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BIOACTIVE PYRAZOLINES: AN UPDATE

Dr. VasudevaRao Avupati[1,*] and Prof. Rajendra Prasad Yejella[2]

[1]Department of Chemistry, Faculty of Pharmacy, Asia Metropolitan University,G-8, Jalan Kemacahaya 11, Taman Kemacahaya, Batu 9, 43200, Cheras, Selangor, Malaysia.

[2]Pharmaceutical Chemistry Division, A U College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, Andhra Pradesh, INDIA, Pin code: 530 003.

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***Correspondence for Author**
Dr. VasudevaRao Avupati
Department of Chemistry, Faculty of Pharmacy, Asia Metropolitan University,G-8, Jalan Kemacahaya 11, Taman Kemacahaya, Batu 9, Cheras, Selangor, Malaysia.

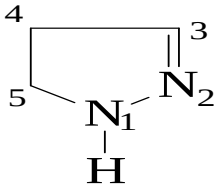
ABSTRACT

In the recent past, substituted pyrazoline derivatives have been extensively studied because of their synthetic feasibility, varied chemical behavior, diverse biological activities and different applications. The current review focuses on the methods of synthesis, spectroscopic characterization and biological activities of pyrazolines. This review mainly summarizes the antimicrobial and anti-inflammatory potential of different synthetic pyrazolines.

KEYWORDS: Pyrazolines, Antimicrobial Activity, Anti-Inflammatory Activity

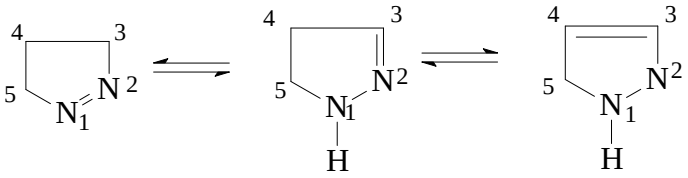
INTRODUCTION

Pyrazole is a π-excessive aromatic monocyclic heterocycle containing two nitrogen atoms in a five membered 1, 2-diazole ring. It was in the late nineteenth century that Fischer and Knovenagel described the reaction of acrolein with phenylhydrazine [1] to provide a 2-pyrazoline type compound (1). Their experiment seems to be the first example of 2-pyrazoline formation by the reaction of an α,β-enone with a hydrazine derivative. Later, Auwers *et al.* [2, 3] corraborated that the product of this reaction was 1-phenyl 2-pyrazoline. During the last century, after these pioneering studies, numerous 2-pyrazolines were synthesized by the reaction of α,β-enones with hydrazines. This simple and convenient procedure has remained one of the most popular methods for the preparation of 2-pyrazolines.



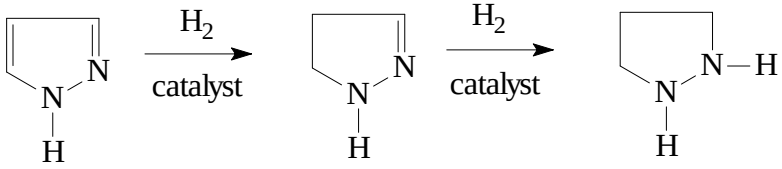
(1)

Pyrazoles exhibit aromatic character with properties resembling those of both pyrrole and pyridine. 1-Pyrazoline, 2-pyrazoline and 3-pyrazoline are the three partially reduced forms of the pyrazole structure with different positions of the double bonds and exists in equilibrium one with the other (Scheme 1). 2- pyrazoline exhibits the monoimino character and hence more stable than the rest eventhough all the three types have been synthesized.[4]



Scheme 1. All the three partially reduced forms of pyrazoline

Pyrazole is feebly basic and forms salts with inorganic acids. The imino hydrogen may be replaced by an acyl group. Pyrazole is very resistant to oxidation and reduction, but may be hydrogenated catalytically, first to pyrazoline and then to pyrazolidine (Scheme 2). Both of these compounds are stronger bases than pyrazole.



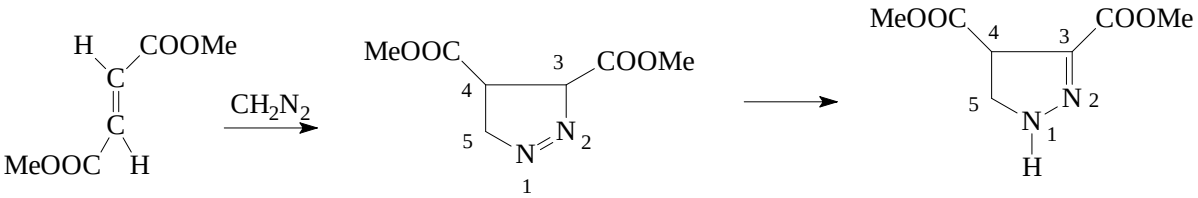
Scheme 2

Pyrazoline derivatives differ considerably in their properties from those of pyrazole, owing to their much lower stability. The pyrazolines give the reactions of aliphatic derivatives, resembling unsaturated compounds in their behavior towards permanganate and nascent hydrogen. They resemble hydrazones in the manner in which they are hydrolyzed by mineral acids, and aldazines in their decomposition into gaseous nitrogen and nitrogen-free substances. Pyrazoline and its homologues are weak bases. In general they only dissolve in concentrated acids, forming unstable salts which dissociate on the addition of water. The

parent substance, pyrazoline, an oil of boiling point 114°C, is the most stable of all these compounds. The pyrazolidines possess strong reducing properties and readily give up hydrogen to form pyrazolines.

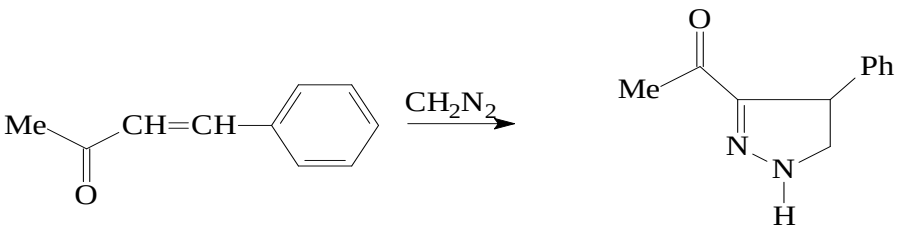
General Methods of Synthesis of Pyrazolines

1. α,β-unsaturated carboxylic acid esters reacts with diazomethane to give 2-pyrazolines. The mechanism of this reaction was correctly anticipated by Pechmann [5] in which the primary product of this reaction is a 1-pyrazoline, formed by 1,3-dipolar cyclo addition, which spontaneously isomerizes into its thermodynamically more stable 2-pyrazoline isomer by a 1,3- H shift (Scheme 3).



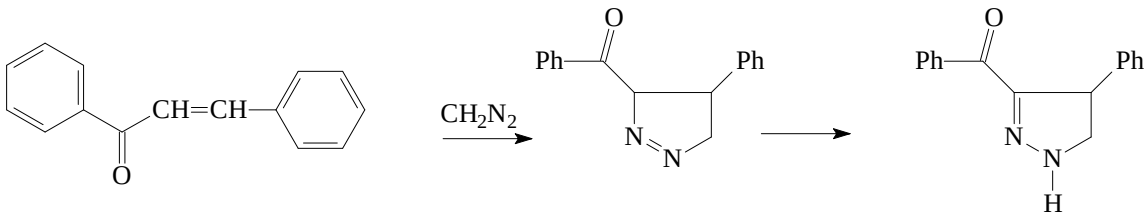
Scheme 3

2. Benzylideneacetone on reaction with diazomethane by 1, 3-dipolar cycloaddition yield 2-pyrazolines (Scheme 4). This is probably the first example of the synthesis of a pyrazoline from the reaction of an α,β-unsaturated ketone and diazomethane and was published by Azzarello. [6] in 1906. Later, this reaction was reinvestigated by Smith and Howard.[7] and by Raju and Rao [8] and the assumption made by Azzarello were corroborated.



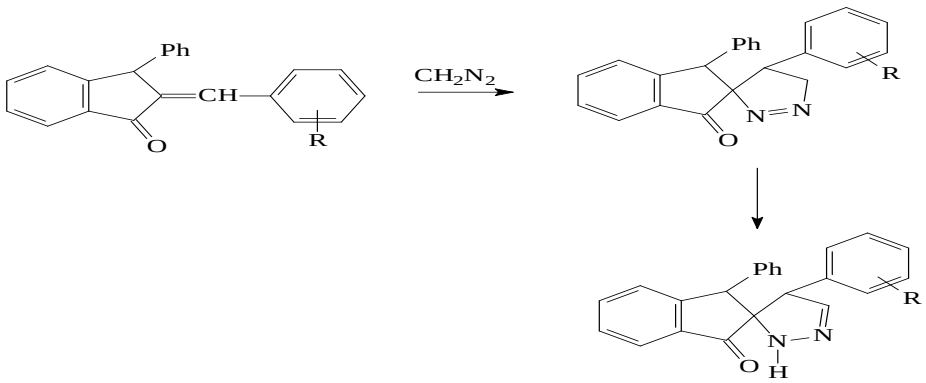
Scheme 4

3. 1, 3-Dipolar cycloaddition of chalcones and diazomethane was first investigated by Smith and Pings [9] and 3-benzoyl- 4-phenyl-1-pyrazoline was prepared as a primary product which was then isomerized into the 3-benzoyl-4-phenyl-2-pyrazoline on gentle heating (**Scheme 5**).



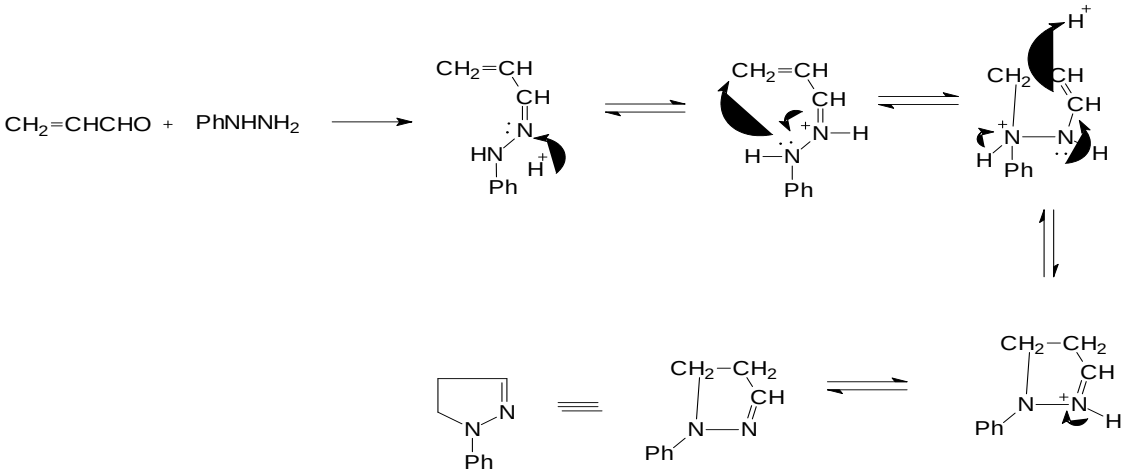
Scheme 5

4. The reaction of 2-arylidene-3-phenyl-1-indanones with diazomethane performed by Mustafa and Hilmy [10] can be considered as the first example of pyrazoline formation by the cycloaddition of an exocyclic α,β- unsaturated ketone and diazomethane (Scheme 6).



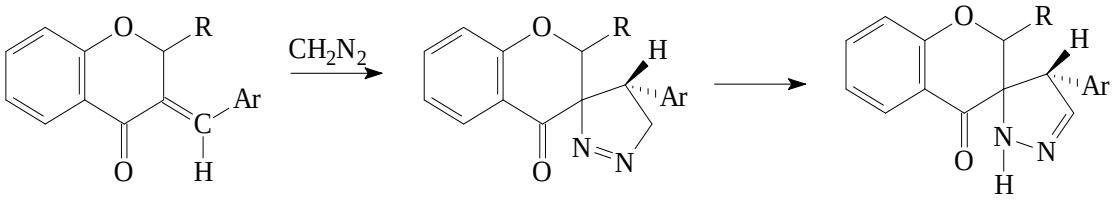
Scheme 6

5. α, β-unsaturated aldehydes or ketones do react with phenylhydrazine to form hydrazones as intermediates. These hydrazone intermediates on treatment with acetic acid or hydrochloric acid in ethanol isomerizes to Δ^2-pyrazolines. The reaction scheme is given below (Scheme 7).



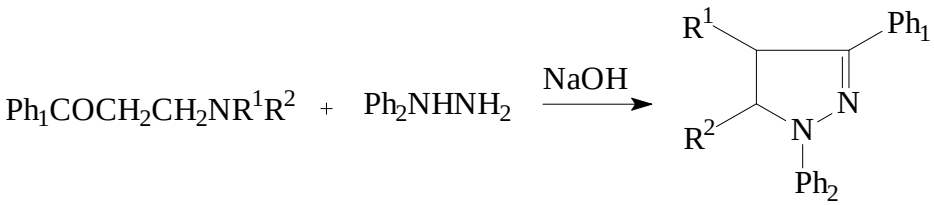
Scheme 7

6. Pijewska *et al*.[11,12] studied the reaction of 3-arylideneflavanones and diazomethane to yield pyrazolines. The structure and stereochemistry of the pyrazolines formed have been elucidated by various NMR techniques. This detailed spectroscopic investigation[13-16] unambiguously proved that the (E) isomers of flavanones provided *trans*-spiro-1-pyrazolines, which were then isomerized to *trans*-spiro-2-pyrazolines (Scheme 8).



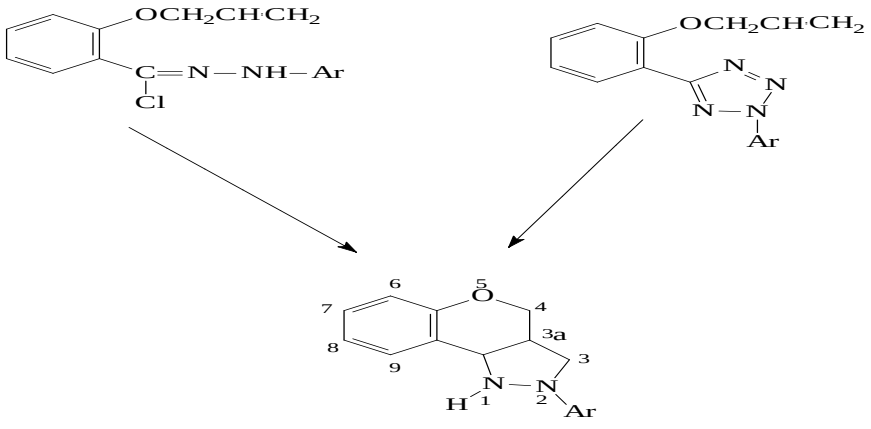
Scheme 8

7. Mannich bases on reaction with phenylhydrazine and aqueous ethanolic NaOH at reflux temperature yield substituted 2-pyrazolines.[17] (Scheme 9).



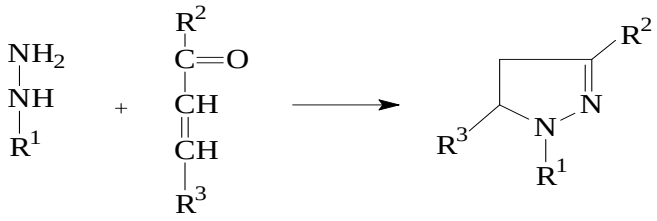
Scheme 9

8. The synthesis of tricyclic 2-pyrazolines by an intramolecular 1,3-dipolar cycloaddition of nitrile imines is well documented in the literature.[18-20] 2, 3, 3a, 4-Tetrahydro- 2-aryl [1] benzopyrano [4,3-c] pyrazolines have been prepared by the intramolecular 1,3-dipolar cycloaddition of nitrile imines generated either from 1-(*o*-allyloxyphenyl)-N-(arylhydrazidoyl) chloride on treatment with triethyl amine or by the irradiation of 2-aryl-5-(*o*-allyloxyphenyl) tetrazole (Scheme 10).



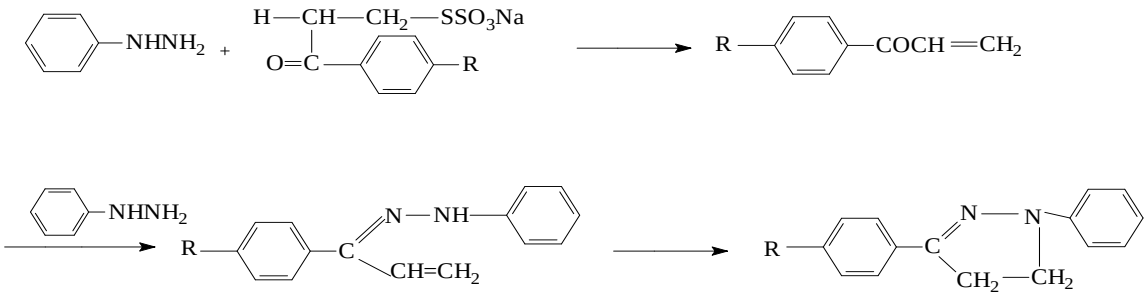
Scheme 10

9. The reaction of chalcones with hydrazines is probably the most popular procedure for the synthesis of 2-pyrazolines. The most commonly used method is the reaction of hydrazine and the chalcones in acetic acid solution to prepare 2-pyrazolines in high yield.[21-23] (Scheme 11). This method is used with or without the isolation of the hydrazone intermediate. Synthesis of 2-pyrazolines can also be achieved under alkaline conditions by using pyridine as catalyst in ethanolic solution [24]. In some cases the two reactants were refluxed in alcoholic solution without a catalyst to provide 2-pyrazolines. [25, 26].



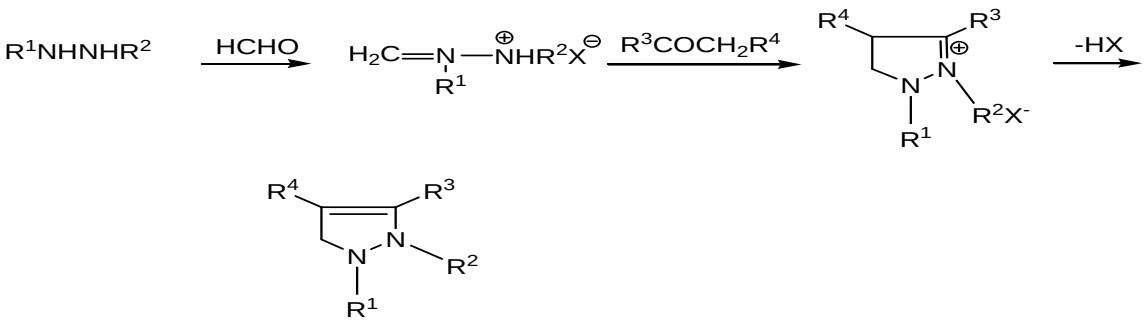
Scheme 11

10. 2-arylcarbonylethylthiosulfates when heated with two equivalents of phenyl hydrazine in water for 0.5-3 hrs under reflux yield 1-phenyl-3-aryl-2-pyrazolines.[27] (Scheme 12).



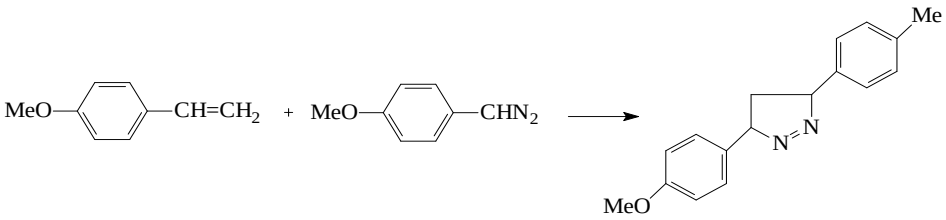
Scheme 12

11. 1,2-disubstituted hydrazine react with formalin and a carbonyl compound (Hinmann synthesis) to yield pyrazolines.[28] (Scheme 13).



Scheme 13

12. Cycloaddition reaction of substituted styrenes with *p*-anisyldiazomethane at low temperature yield *trans*-3, 5-bis-(p-anisyl)-1-pyrazoline.[29] (Scheme 14).

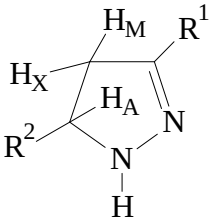


Scheme 14

SPECTRAL FEATURES OF PYRAZOLINES

NMR SPECTRA OF PYRAZOLINES:

A pyrazoline ring is identified by characteristic spectral features.[30] in its ^{1}H NMR spectrum. The three protons in the pyrazoline ring (2) will show AMX splitting pattern, H_A proton appearing at δ 2.98 (dd), J_{AM}= 7.6 Hz and J_{AX} = 12 Hz, H_M proton resonating at δ 3.64 (dd), J_{AM}= 12 Hz and J_{MX}=12 Hz and H_X proton appearing at δ 5.2 (dd), J_{AX}= 7.6 Hz and J_{MX}=12 Hz.



(2)

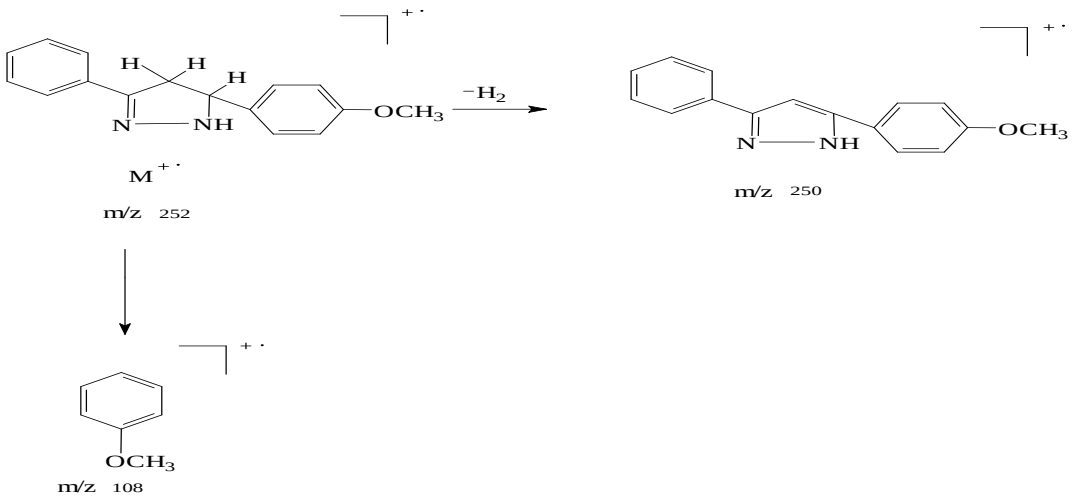
Mass Spectra of Pyrazolines

Srzic *et al.* [31] studied the fragmentation pathway of 1, 3-diphenyl-2-pyrazoline employing ion kinetic energy spectrometry (IKES) and mass analyzed ion kinetic energy spectrometry (MIKES) of the native compound and specifically of isotope (^{2}H, ^{13}C, ^{15}N) labelled compounds, combined with high resolution mass determinations. The results clearly demonstrated that the large majority of ions formed by simple cleavage had the molecular ion as their precursor.

Sayed *et al.* [32] studied the mass spectrometric fragmentations of the 3,5-bisaryl-2- pyrazoline derivatives by high resolution mass spectrometry. The observed ions may be arranged in three main groups according to their assumed mechanistic formation, *viz.* (a) by 1,2-

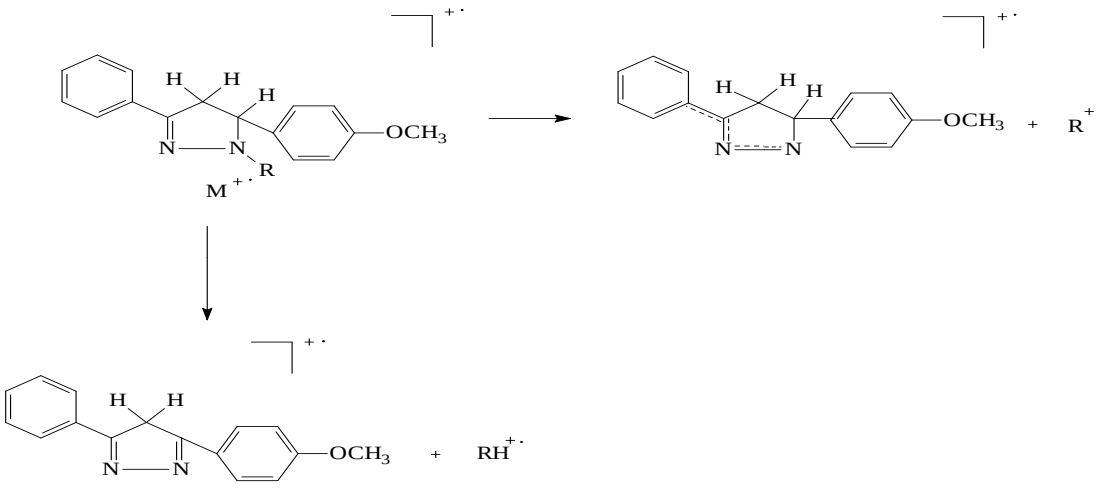
elimination processes (Scheme 15), (b) by α-cleavage (Scheme 16) and (c) by assumed cyclo-reversion (Scheme 17) .

In 1, 2-elimination, as given below, molecular hydrogen and one aryl substituent as anisol were lost from the molecular ion.



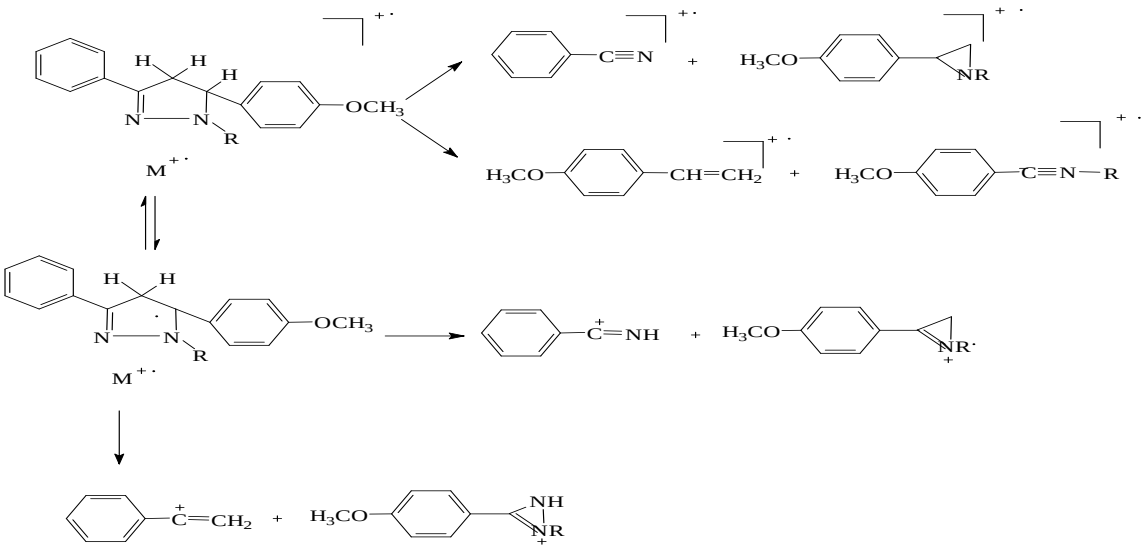
Scheme.15. Mass fragmentation of 3, 5-disubstituted 2-pyrazoline involving 1, 2-elimination process.

The α-cleavage involves the radical loss of the N-1 substituent and this cleavage may be rationalized as one electron transfer with and without hydrogen transfer in either direction initiated by cation radical locations somewhere in the Ar-C=N-N-π orbital system.



Scheme 16. Mass fragmentation of 3, 5- disubstituted 2-pyrazoline involving α-cleavage.

A cyclo-reversion process involves the cleavage of the pyrazoline ring structure and gives rise to a majority of the middle to low mass range fragments.



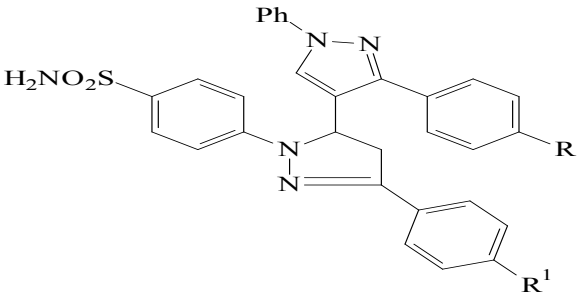
Scheme 17. Mass spectral fragmentation of substituted 2-pyrazolines involving cyclo-reversion

Therapeutic Potential of 2-Pyrazolines

The pyrazoline nucleus is a ubiquitous feature of various compounds possessing many pharmacological and physiological activities and therefore they are useful materials in drug research. It was reported in the literature that different substituted 2-pyrazolines possess antimicrobial, anti-inflammatory, analgesic, antipyretic, antidepressant, antitubercular, antiamoebic, anthelmintic, anticonvulsant, antihypertensive, antidiabetic, antitumor, anti-HIV, local anaesthetic, antioxidant, insecticidal and tranquilizing activities. Given below is a brief account of various modifications reported on 2-pyrazoline nucleus, which showed a variety of biological and pharmacological activities.

ANTIMICROBIAL ACTIVITY

Sharma *et al.*[33] synthesized a new series of pyrazolylpyrazolines (3) by the reaction of appropriate chalcones with 4-hydrazinobenzenesulfonamide hydrochloride in ethanol. The synthesized compounds were evaluated for their *in vitro* antimicrobial activity against *S.aureus* (MTCC 3160) and *B.subtilis* (MTCC 121) representing Gram-positive bacteria and *Pseudomonas aeruginosa* (MTCC 741) and *E.coli* (MTCC 51) representing Gram-negative bacteria. Most of the tested compounds showed better activity against the Gram-positive rather than the Gram-negative bacteria. Compounds with fluoro and bromo as substituents showed good broad spectrum activity against all the tested Gram-positive and Gram-negative bacterial strains.

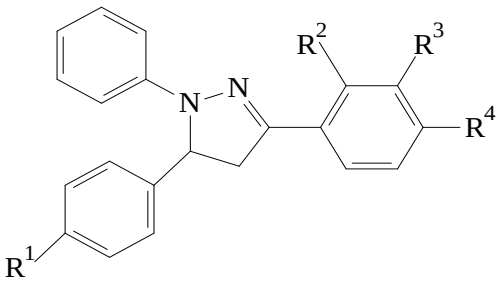


(3)

R= H,-CH_3, -F, -Br

R^1= H, -CH_3, -F, -Br

Sivakumar *et al*. [34] synthesized some novel 1, 3, 5-triphenyl-2-pyrazolines (4) and evaluated their antimicrobial activity. All the compounds showed good activity against *E.coli* and poor activity against *S.aureus*. Compounds possessing chloro, methoxy, dimethoxy and bromo as substituents exhibited reasonable activity against all the organisms tested (< 0.309 µm) except against *S.aureus*. Compounds possessing halogens (-F and -Cl) as substituents showed very good activity (<88% reduction) against the fungi studied at 2 mg/mL. The results proved the importance of halogen substituents for antibacterial and antifungal activities.



(4)

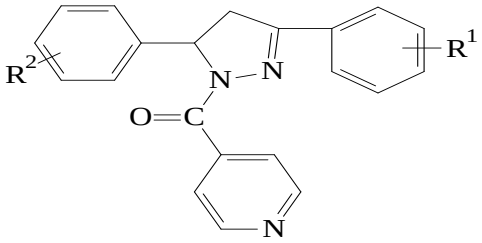
R^1= -SCH_3, -SO_2CH_3;

R^2= -Cl; R^3= -O-CH_2-O-, -NO_2, -OMe, -Br,

-NH_2; R^4= -Cl, -CH_3, -OEt, -OMe, -F, -Br.

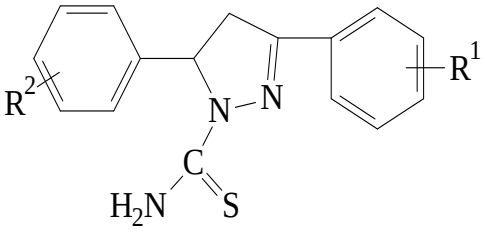
Chawla *et al*. [35] synthesized some novel [3-(4-phenyl)-5-phenyl-4,5-dihydropyrazol-1-yl] (pyridine-4-yl) methanones (5) and 3-substituted phenyl-5-substituted phenyl-4,5-dihydro-pyrazole-1-carbothioamides (6) employing microwave technique and the synthesized compounds were evaluated for antimicrobial activity. Antibacterial activity were screened against *S.aureus*, *B.subtilis*, *E.coli* and *Pseudomonas aeruginosa* and antifungal activity were screened against *C.albicans* and *A.niger*. The compounds exhibited moderate antibacterial

and good antifungal activity. Compounds having chloro and methoxy groups as substituents showed significant antifungal activity against *A.niger* and *C.albicans* respectively.



(A)

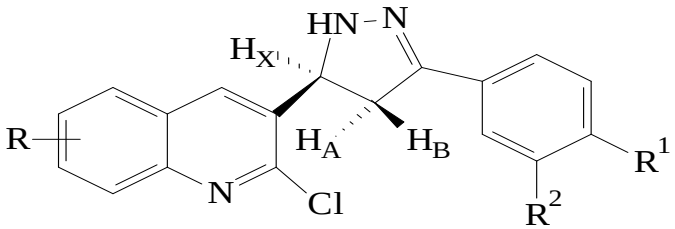
R^1= 4-OCH_3, 4-Cl, 3-NO_2



(B)

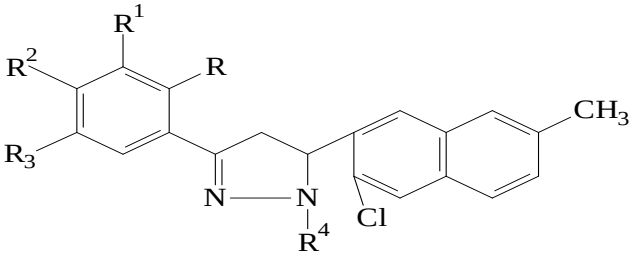
R^2= H, 4-Cl

Bawa *et al*.[36] synthesized a series of 2-chloroquinoline containing pyrazoline derivatives having 3,4-dichloro / 3,4-dimethoxy moiety on the phenyl ring **(7)** and the synthesized compounds were screened for antimicrobial activity. All the compounds were evaluated for their antibacterial activity against *Escherichia coli* (NTCC 10418), *S.aureus* (NCTC 65710) and *P.aeruginosa* (NCTC 10662). The compounds were also evaluated for their antifungal activity against *A.niger* (MTCC 281), *Aspergillus flavus* (MTCC 277), *Monascus purpureus* (MTCC 369) and *Penicillium citrinum* (NCIM 768) by agar cup plate method. From the results it is clearly indicated that the compounds having 3, 4-dichloro moieties were more active in antimicrobial screening when compared to their 3, 4-dimethoxy analogs.



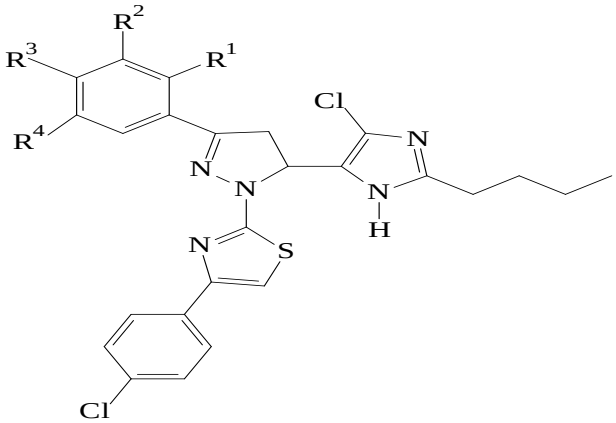
(7) R= H, -CH_3, -OCH_3; R^1= Cl, -OCH_3; R^2= -Cl, -OCH_3

Mokie *et al*. [37] synthesized a series of 2-pyrazolines (8) by cyclization of α,β-unsaturated ketone (chalcones) with hydrazine hydrate / phenylhydrazine using triethanolamine as solvent within 15-20 mins. All the synthesized compounds were evaluated for their antibacterial activity by Agar well diffusion method. The antibacterial activity was carried out against *B.subtilis*, *Escherichia coli*, *Ervinia carotovara* and *Xanthomonas citri*. Most of the compounds showed potent antibacterial activity.



(8) R= H, -OH; R^1= -Cl, -Br, -I; R^2= H, -OH; R^3= $-CH_3$, -Cl, -Br, -I; R^4= H, $-C_6H_5$

Dawane *et al.* [38] synthesized some 1-(4-(4'-chlorophenyl)-2-thiazolyl)-3-aryl-5-(2-butyl-4-chloro-1H-imidazo-5yl)-2-pyrazoline derivatives (9) by the base catalyzed treatment of appropriate chalcones with 4-(4'-chlorophenyl)-2-hydrazino-thiazole in polyethylene glycol (PEG 400) as an alternative reaction solvent. All the synthesized compounds were tested for their antimicrobial activities against *E.coli* (MTCC 2939), *Salmonella typhi* (MTCC 98), *S.aureus* (MTCC 96), *B.subtilis* (MTCC 441), *A.niger* (MTCC 281), *Trichoderma viridae* (MTCC 167), *Penicillium chrysogenum* (MTCC 183). Most of the compounds showed potent antibacterial and antifungal activity.



(9)

R^1= H, -OH;

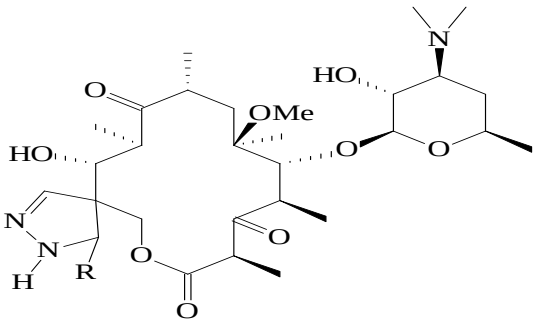
R^2= H, -Cl, -Br, -I;

R^3= H, -Me, -OMe, $-NH_2$, -Cl;

R^4= H, -Me, -Cl, -Br, -I

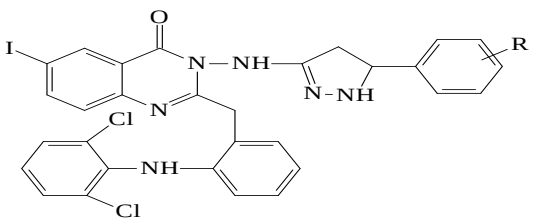
Hu *et al.* [39] synthesized a series of C-12 pyrazolinyl spiroketolide derivatives **(10)**. Compounds with alkane and ester groups at pyrazolinyl spiros were investigated for their antibacterial activities against both erythromycin-susceptible and erythromycin-resistant bacteria. All the derivatives were found to possess better antibacterial activities than erythromycin A and clathriamycin against *S.aureus* strains, and with almost equivalent

bioactivities against *S.pneumonia* and *H.influenza* strains. Among the C-12 pyrazolinyl spiro ketolides, compounds with ester substituents displayed better antibacterial activities than those of compounds with alkyl substituents. The results are useful to aid the designing of new C-12 pyrazolinyl spiro ketolides with better antibacterial activities.



(10) R= H, -CH_3, -$COOCH_3$, -$COOC_2H_5$

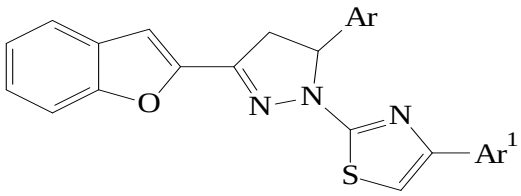
Patel *et al.*[40] synthesized a series of new 2-[2-(2,6-dichlorophenyl)amino] phenylmethyl-3-[(5-substitutedphenyl)-1,5-dihydro-1H-pyrazol-3-yl-amino]-6-iodoquinazolin-4(3H)ones (11) by the reaction of 2-[2-(2,6-dichlorphenyl)amino] phenylmethyl-3-substituted phenyl acryl amido-6-iodoquinazolin-4(3H)ones with hydrazine hydrate in the presence of glacial acetic acid. The synthesized compounds were screened for antibacterial and antifungal activity. The compounds were tested for antibacterial activity *in vitro* by measuring zone of inhibition in mm by cup-plate method. Screening of compounds were done against two Gram-positive bacteria viz. *S.aureus* and *B.subtilis* and two Gram-negative bacteria viz. *E.coli* and *Certium* at a concentration of 100 µg/mL and 50 µg/mL. Almost all the compounds possessed moderate activity against all the tested organisms. Compound with 3-nitrophenyl was active against *E.coli* and *Certium*. Compound with 2-chlorophenyl showed moderate activity against *A.niger* and *C.albicans*.



(11)

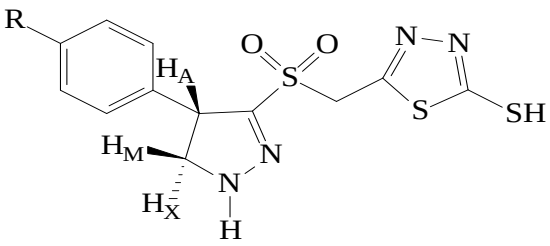
R= H, 2-OH, 3-OH, 4-OH, 2-Cl, 3-Cl, 4-Cl, 2-NO_2, 3-NO_2, 4-NO_2, 4-$N(CH_3)_2$, 2-OCH_3, 4-OCH_3

Abdel-Wahab *et al.*[41] synthesized 3-(benzofuran-2-yl)-4,5-dihydro-5-aryl-1-[4(aryl)-1,3-thiazol-2-yl]-1H-pyrazoles (12) and evaluated for their antimicrobial activity. All the compounds synthesized were screened for their antibacterial and antifungal activities at 100 µg concentration. Compounds with simple phenyl moiety as substituents showed higher inhibition against the Gram-negative bacteria than that of the Gram-positive bacteria. Compound with chloro and bromophenyl as substituents showed inhibiton zones against *C.albicans* more than the reference sample fluconazole.

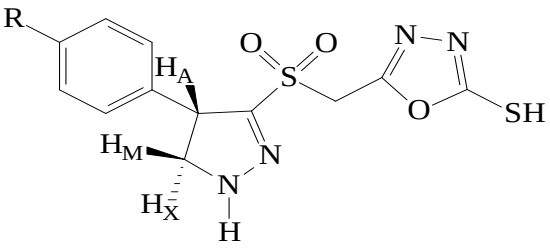


(12) Ar= -C_6H_5, 4-ClC_6H_4; Ar^1= -C_6H_5, 4-BrC_6H_4

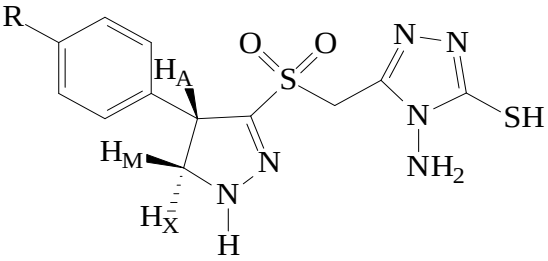
Padmavathi *et al.*[42] synthesized some novel sulfone-linked bis heterocyclic pyrazolines in combination with thiadiazoles (13), oxadiazoles (14) and triazoles (15) from *E*-styryl-sulfonylacetic acid methyl ester and tested for their antimicrobial activity. The antimicrobial activities of the compounds were tested by agar disc-diffusion method. Among the compounds tested, pyrazolines with triazole substituents showed pronounced activity.



(13)

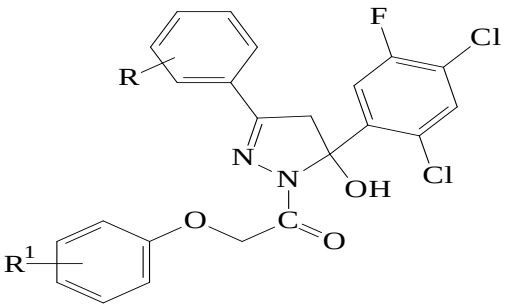


(14)



(15) R= H, -Me, -Cl

Karthikeyan *et al*.[43] synthesized some novel chloro-fluorine containing hydroxy pyrazolines (16) by treating chalcone dibromides with aryloxy acid hydrazides in the presence of triethylamine. All the synthesized compounds were tested for their antibacterial and antifungal activities. The antibacterial activity was screened against *E.coli* (ATCC 25922), *S.aureus* (ATCC 25963), *P.aeruginosa* (ATCC 27853), *Streptococcus pyrogenes* and *Klebsiella pneumoniae* by disc diffusion method. Compounds with chloro, dichloro and methoxy as substituents showed very good activity almost equivalent to that of standard against all the bacterial strains. Compounds were also screened for their antifungal activity against *Aspergillus flavus* (NCIM 524), *Aspergillus fumigatus* (NCIM 902), *C.albicans* (NCIM 300), *Penicillium marneffei* and *Trichophyton mentagrophytes* (recultured). Compounds with methoxy, chloro and dichloro as substituents emerged as very active against all the fungal strains tested.

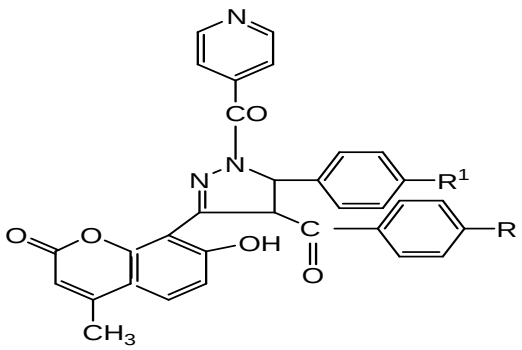


(16)

R= H, 4-OCH_3, 4-Cl, 2,4-$(Cl)_2$, 3,4-$(OCH_3)_2$

R^1= 4-Cl, 4-CH_3, 2, 4-$(Cl)_2$

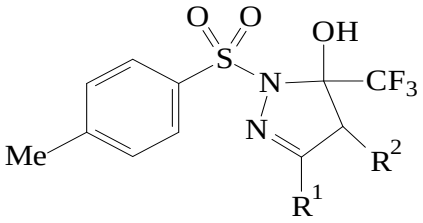
Thakare *et al.* [44] synthesized 3-coumaryl-4-aroyl-5-aryl-2-pyrazolines (17) that showed antimicrobial activity against pathogenic bacteria.



R= H,OCH_3
R^1= H,OCH_3,OH

(17)

Bonacorso *et al.* [45] synthesized a novel series of 4-phenyl- and 3-alkyl(aryl)-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1H-1-tosylpyrazoles (pyrazolinyl *p*-tolyl sulfones) (18), from the cyclocondensation reaction of 3-phenyl- and 4-alkyl(aryl)-1,1,1-trifluoro-4-alkoxy-3-alken-2-ones, [where alkyl = H, methyl and aryl = $–C_6H_5$, 4-$CH_3C_6H_4$, 4-$OCH_3C_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4] with *p*-tosylhydrazine and toluene as solvent. All the synthesized compounds were screened for antimicrobial activity. The best activity was showed by the compound with 4-fluorophenyl as substituents linked at the carbon-3 of the pyrazoline ring.

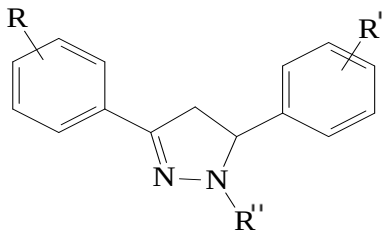


(18)

R^1= H, -Me, -Ph, 4-MePh, 4-OMePh, 4-BrPh, 4-BrPh, 4-ClPh, 4-FPh

R^2= H, -Ph

Bizzarri *et al.*[46] synthesized a series of N_1-substituted 3,5-diphenyl pyrazolines (19) and evaluated for their antibacterial activity. All the synthesized compounds showed less activity against different species of Gram-positive and Gram-negative bacteria of clinical relevance and against various strains of pathogenic fungi. But the same compounds exhibited a significant degree of activity against *H.pylori* strains, including those resistant to the reference compound metronidazole. Among the compounds, those with an N_1-acetyl group and 4-methoxy as substituents on the 5-phenyl ring showed maximum activity against *H.pylori* metronidazole resistant strains at a MIC value of 1-4 µg/mL.



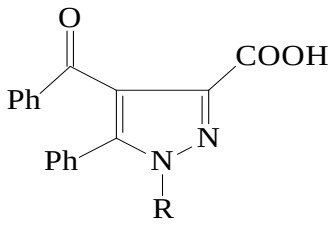
(19)

R= H, 2-OH, 4-OH, 2,6-$(OH)_2$, 2,4-$(OH)_2$.

R'= 4-ClC_6H_4, -$C(O)CH_3$,

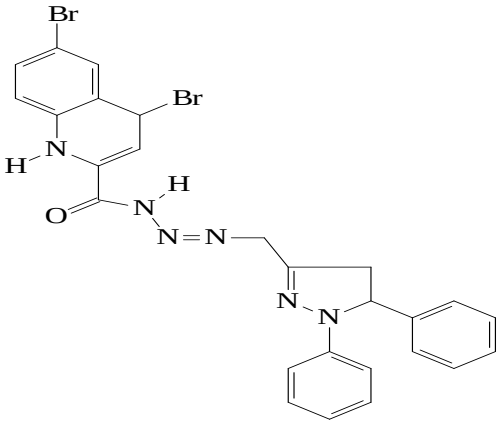
R"= 4-OCH_3, 3,4-$(OCH_3)_2$, 2-OCH_3, 4-OCH_3, 4-CH_3, 4-Cl, 2,4-$(OCH_3)_2$, 2-Cl

Akbas *et al.*[47] reported the synthesis of some new 1 H- pyrazole-3-carboxylic acids (20) and evaluated for their antibacterial activities against *Bacillus cereus* (ATCC 7064), *S.aureus* (ATCC 6538), *E.coli* (ATCC 4230) and *Pseudomonas putida* using tube dilution method. The minimal inhibitory concentration (MIC) experiments revealed that all the compounds showed inhibitory effects on the growth of the test microorganisms.



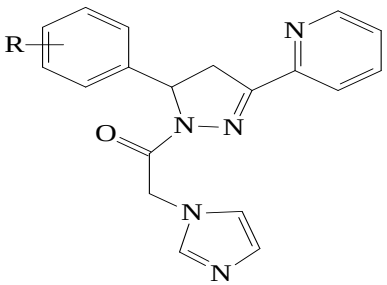
(20)

Saundane *et al.*[48] synthesized some indole derivative containing pyrazoline (21), which were screened for antimicrobial activity against *S. aureus*, *E. coli* and *A. niger*.



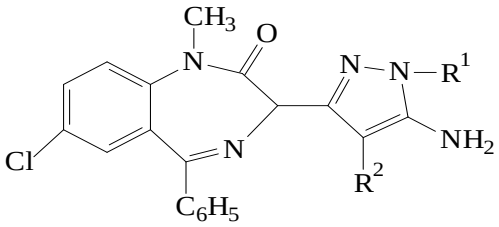
(21)

Mamolo *et al.* [49] synthesized (±)-1-(5-aryl-3-pyridin-2-yl-4, 5-dihydro-pyrazol-1-yl)-2-imidazol-1-yl-ethanone derivatives (22) and tested for their *in vitro* antifungal activity. All the compounds showed moderate activity against *Candida parapsilosis*, *Candida pseudotropicalis* and *Candida glabrata*.

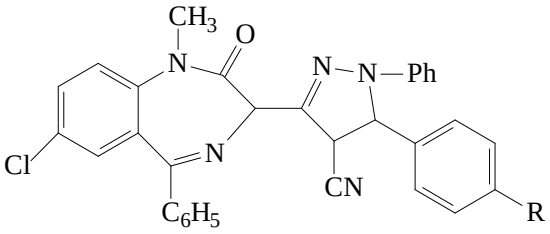


(22) R= H, 2-Cl, 3-Cl, 4-Cl, 2-Br, 3-Br, 4-Br, 2-F, 3-F, 4-F, 2-CH_3, 3-CH_3, 4-CH_3

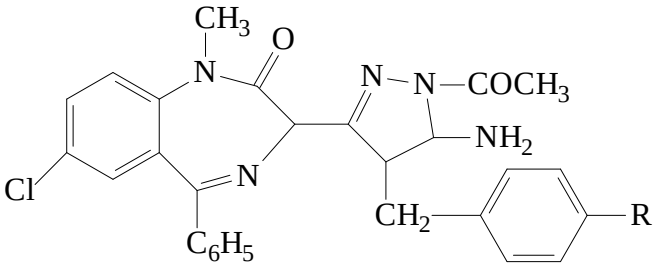
Berghot *et al.* [50] synthesized some polysubstituted pyrazoles (23), pyrazolines (24 and 25) and pyrazolotriazine (26) derivatives of diazepam. Some of these compounds were screened for their antibacterial activity against Gram-positive (*B. subtilis*) and Gram-negative (*P. aeruginosa*). The antibacterial activity was carried out by disc diffusion technique. Pyrazoline with methyl as substituent exhibited potent activity against *B.subtilus* and *P.aeruginosa*.



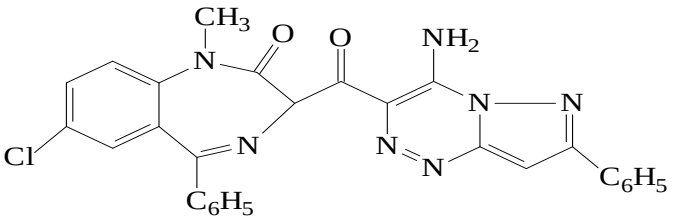
(23)



(24)



(25)



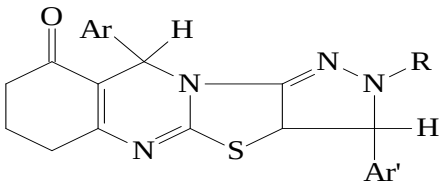
(26)

R= H, CH_3, Cl

R^1= H, -C_6H_5

R^2= H, -N=N-C_6H_5, -N=N-C_6H_4-CH_3(*p*), -N=N-C_6H_4-Cl(*p*)

Gawad *et al.* [51] synthesized some novel pyrazolo [2,3:4,5] thiazolo [2,3-b]quinazolines (27) and evaluated for their antifungal activity against *Aspergillus ochraceus* (AUCC 230), *P.chrysogenum* (AUCC 530), *A. flavus* (AUCC 164) and *C.albicans* (AUCC 1720) using disc diffusion method. Of all the compounds, some of them exhibited moderate antifungal activity.

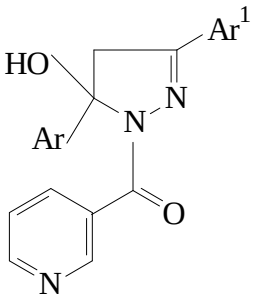


(27)

R= H, -C_6H_5

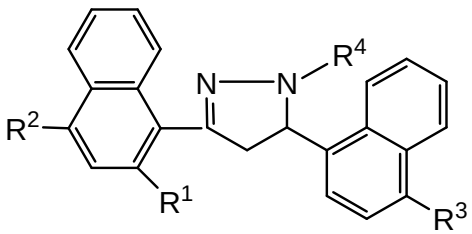
Ar'= -C_6H_4F-*p*

Balakrishna *et al.*[52] synthesized 1-nicotinoyl-3,5-diaryl-5-hydroxy-2-pyrazolines (28) that showed significant antimicrobial activity.



(28) Ar = Ar^1= Ph, C_6H_4X

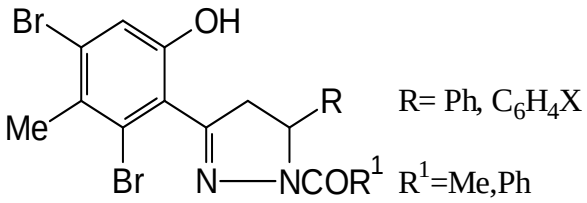
Davood *et al.*[53] synthesized 3,5-dinaphthalene-1-yl-substituted-2-pyrazolines (29) that showed antibacterial activity.



R^1=H,OH
R^2=H,Cl,CH_3
R^3=H,NMe_2
R^4=H,Ph,$CONH_2$,$COCH_3$

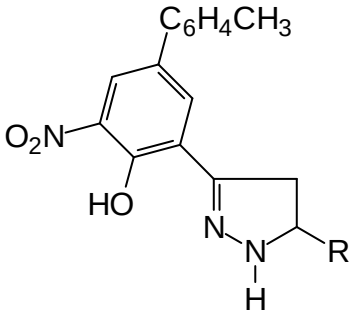
(29)

Naik *et al.*[54] synthesized 1-acyl-3-(2-hydroxy-5-methyl-4,6-dibromophenyl) -5-(substituted phenyl)-2-pyrazolines (30) possessing antibacterial activity.



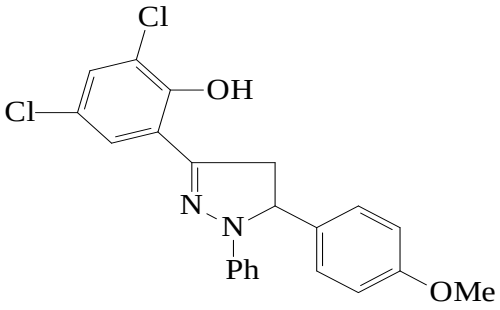
(30)

Desai *et al.*[55] synthesized 1H-3-(2-hydroxy-3-nitro-5-methylphenyl)-5-aryl-2-pyrazolines (31) that exhibited antimicrobial activity against *S. aureus* and *E. coli.*



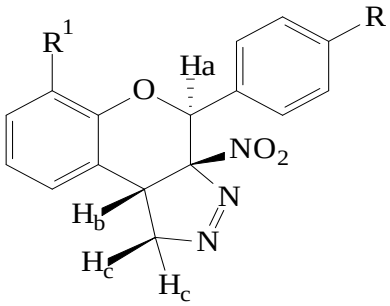
(31)

Deshmukh *et al.*[56] synthesized chlorosubstituted Δ^2-Pyrazolines **(32)** that showed antibacterial activity when assayed against some human pathogens.

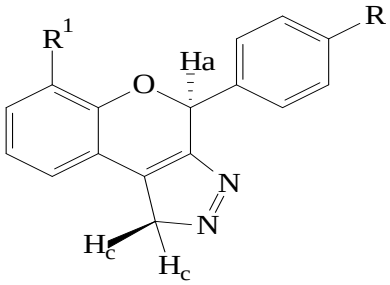


(32)

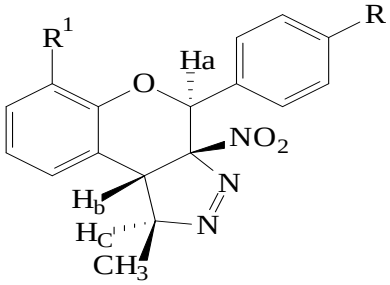
Kodukulla *et al.*[57] synthesized benzopyranopyrazole derivatives (33, 34 and 35) by treating various 3-nitro-2-phenyl-2H-1-benzopyrans with diazomethane and diazoethane. The synthesized compounds were tested for their antimicrobial activities against *S.aureus, S.lutea, B.subtilis, E.coli, S.typhyosa, S.cerevesciae* and *C.albicans*. Compounds with methoxy, methyl and chloro groups exhibited moderate activity against the tested bacterial and fungal strains.



(33)



(34)

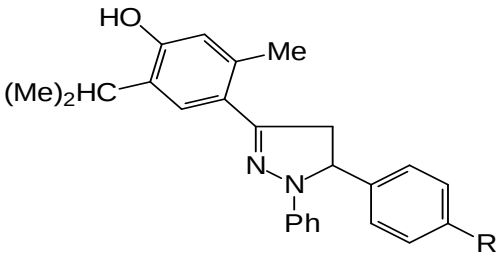


(35)

R= H, Me.OMe, Cl

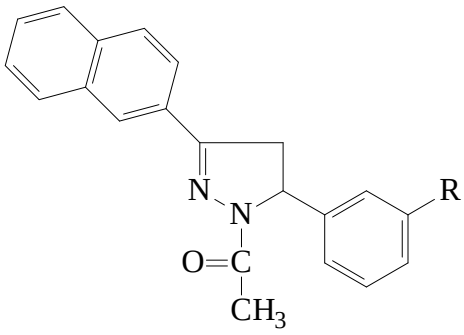
R^1= H

Roda *et al.*[58] synthesized 5-aryl-1-phenyl-3-(3-isopropyl-4-hydroxy-6-methylphenyl)-2-pyrazolines (36) ; these were tested for antimicrobial activity.



(36)

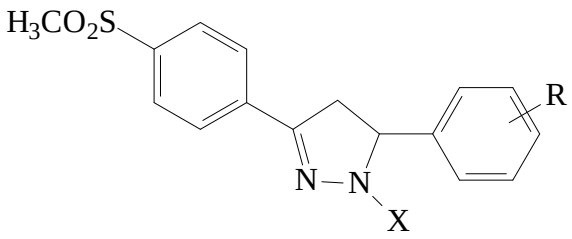
Sim *et al.* [59] synthesized 1-acyl-3-naphthyl-5-substitutedphenyl-2- pyrazolines (37); the antimicrobial activity of these compounds was determined by using ampicillin and clotrimazole a standard.



(37)

Anti-Inflammatory Activity

Fioravanti *et al.* [60] synthesized some new 1-N-substituted-3,5-diphenyl-2-pyrazoline derivatives (38) and the synthesized compounds were evaluated for cyclooxygenase (COX-1 and COX-2) inhibitory activities. N-acetyl derivatives were found to be more potent than the corresponding N-thiocarbomoyl derivatives.

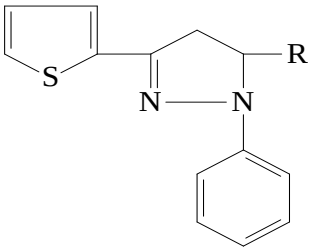


(38)

R= H, 4-Cl, 4-F, 4-CH_3, 4-CF_3, 4-OCH_3, 2-OCH_2Ph, 3-OCH_2Ph, 4-OCH_2Ph

X= -$COCH_3$, -$CSNH_2$

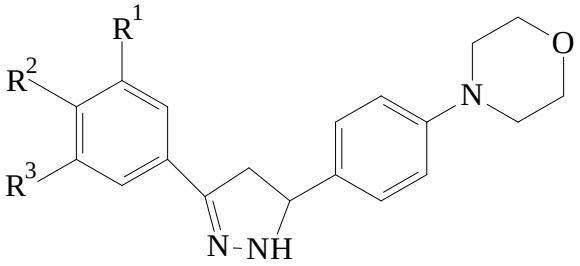
Ramesh *et al.* [61] synthesized some new pyrazoline derivatives (39) by reacting chalcones of 2-acetylthiophene with phenylhydrazine hydrochloride in the presence of alcohol. The synthesized compounds were screened for their anti-inflammatory activity. Some of the compounds showed moderate to considerable anti-inflammatory activity.



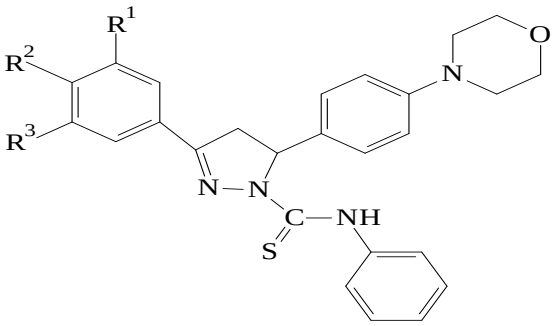
(39)

R= 2-thienyl, 2,4-$(Cl)_2$, 4-$N(CH_3)_2$, 4-F, 4-Cl.

Joshi *et al.* [62] designed and synthesized a new series of 3,2-(4,5-dihydro-5-(4-morphilinophenyl)-1H-pyrazol-3yl) phenols (40) and its N-phenylpyrazol-1-carbothioamide (41) by Claisen-Schmidt condensation followed by the reaction of hydrazine hydrate. All the synthesized compounds were assayed for their *in vivo* anti-inflammatory activity by using carrageenan-induced rat paw edema in rats. Compounds with chloro and bromo as substituents were found to be potent when compared with the standard drug diclofenac.



(40)

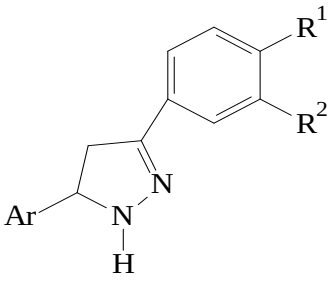


(41)

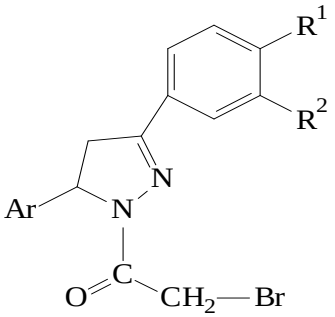
R^1= H, $-CH_3$, -Cl; R^2= H, $-CH_3$; R^3= H, $-CH_3$, -Cl, -Br

Shoman *et al.* [63] synthesized novel 3, 5-diaryl-2-pyrazoline derivatives (42, 43, 44, 45, 46, 47 and 48) by reaction of various chalcones with hydrazine hydrate in ethanol. A group of

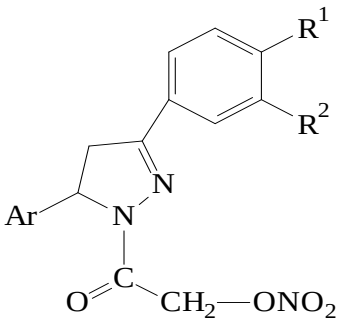
NO-donating-2-pyrazoline derivatives were synthesized by carrying a nitrate ester group or an oxime group onto the prepared pyrazolines derivatives through different spacers. The synthesized compounds were evaluated for their anti-inflammatory activity using carrageenan-induced rat paw edema and compared to a well known NSAID, indomethacin as a reference drug. Most of the prepared compounds showed significant anti-inflammatory activity at the injected dose (100 mg/kg) but they were safer than indomethacin in regard to gastric toxicity. The incorporation of the NO-donating group into the parent pyrazoline derivatives caused a non-significant reduction in the anti-inflammatory activity while a marked decrease in gastric ulcerations induced by their parent pyrazolines was observed.



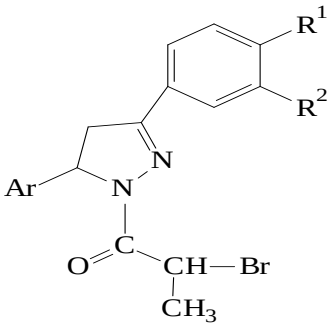
(42)



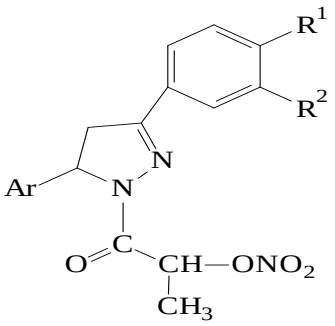
(43)



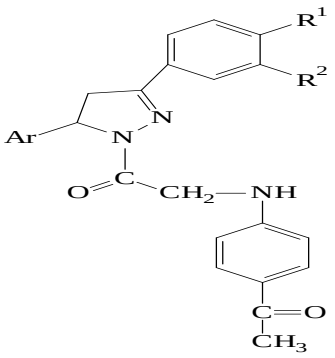
(44)



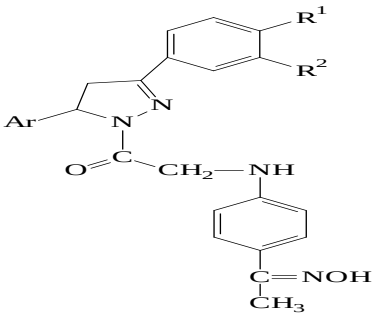
(45)



(46)



(47)



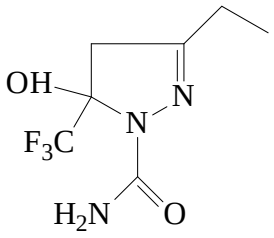
(48)

R^1= H, -OCH_3

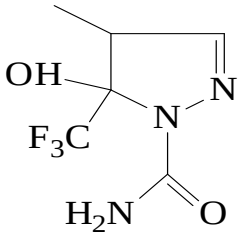
R^2= H, -OCH_3

Ar= furyl, 2,4-$(OCH_3)_2C_6H_3$, 2,6-$(Cl)_2C_6H_3$

Sauzem *et al*. [64] synthesized 3-ethyl-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1H-1-carboxamide pyrazole (EPFCA3) (49) and 4-methyl-5-hydroxy-5-trifluoromethyl-4,5-dihydro-1H-1-carboxamide pyrazole (MPFCA4) (50) and evaluated their anti-inflammatory activity. From the results it was evident that EPFCA3 and MPFCA3 are good candidates for the development of new drugs for pain treatment.

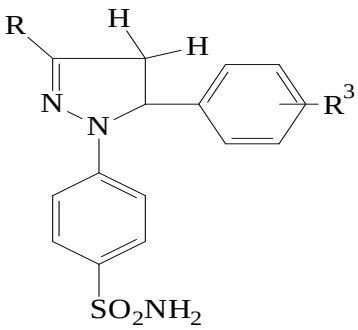


(49)



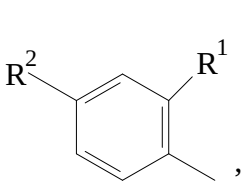
(50)

Rathish *et al*. [65] synthesized new 2-pyrazolines (51) bearing benzenesulfonamide derivatives by condensing chalcones with 4-hydrazinonbenzenesulfonamide hydrochloride. The synthesized compounds were tested at a dose of 20 mg/kg for their anti-inflammatory activity by carrageenan-induced rat paw edema model. Compounds with trimethoxy and N, N-dimethylamino moieties as substituents were found to be more potent than celocoxcib throughout the study.



(51)

R =



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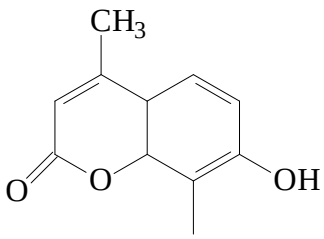
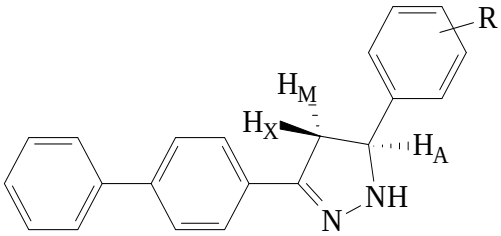


R^1= -OH, -OCH_3

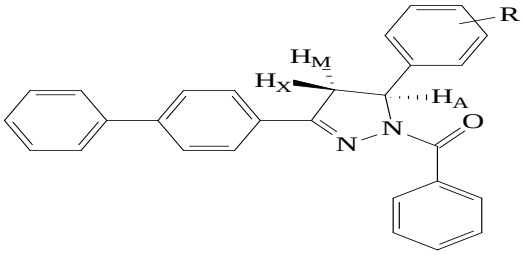
R^2= H, -OH, -OCH_3

R^3= H, 3-OH, 4-OCH_3, 2-Cl, 4-Cl, 3-NO_2, 4- OCH_3, 3,4-$(OCH_3)_2$, 3,4,5-$(OCH_3)_3$

Amir *et al*. [66] synthesized a series of 3-(4-biphenyl)-5-substituted phenyl-2-pyrazolines (52) and 1-benzoyl-3-(4-biphenyl)-5-substituted phenyl-2-pyrazolines (53) by condensation of chalcones with hydrazine hydrate in solvent system ethanol and DMF. The newly synthesized compounds were screened for their anti-inflammatory activity. Among the compounds studied compound having 4-methyl and 2,4,6-trimethoxy group on the phenyl ring at C-5 of pyrazoline nucleus possess highest activity (82.45%), greater than the standard drug flurbiprofen.



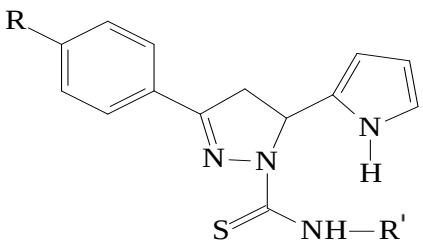
(52)



(53)

R= H, 2-Cl, 4-Cl, 4-$N(CH_3)_2$, 4-CH_3, 4-OCH_3, 3,4-$(OCH_3)_2$, 2,4,6-$(OCH_3)_3$

Kelekci *et al*. [67] synthesized novel series of 1-thiocarbamoyl-3-substituted phenyl-5-(2-pyrrolyl)-4,5-dihydro-(1*H*)-pyrazole derivatives (54). All the synthesized compounds were tested for their *in vivo* anti-inflammatory activity by two different bioassays, carrageenan-induced edema and acetic acid-induced increase in capillary permeability in mice. Compound with methoxy group and allyl group on the thiocarbamoyl moiety exhibited good anti-inflammatory activity comparable to that of indomethacin with no ulcerogenic effects.



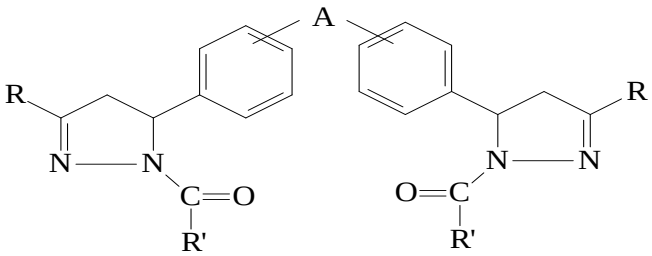
(54)

R= $-CH_3$, -Cl, $-OCH_3$

R'= $-CH_3$, $-C_2H_5$, $-C_3H_5$, $-C_6H_5$

Barsoum *et al*. [68] synthesized novel bis[3-aryl-4,5—dihydro-1*H*-pyrazol-1-carboxaldehydes] by refluxing bis[1-aryl-2-propen-1-ones] with hydrazine hydrate in formic acid and bis[1-acetyl-3-aryl-4,5-dihydro-1*H*-pyrazoles] were obtained by refluxing again with bis[1-aryl-2-

propen-1-ones] and hydrazine hydrate in acetic acid (55). Anti-inflammatory activity of the prepared pyrazolines were evaluated *in vivo* and compared with that of standard drug indomethacin. Most of the compounds showed remarkable anti-inflammatory properties with an ulcerogenic liability lower than that of the standard drug. Bis(2-pyrazoline-1-carboxaldehyde) analogue linked by *para*-phenylene moiety exhibited better activities than those linked by the *ortho*-phenylene residue.



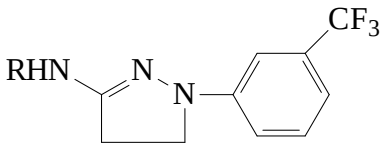
(55)

A= 2-O$(CH_2)_2$O-2', 4-O$(CH_2)_2$O-4'

R= -Ph, 4-ClC_6H_4, 4-FC_6H_4, 4-H_3CC_6H_4, 2-theinyl

R'= H, -CH_3

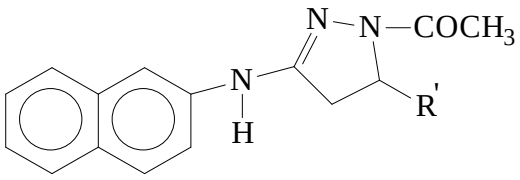
Fredrick *et al.*[69] synthesized 3-N-substituted amino-1-[3-(trifluoromethyl) phenyl]-2-pyrazolines (56) which showed anti-inflammatory activity.



(56)

R= H, methyl, propyl, butyl, -PhMe, 2-butenyl

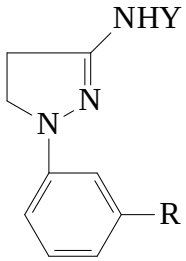
Bansal *et al.*[70] synthesized 1-acetyl-5-substituted aryl-3-(β-aminonaphthyl)-2-pyrazolines by treating β-acetylamino-naphthalene with different aromatic aldehydes followed by cyclization with hydrazine hydrate (57). The synthesized compounds were screened for their anti-inflammatory activity *in vivo* with the standard drug phenylbutazone. Some of the compounds of the series exhibited promising anti-inflammatory activity with lower ulcerogenic liability than the standard drug.



(57)

R'= -C_6H_5, 2-furyl, 4-$OCH_3C_6H_4$, 2-$OCH_3C_6H_4$, 4-$N(CH_3)_2C_6H_4$

Gurar *et al.*[71] synthesized 1-aryl-2-pyrazolines (58) exhibiting anti-inflammatory and analgesic activity.

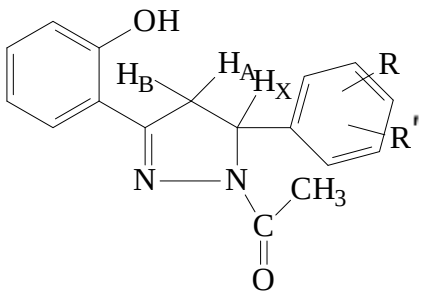


(58)

R= -CF_3, H, -Me, -CH_3PH, -Ph

Y= -CSNHR, -$CSNH_2$, =CHR^1

Manna *et al.*[72] synthesized a series of 1-acetyl-3-(2-hydroxyphenyl)-5-(R,R'-aryl)-4,5-dihydro-(1H) pyrazoles (59). The synthesized compounds were evaluated for their anti-inflammatory activity. From the results it was evident that presence of substituents on the 5-aryl group of the N-acetyl-Δ^2-pyrazoline was necessary for anti-inflammatory activity.

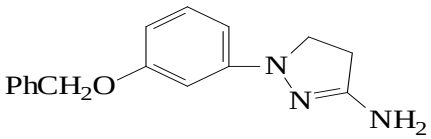


(59)

R= H, 2-Cl, 2-OCH_3

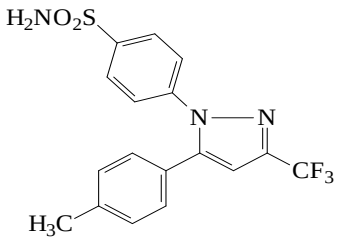
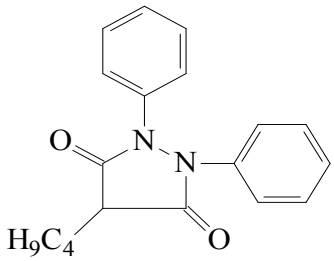
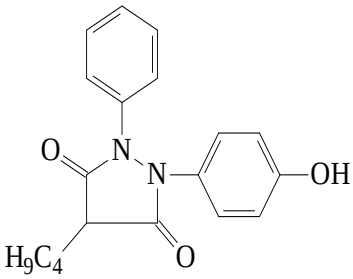
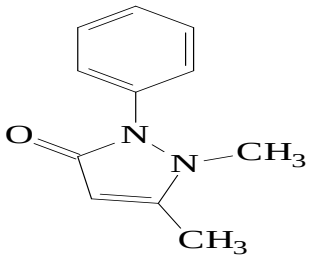
R'= H, 2-Cl, 3-Cl, 4-Cl, 2-Br, 3-Br, 4-Br, 4-CH_3, 2-OCH_3, 4-OCH_3, 5-OCH_3, 4-$N(CH_3)_2$

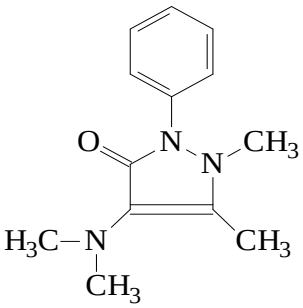
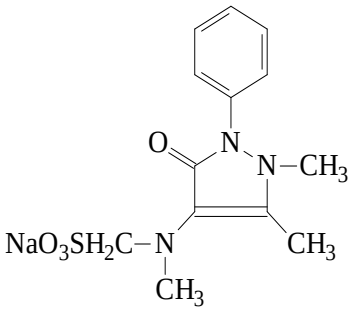
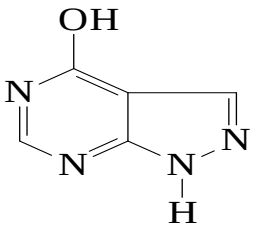
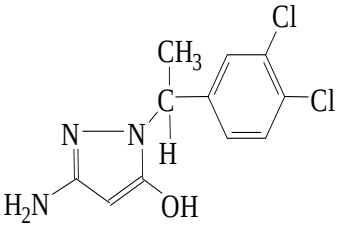
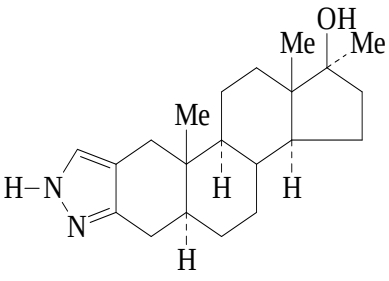
Huang *et al.*[73] synthesized 1-arylalkoxy and 1-arylalkylthioaryl-2-pyrazolines (60) that showed anti-inflammatory and antiallergic activity.

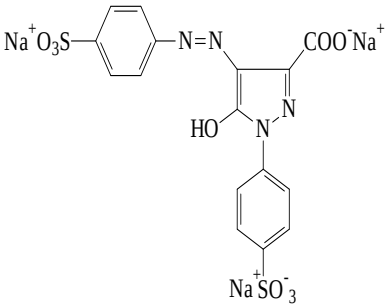
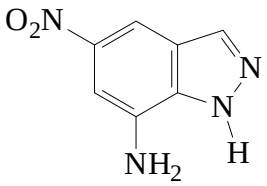
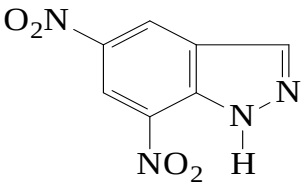
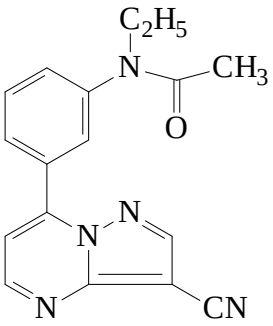


(60)

Drugs [74-77] Containing Pyrazole or Pyrazoline Moiety Along With Their Structures Are Given Below.

DRUG	ACTIVITY
 Celecoxib **(61)**	NSAID
 Phenylbutazone **(62)**	NSAID
 Oxyphenbutazone **(63)**	NSAID
 Antipyrine **(64)**	Analgesic

DRUG	ACTIVITY
 Aminopyrine **(65)**	Analgesic, Antipyretic
 Dipyrone **(66)**	Analgesic, Antipyretic, Antirheumatic
 Allopurinol **(67)**	Treatment of gout
 Muzolimine **(68)**	Diuretic
 Stanozolol **(69)**	Anabolic Androgenic activity

DRUG	ACTIVITY
 Amaranth **(70)**	Used in ulcerative colitis
 7-Amino-5-nitroindazole **(71)**	Antibacterial
 5,7-Dinitroindazole **(72)**	Antibacterial
 Zaleplon **(73)**	Hypnotic and Sedative

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