5.1. INTRODUCTION

Heterocyclic compounds are acquiring more importance in recent years because of their pharmacological activities. Pyrazolones have a particular value due to their broad spectrum of biological activity and their wide ranging utility as synthetic tools to design the various bioactive molecules. Pyrazolone derivatives are an important class of heterocyclic compounds as they play a vital role both in medicinal chemistry and in organic synthesis. Pyrazolone, a derivative of pyrazole that has an additional keto (C=O) group. There are three possible isomers: 3-pyrazolone, 4-pyrazolone, and 5-pyrazolone. Pyrazolones are traditionally synthesized by treatment of β-keto esters with hydrazine substrates under acidic conditions. In the field of organic synthesis, pyrazolones are important intermediates for the synthesis of dihydro[2,3-c]pyrazoles, phenylpyrazoles, and chromeno[2,3-c]pyrazol-4(H)-ones. In addition, they also serve as precursors in agrochemical industries for the preparation of herbicides, fungicides and insecticides, liquid crystals, dyes and thermally stable polymers. Pyrazolone derivatives are useful for the extraction and separation of various metal ions. Chemical oxidation of pyrazolones to azo dienophiles provides suitable substrates for hetero Diels-Alder cycloadditions. They have been found useful as solvent extraction reagents in both acidic and non-acidic media.

The chemistry of pyrazolone has gained increasing attention due to its diverse pharmacological properties such as analgesic, anti-inflammatory, antimicrobial, anticancer, antitubercular, antioxidant and antitumor activities. Antipyrine, synthesized in 1883 was the first pyrazolone derivative that was used for clinical trials. Antipyrine was used as the first agent to reduce fever and also for arthritis. Nowadays a large no. of drugs such as Edaravone, Phenazone, Propyphenazone, ARONIS023059, Metamizole sodium, TELIN and many others are available in the market possess pyrazolone moiety in their structural framework. The biological activities of pyrazol-5-ones depend on the nature of the substituents present on pyrazolone ring. Compounds like 3-alkyl-4-aryl methyl pyrazol-5-ones are reported to exhibit potent antihyperglycemic activity, while 1-phenyl-3-tetrafluoroethylpyrazol-5-one is an anxiolytic. 3-methyl-1-phenyl-2-pyrazolin-5-one (edaravone) a strong novel free radical scavenger is used for the treatment of patients with acute brain infarction. A new derivative of edaravone, 4,4-dichloro-1-(2,4-
dichlorophenyl)-3-methylpyrazol-5-one was identified as a potent blocker of human telomerase and is considered to be a valuable substance for medical treatment of cancer and related diseases.\textsuperscript{25} Thiadiazole substituted pyrazol-5-ones derivatives were found to be potent KDR/VEGFR-2 kinase inhibitors in regulating angiogenesis which is crucial for the proliferation of tumor cells.\textsuperscript{26} The diverse pharmacological properties have encouraged the chemists to develop new synthetic methodologies to synthesize a large number of novel therapeutic agents. Several sophisticated methodologies have been postulated in the literature for the synthesis of a pyrazolone moiety.

**Vijesh et al.\textsuperscript{27}** Reported two-step synthesis of novel pyrazolone derivatives 3(a-f). First they react phenyl hydrazine/2,4 dinitrophenyl hydrazine with ethylacetoacetate in ethanol under reflux condition to form 2-Aryl-5-methyl-2,4-dihydro-3H-pyrazol-3-one (1). Further the targeted pyrazolone derivatives 3(a-f) were obtained in excellent yields by refluxing 2-Aryl-5-methyl-2,4-dihydro-3H-pyrazol-3-one (1) with various substituted heterocyclic aldehydes 2(a-f) in presence of anhydrous sodium acetate in acetic acid (AA) for 8h. The synthesized compounds were also evaluated for antimicrobial activity.

\[
\begin{align*}
\text{C}_2\text{H}_5\text{O} & \quad \text{O} \\
\text{H}_3\text{C} & \quad \text{N} \quad \text{N} \\
\text{Ar} & \quad \text{NH} \\
\text{R} & \quad \text{O} \\
\text{Ar} & \quad \text{NH} \\
\text{R} & \quad \text{O} \\
\text{Ar} & \quad \text{NH} \\
\text{R} & \quad \text{O} \\
\text{Ar} & \quad \text{NH} \\
\end{align*}
\]

\begin{align*}
\text{Ar} & = \text{H}, \text{NO}_2 \\
\text{R} & = \text{2,4-dichlorophenyl, thioanisyl, 2,5-dichlorothiophene, biphenyl, 4-anisyl, 4-chlorophenyl}
\end{align*}

**Mariappan et al.\textsuperscript{28}** carried out the synthesis of 3-methyl pyrazol-5-one derivatives 5(a-j) by reacting ethylacetoacetate and hydrazine hydrate at 60 °C for 1h to yield 3-methyl pyrazol-5-one (3). Further in presence of 20% alcoholic solution of sodium hydroxide, 3-methyl pyrazol-5-one reacts with aromatic and aliphatic aldehydes 4(a-j) to yield 3-methyl pyrazol-5-one derivatives 5(a-j).
Verma and co-workers\textsuperscript{29} synthesized a series of 4-arylidene-3-methyl-1-phenyl-5-pyrazolone derivatives 5(a-j) by reacting various substituted aromatic aldehydes 4(a-j) with 3-methyl-1-phenyl-5-pyrazolone (3) via Knoevenagel condensation by conventional as well as by exposure to microwave irradiations. All the synthesized compounds were also tested for anti-inflammatory as well as antimicrobial activity.

Rasapalli \textit{et al.}\textsuperscript{30} developed a facile one pot approach for synthesis of new pyrazolones derivatives 4(a-j) from the reaction of dimethyl 3-oxopentanedioate (1), phenylhydrazine (2) and aromatic aldehydes 3(a-j) in presence of acetic acid and \textit{NH}_4\textit{OAc} (20% mmol).
Atudosie et al.\textsuperscript{31} documented one-pot approach for the synthesis of new pyrazolones derivatives containing a phenothiazine unit 4(a-d) using 4Å molecular sieves as catalyst in DMA at 60 °C.

Mosaddegh et al.\textsuperscript{32} effectively synthesize a series of 4,4'-(arylmethylene) bis(3-methyl-1-phenyl-1\texttextsuperscript{H}-pyrazol-5-ol) derivatives 3(a-j) by refluxing aromatic aldehydes (2) with 1-phenyl-3-methyl-5-pyrazolone (1) using Ce(SO\textsubscript{4})\textsubscript{2}.4H\textsubscript{2}O as reusable, environmentally friendly catalyst in water/ethanol solution for 5-25 min.

Yang et al.\textsuperscript{33} successfully synthesized 4-amino-5-pyrazolone derivatives (3) bearing a chiral quaternary centre by the reaction of 4-substituted pyrazolones (1) with azodicarboxylates (2) employing \textit{N,N'}-dioxide gadolinium(III) complex as the catalyst.
furanylmethyl, 2-thienylmethyl, 1-naphthylmethyl, 2-naphthylmethyl, Me, Et, n-propyl, allyl, (CH₂)₄; R₂=Me, Ph; R₃= Et, i-Pr, Bu

**Zang** and co-workers³⁴ described a new methodology for the synthesis of 4-[(5-hydroxy-3-methyl-1-phenyl-1H-pyrazol-4-yl)-phenyl-methyl]-5-methyl-2-phenyl-1,2-dihydro-pyrazol-3-ones **3(a-m)** using ionic liquid [HMIM][HSO₄] as a catalyst in ultrasound irradiation at room temperature.

\[
\begin{align*}
\text{NN} & \quad \text{O} \\
\text{Ph} & \quad \text{Ar} \\
\text{O} & \quad \text{EtOH, Ultrasound, RT} \\
\text{HN} & \quad \text{N} \\
\text{N} & \quad \text{O} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

Ar= C₆H₅, 4-ClC₆H₄, 2-ClC₆H₄, 2,4-Cl₂C₆H₃, 2-BrC₆H₄, 4-NO₂C₆H₄, 3-NO₂C₆H₄, 2-NO₂C₆H₄, 2-OHC₆H₄, 4-OHC₆H₄, 2-OCH₃C₆H₄, 4-OCH₃C₆H₄, 4-N(CH₃)₂C₆H₄

**Ziarati et al.**³⁵ reported simple and green four-component reaction of phenylhydrazine, ethyl acetoacetate, aromatic aldehydes **4(a-o)** and β-naphthol in water under ultrasound irradiation using CuI nanoparticles as a catalyst for synthesis of 2-aryl-5-methyl-2,3-dihydro-1H-3-pyrazolones **5(a-o)**.

\[
\begin{align*}
\text{HN} & \quad \text{NH₂} \\
\text{R₁} & \quad \text{Me} \\
\text{O} & \quad \text{OEt} \\
\text{OH} & \quad \text{CHO} \\
\text{HO} & \quad \text{Cu nanoparticles, H₂O, Ultrasound, RT, 30-40 min}
\end{align*}
\]

R₁=H, 4-Cl; R₂=H, 4-Cl, 4-NO₂, 4-Me, 2-Me, 2-Cl, 4-Br, 2-NO₂, 4-OMe

**Gunasekaran et al.**³⁶ developed new protocol for the synthesis of a series of novel 2-aryl-5-methyl-2,3-dihydro-1H-3-pyrazolones **5(a-o)** through one-pot four-component reaction between phenylhydrazine (1), methyl acetoacetate (2), β-naphthol (3) and aromatic aldehydes (4) in the presence of p-toluenesulphonic acid in water.
These 2-aryl-5-methyl-2,3-dihydro-1H-3-pyrazolones were also screened for in-vitro antimycobacterial activity against *mycobacterium tuberculosis* H37Rv (MTB).

\[
\text{RNHNNH}_2 \xrightarrow{\text{Ac}} \xrightarrow{\text{OMe}} \text{ArCHO} \xrightarrow{p\text{-TSA, H}_2\text{O, Reflux, 4-12h}} \text{HN} \xrightarrow{\text{Ar}} \text{O} \xrightarrow{\text{HO}} \text{5(a-o)}
\]

\[
\text{R= C}_6\text{H}_5, 4\text{-FC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4
\]

\[
\text{Ar= 4-NO}_2\text{C}_6\text{H}_4, 2\text{-NO}_2\text{C}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 4\text{-PrC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4, 4\text{-MeC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 4\text{-NO}_2\text{C}_6\text{H}_4, 2,4\text{-Cl}_2\text{C}_6\text{H}_3, 3\text{-NO}_2\text{C}_6\text{H}_4, 4\text{-FC}_6\text{H}_4
\]

Sujatha *et al.*[^37] carried out efficient synthesis of 4,4'- (arylmethylene) bis (1H-pyrazol-5-ols) 3(a-j) by ceric ammonium nitrate (CAN) catalysed tandem Knoevenagel-Michael reaction of two equivalents of 5-methyl-2-phenyl-2,4-dihydro-3H-pyrazol-3-one (1) with various aromatic aldehydes (2) in water.

\[
\text{Ar= C}_6\text{H}_5, 3\text{-CH}_3\text{C}_6\text{H}_4, 4\text{-CH}_3\text{C}_6\text{H}_4, 4\text{-OCH}_3\text{C}_6\text{H}_4, 4\text{-FC}_6\text{H}_4, 4\text{-NO}_2\text{C}_6\text{H}_4, 3,4\text{-}(\text{OCH}_3)_2\text{C}_6\text{H}_3, 3\text{-OCH}_3\text{C}_6\text{H}_4, 2\text{-Furfuryl, 2-Pyridyl}
\]

In light of the above observations, a series of biologically active pyrazolone analogues have been synthesized *via* one pot synthesis of aromatic/heterocyclic aldehydes, ethylacetooacetate and phenylhydrazine/2,4 dinitrophenylhydrazine (2,4-DNP) in water under microwave heating using SiO$_2$/ZnBr$_2$ as a catalyst. This new synthetic eco-friendly approach resulted in a remarkable improvement in synthetic efficiency (94-98%), high purity, minimizing the production of chemical wastes without using highly toxic reagents for the synthesis. The synthesized compounds have been screened for antioxidant study.
5.2. RESULTS AND DISCUSSION

In the present chapter, a library of 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one derivatives 4(a-s) have been synthesized using SiO₂/ZnBr₂ as a recyclable Lewis acid catalyst in water under microwave heating. The molecular structure of compounds 4a and 4d were well supported by single crystal X-ray crystallographic analysis. The present protocol bears a wide substrate tolerance and is believed to be more practical, efficient, eco-friendly and compatible as compared to existing methods. Further all synthesized compounds were tested for antioxidant activity and results obtained were promising.

5.2.1. Characterization of catalyst (SiO₂/ZnBr₂)

The catalyst was prepared by employing standard procedures depicted in the literature. The formation of SiO₂/ZnBr₂ system was evaluated by FT-IR, powder XRD and SEM-EDX analysis. The stability of the catalyst was shown by TGA/DTA analysis. The FT-IR spectrum of the catalyst (SiO₂/ZnBr₂) is depicted in Fig. 1.

![Fig. 1 FT-IR Spectrum of catalyst (SiO₂/ZnBr₂)](image)

The FT-IR spectrum of the catalytic system displayed a symmetrical stretching band at 3483 cm⁻¹ for hydroxyl group and the band resonating at 1632 cm⁻¹ was attributed to the bending vibration of adsorbed water. Moreover, asymmetric and symmetric stretching vibration band for Si-O-Si appeared at 1093 cm⁻¹ and 797 cm⁻¹, respectively. In addition the peak resonating at 910 and 467 cm⁻¹ has been assigned.
for the stretching vibration of Si-OH\textsuperscript{39} and Zn-Br, respectively. Thus, FT-IR spectrum of the catalytic system authenticates the coating of ZnBr\textsubscript{2} on the SiO\textsubscript{2} surface as all the characteristic peaks related to silica and ZnBr\textsubscript{2} has been present in the spectrum of SiO\textsubscript{2}/ZnBr\textsubscript{2}.

Formation of the catalytic system (SiO\textsubscript{2}/ZnBr\textsubscript{2}) was further confirmed by powder XRD analysis (Fig. 2). X-ray diffractograms (XRD) of the catalyst were recorded in the 2\(\theta\) range of 20-80\(^\circ\). A single broad peak in the range of 2\(\theta=20-30^\circ\) ascribed to the amorphous nature of silica. The characteristic diffraction peaks of pure ZnBr\textsubscript{2} were reported to appear at 13.7\(^\circ\), 21.1\(^\circ\), 27.5\(^\circ\), 46.1\(^\circ\) and 53.4\(^\circ\). The XRD analysis of SiO\textsubscript{2}/ZnBr\textsubscript{2} exhibited diffraction peak for ZnBr\textsubscript{2} only at 46.2\(^\circ\) and 53.4\(^\circ\). However, the other characteristic peaks (21.1\(^\circ\) and 27.5\(^\circ\)) were merged with the broad peak of SiO\textsubscript{2} (2\(\theta=20-30^\circ\)). The appearance of these characteristics peaks indicating the dispersion of ZnBr\textsubscript{2} on the silica material and thus confirming the formation of SiO\textsubscript{2}/ZnBr\textsubscript{2} matrix.

![Fig. 2 Powder XRD pattern of catalyst (SiO\textsubscript{2}/ZnBr\textsubscript{2})](image)

SEM analysis was employed to study the surface morphology of the catalytic system (Fig. 3). SEM micrographs of the catalyst showed that the particles of ZnBr\textsubscript{2} were well dispersed on silica surface. The successful incorporation of zinc bromide was also confirmed by EDX analysis (Fig. 4). EDX spectrum showed the presence of Zn and Br in addition to O and Si elements.

The thermal stability of the catalyst was determined by TGA analysis (Fig. 5). The only weight loss of 16.94\% in the range of 40-120 °C was attributed to loss of physically adsorbed water molecules in the silica gel framework. TGA is further
supported by DTA analysis in which a prominent peak at 93.04 °C showed endothermic reaction which help in the removal of water molecule (Fig. 5). Further there is no weight loss upto 800 °C. Therefore it can be concluded that physiosorbed and chemisorbed ZnBr₂ on silica surfaces is stable upto 800 °C.⁴¹

![SEM micrograph of (a) pure SiO₂ (b) SiO₂/ZnBr₂ catalyst.](image)

**Fig. 3** SEM micrograph of (a) pure SiO₂ (b) SiO₂/ZnBr₂ catalyst.

![EDX analysis of the catalyst (SiO₂/ZnBr₂)](image)

**Fig. 4** EDX analysis of the catalyst (SiO₂/ZnBr₂)
Fig. 5 TGA/DTA of catalyst (SiO$_2$/ZnBr$_2$)

5.2.2. Chemistry

In the present chapter, a library of 3-methyl-1-phenyl-1$H$-pyrazol-5(4$H$)-one derivatives 4(a-s) have been synthesized (Scheme 1), via the reaction between aromatic/heterocyclic aldehydes 1(a-s) with phenylhydrazine / 2,4 dinitrophenylhydrazine (2,4-DNP) 2(a-b) and ethylacetoacetate (3) employing SiO$_2$/ZnBr$_2$ as a catalyst in water under microwave heating.
Scheme 1 Synthetic scheme for the synthesis of pyrazolone derivatives 4(a-s)

The structural elucidation of the synthesized compounds 4(a-s) was established on the basis of elemental analysis, IR, $^1$H NMR, $^{13}$C NMR and mass spectral studies. The analytical results for C, H and N were within ±0.3% of the theoretical values. The absence of peak for aldehydic carbonyl in IR spectrum, confirmed the reaction at the carbonyl moiety. Moreover, all the compounds displayed a characteristic peak for C=N and C=O groups, resonating at around 1578-1603 cm$^{-1}$ and 1680-1700 cm$^{-1}$, respectively, which signifies the formation of a pyrazolone ring. Characteristic peaks
for the different functional groups such as methoxy, nitro and hydroxyl etc. have been discussed in experimental section. In $^1$H NMR spectrum, each compound displayed a sharp singlet at around $\delta$ 7.32-7.99 ascribed to the olefinic proton, a broad singlet at around $\delta$ 12.02-12.46 (D$_2$O exchangeable) has been ascribed to -NH proton of indole ring. Similarly, a sharp singlet at around $\delta$ 9.32-9.82 corresponds to the H-2 proton of indole ring (4a-4c). Furthermore, sharp singlets resonating at around $\delta$ 10.64, 10.04, 10.12, 10.10 each integrating for one proton, has been attributed to H-2 proton of $\gamma$-pyrone ring of compounds 4d, 4e, 4f and 4g, respectively. $^{13}$C NMR spectra, showed peaks resonating at around $\delta$ 137.31-153.80 and $\delta$ 162.77-170.16 corresponds to -C=N and -C=O moiety of pyrazolone ring, respectively. Similarly signals at $\delta$ 174.19-174.69 have been attributed to carbonyl group (C=O$_{\gamma$-pyrone}) of compounds (4d-4h). The mass spectral analysis of the synthesized compounds was also in good conformity with the proposed structures.

The FT-IR spectrum of compound 4a (Fig. 6) displayed characteristics peaks at 1594 and 1680 cm$^{-1}$ attributed to C=N and C=O respectively, while the peak resonating at 3251 cm$^{-1}$ attributed to –NH stretching of the indole ring. Other peaks resonating at 1157, 1456 cm$^{-1}$ for C=C stretching, 2928, 3064 cm$^{-1}$ for –C-H and =C-H stretching, respectively. The $^1$H NMR spectrum of compound 4a (Fig. 7) displayed a sharp singlet at $\delta$ 7.91 for one protons ascribed to the =C-H proton. Multiplets at around $\delta$ 7.52-8.02 for five protons have been attributed to phenyl ring. A broad singlet at $\delta$ 12.46 for one proton has been ascribed to -NH proton of the indole ring. A sharp singlet at $\delta$ 9.82 for one proton has been ascribed to H-2 proton of the indole ring. Another sharp singlet at $\delta$ 2.39 for three protons and multiplet at $\delta$ 7.14-7.67 for four protons were attributed to CH$_3$ protons and indole ring respectively.
Fig. 6 FT-IR spectrum of compound 4a

Fig. 7 \(^1\)H NMR spectrum of compound 4a
\(^{13}\)C NMR spectrum of compound 4a (Fig. 8) displayed characteristics absorption bands resonating at around \(\delta\) 162.77, 150.44, 136.40 and 138.90 for C=O, C=N, C-1’ and C-2’, respectively. Further a series of signals resonating at around \(\delta\) 118.40-138.19 and \(\delta\) 112.17-136.56 have been assigned to phenyl ring and indole ring, respectively. The detailed spectral characterizations of all the synthesized compounds have been discussed in experimental section.

![13C NMR spectrum of compound 4a](image)

Fig. 8 \(^{13}\)C NMR spectrum of compound 4a

The selective Z-geometry across C=C was authenticated by single crystal X-ray crystallographic analysis of compound 4a and 4d (Fig. 9), which was found to be stabilized by an intricate array of H-bonding (Fig. 10) and \(\pi\).....\(\pi\) interactions (Fig. 11). The crystallographic data of compound 4a and 4d have been presented in Table 1.
Fig. 9 Asymmetric unit showing thermal ellipsoids (50% probability level) of (a) compound 4a (b) compound 4d.
Fig. 10 2D view showing intricate H-bonding interactions in (a) compound 4a; (b) compound 4d.
Fig. 11 Diagrammatic representation of π...π interactions in (a) compound 4a, π...π and -CH...π interactions in (b) compound 4d
Table 1 Crystallographic data and structure refinement of compounds 4a and 4d

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Compound 4a</th>
<th>Compound 4d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C_{19}H_{15}N_{3}O</td>
<td>C_{20}H_{14}N_{2}O_{3}</td>
</tr>
<tr>
<td>Formula wt.</td>
<td>301.34</td>
<td>330.33</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
<td>Triclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P21/n</td>
<td>P-1</td>
</tr>
<tr>
<td>a, Å</td>
<td>5.810(5)</td>
<td>7.870(5)</td>
</tr>
<tr>
<td>b, Å</td>
<td>9.256(5)</td>
<td>8.298(3)</td>
</tr>
<tr>
<td>c, Å</td>
<td>26.893(5)</td>
<td>11.843(5)</td>
</tr>
<tr>
<td>α (°)</td>
<td>90</td>
<td>85.806(4)</td>
</tr>
<tr>
<td>β (°)</td>
<td>94.997(5)</td>
<td>80.900(5)</td>
</tr>
<tr>
<td>γ (°)</td>
<td>90</td>
<td>89.987(5)</td>
</tr>
<tr>
<td>U, Å³</td>
<td>1440.7(15)</td>
<td>761.6(7)</td>
</tr>
<tr>
<td>Z</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>ρ_{calc} Mg/m³</td>
<td>1.389</td>
<td>1.441</td>
</tr>
<tr>
<td>μ, mm⁻¹</td>
<td>0.089</td>
<td>0.099</td>
</tr>
<tr>
<td>Temperature (K)</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>θ max</td>
<td>25.50</td>
<td>25.50</td>
</tr>
<tr>
<td>F(000)</td>
<td>632</td>
<td>344</td>
</tr>
<tr>
<td>Refl. collected</td>
<td>11010</td>
<td>9548</td>
</tr>
<tr>
<td>Independent refl.</td>
<td>2087</td>
<td>2314</td>
</tr>
<tr>
<td>GOFa</td>
<td>1.038</td>
<td>1.037</td>
</tr>
<tr>
<td>Final R^b indices [I&gt;2σ(I)]</td>
<td>R1 = 0.0501; wR2 =</td>
<td>R1 = 0.0402; wR2 =</td>
</tr>
<tr>
<td></td>
<td>0.1268</td>
<td>0.0970</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>R1 = 0.0675; wR2 =</td>
<td>R1 = 0.0524; wR2 =</td>
</tr>
<tr>
<td></td>
<td>0.1380</td>
<td>0.1038</td>
</tr>
</tbody>
</table>

5.2.3. Optimization of reaction conditions

To optimize the best reaction conditions for synthesis of biologically active pyrazolone derivatives, effect of solvent, catalyst loading, effect of temperature have been investigated on the model reaction. Initially, indole-3-carbaldehyde (1a, 2 mmol), phenylhydrazine (2a, 2 mmol) and ethylacetoacetate (3, 2 mmol) were
refluxed in water (10 mL) at 60 °C without catalyst. The reaction took a longer time period of 24 h to complete and afforded desired product 4a in less yield (Table 2, entry 1), signifying the need of a catalyst. The reaction was then studied in the presence of different catalysts such as AlCl\(_3\), ZnBr\(_2\), FeCl\(_3\), SiO\(_2\)-Cl, SiO\(_2\)/ZnBr\(_2\). Our analysis revealed that the catalytic activity of various catalysts in water at 60 °C was found to be in the order of SiO\(_2\)/ZnBr\(_2\) > AlCl\(_3\) > FeCl\(_3\) > ZnBr\(_2\) > SiO\(_2\)-Cl (Table 2, entries 2-6). To compare the efficiency as well as competence of the reactions under aqueous condition, the model reaction was also examined in the presence of SiO\(_2\)/ZnBr\(_2\) in different solvents like MeOH, EtOH, CH\(_3\)COOH, CH\(_2\)Cl\(_2\), DMF and THF. The use of relatively less polar aprotic solvents CH\(_2\)Cl\(_2\), DMF and THF yielded the product 4a in moderate yield (58-62%), after extended reaction time (Table 2, entries 10-12). However, in polar protic solvents MeOH, EtOH, and AcOH relatively high yield (65-70%) of the product 4a was obtained with dip in reaction time (Table 2, entries 7-9), whereas when reaction was performed in water in the presence of SiO\(_2\)/ZnBr\(_2\), there was remarkable increase in the yield (86%) of the product 4a with prominent fall in reaction time (Table 2, entry 6). In order to further improve the protocol to make it more energy efficient microwaves was introduced. The use of microwaves (Anton Paar, Monowave 300) enhanced the protocol remarkably with high yield of the product 4a (98%) and short reaction period (10 min) (Table 2, entry 13).

Table 2 Effect of different reaction media on model reaction (4a)*

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Solvent</th>
<th>Condition</th>
<th>Time (h)*</th>
<th>Yield (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Water</td>
<td>60 °C, without catalyst</td>
<td>24h</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>Water</td>
<td>60 °C, AlCl(_3)</td>
<td>8h</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>Water</td>
<td>60 °C, ZnBr(_2)</td>
<td>10h</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>Water</td>
<td>60 °C, FeCl(_3)</td>
<td>12h</td>
<td>53</td>
</tr>
<tr>
<td>5</td>
<td>Water</td>
<td>60 °C, SiO(_2)-Cl</td>
<td>16h</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>Water</td>
<td>60 °C, SiO(_2)/ZnBr(_2)</td>
<td>4h</td>
<td>86</td>
</tr>
<tr>
<td>7</td>
<td>MeOH</td>
<td>60 °C, SiO(_2)/ZnBr(_2)</td>
<td>6h</td>
<td>65</td>
</tr>
<tr>
<td>8</td>
<td>EtOH</td>
<td>60 °C, SiO(_2)/ZnBr(_2)</td>
<td>8h</td>
<td>70</td>
</tr>
<tr>
<td>9</td>
<td>CH(_3)COOH</td>
<td>60 °C, SiO(_2)/ZnBr(_2)</td>
<td>6h</td>
<td>68</td>
</tr>
<tr>
<td>10</td>
<td>CH(_2)Cl(_2)</td>
<td>60 °C, SiO(_2)/ZnBr(_2)</td>
<td>10h</td>
<td>62</td>
</tr>
</tbody>
</table>
DMF 60 °C, SiO$_2$/ZnBr$_2$ 14h 60
THF 60 °C, SiO$_2$/ZnBr$_2$ 18h 58
Water 60 °C, SiO$_2$/ZnBr$_2$, MW 10 min 98

*Reaction condition:* indole-3-carbaldehyde (1a, 2 mmol), phenylhydrazine (2a, 2 mmol), and ethylacetoacetate (3, 2 mmol), different solvent (10 mL), different catalyst (0.10 g)

*Reaction progress monitored by TLC; Isolated yield of products*

To achieve the optimum concentration of the catalyst, the model reaction (4a) was investigated at different concentrations 0.02-0.12 g (*Table 3, entries 1-6*) of the catalyst SiO$_2$/ZnBr$_2$ at 60 °C in water under MW. The best results were obtained with the use of 0.10 g of catalyst. Using less than 0.10 g of catalyst, moderate yields of the product 4a (66-83%) were obtained with extended reaction times, while increasing catalyst amount 0.10-0.12 g, there was no further increase in the yield of the product 4a, possibly due to the saturation of the catalyst. The above results signify that 0.10 g of SiO$_2$/ZnBr$_2$ is optimum dose in terms of efficient yield and reduced reaction time.

**Table 3** Effect of catalyst loading on the yield and reaction time of model reaction (4a)*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (g)</th>
<th>Time (min)*</th>
<th>Yield (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.02</td>
<td>35</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>0.04</td>
<td>30</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>0.06</td>
<td>28</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>0.08</td>
<td>25</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>0.10</td>
<td>10</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>0.12</td>
<td>10</td>
<td>98</td>
</tr>
</tbody>
</table>

*Reaction condition: indole-3-carbaldehyde (1a, 2 mmol), phenylhydrozine (2a, 2 mmol), and ethylacetoacetate (3, 2 mmol), water (10 mL), SiO$_2$/ZnBr$_2$ (0.02-0.12 g), MW-60 °C

*Reaction progress monitored by TLC; Isolated yield of products*

To optimize the reaction temperature, the model reaction was carried out at different temperatures in water under microwave heating (*Table 4, entries 1-7*). It was observed that increase in temperature from 25 °C to 60 °C, has a noteworthy effect on the model reaction in terms of yield and reaction time (*Table 4, entries 1-6*). However, no further enhancement in the yield of product 4a was observed when the reaction temperature was raised from 60 °C to 65 °C (*Table 4, entry 7*).
Table 4 Effect of reaction temperature on the model reaction (4a)*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Time (min)b</th>
<th>Yield (%)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>75</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>50</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>35</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>30</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>25</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>10</td>
<td>98</td>
</tr>
<tr>
<td>7</td>
<td>65</td>
<td>10</td>
<td>98</td>
</tr>
</tbody>
</table>

*Reaction condition: indole-3-carbaldehyde (1a, 2 mmol), phenylhydrazine (2a, 2 mmol), and ethylacetoacetate (3, 2 mmol), water (10 mL), SiO2/ZnBr2 (0.10 g), MW, different temperature (25-65 °C)

bReaction progress monitored by TLC

*Isolated yield of products

After optimization of the reaction conditions, the catalyst SiO2/ZnBr2 was examined under the optimized reaction conditions using both conventional and microwave heating. A wide range of aromatic/heterocyclic aldehydes was reacted with ethylacetoacetate and phenylhydrazine/2,4-dinitrophenylhydrazine (2,4-DNP) to afford the target pyrazolone in excellent yields. The catalyst showed good efficiency under conventional heating giving the products in 4-6 h. However, microwave induction produced excellent yields (94-98%) of products in 10-15 min. The above results demonstrate that SiO2/ZnBr2 is an efficient catalyst for the synthesis of wide range of pyrazolones in high yields under mild aqueous conditions.
**Table 5** Synthesis of pyrazolones derivatives 4(a-s)

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Products</th>
<th>Conventional Method&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Microwave irradiation&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Time (h)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Yield (%)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>4a</td>
<td><img src="image1" alt="Image" /></td>
<td>4</td>
<td>81</td>
</tr>
<tr>
<td>4b</td>
<td><img src="image2" alt="Image" /></td>
<td>4.5</td>
<td>77</td>
</tr>
<tr>
<td>4c</td>
<td><img src="image3" alt="Image" /></td>
<td>4.5</td>
<td>80</td>
</tr>
<tr>
<td>4d</td>
<td><img src="image4" alt="Image" /></td>
<td>4</td>
<td>84</td>
</tr>
<tr>
<td>4e</td>
<td><img src="image5" alt="Image" /></td>
<td>5</td>
<td>78</td>
</tr>
<tr>
<td>4f</td>
<td><img src="image6" alt="Image" /></td>
<td>4.5</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>Structure</td>
<td>Yield</td>
<td>Isolation %</td>
</tr>
<tr>
<td>---</td>
<td>---------------------------------</td>
<td>-------</td>
<td>--------------</td>
</tr>
<tr>
<td>4g</td>
<td><img src="image1" alt="Structure" /></td>
<td>6</td>
<td>79</td>
</tr>
<tr>
<td>4h</td>
<td><img src="image2" alt="Structure" /></td>
<td>5.0</td>
<td>76</td>
</tr>
<tr>
<td>4i</td>
<td><img src="image3" alt="Structure" /></td>
<td>5.5</td>
<td>81</td>
</tr>
<tr>
<td>4j</td>
<td><img src="image4" alt="Structure" /></td>
<td>6.0</td>
<td>74</td>
</tr>
<tr>
<td>4k</td>
<td><img src="image5" alt="Structure" /></td>
<td>4.0</td>
<td>83</td>
</tr>
<tr>
<td>4l</td>
<td><img src="image6" alt="Structure" /></td>
<td>4.5</td>
<td>75</td>
</tr>
<tr>
<td>4m</td>
<td><img src="image7" alt="Structure" /></td>
<td>5.5</td>
<td>84</td>
</tr>
<tr>
<td>4n</td>
<td><img src="image1" alt="Structure" /></td>
<td>5</td>
<td>76</td>
</tr>
<tr>
<td>4o</td>
<td><img src="image2" alt="Structure" /></td>
<td>6</td>
<td>74</td>
</tr>
<tr>
<td>4p</td>
<td><img src="image3" alt="Structure" /></td>
<td>4.5</td>
<td>78</td>
</tr>
<tr>
<td>4q</td>
<td><img src="image4" alt="Structure" /></td>
<td>5</td>
<td>76</td>
</tr>
<tr>
<td>4r</td>
<td><img src="image5" alt="Structure" /></td>
<td>4</td>
<td>82</td>
</tr>
<tr>
<td>4s</td>
<td><img src="image6" alt="Structure" /></td>
<td>5.5</td>
<td>75</td>
</tr>
</tbody>
</table>

*a Reaction conditions*: indole-3-carbaldehyde (1a, 2 mmol), phenylhydrazine (2a, 2 mmol), and ethylacetoacetate (3, 2 mmol), water (10 mL), SiO₂/ZnBr₂ (0.10 g), 60 °C

*b Reaction conditions*: indole-3-carbaldehyde (1a, 2 mmol), phenylhydrazine (2a, 2 mmol), and ethylacetoacetate (3, 2 mmol), water (10 mL), SiO₂/ZnBr₂ (0.10 g), MW-60 °C

*c Reaction progress monitored by TLC.*

*d Isolated yield of the products*
5.2.4. Reusability of the catalyst

The reusability of the catalyst (SiO₂/ZnBr₂) was also explored for the selected model reaction in order to reduce the cost of the process (Fig. 12). After the first fresh run with 98% yield, the catalyst was removed by simple filtration, washed with ethylacetate and dried at 160 °C for 10 h. The recovered catalyst was further tested up to five more reaction cycles. The results revealed that there is little drop in the yield of the product after every successive run of the catalyst. This little drop in the catalytic activity is believed to be due to the leaching of ZnBr₂. SEM and EDX analysis of the recovered catalyst was also performed to ascertain its morphology and composition (Fig. 13). It was observed that the composition of the catalytic system was almost consistent with the fresh catalyst (Fig. 3) there have been no significant changes in the morphology of the catalyst.

Fig. 12 Recycling data of the catalyst (SiO₂/ZnBr₂) for the model reaction

Fig. 13 (a) SEM micrograph (b) EDX spectrum of the recovered catalyst (SiO₂/ZnBr₂)
5.2.5. Antioxidant studies

The antioxidant activities of all the synthesized pyrazolone derivatives 4(a-s) were investigated by DPPH scavenging activity. The reduction capability of DPPH radicals was determined by a decrease in their absorbance at 517 nm induced by antioxidants using ascorbic acid as a reference. The potencies for the antioxidant activity of compounds 4(a-s) to the reference compound are shown in Table 6.

Table 6 Antioxidant activity of compounds 4(a-s) by DPPH assay

<table>
<thead>
<tr>
<th>Compounds</th>
<th>2 μg/mL</th>
<th>4 μg/mL</th>
<th>6 μg/mL</th>
<th>8 μg/mL</th>
<th>IC\textsubscript{50}(μg/mL)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>43.94±0.3</td>
<td>47.80±0.4</td>
<td>49.73±0.1</td>
<td>51.44±0.5</td>
<td>6.45</td>
</tr>
<tr>
<td>4b</td>
<td>32.84±0.4</td>
<td>52.19±0.2</td>
<td>59.69±0.3</td>
<td>63.87±0.5</td>
<td>4.57</td>
</tr>
<tr>
<td>4c</td>
<td>36.22±0.2</td>
<td>38.90±0.6</td>
<td>52.84±0.7</td>
<td>56.37±0.2</td>
<td>6.05</td>
</tr>
<tr>
<td>4d</td>
<td>33.44±0.3</td>
<td>37.62±0.3</td>
<td>39.22±0.4</td>
<td>49.30±0.2</td>
<td>9.10</td>
</tr>
<tr>
<td>4e</td>
<td>26.79±0.5</td>
<td>32.58±0.1</td>
<td>39.11±0.4</td>
<td>44.37±0.7</td>
<td>9.82</td>
</tr>
<tr>
<td>4f</td>
<td>41.26±0.4</td>
<td>42.97±0.5</td>
<td>47.90±0.7</td>
<td>49.62±0.6</td>
<td>8.04</td>
</tr>
<tr>
<td>4g</td>
<td>36.58±0.4</td>
<td>39.92±0.5</td>
<td>47.40±0.4</td>
<td>54.96±0.2</td>
<td>6.68</td>
</tr>
<tr>
<td>4h</td>
<td>38.26±0.3</td>
<td>45.58±0.3</td>
<td>50.78±0.5</td>
<td>58.38±0.4</td>
<td>5.53</td>
</tr>
<tr>
<td>4i</td>
<td>21.46±0.6</td>
<td>25.83±0.7</td>
<td>29.36±0.4</td>
<td>31.40±0.3</td>
<td>18.79</td>
</tr>
<tr>
<td>4j</td>
<td>32.26±0.4</td>
<td>35.09±0.5</td>
<td>36.87±0.4</td>
<td>38.47±0.3</td>
<td>19.04</td>
</tr>
<tr>
<td>4k</td>
<td>33.54±0.4</td>
<td>38.69±0.2</td>
<td>44.15±0.6</td>
<td>49.30±0.2</td>
<td>8.25</td>
</tr>
<tr>
<td>4l</td>
<td>25.18±0.3</td>
<td>28.18±0.6</td>
<td>33.65±0.5</td>
<td>37.72±0.1</td>
<td>13.73</td>
</tr>
<tr>
<td>4m</td>
<td>23.68±0.4</td>
<td>29.15±0.2</td>
<td>35.15±0.5</td>
<td>41.58±0.2</td>
<td>10.90</td>
</tr>
<tr>
<td>4n</td>
<td>33.11±0.4</td>
<td>37.19±0.1</td>
<td>43.08±0.6</td>
<td>45.76±0.3</td>
<td>9.66</td>
</tr>
<tr>
<td>4o</td>
<td>26.36±0.2</td>
<td>35.47±0.7</td>
<td>39.65±0.1</td>
<td>42.06±0.3</td>
<td>10.50</td>
</tr>
<tr>
<td>4p</td>
<td>25.18±0.3</td>
<td>28.18±0.6</td>
<td>33.65±0.4</td>
<td>37.72±0.1</td>
<td>13.73</td>
</tr>
<tr>
<td>4q</td>
<td>24.65±0.5</td>
<td>25.83±0.2</td>
<td>32.04±0.6</td>
<td>34.51±0.1</td>
<td>16.59</td>
</tr>
<tr>
<td>4r</td>
<td>21.11±0.4</td>
<td>33.33±0.2</td>
<td>30.86±0.5</td>
<td>39.97±0.2</td>
<td>11.30</td>
</tr>
<tr>
<td>4s</td>
<td>38.15±0.4</td>
<td>41.80±0.7</td>
<td>43.62±0.2</td>
<td>47.37±0.3</td>
<td>9.93</td>
</tr>
<tr>
<td>Control</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(Ascorbic acid)</td>
<td>16.50±0.2</td>
<td>44.35±0.3</td>
<td>57.22±0.4</td>
<td>66.25±0.3</td>
<td>5.48</td>
</tr>
</tbody>
</table>

\textsuperscript{a}IC\textsubscript{50} value represents the concentration of three experiments required to exhibit 50 % antioxidant activity.
Almost all the tested compounds possessed strong scavenging activity against the DPPH with IC$_{50}$ values (4.57-19.04µg/mL). Compounds having indole ring 4(a-c) showed potent antioxidant activity (4.57-6.45 µg/mL). Compound 4b (IC$_{50}$=4.57µg/mL) showed the highest antioxidant activity due to existence of –NH and OH group. Further formyl derivatives having NH$_2$ group on 2$^{\text{th}}$ position showed the high scavenging activity (IC$_{50}$=5.53µg/mL) after compound 4b whereas methyl substitution on 6$^{\text{th}}$ position does not affect on activity. N-N’dimethyl derivatives 4m and 4r showed good inhibitory activity with IC$_{50}$=10.90 and 11.30µg/mL whereas methoxy derivatives showed the less inhibitory activity than other (IC$_{50}$=16.59-19.04µg/mL). Rest of the compounds showed significantly good activity against DPPH.

5.3. EXPERIMENTAL

5.3.1. Materials and methods
All the chemicals and reagents were purchased from Merck and Sigma-Aldrich (India) as ‘synthesis grade’ and used without further purification. The microwave synthesis was performed in Anton Paar, Monowave 300 microwave synthesizer. Melting points were determined on a Kofler apparatus and are uncorrected. The instrumental detail of elemental analysis (C, H, N), IR, NMR and Mass have been discussed in chapter 2. X-ray diffractograms (XRD) of the catalyst were recorded in the 2$\theta$ range of 20-80$^\circ$ with a scan rate of 41 min$^{-1}$ on a Shimadzu-6100 X-ray diffractometer with Ni-filtered Cu Ka radiation at a wavelength of 1.54060 Å. The scanning electron microscope (SEM-EDX) analysis was obtained using a JEOL (JSM-6510) equipped with an energy dispersive X-ray spectrometer at different magnification. TGA has been carried out with DTG-60H (Simultaneous DTA-TG Apparatus), Shimadzu instrument. The progress of the reaction homogeneity of reaction mixture was monitored by Thin layer chromatography (TLC) glass plates 120×5 cm with silica gel G (Merck) using benzene:acetone (8:2) as mobile phase.

5.3.2. Preparation of the silica-supported zinc bromide (SiO$_2$/ZnBr$_2$) catalyst
Silica gel (70-230 mesh) (10 g) was added to a solution of ZnBr$_2$ (12 mmol, 2.7 g) in EtOH (50 mL), and the mixture was heated at reflux for 1 h. The solvent was removed using rotary evaporator, and the product was dried under vacuum at 160 °C for 10 h.
The other catalyst i.e. SiO$_2$-Cl used for the comparative study has been synthesized according to the previously published standard procedures.$^{42}$

5.3.3. General procedure for the synthesis of pyrazolones under microwave irradiation

A mixture of substituted aromatic/heterocyclic aldehyde 1(a-s) (2 mmol), phenylhydrazine/2,4-dinitrophenylhydrazine 2(a-b) (2 mmol), ethylacetoacetate (3, 2 mmol), and SiO$_2$/ZnBr$_2$ (0.10 g) in 10 mL water was taken in a G30 vial and irradiated using microwaves with continuous stirring at 60 $^\circ$C for 10-15 min. After completion of reaction (monitored by TLC), the reaction mixture was allowed to cool at room temperature and diluted with cold water (5 mL). The catalyst was separated by filtration and the resulting solution was extracted with ethyl acetate (3×10 mL). The combined organic layer was washed with water, dried over anhydrous Na$_2$SO$_4$ and evaporated under reduced pressure. The crude product was crystallized with chloroform-methanol to afford the pure product. The recovered catalyst was reused for subsequent cycles without a significant loss in yield.

5.3.4. Spectral characterization of synthesized compounds 4(a-s)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Physical State</th>
<th>Yield</th>
<th>M.p.</th>
<th>Analytical Cal.</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Z)-4-(((1H-Indol-3-yl)methylene)-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (4a)</td>
<td>Orange crystalline solid</td>
<td>98%</td>
<td>245-250 $^\circ$C</td>
<td>C$<em>{19}$H$</em>{15}$N$_3$O: C, 75.73; H, 5.02; N, 13.94; found: C, 75.70; H, 5.03; N, 13.96.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IR (KBr, $\nu_{max}$ cm$^{-1}$): 1157, 1456 (C=C), 1594 (C=N), 1680 (C=O).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$^1$H NMR (400 MHz, DMSO-d$_6$, $\delta$, ppm): 2.39 (s, 3H, -CH$<em>3$), 7.26-7.39 (m, 4H, indole ring), 7.52-8.02 (m, 5H, phenyl ring), 7.91 (s, 1H, -CH=C), 9.82 (s, 1H, H-2$</em>{indole ring}$), 12.46 (brs, 1H, -NH, D$_2$O exchangeable),</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>$^{13}$C NMR (100 MHz, DMSO-d$_6$, $\delta$, ppm): 12.93 (CH$_3$), 112.17-136.56 (indole ring), 118.40-138.19 (phenyl ring), 136.40 (C-1’), 138.90 (C-2’), 150.44 (-C=N), 162.77 (C=O), MS (ESI) (m/z): 301.12 [M$^+$].</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Z)-4-(((5-Hydroxy-1H-indol-3-yl)methylene)-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (4b)</td>
<td>Yellow crystalline solid</td>
<td>95%</td>
<td>256 $^\circ$C</td>
<td>C$<em>{19}$H$</em>{15}$N$_3$O$_2$: C, 71.91; H, 4.76; N, 13.24; found: C, 71.90; H, 4.79; N, 13.22.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IR (KBr, $\nu_{max}$ cm$^{-1}$): 1150, 1450 (C=C), 1578 (C=N), 1685 (C=O).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| | $^1$H NMR (400 MHz, DMSO-d$_6$, $\delta$, ppm): 2.31 (s, 3H, -CH$_3$), 6.86-7.17 (m, 3H, indole ring), 7.23-7.98 (m, 5H, phenyl ring), 7.83 (s, 1H, -CH=C), 9.70 (s, 1H, H-}$
Yellow solid; yield 98%; m.p. 248 °C; Analytical cal. C_{20}H_{17}N_{3}O: C, 76.17; H, 5.43; N, 13.32; found: C, 76.18; H, 5.40; N, 13.34.

IR (KBr, \nu_{\text{max}} \text{ cm}^{-1}): 1152, 1452 (C=C), 1603 (C=N), 1688 (C=O).

1H NMR (400 MHz, DMSO-d_{6}, \delta, ppm): 2.31 (s, 1H, -CH_{3}), 7.26-7.91 (m, 5H, phenyl ring), 6.89-7.27 (m, 3H, indole ring), 7.71 (s, 1H, -CH=C), 9.32 (s, 1H, H-2\text{indole ring}). 12.02 (brs, 1H, -NH, D_{2}O exchangeable).

13C NMR (100 MHz, DMSO-d_{6}, \delta, ppm): 14.23 (CH_{3}), 112.64-135.65 (indole ring), 115.04 (C-8), 118.38-142.54 (phenyl ring), 118.54 (C-3), 123.10 (C-4a), 124.56 (C-6), 125.75 (C-5), 134.67 (C-1', 135.92 (C-7), 137.81 (-C=N), 150.67 (C-2', 155.47 (C-2'), 163.35 (C=O), 174.29 (C-4, C=O \gamma-pyrole ring).

MS (ESI) (m/z): 317.12 \{M^{+}\}.

(Z)-3-Methyl-4-((5-methyl-1H-indol-3-yl)methylene)-1-phenyl-1H-pyrazol-5(4H)-one (4c)

Red crystalline solid; yield 98%; m.p. 222 °C. Analytical cal. C_{20}H_{14}N_{2}O_{3}: C, 72.72; H, 4.27; N, 8.48; found: C, 72.70; H, 4.30; N, 8.47.

IR (KBr, \nu_{\text{max}} \text{ cm}^{-1}): 1153, 1452 (C=C), 1600 (C=N), 1692 (C=O).

1H NMR (400 MHz, DMSO-d_{6}, \delta, ppm): 2.33 (s, 1H, -CH_{3}), 7.12-7.34 (m, 5H, phenyl ring), 7.99 (s, 1H, -CH=C), 8.19-7.27 (m, 4H, chromone ring), 10.64 (s, 1H, H-2\gamma-pyrole ring).

13C NMR (100 MHz, DMSO-d_{6}, \delta, ppm): 14.23 (CH_{3}), 117.59 (C-8), 118.38-142.54 (phenyl ring), 118.54 (C-3), 123.10 (C-4a), 124.56 (C-6), 125.75 (C-5), 134.67 (C-1'), 135.92 (C-7), 137.81 (-C=N), 150.67 (C-2', 161.83 (C-8b), 163.35 (C=O), 174.29 (C-4, C=O \gamma-pyrole ring). MS (ESI) (m/z): 330.10 \{M^{+}\}.

(Z)-3-Methyl-4-((4-oxo-4H-chromen-3-yl)methylene)-1-phenyl-1H-pyrazol-5(4H)-one (4d)

Orange solid; yield 95%; m.p. 230 °C. Analytical cal. C_{21}H_{16}N_{2}O_{3}: C, 73.24; H, 4.01; N, 8.47.
IR (KBr, v<sub>max</sub> cm<sup>-1</sup>): 1156, 1456 (C=C), 1598 (C=N), 1699 (C=O).

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ, ppm): 2.30 (s, 1H, -CH₃), 7.10-7.31 (m, 5H, phenyl ring), 7.69 (s, 1H, -CH=C), 8.09-7.20 (m, 3H, chromone ring), 10.04 (s, 1H, H-2<sub>γ</sub>-pyrone ring).

<sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>, δ, ppm): 14.13 (CH₃), 117.49 (C-8), 118.21-142.24 (phenyl ring), 118.74 (C-3), 123.18 (C-4a), 124.56 (C-6), 125.32 (C-5), 134.17 (C-1'), 135.52 (C-7), 137.61 (-C=N), 150.22 (C-2, γ-pyrene ring), 155.27 (C-2'), 161.53 (C-8b), 163.05 (C=O), 174.19 (C-4, C=O<sub>γ</sub>-pyrone ring).

MS (ESI) (m/z): 344.12 [M+•].

(Z)-4-((6-Fluoro-4-oxo-4H-chromen-3-yl)methylene)-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (4f)
Red solid; yield 96%; m.p. 214 °C; Analytical cal. C<sub>20</sub>H<sub>13</sub>FN<sub>2</sub>O<sub>3</sub>: C, 68.96; H, 3.76; N, 8.04; found: C, 68.97; H, 3.78; N, 8.01.

IR (KBr, v<sub>max</sub> cm<sup>-1</sup>): 1157, 1455 (C=C), 1599 (C=N), 1696 (C=O).

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ, ppm): 2.31 (s, 1H, -CH₃), 7.02-7.11 (m, 5H, phenyl ring), 7.72 (s, 1H, -CH=C), 8.07-7.23 (m, 3H, chromone ring), 10.12 (s, 1H, H-2<sub>γ</sub>-pyrone ring).

<sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>, δ, ppm): 14.18 (CH₃), 117.41 (C-8), 118.27-142.21 (phenyl ring), 118.64 (C-3), 123.38 (C-4a, 124.52 (C-6), 125.30 (C-5), 134.19 (C-1'), 135.56 (C-7), 137.41 (-C=N), 150.29 (C-2, γ-pyrene ring), 155.23 (C-2'), 161.50 (C-8b), 163.25 (C=O), 174.69 (C-4, C=O<sub>γ</sub>-pyrone ring).

MS (ESI) (m/z): 348.09 [M+•].

(Z)-4-((6-Bromo-4-oxo-4H-chromen-3-yl)methylene)-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (4g)
Brown solid; yield 94%; m.p. 248 °C; Analytical cal. C<sub>20</sub>H<sub>13</sub>BrN<sub>2</sub>O<sub>3</sub>: C, 58.70; H, 3.20; N, 6.85; found: C, 58.71; H, 3.22; N, 6.82.

IR (KBr, v<sub>max</sub> cm<sup>-1</sup>): 1158, 1451 (C=C), 1580 (C=N), 1699 (C=O).

<sup>1</sup>H NMR (400 MHz, DMSO-d<sub>6</sub>, δ, ppm): 2.35 (s, 1H, -CH₃), 7.42-7.18 (m, 5H, phenyl ring), 7.76 (s, 1H, -CH=C), 8.03-7.21 (m, 3H, chromone ring), 10.10 (s, 1H, H-2<sub>γ</sub>-pyrone ring).

<sup>13</sup>C NMR (100 MHz, DMSO-d<sub>6</sub>, δ, ppm): 14.22 (CH₃), 117.46 (C-8), 118.19-142.29 (phenyl ring), 118.64 (C-3), 120.41(C-6), 123.34 (C-4a), 125.39 (C-5), 133.19 (C-1').
Brown solid; yield 95%; m.p. 240 °C; Analytical cal. C_{20}H_{15}N_{3}O_{3}: C, 69.56; H, 4.38; N, 12.17; found: C, 69.53; H, 4.39; N, 12.19.  
**IR (KBr, ν_{max} cm^{-1}):** 1157, 1450 (C=C), 1580 (C=N), 1681 (C=O).  
**^{1}H NMR (400 MHz, DMSO-d$_6$, δ, ppm):** 2.33 (s, 1H, -CH$_3$), 7.32-7.17 (m, 5H, phenyl ring), 7.72 (s, 1H, -CH=C), 8.08-7.27 (m, 4H, chromone ring), 8.57 (s, 2H, -NH, D$_2$O exchangeable),  
**^{13}C NMR (100 MHz, DMSO-d$_6$, δ, ppm):** 14.22 (CH$_3$), 117.26 (C-8), 118.61 (C-3), 118.25-142.37 (phenyl ring), 123.28 (C-4a), 123.41 (C-6), 125.33 (C-5), 133.29 (C-1'), 135.16 (C-7), 137.38 (-C=N), 155.34 (C-2'), 161.66 (C-8b), 163.28 (C=O), 170.24 (C-2, γ-pyrone ring), 174.41 (C-4, C=O γ-pyrone ring).  
**MS (ESI) (m/z):** 408.01 [M$^+$].

(Z)-4-((2-Amino-4-oxo-4H-chromen-3-yl)methylene)-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (4h)

Yellow solid; yield 97%; m.p. 208 °C; Analytical cal. C$_{19}$H$_{18}$N$_2$O$_4$: C, 70.79; H, 5.63; N, 8.69; found: C, 70.71; H, 5.60; N, 8.71.  
**IR (KBr, ν_{max} cm^{-1}):** 1157, 1450 (C=C), 1578 (C=N), 1700 (C=O).  
**^{1}H NMR (400 MHz, DMSO-d$_6$, δ, ppm):** 2.31 (s, 1H, -CH$_3$), 3.34 (s, 9H, 3×-OCH$_3$), 7.12 (s, 2H, phenyl ring), 7.19-7.97 (m, 5H, phenyl ring), 7.35 (s, 1H, -CH=C).  
**^{13}C NMR (100 MHz, DMSO-d$_6$, δ, ppm):** 14.62 (CH$_3$), 56.36 (OCH$_3$), 105.13 (C-2 and C-6), 118.52-142.29 (phenyl ring), 122.25 (C-6), 128.24 (C-1), 133.22 (C-1'), 137.32 (-C=N), 148.61 (C-3), 149.41 (C-4), 155.14 (C-2'), 163.26 (C=O).  
**MS (ESI) (m/z):** 322.13 [M$^+$].

(Z)-4-(3,4-Dimethoxybenzylidene)-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (4i)

Yellow crystalline solid; yield 94%; m.p. 214 °C; Analytical cal. C$_{20}$H$_{20}$N$_2$O$_4$: C, 68.17; H, 5.72; N, 7.95; found: C, 68.20; H, 5.70; N, 7.94.  
**IR (KBr, ν_{max} cm^{-1}):** 1150, 1456 (C=C), 1600 (C=N), 1691 (C=O).  
**^{1}H NMR (400 MHz, DMSO-d$_6$, δ, ppm):** 2.32 (s, 1H, -CH$_3$), 3.34 (s, 9H, 3×-OCH$_3$), 7.12 (s, 2H, phenyl ring), 7.19-7.97 (m, 5H, phenyl ring), 7.35 (s, 1H, -CH=C).  
**^{13}C NMR (100 MHz, DMSO-d$_6$, δ, ppm):** 14.89 (CH$_3$), 56.36 (OCH$_3$), 105.13 (C-2 and C-6), 118.52-142.29 (phenyl ring), 122.25 (C-6), 128.24 (C-1), 133.22 (C-1'), 137.32 (-C=N), 148.61 (C-3), 149.41 (C-4), 155.14 (C-2'), 163.26 (C=O).

(Z)-3-Methyl-1-phenyl-4-(3,4,5-trimethoxybenzylidene)-1Hpyrazol-5(4H)-one (4j)

Yellow crystalline solid; yield 94%; m.p. 214 °C; Analytical cal. C$_{20}$H$_{20}$N$_2$O$_4$: C, 68.17; H, 5.72; N, 7.95; found: C, 68.20; H, 5.70; N, 7.94.  
**IR (KBr, ν_{max} cm^{-1}):** 1150, 1456 (C=C), 1600 (C=N), 1691 (C=O).  
**^{1}H NMR (400 MHz, DMSO-d$_6$, δ, ppm):** 2.32 (s, 1H, -CH$_3$), 3.34 (s, 9H, 3×-OCH$_3$), 7.12 (s, 2H, phenyl ring), 7.19-7.97 (m, 5H, phenyl ring), 7.35 (s, 1H, -CH=C).  
**^{13}C NMR (100 MHz, DMSO-d$_6$, δ, ppm):** 14.89 (CH$_3$), 56.36 (OCH$_3$), 105.13 (C-2 and C-6), 118.52-142.29 (phenyl ring), 122.25 (C-6), 128.24 (C-1), 133.22 (C-1'), 134.34 (C-5), 137.32 (-C=N), 148.61 (C-3), 149.41 (C-4), 155.14 (C-2'), 163.26 (C=O).
<table>
<thead>
<tr>
<th>Compound</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>137.38 (-C=N), 154.11 (C-3 and C-4), 155.39 (C-2'), 163.28 (C=O).</td>
<td>MS (ESI) (m/z): 352.14 [M⁺].</td>
</tr>
<tr>
<td>Orange crystalline solid; yield 97%; m.p. 210 ⁰C; Analytical cal. C₁₇H₁₃N₃O₃: C, 66.44; H, 4.26; N, 13.67; found: C, 66.41; H, 4.28; N, 13.68.</td>
<td>IR (KBr, ν&lt;sub&gt;max&lt;/sub&gt; cm⁻¹): 1157, 1456 (C=C), 1578 (C=N), 1687 (C=O), 1522, 1365 (NO₂).</td>
</tr>
<tr>
<td>²H NMR (400 MHz, DMSO-d₆, δ, ppm): 2.36 (s, 1H, -CH₃), 7.20-7.99 (m, 5H, phenyl ring), 7.49 (s, 1H, -CH=C), 8.12 (d, 2H, H-2 and H-6), 8.18 (d, 2H, H-3 and H-5).</td>
<td>¹³C NMR (100 MHz, DMSO-d₆, δ, ppm): 15.09 (CH₃), 118.12-142.22 (phenyl ring), 124.18 (C-3 and C-4), 128.21 (C-1'), 132.17 (C-2 and C-6), 139.24 (C-1), 145.69 (C-2'), 145.88 (-C=N), 148.14 (C-5), 163.25 (C=O).</td>
</tr>
<tr>
<td>MS (ESI) (m/z): 307.10 [M⁺].</td>
<td></td>
</tr>
<tr>
<td>Yellow solid; yield 94%; m.p. 202 ⁰C; Analytical cal. C₁₇H₁₃N₃O₃: C, 66.44; H, 4.26; N, 13.67; found: C, C, 66.41; H, 4.27; N, 13.69.</td>
<td>IR (KBr, ν&lt;sub&gt;max&lt;/sub&gt; cm⁻¹): 1152, 1454 (C=C), 1579 (C=N), 1693 (C=O), 1520, 1360 (NO₂).</td>
</tr>
<tr>
<td>²H NMR (400 MHz, DMSO-d₆, δ, ppm): 2.32 (s, 1H, -CH₃), 7.22-7.95 (m, 5H, phenyl ring), 7.47 (s, 1H, -CH=C), 7.67-8.42 (m, 4H, phenyl ring).</td>
<td>¹³C NMR (100 MHz, DMSO-d₆, δ, ppm): 15.19 (CH₃), 118.15-142.32 (phenyl ring), 123.08 (C-4), 123.36 (C-6), 125.17 (C-2), 127.23 (C-1'), 128.18 (C-5), 133.34 (C-1), 144.63 (C-2'), 146.98 (-C=N), 147.08 (C-3), 163.29 (C=O).</td>
</tr>
<tr>
<td>MS (ESI) (m/z): 307.10 [M⁺].</td>
<td></td>
</tr>
<tr>
<td>Orange crystalline solid; yield 98%; m.p. 194 ⁰C, reported 188-192 ⁰C; Analytical cal. C₁₀H₁₉N₃O: C, 74.73; H, 6.27; N, 13.76; found: C, 74.70; H, 6.28; N, 13.78</td>
<td>IR (KBr, ν&lt;sub&gt;max&lt;/sub&gt; cm⁻¹): 1154, 1452 (C=C), 1591 (C=N), 1689 (C=O).</td>
</tr>
<tr>
<td>²H NMR (400 MHz, DMSO-d₆, δ, ppm): 2.30 (s, 1H, -CH₃), 3.13 (s, 1H, 2×CH₃), 7.13-7.97 (m, 5H, phenyl ring), 6.84-8.66 (m, 4H, phenyl ring), 7.58 (s, 1H, -CH=C).</td>
<td>¹³C NMR (100 MHz, DMSO-d₆, δ, ppm): 15.19 (CH₃), 41.28 (N-CH₃), 111.32 (C-3 and C-5), 118.09-138.84 (phenyl ring), 123.92 (C-1), 128.69 (C-1'), 137.43 (C-2 and C-6), 148.18 (C-4), 151.56 (C-2'), 153.80 (-C=N), 170.16 (C=O).</td>
</tr>
</tbody>
</table>

179
(Z)-4-(4-Fluorobenzylidene)-3-methyl-1-phenyl-1H-pyrazol-5(4H)-one (4n)

<table>
<thead>
<tr>
<th><strong>MS (ESI) (m/z)</strong></th>
<th>305.15 [M+•].</th>
</tr>
</thead>
</table>

Yellow solid; yield 96%; m.p. 104 °C, reported 98-102 °C;\(^{43}\) Analytical cal. C\textsubscript{17}H\textsubscript{13}FN\textsubscript{2}O: C, 72.85; H, 4.67; N, 9.99; found: C, 72.82; H, 4.69; N, 10.00.

**IR (KBr, ν\textsubscript{max} cm\textsuperscript{-1})**: 1156, 1455 (C=C), 1593 (C=N), 1697 (C=O).

**\(^1\)H NMR (400 MHz, DMSO-d\textsubscript{6}, δ, ppm)**: 2.34 (s, 1H, -CH\textsubscript{3}), 7.14-7.86 (m, 4H, phenyl ring), 7.19-7.97 (m, 5H, phenyl ring), 7.42 (s, 1H, -CH=C).

**\(^13\)C NMR (100 MHz, DMSO-d\textsubscript{6}, δ, ppm)**: 15.02 (CH\textsubscript{3}), 115.36 (C-3 and C-5), 118.02-139.81 (phenyl ring), 127.60 (C-1'), 128.91 (C-1), 132.03 (C-2 and C-6), 145.50 (C-2'), 148.85. (-C=N), 162.18 (C-4), 168.12 (C=O). **MS (ESI) (m/z)**: 280.10 [M+•].

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)

(4n)
5(4H) one (4q)

Yellow solid; yield 97%; m.p. 224 °C; Analytical cal. C_{19}H_{16}N_{4}O_{7}: C, 55.34; H, 3.91; N, 13.59; found: C, 55.31; H, 3.93; N, 13.60.

**IR (KBr, v_{max} cm^{-1}):** 1157, 1456 (C=C), 1522, 1362 (NO_{2}), 1594 (C=N), 1688 (C=O).

**^{1}H NMR (400 MHz, DMSO-d_{6}, δ, ppm):** 2.32 (s, 1H, -CH_{3}), 3.36 (s, 6H, 2×-OCH_{3}), 7.20-7.31 (m, 3H, phenyl ring), 7.46 (s, 1H, -CH=C), 8.20-9.04 (m, 3H, phenyl ring).

**^{13}C NMR (100 MHz, DMSO-d_{6}, δ, ppm):** 14.88 (CH_{3}), 56.02 (OCH_{3}), 111.72 (C-5), 115.53 (C-2), 120.21-144.39 (phenyl ring), 122.25 (C-6), 128.14 (C-1), 130.22 (C-1'), 139.32 (-C=N), 148.68 (C-3), 149.45 (C-4), 150.14 (C-2'), 164.26 (C=O).

**MS (ESI) (m/z):** 412.10 [M+•].

(Z)-4-(4-(Dimethylamino)benzylidene)-1-(2,4-dinitrophenyl)-3-methyl-1H-pyrazol-5(4H)-one (4r)

Orange crystalline solid; yield 98%; m.p. 240 °C; Analytical cal. C_{19}H_{17}N_{5}O_{5}: C, 57.72; H, 4.33; N, 17.71; found: C, 57.73; H, 4.30; N, 17.73.

**IR (KBr, v_{max} cm^{-1}):** 1156, 1452 (C=C), 1526, 1361 (NO_{2}), 1593 (C=N), 1691 (C=O).

**^{1}H NMR (400 MHz, DMSO-d_{6}, δ, ppm):** 2.32 (s, 1H, -CH_{3}), 3.10 (s, 1H, 2×CH_{3}), 6.80-8.46 (m, 4H, phenyl ring), 7.49 (s, 1H, -CH=C), 8.28-9.01 (m, 3H, phenyl ring).

**^{13}C NMR (100 MHz, DMSO-d_{6}, δ, ppm):** 15.20 (CH_{3}), 41.31 (N-CH_{3}), 111.48 (C-3 and C-5), 120.14-144.09 (phenyl ring), 123.02 (C-1), 126.69 (C-1'), 136.43 (C-2 and C-6), 148.88 (C-4), 150.56 (C-2'), 150.80 (-C=N), 170.12 (C=O).

**MS (ESI) (m/z):** 395.12 [M^{+}].

(Z)-1-(2,4-Dinitrophenyl)-4-(4-fluorobenzylidene)-3-methyl-1H-pyrazol-5(4H)-one (4s)

Yellow solid; yield 94%; m.p. 162 °C, reported 160-163 °C; Analytical cal. C_{17}H_{11}FN_{4}O_{5}: C, 55.14; H, 2.99; N, 15.13; found: C, 55.15; H, 2.96; N, 15.15.

**IR (KBr, v_{max} cm^{-1}):** 1159, 1453 (C=C), 1526, 1360 (NO_{2}), 1598 (C=N), 1698 (C=O).

**^{1}H NMR (400 MHz, DMSO-d_{6}, δ, ppm):** 2.36 (s, 1H, -CH_{3}), 7.18-7.80 (m, 4H, phenyl ring), 7.42 (s, 1H, -CH=C), 7.96-7.98 (m, 3H, phenyl ring).

**^{13}C NMR (100 MHz, DMSO-d_{6}, δ, ppm):** 15.01 (CH_{3}), 115.31 (C-3 and C-5), 120.23-145.84 (phenyl ring), 127.60 (C-1), 128.91 (C-1'), 132.00 (C-2 and C-6), 145.50 (C-2'), 148.85 (-C=N), 162.18 (C-4), 169.10 (C=O).

**MS (ESI) (m/z):** 370.07 [M^{+}].

5.3.5. Single crystal X-ray crystallographic studies of compound 4a and 4d
The crystal structure of compounds 4a and 4d were determined by X-ray diffraction experiments performed on a Bruker Apex II diffractometer. The instrumentation detail and procedure have been discussed in chapter 2. Pertinent crystallographic data for compounds 4a and 4d have been summarized in Table 1. The crystal data have been deposited at the Cambridge Crystallographic Data Centre (CCDC) with reference number, compound 4a with CCDC 1409997 and compound 4d with CCDC 1432605.

5.3.6. Antioxidant assay
All the synthesized compounds were tested for their antioxidant property by 1,1-diphenylpicrylhydrazyl (DPPH) method. The general procedure for this assay is discussed in chapter 2. In this procedure, drug stock solution (1 mg/mL) was diluted to final concentration of 2, 4, 6, and 8µg/mL in methanol.

5.4. CONCLUSION
This chapter reports a convenient, eco-friendly and sustainable approach for the one-pot synthesis of a series of pyrazolone derivatives 4(a-s) in excellent yields (94-98%) by employing recyclable and reusable SiO₂/ZnBr₂ Lewis acid catalyst in water under microwave heating. The scheme not only offers use of microwave at low temperature and substantial yield of products but also affords mild reaction conditions, water as a green solvent, shorter reaction times, high purity, operational simplicity and easy workup. This green synthetic procedure eliminates the use of toxic solvents and thus makes it attractive one in organic synthesis. All the compounds displayed moderate to good antioxidant activity. The results validate that the nature of substituent attached to the heterocyclic moieties is important for biological activity. Thus, present synthetic approach provides a better scope for the synthesis of pyrazolone analogues and will be a more practical alternative to the other existing methods.
5.5. REFERENCES


