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REVIEW ARTICLE

BIOLOGICALLY ACTIVE OXADIAZOLE

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ABSTRACT

As we know that, Oxadiazole is a heterocyclic compound containing an oxygen atom and two nitrogen atoms in a five-membered ring and is derived from furan by substitution of two methylene groups (=CH) with two pyridine type nitrogen (-N=) [1,2]. There are three known isomers that is 1,2,4-oxadiazole, 1,2,3-oxadiazole and 1,2,5-oxadiazole (Figure 1.0). However, 1,3,4-oxadiazole and 1,2,4-oxadiazole are better known, and more widely studied by researchers because of their many important chemical and biological properties. Among heterocyclic compounds, 1,3,4-oxadiazole has become an important construction motif for the development of new drugs. Compounds containing 1,3,4-oxadiazole cores have a broad biological activity spectrum including antibacterial, antifungal, analgesic, anti-inflammatory, antiviral, anticancer, antihypertensive, anticonvulsant, and anti-diabetic properties. They have also attracted interest in medicinal chemistry as surrogates (bioisosteres) for carboxylic acids, esters and carboxamides. The ability of 1,3,4-oxadiazole heterocyclic compounds to undergo various chemical reactions has made them important for molecule planning because of their privileged structure, which has enormous biological potential. Some examples of compounds containing the 1,3,4-oxadiazole unit currently used in clinical medicine are: Raltegravir as an antiretroviral drug and Zibotentan as an anticancer agent. They possesses various other biological activities and having various synthetic approaches, some of them are presented here in the aritcle.

Keywords: Oxadiazoles synthetic approaches, biologically active ozadiazoles, oxadiazoles as anticancers etc.

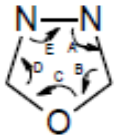
1. NTRODUCTION:

Oxadiazole is a heterocyclic aromatic compound having molecular formula C2H2N2O. It is a five membered ring consisting of 2 nitrogen atoms, 2 carbon atoms,1 oxygen atom and 2 double bonds[1]. It is derived from furan by replacing two -CH= group with 2 pyridine typed nitrogen (-N=). So possibly there are 4 isomers of oxadiazole which depends on the nitrogen atom position in the ring as follows:

Figure 1.0

1,2,4- Oxadiazole, 1,2,5-oxadiazole, and 1,3,4-oxadiazole are known, but the 1,2,3-isomer is unstable and reverts to the diazoketone tautomer.[2] 1, 3, 4-Oxadiazole derivatives shows a wide range of biological activities including antibacterial, antitubercular, vasodialatory, antifungal, cytotoxic, anti-inflammatory, analgesic, hypolipidemic, anticancer and ulcerogenic activities.[3]

1.1 Physical properties of oxadiazole: In 1955 the first monosubstituted 1,3,4-oxadiazoles were reported by two independent laboratories [4,5]. Nature of 1,3,4 oxadiazoles is liquid. They have a boiling point of 150° C [6-8]. 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.



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

Figure 2.0

The IR spectra of 1,3,4-oxadiazole is characterized by bonds present at1640-1650 cm (C=N) and at 1020cm (C=O) [9]. The position of both protons in H-NMR is 1.27.The refractive index n D of 1,3,4- oxadiazole is 1.43 [10]. According to the mass spectra the base peak is the molecular ion peak. The solubility of oxadiazole in water varies with the substituent present: 2,5-dimethyl-1,3,4-oxadiazole is miscible with water in all proportions whereas the solubility of 2,5-diphenyl-1,3,4- oxadiazole in water is less [11].

1.2 Chemistry of oxadiazole

Oxadiazole shows inductive effect because of the presence of heteroatom in the ring 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 as compared to its isomeric partner. Other differences involve metabolic stability, hERG inhibition, and aqueous solubility. All these studies favoured 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. The 1, 3, 4-oxadiazole undergoes number of reactions including electrophillic substitution, nucleophilic substitution, thermal and photochemical.

1.2.1 Electrophillic reaction

Low electron density of carbon atom in 1,3,4-oxadiazole, 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.

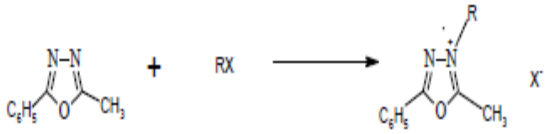


Figure 3.0

1.2.2 Nucleophillic reaction

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

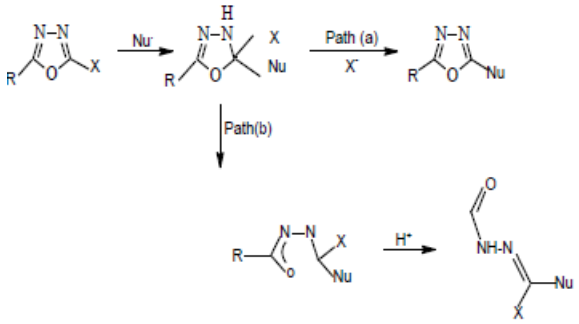


Figure 4.0

1.2.3 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 forms 2-alkoxy-1, 3,4oxadiazoles [2].

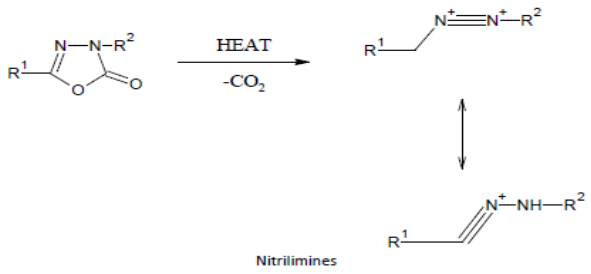


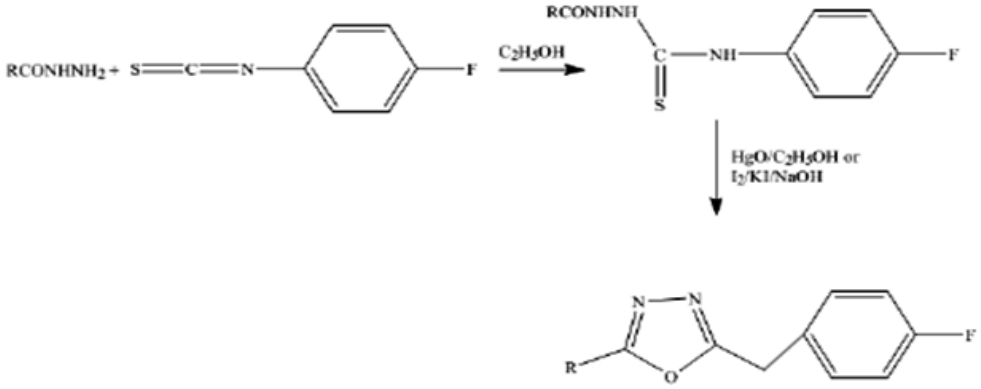
Figure 5.0

2. SYNTHETIC APPROACHES OF OXADIAZOLE

2.1. Scheme 1

From Thiosemicarbazide

Barbuceanu et. al.; (2010); reported the synthesis of oxadiazole by reacting N1-[4-(4- bromophenylsulfonyl) benzoyl]-N4-(4-flourophenyl)-thiosemicarbazide[12] with (a) Mercuric Oxide (HgO) in ethanol media (b) I2/KI in NaOH solution media.

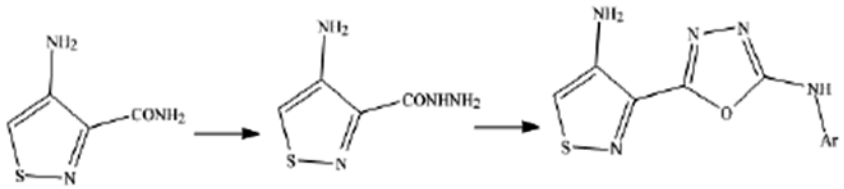


Scheme 1

2.2 Scheme 2

From Isothiazole

Kiselyov et. al.; (2010); 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 [13].

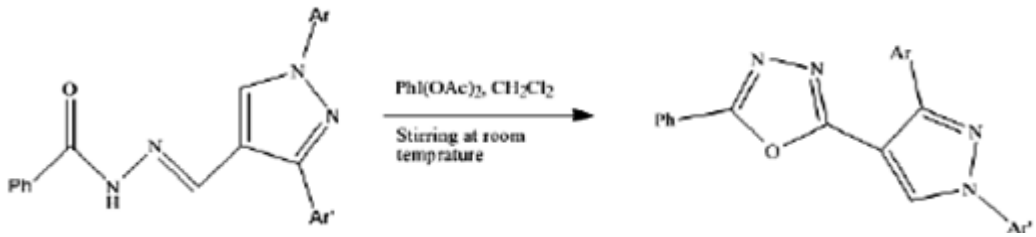


Scheme 2

2.3 Scheme 3

From N-acyl hydrazones

Prakash et. al.; (2010); reported the synthesis of a series of novel 2,5-disubstituted 1,3,4- oxadiazoles, by oxidative cyclization of pyrazolylaldehyde N-acyl hydrazones promoted by iodobenzene diacetate under mild conditions [14].

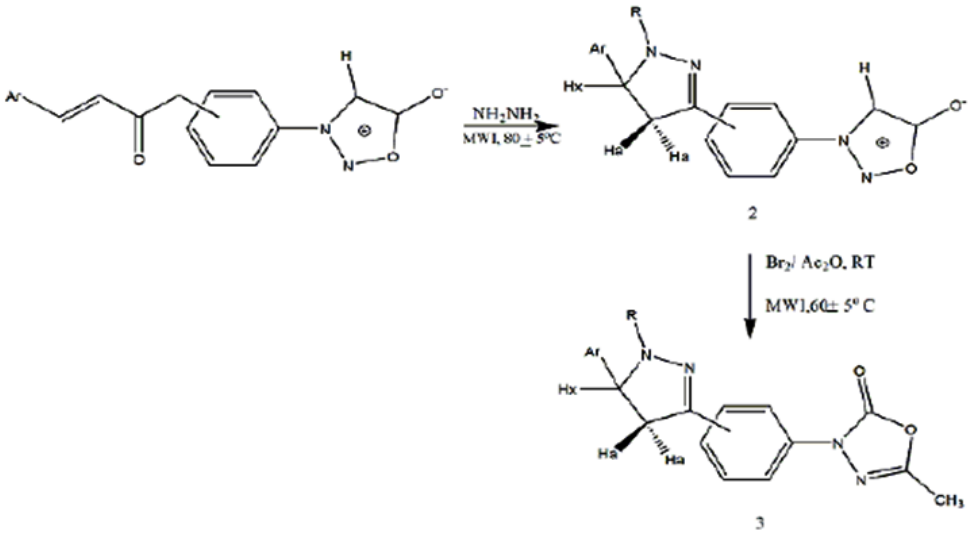


Scheme 3

2.4 Scheme 4

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 hydrate using Polyethylene glycol (PEG 200) and formic acid as solvents. The Compound 2 on bromination and heating with acetic anhydride afforded the Oxadiazole derivatives (compound 3)[15].

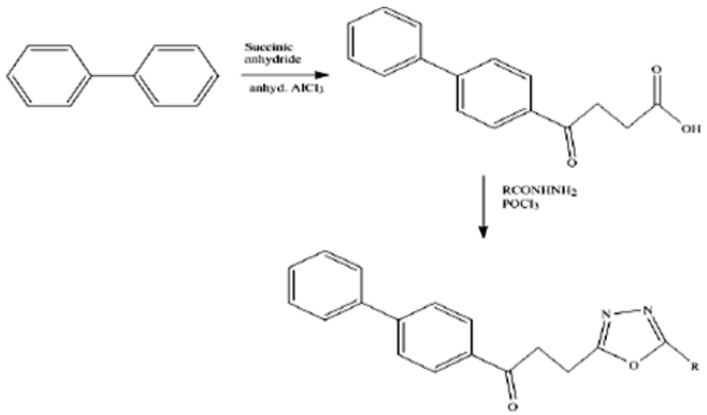


Scheme 4

2.5 Scheme 5

From acid hydrazides

The formation of 1,3,4 –oxadiazole via condensation of various alkyl hydrazides with substituted acids using various cyclodehydrogenating agents 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 [16].

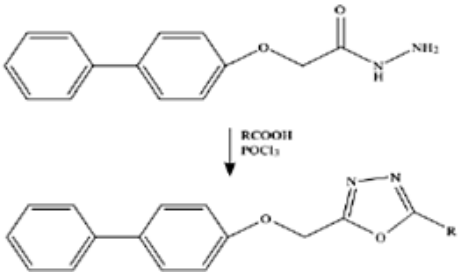


Scheme 5

2.6 Scheme 6

From acetic acid hydrazide

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 [17].



Scheme 6

3. BIOLOGICAL APPROACHES OF OXADIAZOLE

3.1 Calcium Channel Blocker

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 [18].

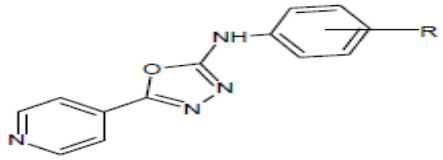


Figure 6.0

3.2 Anti-Osteoporotic Activity

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 [19].

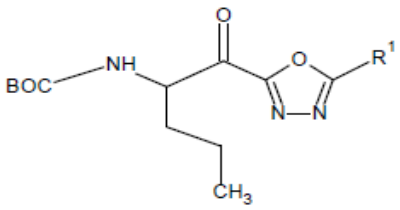


Figure 7.0

3.3 Antiviral Activity

The unsubstituted aromatic sulfonamides of type $ArSO_2NH_2$ act as strong carbonic anhydrase inhibitors and potency of such compounds is drastically increased by N- substitution of the sulphonamide moiety. Iqbal et al. studied the antiviral activity of novel benzene sulfonamides bearing 2,5- disubstituted-1,3,4-oxadiazole moiety[7] by screening them against human immunodeficiency virus type 1(HIV-1) using the XTT assay in MT-4 cells. The antiviral activity of synthesized compounds was evaluated at concentrations of 5, 25 and 50µg/ml. The results showed that one compound was found to be the most active amongst the tested compounds; it produced 14%, 21% and 42% reduction of viral replication at concentrations of 5, 25 and 50µg/ml respectively comparable to that of standard antiviral drug [20]

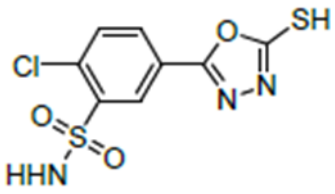


Figure 8.0

3.4 Anticancer activity

Formagio et al. studied some novel 2- substituted-1,3,4-oxadiazole-5-yl bearing β-carboline derivatives (13) for their antitumour activity and evaluated by in- vitro process. Some compounds showed high selectivity and potent anticancer activity against human tumor lines melanoma, breast, lung, leukemia, ovarian, prostate, colon and renal. Assays were performed in a 96-well plate using four concentrations at 10-fold dilutions (0.25 mg/ml to 250 mg/ml) for each test compound. Two compounds showed significant anticancer activity on comparison with standard anticancer drug [21].

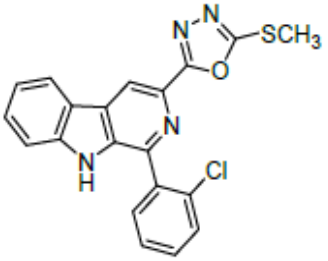


Figure 9.0

3.5 Anti inflammtory activity

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].

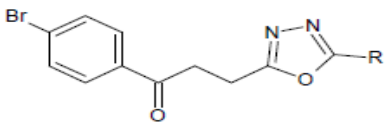
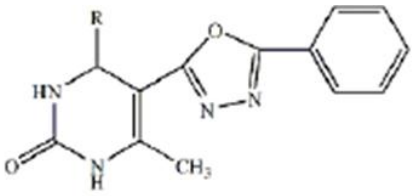


Figure 10.0

3.6 Anti microbial activity

Mishra et. al.; (2010); synthesised a series of Oxadiazole (Compound 8) and then final compounds were tested for their antimicrobial activity by cup and plate method. Among the tested compound 8a showed promising antibacterial activity against Gram +ve bacteria i.e. Streptococcus pneumonia and compound 8b showed promising antibacterial activity against Gram –ve bacteria i.e. Escherichia coli as compared to standard drugs Ofloxacin and Levofloxacin [23].



Where 8a: R = 4-$OCH_3C_6H_5$

8b: R = 4-$N0_2C_6H_5$

Figure 11.0

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