CHAPTER – IV
Chemistry of Pyrazolines
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CHEMISTRY OF PYRAZOLINES

4.1.0 Introduction:

α,β-Unsaturated ketones constitute an important class of naturally occurring flavonoid compounds that exhibit a wide spectrum of biological activities such as anticancer, anti-inflammatory, antiviral and antibacterial activities etc. These are well-known intermediates for the synthesis of a large number of bioactive molecules, such as pyrazolines, pyrimidines, isoxazolines and thiazolines.

Amongst nitrogen containing five membered heterocycles, pyrazolines have proved to be the most useful framework for biological activities. The dihydro pyrazoles are called pyrazolines. Pyrazolines have attracted attention of medicinal chemists for both with regard to heterocyclic chemistry and the pharmacological activities associated with them and various methods have been carried out for their synthesis. Considerable attention has been focused on pyrazolines and substituted pyrazolines due to their interesting biological activities. The pharmaceutical importance of these compounds lies in the fact that they can be effectively utilized as antibacterial, antifungal, antiviral, antiparasitic, antitubercular, herbicidal, fungicidal, analgesic, antioxidant, antipyretic, insecticidal, anticancer, antitumor, anti-diabetic, anticonvulsant, antidepressant and anti-inflammatory agents. Moreover, many selectively fluoro-substituted pyrazolines show promising agrochemical properties.

4.1.1 Synthesis of functionalized pyrazolines using various synthetic approaches:

Pyrazolines were synthesized from a series of substituted chalcones by condensation with phenylhydrazine under phase transfer catalysis technique (PTC) employing tributylbenzylammonium (TBBAB) as a catalyst in 50% aqueous sodium hydroxide in benzene (Scheme-104).
1,3,5-Trisubstituted 2-pyrazolines (Scheme-105)\textsuperscript{204} were synthesized through cyclization of phenylhydrazine with α,β-unsaturated ketones using methanoic acid (formic acid) as catalyst under thermal condition.

Deshmukh et al.\textsuperscript{205} reported the synthesis of chlorosubstituted 3,5-diaryl-1-substituted pyrazolines by treatment of 1,3-aryl-prop-2-ene-1-ones with thiosemicarbazide/isonicotinicacidhydrazide/semicarbazide hydrochloride in ethanol/DMF solvent. A simple, general one-pot synthesis of 3,5-disubstituted pyrazolines and pyrazoles from different type of electron poor olefins/alkyne including Baylis-Hillman adducts and ethyl diazoacetate (EDA) under mild conditions in good to excellent yields, in high regioselective manner in the presence of Indium chloride and/or 1,4-diazabicyclo[2,2,2]octane (DABCO) was reported (Scheme-106).\textsuperscript{206} Amongst the two DABCO and InCl\textsubscript{3}, the reaction was more facile with DABCO to afford products in good yields and in shorter time.
Ragini et al\textsuperscript{207} reported an efficient and convenient procedure for the synthesis of 2-pyrazolines by the cyclization of chalcones and phenylhydrazine in glacial acetic acid under ultrasonic irradiation and screened for their antimicrobial activity (Scheme-107). The electron donating group (CH$_3$) increased the reaction rate as well as the yield whereas in the halogen series, as the electro negativity of halogen atom increased, the time required for the formation of pyrazoline increased. The main advantage of this method is milder reaction conditions, higher yields and shorter reaction time.

![Scheme-107](image)

Razieh et al\textsuperscript{208} synthesized a series of novel 1,3,5-triaryl-2-pyrazoline using H$_3$PW$_{12}$O$_{40}$, as an eco-friendly, inexpensive and efficient catalyst. The advantages of this catalytic system is short reaction times, high product yields, non-toxicity of the catalysts, simple and clean work-up of the desired products (Scheme-108).

![Scheme-108](image)

Shipra et al\textsuperscript{209} synthesized new pyrazolines by microwave irradiation, ultrasound waves and simple conventional methods and compared for reaction time, yield of the compound and avoidance of catalyst. It is observed that using microwave and ultrasonic waves, the reaction time is reduced considerably however percentage
yields increased markedly. Further, the amount of catalyst required in these techniques is very less in comparison to conventional method. Thus, microwave and ultrasonic proved to be better technique than conventional method.

A series of novel 2-pyrazolines were synthesized by condensation of substituted chalcones with hydrazine hydrate/phenylhydrazine in triethanolamine within 15-20min. and screened for their antibacterial activity (Scheme-109).\(^{210}\)

An environmentally benign easy, convenient solvent-free approach for the synthesis of pyrazolines using microwave assisted solid phase technique by condensation of 2,4-dichloro-5-fluoro chalcones with thiosemicarbazide over potassium carbonate was developed.\(^{211}\) The work-up is simple and involves treatment with ice-cold water. A considerable increase in the reaction rate has been observed, with better yields (Scheme-110).

2-Pyrazolines were synthesized by the reaction of chalcone derivatives with hydrazine hydrate in the presence of formic acid (Scheme-111).\(^{212}\)
4.1.2 Reactions of pyrazolines:

A simple, green and an efficient one-pot procedure was developed for the aromatization of 1,3,5-trisubstituted-2-pyrazolines (93) to the corresponding pyrazoles (94) by in situ generation of iodine (I+) from H$_2$O$_2$/CH$_3$COOH or silica sulphuric acid or oxalic acid /KI or NaI system under thermal condition. The advantages of the method are mild and simple experiment, easy isolation procedure, green aspects avoiding hazardous solvents, use of eco-friendly and less toxic reagents, shorter reaction times and high yields of the products (Scheme-112).

Mild oxidation of the pyrazoline derivatives (95) with bromine water led to the formation of the corresponding pyrazoles (96). Condensation of the pyrazolines (95) with the appropriate isocyanate and isothiocyanate in dry acetone gave the corresponding benzenesulfonylurea (97) and thiourea (98) derivatives respectively (Scheme-113).
Reaction of 3-methyl-5-oxo-1-phenyl-Δ²-pyrazoline-4-thiocarbohydrazide (99) with phenyl isothiocyanate in absolute ethanol afforded N¹-(4,5-dihydro-3-methyl-5-oxo-1-phenylpyrazol-4-yl) thiocarbonyl-N⁴-phenylthiosemicarbazide (100). Hydrolysis of (100) with 10% sodium hydroxide solution followed by acidification with dilute hydrochloric acid gave 4-(4,5-dihydro-1-phenyl-5-thioxo-1,3,4-triazol-2-yl)-3-methyl-1-phenyl-Δ²-pyrazolin-5-one (101). Treatment of (99) with sodium nitrite in acetic acid yielded 4-azidothiocarbonyl-3-methyl-1-phenyl-Δ²-pyrazolin-5-one (102). Compound (99) was also subjected to the reaction with carbon disulphide. It was found that (99) reacted with CS₂ in KOH to give 4-(4,5-dihydro-5-thioxo-1,3,4-thiadiazol-2-yl) - 3-methyl-1-phenyl-Δ²-pyrazolin-5-one (103). Compound (103) was reacted with hydrazine hydrate to give 4-(1-amino-4,5-dihydro-5-thioxo-1,3,4-triazol-2-yl)-3-methyl-1-phenyl-Δ²-pyrazolin-5-one (104) (Scheme-114).

4.1.3 Biological activity of substituted pyrazolines:

Anees et al\textsuperscript{216} synthesized some substituted 3,5-diphenyl-2-pyrazoline-1-carboxamide derivatives (105) from appropriate substituted 1,3-diphenylprop-2-en-1-one (chalcone) on reaction with semicarbazide hydrochloride. The final compounds were evaluated for anticonvulsant activity by the maximal electroshock seizure (MES)
method. The neurotoxicity was determined by rotorod toxicity test on male albino mice. All of the tested compounds were found protective against MES-induced seizures at 100-300 mg/kg dose levels.

A new series of acetyl pyrazoline derivatives (106) are reported by conventional method in excellent yields and in less reaction time using ethanol via cyclization reaction of chalcones, hydrazine hydrate and few drops of glacial acetic acid. These newly synthesized compounds were screened for their antimicrobial activities which reflects moderate to good activity against different strains of bacteria and fungi employed. Compounds having pharmacophores such as chloro, bromo, iodo, hydroxyl and methyl groups exhibited best antimicrobial activity.

![Chemical structures](image)

Omenya et al\textsuperscript{218} reported some chalcones (107) and pyrazolines (108) carrying morpholinophenyl moiety as anti-inflammatory agents. All the synthesized compounds were screened for their anti-inflammatory activities against carrageenan-induced rat’s paw edema at 10 mg/kg. The anti-inflammatory properties were compared with that of indomethacin (in a dose of 10 mg/kg) which was used as a reference standard. Report reveals that all chalcone derivatives were found to be more potent than their cyclized pyrazolines. Cyclization of these chalcones into their corresponding pyrazolines showed moderate anti-inflammatory activity. In general, they exhibited less degree of inhibition of edema compared to their parent compounds.
Jyothi et al. synthesized and reported the antimicrobial activity of some novel pyrazolines (109) from chalcones. Chandrashekhar and co-workers synthesized 1,5-disubstituted pyrazoline derivatives (110) bearing p-methoxy-m-chloro phenyl moiety and described their antimicrobial activity. Piperazine-Pyrazoline merged compounds (111) were studied for their antibacterial activity.

Palaska et al. synthesized ten new 3,5-diphenyl-2-pyrazoline derivatives (112) and evaluated their antidepressant activities by the Porsolt behavioral despair test on Swiss-Webster mice. It was found that 4-methoxy and 4-chloro substituents on the phenyl ring at position 3 of the pyrazoline ring increased the antidepressant activity the replacement of these groups by bromo and methyl substituents decreased activity.

Mamolo et al. reported the synthesis of 5-aryl-1-isonicotinoyl-3-(pyridin-2-yl)-4,5-dihydro-1H-pyrazole derivatives (113) and tested for their in vitro antimycobacterial activity. The compounds showed an interesting activity against a strain of *M. tuberculosis* and a human strain of *M. tuberculosis* H4.

Manna et al. synthesized a series of substituted pyrazolines (1-acetyl-3,5-diphenyl-4,5-dihydro-1H-pyrazole) (114) and evaluated for their anticancer activity.
and for their ability to inhibit \(P\)-glycoprotein-mediated multidrug resistance by direct binding to a purified protein domain containing an ATP-binding site and a modulator interacting region.

Wanga and co-workers\textsuperscript{225} synthesized 5-(9-anthryl)-3-(4-nitrophenyl)-1-phenyl-2-pyrazoline (115) and screened for its photoluminescence property. The absorption of anthryl moiety at about 325-400 nm superimposed on the broader absorption of 3-(4-nitrophenyl)-1-phenyl-2-pyrazoline moiety peaked at 420 nm. Photo-induced intramolecular energy transfer from the anthryl to pyrazoline moiety exists simultaneously with the charge transfer from N1 to C3 in the pyrazoline moiety in the excited state and both compete with each other.

Budakoti et al\textsuperscript{226} synthesized a variety of 3-(3-bromophenyl)-5-phenyl-1-(thiazolo \([4,5-b]\) quinoxaline-2-yl)-2-pyrazoline derivatives (116) and screened for their antamoebic activity against HMI: IMSS strain of \textit{E. histolytica} by microdilution method and compared the IC\(_{50}\) values with the standard drug metronidazole. Some of the quinoxaline derivatives showed less IC\(_{50}\) values than metronidazole. All the compounds were found to be non-toxic.
Chimenti et al\textsuperscript{227} synthesized a series of $\text{N}^1$-propanoyl-3,5-diphenyl-4,5-dihydro-$1H$-pyrazole derivatives (117) and assayed as inhibitors of MAO-A and MAO-B isoforms. These showed inhibitory activity with micromolar values and MAO-A selectivity and found to be useful as co-adjuvants in the treatment of Parkinson’s disease and Alzheimer’s disease.

Silver and co-workers\textsuperscript{228} synthesized pyrazoline-type insecticides (118) and examined the mechanism of action of these compounds based on available electrophysiological, pharmacological and toxicological information and found to act at neuronal target sites.

![Chemical structures](image)

4.2.0 Aim of present work:

The present work deals with the synthesis of trisubstituted 4,5-dihydropyrazole derivatives using 4-phenylbut-3-en-2-one as the precursor. A series of compounds (121a–g) were synthesized and evaluated for their antimicrobial activity. The newly synthesized compounds were characterized by $^1$H NMR, $^{13}$C NMR, MS studies, X-ray diffraction and elemental analysis.

A mixture of 4-phenylbut-3-en-2-one (119, 0.001mmol), phenylhydrazine hydrochloride (120a-g, 0.001mmol) and sodium acetate (0.002mmol) in ethyl alcohol was stirred at room temperature for 1 h to get trisubstituted 4,5-dihydropyrazoles (121a-g) in good yield (Scheme-115).
4.3.0 Discussion on the experiments leading to the synthesis of pyrazolines:

The intermediate phenylhydrazones could very rarely be isolated with 4-phenylbut-3-en-2-one. Michael addition (1,4) is one of the most important reactions in the organic synthesis which causes ring closure of the reactant. It might be expected that the reaction of α,β-unsaturated compounds with phenylhydrazine or other substituted hydrazines would proceed through ring closure in a straightforward way to give pyrazolines. \(^{229, 230}\) 4-Phenylbut-3-en-2-ones reacts with substituted phenylhydrazines \((120a-g)\) in the presence of sodium acetate to form trisubstituted 4,5-dihydropyrazoles \((121a-g)\) in good yield.

Brief spectral analysis discussion of the compounds 121a-g:

\(^1H\) NMR, \(^{13}C\) NMR, MS studies, elemental analysis and X-ray diffraction crystallographic studies provide the structure proof for the products \((121a-g)\). The structural assignments were made by NMR analysis by considering compound \((121b)\) as the representative compound. In its \(^1H\) NMR spectra, all the three protons, \(H_A\), \(H_B\) and \(H_X\) are non-equivalent and therefore have different chemical shifts \((Figure-18)\) and gave rise to three separate signals.

All the three protons, \(H_A\), \(H_B\) and \(H_X\) attached to the C-4 and C-5 carbon atoms of the pyrazoline ring gave an ABX spin system and appeared as a doublet of doublet. The methylene protons of pyrazoline ring \((H_A\ \text{and} \ H_B)\) exhibited a typical ABX spin...
system with \( H_X \) as a doublet of doublets. The doublets of \( H_A \) appeared in the region \( \delta \) 2.61-2.67 ppm; doublets of \( H_B \) appeared in the region \( \delta \) 3.47-3.53 ppm and that of \( H_X \) in the region \( \delta \) 5.10-5.14 ppm. Among \( H_A \), \( H_B \) and \( H_X \) protons, \( H_X \) is the most deshielded due to its close proximity to benzene ring and it appeared as a doublet of doublet. Thus, each of the three signals is split into four peaks, a doublet of doublets. A total of twelve peaks are observed for these three protons which supported the formation of \( 121a-g \). A signal at \( \delta \) 2.01 ppm is assigned to methyl protons attached to pyrazoline ring at C-3. Moreover, a collection of signal observed in the aromatic region \( \delta \) 6.62-7.37 ppm is due to aromatic protons at 1\(^{st}\) and 5\(^{th}\) position of the pyrazoline ring.

![Figure-18: Proton chemical shifts and couplings of 121b](image)

In \(^{13}\)C NMR spectrum of compound (121b), a signal at \( \delta \) 15.99 ppm is assigned to methyl carbon attached to pyrazoline ring at C-3. Two signals at \( \delta \) 47.74 and \( \delta \) 63.75 ppm are assigned to C-4 and C-5 respectively. One signal at \( \delta \) 146.04 ppm is attributed to C-3 carbon in the pyrazoline ring which is a carbon attached to electronegative nitrogen by a double bond is deshielded due to its sp\(^2\) hybridization and electronegativity of nitrogen. A collection of signals appeared in the region \( \delta \) 112.97-149.58 ppm which are ambiguously assigned to aryl carbons. The mass spectrum of all the synthesized compounds showed M+1 molecular ion peak corresponding to its molecular formula as base peak which confirmed the formation of these compounds. Further, all showed satisfactorily elemental analysis with a deviation of \( \pm 0.02\% \) from
the theoretically calculated values. These observations strongly favor the formation of the products 121a-g. Further the structure proofs of the products were confirmed by single crystal X-ray diffraction studies. For instance, the structure of one of the compound 121b of the series of the synthesized compounds has been confirmed by X-ray diffraction studies. The ORTEP diagram of 121b as shown in Figure-19 and packing diffraction of the molecule is shown in Figure-20.

**Figure 19:** ORTEP diagram of 124b with 50% probability ellipsoids.

**Figure 20:** Packing diagram of molecule, viewed along the crystallographic b axis.

**Mechanism for the formation of pyrazoline:**

The probable mechanism for the formation of pyrazoline is depicted in scheme-116. The reaction proceed by Michael addition of (nucleophile) R-N\(^{-}\)-NH\(_2\) to the chalcones (1,4-addition) followed by proton transfer, cyclization via Claisen addition, hydrolysis and spontaneous dehydration.
Mass spectral fragmentation of the cycloadducts:

All the synthesized new compounds (121a-g) gave significantly stable molecular ion peaks with a relative abundance ranging from 10-40%. The common fragmentation pattern involves some rearrangement with the removal of simple and smaller molecules (Scheme-117).
4.4.0 Antimicrobial activity:

The reagents required and experimental procedure for *in vitro* antimicrobial properties of synthesized compounds ([121a-g](#)) was described in chapter 2 (refer page 63-77). The solutions were prepared at a concentration ranging between 25 µg/mL to 200 µg/mL for antibacterial and antifungal activities.

Synthesized compounds ([121a-g](#)) were evaluated for their antimicrobial activity (MIC) against fungal species *C. albicans, A. niger, A.flavus* and bacteria species *E. coli, S. typhimurium, B. subtilis*. The antibiotics amphotericin B and ciprofloxacin were used as standard drugs against fungi and bacteria species respectively. DMSO is used as control. The experiments were carried out in triplicate; the results were taken as a mean of three determinations.

4.4.1 Evaluation of antibacterial activity by paper disc method:

The minimum inhibitory concentration (MIC) results of the synthesized compounds ([121a-g](#)) against the bacteria species *E. coli, S. typhimurium, B. subtilis* are summarized in ([Table-12](#)). The test compounds exhibited different degrees of antibacterial activity in relation to the tested microbial species. The activity is considerably affected by substituents present at the *para* position of phenyl ring. The compound ([121a](#)) having only one aromatic ring substituent showed lesser activity against the organisms tested. The compounds ([121d-f](#)) with halogen and methoxy function present at C-6 positions of phenyl ring exerted very good activity. The compounds ([121b](#)) and ([121g](#)) with no substitution and –CH₃ substituent on aromatic ring exerted moderate activity. However the compound ([121c](#)) with –NO₂ substituent on the aromatic ring was found inactive even at a higher concentration of 200µg/ml against all the organisms tested.
Table-12: MIC’s of the synthesized compounds 121a-g against bacteria species

<table>
<thead>
<tr>
<th>Compound</th>
<th>Minimum inhibitory concentration (MIC’s) in µg/ml*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E. coli</td>
</tr>
<tr>
<td>121a</td>
<td>100</td>
</tr>
<tr>
<td>121b</td>
<td>50</td>
</tr>
<tr>
<td>121c</td>
<td>**</td>
</tr>
<tr>
<td>121d</td>
<td>25</td>
</tr>
<tr>
<td>121e</td>
<td>25</td>
</tr>
<tr>
<td>121f</td>
<td>25</td>
</tr>
<tr>
<td>121g</td>
<td>50</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>25</td>
</tr>
</tbody>
</table>

*Results are expressed as mean of three determinations (n=3);
**No activity observed even at a concentration of 200 µg/mL.

4.4.2 Evaluation of antifungal activity by paper disc method:

The results of minimum inhibitory concentration (MIC) of the synthesized compounds (121a-g) against the fungi species C. albicans, A. niger and A. flavus are furnished in (Table-13). The investigated compounds showed different degrees of antifungal activity in relation to the tested microbial species. The extent of antifungal activity depended on the microorganism and the type of functional groups present in the molecule. The activity is considerably affected by substituents present at the para position of phenyl ring. A close investigation of the in vitro antifungal activity profile of the trisubstituted pyrazolines gives a clear picture of the structure activity correlations among the compounds (121a-g) under study. The compounds with halogen and methyl function present at C-6 positions of phenyl ring exert varied range of antifungal activity while the compounds with no substituents or –NO₂ substituent on the phenyl groups did not exhibit significant antifungal activity. Substitution of halogen at the para position of phenyl groups has promoted the activity against C. albicans and A. flavus. However, this introduction did not show any improvement
against *A. niger*. Similarly, compound which has methoxy group at *para* position only recorded a marked potency.

**Table 13: MIC’s of the synthesized compounds 121a-g against fungi species**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Minimum inhibitory concentration (MIC’s) in µg/mL*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C. albicans</td>
</tr>
<tr>
<td>121a</td>
<td>100</td>
</tr>
<tr>
<td>121b</td>
<td>100</td>
</tr>
<tr>
<td>121c</td>
<td>100</td>
</tr>
<tr>
<td>121d</td>
<td>100</td>
</tr>
<tr>
<td>121e</td>
<td>50</td>
</tr>
<tr>
<td>121f</td>
<td>25</td>
</tr>
<tr>
<td>121g</td>
<td>50</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>25</td>
</tr>
</tbody>
</table>

*Results are expressed as mean of three determinations (n=3); **No activity observed even at a concentration of 200 µg/mL.*

**4.5.0 Experimental section:**

The chemicals used were purchased from Aldrich chemicals (India). Melting points were taken in open capillaries using Thomus Hoover melting point apparatus and are uncorrected. The $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker Supercon 400 MHz spectrophotometer in CDCl$_3$; chemical shifts are expressed in δ ppm. The coupling constant ($J$) is expressed in Hz. Mass spectra were obtained on Maspec MSW 9629 spectrophotometer. Elemental analysis was obtained on a Thermo Finnigan Flash EA 1112 CHN analyser. Chromatographic separations were carried out on silica gel (70-230 mesh, Merck) column using benzene: ethyl acetate (8:1 v/v) as eluent.

**4.5.1 General procedure for the preparation of pyrazolines:**

In a typical procedure, a mixture of 4-phenylbut-3-en-2-one (119, 0.001mmol), phenylhydrazine hydrochloride (120a-g 0.001mmol) and sodium acetate in ethyl alcohol was refluxed on water bath for 2 h. The progress of the reaction was
monitored by TLC. After the completion of the reaction, the mixture was poured into ice cold water. The solid formed was separated and crystallized with acetonitrile to get the title compounds (121a-g) in relatively good yield (Scheme-115). The same procedure was used in all the cases.

4.6.0 Experimental results:

3-Methyl-5-phenyl-4,5-dihydro-1H-pyrazole, 121a:

Obtained from 4-phenylbut-3-en-2-one (119) (0.146mg, 0.001mmol) and hydrazine hydrate (120a) (0.05mg, 0.001mmol) as a light brown solid in 58% yield, m.p. 60-62°C. 1H NMR (DMSO): δ 1.98 (s, 3H, CH₃), 2.62 (dd, 1H, Ha), 3.47 (dd, 1H, Hb), 5.11 (dd, 1H, Hc), 6.9 (s, 1H, NH), 6.61-6.63 (t, 1H, Ar-H), 6.78-6.81 (d, 2H, Ar-H), 7.03-7.08 (t, 2H, Ar-H), 7.24-7.35 (m, 5H, Ar-H). 13C NMR (DMSO): δ 15.88 (1C, CH₃), 146.01 (1C, 3-C), 46.82 (1C, CH₂), 61.62 (1C, CH), 126.90-142.54 (6C, C₆H₅-C). Anal. Calcd. for C₁₀H₁₂N₂, %: C, 74.97, H, 7.55, N, 17.48%; Found: C, 74.95, H, 7.52, N, 17.45.

3-Methyl-1,5-diphenyl-4,5-dihydro-1H-pyrazole, 121b:

Obtained from 4-phenylbut-3-en-2-one (119) (0.146mg, 0.001mmol) and phenylhydrazine hydrochloride (120b) (0.14mg, 0.001mmol) as yellow crystals in 62% yield, m.p. 90-92°C. 1H NMR (DMSO): δ 2.01 (s, 3H, CH₃), 2.64 (dd, 1H, Ha), 3.51 (dd, 1H, Hb), 5.13 (dd, 1H, Hc), 6.62-6.65 (t, 1H, Ar-H), 6.80-6.82 (d, 2H, Ar-H), 7.06-7.09 (t, 2H, Ar-H), 7.23-7.37 (m, 5H, Ar-H). 13C NMR (DMSO): δ 15.99 (1C, CH₃), 146.04 (1C, 3-C), 47.74(1C, CH₂), 63.75 (1C, CH), 112.97-149.58 (12C, C₆H₅-C). MS (relative abundance) m/z: 237 (M+1), 221, 144, 66. Anal. Calcd. for C₁₆H₁₅N₂, C, 81.32, H, 6.82, N, 11.85%; Found: C, 81.36, H, 6.80, N, 11.88%.
1-(2,4-Dinitrophenyl)-3-methyl-5-phenyl-4,5-dihydro-1H-pyrazole, 121c:

Obtained from 4-phenylbut-3-en-2-one (119) (0.146mg, 0.001mmol) and 2,4-dinitrophenylhydrazine (120c) (0.198mg, 0.001mmol) as red solid in 55% yield, m.p. 220-222°C. \( ^1 \)H NMR (DMSO): \( \delta \) 2.01 (s, 3H, CH\(_3\)), 2.63 (dd, 1H, Ha), 3.48 (dd, 1H, Hb), 5.12 (dd, 1H, Hc), 6.91-6.94 (t, 1H, Ar-H), 6.97-6.99 (d, 2H, Ar-H), 7.16-7.19 (t, 2H, Ar-H), 8.08-8.22 (m, 5H, Ar-H). \( ^{13} \)C NMR (DMSO): \( \delta \) 16.20 (1C, C\(_{\text{H3}}\)), 146.02 (1C, 3-C\(_\text{H}\)), 48.18 (1C, C\(_{\text{H2}}\)), 63.81 (1C, CH), 112.81-150.37 (12C, C\(_{6\text{H5-C}}\)). Anal. Cacl.d. for C\(_{16}\)H\(_{14}\)N\(_4\)O\(_4\), C, 58.89, H, 4.32, N, 17.17%; Found: C, 58.90, H, 4.32, N, 17.15%.

1-(4-Methoxyphenyl)-3-methyl-5-phenyl-4,5-dihydro-1H-pyrazole, 121d:

Obtained from 4-phenylbut-3-en-2-one (119) (0.146mg, 0.001mmol) and 4-methoxyphenylhydrazine hydrochloride (120d) (0.175mg, 0.001mmol) as a dark brown solid in 51% yield, m.p. 138-140°C. \( ^1 \)H NMR (DMSO): \( \delta \) 1.99 (s, 3H, CH\(_3\)), 3.70 (s, 3H, OCH\(_3\)), 2.56 (dd, 1H, Ha), 3.46 (dd, 1H, Hb), 5.08 (dd, 1H, Hc), 6.54-6.57 (t, 1H, Ar-H), 6.72-6.75 (d, 2H, Ar-H), 7.96-7.999 (t, 2H, Ar-H), 7.07-7.21 (m, 5H, Ar-H). \( ^{13} \)C NMR (DMSO): \( \delta \) 15.91 (1C, C\(_{\text{H3}}\)), 146.03 (1C, 3-C\(_\text{H}\)), 47.63 (1C, C\(_{\text{H2}}\)), 54.90 (1C, OCH\(_3\)), 62.90 (1C, CH), 118.20-148.63 (12C, C\(_{6\text{H5-C}}\)). Anal. Cacl.d. for C\(_{17}\)H\(_{18}\)N\(_2\)O, C, 76.66, H, 6.81, N, 10.52%; Found: C, 76.70, H, 6.82, N, 10.54%.

1-(4-Bromophenyl)-3-methyl-5-phenyl-4,5-dihydro-1H-pyrazole, 121e:

Obtained from 4-phenylbut-3-en-2-one (119) (0.146mg, 0.001mmol) and 4-bromophenyl hydrazine hydrochloride (120e) (0.22mg, 0.001mmol) as off white powder in 54% yield, m.p. 98-100°C. \( ^1 \)H NMR (DMSO): \( \delta \) 2.02 (s, 3H, CH\(_3\)), 2.65 (dd, 1H, Ha), 3.51 (dd, 1H, Hb), 5.13 (dd, 1H, Hc), 6.72-6.75 (t, 1H, Ar-H), 6.89-6.81 (d, 2H, Ar-H), 7.16-7.20 (t, 2H, Ar-H), 7.15-7.39 (m, 5H, Ar-H). \( ^{13} \)C NMR (DMSO): \( \delta \) 15.73 (1C, C\(_{\text{H3}}\)), 146.04 (1C, 3-C\(_\text{H}\)), 47.90 (1C, C\(_{\text{H2}}\)), 63.91 (1C, CH), 112.91-
149.64 (12C, C₆H₅-Ç). Anal. Cacld. for C₁₆H₁₅BrN₂, C, 60.97, H, 4.80, N, 8.89% ; Found: C, 60.97, H, 4.85, N, 8.88%.

1-(4-Chlorophenyl)-3-methyl-5-phenyl-4,5-dihydro-1H-pyrazole, 121f:
Obtained from 4-phenylbut-3-en-2-one (119) (0.146mg, 0.001mmol) and 4-chlorophenyl hydrazine hydrochloride (120f) (0.178mg, 0.001mmol) as a white solid in 56% yield, m.p. 101-103°C. ¹H NMR (DMSO): δ 2.02 (s, 3H, CH₃), 2.61 (dd, 1H, Ha), 3.50 (dd, 1H, Hb), 5.14 (dd, 1H, Hc), 6.71-6.74 (t, 1H, Ar-H), 6.89-6.92 (d, 2H, Ar-H), 7.15-7.19 (t, 2H, Ar-H), 7.22-7.36 (m, 5H, Ar-H). ¹³C NMR (DMSO): δ 15.72 (1C, CH₃), 146.05 (1C, 3-Ç), 47.89 (1C, ÇH₂), 63.92 (1C, ÇH), 112.89-149.69 (12C, C₆H₅-Ç). MS (relative abundance) m/z: 271 (M+1, 35Cl), 273 (M+1, 37Cl), 255, 144, 66. Anal. Cacld. for C₁₆H₁₅ClN₂, C, 70.98, H, 5.58, N, 10.35% ; Found: C, 70.91, H, 5.54, N, 10.36%.

3-Methyl-5-phenyl-1-(p-tolyl)-4,5-dihydro-1H-pyrazole, 121g:
Obtained from 4-phenylbut-3-en-2-one (119) (0.146mg, 0.001mmol) and 4-methylphenylhydrazine hydrochloride (120g) (0.158mg, 0.001mmol) as a light brown solid in 59% yield, m.p. 120-122°C. ¹H NMR (DMSO): δ 1.99 (s, 3H, CH₃), 2.40 (s, 3H, CH₃), 2.64 (dd, 1H, Ha), 3.46 (dd, 1H, Hb), 5.15 (dd, 1H, Hc), 6.63-6.66 (t, 1H, Ar-H), 6.81-6.83 (d, 2H, Ar-H), 7.07-7.10 (t, 2H, Ar-H), 7.24-7.36 (m, 5H, Ar-H). ¹³C NMR (DMSO): δ 15.63 (1C, ÇH₃), 21.07 (1C, ÇH₃), 146.02 (1C, 3-Ç), 47.72 (1C, ÇH₂), 63.81 (1C, ÇH), 112.54-145.54 (12C, C₆H₅-Ç). Anal. Cacld. for C₁₇H₁₈N₂, C, 81.56, H, 7.25, N, 11.19% ; Found: C, 81.54, H, 7.18, N, 11.18%.

4.7.0 Conclusion:
We have demonstrated the crystal and molecular structure of 3-methyl-1, 5-diphenyl-4, 5-dihydro-1H-pyrazole (121b) by the single crystal x-ray diffraction
technique. A series of novel trisubstituted pyrazoles have been synthesized in appreciable yields in an easy accessible method. Results of the antimicrobial activity reveal that some of the compounds particularly with chloro substituents act as potential antimicrobial agents.