WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 12, 731-746. Review Article ISSN 2277– 7105

A REVIEW ON HETEROCYCLIC COMPOUND PYRAZOLE

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Article Received on
11 July 2022,
Revised on 01 August 2022,
Accepted on 22 August 2022
DOI: 10. 20959/wjpr202212-25372

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ABSTRACT

Pyrazole is an important five membered heterocyclic compound. Most of the drugs contain a heterocyclic nucleus. This heterocyclic nucleus play an important role in the activity of that drug. This review deals with the importance of pyrazole moiety as a heterocyclic compounds.

KEYWORDS: Heterocyclic, Pyrazole.

INTRODUCTION

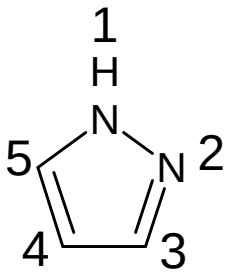
Pyrazoles are five - membered heterocycles that constitute a class of compounds particularly useful in organic synthesis. They are one of the most studied groups of compounds among the azole family. Indeed, a huge variety of synthesis methods and synthetic analogues have been reported over the years. The presence of the pyrazole nucleus in different structures leads to diversified applications in different areas such as technology, medicine and agriculture. In particular, they are described as inhibitors of protein glycation, antibacterial, antifungal, anticancer, antidepressant, anti-inflammatory, anti-tuberculosis, antioxidant as well as antiviral agents. Now a day, pyrazole systems, as biomolecules, have attracted more attention due to their interesting pharmacological properties. This heterocycle can be traced in a number of well-established drugs belonging to different categories with diverse therapeutic activities.[1]

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 fezolamide 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. Studies on the synthesis and biological activity of pyrazole derivatives developed by many scientists around the globe are reported.

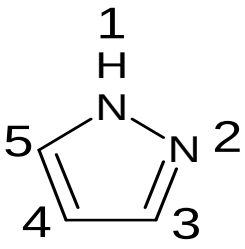
PYRAZOLE[2]

The term Pyrazole was given by Ludwig Knorr in 1883. 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 the 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 the seeds of watermelons.



Pyrazole derivatives have a long history of application in agrochemicals and pharmaceutical industry as herbicides and active pharmaceuticals.

NOMENCLATURE



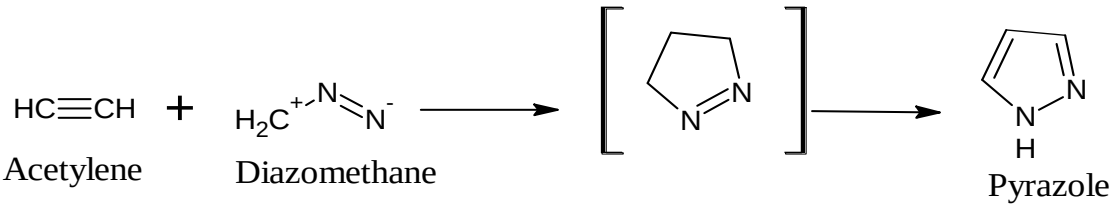
Pyrazole is a π-excessive heterocycle and contain two nitrogen atoms.

The IUPAC name of pyrazole is 1, 2 AZOLES.

SYNTHESIS OF PYRAZOLE[3]

1. FROM ACETYLENE

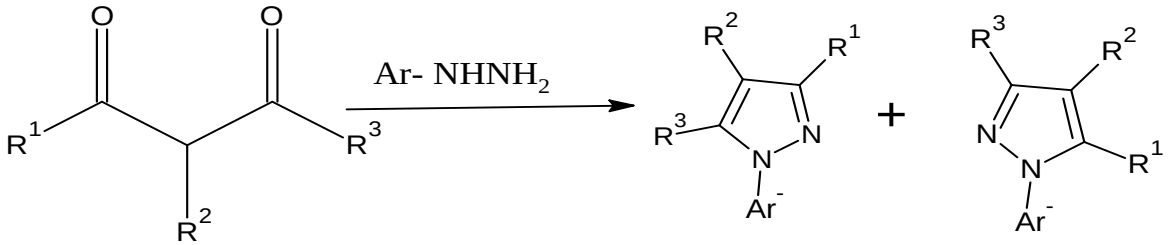
By passing acetylene into a cold ethereal solution of diazomethane.



2. CYCLOCONDENSATION OF HYDRAZINE AND ITS DERIVATIVES ON 1,3 DIFUNCTIONAL SYSTEMS

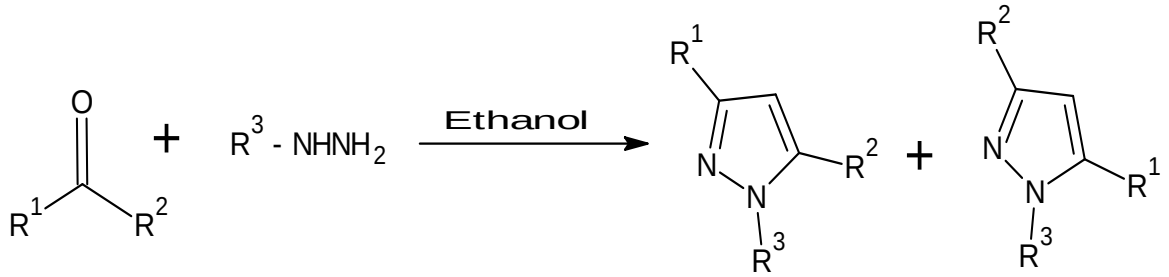
a. From 1, 3 diketones

The cyclocondensation of the 1,3dicarbonyl compounds with the hydrazine derivatives is a simple and rapid approach to obtain polysubstituted pyrazoles. The first synthesis of the substituted pyrazoles was carried out in 1883 by Knorr et al. who reacted beta - diketone with hydrazine derivatives to give two regioisomers.



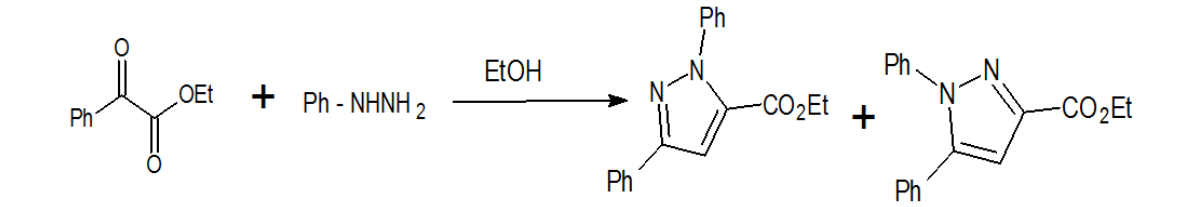
b. From Acetylenic ketone

The cyclocondensation reaction of hydrazine derivatives on acetylenic ketones to form pyrazoles has been known for more than 100 years. However the reaction results in a mixture of regioisomers.



The diacetylene ketones reacted with phenyl hydrazine in ethanol to give two regioisomeric pyrazoles. When phenyl hydrazine was used a mixture of region-isomers was generated in

approximately 3:2 ratio. When hydrazine hydrate was used as the nucleophile, only regioisomer was isolated, presumably due to hydrogen bonding to the ethyl ester group.



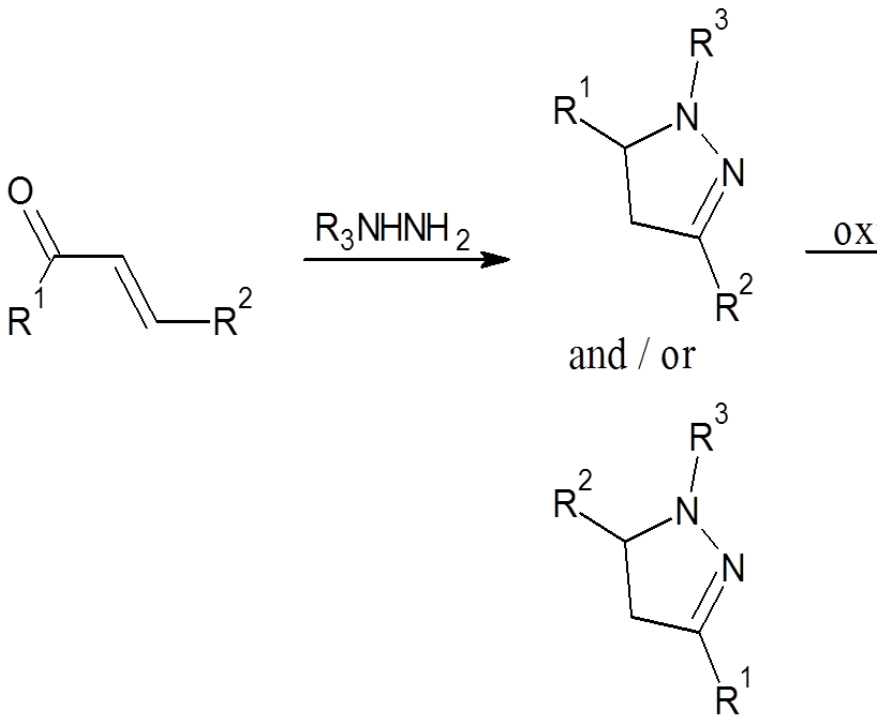
Ethyl oxo (phenyl) acetate

Ethyl 1,3-diphenyl-1*H*-pyrazole-5-carboxylate

Ethyl 1,5-diphenyl-1*H*-pyrazole-3-carboxylate

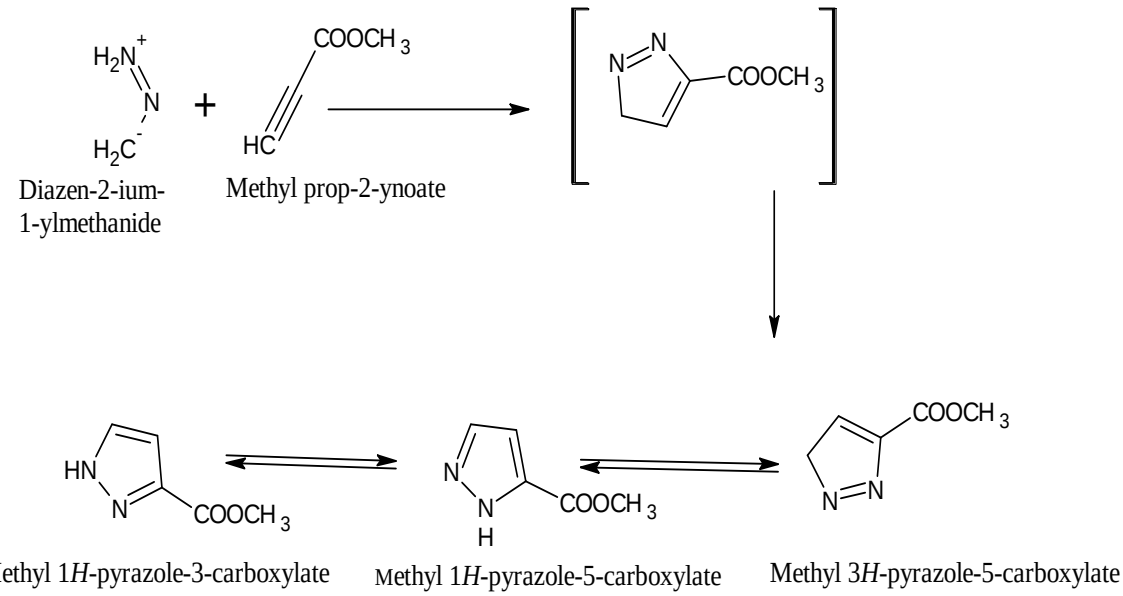
c. From Vinyl Ketones

The cyclocondensation reaction between an α, β-ethylenic ketone and a hydrazine derivative results in the synthesis of pyrazolines which, after oxidation, provide the pyrazole ring.



d. 1, 3-Dipolar Cycloadditions[4]

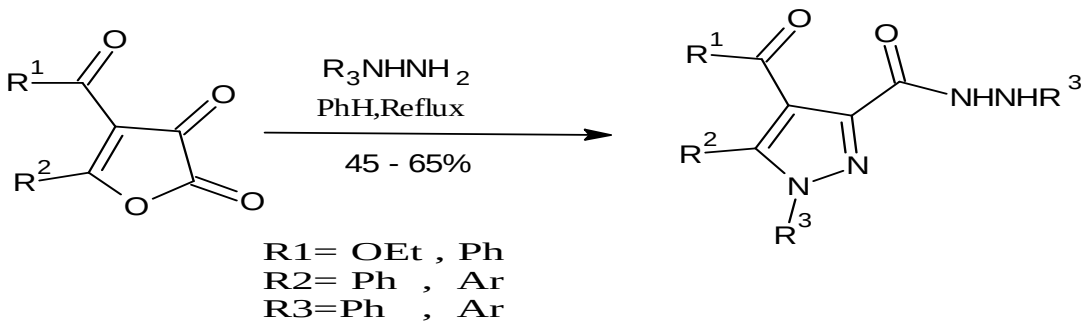
1, 3 Dipolar cycloaddition of diazoalkanes with functionalized alkynes results in the formation of pyrazoles. The reaction proceeds through a transition state involving energetically most favourable interaction of 4π-electrons of 1,3 –dipole [diazoalkane – with electroplilic and neutrophilic centres –ambivalent]with 2π- electrons of dipolarophile.



3. FROM HETEROCYCLIC SYSTEM[3]

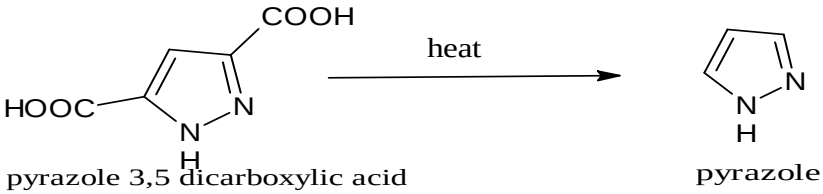
From Furandiones

Ilham et al. carried out condensation in refluxing benzene, furan - 2,3-diones with aryl hydrazines allowing access to pyrazole-3- hydrazides in acceptable to good yields(45-65%). Similarly, condensation of furan - 2,3-dione with N-benzylidene-N'-(4-nitrophenyl)hydrazine afforted 4-benzoyl-1-(4-nitrophenyl)-5-phenyl-1H-pyrazole-3-carboxylic acid in a 45% yield.



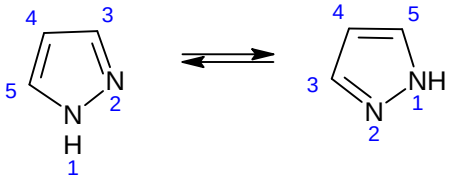
4. FROM PYRAZOLE DERIVATIVES

The simple pyrazole compounds are frequently obtained from their derivatives. Decarboxylation of various pyrazolecarboxylic acids, on heating, give pyrazole.



PHYSICAL PROPERTIES[4]

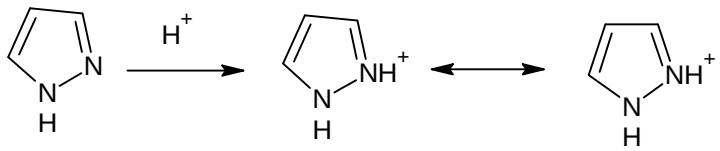
Pyrazole is a colorless solid with melting point 70°C and boiling point 185°C, crystallizes in long needles. The high melting point is due to intermolecular hydrogen bonding. The important physical property of pyrazole is the existence of tautomerism, which can only be demonstrated in pyrazole derivatives and not in the pyrazole itself.



If pyrazole is tautomeric, then the positions 3 and 5 will be identical; if pyrazole is not tautomeric, then these positions are different. Now Knorr *et al* showed that on oxidation, both 3-methyl-1- phenylpyrazole and 5-methyl-1-phenylpyrazole gave the same product. Thus positions 3and 5 must be equivalent in pyrazole, and this can only be explained by assuming that pyrazole is tautomeric.

Pyrazole exhibits aromatic properties, e.g, it is readily halogenated, nitrated, sulphonated; the group enters at position 4. The following resonating structures are possible for pyrazole.

The position 4 in pyrazole carries a large π- electron charge than any of the other nuclear carbon atoms. Hence the position 4 will be the most likely site of attack by an electrophonic reagent. The position 4 is the favoured site for electroplilic attack but the rate of reaction decreases due the positive charge of nitrogen atoms and the electrostatic repulsion between protonated substrate and the nitroniun ion.



The chemical reactivity of the pyrazole molecule can be explained by the effect of individual atoms. The N-atom at position 2 with two electrons is basic and therefore reacts with electrophiles. The N-atom at position 1 is unreactive, but loses its proton in the presence of base. The combined two N-atoms reduce the charge density at C3 and C5, making C4 available for electrophilic attack. Deprotonation at C3can occur in the presence of strong base, leading to ring opening. Protonation of pyrazoles leads to pyrazolium cations that are

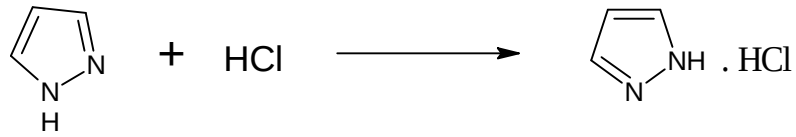
less likely to undergo electrophilic attack at C4, but attack at C3 is facilitated. The pyrazole anion is much less reactive toward nucleophiles, but the reactivity to electrophiles is increased.

Pyrazoles are aromatic molecules due to their planar conjugated ring structures with six delocalized π-electrons. Therefore, many important properties of these molecules were analyzed by comparing with the properties of benzene derivatives like other nitrogen involving heterocycles, different tautomeric structures can be written for pyrazoles. Unsubstituted pyrazole can be represented in three tautomeric forms.

CHEMICAL PROPERTIES[6]

1. Reaction with inorganic acids

Pyrazole is a feebly basic compound and forms salts with inorganic acids.



Pyrazole Pyrazole hydrochloride

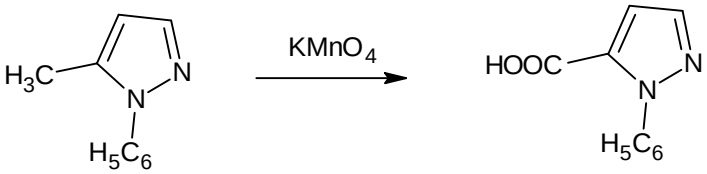
2. Acylation

Pyrazole when treated with acetic anhydride, the imino hydrogen atom of the pyrazole nucleus may be replaced by an acyl group.

Pyrazole N-acetylpyrazole

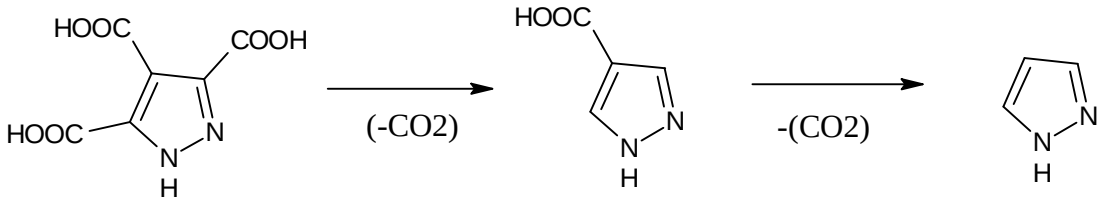
3. Oxidation

Like benzene, pyrazole is very resistant to oxidation. But again like alkylated benzene, C-alkylated pyrazole may be readily oxidised to the corresponding carboxylic acid.



The pyrazole carboxylic acids resemble pyridine carboxylic acids in many points. For example, when polycarboxylic acids of either of them are heated, corresponding mono

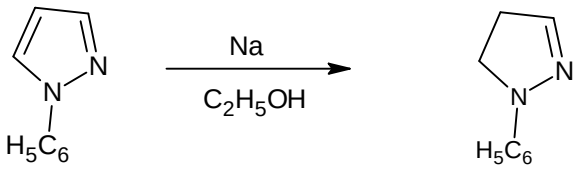
carboxylic acids are obtained and it is observed that the carboxyl group in the α-position to nitrogen is the first to be removed. By a repetition of the decarboxylation process at higher concentration the monocarboxylic acids are converted into the parent compounds.



Pyrazole-3,4,5-tricarboxylic acid — Pyrazole-3-carboxylic acid — Pyrazole

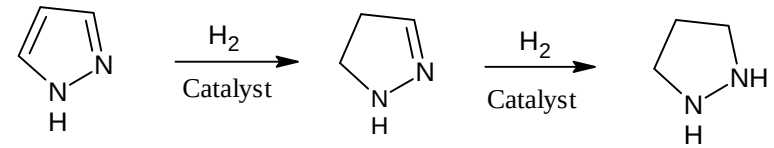
4. Reduction

Although pyrazole itself is resistant to reduction by sodium - ethanol, its N-phenyl derivative may be reduced by sodium – ethanol to the corresponding pyrazoline.



1-Phenyl-1*H*-pyrazole — 1-Phenyl-4,5-dihydro-1*H*-pyrazole

However, pyrazole itself may catalytically be reduced to pyrazoline and pyrazolidine.

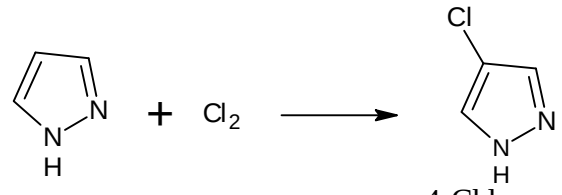


Pyrazole — Pyrazoline — Pyrazolidine

The two reduced products are stronger than pyrazole.

5. Halogenation

Halogenation takes place at position 4 form 4-halopyrazole.

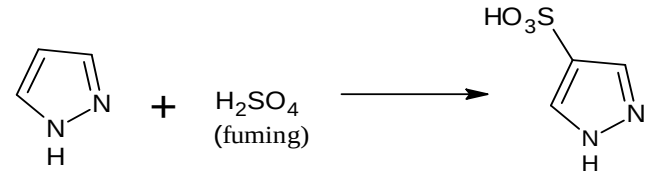


Pyrazole — 4-Chloropyrazole

In halogeno pyrazole, the halogen atom attached to nucleus is even more firmly held than in benzene derivatives.

6. Sulphonation

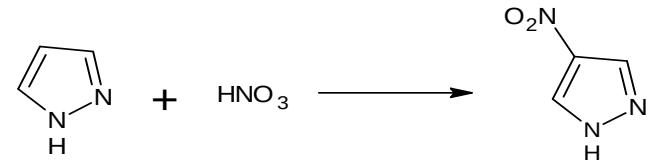
Pyrazole treated with fuming sulphuric acid leads to sulphonation at 4th position.



Pyrazole Pyrazole 4-sulphonic acid

7. Nitration

Pyrazole may readily be nitrated by means of concentrated nitric acid.

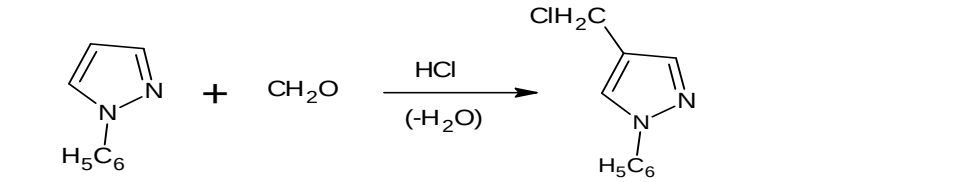


Pyrazole 4-nitropyrazole

Like the aromatic nitro compounds, 4 – nitropyrazole can be reduced to 4 – aminopyrazole which again resembles the aromatic bases in its behaviour, ie; diazotization to form diazo-pyrazole.

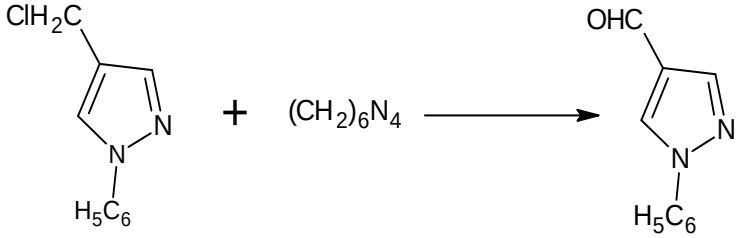
8. Chloromethylation

Pyrazoles having free imino group cannot be chloromethylated; and in such cases carbinols are obtained.



N-Phenylpyrazole 4-Chloromethyl-N-phenylpyrazole

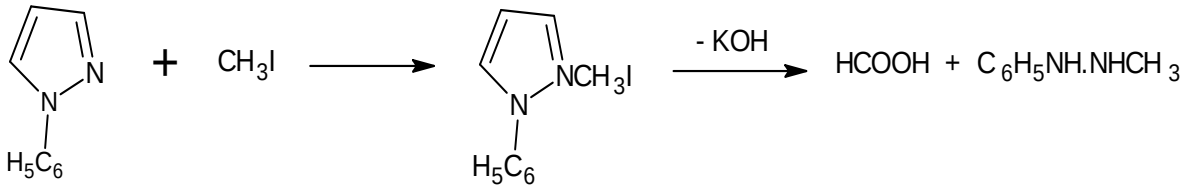
Chloromethyl derivative can be converted into aldehyde by refluxing it with hexamethylenetetramine in aqueous ethanolic solution followed by acidification resemblance with benzyl chloride.



4-Chloromethyl-N-phenylpyrazole N-Phenylpyrazole-4-aldehyde

9. Reaction with alkyl halide

N- Phenylpyrazole when treated with methyl iodide forms quaternary pyrazole which on boiling with concentrated aqueous potassium hydroxide decomposes to substituted hydrazine



1-Phenyl-1*H*-pyrazole

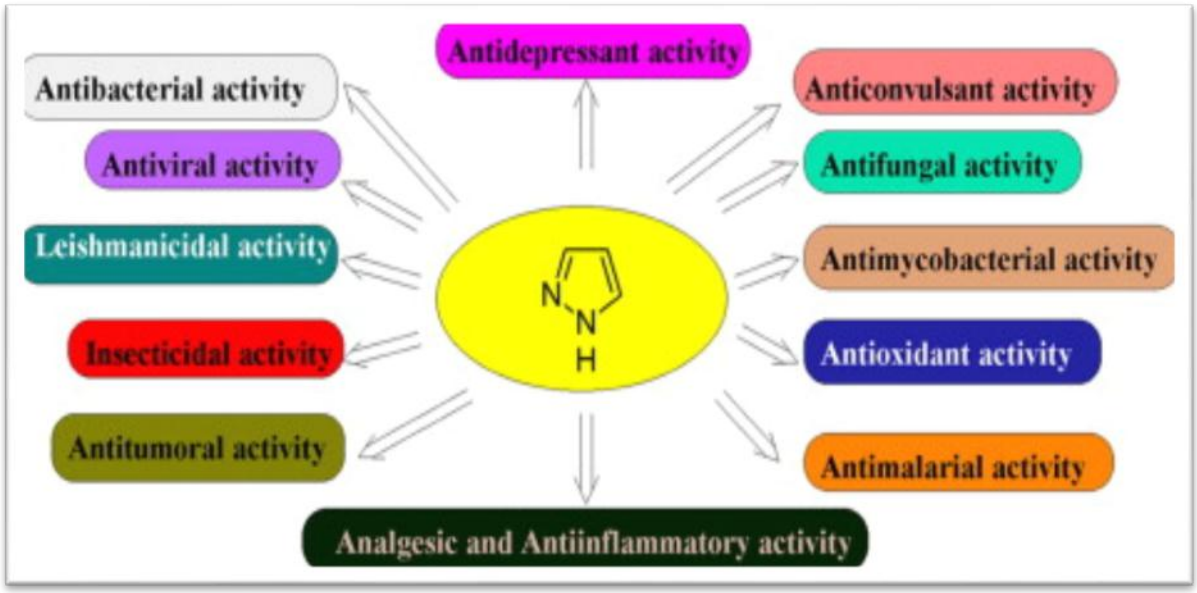
SPECTRAL DATAS OF PYRAZOLE[7]

Basic structural characterization of pyrazole derivatives includes spectroscopy, thermal analysis, and other aspects. Advanced techniques such as two-dimensional (2D) 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).

PHARMACOLOGICAL ACTIVITIES[8]

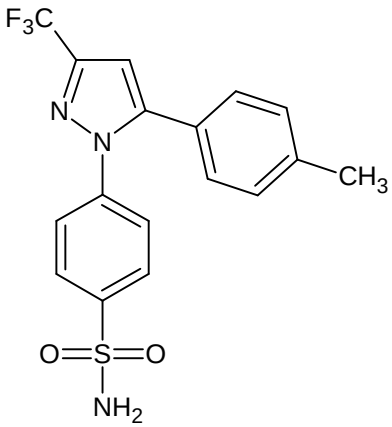
Pyrazole derivatives possess a wide range of bioactivities including anti-inflammatory, anticonvulsant, anticancer, and antifungal behavior. Barret et al. (2011) reported a fluorinated pyrazole derivative that was able to inhibit selective hypoxia-inducible factor prolyl hydroxylase. Hypoxia-inducible factor-α (HIF-α) mediates the cells' 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)-1Hbenzoimidazol-2yl)-1H-pyrazole-4-carboxylic acid. It is used for the treatment of a range of anemic conditions.

The pyrazole moiety has many pharmacological activities. Many drugs contain pyrazole ring in their structure. Some of the important drugs are Celecoxib, Phenylbutazone, Fipronil etc.



DRUGS CONTAINING PYRAZOLE NUCLEUS

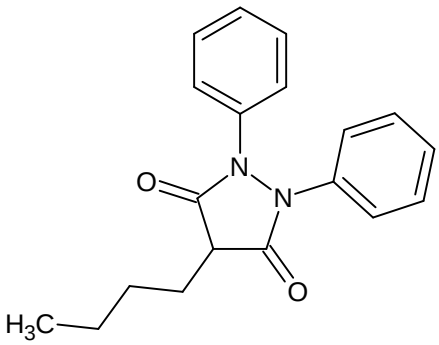
1. Celecoxib[9]



Celecoxib is a non –steroidal anti- inflammatory drug (**NSAID**).

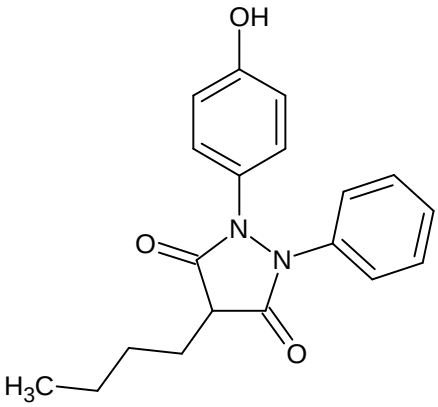
Used in the treatment osteoarthritis, rheumatoid arthritis, acute pain, painful menstruation and menstrual symptoms.

2. Phenyl butazone[7]



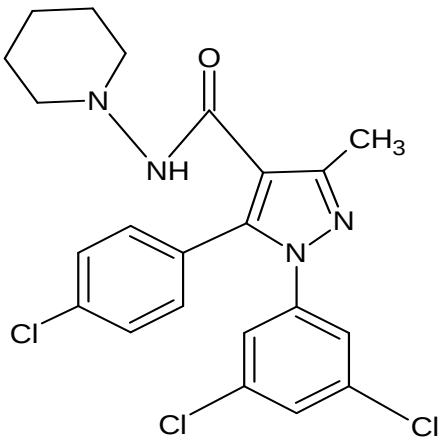
Phenylbutazone is a non-steroidal anti-inflammatory drug (**NSAID**) effective in treating fever, pain, and inflammation in the body. As a group, NSAIDs are non-narcotic relievers of mild to moderate pain of many causes, including injury, menstrual cramps, arthritis and other musculoskeletal conditions.

3. Oxyphenbutazone[10]



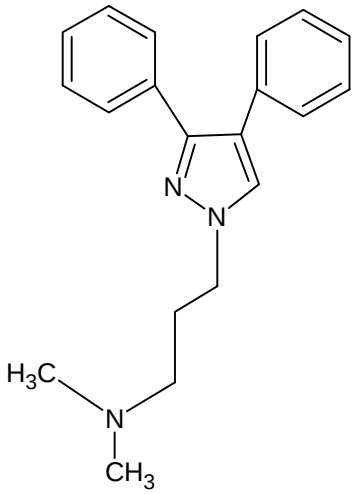
Commonly used (as its hydrate) to treat pain, swelling and stiffness associated with arthritis and gout, it was withdrawn from the market 1984 following assosciation with blood dyscrasis and Stevens-Johnson syndrome. Oxyphenbutazone is a non steroidal anti-inflammatory drug (**NSAID**).

4. Rimonabant



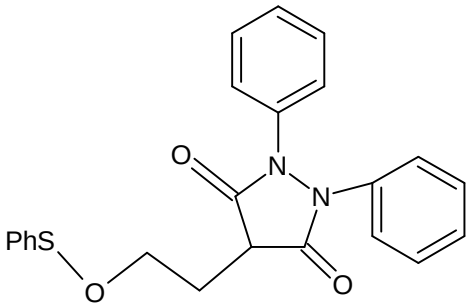
Rimonabant is an **anti-obesity** drug produced and marketed by Sanofi-Aventis. It is an inverse agonist for the cannabinoid receptor CB1. Its main avenue of effect is reduction in appetite. Rimonabant is the first selective CB1 receptor blocker to be approved for use anywhere in the world.

5. Fezolamine[11]



Fezolamine is a new, nontricyclic potential antidepressant.

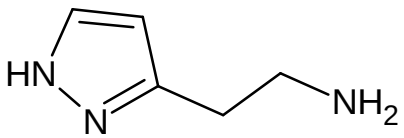
6. Sulphinpyrazone[7]



Sulfinpyrazone belongs to a class of drugs known as **uricosurics**.

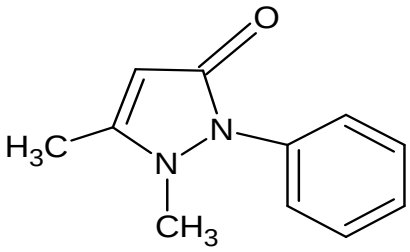
This medication is used to prevent gout and gouty arthritis. It will not treat a sudden/severe attack of gout and may make it worse. Gout occurs when our uric acid level gets too high, forming uric acid crystals in the joints that cause pain.

7. Betazole[12]



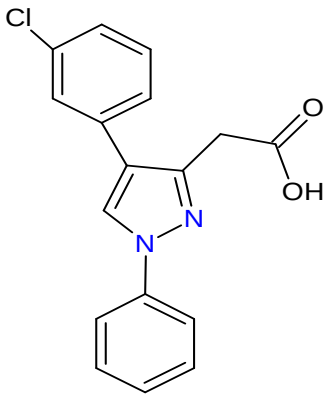
Betazole (also known as ametazole) is a histamine **H_2 receptor agonist**. Betazole hydrochloride is known as gastramine. It has been used as a gastric stimulant to test for maximal production of gastric secretion activity.

8. Phenazone



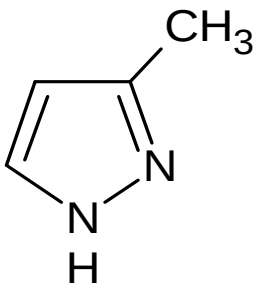
Phenazone, known in the U.S. as Antipyrine, is a pain reliever, and a fever reducer. It is combined in ear drops with benzocaine, a medication used to numb the ear. It is used to relieve ear pain caused by infections, and remove a buildup of ear wax.

9. Lonazolac



Lonazolac is a non-steroidal anti-inflammatory drug (NSAID). A drug that has principally analgesic, antipyretic and anti-inflammatory actions. Non-narcotic analgesics do not bind to opioid receptors.

10. Fomepizole



Fomepizole is an antidote to certain types of poison. Fomepizole is used to treat poisoning with ethylene glycol (antifreeze) or methanol. Fomepizole is sometimes used together with hemodialysis to rid the body of a poison.

CONCLUSION

Pyrazole is five membered heterocyclic rings which is versatile lead compound for designing potent bioactive agent. Pyrazole being heterocyclic planar five membered rings have various pharmacological actions. These Pyrazole skeletons comprise various ranges of pharmacological activities such as analgesic, antipyretic, anticancer, antiviral, anti-inflammatory, antioxidants, antimicrobial, anti-diabetic, anticonvulsant, and arrhythmic activities. Pyrazole is a multipurpose lead compound developed by chemical architecture for effective molecules which are biologically active.

This literature review 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. The docking studies on pyrazole provide an idea about its activity. The heterocyclic compounds undergo the most common synthesis methods such as cyclocondensation and Michael addition when react with hydrazine hydrate to form a pyrazole moiety. Some important drugs containing Pyrazole moiety are also discussed in this review.

REFERENCES

1. Khalid Karrouchi, Smaail Radi, Youssef Raml, Jamal Taoufik. A Review on Synthesis and Pharmacological Activities of Pyrazole Derivatives. Journal of MDPI, 2018; 12: 3-21.
2. Md. Jahangir Alam, Ozair Alam, Perwaiz Alam, Mohd Javed Naim. A Review on Pyrazole chemical entity and Biological Activity. International Journal of Pharma Sciences and Research, 2015; 12(6): 1443- 1144.
3. Seham Y. Hassan. Synthesis, Antibacterial and Antifungal Activity of Some New Pyrazoline and Pyrazole Derivatives. Journal of MDPI, 2013; 18(18): 2683-2711.
4. R.R.Gupta, M.Kumar, V.Gupta, Heterocyclic Chemistry, Volume –II, Page No:435-455
5. IL Finar, Organic Chemistry, Volume –II, Page No: 604.
6. O.P. Agarwal, Organic Chemistry- Reactions and Reagent, Page No: 719.
7. Rajeev Jain, Seema Gupta. Indian J. Heterocyclic Chemistry. 1996; 6:71-72.
8. Samet Mert1, Rahmi Kasimogullari1, Salim. A Short Review on Pyrazole Derivatives and their Applications. Journal of Postdoctoral Research, 2014; 4(2): 64-72.

9. Vishwanadham Yerragunta, Duggi Suman, Kumara swamy, V.Anusha, Pratima Patil, M. Naresh. Pyrazole and Its Biological Activity. Pharma Tutor Magazine, 1(2): 40-48.
10. Recent advances in bioactive pyrazoles, European Journal of Medicinal Chemistry, 2015; 97: 786-815.
11. Baizman Er, Ezrin Am, Ferrari Ra, Luttinger D. Pharmacologic profile of fezolamine fumarate: a nontricyclic antidepressant in animal models, 1989; 40-54.
12. A. Jamwal1, A. Javed, V. Bhardwaj. A Review on Pyrazole Derivatives of Pharmacological Potential. Journal of Pharmaceutical and Bio Science, 2013; 114-123.