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A REVIEW ON SYNTHESIS, BIOLOGICAL ACTIVITIES, AND APPLICATIONS OF OXADIAZOLE DERIVATIVES

[1]Asiya Ibraheem, [2]Bhavana Pandit, [3]Nadeem Alam,
[4]Dr.Sarika Arora
[1]Research Scholar, ,[2]Research Scholar,[3]Research Scholar,
[4]Associate Professor
Department of Chemistry,
IFTM University, Moradabad, U.P. 244001, India

Abstract **:** Oxadiazole is a heterocyclic molecule with an oxygen atom and two nitrogen atoms in a five-membered ring generated from furan by replacing two methylene groups (=CH) with two pyridine type nitrogen (-N=). Oxadiazole and its derivatives have anti-inflammatory, antimicrobial, antifungal, antiviral, analgesic, antimycobacterial, and anti-amoebic properties. Oxadiazoles are common motifs in drug-like compounds and are widely employed as a bio-isosteric replacement for esters and amide functions.

Keywords-Oxadiazole, oxadiazole derivatives, synthesis, biological- activities.

I. INTRODUCTION

The heterocyclic ring oxadiazole is found in a variety of physiologically active compounds, including those with fungicidal, bactericidal, anticancer, and antitubercular properties.[1] Oxadiazole was initially synthesized by Ainsworth in 1965 using the thermolysis of hydrazine. Its chemical formula is $C_2H_2ON_2$ and it has a molecular mass of 70.05g/mol and is water-soluble. The chemical[2] oxadiazole is thermally stable, with estimated resonance energy of 167.4kj/mol. The replacement at the second position improves the thermal stability of oxadiazole.[3] Hormonal heterocyclic molecules with nitrogen atoms, like oxadiazole moieties, are of interest to medical and pharmaceutical chemistry researchers. Oxadiazoles are of great interest in pharmaceutical and pesticide chemistry and polymer and material science. [4] Several compounds having an oxadiazole moiety are in late-stage clinical studies, including zip bosentan as an anticancer agent [5], for the treatment of cystic fibrosis.[6] So far, only one oxadiazole-containing molecule, raltegravir [7], is an antiretroviral medication for the treatment of HIV infection. Oxadiazoles are having a significant influence on several drug development projects in areas such as diabetes, obesity, inflammation, cancer, and infection.[8-12]

Low solubility compounds have a higher risk of failure in drug discovery because insufficient solubility can compromise pharmacokinetics and pharmacodynamic properties and mark other undesirable properties. In some cases, poor solubility can prevent promising drugs from reaching the market [13], and regulatory authorities are currently requiring additional investigations on low soluble compounds when the goal is oral administration. Oxadiazole has a wide range of medical and industrial uses. Several synthetic pathways for oxadiazole conjugated with another biological molecule have been identified, hence ibuprofen conjugated with oxadiazole was investigated for its potential action.

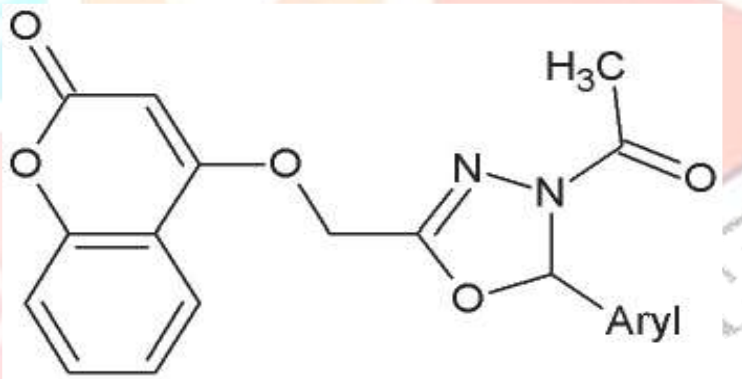
The newly synthesized oxadiazole compounds are crucial in the development of multi-target medicines with specific target action. With nucleophilic alkylation of heterocyclic analogs, novel heterocyclic compounds were produced with benzophenone and oxadiazole cores as backbones. Oxadiazole is a

heterocyclic nucleus that has liquid the curiosity of numerous researchers interested in developing new therapeutic medicines. There are four potential isomers of oxadiazole, the most important of which is 1,3,4-oxadiazole. The 1,2,4-oxadiazole moiety is used in several therapeutically active drugs, such as raltegravir for HIV-integrase inhibition and Furamizole for nitrofuran antibacterial, antihypertensive, antimicrobial, and anticancer activities. Electrophilic substitution, nucleophilic substitution, and photochemical reactions are all possible with the 1,3,4-oxadiazole. [14] Because of the inductive effect of the extra heteroatom, oxadiazole is a very weak base. Oxadiazole, as we know, is made up of 2-pyridine type nitrogen(-N=). As a result of the reaction in the aromaticity of the oxadiazole ring, the oxadiazole ring exhibits conjugated diene characteristics. Due to the lower electron density on the same carbon atom, there is no or very limited opportunity for electrophilic substitution at the carbon atom in the oxadiazole ring. Instead of attacking nitrogen electrophilically, an association of electron releasing groups in the oxadiazole ring is required. In nucleophilic substitution, such as in halogen-substituted oxadiazole, the halogen atom is replaced by nucleophiles.

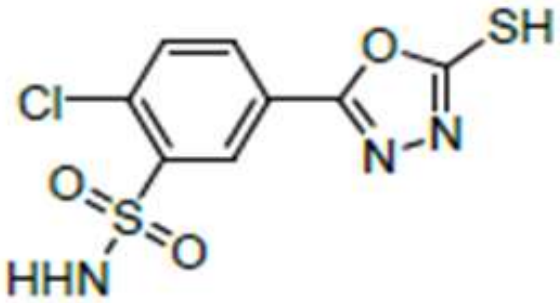
Hutt, et al., [15] previously documented the synthesis of a series of 2-trichloromethyl-5-phenyl-1,3,4-oxadiazoles with various substituents. The compounds were inspired by the chemical structure of 1,4-bis-benzene, which shows antimalarial activity in infected monkeys,[16]test molecules were assayed for antimalarial activity in BALBLC mice infected with P. berghei (n=5groups) the animals were treated with a single subcutaneous dose of test compounds and compared with hetol at the same drug regimen compounds 77a-b display the highest care rates (60-80%).

Feng, et al., (2012), produced and tested a variety of thio-substituted 1,3,4-oxadiazole derivatives. Tumor cell line from a person with leukemia (K-562). Compounds 31 and 32 have been docked into the system.TP-ATPase II's domain.[17]

Hamdi, et al., (2011), looked at the antibacterial and antioxidant properties of 1,3,4-oxadiazole derivatives.[18]



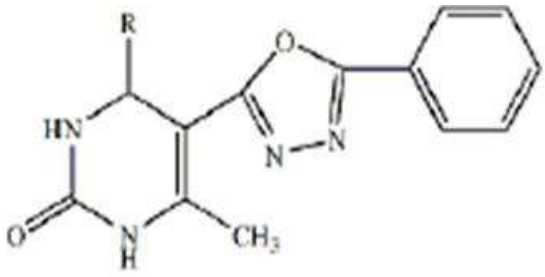
Iqbal, et al., (2006), investigated the antiviral efficacy of new benzene sulfonamides having a 2,5-disubstituted-1,3,4-oxadiazole moiety by screening them against HIV-1 in MT-4 cells using the TXT assay. The antiviral activity of produced compounds were tested at doses of 5, 25, and 50 g/ml. When compared to typical antiviral medicine, one molecule was shown to be the most active among the tested compounds, reducing viral replication by 14 percent, 21 percent, and 42 percent at doses of 5, 25, and 50g/ml, respectively. [19]



Formagio, et al., (2008), investigated the anticancer efficacy of various new 2- substituted-1,3,4-oxadiazole-5-yl containing -carboline derivatives using an in vitro method. Against human tumor lines such as melanoma, breast, lung, leukemia, ovarian, prostate, colon, and kidney, certain drugs exhibited excellent selectivity and powerful anticancer action. Each test chemical was tested in a 96-well plate with

four concentrations at 10-fold dilutions (0.25 mg/ml to 250 mg/ml). In comparison to a typical anticancer medication, two molecules demonstrated substantial anticancer efficacy.[20]

Mishra, et al., (2010), synthesized various Oxadiazole derivatives and used the cup and plate technique to assess their antibacterial properties. When compared to the mainstream medications Ofloxacin and Levofloxacin, 8a showed promising antibacterial action against Gram +ve bacteria, such as Streptococcus pneumonia, while the chemical listed below showed promising antibacterial activity against Gram–ve bacteria, such as Escherichia coli. [21]



By Asif Husain, et al., (2009), the synthesis of a novel series of 2-[3-(4-bromophenyl) propane-3-one] was reported. 3-(4-bromobenzoyl) propionic acid was used to make -5- (substituted phenyl)-1,3,4-oxadiazoles, which are better anti-inflammatory and analgesic medicines with minimal or no adverse effects (electrogenicity). 2- [3-(4-bromophenol)- propan-3-one] and 3- [3-(4-bromophenol)- propan-3-one] 2- [3-(4-bromophenyl) propane-3-one] and -5-(4-chlorophenyl)-1,3,4-oxadiazole with anti-inflammatory action of 59.5 and 61.9 percent, respectively, -5-(3,4-dimethoxy phenyl)-1,3,4-oxadiazole was found to be equivalent to indomethacin, which had 64.3 percent activity at the same dose of 20 mg/kg. [23]

Usman Ghani, et al., (2010), developed a series of cathepsin K inhibitors with a payload of keto-1,3,4-oxadiazole that may create a Hemi thioketal complex with the target enzyme. Selectivity over cathepsins B, L, and S was accomplished by altering binding moieties at the inhibitors' P1, P2, and prime side locations. This group of chemicals thus represents a promising chemotype that might be exploited to treat disorders like osteoporosis that are linked to cathepsin K activity abnormalities. [23]

The synthesis of oxadiazole was described by Kiselyov et al. (2010), who used plain hydrazine hydrate to reflux an isothiazole derivative for 4 hours. The resultant hydrazide can then be treated with isothiocyanates, and the intermediate thiosemicarbazide can subsequently be cyclized in situ with DCC to yield the essential chemicals. [24]

Prakash, et al., (2010), described the oxidative cyclization of pyrazolyl aldehyde N-acyl hydrazones driven by iodobenzene diacetate under mild conditions to produce a variety of novel 2,5-disubstituted 1,3,4- oxadiazoles. [25]

Bhat, et al., (2011), 4-Bromo-N- [(5-(substituted phenyl)-1,3,4-oxadiazol-2yl) methyl] aniline was developed, and its derivatives were tested for antibacterial activity against S. aureus, E. coli, B. subtilis, and P. aeruginosa, with amoxicillin as a positive control. These substances were tested for anti-mycotic activity against A. Niger and Candida albicans using ketoconazole as a reference standard. Different groups of derivatives, such as -OH and -NO2, demonstrate strong antibacterial efficacy against fungal strains.[26]

Gudipati, et al., (2011), a variety of indole-containing oxadiazoles were synthesized. The chemicals inhibited the development of the HeLa cancer cell line in a dose-dependent manner. Between 10.64 and 33.62 m, the ic50 values were discovered. The antitumor activity of compounds 36, 37, and 38 was equivalent to that of cisplatin.[27]

Balaji, et al., (2016), described the synthesis and antimalarial development of 20 new 1,3,4-oxadiazole derivatives. The compounds were tested against P. falciparum strains that were chloroquine-sensitive (nf54) and chloroquine-resistant (Dd2).[28]

Patel, et al., (2010), disclose a series of 1,3,4-oxadiazoles and their synthesis and characterization. Earthworms in a saline solution were used to conduct biological tests. albendazole is used as a reference medication. also discovered anti-helminthic properties.[29]

Kumar, et al., (2016), the synthesis of substituted 1,3,4-oxadiazole derivatives with 4-biphenyl carboxylic acid as starting material yielded 2-((1, 1′-biphenyl)-4-yl)-5-(substituted phenyl)-1,3,4-oxadiazole. Using

ofloxacin as a reference standard, the antibacterial activity of these derivatives was assessed against Gram + ve (S. aureus) and Gram -ve (K. pneumonia, E. coli, and P. aeruginosa) pathogens. The zone of inhibition was determined using the cup plate agar diffusion technique.[30]

Kanthiah, et al., (2011), created 5-(2-aminophenyl)-3-(substituted (disubstituted amino) methyl)-1,3,4-oxadiazole-2(3H)-thione by synthesizing substituted 1,3,4-oxadiazole with 2-aminobenzoic acid as the starting material. Using amikacin as a reference standard, the antibacterial activity of synthesized derivatives was tested against two Gram-positive (S. aureus and S. pyogenes) and gram-negative (E. coli and K. aerogenes) pathogens.[31]

Chikhalia, et al., (2009), synthesised 1-substituted-3-(4-morpholino -6-((5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazol-2-yl) thio)-1,3,5-triazine-2-yl) substituted urea was synthesised utilising a 3,4,5-methoxy benzoic acid starting material and substituted 1,3,4-oxadiazole. utilising ampicillin as a reference standard, for antibacterial activity against diverse organisms such as (Staphylococcus aureus, Bacillus subtilis, Escherichia coli, and Pseudomonas aeruginosa). These compounds' antifungal activity was tested against Candida albicans using fluconazole as a reference standard.[32]

Srinivas, et al., (2018), done the synthesis of substituted 1,3,4-oxadiazole derivatives is used to develop (E)-1-((5-substituted-1,3,4-oxadiazol-2-yl) methyl))-1H-indol-3-yl)-4(thiazol-2-arylamino) but-2-en-1-one. HT-29 (colon), A375 (melanoma), MCF-7 (breast), and A549 (lung) cancer cell lines were tested for anticancer activity using the MTT assay, using combretastatin-A4 as the reference standard. The antitumor activity of all 1,3,4-oxadiazole fused indole ring derivatives was varied.[33]

Kapoor, et al., (2016), synthesised 1,3,4-oxadiazole derivatives, 2-(substituted phenyl)-5-(2-(substituted phenyl)-1Hbenzo[d]imidazol-1-yl) was synthesized. The MTT method was used to synthesize substituted 1,3,4-oxadiazole derivatives phenyl)-1,3,4-oxadiazole using substituted 1,3,4-oxadiazole as a starting material and benzene 1,2-diamine as a starting material. The assay was used to test anticancer efficacy against the MCF-7 (breast) cancer cell line, compound.[34]

Kavitha, et al., (2017), using a 1,3,4-oxadiazole derivative as a starting point, N-substituted-(3-(5-cyclohexyl-1,3,4-oxadiazol-2-yl) phenyl) benzamide, urea, and substituted benzenesulfonamide derivatives were developed. The antitumor efficacy of synthesized compounds was assessed using cisplatin as a reference standard against cancer cell lines such as HeLa and MCF-7.[35]

Chakrapani, et al., (2018), using 1,2,4-oxadiazole derivatives, synthesised 3-(6-chloro-2-methylimidazo[2,1-b] [1,3,4] thiadiazol-5-yl)-5-(substituted phenyl)-1,2,4-oxadiazole. The anticancer efficacy of the synthesized compounds were assessed using the MTT test with doxorubicin as a reference standard against the ACHN (renal), MCF-7 (breast), and A375 (melanoma) tumor cell lines.[36]

Pattan, et al., (2009), synthesised 2-(5-(substituted thio)-1,3,4-oxadiazol-2-yl) phenol and 4-(5-(substituted thio)-1,3,4-oxadiazol-2-yl) phenol (substituted-1-ylmethyl) phenol the synthesis of 1,3,4-oxadiazole derivatives yielded 1H-pyrazole-5 (4H)-one. MB 7H9 agar medium was used to test the antimycobacterial activity of the produced derivatives against Mycobacterium tuberculosis (H37Rv). As a reference standard, streptomycin was utilized.[37]

Das, et al., (2015), carried the synthesis of 6-(pyrazin-2-yl)- [1,3,4]- oxadiazole [3,2-d] synthesised 6-(pyrazin-2-yl)- [1,2,4] triazolo[3,4-b] tetrazole and 6-(pyrazin-2-yl)- [1,2,4] triazolo[3,4-b] tetrazole Synthesis of 1,3,4-oxadiazole coupled triazole and tetrazole molecules yielded [1,3,4] oxadiazole. The antimycobacterial activity of these derivatives was tested using the (LJ) agar technique against Mycobacterium tuberculosisH37Rv (MTCC200) utilizing isoniazid and rifampicin as a reference standard against Mycobacterium tuberculosisH37Rv (MTCC200).[38]

Raval, et al., (2014), proposed the s-(5-(pyridine-4-yl)-1, 3,4-oxadiazol-2yl)-2((substituted phenyl) amino) ethanethiol from substituted 1,3,4-oxadiazole. Synthetic compounds were tested for antitubercular activity against mycobacterium tuberculosis h37rv (atcc27294). As a reference standard, rifampin was employed.[39]

Somani, et al., (2011), developed N'-substituted-2-((5-(pyridine-4-yl)-1,3,4- oxadiazol-2-yl) thio) acetohydrazide. Using MTT test in MT-4 cells, antiviral efficacy against different types of strains such as HIV-2 ROD and HIV-1IIIB was examined using a synthesis of substituted1,3,4-oxadiazole. The reference standard was nevirapine. These compounds were also tested for cytotoxicity in uninfected mt-4 cells using the MTT assay.[40]

Gan, et al., (2016), produced (1e, 4e) -1-(substituted)-5-(4-(2-((5-substituted) -1,3,4-oxadiazol-2-yl) thio) ethoxy) phenyl) Penta-1,4-dien-3-one by utilizing substituted 1,3,4-oxadiazole as a starting material and benzoic acid as a catalyst. Using ribavirin as a reference standard, the antiviral activity of produced compounds was tested against (TMV).[41]

Malhotra, et al., (2017), have tweaked the formula (Z) -2- [(1, 1-biphenyl)-4-yl]-2- [(1, 1-biphenyl)-4-yl]-2- [(1, 1-biphenyl)-4- -3-(1-((substituted)amino) ethyl) -3-(1-((substituted)amino) ethyl) -2,3-dihydro-1,3,4-oxadiazol-2yl) phenol, utilising substituted 1,3,4-oxadiazole as a starting material and 4-biphenyl carboxylic acid as a catalyst. Antioxidant activity was measured in terms of hydrogen peroxide scavenging activity.[42]

Rahul, R., et al., (2016), proposed 5-(4-(4-chlorophenyl) thiazol-2-yl)-3-(4-chlorophenyl) thiazol-2-yl)-3-(4-chlorophenyl) thiazol-2-y (substituted benzyl) -1,3,4-oxadiazole-2(3H)-thione using a substituted 1,3,4-oxadiazole and tested for antioxidant activity utilizing a variety of methodologies, including hydrogen peroxide scavenging, nitric oxide scavenging, and the DPPH assay.[43]

II. CONCLUSION

Different synthetic methods were discussed in this review article, and it is very clear that all the methods discussed for the synthesis of oxadiazole derivatives are efficient it has been found that oxadiazole molecules and their derivatives are present in many biologically active molecules showing broad-spectrum medicinal activity, against a different type of cancer, most of the work is done on cancer and animal viruses, but none on plant viruses.

Hence an attempt should be made in the future to see the impacts of oxadiazole derivatives on different plant viruses. which can give a contribution to protecting different crops against plant viral diseases.

III. ACKNOWLEDGEMENT

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