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Chemistry, Biological and Pharmacological Importance of Pyrazolines Derivatives

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ABSTRACT

The pyrazolines 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.

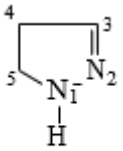
INTRODUCTION

Pyrazoles (pyrazolines) are important nitrogen containing five member heterocyclic ring compounds. Several pyrazole derivatives possess important pharmacological and therefore they are useful materials in drug research development. The simplicity of pyrazoles framework makes it feasible to easily incorporate into more complex structures to design potentially new bioactive compounds. It was reported in the literature that different substituted 2-pyrazolines possess antimicrobial, anti-inflammatory, analgesic, antipyretic, tranquilizing, muscle relaxant, psychoanaleptic, anticonvulsant, anti-hypertensive, antidiabetic and antidepressant activities. Given below is a brief account of various modifications reported on 2-pyrazoline nucleus, which showed a variety of biological and pharmacological activities

The pyrazolines 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.

2.1.1. Chemistry

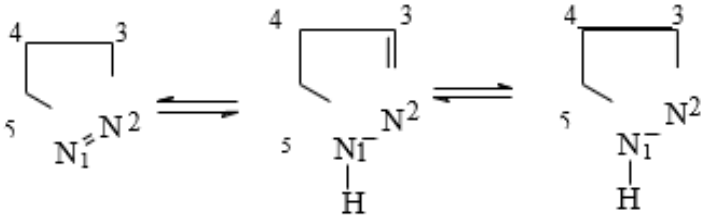
Pyrazole is a π-excessive aromatic monocyclic heterocycle containing two nitrogen atoms in a five membered 1,2-diazole ring. It was in the late nineteenth century that Fischer and Knovenagel described the reaction of acrolein with phenylhydrazine [1] to provide a 2-pyrazoline type compound **1**. Their 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



1

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.

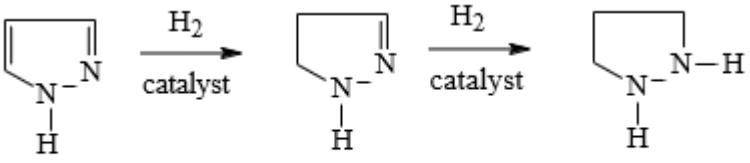
Pyrazoles exhibit aromatic character with properties resembling those of both pyrrole and pyridine. 1-Pyrazoline, 2-pyrazoline and 3-pyrazoline are the three partially reduced forms of the pyrazole structure with different positions of the double bonds and exists in equilibrium one with the other **2**.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



2

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 **3**. Both of these compounds are stronger bases than pyrazole.

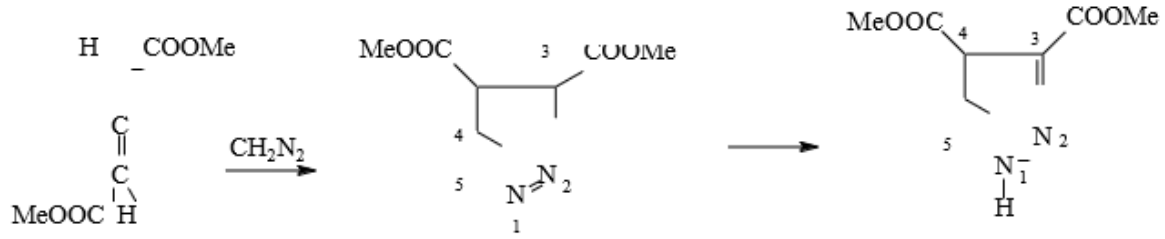


3

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.

2.1.1.1. General method of synthesis

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 cycloaddition, which spontaneously isomerizes into its thermodynamically more stable 2-pyrazoline isomer by a 1,3- H shift **4**.



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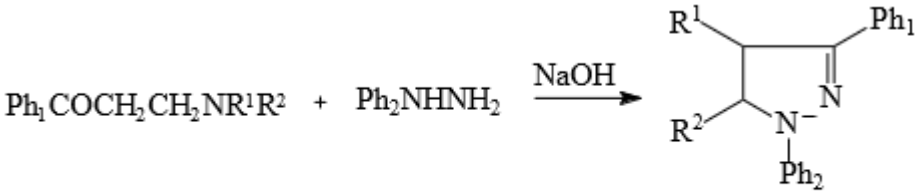
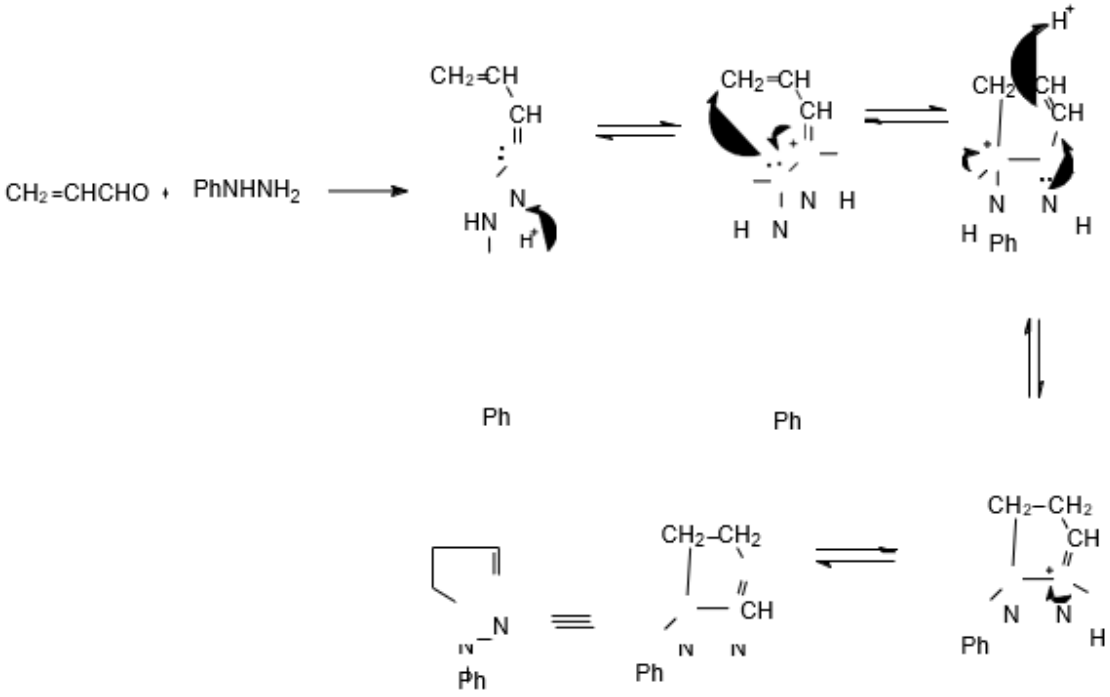
Mannich bases on reaction with phenylhydrazine and aqueous ethanolic NaOH at reflux temperature yield substituted 2-pyrazolines **5** [6].



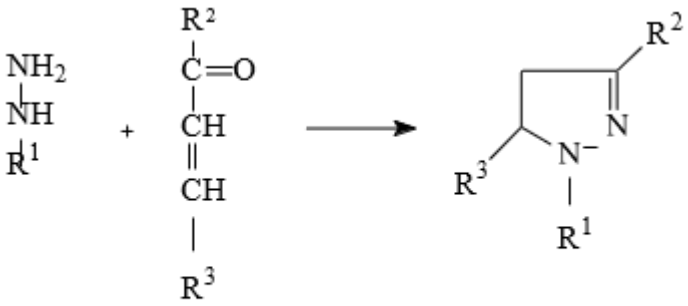
5

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 **6**.



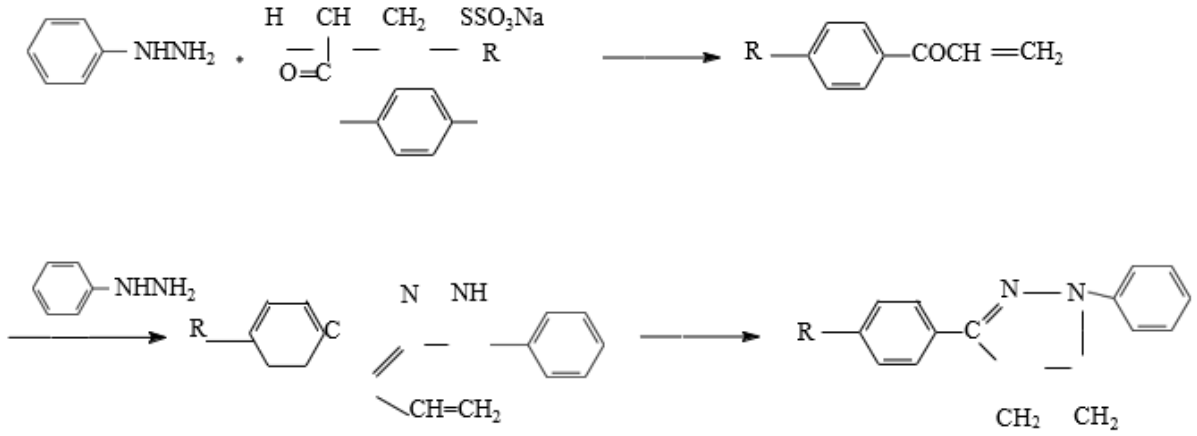
6

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 **7** [7, 8, 9]. 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[16]. In some cases the two reactants were refluxed in alcoholic solution without a catalyst to provide 2-pyrazolines.



7

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 **8** [10].



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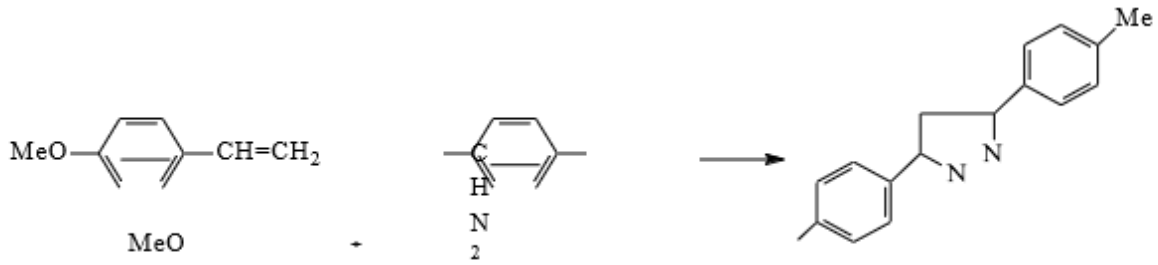
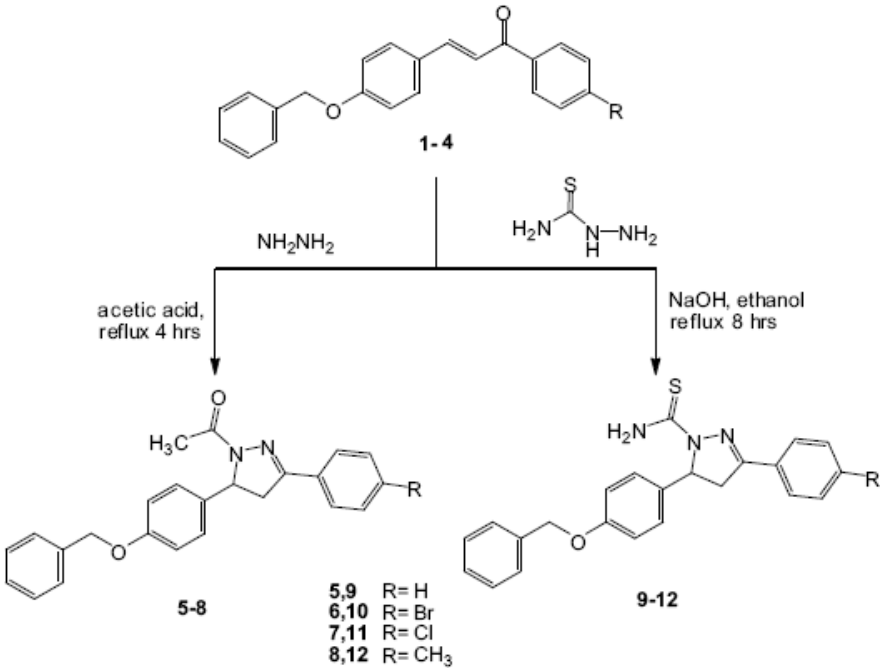
Cycloaddition reaction of substituted styrenes with *p*-anisyldiazomethane at low temperature yield *trans*-3,5-bis-(p-anisyl)-1-pyrazoline **9** [11].



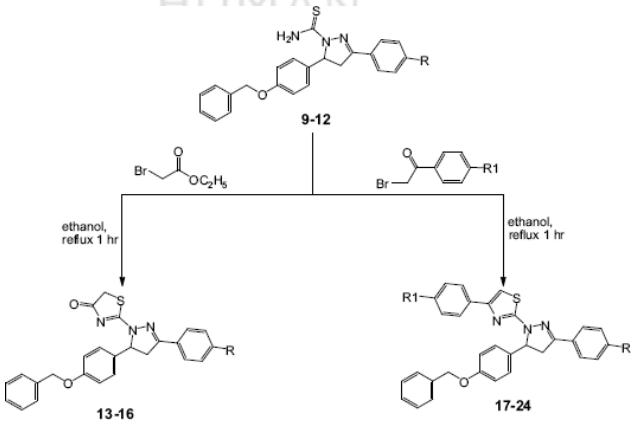
9

The two type of pyrozole derivatives were prepared by utilizing deferent reaction conditions. In acidic media, the novel N-acetyl derivatives were prepared by heating at reflux the chalcones with hydrazine hydrate in acetic acid for 4 h yield N-Acetyl pyrazoles. on the other side, upon using basic media, the novel 1-thio-carbamoyl pyrazole derivatives were obtained by heating at reflux equimolar amounts of thiosemicarbazide and the corresponding ketones in hot ethanol NaOH solution for 8 h to yield 1-thiocarbamoyl pyrazole derivatives **10** [12].



10

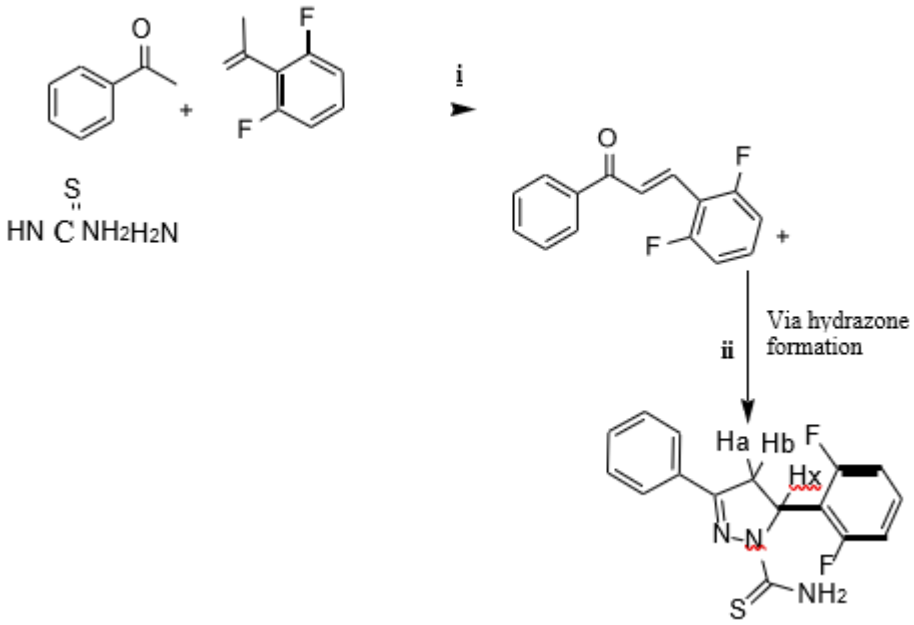
The reaction of 1-thiocarbamoyl pyrazole derivatives were cyclized to pyrazolothiazole-4(5H)-ones or pyrazolothiazole derivatives through their reaction with ethyl bromoacetate or phenacyl bromide derivatives in hot ethanol for 1h **11** [12].



11

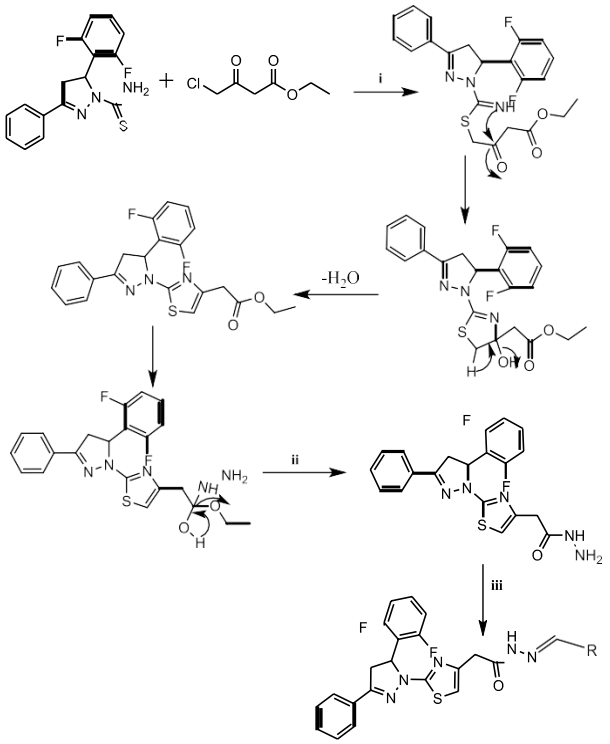
Reacting acetophenone and 2,6-difluoroacetophenone by Claisen–Schmidt reaction yield chalcone on reacting with thiosemicarbazide in basic conditions pursue reaction mechanism involving formation of intermediate (non-isolable) hydrazones and Subsequent addition of

NH on the carbon–carbon double bond of the propenone moiety. The literature's apparent formation of 5-(2,6-difluorophenyl)-3-phenyl-4,5-dihydropyrazole-1-carbothioamide **12** [13].



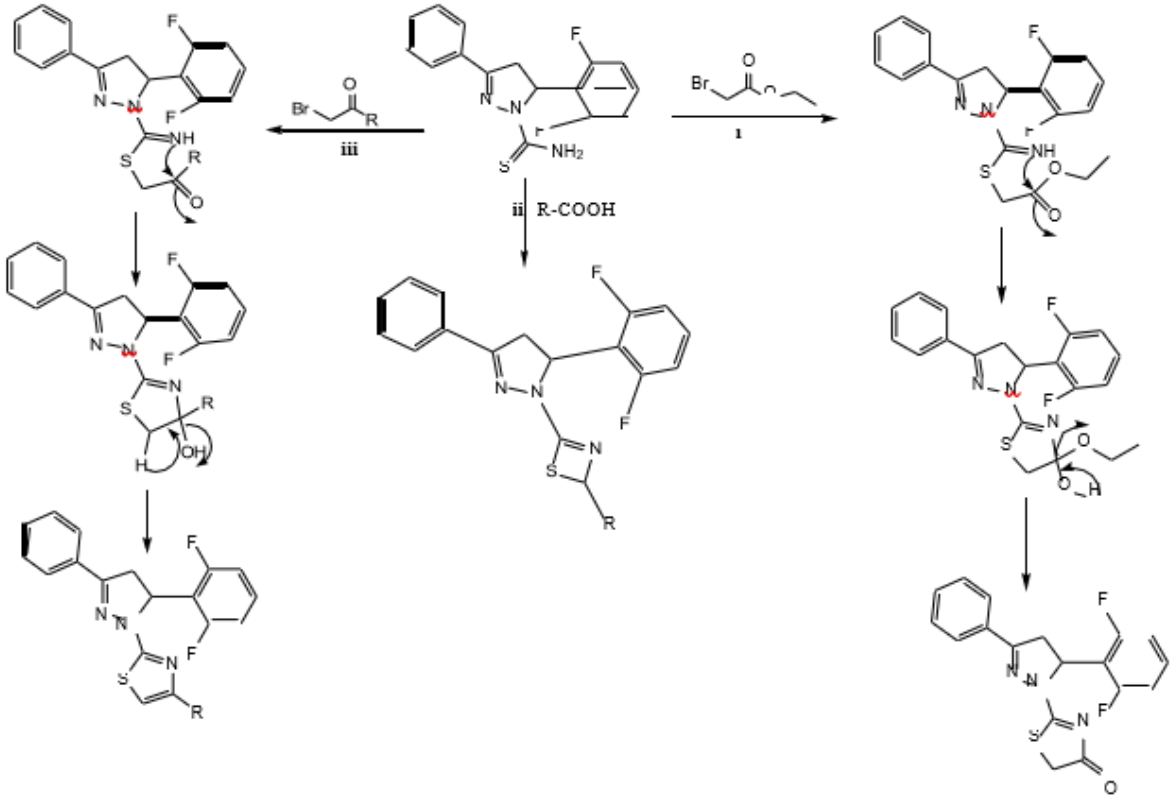
12

5-(2,6-difluorophenyl)-3-phenyl-4,5-dihydropyrazole-1-carbothioamide on reacting with ethyl chloroacetoacetate provides 1-(2-(5-(2,6-difluorophenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)thiazol-4-yl)-3-methoxypropan-2-one via the non isolable intermediate further on reacting with hydrazine hydrate provides acetohydrazide derivative. The treatment of acetohydrazide derivative with several aromatic aldehydes afford 2,6-(difluorobenzylidene)-2-(2-(5-substituted -3-phenyl-4,5-dihydropyrazol-1-yl)thiazol-4-yl) acetohydrazides **13** [13].



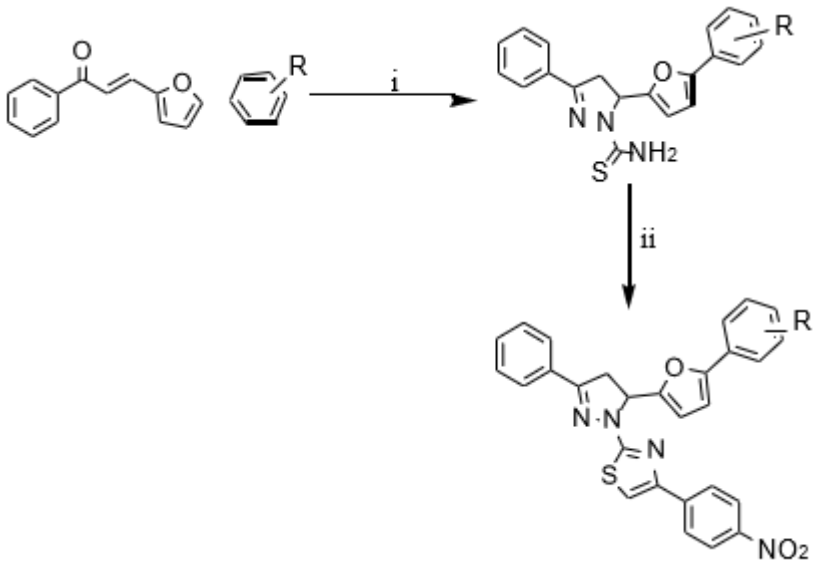
13

The 1-thiocarbamoyl pyrazole derivatives were cyclized to pyrazolothiazol-4(5H)-ones and pyrazolothiazole derivatives through their reaction with ethyl chloroacetate and phenacyl bromide derivatives, respectively, in hot ethanol for 1 h. While 1-thiocarbamoyl pyrazole derivative on reacting with appropriate aromatic acids in Presence of phosphorus oxychloride afforded thiazets **14** [13].



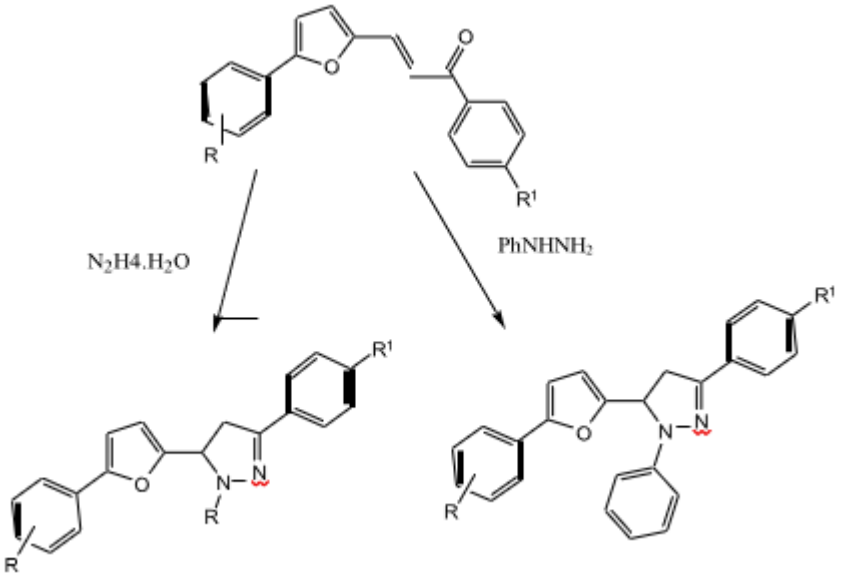
14

1,3-diaryl prop-2-en-1-ones (chalcone) on reacting with thiosemicarbazide in basic conditions in alcoholic medium led to the formation of intermediate 3,5-disubsititued -4,5 –dihydro-1H-pyrazole-1-carbothioamides further treated with 4-nitrophenacyl bromides in alcoholic medium to obtain the title compounds **15** [14].



15

1-Aryl-3-(5-aryl-2-furyl)2-propen-1-ones (chalcone) on reacting with Hydrazine hydrate and phenyl hydrazine in ethanol containing glacial acetic acid to obtain 3-aryl-5-(5-aryl-2-furyl)-4,5-dihydropyrazoles and 1-phenyl-3-aryl-5-(5-aryl-2-furyl)-4,5- dihydro-pyrazoles **16** [15].

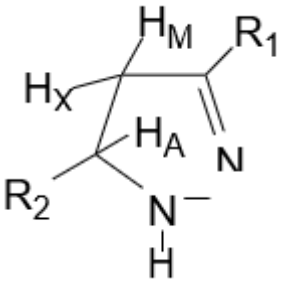


16

2.1.1.2. Spectral features of pyrazolines

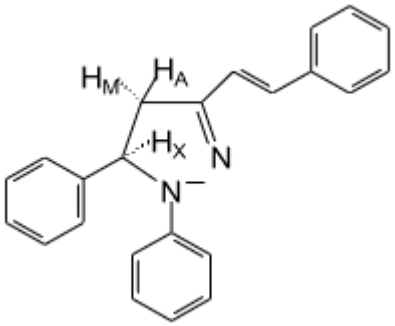
Pyrazoline ring shows special spectral features in its ^{1}H NMR spectrum. The three protons in the pyrazoline ring **17** will show AMX splitting pattern. H_A proton appears at δ

2.98 (dd), J_{AM} = 7.6 Hz and J_{AX} = 12 Hz. H_M proton resonates at δ 3.64 (dd) and coupling constants are J_{AM}= 12 Hz and J_{MX} =12 Hz. H_X proton appears at δ 5.2 (dd), J_{AX}= 7.6 Hz and J_{MX}=12 Hz. In the IR spectrum at 1580-1570 and 3195-3190 cm^{-1} bands appear due to the presence of C=N and N-H vibrations[15].



17

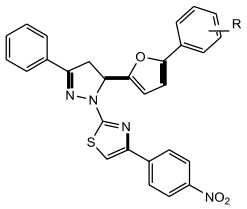
The ^{1}H NMR spectrum of trans-3,5-bis(*p*-anisyl)-1-pyrazoline **18** showed a quartet at δ 7.02 (aromatic protons), a triplet at δ 5.75 (benzylic protons) and a triplet at δ 2.05 (methylene protons). Its IR spectrum showed –N=N- absorption at 1555 cm^{-1}. In case of the cis-isomer, the ^{1}H NMR spectrum showed resonance signals of AMX system. The nonequivalent protons of the methylene group H_M and H_X (cis-form) each appeared as a sixtet at δ2.44 and 1.37 respectively.



18

2.1.2. Pharmacological importance of Pyrazolines

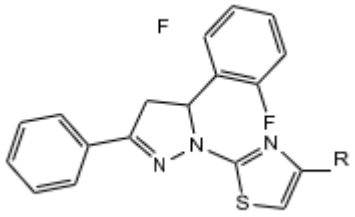
Prajwal. L. Lobo *et al.* [14] synthesized 2-[1-{3,5-diaryl-4,5-dihydro-1H-pyrazolenyl}]-4-(40nitrophenyl)-[1,3]-thiazoles **19** ; their antimicrobial activities against *Escherichia coli* (ATTC-25922), *Staphylococcus aureus* (ATTC-25923), *Pseudo-monas aeruginosa* (ATTC-27853), *Klebsiella pneu-moniae, Aspergilus flavus* (NCIM No.524), *Aspergilus fumigates* (NCIM No.902), *penivillium maneffei* and *Trichophyton mentagrophytes.*



19

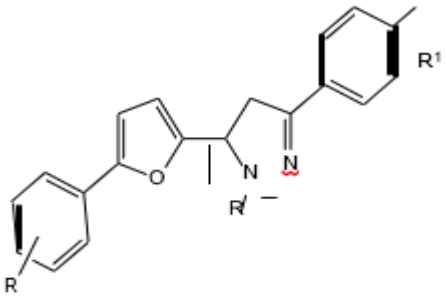
Y. Rajendra Prasad, *et al.* [13] synthesized 4,5-dihydropyrazole derivatives **20** and The antimicrobial susceptibility testing was performed *in vitro* by broth micro dilution method. The MIC determination of the synthesized 4,5-dihydropyrazole derivatives was carried out in side-by-side comparison with ciprofloxacin and norfloxacin against Gram-positive (S. aureus, S. faecalis, B. subtilis) and Gram-negative (K. penumoniae, E. coli. P. aeruginosa) bacteria.

The antifungal activity was assayed against yeasts (C. tropicalis, S. cerevisiae) and moulds (A. niger).



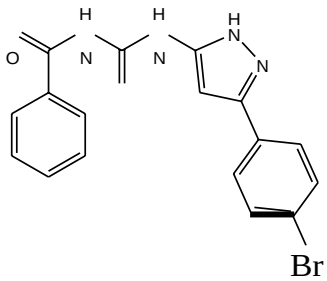
20

B.Shivarama Holla *et al.* [15] synthesized 3-aryl-5-(5-aryl-2-furyl)-4,5-dihydropyrazoles derivatives and 1-phenyl-3-aryl-5-(5-aryl-2-furyl)-4,5- dihydro-pyrazoles derivatives **21** were screened for their in vitro antibacterial activity *against E. Coli, S. aureus, B. subtilis and P. aeruginosa.* Shows promising antibacterial activity Nitrofurazone (Furacin) was used as the standard drug for comparison.



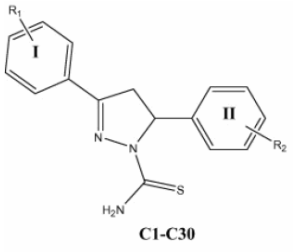
21

G.M. Nitulescu *et al.* [16] synthesized N-Benzoyl-N′-(5-methyl-1H-pyrazol-3-yl)thiourea derivatives **22** were screened for their anti-cancer activity *in vitro* Some of the compounds of the series exhibited promising anti- anti-cancer activity.



22

Peng-Cheng Lv, Huan-Qiu Li, Juan Sun, Yang Zhou, Hai-Liang Zhu [17] synthesized Two series of pyrazole derivatives**(23 and 24)** designing for potential EGFR kinase inhibitors have been discovered. Some of them exhibited significant EGFR inhibitory activity and antiproliferative assay results indicating that some of the pyrazole derivatives own high antiproliferative activity against MCF-7.



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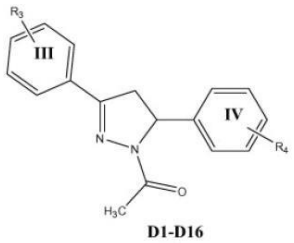

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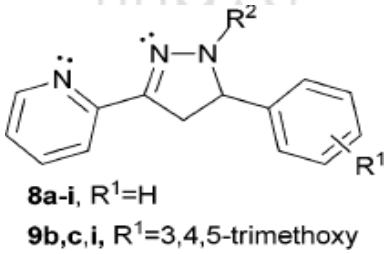
Alexander Ciupa, Paul A. De Bank,a Mary F. Mahon,b Pauline J. Wooda and Lorenzo Caggiano [18] synthesized the some 3-(pyrid-2-yl)-pyrazolines **25** Pyrazoline 8i (NSC 761258) displayed promising GI50 values across the NCI 60 human tumour cell line panel and exhibited sub-micromolar activity in a range of cancer cell lines, including the multidrug resistant ovarian cell line NCI/ADR-RES (0.519 mM).



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