CHAPTER – III

Chemistry of Pyrazoles
CHAPTER – III

CHEMISTRY OF PYRAZOLES

3.1.0 Introduction:

Pyrazoles (65a) 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 and the other is neutral in nature. These are aromatic molecules due to their planar conjugated ring structures with six delocalized \( \pi \)-electrons. The aromatic nature arises from the four \( \pi \) electrons and the unshared pair of electrons on the –NH nitrogen. The partially reduced forms of pyrazole are named as pyrazolines (65b or 65c); while completely reduced form is pyrazolidine (65d).

Pyrazole is a tautomeric substance; the existence of tautomerism cannot be demonstrated in pyrazole itself but it can be inferred by the consideration of pyrazole derivatives. Unsubstituted pyrazole can be represented in three tautomeric forms (Scheme-71). For the pyrazole derivatives in which two carbon atoms neighboring the nitrogen atoms on the ring have different substituents, five tautomeric structures are possible (Scheme-72).
Pyrazoles and its derivatives, a class of well known nitrogen heterocycles, occupy a prime position in medicinal and pesticide chemistry for their diverse biological activities. Pyrazole analogues have found use as building blocks in organic synthesis for designing pharmaceutical and agrochemicals and as bifunctional ligands for metal catalysis. They have been known to exhibit antimicrobial, analgesic, anticancer, anti-tubercular, anti-inflammatory, antidepressant, anticonvulsant, antihyperglycemic, antipyretic, antihelmintic, antioxidant and herbicidal properties. The pyrazole ring is present as the core in a variety of leading drugs such as Celebrex, Sildenafil (Viagra), Ionazlac, Rimonabant and Difenamizole etc.

Pyrazoles have illustrious history; in 1883, a German chemist Ludwig Knorr was the first to discover antipyretic action of pyrazole derivative in man, he named the compound antipyrine. When he attempted to synthesize quinoline derivatives with antipyretic activity, accidentally obtained antipyrine (2,3-dimethyl-1-phenyl-3-pyrazolin-5-one) which has analgesic, antipyretic and antirheumatic activity; which stimulated interest in pyrazole chemistry.

The first natural pyrazole derivative was isolated by Japanese workers Kosuge and Okeda in the year 1954, till their discovery it was thought that pyrazoles could not be obtained naturally. They isolated 3-\(n\)-nonylpyrazole (66) from Houttuynia Cordata, a plant of the “piperaceae” family from tropical Asia, which showed antimicrobial
activity. They also isolated *levo*-β-(1-pyrazolyl) alanine (67) an amino acid from watermelon seeds (Citrullus Vulgaris).

![Chemical structures](image)

3.1.1 Synthesis of functionalized pyrazoles using various synthetic approaches:

The wide range of biological activities associated with pyrazoles has made them popular synthetic targets. Numerous methods have been developed for preparation of substituted pyrazoles. In general, pyrazoles are synthesized by (*i*) the reaction of 1,3-diketones with hydrazines, (*ii*) 1,3-dipolar cycloaddition of diazo compounds with alkynes and (*iii*) the reaction of α,β-unsaturated aldehydes and ketones with hydrazines.

A mild and efficient protocol to access fluoropyrazoles for the first time based on ubiquitous alkyne moieties as backbones involving a gold-catalyzed tandem aminofluorination of alkynes in the presence of selectfluor (an electrophilic fluorine source) was developed by Qian et al (*Scheme-73*). The method has advantages of mild reaction conditions, high yields, broad substrate scope and a simple one-pot procedure.

![Scheme-73](image)

An efficient three-component reaction of an aromatic aldehyde, 3-methyl-1-phenyl-5-aminopyrazole and 1,3-indenedione was designed for the synthesis of indeno[2′,1′:5,6]pyrido[2,3-d]pyrazole derivatives in the presence of sodium dodecyl...
sulfate, an anionic surfactant using water as reaction medium (Scheme-74).\textsuperscript{164} This protocol has an environmentally benign procedure having simple operation.

\begin{center}
\includegraphics[width=\textwidth]{scheme74}
\end{center}

Tandem reactions refer to two reactions operating in succession in the same reaction vessel. An efficient and general one-pot three-component procedure for the construction of pyrazoles via a tandem coupling-cyclocondensation sequence catalyzed by Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2}/CuI was reported (Scheme-75).\textsuperscript{165} Enones were synthesized from acid chlorides and terminal alkynes and were converted \textit{in situ} into pyrazoles by the cycloaddition of hydrazines. The method has easy isolation and simple workup procedures.

\begin{center}
\includegraphics[width=\textwidth]{scheme75}
\end{center}

The pyrazole compounds were constructed through the Huisgen cycloaddition of 2-methylene-1,3,3-trimethylindoline and an \textit{in situ} generated nitrile imine. The newly formed spiro-pyrazoline intermediate presumably then undergoes a ring opening/elimination process to afford a novel 1,3,5-trisubstituted pyrazole derivative (Scheme-76).\textsuperscript{166}

\begin{center}
\includegraphics[width=\textwidth]{scheme76}
\end{center}

Microwave irradiation is pollution free and eco-friendly route in organic synthesis. As microwave irradiation facilitates the polarization of the molecule, the
reactions proceed much faster and with higher yields under microwave irradiation compared to conventional heating. For instance; Mistry et al\textsuperscript{167} reported the synthesis of various pyrazole derivatives both by conventional and microwave-assisted synthesis (\textbf{Scheme-77}). It was found that the reaction carried out in acetone using conventional method requires about 5-7h, while microwave irradiation method requires only 4-7min. The synthesized compounds have been tested of their antibacterial and antifungal activities.

![Scheme-77](image)

The reaction of Baylis–Hillman adduct and phenyl hydrazine in dichloroethane at 50-70°C for about 6 h afforded the tetrasubstituted pyrazole derivatives with very high regioselectivity of products in 89% yield (\textbf{Scheme-78}).\textsuperscript{168} The reaction follows \textit{via} the successive hydrazone formation, cyclization and double bond isomerization sequence under reflux conditions.

![Scheme-78](image)

The nitrile imines generated \textit{in situ} from the hydrazonoyl halides react with 3-propylideneephthalide and 3-benzylideneephthalide in refluxing benzene to afford 1,3,4,5-tetrasubstituted pyrazoles (\textbf{Scheme-79})\textsuperscript{169} which involves initial formation of the spiro intermediates via 1,3-dipolar cycloaddition of nitrile imines, ultimately underwent ring opening via 1,3-hydrogen shift to aromatic pyrazole derivatives.
Alinezhad and coworkers\textsuperscript{170} reported a facile one-pot regioselective preparation of 4-bromopyrazoles with high yields from 1,3-diketones, arylhydrazines and \(N\)-bromosaccharin (NBSac) in the presence of silica gel supported sulfuric acid (\(\text{H}_2\text{SO}_4/\text{SiO}_2\)) under solvent free conditions (Scheme-80). When \(N\)-bromosaccharin was added and mixed thoroughly, 3,5-dimethyl-4-bromo-\(N\)-phenylpyrazole was obtained in excellent yield within 7 min.

A novel Ru (II)-catalyzed oxidative C-N coupling method has been reported for the synthesis of highly diversified tri- and tetrasubstituted pyrazoles from easily accessible starting materials (Scheme-81). Dioxygen gas is employed as the oxidant which plays an essential role in the catalytic cycle of C-H activation. This method is useful for making a variety of multisubstituted pyrazoles, most of which are difficult to access with conventional methods. The reaction demonstrates excellent reactivity, broad scope, high tolerance of functional groups and high yields.\textsuperscript{171}
Silver triflate Ag(I) 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 by Claisen-Schmidt condensation of appropriate acetophenones with imidazole aldehydes in the presence of aqueous solution of potassium hydroxide and ethanol at room temperature. 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-82). The synthesized compounds were tested for their antibacterial and antifungal activities.

![Scheme-82](image)

The synthesis of pyrazolo [3,4-b] quinolines from β-chlorovinylaldehydes and phenyl hydrazine using p-TsOH under microwave irradiation was reported (Scheme-83). It was found that p-TsOH is most adaptable and simplest catalyst that causes noticeable rate enhancement in microwave irradiation synthesis.

![Scheme-83](image)

The highly functionalized 1H-pyrazole derivatives were synthesized by a one-pot isocyanide-based cascade four-component reaction between arylcarbohydrazides, dialkyl acetylenedicarboxylates and cyclohexyl isocyanide (Scheme-84). This approach has the potential in synthesis of various functionalized 1H-pyrazole
derivatives due to the easy availability of the synthetic approach and the neutral ring closure conditions.

Hydrazones were treated with excess dimethylformamide and phosphorous oxychloride and irradiated under microwaves for 30-60 seconds to get 1-(2,4-dinitrophenyl)-3-aryl-4-(arylsulfanyl)-1H-pyrazoles in good yields (Scheme-85). Hydrazones were in turn prepared from 2,4-dinitrophenylhydrazine and substituted phenacyl aryl sulfides.

Mercaptoheterocyclic compounds on treatment with bromo ethylacetate in the presence of base afforded thioacetate derivatives which on subsequent treatment with hydrazine hydrate yielded acylated hydrazine derivatives. Reaction of these acylated hydrazine derivatives with ketene dithioacetal derivatives in methanol under reflux condition afforded sulphur bridged pyrazole derivatives. These synthesized pyrazole derivatives were tested for their antibacterial activity against both gram positive and gram negative bacteria.

In recent times, ultrasonic conditions in organic synthesis has gained prime place. Reactions carried out under silent and ultrasonic conditions reduce the time of reactions from several hours to minutes and improves the yields compared to that of conventional conditions. For example; Tamer S.S. et al reported the synthesis of
novel pyrazoles by the reaction of the carbanions of 1-aryl-2-(phenylsulphonyl) ethanone with different hydrazonyl halides (Scheme-86). It was observed that α-sulphonyl carbanion was found to be a good nucleophile for reaction with different hydrazonyl halides. The reaction evidences that ultrasound irradiations enable some reactions to occur which could not be carried out under silent condition.

Ken-Ichi et al\textsuperscript{178} reported a novel synthesis of pyrazole derivatives using polymer-supported α-silylnitrosoamide derivatives. Pyrazole derivatives were obtained by 1,3-dipolar cycloaddition of polymer-supported azomethine imines with dimethyl acetylenedicarboxylate (DMAD) in good yields (Scheme-87). The azomethine imines were generated from polymer-supported α-silylnitrosoamides by a 1,4-silatropic shift. Intramolecular 1,4-silatropic shift of the α-silylnitrosoamide gave the polymer-supported azomethine imine which underwent 1,3-dipolar cycloaddition with the dipolarophile. The products can be easily separated from the polymer without any cleavage operation.

A simple, efficient and regioselective procedure for the silver(I)-catalyzed formation of 1,3- and 1,5-disubstituted and 1,3,5-trisubstituted pyrazoles from propargyl \textit{N}-sulfonylhydrazone is reported by Lee and co-workers\textsuperscript{179} (Scheme-88). It was observed that during the reaction, migration of sulfonyl groups (Ts, Ms) occur.
The method was found practically useful and good functional group-compatibility under mild reaction conditions.

1,3-Diaryl-4-halo-1H-pyrazoles were found to be important intermediates that can easily be converted into 1,2,4-triaryl- or 1,2,5-triaryl-substituted pyrazoles via a Pd-catalyzed C–C coupling reaction. For instance; Yang et al\textsuperscript{180} reported a convenient and efficient synthesis of a series of 1,3-diaryl-4-halo-1H-pyrazoles in moderate to excellent yields by 1,3-dipolar cycloaddition of 3-arylsydrones and 2-aryl-1,1-dihalo-1-alkenes (Scheme-89).

Fluoro chloro aniline on diazotization forms diazonium salt which on reaction with ethyl cyanoacetate gives the intermediate. The intermediate when cyclized with chloroacetonitrile using triethyl amine as the base gave a series of novel substituted pyrazoles (68) and were screened for their antibacterial and anti-oxidant activity.\textsuperscript{181}

Aggarwal et al\textsuperscript{182} reported a new user-friendly one-pot procedure for regioselective synthesis of 3,5-disubstituted pyrazoles by the 1,3-dipolar cycloaddition reactions of diazo compounds (Scheme-90).
An efficient regioselective synthetic route to multisubstituted pyrazoles by cyclocondensation of β-thioalkyl-α,β-unsaturated ketones with hydrazines was developed by Jin et al.\textsuperscript{183} (Scheme-91). The reactions of β-thioalkyl-α,β-unsaturated ketones with hydrazines were carried out in the presence of t-BuOK or HOAc in refluxing t-BuOH.

![Scheme-90](image)

**Scheme-90**

### 3.1.2 Reactions of pyrazoles:

Metal triflates exhibited high efficiency for the synthesis of benzochromeno-pyrazoles. The catalytic efficiency of Sc(OTf)\textsubscript{3}, Yb(OTf)\textsubscript{3}, La(OTf)\textsubscript{3}, Zn(OTf)\textsubscript{2} and Cu(OTf)\textsubscript{2} was studied extensively. In all cases 10 mol% of the catalyst was used and the reaction was carried out under solvent free condition; the best result was obtained when copper (II) triflate was used as a catalyst. For instance; Saman\textsuperscript{184} developed an efficient and green synthetic route to benzochromeno-pyrazole derivatives via one-pot three component condensation of aldehydes, 3-methyl-1\textit{H}-pyrazol-5(4\textit{H})-one and α- or β-naphthol catalyzed by a series of metal triflates under solvent-free conditions at 80°C (Scheme-92).

![Scheme-91](image)

**Scheme-91**

Pyrazole-1\textit{H}-4-carbaldehydes were prepared by the Vilsmeier-Haack reaction of phenyl hydrazone derivatives. The aldehydes were converted into 3-(1,3-diphenyl-
1\textit{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\textit{H}-4-yl-acrylic acids to 3-(1,3-diphenyl-1\textit{H}-pyrazol-4-yl) propanoic acids was carried out using Pd-charcoal and diimide methods.\textsuperscript{185} The reduction of pyrazole acrylic acids to pyrazole propanoic acids using diimide method was found to have advantages like operational simplicity and good yields.

Pyrazole-tethered Schiffs base ligand (69) and pyrazole-tethered phosphine ligand (70) acts as an efficient catalyst system for Suzuki coupling reactions. For example in the presence of ligand (69), the coupling of aryl bromides/chlorides with phenylboronic acid took place efficiently under mild conditions (Scheme-93).\textsuperscript{186} The catalytic activity depends considerably on the donor atoms and the steric environment around the metal present in the ligands system.

\begin{center}
\begin{tikzpicture}
\node[anchor=west] at (0,0) {MeO-\text{Br} \quad \text{Pd}({\text{dba}})_{3}/\text{Ligand 69} \quad \text{CsF, Dioxane}};
\node[anchor=west] at (0,-1.5) {Pd:2-1:1 Scheme-93};
\end{tikzpicture}
\end{center}

Combination of Pd\textsubscript{2} (dba)\textsubscript{3} and ligand (70) (Pd:6 = 1:2) catalyzed the coupling between aryl bromide and phenylboronic acid at 80-85°C in toluene to produce products in 70-80% yield (Scheme-94).\textsuperscript{187}
A one pot, mild and efficient method for the synthesis of a series of α-aminophosphonates from pyrazolyl imines and triethyl phosphite using TMSCl as a catalyst by both conventional and under ultrasound irradiation conditions was reported by Nagargoje and co-workers.\textsuperscript{188} Their study revealed that non-conventional method offer advantages over conventional process \textit{viz.}, short time span to complete reaction, easy work procedure and excellent yields.

Ibrahim \textit{et al}\textsuperscript{189} reported the direct \textit{N}-arylation of 3,5-disubstituted-pyrazoles with 4-fluoronitrobenzene and 2-fluoronitrobenzene using potassium t-butoxide in DMSO using three methods \textit{viz.}, microwave irradiation with or without solvent and a classical heating. The method affords the α-regioisomers in excellent yields (Scheme-\textbf{95}). But in solvent-free under microwave irradiation conditions, the reaction gives a mixture of isomers. The reaction performed without or with some drops of solvent using microwave irradiation increased reaction rates and improved the regioselectivity.

The thermal reactions of 3-methyl-1(2),4,5,6-tetrahydrocyclopenta[c] pyrazole under FVP (Flash Vacuum Pyrolysis) conditions was reported. All the products arise from a nitrogen extrusion reaction which proceeds through the different rearrangements of the vinylcarbenes. These intermediates are generated from the two possible tautomeric pyrazoles and can undergo 1,2 or 1,4-H-migration and C-H insertion reactions.\textsuperscript{190} Thieno [2,3-\textit{c}] pyrazole was synthesized by the reaction of methyl 4-pyrazoleacetate with carbon disulfide and iodomethane in a new tandem reaction (Scheme-\textbf{96}).\textsuperscript{191}
Direct nitration of a variety of pyrazoles with nitric acid/trifluoroacetic anhydride affords mononitro derivatives in average yield of 60%. Pyrazole (71) on treatment with above nitrating system gave a 41% yield of the 3,4-dinitrated derivative (72) while N-methylpyrazole under the same reaction condition gave a 65% yield of the 3-nitro product (72). 3,5-Dimethylpyrazole (73), on the other hand, give only 3,5-dimethyl-4-nitropyrazole (74) in 76% yield. (Scheme-97).^{192}

Oxidative dehydrogenation of 3-vinyl-4,5-dihydro-3H-pyrazoles (75) with 20equiv of MnO₂ in benzene at room temperature to produce 3-alkenyl-1H-pyrazoles (76) in good yield. While, 4,4′,5,5′-tetrahydro-3H,3′H-3,3′-bipyrazole (77) on oxidative dehydrogenation with MnO₂ in benzene at room temperature produces a mixture of 3,3′-bipyrazoles (78) and 3-cyclopropyl-1H-pyrazole (79) in 27 and 18% yields respectively. The 3-cyclopropyl-1H-pyrazole (79) was presumably formed by the elimination of nitrogen molecule from one dihydropyrazole ring of (77).^{193}
3.1.3 Biological activity of various substituted pyrazole derivatives:

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. A series of 1-acetyl-3,5-diphenyl-4,5-dihydro-(1H)-pyrazoles (80) synthesized 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. In particular 1-acetyl-3-(2,4-dihydroxyphenyl)-5-(3-methylphenyl)-4,5-dihydro-(1H)-pyrazole showed I_{50} values of 40nM accompanied by a selectivity factor of 4000 for MAOs (mitochondrial monoamine oxidases). By replacing the substituted phenyl ring at N₁ by an acetyl group increased the inhibitory activity and selectivity towards MAOs of pyrazoles likely taking part in the interaction with the isoalloxazine nucleus.¹⁹⁴

![Pyrazole Derivative](image)

2-(5-Substituted-1H-pyrazol-3-yl)naphthalen-1-ol derivatives (81), a non vicinal diaryl heterocycle synthesized were evaluated for in-vivo anti-inflammatory activity by acute carrageenan induced paw edema standard method in rats. The compounds containing electron donating methyl and halogen functional group showed more activity than that of electron withdrawing nitro and dinitro functional group.¹⁹⁵
The anticancer activity of the pyrazole analogues of piperine (82) 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 (82) was determined by Human Red Blood Cell (HRBC) membrane stabilization method at doses of 100 μgm, 500 μgm and 1000 μgm. These analogues also showed good binding affinity with cyclooxygenase and farnasyl transferase receptors, which was proved from the docking studies. 196 1-(5-Methyl-4H-pyrazol-3-yl) methanamine derivatives (83) synthesized showed significant antibacterial activity when compared to the standard drug.

Pyrazole derivatives (84) synthesized were screened for anti-tubercular activity. The minimal inhibition concentration was used to evaluate the antituberculosis activity. Shin-Ru-Shih et al199 reported that BPR1P0034 (85) has potent inhibitory activity against influenza virus. They showed that BPR1P0034 is the first pyrazole-based anti influenza compound ever identified and characterized from high through put screening to show potent (sub-μM) antiviral activity.
Abdel Hameed and co-workers\textsuperscript{200} reported 5-Chloro-1-phenyl-3-methyl-pyrazolo-4-methinethiosemicarbazone (86) as corrosion inhibitors for carbon steel in 1M HCl by chemical and electrochemical method. The corrosion rate decreased and inhibition efficiencies and surface coverage degree increased with increasing in inhibitor concentration and temperature. The protective film of these compounds formed on the carbon steel surface is stable at higher temperature. Nitulescu and co-workers\textsuperscript{201} synthesized N-(1-methyl-1$H$-pyrazole-4-carbonyl)-thiourea derivatives (87) and evaluated for their analgesic and sedative effects. The compounds showed promising activities.

The synthesis and structure–activity relationship of pyrazole derivatives (88, 89) 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 (88) 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 anti-proliferative activity against MCF-7 with IC$_{50}$ of 0.08 lM and with potent inhibitory activity in tumor growth inhibition was a potential anticancer agent.\textsuperscript{202}
3.2.0 Aim of present work:

The pyrazole nucleus is present in a wide variety of biologically interesting compounds. Continuous efforts have been devoted to the development of general and versatile synthetic methodologies to this class of compounds. Many research groups have been synthesized pyrazole derivatives using various methods. However, the existing methods suffered with some drawbacks such as long reaction time, product isolation, etc. The 1,3-dipolar cycloaddition reactions of nitrile imine with olefins is a useful reaction for the construction of five membered heterocyclic rings. A series of compounds (91a-h) were prepared and evaluated for their antimicrobial and antioxidant activity. The synthesized new compounds were characterized by IR, $^1$H NMR, $^{13}$C NMR, Mass spectral studies and elemental analysis.

The 4-methoxy cinnamonitrile (60) was used as the precursor for the synthesis of 3-aryl-4-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1$H$-pyrazole-5-carbonitriles (91a-i). Initially aromatic aldehyde phenyl hydrazones (90) were synthesized by reacting aromatic aldehydes with phenyl hydrazine hydrochloride in the presence of sodium acetate in ethanol as a solvent (Scheme-98).

\[
\begin{align*}
\text{Ar} - \text{C} &= \text{O} & \text{Ar'}\text{NHNH}_2\text{HCl} & \xrightarrow{\text{CH}_3\text{COONa/C}_2\text{H}_5\text{OH}} & \text{Ar} - \text{C} &= \text{N} - \text{N}\text{Ar'} \\
\text{Ar} & \text{H} & & \text{Scheme-98} & & \text{Ar} & \text{H} \\
\end{align*}
\]

Chloramine-T was used as a reagent for the generation of nitrile imines from aromatic aldehyde phenyl hydrazones. Oxidative dehydrogenation of (90) by
chloramine-T (CAT) afforded nitrile imine, which was \textit{in situ} trapped by 4-methoxy cinnaminitrile \( \text{(60)} \) to give an isomeric mixture of 3-aryl-4-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1\( H \)-pyrazole-5-carbonitriles \( \text{(91)} \) (major product) and 3-aryl-5-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1\( H \)-pyrazole-4-carbonitriles \( \text{(92)} \) (minor product) (\textbf{Scheme-99}).

\[ 60 + 90 \xrightarrow{\text{Chloramine-T, C}_2\text{H}_5\text{OH, 100°C, 3h}} 91 \cup 92 \]

\textbf{91 and 92} a) \( \text{Ar} = 4\text{-FC}_6\text{H}_4, \text{Ar}' = \text{C}_6\text{H}_5 \) b) \( \text{Ar} = 4\text{-ClC}_6\text{H}_4, \text{Ar}' = \text{C}_6\text{H}_5 \)

c) \( \text{Ar} = 4\text{-BrC}_6\text{H}_4, \text{Ar}' = \text{C}_6\text{H}_5 \) d) \( \text{Ar} = 4\text{-CNc}_6\text{H}_4, \text{Ar}' = \text{C}_6\text{H}_5 \)

e) \( \text{Ar} = \text{C}_6\text{H}_5, \text{Ar}' = \text{C}_6\text{H}_5 \) f) \( \text{Ar} = 4\text{-OCH}_3\text{c}_6\text{H}_4, \text{Ar}' = \text{C}_6\text{H}_5 \)

g) \( \text{Ar} = 3,4\text{(OCH}_3\text{c}_6\text{H}_4, \text{Ar}' = \text{C}_6\text{H}_5 \) h) \( \text{Ar} = \text{Furan-2-yl}, \text{Ar}' = \text{C}_6\text{H}_5 \)

\[ \text{Scheme-99} \]

\textbf{3.3.0 Discussion on the experiment leading to the formation of pyrazolines:}

In a typical 1,3-dipolar cycloaddition, the nitrile imines generated by the catalytic dehydrogenation of aromatic aldehyde phenyl hydrazones \( \text{(90)} \) with chloramine-T were trapped \textit{in situ} by 4-methoxy cinnaminitrile \( \text{(60)} \), the reaction afforded an isomeric mixture of 3-aryl-4-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1\( H \)-pyrazole-5-carbonitriles \( \text{(91)} \) in 60-76% yield and 3-aryl-5-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1\( H \)-pyrazole-4-carbonitriles \( \text{(92)} \) in 10-20% yield (\textbf{Scheme-99}).

Catalytic dehydrogenation of aromatic aldehyde phenyl hydrazones with Chloramine-T in ethyl alcohol generates nitrile imines. The nitrile imines generated \textit{in
situ undergo 1,3-dipolar cycloaddition with an alkenyl moiety of 4-methoxy cinnamonomitrile to produce the title compounds.

**Brief spectral analysis discussion of the compounds 91a-h:**

The structures of the cycloadducts were provided by IR, $^1$H NMR, $^{13}$C NMR, MS studies and elemental analysis. For instance, in IR spectra, the cycloadducts (91a-h) gave the absorption bands in the region 1650-1675 cm$^{-1}$ for C=N (str) group, a strong and sharp absorption bands in the region 2220-2240 cm$^{-1}$ for CN (str) which supports the fact that the C-N triple bond of CN group is unaffected during the cycloaddition reaction. Aromatic and aliphatic C–H stretching vibrations are observed in the range of 2700–3100 cm$^{-1}$.

In $^1$H NMR spectra, all cycloadducts (91a-h) showed the peaks due to aromatic and substituent protons at the expected region. The consistent pattern signals due to C$_4$-H appeared as doublet in the region $\delta$ 5.102-5.279 ppm. While signal due to C$_5$-H appears as doublet in the region $\delta$ 5.485-5.704ppm. The coupling constant ($J$) values calculated for C$_4$-H and C$_5$-H were in range 7.0-9.6 Hz, these values indicating that both C$_4$-H and C$_5$-H are in cis orientation. The appearance of these proton signals in the downfield was expected due to the aromatic ring and strong electron withdrawing –CN group bonded to C$_4$- and C$_5$- atoms respectively. The absorption of the methyl hydrogens attached to single bonded oxygen are seen at about $\delta$ 3.83-3.85 ppm are deshielded due to electro negativity of oxygen. The methoxy peak is unsplit and stands out as a tall, sharp singlet. The aromatic proton signals appeared at down field region due to their ring current or anisotropic effect. Owing to this in compounds 91a-h, the aromatic proton signals resonated in the region $\delta$ 6.89-7.79 ppm as multiplet.
In $^{13}$C NMR, all products gave the signals due to aromatic and substituent carbons at the expected region. The signals due to newly formed C$_4$-carbon appeared in the region $\delta_c$ 41.56-41.88 ppm, while, C$_5$-carbon showed the signals in the region $\delta_c$ 51.24-51.92 ppm. A signal at $\delta_c$ 142.66-144.16 ppm is attributed to C$_3$-carbon in the pyrazoline ring which is a carbon attached to electronegative nitrogen by a double bond and also to a benzene ring is deshielded due to its sp$^2$ hybridization and some diamagnetic anisotropy. One more signal at $\delta_c$ 55.50-55.96 ppm is assigned to methoxy carbon deshielded by electronegative oxygen. The signals due to CN group carbon appear in the region $\delta_c$ 116.2-118.0 ppm which shows that the CN triple bond is unaffected during cycloaddition and is retained in the product. Moreover, a collection of signals appeared in the region $\delta_c$ 114.16-164.38 ppm which are ambiguously assigned to aryl carbons.

The new compounds (91a-h) gave significantly stable molecular ion peaks with a relative abundance ranging up to 40% and base peak at (MH$^+$). Further, all showed satisfactorily CHN analysis with a deviation of ± 0.02% from the theoretically calculated values. The observed molecular ion peak and elemental analysis (C H N analysis) for the compounds (91a-h) are well compatible with proposed molecular formula. All these observations strongly favor the formation of the cycloadducts.

In a 1,3-dipolar cycloaddition, an isomeric cycloadducts (92a-h) were obtained relatively in low yield. Only representative three compounds among the series of the synthesized compounds have been characterized by spectral and elemental analysis. For instance, in IR spectra, the cycloadducts (92a, 92b and 92f) gave the absorption bands in the region 1640-1665 cm$^{-1}$ for C=N (str) group, a strong and sharp
absorption bands in the region 2220-2250 cm\(^{-1}\) for CN (str) which supports the fact that the C-N triple bond of CN group is unaffected during the cycloaddition reaction. Aromatic and aliphatic C–H stretching vibrations are observed in the range of 2800–3000 cm\(^{-1}\).

In \(^1\)H NMR spectra, 3-aryl-5-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1\(H\)-pyrazole-4-carbonitriles (92a, 92b and 92f) showed the peaks due to aromatic and substituent protons at the expected region. The consistent pattern signals due to C\(_4\)-H appeared as doublet in the region $\delta$ 5.280-5.400 ppm. While signal due to C\(_5\)-H appears as doublet in the region $\delta$ 5.600-5.790 ppm. The coupling constant ($J$) values calculated for C\(_4\)-H and C\(_5\)-H were in range 7.0-9.6 Hz, these values indicating that both C\(_4\)-H and C\(_5\)-H are in cis orientation. The appearance of these proton signals in the downfield was expected due to the strong electron withdrawing –CN group and aromatic ring bonded to C\(_4\)- and C\(_5\)- atoms of pyrazole ring respectively. The absorption of the methyl hydrogens attached to single bonded oxygen are seen at about $\delta$ 3.85-3.88 ppm are deshielded due to electro negativity of oxygen. The methoxy peak is unsplit and stands out as a tall, sharp singlet. The aromatic proton signals appeared at down field region due to their ring current or anisotropic effect. Owing to this in compounds (92a, 92b and 92f); the aromatic proton signals resonated in the region $\delta$ 6.80-7.80 ppm as multiplet.

In \(^{13}\)C NMR, all cycloadducts gave the signals due to aromatic and substituent carbons at the expected region. The signals due to newly formed C\(_4\)-carbon appeared in the region $\delta_c$ 40.65-42.73 ppm, while, C\(_5\)-carbon showed the signals in the region $\delta_c$ 52.30-53.10 ppm. A signal at $\delta_c$ 143.51-144.20 ppm is attributed to C\(_3\)-carbon in the pyrazoline ring which is a carbon attached to electronegative nitrogen by a double
bond and also to a benzene ring is deshielded due to its sp$^{2}$ hybridization and some
diamagnetic anisotropy. One more signal at $\delta_c$ 55.41-55.80 ppm is assigned to
methoxy carbon deshielded by electronegative oxygen. The signals due to CN group
carbon appear in the region $\delta_c$ 116.0-118.3 ppm which shows that the CN triple bond
is unaffected during cycloaddition and is retained in the product. Moreover, a
collection of signals appeared in the region $\delta_c$ 114.20-163.90 ppm which are
ambiguously assigned to aryl carbons.

The compounds (92a, 92b and 92f) gave significantly stable molecular ion
peaks with a relative abundance ranging up to 40% and base peak at (MH$^+$). Further,
all showed satisfactorily CHN analysis with a deviation of $\pm$ 0.02% from the
theoretically calculated values. The observed molecular ion peak and elemental
analysis (C H N analysis) for the compounds (92a, 92b and 92f) are well compatible
with proposed molecular formula. All these observations strongly favor the formation
of the cycloadducts.

**Mechanism for the formation of pyrazoline:**

The probable mechanism for the generation of nitrile imine using chloramine-
T is depicted in **scheme-100**. The unshared electrons of the nitrogen atom of
chloramine-T abstracts a proton from =N-NH- of aromatic aldehyde hydrazone to
form nucleophile. The nucleophile abstracts a chlorine atom followed by loss of
sodium chloride to form the intermediate. The abstraction of proton from an
intermediate by a mild base TsNH$^-$ ion produced in a reaction forms nitrile imine.
The probable 1,3-dipolar cycloaddition mechanism for the formation of cycloadducts (91a-h) is given in scheme-101. The nucleophilic attack of nitrile imine to a C^bH= atom of C^aH=C^bH-CN group of 4-methoxy cinnamoinitrile and simultaneous attack of CH=CH pi electrons to triple bonded carbon of nitrile imine leads to the formation of 3-aryl-4-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole-5-carbonitriles (91a-h).

Scheme 101: Proposed mechanism for the 1,3-dipolar cycloaddition of nitrile imine with dipolarophile to get the cycloadducts (91a-h).

The probable mechanism for the formation of cycloadducts (92a-h) is given in scheme-102. The nucleophilic attack of nitrile imine to a C^aH= atom of C^aH=C^bH-CN group of 4-methoxy cinnamoinitrile and simultaneous attack of CH=CH pi electrons to triple bonded carbon of nitrile imine leads to the formation of 3-aryl-5-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole-4-carbonitriles (92a-i).
Scheme 102: Proposed mechanism for the 1,3-dipolar cycloaddition of nitrile imine with dipolarophile to get the cycloadducts (92a-h).

Mass spectral fragmentation of the cycloadducts:

All the products gave significantly stable molecular ion peaks with a relative abundance ranging from 10-38%. Both the isomeric mixture (91a-h and 92a-h) of new pyrazolines showed similar pattern of fragmentation during the mass spectral analysis. The common fragmentation pattern involves some rearrangement with the removal of simple and smaller molecules (Scheme-103).
3.4.0 Biological Activity:

The reagents required and experimental procedure for *in vitro* antimicrobial and antioxidant properties of synthesized compounds (91a-h) was described in chapter 2 (refer page 63-77).

3.4.1 Evaluation of antibacterial activity by paper disc method:

The representative compounds (91a-h) were tested at the concentration (50 µg/mL) in methanol on the nutrient agar media against Gram-negative bacteria species *Escherichia coli, Salmonella typhimurium*, Gram-positive bacteria species *Bacillus subtilis, Staphylococcus aureus*. The screening tests were performed in triplicate and the results were taken as a mean of three determinations. Minimum inhibitory concentrations (MICs) were determined by broth dilution technique. All the experiments were carried out in triplicate and the results were taken as a mean of three determinations.

**Antibacterial activity of 3-aryl-4-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole-5-carbonitriles 91a-h:**

The results of antibacterial activity of the test compounds shows that the compounds 91a-c showed remarkable activity against *E.coli, S.typhimurium* and *B. subtilis* and moderate against *S. aureus*, which is attributed to the presence of fluoro, chloro, bromo substituents at C3-substituted benzene ring. The compounds 91d and 91h showed lesser activity against all the bacterium, this might be expected due to the presence of strong electron withdrawing -CN substituent on the aromatic ring and the 2-furanoyl substituent to the pyrazole nucleus respectively. The compounds 91e-g showed higher activity against *E.coli* and *S.typhimurium*, moderate against *B. subtilis* and weak against *S. aureus*, this was expected to the presence of electron donating –OCH3 groups on the aromatic ring. It was interesting to notice that, with increase in
the number of –OCH₃ groups on the ring; enhanced their activity from 91e to 91g. The results show that the presence of electron donating groups such as –OCH₃, fluoro, chloro and bromo substituents at C₃-substituted benzene ring were better antibacterial agents (Table-7, Figure-11). The results indicate that the compounds 91a-c may be used as control measures against different bacteria. The results of MIC’s determined reveal that some of these test compounds can act as good antibacterial agents at very lower concentrations (Table-7, Figure-12).

**Table-7: Zone of inhibition (X mm) at 50 µg/mL concentrations and MIC’s (Y µg/mL) of the test samples 91a-h tested against bacterial strains.**

<table>
<thead>
<tr>
<th>Compound</th>
<th><em>Escherichia coli</em></th>
<th><em>Salmonella typhimurium</em></th>
<th><em>Bacillus subtilis</em></th>
<th><em>Staphylococcus aureus</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X</td>
<td>Y</td>
<td>X</td>
<td>Y</td>
</tr>
<tr>
<td>91a</td>
<td>30</td>
<td>26</td>
<td>23</td>
<td>28</td>
</tr>
<tr>
<td>91b</td>
<td>33</td>
<td>25</td>
<td>25</td>
<td>27</td>
</tr>
<tr>
<td>91c</td>
<td>27</td>
<td>26</td>
<td>24</td>
<td>29</td>
</tr>
<tr>
<td>91d</td>
<td>18</td>
<td>23</td>
<td>16</td>
<td>38</td>
</tr>
<tr>
<td>91e</td>
<td>23</td>
<td>25</td>
<td>22</td>
<td>30</td>
</tr>
<tr>
<td>91f</td>
<td>24</td>
<td>28</td>
<td>23</td>
<td>33</td>
</tr>
<tr>
<td>91g</td>
<td>26</td>
<td>30</td>
<td>25</td>
<td>31</td>
</tr>
<tr>
<td>91h</td>
<td>20</td>
<td>34</td>
<td>18</td>
<td>36</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>38</td>
<td>16</td>
<td>34</td>
<td>20</td>
</tr>
</tbody>
</table>

Results are expressed as mean of three determinations (n=3); Streptomycin* (50 µg per disc) was used as standard drug.
3.4.2 Evaluation of antifungal activity by paper disc method:

The test compounds (91a-h) were evaluated for their antifungal activity against the fungi species *Aspergillus niger, Aspergillus flavus, C. albicans, Fusarium oxysporium* strains at a concentration (25 µg/mL) in DMF in the potato dextrose agar media. The screening tests were performed in triplicate and the results were taken as a mean of three determinations. Minimum inhibitory concentrations (MICs) were determined by broth dilution technique. All the experiments were carried out in triplicate and the results were taken as a mean of three determinations. 

**Antifungal activity of 3-aryl-4-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole-5-carbonitriles 91a-h:**

The results of antifungal activity of the compounds show that all possess promising antifungal activity against *A. niger* and *A. flavus*; moderate or weak activity against *C. albicans* and *F. oxysporium*. The compound 91d exhibited very weak
inhibition against all the organisms tested, it might be expected due to the presence of electron with drawing –CN group on the aromatic ring. From the results of the study, it was observed that the presence of halogen substituents and electron donating substituents enhances the activity against many fungi organisms (Table-8, Figure-13). The results of MIC’s determined reveal that some of these test compounds can act as good antifungal agents at very lower concentrations (Table-8, Figure-14).

**Table-8: Zone of Inhibition (diameter) (X mm) at 25 µg/mL concentrations and MICs (Y µg/mL) of the compounds 91a-h tested against fungal strains.**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Aspergillus niger</th>
<th>Aspergillus flavus</th>
<th>Candida albicans</th>
<th>Fusarium oxysporium</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>Y</td>
<td>X</td>
<td>Y</td>
<td>X</td>
</tr>
<tr>
<td>91a</td>
<td>24</td>
<td>23</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>91b</td>
<td>25</td>
<td>23</td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td>91c</td>
<td>21</td>
<td>30</td>
<td>19</td>
<td>32</td>
</tr>
<tr>
<td>91d</td>
<td>10</td>
<td>36</td>
<td>10</td>
<td>34</td>
</tr>
<tr>
<td>91e</td>
<td>20</td>
<td>23</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>91f</td>
<td>21</td>
<td>26</td>
<td>21</td>
<td>26</td>
</tr>
<tr>
<td>91g</td>
<td>22</td>
<td>24</td>
<td>20</td>
<td>27</td>
</tr>
<tr>
<td>91h</td>
<td>26</td>
<td>23</td>
<td>27</td>
<td>25</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>31</td>
<td>18</td>
<td>32</td>
<td>20</td>
</tr>
</tbody>
</table>

Results are expressed as mean of three determinations (n=3);
Griseofulvin* (25 µg per disc) was used as standard drug.
3.4.3 Evaluation of antioxidant activity by DPPH radical scavenger method:

Samples dissolved in methanol (0-50 µg/mL for samples (91a-h); 0-5 µg/mL for BHT) in 200 µL aliquot was mixed with 100 mM tris-HCl buffer (800 µL, pH 7.4) and then added 1 mL of 500 µM DPPH in ethanol (final concentration of 250 µM). The mixture was shaken vigorously and left to stand for 20 min at room temperature in the dark. The absorbance of the resulting solution was measured spectrophotometrically at 517 nm. The results of all experiments performed were expressed as mean of the three determinations.

Antioxidant activity of 3-aryl-4-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole-5-carbonitriles 91a-h:

The free radical scavenging ability of samples 91a-h was evaluated by DPPH scavenging model system using the equation-1. All the synthesized compounds showed promising free radical scavenging ability but of lesser activity when compared with the standard antioxidant. At the initial concentrations of (10-20 µg/mL), no much significant variations in the free radical scavenging ability of samples 91a-h was observed. However, when the concentration was increased (30-50 µg/mL) all showed a promising radical scavenging ability. The compounds 91a-d showed radical scavenging ability up to 60%; the compounds 91e, 91f, 91h showed up to 45% and the compound 91g showed 32% with reference to the standard
antioxidant. From the results, it was observed that, the presence of strong electron withdrawing substituents enhanced the antioxidant property of the test compounds; the electron donating substituents retards the antioxidant property of the test compounds (Table-9, Figure-15). The IC$_{50}$ values in µg/mL were determined for the antioxidant activity of the test samples measured at different concentrations (Figure-16). The experimental results indicate the potential electron donating ability of synthesized compounds.

### Table-9: Percentage of Radical Scavenging activity of samples 91a-h relative to the standard antioxidant BHT.

<table>
<thead>
<tr>
<th>Samples</th>
<th>Concentration (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td>91a</td>
<td>10.46</td>
</tr>
<tr>
<td>91b</td>
<td>13.12</td>
</tr>
<tr>
<td>91c</td>
<td>11.22</td>
</tr>
<tr>
<td>91d</td>
<td>14.76</td>
</tr>
<tr>
<td>91e</td>
<td>11.16</td>
</tr>
<tr>
<td>91f</td>
<td>09.32</td>
</tr>
<tr>
<td>91g</td>
<td>8.12</td>
</tr>
<tr>
<td>91h</td>
<td>12.12</td>
</tr>
</tbody>
</table>

*Values are expressed as mean of the three determinations (n=3)
3.4.4 Measurement of reducing power:

The reducing power ability of samples 91a-h was determined by a known method as in chapter-2. All the experiments were carried out in triplicates (n = 3) and the results are expressed as mean of the three determinations.

Reducing power ability of 3-aryl-4-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole-5-carbonitriles 91a-h:

The samples 91a-h is evaluated for their reducing power ability to reduce ferric chloride and potassium ferricyanide complex. It was observed that at the initial concentrations of (10-20 µg/mL), there was no significant variations in the activity.
However, when the concentration was increased (30-50 µg/mL), all showed remarkable reducing power. The compounds 91a-d showed higher reducing power and 91e-h showed moderate reducing power. The increased absorbance at 700 nm indicated the presence of reducing power of the synthesized compounds (Table-10, Figure-17).

**Table-10: Reducing power ability (absorbance) of samples 91a-h measured at 700 nm relative to the standard oxidant BHT.**

<table>
<thead>
<tr>
<th>Sample</th>
<th>Concentration (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td>91a</td>
<td>0.266</td>
</tr>
<tr>
<td>91b</td>
<td>0.301</td>
</tr>
<tr>
<td>91c</td>
<td>0.322</td>
</tr>
<tr>
<td>91d</td>
<td>0.336</td>
</tr>
<tr>
<td>91e</td>
<td>0.228</td>
</tr>
<tr>
<td>91f</td>
<td>0.226</td>
</tr>
<tr>
<td>91g</td>
<td>0.200</td>
</tr>
<tr>
<td>91h</td>
<td>0.253</td>
</tr>
</tbody>
</table>

*Values are expressed as mean of the three determinations (n=3)*
3.5.0 Experimental section:

The chemicals/reagents used were purchased from sigma-aldrich chemicals (India) and Merck Chemicals (India). IR spectra were recorded on a Nujol mull on Shimadzu 8300 spectrometer. The $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker supercon 400 MHz spectrophotometer using CDCl$_3$ as solvent and TMS as an internal standard. The Chemical shifts are expressed in δ ppm. Mass spectra were obtained on Shimadzu LCMS-2010A spectrophotometer (chemical ionization) and the important fragments are given with the relative intensities in the bracket. Elemental analysis was obtained on a Thermo Finnigan Flash EA 1112 CHN analyser. Thin layer chromatography (TLC) was performed on a pre-coated Silica Gel sheets (HF 254, sd-fine) using benzene:ethyl acetate (7:2) eluent and visualization of the spots was done in iodine vapour and UV light. Chromatographic separations were carried out on silica gel (70-230 mesh, Merck) column using hexane:ethyl acetate (8:1) as eluent.

3.5.1 General procedure for the preparation of hydrazones:

Solution of colorless phenyl hydrazine hydrochloride (0.5g) and crystallized sodium acetate (0.8g) in distilled water (10 mL) was mixed with solution of aldehyde (0.5g) in ethyl alcohol. The mixture was then warmed for 5-10 minutes and cooled in ice water. The crystals formed were filtered, washed with a little cold water and recrystallized from ethanol.
### Table-11: Physical constants (Melting points) of hydrazone intermediates

<table>
<thead>
<tr>
<th>Aromatic aldehyde phenyl hydrazone</th>
<th>Melting point</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obs.$^\circ$C</td>
</tr>
<tr>
<td>4-Fluorobenzaldehyde phenylhydrazone</td>
<td>84-86$^\circ$C</td>
</tr>
<tr>
<td>4-Chlorobenzaldehyde phenylhydrazone</td>
<td>121-123$^\circ$C</td>
</tr>
<tr>
<td>4-Bromobenzaldehyde phenylhydrazone</td>
<td>109-111$^\circ$C</td>
</tr>
<tr>
<td>4-Cyanobenzaldehyde phenylhydrazone</td>
<td>170-172$^\circ$C</td>
</tr>
<tr>
<td>Benzaldehyde phenylhydrazone</td>
<td>151-153$^\circ$C</td>
</tr>
<tr>
<td>4-Methoxybenzaldehyde phenylhydrazone</td>
<td>119-121$^\circ$C</td>
</tr>
<tr>
<td>3,4-Dimethoxybenzaldehyde phenylhydrazone</td>
<td>94-96$^\circ$C</td>
</tr>
<tr>
<td>Furfural phenylhydrazone</td>
<td>94-96$^\circ$C</td>
</tr>
</tbody>
</table>

#### 3.5.2 General procedure for the synthesis of pyrazolines:

Substituted aromatic aldehyde phenyl hydrazones prepared by the reaction of aromatic aldehydes and phenyl hydrazine hydrochloride were subjected to 1,3-dipolar cycloaddition reaction with an alkene to get five membered pyrazolines. Aromatic aldehyde hydrazones on catalytic dehydrogenation with different oxidants gives the corresponding nitrile imine, which acts as a 1,3-dipole in cycloaddition reaction.

#### 3.5.2.1 General procedure for the synthesis of pyrazolines using chloramine-T:

A mixture of aromatic aldehyde phenylhydrazone (90) (4.0 mmol), 3-(4-methoxyphenyl) acrylonitrile (60) (4.0 mmol) and chloramine-T trihydrate (4.0 mmol) in ethanol was refluxed on water bath for 3 h. The progress of the reaction was monitored by TLC. After the completion of the reaction, the sodium chloride formed in the reaction mixture was filtered off and washed with ethanol (1 X 15 mL) and then the combined filtrate and washings were evaporated in vacuum. The residual part was extracted into ether (25 mL), washed successively with water (2 X 15 mL),
10% sodium hydroxide (2 \times 15 \text{ mL}) and saturated brine solution (1 \times 10 \text{ mL}). The organic layer was dried over anhydrous sodium sulphate. Evaporation of the solvent yielded the light brown oil, which gave one major spot corresponding to the product 4-(4-methoxyphenyl)-1,3-diphenyl-4,5-dihydro-1H-pyrazole-5-carbonitrile (91) and two minor spots corresponding to the un-reacted precursors in TLC. The product was purified by column chromatography using hexane:ethyl acetate (8:1 v/v) as eluent. The products were obtained in relatively high yields. The same procedure was used in all cases.

3.6.0 Experimental results of the cycloadducts (91a-h):

3-(4-Fluorophenyl)-4-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole-5-carbonitrile, 91a:

Obtained from 3-(4-methoxyphenyl) acrylonitrile (60) (0.64g, 4.0 mmol), 4-fluorobenzaldehyde phenylhydrazone (90a) (0.86g, 4.0mmol) and chloramine-T trihydrate (1.13g, 4.0mmol) as a light brown oil in 62% yield. IR (nujol): 1675 (C=N str.), 2235 (C≡N str.) cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)): 3.846 (s, 3H, OCH\(_3\)), 5.279 (d, 1H, C-4-H), 5.704 (d, 1H, C-5-H), 6.894-6.950 (m, 5H, Ar-H), 7.025 (dd, 2H, Ar-H), 7.299 (dd, 2H, Ar-H), 7.386 (dd, 2H, Ar-H), 7.785 (dd, 2H, Ar-H). \(^1\)C NMR (CDCl\(_3\)): 41.56 (1C, 4-C), 51.24 (1C, 5-C), 55.65 (1C, OCH\(_3\)), 114.16 (2C, Ar-C), 115.42 (2C, Ar-C), 116.32 (1C, C-N), 116.64 (2C, Ar-C), 120.60 (1C, Ar-C), 128.56 (2C, Ar-C), 129.28 (2C, Ar-C), 129.42 (2C, Ar-C), 129.96 (1C, Ar-C), 132.75 (1C, Ar-C), 134.09 (2C, Ar-C), 143.20 (1C, 3-C), 143.66 (1C, Ar-C), 156.36 (1C, Ar-C), 164.38 (1C, Ar-C). MS (relative abundance) m/z: 372 (MH\(^+\), 100), 346 (11), 278 (18), 244 (06), 214 (16), 195 (14), 137(08). Anal. Cacld. for C\(_{23}\)H\(_{18}\)FN\(_3\)O: C, 74.38, H, 4.88, N, 11.31%; Found: C, 74.56, H, 4.79, N, 11.21%.
3-(4-Chlorophenyl)-4-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole-5-carbonitrile, 91b:

Obtained from 3-(4-methoxyphenyl) acrylonitrile (60) (0.64g, 4.0 mmol) and 4-chlorobenzaldehyde phenylhydrazone (90b) (0.92g, 4.0mmol) as a light brown oil in 70% yield. IR (nujol): 1660 (C=N str.) , 2233 (C≡N str.) cm⁻¹. ¹H NMR (CDCl₃): 3.838 (s, 3H, OCH₃), 5.221 (d, 1H, C₄-H), 5.674 (d, 1H, C₅-H), 6.904-6.952 (m, 5H, Ar”-H), 7.050 (dd, 2H, Ar-H), 7.300 (dd, 2H, Ar’-H), 7.398 (dd, 2H, Ar-H), 7.796 (dd, 2H, Ar’-H). ¹³C NMR (CDCl₃): 41.62 (1C, 4-Ć), 51.34 (1C, 5-Ć), 55.55 (1C, OĆH₃), 114.22 (2C, Ar-Ć), 116.12 (2C, Ar-Ć), 116.30 (1C, ĆN), 120.68 (1C, Ar-Ć), 128.12 (2C, Ar-Ć), 128.44 (2C, Ar-Ć), 128.80 (2C, Ar-Ć), 129.51 (2C, Ar-Ć), 131.71 (1C, Ar-Ć), 132.54 (1C, Ar-Ć), 136.80 (1C, Ar-Ć), 142.96 (1C, 3-Ć), 143.78 (1C, Ar-Ć), 157.06 (1C, Ar-Ć). MS (relative abundance) m/z: 389 (M⁺, 37Cl, 33), 387.11 (M⁺, 35Cl, 100), 361 (24), 294 (24), 260 (16), 230 (15), 211 (22), 153 (29). Anal. Cacld. for C₂₃H₁₈ClN₃O, C, 71.22, H, 4.68, N, 10.83%; Found: C, 71.20, H, 4.61, N, 10.74%.

3-(4-Bromophenyl)-4-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole-5-carbonitrile, 91c:

Obtained from 3-(4-methoxyphenyl) acrylonitrile (60) (0.64g, 4.0 mmol) and 4-bromobenzaldehyde phenylhydrazone (90c) (1.10g, 4.0mmol) as a light brown oil in 60% yield. IR (nujol): 1670 (C=N str.) , 2240 (C≡N str.) cm⁻¹. ¹H NMR (CDCl₃): 3.842 (s, 3H, OCH₃), 5.218 (d, 1H, C₄-H), 5.644 (d, 1H, C₅-H), 6.920-6.945 (m, 5H, Ar”-H), 7.010 (dd, 2H, Ar-H), 7.308 (dd, 2H, Ar’-H), 7.412 (dd, 2H, Ar-H), 7.722 (dd, 2H, Ar’-H). ¹³C NMR (CDCl₃): 41.68 (1C, 4-Ć), 51.54 (1C, 5-Ć), 55.50 (1C, OĆH₃), 114.26 (2C, Ar-Ć), 116.12 (2C, Ar-Ć), 116.30 (1C, ĆN), 120.64 (1C, Ar-Ć), 125.24 (1C, Ar-Ć), 128.40 (2C, Ar-Ć), 128.78 (2C, Ar-Ć), 129.46 (2C, Ar-Ć), 131.71 (1C, Ar-Ć), 132.63 (1C, Ar-Ć), 133.02 (1C, Ar-Ć), 142.66 (1C, 3-Ć), 143.70 (1C, Ar-Ć), 157.06 (1C, Ar-Ć). MS (relative abundance) m/z: 389 (M⁺, 37Cl, 33), 387.11 (M⁺, 35Cl, 100), 361 (24), 294 (24), 260 (16), 230 (15), 211 (22), 153 (29). Anal. Cacld. for C₂₃H₁₆ClN₃O, C, 71.22, H, 4.68, N, 10.83%; Found: C, 71.20, H, 4.61, N, 10.74%.
3-(4-Cyanophenyl)-4-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole-5-carbonitrile, 91d:

Obtained from 3-(4-methoxyphenyl) acrylonitrile (60) (0.64g, 4.0 mmol) and 4-cyanobenzaldehyde phenylhydrazone (90d) (0.89g, 4.0mmol) as a light brown oil in 64% yield. IR (nujol): 1675 (C=N str.), 2230 (C≡N str.) cm⁻¹. ¹H NMR (CDCl₃): 3.832 (s, 3H, OCH₃), 5.186 (d, 1H, C⁴-H), 5.626 (d, 1H, C₅-H), 6.090 (dd, 2H, Ar-H), 6.928-7.266 (m, 5H, Ar”-H), 7.300 (dd, 2H, Ar-H), 7.712 (dd, 2H, Ar’-H), 8.010 (dd, 2H, Ar’-H). ¹³C NMR (CDCl₃): 41.76 (1C, 4-C), 52.32 (1C, 5-C), 55.96 (1C, OCH₃), 114.52 (2C, Ar-C), 114.84 (1C, Ar-C), 116.22 (2C, Ar-C), 116.58 (1C, CN), 118.12 (1C, CN), 120.26 (1C, Ar-C), 128.56 (2C, Ar-C), 129.46 (2C, Ar-C), 129.74 (2C, Ar-C), 132.66 (2C, Ar-C), 132.94 (1C, Ar-C), 138.12 (1C, Ar-C), 142.98 (1C, 3-C), 143.82 (1C, Ar-C), 157.08 (1C, Ar-C). MS (relative abundance) m/z: 379 (MH⁺, 100), 353 (20), 285 (14), 251 (26), 221 (19), 202 (32), 144 (30). Anal. Caclld. for C₂₃H₁₈BrN₃O: C, 63.90, H, 4.20, N, 9.72%; Found: C, 63.84, H, 4.12, N, 9.64%.

4-(4-Methoxyphenyl)-1,3-diphenyl-4,5-dihydro-1H-pyrazole-5-carbonitrile, 91e:

Obtained from 3-(4-methoxyphenyl) acrylonitrile (60) (0.64g, 4.0 mmol) and benzaldehyde phenylhydrazone (90e) (0.78g, 4.0mmol) as light brown oil in 58% yield. IR (nujol): 1672 (C=N str.) , 2234 (C≡N str.) cm⁻¹. ¹H NMR (CDCl₃): 3.840 (s, 3H, OCH₃), 5.196 (d, 1H, C⁴-H), 5.638 (d, 1H, C₅-H), 6.930 (dd, 2H, Ar-H), 6.998-7.544 (m, 10H, Ar’, Ar”-H), 7.452 (dd, 2H, Ar-H). ¹³C NMR (CDCl₃): 41.88 (1C, 4-C), 51.92 (1C, 5-C), 55.65 (1C, OCH₃), 114.20 (2C, Ar-C), 116.38 (2C, Ar-C), 116.80 (1C, CN), 120.42 (1C, Ar-C), 128.14 (2C, Ar-C), 128.56 (2C, Ar-C), 128.98 (2C, Ar-C), 129.64 (2C, Ar-C), 131.04 (1C, Ar-C), 131.32 (1C, Ar-C), 132.40 (1C,
Ar-C), 143.48 (1C, Ar-C), 144.16 (1C, 3-C), 157.36 (1C, Ar-C). MS (relative abundance) m/z: 354 (MH⁺, 100), 328 (24), 260 (24), 225 (16), 195 (21), 177 (32), 118 (24). Anal. Calcd. for C₂₃H₁₉N₃O: C, 78.16, H, 5.42, N, 11.89%; Found: C, 78.07, H, 5.34, N, 11.81%.

3,4-Bis(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole-5-carbonitrile, 91f:
Obtained from 3-(4-methoxyphenyl) acrylonitrile (60) (0.64g, 4.0 mmol) and 4-methoxybenzaldehyde phenylhydrazone (90f) (0.90g, 4.0mmol) as a light brown oil in 65% yield. IR (nujol): 1660 (C=N str.), 2235 (C≡N str.) cm⁻¹. ¹H NMR (CDCl₃): 3.854 (s, 6H, OCH₃), 5.166 (d, 1H, C₄-H), 5.526 (d, 1H, C₅-H), 6.890 (dd, 2H, Ar-H), 6.192-7.426 (m, 5H, Ar”-H), 7.010 (dd, 2H, Ar'-H), 7.542 (dd, 2H, Ar-H), 7.992 (dd, 2H, Ar'-H). ¹³C NMR (CDCl₃): 41.68 (1C, 4-C), 51.54 (1C, 5-C), 55.50 (2C, OCH₃), 114.26 (2C, Ar-C), 116.50 (2C, Ar-C), 116.64 (1C, C=N), 120.64 (1C, Ar-C), 125.24 (1C, Ar-C), 128.40 (2C, Ar-C), 128.78 (2C, Ar-C), 129.46 (2C, Ar-C), 131.52 (2C, Ar-C), 132.63 (1C, Ar-C), 133.02 (1C, Ar-C), 142.66 (1C, 3-C), 143.70 (1C, Ar-C), 156.70 (1C, Ar-C). MS (relative abundance) m/z: 384 (MH⁺, 100), 358 (20), 290 (34), 256 (20), 226 (18), 207 (28), 149 (20). Anal. Calcd. for C₂₄H₂₁N₃O₂: C, 75.18, H, 5.52, N, 10.96%; Found: C, 75.11, H, 5.50, N, 10.91%.

3-(3,4-Dimethoxyphenyl)-4-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole-5-carbonitrile, 91g:
Obtained from 3-(4-methoxyphenyl) acrylonitrile (60) (0.64g, 4.0 mmol) and 3,4-dimethoxybenzaldehyde phenylhydrazone (90g) (1.10g, 4.0mmol) as a light brown oil in 61% yield. IR (nujol): 1655 (C=N str.), 2238 (C≡N str.) cm⁻¹. ¹H NMR (CDCl₃): 3.848 (s, 9H, OCH₃), 5.102 (d, 1H, C₄-H), 5.485 (d, 1H, C₅-H), 6.882 (dd, 2H, Ar-H), 7.524 (dd, 2H, Ar-H), 6.998-7.510 (m, 8H, Ar’, Ar”-H). ¹³C NMR (CDCl₃): 41.68 (1C, 4-C), 51.54 (1C, 5-C), 55.50 (2C, OCH₃),
114.26 (2C, Ar-C), 116.50 (2C, Ar-C), 116.64 (1C, CN), 120.64 (1C, Ar-C), 125.24 (1C, Ar-C), 128.40 (2C, Ar-C), 128.78 (2C, Ar-C), 129.46 (2C, Ar-C), 131.52 (2C, Ar-C), 132.63 (1C, Ar-C), 133.02 (1C, Ar-C), 142.66 (1C, 3-C), 143.70 (1C, Ar-C), 156.70 (1C, Ar-C). Anal. Cacl.d. for C_{25}H_{23}N_{3}O_{3}: C, 72.62, H, 5.61, N, 10.16%; Found: C, 72.56, H, 5.54, N, 10.11%.

3-(Furan-2-yl)-4-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole-5-carbonitrile, 91h:

Obtained from 3-(4-methoxyphenyl) acrylonitrile (60) (0.64g, 4.0 mmol) and 2-furaldehyde phenylhydrazone (90h) (0.74g, 4.0mmol) as a light brown oil in 67% yield. IR (nujol): 1670 (C=N str.), 2240 (C≡N str.) cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)): 3.852 (s, 3H, OCH\(_3\)), 5.110 (d, 1H, C\(_4\)-H), 5.502 (d, 1H, C\(_5\)-H), 6.513-6.728 (d, 2H, Ar'-H), 6.898 (dd, 2H, Ar-H), 7.080-7.344 (m, 5H, Ar”-H), 7.326 (dd, 2H, Ar-H), 7.752 (d, 1H, Ar’-H). Anal. Calcd. for C\(_{21}\)H\(_{17}\)N\(_3\)O\(_2\) (m/z 343.13): C, 73.45, H, 4.99, N, 12.24%; Found: C, 73.36, H, 4.93, N, 12.16%.

Spectral and elemental analysis data of the few isomeric compounds 92 are given below.

3-(4-Fluorophenyl)-5-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole-4-carbonitrile, 92a:

IR (Nujol): 1640 (C=N str.), 2230 (C≡N str.) cm\(^{-1}\). \(^1\)H NMR (CDCl\(_3\)): 3.850 (s, 3H, OCH\(_3\)), 5.401 (d, 1H, C\(_4\)-H), 5.790 (d, 1H, C\(_5\)-H), 6.802-6.941 (m, 5H, Ar”-H), 7.033 (dd, 2H, Ar-H), 7.271 (dd, 2H, Ar’-H), 7.397 (dd, 2H, Ar-H), 7.796 (dd, 2H, Ar’-H). \(^13\)C NMR (CDCl\(_3\)): 40.65 (1C, 4-C), 52.30 (1C, 5-C), 55.50 (1C, OCH\(_3\)), 114.20 (2C, Ar-C), 115.63 (2C, Ar-C), 116.0 (1C, CN), 117.53 (2C, Ar-C), 121.24 (1C, Ar-C), 127.36 (2C, Ar-C), 128.19 (2C, Ar-C), 129.30 (2C, Ar-C), 130.81 (1C, Ar-C), 131.63 (1C, Ar-C), 143.51 (1C, 3-C), 144.51 (1C, Ar-C), 154.36 (1C, Ar-C), 163.90 (1C, Ar-C), 179.30 (1C, Ar-C).
(1C, Ar-C). MS (relative abundance) m/z: 372 (MH⁺, 100), 346 (11), 278 (18), 244 (06), 214 (16), 195 (14), 137(08). Anal. Caclld. for C23H18FN3O: C, 74.38, H, 4.88, N, 11.31%; Found: C, 74.56, H, 4.79, N, 11.21%.

3-(4-Chlorophenyl)-5-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole-4-carbonitrile, 92b:

IR (Nujol): 1650 (C=N str.) , 2245 (C≡N str.) cm⁻¹. ¹H NMR (CDCl₃): 3.880 (s, 3H, OCH₃), 5.379 (d, 1H, C₄-H), 5.609 (d, 1H, C₅-H), 6.814-6.922 (m, 5H, Ar”-H), 7.150 (dd, 2H, Ar-H), 7.288 (dd, 2H, Ar’-H), 7.391 (dd, 2H, Ar-H), 7.793 (dd, 2H, Ar’-H). ¹³C NMR (CDCl₃): 41.62 (1C, 4-C), 52.64 (1C, 5-C), 55.80 (1C, OCH₃), 115.27 (2C, Ar-C), 116.20 (2C, Ar-C), 116.40 (1C, C=N), 120.88 (1C, Ar-C), 128.73 (2C, Ar-C), 128.84 (2C, Ar-C), 129.20 (2C, Ar-C), 129.81 (2C, Ar-C), 131.62 (1C, Ar-C), 132.63 (1C, Ar-C), 139.80 (1C, Ar-C), 143.91 (1C, 3-C), 145.98 (1C, Ar-C), 159.28 (1C, Ar-C). MS (relative abundance) m/z: 389 (M⁺, 37Cl, 33), 387.11 (M⁺, 35Cl, 100), 361 (24), 294 (24), 260 (16), 230 (15), 211 (22), 153 (29). Anal. Caclld. for C23H18ClN3O, C, 71.22, H, 4.68, N, 10.83%; Found: C, 71.20, H, 4.61, N, 10.74%.

3,5-Bis(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazole-4-carbonitrile, 92f:

IR (Nujol): 1665 (C=N str.) , 2250 (C≡N str.) cm⁻¹. ¹H NMR (CDCl₃): 3.851 (s, 6H, OCH₃), 5.280 (d, 1H, C₄-H), 5.558 (d, 1H, C₅-H), 6.810 (dd, 2H, Ar-H), 6.991-7.447 (m, 5H, Ar”-H), 7.224 (dd, 2H, Ar’-H), 7.631 (dd, 2H, Ar-H), 7.802 (dd, 2H, Ar’-H). ¹³C NMR (CDCl₃): 42.73 (1C, 4-C), 53.10 (1C, 5-C), 55.41 (2C, OCH₃), 114.16 (2C, Ar-C), 116.22 (2C, Ar-C), 118.30 (1C, C=N), 122.53 (1C, Ar-C), 125.26 (1C, Ar-C), 128.37 (2C, Ar-C), 128.91 (2C, Ar-C), 129.54 (2C, Ar-C), 131.66 (2C, Ar-C), 132.19 (1C, Ar-C), 133.21 (1C, Ar-C), 144.20 (1C, 3-C), 145.69(1C, Ar-C), 159.28 (1C, Ar-C). MS (relative abundance) m/z: 384 (MH⁺, 100), 358 (20), 290 (34), 256 (20), 226
(18), 207 (28), 149 (20). Anal. Cacl.d. for C$_{24}$H$_{21}$N$_3$O$_2$: C, 75.18, H, 5.52, N, 10.96%;
Found: C, 75.11, H, 5.50, N, 10.91%.

3.7.0 Conclusion:

A facile and convenient route of synthesis for substituted pyrazolines based on
the reactions of aromatic aldehyde phenyl hydrazones with 4-methoxy cinnamionitrile
in the presence of chloramine-T has been developed. The present method is concise
and efficient.