A Short Review on 1,3,4 –Oxadiazole and its Pharmacological Activities

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Abstract:
The 1,3,4-oxadiazole nucleus is a biologically important scaffold with a wide range of biological activities. Because of their broad and potent activity, 1,3,4-oxadiazole and its derivatives have become important pharmacological scaffolds, particularly in the treatment of cancer disease. Several di-, tri-, aromatic, and heterocyclic substituted 1,3,4-oxadiazole derivatives with potent anticancer activity have been reported. These substituted 1,3,4-oxadiazoles had different mechanisms of action and were involved in the discovery and development of anticancer drugs. This review is intended to supplement previous reviews by reviewing the work reported on 1,3,4-oxadiazole derivatives from the year 2000 to the beginning of 2020.

Keywords: oxadiazole nucleus, scaffolds, Hemorrhage, anticancer, heterocyclic and discovery.

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Introduction:

The study of heterocyclic compounds has always been an intriguing area of study in the field of chemistry. The carbon atoms are not the most important constituents of heterocyclic compounds. Some of the heteroatoms present in the rings that replace carbon are nitrogen, oxygen, and sulphur.[1] Replacements on the heterocyclic medications gives them more powerful and different functionalization. The significant intensifies present in nutrient B complex, colors, protein, anti-toxins, alkaloids, amino corrosive and medications are heterocyclic intensifies which are having therapeutics use.[2] The five membered oxadiazole core present in heterocyclic compounds is significantly answerable for the differentiated valuable natural impacts.[3] At the point when two methane (- CH=) bunches present in the furan ring are supplanted by two pyridine type nitrogen (- N=) then, at that point, n oxadiazole is derived with the general formula of C2H2ONa.[4] The electrophilic substitution reactions are not possible in oxadiazole because of low density of electrons on carbon atom which causes the electron withdrawal effect of pyridine type nitrogen when any electron releasing group was added to it. The oxadiazole ring is found to be resistant to nucleophilic substitutions. Whereas the halogen substituted oxadiazole can undergo these substitutions by replacing halogen atom by nucleophiles. Four isomers of oxadiazole are

present.[3]

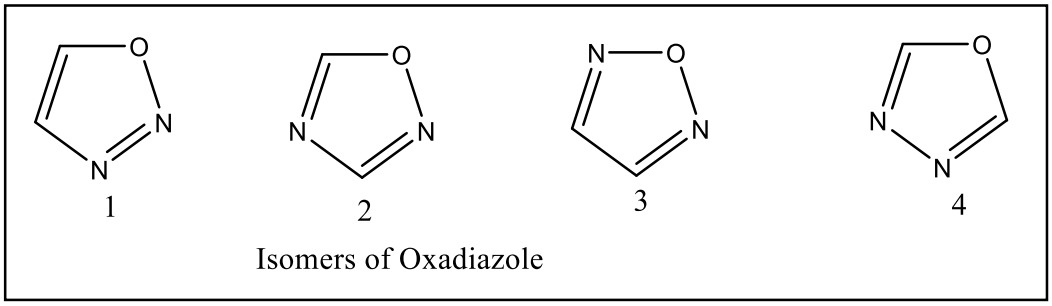


Figure 1: isomers of oxadiazole

Among the various isomers as shown in figure 1, the 1,3,4-oxadiazole isomer exhibits numerous therapeutic activities including antibacterial [4,5], anticonvulsant [6,] antitumor [7,8,9,10,11,12,13,14,15,16,17], hypoglycemic, antipyretic [18], anti-tubercular [5, 19], anti-viral [20], immunosuppressive, spasmolytic, antioxidant [8, 21], anti-inflammatory.

Differences between 1,2,4- and 1,3,4-Oxadiazoles

Although both 1,2,4- and 1,3,4-oxadiazoles satisfy Hückel rule (a cyclic and planar system containing (4n + 2 electrons), there are differences concerning their aromaticity. The idea that 1,2,4-oxadiazoles do not behave as aromatic compounds was experimentally confirmed in 1964 by Moussebois and Oth.[4] when the authors compared UV spectra of several aryl-substituted oxadiazole compounds. The chemical structures and maximum absorption wavelength values (λmax) of 3-phenyl-1,2,4-oxadiazole (1), 5-phenyl-1,2,4-oxadiazole (2) and 3,5-diphenyl-1,2,4-oxadiazole (3) derivatives are shown in figure 2 If the 1,2,4-oxadiazolic ring had considerable aromaticity, the presence of the two phenyl rings would cause a bathochromic effect on the λmax of these substances. This would decrease the amount of energy required for the $\pi \rightarrow \pi^*$ transition due to an increase in the conjugation. However, Moussebois found the λmax values of 238 nm for 1 (3-phenyl substituted), 250 nm for 2 (5-phenyl substituted) and curiously an intermediate value of 245 nm for derivative 3 (3,5-diphenyl substituted). These results indicate that the heterocyclic ring does not have significant aromaticity and is better described as a conjugated diene. 1,3,4-Oxadiazole derivatives, for their part, behave differently. It was observed that the presence of two phenyl rings considerably increases the observed λmax value. For example, 2-phenyl-1,3,4-oxadiazole (4) has a λmax= 245 nm. [27] whereas the 2,5-diphenyl-1,3,4-oxadiazole (5) analogue has a λmax= 276 nm (Figure 1).[28] The analysis of UV spectra information allows us to infer that 1,3,4-oxadiazoles have greater aromaticity, presumably because of their symmetry.

Structural profile of 1,3,4- and 1,2,4-oxadiazoles driving their intermolecular interactions with biomacromolecules

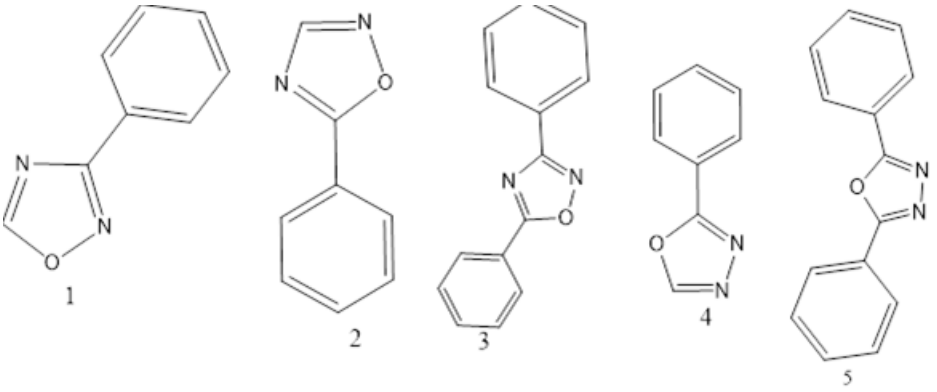


Figure 2: chemical structure of oxidiazoles

Dhumal et al reported 1,3,4-oxadiazole core's properties which are similar to an aromatic heterocycle. Being so, it has typical interactions of aromatic systems, such as π-π stacking with hydrophobic amino acids such as tyrosine, phenylalanine and tryptophan and he synthesized a series of 1,3,4-oxadiazoles aiming to inhibit the mycobacterial enoyl reductase (InhA) of Mycobacterium tuberculosis. Docking studies carried out. On InhA showed that the oxadiazole core of interacts with Phe149 and Tyr158 through a π-π stacking. This kind of interaction also happens in other 1,3,4-oxadiazoles designed by the authors, with relevant changes only at the level of the other structure decorations present, like a pyridine ring.[29] as shown in figure 3

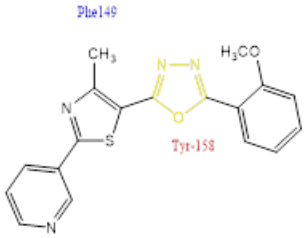


Figure 3: Schematic model of p-p stacking interaction

Synthesis and biological activity of 1, 3, 4-oxadiazole:

Xu WM, et al synthesised 1,3,4-oxadiazole moiety(Scheme:1) figure 4 , containing sulfone groups and were reported to have ability to mycelia growth of Ralstonia solanacearum in vitro also having better control effect against tobacco bacterial wilt so sulfone derivatives containing 1,3,4-oxadiazole can be used to develop potential bactericides for plants.[30]

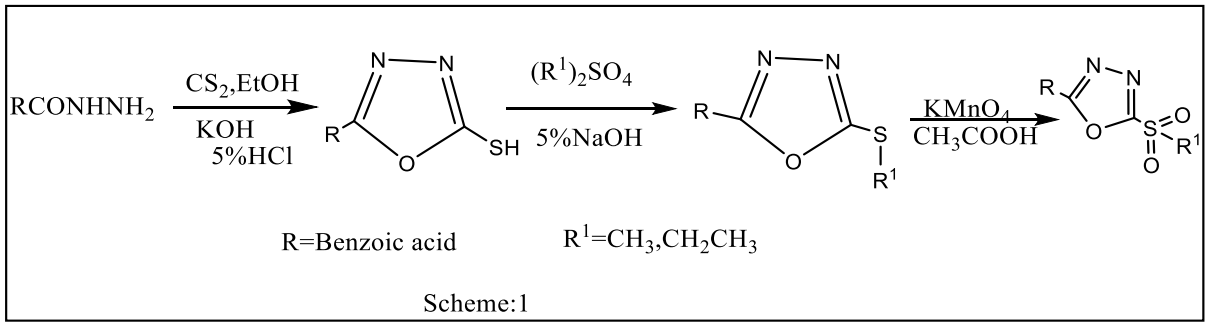


Figure 4: Scheme 1

Baykov et al. reported one-pot synthetic procedure for the synthesis of 3,5-disubstituted-1,2,4-oxadiazoles at room temperature (RT) from corresponding amidoximes and carboxylic acids methyl or ethyl esters in the superbase medium NaOH/DMSO (Scheme 2) figure 5 . [31] This synthetic approach led to obtain diverse oxadiazole analogs isolable via simple purification protocol, although in moderate to long reaction time (4–24h) with poor to excellent yields (11–90%). Moreover, the presence of -OH or -NH2 groups in the structure of carboxylic acid ester limited the formation of desired compound

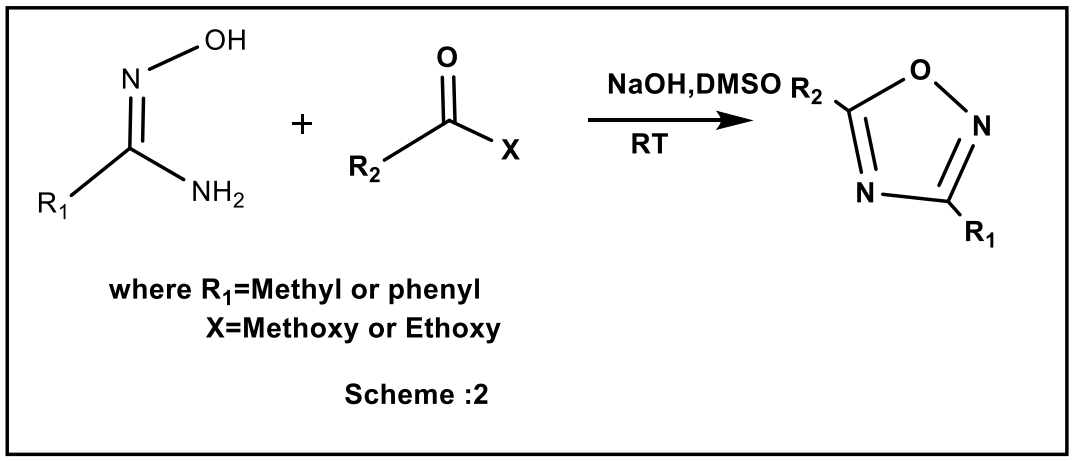


Figure 5: scheme 2

one-pot synthetic procedure of 3,5-disubstituted-1,2,4-oxadiazoles from the corresponding amidoximes and carboxylic acids employing the –COOH group activation via reaction with Vilsmeier reagent (Scheme 3) figure 6 was reported by Zarei M.[32]

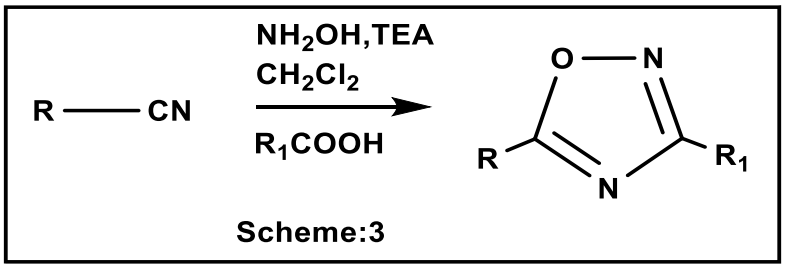


Figure 6 : Scheme 3

Golushko A. et al. developed a novel synthetic method of 1,2,4-oxadiazoles based on tandem reaction of nitroalkenes with arenes and nitriles in the presence of TfOH (Scheme 4) figure7. Despite the excellent yields (~90% in most cases) and short reaction time (10 min), the usage of a superacid requires resistant starting materials, which can be a serious limitation.[33]

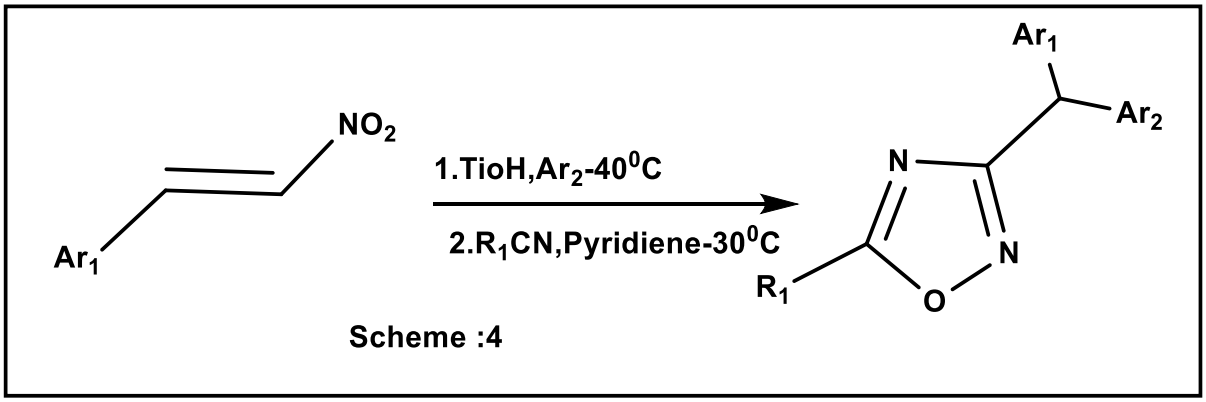
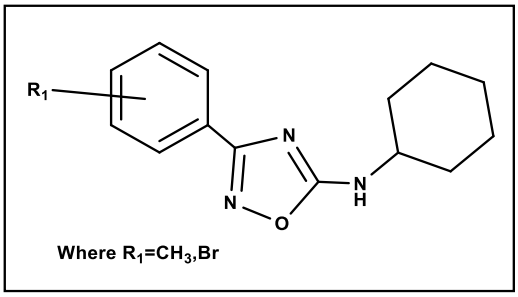


Figure 7: Scheme 4

De Oliveira V. N. M. and collaborators synthesized a series of substituted N-cyclohexyl-3-aryl-1,2,4-oxadiazole-5-amines from corresponding arylamidoximes and DCC under MWI and determined their antitumor activity against HCT-116, human prostate (PC-3) and human astrocytoma (SNB-19) cancer cell lines. Compounds shown in the table exhibited the highest activity and were further evaluated against five cell lines HCT-116, PC-3, SNB-19, mouse melanoma (B16F10) and mouse adipose (L929). Their activity expressed by the IC50 values ranged from 13.6 to48.37 μM, nonetheless, the levels of inhibition were still far from reference compound—doxorubicin, thus additional modifications of a chemical structure are required for improvement of the activity.[34]



Q. Gao, et.al reported a synthesis of direct annulation of hydrazides with methyl ketones for the synthesis of 1,3,4-oxadiazoles, the use of K2CO3 as a base achieves an unexpected and highly efficient C-C bond cleavage(Scheme:5) . This reaction is proposed to go through oxidative cleavage of Csp3-H bonds, followed by cyclisation and deacylation .[35]

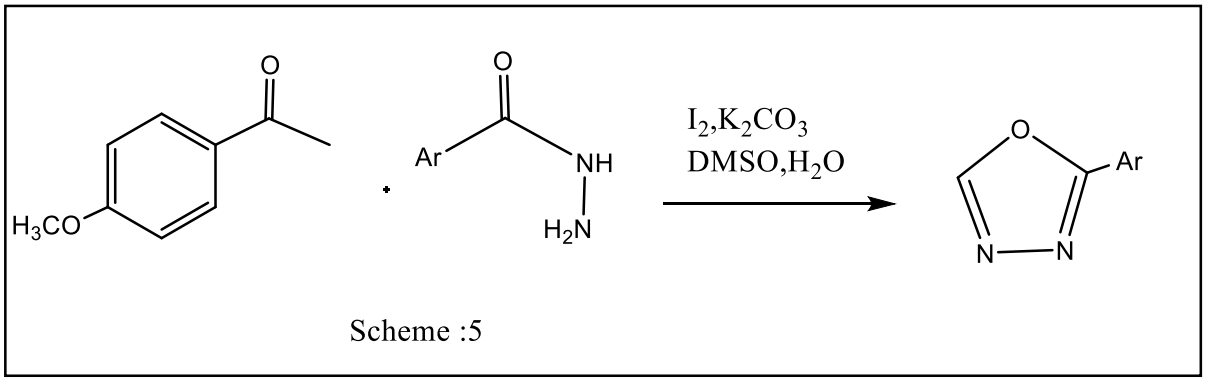


Figure 9: Scheme 5

V. Mercalli et.al reported three-component reaction of Z-chlorooximes, isocyanides, and hydroxylamines. Furthermore, a Mitsunobu-Beckmann rearrangement of aminodioximes yields 1,2,3-oxadiazole-5-amines. [36](Scheme:6)

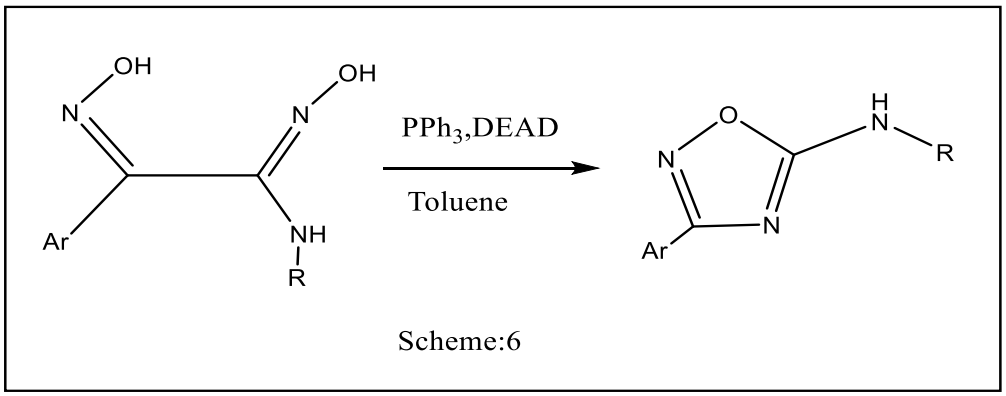
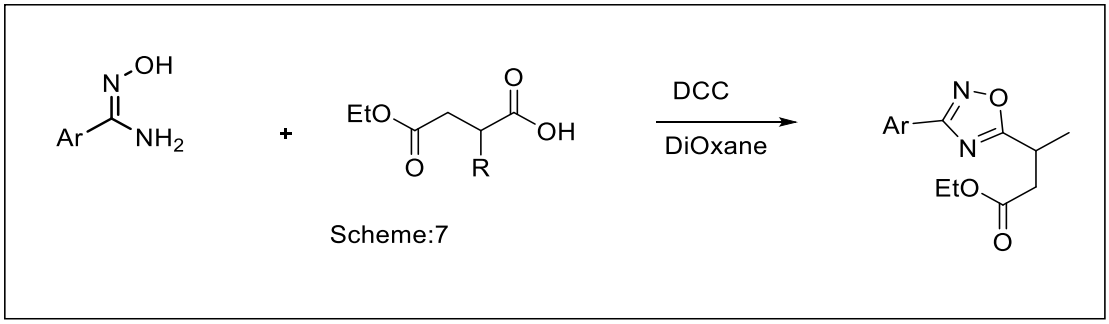


Figure 10: Scheme 6

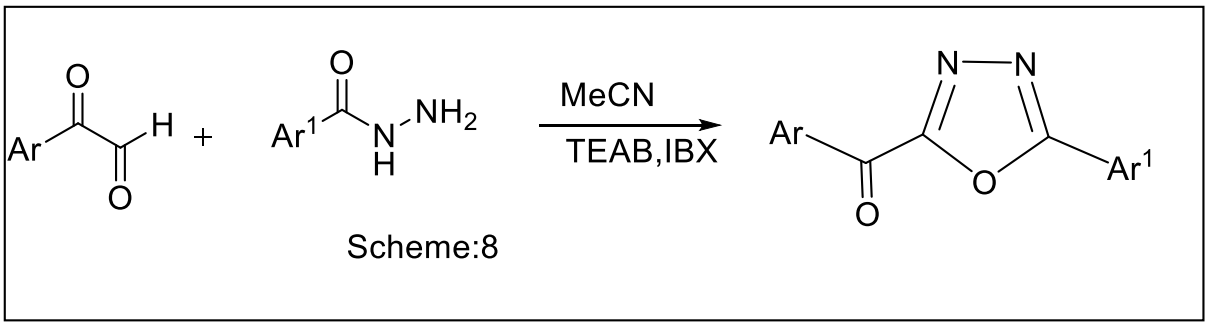
A. L. Braga and his co workers reported a synthesis of α-amino acid-derived 1,2,4-oxadiazoles via a convenient and inexpensive one-pot protocol in good yields and in relatively short reaction time .[37](Scheme :7)



Scheme:7

Figure 11: Scheme 7

D. Kumar and his collegues reported a synthesis of 2-iodoxybenzoic acid/tetraethyl ammonium bromide mediated oxidative cyclization of hydrazide-hydrazones by using aryl glyoxal and hydrazides.[38](Scheme :8)



Scheme:8

Figure 12 : Scheme 8

R. Kapoorr et al reported a synthesis of highly efficient eosin Y catalyzed oxidative heterocyclization of semicarbazones was established under visible-light photoredox catalysis using CBr4 as a bromine source. The protocol renders a rapid, mild, and efficient access to valuable 5-substituted 2-amino-1,3,4-oxadiazoles in an operationally simple way utilizing visible light and atmospheric oxygen.[39](Scheme:9)

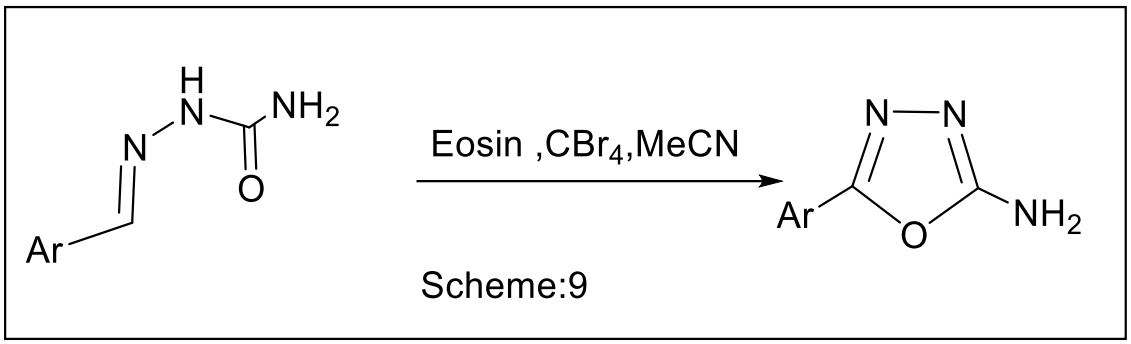


Figure13 : Scheme 9

S. J. Dolman and his coworkers reported a synthesis of 2-amino-1,3,4-oxadiazoles relies on a tosyl chloride/pyridine-mediated cyclization of thiosemicarbazides that consistently outperforms the analogous semicarbazide cyclizations. [40](Scheme:10)

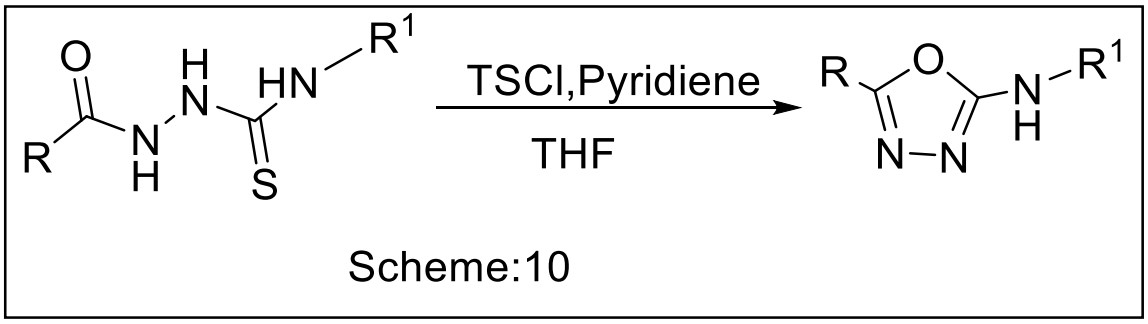


Figure14 : Scheme 10

L. Wang and his Coworkers reported a radical-promoted cross-dehydrogenative coupling strategy enables a metal- and base-free one-pot synthesis of 2,5-diaryl 1,3,4-oxadiazoles via N-acylation of aryl tetrazoles with aryl aldehydes, followed by thermal rearrangement. A broad range of aryl tetrazoles and aryl aldehydes deliver the corresponding products in good yields.[41](Scheme :11)

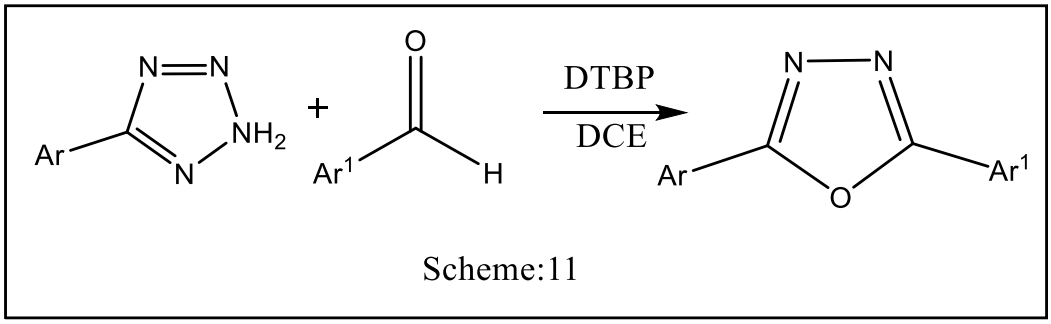


Figure 15: Scheme 11

Mohd Amir et al , synthesized a series of 2-[(5- diphenylmethyl-1,3,4-oxadiazoles-2-yl) sulfanyl-N- (substituted phenyl)-acetamides as antiinflamatory agents using paw edema model in wister rats. Halogen substituted derivatives in aryl ring showed significant anti-inflammatory activity.[42]

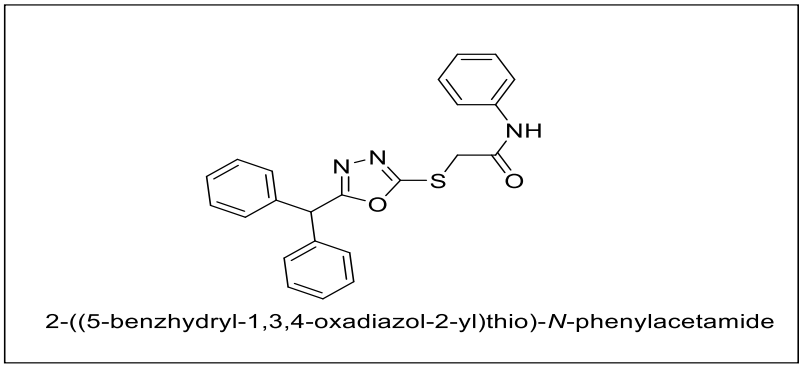


Figure 16: structure of 2-[(5- diphenylmethyl-1,3,4-oxadiazoles-2-yl) sulfanyl-N- (substituted phenyl)-acetamides

Same year he synthesized derivatives of 2- substituted aryl-5-(2,4,6-trichlorophenoxy methyl)-1,3,4- oxadiazole for anti-inflammatory and ulcerogenecity using pylorus ligation method.

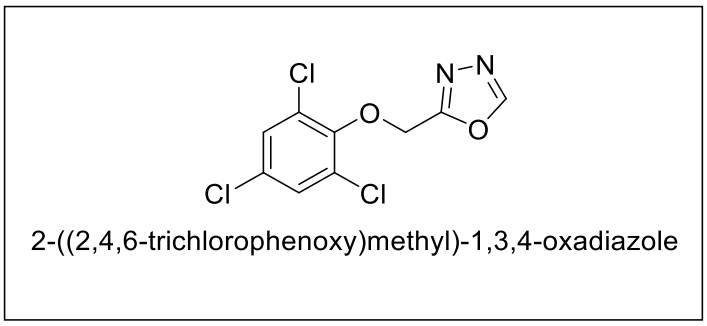


Figure 17: structure of derivatives of 2- substituted aryl-5-(2,4,6-trichlorophenoxy methyl)-1,3,4-oxadiazole.

Shashikant V Bhandari et al reported a synthesis of 5-[2-(2,6- dichloroaniline)benzyl]2-mercapto-1,3,4 oxadiazole and screened for anti-inflammatory activity and ulcerogenicity .[43]

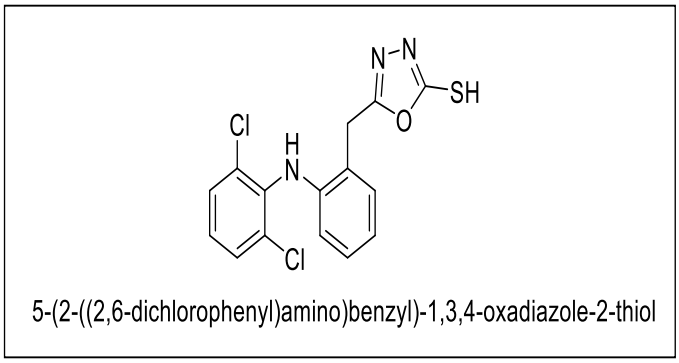


Figure 18: structure of 5- [2-(2,6- dichloroaniline) benzyl]2-mercapto-1,3,4 oxadiazole

Conclusion:

This review focuses on the antimicrobial activity of 1,3,4-oxadiazoles, as well as anti-inflammatory, anti-tumor, analgesic, anti-convulsant, antioxidant, anti-viral activity, and a variety of other activities. This emphasises the importance of investigating the 1,3,4-oxadiazole moiety for further research and screening.

The Department of Chemistry at St. Philomenas College (Autonomous) Mysuru provided all of the necessary resources. Dr. Bernard Prakash, Dr. Alphonsus DSouza,provided excellent technical assistance to this paper.

Conflict of Interest:

The authors declare no conflict of interest.

Acknowledgement:

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