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PHARMACOLOGICAL EVALUATION OF 1,3,4- THIADIAZOLE ANALOGUES

Hemant Dhakne*[1], Sandhya Dhurve[1], Rakesh Chaudhary[2], Diksha Dhandge[2], Yojna Dhuri[3], Sonal Dhonar[3]

*[1]B. R. Harne College of Pharmacy, Karav, Vangani, Next Station, After, Tq, Badlapur, Ambernath, Maharashtra 421503.

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***Corresponding Author**
Hemant Dhakne
B. R. Harne College of Pharmacy, Karav, Vangani, Next Station, After, Tq, Badlapur, Ambernath, Maharashtra 421503.

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ABSTRACT

The 1,3,4-thiadiazole ring stands out as a highly valuable heterocyclic structure in modern drug discovery due to its unique electronic characteristics, flexible tautomerism, and ability to act as a bioisostere. Over recent years, it has served as a foundation for designing compounds with diverse pharmacological activities, such as antimicrobial, anticancer, antidiabetic, anti-inflammatory, antioxidant, and anticonvulsant effects. Advances in synthesis from traditional thiosemicarbazide cyclization to modern green and solvent-free techniques have enabled the development of structurally varied analogues with improved pharmacological performance. Detailed spectroscopic and structure–activity studies have helped clarify how different substituents influence biological activity. Clinically approved drugs like acetazolamide, sulfamethizole, and filanesib further highlight the therapeutic relevance of this scaffold. This review aims to summarize recent progress in the synthesis, bioactivity, and mechanism of 1,3,4- thiadiazole derivatives, emphasizing their continued significance as promising building blocks for future drug development.

KEYWORDS: 1,3,4 thiadiazole, Anti microbial, Anti oxidant, Anti bacterial, Anti cancer.

1. INTRODUCTION

Heterocyclic chemistry plays a crucial role in drug development and discovery, with nitrogen and sulfur containing heterocycles showing significant biological and pharmaceutical importance. Amongest them, 1,3,4-thiadiazoles have appeared as versatile or multifaceted scaffolds due to their wide range of pharmacological and physicochemical properties, as well as synthetic accessibility. These heterocycles were first reported back in the 19th century, and continued to attract attention for their latent applications in medicinal, agricultural, and material sciences.[1,2]

The compound $C_2H_2N_2S$ having molecular weight ~86.11 g/mol is meticulously named 2,3-dihydro-1,3,4- thiadiazole-2-thione according to IUPAC nomenclature.[17] It belongs to the aromatic heterocyclic class which is characterized by a five-membered ring containing two nitrogen atoms and one sulfur atom, imparting unique electronic properties. These structural features promote strong intermolecular interactions and allow for bioisosteric replacement with other heterocycles such as oxadiazoles and triazoles, making thiadiazoles important pharmacophores in drug design and optimization strategies.[3,5] The chemical structure can be represented in different forms, including ball-and-stick models, which help visualize the spatial arrangement of atoms and bonds in the molecule (Fig. 1).[3]

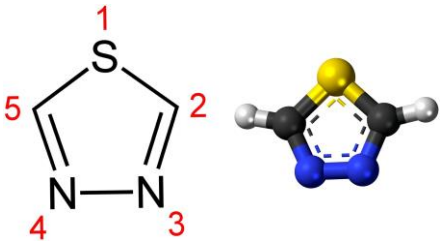


Figure 1: Chemical structure with ball and stick model for 1,3,5 thiadiazole.[3]

of the four thiadiazole isomers 1,2,3-thiadiazole; 1,2,4-thiadiazole; 1,2,5-thiadiazole; and 1,3,4-thiadiazole; the 1,3,4-isomer has demonstrated superior relevance in medicinal and biological applications(Fig.2).[1]

Figure 2: Isomers of 1,3,4 thiadiazole.[1]

The isomer of 1,3,4-thiadiazole was first reported by Fischer in 1882 and later explored by Bush et al., with its structure conclusively elucidated by Goerdler et al. in 1956.[2] The evolution of thiadiazole chemistry was greatly influenced by the discovery of sulfonamide drugs and mesoionic compounds, which inspired extensive exploration of heterocyclic scaffolds with therapeutic potential. Substituted thiadiazoles containing functional groups such as mercapto, hydroxyl, or amino moieties demonstrate tautomeric flexibility, enhancing their reactivity and biological significance.[2]

Over the decades, 1,3,4-thiadiazole derivatives have attracted immense interest due to their wide range of pharmacological activities, including antibacterial, antifungal, anticancer, antiviral, anti-inflammatory, analgesic, and anticonvulsant effects.[1,5–7] Their versatility arises from their ability to interact with diverse biological targets, positioning them as potential leads in drug discovery and design.[10–13] In addition to their biological value, thiadiazoles exhibit unique chemical behaviors such as keto–enol tautomerism, influencing molecular stability and activity profiles.[14–16]

Recent advancements have focused on the development of efficient, eco-friendly, and chemoselective synthesis routes employing elemental sulfur and easily available precursors, consistent with green chemistry principles. Such methods have expanded the chemical diversity of thiadiazoles, facilitating their integration into modern pharmaceutical research. Several reviews have since summarized their synthesis and bioactivity, highlighting the growing pharmacological scope of this nucleus.[19]

India has played a pivotal role in advancing thiadiazole research, with scientists developing innovative synthetic routes and bioactive analogs using cyclization, condensation, and hybridization techniques.[17]

S. N. Pandeya et al. at IIT BHU have made notable contributions, designing thiadiazole-based antitubercular, anticancer, anticonvulsant, antibacterial, and anti-HIV agents that serve as key templates for further modification.[18] Indian researchers have also targeted diseases of national concern, including tuberculosis, leishmaniasis, and drug-resistant infections, through cost-effective and sustainable synthetic approaches.[19]

Several studies further highlight the antibacterial, anti-inflammatory, anticancer, and antidiabetic potential of novel thiadiazole derivatives, reinforcing their therapeutic

versatility.[27,29–38,83] Consequently, 1,3,4- thiadiazoles remain an essential heterocyclic framework with expanding relevance in both medicinal chemistry and global health innovation.

1.1.Pharmacological and Disease Targets

Recent literature has cataloged the therapeutic versatility of 1,3,4-thiadiazoles across a wide range ofdisease states:

1.1.1. Anticancer Activity

Indelicato et al. (2025) reviewed thiadiazole-based anticancer agents developed over the last five years. Notably, 2,5-disubstituted derivatives exhibit nanomolar-range GI_{50} values, targeting cancers such asbreast, ovarian, and pancreatic tumors. These compounds act through various mechanisms like kinase inhibition, microtubule destabilization, and interference with DNA replication stress responses, etc.[11]

1.1.2. Antidiabetic and Metabolic Disorders

Thiadiazole derivatives have shown promising activity against metabolic disease. Vaishnav et al. (2017) highlighted theirstrong inhibitory activity against α-glucosidase and α-amylase enzymes, along with prominent in-vivohypoglycemic effects in animal models.[21]

1.1.3. Antimicrobial and Antitubercular Applications

Multiple studies underscore the antimicrobial capabilities of thiadiazole derivatives. Pal et al. (2020) reported antifungal efficacy against phytopathogenic fungi, while Chandurwala (2025) documented broad-spectrum antimicrobial and antitubercular effects, including activity against drug- resistant Mycobacterium tuberculosis strains.[20,22]

1.1.4. Anti-inflammatory Activity

Jadhav et al. (2008) in their studies stated several derivatives exhibited significant inhibition incarrageenan- induced rat paw edema model, suggesting that the imidazo-thiadiazole scaffold holdspotential as a novel anti-inflammatory pharmacophore.[23]

1.1.5. Antioxidant Activity

Swapna et al. (2013) synthesized a series of sulfonamidomethane-linked 1,3,4-oxadiazoles and 1,3,4-thiadiazoles and studied them for antioxidant potential. Various derivatives showed significant freeradical scavenging activity in DPPH and ABTS assays, indicating the effectiveness of these heterocycles aspromising antioxidant agents.[24]

1.2.Marketed Drugs and Clinical Relevance

Several clinically important drugs contain the 1,3,4-thiadiazole nucleus, reflecting its broad therapeutic potential. For instance, acetazolamide and methazolamide act as carbonic anhydrase inhibitors used to treat glaucoma, altitude sickness, and edema. Sulfamethizole, a sulfonamide antibiotic, inhibits dihydropteroate synthase, while desaglybuzole serves as a hypoglycemic agent. Additionally, litronesib and filanesib are anticancer candidates targeting kinesin spindle proteins. These examples collectively highlight the scaffold's clinical significance and commercial viability.[11]

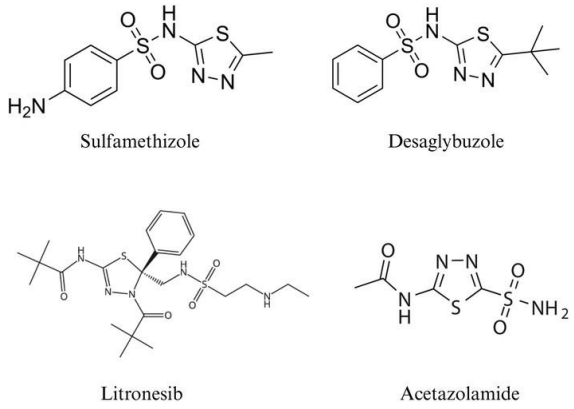


Figure 3: FDA approved marketed preparations having 1,3,4 thiadiazole nucleus.[11]

2. Spectroscopic Characterization

Spectral characterization indicates to the use of various analytical techniques based on the interaction of theelectromagnetic radiation with matter to elucidate the molecular structure, chemical environment, functional groups, and electronic transitions of compounds.[16] Methods such as Nuclear Magnetic Resonance (NMR), Infrared (IR), Fourier Transform Infrared (FTIR), UV–Visible spectroscopy, andMass Spectrometry (MS) offer comprehensive insights into the identity and purity of chemical substances.[16]

Spectral characterization plays a important role in structural validation, particularly for heterocycliccompounds like 1,3,4-thiadiazole derivatives, where tautomerism, substitution patterns, and electrondistribution can widely affect both spectral properties and biological activity.[25]

2.1.Infrared and FTIR Spectroscopy

IR and FTIR spectroscopy serve as powerful tools for identifying functional groups and exploring molecular vibrations in thiadiazole derivatives.[25] In one study, Mohamed et al. conducted detailed spectroscopic and DFT-based analysis of 2-amino-5-(ethylthio)-1,3,4-

thiadiazole, revealing strong NH_2 stretching at 3425 cm^{-1} and C=N stretching near 1616 cm^{-1}. The compound exhibited a planar conformation stabilized by intramolecular hydrogen bonding, and the close agreement between experimental and theoretical frequencies confirmed the reliability of the predicted molecular geometry.[28]

Similarly, Thirunarayanan et al.[26] investigated benzylidene-5-ethyl-1,3,4-thiadiazole-2-amines and reported substituent-dependent shifts in C=N (1600–1620 cm^{-1}) and C–S (680–740 cm^{-1}) stretching bands, with electron-withdrawing groups causing frequency reductions due to altered electron density in the thiadiazole ring. These variations highlighted the influence of resonance and inductive effects on vibrational behavior. Furthermore, Burdzinski et al. utilized ultrafast time-resolved IR spectroscopy to monitor the photochemistry of 1,2,3-thiadiazole, observing rapid (~500 fs) decay of the excited state and formation of a nitrene intermediate, followed by N_2 extrusion and structural rearrangement, offering crucial insight into the ultrafast dynamics of heterocyclic photochemical processes.[28]

2.2.NMR Spectroscopy

Nuclear Magnetic Resonance (NMR) spectroscopy is one of the most powerful analytical techniques for elucidating molecular structure and understanding the chemical environment of atoms within compounds. It has been extensively applied to study the structural and electronic features of 1,3,4-thiadiazole derivatives, providing crucial insights into substitution patterns and the stability of the heterocyclic core.[5,25] For instance, the ^1H NMR spectrum of compound 2a exhibited a broad NH resonance at δ 11.4 ppm, a distinct azomethine (–CH=N) singlet at δ 8.20 ppm, aromatic multiplets in the δ 7.99–7.07 ppm region, and characteristic methylene (–OCH_2–) and S–CH_2 signals at δ 5.16 and δ 4.52 ppm, respectively. Corresponding ^{13}C NMR signals appeared at δ 36.66 (S–CH_2), 69.88 (O–CH_2), 115–147 (Ar–C), 160.35–163.21 (C=N), and 168.38 (C=O). Similarly, compound 2b showed diagnostic resonances for NH (δ 11.64 ppm), CH=N (δ 8.31 ppm), aromatic protons (δ 7.34–6.99 ppm), S–CH_2 (δ 4.55 ppm), and O–CH_3 singlets (δ 3.80–3.72 ppm), with its ^{13}C NMR data confirming C=N (δ 160–165 ppm) and C=O (δ 167– 170 ppm) functionalities.[8]

Beyond conventional proton and carbon spectra, ^{15}N NMR has proven highly valuable in probing tautomerism in thiadiazol-2(3H)-ones, where oxo and hydroxy forms exhibit distinct nitrogen shifts typically δ –80 to –120 ppm for N-2 and δ –140 to –180 ppm for N-4 allowing precise differentiation of tautomers. Advanced multidimensional NMR techniques such as

DEPT, COSY, HSQC, and HMBC further enhance spectral resolution by revealing through-bond and through-space correlations.[19]

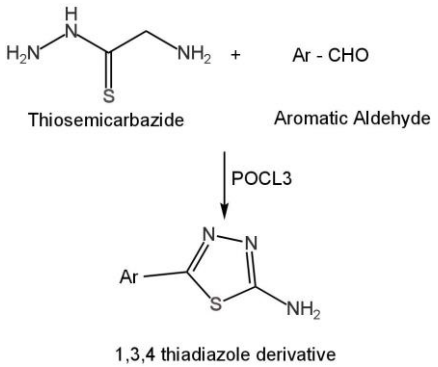
Mohamed et al.[25] reported that ^{1}H and ^{13}C NMR spectra of thiadiazole derivatives displayed downfield shifts for C5 (δ 160–170 ppm) and NH_2 (δ 7.8–8.6 ppm), attributed to the electron-withdrawing nature of the thiadiazole ring. DFT calculations supported these findings, confirming a stable intramolecularly hydrogen-bonded conformation. Likewise, Thirunarayanan et al.[26] observed that azomethine protons (δ 8.0–8.6 ppm) appeared downfield, while aromatic resonances varied depending on substituent effects. In their ^{13}C spectra, thiadiazole carbons were consistently found at δ 155–170 ppm, reinforcing their diagnostic value.[26,27] Collectively, these studies highlight the significance of NMR parameters in elucidating electronic distribution, substitution influence, and structural integrity within 1,3,4-thiadiazole frameworks.

3. Synthetic Methodoloy

3.1. Microwave-Assisted Synthesis of 5-Substituted-2-Arylbenzalamino-1,3,4-Thiadiazoles.

A general method of synthesis involves the cyclization of thiosemicarbazide derivatives in the presence ofdehydrating/cyclizing agents like phosphorus oxychloride ($POCl_3$).[6]

Thiosemicarbazide derivatives contain the –NH–NH–C(=S)–NH_2 group, which undergoes intramolecularcyclization to form the thiadiazole ring system. $POCl_3$ acts as a dehydrating and cyclizing agent, facilitating the elimination of water and HCl during ring closure. The reaction thus leads to formationof the 1,3,4-thiadiazole nucleus, a stable aromatic heterocycle, from thiosemicarbazide derivatives.[82]



Scheme 1: Reaction of Synthesis of 1,3,4 thiadiazole derivative from thiosemicarbazide.

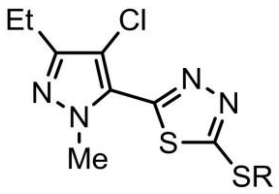
3.2.Procedure

Microwave-assisted synthesis has been effectively employed for the preparation of 5-substituted-2- arylbenzalamino-1,3,4-thiadiazoles. In this method, (3-chloro-4-fluorophenoxy)acetic acid, thiosemicarbazide, and suitable aromatic aldehydes are reacted in the presence of a catalytic amount of $POCl_3$ under microwave irradiation at 600 W for 3–5 minutes. Reaction progress is monitored by TLC, and upon completion, the mixture is cooled, treated with dilute NaOH (pH 9–10), and recrystallized from DMF to afford the desired thiadiazole derivatives in good yield. This protocol demonstrates enhanced efficiency, reduced reaction time, and higher product purity compared to conventional synthetic methods.[6]

4. Activities

4.1.Anti Bacterial Activity

4.1.1. Swamy et al. (2006a) reported the synthesis of pharmaceutically important condensed heterocyclic 4,6-disubstituted-1,2,4-triazolo-1,3,4-thiadiazole derivatives and systematically evaluated their antimicrobial activity. The compounds were screened against both Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacterial strains, as well as against the fungal pathogen *Candida albicans*. Various derivatives showcased moderate to potent antibacterial and antifungal effects, with activity comparable to standard reference drugs. The reported LC_{50} values for the most active molecules showed favorable therapeutic margins, highlighting 1,3,4-thiadiazole as a promising structural scaffold for the design of novel antimicrobial agents.[40]

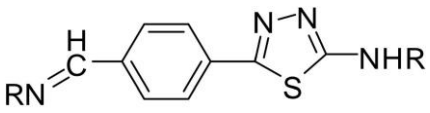


(1)

Compounds: (1a): R= Me; (1b): R= Propyl; (1c): R= Allyl; (1d): R= Amyl Figure 4.

4.1.2. Solak et al. (2006b) synthesized a series of 2-(aryl/alkylamino)-5-(4-aminophenyl)-1,3,4-thiadiazole derivatives and assessed their antitubercular potential against *Mycobacterium tuberculosis* H37Rv using the BACTEC 460 radiometric system. Biological evaluation revealed that compound 2a exhibited the highest level of

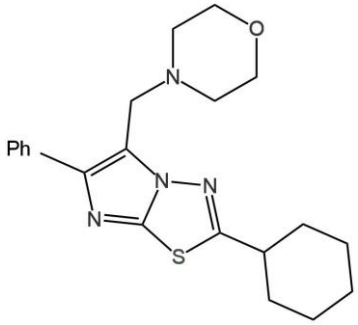
inhibition, suggesting a strong affinity towards the tubercular target. In contrast, compounds 2b–2e displayed only moderate activity, indicating that subtle structural variations within this scaffold markedly influence antitubercular efficacy.[41]



(2)

Compounds: 2a: R=Methyl, R'=2-hydroxyphenyl; 2b: R=Methyl, R'=3-nitrophenyl; 2c:R=benzyl, R'=2- hydroxyphenyl; 2d: R=Benzyl, R'=5-nitrofurfuryl; 2e: R=benzyl, R'=3-nitrophenyl. Figure 5.

4.1.3. Onkol T. et al. (2008a) synthesized a series of imidazo[2,1-b][1,3,4]thiadiazole derivatives specifically compounds (3) (2-cyclohexyl-6-phenyl…), (4) (6-(4-bromophenyl)-2-cyclohexyl…), each bearing a morpholine-linked methylene moiety. These novel structures were studied for in-vitro antimycobacterial activity and demonstrated excellent inhibitory effects against Mycobacterium tuberculosis, underscoring their potential as lead compounds for antitubercular drug development.[42]



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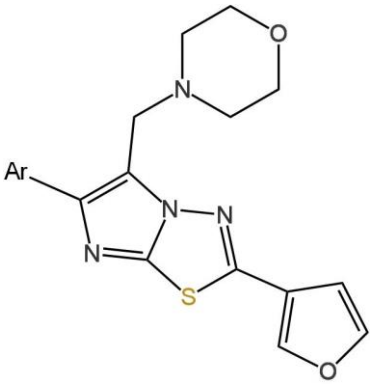
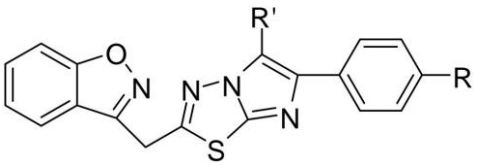


(4) Figure 6.

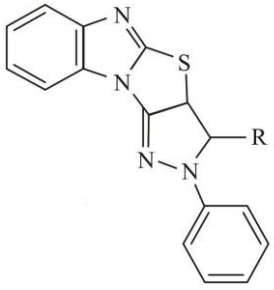
4.1.4. Lamani R.S. et al. (2009) reported the synthesis of a series of novel methylene-bridged benzisoxazolyl-imidazo[2,1-b][1,3,4]thiadiazole derivatives. The antimicrobial activity of the synthesized compounds was evaluated using the agar diffusion method. Antibacterial activity was studied against *Staphylococcus aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Escherichia coli*, while antifungal activity was tested against *Candida albicans* and *Aspergillus fumigatus*. Among the series, compounds (5a– 5e) exhibited moderate to good antibacterial inhibition, whereas compounds (5b), (5f), (5g), (5h), and (5i) displayed significant antifungal efficacy.[43]



(5)

Compounds: 5a: R=Cl, R'=H; 5b: R=Br, R'=H; 5c: R=Cl, R'=Br; 5d: R=O-Me, R'=Br; 5e: R=Cl, R'=SCN; 5f: R=3-coumarinyl, R'=H; 5g: R=O-Me, R'=SCN; 5h:R=H, R'=H; 5i: R=3-coumarinyl, R'=SCN. Figure 7.

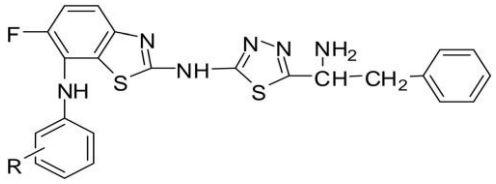
4.1.5. Omprakash et al. (2011a) investigated the antibacterial potential of pyrazolinothiazolidine derivatives using the disc diffusion method. The compounds were tested against Bacillus cereus ATCC11778 and Staphylococcus aureus ATCC9144 (Gram-positive), as well as Escherichia coli ATCC25922 (Gram-negative). Dimethylformamide (DMF) was used as the solvent control, while ciprofloxacin served as the reference drug. Their results demonstrated that all derivatives displayed measurable antibacterial activity, showing that incorporation of the pyrazolinothiazolidine scaffold contributes to broad-spectrum antimicrobial efficacy.[44]



(6) Figure 8.

4.1.6. Sathe et al. (2011b) reported the synthesis of N-[5-(1-amino-2-phenylethyl)-1,3,4-thiadiazol-2-yl]-6- fluoro-7-substituted-1,3-benzothiazol-2-amine derivatives, which

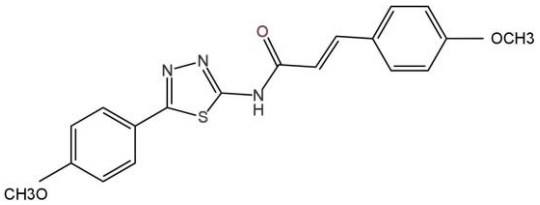
were subsequently studied for their antitubercular activity against *Mycobacterium tuberculosis* H37Rv in BACTEC medium. Biological screening revealed that the compounds 7a–7g exhibited promising inhibition, with several derivatives demonstrating good activity profiles. These findings suggested that incorporation of both the thiadiazole and benzothiazole pharmacophores within a single scaffold enhances their potential as lead scaffolds for antitubercular drug development.[45]



(7)

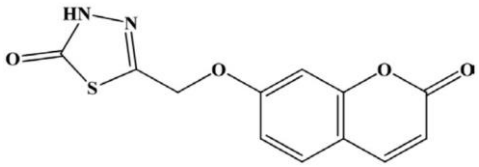
Compounds: 7a: R=o-NO_2; 7b: R=m-NO_2; 7c: R=p-NO_2; 7d: R=o-CH_3; 7e: R=m-OCH_3; 7f: R=p-OCH_3; 7g: R=o-Cl. Figure 9.

4.1.7. Dilmaghani et al. (2012) designed and synthesized a series of 5-(4-aminophenyl)-2- (arylamino)-1,3,4-thiadiazole derivatives along with their Schiff bases, and evaluated their antitubercular activity in vitro against *Mycobacterium tuberculosis*. Various compounds exhibited MIC values comparable to, or in some cases superior to, isoniazid in the primary screening assays. SAR analysis further revealed that aryl substitutions significantly enhanced antimycobacterial potency, supporting this scaffold as a promising lead for anti-TB drug development.[46]



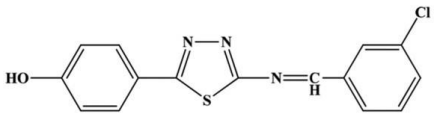
(8) Figure 10.

4.1.8. Al-Amiery et al. (2013) reported the synthesis of novel thiadiazole derivatives containing coumarin moieties and evaluated their antimicrobial potential. The compounds were screened in-vitro for both antibacterial and antifungal activities. Biological assays revealed inhibition against a range of bacterial strains, including *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris*, and *Pseudomonas aeruginosa*, as well as fungal pathogens such as *Aspergillus niger* and *Candida albicans*.[47]



(9) Figure 11.

4.1.9. Baghel et al. (2014) synthesized a new series of thiadiazole derivatives and studied their antibacterial and antifungal activities. The compounds were tested against Gram-positive strains (Bacillus subtilis, Staphylococcus aureus), Gram-negative strains (Pseudomonas aeruginosa, Escherichia coli), and fungal pathogens (Candida albicans, Aspergillus niger). Among the synthesized derivatives, 4-(5-(3- chlorobenzylideneamino)-1,3,4-thiadiazol-2-yl)phenol (10) and 4-(5-(4-chlorobenzylideneamino)-1,3,4- thiadiazol-2-yl)phenol (11) showed the most potent antimicrobial activity, showing significant inhibition compared with the tested microbial species.[48]



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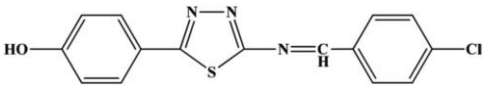
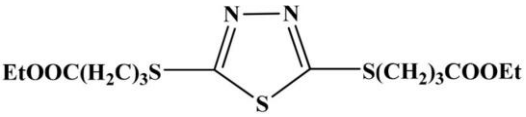


(11) Figure 12.

4.1.10. Nadjet et al. (2015) successfully synthesized two novel thiadiazole derivatives: diethyl 4,4′-[(1,3,4- thiadiazol-2,5-diyl)bis(sulfanediyl)]dibutanoate (12) and its corresponding hydrazide, 4,4′-(1,3,4- thiadiazol-2,5-diyl)bis(sulfanediyl)dibutanehydrazide (13). These compounds were evaluated for their antimicrobial efficacy using the broth dilution method to determine minimum inhibitory concentrations (MICs) against a panel of nine reference strains three Gram-positive bacteria (including Streptococcus pneumoniae, Bacillus subtilis, Staphylococcus aureus), three Gram-negative bacteria (Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae), and three fungi (Aspergillus fumigatus, Candida albicans, Geotrichum candidum). Compound 2 displayed good antibacterial activity, with MICs ranging from 16 to 31.25 µg/mL, and moderate antifungal activity with MICs between 31.25 and 62.5 µg/mL. Its hydrazide analogue, compound 3, demonstrated even stronger antibacterial performance (MICs of 8– 31.25 µg/mL) but somewhat reduced antifungal potency (MICs of 31.25–62.5 µg/mL).[49]



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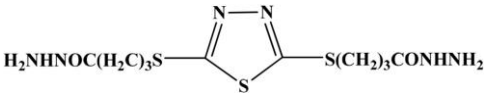
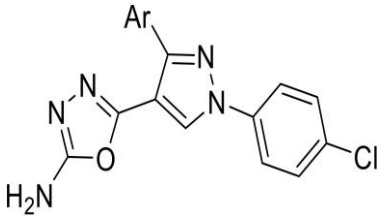


(13) Figure 13.

4.1.11. Gurunanjappa et al. (2016) synthesized a series of 1,3,4-oxadiazoles and 1,3,4-thiadiazoles incorporating pyrazole scaffolds and evaluated their antimicrobial potential against Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, Aspergillus niger, Aspergillus flavus, and Candida albicans, using ciprofloxacin and fluconazole as reference drugs. The compounds demonstrated moderate to excellent antibacterial and antifungal activities. Notably, the chloro-substituted oxadiazole 14d exhibited equipotent activity to both standards (MIC 12.5–25 µg/mL), while 14j showed superior potency against E. coli and C. albicans (MIC 12.5 µg/mL) compared with ciprofloxacin (25 µg/mL) and fluconazole (50 µg/mL). Similarly, chloro-substituted thiadiazoles 15d and 15j displayed stronger activity against S. aureus and E. coli than ciprofloxacin. Comparative analysis highlighted that the sulfur moiety in 1,3,4-thiadiazoles contributes significantly to antimicrobial potency.[50]



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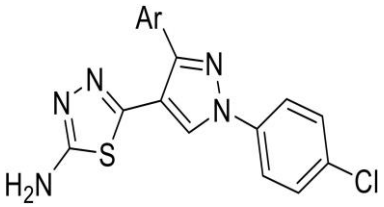
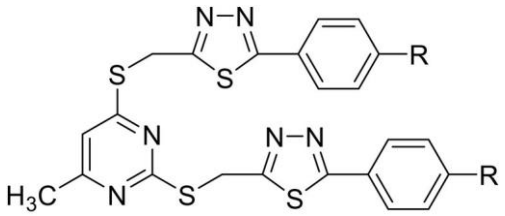


(15) Figure 14.

4.1.12. Sekhar et al. (2018a) developed a new class of methylthio-linked pyrimidinyl 1,3,4-oxadiazoles and 1,3,4-thiadiazoles and evaluated their antibacterial activity. The compounds were generally more potent against Gram-negative bacteria than Gram-positive strains. Notably, pyrimidinyl bis-thiadiazoles (16) demonstrated superior activity

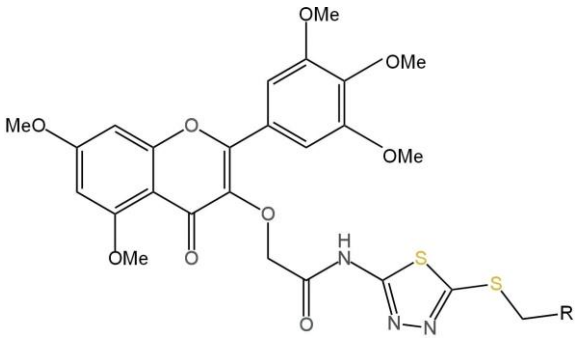
compared to their bis-oxadiazole counterparts. Structure–activity analysis indicated that electron-withdrawing substituents on the aromatic ring enhanced potency, with p-chlorophenyl (16a) and p-nitrophenyl (16b) derivatives (MIC 6.25 µg/well) showing remarkable inhibition against *Pseudomonas aeruginosa*, comparable to the standard drug chloramphenicol (MIC 6.25 µg/well).[51]



(16)

R= a) chloro b) nitro Figure 15.

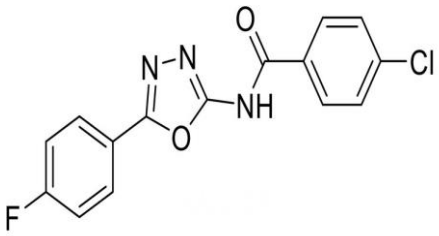
4.1.13. Ruan et al. (2018b) synthesized a series of myricetin derivatives incorporating amide, thioether, and 1,3,4-thiadiazole motifs, and evaluated their antimicrobial activity against plant pathogens Xanthomonas citri (Xac), Ralstonia solanacearum (Rs), and Xanthomonas oryzae (Xoo) using a turbidimetric assay. Compounds 5a, 5f, 5g, 5h, 5i, and 5l exhibited EC_{50} values of 11.5–27.3 µg/mL against Xac, surpassing Bismerthiazol (34.7 µg/mL) and thiadiazole–copper (41.1 µg/mL). Remarkably, compound 5g displayed ~50% antiviral curative effect, outperforming ribavirin. SAR analysis revealed that moderate lipophilicity and electron-withdrawing groups enhanced activity.[52]



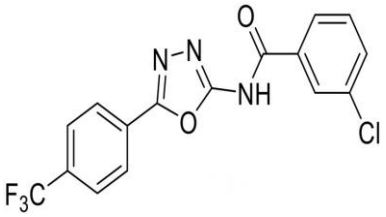
(17) Figure 16.

4.1.14. Tresse et al. (2019) reported the synthesis of novel 1,3,4-oxa-/thiadiazole derivatives as structural analogs of the highly active oxadiazole KKL-35. Among them, compounds 18c and 16a displayed significant antibacterial potential. Compound 18c inhibited *B. fragilis* and showed activity against *M. fortuitum* (MIC 8 mg/L) and M. abscessus, while 18a exhibited superior potency against *E. faecalis, E. faecium,* and *S.*

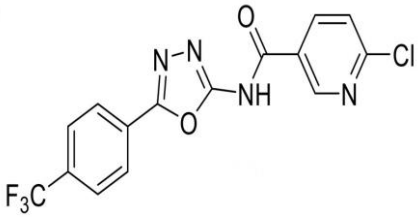
epidermidis with remarkably low MIC values (0.0625–1 mg/L). Both compounds also demonstrated synergistic activity with conventional antibiotics and maintained low cytotoxicity, highlighting their therapeutic promise.[53]



KKL-35

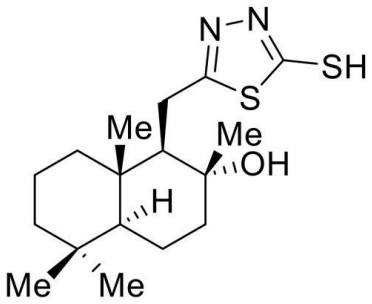


18c



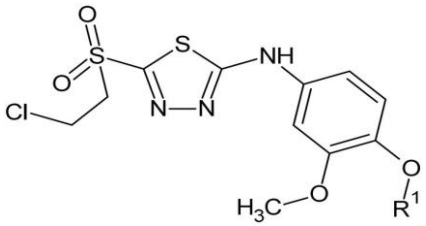
18a Figure 17.

4.1.15. Lungu L. et al. (2020a) reviewed thirteen sclareolide-based homodrimane sesquiterpenoids containing 1,3,4-oxadiazole or 1,3,4-thiadiazole units, which exhibited notable antibacterial and antifungal activity. Thiadiazole derivatives were more effective, with compound 19 (bearing a 2-mercapto group) showing potent broad-spectrum action (MIC 0.032 µg/mL antifungal; 0.094 µg/mL antibacterial). Additionally, thiadiazoles 19 a and 19j inhibited S. aureus and E. coli at MIC 12.5 µg/mL, surpassing ciprofloxacin (25 µg/mL). SAR studies revealed that sulfur-substituted thiadiazoles conferred superior bioactivity compared to oxadiazoles, underscoring their therapeutic promise.[54]



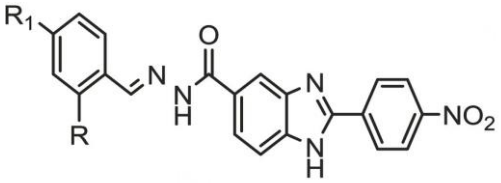
(19) Figure 18.

4.1.16. Qiong Wu et al. (2020b) synthesized thirty-four novel vanillin-based derivatives incorporating the 1,3,4-thiadiazole scaffold and evaluated their antibacterial activity. Among these, compound 20 emerged as the most potent, exhibiting excellent antibacterial activity with EC_{50} values of 3.14 and 8.83 μg/mL. Mechanistic studies indicated that compound 20 significantly reduced exopolysaccharide production while enhancing cell permeability, ultimately leading to increased bacterial cell damage. These findings highlight the therapeutic promise of vanillin–thiadiazole hybrids as effective antibacterial candidates.[55]



(20) Figure 19.

4.1.17. Kumar K.A. et al. (2021) highlighted the importance of chitinase inhibition in developing novel antifungal agents. Their study reported that 4-hydroxycoumarin Schiff bases displayed potent activity against phytopathogenic fungi such as *F. solani, F. oxysporium, A. niger, and Candida species* (*C. krusei, C. albicans, C. tropicalis*), with significant chitinase inhibition (IC_{50} = 1.0 mM). Additionally, benzimidazole hydrazone derivatives (21) showed antimicrobial efficacy against *C. albicans and C. neoformans* (MIC 4–16 μg/mL) without cytotoxicity, while fused pyrazole, pyrazole-integrated 1,3,4-oxadiazoles, and Schiff bases (22) demonstrated notable antimicrobial potential, including inhibition of S. aureus DNA gyrase.[56]



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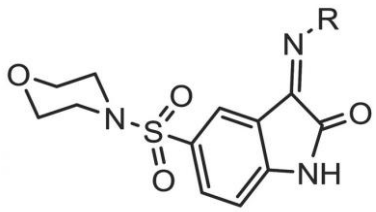
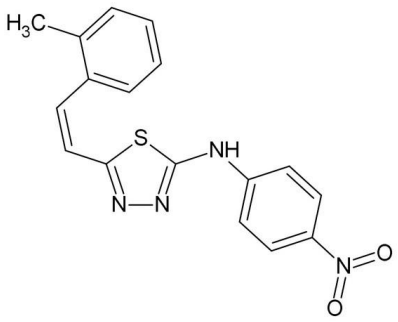


(22) Figure 20.

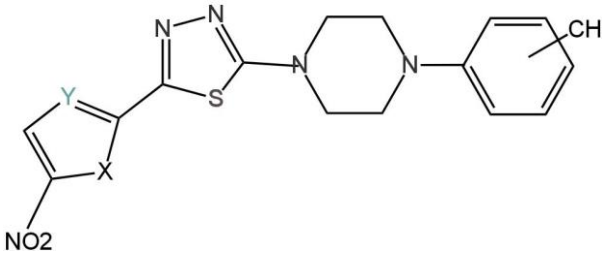
4.1.18. Hakan S. Sayiner et al. (2022a) reported the synthesis and characterization of a novel series of 1,3,4-thiadiazole derivatives, confirmed by UV, FTIR, ^{13}C NMR, and ^{1}H NMR analyses. The antibacterial evaluation revealed that compound 23 displayed a notable inhibitory effect against *Staphylococcus epidermidis*. Furthermore, DNA-binding studies indicated that all synthesized compounds exhibited strong interactions with CT-DNA, suggesting a potential mechanism of antibacterial activity. These findings highlight the dual biological relevance of the thiadiazole scaffold as both antimicrobial agents and DNA-interacting molecules.[57]



(23) Figure 21.

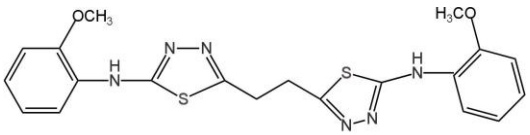
4.1.19. Tahghighi et al. (2022b) conducted an in-depth investigation on nitro-heteroaryl-1,3,4-thiadiazole derivatives functionalized with a piperazinyl-benzonitrile scaffold. The synthesized compounds demonstrated remarkable antibacterial potential in vitro, with activity trends strongly influenced by the presence of electron-withdrawing nitro groups and the flexible piperazine linker. Computational docking studies further confirmed their strong binding affinities toward key bacterial enzyme targets, supporting their

mechanism of action. Collectively, the study provided important insights into structure–activity relationships (SAR), underscoring these thiadiazole derivatives as promising candidates for antimicrobial drug development.[58]



(24) Figure 22.

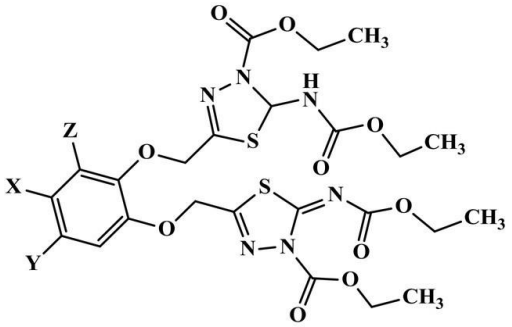
4.1.20. Muğlu et al. (2023) reported the synthesis of seven novel bis-1,3,4-thiadiazole derivatives employing fumaric acid as the central scaffold. Their antibacterial potential was systematically evaluated against eight clinical bacterial strains using broth-dilution MIC/MBC assays. Notably, compounds 25 exhibited significant inhibition of Klebsiella pneumoniae (MIC 2.75 mg·L^{-1}), whereas compounds 4–7 were particularly active against Enterococcus faecium (MIC 1.375 mg·L^{-1}), alongside moderate activity against E. coli and E. faecalis. Furthermore, quantum-chemical descriptors corroborated the experimental findings, highlighting the role of electronic factors in potency.[59]



(25) Figure 23.

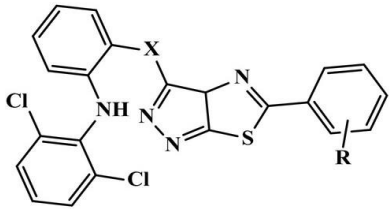
4.2.Cytotoxic Activity

4.1.1. Foroumadi et al. (2006) reported the synthesis and biological evaluation of a novel class of 2- acylamino, 2-aroylamino, and ethoxycarbonyl-imino-1,3,4-thiadiazole derivatives (26), which were designed and assessed for their potential antitumor activity. These compounds demonstrated promising cytotoxic profiles, suggesting their possible utility as chemotherapeutic agents. In the same study, the authors also explored the cytotoxic and antileishmanial properties of 3,6-disubstituted 1,2,4-triazolo[3,4- b]-1,3,4-thiadiazoles.[27] When evaluated against the standard anticancer drug Doxorubicin at a concentration of 10 μM, these triazolo-thiadiazole derivatives exhibited notable activity, highlighting their potential as valuable leads in the development of novel agents with dual antitumor and antileishmanial efficacy.[60]



(26)

X=H, Y=H, Z=H,OCH_3

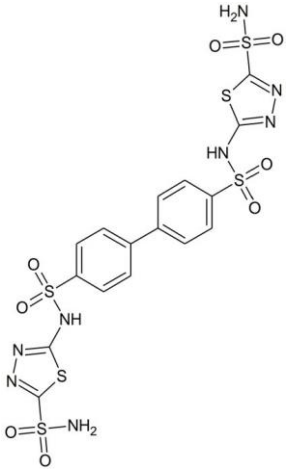


(27)

R=-3-Chloro, -4-Chloro, -4-nitro, -2-methoxy,X= $-CH_2$, $-CH_2COOCH_2$ Figure 24.

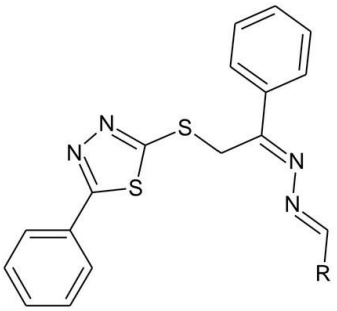
4.2.2. Morsy et al. (2009a) investigated the anticancer potential of a series of bis-sulfonamide derivatives bearing a 1,3,4-thiadiazole heterocyclic core. These compounds were evaluated as inhibitors of multiple human carbonic anhydrase (hCA) isoforms, including CA I, CA II, CA IX, and CA XII. The results revealed that while the derivatives displayed only modest inhibitory activity against CA I and CA XII, they exhibited significantly higher potency toward CA II (cytosolic isozyme) and CA IX (tumor- associated transmembrane isozyme), with inhibition constants (K_i) ranging from 21–129 nM for hCA II and 23–79 nM for hCA IX, respectively.

In addition to enzymatic inhibition, the synthesized compounds demonstrated ex vivo antiproliferative activity against several human tumor cell lines. Notably, they inhibited the growth of the human colon carcinoma cell line (HCT116), non-small cell lung carcinoma cell line (H460), and breast adenocarcinoma cell line (MCF-7), with GI_{50} values between 0.74–10.0 μg/mL. Among the tested derivatives, compound (1) emerged as the most active candidate, particularly against HCT116 (GI_{50} = 3.29 μg/mL) and H460 (GI_{50} = 10 μg/mL), underscoring its potential as a lead molecule for further optimization in anticancer drug discovery.[61]



(28) Figure 25.

4.2.3. Zhang et al. (2009b) described the design, synthesis, and biological evaluation of nine heterocyclic dihydrazone derivatives incorporating a 1,3,4-thiadiazole nucleus. Biological screening revealed that several members of this series exhibited noteworthy antitumor activity. In particular, compounds 29a-f demonstrated significant growth-inhibitory effects against three distinct tumor cell lines, namely CHO (Chinese hamster ovary cells), HL60 (human leukemia cells), and L1210 (mouse leukemia cells). These findings highlight the potential of dihydrazone–thiadiazole hybrids as promising scaffolds for the development of novel antineoplastic agents.[62]



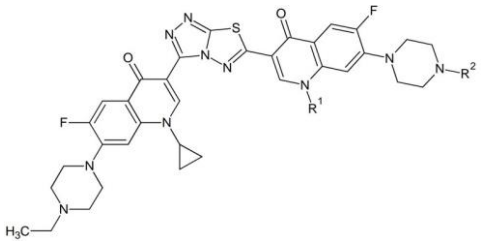
(29)

R = 2H-1,3-benzodioxol-5-yl, a- antracen-5-yl, 2-$CH_3C_6H_4$, 4-$NO_2C_6H_4$, 3-$NO_2C_6H_4$, 4-$OCH_3C_6H_4$ Figure 26.

4.2.4. Hu et al. (2010a) synthesized and evaluated a novel series of 1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles, in which the triazolo–thiadiazole core was covalently linked to a fluoroquinolone scaffold. These hybrid molecules displayed remarkable growth-inhibitory activity against tumor cell lines, particularly HL-60 (human leukemia) and DBA/2 (mouse leukemia), with IC_{50} values of 1.1 μM, 0.25 μM, and 0.15 μM,

respectively.[63] The integration of fluoroquinolone and thiadiazole moieties provided a synergistic effect, contributing to their potent antitumor profile.

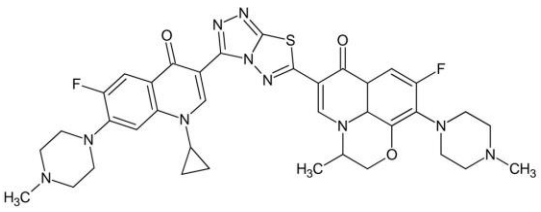
In a subsequent study, the same research group reported the synthesis of five C3/C3 fluoroquinolone dimers tethered to a fused heterocyclic 1,3,4-thiadiazole ring (30). Their anticancer efficacy was tested against L1210 (mouse lymphocytic leukemia) and CHO (Chinese hamster ovary) cells. Among these, derivatives with R_1/R_2 substitutions of cyclopropyl/H (30a), cyclopropyl/CH_3 (30b), and cyclopropyl/C_2H_5 (30c) demonstrated superior cytotoxic activity, with IC_{50} values of 0.20 μM, 1.2 μM, and 2.5 μM, respectively.[64]



(30)

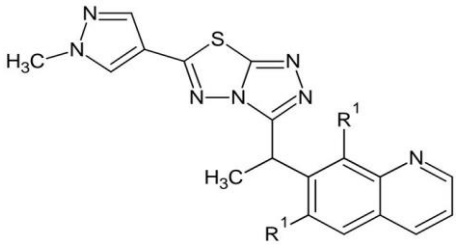
R_1/R_2 = 30a: cyclopropyl/H, 30b: cyclopropyl/CH_3, 30c: cyclopropyl/C_2H_5 Figure 27.

Building upon these promising results, Hu and et al. (2011) extended their work by designing a new set of fluoroquinolone 1,3,4-thiadiazole conjugates and assessing their anticancer activity using the MTT assay. The compounds were evaluated against L1210 (mouse lymphocytic leukemia), CHO (Chinese hamster ovary), and HL-60 (human leukemia) cell lines. Several derivatives showed potent cytotoxicity, with representative IC_{50} values of 1.5 μM (L1210), 0.12 μM (HL-60), and 3.4 μM (CHO), particularly for the methyl-substituted analogs. These findings strongly suggest that fluoroquinolone–thiadiazole hybrids represent a versatile scaffold for the design of next-generation anticancer agents.[65]



(31) Figure 28.

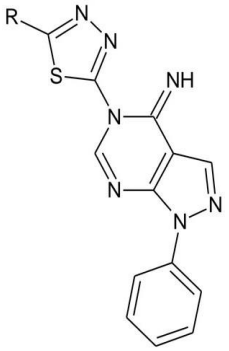
4.2.5. Lauffer et al. (2010b) reported the synthesis and anticancer evaluation of two novel 1,3,4- thiadiazole-fused compounds (32). These complexes demonstrated inhibitory activity against c-Met protein kinase in Snu5 gastric carcinoma cells, with IC_{50} values below 200 nM. Additionally, a new series of [1,2,4]triazolo[3,4-b][1,3,4]thiadiazole derivatives was developed.[66]



(32) R1 = H, F Figure 29.

4.2.6. Song et al. (2011a) designed and synthesized a series of fluorinated pyrazolo[3,4-d]pyrimidine derivatives incorporating a 1,3,4-thiadiazole moiety, and evaluated their in vitro anticancer activity. The cytotoxic potential of the compounds was assessed against the HL-60 human leukemia cell line using the standard MTT assay. Among the series, two derivatives, namely the trifluoromethyl-substituted compound (33a) and the 4-trifluoromethylphenyl-substituted compound (33b), exhibited superior cytotoxic activity compared with the reference drug doxorubicin, highlighting their promise as potent anticancer leads.

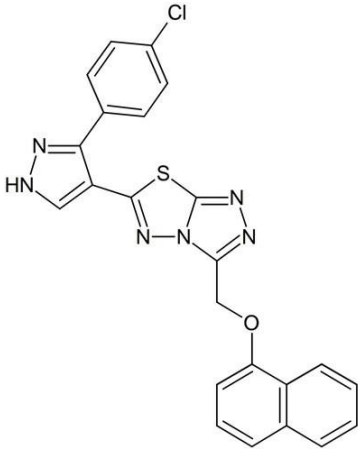
Structure–activity relationship (SAR) analysis provided further insight into their enhanced activity. It was observed that substitution of the hydrogen atom at position 1 of the pyrazole ring with a phenyl group significantly improved the anticancer effect. Moreover, the introduction of a trifluoromethyl ($–CF_3$) group into the molecular framework markedly increased cytotoxic potency, underscoring the importance of fluorine-based substituents in optimizing the pharmacological activity of this scaffold.[67]



(33)

33a: R = CF_3, 33b: R = 4-$CF_3C_6H_4$ Figure 30.

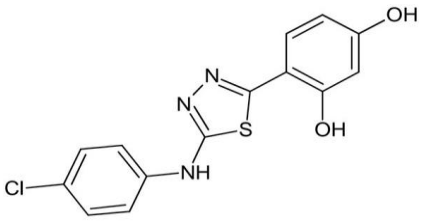
4.2.7. Sunil et al. (2011b) synthesized and evaluated the anticancer activity of a novel compound, 6-[3-(4-chlorophenyl)-1H-pyrazol-4-yl]-3-[(2-naphthyloxy)methyl][1,2,4]triazolo[3,4-b][1,3,4]thiadiazole(34) (Figure 55). This compound exhibited potent growth-inhibitory activity against the HepG2 liver cancer cell line, with an IC_{50} value of 0.8 µg/mL.[68]



(34) Figure 31.

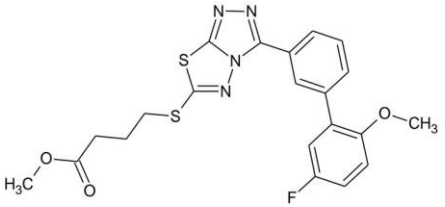
4.2.8. Juszczak et al. (2012a) reported the design, synthesis, and biological evaluation of a novel thiadiazole derivative, 2-(4-chlorophenylamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole (35). The compound was systematically screened for its antiproliferative activity against a broad panel of cancer cell lines representing both peripheral and nervous system malignancies. Among the peripheral cancer models, the compound demonstrated promising cytotoxicity against breast carcinoma (T47D), colon carcinoma (HT-29), thyroid carcinoma (FTC-238), teratoma (P19), and T-cell leukemia (Jurkat E6.1). In addition, significant inhibitory effects were also observed in nervous system–derived cancers, including rhabdomyosarcoma/medulloblastoma (TE671), brain astrocytoma (MOGGCCM), and glioma (C6).

The MTT assay was used to determine the in vitro cytotoxicity, and importantly, compound 35 displayed selective activity toward cancer cells, showing no significant toxicity against normal human cells, including skin fibroblasts, hepatocytes, astrocytes, and neurons. This selective antiproliferative profile highlights compound 35 as a promising lead candidate for further preclinical development in the search for novel anticancer agents with reduced off-target toxicity.[69]



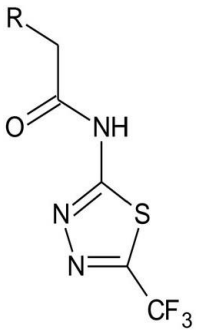
(35) Figure 32.

4.2.9. Ramaprasad et al. (2012b) synthesized a new series of condensed triazolo–thiadiazole analogues using microwave-assisted synthesis and evaluated their anticancer potential against the HT-29 colon cancer cell line by the MTT assay. Among the tested derivatives, the most active compound, 6-((4- fluorobutyl)sulfanyl)-3-(5'-fluoro-2'-methoxy-(1,1'-biphenyl)-3-yl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole, exhibited a notable IC_{50} value of 12 μM, highlighting the significance of fluorinated substituents and microwave-assisted synthesis in developing promising anticancer leads.[70]



(36) Figure 33.

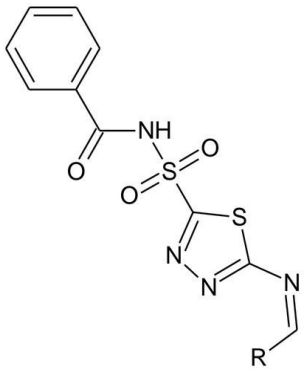
4.2.10. Hosseinzadeh et al. (2013) synthesized novel 1,3,4-thiadiazole derivatives bearing trifluoromethyl groups and evaluated their anticancer potential against PC3 (prostate), MCF7 (breast), and SKNMC (neuroblastoma) cell lines using the MTT assay, with doxorubicin as the reference drug. Among the series, compounds 37 (3-chloro) and 26 (4-chloro) displayed superior cytotoxicity, particularly against MCF7 cells. Mechanistic studies revealed that these derivatives effectively induced apoptosis via caspase-3, -8, and -9 activation, underscoring their potential as promising anticancer leads.[71]



(37)

25: R = 3-ClC_6H_4, 26: R = 3-ClC_6H Figure 34.

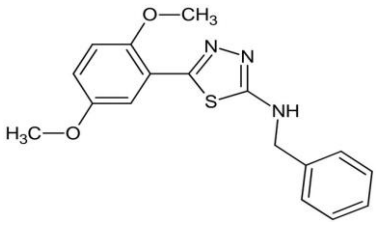
4.2.11. Chhajed et al. (2014) synthesized a series of 5-arylideneamino-1,3,4-thiadiazol-2-[(N-benzoyl)] sulfonamide derivatives, starting from the carbonic anhydrase inhibitor acetazolamide. The newly prepared compounds were evaluated for anticancer activity against HEK293 (human embryonic kidney), BT474 (breast cancer), and NCI-H226 (lung cancer) cell lines, with indisulam (ISL) serving as the reference drug. The study revealed that the compounds exhibited strong dose-dependent growth inhibition. Among them, the most active derivatives were N-({5-[(2-methoxybenzylidene)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)benzamide (38a), showing a CTC50 value of 0.794 µM against the BT474 breast cancer cell line, and N-({5-[(furan-2-ylmethylidene)amino]-1,3,4-thiadiazol-2-yl}sulfonyl)benzamide (38b), with a CTC50 of 0.913 µM against the NCI-H226 lung cancer cell line. However, none of the tested compounds demonstrated potency comparable to the standard drug.[72]



(38)

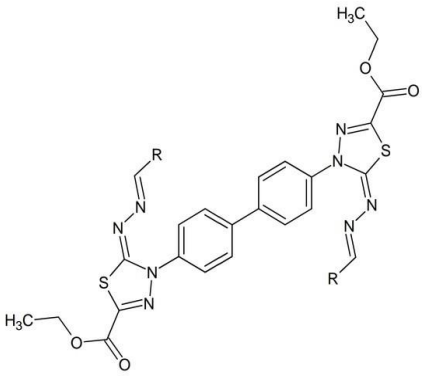
38a: R = 2-$OCH_3C_6H_4$, 38b: R = 2-furyl Figure 35.

4.2.12. Polkam et al. (2015) synthesized a series of 5-(2,5-dimethoxyphenyl)-2-substituted-1,3,4- thiadiazole derivatives and evaluated their in vitro anticancer and antimycobacterial activities. Anticancer activity was assessed using the MTT assay against HT-29 (colon cancer) and MDA-MB-23 (breast cancer) cell lines. Several compounds exhibited promising inhibitory effects, with the benzyl-substituted derivative 39 showing the highest cytotoxicity 68.28% inhibition against HT-29 and 62.95% against MDA-MB-23 (Figure 19). Importantly, the compounds were also tested on normal human cell lines and demonstrated selectivity toward cancer cells.[73]



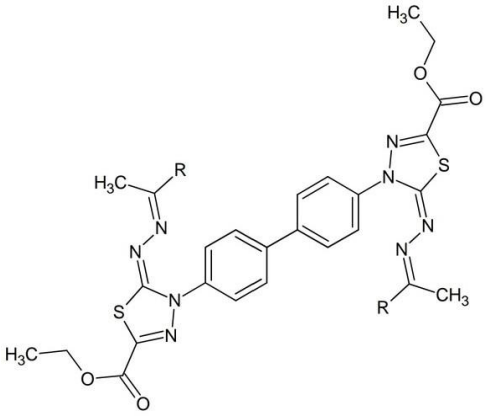
(39) Figure 36.

4.2.13. Gomha et al. (2016) designed, synthesized, and evaluated a new class of bis(1,3,4-thiadiazole) derivatives for their potential as cytotoxic agents. The compounds were tested for anticancer activity against the human breast cancer cell line MCF-7 using the MTT assay. The study revealed that the presence of heteroaryl substituents played a crucial role in modulating biological activity. In particular, derivatives diethyl 4,4'-(biphenyl-4,4'-diyl)bis(5-((thiophen-2-ylmethylene)hydrazono)-4,5-dihydro-1,3,4-thiadiazole2-carboxylate (40a) diethyl 4,4'-(biphenyl-4,4'-diyl)bis(5-((furan-2-ylmethylene)hydrazono)-4,5- dihydro-1,3,4-thiadiazole-2-carboxylate) (40b), incorporating 2-thienyl or 2-furyl groups, as well as compounds diethyl4,4'-(biphenyl-4,4'-diyl)bis(5-((1-(furan-2-yl)ethylidene)hydrazono)-4,5-dihydro-1,3,4- thiadiazole-2-carboxylate (41a) diethyl 4,4'-(biphenyl-4,4'-diyl)bis(5-((1-(pyridin- 3-yl)ethylidene)hydrazono)-4,5-dihydro-1,3,4-thiadiazole-2-carboxylate) (41b), containing 2-furyl or 3- pyridyl moieties, displayed pronounced cytotoxic effects. These derivatives not only showed strong dose- dependent growth inhibition but also demonstrated superior activity compared to the standard anticancer drug imatinib. Such findings suggest that bis(1,3,4-thiadiazole) scaffolds bearing heteroaryl substituents could serve as promising lead structures for the development of more potent breast cancer therapeutics. Furthermore, the work highlights the importance of structural modification on the thiadiazole ring in enhancing anticancer potential, thereby providing valuable insight for future medicinal chemistry optimization.[74]



(40)

40a: R= 2-tienyl, 40b: R = 2-fury

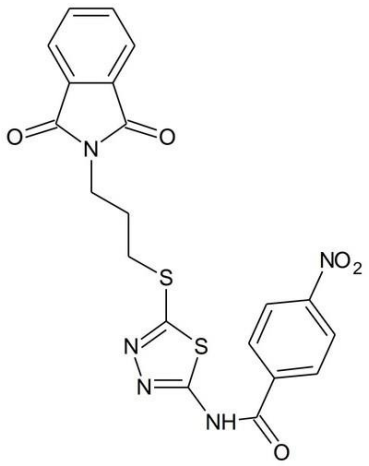


(41)

41a: R = 2-furyl, 41b: R = 3-pirydyl Figure 37.

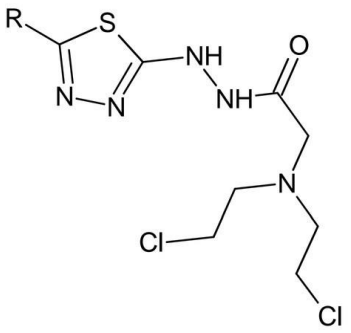
4.2.14.

ezaei et al. (2017) reported the synthesis and biological evaluation of a series of 1,3,4-thiadiazole- linked phthalimide derivatives. Their anticancer activity was assessed using the MTT assay against human colon cancer (HT-29) and breast cancer (MCF-7) cell lines. Among the tested compounds, N-(5-{[3-(1,3- dioxo-1,3-dihydro-2H-isoindol-2-yl)propyl]sulfanyl}-1,2,4-thiadiazol-2-yl)-4-nitrobenzamide (42) exhibited the most potent activity, with IC_{50} values of 23.83 µM (HT-29) and 27.21 µM (MCF-7). The presence of the 4-nitrobenzoyl substituent in compound 42 appears to play a critical role in enhancing cytotoxicity, making this scaffold a valuable lead for further structural optimization.[75]



(42) Figure 38.

4.2.15. Gowramma et al. (2018a) synthesized a series of novel 1,3,4-thiadiazole derivatives and investigated their anticancer potential. The cytotoxic properties of these compounds were evaluated against the human liver cancer (Hep-2) cell line using the CCK-8 assay. Furthermore, derivatives incorporating electron-withdrawing substituents such as nitro and chloro groups demonstrated enhanced activity. In particular, 2-[bis(2-chloroethyl)amino]-N-[5-(3-nitrophenyl)-1,3,4-thiadiazol-2- yl]acetohydrazide (43a) and 2-[bis(2-chloroethyl)amino]-N-[5-(2-chlorophenyl)-1,3,4-thiadiazol-2- yl]acetohydrazide (43b) showed substantial antitumor activity, suggesting that substitution at the 5- position of the thiadiazole ring plays a critical role in modulating cytotoxicity. Collectively, these findings highlight the potential of 1,3,4-thiadiazole scaffolds bearing disulfanyl or arylhydrazide substituents as promising leads for the development of anticancer agents.[76]



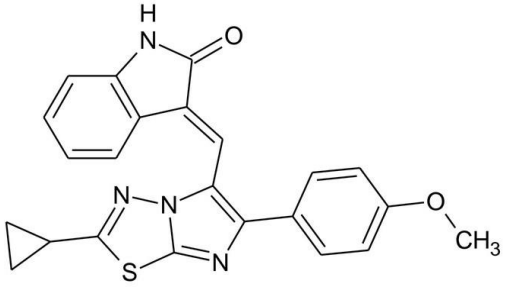
(43)

43a: R = 3-$NO_2C_6H_5$, 43b: R = 2-ClC_6H_5 Figure 39.

4.2.16. Narashika et al. (2018b) reported the design, synthesis, and biological evaluation of a novel series of imidazo[2,1-b][1,3,4]thiadiazole–indolin-2-one conjugates. These compounds were screened for antiproliferative activity against a panel of human cancer cell lines, where they exhibited promising cytotoxicity with GI_{50} values ranging from 0.13 to 3.8 µM. To further investigate their mechanism of action, the most active derivatives were subjected to cell cycle analysis, tubulin polymerization assays, and apoptosis studies. The three most potent conjugates, namely (E)-3-((6-(4-chlorophenyl)-2- cyclopropylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)-5-methoxyindolin-2-one (44), (E)-3-((2- cyclopropyl-6-(4-methoxyphenyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)indolin-2-one (45), and (E)-5-chloro-3-((6-(4-chlorophenyl)-2-cyclopropylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene)indolin- 2-one (46), were found to induce significant accumulation of cells in the G_2/M phase. They also disrupted

the microtubule network and effectively inhibited tubulin assembly, leading to apoptosis in the HeLa cell line.

Molecular docking studies further revealed that these conjugates interact with key amino acid residues αAsn101, αThr179, αSer178, βCys241, βLys254, and βLys352—within the colchicine-binding site of tubulin, providing mechanistic insight into their potent anticancer activity. Taken together, these findings suggest that imidazo[2,1-b][1,3,4]thiadiazole–indolin-2-one hybrids represent a promising class of tubulin-targeting agents with potential for further development as anticancer therapeutics.[77]



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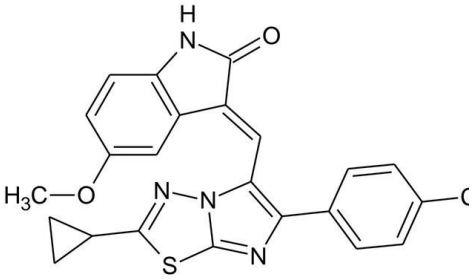

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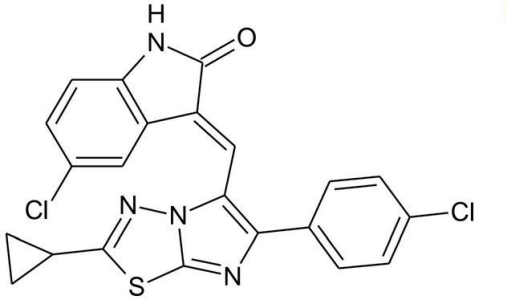


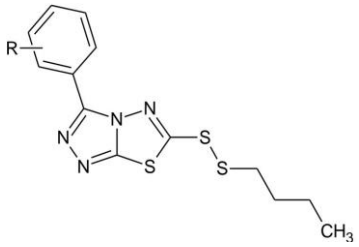
(46) Figure 40.

4.2.17. Liu et al. (2019a) reported the synthesis of twenty-three novel 3,6-disubstituted 1,2,4-triazolo[3,4- b][1,3,4]thiadiazole derivatives and investigated their in vitro antiproliferative activity. The compounds were tested against human hepatocarcinoma

(SMMC-7721), HeLa, human lung carcinoma (A549), and normal mouse fibroblast (L929) cell lines using the CCK-8 assay. The results indicated that all synthesized derivatives displayed varying degrees of antiproliferative activity, with several compounds demonstrating superior effects compared to the reference drug 5-fluorouracil (5-FU).

Among them, 3-phenyl-6-(n-butyldisulfanyl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (47a), 3-(4- methylphenyl)-6-(n-butyldisulfanyl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (47b), and 3-(4- methylphenyl)-6-(isobutyldisulfanyl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (48). These derivatives exhibited potent cytotoxicity across multiple cancer cell lines, outperforming 5-FU in certain assays.

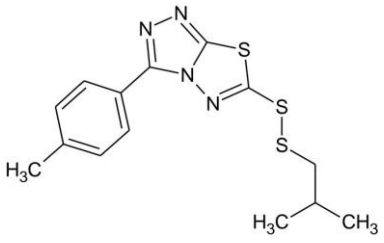
The study highlights the importance of disulfanyl substitution at the 6-position of the triazolothiadiazole core in enhancing anticancer potential, suggesting that such modifications could be a valuable strategy in the development of more effective anticancer agents.[78]



(47)

47a: R = H

47b: R = 4-CH_3

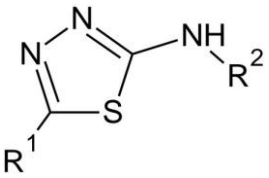


(48) Figure 41.

4.2.18. Chandra et al. (2019b) synthesized and evaluated a new series of 5-phenyl-substituted 1,3,4- thiadiazole-2-amines for their potential antitumor and antitubercular activities. The compounds were screened for cytotoxicity against the MDA-MB-231 human breast cancer cell line. Several derivatives exhibited remarkable activity, with

compounds N-benzyl-5-(4-fluorophenyl)-1,3,4-thiadiazol-2-amine (49a), N-benzyl-5-(4-nitrophenyl)-1,3,4-thiadiazol-2-amine (49b), and 5-phenyl-N-(4-tolyl)-1,3,4- thiadiazol-2-amine (49c) (Figure 49) demonstrating stronger growth inhibition than the standard reference drug cisplatin.

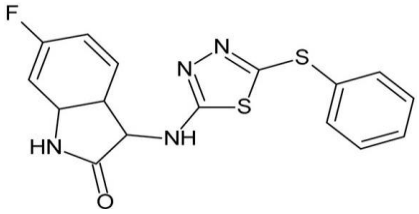
The SAR evaluation revealed that the presence of an aromatic ring at the N-substituted position significantly enhanced activity, while electron-withdrawing substituents such as fluoro and nitro groups further improved the anticancer potential. These findings underscore the importance of electronic effects and aromatic substitution patterns in modulating the cytotoxicity of 1,3,4-thiadiazole derivatives, suggesting that this scaffold could serve as a promising platform for designing potent anticancer agents.[79]



(49)

49a: R1 = C_6H_5 R2 = 4-$CH_3C_6H_4$, 49b: R1 = $C_6H_5CH_2$ R2 = 4-FC_6H_4, 49c: R1 = $C_6H_5CH_2$ R2 = 4- $NO_2C_6H_4$ Figure 42.

4.2.19. Prashant J. et al. (2022) employed an in silico drug design strategy combined with supramolecular green synthesis to develop novel 1,3,4-thiadiazole- and aziridine-based indolin derivatives with potential anticancer activity. Molecular docking studies were performed using C-KIT kinase as the target protein, revealing strong binding interactions with docking scores of –10.915 and –9.662, indicative of high affinity. Guided by these computational findings, several unique indolin-conjugated 1,3,4-thiadiazole scaffolds were synthesized and subsequently screened for anticancer efficacy against a panel of human cancer cell lines. Among the tested derivatives, compound 50 demonstrated particularly potent activity against colon tumor cell lines, highlighting the therapeutic relevance of this hybrid scaffold. The study emphasizes the integration of computational docking with eco-friendly synthetic strategies as an efficient approach to accelerate the discovery of novel anticancer agents.[80]

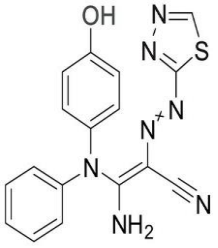


(50) Figure 43.

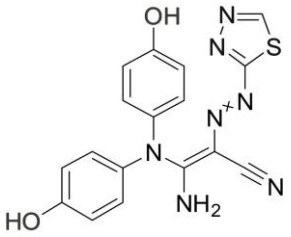
4.2.20. Hanadi A. et al. (2023) synthesized a new series of 1,3,4-thiadiazol-diazenylacrylonitrile derivatives and evaluated their antioxidant and anticancer properties. The antioxidant capacity was assessed using the DPPH free radical scavenging assay, with IC_{50} values calculated relative to ascorbic acid as the reference standard. Compounds 51,52,53,54,55, which incorporated electron-donating substituents, demonstrated excellent antioxidant activity.

The same derivatives were subsequently tested for anticancer activity against HepG2 (human liver cancer) and MCF-7 (human breast cancer) cell lines. Notably, these compounds exhibited IC_{50} values that were comparable to, or in some cases slightly lower than, those of the standard drug doxorubicin, confirming their significant cytotoxic potential. The structure–activity relationship (SAR) suggested that electron-donating groups may enhance reactivity by facilitating addition reactions at unsaturated DNA sites, thereby boosting anticancer efficacy.

To further understand the molecular basis of their activity, docking studies were conducted using Autodock Vina against cyclin-dependent kinase 2 (CDK2, PDB ID: 1PXO). The results indicated that the derivatives displayed more favorable binding energies than the native ligand CK7, and their binding orientation suggested interactions within the ATP-binding pocket of CDK2. These findings support the hypothesis that such derivatives may function as effective dual-action agents with both antioxidant and anticancer potential.[81]



(51)



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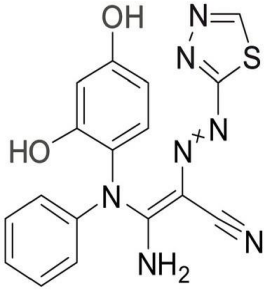

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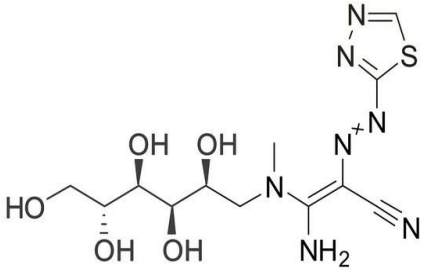

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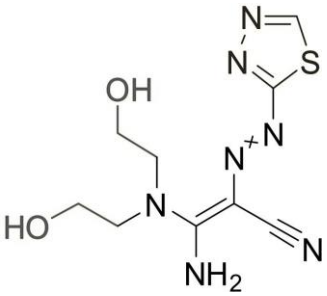
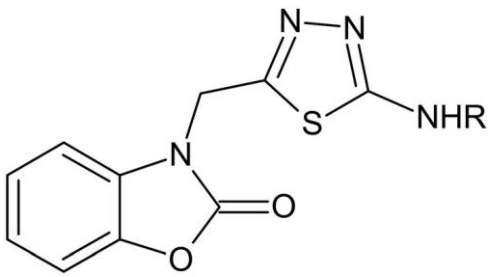


(55) Figure 44.

4.3.Anti Inflammatory Activity

4.3.1. Salgin-Goksen et al. (2007a) reported the synthesis of a series of condensed 2-benzoxazolinone derivatives incorporating substituted thiadiazole moieties (56), which were subsequently evaluated for their anti-inflammatory potential. The biological screening revealed that substitution played a crucial role in modulating activity. In particular, the compound bearing a phenyl substituent demonstrated the most pronounced

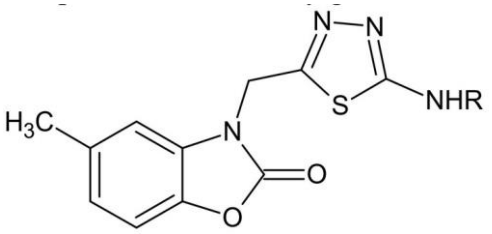
and consistent anti-inflammatory effect, clearly outperforming its analogues with alkyl side chains. Interestingly, a notable increase in activity was observed when the alkyl chain was replaced by a phenyl ring, suggesting that enhanced aromatic interactions and improved structural rigidity may contribute to stronger binding affinity with the biological target. These findings emphasize the importance of aromatic substitution in optimizing the pharmacological profile of this scaffold and provide valuable insights into the structure activity relationship of benzoxazolinone thiadiazole hybrids.[84]



(56)

R= -CH_3, -C_2H_5, -C_6H_5 Figure 45.

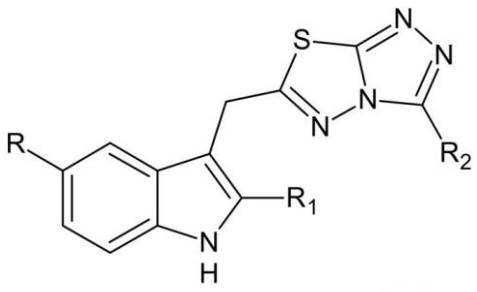
4.3.2. Mathew et al. (2007b) carried out the anti-inflammatory activity screening of several 3,6- disubstituted-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole derivatives along with their dihydro analogues. The pharmacological evaluation indicated that substitution at the sixth position of the triazolothiadiazole nucleus played a decisive role in modulating activity. Among the tested series, compounds incorporating an indole moiety at this position exhibited the highest anti-inflammatory potential. The enhanced activity of indole-substituted derivatives may be attributed to the favorable electronic environment and planar aromatic structure of the indole ring, which likely facilitates better interaction with biological targets involved in the inflammatory cascade. Moreover, the comparison between the parent triazolothiadiazoles and their dihydro analogues suggests that aromatic substitution, particularly with heteroaryl groups like indole, contributes more significantly to pharmacological potency than simple hydrogenation of the system. These results highlight the importance of heteroaryl substitution in designing triazolothiadiazole- based anti-inflammatory agents and provide valuable insights for further structural optimization within this class of heterocycles.[85]



(57)

R= -H, -OCH3; R1= -H, -CH3; R2= 5-methoxy-3-indolylmethyl, 5-methoxy-2-methyl-3-indolylmethyl, 3-indolylmethy Figure 46.

4.3.3. Nesrin et al. (2007c) synthesized a series of 1,3,4-thiadiazole derivatives (58a–c) incorporating a 5- methyl-2-benzoxazolinone moiety and evaluated them for their analgesic and anti-inflammatory activities. Pharmacological screening revealed that all synthesized compounds displayed remarkable anti- inflammatory effects, indicating that the benzoxazolinone substitution contributed significantly to their biological activity. Interestingly, compound 58a demonstrated an exceptionally high analgesic response, surpassing the standard drugs morphine and aspirin, which underscores its strong potential as a lead candidate for further development. The pronounced activity of 58a may be associated with synergistic contributions from both the thiadiazole nucleus and the benzoxazolinone ring, which together could enhance receptor binding or modulate inflammatory mediators more effectively. Overall, the study emphasizes that structural incorporation of the 5-methyl-2-benzoxazolinone framework into the thiadiazole scaffold yields derivatives with promising dual analgesic and anti-inflammatory profiles, making them valuable templates for future drug design.[84]

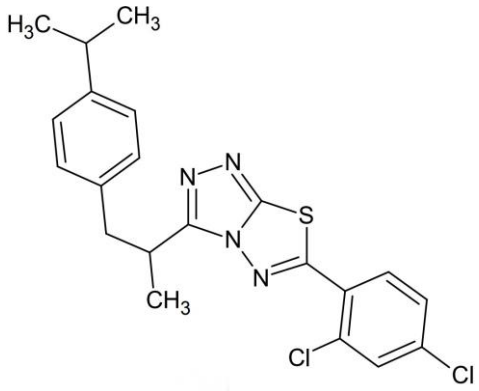


(58)

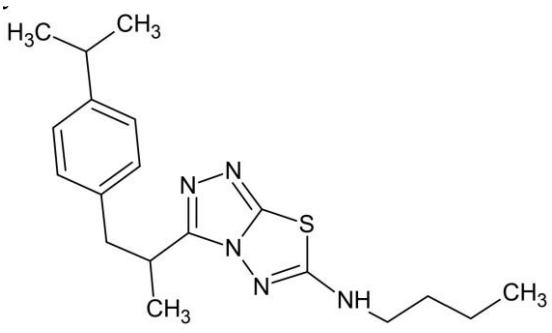
58a: R= -CH_3; 58b: R= -C_2H_5; 58c: R= C_6H_5 Figure 47.

4.3.4. Amir et al. (2008a) synthesized a series of 1,2,4-triazolo[3,4-b][1,3,4]thiadiazole derivatives based on ibuprofen and biphenyl-4-yloxy acetic acid, and subsequently

evaluated their anti-inflammatory potential. Among the tested compounds, derivatives 59 and 60 bearing 2,4-dichlorophenyl and n-butylamino substituents, respectively exhibited the highest activity. Their efficacy was slightly lower than ibuprofen but found to be comparable to flurbiprofen, indicating strong pharmacological relevance. Structure–activity analysis revealed that substitution at the C-6 position of the triazolo-thiadiazole core plays a critical role in modulating activity. In particular, the incorporation of 2,4-dichlorophenyl, 4-chlorophenyl, n- butylamino, or 4-aminophenyl groups enhanced the anti-inflammatory profile of these derivatives. These findings suggest that both halogenated aromatic groups and electron-donating amino substituents contribute positively to activity, likely through a balance of hydrophobic interactions and electronic effects that strengthen target binding. Overall, this study highlights the potential of C-6 substitution in optimizing the anti-inflammatory efficacy of triazolo-thiadiazole frameworks derived from established NSAID scaffolds.[86]



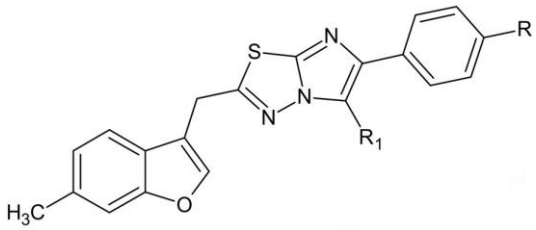
(59)



(60) Figure 48.

4.3.5. Kulkarni et al. (2008b) reported the synthesis of a series of 6-substituted and 5,6-disubstituted 2-(6- methyl-benzofuran-3-ylmethyl)-imidazo[2,1-b][1,3,4]thiadiazole derivatives (61) and evaluated their anti- inflammatory potential. Biological screening demonstrated that the nature of substitution at the R_1 position exerted a significant

influence on activity. In particular, formyl- and hydroxymethyl-substituted analogues exhibited the most pronounced anti-inflammatory effects among the tested series. The superior activity of these groups may be attributed to their ability to engage in hydrogen bonding interactions with biological targets, thereby enhancing receptor affinity. Moreover, the incorporation of polar functionalities such as hydroxymethyl appears to improve the pharmacological profile, likely by balancing lipophilicity with hydrophilicity and facilitating better bioavailability. These observations reinforce the importance of substituent selection in fine-tuning the pharmacological potential of imidazo[2,1-b][1,3,4]thiadiazole scaffolds and provide valuable insights for the rational design of new anti-inflammatory agents.[88]

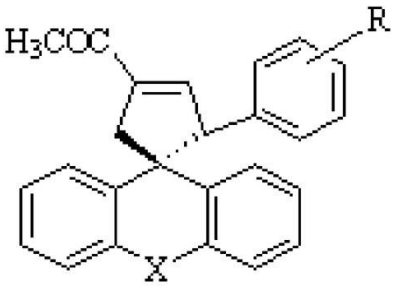


(61)

R= -Cl, -Br, -NO_2; R1= -H, -CHO, -CH_2OH, -CN, -N=OH Figure 49.

4.3.6. Hafez et al. (2008c) synthesized a new class of spiro-thioxanthene and spiro-xanthene-9,0,2- [1,3,4]thiadiazole derivatives (62) and evaluated their anti-inflammatory and analgesic potential in comparison with the standard drug ibuprofen. The anti-inflammatory assay demonstrated that the synthesized compounds exhibited activity in the range of 50–86% inhibition, while ibuprofen produced 92% inhibition at a dose of 70 mg/kg after 4 h. Notably, derivatives bearing a 4-nitrophenyl substituent at position 3 and an acetyl group at position 5 displayed the highest anti-inflammatory response (84–86%), closely approaching that of the reference drug. In addition, spiro derivatives containing two phenyl groups at positions 3 and 5 also showed strong inhibition (85% and 82%, respectively), suggesting that the presence of aromatic substituents contributes significantly to biological activity. Analgesic screening further revealed moderate to strong efficacy, with inhibition ranging from 57% to 73%, compared to 84% for ibuprofen at the same oral dose. These findings highlight that substitution with nitro- or phenyl groups, along with acetyl functionalities, enhances the pharmacological performance of spiro-thioxanthene and spiro-xanthene thiadiazole hybrids, underscoring their potential as promising scaffolds for the development of dual anti-inflammatory and

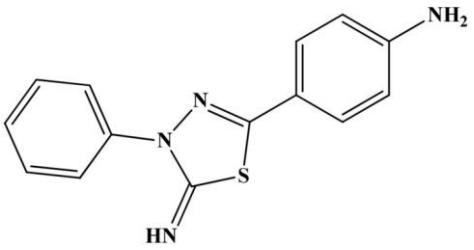
analgesic agents.[86]



(62)

X- O; S Figure 50.

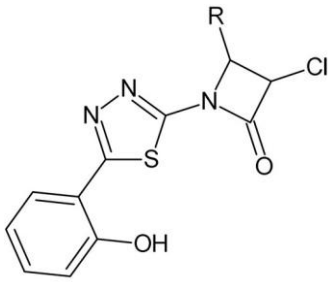
4.3.7. Asif M. et al. (2009) synthesized a series of thiadiazole derivatives bearing an imino moiety and evaluated their pharmacological potential. Among these, the compound 4-(5-imino-4-phenyl-4,5-dihydro- 1,3,4-thiadiazol-2-yl)aniline (63) was specifically assessed for its anti-inflammatory activity using the carrageenan-induced paw edema model in vivo, with Diclofenac employed as the reference drug. The biological evaluation indicated that this compound exhibited notable anti-inflammatory effects, although its activity was slightly lower than that of Diclofenac. The presence of the imino functionality, together with the phenyl substituent, may contribute to improved interaction with inflammatory mediators through a combination of electronic effects and hydrogen bonding capacity. These findings suggest that thiadiazoles incorporating imino groups could serve as valuable templates for further optimization in the search for new anti-inflammatory agents.[88]



(63) Figure 51.

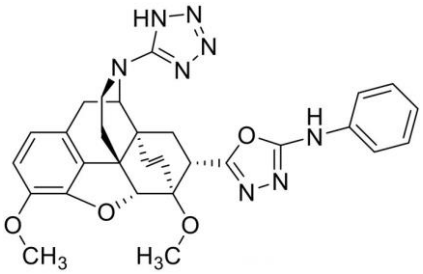
4.3.8. Shiv K. Gupta et al. (2011) synthesized and characterized a series of disubstituted 1,3,4-thiadiazole derivatives and evaluated their anti-inflammatory activity. Biological screening revealed that substitution significantly influenced pharmacological response, with compound 64 exhibiting the highest level of anti- inflammatory activity among the tested series. The superior efficacy of this compound suggests that specific substitution patterns on the thiadiazole nucleus can enhance binding affinity to biological targets

involved in the inflammatory cascade. Although the study primarily emphasized the synthesis and activity screening, the results highlight the importance of rational substituent selection in optimizing the therapeutic potential of thiadiazole-based scaffolds.[89]



(64) Figure 52.

4.3.9. Toma et al. (2013a) designed a series of N-(tetrazol-1H-5-yl)-6,14-endoethenotetrahydrothebaine 7α-substituted 1,3,4-(oxa)thiadiazoles which were synthesized and evaluated for analgesic activity in rats using the hot-plate and tail-flick methods, with Morphine employed as the standard reference drug. Among the tested compounds, the phenylamino-oxadiazole derivative 65 demonstrated remarkable potency, producing reaction times of 9.78 s in the hot-plate test and 21.45 s in the tail-flick test, which were superior to those of Morphine (6.28 s and 15.90 s, respectively). By contrast, the thiadiazole analogue 66 exhibited only moderate analgesic activity. These findings clearly indicated that incorporation of an oxadiazole moiety at the 7α-position of thebaine significantly enhanced analgesic efficacy, highlighting the importance of bioisosteric replacement in modulating pharmacological activity.[90]



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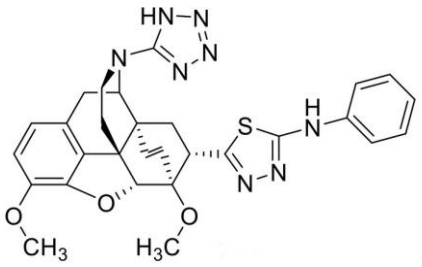
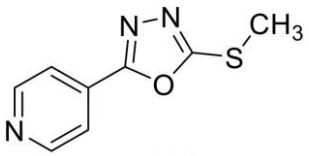
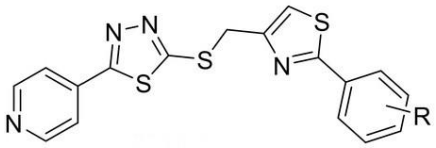


(66) Figure 53.

In a related study, by Yavuz (2013b) a series of polyheterocyclic thioethers incorporating 1,3,4- (oxa)thiadiazole scaffolds were screened for anti-inflammatory potential using the carrageenan-induced rat paw edema assay, with Diclofenac as the reference drug. Notably, compounds 67, 68a, and 68b showed stronger efficacy than Diclofenac in reducing paw edema after 2–4 hours of treatment, with inhibition values ranging from 30–55%. Importantly, no significant difference was observed between the oxadiazole-and thiadiazole-based isosteres, indicating that both heterocyclic frameworks can effectively contribute to anti-inflammatory activity.[91]



(67)



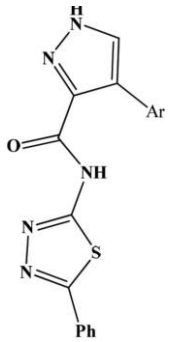
(68)

67a: R= H; 67b: R= methyl Figure 54.

Collectively, these studies emphasize the pharmacological relevance of oxadiazole and thiadiazole moieties as interchangeable bioisosteres for the design of novel analgesic and anti-inflammatory agents, with substitution patterns playing a pivotal role in determining potency.

4.3.10. Maddila S. et al. (2016) reported the synthesis of three novel heterocyclic derivatives, namely 4-(4- nitrophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-1H-pyrazole-3-carboxamide (69), 4-(4-fluorophenyl)-N-(5- phenyl-1,3,4-thiadiazol-2-yl)-1H-pyrazole-3-

carboxamide (70), and 4-(4-nitrophenyl)-N-(5-phenyl-1,3,4- thiadiazol-2-yl)-1H-pyrrole-3-carboxamide (71). These newly designed compounds were subjected to pharmacological evaluation to determine their potential anti-inflammatory activity. Biological screening revealed that all three derivatives exhibited remarkable inhibition of paw edema, indicating strong anti- inflammatory properties. Their activity was found to be significant when compared with indomethacin, which was employed as the standard reference drug. The high percentage of edema inhibition suggests that these compounds could serve as promising scaffolds for the development of more effective anti-inflammatory agents.[92]



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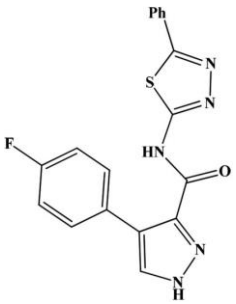
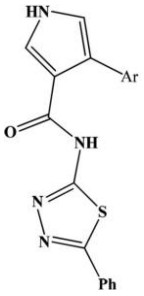


(70)

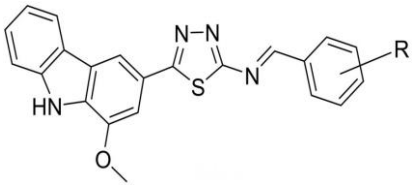


(71) Figure 55.

4.3.11. Mahapatra et al. (2017a) designed and synthesized a novel series of murrayanine–1,3,4-thiadiazole hybrids as potential anti-inflammatory agents. The synthetic route

employed utilized the previously reported starting material (E)-2-((1-methoxy-9H-carbazol-3-yl)methylene)thiosemicarbazide. The resulting compounds (72a–e) were evaluated for anti-inflammatory activity. Among them, compound 72c, bearing 3-OCH_3 and 4-OH substituents, exhibited the most pronounced edema-reducing effect at the 3 h mark. The improved activity was attributed to the possible interaction of hydrophilic substituents, particularly oxygen-containing groups, with the active sites of key pro-inflammatory enzymes such as Cyclooxygenase (COX) and Lipoxygenase (LOX).

Although efforts were made to establish a clear structure–activity relationship (SAR), the results were somewhat inconsistent, preventing a definitive conclusion. Nevertheless, tentative assumptions were drawn, suggesting that the enhanced biological activity may be influenced by specific functional groups capable of engaging with the active sites of inflammatory mediators.[93]

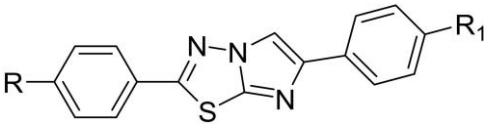


(72)

R= 72a: -H, 72b: -CH(CH_3), 72c: 3-OCH_3;4-OH, 72d: 3,4-OCH_3, 72e: 3,5-OCH_3; 4-OH Figure 56.

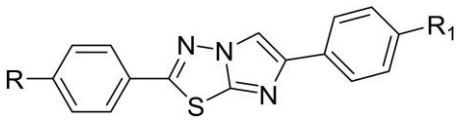
4.3.12. Kumari et al. (2017b) synthesized a series of novel 1,3,4-thiadiazole derivatives (73) and subjected them to pharmacological screening for their anti-inflammatory potential. The selection of the 1,3,4- thiadiazole nucleus as the central scaffold was based on its well-documented role in medicinal chemistry, particularly for its ability to act as a bioisostere of amide and ester functionalities and to interact with multiple biological targets. The newly synthesized compounds were evaluated using standard in vivo models of inflammation, where several derivatives exhibited moderate to significant edema inhibition, comparable in some cases to reference drugs. The enhanced pharmacological effect was attributed to the possible interactions of electronegative substituents with the active site residues of pro-inflammatory enzymes, thereby interfering with the biosynthetic pathways of mediators such as prostaglandins and leukotrienes. While the study highlighted the anti-inflammatory potential of 1,3,4-thiadiazole hybrids, further optimization of substituent pattern and exploration of mechanistic pathways were

suggested to achieve greater potency and selectivity.[94]



(73) Figure 57.

4.3.13. Cristina A. et al. (2018a), stated that Non-steroidal anti-inflammatory drugs (NSAIDs) represent a major class of pharmacological agents employed in the management of inflammatory disorders. Despite their clinical efficacy, their long-term use is often limited by adverse effects such as gastrointestinal ulceration, elevated cardiovascular risk, and renal impairment. To overcome these limitations and to identify safer therapeutic alternatives, a novel series of 2,6-diaryl-imidazo[2,1-b][1,3,4]thiadiazole derivatives (74a–l) was synthesized and evaluated for anti-inflammatory and analgesic activites. The in vivo pharmacological screening was conducted using the carrageenan-induced rat paw edema model. Among the synthesized compounds, 74c demonstrated superior anti-inflammatory efficacy compared to the reference drug diclofenac, while compounds 74g, 74i, and 74j exhibited antinociceptive activity comparable to that of diclofenac. Importantly, none of the derivatives showed ulcerogenic effects, indicating a potentially improved safety profile. Furthermore, molecular docking studies were performed to explore binding interactions with cyclooxygenase isoenzymes (COX-1 and COX-2). Notably, compound 74c displayed higher COX-2 inhibitory potential than diclofenac, providing a molecular basis for its enhanced pharmacological activity.[95]

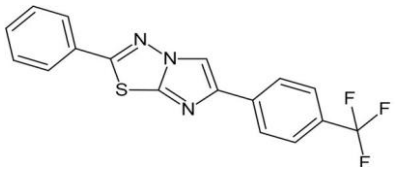


(74)

74a: R = H; R_1 = H, 74b: R = H; R_1 = Br, 74c: R = H; R_1 = CF_3, 74d: R = H; R_1 = OCH_3, 74e: R = Cl, 74f: R = Cl; R_1 = Br, 74g: R = Cl; R_1 = CF_3, 74h: R = Cl; R_1 = OCH_3; 74i: R = OCH_3; R_1 = H, 74j: R = OCH_3; R_1 = Br, 74k: R = OCH_3; R_1 = CF_3, 74l: R = OCH_3; R_1 = OCH_3. Figure 58.

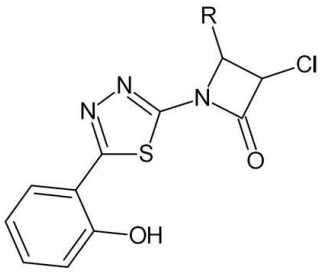
4.3.14. Omar et al. (2018b) reported the synthesis, biological evaluation, and molecular docking studies of 1,3,4-thiadiazole derivatives as potential anti-inflammatory agents with dual inhibition of COX-2 and 15- LOX. All thiadiazole analogs were synthesized and structurally characterized using ^1H NMR, ^13C NMR, and mass spectrometry.

Both in vitro and in vivo anti-inflammatory activities were assessed, and among the tested compounds, compound 75 exhibited superior activity compared to the reference drug celecoxib.[96]



(75) Figure 59.

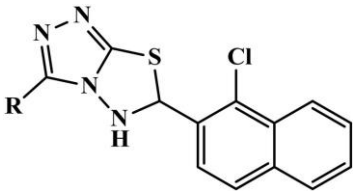
4.3.15. Doshi et al. (2021) investigated the biological potential of 1,3,4-thiadiazole derivatives. A series of these compounds was synthesized, structurally characterized, and evaluated for both in vitro and in vivo anti-inflammatory activities. The in vitro studies included membrane stabilization (48.89%) and proteinase enzyme inhibition (66.78%), while the in vivo activity was assessed using the cotton pellet granuloma model. Among the tested compounds, compound A demonstrated superior anti-inflammatory activity in both assays.[97]



(76) Figure 60.

4.4.Anti Oxidant Activity

4.4.1. Abdel H.et al (2007) synthesized the series of 3-alkyl/aryl-6-(1-chloro-3,4-dihydronaphth-2-yl)-5,6- dihydro-s-triazolo[3,4-b][1,3,4]thiadiazole derivatives were systematically investigated for their biological activities, with particular emphasis on antioxidant and antibacterial potential. The antioxidant activity was assessed in comparison with the standard reference drug Sodium Nitroprusside at a concentration of 5 µM. Furthermore, their antibacterial efficacy was examined against two representative bacterial strains, namely Escherichia coli (a Gram-negative pathogen) and Staphylococcus aureus (a Gram-positive pathogen). The findings suggested that these heterocyclic scaffolds possess promising dual activity, highlighting their potential as lead candidates for further pharmacological development.[98]



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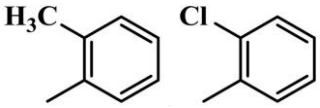
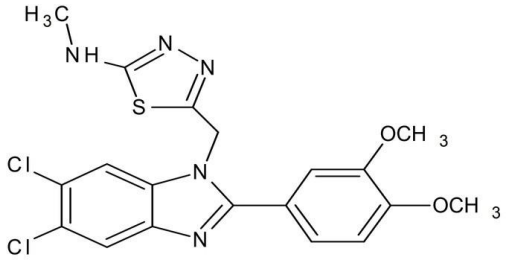


(78)

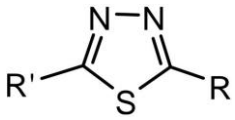
R = Phenyl, CH3, C2H5, CH2CH2CH3R1=H, OH, Cl, NO2 R2=OH, NO2, Cl, R3=OH, H, NO2 R4=H, OH, OCH3 Figure 61.

4.4.2. Kus et al. (2008a) synthesized a series of novel 5-[(2-(substituted phenyl)-1H-benzimidazole-1- yl)methyl]-4-methyl-1,3,4-thiadiazole-2-amines and evaluated their antioxidant activity using different in vitro models. Among them, compound (79) emerged as the most active derivative, showing a mild inhibitory effect on lipid peroxidation at a concentration of 10^{-3} M.[99]



(79) Figure 62.

4.4.3. Kus et al. (2008b) synthesized series of disubstituted 1,3,4-oxadiazoles/thiadiazoles (80) were evaluated for their antioxidant potential using nitric oxide and DPPH assays. The findings revealed that compounds bearing the oxadiazole moiety demonstrated significantly higher antioxidant activity compared to those containing thiadiazole moieties in both assays at a concentration of 100 mM. Furthermore, members of the benzyl series exhibited stronger antioxidant effects than those of the aryl series.[99] Similarly, Padmaja et al. (2012) further studied a set of 5-[(2-(substituted phenyl)-1H- benzimidazole-1-yl)methyl]-N-methyl-1,3,4-thiadiazole-2-amines (81) were also investigated for antioxidant activity across various in vitro systems.[100]



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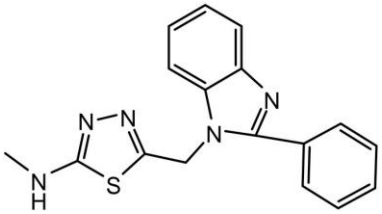
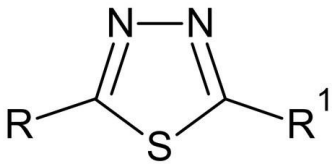


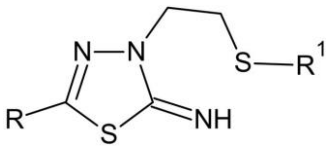
(81) Figure 63.

4.4.4. Cressier et al. (2009) evaluated the antioxidant potential of various thiadiazole derivatives and found that the thiol, thiosulfonic acid, and phosphorothioate derivatives (82-83) exhibited marked antioxidant activity. The notable activity of thiol derivatives supports the hypothesis that the presence of a thiol group directly linked to an aromatic ring plays a crucial role in enhancing radical scavenging ability. In this mechanism, the thiol group captures the free radical, while the aromatic ring stabilizes and traps it further. Additionally, the aminothiol derivative of thiadiazole was reported to display even stronger antioxidant activity.[101]



(82)

R= -SCH_2CH_3, -CH_2CH_3;R1= -SH, -$NHCH_2CH_2SH$

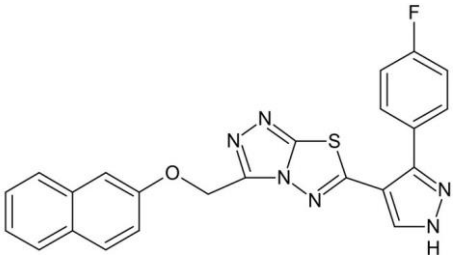


(83)

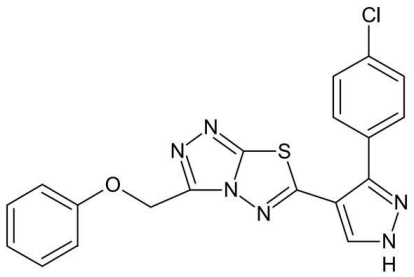
R= -SCH_2CH_3, -CH_2CH; R1= -SO_3H, -$PO(OH)_2$ Figure 64.

4.4.5. Sunil D. et al (2010) investigated the in vitro antioxidant activity of two triazolothiadiazoles, namely 6-[3-(4-fluorophenyl)-1H-pyrazol-4-yl]-3-[(2-naphthyloxy)methyl][1,2,4]triazolo[3,4-b][1,3,4]thiadiazole (FPNT) (84) and 6-

[3-(4-chlorophenyl)-1H-pyrazol-4-yl]-3-[(phenyloxy)methyl][1,2,4]triazolo[3,4-b] [1,3,4]thiadiazole (CPPT) (85). Their antioxidant potential was assessed using spectrophotometric DPPH and ABTS radical scavenging assays, along with a lipid peroxidation assay. Among the tested compounds, FPNT displayed remarkable antioxidant activity, as reflected by its significantly lower IC_{50} values compared to the standard. Results from both radical scavenging assays and the lipid peroxidation test consistently confirmed FPNT as a highly potent antioxidant.[102]

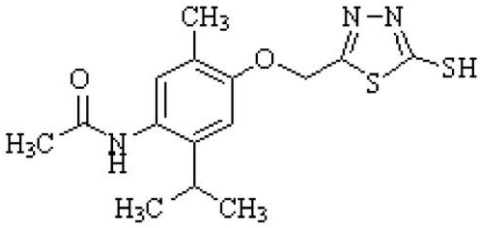


(84)



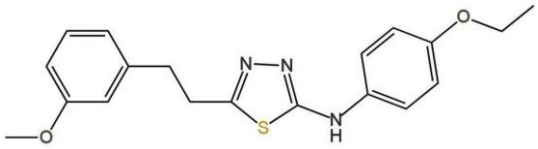
(85) Figure 65.

4.4.6. Suresh et al. (2016) synthesized a series of carvacrol-based novel thiadiazole derivatives (86) and evaluated their in vitro antioxidant potential using the DPPH free radical scavenging assay. All the synthesized compounds demonstrated noteworthy antioxidant activity, with several of them exhibiting activity either comparable to or exceeding that of the reference standard, ascorbic acid. The highest radical scavenging activities recorded were 89.98% and 94.52%, which are on par with or superior to the standard ascorbic acid (94.03%) at the same concentration. In addition, the compounds displayed considerable radical scavenging efficiency, with percentage inhibition values ranging between 63.67% and 67.21%, confirming their significant antioxidant properties.[103]



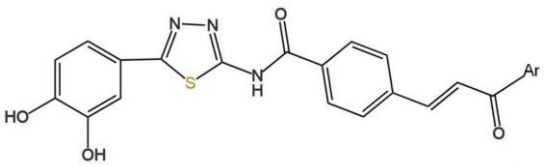
(86) Figure 66.

4.4.7. Gür M et al. (2017) synthesized 1,3,4-thiadiazoles incorporating 2- and 3-methoxycinnamic acidsand characterized structures with spectroscopy and quantum-chemical calculations. Compounds displayedmeaningful antioxidant activities in DPPH and FRAP assays, with methoxy-substituted cinnamatesboosting electron-donation and radical-stabilization through conjugation and resonance effects. DFTparameters (HOMO energies, proton affinity, BDEs) correlated with experimental potency, indicatingmixed single-electron transfer and hydrogen-atom transfer mechanisms. Carboxylate linkages andextended π-systems facilitated charge delocalization, enhancing redox buffering. Findings underscoredcinnamate–thiadiazole hybrids as tunable antioxidants with predictable substituent influences.[104]



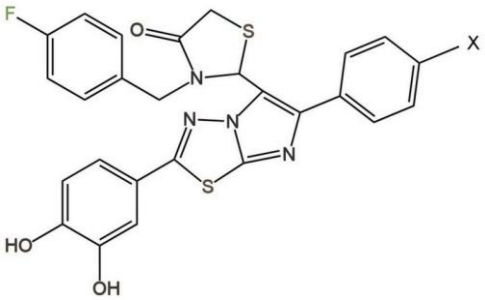
(87) Figure 67.

4.4.8. Jakovljević K et al. (2018) synthesized 1,3,4-thiadiazole–chalcone hybrids bearing catechol groupsand showed strong radical-scavenging in DPPH/ABTS assays, enhanced ferric-reducing power, and metal-chelation consistent with redox-active catechols. Compounds intercalated with DNA and protectedplasmid DNA from oxidative nicking, suggesting ROS-quenching alongside potential redox cycling. Structure–activity indicated electron-donating substituents on chalcone rings and intact catechol motifsimproved activity. Selected hybrids exhibited balanced antioxidant capacity and moderate cytotoxicityagainst tumor lines, implying redox-mediated antiproliferative effects. Electrochemical profiles supportedfacile single-electron transfer. Overall, catechol-decorated thiadiazole–chalcones emerged as dualantioxidant/DNA-interactive scaffolds with tunable potency and safety.[105]



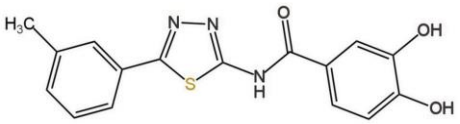
(88) Figure 68.

4.4.9. Taflan E et al. (2019a) designed imidazo[2,1-b][1,3,4]thiadiazole (ITD) hybrids with notableantibacterial potency and complementary antioxidant effects. Hybrids scavenged DPPH/ABTS radicals, showed ferric-reducing antioxidant power, and inhibited lipid peroxidation, indicating both electron-transfer and hydrogen-atom transfer mechanisms. Electron-donating aryl substituents, heteroatom-rich linkers, and extended conjugation enhanced activity by stabilizing radical intermediates. Antioxidantperformance correlated partly with antibacterial efficacy, suggesting redox stress modulation in microbes. Docking supported interactions with oxidoreductase targets. ITD cores provided a compact, rigidplatform enabling favorable π-stacking and redox behavior, positioning these hybrids as multifunctionalanti-infective/antioxidant candidates.[106]



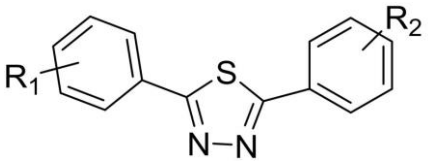
(89) Figure 69.

4.4.10. Jakovljević K et al. (2019b) prepared 1,3,4-thiadiazole conjugates from protocatechuic acid, leveraging a natural catechol antioxidant as a pharmacophore. Conjugates exhibited excellentDPPH/ABTS scavenging, ferric-reducing capacity, and copper-chelating effects, reflecting synergistic catechol–thiadiazole contributions. Cyclic voltammetry indicated reversible redox events and lowoxidation potentials consistent with efficient electron donation. Computational modeling supportedradical stability via delocalization across aromatic and heterocyclic domains. The most potent analogsprotected DNA against oxidative degradation and showed acceptable cytotoxicity.[107]



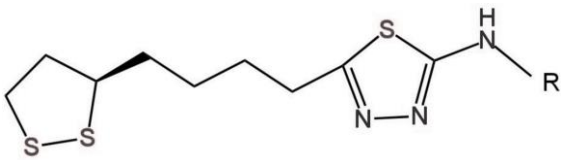
(90) Figure 70.

4.4.11. Ko I. et al. (2019c) studied five-membered heterocyclic scaffolds, particularly thiadiazoles, continue to serve as a vital framework in medicinal chemistry due to their wide applicability in the design of novel therapeutic agents. A convenient two-step, one-pot protocol has been reported for the synthesis of 2,5- disubstituted-1,3,4-thiadiazole derivatives (91), employing aryl hydrazides and aryl aldehydes as starting materials in the presence of Lawesson's reagent. This method affords the desired products in moderate to high yields, highlighting its efficiency and practicality. Preliminary biological evaluations further revealed that several of these newly synthesized thiadiazole derivatives exhibit promising antioxidant activity, underscoring their potential for future pharmacological exploration.[108]



(91) Figure 71.

4.4.12. Bakir TK et al. (2024) developed novel 1,3,4-thiadiazoles conjugated to α-lipoic acid, a clinicallyused antioxidant. Hybrids demonstrated robust free-radical scavenging (DPPH/ABTS), ferric-reducingpower, and protection against lipid peroxidation, outperforming parent fragments in several assays evidence of synergistic redox behavior. Likely mechanisms combined lipoic/dihydrolipoic cycling withthiadiazole-facilitated electron transfer and metal chelation. Spectroscopic and analytical data confirmedintended architectures. The conjugation strategy delivered high antioxidant potency with promisingstability, highlighting thiadiazole–lipoic hybrids as next-generation redox modulators and potentialcytoprotective agents against oxidative stress-related pathologies.[109]



(92) Figure 72.

CONCLUSION

In conclusion, the extensive evaluation of various derivatives and analogues of 1,3,4-thiadiazoles over the past decade underscores their enduring medicinal significance. Among the range of pharmacological activities explored, antimicrobial potential stands out as the most widely investigated and easily evaluated property, reflecting both its clinical importance and the feasibility of experimental assessment. This review consolidates 10–20 years of research, highlighting the systematic exploration of structural modifications and their impact on biological activity, which has led to the identification of highly potent and selective thiadiazole-based molecules. Beyond antimicrobial effects, these scaffolds demonstrate remarkable versatility, exhibiting promising activity across diverse therapeutic areas, including anticancer, anti-inflammatory, antioxidant, and enzyme inhibitory domains. The compiled data collectively emphasize that the 1,3,4-thiadiazole nucleus serves as a robust and adaptable scaffold for rational drug design.

Furthermore, the strategic modification of the thiadiazole core, including hybridization approaches and bioisosteric replacements, has proven to enhance pharmacological profiles significantly, offering a rich template for future drug discovery. The versatility and structural tunability of these scaffolds position them as highly valuable candidates for the development of novel therapeutics. Moving forward, the integration of innovative synthetic methodologies, rational analog design, and targeted pharmacological evaluations promises to accelerate the translation of thiadiazole-based compounds into clinically relevant applications. Collectively, the insights compiled in this review not only reinforce the therapeutic potential of 1,3,4-thiadiazoles but also provide a solid foundation for guiding future research aimed at harnessing their full pharmacological spectrum.

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