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SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF NOVEL-5-(2-(1H-INDOL-3-YL) ETHYL)-1,3,4-THIADIAZOL-2-AMINE DERIVATIVES ITS MOLECULAR DOCKING

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Abstract: The antimicrobial resistance has necessitated the development of novel therapeutic agents with distinct mechanisms of action. the synthesis, characterization, and biological evaluation of a novel 5-(2-(1H-indol-3-yl) ethyl)-1,3,4-thiadiazol-2-amine derivative. The compound was synthesized via condensation of 3-indolepropionic acid with thiosemicarbazide in ethanolic solution using sulfuric acid as a catalyst, yielding 98% of the target product. The Structural confirmation was through FT-IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry. And antimicrobial screening revealed significant antibacterial activity against *Staphylococcus aureus* with an 18 mm zone of inhibition at 25 mg/mL, outperforming chloramphenicol (16 mm), while moderate antifungal activity was observed against *Rhizopus* sp. Molecular docking studies demonstrated strong binding affinities ranging from -4.7 to -8.3 kcal/mol against bacterial and fungal target proteins. ADME analysis indicated favorable drug-like properties with high GI absorption, good solubility, and compliance with Lipinski's rule. These results highlight the potential of indole-thiadiazole hybrids as promising scaffolds for antimicrobial drug discovery.

Keyword: Antimicrobial activity, Molecular docking, ADME prediction

INTRODUCTION

The rapid emergence of antimicrobial resistance (AMR) has become one of the most critical global health challenges of the 21st century [1]. The overuse and misuse of conventional antibiotics have led to the evolution of multidrug-resistant (MDR) bacterial strains [2], rendering many existing drugs ineffective against common pathogens such as antibacterial [3, 4], antifungal, anti -inflammatory [5]. This situation has created an urgent need for the discovery [6] and development of novel antibacterial agents with distinct mechanisms of action [7, 8].

Heterocyclic compounds have historically played a central role in drug discovery due to their diverse biological activities [9, 10]. these, 1,3,4-thiadiazole is a prominent five-membered heterocyclic scaffold containing two nitrogen atoms and one sulfur atom [11, 12]. The presence of the –N=C–S– moiety imparts remarkable pharmacological potential [13]. Precisely, the thiadiazole nucleus is known to interfere with bacterial enzyme systems by forming hydrogen bonds[14] and thereby inhibiting crucial metabolic pathways[15].

The indole nucleus is a advantaged structure widely circulated in nature [16, 17], present in essential amino acid tryptophan and many plant alkaloids [18, 19]. Indole derivatives have demonstrated significant through various mechanisms [20], with DNA embolism, inhibition of bacterial gyrase [21] and disruption of microbial cell membranes [22]. The combination of indole with other bioactive scaffolds often results in synergistic effects, and condensed toxicity [23].

In the present study, we have designed and synthesized a series of novel 5-(2-(1H-indol-3-yl) ethyl)-1,3,4-thiadiazol-2-amine derivatives by linking the indole ring through an ethyl bridge to the 1,3,4-thiadiazole core. This molecular approach aims to combine the pharmacophoric features of both moieties into a single molecular framework, potentially leading to compounds with improved antibacterial activity.

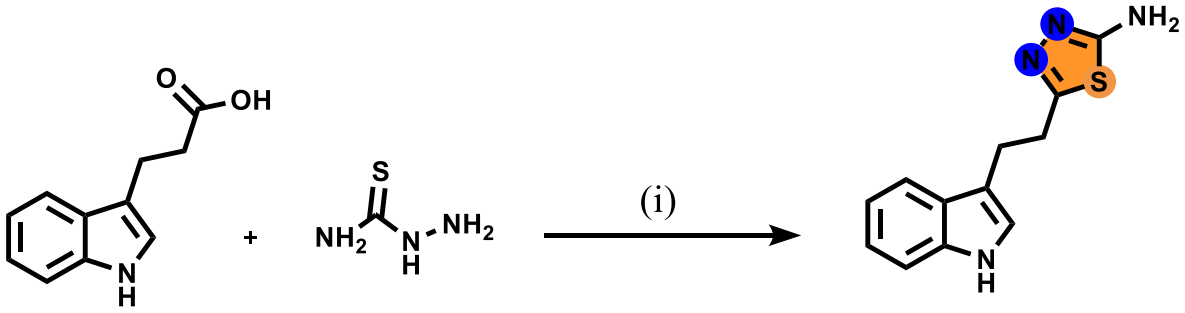
The synthesized compound were characterized using modern analytical techniques, including FT-IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry. Furthermore, to rationalize the observed biological activity and understand the binding interactions at the molecular level, molecular docking studies were performed. The docking studies were carried out against key bacterial target proteins, such as *Rhizopus* fungus or *S. aureus* bacteria, to predict binding affinities, binding modes, and key intermolecular interactions (hydrogen bonds, hydrophobic interactions, π-π stacking) between the synthesized ligands and the active site residues of the target enzyme.

The comprehensive approach adopted in this research encompassing synthesis [24], characterization [25], antibacterial screening [26], and computational docking provides valuable insights into the structure-activity relationships (SAR) of indole-thiadiazole hybrids [26] and paves the way for further optimization of these compounds as potential antibacterial drug candidates [27].

RESULT AND DISCISSION

Chemistry

The synthesis begins with 3-indolepropionic acid, which undergoes a condensation reaction with thiosemicarbazide, followed by a subsequent dehydration step that facilitates cyclization to afford a five-membered 1,3,4-thiadiazole ring. The target compound, 5-(2-(1H-indol-3-yl) ethyl)-1,3,4-thiadiazol-2-amine. The precursor (reactant 1) was refluxed in ethanol for 5–6 hours, yielding compound 2 in an excellent 98% yield, as illustrated in Scheme 1. The structure of the synthesized compound was unequivocally confirmed by FTIR, ^{1}H NMR, and ^{13}C NMR spectroscopy.



3-(1*H*-indol-3-yl)propanoic acid

5-(2-(1*H*-indol-3-yl)ethyl)-1,3,4-thiadiazol-2-amine

Scheme 1: Synthesis of 5-(2-(1H-indol-3-yl) ethyl)-1,3,4-thiadiazol-2-amine.

Reagent and Conditions: **(i) H_2SO_4, EtOH 15 ml 90^{0}C, 5-6 hr, yield 98%**

MATERIAL AND METHOD

3-indolepropionic acid, and thiosemicarbazide, purchased from BLD Pharma and sigma Aldrich all the chemical used further without purification. And Solvent, distilled water, silica gel purchased from S.D. chemicals, India, solvents were purified by distillation method. Muller-Hinton agar, DMSO, petri-disc.

The ^{1}H and ^{13}C NMR nuclear magnetic resonance (NMR) spectra were recorded in DMSO-as the solvent using a Bruker AMU spectrometer at Aligarh, India. Fourier transform infrared (FTIR) analysis was performed at Jiwaji University, Gwalior. The combined spectral data collectively substantiated the assigned structure of the synthesized compound.

Chemistry

Synthesis of 5-(2-(1H-indol-3-yl) ethyl)-1,3,4-thiadiazol-2-amine.

An ethanolic solution of 3-indolic Propionic acid (0.5 mg, 2.60 mm) was added to thiosemicarbazide (0.240 mg, 2.60 mm) with constant stirring. A few drops of conc sulfuric acid were added and heated for 5-6 h at 85-90 ^{0}C, after monitoring TLC then poured to ice cold water and neutralized with 10 % $NaHCO_3$ / NaOH solution and the separated lightly white precipitate was filtered, washed with distilled water, dried, good yield and crystallized from suitable solvent.

Physical State: Brauns's colour and solid room temperature

Spectroscopic analysis: FTIR (cm^{-1}) 3242, N-H Stretching (primary amine NH_2 group), 3083C-H Stretching (Aromatic). 2937 C-H Stretching (Aliphatic). 1614 C=N Stretching. 1510 C=C Stretching (Aromatic). 1217 C-N Stretching and Indole ring., 651 C-S-C Stretching from thiadiazol ring., ^{1}H NMR (400 MHz, DMSO-D_6) δ 10.73, 7.46, 7.44, 7.29, 7.27, 7.06, 7.05, 7.03, 7.01, 6.99, 6.94, 6.92, 6.90, 4.02, 4.00, 3.98, 3.96, 3.52, 3.36, 2.92, 2.91, 2.89, 2.62, 2.60, 2.58, 2.46, 2.45, 2.45, 2.44, 2.44, 1.12, 1.10, 1.08, 1.06.

^{13}C NMR (101 MHz, DMSO-D_6) δ 173.19, 136.74, 127.41, 122.84, 121.48, 118.78, 118.69, 113.60, 111.89, 60.28, 40.60, 40.39, 40.18, 39.97, 39.76, 39.55, 39.34, 35.05, 20.78, 14.60.

Spectral data and Fig

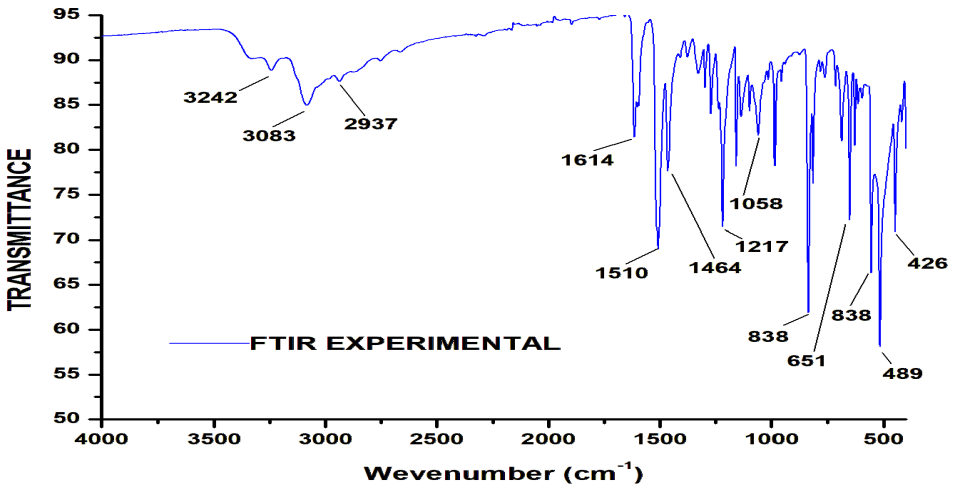


Fig. : FTIR of Compound

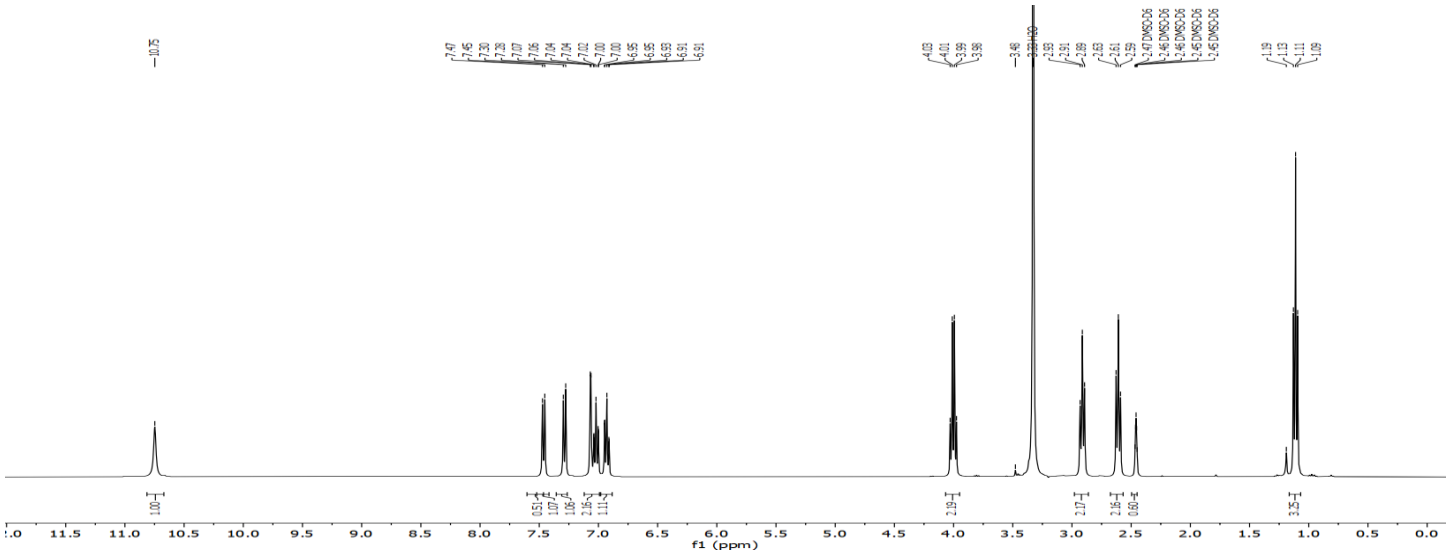


Fig. : ^{1}H NMR of compound

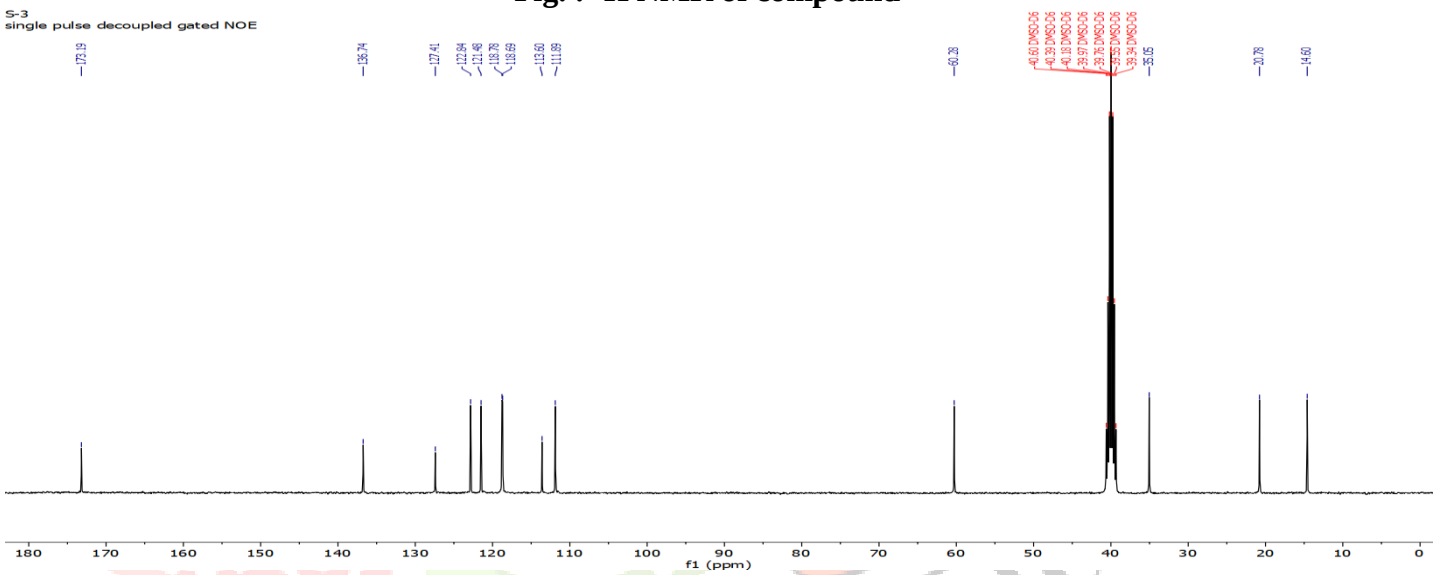


Fig. : ^{13}C NMR of compound

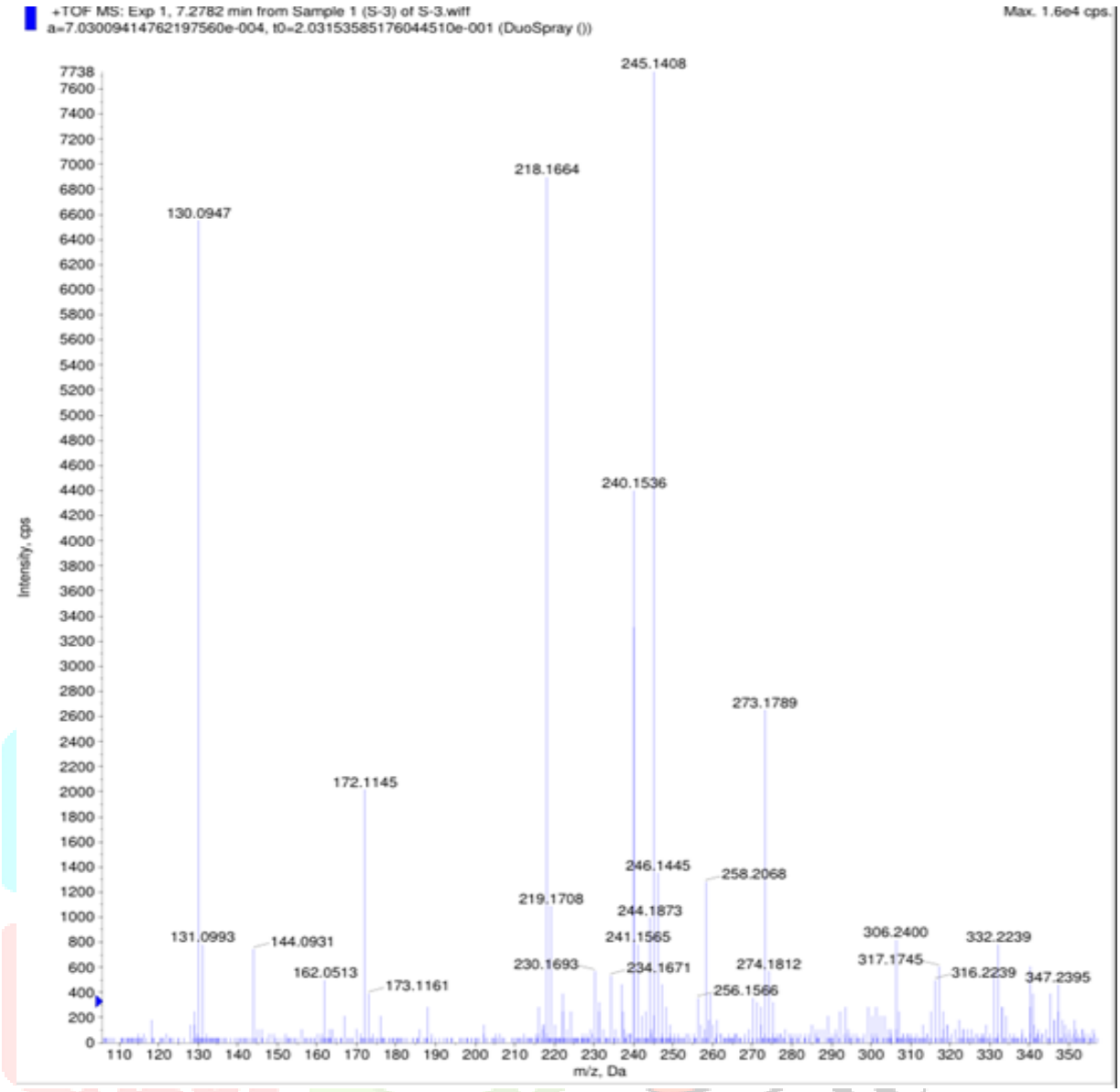


Fig. : HRMS of Compound

Evaluation of Antimicrobial Activity

Table :1 anti- Fungus Activity-

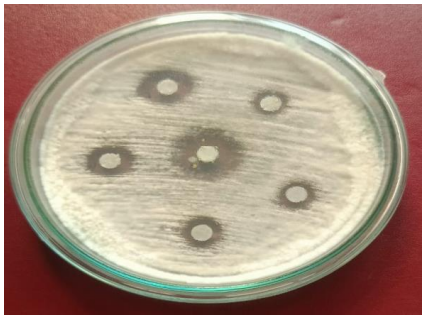
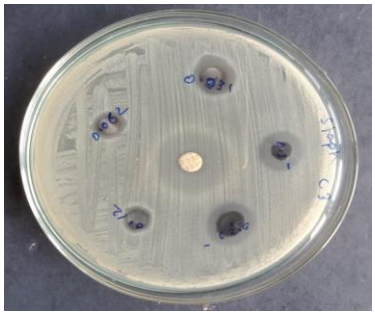
S.N	Sample	Conc	ZOI Against Rhizopus	Image
1	S-2	100	14 mm	
		50	12 mm partial	
		25	11 mm partial	
		12.5	10 mm	
		6.5	8 mm	
Control- Fluconazole		25	10 mm	**Fig. : Anti- Fungus Activity of Synthesized Compound**

Table : 2 Antibacterial Activity

S.N	Sample	Conc	ZOI Against *Staphylococcus aureus*	Image
1	S-2	100	14mm	
		50	13mm	
		25	18mm	
		12.5	8mm	
		6.5	9mm	
Control-Chloramphenicol		25	16mm	**Fig. : Antibacterial Activity of Synthesized Compound**

The biological activity of sample S-2 was evaluated for both antifungal and antibacterial properties. In the antifungal study, S-2 was tested against *Rhizopus* sp., (table-1) and at the highest concentration of 100 mg/ml, S-2 produced a zone of inhibition (ZOI) of 14 mm, indicating good antifungal activity. When the concentration was reduced to 50 mg/ml, a partial inhibition of 12 mm was observed. At 25 mg/ml, the ZOI decreased to 11 mm partial inhibition, followed by 10 mm at 12.5 mg/ml and 8 mm at 6.5 mg/ml. The control drug, fluconazole, at 25 mg/ml produced a 10 mm ZOI, which is comparable to the effect of S-2 at the same concentration (11 mm partial inhibition), suggesting that S-2 has moderate but consistent antifungal potential. In the antibacterial study, S-2 was tested against Staphylococcus aureus. (table-2) The results demonstrated promising antibacterial activity. At 50 mg/ml, S-2 produced a 13 mm ZOI. At concentrations of 25 mg/ml and 18 mg/ml, the ZOI was 18 mm each. Further dilutions to 6.25 mg/ml and 3.125 mg/ml resulted in ZOIs of 8 mm and 9 mm respectively. The control antibiotic, chloramphenicol, at 25 mg/ml gave a 16 mm ZOI, which is lower than S-2's best result. However, S-2 still exhibited consistent and notable activity against *S. aureus*, especially at higher concentrations. Overall, sample S-2 demonstrates moderate antifungal activity against *Rhizopus* and good antibacterial activity against *Staphylococcus aureus*.

Molecular Docking of Synthesized Compound

Molecular docking analysis was showed to evaluate the binding affinity of the synthesized 5-(2-(1H-indol-3-yl) ethyl)-1,3,4-thiadiazol-2-amine derivatives compound against two protein targets each from *Staphylococcus aureus***,** Against Rhizopus. The docking result, including binding affinities (ΔG) and inhibition constants (Ki) are showing in table-1, Staphylococcus Aureus the synthesized -(2-(1H-indol-3-yl) ethyl)-1,3,4-thiadiazol-2-amine derivatives compound show a strong binding affinity toward the 3U2D protein with a ΔG of -7.5 Kal/mol and inhibition constant of -3.1µM, indicating interaction (Table-3). The interacting amino acid residues included ILE 32, ILE 302, ASP31, GLU58, ASN54, ILE36, GLY33, (Fig-1). And the 5EDR protein the -(2-(1H-indol-3-yl) ethyl)-1,3,4-thiadiazol-2-amine derivatives compound exhibited a binding affinity of -7.0 Kal/mol and Ki of 7.3µM, forming interactions with residues GLY796, MET793, LEU792, LEU718, ALA743, LEU844, VAL790, ILE744, GLU762, MET766. For Rhizopus (table-3) -(2-(1H-indol-3-yl) ethyl)-1,3,4-thiadiazol-2-amine derivatives compound in binding affinity of -8.3 kal/mol against IGAL protein with a ki of 8.1µM. the indicating residues were HLY302, GLY97, HPS78, SLR303, YLY250, ALA388, and TYR30.

4IIB protein docking score show reasonably lower binding affinity of -4.7kal/mol and ki of 35.6 µM.

Table 3: show the binding affinity and inhibition constant data for the 5-(2-(1H-indol-3-yl) ethyl)-1,3,4-thiadiazol-2-amine derivatives compound.

Targets	Synthesis of Compound	
	(ΔG) Kcal/ mol Binding Affinity	Inhibition Constant (Ki) µM
Streptococcus aureus		
3U2D	-7.5	3.1
5M18	-7.1	6.1
5EDR	-7.0	7.3
Rhizopus		
1GAL	-8.3	8.1
4WAB	-5.5	9.2
4IIB	-4.7	35.6

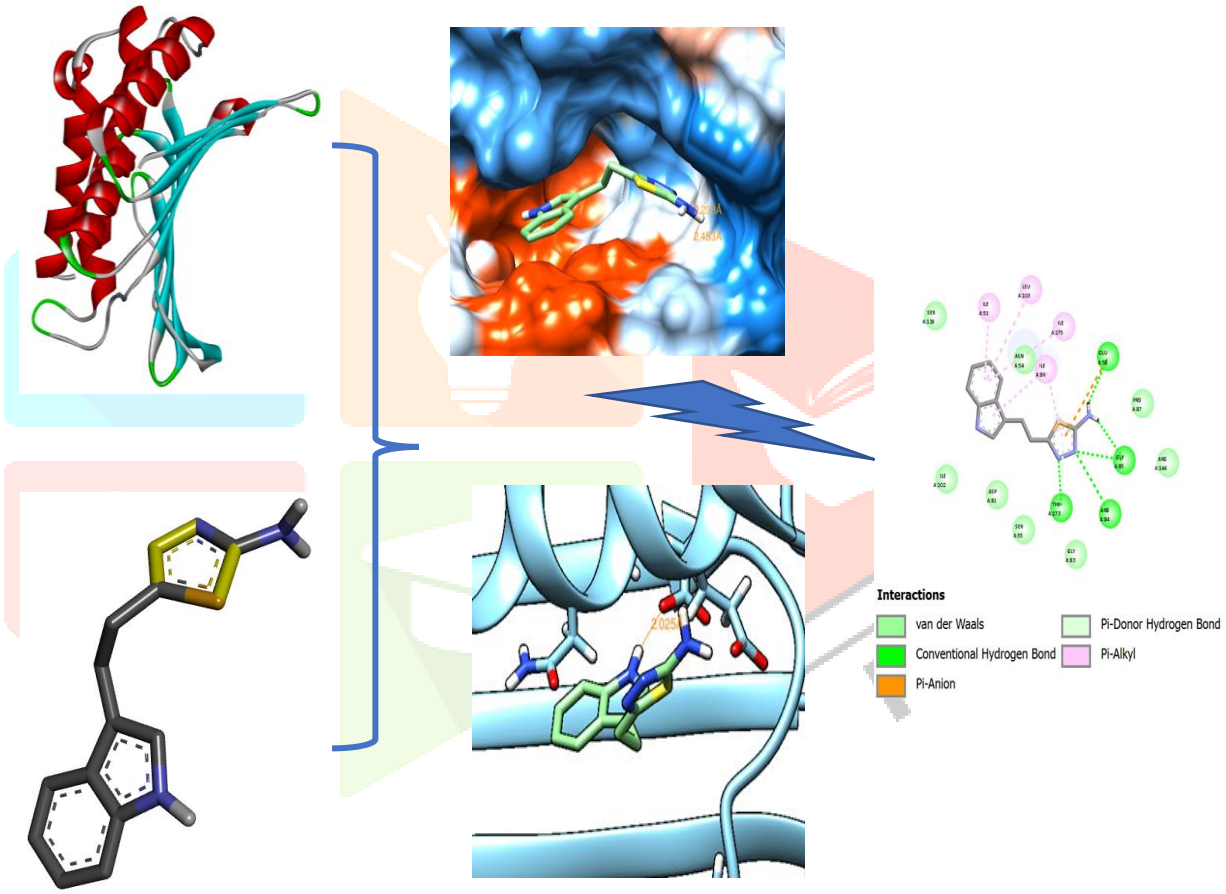


Fig. 1: 2D Interaction of 5-(2-(1H-indol-3-yl) ethyl)-1,3,4-thiadiazol-2-amine derivatives compound and 2U2D

ADME of Synthesized Compound

The drug-likeness and pharmacokinetic properties of the synthesized 5-(2-(1H-indol-3-yl) ethyl)-1,3,4-thiadiazol-2-amine derivatives were evaluated by estimating their ADME (Absorption, Distribution, Metabolism, and Excretion) profile through computational tools. With a molecular weight of 244.32 g/mol slightly exceeding the ideal lead-like range yet still within the limits for oral bioavailability the synthesized molecule 5-(2-(1H-indol-3-yl) ethyl)-1,3,4-thiadiazol-2-amine fully complies with Lipinski's rule of five (zero violations) and also meets the Ghose, Veber, Egan, and Muegge drug-likeness criteria, reflecting satisfactory physicochemical properties. The measured TPSA of 95.83 Å² for the 5-(2-(1H-indol-3-yl) ethyl)-1,3,4-thiadiazol-2-amine molecule correlates with enhanced GI absorption, marking it as a favorable

candidate for oral drug delivery. Due to its inability to permeate the blood-brain barrier (BBB), the 5-(2-(1H-indol-3-yl) ethyl)-1,3,4-thiadiazol-2-amine compound presents a low risk of CNS activity, which may be advantageous in preventing off-target neurological actions based on the desired clinical use.

With an iLOGP value of 0.00 and an ESOL-predicted Log S of -3.26, the compound's solubility appears sufficient for oral formulation development, although additional refinement may boost bioavailability if necessary. Metabolically speaking, the compound 5-(2-(1H-indol-3-yl) ethyl)-1,3,4-thiadiazol-2-amine is expected to inhibit CYP1A2, CYP2C19, and CYP2C9, suggesting a risk of drug-drug interactions upon co-administration with drugs metabolized by these enzymes. Fortunately, it does not act as a P-gp substrate and shows no inhibition of CYP2D6 or CYP3A4, which minimizes concerns over drug efflux and major metabolic clearance routes. The compound 5-(2-(1H-indol-3-yl) ethyl)-1,3,4-thiadiazol-2-amine shows a bioavailability score of 0.55 (moderate oral absorption) and a synthetic accessibility score of 2.62 (easy to synthesize). Even though it violates lead-likeness criteria due to molecular weight above 250 and having more than seven rotatable bonds, these factors do not undermine its potential as a valid drug candidate, particularly considering its excellent all-around ADME characteristics (Table ---).

Overall, these results indicate that the 5-(2-(1H-indol-3-yl) ethyl)-1,3,4-thiadiazol-2-amine derivative possesses encouraging drug-like attributes, particularly suited for oral administration.

Table 2 : ADME analysis of targeted compound5-(2-(1H-indol-3-yl) ethyl)-1,3,4-thiadiazol-2-amine

S. No.	Parameter	Compound
1	Molecular weight	244.32 g/mol
2	Formula	$C_{12}H_{12}N_4S$
3	TPSA	95.83 $Å^2$
4	Log Po/W (iLOGP)	0.00
5	Log S (ESOL)	-3.26
6	Solubility	2.69e-01mg/ml;1.10e-03 mol/l
7	Class	soluble
8	GI absorption	High
9	BBB Permeant	No
10	P-gp substrate	No
11	CYP1A2 inhibitor	Yes
12	CYP2C19 inhibitor	Yes
13	CYP2C9 inhibitor	Yes
14	CYP2D6 inhibitor	No
15	CYP2A4 inhibitor	No
16	Log Kp (skin permeation)	-6.09 cm/s
17	Lipinski	Yes; 0 violation
18	Ghose	Yes
19	Veber	Yes
20	Egan	Yes
21	Muegge	Yes
22	Bioavailability Score	0.55
23	Leadlikeness	No; 1 violation: MW>250
24	Synthetic accessibility	2.62

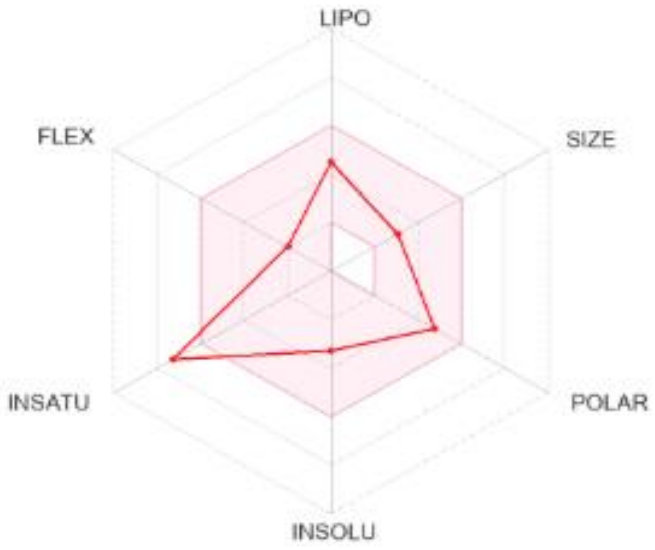


Fig.2 : ADME Synthesized Compound

CONCLUSION

A novel 5-(2-(1H-indol-3-yl) ethyl)-1,3,4-thiadiazol-2-amine derivative compound was successfully synthesized via a condensation reaction between 3-indolepropionic acid and thiosemicarbazide, given an excellent 98% yield. And The compound structure was confirmed through FT-IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry analyses. Biological evaluation confirmed promising antimicrobial activity, with the compound showing sensible antifungal effects against *Rhizopus* sp. (14 mm ZOI at 100 mg/mL) and significant antibacterial activity against *Staphylococcus aureus* (18 mm ZOI at 25 mg/mL), outperforming the standard drug chloramphenicol. Molecular docking studies disclose strong binding affinities toward target proteins, with the highest affinity of -8.3 kcal/mol against the 1GAL protein of *Rhizopus*. Also, ADME predictions indicated favorable drug-like properties with high GI absorption, good solubility, and compliance with Lipinski's rule of five. These conclusions suggest that the indole-thiadiazole hybrid represents a promising scaffold for developing novel antimicrobial agents.

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