

# **A REVIEW ON OXADIAZOLES AS A PHARMACOLOGICALLY ACTIVE NUCLEUS**

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## **ABSTRACT**

The structure of the Oxadiazole skeleton is a biologically/biochemically active nucleus which have multiple number of biological activities. Oxadiazole structure is a five-membered aromatic ring and has been used in multiple number of studies and molecules prepared synthetically in laboratories. The principle structure of Oxadiazole ring with a pair of Pyridine-type of nitrogen atoms has been confirmed to be valuable for Oxadiazole analogues for having efficacious protein interaction with multiple number of enzyme protein and receptor protein present in the organ system of the human body through/via different types of interactions, like Vander walls interaction, thereby producing a huge variety of biological activities or pharmacological properties. Due to the variety in the pharmacological activity of Oxadiazole and their derivatives/analogues, they has are termed as one of the important pharmacological aspects to study. Multiple number of Oxadiazole related synthetic compounds possessing high potent action and therapeutic activity are being widely incorporated for treatment and management of multiple number of diseases and disorders, giving immeasurable progression and establishment value. Oxadiazole derivatives expresses multiple number of pharmacological activities like antimicrobial, anti-inflammatory, analgesic, antifungal, antipyretic, antidepressant, antitubercular, anticonvulsant, anticholinesterase, antihypertensive, antidiabetic, antitumor/ anticancer, anti-HIV, antioxidant, etc. The history of 1,3,4-Oxadiazole is also very interesting. It shows that it attracted many chemists/researchers/scientists to explore the Oxadiazole nucleus as a biologically active molecule having promising potency. This review article mainly focuses on the pharmacological profile of 1,3,4- Oxadiazole with various activities and examples (in form of figures/structures). Expectations are like this article will be like a path showing torch to help and serve as a guidance for new innovations/ideas along the progression of research for the evolution of more n more active/potent and less poisonous/toxic Oxadiazole based derivatives.

## **KEYWORDS**

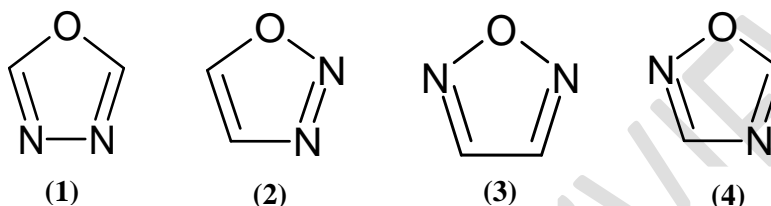
Oxadiazole, Antifungal, Pharmacological activity, Antimicrobial, Antitumor, Antitubercular.

## **INTRODUCTION**

Compounds having different heterocyclic moieties have earned special interest in drug discovery. Among all the heterocyclic compounds, oxadiazoles have influenced remarkable engrossment in medicinal and pharmaceutical chemistry and exhibited a huge scope of biological and pharmacological properties/actions. 1,3,4-oxadiazole derivatives represents an array of synthetic compounds with significant medicinal importance. Oxadiazole analogues are an interesting moiety which has continuously been the principle focus for multiple number of modern studies/researches. This present article narrates

some of the numerous biological and pharmacological activities incorporated with Oxadiazole structural system.

The molecular skeleton of Oxadiazole ring is consisting of 5 atom structure with couple of pyridine-type Nitrogen (N) with single Oxygen (O) atom. Regarding isomerism, four different types of structures for Oxadiazoles are available; such as: 1,3,4-oxadiazoles, 1,2,3-oxadiazoles, 1,2,5-oxadiazoles and 1,2,4-oxadiazoles. The 1,3,4-oxadiazoles variant and 1,2,4-oxadiazoles variant have been more focused and prominently studied due to possessing influential chemical, biological and pharmacological properties. The 1,2,5-oxadiazoles (furazan) is also studied to some extent and it have been found to display some biological activities. The 1,2,3-oxadiazoles (3) are not practically isolated in laboratories because they isomerize simultaneously to  $\alpha$ -diazo ketones (Figure 1).



**Figure 1. Structures of the regioisomeric oxadiazole rings**

Oxadiazole is a very weakly basic in nature owing to the (+/-) I effect (inductive effect) shown by the additional heteroatom. When a couple of  $-CH$  moiety from the structure of furan structure are exchanged by a couple of pyridine variety of Nitrogen atom ( $-N$ ), the Aromaticity property of the emerging Oxadiazole ring reduces by a significant value hence the resulting oxadiazole moiety shows/displays the characteristics/properties of conjugated diene. Because of the presence of comparatively less  $e^-$  (negative charge) cloud over the available Carbon atoms (at different positions for different isomers), the Oxadiazole ring is exceptionally non-favourable for electrophilic substitutions at the two carbon atom present; although the attack of electrophile or electrophilic groups occurs to the pyridine variety of Nitrogen atoms, when Oxadiazole moiety hydrogens are swapped with EDGs like ( $-CH_3$ ). Nucleophile based attack is exceptionally impossible in Oxadiazoles moiety due to presence of two pyridine type Nitrogen atoms with lone pairs of electrons; however, the Oxadiazole rings with halogen groups as side chains can react in nucleophilic substitution reactions.

Oxadiazole moiety is a very resourceful and has continuously been an area of large scale and vast study in the recent years. Compounds possessing Oxadiazoles skeleton in their structures are extensively studied for biological and pharmacological activities such as antiviral, antifungal, antimicrobial, antidiabetic, anticancer, antihypertensive activity, antioxidant, neuroprotective activity, hypolipidemic activities, anticholinesterase activity, inhibition of tyrosinase and anticonvulsant activity. They have also made a valuable contribution for intermediates in organic manufacturing of various compounds and largely used as transporting agents for electrons.

In this present review, emphasis is on the diverse pharmacological properties which are associated and contributed with substituted/derivatized Oxadiazoles in the past two and a half decades (1995- 2020).

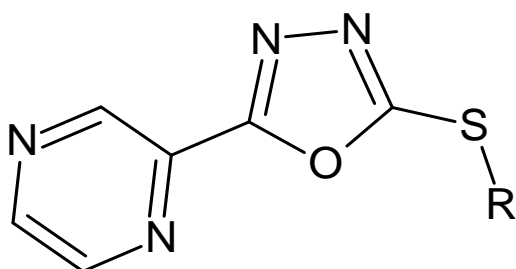
### **Pharmacological scaffolds of Oxadiazoles**

Oxadiazoles have been included into a domain of well- known biologically and pharmacologically active compounds, like, either as a side chain group or in the form of a modification of another heterocyclic ring. There are multiple number of reports in the literatures available describing the oxadiazole derivatives

regarding a multitude of pharmacological and biological effects and few of them are covered in this review.

### 1. Antifungal activity

**Pattan S.R. et al** synthesized 2-[5-(arylthio)-oxadiazole pyrazine analogues. Compounds displayed moderate to good Antifungal activity against *Aspergillus niger* at 200mcg/ml. Griseofulvin was used as standard drug for comparison [1a-1c].



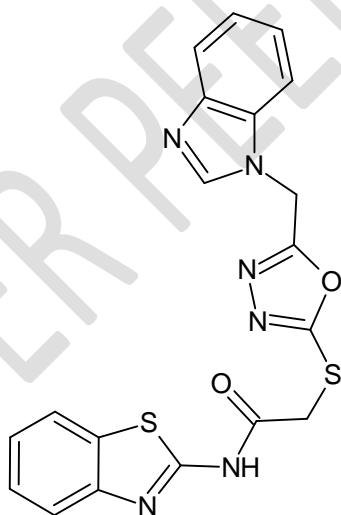
1a-1c

a, **R**= pyridine-2-yl

b, **R**= *o*-hydroxyphenyl

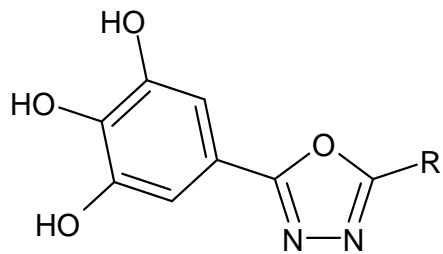
c, **R**= phenyl

**Rahul VP et al** innovated the benzimidazole oxadiazole thio-N-phenyl benzothiazole acetamides analogues. Two compounds showed better activity against *Aspergillus niger* at 12.5µg/ml of minimum inhibitory concentration (MIC) [2].



(2)

**K. Ilango et al** proposed novel set of 2- (trihydroxy phenyl)-5-substituted oxadiazoles analogues. Each of the proposed analogues were screened for antibacterial as well as antifungal activity. Few of the synthesized compounds displayed moderate antifungal action at an MIC value of 100µg/ml against *Aspergillus niger* while Ketoconazole was used as a standard/reference drug [3a-3c].



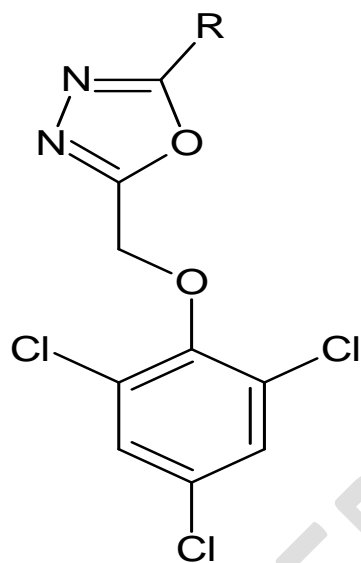
3a-3c

a, R= 2-hydroxy phenyl

b, R= 3-amino phenyl

c, R= 3- methoxy phenyl

**Nadagouda S.G. et al** synthesized 2-substitute-5-[(2,4,6-trichlorophenoxy) methyl]- 1,3,4-oxadiazoles derivatives. Some derivatives displayed promising fungicidal as well as fungistatic actions for *Aspergillus niger* while some showed moderate to weak activity compared with the standards of fluconazole and griseofulvin [4a-4d].



4a-4b

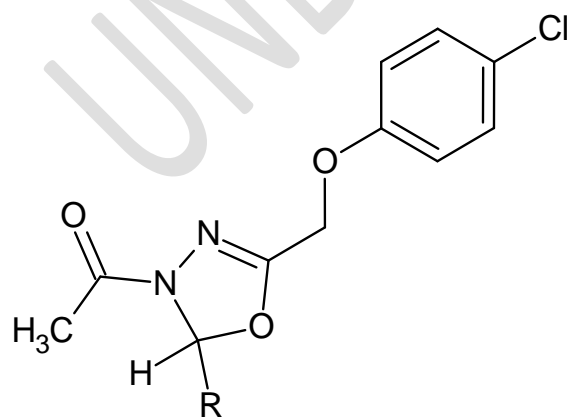
a, R= -S-CH<sub>2</sub>COOC<sub>2</sub>H<sub>5</sub>

b, R= -S-CH<sub>2</sub>COOH

c, R= -C<sub>6</sub>H<sub>5</sub>

d, R= 4-NH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>

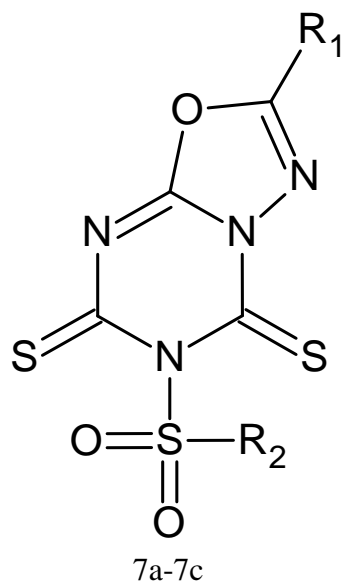
**S.D. Joshi et al** synthesized 2-aryl-3-acetyl-5-[4-chlorophenoxymethyl]-2,3-H-oxadiazoles analogues. One compound showed better antifungal activity against *Aspergillus niger* [5a].



5a

R= C<sub>6</sub>H<sub>5</sub>

**Dayashankar tripathi et al** synthesized 2-arylsulphonyl-oxadiazole-triazine-5,7-dithione derivatives. Three compounds exhibited the antifungal activity nearly parallel to that of Dithane M-45 (standard) at 100ppm conc. against *Aspergillus niger* [7a-7c].

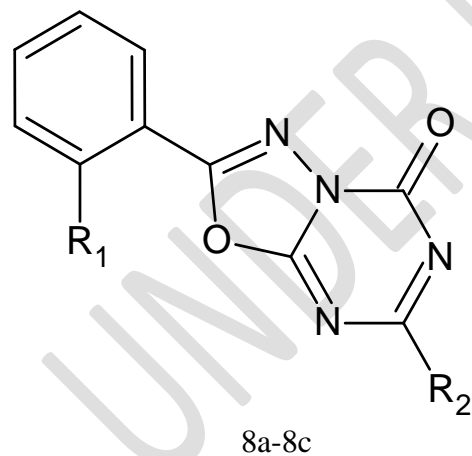


a,  $R_1 = 4\text{-ClC}_6\text{H}_4$ ;  $R_2 = 4\text{CH}_3\text{OC}_6\text{H}_4$

b,  $R_1 = 4\text{-ClC}_6\text{H}_4$ ;  $R_2 = 2\text{-ClC}_6\text{H}_4$

c,  $R_1 = 4\text{-ClC}_6\text{H}_4$ ;  $R_2 = 2\text{-BrC}_6\text{H}_4$

**D.V.Singh et al** synthesized 2-Aryl-7-alkyl or aryl-1,3,4-oxadiazole-triazine-5-thione derivatives. Few compounds had similar activity to Mancozeb at 1000ppm and showed 53-49% growth inhibition against *Aspergillus niger* [8a-8c].



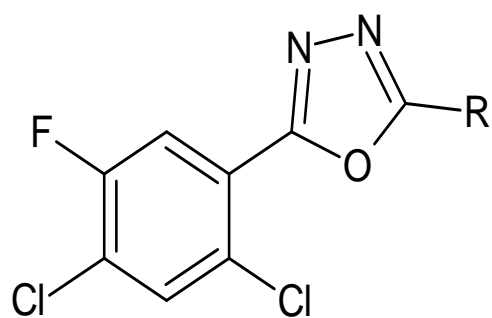
a,  $R_1 = \text{Cl}$ ;  $R_2 = \text{methyl}$

b,  $R_1 = \text{Cl}$ ;  $R_2 = \text{ethyl}$

c,  $R_1 = \text{Cl}$ ;  $R_2 = \text{phenyl}$

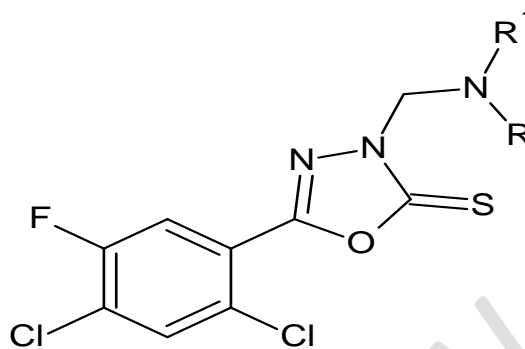
## 2. Anticancer activity

**K. Subrahmanya bhat et al** synthesized 3-(methylamino substituted)-5-(2,4-diCl-5-fluorobenzene)-oxadiazolo derivatives. Two compounds emerged active in the primary anticancer assay against breast cancer MCF-7 cell line [9a-9b].



R = 5-(3-Cl-4-F-C<sub>6</sub>H<sub>3</sub>)-2-furanyl-

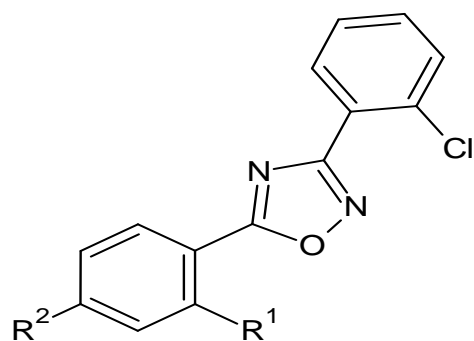
9a



NRR' = Methylpiperazino

9b

**Mrityunjy kundu et al** synthesized 3-(2-Chlorophenyl)-5-substituted-1,2,4- Oxadiazole analogues. Two analogues showed potent anticancer property on Swiss albino mice [10a-10b].

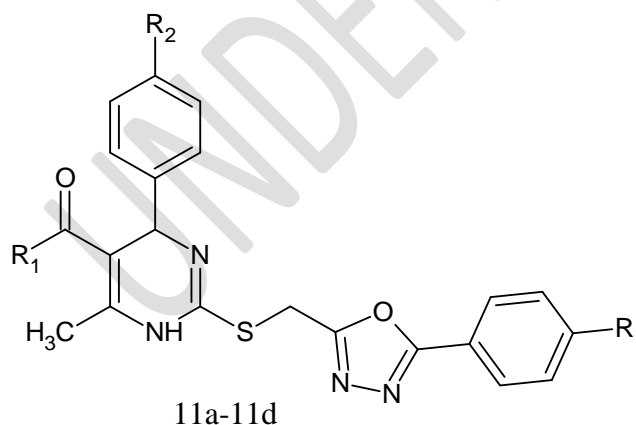


10a-10b

a, R<sup>1</sup> = H ; R<sup>2</sup> = Cl

b, R<sup>1</sup> = Cl ; R<sup>2</sup> = Cl

**Fatma A.F. Ragab et al** synthesized Dihydropyrimidine analogues having oxadiazole ring as monastrol derivatives. Some derivatives displayed action to combat various cancer cell lines [11a-11d].



11a-11d

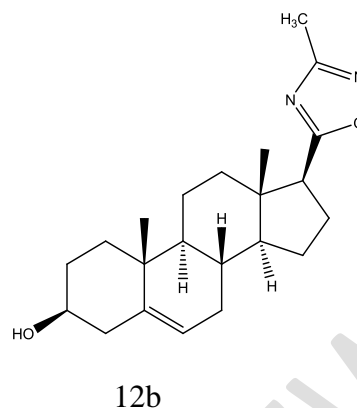
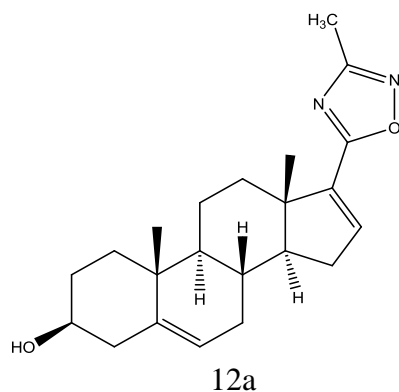
a, R = Cl; R<sub>1</sub> = OC<sub>2</sub>H<sub>5</sub> ; R<sub>2</sub> = 4-Cl

a, R = Cl; R<sub>1</sub> = OC<sub>2</sub>H<sub>5</sub>; R<sub>2</sub> = 4-Br

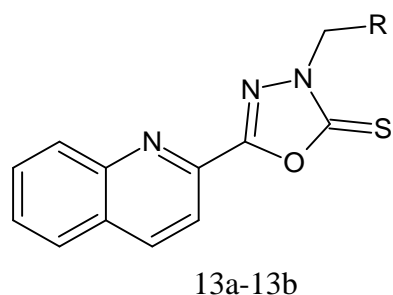
a, R = Cl; R<sub>1</sub> = OC<sub>2</sub>H<sub>5</sub> ; R<sub>2</sub> = 3-Cl

a, R = Cl; R<sub>1</sub> = OC<sub>2</sub>H<sub>5</sub>; R<sub>2</sub> = 2,4-diCl

**Dora kovacs et al** synthesized novel series of Oxadiazole ring in the steroidal structure. Two compounds found to be having antiproliferative activity against 4 cell lines (HeLa, MCF7, A2780 and A431) and inhibition action over rat testicular C<sub>17,20</sub>-lyase [12a-12b].



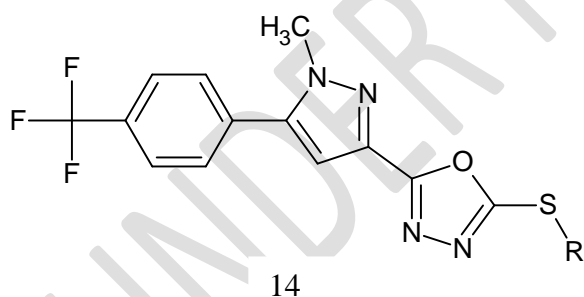
**J. sun et al** synthesized 2-aminomethyl-5-quinoline-oxadiazole-thione quinolone analogues. Two of these innovated compounds showed promising antiangiogenic activity against various cell lines like HepG2, SGC-7901 and MCF-7 [13a-13b].



a, R= -NH-C<sub>6</sub>H<sub>4</sub>(2-F)

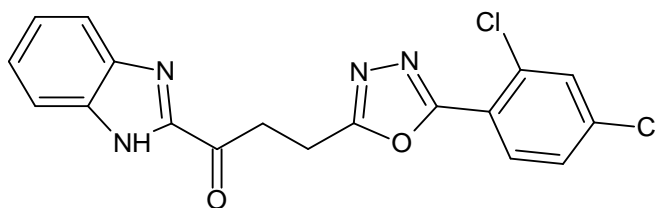
b, R= -NH-C<sub>6</sub>H<sub>4</sub>(4-Cl)

**Pushpan P. et al** synthesized a series of oxadiazolo having N-methyl-4-(CF<sub>3</sub>) phenyl pyrazole group. One compound showed most potent cytotoxic activity with MIC values 15.54 mM in MCF-7 cells [14].

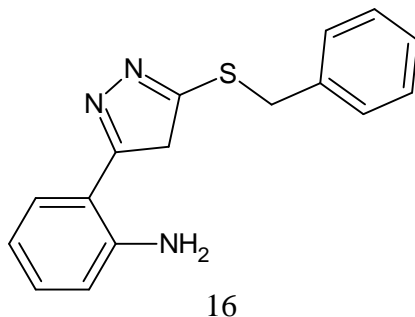


R= 4-CF<sub>2</sub>-C<sub>6</sub>H<sub>4</sub>-CH<sub>2</sub>-

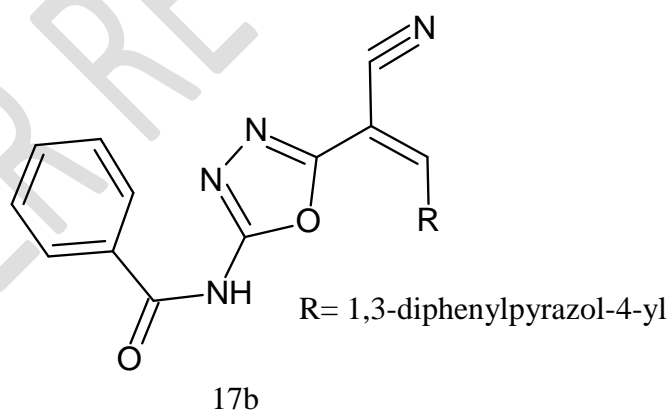
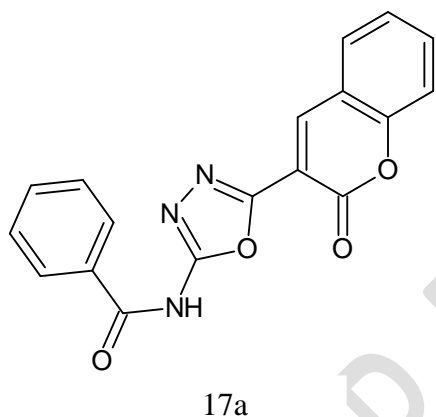
**Mohd. Rashid et al** synthesized novel series of 1-(1*H*-benzimidazole)-3-(5-(aryl)-oxadiazole)-propanone derivatives. One of the derivative exhibited maximum growth inhibition and was screened at 5 different dose concentrations (0.01, 0.1, 1, 10 and 100 mM) [15].



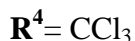
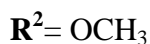
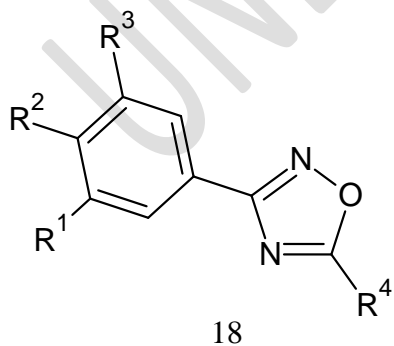
**Kia liu et al** innovated a novel set of 2-(benzylthio)-5-aryloxadiazoles. One derivative was found to have most anti-tumor activity while the evaluation on cell lines like MCF-7 and A549, B16-F10. For reference, Gefitinib was used as standard drug [16].



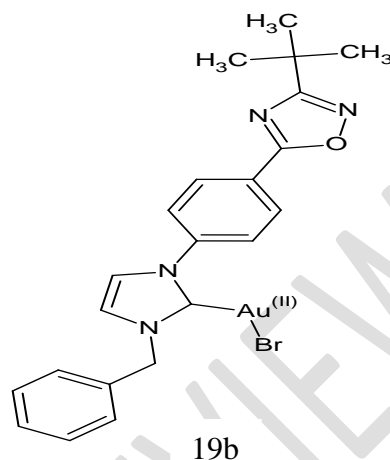
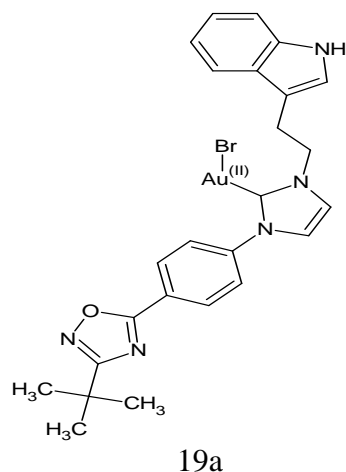
**Samir bondock et al** put forward few oxadiazoles related heterocyclic moiety. Five compounds exhibited prominent potency against HepG2, WI 38, MCF-7, & VERO at different MIC concentrations ranging from 10 to 1000 $\mu$ g/ml [17a-17b].



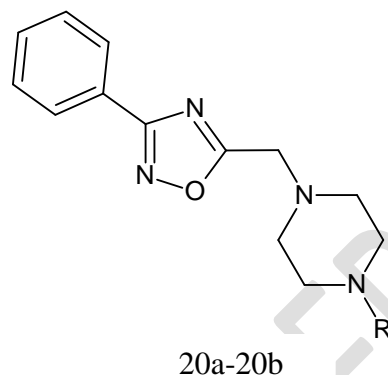
**Dalip kumar et al** innovated a series of 1,2,4-oxadiazolo analogues. The trichloromethyl analogues which were proved to have best activity among the derivatives of the set with significant potent action to combat PC3, DU145, LnCaP, MCF7 MDA-MB-231, PaCa2 and DUP145 with IC<sub>50</sub> 9.2  $\mu$ M [18].



**Catalin V. Maftei et al** synthesized novel set of gold related nitrogen containing heterocycle carbene (NHC) combined with oxadiazole analogues through related imidazolium salts. Few compounds revealed impressive potency and tumor selectivity with  $IC_{50} < 0.1 \mu M$  against a 12 cancer cell lines [19a -19b].



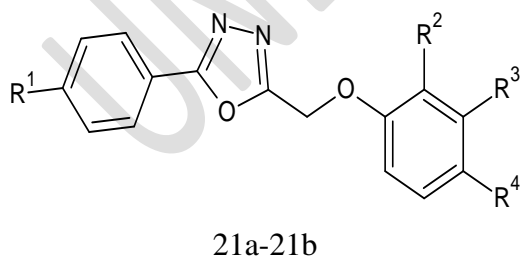
**Wiliam caneschi et al** innovated a series of 1,2,4 and 1,3,4-oxadiazoles consisting of a lipophilic moiety. Two compounds of 1,2,4- oxadiazole derivative was selectively most potent against 4T1 cell line. Few compounds of 1,3,4-oxadiazole analogues with aryl substitutes associated showed quite potent in anticancer assays [20a-20b].



a,  $R = -(CH_2)_9CH_3$

b,  $R = -(CH_2)_{11}CH_3$

**K. Lakshmithendral et al** innovated 2-(phenoxyethyl)-5- phenyl-1,3,4-oxadiazoles. Two analogues showed good to moderate anti- breast cancer action in MDA-MB-453 and MCF-7 cell lines [21a-21b].



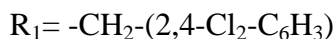
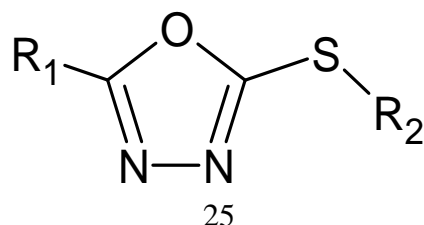
a,  $R^1 = OCH_3$  ;  $R^2 = OCH_3$  ;  $R^3 = H$  ;  $R^4 = CN$

b,  $R^1 = F$  ;  $R^2 = OCH_3$  ;  $R^3 = H$  ;  $R^4 = CN$

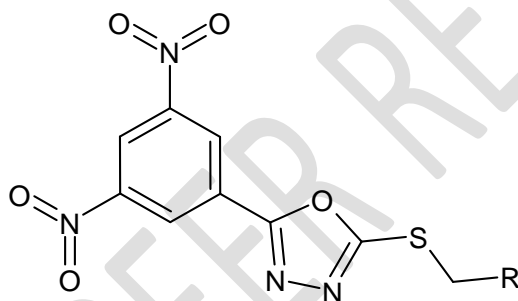
**Zhuang yang et al** synthesized 1,2,4-oxadiazoles comprising of hydroxamic acid analogues regarding a histone deacetylase inhibitor. The most active derivative exhibited optimum HDAC inhibition action, mostly towards HDAC with MIC values ranging 1.8 to 3.0nM, with the antiangiogenic MIC values range 9.8-44.9 nM to combat 12 different cancer cell lines [22].



**Ravi LB et al** innovated 2-(alkyl-thio)-5-(substituted aryl-methyl)-1,3,4-oxadiazole analogues. One of the proposed compound showed almost equipotent anti-mycobacterial activity as that of Isoniazid against nine multidrug-resistant (MDR) & two poly-drug resistant MTB strains [25].



**Galina karabanovich et al** synthesized S-aryl-3,5-dinitrobenzene 1,3,4-oxadiazolo-thiols. Few compounds displayed tremendous anti-tubercular activity with minimum inhibitory concentration values 0.03- 0.06 $\mu$ M and cross resistance was not observed with any of the anti-tubercular drugs [26a-26f].



26a-26f

a,  $R = -(4-OCH_3)C_6H_4$

b,  $R = -(2-Cl) C_6H_4$

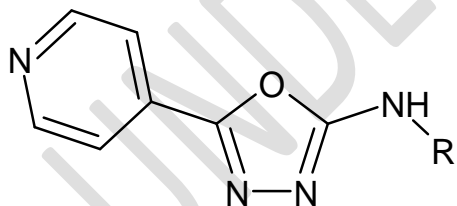
c,  $R = -(3-Cl) C_6H_4$

d,  $R = -(4-Cl) C_6H_4$

e,  $R = -(3,4-diCl) C_6H_4$

f,  $R = -(4-Br) C_6H_4$

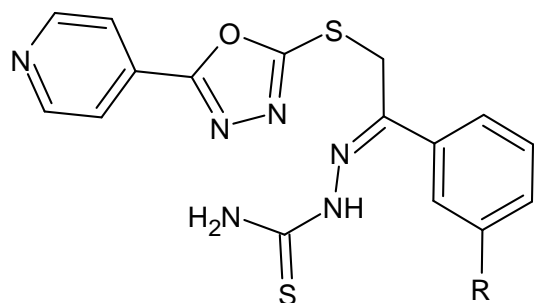
**Rudolf vosatka et al** innovated 1,3,4-oxadiazole analogues of Isoniazid analogues. Results of pharmacological activities were not that promising. The oxadiazole analogues showed very moderate anti-TB activity [27].



27

R= butyl, hexyl, heptyl, tridecyl,  
pentadecyl, hexadecyl, octadecyl

**Ajay N. Ambhore et al** synthesized pyridine-oxadiazole-thio-ethylidene-hydrazinecarbothioamide analogues. Few compounds showed potent growth inhibition and anti-mycobacterium activity and the others showed moderate activities as compared to the drugs Rifampicin and Isoniazid as standard [28a-28c].



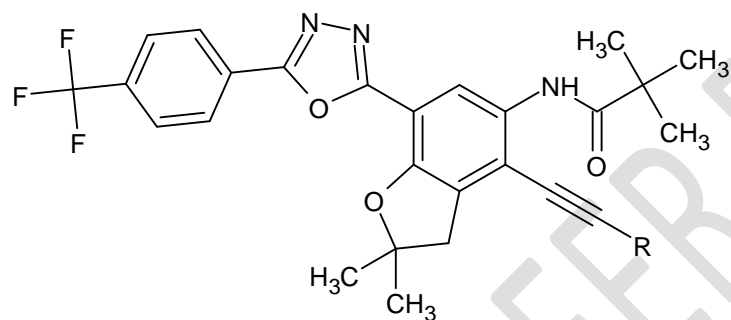
a, **R**= Br

b, **R**= NO<sub>2</sub>

c, **R**= CH<sub>3</sub>

28a-28c

**Somnath gholap et al** synthesized 2,2-diCH<sub>3</sub>-2,3-dihydrobenzofurane linked oxadiazolo analogues. Few of the proposed derivatives exhibited significant potent activity against non-replicating with comparison to that of to combat replicating broth of *M. tuberculosis* H37Ra ex vivo as well as in vitro at MIC values ranging 2.31 to 23.91 µg/ml using the cell lines THP-1, A549 and PANC-1 [29a-29e].



a, **R**= -C<sub>6</sub>H<sub>5</sub>

b, **R**= -cyclopentyl

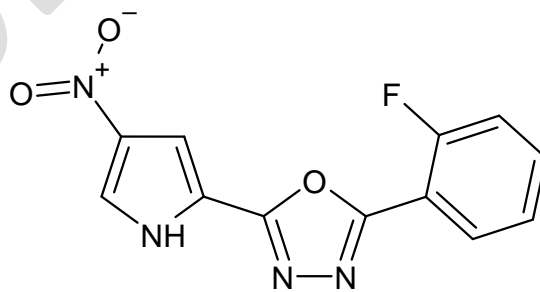
c, **R**= -cyclopropyl

d, **R**= -(4-CF<sub>3</sub>) C<sub>6</sub>H<sub>4</sub>

e, **R**= -CH<sub>2</sub>OH

29a-29e

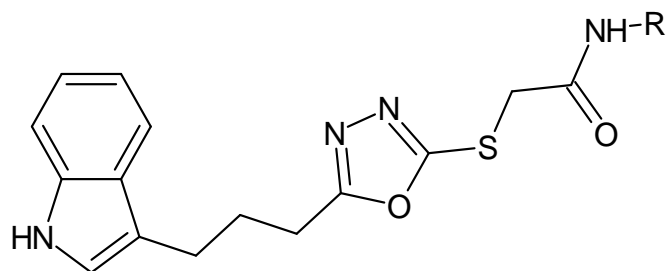
**Rajesh A. Rane et al** synthesized 4-nitropyrole-based 1,3,4-oxadiazole (2-(4-NO<sub>2</sub>-pyrrol-2-yl)-5-substituted-1,3,4-oxadiazolo) analogues. One of the synthesized compounds showed anti-mycobacterial activity (0.46 µg/ml) equivalent to that of reference Isoniazid (0.40 µg/ml) against VERO cell line and was proved non harmful [30].



30

#### 4. Anti-diabetic activity

**Majid nazir et al** synthesized 5-[3-(1*H*-indol-3-yl) propyl]-1,3,4-oxadiazolo-2-thiols analogues. Two of the synthesized compounds were most potent with MIC values ranging  $9.46 \pm 0.03 \mu\text{M}$  to  $9.37 \pm 0.03 \mu\text{M}$ . Remaining derivatives displayed nonsignificant inhibitory property. The MIC values were from  $12.68 \pm 0.04$  to  $37.82 \pm 0.07$ , whereas the reference acarbose (MIC =  $37.38 \pm 0.12 \mu\text{M}$ ) [31a-31b].

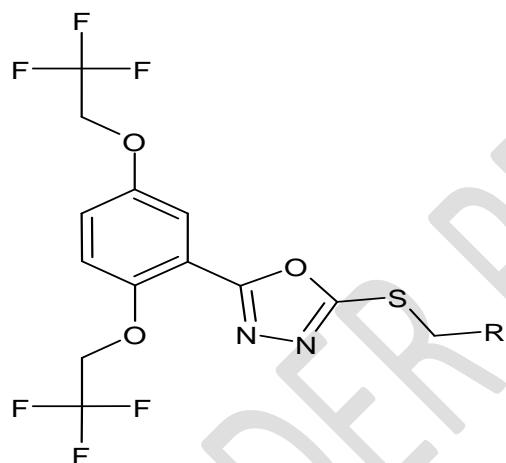


31a-31b

a, **R**= 2,3-dimethylphenyl

b, **R**= 5-methylpyridine-2-yl

**Ramesh S. Gani et al** synthesized new set of 5-(2,5-bis(2,2,2-trifluoroethoxy) phenyl)-1,3,4-oxadiazolo-2-thiols analogues. Two of the synthesized derivatives showed better activity both in vitro as well as in vivo at MIC=40.00- 80.00 $\mu\text{g/ml}$  as compared to the reference acarbose (MIC=34.72 $\mu\text{g/ml}$ ) [32a-32b].



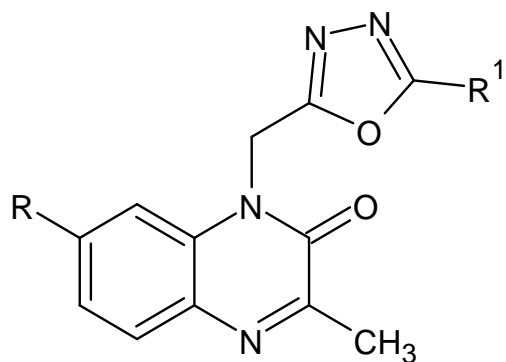
32a-32b

a, **R**= -C<sub>6</sub>H<sub>5</sub>

b, **R**= -(4-NO<sub>2</sub>)C<sub>6</sub>H<sub>5</sub>

## 5. Anti-inflammatory activity

**Shivananda wagle et al** synthesized 2-(3-methyl-7-aryl-2-oxoquinoxaliny)-5-(substituted)-1,3,4-oxadiazoles analogues. Few compound exhibited good anti-inflammatory action at 50mg/kg dose using carrageenan-induced paw edema method. Indomethacin was taken for reference [33a-33d].



33a-33d

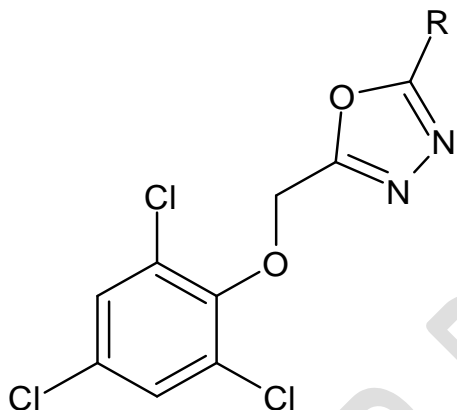
a,  $R = CH_3, Cl, H$  ;  $R^1 = 4(OCH_3)C_6H_4$

b,  $R = CH_3, Cl, H$  ;  $R^1 = 3,4,5(OCH_3)C_6H_2$

c,  $R = CH_3, Cl, H$  ;  $R^1 = -S-CH_3$

d,  $R = CH_3, Cl, H$  ;  $R^1 = -S-C_2H_5$

**Mohd Amir et al** synthesized 2-Substitutedaryl-5-(2,4,6-trichlorophenoxy\_methyl)-1,3,4-oxadiazolo analogues. Two of the proposed derivatives displayed maximum anti-inflammatory action while being checked by carrageenan-induced rat paw edema method with NSAIDs for reference [34a-34b].

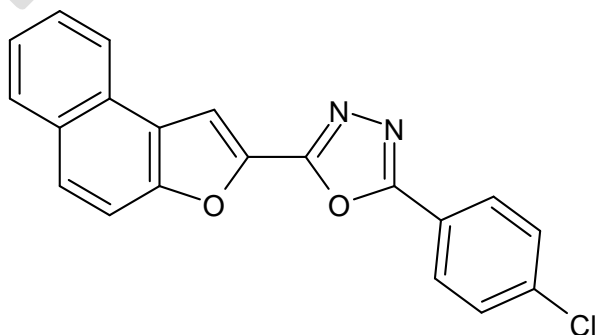


34a-34b

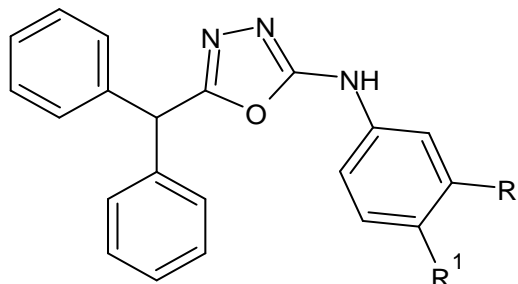
a,  $R = 2,4\text{-Dichlorophenyl}$

b,  $R = 1\text{-(4-isobutylphenyl) ethyl}$

**Ravindra KC et al** innovated 2-Naphtho [2,1-b]furan-2-yl-5-substituted-1,3,4-oxadiazole derivatives. One of the synthesized compounds was displaying higher anti-inflammatory potency while compared with the reference drug using Ibuprofen for reference by carrageenan-induced rat paw edema [35].



**Mohd Amir et al** synthesized 5-(diphenylmethyl)-2-(4-halogenated phenyl) amino-1,3,4-oxadiazolo analogues. Two of the proposed derivatives emerged as most potent compounds (70mg/kg body weight) of the synthesis and were moderate potent, while compared with the reference Ibuprofen, using the carrageenan-induced rat paw edema method in albino rats [36a-36b].

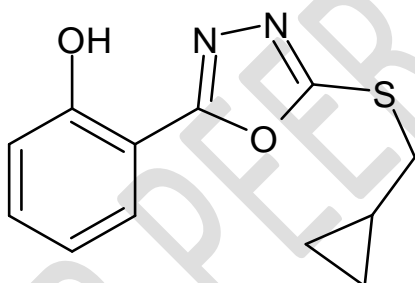


a,  $R = H$  ;  $R^1 = F$

a,  $R = Cl$  ;  $R^1 = F$

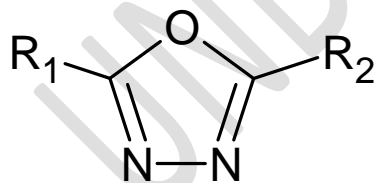
36a-36b

**Kittur B.S. et al** innovated 2-mercapto-1,3,4-oxadiazole analogues. Out of three proposed derivatives, only one of them was showing promising anti-inflammatory activity while the others were exhibiting moderate activity [37].



37

**R.R. Somani et al** proposed 2,5-Disubstituted aryl-1,3,4-oxadiazole scaffolds. All the synthesized derivative was showing inhibitory effects towards the induced inflammation. Few of the synthesized compounds were exhibiting great percentages of inhibition [38a-38b].

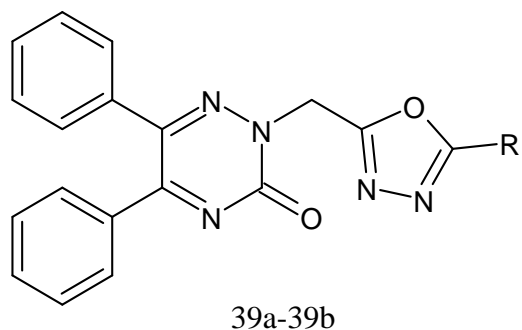


a,  $R_1 = [2-(2,6-Dichloroanilino) Benzyl]$  ;  $R_2 = -4-methyl phenyl$

b,  $R_1 = [2-(2,6-Dichloroanilino) phenyl]$  ;  $R_2 = -(pyridine-4-yl)$

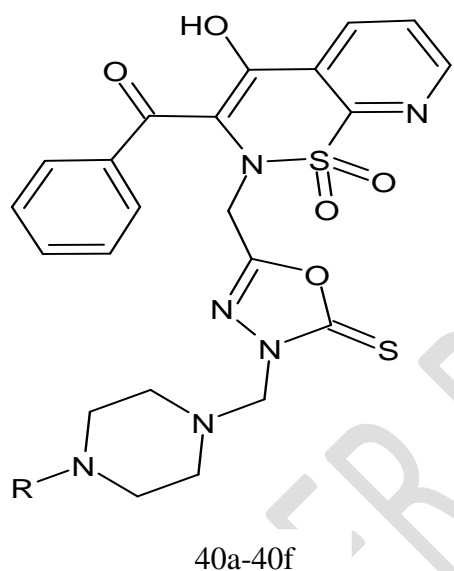
38a-38b

**Anupam G. Banerjee et al** synthesized 5, 6-diphenyl-1,2,4-triazin-3(2H)-one analogues having 5-aryl Oxadiazole analogues. Few of the proposed analogues were showing decent inhibition percentage of the denaturation (80.81-76.70%) of the Bovine serum albumin (BSA) compared to the standard Indomethacin (84.88%) [39a-39e].



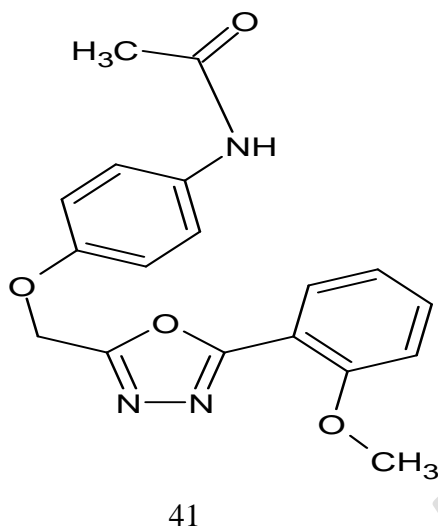
- a, **R**=*o,p*-dihydroxyphenyl
- b, **R**=*p*-aminophenyl
- c, **R**=*p*-chlorophenyl
- d, **R**=*p*-methoxyphenyl
- e, **R**=*p*-nitrophenyl

**Teresa glomb et al** innovated new oxadiazole analogues of pyridothiazine-1,1-dioxide. Few of the synthesized compounds exhibited COX inhibition at a minimum inhibitory concentration of 100 $\mu$ M (either COX-1 or COX-2) while others displayed no inhibitory activity compared to the reference Meloxicam [40a-40f].



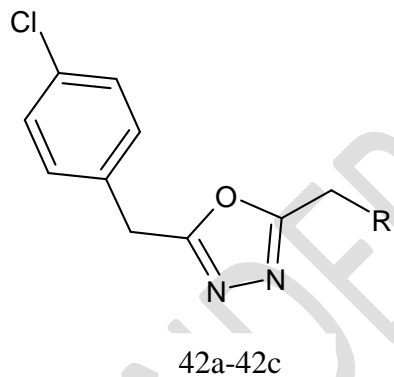
- a, **R**=3-trifluoromethylphenyl
- b, **R**=*o,p*-difluorophenyl
- c, **R**=*o*-cyanophenyl
- d, **R**=*p*-nitrophenyl

**K. Ilango et al** synthesized 2- (4-Acetamido phenoxy methyl) - 5-substituted- oxadiazolo analogues. One of the synthesized compounds displayed the highest anti-inflammatory activity while few of the derivatives exhibited moderate activities against carrageenan induced paw edema in rats at the concentration of 50mg/ml using Diclofenac sodium as standard drug [41].



## 6. Anti-bacterial activity

**N.C. Desai et al** proposed 2-Substitutedamine-5-chlorobenzene-1,3,4-oxadiazole analogues. Out of 9 proposed derivatives, few derivatives showed promising bactericidal action to combat *E. coli* and *S. aureus* at MIC values in the range of 6-18 $\mu$ g/ml. other synthesized compounds were showing moderate activity of inhibition [42a-42c].

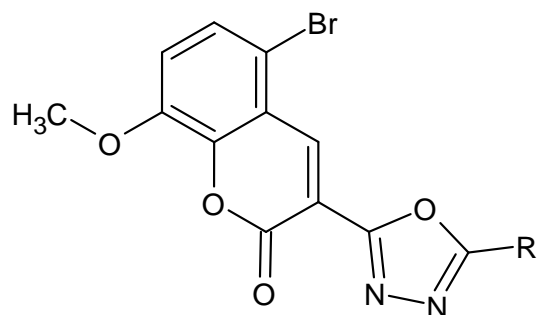


a, **R**= -2-OC<sub>2</sub>H<sub>5</sub>-C<sub>6</sub>H<sub>4</sub>

b, **R**= -2,5-(OCH<sub>3</sub>)<sub>2</sub>-C<sub>6</sub>H<sub>3</sub>

c, **R**= -4-CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>

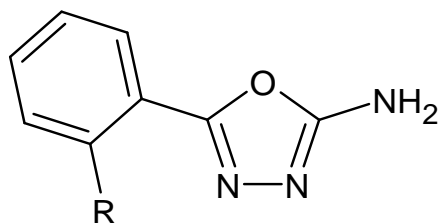
**Devki desai et al** synthesized 2-Aryl-5-(8'methoxy-5'bromo-3'coumarinyl)-1,3,4-oxadiazole analogues. Few of the proposed derivatives showed moderate activity at 500ppm concentration against *E. coli* [43a-43c].



43a-43c

- a,  $R = -p\text{-CH}_3\text{-C}_6\text{H}_4$
- b,  $R = -p\text{-NO}_2\text{-C}_6\text{H}_4$
- c,  $R = -o\text{-NO}_2\text{-C}_6\text{H}_4$

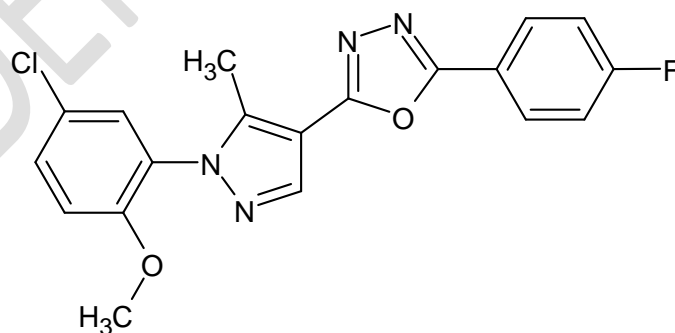
**M.S.Y. Khan et al** proposed 2-NH-5-Substitutedphenyl-oxadiazolo analogues. Few compounds were exhibiting good antibacterial activity while the others were showing moderate activity against *E. coli* at 100µg/ml with Norfloxacin as reference drug (50µg/ml) [44a-44b].



44a-44b

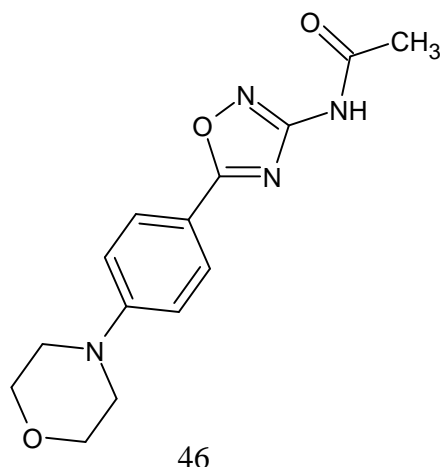
- a,  $R = -\text{OH}$
- b,  $R = -\text{F}$

**Neithnadka Preamsai Rai et al** proposed 2-[1-(5-Chloro-2-methoxy-phenyl)-5-(4-fluorophenyl)-1H-pyrazol-4-yl]-5-(aryl)-oxadiazole analogues. Only one of the synthesized compounds exhibited noticeable bactericidal action with MICs ranging 22.4 to 30.0 mg/mL to combat *Bacillus subtilis* etc. The remaining derivatives displayed moderate activity. Ampicillin was used as standard [45].

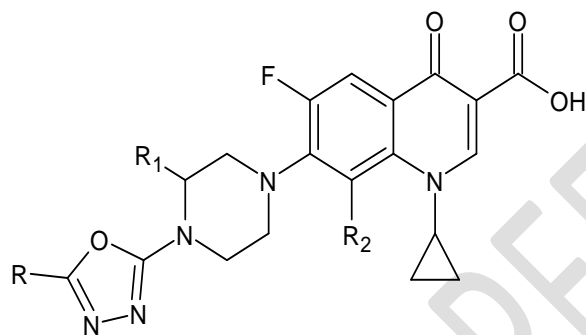


45

**Antonio palumbo piccionello et al** synthesized two sets of 1,2,4-oxadiazoles, having variant side chains and comprising of a different amount of fluorine atoms. Only one of the proposed compounds was found to exhibit a better activity against *S. pyogenes* (64mg/L). Linezolid and Ceftriaxone were used as standard drugs [46].



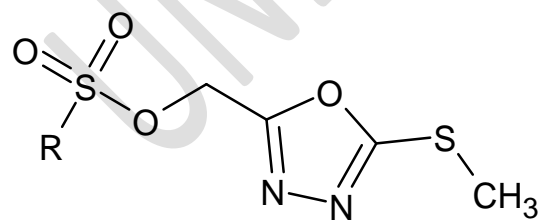
**Rajnish kumar et al** synthesized 7-[4-(5-substituted-1,3,4-oxadiazolo-2-yl)piperazine] quinolone-yl analogues. Few compounds were declared as most potent compounds to combat *S. aureus*, *B. subtilis* & *E. coli*. While the other derivatives showed moderate to average potency [47a-47f].



47a-47f

- a, **R**=4-nitrophenyl ; **R**<sub>1</sub>= CH<sub>3</sub> ; **R**<sub>2</sub>= OCH<sub>3</sub>
- b, **R**= Phenyl; **R**<sub>1</sub>= H ; **R**<sub>2</sub>= H
- c, **R**= 3-nitrophenyl; **R**<sub>1</sub>= CH<sub>3</sub> ; **R**<sub>2</sub>= OCH<sub>3</sub>
- d, **R**=3,4-dinitrophenyl ; **R**<sub>1</sub>= H ; **R**<sub>2</sub>= H
- e, **R**= Phenyl ; **R**<sub>1</sub>= CH<sub>3</sub> ; **R**<sub>2</sub>= OCH<sub>3</sub>
- f, **R**= 3,4-dinitrophenyl; **R**<sub>1</sub>= CH<sub>3</sub> ; **R**<sub>2</sub>=OCH<sub>3</sub>

**Lei Wang et al** synthesized 5-phenyl sulfonate methyl-1,3,4-oxadiazoles analogues. Out of the proposed derivatives, few of them demonstrated good activity against *X. axonopodis* with EC<sub>50</sub> values ranging 95.8-155.2μM. the compounds were also active against rice bacterial leaf blight [48a-48d].

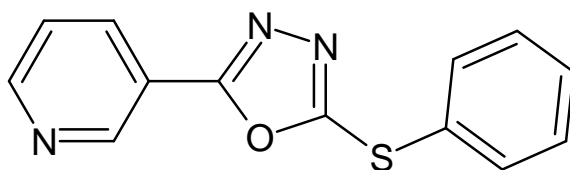


48a-48d

- a, **R**= phenyl
- b, **R**=-4-F-phenyl
- c, **R**=-4-Cl-phenyl
- d, **R**= -4-Br-phenyl

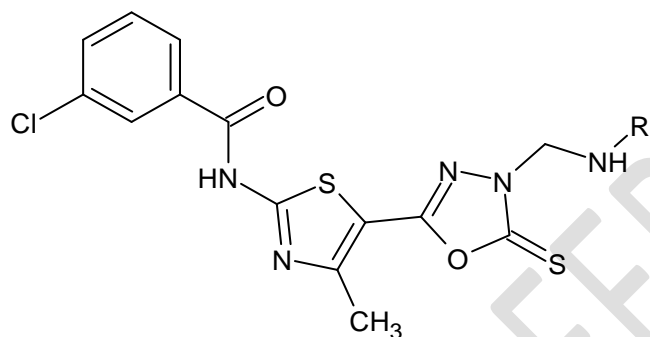
## 7. Anti-microbial activity

**Pattan S.R. et al** proposed Novel aryl 5-(Pyridin-4-yl)-1,3,4-oxadiazolo-2-thiols analogues. Only one from the proposed derivatives showed antibacterial action to combat *E. coli*, *B. subtilis*, *S. aureus*, *A. niger* & *C. albicans* at 200µg/ml [49].



49

**N.C. Desai et al** synthesized 3-chloro-N-(5-(4-((arylphenyl-amino)methyl)-5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)-4-methylthiazol-2-yl)benzamides analogues. Few of the proposed derivatives displayed proficient potency against all bacterial strains with MICs ranging 12.5-100µg/ml with Ciprofloxacin as the standard drug [50a-50d].



50a-50d

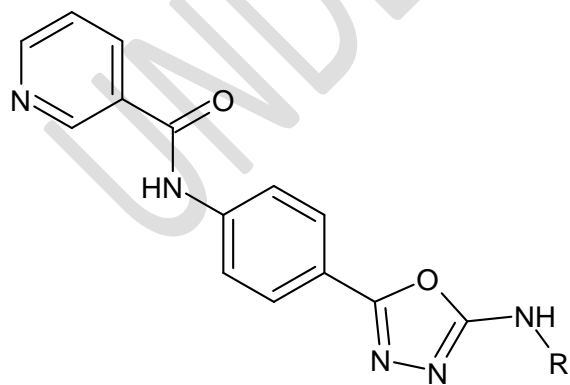
a, **R**=-3-fluorobenzene

b, **R**=-4-fluorobenzene

c, **R**=-3-nitrobenzene

d, **R**=-4-nitrobenzene

**Viral R. shah et al** proposed 2-(*p*-Methoxyphenyl) amino-5-*p*-(nicotinamidophenyl)-1,3,4-oxadiazoles analogues. Few proposed analogues exhibitd highest activity against *E. coli*, *S. typhosa*, *S. citrus* and *B. megaterium* at 50µg/ml concentration with Ampicillin, chloramphenicol, Norfloxacin and Griseofulvin as standard antibiotics [51a-51d].



51a-51d

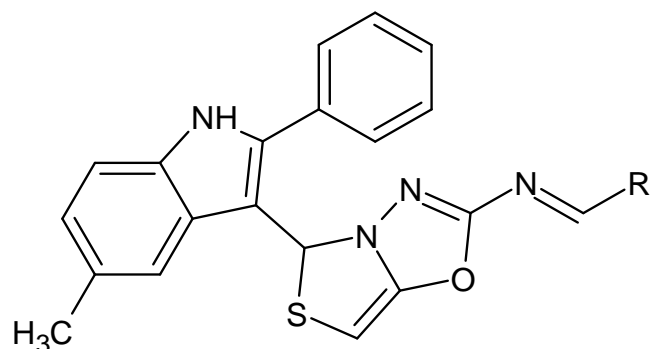
a, **R**= -C<sub>6</sub>H<sub>4</sub>

b, **R**= 2,3-(CH<sub>3</sub>)-C<sub>6</sub>H<sub>4</sub>

c, **R**= -2-OCH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>

d, **R**= -2-C<sub>2</sub>H<sub>5</sub>-C<sub>6</sub>H<sub>4</sub>

**R. Saundane Anand et al** synthesized 2-(Substituted benzylidene)amino-5-(2',5'-diaryl 1*H*-indol-3'-yl)-5*H*-thiazolo[4,3-*b*]-1,3,4-oxadiazoles derivatives. From screening the compounds revealed that few of the proposed derivatives displayed better zone of inhibition against *S. aureus* and *P. aeruginosa* at concentrations 500 and 1000µg/ml [52a-52b].

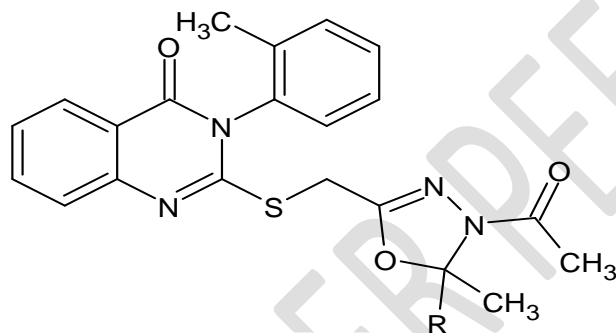


52a-52b

a, **R=** -3-nitrobenzene

b, **R=** -4-methoxybenzene

**D.R. Godhani et al** synthesized a set of 2-((4-acetyl-5-(substituted)-5-methyl-4,5-dihydro-1,3,4-oxadiazol-2-yl) methylthio)-3-*o*-tolylquinazolin-4(3*H*)-one derivatives. Few proposed derivatives showed good potency for *E. coli*, *P. aeruginosa*, *S. aureus* & *S. pyogenus* using Gentamycin, Ampicilin, Chloramphenicol, Ciprofloxacin and Norfloxacin as reference drugs [53a-53b].

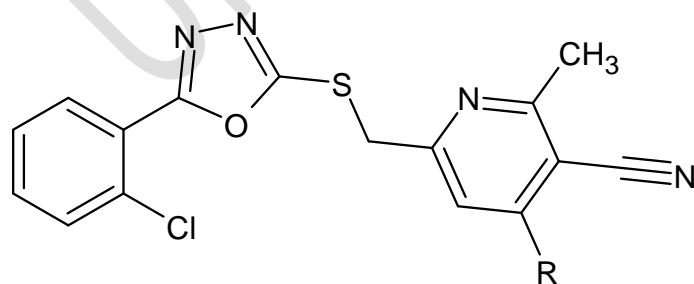


53a-53b

a, **R=** -2-OH-C<sub>6</sub>H<sub>4</sub>

b, **R=** -4-CH<sub>3</sub>-C<sub>6</sub>H<sub>4</sub>

**Niranjan S. Mahajan et al** synthesized a set of 2-NH<sub>2</sub>-6-[(5-(2-chlorophenyl)-1,3,4-oxadiazole-2-yl)-thio]CH<sub>3</sub>-4-aryl nicotinonitrile derivatives. Few of the synthesized compounds displayed promising inhibitory action for Gram -ve like *E. coli* & *P. aeruginosa* and Gram +ve organisms like *B. subtilis* having minimum inhibition concentrations of 5-8µg/ml [54a-54b].

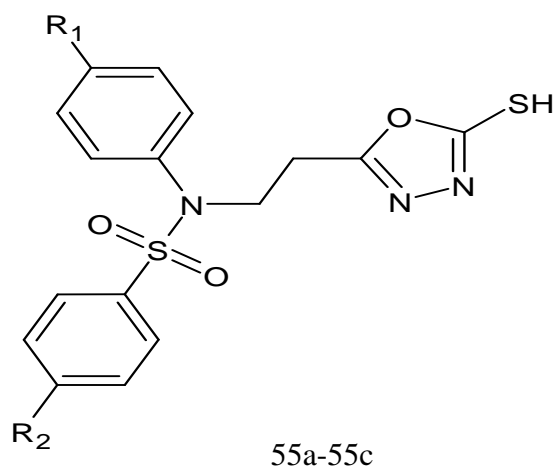


54a-54b

a, **R=** p-OHC<sub>6</sub>H<sub>4</sub>

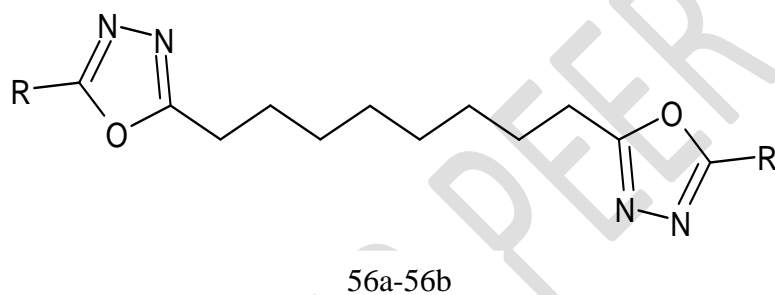
b, **R=** m-ClC<sub>6</sub>H<sub>4</sub>

**Desai S.R. et al** synthesized series of 5-β-[(N-benzenesulphony/tosyl)-4- alkyl anilino] ethyl-2-mercapto-1,3,4-oxadiazoles derivatives. All the proposed derivatives proved to be showing moderately antibacterial activity against *Escherichia coli* and *Bacillus cirroflagellosus* at 100µg/ml [55a-55c].



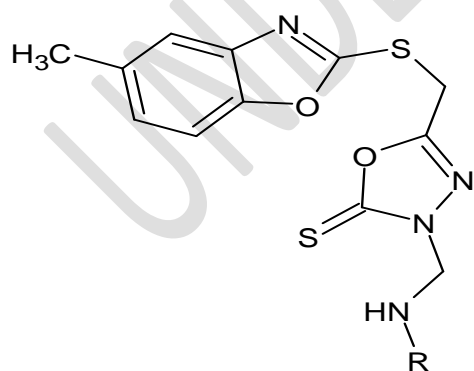
- a,  $R_1 = CH_3$  ;  $R_2 = H$
- b,  $R_1 = CH_3$  ;  $R_2 = CH_3$
- c,  $R_1 = Cl$  ;  $R_2 = CH_3$

**S.G. patil et al** synthesized 1,8-bis (5-aryl-1,3,4-oxadiazol-2-yl) octane analogues. Few of the synthesized derivatives exhibited moderately activity against the bacteria *Staphylococcus aureus* [56a-56b].



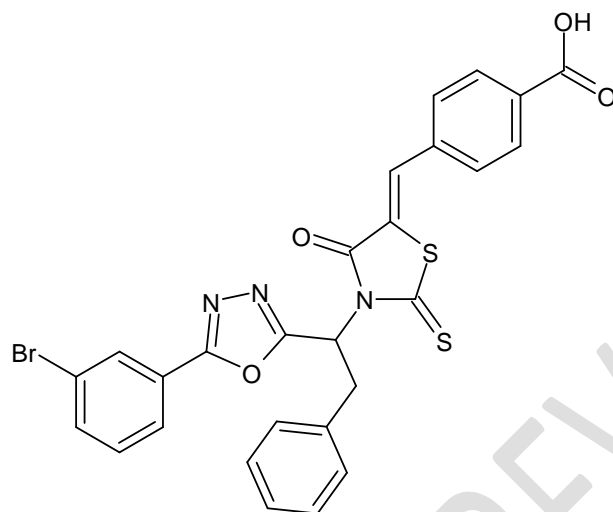
- a,  $R = -4-OCH_3C_6H_4$
- b,  $R = -4-NO_2C_6H_4$

**B.M. Basavaraja et al** synthesized 5-[(1,3-benzoxazol-2-yl-thio) methyl]-3-[[4-alkyl phenyl] amino] methyl-1,3,4-oxadiazolidine-2-thione derivatives. Majority of the compounds showed very good activity against *S. aureus*, *K. pneumonia* and *P. aeruginosa* with Fluoroquinolones as reference [57a-57f].



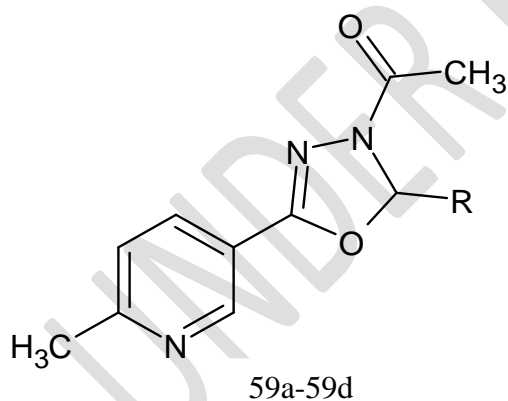
- a,  $R = -2-Cl$
- b,  $R = -3-Cl$
- c,  $R = -2-CH_3$
- d,  $R = -3-CH_3$
- e,  $R = -2-Cl$ ;  $-4-Cl$
- f,  $R = -4-OCH_3$

**Jia-Chun Liu et al** synthesized set of 3-((5-phenyl-1,3,4-oxadiazol-2-yl)methyl)-2-thioxothiazolidin-4-one analogues. The antibacterial evaluation of proposed analogues proved that one derivative displayed better potency with minimum inhibitory concentration values of 1µg/ml to combat MRSA (3167 and 3506) strains. For reference, Fluoroquinolones were used as standard drugs for comparison [58].



58

**Shyma P.C. et al** synthesized set of 3-acetyl-2-substituted-2H/methyl-5-[3-(6-methylpyridinyl)]-2,3-dihydro-[1,3,4]-oxadiazoles analogues. Few of the derivatives exhibited good to moderate potency for *E. coli*, *S. aureus* and *P. aeruginosa* with MIC concentration 0.5-1.5mg/ml. Streptomycin was taken as reference drug for correlation [59a-59d]



a, **R**= *p*-bromophenyl

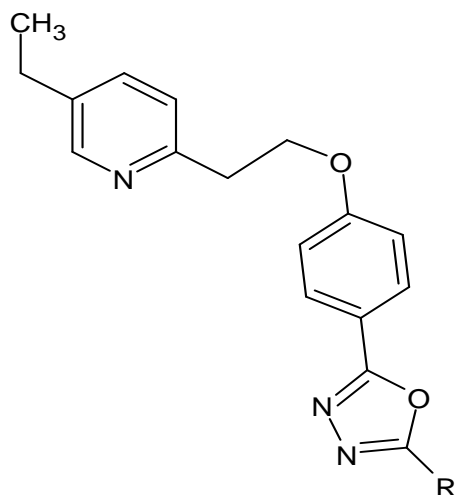
b, **R**= *p*-chlorophenyl

c, **R**= 2,4-dichlorophenyl

d, **R**= 2-fluoro-3-chlorophenyl

59a-59d

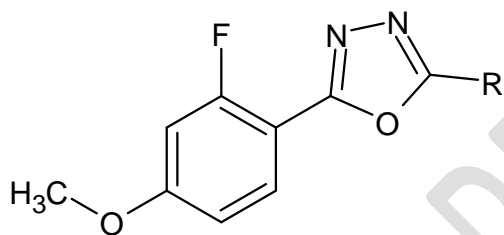
**S.L. Gaonkar et al** innovated a set of 2-{4-[2-(5-ethylpyridin-2-yl) ethoxy] phenyl}-5-aryl-1,3,4-oxadiazolo analogues. The proposed derivatives were found to display good to less potent antimicrobial action. Few of the synthesized derivatives displayed good inhibitory action while some of them showed moderate action with MIC values ranging 8-26µg/ml [60a-60f].



60a-60f

- a, **R**= 4-chlorophenyl
- b, **R**= 2,3-dichlorophenyl
- c, **R**= 2,4-dichlorophenyl
- d, **R**= 4-methoxyphenyl
- e, **R**= 4-nitrophenyl
- f, **R**= 4-pyridinyl

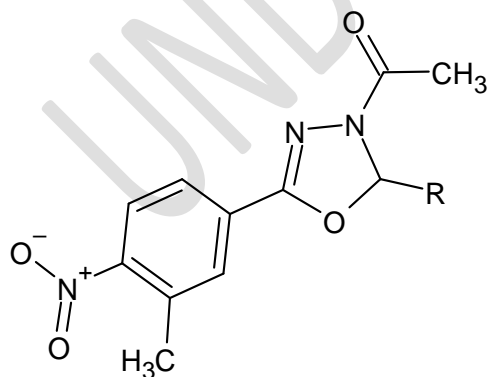
**B. Chandrakantha et al** synthesized novel 1,3,4-oxadiazole ring tethered with 2-F-4-OCH<sub>3</sub> phenyl group. Few of the proposed derivatives displayed significant antibacterial action against *E. coli* & *P. aeruginosa* at quite less minimum inhibitory concentration 3µg/ml [61a-61b].



61a-61b

- a, **R**= -3-bromo-2-methylphenyl
- b, **R**= 2,3,4-trifluorophenyl

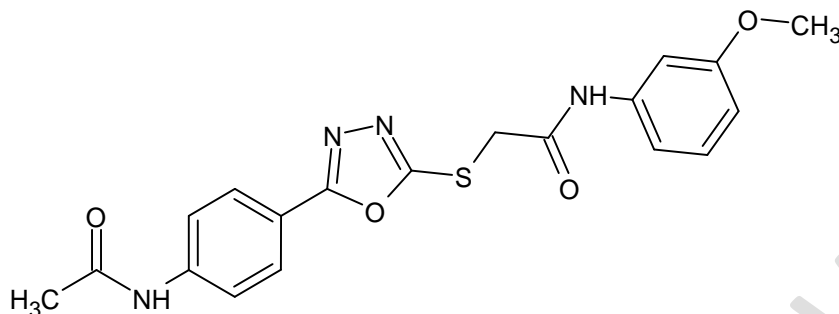
**Kinga paruch et al** synthesized novel 3-Acetyl-2,5-diaryl-1,3,4-oxadiazoline analogues. Most of proposed analogues exhibited bactericidal effect for Gram +ve organism. Two of the proposed derivatives exhibited the significant antibacterial action with minimal inhibitory concentrations (MICs) ranging 0.48µg/ml to 500µg/ml. other compounds showed moderate to poor antibacterial activity [62a-62b].



62a-62b

- a, **R**= -(5-iodofuran-2-yl)
- b, **R**= quinolin-4-yl

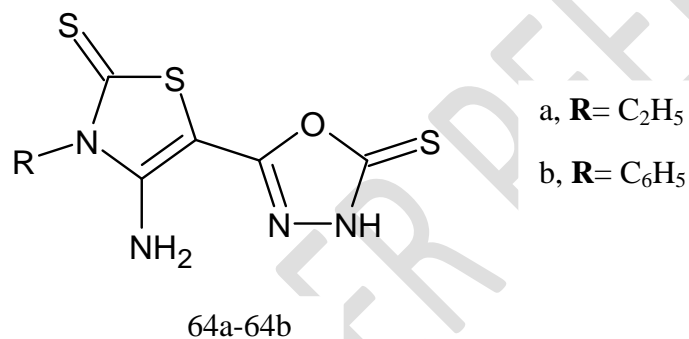
**Shah H.P. et al** innovated set of 2-[[5-(4-acetamidophenyl)-1,3,4-oxadiazol-2-yl]sulfanyl]-*N*-aryl)acetamide derivatives. Out of synthesized derivatives, one exhibited excellent action against *S. aureus* [63].



63

### 8. Anti-viral activity

**Mohammed albratty et al** synthesized thiazole bearing 1,3,4-oxadiazoles analogues. Both the proposed derivatives exhibited promising antiviral actions against various viral strains possibly under the influence of the presence of amino thiazole substituent [64a-64b].



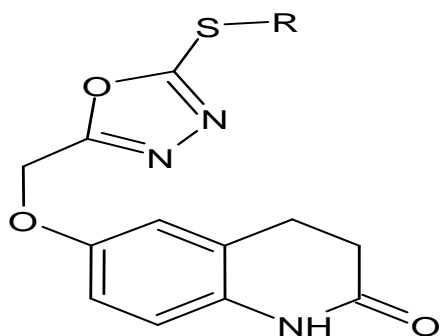
a, R= C<sub>2</sub>H<sub>5</sub>

b, R= C<sub>6</sub>H<sub>5</sub>

64a-64b

### 9. Anti-convulsant activity

**Shiben wang et al** innovated Dihydroquinoline bearing 1,3,4-oxadiazoles analogues. One of the synthesized compound was showing the significant anticonvulsant action better from the actions of carbamazepine and ethosuximide [65].

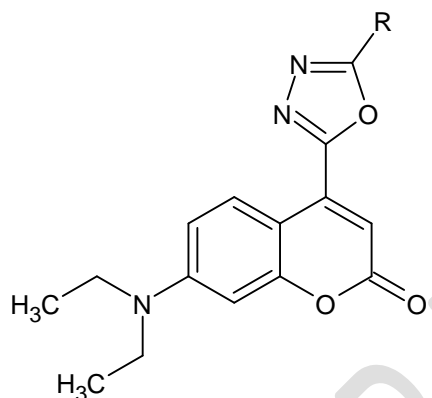


$R = n\text{-C}_5\text{H}_{11}$

65

### 10. Anti-cholinestrase activity

Xiang Yu et al innovated a set of novel 7-diethylaminocoumarin-based 1,3,4-oxadiazoles analogues. Among the derivatives, two of them showed moderate inhibitory activities positively correlated to the concentration [66a-66b].



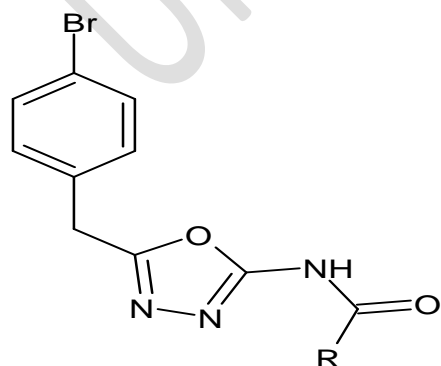
a,  $R =$  -4-chlorophenyl

b,  $R =$  -4bromophenyl

66a-66b

### 11. Anti-salmonella typhii

Eid E. Salama et al innovated 5-substituted-2-NH<sub>2</sub>-1,3,4-oxadiazolo analogues. Out of the proposed derivatives few of them displayed great inhibitory activity against *salmonella typhii* whereas the other compounds displayed moderate activity [67a-67b].



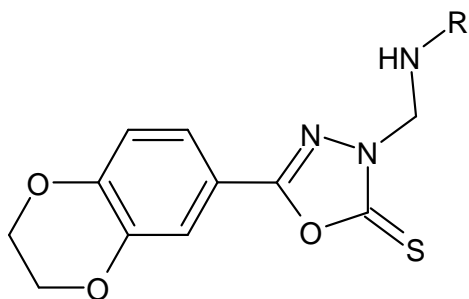
a,  $R =$  -(4-COCH<sub>3</sub>)C<sub>6</sub>H<sub>4</sub>

b,  $R =$  -(3-NO<sub>2</sub>)C<sub>6</sub>H<sub>4</sub>

67a-67b

## 12. Antioxidant

**Liang Ma et al** innovated novel set of oxadiazole analogues having 1,4-benzodioxane moiety. Few of the proposed derivatives were exhibiting excellent radical scavenging action compared to the existing antioxidants, like BHT and Trolox. The synthesized derivatives were assayed using (DPPH), (ABTS+ •) and (FRAP) scavenging assays [68a-68b].

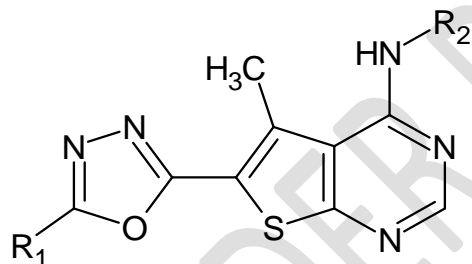


68a-68b

a, **R**= 2,6-Difluorophenyl

b, **R**= 3,4,5-Trifluorophenyl

**Y. Kotaiah et al** innovated set of novel N-substitutedaryl phenyl-1,3,4-oxadiazole-thiazole- pyrimidine amine analogues. Few of these synthesized derivatives displayed good radical scavenging under the influence of EDGs like -CH<sub>3</sub> on either ends of the thienopyrimidine moiety. These synthesized compounds were screened by using DPPH, Hydrogen peroxide and nitric oxide radical scavenging assays [69a-69d].



69a-69d

a, **R**<sub>1</sub>= phenyl ; **R**<sub>2</sub>= 4-fluorophenyl

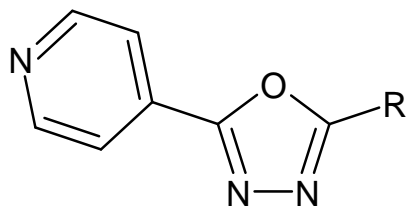
b, **R**<sub>1</sub>= 4-chlorophenyl ; **R**<sub>2</sub>= 4-fluorophenyl

c, **R**<sub>1</sub>= phenyl ; **R**<sub>2</sub>= 2,4-difluorophenyl

d, **R**<sub>1</sub>= 4-chlorophenyl ; **R**<sub>2</sub>= 2,4-difluorophenyl

## 13. Analgesic activity

**Ilango K. et al** innovated 2-substituted-5-(4-pyridyl)-1,3,4-oxadiazoles analogues. Among these proposed analogues, few of them showed good analgesic activity at a concentration of 500mg/ml using Aspirin for reference comparison (40mg/ml) [70a-70b].



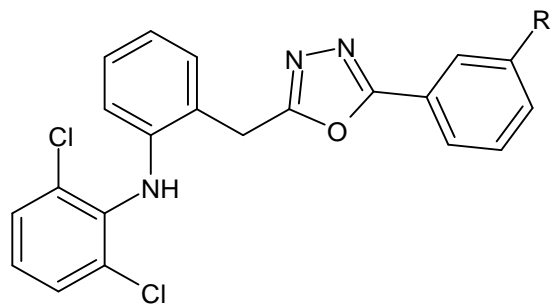
70a-70c

a, **R**= 4-methoxy phenyl

b, **R**= 4-hydroxy phenyl

c, **R**= 4-hydroxy-3,5-Dimethoxyphenyl

**Ilango K. et al** synthesized 2, 6-diCl-N-(2-((5-(alkyl)-1, 3, 4- oxadiazol-yl) methyl) phenyl) benzenamines analogues. Few of the proposed derivatives showed analgesic action while few of them showed central analgesic activity using the acetic acid induced writhing response methods [71a-71d].



71a-71d

- a, **R= NO<sub>2</sub>**
- b, **R= NH<sub>2</sub>**
- c, **R= OCH<sub>3</sub>**
- d, **R= Cl**

## CONCLUSION

This review is focused on the Diversified Pharmacological Properties possessed by and associated with the derivatives of Oxadiazole moiety in last two and a half decades. Synthetic compounds possessing Oxadiazole ring in their chemical structure have been studied for multiple number of biological activities such as antifungal, anticancer, anti HIV, antihypertensive, antibacterial, antimicrobial, anticholinesterase, anticonvulsant, antiviral etc. The studied literatures resulted in getting a conclusion that the Oxadiazole ring has been used in multiple number of synthetic studies now-a-days. Oxadiazole moiety has grabbed the attention of many researchers due to its biological versatility.

## COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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UNDER REVIEW