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MEDICINAL CHEMISTRY RESEARCH

REVIEW ARTICLE

Antimicrobial and antiprotozoal activity of 3-acetyl-2,5-disubstituted-1,3,4-oxadiazolines: a review

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Abstract
In the last 20 years there has been a significant increase in interest in the structure of oxadiazole derivatives, especially 3-acetyl-1,3,4-oxadiazolines. It is known that these derivatives possess: antibacterial, antifungal, antitubercular, antiprotozoal, anticancer and anti-inflammatory activity. Therefore, many medicinal chemists choose 3-acetyl-1,3,4-oxadiazoline scaffold for the synthesis of new potentially active substances with a better effectiveness and less toxicity. This article is a literature review since 2000 presenting new derivatives with proven antimicrobial and antiprotozoal activity, containing in its structure a 3-acetyl-1,3,4-oxadiazoline system.

Keywords 3-acetyl-1,3,4-oxadiazolines · Antimicrobial activity · Antiprotozoal activity

Introduction

The 1,3,4-oxadiazoles constitute an important class of chemical compounds, which possess significant biological activity. The 1,3,4-oxadiazole system is also present in several currently used medicines, e.g. furamizole (Bala et al. 2010), nesapidil (Schlecker and Thieme 1988), raltegravir (Cocohoba and Dong 2008), tiodazosin (Vardan et al. 1983) and zibotentan (James and Growcott 2009) (Fig. 1).

Among 1,3,4-oxadiazoles, the 3-acetyl-1,3,4-oxadiazoline derivatives are currently being synthesized by many medicinal chemists due to the fact that these derivatives exhibit wide spectrum of activities, mainly antibacterial, antifungal, antitubercular, antiprotozoal, anticancer and anti-inflammatory activity (Habibullah et al. 2016). Their mechanism of synthesis is usually based on two step reactions. Firstly, the condensation reaction between appropriate carboxylic acid hydrazide and aldehydes is performed and subsequently obtained hydrazones are subjected to cyclization reaction with acetic anhydride (Desai and Dodiya 2016). The identification and confirmation of the chemical structure of 3-acetyl-1,3,4-oxadiazolines is possible, e.g. by commonly used ^{1}H NMR and ^{13}C NMR spectra analysis. In the ^{1}H NMR spectra we can find characteristic signals for this group of compounds like, singlet signal for CH group, which is present in the 1,3,4-oxadiazoline ring and singlet signal for methyl group present in acetyl substituent. Similarly, in ^{13}C NMR spectra we should seek for carbon signal of CH group and carbon atom of 1,3,4-oxadiazole ring and carbonyl group in acetyl substituent (Popiołek et al. 2019).

This review article gather literature findings since 2000 and is focused on the antimicrobial and antiprotozoal activity of compounds containing 3-acetyl-1,3,4-oxadiazoline scaffold.

Antibacterial activity

Due to the still current problem of bacterial and fungal infections caused by the increasing resistance of microorganisms to commonly used antibiotics and a limited number of drugs effective in combating with them, it is necessary to constantly search for new chemotherapeutic agents that will be more effective in the fight with microorganisms, less toxic and better tolerated by the patients. Many of the currently tested molecules have in their structure a 3-acetyl-1,3,4-oxadiazoline system and microbiological tests confirm great potential of this class of compounds as antimicrobial agents against Gram-positive and Gram-negative bacterial strains.

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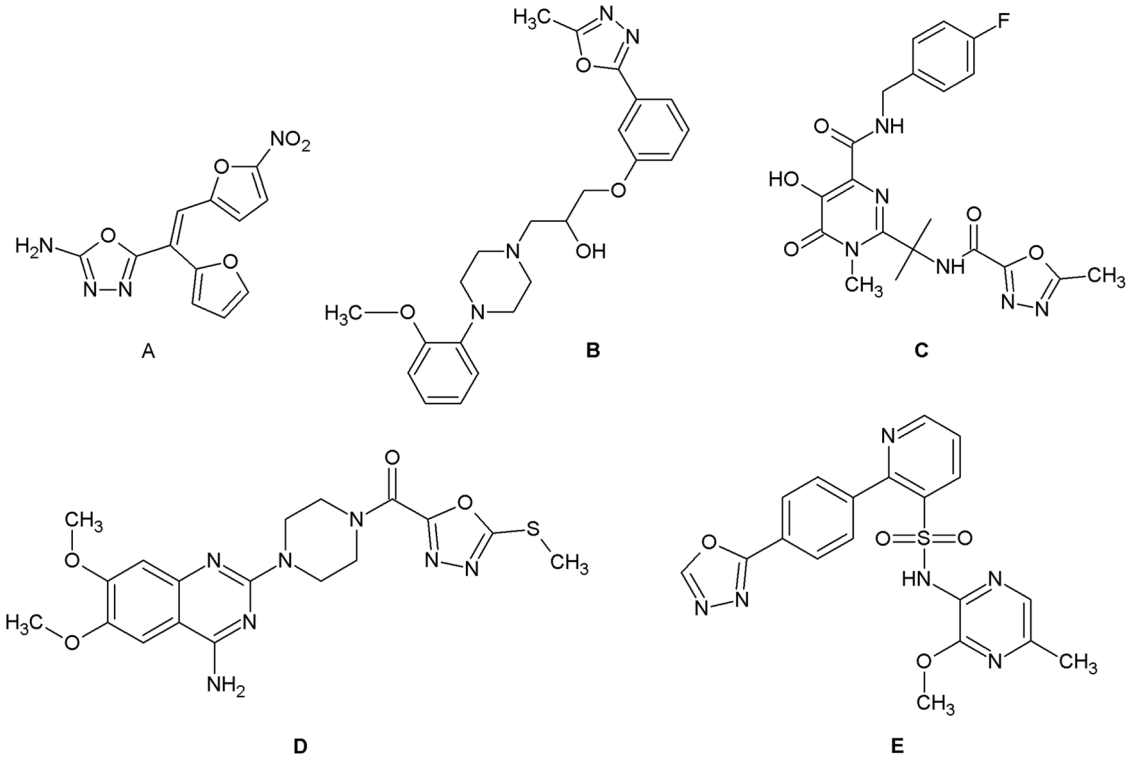

Fig. 1 Chemical structures of furamizole **a**, nesapidil **b**, raltegravir **c**, tiodazosin **d** and zibotentan **e**

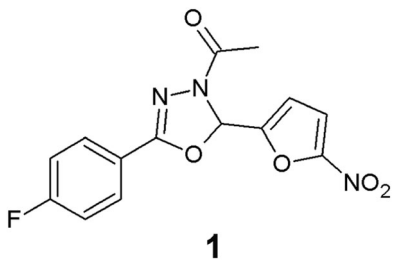

Fig. 2 3-acetyl-2,5-disubstituted-1,3,4-oxadiazoline (**1**) with significant activity against *S. aureus*

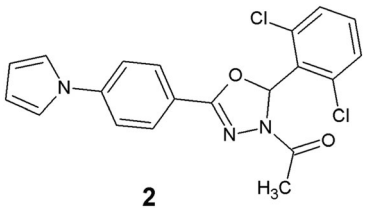

Fig. 3 Novel 3-acetyl-1,3,4-oxadiazoline of 4-(pyrrol-1-yl)benzoic acid hydrazide (**2**) with significant antibacterial activity

According to Zheng et al. (2018) the 1,3,4-oxadiazole derivatives displayed activity against *S. aureus*, which is attributed in part to the presence of a toxophoric –N = C–O– linkage group, which may react with the nucleophilic centers of the microbial cells. The same research group also suggested that 1,3,4-oxadiazole derivatives, which they have synthesized may affect the transcription of biofilm-related genes, such as *sarA*, *icaA*, *spa*, *fnbA* and *fnbB*, which are essential for biofilm formation (Zheng et al. 2018).

Rollas et al. (2002) synthesized a series 4-fluorobenzoic acid derivatives, which were tested against three bacterial strains: *S. aureus*, *E. coli* and *P. aeruginosa*. Ceftriaxone was used as positive control. Tested compounds displayed high activity against *S. aureus* and the most active was **1** with MIC = 8 µg/ml (Fig. 2). Other derivatives showed lower activity but may serve as the basis for future modification in searching for more active substances (Rollas et al. 2002).

Joshi et al. (2008) synthesized new derivatives of 4-(pyrrol-1-yl)benzoic acid hydrazide. Among synthesized 3-acetyl-1,3,4-oxadiazolines compound **2** displayed significant antibacterial activity. Antimicrobial activity assays were performed against three Gram-positive and three Gram-negative bacterial strains. The MIC values of synthesized compound **2** were within the range of 31.25–62.5 µg/ml (Fig. 3). Reference substances: ciprofloxacin and norfloxacin showed MIC values below 5 µg/ml (Joshi et al. 2008).

The series of 1-(2-aryl-5-phenethyl-1,3,4-oxadiazol-3(2*H*)-yl)ethanones were synthesized by cyclization of imines with acetic anhydride (Fuloria et al. 2009). Obtained

derivatives were tested for antibacterial activity against *S. aureus* and *P. aeruginosa*. On the basis of conducted assays it was revealed that obtained derivatives showed similar or better activity than ampicillin, which was used as reference substance. In addition, it was proved that introduction of substituent in *para* position of phenyl ring of 1,3,4-oxadiazole moiety strengthen antimicrobial activity, what was

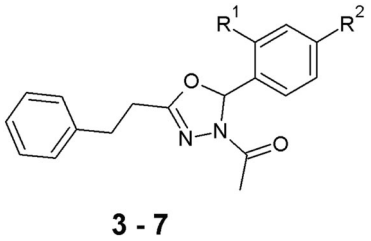

Fig. 4 New 1-(2-aryl-5-phenethyl-1,3,4-oxadiazol-3(2*H*)-yl)ethanones (**3**–**7**) with antibacterial activity

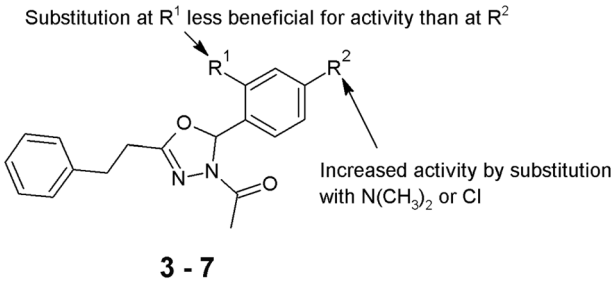

Fig. 5 The influence of substituents of 1,3,4-oxadiazoline derivatives (**3**–**7**) on antibacterial activity

Table 1 Antimicrobial activity-sensitivity testing results of 1-(2-aryl-5-phenethyl-1,3,4-oxadiazol-3(2*H*)-yl)ethanones (**3**–**7**)

Compound number	R^1	R^2	Zone of inhibition in mm	
			S. aureus	*P. aeruginosa*
3	H	$N(CH_3)_2$	24	24
4	H	Cl	25	24
5	OH	OH	23	20
6	H	H	22	23
7	H	OH	19	20
Ampicillin			25	24

especially seen in compounds **3**: ZOI = 24 mm (*S. aureus*) and 24 mm (*P. aeruginosa*) and **4** ZOI = 25 mm (*S. aureus*) and 24 mm (*P. aeruginosa*) (Figs 4 and 5, Table 1) (Fuloria et al. 2009).

Chawla et al. (2010) confirmed that acetyl substituent is crucial to increase antibacterial activity of synthesized 1,3,4-oxadiazole derivatives. Conducted antimicrobial activity research against four species of bacteria revealed that 1,3,4-oxadiazole compounds with acetyl substituent (**8**–**15**) possessed much higher antibacterial activity in comparison with the non-substituted 1,3,4-oxadiazole derivatives (**16**–**23**) (Fig. 6). In addition, it is worth to underline that compounds with methoxy substituent numbered as **10** (zone of inhibition growth—ZOI = 30 mm) and **12** (ZOI = 28 mm) displayed higher activity towards *Staphylococcus aureus* than reference substance—ciprofloxacin (ZOI = 26 mm). Compounds without acetyl substituent were characterized by lower activity: **18** (ZOI = 20 mm) and **20** (ZOI = 18 mm). Similarly, in the case of activity towards *Bacillus subtilis* compounds **10** (ZOI = 27 mm) and **12** (ZOI = 28 mm) showed higher activity than ciprofloxacin (ZOI = 26 mm), whereas compounds **18** (ZOI = 22 mm) and **20** (ZOI = 19 mm) were less active (Fig. 7). Unfortunately, activity against *Escherichia coli* and *Pseudomonas aeruginosa* was weak (ZOI = 9–19 mm) (Table 2) (Chawla et al. 2010).

Dewangan et al. (2010) described the synthesis of 2,5-disubstituted 1,3,4-oxadiazole derivatives, where as a starting material pyridine-4-carbohydrazide was used. Synthesized compounds were evaluated as potent antibacterial agents against *E. coli*. Oxytetracycline was used as reference compound. One derivative among synthesized compounds, derivative with 3-methoxy-4-hydroxyphenyl substituent **24**, showed interesting antibacterial activity at the concentration of 1000 µg/ml (ZOI = 19 mm), whereas control displayed zone of inhibition growth ZOI = 22 mm (Fig. 8) (Dewangan et al. 2010).

New 2-(4-isopropylthiazol-2-yl)-5-substituted-1,3,4-oxadiazoles were tested for antibacterial activity against three Gram-positive bacterial strains (*S. aureus*, *S. faecalis* and *B. subtilis*) and three Gram-negative bacterial strains (*Klebsiella pneumoniae*, *E. coli* and *P. aeruginosa*). Ciprofloxacin and norfloxacin were used as reference substances. Compound **25** (MIC = 8 µg/ml) showed the highest activity against

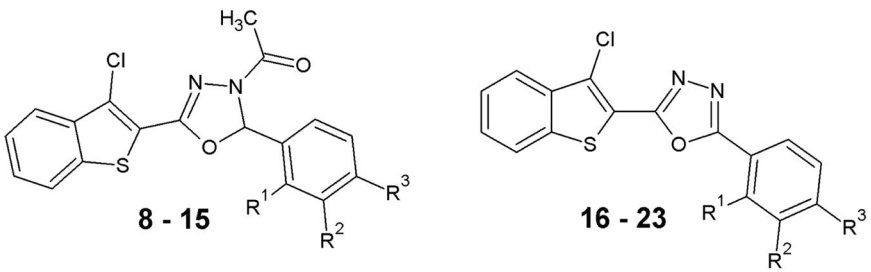

Fig. 6 New oxadiazoles obtained from 3-chloro-1-benzo [b]thiophene-2-carbohydrazine (**8**–**23**) with antibacterial properties

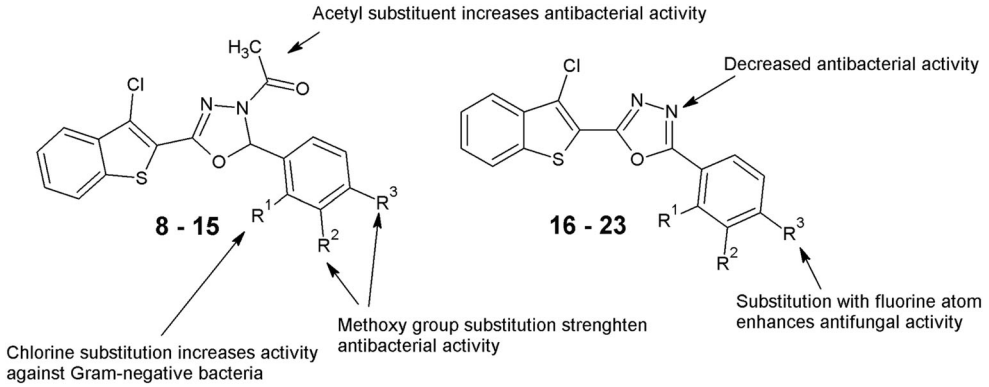

Fig. 7 Influence of substituents of new 1,3,4-oxadiazoline derivatives (**8**–**23**) on antimicrobial activity

Table 2 Antimicrobial activity results of new 1,3,4-oxadiazoline derivatives (**8**–**23**)

Compound number	R^1	R^2	R^3	Zone of inhibition in mm					
				Antibacterial activity				Antifungal activity	
				S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*C. albicans*	*A. niger*
8	H	H	H	14	21	10	17	9	10
9	H	H	F	18	19	12	15	10	11
10	H	OCH_3	H	**30**	**27**	**14**	**18**	9	11
11	Cl	H	H	19	22	11	18	10	11
12	H	H	OCH_3	**28**	**28**	**14**	**14**	10	9
13	H	NO_2	H	14	19	10	15	10	10
14	H	H	Cl	21	23	13	19	11	9
15	H	OCH_3	OH	14	20	10	16	9	10
16	H	H	H	11	12	10	9	11	11
17	H	H	F	10	12	9	11	**12**	**12**
18	H	OCH_3	H	20	21	12	13	11	11
19	Cl	H	H	20	22	16	18	10	11
20	H	H	OCH_3	18	19	11	13	11	10
21	H	NO_2	H	11	13	10	11	10	11
22	H	H	Cl	12	14	9	12	10	10
23	H	OCH_3	OH	10	13	9	11	10	11
Ciprofloxacin				26	26	28	25	–	–
Fluconazole				–	–	–	–	26	25

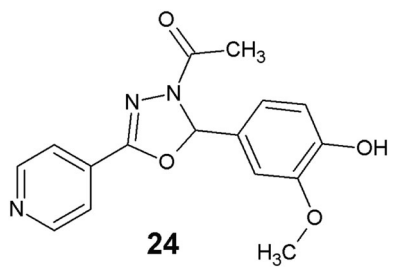

Fig. 8 Novel 3-acetyl-2,5-disubstituted-1,3,4-oxadiazoline (**24**) obtained from pyridine-4-carbohydrazide with activity against *E. coli*

Gram-negative bacterial strains, what may be connected with the substitution of chlorine at position 4 in phenyl ring (Fig. 9). The same compound showed moderate activity against Gram-positive bacteria MIC = 16–62.5 µg/ml. Compounds **26** and **27** with *p*-CH_3 and *p*-OH substituents in the phenyl ring displayed moderate antibacterial activity against Gram-positive bacteria and good activity towards Gram-negative *K. pneumoniae* (MIC = 31.25 µg/ml and 16 µg/ml, respectively) and *E. coli* (MIC = 16 µg/ml) better than against *P. aeruginosa* (MIC = 125 µg/ml and 62.5 µg/ml, respectively) (Fig. 9). Other derivatives tested showed moderate-to-low activity against both Gram-positive and Gram-negative

bacterial strains (MIC = 16–125 µg/ml), whereas ciprofloxacin and norfloxacin displayed high activity (MIC = 1 µg/ml) (Kumar et al. 2010).

Hamdi et al. (2011) synthesized 4-(4-acetyl-5-substituted-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)-2*H*-chromen-2-ones (**28**–**32**) (Fig. 10) with the use of hydroxycoumarin as a starting compound. All of obtained derivatives were tested for potential antimicrobial activity against five bacterial strains: *S. aureus* (CIP 7625), *S. aureus**, *E. coli* (ATCC 25922), *K. pneumoniae* (CIP 104727) and *P. aeruginosa* 27853 (CIP 76110). Antimicrobial activity was assessed on the basis of the mea-

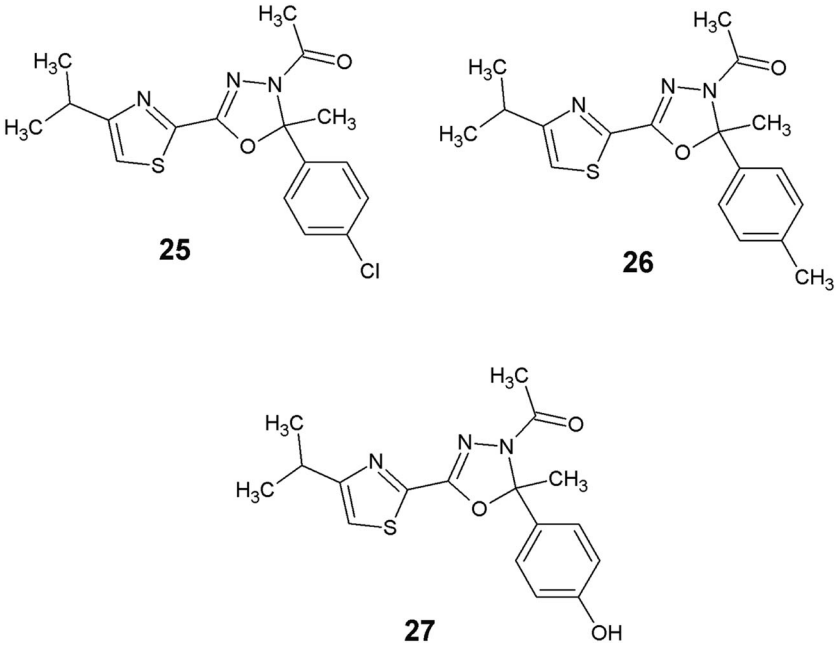

Fig. 9 Novel 3-acetyl-2,5-disubstituted-1,3,4-oxadiazoline derivatives (**25**–**27**) as potential antibacterial agents

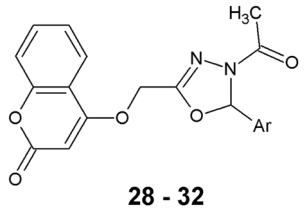

Fig. 10 New 4-hydroxycoumarine derivatives (**28**–**32**) with interesting antibacterial activity

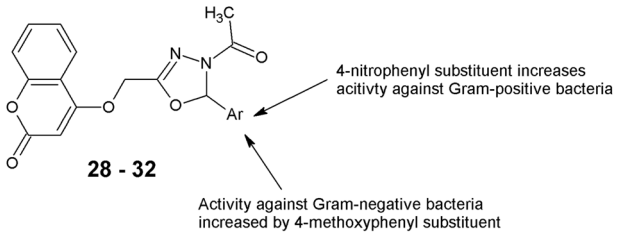

Fig. 11 The impact of substituents on antimicrobial activity of 1,3,4-oxadiazolines (**28**–**32**)

Table 3 Measured zone of inhibition growth of 1,3,4-oxadiazoline derivatives (**28**–**32**)

Compound number	Ar	Inhibition zone (mm)				
		S. aureus (CIP 7625)	*S. aureus*[a]	*E. coli ATCC 25922*	*K. pneumonia (CIP 104727)*	*P. aeruginosa 27853 (CIP 76110)*
28	C_6H_5	34	26	30	25	30
29	4-FC_6H_4	27	28	27	27	26
30	4-$OCH_3C_6H_4$	28	27	35	31	34
31	4-$NO_2C_6H_4$	33	33	32	30	33
32	3,4,5-tri$OCH_3C_6H_2$	34	34	31	28	32
Gentamycin		24–28	24	22–26	21	15–22

[a]Strain obtained from laboratoire de microbiologie, Centre national de Greffe de Moelle Osseuse, Tunis, Tunisia

surement of zones of inhibition growth (ZOI = 26–34 mm) (Table 3). Compounds that contain methoxy or nitro group connected to aromatic ring displayed the highest activity (Fig. 11). Gentamycin was used as reference substance in this research (Hamdi et al. 2011).

El-Emam et al. (2012) synthesized 2-(1-adamantyl)-4-acetyl-5-[5-(4-substituted-phenyl-3-isoxazolyl)]-1,3,4-oxadiazolines, which were tested against *S. aureus*, *B. subtilis*, *Micrococcus luteus* (Gram-positive bacteria), *E. coli* and *P. aeruginosa* (Gram-negative bacteria). Performed antibacterial activity assays showed that only one compound **33** displayed significant antibacterial activity against Gram-positive bacteria (ZOI = 11–12 mm), whereas gentamycin and ampicillin were characterized by the activity in the range of ZOI = 19–26 mm (Fig. 12) (El-Emam et al. 2012).

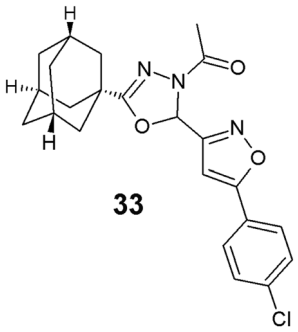

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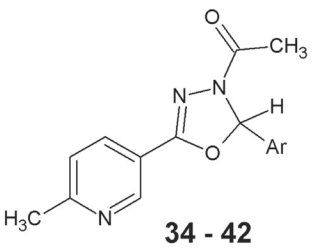
Fig. 12 2-(1-Adamantyl)-4-acetyl-5-[5-(4-chlorophenyl-3-isoxazolyl)]-1,3,4-oxadiazoline (**33**) with antibacterial activity

Shyma et al. (2013) synthesized two series of 1,3,4-oxadiazole derivatives. New 3-acetyl-2-aryl-5-[3-(6-methylpyridinyl)]-2,3-dihydro-1,3,4-oxadiazole (**34**–**42**) and 3-acetyl-2-aryl-2-methyl-5-[3-(6-methylpyridinyl)]-2,3-dihydro-1,3,4-oxadiazole (**43**–**47**) were obtained by four step synthesis (Fig. 13). Newly synthesized compounds were tested for antibacterial activity against: *S. aureus* ATCC 25923, *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853. Results showed that among tested derivatives compounds **40** and **41** were characterized by good activity against all bacterial strains (Fig. 13). Towards *E. coli* they showed following zone of inhibition growth (ZOI) values: 12 and 13 mm, respectively, against *S. aureus* it was for **40**: 9 mm, **41**: 10 mm and for *P. aeruginosa* (**40**: 13 mm, **41**: 13 mm), in concentration of 1 mg/ml similar to reference streptomycin (Fig. 13). Their good activity may be connected with the presence of 2,4-dichlorophenyl **40** and 2-fluoro-3-chlorophenyl **41** substituents in these derivatives. Whereas other compounds showed moderate antibacterial activity against all tested bacteria (Fig. 13) (Shyma et al. 2013).

Mostafa and Kandeel (2014) synthesized 2-oxo-2*H*-chromene-3-carbohydrazide derivatives, which were tested against: *B. subtilis*, *S. aureus*, *E. coli* and *Pseudomonas* spp. Only one derivative **48** among synthesized compounds



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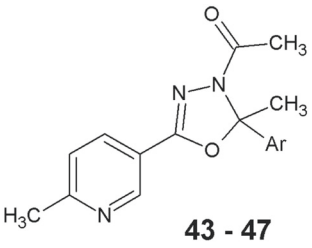

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Fig. 13 New 3-acetyl-1,3,4-oxadiazoline derivatives (**34**–**47**) as potent antimicrobial agents

Compound number	Ar
34	6-metoxynaphthyl
35	4-biphenyl
36	3,4-dihydroxyphenyl
37	2-thiophenyl
38	4-bromophenyl
39	4-chlorophenyl
40	2,4-dichlorophenyl
41	2-fluoro-3-chlorophenyl
42	2,4-dimethoxyphenyl
43	4-nitrophenyl
44	2-bromophenyl
45	3-bromophenyl
46	4-biphenyl
47	4-acetylphenyl

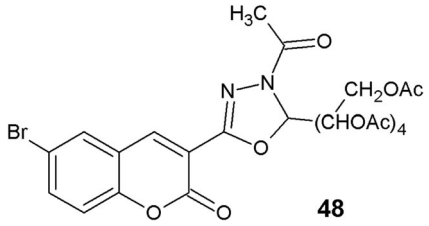


Fig. 14 2-Oxo-2*H*-chromene-3-carbohydrazide derivative (**48**) with antibacterial activity

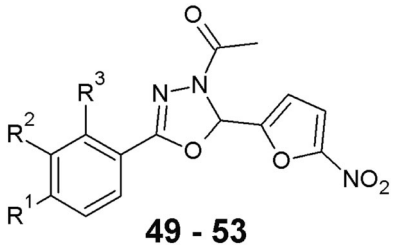


Fig. 15 Novel 3-acetyl-5-(substituted-phenyl)-2-(5-nitrofuran-2-yl)-2,3-dihydro-1,3,4-oxadiazolines (**49**–**53**) with interesting antibacterial activity

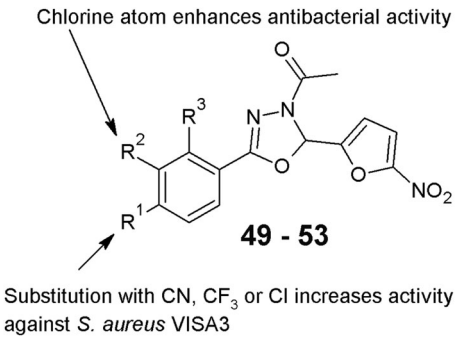


Fig. 16 Structure-activity relationship of 1,3,4-oxadiazoline derivatives (**49**–**53**)

showed good activity towards tested strains (MIC = 25–50 μg/ml). Ampicillin used as reference substance showed activity in the range of MIC = 100–250 μg/ml (Fig. 14) (Mostafa and Kandeel 2014).

Crucial threat to life and health of patients is caused by *S. aureus* strains resistant to methicillin (MRSA). They are thought as the most dangerous pathogens that cause severe hospital infections. Methicillin resistant *S. aureus* is not only resistant to methicillin but also against all β-lactam antibiotics (penicillin, cephalosporins and carbapenems), as well as aminoglycosides, chloramphenicol, clindamycin, fluoroquinolones and macrolides (Stapleton and Taylor 2002). Due to this the most important thing is to discover new molecules with activity against resistant bacterial strains, which are responsible for high morbidity and mortality (Velázquez-Meza 2005).

Zorzi et al. (2014) synthesized two series of 5-nitrofuran derivatives with 3-acetyl-1,3,4-oxadiazole moiety. Their

Table 4 Antibacterial activity of 3-acetyl-5-(substituted-phenyl)-2-(5-nitrofuran-2-yl)-2,3-dihydro-1,3,4-oxadiazole derivatives (**49**–**53**)

Compound number	R^1	R^2	R^3	*S. aureus* VISA3 MIC (μM)
49	Br	H	H	8.0–16.0
50	CN	H	H	4.0–8.0
51	Cl	H	H	4.0–8.0
52	Cl	Cl	H	4.0–8.0
53	CF_3	H	H	4.0–8.0
Nifuroxazide				8.0–16.0
Vancomycin				2

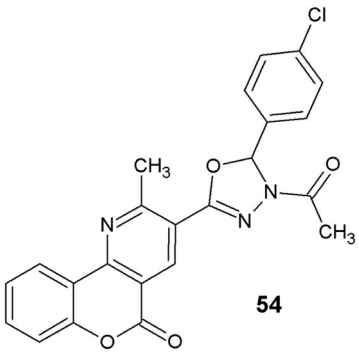


Fig. 17 New 1,3,4-oxadiazoline derivative (**54**) with promising activity against *S. aureus*

antibacterial activity was established on the basis of MIC values against following bacterial strains: *K. pneumoniae*, *Enterococcus faecalis*, *Enterobacter cloacae*, *E. coli*, *Serratia marcescens* and *S. aureus*. Obtained compounds were active mainly against *S. aureus* and the highest activity showed compound **50** towards this bacterium (MIC = 2.0–8.0 μM) (Fig. 15). The most active compounds were also tested towards *S. aureus* VISA3 strain, which is resistant to many antibacterial agents. Four among five derivatives tested showed two times higher activity (MIC = 4.0–8.0 μM) than nifuroxazide (MIC = 8.0–16.0 μM), but lower than vancomycin used as reference compound (MIC = 2.0 μM) (Fig. 16, Table 4) (Zorzi et al. 2014).

New 2,5-disubstituted 1,3,4-oxadiazole derivatives were tested for antibacterial activity against following bacterial strains *Staphylococcus aureus* and *Escherichia coli* with the use of streptomycin as reference substance. Compound **54** possessed good antibacterial activity (MIC = 5 μg/ml, ZOI = 15.9 mm) against *S. aureus* comparable with streptomycin (MIC = 3 μg/ml, ZOI = 17.9 mm). Its activity, as authors suggest, may be connected with the substitution of chlorine atom at *para* position of phenyl ring (Fig. 17) (Jadhav et al. 2016).

Lole et al. (2016) synthesized novel 1,3,4-oxadiazole derivatives and evaluated their antibacterial activity against *E. coli* and *S. aureus*. Streptomycin, as in previous research,

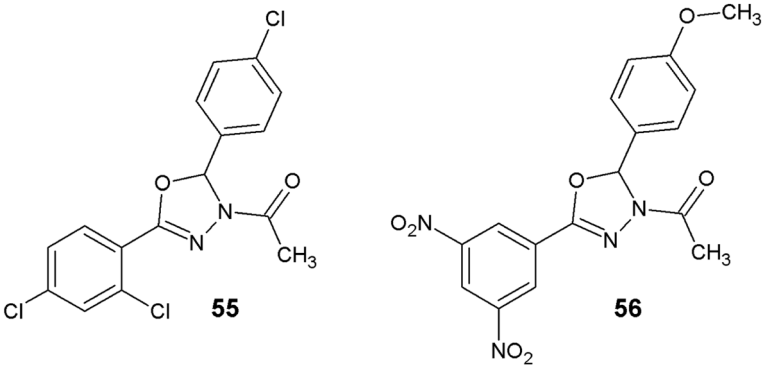


Fig. 18 Novel 3-acetyl-1,3,4-oxadiazolines (**55**, **56**) with antibacterial activity

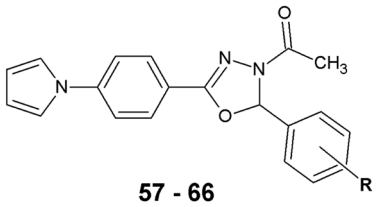


Fig. 19 Novel 3-acetyl-1,3,4-oxadiazolines (**57**–**66**) with antibacterial activity

was used as reference compound. The compounds **55** and **56** showed moderate activity against *E. coli* (ZOI = 12 mm, streptomycin ZOI = 15 mm). Compound **56** displayed good activity against *S. aureus* (ZOI = 12 mm), while streptomycin showed zone of inhibition growth (ZOI = 13 mm). Activity of these compounds was enhanced due to the substitution of electron withdrawing groups NO_2 and chlorine atom at *para* position in the phenyl ring (Fig. 18) (Lole et al. 2016).

Joshi et al. (2017) published interesting research concerning 4-(4-pyrrol-1-yl/2,5-dimethyl-4-pyrrol-1-yl)benzoic acid hydrazide derivatives. Synthesized compounds (**57**–**66**) were tested towards: *S. aureus* ATCC 11632, *B. subtilis* ATCC 60511, *E. coli* ATCC 10536 and *Vibrio cholerae*. All of obtained compounds displayed good activity against tested bacteria and one of them showed activity better than positive controls (ciprofloxacin and norfloxacin). Performed structure-activity relationship analysis proved that compounds with oxadiazole scaffold were more active than starting Schiff bases (Figs 19 and 20, Table 5) (Joshi et al. 2017).

Antitubercular activity

Tuberculosis is a deadly infectious disease caused mainly by *Mycobacterium tuberculosis* (MTB) as well as *Mycobacterium bovis* and *Mycobacterium africanum* (Pasqualoto et al. 2004). According to World Health Organization (WHO) report from 2018 tuberculosis is on the list of ten most frequent causes of death throughout the world. In 2017 10 millions of new evidences of tuberculosis were registered (5.8 million men, 3.2 million women, 1 million children) and 1.6 million of people were dead as a result of tuberculosis (WHO 2018).

The pandemic of AIDS has significant impact on world problem of tuberculosis. One-third of the increase of incidences of tuberculosis in the last 5 years can be attributed to HIV co-infection. Additional factor that is responsible for the increase of morbidity on tuberculosis and for the increase of mortality is the appearance of new strains of *M. tuberculosis* that are resistant to some or all of current medicines against tuberculosis, which are named as multi-drug resistant tuberculosis (MDR-TB) (Pasqualoto et al. 2004).

As a result of increased resistance, new classes of antimicrobial agents with new mechanism of action are needed to combat with infections.

Joshi et al. (2008) synthesized a series of (4-pyrrol-1-yl) benzoic hydrazide derivatives, which were converted to 5-substituted-2-thiol-1,3,4-oxadiazoles. Activity of synthesized compounds was established on the basis of MIC values against *M. tuberculosis* H37Rv with the use of microdilution technique. Antitubercular activity assays showed that compounds **2** and **67** showed significant activity towards *M. tuberculosis* H37Rv (Figs 3 and 21). Isoniazid (INH) was used as reference substance (Joshi et al. 2008).

Baquero et al. (2011) in research article presented two oxadiazole derivatives, which showed antitubercular activity (**68**, **69**) (Fig. 22). MIC values towards *M. tuberculosis* H37Rv for compound **68** was 6.09 µM and for compound **69** it was 81.1 µM, whereas for INH it was 0.438 µM and for rifampicin (RFP): 0.608 µM (Fig. 22) (Baquero et al. 2011).

The series of 1,3,4-oxadiazole derivatives of INH were synthesized and tested for their antimycobacterial activity (Bhat 2014). One of synthesized derivatives **70** displayed significant growth inhibition against *Mycobacterium* strains: *Mycobacterium intercellulare* (ATCC 35734), *Mycobacterium xenopi* (ATCC 14470), *Mycobacterium cheleneo*

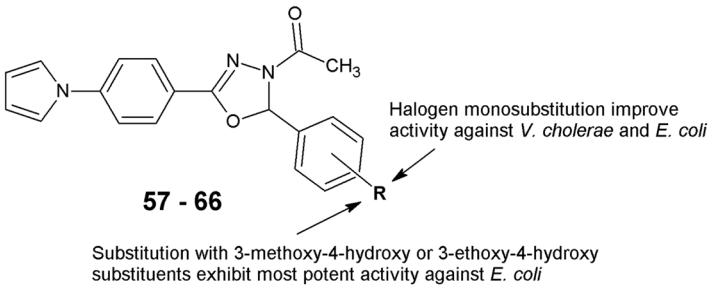


Fig. 20 1,3,4-Oxadiazoline derivatives (**57–66**): influence of substituents on antibacterial activity

Table 5 Results of antibacterial activity screening of synthesized 3-acetyl-1,3,4-oxadiazolines (**57–66**)

Compound number	*R*	MIC (μg/ml)			
		Vibrio cholerae	*Escherichia coli*	*Staphylococcus aureus*	*Bacillus subtilis*
57	4-Cl	0.8	0.8	25	12.5
58	4-Br	0.8	1.6	12.5	50
59	4-F	0.4	0.8	12.5	25
60	2,4-di-Cl	1.6	1.6	25	50
61	2,3-di-Cl	6.25	3.125	50	50
62	2-OH	6.25	6.25	12.5	50
63	3-OH	6.25	12.5	12.5	50
64	3,4-di-OCH_3	1.6	0.8	12.5	25
65	3-OCH_3-4-OH	1.6	0.4	12.5	50
66	3-OC_2H_5-4-OH	0.8	0.4	6.25	25
Ciprofloxacin		1	2	2	2
Norfloxacin		1	12	2	2

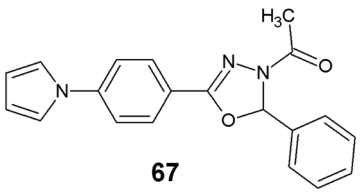


Fig. 21 Novel derivative of 4-(pyrrol-1-yl)benzoic acid hydrazide (**67**) with antitubercular activity

(ATCC 35751) and *Mycobacterium smegmatis* (ATCC 35797) with MIC = 6.0 μg/ml, respectively. Whereas MIC values for INH against all tested strains were 12.5 μg/ml. The authors point out that good activity of this compound makes it a good candidate for the development of a novel antitubercular agent (Fig. 23) (Bhat 2014).

Joshi et al. (2017) synthesized 4-(4-pyrrol-1-yl/2,5-dimethyl-4-pyrrol-1-yl)benzoic acid hydrazide analogues with antitubercular activity. Synthesized compounds had moderate or good activity against MTB as well as MDR-TB. INH, RFP and ethambutol (EB) were used as reference substances. Compound **66** appeared to be strong inhibitor (MIC = 0.2 μg/ml) similar to INH (Fig. 19). Antitubercular activity screening was performed against MDR-TB strain, which is resistant to three medicines: INH, RFP and EB. Most of synthesized compounds showed good activity towards MDR-TB (MIC in the range of 0.4–50 μg/ml) (Table 6). Good activity towards tuberculosis may be connected with the presence of pharmacologically active 1,3,4-oxadiazole scaffold connected to pyrrole ring. The best activity, equal or better than reference substances, showed 1,3,4-oxadiazoles with 3-ethoxy-4-hydroxyphenyl **66**, 2-hydroxyphenyl **62**, 4-bromophenyl **58** and 4-fluorophenyl **59** substituents. All of synthesized compounds were characterized with low toxicity according to MTT cytotoxicity assay (Joshi et al. 2017).

Ghaisas and Patel (2018) synthesized a series of 1,3,4-oxadiazoline derivatives. All of obtained compounds were screened for in vitro antimycobacterial activity against MTB H37Rv. Compound **71** at the concentration of 50 μM showed 92% of inhibition against *M. tuberculosis*, whereas compound **72** showed 62% of inhibition at the same concentration (Ghaisas and Patel 2018) (Fig. 24).

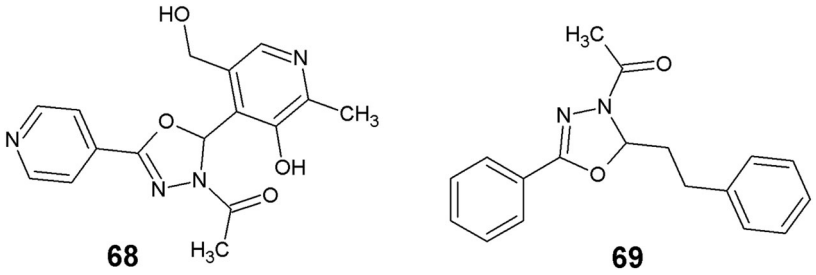


Fig. 22 Novel 3-acetyl-1,3,4-oxadiazolines (**68**, **69**) with antitubercular activity

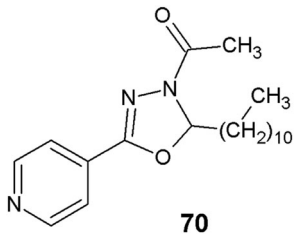


Fig. 23 *N*-acetyl-4-(5-undecyl-1,3,4-oxadiazol-2-yl)pyridine derivative (**70**) with significant activity against *Mycobacterium* strains

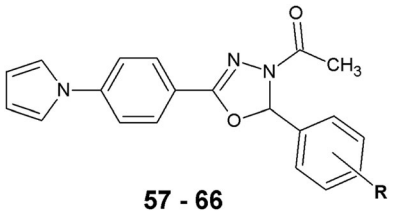
Antiprotozoal activity

Chagas disease is caused by *Trypanosoma cruzi*, which is a crucial problem of public health in endemic geographic regions of Middle and South America. This disease touches about 8–10 millions of people around the world yearly. The possibility of curability of Chagas disease is limited by the toxicity of available medicines, the resistant of parasites and weak activity of medicines during chronic stage of disease. Clinically the pathogenesis of this disease can be divided in three stages: short acute phase, long occult phase and chronic phase at about 10–30% of patients (Astelbauer and Walochnik 2011). Currently in the treatment two medicines are used: benznidazole (BZN) and nifurtimox (NFX), which are effective only in acute and the beginning of the disease (WHO 2002). According to the literature NFX mechanism of action is not fully elucidated, but it is suggested that it is probably connected with the reduction of the nitro group and formation of free toxic radical (Palace-Berl et al. 2013).

Searching for biologically active molecules and effective against Chagas disease is the main topic of many research groups. The series of 15 new 3-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazoles (**73**–**87**) were synthesized in four step synthesis (Fig. 25). All of obtained compounds were tested for its potential activity in the treatment of infections caused by *Trypanosoma cruzi*. The values of IC_{50} of tested derivatives (**73**–**87**) were compared with BZN, which was used as reference compound. The most active compound was the derivative **87** with 4-CO_2CH_3-phenyl substituent $IC_{50} = 7.91$ µM (Table 7). This compound was nearly three times more active than reference substance $IC_{50} = 20.84$ µM (Table 7). Activity decreased with the substitution of following substituents in order: $CO_2CH_3 > CN > NO_2 > C_3H_7$. Only one compound was less active than BZN (Ishii et al. 2011).

The same research group two years later synthesized a series of 5-nitro-2-substituted-furan derivatives. Firstly, hydrazide–hydrazones were synthesized and after that were subjected to cyclization reaction to obtain 3-acetyl-1,3,4-oxadiazolines. Next, all of synthesized compounds were tested in the assay to inhibit the growth of epimastigote stadium of *T. cruzi* (Y strain). The most active was compound with butyl substituent (**88**) $IC_{50} = 8.27$ µM, whereas the activity for NFX was $IC_{50} = 3.59$ µM, and for BZN it was $IC_{50} = 22.69$ µM (Fig. 26). The lower activity showed

Table 6 Antimycobacterial activity of pyrrole derivatives (**57**–**66**)



57 - 66

Compound number	*R*	MIC (µg/ml)	
		M. tuberculosis $H_{37}Rv$	MDR-TB
57	4-Cl	1.6	3.125
58	4-Br	0.4	3.125
59	4-F	0.4	0.4
60	2,4-di-Cl	3.125	6.25
61	2,3-di-Cl	3.125	12.50
62	2-OH	0.4	1.6
63	3-OH	1.6	3.125
64	3,4-di-OCH_3	0.4	3.125
65	3-OCH_3-4-OH	0.8	12.5
66	3-OC_2H_5-4-OH	**0.2**	**0.5**
Isoniazid		0.2	12.5
Rifampicin		0.4	25
Ethambutol		0.5	12.5

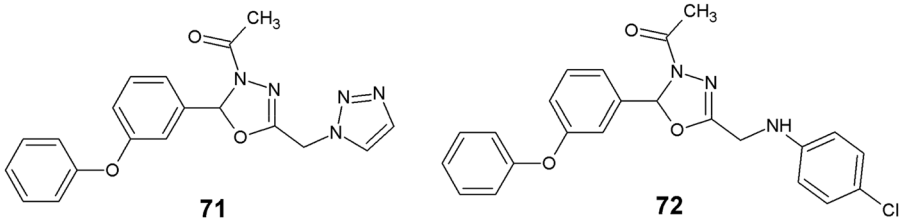


Fig. 24 Novel 3-acetyl-1,3,4-oxadiazolines (**71**, **72**) with antitubercular activity

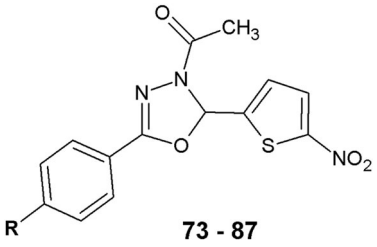


Fig. 25 New derivatives of 3-acetyl-1,3,4-oxadiazole (**73**–**87**) with antiprotozoal activity

compounds with OCH_3 (**89**), Br (**90**), CH_3 (**91**) substituents $IC_{50} = 9.26–9.84\ \mu M$ (Fig. 26). The cytotoxicity assays revealed that obtained compounds were safe and not toxic (Palace-Berl et al. 2013).

Antifungal activity

The incidence of sepsis especially connected with mycosis may also be crucial problem for the health care system. The number of fungal infections increased more than 200% during last two decades and constitute third most frequent of blood infections (Martin et al. 2003). The *Candida* spp. is responsible for 75% of all hospital infections caused by fungi. The currently used medicines include polien (amphotericin B), azoles (fluconazole and itraconazole) and echinocandins. These medicines may cause serious undesirable side effects. As a result of this searching for new chemotherapeutic agents to treat mycosis is very important (Cowen 2008).

Chitin is the integral part of cell wall of fungi that is why the inhibition of the chitin synthesis is the ideal point of handle to design new antifungal agents (Lenardon et al. 2010). Based on the literature findings the 1,3,4-oxadiazoline derivatives may act as chitin biosynthesis inhibitors (Ke et al. 2009).

Rollas et al. (2002) synthesized a series of 3-acetyl-2,5-disubstituted 1,3,4-oxadiazoles obtained from 4-fluorobenzoic acid derivatives in two-step synthesis. Then, their activity was determined on the basis of MIC values against *C. albicans*. The most active compound **1** (Fig. 2) showed MIC value equals 8 µg/ml, whereas miconazole MIC = 0.05 µg/ml (Rollas et al. 2002).

Table 7 In vitro antiprotozoal activity of the series of 3-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazole derivatives (**73**–**87**)

Compound number	*R*	IC_{50} (µM)
73	H	10.24
74	Cl	10.85
75	Br	10.16
76	I	12.10
77	CF_3	14.25
78	CH_3	11.74
79	C_2H_5	10.74
80	C_3H_7	9.90
81	OCH_3	10.67
82	OC_2H_5	26.64
83	OC_3H_7	12.20
84	OC_4H_9	11.47
85	NO_2	9.85
86	CN	8.19
87	CO_2CH_3	7.91
Benznidazole	–	20.84

Fuloria et al. (2009) synthesized a series of 1-(2-aryl-5-phenethyl-1,3,4-oxadiazol-3(2*H*)-yl)ethanones. All of synthesized compounds (**3**–**7**) (Fig. 4) showed antifungal activity comparable to fluconazole used as reference substance (ZOI = 12–16 mm) (Table 8). The most significant activity was displayed by compounds that at *ortho* position of phenyl ring possessed dimethylamine or hydroxyl group. Their activity was only slightly lower than activity of fluconazole against *C. albicans* and *Aspergillus flavus* (Fuloria et al. 2009).

Ke et al. (2009) synthesized new 3-acetyl-1,3,4-oxadiazolines with potential antifungal activity. The bioactivity tests revealed that all of synthesized derivatives inhibited the synthesis of chitin at the level of 250 µM. Compounds **92**, **93** and **94** showed significant inhibition activity of enzymes: 91, 69 and 68% of inhibition, respectively, at a concentration of 250 µM (Fig. 27). Among synthesized derivatives compound with *o*-chlorophenyl substituent showed the highest inhibitory potential (91%). It may be caused by the introduction of halogen atoms in the phenyl ring what increases lipophilicity. Botherless, change of the position of halogen atoms in the same ring (compounds **92**

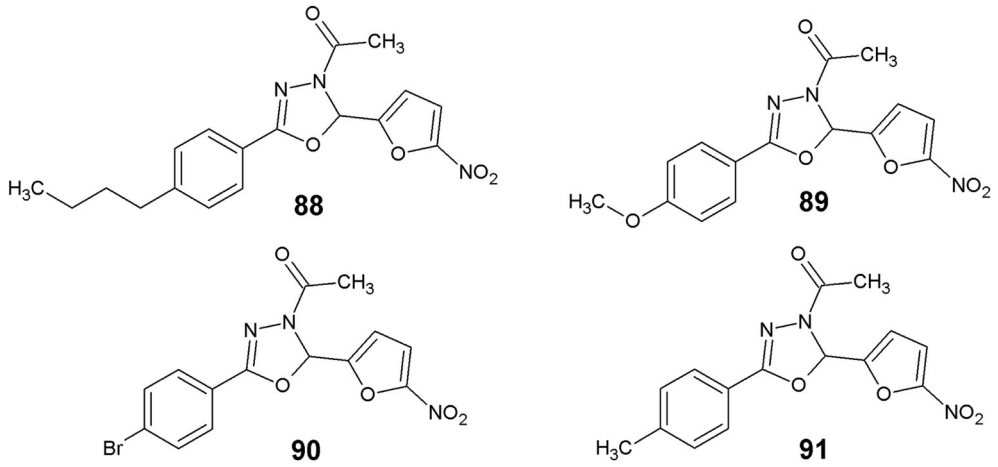
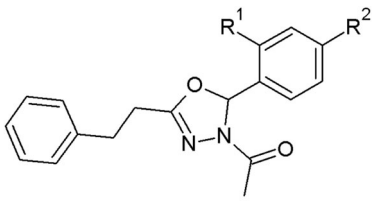


Fig. 26 Novel 3-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazoles (**88**–**91**) with antiprotozoal properties

Table 8 Antifungal activity results of novel 3-acetyl-1,3,4-oxadiazolines (**3**–**7**)



3 - 7

Compound number	R^1	R^2	Zone of inhibition in mm	
			C. albicans	*A. flavus*
3	H	$N(CH_3)_2$	16	15
4	H	Cl	15	13
5	OH	OH	13	12
6	H	H	16	13
7	H	OH	16	15
Fluconazole			17	16

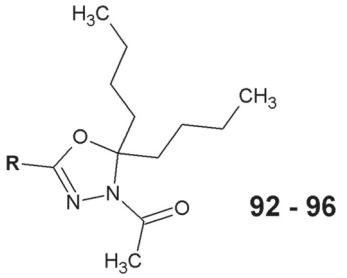
and **93**) dramatically change the activity of inhibition, what may suggest that the substituent in *ortho* position may increase the activity. From the other side, substitution with methyl groups connected to phenyl ring in compound **94** is more beneficial to the inhibition activity than substitution by alkyl or alkoxyl fragment (Fig. 27). Analogues with naphthalene and furan ring (compounds **95** and **96**) showed moderate inhibition activity (Fig. 27). Nikkomycin and diflubenzuron were used as reference substances in this research (Ke et al. 2009).

Chawla et al. (2010) synthesized and compared antifungal activity of oxadiazoles with acetyl substituent (3-acetyl-5-(3-chloro-1-benzo[b]thiophen-2-yl)-2-substituted-phenyl-2,3-dihydro-1,3,4-oxadiazoles) (**8**–**15**) and oxadiazoles without this substituent (2-(3-chloro-1-benzo[b]thiophen-2-yl)-5-substituted-phenyl-1,3,4-oxadiazoles) (**16**–**23**). Antifungal activity screening was performed against: *C. albicans* and *A. niger*. Both series of compounds displayed comparable activity (ZOI = 9–11 mm). Fluconazole used as reference compound showed better activity (ZOI = 25–26 mm). The most active was the derivative with 4-fluorophenyl substituent **17** (Fig. 6, Table 2) (Chawla et al. 2010).

Novel 2-substituted-5-(isopropylthiazole)clubbed-1,3,4-oxadiazoles were synthesized by Kumar et al. (2010) and tested for antifungal activity against three species of fungi: *Saccharomyces cerevisiae* ATCC 9763, *C. tropicalis* ATCC 1369 and *Aspergillus niger* ATCC 6275. One of obtained derivatives with 4-methoxyphenyl substituent (**97**) showed interesting activity (MIC = 4–8 µg/ml) (Fig. 28) Fluconazole, used as reference substance, displayed activity below ≤1 µg/ml (Kumar et al. 2010).

Yang et al. (2011) conducted a series of reactions and obtained 15 bis-heterocyclic compounds containing pyrazole and 1,3,4-oxadiazoline scaffold. Antifungal activity was assessed against five species of fungi: *Fusarium oxysporum, Verticillium dahliae, Rhizoctonia solani, Pychium aphanidermatum, Alternaria solani* and *Sclerotinia sclerotiorum*. All bis-heterocyclic compounds showed good antifungal activity with inhibition growth of fungi from 45.6 to 97.5%. The most active were compounds **98** and **99**, which showed very strong inhibitory activity (>85.5%) towards six strains of fungi (Fig. 29) (Yang et al. 2011).

Kocyigit-Kaymakcıoglu et al. (2012) obtained a series of 3-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazole derivatives starting from 4-fluorobenzoic acid hydrazide. All of synthesized compounds were tested for antifungal activity on the basis of established MIC values against eight species of fungi from *Candida* spp. genus. Ketoconazole was used as reference substance. The most active compound



Compound number	R
92	*o*-Cl-C_6H_4
93	*p*-Cl-C_6H_4
94	3,5-Me-C_6H_3
95	naphthalen-2-yl
96	furan-2-yl

Fig. 27 The structures of new 3-acetyl-1,3,4-oxadiazolines (**92**–**96**) with antifungal activity

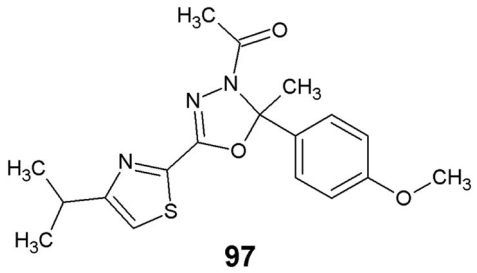


Fig. 28 Novel 2-substituted-5-(isopropylthiazole)clubbed-1,3,4-oxadiazole (**97**) with antifungal activity

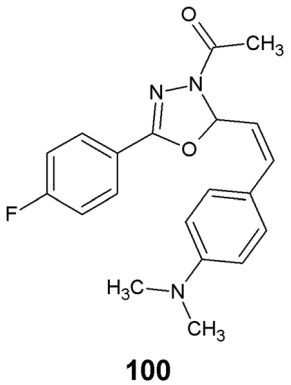
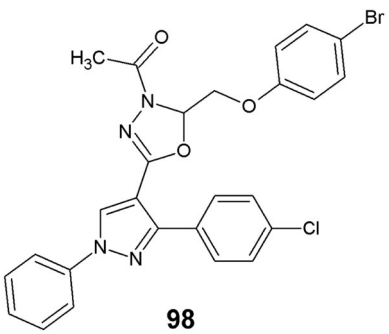


Fig. 30 New 3-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazole (**100**) derivative with antifungal properties



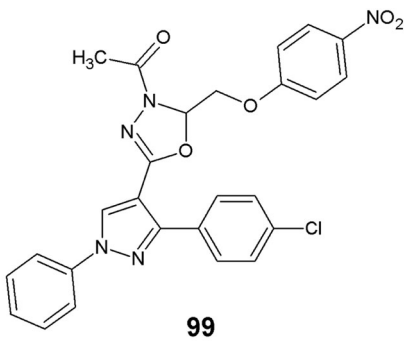


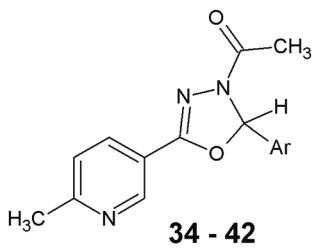
Fig. 29 New bis-heterocyclic compounds (**98**, **99**) with antifungal activity

with moderate inhibitory activity (MIC = 125 µg/ml) against *Candida tropicalis* NRRL Y-12968 and *Candida krusei* NRRL Y-7179 was 3-acetyl-5-(4-fluorophenyl)-2-[2-(4-(dimethylamino)phenyl)ethenyl]-2,3-dihydro-1,3,4-oxadiazole (**100**) (Fig. 30). Ketoconazole showed two times better activity against these fungi (MIC = 62.5 µg/ml). In addition, synthesized compounds were also tested for anti-inflammatory, cytotoxic and antioxidant activity (Koçyiğit-Kaymakçıoğlu et al. 2012).

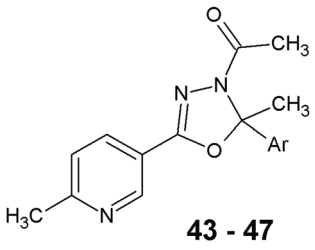
Shyma et al. (2013) synthesized two series of compounds: 3-acetyl-2-aryl-2*H*-5-[3-(6-methylpyridinyl)]-2,3-dihydro-1,3,4-oxadiazoles (**34**–**42**) and 3-acetyl-2-aryl-2-methyl-5-[3-(6-methylpyridinyl)]-2,3-dihydro-1,3,4-oxadiazoles (**43**–**47**) (Fig. 13). Authors in this article analyzed how different substituents influence the antifungal activity. Antifungal activity was assessed against three species of fungi: *A. flavus*, *Chrysosporium keratinophilum* and *C. albicans*. Conducted assays showed that among synthesized derivatives compound **40** showed the best activity against all tested strains (Table 9) (Shyma et al. 2013).

Zorzi et al. (2014) synthesized novel series of 3-acetyl-1,3,4-oxadiazolines, which contained 5-nitrofuran system as substituent and evaluated their activity against *Candida* spp. Two among synthesized compounds **101** and **102** showed antifungal activity higher (MIC = 8–16 µg/ml) than commonly used itraconazole (MIC ≤ 20 µg/ml) (Fig. 31). Authors also suggested that the presence of furan ring increases the antifungal activity of synthesized derivatives (Zorzi et al. 2014).

Table 9 Antifungal activity of novel 1,3,4-oxadiazolines bearing 6-methylpyridine moiety



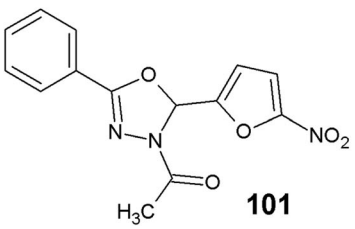
34 - 42



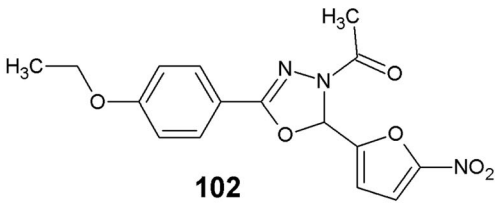
43 - 47

Compound number	Ar	Zone of inhibition growth in mm					
		A. flavus		*C. keratinophilum*		*C. albicans*	
Concentration mg/ml		1.0	0.5	1.0	0.5	1.0	0.5
38	4-Br-C_6H_4	7	5	6	4	4	3
40	2,4-diCl-C_6H_3	10	8	9	7	11	9
41	2-F-3-Cl-C_6H_3	9	7	8	7	6	4
44	2-Br-C_6H_4	10	7	6	4	6	4
45	3-Br-C_6H_4	9	7	8	7	6	4
Fluconazole		13	10	17	15	22	20

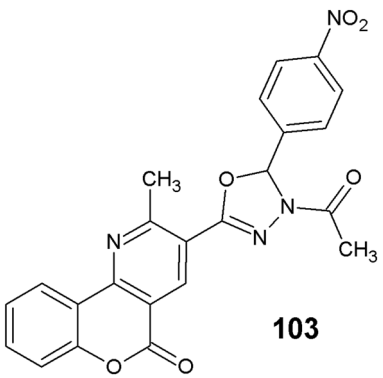
Fig. 31 Novel series of 3-acetyl-1,3,4-oxadiazolines (**101**, **102**) with antifungal activity



101



102



103

Fig. 32 2,5-Disubstituted 1,3,4-oxadiazole derivative (**103**) with activity against *C. albicans* (MTCC 277) and *A. niger* (MCIM 545)

Novel 2,5-disubstituted 1,3,4-oxadiazoline derivatives of chromen[4,3-b]pyridine were synthesized by Jadhav et al. (2016) and tested for antifungal activity against two species of fungi: *C. albicans* (MTCC 277) and *A. niger* (MCIM 545). One of the obtained derivatives with 4-NO_2-phenyl substituent **103** showed interesting activity (MIC = 5 µg/ml, ZOI = 14.4 mm). Griseofulvin used as reference substance displayed similar activity (MIC = 3 µg/ml, ZOI = 16.8 mm) (Fig. 32) (Jadhav et al. 2016).

Ghaisas and Patel (2018) synthesized novel series of 1-(2-(3-phenoxyphenyl)-5-((substitutedaminoaryl)methyl)-1,3,4-oxadiazol-3(2*H*)-yl)ethanone and evaluated their activity against: *C. albicans* (MTCC 227), *A. niger* (MTCC 282) and *A. clavatus* (MTCC 1323). Two among synthesized compounds **104** and **105** showed antifungal activity higher (MIC = 250 µg/ml) than commonly used griseofulvin (MIC = 500 µg/ml) (Fig. 33) (Ghaisas and Patel 2018).

Summary

In summary, this article presents a literature review of 3-acetyl-1,3,4-oxadiazoline derivatives with antibacterial, antitubercular, antifungal and antiprotozoal properties. In general, the antimicrobial activity seemed to be more dependent on the nature of the substituents rather the basic skeleton of 1,3,4-oxadiazoline. Within the 1,3,4-oxadiazoline

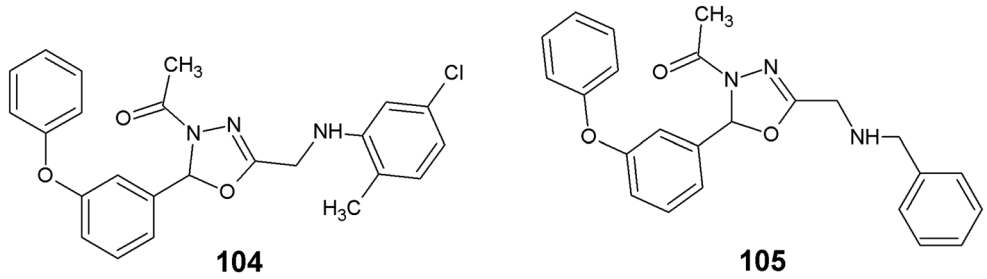


Fig. 33 New 3-acetyl-2,5-disubstituted-1,3,4-oxadiazolines (**104**, **105**) with antifungal activity

series described, it can be concluded that the substitution with acetyl group at the position 3 of the 1,3,4-oxadiazole has great influence on the antimicrobial activity. Whereas substitution at position 2 and/or 5 of various pharmacophores may give rise to the novel molecules with enhanced antimicrobial properties. Based on the collected literature, it can be stated that 3-acetyl-1,3,4-oxadiazoline system has a significant biological activity and shows great potential for the synthesis of new molecules with a broad spectrum of activity, and at the same time, more effective and less toxic.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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