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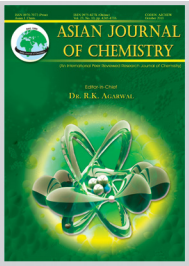

Synthesis and Biological Activity of Heterocycles from Chalcone

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The reaction between aromatic or heteroaromatic *ortho*-diamines and chalcone **1**$_{a,b}$ is a convenient and versatile method for the preparation of condensed 1,4-diazepines **2**$_{a,b}$ and **4**$_{a,b}$. 2,4-Diaryl-2,3-dihydro[1,5]benzothiazepines **5**$_{a,b}$ were obtained from the condensation of chalcone **1**$_{a,b}$ with 2-aminothiophenol in presence of catalytic amount of acid. The reaction of 2,3-diaminopyridine with chalcone dibromides **6**$_{a,b}$ afforded the corresponding enaminoketones **7**$_{a,b}$, which cyclized to 6,8-diaryl-7,8-dihydro-9*H*-pyrido[4,5-b][1,4]diazepine **9**$_{a,b}$ under acid condition. All synthesized compounds were characterized using IR, ^{1}H NMR, ^{13}C NMR, MS and elemental analysis. The compounds were screened for their antibacterial and antifungal activities. The synthesized compounds have shown activity against all the bacterial and fungal strains.

Key Words: Fused 1,4-diazepine, 1,5-Benzothiazepine, Antimicrobial activity.

INTRODUCTION

Infectious diseases are responsible for great number of death in the world population. The reduction of sensibility to antimicrobial agents in current use has been increasing for a great variety of pathogens and the resistance to multiple drugs is common for several microorganisms, especially for gram-positive bacteria. Infection by methicillin-resistant *Staphylococcus aureus* and Vancomycin-resistant Enterococci presents a difficult problem for medicine[1-5]. In addition, the treatment of infectious diseases is much more complicated in immunosuppressed patient such as those infected with HIV, undergoing anticancer therapy or transplants. Given the evidence for the rapid global spread of resistant clinical isolates and the appearance of drug-resistant strains among community acquired infection, the need for discovery or optimization of antimicrobial agents active against these resistant strains are of paramount importance.

Synthesis of chalcone and their derivatives has attracted considerable attention due to their significant biological activity[6]. Chalcone have been reported to have many useful properties like anti-inflammatory, antimicrobial[7], antioxidant[8], cytotoxic, antitumor, anticancer activities[9]. Chalcone shows a highly electrophilic α,β-unsaturated carbonyl moiety, which is responsible for antiinflammatory activity[10]. Synthetic chalcone inhibited the release of chemical mediators from mast cells, neutrophils, macrophages and microglial cells *in vitro* and suppressed the edematous response *in vivo*[11]. Chalcone derivatives exerted acute and chronic antiinflammatory effects related to the inhibition of nitric oxide (NO), 5-LO (5-lipooxygenase) and PGE_2 (prostaglandin E_2) overproduction by blocking the activation of nuclear factor -KB (NF-KB) pathway and cyclooxygenase pathway[12-16].

Condensed pyrimidine derivatives have been reported as antibacterial[17], analgesic antiviral, antiinflammatory[18], anti HIV[19], antitubercular[20], antitumor[21], antineoplastic[22], antiparkinsonian[23], diuretic[24] and antimycobacterial[25]. Pyrimido[4,5-b] [1,4] diazepines derivatives,compounds are characterized by having biological and pharmacological properties[26].

Benzothiazepines are active constituents of a series of new potent bradykinin agonists. Some of these compounds have also shown activity as antibacterial and antimicrobial activity, calming activity, calcium channel antagonists, enzyme inhibitors, muscle relaxants, hypnotics, antipsychotics, coronary vasodilators, calcium antagonists and antidepressants[27-36]. In view of the variety of pharmacological properties exhibited by chalcone, which promoted to undertake its synthesis and conversion to other heterocycles which may show different or better physiological activities.

EXPERIMENTAL

Melting points were measured with Gallenkamp electrothermal melting point apparatus in capillary tubes and are uncorrected ^{1}H and ^{13}C NMR spectra were recorded on a Brucker 400 MHz with (DMSO) as solvent and tetramethylsilane as an internal standard chemical shifts are a δ units (ppm). The

mass spectra were recorded on Ms-S988 operating at 70 eV. The IR spectra were recorded on a pye-unicam SP-3-100 spectrophotometer using KBr Wafer Technique. Elemental analysis was determined using a Perkin-Elmer 240C micro-analyses. The synthesized compounds $\mathbf{1}_{a,b}$-$\mathbf{9}_{a,b}$ were screened for their *in vitro* antibacterial and antifungal activities.

Compounds $\mathbf{1}_{a,b}$ and $\mathbf{6}_{a,b}$ were prepared according to the literature procedure[37,38].

2,4-Diaryl-3,4-dihydro-5*H*-[1,5]benzodiazepine $\mathbf{2}_{a,b}$: A mixture of compound $\mathbf{1}_a$ or **b** (2.20 or 1.88 g, 1 mmol) and *o*-phenylenediamine (1.08 g, 1 mmol) in absolute butanol (20 mol) was heated under reflux and followed up by TLC. The reaction was completed after 12 h and solvent was evaporated to dryness. The precipitate was collected, washed with petroleum ether (40-60 ºC) (5 mL), dried and recrystallized from ethanol.

2a: IR (KBr, ν_{max}, cm^{-1}) 3212 (NH), 3005 (Ar-CH), 1459 (C=N); ^{1}H NMR (DMSO): δ 7.54-7.38 (d, 1H, NH, J = 6.31 Hz) 6.95-7.05 (m, 4H, Ar-H), 7.22-7.34 (m, 6H, thiophene-H), 4.18-4.02 (dd, 1H, H-2, J_{ax} = 5.01, J_{bx} = 11.08 Hz), 3.44-3.18 (dd, 1H, H3-a, J_{ax} = 6.82, J_{ab} = 11.31 Hz), 3.62-3.70 (dd, 1H, J_{bx} = 4.22, J_{ab} = 9.08 Hz), ^{13}C NMR: δ C-2 (58.04), C-3(38.11), C-4 (148.07), C-5a (118.70), C-6 (130.31), C-7 (133.38), C-8 (137.11), C-9 (138.00), C-9a (140.22), thiophene-C (129.82, 139.92, 142.45, 144.56); MS, m/z: 31 (M^+) (1.2 %), 200 (100 %). Anal. calcd. (%) for $C_{17}H_{14}N_2S_2$; C, 65.80; H, 4.51; N, 9.03, S, 20.64; found (%): C, 65.50; H, 4.32; N, 8.95; S, 21.00.

2b: IR (KBr, ν_{max}, cm^{-1}): 3230 (NH), 3030 (Ar-CH), 1640 (C=N); ^{1}H NMR (DMSO): δ 7.77-7.11 (d, 1H, NH, J = 5.11 Hz) 7.20-7.30 (m, 6H, furane-H), 4.28-3.95 (dd, 1H, H-2, J_{ax} = 6.65, J_{bx} = 9.83Hz), 4.20-4.11 (dd, 1H, J_{bx} = 5.02, J_{ab} = 11.13 Hz); ^{13}C NMR: δ C-2 (60.11), C-3 (38.02), C-4 (151.33), C-5a (120.11), C-6 (130.11), C-7 (140.88), C-8 (142.51), C-9 (142.99), C-9a (144.03), furane-C (130.11, 133.88, 134.00, 138.42); MS, m/z: 278 (M^+) (0.8 %), 184 (100 %). Anal. calcd. (%) for $C_{17}H_{14}N_2O_2$: C, 73.38, H, 5.03, N, 10.07, found (%): C, 73.40; H, 5.11; N, 10.00.

2-Aryl benzimidazole $\mathbf{3}_{a,b}$

Method A: Equimolecular amount of the chalcone $\mathbf{1}_a$ or **b** (2.20 or 1.88 g, 1 mmol) and *o*-phenylenediamine (1.08 g, 1 mmol) were fused together on an oil bath at 170-190 °C for 6 h. After cooling, the obtained solid was crushed and extracted with hot ethanol. The ethanol extract was evaporated to dryness and the result solid was crystallized to yield the desired product $\mathbf{3}_{a,b}$.

3a: IR (KBr, ν_{max}, cm^{-1}): 3230 (NH), 3050 (Ar-CH), 1659 (C=N), 1595 (C=C). ^{1}H NMR (DMSO): δ 10.80 (s, 1H, NH), 7.88-7.13 (m, 7H, Ar-H); MS, m/z: 200 (M^+) (1.2 %), 76 (100 %). Anal. calcd. (%) for: $C_{11}H_8N_2S$: C, 66.00, H, 4.00; N, 14.00, S, 16.00. Found (%): C, 66.12, H, 4.80, N,14.11, S, 16.38.

3b: IR (KBr, ν_{max}, cm^{-1}): 3244 (NH), 1460 (C=N), 1600 (C=C); ^{1}H NMR, (DMSO) δ 11.00 (s, 1H, NH), 8.11-7.58 (m, 7H, Ar-H); MS, m/z: 184 (M^+) (3.11 %), 76 (100 %). Anal. calcd. (%) for $C_{11}H_8N_2O$: C, 71.73; H, 4.34; N, 15.21. Found (%): C, 71.70; H, 4.30; N, 15.38.

Method B: A mixture of the acetylthiophene or acetyl furane (1.26 or 11.0 g, 1 mmol) and *o*-phenylene diamine (1.08 g, 1 mmol) was fused in an oil bath at 180-200 °C for 8 h. The obtained solid on cooling was dissolved hot ethanol and recrystallized to give benzimidazole derivatives $\mathbf{3}_{a,b}$, identical to the above described sample with respect to melting point and IR spectrum.

Method C: Benzodiazepine derivatives $\mathbf{2}_{a,b}$ were heated in an oil-bath at 180-200 °C for 6 h. After cooling, the resulted darkness crushed and extracted with boiling benzene. The benzene extract was evaporated to dryness and recrystallized from ethanol to give the benzimidazole derivatives $\mathbf{3}_{a,b}$ in 15 and 20 % yield. The benzimidazole derivatives $\mathbf{3}_{a,b}$ were identified by melting points and mixed melting points and comparison with authentic samples previously obtained by fusion.

6,8-Diaryl-7,8-dihydro-9*H*-pyrimido[4,5-b][1,4]-diazepine ($\mathbf{4}_{a,b}$): A solution of 1,3-diaryl-2-propenone (chalcone) $\mathbf{1}_{a,b}$ (2.20 or 1.8 g, 1 mmol) and 5,6-diaminopyrimidine (1.10 g, 1 mmol) in ethanol (15 mL) and acetic acid (1 mL) was refluxed for 6 h. The reaction mixture was neutralized with ammonia and cooled to 0 ºC. The precipitate that formed overnight was filtered off and recrystallized.

4a: IR (KBr, ν_{max}, cm^{-1}): 3100 (Ar-CH), 3380 (NH), 2700 (aliph.-CH), 1620 (C=N), 1600 (C=C); ^{1}H NMR (DMSO) δ 7.12-7.08 (d 1H, NH, J = 7.11 Hz), 4.48-4.62 (dd, 1H, H-2, J_{ax} = 5.80, J_{bx} = 12.11 Hz), 2.80, 3.18 (dd, 1H, $H_{3\text{-}a}$, J_{ax} = 5,12, J_{ab} = 14.33 Hz); 3.72-3.77 (dd, 1H, $H_{3\text{-}b}$, J_{bx} = 6.22, J_{ab} = 11.01 Hz); MS: m/z 312 (M^+) (3.11 %), 186 (100 %); ^{13}C NMR: δ C-2 (60.11), C-3 (44.00), C-4 (160.82), C-5a (115.50) C-6 (158.11), C-8 (160.12), C-9a (164.18), Ar (144.20, 144.80, 146.00, 148.11). Anal. calcd. (%) for: $C_{15}H_{12}N_2S_2$: C, 57.69; H, 3.84; N, 17.94, S,20.51. Found (%): C, 57.30; H. 3.52; N, 18.00 S, 20.98.

4b: IR (KBr, ν_{max}, cm^{-1}): 3055 (Ar-CH), 3320 (NH), 2840 (aliph. CH). 1635 (C=N), 1600 (C=C); ^{1}H NMR (DMSO) δ 7.60-7.20 (d, 1H, NH, J = 5.00 Hz), 4.43-4.11 (dd, 1H, H-2, J_{ax} = 5.80, J_{bx} = 12.11 Hz), 3.18-2.80 (dd, 1H, $H_{3\text{-}a}$, J_{ax} = 5.12, J_{ab} = 14.33 Hz), 3.80-3.75 (dd, 1H, $H_{3\text{-}b}$, J_{bx} = 4.22, J_{ab} = 9.08 Hz); ^{13}C NMR; δ C-2 (60.50), C-3 (40.44), C-4), (158.70), C-5a (112.40), C-6 (160.20), C-8 (158.22), C-9a (154.17), Ar (147.30, 148.11, 149.50, 149.99); MS: m/z, 280 (M^+) 1.08 %), 186 (100 %). Anal. calcd. (%) for $C_{15}H_{12}N_4O_2$: C, 64.28; H, 4.28; N, 20.00; Found (%): C, 64.50, H, 4.11, N,19.98.

2,4-Diaryl-2,3-dihydro[1,5]benzothiazepine ($\mathbf{5}_{a,b}$): To a solution of chalcone $\mathbf{1}_{a,b}$ (8.80 or 7.52 g, 4 mmol) in ethanol (60 mL) was added *o*-aminothiophenol (4.60 g, 4 mmol). The mixture was heated to reflux for 0.5 h and then CF_3COOH (1.2 mL) was added. Refluxing was continued for 5-6 h. The solvent volume was reduced by half and the resulting mixture was allowed to stand at room temperature. The crystalline solid product was filtered, washed with ethanol (2-3 mL) and dried in air. The crude compound was recrystallized.

5a: IR (KBr, ν_{max}, cm^{-1}): 3050 (Ar-CH), 2885 (aliph.-CH), 1640 (C=N); ^{1}H NMR (DMSO): δ 7.88-7.05 (m, 10H , Ar-H), 3.61-3.59 (dd, 1H, H-2, J_{ax} = 5.22, J_{bx} = 9.13 Hz), 3.59-3.55 (dd, 1H, H_{3a}, J_{ax} = 4.22 Hz, J_{ab} = 10.70 Hz), 3.56-3.55 (dd, 1H, J_{bx} = 5.51, J_{ab} = 10.12 Hz); ^{13}C NMR: δ C-2 (55.55), C-3 (38.80), C-4 (152.50), C-5a (113.00), C-6 (164.43), C-7 (155.39), C-8 (154.00), C-9 (153.11), C-9a (152.80), Ar

(148.26, 135.88, 132.85, 131.66). MS: m/z: 327 (110 %), 217 (1.10 %). Anal. calcd. (%) for: $C_{17}H_{13}NS_3$: C, 62.38, H, 3.97, N, 4.28, S, 29.35. Found (%): C, 62.00; H, 4.00 N, 4.66, S, 30.01.

5b: IR (KBr, ν_{max}, cm^{-1}): 3090 (Ar-CH), 2900 (aliph. -CH), 1635 (C=N); ^{1}H NMR ($CDCl_3$): δ 8.11-7.12 (m, 10H, Ar-H), 3.33-3.12 (dd, 1H, H-2, J_{ax} = 6.13, J_{bx} = 8.55 Hz), 3.55-3.51 (dd, 1H, H-3a, J_{ax} = 4.72, J_{ab} = 9.04), 3.59-3.57 (dd, 1H, J_{bx} = 5.00, J_{ab} = 9.52 Hz); ^{13}C NMR: δ C-2 (50.13) C-3 (36.00), C-4 (150.22), C-5a) (112.12), C-6 (164.00), C-7 (160.88), C-8 (153.02) C-9 (155.99), C-9a (156.10), Ar (144.22, 144.92, 148.70, 148.98). MS: m/z: 295 (2.04 %), 217 (100 %). Anal. calcd. (%) for: $C_{17}H_{13}NO_2S$: C, 69.15, H, 4.40, N, 4.74, S, 10.84. Found (%): C, 70.01; H, 4.66; N, 4.35, S, 11.02.

Formation of β-aminochalcones ($7_{a,b}$) and chalcones ($8_{a,b}$): A mixture of 3-(*p*-nitrophenyl)-1-(theinyl or biphenyl)-2,3-dibromo-propenone $\mathbf{6}_{a,b}$[41] (8.54 or 9.94 g, 2 mmol), 2,6-diaminopyridine (2.18 g, 2 mmol) and (2.0 mL) of triethylamine in (60 mL) of ethanol was refluxed for 6 h. The solvent was removed in a rotary evaporator and the residue was crystallized from 1:3 mixture of chloroform and methanol, obtaining compound $\mathbf{7}_{a,b}$ after few days and second product $\mathbf{8}_{a,b}$[39] was recovered from the mother liquor.

7a: IR (KBr, ν_{max}, cm^{-1}): 3364, 3380, 3474 (NH_2, NH), 1660 (C=O), 1644 (C=N); ^{1}H NMR (DMSO): δ 6.44 (s, 2H, NH), 6.50 (s, 1H, =CH), 7.98-7.12(m, 6H, Ar-H), 7.18-7.12 (d, 2H, Ar-H, *J* = 7.33 Hz) 8.33-8.11 (d, 2H, Ar-H, *J* = 7.85 Hz). Anal: calcd. (%) for: $C_{18}H_{14}N_4O_3S$: C, 59.01; H, 3.82; N, 15.30; S, 8.74. Found (%): C, 59.66; H, 4.01; N, 15.00; S, 9.10.

7b: IR (KBr, ν_{max}, cm^{-1}): 3300, 3285, 3230 (NH2, NH), 1664 (C=O), 1635 (C=N). ^{1}H NMR (DMSO): δ 6.44 (s, 2H, NH_2) 6.70 (s, 1H, =CH), 7.80-7.28 (m, 8H, Ar-H), 8.78-8.68 (d, 2H, Ar-H, *J* = 6.44Hz), 7.28-7.16 (d, 2H, Ar-H, *J* = 11.08Hz). Anal: calcd. (%) for: $C_{26}H_{20}N_4O_3$: C, 71.55; H, 4.58; N, 11.00. Found (%): C, 71.88; H, 5.01, N, 11.82.

6,8-Diaryl-7,8-dihydro-9*H*-pyrido[4,5-b][1,4]diazepine ($9_{a,b}$): A mixture of compound $\mathbf{7}_a$ or $\mathbf{7}_b$ (7.32 or 8.72, 2 mmol) and (60 mL) of acetic acid in 15 mL) of methanol was reflux for 20 min. During this time refluxing, the solution became clear and solid crystalline precipitate of compound $\mathbf{9}_a$ or $\mathbf{9}_b$ was formed.

9a: IR (KBr, ν_{max}, cm^{-1}): 3320 (NH), 3090 (Ar-CH), 2880 (aliph.-CH), 1640 (C=N); ^{1}H NMR ($CDCl_3$), δ 8.22-8.12 (d, 1H, NH, *J* = 6.84 Hz) 5.28-5.24 (dd, 1H, H-5, J_{ax} = 7.11, J_{bx} = 10.07 Hz), 2.98-3.02 (dd, 1H, $H_{3\text{-}a}$. J_{ab} = 6.28, J_{bx} = 13.81 Hz), 3.38-3.32 (dd, 1H, $H_{3\text{-}b}$, J_{bx} = 6.08, J_{ab} = 10.12 Hz); 7.82-7.80 (d, 2H, Ar-H, *J* = 8.82 Hz), 8.00-7.96 (d, 2H, Ar-H, *J* = 10.12 Hz), 7.50-7.22 (m, 6H, Ar-H). ^{13}C NMR: δ C-2 (58.81), C-3 (38.11), C-4 (155.22), (C-5a) (108.11), (C-7) (160.22), (C-8) (161.04), C-9 (162.01), C-9a (166.81), Ar (147.21, 148.02, 148.81, 149.28, 150.33, 151.82, 151.99, 153.48, 153.99, 154.10); MS: m/z (350) (1.08 %). Anal. calcd. (%) for: $C_{18}H_{14}N_4O_2S$: C, 61.71, H, 4.00, N, 16.00; S, 9.14, found (%): C, 61.50; H, 3.98; N, 16.30; S, 9.00.

9b: IR (KBr, ν_{max}, cm^{-1}): 3300 (NH), 3100 (Ar-CH), 2900 (aliph. -CH), 1635 (C=N); ^{1}H NMR (DMSO): δ 6.80-6.76 (d, 1H, NH, *J* = 8.15 Hz), 6.18-5.98 (dd, 1H, H-5, J_{ax} = 8.02, J_{bx} = 11.82 Hz), 3.30-3.28 (dd, 1H, $H_{3\text{-}a}$, J_{ax} = 6.28, J_{ab} = 13.81 Hz), 4.04-3.83 (dd, 1H, $H_{3\text{-}b}$, J_{bx} = 6.08, J_{ab} = (10.12 Hz; 7.80-7.68 (dd, 4H, Ar-H, *J* = 8.11, *J* = 11.13 Hz), 8.11-8.08 (dd, 4H, Ar-H, *J* = 11.02. = 14.13 Hz); ^{13}C NMR: δ C-2 (60.11) C-3 (40.42), C-4 (154.13), $C_{5\text{-}a}$ (112.12), C-7 (118.11), C-8 (120.22), C-9 (128.27), C-9a (128.99), Ar-C (130.11, 130.11, 130.32, 130.89, 133.11, 134.50, 134.80, 135.83, 135.89, 136.11, 136.88, 138.08, 138.11, 138.98, 140.48, 142.22, 144.15, 145.98, 150.22. MS: m/z: 420 (3.83 %). Anal. calcd. (%) for: $C_{26}H_{20}N_4O_2$: C, 74.28; H, 4.76, N, 13.33. Found (%): C, 74.55; H, 4.50, N, 13.80.

RESULTS AND DISCUSSION

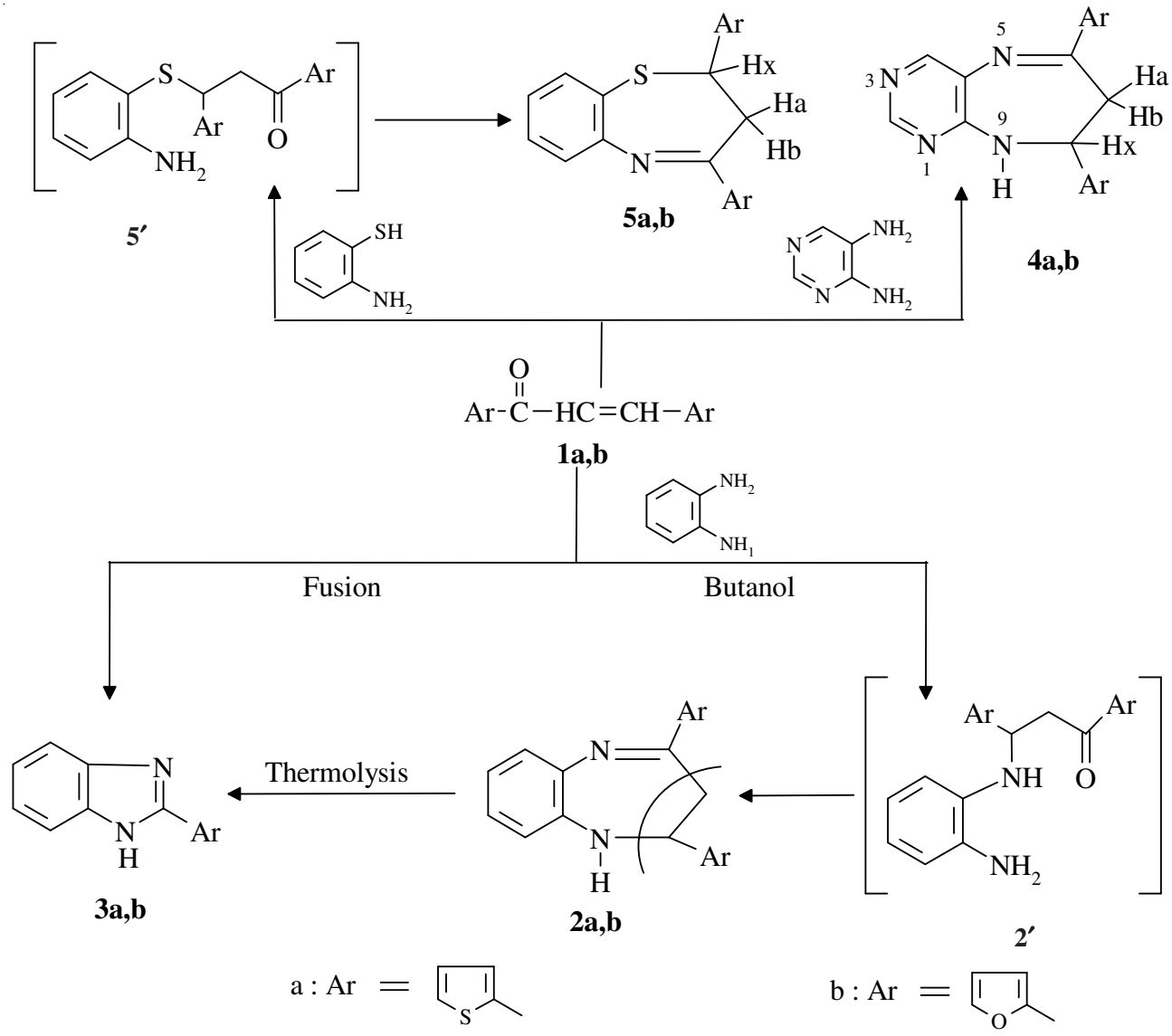
Several publication[40-42] reported the reaction of 1,2-diamines with chalcone and the nature of the products varied according to the experimental conditions. The present work reports the reaction between 1,3-diaryl-2-propenones (chalcones) $\mathbf{1}_{a,b}$ with *o*-phenylenediamine in refluxing butanol afforded the corresponding[1,4]diazepine derivatives $\mathbf{2}_{a,b}$. Formation of **2** is believed to proceed through the initial addition of the diamine to the ethylenic double bond **1** followed by intramolecular condensation of the amino group with the carbonyl function, afforded **2** as the sole product in 42-55 % yield. The structure of **2** was established in light of their elemental analysis and spectral data, the IR spectra of $\mathbf{2}_{a,b}$ showed close similarity with other previously reported analogous compounds[40]. The spectra exhibited (NH) as a single sharp band at 3380, 3350, while bands corresponding to (C=O) or (NH_2) of the diamine were not observed. The mass spectrum of $\mathbf{2}_a$, showed M^+ m/e = 310 (1.2 %) which corresponds to the molecular formula $C_{17}H_{14}N_2S_2$ and the base peak at m/e = 200 (100 %). On the other hand, when equimolar amount of the chalcone $\mathbf{1}_{a,b}$ and *o*-phenylenediamine are fused together without solvent at 170-190 ºC, the benzimidazole derivatives $\mathbf{3}_{a,b}$ were isolated, as the main product. Formation of benzimidazoles **3** is presumed to proceed through the intermediate formation of the corresponding diazepine derivative **2** followed by cleavage of the 1,4-diazacycloheptene ring to give **3**. Moreover, thermolysis of the benzodiazepine derivatives $\mathbf{2}_{a,b}$ at 180-200 °C afforded the same benzimidazole $\mathbf{3}_{a,b}$. these thermolysis showed close similarity with other previously reported analogous compounds[37]. In addition, $\mathbf{3}_{a,b}$ were prepared by fusion of acetyl thiophene or furan with *o*-phenylenediamine at 170 ºC. As regard to the mass spectrum of the benzimidazole derivatives $\mathbf{3}_{a,b}$, it is worthy to mention that its fragmentation pattern appears also with almost the same relative intensities, in the mass spectrum of the diazepine derivatives, which supports the view which previously discussed that benzodiazepines are intermediate compounds in the reaction leading to the benzimidazole formation, in agreement with other finding[40].

Heating of 5,6-diaminopyrimidine with molar quantities of 1,3-diaryl-2-propenones (chalcone) $\mathbf{1}_{a,b}$ in ethanol in the presence of catalytic amounts of acetic acid generates the desired products 6,8-diaryl-7,8-dihydro9*H*-pyrimido[4,5-b][1,4]diazepine $\mathbf{4}_{a,b}$ in yield between 60 and 45 %. 5,6-Diaminopyrimidine contains two type of non-equivalent amino group. Due to the electronic effect of the pyrimidine ring, the

amino group on C-5 has the highest nucleophilicity[42]. It condensation reaction with the carbonyl group of $\mathbf{1}_{a,b}$ can be followed by a Michael type addition of 6-amino group to the double bond. The IR spectra show typical bands at 3420-3380 and 1635-1620 cm^{-1} for NH and C=N stretching vibrations. A super position of other coupled C=C vibration of the ring system is observed for the region of 1600 cm^{-1} the ^1H NMR data of $\mathbf{4}_{a,b}$ showed the four protons on the 1,4-diazepine ring give rise to an ABMX spin system. The coupling of the proton on N-9 with (J = 7.11 Hz) indicates the vicinal position to the proton on C-8. The latter shows two coupling (J_{ax} = 5.80 Hz) and (J_{bx} = 12.11 Hz) to the methylene group (H_2C-7). The geminal proton on C-7 have a coupling constant (J_{ax} = 5.12, J_{ab} = 14.33 Hz) and (J_{bx} = 6.22, J_{ab} = 10.01 Hz) to (2-H) which generates two doublet of doublets.

The importance and utility of benzothiazepines have led to the development of numerous synthetic routes. They are usually prepared by cyclocondensation of 2-aminothiophenol (*o*-ATP) with 1,3-diaryl-2-propenones (chalcone) $\mathbf{1}_{a,b}$ in presence of a catalytic amount of acid[39] gave 2,4-diaryl-2,3-dihydro[1,5]-benzothiazepines $\mathbf{5}_{a,b}$ were obtained as the only products. The ^1H NMR spectrum of compound $\mathbf{5}_a$ showed (H-2) the two doublets of doublets (J_{ax} = 5.22 Hz, J_{bx} = 9.13 Hz). the geminal proton on C-3 have a coupling constant (J_{ax} = 4.72 Hz, J_{ab} = 10.70 Hz) and (J_{bx} = 5.51, J_{ab} =10.12 Hz) to (2-H) which generates two doublets of doublets (**Scheme-I** and Table-1).

Reaction of 2,3-diaminopyridine with 3-(*p*-nitrophenyl)-1-(thienyl or biphenyl)-2,3-dibromopropenone $\mathbf{6}_{a,b}$ in the presence of a basic catalyst leads to the formation of β-aminochalcones $\mathbf{7}_{a,b}$ and chalcone $\mathbf{8}_{a,b}$. This reaction was carried out upon heating with excess of triethylamine accelerate the dihydrobromination of intermediate bromoketone **7′** which lead to the enaminoketone $\mathbf{7}_{a,b}$, its cyclization in a 4:1 mixture of acetic acid and methanol gave 6,8-diaryl-7,8-dihydro-9*H*-pyrido[4,5-b][1,4]diazepine $\mathbf{9}_{a,b}$ (**Scheme-II**). The IR spectrum show typical bands at 3410-3320 and 1640 for the (NH) and (C=N) stretching vibration. The ^1H NMR data the proton on N-9 gives rise to a doublet (J = 6.84 Hz) indicating the vicinal position of the proton C-8. The *geminal* protons on (C-7) have



Scheme-I: Synthetic pathway for compound $\mathbf{2}_{a,b}$, $\mathbf{3}_{a,b}$, $\mathbf{4}_{a,b}$ and $\mathbf{5}_{a,b}$

TABLE-1
CRYSTALLIZATION SOLVENT, MELTING POINTS, YIELD PERCENTAGES, MOLECULAR FORMULAE AND MOLECULAR WEIGHTS OF COMPOUNDS **2**$_{a,b}$, **3**$_{a,b}$, **4**$_{a,b}$, **5**$_{a,b}$, **7**$_{a,b}$ AND **9**$_{a,b}$

Comp. No.	Cryst. solvent	m.p. (ºC)	Yield (%)	m.f. (m.w.)
2a	EtOH	150-2	55	$C_{17}H_{14}N_2S_2$(310)
2b	DMF	>360	42	$C_{17}H_{14}N_2O_2$(278)
3a	EtOH	330-2	72	$C_{11}H_8N_2S$(200)
3b	THF	>360	70	$C_{11}H_8N_2O$(184)
4a	MeOH	170-4	60	$C_{15}H_{12}N_4S_2$(312)
4b	EtOH	150-2	45	$C_{15}H_{12}N_4O_2$(280)
5a	EtOH	140-2	55	$C_{17}H_{13}NS_3$(327)
5b	EtOH	190-3	50	$C_{17}H_{13}NO_2S$(295)
7a	EtOH	160-4	72	$C_{18}H_{14}N_4O_3S$(366)
7b	EtOH/H_2O	110-3	70	$C_{26}H_{20}N_4O_3$(436)
9a	EtOH	240-2	55	$C_{18}H_{14}N_4O_2S$(350)
9b	EtOH	220-4	44	$C_{26}H_{20}N_4O_2$(420)

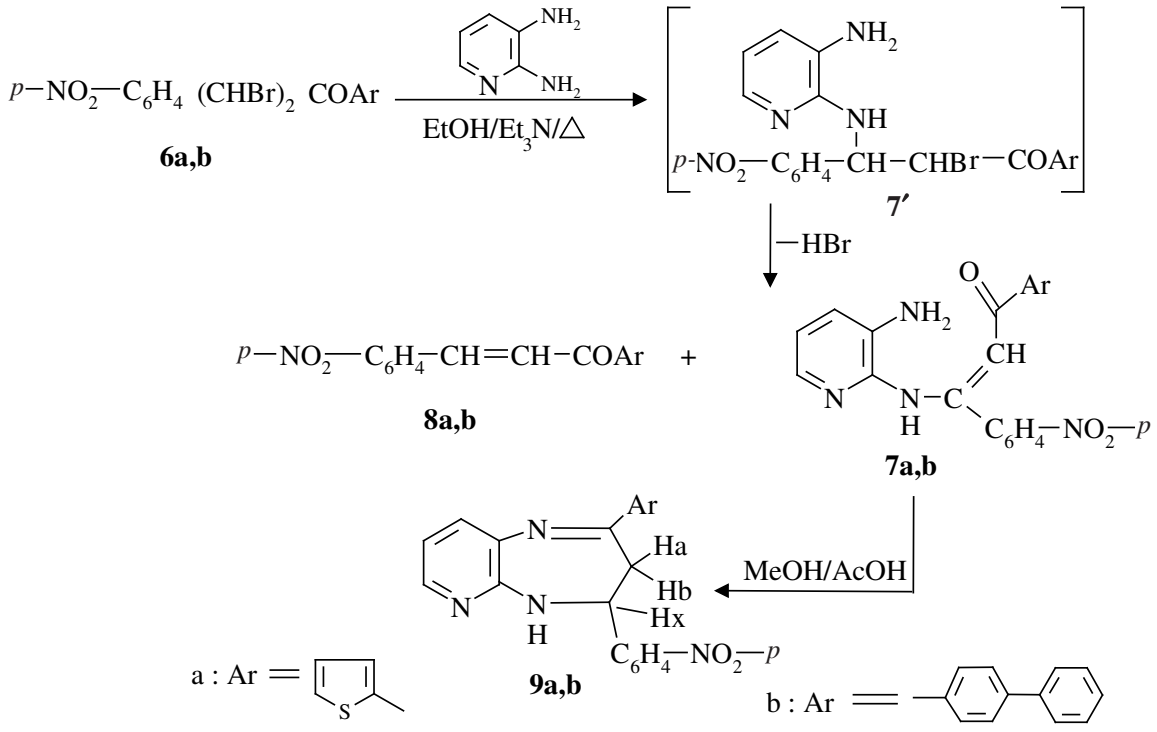
a coupling constant (J_{ab} = 13.81 or 10.12 Hz) and vicinal coupling of (J_{ax} = 6.28 Hz, J_{bx} = 6.08 Hz) to two hydrogen (**Scheme-II** and Table-1).

Biological evaluation

Antibacterial activity: The synthesized compounds **[(2-5)$_{a,b}$, 7$_{a,b}$, 9$_{a,b}$]** were screened for their *in vitro* antibacterial activity against gram-positive bacterial strain *viz*., *Staphylococcus aureus* (ATCC-29213) and gram-negative bacterial strain *viz*., *Escherichia coli* (ATCC-25922) by the agar-well diffusion method[43].

Ciprofloxacin was used as reference standard to compare antibacterial activity. The wells (6 mm in diameter) were dug in the media with the help of a sterile metallic borer with centers at least 24 mm a part. 2-8 h old bacterial inocula containing approximately 10^4-10^6 colony-forming units (CFU/mL) were spread on the surface of the nutrient agar with the help of a sterile cotton swab. The tests were carried out at a concentration of 100, 50 and 25 µg mL. After 48 h of incubation at 37 °C, the zone of inhibition was measured in millimeters. In order to clarify any participating role of DMSO in the biological screening, separate studies were carried out with the solution alone of DMSO and they showed no activity agaist any bacterial strains. Compounds **2**$_a$, **4**$_{a,b}$, **5**$_b$, **7**$_a$ and **9**$_b$ have shown excellent activity against bacterial and the remaining compounds, showed good to moderate activity comparable with standard drugs.

Antifungal activity: The antifungal screening of the compounds was carried out against *Candida albicans*. Sabouraud dextrose agar was seeded with 10^5 (CFU/mL) fungal spore suspensions and transferred to Petri plates, Disco soaked in 20 mL (100 mg/mL in DMSO) of all compounds were placed at different position on the agar surface. The plates were incubated at 37 ºC for 48 h. Dimethyl sulphoxide (DMSO)



Scheme-II: Synthetic pathway for compounds **7**$_{a,b}$, **8**$_{a,b}$ and **9**$_{a,b}$

TABLE-2
IN VITRO ANTIMICROBIAL ACTIVITY OF SYNTHESIZED COMPOUNDS [$(\mathbf{2\text{-}5})_{a,b}$, $\mathbf{7}_{a,b}$ AND $\mathbf{9}_{a,b}$]

Comp. No	Zone of inhibition nm (%)								
	S. aureus concentration (μg mL^{-1})			*E. coli* concentration (μg mL^{-1})			*Candida albicans* concentration (μg mL^{-1})		
	100 (μg)	50 (μg)	25 (μg)	100 (μg)	50 (μg)	25 (μg)	100 (μg)	50 (μg)	25 (μg)
2a	36[a]	23	13	36	22	12	54[a]	22	12
	67[b]	64	54	72	65	60	77[b]	58	50
2b	30	18	Nil	40	25	13	46	22	12
	56	50	–	80	73	65	66	58	50
3a	40	18	Nil	32	21	Nil	62	32	15
	74	50	–	64	62	–	89	84	62
3b	30	22	13	36	17	Nil	50	24	10
	56	61	54	72	50	–	71	63	42
4a	42	24	14	38	24	10	43	25	59
	78	67	58	76	71	50	61	66	38
4b	33	20	12	42	26	12	52	25	13
	61	56	50	84	76	60	74	66	54
5a	30	18	Nil	38	18	Nil	56	24	14
	56	50	–	76	53	–	80	63	58
5b	38	20	11	34	20	11	62	30	16
	70	56	46	68	59	55	80	79	67
7a	40	24	Nil	34	20	Nil	48	20	10
	74	67	–	68	59	–	69	53	42
7b	30	22	Nil	28	17	Nil	54	24	11
	56	61	–	56	50	–	77	63	46
9a	47	26	14	32	18	Nil	54	24	11
	87	72	58	64	53	–	77	63	46
9b	36	20	10	35	22	11	48	19	10
	67	56	42	70	65	55	69	50	42
Ciprofloxacin	54	36	24	50	34	20	–	–	–
Gentamycin	–	–	–	–	–	–	70	38	24
Control	–	–	–	–	–	–	–	–	–

Control – DMSO, (–): Inactive, [a]Zone of inhibition, [b]Percentage inhibition.

was used as solvent control and gentamycin used as standard drug to compare antifungal activity. The tests were carried out at a concentration of 100, 50 and 25 μg mL^{-1} and the zone of inhibition was measured in millimeters. The percentage inhibition of test compounds was related to the standard whose zone of inhibition was taken as 100 %. From the results reported in Table-2, it appears that the compounds $\mathbf{2}_a$, $\mathbf{3}_{a,b}$, $\mathbf{4}_b$, $\mathbf{5}_{a,b}$, $\mathbf{7}_b$ and $\mathbf{9}_a$ showed activity against *Candida albicans* at 100 μmL^{-1} concentration as compared to the standard. Remaining compounds showed moderate antifungal activity against fungal species.

Conclusion

In the present work, new series of condensed 1,4-diazepines and 1,5-thiazepine are reported. The new derivatives were characterized by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The new compounds were tested for *in vitro* antimicrobial activity against a panel of gram-positive bacteria (*Staphylococcus aureus*) and the gram-negative bacteria (*Escherichia coli*) and the yeast-like pathogenic fungus *Candida albicans*. All compounds have shown activity against all the bacterial and fungal strains.

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