Available Online at www.ijpba.in

International Journal of Pharmaceutical and Biological Science Archive 1 (1) 2013, 87-97

REVIEW ARTICLE

ANTIMICROBIAL ACTIVITIES OF 1,3,4-OXADIAZOLE: A REVIEW

Alex Martin

Department of Pharmaceutical Chemistry, St. Joseph's College of Pharmacy, Kerala University of Health Sciences, Cherthala, Kerala, India.

Received 05 July 2013; Revised 15 July 2013; Accepted 30 July 2013

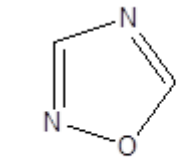
ABSTRACT

Oxadiazole is a five membered heterocyclic ring which is a versatile lead compound for designing potent bioactive agents. It exists in four isomeric forms. One of its four isomers 1,3,4-oxadiazole exhibited a wide range of biological activities which includes anti-bacterial, anti-tubercular, anticonvulsant, hypoglycemic, anti-allergic, enzyme inhibitor, vasodilatory, antifungal, cytotoxic, anti-inflammatory, analgesic, hypolipidemic, anticancer, insecticidal activities, etc. 1,3,4-oxadiazoles have shown significant antibacterial activity against a wide range of microorganisms like fungi, Gram positive strains such as Staphylococcus aureus, Bacillus subtilis and Bacillus lintus and Gram negative strains such as Escheria coli, Vibrio cholera and Pseudomonas aeruginosa. The present review reports the methods of synthesizing some of the 1,3,4-oxadiazole derivatives and their anti-microbial activity.

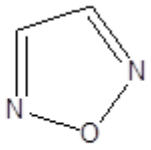
KEYWORDS: 1,3,4-oxadiazole derivatives, Anti-microbial activity.

INTRODUCTION:

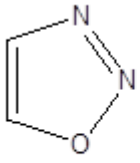
Oxadiazole is a heterocyclic ring and is considered to be derived from furan by the replacement of two methane (-CH=) groups by two nitrogen (-N=) atoms. There are four possible isomers of Oxadiazole, depending on the positions of hetero atoms and they are named as 1,2,3; 1,2,4; 1,2,5; 1,3,4-oxadiazoles. 1,2,4-Oxadiazole, 1,2,5-Oxadiazole, and 1,3,4-Oxadiazole are known, but the 1,2,3-isomer is unstable and reverts to the diazoketone tautomer. The stable oxadiazoles appear in a variety of pharmaceutical drugs including raltegravir, butalamine, fasiplon, oxolamine, and pleconaril.



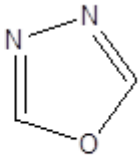
1,2,4-Oxadiazole



1,2,5-Oxadiazole



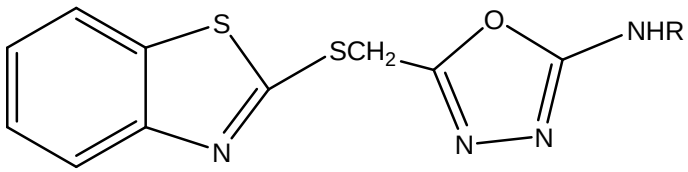
1,2,3-Oxadiazole



1,3,4-Oxadiazole

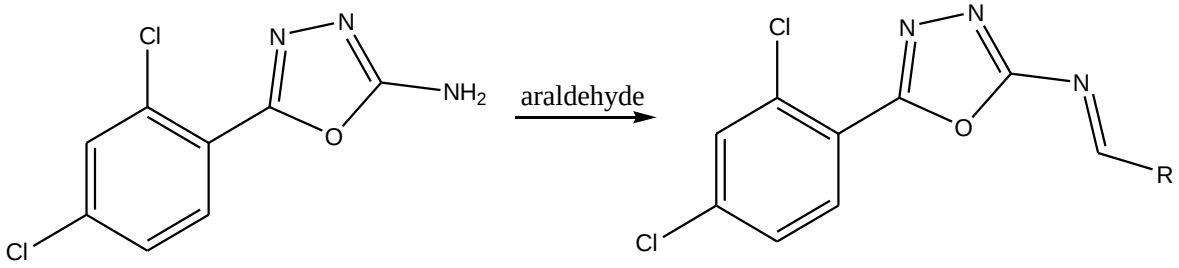
Literature review reveals that the 1,3,4-oxadiazoles undergo a number of reactions such as Electrophilic substitution, Nucleophilic substitution, Thermal and Photochemical. This has been exploited in the preparation of 1,3,4-oxadiazole therapeutic molecules for various applications. In view of this, an attempt has been made to review the antimicrobial activities of 1,3,4-oxadiazole.

Radha *et al*[1] synthesized 5-(benzothiazol-2-yl-thiomethyl)-1,3,4-oxadizole from mercaptobenzothiazole which showed moderate anti-bacterial and anti-inflammatory activities.

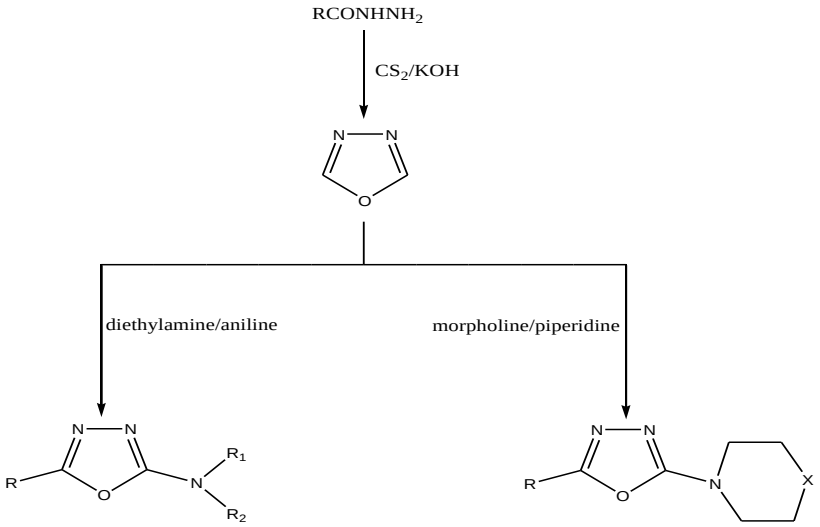


*Corresponding author: Alex Martin, | Email: aalexmartin@rediffmail.com

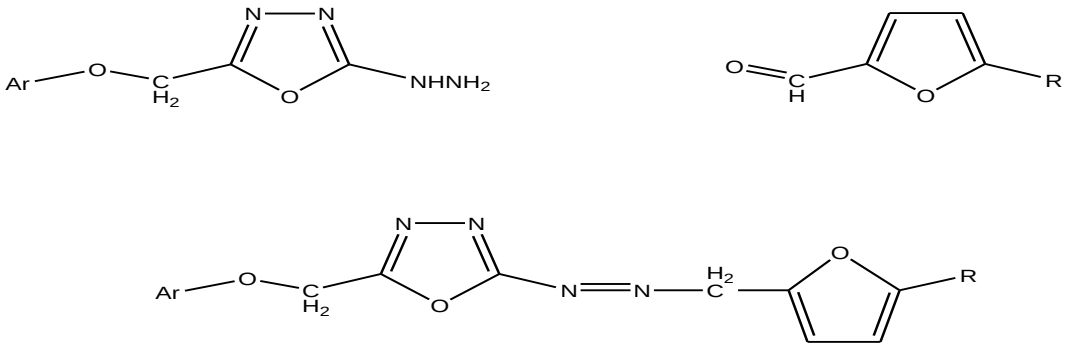
The insecticidal activity of 1,3,4-oxadiazoles was screened by **Kataky *et al*** [2] by the synthesis of 2-amino-5-(2,4-dichlorophenyl)-1,3,4-oxadiazoles. This will give 1,3,4-oxadiazole-2-iminobenzylidine with appropriate araldehydes. The products exhibited good insecticidal activity.



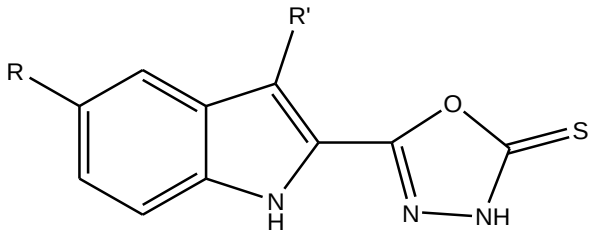
Beenus *et al* [3] synthesized several new 2-mercapto-5-N-methyl/ethyl/ethyl morphilino/piperidino-1,3,4-oxdiazoles. The oxadiazoles formed from acid hydrazides on reaction with CS_2 and alcoholic KOH were condensed with diethylamine/dimethylamine, aniline, morpholine and piperidine to yield 2-dimethyl/ diethylamine /aniline /morpholino/piperidino-5-N-dimethylamine/diethylamine/ aniline-1,3,4-oxadiazole. It was found that the synthesized compounds were active against bacteria but they exhibit good activity against fungal organisms.



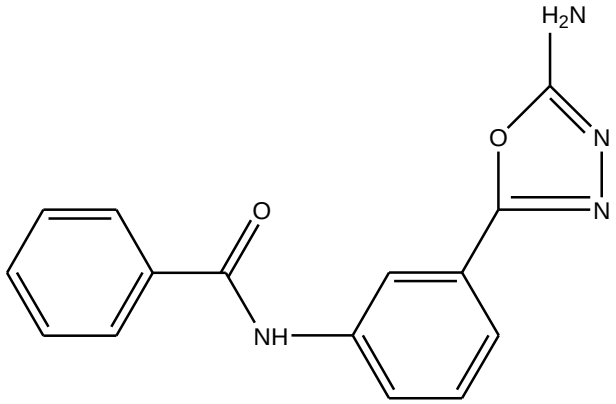
Various 5-substituted-1,3,4-oxadiazol-2-hydrazides were synthesized by **Kalluraya B. *et al*** [4] by the reaction of oxadiazole with hydrazine hydrate. The oxadiazole hydrazide when condensed with 5-substituted-2-furfural gave hydrazones. These compounds were found to be active against gram positive and gram negative bacteria.



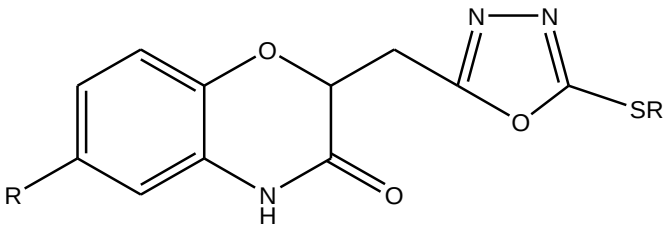
2-(5'-thioxo-1,3,4-oxadiazolin-2-yl) indoles were synthesized by **Sonar VN *et al*** [5] by the reaction of indole-2-carbohydrazides with CS_2 and KOH. Screening of these compounds has shown that they posses moderate activity against S. aureus, E. coli, P. vulgaris and B. subtilis.



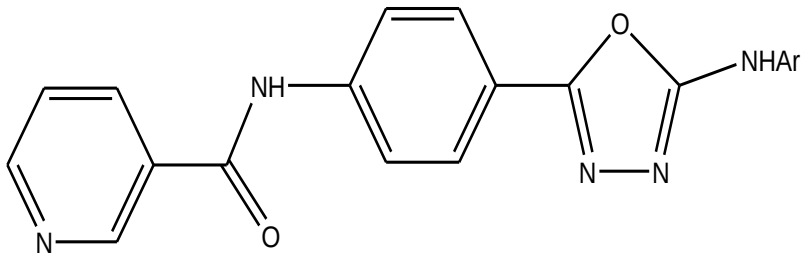
Nailesh Joshi *et al* [6] synthesized some 2,5-disubstituted-1,3,4-oxadiazoles . The compounds have been tested for their anti-microbial and anti-fungal activity.



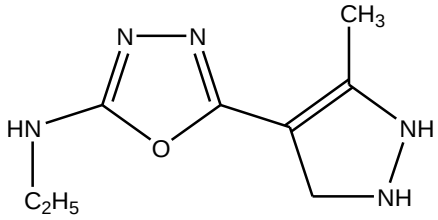
2-(3,4-dihydro-3-2H-1,4-benzoxazin-2-yl)methyl-5-(alkyl/arylthio)-1,3,4-oxadiazoles have been synthesized by **Y. Jayamma *et al*** [7] and screened for their anti-microbial activity.



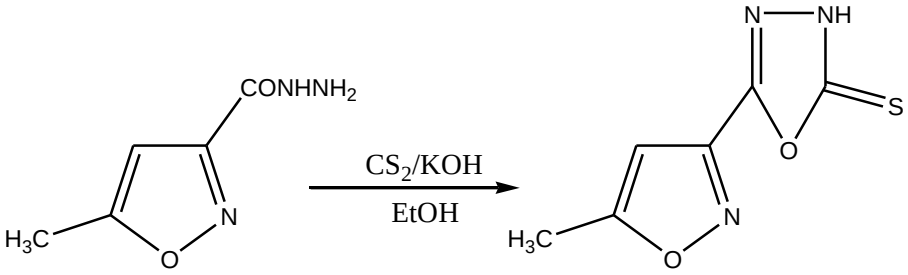
The synthesis of 2-arylamino-5-(p-nicotinamidophenyl)-1,3,4-oxadiazoles was carried out by **Vimal R. Shah *et al*** [8] from ethyl p-nicotinamidobenzoate which in turn was obtained by the treatment of nicotinic acid with thionyl chloride followed by the reaction with ethyl p-aminobenzoate in pyridine. The anti-bacterial activity of the compound was determined by the cup plate method.



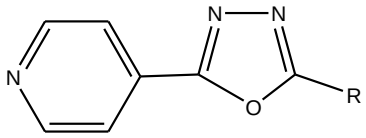
A series of 1,3,4-oxadiazoles were prepared by **Kapoor *et al*** [9] by the cyclisation of respective hydrazides. They were screened for their anti-bacterial, anti-fungal and anti-mycobacterial activities by agar well diffusion method.



Zi Yi Zhang *et al* [10] synthesized 5-(5-methylisoxazol-3-yl)-1,3,4-oxadiazole-2-thione from methylisoxazole-3-aceticacid hydrazide and showed to posses anti-bacterial activity.



A series of 2-(4'-pyridyl)-5-alkyloxyphenyl-1,3,4-oxadiazoles and 2-(4'-pyridyl)-5-p-chlorophenyl-1,3,4-oxadiazole were synthesized by **Lokanatha Rai *et al*** [11] by treating semicarbazones with Chloramine-T under appropriate conditions. The products were screened for anti-microbial activity.

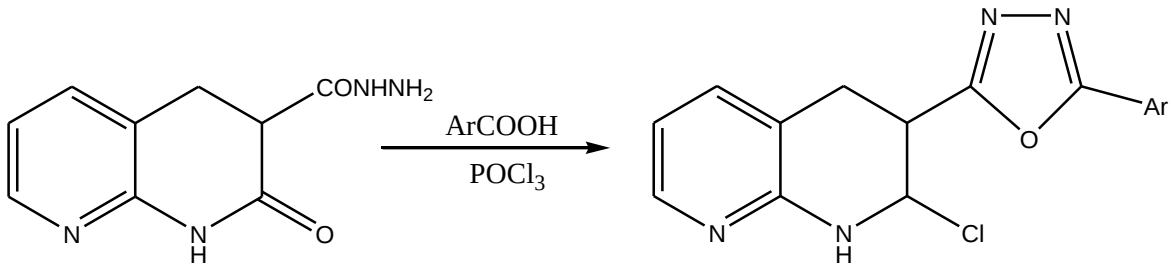


a) R = 4-$MeOC_6H_4$

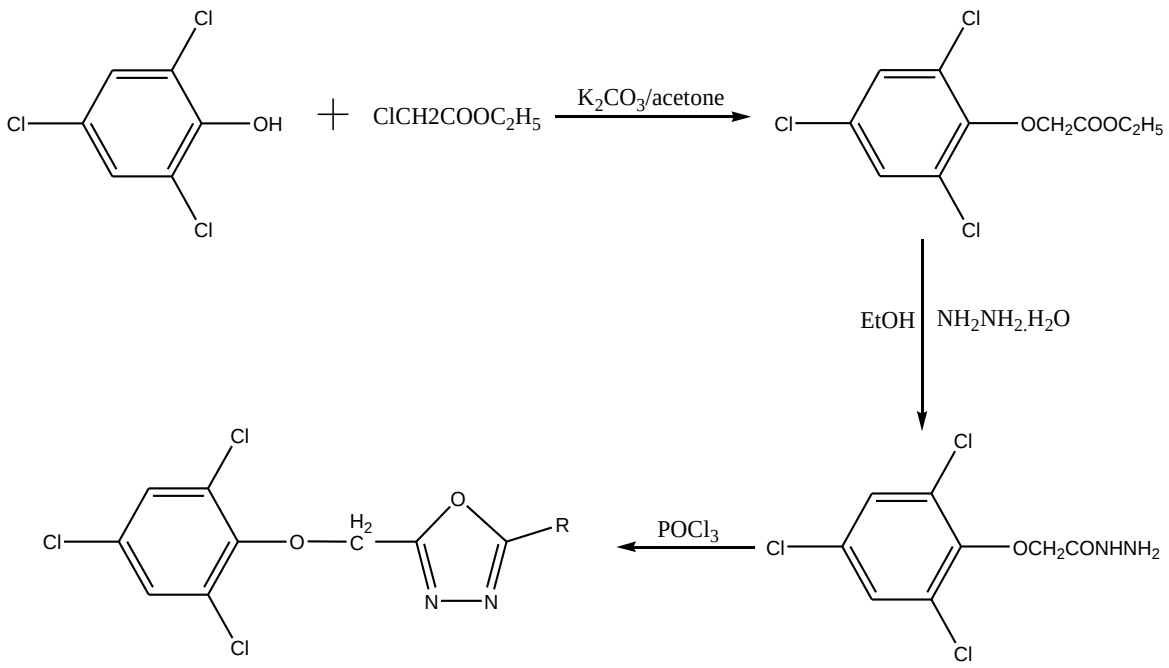
b) R = 3,4-$(MeO)_2C_6H_3$

c) R = p-ClC_6H_4

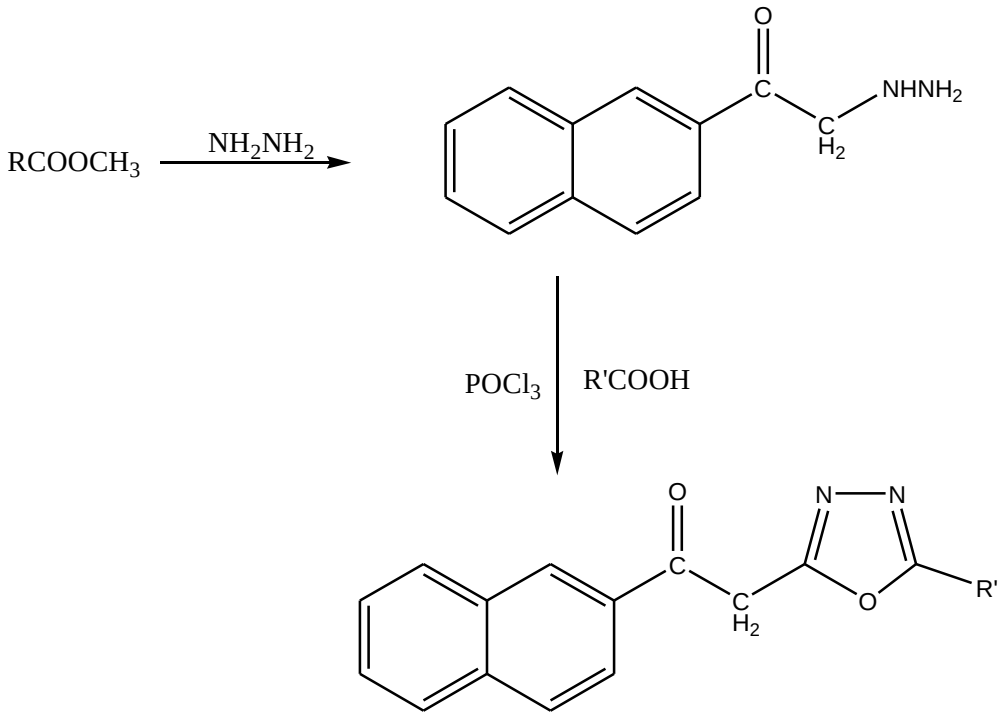
5-Aryl-1,3,4-oxadiazol-2-yl-2-chloro-1,8-naphthyridines were synthesized by **Mogilaiah K. *et al*** [12] on reacting 1,8-Naphthyridin-2-one-3-carboxylic acid hydrazide with aromatic acid in the presence of phosphorous oxychloride. The compounds were screened for their anti-microbial activity.



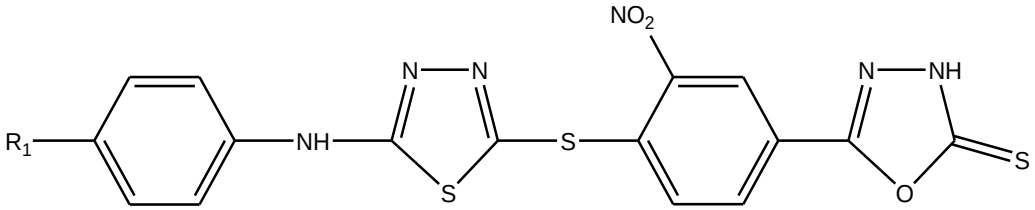
Patel KD *et al* [13] synthesized 2-(2,4,6-trichlorophenoxymethyl)-5-aryl-1,3,4-oxadiazoles from ethyl-2,4,6-trichlorophenoxy acetate and then converting them into corresponding hydrazides. These hydrazides are made to react with various aromatic acids in phosphorous oxychloride. The resultant compound is assayed for anti-bacterial activity.



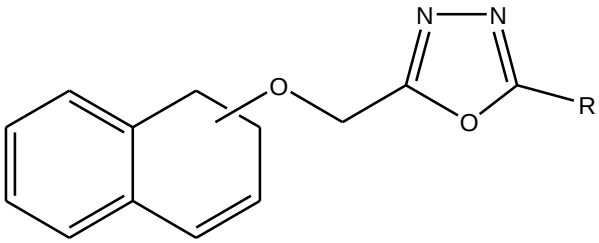
M.S.Y Khan *et al* [14] synthesized hydrazides of appropriate carboxylic acid by reacting their methyl esters with hydrazine hydrate. These hydrazides were now condensed with aromatic acids in presence of phosphorous oxychloride to give 2,5-disubstituted-1,3,4-oxadiazoles. Anti-microbial and anti-convulsant activity of these compounds was studied.



Smitha Nair S.P. *et al* [15] conducted a work wherein 2-(arylamino-5-mercapto-1,3,4-thiadiazolyl)-3-nitrophenyl-4-carboxylic acid hydrazide was cyclised with pentane-2,4-dione to give substituted pyrazoles. The pyrazoles were then converted to 2-(2-arylamino-5-mercapto-1,3,4-thiadiazol)-3-nitrophenyl-1,3,4-oxadiazolin-5-thione. These compounds were evaluated for their anti-microbial and anti-fungal activity.



A series of new derivatives of 5-(1-/2-naphthyloxymethyl)-1,3,4-oxadizol-2(3H)-thione, 5-(1-/2-naphthyloxymethyl)-1,3,4-oxadizol-2-amines and 5-(1-/2-naphthyloxymethyl)-1,3,4-oxadiazol-2(3H)-ones were synthesized by **Sachin *et al*** [16] and they were evaluated for their anti-,microbial activity . All were active against S. aureus, E. coli, P. aeruginosa, C. albicans and C. parapsilosis.

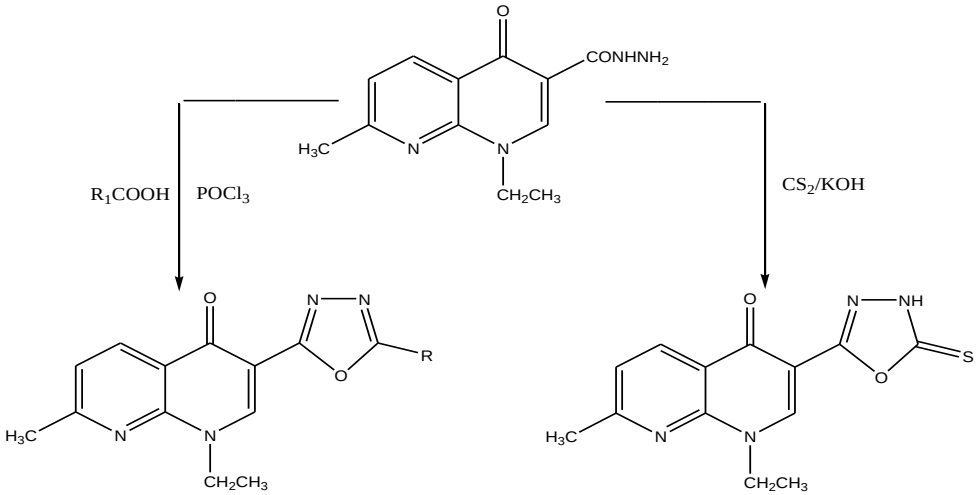


R = SH ; 5-(1-/2-naphthyloxymethyl)-1,3,4-oxadiazol-2(3H)-thione.

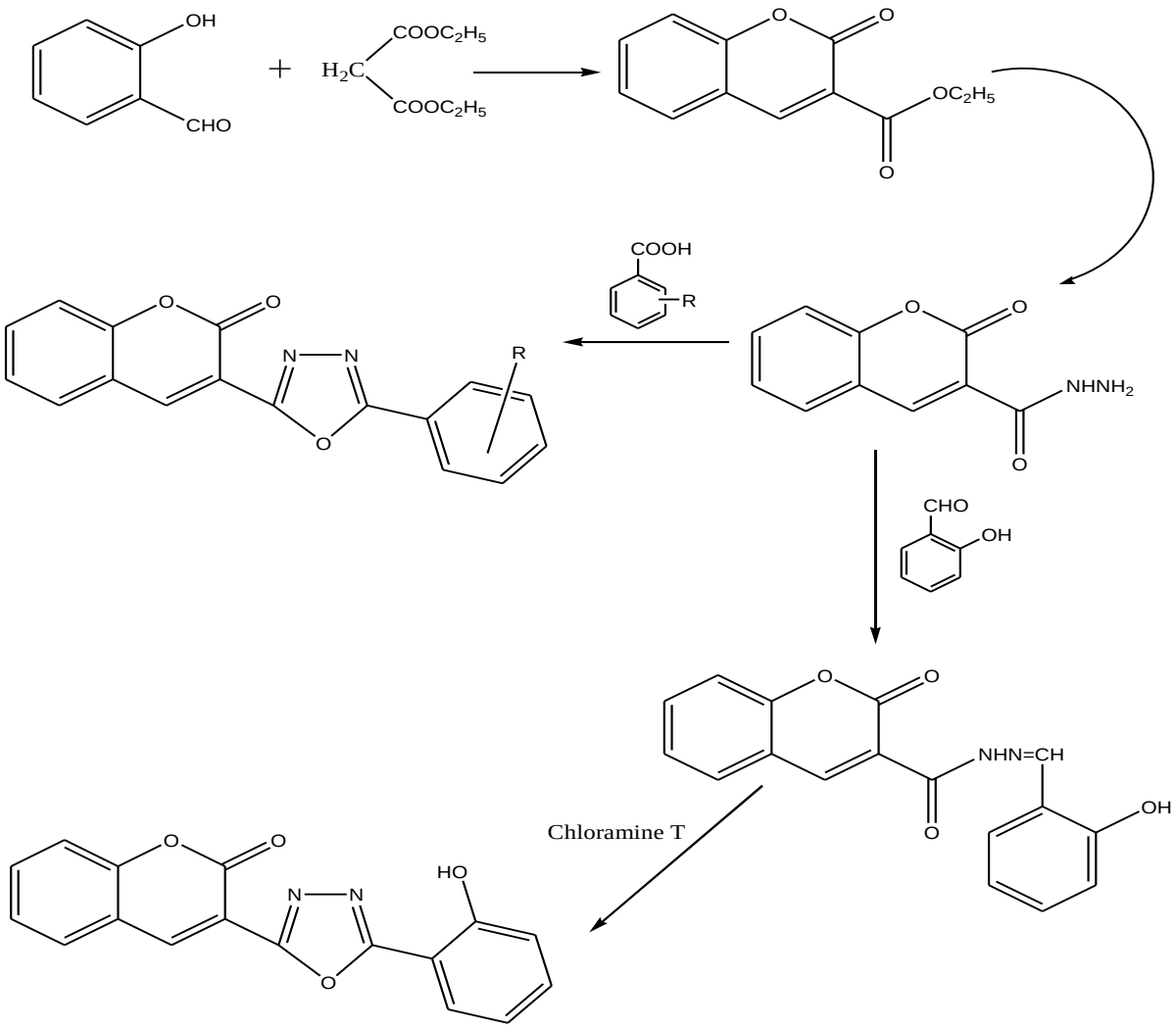
R = NH_2 ; 5-(1-/2-naphthyloxymethyl)-1,3,4-oxadizol-2-amine.

R = OH ; 5-(1-/2-naphthyloxymethyl)-1,3,4-oxadizol-2(3H)-ones.

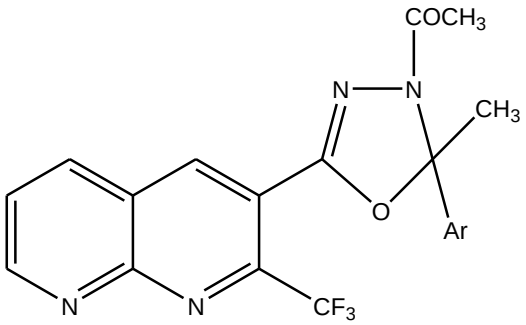
Grover Gaurav and Swarna G. Kini [17] synthesized a series of new nalidixic acid derivatives having 1,3,4-oxadiazole and 1,3,4-oxadiazole thione. These compounds were screened for their anti-bacterial and anti-fungal activity.



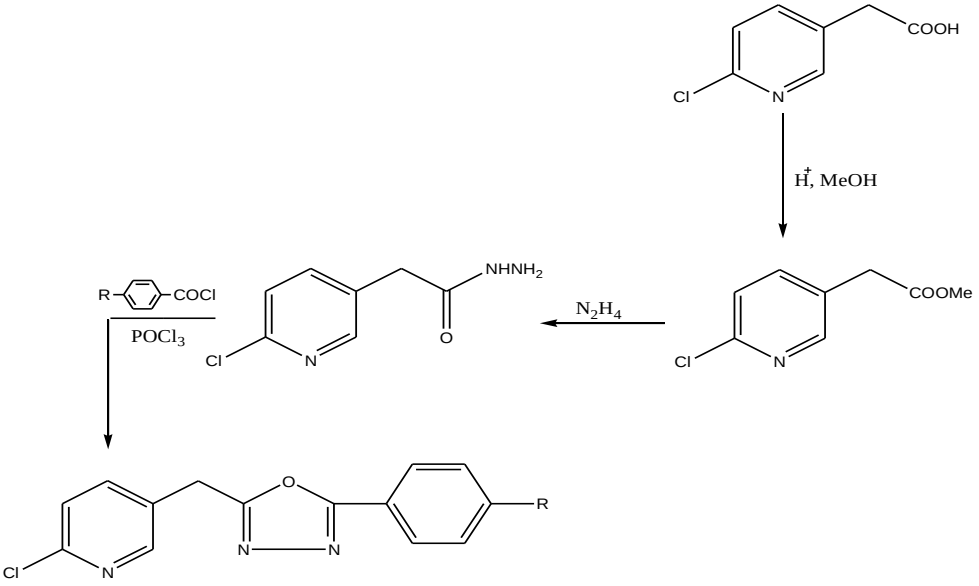
2,5-disustituted-1,3,4-oxadiazoles were synthesized and tested for their anti-inflammatory activity, analgesic and anti-microbial activity by **Khan MSY and Akhtar M.** [18] . These compounds revealed interesting results.



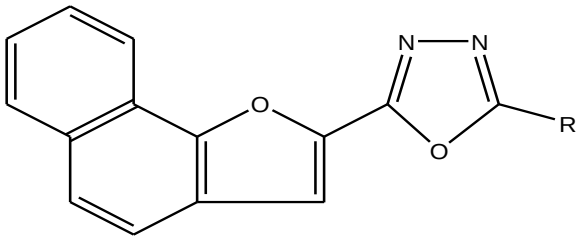
Condensation of 2-(triflouromethyl-1,8-naphthyridine-3-carboxylic acid hydrazide with different acetophenones was carried out by **Mogilaiah. K *et al*** [19] to give corresponding 2-triflouromethyl-1,8-naphthyridine-3-carbonylhydrazones, which on cyclisation with acetic anhydride yields 4-acetyl-2(2-triflouromethyl-1,8-naphthyridine-3-yl)-5-aryl-5-methyl-1,3,4-oxadiazolines. These compounds were analyzed by elemental analysis and were studied for their anti-microbial activity.



B. Shivarama Holla *et al* [20] synthesized some 1,3,4-oxadiazoles from 2-chloropyridine-5-acetic acid. Esterification of 2-chloropyridine-5-acetic acid with methanol in presence of H_2SO_4 gives the corresponding methyl ester, hydrazinolysis of which with hydrazine hydrate affords 2-chloropyridine-5-acetic acid hydrazide. This hydrazide on reacting with aryl chlorides in the presence of $POCl_3$ yields 2-chloro-5-(5-aryl-1,3,4-oxadizol-2-yl)methyl pyridines . The synthesized compounds were screened for their insecticidal activity.

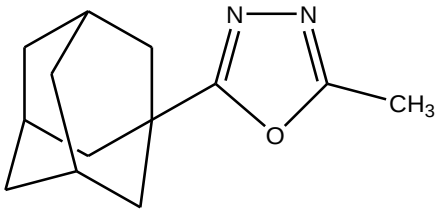


H.M. Vagdevi *et al* [21] reported the synthesis, anti-microbial and anti-inflammatory activity of 1,3,4-oxadiazoles linked to naphthol [2,1-b} furan. They reported that amongst the compounds tested for anti-microbial activity, the compound having R = p-$CH_3C_6H_4$ exhibited promising activity against all six organisms. The compounds having R = p-ClC_6H_4 was active against S. aureus and E. coli.

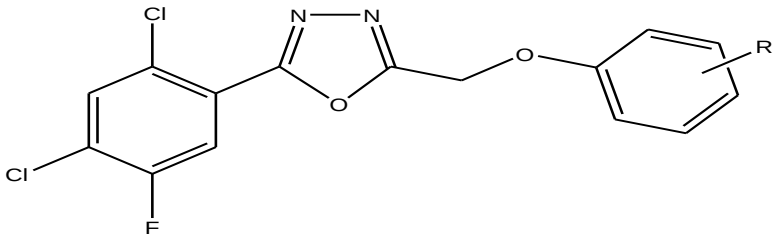


R = C_6H_5, m-ClC_6H_4, p-ClC_6H_4, p-$CH_3C_6H_4$

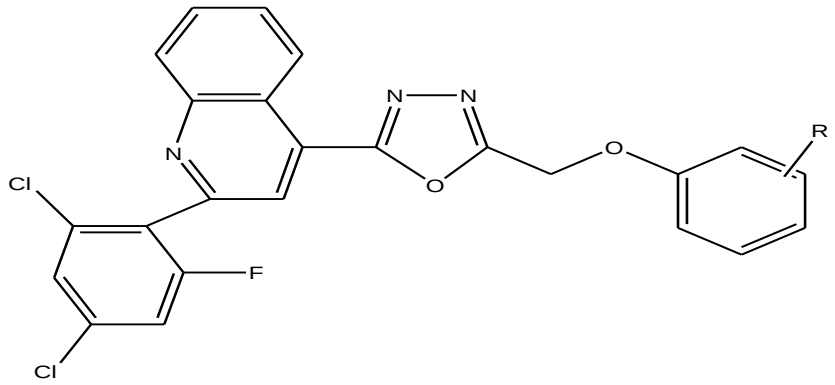
Kadi AA *et al* [22] reported anti-microbial and anti-inflammatory activity in novel 2-substituted-5-1-admantyl)-1,3,4-oxadiazoles and 2-substituted-5-(1-admantyl)-1,3,4-thiadiazoles. Several derivatives showed good to moderate anti-bacterial activity particularly against gram positive organism, Bacillus subtilis and marked antifungal activity against Candida albicans.



Karthikeyan *et al* [23] synthesized some 2,4-dichloro-5-flourophenyl containing oxadiazoles (compound 1 & 2) and then the final compounds were tested for their anti-microbial activity. Among the tested compounds, compound 1a, 1b,1c,2b and 2c showed good inhibition against Staphylococcus aureus, Pseudomonas aeruginosa and Klebsiella pneumonia bacterial strains. Compound 1a, 1c and 2c showed good inhibition against fungal strains. Compound 1c showed good fungicidal activity against Candida albicans, Aspergillus fumigates and Penicillium marneffei strains.

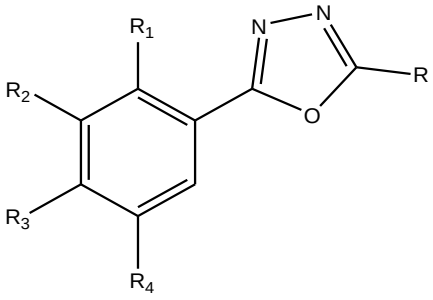


1a) R = 4-CH_3 ; 1b) R = 2-CH_3; 1c) R = 4-Cl-2-CH_3



2a) R = 2-Cl, 2b) R = 4-Cl; 2c) R = 2,4-Cl_2

A series of new oxadiazoles with 2-flouro-4-methoxy moiety were prepared by **B. Chandrakantha *et al*** [24]. Compounds 4a and 4b showed significant anti-bacterial activity against Escherichia coli and Pseudomonas aeruginosa. Compound 4i showed good anti-fungal activity.



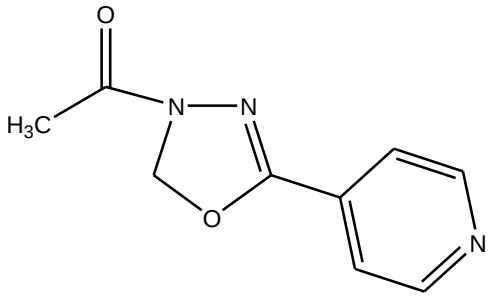
for compounds,

4a : R = 2-flouro-4-methoxyphenyl,R_1 =- CH_3 , R_2 = Br, R_3 = H, R_4 = H

4b : R = 2,3,4-triflourophenyl, R_1 = F, R_2 = H, R_3 = OCH_3, R_4= H

4i: R = 2-flouro-4-methoxyphenyl, R_1 = Br, R_2 = H, R_3= H, R_4=Cl

Shridhar *et al* [25] synthesized a series of 2,5-disubstituted-1,3,4-oxadiazolines by the reaction of isonicotinic acid hydrazide with various substituted aromatic acids in the presence of $POCl_3$. Ten compounds from this series were screened for anti-bacterial and anti-fungal activity. The synthesized compounds showed good anti-fungal with moderate anti-bacterial activity.



CONCLUSION:

The review reports synthetic approaches to some of the Oxadiazole derivatives and it highlights the use of Oxadiazole derivatives having antimicrobial activity. The 1,3,4-oxadiazole derivatives show significant antimicrobial activity against a variety of microorganisms such as fungi, Gram +ve and Gram –ve bacteria.

REFERENCES:

1. Radha R.B and Rao B.U.T. (1990). Synthesis and Biological activities of benzthiazolothiomethyl-oxadiazoles, thiadiazoles and triazoles. *Indian Journal of Chemistry*, 29, 995 – 998.
2. Duita MM and Kataky (1992). Synthesis and biological activities of Azadianesarylphosphate/ thiophosphate derivatives of 1,3,4-oxadiazoles and thiadiazoles. *Indian Journal of Chemical Society*, 69, 599 – 601.
3. Beenus SC, Hosus MC, Talawas MB, Laddi UV and Ranjani S. (1994). Synthesis and evaluation of anti-microbial activity of some new 1,3,4-oxadiazoles. *Indian Journal of Heterocyclic Chemistry*, 3, 237 – 239.
4. Kalluraya B , Ramesh C and Shivaram HB (1995). Synthesis and anti-microbial activity of various 5-substituted-1,3,4-oxadiazole-2-hydrazines. *Indian Journal of Pharmaceutical Sciences*, 5, 37 – 39.
5. Sonar VN , Yadav LDS and Sandhya S. (1995). New Mannich bases from oxadiazolyl indoles and their anti-bacterial activities. *Indian Journal of Heterocyclic Chemistry*, 4, 203 – 205.
6. Nailesh J., Korgaokar S. and Parekh H. (1996). Synthesis and anti-microbial activity of substituted 1,3,4-oxadiazoles. *Indian Journal of Heterocyclic Chemistry*, 5, 241 – 242.
7. Jayamma Y., Sarangapani M. and Reddy V.M. (1996). Synthesis and evaluation of biological activity of novel heterocycles. *Indian Journal of Heterocyclic Chemistry*, 6, 111 – 114.
8. Shah V.R., Vadodaria M. and Parikh A.R. (1997). Synthesis of 1,3,4-oxadiazoles having nicotinamide moiety as potential anti-microbial agents. *Indian Journal of Chemistry*, 36, 101 – 103.
9. Kapoor RP and Batra H (1997). Synthesis of some oxadiazoles and thiadiazoles of potential biological importance. *Indian Journal of Heterocyclic Chemistry*, 6, 1 – 4.
10. Zhang Z.Y., Hui X.P. and Zhang L.M. (1999). Synthesis and anti-fungal activities of 1,3,4-thiadiazoles, 1,3,4-oxadiazoles and 1,2,4-triazole derivatives of 5-methyloxazole. *Indian Journal of Chemistry*, 38, 1066 – 1070.
11. Lokanatha R.K.M., Manoj K.C., Shekar S.H. , Rajendra Prasad K. and Niranjana N. (1999). Synthesis of 2-(4'-pyridyl)-5-alkyloxy-1,3,4-oxadiazoles of potential biological importance. *Indian Journal of Chemistry*, 8, 335 -336.
12. Mogilaiah K. and Prashanthi (2000). A convenient synthesis of 5-aryl-2-[p-(1,8-naphthyridin-2yl)phenoxymethyl]-1,3,4-oxadiazoles under microwave irradiation. *Indian Journal of Heterocyclic Chemistry*, 14, 185 – 188.
13. Patel K.D., Mistry B.D. and Desai K.R. (2001). Synthesis and biological activity of oxadiazolines and oxadiazoles. *Indian Journal of Heterocyclic Chemistry*, 11, 63 - 66.
14. Khan M.S.Y. and Akthar M. (2001). Synthesis of some new 2,5-disubstituted-1,3,4-oxadiazole derivatives and evaluation of their biological activity. *Indian Journal of Heterocyclic Chemistry*, 42, 900 – 904.

15. Smitha N., Garg S.P. and Pramila S. (2002). Synthesis of some pyrazolones and oxadiazoles bearing 2-arylamino-5-mercapto-1,2,3-thiadiazole nuclei as possible anti-microbial agents. *Indian Journal of Heterocyclic Chemistry*, 12, 09 – 12.

16. Sachin G., Palaska E., Ekizoglu M., Ozalp M. (2002). Synthesis and anti-microbial activity of some 1,3,4-oxadiazole derivatives, *Il Farmaco*, 57, 539 – 542.

17. Gaurav G. and Kini S.G. (2002). Synthesis and evaluation of new 1,3,4-oxadiazole and 1,3,4-oxadiazol-2-thione derivatives of nalidixic acid as potential anti-bacterial and anti-fungal agents. *Indian Journal of Heterocyclic Chemistry*, 12, 289 – 290.

18. Khan M.S.Y. and Akthar M. (2003). Synthesis of some new 2,5-disubstituted-1,3,4-oxadiazole derivatives and evaluation of their biological activity. *Indian Journal of Chemistry*, 42, 900 – 904.

19. Mogilaiah K. and Sakram B. (2004). Synthesis and anti-microbial activities of 1,3,4-oxadiazole and pyrazoline derivatives containing 1,8-napthyridine moiety. *Indian Journal of Pharmaceutical Sciences*, 13, 289 – 292.

20. Shivarama H.B., Prasanna C.S. , Boja P. , Rao K.S. , Shridhara K. and Bhat G.U. (2004). Synthesis and insecticidal activity of some 1,3,4-oxadiazoles derived from 2-chloropyridine-5-acetic acid. *Indian Journal of Chemistry*, 43, 864 – 868.

21. Vagdevi H.M., Ravindra K.C., Vaidya V.P. and Basavaraj P. (2006). Synthesis, anti-microbial and anti-inflammatory activities of 1,3,4-oxadiazoles linked to naphthol[2,1-b] furan. *Indian Journal of Chemistry*, 45, 2506 – 2511.

22. Kaddi A.A., Brollosy N.R., Deep O.A., Habib E.E., Ibrahim T.T. and Emam A.A. (2007). Synthesis, anti-bacterial and anti-inflammatory activities of novel 2-(1-adamantyl)-5-substituted-1,3,4-oxadiazoles and 2-(1-adamantylamino)-5-substituted-1,3,4-thiadiazoles. *European Journal of Medicinal Chemistry*, 42, 235 – 242.

23. M.S. Karthikeyan, D.J. Prasad, M. Mahalinga, B.S. Holla and N.S. Kumari (2008). Synthesis, characterization and evaluation of anti-microbial activity of some novel oxadiazole derivatives. *European Journal Of Medicinal Chemistry*, 16, 3632 – 3640.

24. Chandrakantha B., Shetty P., Nambiar V., Isloor N. and Isloor A.M. (2010). Synthesis, characterization and biological activity of some new 1,3,4-oxadiazole bearing 2-flouro-4-methoxyphenyl moiety. *European Journal of Medicinal Chemistry*, 45, 1206 – 1210.

25. Shridhar A.H., Keshavayya and Joy H.H. (2011). Synthesis, characterization and pharmacological studies of novel bis-1,3,4-oxadiazole and 1,2,4-triazole derivatives. *Der Chemica Sinica*, 2, 106 – 114.