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Review Article

SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF 1,3,4-THIADIAZOLE DERIVATIVES: A REVIEW

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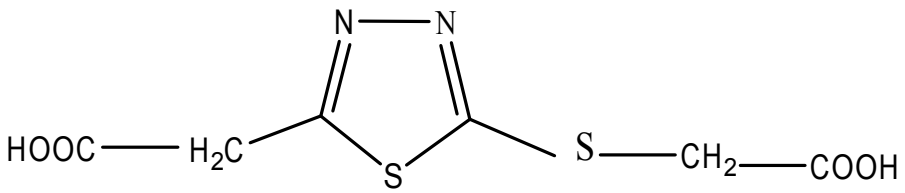
ABSTRACT
1,3,4-Thiadiazole and their derivatives exhibit a broad spectrum of biological effectiveness like antimicrobial, antiinflammatory, antitubercular, antidiabetic, anticancer, antidepressant, anti- parkinson, hypoglycaemic, anti-hypertensive and diuretic activity. This review provide a broad view of chemistry of 1,3,4-thiadiazole system and it includes the literature survey on methods of preparation and pharmacological activities of 1,3,4-thiadiazole moiety. As a result, compounds containing 1,3,4-thiadiazole were attracted much attention in the field of medicines.
Keywords: 1,3,4-thiadiazole, biological effectiveness.

INTRODUCTION

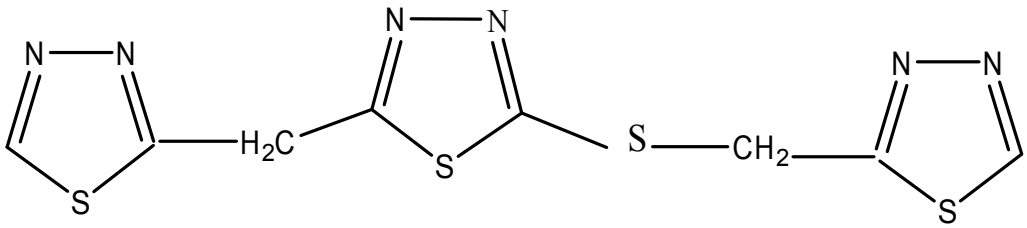
Several five membered aromatic systems having three hetero atoms at symmetrical position have been studied because of their interesting physiological properties. Thiadiazole is a 5-membered ring system containing two nitrogen and one sulphur atom. They occur in nature in four isomeric forms viz. 1,2,3-thiadiazole; 1,2,5-thiadiazole; 1,2,4-thiadiazole and 1,3,4-thiadiazole. The thiadiazoles have occupied an important place in drug industry. 1,3,4-Thiadiazoles have wide applications in many fields. The earliest uses were in the pharmaceutical area as antibacterial with known sulphonamides drugs. Some of the later uses are as antitumor and anti-inflammatory agents, pesticides, dyes, lubricants and analytical reagents. The literature review showed that 1,3,4-Thiadiazole and its derivatives possess wide range of therapeutic effectiveness like antimicrobial, antiinflammatory, antitubercular, anticonvulsant, antidiabetic, anticancer, antidepressant, antiparkinson, hypoglycaemic, antihypertensive and diuretic activity.

Antimicrobial Activity

Salimon et al[1] carried out the successful synthesis of some new 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)** which were screened for their in vitro antibacterial activities against the Gram-positive (S. aureus, S. cerevisiae and C. diphtheriae) and the Gram-negative, (*E.coli* and *P. aeruginosa*) bacteria .

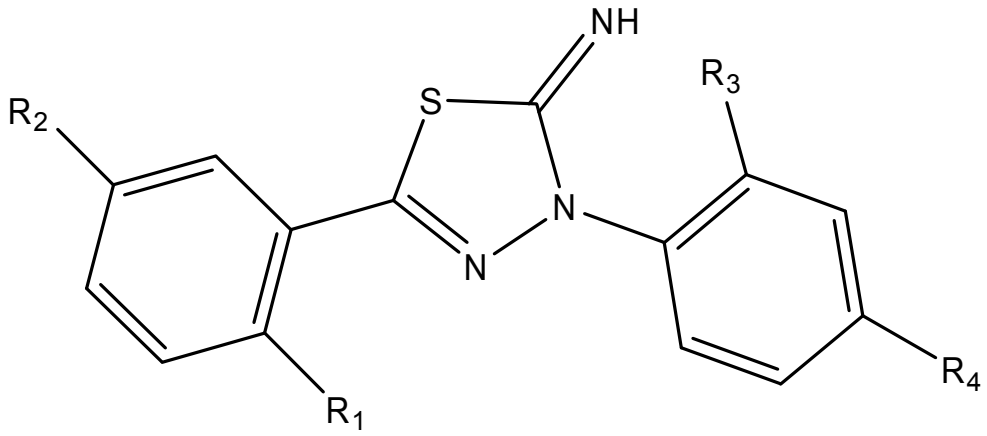


1(a)



1(b)

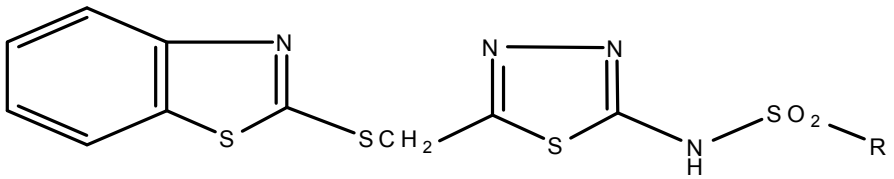
Some new subsituted-2,4-diphenyl-5-imino-1,3,4-thiadiazole derivatives were synthesized by M.Asif et al[2] and all the compounds were evaluated for their *in vitro* antibacterial activity against two Gram negative strains (*Escherichia coli* and *Pseudomonas aeruginosa*) and two Gram positive strains (*Bacillus cereus* and *Staphylococcus aureus*) and their minimum inhibitory concentration (MIC) were determined. The newly synthesized compounds exhibited promising antimicrobial activities.



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

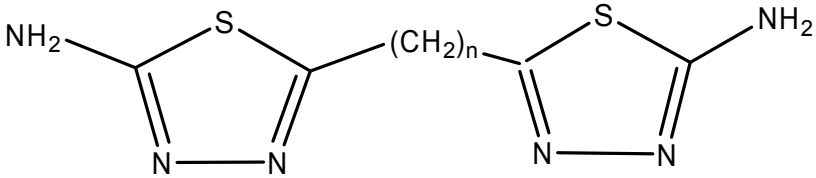
Mehta et al[3] synthesized a series of 2-Arylsulfonamido-5-(Benzthiazol-2'yl-Thiamethyl)-1,3,4-thiadiazoles and were screened for antibacterial activity against gram (+ve) *Bacillus megaterium, B.subtilis* and gram(-ve) *Escherichia coli* and *A.aerogens* and antifungal activity against *A.awamory*.Compounds showed good antibacterial activity and moderate antifungal activity.



3(a –h)

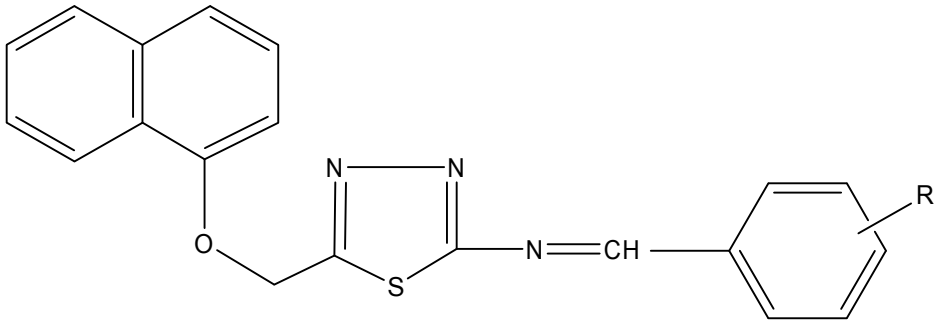
R=Phenyl,4-Chlorophenyl, 4-Iodophenyl,4-Anisyl,3-Carboxyphenyl, 3-Carboxy-4-chlorophenyl, 3-Carboxy-6-chloropheny, 3-Carboxy-4-methoxyphenyl.

Barve 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; Staphylococcus aureus,* Gram-negative bacterial strains: *Escherichia coli*; *Pseudomonas aeruginosa,* Fungal strains *Saccharomyces cerevisiae; Aspergillus niger, Candida albicans*.It is showed that compounds **(4a), (4e), (4f)** and **(4h)** exhibited antibacterial and antifungal activity.



n=1,2,3,4.....8 **4(a-h)**

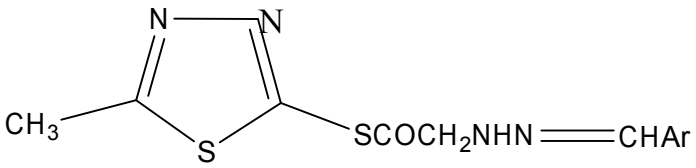
Madhav et al[5] have been synthesized a series of new 2-(substituted benzalamino)-5-(8-quinolinoxy methyl)-1,3,4-thiadiazoles and screened for their antimicrobial activity. Among all the compounds,compound 5g (R = 4-NO2) has been found to be greater inhibitory effect against four strains of bacteria, followed by compound 5f (R= 2-Cl) whereas rest of the compounds were mild to moderately active.



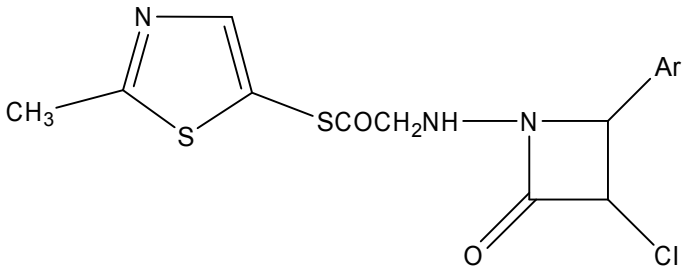
5(a-h)

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

Rajiv Dua et al[6] have synthesized several new 2-(2'-substitutedbenzylidene-hydrazino-acetyl)-mercapto-5-methyl-1,3,4-thiadiazoles,**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, Escherichia coli. Klebsiella pneumoniae* and *Streptococcus aureus* bacteria and antifungal activity against *Aspergillus niger, Aspergillus flavus, Fusarium oxisporium* and *Trichoderma viride* fungi respectively.They have shown significant antibacterial and antifungal activity.

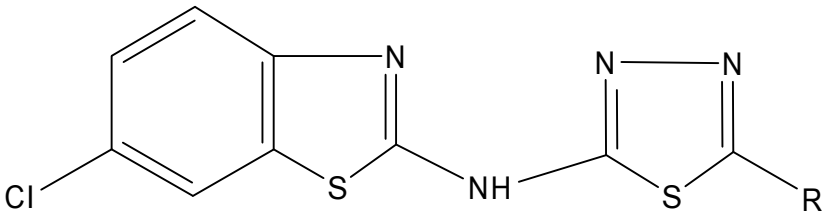


6(a-n)



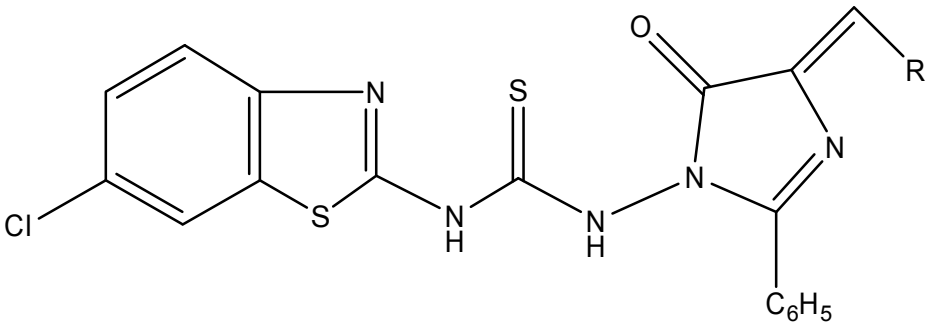
7(a-n)

The research study by Amir et al[7] report 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-dihydroimidazolinones **(9a-e)**.All the compounds showed significant antimicrobial activity.



8(a-j)

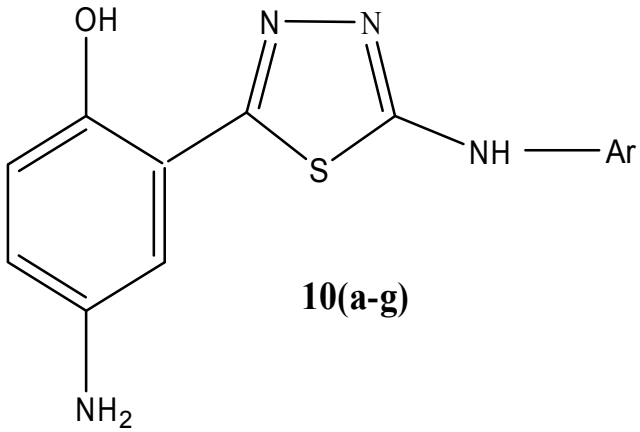
Ar=phenyl,4-Chiorophenyl,2,4-Dichlorophenyl, 4-Nitrophenyl, 2-Aminopheny,2,4-Dichlorophenoxymethyl,2-Napthylmethyl,4-Methoxyphenyl,2-Acetoxyphenyl,3-Pyridyl.



9(a-e)

R= Phenyl,4-Chiorophenyl,4-Fluorophenyl, 4-N,N-dimethyl phenyl,3-Indolyl.

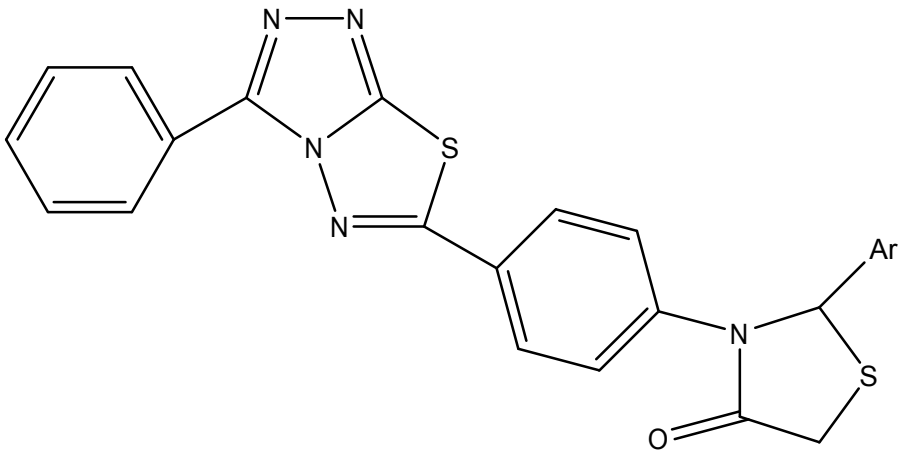
Sabir Hussain et al[8] have synthesized some 4-amino-2-{5-[(4-substituted phenyl)amino]-1,3,4-thiadiazole-2-yl} phenol **10(a-g)** evaluated for their antibacterial and antifungal activity. The compounds showed significant antibacterial activity against *S. aureus* (gram-positive) and *E.coli* (gram-negative) bacteria and antifungal activity against *A. niger* fungi. Compounds **10c, 10f** exhibited promising antibacterial activity against *S. aureus* and *A. niger*.



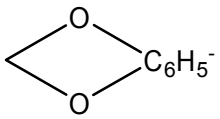
10(a-g)

Ar = 4-Methylphenyl,4-Methoxyphenyl,4-Chlorophenyl,2,5-Dimethylphenyl,3-Chloro-4-fluorophenyl,4-Bromophenyl.

Parmar et al[9] 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*.

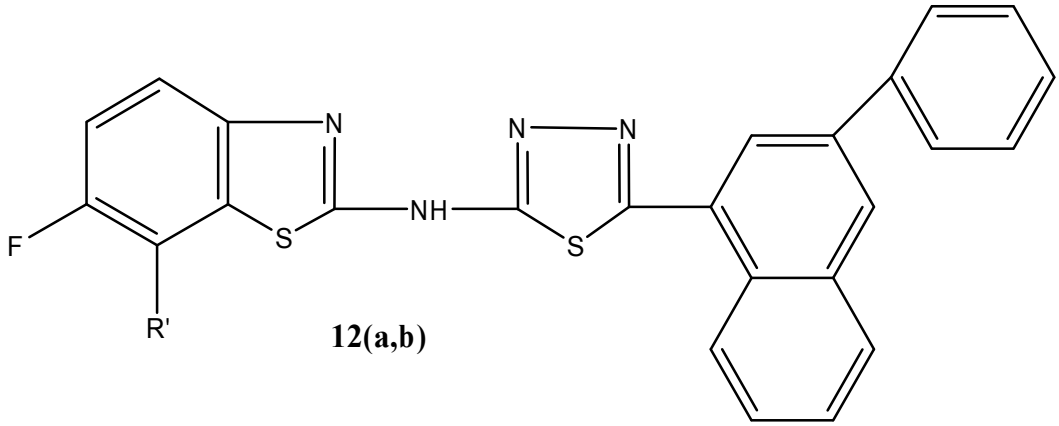


11(a-h)



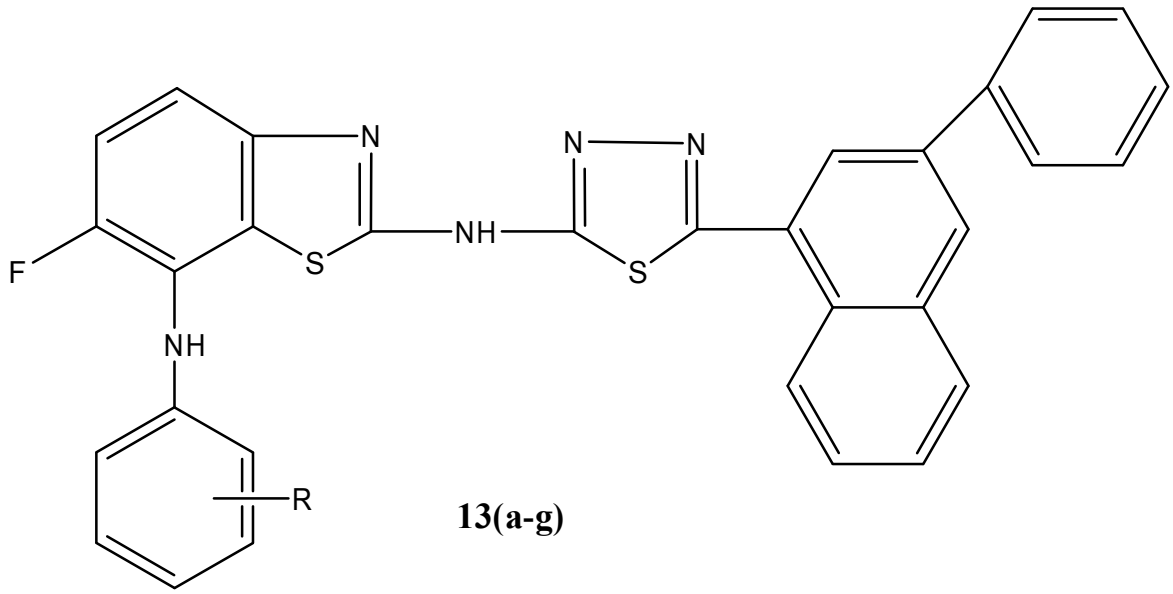
Ar = -C_6H_5 ,4-OCH_3-C_6H_4 , 4-OH-C_6H_4 , 2-OH-C_6H_4, 4-CH_3-C_6H_4 , ,4-OH-3-OCH_3-C_6H_3 , 4-OC_2H_5-3-OC_2H_5-C_6H_3 .

M.Vedavathi et al[10] 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.



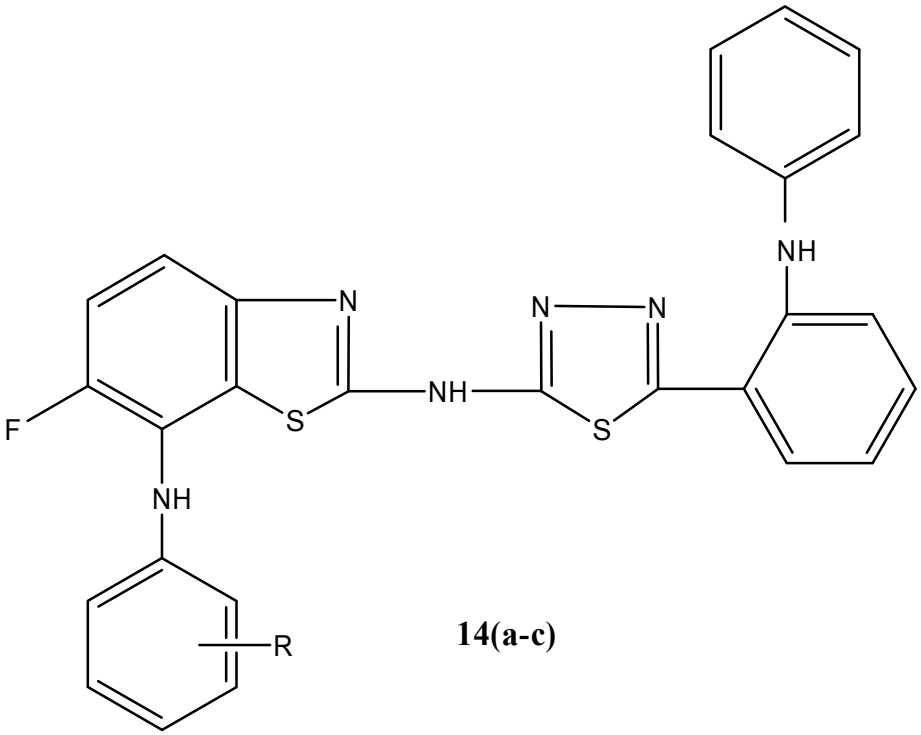
12(a,b)

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



13(a-g)

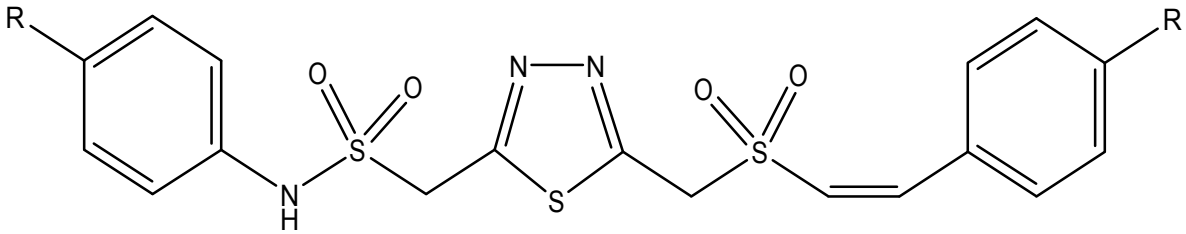
R = o, m, p nitro aniline (a-c)
= o, m, p chloro aniline (d-f)
= aniline (g)



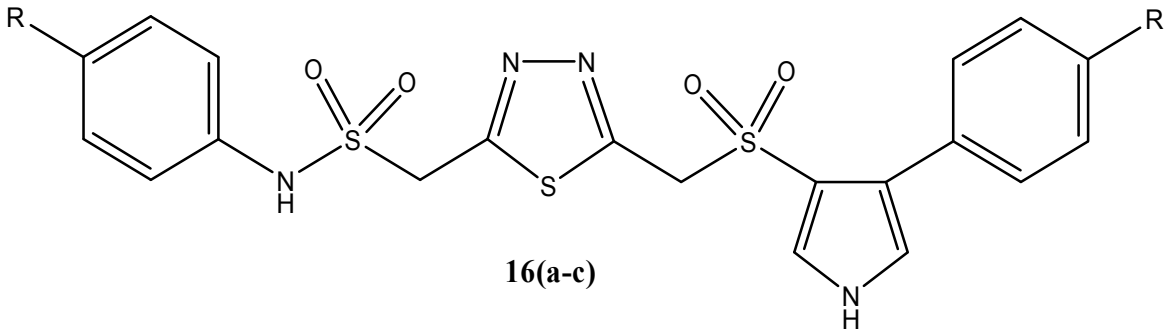
14(a-c)

R= o-anisidine, m-anisidine, p-anisidine

Padmaja et al[11] 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 *Staphylococcus aureus*, *Bacillus subtilis* (Grampositive bacteria) and *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* (Gram-negative bacteria) and antifungal activity evaluated against *Penicillium chrysogenum*, *Curvularia lunata* and *Aspergillus niger*.

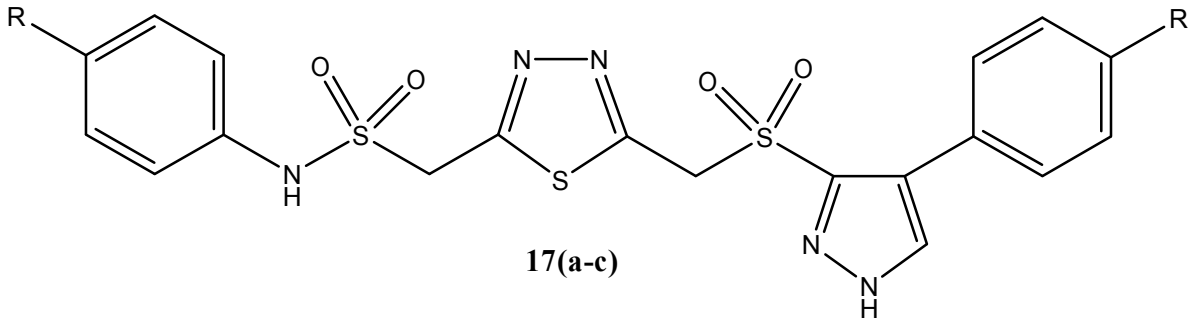


15(a-c)
R = H, Me, Cl



16(a-c)

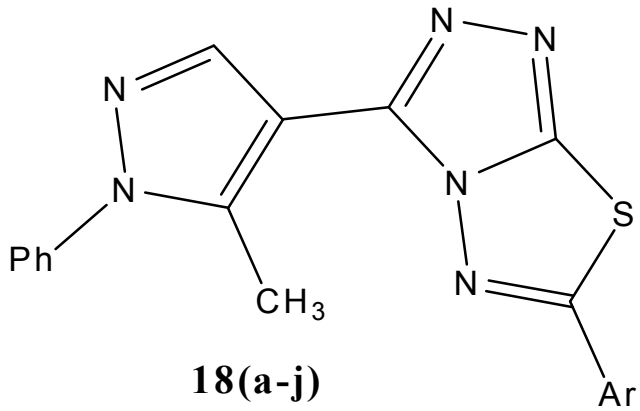
R = H, Me, Cl



17(a-c)

R = H, Me, Cl

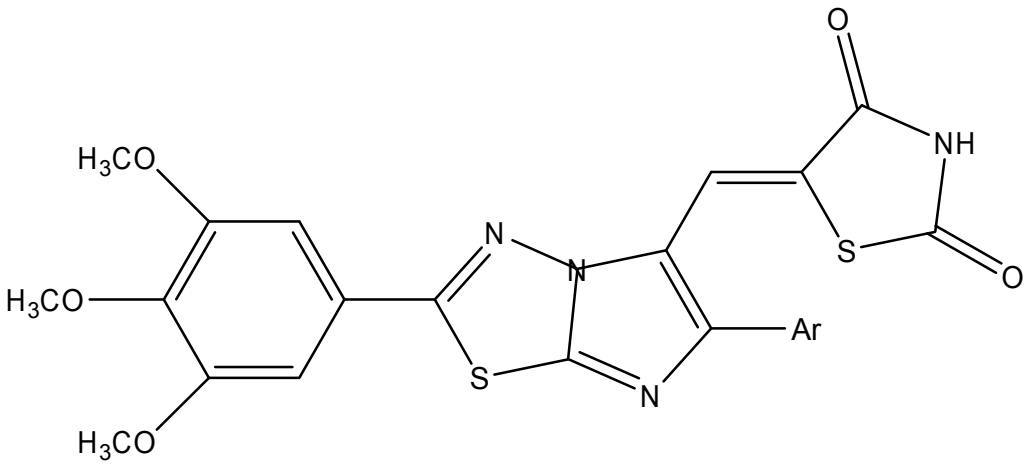
Cherkupally et al[12] synthesized a new series of 6-(aryl/heteryl)-3-(5-methyl-1-phenyl-1*H*-4-pyrazolyl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazoles **18(a—j)**. All the synthesized compounds were tested for *in vitro* activities against certain strains of bacteria such as *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and fungi such as *Aspergillus niger*, *Aspergillus nodulans*, *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.



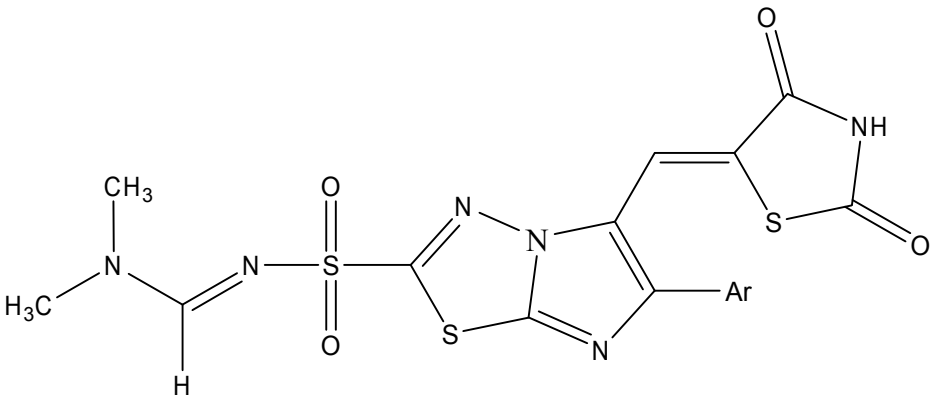
18(a-j)

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

K.R.Alagawadi et al[13] synthesized a new 2,4-thiazolidinediones derivatives bearing imidazo[2,1-b][1,3,4] thiadiazole moeity. All compounds were evaluated for their preliminary in vitro antibacterial and antifungal activity against Gram-positive *Staphylococcus aureus, Enterococcus faecalis*,Gram-negative *Escherichia coli , Pseudomonas aeruginosa bacteria and Candida albicans, Aspergillus flavus , Aspergillus niger ,* and *Cryptococcus neoformans* fungi. The results revealed that most of the compounds showed high or moderate biological activity against tested microorganisms.



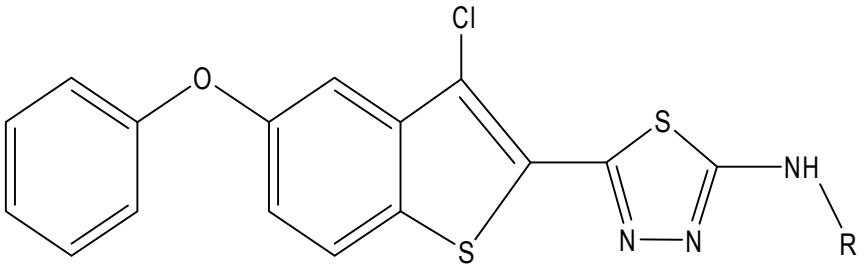
19(a-g)



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.

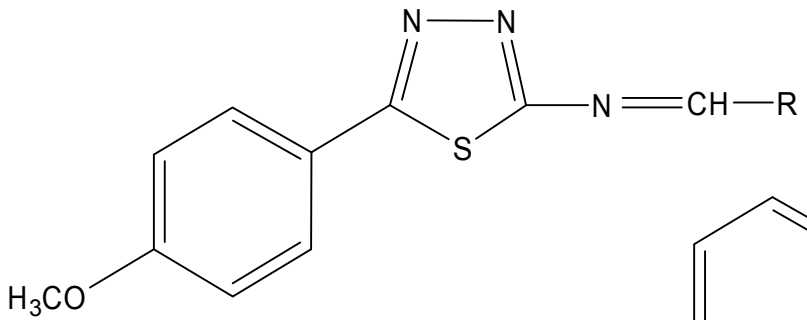
Vasoya et al[14] synthesized 2-(3′-Chloro-5′-phenoxybenzo[b]thiophen-2′-yl)-5-arylamino-1,3,4-thiadiazole derivatives **(21a-h)** by the cyclization of arylthiosemicarbazides with concentrated sulphuric acid. All the compounds were screened for their antimicrobial activity against various microorganisms.



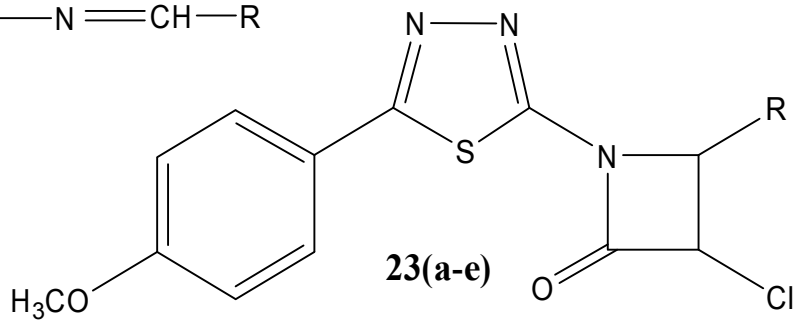
21(a-h)

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

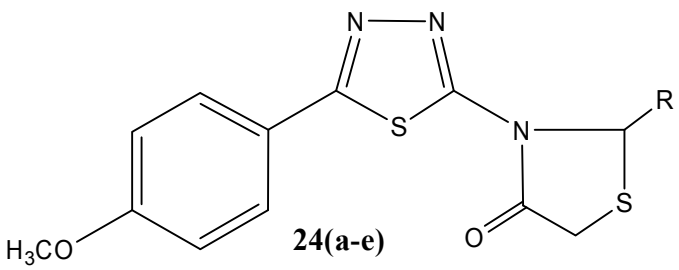
Pratibha Singh et al[15] have been synthesized some thiadiazole derivatives by incorporating azetidinyl and thiazolidinyl moieties at its 2-position such as 5-(*p*-methoxyphenyl)-[2-substituted benzylidenylimino] 1,3,4-thiadiazole **22(a-e)**, 5-(*p*-methoxyphenyl)-[2-(3'-chloro-2'-oxo-4'-substituted 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)



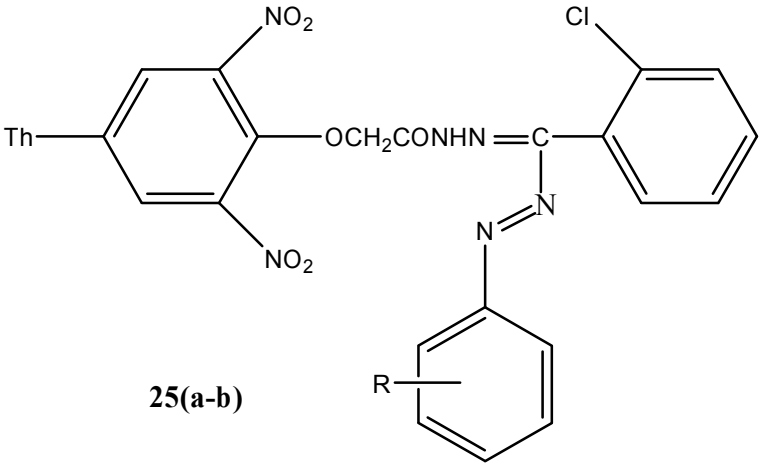
23(a-e)



24(a-e)

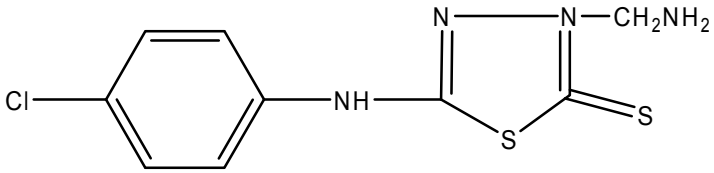
R = 4-OH-C_6H_4 , 4-OCH_3-C_6H_4 , -C_6H_5 , 4-Cl-C_6H_4 , 4-$N(CH_3)_2$-C_6H_4

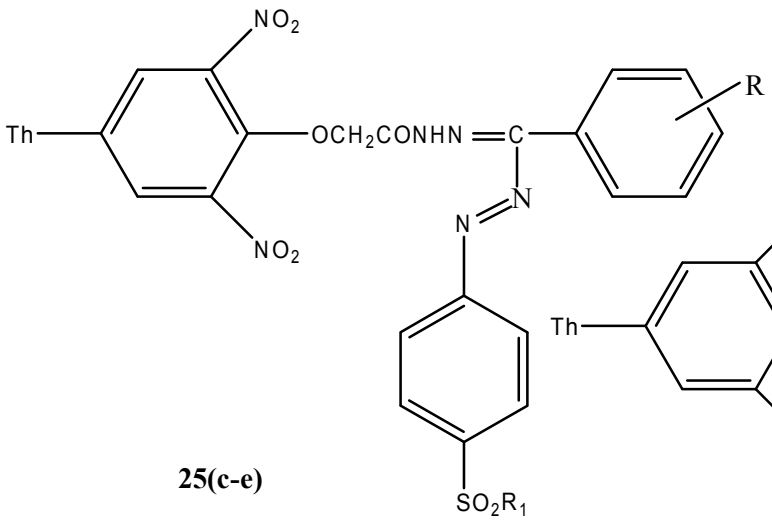
Pramila Shah et al[16] synthesized formazans from Mannich base of 5-(4-chlorophenyl amino)-2-mercapto-1,3,4-thiadiazole. All the compounds (25a-g) were screened for their in vitro antibacterial activity against *Escherichia coli* and *Salmonella typhi*. Antifungal activity was conducted against *Aspergillus niger, Penicillium sp*. and *Candida albicans*



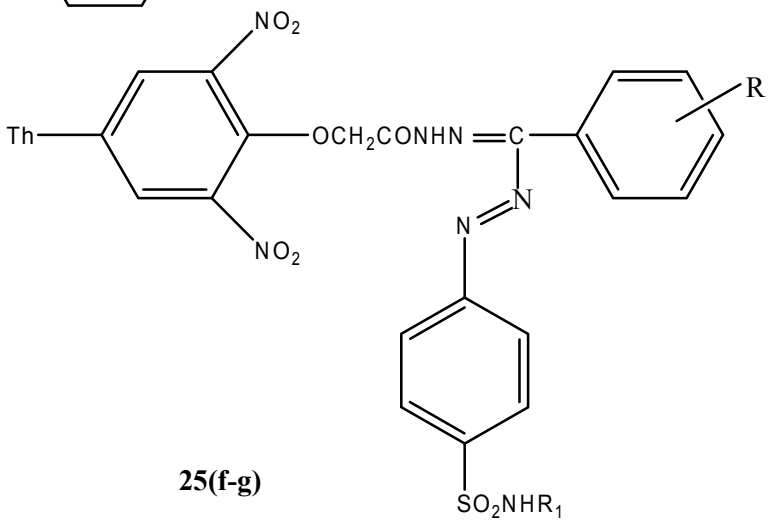
25(a-b)

Th =





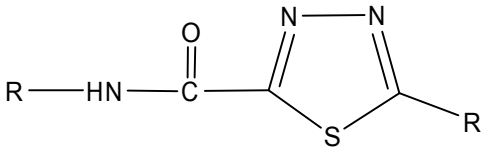
25(c-e)



25(f-g)

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, guanidino
25f-g : R = 3-methoxy, 4-hydroxy, R1 = pyrimidinyl, 4,6 dimethyl pyrimidinyl

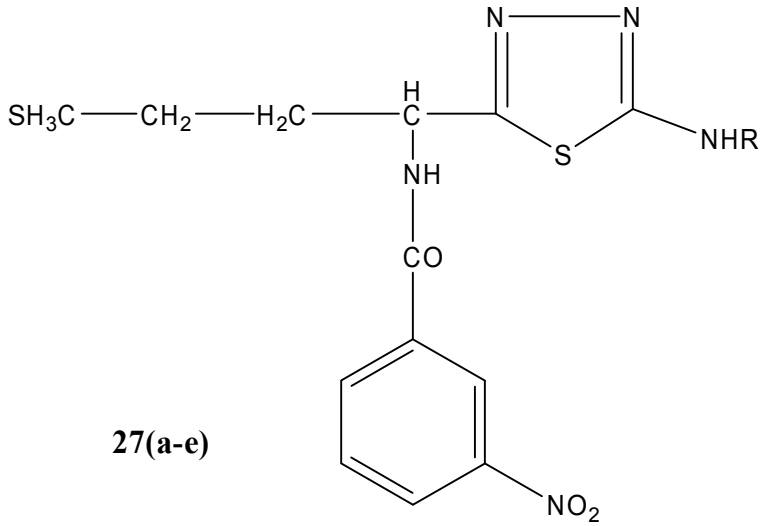
Arvind et al[17] synthesized a series of new 5-substituted-[1,3,4-thiadiazole-2-yl] benzamide.
Antimicrobial activity was carried out using bacterial strain *Staphylococcus aureus* (gram +ve), *E. Coli* (gram -ve) and *A. niger*. All compounds have shown moderate antimicrobial activity against all the 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

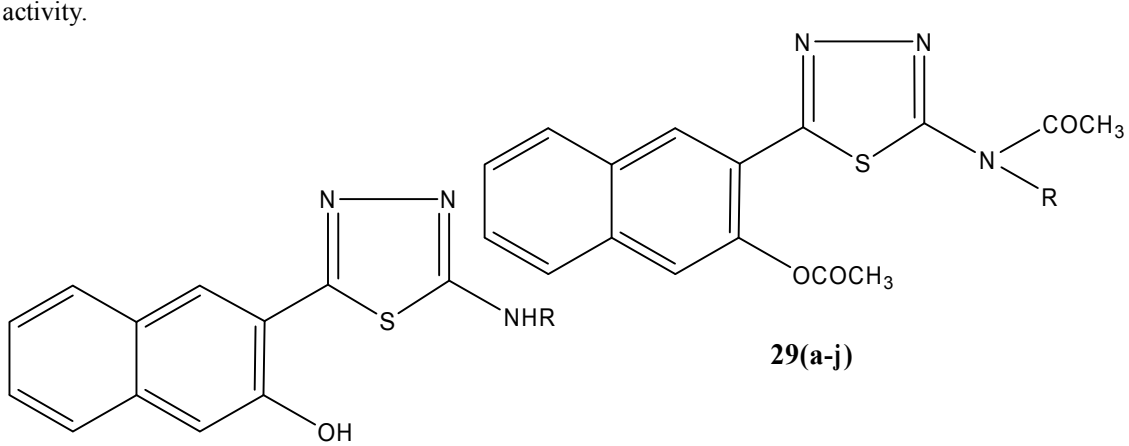
Profire et al[18] synthesized a new 1,3,4-thiadiazole derivatives **(27a-e)** containing a *D,L*-methionine moiety by intramolecular cyclization of 1,4-disubstituted thiosemicarbazides in acid and alkaline media, respectively. The potential antimicrobial effects of the synthesized compounds were investigated using the *Staphylococcus aureus*, *Bacillus antracis*, *Bacillus cereus*, *Sarcina lutea* and *Escherichia coli* strains. The newly synthesized compounds exhibited promising activities against *Bacillus antracis* and *Bacillus 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[19] synthesized the two new series of 2,5-disubstituted-1,3,4-thiadiazoles. All the synthesized products were evaluated for their antibacterial activity against *Bacillus substilis, Escherichia coli. P.aeruginosa* and *Streptococcus aureus* bacteria and antifungal activity against *Candida.albicans* fungi respectively.They have shown significant antibacterial and antifungal activity.

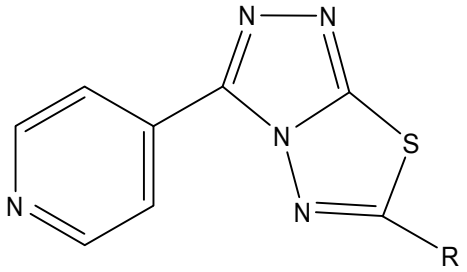


29(a-j)

28(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).

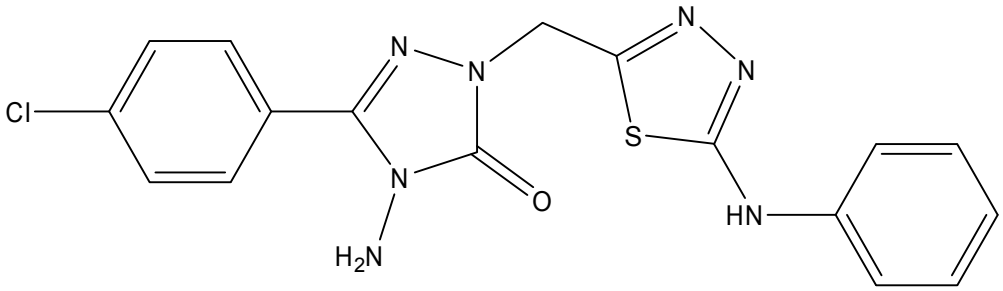
Gilani et al[20] synthesized a series of 6-substituted-1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazole **(30a-g)** derivatives of isoniazid in satisfactory yield and pharmacologically evaluated for their *in vitro* antimicrobial activity. A majority of the tested compounds showed good to moderate antimicrobial activity against all tested pathogenic bacterial and fungal strains.



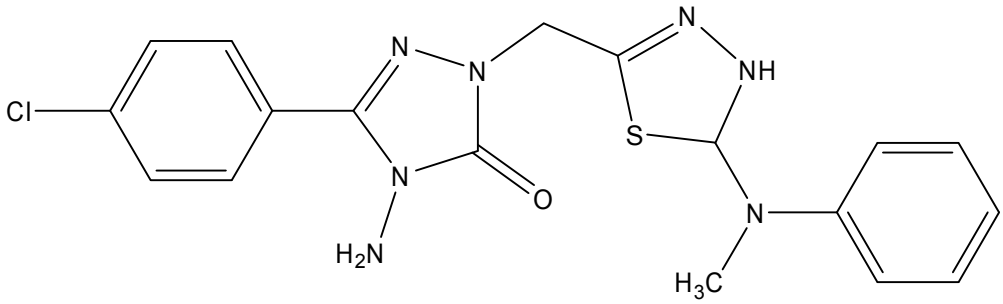
30(a-g)

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[21] 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.

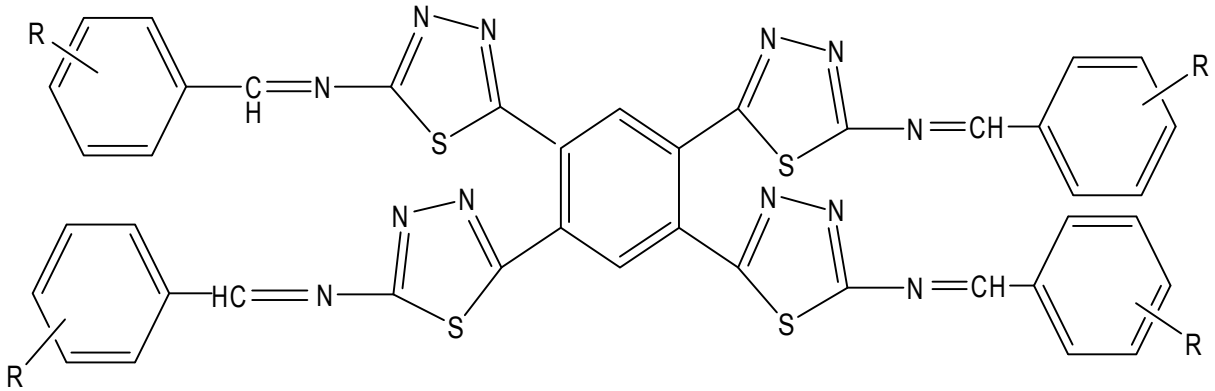


31a



31b

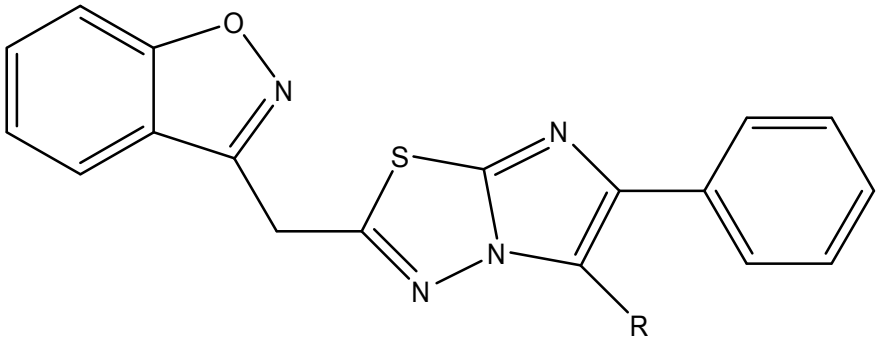
Yousif et al[22] synthesized novel tetra compound Schiff base by condensation of 1,2,4,5-tetra (5-amino-1,3,4-thiadiazole-2-yl)benzene with different aromatic aldehydes. All compounds **(32 a-h).** Were screened for antibacterial (*Staphylococcus aureus*, *Staphylococcus epidermidis*, *icrococcus luteus*, *Bacillus cereus*, *Escherichia coli*, and *Pseudomonas aeruginosa*) and antifungal (*Aspergillus niger* and *Aspergillus fumigatus*) activities.



32(a-h)

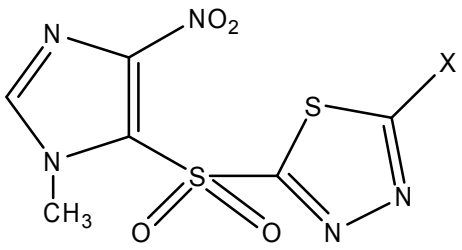
R = *p*-H, *p*-CH_3, *p*-OH, *o*-H, *p*-NO_2, *p*-Br, *p*-OCH_3, *p*-Cl

Lamani et al[23] synthesized novel methylene bridged benzisoxazolyl imidazo[2,1 b][1,3,4] thiadiazoles **(33a-c)** and revealed for their antibacterial and antifungal activities. Allcompounds having nitroso, bromo, thiocynato exhibited significant antibacterial and antifungal activities.



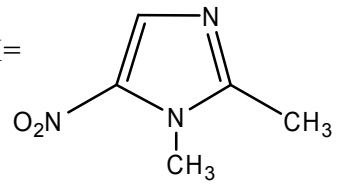
(33a-c)
R = Br, NO, SCN

Bahram et al[24] 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 *Staphylococcus aureus, Staphylococcus epidermidis* and *Bacillus subtilis.*

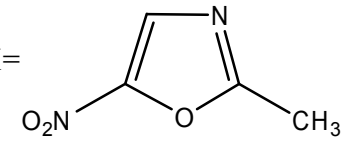


34(a-c)

34(a) X=

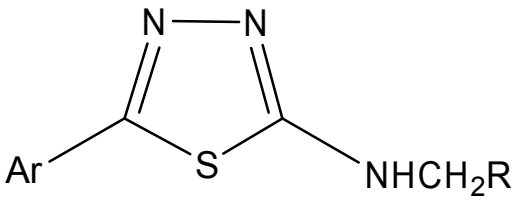


34(b) X=



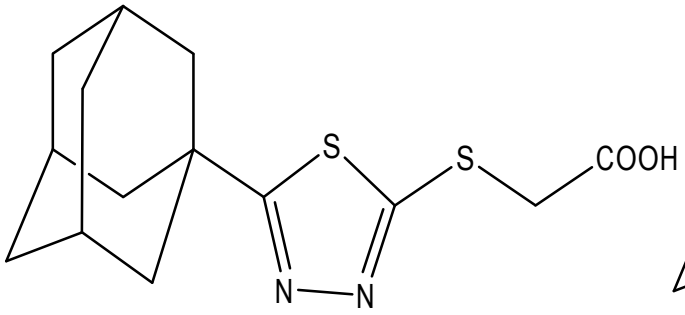
34(c) X= CH_3CONH-

B.Gowramma et al[25] 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.

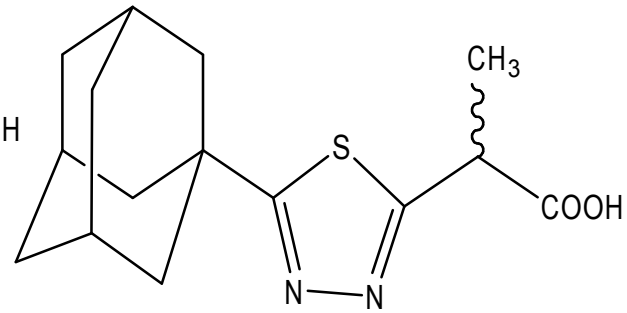


35(a-m)
R = C_6H_6N & C_6H_5NCl
Ar = - C_6H_5, - C_6H_4OH, - $C_6H_4N(CH_3)_2$, - C_6H_4Cl, - $C_6H_4NO_2$, - C_4H_3S

Kadi et al [26] 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 *Candida 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

This literature review reveals that 1, 3, 4 Thiadiazole have diverse biological activity, and very simple synthetic process too. It has shown the good anti-microbial activities. By the present scenario it can be concluded that 1, 3, 4 Thiadiazole have remarkable anti –microbial activity.

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