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PHARMACOLOGICAL ACTIVITIES OF OXADIAZOLE DERIVATIVES: A REVIEW

Vandana Kaur*, Parminder Kaur and Manish Goswami

University Institute of Pharmaceutical Sciences, Chandigarh University, Punjab, India.

***Corresponding Author: Vandana Kaur**
University Institute of Pharmaceutical Sciences, Chandigarh University, Punjab, India.

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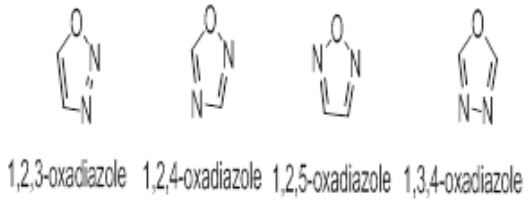
ABSTRACT
Different heterocyclic analogues were evaluated for their different and variety of biological activities that have led to an intense study and research of these compounds. Out of them, the 1,3,4-oxadiazole nucleus is an ubiquitous structural feature of many synthetic compounds with diversified therapeutic efficacy. 1,3,4-oxadizole exhibited a wide range of biological activities which includes antimicrobial activity, anti-tubercular, anticonvulsant, anti-inflammatory, anti-analgesic, antioxidant activity, anti-cancer activity, anti-viral activities, anti-spasmolytic, antimicrobial activities. This article presents a comprehensive review on the pharmacological activities of some novel derivatives of the 1,3,4-oxadiazole moiety.

KEYWORDS: Different heterocyclic analogues 1,3,4-oxadiazole moiety.

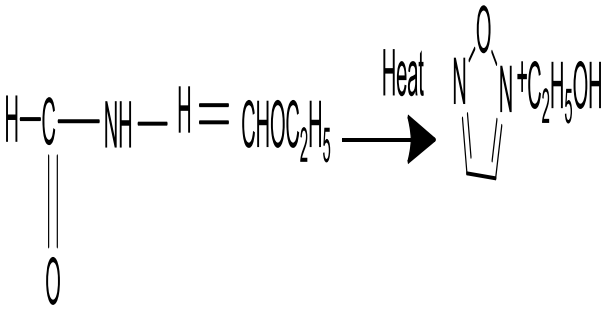
INTRODUCTION
It is well known in the literature that for the treatment of different kinds of fungal and bacterial infections along with the treatment of gastric ulcer, cancer, etc. the nitrogen and oxygen containing compounds are essentially used in medicines.[1] The nitrogen atom present in the organic moiety results in higher efficiency against various diseases.[2] Five membered heterocyclic compounds that show different types of biological activities 2,5-disubstituted 1,3,4-oxadiazoles also display a wide spectrum of activities such as antimicrobial[3], anti-malarial[4], anti-inflammatory[5], antioxidant[6] and anticonvulsant.[7]

Oxadiazole is an aromatic heterocyclic compound which contains an oxygen atom and two nitrogen atoms in a five-membered ring having molecular formula $C_2H_2N_2O$. Oxadiazole has its four known isomers as shown in figure 1. Because of the wide applications 1,3,4-oxadiazole and 1,2,4-oxadiazole are better known by researchers. Furthermore, 1,2,4-oxadiazole-unit-containing compounds such as phidianidine A and phidianidine B which are isolated from the marine opisthobranch mollusk Phidiana militaris and they exhibit high cytotoxicity against tumor and non-tumor mammalian cell lines.[8]



"Fig. 1": Four different types of isomers.

Synthesis of 1,3,4-oxadiazole
Ainsworth in 1965 prepared 1,3,4-oxadiazole for the first time by the thermo-lysis of ethyl formate, formally hydrazine, at atmospheric pressure and is liquid in nature which boils at 150^0C.



Oxybiazole, diazoxole, furo (bb)diazole, and biozole were the first common name known. Common names were replaced by the IUPAC name 1,3,4-oxadiazole. 1,3,4-oxadiazole is a thermally stable aromatic molecule and 1,3,4-oxadiazolium cation and the exocyclic-

conjugated meso ionic-1,3,4-oxadiazole and 1,3,4-oxadizolines are other aromatic system. 2,5-dihydro-1,3,4-oxadiozole and 2,3,4,5-tetrahydro-1,3,4-oxadiazole are considered as derivatives of the non-aromatic reduced system.[9] 1,3,4-Oxadiazole is a decent bio-isoster of amide and ester useful gatherings and is accounted for to contribute significantly to pharmacological activity by participating in hydrogen bonding interactions with different receptors.[10]

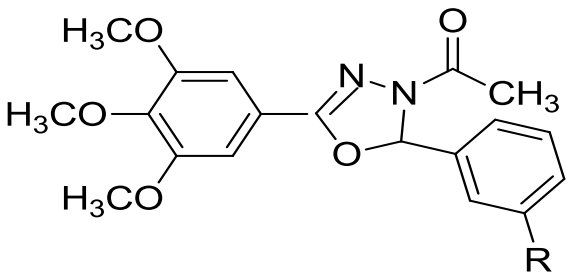
Oxadiazole is an exceptionally weak base because of the inductive impact of the additional heteroatom. The substitution of two –CH= group in furan by two pyridine type nitrogen (-N=) diminishes aromaticity of coming about oxadiazole ring to such an extent, to the point that the oxadiazole ring display character of conjugated diene. Writing study uncovers that the oxadiazoles experiences number of responses, for example, electrophilic substitution, nucleophilic substitution, thermal and photochemical.[11] Presently accessible medications containing oxadiazole unit utilized as a part of clinical medicines are Raltegravir, an antiretroviral medication and Zibotentan, an anticancer specialist.[12-13]

Oxadiazole, a heterocyclic nucleus has attracted wide attention of the chemists in search of new therapeutic molecules. Out of its four possible isomers, 1,3,4-oxadiazole is widely exploited for various applications.[14]

Pharmacological Activities

Anticancer

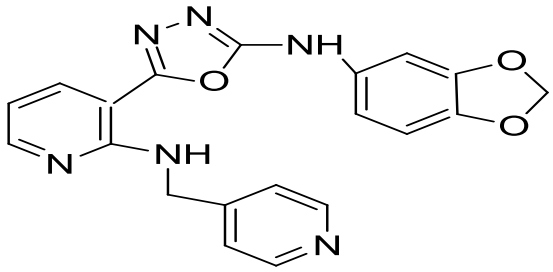
Linhong *et al* synthesized some 3-acetyl-2-substituted phenyl-5-(3,4,5-trimethoxyphenyl)- 2,3-dihydro-1,3,4-oxadiazole derivatives. From the synthesized compounds, six compounds were very dynamic against PC3 cells and very active against Bcap37 and BGC823 cells.[15]



(1)

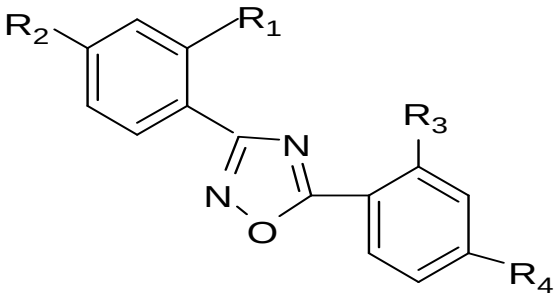
R- 2F, 4F, 2-CF_3, f: 4-CF_3, l: 3,5-2Cl, m: 2,4-3OCH_3

Ouyang *et al* synthesized the derivatives of oxadiazoles and are assessed their ability so as to inhibit tubulin polymerization and to inhibit the mitotic division of tumor cells. Compound 2 showed potent activity.[16]



(2)

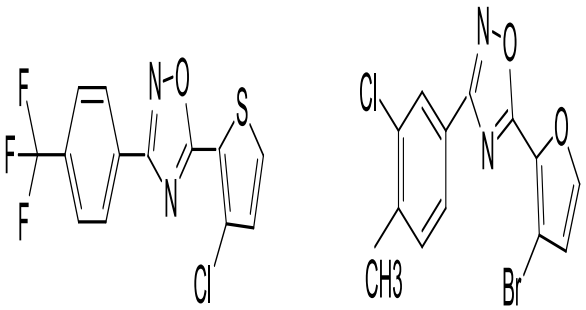
Machado *et al* synthesized the compounds and evaluated for their anticancer activity by using mice specific EhrlicAscites Carcinoma cell (EAC cells) in Swiss albino mice model. 3,5-diaryl-1,2,4-oxadiazole derivatives has the potential for anticancer activity. The compound 3a and 3b has resulted for anticancer activity which has the anticancer potential and reported as the percentage of tumor weight inhibition (%TWI) and percentage of tumor cell count inhibition (%TCI) of the treated ascitic cells in comparison to untreated control ascitic cells.[17]



(3a) and (3b)

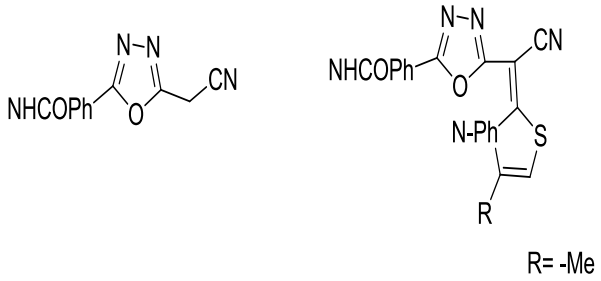
3a- R_1-R_4-Cl, R_2-R_3-H; 3b- R_1-R_3-R_4-Cl, R_2-H

Zhang *et al* investigated the anticancer and apoptosis inducing potential of a series of 3,5-diaryl-1,2,4-oxadiazoles compound 4 was specifically potent against breast and colorectal cancer cell lines by arresting cell cycle in G1 phase took after by initiating apoptosis. Their further explorations to enhance the activity led to the preparation of 5-furyl-1,2,4-oxadiazoles, out of which, the 1,2,4-oxadiazole compound 5 has shown good in vivo efficacy in animal studies.[18]



(4) and (5)

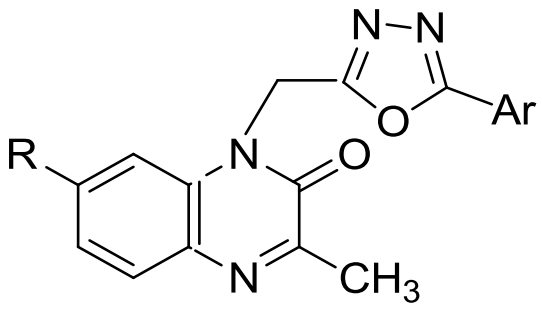
Bondock *et al* used four human tumor cell lines they were heptacelluar carcinoma HepG2, lung fibroblasts WI 38, kidney of a normal adult African green monkey VERO, and breast cancer MCF-7 to evaluate the anti-cancer activity. A thiazole ring to 1,3,4-oxadiazole skeleton has given the better antitumor activities. Compounds 6 and 7 showed a considerable broad spectrum of anticancer activity against the four tested human tumor cell lines. Compound 8 approved to be the most active member in this study with special effectiveness against the human HepG2, VERO, and WI-38. Compound 7 was found to have higher activity against HepG2 and moderate activity against MCF-7.[19]



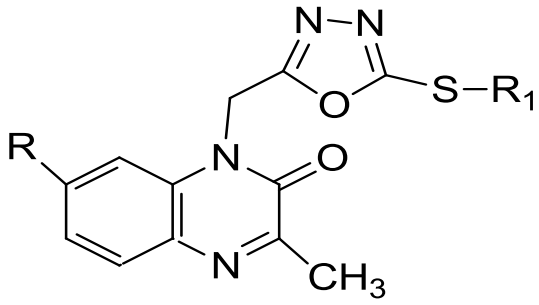
(6) (7)

Anti-inflammatory and Analgesic activity

Wagle *et al* evaluated the anti-inflammatory activity and analgesic activity by carrageenan-induced paw edema method and analgesic activity by hot-plate method. It was observed that the compounds 8a was tested, oxadiazole containing 7-methyl quinoxaline 8a was found to have higher activity than that of un-substituted quinoxaline. It can be presumed that the presence of methyl group on position 7 of quinoxaline moiety and methoxy substitution to phenyl ring increased the activity considerably. The increased hydrophobic nature due to the presence of methyl group and electron releasing nature of methoxy group substituted at phenyl moiety in the structure might be in charge for the higher activity. The Standard drug Pethidine demonstrated analgesic activity in the model used.[20]



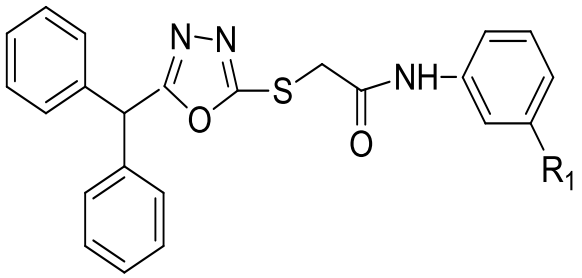
(8a)



(8b)

R-CH_3, H, Cl; R_1-CH_3, C_2H_5 and -$CH_2C_6H_5$

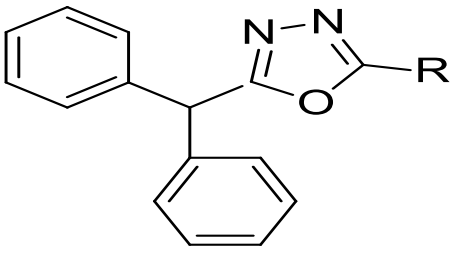
Winter *et al* evaluated this activity. The compounds having 3-chloro-4-fluro-phenyl and 4 methyl-phenyl group individually demonstrated slightly higher activity than the Standard drug Ibuprofen. The compound 9 consisting of 4-fluoro-phenyl group also showed significant anti-inflammatory activity. Hence it was observed that the substitution of phenyl group at second position of 1,3,4-oxadiazole moiety by substituted phenyl acetamido group resulted in enhancement of anti-inflammatory activity.[21]



(9)

9b: R_1-2,4-dichlorophenyl; 9c: R_1-2,4-dichlorophenoxymethyl

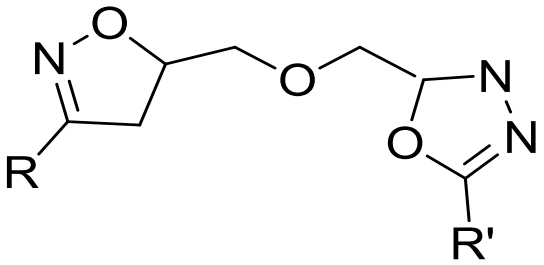
Amir *et al* investigated the analgesic activity and it was evaluated by tail immersion method by using Swiss albino mice. The compound 10 having 3-chloro-4-flouro group has demonstrated maximum analgesic activity. The compound 10 showed significant analgesic activity.[22]



(10)

R- 4-chlorophenyl

Jayashankar *et al* synthesized a series of novel ether-linked bis (heterocycle). All the synthesized compounds were screened for anti-inflammatory and analgesic activities. Hence, compound 11 showed excellent activity against ibuprofen and aspirin.[23]

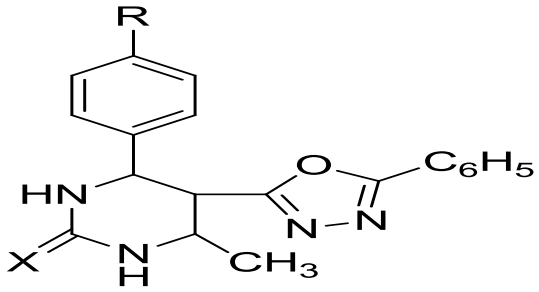


(11)

R, R'-3-$O_2NC_6H_4$; -2,4-$Cl_2C_6H_3$

Oxadiazole as Antimicrobial

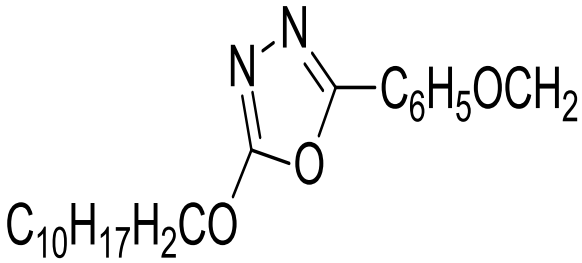
Mishra *et al* synthesized 6–Methyl–4–aryl–5-(5-phenyl-1,3,4–oxadiazol-2-*yl*)-1,2,3,4-tetrahydro pyrimidine-2(1*H*)-one. From all these derivatives 12a has vital effect against *Streptococcus pneumonia* (+ve) and 12b has significant activity effect against *Escheria coli*(-ve).[24]



(12)

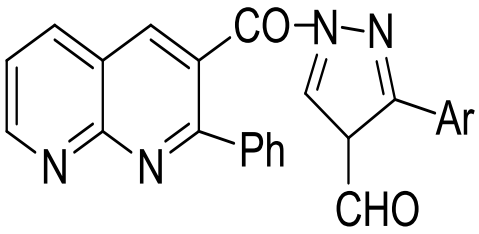
12a: R-OCH_3, X-O**;** 12b: R-NO_2, X-O

Yar *et al* synthesized a series of novel 2,5-disubstituted 1,3,4-oxadiazole derivatives and was tested for *in vitro* anti-microbial activity, 2-(2-naphthyloxymethyl)-5-phenoxymethyl-1,3,4-oxadiazole has exhibited >90% inhibition among all the synthesized compounds.[25]



(13)

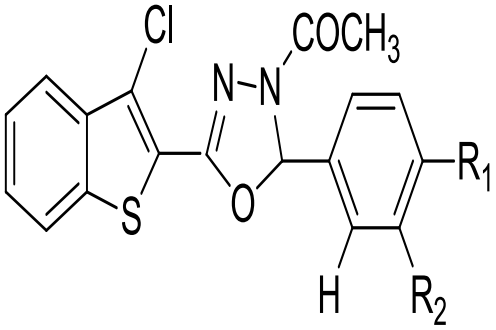
Mogilaiah *et al* screened the compound 14 and 15 for their antibacterial activity against the bacteria *E.coli, pseudomonas aeruginosa, bacillus subtilis and bacillus mycoides* following filter paper disc technique at 400 and 600 microg/disc concentrations. All the compounds were active against both gram (+ve) and gram (-ve) bacteria at concentration of 400 microg/disc. But the the degree of inhibition varied both with test compound and also with the bacterium.[26]



(14) and (15)

Ar:-p-$CH_3C_6H_4$; p-$CH_3OC_6H_4$; p-ClC_6H_4; p-$CH_3C_6H_4$; o-ClC_6H_4; p-ClC_6H_4

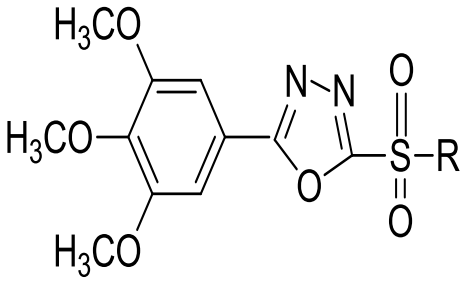
Chawla *et al* synthesized some new 3-acetyl-5-(3-chloro-1-benzo[b]thiophen-2-*yl*)-2-substituted phenyl-2,3-dihydro-1,3,4-oxadiazoles and 2-(3-chloro-1-benzo[b]thiophen-2-*yl*)-5-substituted phenyl-1,3,4-oxadiazoles and which was evaluated for anti-microbial activity. And compounds 16a and 16b were found to be most potent against the activities, even better than the Standard drugs i.e. Ciprofloxacin.[27]



(16)

16a:R_1-H; R_2-OCH_3; 16b:R_1-OCH_3; R_2-H

Bao-An Song *et al* synthesized compounds by using the key intermediates 5-(3,4,5- trimethoxyphenyl)-1,3,4-thiadiazole-2-thiol or the oxadiazole analogue and tested for fungicidal activity. From all the synthesized compounds 17a and 17b can inhibit mycelia growth by approx 50% in vitro against the ten kinds of fungus.[28]

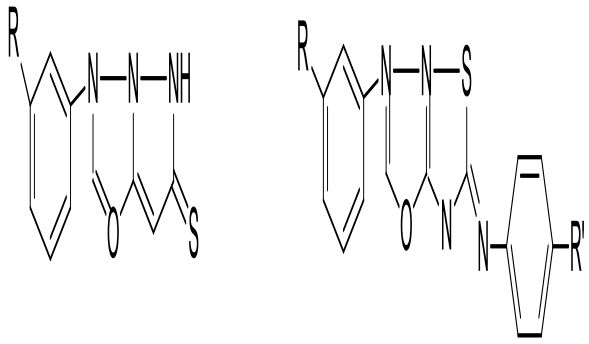


(17)

17a: R-CH_3; 17b: R-C_2H_5

Kumar *et al* evaluated the fungicidal activities of compounds 18 and 19 by agar plate technique by using Czapek's agar medium on the pure cultures of test fungi *Cytospora saccharii*, *Aspergillus niger* and *Fusarium oxyspurum*. At 100ppm and 10ppm concentration the fungicidal toxicity was evaluated using acetone-water

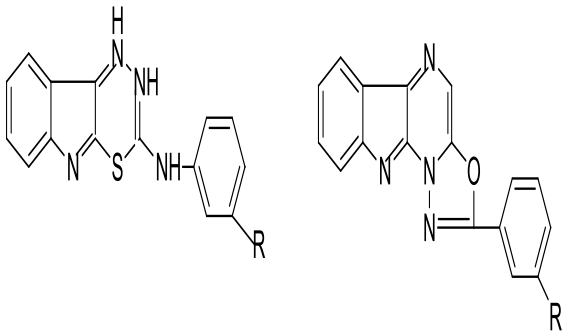
using (20:80 v/v) mixture as eluent. At 100ppm conc. the below compounds showed 80-85% activity against *Cephalosporum sacharii* that is it gives appericiable fungi toxicity, but significant decrease at dilution of 10ppm. And the compounds 18 and 19 were more active against the test fungi.[29]



(18) and (19)

18: R-3F R-2F; 19: R-2F, R'-2Cl; R-3F, R'-4Cl; R-4F, R'-4CH_3

Nizamuddin *et al* evaluated the compounds and were screened for their antifungal activity agains*t Aspergillus flavus, Cephalosporium sacchari, Pyriculariasolani and Phytophthora infestans* at 500ppm and 100 ppm concentration. The inhibitory activities were compared with commercial fungicide Carbendazim tested under similar condition. From the tested compounds 20a and 20b were found to be the most active (> 86%) at 500 ppm. Their activity decreases with dilution.[30]

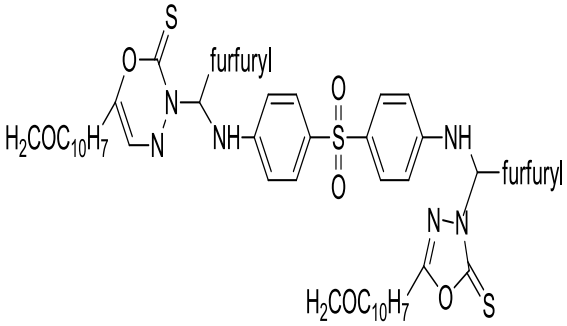


(20)

20a: R-4-OCH_3; 20b: R-4-NO_2

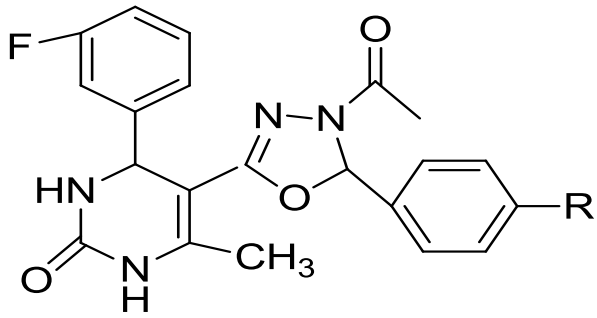
Anti-tubercular activity

Ali *et al* synthesized a series of oxadiazole mannich bases by giving a reaction between oxadiazole derivatives, dapsone and appropriate aldehydes and were evaluated against *Mycobacterium Tuberculosis*. The compound 3-{2-furyl[4-(4-{2-furyl[5-(2-naphthyloxy methyl)-2-thioxo-2,3-dihydro-1,3,4-oxadiazol-3-yl]methylamino}phenylsulfonyl)anilino] meth yl}-5-(2-naphthyloxymethyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione from all the synthesized compounds have shown best activity against *M. Tuberculosis* and Isoniazid resistant *M. Tuberculosis.*[31]



(21)

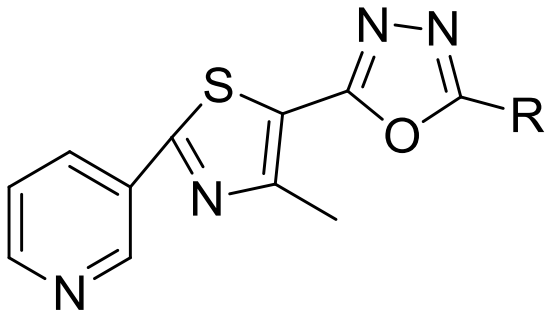
Desai *et al* synthesized the compound 22 and screened for their *in vitro* anti-tubercular activity against *Mycobacterium tuberculosis* H37Rv using Lowenstein–Jensen method. Minimum inhibitory concentration (MIC) for compound 23 was observed to be equipotent (MIC: 0.20lg/ml) to the reference drug Isoniazid. Due to the presence of electron withdrawing group at para position of phenyl ring it enhanced the anti-tubercular activity of synthesized compounds. Compound 23 has 4-NO2 substitution at the phenyl ring of 1,3,4-oxadiazole substitution which was found to be the most potent compound of the series with MIC equivalent to the Standard drug Isoniazid.[32]



(22)

R-4-NO_2

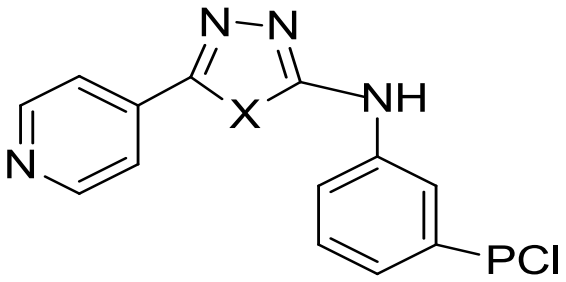
Dhumal *et al* synthesized a new 2-pyridinyl substituted thiazolyl-5-aryl-1,3,4-oxadiazoles by using thionicotinamide as a starting and followed a novel multistep synthetic route. All the synthesized compounds and intermediate acid hydrazide was screened for their *in-vitro* antitubercular activity against *Mycobacterium tuberculosis* H37Ra (MTB) and *Mycobacterium bovis BCG*. Many of the compounds had shown an appreciable activity against *Myobaterium bovis* BCG at concentrations less than 3µg/mL. The newly synthesized compounds displayed excellent selectivity towards *Myobacterium bovis* BCG as compared to *M. tuberculosis* H37Ra.[33]



(23)

Anticonvulsant activity

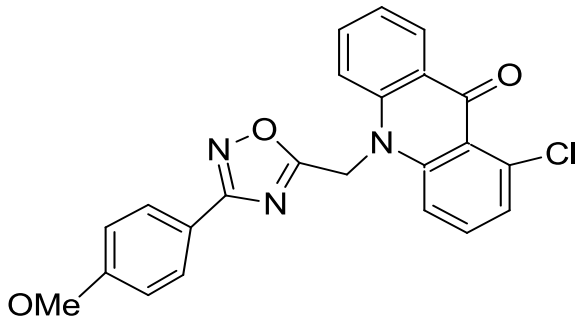
Shaharyar *et al* synthesized a series of five membered heterocyclic and tested for convulsion. From the synthesized compounds, 2-(4-chlorophenyl) amino-5-(4-pyridyl)-1,3,4-thiadiazole and compound 2-(4-chlorophenyl)amino-5-(4-pyridyl)-1,3,4-oxadiazole has given better potent activity.[34]



(24)

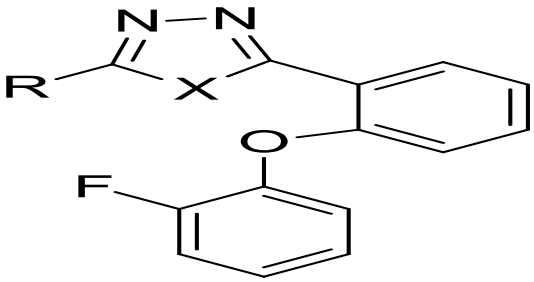
X=S, O

Shabani *et al* synthesized an acridone-based oxadiazoles compounds and evaluated for their anticonvulsant activity against pentylenetetrazole (PTZ) and maximal electroshock (MES)-induced seizures in mice. The neurotoxicity was also evaluated by the rota rod test. And most of the compounds found to exhibit better anticonvulsant activity and higher safety respect to the Standard drug, Phenobarbital. From all the tested derivatives, compound 25 with ED_{50} value of 2.08 mg/kg was one of the most potent.[35]



(25)

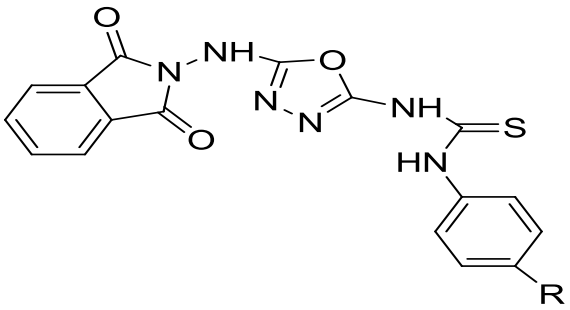
Almasirad *et al* synthesized the compounds for the anticonvulsant activity and was determined by evaluation of the ability of the compounds to protect mice against convulsion induced by a lethal dose of PTZ and electroshock as two routine models. Diazepam was considered to be the reference for benzodiazepine agonist with anticonvulsant effect in both the models. The synthesized compounds, diazepam or vehicle were administered 30min before injection of PTZ 100mg/kg or induction of electroshock (60Hz, 37.2mA and 0.25s) compound 26 with amino substituent on position 2 of oxadiazole ring as the best anticonvulsant activity in both PTZ and MES models.[36]



(26)

X-O; R-NH_2

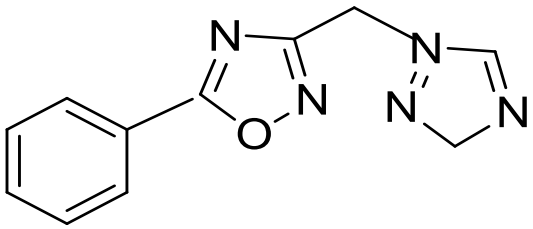
Bhat *et al* synthesized a series of novel 1,3,4-oxadiazole derivatives of phthalimide and evaluated for their anticonvulsant and neurotoxicity studies. By reacting phthalic anhydride with hydrazine hydrate in presence of sodium hydroxide which yields oxadiazole. Among the compounds synthesized, compound with para-methoxy substituent exhibited the highest anticonvulsant activity.[37]



(27)

R=4-OCH_3

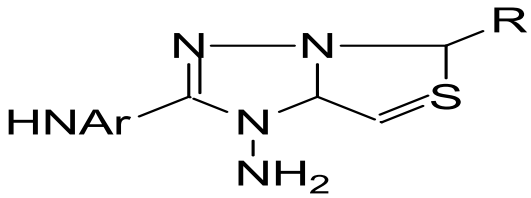
Lankau *et al* synthesized a series of 3 and 5-aryl-1,2,4-oxadiazole derivatives and tested for anticonvulsant activity in a variety of models. These 1,2,4-oxadiazoles derivatives found to exhibit a considerable activity in both pentylenetetrazole (PTZ) and maximal electroshock seizure (MES) models. Compound 28 was protective in the PTZ model with an oral ED_{50} of 25.5 mg/kg and in the MES model with an oral ED_{50} of 14.6 mg/kg. Several oxadiazoles were synthesized that act as a selective GABA potentiating compounds with no interaction to the benzodiazepine binding site.[38]



(28)

Anti-Viral activity

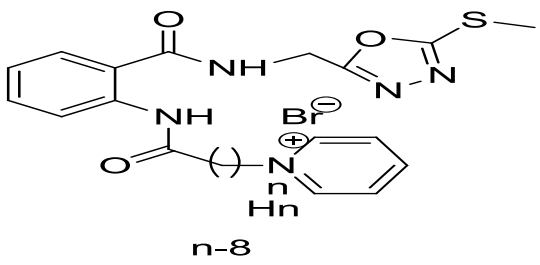
Yadav *et al* evaluated the compounds for their anti-viral activity *in vitro* against the viral species *Chenopodium amaranticolo*. The compounds were applied in the form of their suspensions in acetone-water (20:80, v/v) at 1000 ppm and 100 ppm concentrations. A standard antiviral agent, Virazole (ribofuranosyl-1,2,4-triazole-3-carboxamide) was also tested under similar conditions for comparison. From the tested compounds the most active compound was 29 which exhibited antiviral activity equivalent to that of Virazole at 1000 ppm concentration. Nucleosides which comprise of 1,2,4-triazole nucleus were much more active than the corresponding nucleosides comprising of either 1,3,4-thiadiazole or 1,3,4-oxa-diazole ring. The compounds consisting of D-xylobutyl moiety were found to be more potent than those consisting of D-glucopentyl moiety that enhances the antiviral action.[39]



(29)

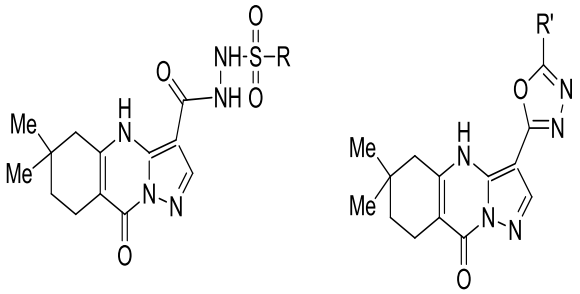
Ar-p-MeOC_6H_4; R-D-xylobutyl; Ar-o-MeC_6H_4; R-D-xylobutyl

Wang *et al* synthesized a series of novel 1,3,4-oxadiazole derivatives having diamides and tested for their antiviral activity. Some of these structures have given good curative activities and moderate protective effects against *tobacco mosaic virus* (TMV) *in vivo*. Among them, compound 30 has given the best chemotherapeutic effect against TMV with the curative rate of 60.0% at 500 μg/mL, which can be compared with those of commercial agricultural antiviral agent ningnanmycin (54.2%).[40]



(30)

Selvakumar *et al* synthesized 6,6-dimethyl-9-oxo-4,5,6,7,8,9-hexahydropyrazolo[5,1-b]quinazoline-3-carbohydrazide and its sulfonyl for compound 31 and 1,3,4-oxadiazole for 32 derivatives and screened their antiviral activity against an avian paramyxovirus (APM V-1) and reported that a 1,3,4-oxadiazole ring attached to pyrazolo-pyrimidinones shows inhibitory activity against PAS kinase. He synthesized, characterized and screened for antiviral activity Sulfonohydrazide and 1,3,4-oxadiazole derivatives of 6,6-dimethyl-9-oxo-4,5,6,7,8,9-hexahydropyrazolo[5,1-b] quinazoline.[41]

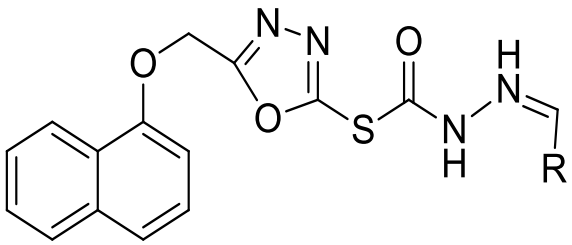


(31) and (32)

31a:2-fluoro phenyl, 2b:2-chloro phenyl, 2c:4-chloro phenyl

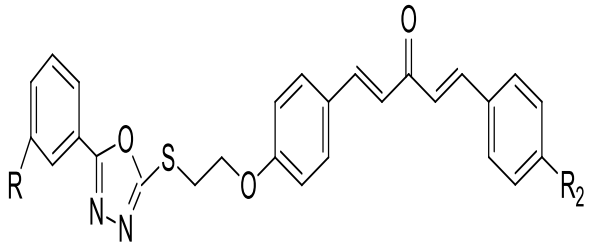
32a:4-fluoro phenyl, 32b:4-chloro phenyl, 32c: 3,5-dimethyl phenyl

Sayed *et al* synthesized compounds which were evaluated for their HIV inhibitory activity as reverse transcriptase inhibitors by using microtiter anti-HIV assays with CEM-SS cells or fresh human peripheral blood mononuclear cells. Compound 33 showed the highest activity with an IC_{50} value of 1.44 μM.[42]



(33)

Xuihai Gan *et al* synthesized and obtained 1,4-pentadien-3-one derivatives containing the 1,3,4-oxadiazole moiety. 1,4-pentadien-3-one and 1,3,4-oxadiazole derivatives possess good antiviral activities. Bioassay results given information about that some of the compounds have shown excellent anti-TMV activity in vivo. Among them, compounds 34a, 34b, 34c, 35a, 35b, 35c, 35d and 35e were considered to be better curative, protective, and inactivation activities than Ribavirin at 500 mg/L.[43]

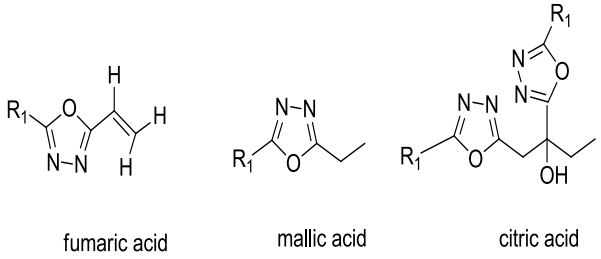


(34) and (35)

34a: R_1-4-F; 34a: 8k: R_1-H
34a: R_2-4-F; 34b: R_2-4-Br; 34c:R_2-2,4-diCl; 35a: R_2-4-Br; 35b: R_2-2-F; 35c:R_2-2-Cl,

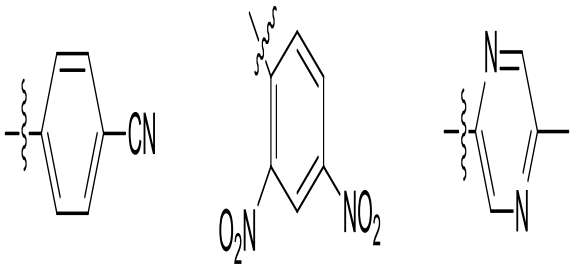
Antioxidant activity

Rabie *et al* synthesized a novel series of 5-(5-substituted-1,3,4-oxadiazol-2-*yl*)benzene-1,2,3-triols and evaluated for its potential antioxidant activities. By some structural modifications at position 5 of the 1,3,4-oxadiazole scaffold (linked to a fixed antioxidant 3,4,5-trihydroxyphenyl moiety at position 2 of the ring) it gave a new 1,3,4-oxadiazole derivatives with a wide spectrum of biological antioxidant activities. The pharmacological screening for evaluation of the antioxidant activity was done for new thirteen target 5-substituted-2-(3,4,5-trihydroxyphenyl)-1,3,4-oxadiazoles by using two of the most common in vitro antioxidant assays. The results of both assays showed that compounds derived from fumaric, malonic and citric acids has exhibited very high and significant antioxidant activities.[44]



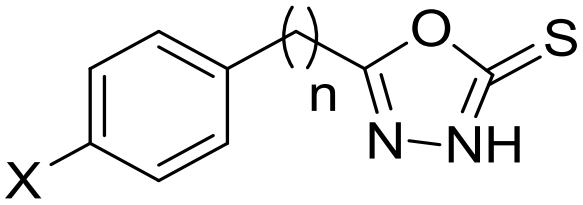
(36)

Chandrashekar *et al* synthesized a series of novel 2,5-disubstituted-1,3,4-oxadiazole derivatives were synthesized and screened for their antioxidant activities. The assay indicated that some of the compounds substituted with below groups exhibited comparable antioxidant activity with first-line drugs.[45]



(37)

Hanif *et al* synthesized a series of eighteen 1,3,4-oxadiazole derivatives & it was observed that in compound 38 having 2-F, 4-Cl phenyl groups showed fourfold DPPH radical scavenging activity as compared to Standard Propyl Gallate. Two other derivative 38b and 38c were also more effective than the propyl gallate having 2-chloro and 4-bromo substitutions on benzene ring next to parent core. The synthesized 1,3,4-oxadiazoles derivatives evaluated in vitro for their urease inhibitory activities, most of the investigated compounds were potent inhibitors of Jack bean urease. The synthesized compounds were tested for antioxidant activities and some derivatives exhibited very good results.[46]

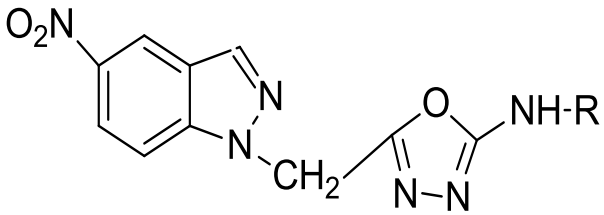


(38)

X-2-F, 4-Cl; n-0; X-2-Cl; n-1; X-4-Br; n-1

Antipyretic activity

Cheptea *et al* synthesized a series of 2-[(5'-nitroindazole-1'-methyl)]-5-(*p*-bromophenylamino)-1,3,4-oxadiazole derivatives. All synthesized compound showed good antipyretic activity, similar to that of acetylsalicylic acid activity.[47]

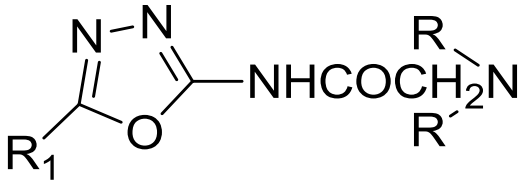


(39)

R-C_6H_4Br; C_6H_4-Cl

Spasmolytic activity

Mishra *et al* synthesized a series 2-(substituted acetyl-amino)-5-alkyl-1,3,4-oxadiazoles derivatives and was found to consist of considerable spasmolytic activity. Compound 40a and 40b showed non-specific spasmolytic activity.[48]



(40)

40a: R_1-methyl, R-ethyl; 40b: R_1-ethyl, R-n-propyl

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