1,3,4-Thiadiazole Derivatives as an Antimicrobial: An Update

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Authors’ contributions
This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information
DOI: 10.9734/JPRI/2021/v33i62A35203

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/81506

ABSTRACT
Persistent and uncontrolled use of antibiotics results in development of bacterial resistant. The situation is getting worsen day by day and scientists are investigating thousands of potentially active drugs like molecule in laboratories around the world every day in search of effective antibiotics. During last decade considerable attention was given to five-member heterocyclic moieties while designing new antimicrobial agents. One of important heterocycle is five-membered 1,3,4-thiadiazole with unique bioisosteric properties displaying unusually wide spectrum of biological activities. This comprehensive review represent the recent 1,3,4-thiadiazole and its derivatives, which can be considered as potential antimicrobial agents in the period of 2015 and onwards. This review may help the medicinal chemists to develop new leads possessing 1,3,4-thiadiazole nucleus with higher efficacy and reduced side effects.

Keywords: 1,3,4-thiadiazole; anti-tubercular activity; antimicrobial activity; thiadiazole.

1. INTRODUCTION
Among organic compounds, heterocyclic compounds stood at front for the use of drugs for different biological activities in human and veterinary medicine or as insecticides and pesticides in agriculture [1]. During the past decade, five-membered heterocyclic moieties remain an important target in search of new lead for different therapeutic areas [2]. Among all the

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heterocycles, five-membered thiadiazole ring system is one of the important heterocycles which comprises different isomers of thiadiazole 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, and 1,3,4-thiadiazole [3]. The hybrid technique is an innovative and strong synthetic tool for the synthesis of two or more different entities in one molecule with novel biological functions, according to the review study. Because of their tremendous potential for displaying notable biological features, -lactams have long been a key component of hybrid molecules. Lactams with four members have been identified as a component of penicillin. The synthesis of -lactams can be done in a variety of ways. For the production of these compounds, the Staudinger reaction of Schiff bases with diphenylketenes is an effective and well-known approach [4]. Several studies have been published on the topic of hybrid molecules, such as the synthesis of The reaction of readily accessible starting materials such as 4-oxo-4H-chromene-3-carbaldehyde, 1-phenyl-2-(1,1,1-triphenyl-5-phosphanylidene)ethan-1-one, and dibromoformaldoxime under mild conditions in the presence of KHCO3 yielded a novel, metal-free, and chemo selective approach for 4,5-dihydroisoxazole derivatives [5-6]. The authors described a one-pot sequential four-component reaction of 4-oxo-4H-chromene-3-carbaldehyde, 2-chloroquinoline-3-carbaldehyde, 1-phenyl-2-(1,1,1-triphenyl-5-phosphanylidene)ethan-1-one, ninhydrin or isatin, and L-proline in EtOH to obtain a library of diverse polycyclic pyrrolizid Excellent chemical yields, great diastereoselectivity, and operational simplicity are all hallmarks of this procedure [7]. An efficient, practical, and generic approach for the synthesis of [1,8] was explored and discussed by a group of researchers. It is described a one-pot four-component reaction of 2-chloroquinoline-3-carbaldehyde and 1-phenyl-2-(1,1,1-triphenyl-5-phosphanylidene)ethan-1-one, 1,1-bis(methylthio)-2-nitroethylene or ketene N,S-acetals, aromatic/alphaic amine or diamines, and aromatic/alphaic amine or diamines under mild and High yields, gentle and catalyst-free conditions, fast reaction durations, and the use of green solvent are all advantages of this protocol [8].

Literature survey revealed that among all the isomer, 1,3,4-thiadiazole have received considerable attention and has been because of their broad spectrum of pharmacological activity. 1,3,4-thiadiazole having high aromatic property is a very weak base because of inductive effect imparted by ring sulfur. 1,3,4-thiadiazole is stable in aqueous acid solution and undergoes ring cleavage in aqueous basic solution. Nucleophilic attack is prevalent as ring is electron deficient because of electronegative ring nitrogen nonreactive towards electrophilic attack. Nucleophilic substitution is favored at 2’ or 5’ position of the ring. 1,3,4-thiadiazole [9,10].

Fig. 1. Isomers of thiadiazole

Fig. 2. Numbering of 1,3,4-thiadiazole ring system

Most of the authors assumed that presence of =N-C-S- moiety is responsible for biological potential of 1,3,4-thiadiazole derivatives [11]. While some other authors supposed that great in vivo stability of 1,3,4-thiadiazole is because of its strong aromatic is responsible for biological activity and low toxicity [12].

1,3,4-thiadiazole is the bioisosteres of pyridazine through the substitution of CH=CH by -S- (Fig. 2) [13, 14]. The thiadiazole derivatives show good lipid solubility attributed to ring sulfur and thereby show oral absorption and good cell permeability leading to a good bioavailability [14-16]. Discovery of heterocyclic sulfonamides established the biological importance of 1,3,4-thiadiazole derivatives [17]. Presently only sulfathiazole is used in clinical practice for the management of Haemophilus vaginalis vaginitis [18]. Importance of 1,3,4 thiadiazole highlighted among researchers with report of acetazolamide synthesis as carbonic anhydrase inhibitor used in glaucoma [19], epileptic seizures [20], hemiplegic migraine [21] etc. Its methylated derivative methazolamide is a more potent carbonic anhydrase inhibitor and displays diuretic, antiglaucoma and potential antineoplastic activity [22], 1,3,4-thiadiazole derivatives displays diverse pharmacological activities including antimicrobial [23], anti-cancer
[24], antifungal [25], antituberculosis [26], local anaesthetic [27], antiglaucoma [28], anticonvulsant [29], anti-inflammatory [30], antidepressant and anxiolytic [31], antihypertensive [32], antiviral [33] and antioxidant activity [34].

This review discusses the antimicrobial potential of 1,3,4-thiadiazole which appeared very recently in literature. Special attention is given to antitubercular activity and discussed under separate heading.

2. ANTIMICROBIAL ACTIVITIES ASSOCIATED WITH 1,3,4-THIADIAZOLE SYSTEM

Infective diseases caused by pathogenic microorganisms such as bacteria, fungi, viruses, protozoa and helminthes affects millions of people worldwide and results in considerable deaths. Interestingly among 1400 different species of microorganisms which are reported in literature only 20 of them (mostly bacteria) accounts for around two thirds of the casualties [35]. Although highly developed countries experiencing fall in death from 16 million in 1990 to approximately 15 million and forecasting 13 million in 2050, death rate is still high in developing countries because of tuberculosis, pneumonia, malaria, HIV/AIDS, diarrhea and many other diseases [36,37]. Powerful immunosuppressive drugs are occasionally prescribed for the management of cancer therapy, organ transplant and spread of HIV infection resulting in increased incidence of fungal infections among immunocompromised patients. Occurrence of systemic fungal infections witnessed sharp rise recently [38,39]. Considering the recent pandemic because of COVID-19 and similar pandemic threat in future and issue of dramatic increase in antibiotics resistance, discovering new effective antibacterial/antiviral drugs and the development of modern therapies are two challenges of top importance.

2.1 Antibacterial and Antifungal Activities

Being bioisosteres of the thiazole ring, thiazole ring acts as a pharmacophore and is the part of the third- and fourth-generation cephalosporins, and this observation makes it possible to use it in the synthesis of antimicrobial agents [40]. Since the discovery of penicillin in 1942) the race of finding new antibiotics continued and became most intense with time [41]. With the passing time microorganisms are becoming more resistant and invasive which resulted in dramatically increased bacterial infections. On other side systemic fungal infection is now more evident with the use of powerful immunosuppressive drugs for cancer therapy and organ transplants [30,31].

As per reported work, synthesized a new series of 1,3,4-thiadiazol-4,5-dihydropyridazin-3(2H)-ones derivatives and evaluated the compounds for antimicrobial potential. Most of the synthesized derivatives were found to be bactericidal. Compounds 1a–e, 2a–c and 3 exhibited moderate activity against B. subtilis. Compounds 1a, 1c–e and 2a–c were potent against S. pneumoniae. Compounds 1a–e exhibited moderate to potent activity against fungal strains A. fumigates, S. racemosum and G. candidum. Authors observed that compounds bearing only thiazole moiety at C-4 of pyridazinone ring were found more active towards all microbial strains except for P. aeruginosa and C. albicans, and the presence of either carbamoyl or thiocarbamoyl group at N-2 improved the activity [42].
As per reported work, the synthesis of Schiff bases clubbed with 1,3,4-thiadiazole moiety and evaluated them for antimicrobial activity. Antimicrobial assay results indicated that most of the synthesized thiadiazole derivatives exhibited good to excellent antimicrobial activity. Schiff bases 4, 5, 6 exhibited excellent bactericidal activities against all the strains with inhibition at MIC 4–16 μg/mL. Compound 7a and 7b comprising fluorine atom displayed remarkable inhibition at MIC 4–8 μg/mL against Gram positive bacteria. The entire above compound displayed good antifungal activity against all examined fungal strains at MIC 16–31.5μg/mL [43].

Author have reported the 1,3,4-thiadiazole derivatives of 2-(4-formyl-2-methoxyphenoxy) acetic acid (6a–s) and tested them against bacteria S. aureus, S. enterica, V. cholera, B. subtilis, P. mirabilis, E. coli V517, M. smegmatics, P. aeruginosa and antifungal activity against C. albicans. Compound 8b exhibited excellent activity against all the strains. It showed maximum activity (97%) against S. enterica (95%), against V. cholera and (87.9%) inhibition of E. coli V517 when compared with standard drug ampicillin. Compound 8a, 8c, 8d and 8e also displayed very good activity. Compound 8b showed maximum inhibition (87.8%) whereas, compound 8a showed (83.3%) inhibition against fungal strain C. albicans [44].

As per reported in literature, synthesized novel pyridine imidazo [2,1b]-1,3,4-thiadiazole derivatives. When investigated for antimicrobial potential it was revealed that compounds, 4(a), 4(b), 4(f), 4(h) and 4(k) exhibited promising candidates against B. pumillus, S. aureus, V. cholera, E. coli, P. mirabilis, P. aeruginosa and C. albicans with reference to standard drugs ampicillin and amphotericin B [45].
Substituted benzimidazoles containing 1,3,4-thiadiazole were synthesized and tested for antimicrobial activity. Compound 10 displayed moderate antibacterial activity [46].

In vitro antimicrobial activity of Novel 4-(5-(10-(3-N, N-dimethylamino) propyl)-10H-phenothiazine3-yl)-1, 3, 4-thiadiazole-2-yl) Azo dye/Schiff base derivative was evaluated against several strains. Compound 13 showed promising anti-microbial activity against various pathogenic microorganisms as compared to the antibiotics Ciprofloxacin and Fluconazole [49].

New 1,3,4-thiadiazole derivatives based on the key precursor 2,5-bis(mercaptoacetichydrazide)-1,3,4-thiadiazole were reported and tested against E. coli and E. faecalis strains. The tested compounds exhibited higher to moderate activity in comparison with ceftriaxone at concentration 30 mg/discs. Compounds 14, 15, and 17 showed higher activity against bacteria E. coli, and compounds 15, 16, 17, and 18 showed higher activity against Enterococcus bacteria [50].
1, 3, 4-thiadiazole-based thioglycosides were synthesized and evaluated for antimicrobial activity against several strains. Among the entire compounds lauric acid and myristic acid derivatives showed good and moderate antimicrobial activity. Compound 19a and 19b were found most potent against Gram-negative bacteria strain *Klebsiella pneumonia* with MIC values 12.5, 25 g/mL respectively when compared with penicillin and streptomycin [51].

Synthesized new a series of novel myricetin derivatives containing 1,3,4-thiadiazole and tested for antibacterial activities against Xoo and Rs and their antiviral activity against TMV. Bioassay results indicated that some target compounds exhibited potential antibacterial and antiviral activities. Among them, compounds 24, 5, 7-Dimethoxy-2-(3,4,5-trimethoxyphenyl)-3-((5-((4-chlorobenzyl)thio)-1,3,4-thiadiazol-2-yl) methoxy)-4H-chromen-4-one exhibited highest activity [53].

Synthesized new 1,2,4-Triazolo [3,4-b][1,3,4]thiadiazole derivatives and evaluated for their in vitro antibacterial and antifungal activities against pathogenic microorganisms using two fold serial dilution method. Compound 25a was most active while compounds 25b and 25c displayed remarkable antimicrobial activity against all the tested microorganisms comparable to reference drugs gentamicin and miconazole. Docking study revealed that test compound 25e had lesser estimated binding free energy and predicted inhibitory constant values when compared with fluconazole. A SAR study indicated that the activity was the highest when halogen groups were substituted at the ortho and Meta positions of the first phenyl ring attached to the 3rd position of the triazolothiadiazole nucleus [54].

1,3,4-thiadiazoles derived from 4-phenoxbutyric acid were synthesized and screened tested against gram negative bacteria, gram positive bacteria and for antifungal potential. However, all the tested compounds showed good antimicrobial activities against *S. aureus* only. The highest antimicrobial activity was exhibited by compound 26a. Compound 26b, 27 and 28 also exhibited significant antimicrobial activity [55].
Sawarkar et al.; JPRI, 33(62A): 232-257, 2021; Article no.JPRI.81506
As per published work, synthesized new series of 1,3,4-thiadiazolyl-sulfanyl-4,5-dihydropyridazin-3(2H)-ones and evaluated them for antimicrobial potential. Compounds 29d, 30 and 31 exhibited potent activity against B. subtilis and found more potent against S. pneumonia compared to control drug. Compounds 29a, 29d, 30, and 31 displayed remarkable activity against E. coli and their bacteriostatic effect has exceeded over control drug. Compounds 29a-c, 5, and 29d exhibited potent antifungal activity against A. fumigates, S. racemosum, G. candidum. Only compound 29d was found potent against C. albicans strain. From the obtained results it was noted that; pyridazinone rings 29a–d and 30 resulted from thia-Michael adduct were generally very potent against all bacterial and fungal strains except for P. aeruginosa and C. albicans. The presence of either carbamoyl or thiocarbamoyl moiety at N-2 significantly increased the activity to precede the control drug [56].

A new class of methylthio linked pyrimidinyl 1,3,4-thiadiazoles 32a-f were synthesized and evaluated for antimicrobial activity. The compounds 32c and 32f displayed strong antibacterial activity against P. aeruginosa at all tested concentrations. It was observed that electron withdrawing groups on the aromatic ring increased the activity. Results indicated that tested compounds were more susceptible towards the Gram negative bacteria than Gram positive ones. All the compounds exhibited very good antifungal activity against A.niger than P. chrysogenum [57].
compounds for antibacterial potential. Compound 33a and 33b displayed good activity against Gram-positive bacteria *Bacillus megaterium, Enterococcus faecalis* and *Streptococcus mutans* MTCC 497 and Gram-negative bacteria *Escherichia coli, Proteus vulgaris* and *Pseudomonas aeruginosa* [58].

1,3,4-thiadiazole derivatives containing pyrazole oximes were synthesized and tested against acaricidal and insecticidal activity. Some of the target compounds showed promising acaricidal and insecticidal properties. Importantly, compound 34a showed 80% acaricidal activity against *Tetranychus cinnabarinus* at the concentration of 50μg/mL and compound 34b exhibited 100% insecticidal activities against *Aphis craccivora* at the concentration of 50 μg/mL. Moreover 100% insecticidal activities against *Plutella xylostella* was exhibited by compound 34c and 34d at the concentration of 50μg/mL. Furthermore, compounds 34c (LC50 = 19.61 μg/mL) and 34d (LC50 = 9.78 μg/mL) possessed comparable or even better insecticidal activities than the control Pyridalyl (LC50 = 17.40 μg/mL) against *Plutella xylostella* [59].

Synthesized new 1,3,4-thiadiazole derivatives and screened for antimicrobial activity. Levofoxacin. Compounds 35, 36a and 36b showed very good antimicrobial activity towards Gram-positive (*Rhodopseudomonas*sp., *Bacillus cereus* and *Micrococcus luteus*) and Gram negative (*E. coli* and *Salmonela typhi*) bacteria with MIC values (1-8) mol mL−1 when compared to Levofoxacin (MIC= 2-5 mol mL−1). Compounds 8, 10a and 10b also exhibited higher antifungal activity against *Alternaria alternate, Aspergillus flavus, Candida albicans* and *Curvularia lunata* comparable to Nystatin [60].

Vanillin derivatives of 1,3,4-thiadiazole were synthesized and screened for antibacterial activity. Compound 37 displayed strong antibacterial activities against *Xanthomonas oryzae pv. oryzae* (Xoo) and *Xanthomonas oryzae pv. oryzicola* (Xoc) in vitro, with the EC50 values of 3.14 and 8.83 μg/mL, respectively [61].
Reported synthesized several 1,3,4-thiadiazole derivatives of 4-phenoxybutyric acid which displayed strong antimicrobial properties against *S. aureus*. The highest antimicrobial activity was exhibited by compound 38. It has been observed that the tested compounds exhibited increased potential antimicrobial activities against *S. aureus* [62].

![Structure of compound 38](image)

1,3,4-thiadiazole derivatives from N-aminobenzyl or N-arylhydrazone series were synthesized and tested against the trypomastigote form of *Trypanosoma cruzi*. Compounds 39, 40 and 41 exhibited outstanding activity and excellent selectivity indexes when compared to reference drug posaconazole. Compound 39 was also active against the intracellular amastigote form of *T. cruzi*. Furthermore, its corresponding hydrochloride, compound 40, showed the most promising profile, producing phenotypic changes similar to those caused by posaconazole, a well-known inhibitor of sterol biosynthesis. Findings of the study indicated compound 118 as a possible prototype for the development of new drug candidates for Chagas disease therapy [63].

![Structures of compounds 39, 40, and 41](image)

Novel 1,3,4-thiadiazole derivatives 42a-h were prepared via cyclization reaction of 2-phenylbutyric acid with N-phenylthiosemicarbazide and POCl3. All the synthesized derivatives were screen against several microbial strains using a disk diffusion method. From the biological finding it was observed that the synthesized 1,3,4-thiadiazole derivatives exhibited antibacterial activity against *S. aureus*, *E. coli*, and *C. albicans* [64].

![Structure of 1,3,4-thiadiazole derivatives 42a-h](image)

Synthesis of 1,3,4-thiadiazole derivatives containing N-aryl 2-aryldiazonono-propanehydrazonoyl chlorides. Among them 43, 44, 45, 46, 47a-b, 48a-b, and 49a-b, were tested for their *in-vitro* antibacterial activity against Gram-positive bacteria (*Staphylococcus pneumoniae* and *Bacillus subtilis*) and Gram-negative bacteria (*Pseudomonas aeruginosa* and *Escherichia coli*). Compounds were also tested for their in vitro antifungal activity against fungi species (*Aspergillus fumigatus*, *Geotrichum candidum*, *Candida albicans* and *Syncephalastrum racemosum*). Ampicillin, Gentamicin and Amphotericin B were used as reference drugs. From the data obtained from experiment it was observed that tested compound exhibited moderate to strong activity against *S. pneumoniae* of *B. subtilis* while have no inhibitory effect toward *P. aeruginosa*. Compounds 45, 46, 47b and 49b exhibited high inhibitory effects against *E. coli*. Moreover all the derivatives exhibited good activity against all fungi strains [65].
Novel quinazolin-4(3H)-one derivatives containing a 1,2,4-triazolo [3,4-b][1,3,4] thiadiazole were synthesized and tested for antibacterial potential. The experimental data indicated that the compounds 50a, 50b, 50c and 50d had the EC50 values of 34.8, 28.2, 41.5 and 42.5µg/mL against the phytopathogenic bacterium Xanthomonas oryzae pv. oryzae (Xoo), respectively, which were significantly better than commercial bactericide Bismuthiazol (EC50 =95.8µg/mL) [66].

Highly potent antimicrobial imidazo [2,1-b][1,3,4] thiadiazole derivatives were reported. Compounds 51a-f were found ten time more potent with MIC values as low as 0.03 mg/ml when compared to control chloramphenicol against Gram-positive (Staphylococcus aureus and Bacillus subtilis) bacteria and Gram negative (Escherichia coli) bacteria. All the compounds fail to show significant antifungal activity. According to the electronic structure calculations, almost all active compounds obey the drug likeness properties [67].

As reported data, synthesis of N-(5-{[(1-Phenyl-5-((thiophen-2-yl)-1H-1,2,4-triazol-3-yl)thio)methyl]-1,3,4- thiadiazol-2-yl)thiophene-2-carboxamide 52 and its evaluation for antimicrobial potential. The compound was found active against gram positive bacteria (Staphylococcus aureus and Bacillus subtilis) and Gram negative bacteria (Escherichia coli and Pseudomonas aeruginosa) [68].
Synthesis of novel 1,3,4 thiadiazole derivatives with potent antifungal activity. Compounds 53a and 53b showed remarkable antifungal activity against all eight Candida species. Compound 53b was the most effective derivative against C. albicans ATCC 10231. It was observed that presence of fluoro and chloro groups at the second position of the phenyl moiety in compounds 53a and 53b was responsible for their potent activity. Moreover compound 53a and 53b exhibited a good predicted pharmacokinetics profile. Furthermore, when investigate for primary mechanism of action it was revealed that inhibition of ergosterol biosynthesis in C. Albicans was the reason behind activity of 53a and 53b. In the docking study, significant interactions were observed between compounds 53a and 53b and 14α-sterol demethylase, which is a key enzyme in ergosterol biosynthesis [69].

New imidazo[2,1-b][1,3,4]thiadiazole derivatives containing benzothiazole moiety were tested against anti-leishmanial and antibacterial activity. Compound 54a exhibited most potent antileishmanial activity (MIC=10000 μg/mL) whereas compound 54b was found to be effective at the highest concentration studied (MIC=20 000 μg/mL). In terms of antibacterial activity, compounds 54b were found to be the most effective compounds against Escherichia coli (MIC = 625 μg/mL) and against Yersinia enterocolitica (MIC=1 250 μg/mL). The docking study revealed that compounds 55, and 54b could be new potential inhibitor compounds for the 2eg7 protein structure [70].

New derivatives of 5-(nitroheteroaryl-2-yl)-1,3,4-thiadiazole were tested for leishmanicidal activity. Entire compounds exhibited potent activity against both promastigote and amastigote forms of Leishmania major (L. major). Compounds, 56 and 57 displayed highest activity. The analysis of redox-related factors indicated that exposure of L. major cells to 56 and 57 led to an increase in reactive oxygen species (ROS). Authors concluded that the anti-leishmanial potential of 56 and 57 is mediated by apoptosis through an imbalance in the redox system resulting in the elevation of ROS [71].

Synthesis of N-(5-(pyridin-4-yl)-1,3,4-thiadiazol-2-yl) cinnamamide 58. The compound was found moderately active against Salmonella typhimurium ATCC14028 [72].
Synthesis of new 2-(6-phenylimidazo[2,1-b][1,3,4]thiadiazol-2-yl)-1H-indoles derivatives and evaluated for their anti-biofilm properties against the Gram-positive and the Gram-negative bacterial strains. Compounds 59a and 59b displayed excellent anti-biofilm activity against S. aureus ATCC 25923 with BIC50 values of 0.5 and 0.8 mg/ml, respectively, whereas compound 59c was the most potent against S. aureus ATCC 6538, with a BIC50 of 0.3 mg/ml. Notably, these compounds showed effects in the early stages of the biofilm formation without affecting the mature biofilm of the same strains and the viability of the planktonic form. Author proposed the derivatives as novel valuable anti-virulence agents because of their ability in counteracting virulence factor (biofilm formation) without interfering with the bacterial growth in the free life form makes them [73].

Novel \[1,2,4\]triazolo[3,4-b][1,3,4]thiadiazole derivatives from aryl acetic acids and tested all the compounds for antimicrobial activity using ciprofloxacin and fluconazole as reference drugs. Compounds 60a and 60b exhibited highest activity against S. aureus and were more potent than standard; 60c and 60d showed remarkable activity against M. luteus. 60d displayed strong antibacterial activity than the reference drug against E. coli. The compound 60e showed significant activity against P. aeruginosa. Among fungal strains, compounds 60c and 60f displayed potent activity against A. niger, and 60d exhibited moderate potency against C. albicans [74].

Some 1,3,4-thiadiazole derivatives derived from azo dye. All the compounds were tested for antimicrobial activity. Compound 61a displayed antimicrobial activity against Candida albicans, Enterobacter aerogenes and Salmonella enteritidis. Compound 61b was found active against Salmonella typhimurium and Enterococcus durans. Compound 61c exhibited activity against Staphylococcus epidermidis and Candida albicans. Compound 61d had antimicrobial activity against Enterobacter aerogenes and Candida albicans [75].

The series of 2-amino-5-(2,4-hydroxyphenyl)-1,3,4-thiadiazole-derived homologues and examined their ability to form metal complexes with Zn(II) and Cu(II) ions. Authors observed strong synergistic antibacterial effect against Staphylococcus aureus, using concomitant treatment of thiadiazole derivatives with the commercial antibiotic kanamycin. Compounds 62 and 63 revealed a promising synergistic interaction with kanamycin resulting in a considerably enhanced activity against S. aureus. The MIC value of 0.5 µg/mL calculated for kanamycin coupled with relatively inactive compound 62, found 8-fold lower compared to that of separately tested kanamycin (3.9µg/mL) and few orders of magnitude lower compared to that of thiadiazole 62 alone. Interestingly, an identical result was received from the mixture of kanamycin with complex 63, suggesting that the interactions between kanamycin may occur via moieties which are not involved in the formation of metal complex [76].
μg/cm³) and twofold (MBC = 312.5 μg/cm³) stronger activity respectively against *P. aeruginosa* when compared to the reference drug ciprofloxacin (MBC = 625 μg/cm³) [77].

Ketoconazol. Compound 66 displayed moderate activity against all tested fungi and bacteria except (*Aspergillus flavus*). Molecular docking study revealed strong binding pattern of compound 65 at active site of target enzymes, Aspartic Proteinase (SAP2) from *Candida albicans* and enoyl-ACP reductase enzyme [78].

New dihydro-1,3,4-thiadiazole derivatives. The antimicrobial screening of newly synthesized compounds revealed that compounds 67 and 68 are the most potent against the Gram positive (*S. aureus*) and the Gram-negative (*E. coli*) bacteria compared to ciprofloxacin. The docking study was carried out using the bacterial DNA gyrase structure. Docking results revealed that compound 67, nicely bound to the substrate binding pocket of 4URO via incorporation of four hydrogen bonds with Arg84, Gly85, Arg144 and Thr173. In addition to five hydrophobic interactions with Glu58, Arg84, Pro87 and Ile102 and this may explain the high antibacterial activity of compound. Compound 68 engaged in two hydrogen bonds, one with Arg84 and Arg144 [79].
Synthesis and antibacterial activity of 2,6-disubstituted and 2,5,6-trisubstituted imidazo [2,1-b][1,3,4] thiadiazole derivatives was reported. The investigation data indicated that compounds bearing morpholine and piperidine exhibited highest activity. Compound 69 containing the piperidine group exhibited highest activity against all species of bacteria and fungi. Also, it was observed that compounds 70 and 69, which displayed higher antibacterial, have the highest docking score (-9.5 and 9.3 kcal/mol, respectively) as well [80].

Synthesis of imidazo[2,1-b][1,3,4]thiadiazoles from carbohydrates with D-ribo and D-xylo configuration was reported. The compounds were tested for the antiviral activity against Junin virus (the etiological agent of Argentine hemorrhagic fever) by a virus yield inhibition assay. The study indicated that only the p-chloro derivatives (71, 72 and 73) displayed moderate and selective antiviral activity with EC50 close to 200 micro molar although they were less effective than the reference compound rivabirin with EC50 19.2 [81].

3. ANTITUBERCULAR ACTIVITY

Increasing bacterial resistance to commonly prescribed antitubercular drugs is one of the major issue while treatment of infections caused by *Mycobacterium tuberculosis* strains. Additionally increase in overlap of the AIDS and tuberculosis pandemics coupled with the multidrug-resistant tuberculosis (MDR-TB) worsens the situation further. Moreover, coupled with the increasing have brought tuberculosis among the major worldwide. The development of new classes of antitubercular drugs containing a core of 1,3,4-thiadiazole moiety is a very challenging task to many scientists.

The discovery and structure-activity relationships of 5-substituted-2-[(3,5-dinitrobenzyl)sulfanyl]-1,3,4-thiadiazoles (74a-l) derivatives with remarkable in vitro activity against *Mycobacterium tuberculosis* CNCTC My 331/88 and six multidrug-resistant clinically isolated strains of *M. tuberculosis*, MIC values as low as 0.03 µM (0.011-0.026 µg/mL) have been reported. 5-substituted 2-[(3,5-dinitrobenzyl)sulfanyl]-1,3,4-thiadiazoles (74k)
exhibited outstanding activity against drug-susceptible and multi drug resistant *M. tuberculosis*, with no cross resistance with first- and second-line anti-TB drugs. Moreover, these compounds exhibited excellent activity against the non-replicating *M. tuberculosis* strain SS18b-Lux. SAR study revealed that 3,5-dinitro substitution plays important role in antimycobacterial activity: any changes to the positions or numbers of nitro groups led to a major decrease in antimycobacterial activity. The antimycobacterial effects of the investigated compounds were selective, as they showed no growth inhibitory activity against other bacteria or against fungi and had low toxicity against proliferating cell lines and isolated human hepatocytes. Moreover, several genotoxicity and mutagenicity assays indicated that these nitro group-containing compounds have low mutagenicity. These results indicate that the reported compounds affect some specific mycobacterial system [82].

Synthesis of novel triazole–imidazo[2,1-b][1,3,4]thiadiazole hybrids derivatives have been reported by Ramprasad et al. exhibiting activity against *Mycobacterium tuberculosis* H37Rv strain. Compound 75 and 76 displayed highest activity with a MIC of 3.125 µg/mL which is comparable with reference drug ethambutol. The active molecules exhibited positive drug-likeness score and their Clog P values are in the range 2.2–2.9. The active derivatives do not shown any kind of cellular toxicity [83].

Synthesis of Schiff bases by reacting a variety of carbonyl compounds with 5-amino-1,3,4-thiadiazole-2-thiol have been reported. All these compounds were evaluated for their antibacterial, antifungal and antitubercular activities. The compounds 77e and 77d substituted with the electron withdrawing fluorine and nitro groups exhibited remarkable inhibitory activity against *Staphylococcus aureus*, *Aspergillus niger* and *Candida tropicalis* with an MIC of 8 µg/mL whereas 77a containing the electron releasing dimethylamine group displayed strong activity against *Proteus vulgaris*. Moreover compounds 77e, 77b, 77c and 77d also displayed outstanding antimycobacterial activity than the standard pyrazinamide [84].
of 2,5-disubstituted-1,3,4-thiadiazole derivatives and in vitro antmycobacterial activity against *Mycobacterium smegmatis* MC-155. Compounds 78 and 79 displayed significant antitubercular activity with MIC value 65.74 and 40.86 respectively. Compound 78 was found to be safe and potent antitubercular agent when tested on human normal cells HEK293T [85].

Synthesis of substituted derivatives of imidazo[2,1-b][1,3,4]thiadiazole. All the synthesized derivatives were screened for anti-TB and anti-fungal activity. The compounds 80a, 80b, 80c, 80f, 80g and 80h with MIC 1.6-6.25µg/ml exhibited strong antitubercular activity. Compounds 80a, 80d, 80e, and 80h showed strong antifungal activity with MIC 5 µgm/ml owing to presence of electron withdrawing groups at 4th position to both phenyl rings which are attached to the thiazole of the imidazo thiadiazole and imidazo thiadiazole ring [86].

Imidazo[2,1-b][1,3,4]thiadiazole derivatives (81a–j) were tested for antitubercular activity against *M. tuberculosis* strain H37Rv by using the MABA method. Compounds 81a, 81b, 81c, 81d, 81f and 81i showed excellent antitubercular activities. Compound 81f containing the nitro phenyl substituent exhibited highest activity with MIC of 3.14 lg mL. Author noticed considerable variation in activity with different substituents at the 6th position of imidazo(2,1-b)-1,3,4-thiadiazole nucleus [87].

Novel triazole–imidazo[2,1-b][1,3,4]thiadiazole hybrids designed by a molecular hybridization approach were synthesized and tested against *Mycobacterium tuberculosis* H37Rv strain. Compounds 82a and 82b exhibited excellent growth inhibitory activity against the bacterial strain with
a MIC of 3.125mcg/mL. It was noticed that the presence of chloro substituent on the imidazo[2,1-b][1,3,4]thiadiazole ring and ethyl, benzyl or cyanomethylene groups on the 1,2,3-triazole ring increase the inhibition activity of the molecules. The active compounds are devoid of any toxicity to a normal cell line makes these compounds safe [88].

Novel substituted 1,3,4-thiadiazole derivatives and tested them for in vitro anti-mycobacterial activity against the Mycobacterium tuberculosis H37Rv and resistance MDR-TB strain. Compound N-(5-(4-nitrophenyl)-1,3,4-thiadiazol-2-yl)furan-2-carboxamide (83c) exhibited highest activity with MIC of 9.87 μM against the MDR-TB strain as compared to the standard isoniazid (> 200 μM). The tested compounds 83a, 83b, 83c, 83d, 83e, 84a, 84b, 84c and 85 also displayed significant MDR inhibitory activity. Compounds were found safe at non-cytotoxic concentrations when assessed for cytotoxicity to a mammalian Vero cell line using the MTT assay. SAR study revealed that activity is significantly influenced by various 5 substituents at the 2nd position of 1,3,4-thiadiazole and electron withdrawing group on aliphatic side chain at 2nd position of 1,3,4-thiadiazole has diminishing effect on anti-mycobacterial and MDR inhibitory activity [89].

New cyrhetrenyl and ferrocenyl 1,3,4-thiadiazoles were designed, synthesized, characterized and evaluated against M. Tuberculosis using Isoniazid as the reference drug in this study. Taking into account the similar MIC values found for the ferrocenyl (86a–c) and cyrhetrenyl (87a–c) TZDs (MIC N 100 μg ml⁻¹), author concluded that the opposite electronic effects of the organometallic fragments are not an important factor in the antitubercular activities of these types of compounds. The MIC values are far higher than those of isoniazid but are comparable [90].
Novel imidazo-[2,1-b][1,3,4]thiadiazole (ITD) derivatives with anti-tubercular properties were reported. Among all the microorganisms *Mycobacterium smegmatis* was found most sensitive microorganism with the MIC value between 0.24 and 0.49 μg/mL concentration compared to reference drug Streptomycin (4 g/mL). It was noticed that Mannich bases 93a, 93b, 93c, 93d, 1,3-thiazolidin-4-one derivatives 94a, 94b and 95 exhibited outstanding antitubercular activity and also exhibited activity against bacteria with high inhibition at low concentrations (< 0.24 μg/mL) compared with standard drug Ampicillin. Compound 96 including piperidin-2,6-dione and compound 95 showed potent activity against entire test microorganisms than that of standard drugs [92].

New compound, N-{3-(methylsulfanyl)-1-[5-(phenylamino)-1,3,4-thiadiazole-2-yl]propyl}benzamide (97) which found active against *Influenza A H3N2* virus with an EC50 value of 20-40 μM [93].

New thiazol-imidazo-[2,1-b]-1,3,4-thiadiazole hybrids with antitubercular activity was reported. Compound 98a, substituted with trifluoromethyl and p-chlorophenyl at 2 and 6 positions of the ITD ring, respectively, exhibited highest activity with an MIC of 6.03 μM comparable with MIC values of standard drugs ethambutol (15.3 μM) and ciprofloxacin (9.4 μM). Compounds 98b, 98c, 98d and 98e also displayed promising inhibitory activity with MIC values in the range of 11.7–13.9 μM. SAR study revealed that the trifluoromethyl substitution at position-2 and p-chlorophenyl substitution at position-6 of the...
imidazol[2,1-b][1,3,4]thiadiazole ring enhanced the inhibitory activity. Also, the methyl, methoxy, fluoro or nitro substituents on the thiazole ring enhanced the activity of the compounds. All the compounds are devoid of general cellular. In silico molecular docking studies revealed the favorable interaction of the potent compounds with the target enzymes InhA and CYP121 [94].

Phenothiazine and 1,3,4-thiadiazole hybrid derivatives were evaluated for their in vitro inhibition activity against *Mycobacterium tuberculosis* H37Rv (MTB). Among the series compounds 99a and 99b came up with most potent derivative with MIC of 0.8µg/mL (~1.9 µM). Moreover, compounds 99c, 99d, 99e, 99f, 99g and 99h (MIC = 1.6 µg/mL), and compounds 99i, 99j and 99k (MIC = 3.125 µg/ml) displayed strong inhibition activity. The SAR study revealed that an alkyl (methyl/n-propyl) or substituted (4-methyl/4-Cl/4-F) phenyl groups on the 1,3,4-thiadiazole ring enhance the inhibition activity of the compounds. The cytotoxicity study demonstrated all the compounds lacks in cellular toxicity. The molecular docking study revealed strong pi-pi stacking interaction of the active molecules with the target enzymes InhA and CYP121 [95].

![Chemical structures of compounds 98a-e](image)

2,5-substituted-1,3,4-thiadiazoles were synthesized and evaluated for antituberculosis activity. Compound 5-phenyl-N-(4-(trifluoromethyl)-phenyl)methyl)-1,3,4-thiadiazole-2-amine 100 exhibited most potent activity against *mycobacterium smegmatis* MC155 (MIC 26.46 µg/mL) compared to the Isoniazid control (12 µg/mL). The SAR analysis demonstrated that a smaller aromatic ring and electron-withdrawing groups favors activity [96].

![Chemical structure of compound 100](image)
5-substituted-1,3,4-thiadiazole-based fluoroquinolone derivatives were designed as potential antibacterial agents using a molecular hybridization approach. Compound 101a was rewarded as the most active agent exhibiting antibacterial activity against *Escherichia coli* and *Staphylococcus aureus* with MIC values of 4µg/mL and 2µg/mL, respectively. Amongst the synthesized fluoroquinolone derivatives, compounds 101b and 101a were displayed significant antitubercular activity with 8 µg/mL MIC values for each. Most potent derivative, compound 101a was docked against *Staphylococcus* aureus and *Mycobacterium tuberculosis* DNA gyrase enzymes and found capable for appropriate binding at target site [97].

\[ \text{O} \]

\[ \text{N} \]

\[ \text{F} \]

\[ \text{R}_2 \]

\[ \text{N} \]

\[ \text{S} \]

\[ \text{R}_1 \]

\[ \text{O} \]

\[ \text{N} \]

\[ \text{HO} \]

\[ \text{O} \]

\[ \text{N} \]

\[ \text{O} \]

\[ \text{N} \]

\[ \text{O} \]

\[ \text{N} \]

\[ \text{O} \]

\[ \text{N} \]

\[ \text{S} \]

\[ \text{N} \]

\[ \text{N} \]

\[ \text{R}_1 \]

\[ \text{F} \]

\[ \text{R}_2 \]

\[ \text{101a}, \text{R}_1 = \text{2,4-dichlorophenyl}; \text{R}_2=\text{Ethyl}; \]

\[ \text{101b}, \text{R}_1 = \text{4-chlorophenyl}; \text{R}_2=\text{Ethyl} \]

4. CONCLUSION

1,3,4-Thiadiazole is a unique pattern associated with various biological activities. The potency of the 4-thiazolidin-1-one core is clearly evident from clinically used drugs such as acetazolamide, metazolamide and megazol. Although antibacterial, anti-tubercular drugs, carbonic anhydrase inhibitors and antilucer are the four main areas of clinical use, other potential targets remain to be explored. Most locations have been explored to improve the antibacterial and anti-tubercular profile of 1,3,4-thiadiazole, but none of the derivatives have shown promising anti-tubercular activity. The literature is extensively analyzed to provide a meaningful overview of the structural requirements for the business whenever possible.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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