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A short review of some pyrazole derivatives and their applications

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ABSTRACT

Pyrazole is a heterocyclic organic compound having a 5-membered cyclic ring structure with two neighbouring nitrogen and three carbon atoms. A large number of pyrazole heteroatom linked derivatives were synthesized for their useful applications. There are several pyrazole heterocyclic motifs found in a number of small molecules that possess a wide range of pharmaceutical and agricultural activities. There is an increase in the interest of synthesizing and analysing different properties shows possible applications of pyrazole derivatives. Our research efforts have been focusing on different aspects of pyrazoles including facile synthesis and their behaviour investigating in their biological activities. In this short review article, the aim is to show the trends in the research on pyrazole derivatives.

KEYWORDS: Pyrazole derivatives, synthesis, applications, characterization, bioactivity, etc.

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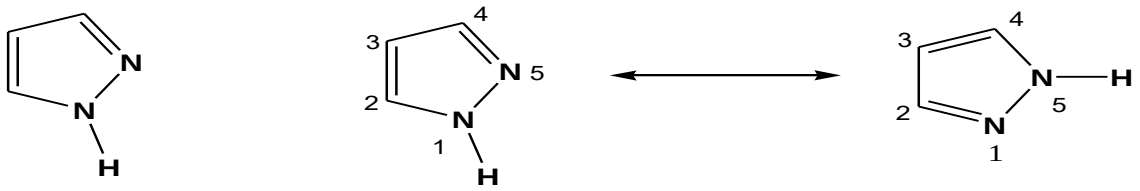
INTRODUCTION

Compounds classified as heterocyclic, probably constitute the largest and most varied family of organic compounds and Heterocycles dominate the fields of biochemistry, medicinal chemistry, dyestuffs, etc. Over the years increasing attention towards pyrazole derivatives which are synthesized based on pyrazole as the central core. The central core contains a five membered heterocyclic compound with two adjacent nitrogen atoms[1] (Scheme 1). Pyrazole derivatives have great interest in agrochemical, pharmaceutical and chemical industries[2].

In this short review, we want to cover the recent studies on pyrazole derivatives mostly published within the last few years. There are several aspects that will be explained referring to the works of the leading groups in the area of pyrazole derivatives shows four different points of description; **i) Different approaches in synthesis, ii) characterization of various properties, iii) bioactivities of pyrazole derivatives, iv) other applications of pyrazole derivatives.**



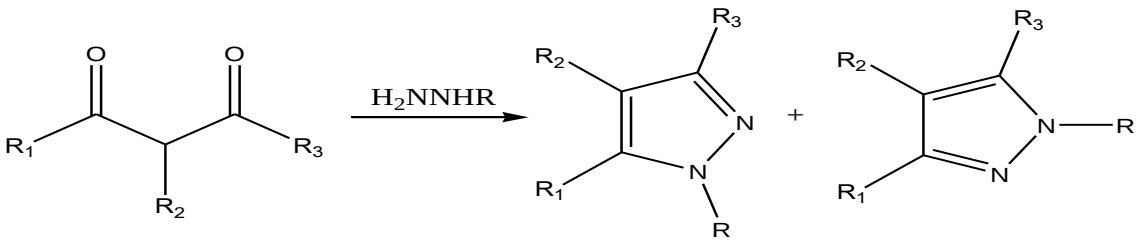
Pyrazole

Resonance structure of pyrazole

Scheme 1

i) Different Approaches in Synthesis

There are various synthetic approaches in synthesizing new pyrazole derivatives. The most common synthetic approach to pyrazole derivatives involves the reaction of 1, 3-diketones with hydrazine derivatives[1, 3] (Scheme 2).



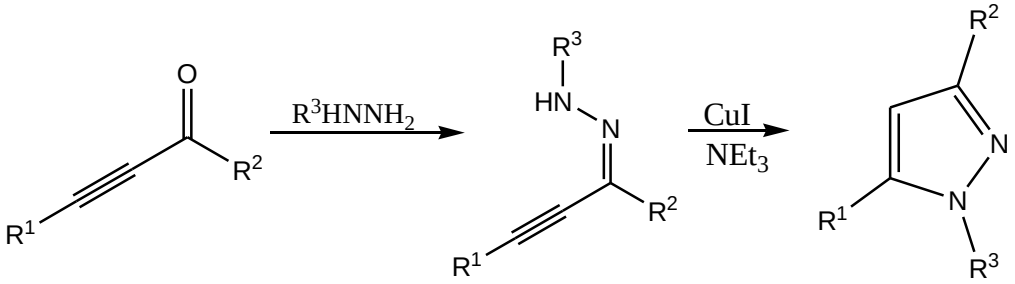
R= alkyl, aryl, heteroaryl, etc.

Scheme 2

Synthesis of Pyrazole via 1, 3-diketones with hydrazine derivatives

One of the major concerns is to exhibit simple routes for the synthesis of pyrazole derivatives. The other important area of research in synthetic organic chemistry is "Green Chemistry''. The Green Chemistry here refers to the reactions that can be carried at room temperature with no organic solvent required and no waste production[4]. For instance, solvent free heterocyclic compound synthesis includes ultrasound and microwave irradiation. Microwave irradiation has been widely exploited in the last decades to run various number of organic synthesis. Usually three types of solvent free procedures can be coupled with dielectric heating provided by a microwave source: reaction amongst neat reagents, reaction among supported reagents on mineral solid supports and phase transfer catalysis reactions. Among the three types of solvent-free procedures, the neat reagent one is the most routinely employed due to its easy work-up and negligible use of solvents. In particular, applying Microwave Assisted Organic Synthesis (MAOS) becomes more common in heterocyclic chemistry and especially in pyrazole derivative synthesis[5]. The other possibility in contributing to green chemistry is to carry the synthesis of pyrazole derivatives in aqueous medium.

Synthesis of pyrazoles via electrophilic cyclization of α, β-alkynic hydrazones by copper (I) iodide was reported. Upone reacting with copper (I) iodide in the presence of triethylamine in refluxing acetonitrile, α, β-alkynic hydrazones underwent electrophilic cyclization to result in novel pyrazole derivatives with high yields[6] (Scheme 3).



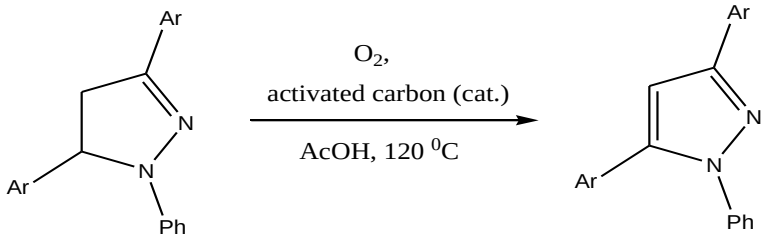
R^1= aryl, alkyl, ferrocenyl
R^2= H, methyl, phenyl
R^3= alkyl, aryl

Scheme 3

Synthesis of pyrazoles via electrophilic cyclization of ?, ?-alkynic hydrazones by copper (I) iodide

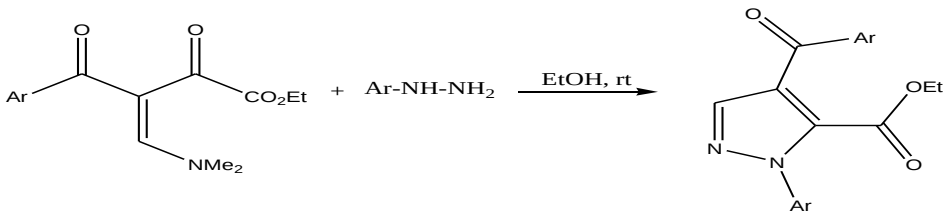
The use of water has many advantages since water is cheap, easily available and environmentally friendly. Water is preferable as a solvent from both an economical and environmental point of view. The unique structure and physicochemical properties of water establish particular interactions of polarity,

hydrogen-bonding, hydrophobic effects in addition to trans-phase interactions that might influence the course of a reaction. In the presence of activated carbon, Hantzsch 1,4-dihydropyridines and 1,3,5-trisubstituted pyrazolines were aromatized with molecular oxygen to the corresponding pyrazole in excellent yields as reported by Nakamichi, N. *et al.*[7] (Scheme 4).



Scheme 4

Usually pyrazole derivatives are synthesized as a series of molecules. For this reason, combinatorial synthesis is also mentioned in the current literature[8]. In addition to green chemistry and combinatorial synthesis approaches to novel pyrazole derivatives generation, there are metal assisted synthetic methods developed[9]. Extension of metalmediated cyclization reaction led to the synthesis of aluminated pyrazoles. Aluminated heteroles can be produced by in parallel addition/ intramolecular 5-endo-dig metal-mediated cyclization enabling the preparation of 1, 3, 5-trisubstituted 4-aluminopyrazoles[10]. A series of 4-substituted 1H-pyrazole-5-carboxylate was synthesized by cyclocondensation reaction of unsymmetrical enaminodiketones with ter-butylhydrazine hydrochloride or carboxymethyl hydrazine by Martin, R. *et al.*[11]. These compounds were obtained regiospecifically and in very good yields (Scheme 5).



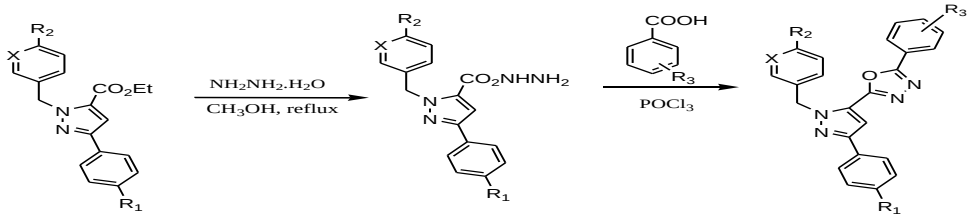
Scheme 5

The other important sub-class of pyrazole derivatives are the fluorinated compounds. There is transition-metal mediated C-F bond formation that has high attention for the construction of organic fluoro compounds[12]. This review is a short description of an on-going research area of pyrazole synthesis, though there are a lot of synthetic methods developed for generating novel pyrazole derivatives. However, generally these methods need organic solvents. In addition to the use of organic

solvents, low yield percentage is another major challenge in pyrazole synthesis. Solvent less reaction are rapid, region or chemo-selective. These reactions result in high yields and have environmental and economic advantages. We believe that these solvent less reactions represent a possible solution to the challenges in the synthesis of pyrazole derivatives. The use of water will also be helpful in overcoming some major issues of pyrazole derivative synthesis[13].

ii) Characterization of various properties

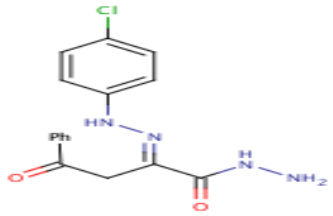
It is necessary to study different properties of pyrazole derivatives since investigation of these properties is compulsory because of wide biological activities of the derivatives. There are various physical properties of pyrazole derivatives which are important. For example, the photochemical property of phthalocyanines substituted with four 3,5-dimethylpyrazole-1-methoxy group and fluorescence activity of metal complexes of 1,3-diphenyl-1H-pyrazole-4-carboxaldehyde Schiff bases have been reported[14]. Cationic surfactants and their tin and copper complexes were derived based on the pyrazole core. Surface activity of these surfactants was studied. The presence of the heterocyclic core led to the relatively higher values of the surface tension of these surfactants. In the study on phthalocyanines with and without metals typical electronic spectra with two strong absorption regions were observed. The pyrazolyl 1,3,4-oxadiazole derivatives, the absorption spectra and fluorescence characteristics were correlated with substituents on benzene rings[15] (Scheme 6).



R^1= H, Cl, OCH_3 R^3= H, Br, CH_3
R^2= H, Cl, t-Bu X= O & N

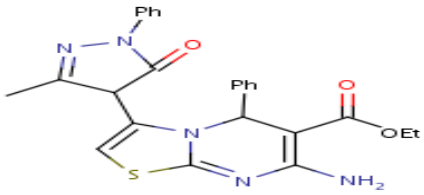
Scheme 6

In a very recent report on pyrazole-metal complexes, UV-Vis was employed for controlling thermodynamic stability. Eman M. Flefel et.al have reported the new substituted pyrazole, thiazole and 1,2,4-triazole derivatives were synthesized. The sugar hydrazones, their acetylated derivatives as well as their derived acyclic C-nucleoside analogs, and the thioglycosides of the 1,2,4-triazole derivatives were also prepared. The antitumor activity of some of the synthesized compounds were studied and a number of the tested compounds showed significant activities[16] (Scheme 7).



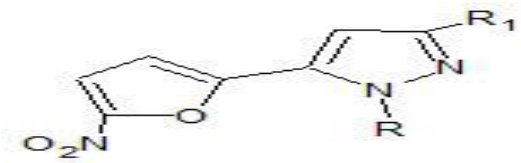
Scheme 7

Mohamed salahk youssef et.al., have synthesized Ethyl 7-amino-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-5-aryl-5*H*-thiazolo[3,2-a]pyrimidine-6-carboxylate was synthesized by the reaction of 4-(2-aminothiazole-4-yl)-3-methyl-5-oxo-1-phenyl-2-pyrazoline with arylidene ethyl cyanoacetate and it transformed to related fused heterocyclic systems *via* reaction with various reagents[17] (Scheme 8).



Scheme 8

Rao Jyothi et al., have synthesized a novel series of 1, 3, 5-trisubstituted pyrazoles by the cyclo condensation reaction of chalcones and substituted hydrazides by irradiation under microwave energy and also by conventional method. Compound 3g showed good activity against E. coli and P.aerugiosa. Compound 3j showed good activity against the fungus A. fumigatus[18] (Scheme 9).



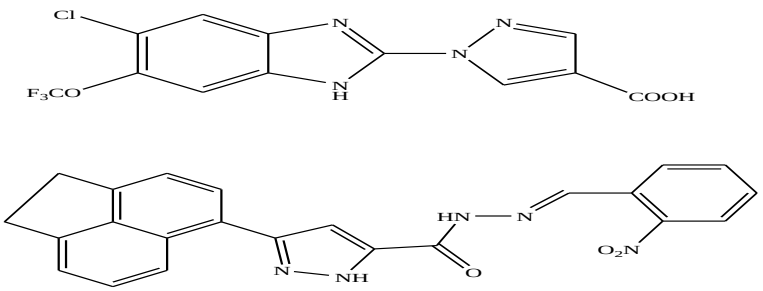
Scheme 9

Basic structural characterization of pyrazole derivatives includes spectroscopy, thermal analysis and other aspects. The detailed characterization by advanced techniques such as two/three- dimensional nuclear magnetic resonance (NMR) spectroscopy is not employed. Further, thermal analysis is done with the thin capillary method. In fact, thermo gravimetric analysis (TGA) measurements are required to

be performed prior to melting temperature determination of new organic molecules by differential scanning calorimeter (DSC). We think that the organic synthetic community and especially the contributors of the synthesis of pyrazole derivatives literature need to benefit from such methods of 2D-NMR, TGA and DSC in order to provide more reliable data on different physical properties of pyrazole derivatives. Overcoming such a challenge will be important for opening new routes for better understanding the properties of novel pyrazole core based organic molecules.

iii) Bioactivities of Pyrazole Derivatives

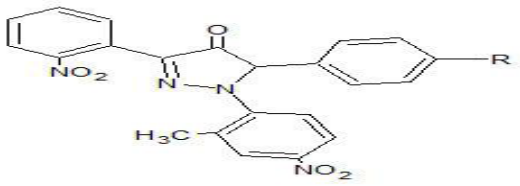
Pyrazole derivatives possess a wide range of bioactivities, including anti-inflammatory, anticonvulsant, anticancer and antifungal behaviour. In this section, we will describe some of the current studies about the inhibition ability of pyrazole derivatives. Barret et al. (2011) reported a fluorinated pyrazole derivative that was able to inhibit selective hypoxia- inducible factor prolyl hydroxylase. Hypoxia-inducible factor-α (HIF- α) mediates the cell's transcriptional response to hypoxia. There is a role of prolyl hydroxylase (PHD) enzymes in the process for the hypoxia- responsive nature of cellular HIF-1α content. The possibility of mimicking the body's coordinated response to hypoxia was shown by the PHD inhibitor, 1-(5-chloro-6-trifluoromethoxy)-1H (benzoimidazole-2-yl)-1H-pyrazole-4-carboxylic acid (JNJ-42041935). The JNJ-42041935 depicted great promise for the treatment of a range of anemic conditions[19] (Scheme 10).



Scheme 10

In glaucoma treatment, there are several side effects of various drugs used. For this reason, there is a need for synthesizing novel molecules with antiglaucoma activity with less side effect. Some of these sulphonamides had higher inhibition ability with respect to drug molecules. Sagar K. Mishra et al., have reported the synthesis of a series of 1-(2, 4-dinitrophenyl)-3-(3-nitrophenyl)-5-(4-substituted phenyl)-2-pyrazolin-4-ones by the oxidation of 1-(2, 4-dinitrophenyl)-3-(3-nitrophenyl)-5-(4-substituted phenyl)-4-bromo-2-pyrazolines with dimethyl-sulfoxide and assayed for in vitro antimicrobial activity.

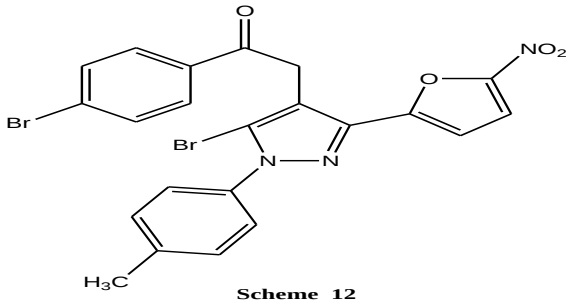
Most of the synthesized compounds did not exhibit significant inhibitory activity against the tested strains[20] (Scheme 11).



R=H,NO 2,OCH 3,Cl,Br
1,3,5 Tri aryl 2 ¯pyrazolines

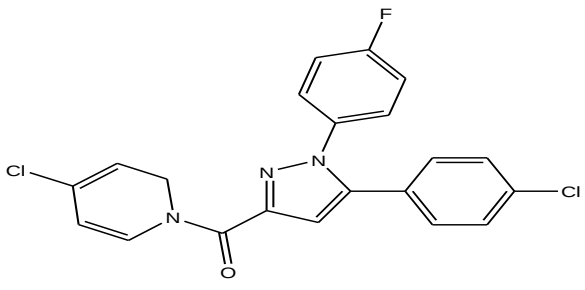
Scheme 11

Satheesha Rai N and Balakrishna Kalluraya et.al., have reported novel series of nitrofuran containing 1, 3, 4, 5 tetra substituted pyrazole derivatives. Compound (Scheme 12) showed highest antibacterial and antifungal activity than all other compounds[21].



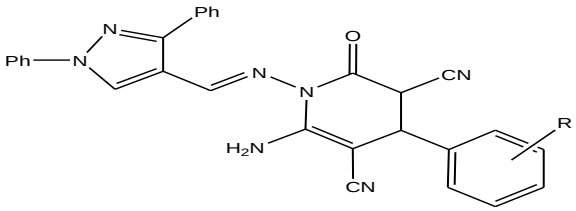
Scheme 12

Venkat Ragavan R et al., have synthesized A group of novel 1, 5-diaryl pyrazoles by altering the active part (amide linkage) and tested for their biological activities. The results of our present study conferred that the aliphatic amide pharmacophore is important for antimicrobial activities of studied pyrazoles specifically the presence of 4-piperidine moiety enhances the activities. Compounds exhibited good antibacterial and antifungal activity[22] (Scheme 13).



Scheme 13

In a recent in vitro study by Desai et al. (2013), some pyrazole derivatives encompassing 2-pyridene depicted potent antibacterial activity against bacterial strains such as Staphylococcus aureus at non cytotoxic concentrations[23] (Scheme 14). Finding such new organic molecules with antibacterial activity is important because of the resistance of pathogenic bacteria towards available antibiotics.

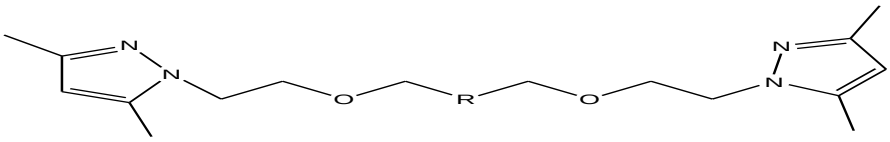


R= H, F, Br, NO_2, CH_2, OH, OCH_2, CF_3

Scheme 14

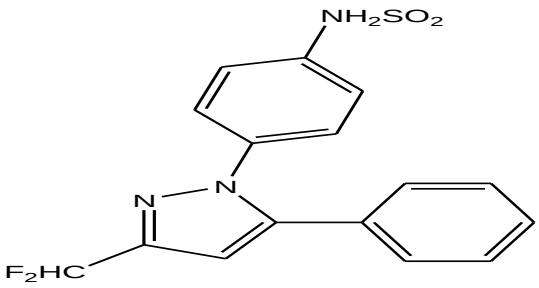
iv) Other Applications of Pyrazole Derivatives

The most studied property of pyrazoles is their bioactivity. In addition to bioactivity, pyrazoles have potential for other applications such as dyes and catalysts. Pyrazole based metal complexes for example have been studied as homogenous or supported catalysts. Oxovanadium (IV) complexes derived from pyrazole were studied for oxidation of cyclohexane under mild conditions. The study focused on applying these complexes as catalyst precursors for the single-pot peroxidative cyclohexane oxidation to cyclohexane oxidation, then to cyclohexanol and to cyclohexanone at 25 ^{0}C under both homogeneous and heterogeneous conditions. The homogeneous reactions were faster than the heterogeneous ones. Guerrero et al. have designed new N, O hybrid pyrazole derived ligands and they investigated their use as stabilizers for the synthesis of Pd nanoparticles[24] (Scheme 15).



Scheme 15

Sunil Singh K et al., studied the microwave promoted condition and optimized to get a 1,5-diaryl-pyrazole and subsequently implemented to the parallel synthesis of different compounds and they concluded that this was the excellent method for the rapid generation of 1,5-diarylpyrazole using microwave in aqueous medium under normal condition[25] (Scheme 16).



1,5 -diaryl pyrazole

Scheme 16

CONCLUSION

The reviewed pyrazole is a unique template that is associated with several biological activities. Mostly, the bioactivity of the pyrazole derivatives was studied in detail. There are recent attempts in understanding different properties of the pyrazole derivatives. This article high lightened research work of many researchers reported in literature for different pharmacological activities on pyrazole compounds synthesized. The review has presented comprehensive details of pyrazole analogues, potent compounds reported for particular pharmacological activity and the method or technique involved in evaluation process. More investigations must be carried out to evaluate more activities of pyrazole for many diseases. Therefore, the new trend in pyrazole derivatives will be towards new applications in various areas.

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