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Diazoles: Promising and Versatile Class To Design Anti Microbial Agents

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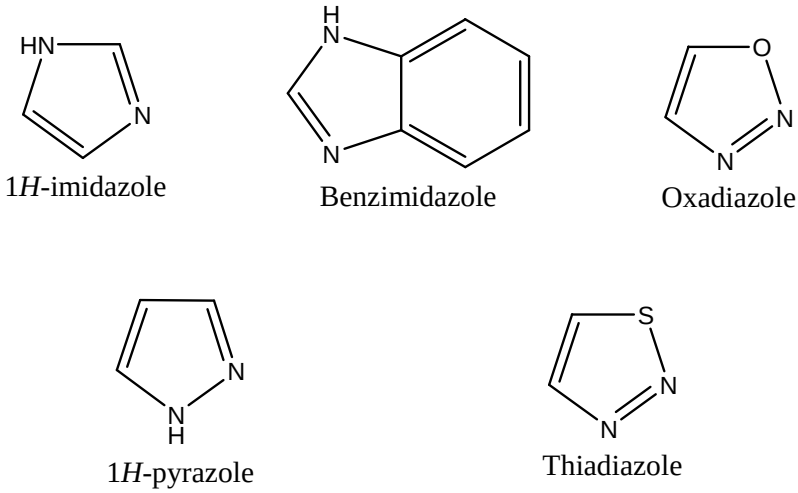
Abstract: Diazoles is highly privileged structure which includes imidazole, benzimidazole, pyrazole and oxadiazole and its derivatives exhibit wide range of pharmacological activity. Various biologically active synthetic compounds have five-membered nitrogen-containing heterocyclic ring in their structures. Given review shows diazoles structural frameworks can be described as privileged structures to design novel antimicrobial agents. Resistant to number of antimicrobial agent among a variety of clinically significant species of bacteria is becoming increasingly important global problem. This review has basic information about general synthesis and antimicrobial activity work for development in medicinal chemistry field.
Key words: Diazole; Imidazole; Benzimidazole; Pyrazole; Oxadiazole; Antimicrobial activity.

1. Introduction

Diazole refers to either one of a pair of isomeric chemical compounds with molecular formula $C_3H_4N_2$, having a five-membered ring consisting of three carbon atoms and two nitrogen atoms. Five membered and two nitrogen heteroatom containing heterocyclic compounds like Imidazole, Benzimidazole, Pyrazole, Oxadiazole, and Thiadiazole possess varieties of biological activity. These entire compounds collectively known as diazole.

Various biologically active synthetic compounds have five-membered nitrogen-containing heterocyclic ring in their structures [1-4]. Structural frameworks have been described as privileged structures and in particular, N containing polycyclic structures have been reported to be associated with a wide range of biological activity.

In the field of five membered heterocyclic structures imidazole (1, 3-Diazole) nucleus shows various properties. The high therapeutic properties of the imidazole related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents. Imidazole drugs have broadened scope in remedying various dispositions in clinical medicines. Medicinal properties of imidazole and benzimidazole include anticancer, b-lactamase inhibitors, 20-HETE (20-Hydroxy-5,8,11,14-eicosatetraenoic acid) synthase inhibitors, carboxypeptidase inhibitors, hemeoxygenase inhibitors, antiaging agents, anticoagulants, anti-inflammatory, antibacterial, antifungal, antiviral, antitubercular, antidiabetic and antimalarial [5-17].



1,3,4-Oxadiazoles are versatile lead compounds for designing potent bioactive agents. This interesting class of heterocyclic compounds shows broad spectrum of biological activities. Substituted 1, 3, 4-oxadiazoles have revealed antimicrobial [18], anti-inflammatory [19], antimycobacterial [20], analgesic [21], anticonvulsant [22], antihypoglycemic [23], and insecticidal properties [24]. Compounds possessing oxadiazole moieties show anticancer [25, 26] and tyrosinase inhibitory activities [27]. Oxadiazoles are used as fluorescent whiteners and also act as muscle relaxants [28].

Thiadiazole is a heterocyclic compound featuring both two nitrogen atom and one sulfur atom as part of the aromatic five-membered ring. Thiadiazole and related compounds are called 1, 3, 4-thiadiazole (two nitrogen and one other heteroatom in a five-membered ring). They occur in nature in four isomeric forms as. 1,2,3-thiadiazole; 1,2,5-thiadiazole; 1,2,4-thiadiazole and 1,3,4-thiadiazole. 1, 3, 4-thiadiazole are important because of their versatile biological actions. In particular, compounds bearing the 1, 3, 4-thiadiazole nucleus is known to have unique antibacterial and anti-inflammatory [29] activities. Differently substituted thiadiazole moieties have also been found to have other interesting activities such as analgesic, antimicrobial [30, 31], antitubercular, anticonvulsant [32], antidiabetic [33] and other activities.

A summarize review of Diazoles associated with large number of antimicrobial activities is presented below.

2. Imidazole and Benzimidazole

2.1 Compounds Having Imidazole or Benzimidazole Nucleus

Imidazole is a planer five-member heterocyclic ring with 3C and 2N atom and in ring N is present in 1st and 3rd positions. The imidazole ring is a constituent of several important natural products, including purine, histamine, histidine and nucleic acid. Imidazole is also known as 1, 3-Diazole.

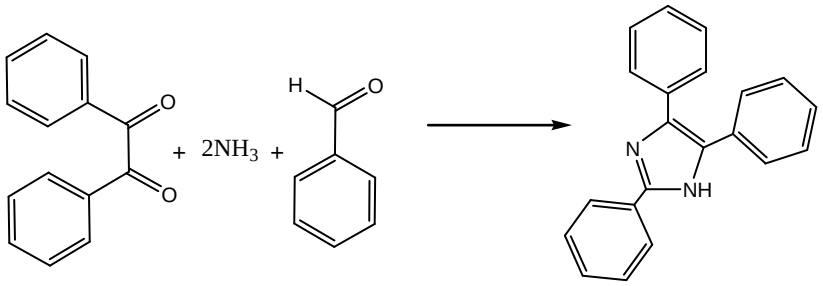
Benzimidazole is a fused aromatic imidazole ring system where a benzene ring is fused to the 4 and 5 positions of an imidazole ring. Benzimidazole is also known as 1, 3-benzodiazoles.

Other then their pharmacological actions they also function as dyestuffs catalysts and polymerizing agents. 2-nitroimidazole (azomycin) and 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole (metronidazole) are anti bacterial agent with particular applications as trichomonacide. Along with metronidazole other nitroimidazoles (misonidazole, metrazole and clotrimazole) are important anti cancer drugs.

2.2 General synthesis of Imidazole

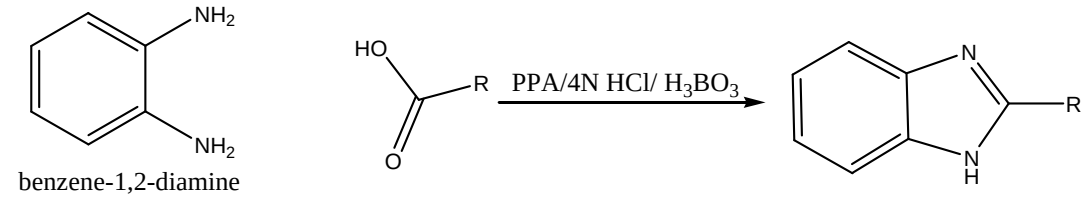
Imidazoles were prepared in 1858 from glyoxal and ammonia. Several approaches are available for synthesis of imidazoles as, Radiszewski synthesis, dehydrogenation of imidazolines, from alpha halo ketones, Wallach synthesis, from aminonitrile and aldehyde and Marckwald synthesis.

It consist of condensing a dicarbonyl compound such as glyoxal, α- keto aldehyde or δ-diketones with an aldehyde in the presence of ammonia, benzyl for instantce, with benzaldehyde and two molecule of ammonia react to yield 2,4,5-triphenylimidazole. Formamide often proves a convenient substitute for ammonia.



Benzil Benzaldehyde 2,4,5-triphenyl-1*H*-imidazole

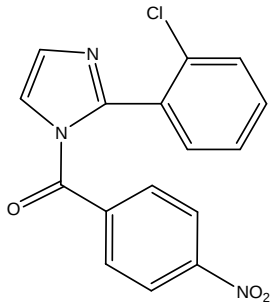
Benzimidazoles have most frequently been prepared from the reaction of 1, 2-diaminobenzenes with carbonyl-containing compounds (Carboxylic acids, Aldehyde, etc.) under harsh dehydrating reaction conditions, utilizing strong acids such as polyphosphoric acid, hydrochloric acid, boric acid, or p-toluenesulfonic acid. The use of milder reagents, particularly Lewis acids, inorganic clays [34], or mineral acids, has improved both the yield and purity of this reaction.



benzene-1,2-diamine (Ortho Phenylenediamine) Carboxylic acid Benzimidazole

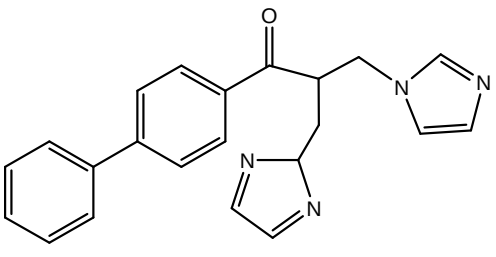
2.3 Antimicrobial activity

Deepika Sharma et al have synthesized 2-(substituted phenyl)-1H-imidazole and (substituted phenyl)-[2-(substituted phenyl)-imidazol-1-yl]-menthanone analogues **(2a)** and screened for antimicrobial activity against gram positive, Gram negative, and fungal species. Norfloxacin used as standard and following compound is most potent. [35]



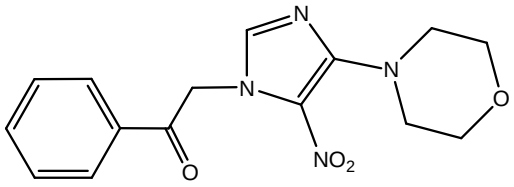
(2a)

Daniele Zampieri et al synthesized bis-imidazole derivative **(2b)** and screened for antifungal and anti mycobacterial activity. All compounds in this series showed moderate to good activity against *Candidaalbicans* and *Candida glabrata.* Miconazole used as reference drug. [36]



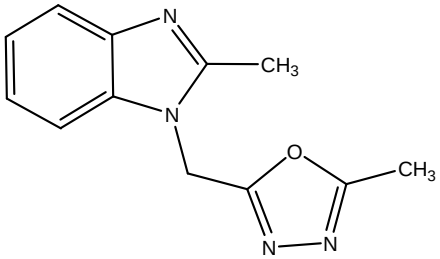
(2b)

Dorota Olender et al. synthesized nitroimidazole derivative **(2c)** and tested for their antifungal activity using the standard nutrient method against *sclerophoma pityophila*. This compound shows more potent fungistatic activity. [37]



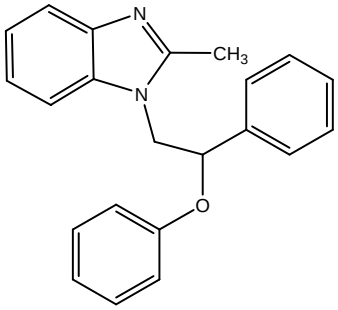
(2c)

K. M. Ansari et. al. Synthesize 2-methyl-1-((5-methyl-1,3,4-oxadiazol-2-yl)methyl)-1H-benzo[d]imidazole **(2d)** which shows antimicrobial activity. [38]



(2d)

Ozden ozel guuven *et. al.* reported synthesis of 2-methyl-1-(2-phenoxy-2-phenylethyl)-1H-benzo[d] imidazole **(2e)** which shows anti bacterial and antifungal activity.[39]



(2e)

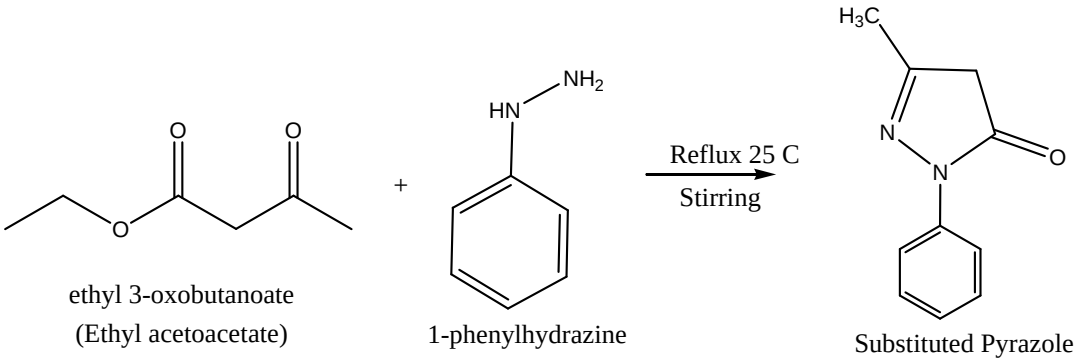
3. Pyrazole (1,2-Diazole)

3.1 Compounds Having Pyrazole Nucleus:

Pyrazole refers to the class of simple aromatic ring organic compounds of the heterocyclic series characterized by a 5-membered ring structure composed of three carbon atoms and two nitrogen atoms in adjacent positions. Being so composed and having pharmacological effects on humans, they are classified as alkaloids, although they are rare in nature. In 1959, the first natural pyrazole, 1- pyrazolyl-alanine, was isolated from seeds of watermelons. [40]

3.2 General synthesis of pyrazole

Pyrazoles are produced synthetically through the reaction of α,β-unsaturated aldehydes with hydrazine and subsequent dehydrogenation.



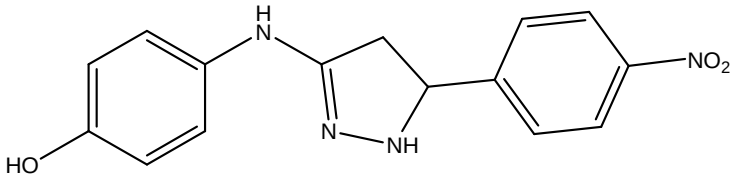
ethyl 3-oxobutanoate
(Ethyl acetoacetate)

1-phenylhydrazine

Substituted Pyrazole

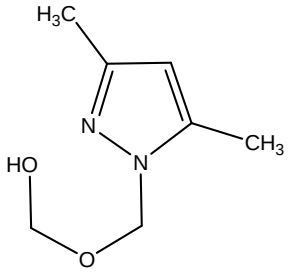
3.3 Antimicrobial activity

S. K. Sahu *et. al.* synthesized novel pyrazoline derivatives. The one derivative **(3a),** showed potent Antimicrobial activity: Antibacterial activity; by muller hinton agar (Hi-media) plates by agar diffusion cup-plate method for Staphylococcus aureus, salmonella typhi & E. coli. Antifungal activity; was tested on sabouraud dextrose agar plates by cup-plate method against Candida albicans & Aspergillus niger). [41]

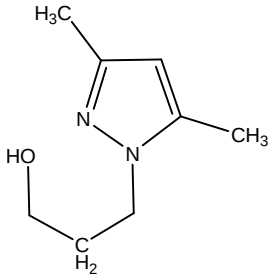


(3a)

Smaail Radi ***et al,*** synthesized novel pyrazole derivatives **(3b-3c)** and these derivatives were evaluated for their antimicrobial activity determined by agar plate diffusion technique. Antibacterial activity: Against antibacterial strains *Escherichia coli* and determined by agar plate diffusion method. Antifungal activity: Against two fungal strains *Saccharomyces cerevisae* and *Fusarium oxysporum f. sp.ablicans*. [42]

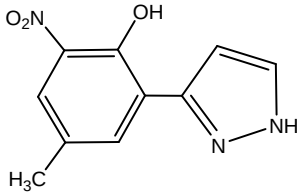


(3b)



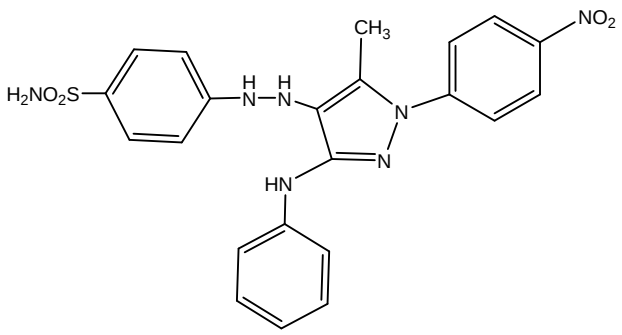
(3c)

J. K. Desai *et. al.* reported synthesis of 4-methyl-2-nitro-6-(1H-pyrazol-3-yl) phenol. [43]



(3d)

Rajiv Jain *et. al.* reported synthesis of 4-(2-(5-methyl-1-(4-nitrophenyl)-3-(phenylamino)-1H-pyrazol-4-yl) hydrazinyl) benzenesulfonamide.[44]



(3e)

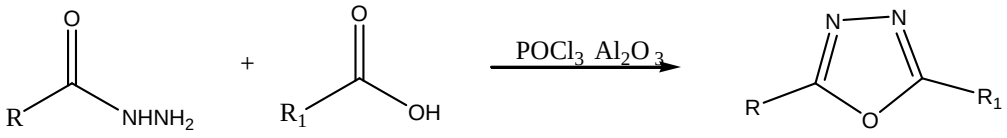
4. Oxadiazole

4.1 Compounds Having Oxadiazole Nucleus

Substituted 1,3,4-oxadiazoles are of considerable pharmaceutical interest. 2,5-Substituted diphenyl-1,3,4-oxadiazoles are associated with diverse biological activities by the virtue of -N = C-O- grouping. In the view of wide range of biological properties associated with 1,3,4-oxadiazole.

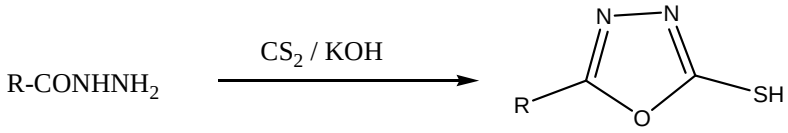
4.2 General synthesis of Oxadiazole

Khalid M. Khan et. al. reported the microwave assisted synthesis of such diaryl-1, 3, 4-oxadiazoles. In this a number of commercially available hydrazides (a) were treated with different carboxylic acids (b) in the presence of phosphorus oxychloride to afford the desired products (c). [45]



(a) **(b)** **(c)**

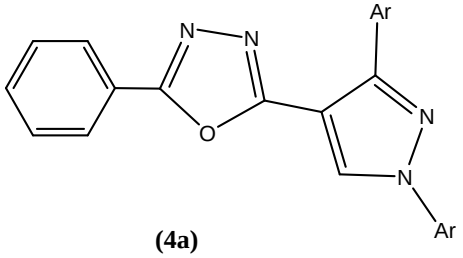
M.C Hosur *et. al.* reported synthesis of 2-mercapto-5-aryl-1, 3, 4-oxadiazole (d) from the properly substituted acid hydrazide (a) in presence of CS2/KOH. [46]



(a) **(d)**

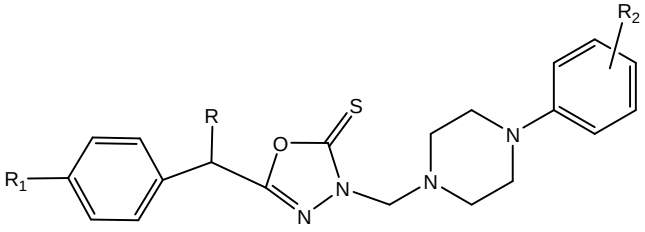
4.3 Antimicrobial activity of some Oxadiazole derivatives

Ajjanna M. Sridhara, Kallam R *et.al*. reported novel 2, 5-disubstituted 1,3,4-oxadiazoles **(4a)** have been conveniently synthesized by oxidative cyclization of pyrazolylaldehyde Nacylhydrazones promoted by iodobenzene diacetate under mild conditions. All the compounds were tested in vitro for their antibacterial activity against Gram positive bacteria namely, Staphylococcus aureus, Bacillus subtilis and two Gram-negative bacteria namely, Escherichia coli and Pseudomonas aeruginosa. All the synthesized compounds were also tested for their inhibitory action against two strains of fungus. [47]



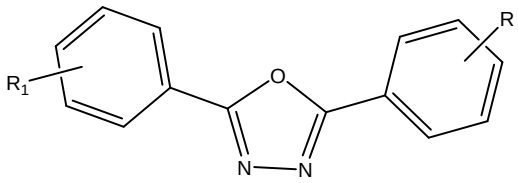
(4a)

Om Prakash *et. al.* reported acid hydrazides derived from ibuprofen and 4-methylthiophenyl acetic acids **(4b)** have been subjected to cyclization with carbon disulphide under basic conditions to yield 1,3,4-oxadiazol-2-thiones which on aminomethylation with formaldehyde and secondary amines afforded a series of Mannich bases.. The newly synthesized compounds were evaluated for their antimicrobial activities. [48]



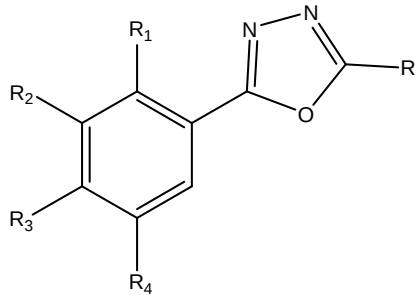
(4b)

K. Manjunatha *et. al*. synthesized 1,3,4-oxadiazole derivatives by the ring closure reactions of various acylhydrazides with carbon disulphide and with aromatic acids in POCl3. After structural elucidation, all the synthesized compounds were evaluated for their antimicrobial activity against Escherichia coli, Staphylococcus aureus and S. epidermidis. [49]



(4c)

B. Chandrakantha *et.al*. reported synthesis, Characterization and biological activity of some 1,3,4-oxadiazole **(4d)** bearing 2-fluoro 4-methoxy phenyl moity. [50]



(4d)

5. Conclusion:

This review thus gives an overview of the various synthetic routes used to form antimicrobial diazoles like imidazole, benzimidazole, pyrazol and oxadiazole moieties as well as the reactions the molecule undergoes to yield various other important molecules. It also highlights the antimicrobial properties of the five member two nitrogen atom containing rings or diazoles collectively and the availability of varied drugs in the market containing the ring. Thus this paper proves to be significant for further research work on the bioactive diazoles ring.

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