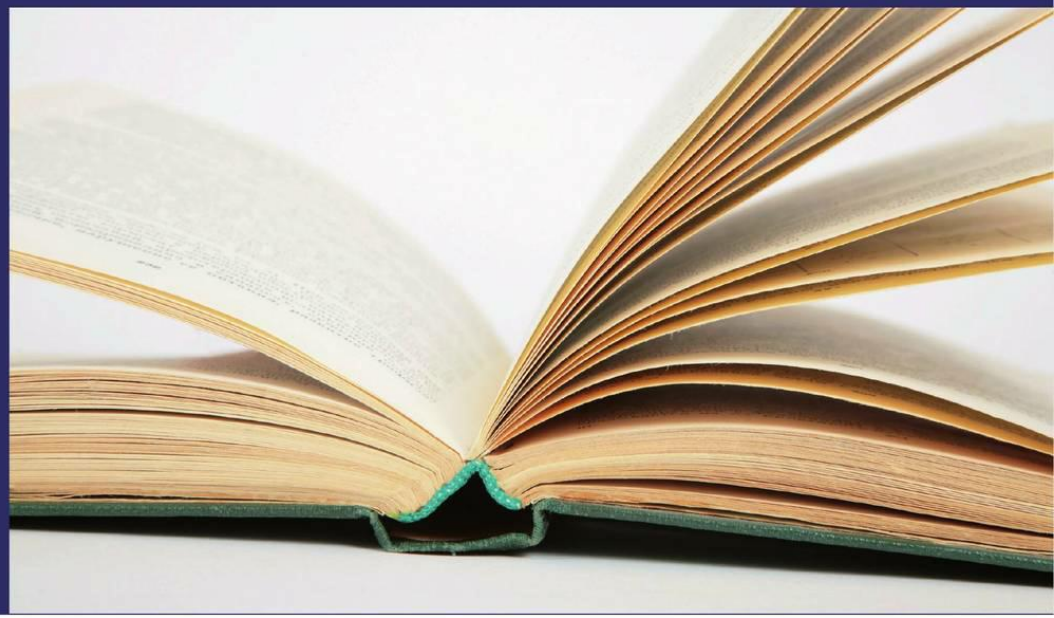
This book includes an introduction to medical Pyrazole compounds and their use as drugs because of their great importance in the treatment of some medical conditions. This book contains naming these compounds and methods of preparation and how to diagnose and also includes the preparation of a series of Pyrazoline vehicles new and diagnosis FT-IR, HNMR, and elements analysis, this book can be used to assist in the teaching of Heterocyclic Compounds as a source decision for the undergraduate students.



Pyrazoline Compounds

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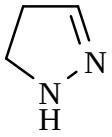
Content

1. Pyrazolines

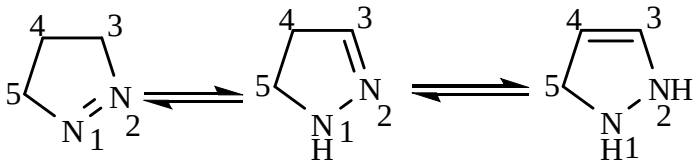
1.1 Introduction

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 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



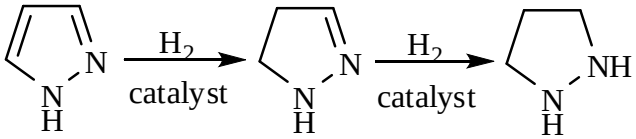
(1)

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.



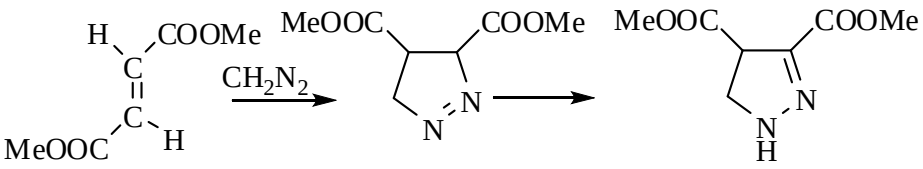
Scheme (2)

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^{o}C, is the most stable of all these compounds. The pyrazolidines possess strong reducing properties and readily give up hydrogen to form pyrazolines.

1.2. General methods of synthesis of pyrazolines

1.2.1. From α,β-unsaturated carboxylic acid esters reacts with diazomethane

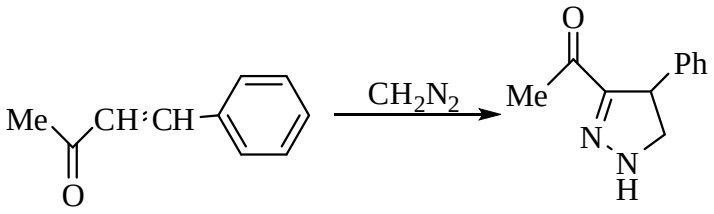
α,β-unsaturated carboxylic acid esters reacts with diazomethane to give 2-pyrazolines. The mechanism of this reaction was correctly anticipated by Pechmann[(5)] in which the primary product of this reaction is a 1-pyrazoline, formed by 1,3-dipolar cyclo addition, which spontaneously isomerizes into its thermodynamically more stable 2-pyrazoline isomer by a 1,3- H shift (**Scheme3**).



Scheme (3)

1.2.2.From Benzylideneacetone on reaction with diazomethane

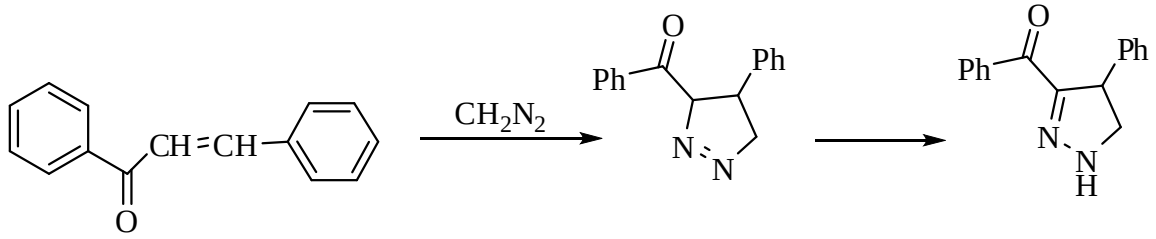
Benzylideneacetone on reaction with diazomethane by 1,3-dipolar cycloaddition yield 2-pyrazolines (**Scheme 4**). This is probably the first example of the synthesis of a pyrazoline from the reaction of an α,β- unsaturated ketone and diazomethane and was published by Azzarello[6] in 1906. Later, this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



Scheme (4)

1.2.3.1,3-Dipolar cycloaddition of chalcones and diazomethane

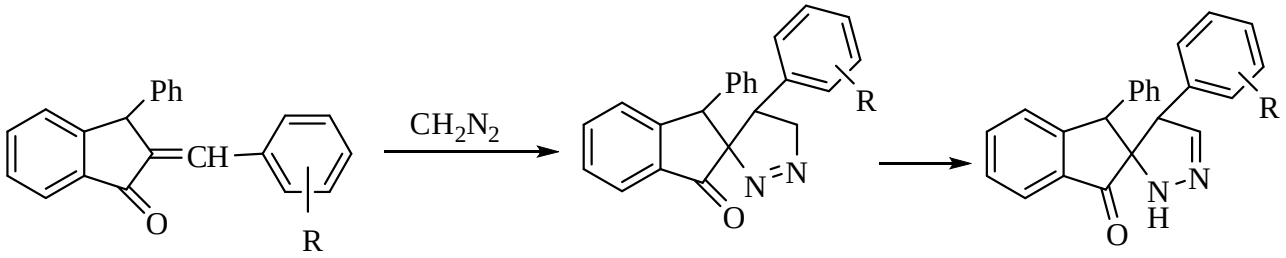
1,3-Dipolar cycloaddition of chalcones and diazomethane was first investigated by Smith and Pings[9] and 3-benzoyl- 4-phenyl-1-pyrazoline was prepared as a primary product which was then isomerized into the 3-benzoyl-4-phenyl-2-pyrazoline on gentle heating (**Scheme 5**).



Scheme (5)

1.2.4.From reaction of 2-arylidene-3-phenyl-1-indanones with diazomethane

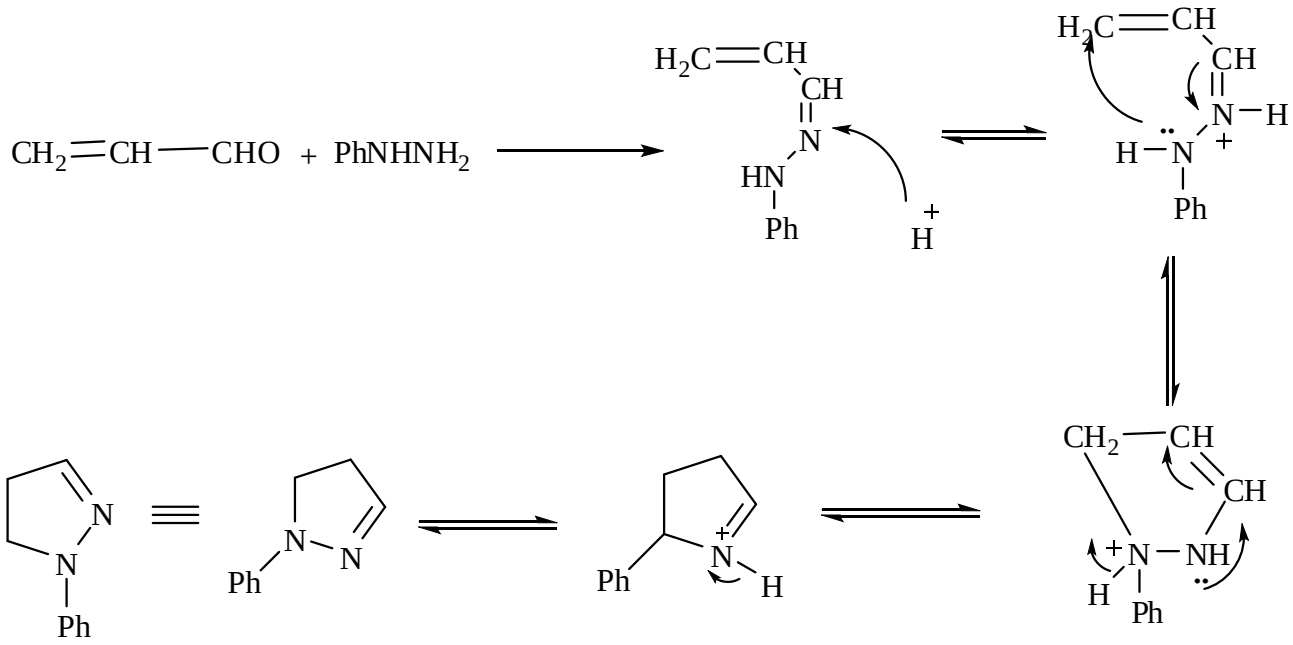
The reaction of 2-arylidene-3-phenyl-1-indanones with diazomethane performed by Mustafa and Hilmy[10] can be considered as the first example of 77 pyrazoline formation by the cycloaddition of an exocyclic α,β- unsaturated ketone and diazomethane (**Scheme 6**).



Scheme (6)

1.2.5.Froα,β-unsaturated aldehydes or ketones with phenylhydrazine

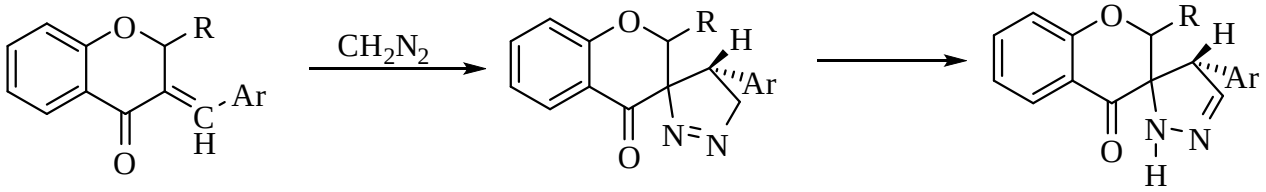
α,β-unsaturated aldehydes or ketones do react with phenylhydrazine to form hydrazones as intermediates. These hydrazone intermediates on treatment with acetic acid or hydrochloric acid in ethanol isomerizes to Δ^2-pyrazolines. The reaction scheme is given below (**Scheme 7**).



(Scheme 7)

1.2.6. From the reaction of 3-arylideneflavanones and diazomethane

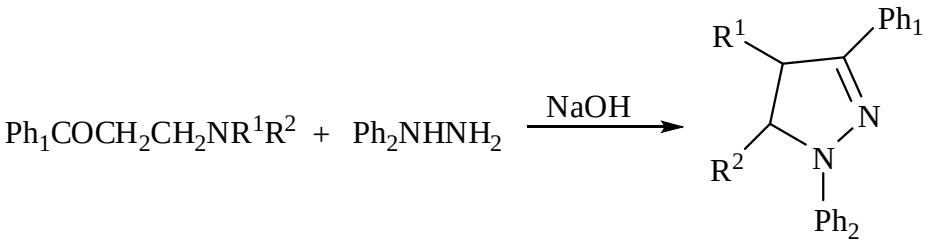
Pijewska *et al.*[11,12] studied the reaction of 3-arylideneflavanones and diazomethane to yield pyrazolines. The structure and stereochemistry of the pyrazolines formed have been elucidated by various NMR techniques. This detailed spectroscopic investigation[13-16] unambiguously proved that the (E)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



Scheme (8)

1.2.7. From Mannich bases on reaction with phenylhydrazine

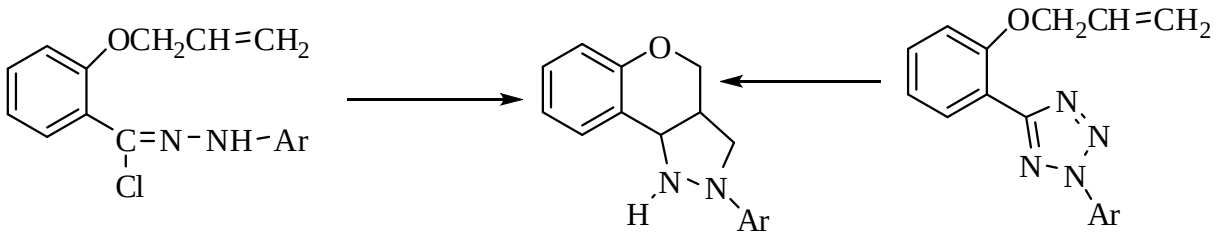
Mannich bases on reaction with phenylhydrazine and aqueous ethanolic NaOH at reflux temperature yield substituted 2-pyrazolines[17] (**Scheme 9).**



Scheme (9)

1.2.8. From intramolecular 1,3-dipolar cycloaddition of nitrile imines

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**).

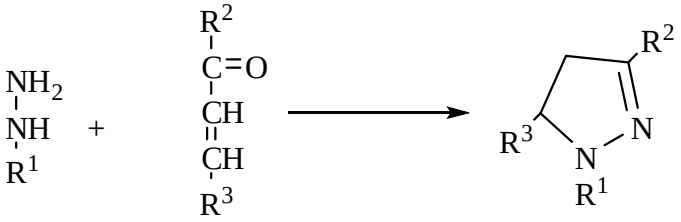


Scheme (10)

1.2.9.From reaction of chalcones with hydrazines

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

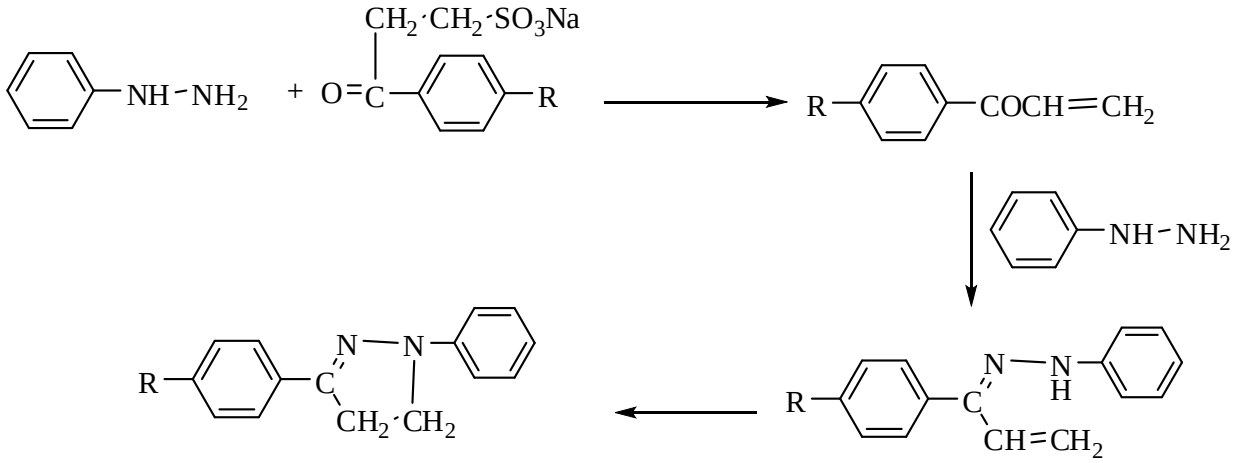
achieved under alkaline conditions by using pyridine as catalyst in ethanolic solution[24]. In some cases the two reactants were refluxed in alcoholic solution without a catalyst to provide 2-pyrazolines[25,26].



Scheme (11)

1.2.10.From 2-arylcarbonylethylthiosulfates

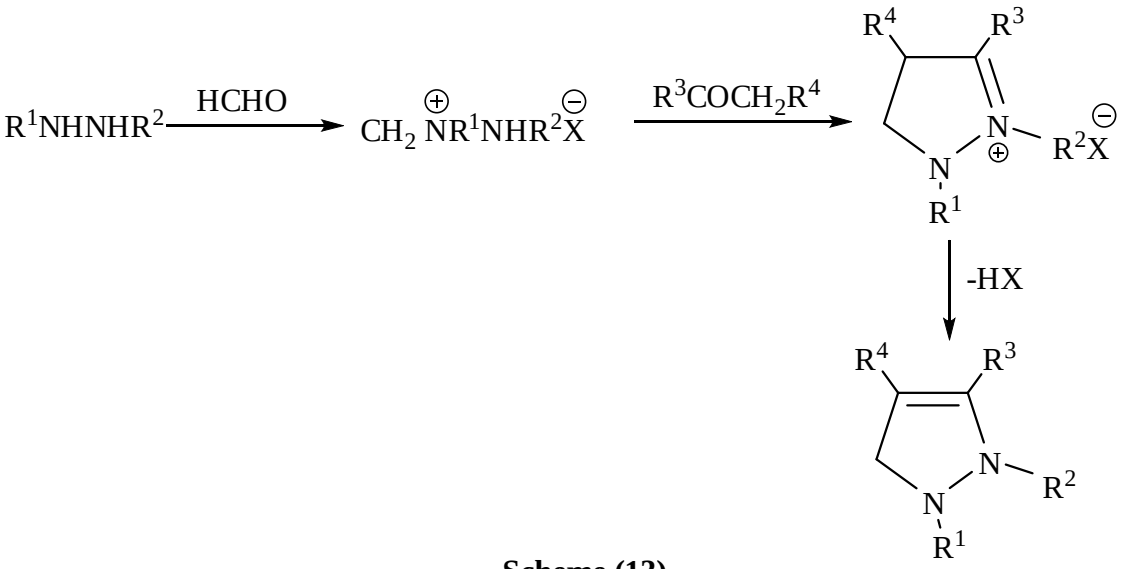
2-arylcarbonylethylthiosulfates when heated with two equivalents of phenyl hydrazine in water for 0.5-3 hrs under reflux yield 1-phenyl-3-aryl-2-pyrazolines[27] (**Scheme 12**).



Scheme (12)

1.2.11.From 1,2-disubstituted hydrazine react with formalin

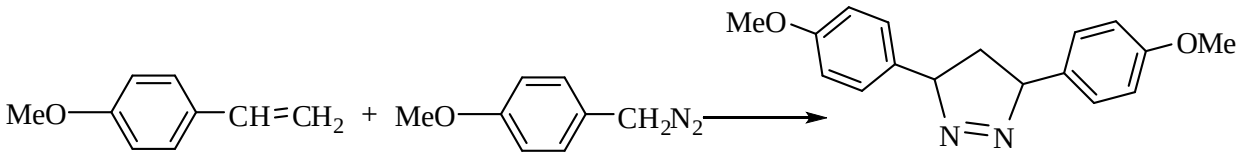
1,2-disubstituted hydrazine react with formalin and a carbonyl compound (Hinmann synthesis) to yield pyrazolines[28] (**Scheme 13**).



Scheme (13)

1.2.12.From Cycloaddition reaction of substituted styrenes with *p*-anisyldiazomethane

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

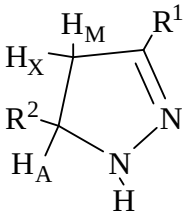


Scheme (14)

2. Spectral features of pyrazolines

2.1 NMR spectra of pyrazolines :

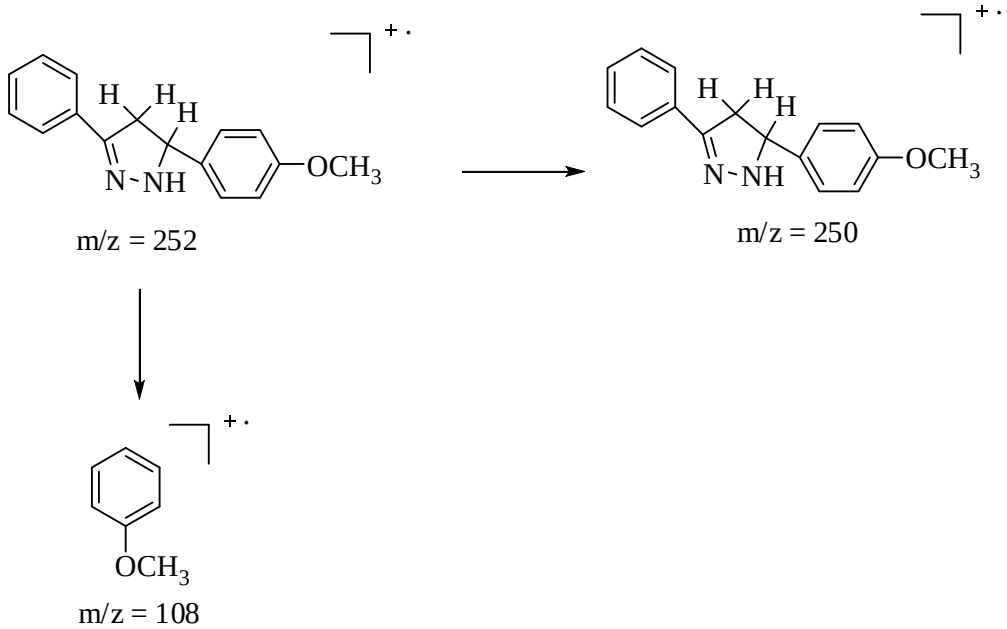
A pyrazoline ring is identified by characteristic spectral features[30] in its ^1H NMR spectrum. The three protons in the pyrazoline ring **(2)** will show AMX splitting pattern, H_A proton appearing at δ 2.98 (dd), J_{AM}= 7.6 Hz and J_{AX} = 12 Hz, H_M proton resonating at δ 3.64 (dd), J_{AM}= 12 Hz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

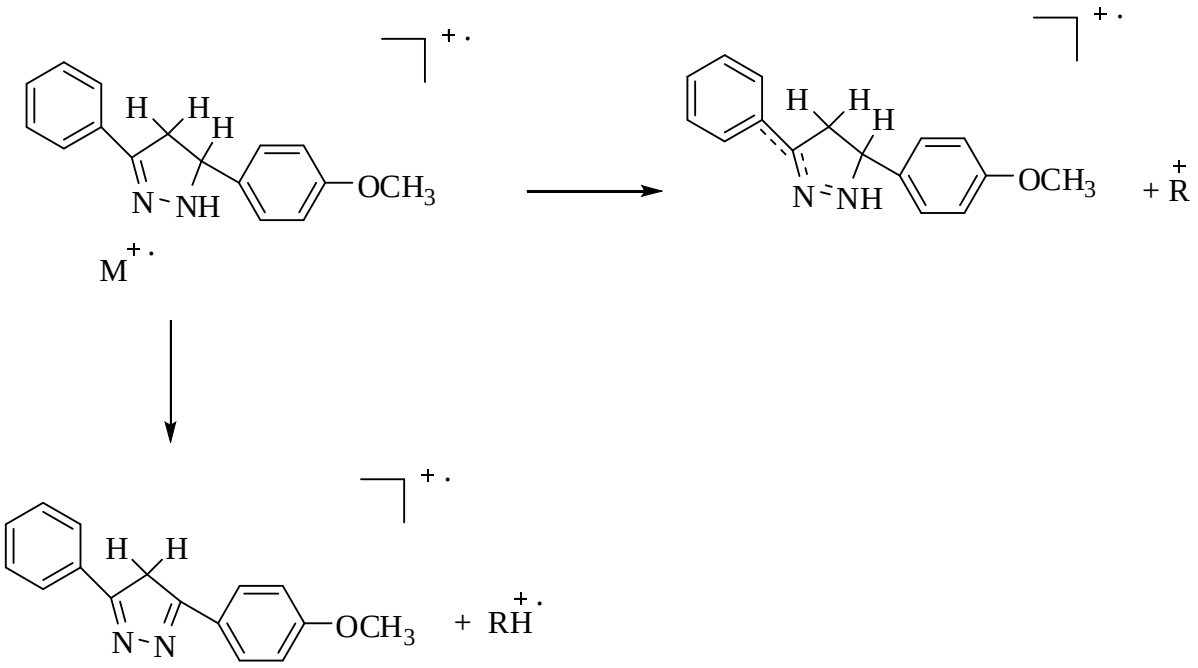
2.2 Mass spectra of pyrazolines:

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.



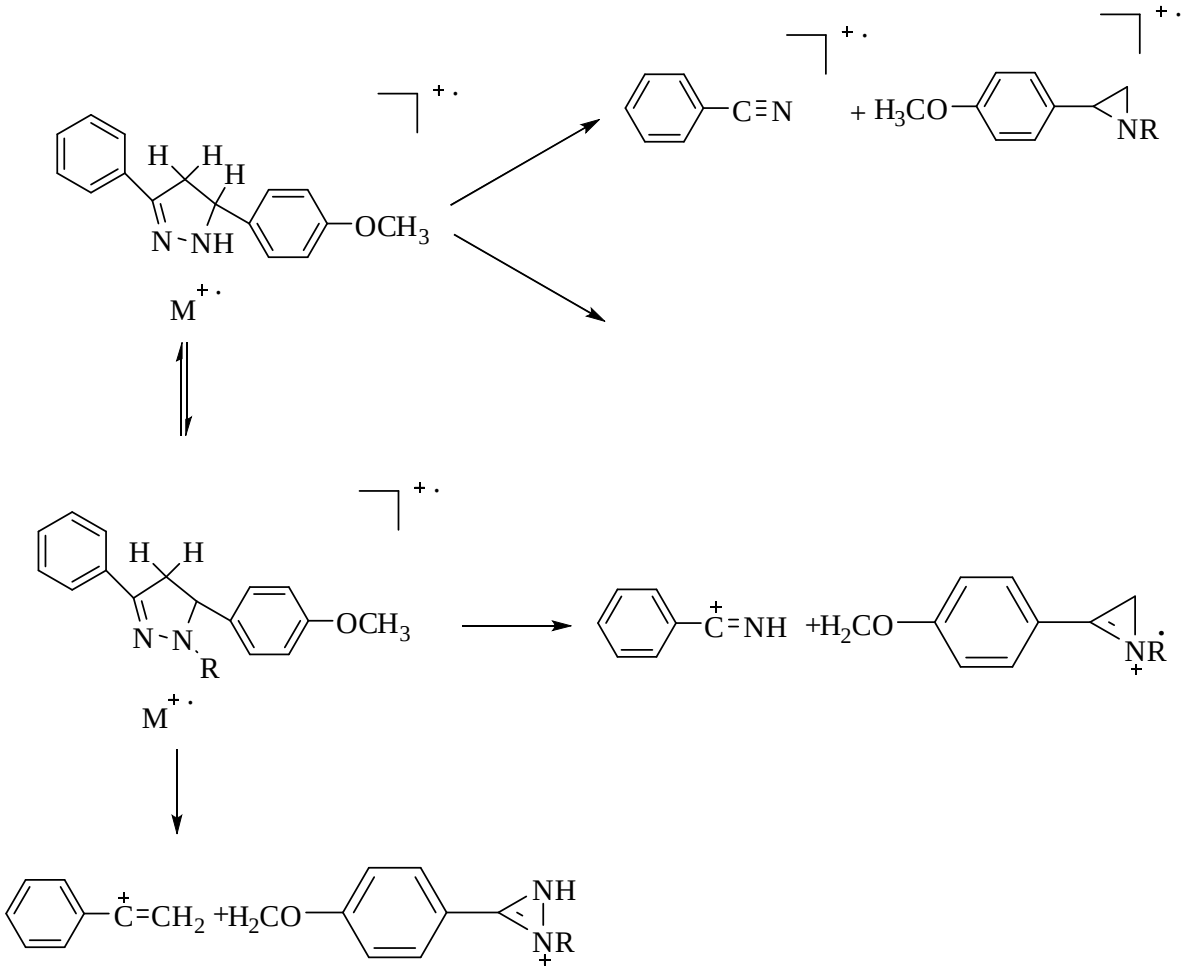
Scheme(15)

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)

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



Scheme (17)

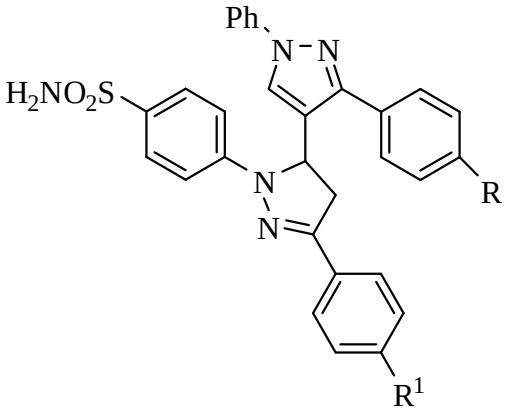
3.Theriputic potential of 2-pyrazolines :

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.

3.1 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*

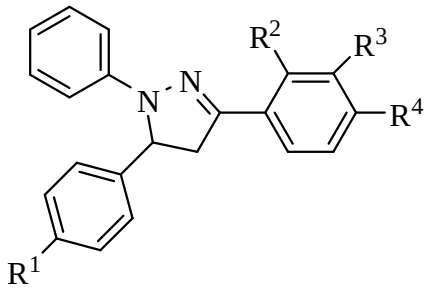
vitro antimicrobial activity against *S.aureus* (MTCC 3160) and *B.subtilis* (MTCC 121) representing Gram-positive bacteria and *Pseudomonas aeruginosa* (MTCC 741) and *E.coli* (MTCC 51) representing Gram-negative bacteria. Most of the tested compounds showed better activity against the Gram-positive 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



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

(3)

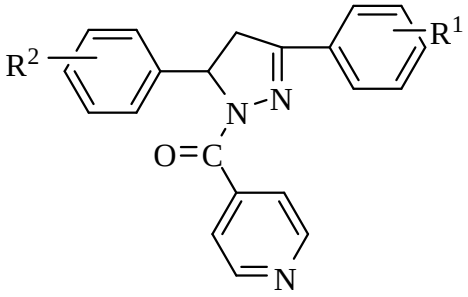
Sivakumar *et al.*[34] synthesized some novel 1,3,5-triphenyl-2-pyrazolines **(4)** and evaluated their antimicrobial activity. All the compounds showed good activity against *E.coli* and poor activity against *S.aureus*. Compounds possessing chloro, methoxy, dimethoxy and bromo as substituents exhibited 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.



R^1=-SCH_3,-SO_2-CH_3
R^2=-Cl, R^3=-O-CH_2-O,-NO_2,-OMe,-Br. R^4=-Cl,-CH_3,-OEt,-OMe,-F

(4)

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.



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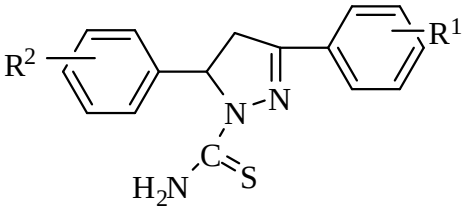
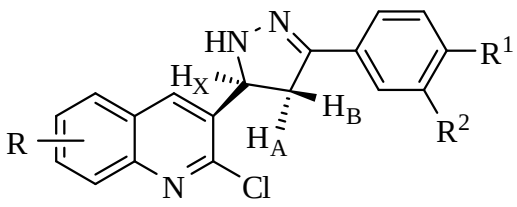


(6)

R^1= 4-OCH_3, 4-Cl, 3-NO_2
R^2= H,4-Cl

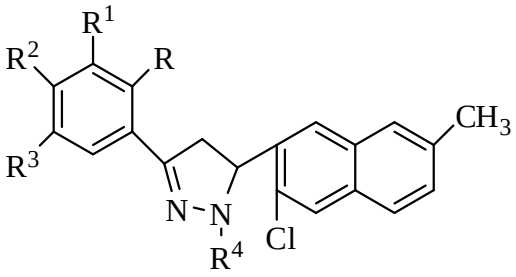
Bawa *et al*.[36] synthesized a series of 2-chloroquinoline containing pyrazoline derivatives having 3,4-dichloro / 3,4-dimethoxy moiety on the phenyl ring **(7)** and the synthesized compounds were screened for antimicrobial activity. All the compounds were evaluated for their antibacterial activity against *Escherichia coli* (NTCC 10418), *S.aureus* (NCTC 65710) and *P.aeruginosa* (NCTC 10662). Thecompounds 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.



R= H,-CH_3,-OCH_3, R^1= Cl,-OCH_3, R^2=Cl,-OCH_3

(7)

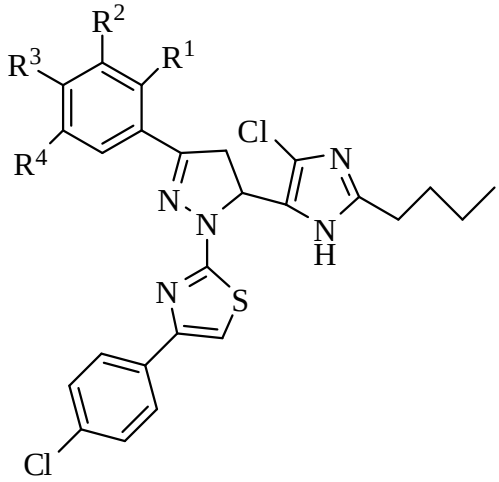
Mokie *et al*.[37] synthesized a series of 2-pyrazolines **(8)** by cyclization of α,β-unsaturated ketone (chalcones) with hydrazine hydrate / phenylhydrazine using triethanolamine as solvent within 15-20 mins. All the synthesized compounds were evaluated for their antibacterial activity by Agar well 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.



R=H,-OH, R^1=Cl, R^2=H,-OH, R^3=-CH_3,-Cl,-Br,-I, R^4=H,-C_6H_5

(8)

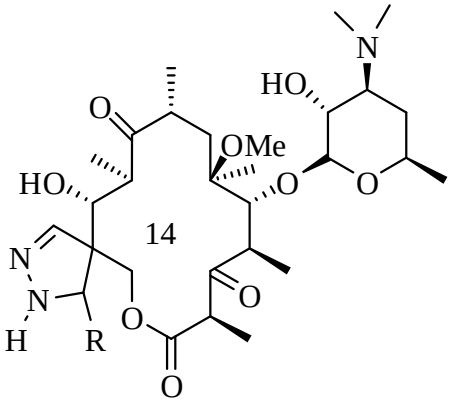
Dawane *et al*.[38] synthesized some 1-(4-(4'-chlorophenyl)-2-thiazolyl)-3-aryl-5- (2-butyl-4-chloro-1H-imidazo-5yl)-2-pyrazoline derivatives **(9)** by the base catalyzed treatment of appropriate chalcones with 4-(4'-chlorophenyl)-2-hydrazino-thiazole in polyethylene glycol (PEG 400) as an alternative reaction89 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.



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

(9)

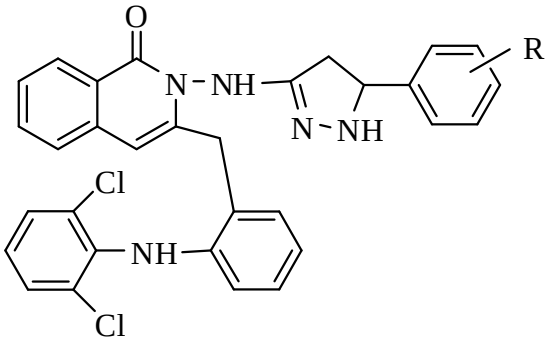
Hu *et al.*[39] synthesized a series of C-12 pyrazolinyl spiroketolide derivatives **(10)**. Compounds with alkane and ester groups at pyrazolinyl spiros were investigated for their antibacterial activities against both erythromycin-susceptible and erythromycin-resistant bacteria. All the derivatives 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.



R= H,-CH_3,-$COOCH_3$, -$COOC_2H_5$

(10)

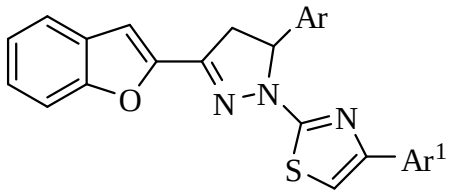
Patel *et al.*[40] synthesized a series of new 2-[2-(2,6-dichlorophenyl)amino] phenylmethyl-3-[(5-substitutedphenyl)-1,5-dihydro-1H-pyrazol-3-yl-amino]-6-iodoquinazolin-4(3H)ones **(11)** by the reaction of 2-[2-(2,6-dichlorphenyl)amino] phenylmethyl-3-substituted phenyl acryl amido-6-iodoquinazolin-4(3H)ones 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*.



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

(11)

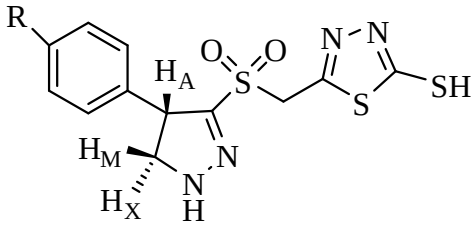
Abdel-Wahab *et al.*[41] synthesized 3-(benzofuran-2-yl)-4,5-dihydro-5-aryl-1-[4(aryl)-1,3-thiazol-2-yl]-1H-pyrazoles **(12)** and evaluated for their antimicrobial activity. All the compounds synthesized were screened for their antibacterial and antifungal activities at 100 µg concentration. Compounds 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.



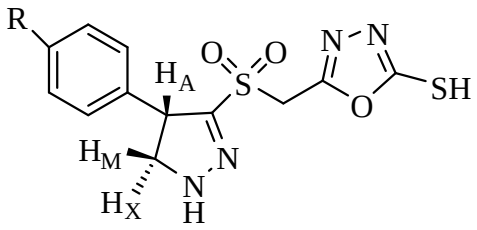
Ar= -C_6H_5,4-ClC_6H_4, Ar^1= -C_6H_5,4-BrC_6H_4

(12)

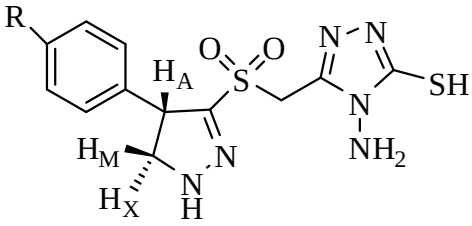
Padmavathi *et al.*[42] synthesized some novel sulfone-linked bis heterocyclic pyrazolines in combination with thiadiazoles **(13)**, oxadiazoles **(14)** and triazoles **(15)** from *E*-styryl-sulfonylacetic acid methyl ester and tested for their antimicrobial activity. The antimicrobial activities of the compounds were tested 92 by agar disc-diffusion method. Among the compounds tested, pyrazolines with triazole substituents showed pronounced activity.



(13)



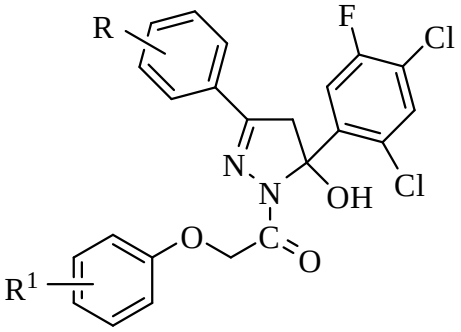
(14)



(15)

R=H,-Me, -Cl

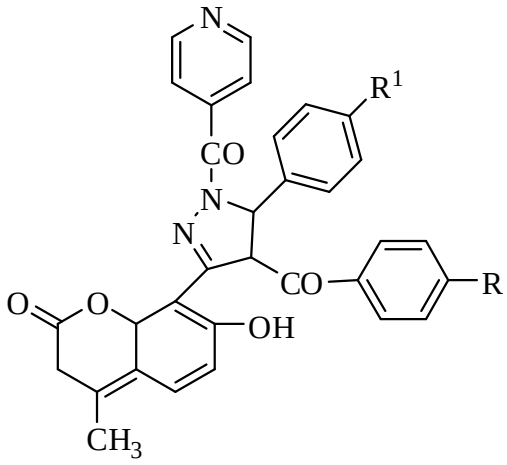
Karthikeyan *et al.*[43] synthesized some novel chloro-fluorine containing hydroxy pyrazolines **(16)** by treating chalcone dibromides with aryloxy acid hydrazides in the presence of triethylamine. All the synthesized compounds were tested for their antibacterial and antifungal activities. The antibacterial 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* 93 (recultured). Compounds with methoxy, chloro and dichloro as substituents emerged as very active against all the fungal strains tested.



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-$(Cl)_2$

(16)

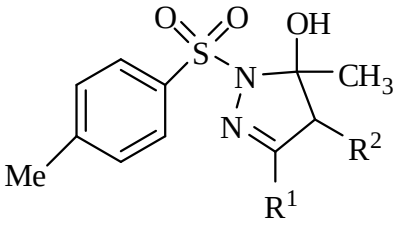
Thakare *et al.*[44] synthesized 3-coumaryl-4-aroyl-5-aryl-2-pyrazolines **(17)** that showed antimicrobial activity against pathogenic bacteria



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 94 *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.

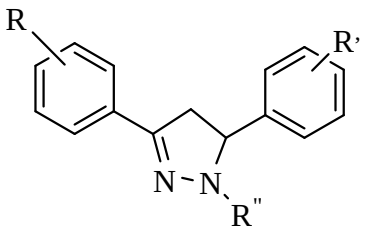


R^1=H,-Me,-Ph,4-MePh,4-OMePh,4-BrPh,4-ClPh,4-FPh
R^2=H,-Ph

(18)

Bizzarri *et al.*[46] synthesized a series of N1-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

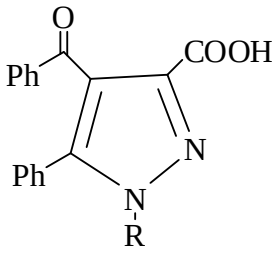
compounds exhibited a significant degree of activity against *H.pylori* strains, including those resistant to the reference compound metronidazole. Among the compounds, those with an N1-acetyl group and 4-methoxy as substituents on the 5-phenyl ring showed maximum activity against *H.pylori* metronidazole resistant strains at a MIC value of 1-4 µg/mL.



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

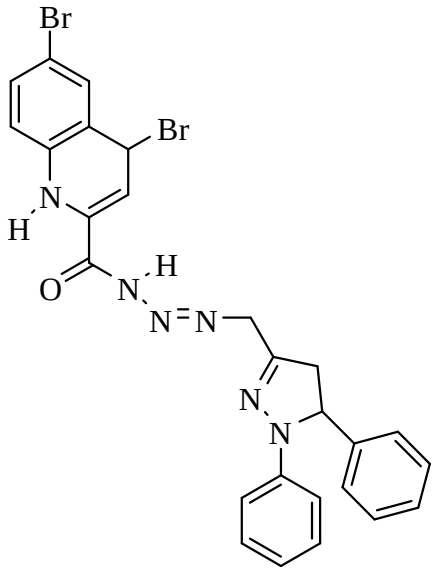
(19)

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.



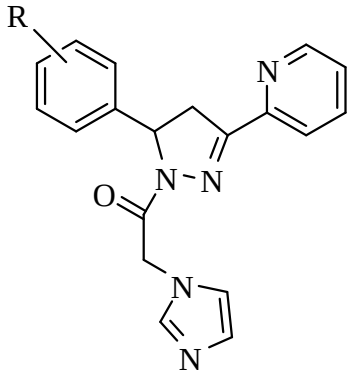
(20)

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)

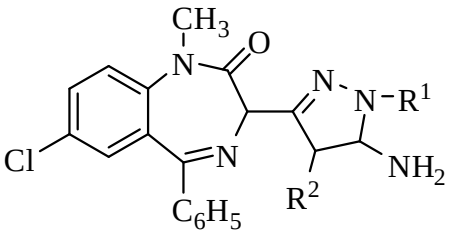
Mamolo *et al*.[49] synthesized (±)-1-(5-aryl-3-pyridin-2-yl-4,5-dihydro-pyrazol-1-yl)-2-imidazol-1-yl-ethanone derivatives **(22)** and tested for their *in vitro* 96 antifungal activity. All the compounds showed moderate activity against *Candida parapsilosis*, *Candida pseudotropicalis* and *Candida glabrata*.



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

(22)

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*



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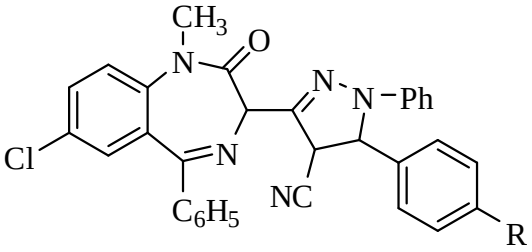
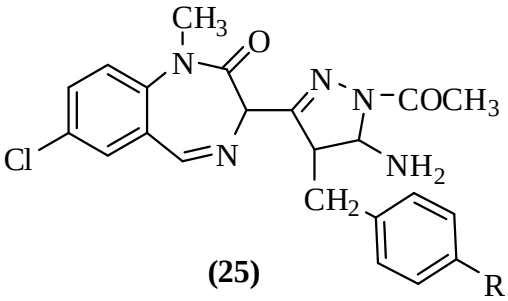


(24)



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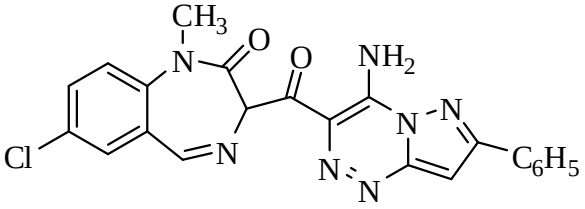


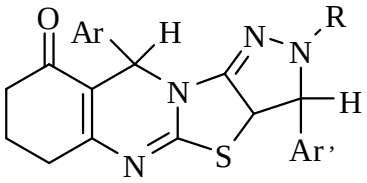
(26)

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.

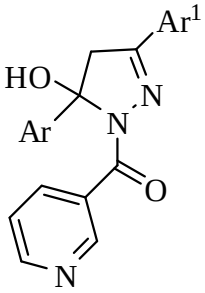


R=H,-C_6H_5

Ar'=-C_6H_4-F(*P*)

(27)

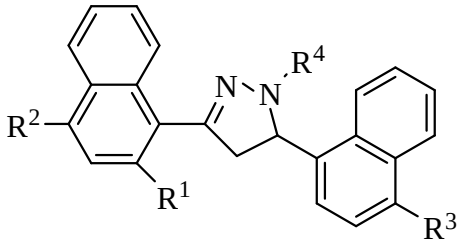
Balakrishna *et al.*[52] synthesized 1-nicotinoyl-3,5-diaryl-5-hydroxy-2-pyrazolines **(28)** that showed significant antimicrobial activity**.**



Ar=Ar^1=Ph,C_6H_4X

(28)

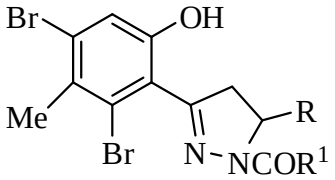
Davood *et al.*[53] synthesized 3,5-dinaphthalene-1-yl-substituted-2-pyrazolines **(29)** that showed antibacterial activity.



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

(29)

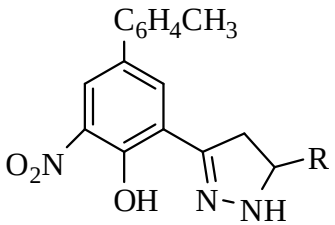
Naik *et al.*[54] synthesized 1-acyl-3-(2-hydroxy-5-methyl-4,6-dibromophenyl) -5-(substituted phenyl)-2-pyrazolines **(30)** possessing antibacterial activity.



R=Ph,C_6H_4X
R^1=Me,Ph

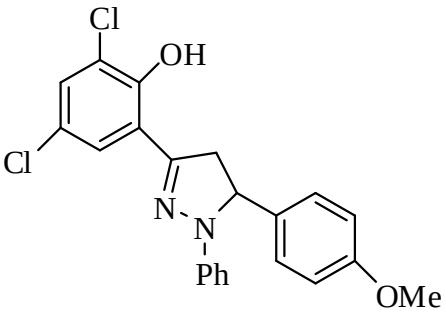
(30)

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.*



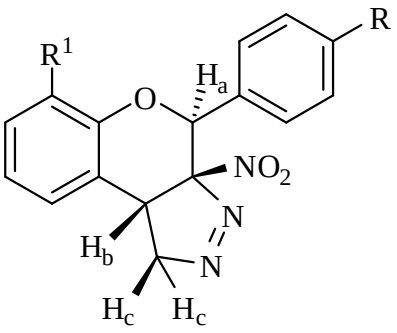
(31)

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

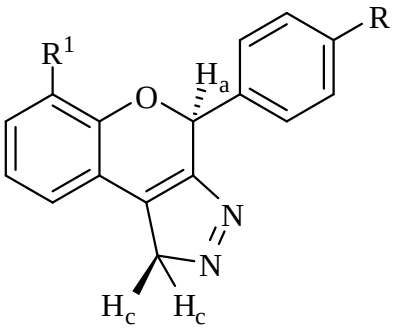


(32)

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)



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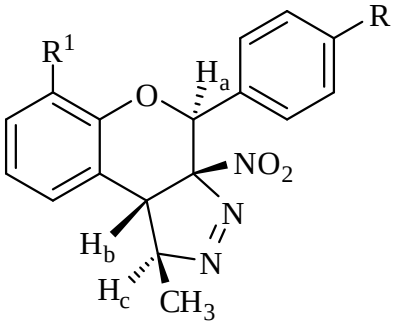
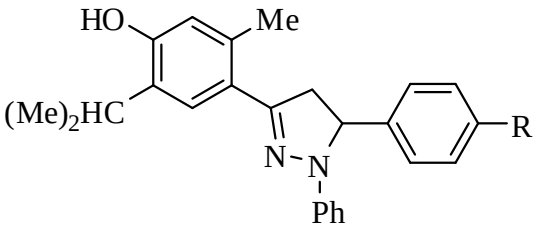


(35)

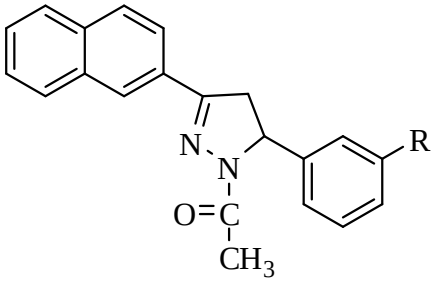
R=H,Me,OMe,Cl
R^1=H

Roda *et al.*[58] synthesized 5-aryl-1-phenyl-3-(3-isopropyl-4-hydroxy-6-methyl phenyl)-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.

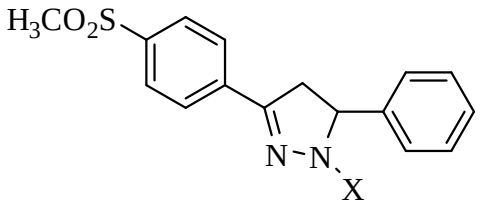


(37)

Nesreen N.Majeed et.al.[60] synthesis 2-(1,5-Diphenyl-4,5-Dihydro-1HPyrazol-3-Yl)Pyridine Derivatives and study as antibacterial it is clear that Gram negative bacteria (E. coli) are more affected than Gram positive bacteria (S. aureus). It has been postulated that the cell membrane of E. coli contains many condensed fat layers as compared to S. aureus. Accordingly, chemicals, antibiotics or antiseptics face difficulty in penetrating these membranes and therefore their effectiveness is diminished.

3.2. Anti-inflammatory activity :

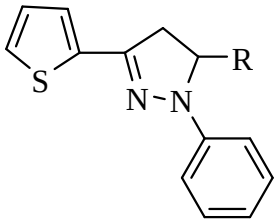
Fioravanti *et al.*[61] synthesized some new 1-N-substituted-3,5-diphenyl-2-pyrazoline derivatives **(38)** and the synthesized compounds were evaluated for cyclooxygenase (COX-1 and COX-2) inhibitory activities. N-acetyl derivatives were found to be more potent than the corresponding N-thiocarbomoyl derivatives.



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= -$COCH_3$, -$CSNH_2$

(38)

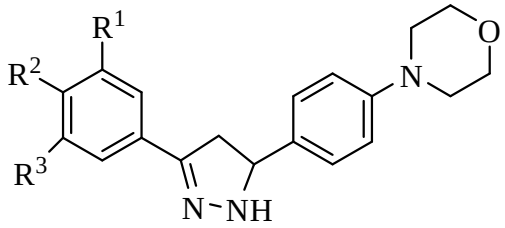
Ramesh *et al*.[62] synthesized some new pyrazoline derivatives **(39)** by reacting chalcones of 2- acetylthiophene with phenylhydrazine hydrochloride in the presence of alcohol. The synthesized compounds were screened for their anti-inflammatory activity. Some of the compounds showed moderate to considerable anti-inflammatory activity.



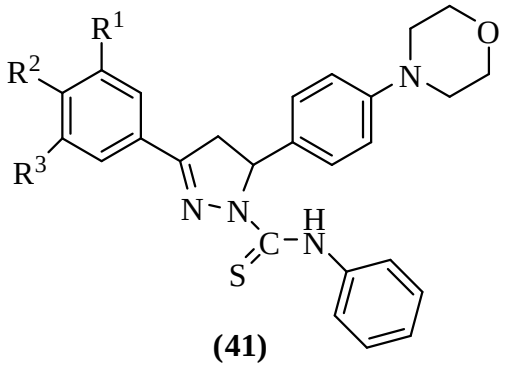
R= 2-thienyl, 2,4-$(Cl)_2$, 4-$N(CH3)_2$, 4-F, 4-Cl.

(39)

Joshi *et al*.[63] 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.



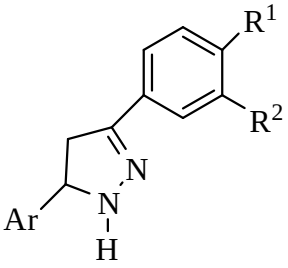
(40)



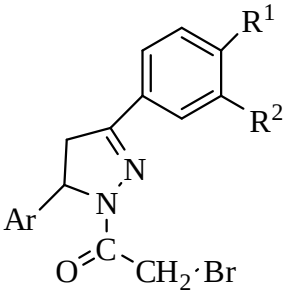
(41)

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

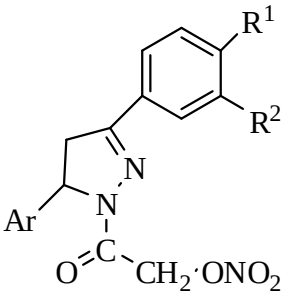
Shoman *et al*.[64] synthesized novel 3,5-diaryl-2-pyrazoline derivatives **(42, 43, 44, 45, 46, 47** and **48**) by reaction of various chalcones with hydrazine hydrate in ethanol. A group of NO-donating-2-pyrazoline derivatives were synthesized by carrying a nitrate ester group or an oxime group onto 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.



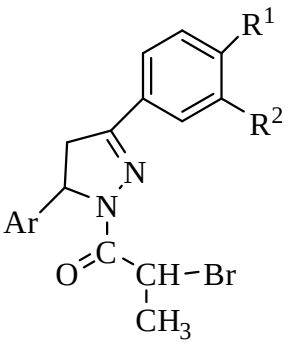
(42)



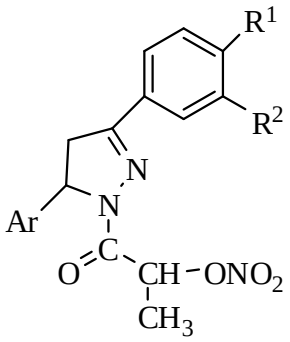
(43)



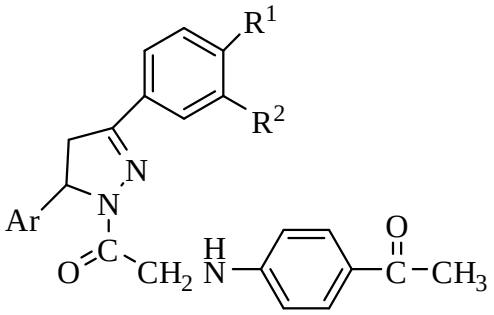
(44)



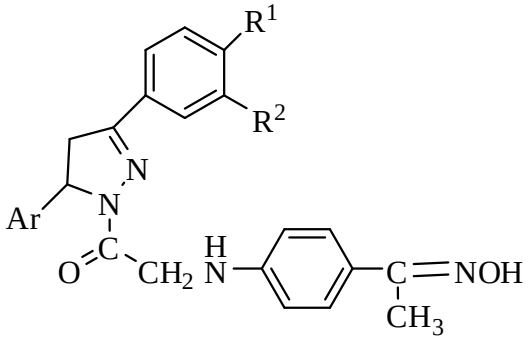
(45)



(46)



(47)

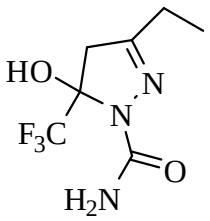


(48)

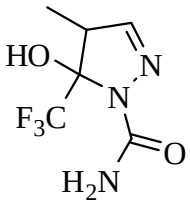
R^1= H, -OCH_3
R^2= H, -OCH_3

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

Sauzem *et al*.[65] 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.

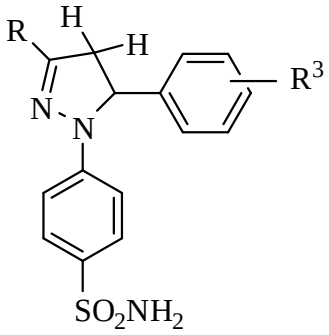


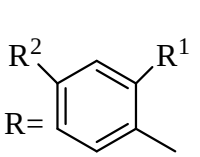
(49)

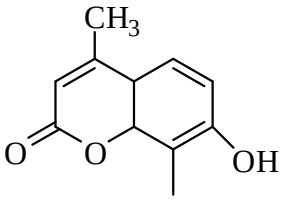


(50)

Rathish *et al*.[66] 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 carrageenaninduced rat paw edema model. Compounds with trimethoxy and N,Ndimethylamino moieties as substituents were found to be more potent than celocoxcib throughout the study.



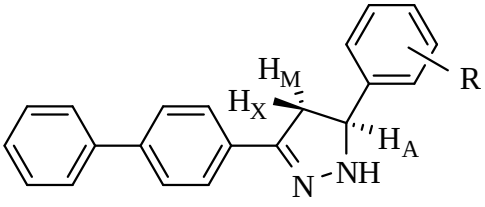


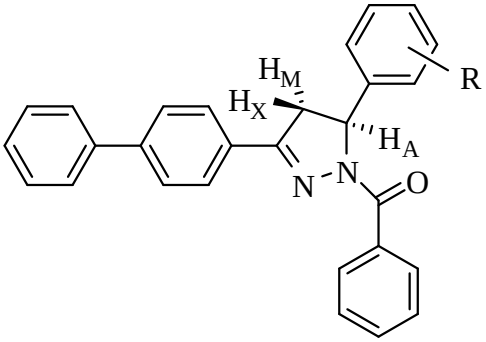


R^1= -OH, -OCH_3
R^2= H, -OH, -OCH_3

(51)

Amir *et al.*[67] 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.

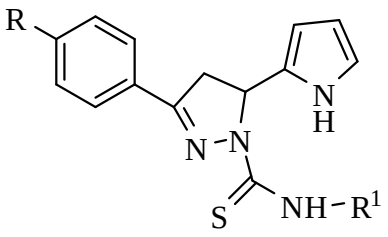




(52) **(53)**

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-$(OCH_3)_3$

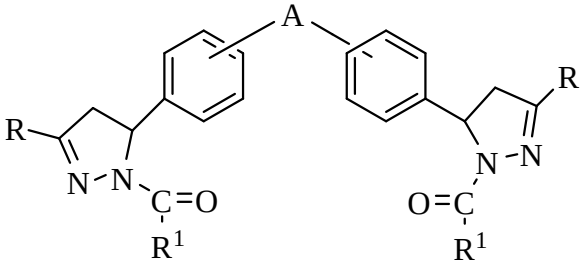
Kelekci *et al.*[68] synthesized novel series of 1-thiocarbamoyl-3-substituted phenyl-5-(2-pyrrolyl)-4,5-dihydro-(1*H*)-pyrazole derivatives **(54)**. All the synthesized compounds were tested for their *in vivo* anti-inflammatory activity by two different bioassays, carrageenan-induced edema and acetic acid-induced 108 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^1= -CH_3, -C_2H_5, -C_3H_5, -C_6H_5

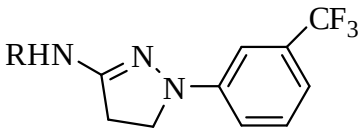
Barsoum *et al*.[69] synthesized novel bis[3-aryl-4,5—dihydro-1*H*-pyrazol-1-carboxaldehydes] by refluxing bis[1-aryl-2-propen-1-ones] with hydrazine hydrate in formic acid and bis[1-acetyl-3-aryl-4,5-dihydro-1*H*-pyrazoles] were obtained by refluxing again with bis[1-aryl-2-propen-1-ones] and hydrazine 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)

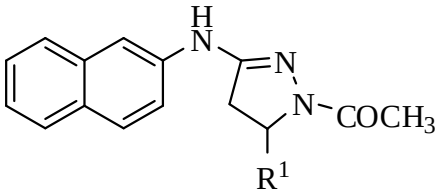
A= 2-$O(CH_2)_2O$-2', 4-$O(CH_2)_2O$-4'
R= -Ph, 4-ClC_6H_4, 4-FC_6H_4, 4-$H_3CC_6H_4$, 2-theinyl
R^1= H, -CH_3

Fredrick *et al*.[70] 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

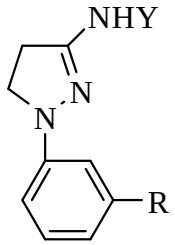
Bansal *et al.*[71] synthesized 1-acetyl-5-substituted aryl-3-(β-aminonaphthyl)-2-pyrazolines by treating β-acetylamino-naphthalene with different aromatic aldehydes followed by cyclization with hydrazine hydrate **(57)**. The synthesized compounds were screened for their anti-inflammatory activity *in 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^1= -C_6H_5, 2-furyl, 4-$OCH_3C_6H_4$, 2-$OCH_3C_6H_4$, 4-$N(CH_3)_2C_6H_4$

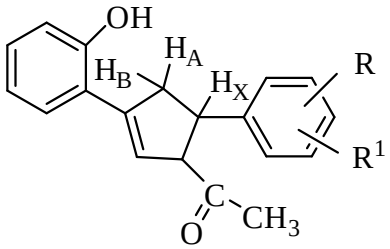
Gurar *et al.*[72] synthesized 1-aryl-2-pyrazolines **(58)** exhibiting anti-inflammatory and analgesic activity.



(58)

R= -CF_3, H, -Me, -CH_3Ph, -Ph
Y= -CSNHR, -$CSNH_2$, =CHR^1

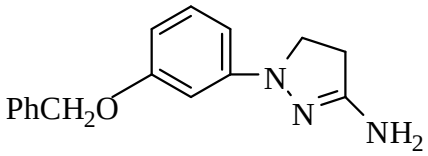
Manna *et al.*[73] synthesized a series of 1-acetyl-3-(2-hydroxyphenyl)-5-(R,R'-aryl)-4,5-dihydro-(1H) pyrazoles **(59)**. The synthesized compounds were evaluated for their anti-inflammatory activity. From the results it was evident that presence of substituents on the 5-aryl group of the N-acetyl-Δ^2-pyrazoline 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.*[74] synthesized 1-arylalkoxy and 1-arylalkylthioaryl-2-pyrazolines **(60)** that showed anti-inflammatory and antiallergic activity.



(60)

4. Computational Study of pyrazoline :

Abbas F. Abbas et.al.[75] Synthesis of 3-(biphenyl-4-yl)-5-(furan-2-yl)-4,5-dihydro-1H-pyrazole and computational study .The theoretical study indicates that these molecules are polare and active molecule and they may interact with its environment strongly in solution. The indications of the theoretical study reveals useful information about the reactivity of such molecules and give good information about the active sites in the molecules and clarify the sites of molecules which undergo nucleophilic substitution or electrophilic substitution reactions.

5. Present work

5.1 Aim and objectives

It is evident from the literature that 2-pyrazolines and their derivatives possess important biological activities. A number of 5-(furan-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazole derivatives earlier synthesized in our laboratory possessed and in continuation of that work it is aimed to synthesize some more new substituted 5-(furan-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazole derivatives.

1. To condense some of the chalcones with hydrazine hydrate in absolute ethanol to obtain pyrazolines and to purify these pyrazolines by chromatographic and crystallization methods.
2. To characterize the compounds using spectral (IR, and ^{1}HNMR) methods and elemental analyses. The data related to structural characterization are given in the form of tables.
3. Computational study of synthesized compounds.

5.2. Experimental

General. Melting points were uncorrected. FT.IR-8400,SHIMADZU. NMR spectra were acquired with a Bruker Ultra Shield (^{1}H : 300 MHz) (University of AL-al-Bayt,Jordan). The chemical shifts were referenced to tetra methyl silane (TMS) as an internal standard. The elemental analysis were performed by using Euro Vector EA3000A (University of AL-al-Bayt,Jordan).

5.2.1. Synthesis of pyrazoine derivatives (62a-f)

General procedure. To a stirred solution of chalcone **(61a–f)** (which was prepared as mentioned in the literature) [76] (1.0 mmol) in 10 ml EtOH (96 %) was added hydrazine hydrate (2.0 mmol) and glacialaceticacid (2.5 ml) at room temperature. The reaction mixture was heated to reflux overnight. The progress of the reaction was monitored by TLC (ethyl acetate/hexane, 8:2). The EtOH was removed under reduced pressure and the residue was recrystalized from EtOH to afford the pure products (**62a–f**).

5.2.1.1. 5-(furan-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazole (62a)

was prepared from the reaction of 3-(furan-2-yl)-1-phenylprop-2-en-1-one (61a) with hydrazine hydrate and gave a 73% yield with a m.p. (202-204)^{o}c. The CHN analysis for $C_{13}H_{12}N_2O$; C 73.56; H 5.70; N 13.20 Found C 73.52; H 5.68; N 13.13, FT-IR spectra (KBr pellet) υ(cm^{-1}) 3330 (NH stretching of pyrazoline ring), 3020 (C–H stretching of aromatic ring), 2880 (C–H stretching of aliphatic), 1614 (C=N stretching of pyrazoline ring), 1595 (C=C stretching of aromatic ring), 1219 (C–N stretching of pyrazoline ring), δ_H($CDCl_3$) (7.912-7.921) ppm (1H,d,1); (7.518-7.581) ppm (5H,m,8,9,10,11,12); 7.065 ppm (1H,s,5) ; (6.211-6.481) ppm (2H,m,2,3); (4.625-4.725) ppm (1H,t,4); (3.927-3.937) ppm (2H,d,7,7\)

5.2.1.2.5-(furan-2-yl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole (62b)

was prepared from the reaction of 3-(furan-2-yl)-1-(4-methoxyphenyl)prop-2-en-1-one (61b) with hydrazine hydrate and gave a 75% yield with a m.p. (200-202)^{o}c. The CHN analysis for $C_{14}H_{14}N_2O_2$; C 69.41; H 5.82; N 11.56 Found C 69.31; H 5.80; N 11.55, FT-IR spectra (KBr pellet) υ(cm^{-1}) 3332 (NH stretching of

pyrazoline ring), 3022 (C–H stretching of aromatic ring), 2883 (C–H stretching of aliphatic), 1619 (C=N stretching of pyrazoline ring), 1594 (C=C stretching of aromatic ring), 1216 (C–N stretching of pyrazoline ring), $\delta_H(CDCl_3)$ (7.912-7.921) ppm (1H,d,1); (7.455-7.465) ppm (2H,d,8,12); (7.259-7.269) ppm (2H,d,9,11); 7.065 ppm (1H,s,5) ; (6.211-6.481) ppm (2H,m,2,3); (4.625-4.725) ppm (1H,t,4); 4.111 ppm (3H,s,10); (3.350-3.360) ppm (2H,d,7,7\)

5.2.1.3.5-(furan-2-yl)-3-(4-bromoxyphenyl)-4,5-dihydro-1H-pyrazole (62c)

was prepared from the reaction of 3-(furan-2-yl)-1-(4-bromophenyl)prop-2-en-1-one (61c) with hydrazine hydrate and gave a 79% yield with a m.p. (206-208)^{o}c. The CHN analysis for $C_{13}H_{11}N_2OBr$; C 53.63; H 3.81; N 9.62 Found C 53.60; H 3.80; N 9.61, FT-IR spectra (KBr pellet) $\upsilon(cm^{-1})$ 3334 (NH stretching of pyrazoline ring), 3023 (C–H stretching of aromatic ring), 2884 (C–H stretching of aliphatic), 1622 (C=N stretching of pyrazoline ring), 1596 (C=C stretching of aromatic ring), 1217 (C–N stretching of pyrazoline ring), $\delta_H(CDCl_3)$ (7.912-7.921) ppm (1H,d,1); (7.709-7.719) ppm (2H,d,8,12); (7.402-7.412) ppm (2H,d,9,11); 7.065 ppm (1H,s,5) ; (6.211-6.481) ppm (2H,m,2,3); (4.625-4.725) ppm (1H,t,4); (3.927-3.937) ppm (2H,d,7,7\)

5.2.1.4. 5-(furan-2-yl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazole (62d)

was prepared from the reaction of 3-(furan-2-yl)-1-(4-nitrophenyl)prop-2-en-1-one (61d) with hydrazine hydrate and gave a 85% yield with a m.p. (205-207)^{o}c. The CHN analysis for $C_{13}H_{11}N_3O_3$; C 60.70; H 4.31; N 16.33 Found C 60.60; H 4.30; N 16.27, FT-IR spectra (KBr pellet) $\upsilon(cm^{-1})$ 3338 (NH stretching of pyrazoline ring), 3021 (C–H stretching of aromatic ring), 2881 (C–H stretching of aliphatic), 1625 (C=N stretching of pyrazoline ring), 1597 (C=C stretching of aromatic ring), 1212 (C–N stretching of pyrazoline ring), $\delta_H(CDCl_3)$ (8.321-8.331) ppm (2H,d,9,11); (8.111-8.121) ppm (2H,d,8,12); (7.912-7.921) ppm (1H,d,1); 7.065 ppm (1H,s,5) ; (6.211-6.481) ppm (2H,m,2,3); (4.625-4.725) ppm (1H,t,4); (3.927-3.937) ppm (2H,d,7,7\)

5.2.1.5. 5-(furan-2-yl)-3-(3-aminophenyl)-4,5-dihydro-1H-pyrazole (62e)

was prepared from the reaction of 3-(furan-2-yl)-1-(3-aminophenyl)prop-2-en-1-one (61e) with hydrazine hydrate and gave a 71% yield with a m.p. (198-200)^{o}c. The CHN analysis for $C_{13}H_{13}N_3O$; C 68.70; H 5.77; N 18.49 Found C 68.65; H 5.71; N 18.45, FT-IR spectra (KBr pellet) υ(cm^{-1}) 3336 (NH stretching of pyrazoline ring), 3020 (C–H stretching of aromatic ring), 2880 (C–H stretching of aliphatic), 1620 (C=N stretching of pyrazoline ring), 1590 (C=C stretching of aromatic ring), 1210 (C–N stretching of pyrazoline ring), $\delta_H(CDCl_3)$ (7.912-7.921) ppm (1H,d,1); (7.218-7.281) ppm (6H,m,2,3,8,10,11,12); 7.065 ppm (1H,s,5) ; 5.500 ppm (2H,s,9); (4.625-4.725) ppm (1H,t,4); (3.927-3.937) ppm (2H,d,7,7\)

5.2.1.6. 5-(furan-2-yl)-3-(3-nitrophenyl)-4,5-dihydro-1H-pyrazole (62f)

Was prepared from the reaction of 3-(furan-2-yl)-1-(3-nitrophenyl)prop-2-en-1-one (61f) with hydrazine hydrate and gave a 87% yield with a m.p. (201-203)^{o}c. The CHN analysis for $C_{13}H_{11}N_3O_3$; C 60.70; H 4.31; N 16.33 Found C 60.65; H 4.28; N 16.30, FT-IR spectra (KBr pellet) υ(cm^{-1}) 3333 (NH stretching of pyrazoline ring), 3024 (C–H stretching of aromatic ring), 2885 (C–H stretching of aliphatic), 1622 (C=N stretching of pyrazoline ring), 1595 (C=C stretching of aromatic ring), 1214(C–N stretching of pyrazoline ring), $\delta_H(CDCl_3)$ 8.711 ppm (1H,s,8), (8.318-8.381) ppm (3H,m,10,11,12); (7.900-7.910) ppm (1H,d,1); 7.065 ppm (1H,s,5) ; (6.211-6.481) ppm (2H,m,2,3); (4.625-4.725) ppm (1H,t,4); (3.927-3.937) ppm (2H,d,7,7\)

5.3. Results and discussion

Treatment of chalcones derivatives **(61a-f)** with hydrazine hydrate in boiling ethanol gave pyrazine derivatives compounds, after purification by recrystallization from ethanol, pure pyrazine derivatives compounds as shown in (scheme 18) in (71-87)% yield. The structures of these products were established from their elemental analysis, FT-IR,C.H.N and ^{1}H NMR spectra. The FT-IR spectra of pyrazoline compounds were characterized by the disappearance of the absorption band that was attributed to the (C=O) stretching which appeared at (1672-1710) cm^{-1}. These fact confirmed the correct expected chemical structure of these compounds. The representative absorption bands are shown in table (1). All the IR spectra of pyrazine derivatives showed a peak at (1614-1625) cm^{-1} which related to (C=N)

stretching of pyrazoline ring , a peak at (1210-1219) cm^{-1} which appeared due to (C-N) stretching of pyrazoline ring and a peak at (1590-1597) cm^{-1} which appeared due to (C=C stretching of aromatic ring). While, the C-H stretching aromatic rings showed a peak within the range (3020-3024) cm^{-1} and the C-H stretching aliphatic showed a peak within the range (2880-2885) cm^{-1}. The N-H stretching showed a peak within the range (3330-3338) cm^{-1}.

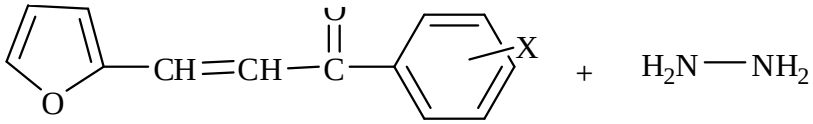
Table (1) : Data of the FT-IR spectra of pyrazoline compounds

Sym.	C=N Str. (w)	C-N Str. (m)	C=C Ar.Str. (w)	C-H Ar.Str. (m)	C-H, alip. Str. (w)	NH.Str.(m)
62a	1614	1219	1595	3020	2880	3330
62b	1619	1216	1594	3022	2883	3332
62c	1622	1217	1596	3023	2884	3334
62d	1625	1212	1597	3021	2881	3338
62e	1620	1210	1590	3020	2880	3336
62f	1614	1219	1595	3020	2880	3333

Str. = stretching, w= weak, m = medium, Ar.=aromatic, alip.= aliphatic

The ^{1}H NMR spectra of pyrazoline compounds are shown in figures **(1-6)**. ^{1}H NMR data of these compounds are summarized in table (2). All the ^{1}H NMR spectra of pyrazoline ring were characterized [77-79] by the presence protons (5) of pyrazoline ring showed singlet signals within the range 7.065 ppm and showed triplet signals within the range (4.625-4.725) ppm which appeared to proton in (4) position because interaction with two protons in (7 and 7\) position , while the two protons in (7 and 7\) position showed doublet signals within the range (3.350-3.937) ppm because interaction with protons in (4) position. These peaks confirmed the correct expected

chemical structure of pyrazoline compounds. The proton in position (1) of furan ring showed doublet signals at (7.900-7.921) ppm , while the other two protons in positions (2 and 3) of furan ring showed multiplet signals within the range (6.211-7.281) ppm. The protons of aromatic rings in compound (62a) showed multiplet signals within the range (7.518-7.581) ppm which appeared to five protons in (8,9,10,11 and 12). While the compounds (62b,62c and 62d) including AB system in ^{1}H NMR spectra therefore showed doublet signals within the range (7.455-8.121) ppm which appeared to the two protons in (8 and 12) positions. The other two protons in positions (9 and 11) showed doublet signals within the range (7.259-8.331) ppm. The four protons in compound (62e) appeared multiplet signals for aromatic ring in (7.218-7.281) ppm, while compound (62f) showed singlet signal at the range 8.711 ppm which related to proton in position (8) and showed multiplet signals within the range(8.318-8.381) ppm which appeared to the three protons in positions (10,11 and 12). The OCH_3 protons showed singlet signal for three protons at 4.111 ppm. The NH_2 protons showed singlet signal for two protons in the region δ= 5.500 ppm..

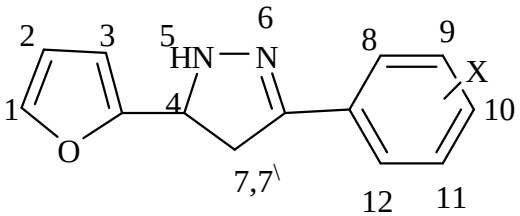


X= H , 4-OCH_3,4-Br ,4- NO_2, 3-NH_2, 3-NO_2

61a, 61b, 61c , 61d , 61e , 61f

glacial acetic acid

ethanol



X= H , 4-OCH_3,4-Br ,4- NO_2, 3-NH_2, 3-NO_2

62a, 62b, ,62c , 62d , 62e , 62f

Scheme (18)

Table (2) : Chemical shift (ppm) of the synthesized pyrazoline compounds

Symb.	δ (ppm) of Proton (1)	δ (ppm) of Protons (2 and 3)	δ (ppm) of Proton (4)	δ (ppm) of Proton (5)	δ (ppm) of Protons (7 and 7\)	δ (ppm) of Protons NH_2	δ (ppm) of Protons OCH_3	δ (ppm) of Aromatic Protons
62a	(7.912-7.921) d	(6.211-6.481) m	(4.625-4.725) t	7.065 s	(3.927-3.937) d	---	---	(7.518-7.581) m (8,9,10,11 and 12)
62b	(7.912-7.921) d	(6.211-6.481) m	(4.625-4.725) t	7.065 s	(3.350-3.360) d	---	4.111 S	(7.455-7.465) d (8 and 12) (7.259-7.269) d (9 and 11)
62c	(7.912-7.921) d	(6.211-6.481) m	(4.625-4.725) t	7.065 s	(3.927-3.937) d	---	---	(7.709-7.719) d (8 and 12) (7.402-7.412) d (9 and 11)
62d	(7.912-7.921) d	(6.211-6.481) m	(4.625-4.725) t	7.065 s	(3.927-3.937) d	---	---	(8.111-8.121) d (8 and 12) (8.321-8.331) d (9 and 11)
62e	(7.912-7.921) d	(7.218-7.281) m Me.wi. arom.	(4.625-4.725) t	7.065 s	(3.927-3.937) d	5.500 S	---	(7.218-7.281) m (8,10,11 and 12) Me.wi. (2 and 3)
62f	(7.900-7.910) d	(6.211-6.481) m	(4.625-4.725) t	7.065 s	(3.927-3.937) d	---	---	8.711 s (8) (8.318-8.381) m (10,11 and 12)

Symb. = symbol, s = singlet, d = doublet, t = triplet, m=multiplet, Me.wi.=merge with

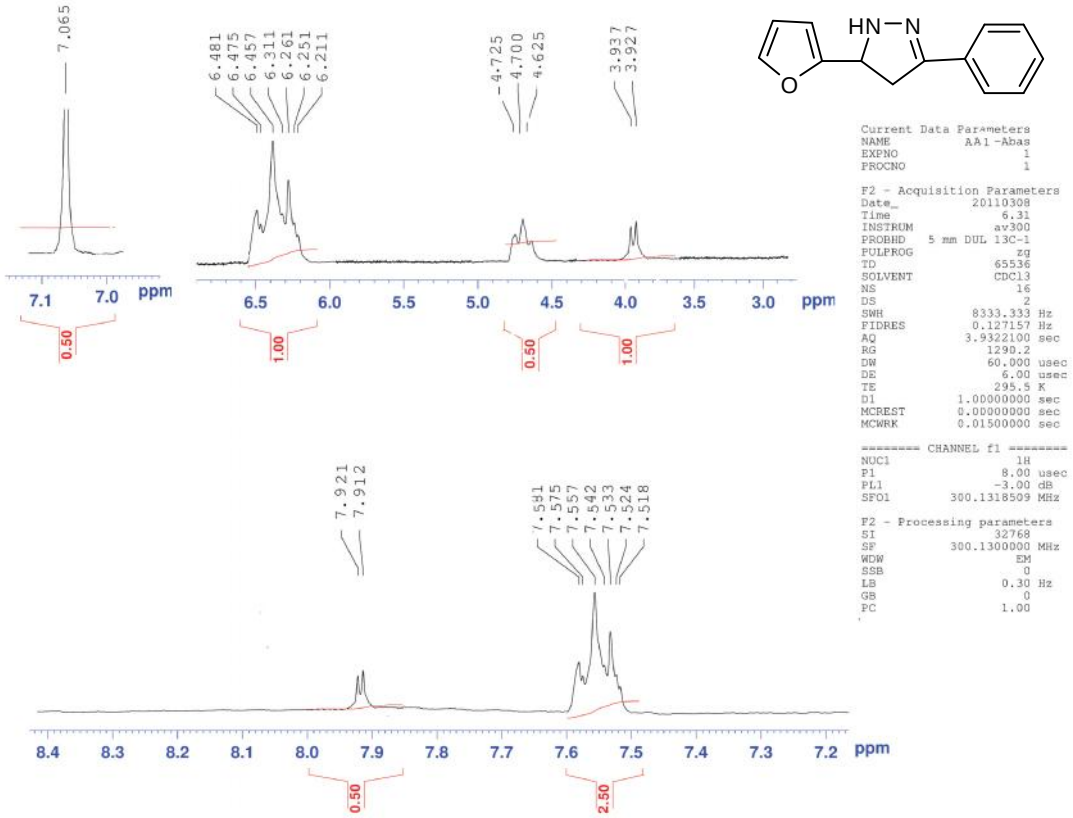


Figure (1) H NMR spectrum of compound (62a)

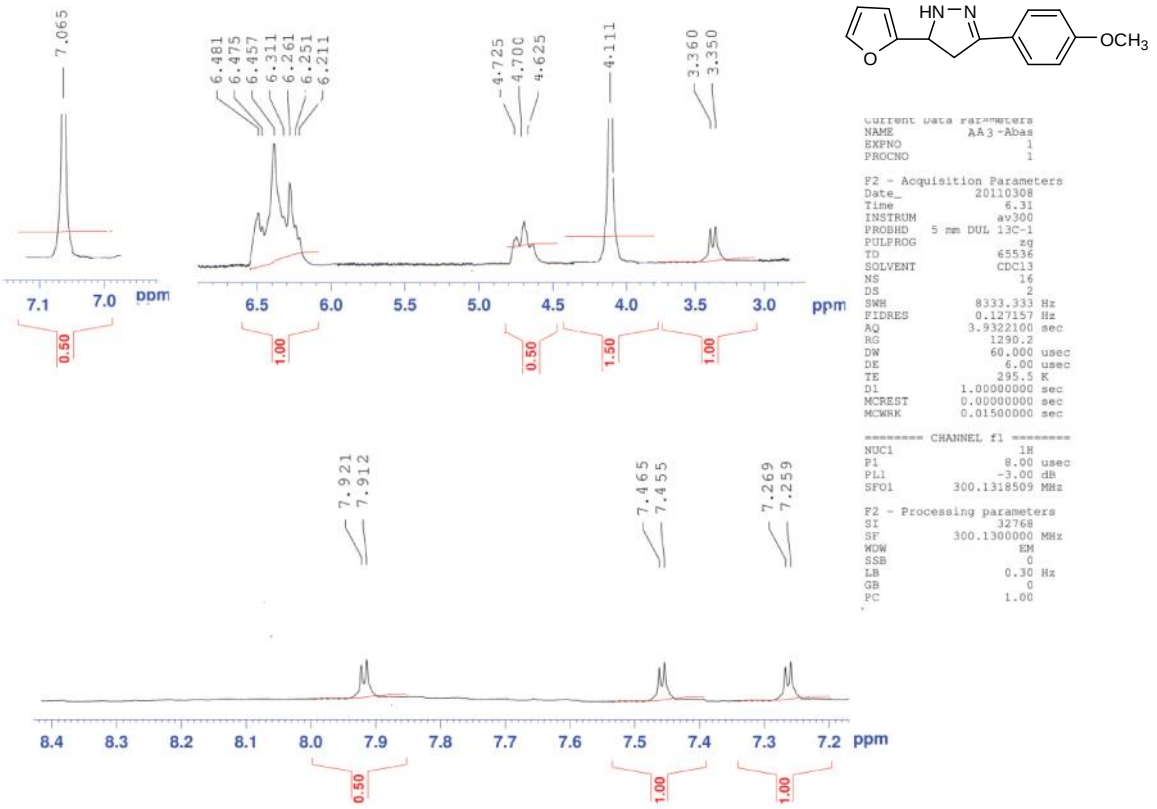


Figure (2) H NMR spectrum of compound (62b)

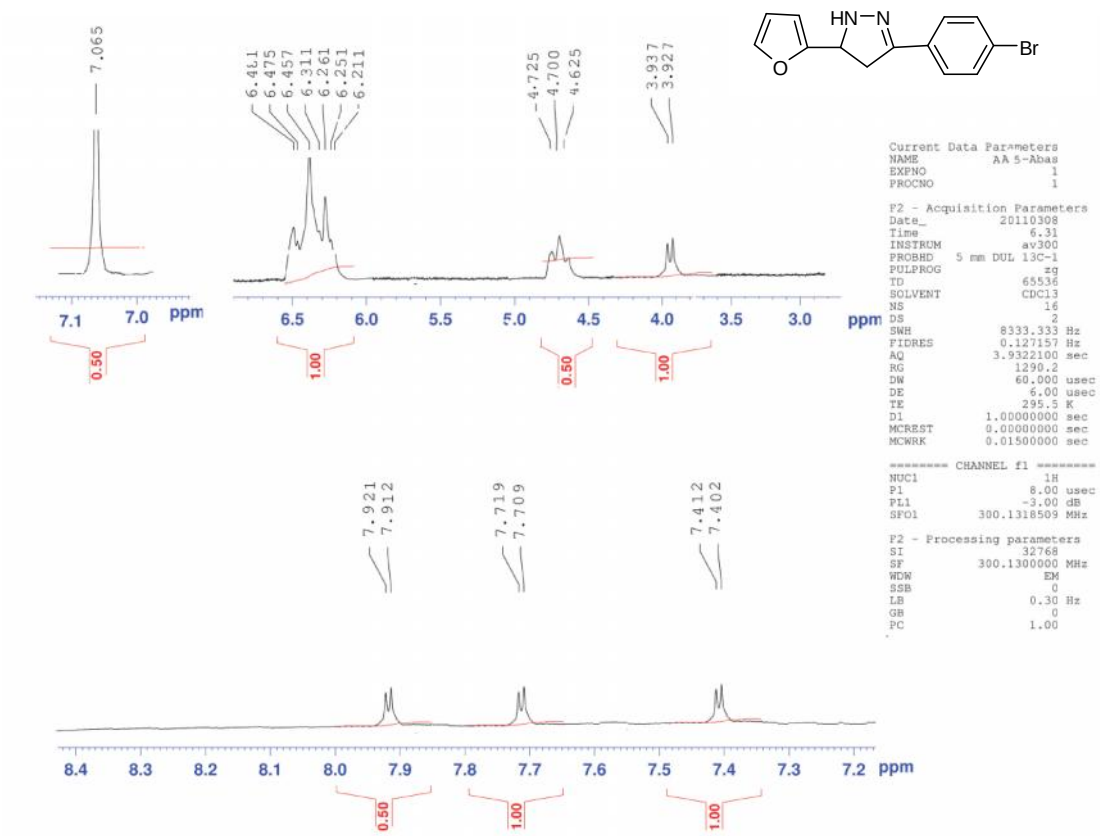


Figure (3) H NMR spectrum of compound (62c)

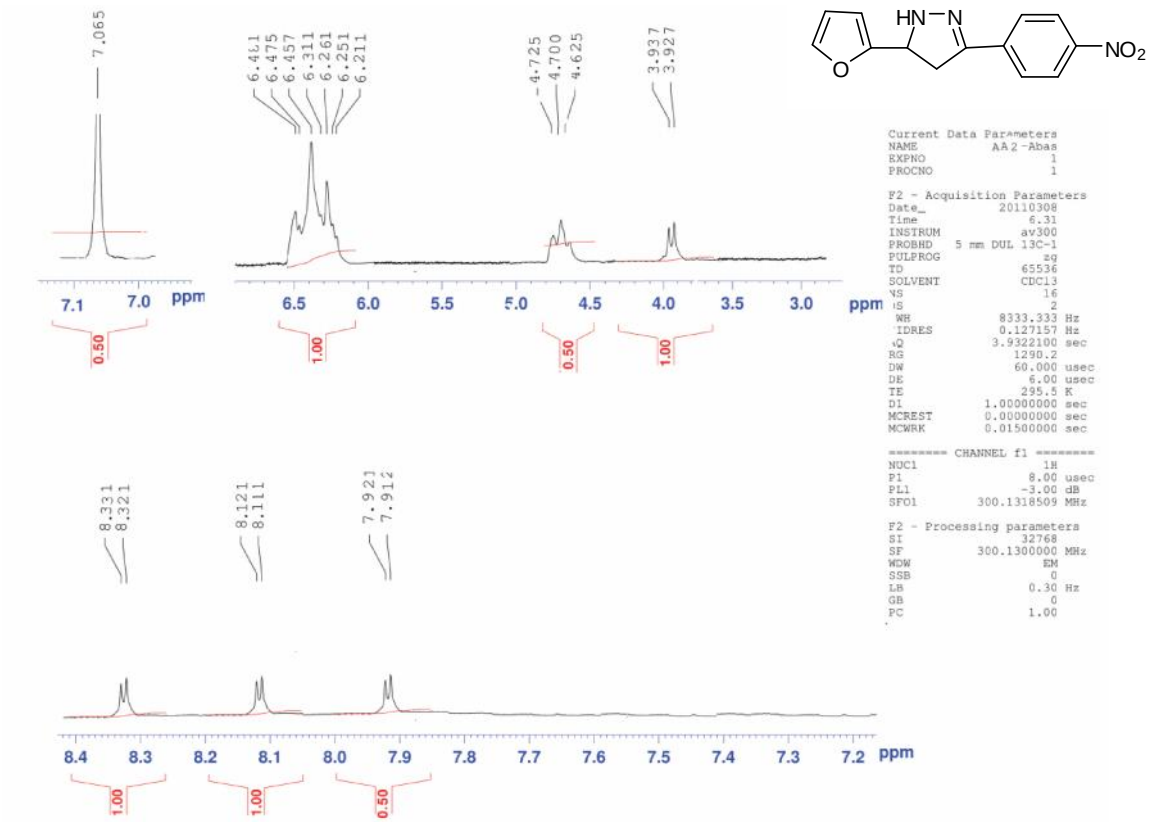


Figure (4) H NMR spectrum of compound (62d)

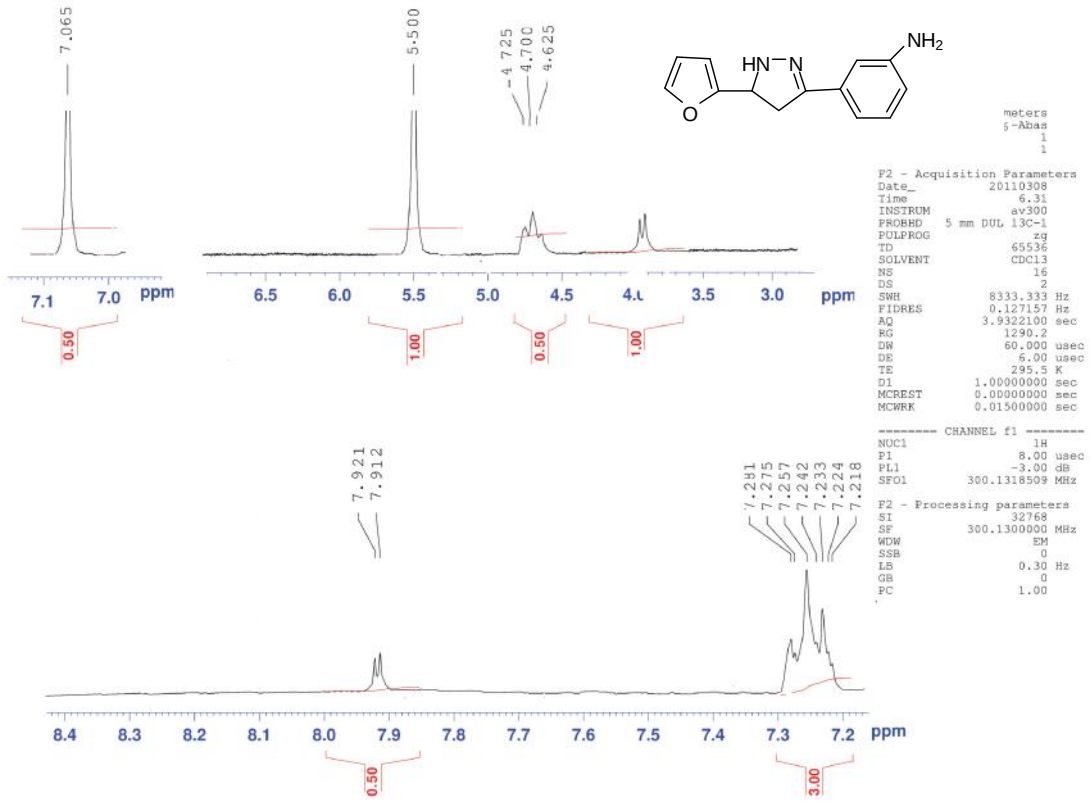


Figure (5) H NMR spectrum of compound (62e)

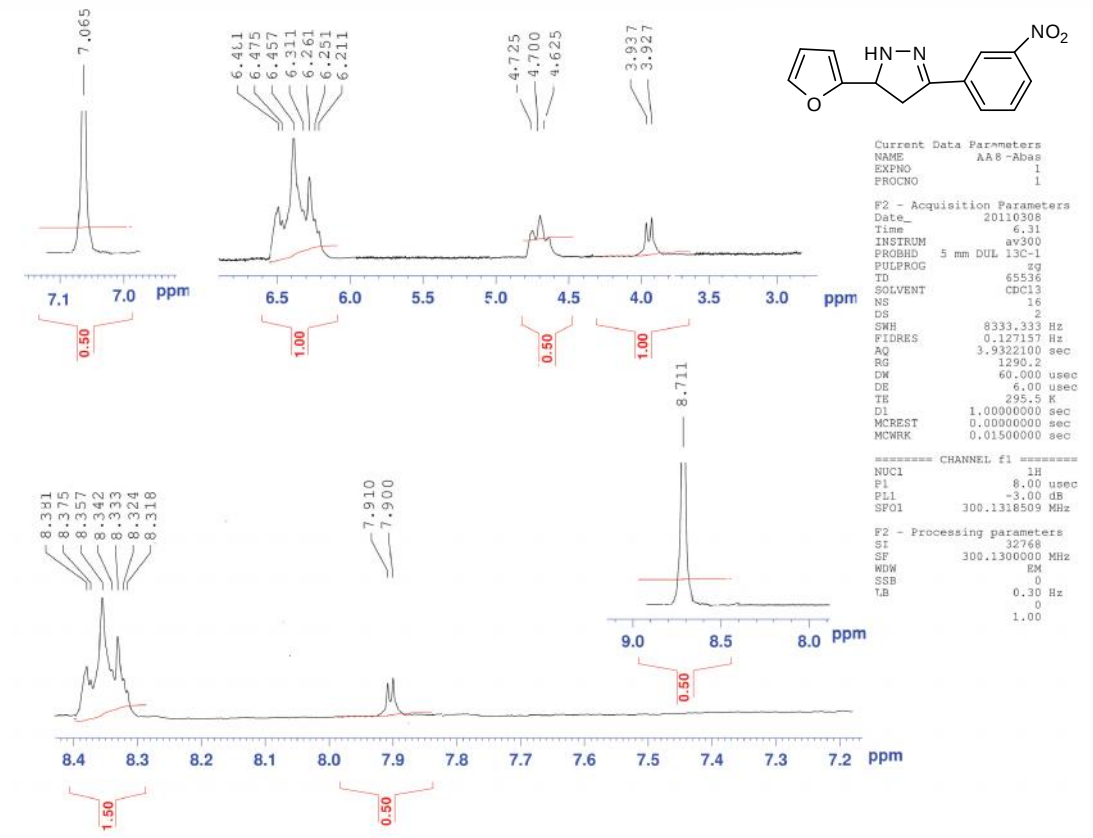


Figure (6) H NMR spectrum of compound (62f)

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