Chapter 2

Synthesis and Biological Studies of Some New Chalcone and 1,4-Dihydropyridine Derivatives Containing Phenothiazine Moiety

2.1 INTRODUCTION

2.1.1 PHENOTHIAZINE

Phenothiazines, nitrogen- and sulfur-containing tricyclic compounds, have been known for over a hundred years. The parent compound, 10H-dibenzo-1,4-thiazine was obtained the first time by Bernthsen in 1883. Till now over 5000 phenothiazine derivatives have been obtained and this class of organic compounds became exceedingly important due to their varied and significant biological as well as chemical properties. Phenothiazines, mostly substituted at position 10 with the dialkylaminoalkyl groups and additionally at position 2 with small groups exhibit valuable activities such as neuroleptic, antiemetic, antihistaminic, antipuritic, analgesic and antihelminthic (Gupta et al., 1988). New derivatives of phenothiazines have been obtained by modifications of the parent phenothiazine structure in several ways by:

- introduction of a new substituent at the thiazine nitrogen atom (at position 10),
- introduction of a new substituent at the benzene ring carbon atom (at positions 1-4 and 6-9),
- oxidation of the sulfide function into sulfoxide and sulfone groups,
- substitution of one or two benzene rings with homoaromatic and heteroaromatic rings (Pluta et al., 2009).

The introduction of different substituents into the phenothiazine skeleton as well as the modification of the tricyclic ring system brings changes in biological activities. Every year hundreds of new phenothiazine derivatives are being synthesized and a part of them has been biologically screened. A simple modification of promazine, chlorpromazine and triflupromazine by their benzylaion led to compounds with enhanced antibacterial activity against Mycobacterium tuberculosis than the parent compounds (Bata et al., 2007; Weinstein et al., 2005). 10H and 10-phthalimidoalkyl
phenothiazines exhibited antitumor activity against HEp-2 and L5178Y tumor cells (Nagy et al., 1996; Motohashi et al., 1996).

2.1.2 CHALCONES

Chalcones are bichromophoric molecules separated by a keto-vinyl chain and constitute an important class of naturally occurring flavanoids exhibiting a wide spectrum of biological activities. The name “Chalcones” was given by Kostanecki and Tambor (Kostanecki et al., 1899). These compounds are also known as benzal acetophenones or benzylidene acetophenones. Chalcones are unsaturated ketones containing reactive ketoethylenic group –CO-CH=CH-. These are coloured compounds because of the presence of the chromophore -CO-CH=CH-. Chalcones are intermediate compounds used for the synthesis of some naturally occurring heterocyclic compounds like flavones, flavanoids, flavanones, dihydro flavanols, benzal coumarinones, anthocyanins. Chalcones contain a keto-ethylenic group and therefore they are reactive towards number of reagents yielding different heterocyclic compounds exhibiting significant biological activities viz. pyrazolines (Sivakumar et al., 2010), cyanopyrans (Mahmoud et al., 2010), pyrimidines (Rostom et al., 2011; Nagaraj et al., 2008), cyanopyridines (Patel et al., 1996), isoxazoles (Voskiene et al., 2009), cyanopyridiones. (Ebtehal et al., 2011), indazole (Sikkandarkani et al., 2013) etc. Different methods are known for the preparation of chalcones (Farzana et al., 2009; Zhang et al., 2008; Prasath et al., 2013). The most convenient method is the Claisen-Schimdt condensation using equimolar quantities of arylmethylketone with aryl aldehyde in the presence of alcoholic NaOH or KOH (Bukhari et al., 2012).

\[
\begin{align*}
\text{Ph} & \quad + \quad \text{Ph} \\
& \quad \xrightarrow{\text{alc.KOH or NaOH}} \quad \text{Ph} - \text{CO} - \text{Ph}
\end{align*}
\]

Chalcone functional group present in some derivatives of flavionoids are given in Fig. 2.1. Chalcones are present in edible plants and are a major classes of natural products
with wide range distribution in vegetables, fruits, tea and soy based food stuffs (Dimmock et al., 1998).

![Flavones and Isoflavones](image)

**Fig. 2.1** Chalcone containing flavionoids compounds

The main functions of chalcone are purifying blood, strengthening immune system, monitoring cholesterol level, regulateing blood pressure, preventing thrombus, suppressing acid secretion, preventing cancer and promoting metabolism. These compounds with the backbone of chalcones have been reported to possess various biological activities such as cytotoxic (Gul et al., 2007), antimalarial (Yadav et al., 2012), antioxidant (Sivakumar et al., 2011), tyrosinase inhibitory (Liu et al., 2013) anti-inflammatory (Xue et al., 2010), cancer chemopreventive (Khatib et al., 2005) and antibacterial (Kazuhiro et al., 2011). Hydroxy and methoxy substituted chalcones showed potent inhibiton of α-glucosidase (Ansari et al., 2005). Paula Boeck (Paula et al., 2006) produced novel chalcone analougs with antileishmanial activity. Analogs containing nitro, bromine or fluorine group respectively displayed increased selectivity against the parasites as compared to natural chalcone.
2.1.3 1,4-DIHYDROPYRIDINE

Nitrogen containing heterocyclic compounds have been known to possess a wide spectrum of biological properties. Synthesis of 1,4-dihydropyridines was first reported by Arthur Hantzsch (Hantzsch, 1882). In recent years, considerable focus has been given to the synthesis of 1,4-dihydropyridines owing to their significant biological activity. (Mauzeral et al., 1955). 1,4-Dihydropyridine-containing drugs (1,4-DHPs), such as nifedipine, nicardipine, amlodipine and others have been found as useful calcium channel blockers, (Aziz et al., 2012; Latifeh et al., 2004; Gordeev et al., 1996; Latifeh et al., 2004) and are most frequently used as cardiovascular agents for treatment of hypertension.

![Amlodipine and Nifedipine](image)

**Fig. 2.2** Biologically active dihydropyridine moiety

1,4-Dihydropyridine is a significant subclass of pyridines, the best known heterocyclic compounds which are associated with good number of pharmacological activities. Oxidative aromatization reactions of DHPs take place in biological systems in the presence of certain enzymes. The nitrogen heterocycles thus prepared by Hantzsch method are of great importance because of their active role in biological systems. They are known as model compounds for the NAD-NAPH biological redox systems.
(Schellenberg et al., 1965; Norcross et al., 1962) possessing neuroprotective, platelet anti-aggregation and antidiabetic activities (Tewari et al., 2004; Briede et al., 2008). Recently, the synthesis of DHPs as Multidrug Resistance (MDR) reversal agent in tumor cell gave a new dimension to their applications (Kawase et al., 2002; Tasaka et al., 2001). It has been found that DHPs posses a wide range of other beneficial biological activities such as anticonvulsant analgesic and are also used as a chemical drug delivery systems, especially in brain delivery (Subudhi, et al., 2009; Mortazavi et al., 2007). Cozzi and co-workers (Cozzi et al., 1993) have prepared unsymmetric 3-cyano-4-[3-imdazo-1-yl]phenyl or 3-(1,2,4-triazol-1-yl)-1,4-DHP derivatives and found the activity of such DHPs in the treatment of prevention of breast endometrial, ovarian or pancreatic cancers, gynecomastia, benign breast disease, endometriosis, ovarian disease, prostatic hyperplasia and in the male fertility or female fertility control.

Aromatization of 1,4-DHP has also attracted considerable attention in recent years after Bocker (Gordeev et al., 1996) has demonstrated that metabolism of those drugs involves a cytochrome P-450 catalyzed oxidation in the liver. Besides reversing activity of DHPs, there are several reports about their intrinsic cytotoxicity. Particularly, some derivatives showed significant cytotoxicity such as dexniguldipine and some dibenzoyl derivatives (Mehdipour et al., 2007; Hahn et al., 1997; Jorjani et al., 2003; Morshed et al., 2005). In addition, there are some reports on the effects of DHPs on potential antitumoral and antimetastatic activity of some common cytotoxic drugs (Fedeli et al., 1989). Mechanistic investigations proved that cytotoxicity of DHPs may not be the result of interaction with Calcium channels although it might be related to other pathways in which calcium is involved such as calcium/calmodulin pathway or other cellular pathways like inhibition of topoisomerase I enzyme (Orth et al., 1996; Straub et al., 1997).
2.2 RESULTS AND DISCUSSION

The present work focuses on the synthesis of new chalcones incorporating phenothiazine moiety. Synthesis of 3-(10-methyl-10H-phenothiazin-3-yl)-1-substituted phenylprop-2-en-1-one by condensation of 10-alkyl-10H-phenothiazine-3-carbaldehyde with different aromatic ketones in the presence of alc. KOH. Ethyl 7,7-dimethyl-4-(10-methyl-10H-phenothiazin-3-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate was carried out by Hantzsch method using dimedone and ethyl acteacetate. All the compounds have been screened for their antioxidant activity using radical scavenging method and in vitro antibacterial studies was carried out using “Gram +ve” and “Gram –ve” bacterial strains.

2.2.1 CHEMISTRY

Phenothiazine (1) was reacted with alkyl iodide (ethyl, methyl) in the presence of potassium tertiary butoxide and dry DMF at 80º C for 24 hours to yield around 80% of N-alkyl phenothiazines 2(a-b) (Scheme 2.1). The \(^1\)H NMR of compound 2a showed a singlet at \(\delta\) 3.40 ppm showing the presence of CH\(_3\) group indicating the formation of 10-methyl-10H-phenothiazine. In the IR spectra of compounds 2(a-b), disappearance of absorption band at 3420 cm\(^{-1}\) clearly indicates formation of alkyl phenothiazine. The \(^1\)H NMR spectrum of compound 2b showed a triplet at \(\delta\) 1.47 ppm and a quartet at \(\delta\) 3.96 ppm indicating the presence of CH\(_3\) and CH\(_2\) groups respectively confirming the formation of 10-ethyl-10H-phenothiazine. The \(^13\)C NMR spectrum of compound 2b shows peaks at \(\delta\) 14.07 ppm and 41.78 ppm indicating presence of CH\(_3\) and CH\(_2\) carbons respectively. The compounds 3(a-b), 10-alkyl-10H-phenothiazine-3-carbaldehyde was obtained from 10-alkyl phenothiazine 2(a-b) via Vilsmeier Hack reaction with yields of around 78%. \(^1\)H NMR spectra of compounds 3a and 3b shows singlet at \(\delta\) 9.79 and 9.77 ppm respectively indicating the formation of formyl proton and in \(^13\)C NMR spectra the peaks at \(\delta\) 190.67 and 190.08 ppm respectively also support the formation of carbonyl carbon. The IR spectra of compounds 3a and 3b show the absorption frequency at 1669 and 1678 cm\(^{-1}\) indicates carbonyl (C=O) group which clearly indicates the formation of compounds 3a and 3b.

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The compounds, 3-(10-methyl-10H-phenothiazin-3-yl)-1-substituted phenylprop-2-en-1-one \(6(a-h)\) were prepared employing Claisen-Schmidt reaction, by condensing \(3a\) with different substituted acetophenones in presence of alcoholic KOH at room temperature (Scheme 2.1). The compounds \(6(a-h)\) in their IR spectra showed bands 1653-1657 cm\(^{-1}\) due to styryl ketone C=O stretching frequency. These compounds in their \(^1\)H-NMR spectra exhibited protons attached to the carbon atoms of \(\alpha,\beta\)-unsaturated ketone moiety at \(\delta\) 7.4-7.8 ppm, that were seen merged with aromatic protons. The disappearance of formyl proton at \(\delta\) 9.79 ppm confirms the formation of compounds \(6(a-h)\).

![Scheme 2.1](image)

**SCHEME 2.1** Synthetic pathway for the preparation of compound 6(a-h).

The compounds \(7(a-d)\) were synthesized by treatment of one equivalent of 10-alkyl-3-formylphenothiazine, one equivalent of dimedone and ammonium acetate with one equivalent of ethylacetoacetate in presence of \(p\)-TSA (10 mol %) under reflux and ultrasonic irradiation giving the hexahydroquinoline-3-carboxylate \(7(a-d)\) represented in Scheme 2.2. Structures of the synthesized compounds \(7(a-d)\) were confirmed by recording their IR, \(^1\)H NMR, \(^{13}\)C NMR and mass spectra. IR spectrum of compound \(7a\) showed absorption at 3282 cm\(^{-1}\) which is due to the NH stretching. The absorption band at 1699 and 1647 cm\(^{-1}\) is due to \(-\text{CO}\) stretching frequency. The \(^1\)H NMR spectrum of \(7a\) showed a singlet at \(\delta\) 5.89 ppm corresponding to the NH proton.
Table 2.1 Physical data of synthesized compounds 6 (a-h) and 7 (a-d)

<table>
<thead>
<tr>
<th>Compound</th>
<th>R$_1$</th>
<th>Reaction Time $^a$ (min)</th>
<th>Yield $^{a,b}$ (%)</th>
<th>m.p. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>H</td>
<td>180/4.0</td>
<td>82/83</td>
<td>161-163</td>
</tr>
<tr>
<td>6b</td>
<td>2,4-OMe</td>
<td>195/4.5</td>
<td>85/84</td>
<td>148-150</td>
</tr>
<tr>
<td>6c</td>
<td>4-OMe</td>
<td>190/4.5</td>
<td>83/85</td>
<td>142-145</td>
</tr>
<tr>
<td>6d</td>
<td>2-OH</td>
<td>185/4.5</td>
<td>80/82</td>
<td>135-138</td>
</tr>
<tr>
<td>6e</td>
<td>2-NH$_2$</td>
<td>190/5.0</td>
<td>78/81</td>
<td>110-112</td>
</tr>
<tr>
<td>6f</td>
<td>2-Naphthyl</td>
<td>195/5.0</td>
<td>80/82</td>
<td>173-175</td>
</tr>
<tr>
<td>6g</td>
<td>2-Thiohenyl</td>
<td>185/4.5</td>
<td>79/80</td>
<td>158-160</td>
</tr>
<tr>
<td>6h</td>
<td>4-Br</td>
<td>180/5.0</td>
<td>83/86</td>
<td>122-124</td>
</tr>
<tr>
<td>7a</td>
<td>CH$_3$-CH$_2$</td>
<td>360/18</td>
<td>82/84</td>
<td>212-215</td>
</tr>
<tr>
<td>7b</td>
<td>CH$_3$</td>
<td>350/19</td>
<td>80/83</td>
<td>225-228</td>
</tr>
<tr>
<td>7c</td>
<td>CH$_3$-CH$_2$</td>
<td>200/14</td>
<td>83/84</td>
<td>245-247</td>
</tr>
<tr>
<td>7d</td>
<td>CH$_3$</td>
<td>190/15</td>
<td>84/86</td>
<td>256-258</td>
</tr>
</tbody>
</table>

$^a$At reflux temperature/ultrasonic irradiation; $^b$Isolated yields
SCHEME 2.2 Synthetic protocol of compounds 7(a-d).

The singlet at δ 4.94 ppm corresponds to the C-4 hydrogen of dihydropyridine ring, which is further supported through the $^{13}$C NMR spectrum and the peak at δ 41.2 ppm corresponds to CH carbon.

2.2.2 BIOLOGICAL ACTIVITY STUDIES

2.2.2.1 SCREENING OF ANTIOXIDANT ACTIVITY

All the synthesized compounds 6(a-h) and 7(a-d) were subjected to in vitro antioxidant activity using DPPH free radical scavenging method using the standard procedure given in Annexure I.

The antioxidant studies revealed that compound 7(a-d) showed least free radical scavenging activity (25.09%, 28.83%, 20.45% and 22.59% respectively) compared to that of BHT (Butylated hydroxy toluene) and ascorbic acid (100%), at 100 µg/mL after 30 minutes of incubation time. Free radical scavenging capacities of the synthesized compounds 7(a-d) and BHT at 100 µg/mL concentration after half an hour (Fig. 2.3) incubation time in dark at room temperature were measured by DPPH assay. The remaining compounds 6(a-h) have not showed radical scavenging activity against DPPH under the same reaction conditions.
Table 2.2 Antioxidant activity of compounds 7a-d using DPPH radical scavenging method

<table>
<thead>
<tr>
<th>Compound</th>
<th>Absorbance</th>
<th>% Antioxidant activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a</td>
<td>1.3848</td>
<td>25.09</td>
</tr>
<tr>
<td>7b</td>
<td>1.3157</td>
<td>28.83</td>
</tr>
<tr>
<td>7c</td>
<td>1.4706</td>
<td>20.45</td>
</tr>
<tr>
<td>7d</td>
<td>1.4311</td>
<td>22.59</td>
</tr>
<tr>
<td>Control</td>
<td>1.8488</td>
<td></td>
</tr>
</tbody>
</table>

*At 100 µg/mL concentration and BHT and ascorbic acid was used as a standard antioxidant.

Fig. 2.3 Antioxidant activity of compounds 7(a-d) and BHT, ascorbic acid using DPPH free radical scavenging method after 30 min. of incubation.

2.2.2.2 SCREENING OF ANTIBACTERIAL ACTIVITY

The in vitro antibacterial activity studies have been carried out for all the synthesized compounds using the standard procedure given in Annexure II.

The compounds 6(a-h) and 7(a-d) were screened for antibacterial activity against three “Gram +ve” bacterial strains, *S. aureus* (MTCC 3381), *P. aeruginosa* (MTCC 2295) and *B. cereus* (MTCC 8372) and two “Gram -ve” bacterial strains, *E. coli* (MTCC 1302), *K. pneumonia* (MTCC 3384) at 25, 50 µg/mL concentration by agar well diffusion method using Muller Hinton agar as the medium.
Compounds 6d, 6g, 7a and 7b showed good activity against *S. aureus*, *P. aeruginosa*, *E. coli* and *K. pneumonia* and moderate activity against *B. cereus* while compounds 6g and 7b exhibited significant activity against *B. cereus*. Compounds 6a, 6f and 7d showed moderate activity against *S. aureus*, *P. aeruginosa*, *E. coli*, *K. pneumonia* while compounds 6b, 6c, 6e, 6h and 7c exhibited significant activity against *S. aureus*, *P. aeruginosa*, *E. coli*, *K. pneumonia* and *B. cereus*. Compounds 6a and 6h showed least activity against *B. cereus* while compounds 6f and 7d showed moderate activity against *B. cereus*.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Zone of bacterial Inhibition in³ (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25 µg/mL</td>
</tr>
<tr>
<td>6a</td>
<td>9</td>
</tr>
<tr>
<td>6b</td>
<td>10</td>
</tr>
<tr>
<td>6c</td>
<td>10</td>
</tr>
<tr>
<td>6d</td>
<td>12</td>
</tr>
<tr>
<td>6e</td>
<td>10</td>
</tr>
<tr>
<td>6f</td>
<td>9</td>
</tr>
<tr>
<td>6g</td>
<td>11</td>
</tr>
<tr>
<td>6h</td>
<td>10</td>
</tr>
<tr>
<td>7a</td>
<td>11</td>
</tr>
<tr>
<td>7b</td>
<td>12</td>
</tr>
<tr>
<td>7c</td>
<td>11</td>
</tr>
<tr>
<td>7d</td>
<td>9</td>
</tr>
</tbody>
</table>

(Ampicillin³ 25 µg/mL)

³zone of inhibition in mm; ²Standard antibacterial drug;

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2.3 CONCLUSIONS

Synthesis and characterization of a series of phenothiazine incorporated Chalcone and 1,4-dihydropyridine derivatives using conventional as well as ultrasonic irradiation methods are reported. All these compounds have been screened for their antioxidant activity using DPPH free radical scavenging method. Out of these compounds, only 1,4-dihydropyridine is found to be moderately active. All these compounds 6(a-h) and 7(a-d) were screened for their in vitro antibacterial activity using agar well diffusion method. The phenothiazine incorporated Chalcone and dihydropyridine derivatives have shown good antibacterial activity.

2.4 EXPERIMENTAL PROCEDURE

2.4.1 GENERAL

All the reagents, solvents used were of analytical grade from commercial sources and purchased from Aldrich, SD-Fine and Sisco Research Laboratory used without further purification. All the melting points were determined using open capillary tubes on a Buchi-530 melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FT-IR 8300 spectrophotometer using KBr pellet. $^1$H and $^{13}$C NMR spectra were recorded on an Bruker Spectrospin DPX 400 MHz spectrometer in CDCl$_3$ and DMSO-$d_6$ as solvents and chemical shift values are recorded in units δ (ppm) relative to tetramethylsilane (Me$_4$Si) as an internal standard. Sonication reaction was performed by SONICS, Vibra Cell, VC 130, ultrasonic processor equipped with a 3 mm wide and 140 mm long probe, which was immersed directly into the reaction mixture. UV spectra were determined on a UV/Vis-spectrophotometer (Model V-670, JASCO UVVISNIR) under thermostatic conditions at 25°C.

2.4.2 Procedure for the preparation of 10-alkyl phenothiazine 2(a-b):

Phenothiazine (1.0 mmol), iodoethane or iodomethane (3.0 mmol), and DMF (30 mL) were added together in a 50-mL two-necked round bottom flask. The solution was warmed to 75°C, treated portion wise with potassium tert-butoxide (1.5 mmol) and
then stirred at 80°C for 24 h. After the reaction was completed (through TLC monitoring), the reaction mixture was cooled to room temperature and poured into ice water and extracted with chloroform (75 mL) and dried over Na₂SO₄. Crude products obtained by removing the solvent were purified by column chromatography by eluting hexane/ethyl acetate (4:1) to give 2 (a-b) as a white solid (yield: 80-84%).

10-methyl-10H-phenothiazine (2a): mp. 95-97 °C; IR (KBr) ν_max: 3053, 2981, 2937, 2826, 1788, 1591, 1570, 1483, 1456, 1440, 1384, 1327, 1280, 1232, 1130, 1109, 1033 cm⁻¹; ¹H NMR (500 MHz, CDCl₃, ppm), δ_H = 6.95-7.28 (m, 6H, Ar-H of phenothiazine ring), 6.84 (d, 2H, J = 8.0Hz, C3 & C6- Ar-H of phenothiazine ring), 3.40 (s, 3H, CH₃); ¹³C NMR (125.757 MHz, CDCl₃, ppm), δ_C = 145.8, 127.4, 123.4, 122.4, 114.0, 35.3; HRMS (EI): m/z [M⁺] calcd. for C₁₃H₁₁NS: 213.0612; found: 212.2038.

10-ethyl-10H-phenothiazine (2b): mp. 101-103ºC; IR (KBr) ν_max: 3055, 2960, 2879, 2816, 2816, 1568, 1489, 1456, 1446, 1330, 1286, 1259, 1163, 1136, 1107, 1039 cm⁻¹; ¹H NMR (500 MHz, CDCl₃, ppm), δ_H = 6.90-7.28 (m, 8H, Ar-H of phenothiazine ring), 3.96 (d, 2H, J = 5.6Hz, CH₂), 1.46 (t, 3H, J = 5.4 Hz, CH₃); ¹³C NMR (125.757 MHz, CDCl₃, ppm), δ_C = 145.0, 127.3, 127.2, 124.5, 122.3, 115.1, 41.7, 13.7; HRMS (EI): m/z [M⁺] calcd. for C₁₄H₁₃NS: 227.0769; found: 227.1685.

2.4.3 Procedure for the preparation of 10-alkyl-3-formylphenothiazine 3(a-b):

Phosphorus oxychloride (POCl₃) (4.1 mmol) was taken in a 50 mL two necked round bottom flask to that of freshly distilled N,N-dimethylformamide (4.7 mmol) added drop wise at 0°C under nitrogen atmosphere. A solution of (1.0 mmol) of N-alkyl-phenothiazine 2(a-b) dissolved in dichloroethane 30 mL was added dropwise to POCl₃/DMF complex at 30°C. The reaction mixture was stirred at 80°C for 16h. After the reaction went to completion (through TLC monitoring), the reaction mixture was cooled.
to room temperature and poured into ice water, neutralized with NaHCO₃, extracted with chloroform (75 mL) and then dried over Na₂SO₄. The solvent was evaporated by vacuum distillation. The crude product was purified by column chromatography by eluting hexane/ethyl acetate (3.5:1.5); yield (78-81%).

10-methyl-10H-phenothiazine-3-carbaldehyde (3a): mp. 105-107°C; IR (KBr) \( \nu_{\text{max}} \): 3056, 2986, 2884, 2819, 2735, 1678, 1641, 1595, 1566, 1327, 1288, 1252, 1144, 1036 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃, ppm), \( \delta_H = 9.79 \) (s, 1H, CHO proton), 7.00-7.74 (m, 7H, Ar-H of phenothiazine ring), 3.37 (s, 3H, CH₃ proton); \(^1^\)C NMR (100.612 MHz, CDCl₃, ppm), \( \delta_C = 190.6, 150.4, 143.6, 130.8, 130.4, 128.0, 127.2, 126.9, 123.5, 122.3, 121.1, 115.4, 114.5, 35.6; HRMS (EI): m/z [M⁺] calcd. for C₁₄H₁₁NOS: 241.0561; found: 241.0069.

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10-ethyl-3-formylphenothiazine (3b): mp. 110-112°C; IR (KBr) \( \nu_{\text{max}} \): 3057, 2977, 2931, 2827, 2738, 1669, 1598, 1572, 1552, 1466, 1368, 1310, 1238, 1199, 1135, 1102, 1042 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃, ppm), \( \delta_H = 9.78 \) (s, 1H, CHO proton), 7.62 (d, 1H, \( J = 8.4 \)Hz C7- Ar-H of phenothiazine ring), 7.56 (s, 1H, C8- Ar-H of phenothiazine ring), 6.89-7.26 (m, 5H, Ar-H of phenothiazine ring), 3.97 (d, 2H, \( J = 6.4 \)Hz, CH₂), 1.45 (d, 3H, \( J = 6.4 \)Hz CH₃); \(^1^\)C NMR (100.612 MHz, CDCl₃, ppm), \( \delta_C = 190.0, 150.3, 143.0, 130.9, 130.2, 128.2, 127.6, 127.5, 124.4, 123.5, 123.2, 115.6, 114.4, 42.4, 12.8; HRMS (EI): m/z [M⁺] calcd. for C₁₅H₁₃NOS: 255.0718; found: 255.2485.

S
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\[ \text{O} \]
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2.4.4 Procedure for the preparation of 3-(10-methyl-10H-phenothiazin-3-yl)-1-substituted phenylprop-2-en-1-one 6(a-h):

**Conventional method**

Equimolar quantities of 10-methyl-10H-phenothiazine-3-carbaldehyde (1 mmol) and substituted acetophenone (1 mmol) were dissolved in minimum amount of alcohol and to this 5 mL of 40% potassium hydroxide solution was added slowly, reaction mixture stirred for 2h until the entire mixture becomes very cloudy. Then it was poured slowly into 400 mL of water with constant stirring and stored in refrigerator for 24 hours. The precipitate obtained was filtered, washed and recrystallized from ethanol to afford the products.

**Ultrasonic method**

To a mixture of 10-methyl-10H-phenothiazine-3-carbaldehyde (1 mmol), substituted acetophenone (1 mmol) in ethanol (10 mL), 2 mmol of KOH was added in a 50 mL beaker. The ultrasonic probe was immersed directly into the reaction mixture. The ultrasound reaction duration was maintained for the period indicated in Table 1.1. Sonication was performed at frequencies of 16 kHz (amplitude of 40%). The completion of the reaction was monitored by TLC. On completion of the reaction, the reaction mixture was poured into water and the solid separated was filtered, dried and purified by recrystallization with ethanol.

2.4.4.1 3-(10-methyl-10H-phenothiazin-3-yl)-1-phenylprop-2-en-1-one (6a):

To a mixture of 10-methyl-10H-phenothiazine-3-carbaldehyde (1 mmol) and acetophenone (1 mmol) in ethanol (10 mL), 2 mmol of KOH was added in a 50 mL round bottomed flask and the reaction was carried out as per general procedure given at 2.4.4. Column chromatographic purification was carried out using ethyl acetate/hexane as solvent to separate the title compound; mp 161-163°C; IR (KBr) νmax: 3059, 1654, 1591, 1571, 1500, 1465, 1442, 1402, 1336, 1292, 1215, 1159 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, ppm), δH = 8.06 (d, 2H, J = 7.2 Hz, CH and Ar-H of phenyl ring), 7.72 (s, 1H, Ar-H of phenyl ring), 7.68 (s, 1H, Ar-H of phenyl ring), 6.78-7.58 (m, 10H, CH, Ar-H of phenyl
and phenothiazine ring), 3.41 (s, 3H, CH$_3$); $^{13}$C NMR (100.645 MHz, CDCl$_3$, ppm), $\delta_C = 190.4, 144.8, 143.9, 138.5, 132.7, 129.4, 129.2, 129.1, 128.7, 128.5, 128.2, 127.7, 127.3, 126.3, 123.2, 122.6, 199.9, 114.5, 114.2, 35.6; HRMS (EI): m/z [M$^+$] calcd. for C$_{22}$H$_{17}$NOS: 343.1031; found: 343.1033.

2.4.4.2 1-(2,4-dimethoxyphenyl)-3-(10-methyl-10H-phenothiazin-3-yl)prop-2-en-1-one (6b):
To a mixture of 10-methyl-10H-phenothiazine-3-carbaldehyde (1 mmol) and 2,4-dimethoxy acetophenone (1 mmol) in ethanol (10 mL), 2 mmol of KOH was added in a 50 mL round bottomed flask and the reaction was carried out as per general procedure given at 2.4.4. Column chromatographic purification was carried using ethyl acetate/hexane as solvent to separate the title compound; mp 148-150ºC; IR (KBr) $\bar{\nu}_{\text{max}}$: 3095, 1659, 1579, 1468, 1400, 1330, 1257, 1184, 1128 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, ppm), $\delta_H = 7.72$ (d, 1H, $J = 8.8$ Hz, Ar-H of phenyl ring), 6.48-7.58 (m, 11H, 2xCH, Ar-H of phenyl and phenothiazine ring), 3.85 (s, 3H, OCH$_3$), 3.89 (s, 3H, OCH$_3$), 3.37 (s, 3H, N-CH$_3$); $^{13}$C NMR (100.645 MHz, CDCl$_3$, ppm), $\delta_C = 190.5, 164.1, 160.4, 147.4, 145.0, 141.2, 132.8, 130.0, 128.8, 127.7, 127.3, 126.3, 125.3, 123.8, 123.0, 122.8, 122.5, 114.4, 114.1, 105.2, 98.75, 55.9, 55.6, 35.6; HRMS (EI): m/z [M$^+$] calcd. for C$_{24}$H$_{21}$NO$_3$S: 403.1242; found: 403.1240.

2.4.4.3 1-(4-methoxyphenyl)-3-(10-methyl-10H-phenothiazin-3-yl)prop-2-en-1-one (6c):
To a mixture of 10-methyl-10H-phenothiazine-3-carbaldehyde (1 mmol) and 4-methoxy acetophenone (1 mmol) in ethanol (10 mL), 2 mmol of KOH was added in a 50 mL round bottomed flask and the reaction was carried out as per general procedure given at 2.4.4. Column chromatographic purification was carried out using ethyl acetate/hexane as solvent to separate the title compound; mp 142-145ºC; IR (KBr) $\bar{\nu}_{\text{max}}$: 3145, 1653, 1589,
1463, 1400, 1330, 1257, 1184, 1124 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃, ppm), \(\delta_H = 8.02\) (dd, 2H, \(J = 2.0 \& 6.8\) Hz, \(o, o'\)- Ar-H of phenyl ring), 7.71 (s, 1H, Ar-H of phenyl ring), 6.77-7.67 (m, 10H, CH, Ar-H of phenyl and phenothiazine ring), 3.88 (s, 3H, OCH₃), 3.38 (s, 3H, N-CH₃); \(^1^3\)C NMR (100.645 MHz, CDCl₃, ppm), \(\delta_C = 188.6, 163.4, 147.7, 144.9, 143.0, 131.4, 130.8, 129.6, 129.0, 127.7, 127.3, 126.2, 124.0, 123.1, 122.1, 119.8, 114.5, 114.1, 113.9, 55.6, 35.6; HRMS (EI): m/z [M⁺] calcd. for C₂₃H₁₉NO₂S: 373.1136; found: 373.1135.

2.4.4.4 1-(2-hydroxyphenyl)-3-(10-methyl-10H-phenothiazin-3-yl)prop-2-en-1-one (6d):
To a mixture of 10-methyl-10H-phenothiazine-3-carbaldehyde (1 mmol) and 2-hydroxy acetophenone (1 mmol) in ethanol (10 mL), 2 mmol of KOH was added in a 50 mL round bottomed flask and the reaction was carried out as per general procedure given at 2.4.4. Column chromatographic purification was carried using ethyl acetate/hexane as solvent to separate the title compound; mp 135-138°C; IR (KBr) \(\nu_{max}\): 3450, 1657, 1627, 1593, 1571, 1498, 1465, 1401, 1336, 1290 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃, ppm), \(\delta_H = 12.94\) (s, 1H, OH), 7.926 (d, 1H, \(J = 7.6\) Hz, CH), 6.81-7.84 (m, 12H, CH, Ar-H of phenyl and phenothiazine ring), 3.42 (s, 3H, N-CH₃); \(^1^3\)C NMR (100.645 MHz, CDCl₃, ppm), \(\delta_C = 193.6, 163.7, 148.3, 144.7, 144.6, 136.3, 129.7, 129.6, 129.1, 127.8, 127.4, 126.5, 124.2, 123.3, 122.6, 120.2, 118.9, 118.7, 117.8, 114.6, 114.2, 114.2, 35.7; HRMS (EI): m/z [M⁺] calcd. for C₂₂H₁₇NO₂S: 359.0980; found: 359.0978.

2.4.4.5 1-(2-aminophenyl)-3-(10-methyl-10H-phenothiazin-3-yl)prop-2-en-1-one (6e):
To a mixture of 10-methyl-10H-phenothiazine-3-carbaldehyde (1 mmol) and 2-amino acetophenone (1 mmol) in ethanol (10 mL), 2 mmol of KOH was added in a 50 mL round bottomed flask and the reaction was carried out as per general procedure given at 2.4.4. Column chromatographic purification was carried out using ethyl acetate/hexane as
solvent to separate the title compound; mp 110-112°C; IR (KBr) \( \nu_{\text{max}} \): 3351, 1629, 1598, 1571, 1465, 1465, 1402, 1336, 1290, 1255, 1224, 1141 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\), ppm), \( \delta_H = 8.32 \) (s, 1H, Ar-H of phenyl ring), 8.06 (d, 1H, \( J = 7.6 \)Hz, CH), 6.68-7.93 (m, 11H, Ar-H of phenyl and phenothiazine ring), 4.13 (s, 2H, NH\(_2\)), 3.40 (s, 3H, N-CH\(_3\)); \(^{13}\)C NMR (100.645 MHz, CDCl\(_3\), ppm), \( \delta_C = 189.2, 151.07, 147.3, 145.2, 141.2, 132.6, 131.0, 128.5, 127.7, 127.5, 126.1, 125.3, 124.7, 123.8, 123.4, 122.6, 122.5, 114.4, 114.1, 35.4; HRMS (EI): m/z [M\(^+\)] calcd. for C\(_{22}\)H\(_{18}\)N\(_2\)O\(_2\): 358.1140; found: 358.1145.

\[ \text{2.4.4.6 3-(10-methyl-10H-phenothiazin-3-yl)-1-(naphthalen-2-yl)prop-2-en-1-one (6f):} \]
To a mixture of 10-methyl-10H-phenothiazine-3-carbaldehyde (1 mmol) and 2-acetyl naphthalene (1 mmol) in ethanol (10 mL), 2 mmol of KOH was added in a 50 mL round bottomed flask and the reaction was carried out as per general procedure given at 2.4.4. Column chromatographic purification was carried out using ethyl acetate/hexane as solvent to separate the title compound; mp 173-175°C; IR (KBr) \( \nu_{\text{max}} \): 3145, 1653, 1589, 1463, 1400, 1330, 1257, 1184, 1124 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\), ppm), \( \delta_H = 8.52 \) (s, 1H, C-1 Ar-H of naphthalene ring), 8.10 (d, 1H, \( J = 2.0 \)Hz, CH), 8.08 (d, 1H, \( J = 1.6 \)Hz, C-5 Ar-H of naphthalene ring), 6.79-8.01 (m, 13H, CH, Ar-H of naphthalene and phenothiazine ring), 3.40 (s, 3H, N-CH\(_3\)); \(^{13}\)C NMR (100.645 MHz, CDCl\(_3\), ppm), \( \delta_C = 190.3, 147.9, 144.8, 143.8, 135.9, 135.5, 132.7, 129.8, 129.6, 129.5, 129.3, 128.6, 128.4, 127.9, 127.8, 127.3, 126.8, 126.3, 124.6, 124.1, 123.2, 122.7, 120.0, 114.5, 114.2, 35.6; HRMS (EI): m/z [M\(^+\)] calcd. for C\(_{26}\)H\(_{19}\)NO\(_2\): 393.1187; found: 393.1183.

\[ \text{2.4.4.7 3-(10-methyl-10H-phenothiazin-3-yl)-1-(thiophen-2-yl)prop-2-en-1-one (6g):} \]
To a mixture of 10-methyl-10H-phenothiazine-3-carbaldehyde (1 mmol) and 2-amino acetophenone (1 mmol) in ethanol (10 mL), 2 mmol of KOH was added in a 50 mL round bottomed flask and the reaction was carried out as per general procedure given at 2.4.4.
Column chromatographic purification was carried out using ethyl acetate/hexane as solvent to separate the title compound; mp 158-160ºC; IR (KBr) νmax: 3044, 1649, 1588, 1561, 1455, 1423, 1402, 1326, 1280, 1232, 1161 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, ppm), δH = 8.12 (s, 1H, C-5 Ar-H of thiophene ring), 7.99 (d, 1H, J = 2.0 Hz, C-3 Ar-H of thiophene ring), 6.69-7.82 (m, 10H, 2CH, Ar-H of thiophene and phenothiazine ring), 3.34 (s, 3H, N-CH₃); ¹³C NMR (100.645 MHz, CDCl₃, ppm), δC = 185.2, 148.1, 144.2, 140.9, 134.6, 132.0, 131.2, 129.5, 128.7, 127.5, 126.8, 125.9, 124.3, 123.6, 123.4, 122.6, 114.9, 114.1, 35.4; HRMS (EI): m/z [M⁺] calcd. for C₂₀H₁₅NOS₂: 349.0595; found: 349.0590.

2.4.4.8 1-(4-bromophenyl)-3-(10-methyl-10H-phenothiazin-3-yl)prop-2-en-1-one (6h): To a mixture of 10-methyl-10H-phenothiazine-3-carbaldehyde (1 mmol) and 4-bromoacetophenone (1 mmol) in ethanol (10 mL), 2 mmol of KOH was added in a 50 mL round bottomed flask and the reaction was carried out as per general procedure given at 2.4.4. Column chromatographic purification was carried out using ethyl acetate/hexane as solvent to separate the title compound; mp 122-124ºC; IR (KBr) νmax: 3023, 1654, 1627, 1593, 1571, 1498, 1465, 1442, 1404, 1336, 1290, 1259, 1215, 1141 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, ppm), δH = 8.01 (s, 1H, C-2 Ar-H of phenothiazine ring), 7.99 (d, 1H, J = 2.0 Hz, CH), 6.77-7.72 (m, 11H, CH, Ar-H of phenyl and phenothiazine ring), 3.38 (s, 3H, N-CH₃); ¹³C NMR (100.645 MHz, CDCl₃, ppm), δC = 190.4, 147.9, 144.8, 143.8, 138.5, 132.7, 129.4, 129.1, 128.6, 128.5, 127.7, 127.3, 126.3, 124.0, 123.1, 122.7, 120.0, 114.5, 114.1, 35.6; HRMS (EI): m/z [M⁺] calcd. for C₂₂H₁₆BrNOS: 421.0136; found: 421.1032.

O
\[
\begin{align*}
\text{N} & \quad \text{S} \\
\text{S} & \quad \text{N} \\
\text{2.4.4.8} & \quad 1-(4\text{-bromophenyl})-3-(10\text{-methyl-10H-phenothiazin-3-yl})\text{prop-2-en-1-one (6h)}
\end{align*}
\]
2.4.5 Procedure for the preparation of ethyl-7,7-dimethyl-4-(10-methyl-10h-phenothiazin-3-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (7a-d):

**Conventional method**

A mixture of 10-alkyl-10H-phenothiazine-3-carbaldehyde (1 mmol), ethyl acetoacetate (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (1 mmol), ammonium acetate (10 mmol) and p-TSA (10 mol%) was stirred in absolute ethanol (5 mL) at 80°C. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into ice cold water and the solid separated was filtered off. The crude product was purified by column chromatography with hexane/ethylacetate as solvent to yield the title compound.

**Ultrasonic method**

Dimedone (1 mmol), ethyl acetoacetate or methyl acetoacetate (1 mmol), 10-alkyl-10H-phenothiazine-3-carbaldehyde (1 mmol), ammonium acetate (3 mmol), p-TSA (10 mol %) and 5 mL of methanol were added in a 50 mL beaker. The reaction mixture was continuously irradiated at room temperature for 13-20 min with a sonic probe with a frequency of 18 kHz. The completion of reaction was followed by TLC using hexane: ethyl acetate (3:2) as eluent and the mixture was poured into ice water. The crude product was purified by column chromatography with hexane/ethylacetate as solvent to yield the title compound.

2.4.5.1 *Ethyl-4-(10-ethyl-10H-phenothiazin-3-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydro quinoline-3-carboxylate (7a):*

Dimedone (1 mmol), ethyl acetoacetate (1 mmol), 10-ethyl-10H-phenothiazine-3-carbaldehyde (1 mmol), ammonium acetate (3 mmol), p-TSA (10 mol %) and 5 mL of methanol were added in a 50 mL round bottomed flask and the reaction was carried out as per general procedure given at 2.4.5. Column chromatographic purification using ethyl acetate/hexane as solvent gave the title compound; mp 212-215°C; IR (KBr) v_max: 3282, 3215, 2960, 2818, 1699, 1647, 1492, 1465, 1381, 1280, 1215, 1141 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, ppm), δ_H = 6.78-7.25 (m, 6H, Ar-H of phenothiazine ring), 6.69 (d, 1H,
$J$ = 7.2 Hz, C-2, Ar-H of phenothiazine ring), 5.89 (s, 1H, NH), 4.94 (s, 1H, CH), 4.05 (d, 2H, $J$ = 1.6 Hz, OCH$_2$), 3.84 (s, 2H, N-CH$_2$), 2.35 (s, 3H, CH$_3$), 2.23 (d, 2H, $J$ = 10.8 Hz, CH$_2$), 2.17 (d, 2H, $J$ = 6.0 Hz, CH$_2$), 1.35 (s, 3H, CH$_3$), 1.21 (s, 3H, CH$_3$), 1.05 (s, 3H, CH$_3$), 0.95 (s, 3H, CH$_3$); $^{13}$C NMR (100.645 MHz, CDCl$_3$, ppm), $\delta_C$ = 195.6, 167.4, 147.9, 145.1, 143.3, 143.1, 141.5, 127.4, 127.3, 127.1, 126.7, 124.4, 123.4, 122.0, 114.9, 114.5, 112.1, 106.0, 60.0, 50.8, 41.7, 41.2, 35.7, 32.9, 29.3, 27.6, 19.7, 14.4, 13.1; HRMS (EI): m/z [M$^+$] calcd. for C$_{29}$H$_{32}$N$_2$O$_3$: 488.2134; found: 488.2138.

2.4.5.2 Ethyl-2,7,7-trimethyl-4-(10-methyl-10H-phenothiazin-3-yl)-5-oxo-1,4,5,6,7,8-hexahydro quinoline-3-carboxylate (7b):
Dimedone (1 mmol), ethyl acetoacetate (1 mmol), 10-methyl-10H-phenothiazine-3-carbaldehyde (1 mmol), ammonium acetate (3 mmol), $p$-TSA (10 mol %) and 5 mL of methanol were added in a 50 mL round bottomed flask and the reaction was carried out as per general procedure given at 2.4.5. Column chromatographic purification using ethyl acetate/hexane as solvent gave the title compound; mp 225-228°C; IR (KBr) $\nu_{\text{max}}$: 3278, 3211, 2960, 2870, 1699, 1647, 1604, 1492, 1465, 1381, 1280, 1215 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, ppm), $\delta_H$ = 7.08-7.26 (m, 3H, Ar-H of phenothiazine ring), 6.74-7.01 (m, 3H, Ar-H of phenothiazine ring), 6.65 (d, 1H, $J$ = 7.6 Hz, C-2, Ar-H of phenothiazine ring), 6.06 (s, 1H, NH), 4.95 (s, 1H, CH), 4.05 (d, 2H, $J$ = 6.0 Hz, OCH$_2$), 3.29 (s, 3H, N-CH$_3$), 2.35 (s, 3H, CH$_3$), 2.04-2.28 (m, 4H, 2xCH$_2$), 1.21 (s, 3H, CH$_3$), 1.04 (s, 3H, CH$_3$), 0.93 (s, 3H, CH$_3$); $^{13}$C NMR (100.645 MHz, CDCl$_3$, ppm), $\delta_C$ = 195.6, 167.4, 148.1, 146.1, 143.9, 143.4, 141.7, 127.5, 127.4, 127.1, 126.6, 123.5, 122.6, 122.2, 113.9,
113.6, 112.1, 105.9, 60.0, 50.8, 41.2, 35.8, 35.3, 32.8, 29.3, 27.5, 19.6, 14.4; HRMS (EI): m/z [M⁺] calcd. for C₂₈H₃₀N₂O₃S: 474.1977; found: 474.1973.

2.4.5.3. Methyl-4-(10-ethyl-10H-phenothiazin-3-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydro quinoline-3-carboxylate (7c):

Dimedone (1 mmol), methyl acetoacetate (1 mmol), 10-ethyl-10H-phenothiazine-3-carbaldehyde (1 mmol), ammonium acetate (3 mmol), p-TSA (10 mol %) and 5 mL of methanol were added in a 50 mL round bottomed flask and the reaction was carried out as per general procedure given at 2.4.5. Column chromatographic purification using ethyl acetate/hexane as solvent gave the title compound; mp 245-247°C; IR (KBr) νₓmax: 3414, 3288, 3217, 2960, 2813, 1701, 1647, 1604, 1492, 1465, 1381, 1330, 1284, 1219 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆, ppm), δH = 9.10 (s, 1H, NH), 6.84-7.17 (m, 7H, Ar-H of phenothiazine ring), 4.76 (s, 1H, CH), 3.84 (s, 2H, N-CH₂), 3.53 (s, 3H, OCH₃), 2.38-2.51 (m, 2H, CH₂), 2.29 (s, 3H, CH₃), 1.98-2.18 (m, 2H, CH₂), 1.25 (s, 3H, CH₃), 1.00 (s, 3H, CH₃), 0.86 (s, 3H, CH₃); ¹³C NMR (100.645 MHz, DMSO-d₆, ppm), δC = 194.3, 167.2, 149.4, 145.2, 144.3, 142.3, 141.8, 127.5, 126.9, 126.5, 122.7, 122.1, 121.8, 115.2, 114., 109.7, 102.9, 50.19, 50.71, 40.92, 34.72, 32.1, 28.9, 26.6, 18.6, 12.6; HRMS (EI): m/z [M⁺] calcd. for C₂₈H₃₀N₂O₃S: 474.1977; found: 474.1974.
2.4.5.4 Methyl-2,7,7-trimethyl-4-(10-methyl-10H-phenothiazin-3-yl)-5-oxo-1,4,5,6,7,8-hexa hydroquinoline-3-carboxylate (7d):

Dimedone (1 mmol), methyl acetoacetate (1 mmol), 10-methyl-10H-phenothiazine-3-carbaldehyde (1 mmol), ammonium acetate (3 mmol), p-TSA (10 mol %) and 5 mL of methanol were added in a 50 mL round bottomed flask and the reaction was carried out as per general procedure given at 2.4.5. Column chromatographic purification using ethyl acetate/hexane as solvent gave the title compound; mp 256-258ºC; IR (KBr) \( \nu_{\text{max}} \): 3277, 3216, 3080, 2960, 2873, 1703, 1647, 1494, 1465, 1381, 1284, 1217, 1111 cm\(^{-1}\); \(^1\)H NMR (400 MHz, DMSO-\(d_6\), ppm), \( \delta^H = 9.11 \) (s, 1H, NH), 6.87-7.20 (m, 6H, Ar-H of phenothiazine ring), 6.80 (d, 1H, \( J = 8.0\)Hz, C-4 Ar-H of phenothiazine ring), 4.77 (s, 1H, CH), 3.5 (s, 3H, OCH\(_3\)), 3.25 (s, 3H, N-CH\(_3\)), 2.38-2.51 (m, 2H, CH\(_2\)), 2.29 (s, 3H, CH\(_3\)), 1.97-2.18 (m, 2H, CH\(_2\)), 1.00 (s, 3H, CH\(_3\)), 0.85 (s, 3H,CH\(_3\)); \(^{13}\)C NMR (100.645 MHz, DMSO-\(d_6\), ppm), \( \delta^C = 194.3, 17.2, 149.4, 145.4, 145.3, 143.2, 142.1, 127.7, 126.7, 126.6, 125.5, 122.2, 121.9, 121.1, 114.4, 114.2, 109.8, 103.0, 50.7, 50.2 35.0, 34.8, 32.2, 29.0, 26.5, 18.3; HRMS (EI): m/z [M\(^+\)] calcd. for C\(_{27}\)H\(_{28}\)N\(_2\)O\(_3\)S: 460.1821; found: 460.1823.
2.5 SPECTRAL DATA

$^1$H NMR, $^{13}$C NMR and Mass Spectra of compound 6b, 6d, 6h, 7a, and 7b
2.5.1 $^1$H NMR spectrum of 1-(2,4-dimethoxyphenyl)-3-(10-methyl-10H-phenothiazin-3-yl)prop-2-en-1-one (6b):

![H NMR spectrum of 1-(2,4-dimethoxyphenyl)-3-(10-methyl-10H-phenothiazin-3-yl)prop-2-en-1-one (6b)](image)

2.5.2 $^{13}$C NMR spectrum of 1-(2,4-dimethoxyphenyl)-3-(10-methyl-10H-phenothiazin-3-yl)prop-2-en-1-one (6b):

![C NMR spectrum of 1-(2,4-dimethoxyphenyl)-3-(10-methyl-10H-phenothiazin-3-yl)prop-2-en-1-one (6b)](image)
2.5.3 Mass spectrum of 1-(2,4-dimethoxyphenyl)-3-(10-methyl-10H-phenothiazin-3-yl)prop-2-en-1-one (6b):

2.5.4 $^1$H NMR spectrum of 1-(4-bromophenyl)-3-(10-methyl-10H-phenothiazin-3-yl)prop-2-en-1-one (6h):
2.5.5 $^{13}$C NMR spectrum of 1-(4-bromophenyl)-3-(10-methyl-10H-phenothiazin-3-yl)prop-2-en-1-one (6h):

![C NMR spectrum of 1-(4-bromophenyl)-3-(10-methyl-10H-phenothiazin-3-yl)prop-2-en-1-one (6h)](image)

2.5.6 Mass spectrum of 1-(4-bromophenyl)-3-(10-methyl-10H-phenothiazin-3-yl)prop-2-en-1-one (6h):

![Mass spectrum of 1-(4-bromophenyl)-3-(10-methyl-10H-phenothiazin-3-yl)prop-2-en-1-one (6h)](image)
2.4.7 $^1$H NMR spectrum of 1-(2-hydroxyphenyl)-3-(10-methyl-10H-phenothiazin-3-yl)prop-2-en-1-one (6d):

![NMR spectrum of 1-(2-hydroxyphenyl)-3-(10-methyl-10H-phenothiazin-3-yl)prop-2-en-1-one (6d)](image)

2.5.8 $^{13}$C NMR spectrum of 1-(2-hydroxyphenyl)-3-(10-methyl-10H-phenothiazin-3-yl)prop-2-en-1-one (6d):

![NMR spectrum of 1-(2-hydroxyphenyl)-3-(10-methyl-10H-phenothiazin-3-yl)prop-2-en-1-one (6d)](image)
2.5.9 Mass spectrum of 1-(2-hydroxyphenyl)-3-(10-methyl-10H-phenothiazin-3-yl)prop-2-en-1-one (6d):

![Mass Spectrum Image]

2.5.10 $^1$H NMR spectrum of Ethyl-4-(10-ethyl-10H-phenothiazin-3-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydro quinoline-3-carboxylate (7a):

![NMR Spectrum Image]
2.5.11 $^{13}$C NMR spectrum of Ethyl-4-(10-ethyl-10H-phenothiazin-3-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydro quinoline-3-carboxylate (7a):

![C NMR spectrum image]

2.5.12 Mass spectrum of Ethyl-4-(10-ethyl-10H-phenothiazin-3-yl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydro quinoline-3-carboxylate (7a):

![Mass spectrum image]
2.5.13 $^1$H NMR spectrum of Ethyl-2,7,7-trimethyl-4-(10-methyl-10H-phenothiazin-3-yl)-5-oxo-1,4,5,6,7,8-hexahydro quinoline-3-carboxylate (7b):

![NMR spectrum](image)

2.5.14 $^{13}$C NMR spectrum of Ethyl-2,7,7-trimethyl-4-(10-methyl-10H-phenothiazin-3-yl)-5-oxo-1,4,5,6,7,8-hexahydro quinoline-3-carboxylate (7b):

![NMR spectrum](image)
2.5.15 Mass spectrum of Ethyl-2,7,7-trimethyl-4-(10-methyl-10H-phenothiazin-3-yl)-5-oxo-1,4,5,6,7,8-hexahydro quinoline-3-carboxylate (7b):