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Pyrazoles in Medicinal Chemistry: A Concise Review of Their Biological Activities and Synthetic Routes

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Abstract:

In the field of medicinal chemistry there is always an urge among researchers to find out some new drugs having properties like antibacterial, antifungal, anti-inflammatory etc. with fewer toxic effects than already existing drugs. As with passage of time the microbes develop resistance against the already existing drugs. So the research for new drugs should always continue. Heterocyclic compounds like benzoxazine, thiazole, pyrazoles and their derivatives have always been studied by the researchers regarding their prominent biological activities. This review has been written with the motive to throw light on the medicinal uses of various pyrazole derivatives and various synthetic methods available to synthesize these compounds. So that researchers are oriented to design and synthesize new compounds containing pyrazole core and developing safer and more efficient drugs.

Keywords:

Pyrazole, anti-tumor, anti-cancer, anti-leukemic, antiproliferative

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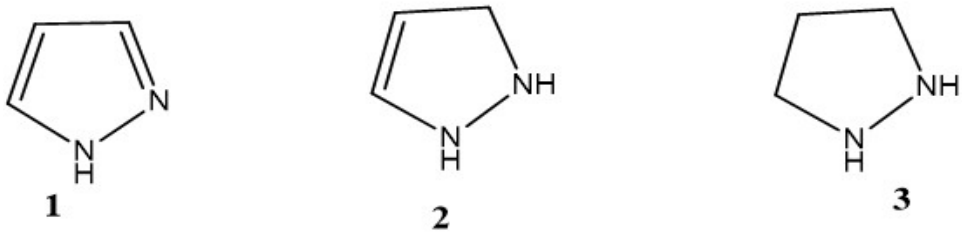
Introduction:

The name Pyrazole was given to this class of compounds by "Ludwig Knorr in 1883. Pyrazole is an organic heterocyclic compound with the molecular formula $C_3H_3N_2H$. Pyrazole 1 is a heterocyclic five-member ring compound having two adjacent nitrogen atoms and three carbon atoms. Pyrazoline 2 and Pyrazolidine 3 are its reduction products.



Buchner in 1889 prepared Pyrazole for the first time by decarboxylation of pyrazole-3,4,5- tricarboxylic acid 4.

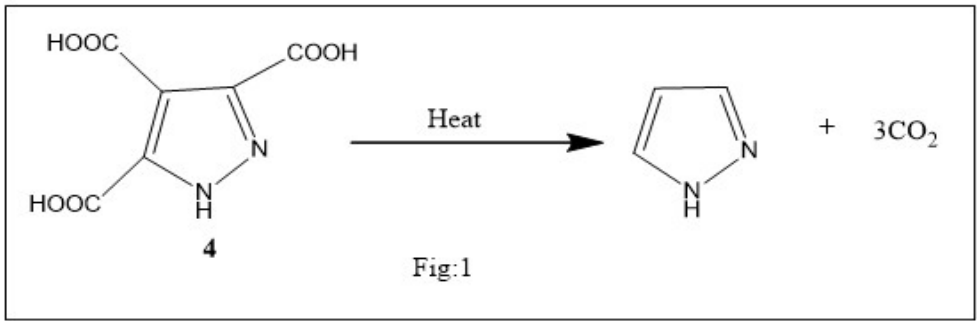
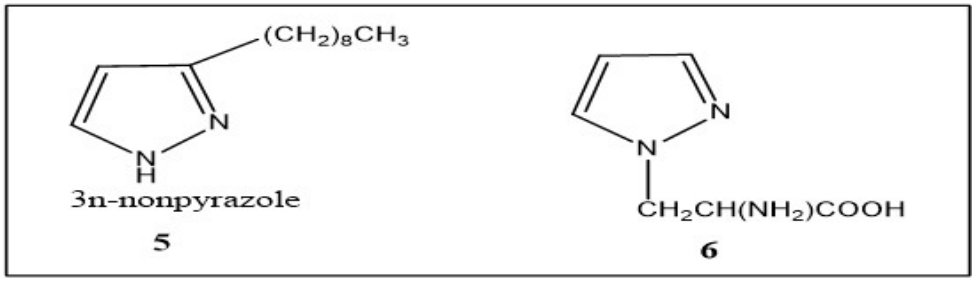


Fig:1

There was no pyrazole derivative found in nature for a long time. Japanese labourers separated 3-n-nonpyrazole **5** from a *Houttuynia Cordata*, a plant of family Piperaceae from tropical Asia. Its antimicrobial actions were observed by them. In 1959 â-(1-Pyrazolyl) alanine **6** was isolated from watermelon seeds (citrullus vulgaris). These are the main pyrazole derivatives occurring naturally at present [1].



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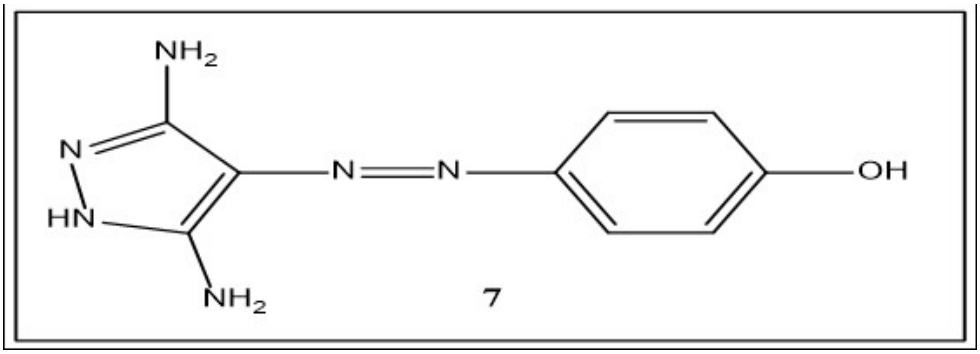
Pyrazole is a colourless solid with melting point 70°C. Pyrazole is an aromatic compound i.e. it undergoes nitration, halogenation and sulphonation. The substitution takes place at position-4. Pyrazole is weakly basic and form salts with inorganic acids. The imino hydrogen present in pyrazole can be substituted with acyl group. Pyrazole is not very active towards oxidising or reducing agents but can be hydrogenated catalytically into pyrazoline and then into pyrazolidine. Pyrazoline and pyrazolidine are stronger bases than pyrazole. Although pyrazole is not susceptible for oxidizing agents but the side chain present on substituted Pyrazoles can be oxidized with potassium permanganate into carboxylic acid group.

In Pyrazole a free N-H group is present. The free N-H group can be alkylated with diazomethane or alkyl halide and dimethyl sulfate etc. Pyrazole derivatives are referred as interesting group of organic compounds having numerous medicinal properties.

Fipronil is a phenyl pyrazole. It is a bug spray and is a non-focused blocker of the ã-amino butyric corrosive receptor [2-8].

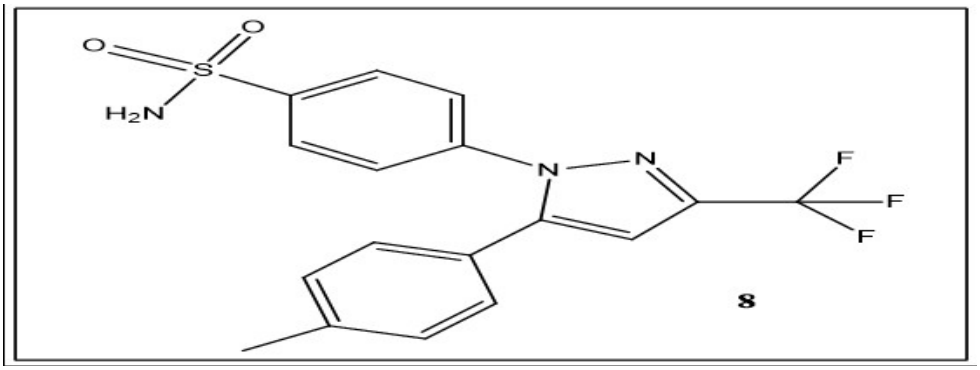
Chauhan et al. [9] have reviewed many pyrazole derivatives that exhibit anticancer activity. Literature shows that many N-substituted pyrazoles are used as antitumor, anti-leukemic, anti-angiogenic, anti-proliferative agents. These compounds show anticancer effects by inhibiting various receptors or proteins or enzymes that are responsible for cell division. Thus pyrazoles were studied more for their structure activity relationship (SAR). By going through it authors got the idea that how structure of compounds are related with binding to various receptors. Various modifications in the structure of pyrazole were done to get the compound having pharmacological activity. Krystof et al. 2011 [10] reported that CAN 508 which is a 3,5- diamino pyrazole **7**, can be used as anticancer drug.



7

Celecoxib **8** is a tricyclic compound having a Pyrazole ring. It is a very good anti-inflammatory agent inhibiting the enzyme cyclooxygenase-2 (COX-2).

Kumar et al. [11] has reviewed its synthesis and development. Its main step of synthesis is condensation of hydrazines with 1,3-diketones. Wei et al. [12] reported that Celecoxib reduces angiogenesis and metastasis of human pancreatic cancer. Xu et al. [13] reported that celecoxib can induce VEGF expression as well as tumor angiogenesis.



8

Antibacterial and antifungal activities of various synthesized quinoline derivatives having pyrazole nucleus were screened. When pyrazole compound **9** was compared with the reference drugs against many human pathogen strains like *C. albicans*, *P. Vulgaris*, *A. Clavatus*; *A. fumigatus* and *S. Flexneri*, it was found to show better results [14] as evidenced by their MIC values (0.12 - 0.98 ìg/ml).

Nada et al. synthesized pyrazole derivatives and studied their properties against bacteria *E. coli* and *S. Aureus*. As revealed by data it was found that pyrazole compound **10** was effective at only 0.075mg/ml against the microorganism used for testing [15].

Mondal et al. synthesized and then studied antimicrobial activity of Ni(II) Hg(II) and Cd(II) complexes of schiff base ligands having pyrazole moiety. The result showed that complex of Hg **11** showed highest antimicrobial activity against bacteria [16].

Various pyrazole-oxindole compounds were synthesized and their anti-proliferative activity on different human cancer cell lines was studied. Compound **12** was found to show significant cytotoxicity [17].

Antimicrobial activity and synthesis of new derivatives of Pyrazole were described by Syed and co-workers. The result of these studies showed that compound **13** had considerable antimicrobial properties against the micro-organisms tested [18].

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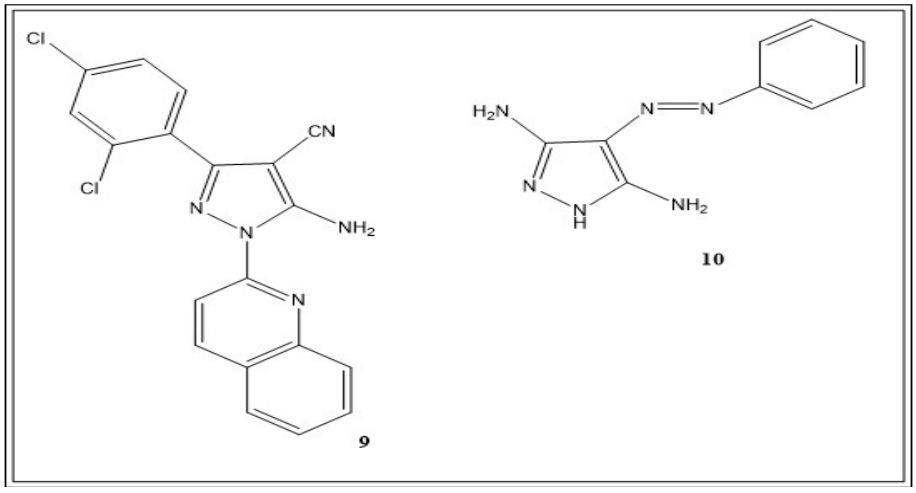
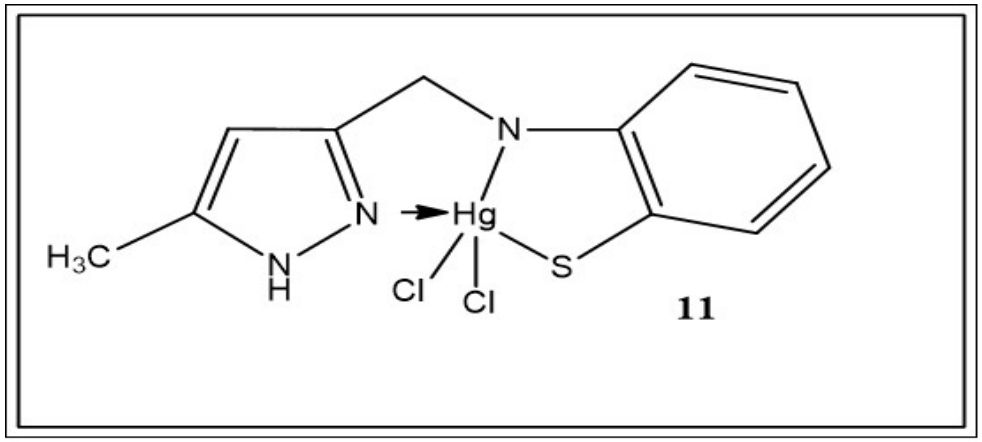
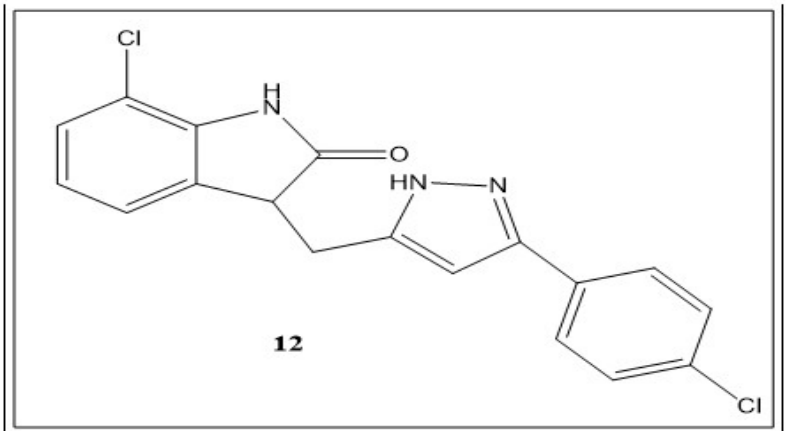
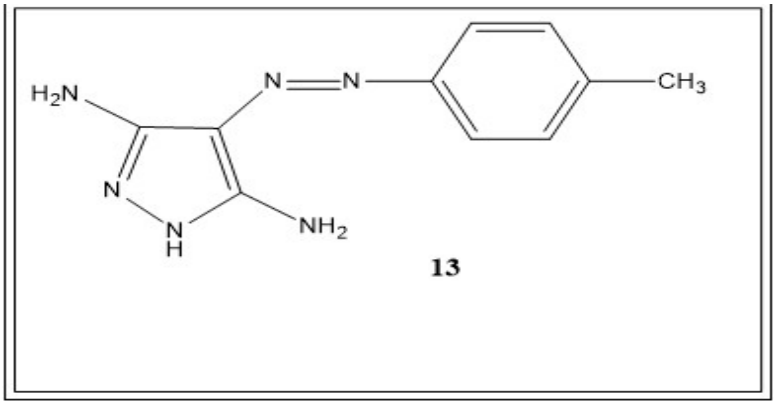






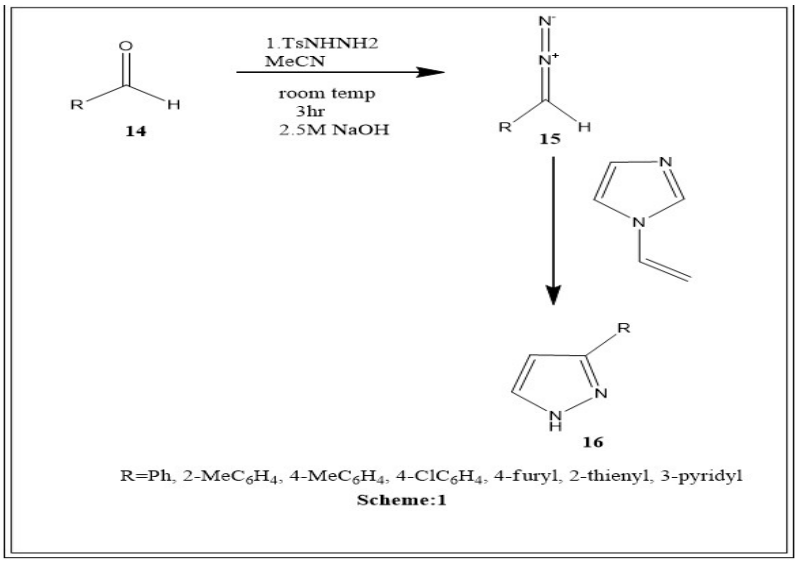


13

Synthesis of Pyrazole:

The first synthesis of Pyrazole nucleus was described by Knorr [19]. Since then numerous modifications were done in various routes applied to get Pyrazole nucleus. Following are the various methods generally employed for synthesizing Pyrazole derivatives:

An important method for the formation of Pyrazoles is 1,3-dipolar cycloaddition of diazo group containing compounds to triple bond. The diazo compounds **15** were generated from tosylhydrazone of aldehydes **14**. Compound **15** reacts with N-vinyl imidazole to give Pyrazole **16** (Scheme-1) [20].



14 **15** **16**

R=Ph, 2-MeC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-furyl, 2-thienyl, 3-pyridyl

Scheme:1

One of the best method to prepare Pyrazole is oxidation of Pyrazoline. Pyrazolines can be synthesised most commonly by doing cycloaddition of diazoalkanes to á, â-unsaturated ketones. Using this concept Silva et al. [21] first prepared 3-benzoyl-

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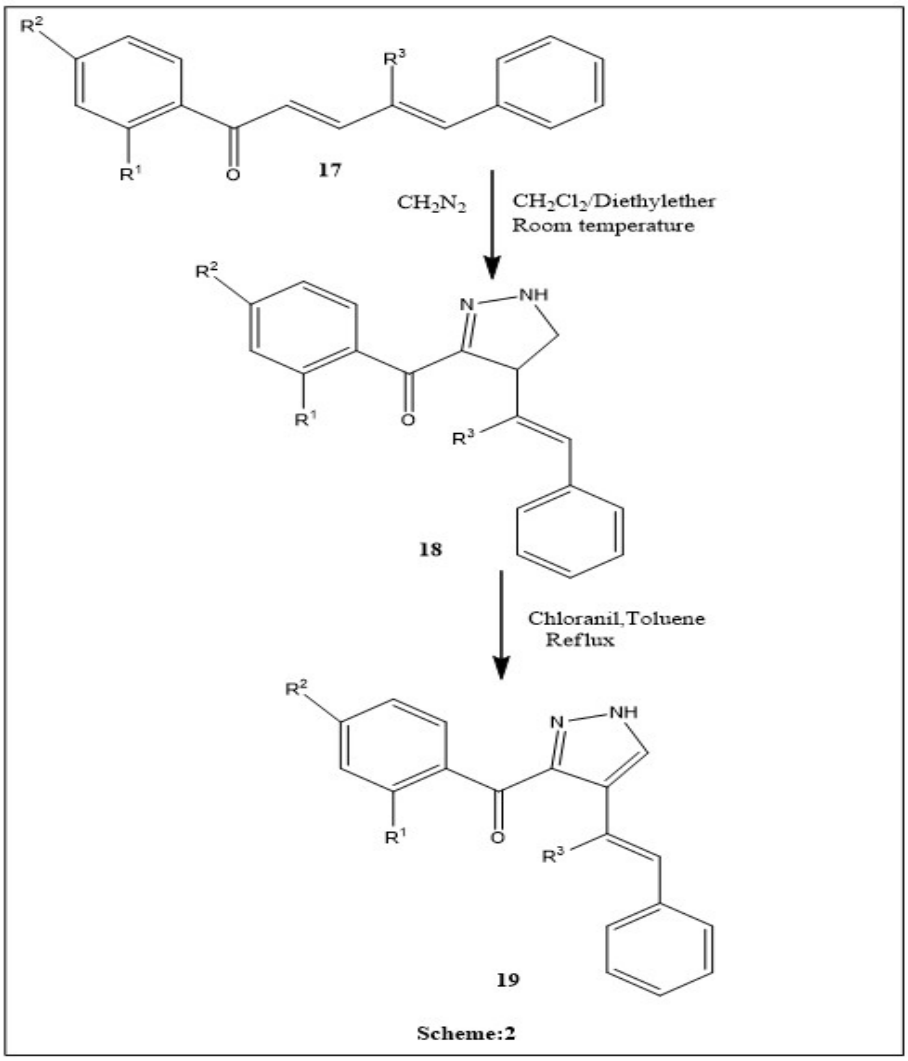
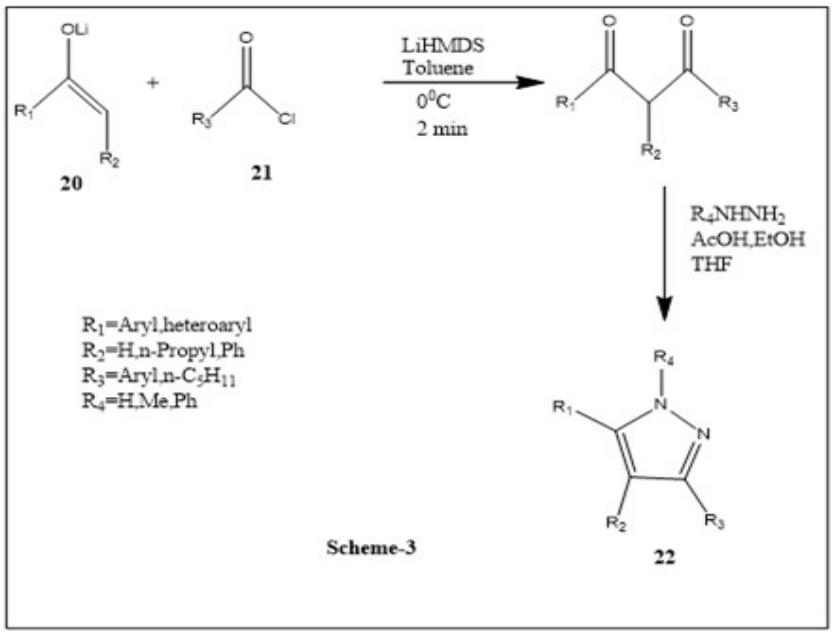
4-styryl-2-pyrazolines **18** by reacting cinnamylideneacetophenones **17** with diazomethane. **18** was subjected to oxidation with chloranil to give 3-(5)-benzoyl-4-styrylpyrazoles **19** (Scheme-2).



Scheme:2

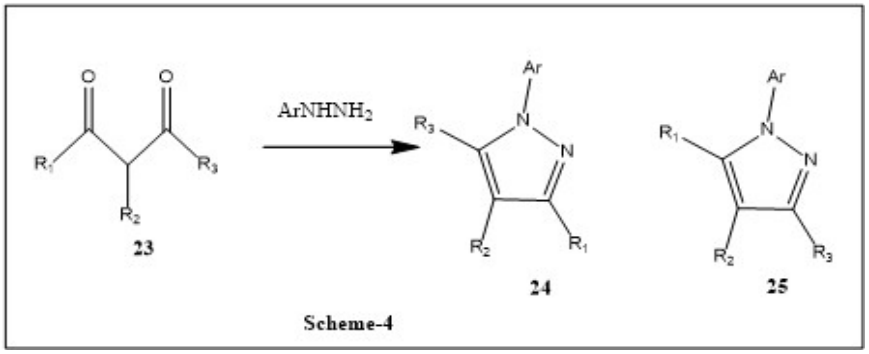
Silva et al. [22] also prepared bis (pyrazoles) by oxidizing pyrazolyl-2-pyrazolines with 2,3-dichloro-5,6-dicyanoquinone.

In an efficient one pot synthesis of substituted pyrazoles, enolates **20** and acid chlorides **21** were reacted to give 1,3-diketone that was subjected in situ to addition of hydrazines to give 3,5-disubstituted pyrazoles **22** (Scheme-3) [23].



Scheme-3

In 1883 the substituted pyrazoles were first synthesized by Knorr [19]. He synthesised two regiomers **24** and **25** by reacting â diketone **23** with hydrazine derivatives (Scheme-4). This cycloaddition reaction of 1,3-dicarbonyl with derivatives of hydrazines is a very simple and rapid method to give poly-substituted pyrazoles.



Scheme-4

1,3-diketone **26** on reacting with hydrazine in presence of sulphuric acid as catalyst gave high yields of 3,5-disubstituted pyrazole **27** .This was a solventless reaction performed by mixing diketone and hydrazine in a mortar with a drop of concentrated sulphuric acid (Scheme-5) [24].

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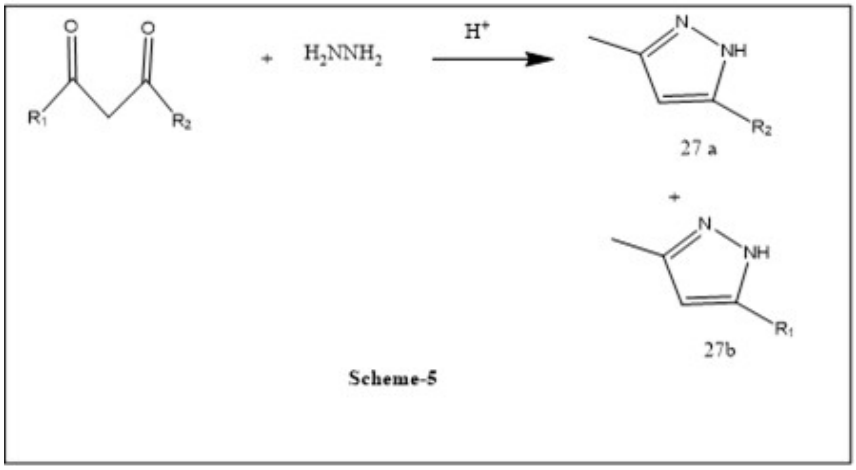
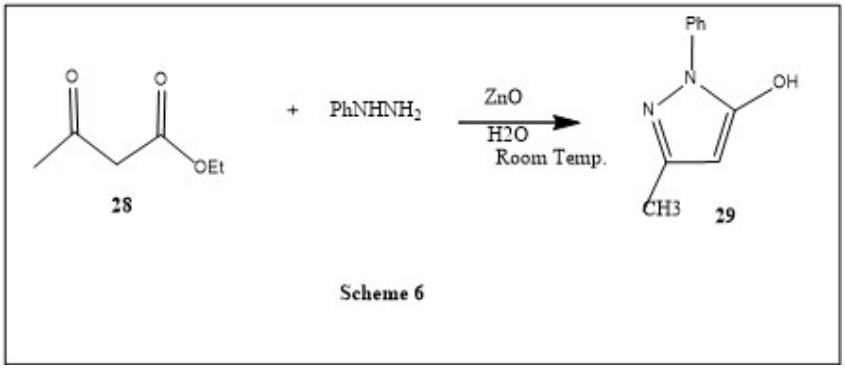


Scheme-5

Girish et al. [25] synthesized 1,3,5-trisubstituted pyrazoles **29** by condensing phenylhydrazine with ethylacetoacetate **28** using nano ZnO as catalyst (Scheme-6). This reaction was having many advantages like small reaction time, high yield 95% and easy workup procedure.



Scheme 6

Conclusion:

When we go through lectures or read various publications we are always surprised by the new informations about the compounds under study that have important applications especially in medicinal chemistry.

In the field of medicinal chemistry Pyrazoles and various compounds having pyrazole rings are the most repetitively found heterocyclic rings. The present review explores medicinal value of various pyrazoles and its derivatives as well as throws light on the various routes of synthesizing pyrazoles derivatives. This review paper is an effort to promote the use of pyrazole scaffold.

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