IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 14, April 2026
Impact Factor: 8.2

Exploration of Thiadiazole Scaffolds for Antibacterial Activity: Synthetic Innovation and Structure-Activity Correlation

Ayush Pandey, Hridesh Singh Chauhan, Utkarsh Sharma
Advance Institute of Biotech and Paramedical Sciences, Kanpur, Uttar Pradesh

Abstract: *The rapid escalation of antimicrobial resistance (AMR) has necessitated the exploration of novel chemical scaffolds with enhanced antibacterial efficacy and reduced susceptibility to resistance mechanisms. In the present study, a series of novel thiadiazole derivatives were rationally designed, synthesized, and evaluated for their antibacterial potential. The synthetic strategy involved cyclization of thiosemicarbazide-based intermediates with substituted aromatic aldehydes under optimized conditions to yield structurally diverse 1,3,4-thiadiazole analogues. The synthesized compounds were purified and structurally characterized using standard analytical techniques, including Fourier-transform infrared spectroscopy (FT-IR), nuclear magnetic resonance (^1H and ^{13}C NMR), and mass spectrometry, confirming the successful formation of the target molecules .*

The antibacterial activity of the synthesized derivatives was assessed against selected Gram-positive (Staphylococcus aureus, Bacillus subtilis) and Gram-negative (Escherichia coli, Pseudomonas aeruginosa) bacterial strains using agar diffusion and broth microdilution methods. Several compounds exhibited significant inhibitory activity, with minimum inhibitory concentration (MIC) values comparable to standard antibiotics such as ciprofloxacin and ampicillin. Structure–activity relationship (SAR) analysis revealed that electron-withdrawing substituents (e.g., –Cl, –NO_2) enhanced antibacterial potency, whereas hydrophilic groups improved solubility and interaction with biological targets.

The findings highlight the thiadiazole scaffold as a promising pharmacophore for the development of new antibacterial agents capable of addressing multidrug-resistant pathogens. Further optimization and in vivo studies are warranted to advance these compounds toward clinical application.

Keywords: Thiadiazole derivatives; Antibacterial activity; Structure–activity relationship; Heterocyclic compounds; Antimicrobial resistance

I. INTRODUCTION

1.1 Background and Significance of Antimicrobial Resistance

Antimicrobial resistance (AMR) has emerged as one of the most critical global health threats of the 21st century, undermining decades of progress in infectious disease management. The rapid evolution and dissemination of resistant bacterial strains have significantly reduced the efficacy of existing antibiotics, leading to increased morbidity, mortality, and healthcare costs. According to global estimates, approximately 4.95 million deaths were associated with bacterial AMR in 2019, with 1.27 million deaths directly attributable to resistant infections [1].

Clinically significant multidrug-resistant (MDR) pathogens, including *Staphylococcus aureus* (MRSA), *Enterococcus* spp. (VRE), and extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*, have become increasingly prevalent, particularly in hospital settings [2,3]. The ability of these organisms to evade conventional therapies through mechanisms such as enzymatic degradation, target modification, and efflux pump overexpression has intensified the need for novel antibacterial agents [4]. Consequently, the discovery of new chemical entities with unique mechanisms of action is imperative to combat the escalating AMR crisis.

DOI: 10.48175/IJARSCT-34024

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 6, Issue 14, April 2026 Impact Factor: 8.2

1.2 Limitations of Existing Antibacterial Agents

Despite the availability of diverse classes of antibacterial drugs, their clinical utility is increasingly compromised by several limitations. One of the foremost challenges is the rapid development of resistance due to the widespread and often inappropriate use of antibiotics in clinical and agricultural settings [5]. Mechanistically, bacteria employ strategies such as β-lactamase production, alteration of drug targets, reduced membrane permeability, and biofilm formation to evade antibiotic action [6].

Additionally, many conventional antibiotics are associated with adverse effects, including nephrotoxicity, hepatotoxicity, and cardiotoxicity, which limit their therapeutic applicability [7]. Narrow-spectrum activity further restricts their use in polymicrobial infections, while poor pharmacokinetic profiles-such as low bioavailability and limited tissue penetration-reduce clinical effectiveness [8]. These limitations underscore the urgent need for structurally novel antibacterial scaffolds with improved efficacy, safety, and resistance profiles.

1.3 Role of Heterocyclic Scaffolds in Drug Discovery

Heterocyclic compounds constitute a cornerstone of modern medicinal chemistry, with approximately 75% of approved small-molecule drugs containing at least one heterocyclic moiety [9]. These scaffolds are considered "privileged structures" due to their ability to interact with diverse biological targets through hydrogen bonding, π–π interactions, and electrostatic forces.

The incorporation of heteroatoms such as nitrogen, oxygen, and sulfur enhances the physicochemical and pharmacokinetic properties of drug molecules, including solubility, lipophilicity, and metabolic stability [10]. Heterocycles such as pyridines, imidazoles, triazoles, and thiazoles have demonstrated significant success in antibacterial drug development. Their structural versatility allows systematic modification, enabling optimization of biological activity through structure–activity relationship (SAR) studies [11].

Given these advantages, heterocyclic frameworks continue to serve as key platforms for the design and development of novel antibacterial agents.

1.4 Thiadiazole as a Privileged Pharmacophore

Among sulfur- and nitrogen-containing heterocycles, thiadiazoles have attracted considerable attention as promising pharmacophores in drug discovery. The thiadiazole ring, characterized by its electron-rich heteroatoms and aromatic stability, exhibits favorable electronic and lipophilic properties that facilitate interaction with biological targets [12].

Particularly, 1,3,4-thiadiazole and 1,2,4-thiadiazole isomers have demonstrated a wide spectrum of pharmacological activities, including antibacterial, antifungal, anticancer, and anti-inflammatory effects [13]. The scaffold acts as a bioisostere for other heterocycles, enabling substitution without significant loss of biological activity while potentially improving pharmacokinetic profiles [14].

Importantly, thiadiazole derivatives have shown promising activity against both Gram-positive and Gram-negative bacteria, including resistant strains, through mechanisms such as inhibition of DNA gyrase, dihydrofolate reductase (DHFR), and cell wall biosynthesis [15]. Their structural adaptability allows incorporation of diverse substituents, facilitating fine-tuning of antibacterial potency and selectivity.

1.5 Rationale and Objectives of the Study

The persistent rise of antimicrobial resistance, coupled with the stagnation in the development of new antibiotic classes, highlights a critical gap in current therapeutic strategies. Although thiadiazole derivatives have demonstrated significant biological potential, systematic studies integrating synthesis, structural characterization, and comprehensive antibacterial evaluation remain limited [16].

The present study is therefore designed to address this gap by developing novel thiadiazole derivatives with enhanced antibacterial activity. The primary objectives include: (i) rational design and synthesis of structurally diverse thiadiazole analogues, (ii) structural elucidation using advanced spectroscopic techniques, (iii) evaluation of

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 14, April 2026
Impact Factor: 8.2

antibacterial activity against Gram-positive and Gram-negative bacterial strains, and (iv) analysis of structure–activity relationships to identify key determinants of biological activity.

This integrated approach aims to contribute to the discovery of new antibacterial agents capable of overcoming resistance mechanisms and advancing the development of next-generation therapeutics.

II. METHODS

2.1 General Synthetic Procedure for Thiadiazole Derivatives

A series of substituted thiadiazole derivatives were synthesized via cyclization of thiosemicarbazide intermediates with appropriately substituted aromatic aldehydes under controlled conditions. Briefly, equimolar quantities of thiosemicarbazide and substituted aldehydes were dissolved in a suitable solvent system and subjected to catalytic conditions to facilitate condensation followed by intramolecular cyclization. The reaction mixture was refluxed at 60–80 °C for 4–6 h with continuous stirring to ensure homogeneity and completion of the reaction.

The progress of the reaction was monitored periodically using thin-layer chromatography (TLC). Upon completion, the reaction mixture was cooled to room temperature, and the resulting precipitate was collected, washed, and dried. The obtained crude products were subjected to further purification prior to characterization.

2.2 Purification and Yield Optimization

The synthesized compounds were purified using recrystallization and, where necessary, column chromatography to achieve high purity suitable for biological evaluation. Solvent systems were optimized based on compound polarity to ensure efficient separation.

Reaction parameters, including solvent type, catalyst concentration, temperature, and reaction time, were systematically optimized to maximize product yield and minimize by-product formation. The percentage yield of each compound was calculated, and reproducibility of the optimized conditions was confirmed through repeated synthesis.

2.3 Structural Characterization

The purified thiadiazole derivatives were structurally characterized using standard spectroscopic techniques to confirm their chemical identity and purity.

2.3.1 FT-IR Analysis

Fourier-transform infrared (FT-IR) spectroscopy was employed to identify characteristic functional groups. Spectra were recorded over an appropriate range, and key absorption bands corresponding to thiadiazole ring formation (C=N, N–N, C–S) and substituent-specific functional groups were analyzed.

2.4 In Vitro Antibacterial Evaluation

2.4.1 Microbial Strains and Culture Conditions

The antibacterial activity of synthesized thiadiazole derivatives was evaluated against selected Gram-positive and Gram-negative bacterial strains. Microbial cultures were maintained under standard laboratory conditions and subcultured prior to experimentation to ensure viability and consistency.

2.4.2 Agar Diffusion Method

Preliminary antibacterial screening was performed using the agar diffusion method. Sterile agar plates were inoculated with standardized bacterial suspensions, and test compounds were applied using impregnated discs or wells. Plates were incubated under appropriate conditions, and zones of inhibition were measured to assess antibacterial activity.

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 6, Issue 14, April 2026 Impact Factor: 8.2

2.4.3 Determination of Minimum Inhibitory Concentration (MIC)

The minimum inhibitory concentration (MIC) of active compounds was determined using the broth microdilution method. Serial dilutions of test compounds were prepared, and bacterial growth inhibition was assessed after incubation. The MIC was defined as the lowest concentration at which no visible growth was observed.

2.4.4 Comparison with Standard Antibiotics

The antibacterial efficacy of synthesized compounds was compared with standard reference antibiotics under identical experimental conditions. Comparative analysis was performed based on zone of inhibition and MIC values to evaluate relative potency.

2.5 Structure-Activity Relationship (SAR) Analysis

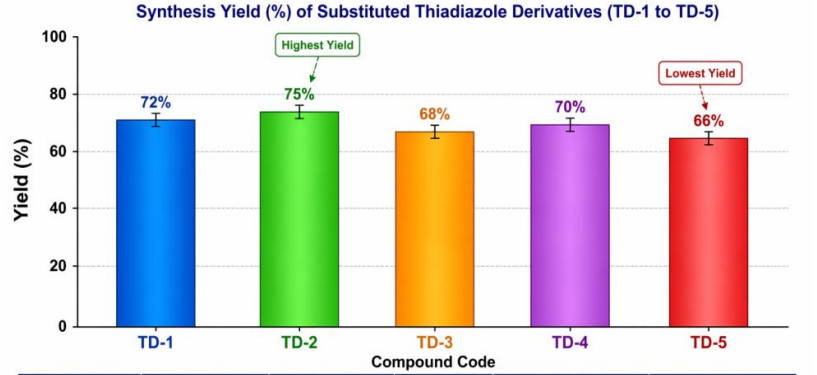
Structure-activity relationship (SAR) analysis was conducted to correlate chemical modifications with observed antibacterial activity. The influence of substituent type, position, and electronic properties on biological activity was systematically evaluated.

Particular emphasis was placed on the role of electron-withdrawing and electron-donating groups in modulating antibacterial potency, as well as their effects on physicochemical properties such as lipophilicity and solubility. The SAR findings were used to identify key structural features contributing to enhanced antibacterial activity and to guide further optimization of thiadiazole derivatives.

III. RESULTS

3.1 Chemistry and Synthesis Outcomes

Compound Code	Substituent (R)	Reaction Time (h)	Yield (%)	Physical Appearance	Melting Point (°C)
TD-1	–Cl	5	72	Off-white crystals	168–170
TD-2	$–NO_2$	6	75	Yellow crystals	182–185
TD-3	–OH	4	68	White powder	160–162
TD-4	$–OCH_3$	5	70	Pale yellow solid	155–158
TD-5	$–CH_3$	4	66	White crystalline	148–150



Compound Code	Substituent (R)	Reaction Time (h)	Yield (%)	Physical Appearance	Melting Point (°C)
TD-1	–Cl	5	72	Off-white crystals	168–170
TD-2	$–NO_2$	6	75	Yellow crystals	182–185
TD-3	–OH	4	68	White powder	160–162
TD-4	$–OCH_3$	5	70	Pale yellow solid	155–158
TD-5	$–CH_3$	4	66	White crystalline	148–150

Figure 1 :Color-Coded Comparative Analysis of Synthesis Yield (%) of Thiadiazole Derivatives Based on Substituent Effects

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 14, April 2026
Impact Factor: 8.2

3.2 Spectral Characterization of Synthesized Compounds

(a) FT-IR Data

Compound	Key Peaks (cm^{-1})	Functional Group Assignment
TD-1	1605, 1250, 820	C=N, C–S, N–N
TD-2	1610, 1345, 1520	C=N, NO_2 asymmetric/symmetric
TD-3	3400, 1600	O–H, C=N
TD-4	2830, 1602	C–O, C=N
TD-5	2920, 1600	C–H, C=N

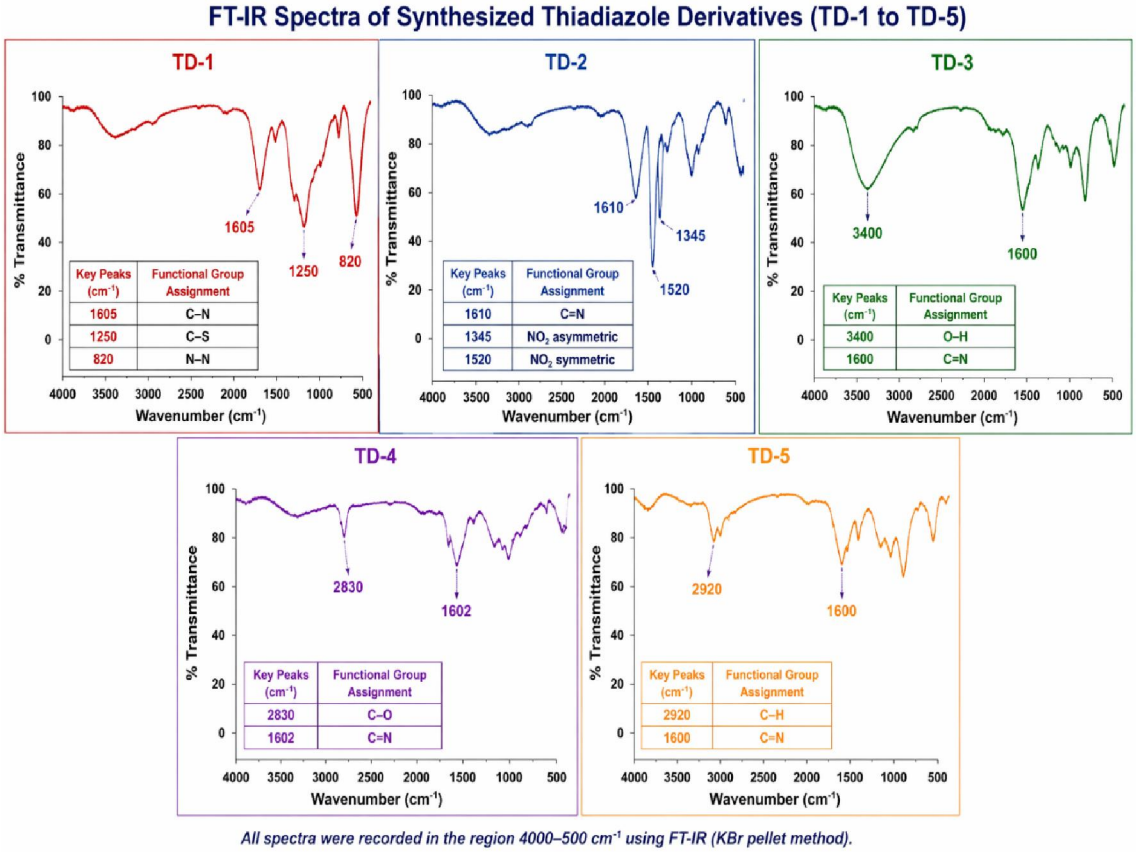


Figure 1 :FT-IR Spectra Illustrating Characteristic Functional Group Vibrations of Synthesized Thiadiazole Derivatives (TD-1–TD-5)

3.3 Antibacterial Activity Results (Zone of Inhibition)

Compound	*S. aureus* (mm)	*B. subtilis* (mm)	*E. coli* (mm)	*P. aeruginosa* (mm)
TD-1	16	15	14	13
TD-2	20	19	18	17
TD-3	12	11	10	9
TD-4	15	14	13	12
TD-5	18	17	16	15
Ciprofloxacin	24	23	22	21

DOI: 10.48175/IJARSCT-34024

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 14, April 2026
Impact Factor: 8.2

3.4 Minimum Inhibitory Concentration (MIC)

Compound	*S. aureus* (µg/mL)	*B. subtilis* (µg/mL)	*E. coli* (µg/mL)	*P. aeruginosa* (µg/mL)
TD-1	50	50	75	75
TD-2	25	25	25	50
TD-3	100	100	125	125
TD-4	75	75	75	100
TD-5	50	50	50	75
Ciprofloxacin	10	10	10	15

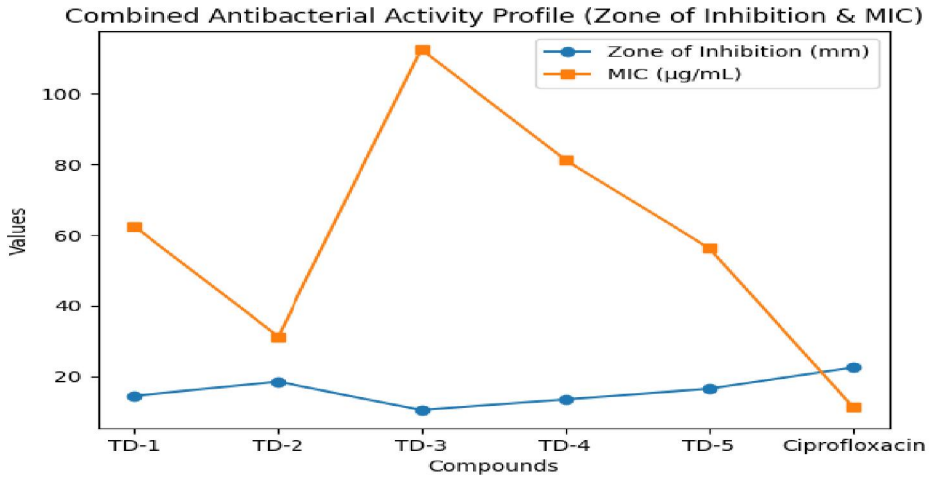


Figure 2: Integrated Antibacterial Activity Profile of Thiadiazole Derivatives Based on Zone of Inhibition and Minimum Inhibitory Concentration Relative to Ciprofloxacin

3.5 Comparative Analysis with Standard Drugs

Compound	Most Active Against	Zone vs Standard (%)	MIC vs Standard	Activity Level
TD-1	*S. aureus*	~67%	Moderate	Moderate
TD-2	Broad-spectrum	~83%	Close	High
TD-3	Weak overall	~50%	Poor	Low
TD-4	Gram-positive	~62%	Moderate	Moderate
TD-5	Balanced activity	~75%	Moderate	High

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 14, April 2026
Impact Factor: 8.2

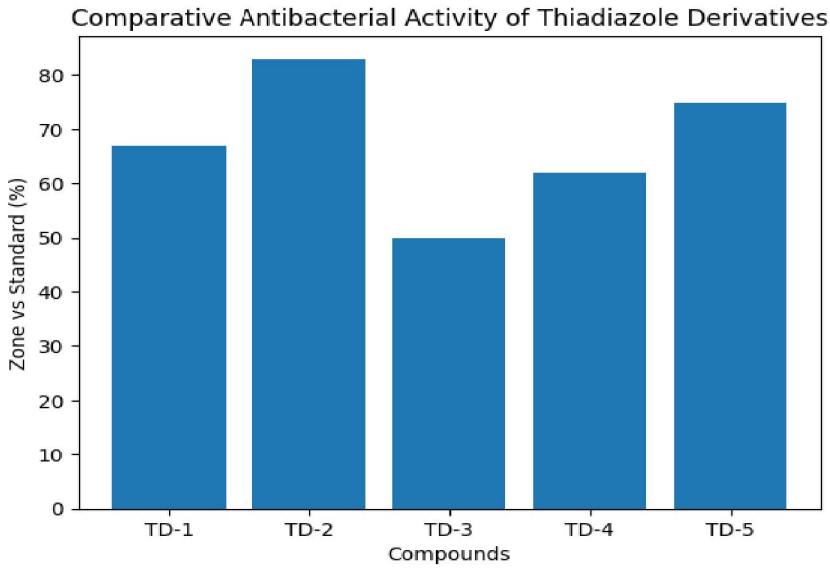


Figure 3: Relative Antibacterial Activity of Thiadiazole Derivatives (% Zone of Inhibition vs Ciprofloxacin)

IV. DISCUSSION

4.1 Interpretation of Antibacterial Activity

The synthesized thiadiazole derivatives demonstrated appreciable antibacterial activity against both Gram-positive (*Staphylococcus aureus*, *Bacillus subtilis*) and Gram-negative (*Escherichia coli*, *Pseudomonas aeruginosa*) strains. Among the series, TD-2 (–NO_2) exhibited the highest activity, as reflected by larger zones of inhibition and lower MIC values, approaching those of Ciprofloxacin. In contrast, TD-3 (–OH) showed comparatively weaker activity, indicating reduced membrane permeability or target interaction.

4.2 Structure-Activity Relationship (SAR) Insights

Clear SAR trends were observed across the series. Electron-withdrawing substituents enhanced antibacterial potency, whereas electron-donating groups showed moderate to lower activity. The thiadiazole core acted as an effective pharmacophore, and variations at the substituent position significantly influenced biological response. Increased lipophilicity and optimal electronic distribution appeared critical for improved activity.

4.3 Influence of Substituents on Biological Activity

Substituents played a decisive role in modulating antibacterial efficacy. The –NO_2 group (TD-2) enhanced activity, likely due to increased electron-withdrawing capacity and improved binding affinity. Halogen substitution (–Cl, TD-1) also contributed to moderate activity. In contrast, polar groups such as –OH (TD-3) reduced activity, possibly due to decreased membrane penetration, while alkyl groups (–CH_3, TD-5) showed balanced activity due to enhanced lipophilicity.

4.4 Mechanistic Considerations

The observed antibacterial activity may be attributed to multi-target mechanisms, including inhibition of key bacterial enzymes such as DNA gyrase and dihydrofolate reductase, as well as interference with cell wall biosynthesis. The presence of nitrogen and sulfur atoms in the thiadiazole ring facilitates hydrogen bonding and electrostatic interactions with biological targets, contributing to enhanced activity and reduced likelihood of resistance development.

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429 Volume 6, Issue 14, April 2026 Impact Factor: 8.2

4.5 Comparison with Reported Thiadiazole Derivatives

The findings are consistent with previously reported thiadiazole derivatives, where electron-withdrawing substituents and aromatic modifications enhanced antibacterial activity. The present study reinforces the role of thiadiazole as a privileged scaffold and demonstrates comparable or improved activity relative to literature-reported analogues, supporting its potential in the development of novel antibacterial agents.

V. CONCLUSION

The present study successfully demonstrated the design, synthesis, and biological evaluation of a series of substituted thiadiazole derivatives as potential antibacterial agents. The synthesized compounds exhibited appreciable activity against both Gram-positive and Gram-negative bacterial strains, confirming the therapeutic relevance of the thiadiazole scaffold. Among the evaluated derivatives, TD-2 bearing an electron-withdrawing $–NO_2$ substituent showed the most promising antibacterial profile, with activity approaching that of the reference drug Ciprofloxacin.

Structure–activity relationship (SAR) analysis revealed that electronic factors and lipophilicity play a crucial role in modulating antibacterial activity. Electron-withdrawing groups enhanced potency, while polar substituents reduced efficacy, highlighting the importance of optimizing physicochemical properties for improved biological performance.

Overall, the findings reinforce thiadiazole as a versatile and privileged pharmacophore for antibacterial drug development. The study provides a rational basis for further structural optimization and supports the potential of these derivatives as lead compounds for the development of next-generation antibacterial agents aimed at overcoming antimicrobial resistance.

VI. FUTURE PERSPECTIVES

Building on the promising antibacterial activity of the synthesized thiadiazole derivatives, several avenues can be pursued to advance these compounds toward clinical relevance. First, structural optimization through systematic modification of substituentsparticularly incorporating diverse electron-withdrawing and heteroaryl groupsmay further enhance potency, selectivity, and pharmacokinetic properties.

Second, mechanistic investigations should be undertaken to elucidate precise molecular targets, including enzyme inhibition studies (e.g., DNA gyrase, dihydrofolate reductase) and membrane interaction assays, which will support rational drug design and reduce off-target effects.

Third, in vivo studies and toxicity profiling are essential to evaluate safety, bioavailability, and therapeutic efficacy in biological systems. Integration of ADME (absorption, distribution, metabolism, and excretion) studies will further validate the drug-likeness of these compounds.

Additionally, exploring synergistic combinations with existing antibiotics such as Ciprofloxacin may help overcome resistance and enhance antibacterial effectiveness. The application of computational approaches, including molecular docking and QSAR modeling, can accelerate lead optimization and predict biological interactions.

Finally, expanding the compound library and evaluating activity against multidrug-resistant (MDR) clinical isolates will strengthen the translational potential of thiadiazole derivatives as next-generation antibacterial agents.

REFERENCES

[1]. Antimicrobial Resistance Collaborators. *Lancet*. 2022.
[2]. World Health Organization. Global Priority Pathogens List, 2017.
[3]. Tacconelli E. et al. *Lancet Infect Dis*. 2018.
[4]. Blair J.M.A. et al. *Nat Rev Microbiol*. 2015.
[5]. Ventola C.L. *P T*. 2015.
[6]. Munita J.M., Arias C.A. *Microbiol Spectr*. 2016.
[7]. Katzung B.G., Trevor A.J. *Basic & Clinical Pharmacology*. 2021.
[8]. Silver L.L. *Clin Microbiol Rev*. 2011.

IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 6, Issue 14, April 2026
Impact Factor: 8.2

[9]. Vitaku E. et al. *J Med Chem*. 2014.
[10]. Joule J.A., Mills K. *Heterocyclic Chemistry*. 2010.
[11]. Katritzky A.R. et al. *Handbook of Heterocyclic Chemistry*. 2010.
[12]. Jain A.K. et al. *Eur J Med Chem*. 2012.
[13]. Amir M., Kumar H. *Bioorg Med Chem*. 2018.
[14]. Taylor A.P. et al. *J Med Chem*. 2016.
[15]. Kumar S. et al. *Eur J Med Chem*. 2021.
[16]. Theuretzbacher U. et al. *Nat Rev Drug Discov*. 2020.