CHAPTER-2
SYNTHESIS OF NOVEL CHROMONYL AND PYRAZOLYL CHALCONES UNDER GREEN CONDITIONS

2.1. REVIEW & LITERATURE

2.1.1. Biological importance

Chalcones are one of the major class of natural products with widespread distribution in fruits, vegetables, spices, tea and soy based foodstuff and has been subject of great interest for possessing interesting pharmacological activities.\(^1\) The chalcones like phloretin, arbutin, chalconaringenin, phloridizin are frequent components of human diet.\(^2\) Representative examples of naturally occurring bioactive chalcones are xanthohumol, cardomonin and flavokawains. Xanthohumol is a principal prenylated flavanoid of the hop plant, and is characterized as ‘broad spectrum’ cancer chemopreventive agents in vitro.\(^3\) Cardomonin is a hydroxychalcones isolated from zingiberous plant species, which possesses antimitagenic, vasorelaxant and anti-inflammatory properties.\(^4\) Flavokawains are found mainly in the kava plant and have been used in traditional medicine practices of the pacific islands.\(^5\)

Chalcones or 1,3-diaryl-2-propene-1-ones, belong to the flavanoid family. Chemically chalcones consist of open-chain flavanoids in which two aromatic or heteroaromatic rings are joined by three carbons \textit{viz} \(\alpha,\beta\)-unsaturated carbonyl system. They display a wide spectrum of biological activities including antioxidant,\(^6\) antibacterial,\(^7\) antileishmanial,\(^8\) anticancer,\(^9\) antiangiogenic,\(^10\) anti-infective, anti-inflammatory,\(^11\) nitric oxide regulation,\(^12\) anti-hyperglycemic,\(^13\) antifungal, antipyretic, bactericidal, insecticidal,\(^14\) phytoestrogenic
activities etc. Some of the naturally occurring chalcones with varied biological activity are listed below.

2.1.2. Naturally occurring and biologically active chalcones

2.1.2a. Antibacterial chalcones

2.1.2b. Antileishmanial chalcones

2.1.2c. Antiviral chalcones
2.1.2d. *Antimalarial chalcones*

- Xanthohumol
- Crotaorixin
- Licoagrochalcone

2.1.2e. *Antifungal chalcones*

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2.1.2f. *Anti-inflammatory chalcones*

- Xanthohumol B
- Xanthohumol D
2.1.3. Chemical relevance

Chalcones are generally synthesized via Claisen-Schmidt condensation carried out in basic or acidic media under homogeneous conditions. The reactions carried out in the presence of bases include aqueous NaOH, KOH, Ba(OH)₂, zeolites, hydrotalcites, LiHDMS, calcined NaNO₃, natural phosphates etc. A number of acid-catalyzed methods are also sited in the literature which includes the use of AlCl₃, dry HCl, Zn(bpy)(OAc)₂, TiCl₄, Cp₂ZrH₂/NiCl₂ and RuCl₃. Recent reports have revealed that catalysts like BF₃·Et₂O, SOCl₂/EtOH, Bronsted acidic ionic liquids etc are also used with more or less success. Unfortunately, many of these methods have drawbacks such as use of expensive stoichiometric amount of reactants, use of hazardous and environmentally polluting solvents, low yields, extended time, tedious procedure etc. Thus, the need for the development of an alternative route to construct biologically active novel heterocycles by reducing time from hours to minutes at ambient temperature is in demand.

One of the major challenges facing chemists this century is to develop new transformations that are not only efficient, selective, and high yielding but also environmentally benign. During the last decade, the topic of ‘green’ chemistry has received increasing attention. ‘Green’ chemistry aims at the total elimination or at least the minimization of waste/side products (atom economy) and the implementation of sustainable processes. The utilization of non-toxic chemicals, renewable materials and solvent-free conditions are the key issues of green synthetic strategy. The application of water as an environmentally benign and economically favorable alternative to organic solvents has developed into a highly active field of research addressing current
requirements in synthetic chemistry and catalysis.\textsuperscript{34} In contrast to common organic reaction media, it is nontoxic, non-flammable and cheap.\textsuperscript{35} Use of water as a solvent is undoubtedly the best alternative as there will be no use of hazardous and toxic organic solvents and no need for vigorous drying of the solvents.

In most chemical processes, major adverse effects towards the environment are due mainly to the consumption of energy for heating. To overcome this problem it is highly desirable to develop efficient methods that use alternative energy sources such as microwave irradiation, to facilitate chemical reactions. Ideal industrial chemical processes require energy saving, high conversion, high selectivity, and solvent-free reaction conditions with minimizing the processes themselves. A microwave heating technique is a promising candidate, replacing conventional boilers because microwave-assisted organic syntheses can lead to large reductions in reaction time and to enhancement in conversion and selectivity compared to conventional heating.\textsuperscript{36} These microwave effects could be attributed to the characteristic heating modes of MW through the interaction of oscillating electric and magnetic fields with ordered assemblies of polar molecules expressed as dielectric loss, leading to unusual phenomenon called superheating or hot-spots.\textsuperscript{37} Instantaneous heat release at the molecular level should favorably induce some thermal reactions between molecules which form a polar charge transfer state or a polar transition state as often observed in photo induced chemical reactions. Recently, the combination of these two prominent green chemistry principles, "microwaves" and "water", has become very popular and received substantial interest.\textsuperscript{38}
2.2. PRESENT WORK

It is worthwhile to mention here that the chromones form an important component of pharmacophores of a number of biologically active molecules of synthetic as well as natural origin having significant medicinal applications.\(^{39}\) Consequently, chromone chemistry continues to draw considerable attention of synthetic organic and medicinal chemists.\(^{40}\) Chromones are widely distributed in nature, especially in the plant kingdom, and a wide spectrum of useful properties of biological importance are associated with them. Some of the biological activities ascribed to chromone derivatives include cytotoxic,\(^{41a-b}\) p-glycoprotein binding,\(^{41c}\) neuroprotective,\(^{41d}\) HIV inhibitory,\(^{41e}\) antimicrobial,\(^{41f}\) cyclin-dependant kinase inhibitory,\(^{41g}\) antifungal\(^{41h}\) and antioxidant\(^{41i}\) activities. Among the chromone moieties 3-formylchromones 1 are an important and well-studied class of 3-substituted chromones, which can serve as the starting materials for the synthesis of a broad range of heterocyclic systems due to the presence of three electrophilic centers in their molecules (The C-2 and C-4 atoms of the chromone system and the carbonyl carbon of 3-formyl group).

Pyrazole derivatives are another important class of heterocyclic compounds and many pyrazole derivatives are reported to have the broad spectrum of biological activities, such as antihyperglycemic, analgesic, anti-inflammatory, antipyretic, antibacterial, hypoglycemic, sedative-hypnotic,\(^{42a}\) and anticoagulant activity.\(^{42b}\) Recently, some arylpyrazoles were reported to show non-nucleoside HIV-1 reverse transcriptase inhibitory activity.\(^{42c}\) Extensive studies have been devoted to arylpyrazole derivatives such as Celecoxib, a well-known cyclo-oxygenase-2 inhibitor.\(^{42d}\)
Keeping in view the biological importance of chalcones, chromone and pyrazole derivatives it was worthwhile to prepare novel chromonyl chalcones and pyrazolyl chalcones by employing 3-formylchromones, 5-chloro-3-methyl-1-phenylpyrazole-4-carboxaldehyde with various acetylbarbituric acid derivatives under green environment.

2.3. RESULTS AND DISCUSSION

Due to the exceptional reactivity of formyl group in 3-formylchromone as well as the versatile biological activities of chromone and barbituric acid derivatives \(^{43}\) several novel chromonyl chalcones (3a-f) were synthesized employing 3-formylchromones (1a-b), 5-acetyl-1,3-dimethylbarbituric acid (2a), 5-acetylbarbituric acid (2b) and 5-acetyl thiobarbituric acid (2c) (Scheme 1). As a preliminary study, we carried out the synthesis of chromonyl chalcones (3a-f) under conventional heating method using ethanol as a solvent in the presence of catalytic amount of pyridine. Although, the reactions were found to proceed smoothly, it took longer period for completion of reaction (7-16 h) with yields (62-79%). Keeping in mind the key principles of ‘green’ chemistry, we attempted the same reactions under microwave irradiation. The results obtained were surprising that most of the reactions were found to be completed within 6-11 min with substantial increase in yield of products (81-90%). Further the generality of reaction was envisaged by using the novel and recently explored Lewis acid catalyst Zn(proline)\(_2\)\(^{44}\) in ‘green solvent’ water. The results were found to be equally effective (Table 1). The Zn(proline)\(_2\) catalyst was easily preparable, stable, inexpensive and recyclable. The solubility nature of the catalyst facilitated the separation of products from the catalyst (Catalyst is soluble in water and insoluble in organic solvents). The used catalyst was recycled up to 3 cycles without significant loss of its catalytic activity and was used for the next reaction.
The infrared (IR) spectrum of 3a (Fig. 1) exhibited a sharp band at 1719 cm\(^{-1}\) for carbonyl groups of barbituric acid moiety. Another strongly absorbed band at 1657 cm\(^{-1}\) accompanied by a notch at 1650 cm\(^{-1}\) was assigned to chromone and propenone carbonyl groups respectively. The \(^1\)H NMR spectrum (Fig. 2) showed trans olefinic protons H\(_a\) and H\(_b\) of \(\alpha,\beta\)-unsaturated carbonyl system as ortho coupled doublets at \(\delta\) 9.26 (\(J=15.7\) Hz) and 7.84 (\(J=15.7\) Hz) respectively. The value of spin-spin coupling constant \(J_{ab}\) in the range 15-16 Hz is indicative of the \(E\)-configuration of chalcone. The presence of chromone ring was established by the characteristic C-2 singlet at \(\delta\) 8.39 and a double doublet for C-5 proton at \(\delta\) 8.32. The three aromatic protons of chromone moiety were discernible in the form of multiplet at \(\delta\) 7.49-7.76. The two N-CH\(_3\) protons of barbituric acid moiety were present as sharp singlets at \(\delta\) 3.37 and 3.39. Further, the structure was confirmed by mass spectrum (Fig. 3), which showed \(M^+\) at \(m/z\) 354. The other important peaks were obtained as depicted in Scheme 2. The spectral data of other compounds followed similar pattern, and are explained in experimental section.

Further, efforts were made to synthesize pyrazolyl chalcones (5a-c) employing 5-chloro-3-methyl-1-phenylpyrazole-4-carboxaldehyde (4) and various 5-acetylbarbituric acid derivatives (2a-c) in presence of piperidine both under conventional and microwave irradiation method (Scheme 1). Chalcones were obtained in excellent yields (87-92\%) under microwave irradiation technique in shorter time (6-10 min) and were comparable with conventional heating technique results (Table 1).

The infrared (IR) spectrum of 5a (Fig. 4) showed the carbonyl absorption band of barbituric moiety at 1715 cm\(^{-1}\). The carbonyl group of propenone moiety appeared as strong and sharp absorption band at 1664 cm\(^{-1}\). Another sharp and strongly absorbed band
at 1618 cm⁻¹ was assigned to carbon-carbon double bond of α,β-unsaturated system. The
¹H NMR spectrum (Fig. 5) showed trans olefinic protons Hₐ and Hₐ as ortho coupled
doublets at δ 8.55 (J=15.9 Hz) and 8.00 (J=16.2 Hz) respectively. The aromatic protons
of pyrazole moiety were present in the form of multiplet at δ 7.42-7.58. The N-CH₃
protons of barbituric acid moiety were discernible as two sharp singlets at δ 3.37 and 3.40
whereas protons of CH₃ group of pyrazole unit appeared as another sharp singlet at δ
2.59. Further confirmation of the structure was established by mass spectrum (Fig. 6),
which showed M⁺ at 400.12 as base peak. The spectral data of other compounds followed
similar pattern.

Table I. Synthesis of chromonyl and pyrazolyl chalcones.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>In refluxing ethanol/ methanol</th>
<th>In refluxing water</th>
<th>Microwave irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Time</td>
<td>Yield (%)</td>
<td>Time</td>
</tr>
<tr>
<td>1</td>
<td>3a</td>
<td>7 h</td>
<td>78</td>
<td>20 min</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>7.5 h</td>
<td>79</td>
<td>20 min</td>
</tr>
<tr>
<td>3</td>
<td>3e</td>
<td>16 h</td>
<td>62</td>
<td>30 min</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>16 h</td>
<td>72</td>
<td>30 min</td>
</tr>
<tr>
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<td>3e</td>
<td>14 h</td>
<td>74</td>
<td>25 min</td>
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<tr>
<td>6</td>
<td>3f</td>
<td>15 h</td>
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<td>30 min</td>
</tr>
<tr>
<td>7</td>
<td>5a</td>
<td>12 h</td>
<td>72</td>
<td>-</td>
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<tr>
<td>8</td>
<td>5b</td>
<td>14 h</td>
<td>70</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>5c</td>
<td>8 h</td>
<td>78</td>
<td>-</td>
</tr>
</tbody>
</table>

- No reaction
Scheme 1. Synthesis of chromonyl chalcones (3a-f) and pyrazolyl chalcones (5a-c).
2.4. CONCLUSION

In conclusion, we have developed green synthetic approaches for the generation of novel series of chromonyl and pyrazolyl chalcones in excellent yields. Further, first time novel synthesis of chromonyl chalcones was achieved under the influence of recyclable
Zn(proline)$_2$ as Lewis acid catalyst in good yields. The experimental simplicity, excellent yields, short reaction times, mild reaction conditions, high purity, solvent-free or usage of water as a 'green solvent' and Zn(proline)$_2$ as an efficient recyclable catalyst etc are the noteworthy advantages of the present procedure.

2.5. EXPERIMENTAL

Melting points were taken in Riechert Thermover instrument and are uncorrected. The IR spectra were recorded on Perkin Elmer RXI spectrometer in KBr, $^1$H NMR on Bruker DRX-300 and Bruker Avance II 400 spectrometer using tetramethyl silane (TMS) as the internal standard and DMSO-d$_6$/CDCl$_3$ as solvent. Mass spectra were obtained Jeol-SX-102 (FAB), JEOL-Accu TOF JMS-T100LC DART-MS and Micro mass Quattro II triple quadrupol mass spectrometer. The microanalytical data were collected on Elementar vario EL III elemental analyzer. 3-Formylchromone and substituted-3-formylchromone,$^{45}$ 5-chloro-3-methyl-1-phenylpyrazole-4-carboxaldehyde,$^{46}$ 5-acetyl-1,3-dimethylbarbituric acid, 5-acetylbarbituric acid, 5-acetylthiobarbituric acid,$^{47}$ Zn(proline)$_2$$^{48}$ were synthesized by reported methods. All other chemicals used were purchased from Merck (Mumbai, India), Fluka Chemicals (Switzerland) and used without further purification. The purity of the compounds was checked by thin layer chromatography (TLC) on glass plates coated with silica gel G$_{254}$ (E.Merck) using chloroform-methanol (3:1) mixture as mobile phase and visualized by iodine vapors. All the experiments under microwave irradiation were carried out in a domestic microwave oven (National, Model NN-S557WF, 1.3 KW, 2450 MHz).

2.5.1. Preparation of chromonyl chalcones (3a-f) under thermal heating condition
To a well stirred solution of 5-acetyl-1,3-dimethylbarbituric acid (5.05 mmol)/5-acetylbarbituric acid (5.05 mmol)/5-acetylthiobarbituric acid (5.05 mmol) in ethanol (25 mL) containing pyridine (0.5 mL), 3-formylchromone/substituted-3-formylchromone (5.05 mmol) was added. The reaction mixture was then refluxed in a heating mantle for 7-16 h (Table 1) and cooled at room temperature. The solid, thus, obtained was filtered, washed with water, alcohol and dried to afford 3a-f.

2.5.2. Preparation of chromonyl chalcones (3a-f) under microwave irradiation condition

3-Formylchromone/substituted-3-formylchromone (5.05 mmol), 5-acetyl-1,3-dimethylbarbituric acid (5.05 mmol)/5-acetylbarbituric acid (5.05 mmol)/5-acetylthiobarbituric acid (5.05 mmol) and pyridine (0.3 mL) were mixed thoroughly in a mortar, and air dried. The reaction mixture was then transferred to an open Pyrex beaker and subjected to microwave irradiation (Multimode, full power). The progress of reaction was monitored by TLC and on completion, the reaction mixture was slurried in water (40 mL). The solid, thus, obtained was filtered, washed with water, alcohol and dried to afford 3a-f.

2.5.3. Zn(proline)$_2$-catalyzed synthesis of chromonyl chalcones (3a-f) in water

A mixture of 3-formylchromone/substituted-3-formylchromone (5.05 mmol), 5-acetyl-1,3-dimethylbarbituric acid (5.05 mmol)/5-acetylbarbituric acid (5.05 mmol)/5-acetylthiobarbituric acid (5.05 mmol) and Zn(proline)$_2$ (0.30 mmol) was dissolved in water (14 mL) and refluxed on a heating mantle for specified time (Table 1). After completion of the reaction (monitored by TLC), it was allowed to cool to room temperature. The reaction mixture was extracted with dichloromethane, dried over
anhydrous Na$_2$SO$_4$, concentrated to furnish crude product, which was then recrystallized from suitable solvents. The catalyst was recovered by simple separation of aqueous and organic phases. The catalyst present in the aqueous layer was used for the subsequent reactions.

**Spectral data**

$(2E)$-1-(1,3-Dimethyl-2,4,6-pyrimidinetione-5-yl)-3-(4-oxo-4H-1-benzopyran-3-yl)-2-propene-1-one (3a)

Purified by recrystallization from chloroform.

Bright yellow crystals.

M.p : >300 °C.

IR (KBr) $v_{max}$/cm$^{-1}$ : 1657 (C=O), 1719 (C=O).

$^1$H NMR (400 MHz, CDCl$_3$) :

$\delta$ (ppm) 3.37 (s, 3H, N-CH$_3$), 3.39 (s, 3H, N-CH$_3$), 7.49-7.76 (m, 3H, Ar-H), 7.84 (d, 1H, $J=15.7$ Hz, $H_b$), 8.32 (dd, 1H, C-5), 8.39 (s, 1H, C-2), 9.26 (d, 1H, $J=15.7$ Hz, $H_a$).

MS-FAB (% rel. Int.) :

$m/z$ 354 (M$^+$, 80), 353 (60), 336 (30), 307 (65), 279 (5), 199 (15), 171 (50), 155 (50) 154 (100), 136 (90), 122 (5), 107 (50).

Elemental analysis for C$_{18}$H$_{14}$N$_2$O$_6$ : Calculated C, 61.02; H, 3.98; N 7.91; Found C, 61.05; H, 3.83; N, 7.84 %.

$(2E)$-1-(1,3-Dimethyl-2,4,6-pyrimidinetione-5-yl)-3-(6-methyl-4-oxo-4H-1-benzopyran-3-yl)-2-propene-1-one (3b)
Purified by recrystallization from chloroform.

Bright yellow crystals.

M.p : >300 °C.

IR (KBr) $\nu_{\text{max}}$/$\text{cm}^{-1}$ : 1666 (C=O), 1716 (C=O).

$^1$H NMR (400 MHz, CDCl$_3$) : $\delta$ (ppm) 2.48 (s, 3H, CH$_3$), 3.38 (s, 3H, N-CH$_3$), 3.40 (s, 3H, N-CH$_3$), 7.31-7.46 (m, 3H, Ar-H), 7.87 (d, 1H, $J$=16.3 Hz, H$_b$), 8.27 (s, 1H, C-2), 9.18 (d, 1H, $J$=15.8 Hz, H$_a$).

MS-FAB (% rel. Int.) : m/z 368 (M$^+$, 30), 367 (10), 213 (5), 212 (20), 155 (30), 154 (100), 136 (60), 122 (30), 108 (50).

Elemental analysis for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}_6$ : Calculated C, 61.95; H, 4.38; N, 7.61; Found C, 61.86; H, 4.27; N, 7.58 %.

(2E)-3-(4-Oxo-4$^H$-1-benzopyran-3-yl)-1-(2,4,6-pyrimidinetrione-5-yl)-2-propen-1-one (3c)

Purified by recrystallization from methanol-DMF (3:2 v/v) mixture.

Bright yellow solid.

M.p : >300 °C.

IR (KBr) $\nu_{\text{max}}$/$\text{cm}^{-1}$ : 1643 (C=O), 1740 (C=O), 3078 (NH) 3200 (NH).

$^1$H NMR (300 MHz, DMSO-$d_6$) : $\delta$ (ppm) 7.40 (d, 1H, $J$=15.2 Hz, H$_b$), 7.55-
7.91 (m, 3H, Ar-H), 8.17 (dd, 1H, $J=8.0$ Hz, 1.6 Hz, C-5), 8.95 (s, 1H, C-2), 9.09 (d, 1H, $J=15.9$ Hz, $H_a$), 11.06 (s, 1H, NH), 11.76 (s, 1H, NH).

MS-FAB (% rel. Int.) : $m/z$ 326 (M$^+$, 60), 325 (5), 279 (25), 251 (5), 206 (10), 199 (70), 171 (65), 143 (40), 99 (5).

Elemental analysis for $C_{16}H_{10}N_2O_6$ : Calculated C, 58.90; H, 3.08; N, 8.58; Found C, 58.57; H, 3.14; N, 8.44 %.

$(2E)$-3-(6-Methyl-4-oxo-4H-1-benzopyran-3-yl)-1-(2,4,6-pyrimidinetrione-5-yl)-2-propen-1-one (3d)

Purified by recrystallization from methanol-DMF (3:2 v/v) mixture.

Yellow solid.

M.p : $>300$ °C.

IR (KBr) $v_{max}$/cm$^{-1}$ : 1647 (C=O), 1746 (C=O), 3025 (NH), 3188 (NH).

$^1$H NMR (400 MHz, DMSO-d$_6$) : $\delta$ (ppm) 2.49 (s, 3H, CH$_3$), 7.43-8.01 (m, 3H, Ar-H), 7.87 (d, 1H, $J=15.8$ Hz, $H_b$), 8.44 (s, 1H, C-2), 8.96 (d, 1H, $J=15.8$ Hz, $H_a$), 10.71 (s, 1H, NH), 11.57 (s, 1H, NH).

MS-ESI : $m/z$ 340.4 (M$^+$), 321.6, 274.6, 214.4, 213.4, 202.6.
Elemental analysis for 
\( \text{C}_{17}\text{H}_{12}\text{N}_{2}\text{O}_{6} \) : Calculated C, 60.00; H, 3.55; N, 8.23;
Found C, 59.91; H, 3.61; N, 8.34 %.

\((2E)-1-(2\text{-Mercapto-4,6-pyrimidinedione-5-yl})-3-(4\text{-oxo-4H-1-benzopyran-3-yl})-2\text{-propene-1-one} \ (3e)\)

Purified by recrystallization from methanol-DMF (3:2 v/v) mixture.

Yellow solid.

\( \text{M.p} \) : >300 °C.

\( \text{IR (KBr) } \nu_{\text{max}}/\text{cm}^{-1} \) : 1060 (C=S), 1648 (C=O), 3027 (NH), 3189 (NH).

\( ^{1}\text{H NMR (300 MHz, DMSO-d}_{6}) \) : \( \delta \) (ppm) 7.55-7.89 (m, 3H, Ar-H), 7.77 (d, 1H, J=16.2 Hz, \( \text{H}_{b} \)), 8.17 (d, 1H, J=7.8 Hz, C-5), 8.99 (s, 1H, C-2), 9.09 (d, 1H, J=15.0 Hz, \( \text{H}_{a} \)), 12.55 (s, 1H, NH), 12.61 (s, 1H, NH).

\( \text{MS-ESI} \) : \( m/z \) 342.07 (M\(^+\)), 341.06, 324.10, 199.07, 171.07, 79.05.

Elemental analysis for 
\( \text{C}_{16}\text{H}_{10}\text{N}_{2}\text{O}_{5}\text{S} \) : Calculated C, 56.14; H, 2.94; N, 8.18.
Found C, 56.04; H, 2.98; N, 8.01 %.

\((2E)-1-(2\text{-Mercapto-4,6-pyrimidinedione-5-yl})-3-(6\text{-methy}-4\text{-oxo-4H-1-benzopyran-3-yl})-2\text{-propene-1-one} \ (3f)\)

Purified by recrystallization from methanol-DMF (2:3 v/v) mixture.
2.5.4. Preparation of pyrazolyl chalcones (5a-c) under thermal heating conditions

To a well stirred solution of 5-acetyl-1,3-dimethylbarbituric acid (5.05 mmol)/5-acetylbarbituric acid (5.05 mmol)/5-acetylthiobarbituric acid (5.05 mmol) in methanol (20 mL) containing piperidine (0.2 mL), 5-chloro-3-methyl-1-phenylpyrazole-4-carboxaldehyde (5.05 mmol) was added. The reaction mixture was then refluxed in a heating mantle for 8-14 h, cooled at room temperature. The bright yellow solid, thus, obtained was filtered, washed with water, alcohol and dried to afford 5a-c.

2.5.5. Preparation of pyrazolyl chalcones (5a-c) under microwave irradiation conditions

5-Chloro-3-methyl-1-phenylpyrazole-4-carboxaldehyde (5.05 mmol), 5-acetyl-1,3-dimethylbarbituric acid (5.05 mmol)/5-acetylbarbituric acid (5.05 mmol)/5-acetylthiobarbituric acid (5.05 mmol) and piperidine (0.2 mL) were mixed thoroughly
with the help of pestle in a mortar, and air dried. The reaction mixture was then transferred to an open Pyrex beaker and subjected to microwave irradiation (Multimode, full power). The progress of reaction was monitored by TLC and on completion, the reaction mixture was slurred in water (30 mL). The solid, thus, obtained was filtered, washed with water, alcohol and dried to afford 5a-c.

\[(2E)-3-(5\text{-chloro-3-methyl-1-phenylpyrazol-4-yl})-1-(1,3\text{-dimethyl-2,4,6-pyrimidinetrione-5-yl})-2\text{-propen-1-one} \ (5a)\]

Purified by recrystallization from chloroform.

Yellow crystals.

M.p. : 263-266 °C.

\[\text{IR (KBr)} \ \nu_{\text{max}}/\text{cm}^{-1}\]

: 1618 (C=C), 1664 (C=O), 1715 (C=O).

\[\text{\textsuperscript{1}H NMR} \ (300 \text{ MHz, CDCl}_3)\]

: \(\delta \ \text{(ppm)} \ 2.59 \ (s, \ 3\text{H, CH}_3), \ 3.37 \ (s, \ 3\text{H, N-CH}_3), \ 3.40 \ (s, \ 3\text{H, N-CH}_3), \ 7.42-7.58 \ (m, 5\text{H, Ar-H}), \ 8.00 \ (d, \ 1\text{H, } J=16.2 \text{ Hz, H}_b), \ 8.55 \ (d, \ 1\text{H, } J=15.9 \text{ Hz, H}_a).\]

\[\text{MS-ESI : } m/z \ 400.12. \ (M^+)\]

Elemental analysis for

\[\text{C}_{19}\text{H}_{17}\text{N}_4\text{O}_4\text{Cl}\]

: Calculated C, 56.93; H, 4.27; N, 13.97.

Found C, 56.76; H, 4.38; N, 13.91 %.

\[(2E)-3-(5\text{-chloro-3-methyl-1-phenylpyrazol-4-yl})-1-(2,4,6-pyrimidinetrione-5-yl)-2-propen-1-one \ (5b)\]

Purified by recrystallization from methanol-DMF (3:2 v/v) mixture.

White powder.
M.p. : >300 °C.

IR (KBr) $\nu_{\text{max}}$/cm$^{-1}$ : 1601 (C=C), 1657 (C=O), 1698 (C=O), 3069 (NH), 3193 (NH).

$^1$H NMR (400 MHz, DMSO-d$_6$) : $\delta$ (ppm) 2.62 (s, 3H, CH$_3$), 7.47-7.85 (m, 5H, Ar-H), 8.32 (d, 1H, $J=15.8$ Hz, H$_b$), 9.01 (d, 1H, $J=15.8$ Hz, H$_a$), 11.45 (s, 1H, NH), 11.60 (s, 1H, NH).

MS-FAB (% rel. Int) : $m/z$ 372 (M$^+$, 75), 371 (55), 336 (10), 261 (20), 260 (10), 232 (40), 214 (15), 157 (100).

Elemental analysis for C$_{17}$H$_{13}$N$_4$O$_4$Cl : Calculated C, 54.77; H, 3.51; N, 15.02. 

Found C, 54.86; H, 3.64; N, 15.08 %.

(2E)-3-(5-Chloro-3-methyl-1-phenylpyrazol-4-yl)-1-(2-mercapto-4,6-pyrimidinedione-5-yl)-2-propen-1-one (5c)

Purified by recrystallization from methanol-DMF (3:2 v/v) mixture.

Yellow powder.

M.p. : >300 °C.

IR (KBR) $\nu_{\text{max}}$/cm$^{-1}$ : 1057 (C=S), 1608 (C=C), 1647 (C=O), 1746 (C=O), 3056 (NH), 3188 (NH).

$^1$H NMR (400 MHz, DMSO-d$_6$) : $\delta$ (ppm) 2.56 (s, 3H, CH$_3$), 7.47-7.97 (m, 5H, Ar-H), 7.87 (d, 1H, $J=15.7$ Hz, H$_b$), 9.04 (d, 1H, $J=15.8$ Hz, H$_a$), 12.19 (s, 1H, NH).
MS-ESI: $m/z$ 388.6 ($M^+$), 361.6, 360.6, 310.6, 274.6, 202.6.

Elemental analysis for $C_{17}H_{13}N_4O_3SCl$:

Calculated C, 52.51; H, 3.36; N, 14.40.

Found: C, 52.57; H, 3.44; N, 14.32 %.
Fig. 1. IR spectrum of 3a.
Fig. 2. $^1$H NMR spectrum of 3a.

Solvent- CDCl$_3$, Frequency- 400.131 MHz
Fig. 3. Mass spectrum of 3a.
Fig. 4. IR spectrum of 5a.
Fig. 5. $^1$H NMR spectrum of 5a.

Solvent- CDCl$_3$, Frequency- 300.130 MHz
Fig. 6. Mass spectrum of 5a.

5a
2.6. REFERENCES


(b) Varma, R. S. Advances in Green Chemistry: Chemical Syntheses using Microwave Irradiation, Astra Zeneca Research Foundation India, Bangalore, 2002.


