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RESEARCH ARTICLE

# Synthesis, *In silico* Studies, and Biological Evaluation of Benzotriazole-Fused Thiazole-containing Schiff Bases as Potential Therapeutic Agents for Microbial Infections in Respiratory Disorders

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**Abstract:** ***Introduction*:** Respiratory disorders pose a significant global health challenge, often worsened by bacterial and fungal infections. Schiff bases have gained attention for their antimicrobial properties, making them promising candidates for drug development and potential patent applications. This study explores the synthesis, computational analysis, and biological evaluation of thiazole-containing Schiff bases as therapeutic agents.

***Materials and Methods*:** A series of Schiff base compounds (9a–9h) was synthesized and characterized using spectroscopy and chromatography techniques. Computational studies, including molecular docking, ADME profiling, and physicochemical analyses, were performed to compare them with standard antimicrobial drugs (Amoxicillin and Fluconazole). Antimicrobial efficacy was assessed against *Escherichia coli*, *Bacillus subtilis*, and *Candida albicans* using the broth microdilution method in 96-well plates to determine minimum inhibitory concentrations (MICs).

***Results*:** Among the synthesized compounds, 9c exhibited potent antimicrobial activity, with MIC values of 12.76 µg/mL against *B. subtilis* and 25.52 µg/mL against *C. albicans*. Compound 9g showed strong activity against *E. coli*, with an MIC value of 12.76 µg/mL. Spectroscopic and computational analyses validated their structural stability and bioactive potential.

***Discussion*:** The observed antimicrobial activity highlights the therapeutic promise of thiazole-containing Schiff bases in combating microbial infections associated with respiratory diseases. Their potency, compared to standard antibiotics and antifungal agents, underscores the need for further pharmacological evaluation, optimization, and patent consideration.

***Conclusion*:** Thiazole-containing Schiff bases demonstrate significant antimicrobial potential, particularly against respiratory-related pathogens. These findings warrant further investigation into their pharmacological properties to develop new treatment options for microbial infections in respiratory disorders, with scope for patentable innovations.

**Keywords:** Schiff base, antimicrobial agents, Broth microdilution method, Docking, Physicochemical parameter, *C. albicans*, *B. subtilis*, *E. coli*, Patent.

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## 1. INTRODUCTION

Respiratory disorders represent a significant global health burden, affecting millions of individuals across all age groups. These conditions, ranging from acute infections like pneumonia to chronic illnesses such as asthma, chronic obstructive pulmonary disease (COPD), and tuberculosis, are often exacerbated by microbial infections [1-3]. Bacteria, fungi, and viruses play a crucial role in the pathogenesis of respiratory diseases, leading to severe complications, reduced quality of life, and increased mortality rates worldwide. Among bacterial infections, *Streptococcus pneumoniae*, *Mycobacterium tuberculosis*, *Klebsiella pneumoniae*, *Bacillus subtilis,* and *Escherichia coli* are known to cause respiratory ailments, ranging from mild infections to life-threatening conditions [4-8]. Fungal infections, primarily caused by species such as *Candida albicans* and *Aspergillus fumigatus*, can lead to pulmonary aspergillosis and other invasive diseases, particularly in immunocompromised individuals [9-13].

The need for effective antimicrobial agents has led to the exploration of Schiff bases, a class of organic compounds characterized by the presence of an imine group (-C=N-) with a substituent attached to the nitrogen atom [14-16]. These compounds are typically formed by the condensation of primary amines with carbonyl compounds (aldehydes or ketones) [17-19]. Schiff bases are of considerable interest due to their diverse biological and chemical properties. They are known for their versatility and have been extensively studied for various applications, including medicinal chemistry, coordination chemistry, and material science [20-24]. Schiff bases exhibit a wide range of biological activities, such as antifungal [25,26], antibacterial [27, 28], antiviral [29, 30], antitumor [31, 32], and anti-inflammatory [33-34], antianxiety [35-36] properties, making them valuable candidates for drug development (Fig. **1**) [37].

To elucidate the antimicrobial potential of thiazole-containing Schiff bases, a comprehensive literature survey is presented, emphasizing key findings from previous research, as a study was conducted on imino-4-methoxyphenol thiazole-derived Schiff base ligands, focusing on their synthesis, spectral characterization, and antimicrobial activity. The research demonstrated that these Schiff bases exhibit moderate antibacterial and antifungal activities, although their effectiveness was found to be less than that of standard drugs [38]. Research was undertaken on the synthesis, antibacterial, and antioxidant activities of thiazole-based Schiff base derivatives. This study combined experimental and computational methods to evaluate the biological activities of these compounds [39]. A study focused on the synthesis, antimicrobial, and antioxidant evaluation of new thiazole Schiff base derivatives was conducted. The research incorporated *in silico* studies to predict their biological activities [40].

BP Sharma *et al.* synthesized an antibacterial Schiff base (Fig. **2** [41]) through a multi-step reaction process. Initially, an aromatic carboxylic acid (*o*-chloro and *o*-hydroxy benzoic acid) was refluxed with methanol at 50°C, leading to the formation of an ester. The ester was then treated with hydrazine hydrate in methanol to yield the corresponding hydrazide. Subsequently, the hydrazide underwent a reaction with KOH, $CS_2$, and hydrazine hydrate in methanol, resulting in the formation of a 1,3,4-triazole derivative. Two distinct triazoles were synthesized from the two different starting aromatic carboxylic acids (*o*-chloro and *o*-hydroxy benzoic acid). These triazole intermediates were further refluxed with the carbonyl compound, Benzil, leading to the formation of two different Schiff bases. Finally, both triazole intermediates were reacted with Benzil to obtain the desired antibacterial Schiff base [42]. Nessma F. Mahmoud synthesized 4-(benzylidene amino)-5-phenyl-4H-1,2,4-triazole-3-thiol ligand (Fig. **2**) from 4-amino-5-phenyl-1,2,4-triazole-3-thiol and benzaldehyde in a 1:1 ratio. Its Fe(III), Cu(II), and Zn(II) complexes were characterized, showing octahedral structures and nanostructural formation. Biological screening revealed antibacterial and antifungal activity, with molecular docking studies conducted against Aspergillus fumigatus and Mycobacterium tuberculosis [43].

In contrast, the current study introduces novel benzotriazole–thiazole Schiff bases that combine the pharmacologically active thiazole core with a benzotriazole scaffold in a single framework, which has not been explored previously. These new derivatives are designed to enhance antimicrobial potency while optimizing drug-likeness

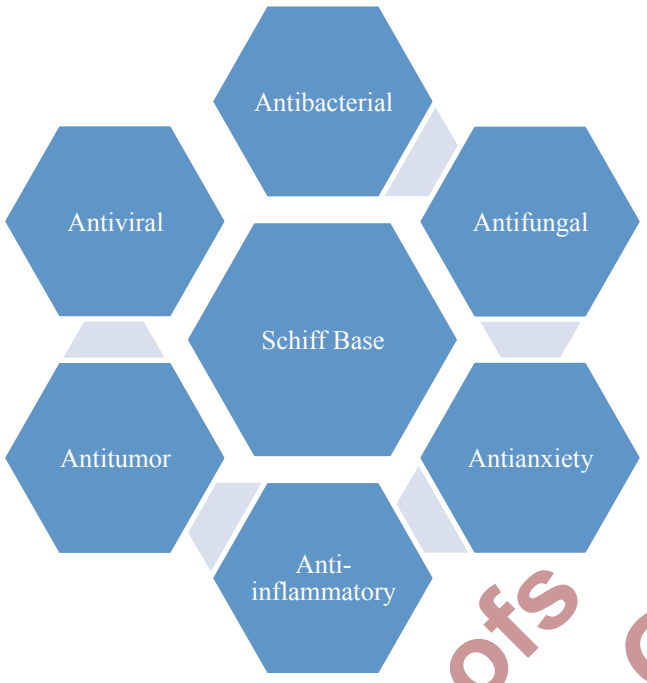



**Fig. (1).** Various Biological Activities demonstrated by Schiff Bases [37]. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*



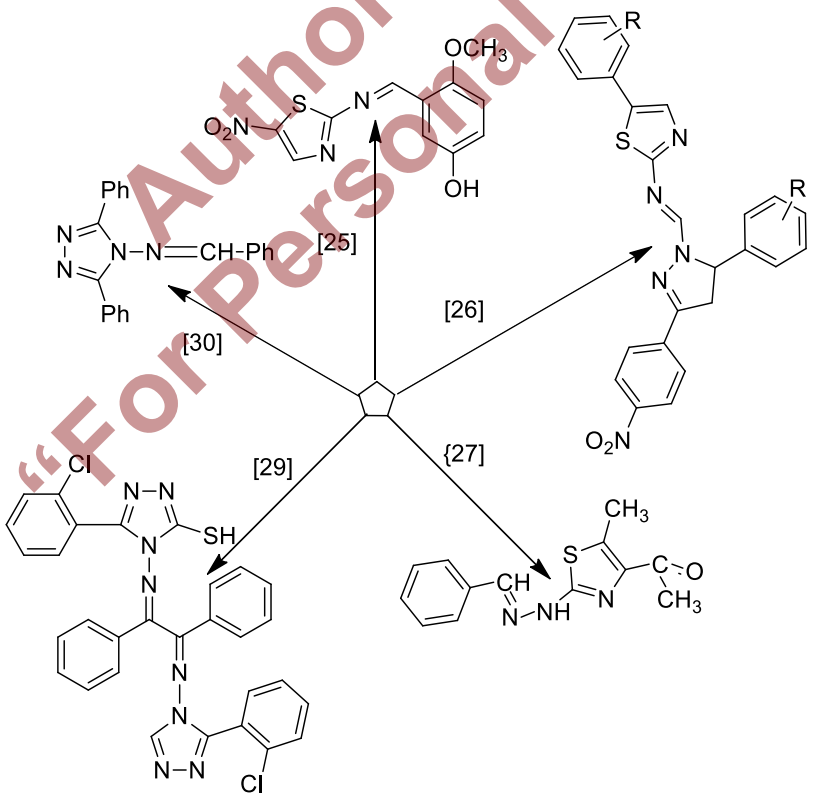



**Fig. (2).** Thiazole-Triazole containing Schiff Base.

and bioavailability. Furthermore, we extend the evaluation beyond conventional assays by performing computational studies, including molecular docking and ADME prediction, to assess their potential as therapeutic agents against respiratory pathogens. This work, therefore, establishes a distinct chemical and functional advancement over previous thiazole/Schiff-base derivatives by integrating structural novelty with targeted antimicrobial activity and *in silico* pharmacokinetic profiling (Fig. **3**).

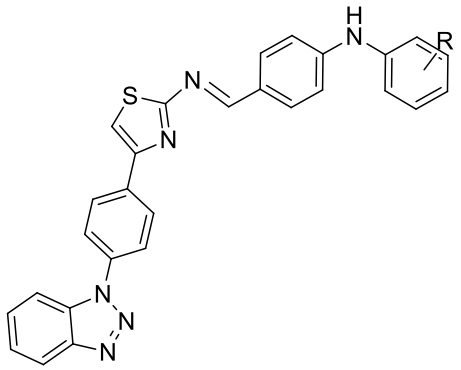



**Fig. (3).** Target compounds.

## 2. MATERIALS AND METHODS

### 2.1 Synthesis and Characterization of Compounds

4-Bromoacetophenone, thiourea, substituted amines, benzotriazole, and 4-chlorobenzaldehyde were purchased from Himedia, and all other chemicals and solvents were purchased from CDH. All chemicals used were of analytical grade and purified before use. Melting points of the synthesized compounds were determined by the open capillary method [44-45]. The IR spectra of synthesized compounds were recorded in potassium bromide discs on a Frontier FTIR (OTL/58) spectrometer [46-50]. The $^1$H NMR spectra were recorded on a Bruker Advanced Neo spectrometer at 500 MHz in $CDCl_3$ and DMSO containing TMS as internal standard. All chemical shift values are reported in ppm ($\delta$) [51-56]. The reaction progress was monitored by thin-layer chromatography (TLC) using silica gel G, and spots were visualized in an iodine chamber [57-60]. All the target compounds were subjected to biological evaluation for their antimicrobial activity.

### 2.2. Computational Studies

Virtual screening for a series of compounds was performed by molecular docking [61-64] for the prediction of binding affinity and preferred orientation of the compounds and the physicochemical properties (MW, MR, CAA, CMA, CSEV, Ovality, LogP, number of rotable bonds, H-bonds, Gastrointestinal absorption, Synthetic Accessibility, Abbott Bioavailability Score, Lipinski Filter, Synthetic Accessibility) of the target compounds (9a-9h) and standard drugs (Amoxicillin, fluconazole) were calculated using Chem 3D Ultra version 12.0 and Swiss ADME free software programs[65-69]. The comparison of physicochemical characteristics was done, and the percentage similarity of target compounds with comparison to reference drugs [70-72].

### 2.3. Antimicrobial Activity of Target Compounds (9a-9h)

*In vitro* tests, such as minimum inhibitory concentration (MIC) and sensitivity tests, are used to screen new agents and determine the effectiveness of drugs against antimicrobials. We performed antimicrobial activity using *E coli, B Substiles,* and *Candida albicans* through the broth dilution method in which 96-well plates, with maximum resistance evaluated against increasing sample concentrations. The absorbance was measured at 600 nm to determine MIC values, which indicate the lowest concentration required to inhibit visible microbial growth. All experiments were performed in triplicate (n = 3), and MIC values are reported as the standard deviation of the ≤10% of the mean [73-75]. The selected microorganisms are opportunistic pathogens frequently associated with respiratory and nosocomial infections. The study aims to identify broad-spectrum anti-infective leads relevant to respiratory complications

## 3. Results and Discussion

### *3.1. Procedure for the Synthesis of Compounds (9a-9h)*

A mixture of 1-(4-bromophenyl) ethenone (0.01 mole), thiourea (0.015 mole), and iodine (0.01 mole) was refluxed in a round-bottom flask at

50°C for 12 hours, yielding 4-(4-bromophenyl) thiazole-2-amine (0.01 mole). This intermediate was then reacted with benzotriazole (0.01 mole) in the presence of anhydrous potassium carbonate (0.02 mole), Copper Iodide in 20ml DMF, and forming 4-(4-(1H-benzo[1,2,3]triazol-1-yl)phenyl) thiazole-2-amine (0.01 mole). Subsequently, this compound (0.01 mole) was dissolved in 40 mL of ethanol with glacial acetic acid (0.005 mole) and refluxed with 4-chlorobenzaldehyde (0.01 mole) for 6 hours, producing 4-(4-(1H-benzo[1,2,3]triazol-1-yl) phenyl)-N-(4-chlorobenzylidene) thiazole-2-amine (0.01 mole). Finally, this product was reacted with various substituted amines (0.01 mole) through the Ullmann reaction to afford the final Schiff bases (9a-9h) as shown in Fig. (**4**).

### *3.1.1. 4-(4-bromophenyl) thiazole-2-amine (3)*

IR (KBr) $cm^{-1}$: 3350 (NH Str.), 2980 (C-H Str. Aromatic), 1590 (C=C Str. Aromatic), 1320 (C=N Str.), 879 (C-Br Str.) Yield: 65.63%, Melting Point: 127-130°C, $R_f$:0.67 (n-Hexane: Ethyl acetate; 3:1).

### *3.1.2. 4-(4-(1H-benzo[1, 2, 3] triazol-1-yl) phenyl) thiazole-2-amine (5)*

IR (KBr) $cm^{-1}$: 3350 (NH Str.), 2980 (C-H Str. Aromatic), 1584 (C=C Str. Aromatic), 1394 (C=N Str.), 1197 (C-N Str). $^1$H NMR (500 MHz, $CDCl_3$) δ: 7.82–6.70 (m, 8H, Ar–H), 5.29 (s, 2H, $NH_2$), 4.84 (s, 1H, CH)Yield: 71.73%, Melting Point: 138-140°C. $R_f$:0.57 (n-Hexane: Ethyl acetate; 3:1).

4-(4-(1H-benzo[d] [1, 2, 3] triazol-1-yl) phenyl)-N-(4-chloro benzylidene) thiazole-2-amine (7)

IR (KBr) $cm^{-1}$: 2970 (C-H Str. Aromatic), 1404 (C=N Str.), 1210 (C-N Str). $^1$H NMR (500 MHz, $CDCl_3$) δ: 9.61 (s, 1H, CH=N), 7.83–7.25 (m, 12H, Ar–H), 4.84 (s, 1H, CH)Yield: 61.33%, Melting Point: 98-100°C. $R_f$ :0.80 (n-Hexane: Ethyl acetate; 3:1).

### *3.1.3. 4-(4-(1H-benzo [1, 2, 3] triazol-1-yl) phenyl)-N-(4-(phenylamino) benzylidene) thiazole-2-amine(9a)*

IR (KBr) $cm^{-1}$: 3340 (NH Str.), 3010 (C-H Str. Aromatic), 2916 (C-H Str. Aliphatic), 1378 (C=N Str.), 1209 (C-N Str). $^1$H-NMR (500 MHz, $CDCl_3$) δ 9.84 (s, 1H, N=CH), 7.26 (d, J = 8.4 Hz, 2H, Ar–H), 7.84–7.24 (m, 15H, Ar–H), 6.54 (s, 1H, NH), 3.84 (s, 1H, CH)Yield: 64.33%, Melting Point: 133-135°C, $R_f$:0.91 (n-Hexane: Ethyl acetate; 3:1).

### *3.1.4. 4-(4-(1H-benzo[1, 2, 3] triazol-1-yl) phenyl)-N-(4-((2- methoxy phenyl) amino) benzylidene) thiazole-2-amine(9b)*

IR (KBr) $cm^{-1}$: 3356 (NH Str.), 3010 (C-H Str. Aromatic), 2916 (C-H Str. Aliphatic), 1398 (C=N Str.), 1247 (C-N Str.), 1089 (C-O-C Str). $^1$H-NMR (500 MHz, $CDCl_3$) δ 9.79 (s, 1H, N=CH), 7.84–7.01 (m, 16H, Ar–H), 6.42 (s, 1H, NH), 3.76 (s, 1H, CH–thiazole), 3.68 (s, 3H, $OCH_3$). Yield: 68.32%, Melting Point: 123-125°C, $R_f$ :0.90 (n-Hexane: Ethyl acetate; 3:1).

### *3.1.5. 4-(4-(1H-benzo[1, 2, 3] triazol-1-yl) phenyl)-N-(4-((3-methoxyphenyl) amino) benzylidene) thiazole-2-amine(9c)*

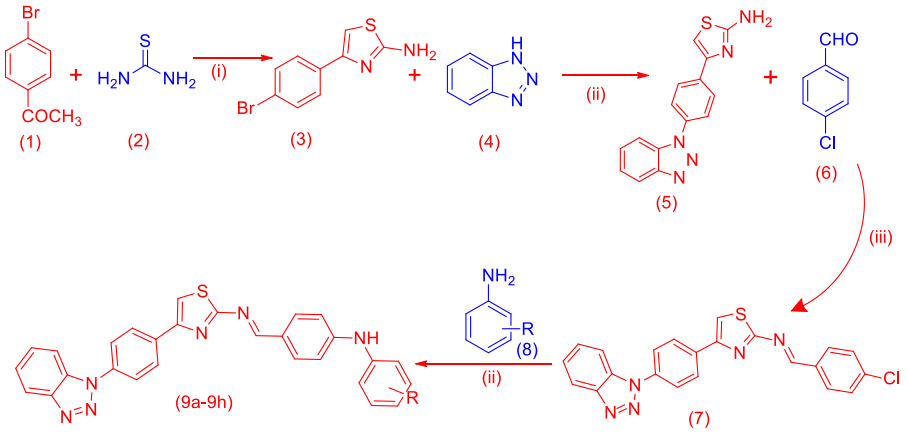
IR (KBr) $cm^{-1}$: 3366 (NH Str.), 3010 (C-H Str. Aromatic), 2916 (C-H Str. Aliphatic),1398 (C=N Str.), 1204 (C-N Str.), 1089 (C-O-C Str).$^1$H-NMR (500 MHz, $CDCl_3$) δ 9.64 (s, 1H, N=CH), 7.84–7.01 (m, 16H, Ar–H), 6.34 (s, 1H, NH), 3.76 (s, 1H, CH–thiazole), 3.68 (s, 3H, $OCH_3$)Yield: 64.00%, Melting Point: 140-141°C, $R_f$ : 0.84(n-Hexane: Ethyl acetate; 3:1).

### *3.1.6. 4-(4-(1H-benzo[1,2,3]triazol-1-yl)phenyl)-N-(4-((4-methoxyphenyl)amino)benzylidene) thiazole-2-amine (9d)*

IR (KBr) $cm^{-1}$: 3366 (NH Str.), 3010 (C-H Str. Aromatic), 2916 (C-H Str. Aliphatic), 1403 (C=N Str.), 1242 (C-N Str.), 1092 (C-O-C Str.) $^1$H-NMR (500 MHz, $CDCl_3$) δ 9.78 (s, 1H, N=CH), 8.44–6.92 (m, 16H, Ar–H), 7.93 (s, 1H, NH), 3.84 (s, 1H, CH–thiazole), 3.74 (s, 3H, $OCH_3$). Yield: 69.30%,Melting Point: 130-131°C, $R_f$ : 0.81(n-Hexane: Ethyl acetate; 3:1).

### *3.1.7. 4-(4-(1h-benzo[1,2,3]triazol-1-yl)phenyl)-n-(4-((4-methylphenyl)amino)benzylidene) thiazole -2-amine (9e)*

IR (KBr) $cm^{-1}$: 3366 (NH Str.), 3010 (C-H Str. Aromatic), 2917 (C-H Str. Aliphatic), 1396 (C=N Str.), 1261 (C-N Str.), 1087 (C-O-C Str.) $^1$H-NMR (500 MHz, $CDCl_3$) δ 9.56 (s, 1H, N=CH), 8.42–7.12 (m, 16H, Ar–H), 7.63 (s, 1H, NH), 3.84 (s, 1H, CH–thiazole), 3.68 (s, 3H, $CH_3$)Yield: 67.30%, Melting Point: 134-136°C, $R_f$ : 0.89(n-Hexane: Ethyl acetate; 3:1).




| R | H | 2-$OCH_3$ | 3-$OCH_3$ | 4-$OCH_3$ | 4- $CH_3$ | 4- F | 4- Cl | 4- Br |
|---|---|---|---|---|---|---|---|---|
| Cpd Code | 9a | 9b | 9c | 9d | 9e | 9f | 9g | 9h |

**Fig. (4). Scheme:** Synthesis of the target compounds. Reagents and conditions: (**i**) Iodine, Reflux (**ii**) CuI, $K_2CO_3$, DMF (**iii**) Ethanol and glacial acetic acid, Reflux.



### *3.1.8. 4-(4-(1H-benzo[1, 2, 3] triazol-1-yl) phenyl)-N-(4-((4-fluorophenyl) amino) benzylidene) thiazole-2-amine(9f)*

IR (KBr) $cm^{-1}$: 3366 (NH Str.), 3010 (C-H Str. Aromatic), 2917 (C-H Str. Aliphatic), 1396 (C=N Str.), 1214 (C-N Str.), 778 (C-F Str.)$^1$H-NMR (500 MHz, $CDCl_3$) δ: 9.57 (s, 1H, N=CH), 8.40–7.08 (m, 16H, Ar–H), 7.65 (s, 1H, NH), 3.86 (s, 1H, CH–Thiazole), Yield: 68.37%, Melting Point: 144-146°C, $R_f$:0.92(n-Hexane: Ethyl acetate; 3:1).

### *3.1.9. 4-(4-(1H-benzo [1, 2, 3] triazol-1-yl) phenyl)-N-(4-((4- chloro phenyl) amino) benzylidene) thiazole-2-amine (9g)*

IR (KBr) $cm^{-1}$: 3348 (NH Str.), 3010 (C-H Str. Aromatic), 2917 (C-H Str. Aliphatic), 1396 (C=N Str.), 1277 (C-N Str.) $^1$H NMR (δ, ppm): 9.87 (s, 1H, N=CH), 7.81–6.92 (m, 16H, Ar–H), 7.14 (s, 1H, NH), 3.86 (s, 1H, CH–Thiazole), Yield: 61.37%, Melting Point: 142-143°C, $R_f$: 0.81(n-Hexane: Ethyl acetate; 3:1).

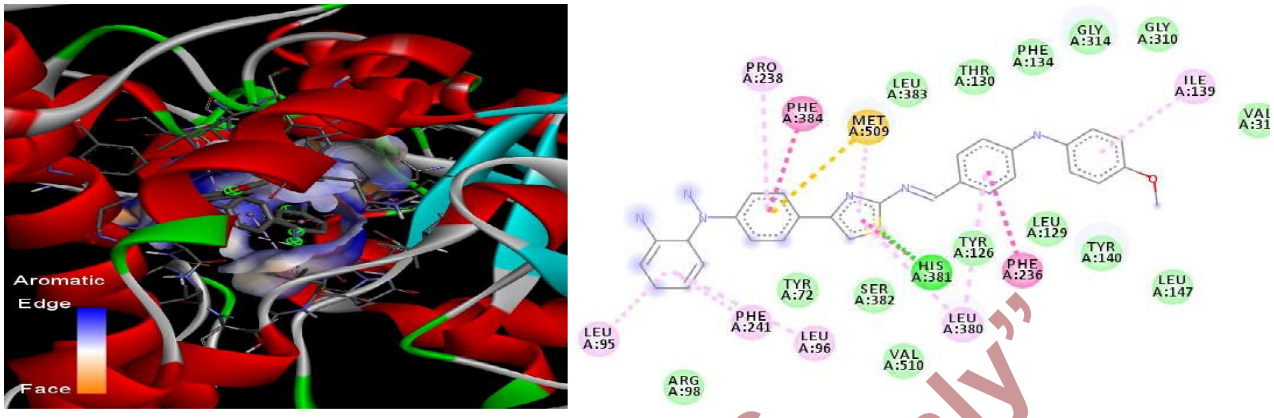
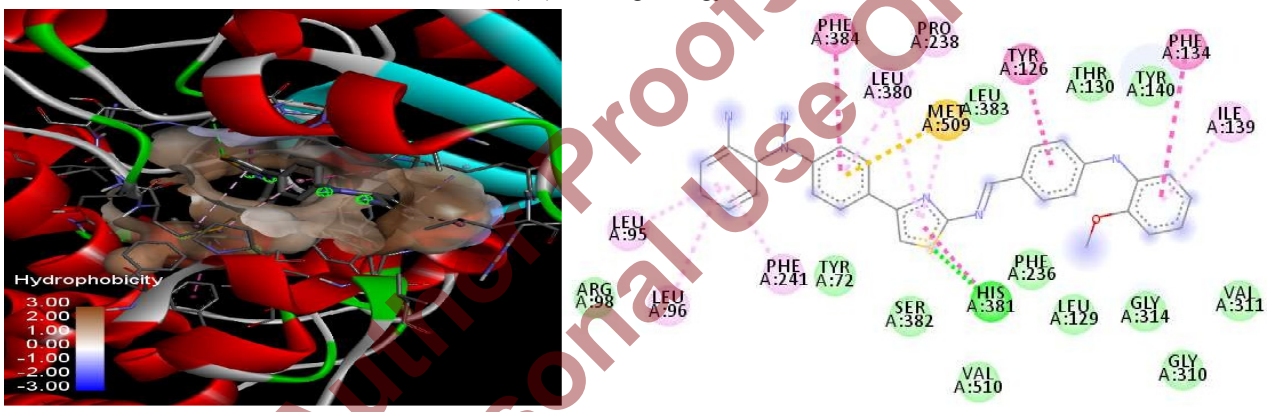
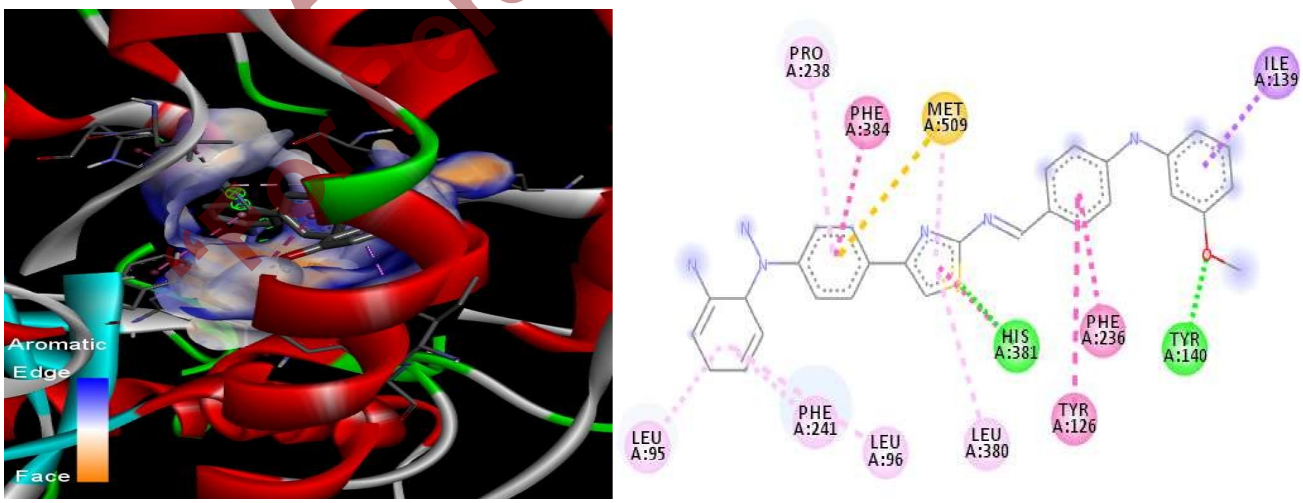
### *3.1.10. 4-(4-(1H-benzo[d] [1, 2, 3] triazol-1-yl) phenyl)-N-(4-((4-bromophenyl) amino) benzylidene) thiazole-2-amine (9h)*

IR (KBr) $cm^{-1}$: 3332 (NH Str.), 3010 (C-H Str. Aromatic), 2975 (C-H Str. Aliphatic), 1376 (C=N Str.), 1275 (C-N Str.)$^1$ $^1$H NMR (500 MHz, $CDCl_3$) δ: 9.78 (s, 1H, N=CH), 7.98 (s, 1H, NH), 7.44–7.16 (m, 16H, Ar–H), 3.86 (s, 1H, CH–Thiazole). Yield: 60.47%,Melting Point: 132-1433°C,$R_f$: 0.93(n-Hexane: Ethyl acetate; 3:1).

## 3.2. Molecular Docking

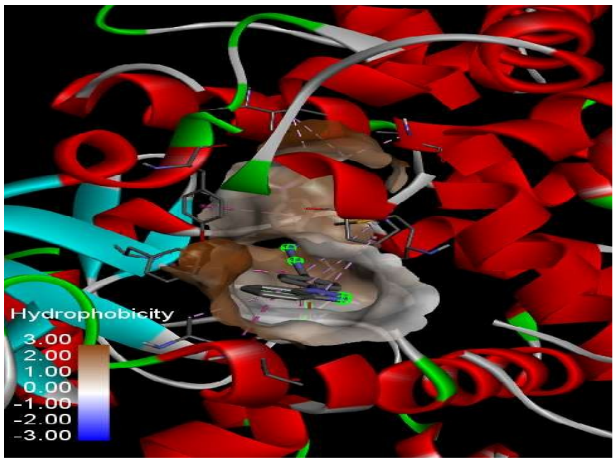
In this study, molecular docking analysis was carried out on compounds 9a-9h. The MD analysis aimed to understand the binding modes and estimate the binding affinity of these compounds against the 3D structures of receptors downloaded from the Protein Data Bank (PDB). The receptors used were E. coli DNA gyrase (PDB ID: 1Zi0), a Gram-negative bacterial strain, and C. albicans Lanosterol alpha-demethylase (PDB ID: 4WMZ), a fungal strain, as shown in Tables **1** and **2**. DNA gyrase and lanosterol 14α-demethylase were chosen as molecular targets because they play essential and distinct roles in bacterial and fungal survival, respectively. DNA gyrase is a unique bacterial enzyme responsible for maintaining DNA supercoiling during replication and transcription, making it an established antibacterial target. Lanosterol 14α-demethylase (CYP51) is a key fungal enzyme in ergosterol biosynthesis, and its inhibition disrupts membrane integrity, a mechanism exploited by clinically used azole antifungals.

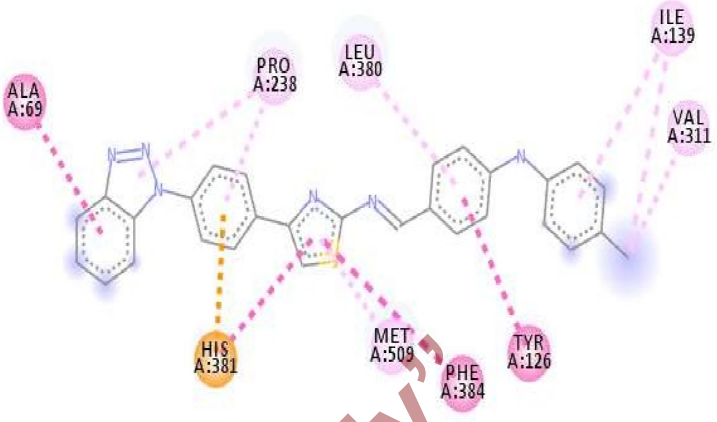
**Table 1. Docking results of target compounds on the active site of Lanosterol alpha demethylase (PDB ID-4WMZ).**

| 3D and 2D interaction |
|---|
| (9a) Binding Energy : -11.5   |
| (9b) Binding Energy : -11.0   |
| (9c) Binding Energy : -11.2   |

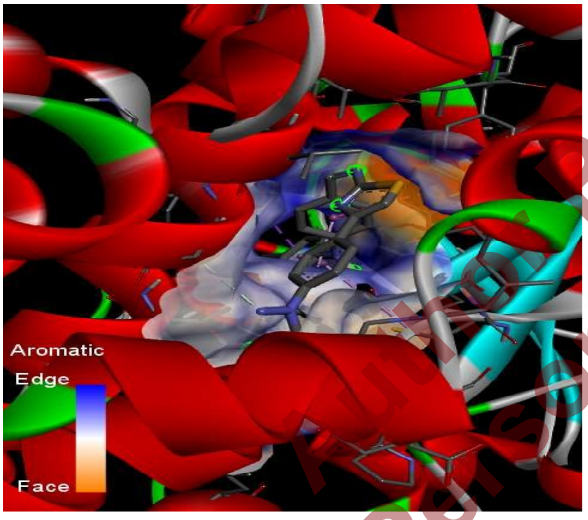
**3D and 2D interaction**

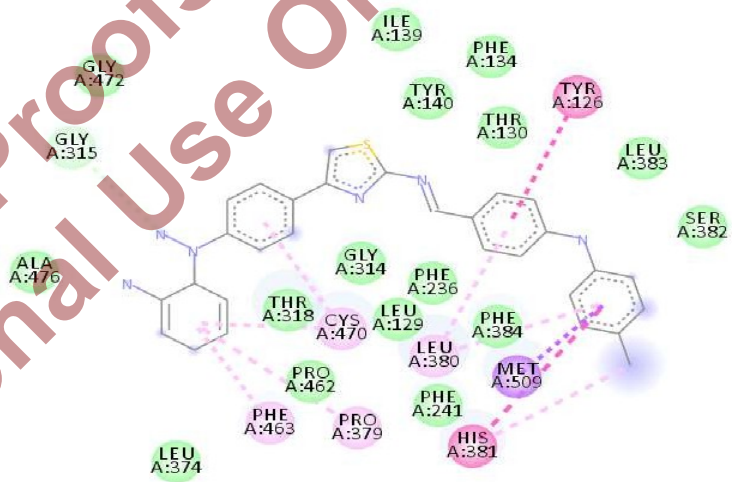
(9d) Binding Energy : -11.0



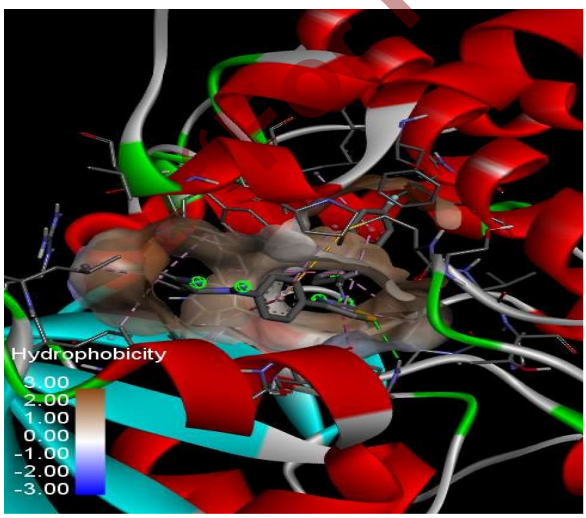



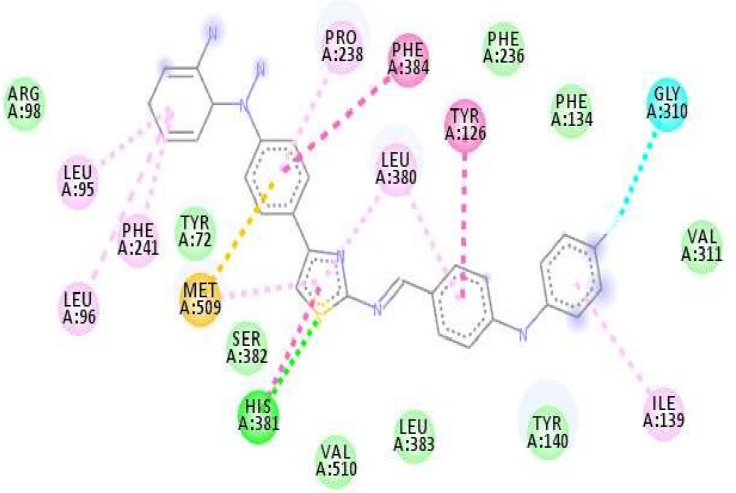

(9e) Binding Energy : -10.8




(9f) Binding Energy : -11.5



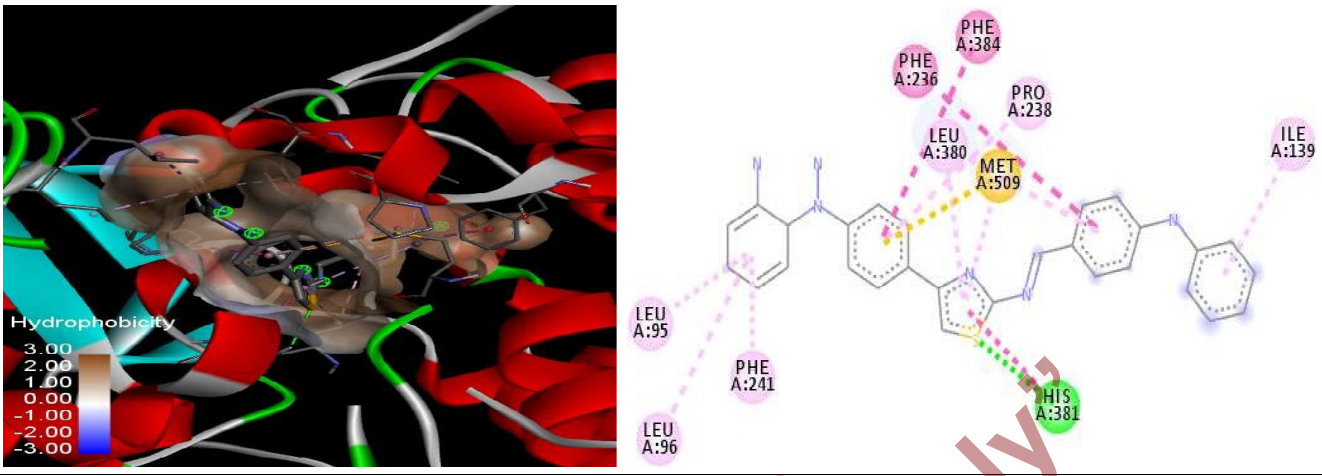
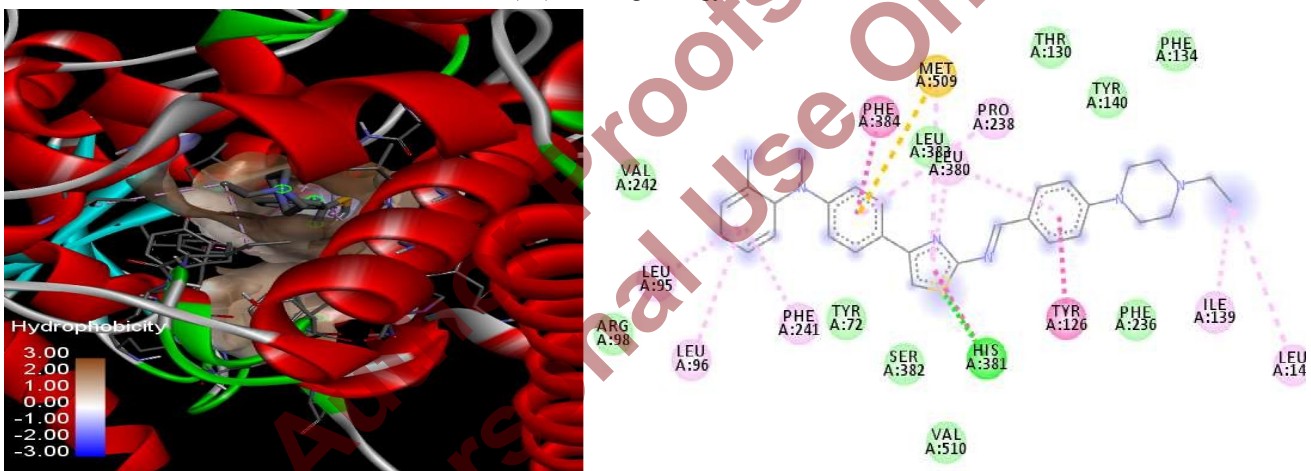
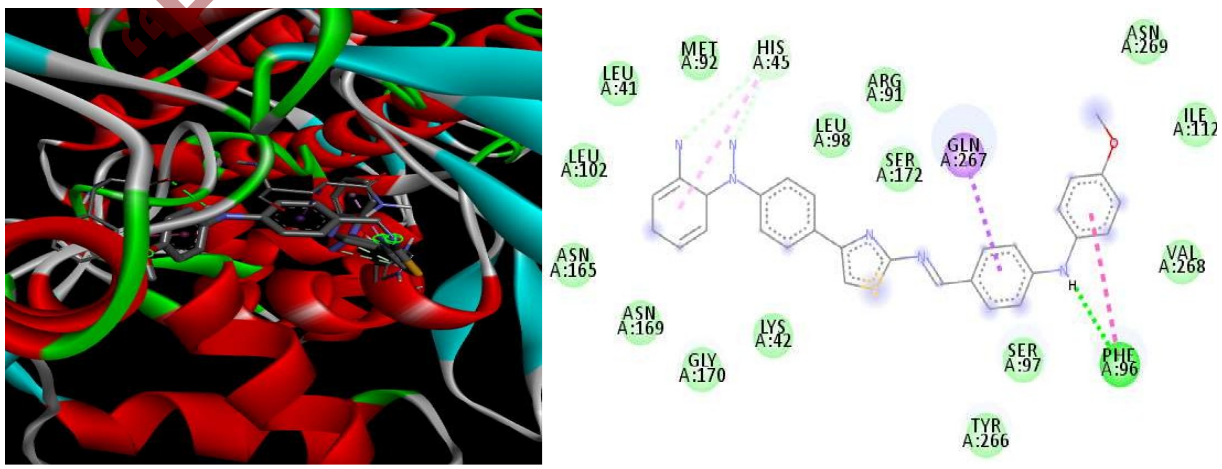
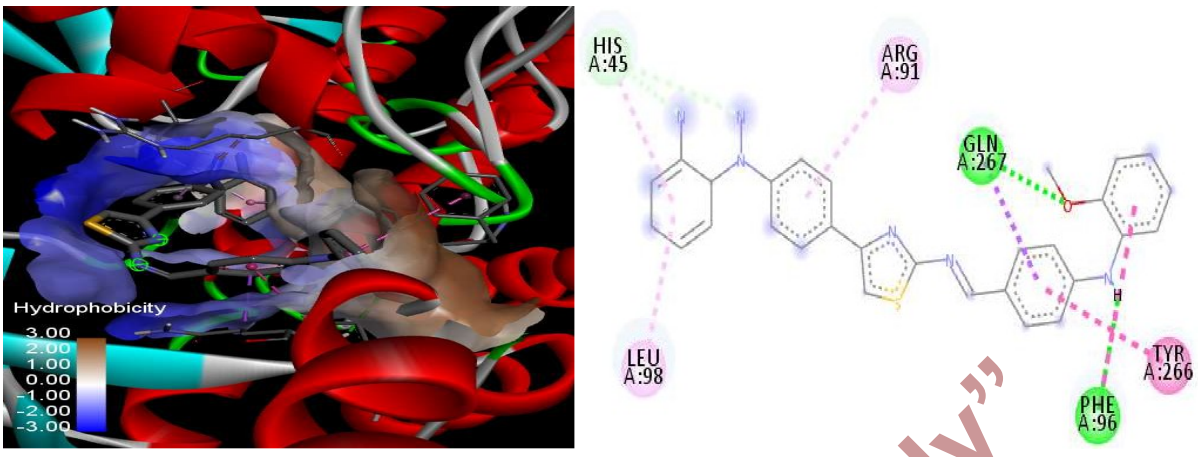
| **3D and 2D interaction** |
|---|
| (9g) Binding Energy : -11.5 |
|   |
| (9h) Binding Energy : -10.9 |
|   |

**Table 2. Docking results of target compounds on the active site of DNA gyrase (PDB ID-1Zi0).**

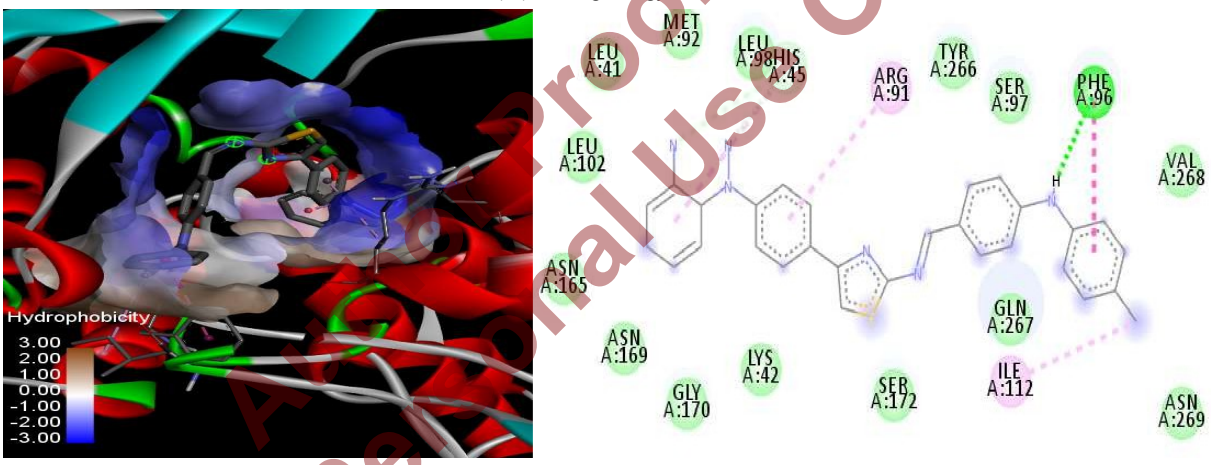
| **3D and 2D interaction** |
|---|
| (9a) Binding Energy : -9.5 |
|   |

**3D and 2D interaction**

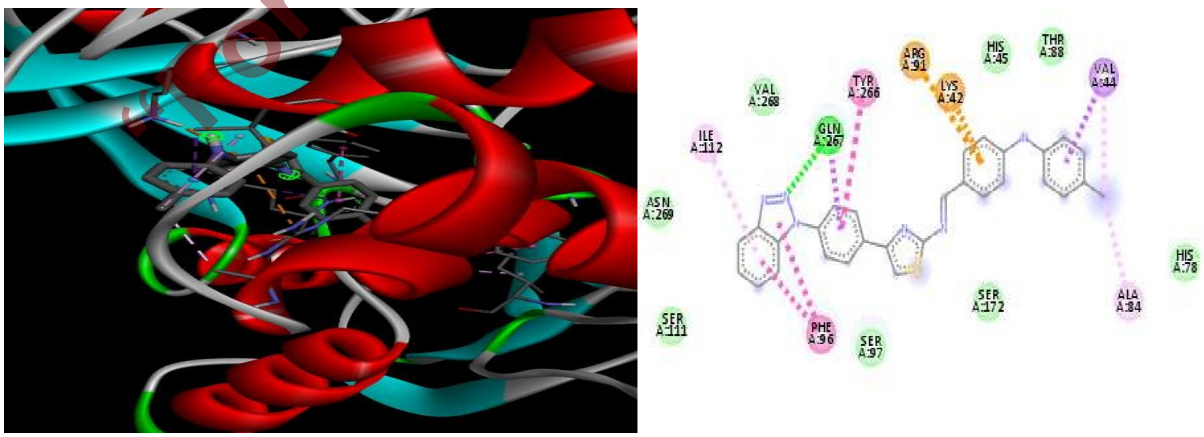
(9b) Binding Energy : -9.6




(9c) Binding Energy : -9.6

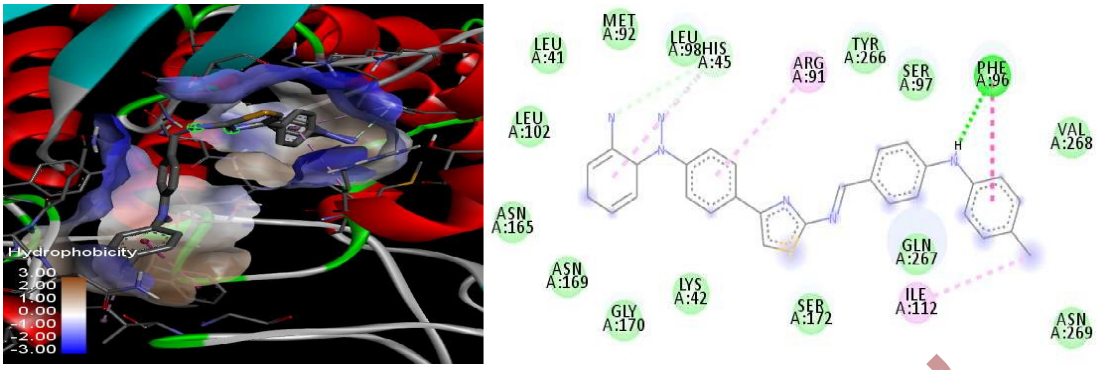



(9d) Binding Energy : -9.0

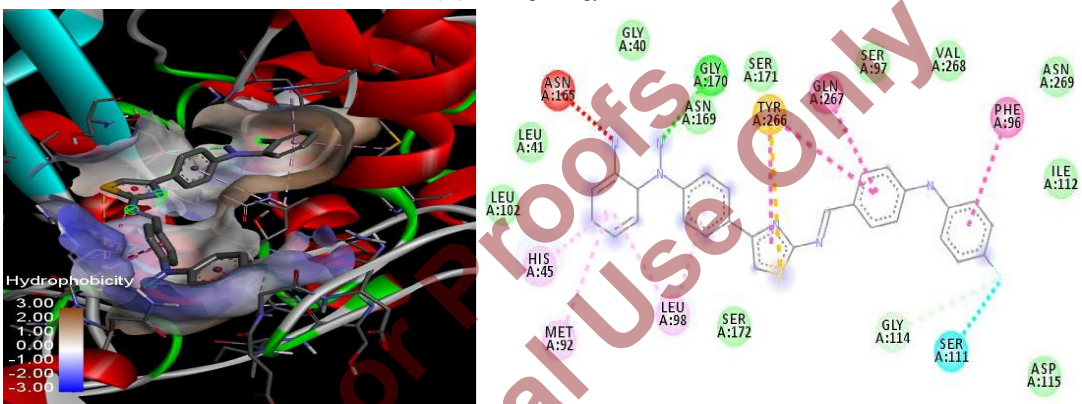


**3D and 2D interaction**

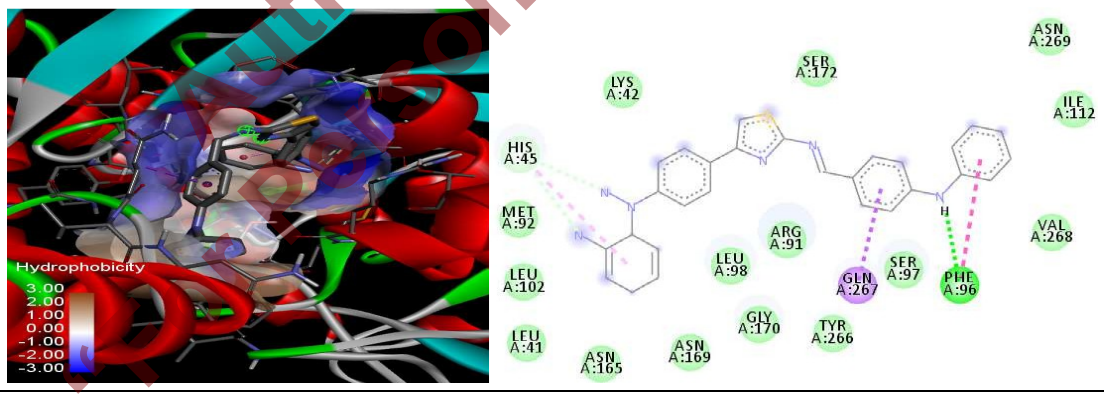
(9e) Binding Energy : -9.4




(9f) Binding Energy : -9.2




(9g) Binding Energy : -9.5




(9h) Binding Energy : -9.2

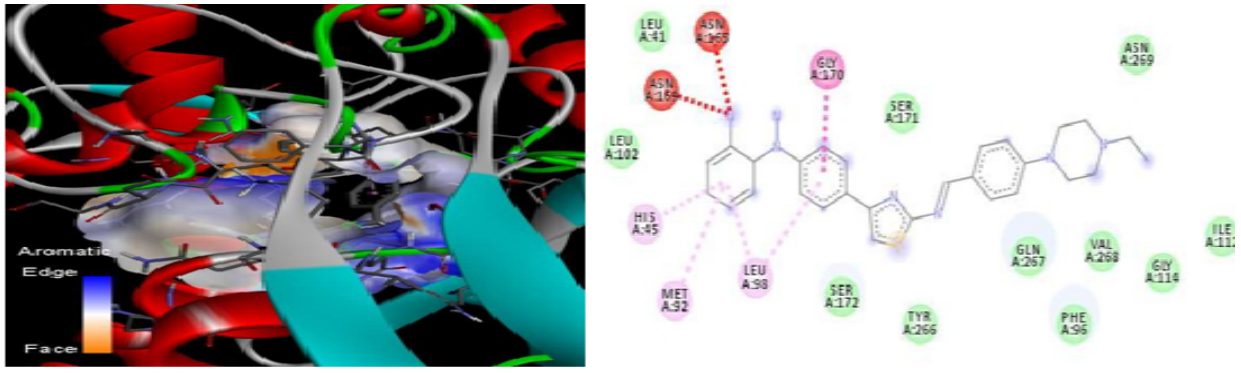


**Table 3. Physicochemical Parameters of Target Compounds (9a-9h).**

| Cpd. Code | LogP | MR[b] | TPSA[c] | CAA[d] | CMA[e] | CSEV[f] | Ov[g] | Bio-Aviavility | SA | Lipinski Filter |
|---|---|---|---|---|---|---|---|---|---|---|
| 9a | 5.84 | 143.21 | 96.23 | 643.287 | 350.567 | 320.029 | 1.5493 | 0.55 | 3.71 | Yes; 1 violation |
| 9b | 5.86 | 149.70 | 105.46 | 660.784 | 363.552 | 332.46 | 1.5665 | 0.17 | 3.87 | No; 2 violation |
| 9c | 5.82 | 149.70 | 105.46 | 667.85 | 365.377 | 334.361 | 1.5683 | 0.17 | 3.85 | No; 2 violation |
| 9d | 5.82 | 149.70 | 105.46 | 675.185 | 369.517 | 335.155 | 1.5836 | 0.17 | 3.85 | No; 2 violation |
| 9e | 6.16 | 148.18 | 96.23 | 680.075 | 377.228 | 350.385 | 1.5694 | 0.55 | 3.82 | Yes; 1 violation |
| 9f | 6.14 | 143.17 | 96.23 | 640.98 | 367.76 | 356.87 | 1.8765 | 0.55 | 3.67 | Yes; 1 violation |
| 9g | 6.36 | 148.22 | 96.23 | 687.76 | 365.765 | 354.76 | 1.7534 | 0.17 | 3.70 | No; 2 violations |
| 9h | 6.43 | 150.91 | 96.23 | 654.89 | 379.876 | 387.85 | 1.8464 | 0.17 | 3.71 | No; 2 violations |
| Fluconazole | 0.88 | 70.71 | 81.65 | 675.65 | 356.76 | 366.54 | 1.7234 | 0.55 | 2.45 | Yes; 0 violation |
| Amoxicillin | -0.29 | 94.59 | 158.26 | 623.65 | 346.65 | 376.45 | 1.5476 | 0.55 | 4.17 | Yes; 0 violation |

**Abbreviations:** MW[a]: Molecular Weight; MR[b]: Molar Refractivity; TPSA[c]: Topological Polar; CAA[d]: Connolly Accessible; CMA[e]: Connolly Molecular Area; CSEV[f] : Connolly Solvent Excluded Volume; Ov[g] : Ovality.



Targeting these enzymes allows evaluation of both antibacterial and antifungal potential, addressing the need for agents active against resistant microbial strains.

Compounds 9a, 9f, and 9g demonstrated the highest binding affinity toward lanosterol α-demethylase (PDB ID: 4WMZ), indicating a strong potential to interfere with ergosterol biosynthesis, a validated antifungal target. Notably, the binding energies of these compounds were comparable to or better than the reference drug fluconazole (−8.5 kcal/mol), suggesting enhanced stabilization within the enzyme's active pocket through favorable hydrogen bonding and hydrophobic interactions. In contrast, compounds 9b and 9c exhibited superior binding affinity toward DNA gyrase (PDB ID: 1ZI0), a key bacterial target involved in DNA replication, with docking scores that approached or exceeded that of the standard antibacterial agent amoxicillin (−7.5 kcal/mol).

### 3.3. Physicochemical Parameters

In this study, a set of physicochemical properties was computed for the target compounds and standard drugs Fluconazole and Amoxicillin using Chem3D Ultraversion 12.0 and Swiss ADME software. Key descriptors such as LogP, topological polar surface area (TPSA), Connolly molecular surface area, solvent excluded volume, molecular weight (MW), molar refractivity (MR), and ovality were calculated as shown in Table **3**. These properties, crucial for determining biological activity, lipophilicity, and pharmacokinetic behavior, indicated that the target compounds (9a-9h) have comparable lipophilicity and molar refractivity to standard drugs. The results align with Lipinski's rule of five, suggesting favorable absorption, distribution, metabolism, and excretion (ADME) properties. Additionally, the Synthetic Accessibility (SA) Score and similarity to standard drugs were evaluated, confirming the potential of the target compounds as drug candidates.

**Table 4. Similarity of Target Compounds (9a-9h) With Respect to the Standard Drugs.**

| Cpd. Code | Similarity (in %) | |
|---|---|---|
| | Fluconazole | Amoxicillin |
| 9a | 55.45 | 72.60 |
| 9b | 49.90 | 69.85 |
| 9c | 50.00 | 69.42 |
| 9d | 49.93 | 69.25 |
| 9e | 51.00 | 70.78 |
| 9f | 44.06 | 58.37 |
| 9g | 52.00 | 57.10 |
| 9h | 46.90 | 52.18 |

**Table 5. *In vitro* antimicrobial evaluation of target compounds (9a-9h).**

| Compound | *E. coli* (µg/mL) | *B. subtilis* (µg/mL) | *C. albicans* (µg/mL) |
|---|---|---|---|
| 9a | 25.52 ± 1.28 | 25.52 ± 1.31 | 25.52 ± 1.22 |
| 9b | 25.52 ± 1.34 | 25.52 ± 1.26 | 25.52 ± 1.18 |
| 9c | 25.52 ± 1.29 | 12.76 ± 0.64 | 25.52 ± 1.21 |
| 9d | 51.04 ± 2.10 | 51.04 ± 2.05 | 51.04 ± 2.18 |
| 9e | 51.04 ± 2.22 | 51.04 ± 2.11 | 51.04 ± 2.06 |
| 9f | 25.52 ± 1.33 | 25.52 ± 1.27 | 51.04 ± 2.09 |
| 9g | 12.76 ± 0.62 | 25.52 ± 1.24 | 51.04 ± 2.15 |
| 9h | 51.04 ± 2.08 | 51.04 ± 2.14 | 51.04 ± 2.12 |
| Amoxicillin | 6.38 ± 0.31 | 6.38 ± 0.29 | – |
| Fluconazole | – | – | 6.42 ± 0.33 |



*In silico* ADME analysis indicated that compounds 9a–9h exhibit relatively high lipophilicity (LogP > 5), leading to one or two Lipinski rule-of-five violations compared with fluconazole and amoxicillin. While compounds 9a, 9e, and 9f showed acceptable predicted bioavailability, others displayed reduced absorption profiles. Overall, these derivatives should be considered lead-like molecules, requiring further structural optimization to improve pharmacokinetic properties before advancement as drug-like candidates.

### 3.4. Similarity Calculations

The physicochemical characteristics of the target compounds were compared to standard drugs, and their similarity was calculated based on several properties, as shown in Table **4**. These properties include molecular weight, molar refractivity, topological polar surface area, Connolly solvent accessible surface area, Connolly molecular surface area, Connolly solvent excluded volume, and ovality.

### 3.5. Antimicrobial Activities of Target Compounds (9a-9h)

In this study, a variety of test compounds were evaluated for their antimicrobial potential against different microbial strains. Among the compounds tested, several exhibited significant potencies. Specifically compound 9c exhibited good potency against both bacterial and fungal strains, with MIC values of 12.76 µg/mL against B. subtilis and

**Table 6. SAR of the compounds.**

| Cpd Code | Substituent (R) | Electronic Effect | Antimicrobial Activity (MIC, µg/mL) | Binding Affinity | Observations |
|---|---|---|---|---|---|
| 9a | H | Neutral | – | Lanosterol α-demethylase (4WMZ) – High | Highest binding affinity on 4WMZ |
| 9b | 2-$OCH_3$ | Electron-donating | – | DNA Gyrase (1Zi0) – High | Highest binding affinity on 1Zi0 |
| 9c | 3-$OCH_3$ | Electron-donating | B. subtilis: 12.76 °C. albicans: 25.52 | DNA Gyrase (1Zi0) – High | Good potency against bacterial & fungal strains |
| 9d | 4-$OCH_3$ | Electron-donating | – | – | Moderate effect expected due to para substitution |
| 9e | 4-$CH_3$ | Electron-donating | – | – | Slightly increased lipophilicity; moderate activity |
| 9f | 4-F | Electron-withdrawing | – | Lanosterol α-demethylase (4WMZ) – High | Strong binding affinity due to halogen interaction |
| 9g | 4-Cl | Electron-withdrawing | E. coli: 12.76 | Lanosterol α-demethylase (4WMZ) – High | Excellent antibacterial activity; halogen effect enhances binding |
| 9h | 4-Br | Electron-withdrawing | – | – | Bulky substituent; may affect binding sterically. |



25.52 µg/mL against C. *albicans*. Compound 9g demonstrated excellent activity against *E. coli* with an MIC value of 12.76 µg/mL, as shown in Table **5**.

### 3.6. Structure Activity Relationship

The observed SAR indicates that compound 9c, bearing a 3-$OCH_3$ group, exhibits good potency against *B. subtilis* (MIC 12.76 µg/mL) and moderate antifungal activity against *C. albicans* (MIC 25.52 µg/mL), likely due to the electron-donating and H-bond-accepting nature of the methoxy group, which increases local electron density, supports π–π and hydrogen-bonding interactions with Gram-positive or fungal targets, and maintains moderate lipophilicity for cell penetration. In contrast, compound 9g, containing a chloro substituent, shows excellent activity against *E. coli* (MIC 12.76 µg/mL), which can be attributed to chlorine's ability to enhance lipophilicity, improve outer membrane permeation, and engage in hydrophobic or halogen-bond interactions with bacterial proteins, properties particularly advantageous for Gram-negative activity. The meta position of the $OCH_3$ in 9c minimizes steric hindrance while still influencing ring electronics, whereas the small, hydrophobic Cl in 9g creates a favorable binding surface without disrupting planarity. Overall, the data suggest that electron-donating polar substituents such as $OCH_3$ favor Gram-positive and antifungal potency, while lipophilic halogens enhance Gram-negative activity, highlighting the importance of balancing electronic effects and membrane permeability for broad-spectrum optimization as shown in Table **6**.

## CONCLUSION

The molecular docking study showed that compounds 9a, 9f, and 9g exhibited the highest binding affinity (-11.5 kcal/mol) for Lanosterol alpha demethylase (PDB ID: 4WMZ), while compounds 9b and 9c had the strongest interaction (-9.6 kcal/mol) with DNA gyrase (PDB ID: 1Zi0). Physicochemical analysis revealed that these compounds possess favorable lipophilicity, with LogP values ranging from 5.82 to 6.43, suggesting good membrane permeability. Most compounds adhered to Lipinski's rule, enhancing their drug-likeness. In antimicrobial assays, compound 9g exhibited potent activity against E. coli (MIC = 12.76 µg/mL), while compound 9c showed the best inhibition of B. subtilis (MIC = 12.76 µg/mL) and also demonstrated antifungal potency against C. albicans (MIC = 25.52 µg/mL). These findings highlight their strong binding affinity, favorable physicochemical properties, and promising biological activity, supporting further research for drug development.

## LIMITATIONS OF THE STUDY

This study is limited to *in vitro* antimicrobial evaluation and lacks *in vivo* validation of efficacy

and safety. Cytotoxicity against normal mammalian cells was not assessed, preventing the determination of selectivity indices. The molecular docking results provide only predictive insights and were not experimentally validated through enzymatic or mechanistic assays. Pharmacokinetic behavior, metabolic stability, and long-term toxicity were not investigated. Additionally, the limited number of synthesized derivatives restricts comprehensive structure–activity relationship (SAR) conclusions.

## CURRENT AND FUTURE DEVELOPMENT

Compounds 9c and 9g exhibited meaningful activity against Bacillus subtilis, Candida albicans, and Escherichia coli, and thiazole-containing Schiff bases can be a novel class of strong antimicrobial agents. These reports by various spectroscopic and computational methods have already proved promising in the structural stability and bioactivity profiles of these compounds, which can be a potential alternative to existing drugs. Further evaluation is needed in terms of safety, *in vivo* studies, pharmacological optimizations, predictive toxicity studies, administration route, and predictive computational algorithms. They might particularly be used to help identify new classes of treatment for respiratory tract infections, such as Schiff bases, in the face of an acute antimicrobial resistance crisis.

## AUTHOR'S CONTRIBUTION

The authors confirm their contribution to the paper as follows: study conception and design: S K. Data Collection: N G, J K S. Analysis and Interpretation: N G, A K. Draft Manuscript: N G, S K.

## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

## HUMAN AND ANIMAL RIGHTS

Not applicable.

## CONSENT FOR PUBLICATION

Not applicable.

## AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the article are available within the article.



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None.

## CONFLICT OF INTEREST

The authors declared no conflict of interest, financial or otherwise.

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