain. Violations of Lipinski's Rule (nviolations = 1) were observed for compounds 5l (miLogP = 5.30), 5p (miLogP = 5.16), and 5t (miLogP = 5.86), where miLogP exceeds the threshold of 5.

Discussion

The obtained results enable a detailed assessment of the impact of structural modifications on the physicochemical properties of the studied compounds. In the 3a–3d group, the increase in lipophilicity (miLogP) from 3.02 to 3.33 is associated with the introduction of hydrophobic alkyl (methyl, ethyl) or phenyl groups, consistent with the well-established relationship between substituent size and molecular hydrophobicity. The reduction in TPSA from 50.81 Å^2 (3a) to 39.95 Å^2 (3b–3d) indicates decreased polarity due to the substitution of the thiol hydrogen, which may negatively affect water solubility but enhance penetration through lipid membranes. The increase in the number of rotatable bonds in compounds 3c and 3d (to 3) compared to 3a and 3b (2) suggests greater conformational flexibility, potentially influencing interactions with biological targets.

Compounds in the second group (4a–4d) exhibit lower lipophilicity (miLogP ranging from 2.46 to 3.81) compared to their counterparts in groups 3 and 5, likely due to the incorporation of a polar carboxyl group

Tab. 1. *Physicochemical Properties and Drug-Likeness Parameters of 5-(2-Bromo-5-Methoxyphenyl)-4-R-1,2,4-Triazole-3-Thiol Derivatives*

№	Compound	Name of structure	mi Log P	TPSA	n atoms	MW	n ON	n OHNH	n violations	n rotb	volume
1	3a	5-(2-bromo-5-methoxyphenyl)-4H-1,2,4-triazole-3-thiol	3.02	50.81	15	286.15	4	1	0	2	193.22
2	3b	5-(2-bromo-5-methoxyphenyl)-4-methyl-4H-1,2,4-triazole-3-thiol	3.08	39.95	16	300.18	4	0	0	2	210.16
3	3c	5-(2-bromo-5-methoxyphenyl)-4-ethyl-4H-1,2,4-triazole-3-thiol	3.33	39.95	17	314.21	4	0	0	3	221.16
4	3d	5-(2-bromo-5-methoxyphenyl)-4-phenyl-4H-1,2,4-triazole-3-thiol	3.33	39.95	17	314.21	4	0	0	3	221.16
5	4a	2-((5-(2-bromo-5-methoxyphenyl)-4H-1,2,4-triazol-3-yl)thio)acetic acid	2.46	88.11	19	344.19	6	2	0	5	237.49
6	4b	2-((5-(2-bromo-5-methoxyphenyl)-4-methyl-4H-1,2,4-triazol-3-yl)thio)acetic acid	2.53	77.25	20	358.22	6	1	0	5	254.43
7	4c	2-((5-(2-bromo-5-methoxyphenyl)-4-ethyl-4H-1,2,4-triazol-3-yl)thio)acetic acid	2.91	77.25	21	372.24	6	1	0	6	271.23
8	4d	2-((5-(2-bromo-5-methoxyphenyl)-4-phenyl-4H-1,2,4-triazol-3-yl)thio)acetic acid	3.81	77.25	25	420.29	6	1	0	6	309.28
9	5a	Methyl 2-((5-(2-bromo-5-methoxyphenyl)-4H-1,2,4-triazol-3-yl)thio)acetate	3.08	77.11	20	358.22	6	1	0	6	255.01
10	5b	Methyl 2-((5-(2-bromo-5-methoxyphenyl)-4-methyl-4H-1,2,4-triazol-3-yl)thio)acetate	3.15	66.26	21	372.24	6	0	0	6	271.96
11	5c	Methyl 2-((5-(2-bromo-5-methoxyphenyl)-4-ethyl-4H-1,2,4-triazol-3-yl)thio)acetate	3.52	66.26	22	386.27	6	0	0	7	288.76
12	5d	Methyl 2-((5-(2-bromo-5-methoxyphenyl)-4-phenyl-4H-1,2,4-triazol-3-yl)thio)acetate	4.42	66.26	26	434.31	6	0	0	7	326.81
13	5e	Ethyl 2-((5-(2-bromo-5-methoxyphenyl)-4H-1,2,4-triazol-3-yl)thio)acetate	3.46	77.11	21	372.24	6	1	0	7	271.82
14	5f	Ethyl 2-((5-(2-bromo-5-methoxyphenyl)-4-methyl-4H-1,2,4-triazol-3-yl)thio)acetate	3.52	66.26	22	386.27	6	0	0	7	288.76
16	5g	Ethyl 2-((5-(2-bromo-5-methoxyphenyl)-4-ethyl-4H-1,2,4-triazol-3-yl)thio)acetate	3.90	66.26	23	400.30	6	0	0	8	305.56
16	5h	Ethyl 2-((5-(2-bromo-5-methoxyphenyl)-4-phenyl-4H-1,2,4-triazol-3-yl)thio)acetate	4.80	66.26	27	448.34	6	0	0	8	343.61
17	5i	Propyl 2-((5-(2-bromo-5-methoxyphenyl)-4H-1,2,4-triazol-3-yl)thio)acetate	3.96	77.11	22	386.27	6	1	0	8	288.62
18	5j	Propyl 2-((5-(2-bromo-5-methoxyphenyl)-4-methyl-4H-1,2,4-triazol-3-yl)thio)acetate	4.03	66.26	23	400.30	6	0	0	8	305.56
19	5k	Propyl 2-((5-(2-bromo-5-methoxyphenyl)-4-ethyl-4H-1,2,4-triazol-3-yl)thio)acetate	4.40	66.26	24	414.32	6	0	0	9	322.36
20	5l	Propyl 2-((5-(2-bromo-5-methoxyphenyl)-4-phenyl-4H-1,2,4-triazol-3-yl)thio)acetate	5.30	66.26	28	462.37	6	0	1	9	360.41
21	5m	Isopropyl 2-((5-(2-bromo-5-methoxyphenyl)-4H-1,2,4-triazol-3-yl)thio)acetate	3.82	77.11	22	386.27	6	1	0	7	288.40
22	5n	Isopropyl 2-((5-(2-bromo-5-methoxyphenyl)-4-methyl-4H-1,2,4-triazol-3-yl)thio)acetate	3.89	66.26	23	400.30	6	0	0	7	305.35
23	5o	Isopropyl 2-((5-(2-bromo-5-methoxyphenyl)-4-ethyl-4H-1,2,4-triazol-3-yl)thio)acetate	4.26	66.26	24	414.32	6	0	0	8	322.15
24	5p	Isopropyl 2-((5-(2-bromo-5-methoxyphenyl)-4-phenyl-4H-1,2,4-triazol-3-yl)thio)acetate	5.16	66.26	28	462.37	6	0	1	8	360.19
25	5q	Butyl 2-((5-(2-bromo-5-methoxyphenyl)-4H-1,2,4-triazol-3-yl)thio)acetate	4.52	77.11	23	400.30	6	1	0	9	305.42
26	5r	Butyl 2-((5-(2-bromo-5-methoxyphenyl)-4-methyl-4H-1,2,4-triazol-3-yl)thio)acetate	4.59	66.26	24	414.32	6	0	0	9	322.36
27	5s	Butyl 2-((5-(2-bromo-5-methoxyphenyl)-4-ethyl-4H-1,2,4-triazol-3-yl)thio)acetate	4.96	66.26	25	428.35	6	0	0	10	339.17
28	5t	Butyl 2-((5-(2-bromo-5-methoxyphenyl)-4-phenyl-4H-1,2,4-triazol-3-yl)thio)acetate	5.86	66.26	29	476.40	6	0	1	10	377.21

into the thioacetic fragment. Elevated TPSA values (88.11 Å² for 4a and 77.25 Å² for 4b–4d) and the presence of 6 hydrogen bond acceptors underscore the higher polarity of these molecules, which may improve water solubility but hinder cellular membrane permeability. The increase in molecular weight and volume in this group correlates with the addition of a phenyl substituent (4d), while the higher number of rotatable bonds (5–6) compared to the 3a–3d group reflects the flexibility of the thioacetic chain.

The third group (5a – 5t) is characterized by considerable variability in lipophilicity, dependent on the ester group type. For instance, the transition from a methyl ester (5a, miLogP = 3.08) to a butyl ester (5q,

miLogP = 4.52) or phenyl derivative (5t, miLogP = 5.86) demonstrates a clear trend of increasing hydrophobicity with elongation of the alkyl chain. The decrease in TPSA to 66.26 Å^2 in compounds with substituted triazoles (e.g., 5b–5t) compared to 77.11 Å^2 in unsubstituted analogs (5a, 5e) may suggest a reduced capacity for hydrogen bonding. The rise in rotatable bonds (up to 10 in 5s–5t) reflects increasing conformational flexibility, which could be advantageous (e.g., adaptability to receptors) or disadvantageous (e.g., reduced conformational stability). Violations of Lipinski's Rule in compounds 5l, 5p, and 5t (miLogP > 5) indicate potential challenges with oral bioavailability, necessitating further investigation, such as evaluation of metabolism or alternative administration routes. Overall, varying substituents in the triazole core and ester groups allows precise tuning of key molecular parameters, offering opportunities for optimization in the context of pharmacological properties.

Conclusion

This study confirmed that structural modifications of 5-(2-bromo-5-methoxyphenyl)-4H-1,2,4-triazole-3-thiol derivatives effectively influence their physicochemical properties, including lipophilicity, polarity, and conformational flexibility. Compounds bearing carboxyl groups (4a–4d) exhibit increased polarity, whereas esters (5a–5t) demonstrate a dependence of lipophilicity on the type of alkyl chain. The identified violations of Lipinski's Rule for compounds 5l, 5p, and 5t highlight the need for further investigation of their pharmacokinetic profiles. The obtained results underscore the potential of these compounds as candidates for pharmaceutical development and provide a foundation for subsequent biological and pharmacological studies.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

AUTHORS' CONTRIBUTION

Conceptualized: Mykola Skoryi, Roman Shcherbyna.

Designed the methodology: Roman Shcherbyna, Olexandra Cherchesova.

Software and data curation: Volodymyr Salionov, Olexandra Cherchesova.

Performed the formal analysis and experiments: Roman Shcherbyna, Sergii Kulish.

Collected the data. Mykola Skoryi, Sergii Kulish, Volodymyr Salionov.

Wrote the initial draft and supervised the research: Mykola Skoryi, Olexandra Cherchesova.

Prepared the data presentation. Mykola Skoryi, Roman Shcherbyna, Sergii Kulish, Volodymyr Salionov, Olexandra Cherchesova.

Coordinated the project. Mykola Skoryi, Roman Shcherbyna.

REFERENCES

1. Ekins S, Lane TR, Urbina F, Puhl AC. In silico ADME/tox comes of age: twenty years later. Xenobiotica. 2024;54(7):352-358.
2. Maver T, Vihar B, Maver U. A narrative review of ADME testing platforms. Acta Med Biotech. 2024;17(2):9-17.
3. Lohit N, Singh AK, Kumar A, Singh H, Yadav JP, Singh K, et al. Description and in silico ADME studies of US-FDA approved drugs or drugs under clinical trial which violate the Lipinski's Rule of 5. Lett Drug Des Discov. 2024;21(8):1334-1358.
4. Johnson DB, Singh G, Sharma D, Natarajan V, Lakshmi KNVC, Dhakar RC, et al. Exploring computational advancements in ADME: essential insights for drug disposition. Chin J Appl Physiol. 2024;40:e20240033.
5. Paggi JM, Pandit A, Dror RO. The art and science of molecular docking. Annu Rev Biochem. 2024;93:261-284.
6. De P, Kar S, Ambure P, Roy K. Prediction reliability of QSAR models: an overview of various validation tools. Arch Toxicol. 2022;96(5):1279-95.
7. Tiwari S, Nagarajan K, Gupta A. SwissADME: an in silico ADME examination tool. In: Alam S, Gupta A, editors. Computational biology in drug discovery. Boca Raton (FL): CRC Press; 2024. p. 415-424.
8. Shcherbyna R, Pruhlo Y, Duchenko M, Kulagina M, Kudria V, Vashchuk V. Evaluation of antioxidant activity of 1, 2, 4-triazole derivatives with morpholine moiety. Hacettepe Univ J Fac Pharm. 2022;42(2):73-82.
9. Shcherbyna R, Panasenko O, Polonets O, Nedorezaniuk N, Duchenko M. Synthesis, antimicrobial and antifungal activity of ylidenehydrazides of 2-((4-R-5-R1-4H-1,2,4-triazol-3-yl)thio)acetaldehydes. J Fac Pharm Ankara Univ. 2021;45(3):504-514.
10. Shcherbyna R. An investigation of the pharmacokinetics and potential metabolites of potassium 2-((4-amino-5-(morfolinometyl)-4H-1,2,4-triazol-3-yl)thio) acetate on rats. J Fac Pharm Ankara Univ. 2020;44(2):233-241.
11. Usenko DL, Varynskyi BO, Kaplaushenko AH, Safonov AA, Panasenko OI, Morozova LP, et al. The research of pharmacokinetic parameters and metabolism of sodium 2-((4-amino-5-(thiophen-2-ylmethyl)-4H-1,2,4-triazol-3-yl)thio)acetate for use in military and civilian medicine. Ukr J Mil Med. 2024;5(4):159-167.
12. Sameliuk Y, Kaplaushenko A, Diakova F, Ostretsova L, Nedorezaniuk N, Gutyj B. Prospects for the search for new biologically active compounds among the derivatives of the heterocyclic system of 1,2,4-triazole. Hacettepe Univ J Fac Pharm. 2022;42(3):175-186.
13. Hotsulia AS, Brytanova TS, Fedotov SO, Ubogov SG, Pidlisnyi OV, Yaroshenko IV. The pharmacological potential of 1-alkyl derivatives of 4-((4-nitrobenzylidene)amino)-1,2,-4-triazole. Ukr J Mil Med. 2024;5(3):85-94.
14. Zvenihorodska T, Hotsulia A, Kravchenko S, Fedotov S, Kyrychko B. Synthesis and antimicrobial action of 1,2,4-triazole derivatives containing theophylline and 1,3,4-thiadiazole fragments in their structure. Afr J Biomed Res. 2021;24(1):159-163.
15. Safonov A, Demianenko D, Vashchyk Y, Larianovska Y, Lytkin D, Shcherbyna R, et al. Histological study of a corrective influence of sodium 2-((4-amino-5-(thiophen-2-ylmethyl)--4H-1,2,4-triazol-3-yl)thio) acetate on the state of rats liver under conditions of acute immobilization stress. J Fac Pharm Ankara Univ. 2022;46(2):330-341.
16. Isaicheva K, Kaplaushenko A, Sameliuk Y. Synthesis, determination of physico-chemical parameters, structure confirmation, and antioxidant activity of compounds based on 3,5-bis(5-mercapto-4-R-4H-1,2,4-triazole-3-yl)phenol. Sci Rise Pharm Sci. 2024;51(5):63-70.
17. Zafar W, Sumrra SH, Chohan ZH. A review: pharmacological aspects of metal based 1,2,4-triazole derived Schiff bases. Eur J Med Chem. 2021;222:113602.
18. Kaur R, Ranjan Dwivedi A, Kumar B, Kumar V. Recent developments on 1,2,4-triazole nucleus in anticancer compounds: a review. Anticancer Agents Med Chem. 2016;16(4):465-489.
19. Mohamed MS, Ibrahim NA, Gouda AM, Badr M, El-Sherief HAM. Design, synthesis and molecular docking of 1,2,4-triazole schiff base hybrids as tubulin, EGFR inhibitors and apoptosis-inducers. J Mol Struct. 2023;1286:135621.
20. Sadeghian S, Emami L, Mojaddami A, Khabnadideh S, Faghih Z, Zomorodian K, et al. 1,2,4-Triazole derivatives as novel and potent antifungal agents: design, synthesis and biological evaluation. J Mol Struct. 2023;1271:134039.
21. Kiran PVR, Waiker DK, Verma A, Saraf P, Bhardwaj B, Kumar H, et al. Design and development of benzyl piperazine linked 5-phenyl-1,2,4-triazole-3-thione conjugates as potential agents to combat Alzheimer's disease. Bioorg Chem. 2023;139:106749.
22. Gitto R, Vittorio S, Bucolo F, Peña-Díaz S, Siracusa R, Cuzzocrea S, et al. Discovery of neuroprotective agents based on a 5-(4-pyridinyl)-1,2,4-triazole scaffold. ACS Chem Neurosci. 2022;13(5):583-591.
23. Skoryi M, Shcherbyna R, Salionov V. Synthesis and biological potential of 1,2,4-triazole derivatives with a 2-bromo-5-methoxyphenyl fragment. In: Proceedings of the scientific conference. Zaporizhzhia: Zaporizhzhia State Medical and Pharmaceutical University; 2023. p. 162-164.
24. Skoryi MP, Shcherbyna RO. QSAR prediction of toxicity for a new 1,2,4-triazole derivatives with 2-bromo-5-methoxyphenyl fragment. Curr Issues Pharm Med Sci Pract. 2024;17(3):226-230.
25. Suganya M, Hemamalini M, Jose Kavitha S, Rajakannan V. In silico studies of molecular property and bioactivity of organic crystalline compounds using Molinspiration. Int Res J Eng Technol. 2020;7(2):519. [cited 2025 Apr 20]. Available from: https://www.irjet.net
26. Mishra SS, Kumar N, Pandiya H, Singh HP, Sharma CS. In silico pharmacokinetic, bioactivity and toxicity study of some selected anti-anginal agents. Int J Appl Pharm Biol Res. 2017;2(4):57-60. [cited 2025 Apr 20]. Available from: http://www.ijapbr.com/