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1, 3, 4-Oxadiazole as antimicrobial agents: An overview

Shivi Bhatia and Monika Gupta*

ASBASJSM College of Pharmacy, Bela, Punjab, India

ABSTRACT

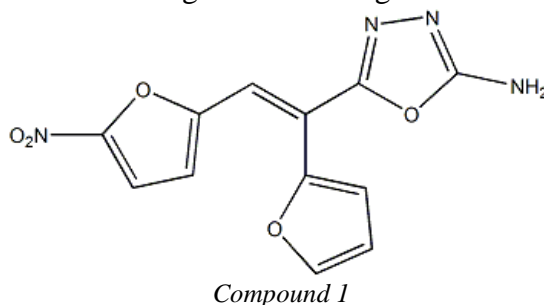
Oxadiazole derivatives have been extensively studied in the past few decades. It is a five membered heterocyclic ring that exist in four isomeric forms. Out of its four isomers 1, 3, 4-oxadiazole exhibited a wide range of biological activities which includes antibacterial, antitubercular, vasodialatory, antifungal, cytotoxic, antiinflammatory, analgesic, hypolipidemic, anticancer and ulcerogenic activities. The present review deals with the various chemical aspects of 1,3,4-oxadiazoles. It includes the a rigorous literature survey on method of preparation and physicochemical properties of the said moiety. The methods of preparation discussed in this review have an extra edge over the conventional method of the synthesis like small reaction time, higher yield and cleaner reactions. The 1,3,4-oxadiazole have shown significant antimicrobial activity against a wide variety of microorganisms like fungi, Gram +ve and Gram -ve bacteria. Keeping this in mind the special emphasis is given on recently reported oxadiazoles possessing antimicrobial activity.

Keywords: Oxadiazole, Antimicrobial activity, Acid hydrazides.

INTRODUCTION

Resistance to number of antimicrobial agents among a variety of clinically significant species of bacteria is becoming increasingly important global problem [1]. There are various problems arising with the use of antimicrobials such as local tissue irritation, interference with wound healing process, hypersensitivity reactions, systemic toxicity, narrow antimicrobial spectrum, emergence of resistance [2]. So the increasing clinical importance of drug-resistant microbial pathogens has lent additional urgency in microbiological and antifungal research. A wide variety of heterocyclic systems have been explored for developing pharmaceutically important molecules. Among them the derivatives of oxadiazoles have been playing an important role in the medicinal chemistry [3]. Oxadiazole moiety and its various derivatives studied frequently in

the past few decades and found potent in various pharmacological and pathological conditions [4]. Literature reveals that 1, 3, 4-Oxadiazole is a highly privileged structure the derivatives of which exhibit a wide range of biological activities including antibacterial [5], antitubercular [6], vasodialatory [7], antifungal [8], cytotoxic [9], anti-inflammatory and analgesic [10,11], hypolipidemic [12], anticancer [13] and ulcerogenic [14] activities. Oxadiazole derivatives have been found to possess broad spectrum antimicrobial activity and therefore are useful substructures for further molecular exploration [15]. Furamizole (Compound 1) is a compound which is based upon 1,3,4-oxadiazole ring and has strong antibacterial activity.



Physical Properties of Oxadiazole

Oxadiazole is a five membered heterocycle having two carbons, two nitrogens, one oxygen and two double bonds. The first monosubstituted 1,3,4-Oxadiazoles were reported in 1955 by two independent laboratories [16, 17]. Since 1955 other workers have extended this reaction 1, 3, 4-Oxadiazole boils at 150° C [18-20]. The percentage of C, H, N present in 1, 3, 4-Oxadiazole is given in table 1 [21].

Table: 1 Percentage of C, H, N present in 1, 3, 4-oxadiazole

Calculated %			Found %		
C	H	N	C	H	N
34.29	2.88	40.00	34.56	3.19	39.71

The IR spectra of 1, 3, 4-oxadiazole is characterized by the bonds at 1640-1560 cm^{-1} (C=N) and 1020 cm^{-1} (C=O) [22]. The position of both protons of 1, 3, 4-Oxadiazole in $^1\text{H-NMR}$ (τ^a) is 1.27. The refractive index ($n^{25\text{D}}$) of 1, 3, 4-Oxadiazole is 1.43 [21]. The mass spectra showed that the base peak is the molecular ion peak.

Chemistry of Oxadiazole

Ainsworth prepared 1, 3, 4-Oxadiazole in 1965 by the thermolysis of ethylformate formly hydrazine [Figure 1] at atmospheric pressure [21].

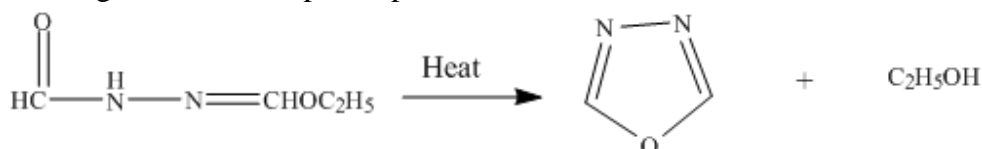


Figure 1: Synthesis of 1, 3, 4-oxadiazole

Oxadiazole exist in four isomeric forms as shown in Figure 2.

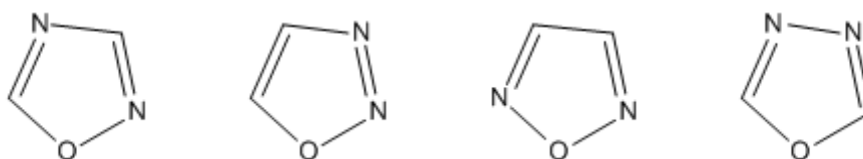


Figure 2: Isomers of oxadiazole

1, 3, 4-oxadiazole is a thermally stable molecule. Oxadiazole is a very weak base due to the inductive effect of the extra heteroatom. The 1, 3, 4-Oxadiazole undergoes number of reactions including electrophilic substitution, nucleophilic substitution, thermal and photochemical. The electrophilic substitution in oxadiazole ring is extremely difficult at the carbon atom because of the relatively low electron density on the carbon atom which can be attributed to electron withdrawing effect of the nitrogen atom. If oxadiazole ring is substituted with electron releasing groups then the attack of electrophiles occurs at nitrogen. Oxadiazole ring is generally resistant to nucleophilic attack. Halogen substituted oxadiazole, however, undergo nucleophilic substitution similarly as occurring at an aliphatic sp^2 carbon atom [15].

Methods of Preparation

The most popular reported method for the synthesis of 1,3,4-Oxadiazole backbone is the reaction between the properly substituted acid hydrazide, carbon disulphide (CS_2) and potassium hydroxide (KOH) [23]. However the long reaction time is a limiting factor over the high and consistent yields obtained with this method. Various other synthetic methods have been reported in literature to overcome this limitation. We are hereby reporting some recent modification in the synthesis of the said nucleus.

From Isothiazole

Kiselyov *et. al.*; (2010); reported the synthesis of oxadiazole by refluxing isothiazole derivative with neat hydrazine hydrate for 4 hrs. The hydrazide so obtained can be further reacted with isothiocyanates followed by *in situ* cyclization of the intermediate thiosemicarbazides with DCC [Figure 3] to afford the key molecules [24].

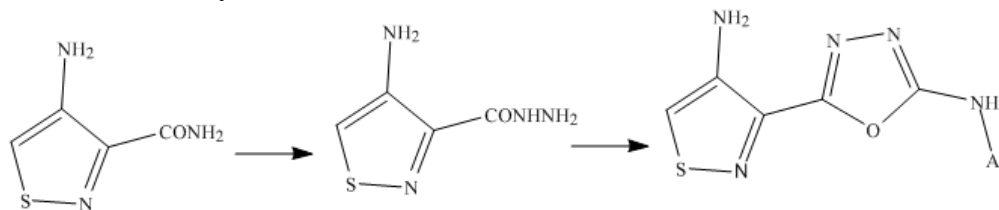


Figure: 3 Synthesis of 1,3,4-Oxadiazole from Isothiazole

From Thiosemicarbazide

Barbuceanu *et. al.*; (2010); reported the synthesis of oxadiazole [Figure 4] by reacting N^1 -[4-(4-bromophenylsulfonyl)benzoyl]- N^4 -(4-fluorophenyl)-thiosemicarbazide [5] with (a) Mercuric Oxide (HgO) in ethanol media (b) I_2/KI in NaOH solution media.

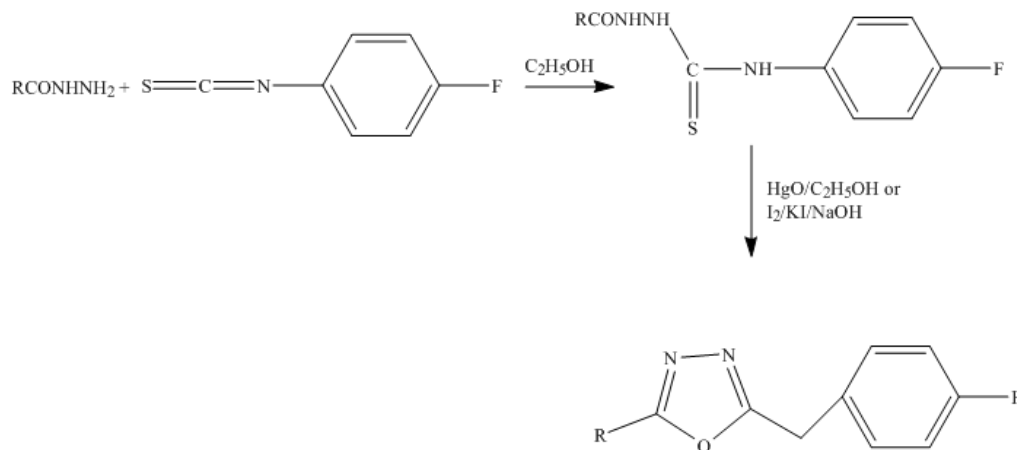


Figure: 4 Synthesis of Oxadiazole from Thiosemicarbazide

From N-acyl hydrazones

Prakash *et. al.*; (2010); reported the synthesis of a series of novel 2,5-disubstituted 1,3,4-oxadiazoles [Figure 5] by oxidative cyclization of pyrazolylaldehyde N-acyl hydrazones promoted by iodobenzene diacetate under mild conditions [8].

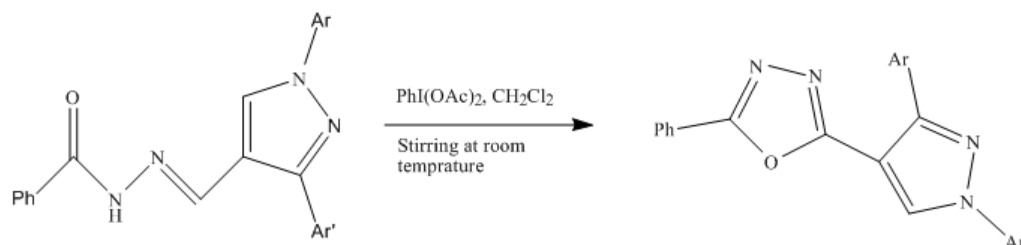


Figure: 5 Synthesis of Oxadiazole from N-acyl hydrazones

From acid hydrazides

The formation of 1,3,4-oxadiazole via condensation of various alkyl hydrazides with substituted acids using various cyclodehydrogenating agents are reported in literature. A few of them are mentioned below.

Husain *et. al.*; (2010); reported the synthesis of 1,3,4-Oxadiazole [Figure 6] by reacting 4-oxo-4(biphenyl-4-yl)butanoic acid (fenbufen) with aryl acid hydrazides in phosphorous oxychloride [25].

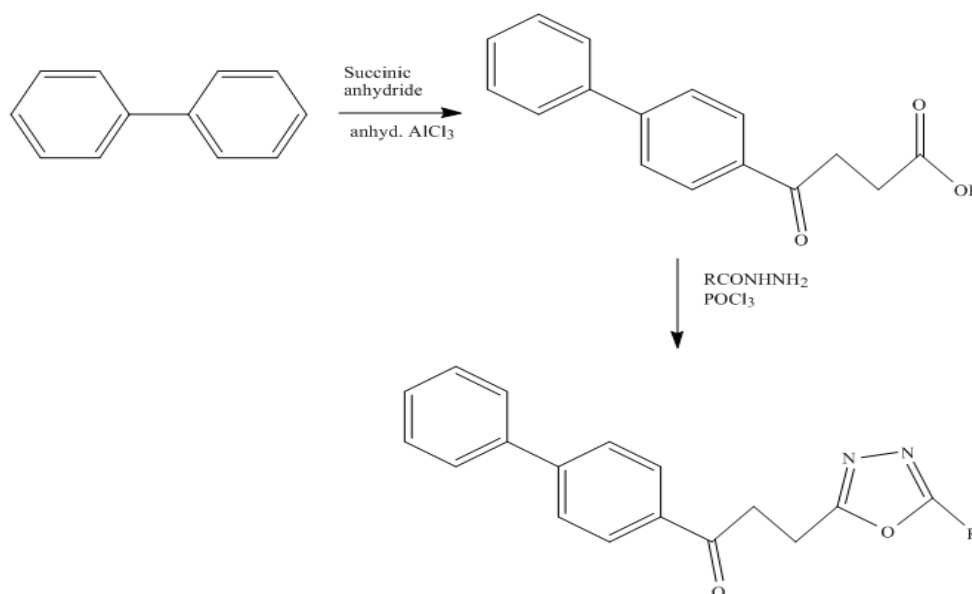


Figure: 6 Synthesis of Oxadiazole using phosphorus oxychloride

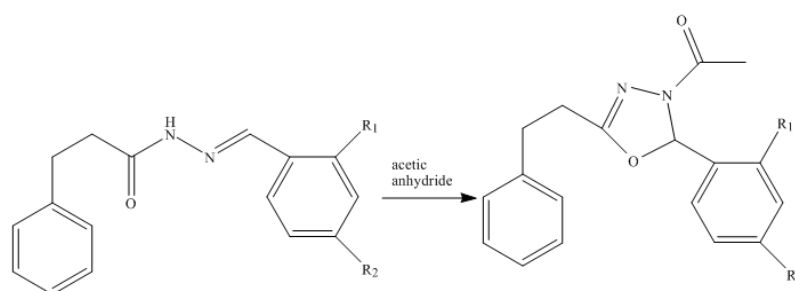


Figure: 7 Synthesis of Oxadiazole using acetic anhydride

Fuloria *et. al.*; (2010); reported the synthesis of 1-(2-aryl-5-phenethyl-1,3,4-oxadiazol-3(2H)-yl)ethanones [Figure 7] by reacting N-(substituted benzylidene)-3-phenyl propionohydrazides with *acetic anhydride* [26].

From Chalcones

Kamble *et. al.*; (2010); reported the microwave assisted synthesis of 1,3,4-oxadiazole [Figure 8] from Chalcones. This microwave assisted synthesis lead to the cleaner reactions as well as afforded high yields and shorter reaction times. The chalcones underwent a rapid cyclisation with hydrazine hydrate using Polyethylene glycol (PEG 200) and formic acid as solvents. The Compound 2 on bromination and heating with acetic anhydride afforded the Oxadiazole derivatives (compound 3) [27].

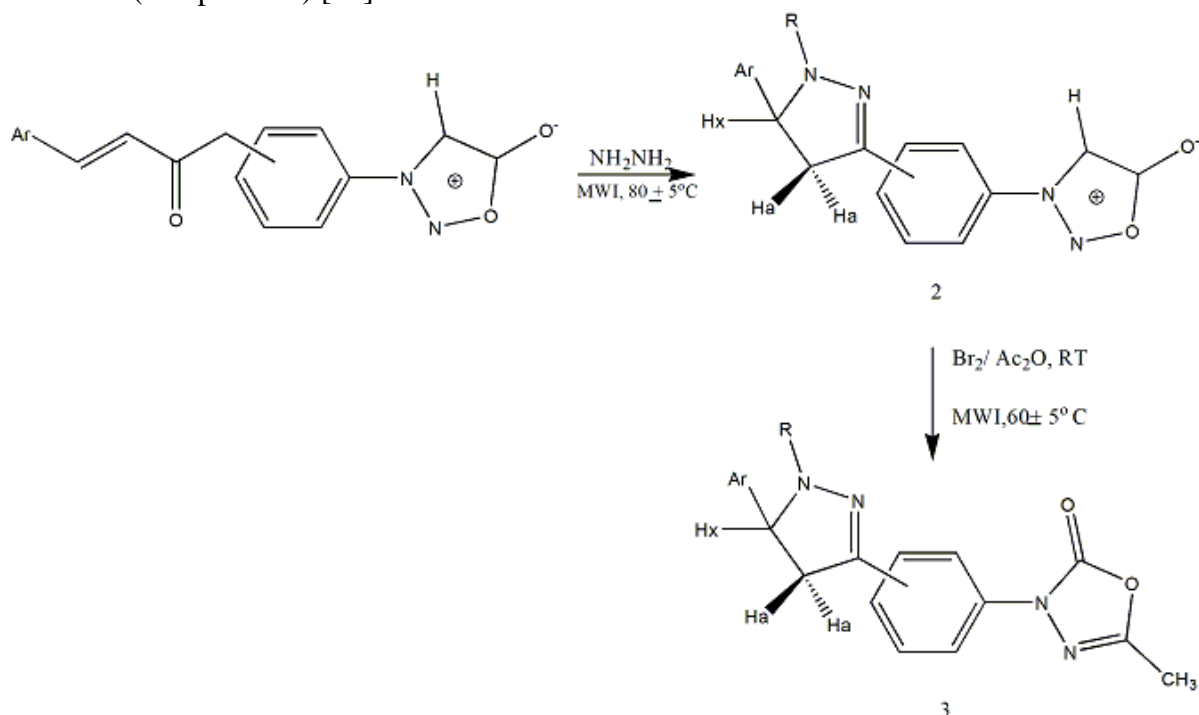


Figure: 8 Synthesis of Oxadiazole from Sydnones

From acetic acid hydrazide

Kumar *et. al.*; (2010); reported the synthesis of 5-[(biphenyl-4-yloxy)-methyl]-2-substituted-1,3,4-oxadiazoles [Figure 8] by treatment of 2-(biphenyl-4-yloxy) acetic acid hydrazide with appropriate aromatic acid in presence of phosphorous oxychloride [28].

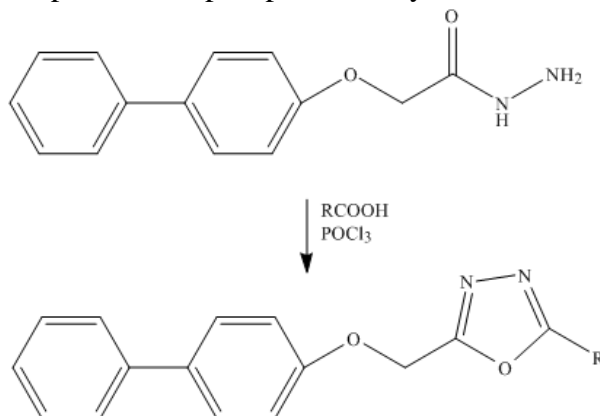
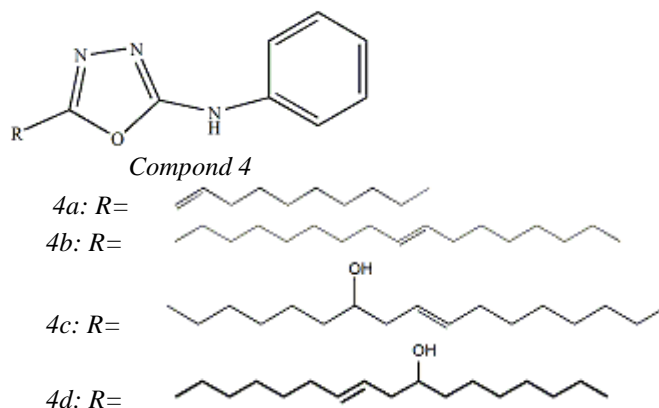


Figure: 9 Synthesis from acetic acid hydrazide

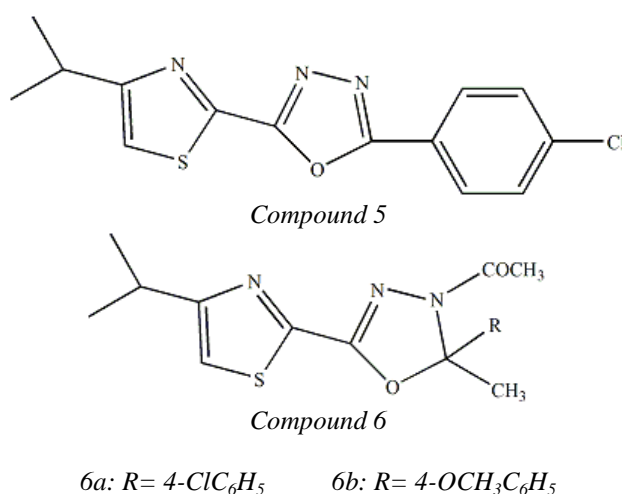
OXADIAZOLE AS ANTIMICROBIAL AGENTS

Farshori *et. al.*; (2010); synthesised 5-alkenyl/hydroxyalkenyl-2-phenylamine-1,3,4-Oxadiazoles (compound 4) and tested for in vitro antimicrobial activities by disc diffusion method.

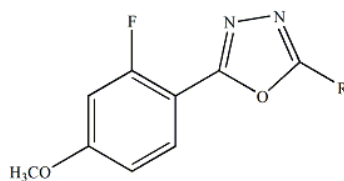


Among the synthesised compounds, compound 4b was found to be more active against fungal strain i.e. *Penicillium marneffeii* and was compared with greseofulvin as standard drug. Compound 4c, 4d was found to be more active against bacterial strains i.e. *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus pyogenes*, *Klebsiella pneumoniae* and was compared with chloramphenicol as standard drug [3].

Kumar *et. al.*; (2010); synthesised some novel 2-substituted-5-[isopropylthiazole] clubbed 1,3,4-Oxadiazoles (Compound 5 and 6) and tested for antimicrobial activity by broth microdilution method. Among the various synthesised compounds 5 showed improved antibacterial activity against tested Gram-positive bacteria i.e. *Staphylococcus aureus*, *Staphylococcus faecalis*, *Bacillus subtilis* and compound 6b having *p*-methoxy substitution showed excellent antifungal activity against *Saccharomyces cerevisiae*, *Candida tropicalis*, *Aspergillus Niger*. Compound 6a exhibited good inhibition against Gram-positive bacteria. These tested compounds were compared with standard drugs i.e. Ciprofloxacin, Norfloxacin, Flucanazole [6].



Chandrakantha *et. al.*; (2010); synthesised some novel 1,3,4-Oxadiazole bearing 2-flouro-4-methoxy phenyl moiety (compound 7) and tested for antimicrobial activity by serial dilution method.



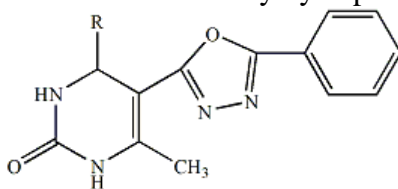
Compound 7

7a: R = 2-CH₃-3-BrC₆H₅7c: R = 2-Br-5-ClC₆H₅7b: R = 2,3,4-F₃C₆H₅

7d: R = 5-methylisoxazole

Among the various synthesised compounds 7a, 7b showed excellent antibacterial activity against *Escherichia coli* and *Pseudomonas aeruginosa* and 7c, 7d showed excellent antifungal activity against *Candida albicans*. Compounds tested for antibacterial activity was compared with standard drug Furacin and for antifungal activity standard drug was Flucanazol [29].

Mishra *et. al.*; (2010); synthesised a series of Oxadiazole (Compound 8) and then final compounds were tested for their antimicrobial activity by cup and plate method.

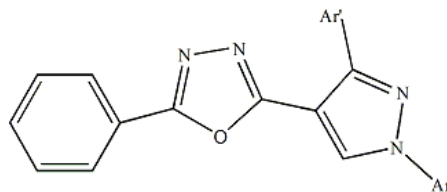


Compound 8

8a: R = 4-OCH₃C₆H₅8b: R = 4-NO₂C₆H₅

Among the tested compound 8a showed promising antibacterial activity against Gram +ve bacteria i.e *Streptococcus pneumonia* and compound 8b showed promising antibacterial activity against Gram –ve bacteria i.e *Escherichia coli* as compared to standard drugs Ofloxacin and Levofloxacin [30].

Prakash *et. al.*; (2010); synthesised a series of novel unsymmetrical 2,5-disubstituted 1,3,4-Oxadiazoles (Compound 9) and then the final compounds were tested for their antibacterial and antifungal activities.



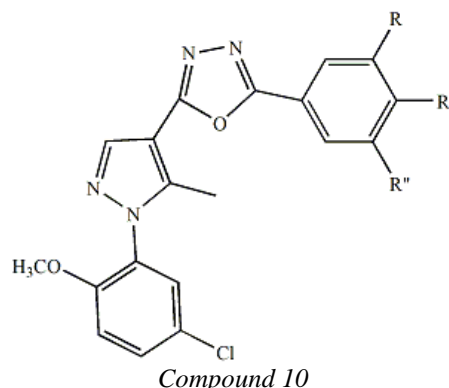
Compound 9

9: Ar = Ar' = C₆H₅9c: Ar = 4-NO₂C₆H₅ Ar' = C₆H₅9b: Ar = C₆H₅ Ar' = 4-NO₂C₆H₅9d: Ar = 4-NO₂C₆H₅ Ar' = 4-OCH₃C₆H₅

Among the tested compounds, compound 9a, 9b showed maximum antibacterial activity against *Staphylococcus aureus* and was compared with ciprofloxacin as standard drug. Compound 9c, 9d showed maximum inhibition against both of the fungi *Aspergillus niger* and *Aspergillus flavus* and was compared with Fluconazole as standard drug [8].

Rai *et. al.*; (2009); synthesized 2-[1-(5-chloro-2-methoxyphenyl)-5-methyl-1H-pyrazol-4-yl]-5-(substitutedphenyl)-[1,3,4-oxadiazole (Compound 10) and tested for their antibacterial activity. From the tested compounds, compound 10a which is unsubstituted showed significant activity against *Bacillus subtilis* and moderate activity against *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumonia*. Fluorine incorporated in phenyl ring of 1,3,4-oxadiazole showed improved

activity against both Gram +ve bacteria i.e *Bacillus subtilis*, *Staphylococcus aureus* and Gram – ve bacteria i.e against *Escherichia coli*, *Klebsiella pneumonia*. These compounds were compared with Ampicillin as standard drug [31].

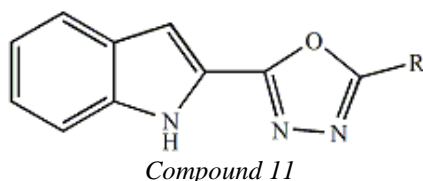


10a: $R = R' = R'' = H$

10b: $R = R'' = H, R' = F$

10c: $R = F, R' = R'' = H$

Bhardwaj *et. al.*; (2009); synthesized 1,3,4-Oxadiazoles (Compound 11) and tested for their antimicrobial activity on different strains. A total of four compounds were synthesized, out of those only three found to be active against bacterial strains i.e *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa* and none of the compound were found to be effective against fungal strains. Standard Drug used were Norfloxacin and Fluconazole [32].



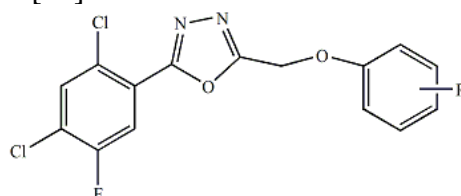
11a: $R = H$

11c: $R = 2\text{-ClC}_6\text{H}_5$

11b: $R = 3\text{-ClC}_6\text{H}_5$

11d: $R = \text{C}_6\text{H}_5$

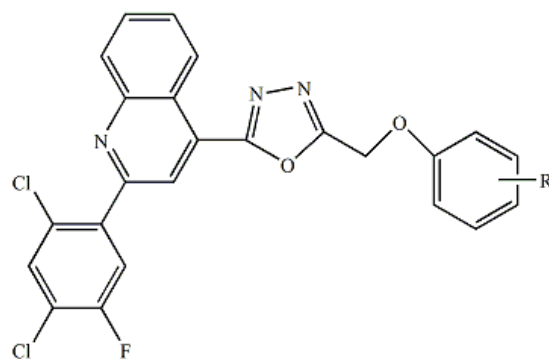
Karthikeyan *et. al.*; (2008); synthesized 2,4-dichloro-5-fluorophenyl containing Oxadiazoles (Compound 12 and 13) and then final compounds were tested for their antimicrobial activity. Among the tested compounds, compound 12a, 12b, 12c, 13a, 13b and 13c showed good inhibition against *Staphylococcus aureus*, *Escherichia coli*. Compounds 12a, 12b, 12c, 13b and 13c exhibited good antibacterial activity almost equal to the standard i.e Ciprofloxacin. Compound 12c showed good bactericidal activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* bacterial strains. Compound 12a, 12c, 13c showed good inhibition against all the fungal strains. Compound 12c showed good fungicidal activity against *Candida albicans*, *Aspergillus fumigatus* and *Penicillium marneffe* fungal strains and compared with standard drug Greseofluvin[33].



12a: $R = 4\text{-CH}_3$

12b: $R = 2\text{-CH}_3$

12c: $R = 4\text{-Cl-2-CH}_3$



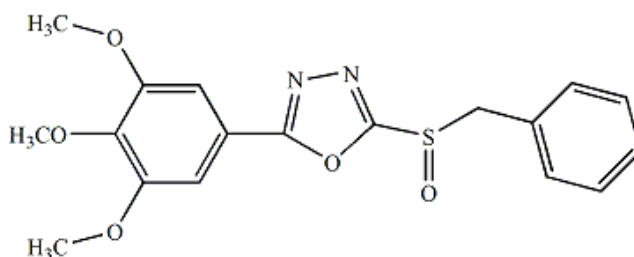
Compound 13

13a: R= 2-Cl

13b: R= 4-Cl

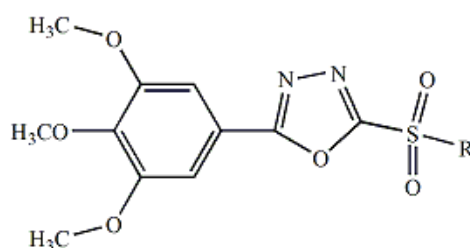
13c: R= 2,4-Cl₂

Liu *et. al.*; (2008); synthesized sulfoxide derivatives containing trimethoxyphenyl substituted 1,3,4-Oxadiazole moiety (Compound 14) and tested for their antifungal activity. From the data it was obtained that introduction of 1,3,4-Oxadiazole in sulfoxide might improve their antifungal activities. Among the tested compounds, compound 14 was found to be more active against *Gibberella zeae*, *F. oxysporum* and *C. mandshurica* than other ones. Hymexazol was used as standard drug [34].



Compound 14

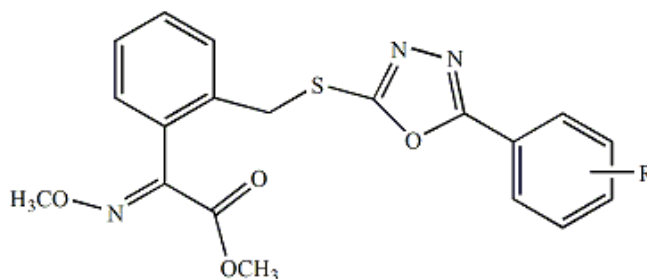
Chen *et. al.*; (2007); synthesized 5-(3,4,5-trimethoxyphenyl)-2-sulfonyl-1,3,4-oxadiazole derivatives (Compound 15) and tested for their antifungal activity against *Gibberella zeae*, *Botrytis cinerea*, *Sclerotinia sclerotiorum*. Among the tested compounds 15a and 15b exhibiting promising antifungal activities even better than that of the commercial fungicide Hymexazol [35].



Compound 15

15a: R= CH₃15b: R= -CH₂-CH₃

Li *et. al.*; (2006); synthesized (E)- α -(methoxyimino)-benzeneacetate derivatives containing 1,3,4-Oxadiazole ring (Compound 16) and tested for their fungicidal activities. All the compounds 16a-16o showed potent fungicidal activities against *Rhizoctonia solani*, *Botrytis cinereapers*, *Gibberesapers zeae*, *Physalospora piricola* and *Bipolaris mayclis*. The fluorinated compounds 16j and 16l showed activity higher than kresoxim-methyl and compounds 16a-16o had higher fungicidal activity against *R. solani* than kresoxim-methyl [36].



Compound 16

16a: R= H	16f: R= 2,4-Cl ₂	16k: R= 2-F-4-Br
16b: R= 4-OCH ₃	16g: R= 2,5-Cl ₂	16l: R= 2,3-F ₂
16c: R= 4-C ₆ H ₅ -CH ₂ O	16h: R= 2,4-Cl ₂ -5-F	16m: R= 4-CF ₃
16d: R= 3-Cl	16i: R= 2-F	16n: R= 2-I
16e: R=2,3-Cl ₂	16j: R=4-F	16o: R= 4-NO ₂

CONCLUSION

In present work an attempt has been made to discuss various aspects such as physicochemical properties, method of preparation and antimicrobial activity of 1,3,4-oxadiazole derivatives. The work concludes that although a number of methods are available for the synthesis of oxadiazole the most common method is condensation of various alkyl hydrazides with substituted acids using various cyclodehydrogenating agents like phosphorus oxychloride. This review has highlighted the use of Oxadiazole derivatives having antimicrobial activity. Furamizole is a compound which is based upon 1,3,4-oxadiazole ring and has strong antibacterial activity.

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