4.1. INTRODUCTION

Heterocyclic compound attracts more interest for synthetic organic chemists due to the interesting biological activities from the last decades\(^1\). Many of the synthetic drugs contain heterocyclic rings\(^2\) like pyridine, pyrimidine, thiazole, pyrazole, indole etc. Many natural compounds have interesting biological properties and they have been chosen as a lead compound for further SAR studies. Due to these facts, the conversion of a natural product into heterocyclic derivatives attracts much more interest in medicinal chemistry.

Curcumin (41) possessing various biological activities\(^3\), which is also attempted in the same manner. The heterocyclic derivatives of curcumin (41) are pyrazole\(^4\), oxazole\(^5\), pyrimidine\(^6\) and pyridone\(^7\). Among the various curcumin derivatives, hydrazinocurcumin is a vital in drug discovery due to its various biological activities of initial studies\(^3\). Hydrazinocurcumin was prepared by converting the 1,3-diketone of curcumin (41) into pyrazole i.e., curcumin (41) was converted into distryryl pyrazole.

Though curcumin (41) was first isolated\(^8\) in 1815, its potential derivatives were synthesised almost after the two centuries due to the complex nature of the molecule. The complex nature of curcumin (41) restricts the formation of derivatives to the greater extent.
For e.g.,

\[
\begin{align*}
\text{pentane-2,4-dione} & \quad + \quad \text{hydrazine} \\
\text{3,5-dimethyl-1H-pyrazole}
\end{align*}
\]

The formation of 3,5-dimethyl-1H-pyrazole can be easily achieved from 2,4-diketone and hydrazine with a very mild condition\(^9\).

But at the same time, the same kind of cyclisation with curcumin is not possible with such mild condition due to the complex nature of 1,3-diketone. i.e., the keto group is \(\alpha, \beta\)-unsaturated ketone in curcumin.

This is making trouble in two ways, i.e., this reduces the reactivity of 1,3-diketone. On the other hand, the hydrazine may cyclise with double bond under drastic conditions. This structural feature restricts the synthesis of hydrazinocurcumin.

Hydrazinocurcumin (33) was first synthesised by Flynn et al\(^{10}\) in 1991 by treating alcoholic solution of curcumin (41), acetic acid and hydrazine hydrate under 60° C for 24 h. The yield of the reaction is just 5%.
Arylhydrazinocurcumin (34) were synthesised later to establish the various biological activities. The aryl substituted hydrazines gave arylhydrazinocurcumin (34) under similar conditions. These arylhydrazinocurcumin (34) are vital in a view of SAR based drug discovery.

On the other hand, the heteroarylhydrazinocurcumin was not appeared much in the literature due to sluggish reactivity of heteroaryl hydrazines compared to aryl hydrazines along with the complexity of curcumin structural feature. The heteroarylhydrazinocurcumin, a new class is important due to an additional hetero atom compared to hydrazinocurcumin.

In the present work, the new classes of curcumin derivatives were synthesized by microwave assisted reaction. Consequently deals with the microwave assisted synthesis of heteroarylhydrazinocurcumin, optimisation of the reaction time and the accelerated synthesis of arylhydrazinocurcumin.
Hydrazinocurcumin (33) was first synthesised by Flynn et al\textsuperscript{10} in 1991 by treating alcoholic solution of curcumin (41), acetic acid and hydrazine hydrate under 60°C for 24 h. The yield of the reaction is just 5%, investigated for cyclooxygenase inhibition and found to be more active ($IC_{50} = 1.0 \mu M$).

Hydrazinocurcuminoids (35) and Benzoylhydrazinocurcuminoids (36) were synthesised by J. S. Shim et al\textsuperscript{4} in 2002 by treating curcumin, acetic acid and hydrazine hydrochloride under room temperature for 24 h to get 65% yield. Then it is investigated for inhibition of endothelial cell proliferation. Out of these six compounds, hydrazinocurcumin was found to be most potent inhibitory against BAECs.
Hydrazinocurcuminoids (35) were also synthesised and investigated for its antioxidant and anti-inflammatory activity by C. Selvam et al in 2005 by treating curcumin acetic acid and hydrazinehydrate at room temperature for 7 h. The antioxidant activity was measured using DPPH radical scavenging assay. Hydrazinocurcumin shown more antioxidant activity (IC\(_{50}\) = 9.7 µM) than Trolox\(^{11}\) (an antioxidant standard). It was shown high anti-inflammatory activity 68.8% than curcumin itself.

\[
\begin{align*}
\text{R} & \quad \text{R} & \quad \text{R} \\
a & \text{H} & \text{H} & \text{H} \\
b & \text{H} & \text{H} & \text{F} \\
c & \text{H} & \text{NO}_2 & \text{H} \\
d & \text{Cl} & \text{H} & \text{Cl} \\
e & \text{H} & \text{H} & \text{OCH}_3
\end{align*}
\]

Arylhydrazinocurcumins (37) were synthesized by S.Mishra et al\(^{12}\), Indian Institute of Science, Bangalore (2008) by refluxing curcumin and arylhydrazine in acetic acid for 8 h. The yield of the reaction was observed between 60-70% in most of the cases. Compound (37c) exhibited remarkable antimalarial activity (IC\(_{50}\) = 9.7 µM) against \textit{P.falciparum}. 
Methylhydrazinocurcumin (38b) was synthesized by J. R. Fuchs et al.\textsuperscript{13}, 2009 by refluxing curcumin (41) and substituted hydrazine at 85\degree C for 6 h. These compounds were tested against prostate and breast cancer cell lines and exhibited good activities.

| b | R= benzyl |
| c | R= Phenyl |
| d | R= 4-nitrophenyl |
| e | R= 6-chloropyridazin-3-yl |
| f | R=4-tolyl |
| g | R= 4-isopropylphenyl |
| h | R= methyl |
| i | R=hydroxymethyl |
| j | R= 3-nitrophenyl |
| k | R= 3,5-dichlorophenyl |

B. Schmidt et al.\textsuperscript{14}, 2008 synthesized arylhydrazinocurcumins (39) using the above mentioned procedures as well as TFA toluene reflux conditions from 24 to 72 h.
reaction time. This group synthesised a heteroarylhydrazinocurcumin, compound (39c) with long reaction time and low yield (54%).

\[
\begin{align*}
\text{OH} & \quad \text{O} \\
\text{HO} & \quad \text{N} \\
& \quad \text{N} \\
& \quad \text{R}
\end{align*}
\]

(40)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Me</td>
</tr>
<tr>
<td>b</td>
<td>Ph</td>
</tr>
<tr>
<td>c</td>
<td>t-Bu</td>
</tr>
<tr>
<td>d</td>
<td>2-F-Ph</td>
</tr>
<tr>
<td>e</td>
<td>3-F-Ph</td>
</tr>
<tr>
<td>f</td>
<td>4-F-Ph</td>
</tr>
<tr>
<td>g</td>
<td>3-NO2-Ph</td>
</tr>
<tr>
<td>h</td>
<td>4-Ome-Ph</td>
</tr>
<tr>
<td>i</td>
<td>4-CF3-Ph</td>
</tr>
<tr>
<td>j</td>
<td>2,5-DiF-Ph</td>
</tr>
</tbody>
</table>

Schubert et al.\textsuperscript{15}, 2009 has synthesised arylhydrazinocurcumin (40) under TFA, toluene refluxing conditions for 48 h, with 40-55% yields, and evaluated as potential compounds against neural disorders.

4.1.2. MICROWAVE ASSISTED ORGANIC SYNTHESIS (MAOS)

MICROWAVES THEORY
A microwave is a form of electromagnetic energy defined within the frequency range between 300 and 3,000,000 MHz and with a wave length interval between 1 mm and 30 cm. Within this region of electromagnetic energy, only molecular rotation is affected, not molecular structure. The no. of Microwave Assisted Organic Reaction (MAOS) citations from Pubmed clearly indicates the importance of microwave assisted organic synthesis in modern days.

Fig. 4.1. Pubmed Citations on Microwave Assisted Organic Synthesis

MICROWAVE HEATING AND ITS MECHANISM
Microwave is an electromagnetic radiation, only its electric field is responsible of the energy transfer to heat substances, since magnetic interactions do not occur in chemical synthesis. This electric field can heat the matter through three different mechanisms:\textsuperscript{17}

i) \textbf{Dipole rotation:} This is an interaction in which polar molecules try to align themselves with the rapidly changing electric field of the microwave. The rotational motion of the molecule as it tries to orient itself with the field results in a transfer of energy. The coupling ability of this mechanism is related to the polarity of the molecules and their ability to align with the electric field.

ii) \textbf{Ionic conduction:} This is an interaction that occurs when there are free ions or ionic species present in the substance being heated. The electric field generates ionic motion as the molecules try to orient themselves to the rapidly changing field. This causes the instantaneous superheating as in the previous case. The temperature of the substance also affects ionic conduction: as the temperature increases, the transfer of energy becomes more efficient. In case of metals, very conducive substances, the main microwaves energy does not penetrate the metal surface, it is reflected and the induced voltage generates electrical discharges that could cause an explosion. That is the reason why metals should not be introduced in a microwave oven.

iii) \textbf{Interfacial ionization:} This third mechanism is less common than the other two. This interaction occurs in systems with inclusions of conductive materials in a non-conductive matrix. The combination of these products causes that the whole material behaves as a good microwave absorbent as a combination of the other two mechanisms explained above.
In conductive heating, there is an external heating source and the heat is driven into the substance, passing first through the walls of the vessel in order to reach the solvent and the reactants. This is a slow and inefficient method for transferring energy into the system and this lack of efficiency causes some drawbacks\textsuperscript{17}:

1. The temperature of the vessel is always higher than the temperature of the reaction mixture inside. Thus, there is generation of thermal gradients.

2. The energy transfer depends on the thermal conductivity of the vessel and the materials being heated present in the reaction medium.

3. The reaction times are longer due to the difficulty to reach a thermal equilibrium.

\begin{figure}[h]
\centering
\includegraphics[width=\linewidth]{microwave_vs_thermal_heating.png}
\caption{Microwave heating Vs. Thermal heating}
\end{figure}

Microwave heating, as it has been explained, is a very different process. The microwaves couple directly with the polar molecules or ions that is present in the reaction medium, leading to a rapid increase in the temperature. Thus, in this case, the heat does not go from outside to inside. The heat is directly generated inside the material and it is driven to its surface. Furthermore, as stated before, there are materials\textsuperscript{17} transparent to this kind of
radiation and these materials can be used to construct the vessel and the oven cavity, minimizing the lost of heat in the energy transfer to the system. So the lost of heat in the energy transfer to the system is minimized.

**Advantages of microwave heating in comparison with conductive heating**\(^{18}\)

Microwave causes reduction of the reaction times due to its higher efficiency to transfer energy to the reactants\(^{19}\). Furthermore, in some cases it makes possible to overcome high energetic barriers and promote transformations that are currently not possible using conventional heating. This is creating new perspectives in synthetic chemistry.

It is easy to reach the temperature equilibrium and also the chemical control of the reaction, due to the homogeneity of the electrical field.

It is a selective heating source, since its ability to heat depends on the dielectric constant of every substance. It causes high localized temperatures (“hot spots”) inside the reaction medium.

Due to the fact that the energy is transferred through molecular excitation, the heating is fast and it has a high penetration power. As a consequence, reactions are more uniform\(^{20}\).

Industrial application of microwave is cleaner and cheaper because it is possible to work continuously. Furthermore, because of the increase in reaction rates, it causes a reduction in the production lines length, which implies a reduction in space and costs\(^{20}\).

**4.2. RESULTS AND DISCUSSION**
The microwave assisted synthesis of heteroarylhydrazinocurcumin (44a-d) and arylhydrazinocurcumin (45a-h) were achieved by subjecting in to 120ºC heating with the help of microwave radiation in acetic acid with high yields (75-91%). Further, the reaction time optimisation also discussed by setting model reaction with curcumin (41) and 2-pyridyl hydrazine (47a) to form compound (44a). The starting material curcumin (41) was extracted from nutraceutical (turmeric).

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Compound</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44a</td>
<td>2-pyridyl</td>
</tr>
<tr>
<td>2</td>
<td>44b</td>
<td>2-Me-4-pyridyl</td>
</tr>
<tr>
<td>3</td>
<td>44c</td>
<td>3-Me-4-pyridyl</td>
</tr>
<tr>
<td>4</td>
<td>44d</td>
<td>7-chloroquinolin-4-yl</td>
</tr>
<tr>
<td>5</td>
<td>45a</td>
<td>H</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phenyl</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>----------</td>
</tr>
<tr>
<td>6</td>
<td>45b</td>
<td>Phenyl</td>
</tr>
<tr>
<td>7</td>
<td>45c</td>
<td>2-NO₂-phenyl</td>
</tr>
<tr>
<td>8</td>
<td>45d</td>
<td>3-Br-phenyl</td>
</tr>
<tr>
<td>9</td>
<td>45e</td>
<td>5-bromo-2-methoxyphenyl</td>
</tr>
<tr>
<td>10</td>
<td>45f</td>
<td>2-bromo-5-chlorophenyl</td>
</tr>
<tr>
<td>11</td>
<td>45g</td>
<td>2-bromo-5-(trifluoromethyl)phenyl</td>
</tr>
<tr>
<td>12</td>
<td>45h</td>
<td>4-chlorophenyl</td>
</tr>
</tbody>
</table>

**Scheme 4.1.** Microwave assisted synthesis of aryl and heteroarylhydrazinocurcumin (44a-d) and (45a-h)

The structures of the compounds were elucidated by using $^1$H, $^{13}$C NMR and LCMS data. The $^1$H and $^{13}$C NMR spectroscopic data of (44a-d) and (45a-h) are given in Tables 4.1. and 4.2. respectively.

**$^1$H NMR spectra**

**Table 4.1.** $^1$H NMR spectral data of heteroarylhydrazinocurcumin (44a-d) and arylhydrazinocurcumin (45a-h)
### Table 4.1

<table>
<thead>
<tr>
<th>44a</th>
<th>3.90, 3.93</th>
<th>6.80</th>
<th>7.57, 7.81, 7.98, 8.56</th>
<th>6.80, 6.96, 7.09, 7.15, 7.39</th>
<th>-</th>
</tr>
</thead>
<tbody>
<tr>
<td>44b</td>
<td>3.81, 3.84</td>
<td>6.77</td>
<td>7.35, 7.49, 8.57</td>
<td>6.77, 6.98, 7.06, 7.11, 7.35</td>
<td>2.57 (Me)</td>
</tr>
<tr>
<td>44c</td>
<td>3.84, 3.93</td>
<td>6.42</td>
<td>7.44, 8.61, 8.69</td>
<td>6.75, 6.81, 6.90, 6.97, 7.15</td>
<td>2.25 (Me)</td>
</tr>
<tr>
<td>44d</td>
<td>3.80, 3.94</td>
<td>6.50</td>
<td>7.65, 7.69, 7.88, 8.24, 9.11</td>
<td>6.73, 6.82, 6.95, 7.18, 7.28</td>
<td></td>
</tr>
<tr>
<td>45a</td>
<td>3.92</td>
<td>6.65</td>
<td>-</td>
<td>6.80, 6.88, 6.99, 7.08</td>
<td>-</td>
</tr>
<tr>
<td>45b</td>
<td>3.81, 3.88</td>
<td>6.61</td>
<td>7.46, 7.55</td>
<td>6.75, 6.86, 6.93, 7.08</td>
<td>-</td>
</tr>
<tr>
<td>45c</td>
<td>3.82, 3.82</td>
<td>6.49</td>
<td>7.64, 7.73, 7.85, 8.14</td>
<td>6.73, 6.85, 6.99, 7.09</td>
<td>-</td>
</tr>
<tr>
<td>45d</td>
<td>3.85, 3.91</td>
<td>6.67</td>
<td>7.46, 7.63, 7.65</td>
<td>6.77, 6.92, 6.99, 7.01</td>
<td></td>
</tr>
<tr>
<td>45e</td>
<td>3.81, 3.91</td>
<td>6.38</td>
<td>7.56, 7.66</td>
<td>6.72, 6.81, 6.93, 7.11</td>
<td>3.84 (OMe)</td>
</tr>
<tr>
<td>45f</td>
<td>3.83, 3.92</td>
<td>6.29</td>
<td>7.56, 7.65, 7.86</td>
<td>6.78, 6.85, 6.92, 6.96, 7.00, 7.10</td>
<td>-</td>
</tr>
<tr>
<td>45g</td>
<td>3.82, 3.93</td>
<td>6.30</td>
<td>7.84, 7.92, 8.10</td>
<td>6.72, 6.81, 6.85, 6.90, 7.00, 7.12, 7.17</td>
<td>-</td>
</tr>
<tr>
<td>45h</td>
<td>3.87, 3.93</td>
<td>6.66</td>
<td>7.52, 7.59</td>
<td>6.78, 6.92, 6.96, 7.00,</td>
<td>-</td>
</tr>
</tbody>
</table>

The $^1$H NMR spectrum of compounds (44a-d) and (45a-h) were in accordance with the expected protons shift values. This proton shift values were tabulated in Table 4.1. The symmetric structure of curcumin (41) was changed to asymmetric after conversion into aryl and heteroarylhydrazinocurcumins except the compound (45a). This is illustrated in the Fig. 4.3.
This structural change reflects as expected in the $^1$H NMR. The two Methoxy groups of compounds (44a-d) and (45b-h) were observed as two peaks between 3.8 and 4.0 ppm. The pyrazol proton was observed between 6.2 and 6.8 ppm. The aryl and allyl protons were observed the range between 6.7 and 7.4 ppm. This 10 different protons overlap in a small region makes the NMR spectra very complex to understand. The hydrazino aryl protons were observed in the range between 7.3 and 9.5 ppm, with respect to the substitution.

Scheme 4.2. Synthesis of heteroarylhydrazines
The heteroarylhydrazines (47a-d) were synthesised from corresponding chloro compound (46a-d) by hydrazination by refluxing with hydrazine hydrate. The $^1$H NMR of hetero arylhydrazines (47a-h) were in accordance with the expected proton shift values.

\[
\begin{align*}
\text{(48c-h)} & \xrightarrow{\text{H}_2\text{SO}_4, \text{HCl, 0 C}} \text{(49c-h)} & \xrightarrow{\text{Sn/HCl}} \text{(50c-h)}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Compound</th>
<th>( R )</th>
</tr>
</thead>
<tbody>
<tr>
<td>50c</td>
<td>2-NO₂</td>
</tr>
<tr>
<td>50d</td>
<td>3-Br</td>
</tr>
<tr>
<td>50e</td>
<td>5-bromo-2-methoxy</td>
</tr>
<tr>
<td>50f</td>
<td>2-bromo-5-chloro</td>
</tr>
<tr>
<td>50g</td>
<td>2-bromo-5-(trifluoromethyl)</td>
</tr>
<tr>
<td>50h</td>
<td>4-chloro</td>
</tr>
</tbody>
</table>

**Scheme 4.3.** Synthesis of arylhydrazines

The arylhydrazines (50c-h) were synthesised from corresponding amine (48c-h) via conversion in to diazonisation (49c-h) followed by reduction with hydrogen source. The $^1$H NMR of arylhydrazines (50c-h) were in accordance with the expected proton shift values.
### Table 4.2. $^{13}$C NMR spectral data of heteroarylhydrazinocurcumins (44a-d) and arylhydrazinocurcumins (45a-h)

<table>
<thead>
<tr>
<th>Compd.</th>
<th>OMe</th>
<th>Pyrazol</th>
<th>Hydrazino R -aryl</th>
<th>Aryl and allyl</th>
<th>Other protons</th>
</tr>
</thead>
<tbody>
<tr>
<td>44a</td>
<td>56.42</td>
<td>102.53</td>
<td>149.12, 149.23, 149.28, 153.84, 154.20</td>
<td>110.52, 111.03, 115.34, 116.40, 116.48, 117.93, 118.84, 121.59, 123.45, 130.38, 130.48, 133.50, 134.19, 140.33, 145.64, 148.21, 148.47</td>
<td>-</td>
</tr>
<tr>
<td>44b</td>
<td>56.39</td>
<td>100.99</td>
<td>149.18, 149.27, 149.42, 153.27, 153.98</td>
<td>110.37, 110.89, 111.59, 116.39, 116.59, 117.39, 121.54, 121.72, 123.74, 129.05, 130.10, 132.98, 133.31, 135.57, 145.37, 147.16, 148.37, 149.05</td>
<td>20.01 (Me)</td>
</tr>
<tr>
<td>44c</td>
<td>56.41</td>
<td>100.91</td>
<td>149.40, 149.49, 149.64, 153.49, 154.20</td>
<td>110.48, 110.00, 111.70, 116.50, 116.70, 117.50, 121.65, 121.83, 123.85, 129.16, 130.21, 133.07, 133.42, 135.68, 145.39, 147.38, 148.59, 149.27</td>
<td>15.04 (Me)</td>
</tr>
<tr>
<td>44d</td>
<td>56.40</td>
<td>100.83</td>
<td>149.12, 149.23, 149.28, 151.21, 153.84, 154.20, 155.11</td>
<td>110.50, 111.01, 115.32, 116.42, 116.45, 117.90, 118.81, 121.56, 123.40, 130.38, 130.48, 133.50, 134.19, 140.33, 145.61, 148.17, 148.37</td>
<td>-</td>
</tr>
<tr>
<td>45a</td>
<td>56.9</td>
<td>98.8</td>
<td>-</td>
<td>110.9, 113.81, 116.72, 117.4, 122.65, 122.89, 130.03, 136.61, 137.84, 148.21, 148.33, 151.43, 151.84</td>
<td>-</td>
</tr>
<tr>
<td>45b</td>
<td>56.41</td>
<td>101.22</td>
<td>140.61, 144.58, 148.09, 148.62, 149.26, 153.11</td>
<td>110.49, 110.99, 113.31, 116.41, 116.53, 117.95, 121.54, 126.83, 129.44, 129.93, 130.47, 130.58, 132.83, 134.1</td>
<td>-</td>
</tr>
<tr>
<td>45c</td>
<td>56.33, 56.46</td>
<td>101.31</td>
<td>145.89, 147.86, 148.24, 148.96, 149.28, 154.35</td>
<td>110.49, 110.94, 111.03, 111.03, 111.80, 116.51, 117.59, 121.68, 126.55, 129.57, 130.40, 131.11, 131.38, 133.45, 134.95, 135.71</td>
<td>-</td>
</tr>
</tbody>
</table>
The $^{13}$C NMR spectrum of compounds (44a-d) and (45a-h) were in accordance with the expected chemical shift values. This chemical shift values were tabulated in the above Table 4.2. The Methoxy carbons were observed between 55 and 56 ppm. In most of the cases, both the Methoxy peaks overlap and observed as single signal except compounds (45c) and (45g).
Fig. 4.4. Asymmetric carbon environment of hydrazinocurcumin.

The asymmetric nature of the compounds (44a-d) and (45a-h) results of 12 phenyl carbons, 4 allyl carbons and 3 pyrazol carbons (environment 9 & 11) were observed in the region between 110 and 140 ppm. These signals were observed as overlap with each other. The pyrazole carbon environment 10 was observed slightly down field around 99 - 102 ppm. The hydrazino aryl protons were observed up field region between 140 and 160 ppm.

Optimisation of reaction time for the synthesis of heteroarylyhydrazinocurcumin

(44a-d)

The reaction time was optimized by setting a model reaction with 2-hydrazino pyridine (47a) and curcumin (41) in acetic acid under microwave condition with 120°C. The reaction was carried out as described in general procedure and 2-hydrazino pyridine (47a) was taken as heteroarylyhydrazine. The reaction was monitored for each 15 minutes with HPLC. The percentage of product formed was tabulated in Table 4.3.
Table 4.3. Reaction time and conversion of curcumin (41) into compound (44a)

<table>
<thead>
<tr>
<th>Sl.No</th>
<th>Time (Mins)</th>
<th>Product (in %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>53.3</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>75</td>
<td>88.4</td>
</tr>
<tr>
<td>6</td>
<td>90</td>
<td>100</td>
</tr>
</tbody>
</table>

From the Table 4.3., it is evident that the reaction requires 90 minutes to complete the conversion. The first 15 minutes, the reaction progress was very fast and it reaches 40% conversion whereas in the second 15 minutes, the reaction progress was additional by 13% and consequently reaches 11%, 10% 13% and 12%.

Advantages of microwave assisted reaction

Table 4.4. Reaction time and yield for the conversion of curcumin (41) into compounds (44a-d)

<table>
<thead>
<tr>
<th>Sl.no</th>
<th>Compound No</th>
<th>Molecular weight</th>
<th>Molecular formula</th>
<th>Yield</th>
<th>Reaction time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44a</td>
<td>441.48</td>
<td>C26H23N3O4</td>
<td>87%</td>
<td>1.5 h</td>
</tr>
<tr>
<td>2</td>
<td>44b</td>
<td>455.51</td>
<td>C27H25N3O4</td>
<td>78%</td>
<td>1.5 h</td>
</tr>
<tr>
<td>3</td>
<td>44c</td>
<td>455.51</td>
<td>C27H25N3O4</td>
<td>77%</td>
<td>1.5 h</td>
</tr>
<tr>
<td>4</td>
<td>44d</td>
<td>491.18</td>
<td>C30H25N3O4</td>
<td>84%</td>
<td>1.5 h</td>
</tr>
</tbody>
</table>
The synthesis of arylhydrazinocurcumin with the help of microwave condition reduced the reaction time drastically with very good yields.

**General procedure for the synthesis of arylhydrazinocurcumin:**

To a solution of curcumin (41) (1 eq) in glacial acetic acid 5 volume, added 1.2 eq of aryl hydrazine. The reaction mixture was heated to 120°C in microwave for 10 minutes. TLC compiled shows clear formation of polar spot. The excess acetic acid evaporated to dryness using high vaccum pump. The crude material was purified by preparative TLC plate using MeOH: DCM as an eluent system.

**Table 4.5.** Reaction time and yield for the conversion of curcumin (41) into compounds (45a-h)

<table>
<thead>
<tr>
<th>Sl. No</th>
<th>Compound No.</th>
<th>Mol. Wt.</th>
<th>Molecular formula</th>
<th>Yield (%)</th>
<th>Reaction time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Actual</td>
<td>Lit.</td>
</tr>
<tr>
<td>1</td>
<td>45a</td>
<td>364.39</td>
<td>C_{21}H_{20}N_{2}O_{4}</td>
<td>80</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>45b</td>
<td>440.49</td>
<td>C_{27}H_{24}N_{2}O_{4}</td>
<td>83</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>45c</td>
<td>485.49</td>
<td>C_{27}H_{23}N_{3}O_{6}</td>
<td>79</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>45d</td>
<td>519.39</td>
<td>C_{27}H_{23}BrN_{2}O_{4}</td>
<td>92</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>45e</td>
<td>549.41</td>
<td>C_{28}H_{25}BrN_{2}O_{5}</td>
<td>78</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>45f</td>
<td>553.83</td>
<td>C_{27}H_{22}BrClN_{2}O_{4}</td>
<td>77</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>45g</td>
<td>587.38</td>
<td>C_{28}H_{22}BrF_{3}N_{2}O_{4}</td>
<td>77</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>45h</td>
<td>474.94</td>
<td>C_{27}H_{23}ClN_{2}O_{4}</td>
<td>73</td>
<td>-</td>
</tr>
</tbody>
</table>
The novel method for the synthesis of arylhydrazinocurcumin and heteroarylhydrazinocurcumin reduced the reaction time drastically. The yields of the reaction were also good as compared to the classical reaction conditions.

Fig. 4.8. Comparison of reaction time of microwave assisted reaction with thermal heating

4.3. CONCLUSION

The present work describes the synthesis of ten novel compounds with novel methodology. This microwave assisted novel synthetic method will be helpful for the acceleration of drug discovery in the antitumor and anti-inflammatory research pertains to curcumin derivatives. The advantages of heteroarylhydrazinocurcumin are as follows,

i) Synthesis of new class of curcumin derivative opens the opportunities in drug discovery.

ii) Reduced reaction time will accelerate the drug discovery process.
iii) Complex structural features will be interesting fact for biological activity ie., additional heteroatom.

iv) Yields are more than 79-87%.

v) The microwave assisted arylhydrazinocurcumin synthesis becomes rapid synthesis. It will be useful for the library synthesis. It helps to reduce the reaction time drastically and hence accelerate the research.

vi) Industrial application of microwave reaction is cleaner and cheaper because it is possible to work continuously.

vii) Due to the increase in reaction rates, it causes a reduction in the production lines length, which implies a reduction in space and costs.

4.4. EXPERIMENTAL

4.4.1. General Data

The $^1$H and $^{13}$C NMR spectra of the heteroarylhazinocurcumin (44a-d) and arylhydrazinocurcumin (45a-h) were measured at 400 MHz and 100 MHz respectively using Bruker (Avance) NMR instrument in CD$_3$OD unless otherwise specified and the chemical shifts referenced to tetramethylsilane. All the NMR spectra were measured using standard Bruker software throughout. CEM® Microwave parallel synthesiser 200 W is used for the entire microwave assisted reactions.
4.4.2. Phytochemical studies

Drying the Rhizome

The fresh turmeric samples (Curcuma longa rhizome) were purchased from Vickramasingapuram market, Tirunelveli district, TamilNadu, India. The rhizome was washed with water to remove the mud. The rhizome was dried under shade for 2 weeks. The rhizomes were pulverized into fine powder.

Defatification:

The dried powder of the Curcuma longa rhizome was stirred well with petroleum ether in a round bottom flask for 30 minutes. Then the content was allowed to settle. Then it was filtered through a filtration funnel. The solid portion was collected in a round bottom flask. This petroleum ether washing were repeated thrice to completely remove the fat materials.

Isolation of curcuminoids\(^\text{16}\):

The fine powder of Curcuma longa rhizome after defatification was collected in a round bottom flask. Then it was stirred with methanol for 30 minutes. Then it was filtered through a filtration funnel. This procedure repeated until to get colourless methanol extract which indicates the complete extraction of curcuminoids. The filtrate was collected in a round bottom flask and concentrated in rotoevaporator under high vacuum pump at 50°C. This crude curcuminoid mixture was examined by TLC and LCMS. The TLC with 3% Methanol: DCM indicates three separate spots as shown in the figure. Curcumin with
0.8 R_f, demethoxycurcumin with 0.45 R_f, bisdemethoxycurcumin at 0.30 R_f were observed. The LCMS shows three major masses corresponds to the curcuminoids m/e are 369, 339 and 309.

Fig. 4.9. TLC of curcuminoids

This crude curcuminoid extract was purified by combiflash\textsuperscript{®} column purifier using Methanol: DCM system as a mobile phase and silica gel column as stationary phase. The curcuminoids were isolated from 0.5\% to 4\% Methanol: DCM as eluent. The roughly purified compounds were loaded in to preparative TLC plate using 3\% Methanol: dichlormethane system.

**General procedure for the synthesis of heteroarylhydrazinocurcumin (44a-d)**

To a solution of curcumin (41) (1 eq) in glacial acetic acid 5 volume, added 1.2 eq of heteroarylhydrazine. The reaction mixture was heated to 120°C in microwave for 1.5 h. TLC compiled shows clear formation of polar spot. The excess acetic acid evaporated to dryness, purified by preparative TLC plate.
General procedure for the synthesis of arylhydrazinocurcumins (45a-h)

To a solution of curcumin (41) (1 eq) in glacial acetic acid 5 volume, added 1.2 eq of aryl hydrazine. The reaction mixture was heated to 120°C in microwave for 10 minutes. TLC compiled shows clear formation of polar spot. The excess acetic acid evaporated to dryness, purified by preparative TLC plate.

General Procedure for the synthesis of Heteroarylhydrazines (47a-d)

A mixture of chloro compound (1 eq) (46a-d) in hydrazine hydrate (5 eq) was allowed to reflux for 16h. TLC compiled shows clear formation of polar spot. The solution was cooled to room temperature, excess hydrazine hydrate was evaporated under reduced pressure and the residue was poured into water. The solution was made alkaline by the addition of 1 N NaOH solution, and extracted with chloroform. The combine organic layer dried over Na₂SO₄, evaporated under reduced pressure.

General Procedure for the synthesis of arylhydrazines (50c-h)

To a suspension of amine (1 eq) (48c-h) in con. HCl (5 vol) was added dropwise a solution of sodium nitrite (1.1 eq) in water (5 vol) over 30 min at 0 °C. The reaction mixture was allowed to stir for 30 min. To the reaction mixture was added dropwise a solution of SnCl₂. 2H₂O (3 eq) in con. HCl (2 vol) over 1 h. The reaction mixture was allowed to stir at 0 °C for 1 h. TLC compiled shows clear polar spot formation. The reaction mixture was made alkaline with 1.5 N NaOH solution, extracted with
diethylether. The combined organic layers were dried over Na$_2$SO$_4$, evaporated under reduced pressure.

**Curcumin (41)**

![Curcumin](image)

Analytical data:
$^1$H NMR (400 MHz, D$_6$-DMSO) 6.06 (s, 1H), 6.73 (d, J = 16 Hz, 2H), 6.82 (d, J = 16 Hz, 2H), 7.14 (m, 2H), 7.32 (d, J = 1.6 Hz, 2H), 7.53 (d, J = 16 Hz, 2H), 9.65 (s, 2H);
$^{13}$C NMR (100 MHz) δ 56.17, 101.26, 111.85, 116.18, 121.55, 123.57, 126.79, 141.15, 148.47, 148.85, 183.66;
LCMS (m/z):369.2 [M$^+$];

**Demethoxycurcumin (42)**

![Demethoxycurcumin](image)

Analytical data:
$^1$H NMR (400 MHz, D$_6$-DMSO) 3.83 (s, 3H), 6.00 (s, 1H), 6.75 (m, 3H), 6.81 (t, J = 3.6 Hz, 2H), 7.12 (d, J = 7.6 Hz, 1H), 7.30 (s, 1H), 7.51 (m, 4H); $^{13}$C NMR (100 MHz) δ
56.13, 101.36, 111.67, 116.27, 116.49, 121.26, 123.81, 126.01, 126.35, 130.74, 140.63, 141.06, 148.64, 150.65, 160.78, 183.49;
LCMS (m/z):337.0 [M]+;

Bisdemethoxycurcumin (43)

Analytical data:
^1^H NMR (400 MHz, D6-DMSO) 6.03 (s, 1H), 6.84 (d, J = 8.2 Hz, 4H), 7.55 ( d, J = 15.9 Hz, 4H), 7.56 ( d, J = 8.2 Hz, 4H), 10.03 (s, 2H) ; ^13^C NMR (100 MHz) δ 56.10, 100.91, 115.90, 120.82, 125.84, 130.33, 140.81, 159.83, 183.21;
LCMS (m/z):307.2 [M]+;

4-((E)-2-(5-((E)-4-hydroxy-3-methoxystyryl)-1-(pyridin-2-yl)-1H-pyrazol-3-yl)vinyl)-2-methoxyphenol (44a)
This compound was synthesized by using the general procedure described in

**Scheme 4.1.** This compound was purified by preparative TLC plate using 2.0% Methanol: DCM as eluent system to get reddish brown solid of 87.0% yield

Analytical data:

$^1$H NMR (400 MHz, CD$_3$OD) δ 3.90 (s, 3H), 3.93 (s, 3H), 6.80 (m, 2H), 6.96 (m, 4H), 7.09 (d, J = 1.6 Hz, 1H), 7.15 (m, 3H), 7.42 (dd, J = 6.8, 5.2 Hz, 1H), 7.57 (d, J = 16.4 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 8.00 (dd, J = 7.8, 1.4 Hz, 1H), 8.56 (s, 1H); $^{13}$C NMR (100 MHz, CD$_3$OD) δ 56.42, 102.53, 110.52, 111.03, 115.34, 116.40, 116.48, 117.93, 118.84, 121.59, 123.45, 130.38, 130.48, 133.50, 134.19, 140.33, 145.64, 148.21, 148.47, 149.12, 149.23, 149.28, 153.84, 154.20;

LCMS (m/z): 442.2 [M$^+$].
This compound was synthesized by using the general procedure described in Scheme 4.1. This compound was purified by preparative TLC plate using 2.0% Methanol: DCM as eluent system to get reddish brown solid of 78.0% yield.

Analytical data:

$^1$H NMR (400 MHz, CD$_3$OD) δ 2.57 (s, 3H), 3.81 (s, 3H), 3.84 (s, 3H), 6.80 (dd, $J = 8.0$, 1.6 Hz, 2H), 7.02 (m, 3H), 7.11 (m,1H), 7.19 (m, 3H), 7.49 (m, 1H), 8.69 (s, 1H);

$^{13}$C NMR (100 MHz, CD$_3$OD) δ 20.01, 56.39, 100.99, 110.37, 110.89, 111.59, 116.39, 116.59, 117.39, 121.54, 121.72, 123.74, 124.05, 130.10, 132.98, 133.31, 135.57, 145.37, 147.16, 148.37, 149.05, 149.18, 149.27, 149.42, 153.27, 153.98;

LCMS (m/z): 456.2 [M$^+$].
4-((E)-2-(5-((E)-4-hydroxy-3-methoxystyryl)-1-(3-methylpyridin-4-yl)-1H-pyrazol-3-yl)vinyl)-2-methoxyphenol (44c)

This compound was synthesized by using the general procedure described in Scheme 4.1. This compound was purified by preparative TLC plate using 2.0% Methanol: DCM as eluent system to get reddish brown solid of 77.0% yield.

Analytical data:

$^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 2.25 (s, 3H), 3.84 (s, 3H), 3.93 (s, 3H), 6.42 (d, $J = 16.4$ Hz, 1H), 6.75 (d, $J = 8.4$ Hz, 1H), 6.81 (d, $J = 8.0$ Hz, 1H), 6.90 (m, 1H), 6.97 (m, 4H), 7.15 (m, 3H), 7.44 (d, $J = 5.2$ Hz, 1H), 8.61 (d, $J = 5.2$ Hz, 1H), 8.69 (s, 1H); $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 15.04, 56.41, 100.91, 110.48, 111.00, 111.70, 116.50, 116.70, 117.50, 121.65, 121.83, 123.85, 129.16, 130.21, 133.07, 133.42, 135.68, 145.59, 147.38, 148.59, 149.27, 149.40, 149.49, 149.64, 153.49, 154.20;

LCMS (m/z): 456.2 [M$^+$].

4-((E)-2-(5-((E)-4-hydroxy-3-methoxystyryl)-1-(7-chloroquinolin-4-yl)-1H-pyrazol-3-yl)vinyl)-2-methoxyphenol (44d)
This compound was synthesized by using the general procedure described in Scheme 4.1. This compound was purified by preparative TLC plate using 2.0% Methanol: DCM as eluent system to get reddish brown solid of 84.0% yield.

Analytical data:

$^{1}H$ NMR (400 MHz, D6-DMSO) $\delta$ 3.80 (s, 3H), 3.94 (s, 1H), 6.54 (d, $J = 16$ Hz, 1H), 6.75 (d, $J = 7.6$ Hz, 1H), 6.84 (d, $J = 8.0$ Hz, 1H), 6.88 (d, $J = 8.4$ Hz, 1H), 7.07 (m, 4H), 7.66 (d, $J = 4.8$ Hz, 2H), 7.71 (dd, $J = 9.2$, 2.0 Hz, 1H), 7.90 (d, $J = 9.2$ Hz, 2H), 8.24 (d, $J = 2.0$ Hz, 2H), 9.12 (d, $J = 4.4$ Hz, 1H); $^{13}C$ NMR (100 MHz, D6-DMSO) $\delta$ 56.40, 100.83, 110.50, 111.01, 115.32, 116.42, 116.45, 117.90, 118.81, 121.56, 123.40, 130.38, 130.48, 133.50, 134.19, 140.33, 145.61, 148.17, 148.37, 149.12, 149.23, 149.28, 151.21, 153.84, 154.20, 155.11;

LCMS (m/z): 526.2 [M$^+$].

$4-((E)-2-(5-((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-3-yl)vinyl)-2$-methoxyphenol (45a)
This compound was synthesized by using the general procedure described in 

**Scheme 4.1.** This compound was purified by preparative TLC plate using 2.0% Methanol: DCM as eluent system to get brown solid of 80.0% yield

Analytical data:

$^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 3.92 (s, 6H), 6.65 (s, 1H), 6.80 (d, $J = 8.0$ Hz, 2H), 6.88 (m, 2H), 6.99 (d, $J = 7.6$ Hz, 2H), 7.08 (m, 4H); $^{13}$C NMR (100 MHz, D6-DMSO) $\delta$ 56.9, 98.8, 110.9, 113.81, 116.72, 117.4, 122.65,122.89, 130.03, 136.61, 137.84, 148.21, 148.33,151.43, 151.84;

LCMS (m/z): 365.2 [M$^+$].

**4-((E)-2-(5-((E)-4-hydroxy-3-methoxystyryl)-1-phenyl-1H-pyrazol-3-yl)vinyl)-2-methoxyphenol (45b)**

This compound was synthesized by using the general procedure described in 

**Scheme 4.1.** This compound was purified by preparative TLC plate using 2.0% Methanol: DCM as eluent system to get dark green solid of 83.0% yield
Analytical data:

$^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 3.81 (s, 3H), 3.88 (s, 3H), 6.61 (d, $J = 16.4$ Hz, 1H), 6.75 (m, 2H), 6.86 (m, 5H), 7.08 (m, 3H), 7.46 (m, 3H), 7.55 (m, 2H); $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 56.41, 101.22, 110.49, 110.99, 113.31, 116.41, 116.53, 117.95, 121.54, 126.83, 129.44, 129.93, 130.47, 130.58, 132.83, 134.1, 140.61, 144.58, 148.09, 148.62, 149.26, 153.11; 
LCMS (m/z): 441.6 [M$^+$].

4-((E)-2-(5-((E)-4-hydroxy-3-methoxystyryl)-1-(2-nitrophenyl)-1H-pyrazol-3-yl)vinyl)-2-methoxyphenol (45c)

![Compound 45c](image)

This compound was synthesized by using the general procedure described in Scheme 4.1. This compound was purified by preparative TLC plate using 2.0% Methanol: DCM as eluent system to get brown solid of 79.0% yield.

Analytical data:

$^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 3.82 (s, 3H), 3.89 (s, 3H), 6.49 (d, 1H), 6.73 (m, 2H), 6.85 (m, 2H), 6.99 (m, 3H), 7.09 (t, 3H), 7.64 (d, 1H), 7.73 (t, 1H), 7.85 (t, 3H), 8.14 (d, 1H);
$^{13}$C NMR (100 MHz, CD$_3$OD) δ 56.33, 56.46, 68.41, 101.31, 110.41, 110.49, 110.94, 111.03, 111.03, 111.80, 116.51, 117.59, 121.68, 126.55, 129.57, 130.40, 131.11, 131.38, 133.45, 134.95, 135.71, 145.89, 147.86, 148.24, 148.96, 149.28, 154.35;

LCMS (m/z): 485.9 [M$^+$].

4-((E)-2-(5-((E)-4-hydroxy-3-methoxystyryl)-1-(3-bromophenyl)-1H-pyrazol-3-yl)vinyl)-2-methoxyphenol (45d)

This compound was synthesized by using the general procedure described in Scheme 4.1. This compound was purified by preparative TLC plate using 2.0% Methanol: DCM as eluent system to get brown solid of 92.0% yield.

Analytical data:

$^1$H NMR (400 MHz, CD$_3$OD) δ 3.85 (s, 3H), 3.91 (s, 3H), 6.67 (d, J = 16.0 Hz, 1H), 6.77 (m, 2H), 6.92 (m, 5H), 7.01 (m, 3H), 7.46 (m, 2H), 7.63 (m, 1H), 7.65 (s, 1H); $^{13}$C NMR (100 MHz, CD$_3$OD) δ 56.43, 66.89, 101.83, 110.53, 110.86, 112.99, 116.41, 116.53, 117.74, 121.60, 121.77, 123.60, 125.22, 129.42, 129.81, 130.47, 131.96, 132.18, 133.23, 135.14, 141.87, 144.71, 148.21, 148.80, 149.30, 153.66;

LCMS (m/z): 519.2 [M$^+$].
4-((E)-2-(5-((E)-4-hydroxy-3-methoxystyryl)-1-(5-bromo-2-methoxyphenyl)-1H-pyrazol-3-yl)vinyl)-2-methoxyphenol (45e)

This compound was synthesized by using the general procedure described in Scheme 4.1. This compound was purified by preparative TLC plate using 2.0% Methanol: DCM as eluent system to get reddish brown solid of 78.0% yield

Analytical data:

$^1$H NMR (400 MHz, CD$_3$OD) $\delta$ 3.81 (s, 3H), 3.84 (s, 3H), 3.91 (s, 3H), 6.38 (d, $J = 13.6$ Hz, 1H), 6.72 (m, 1H), 6.81 (m, 3H), 6.93 (m, 5H), 7.11 (m, 5H), 7.56 (d, $J = 1.6$ Hz, 1H), 7.66 (d, $J = 8.8$ Hz, 1H); $^{13}$C NMR (100 MHz, CD$_3$OD) $\delta$ 56.44, 56.81, 100.16, 110.51, 110.98, 111.72, 113.03, 113.21, 115.57, 116.43, 116.82, 117.85, 121.42, 121.55, 129.84, 130.36, 130.53, 132.83, 132.96, 134.32, 134.78, 146.11, 148.19, 148.77, 149.30, 149.70, 153.43, 155.73;

LCMS (m/z): 549.2 [M$^+$].

4-((E)-2-(5-((E)-4-hydroxy-3-methoxystyryl)-1-(2-bromo-5-chlorophenyl)-1H-pyrazol-3-yl)vinyl)-2-methoxyphenol (45f)
This compound was synthesized by using the general procedure described in Scheme 4.1. This compound was purified by preparative TLC plate using 2.0% Methanol: DCM as eluent system to get greenish yellow solid of 77.0% yield

Analytical data:

$^1$H NMR (400 MHz, D$_6$-Acetone) $\delta$ 3.81 (s, 3H), 3.93 (s, 3H), 6.55 (d, $J = 16$ Hz, 1H), 6.79 (d, $J = 8.4$ Hz, 1H), 6.84 (d, $J = 8.0$ Hz, 1H), 6.94 (m, 1H), 7.03 (m, 4H), 7.15 (m, 3H), 7.58 (m, 1H), 7.60 (d, $J = 3.2$ Hz, 1H), 7.87 (d, $J = 8.8$ Hz, 1H); $^{13}$C NMR (100 MHz, D$_6$-Acetone) $\delta$ 55.39, 99.33, 109.12, 110.07, 111.86, 115.11, 115.27, 117.79, 120.38, 120.41, 128.55, 129.29, 130.34, 130.85, 130.95, 132.88, 133.48, 134.67, 140.18, 144.04, 146.95, 147.52, 147.73, 147.83, 152.06;

LCMS (m/z): 553.0 [M$^-$].

4-((E)-2-((5-((E)-4-hydroxy-3-methoxystyryl)-1-(2-bromo-5-(trifluoromethyl)phenyl)-1H-pyrazol-3-yl)vinyl)-2-methoxyphenol (45g)
This compound was synthesized by using the general procedure described in Scheme 4.1. This compound was purified by preparative TLC plate using 2.0% Methanol: DCM as eluent system to get greenish yellow solid of 77.0% yield.

Analytical data:

$^1$H NMR (400 MHz, D$_6$- Acetone) $\delta$ 3.80 (s, 3H), 3.93 (s, 3H), 6.53 (d, J = 16.4 Hz, 1H), 6.79 (d, J = 3.6 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.94 (dd, J = 8.4, 1.6 Hz, 1H), 7.045 (m, 4H), 7.16 (m, 3H), 7.89 (dd, J = 8.4, 1.6 Hz, 1H), 7.94 (d, J = 2.0 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H); $^{13}$C NMR (100 MHz, D$_6$- Acetone) $\delta$ 35.32, 55.32, 55.39, 99.41, 109.16, 110.03, 111.49, 115.16, 115.36, 117.58, 120.48, 122.21, 124.92, 126.54, 127.27, 127.31, 127.43, 127.62, 128.10, 129.06, 129.88, 130.21, 130.55, 130.88, 131.05, 133.13, 134.86, 139.89, 144.24, 147.20, 147.89, 148.07, 152.31, 162.07;

LCMS (m/z): 587.2 [M$^+$].

$4$-((E)$-2$-((5$-$(E)$-4$-hydroxy$-3$-methoxystyrlyl)$-1$-((4$-chlorophenyl)$-1$-H-pyrazol$-3$-yl)vinyl)$-2$-methoxyphenol (45h)
This compound was synthesized by using the general procedure described in 

**Scheme 4.1.** This compound was purified by preparative TLC plate using 2.0% Methanol: DCM as eluent system to get greenish yellow solid of 73.0% yield

Analytical data:

$^1$H NMR (400 MHz, D$_6$-CD$_3$OD) $\delta$ 3.87 (s, 3H), 3.93 (s, 3H), 6.72 (d, $J = 8.4$ Hz, 1H), 6.82 (dd, $J = 10.8$, 8.4 Hz, 2H), 6.92 (m, 3H), 7.00 (m, 2H), 7.96 (m, 3H), 7.52 (m, 2H), 7.60 (m, 2H); $^{13}$C NMR (100 MHz, D$_6$-DMSO) $\delta$ 55.52, 55.61, 100.31, 109.70, 110.74, 118.74, 115.53, 116.61, 120.12, 120.44, 120.74, 124.32, 125.04, 126.35, 127.51, 128.04, 132.02, 133.91, 145.44, 146.98, 147.62, 147.83, 152.45, 159.72;

LCMS (m/z): 475.2 [M$^+$].

**1-(pyridin-2-yl)hydrazine (47a)**

This compound was synthesized by using the general procedure described in

**Scheme 4.2.** with 97% yield.

Analytical data:
\[ \delta 4.07 \text{ (s, 2H), 6.54 (m, 1H), 6.67 (d, J = 4.4 \text{ Hz}, 1H), 7.33 \text{ (s, 1H), 7.41 (m, 1H), 7.97 (d, J = 4.8 \text{ Hz}, 1H);} \]

LCMS (m/z): 109.7 [M⁺].

1-(2-methylpyridin-4-yl)hydrazine (47b)

\[
\begin{array}{c}
H_2N\text{.}_NH_2 \\
\text{N} \\
\text{N} \\
\hline
(47b)
\end{array}
\]

This compound was synthesized by using the general procedure described in Scheme 4.2. with 95% yield.

Analytical data:

\[ \delta 2.41 \text{ (s, 3H), 4.87 (s, 2H), 6.61 (bs, 1H), 6.96 \text{ (bs, 1H), 7.95 (bs, 1H), 9.56 (s, 1H), 12.88 (bs,1H);} \]

LCMS (m/z): 123.7 [M⁺].

1-(3-methylpyridin-4-yl)hydrazine (47c)

\[
\begin{array}{c}
H_2N\text{.}_NH_2 \\
\text{N} \\
\text{N} \\
\hline
(47c)
\end{array}
\]

This compound was synthesized by using the general procedure described in Scheme 4.2. with 96% yield.

Analytical data:
\(^1\)H NMR (400 MHz, D\(^6\)-DMSO) \(\delta\) 2.09 (s, 3H), 7.20 (d, \(J = 6.8\) Hz, 1H), 8.02 (s, 1H), 8.16 (d, \(J = 6.8\) Hz, 1H), 9.25 (s, 1H), 13.39 (s, 1H);

LCMS (m/z): 123.7 [M\(^+\)].

1-(7-chloroquinolin-4-yl)hydrazine (47d)

![Image of compound 47d]

This compound was synthesized by using the general procedure described in Scheme 4.2, with 91% yield.

Analytical data:

\(^1\)H NMR (400 MHz, D\(^6\)-DMSO) \(\delta\) 4.45 (s, 2H), 6.89 (s, 1H), 7.38 (d, \(J = 8.8\) Hz, 1H), 7.77 (s, 1H), 8.15 (d, \(J = 9.2\) Hz, 1H), 8.42 (s, 1H), 8.60 (s, 1H);

LCMS (m/z): 194.0 [M\(^+\)].

1-(2-nitrophenyl)hydrazine hydrochloride (50c)
This compound was synthesized by using the general procedure described in **Scheme 4.3.** with 90% yield.

Analytical data:

\[^1\text{H NMR (400 MHz, D}^6\text{-DMSO)} \delta 7.02 (m, 1H), 7.34 (m, 1H), 7.71 (m, 1H), 8.14 (m, 1H), 9.22 (s, 1H); \]**

LCMS (m/z): 154.14 [M^+].

**1-(5-bromo-2-methoxyphenyl)hydrazine hydrochloride (50d)**

This compound was synthesized by using the general procedure described in **Scheme 4.3.** with 91% yield.

Analytical data:

\[^1\text{H NMR (400 MHz, D}^6\text{-DMSO)} \delta 3.82 (d, J = 4.4 \text{ Hz}, 3H), 6.94 (d, J = 8.4 \text{ Hz}, 1H), 7.10 (dd, J = 8.4, 2.4 \text{ Hz}, 1H), 7.21 (d, J = 2.4 \text{ Hz}, 1H), 7.86 (s, 1H), 10.13 (s, 2H); \]**

LCMS (m/z): 218.2 [M^+].

**1-(2-bromo-5-chlorophenyl)hydrazine hydrochloride (50e)**
This compound was synthesized by using the general procedure described in Scheme 4.3. with 93% yield.

Analytical data:

$^1$H NMR (400 MHz, D$_6$-DMSO) $\delta$ 6.97 (dd, $J = 8.4, 2.4$ Hz, 1H), 7.21 (d, $J = 2.4$ Hz, 1H), 7.59 (d, $J = 8.4$ Hz, 1H), 8.19 (s, 1H), 10.56 (bs, 2H);

LCMS (m/z): 221.0 [M$^-$].

1-(2-bromo-5-(trifluoromethyl)phenyl)hydrazine hydrochloride (50f)

This compound was synthesized by using the general procedure described in Scheme 4.3. with 95% yield.

Analytical data:

$^1$H NMR (400 MHz, D$_6$-DMSO) $\delta$ 7.24 (dd, $J = 8.2, 1.4$ Hz, 1H), 7.40 (d, $J = 1.2$ Hz, 1H), 7.82 (dd, $J = 8.2, 0.4$ Hz, 1H), 8.26 (s, 1H), 10.18 (bs, 2H);

LCMS (m/z): 256.2 [M$^-$].

1-(3-bromophenyl)hydrazine hydrochloride (50g)
This compound was synthesized by using the general procedure described in Scheme 4.3. with 93% yield.

Analytical data:

\[ ^1H\text{ NMR (400 MHz, D}_6\text{-DMSO)} \delta 6.96 \text{ (m, 1H), 7.12 \text{ (m, 1H), 7.26 \text{ (m, 2H), 8.54 \text{ (s,1H), 10.31 \text{ (s, 2H);}}}} \]

LCMS (m/z): 188.2 [M\text{+}].

**1-(4-chlorophenyl)hydrazine hydrochloride (50h)**

This compound was synthesized by using the general procedure described in Scheme 4.3. with 91% yield.

Analytical data:

\[ ^1H\text{ NMR (400 MHz, D}_6\text{-DMSO)} \delta 6.96 \text{ (m, 1H), 7.56 \text{ (m, 2H), 7.66 \text{ (m, 2H), 10.31 \text{ (s, 2H);}}}} \]

LCMS (m/z): 143.2 [M\text{+}].

4.4. REFERENCES

2. Yadav M. S; Tyagi O. D; A Texbook of Synthetic Drugs, 2004, p-16.


