



1, 3, 4 OXADIAZOLE: A POTENT DRUG CANDIDATE WITH VARIOUS PHARMACOLOGICAL ACTIVITIES

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ABSTRACT

Oxadiazoles were discovered in 2008, against the schistosomiasis-causing fluke are effective without any evidence of negative effects on humans. Oxadiazole is a five membered heterocyclic aromatic lead compound having various pharmacological actions. Derivatives of oxadiazole are used in the market such as (Tiodazosin, Nosapidil, Furamizole), in the preparation of dyes, liquid crystals and scintillators etc. Results of various derivatives of different oxadiazole and their substitutions with diverse biological activities are reviewed in present article.

Keywords: Oxadiazole, Review

INTRODUCTION

Oxadiazole is a heterocycle nucleus and is considered to be derived from furan by replacement of two methane (-CH=) group by two

pyridine type nitrogen (-N=). There are four possible isomers of oxadiazole (1, 2, 3, 4) depending on the position of nitrogen atom in the ring and are numbered as shown in Fig. 1.

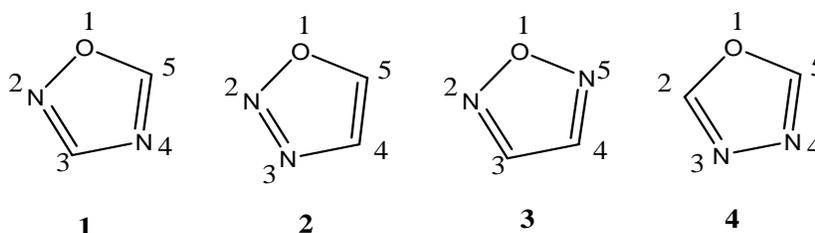


Fig 1. Isomers of Oxadiazole

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. The electrophilic substitutions in oxadiazole ring are extremely difficult at the carbon atom because of the relatively low electron density on the carbon atom which can be attributed to electron withdrawal effect of the pyridine type nitrogen atom. However the attack of electrophiles occurs at nitrogen, if oxadiazole ring is substituted with electron-releasing groups. Oxadiazole ring is generally resistant to nucleophilic attack. Halogen-substituted oxadiazole, however, undergo nucleophilic substitution with replacement of halogen atom by nucleophiles. Oxadiazole undergo nucleophilic substitution similarly as occurring at an aliphatic sp² carbon atom.

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

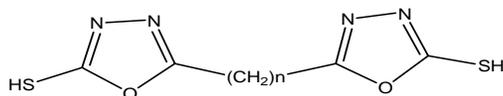
Synthesis and various pharmacological activities

Anti-microbial activity:

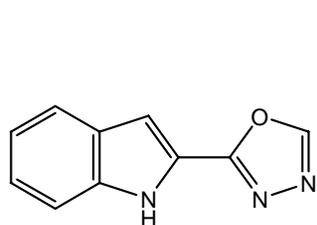
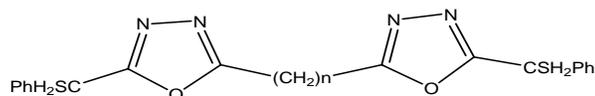
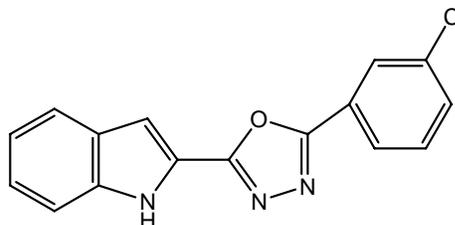
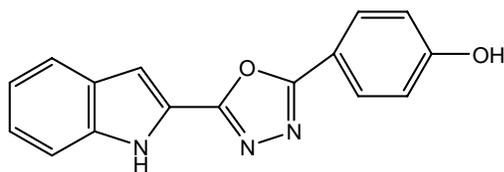
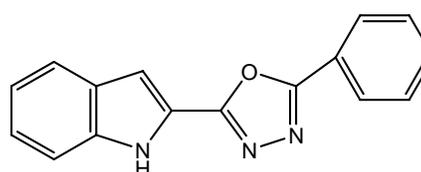
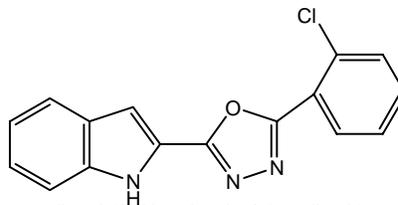
- A series of 1,3,4-bis-oxadiazole derivatives were developed by Ahmed O. Maslat¹ et al as potential antimicrobial agents.

The compounds are: 5,5'-dimercapto- bis-[1,3,4-oxadiazol-2-yl]propane, 5,5'-dimercapto-bis-[1,3,4-oxadiazol-2-yl]butane, 5,5'-dimercapto-bis-[1,3,4-oxadiazol-2-yl]octane and 5,5'-dibenzylthio-bis-[1,3,4-oxadiazol-2-yl]butane. These newly synthesized compounds were investigated for their antibacterial, antifungal activities against *S. aureus* and *B. subtilis*. Compound 2a also showed activity against *P. aeruginosa*. All the above compounds and compound 3 exhibited activity against *C. albicans*.

- Niti Bhardwaj² et al have synthesized derivatives of 1,3,4-oxadiazoles by incorporating indole nucleus at one of the two free positions in the oxadiazole ring system. These synthesized compounds evaluated for antimicrobial activity by Punched-hole method against MTCC 441 (*Bacillus subtilis*), MTCC 1430 (*Staphylococcus aureus*), MTCC 424 (*Pseudomonas aeruginosa*), MTCC 1573 (*Escherichia coli*) and MTCC 2546 (*A. niger*) respectively using the standard drugs norfloxacin and fluconazole. The activity was observed in compound R1 (against *B. subtilis* and *P. aeruginosa*), R2 (against *S. aureus*, *E. coli* and *B. subtilis*) and R5 (against *S. aureus*). None of the compounds were found effective against *A. niger*. Out of these 4 compounds, only three were found effective against bacterial strains and none of the synthesized compound was found effective against fungal strain. The compounds which were active against bacterial strains were effective at a much higher concentration as compared to the standard drug.

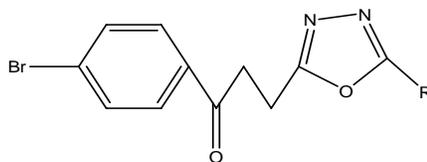


2a (n=3)
2b (n=4)
2c (n=8)

R₁ = 5-Indole-1,3,4-oxadiazoleR₂ = 2-(3-chlorophenyl)-5-indole-1,3,4-oxadiazoleR₃ = 2-(4-hydroxyphenyl)-5-indole-1,3,4-oxadiazoleR₅ = 2-phenyl-5-indole-1,3,4-oxadiazoleR₅ = 2-(2-chlorophenyl)-1,3,4-oxadiazole

AsifHusain³et al have synthesized a novel series of 2-[3-(4-bromophenyl) propan-3-one]-5-(substituted phenyl)-1,3,4-oxadiazoles from 3-(4-bromobenzoyl) propionic acid as starting material in the reaction with different aryl acid hydrazides in phosphorous oxychloride and screened for antibacterial activity by using Gram positive (*Staphylococcus aureus*) and Gram negative (*Escherichia coli*) bacterial strains. The test was carried out in meat peptone agar medium at a concentration of 100 mg mL⁻¹ by the cup plate method. Nitrofurazone was used as standard drug for comparison. Compound 4f, 2-[3-(4-bromophenyl) propan-3-one]-5-(4-

fluorophenyl)-1,3,4-oxadiazole showed very good activity against *S. aureus* (MIC = 12.5 mg mL⁻¹) and good activity against *E. coli* (MIC = 25 mg mL⁻¹), whereas 2-[3-(4-bromophenyl)propan-3-one]-5-(4-chlorophenyl)-1,3,4-oxadiazole (4c) showed good activity against *S. aureus* (MIC = 25 mg mL⁻¹). The reference drug, nitrofurazone showed MIC of 12.5 mg mL⁻¹ against *S. aureus* and 6.5 mg mL⁻¹ against *E. coli*. None of the compounds showed activity equivalent to that of the standard drug Nitrofurazone except compound 4f, which showed at par activity to that of the standard against *S. aureus* with MIC of 12.5 mg mL⁻¹.

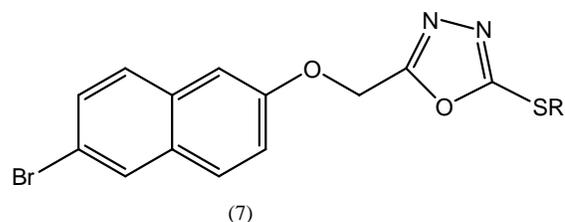
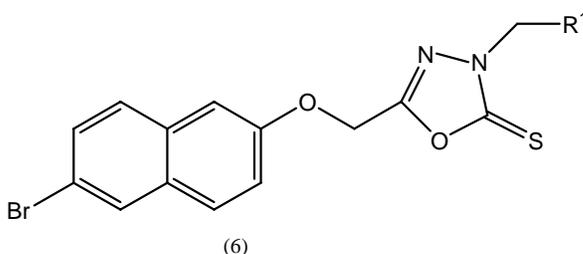
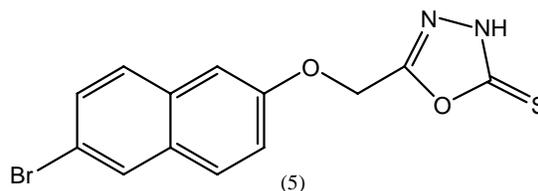
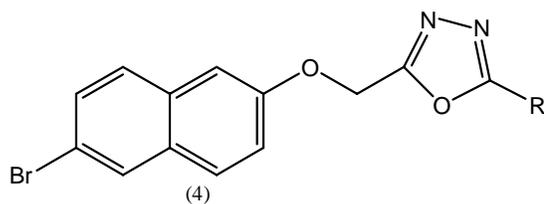


4a-n

R: C₆H₄, 2-ClC₆H₄, 2-HOC₆H₄, 4-NO₂C₆H₄, 4-FC₆H₄, 4-CH₃C₆H₄, 4-OCH₃C₆H₄, 3,4-(OCH₃)₂C₆H₃, C₆H₅CH₂, C₆H₅OCH₂, 2-C₆H₅COC₆H₄, 1-C₁₀H₇OCH₂, 2-C₁₀H₇OCH₂

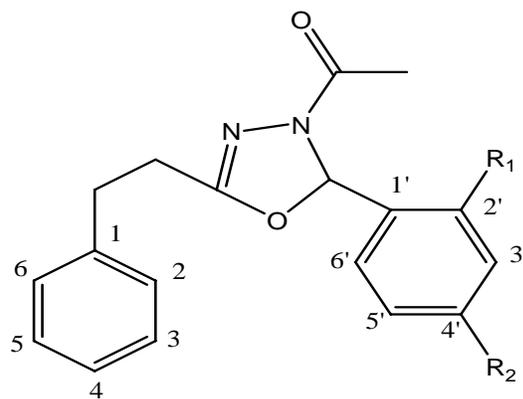
➤ A series of new 1,3,4-oxadiazole derivatives having 6-bromonaphthalene moiety are synthesized by H. S. Yathirajan⁴ et al using 2-[(6-bromo-2-naphthyl)oxy]aceto-hydrazone and various substituted aromatic acids in the presence of POCl_3 . They also synthesized 5-[[6-bromo-2-naphthyl]oxy]methyl]-1,3,4-oxadiazole-2(3H)-thione using hydrazide, CS_2 and KOH. These synthesized compounds were further subjected to Mannich reaction to get a series of Mannich bases. All the newly synthesized compounds were screened for their antimicrobial activity. The investigation of antibacterial and antifungal screening data revealed that all the tested compounds (4a-r) and (6a-j) showed moderate to good inhibition at $\mu\text{g ml}^{-1}$ in DMSO. The compounds 4p and 4r showed comparatively good activity against all the bacterial strains. The good activity is attributed to the presence of

pharmacologically active group attached to phenyl group at position 5 of the oxadiazole ring. Introduction of aryl moiety carrying chloro and dichloro group enhanced activity compared to the standard against *T. mentagrophytes*, *A. flavus* and *A. fumigatus*. The presence of N-Mannich base has shown good antibacterial and antifungal activity. Among the tested compounds, Mannich bases 6a, 6b, 6f, 6g, and 6h have shown remarkable activity against all tested microorganisms. This may be attributed to the presence of pharmacologically active morpholine, 4-methylpiperazine, 2-fluorophenyl, 4-chlorophenyl and 2-methylphenyl groups associated with oxadiazole ring, while S-methylation caused decrease in activity against most of the strains. The compounds 7c-g were inactive compared to that of standard against all the bacterial and fungal strains.



➤ Neeraj Kumar Fuloria⁵ et al have made a series new 1-(2-aryl-5-phenethyl-1,3,4-oxadiazol-3(2H)-yl)ethanones 2a-e was synthesized by the cyclization of imines 1a-e using acetic anhydride. These products were evaluated for antibacterial and anti-fungal activity against freshly cultured strains of *S. aureus* (SA) and *P. aeruginosa* (PA) using sterile nutrient agar media and for antifungal activity against freshly cultured strains of *C. albicans* (CA) and *A. flavus* (AF) using sterile sabouraud's agar medium by the disk diffusion method at a concentration of 2 mg per mL using DMF as

solvent. The results were recorded in duplicate using ampicillin and fluconazole at a concentration of 1 mg per mL as standards. compounds 2a and 2b were found to be equipotent to ampicillin when tested against the strains of *S. aureus*, and *P. aeruginosa*, whereas some of the newly synthesized compounds like 2a, 2d and 2e were found to possess good antibacterial and antifungal activity when tested against *S. aureus*, *P. aeruginosa*, *C. albicans* and *A. flavus*. Finally they conclude that para-substitution enhances the activity of synthesized oxadiazoles.



(2a-e) oxadiazoles

where

a $R_1 = \text{H}$, $R_2 = \text{N}(\text{CH}_3)_2$

b $R_1 = \text{H}$, $R_2 = \text{Cl}$

c $R_1 = \text{OH}$, $R_2 = \text{OH}$

d $R_1 = \text{OH}$, $R_2 = \text{H}$

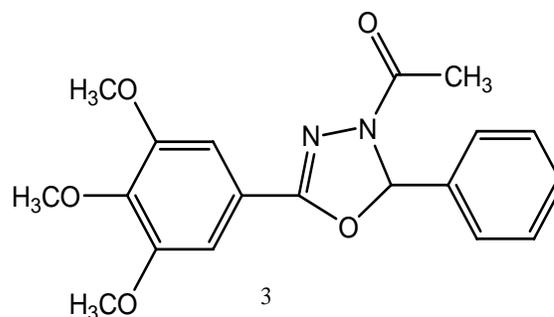
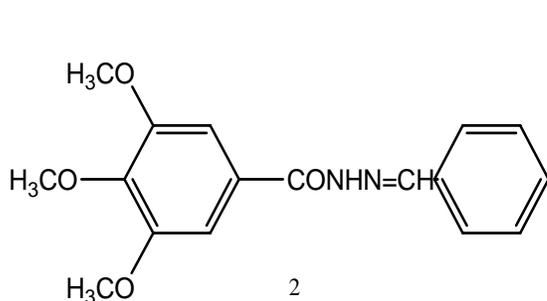
e $R_1 = \text{H}$, $R_2 = \text{OH}$

- Some new 3-acetyl-5-(3-chloro-1-benzo[b]thiophen-2-yl)-2-substituted phenyl-2,3-dihydro-1,3,4-oxadiazoles and 2-(3-chloro-1-benzo[b]thiophen-2-yl)-5-substituted phenyl-1,3,4-oxadiazoles have been synthesized by RakeshChawla⁶ et al. Initially, 3-chloro-1-benzo[b]thiophene-2-carbonyl chloride (1) was prepared from cinnamic acid in the presence of chlorobenzene and thionyl chloride. This compound (1) was treated with hydrazine hydrate to afford 3-chloro-1-benzo[b]thiophene-2-carbohydrazine (2) which was further reacted with various aromatic aldehydes to yield hydrazones (3a-h). Further reaction of these hydrazones (3a-h) with acetic anhydride gave 3-acetyl-5-(3-chloro-1-benzo[b]thiophen-2-yl)-2-substituted phenyl-2,3-dihydro-1,3,4-oxadiazoles (4a-h). Reaction of the same compounds (3a-h) in the presence of chloramine-T afforded 2-(3-chloro-1-benzo[b]thiophen-2-yl)-5-substituted phenyl-1,3,4-oxadiazoles (5a-h). All the compounds were screened for their antibacterial activities against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa* and for antifungal activity against *Candida albicans* and *Aspergillus niger*. The compounds exhibited significant antibacterial and moderate

antifungal activities. Compounds 4c and 4e were found to be most potent with activities, even better than standard drug ciprofloxacin against *S. aureus* and *B. subtilis*.

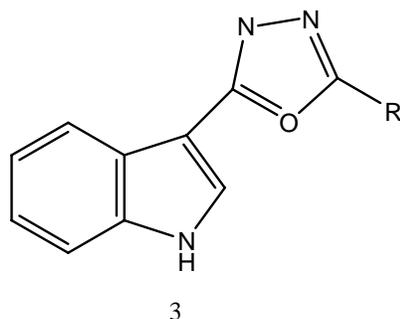
Anti-proliferative activity:

- LinhongJin⁷ et al have synthesized some 3-acetyl-2-substituted phenyl-5-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1,3,4-oxadiazole derivatives by cyclization reaction of N'-substituted benzylidene-3,4,5-trimethoxybenzohydrazide in acetic anhydride. The antitumor activities *in vitro* of these compounds were evaluated against PC3, BGC823, and Bcap-37 cells by MTT method. They found that compounds 2c, 2a, 2b, and 2f have strong inhibitory activity against PC₃ cells. Among these compounds, 2a (R = 2-F) and 2c (R = 4-F) are much more active against PC₃ cells than the other ones, with inhibition rate of 70.6% (2a, 1 μM), 81.8% (2a, 5 μM) and 76.0% (2c, 1 μM), 82.80% (2c, 5 μM), respectively. For the high active compounds 2a, 2b, 2c, and 2f, further bioassay was conducted and their IC₅₀ values against PC₃ cells were 0.2, 1.8, 0.2, and 1.2 μM, respectively.



- DalipKumar⁸ et al have made a facile, convenient and high yielding synthesis of a series of novel 5-(3'-indolyl)-2-(substituted)-1,3,4-oxadiazoles from readily available starting materials. The key step of this protocol is oxidative cyclization of N-acylhydrazones using [bis(trifluoroacetoxy)iodo]benzene under solventfree condition. They studied the Structure Activity Relationship (SAR) of synthesized indolyl-1,3,4-oxadiazoles 3a-m by screening *in vitro* for their anticancer potential against human cancer cell lines from prostate (PC₃, DU145 and LnCaP), breast (MCF7 and MDMDA231), and pancreas (PaCa2). Most of the compounds decreased cell viability significantly as established by colorimetric MTT

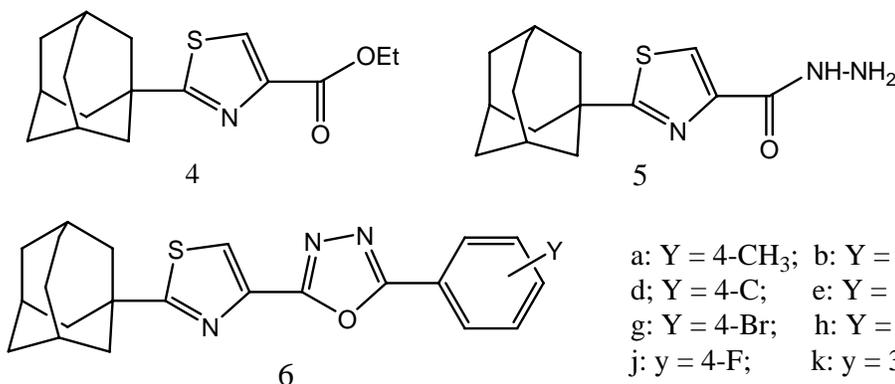
mitochondrial assay with IC₅₀ values ranging from 1 μM to 1 mM concentration. The SAR study reveals that substitution at the C-2 position of the 1,3,4-oxadiazole ring plays an important role. The compound 3a with C-2 phenyl group exhibited moderate activity against MCF7 (388.4 μM) and poor activity against other cell lines. Also, N-methylation of indole ring nitrogen dramatically improved the cytotoxic activity. Studies are being conducted to determine mode of action of 5-(3'-indolyl)-2-(substituted)-1,3,4-oxadiazoles, and further modification of these compounds may successfully lead to development of a potent anticancer agent.



- 3a: R = C₆H₅
 3b: R = CH₂C₆H₅
 3c: R = 4-pyridyl
 3d: R = 3-pyridyl
 3e: R = 4-CH₃OC₆H₄
 3f: R = 4-ClC₆H₄
 3g: R = 3,4-di-CH₃OC₆H₃
 3h: R = 2,3,4-tri-CH₃OC₆H₂
 3i: R = 4-BnO-3-CH₃OC₆H₃
 3j: NH = NCH₃; R = 4-BnO-3-CH₃OC₆H₃,
 3k: R = 4-HO-3-CH₃OC₆H₃
 3l: R = CH₃
 3m: R = CF₃

- A new series of adamantanyl-1,3-thiazole and 1,3,4-oxadiazole derivatives (6a-l), bearing various aryl groups has been synthesized from adamantan-1-nitrile in four steps by MaryamZahid⁹ et al. They used Adamantan-1-nitrile as a starting material for the synthesis of target compounds. The nitrile was converted into thioamide, using P₄S₁₀ followed by its treatment with ethyl bromopyruvate to afford Ethyl 2-adamantyl-1,3-thiazole-4-carboxylate 4. Hydrazinolysis of 4 gave the carbonylhydrazone-1,3-thiazole 5. Heating 5 with substituted benzoic acids in the presence of polyphosphoric

acid (PPA) furnished 1,3,4-oxadiazole derivatives 6a-l. They evaluated all the compounds, *in vitro*, for antiproliferative activity against a large panel of human tumor-derived cell lines. Compounds 6e exhibited activity against human splenic B-lymphoblastoid (WIL-2NS) and human acute B-lymphoblastic leukemia (CCRF-SB) cell lines with CC₅₀ = 68 and 42 μM, respectively. Compound 6l showed activity against CCRF-SB cell lines with CC₅₀ = 51 μM. All the other compounds were found inactive.

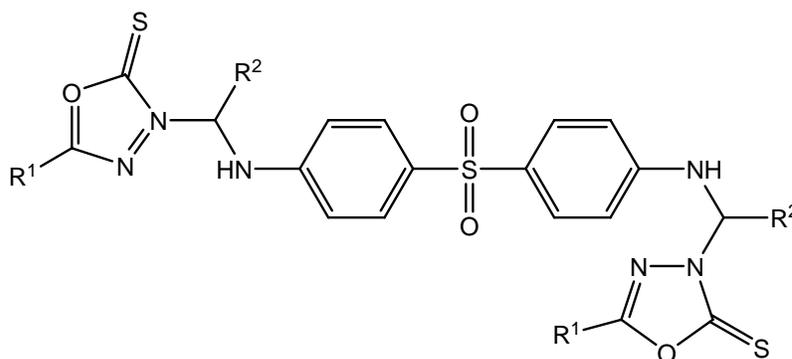


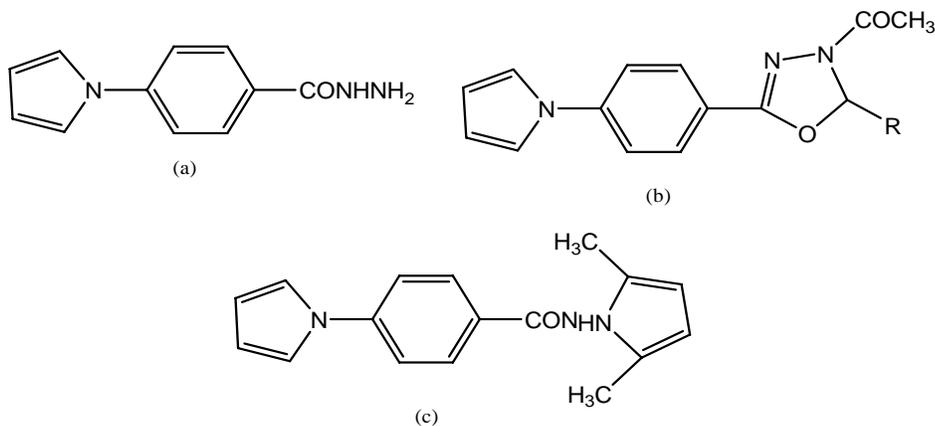
Antitubercular activity:

- MohamedAshrafAli¹⁰ et al have synthesized a series of oxadiazole mannich bases derivatives, dapsone and appropriate aldehyde in the presence of methanol. The reaction procedure is based on the condensation and ring closure reaction of appropriate acid hydrazide with carbondisulfide (CS₂). All the synthesized oxadiazole underwent condensation with appropriate aromatic aldehyde and dapsone in methanolic solution (reaction time varies from 8 to 22 h) affording titled mannich bases. The synthesized compounds (1-14) were tested for their antimycobacterial activity *in vitro* against MTB and INHR-MTB by agar dilution method using double dilution technique. They reported that eleven compounds exhibited excellent antimycobacterial activity with MIC ranging from 0.1 to 5.96 μM. Among the synthesized compounds, 3-{2-furyl}[4-(4-{2-furyl}[5-(2-naphthylloxymethyl)-2-thioxo-2,3-dihydro-1,3,4-oxadiazol-3-yl]methylamino)phenylsulfonyl]anilino]methyl)-5-(2-naphthylloxymethyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione was found to be most potent compound and was 7.3-fold

against MTB and 10.3-fold against INH resistant MTB more active than isoniazid. These antimycobacterial data clearly show that the presence of furfuryl with 2-naphthoxymethyl substitution at mannich bases causes remarkable improvement in Antitubercular activity against both M. tuberculosis H37Rv and INH resistant M. tuberculosis.

- S.D. Joshi¹¹ et al reported a novel series of 4-pyrrol-1-yl benzoic acid hydrazide (a) analogs, some derived 5-substituted-2-thiol-1,3,4-oxadiazoles (b), 5-substituted-4-amino-1,2,4-triazolin-3-thione and 2,5-dimethyl pyrroles (c) and these have been synthesized in good yields and characterized by IR, NMR, mass spectral and elemental analyses. These compounds were screened for antitubercular activity against Mycobacterium tuberculosis H37Rv strain by broth dilution assay method. compounds containing the 1,3,4-oxadiazoline ring and acetyl group, show better activity against M. tuberculosis H37Rv and compound 3 showed highest activity (MIC 16 mg/mL). They selected these compounds for further development to acquire more information about structure-activity relationships in their laboratories.

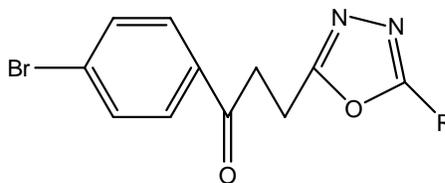




- *Krishna Kant Jha¹² et al* reported 3D QSAR studies for the 41 molecules of 1,3,4-oxadiazoles by using k-Nearest Neighbor Molecular Field Analysis (kNN-MFA) combined with various selection procedures using kNN-MFA approach 52 3D-QSAR models were generated. This model can be used for preliminary screening of large diversified compound libraries. The model has shown that presence of sulphur is must for activity, however the larger bulky substituents reduce the activity. The presence of halogen and other non-halogen groups have also contributed to the activity. Hence the future schemes with smaller groups on sulphur and electronegative groups in the molecule would result in potentially active molecules.

Anti-inflammatory activity:

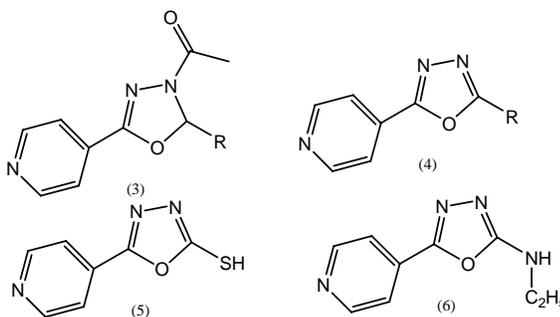
- *Asif Hussain³ et al* reported a novel series of 2-[3-(4-bromophenyl)propan-3-one]-5-(substituted phenyl)-



- 1,3,4-oxadiazole and its derivatives (3a-3e) were synthesized by *Dhansay Dewangan¹³ et al* using intermediate pyridine-4-Carbohydrazide. Schiff's base were obtained on treatment with various aromatic aldehyde, further on condensation with acetic anhydride produced the title compounds. They also synthesized derivative of 1,3,4 oxadiazole (4,5,6) using same intermediate as above by different methods. They also studied SAR of these synthesized compounds. The 2-position and 5-position is an extremely important site of molecular

1,3,4-oxadiazoles and have been synthesized from 3-(4-bromobenzoyl)propionic acid with the aim to get better anti-inflammatory agents with minimum or without side effects. These were evaluated them for anti-inflammatory activity according to the method of Winter *et al.* on Wistar rats. The rats were divided into thirteen groups of six animals each. Freshly prepared aqueous suspension of carrageenan (1 % *m/V*, 0.1 mL) was injected in the planta aponeurosis of the right hind paw of each rat. One group was kept as a control and the animals of other groups were pretreated with test drugs (20 mg kg⁻¹ body mass) given orally 30 minutes before carrageenan injection. The foot volume was measured before and 4 h after carrageenan injection with a plethysmograph. The mean increase in the paw volume in each group was calculated. Indomethacin used as standard drugs for comparison.

modification, which play a dominant role in determining the pharmacological activities of 1,3,4-oxadiazole derivatives. The synthesized compounds were screened using carrageenan induced rat paw edema. Direct substitution of the 2-position with an -C₅H₄N and -2-COOH-C₆H₄, with pyridine in 5-position enhance the anti-inflammatory activity of 1, 3, 4-oxadiazole derivative. Few compounds like compound 3c, 4 and 4j were shows good anti-inflammatory activity against standard.



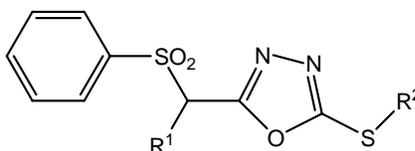
Anti-viral activity:

- *TheresaMayChinTan¹⁴ et al* have synthesized a series of 2-benzenesulfonylalkyl-5-substituted-sulfanyl-[1,3,4]-oxadiazoles. Among the oxadiazoles, compound 1 showed the most promising antiviral activity with no cytotoxic effects. Treatment with compound 1 did not lead to changes in the expression of viral transcripts but there was significant reduction in the amount of virus secreted by the cells as well as the amount of intracellular virion particles suggesting that there is an overall inhibition of virion replication. The reduced virion production also corresponded with markedly reduced levels of the HBV antigens; namely HBsAg and HBeAg. In contrast, the production and secretion of albumin by the 2.2.15 cells were not affected. Inhibition of virion production by compound 1 was comparable to that of the nucleoside analog 3TC with EC₅₀ values of 1.63 and 2.96 μM, respectively. Having observed no changes in the expression of viral transcripts, it is evident that transcription was not affected by compound 1. Thus, compound 1 is likely to affect events downstream of transcription in the viral replication process. Further

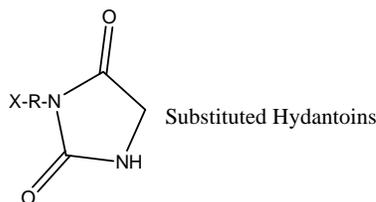
investigation is necessary to fully evaluate and to understand the mechanism of action of oxadiazoles as anti-HBV agents.

Anti-convulsant activity:

- *SangeetaBhatnagar¹⁵ et al* reported fifteen different substituted hydantoin derivatives and were prepared by condensation of different chloro-acetylated heterocyclic moieties with alkali metal-cyanate in the presence of quaternary ammonium salt. The reaction was found to proceed best in polar solvents. These compounds were screened for anticonvulsant activity by maximum electroshock seizures (MES). N³-(5-*p*-dimethyl-aminophenyl)-1,3,4-oxadiazol-2-yl) hydantoin exhibited a potent anticonvulsant activity. Diphenyl hydantoin sodium was used as the reference drug. They also reported substituted hydantoin with oxadiazole moiety are potent anticonvulsants and merit further investigation on other models of antiepileptic drug screening, mechanism of action and toxicity.

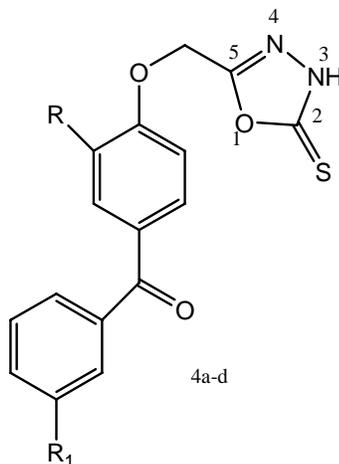


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- 5-(4-Aroyl)-aryloxy methyl-2-thio-1,3,4-oxadiazole (4a-d) were synthesized by *B.S.Sudha¹⁶ et al* by the intramolecular cyclization of thiosemicarbazides generated by the action of hydrazides on carbon disulphide in the presence of potassium hydroxide. These compounds were screened for anticonvulsant

activity based on maximal electroshock induced convulsions in rats. The mean value for each group was calculated and compared with control. They concluded that compound 4c and 4d were shown promising activity compared to that of standard phenytoin.



- a: R, R₁ = H
 b: R=CH₃, R₁=H
 c: R=H, R₁=Cl
 d: R=CH₃, R₁=Cl

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