Review Article

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Pyrazole: Their Chemistry and Pharmacological Potentials: A Review.

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Abstract
Pyrazole is a five membered heterocyclic ring which is a versatile lead compound for designing potent bioactive agents. This interesting group of compound has diverse biological activities such as antimicrobial, anti-inflammatory, analgesic, anticonvulsant, anticancer, antihelmintic, antioxidant, and herbicidal. Given data represents that pyrazole being heterocyclic planar five membered ring systems have various pharmacological actions. Results of various derivatives of different pyrazole and their substitutions are reviewed in present article. Various methods for synthesizing pyrazole are discussed with their pharmacological actions. These derivatives of pyrazole are analysed here for varying pharmacological activities.

Key Words
Pyrazole, Antimicrobial, Anti-inflammatory, Analgesic, Anticonvulsant, Anticancer.

Introduction
Pyrazole refers both to the class of simple aromatic ring organic compounds of the heterocyclic diazole series characterized by a 5-membered ring structure composed of three carbon atoms and two nitrogen atoms in adjacent positions, and to the unsubstituted parent compound. Being so composed and having pharmacological effects on humans, they are classified as alkaloids, although they are rare in nature.

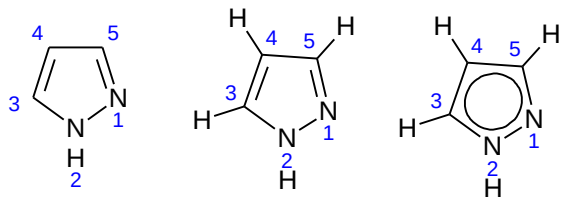

Figure No.-1

Molecular Formula	$C_3H_4N_2$
Formula Weight	68.07726
Composition	C (52.93%) H (5.92%) N (41.15%)
Molar Refractivity	18.77 ± 0.3 cm^3
Molar Volume	60.9 ± 3.0 cm^3
Parachor	161.0 ± 4.0 cm^3
Index of Refraction	1.528 ± 0.02
Surface Tension	48.6 ± 3.0 dyne/cm
Dielectric Constant	Not available
Polarizability	7.44 ± 0.5 $10^{-24}cm^3$
Monoisotopic Mass	68.037448 Da
Nominal Mass	68 Da
Average Mass	68.078461 Da

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Pyrazole, like its structural isomer imidazole, contains a pyrrole-like and a pyridine-like N atom, but in the 1- and 2-positions (1,2-diazole). The pyrazole molecule is planar. Bond lengths and bond angles have been calculated from microwave spectra. Consistent with the structural formula, the bond between atoms 3 and 4 is the longest. The ionization energy of pyrazole is 9.15 eV. It follows from a comparison with pyrrole (8.23 eV) that the pyridine-like N-atom reduces the energy of the HOMO, indeed even more so than in the case of imidazole (8.78 eV). The dipole moment of pyrazole in benzene was calculated to be 1.92 D. This value depends on the concentration, because cyclic dimers form at higher concentrations. The dipole moment is directed from the centre of the molecule to the bond between atoms 2 and 3. In most reactions of pyrazoles, an analogy with imidazoles is apparent, and comparisons are possible.

Acid— base reactions

Pyrazoles are much weaker bases than imidazoles, but can be precipitated as picrates. The conjugate acid of pyrazole has a *pKa* value of 2.52. The difference is due to the fact that the positive charge in the pyrazolium ion is less delocalized than in the imidazolium ion.

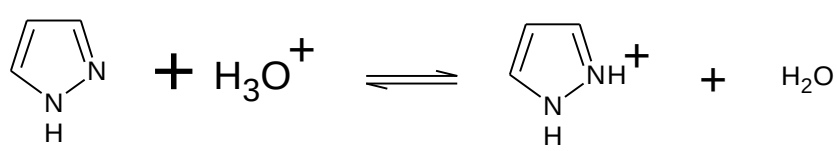


Figure No.-2

The gas-phase basicity (intrinsic basicity) for pyrazoles and imidazoles has been determined, as have their thermodynamic and kinetic basicities and proton affinities. Pyrazoles unsubstituted in the 1 -position show NH-acidity. The *pKa* value of pyrazole is 14.21 and equals that of imidazole. Pyrazole reacts with sodium to give the sodium salt. The sparingly soluble silver salt is formed with aqueous silver nitrate solution.

Annular tautomerism

Pyrazoles unsubstituted in the 1,2-position undergo tautomerism.

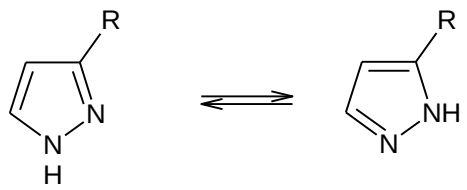


Figure No.-3

In solution, equilibrium is attained so rapidly that the existence of tautomers can only be demonstrated by means of ^{13}C and ^{15}N NMR spectroscopy. Other than for R = CH3, the equilibrium lies to the left i.e. the 3-substituted isomer predominates.

Reactions with electrophilic reagents

The best procedure for methylation of pyrazole is via the sodium salt which reacts with iodomethane or dimethyl sulfate,

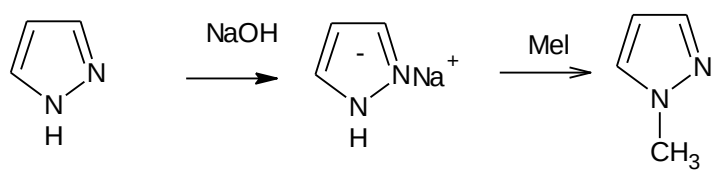


Figure No.-4

Benzylation, acetylation, benzoylation, methylsulfonation, methoxycarbonylation and trimethylsilylation of pyrazole are affected by analogous methods. Mixtures of 1,3- and 1,5-disubstituted pyrazoles are formed from 3- and 5-substituted pyrazoles because of the ambient nature of the pyrazolyl anion, e.g.:

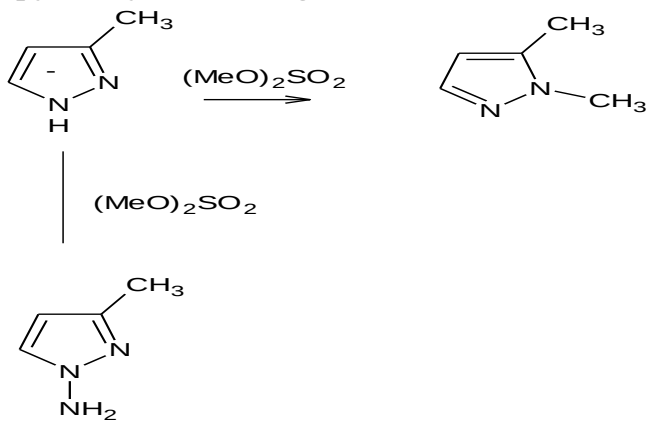


Figure No.-5

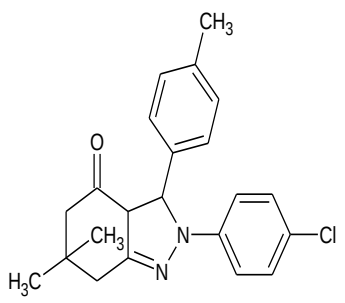
Electrophilic substitution on the C-atoms of pyrazole proceeds more slowly than for pyrrole and at about the same rate as for benzene. The pyrazole anion reacts faster and the pyrazolium ion much more slowly. The corresponding 4-halopyrazoles are produced by the action of chlorine or bromine in acetic acid. Nitrating acid yields 4-nitropyrazoles and, dependent on the substituents in the pyrazole ring, reaction takes place either with pyrazole itself or the pyrazolium ion. Sulfonation involves the pyrazolium ion. For this reason, heating in oleum is necessary, which leads to pyrazole-4-sulfonic acid. Pyrazoles with substituents in the 1 -position yield pyrazole-4-carbaldehyde in the VlLSMElER-HAACK formylation and are amenable to FRIEDEL-CRAFTS acylation. 4- and 5 aminopyrazoles can be diazotized.

Reactions with nucleophilic reagents

Pyrazoles either do not react with nucleophiles, or react with them only very slowly. For instance, pyrazoles unsubstituted in the 3 -position undergo ring opening on heating with alkali hydroxides. Nucleophilic substitution of a halogen in halopyrazoles is also difficult.

Pyrazole as Anti-Microbial Activity

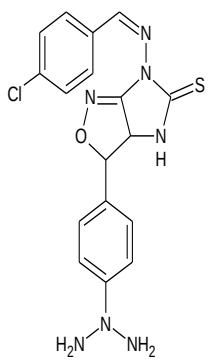
Vijay v. Dabholkar et.al[1]. Synthesized a series of fused isoxazole and pyrazole derivatives and the newly synthesized compounds (5(a–c)–8(a–c)) were screened for their antibacterial activity against *Escherichia coli (ATCC-25922), Staphyllococcus aureus (ATCC-27853), Corynebacterium diphtheriae and Proteus aeruginosa*. Out of all the synthesized compounds 6a, 7b showing good activity against S. aureus and 7c against C. diphtheriae as compaired to other derivatives.



2-(4-chlorophenyl)-6,6-dimethyl-3-(4-methylphenyl)-2,3,3a,5,6,7-hexahydro-4*H*-indazol-4-one

6a

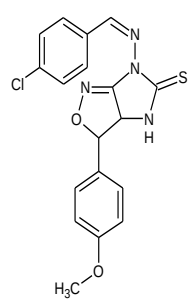
Figure No.-6



3-[4-(1-aminohydrazino)phenyl]-6-{[(1*Z*)-(4-chlorophenyl)methylene]amino}-3a,4-dihydro-3*H*-imidazo[4,5-*c*]isoxazole-5(6*H*)-thione

7b

Figure No.-7

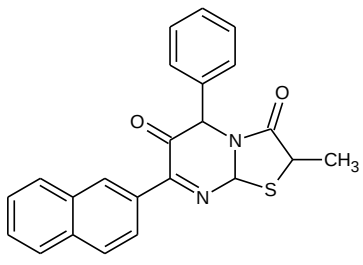


6-{[(1*Z*)-(4-chlorophenyl)methylene]amino}-3-(4-methoxyphenyl)-3a,4-dihydro-3*H*-imidazo[4,5-*c*]isoxazole-5(6*H*)-thione

7c

Figure No.-8

M.M. Youssef et.al[2] synthesized a series of some new pyrimidine, thiazolopyrimidine and pyrazole derivatives using diarylpoxypropaneone as precursors. The antimicrobial activity of the compounds considered was tested on 1) *Escheria coli*, 2) *Pseudomonas puticle,* 3) *Bacillus subtilis*, 4) *Streptococcus lactus,* 5) *Aspergillus niger*, 6) *Penicillium sp.* and 7) *Candida albicans.* Out of all the synthesized compound 5d showing good activity against all m'organism as compaired to other derivatives.

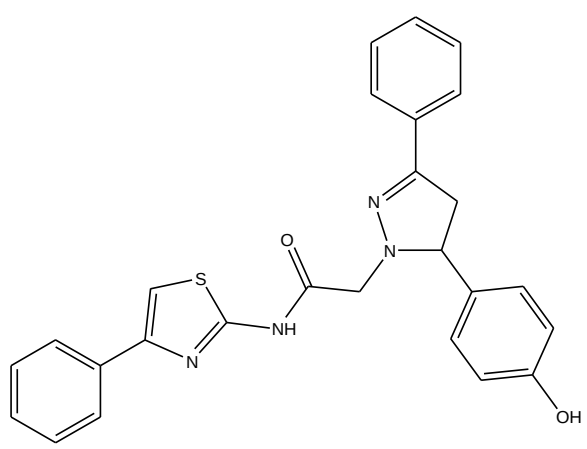


2-methyl-7-(2-naphthyl)-5-phenyl-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidine-3,6(2*H*,8a*H*)-dione

5d

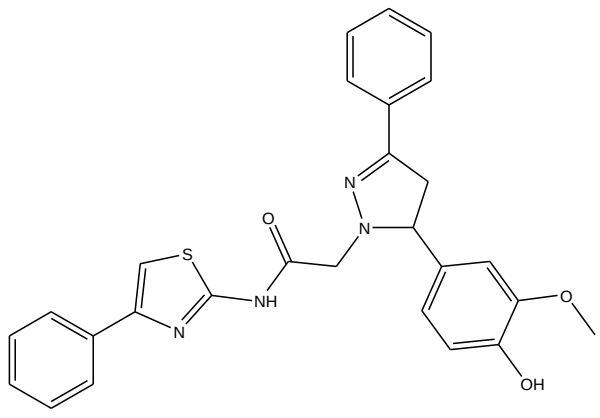
Figure No.-9

G. Saravanan *et. al*[3], synthesized a series of novel pyrazole derivatives. These compounds were screened for anti-bacterial (*Staphylococcus aureus* ATCC 9144, *Staphylococcus epidermidis* ATCC 155, *Micrococcus luteus* ATCC 4698, *Bacillus cereus* ATCC 11778, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 2853, and *Klebsiella pneumoniae* ATCC 11298)) and anti-fungal (*Aspergillus niger* ATCC 9029 and *Aspergillus fumigatus* ATCC 46645) activities by paper disc diffusion technique. Most of the synthesized compounds exhibited significant anti-bacterial and anti-fungal activities. Among the synthesized compounds, 2-(5-(4-hydroxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)-N-(4phenylthiazol-2-yl)acetamide (8f) was found to exhibit the highest anti-bacterial activity and 2-(5-(4-hydroxy-3-methoxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)-N-(4-phenylthiazol-2-yl)acetamide(8j) exhibited highest anti-fungal activity.



2-(5-(4-hydroxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)-N-(4- phenylthiazol-2-yl)acetamide

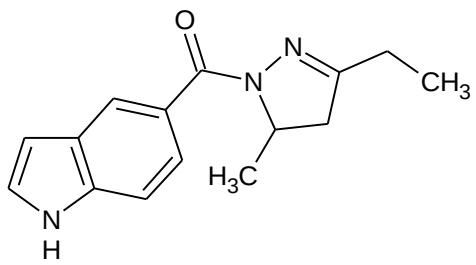
Figure No.-10



2-(5-(4-hydroxy-3-methoxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)-N-(4-phenylthiazol-2-yl)acetamide

Figure No.-11

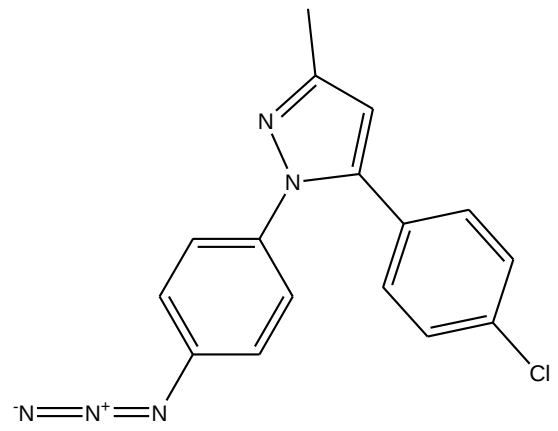
K. Narasimha Sarma *et. al*[4] , synthesized a series of pyrazole derivatives by by esterification of indole-5-carboxylic acid. All the newly synthesized compounds are by elemental analysis and spectral studies and evaluated for antimicrobial activities. The Compounds 7a and 7d exhibiting good activity against *E. coli* and compounds 7c and 7f show good activity of against *P. aeruginosa*, and compounds 7b, 7e and 7h showing good activity against *S. aureus*



5-[(3-ethyl-5-methyl-4,5-dihydro-1*H*-pyrazol-1-yl)carbonyl]-1*H*-indole

Figure No.-12

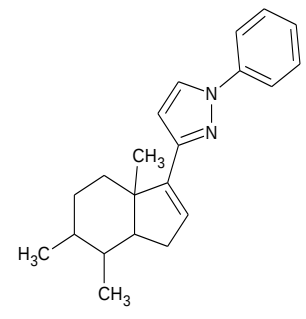
Vertika Gautam *et.al*[5] synthesized a series of 1, 3, 5-Trisubstituted Pyrazole Derivatives and screened for antimicrobial activity. The activity of the derivatives is more pronounced for Gram-negative microorganisms than for the Gram-positive ones. The compounds (2j-o) were evaluated against two gram-positive and two gram-negative bacteria and one fungus, at concentrations of 10 μg/mL and 50 μg/mL. The compounds were founds to be inactive against *P. aeruginosa* and *A. niger* but exhibited moderate activity against *B. subtilis*, *E. coli* and *S. aureus*. It can be concluded that the newly synthesized compounds possess promising antimicrobial activity.



1-(4-Azidophenyl)-5-(4-chlorophenyl)-3-methyl-1H-pyrazole

Figure No.-13

Rafat m. Mohareb *et. al*[6], synthesized a series of pyrazole derivatives of potential antimicrobial activity. Out of all compounds, compound 3b showing better activity.



1-phenyl-3-(3a,6,7-trimethyl-3a,4,5,6,7,7a-hexahydro-1*H*-inden-3-yl)-1*H*-pyrazole

Figure No.-14

R.N. Sharma, *et. al*[7], synthesized a series of aryl azopyrazoles derivatives synthesized compounds[*5a-t*] have been tested for their antibacterial activity against gram positive bacteria *S.albus* , *S.aureus* and gram negative bacteria *E.Coli* and *Pseudomonas piosineus* .The compound *5a,5c,5d,5e,5g and 5h* shown significant activity and compound *5b,5f,5i,5j,5k,5n and 5p* have shown moderate activity. The same compounds were tested for their antifungal activity against *candida albicans, aspergillus niger and alternaria alternata* at concentration of 30 mg/ml using sabouraud dextrose agar media. Compounds *5a,5c,5d,5g,5j,5m, and 5p* were found to be moderately active against *candida albicans* and *aspergillus niger*.

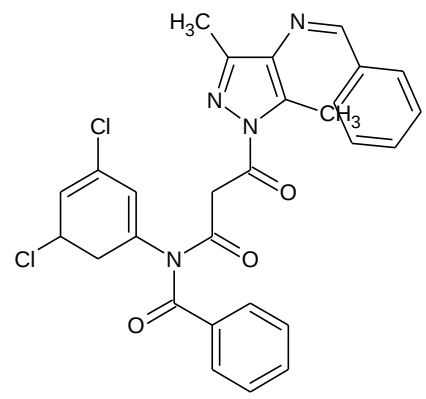
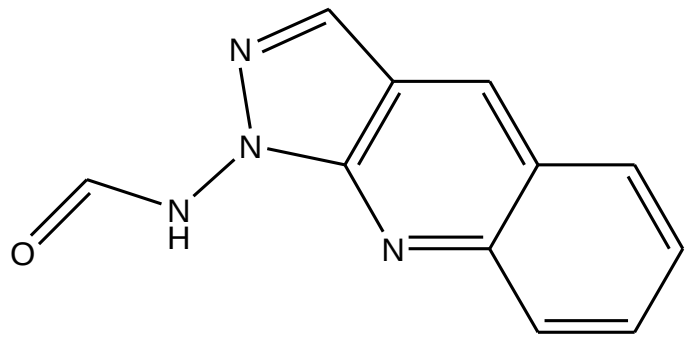


Figure No.-15

Vetrivel Nadaraj *et,al*[8] ,synthesized a series condensed pyrazole derivatives *in one pot by condensing various quinolines and semicarbazide in presence of catalytic amount of PTSA. All the synthesised compound have been characterised by their percentage yield, melting points, elemental analysis, 1H-NMR and 13C-NMR and IR spectra. These compounds have been screened for their antimicrobial activities*. Among them, compound 3a registered good antibacterial activity against most of the bacteria and fungi. The compound 3e and 3g showed excellent *in vitro* activity against *Escherichia coli*, and displayed moderate inhibition against other bacteria such as *Pseudomonas aeruginosa, Klebsiella aerogenes*, *Bacillus subtilis,* and *Staphylococcus albus.*



1-carbonamidopyrazolo[3,4-b]quinoline

Figure No.-16

Raj Narayan Sharma *et,al*[9], synthesized a series of 1-[(N-cinnamoyl) 2, 3-dichloroanilinomalonyl] 3, 5-dimethyl-4-(Unsubstituted/substituted phenylazo) pyrazoles derivatives. Newly synthesized compounds [5a-t] have been tested for their antibacterial activity against gram positive bacteria *S.albus, S.aureus* and gram negative bacteria *E.Coli* and *Pseudomonas piosineus*. The compound 5a, 5c, 5d, 5e, 5g and 5h shown significant activity and compound 5b, 5f, 5i, 5j, 5k, 5n and 5p have shown moderate activity.

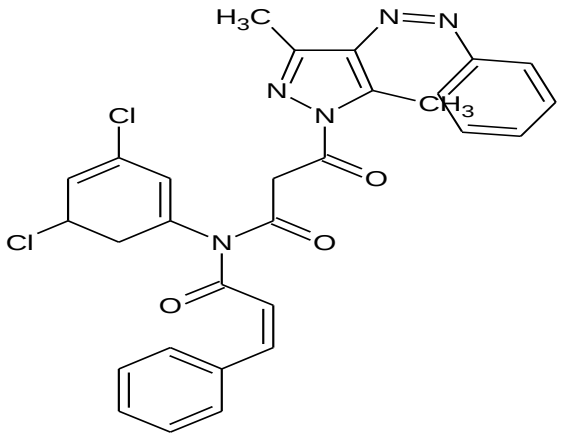


Figure No.-17

Nirav K Shah *et.al*[10], synthesized a series of pyrazole derivatives bearing quinoline derivatives and screened for their antimicrobial activity. In that all synthesized compounds, a differences derivative shows different activities against dram +ve and gram –ve bacteria.

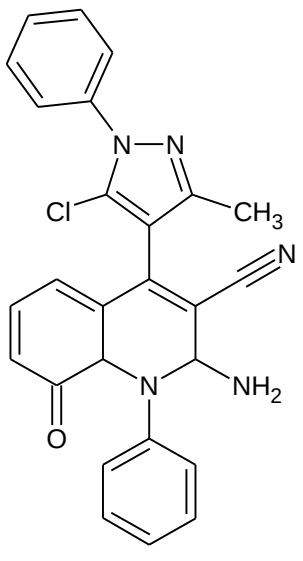
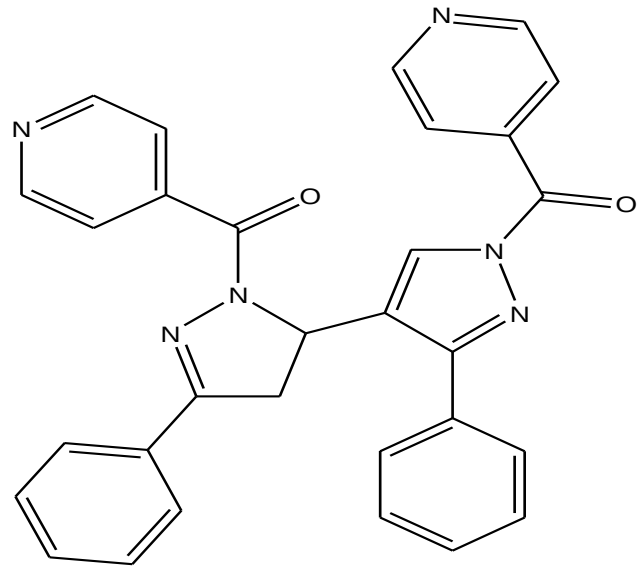


Figure No.-18

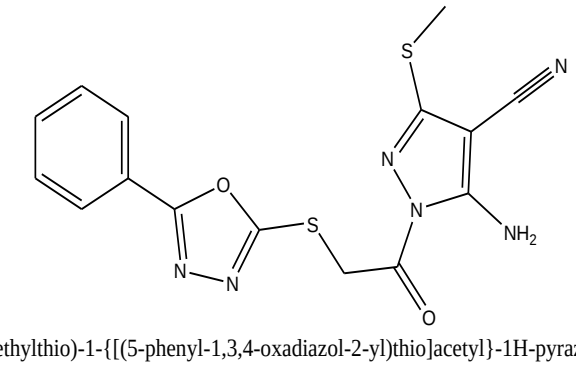
Ujjwal Sahoo *et.al*[11], synthesized a series of Microwave assisted certain novel bipyrazole derivatives All compounds have been screened *in vitro* for their antibacterial activity against *Staphylococcus aureus, Bacillus subtilis, Escherchia coli* and *Pseudomonas aeruginosa*, and also for their antifungal activity against *Candida albicans and Asperigillus niger*. Among the synthesized compounds, 4b, 4c and 4f showed better activity against *Candida albicans* and compounds, 4a, 4e and 4f showed better activity than rest of compounds against *Asperigillus niger* when compared with standard drug.



5,3'-diphenyl-1',2-diisonicotinoyl-3,4-dihydro-1'H,2H-3,4'-bipyrazole

Figure No.-19

Singaravel Mohan *et al*[12], synthesized a series of Some Novel Sulphur Bridged Pyrazoles derivatives. The synthesized pyrazole derivatives 5-10(a-b) were tested for antibacterial activity against both gram positive and gram negative bacteria such as *Staphylococcus aureus, Bacillus subtilis* from gram positive organisms and *Escherichia Coli, Pseudomonas aeruginosa* from gram negative organisms as well as for antifungal activity against Candida albicans. Among the various pyrazoles prepared above, the pyrazole derivative, 8b showed activity against *Bacillus subtilis* from gram positive organisms and Escherichia Coli from gram negative organism.

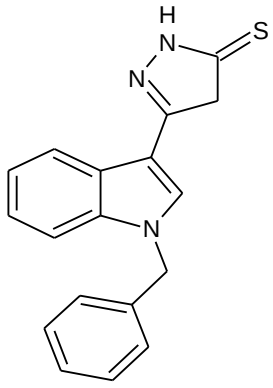


5-Amino-3-(methylthio)-1-{[(5-phenyl-1,3,4-oxadiazol-2-yl)thio]acetyl}-1H-pyrazole-4-carbonitrile

Figure No.-20

Abdel-Rahman *et. al*[1], synthesized a series of pyrazole derivatives and screened for their antibacterial activity. Some selected representatives of the newly synthesized compounds were screened in vitro for their antimicrobial activities against four strains of bacteria* (*Staphylococcus aureus, Serratia*

marcescens, Streptococcus, Pseudomonas aeruginosa) and two species of fungi (*Aspergillus parasitcus, Penicillium oxalicum*) Compound 30 exhibits a moderate activity against *Serratia marcescns.*

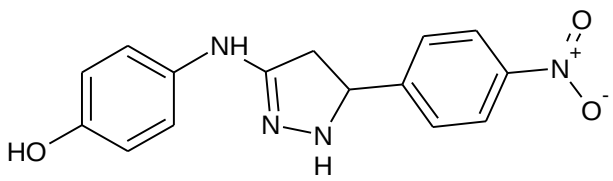


5-(1-benzyl-1*H*-indol-3-yl)-2,4-dihydro-3*H*-pyrazole-3-thione

Figure No.-21

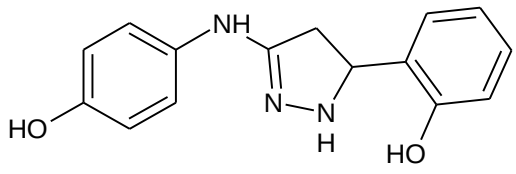
Pyrazole as Analgesic Activity:

SK Sahu *et.al*[14] synthesized a series of pyrazole derivatives and screened for their analgesic activity. The introduction of p-nitro and p-hydroxy group in aryl moiety of the pyrazole analogs 2c and 2e produce compounds with potent analgesic activity.



4-{[5-(4-nitrophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]amino}phenol

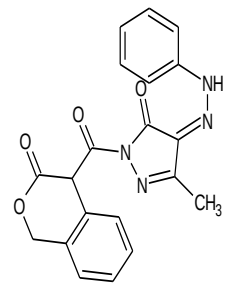
Figure No.-22



2-{3-[(4-hydroxyphenyl)amino]-4,5-dihydro-1*H*-pyrazol-5-yl}phenol

Figure No.-23

K. K. Sivakumar,*et.al*[15], synthesized a series of (4*Z*)-3-methyl-1-[(2-oxo-2*H*-chromen-4-yl) carbonyl]-1*H*-pyrazole-4, 5-dione 4-[(4- substitutedphenyl) hydrazone] (5a-i). The titled compounds were screened for their anti-inflammatory and analgesic activity. Among the synthesized compounds, compound 5a, 5c, 5g and 5h exhibited significant anti-microbial activity and compound 5a, 5b, 5d, 5h and 5i exhibited significant analgesic activity compared with the standard drug (indomethacin 5mg/kg) at the dose level of 50mg/kg on oral administration.

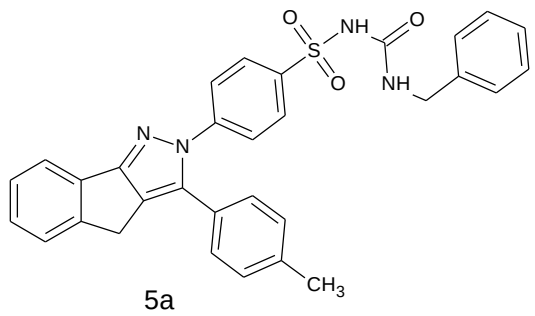


(4*Z*)-3-methyl-1-[(3-oxo-3,4-dihydro-1*H*-isochromen-4-yl)carbonyl]-1*H*-pyrazole-4,5-dione 4-(phenylhydrazone)

Figure No.-24

Pyrazole as Anticancer Activity

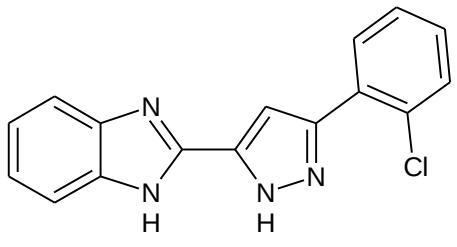
Mohammed S. M. Al-Saadi, *et al*[16], synthesized a series of pyrazole and pyrazoline fused ring systems substituted with variable biologically-active chemical species. Compound 5a proved to be the most active antitumor agent in the present study with GI50, TGI and LC50 MG-MID values of 8.12, 25.7 and 69.2 μM, respectively, with high sensitivity towards some leukemia, melanoma and renal cell lines.



5a

Figure No.-25

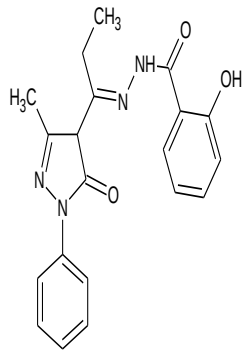
R. Kalirajan, *e .al*[17], synthesized a series of pyrazole derivatives. All the eight compounds were screened for their anticancer activity against MCF7 human breast cell line used in in-vitro methods. Only the Compounds (IV-b, g) have significant activity when compared with standard drug.



2-[3-(2-chlorophenyl)-1*H*-pyrazol-5-yl]-1*H*-benzimidazole

Figure No.-26

Xiao Hong Wang *et al.*[18], synthesized a series of pyrazole derivatives. Derivatives were reported to have a potent cytotoxicity against some tumor cells. A compound 9 was the most promising antitumor agent.

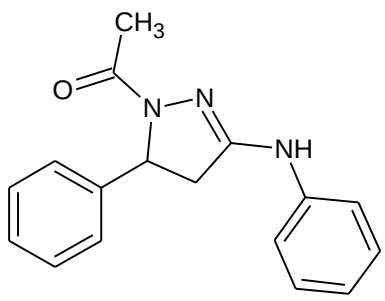


2-hydroxy-*N*'-[(1*E*)-1-(3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)propylidene]benzohydrazide

Figure No.-27

Pyrazole as Anticonvulsant Agent

Anoop Singh, *et al*[19], synthesized a series of 1-[(4, 5-dihydro-5-phenyl-3-(phenylamino) pyrazol-1yl)] ethanone derivatives I-VI were synthesized and evaluated for their anticonvulsant activity against electric shock induced convulsion method. Compounds III and V are found to be the most potent compounds of all synthesized compounds.



1-acetyl-*N*,5-diphenyl-4,5-dihydro-1*H*-pyrazol-3-amine

Figure No.-28

Pyrazole as Antihelmintic Agent

Sreenivasa G.M, *et al*[20], synthesized a series of pyrazole derivatives and and evaluated for their anthelmentic activity. Synthesized compounds of pyrazole derivatives were tested for anthelmintic activity against earthworms, *Perituma posthuma* compared to standard Albendazole. VII P8, VIII P6, VIII P7, VIII P8, VIII P9, VIII P10, VIII P11, VIII P12 showed significant activity compared to standard Albendazole.

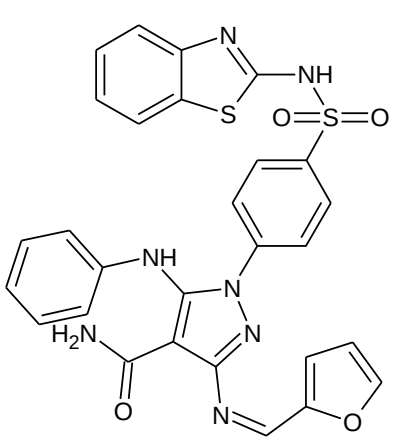
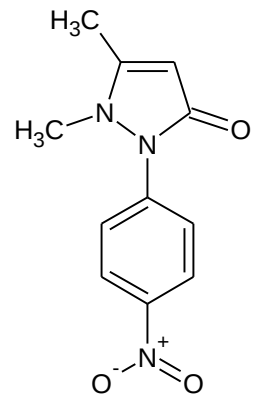


Figure No.-29

Pyrazole as Antiflammatory Agent

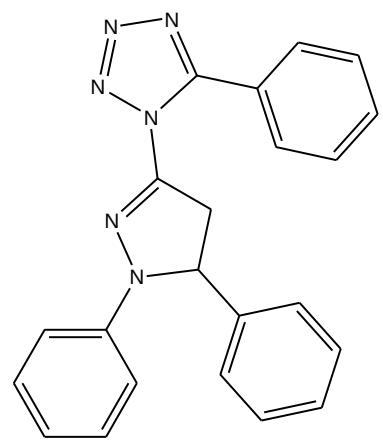
Shilpa Ailawadi,*et.al*[21], synthesized a series of new substituted 3,5- dimethyl pyrazole (4a-c), 3-methyl pyrazol-5-one derivatives (5a-c), 3-Methyl-1-(substituted phenyl) pyrazol-5-ones (7a-b) and 2,3-dimethyl-1-(substituted phenyl)pyrazol-5-ones (8a-b) have been synthesized. All the newly synthesized compounds were tested for their in vivo anti-inflammatory and analgesic activity by bioassays namely: Carrageenan-induced paw edema method and acetic acid induced writhing method respectively. Compound 8b exhibited promising and significant inhibitory activity against COX-2 enzyme.



1,5-dimethyl-2-(4-nitrophenyl)-1,2-dihydro-3*H*-pyrazol-3-one

Figure No.-30

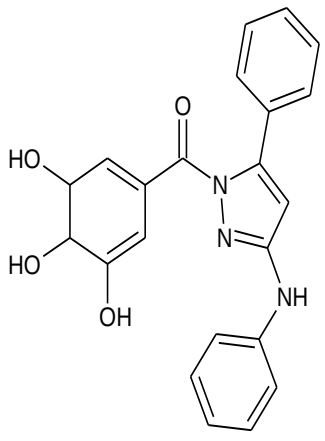
V. H. Bhaskar *et al*[22], synthesized a series of pyrazole derivatives and examined for their anti-iflammatory activity. All the compounds exhibited weak to potent anti-inflammatory activity. Some derivatives bearing a methoxy group exhibited very good anti-inflammatory activity.



1-(1,5-diphenyl-4,5-dihydro-1H-pyrazol-3-yl)-5-phenyl-1H-tetrazole

Figure No.-31

S. Arunkumar, *et al*[23], synthesized a series of pyrazole derivatives. The compounds were evaluated for in vivo anti-inflammatory activity by carrageenan induced paw edema test. In general all compounds were found to exhibit good anti-inflammatory activity.

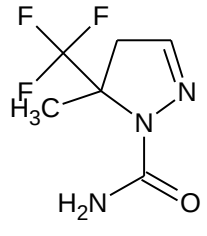


5-[(3-anilino-5-phenyl-1*H*-pyrazol-1-yl)carbonyl]cyclohexa-3,5-diene-1,2,3-triol

Figure No.-32

Pyrazole as Antioxidant Activity

J.S.M. Pasin, *et al*[24], synthesized a series of pyrazole derivatives and screened for their antioxidant activity. All compound showing good activity.



5-methyl-5-(trifluoromethyl)-4,5-dihydro-1*H*-pyrazole-1-carboxamide

Figure No.-33

Pyrazole as Cytotoxic Agent

Magdy I. El-Zahar, *et al*[25], synthesized a series of pyrazole derivatives, they showed good activity.

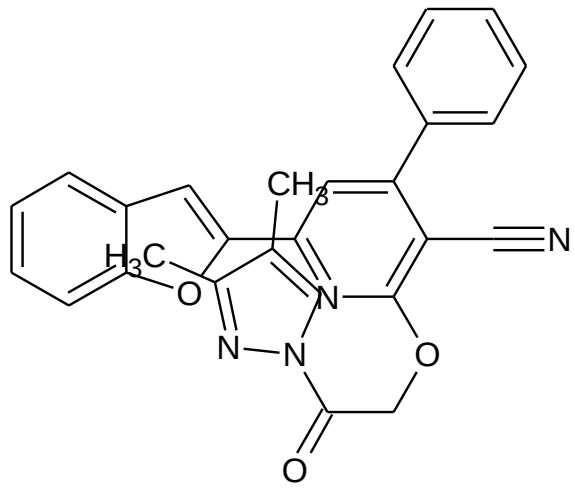
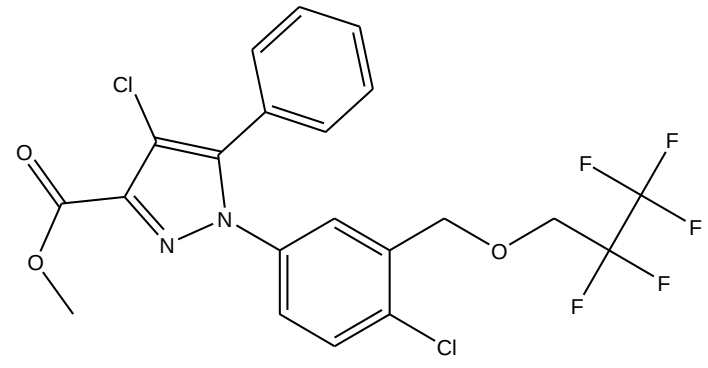


Figure No.-34

Pyrazole as Herbicidal:

Noriaki Kudo, *et al*[26], synthesized a series of 1,5-Diarylpyrazole Derivatives Some of these compounds showed noticeable pre-emergent herbicidal activities against various kinds of weeds. Among the synthesized compounds, methyl 4-chloro-1-(2,5-difluorophenyl)-5-(4-flurophenyl)-pyrazole-3-carboxylate 19t exhibited good activity. Diarylimidazolecarboxylates and carboxamides were also synthesized, but they did not show any herbicidal activities.



Methyl 4-Chloro-1-[4-chloro-3-(2,2,3,3,3-pentafluoropropoxymethyl)-phenyl]-5-phenylpyrazole-3-carboxylate

Figure No.-35

Conclusion

Pyrazole moiety and its various derivatives studied frequently in the past time and found potent in various pharmacological and pathological conditions, which are discussed in brief in this article. This article mainly focused on the various derivatives of pyrazole showed various important pharmacological activities, like compound 2-(5-(4-hydroxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)-N-(4- phenylthiazol-2-yl)acetamide have shown best activity against *Staphylococcus aureus* ATCC 9144, *Staphylococcus epidermidis* ATCC 155, *Micrococcus luteus* ATCC 4698, *Bacillus cereus* ATCC 11778, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* and significant effects of different compounds as analgesic like (4*Z*)-3-methyl-1-[(2-oxo-2*H*-chromen-4-yl) carbonyl]-1*H*-pyrazole-4,5-dione4-[(4-substitutedphenyl) hydrazone] derivative. Anti-inflammatory activity is also been studied. Compounds that are found to be active as anti-inflammatory is 2-(5-(4-methoxyphenyl)-3-phenyl-4, 5- dihydropyrazol-1-yl)-N-(4-phenylthiazol-2-yl) acetamide. Various other activities are also been studied like anticonvulsant, anticancer, antihelmintic etc. Thus by studying all the derivatives showing variety of activities can say that pyrazole ring have been explored in past years and is still be used for future development of new drugs against many more pathological conditions.

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