Pharmedico Publishers
International Journal of Pharmaceutical Science and Medicine
Volume 3, Issue 1 (2025): 43-52
DOI: 10.70199/IJPSM.3.1.43-52

REVIEW ARTICLE

ISSN: 2584-1610 (Online)

A REVIEW ON THIADIAZOLE-DERIVED COMPOUNDS: DESIGN, SYNTHESIS, AND ANTIMICROBIAL POTENTIAL

Hridesh Singh Chauhan*, Manish Thimmaraju, Jitendra Kumar Malik, Vivek Gupta, Gyan Singh

Faculty of Pharmacy, P.K. University, Thanra - 473665, Shivpuri, Madhya Pradesh, India.

Article History
Received: 07 October 2024
Revised: 12 November 2024
Accepted: 07 January 2025
Published: 25 March 2025

Correspondence should be addressed to
Hridesh Singh Chauhan,
Research Scholar, Faculty of Pharmacy, PK University, Thanra - 473665, Madhya Pradesh, India.

Email- hrideshsingh.006@gmail.com

ABSTRACT: There is increasing demand for new treatment agents in the recent past, attributed to alarming increase in antimicrobial resistance globally. In this confrontation, candidates with broad-spectrum antibacterial performance and a high level of structural variability appeared; one of them is thiadiazole derivatives with the participation of sulfur-nitrogen cycles. That is why they can become a kind of stents for fighting infections that are unaffected by multiple drugs. This review seeks to include the background on thiadiazole derived compounds beginning with the simple heterocyclic derivatives to the potent bioactive agents, and their antibacterial alternatives. Modern fabrication processes in chemistry have embraced microwave assisted synthesis and green chemistry which in molecules' fabrication offer structural variety, great productivity and minimal environmental impact. There is an indication of an important role of functional group changes in increasing the potency of the antibiotics by performing an analysis of the structure-activity relationship (SAR). Other aspects are treated in the review, such as enzyme inhibition, microbial membrane disruption, and the inhibition of biofilm formation. Ongoing challenges include toxicity and bioavailability issues, which for several years have raised questions about the future of new directions like the synthesis of hybrid molecules and the application of nanotechnology. The thiadiazole class of compounds meets the traditional requirements of medicinal chemistry and the new frontiers of today's pharmaceutical industry. In order to proving their value in current antibiotic resistance struggle, this review collects current information and looks at future research possibilities. Thiadiazole molecules can be positioned to radically transform the antimicrobial therapeutics through addressing a significant challenge in the world health care sector by wise chemistry and utilization.

Keywords: Thiadiazole derivatives, Antimicrobial resistance, Synthesis strategies, Structure-activity relationships, Drug design

I. INTRODUCTION

Sulfur and nitrogen containing thiadiazoles are a very interesting group of five membered heterocycles which have come to be widely recognized for their diverse chemical and biological uses [1]. Thiadiazole as a core structural motif is highly extensible in medicinal chemistry as a result of its diverse functionalization applicable by its unique electric and structural characteristics. Owing to low synthesis cost and tight binding to biological targets, the identification of thiadiazoles as a versatile scaffold for designing new drugs. Not all properties of thiadiazole derivatives amaze because of many other purposes they serve; those compounds show a high level of antibacterial activity and can influence various types of microorganisms, such as bacteria, fungi, or even viruses in some cases [2].

However, overuse and misuse of older antimicrobial through social abuse contributed to the worsening of the global AMR in prior years. Multidrug-resistant or 'superbugs' are a problem today because bacteria are developing antibiotics faster than new drugs [3]. Therefore, it has become an emergency for research institutions to develop new treatment medicines with diverse mode of action in view of this perilous situation.

The bioactivity coupled with the availability to modify the chemistry of thiadiazole derivatives make it a reasonable answer to this problem [4]. This review provides a comprehensive study of various derivatives of thiadiazole and its compounds, especially antibacterial properties, synthesis methods, and design concepts [5]. The new synthetic tetrazole async themes are discussed that are retrospective of the newest, less prejudicial to the environment, and exciting new ways to rapidly construct thiadiazole libraries. Optimisation strategies of some functional groups can be learned from rational drug design by closer examination of SAR, modern trends of structure-activity relationships [6]. The paper then continues to explain how thiadiazole chemicals function as antimicrobials such as; by inhibiting enzyme activity, disrupting the microbial cell membranes and interfering with metabolic activities [7]. This work discusses challenges faced by their development including bioavailability, stability, and toxicity issues. Lastly, the author gives some idea about what is in store for the reader by reviewing what has been done so far and how thiadiazoles may be incorporated optimally in the future by the use of nanotechnology, combination therapy, or hybrid molecules [8]. To this end, this study will present current state knowledge to researchers and pharmaceutical developers in a guide manner while focusing on thiadiazole derivatives as one of the key

chemicals in the fight against AMR. It well may be that one of the most pressing problems in the world today can be addressed with thiadiazole based new product development and with focused R & D research [9].

2. Thiadiazole Chemistry and Core Structure

2.1 Overview of Thiadiazole Framework

Thiadiazoles are the five-membered heterocyclic compounds where the ring formed by comprising two nitrogen atoms and one sulfur atom. The electrical structures and/or reactivity of the three most investigated isomers comprising of 1,2,3-thiadiazole, 1,2,4- thiadiazole and 1,3,4-thiadiazole are distinctive. Out of all the given isomers of 1,3,4-thiadiazole, the 1,3,4-thiadiazole isomer of great interest in medicinal chemistry due to its stability and biochemical compatibility [10]. Electron delocalization and Hydrogen bonding are some electrical characteristics of thiadiazoles; each offers extra medicinal value. They have a stiffening property due to their aromatic nature and can engage with biochemical targets through a number of mechanisms such as interacting with the active sites of enzymes or through coordinated metal sequestering. They are more soluble and ease to pass across cell membranes because, their heteraoatoms provide polarity [11].

2.2 Functionalization of Thiadiazoles

Modifications of the thiadiazole ring are also easy to achieve and these modifications can easily lead to formation of products with different physical and biological properties. In general, substitutes allow for the modulation of the antibacterial efficacy by functionalising at positions in the proximity to the heteroatoms [12, 13]. As earlier noted, aryl, amino, halogen and heteroaryl are some of the most common replacements or substituents that must be used to enhance electron density, microbe targets binding or lipophilicity of a given molecule.

The antibacterial activity spectral range of the thiadiazole compounds have been further expanded by modifying the structure. One of the examples of such groups includes halogens, which enhances the activity against the Gram-positive bacteria, and bulky aromatic group which enhance the interaction with bacterial membranes. In addition, through functionalisation, compound hybrids that exhibit summative or potentially additive activity against resistant bacteria to the azoles or quinolones has been incorporated [14]. This is calculated with the help of functionalization which enables thiadiazoles to attain structural diversity – a pointer to their versatility as antimicrobial agents. By the same token, not only can activity be maximised but also other derivatives that may be designed to act on certain pathogens or able to overcome certain resistances may be derived more easily [15].

3. Synthesis Strategies for Thiadiazole-Derived Compounds

3.1 Conventional Synthetic Methods

Traditional routes for the synthesis of thiadiazole derivatives obtain their starting point in cyclization reactions which form the central ring structure. In these classical approaches, thiosemicarbazides, hydrazine derivatives, or isothiocyanates are employed which reacts with different electrophilic agents at desired condition [16]. The chemical procedure common to Thiosemicarbazide is cyclization with carboxylic acids, esters, or acid chlorides in either acidic or basic conditions [17]. An example of this is synthesis of 1,3,4-thiadiazole derivatives using thiosemicarbazides mixed with phosphoryl chloride or acetic acid on heating. The reaction between thiourea derivatives and halogenating agents such as bromine or iodine to form thiadiazoles is also popular [18].

Reaction circumstances such catalysts, temperature and type of solvent can have a direct impact on the efficiency of the reaction and on the yield of the product. Regarding rate accelerations, for instance, workers often select aprotic solvents, which may consist of dimethyl formamide DMF or dimethyl sulfoxide DMSO [19].

Examples of classic synthetic methods include

- **Oxidative Cyclization:** Sulphurisation of thiourea derivatives to thiadiazoles employing reagents such as iodine or hydrogen peroxide [20].
- **Condensation Reactions:** The synthesis of functionalized thiadiazoles without mediated intermediates starting from thiosemicarbazides and aldehydes or ketones [21].

3.2 Recent Advances in Synthesis

Optimization and the ability to create sustainable and cost affective processes were the driving factors behind the modern developments in the synthesis's methods. Many novel methods have been adopted in the synthesis of thiadiazole including flow chemistry, ultrasound-assisted process, microwave assisted synthesis and so on [22].

Microwave-Assisted Synthesis

Microwave irradiation has greatly increased yields while at the same time minimising reaction times since it offers uniform and rapid heating. For instance, 1,3,4-thiadiazole derivatives can be synthesised within few minutes using microwave assisted cyclization of thiosemicarbazides with carbonyl compounds [23].

Green Chemistry Approaches

Stimuli have been given towards green processes including the use of bio-catalysts coupled with biologically friendly solvents like water or ethanol. Ionic liquids and DES are examples of green solvents that are taking a large amount of space in reaction media as a replacement to carcinogenic organic solvents [24].

Ultrasound-Assisted Reactions

Ultrasound irradiation has been utilised in increasing the frequency of molecular collisions to enhance reaction rates. For

instance, synthesis of several thiadiazole derivatives in mild condition from the thiosemicarbazones has been achieved with high rate employing the ultrasonic activation [25].

Flow Chemistry and Continuous Processing

Thus, accurate control of parameters during flow synthesis enables efficient and large-scale preparation of thiadiazole derivatives. Nevertheless, in an industrial application where both speed of production and quality of products matter, this method is highly effective. When implemented, these new approaches improve synthetic efficiency and minimize the environmental footprint as well as overall resource utilization that characterizes green chemistry [26].

Table 1: Comparison of Synthetic Methods for Thiadiazole Derivatives [27]

Synthetic Method	*Reagents/Conditions*	*Yield (%)*	*Reaction Time*	*Scalability*	*Remarks*
Oxidative Cyclization	Thiourea, iodine, ethanol, heating	60–80	3–6 hours	Moderate	Simple but requires halogen-based oxidants.
Cyclization with Acids	Thiosemicarbazides, acetic acid, reflux	50–75	4–8 hours	Moderate	Commonly used, requires high temperatures.
Phosphoryl Chloride Cyclization	Thiosemicarbazides, $POCl_3$, heating	70–90	2–4 hours	High	High yield; efficient for large-scale synthesis.
Microwave-Assisted Cyclization	Thiosemicarbazides, aldehydes, microwave irradiation	80–95	5–20 minutes	High	Rapid synthesis with excellent yields.
Ultrasonic Cyclization	Thiosemicarbazides, acids, ultrasonic bath	65–85	1–2 hours	Low to Moderate	Reduces energy usage; suitable for small-scale synthesis.
Condensation Reactions	Thiosemicarbazides, ketones, acidic catalyst	55–75	6–10 hours	Moderate	Prolonged reaction time; scalable but less efficient.
Halogen-Based Oxidation	Thiourea, bromine, acidic medium	60–78	3–5 hours	Low	Requires careful handling of halogens.
Hydrogen Peroxide Oxidation	Thiourea, H_2O_2, ethanol	70–85	3–4 hours	Moderate	Safer oxidant; moderate scalability.
Solvent-Free Cyclization	Thiosemicarbazides, aldehydes, grinding	75–90	20–40 minutes	High	Green method with no solvent usage; efficient for small-scale production.
Ionic Liquid Catalysis	Thiosemicarbazides, ionic liquid catalyst, heating	80–92	2–5 hours	Moderate	Eco-friendly but high cost of ionic liquids.
Deep Eutectic Solvent Approach	Thiourea, DES, heating	70–88	3–6 hours	Low to Moderate	Sustainable, but still in experimental stages.
Microwave-Assisted Green Methods	Thiosemicarbazides, green solvents, microwave	85–97	5–15 minutes	High	Combines rapid synthesis and eco-friendliness.
Continuous Flow Chemistry	Thiosemicarbazides, acid chlorides, flow reactor	75–90	10–30 minutes	Very High	Industrially scalable; precise control over conditions.
Water-Mediated Cyclization	Thiosemicarbazides, water, mild heating	60–80	6–12 hours	Moderate	Eco-friendly but longer reaction time.
Metal-Free Green Synthesis	Thiosemicarbazides, bio-catalyst, mild conditions	50–70	8–12 hours	Low	Sustainable, but lower yield and longer reaction time.

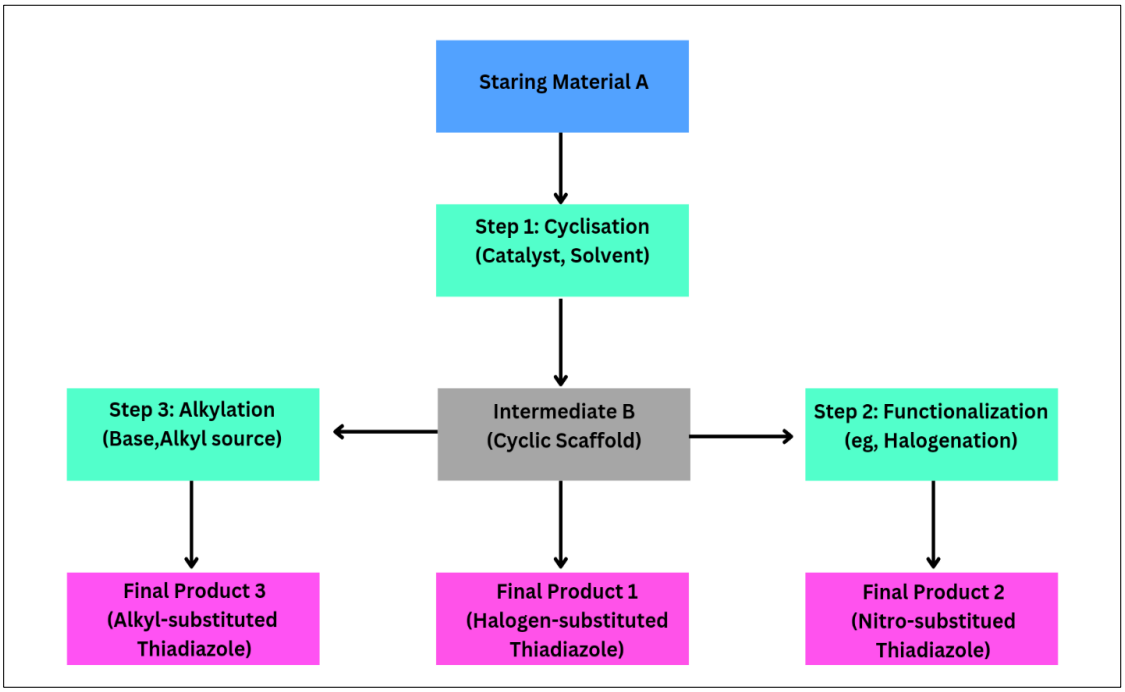

Fig. 1: Flowchart of representative synthetic routes for thiadiazole derivatives. [28]

4. Antimicrobial Potential of Thiadiazole Derivatives

4.1 Antibacterial Activity

Gram positive and negative bacteria are known to be sensitive to antibacterial properties belonging to thiadiazole derivatives. These chemicals have antibacterial action due to their ability to adhere with definite bacterial cell components and affect important biochemical processes [29]. Tiadiazoles are more toxic to S. aureus particularly MRSA than other G +ve bacteria because they can enter into direct contact with the cell membranes and cross the thicker peptidoglycan layer. Thiadiazole derivatives interfere with outer-membrane protein or cell-wall synthesis in Gram-negative organisms comparable to *E. coli* and *P. aeruginosa* [30].

The SAR remains central to controlling how effective thiadiazole derivatives are against bacteria. However, to enhance the effectiveness of the compounds against Gram-negative organisms, it is possible to enhance the bacterial cell membrane permeability by attaching the functional groups such as halogens (fluorine or chlorine) to the positions 4 or 5 of the thiadiazole [31]. To increase the interaction with bacterial DNA or replication-enzyme-related enzymes, electron-withdrawing nitro or cyano groups can be added to the phenyl ring bound to the thiadiazole ring. This in turn raises the electron density. On the other hand, increasing the size of the substituent on the thiadiazole rings and nitrogen atoms leads to higher antibacterial activity due to stronger affinity of the enzymes, DNA gyrase and RNA polymerase, in bacteria [32].

4.2 Antifungal Activity

however, thiadiazole compounds have shown moderate to good level antifungal activity predominantly *Aspergillus flavus, Candida albicans* and *Trichophyton rubrum*. Also, the most widespread method of the usage of antifungal agents is based on the ability to hinder the formation of the fungal cell wall or the destructing of the growing fungal cell membrane [33]. Lanosterol 14α-demethylase is grouped under thiadiazole derivatives which catalyzes fungi enzymes. This enzyme is essential to the biosynthesis of ergosterol – with the help of which the required rigidity of the membranes of fungal cells is maintained, and the necessary fluidity is reached [34].

Scientific work on surface plasmon resonance (SAR) in antifungal studies indicated that groups which attract electrons like fluorine and chlorine might enhance antifungal efficacy through enhancing lipophilicity to increase membrane penetration [35]. Substitution by hydrophobic groups such as alkyl or aryl groups enhances the antifungal efficacy of the compounds under consideration. These groups improve the relations with components on the outer surface of the fungal cell. To enhance the solubility and the antifungal effect of the prepared compounds, the thiadiazole ring may be appended with -OH or NH_2. This it has also been shown that the addition of fused aromatic systems will further draw the ability of the compound to disrupt membranes because of the improved binding affinity of the compounds to fungal sterols [36].

Table 2: Summary of thiadiazole derivatives with their antimicrobial spectrum and potency (MIC or IC_{50} Values) [42]

Thiadiazole Derivative	*Microorganism Tested*	*Antimicrobial Activity*	*MIC (μg/mL) / IC_{50} (μM)*	*Remarks*
1,3,4-Thiadiazole (Compound A)	*Staphylococcus aureus*	Antibacterial	8 μg/mL	Effective against Gram-positive bacteria.
2-Phenyl-1,3,4-thiadiazole (Compound B)	*Escherichia coli*	Antibacterial	16 μg/mL	Potent against Gram-negative bacteria.
4-Fluoro-1,3,4-thiadiazole (Compound C)	*Candida albicans*	Antifungal	12 μg/mL	Effective against Candida species.
5-Nitro-1,3,4-thiadiazole (Compound D)	*Aspergillus flavus*	Antifungal	20 μg/mL	Inhibits fungal growth in vitro.
4-Methyl-1,3,4-thiadiazole (Compound E)	*Pseudomonas aeruginosa*	Antibacterial	10 μg/mL	Active against resistant Gram-negative bacteria.
1-(4-Chlorophenyl)-1,3,4-thiadiazole (Compound F)	*Mycobacterium tuberculosis*	Antibacterial	25 μg/mL	Active against tuberculosis pathogens.
5-Bromo-1,3,4-thiadiazole (Compound G)	*Trichophyton rubrum*	Antifungal	15 μg/mL	Broad-spectrum antifungal activity.
2,5-Dimethyl-1,3,4-thiadiazole (Compound H)	*HIV-1* (in vitro)	Antiviral	IC50 = 5.4 μM	Inhibits HIV reverse transcriptase.
4-Hydroxy-1,3,4-thiadiazole (Compound I)	*Streptococcus pneumoniae*	Antibacterial	18 μg/mL	Strong activity against Gram-positive bacteria.
3-(Pyridin-2-yl)-1,2,4-thiadiazole (Compound J)	*Influenza virus*	Antiviral	IC50 = 7.2 μM	Exhibits antiviral properties against influenza.
1,2,4-Thiadiazole-3-carboxylic acid (Compound K)	*Salmonella typhimurium*	Antibacterial	12 μg/mL	Broad-spectrum antibacterial activity.
5-(Methylthio)-1,3,4-thiadiazole (Compound L)	*Aspergillus niger*	Antifungal	17 μg/mL	Effective against a wide range of fungal pathogens.
2-(Chloromethyl)-1,3,4-thiadiazole (Compound M)	*E. coli*, *S. aureus*	Antibacterial	11 μg/mL	Exhibits selective activity against both Gram-positive and Gram-negative bacteria.
3-(Benzyloxy)-1,3,4-thiadiazole (Compound N)	*Pseudomonas aeruginosa*, *S. aureus*	Antibacterial	8 μg/mL	Broad-spectrum antibacterial activity, effective against MDR strains.
1,3,4-Thiadiazole-2-thiol (Compound O)	*Candida albicans*, *Cryptococcus neoformans*	Antifungal	14 μg/mL	Effective against both yeasts and molds

4.3 Antiviral Properties

The antiviral properties of thiadiazole derivatives are emerging as an interesting area of research, but the development of such compounds as antiviral agents has not been as active as the development of compounds with antibacterial and antifungal activities [37]. Organic thiadiazoles have anti-viral capabilities; HSV, HIV and the influenza virus have been known to be retarded by thiadiazoles. They act against viruses through inhibiting virus replication, through deblocking viral proteases and through inhibition of virus penetration into host cell [38].

For example, thiadiazole derivatives are active against herpes simplex virus since the virus cannot penetrate host cell when the agent is present. The SAR studies show that the antiviral activity increases with the increase of the electron density on the phenyl ring and the 5-position of the thiadiazole ring [39]. This enhancement happens either by inhibiting the viral DNA polymerase enzyme or by increasing the affinity to the viral glycoprotein. Thiadiazoles have similar action on HIV, as it inhibits the reverse transcriptase enzyme, which is crucial for the replication of HIV virus [40].

They substantiate that hydrophobic group functionalization enhanced their ability to cross the lipid bilayer of the host cell and interfere with viral replication. Thiadiazole derivatives exhibit low toxicity, good activity against a wide range of viruses, and represent a new direction for the development of antiviral drugs, but at the same time, research on them is relatively limited [41].

5. Structure-Activity Relationships (SAR) of Thiadiazole Derivatives

In the case of thiadiazole derivatives antibacterial activity is extremely sensitive to the structure activity relationship (SAR). To enhance these molecules for selective antimicrobial activity, modification of the core thiadiazole ring and changes in specific functional groups will prove interesting, as the simple changes can drastically affect biological properties. In this part, the effects of different functional groups on the antibacterial activity of thiadiazole derivatives will be discussed, and the key structural features responsible for such activity will be determined [44].

Impact of Functional Groups on Antimicrobial Activity

1. Halogen Substituents (Cl, F, Br)

An integral part of the thiadiazine ring is to attach halogen atoms at different areas (including 4 or 5 area)—Chlorine, Fluorine and Bromide. These halogens enhance the lipophilicity of the compound, thus permitting enhanced entry into cells across membranes. Especially if the compound contains fluorine, its electronegativity rises, which allows interactions with two bacterial enzymes – gyrase and topoisomerase. The introduction of halogens in the molecule increases the overall efficiency of the molecule to disturb bacterial cell wall or membrane positively charging it for better antibacterial action [45].

2. Electron-Withdrawing Groups (NO_2, CN)

The reactivity is higher towards bacterial nucleic acids and enzymes when the phenyl or thiadiazole is substituted with one or more electron-withdrawing groups (EWGs) such as nitro (NO_2) or cyano (CN) group that withdraw electron density of the molecule. In other areas they help in the inhibition process of DNA replication process or protein synthesis and this in turn increases the antibacterial properties of the drug. Nitro-substituted thiadiazoles act in several ways, but the ability to halt the division of Mycobacterium tuberculosis cells is a primary function [46].

3. Aromatic/Alkyl Groups (Phenyl, Methyl, Ethyl)

Thiadiazoles bearing aromatic or alkyl substituents directly attached to the core structures are more lipophilic, and can transverse the bacterial lipid layers more efficiently especially in Gram-negative bacteria. It has also been established that the addition of methyl or ethyl groups at 2 or at 5 positions on the thiadiazole ring enhances the antibacterial activity either by prolonging the interaction with lipids present in bacterial cell membrane or by opposing various metabolic activities. In addition, large aromatic groups are capable of increasing the measure of antibacterial impact through interaction with bacterial DNA or proteins by π-π stacking effects [47].

4. Hydroxyl (-OH) and Amino ($-NH_2$) Groups

Of course, Positions 2, 3, or 5 on the ring structure, for instance, are the best places for attaching more hydroxyl (-OH) and amino ($-NH_k$) groups, which increase the water solubility and bioavailability. Certain or members of bacterial enzymes or portions of their cell membranes can be improved in binding force and overall functionality by hydrogen bond—forming -OH group. The 3 steps such as the interaction of amino groups with bacterial ribosome or the acivity of enzymes which are crucial in bacterial life may improve the antibacterial efficiency whereby halogen or nitro substituents [48].

5. Thioether and Sulfonyl Groups

Also, the addition of thioether (-S-) or sulfonyl ($-SO_2-$) to the thiadiazole ring serves to increase the interaction profile of the compound with bacterial proteins even further. This sulfur containing functional groups inhibit formation of peptidoglycan and compromise the cell wall stability, more efficient against Gram positive bacteria. Sulfonyl groups appear particularly effective for enhancing the stability and solubility of thiadiazole derivatives and thus, their activity spectrum [49].

Key Pharmacophores and Their Role in Enhancing Potency

The pharmacophore is the essential part of the molecule responsible for its biological activity. In thiadiazole derivatives, the following pharmacophores are critical for their antimicrobial efficacy:

1. Thiadiazole Ring

The biological activity of these compounds depends solely on the thiadiazole ring at the central core of the structure. Notably, nitrogen and sulfur of the ring engage enzymes, and metal ions to break cycles within bacterial cells. Essential to its antibacterial activity is the ability of the thiadiazole ring to chelate biological macromolecules such as nucleic acids or enzymes by means of hydrogen bonding and π-cation stacking [50].

2. Aromatic/Alkyl Substituents

This is because the groups of aromatic or alkyl linked to the thiadiazole ring bring the compound close enough to make the interaction with the hydrophobic regions of bacterial enzymes or membrane proteins. Ability to increase the compounds solubility is something these substituents can do, which is a key factor to increase bioavailability in vivo [51].

3. Functional Groups (Halogens, Nitro, Amino)

Halogenated, nitro and amino substituted thiadiazole rings have tunable electrical properties based on the position of the substituents on the rings, these properties can be optimised to enhance interaction with DNA, bacterial cell membrane and enzymes. These alterations not only improve the antibacterial activity, but also the scope of action, make thiadiazole derivatives effective against not only bacteria but also fungi and viruses, both Gram-positive and Gram-negative [52].

4. Sulfur and Oxygen-Based Modifications

Thioether and sulfonyl groups on the thiadiazole ring interfere with bacterial proteins or cell wall formation especially with Gram positive bacteria. These changes also enhance the stability and solubility of the thiadiazole derivatives in which make them better for pharmed formulations [53].

6. Challenges and Future Perspectives

6.1 Challenges in Synthesis and Biological Evaluation

The development and optimization of thiadiazole-derived compounds for antimicrobial applications face several significant challenges that need to be addressed for better therapeutic outcomes:

1. Synthetic Complexity

Despite such achievements, thiadiazole derivative synthesis often poses challenges as a result of the need to effect precise functional group transformations and to form the heterocyclic nucleus. In specific, the synthesis of multi-substituted thiadiazoles, especially of moiety 2, may require time-consuming and experimentally laborious procedures that involve multiple steps to obtain the compounds of desirable yield and high purity. Some synthetic methods involve toxic reagents or exceedingly severe reaction conditions, which may also cause some methods to be applied on an industrial scale. But it remains equally important to strive for the development of synthetic strategies that are more efficient, greener, and easily large scale-able [54].

2. Poor Bioavailability and Solubility

Tiadiazole derivatives could be potentially good antibacterial drugs but the problem always arises with their solubility which significantly affects their bioavailability. A number of these chemicals are insoluble in water and its implication is that the oral/intravenous administration of several of these chemicals is difficult to affect. Thus, in order to receive the necessary concentrations in living organisms, we may need to introduce enormous amounts of them, which leads to the toxic effects. Secondly, the therapeutic efficacy of the active ingredient can be reduced simply because its plasma levels are not sufficient because of poor bioavailability. Therapeutic effects of thiadiazole derivatives require increased solubility, stability, and bioavailability improvements. Such approaches can embrace designing of prodrug approaches, or using solubility enhancing/accessibility agents [55].

3. Antimicrobial Resistance

The other challenge is in relation to the possible emergence of resistance to thiadiazole derivatives. However, since these chemicals can affect life in many ways, one can envisage that microbes can also become resistant to them. Worse thiadiazole-based treatments could be developed if mechanisms of drug resistance, as for example modification of the drug target, activation of efflux pumps, or enzymatic drug degradation are to appear. Therefore, to ensure the long-term efficacy of thiadiazole derivatives, constant resistance pattern observation is important [56].

4. *In Vivo* Toxicity and Side Effects

Even though new thiadiazole compounds may show high antibacterial activity in vitro their toxicity in vivo can become a problem. Certain functional groups of these compounds produce unwanted reactions or organ toxicity when administered at high dosages, and as such, their toxicity has to be evaluated. Thiadiazole derivatives could only be considered for an administration trial, after evaluating the safety of thiadiazole derivatives for the intended treatments of the diseases through preclinical studies using suitable animal models and in vitro toxicity test [57].

6.2 Future Directions in Research

Despite the challenges, research into thiadiazole-derived compounds continues to evolve, with several emerging trends and strategies offering promising avenues for enhancing their therapeutic potential:

1. Hybrid Thiadiazole Molecules

The concept of developing multitarget-directed ligands through the integration of the multiple pharmacophores into the central thiadiazole core warrants optimism. One chemical that could be employed in combating resistant bacteria is a thiadiazole–

antimicrobial hybrid product; β-lactams; quinolines; or peptides. It is postulated that these chemicals may synergistically enhance the efficacy, reduce bacterial resistance and expand the antibacterial spectrum [58].

2. Nanotechnology in Drug Delivery

Thiadiazole derivatives and other bioactive chemicals are generally characterized by low solubility and bioavailability; though nanotechnology has emerged as a solution to this problem. To improve solubility, stability and competent release of thiadiazole derivatives, new nanoformulation that may include lipid nanoparticle, micelles or polymeric nanoparticle can be prepared and incorporated in the formulations. Pharmacokinetics of thiadiazole derivatives may be sustained with nanocarriers resulting in reduced toxicity and enhanced therapeutic efficacy. Graphene based materials or metal-organic frameworks (MOFs) based nanocarriers for thiadiazole derivatives increase their antibacterial activity [59].

3. Combinatorial Approaches for Drug Discovery

The concern has emerged whether it is possible to use thiadiazole derivatives together with other kinds of antibacterial drugs. In the context of combinatorial drug design; further research should be carried out to determine if thiadiazole derivatives exhibit any synergistic interactions with other antifungal or antibiotic compounds. Relative to other traditional treatment approaches, this method may improve the effectiveness of treatment as well as slow down the rate at which strains of microbes evolve resistance to the drugs. Research may also be able to further dilute each chemical since they work optimally with other chemicals in order to ensure efficacy extra of their side effects [60].

4. Targeting Specific Bacterial Enzymes or Pathways

Scientists are now focusing on developing new thiadiazole molecules that either inhibit hitherto untargeted bacterial enzymes or interfere with the resistance mechanism. For example, thiadiazoles which act on bacterial protein synthesis or which affect the biosynthesis of bacterial cell wall have proved promising. Any future work may occur in the design of compounds that inhibit bacterial efflux pump or other mechanisms of resistance that diminish the effectiveness of regular antibiotics [61].

5. Exploring Antiviral and Antifungal Potential

While the antibacterial properties of thiadiazole have dominated numerous more recent studies, new evidence points that these derivatives are also valuable as antiviral and antifungal agents. Thiadiazole derivatives for viruses including HIV, herpes simplex, and influenza, as well as fungi like Candida albicans and Aspergillus can be enhanced as the next direction for research. Since the emergence of resistant to the antiviral drugs in the recent past is becoming a serious issue thiadiazole derivative may offer a better prospect with regard to viruses [62].

CONCLUSION

Studies have revealed that thiadiazole based compounds have very high potential for use as antimicrobial since they are effective on bacteria, fungi, and viral infections. These compounds have substantial antibacterial activity due to the inherent uniqueness of the thiadiazole ring and the versatility of the functional group modifications. The task is improving the quality characteristics of such compounds such as potency, solubility, and stability, which would assist with defeating a new issue of microbial resistance.

As derived from some important findings of this review, certain structural modifications such as halogenation, electron with drawing groups or functional group substitutions can significantly alter the biological potency of thiadiazole derivatives. These changes make them more therapeutically useful since the alterations in their pharmacokinetics make them more effective against bacteria and fungi. Additionally, a possibility to increase the effectiveness of the treatment by avoiding the discovered resistance mechanisms may be considered in further development of the hybrid molecule design or in combinatorial approaches based on incorporating thiadiazole derivatives and other antimicrobial agents.

However, even though thiadiazole derivatives appear to demonstrate considerable potential, there remain challenges that must be met before the full therapeutic potential of the compounds can be fully realised. These are synthetic complexity, low bioavailability, and the emergence of resistance to them. If these molecules are to be developed further, there has to be advancement in synthetic chemistries, drug delivery nano technologies and strategizing of the identified microbial enzymes or modes of resistance.

Last but not least, thiadiazole derivatives are the new attractive entry for the field of infection management, which can be referred to as a versatile and potent group of antimicrobials. The long-term problem of clinical efficiency of these compounds and the global crises of antimicrobial resistance means that constant research and favourable developments in their design, synthesis and delivery will be required.

ACKNOWLEDGEMENT: Nil

CONFLICT OF INTEREST: Nil

REFERENCES:

1. Shrivastava K, Purohit S, Singhal S. Studies on nitrogen and sulphur containing heterocyclic compound: 1, 3, 4-thiadiazole. Asian J. Biomed. Pharm. Sci. 2013 Jul 10;3(21):18.
2. Babalola BA, Sharma L, Olowokere O, Malik M, Folajimi O. Advancing drug discovery: Thiadiazole derivatives as multifaceted agents in medicinal chemistry and pharmacology. Bioorganic & Medicinal Chemistry. 2024 Aug 16:117876.
3. Khan SN, Khan AU. Breaking the spell: combating multidrug resistant 'superbugs'. Frontiers in microbiology. 2016 Feb 18;7:174.

4. Ahmad S, Alam MZ, Salma U, Mohasin M, Rahaman PF, Parveen H, Khan SA. A review on recent progress in synthesis and biological activities of thiadiazole and its derivatives. Journal of Molecular Structure. 2024 Apr 23:138438. https://www.sciencedirect.com/science/article/abs/pii/S002228602400958X
5. Hu Y, Li CY, Wang XM, Yang YH, Zhu HL. 1, 3, 4-Thiadiazole: synthesis, reactions, and applications in medicinal, agricultural, and materials chemistry. Chemical reviews. 2014 May 28;114(10):5572-610. https://pubs.acs.org/doi/full/10.1021/cr400131u
6. Kumar D, Aggarwal N, Kumar V, Chopra H, Marwaha RK, Sharma R. Emerging synthetic strategies and pharmacological insights of 1, 3, 4-thiadiazole derivatives: A comprehensive review. Future Medicinal Chemistry. 2024 Mar 1;16(6):563-81.
7. Jain AK, Sharma S, Vaidya A, Ravichandran V, Agrawal RK. 1, 3, 4-Thiadiazole and its derivatives: A review on recent progress in biological activities. Chemical biology & drug design. 2013 May;81(5):557-76.
8. Knall AC, Slugovc C. Inverse electron demand Diels–Alder (iEDDA)-initiated conjugation: a (high) potential click chemistry scheme. Chemical Society Reviews. 2013;42(12):5131-42.
9. Bhati S. Synthesis, characterization, antimicrobial screening and in-silico studies of thiadiazole derivatives. Journal of Molecular Structure. 2024 Nov 15;1316:138793. https://doi.org/10.1016/j.molstruc.2024.138793
10. Moussa Z, Paz AP, Judeh ZM, Alzamly A, Saadeh HA, Asghar BH, Alsaedi S, Masoud B, Almeqbaali S, Estwani S, Aljaberi A. First X-ray Crystal Structure Characterization, Computational Studies, and Improved Synthetic Route to the Bioactive 5-Arylimino-1, 3, 4-thiadiazole Derivatives. International journal of molecular sciences. 2023 Feb 13;24(4):3759.
11. Pakulski P, Pinkowicz D. 1, 2, 5-Thiadiazole 1, 1-dioxides and their radical anions: structure, properties, reactivity, and potential use in the construction of functional molecular materials. Molecules. 2021 Jan;26(16):4873. https://doi.org/10.3390/molecules26164873
12. Asif M. Chemistry, synthesis and progress report on biological activities of thiadiazole compounds-a review. Mediterranean Journal of Chemistry. 2016 Jun 25;5(5):568-88.
13. Irfan A, Ullah S, Anum A, Jabeen N, Zahoor AF, Kanwal H, Kotwica-Mojzych K, Mojzych M. Synthetic transformations and medicinal significance of 1, 2, 3-thiadiazoles derivatives: An update. Applied Sciences. 2021 Jun 21;11(12):5742.
14. Dong A, Wang YJ, Gao Y, Gao T, Gao G. Chemical insights into antibacterial N-halamines. Chemical reviews. 2017 Mar 22;117(6):4806-62.
15. Khamitova Ц1, Berillo D, Lozynskyi A, Konechnyi Y, Mural D, Georgiyants V, Lesyk R. Thiadiazole and thiazole derivatives as potential antimicrobial agents. Mini Reviews in Medicinal Chemistry. 2024 Mar 1;24(5):531-45.
16. Aly AA, Hassan AA, AbdEl-latief ES. An update of the use of thiocarbohydrazides and thiosemicarbazides in the preparation of heterocycles and their biological importance. Journal of Heterocyclic Chemistry. 2018 Oct;55(10):2196-223.
17. Majumdar P, Pati A, Patra M, Behera RK, Behera AK. Acid hydrazides, potent reagents for synthesis of oxygen-, nitrogen-, and/or sulfur-containing heterocyclic rings. Chemical reviews. 2014 Mar 12;114(5):2942-77.
18. Kokovina TS, Gadomsky SY, Terentiev AA, Sanina NA. A novel approach to the synthesis of 1, 3, 4-thiadiazole-2-amine derivatives. Molecules. 2021 Aug 25;26(17):5159. https://doi.org/10.3390/molecules26175159
19. Varghese JJ, Mushrif SH. Origins of complex solvent effects on chemical reactivity and computational tools to investigate them: a review. Reaction Chemistry & Engineering. 2019;4(2):165-206.
20. Aljamali NM. Survey on methods of preparation and cyclization of heterocycles. International Journal of Chemical and Molecular Engineering. 2020 Dec 16;6(2):19-36p.
21. Ibrahim AM, Shoman ME, Mohamed MF, Hayallah AM, El-Din A. Abuo-Rahma G. Chemistry and applications of functionalized 2, 4-thiazolidinediones. European Journal of Organic Chemistry. 2023 May 12;26(19):e202300184. https://doi.org/10.1002/ejoc.202300184
22. Meramo-Hurtado SI, González-Delgado ÁD. Process synthesis, analysis, and optimization methodologies toward chemical process sustainability. Industrial & Engineering Chemistry Research. 2021 Mar 10;60(11):4193-217.
23. Majhi S, Mitra P, Mondal PK. Green Synthesis of Thiazoles and Thiadiazoles having Anticancer Activities under Microwave Irradiation. Current Microwave Chemistry. 2024 Sep;11(2):74-94.
24. Migowski P, Lozano P, Dupont J. Imidazolium based ionic liquid-phase green catalytic reactions. Green Chemistry. 2023;25(4):1237-60.
25. Sahoo BM, Banik BK, Tiwari A, Tiwari V, Mahapatra MK. Greener Approaches for Synthesis of Bioactive Thiadiazole Scaffolds. Current Organocatalysis. 2023 Sep 1;10(3):237-49.
26. Pirotte G, Agarkar S, Xu B, Zhang J, Lutsen L, Vanderzande D, Yan H, Pollet P, Reynolds JR, Maes W, Marder SR. Molecular weight tuning of low bandgap polymers by continuous flow chemistry: increasing the applicability of PffBT4T for organic photovoltaics. Journal of Materials Chemistry A. 2017;5(34):18166-75. https://pubs.rsc.org/en/content/articlelanding/2017/ta/c7ta05627c/unauth
27. El-Masry RM, Kadry HH, Taher AT, Abou-Seri SM. Comparative study of the synthetic approaches and biological activities of the bioisosteres of 1, 3, 4-oxadiazoles and 1, 3, 4-thiadiazoles over the past decade. Molecules. 2022 Apr 22;27(9):2709.
28. Eissa IH, Elgammal WE, Mahdy HA, Zara S, Carradori S, Husein DZ, Alharthi MN, Ibrahim IM, Elkaeed EB, Elkady H, Metwaly AM. Design, synthesis, and evaluation of novel thiadiazole derivatives as potent VEGFR-2 inhibitors: a comprehensive *in vitro* and in silico study. RSC advances. 2024;14(48):35505-19. https://doi.org/10.1039/D4RA04158E
29. Serban G, Stanasel O, Serban E, Bota S. 2-Amino-1, 3, 4-thiadiazole as a potential scaffold for promising antimicrobial agents. Drug design, development and therapy. 2018 May 31:1545-66.
30. De Benedetti S, Fisher JF, Mobashery S. Bacterial cell wall: Morphology and biochemistry. InPractical Handbook of Microbiology 2021 May 4 (pp. 167-204). CRC Press. https://www.taylorfrancis.com/chapters/edit/10.1201/9781003099277-20
31. Guo J, Xie Z, Ruan W, Tang Q, Qiao D, Zhu W. Thiazole-based analogues as potential antibacterial agents against methicillin-resistant Staphylococcus aureus (MRSA) and their SAR elucidation. European Journal of Medicinal Chemistry. 2023 Nov 5;259:115689.

32. Sayiner HS, Yilmazer MI, Abdelsalam AT, Ganim MA, Baloglu C, Altunoglu YC, Gür M, Saracoglu M, Attia MS, Mahmoud SA, Mohamed EH. Synthesis and characterization of new 1, 3, 4-thiadiazole derivatives: study of their antibacterial activity and CT-DNA binding. RSC advances. 2022;12(46):29627-39.
33. Khan MS, Ahmad I. Antifungal activity of essential oils and their synergy with fluconazole against drug-resistant strains of Aspergillus fumigatus and Trichophyton rubrum. Applied microbiology and biotechnology. 2011 May;90:1083-94.
34. Singh A, Singh K, Sharma A, Kaur K, Chadha R, Bedi PM. Recent advances in antifungal drug development targeting lanosterol 14α-demethylase (CYP51): A comprehensive review with structural and molecular insights. Chemical Biology & Drug Design. 2023 Sep;102(3):606-39.
35. Mousavi SM, Hashemi SA, Kalashgrani MY, Rahmanian V, Gholami A, Chiang WH, Lai CW. Biomedical applications of an ultra-sensitive surface plasmon resonance biosensor based on smart MXene quantum dots (SMQDs). Biosensors. 2022 Sep 9;12(9):743.
36. Bhandare RR, Munikrishnappa CS, Kumar GS, Konidala SK, Sigalapalli DK, Vaishnav Y, Chinnam S, Yasin H, Al-Karmalawy AA, Shaik AB. Multistep synthesis and screening of heterocyclic tetrads containing furan, pyrazoline, thiazole and triazole (or oxadiazole) as antimicrobial and anticancer agents. Journal of Saudi Chemical Society. 2022 May 1;26(3):101447.
37. Farghaly TA, Alsaedi AM, Alenazi NA, Harras MF. Anti-viral activity of thiazole derivatives: an updated patent review. Expert opinion on therapeutic patents. 2022 Jul 3;32(7):791-815.
38. Singh IP, Gupta S, Kumar S. Thiazole compounds as antiviral agents: An update. Medicinal Chemistry. 2020 Feb 1;16(1):4-23.
39. Laxmikeshav K, Kumari P, Shankaraiah N. Expedition of sulfur-containing heterocyclic derivatives as cytotoxic agents in medicinal chemistry: A decade update. Medicinal Research Reviews. 2022 Jan;42(1):513-75.
40. Berdis AJ. DNA polymerases as therapeutic targets. Biochemistry. 2008 Aug 12;47(32):8253-60.
41. Nieto-Garai JA, Contreras FX, Arboleya A, Lorizate M. Role of protein–lipid interactions in viral entry. Advanced Biology. 2022 Mar;6(3):2101264.
42. Mhaidat NM, Al-Smadi M, Al-Momani F, Alzoubi KH, Mansi I, Al-Balas Q. Synthesis, antimicrobial and in vitro antitumor activities of a series of 1, 2, 3-thiadiazole and 1, 2, 3-selenadiazole derivatives. Drug Design, Development and Therapy. 2015 Jul 16:3645-52.
43. Verma SK, Verma R, Verma S, Vaishnav Y, Tiwari SP, Rakesh KP. Anti-tuberculosis activity and its structure-activity relationship (SAR) studies of oxadiazole derivatives: A key review. European Journal of Medicinal Chemistry. 2021 Jan 1;209:112886.
44. Atmaram UA, Roopan SM. Biological activity of oxadiazole and thiadiazole derivatives. Applied microbiology and biotechnology. 2022 May;106(9):3489-505.
45. Holla BS, Sarojini BK, Rao BS, Akberali PM, Kumari NS, Shetty V. Synthesis of some halogen-containing 1, 2, 4-triazolo-1, 3, 4-thiadiazines and their antibacterial and anticancer screening studies—Part I. Il Farmaco. 2001 Aug 1;56(8):565-70.
46. Kaur K, Utreja D, Dhillon NK, Anupam, Buttar HS. Heterocyclic moieties as prospective nematicides: an overview. Current Organic Chemistry. 2022 Sep 1;26(18):1703-24.
47. Nancy DK, Soam A. A Review On Anti-Bacterial Activity Of Substituted Azetidinone, Benzothiazole, Thiazole, Thiadiazole, Triazole, Triazolothiazole And Naphthalene Derivatives. Journal of Survey in Fisheries Sciences. 2022;8(2):634-75.
48. Ghosh I, Nau WM. The strategic use of supramolecular pKa shifts to enhance the bioavailability of drugs. Advanced drug delivery reviews. 2012 Jun 15;64(9):764-83. https://doi.org/10.1016/j.addr.2012.01.015
49. Wang F, Yang BX, Zhang TH, Tao QQ, Zhou X, Wang PY, Yang S. Novel 1, 3, 4-oxadiazole thioether and sulfone derivatives bearing a flexible N-heterocyclic moiety: Synthesis, characterization, and anti-microorganism activity. Arabian Journal of Chemistry. 2023 Feb 1;16(2):104479. https://doi.org/10.1016/j.arabjc.2022.104479
50. Zhang L, Peng XM, Damu GL, Geng RX, Zhou CH. Comprehensive review in current developments of imidazole-based medicinal chemistry. Medicinal research reviews. 2014 Mar;34(2):340-437. https://doi.org/10.1002/med.21290
51. Li Y, Geng J, Liu Y, Yu S, Zhao G. Thiadiazole—A promising structure in medicinal chemistry. ChemMedChem. 2013 Jan;8(1):27-41.
52. Yusuf M, Khan RA, Khan M, Ahmed B. Stereo-Electronic, Molecular Connectivity, and Geometric Configuration Approaches towards Designing Antibacterial Agents from 1, 3, 4-Thiadiazole as the Starting Molecular Template. ChemistrySelect. 2017 Feb 1;2(4):1323-35.
53. Nancy DK, Soam A. A Review On Anti-Bacterial Activity Of Substituted Azetidinone, Benzothiazole, Thiazole, Thiadiazole, Triazole, Triazolothiazole And Naphthalene Derivatives. Journal of Survey in Fisheries Sciences. 2022;8(2):634-75.
54. Besson T, Brain CT. Heterocyclic chemistry using microwave-assisted approaches. Microwave assisted organic synthesis. 2005 May 24:44-74.
55. Rusu A, Moga IM, Uncu L, Hancu G. The role of five-membered heterocycles in the molecular structure of antibacterial drugs used in therapy. Pharmaceutics. 2023 Nov;15(11):2554.
56. Rodrigues L, Cravo P, Viveiros M. Efflux pump inhibitors as a promising adjunct therapy against drug resistant tuberculosis: a new strategy to revisit mycobacterial targets and repurpose old drugs. Expert review of anti-infective therapy. 2020 Aug 2;18(8):741-57.
57. Rashdan HR, Abdelrahman MT, Shehadi IA, El-Tanany SS, Hemdan BA. Novel thiadiazole-based molecules as promising inhibitors of black fungi and pathogenic bacteria: in vitro antimicrobial evaluation and molecular docking studies. Molecules. 2022 Jun 4;27(11):3613.
58. Hu X, Zhang H, Wang Y, Shiu BC, Lin JH, Zhang S, Lou CW, Li TT. Synergistic antibacterial strategy based on photodynamic therapy: Progress and perspectives. Chemical Engineering Journal. 2022 Dec 15;450:138129.
59. Patel S, Mishra S. Synthesis of bile acid-thiadiazole conjugates as antibacterial and antioxidant agents. Steroids. 2023 Oct 1;198:109273.
60. Aziz DM, Hassan SA, Amin AA, Qurbani K, Aziz SB. A synergistic investigation of azo-thiazole derivatives incorporating thiazole moieties: a comprehensive exploration of their synthesis, characterization, computational insights, solvatochromism, and multimodal biological activity assessment. RSC advances. 2023;13(49):34534-55.

61. Dawood KM, Farghaly TA. Thiadiazole inhibitors: a patent review. Expert opinion on therapeutic patents. 2017 Apr 3;27(4):477-505.

62. Husain A, Asif M, Bhutani R, Dutta M. Triazolothiadiazoles as antimicrobial agent: a short riview. World Journal of Pharmaceutical Sciences. 2013 Dec 3;1(4):138-50.

How to Cite this article:
Chauhan HS, Thimmaraju M, Malik JK, Gupta V, Singh G. A review on thiadiazole-derived compounds: design, synthesis, and antimicrobial potential. International Journal of Pharmaceutical Science and Medicine 2025; 3(1): 43-52.