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VISTAS ON ANTIMICROBIAL POTENTIAL OF NOVEL OXADIAZOLE DERIVATIVES IN MODERN MEDICINAL CHEMISTRY

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ABSTRACT

1,3,4-Oxadiazole is a versatile heterocyclic nucleus containing two nitrogen and one oxygen atom which shows antimicrobial, anticancer, anti-inflammatory and antioxidant activities etc. In recent time, microbial resistance to large number of antibiotics is observed so search of newer potent antimicrobial agent with different mechanism of action is a great need. This review article has summarized vital information on antimicrobial activity of 1,3,4-oxadiazole heterocyclic nucleus to provide effective antimicrobial drugs by solving the problem of microbial resistance towards currently used antibiotics.

KEYWORDS: Oxadiazole, antibacterial, antifungal activity.

INTRODUCTION

Microbes are of two types prokaryotic and eukaryotic. Prokaryotic organisms are conventionally classified as lacking membrane- bound organelles and include eubacteria and archaebacteria. Eukaryotic microorganisms possess membrane-bound cell organelles and include fungi and protists [1]. Bacteria are grouped as 'Gram positive' and 'Gram negative' bacteria, based on the results of Gram staining method. Peptidoglycans are the main contents of the cell walls of Gram-positive bacteria (almost 95%) for example *Staphylococcus epidermidis, S. aureus, S. pyogenes, Clostridium tetani*while Gram-negative bacteria have an additional layer of phospholipids and lipopolysaccharides for example *Escherichia coli,*

Bordetella pertussis, Salmonella typhi, Vibrio cholera. Several species of bacteria are pathogenic and cause infectious diseases. Bacterial infections can be much more severe as bacteria can cause organ damage or other severe complications including cholera, syphilis, anthrax, leprosy, and bubonic plague [2,3].

Some commonly found species of fungi include yeasts, rusts, musts, mushrooms, puffballs, truffles, morels and molds. They are generally distinguished by the types of spores and structure of fruiting bodies that they produce for reproduction [4]. Fungi are harmless but some time they cause serious infection called fungal infection for exampleTinea, Candida, Athlete's foot Different types of antimicrobial agents are used for bacterial and fungal infection but many of them have become resistant. Antimicrobial resistance (AMR) is resistance of a microorganism to an antimicrobial medicine to which it was originally sensitive. Resistant microorganisms including bacteria, fungi, viruses and some parasites are able to withstand attack by antimicrobial medicines such as antibiotics, antifungals, antivirals and antimalarials so that standard treatments have become ineffective and infections persist increasing risk of spread to others. The evolution of resistant strains is a natural phenomenon that happens when microorganisms are exposed to antimicrobial drugs and resistant traits can be exchanged between certain types of bacteria. The misuse of antimicrobial medicines accelerates this natural phenomenon of development of microbial resistance against currently used antibiotics [5]. Some of the most common methods of resistance against antibiotics and resistant microbial species have been summarized in the **Table no. 1**.

Table 1: Methods of Resistance against Antibiotics and Resistant Microbial Species [6-12].

S. No.	Antibiotic	Resistant Species	Method of Resistance
1.	Chloramphenicol	*Pseudomonas aeruginosa*	Reduced uptake into cell
2.	Tetracycline	*E.coli, Helicobactor pylori*	Active efflux from the cell
3.	ß-lactams, Erythromycin, Lincomycin	*Legionella*	Reduces binding of antibiotic to cell target
4.	Aminoglycosides, Chloramphenicol	*E.coli, Pseudomonas aeruginosa*	Modification to inactivate antibiotic molecule
5.	Sulfonamides, Trimethoprim	*E. coli*	Metabolic bypass of antibiotic target

Bacterial infections can be much more severe as bacteria can cause organ damage or other severe complications. Common bacterial infections are Otitis Media,Conjunctivitis/Pink Eye,Strep throat or pharyngitis, Cellulitis, Septic Arthritis, Pneumonia, Acute Bronchitis [13]. There were 95 patients with heterotaxy syndrome (88 with right atrial isomerism and 7 with left atrial isomerism) and 142 patients with complex CHD. With 1026 person-years follow-up, the 5-year survival was 52% and 65.7% in heterotaxy and complex CHD groups, respectively. Community-acquired severe bacterial infection occurred only in heterotaxy syndrome with 2- and 5 years cumulative severe bacterial infection rate of 9.6% and 14.5%, respectively. The overall mortality rate of those with community-acquired severe bacterial infection was 31%. *Pneumococcus* and *Citrobacter freundii* were the most common pathogens [14]. 1,3,4-oxadiazole **(1)** is a novel heterocyclic nucleus which has attracted the attention of medicinal chemist to search for newer therapeutic molecules as it has a wide range of pharmacological activities like antibacterial, antifungal, anti-tubercular, immunosuppressant, cytotoxic, antioxidant and antiobesity activities etc.[15,16].

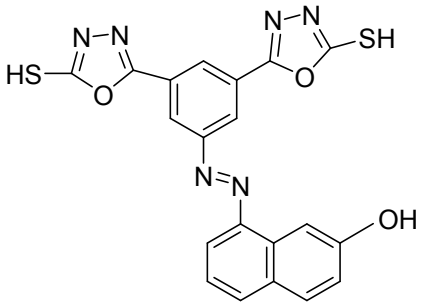
1,3,4-Oxadiazole

(1)

ANTIMICROBIAL ACTIVITY

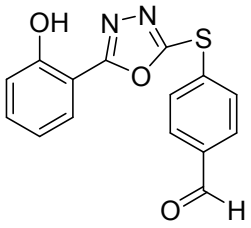
1,3,4-Oxadiazole is a well known heterocyclic nucleus because of its broad spectrum of pharmacological activities especially potent antimicrobial activities. The most recent literature survey on antimicrobial potential of novel oxadiazole derivatives has been presented in this section as given below:

Shridhar *et al* synthesized 1,3,4-oxadiazole incorporated azo dye derivatives **(2)** and evaluated their antimicrobial activity. The antimicrobial activity of newly synthesized compounds was determined by well plate method in nutrient agar (antibacterial activity) and Sabouraud dextrose agar (antifungal activity). *E. coli, Staphylococcus aureus, Bacillus subtilis, Salmonella typhi*, were used to investigate the antibacterial activities and *Pseudomonas Aeruginosa, Candida albicans, Candida parapsilosis,* were used to investigate the antifungal activities. One compound showed maximum inhibitory activity against *Pseudomonas aureginosa* and *Candida parapsilosis* at MIC 2.5 mg/ml. Antibacterial drug Ampicillin and antifungal drug Fluconazole were used as standard drug [17].



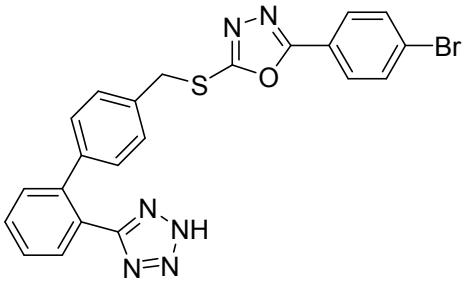
(2)

A novel series of 4-((5-2-hydroxyphenyl)-1,3,4-oxadiazol-2-yl)sufanyl)benzaldehyde derivatives **(3)** were synthesized and screened for antimicrobial activity byfilter paper disc method by **Parikh *et al***. Stains used were *Staphylococcus aureus*, *Pseudomonas aeruginosa, Bacillus subtillis, Escherichia coli* for the antibacterial activity and for the antifungal activity fungi *Candida albicans.* Ciprofloxacin and Ampicillin as standard antibacterial drug and Ketoconazole and Fluconazole as standard antifungal drug were used. From the result it was found that some compounds showed excellent antibacterial activity against *P. aeruginosa* whereas other compounds displayed better antibacterial activity against *B. subtilis* [18].



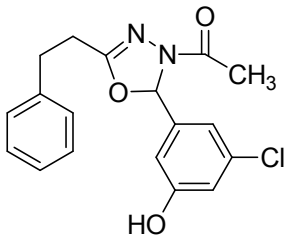
(3)

The series of several new 5-[4'-(5-phenyl-1,3,4-oxadiazole-2-yl-sulfonylmethyl)-biphenyl-2-yl]- tetrazole derivatives **(4)** were synthesized and these compounds were evaluated for their antimicrobial activity against *B. subtilis*and *E. coli* at the concentration of 100µg/ml in nutrient agar media by **Jun-Shu *et al*** . These compounds demonstrated significant antimicrobial activities as compared with standard drug [19].



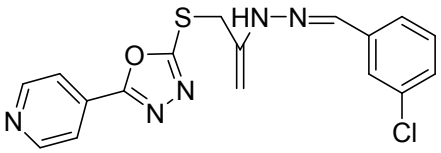
(4)

Fuloria *et al*. synthesized a new series 1-(2-aryl-5-phenethyl-1,3,4-oxadiazole-3(2*H*)-yl)-ethanones **(5)** and investigated for their antimicrobial activities. These newly synthesized compounds showed good antibacterial activity against the stains of micro-organisms like *S. aureus, P. aeruginosa* as compared with standard drug [20].



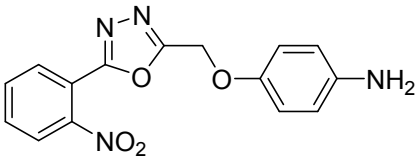
(5)

A novel series of 2-(3-chlorobenzylidene)-1-(1-(5-(pyridine-4-yl)-1,3,4-oxadiazol-2-ylthio)prop-2-en-2 yl)hydrazine derivatives **(6)** were synthesized and evaluated for their antimicrobial activity by **Somani *et al***. The *in vitro* antibacterial activity against *S. aureus* and *E. coli*.was determined by cup-plate method by using Ampicillin as standard drug. The *in vitro* antifungal activity of titled compounds was carried out against *C. albicans* and *A. niger* by using Fluconazole as standard drug. The tests were repeated thrice to confirm the findings that the some compounds exhibited good antibacterial activities against *S. aureus* while some compounds were effective against *E. coli*. One compound was found to be the most potent against *C. albicans* and two compounds were more active as antifungal agents against *A. niger* on comparision with standard drug [21].



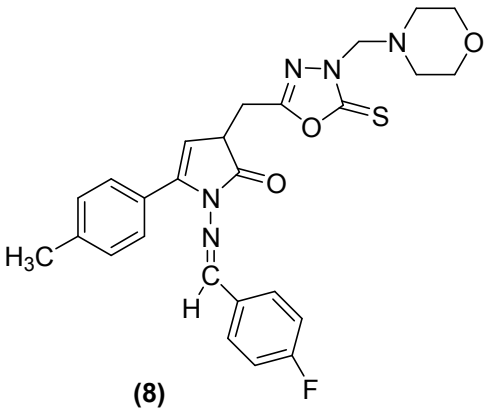
(6)

Patel *et al* synthesized 4-thiazolidinone incorporated 1,3,4-oxadiazoles **(7)** and screened them for their antibacterial and antifungal *in vitro* activity against *E. coli*, *P.aeruginosa*, *S. aureus*, *S. pyogenes*, *C.albicans, A. niger*, *A. clavatus* respectively by using broth microdilution method . Minimum inhibitory concentration was determined and compared with standard drugs Ampicillin and Griseofulvin. Some compounds showed good antimicrobial activity and other compounds depicted moderate activity [22].



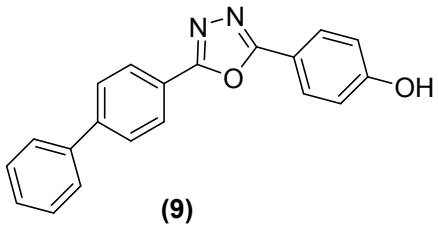
(7)

2-(5-mercapto)-1,3,4-oxadiazol-2-ylmethyl-1,2,4-triazol-3-one derivatives **(8)** were synthesized by **Demirbas *et al***. The antimicrobial effects of the substances were tested quantitatively in their respective broth media by using double dilution and the minimal inhibition concentration (MIC) values were determined. Ampicillin and fluconazolewere used as standard antibacterial and antifungal drugs, respectively. Few compounds displayed good to moderate antimicrobial activity [23].



(8)

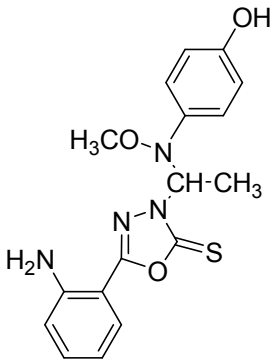
Kumar *et al* synthesized some novel 5-biphenyl,2-(-4-hydroxy)phenyl,1,3,4-oxadiazoles **(9)** derived synthesized and antimicrobial activity evaluated **.** Two Gram-positive bacteria (*Staphylococcus aurous*and *Bacillus subtitles*), two Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeroginosa*) were used. The zone of inhibition values were determined by cup plate agar diffusion method. Zone of inhibition values of the synthesized compounds and the standard drugs. Ofloxacin was compared at concentration of 100µg/ml. One compound showed good activity and other moderate activity [24].



(9)

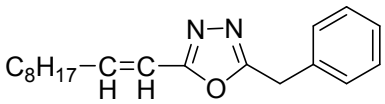
Kanthiah *et al* synthesized (2-aminophenyl)-1,3,4-oxadiazole-2(3*H*)-thione derivatives **(10)** and screened for their antimicrobial activities. Gram positive microorganisms such as

Staphylococcus aureus, *Streptococcus pyogenes*, Gram negative microorganisms such as *Escherchia coli*, *Klebsiellaaerogenes*and fungus *Candida albicans* were used for antibacterial studies. The disc diffusion method was used to evaluate antimicrobial activities. Compounds at a concentration of 100µg/ml showed good antibacterial and antifungal activitiesagainst all the tested microorganisms. Amikacin and Ketoconazole were used as standard drugs for antibacterial and antifungal activities respectively [25].



(10)

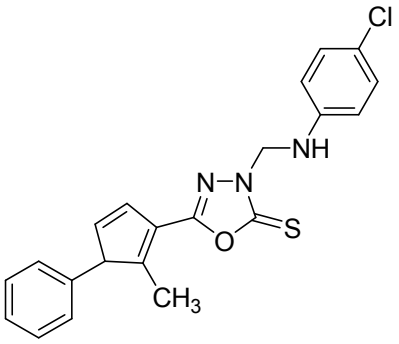
Farshori *et al* synthesized 5-alkenyl/hydroxyalkenyl-2-phenylamine-1,3,4-Oxadiazoles**(11)** and tested for their *in vitro* antimicrobial activities by disc diffusion method. Among the synthesized compounds, some compounds were found to be active against fungal stain i.e *Penicillium marneffei* and was compared with Griseofulvin as standard drug whereas other compounds were found to be active against bacterial stains like *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus pyogenes*, *Klebsiella pneumoniae* and were compared with Chloramphenicol as standard drug [26].



(11)

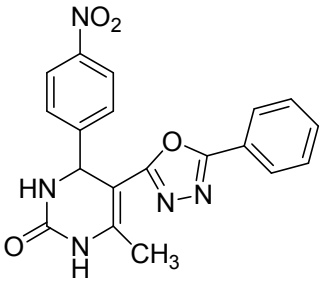
Reddy *et al* synthesized 4-fluoroanilinomethyl, 4-chloroanilinomethyl, 2-trifluoromethylanilinomethyl-oxadiazole derivatives **(12)**. The synthesized compounds were evaluated for their antibacterial activity against three representative Gram positive bacteria *Bacillus subtilis, Bacillus sphaericus*, *Staphylococcus aureus* and three Gram negative bacteria *Pseudomonas aeruginosa*, *Klobsinella aerogenes* and *Chromobacterium violaceum*. In addition, these compounds were also screened for their antifungal activity against four fungal microorganisms *Candida albicans*, *Aspergillus fumigatus, Trichophyton*

rubrum and *Trichophyton mentagrophytes*. Most of the compounds showed excellent antimicrobial activities when compared with their respective standard drugs [27].



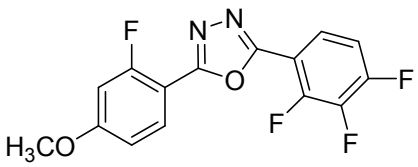
(12)

A series of 3,4-dihydro-6-methy-4-(4-nitrophenyl)-5-(5-pheny-1,3,4-oxadiazol-2-yl)pyrimidin-2-(1*H*)-one derivatives **(13)** were synthesized and tested for their antimicrobial activity by cup and plate method by **Mishra *et al***. Some compounds showed promising antibacterial activity against gram positive bacteria *Streptococcus pneumonia* and other compounds displayed promising antibacterial activity against gram positive bacteria *Escherichia coli* as compared to standard drugs Ofloxacin and Levofloxacin [28].



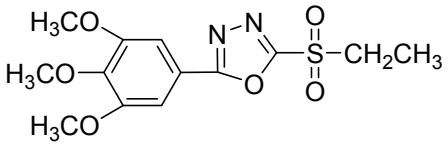
(13)

Some novel 1,3,4-oxadiazole derivatives bearing 2-flouro-4- methoxy phenyl moiety **(14)** were synthesized and screened for antimicrobial activity through serial dilution method by **Chandrakantha *et al.*** Amongst the various compounds synthesized, two compounds showed excellent antibacterial activity against *Escherichia coli* and *Pseudomonas aeruginosa* and other compounds displayed excellent antifungal activity against *Candida albicans.* Compounds tested for antibacterial activity were compared with standard drug Furacin and for antifungal activity standard drug was Flucanazole [29].



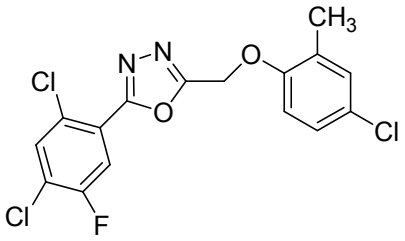
(14)

Chen *et al.* synthesized 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-oxadiazole derivatives **(15)** and investigated for their antifungal activity against *Gibberellazeae,Botrytis cinerea, Sclerotiniasclerotiorum*. Amongst the tested compounds, two compounds depicted promising antifungal activities when compared with standard drug Hymexazol [30].



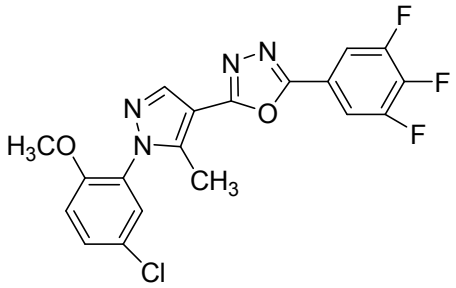
(15)

Karthikeyan *et al.* synthesized 2,4-dichloro-5-flourophenyl containing oxadiazoles **(16)** and then final compounds were demonstrated for their antimicrobial activity. Few compounds displayed good inhibition against *Staphylococcus aureus*, *Escherichia coli* when compared with standard drug Ciprofloxacian. Some other compounds also showed good inhibition aganist all the fungal stains *Candida albicans*, *Aspergillus fumigatus* and *Penicillium marneffei* when compared with standard drug Greseofluvin [31].



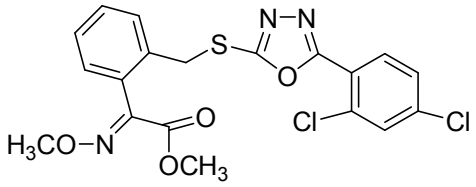
(16)

A novel series of 2-[1-(5-chloro-2-methoxyphenyl)-5-methyl-1*H*-pyrazol-4-yl]-5-(substitutedphenyl)-1,3,4-oxadiazole derivatives **(17)** was synthesized and invesigated for their antibaterial activity by **Rai *et al***. From the tested compounds, few compounds showed significant activity against *Bacillus subtilis* and *Escherichia coli*, *Staphylococcus aureus* and *Klebsiella pneumonia*. These compounds were compared with Ampicillin as standard drug [32].



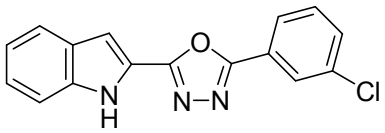
(17)

(E)-α-(metheoxyimino)-benzeneacetate derivatives containing 1,3,4-Oxadiazole ring **(18)** were synthesized and investigated for their fungicidal activities by **Li *et al***. All of the compounds exhibited significant fungicidal activities against *Rhizoctonia solani*, *Botrytis cinereapers*, *Gibbereapers zeae*, *Physalospora piricola* and *Bipolaris mayclis* when compared with standard drug [33].



(18)

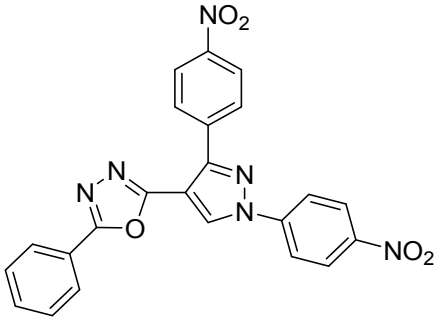
Bhardwaj *et al.* synthesized a novel series of 2-(5-(3-chlorophenyl)-1,3,4-oxadiazol-2-yl)-1*H*-indole derivatives **(19)** and demonstrated for their antimicrobial activity on different stains. Out of total of compounds synthesized, three compounds were found to be active against bacterial stains like *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa* whereas none of the compound was found to be effective against fungal stains. Standard Drugs used for comparision of antimicrobial activities were Norfloxacin and Fluconazole [34].



(19)

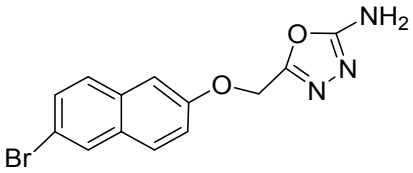
A series of novel unsymmetrical2,[1,3-bis(4-nitrophenyl)-1*H*-pyrazol-4-yl)-5-phenyl-1,3,4-oxadiazoles **(20)** were synthesized and tested for their antibacterial and antifungal activities by **Prakash *et al***. Amongst the tested compounds, two compounds depicted most potent antibacterial activity against *Staphylococcus aureus* and was compared with ciprofloxacin as

standard drug. Two compounds displayed maximum inhibition against both of the fungi *Aspergillus niger* and *Aspergillus flavus* when compared with Fluconazole as standard drug [35].



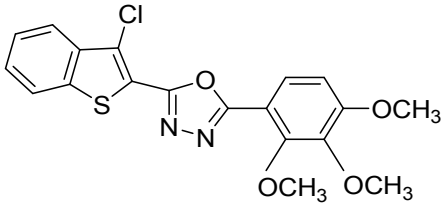
(20)

A series of new 5-amino,2-(-5-bromo)naphthalene)carboxalate,1,3,4-oxadiazole derivatives having 6-bromonaphthalene moiety **(21)** were synthesized by **Mayekar *et al***. The antimicrobial activities of title compounds were examined against two gram positive bacteria (*S. aureus*, *S. pyogenes*), two gram negative bacteria (*E. coli*, *P. aeruginosa*) and three fungi (*C. albicans*, *A. niger*, *A. clavatus*) by using the broth microdilution method. Some of the tested compounds displayed significant antimicrobial activities when compared with their respective standard drugs [36].



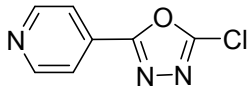
(21)

Ansari *et al* synthesized some new 3-acetyl-5-(3-chloro-1- benzo[*b*]thiophen-2-yl)-2-substituted phenyl-2,3- dihydro-1,3,4-oxadiazoles **(22)** and evaluated for their antimicrobial activities. All the compounds were screened for their antibacterial activities against *Staphylococcus aureus, Bacillus subtilis, Escherichia coli* and *Pseudomonas aeruginosa* and for antifungal activity against *Candida albicans* and *Asperigillus niger.* Some compounds exhibited significant antibacterial and moderate antifungal activities on comparision with their respective standard drugs [37].



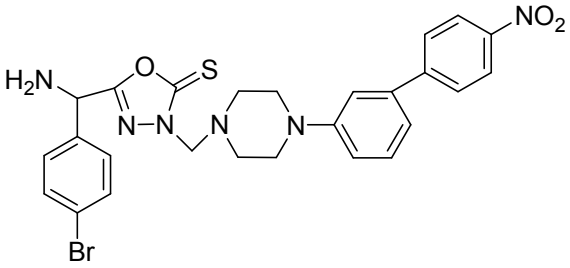
(22)

Novel derivatives of 4-(5-chloro-1,3,4-oxadiazole-2-yl)pyridine **(23)** synthesized and evaluated for antimicrobial activities by **Dewangan *et al***. The antimicrobial activities of title compounds were examined against two gram positive bacteria (*S. aureus*, *S. pyogenes*), two gram negative bacteria (*E. coli*, *P. aeruginosa*) and three fungi (*C. albicans*, *A. niger*, *A. clavatus*) using the broth microdilution method. Some derivatives exhibited excellent antimicrobial activities on comparision with their respective standard drugs [38].



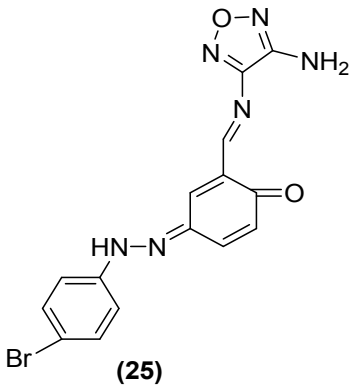
(23)

A novel series of 5-(amino(4-bromophenyl)methyl)-3-((4-phenylpiperazin-1-yl)methyl)-1,3,4-oxadiazole-2(3*H*) thiones **(24)** were synthesized by **Prakash *et al***. The newly synthesized compounds were invesigated for their antimicrobial activities. Microbial stains used for antibacterial activity were *Staphylococcus aureus, Bacillus subtilis, Escherichiacoli* and *Pseudomonas aeruginosa*and for antifungal activity *Candida albicans* and *Asperigillus niger*. Few compounds showed good antimicrobial activity on comparision with standard drug Norfloxin [39].



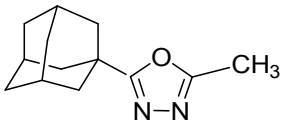
(24)

Kakanejadifard *et al* synthesized some novel 2-((4-amino-1,2,5-oxadiazol-3-ylimino)methyl)-4-(phenyldiazenyl) phenol derivatives **(25)** and evaluated their antimicrobial activities. The synthesized compounds were screened for their *in vitro* antimicrobial activity against both Gram-positive (*Staphylococcus aureus* and *Bacillus cereuss*) and Gram negative (*Escherichia coli* and *Klebsiella pneumonia*) bacteria by using disc diffusion method. The antibacterial activity was reported as the minimum inhibitory concentration (MIC) in mg/ml. One compound showed the most potent antimicrobial activity with MIC value of 57 mg/ml against *S. aureus* and *B. cereuss* as compared with standard drug [40].



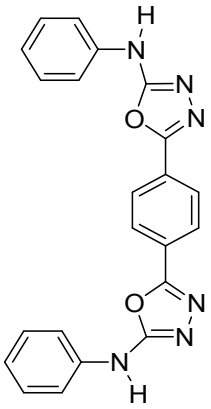
(25)

A novel series of 2-(1-adamantylamino)-5-substituted-1,3,4-oxadiazole derivatives **(26)** were synthesized and screened their antimicrobial activity by **Kadi *et al***.. The primary screening was carried out using the agar disc diffusion method using Muller Hinton agar medium. Antimicrobial activity of compounds was compared with antibacterial drug Ampicillin and the antifungal drug Clotrimazole against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeuroginosa* and *Candida albicans.* Some compounds depicted good to moderate antimicrobial activity relative to standard drug [41].



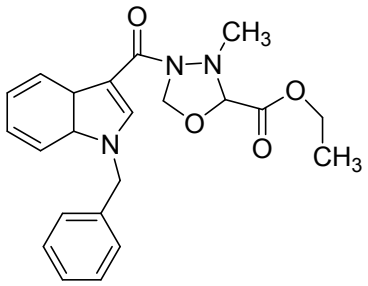
(26)

Shaker *et al* synthesizedN-phenyl-5-(-4-(5-phenylamino-1,3,4-oxadiazol-2-yl)phenyl)-1,3,4-oxadiazol-2-amine**(27)** and examined their antimicrobial activity. Gram-negative bacteria (*Seratia*), gram-positive bacteria (*Bacillus cereus*), as well as two different fungi, *Fusarium monoiliforum* and *Aspergillus flavus* were used for this purpose. Some compounds showed good antimicrobial activity whereas other compounds displayed moderate antimicrobial activity as compared with standard drug [42].



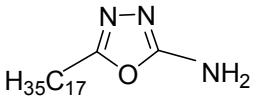
(27)

Rahman *et al.* synthesized compounds some new(3a,7a-dihydro-1*H*-indol-3-yl)(4-methyl-1,3,4-oxadiazolidin-3-yl)methanone derivatives **(28)** and screened *in vitro* for their antimicrobial activities against four stains of bacteria (*Staphylococcus aureus, Serratia marcescens, Streptococcus, Pseudomonas aeruginosa*) and two species of fungi (*Aspergillu sparasitcus, Penicillium oxalicum*) using the filter paper disc method. Most of the compounds exhibited considerable activities against two bacterial species, *Serratia marcescens* and *Streptococcus*. Some compounds exhibited a moderate activity against *Staphylococcus aureus*. All the screened compounds were inactive against *Pseudomonas aeruginosa.* Some compounds showed moderate antibacterial activity against *Penicillium oxalicum* [43].



(28)

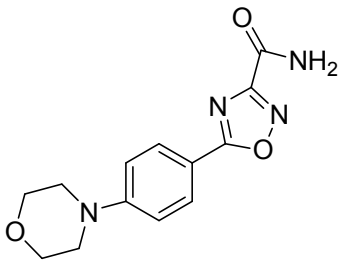
El-Sayed *et al* synthesized a novel series of 2,5-disubsituted, 1,3,4- oxadiazole derivatives **(29)**. Some of the synthesized compounds were screened *in vitro* against some bacteria such as *Escherichia coli, Staphylococcus aureus*and some fungi such as *Aspergillus flavus* and *Candida albicans*. Gentamycin was taken as standard drug for antibacterial activity. Some compounds had high antibacterial and moderate antifungal activities against tested microorganisms. The results revealed that some compounds were found to have an excellent antibacterial activity against *E. coli* and *S. aureus*, while other compounds exhibited moderate antibacterial activity and remaining compounds showed mild antibacterial activity. Furthermore, some compounds were found to be excellent antifungals as compared with standard drug [44].



(29)

Piccionello *et al* synthesized a novel series of 2-(4-morpholinophenyl)1,2,4-oxadiazole-5-carboxamide derivatives **(30)** and evaluated for antibacterial activity. Stains used were Gram-positive and Gram-negative bacterial pathogens including *Streptococcus pyogenes,*

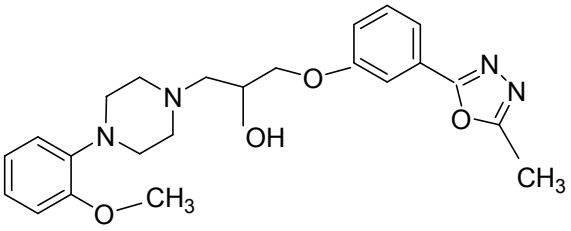
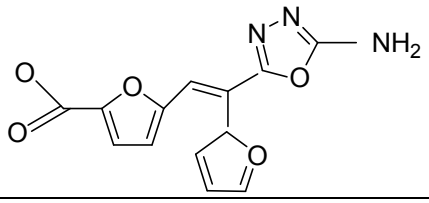
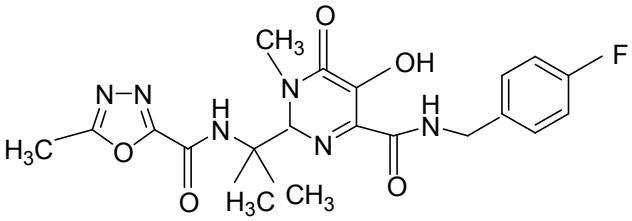
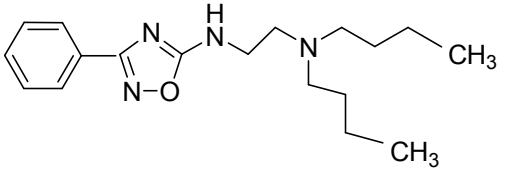
Streptococcus pneumoniae, Staphylococcus aureus, Escherichia coli, and *Serratia marcescens*. Antibacterial activity was determined by the microbroth dilution method using the MIC (Minimal Inhibition Concentrations) values which were expressed in mg/ml. Some compounds showed good to moderate antibacterial activity on comparision with standard drug [45].

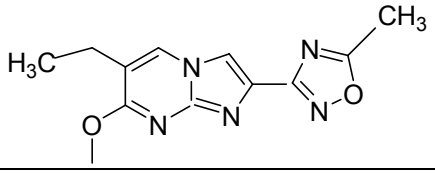
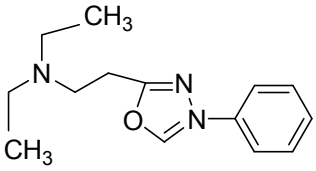
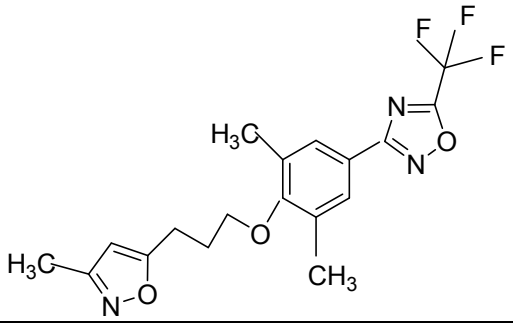


(30)

Some of the successfully used clinical drugs containing oxadiazole nucleus have been compiled in the **Table no. 2**.

Table no. 2: Clinically Used Drugs Containing Oxadiazole Nucleus [46-51].

S. No.	Drug	Chemical Sturucture	Pharmacological Activity
1.	Nesapidil®		Antimicrobial
2.	Furamizol®		Antimicrobial
3.	Raltegravir®		Anti-HIV
4.	Butalamine®		Vasodialator

5.	Fasiplon®		Anxiolytic
6.	Oxolamine®		Cough supressant
7.	Pleconaril®		Antiviral

CONCLUSION

Various oxadiazole derivatives have been placed as succefully used antimicrobial drugs in clinical practice for the treatment of microbial infections. This review article has highlighted the antimicrobial potential of novel 1,3,4-oxadiazole derivatives as per the latest literature survey. Scientific information provided in this manuscript may be exploited in modern medicinal chemistry for the drug design and discovery of novel antimicrobial agents of clinical importance having different mode of action to deal with the challenge of microbial resistance which is the ultimate objective of medicinal chemists.

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