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Visit Journal at <https://www.jacsdirectory.com/jacs>Synthesis, Spectral Characterization, and In-Silico Evaluation of a Thiazole-Based Hydrazone as a Potential Inhibitor of *Mycobacterium tuberculosis* InhAChandrakant S. Aher^{1,*}, Jay S. Khandebharad², Narendra A. Dhoke¹, Rahul A. Shinde^{1,*}¹Dept. of Chemistry, M.G.V's M.S.G. Arts, Science and Commerce College, Malegaon Camp, Malegaon, Nashik – 423 105, Maharashtra, India.²Dept. of Chemistry, Mahatma Gandhi Vidyamandir's Arts, Science and Commerce Colleg, Manmad, Nashik – 423 104, Maharashtra, India.

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ABSTRACT

A thiazole-based hydrazone derivative, (E)-4-(4-chlorophenyl)-2-(2-(2,3-dihydro-1H-inden-1-ylidene)hydrazinyl)thiazole (CPIHT), was synthesized via a one-pot multicomponent reaction. The structure of the synthesized compound was confirmed using FT-IR, ¹H NMR, and ¹³C NMR spectroscopic techniques. The pharmacokinetic properties of CPIHT were evaluated using the SwissADME web tool. The results indicated favourable physicochemical parameters, including a topological polar surface area (TPSA) of 65.52 Å², a consensus Log Po/w value of 4.71, and moderate water solubility (Log S = -5.74). The compound exhibited high gastrointestinal absorption and predicted blood-brain barrier permeability, while it was not identified as a substrate for P-glycoprotein. Furthermore, CPIHT satisfied major drug-likeness criteria, including Lipinski, Ghose, Veber, and Egan rules. The bioavailability radar and BOILED-Egg models further supported the favourable pharmacokinetic and oral bioavailability profile of the compound. Molecular docking studies were performed against *Mycobacterium tuberculosis* enoyl-acyl carrier protein reductase (InhA) (PDB ID: 4TZK), a key enzyme involved in the biosynthesis of mycolic acids essential for the mycobacterial cell wall. The docking results revealed that CPIHT binds strongly within the active site of the enzyme with a binding affinity of -9.5 kcal/mol. The ligand forms a stable ligand-protein complex through several non-covalent interactions, including a π-sulphur interaction with MET199 and a π-π T-shaped interaction with TYR158. In addition, multiple hydrophobic contacts such as alkyl and π-alkyl interactions with residues PHE149 and LEU207 further stabilize the complex. These interactions contribute to the effective stabilization of the ligand within the enzyme binding pocket, indicating favourable binding affinity. Overall, the combined ADME and molecular docking results suggest that CPIHT possesses promising drug-like characteristics and may serve as a potential lead compound for the development of new antitubercular agents.

1. Introduction

Heterocyclic compounds represent an important class of organic molecules characterized by the presence of one or more heteroatoms such as nitrogen, oxygen, or sulphur within a cyclic framework [1]. These heteroatoms significantly influence the chemical reactivity, physicochemical properties, and biological activities of the compounds. Due to these unique features, heterocyclic systems occupy a central position in modern organic and medicinal chemistry. They are widely utilized in pharmaceutical, agrochemical, and biological research because of their ability to interact with diverse biological targets and participate in various biochemical processes [2, 3].

Heterocyclic rings are fundamental structural components of numerous biologically important molecules. For instance, the nucleic acid bases present in DNA and RNA are heterocyclic in nature, while many naturally occurring biomolecules such as chlorophyll, haemoglobin, vitamins, alkaloids, and coenzymes also contain heterocyclic frameworks. These compounds play essential roles in biological processes including metabolism, enzymatic activity, and cellular communication [4]. Owing to their structural diversity and functional versatility, heterocyclic compounds have become indispensable scaffolds in drug discovery and development. Medicinal chemistry extensively utilizes heterocyclic compounds because a large proportion of clinically approved drugs contain heterocyclic rings. These molecules exhibit a wide spectrum of pharmacological activities and are used in the treatment of numerous diseases such as microbial infections, cancer, inflammatory disorders, and neurological diseases.

Literature reports indicate that heterocyclic chemistry remains one of the most productive areas in the design and development of new therapeutic agents. By integrating organic synthesis with biological and pharmaceutical sciences, medicinal chemistry aims to design molecules capable of interacting selectively with biological targets, thereby contributing to improved therapeutic strategies. Among the different heteroatoms incorporated into heterocyclic compounds, sulphur-containing molecules have attracted significant interest due to their diverse biological properties. Sulphur atoms can influence the electronic distribution, lipophilicity, and molecular interactions of compounds, which often results in enhanced biological activity.

Sulphur-containing heterocycles are widely distributed in natural products and pharmaceutical agents and play important roles in medicinal chemistry [5-7]. One of the most important sulphur-containing heterocyclic systems is the thiazole ring, a five-membered heterocycle containing both nitrogen and sulphur atoms. Thiazole derivatives have gained considerable attention because of their broad spectrum of biological activities [8, 9].

In particular, compounds containing the hydrazinylthiazole nucleus have been reported to exhibit diverse pharmacological properties such as antioxidant, antitubercular, antimicrobial, anti-inflammatory, activities [10-13]. Owing to these promising biological activities, hydrazinylthiazole derivatives have attracted considerable interest from both medicinal and industrial chemists. Another pharmacologically important scaffold is 2,3-dihydro-1H-inden-1-one, commonly known as 1-indanone. This fused bicyclic system consists of a benzene ring condensed with a cyclopentanone ring, providing a rigid and versatile structural framework. Indanone derivatives have been extensively investigated due to their wide range of pharmacological properties. Various indanone-based compounds have been reported to possess antimicrobial, antimalarial, anti-inflammatory [14-16] activities.

Furthermore, the indanone scaffold serves as an important intermediate for the synthesis of numerous heterocyclic and carbocyclic

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compounds and is widely used in the preparation of biologically active molecules and natural products. In addition to heterocyclic frameworks, the incorporation of halogen atoms into organic molecules is a well-established strategy in medicinal chemistry to enhance biological activity and improve pharmacokinetic properties. Halogen substitution often increases the lipophilicity, metabolic stability, and membrane permeability of organic molecules, thereby improving their interaction with biological targets [17].

Among the halogens, chlorine is one of the most frequently introduced substituents in drug molecules. Chlorine atoms can influence the electronic distribution of aromatic rings and promote stronger binding interactions with biological receptors through hydrophobic and halogen-bonding interactions. The presence of chlorine in pharmaceutical compounds has been reported to enhance biological potency, selectivity, and metabolic stability, making chlorinated derivatives valuable candidates in drug design and development.

In recent years, computational approaches have become important tools in modern drug discovery. The molecular docking and ADME studies are important tools in modern drug discovery. Molecular docking helps to predict the binding interactions and affinity of a compound with the active site of a target protein, providing insight into its possible biological activity [18].

ADME analysis (Absorption, Distribution, Metabolism, and Excretion) evaluates the pharmacokinetic behaviour and drug-likeness of a compound, including properties such as solubility, permeability, and metabolic stability [19]. These computational approaches help identify promising drug candidates at an early stage and reduce the risk of failure during later stages of drug development. Considering the significant pharmacological importance of hydrazinylthiazole derivatives, the 2,3-dihydro-1*H*-inden-1-one scaffold, and the beneficial effects of halogen substitution, the present study was designed to combine these structural features within a single molecular framework. In this work, we report the synthesis and characterization of a novel compound, (*E*)-4-(4-chlorophenyl)-2-(2-(2,3-dihydro-1*H*-inden-1-ylidene)hydrazinyl)thiazole (CPIHT), which incorporates the indanone nucleus, hydrazinylthiazole moiety, and a chlorine-substituted phenyl ring. The integration of these pharmacologically important structural units is expected to provide a promising scaffold for further investigation of its physicochemical properties and potential biological applications.

2. Experimental Methods

2.1 Materials and Characterization Methods

All chemicals used in this study were procured from Sigma Laboratory, Nashik (Make: SD Fine Chemicals and Avra Synthesis) and were used without further purification. The NMR spectra were recorded on a sophisticated multinuclear FT-NMR spectrometer. The samples were prepared by dissolving the compounds in DMSO-*d*₆, and tetramethylsilane (TMS) was employed as the internal standard. Chemical shifts were recorded in parts per million (ppm). The progress of the reactions was monitored by thin-layer chromatography (TLC) using Merck aluminium TLC plates coated with silica gel containing the fluorescent indicator F254. Prior to use, all glassware was thoroughly cleaned and dried in an oven to remove any moisture or impurities.

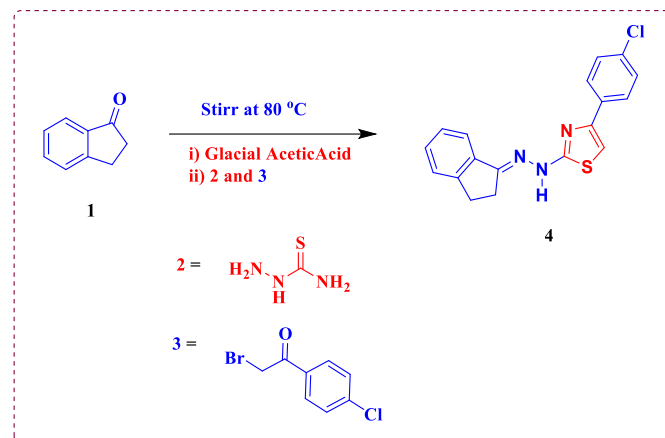
2.2 General Methodology for the Synthesis of (*E*)-4-(4-Chlorophenyl)-2-(2-(2,3-dihydro-1*H*-inden-1-ylidene)hydrazinyl)thiazole (CPIHT)

The target compound (*E*)-4-(4-chlorophenyl)-2-(2-(2,3-dihydro-1*H*-inden-1-ylidene)hydrazinyl)thiazole (CPIHT) was synthesized via a one-pot multicomponent reaction. In this method, 2,3-dihydro-1*H*-inden-1-one (1, 10 mmol), thiosemicarbazide (2, 10 mmol), and 4-chlorophenacyl bromide (3, 10 mmol) were reacted together in ethanol in the presence of a catalytic amount of glacial acetic acid. Initially, 2,3-dihydro-1*H*-inden-1-one reacts with thiosemicarbazide to form the corresponding thiosemicarbazone intermediate, which subsequently undergoes cyclization with 4-chlorophenacyl bromide in the same reaction medium to afford the desired hydrazinylthiazole derivative, CPIHT. The progress of the reaction was monitored by thin-layer chromatography (TLC). The synthesized compound was purified and characterized using ¹H NMR and ¹³C NMR spectroscopic techniques. The synthetic pathway for the preparation of the target compound is presented in Scheme 1.

2.3 Physical and Spectral Data for Synthesized Compounds

Pale Yellow colour; Yield 86%; FT-IR (KBr, cm⁻¹): 3510.97, 3321.75, 3215.03, 3047.49, 2922.84, 2516.12, 1614.53, 1555.79, 1485.03, 1437.22, 1404.34, 1371.52, 1283.29, 1212.28, 1155.98, 1093.76, 1005.50, 824.52, <https://doi.org/10.30799/jacs.S301.26120401>

766.48, 698.24, 626.29, 552.94.; ¹H NMR (500 MHz, DMSO-*d*₆) δ 1H NMR (500 MHz, DMSO-*d*₆) δ 11.27 (s, 1H), 7.90 (d, *J* = 8.6 Hz, 2H), 7.63 (m, 1H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.43–7.38 (m, 2H), 7.36 (s, 1H), 7.31 (m, 1H), 3.10 (t, *J* = 7.8 Hz, 2H), 2.90 (t, *J* = 7.8 Hz, 2H).; ¹³C NMR (126 MHz, DMSO-*d*₆) δ 170.01, 157.33, 148.48, 138.10, 132.47, 130.55, 130.03, 129.11, 128.86, 127.78, 127.48, 126.21, 121.23, 105.12, 28.64, 28.06.



Scheme 1 Synthesis of compound CPIHT

2.4 ADME Study

The pharmacokinetic behaviour of potential drug candidates is largely evaluated through ADME (Absorption, Distribution, Metabolism, and Excretion) analysis during the drug discovery and development process. SwissADME is a freely accessible web-based tool developed by the Molecular Modeling Group of the Swiss Institute of Bioinformatics (SIB) that provides a comprehensive set of predictive models for assessing pharmacokinetics, drug-likeness, and medicinal chemistry suitability [20]. This platform allows researchers to rapidly evaluate the ADME properties of compounds based on their molecular structures, enabling early-stage screening in the drug development pipeline. Such *in silico* evaluation helps identify the most promising candidates for further experimental studies, thereby saving time and increasing the likelihood of successful drug development.

SwissADME calculates several important physicochemical parameters, including the number of hydrogen bond donors (HBDs) and hydrogen bond acceptors (HBAs), rotatable bonds, topological polar surface area (TPSA), and solubility. The tool also provides lipophilicity estimations using multiple logP calculation methods such as iLOGP, XLOGP3, WLOGP, MLOGP, and SILICOS-IT. These parameters are essential for understanding the ability of a molecule to permeate biological membranes. Water solubility, another key factor affecting oral bioavailability, is also predicted by the platform.

In addition, SwissADME evaluates several pharmacokinetic properties, including gastrointestinal absorption, blood–brain barrier permeability, p-glycoprotein substrate status, and potential interactions with cytochrome P450 enzymes, which are important for predicting metabolism and possible drug–drug interactions. The structural properties of compounds are also assessed according to Lipinski's rule of five, which is widely used to evaluate drug-likeness for orally active molecules. According to this rule, a compound should generally contain no more than ten hydrogen bond acceptors and not more than five hydrogen bond donors. Furthermore, the topological polar surface area (TPSA), which represents the surface area contributed by polar atoms in a molecule, should typically remain below 140 Å². Exceeding this limit may reduce membrane permeability and limit the ability of the compound to cross biological barriers such as the blood–brain barrier.

2.5 Molecular Docking Studies

Molecular docking studies were performed to investigate the binding interactions, orientation within the active site, and potential inhibitory activity of the synthesized compound (*E*)-4-(4-chlorophenyl)-2-(2-(2,3-dihydro-1*H*-inden-1-ylidene)hydrazinyl)thiazole (CPIHT). Molecular docking is an essential tool in contemporary drug discovery and development, providing valuable insights into the interactions between small molecules (ligands) and biological targets. The docking analysis was carried out against the target protein (PDB ID: 4TZK) to evaluate the binding affinity and molecular interactions of CPIHT with the active site residues of the selected protein. The protein 4TZK corresponds to the crystal structure of *Mycobacterium tuberculosis* enoyl-acyl carrier protein reductase (InhA) complexed with 1-cyclohexyl-N-(3,5-dichlorophenyl)-5-

oxopyrrolidine-3-carboxamide. InhA is a key enzyme involved in the biosynthesis of mycolic acids, which are essential components of the mycobacterial cell wall. Because of its crucial role in the survival and pathogenicity of *Mycobacterium tuberculosis*, InhA is considered an important target for the development of antitubercular drugs. Therefore, docking the synthesized compound CPIHT with this protein helps to predict its potential inhibitory interactions with the active site of the enzyme. Docking simulations were carried out using AutoDockTools version 1.5.6 [21], which included protein and ligand preparation, grid generation, and docking procedures. The stability of the ligand structure was ensured through energy minimization at the MM2 level using Chem3D Pro [22]. The three-dimensional crystal structure of the target protein was obtained from the Protein Data Bank (<https://www.rcsb.org/>). Furthermore, to better understand the binding mechanism, 2D and 3D ligand-receptor interactions were visualized and analysed using Discovery Studio Visualizer (DSV) [23].

3. Results and Discussion

3.1 Chemistry

The synthesized compound (*E*)-4-(4-chlorophenyl)-2-(2-(2,3-dihydro-1H-inden-1-ylidene)hydrazinyl)thiazole (CPIHT) was obtained as a pale yellow solid with a good yield of 86%, indicating the efficiency of the one-pot multicomponent synthetic approach. The structure of the compound was confirmed through FT-IR, ^1H NMR, and ^{13}C NMR spectroscopic techniques, which provided detailed information about the functional groups and molecular framework. The corresponding spectra are presented in Fig. 1 (FT-IR), Fig. 2 (^1H NMR), and Fig. 3 (^{13}C NMR).

The FT-IR spectrum of CPIHT exhibited characteristic absorption bands corresponding to the functional groups present in the molecule. The strong absorption bands observed at 3321.75 and 3215.03 cm^{-1} are attributed to N-H stretching vibrations of the hydrazinyl group. The band at 3047.49 cm^{-1} corresponds to aromatic C-H stretching, while the absorption at 2922.84 cm^{-1} is assigned to aliphatic C-H stretching of the indanone moiety. The prominent band at 1614.53 cm^{-1} indicates the presence of C=N stretching, confirming the formation of the hydrazone linkage. Additional bands observed in the region 1555–1485 cm^{-1} correspond to aromatic C=C stretching vibrations, while the peaks around 1283–1093 cm^{-1} are associated with C-N and C-S stretching vibrations of the thiazole ring. The absorption bands in the lower region (824–552 cm^{-1}) are characteristic of aromatic C-H bending and C-Cl stretching, supporting the presence of the chlorophenyl substituent.

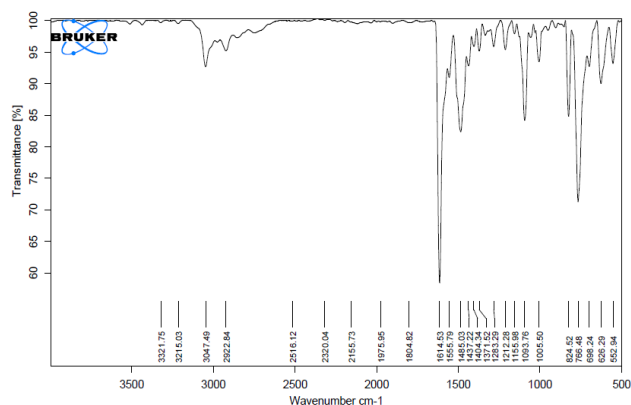


Fig. 1 FT-IR spectrum of CPIHT

The ^1H NMR spectrum (500 MHz, DMSO-d_6) further confirmed the structure of CPIHT. A singlet observed at δ 11.27 ppm corresponds to the -NH proton of the hydrazinyl group, indicating the presence of the hydrazone functionality. The aromatic protons of the 4-chlorophenyl and indene rings appeared in the region δ 7.90–7.31 ppm as doublets, triplets, and multiplets. The doublet signals at δ 7.90 and 7.48 ppm ($J = 8.6$ Hz) are attributed to the aromatic protons of the para-chlorophenyl ring, showing the expected splitting pattern for a substituted benzene ring. The remaining multiplets and triplet signals between δ 7.63–7.31 ppm correspond to the aromatic protons of the indanone framework and thiazole ring. The aliphatic methylene protons of the 2,3-dihydroindanyl moiety appeared as triplets at δ 3.10 ppm and δ 2.90 ppm ($J = 7.8$ Hz), confirming the presence of the saturated methylene groups in the fused indanone structure.

The ^{13}C NMR spectrum (126 MHz, DMSO-d_6) also supported the proposed structure of CPIHT. The signal at δ 170.01 ppm corresponds to

the imine (C=N) carbon, confirming the formation of the hydrazone linkage. Signals observed in the region δ 157.33–121.23 ppm are attributed to the aromatic carbons of the thiazole ring, chlorophenyl ring, and indene moiety. The resonance at δ 105.12 ppm is assigned to the C-2 carbon of the thiazole ring, which is characteristic for heteroaromatic carbons. Additionally, the signals at δ 28.64 and 28.06 ppm correspond to the methylene carbons of the 2,3-dihydroindanone ring system. Overall, the combined FT-IR, ^1H NMR, and ^{13}C NMR spectral data clearly confirm the successful synthesis of the target compound CPIHT, and the observed spectral features are consistent with the proposed molecular structure.

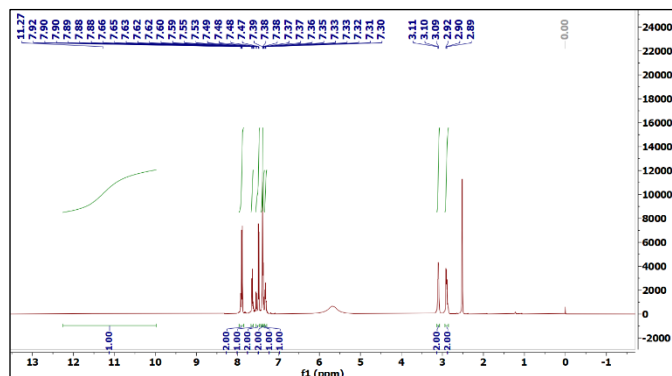


Fig. 2 ^1H NMR spectrum of CPIHT

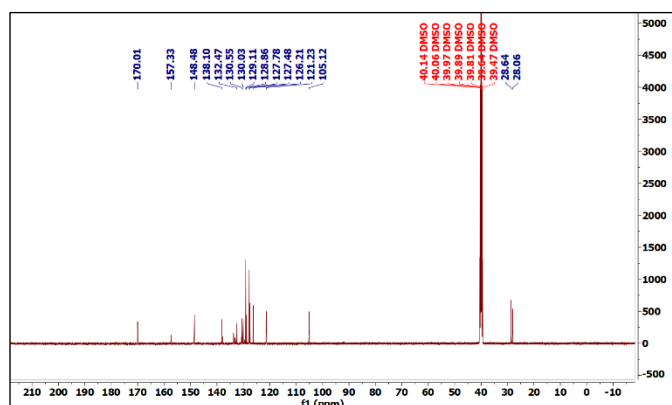


Fig. 3 ^{13}C NMR spectrum of CPIHT

3.2 ADME Study

The ADME (Absorption, Distribution, Metabolism, and Excretion) properties of the synthesized compound CPIHT were evaluated using the SwissADME online tool, and the calculated parameters are summarized in Table 1. These physicochemical parameters provide important information regarding the pharmacokinetic behavior, membrane permeability, and drug-likeness of the compound.

Table 1 The ADME parameters of compound CPIHT

Parameters	Values
Number of Hydrogen bond donors (nHD)	1
Number of Hydrogen bond acceptors (nHA)	2
Molecular Polar surface area (TPSA), \AA^2	65.52
Consensus Log Po/w	4.71
Log S (ESOL)	-5.74
Water Solubility	Moderately soluble
Gastrointestinal absorption	High
BBB permeability	Yes
P-gp substrate	No
Metabolic enzymes inhibition	CYP1A2, CYP2C19 CYP2C9, CYP3A4
Drug likeness matching	Lipinski, Ghose, Veber, Egan

The calculated ADME parameters provide valuable insight into the pharmacokinetic profile and drug-likeness of compound CPIHT. The molecule possesses 1 hydrogen bond donor (nHD) and 2 hydrogen bond acceptors (nHA), indicating limited hydrogen bonding capacity, which may favor membrane permeability and interaction with biological targets. The topological polar surface area (TPSA) of 65.52 \AA^2 suggests good potential for membrane permeation and oral bioavailability, as compounds with TPSA below 140 \AA^2 generally exhibit better absorption. The consensus Log Po/w value of 4.71 indicates relatively high

lipophilicity, which may enhance membrane permeability but could also influence solubility.

The LogS (ESOL) value of -5.74 classifies the compound as moderately soluble in water, suggesting moderate aqueous solubility that may affect dissolution and absorption characteristics. The compound shows high gastrointestinal absorption, indicating good potential for oral administration. Additionally, it is predicted to be BBB permeant, suggesting its ability to cross the blood–brain barrier, which could be relevant for central nervous system activity. The compound is not a substrate for P-glycoprotein (P-gp), implying that it may not be actively effluxed from cells, potentially improving intracellular retention. Furthermore, compound CPIHT is predicted to inhibit several cytochrome P450 enzymes, including CYP1A2, CYP2C19, CYP2C9, and CYP3A4, indicating the possibility of metabolic interactions that should be considered during further drug development. The compound satisfies multiple drug-likeness rules, including Lipinski, Ghose, Veber, and Egan, suggesting favorable characteristics for an orally active drug candidate.

Overall, the ADME profile of compound CPIHT highlights a balance between lipophilicity, permeability, and solubility, indicating promising pharmacokinetic properties while also suggesting aspects that may require optimization during further drug development.

The ADME radar plot (Fig. 4) illustrates the drug-likeness profile of the synthesized compound CPIHT based on six physicochemical parameters: lipophilicity (LIPO), size (SIZE), polarity (POLAR), solubility (INSOLU), flexibility (FLEX), and saturation (INSATU). Most of the parameters of CPIHT fall within the optimal pink region, indicating favourable properties for oral bioavailability.

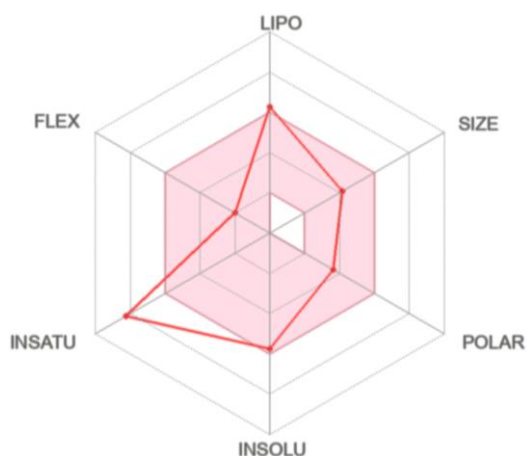


Fig. 4 Bioavailability radar chart for the CPIHT

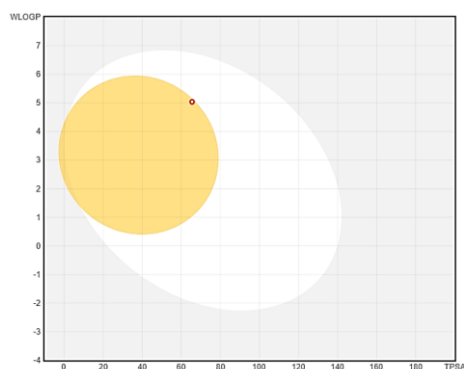


Fig. 5 BOILED-Egg plot of the CPIHT

The compound shows acceptable lipophilicity, molecular size, polarity, and solubility, which are important for membrane permeability and absorption. However, the saturation parameter slightly exceeds the optimal range, reflecting the presence of multiple aromatic rings in the molecule. Additionally, the flexibility value is relatively low, suggesting a rigid molecular structure due to fused ring systems. Overall, the radar analysis suggests that CPIHT possesses promising drug-like characteristics with acceptable pharmacokinetic properties. The BOILED-Egg model was used to predict gastrointestinal absorption and blood–brain barrier penetration of the compound based on lipophilicity (WLOGP) and topological polar surface area (TPSA). As shown in Fig. 5, the red point representing CPIHT is located within the yellow yolk region of the plot, indicating a high probability of blood–brain barrier permeation. Furthermore, the compound also falls within the egg region, suggesting favourable passive gastrointestinal absorption. The TPSA value of <https://doi.org/10.30799/jacs.S301.26120401>

approximately $60\text{--}70 \text{ \AA}^2$ supports good membrane permeability, while the WLOGP value around 5 indicates relatively high lipophilicity that facilitates diffusion across biological membranes. These results suggest that CPIHT may possess good oral absorption and the ability to penetrate the central nervous system.

3.3 Molecular Docking

The molecular docking analysis of compound CPIHT against the target protein *Mycobacterium tuberculosis* enoyl–acyl carrier protein reductase (InhA, PDB ID: 4TZK) revealed the formation of a stable ligand–protein complex within the active site of the enzyme. The compound interacts strongly with the active site through several non-covalent interactions, exhibiting a binding affinity of -9.5 kcal/mol . The binding mode of compound CPIHT is predominantly governed by hydrophobic and π -based interactions, which play a key role in stabilizing the ligand inside the enzyme binding pocket. A significant stabilizing interaction observed in the docking complex is the π -sulphur interaction between the aromatic system of the ligand and the sulphur atom of MET199, which contributes to anchoring the ligand within the active site. In addition, the aromatic ring of CPIHT forms a π - π T-shaped interaction with TYR158, further reinforcing the stability of the ligand–protein complex.

Several alkyl interactions were also observed with residues ALA198, ILE202, LEU207, MET199, and LEU218, indicating that the ligand effectively occupies the hydrophobic region of the active site. Furthermore, the 4-chlorophenyl moiety of the compound contributes to ligand stabilization through π -alkyl interactions with PHE149 and MET161, highlighting the role of the halogenated aromatic ring in strengthening hydrophobic contacts within the binding cavity. Overall, the combined contribution of π -sulphur, π - π stacking, alkyl, and π -alkyl interactions result in effective stabilization of compound CPIHT within the active site of the InhA enzyme, suggesting its potential as a promising inhibitor targeting *Mycobacterium tuberculosis* enoyl reductase. The 3D and 2D binding interactions of CPIHT within the active site of the InhA enzyme is illustrated in Figs. 6 and 7 respectively.

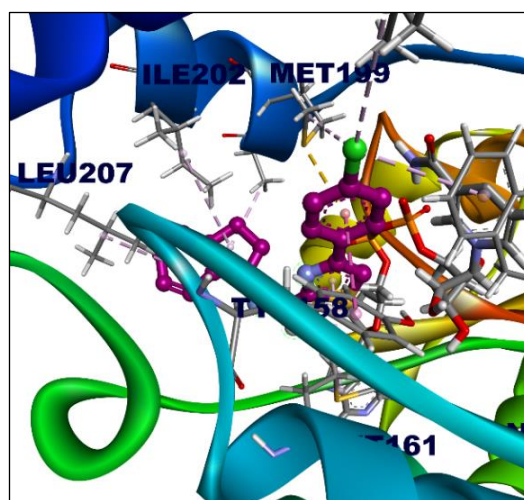


Fig. 6 3D binding interaction between *Mycobacterium tuberculosis* enoyl–acyl carrier protein reductase (InhA) (PDB ID: 4TZK) and CPIHT

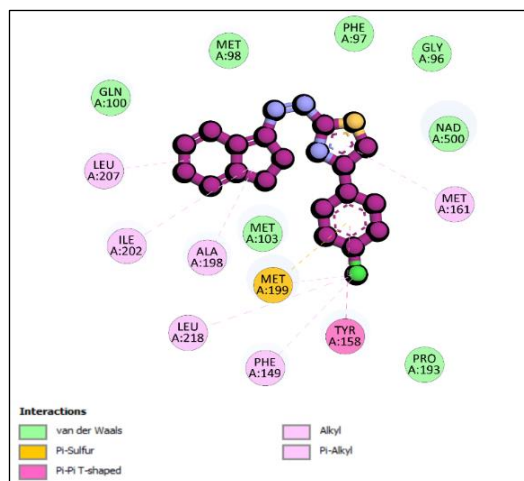


Fig. 7 2D binding interaction between *Mycobacterium tuberculosis* enoyl–acyl carrier protein reductase (InhA) (PDB ID: 4TZK) and CPIHT

4. Conclusion

A thiazole-based hydrazone derivative, (*E*)-4-(4-chlorophenyl)-2-(2-(2,3-dihydro-1H-inden-1-ylidene)hydrazinyl)thiazole (CPIHT) was successfully synthesized through a one-pot multicomponent reaction with a good yield. The structure of the synthesized compound was confirmed by FT-IR, ¹H NMR, and ¹³C NMR spectroscopic analyses, which verified the presence of the expected functional groups and the proposed molecular framework.

The *in silico* pharmacokinetic evaluation using the SwissADME tool revealed favourable physicochemical and ADME properties. The compound exhibited suitable lipophilicity, moderate water solubility, and a topological polar surface area within the acceptable range for good membrane permeability. Additionally, CPIHT demonstrated high gastrointestinal absorption, predicted blood–brain barrier permeability, and compliance with major drug-likeness rules such as Lipinski, Ghose, Veber, and Egan criteria, suggesting good oral bioavailability and drug-like characteristics.

Molecular docking analysis against *Mycobacterium tuberculosis* enoyl-acyl carrier protein reductase (InhA) (PDB ID: 4TZK) showed that CPIHT interacts strongly with the active site of the enzyme with a binding affinity of –9.5 kcal/mol. The ligand forms several stabilizing interactions, including π -sulphur, π - π T-shaped, alkyl, and π -alkyl interactions with key amino acid residues such as MET199, TYR158, PHE149, and LEU207. These interactions contribute to stable ligand–protein complex formation and indicate favourable binding within the enzyme binding pocket.

The combined synthetic, spectroscopic, ADME, and molecular docking results suggest that CPIHT possesses promising drug-like properties and may serve as a potential lead molecule for the development of new antitubercular agents targeting the InhA enzyme.

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References

[1] P.K. Sharma, A. Amin, M. Kumar, A review: Medicinally important nitrogen sulphur containing heterocycles, *Open Med. Chem. J.* 14(1) (2020) 1–13.
 [2] E. Kabir, M. Uzzaman, A review on biological and medicinal impact of heterocyclic compounds, *Results Chem.* 4 (2022) 100606.
 [3] J. Baranwal, S. Kushwaha, S. Singh, A. Jyoti, A review on the synthesis and pharmacological activity of heterocyclic compounds, *Curr. Phys. Chem.* 13(1) (2023) 2–19.
 [4] N. Kumar, N. Goel, Heterocyclic compounds: importance in anticancer drug discovery, *Anti-Cancer Agents Med. Chem.* 22(19) (2022) 3196–3207.

[5] K. Kapoor, N. Kaur, H.S. Sohal, M. Kaur, K. Singh, et al., Drugs and their mode of action: a review on sulphur-containing heterocyclic compounds, *Polycycl. Aromat. Compd.* 45(1) (2025) 136–175.
 [6] M. Mustafa, J.Y. Winum, The importance of sulphur-containing motifs in drug design and discovery, *Expert Opin. Drug Discov.* 17(5) (2022) 501–512.
 [7] K. Laxmikeshav, P. Kumari, N. Shankaraiah, Expedition of sulphur-containing heterocyclic derivatives as cytotoxic agents in medicinal chemistry: A decade update, *Med. Res. Rev.* 42(1) (2022) 513–575.
 [8] M.F. Arshad, A. Alam, A.A. Alshammari, M.B. Alhazza, I.M. Alzimir, et al., Thiazole: A versatile standalone moiety contributing to the development of various drugs and biologically active agents, *Molecules* 27(13) (2022) 3994.
 [9] T.A. Farghaly, G.H. Alfafi, S.M. Gomha, Recent literature on the synthesis of thiazole derivatives and their biological activities, *Mini Rev. Med. Chem.* 24(2) (2024) 196–251.
 [10] Y. Zhu, Y. Wang, H. Zhao, J. Wei, H. Chen, et al., Synthesis, antioxidant activity, DFT simulations, molecular docking studies of Schiff base derivatives containing 2-(2-hydrazinyl) thiazole moiety, *J. Mol. Struct.* 1336 (2025) 142150.
 [11] L.H.B. Maganti, D. Ramesh, B.G. Vijayakumar, M.I.K. Khan, A. Dhayan, et al., Acetylene containing 2-(2-hydrazinyl) thiazole derivatives: design, synthesis, and *in vitro* and *in silico* evaluation of antimycobacterial activity against *Mycobacterium tuberculosis*, *RSC Adv.* 12(14) (2022) 8771–8782.
 [12] A.M. El-Naggar, A. Zidan, E.B. Elkhaed, M.S. Taghour, W.A. Badawi, Design, synthesis and docking studies of new hydrazinyl-thiazole derivatives as anticancer and antimicrobial agents, *J. Saudi Chem. Soc.* 26(4) (2022) 101488.
 [13] D.G. Raut, R.B. Bhosale, A.S. Lawand, M.G. Hublikar, V.D. Kadu, et al., Syntheses, molecular docking and biological evaluation of 2-(2-hydrazinyl) thiazoles as potential antioxidant, anti-inflammatory and significant anticancer agents, *Recent Adv. Inflamm. Allergy Drug Discov.* 16(2) (2022) 96–106.
 [14] X.S. Tang, L.Y. He, S.N. Li, W.C. Zhang, Z.Y. Wu, et al., Design, synthesis, and anti-inflammatory activity evaluation of novel indanone derivatives for the treatment of vascular dementia, *Chem. Biodivers.* 22(3) (2025) e202401931.
 [15] M. Zuo, Y. Chen, H. Zhao, T. Wu, S. He, et al., Synthesis, X-ray, DFT and antibacterial activity of a novel 1-indanone derivative, *J. Mol. Struct.* 1339 (2025) 142422.
 [16] A. Mijoba, E. Fernandez-Moreira, N. Parra-Giménez, S. Espinosa-Tapia, Z. Blanco, et al., Synthesis of benzocycloalkane-based Michael acceptors and biological activities as antimalarial and antityrosinase agents, *Molecules* 28(14) (2023) 5569.
 [17] D.B. Tiz, M. D'Ali, N. Iraci, C. Santi, L. Sancineto, Halogen-containing drugs in 2025: A record year for the therapeutic use and synthesis of FDA-approved small molecules, *Biomolecules* 16(3) (2026) 381.
 [18] I. Asiamah, S.A. Obiri, W. Tamekloe, F.A. Armah, L.S. Borquaye, Applications of molecular docking in natural products-based drug discovery, *Sci. Afr.* 20 (2023) e01593.
 [19] P. Sucharitha, K.R. Reddy, S.V. Satyanarayana, T. Garg, Absorption, distribution, metabolism, excretion, and toxicity assessment of drugs using computational tools, in: *Computational approaches for novel therapeutic and diagnostic designing to mitigate SARS-CoV-2 infection*, Academic Press, USA, 2022, pp.335–355.
 [20] A. Daina, O. Michielin, V. Zoete, SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules, *Sci. Rep.* 7(1) (2017) 42717.
 [21] O. Trott, A.J. Olson, AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading, *J. Comput. Chem.* 31(2) (2010) 455–461.
 [22] M.B. Alhawarri, Exploring the anticancer potential of Furanpydone A: A computational study on its inhibition of MTHFD2 across diverse cancer cell lines, *Cell Biochem. Biophys.* 83(1) (2024) 437–454.
 [23] D.A.E. Pitaloka, D.S.F. Ramadhan, Arfan, L. Chaidir, T.M. Fakhri, Docking-based virtual screening and molecular dynamics simulations of quercetin analogs as enoyl-acyl carrier protein reductase (InhA) inhibitors of *Mycobacterium tuberculosis*, *Sci. Pharm.* 89(2) (2021) 20.