1,3,4-OXADIAZOLE: A THERAPEUTICAL EMERGING SCAFFOLD

[1]Geetanjali Mehara, [2]Kumud Upadhyaya, [3]Amita Joshi Rana

Department of Pharmaceutical Sciences
Sir J.C Bose Technical Campus
Kumaun University Bhimtal, (263136), Uttarakhand, India.

Abstract- **The five-membered heterocyclic ring oxadiazole symbolizes the significance of a structural key in pharmaceutical and medicinal chemistry. Four distinct isomers of oxadiazole exist 1,2,3-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole and 1,2,4-oxadiazole. Due to their extensive spectrum of chemical and biological properties, the 1,3,4-oxadiazole and 1,2,4-oxadiazole are better and are extensively investigated by researchers. The aromatic heterocyclic 1,3,4-oxadiazole has two nitrogen and one oxygen in its nucleus. The nucleus of the 1,3,4-oxadiazole is a biological scaffold with a wide range of pharmacological activities such as anti-cancer, anti-inflammation, analgesic, anti-HIV, anti-bacterial, anti-hypertensive, anti-tubercular, ant-microbial, anti-helminthic, anti-oxidant, anti-diabetic, anti-viral, anti-parkinsonian and anti-convulsant etc. The 1,3,4-oxadiazole scaffold is present in many marketed formulations such as nitrofuran derivative (Furamizole) which has potent anti-bacterial activity, Raltegravir as an anti-viral treatment, Nesapidil as an anti-hypertensive and Zobitentan as an anti-cancer medication. The 1,3,4-oxadiazole nucleus drew researchers from around the world to work in this field of developing new drugs. The present review summarized some pharmacological activities and various synthesis routes for 2,5-disubstituted 1,3,4-oxadiazole.**

Keywords: **Anti-inflammation, Anti-cancer, Anti-arrhythmic, Heterocyclic ring, Anticonvulsant, 1,3,4-Oxadiazole.**

1-INTRODUCTION

Oxadiazole is a five-membered aromatic heterocyclic ring having -N=C=O- linkage and contains one oxygen and two nitrogen atoms [1]. It is found in four different isomeric forms such as 1,2,3-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole and 1,2,4-oxadiazole shown in fig.1 [2]. In 1965, Ainsworth first synthesized oxadiazole through hydrazine thermolysis which is soluble in water and has a molecular mass of 70.05g/mol [3]. The 1,3,4-oxadiazole can be synthesized in a number of methods. Mostly, 1,3,4-oxadiazole is synthesized when the reaction of acid hydrazide or hydrazine along with carboxylic acid/acid hydrazide and direct the ring closure of diacyl hydrazines occur by adding different kinds of a cyclizing agent such as phosphorus oxychloride, thionyl chloride, phosphorus pentaoxide, triflic anhydride, phosphorus acid, acetic acid and the direct reaction of an acid with (N-isocyananimino-) triphenyl phosphorane [4]. In some methods, carbon disulfide is employed as ring closure [5]. The 1,3,4-oxadiazole a broad spectrum of activities such as anti-cancer [6], [7], anti-inflammation [8], analgesic [9], anti-bacterial[10], anti-HIV [11], anti-hypertensive [12], anti-tubercular [13]–[16], anti-microbial [17]–[25], anti-oxidant[26], [27], anti-diabetic [28] and anti-convulsant[29], [30] etc. There are some commercially available marketed drugs such as Furamizole (anti-bacterial), Raltegravir (anti-viral), Nesapidil (anti-hypertensive), Tiodazosin (anti-hypertensive) [31] and Zibotentan (anti-cancer)[32] having a 1,3,4-oxadiazole nucleus.

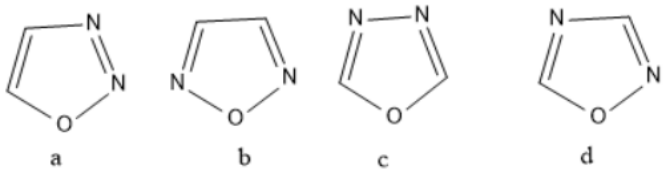


Fig.1 Isomers of oxadiazole [2]

2-Structure-activity relationship of 1,3,4-oxadiazole

Figure.2 exhibits the structure-activity relationship of 1,3,4-oxadiazole. When the phenyl ring is substituted with other substituents such as p-Cl, p-NO_2, and p-Bu increased the activity. The activity is also increased by the conversion of the methylthio group into the methyl-sulfonyl group. The activity is reduced when the pyridine ring and phenyl ring are replaced. The activity was significantly affected by the presence of an acetyl group on the nitrogen atom of the oxadiazole ring [33].

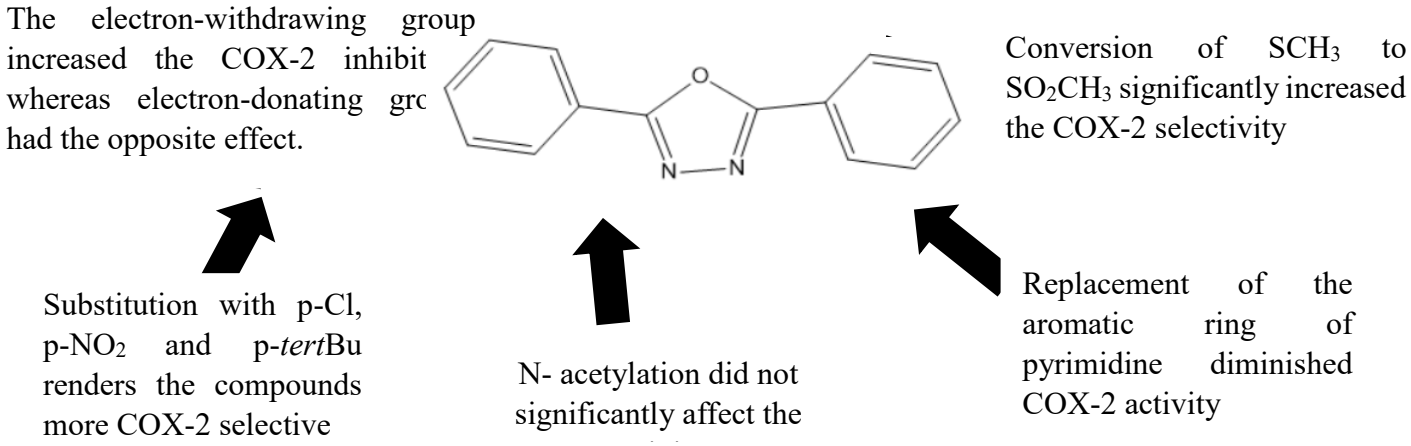


Fig. 2 Structure-activity relationship of 1,3,4-Oxadiazole[33]

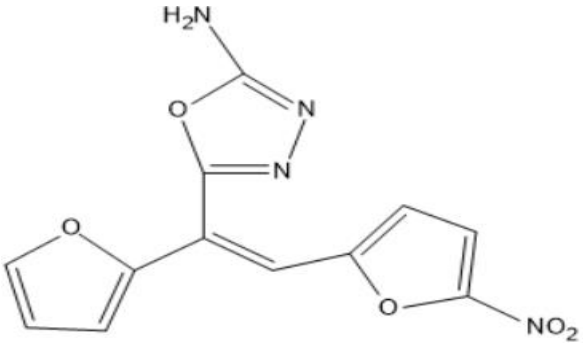
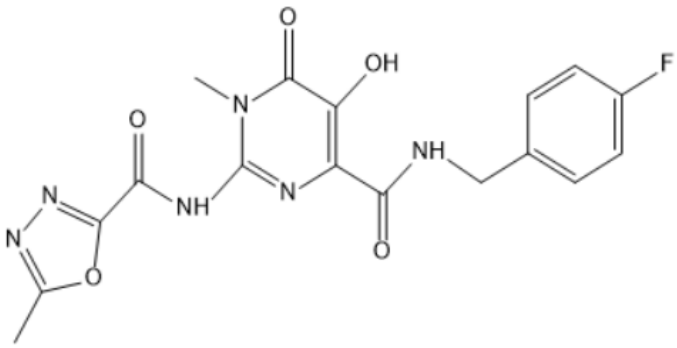
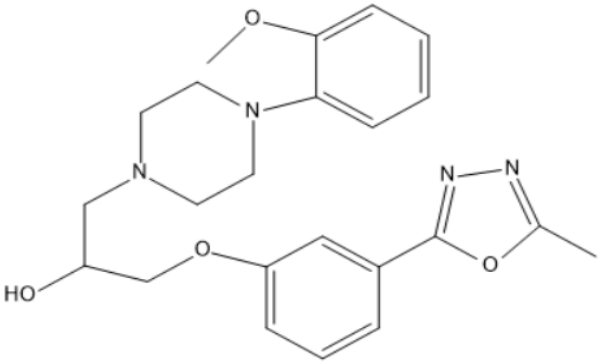
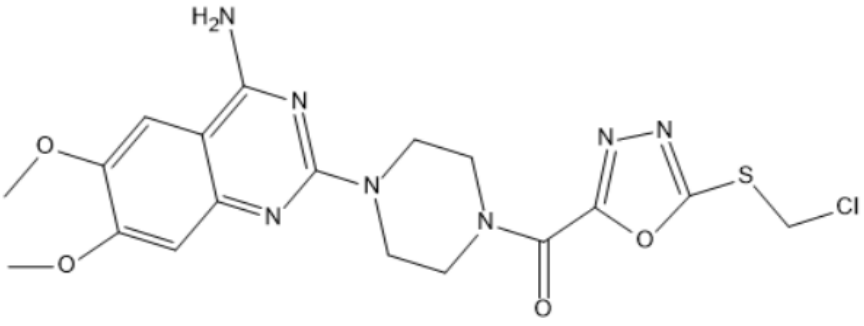
Furamizole	
Raltegravir	
Nesapidil	
Tiodazosin	

Table 1. Commercially available marketed drugs having a 1,3,4-oxadiazole moiety [31]

3-PHARMACOLOGICAL ACTIVITIES OF 1,3,4-OXADIAZOLE

3.1- ANTI-CANCER ACTIVITY

Pidugu *et al.,* (2016) designed and synthesised a novel HDAC8 inhibitor of 2,5-disubstituted-1,3,4-oxadiazole derivatives containing glycine and alanine hybrids. The series of (3a-j) compounds were designed using the silico tool and docking was performed by glide software (Schrodinger). The compounds 3a-j were assessed for their binding affinity towards HDAC8 crystal protein for its catalytic activity inhibition followed by docking with other class 1 enzymes HDAC1, 2, and 3 respectively and showing a good docking score towards the HDAC8 protein. In HDAC *In-Vitro* inhibitory activity of synthesized oxadiazoles linked with glycine/ alanine assay was purified and carried out using HDAC8 and HDAC fluorophore substrate. When compared to other compounds including SAHA the *In-Silico* study of the 3b showed sustained HDAC8 inhibitory activity with IC_{50} of 98 nM. 3b showed the same or more potent and better HDAC8 selectivity than SAHA. The *In-Vitro* anti-cancer activity of linked oxadiazoles with glycine/alanine (fig.3 3a-j) was assessed against breast cancer MDA-MB-231 cells by MTT assay and all tested compounds showed noteworthy anti-cancer activity. In all tested compounds, 3b was the most potent and active compound against MDA-MB-231 cancer cells[34].

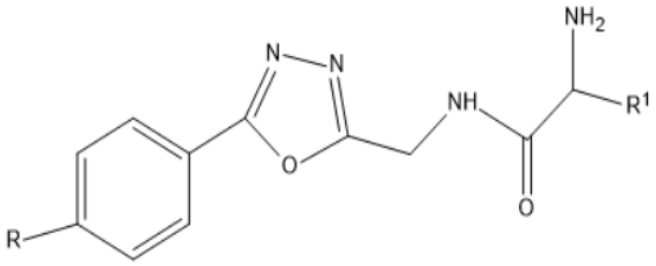
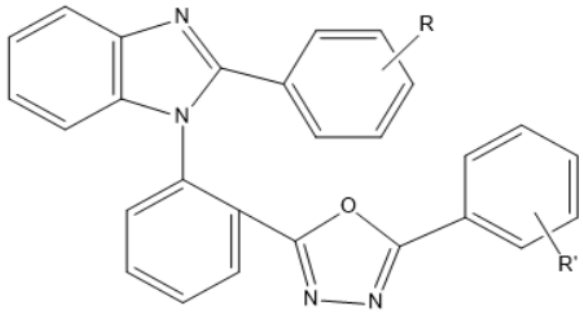


Fig.3

Compound	R	R^1
3a	H	H
3b	H	CH_3
3c	F	H
3d	F	CH_3
3e	CH_3	H
3f	CH_3	CH_3
3g	OCH_3	H
3h	OCH_3	CH_3
3i	NO_2	H

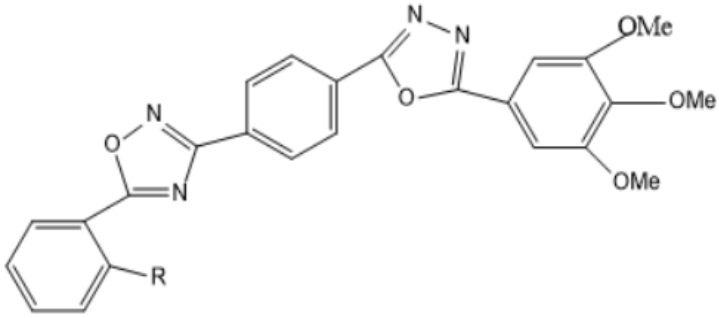
They developed (fig.4) 2-substituted-1-(2-(5-substituted phenyl-1,3,4 oxadiazol-2yl)-phenyl)-1H-benzimidazole and evaluated its anti-cancer activity in human breast cancer cell line MCF-7 by MTT assay. Compound 4e was better cytotoxic as compared to 4a, 4b and 4c. The compounds 4f and 4h also have significant cytotoxic activity as compared to other derivatives which were synthesized by Kapoor *et al.,* (2016) [35]



Compound	R	R'
4a	3,4-OCH_3	4-NO_2
4b	3,4-OCH_3	4-NO_2
4c	3,4-OCH_3	3,4-CH_3NH_2
4d	4-OCH_3	4-NO_2
4e	4-OCH_3	4-OCH_3
4f	4-F	4-NO_2
4g	4-F	4-OCH_3
4h	4-F	3,4-CH_3NH_2

Fig.4

Polothi et al., (2019) synthesized 1,2,4-oxadiazole linked with 1,3,4-oxadiazole derivatives as tubulin binding agents and evaluated its anti-cancer activity on human cell line MCF-7 (lung cancer), A549 and MDA MB-231 (breast cancer) by MTT assay using doxorubicin as a reference drug. The compounds 5b, 5g, 5h and 5j showed significant anti-cancer activity with IC_{50} values having the range between 0.34±0.025 to 2.45 ±0.23µM as compared to the standard drug doxorubicin. The derivatives (5a-j) were investigated by the structure-activity relationship and showed good anti-cancer activity towards two human cancer cell lines (MCF-7= 1.76±0.34µM and A549 =0.45±0.03µM). The compounds 5g (4-NO_2) having an electron-withdrawing group exhibit potent anti-cancer activity against cell lines (MCF= 1.23±0.30 µM, A549= 1.03±0.17µM and MDA MB-231= 1.89±0.35µM. The compound 11h when introduced with $3NO_2$ on the phenyl ring increased the anti-cancer activity in the lung and breast cancer cell lines (MCF-7= 0.34±0.0025 µM) & MDA MB-231=1.11±0.81µM) and 4-OCH_3 group, when introduced into the phenyl ring of the compound 11i, showed significant anti-cancer activity (MCF-7=1.90±0.41µM and A549= 1.89±0.38µM) then the reference drug doxorubicin.[36]



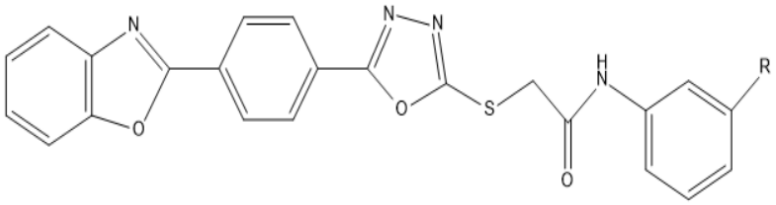
Compound	R
5a	H
5b	3,4,5-trimethoxy
5c	4-methoxy
5d	4-chloro
5e	4-bromo
5f	4-fluoro
5g	4-nitro
5h	3-nitro
5i	4-cyano
5j	4-trifluoromethyl

Fig.5

Ravinaik et al., (2019) A amide derivatives linked with1,3,4-oxadiazole were tested by MTT assay for their anti-cancer activity cancer cell lines A559 (lung cancer), MCF7 (breast cancer), A375 (melanoma cancer) and HT-29 (colon cancer). The synthesized compounds (6a-j) showed good anti-cancer activity with IC_{50} value between 0.01 to 10.40µM and the reference drug showed IC_{50} was between 0.11-0.93µM. The compounds 12c,12g and 12b demonstrated the most significant anti-cancer activity against HT-29 human cancer cell line which showed IC_{50} values 0.018, 0.093 and 0.22µM respectively. The compounds 6f,6g,6b and 6i reflect potent anti-cancer activity against the MCF-7 cancer cell line and 12b and 12i showed good anti-cancer activity against the A549 cell line as compared to combretastatin-A4[37].

3.2 ANTI-INFLAMMATORY ACTIVITY

Kavitha S *et al.,* (2016) synthesized 2,5-substituted-1,3,4-oxadiazole derivatives and evaluated its *In-Vitro* anti-inflammatory activity by serum albumin denaturation with four different concentrations such as 50µm, 100µm, 300µm and 500µm respectively. The compounds 7a,7c, and 9b showed significant anti-inflammatory activity with urea and sulphonamide group and 7b,8a,8c,8g and 8i showed mild activity. The remaining derivatives have moderate activity against reference drug. [38]



Compound	R
6a	H
6b	3,45-trimethoxy
6c	4-methoxy
6d	4-chloro
6e	4-bromo
6f	4-fluoro
6g	4-nitro
6h	4-methyl
6i	4-cyano
6j	3,5-dimethoxy

Fig.6

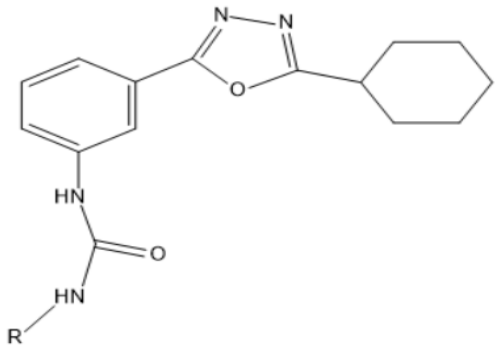


Fig.7

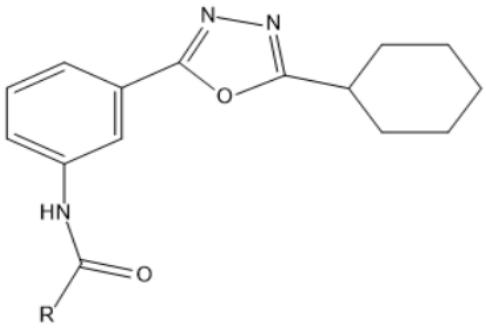


Fig.8

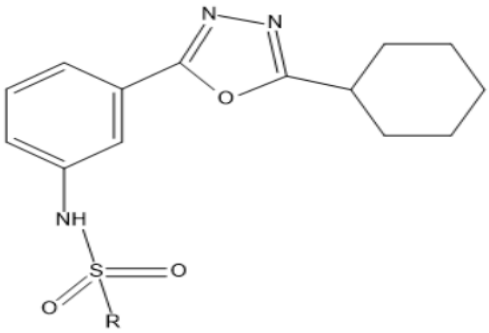


Fig.9

Banerjee *et al.,* designed, synthesized and evaluated its *in-vitro* and *in-vivo* activity against the standard drug indomethacin. The *in-vitro* anti-inflammatory activity was done by the albumin denaturation method and 2-((5-(2-4-dihydroxy phenyl)-1,3,4-oxadiazole-2yl) methyl)-5,6-diphenyl-1,2,4-triazine-3 (2H)-one **(fig.10)** showed the inhibition of heat-induced protein (albumin) denaturation (80.81%) as compared to standard drug indomethacin (84.88%). The *in-vivo* studies showed the highest inhibition of 94.30% **(fig.11)** as compared to indomethacin (100 %). The molecular docking investigation was carried out using the COX-2 crystal structure (PDB: 1CX2), and they revealed anti-inflammatory action by manipulation of the amino acid residues such as Tyr 355 and Arg 120, which were located inside an active site comparable to the common medication indomethacin [39].

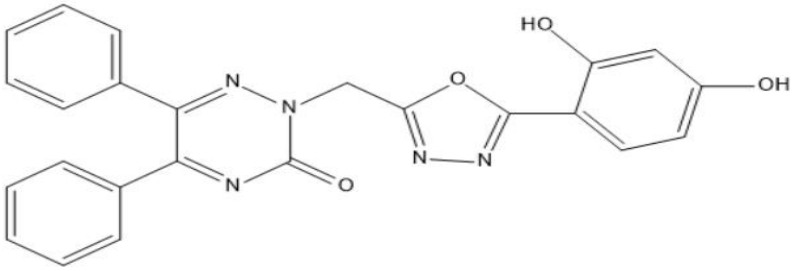


Fig.10

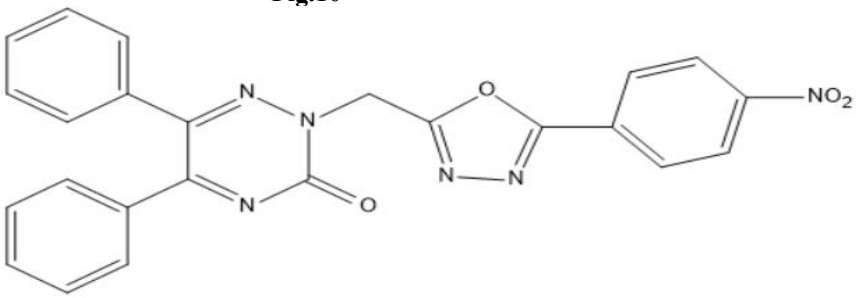


Fig.11

Kashid BB *et al.*,(2020) synthesised a series of novel 2,5-Disubstitiuted-1,3,4-oxadiazole and performed its *in-vitro* anti-inflammatory activity against the reference drug diclofenac. The molecular docking of 2,5-Disubstituted-1,3,4-oxadiazole derivatives showed good to moderate results ranging from -9.692 to the active compound to the moderately active compound docking score of -8.063. The *in-vitro* anti-inflammatory activity of compounds with IC_{50} values of fig.12 (50.54), fig.13 (56.70) and fig.14 (45.69) µM/ml respectively having fig.12, fig.13 and fig.14 has significant activity with reference drug diclofenac sodium (IC_{50}=90.11µM/ml). They all showed good anti-inflammatory activity while the other compounds showed comparable results against the reference drug diclofenac. [40]

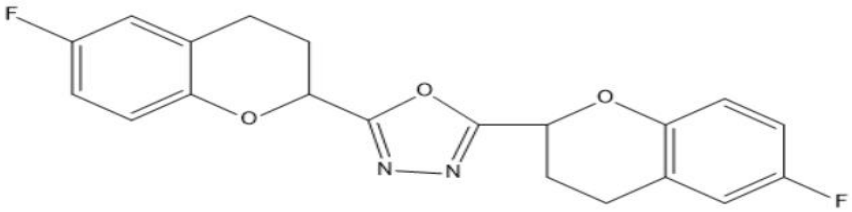


Fig.12

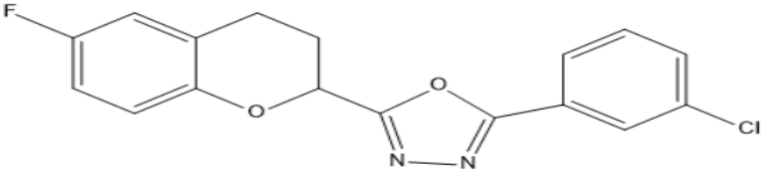


Fig.13

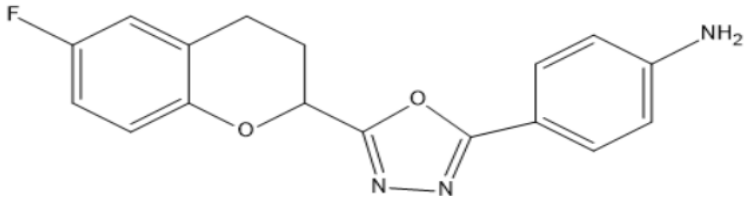
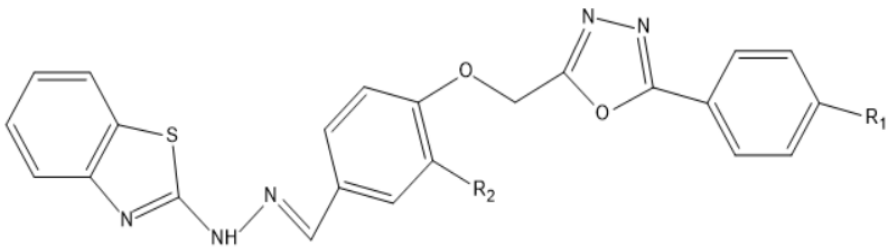


Fig. 14

Zheng XJ *et al.,* synthesized the benzothiazole derivatives having a 1,3,4-oxadiazole nucleus and evaluated their anti-inflammatory activity. The Compound 15 at the highest dose of 100 mg/kg showed the highest anti-inflammatory activity (59.44%) which was equipotent to the reference drug indomethacin (58.28%) [41]

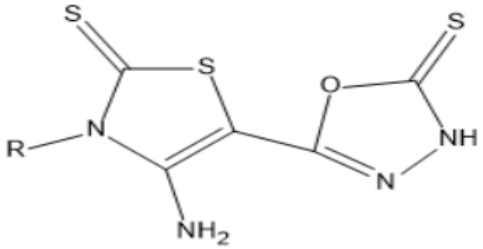
Fig.15

3.3 ANTI-VIRAL ACTIVITY



Albratty *et al.,* (2019) synthesized some new 1,3,4-oxadiazole bearing thiophene, thiazole, coumarin, pyridine and pyridazine ring and evaluated its anti-viral activity. The compounds (fig 16a and b) with an aminothiazole substitution were most active against the Feline herpes virus (FHV), Feline coronavirus (FCoV), Herpes simplex virus-1 (HSV-1 KOS) and Simplex virus-2 (G). The Herpes stains had a 2µmol/L IC_{50} value, so they were weaker than acyclovir (IC_{50}=4.041 µmol/L) but stronger than cidofovir (IC_{50}=125-250µmol/L. The compound fig.17 containing the phenyl hydrazonyl group was most active against vaccinia virus, Herpes simplex virus-1, vesicular stomatitis virus and Coxsackie virus B4 and IC_{50} value was 4µmol/L which was lower than the standard drug acyclovir (IC_{50}=50-250 µmol/L) and cidofovir (IC_{50}=10-250µmol/L) [42].

Compound	R
R_1	3-CH_3
R_2	H



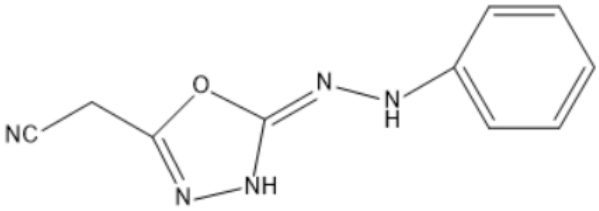
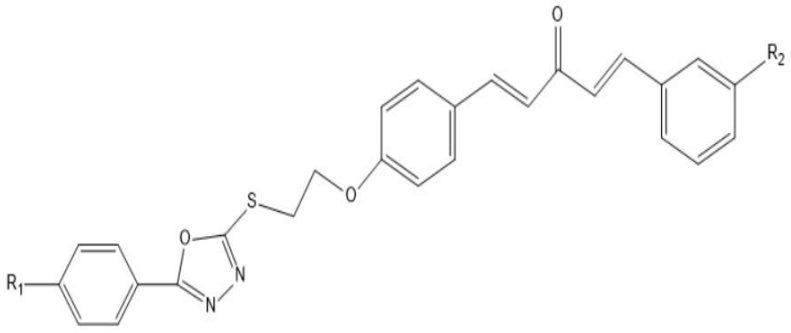


Fig.16 R- a- C_2H_5 **Fig 17**

b-C_6H_5

X Gan *et al*., (2016) designed, synthesized and performed the anti-viral activity of the three-dimensional quantitative structure-activity relationship of novel 1,4-pentadiene-3-one derivative containing 1,3,4-oxadiazole nucleus against TMV using standard drug ribavirin. The synthesized derivatives (Fig.18) 1a, 1c, 1f, 2a, 2c, 2d, 2e, 2f, 2g, 2h, 2i, 3e and 3f had potent activity as compared to standard drug ribavirin. The 1a-1h and 2a-2g had potent curative against TMV. The most active and potent anti-viral compound 2f showed protective activity against the standard drug ribavirin [43]

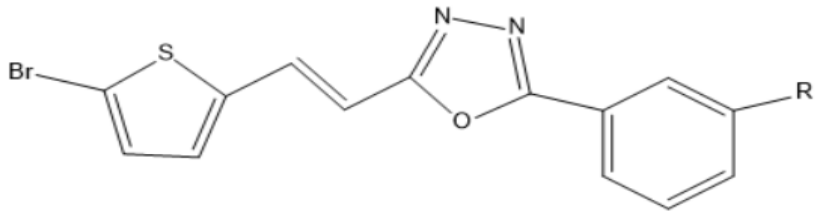


Compounds	R_1
1a-j	4F
2a-k	H
3a-j	4-OCH_3

Compounds	R_2
(a)	4-F
(b)	4-Cl
(c)	4-Br
(d)	2-F
(e)	2-Cl
(f)	2,4-dichloro
(g)	H
(h)	4-CH_3
(I)	4-OCH_3
(j)	2-CF_3
(k)	2,4-difluoro

Fig.18

Benmansour *et al.,* (2016) synthesized the new 1,3,4-oxadiazole derivatives bearing a thiofen nucleus and evaluated their anti-viral activity. They performed the effectiveness of the new compounds as dengue virus (DENV) inhibitors targeting NS5 (nonstructural protein 5) polymerase which was an essential RNA-dependent RNA polymerase (RdRp) that was required for the replication of the virus. The 19a-d compounds were active against the DENV-2 RdRp virus. Furthermore, the activity was also treated in four different clinically isolated serotypes (DENV 1-4) and the 19d was the most effective compound[44]



Compound	R
19a	3-Cl
19b	3,4-diCl
19c	4-CF_3
19d	3-Br

Fig.19

3.4 ANTI-FUNGAL ACTIVITY

Nimbalkar *et al*., (2016) synthesized ultrasound and molecular sieves-assisted compounds and evaluated their anti-fungal activity against fluconazole. The *in-vitro* anti-fungal activity of compounds 21i and 21e showed better activity than the reference drug fluconazole against filamentous Aspergillus fumigatus and Aspergillus niger respectively. The molecular docking of the compounds 21c, 21f and 21i had the lowest and most active interaction[45].

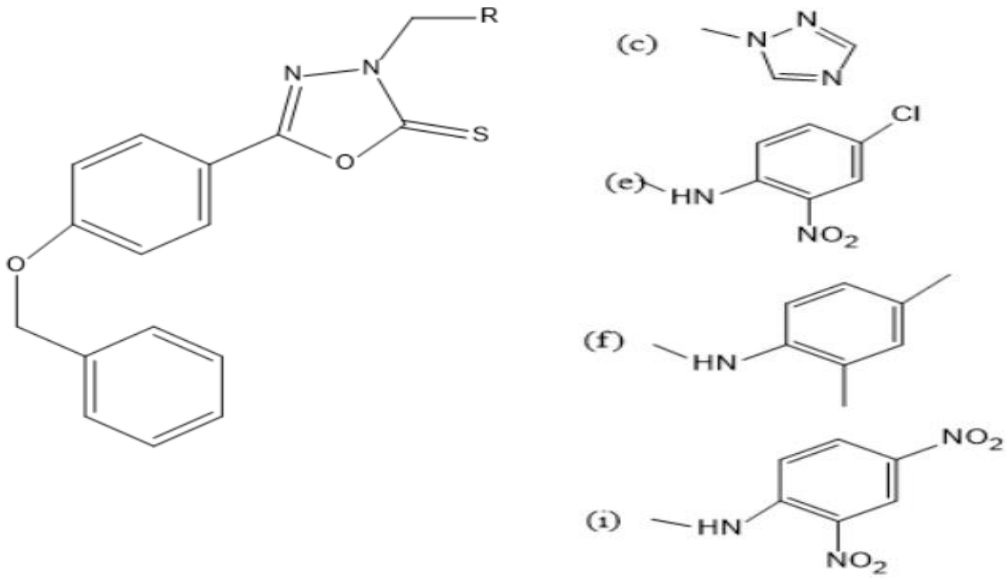


Fig.21

Karaburun *et al.,* synthesized the novel benzimidazole-1,3,4-oxadiazole hybrids and evaluated their *in-vitro* anti-fungal activity using ketoconazole and amphotericin B as reference drugs against Candida strains including C. albicans (ATCC 90030), C.krusei (ATCC 6258), and C. parapsilopsis (ATCC 22019). Among all the strains C. albicans were the most resistant strains towards all compounds. The compounds 22a and 22b showed comparable results as reference drugs which were MIC_{50} value of 1.95µg/mL against C. albicans whereas amphotericin B and ketoconazole showed MIC_{50} values of 1.95µg/mL and 7.8 µg/mL respectively. Compound 22b showed MIC_{50} values 1.95µg/mL, 7.8 µg/mL and 31.25 µg/mL against C. albicans, C. krusei and C. parapsilopsis respectively. Ketoconazole exhibited MIC_{50} values 7.8 µg/mL, 1.95 µg/mL and 1.95 µg/mL against C. albicans, C. krusei and C. parapsilopsis respectively. Docking studies showed that 22a and 22b contained the most active compounds and an ergosterol-qualifying assay revealed the effectiveness of these compound's ergosterol inhibition [46].

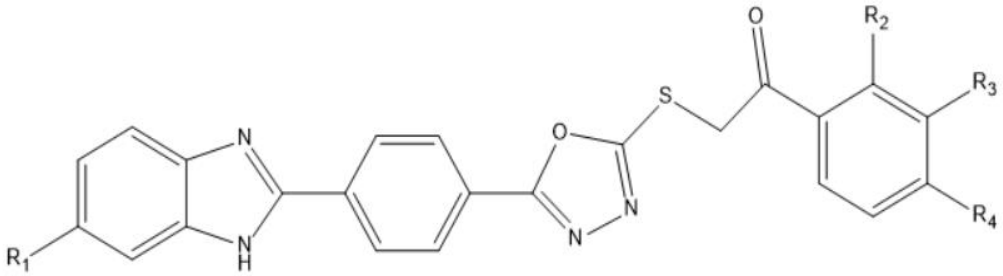
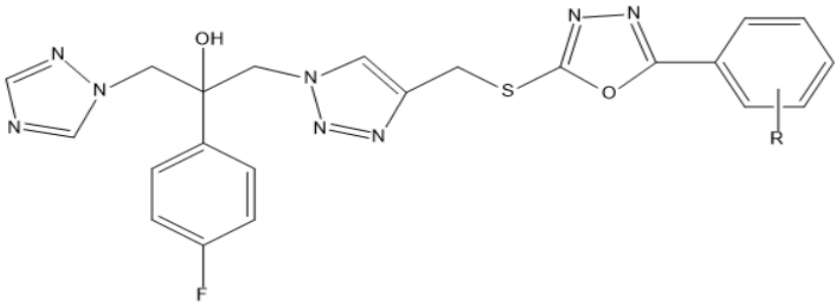


Fig.22

Liao Jun *et al.,* synthesized eighteen (23a-r) novel fluconazole analogues having a 1,3,4-oxadiazole nucleus and evaluated its anti-fungal activity using fluconazole and itraconazole as a reference drug against human pathogenic fungi such as Candida albican SC5314, Candida albican Y0109, Cryptococcus neoformans, Candida parapsilosis, Candida glabrata, Trichophyton rubrum and Microsporum gypseum. The compounds 23a and 23b exhibited good inhibitory action in all pathogenic fungi except M. gypseum with minimum inhibitory concentration (MIC_{80}) value equal to or lower than 0.125µg/mL. The compounds 23a and 23b showed potent MIC_{80} activity as compared to the positive control[47].



Compound	R
23a	2-Br
23b	3-OCH_3

Fig.23

3.5 ANTI-CONVULSANT ACTIVITY

Wang S *et al.,* (2020) synthesized the 1,3,4-oxadiazole with anti-convulsant activity and their binding to the GABAA receptor. The *in-silico* study (fig.24) showed the interaction with amino acid residues around BZ-S of the GABAA receptor. The synthesized compound 24 showed good anti-convulsant activity in MES and scPTZ models as compared to standard drugs. The radioreceptor binding affinity assay showed that the 24 compound has most suitable with an IC_{50} value of 0.11 µm and higher binding affinity towards GABAA receptors[48].

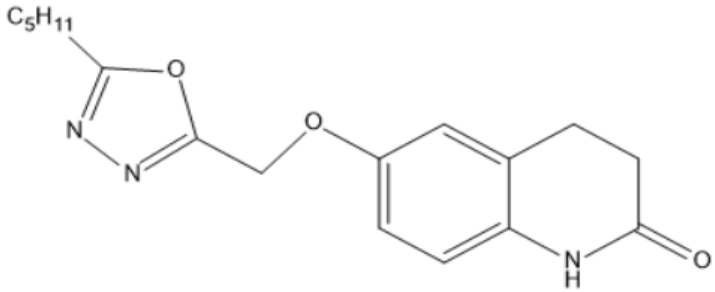


Fig.24

Almasirad A *et al.,* (2004) synthesized and performed its anti-convulsant activity on 2- substituted-5-[2-(2-fluorophenoxy) phenyl]-1,3,4-oxadiazole by MES and PTZ models against the reference drug diazepam. Compound Fig. 25 has effective results in both MES and PTZ[49].

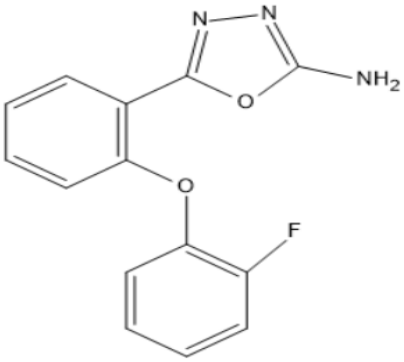
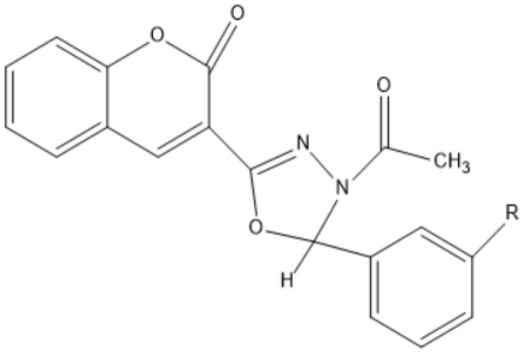


Fig.25

Dureja A *et al.,* (2011) synthesized and evaluated its anti-convulsant activity by the MES model against the standard drug phenytoin. The 26 b, e, f, g and h had significant activity as phenytoin and other derivatives showed mild activity as compared to the reference drug[50].



Compound	R
26a	H
26b	3-NO_2
26c	2-NO_2
26d	2-Cl
26e	4-Cl
26f	4-F
26g	4-OCH_3
26h	4-OH

Fig. 26

CONCLUSION

The reviews compile the broad-spectrum activities associated with the 1,3,4-oxadiazole nucleus. 1,3,4-oxadiazole derivatives are considered an important class of biologically active compound that has various pharmacological activities such as anti-cancer, anti-diabetic, anti-inflammatory, anti-viral, anti-tubercular, anti-fungal, anti-bacterial, anti-oxidant and anti-microbial, anti-convulsant etc. The study revealed the potential value of 1,3.4-oxadiazole as a template for further modification to create compounds with higher biological activity. The 1,3,4-oxadiazole nucleus's new structure attests to the development of cutting-edge medication to treat various diseases. The review approach is currently employed to ignite future secure utilization of the crucial chemical moiety with little or no inflammatory activity.

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