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1, 3, 4-OXADIAZOLE NUCLEUS WITH VERSATILE PHARMACOLOGICAL APPLICATIONS: A REVIEW

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ABSTRACT: Oxadiazole is a heterocyclic compound containing an oxygen atom and two nitrogen atoms in a five membered ring. It is derived from furan by substitution of two methylene groups (=CH) with two pyridine type nitrogens (-N=). It is also termed as a lead compound for designing the potent bioactive agents. It has been reported as a surrogate of carboxylic acid and an important synthons in organic chemistry. It exists in four isomeric forms 1,3,4-oxadiazole, 1,2,4-oxadiazole, 1,2,3-oxadiazole and 1,2,5-oxadiazole. Out of all four isomers of oxadiazole, 1,3,4-Oxadiazole is found to possess variety of chemical and biological applications. 1,3,4-oxadiazole nucleus have been reported a very important nucleus in organic and medicinal chemistry and more widely studied by researchers because of its versatile chemical and biological properties. It has been found to possess antimicrobial, antioxidant, antifungal, cytotoxicity, anticonvulsant, antitumor, tyrosinase enzyme activity, DENV2 inhibitory activity, anti-Trypanosoma cruzi, focal adhesion kinase (FAK) inhibitors, analgesic, HIV-1 integrase inhibitors, XDR and MDR tuberculosis, immunosuppressive activity. This review article describes the various biological activities associated with 1,3,4-oxadiazole ring system and is useful in guiding the researchers across the world working on this moiety and consequently have been instrumental in the advancement of 1,3,4-oxadiazole chemistry.

INTRODUCTION: 1,3,4-Oxadiazole (**1**, **Figure-1**) is a heterocyclic compound containing an oxygen atom and two nitrogen atoms in a five membered ring.

It is derived from furan by substitution of two methylene groups (=CH) with two pyridine type nitrogens (-N=) [1-2].

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There are three known isomers: 1,2,4-oxadiazole (**2**), 1,2,3-oxadiazole (**3**) and 1,2,5-oxadiazole (**4**) (**Figure 1**). However, 1,3,4-oxadiazole and 1,2,4-oxadiazole are better known, and more widely studied by researchers because of their many important chemical and biological properties.

Compounds containing oxadiazole ring possess a variety of biological activities such as Anti-inflammatory, Analgesic, Antimicrobial, Anti-convulsant, Anti-proliferative, Anti-mycobacterial, Anti-protozoal, Anti-diabetic, Anthelmintic, Hypo-glycemic, antiallergic, Enzyme inhibitors, insecticidal, anticancer, antineoplastic, CNS depressant and pesticidal property [3-24].

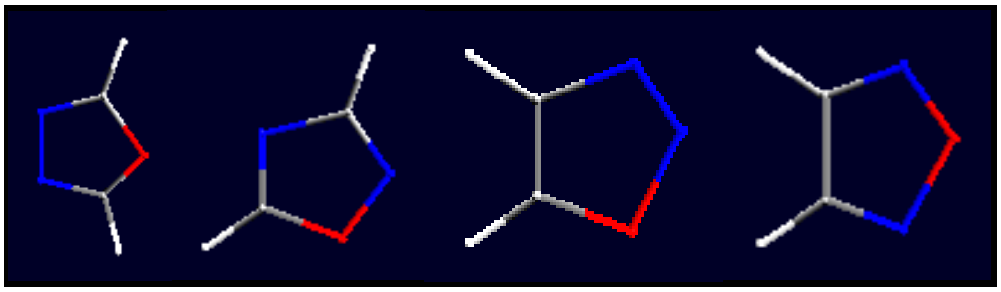


FIGURE 1: REPRESENTING THE 3D IMAGES FOR ISOMERS OF OXADIAZOLE

1,3,4-Oxadiazole is a very good bioisostere of amide and ester functional groups and is reported to contribute substantially to pharmacological activity by participating in hydrogen bonding interactions with various receptors [25]. Oxadiazole is a very weak base due to the inductive effect of the extra heteroatom. The replacement of two –CH= groups in furan by two pyridine type nitrogen (-N=) reduces aromaticity of resulting oxadiazole ring to such an extent that the oxadiazole ring exhibit character of conjugated diene. Literature survey reveals that the oxadiazoles undergoes number of reactions such as electrophilic substitution, nucleophilic substitution, thermal and photo-chemical [1]. Currently available drugs containing oxadiazole unit used in clinical medicines are Raltegravir, an antiretroviral drug and Zibotentan, an anticancer agent [26-27].

Synthesis and Pharmacology of 1,3,4-oxadiazole derivatives: Ming-Zhi Z *et al* [28] have synthesized three series of indole-based 1,3,4-oxadiazole derivatives and designed them as analogues of the antifungal natural product pimprinine. The authors also evaluated their antifungal activities and results showed that the synthesized derivatives displayed an altered pattern of biological activity on comparison with the natural product pimprinine **[Figure 2]**.

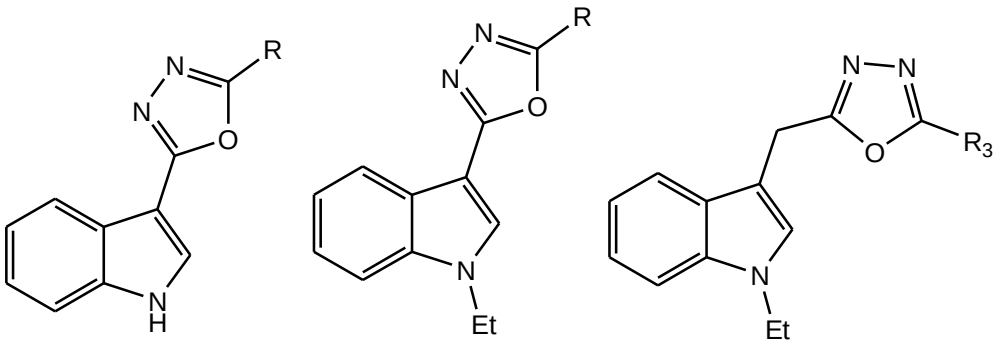


Figure-2

Shyma PC *et al* [29] have synthesized a new series of 3-acetyl-2-aryl-2H/methyl-5-[3-(6-methyl pyridinyl)]-2,3-dihydro-[1,3,4]-oxadiazole derivatives from 6-methyl nicotinate through a multistep reaction sequence. All the synthesized compounds were screened for their antimicrobial activity and antioxidant activity. The final compounds were subjected to molecular docking studies for the inhibition of enzyme L-glutamine: D-fructose-6-phosphate amidotransferase [GlcN-6-P] (EC 2.6.1.16). The *in silico* molecular docking results were matched with the *in vitro* studies and they may be considered as good inhibitor of GlcN-6-P synthase-6-methylpyridine **[Figure 3]**.

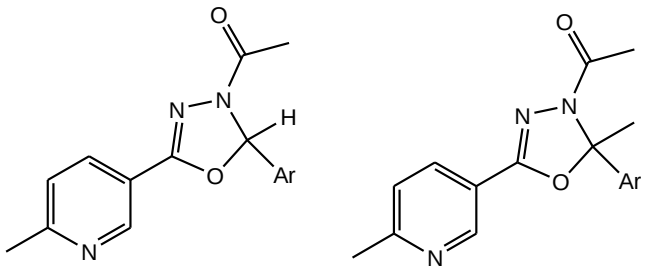


Figure-3

Tyrosinase enzyme is a monophenol monoxygenase enzyme, which plays an important role in human as a rate limiting step enzyme for different specific metabolic pathways, as well as its useful application in industry and agriculture. Therefore, Mohamed M El S *et al* [30] reported the synthesis and bioassay of a New Class of furanyl-1,3,4-oxadiazole derivatives and also tested on tyrosinase enzyme activity, hoping to use them in the treatment of some diseases arising from tyrosinase activity disorders such as Parkinson's disease, schizophrenia, autism, attention deficit, hyperactivity disorder, and cancer **[Figure 4]**.

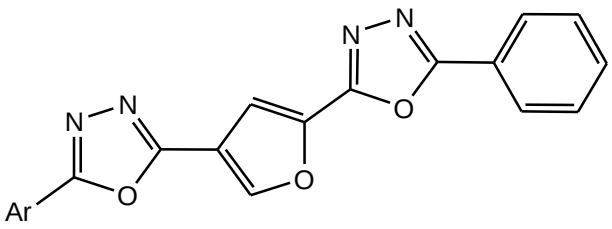


Figure-4

Huiguo L *et al* [31] have synthesized a focused library of 1,2-benzisothiazol-3(2H)-one-1,3,4-oxadiazole hybrid derivatives and have investigated their inhibitory activity against DENV2 NS2B/NS3pro and WNV NS2B/NS3pro. Molecular modeling studies were also performed to delineate the putative binding mode of this series of compounds. Several members of this series of compounds were found to inhibit the two enzymes, and a low micromolar inhibitor capable of inhibiting both enzymes has been identified. Importantly, biochemical studies indicate that the compounds act as competitive inhibitors. It was observed that ten out of twenty-four compounds showed greater than 50% inhibition against DENV2 and WNV proteases **[Figure 5]**.

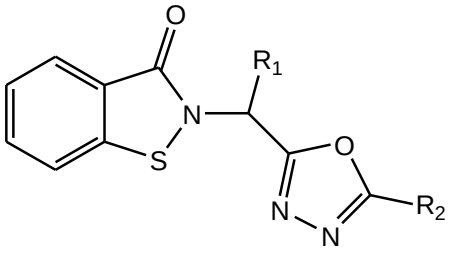


Figure-5

Desai NC *et al* [32] reported the synthesis, characterization, antimicrobial screening and cytotoxicity activities of thiazole clubbed 1,3,4-oxadiazole derivatives. The results indicated that, some compounds exhibited the most potent antibacterial activity. The structure activity relationship revealed that the presence of electron withdrawing groups at para position of phenyl ring remarkably enhanced the antibacterial activity of synthesized compounds. Further, the results of preliminary MTT cytotoxicity studies on HeLa cells suggested that potent antimicrobial activity of the synthesized compounds is accompanied by low cytotoxicity **[Figure 6]**.

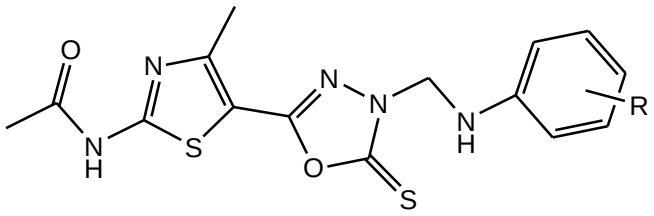


Figure-6

Kikkeri PH *et al* [33] reported the synthesis of a series of novel 1-[5-(4-methoxy-phenyl)-[1,3,4] oxadiazol-2-yl]-piperazine derivatives and characterized by elemental analyses, ^{1}H NMR, ^{13}C NMR and mass spectral studies. The newly synthesized compounds were screened for their anticonvulsant activity against maximal electroshock seizure (MES) model in male wistar rats and compared with the standard drug phenytoin. Results showed that some compounds were found to be most potent **[Figure 7]**.

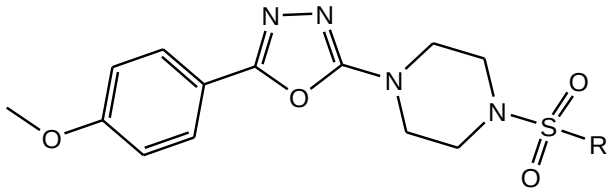


Figure-7

Juan S *et al* [34] have synthesized a series of quinoline derivatives and also evaluated their biological activities as potential telomerase inhibitors. Bioassay tests demonstrated that most of the compounds exhibited substantial broad-spectrum of antitumor activity against the three cancer cell lines (HepG2, SGC-7901 and MCF-7). Moreover, all the title compounds were assayed for telomerase inhibition using the TRAP-PCR-ELISA assay. Some compounds from the series displayed the most potent anticancer activities, which were comparable to the positive control.

Docking simulation was performed to position the title compounds into the telomerase structure active site to determine the probable binding model. Antiproliferative and enzyme assay results suggested that these compounds were potential antitumor agents. From the results, it could be concluded that some quinoline derivatives are good candidates for antitumor agents screening and research. The template quinoline with 1,3,4-oxadiazole moiety was suitable to reconstruct and design for development of more potential therapeutic drugs against cancer **[Figure 8]**.

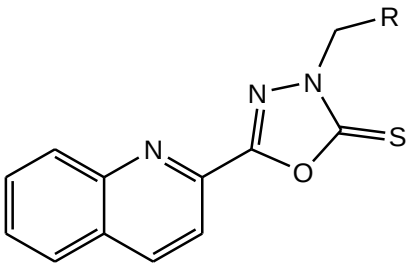


Figure-8

In a recent study Rajesh AR *et al* [35] reported the synthesis and antimicrobial evaluation of 42 novel 4-nitropyrrole-based 1,3,4-oxadiazoles. The synthesized molecules were evaluated for anti-bacterial, anti-fungal and anti-tubercular activities. Promisingly, most of the compounds showed equal or more potency than standard ciprofloxacin against *S. aureus*, *B. subtilis* and *E. coli*. One compound exhibited highest anti-tubercular activity **(**0.46 μg/mL**)** close to that of standard Isoniazid **(**0.40 μg/mL**)**. Equal antifungal activity (1.56 μg/mL) compared to standard Amphotericin-B was shown by most of the compounds. All the N-methylated compounds showed more potent to equal activity against MSSA (MIC 0.39-1.56 μg/mL) and MRSA (MIC 0.78-1.56 μg/mL). All compounds were tested for mammalian cell toxicity using VERO cell line and were found to be non-toxic **[Figure 9]**.

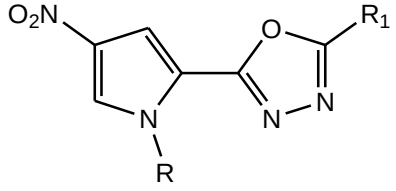


Figure-9

Fanny PB *et al* [36] reported the synthesis and biological evaluation of 5-nitro-2-furfuriliden derivatives and also evaluated the anti-*Trypanosoma cruzi* activity of 5-nitro-2-furfuriliden derivatives. All the synthesized active compounds were evaluated for the cytotoxicity assay of on J774 macrophages cell line and FN1 human fibroblast cells. The findings indicated that the anti-*T. cruzi* activity of the investigated compounds regarding the two series is strongly influenced by the physicochemical properties of the substituent group attached to the benzene ring and the cytotoxicity assay shown that some compounds have presented interesting selectivity indices **[Figure 10]**.

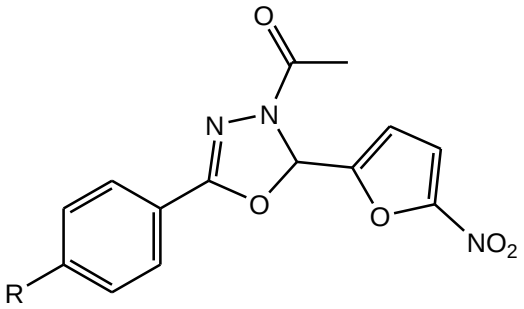


Figure-10

Shuai Z *et al* [37] have designed and synthesized a series of new 1,3,4-oxadiazole derivatives containing benzotriazole moiety as potential focal adhesion kinase (FAK) inhibitors. All the synthesized compounds were evaluated for their anticancer activity against MCF-7 (human breast cancer) and HT29 (human colorectal cancer) cell lines. Some compounds showed the potent inhibitory activity against MCF-7 and HT29 cell lines with IC_{50} values of 5.68 lg/ml and 10.21 lg/ml, respectively. All the compounds were also assayed for FAK inhibitory activity using the TRAP–PCR–ELISA assay and results showed that some compounds found to have potent FAK inhibitory activity with IC_{50} values of 1.2 ± 0.3 lM **[Figure 11]**.

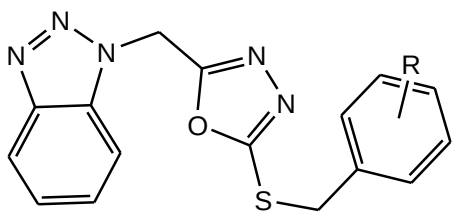


Figure-11

Qian-Ru D *et al* [38] reported that a series of novel 1,3,4-oxadiazole thioether derivatives were designed and synthesized as potential inhibitors of thymidylate synthase (TS) and as anticancer agents. The in vitro anticancer activities of these compounds were evaluated against three cancer cell lines by the MTT assay. Among all the designed compounds, compound bearing a nitro substituent exhibited more potent in vitro anticancer activities. The SAR for these designed compounds against human TS reveals that the sort and position of the substituent(s) on the phenyl ring or heterocycle are important and it was observed that the nature of the electron withdrawing group at 4-position of the phenyl ring is detrimental to potent TS inhibition **[Figure-12]**.

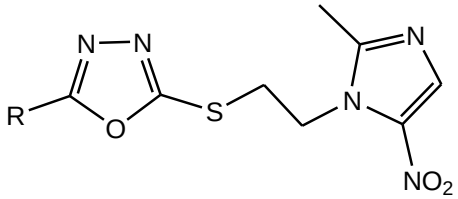


Figure-12

Liang M *et al* [39] reported that a new series of Mannich base of 1,3,4-oxadiazole derivatives possessing 1,4-benzodioxan were synthesized and screened for their *in vitro* antioxidant activity employing 2,20-diphenyl-1-picrylhydrazyl radical (DPPH), 2,20-azinobis (3-ethylbenzothiazoline-6-sulfonate) cationic radical (ABTS+.) and ferric reducing antioxidant power (FRAP) scavenging assays. It was observed that the combination of 1,4-benzodioxan, 1,3,4-oxadiazoles and substituted phenyl ring was fruitful and most of the synthesized compounds exhibited nice antioxidant activities **[Figure 13]**.

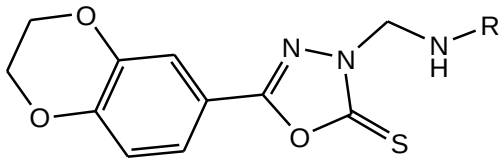


Figure-13

Chandrakantha B *et al* [40] reported that a series of new 1,3,4-oxadiazole derivatives containing 2-fluoro-4-methoxy moiety were synthesized leading to their characterization by NMR, mass spectral, IR spectral study and also by C, H, N analyses.

All the newly synthesized compounds were screened for their antibacterial and antifungal studies. Antimicrobial studies revealed that two compounds showed significant antibacterial activity against *E*. coli and *P*. *aeruginosa* and some compounds showed significant antifungal activity against *C*. albicans **[Figure 14]**.

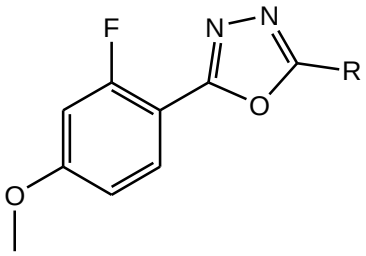


Figure-14

Kumar H et al.[41] have synthesized a series of 1,3,4-oxadiazole of biphenyl-4-yloxy acetic acid in order to obtain new compounds with potential anti-inflammatory activity, analgesic activity and lower ulcerogenic potential. All the compounds were evaluated for their anti-inflammatory activity by the carrageenan induced rat paw edema test method.

The compounds possessing potent anti-inflammatory activity were further tested for their analgesic, ulcerogenic and antioxidant activities. Out of all tested compounds some compounds, showed significant reduction in rat paw edema induced by carrageenan treatment. These compounds showed significant analgesic effect and at an equimolar oral doses relative to flurbiprofen were also found to be non-gastrotoxic in rats **[Figure 15]**.

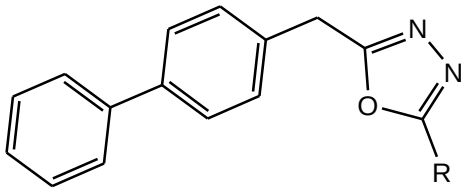


Figure-15

Ravichandran V *et al* [42] reported the synthesis and QSAR study of substituted 1,3,4-oxadiazole naphthyridines as HIV-1 integrase inhibitors **[Figure 16]**.

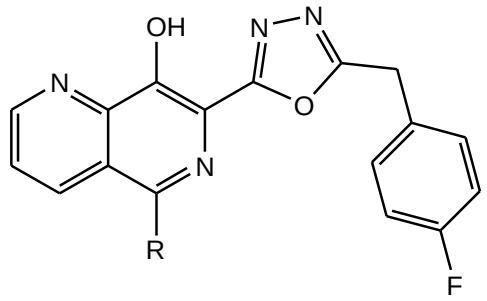


Figure-16

Bondock S *et al* [43] reported the synthesis of a novel series of 1,3,4-oxadiazole analogues and evaluated for anti-cancer activity. The results of the anticancer screening revealed that five compounds were found to exhibit variable degrees of anticancer activities against the four used cell lines **[Figure-17]**.

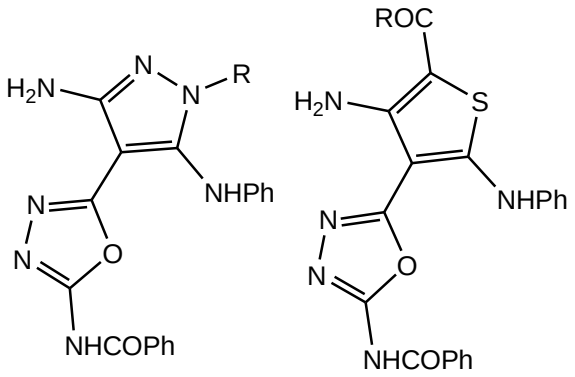


Figure-17

Keshari K J *et al* [44] have been synthesized a novel series of 1,3,4-oxadiazole derivatives and screened for their antibacterial activity against *E*. coli (MTCC 443), *S*. epidermidis (ATCC12228) and *S*. aureus (ATCC25923) bacterial strains by disc diffusion method. In all the determinations, tests were performed in triplicate and the results were taken as a mean of three determinations. Some compounds have shown significant inhibition comparable to standard while some of them showed moderate activity **[Figure 18]**.

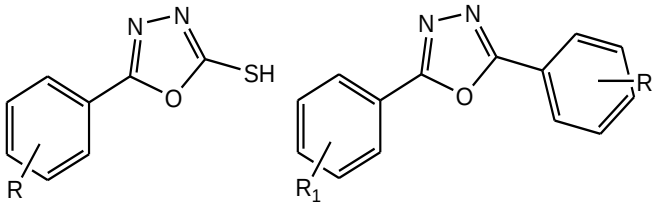


Figure-18

Manjunatha K *et al* [45] reported that various oxadiazole Mannich bases derived from ibuprofen and 4-methylthiophenyl acetic acid were prepared with the objective of developing better anti-inflammatory molecules with minimum ulcerogenic activity and also to evaluate their antimicrobial potency. It was interesting to note that five compounds from the series were found to have anti-inflammatory activity greater than the standard drug, diclofenac at 10 mg/kg p.o. Furthermore, some compounds exhibited anti-inflammatory activity equivalent to the standard drug against carrageenan induced paw oedema test in rats **[Figure 19]**.

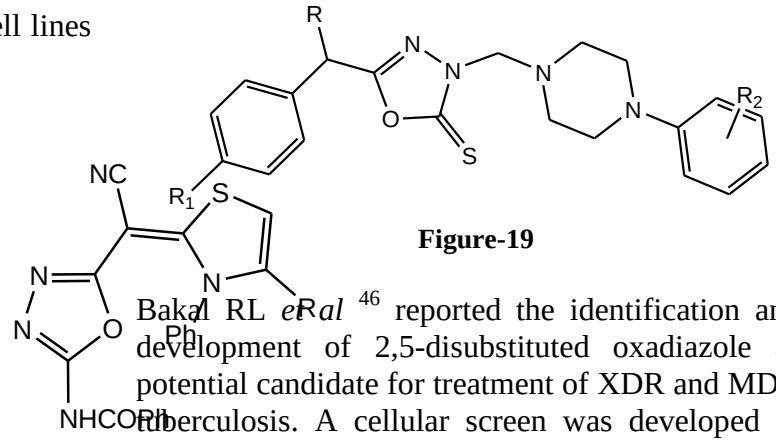


Figure-19

Bakal RL *et al* [46] reported the identification and development of 2,5-disubstituted oxadiazole as potential candidate for treatment of XDR and MDR tuberculosis. A cellular screen was developed to identify mycobacterial growth inhibitors. The screen was carried out against Mycobacterium bovis (M. bovis) BCG using intracellular ATP content as a surrogate marker of bacillary growth. The compound hits with confirmed activity against M. tuberculosis were chemically clustered to identify any emerging SAR **[Figure 20]**.

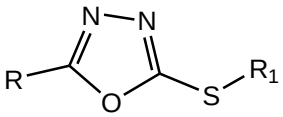


Figure-20

Jayashankar B *et al* [47] reported a series of novel ether-linked bis(heterocycle)s have been synthesized via [3+2]-cycloaddition reaction of nitrile oxide with allyl alcohol followed by intramolecular 1,3-diploar cycloaddition reaction of nitrile imine with carbonyl group. All the newly synthesized compounds were screened for their anti-inflammatory and analgesic activities. Among the list of compounds some exhibited excellent activity comparable to ibuprofen and aspirin at the similar dosages **[Figure 21]**.

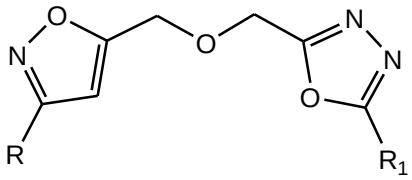


Figure-21

Kadi AA *et al* [48] reported the antimicrobial and anti-inflammatory activities of novel 2-substituted-5-(1-adamantyl)-1,3,4-oxadiazoles and 2-substituted-5-(1-adamantyl)-1,3,4-thiadiazoles. Several derivatives showed good or moderate antibacterial activities particularly against the tested Gram-positive bacteria Bacillus subtilis and marked antifungal activity against Candida albicans **[Figure 22]**.

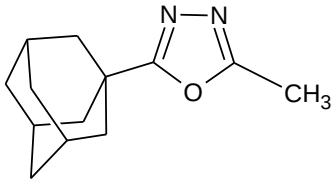


Figure-22

Aboraia AS *et al* [49] reported some novel 5-(2-hydroxyphenyl)-3-substituted-2,3-dihydro-1,3,4-oxadiazole-2-thione derivatives promising anticancer agents. These seven oxadiazole compounds were selected for a full anticancer screening against a 60-cell panel assay where they showed non-selective broad spectrum and promising activity against all cancer cell lines. As a result of 60-cell panel assay two oxadiazole compounds were identified as promising lead compounds **[Figure 23]**.

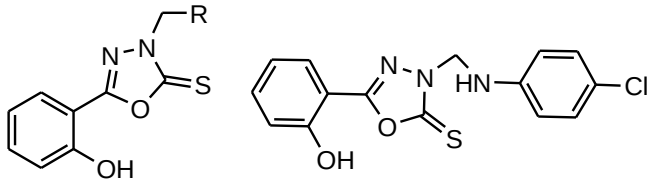


Figure-23

Harish R *et al* [50] reported the synthesis, characterization and antimicrobial properties of novel 2,5-disubstituted 1,3,4-oxadiazoles. All the compounds were screened for their antimicrobial potential using disk diffusion method. Most active compound demonstrated antimicrobial activity against all six microbial strains used with zone of inhibition in disk diffusion method- 18 mm against *S. aureus*, 15 mm against *B. subtilis*, 16 mm against *P. mirabilis*, 17 mm against *P. aeruginosa*, 16 mm against *A. niger* and 17 mm against *C. albican*. In general, compounds bearing the groups like nitro, hydroxy on distant phenyl ring showed high potency in disk diffusion tests. Whereas replacement of these groups with methoxy and chloro groups on the distant phenyl ring has resulted in compounds with decrease in antimicrobial activity.

Replacement of the proton on the carbimino carbon atom by methyl leads to increase in the dimension of the group at this position of the molecule has demonstrated variation in activity. Compounds with phenyl ring were found to possess considerable activity in comparison to methyl group.

The increase in the antimicrobial activity with phenyl substitution might be due to increased lipophilic character of the molecules. The results obtained showed that the majority of the compounds exhibited antimicrobial activity **[Figure 24]**.

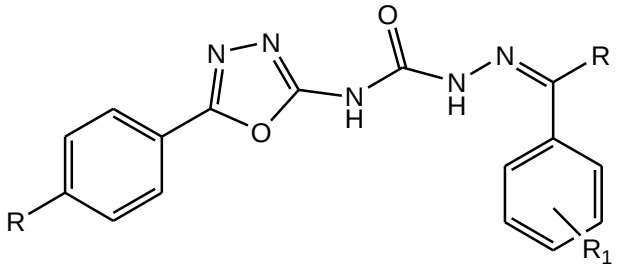


Figure-24

Pudota PT *et al* [51] reported that a series of novel bis-1,3,4-oxadizaoles were synthesized by oxidative cyclisation of respective Schiff bases derived from dicarbohydrazide using ceric ammonium nitrate (CAN) as catalyst.

The synthesized compounds were screened for *in vitro* antibacterial activity against *Staphylococcus aureus* (MTCC 87), *Escherichia coli* (MTCC 46) and antifungal activity against *Candida albicans* (NCIM 3471) by two fold serial tube dilution method. The compounds were evaluated for in vitro cytotoxicity activity against human lung carcinoma cells (A-549) by standard MTT assay method. The DNA cleavage analysis of some compounds was also performed **[Figure 25]**.

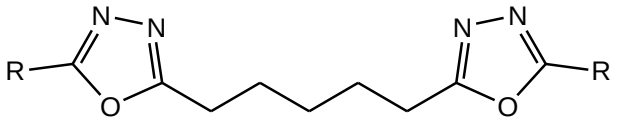


Figure-25

Modh RP *et al* [52] reported that a series of novel hybrid 2-(7-chloroquinolin-4-ylthio)-5-(substituted) -1,3,4-oxadiazole derivatives have been designed, synthesized which contains different pharmacophores like quinoline and 1,3,4-oxadiazole linked via sulfur atom. All the final synthesized scaffolds have been subjected to *in vitro* antimicrobial activity against several bacteria (*E.coli, P.aeruginosa, S.aureus, S.pyogenus*) and fungi (*C.albicans, A.niger, A.clavatus*) using broth dilution technique. Among the tested compounds, compounds with amine group at second position of phenyl to oxadiazole moiety are found to be most potent **[Figure 26]**.

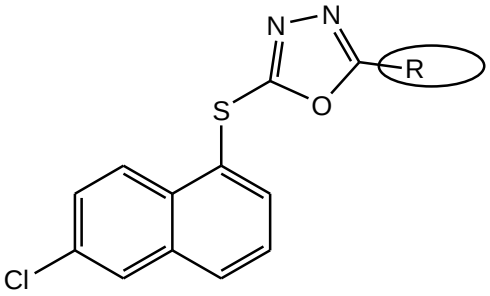


Figure-26

Kumar R *et al* [53] reported a new class of 2-(biphenyl-4-yl)-5-phenyl-1,3,4-oxadiazole derivatives. Furthermore, compounds were screened for in vitro antimicrobial activity against the representative panel of gram positive and gram negative bacteria. The various compounds show potent inhibitory action against test organism **[Figure 27]**.

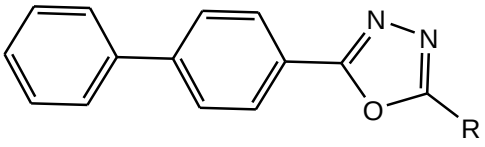


Figure-27

Fliur Macaev *et al* [54] reported that a series of 5-aryl-2-thio-1,3,4-oxadiazole derivatives were synthesized and screened for their anti-mycobacterial activities against Mycobacterium tuberculosis H37Rv.

The synthesized compounds were appeared to exhibit more than 90% inhibition of mycobacterial growth at 12.5 lg/mL. Structure–activity relationships study was performed for the given series by using the electronictopological method combined with neural networks (ETM–NN). A system for the anti-mycobacterial activity prediction was developed as the result of training associative neural network (ASNN) with weights calculated from projections of a compound and each pharmacophoric fragment found on the elements of the Kohonen's self-organizing maps (SOMs).

From the detailed analysis of all compounds under study, the necessary requirements for a compound to possess antituberculosis activity have been formulated. The analysis has shown that any requirement's violation for a molecule implies a considerable decrease or even complete loss of its activity. Molecular docking studies of the compounds allowed shedding light on the binding mode of these novel anti-mycobacterial inhibitors **[Figure 28]**.

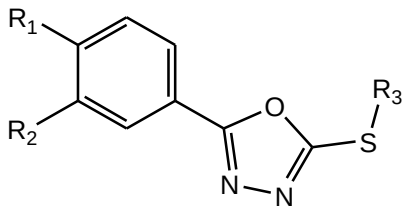


Figure-28

Navarrete-Va´zquez G et al.[55] reported the synthesis of 4-(5-substituted-1,3,4-oxadiazol-2-yl)pyridine derivatives and evaluated for their *in vitro* antimycobacterial activity. Some compounds showed an interesting activity against Mycobacterium tuberculosis H37Rv and five clinical isolates (drug-sensitive and -resistant strains) **[Figure 29]**.

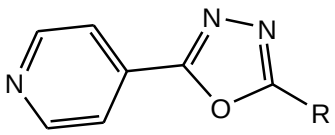


Figure-29

Yan-Ping L *et al* [56] reported the discovery of a new series of tetrazolinone derivatives in good yields by a multiple-step synthetic procedure and also evaluated them all for insecticidal property.

The results of greenhouse *in vivo* test indicated that all the target compounds did not displayed herbicidal activity; however, some of them exhibited excellent *in vivo* insecticidal activity against *Tetranychus cinnabarinus* at the concentration of 250 mgL^{-1} **[Figure 30]**.

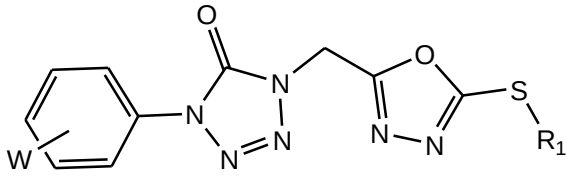


Figure-30

Maria GM *et al* [57] reported that a series of 1,3,4-oxadiazole-2-thione and 1,3,4-oxadiazol-2-one derivatives have been synthesized with the aim to evaluate their antimycobacterial activity toward a strain of *M. tuberculosis* H37Rv sensitive to isoniazid. The results of the in vitro evaluation of antimycobacterial activity of compounds revealed that the oxadiazolone derivatives exhibit an interesting activity against the tested strain, reaching MIC values of 1.25 lg/mL. However, the antimycobacterial activity of the 1,3,4-oxadiazole-2-thione derivatives is very low or absent. The authors also reported that the presence in the active compounds of the carbonyl function seems to be responsible for the greatest potency of these compounds with respect to the corresponding thione derivatives **[Figure 31]**.

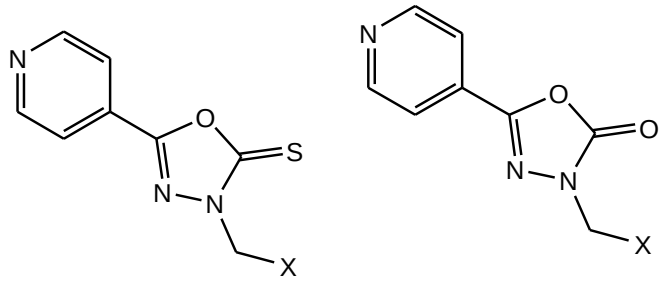


Figure-31

Marina I *et al* [58] have synthesized a series of 3-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazole derivatives and screened them all for in vitro activity against Staphylococcus aureus, Trypanosoma cruzi, and Candida albicans. The bioactivity was expressed as minimum inhibitory concentration (MIC) for S. aureus strains, and as fifty-percent inhibitory concentration (IC50) of parasite population growth for *T. cruzi*.

A molecular modeling approach was performed to establish qualitative relationships regarding the biological data and the compounds' physico-chemical properties. In this study it was observed that all the synthesized 3-acetyl-2,5-disubstituted-2,3-dihydro-1,3,4-oxadiazole derivatives were active against all microorganisms tested **[Figure 32]**.

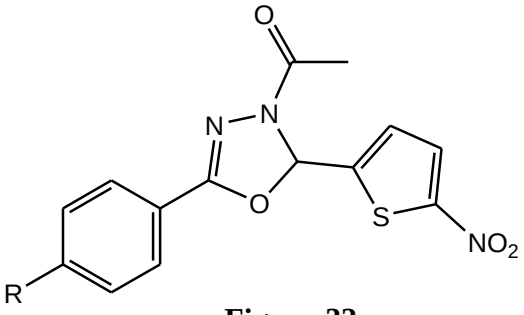


Figure-32

Ru Y *et al* [59] have reported that a series of novel 1,3,4-oxadiazole derivatives have been designed, synthesized and evaluated for their immunosuppressive activity. Most of these synthesized compounds were proved to have potent immunosuppressive activity and low toxicity. Among them some compounds showed the potent biological activity against lymph node cells. The authors also molecular docking was performed to position most active compound into PI3Kc binding site in order to explore the potential target **[Figure 33]**.

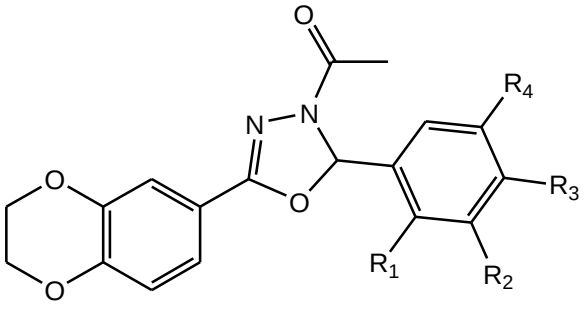


Figure-33

Fang L *et al* [60] have synthesized and screened antifungal activity of novel sulfoxide derivatives containing trimethoxyphenyl substituted 1,3,4-thiadiazole and 1,3,4-oxadiazole moiety. Antifungal screening of all the synthesized compounds was done against Gibberella zeae, Fusarium oxysporium and Cytospora mandshurica. The bioassay results showed that title compound possess good antifungal activities **[Figure 34]**.

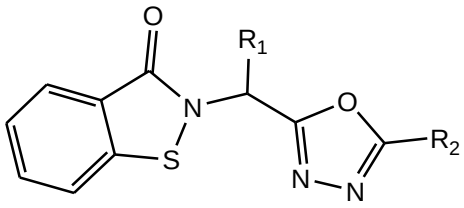


Figure-34

Jian-Feng T *et al* [61] have synthesized a series of novel 1,3,4-oxadiazole derivatives and evaluated their immunosuppressive activity against ConA stimulated T cells. It was observed that most of these synthesized compounds were proved to have potent immunosuppressive activity and low toxicity **[Figure 35]**.

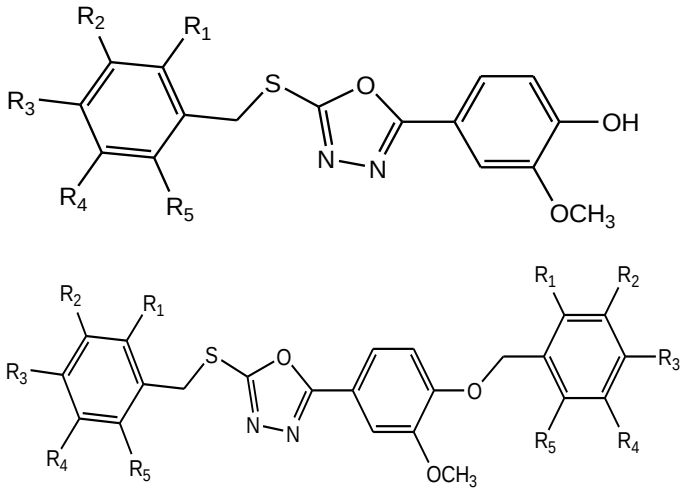


Figure-35

Pushpan P *et al* [62] have been synthesized a novel combinatorial library of S-substituted-1,3,4-oxadiazole derivatives bearing N-methyl-4-(trifluoromethyl) phenyl pyrazole moiety and tested for in-vitro cytotoxic activity by MTT assay **[Figure 36]**.

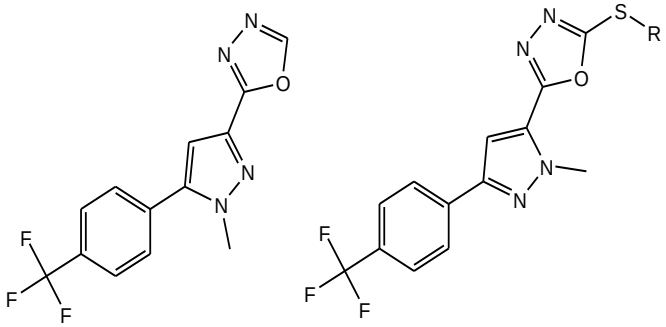


Figure-36

Priscilla P *et al* [63] reported that a new series of 1-(substituted)-2-({5-[(naphthalen-1/2-yloxy) methyl]-1,3,4-oxadiazol-2-yl}sulfanyl)ethanone derivatives was synthesized by reacting 5-[(naphthalen-1/2-yloxy)methyl]-1,3,4-oxadiazole-2-thiol with appropriate α-haloketones by multistep organic synthesis. They were evaluated for antioxidant properties. Results revealed that few of them exhibited promising activities **[Figure 37]**.

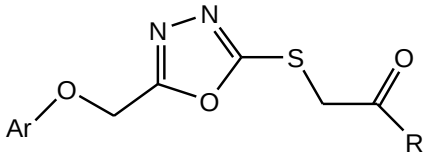


Figure-37

Ramaprasad GC *et al* [64] reported the synthesis of 5-(50-fluoro-20-methoxybiphenyl-3-yl)-1,3,4-oxadiazol-2(3H)-one derivatives. The synthesized compounds were characterized by elemental and spectral analysis and tested for their in vivo anti-inflammatory, analgesic, and *in vitro* antimicrobial activities. Some compounds were found to have promising anti-inflammatory, analgesic, anti-bacterial and antifungal activities **[Figure 38]**.

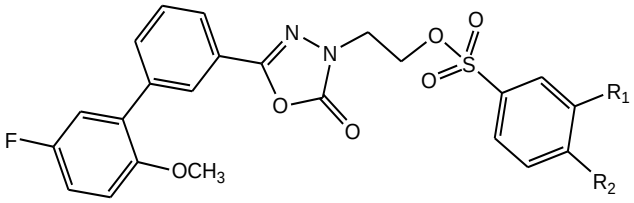


Figure-38

Rajnish K *et al* [65] have been synthesized a series of 7-[4-(5-aryl-1,3,4-oxadiazole-2-yl)piperazinyl] quinolones derivatives using an appropriate synthetic route and characterized by elemental and spectral analysis. The antibacterial activities of all the synthesized compounds were evaluated against identifiable bacterial strains. Many compounds from the series showed better activity than parent compound against all the selected strains. QSAR study on the synthesized molecules for their antibacterial activity was performed using multiple linear regression method. Generated models revealed a decrease in HOMO energy as favourable descriptor for determining and predicting the antibacterial activity of the synthesized compounds. Further, the developed models were cross validated using LOO method for their predictive nature **[Figure 39]**.

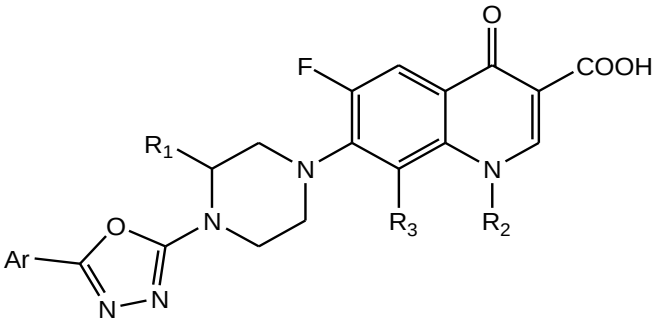
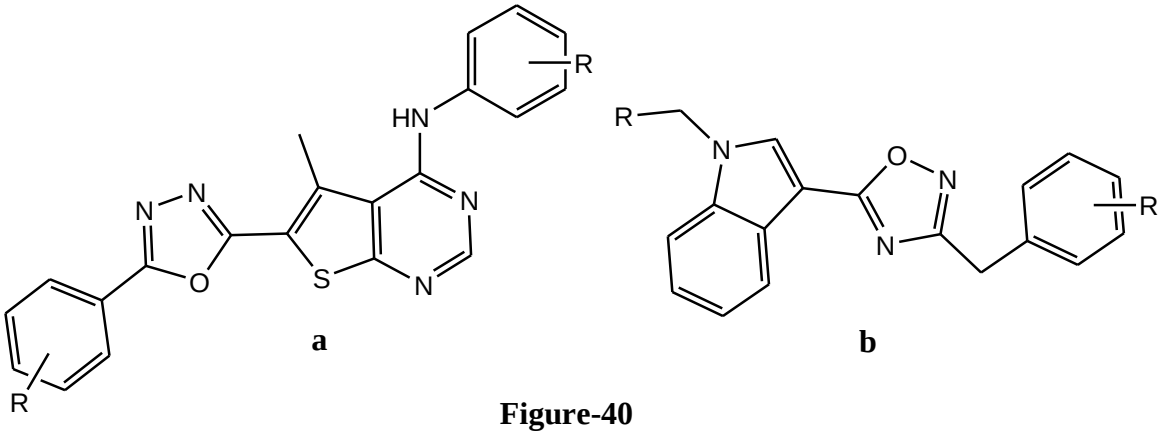


Figure-39

Kotaiah Y *et al* [66] reported the synthesis of a new series of N-substituted phenyl-5-methyl-6-(5-(4-substituted phenyl)-1,3,4-oxadiazol-2-yl)thieno [2,3-d]pyrimidin-4-amine and substituted phenyl amino-5-methylthieno[2,3-d]pyrimidine-6-carboxylic acid derivatives. All these novel compounds were screened for their in vitro antioxidant activity by employing DPPH, hydrogen peroxide, and nitric oxide radical scavenging assays. Many compounds showed significant radical scavenging activity due to the presence of electron donating substituent on both sides of the thienopyrimidine ring enhances the activity and electron withdrawing groups like nitro decrease **[Figure-40a]**. Gerard PM *et al* [67] have been reported the synthesis and cannabinoid activity of 1-substituted-indole-3-oxadiazole derivatives as novel agonists for the CB1 receptor **[Figure 40b]**.



a **b**

Figure-40

Ramaprasad GC *et al* [68] reported that a series of 1,3,4-oxadiazoles, namely 5-[substituted-(1,10-biphenyl)-3-yl]-1,3,4-oxadiazole-2(3H)-thiones and its S-alkyl derivatives have been synthesized in good yield and screened for their antibacterial, antifungal and analgesic activities. The antibacterial screening showed that among the tested compounds, the fluoro substituted compound exhibited the highest activity against all the tested microorganisms. Analgesic activity screening indicated that the compounds bearing ester functional group in the S-alkylated derivatives gave the highest activities **[Figure 41]**.

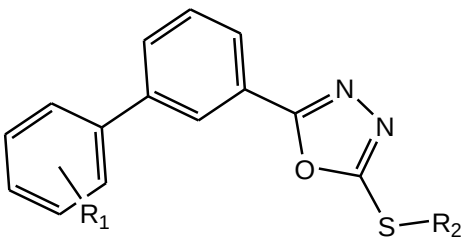


Figure-41

Dabholkar VV *et al* [69] have reported the reaction of diethyladipate with hydrazine hydrate to give succinohydrazide which on further treatment with carbon disulfide, aromatic aldehydes and cynogen bromide yielded 1,2[di-(2-Mercapto-1,3,4-oxadiazole-5yl)] ethane [R= SH], 1,2[di-(2-Phenyl-1,3,4-oxadiazole-5yl)] ethane [R= substituted phenyl] and 1,2[di-(2-Amino-1,3,4-oxadiazole-5 yl)] ethane [R=NH_2] respectively. The structures of the compounds have been elucidated on the basis of spectral analysis **[Figure 42]**.

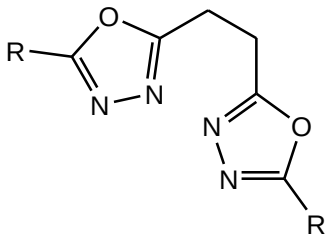


Figure-42

Saini R *et al* [70] have synthesised (ethyl 2-(1H Benzo [d] [1, 2, 3] triazole-1-yl] acetate) and (2H-benzo [d] [1, 2, 3] triazole-1-yl-acetohydrazine)

along with their derivatives. The entire synthesized compounds were characterized by UV, IR and ^{1}H-NMR spectroscopy. The Antimicrobial activity of the synthesized compounds was evaluated on *S. aureus* and *E. coli* **[Figure 43]**.

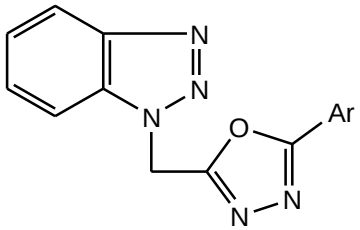


Figure-43

CONCLUSION: The pharmacological potential of 1,3,4-oxadiazole nucleus is cleared from the literature and clinically used drugs. The literature revealed that 1,3,4-oxadiazole possess diverse biological potential, easy synthetic routes for the synthesis and taken the attention of researchers. Though it can be concluded that antimicrobial, antifungal, anti-inflammatory and anti-cancer are the four major areas of clinical use in which much efforts has been done, some other potential targets also showed good results such as enzyme inhibitors and antiviral but these are still to be explored. From these observations important of the nucleus is highlighted.

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