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REVIEW ARTICLE

A Review on Thiadiazoles

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ABSTRACT

Thiadiazoles has two N-atoms and one sulfur particularly at 1,3,4th position generally exhibits a wide range of pharmacological applications including anti-bacterial, anti-fungal, anti-cancer, anti-depressants, and sugar controlling agents, and also has suppressing effects on diseased part of kidney, lungs, etc. In this article, we provide an elaborate sketch of chemical structures of 1,3,4-thiadiazole moiety including its literatures, synthesis, and biological activities reported so far. As a results, drugs with 1,3,4-thiadiazole are attracted a much attention to the medicinal chemists.

Keywords: Antimicrobials, literature, medicinal chemist, nitrogen containing moiety, pharmacological activity

INTRODUCTION

There are number of heterocyclic compounds containing five member ring structure with more than one nitrogen as hetero atoms have hetero aromatic properties. It has three nitrogen atoms in a symmetrical way which was explored since it has wide pharmacological applications. 1,3,4-thiadiazole has five member ring structure consists of two nitrogen and one sulfur atom. In general, these five member moiety are wide spread in nature and it can exist in different isomeric forms based on the position of nitrogen and sulfur atoms, it may be at 1,3,4 1,2,3 1,2,5, and 1,2,4 positions, respectively. This heterocyclic ring system has plays key role in the Pharma industry and other medical, veterinary, and pesticide and insecticide industry. Previously, this heterocyclic ring system had wide applications in the drug manufacturing sector which produced some kinds of sulfa drugs which has anti-bacterial and anti-fungal effects. In addition to these applications, it also has other pharmacological applications such as anti-cancer, anti-diabetics, anti-hypertensive, analgesics, and anti-inflammatory agents. It has also has broad applications in food industry, chemical industry, dye manufacturing, and oil and lubricants industries. The literature review showed that 1,3,4-thiadiazole and its derivatives possess wide range of therapeutic effectiveness such as antimicrobial, anti-inflammatory, anti-tubercular, antiepileptic, anti-diabetic, anti-tumor, antidepressant, anti-parkinsonism, hypoglycemic, antihypertensive, and anti-diuretic activity.

ANTIMICROBIAL ACTIVITY

Jumat *et al.*,[1] in the year 2010, reported the preparation of 2,5-(dithioacetic acid)-1,3,4-thidiazole 1(a), and 2,5-di-5-amino-1,3,4- thiadiazole-2-thiomethyl-1,3,4-thiadiazole 1(b). All the synthesized compounds were evaluated for their *in vitro* anti-bacterial studies using various Gram-positive (*Staphylococcus aureus*, *Streptococcus cerevisiae* and *Corynebacterium diphtheria*) and the Gram-negative (*Escherichia coli* and *Pseudomonas aureginosa*) microorganisms.

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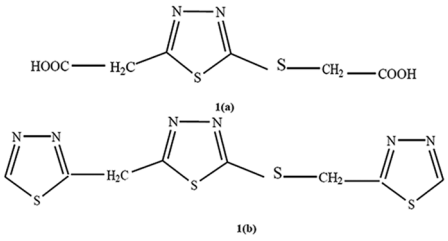
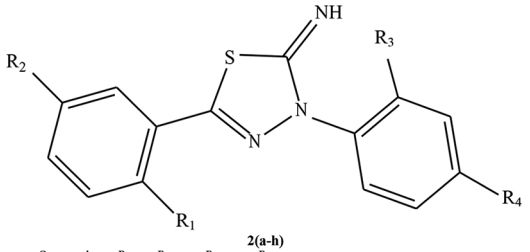


1(a)

1(b)

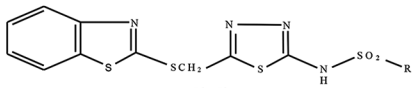
Asif and Asthana[2] has reported the subsituted-2,4-diphenyl-5-imino-1,3,4-thiadiazoles in the year 2010 and performed the *in vitro* anti-microbiological activity using various Gram-negative organisms (*E. coli* and *Pseudomonas aeruginosa*) and Gram-positive strains (*Bacillus cereus* and *S. aureus*) and also performed minimum inhibitory concentration (MIC) studies. The tested compounds all are shown to have good antimicrobial property.



2(a-h)

Compounds	R_1	R_2	R_3	R_4
(2a)	H	H	H	H
(2b)	H	H	NO_2	NO_2
(2c)	Cl	H	H	H
(2d)	Cl	H	NO_2	NO_2
(2e)	H	Cl	H	H
(2f)	H	Cl	NO_2	NO_2
(2g)	H	NH_2	H	H
(2h)	H	NH_2	NO_2	NO_2

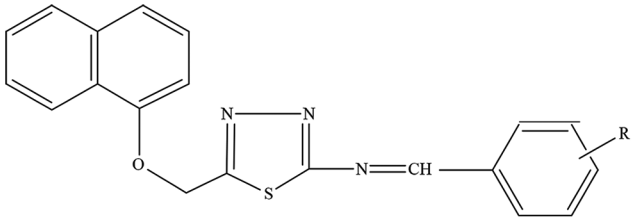
Mehta *et al.,*[3] synthesized a series of 2-arylsulfonamido-5-(benzthiazol-2yl-thiamethyl) -1,3,4-thiadiazoles and were screened for antibacterial activity against Gram-positive *Bacillus megaterium*, *Bacillus subtilus,* and Gram-negative *E. coli* and *A. aerogens* and antifungal activity against *A. awamory*. Compounds showed good antibacterial activity and moderate antifungal activity.



3(a –h)

R=Phenyl,4-Chlorophenyl, 4-Iodophenyl,4-Anisyl,3-Carboxyphenyl, 3-Carboxy-4-chlorophenyl, 3-Carboxy-6-chlorophenyl, 3-Carboxy-4-methoxyphenyl.

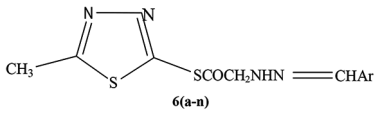
Ashutosh *et al.,*[4] have synthesized a series of eight novel 1,3,4-thiadiazol-2-amine (4a-h) derivatives and investigated for *in vitro* antibacterial and antifungal activity against various Gram-positive bacterial strains: *Bacillus subtillis; S. aureus,* Gram-negative bacterial strains: *E. coli*; *P. aeruginosa,* Fungal strains *Saccharomyces cerevisiae; and Aspergillus niger and Candida albicans*. It is showed that compounds **(4a), (4e), (4f),** and **(4h)** exhibited antibacterial and antifungal activity.



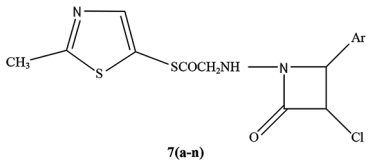
5(a-h)

R= 3-$OCH_3$4-OH, 2-OH ,4-OCH_3 , 3-$OCH_3$4-OCH_3 ,4-N,N-dimethyl, 2-Cl, 4-NO_2 , -H

Dua *et al.,*[5] have synthesized several new 2-(2'-substitutedbenzylidene-hydrazino-acetyl)-mercapto- 5-methyl-1,3,4-thiadiaz oles, **6(a-n)** and 2-[2'-{4-substituted-aryl-3-chloro-2-oxo-azetidine}-acetyl-amino- mercapto]-5-methyl-1,3,4- thiadiazoles,7(a-n). All the synthesized products were evaluated for their antibacterial activity against *Bacillus substilis, E. coli. Klebsiella pneumonia,* and *Streptococcus aureus* bacteria and antifungal activity against *A. niger, Aspergillus flavus, Fusarium oxisporium,* and *Trichoderma viride* fungi, respectively. They have shown significant antibacterial and antifungal activity.

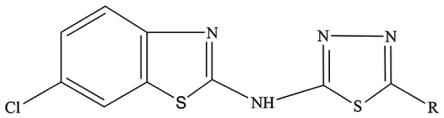


6(a-n)



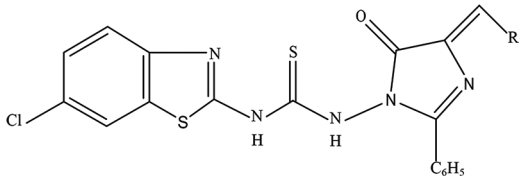
7(a-n)

The research study by Amir *et al.,*[6] reports the synthesis and antimicrobial activity of new 2-aryl-5-(6' - chloro-1',3'- benzothiazole-2- yl-amino)-1,3,4-thiadiazoles **(8a-j)** and 4-(4'-arylidene) -2-phenyl-1-(6'-chloro-1',3'- benzothiazol-2-yl- thiourido)-4,5-dihydro imidazolinones **(9a-e)**. All the compounds showed significant antimicrobial activity.



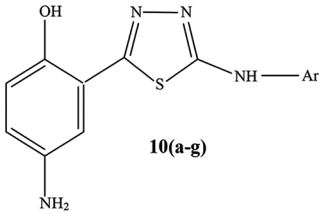
8(a-j)

Ar=phenyl,4-Chiorophenyl,2,4-Dichlorophenyl, 4-Nitrophenyl, 2-Aminopheny,2,4-Dichlorophenoxymethyl,2-Napthylmethyl,4-Methoxyphenyl,2-Acetoxyphenyl,3-Pyridyl.



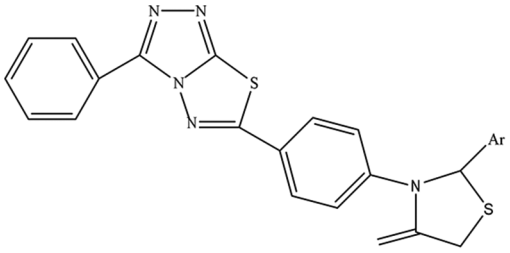
9(a-e)
R= Phenyl,4-Chiorophenyl,4-Fluorophenyl, 4-N,N-dimethyl phenyl,3-Indolyl.

Hussain *et al.,*[7] have synthesized some 4-amino-2-{5-[(4-substituted phenyl)amino]-1,3,4- thiadiazole-2-yl} phenol **10(a-g)** evaluated for their antibacterial and antifungal activity. The compounds showed significant antibacterial activity against *S. aureus* (Gram-positive) and *E. coli* (Gram-negative) bacteria and antifungal activity against *A. niger* fungi. Compounds **10c and 10f** exhibited promising antibacterial activity against *S. aureus* and *A. niger*.



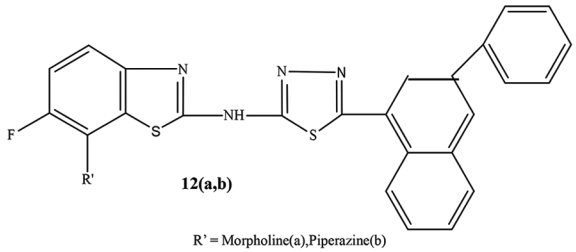
10(a-g)
Ar = 4-Methylphenyl,4-Methoxyphenyl,4-Chlorophenyl,2,5-Dimethylphenyl,3-Chloro-4-fluorophenyl,4-Bromophenyl.

Parmar *et al.,*[8] synthesized some new and biologically active [1,2,4] triazolo[3,4-b][1,3,4] thiadiazole-2- aryl thiazolidinone-4- ones by reaction of Schiff bases with mercapto acetic acid in presence of THF with adding anhydrous $ZnCl_2$. The compounds have been evaluated for antibacterial activity against *B. subtilis, S. aureus*, *P. aeruginosa,* and *E. coli*.

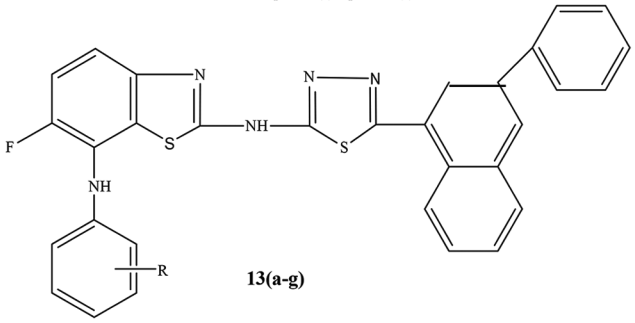


11(a-h)
Ar = -C_6H_5 ,4-OCH_3-C_6H_4 , 4-OH-C_6H_4 , 2-OH-C_6H_4, 4-CH_3-C_6H_4 ,

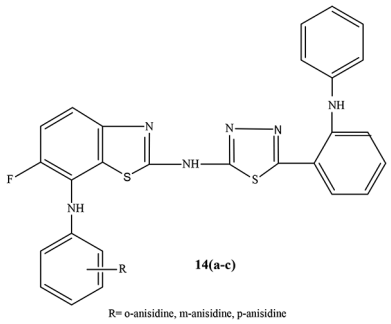
Vedavathi *et al.,*[9] synthesized Fluorobenzothiazole incorporated with 1,3,4-thiadiazole derivatives and evaluated for their anti-microbial activity. Significant antimicrobial activities were observed for members of this series.



12(a,b)
R' = Morpholine(a),Piperazine(b)

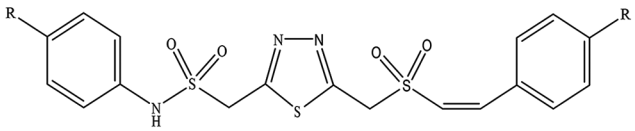


13(a-g)
R = o, m, p nitro aniline (a-c)
= o, m, p chloro aniline (d-f)
= Aniline (g)

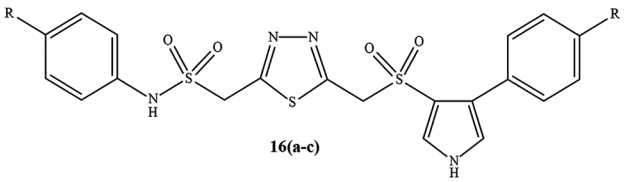


14(a-c)
R= o-anisidine, m-anisidine, p-anisidine

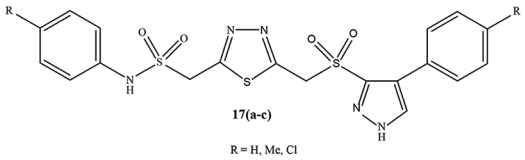
Padmaja *et al.,*[10] have been synthesized a new class of pyrrolyl/pyrazolyl arylaminosulfonyl methyl, 1,3,4-thiadiazoles and tested for antimicrobial activity. The antibacterial activity was carried out against *S. aureus*, *Bacillus subtilis* (Gram-positive bacteria) and *P. aeruginosa*, *K. pneumoniae* (Gram-negative bacteria), and antifungal activity evaluated against *Penicillium chrysogenum*, *Curvularia lunata,* and *A. niger.*



15(a-c)
R = H, Me, Cl



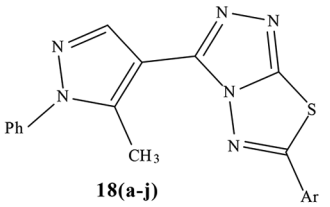
16(a-c)
R = H, Me, Cl



17(a-c)

R = H, Me, Cl

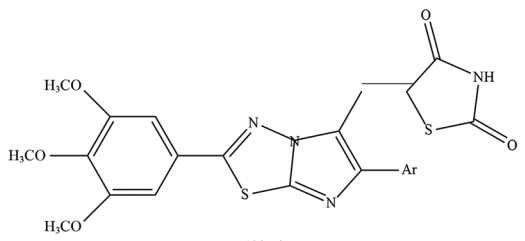
Cherkupally *et al.,*[11] synthesized a new series of 6-(aryl/heteryl)-3-(5-methyl-1-phenyl-1*H*-4- pyrazolyl) [1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **18(a—j)**. All the synthesized compounds were tested for *in vitro* activities against certain strains of bacteria such as *S. aureus*, *B. subtilis*, *E. coli* and fungi such as *A. niger*, *Aspergillus nodulans*, and *Alternaria alternate*. Compounds having 4-chlorophenyl **(18d)**, 4-aminophenyl **(18f)**, 4-nitrophenyl **(18h)** and 3- pyridyl **(18i)** substituents at 6-position of thiadiazole ring, showed marked inhibition of bacterial and fungal growth. The other new compounds also showed appreciable activity against the test bacteria and fungi.



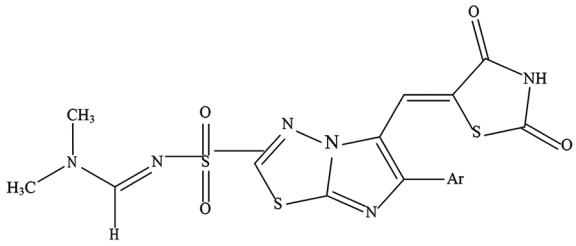
18(a-j)

Ar = phenyl, 4-methylphenyl, 4-methoxyphenyl, 4-chlorophenyl, 2-chloropheyl, 4-aminophenyl, 4-hydroxyphenyl, 4-nitrophenyl, 3-pyridyl, 4-pyridyl.

Alagawadi *et al.,*[12] synthesized a new 2,4-thiazolidinediones derivatives bearing imidazo[2,1-b][1,3,4] thiadiazole moiety. All compounds were evaluated for their preliminary *in vitro* antibacterial and antifungal activity against Gram-positive *S. aureus, Enterococcus faecalis*, Gram-negative *E. coli*, *P. aeruginosa* bacteria and *C. albicans, A. flavus*, *A. niger,* and *Cryptococcus neoformans* fungi. The results revealed that most of the compounds showed high or moderate biological activity against tested microorganisms.



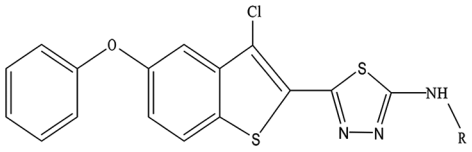
19(a-g)



20(a-g)

Ar = C_6H_5 ,4-CH_3-C_6H_4 ,4-OCH_3-C_6H_4 , 4-NO_2-C_6H_4 ,4-Br-C_6H_4 , 4-Cl-C_6H_4 ,2,5-(OCH_3)- C_6H_3.

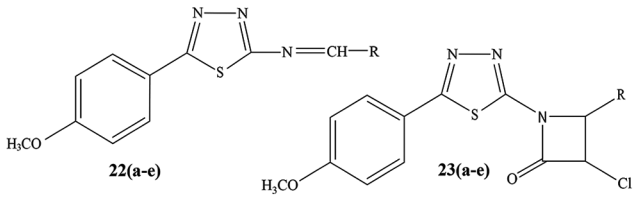
Vasoya *et al.,*[13] synthesized 2-(3′-Chloro-5′-phenoxybenzo[b]thiophen-2′-yl)-5-arylamino-1,3,4-thiadiazole derivatives **(21a-h)** by the cyclization of arylthiosemicarbazides with concentrated sulfuric acid. All the compounds were screened for their antimicrobial activity against various microorganisms.



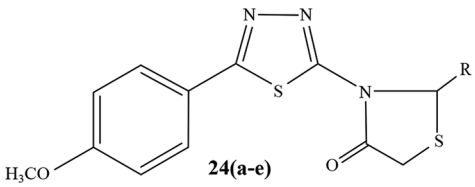
21(a-h)

R = -C_6H_5, 3-Cl-C_6H_4, 4-Cl-C_6H_4 ,2-CH_3-C_6H_4 ,4-CH_3-C_6H_4 , 2-OCH_3- C_6H_4 , 4-OCH_3-C_6H_4 , 2-NO_2- C_6H_4

Singh *et al.,*[14] have been synthesized some thiadiazole derivatives by incorporating azetidinyl and thiazolidinyl moieties at its 2-position such as 5-(*p*-methoxyphenyl)-[2-substituted benzylidenylimino] 1,3,4-thiadiazole **22(a-e)**, 5-(*p*- methoxyphenyl)-[2-(3’-chloro-2’-oxo-4’-substituted aryl-1’-azetidinyl)]- 1,3, 4- thiadiazole **23(a-e)** and 5-(*p*-methoxyphenyl)-[2-(2’ -substituted aryl-4’-oxo-1’,3’-thiazolidin-3’-yl)] -1, 3,4-thiadiazole **24(a-e)**.



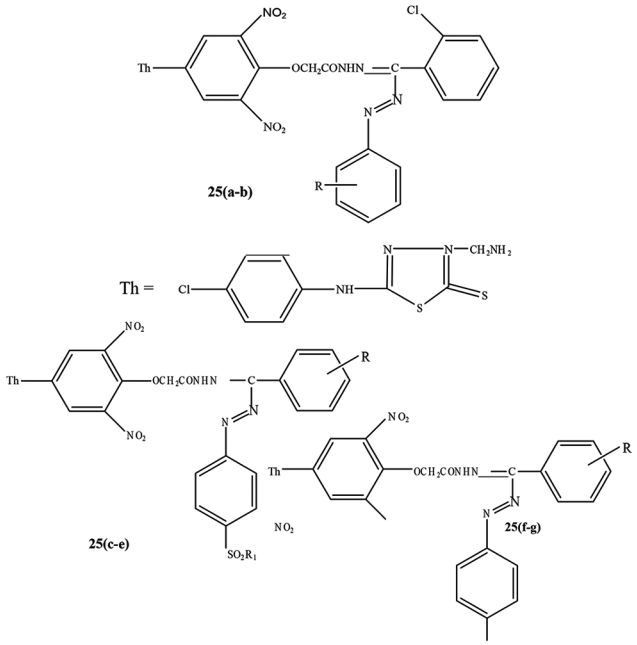
22(a-e) **23(a-e)**



24(a-e)

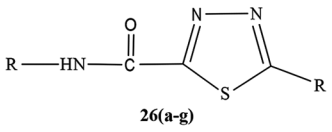
R = 4-OH-C_6H_4 , 4-OCH_3-C_6H_4 , -C_6H_5 , 4-Cl-C_6H_4 , 4-$N(CH_3)_2$-C_6H_4

Shah *et al.,*[15] synthesized formazans from Mannich base of 5-(4-chlorophenyl amino)-2-mercapto- 1,3,4-thiadiazole. All the compounds (25a-g) were screened for their in vitro antibacterial activity against *E. coli* and *Salmonella typhi*. Antifungal activity was conducted against *A. niger, Penicillium* spp., and *C. albicans*



25a : R = 2-chloro, VIb : R = 3-methoxy, 4-hydroxy 25a-b : R = 2-chloro, R1 = 4-nitro, 2-methyl-4-nitro 25c-e : R = 2-chloro, R1 = hydroxyl, amino, guanidine 25f-g : R = 3-methoxy, 4-hydroxy, R1 = pyrimidinyl, 4,6 dimethyl pyrimidinyl

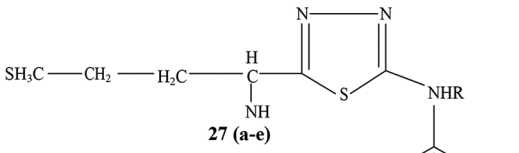
Arvind *et al.,*[16] synthesized a series of new 5-substituted-[1,3,4-thiadiazole-2-yl] benzamide. Antimicrobial activity was carried out using bacterial strain *S. aureus* (Gram-positive), *E. coli* (Gram-positive), and *A. niger*. All compounds have shown moderate antimicrobial activity against all the organism.



26(a-g)

R=C_6H_5, 2- Cl- C_6H_4, 3- Cl- C_6H_4, 4- Cl- C_6H_4,2- $NO_2C_6H_4$,3- NO_2-C_6H_4,4- NO_2- C_6H_4

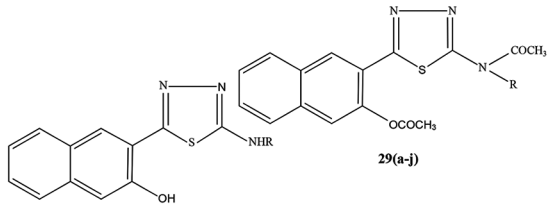
Profire *et al.,*[17] synthesized a new 1,3,4-thiadiazole derivatives **(27a-e)** containing a *D,L*-methionine moiety by intramolecular cyclization of 1,4-disubstituted thiosemicarbazides in acid, and alkaline media, respectively. The potential antimicrobial effects of the synthesized compounds were investigated using the *S. aureus*, *Bacillus antracis*, *B. cereus*, *Sarcina lutea,* and *E. coli* strains. The newly synthesized compounds exhibited promising activities against *B. antracis* and *B. cereus*.



27 (a-e)

R= -CH_3, -C_6H_5 , 4-CH_3-C_6H_4, 4-Br-C_6H_4 ,-CH_2-CH=CH_2.

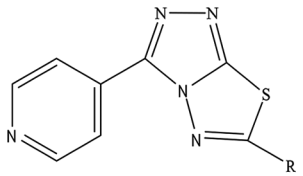
Dogan *et al.,*[18] synthesized the two new series of 2,5-disubstituted-1,3,4-thiadiazoles. All the synthesized products were evaluated for their antibacterial activity against *B. substilis, E. coli. P. aeruginosa,* and *Streptococcus aureus* bacteria and antifungal activity against *Candida albicans* fungi, respectively. They have shown significant antibacterial and antifungal activity.



28(a-j) **29(a-j)**

R= ethyl (a), phenethyl (b), phenyl (c), p-bromophenyl (d), p-chlorophenyl (e), p-fluorophenyl (f), m-fluorophenyl(g), p-methoxyphenyl (h), p-methylphenyl (i), m-trifluoromethylphenyl (j).

Gilani *et al.,*[19] synthesized a series of 6-substituted-1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazole **(30a-g)** derivatives of isoniazid in satisfactory yield and pharmacologically evaluated for their *in vitro* antimicrobial activity. A majority of the tested compounds showed good to moderate antimicrobial activity against all tested pathogenic bacterial and fungal strains.



30(a-g)

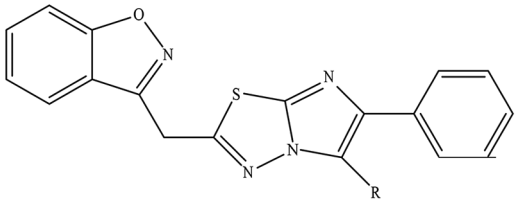
R= -C_6H_5, 2-Cl-C_6H_4, 2,4-Cl-C_6H_3, 2-CH_3-C_6H_4, 2-$OCOCH_3$-C_6H_3, -OC_6H_5 , 4-NO_2-C_6H_4

Demirbas *et al.,*[20] synthesized 4-Amino-2-[(5 -anilino-1,3,4-thiadiazol-2-yl)methyl]-5-(4-chlorophenyl)- 2,4-dihydro-3*H*- 1,2,4- triazol-3 -one **(31a)** and 4-Amino-5-(4- chlorophenyl) -2-({5- [methyl(phenyl)amino]-4,5-dihydro-1,3,4-

thiadiazol-2-yl} methyl)- 2,4-dihydro-3*H*-1,2,4-triazol-3-one **(31b)**. These synthesized compounds were evaluated for antimicrobial activity. Compound **31a** showed good antimicrobial activities against the test microorganisms as compared with ampicillin.

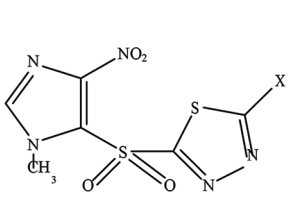
Yousif *et al.,*[21] synthesized novel tetra compound Schiff base by condensation of 1,2, 4,5-tetra (5-amino- 1,3,4-thiadiazole-2- yl) benzene with different aromatic aldehydes. All compounds **(32 a-h)** were screened for antibacterial (*S. aureus*, *Staphylococcus epidermidis*, *Icrococcus luteus*, *B. cereus*, *E. coli*, and *P. aeruginosa*) and antifungal (*A. niger* and *Aspergillus fumigatus*) activities.

Lamani *et al.,*[22] synthesized novel methylene bridged benzisoxazolyl imidazo[2,1 b][1,3,4] thiadiazoles **(33a-c)** and revealed for their antibacterial and antifungal activities. All compounds having nitroso, bromo, and thiocynato exhibited significant antibacterial and antifungal activities.



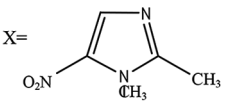
(33a-c)
R = Br, NO, SCN

Bahram *et al.,*[23] introduced the synthesis and antibacterial activity of a new series of 2-(1- methyl-4 -nitro- 1*H*-imidazol-5- ylsulfonyl)-1,3,4-thiadiazoles **(34a-c)**. Three compounds were tested *in vitro* against a panel of microorganisms including Gram-negative and Gram-positive bacteria. Compound **(34b)** with 5-(5- nitrofuran-2-yl)-residue on 1,3,4- thiadiazole scaffold had shown promising antibacterial activities against Gram-positive bacteria including *S. aureus, S. epidermidis,* and *B. subtilis.*

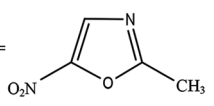


34(a-c)

34(a) X=

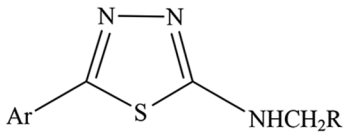


34(b) X=



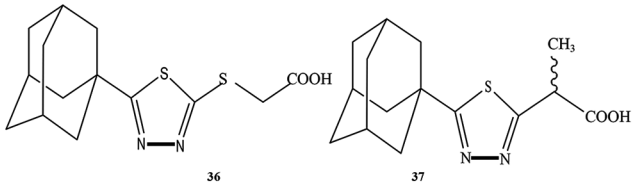
34(c) X= CH_3CONH-

Gowramma *et al.*,[24] synthesized a series of 1,3,4-thiadiazole derivatives. All the compounds were evaluated for antibacterial and antifungal activities. Most of the compounds have shown significant antibacterial and antifungal activity when compared with the standard drugs.



35(a-m)
R = C_6H_6N & C_6H_5NCl
Ar = - C_6H_5, - C_6H_4OH, - $C_6H_4N(CH_3)_2$, - C_6H_4Cl, - $C_6H_4NO_2$, - C_4H_3S

Kadi *et al.*,[25] synthesized a new series of 1-adamanyl-1,3,4-thiadiazole derivatives **(36-37)** and tested for *in vitro* antimicrobial activities against a panel of Gram-positive and Gram-negative bacteria and the pathogenic fungus *C. albicans*. Compounds **(36)** and **(37)** were found to show marked activity against Gram-positive bacteria, whereas compound **(37)** was highly active against the tested Gram-negative bacteria. However, Compounds **(36)** and **(37)** were found to show weakly or moderate activity against *C. albicans.*



36 **37**

CONCLUSION

Based on the literatures cited, 1,3,4-thiadiazole has a diverse biological activities in medical and chemical part. It has enormous applications in agriculture, pesticides, cosmetics, pharmaceuticals, and medical field.

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