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Journal of Advanced Scientific Research

Available online through https://sciensage.info

ISSN: 0976-9595
Review Article
DOI: 10.55218/JASR.202213101

ANTIMICROBIAL ACTIVITY AND SAR OF 2,5-DISUBSTITUTED 1,3,4-OXADIAZOLE DERIVATIVES

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ABSTRACT
1,3,4-oxadiazole is a five membered heterocyclic aromatic moiety, present in a number of antimicrobial agents. 2,5-disubstituted 1,3,4-oxadiazole derivatives have shown broad spectrum of antibacterial and antifungal activities. Many scientific groups have synthesized and screened their antimicrobial potential. Reported activity data showed that some 1,3,4-oxadiazole derivatives exhibited better activity than already known antibiotics. Hence, they can be used as lead for development of promising antimicrobial agents. In present review, antimicrobial activities and SAR of 2,5-disubstituted 1,3,4-oxadiazole derivatives reported by different research groups in last ten years have been summarized.

Keywords: 2,5-Disubstituted 1,3,4-oxadiazole derivatives, Antibacterial activity, Antifungal activity, SAR.

1. INTRODUCTION

Oxadiazoles are heterocyclic aromatic moiety with two carbon, two nitrogen, one oxygen and two double bonds (Fig. 1) [1]. Tiemann and Kruger discovered oxadiazole moiety in 1884 and named furo[ab]diazole [2, 3]. The inductive action of the extra heteroatom makes oxadiazole an extremely weak base [4]. Electrophilic substitution occurs on the nitrogen molecule rather than the carbon molecule due to the electron richness of nitrogen atoms. The oxadiazole ring is resistant to nucleophilic attack, as it lowers its aromaticity and rendering certain of their isomers electrically equivalent to conjugated diene systems [5]. However, nucleophilic substitution occurs in halogen-substituted oxadiazole on replacement of halogen by nucleophiles [4].

The position of the nitrogen and oxygen atoms in the ring structure determines the type of oxadiazole. There are four types of oxadiazoles; 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole and 1,3,4-oxadiazole (Fig. 2). Among these, 1,3,4-oxadiazole derivatives showed most promising antimicrobial activity [6]. 1,3,4-oxadiazole is a thermally stable molecule and can be used to prepare wide range of derivatives [7, 8]. Two distinct laboratories independently reported the first monosubstituted 1,3,4-oxadiazoles in 1955 [9]. 1,3,4 oxadiazoles are liquid at room temperature and its boiling point is 150°C [10].

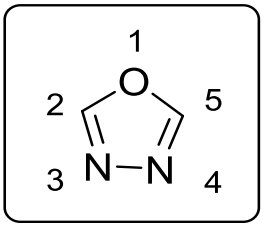


Fig. 1: Chemical structure of 1,3,4-oxadiazole

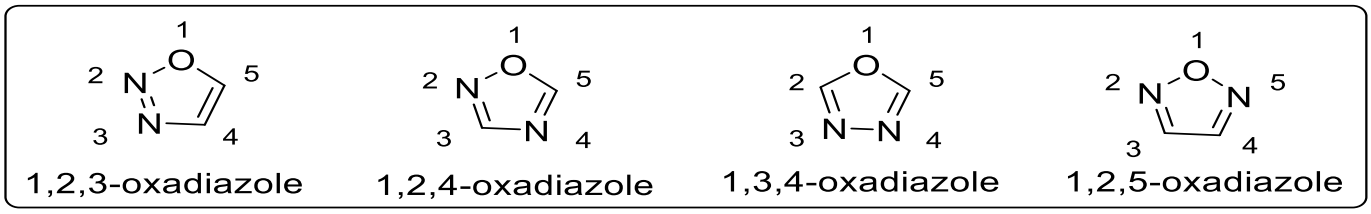


Fig. 2: Chemical structures of different types of oxadiazoles

Molecules with 1,3,4-oxadiazole moieties were used in a variety of applications, including luminescent materials [11], corrosion inhibitors, polymers, herbicides, and electron-transport materials [12, 13].

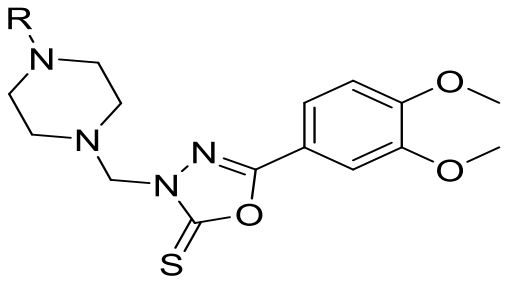
1,3,4-oxadiazole containing molecules showed wide range of biological activities *viz.* anti-inflammatory [14, 15], antioxidant [14, 16-17], anticonvulsant [18, 19], antibacterial [20, 21], antiviral [22], anticancer [23-26], antifungal [21, 27], anti-HIV [28, 29], antituberculosis [30, 31], antimalarial [32, 33], insecticidal [34, 35], herbicidal [36, 37], analgesic [38], ulcerogenic liability [39], muscle relaxant [40], antidepressant agents [41] and sedative-hypnotic [42]. However, more emphasis is reported on the molecules relevant to medicinal chemistry, specifically in the discovery of new chemical entities with antiparasitic [12] and antimicrobial properties [43].

1,3,4-oxadiazole ring has not any freely rotatable bonds [44]. Even though, three hydrogen bond acceptor atoms in 1,3,4-oxadiazole can be involved in interaction with target site [45].

In view of aforementioned facts, in the present study, we have compiled antibacterial and antifungal activities, reported by different research groups in last ten years and summarized the effect of different substituents on 2,5-disubstituted-1,3,4-oxadiazole derivatives.

2. ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES OF 2,5-DISUBSTITUTED-1,3,4-OXADIAZOLE DERIVATIVES

Al-wahaibi et al. (2021) [46] screened 1,3,4-oxadiazole *N*-mannich bases and tested their antibacterial and antifungal activities against various strains. Antibacterial data revealed that compounds **1** and **2** (ZOI range = 18-30 mm) found to be more active among synthesized compounds and displayed better activity as compared to standard drugs Gentamycin sulfate and Ampicillin trihydrate (Table 1). Compound **1** exhibited excellent activity against *Bacillus subtilis* (ZOI = 30 mm), whereas compound **2** showed better activity against *Staphylococcus aureus* (ZOI = 28 mm), *Pseudomonas aeruginosa* (ZOI = 20 mm), *Escherichia coli* (ZOI = 22 mm) and *Micrococcus luteus* (ZOI = 26 mm). SAR analysis revealed that replacement of phenyl ring with benzyl moiety enhanced the activity of compounds (**1-2**). However, in case of antifungal studies, both compounds **1** and **2** found to be inactive against *Candida albicans* (**Table 1**).



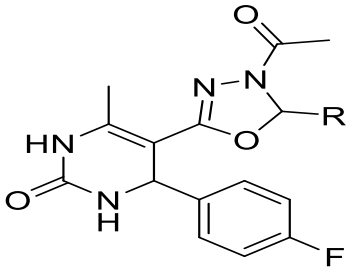
1-2

Table 1: Zone of inhibition of 1,3,4-oxadiazole linked *N*- Mannich bases (mm)

Comp.	R	*S. aureus*	*B. subtilis*	*P. aeruginosa*	*E. coli*	*M. luteus*	*C. albicans*
1	$C_6H_5CH_2$	26	30	18	19	22	-
2	2-$CF_3C_6H_4CH_2$	28	29	20	22	26	-
Gentamycin sulfate	-	27	26	21	22	20	NT
Ampicillin trihydrate	-	22	23	16	16	20	NT
Clotrimazole	-	NT	NT	NT	NT	NT	21

NT: not tested

Desai et al. (2021) [47] synthesized 1,3,4-oxadiazole clubbed 3,4-dihydropyrimidine derivatives and evaluated their activity against various bacterial and fungal strains. Antibacterial data showed compound **3** with *ortho*-hydroxy phenyl exhibited better activity against *E. coli* (MIC = 12.5 µg/mL) and *S. pyogenes* (MIC = 50 µg/mL) as compared to standard drug Ciprofloxacin (Table 2). While in case of antifungal activity compound **4** with *para*-nitro phenyl group exhibited excellent activity against *A. niger* (MIC = 50 µg/mL), *A. clavatus* (MIC = 100 µg/mL) and *C. albicans* (MIC = 100 µg/mL) and showed better activity as compared to standard drug Griseofulvin (Table 2).

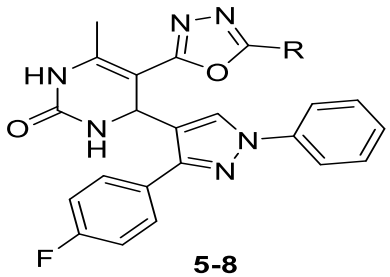


3-4

Table 2: Antimicrobial data of 1,3,4-oxadiazole clubbed 3,4-dihydropyrimidines (µg/mL)

Comp.	R	*S. aureus*	*E. coli*	*P. aeruginosa*	*S. pyogenes*	*A. niger*	*A. clavatus*	*C. albicans*
3	2-OHC_6H_4	100	12.5	500	50	1000	1000	1000
4	4-NO_2 C_6H_4	500	100	200	100	50	100	100
Ciprofloxacin	-	50	25	25	50	-	-	-
Griseofulvin	-	-	-	-	-	100	100	500

Patel *et al.* (2021) [48] investigated a series of 2,5-disubstituted 1,3,4-oxadiazole carrying dihydro-pyrimidines for *in vitro* antimicrobial activity. The antibacterial data showed that compound **6** exhibited maximum potency against *E. coli* and *P. aureginosa* (MIC = 12.5 and 25 µg/mL), whereas compound **8** showed better activity against *S. aureus* (MIC = 25 µg/mL) and compound **7** towards *Streptococcus pyogene* (MIC = 12.5 µg/mL) (**Table 3**). In case of antifungal activity compound **5** exhibited excellent activity against *Aspergillus niger* and *Aspergillus clavatus* (MIC = 100 and 12.5 µg/mL), compound **7** displayed better activity against *C. albicans* (MIC = 50 µg/mL) and compound **8** displayed promising results against *C. albicans* and *A. niger* (MIC = 100 and 12.5 µg/mL) (**Table 3**).



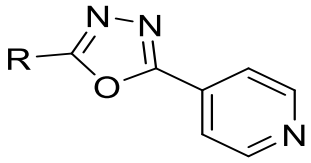
5-8

SAR investigations concluded that electron donating group on phenyl nucleus of 1,3,4-oxadiazole enhances the potency of compounds **(5-8)**, whereas electron withdrawing substituents decreases the potency.

Compounds **(5-8)** showed reduced activity as compared to standard drugs Chloramphenicol, Ciprofloxacin, Griseofulvin and Nystatin (**Table 3**).

Katiyar et al. (2020) [49] screened 2,5-disubstituted 1,3,4-oxadiazole derivatives linked with pyridine ring and evaluated their antimicrobial activity against various pathogenic bacteria and fungi. The antibacterial data revealed that compound **9** with two NO_2 groups at 3rd and 5th position of phenyl ring exhibited good activity against various bacterial strains (MIC range = 12.5-100 µg/mL) (**Table 4**). In case of antifungal activity, compound **10** with -OCH_3 group at 4th position of phenyl ring showed good activity against *C. albicans* and *Aspergillus flavus* at different concentrations (**Table 5**).

SAR data showed that attachment of pyridine moiety to 1,3,4-oxadiazole improved the antimicrobial activity of compound. Furthermore, introduction of electron-withdrawing group at phenyl ring increases the antibacterial activity, whereas presence of electron donating group enhances the antifungal activity. Both compounds **9** and **10** showed comparable activity to standard antifungal drug Econazole (**Table 5**).



9-10

Table 3: Antimicrobial data of Dihydropyrimidines analogues

Comp.	R	Minimum inhibitory concentration (MIC) in µg/mL						
		E. coli	*P. aureginosa*	*S. aureus*	*S. pyogene*	*C. albicans*	*A. niger*	*A. clavatus*
5	-2-OH-C_6H_4	100	1000	1000	500	NA	100	12.5
6	-4-OH- C_6H_4	12.5	25	1000	100	1000	1000	100
7	-4-OCH_3- C_6H_4	100	250	500	12.5	50	1000	1000
8	-4-CH_3- C_6H_4	500	500	25	1000	100	12.5	NA.
Griseofulvin	-	-	-	-	-	500	100	100
Nystatin	-	-	-	-	-	100	100	100
Ciprofloxacin	-	25	25	50	50	-	-	-
Chloramphenicol	-	50	50	50	50	-	-	-

NA. = No activity

Table 4: Antibacterial data of 2,5-disubstituted-1,3,4-oxadiazoles linked with pyridine

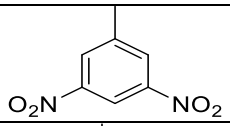
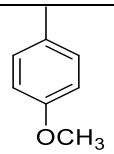
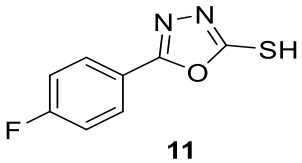
		MIC in (µg/mL)			
Comp.	**R**	***S. aureus***	***B. subtilis***	***E. coli***	***P. aeureginosa***
9		25	50	12.5	100
10		100	100	25	400
Cefixime		25	50	12.5	100

Table 5: Antifungal data of pyridine clubbed 2,5-disubstituted-1,3,4-oxadiazoles

	Zone of inhibition in mm									
Comp.	***C. albicans***					***A. flavus***				
	50	**100**	**250**	**500**	**1000**	**50**	**100**	**250**	**500**	**1000**
9	12.6	14.4	18.0	20.9	22.3	10.0	15.1	19.0	20.2	24.6
10	10.6	15.2	17.9	21.7	24.6	14.0	17.4	21.2	22.0	26.5
Econazole	14.0	17.9	18.0	20.9	25.5	15.0	18.4	21.5	25.4	27.2

Yarmohammadi et al. (2020) [50] investigated 2,5-substituted 1,3,4-oxadiazole-2-thiols and evaluated their antimicrobial activity against various bacterial and fungal pathogens. Among all synthesized derivatives, compound **11** with 4-fluorophenyl moiety displayed best antibacterial activity against *P. aeruginosa, E. coli* and *Streptococcus pneumoniae* (MIC range = 2-8 µg/mL) but weaker towards *Acinetobacter baumannii, Streptococcus epidermidis* and *Bacillus cereus* (MIC range= 256-512 µg/mL). In case of antifungal activity, compound **11** also showed good activity against *C. albicans, A. fumigatus* and *F. oxysporum* (MIC range = 8-128 µg/mL) (**Table 6**).



11

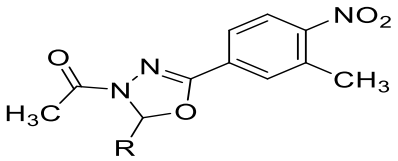
Active compound **11** showed comparable activity as compared to standard drugs Ampicillin and Terbinafine (**Table 6**).

Paruch et al. (2020) synthesized 2,3,5-trisubstituted-1,3,4-oxadiazolines and tested their antimicrobial activity against various bacterial and fungal strains. Compounds (**12-13**) with 1-(*p*-tolyl)-1H-imidazole and 2-(*p*-tolyl)pyridine moieties at 2nd position and 3-methyl-4-nitrophenyl at 5th position of 1,3,4-oxadiazole showed most potent activity among the synthesized compounds (**Table 7**). Based on antimicrobial data it can be concluded that presence of two heterocyclic rings in a compound showed better activity than presence of one heterocyclic ring. Substitution at 2nd and 5th position of 1,3,4-oxadiazole plays an important role in affecting the antimicrobial activity of 1,3,4-oxadiazole derivatives. In general, compounds (**12-13**) showed less activity as compared to standard drugs Ciprofloxacin, Vancomycin, Nitrofurantoin, Cefuroxime and Nystatin (**Table 7**) [51].

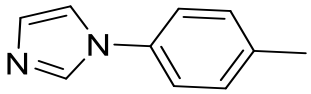
Table 6: Antimicrobial activity data of 2,5-substituted 1,3,4-oxadiazole-2-thiols

	MIC in (µg/mL)								
Comp.	***P.a.***	***E.c.***	***A.b.***	***S.p.***	***S.e.***	***B.c.***	***C.a.***	***A.f.***	***F.o.***
11	8	2	256	2	512	512	128	8	128
Ampicillin	1024	32	64	8	0.25	32	-	-	-
Terbinafine	-	-	-	-	-	-	128	8	128

P.a. = P. aeruginosa, E.c. = E. coli, A.b. = A. baumannii, S.p. = S. pneumoniae, S.e. = S. epidermidis, B.c. = B. cereus, C.a. = C. albicans, A.f. = A. fumigatus and *F.o. = F. oxysporum.*



12-13



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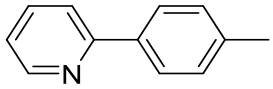


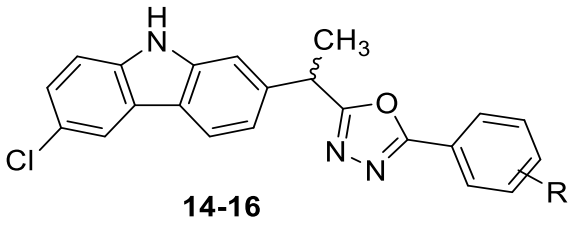
13

Table 7: MIC values of 2,3,5-substituted-1,3,4-oxadiazolines (µg/mL)

Species / Comp.	12	13	CIP/VA/NY	NIT	CFX	APC
S. aureus ATCC 25923	15.62	7.81	0.48	15.62	0.49	-
S. aureus ATCC 6538	15.62	7.81	0.24	15.62	0.98	-
S. aureus ATCC 43300	15.62	15.62	0.24	7.81	-	-
S. aureus ATCC 29213	15.62	15.62	0.48	-	-	-
S. epidermidis	1.95	0.48	0.12	3.91	0.24	-
E. faecalis	125	500	0.98	-	-	-
M. luteus	125	62.5	0.98	62.5	0.98	-
B. subtilis	31.25	31.25	0.03	3.91	15.62	62.5
B. cereus	31.25	31.25	0.06	7.81	31.25	-
B. bronchispetica	125	1000	0.98	125	-	-
C. albicans	31.25	15.62	0.24	-	-	-
C. parapsilosis	125	250	0.24	-	-	-

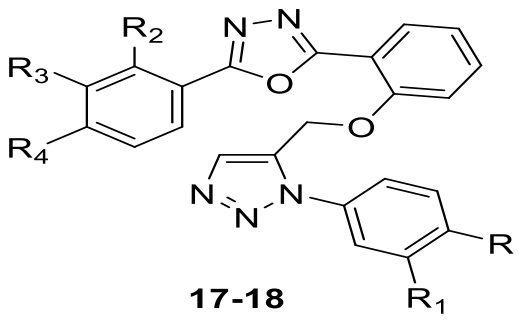
CIP-ciprofloxacin, VA-Vancomycin, NY-Nystatin, NIT-Nitrofurantoin, CFX-Cefuroxime and APC-Ampicillin.

Telehoiu et al. (2020) synthesized 1,3,4-oxadiazole derivatives and tested their antimicrobial activity against various bacterial and fungal strains. Antibacterial data revealed that compounds **(14-16)** showed good activity against *P. aeruginosa* (MIC = 2.5 mg/mL) and compound **14** with unsubstituted phenyl ring displayed better activity against *S. aureus*, *P. aeruginosa* and *E. coli* (MIC = 2.5 mg/mL) except in case of *Enterococcus faecalis* (MIC= 5 mg/mL). Whereas, compound with trifluoromethylphenyl ring (**16**) improved the activity against *E. faecalis* (MIC = 2.5 mg/mL) as compared with another analogues of series. In case of antifungal activity compound **16** showed maximum potency against *C. albicans* (MIC = 0.625 mg/mL) among the studied derivatives (**Table 8**) [52].



14-16

Bitla et al. (2020) screened triazole clubbed 2,5-diaryl 1,3,4-oxadiazole derivatives against various bacterial (*B. subtilis*, *S. aureus* and *E. coli*) and fungal strains (*A. niger* and *Saccharomyces cerevisiae*). The results revealed that compounds (**17-18**) exhibited better antibacterial activity than standard drug Ampicillin except against *E. coli* (**Table 9**). In case of antifungal activity compounds (**17-18**) showed reduced activity as compared to standard drug Miconazole (**Table 10**). Molecular docking studies were also performed on different Penicillin binding protein's (PDB ID: 3HUN, 3ITA). Compounds **17** and **18** displayed excellent docking score (-162.38, -163.56 Kcal/mol) and (-165.92, -165.83 Kcal/mol) with good binding affinity as compare to other studied derivatives. Hence the docking results showed that studied compounds may act by interacting with proteins involved in peptidoglycan and cell wall synthesis and can act as a lead for further development [53].



17-18

Table 8: MIC values of 1,3,4-oxadiazole derivatives (mg/mL)

Comp.	R	*E. faecalis*	*S. aureus*	*P. aeruginosa*	*E. coli*	*C. albicans*
14	-H	5	2.5	2.5	2.5	2.5
15	4-Cl	5	5	2.5	2.5	2.5
16	3-CF_3	2.5	5	2.5	5	0.625

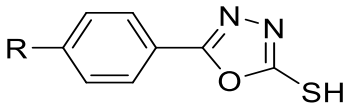
Table 9: MIC values of triazole clubbed 2,5-diaryl 1,3,4-oxadiazoles (µg/ml)

Comp.	R	R_1	R_2	R_3	R_4	*S. aureus*	*B. subtilis*	*E. coli*
17	OCH_3	H	H	OCH_3	OCH_3	8.8	5.7	>50
18	OCH_3	H	Cl	H	Cl	7.9	5.5	9
Ampicillin	-	-	-	-	-	10	10	4

Table 10: Fungal Zone of inhibition (mm) of triazole clubbed 2,5-diaryl 1,3,4-oxadiazoles

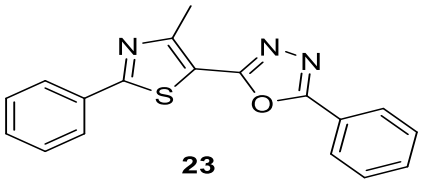
Comp.	Zone of inhibition (Concentration in µM)					
	A. niger			*S. cerevisiae*		
17	4 (10.2)	4.2 (20.5)	4.2 (30.8)	2 (10.2)	2.2 (20.5)	3 (30.8)
18	3 (10.1)	3.5 (20.2)	3.7 (30.3)	3 (10.1)	4 (20.2)	5 (30.3)
Miconazole	8 (12)	10 (24)	12 (36)	8 (12)	9 (24)	12 (36)

Upadhyay et al. (2019) investigated 5-(4-substituted phenyl)-1,3,4-oxadiazole-2-thiols and tested their activity against various bacterial and fungal strains. Compound **19** found to be active against both bacterial and fungal strains with 70-90% inhibition at 100 µg/ml and 200 µg/ml concentration. Compound **20** showed good inhibition (70-85%) towards bacterial strains but weaker against fungal strains (48-56%). However, compounds **21** and **22** displayed good inhibition (73-86%) against fungal strains but weaker towards bacterial strains (43-63%) (**Table 11**). The substituted phenyl group on 5th position of 1,3,4-oxadiazole affects the antimicrobial activity of compounds. In compound **19** the *p*-fluorophenyl substituent on 5th position of 1,3,4-oxadiazole exhibited excellent antimicrobial activity. Therefore, substitution of electron withdrawing groups (Cl, Br and F) at para position of phenyl ring attached to C-5 position of 1,3,4-oxadiazole are important for better antibacterial activity. Whereas, compounds with electron donating group such as (-OCH_3, -OH and -OC_2H_5) increases the antifungal activity of the compounds (**21** and **22**). Compounds **19-22** showed reduced activity as compared to standard drugs Ciprofloxacin and Fluconazole (**Table 11**) [54].



19-22

Araniciu et al. (2019) synthesized 2-(thiazol-5-yl)-1,3,4-oxadiazole scaffold and screened their *in vitro* antibacterial activity against *E. faecali*, *S. aureus*, *Staphylococus saprophyticus*, *B. subtilis*, *E. coli, P. aeruginosa* and antifungal activity against *C. albicans* and *Candida parapsilopsis*. Most of the compounds of the series found to be inactive except compound **23.** Compound **23** displayed lesser activity against most of the bacterial strains, but showed better activity in case of *B. subtilis* (ZOI = 13 mm), equipotent to Ciprofloxacin. In case of antifungal activity compound **23** showed very less or no activity **(Table 12)** [55].



23

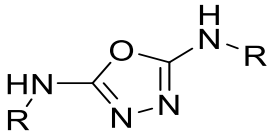
Table 11: Percentage growth inhibition of thiol linked 1,3,4-oxadiazole derivatives

Comp.	R	*S. aureus*		*B. subtilis*		*E. coli*		*P. aeruginosa*		*A. niger*		*C. albicans*	
(µg/ml)		**100**	**200**	**100**	**200**	**100**	**200**	**100**	**200**	**100**	**200**	**100**	**200**
19	-F	90	88	86	88	78	78	70	75	73	80	71	76
20	-Cl	85	83	77	80	74	78	70	71	50	52	48	56
21	-OCH_3	50	58	50	56	43	48	45	50	73	76	86	84
22	-OC_2H_5	60	63	59	60	52	59	50	54	77	84	81	80
Ciprofloxacin	-	100	100	100	100	100	100	100	100	-	-	-	-
Fluconazole	-	-	-	-	-	-	-	-	-	100	100	100	100

Table 12: Antimicrobial data of 2-(thiazol-5-yl)-1,3,4-oxadiazole scaffold

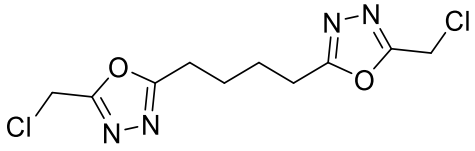
Compd.	Zone of inhibition (mm)								
	E. faecali	*S. aureus* ATCC 6538	*S. aureus* BAA 1026	*S. saprophyticus*	*B. subtilis*	*E. coli*	*P. aeruginosa*	*C. albicans*	*C. parapsilopsis*
23	4	6	5	5	13	3	3	1	0
Ciprofloxacin	15	14	15	16	14	14	16	-	-
Fluconazole	-	-	-	-	-	-	-	18	20

Hkiri *et al.* (2019) synthesized 2,5-difunctionalized 1,3,4-oxadiazole derivatives and investigated their *in vitro* antibacterial and antifungal potential. Antibacterial data revealed that compound **25** showed maximum potency against *S. aureus, Enterococcus faecium, Streptococcus agalactiae* (MIC = 0.015 µg/mL), whereas in case of *E. coli* and *Salmonella typhimurium* both compound **24** and **25** exhibited low activity (MIC = 0.500 µg/mL). In case of antifungal activity, compound **25** exhibited good activity against *C. albicans* (MIC = 0.15 µg/mL) (**Table 13**). SAR data showed that amidine containing 1,3,4-oxadiazole derivatives can be considered as a lead for the development of effective antimicrobial molecules against various fungal and bacterial strains. However, compounds (**24-25**) showed reduced activity as compared to standard drugs Ampicillin and Nystatin (**Table 13**) [56].

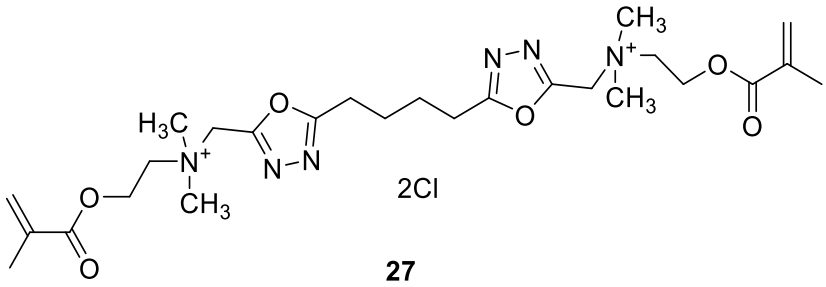


24-25

Rohand et al. (2019) synthesized bis-1,3,4-oxadiazole derivatives from hexanedioic acid dihydrazide and studied antimicrobial activity against various bacterial strains. The findings revealed that conversion of dihydrazides into 1,4-bis(5-chloromethyl-1,3,4-oxadiazole-2-yl)butane (**26)** decreases the activity, whereas further introduction of 2-(dimethylamino)ethyl methacrylate (**27)** group has not improve the activity except against *Citrobacterfreundii*. SAR analysis revealed that lipophilicity of compounds has an essential role in improvement of antibacterial activity. (**Table 14**) [57].



26



27

Table 13: Antimicrobial activity data of 2,5-difunctionalized 1,3,4-oxadiazole derivatives

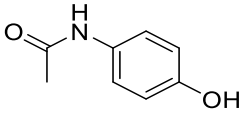
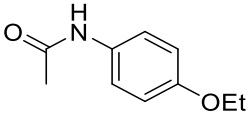
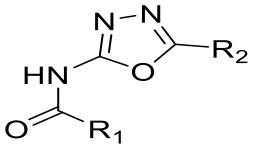
Comp.	R	Minimum inhibitory concentration in µg/mL					
		E. coli	*S. typhimurium*	*S. aureus*	*E. faecium*	*S. agalactiae*	*C. albicans*
24		0.500	0.500	0.031	0.031	0.031	0.500
25		0.500	0.500	0.015	0.015	0.015	0.015
Ampicillin	-	0.031	0.015	0.004	0.004	0.003	-
Nystatin	-	-	-	-	-	-	0.003

Table 14: Antibacterial activity of bis-1,3,4-oxadiazole derivatives

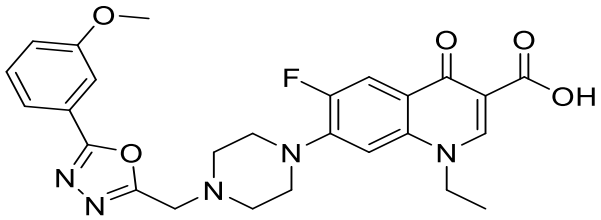
Bacterial strains	MIC (mg/mL) of compound		
	26	**27**	**Gentamicin (µg/mL)**
Enterobacteraerogenes	10.2	31	3.12
Citrobacterfreundii	0.74	0.27	12.5
Acetobacteraceti	7.25	7.25	50
Escherichia coli	2.56	100	12.5
Klebsiellapneumoniae	0.98	33	12.5
Enterobacter cloacae	10.7	10.7	50
Pseudomonas aeruginosa	10.7	10.7	50
Salmonella enterica	10.7	19.6	6.25
MR-Staphylococcus aureus	0.98	0.98	100
Curtobacteriumflaccumfaciens	10.7	31	6.25
Staphylococcus wavy	10.7	10.7	6.25

Li et al. (2019) synthesized 2-acylamino bearing 1,3,4-oxadiazoles and studied their antibacterial activity against *B. subtilis, S. aureus* and *E. coli*. Among the synthesized compounds **28** and **30** have more activity against *B. subtilis* (MIC = 0.78 mg/mL), whereas compound **29** showed better activity against *S. aureus* (MIC = 1.56 mg/mL) (**Table 15**). SAR data revealed that introduction of electron donating group CH_3 and electron withdrawing NO_2 at *para* position of phenyl ring attached to 1,3,4-oxadiazole ring improved the antibacterial activity of compounds except against *E. coli*. Compounds (**28-30**) showed very less potency as compared to Levofloxacin (**Table 15**) [58].

Guo et al. (2019) evaluated antibacterial activity of Norfloxacin and 1,3,4-oxadiazoles hybrids against methicillin-resistant *Staphylococcus aureus* (MRSA). The biological data revealed that compound **31** destroyed the bacterial membranes in a short time and also showed very low toxicity among the studied derivatives. SAR studies indicated that substitution of OCH_3 groups at 3rd position of phenyl group leads to more potent activity as compared to other substituents. Compound **31** showed better results as compared to standard drugs Norfloxacin and Vancomycin (**Table 16**) [59].



28-30



31

Table 15: Antibacterial activity data of 2-acylamino 1,3,4-oxadiazoles

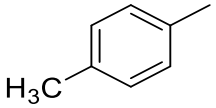
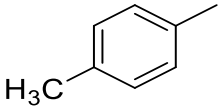
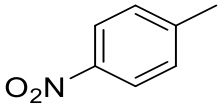
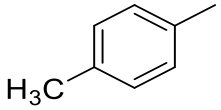
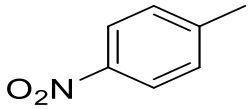
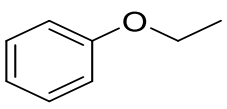
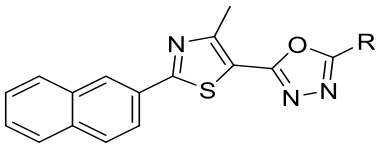
			MIC in (mg/mL)		
Comp.	**R_1**	**R_2**	***B. subtilis***	***S. aureus***	***E. coli***
28			0.78	3.12	>100
29			1.56	1.56	>100
30			0.78	3.12	>100
Levofloxacin	-	-	0.05	0.20	0.02

Table 16: MIC values of 1,3,4-oxadiazoles hybrids (µg/mL)

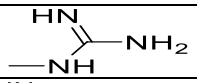
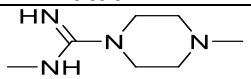
Comp.	*S. aureus*	*MRSA-1	*MRSA-2	*MRSA-3
31	2	0.5	0.25	1
Norfloxacin	1	1	2	1
Vancomycin	2	2	1	2

Hannoun *et al.* (2019) synthesized and investigated thiazole clubbed 1,3,4-oxadiazole and tested their activity against MRSA. The antibacterial activity data revealed that polar guanidine chain enhances the activity of compound **32** and showed similar (MIC = 1.95 µg/mL) value when compared with standard drug Vancomycin (**Table 17**). The replacement of amine group with 1-methyl-piperazine on guanidine group (**33)** retains the antibacterial activity [60].



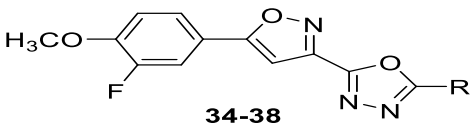
32-33

Table 17: MIC value of thiazole clubbed 1,3,4-oxadiazoles (µg/mL)

Comp.	R	MRSA
32		1.95
33		1.95
Vancomycin	-	1.95

Shingare et al. (2018) synthesized 1,3,4-oxadiazole clubbed isoxazoles and studied their activity against various bacterial and fungal strains. Antibacterial data showed that compounds (**34-38**) displayed good potency against *E. coli, S. aureus* and *S. pyogenes* (MIC range = 62.5-125 µg/mL) except **35** showed low activity against *S. pyogenes* (MIC=250 µg/mL) (**Table 18**). Furthermore, compounds **35** and **38** displayed highest activity against *P. aeruginosa* (MIC = 62.5 and 100 µg/mL) among studied derivatives. The antibacterial activity of compounds was increased by 4-chlorophenyl **(34)** and 2-indolyl moieties (**38)**.

Compounds with extra heterocyclic ring *i.e.,* pyridyl (**37**) and indolyl (**38**) moieties showed strong activity against *C. albicans* (MIC = 200 and 250 µg/mL). Whereas all synthesized compounds were found to be less effective against *A. niger* and *A. clavatus*. Compounds **34** with -Cl substitution at 4th position of phenyl ring and **35** with two -Cl groups substituted at 3rd and 4th positions showed decrease in antifungal activity, indicated that halogen substituent on phenyl ring decreases the antifungal activity. Active compounds (**34-38**) showed almost better antibacterial activity as compared to standard drug Ampicillin and lesser towards antifungal drug Griseofulvin (**Table 18**) [61].

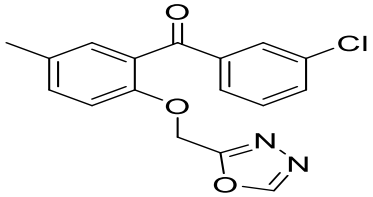


34-38

Table 18: MIC value of isoxazole clubbed 1,3,4-oxadiazoles (µg/mL)

Comp.	R	*E. coli*	*P. aeruginosa*	*S. aureus*	*S. pyogenes*	*C. albicans*	*A. niger*	*A. clavatus*
34	4-Cl-C_6H_4	62.5	125	125	100	1000	1000	1000
35	3,4-Di-Cl-C_6H_3	100	62.5	100	250	1000	1000	1000
36	2-F-C_6H_4	62.5	1000	100	100	500	250	250
37	4-pyridinyl	125	200	62.5	100	200	250	500
38	2-indolyl	62.5	100	100	62.5	250	500	1000
Ampicillin	-	100	100	250	100	-	-	-
Griseofulvin	-	-	-	-	-	500	100	100

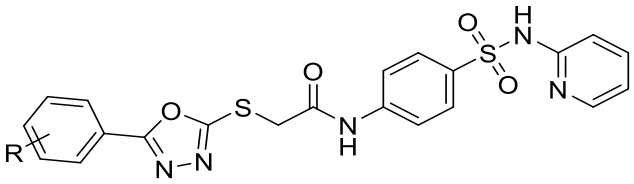
Al-Ostoot et al. (2018) synthesized and screened antimicrobial activity of 2-substituted 1,3,4-oxadiazoles analogues. Among the synthesized derivatives, compound **39** with *para* methylphenoxy and 3-chlorobenzoyl moieties exhibited excellent activity against most of the bacterial strains and equipotent to standard drug, Streptomycin (**Table 19**).



39

Compound **39** exhibited better antifungal activity against *B. cinerea* and *C. krusei* (ZOI = 16 and 22 mm), but lower against *C. albicans* and *M. pachydermatis* (ZOI = 19 and 20 mm) as compared with standard drug Ketoconazole (**Table 19**) [62].

Dholaria et al. (2018) investigated 1,3,4-oxadiazoles linked with pyridine and evaluated their *in vitro* antifungal and antibacterial activities. Antimicrobial results showed that among the compounds (**40-48**), **43** found to be most active against various bacterial and fungal strains (MIC range = 62.5-125 µg/mL) (**Table 20**). In case of antifungal activity, both electron donating and accepting groups **43-47** (*viz.*-Cl, -Br, -I, -NO_2, OH and CH_3) showed good activity against *C. albicans* and *A. niger* (MIC = 125 µg/mL), although all the compounds (**40-48**) displayed low activity towards *A. niger* (MIC range = 125-250 µg/mL) as compared to standard drug Fluconazole (**Table 20**). In general, SAR studies showed that the presence of electron withdrawing groups (*viz.*-Cl, -Br and -NO_2) at *para* and *ortho* positions (R) improved the antibacterial activity as compared to electron-releasing groups, except in compound **47**, with CH_3 group increased the activity. In view of above findings, it can be concluded that position of different substituents on phenyl ring of 1,3,4-oxadiazole derivatives affecting the antibacterial and antifungal activities (**Table 20**) [63].



40-48

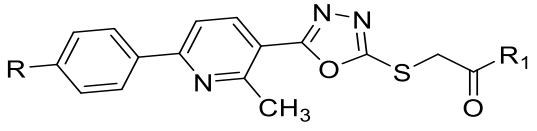
Table 19: Antibacterial Zone of inhibition (mm)

Comp.	*S. aureus*	*E. aerogenes*	*M. luteus*	*K. pneumonia*	*S. typhimurium*	*S. paratyphi*	*P. vulgaris*	*C. albicans*	*B. cinerea*	*M. pachydermatis*	*C. krusei*
39	19	22	23	25	26	29	27	19	16	20	22
Streptomycin/ Ketoconazole	17	24	26	22	25	19	24	22	10	26	16

Table 20: Antimicrobial activity data of 1,3,4-oxadiazole linked pyridine derivatives

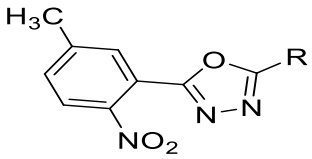
		MIC in µg/mL					
Comp.	**R**	***S. aureus***	***E. faecalis***	***E. coli***	***P. aeruginosa***	***C. albicans***	***A. niger***
40	H	125	125	250	250	250	250
41	-4-Cl	250	250	62.5	125	250	250
42	-2-Cl	500	125	62.5	125	500	250
43	-2-Cl-5-NO_2	125	125	62.5	62.5	125	125
44	-4-Br	125	125	250	250	125	125
45	-2-I	250	250	250	250	125	250
46	-4-OH	250	250	250	250	125	125
47	-3-CH_3	125	125	125	125	125	125
48	-3-OCH_3	250	250	250	250	250	250
Ciprofloxacin	-	62.5	125	125	125	-	-
Fluconazole	-	-	-	-	-	125	62.5

Vasantha et al. (2018) introduced a series of arylpyridine based 1,3,4-oxadiazoles and evaluated their antibacterial activity against various bacterial strains. Among the studied compounds, **50** with *p*-bromo phenyl group demonstrated the good activity against *E. coli* and *P. aeruginosa* (MIC = 6.25 µg/mL) but lesser against *B. subtilis* (MIC= 12.5 µg/mL) (**Table 21**). Furthermore, compound **49** showed better activity against *B. subtilis* (MIC = 6.25 µg/mL) but very less against *P. aeruginosa* and *E. coli* (MIC = 50 µg/mL). Active compounds (**49-50**) showed very less potency as compared to standard drug Ciprofloxacin (**Table 21**) [64].



49-50

Mutchu et al. (2018) screened 2-(5-methyl-2-nitrophenyl) and 5-substituted 1,3,4-oxadiazoles for their antibacterial activities against *Bacillus megaterium, E. faecalis, Streptococcus mutans, E. coli, Proteus vulgaris* and *P. aeruginosa*. Antibacterial data showed compounds **51** and **52** with furan and thiophene moiety at 5th position of 1,3,4-oxadiazole exhibited significant activity against most of the tested strains as compare to other substituents. The presence of a chlorine group on pyridine ring may be responsible for activity of the compound **53** (**Table 22**). However, compounds (**51-53**) showed reduced activity as compared to standard drugs Chloramphenicol and Ampicillin (**Table 22**) [65].



51-53

Table 21: Antibacterial activity data of arylpyridine based 1,3,4-oxadiazoles

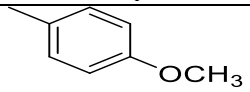
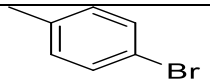
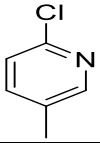
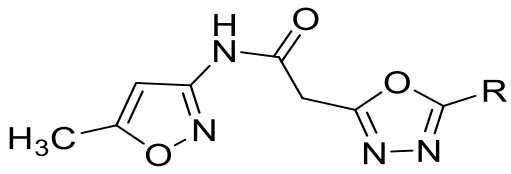
			MIC in µg/mL		
Comp.	**R**	**R_1**	***B. subtilis***	***E. coli***	***P. aeruginosa***
49	-Cl		6.25	50	50
50	-Br		12.5	6.25	6.25
Ciprofloxacin	-	-	2	2	4

Table 22: Zone of inhibition of 2-(5-methyl-2-nitrophenyl) 1,3,4-oxadiazoles (mm)

Comp.	**R**	***B. megaterium***	***E. faecalis***	***S. mutans***	***E. coli***	***P. vulgaris***	***P. aeruginosa***
51		5	5	4	6	4	5
52		4	3	3	0	3	4
53		4	5	4	6	4	3
Chloramphenicol and ampicillin	-	7	7	8	8	7	7

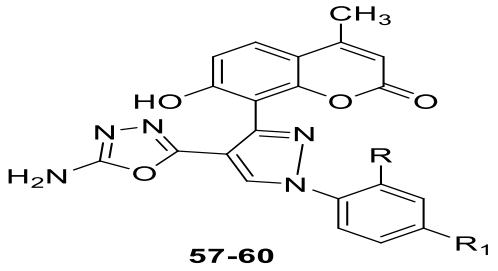
Marri et al. (2018) screened 1,3,4-oxadiazole clubbed isoxazoles and screened their activity against various bacterial and fungal pathogens. The antibacterial studies revealed that introduction of electron withdrawing groups at *para* position of phenyl ring (-Cl and -NO_2) in **54** and **55** improved the activity against all bacterial strains (MIC range = 6-11 µg/mL). On the other hand, introduction of electron withdrawing group (-Br) at *meta* position of phenyl ring (**56)** decreased the activity (**Table 23**). Compound **55** found to be most active (ZOI = 69.5-80.5 mm) against most of the tested fungal strains among synthesized derivatives (**Table 24**). Overall active compounds (**54-56**) showed excellent activity as compared to standard drugs Clotrimazole and Ciprofloxacin (**Table 23, 24**) [66].



54-56

Renuka et al. (2017) investigated a series of pyrazole and coumarin clubbed 1,3,4-oxadiazoles for their antimicrobial activities. Antibacterial studies showed that compounds (**57-60**) exhibited good activity against *S. aureus, E. coli* and *P. aeruginosa* (MIC range = 12.5-25 µg/mL) except **57** against *E. coli* (MIC = 50 µg/mL)

among studied compounds. However, in case of antifungal activity compound **60** found to be most active against *C. albicans* (MIC = 12.5 µg/mL) and compound **57** displayed better activity against all tested fungal strains (MIC range = 25-50 µg/mL) (**Table 25**). Active compounds (**57-60**) showed almost similar activity as compared to standard drugs Ciprofloxacin and Fluconazole (**Table 25**) [67].



57-60

Table 23: Antibacterial activity data of 1,3,4-oxadiazole clubbed isoxazoles

Comp.	R	MIC in (µg/mL)					
		P. aeruginosa	*K. aerogenes*	*C. violaceum*	*B. subtilis*	*B. sphaericus*	*S. aureus*
54	4-Cl-C_6H_4	11	11	8	9	8	7
55	4-NO_2-C_6H_4	10	8	7	6	8	6
56	3-Br-C_6H_4	13	11	14	11	12	10
Ciprofloxacin		30	25	25	20	20	25

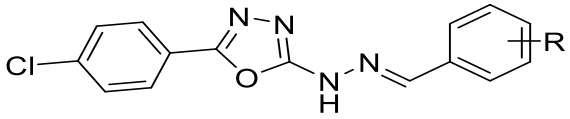
Table 24: Antifungal activity data of 1,3,4-oxadiazole clubbed isoxazoles

Comp.	Zone of Inhibition zone (mm)				
	A. niger	*C. tropicum*	*R. oryzae*	*F. moniliforme*	*C. lunata*
54	69.1	70.1	72.5	69.8	65.5
55	75.0	77.2	80.5	73.2	69.5
56	63.2	65.0	72.5	60.5	73.5
Clotrimazole	26.5	30.6	33.5	25.5	35.8

Table 25: Antimicrobial activity data of pyrazole and coumarin clubbed 1,3,4-oxadiazoles

Comp.	R	R_1	MIC in (µg/mL)					
			S. aureus	*E. coli*	*P. aeruginosa*	*A. niger*	*A. flavus*	*C. albicans*
57	H	H	12.5	50	25	25	25	50
58	OCH_3	H	25	25	12.5	25	75	50
59	CH_3	H	25	25	25	50	25	25
60	H	Cl	25	12.5	12.5	25	50	12.5
Ciprofloxacin	-	-	25	25	12.5	-	-	-
Fluconazole	-	-	-	-	-	25	25	50

Joshi et al. (2017) synthesized Schiff base bearing 1,3,4-oxadiazole derivatives and tested their antibacterial and antifungal activities against various strains. The antibacterial data showed that compounds (**61-65**) exhibited better activity against *S. aureus*, *E. coli* and *P. aeruginosa* (MIC range = 62.5-125 µg/mL) among synthesized derivatives and comparable to standard drug Ciprofloxacin but lower against *E. faecalis* (MIC = 250 µg/mL) (**Table 26**). Whereas, compounds (**61-65**) showed less antifungal activity against *C. albicans* and *A. niger* (MIC = 250 µm/mL) as compared to standard drug Fluconazole. Overall it can be concluded that electron-donating substituents 2,5-dimethoxy (**61**), 2,4,5-trimethoxy (62), 2-OH-1-napthaldehyde (**64**), and N,N-dimethyl (**65**) improved the antibacterial activity except compound **63,** where electron withdrawing group improved the antibacterial activity (**Table 26**) [68].



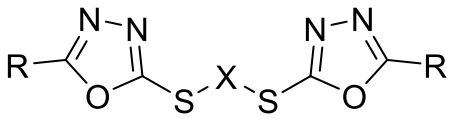
61-65

Table 26: Antimicrobial activity data of Schiff base bearing 1,3,4-oxadiazole derivatives

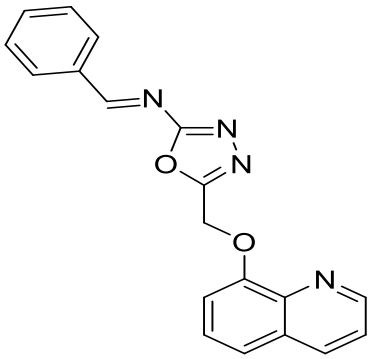
Comp.	R	MIC in (µg/mL)					
		S. aureus	*E. faecalis*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
61	2,5-diOCH_3	62.5	250	62.5	125	250	250
62	2,4,5-triOCH_3	62.5	250	62.5	125	250	250
63	2-NO_2	62.5	250	62.5	125	250	250
64	2-OH-1-Napthaldehyde	62.5	250	125	125	250	250
65	N,N-diCH_3	62.5	250	125	125	250	250
Ciprofloxacin	-	62.5	125	125	125	-	-
Fluconazole	-	-	-	-	-	125	62.5

Ahmed et al. (2017) synthesized bis ((5-aryl-1,3,4-oxadiazol-2-yl)thio) alkanes and tested for their antibacterial and antifungal activity. Compounds **67**, **68** (R = 4-methylphenyl, X = -$(CH_2)_3$, - $CH_2(CH_2)_6CH_2$) and **69** (R = 2-bromophenyl, X = $CH_2(CH_2)_6CH_2$) exhibited better activity against *B. septic, M. Luteus,* and *S. typhimurium* as compare to other synthesized compounds (**Table 27**). Similarly, **67** (R = 4-methylphenyl, X = -$(CH_2)_3$) showed moderate antifungal activity against *A. flavus* and *A. niger* (ZOI = 15 and 19 mm) while **68** (R =4-methylphenyl, X = $CH_2(CH_2)_6CH_2$) depicted significant activity against *A. niger* and *Mucor sp*. (ZOI = 18.5 and 16.5 mm) than other analogues of series. SAR studies showed that length of methylene groups between two 1,3,4-oxadiazole nucleus affects the antifungal activity against *A. flavus*. Compounds (**66-69**) exhibited lesser activity as compared to standard drugs Cefixime and Terbinafine (**Table 27**) [69].

Dhara et al. (2017) investigated 2,5-substituted 1,3,4-oxadiazole for antimicrobial efficacy against *S. aureus, E. coli, M. smegmatis* and *C. albicans*. Among the studied derivatives most active compound **70** showed comparable antimicrobial activity to Ciprofloxacin and Fluconazole (**Table 28**). SAR studies displayed that replacement of naphthalene moiety with quinoline in 1,3,4-oxadiazole derivatives **(70)** improved the antimicrobial activity against all the microorganism. Docking studies were also reported and compound **70** showed the good affinity by acting as ATP-competitive inhibitor on microbial D-alanine:d-alanine ligase enzyme (-58.4434 Kcal/mol) [70].



66-69



70

Table 27: Antimicrobial activity data of bis((5-aryl-1,3,4-oxadiazol-2-yl)thio)alkanes

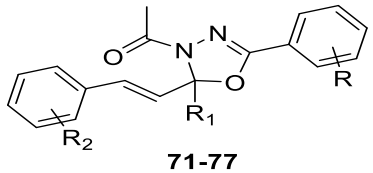
Comp.	R	X	Zone of inhibition (mm)					
			S. typhimurium	*M. Luteus*	*B. septica*	*A. niger*	*Mucor sp.*	*A. flavus*
66	4-pyridyl	$(CH_2)_3$	11.5	8.5	9	15	15.5	14
67	4-Me-C_6H_4	$(CH_2)_3$	14	12.5	10.5	19	14.5	15
68	4-Me-C_6H_4	$CH_2(CH_2)_6CH_2$	12	13	10	18.5	16.5	12.5
69	2-Br-C_6H_4	$CH_2(CH_2)_6CH_2$	13	10	11.5	15.5	11.5	10.5
Cefixime	-	-	22	15	19	-	-	-
Terbinafine	-	-	-	-	8	30	28	33

Table 28: Antimicrobial data of 2,5-substituted 1,3,4-oxadiazoles

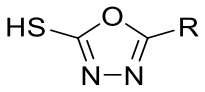
	MIC in (mM)			
Comp.	***S. aureus***	***M. smegmatis***	***E. coli***	***C. albicans***
70	0.025	0.025	0.1	0.025
Ciprofloxacin/ Fluconazole	<0.024	<0.024	<0.024	<0.024

Channigarayappa et al. (2017) studied *in vitro* antimicrobial activity of 1,3,4-oxadiazole-3(2H)-yl-ethanone derivatives against bacterial strain *E. coli* and *S. aureus*; fungal strain *C. albicans* and *T. equinum*. All compounds displayed effective inhibitory activity against all the tested strains. SAR analysis showed that among active compounds (**71-77**), **76** exhibited maximum potency against *E. coli* (ZOI = 12.83 mm) having 2-fluoro-5-trifluoromethoxy moiety at R, 4-OH at R_1 and R_2 (**Table 29**). In case of *T. equinum* (ZOI = 17.57) and *C. albicans* (ZOI = 15.17), compound **71** having 4-OH at R, naphthalene at R_1 and -3-OH-5-OCH_3 at R_2 of 1,3,4-oxadiazole and comparable to Nystatin. In case of *S. aureus*, compound **71** also exhibited comparable activity (ZOI = 13.97) to standard drug Chloramphenicol (**Table 29**) [71].

Sudha et al. (2017) synthesized 5-N-alkyl-1,3,4-oxadiazole-2-thiol derivatives and screened *in vitro* activity against *S. aureus, E. coli, P. aeruginosa* and *B. subtilis*. Among the reported compounds **78** and **79** showed significant activity. SAR studies revealed that presence of fatty acid moiety is essential for good antibacterial activity and presence of double bonds in fatty acid chain further improved the activity. However, reported compounds showed less activity as compared to standard drug Streptomycin except in case of *B. subtilis* (**Table 30**) [72].



71-77



78-79

Table 29: Zone of inhibition of 1,3,4-oxadiazole-3(2H)-yl-ethanone derivatives (mm)

Comp.	**R**	**R_1**	**R_2**	***E. coli***	***S. aureus***	***T. equinum***	***C. albicans***
71	-4-OH	-Naph	-3-OH-5-OCH_3	11.17	13.97	17.57	15.17
72	-2-F-5-OCF_3	-Naph	-4-F	10.67	12.57	17.97	14.17
73	-4-OH	-Naph	-4-F	12.33	11.17	14.17	15.17
74	-2-F-5-OCF_3	-4-OH	-3-OH-5-OCH	11.17	10.17	12.83	13.97
75	-2-F-5-OCF_3	-Naph	-3-OH-5-OCH	8.50	9.67	15.33	14.83
76	-2-F-5-OCF_3	-4-OH	-4-OH	12.83	11.67	13.67	10.17
77	-2-F-5-OCF_3	-Naph	-4-Br	11.97	12.50	16.67	15.97
Chloramphenicol	-	-	-	13.00	14.17	-	-
Nystatin	-	-	-	-	-	18.17	16.33

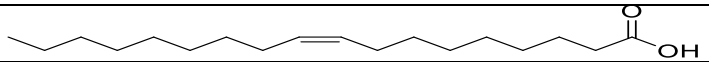
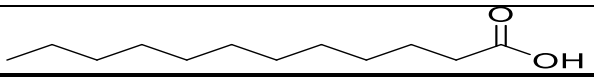
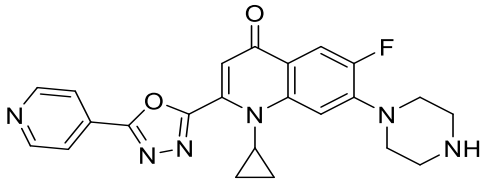
Comp.	**R**
78	
79	

Table 30: Zone of inhibition in mm

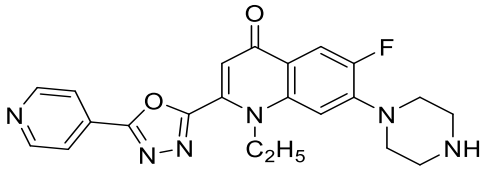
Comp.	***S. aureus***		***B. subtilis***		***P. aeruginosa***		***E. coli***	
Conc. (µg/mL)	**50**	**100**	**50**	**100**	**50**	**100**	**50**	**100**
78	10	15	20	25	12	18	24	27
79	N*	N*	22	27	N*	8	14	20
Streptomycin	25		22		21		28	

** No inhibition*

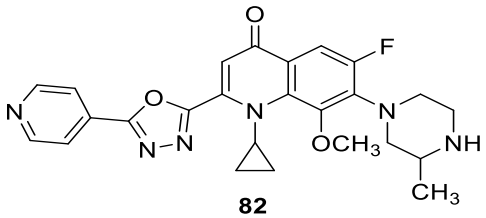
Khan et al. (2017) synthesized 1,3,4-oxadiazoles clubbed with isoniazid and fluoroquinolones as antibacterial agent. Among the synthesized compounds, **80-83** exhibited maximum potency against all tested bacterial strains. SAR studies showed conversion of fluoroquinolones carboxylic group to 1,3,4-oxadiazole has not improved the antibacterial activity. Most of the active compounds (**80-83**) exhibited similar range of activities, as shown by standard drugs, Ciprofloxacin, Norfloxacin, Gatifloxacin and Ofloxacin (**Table 31**) [73].



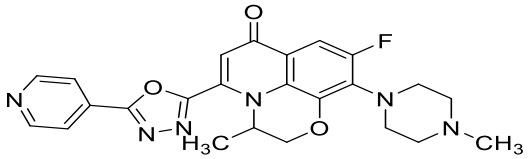
80



81



82



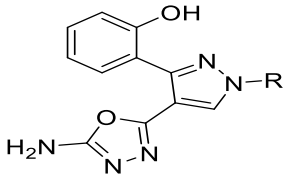
83

Table 31: Antibacterial activity data of 2,5-disubstituted-1,3,4-Oxadiazoles

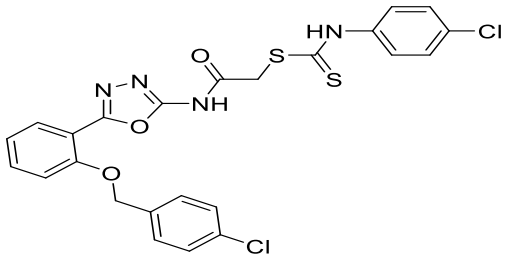
	MIC in µg/mL		
Comp.	***S. aureus***	***P. aeruginosa***	***E. coli***
80	6.25	3.12	6.25
81	6.25	6.25	3.12
82	6.25	6.25	12.5
83	3.12	3.12	6.25
Ofloxacin	3.12	3.12	3.12
Norfloxacin	6.25	6.25	6.25
Gatifloxacin	6.25	6.25	6.25
Ciprofloxacin	6.25	6.25	6.25

Gurunanjappa et al. (2016) synthesized 1,3,4-oxadiazole clubbed pyrazole scaffold and studied their antimicrobial activity against various bacterial and fungal strains. SAR studies showed among the studied derivatives, compound **84** with *p*-chlorophenyl substitution at pyrazole ring exhibited the excellent antibacterial and antifungal activity, which was equipotent to standard drugs Ciprofloxacin and Fluconazole, respectively (**Table 32**). Therefore, *p*-chlorophenyl substitution found to be significant for the better antimicrobial activity of the compounds [74].

Rajak et al. (2015) evaluated antimicrobial potential of 1,3,4-oxadiazole analogues. SAR analysis revealed that, attachment of *para*-Cl group to phenyl ring **85** improved the antimicrobial activity against all tested bacterial and fungal strains, whereas the presence of unsubstituted phenyl ring reduced the activity (**Table 33**). However, active compound **85** showed less activity as compared to standard drugs Norfloxacin and Clotrimazole (**Table 33**) [75].



84



85

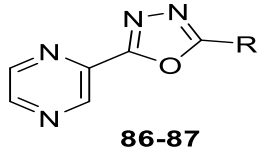
Table 32: Antimicrobial data of 1,3,4-oxadiazole clubbed pyrazole scaffold

Comp.	R	MIC in µg/mL					
		S. aureus	*E. coli*	*P. aeruginosa*	*A. niger*	*A. flavus*	*C. albican*
84	4-Cl-C_6H_4	25	12.5	12.5	12.5	25	25
Ciprofloxacin	-	25	12.5	12.5	-	-	-
Fluconazole	-	-	-	-	12.5	25	25

Table 33: Antimicrobial activity data of 1,3,4-oxadiazole analogues

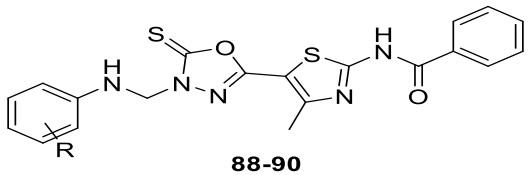
Zone of inhibition in mm (100 µg/8mm disk)						
Comp.	***S. aureus***	***B. subtilis***	***P. mirabilis***	***P. aeruginosa***	***A. niger***	***C. albicans***
85	18	17	16	16	15	17
Norfloxacin	24	21	22	20	-	-
Clotrimazole	-	-	-	-	21	23

Das et al. (2015) investigated and synthesized the 2,5-disubstituted 1,3,4-oxadiazole derivatives carrying pyrazine moiety and evaluated for antimicrobial activity against various strains. Compounds (**86-87**), showed maximum activity among the synthesized derivatives. SAR analysis revealed that introduction of hydrazine group at 2nd position of 1,3,4-oxadiazole (**87**) depictedmore antibacterial and antifungal activities as compare to presence of sulfanyl group at same position (**86**), except in case of B. *subtilis*. However, compounds (**86-87**) showed less activity as compare to standard drug Amoxicillin and Miconazole (**Table 34**) [76].



86-87

Desai et al. (2015) screened thiazole linked 1,3,4-oxadiazoles for antimicrobial activity against bacterial strains and fungal stains. Antibacterial data revealed that compounds **89** and **90** showed better activity against all bacterial strains (MIC range = 12.5-100 µg/mL). However, in case of antifungal activity compound **88** exhibited excellent activity against all fungal strains (MIC range = 12.5-25 µg/mL) (**Table 35**) Reported activity data showed thiazole ring is important for antimicrobial activity and electron donating group at (R = OCH_3 (**89**), CH_3 (**90**)) improved the bacterial activity. On the other hand, compound **88** with electron withdrawing (R = F) group at *para* position improved antifungal activity. Compounds (**88-90**) showed better activity as compared to standard drugs Ampicillin and Griseofulvin (**Table 35**) [77].



88-90

Table 34: Antimicrobial activity data of triazole and tetrazole fused 1, 3, 4-oxadiazoles

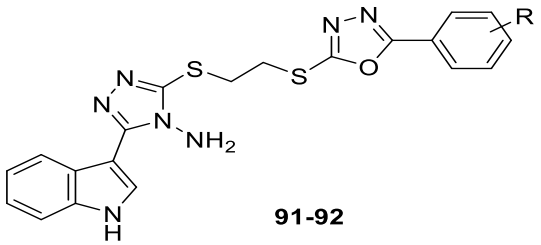
Comp.	MIC in µg/mL						
	R	***B. subtilis***	***S. aureus***	***E. coli***	***P. aeruginosa***	***C. albicans***	***A. niger***
86	-SH	200	400	100	800	100	200
87	-NH-NH_2	200	200	50	400	50	50
Amoxicillin	-	100	100	12.5	200	-	-
Miconazole	-	-	-	-	-	25	12.5

Table 35: Antimicrobial data of thiazole linked 1,3,4-oxadiazoles

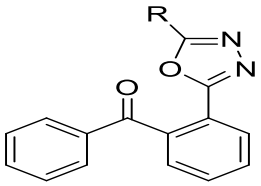
		MIC in µg/mL						
Comp.	**R**	***E. coli***	***P. aeruginosa***	***S. aureus***	***S. pyogenes***	***C. albicans***	***A. niger***	***A. clavatu***
88	-4-F	500	1000	500	1000	25	25	12.5
89	-4-OCH_3	12.5	25	25	100	>1000	250	500
90	-3-CH_3	50	100	50	12.5	500	500	>1000
Ampicillin	-	100	100	250	100	-	-	-
Griseofulvin	-	-	-	-	-	500	100	100

Shi et al. (2015) synthesized 1,3,4-oxadiazole derivatives clubbed with indole moiety and tested their activity against various bacterial strains. Compound **92** with (-NH_2) group showed excellent activity against *S. aureus* (MIC = 2 µg/mL) and *E. coli* (MIC = 8 µg/mL) but, lower against *B. subtilis* (MIC = 8 µg/mL) and *P. aeruginosa* (MIC = 16 µg/mL) as compared to standard drug Amoxicillin (**Table 36**). The SAR studies showed that the presence of electron donating groups **91** (-OCH_3) and **92** (-NH_2) at 4th position of phenyl ring improved the antibacterial activity of compounds. However, all the studied compounds showed very less potency as compared to Ciprofloxacin (**Table 36**) [78].

Bala et al. (2014) investigated the antimicrobial ability of 1,3,4-oxadiazole derivatives against various microbial strains. Antimicrobial results displayed that the introduction of electron withdrawing halogen (Cl, **93)** and resonance electron donating groups (-OH, OCH_3) on phenyl ring (**94**) increased the antimicrobial activity of compound (**Table 37**). Compounds (**93-94**) showed better results as compared to standard drug Amoxicillin, Cefixime and Fluconazole (**Table 37**) [79].



91-92

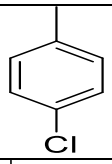
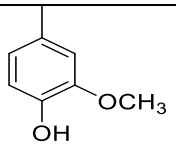


93-94

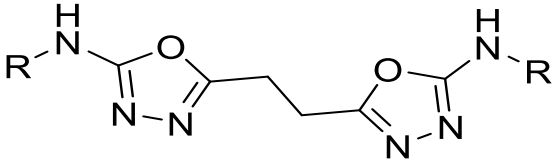
Table 36: MIC values of 1,3,4-oxadiazole derivatives clubbed with indole ring (µg/mL)

Comp.	R	*B. subtilis*	*S. aureus*	*E. coli*	*P. aeruginosa*
91	4-OCH_3	32	8	8	32
92	4-NH_2	8	2	8	16
Amoxicillin	-	2	16	16	4
Ciprofloxacin	-	0.128	3.12	0.25	0.5

Table 37: MIC values in (µg/mL)

Comp.	R	*E. coli*	*P. aeruginosa*	*S. aureus*	*S. epidermidis*	*C. albicans*	*A. niger*
93		12.5	12.5	100	12.5	12.5	10
94		12.5	25	25	25	100	10
Amoxicillin	-	12.5	200	100	12.5	-	-
Cefixime	-	50	400	400	50	-	-
Fluconazole	-	-	-	-	-	12.5	400

Sharma et al. (2014) screened bis-1,3,4-oxadiazoles for fungicidal activity against various fungal strains. Among the synthesized compounds (**95-100**)**,** compound **96** with 2-OCH_3 and **97** with 3-Cl group on phenyl ring showed better activity against *Alternaria solani* (46-94% inhibition) and *Aspergillus flavus* (48-96% inhibition). Overall compounds (**95-100**) showed less activity as compared to standard drug Dithane (**Table 38**) [80].

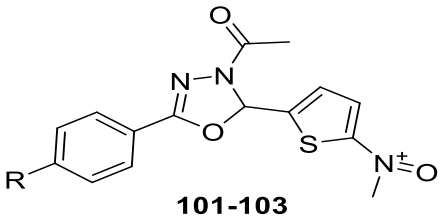


95-100

Table 38: Percent Inhibition of fungal growth after 96 h

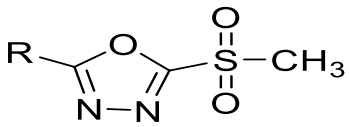
Comp.	R	*Alternaria solani*			*Aspergillus flavus*		
		1,000 ppm	100 ppm	10 ppm	1,000 ppm	100 ppm	10 ppm
95	C_6H_5	60	36	16	62	39	18
96	2-$CH_3OC_6H_4$	88	71	46	90	72	48
97	3-ClC_6H_4	94	75	52	96	74	51
98	3-$CH_3C_6H_4$	60	37	16	61	38	17
99	4-$CH_3C_6H_4$	63	38	19	64	40	20
100	$C_{10}H_7$	49	20	08	50	21	10
Dithane	-	100	85	66	100	83	63

Ishii et al. (2011) synthesized 2-nitrothiazole clubbed 1,3,4-oxadiazole derivatives and evaluated their antibacterial activity against different strains of *S. aureus*. SAR studies showed that among active compounds (**101-103**), **103** exhibited maximum potency against different strains of *S. aureus* (MIC range = 3.38–2.95, 2.50–1.25, 2.50-1.25 µg/mL) having -CO_2CH_3 group attached to phenyl moiety (**Table 39**). Compounds with 5-(4-phenyl butoxy) **102** and 5-(4-phenylmethyl formate) **103** moieties were found to be most active among studied derivatives [81].



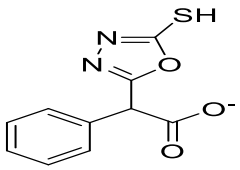
101-103

Xu et al. (2011) studied *in vitro* anti-fungal activity of 1,3,4-oxadiazole clubbed with sulfone moiety against pathogenic fungi, *Fusarium oxysporum* and *Cytospora mandshurica*. Among the active compounds (**104-106**), **106** displayed maximum inhibition against *F. oxysporum* (98.8%) and *C. mandshurica* (97.8%), having 2,6-difluoro substituents on benzene ring (**Table 40**). In general, it was concluded that the presence of electron withdrawing groups specially fluorine moiety at various positions of benzene ring improved the activity as compared to other substituents. Studied compounds exhibited better activity as compare to standard drug Hymexazol (**Table 40**) [82].

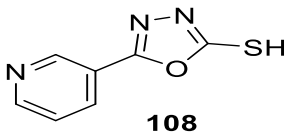


104-106

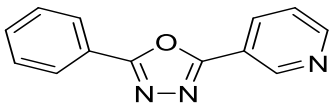
Jha et al. (2010) synthesized 2,5-substituted-1,3,4-oxadiazole derivatives and investigated their antibacterial activity. Among the studied compounds **107**, **108** and **109** showed maximum efficacy against tested bacterial strains. However, the active compounds (**107-109**) displayed reduced activity as compared to Ciprofloxacin (**Table 41**) [83].



107



108



109

Table 39: MIC values of 2-nitrothiazole clubbed 1,3,4-oxadiazoles (µg/mL)

Comp.	R	*S. aureus*		
		ATCC 25923	SP3/R33	VISA3
101	-CF_3	3.28-2.62	2.50-1.25	5.00-2.50
102	-OC_4H_9	1.95-1.25	2.50-1.25	10.00-5.00
103	-CO_2CH_3	3.38-2.95	2.50-1.25	2.50-1.25
Vancomycin	-	-	1.00-0.50	1.00-0.50
Ampicilin	-	0.10-0.20	32.00-16.00	32.00-16.00
Nifuroxazide	-	6.59-5.90	-	10.00-5.00

Table 40: The effect of 1,3,4-oxadiazole methyl sulfones on phytopathogenic fungi inhibition

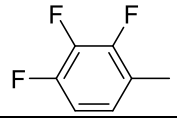
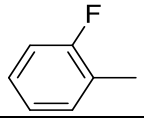
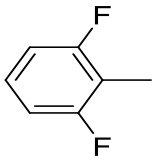
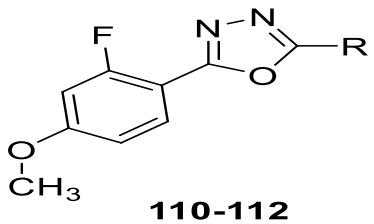
Comp.	R	Inhibition (%)	
		F. oxysporum	*C. mandshurica*
104		97.5 ± 3.3	89.7 ± 3.1
105		70.1 ± 4.9	64.0 ± 1.3
106		98.8 ± 8.0	97.8 ± 11.8
Hymexazol	-	58.4	57.3

Table 41: Antibacterial activity data of 2,5-substituted-1,3,4-oxadiazoles

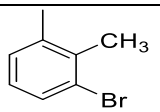
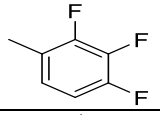
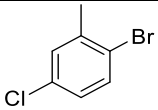
Comp.	Zone of inhibition in (mm)		
	S. aureus	*S. epidermidis*	*E. coli*
107	24	26	25
108	25	26	21
109	24	25	24
Ciprofloxacin	29	30	26

Chandrakantha et al. (2009) synthesized 1,3,4-oxadiazole derivatives bearing 2-fluoro-4-methoxy moiety and evaluated their antifungal and antibacterial activities. Among the investigated compounds, **110-112** exhibited maximum efficacy against all tested strains. Compound **110** with 3-bromo-2-methyl phenyl and **111** with 2,3,4-trifluoro phenyl moieties displayed excellent antibacterial activity against *P. aeruginosa* and *E. coli* (MIC = 3 μg/ml, **Table 42**). Further activity data showed, presence of electron withdrawing groups at different positions of phenyl ring improved antibacterial activity. In case of anti-fungal activity compound **112** with 2-bromo-5-chloro phenyl moiety showed the highest inhibition (MIC = 3 μg/ml) among the studied derivatives. Compounds (**110-112**) exhibited better activity as compared to standard drugs Furacin and Fluconazole (**Table 42**) [84].



110-112

Table 42: MIC values of 1,3,4-oxadiazole derivatives (μg/mL)

Comp.	R	Antibacterial activity				Antifungal activity
		S. aureus	*P. aeruginosa*	*E. coli*	*B. subtilis*	*C. albicans*
110		6	3	3	6	6
111		6	3	3	6	6
112		6	6	6	6	3
Furacin/Fluconazole*	-	12.5	6	12.5	12.5	6*

3. CONCLUSION

1,3,4-oxadiazole is a five membered heterocyclic aromatic ring, exhibited promising antibacterial and antifungal activities against various pathogens. Many scientific groups have synthesized and screened antimicrobial potential of 2,5-disubstituted 1,3,4-oxadiazole derivatives. Reported data revealed that substitution of different moieties at 2nd and 5th position of 1,3,4-oxadiazole ring improved their antibacterial and antifungal potential. In general, SAR analysis displayed the presence of electron withdrawing groups enhanced antibacterial activity, whereas introduction of electron donating groups enhanced antifungal activity. Summarizing, 2,5-disubstituted 1,3,4-oxadiazole is an important class of lead compounds for development of new antimicrobial agents.

Conflict of interest

None declared

4. REFERENCES

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