3.1. INTRODUCTION

This chapter describes the synthesis and characterization of 4-(1-benzofuran-2-yl)-2-methyl-6-substituted phenyl pyrimidine [3a-f] and 5-(4-N-alkyl-piperazin-1-yl)-1-benzofuran-2-yl)-3-phenylprop-2-en-1-one [5a-f] derivatives. A brief literature survey on the importance of pyrimidine, piperazine and chalcone derivatives containing benzofuran nucleus are discussed in the following section.

Pyrimidine represents an important class of heterocycle and they have widespread therapeutic applications because they are present in thymine, cytosine and uracil which are essential building blocks of nucleic acids DNA and RNA. Pyrimidine derivatives possess a wide variety of potential biological properties and are well known to work as herbicides\(^1\),\(^2\) and pesticides\(^3\). In recent years, pyrimidine derivatives have received significant attention owing to their diverse biological properties such as cytostatic\(^4\)–\(^7\), immune modulating\(^8\),\(^9\) antitubercular\(^10\), calcium channel blockers\(^11\) and antimicrobial properties\(^12\)–\(^15\). In most cases, synthesis of pyrimidines is based on the condensation reactions between C-C-C and N-C-N components or cross coupling reactions\(^16\). Fused pyrimidine containing furan ring systems are known to exhibit wide range of pharmacological activities. A brief account of literature survey on the importance of benzofuran pyrimidines are given below.

In search of better antimicrobial agents, B. Raga \textit{et al.} synthesized benzofuran pyrimidines\[1\] exhibiting antimicrobial activity\(^17\). V.P. Vaidya \textit{et al.} prepared some 2, 4, 6-substituted pyrimidines\[2\] and evaluated for their analgesic and anti-inflammatory activities\(^18\).
A.R. Mishra et al. prepared some new pyrimidines [3] and reported that the synthesized compounds possess antifungal activity\textsuperscript{19}. Amino pyrimidine-benzofuran derivatives [4] were prepared under microwave assisted synthetic protocols and tested for their antimicrobial activity against \textit{P. aeruginosa} and \textit{S. aureus}. The result reveals that none of the compounds exhibit good antimicrobial activity\textsuperscript{20}.

Benzofuro[3,2-d]pyrimidine derivative [5] were synthesized by J. Welsh et al. and observed that they play a significant role in enhancement of long-term memory by potentiating the CREB (cAMP response element binding) signaling pathway\textsuperscript{21}.
Benzofuropyrimidine derivative [6] was found to act as modulators of the histamine H4 receptor\textsuperscript{22}.

\[
\begin{array}{c}
\text{NH}_2 \\
\text{Cl} & \text{N} & \text{N} \\
\text{O} \\
\end{array}
\]

[6]

V.K. Tirlapur \textit{et al.} have synthesized biheterocyclic benzofuran pyrimidines [7], [8] and evaluated the compounds for analgesic, anti-inflammatory and antimicrobial activities\textsuperscript{23}. The results of these studies revealed that the compounds showed significant activities.

\[
\begin{array}{c}
\text{Br} \\
\text{O} & \text{N} & \text{N} \\
\text{OH} \\
\end{array}
\quad \begin{array}{c}
\text{Br} \\
\text{O} & \text{N} & \text{N} \\
\text{SH} \\
\end{array}
\]

[7] \quad [8] \quad R = H, OH, Cl, OMe, N(Me)\textsubscript{2}

In search of new antimicrobial agents, pyrimidines derivatives having benzofuryl ring were reported by D.B. Yadav \textit{et al.} and evaluated the in vitro antimicrobial activity of the compounds\textsuperscript{24}. The compounds [9–11] showed good activity against \textit{B. subtilis}, \textit{E. coli}, \textit{A. niger} and \textit{C. albicans}. 
Some substituted pyrimidines derivatives containing benzofuran have been synthesized by V.H. Babu et al. and screened for the in vitro antimicrobial activity\textsuperscript{25}. Results revealed that the compounds [12–14] if suitably substituted were found to show antibacterial and antifungal activity.

Piperazine is the most important building block on drug discovery with high potential biological applications. Piperazine derivatives are important pharmacophore in different therapeutic areas\textsuperscript{26} and they also acts as antifungal\textsuperscript{27}, antipsychotic\textsuperscript{28}, antimicrobial\textsuperscript{29} and anti-HIV protease\textsuperscript{30}. Literature survey revealed that the benzofuran containing piperazine ring compounds known to possess some important biological properties.

Some of the findings are discussed in the following section. Befuraline [15] a psychoactive drug possess both benzofuran and piperazine moiety. It is a member of the piperazine chemical class which possesses stimulant and antidepressant effects\textsuperscript{31}.
P.S. Desai et al. synthesized derivatives of piperazine (Tert-butyl-4-(2-ethoxycarbonyl) benzofuran-5-yl)piperazine-1-carboxylate [16], Ethyl 5-(piperazin-1-yl) benzofuran-2-carboxylate [17] and tert-butyl 4-(2-carbamoylbenzofuran-5-yl) piperazine-1-carboxylate) [18]. The results showed that they were used as corrosion inhibitors for mild steel in hydrochloric acid solution.

Synthesis of novel benzofuranyl acryloylpiperazines [19] with structural similarity to both cinnamamide derivatives and befuraline having antidepressant activities against tetrabenzazine-induced palpebral ptosis have been evaluated in mice. Some of them revealed interesting potencies with that of the reference drugs.
A series of benzofuran derivatives with neuroprotective activity in collaboration with IGF-1 was discovered using a newly developed cell-based assay involving primary neural cells prepared from rat hippocampal and cerebral cortical tissues. A structure–activity relationship study identified compound [20] as exhibiting potent neuroprotective activity and brain penetrability.

The first condensation was reported by Kostanecki and gave the name “Chalcones” a general term given to compounds bearing 1, 3-diphenyl-2-propen-1-one framework. They are open-chain flavonoids bearing two aromatic rings joined by a three carbon α, β-unsaturated carbonyl system. Several chemical methods were used to obtain chalcone derivatives, among them Claisen–Schmidt’s condensation method is the most used one. The compounds bearing chalcone as backbone have been reported to show a broad spectrum of biological activities including anti-inflammatory, antimalarial, anti-invasive, antibacterial, anticancer and pharmacological activities including cytotoxicity toward cell lines, antimitotic and antimutagenic properties, they are also capable of inducing apoptosis. On the other hand, chalcones are well known precursor for synthesis of various heterocyclic compounds and also a very good Michael acceptors. Thus, chalcones continue to attract considerable scientific attention because of their association with a variety of biological activities.
Given below is a brief account of various modifications reported on benzofuran chalcones, which resulted in a variety of biological and pharmacological activities.

In search of new anticancer agents F. Epifano et al. synthesized furanochalcones [21] possessing anticancer activity\(^5\).

![Furanochalcone structure](image1.png)

J.B. Baell et al. synthesized a chalcone [22] having potassium channel modulatory activity\(^6\).

![Chalcone structure](image2.png)

A new series of 4-methoxy-2-acetyl benzofuran based chalcones were synthesized by aldol base condensation reaction and were evaluated for their antioxidant potential\(^7\). The result revealed that the compound [23] with electron donating substituents like hydroxy and methoxy group on the phenyl moiety showed predominant and more activity than the standard.
P.M.G. Swamy et al. reported the synthesis of 3-hydroxy benzofuran substituted chalcones [24]. The synthesized compounds were screened for antimicrobial activity against both gram positive *S.aureus* and gram negative *E.coli* bacteria

A series of fluorine-substituted benzofuran chalcones were synthesized and screened for their antibacterial and antifungal activity [59]. Compound [25] displayed good activity with MIC = 62.5 μg/mL against *S. typhi* and *S. pyogenes*, whereas compound [26] showed similar antibacterial activity with reference drug ampicillin. For antifungal activity, compound [27] evinced better activity against *C. albicans* than reference drug greseofulvin.

A class of novel 1-(7-ethoxy-1-benzofuran-2-yl) substituted chalcone derivatives were designed, synthesized and their cytotoxic activity was evaluated on breast, lung and prostate cancer cell lines. Among the chalcone derivatives, compound [28] showed strong inhibitory
effects on cancer cells with IC$_{50}$ = 9, 2 and 10 µM for A549, MCF-7 and PC-3 cell lines respectively$^{60}$.

A new series of novel chalcones containing piperazine nucleus $^{29}$ were synthesized through Claisen-Schimdt reaction by P.M. Ranjit et al. and the synthesized chalcones exhibited good antimicrobial activity$^{61}$.

In view of the pharmacological significance of pyrimidine, piperazine and chalcone derivatives along with benzofuran ring system. We focused our interest in synthesizing 2, 4, 6-trisubstituted pyrimidine system encompassing methyl group at 2$^{nd}$, phenyl ring at 4$^{th}$ and benzofuran ring at 6$^{th}$ positions. Also an attempt was made to incorporate piperazine moiety at 5$^{th}$ position in the benzofuran chalcone derivatives and investigated the synthesized compounds for their in-vitro antimicrobial properties.

**Present work**

In the present investigation, we focused our interest in the synthesis and characterization of 4-(1-benzofuran-2-yl)-2-methyl-6-substituted phenyl pyrimidine $^{3a-f}$ and 5-(4-N-alkyl-piperazin-1-yl)-1-benzofuran-2-yl)-3-phenylprop-2-en-1-one derivatives
[5a-f] in two separate sections A and B respectively. The synthetic strategies towards the preparation are discussed in detail in the following sections

**Section A:** Synthesis and characterization of 4-(1-benzofuran-2-yl)-2-methyl-6-substituted phenyl pyrimidine [3a-f] derivatives.

![Diagram of reaction for section A]

**Section B:** Synthesis and characterization of 5-(4-N-alkyl-piperazin-1-yl)-1-benzofuran-2-yl)-3-phenylpropenone [5a-f] derivatives.

![Diagram of reaction for section B]
SECTION A

Detailed sequence of reaction carried out for the synthesis and characterization of 4-(1-benzofuran-2-yl)-2-methyl-6-substituted phenyl pyrimidine [3a-f] derivatives have been discussed in this section as given below.

**Step-1:** Reaction of substituted salicylaldehyde with bromoacetone in the presence of base affords substituted-2-acetylbenzofuran [1a-b] derivatives.

**Step-2:** Substituted-2-acetylbenzofuran [1a-b] undergoes crossed aldol condensation with p-substituted aromatic aldehydes in presence of base at room temperature to form chalcone derivatives [2a-f].

**Step-3:** Synthesis of 4-(1-benzofuran-2-yl)-2-methyl-6-substituted phenyl pyrimidine [3a-f] derivatives was carried out through cyclization reaction of chalcone [2a-f] derivatives with acetamidine hydrochloride in presence of base.

The overall reaction for the synthesis of 4-(1-benzofuran-2-yl)-2-methyl-6-substituted phenyl pyrimidine [3a-f] derivatives has been schematically represented in the **scheme-4**.
Scheme-4: Synthetic route for the preparation of 4-(1-benzofuran-2-yl)-2-methyl-6-substituted phenyl pyrimidine [3a-f] derivatives

Reagents and conditions: i) BrCH₂COCH₃, K₂CO₃, Acetone, reflux, 9-10h; ii) p-substituted benzaldehyde, NaOH, Grind, rt, 30min; iii) Acetamidine hydrochloride, KOH, EtOH, reflux, 6h.
3.2. MATERIALS AND METHODS

- **Introduction**
  A brief description of purification of solvents, the analytical procedure followed for the characterization of the synthesized compounds is given below.

- **Organic solvents and Reagents**
  The organic solvents such as methanol, dichloromethane, N,N-dimethylforamide, hexane, ethyl acetate, acetonitrile, ethanol, acetone, acetic acid, dimethyl sulphoxide, etc and the reagents like substituted salicylaldehyde, p-substituted benzaldehyde, methyl/ethyl piperazine, triethylamine, CuI, L-proline, potassium carbonate, sodium sulphate, sodium hydroxide etc., were obtained from SD Fine, Spectrochem, Sigma Aldrich and standard commercial sources are used without further purification.

- **Reaction conditions**
  Room temperature mentioned ranges between 15-35°C (throughout the year). An ice-water bath (0°C) was used to obtain low temperatures. Heating reactions were conducted in a magnetically stirred oil bath (or) heated on a hotplate.

- **Analytical techniques**

- **Melting point**
  Solid compounds melting point range were determined in open capillary tubes using a hot stage apparatus.

- **Thin layer Chromatography (TLC)**
  All reactions were monitored by TLC using Merck silica gel 60 F\textsubscript{254} precoated on aluminium backed plates. The following mobile phases were used for elution-hexane: ethyl acetate in different ratios. TLC plates were visualized with ultraviolet light (254 or 366 nm) or iodine vapors or by staining with 2% aqueous potassium permanganate solution.
- **Column chromatography**
  Silica gel (60-120 mesh) or neutral alumina was used for purification.

- **Instrumentation**
  Characterizations of synthesized compounds were carried out by FTIR, $^1$H, $^{13}$C-NMR, and Mass analysis.

- **FT-IR**
  The spectra were recorded using JASCO FTIR-4100 spectrophotometer as KBr pellets in the range of 4000-400 cm$^{-1}$. FTIR plotted in logarithmic scale and data are reported in the following order: Frequency (bond stretching, functional group, intensity).

- **$^1$H-NMR and $^{13}$C-NMR**
  The $^1$H and $^{13}$C-NMR spectra were recorded on JEOL-400 MHz spectrometers, using deuterated solvents (CDCl$_3$ & DMSO-$d_6$) and TMS as an internal standard. Data expresses the chemical shift values in $\delta$ ppm from downfield to upfield in both $^1$H-NMR (0-15ppm) and $^{13}$C-NMR (0-200ppm) spectra.
  $^1$H-NMR data is reported in the following order: chemical shift (multiplicity, number of protons, $J$ value and nature of proton). $^{13}$C-NMR data are reported in the following order: chemical shift (numbered carbon atom).

- **X-Ray diffraction**
  Single crystal studies were done on Bruker APEXII CCD diffractometer.

- **Mass analyses**
  The mass spectra were recorded using a waters Alliance separation module with C18 column and Shimadzu-LCMS with APCI and ESI probes.
3.3. EXPERIMENTAL

Step-1: Synthesis of 1-(benzofuran-2-yl) ethanone [1a]

To a well stirred solution of salicylaldehyde (10.0 g, 0.0012 mol) and K₂CO₃ (10 g) taken in round bottom flask containing acetone (50 mL), bromoacetone (14.3 mL, 0.0012 mol) was added drop-wise and mixture was refluxed for 10h. After the completion of the reaction as indicated by disappearance of precursor through thin layer chromatography, reaction mixture was poured into crushed ice and extracted to ethyl acetate (2 x 50 mL). The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated invaccu to get crude product. Finally, the pure compound [1a] was obtained by column chromatography on silica gel (60-120 mesh) using ethyl acetate: petroleum ether (9:1) as eluent.

Similar procedure was adopted for the synthesis of 1-(5-Bromo-benzofuran-2-yl) ethanone [1b].

Mechanism for the formation of [1a-b]

Possible mechanism for the formation of 2-acetylbenzofuran [1a-b] derivatives involves the base promoted nucleophilic substitution reaction followed by intramolecular aldol condensation reaction as depicted below.

2-acetylbenzofuran [1a] (0.5 g, 0.00193 mol), benzaldehyde (0.20 g, 0.00193 mol) and NaOH (0.15 g, 0.00386 mol) were taken in clean, dry mortar and grinded well using pestle with minimum amount of EtOH (1 mL) for 30mins. Progress of the reaction was monitored by thin layer chromatography. After the completion of the reaction checked by TLC, the reaction mixture was poured into ice cold water to get yellow colored solid and the obtained solid was washed with ice cold water, filtered and dried. The obtained solid was subjected to column chromatography on silica gel (60-120 mesh) using petroleum ether and ethyl acetate (7:3) as an eluent to obtain pure yellow solid compound [2a]. By adopting the similar procedure remaining 1-benzofuran-2-yl)-3-phenylprop-2-en-1-one [2b-f] derivatives were prepared.
Mechanism for the formation of [2a-f] from [1a-b]

Mechanism for the synthesis of 1-benzofuran-2-yl)-3-phenylprop-2-en-1-one [2a-f] derivatives involves Claisen-Schmidt’s condensation of compound [1a-b] with different p-substituted aromatic aldehydes is presented below.

Step-3: Synthesis of 4-(1-benzofuran-2-yl)-2-methyl-6-phenylpyrimidine [3a]

(1-benzofuran-2-yl)-3-phenylprop-2-en-1-one [2a] (0.5 g, 0.010 mol), acetamidine hydrochloride (0.15 g, 0.010 mol) and KOH (0.22 g, 0.020 mol) were taken in round bottom flask containing 5 mL of ethanol: water (4:1) mixture and refluxed for 6h. The reaction was monitored by thin layer chromatography. After completion of reaction, the reaction mixture was poured into ice cold water and extracted to ethyl acetate layer (3 x 25 mL). Then the
organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated under vacuum to get crude solid product. The crude product was purified by column chromatography using silica gel (60-120 mesh) using ethyl acetate: petroleum ether (1:9) as eluent to get pure solid of 4-(1-benzofuran-2-yl)-2-methyl-6-phenyl pyrimidine [3a]. The remaining 4-(1-benzofuran-2-yl)-2-methyl-6-phenyl pyrimidine [3b-f] derivatives were prepared by following the same procedure.

**Mechanism for the formation of [3a-f] from [2a-f]**

Possible mechanism for the formation of 4-(1-benzofuran-2-yl)-2-methyl-6-phenyl pyrimidine [3a-f] derivatives involves cyclization reaction followed by aromatization of 1-benzofuran-2-yl)-3-phenylprop-2-en-1-one [2b-f] derivatives with acetamidine hydrochloride is presented below.
3.4. RESULTS AND DISCUSSION

The key intermediate substituted-2-acetylbenzofuran [1a-b] was prepared by reaction of substituted salicylaldehyde with bromoacetone in presence of anhydrous K$_2$CO$_3$ under reflux condition. Further, substituted-2-acetylbenzofuran [1a-b] derivatives underwent Claisen-Schmidt’s condensation reaction with p-substituted aromatic aldehydes (1:1 ratio) in presence of base by grinding at room temperature to get 1-benzofuran-2-yl)-3-phenylprop-2-en-1-one [2a-f] derivatives. Finally, cyclization followed by aromatization of product [2a-f] with acetamidine hydrochloride in presence of base under reflux condition afforded corresponding 4-(1-benzofuran-2-yl)-2-methyl-6-substituted phenyl pyrimidine [3a-f] derivatives as shown in scheme-4. The physical characterization data along with yield of the synthesized compounds are tabulated in the table-12.

The assigned structures of the compound were confirmed by the spectroscopic characterization such as FTIR, $^1$H-NMR, $^{13}$C-NMR and LCMS/mass spectrometric techniques.

Crystalline compound [3a] was subjected to single crystal X-ray diffraction study to get additional structural information and to confirm the assigned structure without any ambiguity. The details of spectral characterization data along with X-ray diffraction study have been discussed in the following section.

Finally in chapter-5, the newly synthesized derivatives were screened for their in-vitro antibacterial and antifungal activities along with in-silico ADMET and molecular docking studies with target protein GlcN-6-P synthase.
Table-12: Physical characterization data of Compounds [3a-f]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mol. Formula (Mol. Wt)</th>
<th>Nature</th>
<th>Yield (%)</th>
<th>Melting point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>C₁₉H₁₄N₂O (286.33)</td>
<td>Pale yellow solid</td>
<td>69</td>
<td>130-133</td>
</tr>
<tr>
<td>3b</td>
<td>C₁₉H₁₃ClN₂O (320.77)</td>
<td>White solid</td>
<td>70</td>
<td>115-117</td>
</tr>
<tr>
<td>3c</td>
<td>C₂₀H₁₆N₂O₂ (316.35)</td>
<td>Light Brown solid</td>
<td>65</td>
<td>90-92</td>
</tr>
<tr>
<td>3d</td>
<td>C₁₉H₁₂BrClN₂O (399.67)</td>
<td>Reddish solid</td>
<td>55</td>
<td>118-120</td>
</tr>
<tr>
<td>3e</td>
<td>C₁₉H₁₃BrN₂O (365.22)</td>
<td>Yellow solid</td>
<td>60</td>
<td>110-112</td>
</tr>
<tr>
<td>3f</td>
<td>C₂₀H₁₃BrN₂O₂ (395.25)</td>
<td>Yellow solid</td>
<td>45</td>
<td>105-107</td>
</tr>
</tbody>
</table>

3.5. SPECTRAL INTERPRETATION

1-(Benzofuran-2-yl) ethanone [1a]

FTIR (KBr, ν cm⁻¹): 3086 (C-H, Aromatic, m), 2960 (C-H, Alkyl, m), 1672 (C=O, Ketone, s), 1614 (C=C, Aromatic, m), 1077-1174 (C-O-C, Furan, m).

¹H-NMR (400 MHz, CDCl₃, δ ppm): 7.70-7.72 (d, 1H, J = 7.92 Hz, Ar-H), 7.59 (d, 1H, J = 7.56 Hz, Ar-H), 7.45-7.50 (m, 2H, Ar-H), 7.33 (t, 1H, J = 7.07 Hz, Ar-H), 2.61 (s, 3H, -CH₃).

MS: m/z 160 (M⁺).
The IR spectrum (Fig 36) of compound [1a] showed the presence of characteristic intense absorption bands at 1672 cm\(^{-1}\) attributed to C=O stretching of acetyl group and absence of band due to -OH stretching of the precursor indicates the conversion.

The \(^1\)H-NMR spectrum (Fig 37) of compound [1a] showed the absence of singlets due to OH as well aldehyde proton in the downfield region and presence of signals in the range of \(\delta\) 7.70-7.33 ppm integrated to the five aromatic protons of benzene as well as furan ring. A singlet at \(\delta\) 2.61 ppm is integrated for the three protons of acetyl group confirm the formation of [1a]. The mass spectrum (Fig 38) of compound [1a] showed the peak at \(m/z\) 160 corresponding to its molecular weight. Based on these spectroscopic data the structure of compound [1a] was confirmed and also data are consistent with the literature. Similarly, 1-(5-Bromo-benzofuran-2-yl) ethanone [1b] also characterized and spectral data are given in the following section.

1-(5-Bromo-benzofuran-2-yl) ethanone [1b]

**FTIR (KBr, \(\nu\) cm\(^{-1}\))**: 3104 (C-H, Aromatic, m), 2963 (C-H, Alkyl, m), 1667 (C=O, Ketone, s), 1083-1174 (C-O-C, Furan, m) (Fig 39).

**\(^1\)H-NMR (400 MHz, CDCl\(_3\), \(\delta\) ppm)**: 7.85 (s, 1H, Ar-H), 7.56 (d, 1H, \(J = 7.69\) Hz, Ar-H), 7.45 (t, 2H, \(J = 6.9\) Hz, Ar-H), 2.61 (s, 3H, CH\(_3\)) (Fig 40).

**MS**: \(m/z\) 239 (M\(^+\)) (Fig 41).
Figure-36: FTIR spectrum of 1-(benzofuran-2-yl) ethanone [1a] in KBr
Figure-37: $^1$H-NMR spectrum of 1-(benzofuran-2-yl) ethanone [1a] in CDCl$_3$
Figure-38: Mass spectrum of 1-(benzofuran-2-yl) ethanone [1a]
Figure-39: FTIR spectrum of 1-(5-Bromo-benzofuran-2-yl) ethanone [1b] in KBr
Figure-40: $^1$H-NMR spectrum of 1-(5-Bromo-benzofuran-2-yl) ethanone [1b] in CDCl$_3$
Figure-41: Mass spectrum of 1-(5-Bromo-benzofuran-2-yl) ethanone [1b]
1-(1-Benzofuran-2-yl)-3-phenylpropenone [2a]

**FTIR (KBr, v cm⁻¹):** 3078 (C-H, Aromatic, m), 2955 (C-H, Alkyl, m), 1616 (C=O, Ketone, s), 1681 (C=C, Aromatic, m), 1075-1176 (C-O-C, Furan, m).

**¹H NMR (400 MHz, CDCl₃, δ ppm):** 7.85-7.83 (d, 1H, J = 7.1 Hz, CO-C=CH₂), 7.71-7.29 (m, 10H, Ar-H), 7.27-7.11 (d, 1H, J = 18.5 Hz, CH=CH-Ar).

**MS:** m/z 247 (M⁺).

The IR spectrum (Fig 42) of compound [2a] showed decrease in the C=O stretching band from 1672 to 1616 cm⁻¹ due to conjugation indicates the condensation reaction. Proton nuclear magnetic resonance spectrum (Fig 43) of compound [2a] shows characteristic multiplet signals in the region δ 7.71-7.29 ppm corresponds to ten protons of both benzofuran and phenyl ring. Characteristic two doublets were observed for conjugated protons in the region δ 7.85–7.83 and 7.21–7.11 ppm with coupling constants (J) of 7.1 and 18.5 Hz confirm the formation of chalcone. Additionally mass spectrum was recorded (Fig 44) for compound [2a] displayed molecular ion peak at m/z 247 corresponding to its molecular weight. Based on these spectroscopic data the structure of compound [2a] was confirmed and also data are consistent with the literature. Similarly the remaining derivatives [2b-f] were characterized and the spectral data are presented below.

1-(1-Benzofuran-2-yl)-3-(4-chlorophenyl) propenone [2b]

**FTIR (KBr, v cm⁻¹):** 3060 (C-H, Aromatic, m), 2958 (C-H, Alkyl, m), 1666 (C=O, Ketone, s), 1611 (C=C, Aromatic, m), 1080-1137 (C-O-C, Furan, m) (Fig 45)

**¹H-NMR (400 MHz, CDCl₃, δ ppm):** 7.54-7.55 (d, 1H, J = 7.1 Hz, CO-CH=CH₂), 7.47-7.19 (m, 9H, Ar-H), 7.18-7.07 (d, 1H, J = 18.5 Hz, CH=CH-Ar) (Fig 46)
MS: m/z 282.8 (M⁺) (Fig 47)

1-(1-Benzofuran-2-yl)-3-(4-methoxyphenyl) propenone [2c]

FTIR (KBr, ν cm⁻¹): 3055 (C-H, Aromatic, m), 2955 (C-H, Alkyl, m), 1668 (C=O, Ketone, s), 1613 (C=C, Aromatic, m), 1080-1095 (C-O-C, Furan, m).

¹H-NMR (400 MHz, CDCl₃, δ ppm): 7.84-7.81 (d, 1H, J = 7.1 Hz, CO-CH=CH), 7.71-7.29 (m, 9H, Ar-H), 7.27-7.11 (d, 1H, J = 18.5 Hz, CH=CH-Ar), 3.86 (s, 3H, -OCH₃).

1-(5-Bromobenzofuran-2-yl)-3-phenyl propenone [2d]

FTIR (KBr, ν cm⁻¹): 3062 (C-H, Aromatic, m), 2958 (C-H, Alkyl, m), 1661 (C=O, Ketone, s), 1613 (C=C, Aromatic, m), 1080-1095 (C-O-C, Furan, m).

¹H-NMR (400 MHz, CDCl₃, δ ppm): 7.83-7.81 (d, 1H, J = 8.7 Hz, CO-CH=CH), 7.70-7.28 (m, 9H, Ar-H), 7.22-7.19 (d, 1H, J = 10.6 Hz, CH=CH-Ar).

1-(5-Bromobenzofuran-2-yl)-3-(4-chlorophenyl) propenone [2e]

FTIR (KBr, ν cm⁻¹): 3060 (C-H, Aromatic, m), 2954 (C-H, Alkyl, m), 1656 (C=O, Ketone, s), 1611 (C=C, Aromatic, m), 1080-1095 (C-O-C, Furan, m).

¹H-NMR (400 MHz, CDCl₃, δ ppm): 7.84-7.82 (d, 1H, J = 8.7 Hz, CO-CH=CH), 7.70-7.28 (m, 8H, Ar-H), 7.20-7.17 (d, 1H, J = 10.6 Hz, CH=CH-Ar).

1-(5-Bromobenzofuran-2-yl)-3-(4-methoxyphenyl) propenone [2f]

FTIR (KBr, ν cm⁻¹): 3061 (C-H, Aromatic, m), 2958 (C-H, Alkyl, m), 1666 (C=O, Ketone, s), 1611 (C=C, Aromatic, m), 1080-1095 (C-O-C, Furan, m).

¹H-NMR (400 MHz, CDCl₃, δ ppm): 7.80-7.78 (d, 1H, J = 8.7 Hz, CO-CH=CH), 7.71-7.26 (m, 8H, Ar-H), 7.15-6.72 (d, 1H, J = 10.6 Hz, CH=CH-Ar), 3.73 (s, 3H, -OCH₃).
Figure-42: FTIR spectrum of 1-(1-benzofuran-2-yl)-3-phenylpropenone [2a] in KBr
Figure-43: $^1$H-NMR spectrum of 1-(1-benzofuran-2-yl)-3-phenylpropenone [2a] in CDCl$_3$
Figure-44: Mass spectrum of 1-(1-benzofuran-2-yl)-3-phenylpropenone [2a]
Figure-45: FTIR spectrum of 1-(1-benzofuran-2-yl)-3-(4-chlorophenyl) propenone [2b] in KBr
Figure-46: $^1$H-NMR spectrum of 1-(1-benzofuran-2-yl)-3-(4-chlorophenyl) propenone [2b] in CDCl$_3$
Figure-47: Mass spectrum of 1-(1-benzofuran-2-yl)-3-(4-chlorophenyl) propenone [2b]
4-(1-Benzofuran-2-yl)-2-methyl-6-phenyl pyrimidine [3a]

**FTIR (KBr, ν cm⁻¹):** 3051 (C-H, Aromatic, m), 2925 (C-H, Alkyl, m), 1601 (C=O, Aromatic, m), 1585 (C=N, Pyrimidine, s), 1110-1070 (C-O, Furan, m).

**¹H-NMR (400 MHz, CDCl₃, δ ppm):** 8.20-8.17 (m, 2H, Ar-H), 8.05 (s, 1H, Py-H), 7.71-7.69 (dd, 2H, J = 4.6 & 8.0 Hz, Ar-H), 7.62-7.53 (m, 4H, Ar-H), 7.43-7.39 (m, 1H, Ar-H), 7.32 (s, 1H, Ar-H), 2.86 (s, 3H, Py-CH₃).

**¹³C-NMR (100 MHz, CDCl₃, δ ppm):** 168.576 (C₁₂), 165.217 (C₉), 156.213 (C₁₁), 155.642 (C₁), 153.310 (C₈), 136.973 (C₁₃), 130.901 (C₁₄ & C₁₈), 128.915 (C₁₅ & C₁₇), 128.295 (C₁₆), 127.278 (C₅), 126.313 (C₄), 123.510 (C₂), 122.248 (C₃), 111.670 (C₆), 108.906 (C₇), 108.124 (C₁₀), 26.204 (C₁₉).

**MS:** m/z 287.59 (M⁺), 263.64, 201.53.

IR spectrum (Fig 48) of compound [3a] showed the absence of absorption band at 1681 cm⁻¹ due to carbonyl stretching frequency and presence of absorption band at 1585 cm⁻¹ attributed to C=N stretching frequency indicates cyclization. Proton-NMR spectrum (Fig 49) of the compound [3a] shows absence of doublets due to α, β-unsaturated carbonyl protons and existence of singlet at δ 8.05 ppm integrated to one proton of pyrimidine ring. Multiplets in the range of δ 8.21-7.32 ppm were integrated for benzene and furan ring protons respectively. A singlet at δ 2.86 ppm due to three protons of methyl group attached to C-2 position of pyrimidine ring confirms the cyclization. Carbon-13 NMR spectrum (Fig 50) of the compound [3a] showed signals at δ 168.576 (C₁₂), 165.217 (C₉) ppm due to pyrimidine ring carbon, 155.642 (C₁), 153.310 (C₈), 127.278 (C₅), 126.313 (C₄), 123.510 (C₂), 122.248 (C₃), 111.670 (C₆), 108.906 (C₇) ppm were characteristic carbons of benzofuran ring and signals at δ 136.973 (C₁₃), 130.901 (C₁₄ & C₁₈), 128.915 (C₁₅ & C₁₇), 128.295 (C₁₆), 108.124 (C₁₀) ppm were
observed for carbon atoms of the benzene ring. Methyl group attached to C-2 position of pyrimidine ring was observed at $\delta$ 26.204 (C19) ppm. Finally, the mass spectrum (Fig 51) of the compound [3a] showed m/z peak at 287.5 (M+) with 100% abundance is consistent with the calculated molecular weight. From these result of above spectral characterization, the assigned structure of the compound [3a] was confirmed. In addition to spectral characterization, the compound [3a] subjected to single crystal X-ray diffraction study and the details of crystallographic data are discussed in the following section.

Similarly other derivatives of 4-(1-benzofuran-2-yl)-2-methyl-6-phenyl pyrimidine [3b-f] were characterized by FTIR, $^1$H-NMR, $^{13}$C-NMR and the spectral data are presented below.

4-(Benzofuran-2-yl)-2-methyl-6-(4-chlorophenyl)pyrimidine [3b]

FTIR (KBr, ν cm$^{-1}$): 3058 (C-H, Aromatic, m), 2930 (C-H, Alkyl, m), 1601 (C=C, Aromatic, m), 1586 (C=N, Pyrimidine, s), 1010-1069 (C-O-C, Furan, m).

$^1$H-NMR (400 MHz, CDCl$_3$, $\delta$ ppm): 8.18-8.16 (m, 2H, Ar-H), 8.03 (s, 1H, Py-H), 7.82 (s, 1H, Ar-H), 7.62 (s, 1H, Ar-H), 7.55-7.48 (m, 5H, Ar-H), 2.85 (s, 3H, Py-CH$_3$).

4-(Benzofuran-2-yl)-2-methyl-6-(4-methoxyphenyl)pyrimidine [3c]

FTIR (KBr, cm$^{-1}$): 3055 (C-H, Aromatic, m), 2928 (C-H, Alkyl, m), 1600 (C=C, Aromatic, m), 1588 (C=N, Pyrimidine, s), 1008-1071 (C-O-C, Furan, m).

$^1$H-NMR (400 MHz, CDCl$_3$, $\delta$ ppm): 8.39 (s, 1H, Ar-H), 8.23 (s, 1H, Ar-H), 8.11 (s, 1H, Py-H), 7.87-7.76 (m, 4H, Ar-H), 7.65-7.62 (m, 1H, Ar-H), 7.52 (s, 1H, Ar-H), 7.38-7.26 (m, 2H, Ar-H), 3.38 (s, 3H, OCH$_3$), 2.91 (s, 3H, Py-CH$_3$).
4-(5-Bromobenzofuran-2-yl)-2-methyl-6-(4-chlorophenyl)pyrimidine [3d]

FTIR (KBr, v cm⁻¹): 3087 (C-H, Aromatic, m), 2954 (C-H, Alkyl, m), 1602 (C=C, Aromatic, m), 1555 (C=N, Pyrimidine, s), 1116-1072 (C-O-C, Furan, m) (Fig 52).

¹H-NMR (400 MHz, CDCl₃, δ ppm): 8.01-7.98 (m, 1H, Ar-H), 7.91-7.77 (m, 3H, Ar-H & Py-H), 7.56-7.46 (m, 3H, Ar-H), 7.35-7.32 (m, 1H, Ar-H), 6.71-6.68 (dd, 1H, J = 4.5 & 8 Hz, Ar-H), 3.04 (s, 3H, Py-CH₃) (Fig 53).

¹³C-NMR (400 MHz, CDCl₃, δ ppm): 168.576 (C12), 165.217 (C9), 156.213 (C11), 155.642 (C1), 153.310 (C8), 136.973 (C13), 130.901 (C14 & C18), 128.915 (C15 & C17), 128.295 (C16), 127.278 (C5), 126.313 (C4), 123.510 (C2), 122.248 (C3), 111.670 (C6), 108.906 (C7), 108.124 (C10), 26.204 (C19) (Fig 54).

MS: m/z 401.67 (M+2) (Fig 55).

4-(5-Bromobenzofuran-2-yl)-2-methyl-6-phenyl pyrimidine [3e]

FTIR (KBr, v cm⁻¹): 2954 (C-H, Aromatic, m), 2922 (C-H, Alkyl, m), 1615 (C=C, Aromatic, m), 1553 (C=N, Pyrimidine, s), 1110-1070 (C-O-C, Furan, m) (Fig 56).

¹H-NMR (400 MHz, DMSO-d₆, δ ppm): 8.34-8.31 (m, 1H, Ar-H), 7.98 (s, 1H, Py-H), 7.83-7.75 (m, 3H, Ar-H), 7.608-7.601 (m, 3H, Ar-H), 7.59-7.46 (m, 1H, Ar-H), 7.38-7.34 (m, 1H, Ar-H), 2.77 (s, 3H, Py-CH₃) (Fig 57).

MS: m/z 364 (M⁺) (Fig 58).

4-(5-Bromobenzofuran-2-yl)-2-methyl-6-(4-methoxyphenyl)pyrimidine [3f]

FTIR (KBr, v cm⁻¹): 3085 (C-H, Aromatic, m), 2955 (C-H, Alkyl, m), 1605 (C=C, Aromatic, m), 1551 (C=N, Pyrimidine, s), 1009-1071 (C-O-C, Furan, m).
$^1$H-NMR (400 MHz, CDCl$_3$, δ ppm): 8.22 (s, 1H, Ar-H), 8.00 (s, 1H, Py-H), 7.99-7.92 (m, 2H, Ar-H), 7.84-7.70 (m, 2H, Ar-H), 7.67-7.61 (m, 2H, Ar-H), 7.36-7.26 (m, 1H, Ar-H), 3.42 (s, 3H, OCH$_3$), 2.63 (s, 3H, Py-CH$_3$).
Figure-48: FTIR spectrum of 4-(1-benzofuran-2-yl)-2-methyl-6-phenyl pyrimidine [3a] in KBr
Figure-49: $^1$H-NMR spectrum of 4-(1-benzofuran-2-yl)-2-methyl-6-phenyl pyrimidine [3a] in CDCl$_3$
Figure-50: $^{13}$C-NMR spectrum of 4-(1-benzofuran-2-yl)-2-methyl-6-phenyl pyrimidine [3a] in CDCl$_3$
Figure-51: Mass spectrum of 4-(1-benzofuran-2-yl)-2-methyl-6-phenyl pyrimidine [3a]
Figure-52: FTIR spectrum of 4-(5-bromobenzofuran-2-yl)-2-methyl-6-(4-chlorophenyl) pyrimidine [3d] in KBr
Figure-53: $^1$H-NMR spectrum of 4-(5-bromobenzofuran-2-yl)-2-methyl-6-(4-chlorophenyl) pyrimidine [3d] in CDCl$_3$
Figure 54: $^{13}\text{C}$-NMR spectrum of 4-(5-bromobenzofuran-2-yl)-2-methyl-6-(4-chlorophenyl) pyrimidine [3d] in CDCl$_3$
Figure-55: Mass spectrum of 4-(5-bromobenzofuran-2-yl)-2-methyl-6-(4-chlorophenyl) pyrimidine [3d]
Figure-56: FTIR spectrum of 4-(5-bromobenzofuran-2-yl)-2-methyl-6-phenyl pyrimidine [3e] in KBr
Figure-57: $^1$H-NMR spectrum of 4-(5-bromobenzofuran-2-yl)-2-methyl-6-phenyl pyrimidine [3e] in DMSO-$d_6$
Figure-58: Mass spectrum of 4-(5-bromobenzofuran-2-yl)-2-methyl--6-phenyl pyrimidine [3e]
X-ray diffraction studies of 4-(1-benzofuran-2-yl)-2-methyl-6-phenyl pyrimidine [3a]

**Method of Crystallization:**

100 mg of 4-(1-benzofuran-2-yl)-2-methyl-6-phenyl pyrimidine [3a] was dissolved in 5 mL of ethyl acetate. The solution was filtered through Whatmann filter paper and the resulting solution was kept in a stopper conical flask slightly opened at room temperature. After 7 days, colorless crystals of 4-(1-benzofuran-2-yl)-2-methyl-6-phenyl pyrimidine [3a] were formed. They were filtered, dried and suitable crystals were selected for X-ray diffraction study.

**Crystal structure determination:**

The details of the device, programs and software’s used in the crystal structure determination were mentioned in the page no-63 of chapter-2 under section-A.

The molecular structure of 4-(1-benzofuran-2-yl)-2-methyl-6-phenyl pyrimidine [3a] was determined by single crystal XRD analysis and is depicted in Fig 59. The compound [3a] crystallizes in the monoclinic space group $P2_1$ with cell dimensions $a = 4.803(3) \text{ Å}$, $b = 9.498(5) \text{ Å}$, $c = 15.557(9) \text{ Å}$, $\beta = 93.25 (4)^\circ$ and $Z = 2$. The molecule is almost planar with root mean squared deviation (considering non-H atoms) being 0.101 Å. The dihedral angle between the benzene (A), the pyrimidine ring (B) and the benzofuran ring (C) are 4.79 (A/B), 10.76 (A/C) and 8.42(1)$^\circ$ (B/C) respectively. The crystal structure is stabilized by weak C-H…N intermolecular interactions (Fig 60) running into C(4) chains along [100] i.e., a axis and two pi…pi interactions$^{62}$. Hence, the supra molecular architecture exhibited is one dimensional. The details of crystallographic data, structural refinements of the 4-(1-benzofuran-2-yl)-2-methyl-6-phenyl pyrimidine [3a] are as shown in table-13. The selected coordination and hydrogen bomb geometry were tabulated in table-14 and table-15 respectively.
Figure-59: ORTEP view of the 4-(1-benzofuran-2-yl)-2-methyl-6-phenyl pyrimidine [3a] with atom labeling in color. Atoms are shown as 40% thermal ellipsoids.

Figure-60: Intermolecular and weak pi…pi interactions in the crystal structure of the 4-(1-benzofuran-2-yl)-2-methyl-6-phenyl pyrimidine [3a] leading to the formation of one dimensional network along a axis.
Table-13: Crystallographic data and structure refinement for the compound [3a]

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula</td>
<td>C_{19}H_{14}N_{2}O</td>
</tr>
<tr>
<td>Formula weight</td>
<td>286.32</td>
</tr>
<tr>
<td>Wavelength(Å)</td>
<td>0.71073</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>a (Å)</td>
<td>4.803(3)</td>
</tr>
<tr>
<td>b (Å)</td>
<td>9.498(5)</td>
</tr>
<tr>
<td>c (Å)</td>
<td>15.557(9)</td>
</tr>
<tr>
<td>α (°)</td>
<td>90</td>
</tr>
<tr>
<td>β (°)</td>
<td>93.25(4)</td>
</tr>
<tr>
<td>γ (°)</td>
<td>90</td>
</tr>
<tr>
<td>Volume (Å³)</td>
<td>708.6(6)</td>
</tr>
<tr>
<td>Space group</td>
<td>P2₁</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>T(K)</td>
<td>293(2)</td>
</tr>
<tr>
<td>Crystal size (mm)</td>
<td>0.36 x 0.20 x 0.16</td>
</tr>
<tr>
<td>ρ_{calcd} (g cm⁻³)</td>
<td>1.342</td>
</tr>
<tr>
<td>μ (mm⁻¹)</td>
<td>0.084</td>
</tr>
<tr>
<td>Tmin, Tmax</td>
<td>0.730, 0.793</td>
</tr>
<tr>
<td>θ range (°)</td>
<td>2.62 - 61.5</td>
</tr>
<tr>
<td>h / k / l indices</td>
<td>-6 →6, -12 →13, -22 →22</td>
</tr>
<tr>
<td>R_{int}</td>
<td>0.114</td>
</tr>
<tr>
<td>Goodness-of-fit on F²</td>
<td>0.785</td>
</tr>
<tr>
<td>Final R [I &gt; 2σ(I)]</td>
<td>R1 = 0.0611</td>
</tr>
<tr>
<td></td>
<td>wR2 = 0.1297</td>
</tr>
</tbody>
</table>
**Table-14**: Selected Bond length [Å] and angles [°] in compound [3a]

<table>
<thead>
<tr>
<th>Bond length [Å]</th>
<th>Bond angles [°]</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1-O14 1.372(4)</td>
<td>C1-O14-C7 106.2(2)</td>
</tr>
<tr>
<td>O14-7C 1.377(3)</td>
<td>O14-C7-C8 110.9(3)</td>
</tr>
<tr>
<td>C7-C8 1.333(4)</td>
<td>O14-C7-C15 116.4(2)</td>
</tr>
<tr>
<td>C8-C2 1.429(4)</td>
<td>C16-C15-N31 122.1(3)</td>
</tr>
<tr>
<td>C1-C2 1.388(4)</td>
<td>N31-C19 126.8(3)</td>
</tr>
<tr>
<td>C2-C3 1.388(4)</td>
<td>N32-C17 126.8(3)</td>
</tr>
<tr>
<td>C3-C4 1.372(4)</td>
<td>C19-N32 134.1(4)</td>
</tr>
<tr>
<td>C4-C5 1.374(5)</td>
<td>C19-N32 134.1(4)</td>
</tr>
<tr>
<td>C5-C6 1.369(5)</td>
<td>C17-C16 138.1(4)</td>
</tr>
<tr>
<td>C1-C6 1.372(4)</td>
<td>C17-C16 138.1(4)</td>
</tr>
<tr>
<td>C7-C15 1.447(4)</td>
<td>C17-C20 147.0(4)</td>
</tr>
<tr>
<td></td>
<td>C20-C21 137.6(5)</td>
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<tr>
<td>Bond angles [°] C22-C20-C21 118.5(3)</td>
<td>C23-C27 136.7(5)</td>
</tr>
<tr>
<td>Bond angles [°] C25-C27-C23 118.9(3)</td>
<td>C25-C22 139.0(5)</td>
</tr>
<tr>
<td>Bond angles [°] C1-C2-C3 118.5(3)</td>
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</tr>
</tbody>
</table>
Table-15: Hydrogen-bond geometry [Å, °] in compound [3a]

<table>
<thead>
<tr>
<th>D—H⋯A</th>
<th>D—H</th>
<th>H⋯A</th>
<th>D⋯A</th>
<th>D—H⋯A</th>
</tr>
</thead>
<tbody>
<tr>
<td>C33-H33B-N31^i</td>
<td>0.96</td>
<td>2.61(1)</td>
<td>3.5355(1)</td>
<td>162(1)</td>
</tr>
<tr>
<td>Cg1…Cg2^ii</td>
<td>-</td>
<td>-</td>
<td>3.5644(1)</td>
<td>-</td>
</tr>
<tr>
<td>Cg1…Cg3^I</td>
<td>-</td>
<td>-</td>
<td>3.6945(1)</td>
<td>-</td>
</tr>
</tbody>
</table>

(D-donor; A-Acceptor; H-hydrogen)

Cg1, Cg2 and Cg3 are the centroid of the furan ring, pyrimidine and the benzene ring (of benzofuran ring) respectively.

Symmetry codes: (i) -1+x, y, z; (ii) 1+x, y, z.
SECTION B

This section describes the synthesis and characterization of 5-(4-N-alkyl-piperazin-1-yl)-1-benzofuran-2-yl)-3-substituted phenylpropenone [5a-f] derivatives through the following steps.

**Step-1:** Reaction of 5-bromo-salicylaldehyde with bromoacetone in presence of base afforded 5-bromo-2-acetylbenzofuruan [1b].

**Step-2:** CuI / L-proline catalyzed Ullaman type C-N bond coupling reaction of 5-bromo-2-acetylbenzofuruan [1b] with N-alkyl-piperazine in presence of K₂CO₃ gave N-alkyl-piperazine-2-acetylbenzofuruan [4a-b].

**Step-3:** Synthesis of 5-(4-N-alkyl-piperazin-1-yl)-1-benzofuran-2-yl)-3-substituted phenylprop-2-en-1-one [5a-f] derivatives was carried out via Claisen-Schmidt’s condensation reaction between N-alkyl-piperazine-2-acetylbenzofuran [4a-b] and p-substituted benzaldehydes (1:1 ratio) in presence of base by grinding technique at room temperature.

The overall reaction for the synthesis of 5-(4-N-alkyl-piperazin-1-yl)-1-benzofuran-2-yl)-3-substituted phenylpropenone [5a-f] derivatives has been depicted in the scheme-5.
Scheme-5: General synthetic strategy towards the preparation of 5-(4-N-alkyl-piperazin-1-yl)-1-benzofuran-2-yl)-3-substituted phenylpropenone [5a-f] derivatives

Reagents and conditions: i) BrCH$_2$COCH$_3$, K$_2$CO$_3$, Acetone, reflux, 10h; ii) N-methyl/ethylpiperazine, Cul/L-Proline, K$_2$CO$_3$, DMSO, 80°C, 48h; iii) p-substituted benzaldehyde, NaOH, Grind, rt, 30 min.
3.6. EXPERIMENTAL

Step-1: Synthesis of 1-(5-Bromo-benzofuran-2-yl) ethanone [1b]

\[
\begin{align*}
\text{Br} & \quad \text{CHO} & \quad \text{Bromoacetone} & \quad \text{K}_2\text{CO}_3, \text{Acetone} & \quad \text{Reflux} & \quad \text{Br} \quad \text{O} \\
\text{O} & \quad \text{OH} & & \quad & & \quad \text{O}
\end{align*}
\]

[1b]

The procedure for the synthesis of 1-(5-Bromo-benzofuran-2-yl) ethanone [1b] derivative and possible mechanism for the formation has been given in this chapter-3 under section-A.

Step-2: Synthesis of 1-[5-(4-N-methyl-piperazin-1-yl)-1-benzofuran-2-yl] ethanone [4a]

\[
\begin{align*}
\text{Br} & \quad \text{Me} & \quad \text{N} & \quad \text{NH} & \quad \text{CuI} / \text{L-Proline} & \quad \text{K}_2\text{CO}_3, \text{DMSO, 80}^\circ\text{C} & \quad \text{Br} \quad \text{O} \\
\text{O} & \quad \text{O} & & & & & \quad \text{O} \quad \text{N} \quad \text{NH} \\
\quad & & & & & & \quad \text{Me}
\end{align*}
\]

[1b] [4a]

1-(5-Bromo-benzofuran-2-yl) ethanone (0.2 g, 0.010 mol), N-methyl piperazine (0.12 g, 0.015 mol), CuI (0.015 g, 0.001 mol), L-Proline (0.01 g, 0.001 mol) and K\textsubscript{2}CO\textsubscript{3} (0.57 g, 0.005 mol) were taken in round bottom flask containing DMSO (5 mL). The resulting mixture was stirred at 80\textdegree C for 48h. After completion of the reaction, the reaction mixture was poured into water and extracted to ethyl acetate layer (3 x 25 mL). The organic layer was washed with brine solution, dried over anhydrous sodium sulfate and concentrated under vacuum to get crude product. The crude product was purified by column chromatography on neutral alumina using chloroform: methanol (9:1) to get pure solid 1-[5-(4-N-methyl-piperazin-1-yl)-1-benzofuran-2-yl] ethanone [4a].
Similar reaction condition and procedure was followed for the synthesis of 1-[5-(4-N-ethylpiperazin-1-yl)-1-benzofuran-2-yl] ethanone [4b].

**Mechanism for the formation of [4a-b] from [1b]**

Possible mechanism for CuI and L-proline catalyzed C-N bond coupling reaction of 1-(5-Bromo-benzofuran-2-yl) ethanone with substituted piperazine involves coordination of L-proline to CuI followed by elimination of HI by base to form Cu-piperazine complex. Oxidative addition of compound [1b] to Cu-piperazine complex results in increase in oxidation state of Cu(I) to Cu(III) as well as coordination number 3 to 5. Finally, reductive elimination gives 1-[5-(4-N-methyl/ethylpiperazin-1-yl)-1-benzofuran-2-yl] ethanone [4a-b] as depicted below.\(^{63}\)
Step-3: Synthesis of 5-(4-N-methyl-piperazin-1-yl)-1-benzofuran-2-yl)-3-(4-chlorophenyl) propenone [5a]

1-[5-(4-N-methyl-piperazin-1-yl)-1-benzofuran-2-yl] ethanone [4a] (0.2 g, 0.010 mol), p-chlorobenzaldehyde (0.1 g, 0.010 mol) and NaOH (0.06 g, 0.020 mol) were taken in clean, dry mortar and mixture was grinded well using pestle with minimum amount of EtOH (1 mL) for 30min at room temperature. After completion of reaction indicated by thin layer chromatography, the reaction mixture was poured into ice cold water to get brown colored solid. The solid was washed with ice cold water, filtered and dried. The obtained solid was subjected to column chromatography on silica gel (60-120 mesh) using petroleum ether and ethyl acetate (7:3) as an eluent to obtain pure solid 5-(4-N-methyl-piperazin-1-yl)-1-benzofuran-2-yl)-3-(4-chlorophenyl)propenone [5a].

Similar reaction condition and procedure was followed for the synthesis of remaining derivatives [5b-f].
Mechanism for the formation of [5a-f] from [4a-b]

Mechanism for the synthesis of 5-(4-N-alkyl-piperazin-1-yl)-1-benzofuran-2-yl)-3-substituted phenylpropanone [5a-f] derivatives involves Claisen-Schmidt’s condensation of compound [4a-b] with different p-substituted aromatic aldehydes is presented below.

\[
\begin{align*}
\text{R} & = \text{CH}_3, \text{C}_2\text{H}_5 \\
\text{R}_1 & = \text{Cl}, \text{H}, \text{OCH}_3
\end{align*}
\]
3.7. RESULTS AND DISCUSSION

Synthesis of 5-(4-N-alkyl-piperazin-1-yl)-1-benzofuran-2-yl)-3-substituted phenylpropenone [5a-f] is depicted in the scheme-5. The key starting material for the synthesis 5-bromo-2-acetylbenzofuran [1b] was obtained by the reaction of 5-bromosalicylaldehyde with bromoacetone in presence of base under reflux condition. Further, N-alkyl-piperazine-2-acetylbenzofuran [4a-b] was synthesized through CuI / L-proline promoted Ullmann type C-N bond coupling reaction with 5-bromo-2-acetylbenzofuran [1b] in presence of base.

Finally, N-alkyl-piperazine-2-acetylbenzofuran [4a-b] underwent base catalyzed crossed aldol condensation reaction with p-substituted benzaldehyde (1:1 ratio) by grinding technique at room temperature to get 5-(4-N-alkyl-piperazin-1-yl)-1-benzofuran-2-yl)-3-phenylpropenone [5a-f] derivatives with percentage yield in the range 45-65% as shown in table-16 along with physical characterization data.

The spectroscopic evidences such as FTIR, $^1$H-NMR, $^{13}$C-NMR and mass spectral characterization were carried out to confirm the assigned structures of the compound without any ambiguity. The details of the spectral characterization are discussed below.

Further, the newly synthesized derivatives [4a-b] and [5a-f] were screened for their in-vitro antimicrobial studies along with in-silico ADMET and molecular docking studies. The detailed results are discussed in chapter-5.
Table-16: Physical characterization data of Compounds [4a-b] and [5a-f]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Mol. Formula</th>
<th>Nature</th>
<th>Yield (%)</th>
<th>Melting point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>C_{15}H_{18}N_{2}O_{2} (258.32)</td>
<td>Yellow solid</td>
<td>50</td>
<td>209-210</td>
</tr>
<tr>
<td>4b</td>
<td>C_{16}H_{20}N_{2}O_{2} (272.34)</td>
<td>Brown solid</td>
<td>45</td>
<td>220-222</td>
</tr>
<tr>
<td>5a</td>
<td>C_{22}H_{21}ClN_{2}O_{2} (380.87)</td>
<td>Light Brown solid</td>
<td>65</td>
<td>274-276</td>
</tr>
<tr>
<td>5b</td>
<td>C_{22}H_{22}N_{2}O_{2} (346.42)</td>
<td>yellow solid</td>
<td>50</td>
<td>263-265</td>
</tr>
<tr>
<td>5c</td>
<td>C_{23}H_{24}N_{2}O_{3} (376.45)</td>
<td>Reddish solid</td>
<td>55</td>
<td>277-279</td>
</tr>
<tr>
<td>5d</td>
<td>C_{23}H_{23}ClN_{2}O_{2} (394.89)</td>
<td>Yellow solid</td>
<td>60</td>
<td>273-274</td>
</tr>
<tr>
<td>5e</td>
<td>C_{23}H_{24}N_{2}O_{2} (360.45)</td>
<td>Yellow solid</td>
<td>55</td>
<td>283-285</td>
</tr>
<tr>
<td>5f</td>
<td>C_{24}H_{26}N_{2}O_{3} (390.47)</td>
<td>Yellow solid</td>
<td>45</td>
<td>268-269</td>
</tr>
</tbody>
</table>
3.8. SPECTRAL INTERPRETATION

1-[5-(4-N-methylpiperazin-1-yl)-1-benzofuran-2-yl]ethanone [4a]

**FTIR (KBr, ν cm⁻¹):** 3088 (C-H, Aromatic, m), 2966 (C-H, Alkyl, m), 1672 (C=O, Ketone, s), 1307 (C-N, amine, m), 1078-1157 (C-O-C, Furan, m).

**¹H-NMR (400 MHz, CDCl₃, δ ppm):** 7.47-7.41 (m, 2H, Ar-H), 7.23-7.19 (m, 1H, Ar-H), 7.12-7.11 (d, 1H, J = 2.3 Hz, Ar-H), 3.21-3.19 (t, 4H, J = 4.8 Hz, (CH₂)₂-N-Ar), 2.63-2.61 (t, 4H, J = 4.8 Hz, (CH₂)₂-N-Me), 2.58 (s, 3H, N-CH₃), 2.37 (s, 3H, COCH₃).

**MS:** m/z 258.8 (M⁺).

The IR spectrum (**Fig 61**) of compound [4a] exhibited characteristic strong absorption bands at 1672 cm⁻¹ corresponds to C=O stretching of acetyl group, 1307 cm⁻¹ due to C-N stretching vibrations and absence of band at 670 cm⁻¹ due to C-Br indicates coupling reaction.

Proton nuclear magnetic resonance spectrum (**Fig 62**) of compound [4a] shows a multiplet in the range of δ 7.47-7.11 ppm integrated to four protons of benzofuran ring. Two triplets at δ 3.21-3.19 and 2.63-2.61 ppm were integrated for eight protons of piperazine ring. A singlet was observed at δ 2.58 ppm due to three N-methyl protons confirm the C-N bond formation. A singlet integrated for three methyl protons of acetyl group were observed in the upfield region at δ 2.37 ppm. Further, mass spectrum (**Fig 63**) of compound [4a] exhibited a molecular ion peak at m/z 258.8 of 100% abundance corresponding to its calculated molecular mass of 258.3.

Based on these spectroscopic data the assigned structure of compound [4a] was confirmed. Similarly the compound [4b] was characterized and the spectral data are presented below.
1-[5-(4-N-ethylpiperazin-1-yl)-1-benzofuran-2-yl]ethanone [4b]

FTIR (KBr, ν cm⁻¹): 3088 (C-H, Aromatic, m), 2966 (C-H, Alkyl, m), 1672 (C=O, Ketone, s), 1049-1158 (C-O-C, Furan, m) (Fig 64).

¹H-NMR (400 MHz, CDCl₃, δ ppm): 7.48-7.45 (d, 1H, J = 7.0 Hz, Ar-H), 7.42 (s, 1H, Ar-H), 7.22-7.19 (dd, 1H, J = 2.9 & 6.9 Hz, Ar-H), 7.13-7.12 (d, 1H, J = 6.5 Hz, Ar-H), 3.25-3.23 (t, 4H, J = 5.1 Hz, (CH₂)₂-N-Ar), 2.74-2.71 (t, 4H, J = 4.3 Hz, (CH₂)₂-N-Me), 2.62-2.54 (m, 5H, CH₃ & N-CH₂), 1.19-1.15 (t, 3H, J = 7.3 Hz, N-CH₂CH₃) (Fig 65).

MS: m/z 272 (M⁺) (Fig 66).
Figure-61: FTIR spectrum of 1-[5-(4-N-methylpiperazin-1-yl)-1-benzofuran-2-yl]ethanone [4a] in KBr
Figure-62: $^1$H-NMR spectrum of 1-[5-(4-N-methylpiperazin-1-yl)-1-benzofuran-2-yl]ethanone [4a] in CDCl$_3$
Figure-63: Mass spectrum of 1-[5-(4-N-methylpiperazin-1-yl)-1-benzofuran-2-yl]ethanone [4a]
Figure-64: FTIR spectrum of 1-[5-(4-N-ethylpiperazin-1-yl)-1-benzofuran-2-yl]ethanone [4b] in KBr
Figure-65: $^1$H-NMR spectrum of 1-[5-(4-N-ethylpiperazin-1-yl)-1-benzofuran-2-yl]ethanone [4b] in CDCl$_3$
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Figure-66: Mass spectrum of 1-[5-(4-N-ethylpiperazin-1-yl)-1-benzofuran-2-yl]ethanone [4b]
3-(4-Chlorophenyl)-1-[5-(4-N-methylpiperazin-1-yl)-1-benzofuran-2-yl]propenone [5a]

**FTIR (KBr, \( \nu \text{ cm}^{-1} \)):** 2927 (C-H, Aromatic, m), 2871 (C-H, Alkyl, m), 1661 (C=O, Ketone, s), 1654 (C=C, Aromatic, m), 1078-1174 (C-O-C, Furan, m).

**\(^1\)H-NMR (400 MHz, CDCl\(_3\), \( \delta \text{ ppm} \)):** 7.93-7.78 (m,1H, -CO-CH=CH), 7.73-7.11 (m, 8H, Ar-H), 6.80-6.74 (m,1H, -CH=CH-Ar), 3.25-3.11 (t, 4H, (CH\(_2\))_2-N-Ar), 2.69-2.58 (t, 4H, (CH\(_2\))_2-N-Me), 2.47 (s, 3H, N-CH\(_3\)).

**MS:** \( m/z \) 380.8 [M+1]

The IR spectrum (Fig 67) of compound [5a] showed decrease in the carbonyl stretching from 1672 to 1661 cm\(^{-1}\) due to conjugation.

Proton nuclear magnetic resonance spectrum (Fig 68) of compound [5a] shows characteristic multiplet signals in the region \( \delta \) 7.73-7.11 ppm belong to six protons of benzofuran ring. Two doublets in the region \( \delta \) 7.93–7.78 and 6.80–6.74 ppm were due to \( \alpha, \beta \)-unsaturated protons confirms the formation of chalcones. A triplet at \( \delta \) 3.25-3.11 and a multiplet at 2.69-2.58 ppm were observed correspond to eight protons of piperazine ring. Three protons of methyl group observed at \( \delta \) 2.47 ppm. Additionally mass spectrum was recorded (Fig 69) for compound [5a] displayed a molecular ion peak at \( m/z \) 380.9 corresponding to its molecular weight. Based on these spectroscopic data the structure of compound [5a] was confirmed.

Similarly the remaining compounds [5b-f] were characterized and the spectral data are presented below.
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1-[5-(4-N-Methylpiperazine-1-yl)-1-benzofuran-2-yl]-3-phenylpropenone [5b]

FTIR (KBr, ν cm⁻¹): 3052 (C-H, Aromatic, m), 2977 (C-H, Alkyl, m), 1651 (C=O, Ketone, s), 1615 (C=C, Aromatic, m), 1078-1160 (C-O-C, Furan, m) (Fig 70).

¹H-NMR (400 MHz, CDCl₃, δ ppm): 8.09-8.07 (m, 2H, Ar-H), 8.04-8.00 (m, 1H, CH=CH), 7.86-7.84 (d, 1H, J = 14.0 Hz, CH=CH), 7.75-7.53 (m, 6H, Ar-H), 7.40-7.36 (m, 1H, Ar-H), 3.36 (s, 4H, (CH₂)₂-N-Ar), 2.66 (s, 4H, (CH₂)₂-N-Me), 2.38 (s, 3H, N-CH₃) (Fig 71).

MS: m/z 347 (M⁺) (Fig 72).

3-(4-Methoxyphenyl)-1-[5-(4-N-methylpiperazin-1-yl)-1-benzofuran-2-yl]propenone [5c]

FTIR (KBr, ν cm⁻¹): 2957 (C-H, Aromatic, m), 2923 (C-H, Alkyl, m), 1660 (C=O, Ketone, s), 1654 (C=C, Aromatic, m), 1078-1174 (C-O-C, Furan, m) (Fig 73).

¹H-NMR (400 MHz, CDCl₃, δ ppm): 7.93-7.86 (m, 1H, CH=CH), 7.67-7.54 (m, 2H, Ar-H), 7.53-7.11 (m, 6H, Ar-H), 6.97-6.94 (d, 1H, J = 14.0 Hz, CH=CH), 3.87 (s, 3H, OCH₃), 3.49 (s, 4H, (CH₂)₂-N-Ar), 2.65 (s, 4H, (CH₂)₂-N-Me), 2.44 (s, 3H, N-CH₃) (Fig 74).

MS: m/z 377.0 (M⁺) (Fig 75).

3-(4-Chlorophenyl)-1-[5-(4-N-ethylpiperazine-1-yl)-1-benzofuran-2-yl]phenylpropenone [5d]

FTIR (KBr, ν cm⁻¹): 3104 (C-H, Aromatic, m), 2922 (C-H, Alkyl, m), 1660 (C=O, Ketone, s), 1655 (C=C, Aromatic, m), 1073-1170 (C-O-C, Furan, m).

¹H-NMR (400 MHz, CDCl₃, δ ppm): 7.86-7.70 (m, 5H, Ar-H & CH=CH), 7.66-7.57 (m, 2H, Ar-H), 7.40-7.32 (m, 2H, Ar-H), 6.85-6.81 (d, 1H, J = 14.0 Hz, CH=CH), 3.54-3.51 (t, 4H, (CH₂)₂-N-Ar), 2.67 (s, 4H, (CH₂)₂-N-Me), 2.43-2.38 (q, 2H, N-CH₂), 1.40-1.36 (t, 3H, N-CH₂CH₃).
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1-[5-(4-N-ethylpiperazine-1-yl)-1-benzofuran-2-yl]phenylpropenone [5e]

**FTIR (KBr, ν cm⁻¹):** 3058 (C-H, Aromatic, m), 2928 (C-H, Alkyl, m), 1666 (C=O, Ketone, s), 1648 (C=C, Aromatic, m), 1080-1148 (C-O-C, Furan, m).

**¹H-NMR (400 MHz, CDCl₃, δ ppm):** 7.79-6.56 (m, 9H, Ar-H), 8.45 (d, 1H, J = 14.4 Hz, CH=CH), 6.45 (d, 1H, J = 14.0 Hz, CH=CH), 3.24 (t, 4H, (CH₂)₂-N-Ar), 2.60 (t, 4H, (CH₂)₂-N-Me), 2.39-2.26 (q, 2H, N-CH₂), 1.38-1.26 (t, 3H, N-CH₂CH₃).

3-(4-Methoxyphenyl)-1-[5-(4-N-ethylpiperazine-1-yl)-1-benzofuran-2-yl]phenylpropenone [5f]

**FTIR (KBr, ν cm⁻¹):** 2988 (C-H, Aromatic, m), 2852 (C-H, Alkyl, m), 1665 (C=O, Ketone, s), 1645 (C=C, Aromatic, m), 1088-1135 (C-O-C, Furan, m).

**¹H-NMR (400 MHz, CDCl₃, δ ppm):** 8.08-7.95 (m, 3H, Ar-H & CH=CH), 7.82-7.56 (m, 3H, Ar-H), 7.34-7.32 (m, 2H, Ar-H), 6.98-6.96 (d, 2H, J = 12.0 Hz, CH=CH), 3.86 (s, 3H, OCH₃), 3.43 (s, 4H, (CH₂)₂-N-Ar), 2.65 (s, 4H, (CH₂)₂-N-Me), 2.51-2.46 (q, 2H, N-CH₂), 1.13-1.09 (t, 3H, N-CH₂CH₃).
Figure-67: FTIR spectrum of 3-(4-Chlorophenyl)-1-[5-(4-N-methylpiperazin-1-yl)-1-benzofuran-2-yl]propenone [5a] in KBr
Figure-68: $^1$H-NMR spectrum of 3-(4-Chlorophenyl)-1-[5-(4-N-methylpiperazin-1-yl)-1-benzofuran-2-yl]propenone [5a] in CDCl$_3$
Figure-69: Mass spectrum of 3-(4-Chlorophenyl)-1-[5-(4-N-methylpiperazin-1-yl)-1-benzofuran-2-yl]propenone [5a]
Figure-70: FTIR spectrum of 1-[5-(4-N-methylpiperazine-1-yl)-1-benzofuran-2-yl]-3-phenylpropenone [5b] in KBr
Figure 71: $^1$H-NMR spectrum of 1-[5-(4-N-methylpiperazine-1-yl)-1-benzofuran-2-yl]-3-phenylpropenone [5b] in CDCl$_3$
Figure-72: Mass spectrum of 1-[5-(4-N-methylpiperazine-1-yl)-1-benzofuran-2-yl]-3-phenylpropenone [5b]
Figure-73: FTIR spectrum of 3-(4-Methoxyphenyl)-1-[5-(4-N-methylpiperazin-1-yl)-1-benzofuran-2-yl]propenone [5c] in KBr
Figure-74: $^1$H-NMR spectrum of 3-(4-Methoxyphenyl)-1-[5-(4-N-methylpiperazin-1-yl)-1-benzofuran-2-yl]propenone [5c] in CDCl$_3$
Figure-75: Mass spectrum of 3-(4-Methoxyphenyl)-1-[5-(4-N-methylpiperazin-1-yl)-1-benzofuran-2-yl]propenone [5c]
3.9. REFERENCES


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