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Suzuki-Miyaura Coupling Mediated Synthesis and Spectral Characterization of Novel Chalcones Derived from Substituted Phenothiazines

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A new series of chalcone-functionalized 10*H*-phenothiazine derivatives (**3a-h** and **4a-h**) was synthesized and characterized to explore their potential in medicinal chemistry. The compounds **3a-h** and **4a-h** were synthesized through Suzuki–Miyaura cross-coupling, subsequently acylated with appropriate cinnamic acid derivatives to afford the desired products. Spectral characterization using FTIR, ^{1}H NMR, mass spectrometry and HPLC confirmed the successful synthesis of all the derivatives. FTIR revealed the characteristic C=O and C=C stretches, while ^{1}H NMR indicated *trans*-olefinic protons (J = 15.6 Hz), confirming the *E*-configuration of the chalcone moiety. HRMS data aligned with theoretical molecular weights and HPLC showed excellent purity ranging from 94.2% to 99.3%. Notably, electron-withdrawing substituents such as Cl and CF_3 influenced melting points and yields, suggesting significant structural impact on physico-chemical properties. These findings not only validate the synthetic strategy but also offer a structurally diverse framework for future bioactivity studies, particularly in anticancer or CNS-related drug development.

Keywords: Chalcone derivatives, Phenothiazine, Suzuki–Miyaura coupling, HPLC purity.

INTRODUCTION

Chalcones, a prominent class of open-chain flavonoids, have attracted considerable attention in medicinal and synthetic chemistry due to their structural versatility and broad spectrum of biological activities [1]. Chemically characterized by the α,β-unsaturated carbonyl system linking two aromatic rings, chalcones serve as precursors for several heterocyclic compounds and are known for their antioxidant, antimicrobial, anti-inflammatory, anticancer and antiviral properties [2,3]. Moreover, the strategic modification of chalcone scaffolds has also enabled the development of potent bioactive molecules with enhanced therapeutic potential [4,5].

Phenothiazines, on the other hand, are tricyclic heteroaromatic compounds that exhibit a wide array of pharmacological properties including antipsychotic, antiemetic and antimicrobial effects [6,7]. The core phenothiazine nucleus possesses a rigid planar structure and electron-rich sulphur and nitrogen atoms, which contribute to its significant bioactivity. Structural modification of phenothiazine derivatives has been a fruitful approach in the design of new therapeutic agents, especially when combined with other pharmacophores [8,9].

The synthesis of chalcones incorporating the phenothiazine moiety represents an innovative approach to the design of hybrid molecules with dual pharmacological functionality [10]. By introducing substituted aryl groups on both the phenothiazine ring and its counterpart through Suzuki-Miyaura cross-coupling, followed by acylation with appropriate cinnamic acid derivatives, the physico-chemical and biological properties of the resulting chalcones can be effectively tailored. Such hybrid compounds hold promise not only for enhanced bioactivity but also for improved selectivity and pharmacokinetic behaviour [11,12].

The present study aims to synthesize a novel series of substituted chalcones derived from substituted phenothiazine derivatives through conventional base-catalyzed condensation [13]. The synthesized compounds were structurally confirmed through spectroscopic techniques including FTIR, ^{1}H NMR and mass spectrometry.

EXPERIMENTAL

All reagents and solvents used in the synthesis were of analytical grade and procured from reputed commercial supp-

liers. 2-Chloro-10*H*-phenothiazine, phenylboronic acid, *p*-tolylboronic acid, substituted cinnamic acids, thionyl chloride, potassium phosphate tribasic (K_3PO_4), *N*,*N*-diisopropylethylamine (DIPEA) and sodium hydride were purchased from Sigma-Aldrich, Merck, or Loba Chemie. Solvents including ethanol, dichloromethane (DCM), N,N-dimethylformamide (DMF) and ethyl acetate were dried prior to use as per standard protocols. Palladium(II) acetate and 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (XPhos) were obtained from commercial sources and used without further purification.

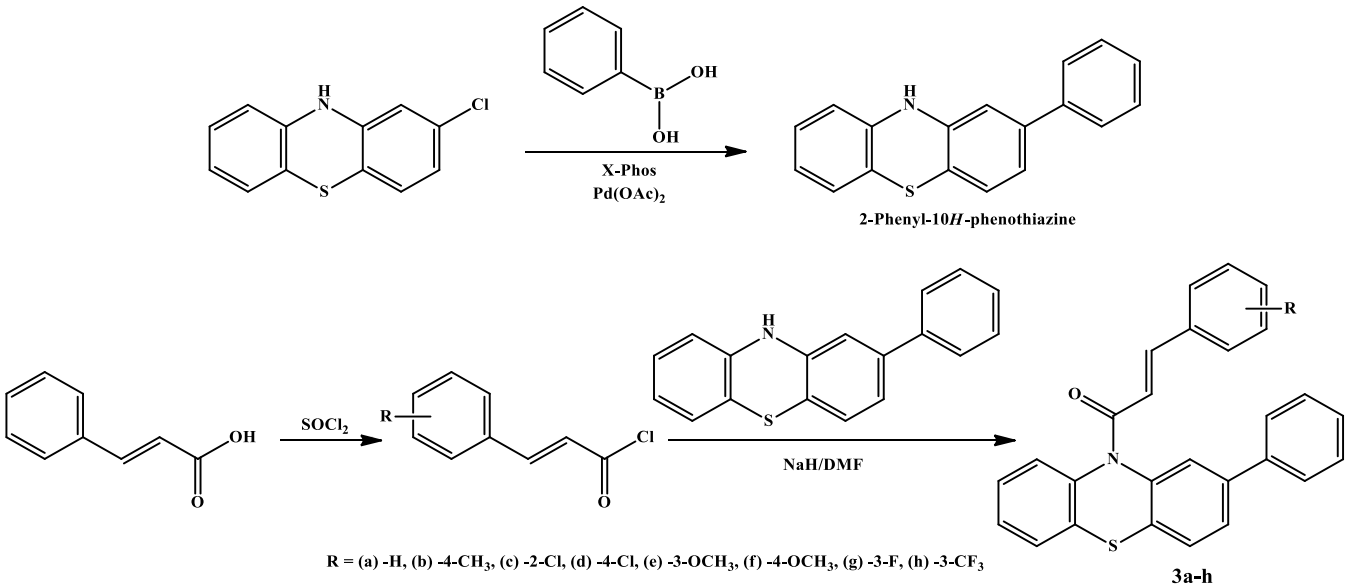
Characterization: TLC was performed on silica gel 60 F_{254} pre-coated plates (Merck) using 2-5% ethyl acetate in petroleum ether or 5% methanol in methylene dichloride as the mobile phase. R_f values were determined by UV visualization at 254 nm using a CAMAG UV cabinet. The melting points of all synthesized compounds were determined using a melting point apparatus (Model: Veego VMP-D, India) and are reported uncorrected. IR spectra were recorded using a Bruker Alpha II FTIR spectrophotometer in the range of 4000-400 cm^{-1} using KBr pellets. ^1H NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer using $CDCl_3$ as the solvent and tetramethylsilane (TMS) as the internal standard. The chemical shifts (δ) were reported in ppm and coupling constants (*J*) were expressed in Hertz (Hz). Mass spectra were obtained using a Waters Xevo G2-XS QTof Mass Spectrometer equipped with an electrospray ionization (ESI) source. The purity of the synthesized compounds was determined using an Agilent 1260 Infinity II HPLC system equipped with a UV-Vis detector. Separation was achieved on a C_{18} reverse-phase column (250 mm × 4.6 mm, 5 μm) at ambient temperature. The mobile phase consisted of acetonitrile and water in a gradient mode and the flow rate was maintained at 1.0 mL/min. Detection was carried out at 254 nm. Purity values exceeding 94% confirmed compound integrity [14,15].

Synthesis of 2-aryl-10*H*-phenothiazine intermediates: In a nitrogen-purged, oven-dried 10 mL round-bottom flask, 2-chloro-10*H*-phenothiazine (5 g, 1 equiv.), arylboronic acid (phenylboronic acid for **3a-h**; *p*-tolylboronic acid for **4a-h**, 1.2 equiv.) and K_3PO_4 (3 equiv.) were dissolved in a mixture of ethanol and water (10:5 v/v). $Pd(OAc)_2$ (4 mol%) and XPhos (7 mol%) were added and the reaction mixture was stirred at 80 ºC for 12-14 h. The progress of the reaction was monitored by thin-layer chromatography (TLC) using silica gel 60 F_{254} plates and visualized under UV light (254 nm). Upon completion, the reaction was cooled to room temperature, filtered through a celite bed and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by flash column chromatography (2-3% ethyl acetate in petroleum ether) to afford the corresponding 2-aryl-10*H*-phenothiazine derivatives as pale-yellow solids [16,17].

Synthesis of substituted cinnamoyl chlorides: To a solution of substituted cinnamic acid (1.2 equiv.) in $SOCl_2$ (5 equiv.), the reaction mixture was refluxed at 70 ºC for 1 h under a fume hood. The completion of acid chloride formation was monitored by TLC using 5% methanol in methylene dichloride as the mobile phase. After completion, the reaction mixture was concentrated under reduced pressure to obtain the substituted cinnamoyl chlorides, which were used directly in the next step without further purification.

Synthesis of chalcone derivatives (3a-h): To a solution of 2-phenyl-10*H*-phenothiazine (1 equiv.) in dry DMF, NaH (1.5 equiv.) was added slowly under nitrogen atmosphere at room temperature [18]. The mixture was stirred for 30 min to allow deprotonation. Substituted cinnamoyl chloride (1.2 equiv.) was then added dropwise and the reaction mixture was heated at 80 ºC for 12 h. After cooling to room temperature, the reaction mixture was poured into ice-cold water and extracted with ethyl acetate (**Scheme-I**). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography using 2-3% ethyl acetate in petroleum ether to yield the chalcone derivatives **3a-h** [19,20].

(*E*)-3-Phenyl-1-(2-phenyl-10*H*-phenothiazin-10-yl)-prop-2-en-1-one (3a): Yield: 68%, m.p.: 222-224 ºC, HPLC



Scheme-I: General synthetic route for the preparation of 2-aryl-10*H*-phenothiazine chalcone derivatives (**3a-h**)

purity: 98.677%, IR (KBr, ν_{max}, cm^{-1}): 3059.78 (Ar-CH), 1656.46 (C=O), 3030.77 (aliph. C–H), 1535.62, 1463.46 (C=C), 1581.42 (C–N), 674.76 (Ar C–S). ^{1}H NMR ($CDCl_3$, δ ppm): 6.80 (1H, d, *J* = 15.6 Hz), 7.33 (1H, ddd, *J* = 7.9, 7.5, 1.3 Hz), 7.12-7.90 (13H, 7.51 ddd, *J* = 7.9, 1.7, 1.3, 0.6 Hz), 7.41 (ddd, *J* = 8.3, 7.5, 1.7 Hz), 7.44 (tt, *J* = 7.9, 1.7, 0.6 Hz), 7.41 (ddd, *J* = 8.1, 2.3, 1.6, 0.5 Hz), 7.59 (dd, *J* = 1.7, 0.5 Hz), 7.37 (dd, *J* = 8.6, 0.5 Hz), 7.83 (ddd, *J* = 8.3, 1.3, 0.6 Hz), 7.37 (tt, *J* = 7.2, 1.6 Hz), 7.49 (dddd, *J* = 7.9, 7.2, 1.5, 0.4 Hz), 7.40-7.90 (4H, 7.36 (d, *J* = 15.6 Hz), 7.40 (dd, *J* = 8.6, 1.7 Hz), 7.90 (dtd, *J* = 7.9, 1.4, 0.4 Hz); ESI-MS (positive): *m/z* 406.30 $[M+H]^+$ (calcd. for $C_{27}H_{19}NOS$: 405.51).

1-(2-Phenyl-10*H*-phenothiazin-10-yl)-3-*o*-tolylprop-2-en-1-one (3b): Yield: 72%, m.p.: 235-238 ºC, HPLC purity: 96.77%, IR (KBr, ν_{max}, cm^{-1}): 3056.44 (Ar-CH), 1663.67 (C=O), 2920.97 (aliphatic C–H), 1558.82, 1618.18 (C=C), 1459.41 (C–N), 665.04 (Ar C–S), 1618.18 (ali-C=C), 751.13 (751.13). ^{1}H NMR ($CDCl_3$, δ ppm): 2.34 (3H, s), δ 6.80 (1H, d, *J* = 15.6 Hz), 7.33 (1H, ddd, *J* = 7.9, 7.5, 1.3 Hz), 7.12-7.90 (16H, 7.47 (ddd, *J* = 8.0, 1.4, 0.4 Hz), 7.51 (ddd, *J* = 7.9, 1.7, 0.6 Hz), 7.41 (ddd, *J* = 8.3, 7.5, 1.7 Hz), 7.44 (tt, *J* = 7.2, 1.4 Hz), 7.12 (dd, *J* = 1.7, 0.5 Hz), 7.37 (dd, *J* = 8.6, 0.5 Hz), 7.83 (ddd, *J* = 8.3, 1.3, 0.6 Hz), 7.49 (dddd, *J* = 7.9, 7.2, 1.5, 0.4 Hz), 7.59 (ddd, *J* = 8.1, 1.4, 0.5 Hz), 7.62 (ddd, *J* = 8.1, 1.3, 0.5 Hz), 7.36 (d, *J* = 15.6 Hz), 7.40 (dd, *J* = 8.6, 1.7 Hz), 7.90 (dtd, *J* = 7.9, 1.4, 0.4 Hz); ESI-MS (positive): *m/z* 420.00 $[M+H]^+$ (calcd. for $C_{28}H_{21}NOS$: 419.54).

(*E*)-3-(2″-Chlorophenyl)-1-(2′-phenyl-10*H*-phenothiazin-10-yl)prop-2-en-1-one (3c): Yield: 74%, m.p.: 245-247 ºC, HPLC purity: 98.21%, IR (KBr, ν_{max}, cm^{-1}): 3319.03 (Ar-CH), 1594.19 (C=O), 3029.10 (aliphatic C–H), 1558.11, 1594.19 (C=C), 1462.16 (C–N), 693.97 (Ar C–S), 744.68 (Ar-C-Cl). ^{1}H NMR ($CDCl_3$, δ ppm): 6.78 (1H, d, *J* = 15.6 Hz), 7.33 (1H, ddd, *J* = 7.9, 7.5, 1.3 Hz), 7.12-7.90 (16H, 7.51 (ddd, *J* = 7.9, 1.7, 0.6 Hz), 7.41 (ddd, *J* = 8.3, 7.5, 1.7 Hz), 7.44 (tt, *J* = 7.2, 1.4 Hz), 7.12 (dd, *J* = 1.7, 0.5 Hz), 7.31 (ddd, *J* = 7.8, 7.4, 1.1 Hz), 7.37 (dd, *J* = 8.6, 0.5 Hz), 7.83 (ddd, *J* = 8.3, 1.3, 0.6 Hz), 7.49 (dddd, *J* = 7.9, 7.2, 1.5, 0.4 Hz), 7.59 (ddd, *J* = 8.1, 1.1, 0.5 Hz), 7.36 (d, *J* = 15.6 Hz), 7.29 (ddd, *J* = 8.1, 7.4, 1.5 Hz), 7.40 (dd, *J* = 8.6, 1.7 Hz), 7.90 (dtd, *J* = 7.9, 1.4, 0.4 Hz), 7.35 (ddd, *J* = 7.8, 1.5, 0.5 Hz); ESI-MS (positive): *m/z* 440.90 $[M+H]^+$ (calcd. for $C_{27}H_{18}NOSCl$: 439.96).

(*E*)-3-(4″-Chlorophenyl)-1-(2′-phenyl-10*H*-phenothiazin-10-yl)prop-2-en-1-one (3d): Yield: 68%, m.p.: 248-250 ºC, HPLC purity: 94.95%, IR (KBr, ν_{max}, cm^{-1}): 3057.65 (Ar-CH), 1658.45 (C=O), 3029.10 (aliphatic C–H), 1551.80, 1590.88 (C=C), 1463.763 (C–N), 695.72 (Ar C–S), 748.13 (Ar-C-Cl). ^{1}H NMR ($CDCl_3$, δ ppm): 6.75 (1H, d, *J* = 15.6 Hz), 7.12-7.90 (17H, 7.33 (ddd, *J* = 7.9, 7.5, 1.3 Hz), 7.51 (ddd, *J* = 7.9, 1.7, 0.6 Hz), 7.41 (ddd, *J* = 8.3, 7.5, 1.7 Hz), 7.44 (tt, *J* = 7.2, 1.4 Hz), 7.12 (dd, *J* = 1.7, 0.5 Hz), 7.37 (dd, *J* = 8.6, 0.5 Hz), 7.83 (ddd, *J* = 8.3, 1.3, 0.6 Hz), 7.49 (dddd, *J* = 7.9, 7.2, 1.5, 0.4 Hz), 7.59 (ddd, *J* = 8.1, 1.4, 0.5 Hz), 7.62 (ddd, *J* = 8.1, 1.3, 0.5 Hz), 7.36 (d, *J* = 15.6 Hz), 7.40 (dd, *J* = 8.6, 1.7 Hz), 7.90 (dtd, *J* = 7.9, 1.4, 0.4 Hz); ESI-MS (positive): *m/z* 440.90 $[M+H]^+$ (calcd. for $C_{27}H_{18}NOSCl$: 440.90).

(*E*)-3-(3″-Methoxyphenyl)-1-(2′-phenyl-10*H*-phenothiazin-10*H*-yl)prop-2-en-1-one (3e): Yield: 68%, m.p.: 250-253 ºC, HPLC purity: 94.80%, IR (KBr, ν_{max}, cm^{-1}): 3028.03 (Ar-CH), 1661.15 (C=O), 2836.02 (aliphatic C–H), 1597.01, 1553.00 (C=C), 1458.96 (Ar-sC–N), 693.50 (Ar C–S), 1222.46 (C-O-C), 2321.30 (aliph. C–H). ^{1}H NMR ($CDCl_3$, δ ppm): 3.81 (3H, s), 6.80 (1H, d, *J* = 15.6 Hz), 6.86 (1H, ddd, *J* = 8.2, 1.8, 1.4 Hz), 7.33 (1H, ddd, *J* = 7.9, 7.5, 1.3 Hz), 7.12-7.90 (11H, 7.51 (ddd, *J* = 7.9, 1.7, 0.6 Hz), 7.32 (ddd, *J* = 8.3, 7.5, 1.7 Hz), 7.41 (ddd, *J* = 8.2, 7.5, 0.5 Hz), 7.44 (tt, *J* = 7.2, 1.4 Hz), 7.12 (dd, *J* = 1.7, 0.5 Hz), 7.37 (dd, *J* = 8.6, 0.5 Hz), 7.25 (ddd, *J* = 8.3, 1.3, 0.6 Hz), 7.83 (ddd, *J* = 1.8, 1.7, 0.5 Hz), 7.44 (ddd, *J* = 7.5, 1.7, 1.4 Hz), 7.49 (dddd, *J* = 7.9, 7.2, 1.5, 0.4 Hz), 7.36-7.90 (4H, 7.40 (dd, *J* = 8.6, 1.7 Hz), 7.90 (dtd, *J* = 7.9, 1.4, 0.4 Hz), 7.36 (d, *J* = 15.6 Hz); ESI-MS (negative): *m/z* 434.30 $[M-H]^-$ (calcd. for $C_{28}H_{21}NO_2S$: 435.54).

(*E*)-3-(4″-Methoxyphenyl)-1-(2′-phenyl-10*H*-phenothiazin-10*H*-yl)prop-2-en-1-one (3f): Yield: 70%, m.p.: 252-255 ºC, HPLC purity: 97.45%, IR (KBr, ν_{max}, cm^{-1}): 2959.80 (Ar-CH), 1661.18 (C=O), 2834.77 (aliph. C–H), 1597.29, 1618.18 (C=C), 1458.96 (Ar C–N), 693.38 (Ar C–S), 1249.81 (C-O-C), 2333.95 (aliph. C–H); ^{1}H NMR ($CDCl_3$, δ ppm): 3.81 (3H, s), 6.80 (1H, d, *J* = 15.6 Hz), 7.12-7.90 (17H, 7.33 (ddd, *J* = 7.9, 7.5, 1.3 Hz), 7.32 (ddd, *J* = 8.8, 1.2, 0.5 Hz), 7.51 (ddd, *J* = 7.9, 1.7, 0.6 Hz), 7.41 (ddd, *J* = 8.3, 7.5, 1.7 Hz), 7.44 (tt, *J* = 7.2, 1.4 Hz), 7.12 (dd, *J* = 1.7, 0.5 Hz), 7.37 (dd, *J* = 8.6, 0.5 Hz), 7.83 (ddd, *J* = 8.3, 1.3, 0.6 Hz), 7.49 (dddd, *J* = 7.9, 7.2, 1.5, 0.4 Hz), 7.59 (ddd, *J* = 8.8, 1.8, 0.5 Hz), 7.36 (d, *J* = 15.6 Hz), 7.40 (dd, *J* = 8.6, 1.7 Hz), 7.90 (dtd, *J* = 7.9, 1.4, 0.4 Hz); ESI-MS (positive): *m/z* 436.30 $[M+H]^+$ (calcd. for $C_{28}H_{21}NO_2S$: 435.54).

(*E*)-3-(3″-Fluorophenyl)-1-(2′-phenyl-10*H*-phenothiazin-10*H*-yl)prop-2-en-1-one (3g): Yield: 68%, m.p.: 253-256 ºC, HPLC purity: 97.45%, IR (KBr, ν_{max}, cm^{-1}): 2959.80 (Ar-CH), 1661.18 (C=O), 2834.77 (aliphatic C–H), 1597.29, 1618.18 (C=C), 1458.96 (Ar C–N), 693.38 (Ar C–S), 1249.81 (C-O-C), 2333.95 (aliph. C–H). ^{1}H NMR ($CDCl_3$, δ ppm): 3.81 (3H, s), 6.80 (1H, d, *J* = 15.6 Hz), 7.12-7.90 (17H, 7.33 (ddd, *J* = 7.9, 7.5, 1.3 Hz), 7.32 (ddd, *J* = 8.8, 1.2, 0.5 Hz), 7.51 (ddd, *J* = 7.9, 1.7, 0.6 Hz), 7.41 (ddd, *J* = 8.3, 7.5, 1.7 Hz), 7.44 (tt, *J* = 7.2, 1.4 Hz), 7.12 (dd, *J* = 1.7, 0.5 Hz), 7.37 (dd, *J* = 8.6, 0.5 Hz), 7.83 (ddd, *J* = 8.3, 1.3, 0.6 Hz), 7.49 (dddd, *J* = 7.9, 7.2, 1.5, 0.4 Hz), 7.59 (ddd, *J* = 8.8, 1.8, 0.5 Hz), 7.36 (d, *J* = 15.6 Hz), 7.40 (dd, *J* = 8.6, 1.7 Hz), 7.90 (dtd, *J* = 7.9, 1.4, 0.4 Hz).

(*E*)-1-(2′-Phenyl-10'*H*-phenothiazin-10*H*-yl)-3-(3″-(trifluoromethyl)phenyl)prop-2-en-1-one (3h): Yield: 67%, m.p.: 257-260 ºC, HPLC purity: 97.45%, IR (KBr, ν_{max}, cm^{-1}): 2959.80 (Ar-CH), 1661.18 (C=O), 2834.77 (aliphatic C–H), 1597.29, 1618.18 (C=C), 1458.96 Ar-(C–N), 693.38 (Ar C–S), 1249.81 (C-O-C), 2333.95 (aliph. C–H). ^{1}H NMR ($CDCl_3$, δ ppm): 3.81 (3H, s), 6.80 (1H, d, *J* = 15.6 Hz), 7.12-7.90 (17H, 7.33 (ddd, *J* = 7.9, 7.5, 1.3 Hz), 7.32 (ddd, *J* = 8.8, 1.2, 0.5 Hz), 7.51 (ddd, *J* = 7.9, 1.7, 0.6 Hz), 7.41 (ddd, *J* = 8.3, 7.5, 1.7 Hz), 7.44 (tt, *J* = 7.2, 1.4 Hz), 7.12 (dd, *J* = 1.7, 0.5 Hz), 7.37 (dd, *J* = 8.6, 0.5 Hz), 7.83 (ddd, *J* = 8.3, 1.3, 0.6 Hz), 7.49 (dddd, *J* = 7.9, 7.2, 1.5, 0.4 Hz), 7.59 (ddd, *J* = 8.8, 1.8, 0.5 Hz), 7.36 (d, *J* = 15.6 Hz), 7.40 (dd, *J* = 8.6, 1.7 Hz), 7.90 (dtd, *J* = 7.9, 1.4, 0.4 Hz).

Synthesis of chalcone derivatives (4a-h): In a separate procedure, 2-(*p*-tolyl)-10*H*-phenothiazine (1 equiv.) was diss-

olved in dry DCM (10 mL) and DIPEA (1.5 equiv.) was added. The mixture was stirred at room temperature for 15 min. The reaction flask was cooled to 0 ºC in an ice bath and substituted cinnamoyl chloride (1.2 equiv.) in DCM was added dropwise. The mixture was allowed to stir at room temperature for 10-12 h. The reaction was quenched with cold water and the product was extracted with DCM. The organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum (**Scheme-II**). The crude product was purified by flash chromatography using 2-3% ethyl acetate in petroleum ether to yield compounds **4a-h**.

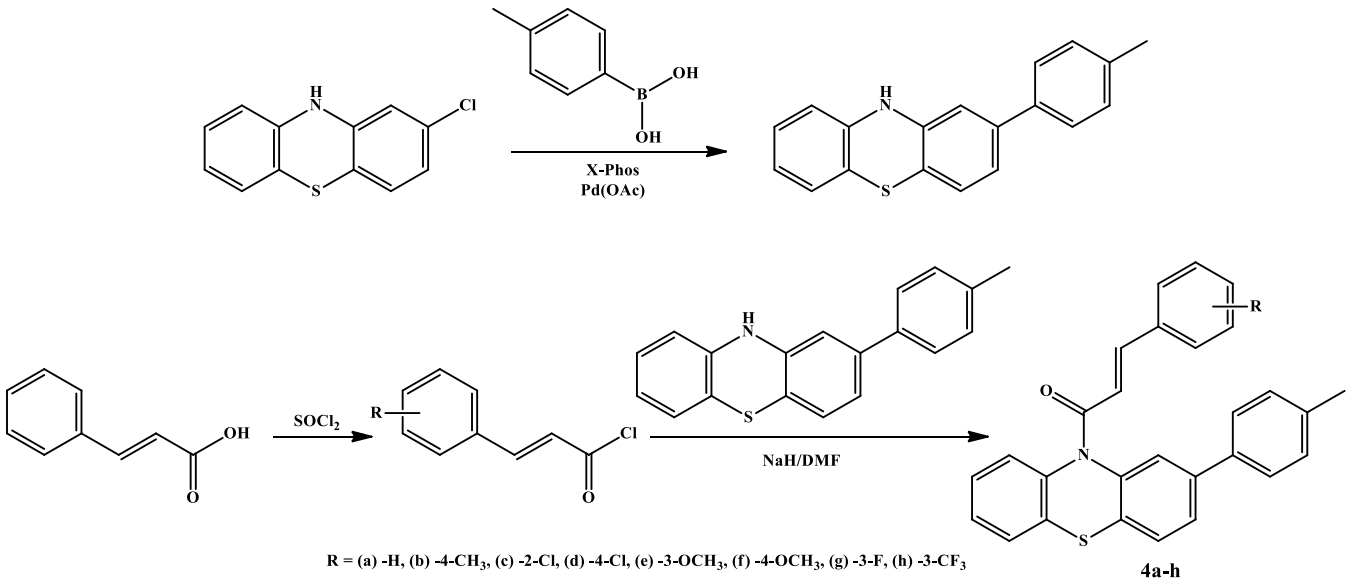
(*E*)-3-Phenyl-1-(2-(*p*-tolyl)-10*H*-phenothiazin-10-yl)-prop-2-en-1-one (4a): Yield: 65%, m.p.: 221-223 ºC, HPLC purity: 95.570%, IR (KBr, ν_{max}, cm^{-1}): 2959 (N–H), 2922 (Ar-CH), 1659 (C=O), 1461 (C=C), 1336 (C–N), 806 (Ar C–S); ^{1}H NMR ($CDCl_3$, δ ppm): 2.38 (3H, s), 6.75 (1H, d, *J* = 15.6 Hz), 7.33 (1H, ddd, *J* = 7.9, 7.5, 1.3 Hz), 7.17-7.51 (11H, 7.23 (ddd, *J* = 8.1, 1.3, 0.5 Hz), 7.26 (ddd, *J* = 7.9, 1.7, 0.6 Hz), 7.30 (ddd, *J* = 8.3, 7.5, 1.7 Hz), 7.36 (dddd, *J* = 8.1, 2.3, 1.6, 0.5 Hz), 7.35 (dd, *J* = 1.7, 0.5 Hz), 7.40 (ddd, *J* = 8.3, 1.3, 0.6 Hz), 7.43 (dddd, *J* = 8.1, 7.2, 2.0, 0.5 Hz), 7.45 (tt, *J* = 7.2, 1.6 Hz)), 7.54-7.79 (5H, 7.61 (dd, *J* = 8.6, 0.5 Hz), 7.65 (d, *J* = 15.6 Hz), 7.65 (dd, *J* = 8.6, 1.7 Hz), 7.73 (ddd, *J* = 8.1, 1.1, 0.5 Hz); ESI-MS (positive): *m/z* 419.40 $[M+H]^+$ (calcd. for $C_{28}H_{21}NOS$: 419.54).

(*E*)-3-(*p*-Tolyl)-1-(2-(*p*-tolyl)-10*H*-phenothiazin-10-yl)-prop-2-en-1-one (4b): Yield: 70%, m.p.: 228-230 ºC, HPLC purity: 94.229%, IR (KBr, ν_{max}, cm^{-1}): 2923 (N–H), 2855 (Ar-CH), 1657 (C=O), 1459 (C=C), 1330 (C–N), 805 (Ar C–S); ^{1}H NMR ($CDCl_3$, δ ppm): 2.34-2.38 (6H, 2.28 (s), 2.34 (s)), 6.73 (1H, d, *J* = 15.6 Hz), 7.08 (1H, ddd, *J* = 7.9, 7.5, 1.3 Hz), 7.17-7.46 (8H, 7.23 (ddd, *J* = 8.1, 1.3, 0.5 Hz), 7.24 (ddd, *J* = 8.0, 1.4, 0.4 Hz), 7.26 (ddd, *J* = 7.9, 1.7, 0.6 Hz), 7.30 (ddd, *J* = 8.3, 7.5, 1.7 Hz), 7.35 (dd, *J* = 1.7, 0.5 Hz), 7.40 (ddd, *J* = 8.3, 1.3, 0.6 Hz)), 7.53-7.79 (7H, 7.59 (ddd, *J* = 8.0, 1.7, 0.4 Hz), 7.61 (dd, *J* = 8.6, 0.5 Hz), 7.66 (d, *J* = 15.6 Hz), 7.65 (dd, *J* = 8.6, 1.7 Hz), 7.73 (ddd, *J* = 8.1, 1.1, 0.5 Hz); ESI-MS (positive): *m/z* 434.0000 $[M+H]^+$ (calcd. for $C_{29}H_{23}NOS$: 434.1573).

(*E*)-3-(3-Chlorophenyl)-1-(2-(*p*-tolyl)-10*H*-phenothiazin-10-yl)prop-2-en-1-one (4c): Yield: 64%, m.p.: 230-233 ºC, HPLC purity: 95.511%, IR (KBr, ν_{max}, cm^{-1}): 39057 (N–H), 2741 (Ar-CH), 1657 (C=O), 1464 (C=C), 1337 (C–N), 801 (Ar C–S); ^{1}H NMR ($CDCl_3$, δ ppm): 6.75 (1H, d, *J* = 15.6 Hz), 7.12-7.90 (17H, 7.33 (ddd, *J* = 7.9, 7.5, 1.3 Hz), 7.51 (ddd, *J* = 7.9, 1.7, 0.6 Hz), 7.41 (ddd, *J* = 8.3, 7.5, 1.7 Hz), 7.44 (tt, *J* = 7.2, 1.4 Hz), 7.12 (dd, *J* = 1.7, 0.5 Hz), 7.37 (dd, *J* = 8.6, 0.5 Hz), 7.83 (ddd, *J* = 8.3, 1.3, 0.6 Hz), 7.49 (dddd, *J* = 7.9, 7.2, 1.5, 0.4 Hz), 7.48 (ddd, *J* = 8.1, 1.4, 0.5 Hz), 7.33 (ddd, *J* = 8.1, 1.3, 0.5 Hz), 7.35 (d, *J* = 15.6 Hz), 7.40 (dd, *J* = 8.6, 1.7 Hz), 7.90 (dtd, *J* = 7.9, 1.4, 0.4 Hz); ESI-MS (positive): *m/z* 455.0000 $[M+H]^+$ (calcd. for $C_{28}H_{20}NOSCl$: 454.1027).

(*E*)-3-(4-Chlorophenyl)-1-(2-(*p*-tolyl)-10*H*-phenothiazin-10-yl)prop-2-en-1-one (4d): Yield: 68%, m.p.: 233-235 ºC, HPLC purity: 97.259%; IR (KBr, ν_{max}, cm^{-1}): 2953 (N–H), 2922 (Ar-CH), 1656 (C=O), 1461 (C=C), 1324 (C–N), 805 (Ar C–S); ^{1}H NMR ($CDCl_3$, δ ppm): 2.38 (3H, s), 6.71 (1H, d, *J* = 15.6 Hz), 7.62 (1H, ddd, *J* = 7.9, 7.5, 1.3 Hz), 7.17-7.46 (6H, 7.23 (ddd, *J* = 8.1, 1.3, 0.5 Hz), 7.26 (ddd, *J* = 7.9, 1.7, 0.6 Hz), 7.30 (ddd, *J* = 8.3, 7.5, 1.7 Hz), 7.35 (dd, *J* = 1.7, 0.5 Hz), 7.39 (ddd, *J* = 8.3, 1.3, 0.6 Hz), 7.48-7.79 (9H, 7.54 (ddd, *J* = 8.1, 1.4, 0.5 Hz), 7.55 (ddd, *J* = 8.1, 1.3, 0.5 Hz), 7.61 (dd, *J* = 8.6, 0.5 Hz), 7.64 (d, *J* = 15.6 Hz), 7.65 (dd, *J* = 8.6, 1.7 Hz), 7.73 (ddd, *J* = 8.1, 1.1, 0.5 Hz).

(*E*)-3-(3-Methoxyphenyl)-1-(2-(*p*-tolyl)-10*H*-phenothiazin-10-yl)prop-2-en-1-one (4e): Yield: 71%, m.p.: 245-248 ºC, HPLC purity: 95.152%; IR (KBr, ν_{max}, cm^{-1}): 2920 (N–H), 2855 (Ar-CH), 1659 (C=O), 1459 (C=C), 1339 (C–N), 799 (Ar C–S); ^{1}H NMR ($CDCl_3$, δ ppm): 2.38 (3H, s), 3.83 (3H, s), 6.73 (1H, d, *J* = 15.6 Hz), 6.95 (1H, ddd, *J* = 8.2, 1.8, 1.4 Hz), 7.08 (1H, ddd, *J* = 7.9, 7.5, 1.3 Hz), 7.17-7.50 (9H, 7.23 (ddd, *J* = 8.1, 1.3, 0.5 Hz), 7.26 (ddd, *J* = 7.9, 1.7, 0.6 Hz),



Scheme-II: Synthesis pathway of 2-aryl-10*H*-phenothiazine chalcone derivatives (**4a-h**) *via* Suzuki–Miyaura coupling, acid chloride formation and final amide bond formation

7.30 (ddd, *J* = 8.3, 7.5, 1.7 Hz), 7.30 (ddd, *J* = 8.2, 7.5, 0.5 Hz), 7.35 (dd, *J* = 1.7, 0.5 Hz), 7.40 (ddd, *J* = 8.3, 1.3, 0.6 Hz), 7.39 (ddd, *J* = 1.8, 1.7, 0.5 Hz), 7.41 (ddd, *J* = 7.5, 1.7, 1.4 Hz)), 7.54-7.79 (5H, 7.61 (dd, *J* = 8.6, 0.5 Hz), 7.65 (dd, *J* = 8.6, 1.7 Hz), 7.72 (d, *J* = 15.6 Hz), 7.73 (ddd, *J* = 8.1, 1.1, 0.5 Hz); ESI-MS (positive): *m/z* 450.3000 $[M+H]^+$ (calcd. for $C_{29}H_{23}NO_2S$: 450.1522).

(*E*)-3-(4-Methoxyphenyl)-1-(2-(*p*-tolyl)-10*H*-phenothiazin-10-yl)prop-2-en-1-one (4f): Yield: 66%, m.p.: 247-250 ºC, HPLC purity: 95.616%; IR (KBr, ν_{max}, cm^{-1}): 2920 (N–H), 2850 (Ar-CH), 1659 (C=O), 1457 (C=C), 1334 (C–N), 803 (Ar C–S); ^1H NMR ($CDCl_3$, δ ppm): 2.38 (3H, s), 3.78 (3H, s), 6.75 (1H, d, *J* = 15.6 Hz), 7.12 (1H, ddd, *J* = 7.9, 7.5, 1.3 Hz), 7.17-7.46 (6H, 7.23 (ddd, *J* = 8.1, 1.3, 0.5 Hz), 7.26 (ddd, *J* = 7.9, 1.7, 0.6 Hz), 7.30 (ddd, *J* = 8.3, 7.5, 1.7 Hz), 7.35 (dd, *J* = 1.7, 0.5 Hz), 7.40 (ddd, *J* = 8.3, 1.3, 0.6 Hz), 7.50-7.79 (8H, 7.57 (ddd, *J* = 7.7, 7.4, 0.4 Hz), 7.61 (dd, *J* = 8.6, 0.5 Hz), 7.49 (ddd, *J* = 7.7, 1.6, 1.1 Hz), 7.49 (dd, *J* = 8.6, 1.7 Hz), 7.70 (ddd, *J* = 7.4, 1.5, 1.1 Hz), 7.72 (d, *J* = 15.6 Hz), 7.73 (ddd, *J* = 8.1, 1.1, 0.5 Hz), 7.90 (1H, td, *J* = 1.5, 0.4 Hz); ESI-MS (positive): *m/z* 450.1000 $[M+H]^+$ (calcd. for $C_{29}H_{23}NO_2S$: 450.1522).

(*E*)-3-(3-Fluorophenyl)-1-(2-(*p*-tolyl)-10*H*-phenothiazin-10-yl)prop-2-en-1-one (4g): Yield: 69%, m.p.: 255-258 ºC, HPLC purity: 98.256%; IR (KBr, ν_{max}, cm^{-1}): 2921 (N–H), 2813 (Ar-CH), 1660 (C=O), 1443 (C=C), 1334 (C–N), 804 (Ar C–S). ^1H NMR ($CDCl_3$, δ ppm): 2.38 (3H, s), 6.75 (1H, d, *J* = 15.6 Hz), 7.03 (1H, ddd, *J* = 7.9, 7.5, 1.3 Hz), 7.16-7.80 (15H, 7.23 (ddd, *J* = 8.3, 1.5, 1.3 Hz), 7.23 (ddd, *J* = 8.1, 1.3, 0.5 Hz), 7.24 (ddd, *J* = 1.6, 1.5, 0.5 Hz), 7.26 (ddd, *J* = 7.9, 1.7, 0.6 Hz), 7.30 (ddd, *J* = 8.3, 7.5, 1.7 Hz), 7.35 (dd, *J* = 1.7, 0.5 Hz), 7.40 (ddd, *J* = 8.3, 1.3, 0.6 Hz), 7.43 (ddd, *J* = 8.3, 7.8, 0.5 Hz), 7.49 (ddd, *J* = 7.8, 1.6, 1.3 Hz), 7.61 (dd, *J* = 8.6, 0.5 Hz), 7.65 (dd, *J* = 8.6, 1.7 Hz), 7.73 (d, *J* = 15.6 Hz), 7.73 (ddd, *J* = 8.1, 1.1, 0.5 Hz); ESI-MS (positive): *m/z* 438.1000 $[M+H]^+$ (calcd. for $C_{28}H_{20}NOSF$: 438.1322).

(*E*)-1-(2-(*p*-Tolyl)-10*H*-phenothiazin-10-yl)-3-(3-(trifluoromethyl)phenyl)prop-2-en-1-one (4h): Yield: 72%, m.p.: 258-261 ºC, HPLC purity: 99.327%; IR (KBr, ν_{max}, cm^{-1}): 3048 (N–H), 2925 (Ar-CH), 1673 (C=O), 1439 (C=C), 1339 (C–N), 811 (Ar C–S); ^1H NMR ($CDCl_3$, δ ppm): 2.38 (3H, s), 6.75 (1H, d, *J* = 15.6 Hz), 7.12 (1H, ddd, *J* = 7.9, 7.5, 1.3 Hz), 7.17-7.46 (6H, 7.23 (ddd, *J* = 8.1, 1.3, 0.5 Hz), 7.26 (ddd, *J* = 7.9, 1.7, 0.6 Hz), 7.30 (ddd, *J* = 8.3, 7.5, 1.7 Hz), 7.35 (dd, *J* = 1.7, 0.5 Hz), 7.40 (ddd, *J* = 8.3, 1.3, 0.6 Hz)), 7.50-7.79 (8H, 7.57 (ddd, *J* = 7.7, 7.4, 0.4 Hz), 7.61 (dd, *J* = 8.6, 0.5 Hz), 7.49 (ddd, *J* = 7.7, 1.6, 1.1 Hz), 7.49 (dd, *J* = 8.6, 1.7 Hz), 7.70 (ddd, *J* = 7.4, 1.5, 1.1 Hz), 7.72 (d, *J* = 15.6 Hz), 7.73 (ddd, *J* = 8.1, 1.1, 0.5 Hz)), 7.90 (1H, td, *J* = 1.5, 0.4 Hz); ESI-MS (positive): *m/z* 486.3000 $[M+H]^+$ (calcd. for $C_{29}H_{20}NOSF_3$: 486.1134).

RESULTS AND DISCUSSION

The synthesis of chalcone-based 2-aryl-10*H*-phenothiazine derivatives (**3a-h**) was achieved through a concise three-step process. First, 2-chloro-10*H*-phenothiazine underwent Suzuki–Miyaura cross-coupling with substituted arylboronic acids using a $Pd(OAc)_2$/XPhos catalyst in ethanol-water (10:5) system under an inert nitrogen atmosphere to yield the corresponding 2-aryl-10*H*-phenothiazines. These intermediates were then treated with substituted cinnamic acid chlorides (prepared *in situ* from the corresponding acids using $SOCl_2$) in the presence of NaH and DMF, leading to the formation of the desired chalcone derivatives **3a-h** (**Scheme-I**). All synthesized compounds were obtained in moderate to good yields, ranging from 67% to 74% and showed sharp melting points, confirming their purity. The R_f values (~0.5) remained relatively constant across the series, indicating a consistent level of polarity. The increase in the melting points across the series, especially for halogenated derivatives (**3c**, **3d**, **3g**, **3h**), reflects increased intermolecular interactions due to electron-withdrawing effects. The chloro- and trifluoromethyl-substituted derivatives exhibited higher melting points, indicative of stronger molecular packing and potentially enhanced stability.

The spectroscopic data confirm the successful formation of the phenothiazine-based chalcone derivatives. FTIR spectra consistently showed the α,β-unsaturated ketone C=O stretch at 1663-1656 cm^{-1}, along with aromatic and aliphatic C–H bands and characteristic C=C absorptions; the aryl C–S vibrations supported the presence of the phenothiazine nucleus. The ^1H NMR spectra further substantiated the chalcone framework, with all compounds displaying the expected *trans*-olefinic doublets ($J \approx 15.6$ Hz) and aromatic multiplets between δ 6.7-8.0 ppm, while substituent signals such as $-CH_3$ and $-OCH_3$ appeared at δ 2.3 and 3.8 ppm, respectively. Mass spectrometry showed the molecular ion peaks in close agreement with calculated masses, exemplified by compound **3a** giving *m/z* 406.12 $[M+H]^+$ and halogenated derivatives such as **3c** and **3d** exhibiting peaks at *m/z* 440.90, consistent with their formulas. HPLC analysis indicated high purity (94.80-98.67%), supporting clean synthesis and isolation. Together, the IR, NMR, MS, and HPLC results confirm the intended structures and purity of all chalcone derivatives.

In other series, the chalcone-functionalized 2-aryl-10*H*-phenothiazine derivatives (**4a-h**) were synthesized through an efficient three-step procedure. Initially, 2-chloro-10*H*-phenothiazine was subjected to Suzuki-Miyaura cross-coupling with *p*-tolylboronic acid using K_3PO_4 as base and a $Pd(OAc)_2$/XPhos catalytic system. The reaction was performed in an ethanol-water mixture (10:5, v/v) under a N_2 atmosphere at 80 ºC for 12-14 h, affording 2-(*p*-tolyl)-10*H*-phenothiazine. In the second step, the required substituted cinnamic acids were converted into their corresponding acid chlorides by refluxing with thionyl chloride. The final step involved coupling the acid chlorides with the phenothiazine intermediate in DCM using DIPEA as base to obtain the chalcone-derived phenothiazine–amide analogues (**4a-h**).

All target compounds were isolated as solid products and purified by flash chromatography. The isolated yields ranged from 64% to 72%, while melting points were recorded between 221 ºC and 261 ºC. Electron-withdrawing substituents (*e.g.* -Cl, $-CF_3$) were associated with higher melting points, reflecting enhanced molecular rigidity and stronger intermolecular interactions. In contrast, electron-donating groups ($-CH_3$, $-OCH_3$) resulted in slightly reduced melting points due to increased

molecular flexibility. The R_f values remained consistent (~0.5), indicating comparable chromatographic behaviour across the series.

The spectroscopic analyses collectively verified the structural features of the phenothiazine–amide derivatives. The FTIR spectra showed the expected characteristics peaks of the newly formed amide linkage, most notably a strong carbonyl stretch in the 1673-1656 cm^{-1} region, accompanied by N–H and aromatic C–H stretching bands that further confirmed the integrity of both the phenothiazine nucleus and the cinnamoyl fragment. Additional absorptions associated with C=C, C–N and C–S functionalities were observed at their characteristic positions, indicating that no structural alterations occurred during the coupling steps. The ^{1}H NMR data reinforced these observations, with the cinnamoyl double bonds consistently giving rise to two well-resolved doublets ($J \approx$ 15.6 Hz), a clear indication of the *E*-configured olefin. The aromatic regions exhibited the expected complex multiplets, while substituent-specific singlets such as those from methoxy and methyl groups, appeared at predictable chemical shifts, aligning with the proposed substitution patterns. High-resolution mass spectrometry further substantiated the molecular structures, as all compounds displayed protonated or deprotonated molecular ions that matched the calculated masses, including the anticipated mass shifts in halogenated or CF_3–substituted analogues. Taken together, the IR, NMR, HRMS and chromatographic profiles collectively validate the successful construction and chemical integrity of the synthesized phenothiazine–amide conjugates.

Conclusion

In this study, two novel series of 2-aryl-10*H*-phenothiazine chalcone derivatives (**3a-h** and **4a-h**) were successfully synthesized *via* palladium-catalyzed Suzuki–Miyaura cross-coupling followed by acylation strategies. The structural confirmation and purity of these compounds were thoroughly established through FTIR, ^{1}H NMR, mass spectrometry and HPLC analysis. The consistent spectral features particularly *trans*-olefinic protons, carbonyl signals and phenothiazine-specific absorptions validated the designed framework. Substituent variations significantly influenced the physico-chemical properties, such as melting point and yield, suggesting the potential structure-activity relationships. The high purity and yields of these derivatives lay a promising foundation for further biological screening and pharmaceutical development, especially in the context of anticancer or neuroprotective therapeutics.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

DECLARATION OF AI-ASSISTED TECHNOLOGIES

During the preparation of this manuscript, the authors used an AI-assisted tool(s) to improve the language. The authors reviewed and edited the content and take full responsibility for the published work.

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