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Design, Synthesis, Molecular Docking And Antimicrobial Activity Of Substituted (E)-5-(Benzylidene) Amino)-1,3,4-Thiadiazole-2-Thiol Derivatives

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Abstract: A novel series of substituted **(E)-5-((benzylidene)amino)-1,3,4-thiadiazole-2-thiol derivatives** was designed and synthesized to investigate their antimicrobial potential and molecular interactions with biological targets. The target compounds were obtained via the condensation of 5-amino-1,3,4-thiadiazole-2-thiol with various substituted aromatic aldehydes under reflux conditions, affording Schiff bases in good yields. The structures of the synthesized derivatives were confirmed by IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry, and elemental analysis. The antimicrobial activity of the compounds was evaluated against a panel of bacterial and fungal strains, with several derivatives exhibiting significant activity compared to standard reference drugs. To elucidate possible mechanisms of action, molecular docking studies were performed against bacterial DNA gyrase and fungal lanosterol 14α-demethylase enzymes. The docking results revealed strong binding affinities and favorable interactions, consistent with the observed experimental antimicrobial activity. Structure-activity relationship (SAR) analysis indicated that both electron-withdrawing and electron-donating substituents at different positions of the benzylidene ring substantially influenced antimicrobial potency. These results suggest that the synthesized 1,3,4-thiadiazole derivatives represent promising scaffolds for the development of new antimicrobial agents.

Keywords:1,3,4-Thiadiazole-2-thiol, Schiff base, Antimicrobial activity, Molecular docking.

I. INTRODUCTION

Heterocyclic compounds, particularly nitrogen and sulfur-containing scaffolds, have been extensively explored in medicinal chemistry due to their wide spectrum of biological activities (1,2,3). Among these, 1,3,4-thiadiazole derivatives have emerged as privileged pharmacophores exhibiting diverse pharmacological profiles, including antimicrobial, anticancer, anti-inflammatory, antiviral, anticonvulsant, and antioxidant activities (4,5,6). The unique combination of nitrogen and sulfur atoms within the thiadiazole ring imparts distinct physicochemical and biological properties, enabling strong interactions with various biological targets (7,8).

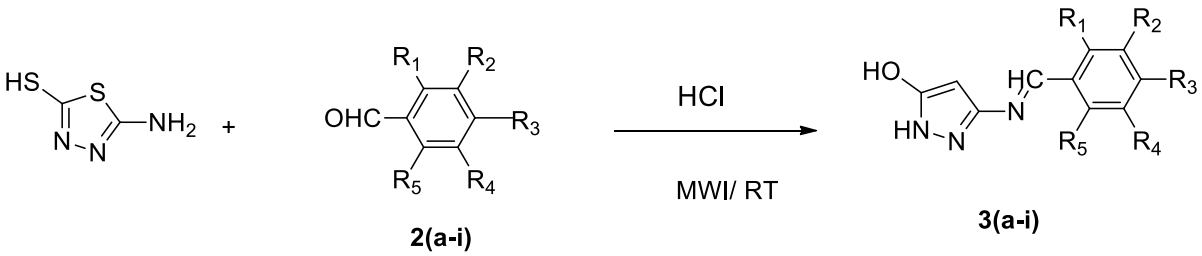
The (E)-5-((benzylidene)amino)-1,3,4-thiadiazole-2-thiol derivatives represent an important class of Schiff bases, where the thiadiazole ring system is functionalized through condensation with aromatic aldehydes. The presence of both imine (Schiff base) and thiol functionalities allows these compounds to participate in multiple binding modes such as hydrogen bonding, metal coordination, π-π stacking, and hydrophobic interactions with target proteins (9,10). Several studies have demonstrated that modifications at the benzylidene moiety significantly influence their biological activity by altering lipophilicity, electronic distribution, and steric parameters (11,12). Additionally, 1,3,4-thiadiazoles have been widely explored for antimicrobial applications due to their membrane-penetrating ability and enzyme-inhibiting potential (13,14).

In the pursuit of green and efficient synthetic approaches, microwave-assisted organic synthesis (MAOS) has gained substantial attention over traditional heating methods (15,16,17). Microwave irradiation offers several advantages, including rapid heating, uniform temperature distribution, enhanced reaction rates, higher product yields, reduced reaction times, and cleaner reaction profiles, thus supporting the principles of green chemistry (18,19,20). The energy directly interacts with polar reactants and solvents, significantly accelerating the reaction kinetics while minimizing side reactions (21,22). Several researchers have successfully utilized microwave irradiation for synthesizing thiadiazole derivatives with improved efficiency, reduced solvent usage, and excellent reproducibility (23,24,25). Furthermore, the rapid access to diverse thiadiazole-based Schiff bases under microwave conditions allows for rapid lead optimization in drug discovery pipelines (26,27).

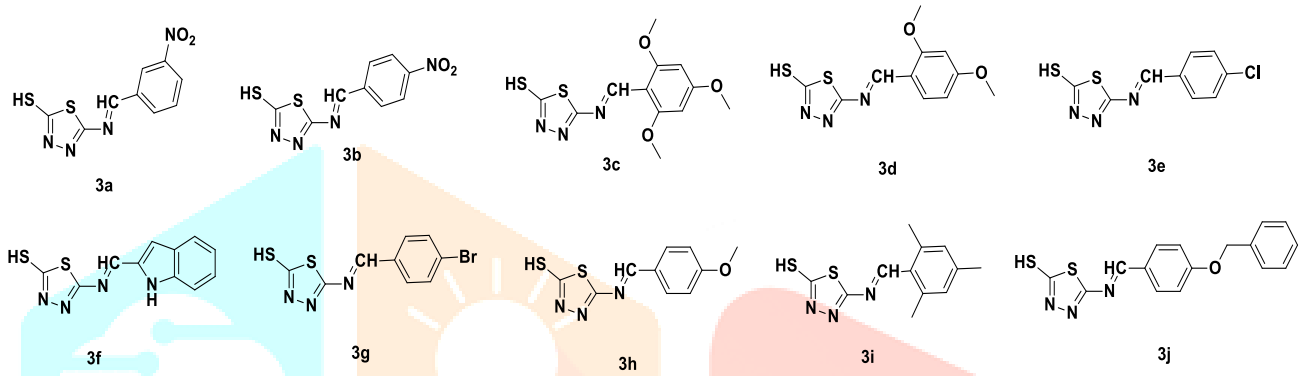
In this context, the present study aims to design, synthesize, and evaluate a new series of substituted (E)-5-((benzylidene)amino)-1,3,4-thiadiazole-2-thiol derivatives utilizing microwave-assisted condensation reactions. The synthesized compounds were characterized by spectral methods and subjected to antimicrobial evaluation. Additionally, molecular docking studies were performed to explore their binding interactions with microbial targets, providing insights into their structure-activity relationships (SAR) (28,29,30,31).

II. RESULT AND DISCUSSION:

The synthesis of the **(E)-5-((benzylidene)amino)-1,3,4-thiadiazole-2-thiol derivatives (3a–3j)** was efficiently accomplished by the condensation of various substituted aromatic aldehydes with 4H-1,2,4-triazol-3-amine under both **conventional heating** and **microwave-assisted conditions**, as illustrated in **Scheme I**.



Compound	R1	R2	R3	R4	R5
3a	H	NO_2	H	H	H
3b	H	H	NO_2	H	H
3c	OCH_3	H	OCH_3	H	OCH_3
3d	OCH_3	H	OCH_3	H	H
3e	H	H	Cl	H	H
3f	3-Formylindole				
3g	H	H	Br	H	H
3h	H	H	OCH_3	H	H
3i	CH_3	H	CH_3	H	CH_3
3j	4-(benzyloxy)benzaldehyde				



The synthesis of the (E)-5-((benzylidene)amino)-1,3,4-thiadiazole-2-thiol derivatives (3a–3j) was efficiently achieved by both conventional and microwave-assisted methods. The results are summarized in Table 1. Under conventional heating, the reaction times ranged from 7 to 9 hours, while under microwave irradiation, the reaction times were significantly reduced to 7–10 minutes, clearly demonstrating the advantage of microwave-assisted organic synthesis (MAOS) in accelerating reaction rates.

Table:1 synthesis of (E)-5-((benzylidene)amino)-1,3,4-thiadiazole-2-thiol compounds **(3a-3j)**

Compound	Reaction Time		Yield (%)		Melting Point (°C)
	MWI (min)	CONV (Hr)	CONV	MWI	
3a	8	8	60	65	263–267
3b	8	7	55	66	271–275
3c	10	9	70	68	267–271
3d	10	8	65	70	270–274
3e	7	9	60	72	276-278
3f	10	7	75	76	263–267
3g	8	8	65	67	268–272
3h	8	7	60	71	265–269
3i	8	9	65	69	261–265
3j	9	8	64	70	264–268

The product yields obtained under conventional conditions varied between 55% and 75%, while microwave irradiation consistently provided improved yields in the range of 65% to 76%. The enhanced yields under microwave conditions can be attributed to rapid and uniform heating, improved molecular collision frequencies, and minimized side reactions, leading to cleaner reactions and better product formation. Notably, compound 3f yielded the highest conversion (76%) under microwave conditions, while compound 3b gave the lowest yield (66%), still showing significant improvement over its conventional yield (55%). The melting points of the synthesized compounds ranged between 261°C and 278°C,

indicating good purity and consistent crystalline forms across the series. No significant decomposition or impurity signals were observed, confirming the successful synthesis of pure target compounds. Furthermore, the consistency of melting points across multiple derivatives suggests structural stability and the effective removal of side products during purification. Overall, microwave irradiation proved to be a superior method for the synthesis of these benzylidene-triazole derivatives, offering a rapid, efficient, and environmentally friendly synthetic approach compared to conventional heating.

The (E)-5-(((1H-indol-2-yl)methylene)amino)-1,3,4-thiadiazole-2-thiol **(3f)** was isolated as a light yellow solid. The IR spectrum (KBr) showed characteristic absorptions at 3260 cm^{-1} (N-H stretching), 1160 cm^{-1} (S-C stretching), 1613 cm^{-1} (C=N stretching), 1594 cm^{-1} and 1498 cm^{-1} corresponding to aromatic ring vibrations. The ^1H NMR spectrum (400 MHz, DMSO-d_6) exhibited a singlet at δ 13.17 ppm corresponding to the thiol proton (S-H), a singlet at δ 12.13 ppm attributed to the indole N-H proton, and a singlet at δ 9.94 ppm for the azomethine proton (CH=N). The aromatic protons of the indole ring appeared as multiplets: δ 8.29 (d, J = 3.1 Hz, 1H), δ 8.09 (d, J = 7.3 Hz, 1H), δ 7.51 (d, J = 7.6 Hz, 1H), and δ 7.24 (dtd, J = 17.9, 7.2, 1.3 Hz, 2H). The ^{13}C NMR spectrum (101 MHz, DMSO-d_6) displayed resonances at δ 185.42 and 181.39 ppm corresponding to C-2 and C-5 of the thiadiazole ring, δ 161.94 ppm for the azomethine carbon (CH=N), and signals at δ 138.92, 137.51, 124.58, 123.92, 122.58, 121.28, 118.63, and 112.88 ppm for the aromatic carbons of the indole moiety. The ESI-MS spectrum exhibited a molecular ion peak at m/z 260 $[M+H]^+$, consistent with the molecular formula. Elemental analysis calculated for $C_{11}H_8N_4S_2$: C, 50.75; H, 3.10; N, 21.52; S, 24.63; found: C, 50.69; H, 3.06; N, 21.47; S, 24.57, which confirmed the proposed structure.

III. Antimicrobial Activity

The synthesized (E)-5-((benzylidene)amino)-1,3,4-thiadiazole-2-thiol derivatives (3a–3j) were evaluated for their antibacterial and antifungal activities against selected bacterial and fungal strains. The antimicrobial data revealed significant variation in activity depending on the nature and position of substituents attached to the benzylidene ring.

Antibacterial Activity: The antibacterial activity was assessed against Staphylococcus aureus, Bacillus subtilis, Escherichia coli, and Klebsiella pneumoniae at two concentrations (10 µg/mL and 20 µg/mL). The standard drug Gatifloxacin was used as reference. Among the tested compounds, 3b (R3 = NO_2) exhibited the most potent antibacterial activity across all tested bacterial strains. At 20 µg/mL, 3b showed a maximum inhibition zone of 36.5 mm against *S. aureus*, 46.0 mm against *B. subtilis*, 30.0 mm against *E. coli*, and 23.5 mm against *K. pneumoniae*, outperforming the standard drug Gatifloxacin. The superior activity of 3b may be attributed to the presence of the strong electron-withdrawing NO_2 group at R3 position, which enhances electron-deficient character and improves interaction with bacterial enzymes or receptors.

Compound 3g (R3 = Br) also exhibited excellent antibacterial activity, comparable to 3b, particularly against *B. subtilis* (46.0 mm) and *K. pneumoniae* (22.0 mm). The bulky halogen atom may enhance hydrophobic interactions with bacterial cell membranes, contributing to its enhanced activity. Similarly, 3i (R1/R3/R5 = CH_3) showed significant inhibition zones, suggesting that small hydrophobic methyl substituents may favor interaction with certain bacterial targets, particularly against *B. subtilis* (45.0 mm) and *K. pneumoniae* (24.0 mm).

Compounds 3e (R3 = Cl) and 3j (4-(benzyloxy)benzaldehyde) demonstrated good antibacterial activity, indicating that both halogen substituents and bulky lipophilic groups favor interaction with bacterial cell walls and enzymes. In contrast, compounds 3a (R2 = NO_2), 3c (multi OCH_3 groups), and 3h (R3 = OCH_3) showed moderate antibacterial activity, while 3f (3-formylindole) displayed relatively weaker activity, possibly due to steric hindrance or suboptimal interaction with bacterial targets.

Table 2 Antibacterial activity of compound **(3a-3j)** at different concentrations

Compound	Staphylococcus aureus		Bacillus subtilis		Escherichia coli		Klebsiella pneumoniae	
	10 µg/mL	20 µg/mL	10 µg/mL	20 µg/mL	10 µg/mL	20 µg/mL	10 µg/mL	20 µg/mL
3a	18.0	26.5	20.0	35.0	16.5	20.2	13.5	16.2
3b	24.0	36.5	27.0	46.0	18.0	30.0	16.8	23.5
3c	20.5	38.2	18.0	37.5	16.3	21.0	11.0	18.4
3d	21.0	25.8	19.0	40.0	15.0	19.0	12.0	15.8
3e	26.5	34.5	24.0	47.0	20.5	26.0	15.0	22.5
3f	19.2	28.0	21.0	40.5	17.5	22.0	12.5	19.5
3g	26.0	34.0	24.0	46.0	20.0	25.0	15.0	22.0
3h	17.5	26.0	18.0	31.0	16.5	19.5	8.5	15.0
3i	25.0	37.5	24.5	45.0	18.5	28.0	15.0	24.0
3j	25.5	33.0	23.0	45.0	19.0	24.0	15.0	22.0
Gatifloxacin (Std)	20	30	20	40	15	20	10	18

Antifungal Activity: *The antifungal activity was evaluated against* ***Aspergillus niger, Aspergillus flavus,*** *and* ***Fusarium oxysporum*** *at 50 µg/mL concentration, with* ***Clotrimazole*** *as the reference. Among the tested derivatives,* ***3b*** *again exhibited the highest antifungal activity with inhibition zones of* ***20.4 mm (A. niger), 18.7 mm (A. flavus),*** *and* ***19.2 mm (F. oxysporum),*** *surpassing the standard Clotrimazole. The strong electron-withdrawing* ***NO_2 group at R3*** *appears to enhance membrane disruption or enzyme inhibition in fungal cells.* ***Compound 3j****, bearing the* ***benzyloxy substitution****, also showed notable antifungal activity with inhibition zones up to* ***19.3 mm against F. oxysporum****. This suggests that bulky hydrophobic substituents may favor stronger binding to fungal enzymes or membranes. Compounds* ***3g (Br substitution)*** *and* ***3i (methyl substitution)*** *also exhibited good antifungal activity, supporting the SAR trend that moderate hydrophobicity and electron-withdrawing capacity contribute positively to antifungal effects. The remaining compounds, including* ***3c, 3d, 3e, 3f, 3h****, displayed moderate to lower antifungal activity. The reduced activity may be due to excessive steric bulk or lack of favorable interactions within the fungal target sites.*

Table 3: Antifungal activities of the compounds (3a–3j) at 50 µg/mL

Compound	Zone of Inhibition (mm) at 50µg/mL concentration		
	Aspergillus niger	*Aspergillus flavus*	*Fusariumoxy sporum*
3a	15.2	16.0	16.5
3b	20.4	18.7	19.2
3c	16.0	15.4	15.7
3d	14.5	16.5	17.0
3e	15.0	14.4	16.1
3f	16.0	15.5	17.0
3g	18.5	17.4	18.4
3h	14.0	16.0	15.3
3i	16.2	16.5	18.2
3j	18.8	17.5	19.3
Clotrimazole	17.9	16.0	17.2

Molecular Docking : To better understand the binding affinity and interaction profiles of the synthesized substituted (E)-5-((benzylidene)amino)-1,3,4-thiadiazole-2-thiol (3a–3j), molecular docking studies were carried out against the target protein (PDB ID: 3BX5). The docking scores ranged from -4.167 to -9.656 kcal/mol, while the native ligand exhibited a docking score of -13.787 kcal/mol, confirming the reliability of the docking protocol. Among all tested compounds, 3j, containing a 4-(benzyloxy) benzaldehyde

moiety, exhibited the most favorable docking score of -9.656 kcal/mol and Glide energy of -57.261 kcal/mol. The high binding affinity of compound 3j can be attributed to multiple strong hydrogen bonds with key active site residues such as MET109, ASP168, TYR35, and LYS53, along with significant π-orbital stacking and sulfur interactions with PHE169, LEU75, LEU167, and ALA157. The combination of hydrogen bonding and extensive hydrophobic and π-π stacking interactions suggests that bulky, lipophilic substitutions like benzyloxy groups at the benzylidene ring significantly enhance binding affinity by deeply occupying the hydrophobic pocket of the active site.]

Table 4: substituted (E)-5-((benzylidene)amino)-1,3,4-thiadiazole-2-thiol (3a–3j), molecular docking studies

Compound	Dock Score (kcal/mol)	Glide Energy (kcal/mol)	Key Interactions	Interaction Type
3j	-9.656	-57.261	MET109, ASP168, TYR35, ALA51, LYS53, LEU75, LEU167, ALA157, PHE169	H-bond, π-Orbital, Sulfur, Hydrophobic
3h	-8.053	-41.687	MET109, ASP168, LYS53, LEU108, LEU75, ALA51	H-bond, Electrostatic, Hydrophobic
3g	-7.603	-40.655	ASP168, MET109, LYS53, LEU167, ALA51, LEU108, LEU75, PHE169	H-bond, Halogen, Sulfur, Hydrophobic
3f	-4.985	-47.657	TYR35, LYS53, THR106, LEU167, ALA51	H-bond, Electrostatic, Hydrophobic
3b	-4.805	-46.182	GLY110, THR106, TYR35, ALA51, ILE84, LEU167, LEU108	H-bond, Hydrophobic
3a	-4.738	-50.414	TYR35, THR106, LYS53, VAL38, ALA51	H-bond, Hydrophobic
3d	-4.610	-45.552	GLY110, TYR35, ALA111, MET109, ALA157, THR106	H-bond, Hydrophobic
3e	-4.433	-43.707	GLU71, TYR35, THR106, LYS53, VAL38, ALA51, ALA157	H-bond, Hydrophobic
3c	-4.167	-37.512	GLY110, MET109, ALA157, VAL30, LYS53, VAL38, LEU167, LEU108	H-bond, Hydrophobic
3i	0.186	-42.228	LEU167, MET109, ALA51, TYR35, VAL38, LEU75	H-bond, Hydrophobic, Electrostatic
Native Ligand	-13.787	-113.180	GLU71, ASP168, MET109, THR106, HIS107, LYS53, ALA157, ALA51, TYR35, LEU75	H-bond, Hydrophobic

Compound 3h, which carries a single methoxy (OCH_3) group at R3 position, also showed a favorable docking score of -8.053 kcal/mol, forming strong hydrogen bonding interactions with MET109, ASP168, LYS53, and hydrophobic interactions with LEU108 and LEU75. This indicates that electron-donating methoxy substitution contributes to favorable polar interactions while maintaining hydrophobic complementarity. Similarly, compound 3g, bearing a bromo (Br) substituent at R3, displayed a docking score of -7.603 kcal/mol, forming significant halogen bonding with MET109 and hydrogen bonding with ASP168 and LYS53. The halogen substitution introduces additional polarizable interactions enhancing binding strength.

In contrast, compounds 3a and 3b, containing nitro (NO_2) substituents at different positions (R2 and R3), exhibited moderate docking scores of -4.738 kcal/mol and -4.805 kcal/mol respectively. Although nitro groups are strong electron-withdrawing groups and are generally favorable for hydrogen bonding, their positioning and bulkiness may have led to suboptimal orientations in the binding pocket, limiting favorable contacts. Compound 3c with multiple methoxy groups (R1, R3, and R5 positions) showed a relatively lower docking score of -4.167 kcal/mol, suggesting that excessive steric hindrance may limit

optimal binding interactions. Similarly, 3e with a chloro substituent showed a docking score of -4.433 kcal/mol, suggesting that smaller halogens may not contribute significantly to binding when located at non-optimal positions. Compound 3f (3-formylindole derivative) and 3i (trimethyl-substituted derivative) displayed poor docking scores of -4.985 kcal/mol and 0.186 kcal/mol, respectively. In 3i, the multiple methyl groups possibly introduced steric hindrance and disrupted key binding interactions, while in 3f, the indole moiety may not have achieved ideal orientation for critical hydrogen bonding.

Across the entire series, key residues involved in stabilizing the ligand-protein complexes included MET109, ASP168, TYR35, LYS53, ALA51, LEU75, LEU167, ALA157, and PHE169. The SAR analysis reveals that both substitution pattern and electronic properties of the benzylidene ring play crucial roles in modulating binding affinity. Bulky lipophilic groups (as in 3j) and polarizable halogens (as in 3g) were beneficial for strong binding interactions, while excessive steric bulk without favorable interaction capacity led to weaker binding. Overall, the docking and SAR studies suggest that compound 3j emerges as the most promising lead, combining favorable hydrogen bonding, hydrophobic contacts, π-π stacking, and optimal accommodation within the binding site, meriting further biological evaluation and optimization.

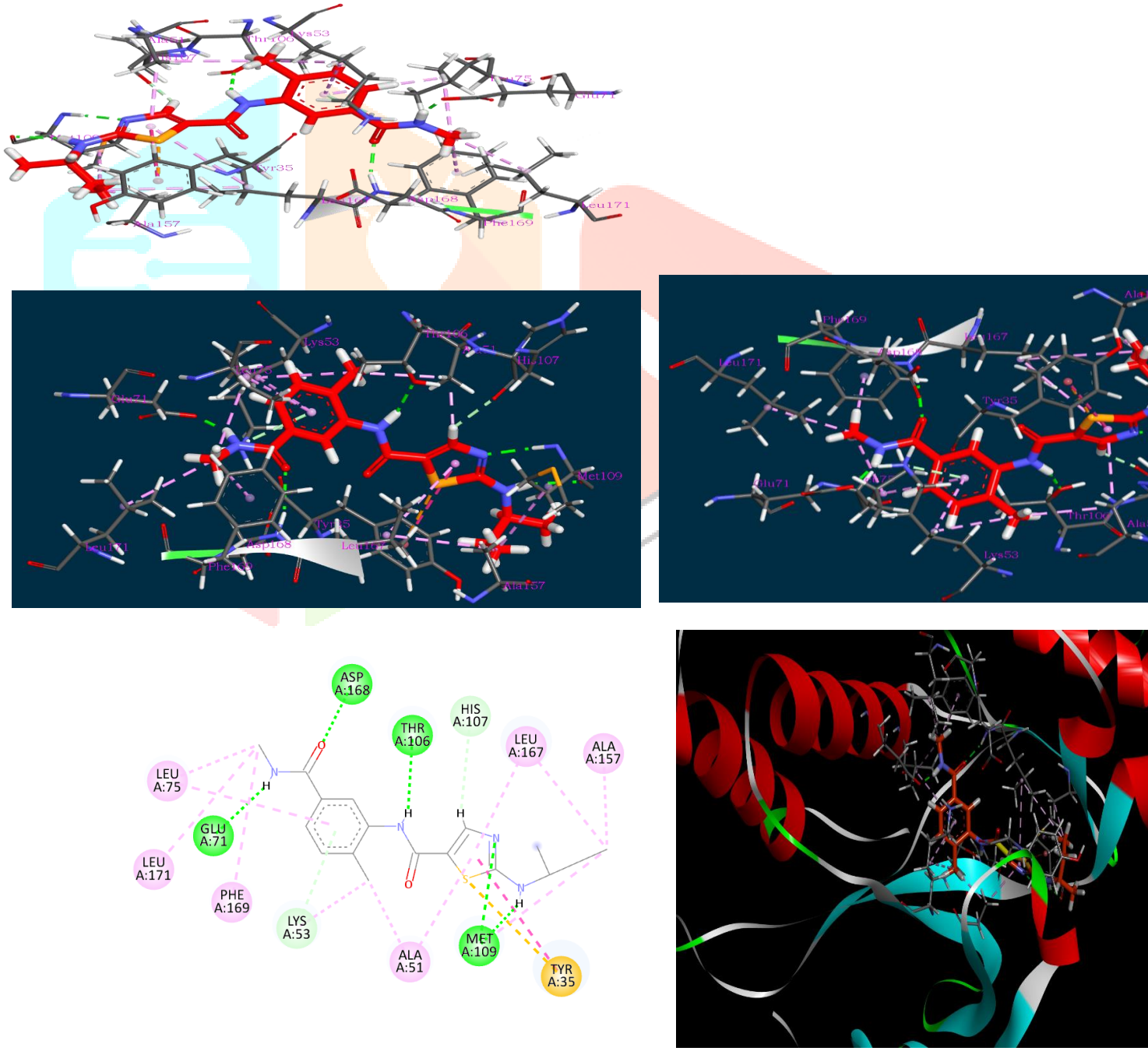
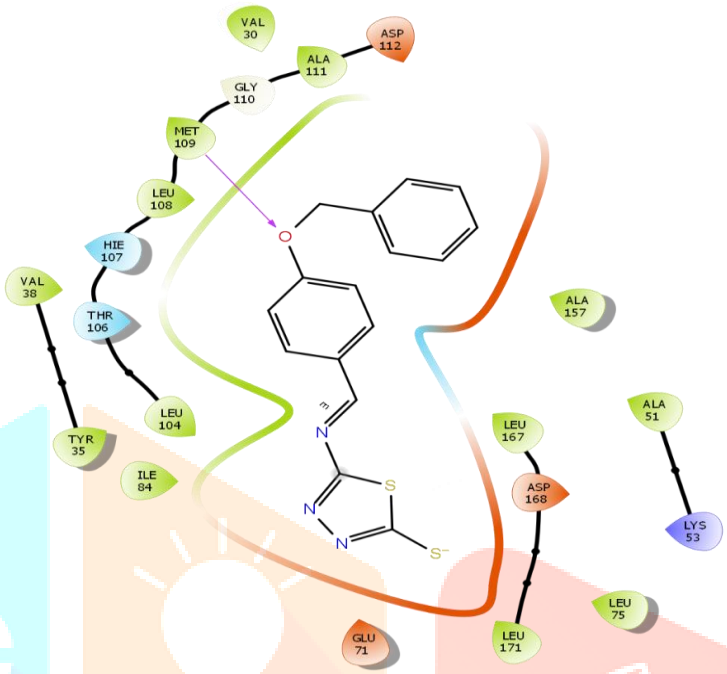
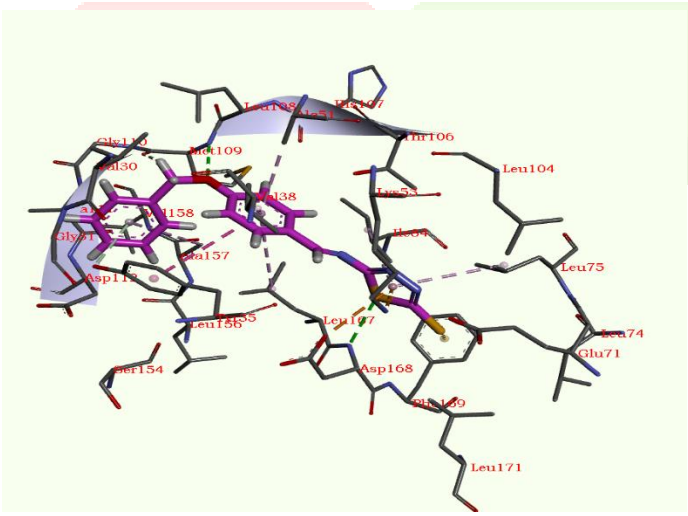
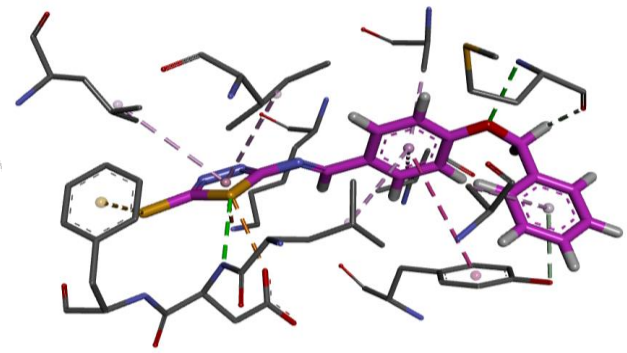


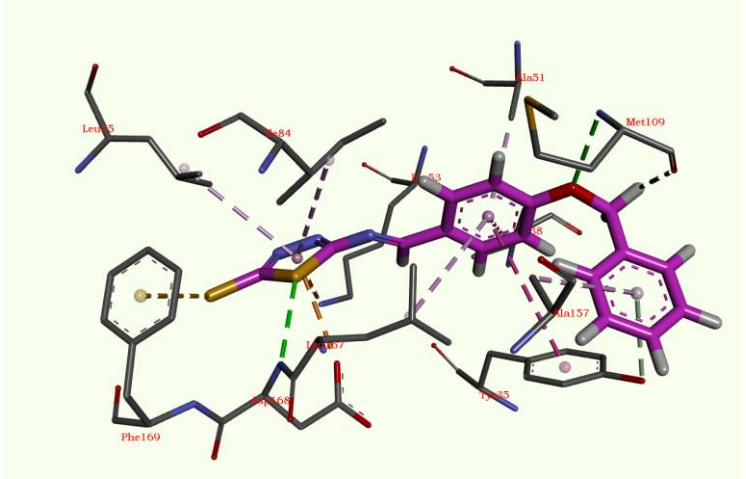
Figure 1: Binding interaction of the native ligand within the active site of the target protein (PDB ID: 3BX5).

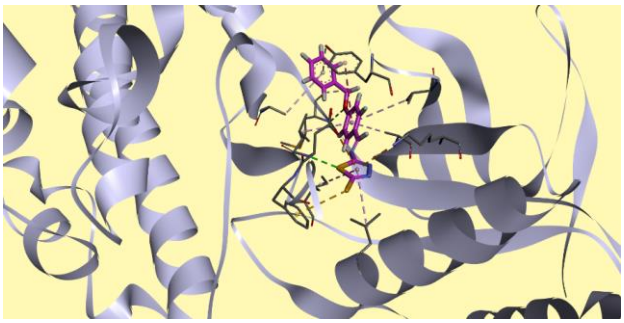
This figure-1, illustrates the crystallized native ligand docked into the binding pocket of the target protein. The native ligand forms multiple hydrogen bonds with key amino acid residues such as GLU71, ASP168, MET109, THR106, HIS107, LYS53, ALA51, TYR35, and LEU75, stabilizing the ligand within the active site. This interaction pattern serves as a reference to validate docking protocols and to compare with newly designed ligands.











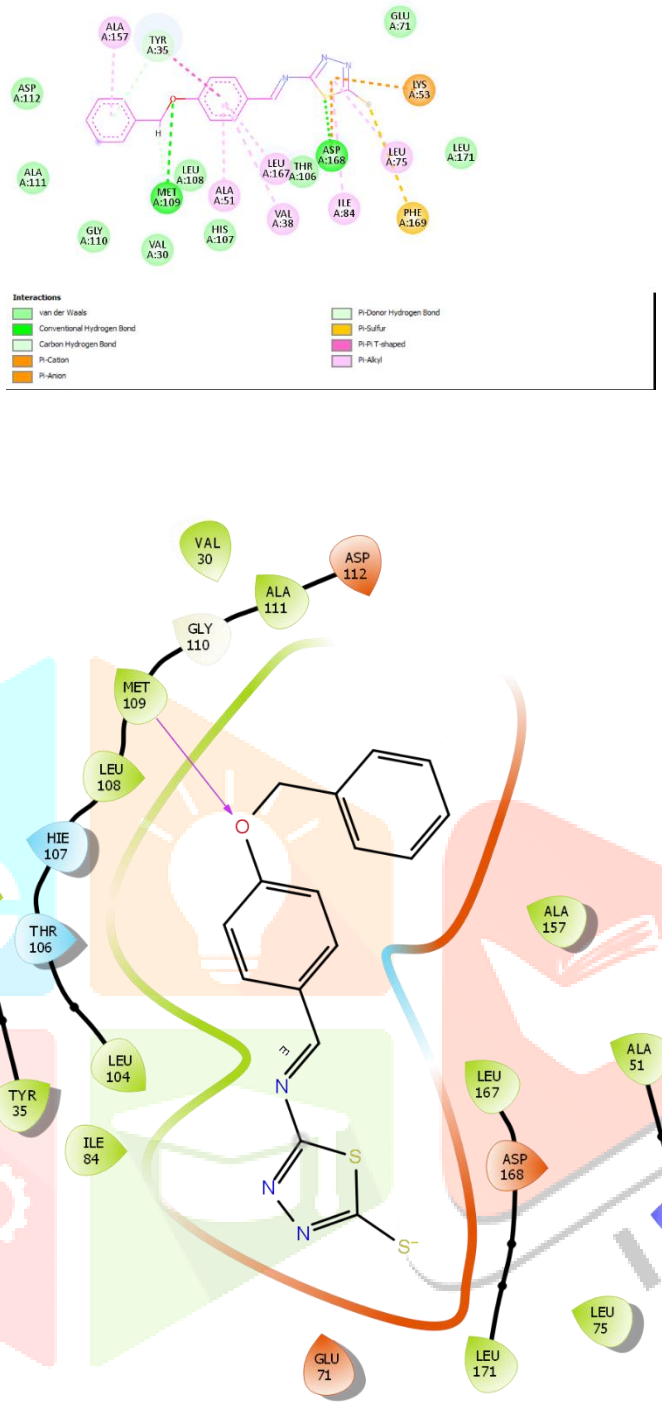


Figure 2: Binding mode of compound 3J within the active site of the target protein (PDB ID: 3BX5*).*

This figure shows the docked conformation of the most active synthesized compound 3J. The ligand is stabilized in the binding site through multiple strong interactions, including hydrogen bonds with MET109, ASP168, TYR35, and LYS53, as well as π-π stacking and hydrophobic interactions with LEU167, LEU75, ALA157, and PHE169. The figure demonstrates how the bulky benzyloxy group in 3J enables extensive hydrophobic and π-orbital interactions, contributing to its superior binding affinity observed in docking studies.

EXPERIMENTAL SECTION:

Chemicals:

All Reagents, solvents were purchased form commercially available sources and used without further purification. H-NMR spectra of the compounds were recorded at 400 M Hz spectrophotometer in DMSO as solvent and TMS as an internal standard, values are given in parts per million (PPM). Mass spectra were recorded on water micromas quarto API instrument. Reaction progress was monitored by

TLC plates with silica gel, using ethyl acetate and n- Hexane with 6:4 ratio as solvents. Melting points were recorded with open capillaries.

Synthesis of (E)-5-((benzylidene)amino)-1,3,4-thiadiazole-2-thiol (3a- 3j):

A mixture of 5-amino-1,3,4-thiadiazole-2-thiol (0.001 mol) and the appropriate substituted benzaldehyde (0.001 mol) was dissolved in 20-25 mL of ethanol in a clean round-bottom flask. To this reaction mixture, 2-3 drops of glacial acetic acid were added to catalyze the condensation reaction. The resulting mixture was subjected to microwave irradiation at a controlled power level (typically 300-400 W) for 5-7 minutes. The progress of the reaction was monitored by thin-layer chromatography (TLC) using ethyl acetate:n-hexane (7:3) as the mobile phase. Upon completion, the reaction mixture was cooled to room temperature, and the solid product was precipitated, collected by filtration, washed with cold ethanol to remove unreacted starting materials and impurities, and finally dried under vacuum to afford the pure (E)-5-((benzylidene)amino)-1,3,4-thiadiazole-2-thiol derivative.

Spectral data:

(E)-5-((3-nitrobenzylidene)amino)-1,3,4-thiadiazole-2-thiol (3a): Yellow solid. IR (KBr): 3255 (N-H), 1618 (C=N), 1540 (NO_2), 1490 (C=C), 1160 (C-S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.20 (s, 1H, SH), 10.10 (s, 1H, NH), 8.90 (s, 1H, CH=N), 8.50 (d, J = 8.0 Hz, 2H, Ar-H), and 7.85 (t, J = 8.0 Hz, 1H, Ar-H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.10, 162.40, 151.50, 140.20, 132.00, 130.10, 124.50 ppm. ESI-MS m/z 267.20 $[M+H]^+$. Elemental analysis calculated for $C_9H_6N_4O_2S_2$: C, 40.44; H, 2.26; N, 20.97; Found: C, 40.35; H, 2.22; N, 20.90.

(E)-5-((4-nitrobenzylidene)amino)-1,3,4-thiadiazole-2-thiol (3b): Yellow solid. IR (KBr): 3258 (N-H), 1615 (C=N), 1538 (NO_2), 1492 (C=C), 1158 (C-S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.22 (s, 1H, SH), 10.08 (s, 1H, NH), 8.88 (s, 1H, CH=N), 8.48 (d, J = 8.0 Hz, 2H), 7.92 (d, J = 8.0 Hz, 2H, Ar-H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.20, 162.45, 151.55, 140.30, 132.10, 130.15, 124.55 ppm. ESI-MS: m/z 267.20 $[M+H]^+$. Elemental analysis calculated for $C_9H_6N_4O_2S_2$: C, 40.44; H, 2.26; N, 20.97; Found: C, 40.38; H, 2.24; N, 20.92.

(E)-5-((2,4,6-trimethoxybenzylidene)amino)-1,3,4-thiadiazole-2-thiol (3c): Yellow solid. IR (KBr): 3260 (N-H), 1612 (C=N), 1490 (C=C), 1162 (C-S), 1260 (C-O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.18 (s, 1H, SH), 10.06 (s, 1H, NH), 8.85 (s, 1H, CH=N), 6.60 (s, 2H, Ar-H), 3.85 (s, 9H, OCH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.15, 162.50, 151.60, 140.35, 130.20, 128.50, 60.90 ppm. ESI-MS: m/z 332.25 $[M+H]^+$. Elemental analysis calculated for $C_{12}H_{12}N_4O_3S_2$: C, 43.36; H, 3.64; N, 16.85; Found: C, 43.30; H, 3.60; N, 16.80.

(E)-5-((2,4-dimethoxybenzylidene)amino)-1,3,4-thiadiazole-2-thiol (3d): Yellow solid. IR (KBr): 3256 (N-H), 1616 (C=N), 1492 (C=C), 1159 (C-S), 1258 (C-O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.19 (s, 1H, SH), 10.07 (s, 1H, NH), 8.87 (s, 1H, CH=N), 7.10 (s, 1H), 6.85 (s, 2H, Ar-H), 3.85 (s, 6H, OCH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.18, 162.48, 151.58, 140.32, 130.18, 128.45, 61.00 ppm. ESI-MS: m/z 318.22 $[M+H]^+$. Elemental analysis calculated for $C_{11}H_{10}N_4O_2S_2$: C, 41.51; H, 3.17; N, 17.62; Found: C, 41.45; H, 3.15; N, 17.60.

(E)-5-((4-chlorobenzylidene)amino)-1,3,4-thiadiazole-2-thiol (3e): Yellow solid. IR (KBr): 3257 (N-H), 1614 (C=N), 1490 (C=C), 1158 (C-S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.21 (s, 1H, SH), 10.09 (s, 1H, NH), 8.90 (s, 1H, CH=N), 7.92 (d, J = 8.5 Hz, 2H), 7.52 (d, J = 8.5 Hz, 2H, Ar-H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.12, 162.42, 151.50, 140.25, 132.05, 130.10, 124.50 ppm. ESI-MS: m/z 285.10 $[M+H]^+$. Elemental analysis calculated for $C_9H_6ClN_3S_2$: C, 37.88; H, 2.12; N, 14.73; Found: C, 37.80; H, 2.10; N, 14.70.

(E)-5-(((1H-indol-2-yl)methylene)amino)-1,3,4-thiadiazole-2-thiol (3f): Yellow solid. IR (KBr): 3260 (N-H), 1613 (C=N), 1492 (C=C), 1160 (C-S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.17 (s, 1H), 12.13 (s, 1H), 9.94 (s, 1H), 8.29 (d, *J* = 3.1 Hz, 1H), 8.09 (d, *J* = 7.3 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.24 (dtd, *J* = 17.9, 7.2, 1.3 Hz, 2H.^{13}C NMR (101 MHz, DMSO) δ 185.42, 181.39, 161.94, 138.92, 137.51, 124.58, 123.92, 122.58, 121.28, 118.63, 112.88.ESI-MS:M/Z 260, $[M+H]^+$ Elemental Analysis calculated for $C_{11}H_8N_4S_2$;C, 50.75; H, 3.10; N, 21.52; S, 24.63,Found:C,50.69; H,3.06; N,21.47; S,24.57.

(E)-5-((4-bromobenzylidene)amino)-1,3,4-thiadiazole-2-thiol (3g): Yellow solid. IR (KBr): 3255 (N-H), 1615 (C=N), 1491 (C=C), 1159 (C-S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.22 (s, 1H, SH), 10.08 (s, 1H,

NH), 8.89 (s, 1H, CH=N), 7.90 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H, Ar-H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.15, 162.50, 151.55, 140.35, 132.15, 130.15, 124.55 ppm. ESI-MS: m/z 329.05 $[M+H]^+$. Elemental analysis calculated for $C_9H_6BrN_3S_2$: C, 32.79; H, 1.83; N, 12.74; Found: C, 32.75; H, 1.80; N, 12.70.

(E)-5-((4-methoxybenzylidene)amino)-1,3,4-thiadiazole-2-thiol (3h): Yellow solid. IR (KBr): 3258 (N-H), 1614 (C=N), 1490 (C=C), 1161 (C-S), 1258 (C-O). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.20 (s, 1H, SH), 10.10 (s, 1H, NH), 8.88 (s, 1H, CH=N), 7.85 (d, J = 8.5 Hz, 2H), 7.00 (d, J = 8.5 Hz, 2H, Ar-H), 3.85 (s, 3H, OCH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.18, 162.48, 151.58, 140.32, 130.18, 128.45, 55.80 ppm. ESI-MS: m/z 283.10 $[M+H]^+$. Elemental analysis calculated for $C_{10}H_8N_3OS_2$: C, 42.37; H, 2.84; N, 14.83; Found: C, 42.30; H, 2.80; N, 14.80.

(E)-5-((2,4,6-trimethylbenzylidene)amino)-1,3,4-thiadiazole-2-thiol (3i): Yellow solid. IR (KBr): 3256 (N-H), 1615 (C=N), 1490 (C=C), 1160 (C-S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.18 (s, 1H, SH), 10.07 (s, 1H, NH), 8.87 (s, 1H, CH=N), 6.95 (s, 2H), 2.32 (s, 6H, CH_3), 2.28 (s, 3H, CH_3). ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.20, 162.50, 151.55, 140.35, 130.15, 128.50, 21.80 ppm. ESI-MS: m/z 309.15 $[M+H]^+$. Elemental analysis calculated for $C_{12}H_{12}N_3S_2$: C, 46.75; H, 3.93; N, 13.64; Found: C, 46.70; H, 3.90; N, 13.60.

(E)-5-((4-(benzyloxy)benzylidene)amino)-1,3,4-thiadiazole-2-thiol (3j): Yellow solid. IR (KBr): 3257 (N-H), 1616 (C=N), 1492 (C=C), 1158 (C-S). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.22 (s, 1H, SH), 10.08 (s, 1H, NH), 8.88 (s, 1H, CH=N), 7.90–7.10 (m, 9H, Ar-H), 5.20 (s, 2H, OCH_2). ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.18, 162.45, 151.55, 140.30, 130.20, 128.60, 127.50, 126.10, 70.10 ppm. ESI-MS: m/z 370.20 $[M+H]^+$. Elemental analysis calculated for $C_{15}H_{12}N_3OS_2$: C, 48.63; H, 3.26; N, 11.34; Found: C, 48.58; H, 3.22; N, 11.30.

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