Section A-Research paper
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COMBINED STUDY ON MEDICINAL SIGNIFICANCE OF OXADIAZOLE AND TRIAZOLE ANALOGUES

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Abstract

Oxadiazole and triazole, along with their other derivatives that have been investigated, are members of an important family of compounds that are used in the process of creating new pharmaceuticals. A wide range of pharmacological effects may be attributed to these substances. In recent years, the importance of newly synthesised oxadiazole and triazole derivatives, which have been investigated for their chemical and biological activity, has become increasingly evident. These compounds have been the subject of production and research efforts. In the previous study, it was shown that a synthetic modification of an oxadiazole and triazole ring had

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a greater efficacy along with enhanced potency and decreased toxicity. This discovery was made possible by the fact that the modification was synthetic. The purpose of this review is to present you with an overview of the research that has been conducted up to this point on oxadiazole and triazole and the biological roles that they serve.

Keywords: Oxadiazole, Triazole, Chemical analogs, Biological activities

INTRODUCTION

The pharmaceutical industry has investigated heterocyclic moieties in an effort to create new types of pharmaceutically active compounds. In particular, oxadiazole derivatives have proven useful in medicinal chemistry [1]. The usual formula for oxadiazole is $C_2H_2ON_2$, and it consists of two carbons, two nitrogens, one oxygen, and two double bonds. These dehydrating agents include phosphorous oxychloride, thionyl chloride, phosphorous pentaoxide, triflic anhydride, polyphosphoric acid, and the direct reaction of acid with (N-isocyanimino-)-triphenylphosphine, among others [2]. These reactions are used to prepare 1,3,4-oxadiazoles. Additional interesting properties, such as analgesic, antibacterial, antitubercular, anticonvulsant, and anti-hepatitis B viral activity, have been discovered in molecules containing variously substituted oxadiazole moieties [3].

For a medicinal chemist, investigating a novel agent is a formidable challenge [4]. Over the last decade, there has been an increase in the synthesis of heterocyclic systems with high nitrogen because of their value in a variety of applications, including propulsion, explosives, pyrotechnics, and chemotherapy [5]. Due to their synthetic and practical biological value, triazoles and their fused heterocyclic derivatives have attracted a lot of interest in recent years in the field of chemistry [6]. Since azolic derivatives like thiazole, triazole, oxadiazole, and thiadiazole are so useful in medicinal chemistry, they've been the subject of much research into their biological effects [7].

OXADIAZOLE DERIVATIVES AND CHEMICAL ANALOGS

New oxadiazole derivatives were synthesised by Dhara *et al.*, [Figure 1], and many of these compounds showed potent growth suppression against Mycobacterium smegmatis, Staphylococcus aureus, and Escherichia coli, as well as the fungus Candida albicans. A later minimum inhibitory concentration (MIC) experiment using the same bacteria verified the antibiotic activity [8]. The compound 5 g showed the most promise, with a MIC of 0.025 mM against two bacteria and fungus and a MIC of 0.1 mM against E. coli. The minimum inhibitory concentrations (MICs) of other active drugs against the chosen bacteria ranged from 0.313 to 5.0 mM. The binding modes of ligand 5g to the D-alanine: d-alanine ligase protein of *E. coli* and *S. aureus* were explored by docking simulations [9].

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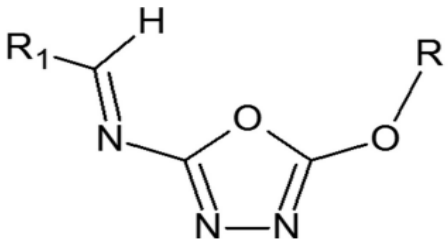

Fig. 1: 2-[2-substituted ethenyl]-5-(substituted methoxy)-1,3,4-oxadiazole derivatives

To create more effective cytotoxic and antibacterial drugs, Kaya *et al.*, developed and synthesised a variety of hydrazide and oxadiazole derivatives [Figure 2]. Compound 7c, which has a 1,3,4-oxadiazole ring and a 6-methoxy benzothiazole moiety, was the most effective inhibitor of A549 and MCF-7 tumour cell lines compared to the NIH/3T3 cell line [10].

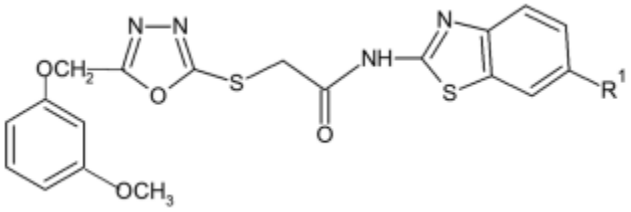

Fig. 2: N-(6-substitutedbenzothiazol-2-yl)-2-[(5-[(3-methoxyphenoxy)methyl]-1,3,4-oxadiazol-2-yl)thio] acetamide derivatives

Eight novel 1,3,4-oxadiazole derivatives with phenolic acid moieties and their diacylhydrazine precursors were reported by Mihailovic *et al.,* [Figure 3]. These compounds were characterised using spectroscopic methods and tested for their ability to scavenge stable 2,2-diphenyl-1-picrylhydrazyl (DPPH) radicals. The aromatic rings and the 1,3,4-oxadiazole contribute to resonance stabilisation of the generated phenoxyl radical, making phenolic 1,3,4-oxadiazoles derivatives much more effective DPPH scavengers than their comparable diacylhydrazine predecessors [11].

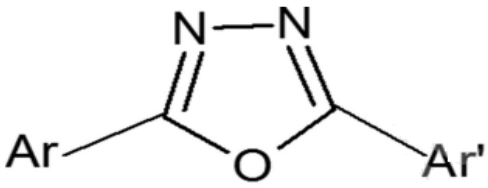

Fig. 3: 2,5-disubstituted-1,3,4-oxadiazole derivatives

Under standard thermal heating and microwave irradiation settings, Doronells *et al.,* [Figure 4] produced a series of novel 2,5-disubstituted 1,3,4-oxadiazoles by the reaction of acyl hydrazides with N-protected -amino acid [12].

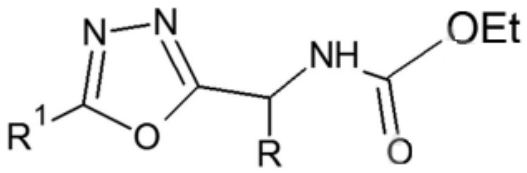

Fig. 4: 2,5-disubstituted-1,3,4-oxadiazole derivatives

1,3,4-oxadiazole compounds were described by Bala *et al.*, and their antibacterial effectiveness against chosen microbiological strains was compared to that of Penicillin and Cefixime [Figures 5 and 6]. Using QSAR analysis and a computer-assisted multiple regression analysis, they analysed the compounds' physicochemical and structural features, and came up with four reliable prediction models with high values of R2, R2adj, and the Fischer statistic [13].

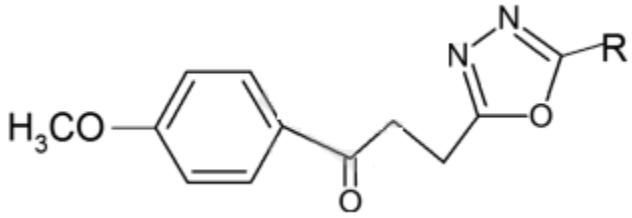

Fig. 5: 1-(4-methoxy-phenyl)-3-[5-(substitutedphenyl)-1,3,4-oxadiazol-2-yl]propan-1-one

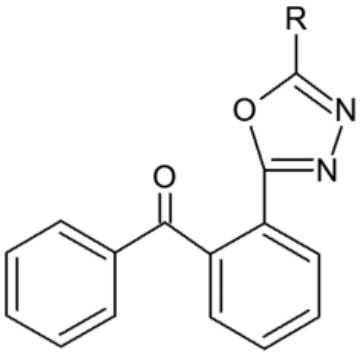

Fig. 6: [2-(5-substituted-phenyl-[1,3,4]oxadiazol-2-yl)-phenyl]phenyl-methanone

Thasneem *et al.*, synthesised chalcone-linked 1,3,4-oxadiazole derivatives and analysed them using IR, 1H NMR, and MASs SPECTRAL for characterization before testing them for anticancer efficacy against the human breast cancer cell line MCF 7. The MCF 7 cell line was very responsive to the derivatives [Figure 7] [14].

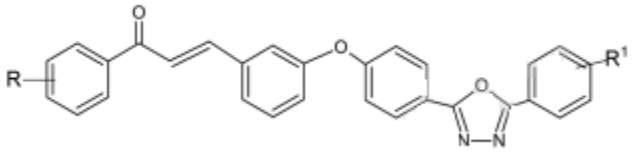

Fig. 7: Chalcone linked 1, 3, 4 – oxadiazole derivatives

By reacting different acid hydrazides with 4-(chlorophenyl) isocyanodichloride, Rashidi and Berad synthesised several new derivatives of N-(4-chlorophenyl) amino-5- aryl-1,3,4-oxadiazole [Figure 8]. All of the newly synthesised compounds had their structures verified using infrared spectroscopy (1H NMR), nuclear magnetic resonance (NMR), and mass spectrometry [15].

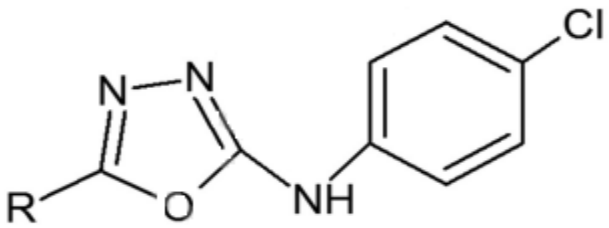

Fig. 8: N-(4-chlorophenyl) amino-5-aryl-1,3,4-oxadiazole

A variety of 2-substituted-5- thiopropylpiperazine (Piperidine)-1,3,4-Oxadiazoles derivatives were produced and analysed by Chen *et al.*, [Figure 9]. Compound 22, which was discovered to have atypical antipsychotic action without propensity for extrapyramidal symptoms, may serve as a starting point for the development of a new class of medicine for the treatment of schizophrenia based on the results of binding affinity studies with various receptors [16].

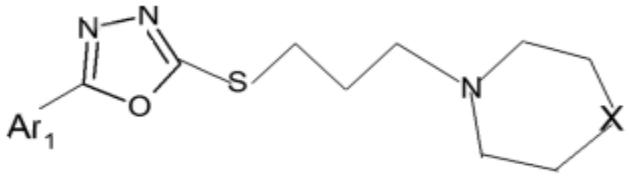

Fig. 9: 2-Substituted-5Thiopropylpiperazine (Piperidine)-1,3,4-Oxadiazoles Derivatives

Malhotra *et al.*, synthesised novel isonicotinohydrazide oxadiazole compounds [Figure 10]. The hydrazide moiety of isoniazid is substituted by 1,3,4-oxadiazole heterocycles in these structural changes of the first-line antitubercular medication to prevent in vivo acetylation by arylamine N-acetyltransferase, which forms the inert acetylated drug. Two Gram-positive bacterial strains (*Bacillus subtilis* and *S. aureus*), two Gram-negative bacterial strains (*Pseudomonas aeruginosa* and *E. coli*), and two fungus strains were tested for their susceptibility to the novel derivatives using the broth dilution technique (*C. albicans* and *A. niger*) [17].

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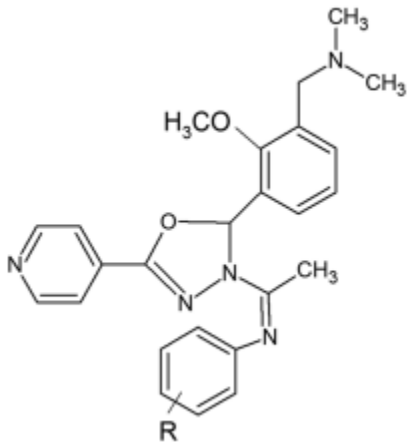


Fig. 10: (Z)-N-(1-(2-(3-((dimethylamino)methyl)-2- methoxyphenyl)-5-(pyridin-4-yl)- -1,3,4-oxadiazol-3(2H)- yl)ethylidene)benzenamine derivative

The intramolecular aza-Wittig reaction of the iminophosphorane intermediates under neutral circumstances was studied and synthesised by Ali *et al.*, yielding excellent products in the disubstituted 1,3,4-oxadiazole derivatives [Figure 11]. This novel synthetic strategy offers great promise in the synthesis of diverse 2,5-disubstituted 1,3,4-oxadiazoles, which might play an important role in the development of important physiologically active molecules or medications [18].

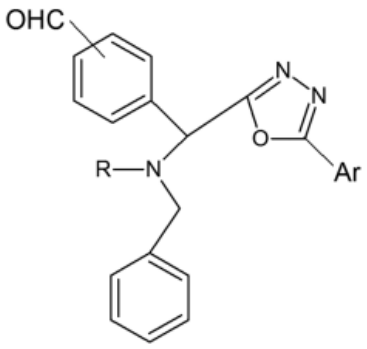


Fig. 11: Sterically congested 1,3,4-oxadiazole derivatives

Two-substituted-1,3,4-oxadiazole derivatives were produced by Dabholkar and Bhusari [Figures 12-14], and spectrum analysis was used to determine their structures. Additionally, the compounds were tested for antibacterial activity, and they showed promising results against both Gram-negative and Gram-positive bacteria [19].

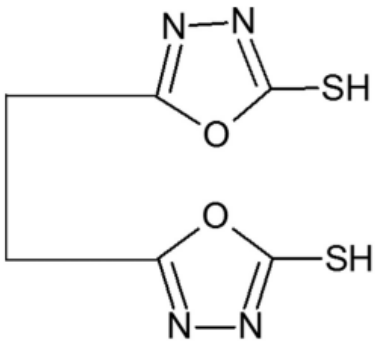


Fig. 12: 1,2[di-(2-Mercapto-1,3,4-oxadiazole-5yl)] ethane

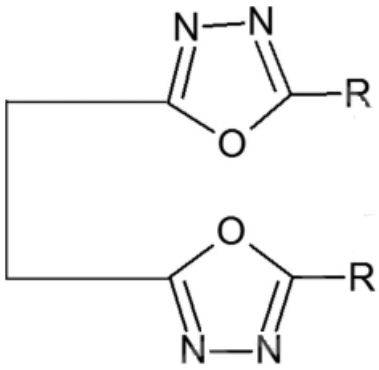


Fig. 13: 1,2[di-(2-Phenyl-1,3,4oxadiazole-5yl)] ethane

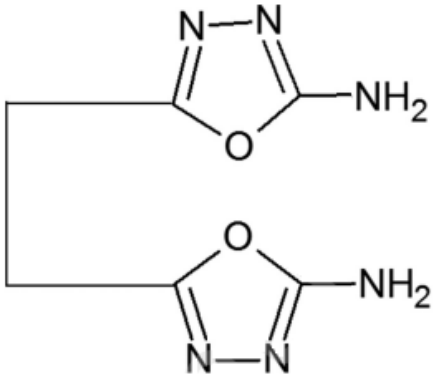


Fig. 14: 1,2[di-(2-Amino-1,3,4-oxadiazole-5 yl)] ethane

A series of 2-aryl-7-alkyl [Figure 15] or aryl-(1,3,4-)oxadiazole(3,2-a) (1,3,5) triazine-5-one, and 2-aryl-7-alkyl [Figure 16] or aryl- (1,3,4-)oxadiazole(3,2-a) (1,3,5)triazine-5-thione, were developed and synthesised by Deshmukh *et al.*, Spectral and analytical data have verified the structures of novel substances. Testing for antibacterial efficacy has been done on the newly synthesised chemicals [20].

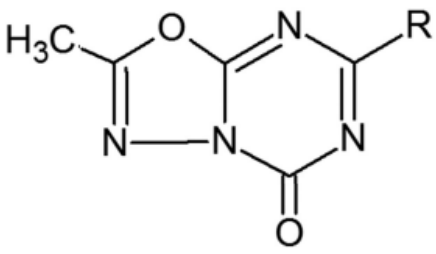


Fig. 15: 2-aryl-7alkyl or aryl-[1,3,4]-oxadiazolo[3,2-a] [1,3,5]triazin-5-one and 2-aryl-7alkyl

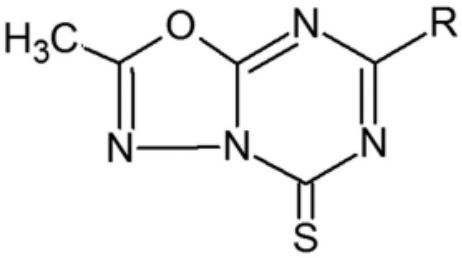


Fig. 16: 2-aryl-7alkyl or aryl–[1,3,4]oxadiazolo[3,2-a] [1,3,5]triazine-5-thione

In his research, Kaplancikli used carbon disulfide to aid in the ring closure process of 2-(pyrimidin-2-ylthio)acetohydrazide, yielding 5-[(pyrimidin2-ylthio)methyl)-1,3,4-oxadiazole-2(3H)-thione [Figure 17]. *Candida albicans*, *C. glabrata*, *C. tropicalis*, *C. krusei*, and *C. parapsilosis* were used in *in vitro* tests of the newly synthesised compounds, and the results were compared to those obtained with ketoconazole [21].

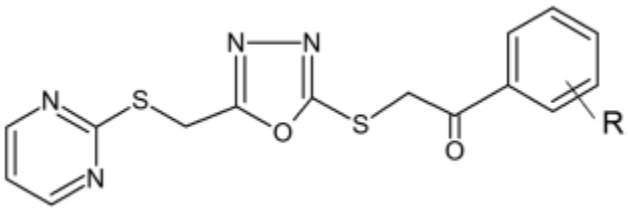


Fig. 17: 2-[5-[(Pyrimidin-2-ylthio)methyl]-1,3,4- oxadiazol-2-ylthio]acetophenone derivatives

Using ring closure reactions of benzohydrazides with carbon disulfide in the presence of ethanolic KOH, followed by an exchange with secondary amines at the 2nd position, Sahoo *et al.,* [Figure 18] synthesised some of the unique 5- phenyl- 1, 3, 4- oxadiazole- 2- thiol derivatives. IR, nuclear magnetic resonance, and liquid chromatography-mass spectrometry were used for spectral characterization of the newly produced substances. Anti-inflammatory and antimicrobial action was found in almost all of them [22].

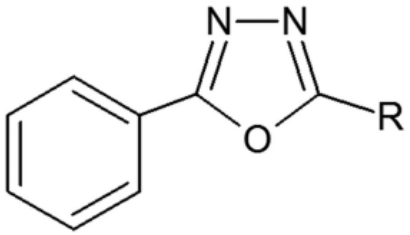


Fig. 18: 5- phenyl- 1, 3, 4- oxadiazole- 2- thiol derivative

Mayekar synthesised a series of new 6-bromonaphthalene-containing 1,3,4-oxadiazole derivatives (Figures 19 and 20). The freshly synthesised substances were analysed and characterised using analytical and spectral data. Several of these chemicals have shown promising antimicrobial action in tests [23].

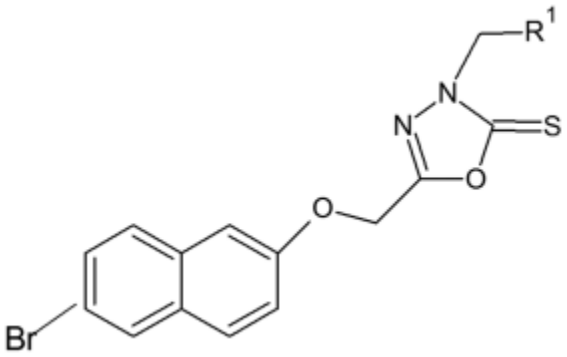


Fig. 19: 2-{[(6-bromo-2-naphthyl)oxy]methyl}-5- [(alkyl)thio]-1,3,4-oxadiazole

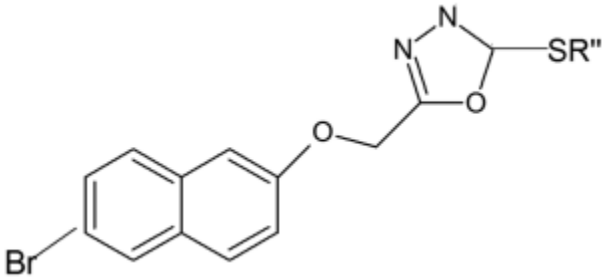


Fig. 20: 2-{[(6-bromo-2-naphthyl)oxy]methyl}-5-[(aryl) thio]-1,3,4-oxadiazole

TRIAZOLE DERIVATIVES AND CHEMICAL ANALOGS

The chemical formula for triazole is $C_2H_3N_3$, and it is a five-membered heterocyclic ring composed of two carbon and three nitrogen atoms. In addition, it occurs as the pyrrodiazole isomers 1,2,3-triazole and 1,2,4-triazole. (Fig. 21). Triazoles are odourless, colourless, or light yellow crystals that dissolve in water and alcohol and melt between 120 and 260 degrees Celsius. Compounds with five nitrogen atoms, like triazole, are extremely useful in medicinal chemistry

because of their many biological effects. These include, but are not limited to, anticonvulsant, antimicrobial, antiviral, antitubercular, antidiabetic, anti-inflammatory, anti-proliferative, antioxidant, anti-urease, and antimalarial properties [24].

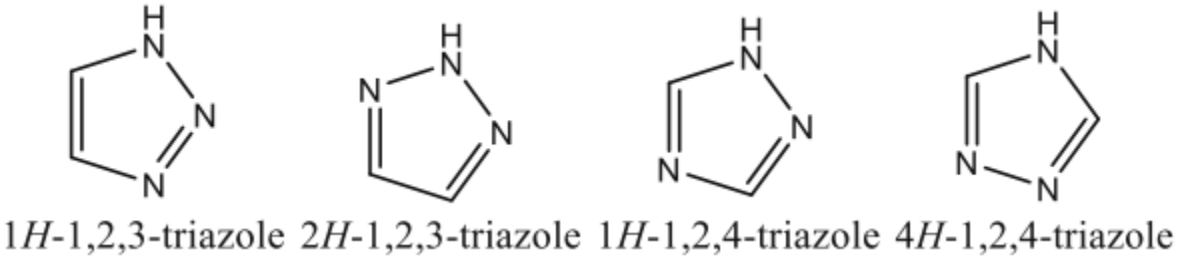
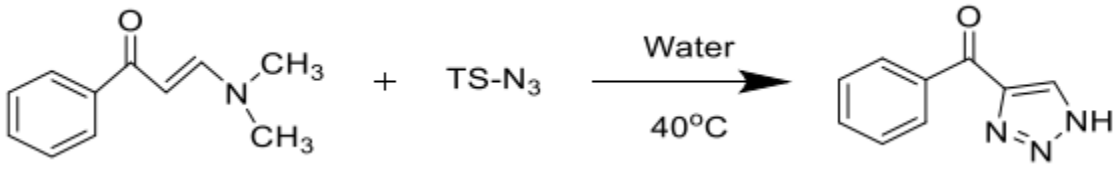


Fig. 21: Different isomeric forms of triazole

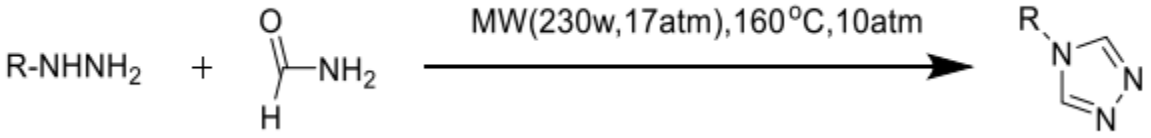
Synthetic approaches of triazoles

The article provides a concise summary of the methods used to synthesise and characterise triazole, as well as its pharmacological action. Water-mediated cycloaddition reactions of enaminone and tosilazide were described by Lu yang *et al.*, which allowed for the synthesis of 4-acyl-NH-1,2,3-triazole under moderate conditions (40 °C) and at a practical scale (Scheme 1) [25].



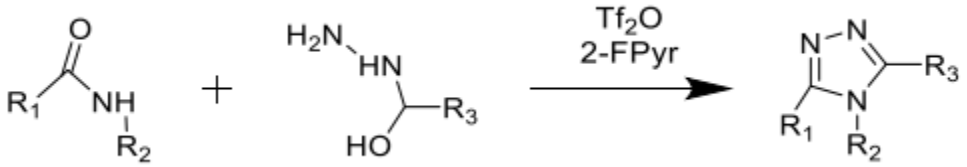
Scheme 1

The synthesis of 1,2,4 triazole from hydrazine and formamide under microwave irradiation and the observation that this reaction occurs in the lack of a catalyst efficiently demonstrates high functional group tolerance; Shelke *et al.,* (Scheme 2) [26].



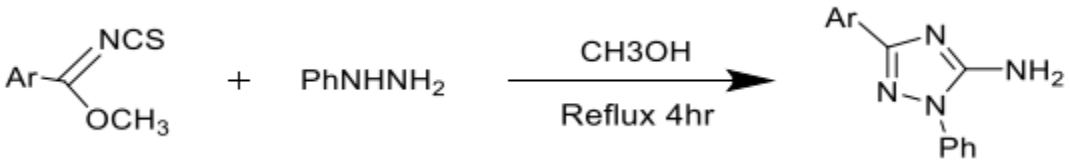
Scheme 2

The 3,4,5-trisubstituted 1,2,4-triazole moiety is a suitable leading group of Ru-catalyzed C-H arylation, as described by Bechara *et al.,* who synthesised it from 2^0 amides and hydrazides by triflic anhydride activation followed by the microwave cyclodehydration (Scheme 3) [27].



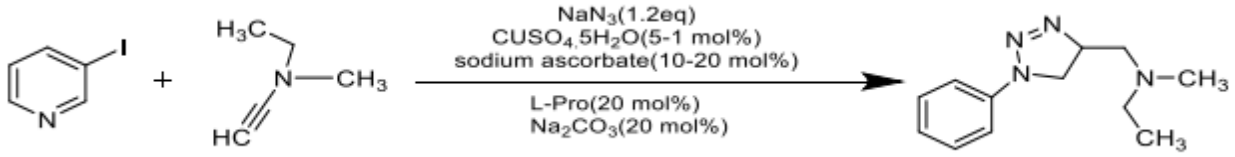
Scheme 3

By using cyanamide as the nitrogen source and NBS as the oxidant, Yin *et al.*, were able to synthesis a substituted triazole in high yield in the absence of a catalyst. High yields of 1,2,4-triazole derivatives may be made by cyclizing the substituted product N-cyanobenzimidate (Scheme 4) [28].



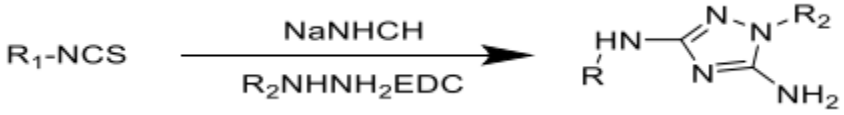
Scheme 4

Disubstituted 1,2,3 triazoles were described by Faldiman *et al.*, from azides. Without the generation of potentially unstable organic azide intermediates, they are produced in high yield from readily accessible aromatic and aliphatic halides (Scheme 5) [29].



Scheme 5

Isothiocynate, mono-substituted hydrazines, and sodium hydrogen cyanamide were used to create a new substituted 3,5-diamine-1,2,4- triazole, as described by Liu *et al.*, (Scheme 6) [30].



Scheme 6

CONCLUSION:

This review article focuses on research work that was published in the literature for chemical analogues of oxadiazole and triazole compounds. The literature includes studies that were

conducted on a variety of compounds. A wide number of researchers contributed to the study's findings and findings. A specific moiety of the triazole molecule is responsible for a range of biological functions, and this moiety is present in the molecule. It is possible to raise the relevance of the triazole moiety by doing further study on the many different ways in which it may be replaced. This will make it possible to build more effective treatments that are able to make large long-term commitments. Detailed information on oxadiazole and triazole analogues, which are potent compounds that have been reported for particular pharmacological activity, has been presented in this research. Additionally, the approach or methodology that was used in the evaluation procedure has also been discussed. There is an urgent need for further study to be carried out in order to investigate the effects of oxadiazole and triazole for a broad variety of conditions that are notoriously difficult to treat using the information that is currently available in the field of medicine.

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