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One-Pot Synthesis of a Hydrazone-Linked Thiazole: Structural Elucidation, Pharmacokinetic Evaluation and *In-Silico* Antitubercular Assessment

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ABSTRACT

In the present study, a hydrazone-linked thiazole derivative, (*E*)-4-(4-chlorophenyl)-2-(2-(1-(2,4-difluorophenyl)ethylidene)hydrazineyl)thiazole (**4**), was successfully synthesized via a one-pot multicomponent reaction involving 1-(2,4-difluorophenyl)ethan-1-one, thiosemicarbazide, and 2-bromo-1-(4-chlorophenyl)ethan-1-one in ethanol using glacial acetic acid as a catalyst. The structure of the synthesized compound was confirmed through detailed spectroscopic analysis using ^{1}H NMR and ^{13}C NMR techniques. The pharmacokinetic properties of the compound were evaluated using in-silico ADME analysis via SwissADME, indicating favourable drug-like characteristics, including high gastrointestinal absorption, moderate solubility, acceptable polarity and compliance with major drug-likeness rules with minimal violations. The compound exhibited relatively high lipophilicity and was predicted to be non-permeable to the blood–brain barrier, suggesting selective peripheral activity. Molecular docking studies against Cytochrome P450 14α-sterol demethylase (CYP51), a key enzyme involved in sterol biosynthesis in Mycobacterium tuberculosis, demonstrated a strong binding affinity (–9.9 kcal/mol). The ligand exhibited a stable binding conformation within the active site, stabilized by a combination of hydrogen bonding, halogen interactions, π–π stacking, π–sulfur interactions, and extensive hydrophobic contacts with key amino acid residues and the heme group. The presence of fluorine and chlorophenyl substituents significantly contributed to enhanced binding interactions and stability. The combined synthetic, spectral, pharmacokinetic, and molecular docking results suggest that the synthesized thiazole-based hydrazone derivative represents a promising scaffold for further development as a potential antitubercular agent, warranting additional biological evaluation and optimization studies.

1. Introduction

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, remains one of the most serious infectious diseases worldwide, posing a significant threat to global health [1-3]. Despite the availability of established treatment regimens, the disease continues to account for a high rate of morbidity and mortality, particularly in developing countries. The emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains has further complicated TB control efforts [4, 5]. Additionally, the long duration of therapy, associated side effects, and patient non-compliance contribute to treatment failure and the spread of resistant strains. These challenges necessitate the continuous search for new antitubercular agents with novel mechanisms of action and improved therapeutic profiles. Heterocyclic compounds constitute a fundamental class of organic molecules that play a crucial role in medicinal chemistry and drug discovery. These compounds, characterized by the presence of one or more heteroatoms such as nitrogen, sulfur, or oxygen within a cyclic framework, exhibit remarkable structural diversity and a wide range of biological activities [6-8]. Due to their ability to mimic natural biomolecules and interact effectively with biological targets, heterocycles form the backbone of many clinically important drugs. Their versatility in chemical modification and functionalization makes them highly attractive scaffolds for the design and development of novel therapeutic agents with improved efficacy and selectivity. Among the various heterocyclic systems, thiazole derivatives have emerged as an important class of bioactive compounds owing to their significant pharmacological potential [9-13]. The thiazole ring, a five-membered heterocycle containing both nitrogen and sulfur atoms, possesses unique electronic and structural features that facilitate strong interactions with biological macromolecules. Thiazole-based compounds are known to exhibit a broad spectrum of biological activities, including antimicrobial, anticancer, anti-inflammatory, antiviral, and antitubercular properties [14-18]. The presence of heteroatoms enhances their ability to participate in hydrogen bonding, and other interactions, thereby improving their binding affinity toward various biological targets. Hydrazone derivatives represent another important class of compounds widely investigated for their diverse biological activities and pharmacological relevance. These compounds contain the characteristic azomethine linkage, which plays a key role in their reactivity and biological function. Hydrazones are known for their antimicrobial, antitubercular, anticancer, and antioxidant activities, and they often act as effective enzyme inhibitors [19-22]. The incorporation of hydrazone moieties into heterocyclic frameworks has been shown to enhance biological activity by increasing molecular flexibility and facilitating stronger interactions with target proteins through hydrogen bonding and coordination with active site residues. In recent years, the strategic incorporation of halogen atoms into organic molecules has gained considerable importance in rational drug design [23, 24].

Halogen substituents, particularly fluorine and chlorine, can significantly influence the physicochemical and biological properties of compounds. Fluorine atoms are known to enhance lipophilicity, metabolic stability, and membrane permeability, while also improving binding interactions with target proteins due to their strong electronegativity. Chlorine substitution can modulate electronic distribution and increase molecular stability, thereby contributing to enhanced biological activity. The presence of halogenated aromatic rings is often associated with improved pharmacokinetic properties and increased drug-likeness. Molecular docking has emerged as a powerful and indispensable computational tool in modern drug discovery, facilitating the rational design of bioactive molecules [25-27]. It enables the prediction of the preferred orientation and binding conformation of small molecules within the active site of target proteins, thereby providing valuable insights into ligand–protein interactions at the molecular level. This approach significantly reduces the time, cost, and experimental effort associated with conventional drug development processes by allowing rapid screening and optimization of potential lead compounds. Molecular

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docking also aids in understanding key interactions such as hydrogen bonding, hydrophobic contacts, electrostatic interactions, and π–π stacking, which are essential for binding affinity and biological activity.

Overall, the application of computational techniques like molecular docking plays a crucial role in accelerating the identification and development of promising therapeutic candidates. In addition to molecular docking, in-silico ADME (Absorption, Distribution, Metabolism, and Excretion) analysis plays a vital role in the early stages of drug development [28, 29]. ADME studies provide important information regarding the pharmacokinetic behaviour and drug-likeness of compounds, including parameters such as oral bioavailability, solubility, permeability, metabolic stability, and potential toxicity. These predictions help in identifying promising lead candidates while minimizing the risk of late-stage failure. The integration of ADME evaluation with molecular docking offers a comprehensive approach for assessing both the biological activity and pharmacokinetic suitability of newly synthesized compounds.

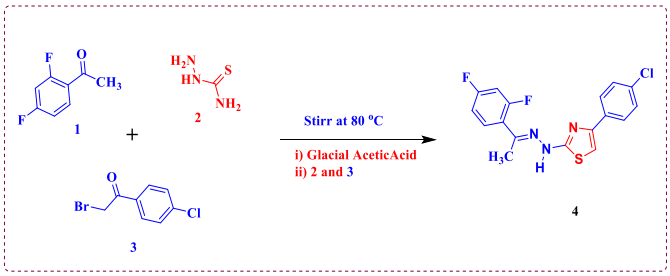
2. Experimental Methods

2.1 Materials and Methods

All reagents and solvents employed in the present work were obtained from Sigma Laboratory, Nashik (SD Fine Chemicals and Avra Synthesis) and utilized as received without any additional purification. Nuclear magnetic resonance (NMR) spectra were acquired using an advanced multinuclear FT-NMR instrument. For analysis, the compounds were dissolved in deuterated dimethyl sulfoxide (DMSO-d_6), with tetramethylsilane (TMS) serving as the internal reference standard, and the chemical shift values were expressed in parts per million (ppm). Reaction progress was routinely assessed by thin-layer chromatography (TLC) on Merck aluminum plates pre-coated with silica gel incorporating a fluorescent indicator (F254). All laboratory glassware was meticulously washed and subsequently oven-dried before use.

*2.2 General Methodology for the Synthesis of (E)-4-(4-chlorophenyl)-2-(2-(1-(2,4-difluorophenyl)ethylidene)hydrazineyl)thiazole (**4**)*

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



Scheme 1 Synthesis of compound **4**

*2.3 Physical and Spectral Data for Synthesized Compounds: (E)-4-(4-Chloro phenyl)-2-(2-(1-(2,4-difluorophenyl)ethylidene)hydrazineyl)thiazole (**4**)*

Yellow colour; Yield 82%; ^{1}H NMR (500 MHz, DMSO) δ 11.68 (s, 1H), 7.55 (d, *J* = 8.6 Hz, 2H), 7.48 (d, *J* = 8.6 Hz, 2H), 7.42 (s, 1H), 7.40 – 7.38 (m, 1H), 7.34 (m, 1H), 7.32 – 7.30 (m, 1H), 2.52 (s, 3H).; ^{13}C NMR (126 MHz, DMSO) δ 170.03, 159.37, 157.45, 155.50, 143.65, 133.92, 133.25, 132.85, 132.43, 132.33, 130.04, 129.11, 128.90, 127.73, 118.46, 118.39, 115.94, 105.73, 17.50.

2.4 ADME Study

The pharmacokinetic properties of the synthesized compounds were evaluated using ADME (Absorption, Distribution, Metabolism, and Excretion) analysis to assess their suitability as potential drug candidates. For this purpose, the online tool SwissADME, developed by the Swiss Institute of Bioinformatics, was employed to predict key pharmacokinetic, physicochemical, and drug-likeness parameters based on molecular structures. The analysis included the determination of important descriptors such as hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), number of rotatable bonds, topological polar surface area (TPSA), and water solubility. Lipophilicity was estimated using various computational models, including iLOGP, XLOGP3, WLOGP, MLOGP, and SILICOS-IT, which are indicative of membrane permeability.

In addition, pharmacokinetic parameters such as gastrointestinal absorption, blood–brain barrier permeability, P-glycoprotein interaction, and cytochrome P450 enzyme involvement were predicted. The drug-likeness of the compounds was further evaluated based on Lipinski's rule of five, which recommends that orally active molecules should generally have no more than ten hydrogen bond acceptors, no more than five hydrogen bond donors, and a TPSA value below 140 Å^2 for optimal biological permeability.

2.5 Molecular Docking Studies

Molecular docking studies were carried out to explore the binding interactions, orientation within the active site, and potential inhibitory activity of the synthesized compound **4**. Molecular docking is a widely used computational technique in drug discovery that provides insights into ligand–protein interactions and helps predict the binding affinity of small molecules toward biological targets. In the present work, docking analysis was performed against the target protein Cytochrome P450 14α-sterol demethylase (CYP51) (PDB ID: 1E9X) to evaluate the binding affinity and interaction pattern of 4 within the active site. The selected protein corresponds to the crystal structure of *Mycobacterium tuberculosis* CYP51 complexed with 4-phenylimidazole. CYP51 is a crucial enzyme involved in sterol biosynthesis and plays an important role in maintaining membrane integrity and cellular function in mycobacteria. Owing to its essential biological role and involvement in pathogen survival, CYP51 is considered a promising target for the development of antitubercular agents. Therefore, docking of 4 with this protein provides valuable insights into its possible inhibitory potential and binding efficiency. Docking simulations were performed using AutoDockTools 1.5.6, [30] including protein and ligand preparation, grid box generation, and docking procedures. The ligand geometry was optimized by energy minimization at the MM2 level using Chem3D Pro to ensure structural stability [31, 32]. The three-dimensional structure of the target protein was retrieved from the Protein Data Bank. Furthermore, the binding interactions and molecular conformations were analysed and visualized using both 2D and 3D representations through Discovery Studio Visualizer [33, 34].

3. Results and Discussion

3.1 Chemistry

The synthesized compound (*E*)-4-(4-chlorophenyl)-2-(2-(1-(2,4-difluorophenyl)ethylidene)hydrazineyl)thiazole (**4**) was obtained as a yellow-colored solid in a good yield of 82%, suggesting the successful formation of a highly conjugated system incorporating thiazole, hydrazone, and substituted aromatic rings. The ^{1}H NMR spectrum (500 MHz, DMSO-d_6) revealed a distinct singlet at δ 11.68 ppm integrating for one proton, which is characteristic of the hydrazone –NH group, thereby confirming the formation of the azomethine linkage. The aromatic region displayed two well-defined doublets at δ 7.55 and 7.48 ppm (J = 8.6 Hz, 2H each), corresponding to the protons of the para-substituted 4-chlorophenyl ring, exhibiting a typical AA′BB′ splitting pattern. A singlet observed at δ 7.42 ppm was attributed to the C5–H proton of the thiazole ring, confirming the integrity of the heterocyclic core. The remaining aromatic signals appearing as multiplets at δ 7.40–7.38, 7.34, and 7.32–7.30 ppm were assigned to the protons of the 2,4-difluorophenyl moiety, where the observed complexity in splitting arises from both proton–proton and long-range proton–fluorine coupling interactions, thus supporting the presence and substitution pattern of fluorine atoms on the aromatic ring. Furthermore, a singlet at δ 2.52 ppm integrating for three protons was assigned to the methyl group attached to the azomethine carbon (–CH_3–C=N), confirming the ethylidene fragment. The ^{13}C NMR spectrum (126 MHz, DMSO-d_6) further substantiated the proposed structure, showing a characteristic downfield signal at δ 170.03 ppm corresponding to the azomethine (C=N) carbon. The signals observed at δ 159.37, 157.45, and 155.50 ppm were attributed to aromatic carbons directly bonded to fluorine atoms, reflecting the strong electron withdrawing effect of fluorine. The remaining aromatic carbons of the chlorophenyl, difluorophenyl, and thiazole rings appeared in the region δ

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143.65–127.73 ppm, consistent with substituted aromatic systems. Additional signals at δ 118.46, 118.39, and 115.94 ppm further confirmed the presence of fluorinated aromatic carbons due to characteristic C–F coupling effects, while the signal at δ 105.73 ppm was assigned to an aromatic CH carbon within the difluorophenyl ring. Finally, the methyl carbon resonated at δ 17.50 ppm, supporting the presence of the ethylidene substituent. Overall, the combined spectral data are in excellent agreement with the proposed structure, thereby confirming the successful synthesis of the target hydrazone-linked thiazole derivative with the expected (*E*)-configuration. The corresponding spectra are presented in Figs. 1 (^{1}H NMR), and 2 (^{13}C NMR).

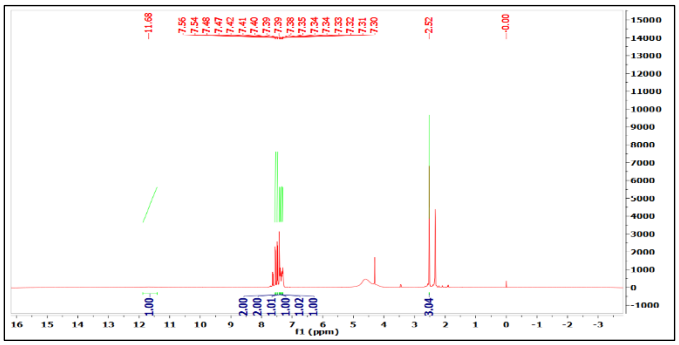

Fig. 1 ^{1}H NMR spectrum of compound **4**

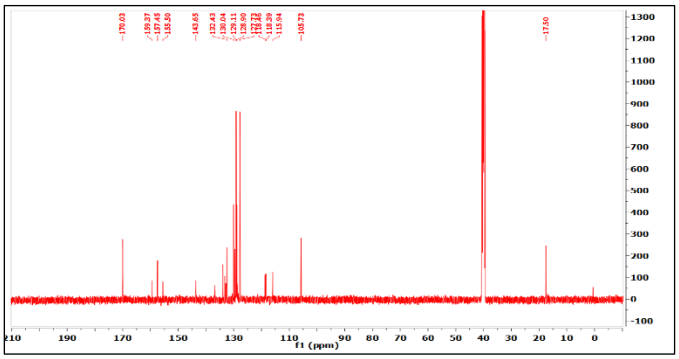

Fig. 2 ^{13}C NMR spectrum of compound **4**

3.2 ADME Study

The ADME (Absorption, Distribution, Metabolism, and Excretion) properties of the synthesized compound (*E*)-4-(4-chlorophenyl)-2-(2-(1-(2,4-difluorophenyl)ethylidene)hydrazineyl)thiazole (**4**) were evaluated using the SwissADME, and the calculated parameters are summarized in Table 1. These parameters provide important insight into the pharmacokinetic profile, membrane permeability, and drug-likeness of the compound.

Table 1 The ADME parameters of compound **4**

Parameters	Values
Number of Hydrogen bond donors (nHD)	1
Number of Hydrogen bond acceptors (nHA)	4
Molecular Polar Surface Area (TPSA), Å^2	65.52
Consensus Log Po/w	5.16
Log S (ESOL)	-5.89
Water Solubility	Moderately soluble
Gastrointestinal absorption	High
BBB permeability	No
P-gp substrate	No
Metabolic enzymes inhibition	CYP1A2, CYP2C19, CYP2C9
Drug likeness matching	Lipinski (1 violation), Ghose (1), Veber (0), Egan (1)

The predicted ADME profile of compound (**4**) reveals important pharmacokinetic characteristics. The molecule contains 1 hydrogen bond donor and 4 hydrogen bond acceptors, indicating moderate polarity and a balanced hydrogen bonding capacity, which is favourable for membrane permeability. The topological polar surface area (TPSA) of 65.52 Å^2 is well below the threshold of 140 Å^2, suggesting good oral bioavailability and efficient permeation across biological membranes. The consensus Log Po/w value of 5.16 indicates relatively high lipophilicity, which may enhance passive diffusion through lipid membranes but could also slightly limit aqueous solubility. The ESOL LogS value of −5.89 classifies the compound as moderately soluble, indicating acceptable solubility for oral absorption. The compound exhibits high gastrointestinal absorption, supporting its suitability for oral administration. However, it is predicted to be non-permeant to the blood–brain barrier, suggesting limited central nervous system penetration. Additionally, the compound is not a substrate of P-glycoprotein, indicating a lower likelihood of active efflux from cells. From a metabolic perspective, the compound is predicted to inhibit cytochrome P450 enzymes CYP1A2, CYP2C19, and CYP2C9, which may lead to potential drug–drug interactions and should be considered in further studies. Drug-likeness evaluation indicates minor deviations, with one violation each in Lipinski, Ghose, and Egan rules, while fully satisfying Veber criteria. The bioavailability score of 0.55 suggests moderate oral bioavailability.

The ADME radar plot (Fig. 3) represents the drug-likeness profile of compound (**4**) based on six physicochemical parameters: lipophilicity (LIPO), size (SIZE), polarity (POLAR), solubility (INSOLU), flexibility (FLEX), and saturation (INSATU). Most parameters fall within the optimal range, indicating favourable oral drug-like properties.

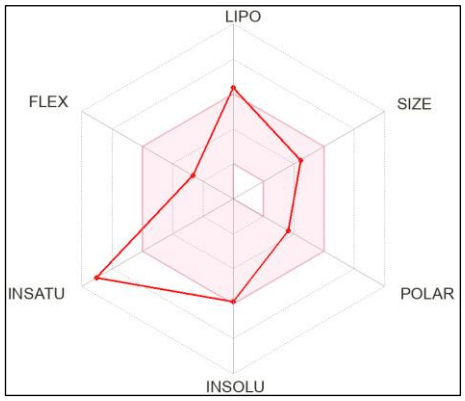

Fig. 3 Bioavailability radar chart for the compound **4**

The compound exhibits suitable lipophilicity, molecular size, polarity, and solubility. However, the saturation parameter is slightly outside the optimal region, reflecting a high degree of aromaticity. Additionally, low flexibility suggests a relatively rigid molecular structure. The BOILED-Egg model (Fig. 4) further supports these findings. The compound is positioned within the white region of the plot, indicating high probability of gastrointestinal absorption, but outside the yellow yolk, confirming its inability to cross the blood–brain barrier. The TPSA (65.52 Å^2) and high lipophilicity contribute to efficient passive membrane permeability. Overall, the ADME analysis of compound (**4**) indicates a favorable balance between permeability, lipophilicity, and solubility, with good oral absorption potential but limited brain penetration, making it a promising candidate for further drug development with scope for optimization in metabolic stability.

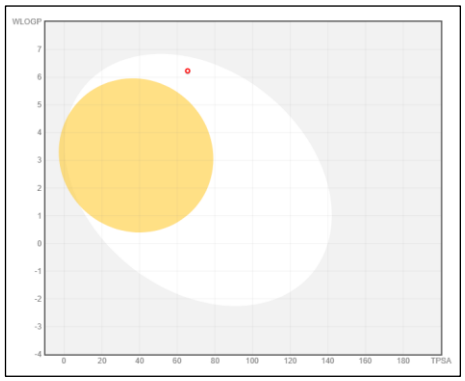

Fig. 4 Boiled-egg plot of the compound **4**

3.3 Molecular Docking

The molecular docking analysis of (*E*)-4-(4-chlorophenyl)-2-(2-(1-(2,4-difluorophenyl)ethylidene)hydrazineyl)thiazole **(4)** with the target protein Cytochrome P450 14α-sterol demethylase (CYP51) (PDB ID: 1E9X) reveals the formation of a stable ligand–protein complex within the active site, exhibiting a binding affinity of −9.9 kcal/mol. The binding mode of 4 is governed by a combination of hydrogen bonding, halogen interactions, π-based interactions, and extensive hydrophobic contacts, which collectively contribute to the stabilization of the ligand within the enzyme binding pocket. A key anchoring interaction is observed in the

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form of a conventional hydrogen bond between the fluorine atom of the ligand and the hydroxyl group of THR80, which plays a crucial role in stabilizing the ligand at the active site.

In addition, a halogen interaction involving the fluorine atom and the oxygen atom of TYR76 further enhances the binding specificity and directional orientation of the ligand. These interactions emphasize the significant role of the difluorophenyl moiety in facilitating strong intermolecular contacts with the protein. The ligand also exhibits a π–sulfur interaction with the sulfur atom of MET79, which contributes to maintaining the proper orientation of the ligand within the hydrophobic environment of the active site.

Aromatic interactions are prominently involved in the binding mechanism, as evidenced by the presence of π–π stacked interaction with TYR76 and a π–π T-shaped interaction with the heme prosthetic group (HEM460). These interactions provide additional stabilization through effective overlap of π-electron systems.

Hydrophobic interactions play a dominant role in the stabilization of the ligand–protein complex. The 4-chlorophenyl ring of 4 participates in alkyl and π–alkyl interactions with key residues such as LEU321, TYR76, and PHE78, indicating that this moiety effectively occupies the hydrophobic pocket of the enzyme.

Furthermore, additional π–alkyl interactions with residues such as LYS97 and the heme group further reinforce the binding stability. Overall, the combined contribution of hydrogen bonding, halogen bonding, π–sulfur interaction, π–π stacking, and extensive hydrophobic interactions ensures strong binding of 4 within the CYP51 active site. The observed binding affinity of –9.9 kcal/mol, along with the diverse interaction profile, suggests that 4 has significant potential as an effective inhibitor of CYP51 and may serve as a promising candidate for antitubercular drug development. The 3D and 2D binding interactions of compound **4** and Cytochrome P450 14α-sterol demethylase (CYP51) (PDB ID: 1E9X) are presented in Figs. 5 and 6 respectively.

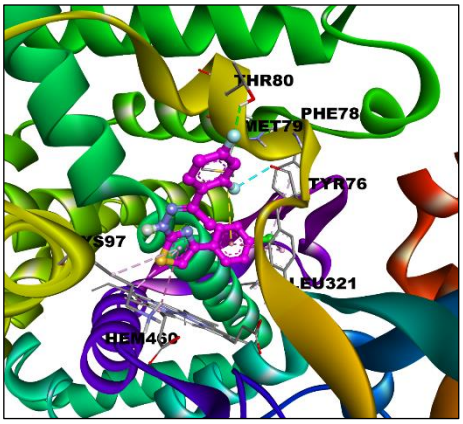

Fig. 5 3D binding interaction between protein Cytochrome P450 14α-sterol demethylase (CYP51) (PDB ID: 1E9X) and compound **4**

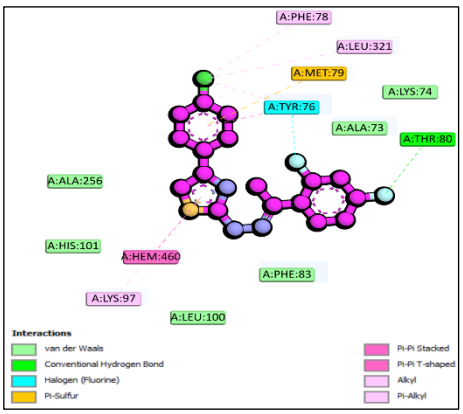

Fig. 6 2D binding interaction between protein Cytochrome P450 14α-sterol demethylase (CYP51) (PDB ID: 1E9X) and compound **4**

4. Conclusion

In summary, a novel hydrazone-linked thiazole derivative, (*E*)-4-(4-chlorophenyl)-2-(2-(1-(2,4-difluorophenyl)ethylidene)hydrazineyl)thiazole (**4**), was successfully synthesized through a simple and efficient one-pot multicomponent strategy, affording the target compound in good yield. The structure of the synthesized molecule was conclusively established using ^{1}H NMR and ^{13}C NMR spectroscopic techniques, which confirmed the presence of the hydrazone linkage, substituted aromatic systems, and thiazole framework. The in-silico ADME evaluation revealed favourable pharmacokinetic properties, including good gastrointestinal absorption, acceptable polarity, and compliance with major drug-likeness criteria, indicating its potential as an orally active compound. Although the compound exhibited relatively high lipophilicity and limited blood–brain barrier permeability, these characteristics may be advantageous for selective peripheral activity. Furthermore, molecular docking studies against Cytochrome P450 14α-sterol demethylase (CYP51) demonstrated a strong binding affinity and stable ligand–protein interactions mediated by hydrogen bonding, halogen interactions, π–π stacking, π–sulfur interactions, and hydrophobic contacts. These findings highlight the significant role of fluorine and chlorophenyl substituents in enhancing binding efficiency and interaction stability. Overall, the findings suggest that the synthesized compound holds significant potential as a lead scaffold for antitubercular drug development and merits further biological investigation and structural refinement.

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