CHAPTER-4

**Zn(PROLINE)$_2$-CATALYZED KNOEVENAGEL CONDENSATION UNDER SOLVENT-FREE/AQUEOUS CONDITIONS**

4.1. REVIEW & LITERATURE

Developing a simple, ecofriendly reaction protocol for the synthesis of compound libraries of medicinal scaffolds is an attractive area of research in both academic and pharmaceutical R&D.\(^1\) Hence, the challenge for sustainable environment calls for the use of clean procedures, which can avoid the use of harmful solvents. The chemists are therefore, more interested in seeking new processes involving solvent-free reactions which are devoid of pollution, low cost and simplicity in processing.\(^2\) Microwave-assisted organic reactions are nowadays a well established green protocol for synthesis of various heterocycles. The shorter reaction time, experimental simplicity, selectivity and easy work-up have given clear indication on the potentialities of this technique over conventional heating.\(^3\) Nowadays water has emerged as an ecofriendly solvent for the reaction medium because of its easy availability, noninflammability, nontoxicity and negligible cost.\(^4\)

The Knoevenagel condensation reaction is an effective C=C bond formation reaction between carbonyl or heterocarbonyl compounds and any compounds having an active methylene group.\(^5\) This reaction has been widely used for the synthesis of several intermediates which are useful in perfumes, cosmetics, and bioactive compounds.\(^6\) This reaction has also application in the preparation of natural products,\(^7\) functional polymers,\(^8\) finechemicals\(^9\) and so forth.
The Knoevenagel condensation products also have widespread applications including inhibition of antiphosphorylation of EGF-receptor and antiproliferative activity. Because of the importance from pharmacological, industrial and synthetic point of view several methods have been reported for this reaction which includes homogeneous condition catalyzed by base such as a piperidine, ethylenediamine or corresponding ammonium salts, dimethylaminopyridine, organocatalysts like L-proline, natural and synthetic phosphates, resins, montmorillonite KSF, Lewis acid, Al₂O₃, ZnCl₂, CdI₂, I₂-K₂CO₃, K₃PO₄, KF-Al₂O₃, AlPO₄-Al₂O₃, H₂O-Cetyl trimethylammonium bromide (CTMAB), montmorillonite K10-ZnCl₂, Zinc acetate, diammonium hydrogen phosphate, USY zeolite, xonotlite, silica gel, silica gel functionalized with amino groups, aminopropyl-functionalized MCM-41, ionic liquid-functionalized silica gel, ionic liquid-functionalized SBA-15, basic ionic liquid etc. Unfortunately, many of these methods have some drawbacks such as use of expensive, stoichiometric amount of reactants, low yields, extended time, tedious procedure etc. Thus, the need for the development of an alternative route to construct substituted electrophilic alkenes by reducing time from hours to minutes at ambient temperature is in demand.

4.1.1. Some recent examples of Knoevenagel condensation under green environment

4.1.1a. n-Butyl pyridinium nitrate as reusable ionic liquid medium

The Knoevenagel condensation of carbonyl substrates with active methylene compounds proceeds smoothly with ammonium acetate as catalyst in n-butyl pyridinium nitrate to afford the desired products of good purity in moderate yields.
The Knoevenagel condensation of Meldrum's acid with aromatic aldehydes proceeded efficiently in the recyclable ionic liquid [Bmim]BF₄ (1-Butyl-3-methylimidazolium tetrafluoroborate) at room temperature in the presence of catalytic amount of piperidine.

A simple, efficient, and green protocol for synthesis of coumarin-3-carboxylic acids and substituted electrophilic alkenes are reported through Knoevenagel condensation of Meldrum’s acid with ortho-hydroxyaryl aldehydes and aromatic aldehydes respectively, in presence of reusable [Hmim]TFA (1-Methylimidazolium trifluoroacetate) ionic liquid, which was found to give better results than other ionic liquids.
4.1.1d. Ionic liquid mediated Knoevenagel condensation of aromatic aldehydes with (2-thio)barbituric acids

The Knoevenagel condensation of aromatic aldehydes with (2-thio)barbituric acids proceeded efficiently in reusable ionic liquids, EAN (Ethylammonium nitrate), BmimBF₄ (1-Butyl-3-methylimidazoliumtetrafluoroborate) and BmimPF₆ (1-Butyl-3 methylimidazoliumhexafluorophosphate) at room temperature in the absence of any catalyst with high yields.
4.1.1e. Borate-Zirconia as a recyclable catalyst

Knoevenagel condensation of 4-oxo-(4H)-1-benzopyran-3-carbaldehydes, 1,3-diphenyl-1H-pyrazol-4-carboxaldehyde and aromatic aldehyde has been carried out with 3-methyl-1-phenylpyrazolin-5-(4H)-one as condensing agent in moderate to good yields by using Borate Zirconia (B$_2$O$_3$/ZrO$_2$) solid acid catalyst in water medium. In each conversion, the catalyst was successfully recovered and recycled without significant loss in yield and selectivity.

4.1.1f. Mn (III) salen as a recyclable catalyst

Knoevenagel condensations were catalysed by Mn(III) salen complex in quantitative yields under mild reaction conditions. The catalyst was reused for several cycles with consistent activity.
A facile method for Knoevenagel condensation has been developed by using recyclable Leucoemeraldine base as a catalyst to give substituted alkenes in excellent yields.

4.1.1g. Leucoemeraldine base as a recyclable catalyst

Leucoemeraldine base

4.1.1 h. 12-Tungstophosphoric acid as reusable catalyst

12-Tungstophosphoric acid is used as a reusable catalyst for Knoevenagel condensation of malononitrile and ethylcyanoacetate with various aldehydes in water.
4.2. PRESENT WORK

As a part of our ongoing research program aimed at developing new catalysts and subsequent application for various organic transformations, herein this chapter we report the recently explored Zn(proline)$_2$ complex as an efficient and recyclable catalyst in Knoevenagel condensation reaction. To the best of our knowledge Zn(proline)$_2$ has not been used as a catalyst before, for Knoevenagel condensation reaction. This prompted us to test the catalytic activity of the viable catalyst for this reaction employing heteroaldehydes with various cyclic active methylene compounds both under solvent-free condition using microwave irradiation and by using water as an ecofriendly reaction medium.

4.3. RESULTS AND DISCUSSION

Ever since the exploration of water soluble Zn(proline)$_2$ complex by Darbre's group\textsuperscript{47} only few reports have so far appeared employing Zn(proline)$_2$ as a Lewis acid catalyst for different organic reactions.\textsuperscript{48} Thus, there is a lot of scope to further explore the catalyst for its application in forming various heterocyclic rings. The Zn(proline)$_2$ catalyst is easily preparable, stable, inexpensive and recyclable. The solubility nature of the catalyst facilitated the separation of products from the catalyst. The used catalyst can be recycled and used for the next reaction without any further purification. We carried out first the reaction of 5-chloro-3-methyl-1-phenylpyrazole-4-carboxaldehyde 1 with various cyclic active methylene compounds 2a-i in conventional method using ethanol as a solvent in acidic/basic medium (Scheme 1). The reactions took longer period of time for completion (3-12 h) with lower yields. Then we studied the efficacy of the Zn(proline)$_2$ complex by carrying reactions in green solvent, water. The reactions were completed
within 1-2 h and the products obtained were in good yield (81-89%). Further, the catalytic activity of the complex was tested under solvent-free condition by employing microwave irradiation. To our pleasant surprise, the reactions were completed in much shorter period of time (5-9 min) in excellent yields (90-95%) (Table 1).

The reaction of 5-chloro-3-methyl-1-phenylpyrazole-4-carboxaldehyde 1 with indane-1,3-dione 2a in the presence of Zn(proline)2 in water as well as in microwave irradiation was taken as model reaction for recycling studies. After completion of reaction in specified time, the crude product obtained was extracted by dichloromethane and the catalyst was recovered by separation of aqueous and organic phases. The catalyst present in the aqueous medium was used for the subsequent cycle. The same procedure was applied for all recycling studies. The results (Table 2) revealed that catalyst exhibited good catalytic activity up to three cycles. The scope of the reaction was further investigated with different cyclic active methylene compounds with viable catalyst, and the results obtained were satisfactory. The reactions of heteroaldehyde with triacetic acid lactone 2h and 4-hydroxycoumarin 2i did not give the expected Knoevenagel condensation products, instead it afforded pyrazolo pyrones 3h and 3i as reported by us earlier49 in a very short period of time (Table 1).

Similar type of Knoevenagel condensation was also carried out by treating 5-azido-3-methyl-1-phenylpyrazole-4-carboxaldehyde 4 with various cyclic active methylene compounds (5a-f) in aqueous medium (Scheme 2). All reactions were found to be completed within 25 min-1 h with considerable increase in the yields of products (Table 3) as compared to conventional method which took longer time period (2.5-6 h). Here again when the reaction of heteroaldehyde (4) was extended to 4-hydroxycoumarin (5e)
and triacetic acid lactone (5f) expected Knoevenagel condensation products were not obtained. Instead it afforded pyrazolo pyrones 6e and 6f as reported earlier from our lab in conventional organic solvent. This time, under the influence of the viable Zn(proline)\textsubscript{2} complex, the reaction time was considerably reduced, and yield of products was also increased from the reported values (Table 3). The recycling studies results of the reaction of 5-azido-3-methyl-1-phenylpyrazole-4-carboxaldehyde (4) with 1,3-dimethylbarbituric acid (5c) are presented in Table 4. The reactions carried under microwave irradiation were not neat probably because of decomposition of much low melting 5-azido-3-methyl-1-phenylpyrazole-4-carboxaldehyde 4 and aqueous medium was, therefore, better alternative for the reactions.

All the products obtained were recrystallized from suitable solvents, and characterized by spectroscopic data. The IR spectrum of 3a (Fig. 2) showed sharp and strong absorption band at 1689 cm\textsuperscript{-1} for α,β unsaturated carbonyl group. The band for carbon-carbon double bond was present at 1623 cm\textsuperscript{-1}. The proton nuclear magnetic resonance spectroscopy (\textsuperscript{1}H NMR) (Fig. 3) exhibited a sharp singlet at δ 2.40 for methyl group of pyrazole moiety. Nine aromatic protons appeared as multiplet in the aromatic region δ 7.45-8.04. The five aromatic protons of phenyl group of pyrazole moiety were present in the form of three multiplets in the range of δ 7.45-7.47, 7.50-7.54 and 7.61-7.63. Three multiplets may be due to H-2'/H-6', H-3'/H-5' and H-4' protons. However four protons of benzene ring of indanedione moiety were visible in the form of two multiplets in the range δ 7.81-7.84 and 7.99-8.04, each multiplet integrating for two protons. These multiplets may be due to H-4, H-5 and H-6, H-7 protons. The olefinic proton was discernible as a sharp singlet at δ
Further confirmation of the structure was provided by mass spectrometry (Fig. 4) which showed $M^+$ at $m/z$ 348.

![Figure-1](image)

**Figure-1.** 2-(5-Chloro-3-methyl-1-phenylpyrazol-4-yl)methylene-1,3-indanedione (3a).

The IR spectrum of 6c (Fig. 5) showed sharp and strong absorption band at 1683 cm$^{-1}$ for $\alpha,\beta$ unsaturated carbonyl group. Two other bands at 1596 and 1524 cm$^{-1}$ were assigned to C=C and C=N bonds. The proton nuclear magnetic resonance spectroscopy ($^1$H NMR) (Fig. 6) exhibited three sharp singlets at $\delta$ 2.40, 3.40 and 3.45 for methyl protons of pyrazole and barbituric acid units. Five aromatic protons of pyrazole unit were appeared as multiplet in the region $\delta$ 7.40-7.69. The olefinic proton was discernable as a sharp singlet at $\delta$ 8.44. The $^{13}$C NMR spectrum (Fig. 7) was informative in assigning the structure. The peaks were observed at $\delta$ 114.9 and 139.0 for the trisubstituted and tetrasubstituted olefinic carbon atoms respectively. Further confirmation of the structure was provided by mass spectrometry (Fig. 8), which showed $M^+$ at $m/z$ 365 followed by subsequent fragmentation pattern. The spectral data of other compounds followed similar pattern and are given in experimental section.

The proposed mechanism for the Zn(proline)$_2$-catalyzed synthesis of Knoevenagel products can be visualised as given in Scheme 3.
Scheme 1. Synthesis of compounds 3a-i.
Scheme 2. Synthesis of compounds 6a-f.
Scheme-3. Mechanism of Zn(proline)$_2$-catalyzed Knoevenagel condensation.
### Table- 1. Synthesis of products 3a-i in refluxing water or microwave irradiation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>product&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Thermal heating in aqueous medium</th>
<th>Microwave irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Time (h)</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>1</td>
<td>3a&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1 h</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>45 min</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>45 min</td>
<td>89</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>1 h</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>3e&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.5 h</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>3f&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2 h</td>
<td>81</td>
</tr>
<tr>
<td>7</td>
<td>3g</td>
<td>45 min</td>
<td>86</td>
</tr>
<tr>
<td>8</td>
<td>3h</td>
<td>1 h</td>
<td>84</td>
</tr>
<tr>
<td>9</td>
<td>3i</td>
<td>1 h</td>
<td>83</td>
</tr>
</tbody>
</table>

<sup>a</sup> The products were confirmed by elemental analysis, spectral data and compared with reported literature.<sup>49, 50, 51</sup>

<sup>b</sup> New compounds.

### Table- 2. Recycling data of Zn(proline)_2 complex for the Knoevenagel condensation of 5-chloro-3-methyl-1-phenyl-4-carboxaldehyde (1) with 1,3-indanedione (2a).

<table>
<thead>
<tr>
<th>Catalyst recycle</th>
<th>Conventional method (Aqueous medium)</th>
<th>Microwave irradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time (h)</td>
<td>Yield (%)</td>
</tr>
<tr>
<td>I</td>
<td>1</td>
<td>85</td>
</tr>
<tr>
<td>II</td>
<td>1</td>
<td>85</td>
</tr>
<tr>
<td>III</td>
<td>1</td>
<td>85</td>
</tr>
<tr>
<td>IV</td>
<td>1</td>
<td>82</td>
</tr>
</tbody>
</table>
Table 3. Synthesis of products 6a-f in refluxing water.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Mol. formula</th>
<th>Time</th>
<th>Yield (%)</th>
<th>M.p (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6a&lt;sup&gt;a&lt;/sup&gt;</td>
<td>C&lt;sub&gt;15&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;N&lt;sub&gt;7&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>25 min</td>
<td>82</td>
<td>167(dec)</td>
</tr>
<tr>
<td>2</td>
<td>6b&lt;sup&gt;a&lt;/sup&gt;</td>
<td>C&lt;sub&gt;15&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;N&lt;sub&gt;7&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;S</td>
<td>45 min</td>
<td>76</td>
<td>174-176</td>
</tr>
<tr>
<td>3</td>
<td>6c&lt;sup&gt;a&lt;/sup&gt;</td>
<td>C&lt;sub&gt;17&lt;/sub&gt;H&lt;sub&gt;15&lt;/sub&gt;N&lt;sub&gt;7&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>35 min</td>
<td>81</td>
<td>201-204</td>
</tr>
<tr>
<td>4</td>
<td>6d&lt;sup&gt;a&lt;/sup&gt;</td>
<td>C&lt;sub&gt;20&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;N&lt;sub&gt;5&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;</td>
<td>30 min</td>
<td>82</td>
<td>234(dec)</td>
</tr>
<tr>
<td>5</td>
<td>6e&lt;sup&gt;b&lt;/sup&gt;</td>
<td>C&lt;sub&gt;29&lt;/sub&gt;H&lt;sub&gt;18&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;6&lt;/sub&gt;</td>
<td>1 h</td>
<td>84</td>
<td>290-292</td>
</tr>
<tr>
<td>6</td>
<td>6f&lt;sup&gt;b&lt;/sup&gt;</td>
<td>C&lt;sub&gt;23&lt;/sub&gt;H&lt;sub&gt;18&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;6&lt;/sub&gt;</td>
<td>1 h</td>
<td>80</td>
<td>231-233</td>
</tr>
</tbody>
</table>

<sup>a</sup> New compounds.

<sup>b</sup> The products were confirmed by elemental analysis, spectral data and compared with reported literature.<sup>49</sup>

Table-4. Recycling data of Zn(proline)<sub>2</sub> complex for the Knoevenagel condensation of 5-azido-3-methyl-1-phenylpyrazol-4-carboxaldehyde (4) with 1,3-dimethylbarbituric acid (5c) in aqueous medium.

<table>
<thead>
<tr>
<th>Catalyst recycle</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>35 min</td>
<td>81</td>
</tr>
<tr>
<td>II</td>
<td>35 min</td>
<td>81</td>
</tr>
<tr>
<td>III</td>
<td>35 min</td>
<td>81</td>
</tr>
<tr>
<td>IV</td>
<td>35 min</td>
<td>77</td>
</tr>
</tbody>
</table>
4.4. CONCLUSION

In brief, we developed an efficient procedure for the synthesis of substituted alkenes through Knoevenagel condensation from various cyclic active methylene compounds and heteroaromatic aldehydes using stable, inexpensive, easily preparable and recyclable Zn(proline)₂ complex in green solvent “water” and under solvent-free condition. The present protocol is devoid of pollution and involves mild reaction condition, excellent yields, short reaction time and simple operational and experimental procedure.

4.5. EXPERIMENTAL

Melting points were taken in Riechert Thermover instrument and are uncorrected. The IR spectra were recorded on Perkin Elmer spectrometer in KBr. ¹H NMR spectra on a Bruker DRX-300 and Bruker Avance 400 Spectrometer using tetra methyl silane (TMS) as an internal standard. Mass spectra were recorded on JEOL-Accu TOF JMS-T100LC DART-MS spectrometer, Micromass Quattro II (ESI) and Jeol-SX-102 (FAB) spectrometer. The microanalytical data were collected on Elementar vario EL III elemental analyzer. The Zn(proline)₂ catalyst and the compounds ¹, ², ³, ²⁴ were synthesized by reported procedures. Other chemicals were of commercial grade and used without further purification. The purity of all compounds was checked by TLC on glass plates coated with silica gel (E-Merck G₂₅₄). The plates were run in chloroform-methanol (4:1) mixture and were visualized by iodine vapours. All the experiments under microwave irradiation were carried out in a domestic microwave oven (National, Model NN-S557WF 1.3 KW, 2450 MHz).

4.5.1. Synthesis of bis[(L) prolinato-N,O]Zn complex
Ten mmol of L-proline was dissolved in 25 mL absolute ethanol containing 10 mmol potassium hydroxide and stirred well for 15 min. In order to maintain the metal to ligand ratio 1:2, 5 mmol of Zn(NO$_3$)$_2$·6H$_2$O was dissolved in a small quantity of double distilled water and this solution was added in drops to the solution of L-proline. The contents were vigorously stirred at room temperature for 8 h. The Zn(proline)$_2$ complex was obtained as white solid, was filtered and dried. Yield: 91%.

**4.5.2. Thermal heating in aqueous medium**

A mixture of 5-chloro-3-methyl-1-phenylpyrazole-4-carboxaldehyde (1)/5-azido-3-methyl-1-phenylpyrazol-4-carboxaldehyde (4) (1.00 mmol), active methylene compounds 2a-i, 5a-f (1.00 mmol) and Zn(proline)$_2$ (0.30 mmol) was dissolved in minimum volume of methanol and water (7 mL) was added. The reaction mixture was then refluxed on a heating mantle for specified time (Table 1, 3) and cooled to room temperature. The solid product was extracted with dichloromethane, dried over anhydrous Na$_2$SO$_4$, concentrated to furnish crude product, which was recrystallized from ethanol-chloroform mixture/methanol-chloroform mixture. The catalyst was recovered by simple separation of aqueous and organic phases. The catalyst present in the aqueous layer was used for the subsequent cycle.

**4.5.3. Microwave irradiation**

A mixture of 5-chloro-3-methyl-1-phenylpyrazole-4-carboxaldehyde 1 (1.00 mmol) and active methylene compounds 2a-i (1.00 mmol) was mixed with Zn(proline)$_2$ (0.30 mmol) and ground well using a mortar and pestle. The mixture was then taken in 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, extracted with dichloromethane, dried over anhydrous Na₂SO₄ and concentrated. The crude product as obtained was recrystallized from ethanol-chloroform mixture. The catalyst was recovered by simple separation of aqueous and organic phases. The catalyst present in the aqueous layer was used for the subsequent cycle.

**Spectral data**

2-(5-Chloro-3-methyl-1-phenylpyrazol-4-yl)methylene-1,3-indanedione (3a)

Purified by recrystallization from ethanol-chloroform (3:2 v/v) mixture.

Pale greenish crystals.

**M.p**: 199-202 °C.

IR (KBr) ν max/cm⁻¹ : 1623 (C=C), 1689 (C=O).

¹H NMR (400 MHz, CDCl₃) : δ (ppm) 2.40 (s, 3H, CH₃), 7.45-8.04 (m, 9H, Ar-H), 7.80 (s, 1H, -CH=C).

MS-FAB (% rel. Int.) : m/z 348 (M⁺, 100).

**Elemental analysis**

for C₂₀H₁₃N₂O₂Cl : Calculated C, 68.89; H, 3.72; N, 8.03.

Found C, 68.96; H, 3.77; N, 8.08 %.

5-(5-Chloro-3-methyl-1-phenylpyrazol-4-yl)methylene-2,4,6-pyrimidinetrione (3b)

Purified by recrystallization from chloroform-ethanol (4:1 v/v) mixture.

Bright yellow crystals.

**M.p**: >300 °C.

IR (KBr) ν max/cm⁻¹ : 1572 (C=C), 1679 (C=O), 3195 (NH).

¹H NMR (300 MHz, DMSO-d₆) : δ (ppm) 2.29 (s, 3H, CH₃), 7.31-7.82 (m, 5H, Ar-H), 8.12 (s, 1H, -CH=C), 11.05 (s, 1H, Ar-O).
1H, NH), 11.36 (s, 1H, NH).

MS-ESI : \( m/z \ 330.20 \ (M^+) \).

Elemental analysis

for C_{15}H_{11}N_{4}O_{3}Cl : Calculated C, 54.49; H, 3.32; N, 16.94.

Found C, 54.56; H, 3.36; N, 16.87 %.

5-(5-Chloro-3-methyl-1-phenylpyrazol-4-yl)methylene-1,3-dimethyl-2,4,6-
pyrimidinetrione (3c)

Purified by recrystallization from ethanol-chloroform (3:2 v/v) mixture

Shining yellow crystals.

M.p : 208-210 °C.

IR (KBr) \( \nu_{\text{max}}/\text{cm}^{-1} \) : 1587 (C=C), 1664 (C=O).

\( ^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3) \) : \( \delta \ (\text{ppm}) \) 2.43 (s, 3H, CH₃), 3.42 (s, 3H, N-CH₃), 3.45 (s, 3H, N-CH₃), 7.32-7.84 (m, 5H, Ar-H), 8.48 (s, 1H, -CH=C).

MS-FAB ( % rel. Int) : \( m/z \ 358 \ (M^+, 90) \).

Elemental analysis

for C_{17}H_{15}N_{4}O_{3}Cl : Calculated C, 56.93; H, 4.18; N, 15.61.

Found C, 56.99; H, 4.16; N, 15.56.

5-(5-Chloro-3-methyl-1-phenylpyrazol-4-yl)methylene-2-mercapto-4,6-
pyrimidinedione (3d)

Purified by recrystallization from chloroform-ethanol (4:1 v/v) mixture.

Pale yellow solid.

M.p : >300 °C.
IR (KBr) $\nu_{\text{max}}$/cm$^{-1}$: 1007 (C=S), 1618 (C=C), 1674 (C=O), 3124 (NH).

$^1$H NMR (300 MHz, DMSO-$_d_6$): $\delta$ (ppm) 2.32 (s, 3H, CH$_3$), 7.34-7.84 (m, 5H, Ar-H), 8.22 (s, 1H, -CH=C), 11.12 (s, 1H, NH), 11.43 (s, 1H, NH).

MS-ESI: $m/z$ 346.15 (M$^+$).

Elemental analysis for C$_{15}$H$_{11}$N$_4$O$_2$SCl: Calculated C, 51.97; H, 3.17; N, 16.15. Found C, 51.99; H, 3.13; N, 16.07%.

2-(5-Chloro-3-methyl-1-phenylpyrazol-4-yl)methylene-1,4-benzothiazine-3-one (3e)

Purified by recrystallization from ethanol-chloroform (3:2 v/v) mixture.

Greenish yellow solid.

M.p: 114-116 °C (dec).

IR (KBr) $\nu_{\text{max}}$/cm$^{-1}$: 1597 (C=C), 1653 (C=O), 3185 (NH).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ (ppm) 2.33 (s, 3H, CH$_3$) 7.12-8.02 (m, 10H, Ar-H + CH=C), 9.61 (br s, 1H, NH).

MS-FAB (% rel. Int): $m/z$ 368 (M$^+$, 70).

Elemental analysis for C$_{19}$H$_{14}$N$_3$OSCl: Calculated C, 62.06; H, 3.80; N, 11.42. Found C, 62.08; H, 3.83; N, 11.39%.
5-(5-Chloro-3-methyl-1-phenylpyrazol-4-yl)methylene-2,2-dimethyl-1,3-dioxane-4,6-dione (3f)

Purified by recrystallization from ethanol-chloroform (2:3 v/v) mixture.

Pale yellow crystals.

\[
\begin{align*}
\text{M.p} : & 240-242 \, ^\circ C. \\
\text{IR (KBr) } \nu_{\text{max}}/\text{cm}^{-1} : & 1582 (C=C), 1725 (C=O). \\
^1\text{H NMR (300 MHz, CDCl}_3) : & \delta (\text{ppm}) 1.59 (s, 6H, 2 CH}_3), 2.52 (s, 3H, CH}_3), 7.00-7.73 (m, 6H, Ar-H + CH=C). \\
\text{MS-FAB (% rel. Int) : } & m/z 347 (M^+, 90). \\
\text{Elemental analysis for C}_{17}\text{H}_{15}\text{N}_2\text{O}_4\text{Cl} : & \text{Calculated C, 58.90; H, 4.32; N, 8.07.} \\
& \text{Found C, 58.94; H, 4.35; N, 8.03 \%}. \\
\end{align*}
\]

4-(5-Chloro-3-methyl-1-phenylpyrazol-4-yl)methylene-3-methyl-1-phenylpyrazol-5-one (3g)

Purified by recrystallization from chloroform-ethanol (4:1 v/v) mixture.

White powder.

\[
\begin{align*}
\text{M.p} : & 186-188 \, ^\circ C. \\
\text{IR (KBr) } \nu_{\text{max}}/\text{cm}^{-1} : & 1602 (C=C), 1730 (C=O). \\
^1\text{H NMR (400 MHz, CDCl}_3) : & \delta (\text{ppm}) 2.41 (s, 6H, 2 CH}_3), 4.93 (s, 1H, -CH=C), 7.23-7.76 (m, 10H, Ar-H). \\
\text{MS-FAB (% rel. Int) : } & m/z 376 (M^+, 100). \\
\text{Elemental analysis for C}_{21}\text{H}_{17}\text{N}_4\text{O}_3\text{Cl} : & \text{Calculated C, 66.96; H, 4.51; N, 14.86.}
\end{align*}
\]
Found C, 66.92; H, 4.49; N, 14.83 %.

5-(5-Azido-3-methyl-1-phenylpyrazol-4-yl)methylene-2,4,6-pyrimidinetrione (6a)

Purified by recrystallization from chloroform-methanol (4:1 v/v) mixture.

Pale yellow crystals.

\[
\text{M.p} : 167^\circ \text{C (dec)}
\]

\[
\text{IR (KBr) } v_{\text{max}}/\text{cm}^{-1} : 1381 (\text{C-N}), 1528 (\text{C=N}), 1574 (\text{C=C}), 1655 (\text{C=O}), 3067 (\text{NH}), 3194 (\text{NH}).
\]

\[
\text{\textsuperscript{1}H NMR (300 MHz, DMSO-d\textsubscript{6})} : \delta (\text{ppm}) 2.37 (s, 3H, \text{CH}_3), 7.36-7.65 (m, 5H, \text{Ar-H}), 8.32 (s, 1H, -\text{CH=C}), 11.10 (s, 1H, NH), 11.20 (s, 1H, NH).
\]

\[
\text{\textsuperscript{13}C NMR (100 MHz, DMSO-d\textsubscript{6})} : \delta (\text{ppm}) 12.6, 115.9, 123.3, 127.7, 128.7, 136.9, 138.7, 142.2, 150.0, 151.4, 161.2, 162.6.
\]

\[
\text{MS-FAB (% rel. Int.)} : m/z 337 (M\textsuperscript{+}, 80), 336 (45), 309 (15), 308 (65), 212 (5), 135 (80), 120 (15), 92 (20).
\]

Elemental analysis

for C\textsubscript{15}H\textsubscript{11}N\textsubscript{7}O\textsubscript{3} : Calculated C, 53.41; H, 3.28; N, 29.60.

Found C, 53.59; H, 3.44; N, 29.45 %.

5-(5-Azido-3-methyl-1-phenylpyrazol-4-yl)methylene-2-mercapto-4,6-
pyrimidinedione (6b)

Purified by recrystallization from chloroform-methanol (4:1 v/v) mixture.

Pale yellow solid.
M.p : 174-176 °C.

IR (KBr) $\nu_{\text{max}}$/cm$^{-1}$ : 1009 (C=S), 1350 (C-N), 1508 (C=N), 1594 (C=C), 1648 (C=O), 3057 (NH), 3140 (NH).

$^1$H NMR (300 MHz, DMSO-$d_6$) : $\delta$ (ppm) 2.43 (s, 3H, CH$_3$), 7.39-7.67 (m, 5H, Ar-H), 8.44 (s, 1H, -CH=C), 11.14 (s, 1H, NH), 11.16 (s, 1H, NH).

$^{13}$C NMR (100 MHz, CDCl$_3$) : $\delta$ (ppm) 12.6, 115.7, 122.3, 127.7, 128.9, 136.2, 138.4, 141.2, 150.0, 151.8, 161.6, 172.1

MS-FAB (% rel int) : m/z 353 (M$^+$, 80), 352 (60), 325 (15), 135 (50), 120 (5).

Elemental analysis

for C$_{15}$H$_{11}$N$_7$O$_2$S : Calculated C, 50.98; H, 3.13; N, 27.74.

Found C, 50.89; H, 3.04; N, 27.70 %.

5-(5-Azido-3-methyl-1-phenylpyrazol-4-yl)methylene-1,3-dimethyl-2,4,6-pyrimidinetrione (6c)

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

Bright yellow crystals.

M.p : 201-204 °C.

IR (KBr) $\nu_{\text{max}}$/cm$^{-1}$ : 1342 (C-N), 1524 (C=N), 1596 (C=C), 1683 (C=O).

$^1$H NMR (400 MHz, CDCl$_3$) : $\delta$ (ppm) 2.40 (s, 3H, CH$_3$), 3.40 (s, 3H, N-CH$_3$), 3.45 (s, 3H, N-CH$_3$), 3.40 (s, 3H, N-CH$_3$), 7.40-7.69 (5H,
2-(5-Azido-3-methyl-1-phenylpyrazol-4-yl)methylene-1,3-indanedione (6d)

Purified by recrystallization from methanol-chloroform (4:1 v/v) mixture.

Red crystals.

M.p : 234 °C (dec)

IR (KBr) $\nu_{\text{max}}$/cm$^{-1}$ : 1358 (C-N), 1520 (C=N), 1576 (C=C), 1671 (C=O).

$^1$H NMR (400 MHz, CDCl$_3$) : $\delta$ (ppm) 2.43 (s, 3H, CH$_3$), 7.39-8.03 (m, 9H, Ar-H), 7.83 (s, 1H, -CH=C).

$^{13}$C NMR (100 MHz, CDCl$_3$) : $\delta$ (ppm) 13.0, 122.9, 123.3, 128.0, 128.2, 131.6, 135.0, 135.3, 137.2, 138.9, 141.9, 152.1, 188.5, 189.4

FAB-MS (% rel. Int.) : m/z 355 (M$^+$, 90), 354 (60), 327 (5), 306 (70), 135 (75), 120 (10).

Elemental analysis for C$_{17}$H$_{15}$N$_2$O$_3$ : Calculated C, 55.89; H, 4.13; N, 26.83.

Found C, 55.81; H, 4.26; N, 26.74%.
for $\text{C}_{20}\text{H}_{13}\text{N}_{3}\text{O}_{2}$

: Calculated C, 67.60; H, 3.68; N, 19.70.

Found C, 67.71; H, 3.75; N, 19.64 %.
Fig. 2. IR spectrum of 3a.
Fig. 3. $^1$H NMR spectrum of 3a.

Solvent-CDCl$_3$, Frequency- 400.130 MHz
Fig. 4. Mass spectrum of 3a.
Fig. 5. IR spectrum of 6c.
Fig. 6. $^1$H NMR spectrum of 6c.

![NMR Spectrum](image)

Solvent-CDCl$_3$, Frequency- 400.130 MHz
Fig. 7. $^{13}$C NMR spectrum of 6c.

$^{13}$C NMR spectrum of 6c.

Solvent- DMSO, Frequency- 100.612 MHz

6c
Fig. 8. Mass spectrum of 6c.
4.6. REFERENCES


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