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Pyrazolines: Versatile Molecules of Synthetic and Pharmaceutical Applications-A Review

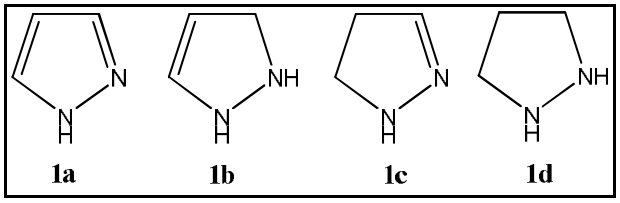
K. Ajay Kumar*, M. Govindaraju

Post Graduate Department of Chemistry, Yuvaraja's College, University of Mysore, Mysore 570005, India.

Abstract: The five membered heterocyclic compounds pyrazolines were found as the core structure in a large variety of compounds. Pyrazoles have been the recent target of numerous methodologies, mostly due to their prevalence as scaffolds in synthesis of bioactive compounds and reactions in different media. In this review, an attempt is made to provide an up to date developments in the synthetic strategies, biological activities associated with these classes of compounds. Synthetic strategies developed, chemical and biological applications shown by the pyrazoline analogues in recent years were critically discussed.
Key Words: Antimicrobial, Anti-depressant, Anti-convulsant Anti-inflammatory, Microwave, Pyrazolines.

Introduction

Pyrazoles (**1a**) are the important members of heterocyclic compounds with two adjacent nitrogens in a five-membered ring system. Among the two nitrogen atoms; one is basic one the other is neutral in nature. The partially reduced forms of pyrazole are named as pyrazolines (**1b** or **1c**); while completely reduced form is pyrazolidine (**1d**)[1].



Pyrazoline is a tautomeric substance; the existence of tautomerism can be demonstrated by the consideration of pyrazoline derivatives. Unsubstituted pyrazoline can be represented in three tautomeric forms (Fig-1). Pyrazoline derivatives in which two carbon atoms neighboring the nitrogen atoms on the ring have different substituents, five tautomeric structures are possible (Fig-2).

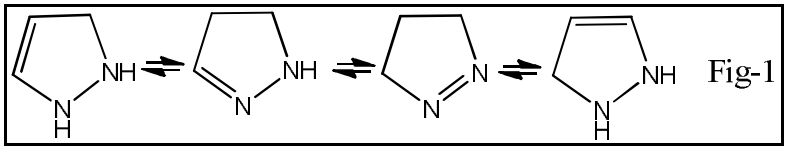


Fig-1

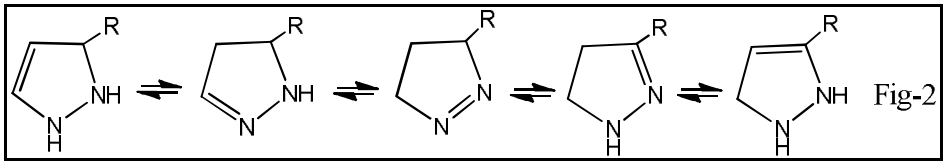


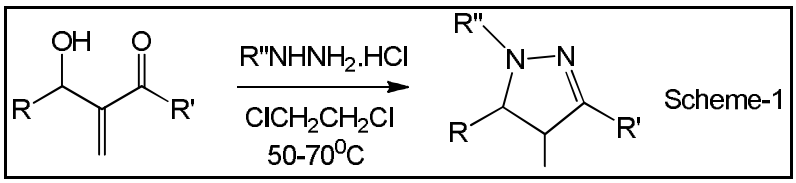
Fig-2

Pyrazoline derivatives are considered as useful building blocks in organic synthesis for designing pharmaceutical and agrochemicals. Pyrazolines were synthesised by adopting various synthetic methodologies. These compounds play a prime role in medicinal and agricultural chemistry for their potent biological activities. Literature reveals that these classes of compounds have been known to possess antimicrobial, analgesic, anticancer, anti-tubercular, anti-inflammatory, antidepressant, anticonvulsant, antipyretic, antihelmintic, antioxidant and herbicidal properties. They also found to show antiviral, antitumor and antiangiogenic activities.

In this review article, critical discussion has made with a more emphasis on strategies adopted for the synthesis of pyrazolines; chemical application to transform them in to biologically potent molecules and pharmaceutical applications associated with them in a chronological manner.

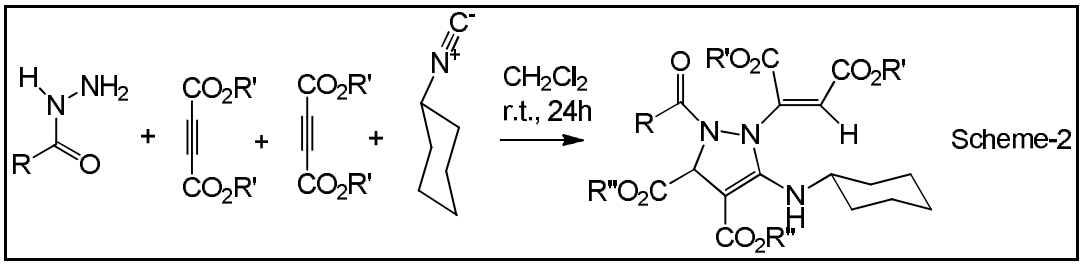
Synthesis of Pyrazolines:

Biological activity potency associated with pyrazolines has made them popular synthetic targets. Literature reveals numerous methods developed for preparation of substituted pyrazolines most common being the cyclocondensation reaction between α, β-unsaturated compounds and hydrazine, phenylhydrazines etc. For instance, the reaction of Baylis–Hillman adduct and phenyl hydrazine in dichloroethane at 50-70°C afforded the tetrasubstituted pyrazole derivatives with very high regioselectivity of products in 89% yield (Scheme-1)[2]. The reaction follows via the successive hydrazone formation, cyclisation and double bond isomerisation sequence under reflux conditions.



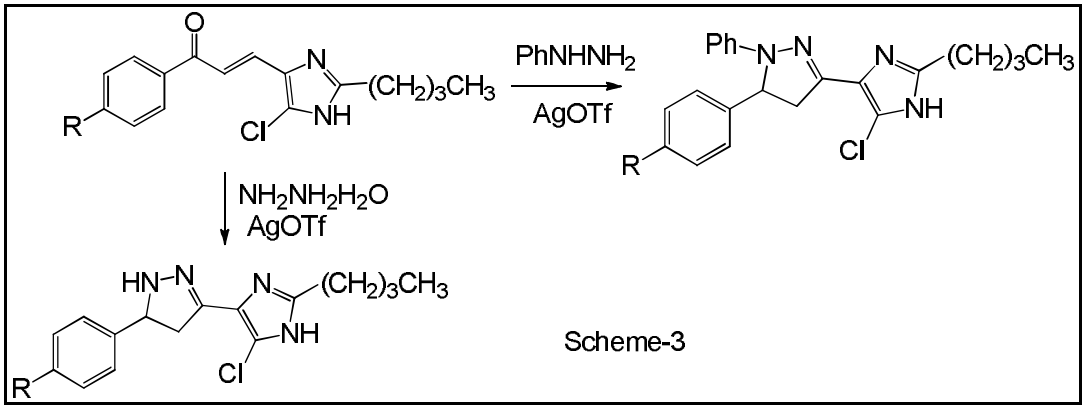
Scheme-1

The highly functionalized 1*H*-pyrazole derivatives were synthesised by a one-pot isocyanide-based cascade four-component reaction between arylcarbohydrazides, dialkyl acetylenedicarboxylates, and cyclohexyl isocyanide (Scheme-2)[3]. The approach has the potential in synthesis of various functionalized 1*H*-pyrazole derivatives due to the easy availability of the synthetic approach and the neutral ring closure conditions.



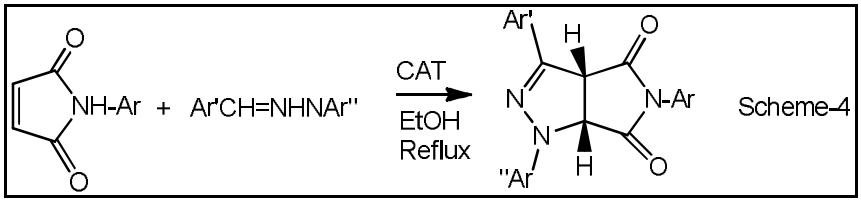
Scheme-2

Silver triflate Ag (I) was used as Lewis acid catalyst in organic reactions for effective and novel transformations in organic synthesis. A series of imidazole-pyrazole derivatives were synthesized using silver triflate as catalyst from chalcones. Silver activates the carbonyl carbon of the chalcone and add hydrazine hydrate or phenyl hydrazine followed by cyclo-reversion to provide products in good yields in short reaction time (Scheme-3)[4]. The synthesized compounds were tested for their antibacterial and antifungal activities.



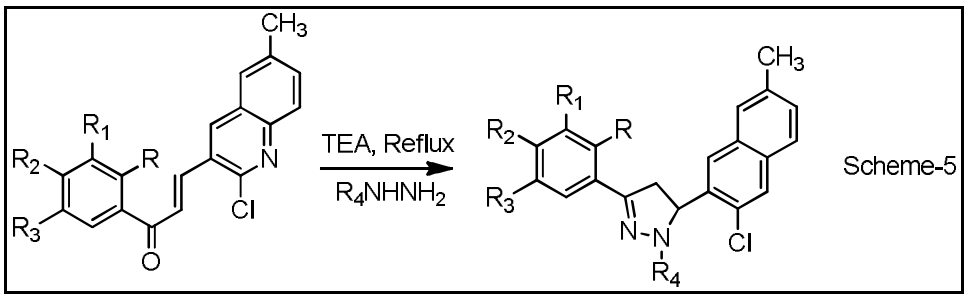
Scheme-3

A series of 3-chloro-1-{4-[5-(Substitutedphenyl)-4,5-dihydro-pyrazol-3-yl]phenyl}-4-(4-hydro xyphenyl) azetidin-2-ones were synthesized by reacting 3-chloro-1-{4-[3-(Substituted phenyl)prop-2-enoyl]phenyl}-4-(4-hydroxyphenyl)azetidin-2-one with 99% hydrazine hydrate. The synthesized products were tested for their antibacterial and antifungal activities by broth dilution method [5]. Rai and co-workers [6] reported a new approach for the synthesis of pyrazoles via 1,3-dipolar cycloaddition of acetyl acetone and *in situ* generated nitrile imines. Their reaction afforded the regioselective cycloadducts in good yield. Very recently Kumar *et al* reported the synthesis of 1,3,5-triaryl-4,6-dioxo-pyrrolo[3,4-*d*]-7,8-dihydropyrazoles by Huisgen cycloaddition of *in situ* generated nitrile imines and *N*-aryl maleimides, the cycloadducts obtained showed promising antibacterial, antifungal and antioxidant activities (Scheme-4)[7-8].



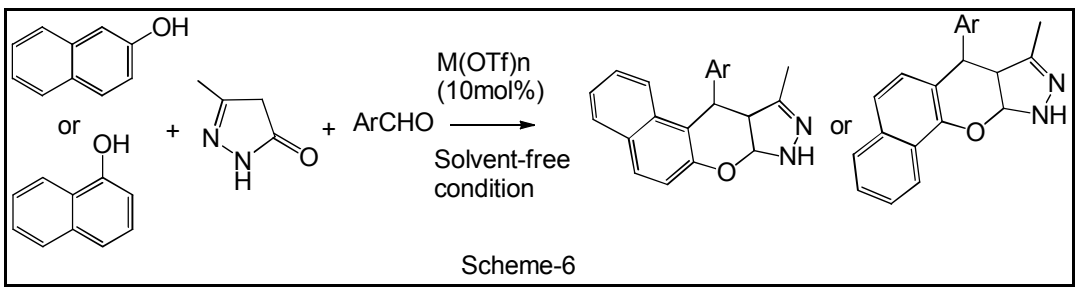
Scheme-4

An efficient method for the regioselective synthesis of potentially biologically active tetrasubstituted 1-pyrazolines has been achieved via 1,3-dipolar cycloaddition reaction. A range of tetrasubstituted 1-pyrazolines bearing one Boc group and two ester groups were obtained in high yields. The structure and relative stereochemistry of cycloadducts were confirmed by NMR spectra and single crystal X-ray diffraction [9]. Shyam and coworkers [10] prepared a series of 2-pyrazolines by the cyclisation of hydrazine hydrate with α, β-unsaturated ketones using triethanalamine solvent within 15-20 min (Scheme-5). All these compounds showed potential biological activity.



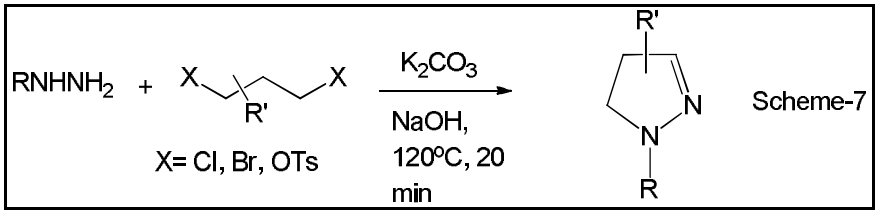
Scheme-5

Metal triflates exhibited high efficiency for the synthesis of benzochromeno-pyrazolines. The studies on the catalytic efficiency of $Sc(OTf)_3$, $Yb(OTf)_3$, $La(OTf)_3$, $Zn(OTf)_2$ and $Cu(OTf)_2$ revealed that in all cases 10 mol% of the catalyst was found efficient for the reaction carried out under solvent free condition; however, the best result was obtained with copper(II) triflate. For instance; an efficient and green synthetic route to benzochromeno-pyrazole derivatives via one-pot three component condensation of aldehydes, 3-methyl-1*H*-pyrazol-5(4*H*)-one and α-or β-naphthol catalyzed by metal triflates under solvent-free conditions at 80°C (Scheme-6) [11].



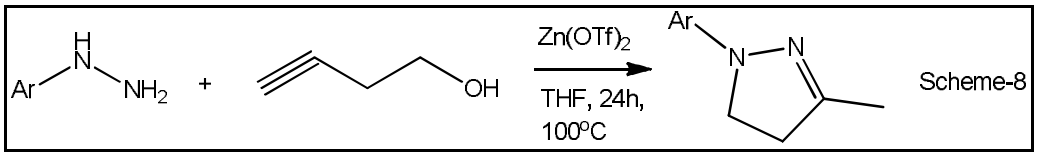
Scheme-6

A series of 3,5-diphenyl and 1,3,5-triphenyl-2-pyrazolines derivatives were synthesized by reacting 1,3-diphenyl-2-propen-1-ones with hydrazine hydrates and phenyl hydrazine in ethanol have showed appreciable antibacterial activity [12]. A one-pot synthesis of nitrogen-containing heterocycles from alkyl dihalides and primary amines and hydrazines occurs under microwave irradiation via a simple and efficient cyclocondensation in an alkaline aqueous medium (Scheme-7) [13].



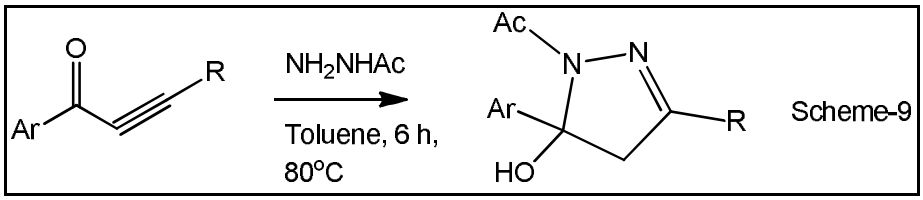
Scheme-7

The reaction of phenyl hydrazine with the chalcones obtained from substituted benzaldehydes and acetophenones under phase transfer catalysis (PTC) conditions employing tetrabutyl ammonium iodide (TBAI) as a catalyst afforded 1,3,5-pyrazolines [14]. Arylhydrazines regioselectively react with 3-butynol in the presence of a catalytic amount of zinc triflate to give aryl-substituted pyrazolines. The resulting products are easily oxidized in a one-pot procedure to the corresponding pyrazoles (Scheme-8) [15].



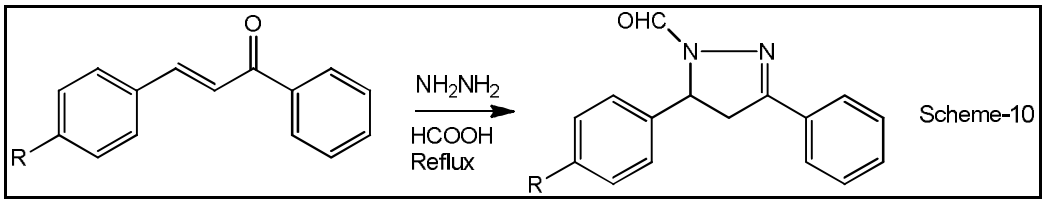
Scheme-8

Starting from easily accessible *gem*-difluoropropargylic derivatives, a DBU-mediated isomerisation affords enones with a *gem*-difluoroalkyl chain. These derivatives were used to prepare pyrazolines and pyrrolines with the desired *gem*-difluoroalkyl side chain by cyclocondensations in good yields and with excellent stereoselectivity. A one-pot process was also successfully developed for these sequential reactions [16]. Various 1-acyl-5-hydroxy-4,5-dihydro-1*H*-pyrazoles have been prepared in good yields from the corresponding 2-alkyn-1-ones. The resulting dihydropyrazoles undergo dehydration and iodination in the presence of ICl and Li_2CO_3 at room temperature to provide 1-acyl-4-iodo-1*H*-pyrazoles (Scheme-9) [17].



Scheme-9

1-[(N,N-disubstitutedthiocarbamoylthio)acetyl]-3-(2-thienyl)-5-aryl-2-pyrazolines were synthesized by reacting 1-(chloroacetyl)-3-(2-thienyl)-5-aryl-2-pyrazolines and appropriate sodium salts of N,N-disubstituted dithiocarbamoic acids in acetone. The synthesised compounds were evaluated for *in vitro* antimycobacterial activity against *M. tuberculosis* H37Rv using the BACTEC 460 radiometric system and BACTEC 12B medium. The preliminary results showed that all of the tested compounds were inactive against the test organism [18]. Reaction of chalcone derivatives with hydrazine hydrate in presence of formic acid yielded 2-pyrazolines in a moderate yield (Scheme-10) **[**19**]**.

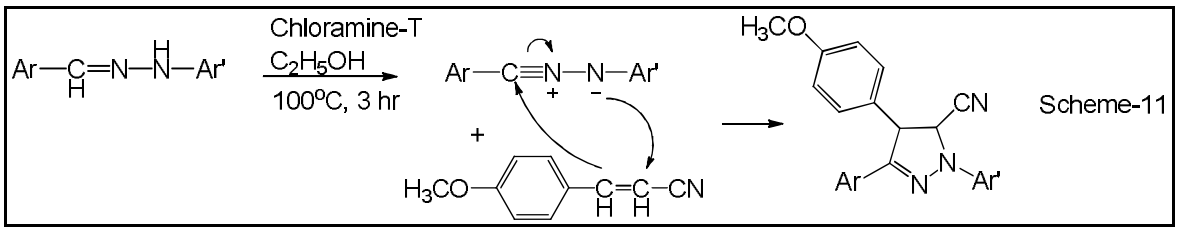


Scheme-10

The exocyclic α, β, γ, δ-unsaturated ketones synthesized by the base-catalyzed reaction of chromanone, flavanone, their 1-thio analogues and *trans*-cinnamaldehydes reacted with diazomethane at ca. 4°C to afford spiro-1-pyrazolines in regioselective and stereospecific reaction. Structure and stereochemistry of all these compounds were elucidated by NMR techniques [20]. A series of chlorinated 3,5-diaryl-2-pyrazolines has been synthesized by the reaction of appropriately substituted chlorochalcones and mono-substituted hydrazines in hot acetic acid solution [21].

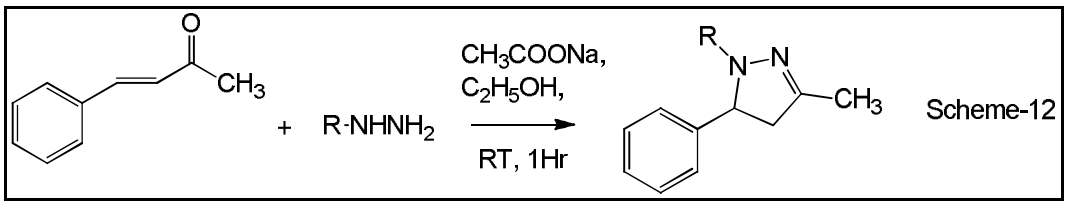
The synthesis of pyrazolines by 1,3-dipolar cycloaddition reactions was discussed comprehensively in the literature [22]. The nitrile imines were considered as useful reactive intermediates in 1,3-dipolar cycloaddition reactions for the synthesis of pyrazolines [23]. In a typical 1,3-dipolar cycloaddition, the nitrile imines generated by the catalytic dehydrogenation of aromatic aldehyde phenylhydrazones with chloramine-T

were trapped *in situ* by 4-methoxy cinnamonitrile, the reaction afforded 3,4-diaryl-1-phenyl-4,5-dihydro-*1H*-pyrazole-5-carbonitriles **3** in 60-76% yield (Scheme-11) [24].



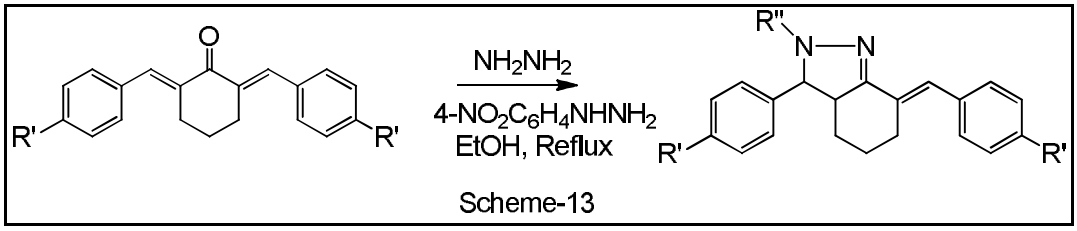
Scheme-11

An efficient one pot synthesis of 4,5-dihydropyrazoles was achieved by the reaction of 4-phenylbut-3-en-2-one and phenyl hydrazine hydrochloride in ethyl alcohol at room temperature (Scheme-12) [25]. The synthesised compounds exhibited moderate antimicrobial activity.



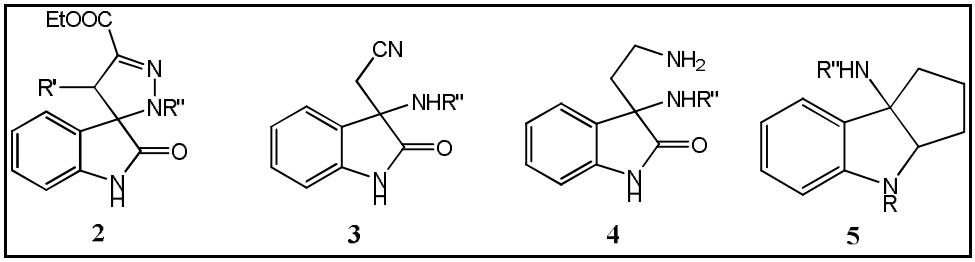
Scheme-12

2-Substituted-3-thiophene-2-yl-prop-2-en-1-one on treatment with hydrazine hydrate in presence of catalytic amount of piperidine yielded 2-substituted-3-thiophene-2-yl-4,5-dihydro-1*H*-pyrazoles. The results of antimicrobial activity studies revealed that these showed very good antibacterial activity [26]. A series of 1-phenyl-3-aryl-5-(4-(3-propanoloxy)phenyl)-1*H*-pyrazoles synthesized by the reaction of 1-aryl-3-(4-hydroxy phenyl) prop-2-en-1-ones and phenyl hydrazine in presence of acetic acid and few drops of HCl were evaluated for their *in vitro* antibacterial activity against gram negative strains and gram positive strains [27]. A series of 2-pyrazolines were obtained in good yield by the reaction 1,3-dipolar cycloadditions of α,β-unsaturated cyclohexanone derivatives with hydrazine hydrate and 4-nitrophenylhydrazine in the presence of acetic acid and ethanol as solvents (Scheme-13) [28].



Scheme-13

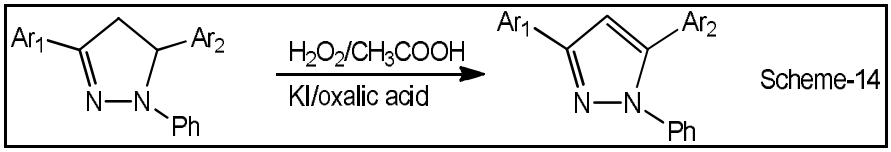
The [3 + 2] dipolar cycloaddition reaction of nitrile imines with 3-alkylidene oxindoles leads to the formation of pyrazoline spiroadducts in high yields and with excellent regio- and diastereoselectivities. These spirocyclic intermediates (**2**) have been elaborated to synthetically versatile 3-amino oxindole building blocks such as β-amino nitrile (**3**), 1,3-diamine (**4**), and pyrrolo[2,3-*b*]indoline (**5**) derivatives [29].



Reactions of Pyrazoles:

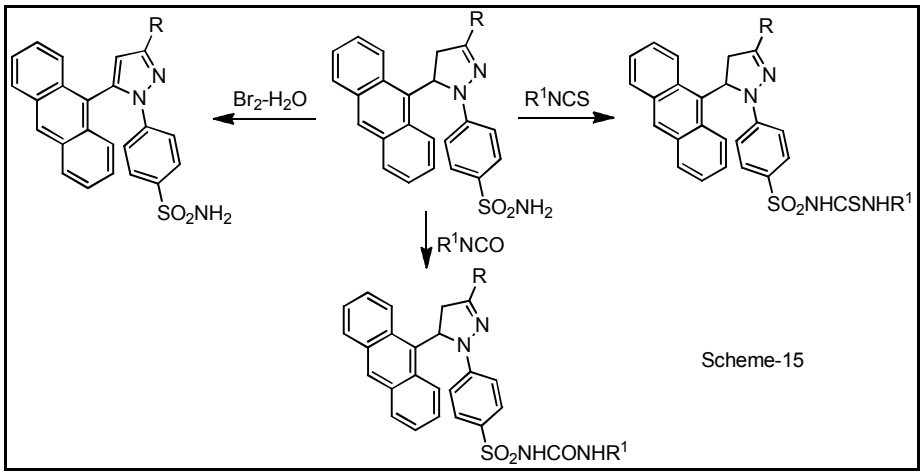
Pyrazole-1*H*-4-carbaldehydes prepared by the Vilsmeier-Haack reaction of phenyl hydrazones were converted into 3-(1,3-diphenyl-1*H*- pyrazol-4-yl) acrylic acids by heating with malonic acid in pyridine and in the presence of catalytic amounts of piperidine. The reduction of pyrazole-1*H*-4-yl-acrylic acids to 3-(1,3-diphenyl-1*H*-pyrazol-4-yl) propanoic acids was carried out using Pd-charcoal and diimide methods. The reduction out by diimide method was found to have advantages of operational simplicity and good yields [30].

An important reaction of pyrazoline is aromatization. It was achieved by heating 1,3,5-trisubstituted-2-pyrazoline with H_2O_2/CH_3COOH or silica/H_2SO_4 to get corresponding pyrazoles. The method was found efficient and convenient for its easy isolation procedures and use of eco-friendly reagents (Scheme-14) [31].



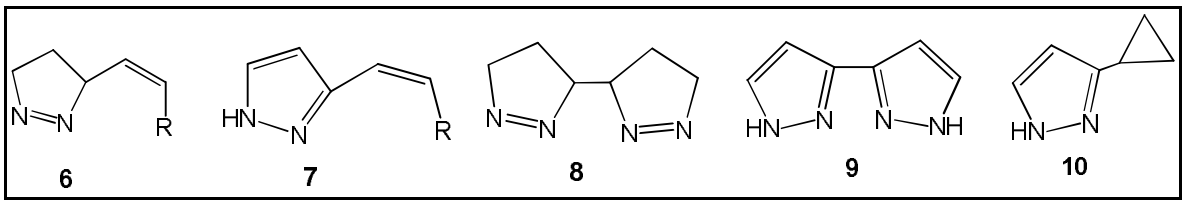
Scheme-14

Pyrazoline derivatives can be oxidized to corresponding pyrazoles with weak oxidizing agents like bromine water and also with suitable isocyanates and isothiocyanates in dry acetone to get the corresponding benzene sulphonyl urea and thiourea derivatives respectively (Scheme-15)[32].



Scheme-15

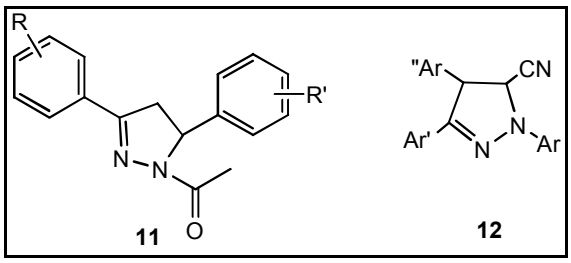
Oxidative dehydrogenation of 3-vinyl-4,5-dihydro-3*H*-pyrazoles (**6**) with 20eq of MnO_2 in benzene at room temperature to produce 3-alkenyl-1*H*-pyrazoles (**7**) in good yield. While, 4,4′,5,5′-tetrahydro-3*H*,3′*H*-3,3′-bipyrazole (**8**) on oxidative dehydrogenation with MnO_2 in benzene at room temperature produces a mixture of 3,3′-bipyrazoles (**9**) and 3-cyclopropyl-1*H*-pyrazole (**10**). The 3-cyclopropyl-1*H*-pyrazole (**10**) was presumably formed by the elimination of nitrogen molecule from one dihydropyrazole ring of (**8**) [33].



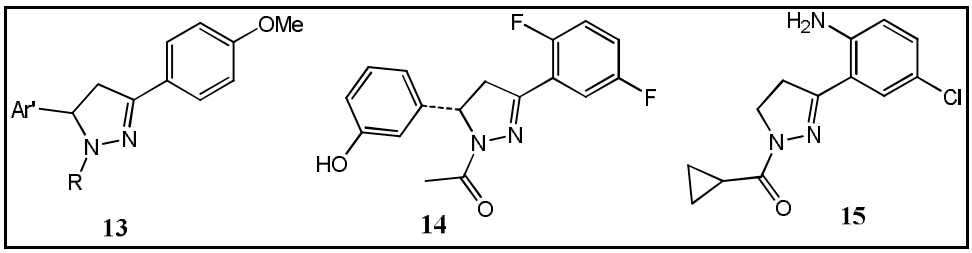
6 **7** **8** **9** **10**

Applications of Pyrazoles:

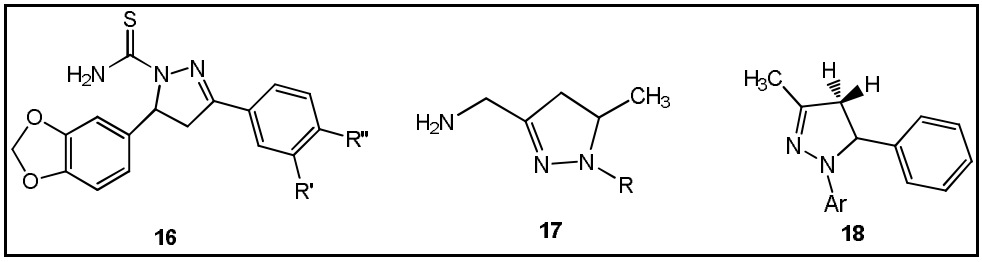
Derivatives of pyrazoles have played a crucial role in the history of heterocyclic chemistry and been used as important pharmacores and synthons in the field of organic chemistry and drug designing. For instance, a series of 1-acetyl-3,5-diphenyl-4,5-dihydro-(1*H*)-pyrazoles (**11**) synthesised were investigated for their ability to inhibit selectively monoamine oxidases, swine kidney diamine oxidase (SKDAO) and bovine serum amine oxidase (BSAO). These compounds were reversible and non-competitive inhibitors of all types of the assayed amine oxidases. The study reported that replacing the substituted phenyl ring at N_1 by an acetyl group increased the inhibitory activity and selectivity towards MAOs of pyrazoles likely taking part in the interaction with the isoalloxazine nucleus [34]. A series of tetrasubstituted pyrazolines (**12**) synthesised by 1,3-dipolar cycloaddition of aromatic aldehyde phenylhydrazones and cinnamonitrile with chloramine-T as catalytic dehydrogenating agent have showed promising antifungal, antibacterial and antioxidant activities [35].



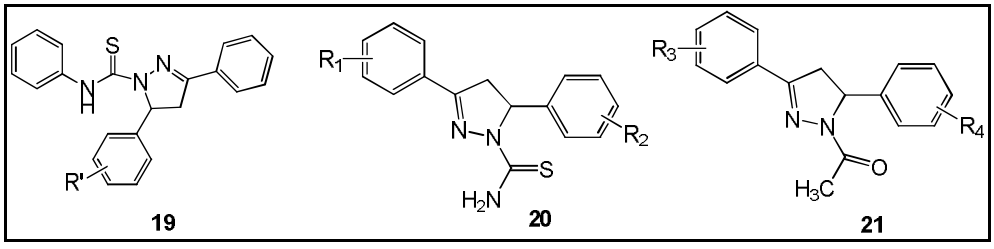
The solution-phase approach avoids the need to re-optimize the chemistry to the solid-phase prior to library generation. Δ^2-Pyrazolines are an important class of heterocyclic small molecules that have shown potential bioactivity in numerous screening tests. For example, pyrazolines (**13**) have demonstrated moderate to good MIC_{90} values against *Helicobacter pylori*. The optimized pyrazoline (**14**) showed nanomolar inhibition (IC_{50} = 26 nM) against kinesin spindle protein (KSP). Pyrazoline (**15**) displayed 70% inhibitory activity against neuronal nitric oxide synthase (nNOS). Such selective inhibition is indicative of potential neuroprotective properties [36].



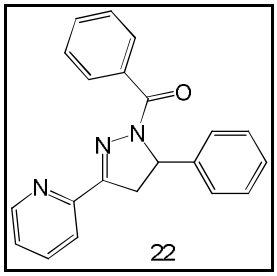
The anticancer activity of the pyrazole analogues of piperine (**16**) were determined by MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-di phenyl tetrazolium bromide) assay method. The anti inflammatory activity of the compounds (**16**) was determined by Human Red Blood Cell (HRBC) membrane stabilization method at doses of 100 µg, 500 µg and 1000 µg. These analogues also showed good binding affinity with Cycloxygenase and farnasyl transferase receptors, which was proved from the docking studies [37]. 1-(5-Methyl-4*H*-pyrazol-3-yl)methanamine derivatives (**17**) [38] synthesised showed significant antibacterial activity when compared to the standard drug. Trisubstituted pyrazolines (**18**) [39] obtained by one pot route have exhibited promising antifungal activities against different organism.



Pyrazole derivatives (**19**) [40] synthesized were screened for anti-tubercular activity. The minimal inhibition concentration was used to evaluate the anti-tuberculosis activity. The synthesis and structure–activity relationship of pyrazole derivatives (**20, 21**) as anticancer agents that may function as inhibitors of EGFR and kinases was reported. Some of them exhibited significant EGFR inhibitory activity. 3-(3,4-Dimethylphenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (**20**) displayed the most potent EGFR inhibitory activity with IC_{50} of 0.07 lM, which was comparable to the positive control erlotinib. The compound also showed significant antiproliferative activity against MCF-7 with IC50 of 0.08 lM and potent inhibitory activity in tumor growth inhibition [41].

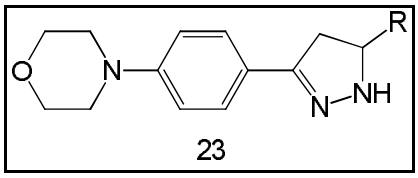


2-Pyrazolines display a broad spectrum of potential pharmacological activities and are present in a number of pharmacologically active molecules such as phenazone/ amidopyrene/ methampyrone (analgesic and antipyretic), azolid/tandearil (anti-inflammatory), indoxacarb (insecticide) and anturane (uricosuric). Changes in their structure have offered a high degree of diversity that has proven useful for the development of new therapeutic agents having improved potency and lesser toxicity [42]. The synthesis and antiproliferative activity of series of 3-(pyrid-2-yl)-pyrazolines (**22**) in two cancer cell lines are reported. Some of the synthesised compounds screened in the NCI 60 human tumour cell line and displayed sub-micromolar activity. Cell cycle analysis, *in vitro* tubulin assay and confocal microscopy are also reported and suggest that the lead compound disrupts microtubule formation [43].



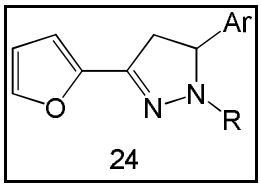
22

A number of synthesized compounds 4-bromo-3(substituted phenyl)-5(substituted phenyl)-1-phenyl-2-pyrazolines were screened for anti-oxidant and anti-inflammatory activity. The free radical scavenging properties were screened by DPPH free radical method using ascorbic acid as standard antioxidant. The anti-inflammatory activities were evaluated by against carragenan induced edema in rat paw using diclofenac sodium as a standard dug. Results of the investigation revealed that some of the tested compounds exhibited promising antioxidant and anti-inflammatory activities [44]. A series of pyrazolines (**23**) prepared from the corresponding chalcones synthesized were evaluated for their anti-inflammatory activity against carrageenan edema in albino rats at a dose of 10 mg/kg. Results of the investigation indicated that all the compounds of this series showed promising anti-inflammatory activity. The most of the compounds of this series were found to be potent. They showed higher percentage of inhibition of edema than the standard drug indomethacin [45].



23

Pyrazoline derivatives obtained from chalcones of 2-acetyl thiophene and phenyl hydrazine hydrochloride in the presence of alcohol were screened for anti-inflammatory activity. Results of the study indicated that some of the compounds show moderate to considerable anti-inflammatory activity [46]. Twelve 1-phenyl-, 1-thiocarbamoyl- and 1-N-substituted thiocarbamoyl-3-(2-furyl)-5-phenyl/(2-furyl)-2-pyrazoline derivatives (**24**)[47] synthesized were screened for their antidepressant activities by Porsolt's behavioural despair test on albino mice. Among the series of the tested compounds 1-N-Ethylthiocarbamoyl-3-(2-furyl)-5-phenyl-2-pyrazoline and 1-N-allylthiocarbamoyl-3,5-di(2-furyl)-2-pyrazoline were reduced 33.80-31.42% duration of immobility times at 10 mg/kg dose level. Anticonvulsant activities of the compounds were determined by maximal electroshock seizure (MES) and subcutaneous pentylenetetrazole (metrazol) (scMet.) tests, neurotoxicities were determined by rotarod toxicity test on albino mice. Some among the tested were found protective against MES and scMet at 30-300 mg/kg dose levels.



24

The synthesised 1,3,5-triphenyl-2-pyrazolines and 3-(2"-hydroxy naphthalen-1"-yl)-1,5-diphenyl-2-pyrazolines were evaluated for their antidepressant activity by the 'Porsolt behavioural despair test' on Swiss-Webster mice. The study revealed that these compounds possess remarkable antidepressant activity at 100mg/kg dose level. In addition, it was found that the compounds possessing electron-releasing groups such as dimethyl amino, methoxy and hydroxyl substituents, on both the aromatic rings at positions 3 and 5 of

pyrazolines, considerably enhanced the antidepressant activity when compared to the pyrazolines having no substituents on the phenyl rings [48].

Conclusion:

Pyrazole moiety is a core skeleton in many of the biologically active heterocycles. These derivatives have a long history of their application in agrochemicals and pharmaceutical industry. The intensity of their diverse biological applications made them has popular drugs that created an interest among the scientists to work in this area. Although chemists devised a broad range of methods for the synthesis of pyrazolines, certainly new methods continue to appear, especially for design of novel regioselective pyrazolines forming reactions. The prevalence of pyrazole cores in biologically active molecules has stimulated the need for elegant and efficient ways to make these heterocyclic lead.

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