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REVIEW: 1,3,4-OXADIAZOLE AS ANTICANCER AGENT

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Abstract: Oxadiazole moiety and its various derivatives studied frequently in the past few decades and found potent in various pharmacological and pathological conditions. Oxadiazole is a versatile heterocyclic nucleus which has attracted a wide attention of the medicinal chemists in search for new therapeutic molecules. Oxadiazoles are five membered heterocyclic compounds with two nitrogen atoms and one oxygen atom. Oxadiazole possess a number of biological activities like anticancer, muscle relaxant, antimicrobial, anticonvulsant, antiviral, anti-tubercular, anti-amoebic, antiobesity, anti-inflammatory activities etc. The present review describes the Chemistry, sources, synthetic review and pharmacological profile of 1,3,4-oxadiazole. The aim of the present paper is to review the available information on 1,3,4-oxadiazole.

Keywords: Oxadiazole, Anticancer, Cytotoxic, Pharmacology

PAPER-QR CODE

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INTRODUCTION

Cancer is the second leading cause of death in Europe and North America. World Health Organization has estimated over 11 million global deaths due to cancer in 2030. Discovery and development of anticancer agents are the key focus of several pharmaceutical companies as well as non-profit government and non-government organizations, like the National Cancer Institute (NCI) in the United States, the European Organization for Research and Treatment of Cancer (EORTC) and the British Cancer Research Campaign (BCRC) [1]. Cancer is a genetic disease resulting from faulty DNA. Mutations can occur in genes, causing normal cell to become cancerous. More specifically, a defective gene can lead to increased cellular proliferation in one cell and it can be passed down to a daughter cell. The accumulation of mutations in subsequent generations of daughter cells can cause cells to proliferate even more rapidly and eventually undergo structural changes to become malignant. Cancer cells are believed to be result from at least two genetic mutations to a normal cell. These mutations cause the cells to divide uncontrollably [2]. Only 5‑10% of all cancer cases can be attributed to genetic defects, whereas the remaining 90‑95% has their roots in the environment and lifestyle. The lifestyle factors include cigarette smoking, diet (fried foods, red meat), alcohol, sun exposure, environmental pollutants, infections, stress, obesity, and physical inactivity[3]. The most numerous and important heterocyclic systems are those having five and six membered rings having hetero atoms such as N, O, S, P, Si, B etc. Heterocyclic compounds have attracted the attention of medicinal chemists because of having broad spectrum of pharmacological activities and hence it continues to yield new medicinal agents. One such heterocyclic nucleus of medicinal importance is oxadiazole nucleus. Oxadiazole is a versatile heterocyclic nucleus which has attracted a wide attention of the medicinal chemists in search for new therapeutic molecules. Oxadiazoles are five membered heterocyclic compounds with two nitrogen atoms and one oxygen atom. Depending on the position of hetero atoms; they are named as 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole and 1,3,4-oxadiazole [Figure 1]. Out of its possible isomers; 1,3,4-oxadiazole is widely exploited for various applications as medicinal agents. This interesting group of compounds has diverse biological activities such as antibacterial, antifungal, antiviral, anticonvulsant, anticancer activities etc.

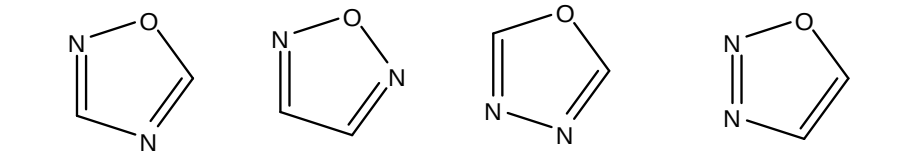


Figure 1: Chemical structures of isomers of oxadiazole nucleus

Biologically active molecules containing oxadiazole moiety includes antimicrobial, anticancer, anticonvulsant, anti-inflammatory and antiviral agents [4].

Physical Properties of Oxadiazole

Oxadiazole is a five membered heterocycle having two carbons, two nitrogens, one oxygen and two double bonds. The first monosubstituted 1,3,4-Oxadiazoles were reported in 1955 by two independent laboratories. Since 1955 other workers have extended this reaction; 1,3,4-Oxadiazole boils at 150^0 C. The percentage of C, H, N present in 1,3,4-Oxadiazole is given in table 1.

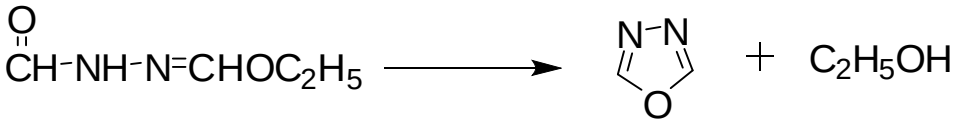
Table: 1 Percentage of C, H, N present in 1,3,4-oxadiazole

Calculated %			Found %		
C	H	N	C	H	N
34.29	2.88	40.00	34.56	3.19	39.71

The IR spectra of 1,3,4-oxadiazole is characterized by the peaks at 1640-1560 cm^{-1} (C=N) and 1020 cm^{-1} (C=O). The position of both protons of 1,3,4-Oxadiazole in ^{1}H-NMR is 1.27. The refractive index of 1,3,4-Oxadiazole is 1.43. The mass spectra showed that the base peak is the molecular ion peak.

Chemistry of Oxadiazole

Ainsworth, *et al*.; (1965) prepared 1,3,4-Oxadiazole by the thermolysis of ethylformate formly hydrazine at atmospheric pressure [Scheme 1].



Scheme 1: Synthesis of 1,3,4-oxadiazole

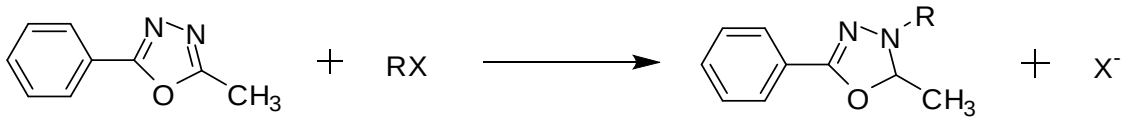
1,3,4-oxadiazole is a thermally stable molecule. Oxadiazole is a very weak base due to the inductive effect of the extra heteroatom. The 1,3,4-Oxadiazole undergoes number of reactions including electrophilic substitution, nucleophilic substitution, thermal and photochemical. The electrophilic substitution in oxadiazole ring is extremely difficult at the carbon atom because of the relatively low electron density on the carbon atom which can be attributed to electron withdrawing effect of the nitrogen atom. If oxadiazole ring is substituted with electron releasing groups then the attack of electrophiles occurs at nitrogen. Oxadiazole ring is generally resistant

to nucleophilic attack. Halogen substituted oxadiazole, however, undergo nucleophilic substitution similarly as occurring at an aliphatic sp^2 carbon atom [5].

Chemical Reactivity of 1,3,4-Oxadiazole

- **Electrophilic substitution reaction**

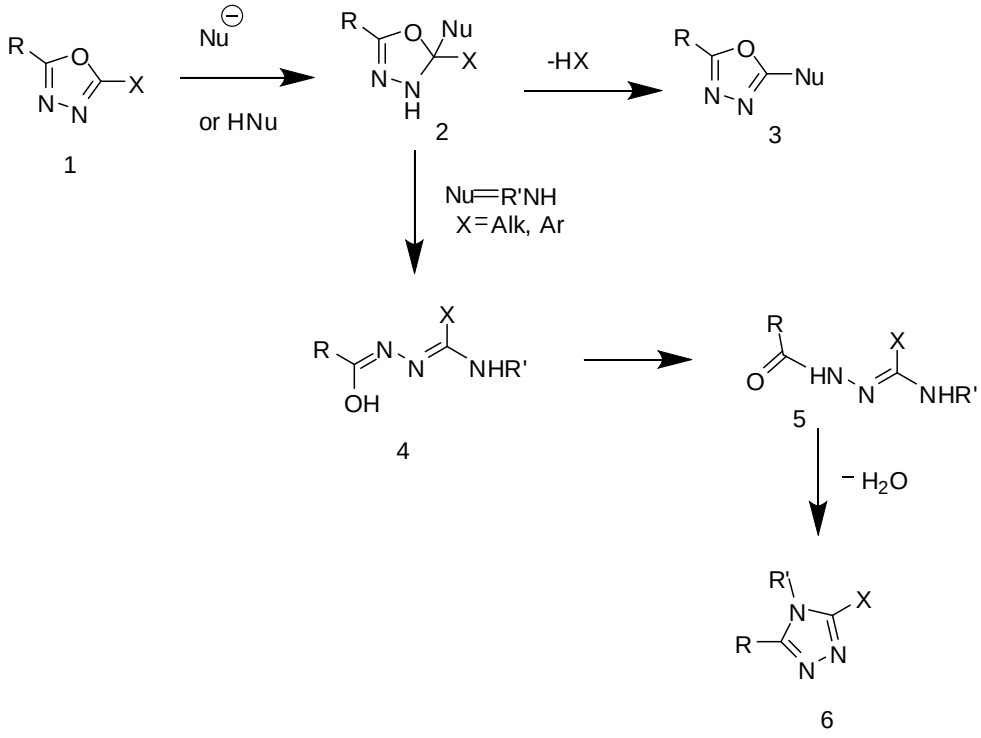
Due to low electron density on the carbon atom, electrophilic attack is favorable at the 3rd position and results in the formation of 1,3,4-oxadiazonium salts [Scheme 2].



Scheme 2: Electrophilic substitution reaction of 1,3,4-oxadiazole

- **Nucleophilic substitution reaction:**

Nucleophilic attack at ring carbon is a major reaction mode of 1,3,4-oxadiazole. Such reaction lead to Nucleophilic products **3** or to the ring cleavage with the formation of intermediates **4** and **5**, which, in case of Nucleophiles, frequently recyclise into 1,2,4-triazole **6** [Scheme 3][6a,b].



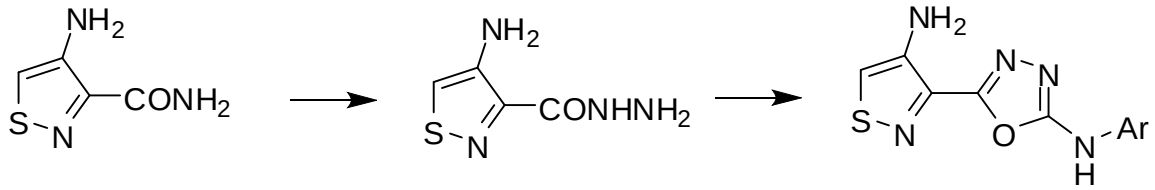
Scheme 3: Nucleophilic substitution reaction of 1,3,4-oxadiazole

SYNTHETIC REVIEW OF 1,3,4-OXADIAZOLE

The most popular reported method for the synthesis of 1,3,4-Oxadiazole backbone is the reaction between the properly substituted acid hydrazide, carbon disulphide (CS_2) and potassium hydroxide (KOH). However the long reaction time is a limiting factor over the high and consistent yields obtained with this method. Various other synthetic methods have been reported in literature to overcome this limitation.

From Isothiazole

Kiselyov, A. S. *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 [Scheme 4].



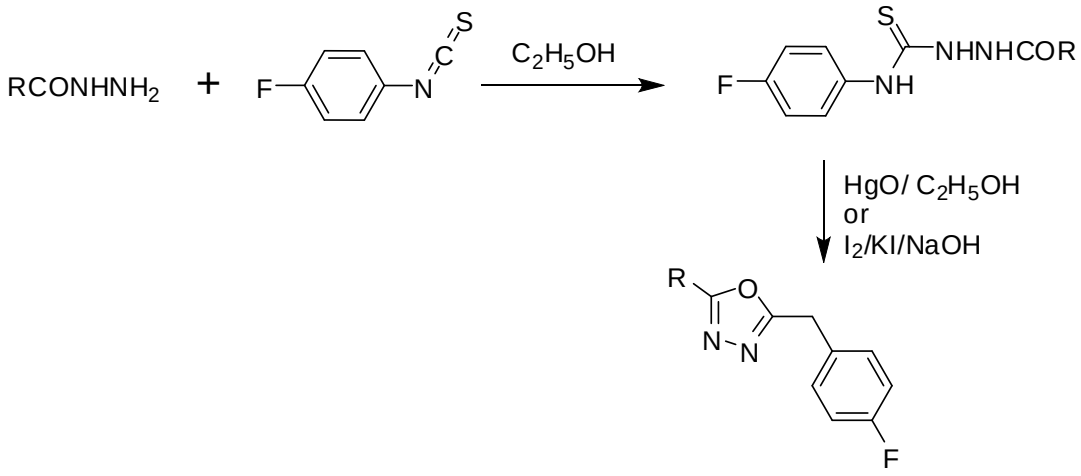
Scheme 4: Synthesis of 1,3,4-Oxadiazole from Isothiazole

From Thiosemicarbazide

Barbuceanu, S. F. *et al.*; (2010) reported the synthesis of oxadiazole by reacting N-1-[4-(4-bromophenylsulfonyl)benzoyl]-N-4-(4-flourophenyl)-thiosemicarbazide with:

(a) Mercuric Oxide (HgO) in ethanol media

(b) I_2/KI in NaOH solution media [Scheme 5].

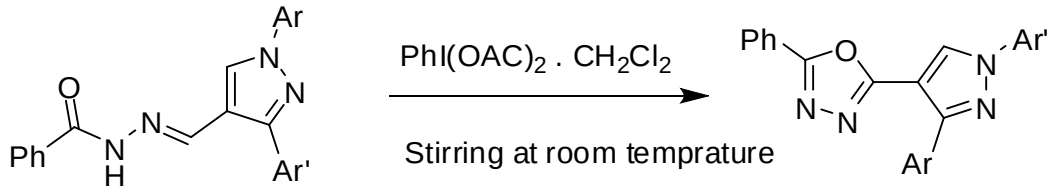


Scheme 5: Synthesis of Oxadiazole from Thiosemicarbazide

From N-acyl hydrazones

Prakash, O. *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 [Scheme 6].

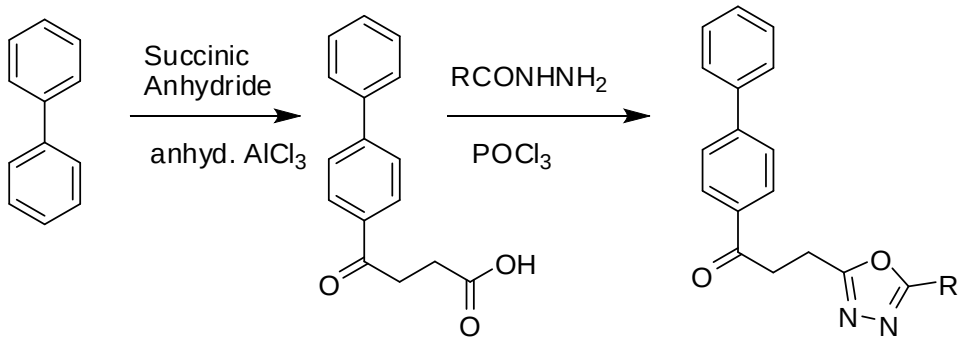


Scheme 6: Synthesis of Oxadiazole from N-acyl hydrazones

From Acid hydrazides

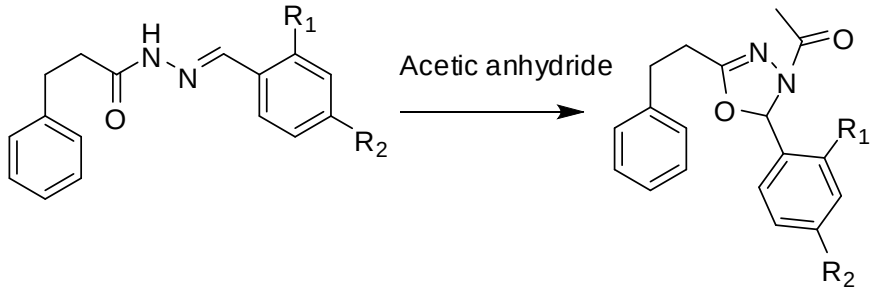
The formation of 1,3,4–oxadiazole via condensation of various alkyl hydrazides with substituted acids using various cyclodehydrogenating agents are reported in literature. A few of them are mentioned below.

Husain, A. *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 [Scheme 7].



Scheme 7: Synthesis of Oxadiazole using phosphorus oxychloride

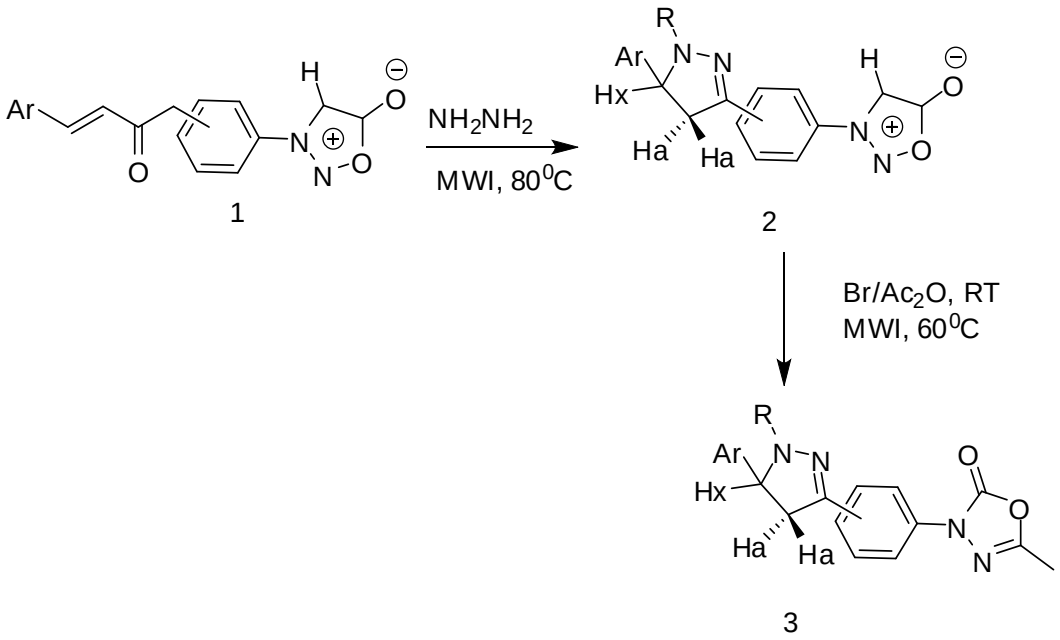
Fuloria, N. K. *et al.*; (2010) reported the synthesis of 1-(2-aryl-5-phenethyl-1,3,4-oxadiazol-3-(2*H*)-yl)ethanones by reacting N-(substituted benzylidene)-3-phenyl propionohydrazides with acetic anhydride [Scheme 8].



Scheme 8: Synthesis of Oxadiazole using acetic anhydride

From Chalcones

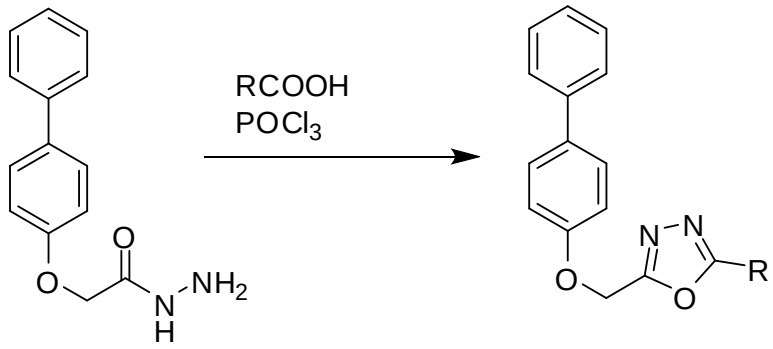
Kamble, R. R. *et al.*; (2010) reported the microwave assisted synthesis of 1,3,4-oxadiazole from chalcones. This microwave assisted synthesis lead to the cleaner reactions as well as afforded high yields and shorter reaction times. The chalcones underwent a rapid cyclization with hydrazine hydrate using 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**) [Scheme 9].



Scheme 9: Synthesis of Oxadiazole from Sydnones

From Acetic acid hydrazide

Kumar, H. *et al.*; (2010) reported the synthesis of 5-[(biphenyl-4-yloxy)-methyl]-2-substituted-1,3,4-oxadiazoles by treatment of 2-(biphenyl-4-yloxy) acetic acid hydrazide with appropriate aromatic acid in presence of phosphorous oxychloride [Scheme 10] [7].



Scheme 10: Synthesis from acetic acid hydrazide

PHARMACOLOGICAL PROFILE OF 1,3,4-OXADIAZOLE

1,3,4-oxadiazole derivatives are having a broad spectrum of pharmacological activities such as anticancer, muscle relaxant, antimicrobial, anticonvulsant, antiviral, anti-tubercular, anti-amoebic, antiobesity and anti-inflammatory activities etc. which are briefly discussed as below:

Anticancer Activity

Cancer treatment has been a major endeavor of research and development in academia and pharmaceutical industry for the last many years as it is one of the leading causes of death. Many of the available anticancer agents exhibit undesirable side effects such as reduced bioavailability, toxicity and drug-resistance. Therefore, the search for novel and selective anticancer agents is urgently required due to problems associated with currently available anticancer drugs [8].

Zhang, F. *et al.*; (2014) reported a series of new 1,3,4-oxadiazole derivatives containing pyridine and acylhydrazone moieties (Figure 2) as potential telomerase inhibitors. The bioassay tests demonstrated that compounds exhibited significant broad-spectrum anticancer activity with IC_{50} range from 0.76 to 9.59 lM against the four cancer cell lines (HEPG2, MCF7, SW1116 and BGC823). Moreover, all the title compounds were assayed for telomerase inhibition using the TRAP-PCR-ELISA assay. The docking simulation was carried out to investigate a possible binding mode of compound into the active site of telomerase (pdb. 3DU6) while the QSAR model was built to check the previous work as well as to introduce new directions [9].

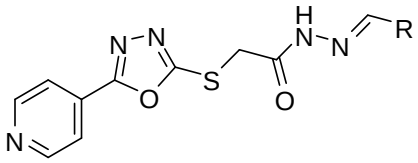


Figure 2: General structure of 1,3,4-oxadiazole derivatives containing pyridine and acylhydrazone moieties

Zhang, S. *et al.*; (2013) reported a series of new 1,3,4-oxadiazole derivatives containing benzotriazole moiety as potential Focal Adhesion Kinase (FAK) inhibitors. Some compounds showed the most potent inhibitory activity against MCF-7 and HT29 cell lines with IC_{50} values of 5.68 lg/ml and 10.21 lg/ml, respectively. Besides, all the compounds were assayed for FAK inhibitory activity using the TRAP–PCR–ELISA assay. The results showed compound **4** (Figure 3) exhibited the most potent FAK inhibitory activity with IC_{50} values of 1.2 ± 0.3 lM. Docking simulation by positioning compound 4 into the FAK structure active site was performed to explore the possible binding mode. Apoptosis which was analyzed by flow cytometry, demonstrated that compound **4** induced apoptosis against MCF-7 cells. Therefore, compound **4** may be a potential anticancer agent against MCF-7 cancer cell [10].

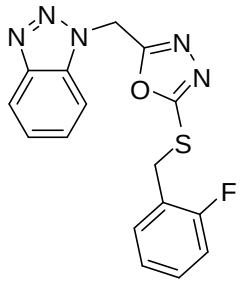


Figure 3: Structure of compound 4

Sun, J. *et al.*; (2013) reported synthesis of a series of quinoline derivatives (Figure 4) and their biological activities were also evaluated as potential telomerase inhibitors. Bioassay tests demonstrated that most of the compounds exhibited substantial broad-spectrum antitumor activity against the three cancer cell lines (HepG2, SGC-7901 and MCF-7) [11].

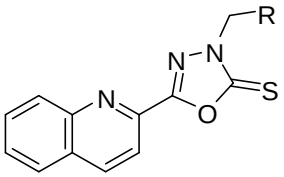


Figure 4: General structure of quinoline derivatives

Sun, J. *et al.*; (2013) reported synthesis of a series of 1,3,4-oxadiazole derivatives containing 1,4-benzodioxan moiety (Figure 5) and evaluated for their antitumor activity. Most of the synthesized compounds were proved to have potent antitumor activity and low toxicity. Among them, one of the compounds showed the most potent biological activity against Human Umbilical Vein Endothelial cells, which was comparable to the positive control. The results of apoptosis and flow cytometry (FCM) demonstrated that compound induce cell apoptosis by the inhibition of MetAP2 pathway [12].

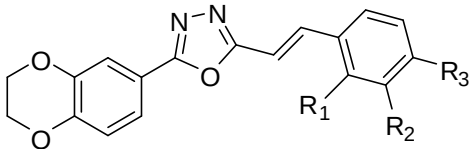
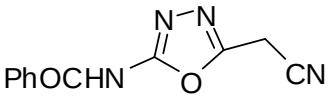


Figure 5: General structure of 1,4-benzodioxan moiety

Bondock, S. *et al.*; (2012) studied the synthetic strategies of some novel 1,3,4-oxadiazole derivatives like N-[5-(cyanomethyl)-1,3,4-oxadiazol-2-yl]benzamide (Figure 6) and N-{5-[Cyano(4-methyl-3-phenylthiazol-2-ylidene)methyl]-1,3,4-oxadiazol-2-yl}benzamide (Figure 7). Out of the newly synthesized compounds, seventeen analogs were selected to be evaluated for their *in-vitro* anticancer effect via the standard MTT method against a panel of four human

tumor cell lines namely: heptacelluar carcinoma HepG2, lung fibroblasts WI 38, kidney of a normal adult African green monkey VERO and breast cancer MCF-7. Two compounds showed considerable broad spectrum of anticancer activity against the four tested human tumor cell lines as compared with standard drug [13].



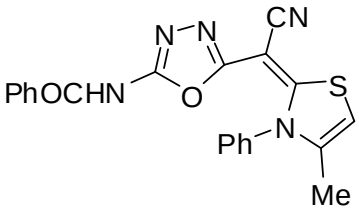


Figure 6 **Figure 7**

Zhang, X. M. *et al*.; (2011) reported the synthesis of a series of new 1,3,4-oxadiazole derivatives containing 1,4-benzodioxan moiety (Figure 8) as potential telomerase inhibitors. The bioassay tests demonstrated that some of the compounds exhibited broad-spectrum antitumor activity with IC_{50} concentration range from 7.21 lM to 25.87 lM against the four cancer cell lines, HEPG2, HELA, SW1116 and BGC823 [14].

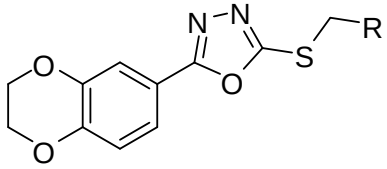


Figure 8: General structure of 1,4-benzodioxan moiety

Gudipati, R. *et al*.; (2011) reported the synthesis of a series of 5- or 7-substituted 3-{4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenylimino}-indolin-2-one derivatives (Figure 9) and screened for their anticancer activity against HeLa cancer cell lines using MTT assay. All the synthetic compounds produced a dose dependant inhibition of growth of the cells. The IC_{50} values of all the synthetic test compounds were found between 10.64 and 33.62 lM. Among the synthesized 2-indolinones, compounds with halogen atom (electron withdrawing groups) at C5 position showed the most potent activity. These results indicate that C5 substituted derivatives may be useful leads for anticancer drug development in the future [15].

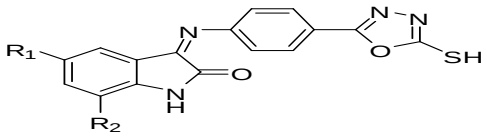


Figure 9: General structure of 5- or 7-substituted 3-{4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenylimino}-indolin-2-one derivatives

Formagio, A. S. N. *et al*.; (2008) studied some novel 2-substituted-1,3,4-oxadiazole-5-yl bearing β-carboline derivatives (Figure 10) 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 [16].

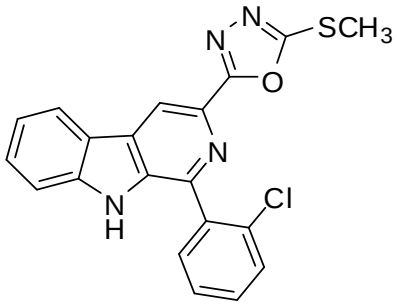


Figure 10

Muscle Relaxant Activity

The classical 1,4-benzodiazepines such as diazepam produce unwanted side effects including sedation, development of tolerance and dependence, rebound symptoms at withdrawal and amnesic effects; therefore, search continues for new benzodiazepine (BDZ)-receptor ligands with enhanced selectivity, safety and efficacy [17].

Almasirad, A. *et al.*; (2007) studied a series of 5-[2-(phenylthio) phenyl]-1,3,4-oxadiazole derivatives (Figure 11) and evaluated them *in-vivo* for their anticonvulsant and muscle relaxant activities. One compound showed muscle relaxant activity comparable to that of standard drug Diazepam [18].

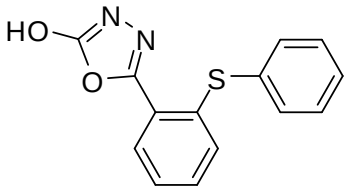


Figure 11

Antibacterial and Antifungal Activities

Liu, J. C. et al.; (2014) synthesized two novel series of 3-((5-phenyl-1,3,4-oxadiazol-2-yl)methyl)-2-thioxothiazolidin-4-one derivatives (Figure 12) and these compounds showed broad-spectrum

inhibitory activities against both Gram-positive and Gram-negative bacteria with minimum inhibitory concentration (MIC) values in the range of 1e64 mg/ml. One of the compounds was the more potent with MIC values of 1 mg/ml against the MRSA (3167 and 3506) strains than those of gatifloxacin, oxacillin, and norfloxacin. Compared to the previously reported rhodanine derivatives, 2-thioxothiazolidin-4-one derivatives exhibited an inhibition against Gram-negative strains due to the introduction of a 1,3,4-oxadiazole moiety, showed moderate activities against the Gram-negative bacteria (*Escherichia coli* 1924) with MIC values of 16 mg/ml [19].

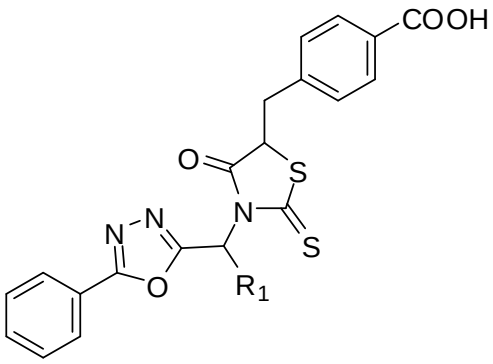


Figure 12

Kumar, H. *et al*.; (2008) synthesized some novel 2-substituted-5-[isopropylthiazole] clubbed 1,3,4-oxadiazoles (Figure 13) and tested them for antibacterial against *Staphylococcus aureus*, *Staphylococcus faecalis, Bacillus subtillis* and antifungal activity against *Saccharomyces cerevisiae*, *Candida tropicalis* and *Aspergillus niger*. Two compounds exhibited good antibacterial and antifungal activities when compared to their respective standard drugs like Ciprofloxacin, Norfloxacin and Flucanozole [20].

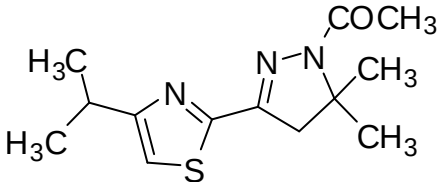


Figure 13

Li, Y. *et al*.; (2006) studied some novel (E)-α-(methoxyimino)-benzeneacetate derivatives containing 1,3,4-oxadiazole nucleus (Figure 14) and screened them for their fungicidal activity against fungal stains like *Rhizoctonia solani*, *Botrytis cinereapers*, *Gibberella zeae*, *Physalospora piricola* and *Bipolaris mayclis* at a concentration of 50μg/ml. Some compounds showed potent fungicidal activity when compared with standard drug [21].

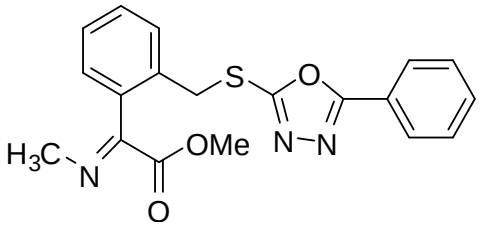


Figure 14

Anticonvulsant Activity

Anticonvulsant activity effect is mediated through benzodiazepine receptors mechanism. BZD agonists are widely used in the treatment of central nervous system disorders such as anxiety, insomnia and epilepsy. The pharmacological effects of BZDs result from their affinity for a specific binding domain on the GABA receptors known as BZD receptor. BZD agonists increase the frequency of the opening of chlorine channel in response to GABA action, causing anxiolytic, sedative and muscle relaxant effects.

Zarghi, A. *et al.*; (2008) synthesized and studied a novel group of 2-substituted-5-[2-(2-halobenzyloxy)phenyl]-1,3,4-oxadiazoles (Figure 15) for their anticonvulsant activity. Anticonvulsant activity of the synthesized compounds was determined through the evaluation of the ability of the compounds to protect mice against convulsion induced by a lethal dose of pentylenetetrazole (PTZ) and electroshock at dose of 100mg/kg. One compound having an amino group at position 2 of 1,3,4- oxadiazole ring and fluoro substituted at ortho position of benzyloxy moiety had the best anticonvulsant activity as compared with standard drug [22].

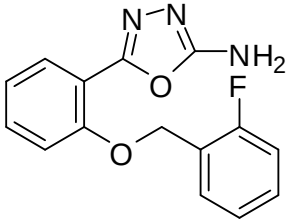


Figure 15

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, R. *et al.*; (2006) studied the antiviral activity of novel benzene sulfonamides bearing 2, 5-disubstituted-1,3,4-oxadiazole moiety (Figure 16) 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 [23].

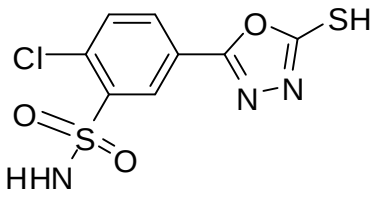


Figure 16

Anti-tubercular Activity

The emergence of multidrug resistant strains (MDR) of *Mycobacterium tuberculosis* together with the spread of severe opportunistic disseminated infections produced by *Mycobacterium* other than tuberculosis (MOTT), particularly *Mycobacterium avium* in immune compromised patients prompted the search for new anti-tubercular agents. WHO considers communicable disease caused by *Mycobacterium* in the world and estimates that about 30 million people would be infected within next 20 years [24].

Vazquez, G. N. *et al*.; (2007) presented the synthesis of novel 4-(5-substituted-1,3,4-oxadiazole-2-yl)pyridine derivatives (Figure 17) and evaluated them for antimycobacterial activity at concentration of 62.5µg/ml. One compound was found to be more potent and active than standard drugs like Isoniazid, Streptomycin and Ethambutol against *Mycobacterium tuberculosis*. The high bioactivity of compounds makes them suitable as lead compounds for additional *in-vitro* and *in-vivo* evaluations in order to develop new antimycobacterial drugs which may be used in the treatment of tuberculosis [25].

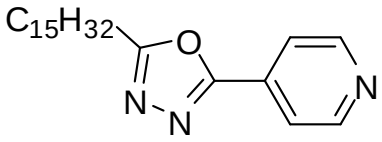


Figure 17

Mamolo, M. G. *et al*.; (2005) synthesized some new 3-substituted-5-(pyridin-4-yl)-3*H*-1,3,4-oxadiazol-2-one derivatives (Figure 18) and tested for their *in-vitro* antitubercular activity. Oxadiazolone derivatives showed an interesting antimycobacterial activity against the tested strain of *Mycobacterium tuberculosis* H37Rv. Some compounds having carbonyl functional

group showed better potency as antitubercular agents comparable to that of standard drugs Isoniazid and Rifampicin [26].

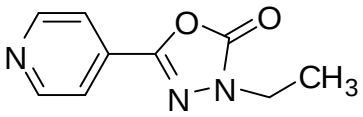


Figure 18

Macaev, F. *et al*.; (2005) designed and synthesized a novel series of 5-aryl-2-thio-1,3,4-oxadiazoles (Figure 19) and tested for their *in-vitro* antimycobacterial activity against *Mycobacterium tuberculosis* using the alamar blue assay method. One compound showed potent antitubercular activity when compared with standard drug [27].

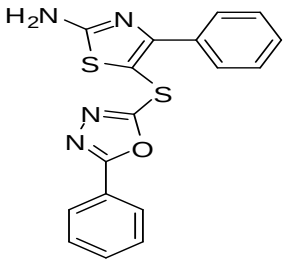


Figure 19

Anti-amoebic activity

Human amoebiasis is caused by *Entamoeba histolytica*; this infection is mainly associated with morbidity thus affecting the quality of life and pace of developmental activities of countries with warm climatic conditions. A consistently high global incidence of this disease has been reported from surveys carried out at different intervals of time. This disease also poses a challenge to our national health programs [7].

Kachroo, P. L. *et al*.; (1990) synthesised some 2-amino-5-aryl-1,3,4-oxadiazoles (Figure 20) with various substitution and varying length of alkyl chain in the benzene ring and screened them for antiamoebic activity. The *in-vitro* antiamoebic activity of compounds was evaluated against *E. histolytica* at pH 7.2- 7.4. Some compounds showed significant antiamobeic activity with MIC ranging between 250-1000µg/ml when compared with standard drug [28].

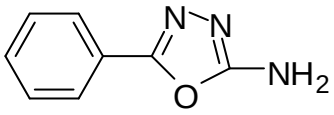


Figure 20

Antiobesity Activity

Obesity is characterized by excess of body fat and includes pro-inflammatory state eventually resulting in type 2 diabetes, coronary heart disease and hypertension. Obesity elevates the relative risk of mortality owing to cardiovascular disease and obesity now ranks as the second leading cause of preventable death after smoking in the United States. Eventually, the discovery was made that modulation of the endocannabinoid system by specifically blocking the cannabinoid receptor 1 (CB1) in both the brain and periphery can provide a novel target for the treatment of obesity. The endocannabinoid system includes endogenous ligands (such as anandamide and 2-AG) and two cannabinoid receptor subtypes (CB1 and CB2). These receptors (CB1 and CB2) belong to the G-protein coupled receptor super family. CB1 antagonism has become a new therapeutic target for the treatment of obesity [29].

Lee, S. H. *et al.*; (2008) investigated some novel biarylpyrazole analogues coupled with 1,3,4-oxadiazole (Figure 21) and tested for CB1 receptor binding affinity as antiobesity agents. SAR proved that replacement of the amide moiety into 1,3,4-oxadiazole ring could impart increase in potency by increasing binding affinity with CB1 receptors. The Fluorine substituent might be involved in a hydrogen bond interaction with receptor that shows high affinity. The addition of 1,2,4-triazole substituent resulted in increased CB1 receptor binding affinity in the biarylpyrazolyl oxadiazole series. Substitution of methyl with triazolylmethyl group on C-4 of pyrazole ring improved *in-vitro* binding affinity and potential for the treatment of obesity. One compound showed highest antiobesity activity comparable to that of standard drug [30].

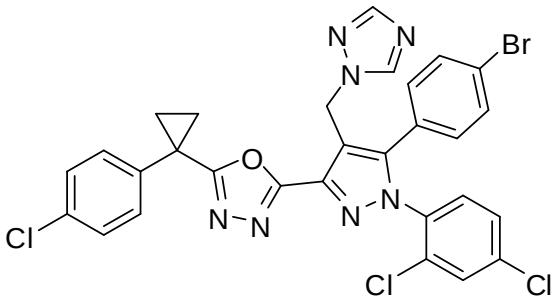


Figure 21

Analgesic and Anti-inflammatory Activities

The pharmacological activity of NSAIDs is related to the suppression of prostaglandin biosynthesis from arachidonic acid by inhibiting the enzyme prostaglandin endoperoxidase, popularly known as cyclo-oxygenase (COX). It was discovered that COX exists in two isoforms: COX-1 and COX-2, which are regulated and expressed differently. COX-1 provides

cytoprotection in the gastrointestinal tract (GIT), whereas inducible COX-2 selectively mediates inflammatory signals [31].

Gilani, S. J. *et al*.; (2010) synthesized a series of 4-[5- (2,4-dichlorophenyl)-1,3,4-oxadiazol-2-yl]pyridine derivatives (Figure 22) and evaluated them for their anti-inflammatory, analgesic, ulcerogenic and lipid peroxidation activities. One compound showed maximum anti-inflammatory & analgesic activities with reduced ulcerogenicity and lipid peroxidation as compared with standard drug [32].

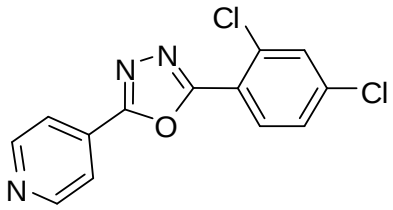


Figure 22

Akhter, M. *et al*.; (2009) synthesized a series of 2,5-disubstituted-1,3,4-oxadiazoles based on aroylpropionic acid moiety (Figure 23) and screened them for anti-inflammatory, analgesic, ulcergenic and lipid peroxidation activities. Some compounds showed better anti-inflammatory activity comparable to standard drug Ibuprofen [33].

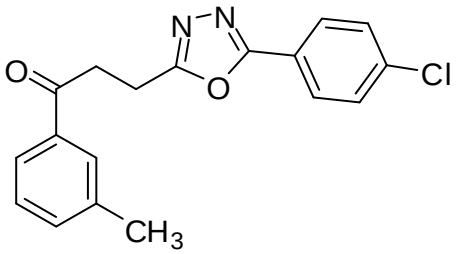


Figure 23

Kumar, H. *et al*.; (2008) designed and synthesized a novel series of 1,3,4-oxadiazole derivatives of biphenyl-4-yloxyacetic acid (Figure 24) and evaluated for their anti-inflammatory activity, analgesic activity and lower ulcerogenic potential. The anti-inflammatory activity was evaluated by the carrageenan induced paw edema test. One compound showed most prominent anti-inflammatory activity when compared with standard drug [20].

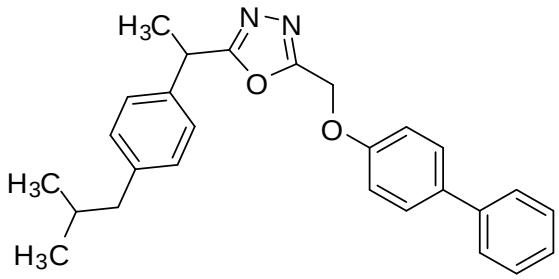


Figure 24

Burbuliene, M. N. *et al*.; (2004) synthesized a series of 5-[(2-disubstitutedamino-6-methyl-pyrimidin-4-yl)-sulfanylmethyl]-3*H*-1,3,4-oxadiazole-2-thione derivatives (Figure 25) and evaluated them for their *in-vivo* anti-inflammatory activity by carrageenan induced paw oedema method. Amongst the synthesized compounds, one compound was found to be the most potent compound [34].

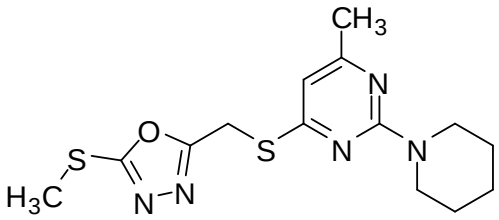


Figure 25

Boschelli, D. H. *et al*.; (1993) synthesized a novel series of 1,3,4-oxadiazole derivatives (Figure 26) and evaluated for their anti-inflammatory activity by inhibition of cyclooxygenase and 5-lipoxygenase enzymes. One compound was found to be the most potent inhibitor of 5-lipoxygenase and cyclooxygenase enzymes and showed best anti-inflammatory activity [35].

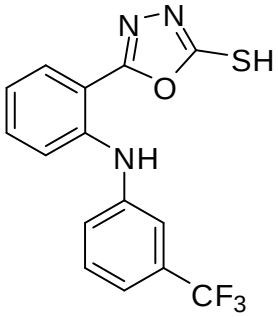


Figure 26

CONCLUSION

In the present review, we have attempted to congregate the chemistry, sources, synthetic review and pharmacological review on 1,3,4-oxadiazole. It comprises a vast array of applications such as anticancer, muscle relaxant, antimicrobial, anticonvulsant, antiviral, anti-tubercular, anti-amoebic, antiobesity, anti-inflammatory activities etc. Modifications on 1,3,4-oxadiazole nucleus have resulted in a large number of compounds, having diverse pharmacological profile; mostly used for the synthesis of compounds having anticancer activity.

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