PART- III

SYNTHESIS OF SUBSTITUTED CHROMONES, BENZOTHIAZINES, CHALCONES & PYRAZOLES
SECTION - A

SYNTHESIS OF 2-ETHYL-3-(1-METHYL-3-n-PROPYL-1H-PYRAZOL-5-CARBONYL) CHROMON-4-ONES
3.1.1. INTRODUCTION :-

Chromones have achieved great importance due to their diverse biological activities e.g. antiallergic, diuretics, antidiabetics, antibacterial, antifungal and anticholesterenic.\(^{(1-14)}\)

Pyrazole chemistry has been focus of high attention for more than three decades due to versatile biological activities of pyrazole derivatives such as anti-microbial, anti-inflammatory, antihistaminic, antidepressant and anticonvulsant agent\(^{(5-14)}\).

Pyrazoles are reported as well known pharmaceuticals.\(^{(15-16)}\) The selection of pyrazole derivative in the field of clinical medicine is undoubted. The principle practical application that one can come across because of their considerable anti-tumor and antiviral action \(^{(17-18)}\).

Dorothy Donelly has suggested that chromones having heterocyclic substituents at 2-position possess anticancer activity.\(^{(19)}\) Ellis and Nohara reported various natural and synthetic chromones, especially those having heterocyclic substituents at C-2 & C-3 position have good pharmacological activities\(^{(20-21)}\).

The base catalyzed claisen condensation of 2-hydroxy acetophenone with esters leads to formation of a 1,3 diketone, which can be isolated as its sodium salt. Cyclisation to the chromones occur readily under acidic conditions (scheme I)\(^{(22)}\).

\[ \text{scheme I} \]

\[
\begin{align*}
\text{RCOOC}_2H & \quad \text{OH} \\
\text{i) Base} & \quad \text{RCOOC}_2H - C - O \text{R} \\
\text{ii) RCOOEt} & \quad \text{RCOOC}_2H - C - O \text{R} \\
\text{H}^+ & \quad \text{RCOOC}_2H - C - O \text{R} \\
\end{align*}
\]
An alternative source of 1,3 diketones and chromones precursor is an ortho acyloxy acyl benzene, which is readily prepared by the acylation of 2-hydroxy acetophenones\(^{(23)}\).

A base catalyzed Baker-Venkataraman rearrangement yield the β-diketones (scheme II) which upon cyclisation in acidic medium leads to the formation of chromones.

**scheme II**

\[\begin{align*}
\text{R-COCI} & \xrightarrow{\text{Pyridine}} \text{R-CO}_{-}\text{O}
\end{align*}\]

\[\begin{align*}
\text{KOH} & \xrightarrow{\text{Heat}} \text{R-CO}_{-}\text{O}
\end{align*}\]

In the Kostanecki Robinson synthesis of chromones and flavones, 2-hydroxy acetophenones are heated with anhydride and sodium salt of an aliphatic acid\(^{(24)}\) (scheme III).

**scheme III**

\[\begin{align*}
\text{R-CO}_{-}\text{O} & \xrightarrow{\text{AC}_2\text{O}} \text{R-CO}_{-}\text{O}
\end{align*}\]

\[\begin{align*}
\text{NaOAC} & \xrightarrow{\text{Heat}} \text{R-CO}_{-}\text{O}
\end{align*}\]
The Kostanecki-Robinson reaction proceeds by both C & O acylation followed by Baker-Venkataraman rearrangement to the 1,3-diketone and subsequent cyclisation\textsuperscript{(25)} to respective chromone.

The mixed anhydride of acetic acid and formic acid acts as a one-carbon synthon and enables chromones unsubstituted at C-2 to be synthesized under mild conditions. This approach is exemplified by formation of isoflavones and 3 (2-benzo-thiazolyl) chromones\textsuperscript{(26-27)}.

\[
\begin{array}{c}
\text{OH} & \text{O} \\
\text{Ar} & \text{AC}_2\text{O} \\
\text{HO} & \text{HCOOH} \\
\end{array}
\]

The use of triethyl ortho formate also yield chromones unsubstituted at 2 position, a route which has been used to prepare 3(3-isoxazolyl) chromones and isoflavones\textsuperscript{(28-29)}.

The Simonis reaction involves the reaction of phenol with 3-keto ester and is closely allied to the Pechmann synthesis of coumarins\textsuperscript{(30)}. Unfortunately the initially formed esters can cyclise to either a chromone or a coumarin and in many cases both are formed.
In the present investigation 2-ethyl, 3 (1-methyl, 3-n-propyl-1H-pyrazol-5 carbonyl) chromon-4-ones are prepared by reaction of 1-(2-hydroxyl phenyl) 3- (1-methyl 3-n-propyl-1H-pyrazol-5-yl)-1,3-propan-diones with propionic anhydride in presence of alcohol and triethyl amine.

\[ \text{Alcohol / Triethyl amine} \]

\[ \text{1} \quad + \quad \text{2} \]

3.1.2. PRESENT WORK :-

In the present investigation 2-ethyl, 3 (1-methyl, 3-n-propyl-1H-pyrazol-5 carbonyl) chromon-4-ones are prepared by reaction of 1-(2-hydroxyl phenyl) 3-(1-methyl 3-n-propyl-1H-pyrazol-5-yl)-1,3-propan-diones with propionic anhydride in presence of alcohol and triethyl amine.
3.1.3. EXPERIMENTAL :-

General procedure for synthesis of 2-ethyl 3-(1-methyl, 3-n-propyl -1H-pyrazol -5-carbonyl) chromon -4-ones

Mixture of compound 1 (0.001 mole) & 10 ml propionic anhydride was taken in a round bottomed flask. It was dissolved in ethyl alcohol & 0.5 ml triethyl amine was added. The reaction mixture was then heated under reflux for 2 hrs. After completion of heating, contents were cooled and poured over crushed ice. The resulting product was separated by filtration and recrystallised from ethanol.

The compounds synthesized by above procedure are listed in Table 8 with their physical constant and percentage yield. Their structures have been confirmed by I.R. & NMR spectral studies.

Table 8

<table>
<thead>
<tr>
<th>Compound no.</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>M.P. oC</th>
<th>% Yield</th>
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<tr>
<td>2a</td>
<td>Cl</td>
<td>H</td>
<td>Cl</td>
<td>159</td>
<td>66</td>
</tr>
<tr>
<td>2b</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
<td>151</td>
<td>62</td>
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<tr>
<td>2c</td>
<td>H</td>
<td>H</td>
<td>CH₃</td>
<td>146</td>
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<td>2d</td>
<td>CH₃</td>
<td>H</td>
<td>CH₃</td>
<td>157</td>
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<td>2e</td>
<td>H</td>
<td>H</td>
<td>Br</td>
<td>163</td>
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3.1.4. DISCUSSION OF SPECTRA :

IR. Spectra:
I.R. spectra of representative compounds of this series were scanned by using Perkin Elmer FT spectrophotometer.
I.R. spectrum (KBr disc) of 2a showed following characteristic absorption bands.

- 1635 cm\(^{-1}\) due to C=O stretching
- 1602 cm\(^{-1}\) due to C=O stretching
- 1508 cm\(^{-1}\) due to C=N stretching
- 1429 cm\(^{-1}\) due to Ar-N stretching
- 754 cm\(^{-1}\) due to C-Cl stretching
NMR Spectra:
The NMR spectra of representative compounds of this series were scanned on Varian 300 MHz spectrophotometer in DMSO as solvent and TMS is used as an internal standard. Peak values are shown in δ ppm.

Compound 2a showed following characteristic signals in δ ppm.

<table>
<thead>
<tr>
<th>δ ppm</th>
<th>Multiplicity</th>
<th>Proton Type</th>
<th>Assignment</th>
</tr>
</thead>
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<td>(of n-propyl group)</td>
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<tr>
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<td>3H triplet</td>
<td>CH₃</td>
<td>(of ethyl group)</td>
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<td>1.56</td>
<td>2H multiplet</td>
<td>CH₂</td>
<td></td>
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<tr>
<td>2.46</td>
<td>2H quartet</td>
<td>CH₂</td>
<td></td>
</tr>
<tr>
<td>2.61</td>
<td>2H triplet</td>
<td>CH₂</td>
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<td>6.90</td>
<td>1H singlet</td>
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<td>7.92</td>
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<td>8.26</td>
<td>1H singlet</td>
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Peaktable of M-SHA2 IRS, 25 Peaks
Threshold: 100, Noise: 1, File Range Selection

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<th>Inten.</th>
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<td>25</td>
<td>3122.5</td>
<td>97.079</td>
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</table>
3.1.5. REFERENCES :-


PART - III

SECTION - B

SYNTHESIS OF (2-HYDROXY PHENYL),(3-(1-METHYL-3-n-PROPYL-1H-PYRAZOL-5-YL)-4H-BENZO[b][1,4]THIAZIN-2-YL) METHANONES
3.2.1. INTRODUCTION :-

Heterocyclic compounds containing nitrogen, such as alkaloids, amides, nucleosides & nucleotides etc. are widely distributed in nature and play vital role in the metabolism of all living cells. However, very few pyrazoles, particularly 1,2 pyrazoles and their derivatives occur naturally. This may be due to the difficulty of living organisms to construct the N-N bond. Like other nitrogen heterocycles pyrazoles also exhibit a wide range of biological activities, like antioxidants, antiinvasive, antiviral, antipyretic, antiinflammatory, antidepressant, blood pressure lowering\(^{[1-7]}\). Pyrazoles are also used as an agrochemicals, dyestuffs etc\(^{[8-10]}\).

Benzothiazepines are of two types 1,4-benzothiazines and 1,5-benzothiazepines. 1,4-benzothiazines are of much interest as the starting substrate for the synthesis of new molecules with potential pharmacological activity\(^{[11]}\) such system also occur in natural pigments and dyes\(^{[12-14]}\). The 1,4-benzothiazine moiety possess interesting analgesic, antimicrobial\(^{[15-16]}\) and antiinflammatory activity\(^{[17]}\). Recently the antiviral activity of 1,4 benzothiazine against human immuno-deficiency virus I & II has been reported\(^{[18-19]}\).

In 1963 Krapcho and co-workers\(^{[20]}\) synthesized 2,3,dihydro and 2,5-dihydro-1-5-benzothiazepine-4(5H)-ones.1,5-Benzothiazepine derivatives are found to possess tranquilizing\(^{[21]}\), antispasmodic \(^{[22]}\) and antibacterial \(^{[21]}\) activities.

1,5- Benzothiazepine derivatives are well known to possess antifungal \(^{[23]}\) and psycotropic \(^{[24]}\) activities.

1,5-Benzothiazepine derivatives showed antiallergic and antidepressant \(^{[25-27]}\) activities, upon substitution at the amino-nitrogen or aliphatic carbon.
Kugita et al reported various benzothiazepine analogs of pharmaceutical interest. They reported antidepressant, tranquilizing, anticonvulsive properties, and dilating action on the coronary blood vessels. They also reported psychotropic coronary vasodilators and ganglion blocking properties.

2,3, dihydro-5-(2-(N-methyl and adamantyl amino)-ethyl ) -2- phenyl -1,5-benzothiazepine found to have central nervous system activity.

Renz et al reported sedative properties of 4-(4-substituted-1-pyrazinyl)-thieno (2,3,-b) 1,5-benzothiazepines.

Pyrido derivatives of benzothiazepines have shown antihistaminic activities. Ingale et al have studied fungicidal activities of 1,5-benzothiazepine derivatives.

Pyrazole moiety containing compounds are associated with bactericidal anti-inflammatory and hepato-protective activities.

B.K Karale et al synthesized 2,3-dihydro-1,5-benzothiazepines by the reaction of chalcones with 2-amino thiophenol.
Sandeep Nigam & Y.C. Joshi\cite{43} reported 1,4-benzothiazines by reaction of β-diketone with 2-amino thiophenol.
S.V. Agarkar\(^{(44)}\) reported synthesis of 1,5 benzothiazepines by reaction of chalcone with 2-amino thiophenol.
3.2.2. PRESENT WORK :-

In the present investigation (2-hydroxy phenyl) (3-(1-methly-3-n-propyl-1H-pyrazol-5-yl) -4H-benzo[b][1,4] thiazin-2-yl) methanones are prepared by reaction of 1(2-hydroxy phenyl) 3-(1-methyl-3-n-propyl-1H-pyrazol-5-yl)1,3-propan-diones with ortho amino thiophenol in DMSO.
3.2.3. EXPERIMENTAL :

General procedure for synthesis of (2-hydroxy phenyl) (3-(1-methyl-3-n-propyl-1H-pyrazol-5-yl)-4H-benzo[b][1,4]thiazin-2-yl) methanones.

2-Aminothiophenol (0.002 mole) was taken in a round bottomed flask containing 10 ml dimethyl sulphoxide and stirred at room temperature for 40 minutes. Then to this reaction mixture 1(2-hydroxy phenyl)-3(1-methyl-3-n-propyl-1H-pyrazol-5-yl) 1,3-propan-dione (0.001 mole) was added and the contents of the flask were refluxed for two hours. After completion of heating reaction mixture was poured over crushed ice. The product thus obtained was separated by filtration and crystallized from ethanol.

Products obtained(3a-3e) were identified with the help of spectral data. The compounds synthesized by above procedure are listed in table 9 with their physical constant and percentage yield.

Table 9

<table>
<thead>
<tr>
<th>Compound no.</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>M.P. °C</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>Cl</td>
<td>H</td>
<td>Cl</td>
<td>173</td>
<td>61</td>
</tr>
<tr>
<td>3b</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
<td>161</td>
<td>57</td>
</tr>
<tr>
<td>3c</td>
<td>H</td>
<td>H</td>
<td>CH₃</td>
<td>152</td>
<td>49</td>
</tr>
<tr>
<td>3d</td>
<td>CH₃</td>
<td>H</td>
<td>CH₃</td>
<td>166</td>
<td>55</td>
</tr>
<tr>
<td>3e</td>
<td>H</td>
<td>H</td>
<td>Br</td>
<td>179</td>
<td>59</td>
</tr>
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</table>
3.2.4. DISCUSSION OF SPECTRA:

I.R. spectra:

I.R. spectra of representative compounds of this series were scanned by using Perkin Elmer FT spectrophotometer.

I.R. spectrum (KBr disc) of 3a showed following characteristic absorption bands.

<table>
<thead>
<tr>
<th>Wavenumber (cm(^{-1}))</th>
<th>Attributed to</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>3437</td>
<td>O-H &amp; N-H</td>
<td>stretching</td>
</tr>
<tr>
<td>1667</td>
<td>C=O</td>
<td>stretching</td>
</tr>
<tr>
<td>1598, 1567</td>
<td>C=N</td>
<td>stretching</td>
</tr>
<tr>
<td>747</td>
<td>Ar-H</td>
<td>stretching</td>
</tr>
</tbody>
</table>
NMR spectrum:

The NMR spectrum of representative compounds of this series were scanned on Varian 300 MHz spectrophotometer in DMSO as a solvent & TMS is used as an internal standard. Peak values are shown in δ ppm.

Compound 3a showed following characteristic NMR peaks in δ ppm.

<table>
<thead>
<tr>
<th>Peak Value</th>
<th>Multiplicity</th>
<th>Proton Type</th>
<th>Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.93</td>
<td>3H triplet</td>
<td>CH₃</td>
<td></td>
</tr>
<tr>
<td>1.64</td>
<td>2H multiplet</td>
<td>CH₂</td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td>2H triplet</td>
<td>CH₂</td>
<td></td>
</tr>
<tr>
<td>3.96</td>
<td>3H singlet</td>
<td>CH₃</td>
<td></td>
</tr>
<tr>
<td>6.5</td>
<td>1H singlet</td>
<td>pyrazole -H</td>
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<tr>
<td>7.00 - 7.40</td>
<td>6H multiplet</td>
<td>Ar-H</td>
<td></td>
</tr>
<tr>
<td>7.9</td>
<td>1H singlet</td>
<td>N-H</td>
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<tr>
<td>8.00</td>
<td>1H singlet</td>
<td>OH</td>
<td></td>
</tr>
</tbody>
</table>

Mass spectra:

m/e (M⁺)  442
3.2.5. REFERENCES:


PART - III

SECTION - C

SYNTHESIS OF 1-(2-HYDROXY-PHENYL)-3-
{4-[2-METHYL-PYRIDIN-2-YL-AMINO]-
ETHOXY]-PHENYL}-PROPENONES
3.3.1. INTRODUCTION:

The chemistry of chalcones has great importance due to their versatility as an effective synthon in the synthesis of many organic compounds. Chalcones are also associated with wide spectrum of pharmacological activities.

Chalcones are the compounds which contain α, β-unsaturated ketone group. These compounds are generally prepared by condensation of acetophenone with aromatic aldehyde in basic conditions.

\[
\text{R} \quad \begin{array}{c} \text{CH}_3 \\ \text{O} \end{array} + \begin{array}{c} \text{H} \\ \text{O} \end{array} \quad \xrightarrow{\text{NaOH}} \quad \begin{array}{c} \text{R} \\ \text{O} \end{array}
\]

Chalcones were found to possess germicidal\(^{(1)}\), fungicidal\(^{(2)}\) and carcinogenic\(^{(3)}\) properties.

Gieger and Conn\(^{(4)}\) asserted that the presence of α, β-unsaturated system is the cause of their activity. They argued that such unsaturated carbonyl system in the compounds are capable of reacting with sulphadryl functions which are constituents of enzymes and proteins thereby destroying the
essential metabolites or interfering with enzyme system and thus producing the antibacterial activity.

Kushawaha\(^6\) and coworkers have reported antibacterial and antifungal activities in substituted 3-(2-furyl)-acrylophenones. Similar activities\(^6\text{--}^9\) have been possessed by acrylophenones having 2 and 4-pyridyl, quinolyl, furyl substituents at 3-position.

Some pyridyl, thienyl and furyl substituted acrylophenones have claimed bacteriostatic and tuberculostatic activities.

Schraufstatter\(^10\) and Agasimudin\(^11\) have synthesized number of acrylophenones and reported the importance of halogen and hydroxyl substituents in benzenoid part for increasing the bacteriostatic activity.

Koo\(^12\) reported coronary dilating properties in 3-(2-furyl) and 3-(2 and 3-pyridyl) acrylophenones. The anticancer activity against friend virus Leukemia were searched by Donnelly and coworkers\(^13\) in a series of acrylophenones having heterocyclic substituents at 3-position.

T. Vandana and K.J. Rajendra Prasad\(^14\) reported synthesis of chalcones from cyclic ketone and aromatic aldehydes in alcoholic KOH.
V. Harinadha & Varadhraj\cite{15} reported synthesis of \(\alpha, \beta\)-unsaturated ketones by condensation of 2-acetyl benzofuran with aromatic aldehydes in alcoholic NaOH.

\[
\text{O CHO O} \quad \xrightarrow{\text{CH}_2} \quad \text{O} \quad \text{CH}_2
\]

Gheorghe Roman\cite{16} and et al synthesized chalcones by the reaction of aldehyde with 2-acetyl benzimidazole.

Mohd. Imran and Suroor A.Khan\cite{17} reported synthesis of isoxazolines from chalcones by the reaction with hydroxylamine hydrochloride.
Manohar Kulkarni et al\textsuperscript{(18)} reported preparation of pyrazoles from chalcones and phenyl hydrazine.

A.R. Bhat\textsuperscript{(19)} et al synthesized pyrazolines from chalcone and hydrazine hydrate in ethanol.
3.3.2. PRESENT WORK :

In the present investigation the 1-(2-hydroxy -phenyl)-3-{4-[2-methyl-
pyridin-2-yl-amino)-ethoxy]-phenyl}-propenones 3 were prepared by
condensation of 2-hydroxy acetophenones 1 with 4[2-(methyl-pyridin-2-yl-
amino)-ethoxy] benzaldehyde 2

![Chemical Structures]

1 + 2 → Alco.KOH → 3
3.3.3. EXPERIMENTAL:


A mixture of 1 (0.001 mole) and 2 (0.001 mole) was dissolved in 40 ml ethanol. To this mixture 5 g of KOH pellets were added. The reaction mixture was stirred at room temperature for 48 hrs. Then reaction mixture was poured over crushed ice and contents were acidified with concentrated HCl. Product thus obtained was crystallized from acetic acid.

The compounds synthesized by above procedure are listed in table 10 with their physical constant and percentage yield. Their structures have been confirmed by IR, NMR and mass spectral studies.

Table 10

<table>
<thead>
<tr>
<th>compound no.</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>M.P. °C</th>
<th>%Yield</th>
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3.3.4. DISCUSSION OF SPECTRA:

IR spectra:

IR spectra of representative compounds of this series were scanned by using Perkin Elmer FT spectrophotometer. IR spectrum (KBr disc) of 3b showed following characteristic absorption bands.

- 3446 cm\(^{-1}\) due to O-H stretching
- 1633 cm\(^{-1}\) due to C=O stretching
- 1608 & 1547 cm\(^{-1}\) due to C=N stretching
- 766 cm\(^{-1}\) due to O-H stretching

NMR spectra:

The NMR spectra of representative compounds in this series of 3b were scanned on Varian 300 MHz spectrophotometer using DMSO as a solvent and TMS as an internal standard.
Compound 3b exhibited following characteristic signals in δ ppm.

<table>
<thead>
<tr>
<th>δ</th>
<th>nH</th>
<th>Multiplicity</th>
<th>Assignments</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.6</td>
<td>1H</td>
<td>singlet</td>
<td>OH (exchangeable with D$_2$O)</td>
</tr>
<tr>
<td>7.00-8.39</td>
<td>11H</td>
<td>multiplet</td>
<td>Ar-H and pyridyl-H</td>
</tr>
<tr>
<td>6.60</td>
<td>2H</td>
<td>quartet</td>
<td>Olefinic protons</td>
</tr>
<tr>
<td>4.23</td>
<td>2H</td>
<td>triplet</td>
<td>CH$_2$</td>
</tr>
<tr>
<td>3.95</td>
<td>2H</td>
<td>triplet</td>
<td>CH$_2$</td>
</tr>
<tr>
<td>3.1</td>
<td>3H</td>
<td>singlet</td>
<td>N-CH$_3$</td>
</tr>
</tbody>
</table>

Mass Spectra:

Mass spectrum of 3b showed (M$^+$) at 410, 411
3.3.5. REFERENCES :-

PART - III

SECTION - D

SYNTHESIS OF 2(5-{4-[2-(METHYL-PYRIDIN-2-YL-AMINO)-ETHOXY]-PHENYL}-4,5-DIHYDRO-1H- PYRAZOL-3-YL)-PHENOLS
3.4.1. INTRODUCTION :-

Substituted pyrazolines are known for their insecticidal\(^1\), anti-inflammatory\(^2\) and analgesic\(^3\) activities. Anti-inflammatory activity is also associated with several compounds possessing pyrazole and benzothiazole ring system\(^4\)-\(^5\). A dramatic increase in anti-inflammatory activity of cortisone and other steroids incorporating pyrazole in the molecules has been reported\(^6\).

The different pyrazoline derivatives were found to possess important pharmacological & biological activities.

Some pyrazolines & their derivatives are found to be associated with antiproteolytic\(^7\), antibacterial, antifungal\(^8\) and antiviral\(^9\) activities. Many of the pyrazolines are reported to possess acaricidal\(^10\) activities.

In nineteenth century Fisher & Knovenagel described the reaction of acrolein with phenyl hydrazine\(^11\) to produce pyrazolines. Their experiment seems to be first example of pyrazoline formation, by the reaction of an \(\alpha, \beta\) enone with a hydrazine derivatives.

Auwers & et al\(^12\)-\(^13\) corroborated that the product of this reaction was 1-phenyl-2-pyrazoline. This simple and convenient procedure has remained one of the most popular method for the preparation of 2-pyrazolines.

The second milestone in the synthesis of pyrazolines was the discovery of the reaction of diazoalkanes with \(\alpha, \beta\)-unsaturated carboxylic acid derivatives\(^14\)-\(^17\) and \(\alpha, \beta\)-enones\(^18\)-\(^19\) in the early twentieth century.

Among diazoalkanes, diazomethanes proved to be the most convenient, nitrogen-containing reagent for the preparation of a wide variety of 1-pyrazolines as primary product, which spontaneously isomerize or can be converted in to their appropriate 2-pyrazolines\(^20\)-\(^24\).

The reaction of chalcones and related \(\alpha, \beta\)-unsaturated ketones with hydrazines is the most popular procedure for the synthesis of 2-pyrazolines.
N.S. Joshi et al synthesized pyrazolines\textsuperscript{(25)} by the reaction of fluorine-substituted chalcones with hydrazine hydrate.

T. Vandana and K.J. Rajendraprasad\textsuperscript{(26)} synthesized pyrazolines by the reaction of hydrazine hydrate with $\alpha$- $\beta$-unsaturated ketones.
B.P. Chetan and A.R. Bhat reported synthesis of pyrazolines from chalcones & hydrazine hydrate (27).

\[
\begin{align*}
\text{Hydrazine hydrate} & \\
\text{Ethanol} & \\
\rightarrow & \\
\end{align*}
\]

P.S. Pande & Wadodkar (28) synthesized substituted pyrazolines by the reaction of Benzothiazole hydrazine with chalcones.

Deepika Vijay Vergiya & B.L. Varma (29) reported preparation of pyrazolines from chalcone & phenyl hydrazines.
K. Mogilaiah and B. Sakram reported synthesis of pyrazolines by the reaction of chalcones with substituted acid hydrazides.
3.4.2. PRESENT WORK:

In the present investigation the $2-(5-{4-[2-(methyl-pyridin-2-yl-amino)-ethoxy]-phenyl})-4,5$-dihydro-$1H$-pyrazol-3-yl)-phenols were prepared by condensation of $1-(2$-hydroxy-phenyl)-$3-{4-[2$-methyl-pyridin-2-yl-amino)-ethoxy]$ phenyl)-propenones 3 with hydrazine hydrate in dioxane as solvent.

\begin{center}
\begin{tikzpicture}
  \node (3) at (0,0) {
    \begin{tikzpicture}
      \draw[thick] (0,0) -- (1,0) -- (1,1) -- (0,1) -- cycle;
      \draw[thick] (0,0.5) -- (1,0.5);
      \draw[thick] (0,1) -- (1,0);
      \node at (0.5,0.5) {$\text{OH}$};
      \node at (0.5,0.75) {$\text{CH}_3$};
      \node at (0.5,0.25) {$\text{N}$};
      \node at (0.5,0) {$\text{N}$};
      \node at (0,0) {$\text{R}_1$};
      \node at (1,0) {$\text{R}_2$};
      \node at (1,1) {$\text{R}_3$};
      \node at (0.5,1.5) {$\text{N}$};
    \end{tikzpicture}
  };
  \node (4) at (2,0) {
    \begin{tikzpicture}
      \draw[thick] (0,0) -- (1,0) -- (1,1) -- (0,1) -- cycle;
      \draw[thick] (0,0.5) -- (1,0.5);
      \draw[thick] (0,1) -- (1,0);
      \node at (0.5,0.5) {$\text{OH}$};
      \node at (0.5,0.75) {$\text{CH}_3$};
      \node at (0.5,0.25) {$\text{N}$};
      \node at (0.5,0) {$\text{N}$};
      \node at (0,0) {$\text{R}_1$};
      \node at (1,0) {$\text{R}_2$};
      \node at (1,1) {$\text{R}_3$};
      \node at (0.5,1.5) {$\text{N}$};
    \end{tikzpicture}
  };
  \node at (1,0.5) {$\text{Dioxane}$};
  \node at (1,-0.5) {$\text{Hydrazine hydrate}$};
\end{tikzpicture}
\end{center}
3.4.3. EXPERIMENTAL: -

General procedure for synthesis of 2(5-{4-[2-(methyl-pyridin-2-yl-amino)-ethoxy]-phenyl}-4,5-dihydro-1H-pyrazol-3-yl)-phenols.

0.001 mole of 3 was dissolved in 15 ml of dioxane. To this reaction mixture 0.002 mole of hydrazine hydrate was added. The contents were heated under mild reflux for 3 hrs and then to the reaction mixture 1 ml of glacial acetic acid was added and heating was continued further for two hours and then cooled to room temperature. 100 ml cold water was added slowly in the reaction flask and separated product was crystallized from ethanol.

The compounds synthesized by above procedure are listed in table 11 with their physical constant & percentage yield. Their structures are confirmed by I.R. & NMR spectral studies.

Table 11

<table>
<thead>
<tr>
<th>compound no.</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>M.P. °C</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>Cl</td>
<td>H</td>
<td>Cl</td>
<td>176</td>
<td>76</td>
</tr>
<tr>
<td>4b</td>
<td>H</td>
<td>H</td>
<td>Cl</td>
<td>154</td>
<td>50</td>
</tr>
<tr>
<td>4c</td>
<td>H</td>
<td>H</td>
<td>Br</td>
<td>173</td>
<td>55</td>
</tr>
<tr>
<td>4d</td>
<td>H</td>
<td>CH₃</td>
<td>Cl</td>
<td>194</td>
<td>47</td>
</tr>
<tr>
<td>4e</td>
<td>H</td>
<td>H</td>
<td>CH₃</td>
<td>129</td>
<td>49</td>
</tr>
</tbody>
</table>
3.4.4. DISCUSSION OF SPECTRA:

IR spectra:

IR spectra of representative compounds in this series were scanned by using Perkin Elmer FT spectrophotometer.

IR spectrum (KBr disc) of (4a) showed following characteristic absorption bands.
- \(3319 \text{ cm}^{-1}\) due to OH stretching
- \(3072 \text{ cm}^{-1}\) due to NH stretching
- \(2959 \text{ cm}^{-1}\) due to CH stretching
- \(1501 \text{ cm}^{-1}\) due to C=N stretching
- \(769 \text{ cm}^{-1}\) due to C-Cl stretching

NMR spectra:

The NMR spectra of representative compounds in this series of 4a were scanned on Varian 300 MHz spectrophotometer using DMSO as a solvent and TMS as an internal standard.
Compound 4a exhibited following characteristic signals in δ ppm.

12.00  1H singlet  OH
8.1    1H doublet  N-H
6.6 -7.5  10H multiplet  Ar-H and pyridyl-H
4.82   2H triplet  CH2 (pyrazoline)
4.12   2H triplet  CH2
3.9    2H triplet  CH2
3.5    1H quartet  CH (pyrazoline)
3.1    3H singlet  N-CH3

Mass spectra:

m/e  (M⁺)  457
3.4.5. REFERENCES :-