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Synthesis and Antimicrobial Activities of Chalcones and Indole Derived from Acetyl Pyridines

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In the present study, chalcones and indole bearing nitrogen containing heterocyclic ring such as pyridine ring have been synthesized and characterized by elemental analysis and spectral studies. Attempts were made to prepare chacones *via* condensation of 2-acetyl pyridines/3-acetyl pyridines/4-acetyl pyridines with substituted benzaldehydes in presence of a number of different inorganic and organic bases. Out of different bases methanolic sodium hydroxide was found best both in terms of rate of reaction and percentage of yield. Synthesized chalcones and indoles were purified by flash column chromatography under nitrogen pressure. Purity of the isolated compounds was checked by HPLC. Compounds with HPLC purity of more than 98 % have been characterized and reported. Synthesized chalcones were tested against the bacteria strains *Staphylococcus aureus* and *E. coli* with reference to the standard drug ciprofloxacin at the concentration 1 µg/mL. Synthesized chalcones were further tested against the fungal strains *Aspergillus niger* and *Penicillium funiculosum* with reference to the standard ketoconazole at the concentration 1 µg/mL.

Keywords: Acetyl pyridine, Benzaldehyde, Chalcone, Indole, Antibacterial activity, Antifungal activity.

INTRODUCTION

Chalcones due to its diverse biological and pharmacological activities have generated extensive scientific studies throughout the world. Chalcones having substitution on two aryl rings exhibit anticancer, antioxidant, anti-inflammatory, antimicrobial, antiulcer, antimalaria and many other activities [1-9]. Chalcones and their derivatives have also been seen to find applications in large varieties of diverse areas such as artificial sweeteners [10], scintillator [11], stabilizer against heat, visible light, ultraviolet light and aging [12,13]. In agriculture, chalcones are used to destroy phytopathogenic organisms [14]. Similarly in industry chalcones are also used in anti-sunburn oil [15].

Indole nucleus is a biologically accepted pharmacophore in medicinal compounds. Compounds bearing indole nucleus exhibit wide spectrum of biological activities such as antifungal, antimicrobial, antiviral, antitubercular, anticancer *etc*. [16,17]. In the present study, it was thus been decided to synthesize and characterize chalcones and indole bearing nitrogen containing heterocyclic ring such as pyridine ring with substitutions selected from -F, $-NO_2$, $-NH_2$ and to screen the antibacterial and antifungal activity of the synthesized compounds.

EXPERIMENTAL

The organic solvents of spectral grade were used without further purification. All key raw materials and the reagents used in the synthesis were of LR grade and were procured from standard sources. Reactions were monitored by TLC using pre-coated TLC plates and by determining the mass of molecular ion of desired molecule in the reaction mass. Silica gel of mesh size 230-400 was used for purification by flash column chromatography under nitrogen pressure. IR spectra were recorded on Perkin-Elmer FT-IR Spectrum 2 using KBr pellets and the values are presented in cm^{-1}. The ^1H NMR spectra of the compounds were recorded on Bruker DPX 300 NMR spectrophotometer using TMS as an internal standard and the values are expressed in δ ppm. The mass spectra of the compounds were recorded on Agilent G1946 MSD Mass Spectrometer using both positive and negative modes. Elemental analysis (C, H and N) was carried out on a Perkin-Elmer 2400 CHN analyzer. Purity was checked in Agilent 1260 series HPLC.

Synthesis of chalcones and indole

3-(4-Fluoro-3-nitro-phenyl)-1-pyridin-2-yl-prop-2-en-1-one (1): To a stirred solution of 2-acetylpyridine (2.00 g, 16.52 mmol) in methanol (80 mL) was added 4-fluro-3-nitro-

benzaldehyde (2.79 g, 16.52 mmol) at 0 °C followed by addition of 3.30 mL of 1 N NaOH (0.13 g, 3.30 mmol). The resultant reaction mixture was stirred for 12 h at room temperature. The progress of the reaction was monitored by TLC (mobile phase: 70 % EtOAc in hexane). The reaction mixture was cooled to 0 °C. 10 mL of 1 N HCl was added slowly to the reaction mixture. The reaction mixture was further diluted with distilled water (80 mL) and was stirred for 1 h. Desired compound 3-(4-fluoro-3-nitro-phenyl)-1-pyridin-2-yl-prop-2-en-1-one was slowly precipitated out. The compound was filtered and isolated as an off white solid (yield 3.5 g, 77.88 %). HPLC purity: 99.11 %, Mass: 271.1 (M–1). IR (KBr, ν_{max}, cm^{-1}): 1698 (C=O), 1590 (C=N), 1532 (C=C quadrant of Ar), 1419 (CH=CH); ^{1}H NMR in DMSO-d_6 (value in δ): 8.80 (d, *J* = 6.00 Hz, 1H), 8.39 (d, *J* = 2.10 Hz, 1H), 8.25 (d, *J* = 16.20 Hz, 1H), 8.18-8.02 (m, 3H), 7.86 (d, *J* = 15.90 Hz, 1H), 7.73-7.67 (m, 1H), 7.45 (d, *J* = 9.00 Hz, 1H).

3-(4-Fluoro-3-nitro-phenyl)-1-pyridin-3-yl-prop-2-en-1-one (2): To a stirred solution of 3-acetylpyridine (1.50 g, 12.93 mmol) in 60 mL methanol was added 4-fluoro-3-nitro-benzaldehyde (2.09 g, 12.39 mmol) at 0 °C, followed by addition of 1 N NaOH (0.09 g, 2.47 mmol). The resultant reaction mixture was stirred for 12 h at 0 °C to room temperature. Reaction was monitored by TLC (mobile phase: 80 % EtOAc in hexane). The reaction mixture was cooled to 0 °C, added slowly 1 N HCl (10 mL) and finally diluted with 80 mL distilled water. After stirring of 1 h the compound 3-(4-fluoro-3-nitro-phenyl)-1-pyridin-3-yl-prop-2-en-1-one was precipitated out which was filtered and isolated as a pale yellow solid (yield 2.1 g, 62.29 %). HPLC purity: 99.06 %, Mass: 271.1 (M–1), IR (KBr, ν_{max}, cm^{-1}): 1698 (C=O), 1582 (C=N), 1532 (C=C quadrant of Ar), 1410 (CH=CH), ^{1}H NMR in DMSO-d_6: 9.15 (dd, *J* = 2.40 Hz, 0.90 Hz, 1H), 8.79 (dd, *J* = 4.80 Hz, 1.80 Hz, 1H), 8.32 (dt, *J* = 9.00 Hz, 1.80 Hz, 1H), 8.22 (dd, *J* = 7.50 Hz, 2.40 Hz, 1H), 7.91-7.85 (m, 1H), 7.60-7.58 (m, 2H), 5.80 (d, *J* = 4.80 Hz, 1H), 5.27 (t, *J* = 4.20 Hz, 1H).

3-(4-Fluoro-3-nitro-phenyl)-1-pyridin-4-yl-prop-2-en-1-one (3): To a stirred solution of 4-acetylpyridines (2.0 g, 16.52 mmol) in methanol (80 mL) was added 4-fluro-3-nitro-benzaldehyde (2.79 g, 16.52 mmol) at 0 °C followed by addition of 3.30 mL of 1 N NaOH (0.13 g, 3.30 mmol). The resultant reaction mixture was stirred for 12 h at 0 °C to room temperature. The progress of the reaction was monitored by TLC (mobile phase: 70 % EtOAc in hexane). The reaction mixture was cooled to 0 °C. 10 mL of 1 N HCl was added slowly to the reaction mixture. The reaction mixture was diluted by distilled water (80 mL). The reaction mixture was stirred for 1 h. Subject compound was slowly precipitated out as an off white solid. Subject compound 3-(4-fluoro-3-nitro-phenyl)-1-pyridin-4-yl-prop-2-en-1-one was filtered and isolated as an off white solid (yield 3.80 g, 84.82 %). HPLC purity: 99.35 %, Mass: 271.1 (M–1), IR (KBr, ν_{max}, cm^{-1}): 1694 (C=O), 1592 (C=N), 1532 (C=C quadrant of Ar), 1428 (CH=CH), ^{1}H NMR in DMSO-d_6 (value in δ): 8.80 (d, *J* = 3.00 Hz, 2H), 8.21 (dd, *J* = 7.20 Hz, 2.10 Hz, 1H), 7.89-7.84 (m, 3H), 7.57 (dd, *J* = 11.40 Hz, 8.70 Hz, 1H), 5.81 (d, *J* = 4.80 Hz, 1H), 5.26 (t, *J* = 4.20 Hz, 1H).

(1*H*-Indol-2-yl)-pyridin-4-yl-methanone (4): To a stirred solution of 4-acetylpyrdine (2 g, 16.52 mmol) in 60 mL methanol was added 2-nitro-benzaldehyde (2.49 g, 16.52 mmol) at 0 °C followed by addition of 3.30 mL of 1 N NaOH (0.13 g, 3.30 mmol) solution. The resultant reaction mixture was stirred for 12 h at 0 °C to room temperature. Progress of the reaction was monitored by TLC (mobile phase: 80 % EtOAc in hexane). The reaction mixture was cooled to 0 °C. 10 mL 1 N HCl was added to the reaction mixture. The reaction mixture was diluted with 80 mL distilled water. Reaction mixture was stirred for 1 h. 3-(2-Nitro-phenyl)-1-pyridin-4-yl-prop-2-en-1-one was precipitated out as a reddish brown solid which was filtered and dried under vacuum (yield 1.60 g, 38.09 %). Mass: 255.3 (M+1), ^{1}H NMR in $CDCl_3$ (value in δ): 8.76 (t, *J* = 3.00 Hz, 1H), 8.75-8.18 (m, 3H), 7.93-7.83 (m, 3H), 7.54-7.49 (m, 1H), 7.26 (s, 1H), 7.19 (t, *J* = 3.27 Hz, 1H).

To stirred a solution of 3-(2-nitro-phenyl)-1-pyridin-4-yl-prop-2-en-1-one (0.50 g, 1.97 mmol) in ethanol (20 mL) was added iron dust (0.44 g, 7.87 mmol) at room temperature. 4 mL of 10 N HCl was added to the reaction mixture. The resultant reaction mixture was heated and stirred for 12 h at 70 °C. The progress of the reaction was monitored by TLC (mobile phase: 100 % EtOAc). The reaction mixture was allowed to cool to room temperature and pH of reaction mixture was adjusted to 9 by aqueous NH_3. The reaction mixture was diluted with distilled water (10 mL). The reaction mixture was extracted with ethyl acetate (2 × 50 mL). Combined organic extract was concentrated to afford a brown subject compound 1*H*-indol-2-yl)-pyridine-4-yl-methanone (yield 0.4 g, 91 %). HPLC purity: 99.06 %, Mass: 221.1 (M–1), IR (KBr, ν_{max}, cm^{-1}): 3414 (C-NH), 1620 (C=O), 1594 (C=N), 1490 (C=C quadrant of Ar), 1424 (CH=CH), ^{1}H NMR in DMSO-d_6 (value in δ): 8.78 (d, *J* = 5.70 Hz, 2H), 8.57 (d, *J* = 8.70 Hz, 1H), 8.37-8.28 (m, 3H), 8.16-8.05 (m, 2H), 7.84 (t, *J* = 7.59 Hz, 1H), 7.67 (t, *J* = 7.87 Hz, 1H).

3-(2-Amino-phenyl)-1-pyridin-4-yl-propan-1-one (5): To stirred a solution of 3-(-2-nitro-phenyl)-1-pyridin-4-yl-prop-2-en-1-one (0.50 g, 1.97 mmol) as prepared above in methanol (20 mL) was added Pd/C (0.42 g) at room temperature. Reaction mixture was stirred overnight at room temperature. The progress of the reaction was monitored by TLC (mobile phase: 5 % MeOH in DCM). The reaction mixture was filtered through celite bed and washed twice with MeOH. The filtrate was concentrated and crude thus obtained was purified by flash column chromatography (mobile phase: 0-80 % EtOAc in *n*-hexane). Subject compound 3-(2-amino-phenyl)-1-pyridin-4-yl-propan-1-one was isolated as a red solid (yield: 0.12 g, 26.96 %). HPLC purity: 99.23 % Mass: 227 (M+1), IR (KBr, ν_{max}, cm^{-1}): 3373 (C-NH_2), 1669 (C=O), 1604 (C=N), 1491 (C=C quadrant of Ar), 1414 (CH=CH), ^{1}H NMR in DMSO-d_6 (value in δ): 8.95-8.90 (m, , 2H), 8.02-7.99 (m, 2H), 7.42-7.37 (m, 3H), 6.45 (d, *J* = 6.01 Hz, 1H), 5.23 (br, s, 2H), 2.75 (t, *J* = 5.98 Hz, 2H), 2.13 (t, *J* = 8.99 Hz, 2H).

3-(2-Nitro-phenyl)-1-pyridin-4-yl-prop-2-en-1-ol (6): To stirred a solution of 3-(2-nitro-phenyl)-1-pyridin-4-yl-prop-2-en-1-one (0.50 g, 1.97 mmol) in methanol (20 mL) was added $NaBH_4$ (0.74 g, 19.68 mmol) at room temperature. Reaction mixture was stirred overnight at room temperature. The progress of the reaction was monitored by TLC (mobile phase: 5 % MeOH in DCM). The reaction mixture was quenched with water and was extracted with EtOAc (2 × 100 mL). Combined organic extract was washed with brine, dried on

Na_2SO_4 and concentrated to get crude. Compound was purified by flash column chromatography (mobile phase: 0-80 % EtOAc in *n*-hexane). Desired compound 3-(2-nitro-phenyl)-1-pyridin-4-yl-prop-2-en-1-ol was isolated as a brown solid (yield 0.10 g, 19.86 %). HPLC purity: 99.03 %, Mass: 257.3 (M+1), IR (KBr, ν_{max}, cm^{-1}): 3435 (O-H), 1582 (C=N), 1357 (N-O), ^{1}H NMR in DMSO-d_6 (value in δ): 8.82-8.97 (m, 1H), 8.40-8.37 (m, 3H), 7.95-7.90 (m, 3H), 7.45=7.41 (m, 1H), 7.23 (d, *J* = 14.99 Hz, 1H), 6.28 (d, *J* = 15.10 Hz, 1H), 5.21 (s, 1H), 2.12 (s, 1H).

3-(2-Nitro-phenyl)-1-pyridin-4-yl-propane-1-ol (7): To stirred a solution of 3-(-2-nitro-phenyl)-1-pyridin-4-yl-prop-2-en-1-one (0.50 g, 1.97 mmol) in methanol (20 mL) was added $NaBH_4$ (0.74 g, 19.68 mmol) at room temperature. Reaction mixture was stirred for overnight at reflux temperature. The progress of the reaction was monitored by TLC (mobile phase: 5 % MeOH in DCM). The reaction mixture was quenched with water and was extracted with EtOAc (2 × 100 mL). Combined organic extract was washed with brine, dried on Na_2SO_4 and concentrated to get crude. Crude was purified by flash column chromatography (mobile phase: 100 % EtOAc). Desired compound 3-(2-nitro-phenyl)-1-pyridin-4-yl-propane-1-ol was isolated as a brown solid (yield: 0.32 g, 63.01 %). HPLC purity: 99.01 %, Mass: 259.3 (M+1), IR (KBr, ν_{max}, cm^{-1}): 3373 (O-H), 1564 (C=N), 1524 (C-C quadrant of Ar), 1348 (N-O), ^{1}H NMR in DMSO-d_6 (value in δ): 8.84-8.79 (m, 1H), 8.42-8.39 (m, 2H), 7.93-7.88 (m, 2H), 7.43-7.40 (m, 1H), 7.20-7.17 (m, 2H), 2.72 (t, *J* = 5.96 Hz, 2H), 2.19 (t, *J* = 5.95 Hz, 2H), 2, 10 (s, 1H).

3-(2-Nitro-phenyl)-1-pyridin-3-yl-prop-2-en-1-ol (8): To a stirred solution of 3-acetylpyridine (2.00 g, 16.50 mmol) in 60 mL methanol was added 2-nitro-benzaldehyde (2.49 g, 16.47 mmol) at 0 °C followed by addition of 3.3 mL of 1 N NaOH (0.13 g, 3.25 mmol) solution. Reaction mixture was stirred for 12 h at 0 °C to room temperature. Progress of the reaction was monitored by TLC (mobile phase: 80 % EtOAc in *n*-hexane). The reaction mixture was cooled to 0 °C. 10 mL of 1 N HCl was added to the reaction mixture. The reaction mixture was further diluted with 80 mL with distilled water. Reaction mixture was stirred for 1 h. Reddish brown compound was precipitated out and it was filtered. 1.60 g of 3-(2-nitro-phenyl)-1-pyridin-3-yl-prop-2-en-1-one was isolated as a reddish brown solid (yield 1.60 g, 47.55 %). Mass: 255.3 (M+1), ^{1}H NMR in DMSO-d_6 (value in δ): 9.35 (d, *J* = 1.50 Hz, 1H), 8.86 (dd, *J* = 4.65 Hz, 1.50 Hz, 1H), 8.49 (dt, *J* = 8.10 Hz, 1.80 Hz, 1H), 8.23 (d, *J* = 7.20 Hz, 1H), 8.14-8.00 (m, 1H), 7.99-7.82 (m, 2H), 7.73 (t, *J* = 7.50 Hz, 1H), 7.67-7.60 (m, 1H)), 6.65-6.50 (m, 1H).

To a stirred solution of 3-(2-nitro-phenyl)-1-pyridin-3-yl-prop-2-en-1-one (0.20 g, 0.79 mmol) in 30 mL methanol and 30 mL THF was added $NaBH_4$ (0.089 g, 2.362 mmol) at room temperature. Reaction mixture was stirred over night at room temperature. Reaction was monitored by TLC (mobile phase: 5 % MeOH in DCM)). After completion of reaction, reaction mixture was quenched by water and extracted twice with ethyl acetate (2 × 100 mL). Combined organic extract was washed with brine and concentrated to get crude. Crude was purified by flush chromatography (mobile phase: 0-100 % EtOAc in *n*-hexane) to give 3-(2-nitro-phenyl)-1-pyridin-3-yl-prop-2-en-1-ol as brown solid (yield 0.11 g, 56 %). HPLC purity: 99.03 %, Mass: 257.3 (M+1), IR (KBr, ν_{max}, cm^{-1}): 3425 (O-H), 1610 (C=N), 1513 (C=C quadrant of Ar), 1424 (CH=CH), 1349 (N-O), ^{1}H NMR in DMSO-d_6 (value in δ): 8.63 (s, 1H), 8.48 (dd, *J* = 4.80 Hz, 1.50 Hz, 1H), 7.96-7.89 (m, 1H), 7.82-7.77 (m, 2H), 7.66 (t, *J* = 7.35 Hz, 1H), 7.51 (t, *J* = 7.65 Hz, 1H), 7.42-7.37 (m, 1H), 7.00 (d, *J* = 14.76 Hz, 1H), 6.55 (dd, *J* = 16.5 Hz, 5.70 Hz, 1H), 5.41 (d, 5.40 Hz, 1H), 1.98 (s, 1H).

3-(3-((2-Chloropyrrolo[2,1-f][1,2,4]triazin-4-yl)amino)-phenyl)-1-(pyridin-2-yl)propan-1-ol (9): To a stirred solution of 3-(3-aminophenyl)-1-(pyridin-2-yl)propan-1-ol ((0.2 g, 0.87 mmol) in 20 mL ethanol were added 2,4-dichloropyrrolo[2,1-f][1,2,4]triazine (0.197 g, 1.05 mmol) and DIPEA (0.339 g, 2.62 mmol) at room temperature. The reaction mixture was stirred for 12 h at room temperature. The progress of the reaction was monitored by TLC (mobile phase: 5 % MeOH in DCM). The reaction mixture was concentrated and crude thus obtained was purified by flash column chromatography (mobile phase: 5 % MeOH in DCM). Subject compound 3-(3-((2-chloropyrrolo-[2,1-f][1,2,4]triazin-4-yl)amino)phenyl)-1-(pyridin-2-yl)-propan-1-ol (180 mg, 54.21 %) was isolated as a yellow solid. HPLC purity: 99.12 %, Mass: 378.1 (M–1), IR (KBr, ν_{max}, cm^{-1}): 3322 (N-H), 1610 (C=N), 1609 (C=C), 3322 (N-H), 1350 (C-N), ^{1}H NMR in DMSO-d_6 (value in δ): 10.23 (s, 1H), 8.60-8.31 (m, 1H), 7.90-7.76 (m, 2H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.53 (dd, *J* = 5.4, 2.7 Hz, 2H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.29-7.14 (m, 2H), 7.04 (d, *J* = 7.5 Hz, 1H), 6.75 (dd, *J* = 4.5, 2.6 Hz, 1H), 5.51 (d, *J* = 5.1 Hz, 1H), 4.81-4.38 (m, 1H), 2.70 (t, *J* = 7.9 Hz, 2H), 2.18-1.75 (m, 2H).

3-(3-((2-Chloropyrrolo[2,1-f][1,2,4]triazin-4-yl)-amino)phenyl)-1-(pyridin-3-yl)propan-1-one (10): To a stirred solution of 3-(3-aminophenyl)-1-(pyridin-3-yl)propan-1-one ((0.2 g, 0.88 mmol) in 20 mL ethanol were added 2,4-dichloro-pyrrolo[2,1-f][1,2,4]triazine (0.21 g, 1.05 mmol) and DIPEA (0.34 g, 2.64 mmol) at room temperature. The reaction mixture was stirred 12 h at room temperature. The progress of the reaction was monitored by TLC (mobile phase: 5 % MeOH in DCM). The reaction mixture was concentrated and crude thus obtained was purified by flash column chromatography (mobile phase: 5 % MeOH in DCM). Subject compound 3-(3-((2-chloropyrrolo[2,1-f][1,2,4]triazin-4-yl)amino)phenyl)-1-(pyridin-3-yl)propan-1-one (200 mg, 60.24 %) was isolated as a yellow solid. HPLC purity: 99.51 %, Mass: 376.0 (M–1), IR (KBr, ν_{max}, cm^{-1}): 1621 (C=O), 1682 (C=N), 3359 (N-H), 1174 (C-Cl), 1679 (C=N), 1352 (C-N), ^{1}H NMR in DMSO-d_6 (value in δ): 10.28 (s, 1H), 9.17 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.79 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.33 (dt, *J* = 8.1, 1.9 Hz, 1H), 7.78 (dd, *J* = 2.6, 1.5 Hz, 1H), 7.69-7.59 (m, 2H), 7.57-7.52 (m, 1H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.28-7.09 (m, 2H), 6.75 (dd, *J* = 4.5, 2.6 Hz, 1H), 3.49 (t, *J* = 7.3 Hz, 2H), 3.00 (t, *J* = 7.3 Hz, 2H).

3-(3-((2-Chlorothieno[3,2-d]pyrimidin-4-yl)amino)-phenyl)-1-(pyridin-3-yl)propan-1-one (11): To a stirred solution of 3-(3-aminophenyl)-1-(pyridin-3-yl)propan-1-one (0.3 g, 1.32 mmol) in 20 mL ethanol were added 2,4-dichlorothieno[3,2-d]pyrimidine (0.326 g, 1.58 mmol) and DIPEA (0.511 g, 3.96 mmol) at room temperature. The reaction mixture was stirred for 12 h at room temperature. The progress of the reaction was monitored by TLC (mobile phase: 5 % MeOH in DCM). The reaction mixture was concentrated and crude thus obtained was purified by flash column chromatography (mobile phase

5 % MeOH in DCM). Subject compound 3-(3-((2-chlorothieno-[3,2-d]pyrimidin-4-yl)amino)phenyl)-1-(pyridin-3-yl)propan-1-one (250 mg, 47.70 %) was isolated as a brown solid. HPLC purity: 99.22 %, Mass: 393.9 (M–1), IR (KBr, ν_{max}, cm^{-1}): 3230 (N-H), 695 (C-S), 1308 (C=N), 1161 (C-Cl), 1686 (C=O), ^{1}H NMR in DMSO-d_6 (value in δ): 9.95 (s, 1H), 8.94 (d, *J* = 2.2 Hz, 1H), 8.57 (dd, *J* = 4.8, 1.7 Hz, 1H), 8.27-7.91 (m, 2H), 7.34 (dd, *J* = 7.8, 4.2 Hz, 2H), 7.30-7.06 (m, 3H), 6.94 (d, *J* = 7.6 Hz, 1H), 3.27 (t, *J* = 7.4 Hz, 2H), 2.78 (t, *J* = 7.4 Hz, 2H)),

3-(3-((2-Chlorothieno[3,2-d]pyrimidin-4-yl)amino)-phenyl)-1-(pyridin-3-yl)propan-1-ol (12): To a stirred solution of 3-(3-aminophenyl)-1-(pyridin-3-yl)propan-1-ol (0.2 g, 0.876 mmol) in 20 mL ethanol were added 2,4-dichlorothieno[3,2-d]pyrimidine (0.215 g, 1.051 mmol) and DIPEA (0.339 g, 2.62 mmol) at room temperature. The reaction mixture was stirred for 12 h at room temperature. The progress of the reaction was monitored by TLC (mobile phase: 5 % MeOH in DCM). The reaction mixture was concentrated and crude thus obtained was purified by flash column chromatography (mobile phase: 5 % MeOH in DCM). Subject compound 3-(3-((2-chlorothieno-[3,2-d]pyrimidin-4-yl)amino)phenyl)-1-(pyridin-3-yl)propan-1-one (250 mg, 72.25 %) was isolated as an off white solid. HPLC purity: 99.29 %, Mass: 396.0 (M–1), IR (KBr, ν_{max}, cm^{-1}): 3240 (N-H), 693 (C-S), 1350 (C=N), 1191 (C-Cl), 1078 (C-N), 946 (O-H), ^{1}H NMR in DMSO-d_6 (value in δ): 10.12 (s, 1H), 8.48 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 8.26 (d, *J* = 5.4 Hz, 1H), 7.79 (td, *J* = 7.7, 1.9 Hz, 1H), 7.61-7.50 (m, 2H), 7.47 (t, *J* = 1.9 Hz, 1H), 7.40 (d, *J* = 5.4 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.24 (ddt, *J* = 8.1, 4.9, 1.7 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 5.46 (dd, *J* = 23.0, 5.1 Hz, 1H), 4.62 (dt, *J* = 8.9, 4.6 Hz, 1H), 2.70 (t, *J* = 7.9 Hz, 2H), 2.24-1.55 (m, 2H).

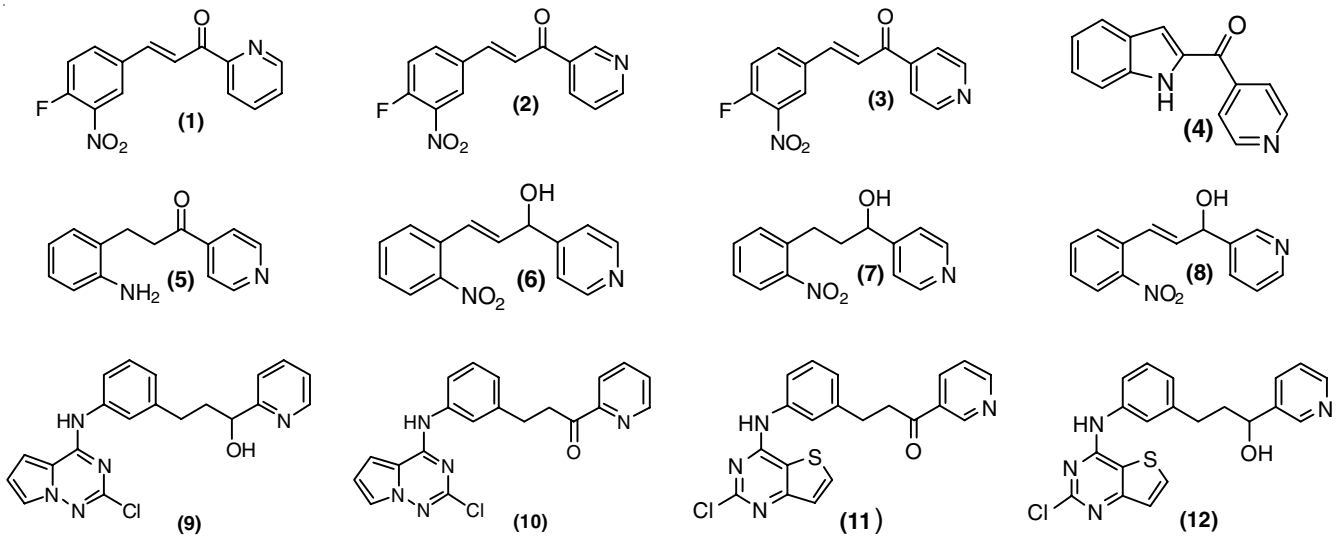
Antibacterial and antifungal activities: The synthesized compounds were screened for antibacterial activity against the bacteria *Staphylococcus aureus, E. coli* and *Bacillus sphaericus.* Antifungal activities of the synthesized compounds were studied against the fungus *Aspergillus niger, Penicillium funiculosum* and *Fusarium oxysporum.*

Determination of antibacterial assay: *In vitro* antibacterial activity of the crude methanol solution was studied against bacterial strains by the agar well diffusion method [18]. Mueller Hinton agar no.2 (Hi Media, India) was used as the bacteriological medium. The extracts were diluted in 100 % dimethyl sulphoxide at the concentrations of 5 mg/mL. The Mueller Hinton agar was melted and cooled to 48-50 °C and standardized inoculums (1.5×10^8 CFU/mL, 0.5 McFarland) was then added aseptically to the molten agar and poured into sterile petri dishes to give a solid plate. Wells were prepared in the seeded agar plates. The test compound (100 µL) was introduced in the well (6 mm). The plates were incubated overnight at 37 °C. The antimicrobial spectrum of the extract was determined for the bacterial species in terms of zone sizes around each well. The diameters of zone of inhibition produced by the agent were compared with standard ciprofloxacin. For each bacterial strain controls were maintained where pure solvents were used instead of the extract. The control zones were subtracted from the test zones and the resulting zone diameter was measured with antibiotic zone reader to nearest mm. The experiments were performed in triplicate.

Determination of antifungal assay: Antifungal activity of the synthesized compounds was investigated by agar well diffusion method [19]. Suspensions of fungal spores were prepared in sterile PBS and adjusted to a concentration of 10^6 cells/mL by dipping a sterile swab into the fungal suspension and rolled on the surface of the agar medium. The plates were dried at room temperature for 15 min. Wells of 10 mm diameter and about 7 mm apart were punctured in the culture media using sterile glass tube. 0.1 mL of several dilutions of fresh solutions was administered to fullness for each well. Plates were incubated at 37 °C. After incubation of 24 h bioactivities were determined by measuring the diameter of inhibition zone (in mm). All experiments were performed in triplicate.

RESULTS AND DISCUSSION

Purity of the chalcones was determined by HPLC. Chalcones with purity more than 98 % were submitted for spectral analysis. The structures of the product were deduced from elemental analysis and spectral analysis. HPLC purity of synthesized chalcones are given in Table-1.



Structure of synthesized compounds **1-12**

The mass spectrum are recorded both in positive and negative mode. Mass spectrum revealed mainly the [M+H] and [M-H] ions without much fragmentation and supported the molecular weight corresponding to the molecular formula suggested for synthesized chalcones and indole. The elemental analysis of the reported compounds supported the suggested molecular formulae. Elemental analysis and molecular ions observed in Mass spectrum are presented in Table-1.

All the synthesized chalcones exhibited characteristic absorption bands in the IR spectra from 1656-1650 cm^{-1} for (C=O), 1507-1503 cm^{-1} for (C=C quadrant of Ar), 1467-1461 cm^{-1} for (CH=CH) and at other regions of the spectrum depending upon the specific substitutions present in the chalcones and indole. IR frequencies observed for different compounds are presented with their respective synthesis.

The ^1H NMR spectrum of the synthesized chalcones exhibited signals for aromatic proton in between 8.69 to 7.10 regions. Number of peaks and their relative intensity comply with the molecular formula and predicted structure of the reported molecules. The ^1H NMR spectra of different chalcones also exhibited two doublets with high *J* value around 9-15 Hz indicating the *trans* relationship of =CH-Ar and –CO-CH= protons. NMR data of synthesized compounds are presented with their respective synthesis.

The synthesized chalcones were screened for antibacterial activity against the bacteria *Staphylococcus aureus, E. coli* and *Bacillus sphaericus. A*ntifungal activities of the synthesized compounds were studied against the fungus *Apergillus niger*, *Penicillium funiculosum* and *Fusarium oxysporum*. Significant antibacterial activities were observed with compounds **4**, **5**, **11** and **12.** Antibacterial activities of different synthesized compounds have been presented in Table-2. Again significant antifungal activities were observed with compound **4**, **5**, **6**, **8**, **9**, **10**, **11** and **12**. Antifungal activities of different synthesized compounds have been presented in Table-2.

Conclusion

Novel chalcones and indole derivatives (**1-12**) were synthesized and tested against the bacteria strains *Staphylococcus aureus, E. coli* and *Bacillus sphaericus* with reference to the standard drug Ciprofloxacin at the concentration 1 µg/mL. Again synthesized compounds were tested against the fungal strains *Apergillus niger*, *Penicillium funiculosum* and *Fusarium oxysporum* with reference to the standard ketoconazole at the

TABLE-1
ELEMENTAL ANALYSIS AND MOLECULAR MASS IONS OF SYNTHESIZED COMPOUNDS

Compd. No.	m.f.	m.w.	Appearance	Molecular mass	HPLC purity (%)	Elemental analysis (%): Found (calcd.)		
						C	H	N
1	$C_{14}H_9N_2O_3F$	272.23	Off white solid	271.1 (M–1)	99.11	61.79 (61.75)	3.37 (3.34)	10.31 (10.29)
2	$C_{14}H_9N_2O_3F$	272.23	Pale yellow solid	271.1 (M–1)	99.06	61.78 (61.75)	3.36 (3.34)	10.32 (10.29)
3	$C_{14}H_9N_2O_3F$	272.23	Off white solid	271.1 (M–1)	99.35	61.78 (61.75)	3.37 (3.34)	10.33 (10.29)
4	$C_{14}H_{10}N_2O$	222.24	Brown solid	221.1 (M–1	99.06	75.68 (75.66)	4.56 (4.54)	12.63 (12.60)
5	$C_{14}H_{14}N_2O$	226.27	Red solid	227.0 (M+1)	99.23	74.36 (74.30)	6.27 (6.25)	12.40 (12.38)
6	$C_{14}H_{12}N_2O_3$	256.26	Brown solid	257.3 (M+1)	99.03	65.66 (65.60)	4.74 (4.73)	10.95 (10.93)
7	$C_{14}H_{14}N_2O_3$	258.10	Brown solid	259.3 (M+1)	99.01	65.10 (65.09)	5.48 (5.47)	10.86 (10.84)
8	$C_{14}H_{12}N_2O_3$	256.26	Brown solid	257.3 (M+1)	99.03	65.65 (65.60)	4.74 (4.73)	10.96 (10.93)
9	$C_{20}H_{18}N_5OCl$	379.85	Yellow solid	378.1 (M–1)	99.12	63.65 (63.35)	4.79 (4.78)	18.44 (18.46)
10	$C_{20}H_{16}N_5OCl$	377.83	Yellow solid	376.0 (M–1)	99.51	63.57 (63.64)	4.27 (4.24)	18.54 (18.56)
11	$C_{20}H_{15}N_4OSCl$	394.88	Brown solid	393.9 (M–1)	99.22	60.90 (60.83)	3.80 (3.83)	14.21 (14.19)
12	$C_{20}H_{17}N_4OSCl$	396.89	Off white	396.0 (M–1)	99.29	60.52 (60.53)	4.30 (4.32)	14.10 (14.12)

TABLE-2
MICROBIAL ACTIVITIES OF SYNTHESIZED COMPOUNDS

Compound No.	Diameter of inhibition zone (mm)					
	Antibacterial activity			Antifungal activity		
	Escherichia coli	*Staphylococcus aureus*	*Bacillus sphaericus*	*Aspergillus niger*	*Fusarium oxysporum*	*Penicillium funiculosum*
1	NIL	NIL	–	NIL	–	NIL
2	NIL	NIL	–	NIL	–	NIL
3	NIL	NIL	–	NIL	–	NIL
4	A: NIL; B: 16	A: 14; B: 16	–	A: 22; B: 26	–	A: 28; B: 28
5	A-12; B: 16	NIL	–	A: 18; B: 24	–	A: 32; B: 34
6	NIL	NIL	–	A: 10; B: 12	–	A: 6; B: 6
7	NIL	NIL	–	NIL	–	NIL
8	NIL	NIL	–	A: 06; B: 06	–	NIL
9	NIL	–	A: 6; B: 16	–	A: 12; B: 14	NIL
10	NIL	–	A: 10; B: 14	–	A: 8; B: 10	NIL
11	A: 16; B: 18	–	NIL	–	NIL	A: 4; B: 11
12	A: 8; B: 10	–	NIL	–	NIL	A: 4; B: 10
Ciprofloxacin standard	22	–	22	–	–	–
Ketoconazole standard	–	–	–	–	22	22

Stock solution: 1 mg/mL (DMSO) A = 40 µL, B = 80 µL

concentration 1 µg/mL. Significant antibacterial and antifungal activities were observed in some of the synthesized compounds.

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