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Review Article

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# SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF SOME NEW PYRAZOLE ANALOGUES: A REVIEW

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**ABSTRACT**

Pyrazole and its derivatives are considered a pharmacologically important active scaffold that possesses almost all types of pharmacological activities. The presence of this nucleus in pharmacological agents of diverse therapeutic categories such as celecoxib, a potent anti- inflammatory, the antipsychotic CDPPB, the anti-obesity drug Rimonabant, Difenamizole, an analgesic, Betazole, a H2-receptor agonist and the antidepressant agent Fezolamine have proved the pharmacological potential of the pyrazole moiety. Owing to this diversity in the biological field, this nucleus has attracted the attention of many researchers to study its skeleton chemically and biologically. This review highlights the different synthesis methods and the pharmacological properties of pyrazole derivatives. Studies on the synthesis and biological activity of pyrazole derivatives developed by many scientists around the globe are reported.

**KEYWORDS:** Pyrazole, anti-inflammatory, anti-obesity.

## INTRODUCTION

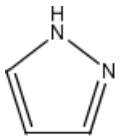
Pyrazole is a five membered heterocyclic ring containing two neighboring nitrogen atom in their ring structure. Pyrazole associated with group of azole in which two double bond present in molecular formula $C_3H_3N_2H$. Pyrazole undergo number of reactions including electrophilic substitution, nucleophilic substitution, halogenation, cycloaddition reaction.

Pyrazole shows different pharmacological activities like antimicrobial, antibacterial, anesthetic, antidiabetic, analgesic, anti-inflammatory, antiepileptic, antioxidant, anticancer, anti-amoebic, anti- tuberculosis.[1]

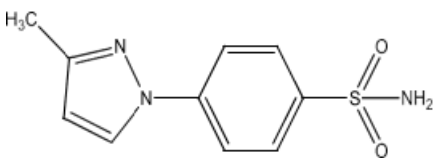
Pyrazole shows versatile pharmacological activity so its nucleus attracts the researcher to study the chemistry and biological activity. Selection of pyrazole for review is because of its different pharmacological property.

## CHEMISTRY OF PYRAZOLE

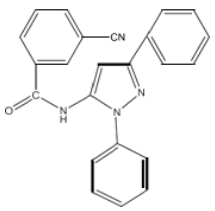
Pyrazole is a weak base and it is tautomeric substances. The structure of pyrazole having two nitrogen atoms among two nitrogen atom one is basic and other one is neutral in nature. Pyrazole is an unsaturated cyclic compound. These are aromatic molecule due to their planar conjugated ring structures with six delocalized pi-electrons.



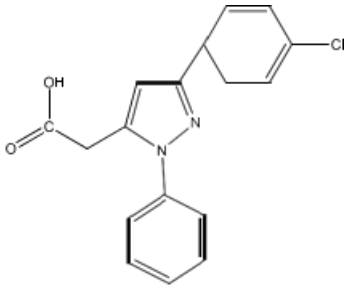

## SOME DRUGS CONTAINING PYRAZOLE NUCLEUS



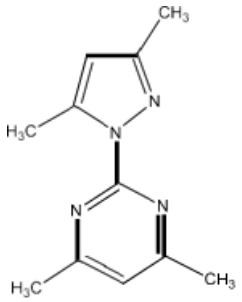

**Celecoxib**
**(Anti-inflammatory)**



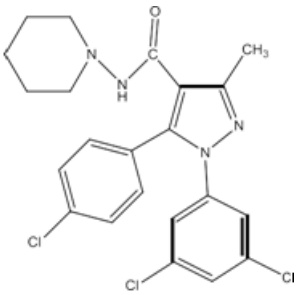

**CDPPB**
**(Antipsychotic)**



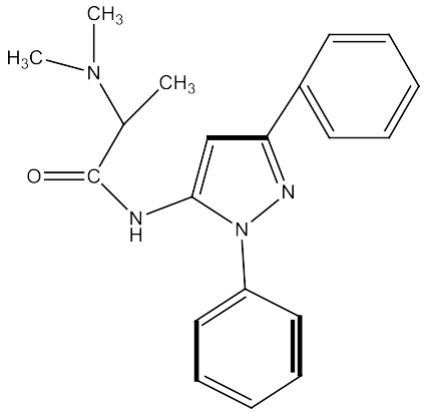
**Lonazolac**
**(Anti-inflammatory)**



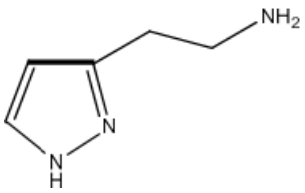
**Meprizole**
**(Anti-inflammatory)**



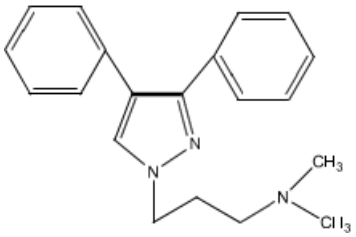
**Rimonabant**
**(Anti-obesity)**



**Difenamizole**
**(Analgesic)**



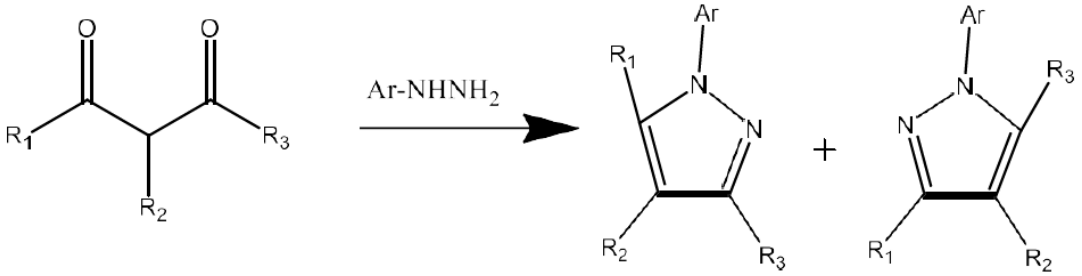
**Betazole**
**($H_2$-receptore agonist)**



**Fezolamine**
**(Antidepressant)**

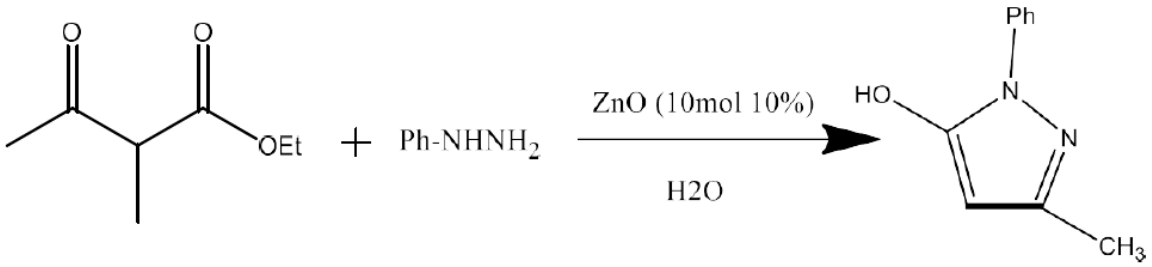
**DIFFERENT METHOD OF SYNTHESIS OF PYRAZOLE**

1. Knorr *et al*.,[2] first synthesis the substituted pyrazoles in 1883. Reaction of β-diketone with hydrazine derivatives gives two regioisomers (Scheme 1).



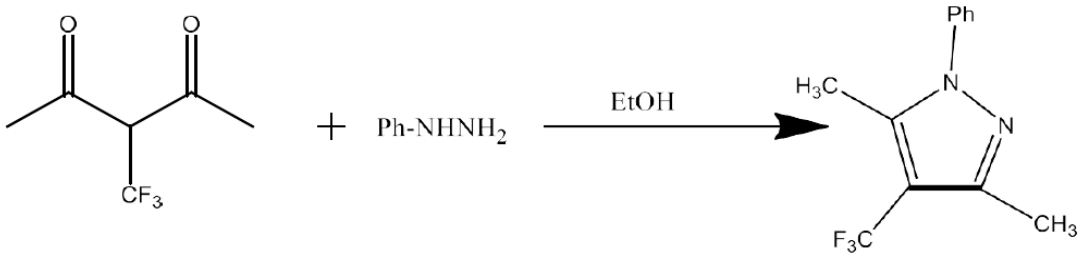

**Scheme 1: Synthesis of polysubstituted pyrazoles form 1,3-dicarbonyl compounds.**

2. Girish et al.,[3] Described an efficient nano-ZnO catalyzed green protocol for the synthesis of 1, 3,5 - substituted pyrazole derivatives by condensation of phenylhydrazine with ethyl acetoacetate (Scheme 2). The main advantage of this protocol is the excellent yield (95%) achieved short reaction time and easy work-up procedure**.**



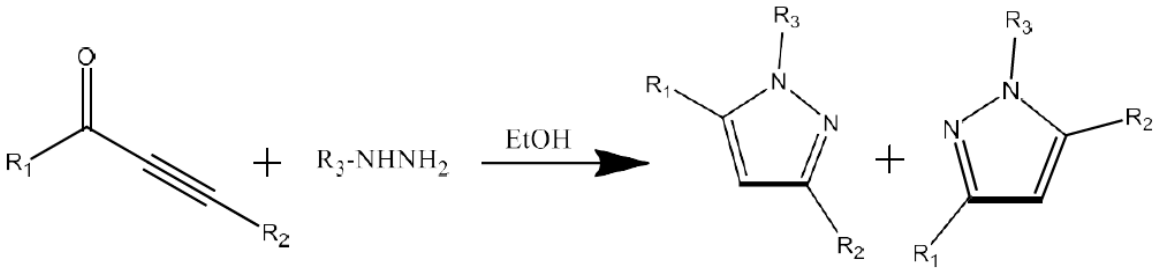

**Scheme 2: Synthesis of 1,3,5-substituted pyrazoles from ethyl acetoacetate.**

3. Ohtsuka *et al.*,[4] studied the condensation of phenylhydrazine with the 2-(trifluoromethyl)- 1,3-diketone in ethanol, affording 1,3,4,5-substituted pyrazole in good yield (63%) Compound was exclusively formed presumably owing to the fact that the sterically small $NH_2$ is more nucleophilic than NHPh (Scheme 3).



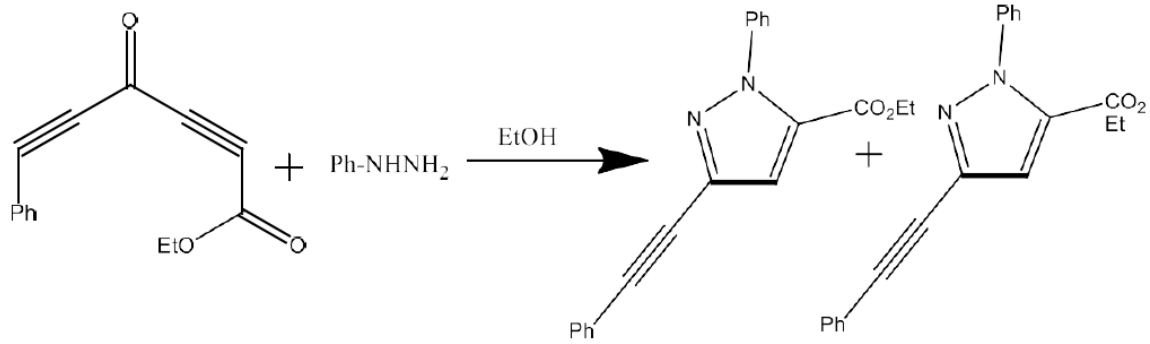

**Scheme 3: Synthesis of 1,3,4,5-substituted pyrazoles from 2-(trifluoromethyl)-1,3-diketone.**

4. The cyclocondensation reaction of hydrazine derivatives on acetylenic ketones to form pyrazoles has been known for more than 100 years.[5] However, the reaction again results in a mixture of two regioisomers (Scheme 4).



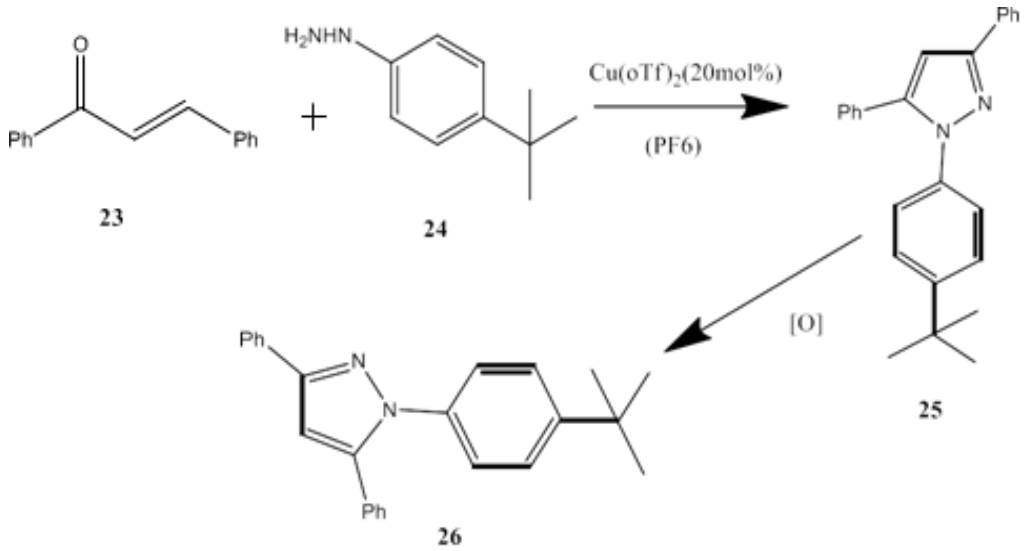

**Scheme 4: Synthesis of pyrazoles from acetylenic ketones.**

5. The diacetylene ketones reacted with phenylhydrazine in ethanol to give two regioisomeric pyrazoles. When phenylhydrazine was used, a mixture of regio-isomers was generated in approximately 3:2 ratios. When hydrazine hydrate was used as the nucleophile, only one regioisomers was isolated, presumably due to hydrogen bonding to the ethyl ester group (Scheme 5).[6]



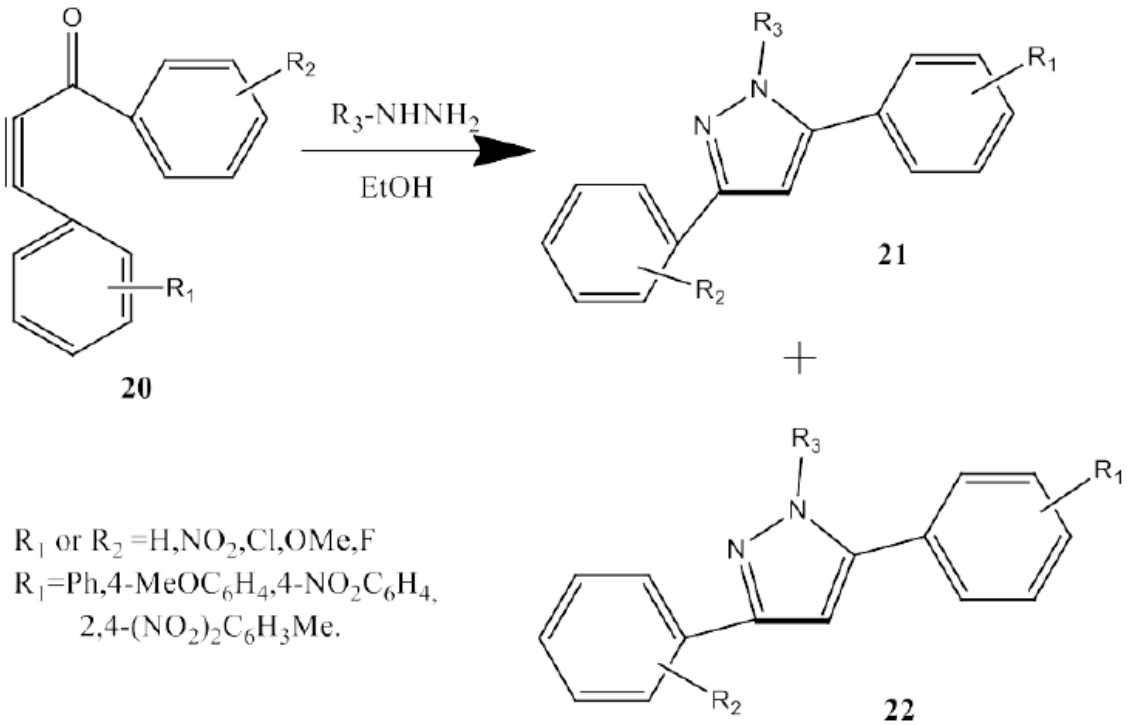

**Scheme 5: Synthesis of pyrazoles from diacetylene ketones.**

6. Guojing *et al.* reported a new efficient method for the synthesis of 3-trifluoromethylpyrazoles with good yields *via* trifluoromethylation/cyclization of acetylenic ketones on phenylhydrazine using a hyper valent iodine reagent under transition-metal-free conditions. The optimal conditions were obtained when the ratio 24/Togni reagent was maintained at 1:1.3, giving in 70% isolated yield (Scheme 6).[7]



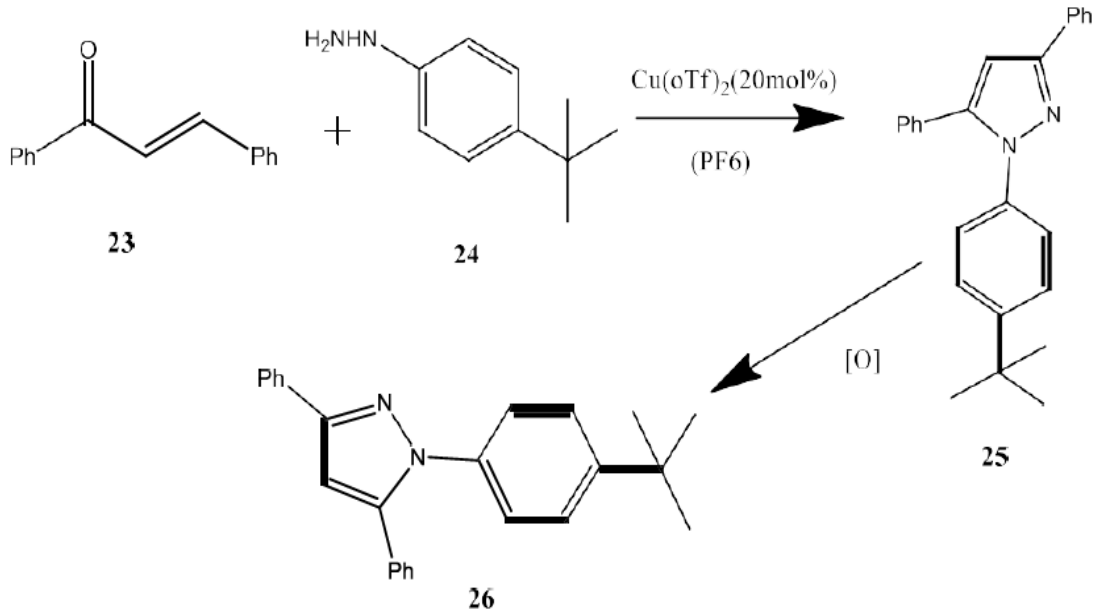

**Scheme 6: Synthesis of 3-trifluoromethylpyrazoles via cyclization of acetylenic ketones.**

7. Bishop et al. were interested in the factors determining the regioselectivity of this type of reaction in the framework of the synthesis of 3,5-diarylpyrazoles. They studied the cyclocondensation of acetylenic ketones on methyl hydrazine or aryl hydrazine in ethanol, which provides two difficultly separable regioisomeric pyrazoles (Scheme 7).[8]



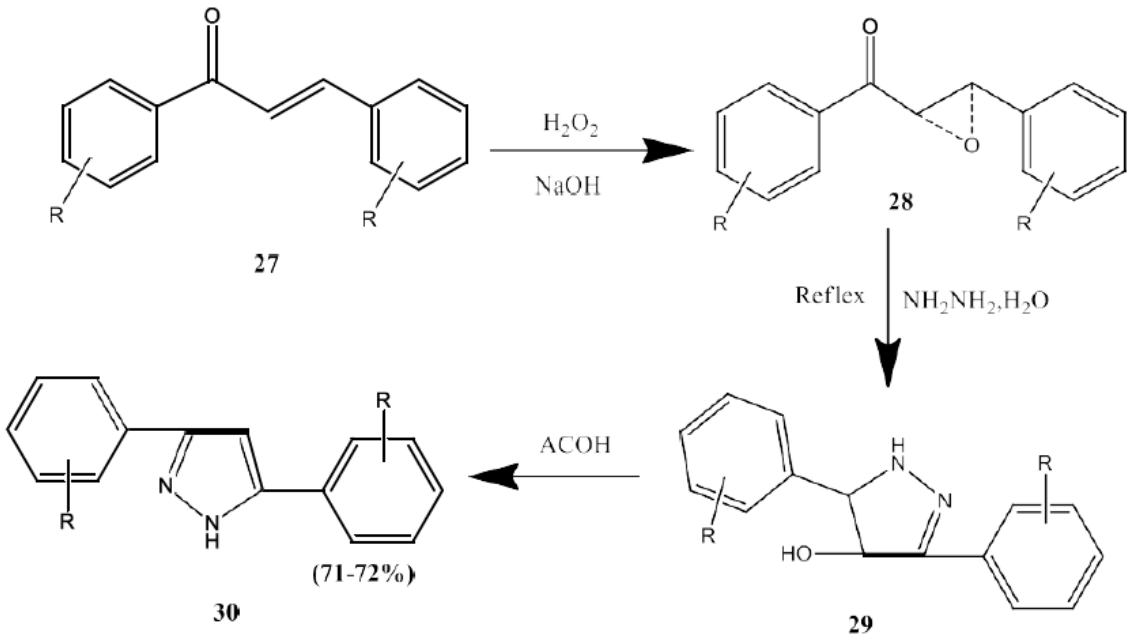

**Scheme 7: Synthesis of 3,5-diarylpyrazoles from acetylenic ketones and hydrazine derivatives.**

8. Rao *et al.*, described the condensation of an α,β-ethylenic ketone with p-(4-(tert-butyl) phenyl)hydrazine in the presence of copper triflate and 1-butyl-3-methylimidazolium hexafluorophosphate as catalysts, to access pyrazoline. The corresponding 1,3,5-trisubstituted pyrazole was obtained after oxidation *in situ* of this pyrazoline (Scheme 8).[9]



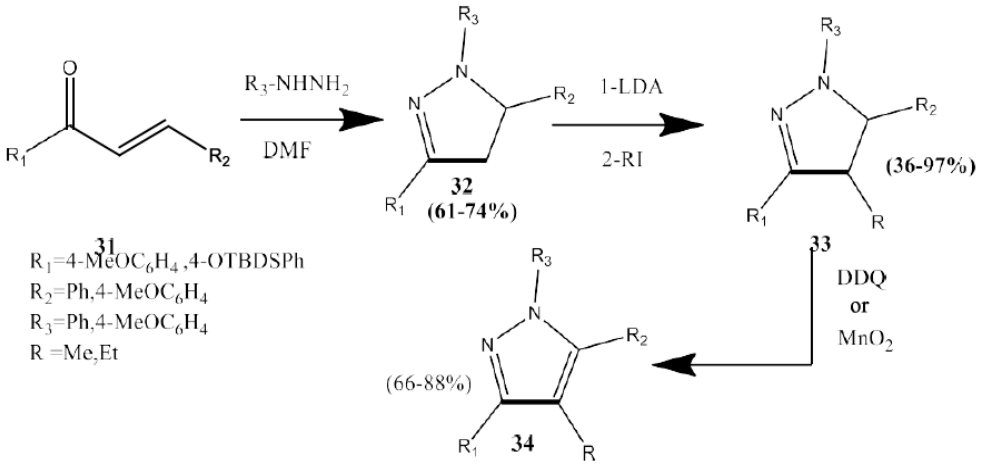

**Scheme 8: Synthesis of pyrazoles from α,β-ethylenic ketone.**

9. On the other hand, Bhat *et al*. described a method for the synthesis of 3,5-diaryl-1H- pyrazoles from the reaction β-arylchalcones with hydrogen peroxide that gave epoxides. Then, addition of hydrazine hydrate afforded pyrazoline intermediates, dehydration of which yielded desired 3,5-diaryl-1H- pyrazoles (Scheme 9).[10]




**Scheme 9: Synthesis of 3,5-diaryl-1H-pyrazoles fromβ-arylchalcones.**

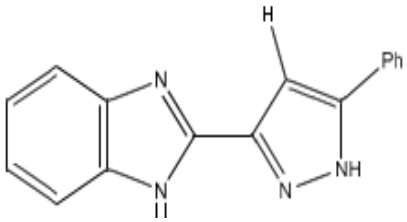
10. Huang *et al*. developed a new regioselective synthesis of 4-alkyl-1,3,5- triarylpyrazoles for the preparation of unsymmetrically substituted systems of interest as ligands for the estrogen receptor. The condensation of hydrazine with α,β-ethylenic ketones in DMF gave pyrazolines. However, the corresponding pyrazole derivatives were obtained in good yield (66–88%) by alkylation of the pyrazolines in the presence of LDA, before undergoing the oxidation reaction (Scheme 10).[11]



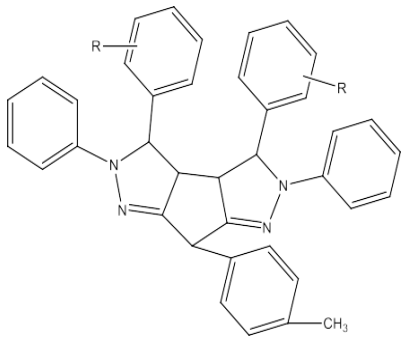

**Scheme 10: Synthesis of 4-alkyl-1,3,5-triarylpyrazoles from α,β-ethylenic ketones.**

**PHARMACOLOGICA ASPECTS OF PYRAZOLE ANTIMICROBIAL ACTIVITY**

1. Sallendra Jaln., (2018), synthesized series of 3-Benzimidazoylyl-5-aryl-2- Pyrazole (3a-f) derivatives and evaluated for their antifungal activity against *Candida albicans and Aspergillus Niger* and antibacterial against *E. coli, P. aeruginosa, B. subtilis and K. Pneumoniae*. The result shows that phenyl substituted derivative shows good antifungal activity at 300mg/ml and 3,4-dimethylphenyl,4- chlorophenyl,2-furanyl derivatives shows good antibacterial activity.[12]

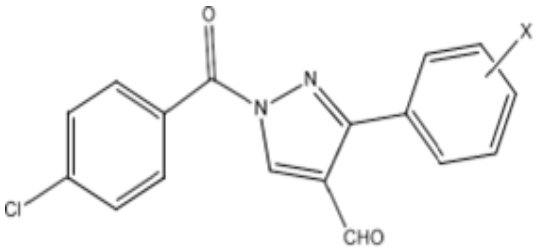


2. Patol & Rajput., (2018), synthesized new series of *bis*-pyrazoles derivatives from 1-p- tollylpyrrolidine-2,5dione and evaluated for their antibacterial activity. The antibacterial evaluation of synthesized compounds have concluded that 3,4-*bis*(2-chlorophenyl)2,5-diphenyl-7-(p-tolyl)-3,3a,3b,4,5,7- hexahydro-2Hpyrrolo-[2,3-c:5,4-c']-dipyrazol shown good antibacterial activities against *S. aureus* and *B. subtilis*. The compound 3,4-*bis*(4methyl phenyl)-2,5-diphenyl-7-(p-tolyl)- 3,3a,3b,4,5,7-hexahydro-2H-pyrrolo- [2,3-c:5,4c']-dipyrazole showed promising antibacterial activities against *B. subtilis* and exhibited potent antibacterial activities against *S. aureus* (100*microgram per disk).*[13]



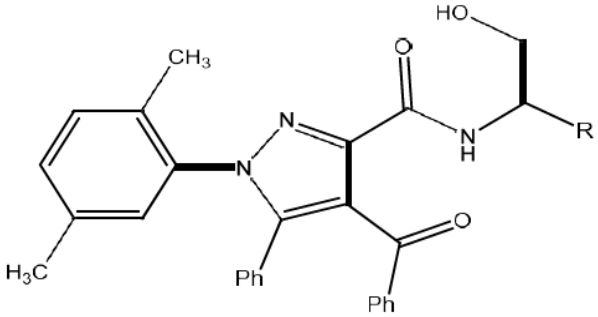
R=OH, $NH_2$, Cl *etc.*

3. Rashmi *et al*., (2018), synthesized series of 1-(4-chlorobenzoyl)-3-(4-substituted phenyl)-1H- pyrazole- 4-carbaldehyde derivatives and evaluated for their antibacterial activity against S.*Aureus* (Gram+) and *E.coli* (Gram-). All derivatives exhibited significant to moderate antibacterial activity. Derivatives substituted with 4-Methoxy, 4-Methane shows good activity against Gram+ and substituted with 4- Bromo and 4-Chloro derivatives shows good activity against Gram- organisms (100mg/ml).[14]

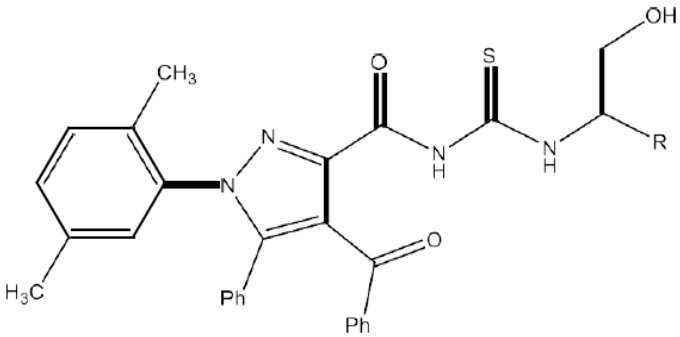



R=I, Br, Cl, F.

4. Ishak *et al*., (2018), reported a synthesis of series of tetra substituted pyrazole-3- carboxamides and pyrazole-3-carbonyl thioureides and evaluated for their antibacterial potential against *Enterobacter aerogenes ATCC 13048, Bacillus subtilis ATCC 6633, Staphylococcus aureus 6538, Bacillus megaterium DSM 32, Pseudomonas aeruginosa 9027, Klebsiella pneumoniae RSKK 574, Escherichia coli,* and antifungal activity against *Candida albicans, Yarrovia lipolytica and Saccharomyces cerevisiae ATCC 10231.* Synthesized compounds were active in a broad spectrum against important human pathogenic microorganisms. Among the synthesized compounds 3b and 6a shows highest activities.[15]

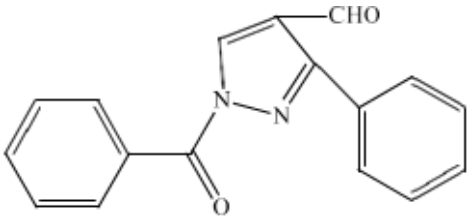



**R**
**a-Ph**
**b-$CH(CH_3)_2$**
**c-$C_2H_5$**



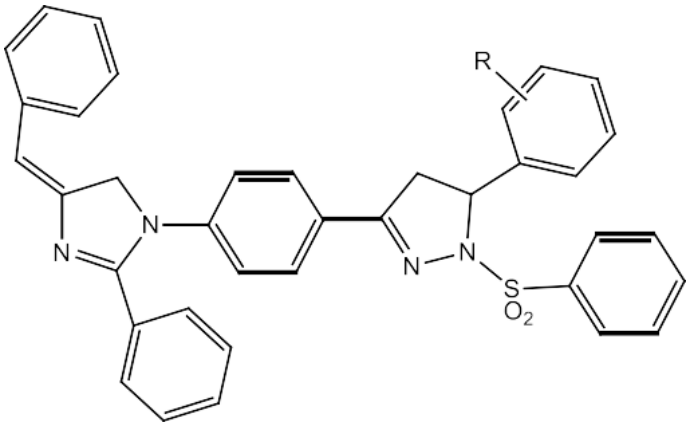

**R**
**a-Ph**
**b-$CH(CH_3)_2$**
**c-$C_2H_5$**

5. Jyothi *et al*., (2017), reported a synthesis of pyrazole derivatives by Vilsmeier Haack reaction and evaluated for their antifungal activity of newly synthesized 1-(34-methoxy phenyl-4- formyl pyrazole-1- carbonyl)benzene and 1-(3-4-methoxy phenyl-4-formyl pyrazole-1-carbonyl) 4-bromobenzene are screened against the *Aspergillus niger* and *Candida albicans.* Ketoconazole is tested as reference drug to compare the activity. The result was recorded for each tested compound as the average diameter zone of inhibition of bacterial or fungal growth around the disks in mm. All tested compounds shows good antifungal activity.[16]




6. Rajiv *et al*., synthesized a series of 1-phenylsulfonyl pyrazoles and evaluated for their antifungal activity against *candida albicans*. Among synthesized derivatives 3b-4-chloro derivative shows good antifungal activity.[17]

3a R= 4-Cl 3b R= 2-Cl 3c R= 2- NO2 3d R= 2-OH
3e R= 4- OH 3f R= 4-(NCH3)2 3g R= 4-OCH3

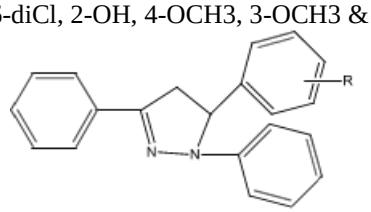



(**3a-g)**

**ANTI-INFLAMMATORY**

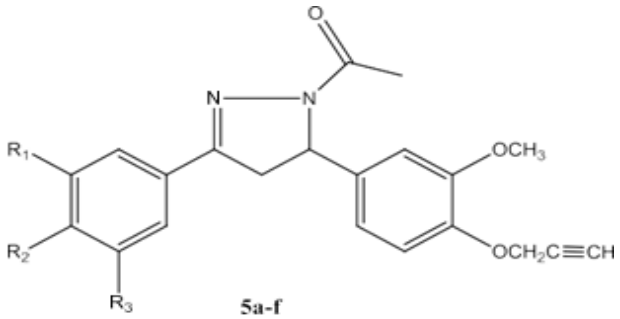
1. Indu Singh., (2018), reported a synthesis of series of 5-substituted(R)1,3-diphenyl-4,5- dihydro-1H pyrazole by the reaction of substituted chalcones with phenylhydrazine, The synthesized compounds evaluated for their anti-inflammatory activity. The anti-inflammatory activity of synthesized compounds is compared by phenylbutazone, some series of compound like 5-(2,6-dichlorophenyl)-1,3,diphenyl-4,5- dihydro-1Hpyrazole, 5-(2,6-dibromophenyl)- 1,3,diphenyl-4,5-dihydro-1Hpyrazole,5-(4- methoxyphenyl)-1,3,diphenyl-4,5-dihydro- 1Hpyrazole,4-(1,3,diphenyl-4,5-dihydro-1H-pyrazol-5-yl)- 2methoxyphenol, showed good anti-inflammatory activity than standard drug.[18]

R = H, 2-Cl, 4-Cl, 2,6-diCl, 2-Br, 4-Br, 2,6-diCl, 2-OH, 4-OCH3, 3-OCH3 & 4-OH

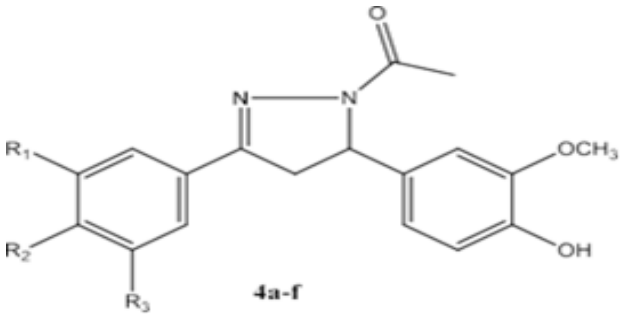



2. Ashwani Kumar Dhingra *et al*., synthesized a novel O-propargylated-N-acetylpyrazole analogs (5a–j) from N-acetylpyrazole (4a–j) derived from 1,3-diarylpropenones (3a–j) with propargyl bromide and evaluated for their anti-inflammatory activities. Among the synthesized derivatives 5e-Nitro substituted derivative shows good activity.[19]

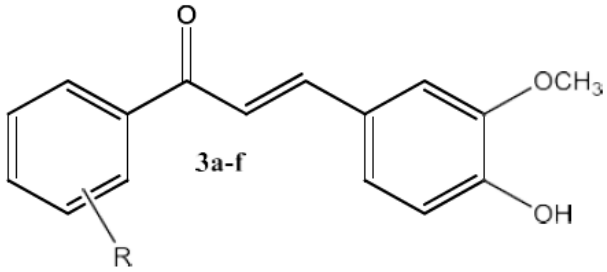
5aR1, R2, R3 = H 5bR2 = Br, R1, R3 = H 5cR2 = Cl, R1, R3 = H
5dR2 = OCH3, R1, R3 = H 5eR2 = NO2, R1, R3 = H 5f R1, R2, R3 = OCH3




**5a-f**



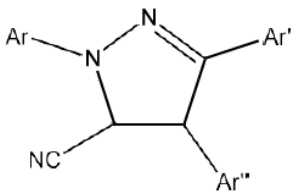

**4a-f**




**3a-f**

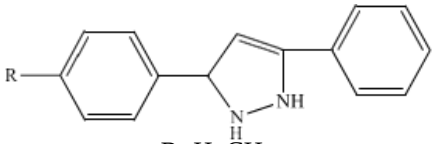
**ANTIOXIDANT**

1. Jayaroop *et al*., (2013), synthesized a series of new 3-Aryl-4-(4-methoxyphenyl)-1-phenyl- 4,5-dihydro- 1H-pyrazole-5-carbonitriles they were screened *in vitro* for their antibacterial and antifungal activities against four different organisms. The minimal inhibitory concentration (MIC's) was determined against each organism. The compounds were tested for their antioxidant activity by evaluating their DPPH radical scavenging ability. Butylated hydroxyl toluene (BHT) is used as an antioxidant and reducing power ability. The effect of substitution on the activity, and the possible structure activity relationship mechanism of the compounds for their antioxidant activity are presented.[20]




Ar=Ph
Ar'=4-$FC_6H_4$,4-$ClC_6H_4$,4-$BrC_6H_4$
Ar''=4-$H_3COC_6H_4$

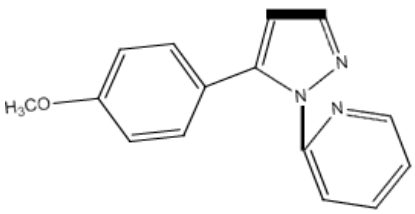
2. Esvet *et al*., synthesized a 3,5-diphenyl-1H-pyrazole and evaluated for antioxidant and oxidant properties. Antioxidant properties have not been investigated on human peripheral blood cells. To determine antioxidant/oxidant potentials, TAC and TOS assays performed using automated colorimetric measurement methods. The obtained results showed that the 3,5-diphenyl-1H-pyrazole did not change the TAC levels in cultured human whole blood cells in any concentrations. Besides, it increased TOS levels in a dose-dependent manner. Result shows that 3,5-diphenyl-1H-pyrazole derivatives increased the production of reactive Oxygen species.[21]



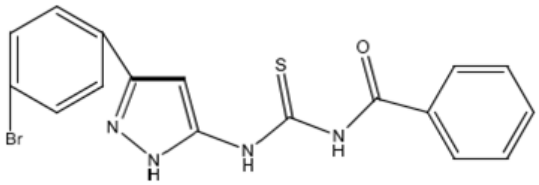

R=H, $CH_3$.

**ANTICANCER**

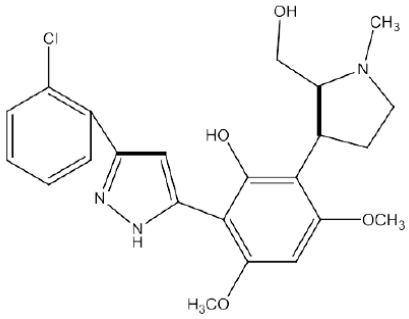
1. Balbi *et al.,* synthesized a series of pyrazole derivatives and studied their anti-proliferative activity in human ovarian adenocarcinoma A2780 cells, human lung carcinoma A549 cells, and murine P388 leukemia cells. Compound demonstrated significant anti proliferative agent.[22]




2. Nitulescu *et al.,* synthesized a series of substituted pyrazole compounds and evaluated in vitro for their anticancer effects on a panel of 60 cellular lines. Results showed that the compound presented significant growth inhibitory effects on the tested cancer cells.[23]

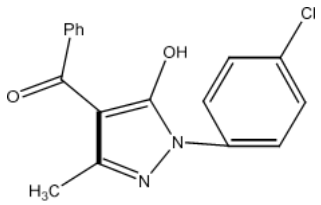


3. Bandgar *et al.,* synthesized a series of 3,5-diarylpyrazole derivatives were and evaluated for their anticancer activity against five cell lines (breast cancer, prostate cancer, promyelocytic leukemia, lung cancer, colon cancer). Compound identified as a potent anticancer agent against all selected cell lines.[24]

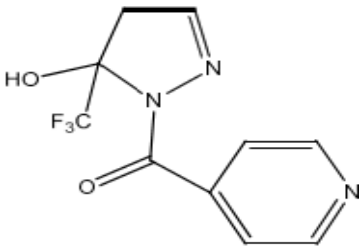


**ANTI-TUBERCULOSIS**

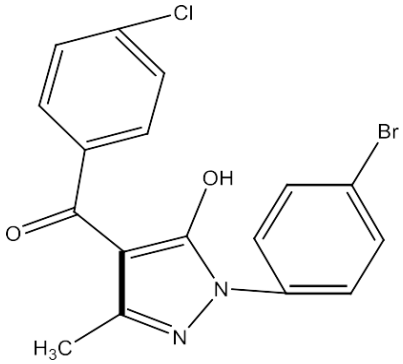
1. Manetti *et al,*. Identified new inhibitors of Mycobacterium tuberculosis. Compound found to be most active agent with a MIC value of 25 µg/mL.[25]



2. A series of 3-substituted 5-hydroxy-5-trifluoro [chloro] methyl-1H-1-isonicotinoyl-4,5-dihydropyrazoles were synthesized by Almeida da Silva *et al.*, and tested for their in vitro antimicrobial activity against *Mycobacterium tuberculosis* H37Rv, INH-resistant clinical M. tuberculosis isolates non-tuberculous mycobacteria. Amongst the synthesized compounds, below compound found to be the most active agents against susceptible *M. tuberculosis* and several INH-resistant strains.[26]

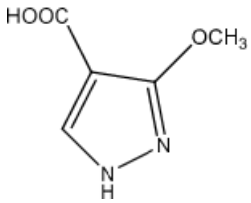


3. Two series of pyrazole derivatives were synthesized by Castagnolo *et al*. And assayed as inhibitors of *M. tuberculosis* H37Rv. The pyrazole derivative (figure-6), with the p- bromophenyl group at the N1 position, is showed to be very active (MIC = 4 µg/mL).[27]

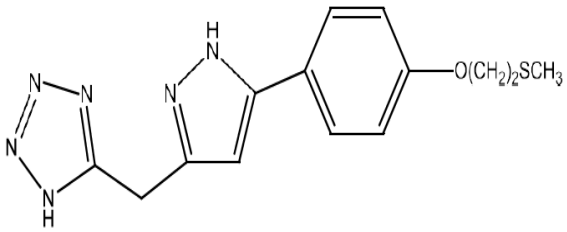


**ANTIDIABETIC**

1. A new series of substituted pyrazole-4-carboxylic acids were synthesized by Cottineau *et al.,* and evaluated for their antidiabetic activity. The results indicated that compound emerges as the best hypoglycemic agent in the series.[28]



2. Sharon *et al.*, synthesized a new series of 5-[(5-aryl-1H-pyrazol-3-yl) methyl]-1H-tetrazoles and evaluated them for their in vivo anti- hyperglycemic activity. Out of screened compounds, compound demonstrated 24.6% of blood glucose lowering activity at 100 mg/kg.[29]



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