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Research Article

THERAPEUTIC IMPACT OF NOVEL THIADIAZOLE SCAFFOLDS IN DRUG DESIGN AS POTENT ANTIMICROBIAL AGENTS

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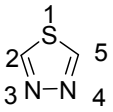
ABSTRACT

Microbial resistance against clinically used antibiotics has become a global threat in the treatment of microbial infections. 1,3,4-thiadiazole is a versatile heterocyclic nucleus which exhibit a wide range of pharmacological activities which includes antibacterial, antifungal, antitubercular, anti-inflammatory and anticancer activities etc. This review article has highlighted the most potent thiadiazole derivatives that have shown substantial antimicrobial activities having different mode of action as per the recent literature survey. Therefore, as a sincere endeavor this manuscript provides information about antimicrobial profile of thiadiazole derivatives in search of better antimicrobial agents.

Keywords: Thiadiazole, antibacterial, antifungal activities.

INTRODUCTION

Bacterial infections are life threatening which include cholera, syphilis, anthrax, leprosy and plague etc[1] whereas fungal infections are related with Tinea, Candida and Athlete's foot. Therefore, pathogenic microbes and their resistance to antibiotic therapy is causing increase in worldwide public health problems[2,3]. Antibiotic resistance may take place due to several bacterial species which are able to survive after exposure to one or more antibiotics and in some cases pathogens become resistant to multiple antibiotics to become multidrug resistant (MDR) species. Considering the extent of lethal effect as well as significant impact on morbidity and mortality, multi-drug-resistant (MDR) pathogens are responsible for global deaths of millions of patients every year. All these facts and problems call for urgent requirement of development of potent antibiotics with unique mode of action[4,5]. Thiadiazole is a 5-membered heterocyclic ring system containing two nitrogen and one sulphur atom which occur in nature as four isomeric forms viz. 1,2,3-thiadiazole; 1,2,5-thiadiazole; 1,2,4-thiadiazole and 1,3,4-thiadiazole **(Fig. 1)**. The recent literature review has proved that the thiadiazole scaffold is having a broad spectrum of pharmacological activities like antimicrobial, anti-inflammatory, anticancer, anticonvulsant, antidepressant and antioxidant activities[6,7].

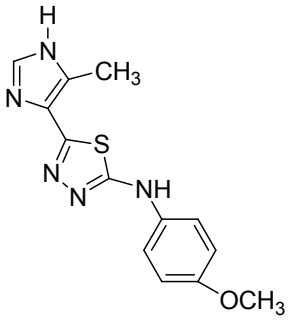


(1)

ANTIMICROBIAL ACTIVITIES

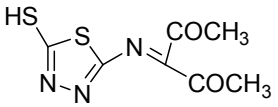
Recent literature survey has demonstrated that thiadiazole derivatives have broad spectrum of pharmacological activities exclusively potent antimicrobial activities which have been presented in this section as given below:

Liesen *et al* synthesized N-(4-methoxyphenyl)-5-(5-methyl-1*H*-imidazol-4-yl)-1,3,4-thiadiazole-2-amine derivatives **(2)**. The synthesized derivatives were tested for antimicrobial activity by the disc diffusion method. In general, these results indicated weak antimicrobial activities for all compounds. However, some compounds showed significant mean zone inhibition (MZI), for bacterial stains *Staphylococcus aureus*and *Bacillus subtilis*, *Escherichia coli* and *Mycobacterium smegmatis*. One compound was found to be the most potent compound with MIC value 130µg/ml as compared with standard drug[8].



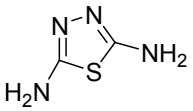
(2)

Dubey *et al* synthesized 1,3,4 thiadiazole-1,3,5-triazine derivatives **(3)** and evaluated their antimicrobial activity against bacterial stains like *Pseudomonas aeruginosa*, *Bacillus cereus, Escherichia coli* and *Bacillus subtilis*. The resultant MIC value for the title compounds were found in good agreement with the results of zone of inhibition.The tested compounds showed moderate antibacterial activity in comparison with cefixime as standard drug[9].



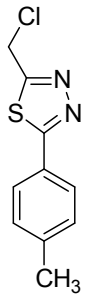
(3)

A novel series of Mn (II) and Fe (III) complexes of 1,3,4-thiadiazole-2,5-diamine **(4)** were synthesized and demonstrated their antimicrobial activityby **Gupta *et al***. The bacteria species used for this test included clinical cultures of *Escherichia coli, Staphylococcus aureus, Klebsiella species, Niesseria gonorrhoea, Salmonella typhi, Shigella, Penicillium, Pseudomonas aeruginosa* and *Aspergillus species*. The antibacterial activities of the compounds were measued by determining their minimum inhibitory concentration (MIC) values. One compound showed most potent antimicrobial activities whereas remaining compounds displayed significant antimicrobial activities when compared with their respective standard drugs[10].



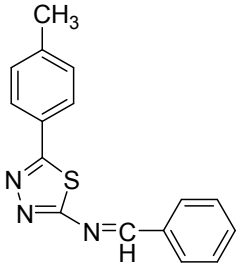
(4)

Some new (3,5-dichloro-4-((5-aryl-1,3,4-thiadiazol-2-yl)methoxy)phenyl) aryl methanones **(5)** were synthesized and investigated for their antimicrobial activities by **Murthy *et al.*** The antimicrobial activity ofthe newly synthesized compoundswere evaluated by agar well diffusion method. Antimicrobial activity of all the synthesizedcompounds was evaluated by measuring the zone of inhibition against the test microorganisms**.** Gentamicin (standard antibacterial drug) andNystatin (standard antifungal drug) were used for comparision. The minimum inhibitory concentrations (MIC) were evaluated by the microbroth dilution technique. Some compounds showed good and other compounds showed moderate antimicrobial activities on comparision with their respective standard drugs[11].



(5)

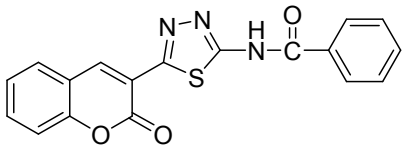
Seelam *et al* synthesized a novel series of N-benzylidene-5-ptolyl-1,3,4-thiadiazole derivatives **(6)** and screened their antimicrobial activity. The screened compounds showed high antibacterial activity against all the stains employed. In this view some compoundsshowed potent activity as compared with standard drug Streptomycin against *B. subtilis*and *B. thuringiensis*[12].



(6)

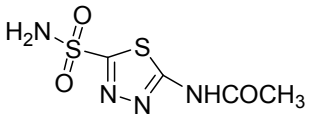
A novel series of N-(5-(2-oxo-2*H*-chromen-3-yl)-1,3,4-thiadiazole-2-yl)benzamide derivatives **(7)** were synthesized and evaluated for their antimicrobial activity by **Wardakhan *et al***. The *in vitro* antimicrobial activity of the structurally promising heterocyclic derivatives were tested against two stains of Gram-positive bacteria *Bacillus subtilis* and *Bacillus cereus*, two stains of Gram-negative bacteria *Escherichia coli* and

Pseudomonas aeruginosa. Ampicillin and Cycloheximide were used as standard drugs. Some compounds showed good antimicrobial activities[13].



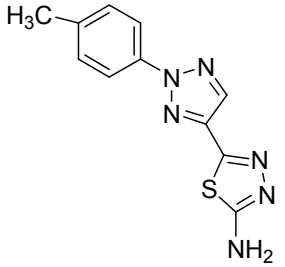
(7)

A novel series of thiadiazole derivatives contaning Zn (II) complex **(8)** were synthesized and evaluated for their antimicrobial activities by **Malik *et al.*** The synthesized compounds were screened against bacteria *Escherichia coli* and *Pseudomonas aeruginosa* by the filter paper disc method at various concentrations using nutrient agar as medium. Some compounds showed significant antimicrobial activities as compared with Ciprofloxin as standard drug[14].



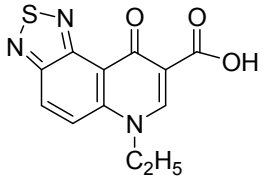
(8)

Atta *et al* synthesized novel imidazo[2,1-b]-1,3,4-thiadiazoles **(9)** and evaluated for their antimicrobial activity. The antibacterial activities of compounds were tested against the micro-organisms *Staphylococcus aureus*, *Candida albicans*, *Pseudomonas aeruginosa* and *Escherichia coli*. Agar diffusion method was used for antibacterial screening. Ampicillin and Clotrimazole were used as reference drugs. Some of the tested compounds showed moderate to good antimicrobial activities[15].



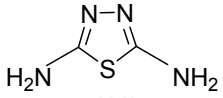
(9)

Al-Qawasmeh *et al* synthesized 9-cyclopropyl-4-fluoro-6-oxo-6,9-dihydro-[1,2,5]thiadiazolo[3,4-h]quinoline-7-carboxylic acid and ethyl ester derivatives **(10)** and tested for their antimicrobial activities. The new fluoroquinoloneand their ester parent compounds were tested *in vitro* against a wide spectrum of Gram-positive and Gram-negative bacteria, yeasts and moulds. The minimum inhibitory concentrations (MIC) and the minimum bactericidal concentrations (MBC), both expressed in µg/mL were determined and compared to those of Ciprofloxacinas reference drug. Some compound showed excellent activity against Gram-positive *bacilli* and *staphylococci* (MICs = 0.015-1.5 µg/mL), including methicillin-resistant *Staphylococcus aureus*, and against most of the Gram-negative bacteria tested (MICs = 0.07-3 µg/mL)[16].



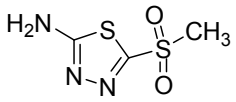
(10)

Adediji *et al* synthesized Cu(II) Metal Complexes of 1,3,4-thiadiazole-2,5-diamine **(11)** with some semicarbazide derivatives and investigated their antimicrobial activity. Antitubercular activity was investigated against *Mycobacterium tuberculosis* using Microplatealamar blue assay. Amoxicillin was used as standard drug. Some compounds showed excellent antimicrobial activities on comparision with standard drug[17].



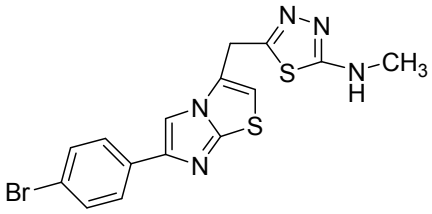
(11)

The 2-amino-5-mercapto-1,3,4-thiadiazole derivatives **(12)** were synthesized by **Ameen *et al.*** The synthesized compounds were screened for the presence of antibacterial constituents against four stains of bacteria i.e. *Staphylococcus aureus, Escherichia coli, Klebsiella pneumonia, β-hemolytic-Streptococcus pyogenes* and one species of fungi *Candida albicans* by disc diffusion method. Gentamycin, Amoxicillin/clavulanic acid, and Ketoconozole were used as standard drugs. Some of the tested compounds displayed excellent antimicrobial activities[18].



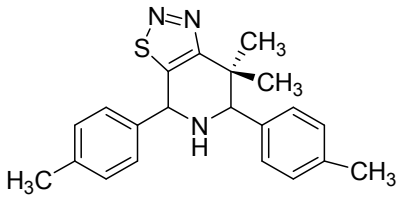
(12)

A novel series of 1,3,4-thiadiazoles bearing imidazo[2,1-b]thiazole derivatives **(13)** were synthesized and examined for their antitubercular activity by **Guzeldemirci *et al***. MICs were determined by the microbroth dilution method. Mueller–Hinton broth was used as the test medium. A primary screening was conducted at 6.25 mg/ml (or molar equivalent of highest molecular weight compound in a series of congeners) against *M. tuberculosis*. One compound showed the most potent antitubercular activity by having MIC value of 0.25µg /mL and 97-99% inhibition as compared with standard antitubercular drug[19].



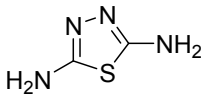
(13)

Gopalakrishnan *et al*. synthesized 5,7-diaryl-4,4- dimethyl-4,5,6,7-tetrahydropyridino[3,4-d]-1,2,3- thiadiazoles **(14)**. All of the newly synthesized novel target molecules were tested for their antibacterial activity *in vitro* against *Staphylococcus aureus, β-Haemolytic streptococcus, Vibreo cholerae, Salmonella typhii, Shigella felxneri, Escherichia coli, Klebsiella pneumonia*, and *Pseudomonas* by using Ciprofloxacin as standard drug for comparison. Some compounds showed good whereas other compounds demonstrated moderate antimicrobial activities[20].



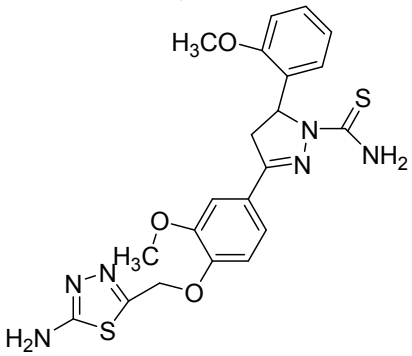
(14)

A novel series of Fe(III) complex of 2,5 diamino-1,3,4- thiadiazole derivatives **(15)** were synthesized and their antimicrobial activities were performed against *Escherichia coli, Staphylococcus aureus, Klebsiella species, Niesseria gonorrhoea, Salmonella typhi, Shigella species, Penicillium species, Pseudomonas aeruginosa* and *Aspergillus species* by **Adediji *et al***. The antibacterial activities of the compounds were determined using sensitivity test, minimum inhibition concentration and minimum bacterial concentration. Some compounds showed significant antimicrobial activities by having MIC values ranging from 15 to 700 µg/mL on comparision with Amoxicillin as standard drug[21].



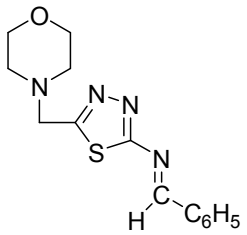
(15)

Noolvi *et al* synthesized a series of 1,3,4-thiadiazole derivatives of 2-(4-formyl-2-methoxyphenoxy) acetic acid **(16)** and screened for their antimicrobial activity against *S. aureus, S. enterica, V. cholera, B. subtilis, P. mirabili, E. coli , M. smegmatics, P. aeruginosa* and antifungal activity against *C. albicans*. Most of the screened compounds showed excellent antimicrobial activities by having % inhibition in range of 83%-97% in comparision with Ampicillin as standard drug[22].



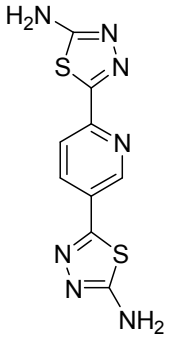
(16)

Some novel N-benzylidene-5-(morpholinomethyl)-1,3,4-thiadiazole-2-amine derivatives **(17)** were synthesized and evaluated for their antibacterial studies against *Staphylococcus aureus, Bacillus cereus* and *Escherichia coli* by **Raj *et al*.** Microbial studies were assessed by Minimum Inhibitory Concentration (MIC) by serial dilution method. Streptomycin was used as standard drug. Some compounds showed good whereas other compounds moderate antimicrobial activities[23].



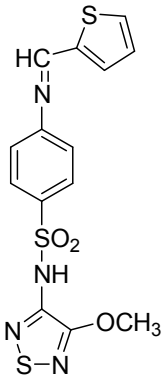
(17)

Bhardwaj *et al* synthesized new pyridine imidazo [2,1b]-1,3,4-thiadiazole **(18)** derivatives. The synthesized compounds were screened for their antimicrobial activity using cup-plate agar diffusion method against bacteria *B. pumillus, S. aureus, V. cholera, E. coli, P. mirabilis,* and *P. aeruginosa* and fungal culture of *C. albicans*. Some compound showed excellent inhibition of *B. pumillus* (95.1%), *P. aeruginosa* (94.6%), *V. cholera* (91.0%), *S. aureus* (88.8%), and one compound demonstrated inhibition of *P. mirabilis* (87.8%) when compared with standard drug Ampicillin[24].



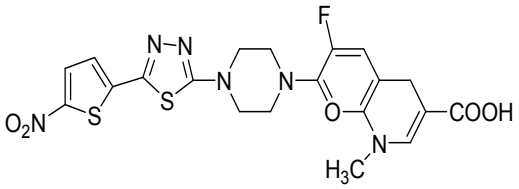
(18)

A series of some novel metal complexes of Schiff base derived from [N1-(4-methoxy-1,2,5-thiadiazol-3-yl)sulfanilamide]and 2-thiophene carboxaldehyde derivatives **(19)** were synthesized and demonstrated their antimicrobial activities against *Escherichia coli*, *Salmonella typhi, Staphylococcus aureus* and *Bacillus subtillus* (bacteria) or *Aspergillus terreus* and *Aspergillus flavus* (Fungi) by **Sharaby *et al.*** The antibacterial and antifungal tests were carried out by using the disc diffuse method at different concentrations 1, 2.5 and 5 µg/ml. Chloramphenicol and Grisofluvin were used as reference drugs for antbacterial and antifungal activities respectively. Some of the tested compounds showed significant antimicrobial activities[25].



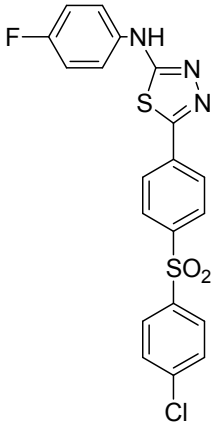
(19)

Foroumadi *et al* synthesized some novel N-[5-(5-nitro-2- thienyl)-1,3,4-thiadiazole-2-yl] piperazinyl quinolones **(20)** and tested for their antimicrobial activity against some Gram-positive *(S. aureus, S. epidermidis, B. subtilis*) and Gram-negative (*E. coli , K. peneumoniae, P. aeruginosa, E. cloacae*) bacteria using conventional agar dilution procedure. Two compounds displayed excellent antimicrobial activities on comparision with standard drugs like Ciprofloxacin, Norfloxacin and Enoxacin[26].



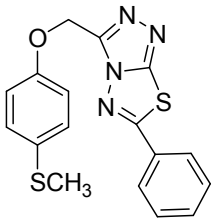
(20)

A new series of 5-(4-(4-chlorophenylsulfonyl)phenyl)-N-(-4-fluorophenyl)-1,3,4-thiadiazol-2-amine derivatives **(21)** were synthesized and investigated for antimicrobial activity by **Barbuceanu *et al***. The *in vitro* testing of the antibacterial activity of compounds was performed using the broth microdilution method, in order to detect the minimum inhibitory concentrations (MIC). The antibacterial activity of the compounds was tested against the following stains of oral streptococci: *S. anginosus*, *S. mitis*, *S. mutans*, *S. parasanguinis, S. salivarius*, *S. sanguinis* and *S. vestibularis.* The MIC values of the tested compounds were found to be in range of 32-64 µg /ml when compared with their respective standard drugs[27].



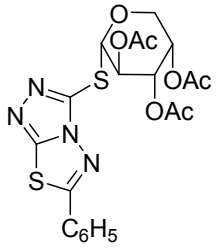
(21)

Some novel 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles **(22)** were synthesized by **Karabasanagouda *et al.*** The newly synthesized compounds were screened for their antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Klebsiella pneumonia* bacterial stains by serial plate dilution method. One compound was found to be the most potent compound of the series by having MIC value of 6.25*µ*g/ml on comparision with Ciprofloxacin as standard drug[28].



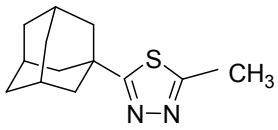
(22)

A novel series of N and S-arabinopyranosyl[3,4-b][1,3,4]thiadiazoles **(23)** were synthesized by **Nasser *et al*** and tested for their antimicrobial activity against selected two Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*), two Gram-negative bacteria (*Pseudomonas aeruginosa* and *Escherichia coli*), one yeast (*Candida albicans*) and three fungal stains *(Aspergillus fumigatus, Penicillium italicum* and *Syncephalastrum racemosum*). The broth dilution method was used to determine the minimum inhibitory concentrations (MICs) of the tested compounds which showed higher inhibitory effect against *A. fumigatus, P. italicum, S. racemosum, S. aureus, P. aeruginosa, B. subtilis* and *E. coli.* One compound was found to be the most potent compound which displayed MIC value of 1.6µg /ml as compared with standard drug[29].



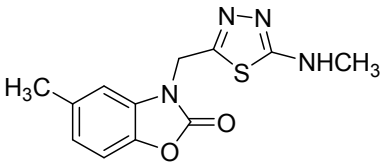
(23)

Some novel 2-(1-adamantylamino)-5-substituted-1,3,4-thiadiazoles **(24)** were synthesized and evaluated for their antimicrobial activity by **Kadi *et al*.** The primary screening was carried against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeuroginosa*, and *Candida albicans* by using the agar disc diffusion method. Some compounds exhibited excellent antimicrobial activity on comparision with standard drugs like Ampicillin and Clotrimazole respectively[30].



(24)

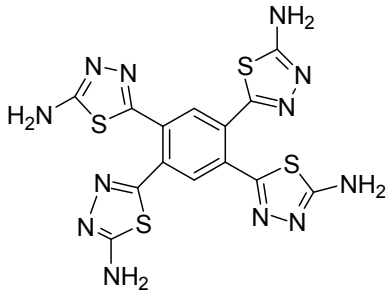
Salgin-Goksen *et al* synthesized acylthiosemicarbazides, 1,2,4-triazole-5(4*H*)-thiones, 1,3,4-thiadiazoles and hydrazones containing 5-methyl-2-benzoxazolinones **(25)** and examined their antimicrobial activity. The assessment of the antimicrobial activities of the synthesized compounds was performed using the broth microdilution test in Mueller-Hinton Broth and RPMI 1640 against *Candida krusei*, *Candida albicans* and *Candida parapsilosis* stains. Some compounds showed significant antimicrobial activity on comparision with standard drugs[31].



(25)

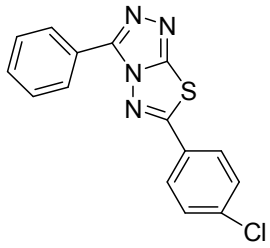
Some novel 1,2,4,5-tetra-(5-amino-1,3,4-thiadiazole-2-yl)benzene derivatives **(26)** were synthesized and demonstrated for their antimicrobial activity by **Yousif *et al***. Some

compounds showed significant antimicrobial activities by having MIC values for *S. aureus* (3.4–29.4 µg/ml), *S. epidermidis* (2.1–28.2 µg/ml), *M. luteus* (1.2–28.7 µg/ml), *B. cereus* (2.0–27.7 µg/ml), *E. coli* (3.1–32.8 µg/ml), *P. aeruginosa* (2.4–36.2 µg/ml), *A. niger* (1.1–34.2µg /ml) and *A. fumigatus* (1.7– 31.8 µg/ml) on comparision with Ciprofloxin and Ketoconazole as standard drugs[32].



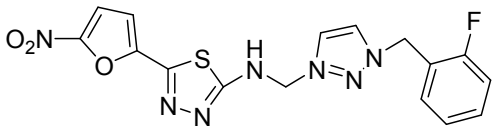
(26)

Mathew *et al* synthesized 2,4-triazolo[3,4-b]-1,3,4-thiadiazoles **(27)** and evaluated their antibacterial activity. The antibacterial activity of titled compounds was determined *in vitro* by using paper disc method against variety of pathogenic microorganisms like *E. coli, P. aeruginosa*, *S. aureus, B. subtilis* at 25, 50, 100 µg/ml concentrations, respectively. Vancomycin and Amikacin were used as standard antimicrobial drugs. Some of the tested compounds exhibited considerable antimicrobial activities[33].



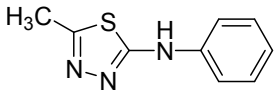
(27)

A novel series of 5-(5-nitrofuran-2-yl)-1,3,4-thiadiazol- 2-amines containing N-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]moieties **(28)** were synthesized by **Tahghighi *et al***. For evaluation of anti-leishmanial properties of target compounds, the *in vitro* activity was assessed against *promastigote* (extracellular parasite) and *amastigote* (intramacrophage parasite) forms of *L. major*. Also, the *in vitro* anti-amastigote activity of compounds was determined in mouse peritoneal macrophages. Some compounds showed significant anti-leishmanial activity when compared with standard drug[34].



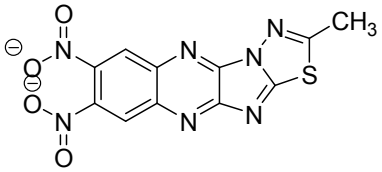
(28)

Farshori *et al* synthesized a novel series of 5-alkenyl/hydroxyalkenyl-2-phenylamine-1,3,4-thiadiazoles **(29)** and screened for their antimicrobial activity against *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus pyogenes* and *Klebsiella pneumoniae* bacterial stains by disc diffusion method. Minimum inhibitory concentrations (MICs) were determined by broth dilution techniques which were in range of 6.25-12.5µg/ml by using Chloramphenicol and Greseofulvin as standard antimicrobial drugs. Most of the tested compounds depicted excellent antimicrobial activities on comparision with standard drugs[35].



(29)

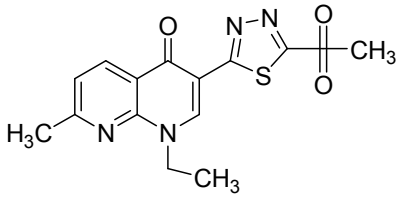
Teja *et al* synthesized some novel thiadiazolo [2,3] imidazo[4,5-B]quinoxaline derivatives **(30)** and evaluated their antimicrobial activity by paper disc diffusion method. The antibacterial activity for the synthesized compounds was screened against gram positive (*S. aureus*and *Bacillus cereus*) and Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*). The minimum inhibitory concentrations (MIC) of the compounds were also determined by using the agar streak dilution method.Ciprofloxin was used as reference drug. Many compounds showed good antimicrobial activities[36].



(30)

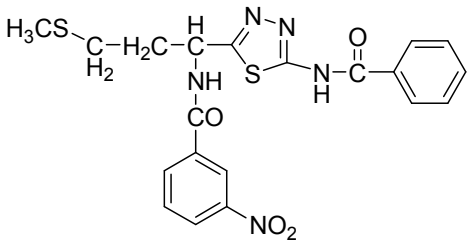
Aggarwal *et al* synthesized novel nalidixic acid-based1,3,4-thiadiazoles **(31)** and demonstrated their antimicrobial activity. Disk diffusion was used for the demonstration of the antibacterial activity. The bacterial stains used included Gram-positive bacteria, namely

Staphylococcus aureus and *Bacillus subtilis*, and Gram-negative bacteria, namely *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae*. Streptomycin was used as standard drug. Some compounds depicted significant antimicrobial activities on comparision with standard drugs[37].



(31)

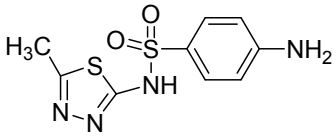
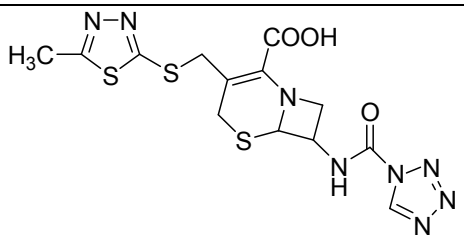
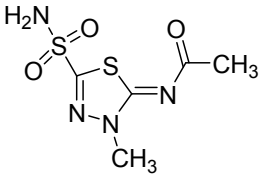
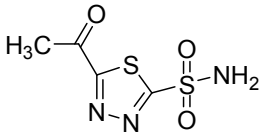
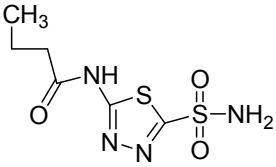
Pintilie *et al* synthesized some novel N-(5-(3-(methylthio)propyl)-1,3,4-thiadiazol-2yl)benzamide derivatives **(32)** investigated for their antimicrobial activities. The potential antimicrobial activity of compounds towards five standard bacterial stains was investigated against *Staphylococcus aureus, Bacillus antracis*, *Bacilluscereus*, *Sarcinalutea* and *Escherichia coli*. The antimicrobial effectsof the substances were quantitatively tested in their respective broth media by using double dilution and the Minimal Inhibitory Concentration (MIC) values in µg/mL. Some of the investigated compounds exhibited excellent antimicrobial activities on comparision with their respective standard drugs[38].

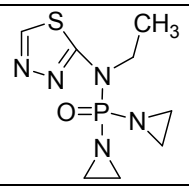
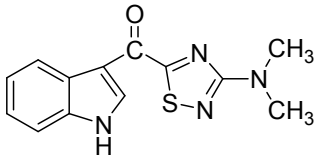


(32)

Some of the successful clinically used drugs having thiadiazole heterocyclic ring system have been compiled in **Table no. 1** which demonstrates its medicinal importance for the treatment of various deadly diseases.

Table 1: Clinically Used Drugs Containing Thiadiazole Nucleus[39-44]

S. No.	Drug	Chemical Structure	Pharmacological Activity
1.	Sulphamethizole®		Antibiotic
2.	Cefazoline®		Antibiotic
3.	Methazolamide®		Diuretic
4.	Acetazolamide®		Diuretic
5.	Butazolamide®		Diuretic

6.	Azetepa®		Antineoplastic
7.	Dendrodoine®		Antioxidant

CONCLUSION

On the basis of recent literature survey and the significant information about potent antimicrobial potential of novel thiadiazole derivatives which have been provided in this manuscript, it may be concluded that these derivatives have a great promise for the treatment of lethal microbial infections and also to deal with the problem of microbial resistance by having different mode of action. Therefore, this review article may give a new hope and significantly different stretegy to the medicinal chemists to attempt drug design and development of better and safer antimicrobial agents for future.

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