Tuijin Jishu/Journal of Propulsion Technology
ISSN: 1001-4055
Vol. 47 No.01 (2026)

Design and Eco-Friendly Synthesis of 4-Oxothiazolidinone-Thiourea Derivative: In Silico Antimicrobial Evaluation and DFT Studies

Karpagam Ezhilarasan[a], Satheeshkumar Nagaraj[a] and Rajalakshmi Ramarajan[*a],

[a]*Department of Chemistry, Annamalai University, Annamalai Nagar, Chidambaram, Tamil Nadu- 608 002, India.*

Abstract: A novel 1-(2-(4-methylphenyl)-4-oxothiazolidin-3-yl)thiourea derivative is synthesized through a tetrabutylammonium bromide catalyzed multicomponent condensation involving 4-methyl substituted aldehydes, amines, and thioglycolic acid. The molecular structures of the obtained 4CTA derivatives are confirmed using FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopic techniques. In silico studies target *Orientia tsutsugamushi*, the causative agent of scrub typhus, to evaluate the potential biological activity and to correlate computational results with experimental findings. The developed synthetic protocol demonstrates environmental sustainability and operational simplicity, affording excellent yields (>95%), reduced reaction times, and a broad substrate scope, which highlights its suitability for the rapid synthesis of biologically relevant thiazolidinone frameworks. ADMET and ProTox computational evaluations are carried out to assess pharmacological relevance, indicating favorable pharmacokinetic properties and low predicted toxicity. Density Functional Theory (DFT) calculations are employed to investigate the electronic properties and reactivity profiles of the active compounds, providing insight

1. Introduction

Recent research in drug development has focused on organic compounds that possesheteroatoms oxygen, sulphur, and nitrogen due to their critical roles in biological processes[1-3]. One class of these compound is thiazolidine and consisting of a carbonyl group, a nitrogen atom at position 3, and a sulphur atom at position at positions 1, 2, 4, or 5. These compounds and their derivatives are widely studied. The first discovery of thiazolidinones in nature was in penicillin, which contains this structure [4-5]. Many approved medicines have been developed with the 4-thiazolidinone in the core structure.

Thiazolidinone derivatives are known for their many biological effects, including anti-HIV1, antibacterial [6], anti-tuberculosis [7], anti-cancer [8], anti-inflammatory [9], anticonvulsant [10], antioxidant [11], and anti-breast cancer[12], properties. Drugs like thiazolidinone derivatives, which target Streptomyces species, as well as etozoline (used for high blood pressure), pioglitazone (for lowering blood sugar), and ralitoline (an anticonvulsant), have been developed using this structure[13]. There are many ways to produced 4-thiazolidinones, usually involving three main ingredients: A mercapto acid, a carbonyl compound, and an amine [14], Some of the common methods for making these compounds are one-pot, three-component reactions [15–16]. or two-step processes [17–18], each with its own advantages The procedure generally starts with imine formation, followed by its reaction with sulfur, leading to ring closure accompanied by water elimination. Various solvents like diethyl formamide (DMF) [19], 1,4-dioxane ([20].), benzene([21].) and DMSO[22].

Recent developments in thiazolidinone derivatives have led to drugs with lower toxicity and better effectiveness. The 4-thiazolidinone ring structure is still very important in drug development. Small changes to the thiazolidinone structure can greatly improve its biological effects. introduce another heterocyclic group to the thiazolidinone structure has been shown to enhance its biological activity [25–30].

The present study focuses on the synthesis of a novel 1-(2-(4-methylphenyl)-4-oxothiazolidin-3-yl)thiourea derivative via an eco-friendly multicomponent strategy, followed by comprehensive structural, computational, and pharmacological evaluation. The integration of green chemistry principles with in silico biological and electronic analyses aims to establish a robust framework for the rapid identification of thiazolidinone-based candidates with potential activity against O. tsutsugamushi.

2. Experimental Section

2.1 General

High- purity All of the study substances are of comparable quality. To track every reaction, Merck silica gel 60-coated plates are used for thin-layer chromatography (TLC). The mobile phase is a combination of ethyl acetate and petroleum ether. A Bruker 400 MHz NMR spectrometer records ^{1}H and ^{13}C NMR spectra in $CDCl_3$, while a Thermo Nicolet iS5 spectrophotometer using KBr pellets records FT-IR spectra, with absorption bands reported in cm^{-1}. The internal standard is tetramethylsilane (TMS), and chemical shifts (δ) are measured in parts per million (ppm). Singlet, doublet, triplet, quartet, and broad signals are represented by the symbols s, d, t, q, and br, respectively; multiplets and broad singlets are represented by the symbols m and br s.

2.2. Synthesis

2.2.1 (E)-1-(4-methylbenzylidene)thiosemicarbazide

One mole of thiosemicarbazide and 4-methylbenzaldehyde is mixed in the presence of anhydrous zinc chloride as a catalyst and stirred at 60 °C for 20 min. After the reaction is complete, the mixture is cooled, and the solid product is recrystallized from methanol.

2.2.2 1-(2-(4-methylphenyl)-4-oxothiazolidin-3-yl)thiourea

Equimolar amounts of (E)-1-(4-methylbenzylidene)thiosemicarbazide and thioglycolic acid are mixed with tetrabutylammonium bromide as a catalyst. The mixture is refluxed at 110 °C for 25–35 min to form 1-(2-(4-methylphenyl)-4-oxothiazolidin-3-yl)thiourea. The reaction mixture is poured into cold water and kept at 0 °C for 48 h. The solid product is collected by filtration and purified by recrystallization from benzene.

2.2.3 1-(2-(4-methylphenyl)-4-oxothiazolidin-3-yl)thiourea

The title compound was synthesized, yielding 93% of an orange solid. The melting point was observed between 295 and 312 degrees Celsius. The IR (KBr) spectrum showed characteristic absorptions at 3029 cm^{-1} (aromatic C-H), 1628 cm^{-1} (C=O) of the thiazolidinone, 1595 cm^{-1} (C=C), 1509 cm^{-1} (C=S), 1274 cm^{-1} (C-N), 3440 cm^{-1} NH, 3216-3328 cm^{-1} NH2.

The ^{1}H NMR (DMSO) spectrum displayed signals at δ 5.482 ppm (singlet, 2H, SCH_2 of the thiazolidinone), 3.527 ppm (singlet, 1H, NCH of the thiazolidinone), (singlet, 2H, NH2)11.105, (singlet, 1H, NH)10.368, (singlet, 3H, CH3)2.086 and 7.612-7.994 ppm (multiplet, 4H, aromatic protons).

The ^{13}C NMR spectrum showed signals at δ 38.71 ppm (C5 of the thiazolidinone), 161.64 ppm (C=O of the thiazolidinone), 19.74 ppm (methyl carbon),61.19 ppm (C2 of the thiazolidinone),171.78 ppm (C=S of the thiazolidinone) and a range of signals from 127.48 to128.83 ppm, consistent with aromatic carbons.

2. 3 Computational methodology

The structures of the compounds are optimized using density functional theory (DFT) with the Gaussian09 and GaussView5 software. Molecular properties such as the molecular electrostatic potential (MEP), HOMO–LUMO energy gap, and geometric parameters are analyzed to determine the most stable structures. The optimized geometries meet the requirements for further study. Electron distribution in the molecules is visualized using electron localization function (ELF) plots generated with the Multiwfn program based on atoms-in-molecules (AIM) theory

2.4 Molecular Docking

The Protein Data Bank (PDB ID: 6UPU) provided the tubulin–combretastatin A-4 complex's X-ray crystal structure, which has an R-value of 0.192 and a resolution of 2.40 Å. For docking investigations, the D-chain is chosen because it contains the combretastatin A-4 binding site. Molecular docking is carried out using methods described in earlier research.

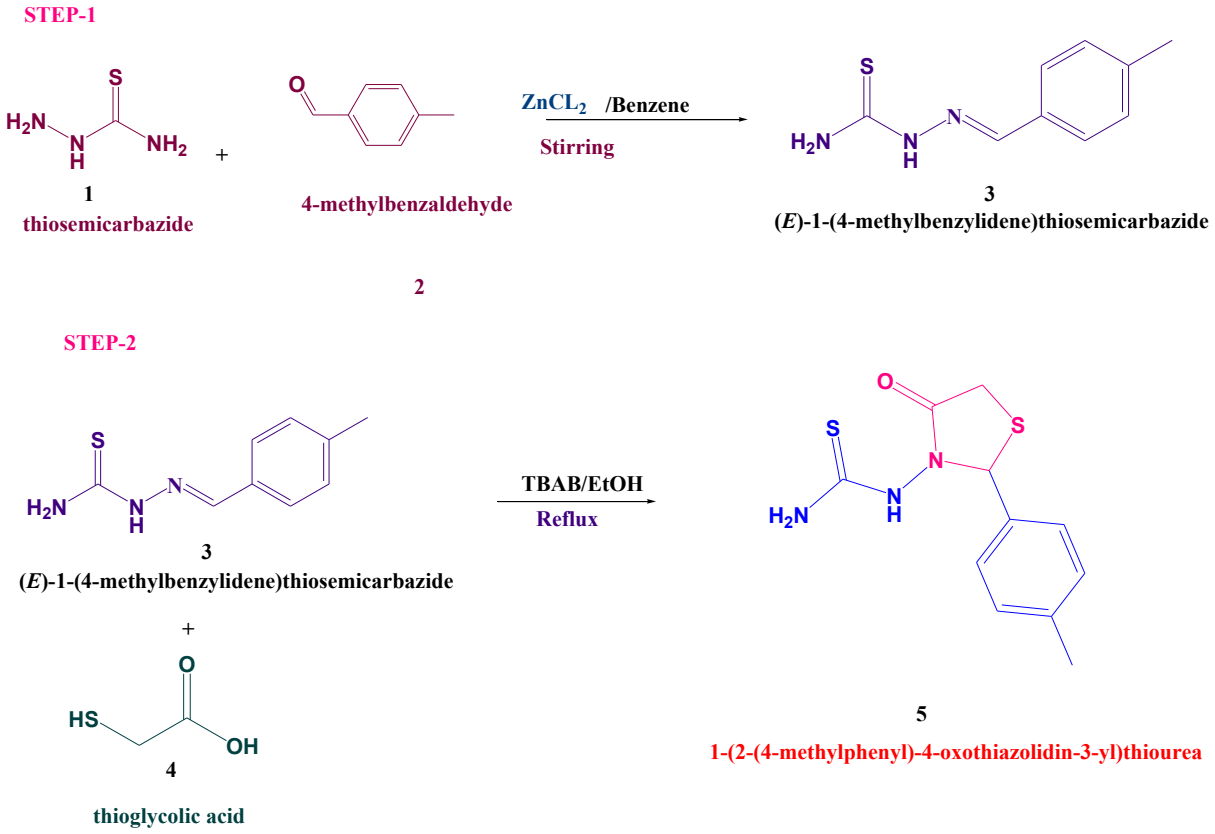
2.5 ADME and Toxicity Prediction

The ADME (absorption, distribution, metabolism, and excretion) properties were predicted using the SwissADME tool available online . Toxicity predictions, including LD50 values and toxicity class, were carried out using the ProTox-II platform.

3. Results and discussion

3.1 Chemistry

Thiosemicarbazide (1), when condensed with 4-methylbenzaldehyde (2) in the presence of anhydrous zinc chloride, forms the corresponding Schiff's bases (E)-1-(4-methylbenzylidene)thiosemicarbazide (3). An Efficient Synthesis of Thiazolidinone Derivatives via Cyclo-Condensation of Schiff Bases with Thioglycolic Acid in the Presence of Tetrabutylammonium hydroxide. An efficient method has been developed for synthesizing thiazolidinone derivatives through the cyclo-condensation of Schiff bases with thioglycolic acid in a water-ethanol medium, using tetrabutylammonium Bromide (Bu_4NBr) as a basic ionic liquid. Initially, we evaluated the reaction between thioglycolic acid and the Schiff base under these conditions. The reaction proceeds via nucleophilic attack by the sulfur atom of thioglycolic acid on the electrophilic carbon of the imine (C=N) group in the Schiff base, followed by ring closure with the elimination of water molecule. This annulation was carried out using 1 mL of 50% aqueous Bu_4NOH at 70°C for 2 hours, affording the desired thiazolidinone derivative(5) in high yields. The general synthetic method for 1-(2-(4-methylphenyl)-4-oxothiazolidin-3-yl)thiourea derivative is presented in scheme-1.



Scheme-1

3.2 Spectral analysis for compound 5

FT-IR, ^1H NMR, ^{13}C NMR, and mass spectrum analysis are used to describe the product. For the representative compound 5, the FT-IR spectrum showed key characteristic peaks. The carbonyl (>C=O) stretching frequency of the thiazolidinone ring is detected at 1628 cm^{-1} in compound 5 infrared spectra. The >C-S- in the thiazolidinone ring was identified as the cause of the absorption band at 1189 cm^{-1}. The thiazolidinone ring (C-N) stretching frequency is found at 1274 cm^{-1}. The >C=S- in the thiazolidinone was identified as the source of the absorption band at 1502 cm^{-1}. The thiazolidinone (NH) stretching frequency is found to be 3440 cm^{-1}. The thiazolidinone (NH_2) stretching frequency is found at 3216–3328 cm^{-1}. The IR Spectrum of compound 5 is shown in Figure- 1.

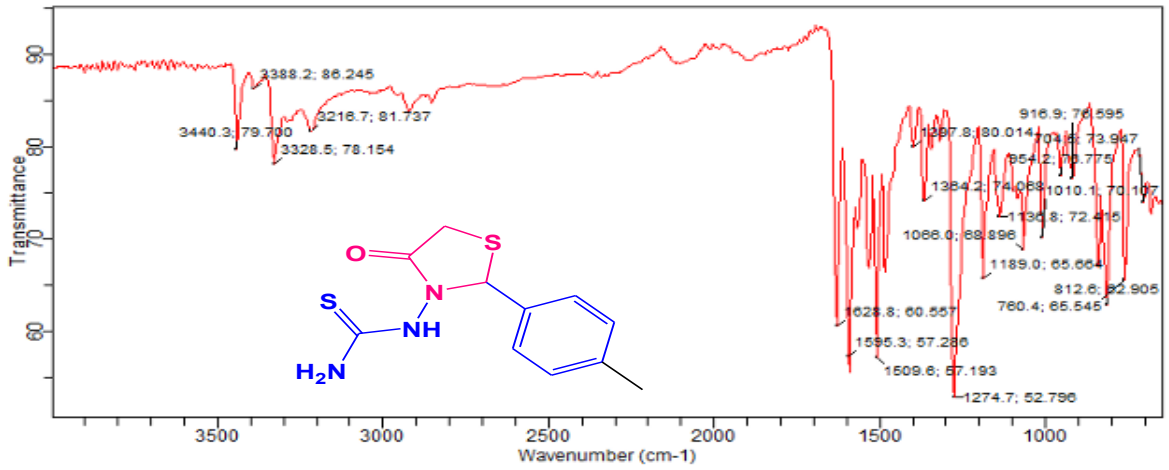


Figure-1- IR Spectrum of compound 5

In the ^{1}H NMR spectrum of compound 5. The singlet with a two-proton integral at 5.482 ppm in compound 5 ^{1}H spectra is attributed to the thiazolidinone ring methine proton. The methylene protons of the thiazolidinone ring are represented by the singlet at 3.527 ppm, which integrates for one proton. The amine (NH_2) protons are attributed to the singlet with a two-proton integral at 11.105 ppm. The amine (NH) proton is identified as a singlet at 10.368 ppm, integrating for one proton. The methyl (CH_3) proton is identified as the source of a singlet at 2.086 ppm that integrates for three protons. The aromatic protons are responsible for the multiplet that appears in the range of 7.612–7.994 ppm. The ^{1}H NMR Spectrum of compound 5 is shown in Figure- 2.

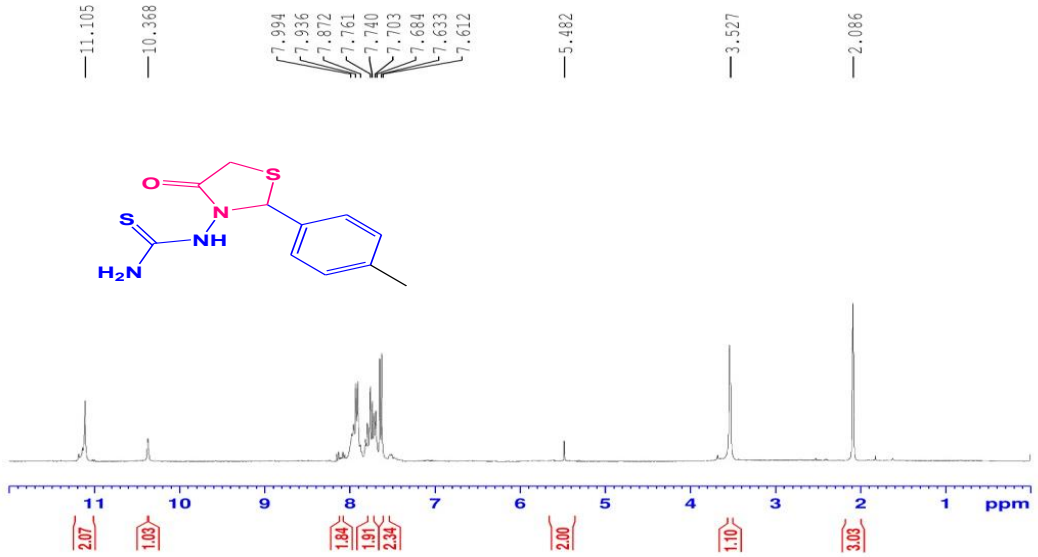


Figure-2- ^{1}H NMR Spectrum of compound 5

In the ^{13}C NMR spectrum of compound 5. The carbonyl carbon (>C=O) of the thiazolidinone ring is responsible for the downfield carbon signal in compound 5 ^{13}C NMR spectra at 161.64 ppm. The thiazolidinone ring methylene carbon can be found at 38.71 ppm. The thiazolidinone ring methine carbon can be found at 61.19 ppm. The thio carbonyl (>C=S) is attributed to the downfield carbon signal at 171.78 ppm. The signal between 127.48 and 128.83 ppm was clearly attributed to an aromatic proton. The ^{13}C NMR Spectrum of compound 5 is shown in Figure- 3

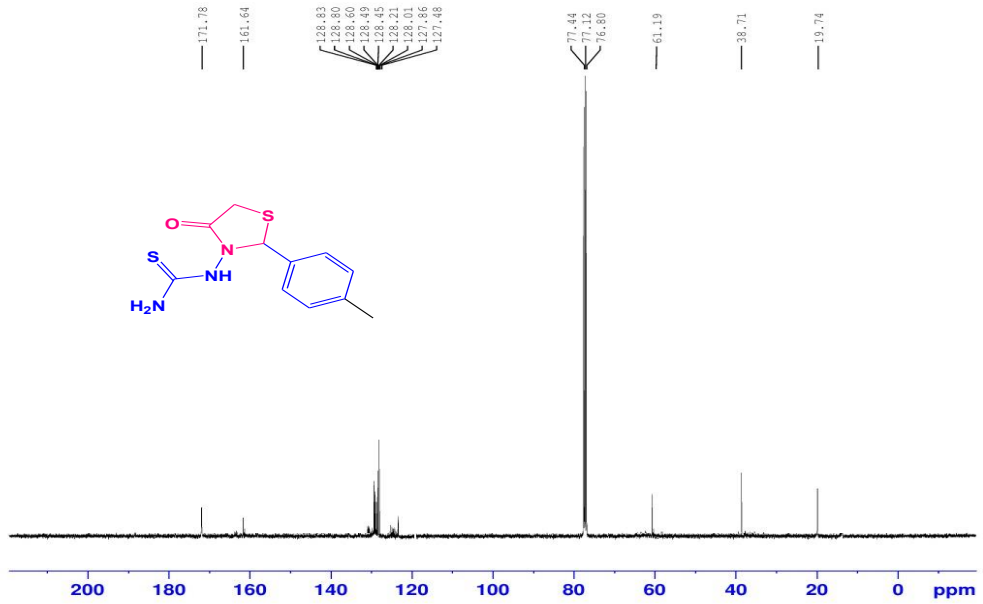


Figure- 3- ^{13}C NMR Spectrum of compound 5

3.3 Molecular docking analysis thaizolidinones against protein (6UPU)

The computational study begins with molecular docking simulations using AutoDock 4.2 and BIOVIA Discovery Studio to determine the binding orientation and binding affinity of compound 5 toward the deubiquitinase enzyme of Orientia tsutsugamushi (OtDUB). The crystal structure of the target protein (PDB ID: 6UPU) is used as the docking model. Before docking, the protein structure is prepared by removing crystallographic water molecules, co-crystallized ligands, and other heteroatoms to ensure accurate interaction analysis at the active site.

Orientia tsutsugamushi is an obligate intracellular Gram-negative bacterium transmitted by infected chigger mites of the Leptotrombidium genus and is the causative agent of scrub typhus. This disease is prevalent in the Asia Pacific region and presents with nonspecific symptoms such as fever, headache, muscle pain, rash, and eschar formation at the bite site. If left untreated, the infection may lead to severe complications, including pneumonitis, meningoencephalitis, multiple organ failure, and death. The high antigenic variability of the pathogen also complicates accurate diagnosis and vaccine development. Docking results **(Table 1**) show that compound 5 binds effectively to the target protein 6UPU with a binding energy of −8.89 kcal/mol, indicating a strong and thermodynamically favorable interaction. This result suggests that compound 5 has a high affinity for the enzyme's active site. Analysis of the binding pose reveals that compound 5 fits well within the binding pocket of 6UPU and interacts with key amino acid residues, including Val533(A), Cys530(A), Lys529(A), Gln600(A), Met528(A), Leu525(A), Met522(A), Tyr526(A), and Leu536(A). Hydrophobic interactions involving Val, Leu, Met, and Tyr residues play a major role in stabilizing the ligand–protein complex. In addition, Lys529 and Gln600 contribute through polar and possible hydrogen-bond interactions, which further strengthen binding.

Overall, the strong binding affinity and effective interaction with critical active-site residues indicate that compound 5 forms a stable and well-oriented complex with 6UPU. These findings highlight its potential as a promising lead compound and provide a solid foundation for further biological evaluation and structure–activity relationship studies. . The **Docking images of compound 5 against 6UPU** is illustrated in Figure 4.

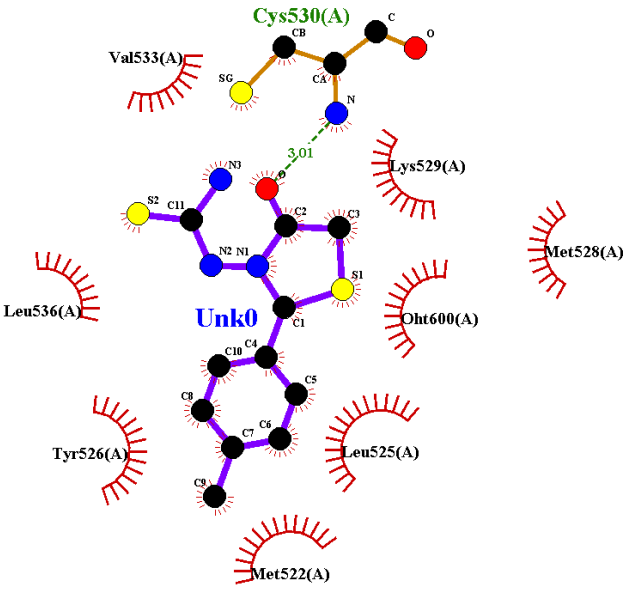


Figure 4. Docking images of compound 5 against 6UPU

Table 1. Binding affinity of the synthesized compound 5 against 6UPU

COMPOUND	BINDING AFFINITY	AMINO ACID RESIDUES
5	-8.89	Val533(A), Cys530(A), Lys529(A), Oht600(A), Met528(A), Leu525(A), Met522(A), Tyr526(A), Leu536(A).

3.4. *In silico* ADMET study

The predicted ADMET parameters of compound 5, presented in Table 2, provide an overview of its physicochemical properties, pharmacokinetic behavior, and drug-likeness. Compound 5 has a molecular formula of $C_{11}H_{13}N_3OS_2$ and a molecular weight of 267.37 g/mol, which falls within the preferred range for small-molecule drugs and supports efficient absorption and distribution.

SwissADME analysis shows that compound 5 has a balanced hydrogen-bonding capacity, with one hydrogen-bond acceptor and two hydrogen-bond donors, which supports effective target interaction while maintaining membrane permeability. The iLogP value of 1.74 indicates moderate lipophilicity and suggests good oral bioavailability. The compound also shows moderate water solubility (1.09 mg/mL), indicating favorable formulation potential.

Pharmacokinetic predictions indicate high gastrointestinal absorption, supporting the suitability of compound 5 for oral administration. The topological polar surface area (TPSA) of 115.75 Å² remains within an acceptable range for drug-like molecules and supports adequate intestinal absorption and polar interactions with the target protein. Compound 5 satisfies the drug-likeness criteria applied by SwissADME and shows no structural features that limit its development. Overall, compound 5 displays a well-balanced ADMET profile with favorable physicochemical and pharmacokinetic properties, supporting its potential as a lead compound. The bioavailability radar of compound 5 is shown in Figure- 5.

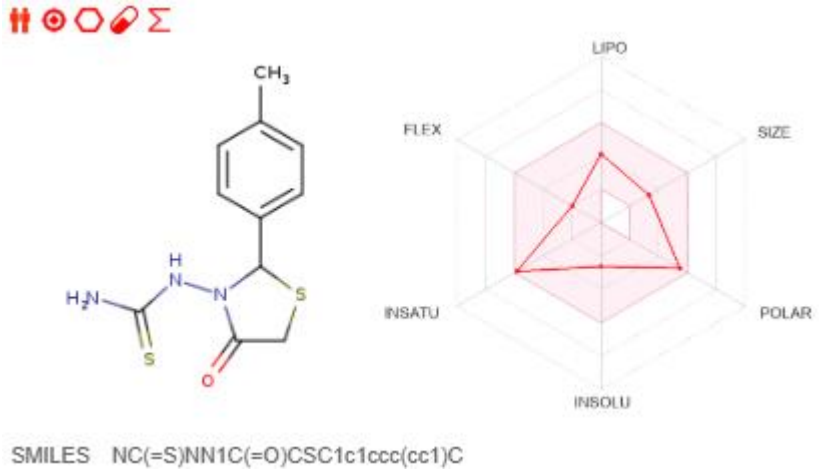


Figure 5. The Bioavailability Radar for compound 5

Table 2: Complete ADMET profile of (5), including pharmacokinetics, physicochemical properties, lipophilicity, water-solubility, pharmacokinetics, drug-likeness and medicinal chemistry.

Ligand	Chemical Formula	Swiss ADME Filters							
		Molar mass (g/mol)	H bond acceptor	H bond donor	iLogP	Water Solubility mg/ml	GI absorption	TPSA (Å2)	Drug-like ness
17	$C_{11}H_{13}N_3OS_2$	267.37	1	2	1.74	1.09(Moderate)	High	115.75	Yes

3.2.5. *In silico* toxicological assessment

The toxicity profile of compound 5, predicted using the ProTox-III platform and summarized in Table 3, provides early insight into its safety characteristics. Compound 5 shows a predicted oral LD_{50} value of 1500 mg/kg and falls into toxicity class 4, which is associated with low acute toxicity. This result suggests that compound 5 is unlikely to cause severe toxic effects at therapeutically relevant doses.

Endpoint-specific toxicity predictions indicate that compound 5 is inactive toward major toxicity risks, including hepatotoxicity, cardiotoxicity, immunotoxicity, mutagenicity, and cytotoxicity. The probability scores (0.51–0.99) support a high level of confidence in these predictions. Notably, the absence of predicted liver and cardiac toxicity is significant, as these effects commonly limit drug development.

ProTox-III analysis also reports 100% average similarity and prediction accuracy, confirming the reliability of the computational model used for compound 5. Overall, compound 5 shows a favorable toxicity profile with a low risk of acute oral toxicity and organ-specific adverse effects.

When considered together with its promising pharmacokinetic and binding properties, the predicted safety profile supports the potential of compound 5 as a viable lead compound and justifies further experimental validation and preclinical evaluation. The overall toxicity radar of compound 5 is shown in Figure 6.

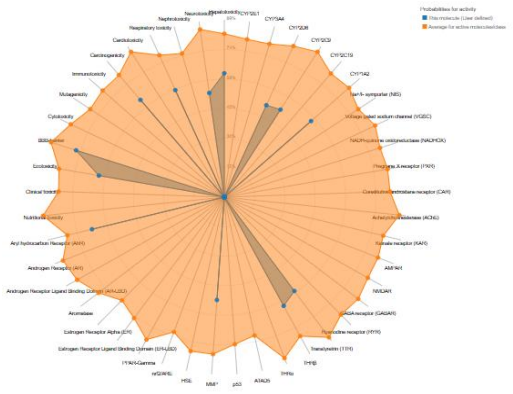


Figure 6. Overall toxicity radar chart of compound 5

Table 3: ProTox-III predicts bioactive chemical oral organ and endpoint toxicity of compound 5

Compound No	Const.LD50 dos (mg/kg) prediction	Prediction toxicity The toxicity prediction criteria and % probability value of bioactive molecules						Average similarity %	Prediction Accuracy %
		class	Hepato	Cardio	Immuno.	Mutag.	Cyto.		
5	1500	4	Inactive (0.51)	Inactive (0.70)	Inactive (0.99)	Inactive (0.57)	Inactive (0.71)	100	100

3.6 Frontier Molecular Orbitals

Frontier molecular orbital (FMO) analysis of compound 5, shown in **Table 4**, provides insight into its electronic properties and reactivity. The calculated HOMO energy (−6.979 eV) indicates the ability of the molecule to donate electrons, while the LUMO energy (−1.714 eV) reflects its tendency to accept electrons during molecular interactions. The relative positions of these orbitals play an important role in predicting charge-transfer behavior during binding with biological targets.

The HOMO–LUMO energy gap (ΔE = 5.265 eV) suggests that compound 5 possesses good electronic stability with controlled reactivity. This energy gap indicates resistance to unwanted chemical changes while allowing effective interaction with target proteins under physiological conditions.

The chemical potential ($\mu = -4.347$ eV) and electronegativity ($\chi = 4.347$ eV) show a moderate tendency of the molecule to attract electron density, supporting stable non-covalent interactions. The global hardness value ($\eta = 2.633$ eV) confirms the structural stability of the compound, while the softness value ($S = 0.190$ eV^{-1}) indicates sufficient polarizability for adaptive binding in a biological environment.

The electrophilicity index ($\omega = 3.589$ eV) indicates moderate electrophilic behavior, allowing the compound to participate in electron-accepting interactions without excessive reactivity. Overall, the FMO descriptors demonstrate a balanced electronic structure that agrees well with the docking results, ADMET profile, and toxicity predictions of compound 5. The HOMO–LUMO distribution of compound 5 is illustrated in Figure 7.

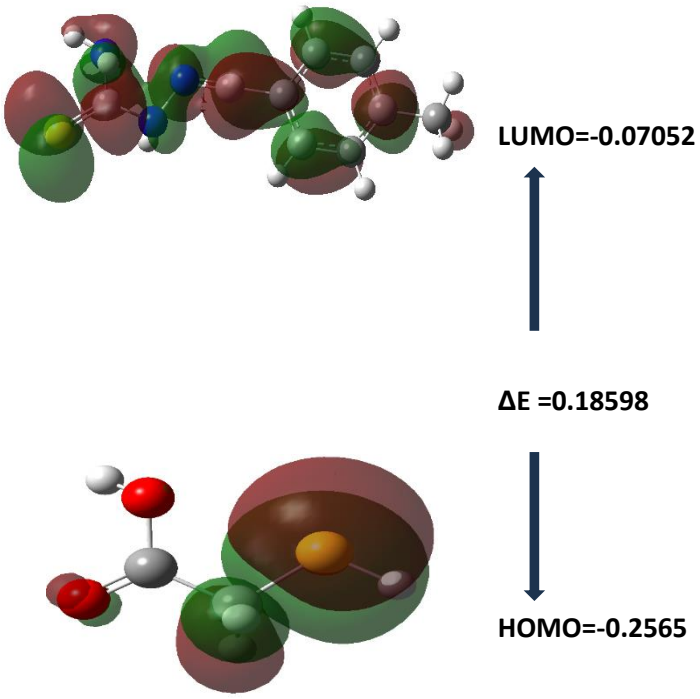


Figure-7 HOMO–LUMO of Compound 5

Table 4. Frontier Molecular Orbitals values of compound 5

Compound	Homo	Lumo	Energy Gap (Δ)(eV)	Chemical potential (μ)	Electro-negativity (χ)	Hardness (η)	Softness (S)	Elecro-philicity (ω)
5	-6.979	-1.714	5.265	4.347	-4.347	2.633	0.190	3.589

5. Conclusion

In conclusion, an efficient and environmentally friendly multicomponent strategy is developed for the synthesis of a novel 1-(2-(4-methylphenyl)-4-oxothiazolidin-3-yl)thiourea derivative, achieving excellent yields in reduced reaction times. Spectroscopic techniques (FT-IR, ^{1}H NMR, and ^{13}C NMR) confirm the proposed molecular structures. In silico studies against *Orientia tsutsugamushi* reveal favorable binding interactions, suggesting potential biological activity of the synthesized thiazolidinone scaffold. ADMET and ProTox analyses predict good pharmacokinetic properties and low toxicity, indicating a safe and drug-like profile. Additionally, DFT calculations provide insights into the electronic characteristics, reactivity, and stability of the molecules, supporting their observed interactions with the target. Overall, this combined experimental and computational study highlights the thiazolidinone–thiourea framework as a promising lead for further optimization and the development of new therapeutic agents against scrub typhus.

References

[1] VL. Maruthanila, R. Elancheran, A.B. Kunnumakkara, S. Kabilan, J. Kotoky, "Recent development of targeted approaches for the treatment of breast cancer,"*Breast Cancer*, 191-219. Mar. 24, (2017),

[2] I. Gomez-Monterrey, G. Santelli, P. Campiglia, D. Califano, F. Falasconi, C. Pisano, & E. Novellino, " Synthesis and cytotoxic evaluation of novel spirohydantoin derivatives of the dihydrothieno [2, 3-b] naphtho-4, 9-dione system,".*Journal of medicinal chemistry*, *48*(4), 1152-1157, (2005)..

[3] R. Rajalakshmi, R.Santhi and T.Elakkiya, "Synthesis, Characterization, Docking studies, Evaluation of Thiazinyl-thiazolidinone derivatives as potential in vitro antidiabetic and antioxidant agents," *Nature Synthesis*, *29*(08), 6091-6103, (2020).

[4] S. P. Singh, S. S .Parmar, K. Raman and V. I. Stenberg, "Chemistry and biological activity of thiazolidinones," *Chemical Reviews*, *81*(2), 175-203, (1981).

[5]. F. C. Brown, "4-Thiazolidinones," *Chemical Reviews*, *61*(5), 463-521, (1961).

[6]. C. J. Andres, J. J Bronson, S. V. D'Andrea, M. S. Deshpande, P. J. Falk, K. A. Grant-Young, and A. W. Walsh, "

4-Thiazolidinones: novel inhibitors of the bacterial enzyme," MurB. *Bioorganic & medicinal chemistry letters*, *10*(8), 715-717, (2000).

[7]. S. Grasso, A. Chimirri, P. Monforte, G. Fenech, M. Zappalà, & A. M. Monforte, "Compounds with potential antitumor activity VI--2-Alkyl-3-[2-(1, 3, 4-thiadiazolyl)]-4-thiazolidinones, " *Il Farmaco; Edizione Scientifica*, *43*(10), 851-856, (1988).

[9]. M. V. Diurno, O. Mazzoni, E. Piscopo, A. Calignano, F. Giordano, and A. Bolognese, "Synthesis and antihistaminic activity of some thiazolidin-4-ones," *Journal of medicinal chemistry*, *35*(15), 2910-2912, (1992).

[10] G. C. Look, J. R. Schullek, C. P. Holmes, J. P. Chinn, E. M. Gordon and M. A. Gallop, ,"The identification of cyclooxygenase-1 inhibitors from 4-thiazolidinone combinatorial libraries," *Bioorganic & medicinal chemistry letters*, *6*(6), 707-712, (1996).

[11] A. Chimirri, S. Grasso, A. M. Monforte, M . Zappala, A. De Sarro, and G. B. De Sarro, "Synthesis and anticonvulsant properties of 3-(1, 3, 4-thiadiazol-2-yl) thiazolidin-4-ones," *Farmaco (Societa Chimica Italian,: 1989)*, *46*(7-8), 935-943, (1991).

[12] N. Hamdi, A. S. Al-Ayed, R. B Said, and A. Fabienne," Synthesis and characterization of new thiazolidinones containing coumarin moieties and their antibacterial and antioxidant activitie," *Molecular Diversity Preservation International (MDPI).* *17*(8), 9321-9334, (2012).

[13] R., Tahmasvand, P. Bayat, S. M. Vahdaniparast, S. Dehghani, Z. Kooshafar, S. Khaleghi, ... and M. Salimi, "Design and synthesis of novel 4-thiazolidinone derivatives with promising anti-breast cancer activity Synthesis, characterization, in vitro and in vivo results," *Bioorganic chemistry*, *104*, 104276, (2020).

[14]. H., Wu. Zhou, S. Zhai, A. Liu, Y. Sun, Li, R., and B. Yan, "Design, synthesis, cytoselective toxicity, structure–activity relationships, and pharmacophore of thiazolidinone derivatives targeting drug-resistant lung cancer cells," *Journal of medicinal chemistry*, *51*(5), 1242-1251, (2008).

[15] P. Ramachandra Reddy, A. Padmaja, and V. Padmavathi, "Synthesis of heteroaryl thiazolidinones and azetidinones under conventional and ultrasonication methods," *Journal of Heterocyclic Chemistry*, *52*(5), 1474-1482, (2015).

[16] L. V. Chanu, , K. Nongalleima, S. P. Singh, W. K. Chanu, C. B. Singh, and O. M. Singh, " Synthesis, anti-inflammatory evaluation and in silico studies of naphtho [1, 2-e][1, 3] oxazine derivatives as potential non-steroidal anti-inflammatory agents," *Medicinal Chemistry Research*, *29*(2), 229-242, (2020).

[17]. A. Preetam and M. Nath,"Ambient temperature synthesis of spiro [indoline-3, 2′-thiazolidinones] by a DBSA-catalyzed sequential reaction in water,"*Tetrahedron Letters*, *57*(13), 1502-1506, (2016).

[18]. J. Fraga-Dubreuil and J. P. Bazureau, " Efficient combination of task-specific ionic liquid and microwave dielectric heating applied to one-pot three component synthesis of a small library of 4-thiazolidinones". *Tetrahedron*, *59*(32), 6121-6130, (2003).

[19]. M. Ehsanifar and Z. Montazeri,"Neuroprotective effects of thiazolidine-4-carboxylic acid derivatives on memory impairment and neurodegeneration,"*Journal International Standard Serial Number 2766*, 2276, (2022).

[21]. E. L. Carpenter, B. A. Vance, R. S. Klein, A. Voloschin, J. Dalmau and R. H. Vonderheide," Functional analysis of CD8+ T cell responses to the onconeural self protein cdr2 in patients with paraneoplastic cerebellar degeneration" *Journal of neuroimmunology*, *193*(1-2), 173-182, (2008).

[22]. R. Subramaniyan, R. Ramarajan, A. Ramalingam, S. Sambandam, A. Petersamy, A. R., Guerroudj, ... and A. Chouaih, " Microwave assisted synthesis, vibrational spectra, Hirshfeld surface and interaction energy, DFT, topology, in silico ADMET and molecular docking studies of 1, 2-bis (4-methoxybenzylidene) hydrazine," *Journal of Molecular Structure*, *1278*, 134946, (2023).

[23]. H. Meiselbach and H. Sticht, "Effect of the SH3-SH2 domain linker sequence on the structure of Hck kinase," *Journal of molecular modeling*, *17*(8), 1927-1934, (2011).

[24]. F. Henot, E. Rioual, A. Favier, P. Macek, E. Crublet, P. Josso, and J. Boisbouvier, "Visualizing the transiently populated closed-state of human HSP90 ATP binding domain," *Nature Communications*, *13*(1), 7601, (2022).

[25]. S. Ramkumar and R. Ramarajan, "Design, synthesis, spectral characterization, antioxidant activity, molecular docking and in silico ADMET studies of 1, 3 Oxazepines," *ChemistrySelect*, *8*(9), e202204818, (2023).

[26]. S. Ramkumar and R. Ramarajan,"Green synthesis, Single-Crystal X-RD, Hirshfeld Analysis and Anti-Covid-19 Molecular Docking Investigation of Symmetrical Azines," *ChemistrySelect*, *8*(6), e202204494, (2023).

[27]. S. Pawar, A. Kale, P. Zori & D. Zope, "Synthesis, Molecular Docking, and Antimicrobial Evaluation of 2-(Substituted Amino)-N-(6-Substituted-1, 3-Benzothiazol-2yl) Acetamide," *Current Drug Discovery Technologies*, *22*(3), E200624231065, ,(2023).

[28]. C. G., Bonde and N. J. Gaikwad, "Synthesis and preliminary evaluation of some pyrazine containing thiazolines and thiazolidinones as antimicrobial agents," *Bioorganic & medicinal chemistry*, *12*(9), 2151-2161, (2004).

[29]. B. Singh, A. Maheshwari, G. Dak, K. Sharma, and G. L. Talesara,"Studies of antimicrobial activities of some 4-thiazolidinone fused pyrimidines,[1, 5]-benzodiazepines and their oxygen substituted hydroxylamine

derivatives," *Indian journal of pharmaceutical sciences*, *72*(5), 607, (2010).

[30]. C. K. Belwal and K. A Joshi, "Synthesis and antifungal activity of some novel thiazolidinone derivatives of 4-(4-oxo-2-phenylthiazolidin-3-yl) benzoic acid," *International Journal of Chemistry, Tech. Res*, *4*(4), 1758-1764, (2012).