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A Review on Oxadiazole.

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ABSTRACT

Oxadiazoles are important five membered heterocyclic classes of compounds with 2 azo groups and one oxygen in its ring system. It is widely researched as a lead compound for designing potent bioactive agents. In this article we have reviewed on physical and chemical properties of oxadiazole, spectra and some methods for its synthesis. We have explored various pharmacological activities of oxadiazole derivatives like anti- inflammatory, anti-cancer, anti-fungal, anti-osteoporotic and anti-microbial. A brief on drugs containing oxadiazole ring and naturally occurring oxadiazole moiety have also been mentioned.

Keywords: Oxadiazole, Anti-inflammatory, Anti-microbial, Anticancer, Anti-osteoporotic.

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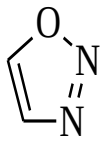
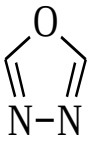
INTRODUCTION

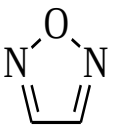
Oxadiazole is a heterocyclic aromatic compound of molecular formula $C_2H_2N_2O$. It is a five membered ring consisting of 2 nitrogen atoms, 2 carbon atoms, 1 oxygen atom and 2 double bonds. There are 4 isomers of oxadiazole as shown in the figures below.



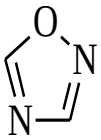
1, 2, 3 oxadiazole
(Diazo-oxides)



1, 2, 5 oxadiazole
(Furazan)



1, 3, 4 oxadiazole
(Biazole)



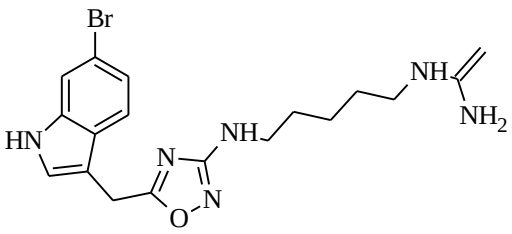
1, 2, 4 oxadiazole
(Azoxime)

The 1, 2, 3-isomer is unstable and reverts to the diazoketone tautomer [1].Oxadiazoles were discovered against the schistosomiasis-causing fluke in the year 2008. It did not show any negative effects on humans. The stable oxadiazoles appear in a variety of pharmaceutical drugs including raltegravir (anti-retroviral), butalamine, fasiplon, oxolamine, and pleconaril. Tiodazosin, nosapidil, furamizole are other examples. The oxadiazoles were successfully tested against various diseases and hence are of importance in pharmaceutical chemistry due to their diverse medicinal potential. Nitrogen and oxygen containing compounds are always of synthetic interest. This is because there are large number of natural and synthetic compounds having nitrogen and oxygen with useful biological properties [2].

Literature survey reveals that the 1, 3, 4 oxadiazole undergoes a couple of reactions such as electrophilic substitution, nucleophilic substitution, thermal and photochemical reactions etc. Due to this reason it has been used in the preparation of 1, 3, 4 oxadiazole therapeutic molecules for various applications [3]. The compounds containing the 1,3, 4 oxadiazole nucleus was found to have unique anti-edema and anti-inflammatory activities [4].

NATURALLY OCURRING OXADIAZOLES:

There are only few examples of natural products with oxadiazole core or a structure based on it. One among this is phidianidines A and B (Figure 1), this is a 3-substituted indole alkaloid. Phidianidines A and B have been isolated by Carbone et al. from the aeolid opisthobranch Phidiana militaris [5]. They selectively inhibits dopamine transporter DAT and also acts as partial agonists of the μ opioid receptor [6]. Phidianidine A and B do not have cytotoxic action and therefore it can be used as CNS targets. Quisqualic acid is another example for naturally occurring oxadiazole. (Figure 1). This is a metabolite which is obtained from the seeds of Quisqualis indica and Q. fructus .Quisqualic acid is a strong agonist for α-amino-3-hydroxy-5- methyl-4-isoxazolepropionic acid receptors and group I metabotropic glutamate receptors [7].



PHIDIANIDINE A

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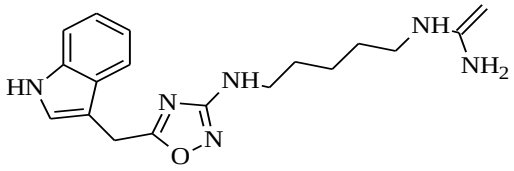
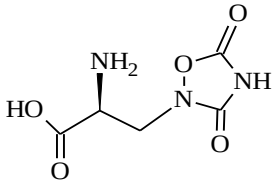


PHIDIANIDINE B



QUISQUALIC ACID

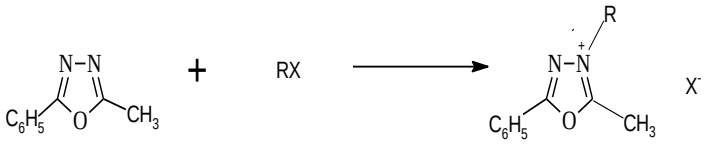
Chemistry

Due to the presence of a heteroatom in the ring, oxadiazole shows inductive effect and thus it is considered to be a weak base. It consists of 2 pyridine like nitrogen, due to which it exhibits conjugate diene type character. Electrophillic substitution at carbon is very difficult in this case due to less electron density which is mainly due to the presence of pyridine like nitrogen in the ring that shows electron withdrawal effect.

Due to the presence of two pyridine type nitrogen, the aromaticity will be removed. Many studies on comparison between 1,2,4- and 1,3,4-oxadiazole pairs shows that ,in all cases,1,3,4-oxadiazole isomer shows lower magnitude lipophilicity (log D) as compared to its isomeric partner. Other differences involve metabolic stability, hERG inhibition, and aqueous solubility. All these studies favored the 1, 3, 4-oxadiazole isomers. The difference in profile between the 1, 2, 4 and 1, 3, 4 regioisomers can be rationalized by their intrinsically different charge distributions.

Reactions with Electrophiles

As mentioned above because of low electron density of carbon atom owing to the electron withdrawal by pyridine type nitrogen atom and also because of protonation possibility at nitrogen atom, the electrophilic substitution reactions are very difficult in oxadiazoles. Association with electron releasing groups in the ring can lead to electrophilic attack at nitrogen. No examples of nitration and sulphonation are yet found though research is being carried out.



Reactions with Nucleophiles

Oxadiazoles normally are resistant to nucleophilic substitution reactions except for halogen-substituted oxadiazoles. In this reaction halogen atom will be replaced by a nucleophile. Due to electron density at C2and C5 many nucleophilic reagents can cause ring cleavage reactions.

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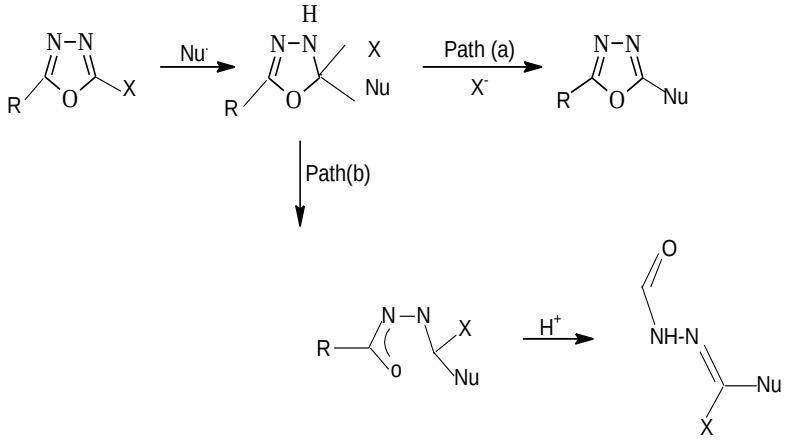
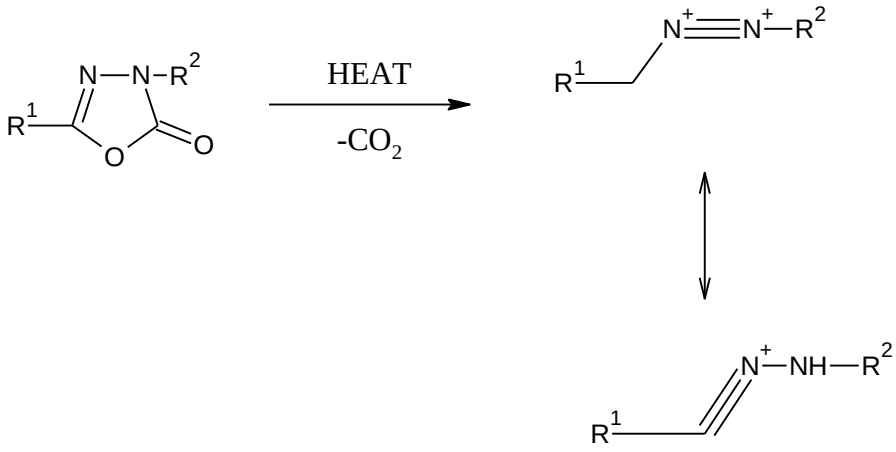


Thermal and Photochemical Reactions

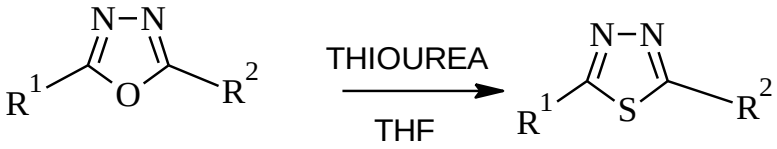
Oxadiazoles, specifically 1, 3,4oxadiazoles are thermally stable. On substitution by aryl and perfluroalkyl groups the thermal stability of oxadiazole increases. When heated at high temperature (210 - 230°C) oxadiazolinones get decarboxylated to form nitrilimines, which when recycled forms2-alkoxy-1, 3,4oxadiazoles [1].



Nitrilimines

Formation of Other Heterocyclic Ring Compounds

1,3,4 oxadiazoles can form other heterocyclic ring compounds like triazoleamine and thiadiazole derivatives.



Physical Properties of 1,3,4 Oxadiazoles

In 1955 the first monosubstituted 1,3,4-oxadiazoles were reported by two independent laboratories [8][9]. 1,3,4 oxadiazoles are liquid in nature. They have a boiling point of 150^0 C [10-12].It does not have any freely rotating bonds. It has 3 hydrogen bond acceptors. Derivatives of 1,3,4 oxadiazoles like 2,5-disubstituted -1,3,4-oxadiazoles are found to be colorless.

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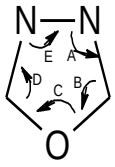
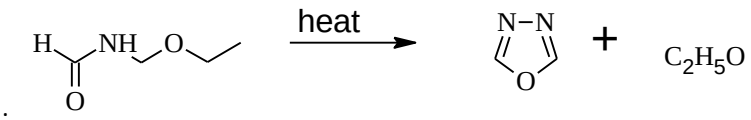


ANGLES	BOND ANGLE(°)
A	105.6
B	113.4
C	102.0
D	113.4
E	105.6

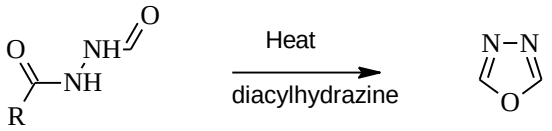
The IR spectra of 1,3,4-oxadiazole is characterized by bonds present at1640-1650 cm^{-1} (C=N) and at 1020cm^{-1} (C=O) [13]. The position of both protons in ^{1}H-NMR is 1.27.The refractive index $n^{25}D$ of 1,3,4-oxadiazole is 1.43 [14]. According to the mass spectra the base peak is the molecular ion peak.

1,3,4 Oxadiazole

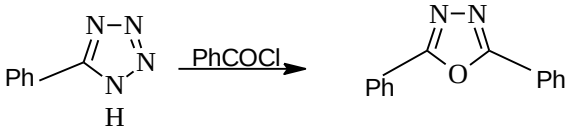
It was first prepared in 1965 by Ainsworth. It was prepared using thermolysis of ethyl formate formyl hydrazone at atmospheric pressure [1].



By heating diacyl hydrazines with thionyl chloride ($SOCl_2$) yields an oxadiazole [1]



1,3,4 oxadiazoles are also obtained on heating tetrazoles with acid chlorides (in C_6H_5N at 50°C)



Synthesis of Substituted 1,3,4 Oxadiazoles:

From Isothiazole

Kiselyov et al reported the synthesis of oxadiazole by refluxing isothiazole derivative with neat hydrazine hydrate for 4 hrs. The hydrazide so obtained can be further reacted with isothiocynates followed by in situ cyclization of the intermediate thiosemicarbazides with DCC to afford the key molecules [15].

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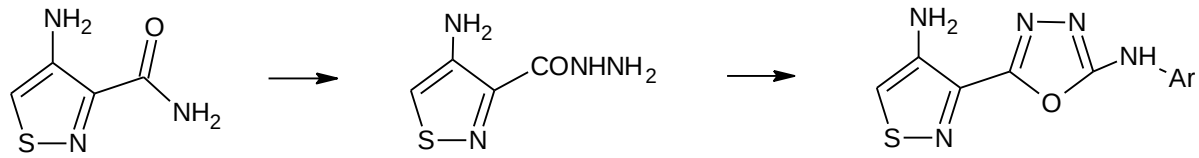
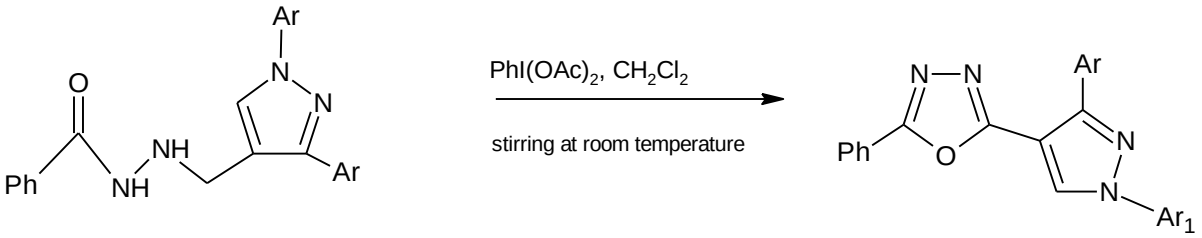


From N-Acyl Hydrazones

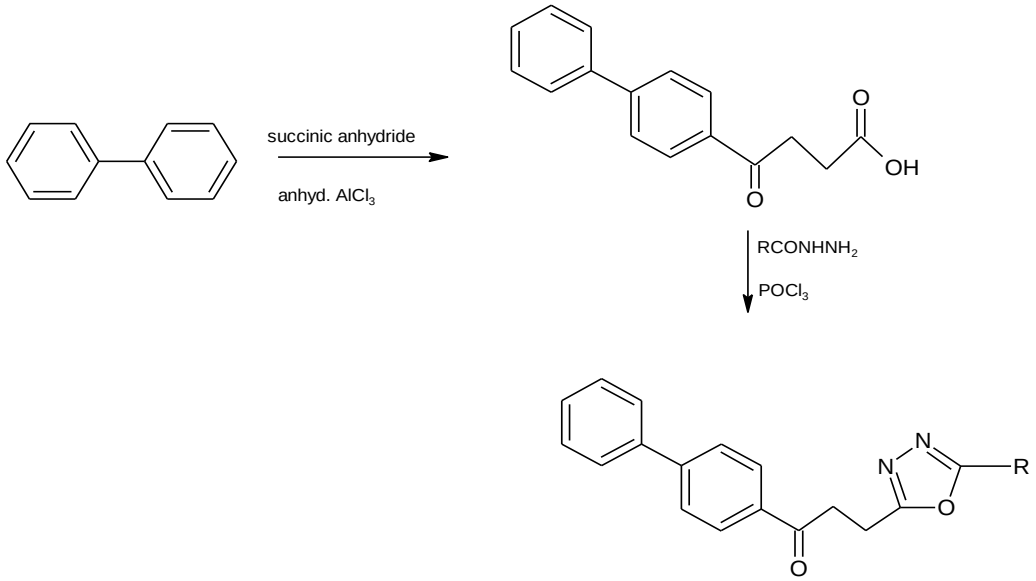
Prakash et. al.; (2010); reported the synthesis of a series of novel 2,5-disubstituted 1,3,4-oxadiazole by oxidative cyclization of pyrazolylaldehyde N-acyl hydrazones catalyzed by iodobenzene diacetate under mild conditions [16].



From Acid Hydrazides

The formation of 1,3,4 -oxadiazole via condensation of various alkyl hydrazides with substituted acids are reported in literature. A few of them are mentioned below.

Husain et. al.; (2010); reported the synthesis of 1,3,4-Oxadiazole by reacting 4-oxo-4(biphenyl-4-yl)butanoic acid (fenbufen) with aryl acid hydrazides in phosphorous oxychloride [17].



Fuloria et. al.; (2010); reported the synthesis of 1-(2aryl-5-phenethyl-1, 3, 4-oxadiazol-3(2H)-yl)ethanones by reacting N-(substituted benzylidene)-3-phenyl propionohydrazides with acetic anhydride [18].

From Acetic Acid Hydrazides

Kumar et. al.; (2010); reported the synthesis of 5-[(biphenyl-4-yloxy)-methyl]-2-substituted- 1,3,4-oxadiazoles [Figure 8] by treatment of 2-(biphenyl-4-yloxy) acetic acid hydrazide with appropriate aromatic acid in presence of phosphorous oxychloride [19].

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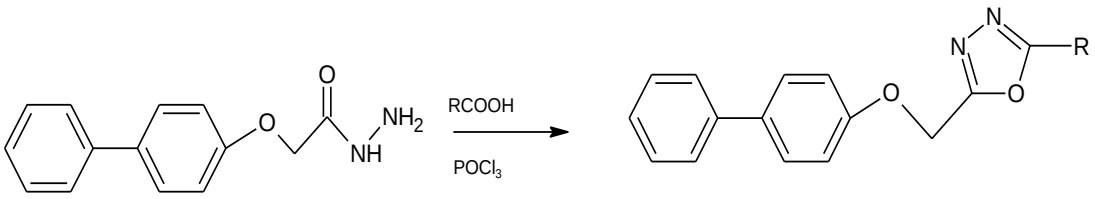
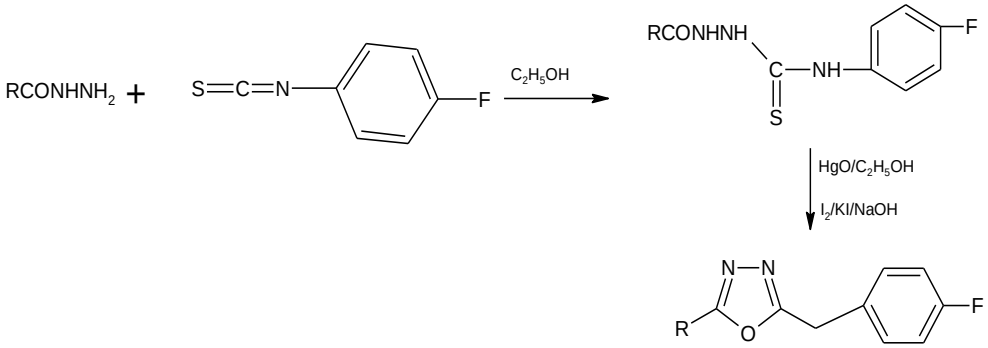


From Chalcones

Kamble et. al.; (2010); reported the microwave assisted synthesis of 1, 3, 4-oxadiazole from Chalcones. This microwave assisted synthesis lead to the cleaner reactions as well as afforded high yields and shorter reaction times. The chalcones underwent a rapid cyclisation with hydrazine hydrates using Polyethylene glycol (PEG 200) and formic acid as solvents. This Compound on bromination and heating with acetic anhydride afforded the Oxadiazole derivatives [20].

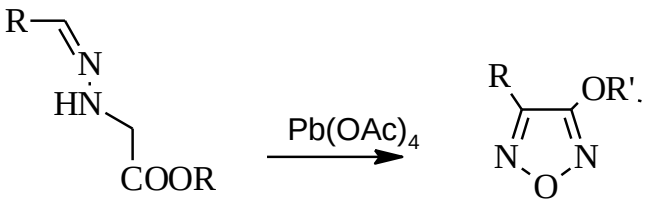
From Thiosemicarbazide

Barbuceanu et. al.; (2010); reported the synthesis of oxadiazole by reacting N1-[4-(4-bromophenylsulfonyl) benzoyl]-N4-(4-flourophenyl)-thiosemicarbazide with (a) Mercuric Oxide (HgO) in ethanol media (b) I2/KI in NaOH solution media [21].



From Hydrazine

Disubstituted 1, 3, 4 oxadiazoles are obtained from oxidative cyclisation of hydrazones by lead acetate

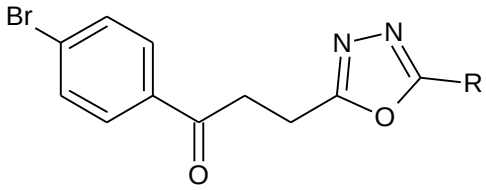


Pharmacology of Oxadiazole

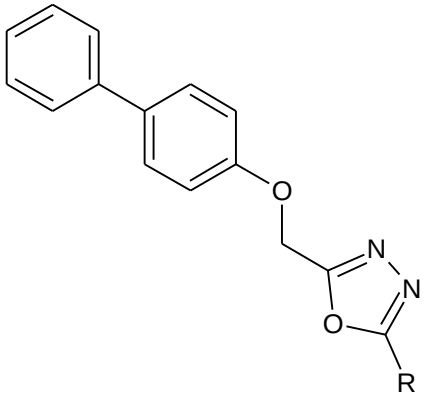
Anti-Inflammatory

1. Asif Husain et al reported the synthesis of novel series of 2-[3-(4-bromophenyl)propan-3- one]-5-(substituted phenyl)-1,3,4-oxadiazoles from 3-(4-bromobenzoyl) propionic acid with the aim to get better anti-inflammatory and analgesic agents with minimum or without side effects (ulcerogenicity).

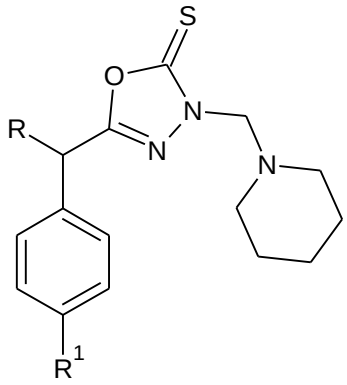
Two compounds, 2-[3-(4- bromophenyl)- propan-3-one]-5-(4-chlorophenyl)- 1,3,4-oxadiazole and 2-[3-(4-bromophenyl)propan-3- one]-5-(3,4-dimethoxy phenyl)-1,3,4-oxadiazole with anti-inflammatory activity of 59.5 and 61.9 %, respectively, were found to have comparable activity with that of indomethacin which showed 64.3 % activity at the same dose of 20 mg/kg [22].



2. Harish Kumar et al reported a series of 1,3,4-oxadiazole and 1,2,4-triazole derivatives of biphenyl-4-yloxy acetic acid and screened for anti-inflammatory activity, analgesic activity and lower ulcerogenic potential. All compounds were evaluated for their anti- inflammatory activity by the carrageenan induced rat paw edema test method. The Compound was evaluated as the lead compound having inflammatory activity (81.81%) than the reference drug (79.54%), it had low ulcerogenic potential and protective effect on lipid peroxidation [23].



3. K. Manjunatha et al carried out the synthesis and evaluation of some 1,3,4-oxadiazole derivatives. They found that the compounds having 4- chlorophenylpiperazin-4-ylmethyl (5h) and 4-fluorophenylpiperazin-4-ylmethyl showed good anti-inflammatory activity [24].



4. Trilok Chandra et al carried out the synthesis of substituted acridinyl pyrazoline derivatives. All the newly synthesized compounds were screened for their anti-inflammatory and analgesic activities. All the compounds have shown anti-inflammatory activity ranging from 10.8 to 40.8% at the dose of 50 mg/kg, p.o. In addition of anti-inflammatory activity these compounds have also exhibited analgesic activity in the ranging from 8.6 to 33.5% at the dose of 50 mg/kg, i.p [25].

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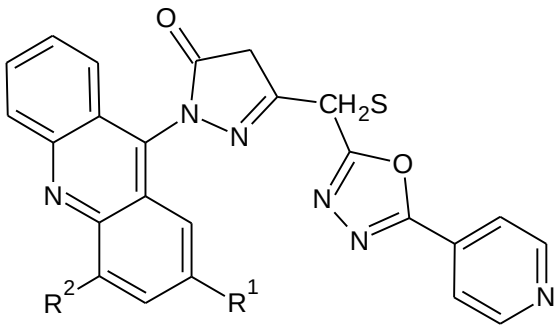
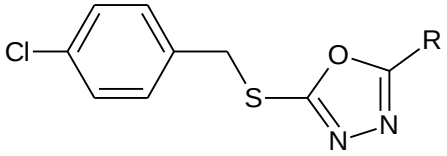
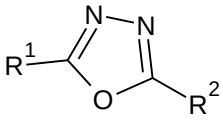


Anti-Cancer Activity

1. A series of new 2-chloropyridine derivatives possessing 1,3,4-oxadiazole moiety were synthesized by Qing-Zhong Zheng et al. Antiproliferative assay results indicated that compounds 6o and 6u exhibited the most potent activity against gastric cancer cell SGC-7901, which was more potent than the positive control. Especially, compound 6o exhibited significant telomerase inhibitory activity (IC50 = 2.3 ± 0.07 lM), which was comparable to the positive control ethidium bromide. Docking simulation was performed to position compound 6o in to the active site of telomerase (3DU6) to determine the probable binding model [26].

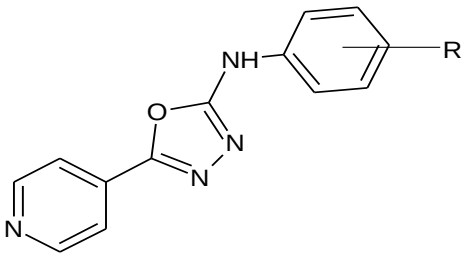


2. Alex S. Kiselyov et al carried out the design and synthesis of a series of novel 1,3,4-oxadiazole derivatives based on structural and electronic overlap with combretastatin A-2. It was tested in vivo using the sea urchin embryo development assay. The effect of these agents were monitored on two specific developmental stages of the embryo, namely i) fertilized egg to assess anti- mitotic activity; ii) free swimming blastulae to detect behavioral changes in the embryo swimming pattern [27].

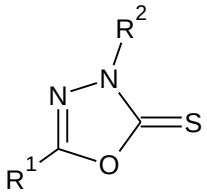


Calcium Channel Blocker

1. Girish R. BankaraIn investigated whether the correction of endothelial dysfunction is dependent on the normalization of high blood pressure levels by 1,3,4-oxadiazole derivative (NOX-1) in deoxycorticosterone acetate (DOCA-salt) and NG-nitro-l-arginine (L-NNA) hypertensive rats. In DOCA-salt and L-NNA hypertensive rats, the mean systolic blood pressure (MSBB) was 185.3±4.7 and 170.2±4.1mmHg, whereas after administration of NOX-1 to hypertensive rats, MSBB was 127.8±4.5 and 120.2±5.1mmHg, respectively [28].

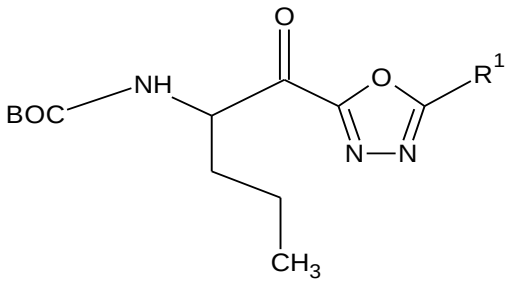


Activity Against Snake Venom

1. Ramya V. Shingalapur et al synthesized and evaluated a series of 1,3,4-oxadiazole-2 (3H)-thiones and 1,3,4-thiadiazole-2 (3H)-thiones for their inhibitory activities against the two nucleotide pyrophosphates phosphodiesterase 1 enzymes. Dixon, as well as Lineweaver–Burk plots, and their secondary reports have indicated that the inhibition was of pure non-competitive type, against both snake venom and pure human recombinant enzymes as the Vmax values decreases without affecting the Km values. 5-[4-(t- Butyldimethylsilyloxy)- phenyl]-1,3,4-thiadiazole-2 (3H)-thione and [4-(t-butyldimethylsilyloxy)- phenyl]-1,3,4- oxadiazole-2 (3H)-thione were found to be the most active compounds with IC50 values 66.47 and 368 lM, respectively [29].
2. 

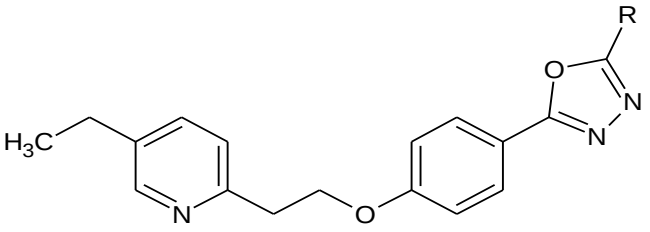
Anti-Osteoporotic Activity

1. Usman Ghani et al have prepared a series of cathepsin K inhibitors bearing the keto-1,3,4-oxadiazole warhead capable of forming a hemithioketal complex with the target enzyme. By modifying binding moieties at the P1, P2, and prime side positions of the inhibitors, selectivity over cathepsins B, L, and S are achieved and also sub-nanomolar potency against cathepsin K. This series thus represents a promising chemotype that could be used in diseases implicated by imbalances in cathepsin K activity such as osteoporosis [30].



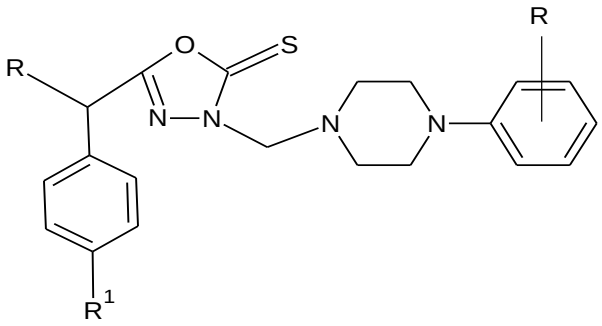
Anti-Microbial Activity

1. G.C. Ramaprasad et al synthesized a series of novel 2-{4-[2-(5-ethylpyridin-2- yl)ethoxy]phenyl}-5-substituted-1,3,4-oxadiazoles by the oxidative cyclisation of hydrazones derived from 4-[2-(5-ethylpyridin-2-yl)ethoxy]benzaldehyde and arylhydrazines using chloramine-T as oxidant. IR, NMR and elemental analysis characterized the newly synthesized compounds. The synthesized compounds were evaluated for their antimicrobial activity and were compared with standard drugs. The compounds demonstrated potent to weak antimicrobial activity [31].

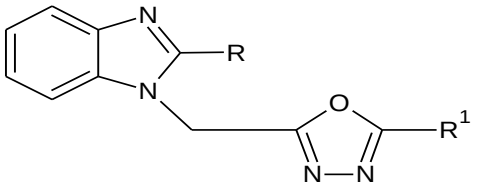


2. Om Prakash et al carried out the hypervalent iodine (III) mediated synthesis of novel unsymmetrical 2,5-disubstituted 1,3,4- oxadiazoles . The acid hydrazides derived from ibuprofen and 4-methylthiophenyl acetic acids have been subjected to cyclization with carbon disulphide under basic

conditions to yield 1,3,4-oxadiazol-2-thiones (3) which on aminomethylation with formaldehyde and secondary amines afforded a series of Mannich bases . Purity of the compounds has been confirmed by TLC. Structures of these compounds were established on the basis of elemental analyses and spectral studies. The newly synthesized compounds were evaluated for their anti-inflammatory, analgesic, ulcerogenic and antimicrobial activities [32].



3. Keshari Kishore Jha et al synthesized some derivatives of benzimidazole by nucleophilic substitution of 2- substituted-1H benzimidazole. The resulting ethyl (2- substituted-1H-benzimidazol-1-yl) acetate on treatment with hydrazine hydrate yielded 2-(2- substituted-1H-benzimidazol-1-yl) acetohydrazide, which on further reaction with one equivalent of different aliphatic or aromatic carboxylic acids in the presence of phosphoryl chloride afforded the corresponding target compounds, 2-substituted-1-[{(5-substitutedalkyl/aryl)-1,3,4-oxadiazol-2-yl} methyl]- 1H-benzimidazole. The structures of the synthesized compounds were evaluated by spectral and elemental methods of analyses. All the synthesized compounds were screened for their antimicrobial activities. All of the derivatives showed good activity towards Gram- positive bacteria and negligible activity towards Gram- negative bacteria. Some of the synthesized compounds showed moderate activity against tested fungi [33].



Drugs Containing Oxadiazole Moeity

Raltegravir (Anti-retroviral drug)

IUPAC Name: N-(2-(4-(4-fluorobenzylcarbamoyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)propan-2-yl)

It is produced by Merck & Co. and received approval by U.S FDA on 12 October 2007, the first of a new class of integrase inhibitors to receive such approval.

Mechanism: It targets the enzyme integrase which is used by the HIV to integrate the viral genetic material to human chromosome. The drug is metabolized via glucuronidation.

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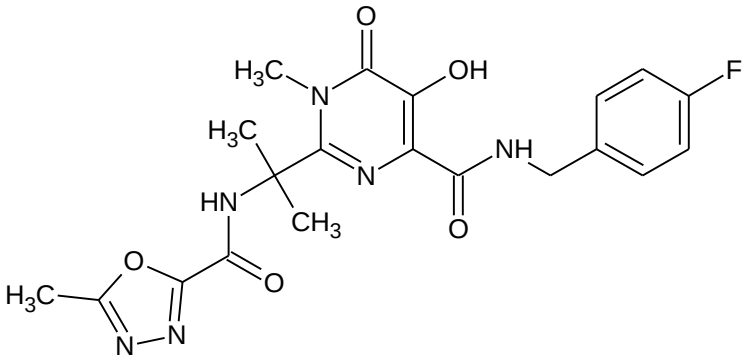
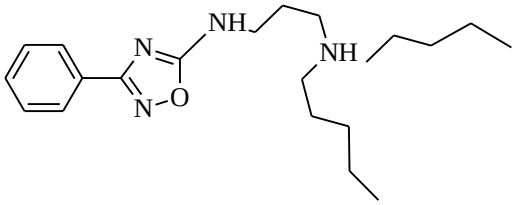
Dose: 200,400 and 600mg. Used orally twice a day [34].



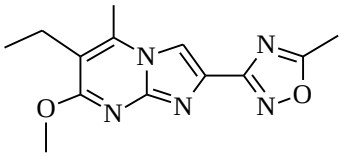
BUTALAMINE (Vasodilator)

IUPAC Name: N, N-Dibutyl-N'-(3-phenyl-1,2,4-oxadiazol-5-yl) ethane-1,2-diamine



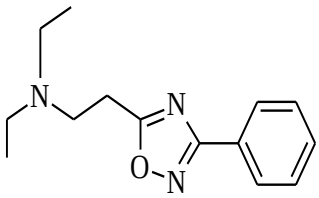
Fasiplon (Anti-Anxiety)

IUPAC Name: 6-Ethyl-7-methoxy-5-methyl-2-(5-methyl-[1,2,4]oxadiazol-3-yl)-imidazo[1,2-a]pyrimidine
Mechanism: It binds strongly to the benzodiazepine sites on the GABA receptor and produces anxiolytic effect [35].



Oxolamine (Cough Suppressant)

IUPAC Name: N,N-diethyl-2-(3-phenyl-1,2,4-oxadiazol-5-yl)ethanamine



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Pleconaril (Anti-Viral Drug)

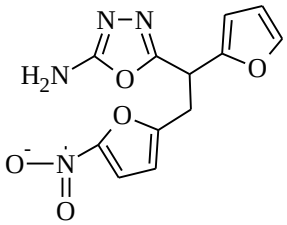
IUPAC Name: 3-{3,5-dimethyl-4-[3-(3-methylisoxazol-5-yl)propoxy] phenyl}-5-(trifluoromethyl)-1,2,4-oxadiazole

Mechanism: Pleconaril binds to a hydrophobic pocket in VP1, the major protein which comprises the capsid (the outer "shell") of picornaviruses. In enteroviruses, this prevents the virus from exposing its RNA, and in rhinoviruses it also prevents the virus from attaching itself to the host cell [36].

Pleconaril was originally developed by Sanofi-Aventis and licensed to viropharma in 1997. Viro pharma developed it further developed and relicensed to Schering-plough in 2003. The phase 2 clinical trials were completed in 2007[37]. Results are yet to be reported.

Furamizole

IUPAC Name: 5-[(E)-1-(furan-2-yl)-2-(5-nitrofuran-2-yl) ethenyl]-1,3,4-oxadiazol-2-amine



CONCLUSION

This article deals about introduction of oxadiazole along with its basic chemistry and its physical and chemical properties. We further discuss about synthesis of oxadiazole and its substitutes. We also explore the common pharmacological properties and mention few of the currently used drugs of oxadiazole moiety. We are able to understand that oxadiazole is potential chemical with many useful properties and currently the topic of many undergoing research projects.

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