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A REVIEW ON PYRAZOLE AN ITS DERIVATIVE

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ABSTRACT:-

Pyrazole is a 2-neighbour nitrogen containing 5-membered heterocyclic organic compound with three carbon atoms. Pyrazole commonly known as 1,2 diazoles has been very popular now a days due to manifold uses. There are number of pyrazole derivatives which has broad spectrum of biological activities like anti-bacterial, anti-microbial, anti-inflammatory, anti-convulsant, analgesic, anti-diabetic, anti-rheumatic, anti-cancer, and anti- tuberculosis. There is various method used for manufacture of pyrazole and its derivative. The purpose of the review was to collect various pharmacological actions which was reported in recent years made on its moiety. Pyrazole and its derivatives are prepared by dehydrogenating 2-pyrazoline or its derivative by process in which the reaction is carried out using sulfuric acid in the presence of iodine or of an iodine compound. Taking into considerations diversity in the biological activity, this nucleus has attracted 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. Development of pyrazole an its derivative has been reported by many scientists in decades.

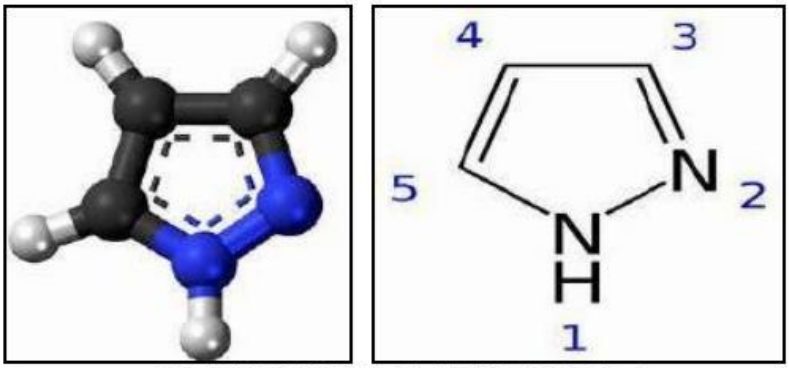
KEYWORDS:-

Pyrazole, Its derivative, 1, 2 Diazole, Anti-microbial, Anti-inflammatory, Analgesic, Anti-diabetic, Anti-cancer, and Anti- tuberculosis, Anti-TMV Activity ACE Inhibitors .

INTRODUCTION:-

- Pyrazole can be any type of organic compound that has a heterocyclic ring consisting of a carbon atom and a nitrogen atom parallel to its structure.
- A compound with the molecular formula **C3H4N2**. [1]
- The chemical reactivity of the pyrazole molecule can be explained by the action of each atom.
- The N atom in position 2 with two electrons is a basic atom and therefore reacts with electrophiles.
- The N atom at position 1 does not react but loses protons when present base.
- Two N atoms combine to reduce the charge density at C3 and C5, making electrophilic attack possible.
- Pyrazole derivatives play an important role in anticancer drugs due to their good inhibitory activity.
- In addition, pyrazole derivatives also have good anti-inflammatory and antibacterial effects.
- Pyrazoles are five-membered heterocycles that form a group of compounds that are particularly useful in organic synthesis.[2]
- They form one of the maximum studied organizations of compounds in the azole family.
- Antitumor, herbicides, Antibacterial, antifungal, hypoglycemic, antidepressant, Analgesic, anti-inflammatory, anti-cancer, enzyme Inhibitor activity are shown among the pyrazoles.[3,4]

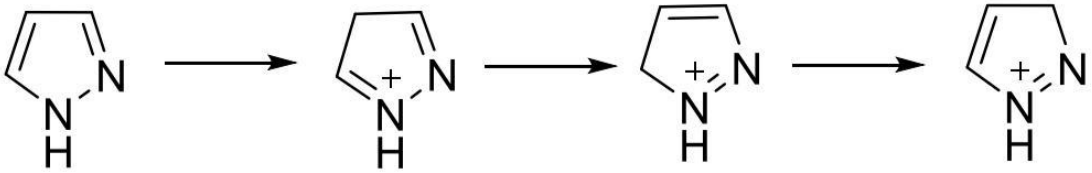
- yrazole is the name given by **"LUDWIG KNORR"** in **1883** to this compound.



STRUCTURE OF PYRAZOLE

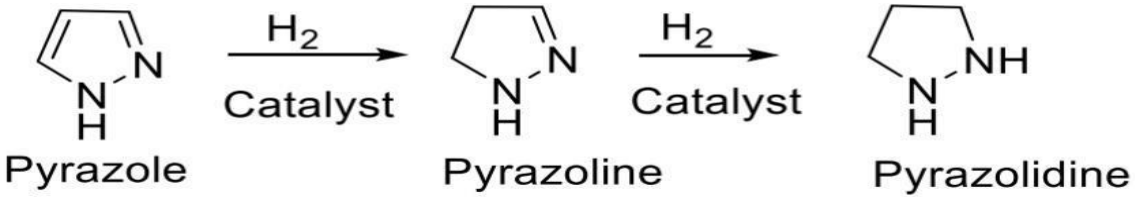
STRUCTURE CHARACTERISTICS:-

- With a melting point of 70°C, Pyrazole is a colourless solid.
- Pyrazole is a tautomeric substance:
  in pyrazole itself, the presence of tautomerism cannot be shown but can be inferred by considering pyrazole derivatives.
- Pyrazole exhibits aromatic properties, e.g., it is readily halogenated, nitrated and sulphonated; the group enters at position 4.
- The following resonating structures are possible for pyrazole.



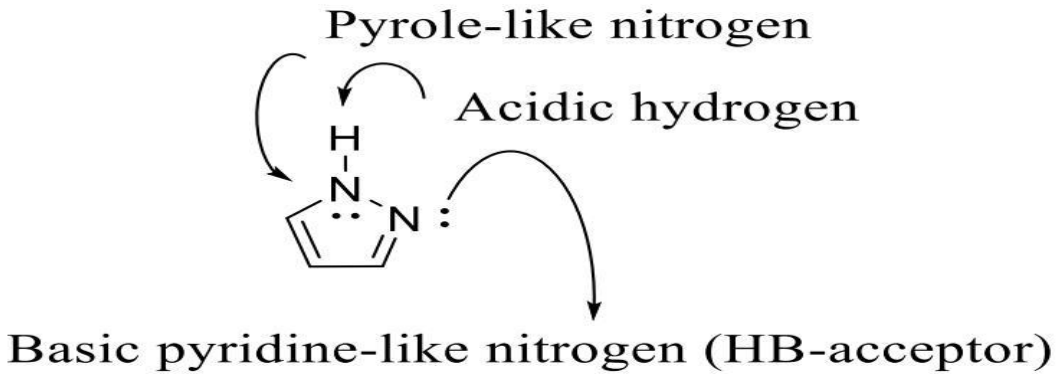
- Pyrazole resist oxidation and reduction reaction due to loss Of aromaticity, but may be hydrogenate catalytically, first to Pyrazoline, and then to pyrazolidine.
- Pyrazole has a weak base and forms salts with inorganic acids; it is possible to substitute imino hydrogen with an acyl group.
- Pyrazole is highly resistant to oxidizing and reducing agents, but can be catalytically hydrogenated, first with pyrazoline and then with pyrazolidine.

- But stronger bases than pyrazole are among these compounds.



PROPERTIES:-

- N-unsubstituted pyrazoles possess amphoteric properties, acting as both acids and bases, considering the presence of nitrogen.
- While the proton is easily donated by the acidic pyrrole-like NH group, the simple pyridine-like nitrogen can accept protons even more readily, and thus the basic character is typically prevalent.



PHYSICAL PROPERTIES:-

1. It is a crystalline solid having pyridine like odour & bitter taste.
2. It is melting point is 70°C.
3. Its boiling point is 187°C.
4. It is soluble in water & organic solvents.

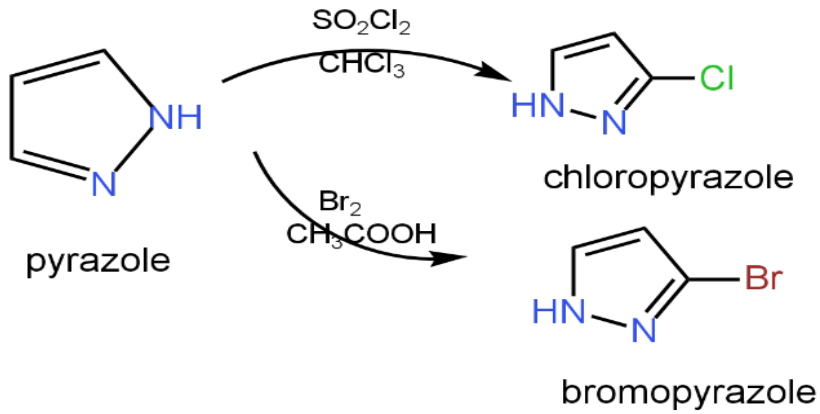
Chemical reaction of pyrazole

1. Ring opening reaction

When pyrazolium salts are treated with caustic alkalis, disubstituted hydrazine's are formed.

2. Halogenation

Pyrazole can be chlorinated by chlorinating reagent such as chlorine water, chlorine in carbon tetrachloride hypochlorous acid. Chlorine in acetic acid & sulfuryl chloride in chloroform. Pyrazole is brominated by bromine in chloroform bromine in acetic acid.



3. Oxidation

Pyrazole ring is generally stable to oxidation, however with peroxide transformed into its 2-oxide.

4. Reduction

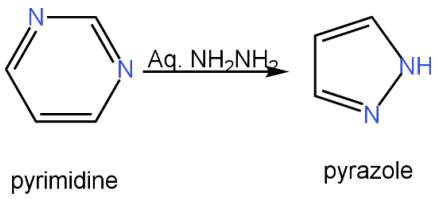
The reduction of pyrazole with sodium & alcohol or by catalytic hydrogenation over palladium results in 2-pyrazolines.

SYNTHESIS:-

Scheme 1

1. From pyrimidine

Pyrimidine reacts with hydrazine solution to give pyrazole.



pyrimidine pyrazole

Scheme 2

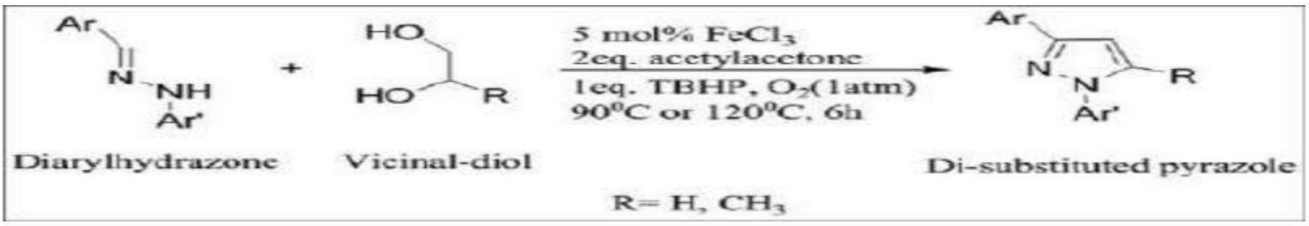
2. Knorr pyrazole synthesis

In this reaction, hydrazine & 1,3-dicarbonyl compound are converted into a pyrazole using an acid catalyst.

Scheme 3

Synthesis of 1, 3 Substituted Pyrazole

An iron catalysed route for region selective synthesis of 1, 3 substituted pyrazoles from the reaction of diarylhydrazones and vicinal diol.



Synthesis of 1,3- and 1,3,5-substituted pyrazoles.

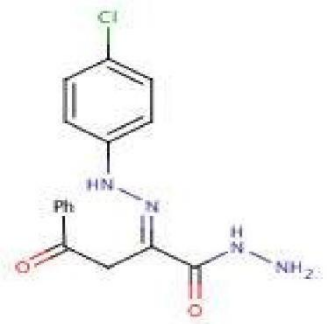
GENERAL SYNTHESIS:-

Pyrazole and their derivatives were synthesized from hydrazine or its derivative and 1, 3 – dicarbon compound using an acid catalyst, the reaction is also known Knorr pyrazole synthesis.Sucrow reported the synthesis of pyrazole using monomethyl hydrazones of dialkyloxalocete Hart an Brew have described the cyclization of 1, 3- bis (diazopropane) to pyrazole by concerted intermolecular 1,3-dipolar cycloaddition reaction.

Literature Review of Pyrazole and Its Derivatives-

Eman M Flefel et al. [5]

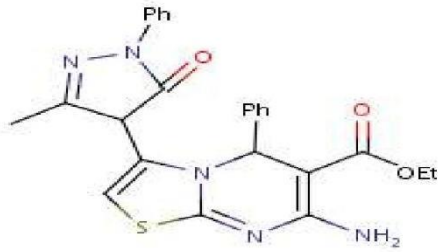
have reported new substitutes pyrazole thiazole and 1,2,4-traizole derivatives. The sugar



hydrazones acetylated derivatives as well as their derived acyclic C-nucleoside analogues, and the thioglycosides 1,2,4 -triazole derivatives were also prepared. The **antitumor activity** of some of the compounds showed significant activities.

Mohamedsalahk Youssef et al. [6]

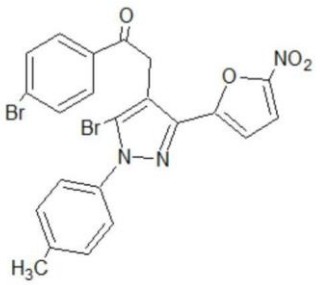
Have synthesized Ethyl 7-amino-3-(3-methyl-5-oxo-1-phenyl-2-pyrazolin-4-yl)-5-aryl-5H-thiazolo [3,2-a] pyrimidine-6-carboxylate was synthesized by the reaction of 4-(2-aminothiazol-4-yl)-3-methyl-5-oxo-1-phenyl-2-pyrazoline with arylidene ethyl cyanoacetate and it



transformed to related fused heterocyclic systems via reaction with various reagents.

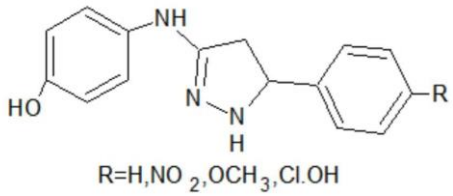
Satheesha Rai N [7]and Balakrishna Kalluraya et al. [7],

have reported novel series of nitrofuran containing 1,3,4,5 tetra substituted pyrazole derivatives. Compound showed highest anti-bacterial and **antifungal activity** than all other compounds.



Sahu SK et al.,[8]

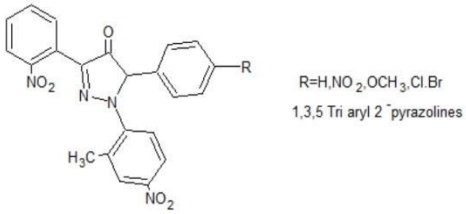
have synthesized a series of novel 4-(5-Substituted aryl-4, 5-dihydropyrazole-3-yl-amino) phenols By treating substituted aryl-N-chalcone amino phenols with Hydrazine hydrate. It was observed increase in **analgesic, Anti-inflammatory and anti -microbial activities** are Attributed to the presence of 4-NO2, 2-OH and 4-Cl in Phenyl ring at 5-position of pyrazoline



ring of synthesized Compounds.

Sagar K. Mishra et al.,[9]

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

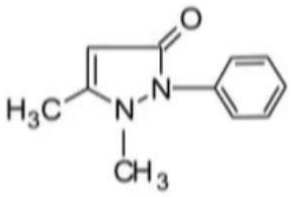


assayed for in vitro **antimicrobial activity.** Most of the synthesized compounds did not exhibit significant inhibitory activity against the tested strains

MEDICINAL USES OF PYRAZOLE:-

Antipyrine/phenazone

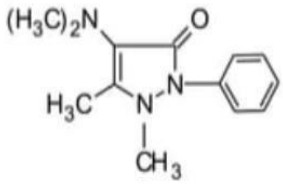
Antipyrine is an antipyretic agent used for the symptomatic treatment of acute otitis media, most commonly in combination with benzocaine.



Antipyrine (Phenazone)

Aminophenazone/aminopyrine

Aminophenazone is an analgesic drug used to treat acute migraine attacks in combination with

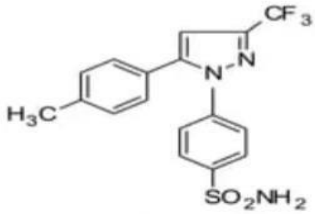


Aminophenazone (Aminopyrine)

ergotamine and caffeine.

Celecoxib

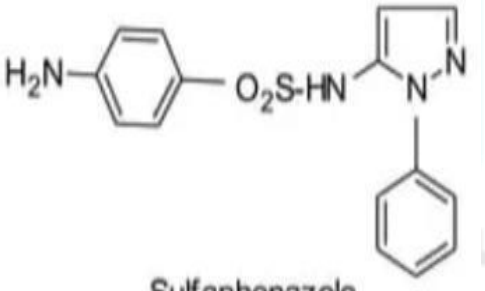
Celecoxib is used to relieve pain, tenderness, swelling and stiffness caused by osteoarthritis, rheumatoid arthritis and ankylosing spondylitis.



Celecoxib

Sulfaphenazole

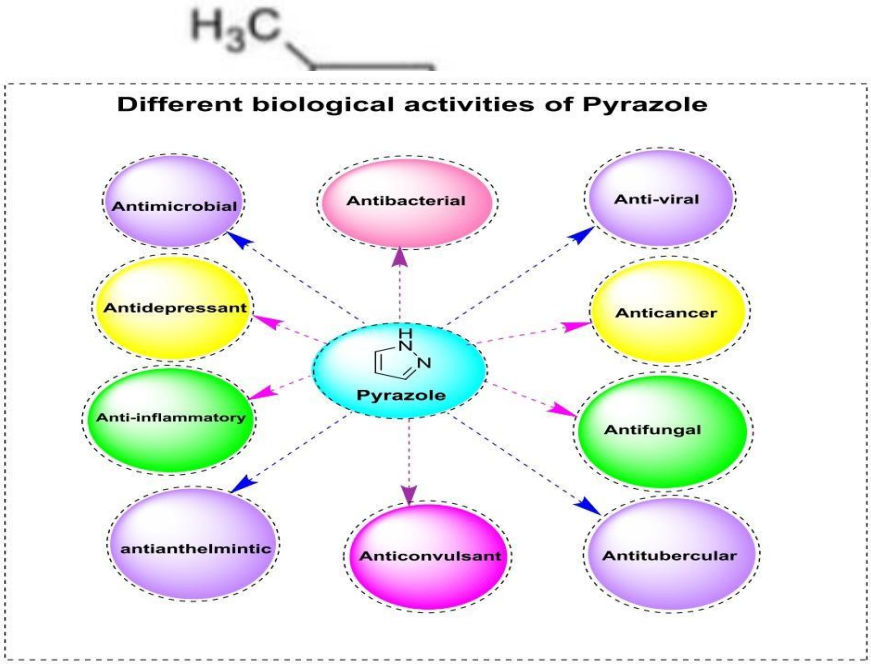
Sulfaphenazole is used for the treatment bacterial infections



Sulfaphenazole

Fomepizole

Fomepizole is indicated as an antidote for ethylene glycol or methanol poisoning, or for use in suspected ethylene glycol or methanol ingestion, either alone or in combination with hemodialysis.

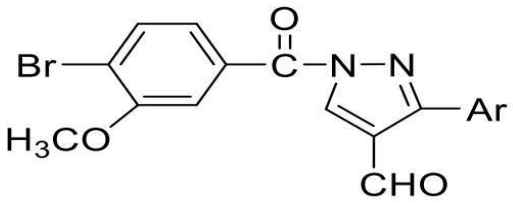


BIOLOGICAL ACTIVITY OF PYRAZOLE:-

Anti-Inflammatory Activity

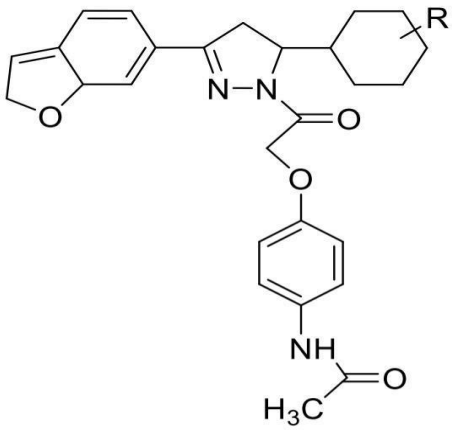
- Inflammation is a multi-stage process that in critical step is supposed to be powered acutely released arachidonic acid and its prostaglandin like metabolites.
- NSAIDS (non-steroidal ant inflammatory drugs is used for counteracting the pain of inflammation by counteracting cyclooxygenase enzyme.
- Some common examples of NSAIDs is aspirin, ibuprofen and naproxen.
- Carbaldehydes were prepared and tested ant inflammatory an analgesics activity.
- Among the prepared compound exhibit maximum ant inflammatory activity.

1) **Freddy et al (2001)[10]** have synthesized the series of 1-(3-bromo-4-methoxybenzyl)-4-formyl-3-(substituted phenyl) pyrazole and their anti-inflammatory activity.



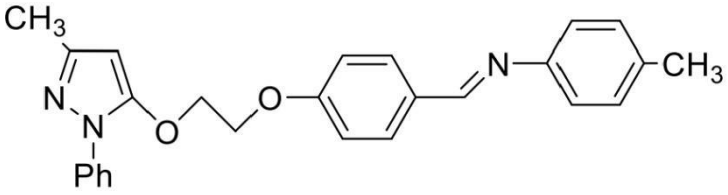
1-(3-bromo-4-methoxybenzyl)-4-formyl-3-(substituted phenyl) pyrazole

2) **Nargund et al (1992)[11]** evaluated the fluorinated phenyl styryl ketones and N phenyl-5-substituted aryl-3-P-(fluorophenyl) pyrazoline and reported anti-inflammatory activity in vivo.



N-Phenyl-5-substituted aryl-3-P-(fluorophenyl) pyrazoline

3) A novel series of pyrazole derivatives were reported by **Tewari et al (2014)[12]** and evaluated in vivo for their anti-inflammatory activity. Among the compoundsN-(4-(2-(3-methyl-1-phenyl-1H-pyrazol-5-yloxy)benzylidene)-4-methylbenzenamine showed comparable anti-inflammatory.

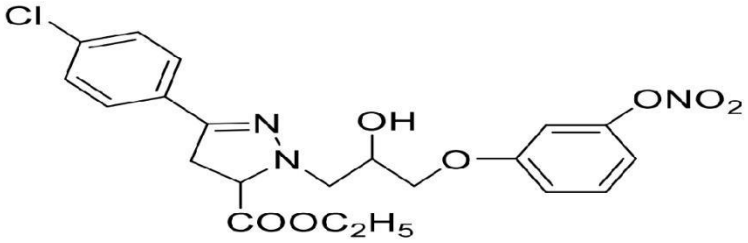


(E)-N-(4-(2-(3-methyl-1-phenyl-1H-pyrazol-5-yloxy)ethoxy)benzylidene)-4-methylbenzenamine

Anticancer Activity

- Different pyrazole derivative is linked with pyrimidine, carbohydrazide, as well as ferrocenyl molecule with pyrazole which is effective with carcinoma of lung cell.

- **Wei et al (2006) [13]** reported a series of novel small molecules of compound ethyl1-[20-hydroxy-30-aroxypropyl]-3-aryl-1H-pyrazole-5-carboxylate derivatives which have its potency to suppress lungs cancer cell growth.



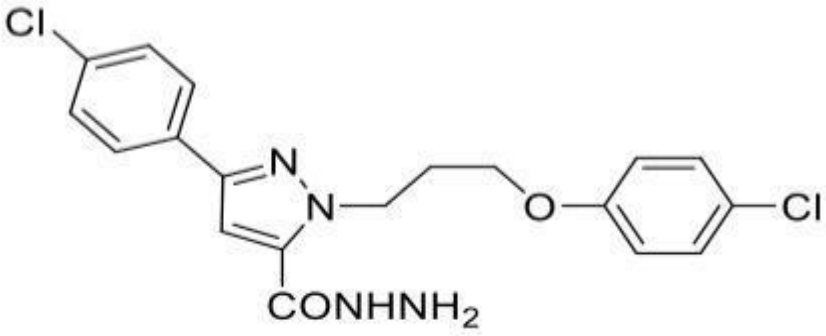
Ethyl1-[20-hydroxy-30-aroxypropyl]-
3-aryl-1H-pyrazole-5-carboxylate

- **Xia et al (2007)[14]** prepared a series of novel1-arylmethyl-3-aryl-1H-pyrazole-5-carbohyrazide derivatives which had inhibitory effects on the growth of A549 cells and induced the cell apoptosis.

R1,R2 = CH3, NH3

1-Arylmethyl-3-aryl-1H-pyrazole-5-carbohyrazide

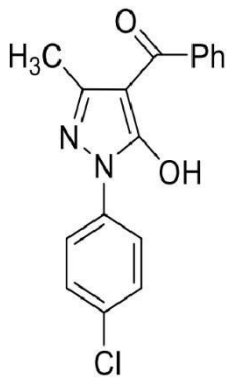
- **Fan et al (2008) [15]**reported a series of novel 1-(3-(4-chlorophenoxy)phenyl)-3-(4-chlorophenyl)-1H-pyrazole-5-carbohydrazide which is inhibiting the growth of A549 cells.46



1-(3-(4-chlorophenoxy)propyl)-3-(4-chlorophenyl)-1H-pyrazole-5-carbohydrazide

Anti-Tubercular Activity

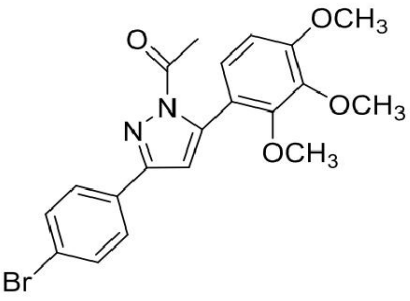
Manetti et al. (2006) [15] developed new inhibitors of mycobacterium tuberculosis. The compound 1-chlorophenyl-5- hydroxy-3-methyl-1h-pyrazol-4-yl)(phenyl)methanone was found to be the most active compound against mic value 25 µM/ mL.50 As per continuation of previous work turned towards the identification of antimycobacterial compound with innovative structure, the compound (1-(4-bromophenyl)-5-hydroxy3-methyl-1H pyrazol-4-yl)(4-chlorophenyl)methanone of pyrazole derivative were synthesized .



(1-(4-chlorophenyl)-5-hydroxy-3-methyl-1H-pyrazol-4-yl)(phenyl)methanone

castagnolo et al. (2008) [16]an was assayed as inhibitor of **m tuberculosis H37Rv** .The pyrazole derivatives with the p-bromophenyl group at the N1 position was showed to be very active.

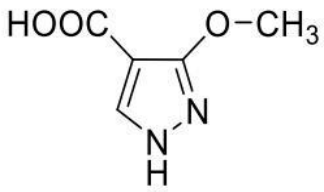
Pathak et al.(2014) [17]synthesized the various substituted 1-(3, 5-diary-4,5-dihydro-1H-pyrazol-1- yl) ethenone derivatives for their in vitro **anti-tubercular activity** against M. tuberculosis H37Rv strain.



1-(3-(4-bromophenyl)-5-(2,3,4-trimethoxyphenyl)-1H-pyrazol-1-yl)ethanone

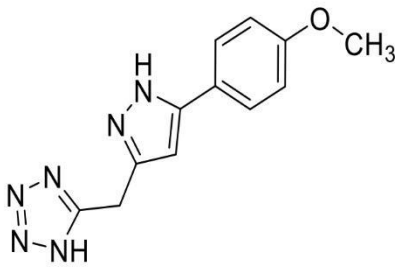
Antidiabetic Activity

Cottineau et al. (2002) [18] were reported and developed a new series of substituted pyrazole-4-carboxylic acid for their **antidiabetic activity.** The results indicated that the prepared compound 3-methoxy-1Hpyrazole-4-carboxylicacid emerges as best hypoglycaemic agent the results indicated that the prepared compound 3-methoxy-1H-pyrazole-4-carboxylic acid emerges as the best hypoglycaemic agent in the series.



3-methoxy-1H-pyrazole-4-carboxylic acid

Sharon et al. (2005) [19] were prepared a new series of 5-[(5-arly-1H-pyrazol-3-yl) methyl]-1H-tetrazoles and isolated them for their in vivo **anti-hyperglycaemic activity.** Out of screen compound demonstrated 24.6% of blood glucose-lowering activity at 100 mg/kg.



5-((5-(4-methoxyphenyl)-1H-pyrazol-3-yl)methyl)-1H-tetrazole

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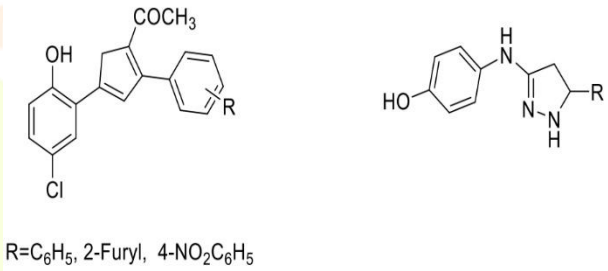
Analgesic Activity

Rajasekaran et al (2012)[20] novel [1-(3-(5-chloro-2-hydroxy phenyl)-5-aryl-4,5-dihydro pyrazol-1-yl] ethanone derivatives has been synthesized and were screened for **analgesic activity** by acetic acid-induced writhing inhibition method. Results showed that all the synthesized compounds shown significant activity when compared with that of standard drug.

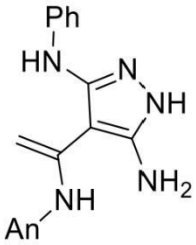


R=C_6H_5, 2-Furyl, 4-$NO_2C_6H_5$

Antimicrobial Activity

Bondock et al (2008)[21] reported the synthesis and **antimicrobial activity** of some new heterocycles incorporating **antipyrine** moiety. 2-cyano-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-

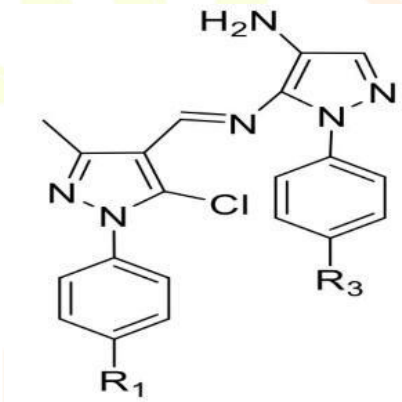
dihydro-1H-pyrazol-4-yl) acetamide was utilized as a key intermediate for the synthesis of some new coumarin, pyridine, pyrrole, thiazole, pyrido, pyrazolo triazine and amino pyrazole.



Anti-TMV Activity

The commercially available plant virucide Ningnammycin was used as a positive control. The anti-viral bioassay against TMV is assayed by the reported method and the

anti-viral results of all the compounds. the results showed that most of the targets compound present excellent anti-TMV activities at 500mg/L.89

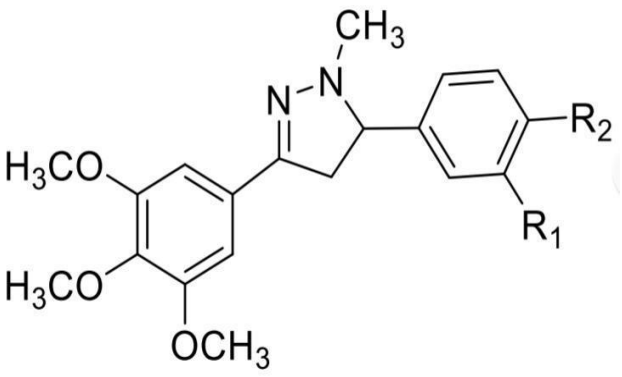


R_1=-H, -Cl, $-CH_3$

R_3=-F, $-CH_3$, -H, $-CF_3$

ACE Inhibitors

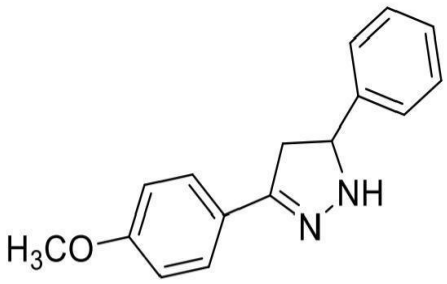
Bonesi et al (2010)[22] produced a series of pyrazole derivatives and examined their potential activity as Angiotensin-I-converting enzyme inhibitory (ACE inhibitors) activity by performance evaluation.



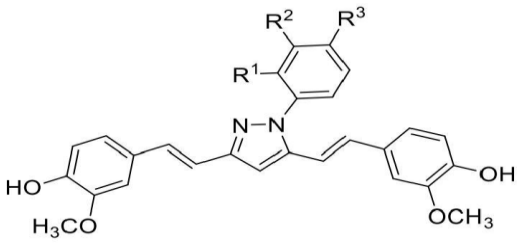
$R_1 = NO_2$ $R_2 = OCH_3$

Neuroprotective Activity

Cocconcelli et al (2008), have described the parallel synthesis of aryl azoles. Here substituted phenylhydrazine is made to react with an α, β-unsaturated ketones, which leads to the regioselective formation of 4,5-dihydro-1Hpyrazole and acetic acid was used as a catalyst. Compounds possess good neuroprotective activity.92



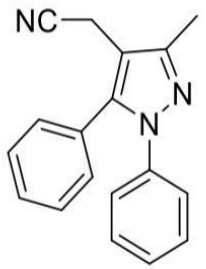
Scientist reported the therapeutic potential of Curcuminoid pyrazole in the treatment of Parkinson disease. Curcuminoid pyrazole, inhibits the deposition of the neurotoxic α-synuclein aggregates in the brain.93



R^1= -H,-Cl R^2= -H, $-NO_2$
R^3=-H, -F

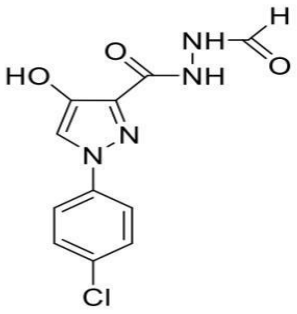
Anti-viral Activity

Genin et al (2000) were synthesized a novel 1,5-diphenylpyrazole class of HIV-1 nonnucleoside reverse transcriptase inhibitors. Compound 2-(3-methyl-1,5-diphenyl-1H-pyrazol-4-yl)acetonitrile was found to have good activity verse wild-type and delaviridine-resistant P236L reverse transcriptase.72



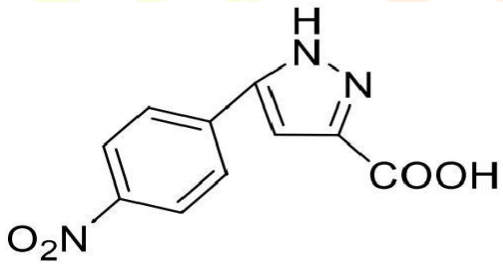
2-(3-Methyl-1,5-diphenyl-1H-pyrazol-4-yl)acetonitrile

Rostom et al (2003) were reported a new series of 1-(4-chlorophenyl)-4-hydroxy-1Hpyrazole-3-carboxylic acid hydrazide analogs and were tested for their in vitro effect on the replication of hepatitis-C virus (HCV) in HepG2 hepatocellular carcinoma cell line infected with the virus using the reverse transcriptase-polymerase chain reaction technique. The results revealed that compound 1-(4-chlorophenyl)-Nformyl-4-hydroxy-1H-pyrazole-3-carbohydrazide were capable of inhibiting the replication of both the HCV RNA(+) and (-) stands at 10-100 µg/mL concentration range.74



1-(4-Chlorophenyl)-N'-formyl-4-hydroxy-1H-pyrazole-3-carbohydrazide

Zeng et al (2008) have been reported novel phenylsubstituted 1H-pyrazole-3-carboxylic acids and were conveniently examined concerning the effect on the IN inhibition and HIV replication. The best antiviral effect was exhibited by 5-(4-nitrophenyl)-1H-pyrazole-3-carboxylic acid and 3-(3-(benzyloxy)phenyl)isoxazole-5-carboxylic acids 46 with an EC50 value of 3.7 and 254 μM.75



5-(4-nitrophenyl)-1H-pyrazole-3-carboxylic acid

CONCLUSION:-

Pyrazole represents a major pharmacophore with various biological properties, and some pyrazole- containing derivatives have already been used for therapeutic purposes. This shows that pyrazole derivatives are pharmacologically very potent and, therefore their design and synthesis is the potential area of research. It has been noted so far that the structural modifications of the basic structure of pyrazole, have allowed the preparation of new derivatives with a broad spectrum of biological activity, with the most important structural variations concerning the substituent at the 1- position, the carbon at the 3-position and the substituents at the 5-position.Previous studies have shown that the structural modification on the different positions of basic molecule allows for improving its pharmacological profile, giving it antimicrobial,

anticonvulsant, analgesic, anti-inflammatory,anti-viral anti-malarial and anti- malarial and anti-cancer properties. For the moment, researchers have been drawn to the design of more potent pyrazole derivatives having great diversity. The pyrazole compounds were designed to have antibiotic activity which used docking studies.

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