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Synthesis and Antimicrobial Activity of Heterocycle based Chalcone Derivatives

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An efficient procedure for the synthesis of novel chalcones containing heterocyclic ring by Claisen-Schmidt condensation of 2-acetyl thiophene with heterocyclic carboxaldehyde, substituted benzaldehyde in the presence of aqueous alkaline bases produced chalcones in good yield (**3a-f**) is developed. These chalcones undergoes hydroamination with N-protected N-Boc piperazine followed by deprotection with trifluoroacetic acid gives corresponding amino derivatives with good yield (**7a-f**). The synthesized compounds were characterized by melting point, FTIR, ^{1}H & ^{13}C NMR and MS spectroscopic data. The synthesized compounds were also evaluated *in vitro* for their antibacterial activity against different bacterial and fungal species. Among the sythesized compounds, compound **7c** showed the maximum potent antibacterial and antifungal activities.

Keywords: Chalcone, Hydroamination, N-Boc piperazine, Inhibition, Antibacterial, Antifungal.

INTRODUCTION

Chalcones can be synthesized easily by Claisen–Schmidt condensation and its compounds are biologically active molecules. Due to their high solubility, they have been used as intermediate in multiple organic reactions and synthesis of flavonoids and isoflavonoids [1]. The α,β-unsaturation is responsible for the pharmacological properties of chalcones with substantial therapeutic application including antimicrobial [2], antibacterial [3], antifungal [4], anti-inflammatory [5], anticancer activities [6] and enzyme inhibition [7]. The α,β-unsaturated carbonyl system of chalcones are considered as open chain flavonoids in which two aromatic rings are joined by a three carbon, which acts as a Michael acceptor group, allowing nucleophiles or ligands to effectively bind to various biological targets [8,9].

Hydroamination is the addition reaction of alkene, alkyne, diene or allenes with amines to form new hetero C-N bond by adding N-H bond across a carbon, carbon multiple bonds [10,11] and can be used to develop a heterocycles intramolecularly or intermolecularly with a separate amine and unsaturated compound. Amines that are formed from this amination represent highly valuable chemicals for applications [12].

Several biologically active compounds containing the piperazine ring, which is a major class of N-heterocyclic bioactive natural products, has gathered a much attention in the field of medicinal chemistry. With the addition of a stereocenter, the N-4 nitrogen of piperazine can participate in hydrogen bonding with other heterocyclic compounds, allowing it to behave as a basic amine [13]. In the process of creating new medications, the nitrogen heterocycle piperazine is often utilized in the preparation of the several pharmaceutical compounds that have effects such as anxiety reduction, antiviral, anticancer, cardioprotective and depression [14,15]. Furthermore, it serves as the primary constituent in some drugs, including imatinib (commonly known as Gleevec) and Sildenafil.

Piperazine is structurally defined by the presence of a six-membered ring with two nitrogen atoms in a 1,4-relationship. The presence of extra-nitrogen in piperazines enables for altering the 3D geometry at a remote position of the six-membered ring. This is not easily achievable with morpholines or piperidines, which are neighbouring six-membered ring heterocyclic counterparts of piperazines. Therefore, it is important to emphasize the impact of the piperazine ring on bioactive molecules and medications, which reduces the effectiveness of the pharma-

cophore method. Therefore, it is not surprising that piperazine has emerged as the preferred structure in the medication design of many biologically active molecules. The presence of an extra nitrogen atom at the 4-position is responsible for the biological characteristics of piperazines [16]. These methods enable the production of piperazine derivatives with a significant level of substitution on the ring. However, the structural complexity of the piperazine moiety varies significantly in physiologically active compounds [17].

The enormous pharmacological applications associated with heterocycle based chalcones prompt us to work in this area. In continuation of our work on the synthesis of thiophene chalcones with new basic condition, a series of new N-Boc piperazine thiophene chalcone derivatives and a series of novel 3-phenyl-3-(piperazin-1-yl)-1-(thiophen-2-yl) propan-1-one derivatives in moderate to excellent yields *via* Claisen-Schmidt condensation of thiophene ketone and aromatic aldehydes is carried out and also screened for their antibacterial and anti-fungal activity by modified agar well diffusion assay method. However, in a piperazine N-Boc protecting enables N-4 to undergo selective reaction with α,β-unsaturated alkene where as the protecting amino group is left intract and followed by a deprotection, get final product. In addition, continuing the synthesis of heterocycle-based chlcone derivatives with nitrogen as a free hydrogen atom will result in a more potent medication with broader applicability.

EXPERIMENTAL

The melting points were obtained using an uncorrected open capillary tube method. A solvent system consisting of ethyl acetate and benzene in 0.5:7 v/v ratio was used to analyze the purity of the synthesized compounds on TLC plates pre-coated with the silica gel. The spots were visualized under UV light. IR spectra were recorded on Perkin-Elmer spectrum 100 IR spectrometer in the of 4000-400 cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded on Agilent-NMR 400 MHz and Bruker-NMR 400 MHz spectrometer using $CDCl_3$ solvent with TMS as internal standard. The mass spectra were obtained on Lynx SCN781 spectrometer TOF mode and the purification of compounds was done by column chromatography on silica gel (60-120 mesh Merck).

Synthesis of chalcones (3a-f): A solution containing 2-acetyl thiophene (**1**, 5 mmol), substituted benzaldehyde (**2a-f**, 5 mmol) and aqueous NaOH (5 mmol) in 95% ethyl alcohol (12 mL) was stirred at room temperature for 4 h. The progress of the reaction was monitored by TLC. Following the completion of the reaction, the mixture was placed into ice water and subsequently stored in the refrigerator for overnight. The obtained solid was separated by filtration and then rinsed with cold water. The resulting crude products (**3a-f**)were recrystallizated using ethyl alcohol to obtain chalcones in the pure form.

(*E*)-3-Phenyl-1-(thiophen-2-yl)prop-2-en-1-one (3a): By reacting 2-acetyl thiophene (**1**, 10 mmol) and benzaldehyde (**2a**, 10 mmol), white solid was obtained in 87% yield, m.f.: $C_{13}H_{10}OS$, m.p.: 68-70 ºC; IR (KBr, ν_{max}, cm^{-1}): 1647 (C=O), 1592 (C=C), 718 (C-S-C), ^1H NMR ($CDCl_3$, δ ppm): 6.859 (d, 1H, *J* = 15.3 Hz, HC=C), 7.300 (d, 1H, *J* = 15.5 Hz, C=CH), 7.319-7.348 (m, 5H, *J* = 7.6 Hz, Ar-H), 7.111-7.541 (m, 3H, *J* = 6.5 Hz, Th-H); ^{13}C NMR ($CDCl_3$, δ ppm): 121.6 (1C), 121.8 (1C, C-2), 128.4 (2C), 129.4 (2C), 129.5 (1C), 129.9 (1C), 132 (1C), 134 (1C), 144 (1C), 146 (1C, C-3), 182.5 (1C, C-1); MS *m/z*: 215.01 (M+1).

(*E*)-1-(Thiophen-2-yl)-3-(*p*-tolyl)prop-2-en-1-one (3b): By reacting 2-acetyl thiophene (**1**, 10 mmol) and 4-methyl benzaldehyde (**2b**, 10 mmol), white solid was obtained in 89% yield, m.f.: $C_{14}H_{12}OS$, m.p.: 130-132 ºC; IR (KBr, ν_{max}, cm^{-1}): 1640 (C=O), 1592 (C=C), 719 (C-S-C), ^1H NMR ($CDCl_3$, δ ppm): 2.416 (s, 3H), 7.192 (d, 1H, *J* = 15.3 Hz, HC=C), 7.558-7.698 (m, 4H, *J* = 7.6 Hz, Ar-H), 7.842 (d, 1H, *J* = 15.5 Hz, C=CH), 7.203-7.892 (m, 3H, *J* = 6.5 Hz, Th-H); ^{13}C NMR ($CDCl_3$, δ ppm): 21.5 (1C), 120.6 (1C, C-2), 128.2 (2C), 128.5 (2C), 129.7 (1C), 131.6 (1C), 131.9 (1C), 133.7 (1C), 141.1 (1C), 144.1 (1C), 145.6 (1C, C-3), 182.1 (1C, C-1); MS *m/z*: 229.04 (M+1).

(*E*)-3-(4-Fluorophenyl)-1-(thiophen-2-yl)prop-2-en-1-one (3c): By reacting 2-acetyl thiophene (**1**, 10 mmol) and 4-fluoro benzaldehyde (**2c**, 10 mmol), white solid was obtained in 90% yield, m.f.: $C_{13}H_9OSF$, m.p.: 120-122 ºC; IR (KBr, ν_{max}, cm^{-1}): 1582 (C=O), 1509 (C=C), 979 (Ar-F), 726 (C-S-C), ^1H NMR ($CDCl_3$, δ ppm): 6.839 (d, 1H, *J* = 15.3 Hz, HC=C), 7.439 (d, 1H, *J* = 15.5 Hz, C=CH), 7.381-7.579 (m, 4H, *J* = 8 Hz, Ar-H), 7.000-7.614 (m, 3H, *J* = 6.6 Hz, Th-H); ^{13}C NMR ($CDCl_3$, δ ppm): 115.5 (2C), 122.4 (1C, C-2), 129.4 (1C), 130.7 (1C), 131.3 (2C), 132.3 (1C), 134.6 (1C), 142.2 (1C), 143.2 (1C, C-3), 145.9 (1C, C-F), 182.3 (1C, C-1); MS *m/z*: 233.03 (M+1).

(*E*)-3-(4-Chlorophenyl)-1-(thiophen-2-yl)prop-2-en-1-one (3d): By reacting 2-acetyl thiophene (**1**, 10 mmol) and 4-chloro benzaldehyde (**2d**, 10 mmol), white solid was obtained in 92% yield, m.f.: $C_{13}H_9OSCl$, m.p.: 128-130 ºC; IR (KBr, ν_{max}, cm^{-1}): 1637 (C=O), 1598 (C=C), 718 (C-S-C), 700 (Ar-Cl), ^1H NMR ($CDCl_3$, δ ppm): 6.854 (d, 1H, *J* = 15.3 Hz, HC=C), 7.031-7.069 (m, 4H, *J* = 7.6 Hz, Ar-H), 7.362 (d, 1H, *J* = 15.5 Hz, C=CH), 6.929-7.529 (m, 3H, *J* = 6.6 Hz, Th-H); ^{13}C NMR ($CDCl_3$, δ ppm): 122 (1C, C-2), 129.3 (2C), 129.8 (1C), 130.3 (2C), 132.4 (1C), 133.7 (1C), 134.4 (1C), 134.7 (1C, C-Cl), 143.1 (1C), 145.9 (1C, C-3), 182.2 (1C, C-1); MS *m/z*: 249 (M+1).

(*E*)-3-(4-Bromophenyl)-1-(thiophen-2-yl)prop-2-en-1-one (3e): By reacting 2-acetyl thiophene (**1**, 10 mmol) and 4-bromo benzaldehyde (**2e**, 10 mmol) white solid was obtained in 95% yield, m.f.: $C_{13}H_9OSBr$, m.p.: 131-133 ºC; IR (KBr, ν_{max}, cm^{-1}): 1637 (C=O), 1404 (C=C), 703 (C-S-C), 635 (Ar-Br), ^1H NMR ($CDCl_3$, δ ppm): 6.858 (d, 1H, *J* = 15.3 Hz, HC=C), 7.371 (d, 1H, *J* = 15.5 Hz, C=CH), 7.356-7.463 (m, 4H, *J* = 7.6 Hz, Ar-H), 7.048-7.536 (m, 3H, *J* = 6.6 Hz, Th-H); ^{13}C NMR ($CDCl_3$, δ ppm): 122.3 (1C, C-2), 125.4 (2C), 128.1 (1C), 129.5 (1C), 130.2 (1C), 130.7 (1C, C-Br), 132.4 (1C), 133 (1C), 134.2 (1C), 134.7 (1C), 143.1 (1C, C-3), 182.2 (1C, C-1); MS *m/z*: 292.9 (M+1).

(*E*)-3-(4-Nitrophenyl)-1-(thiophen-2-yl)prop-2-en-1-one (3f): By reacting 2-acetyl thiophene (**1**, 10 mmol) and 4-nitro benzaldehyde (**2f**, 10 mmol), pale brown solid was

obtained in 75% yield, m.f.: $C_{13}H_9NO_3S$, m.p.: 140-143 ºC; IR (KBr, ν_{max}, cm^{-1}); 1637 (C=O), 1418 (C=C), 1335 (N-O), 742 (C-S-C), ^{1}H NMR ($CDCl_3$, δ ppm): 7.061 (d, 1H, *J* = 15.3 Hz, HC=C), 7.812 (d, 1H, *J* = 15.5 Hz, C=CH), 7.131-8.125 (m, 3H, *J* = 6.6 Hz, Th-H), 8.144-8.176 (m, 4H, *J* = 7.6 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 124.1 (1C, C-2), 126.8 (2C), 127.3 (1C), 128.2 (1C), 129.5 (2C), 129.6 (1C), 133.3 (1C), 133.5 (1C), 135.4 (1C, C-3), 150.5 (1C, C-NO_2), 192.5 (1C, C-1); MS *m/z*: 259.9 (M^+).

General procedure for the synthesis of *N*-Boc amino chalcones (5a-f): A stirred homogeneous solution of chalcones (**3a-f**, 0.01 mol) in ethyl alcohol with *N*-Boc piperazine (**4**, 0.01 mol) was allowed to stand for (stoppered) overnight. The progress of the reaction was monitored by TLC and after the completion, the reaction mixture was cooled in an ice bath. The solid formed was separated and dried. Crude products obtained were recrystallized from ethyl alcohol to obtain pure *N*-Boc amino chalcones (**5a-f).**

***tert*-Butyl 4-(3-oxo-1-phenyl-3-(thiophen-2-yl)propyl)-piperazine-1-carboxylate (5a):** By reaction of (*E*)-3-phenyl-1-(thiophen-2-yl)prop-2-en-1-one (**3a**, 10 mmol) and *N*-Boc piperazine (**4**, 10 mmol) obtained white solid in 82% yield, m.f.: $C_{22}H_{28}N_2O_3S$, m.p.: 48-50 ºC. IR (KBr, ν_{max}, cm^{-1}): 1689 (N-C=O), 1624 (C=O), 721 (C-S-C); ^{1}H NMR ($CDCl_3$, δ ppm): 1.433 (s, 9H), 2.110 (t, 4H, *J* = 7.2 Hz), 2.788 (t, 4H *J* = 7.2 Hz), 3.188 (d, 2H *J* = 7.0 Hz), 4.071 (t, 1H *J* = 7.1 Hz), 7.321-7.420 (m, 5H, *J* = 7.6 Hz, Ar-H), 7.209-7.893 (m, 3H, *J* = 6.6 Hz, Th-H); ^{13}C NMR ($CDCl_3$, δ ppm): 28.4 (3C), 42.8 (2C), 61.5 (2C), 76.7 (1C, C-1), 77.4 (1C, C-2), 79.1 (1C), 122.7 (1C), 128.3 (1C), 128.9 (2C), 129.1 (2C), 133.6 (1C), 133.9 (1C), 138.5 (1C), 145.3 (1C), 154.3 (1C, N-C=O), 185.2 (1C, C-3); MS *m/z*: 401.3 (M+1).

***tert*-Butyl 4-(3-oxo-3-(thiophen-2-yl)-1-(*p*-tolyl)propyl)-piperazine-1-carboxylate (5b):** By reaction of (*E*)-1-(thiophen-2-yl)-3-(*p*-tolyl)prop-2-en-1-one (**3b**, 10 mmol) and *N*-Boc piperazine (**4**, 10 mmol) obtained white solid in 81% yield, m.f.: $C_{23}H_{30}N_2O_3S$, m.p.: 89-90 ºC. IR (KBr, ν_{max}, cm^{-1}): 1680 (N-C=O), 1634 (C=O), 723 (C-S-C); ^{1}H NMR: δ 1.430 (s, 9H), 1.773 (s, 3H), 2.332 (t, 4H *J* = 7.2 Hz), 2.368 (t, 4H *J* = 7.2 Hz), 2.418 (d, 2H *J* = 7.0 Hz), 4.233 (t, 1H *J* = 7.1 Hz), 7.117-7.243 (m, 4H, *J* = 7.6 Hz, Ar-H), 7.286-7.895 (m, 3H, *J* = 6.6 Hz, Th-H); ^{13}C NMR ($CDCl_3$, δ ppm): 21.7 (1C), 28.6 (3C), 42.9 (2C), 64.1 (2C), 76.7 (1C, C-1), 77.2 (1C, C-2), 79.8 (1C), 127.5 (2C), 128.3 (1C), 129.6 (2C), 133.6 (1C), 134.1 (1C), 135.6 (1C), 138.5 (1C), 145.3 (1C), 154.5 (1C, N-C=O), 188.5 (1C, C-3); MS *m/z*: 415.2 (M+1).

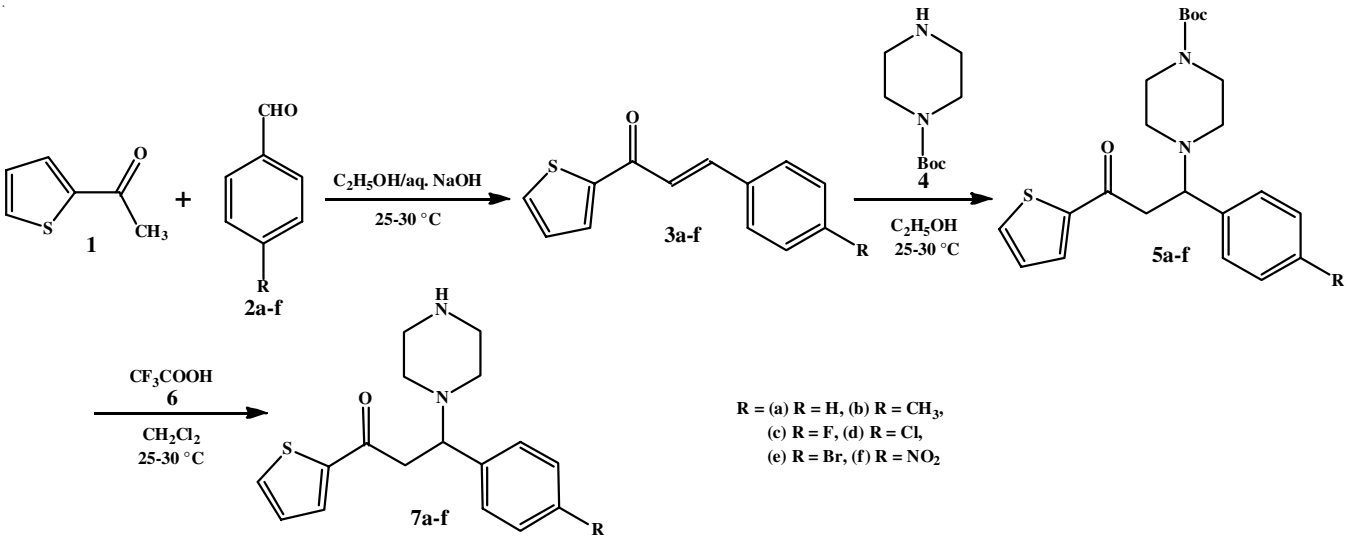
***tert*-Butyl 4-(1-(4-fluorophenyl)-3-oxo-3-(thiophen-2-yl)propyl)piperazine-1-carboxylate (5c):** By reaction of (*E*)-3-(4-fluorophenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**3c**, 10 mmol) and *N*-Boc piperazine (**4**, 10 mmol) obtained white solid in 85% yield, m.f.: $C_{22}H_{27}N_2O_3SF$, m.p.: 94-96 ºC. IR (KBr, ν_{max}, cm^{-1}): 1678 (N-C=O), 1646 (C=O), 728 (C-S-C), 850 (Ar-F); ^{1}H NMR ($CDCl_3$, δ ppm): 1.432 (s, 9H), 2.731 (t, 4H *J* = 7.2 Hz), 2.984 (t, 4H *J* = 7.2 Hz), 3.081 (d, 2H *J* = 7.0 Hz), 4.208 (t, 1H *J* = 7.1 Hz), 7.191-7.28 (m, 4H, *J* = 8 Hz, Ar-H), 7.209-7.788 (m, 3H, *J* = 6.6 Hz, Th-H); ^{13}C NMR ($CDCl_3$, δ ppm): 28.2 (3C), 42.5 (2C), 63.9 (2C), 77.0 (1C, C-1), 77.6 (1C, C-1), 79.6 (1C), 117.5 (2C), 128.3 (1C), 130.6 (2C), 133.6 (1C), 134.1 (1C), 135.5 (1C), 145.3 (1C), 154.5 (1C, N-C=O), 160.1 (1C, C-F), 190.7 (1C, C-3); MS *m/z*: 419.2 (M+1).

***tert*-Butyl 4-(1-(4-chlorophenyl)-3-oxo-3-(thiophen-2-yl)propyl)piperazine-1-carboxylate (5d):** By reaction of (*E*)-3-(4-chlorophenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**3d**, 10 mmol) and *N*-Boc piperazine (**4**, 10 mmol) obtained white solid in 91% yield, m.f.: $C_{22}H_{27}N_2O_3SCl$, m.p.: 96-97 ºC. IR (KBr, ν_{max}, cm^{-1}): 1681 (N-C=O), 1636 (C=O), 729 (C-S-C), 690 (Ar-Cl); ^{1}H NMR ($CDCl_3$, δ ppm): 1.448 (s, 9H), 2.711 (t, 4H *J* = 7.2 Hz), 2.864 (t, 4H *J* = 7.2 Hz), 3.091 (d, 2H *J* = 7.0 Hz), 4.070 (t, 1H *J* = 7.1 Hz), 7.322-7.394 (m, 4H, *J* = 7.6 Hz, Ar-H), 7.219-7.922 (m, 3H, *J* = 6.6 Hz, Th-H); ^{13}C NMR ($CDCl_3$, δ ppm): 28.3 (3C), 42.5 (2C), 64.1 (2C), 76.9 (1C, C-1), 77.8 (1C, C-2), 79.6 (1C), 122.1 (1C), 128.5 (2C), 129.7 (2C), 131.8 (1C, C-Cl), 133.7 (1C), 134.4 (1C), 138.5 (1C), 145.3 (1C), 154.8 (1C, N-C=O), 190.4 (1C, C-3); MS *m/z*: 435.2 (M+1).

***tert*-Butyl4-(1-(4-bromophenyl)-3-oxo-3-(thiophen-2-yl)propyl)piperazine-1-carboxylate (5e):** By reaction of (*E*)-3-(4-bromophenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**3e**, 10 mmol) and *N*-Boc piperazine (**4**, 10 mmol) obtained white solid in 92% yield, m.f.: $C_{22}H_{27}N_2O_3SBr$, m.p.: 97-99 ºC; IR (KBr, ν_{max}, cm^{-1}): 1679 (N-C=O), 1634 (C=O), 729 (C-S-C), 666 (Ar-Br); ^{1}H NMR ($CDCl_3$, δ ppm): 1.481 (s, 9H), 2.735 (t, 4H *J* = 7.2 Hz), 2.866 (t, 4H *J* = 7.2 Hz), 3.010 (d, 2H *J* = 7.0 Hz), 4.809 (t, 1H *J* = 7.1 Hz), 7.187-7.711 (m, 4H, *J* = 7.6 Hz, Ar-H), 7.286-7.760 (m, 3H, *J* = 6.6 Hz, Th-H); ^{13}C NMR ($CDCl_3$, δ ppm): 28.4 (3C), 42.5 (2C), 64.6 (2C), 77.0 (1C, C-1), 77.4 (1C, C-2), 79.6 (1C), 121.3 (1C, C-Br), 128.3 (1C), 129.8 (2C), 131.6 (2C), 133.6 (1C), 134.1 (1C), 138.5 (1C), 142.6 (1C), 154.5 (1C, N-C=O), 190.5 (1C, C-3); MS *m/z*: 479.1 (M+1).

***tert*-Butyl 4-(1-(4-nitrophenyl)-3-oxo-3-(thiophen-2-yl)propyl)piperazine-1-carboxylate (5f):** By reaction of (*E*)-3-(4-nitrophenyl)-1-(thiophen-2-yl)prop-2-en-1-one (**3f**, 10 mmol) and N-Boc piperazine (**4**, 10 mmol) obtained white solid in 71% yield, m.f.: $C_{22}H_{27}N_3O_5S$, m.p.: 100-102 ºC; IR (KBr, ν_{max}, cm^{-1}): 1671 (N-C=O), 1634 (C=O), 1350 (N-O), 732 (C-S-C); ^{1}H NMR ($CDCl_3$, δ ppm): 1.432 (s, 9H), 2.834 (t, 4H *J* = 7.2 Hz), 2.986 (t, 4H *J* = 7.2 Hz), 3.021 (d, 2H *J* = 7.0 Hz), 4.717 (t, 1H *J* = 7.1 Hz), 7.250-7.990 (m, 3H, *J* = 6.6 Hz, Th-H), 7.461-8.202 (m, 4H, *J* = 7.6 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 28.5 (3C), 43.5 (2C), 62.9 (2C), 76.8 (1C, C-1), 77.6 (1C, C-2), 79.6 (1C), 123.5 (2C), 125.8 (2C), 128.7 (1C), 131.6 (2C), 134.1 (1C), 138.5 (1C), 146.6 (1C, C-NO_2), 152.4 (1C, N-C=O), 191.9 (1C, C-3); MS *m/z*: 446.3 (M+1).

General procedure for the synthesis of amino derivatives of chalcones (7a-f): A stirred solution of *N*-Boc amino chalcones (**5a-f**, 0.01 mol) with trifluoroacetic acid (**6**, 0.01 mol) in the presence of dichloromethane was allowed to stand for 4 h. The progress of the reaction was monitored by TLC and after the completion, the reaction mixture was cooled in an ice bath (**Scheme-I**). The obtained solid products was separated and dried. The products were purified by column chromatography using silica gel (60-120 mesh) and ethyl acetate: benzene (0.5:7 v/v) as eluent.



Scheme-I: Schematic diagram for the synthesis of amino derivatives (**7a-f**)

3-Phenyl-3-(piperazin-1-yl)-1-(thiophen-2-yl)propan-1-one (7a): By reaction of *tert*-butyl 4-(3-oxo-1-phenyl-3-(thiophen-2-yl)propyl)piperazine-1-carboxylate (**5a**, 10 mmol) and trifluoroacetic acid (**6**, 10 mmol) obtained white solid in 86% yield, m.f.: $C_{17}H_{20}N_2OS$, m.p.: 68-70 ºC; IR (KBr, ν_{max}, cm^{-1}): 3405 (N-H), 1672 (C=O), 733 (C-S-C); ^1H NMR ($CDCl_3$, δ ppm): 1.478 (s, 1H, NH), 3.143-3.150 (t, 4H *J* = 7.2 Hz), 3.155-3.168 (t, 4H *J* = 7.2 Hz), 3.698 (d, 2H *J* = 7.0 Hz), 3.723 (t, 1H *J* = 7.1 Hz), 7.286-7.441 (m, 5H, *J* = 7.6 Hz, Ar-H), 7.210-7.894 (m, 3H, *J* = 6.6 Hz, Th-H); ^{13}C NMR ($CDCl_3$, δ ppm): 43.2 (2C), 45.8 (2C), 77.3 (1C, C-3), 81.2 (1C, C-2), 128.4 (2C), 128.7 (1C), 129.6 (2C), 132.4 (1C), 133.1 (1C), 134.1 (1C), 136.5 (1C), 145.3 (1C), 182.1 (1C, C-1); MS *m/z*: 301.1 (M+1).

3-(Piperazin-1-yl)-1-(thiophen-2-yl)-3-(*p*-tolyl)propan-1-one (7b): By reaction of *tert*-butyl 4-(3-oxo-3-(thiophen-2-yl)-1-(*p*-tolyl)propyl)piperazine-1-carboxylate (**5b**, 10 mmol) and trifluoroacetic acid (**6**, 10 mmol) obtained white solid in 90% yield, m.f.: $C_{18}H_{22}N_2OS$, m.p.: 88-90 ºC; IR (KBr, ν_{max}, cm^{-1}): 3399 (N-H), 1681 (C=O), 749 (C-S-C); ^1H NMR ($CDCl_3$, δ ppm): 1.493 (s, 1H, NH), 2.405 (s, 3H), 3.133-3.145 (t, 4H *J* = 7.2 Hz), 3.157-3.371 (t, 4H *J* = 7.2 Hz), 3.713 (d, 2H, *J* = 7.0 Hz), 4.822 (t, 1H *J* = 7.1 Hz), 7.387-7.426 (m, 4H, *J* = 7.6 Hz, Ar-H), 7.206-7.889 (m, 3H, *J* = 6.6 Hz, Th-H); ^{13}C NMR ($CDCl_3$, δ ppm): 21.5 (1C), 43.2 (2C), 45.8 (2C), 77.4 (1C, C-3), 81.2 (1C, C-2), 128.2 (2C), 128.5 (1C), 129.7 (2C), 131.8 (1C), 133.1 (1C), 141.1 (1C), 144.5 (1C), 145.6 (1C), 182.1 (1C, C-3); MS *m/z*: 315.4 (M+1).

3-(4-Fluorophenyl)-3-(piperazin-1-yl)-1-(thiophen-2-yl)-propan-1-one (7c): By reaction of *tert*-butyl 4-(1-(4-fluorophenyl)-3-oxo-3-(thiophen-2-yl)propyl)piperazine-1-carboxylate (**5c**, 10 mmol) and trifluoroacetic acid (**6**, 10 mmol) obtained white solid in 93% yield, m.f.: $C_{17}H_{19}FN_2OS$, m.p.: 90-91 ºC; IR (KBr, ν_{max}, cm^{-1}): 3398 (N-H), 1671 (C=O), 1064 (Ar-F), 767 (C-S-C); ^1H NMR ($CDCl_3$, δ ppm): 1.464 (s, 1H, NH), 3.126-3.132 (t, 4H *J* = 7.2 Hz), 3.145-3.158 (t, 4H *J* = 7.2 Hz), 3.705 (d, 2H *J* = 7.0 Hz), 6.420 (t, 1H *J* = 7.1 Hz), 7.188-7.786 (m, 4H, *J* = 8 Hz, Ar-H), 7.285-7.867 (m, 3H, *J* = 6.6 Hz, Th-H); ^{13}C NMR ($CDCl_3$, δ ppm): 43.2 (2C), 45.8 (2C), 77.4 (1C, C-3), 81.2 (1C, C-2), 116.2 (2C), 128.3 (1C), 130.3 (2C), 134.0 (1C), 142.8 (1C), 145.3 (1C), 153.9 (1C), 162.8 (1C, C-F), 181.9 (1C, C-1); MS *m/z*: 319.1 (M+1).

3-(4-Chlorophenyl)-3-(piperazin-1-yl)-1-(thiophen-2-yl)propan-1-one (7d): By reaction of *tert*-butyl 4-(1-(4-chlorophenyl)-3-oxo-3-(thiophen-2-yl)propyl)piperazine-1-carboxylate (**5d**, 10 mmol) and trifluoroacetic acid (**6**, 10 mmol) obtained white solid in 95% yield, m.f.: $C_{17}H_{19}N_2OSCl$, m.p.: 95-97 ºC; IR (KBr, ν_{max}, cm^{-1}): 3386 (N-H), 1672 (C=O), 794 (Ar-Cl), 768 (C-S-C); ^1H NMR ($CDCl_3$, δ ppm): 1.472 (s, 1H, NH), 3.133-3.145 (t, 4H *J* = 7.2 Hz), 3.157-3.371 (t, 4H *J* = 7.2 Hz), 3.713 (d, 2H *J* = 7.0 Hz), 4.598 (t, 1H *J* = 7.1 Hz), 7.380-7.419 (m, 4H, *J* = 7.6 Hz, Ar-H), 7.201-7.883 (m, 3H, *J* = 6.6 Hz, Th-H); ^{13}C NMR ($CDCl_3$, δ ppm): 43.2 (2C), 45.8 (2C), 77.3 (1C, C-3), 81.2 (1C, C-2), 128.4 (2C), 128.7 (1C), 129.6 (2C), 132.4 (1C, C-Cl), 133.1 (1C), 134.1 (1C), 136.5 (1C), 145.3 (1C), 181.8 (1C, C-1); MS *m/z*: 335.8 (M+1).

3-(4-Bromophenyl)-3-(piperazin-1-yl)-1-(thiophen-2-yl)-propan-1-one (7e): By reaction of *tert*-butyl4-(1-(4-bromophenyl)-3-oxo-3-(thiophen-2-yl)propyl)piperazine-1-carboxylate (**5e**, 10 mmol) and trifluoroacetic acid (**6**, 10 mmol) obtained white solid in 95% yield, m.f.: $C_{17}H_{19}N_2OSBr$, m.p.: 99-100 ºC; IR (KBr, ν_{max}, cm^{-1}): 3381 (N-H), 1672 (C=O), 763 (C-S-C), 723 (Ar-Br); ^1H NMR: δ 1.481 (s, 1H, NH), 3.137-3.148 (t, 4H *J* = 7.2 Hz), 3.687-3.699 (t, 4H *J* = 7.2 Hz), 3.711 (d, 2H *J* = 7.0 Hz), 4.809 (t, 1H, *J* = 7.1 Hz), 7.187-7.714 (m, 4H, *J* = 7.6 Hz, Ar-H), 7.286-7.760 (m, 3H, *J* = 6.6 Hz, Th-H); ^{13}C NMR ($CDCl_3$, δ ppm): 42.5 (2C), 45.2 (2C), 77.4 (1C, C-3), 79.6 (1C, C-2), 80.1 (1C), 122.1 (1C, C-Br), 128.3 (2C), 132.2 (2C), 133.6 (1C), 134.1 (1C), 142.6 (1C), 145.3 (1C), 190.5 (1C, C-1); MS *m/z*: 379.1 (M+1).

3-(4-Nitrophenyl)-3-(piperazin-1-yl)-1-(thiophen-2-yl)-propan-1-one (7f): By reaction of *tert*-butyl 4-(1-(4-nitrophenyl)-3-oxo-3-(thiophen-2-yl)propyl)piperazine-1-carboxylate (**5f**, 10 mmol) and trifluoroacetic acid (**6**, 10 mmol) obtained white solid in 70% yield, m.f.: $C_{17}H_{19}N_3O_3S$, m.p.: 105-107 ºC; IR (KBr, ν_{max}, cm^{-1}): 3077 (N-H), 1640 (C=O), 1352 (N-O), 720

(C-S-C); ^{1}H NMR ($CDCl_3$, δ ppm): 1.480 (s, 1H, NH), 3.201-3.211 (t, 4H *J* = 7.2 Hz), 3.699-3.689 (t, 4H *J* = 7.2 Hz), 3.711 (d, 2H *J* = 7.0 Hz), 4.902 (t, 1H, *J* = 7.1 Hz), 7.241-7.817 (m, 3H, *J* = 6.6 Hz, Th-H), 7.680-8.263 (m, 4H, *J* = 7.6 Hz, Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 42.6 (2C), 45.9 (2C), 77.4 (1C, C-3), 79.6 (1C, C-2), 80.1 (1C), 122.1 (1C), 128.3 (2C), 132.2 (2C), 133.6 (1C), 134.1 (1C), 142.6 (1C), 146.1 (1C, C-NO_2), 192.5 (1C, C-1); MS *m/z*: 345.1 (M+1).

Antibacterial activity: The antibacterial activity of compounds **7a**, **7b**, **7c**, **7d**, **7e** and **7f** was assessed using a modified agar well-diffusion assay. For this investigation, we used both freshly subcultured bacteria and bacteria that had been in culture for 18 to 24 h. Mueller-Hinton agar (MHA) was employed as medium and the bacterial pathogens tested included *E. coli*, *S. aureus* and *P. aeruginosa*. Wells with a diameter of 6 mm were created in the agar using a sterile borer and different concentrations of compounds **7a**, **7b**, **7c**, **7d**, **7e** and **7f** stock solutions (5, 2.5 and 1.25 mg/mL) were added to the wells. Streptomycin, ciprofloxacin and chloramphenicol at a concentration of 1 mg/mL were used as positive control, while DMSO served as negative control. After incubation for 24 h at 37 ºC, the zone of inhibition was measured.

Antifungal activity: The antifungal efficacy of compounds **7a**, **7b**, **7c**, **7d**, **7e** was investigated using the agar well diffusion approach, with *Candida albicans* (MTCC-1637), *Aspergillus brassiliensis* (MTCC- 1344) and *Aspergillus flavus* (MTCC-9606) as fungal pathogens. The spore suspension from the test fungus culture was swabbed onto sterile (SDA) Sabouraud Dextrose Agar (Himedia Laboratories Pvt. Ltd., India) medium. The wells were dveloped with a sterile borer on Sabouraud dextrose agar medium plates and loaded with different concentrations (5 mg/mL and 2.5 mg/mL). Standard antibiotic (fluconazole, 1 mg/mL) were used as a positive control and DMSO was used as a negative control under aseptic circumstances. After being incubated upright for 2-3 days at 27 ºC.

RESULTS AND DISCUSSION

The synthesis of heterocyclic chalcones (**3a-f**) involves the reaction between 2-acetyl thiophene and *p*-substituted benzaldehyde in the presence of NaOH base in ethyl alcohol-water solvent system. Adopting this synthetic methodology, the product yield in the 75-95% range was achieved in the presence of ethanol and water, which recognized as effective and environmentally friendly solvents.

The structural elucidation of the synthesized compounds were done by mass, IR, NMR analysis by considering compound **3b** as the representative compound among the series. In IR spectra, the major peaks at 1640, 1592 and 719 cm^{-1} are attributed due to C=O group, alkenyl C=C group and C-S-C group, respectively. Compound **3b** showed M^+ ion peak corresponding to molecular mass at *m/z* (M+1) value. In ^{1}H NMR spectra, the alkenyl proton each for HC=C and C=CH appeared as doublets at δ 7.192 (*J* = 15.3 Hz) and 7.842 (*J* = 15.5 Hz) ppm, respectively. The signals appeared as singlet for three protons at δ 2.416 ppm were assigned to CH_3 protons while as multiplet for three protons at δ 7.203 -7.892 (*J* = 6.5 Hz) was due to thiophene ring and multiplet for four protons at 7.558-7.698 (*J* = 7.6 Hz) ppm were due to aromatic protons. In ^{13}C NMR spectrum, compound **3b** showed a signal at δ 182.1, 120.6 and 145.6 ppm due to C-1, C-2 and C-3 carbons of the carbonyl propene. A signal appeared for one methyl carbons at δ 21.5 ppm was assigned to CH_3 carbon. An array of signals appeared at δ 129.7, 131.6, 133.7, 144.1 ppm were ambiguously assigned to thiophene ring carbons. An array of signals appeared at δ 128.2, 128.2, 128.5, 128.5, 131.9, 141.1 ppm were ambiguously assigned to aromatic carbons. Similar and consistent pattern signals were also observed in the IR, ^{1}H NMR, ^{13}C NMR and mass spectra of a synthesized compounds (**3a-f**), which strongly supports the structure for the synthesized compounds.

The synthesis of chalcone *N*-Boc piperazine derivatives (**5a-f**) involves the reaction between heterocyclic chalcones and *N*-Boc piperazine in ethyl alcohol solvent medium, product yield in the range 71-92% has been achieved. The structural assignments were characterized by considering compound **5e** as the representative compound among the series. In IR spectra, the major peaks at 1679, 1634, 729 and 666 cm^{-1} are due to nitrogen linked carbonyl group N-C=O, C=O group, C-S-C due to thiophene and C-Br group, respectively. Compound **5e** showed M^+ ion peak corresponding to is molecular mass at *m/z* (M+1) value. In ^{1}H NMR spectra, the methylene proton for H_2C-C appeared as doublets at δ 3.010 (*J* = 7.0 Hz) ppm and for C-CH appeared as triplets at δ 4.809 (*J* = 7.1 Hz) ppm, respectively. The signals appeared as triplet for four hydrogens at δ 2.735 (*J* = 7.2 Hz) ppm and for four hydrogens at δ 2.866 (*J* = 7.2 Hz) ppm of the piperazine ring. The signals appeared as singlet for nine protons at δ 1.481 ppm were assigned to *tertiary* butyl protons while as multiplet for three protons at δ 7.286-7.760 (*J* = 6.6 Hz) ppm due to thiophene ring and four protons at δ 7.187-7.711 (*J* = 7.6 Hz) ppm were due to aromatic protons. In ^{13}C NMR spectrum, compound **5e** showed a signal at δ 77.0, 77.4 and 190.5 ppm due to C-1, C-2 and C-3 carbons of the carbonyl propane. A signal carbonyl carbon N-C=O showed at δ 154.5 ppm and for *tertiary* carbon at δ 79.6 ppm and for three carbons at δ 28.4 ppm due to N-Boc *tertiary* butyl groups. A signal appeared for two carbons at δ 42.5 ppm and for two carbons at δ 64.6 ppm were assigned to piperazine ring. An array of signals appeared at δ 128.3, 133.6, 134.1, 142.6 ppm were ambiguously assigned to the thiophene ring carbons. An array of signals appeared at δ 129.8, 129.8, 131.6, 131.6, 138.5 ppm were ambiguously assigned to the aromatic carbons. Similar and consistent pattern signals were also observed in the IR, ^{1}H NMR, ^{13}C NMR and mass spectra of a synthesized series compounds (**5a-f**), which strongly supports the structure proof for the synthesized compounds.

In amino derivatives of chalcones (**7a-f**), the structural assignments were confirmed by mass, IR, NMR analysis by considering compound **7d** as the representative compound among the series. In IR spectra, the major peaks at 3386, 1672, 794 and 768 cm^{-1} are due to N-H stretching, carbonyl group, Ar-Cl and thiophene C-S-C group, respectively. Compound **7d** showed M^+ ion peak corresponding to its molecular mass at *m/z* (M+1) value. In ^{1}H NMR spectra, the methylene proton for H_2C-C appeared as doublets at δ 3.713 (*J* = 7.0 Hz) ppm and for C-CH appeared as triplets at δ 4.598 (*J* = 7.1 Hz) ppm,

respectively. The signals appeared as triplet for four hydrogens at δ 3.133-3.145 (J = 7.2 Hz) ppm and for four hydrogens at δ 3.157-3.371 (J = 7.2 Hz) ppm of the piperazine ring. The signal appeared as singlet for one proton at δ 1.472 ppm were assigned to N-H protons while as multiplet for three protons at δ 7.201-7.883 (J = 6.6 Hz) ppm due to thiophene ring and for four protons at 7.380-7.419 (J = 7.6 Hz) ppm were due to aromatic protons. In ^{13}C NMR spectrum, compound **7d** showed a signal at δ 181.1, 81.2 and 77.3 ppm due to C-1, C-2 and C-3 carbons of the carbonyl propane. A signal appeared for two carbons at δ 43.2 and two carbons at δ 45.8 ppm were assigned to piperazine ring. An array of signals appeared at δ 128.7, 133.1, 134.1, 145.3 ppm were ambiguously assigned to the thiophene ring carbons. An array of signals appeared at δ 128.4, 128.4, 129.6, 129.6, 136.5 ppm were ambiguously assigned to the aromatic carbons. Similar and consistent pattern signals were observed in the IR, ^{1}H NMR, ^{13}C NMR and Mass spectra of a synthesized series compounds **7a-f**, which strongly supports the structure for the synthesized compounds.

Antibacterial activity: The antibacterial activity of compound **7a** was found to be significant for all the studied bacteria species. However, it is almost comparable to compounds **7c** and **7e**. For *E. coli* antibacterial effect of compounds **7a** and **7c** are similar, however, compound **7e** has slightly lesser effect. Thus, the observed order of antibacterial activity, compound **7a** (R = H) > compound **7c** (R = F) > compound **7e** (R = Br) > compound **7d** (R = Cl) > compound **7f** (R = NO_2) was observed. For *S. aureus* antibacterial activity is in the order: **7a > 7e > 7c > 7b > 7d > 7f**, whereas For *P. aeruginosa* antibacterial activity is in the order of **7a, 7c > 7d > 7b > 7e > 7f** (Table-1).

Antifungal activity: All the synthesized compounds (**7a-f**) show more antifungal effect towards *Aspergillus brassiliensis* when compared to *Candida albicans* and *Aspergillus flavus.* For *Candida albicans* antifungal activity is in the order of **7b**, **7c > 7a > 7e > 7d > 7f**. Here **7b** and **7c** are equal antifungal effect. For *Aspergillus brassiliensis* antifungal activity is in the order of **7a > 7d > 7e > 7b > 7c > 7f**. Here **7b** is slightly greater than **7c**. For *Aspergillus flavus* the activity is in the order of **7c > 7a**, **7b**, **7d > 7e > 7f** (Table-2).

Conclusion

The simple easy accessible procedure for the synthesis of amino chalcone derivatives *via* Claisen-Schmidt condensation of substituted aromatic aldehydes and heterocyclic ketones followed by hydroamination and their *in vitro* antibacterial and antifungal activity results revealed the significance of the study. The newly synthesized compounds exhibited moderated to good antibacterial activity and antifungal activity against the tested microorganisms, compounds having halo substituted in which fluoro substitutent in the benzene ring demonstrated potent antibacterial and antifungal activity due to negative inductive effect, whereas nitro substitutent showed poor activity due to both the negative inductive effect and resonance effect.

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CONFLICT OF INTEREST

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

TABLE-1
ZONE OF INHIBITION VALUES OF THE ANTIBACTERIAL ACTIVITY OF **7a-f** AND STANDARD ANTIBIOTICS AT DIFFERENT CONCENTRATIONS AGAINST BACTERIAL PATHOGENS

Bacteria	Measurement of zone of inhibition in diameter (mm)											
	7a (mg/mL)			**7b** (mg/mL)			**7c** (mg/mL)			**7d** (mg/mL)		
	5.0	2.5	1.25	5.0	2.5	1.25	5.0	2.5	1.25	5.0	2.5	1.25
E. coli	15	13	12	14	13	12	15	14	12	14	13	12
S. aureus	16	13.5	12	15	13	10	14	13	11	13	12	11
P. aeruginosa	17	15	14	14	13	12	17	16	15	15	14	13

	7e (mg/mL)			**7f** (mg/mL)			Streptomycin	Ciprofloxacin	Chloramphenicol
	5.0	2.5	1.25	5.0	2.5	1.25			
E. coli	14.5	13.5	11	10	9	8	19.10	28.13	23.06
S. aureus	15	14	13	12	11	10	10.16	33.93	26.03
P. aeruginosa	14	13	12	13	12	11	22.06	23.96	24.10

TABLE-2
ZONE OF INHIBITION VALUES OF THE ANTIFUNGAL ACTIVITY OF **7a-f** AND STANDARD ANTIFUNGAL AT DIFFERENT CONCENTRATIONS AGAINST FUNGAL PATHOGENS

Fungi	Measurement of zone of inhibition in diameter (mm)												
	7a (mg/mL)		**7b** (mg/mL)		**7c** (mg/mL)		**7d** (mg/mL)		**7e** (mg/mL)		**7f** (mg/mL)		Fluconazole
	5.0	2.5	5.0	2.5	5.0	2.5	5.0	2.5	5.0	2.5	5.0	2.5	
Candida albicans	11.10	10.00	12.00	10.05	12.00	11.00	10.10	10.00	10.20	10.00	9.00	8.00	17.5
Aspergillus brassiliensis	15.05	12.10	12.10	11.00	12.05	10.00	13.10	11.00	13.00	12.00	10.00	9.00	16.0
Aspergillus flavus	11.00	10.00	11.10	10.00	13.10	10.00	11.10	10.00	11.00	10.00	8.00	7.00	20.5

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