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Synthesis of Isomeric Subtituted 6-acetyl-3-benzoylindolizine-1-carboxylate and 8-acetyl-3-benzoylindolizine-1-carboxylate from subtituteded 3-acetyl pyridinium bromides and their antimicrobial activity

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ABSTRACT

*A series of substituted 6-acetyl-3-benzoylindolizine-1-carboxylates **(2a-l)** and 8-acetyl-3-benzoylindolizine-1-carboxylate **(3a-l)** from subtitled 3-acetyl pyridinium bromides **(1a-f)** using 1,3-dipolar cycloaddition methods with electron withdrawing Alkynes. The structures of newly synthesized compounds were characterized by analytical spectral data. The synthesized indolizine derivatives were evaluated for qualitative and quantitative antimicrobial activity. Preliminary pharmacological observations revealed that some of the derivatives shown promising in vitro antibacterial and antifungal activity.*

Keywords: Indolizine, Alkynes, Antibacterial activity, Pyridinium bromides, 3-acetylpyridine.

INTRODUCTION

Organic compounds containing two condensed rings (5-and 6-membered) and a bridging nitrogen atom are known as indolizines. Indolizines are such parent system, which contain ring junction nitrogen and very rare in nature. Indolizines are structurally and chemically isomeric with indoles. It is this analogy between indole and indolizine nucleus that has prompted speculation that indolizine analogs of biologically important indoles could conceivably have potent physiological activity,[1,2]. This system is isoelectronic with indole and represents a group of heterocyclic compounds structurally related to purines. Therefore, indolizines can be considered as a 10-π electron system. A lot of modifications, observations and investigation have been reported in this area. Several biologically active indolizines were reported to possess biological activities like anti-inflammatory [3], hypoglycaemic activities [4,5], Other activities reported are 5HT3 receptor antagonist [6], anti acetylcholine [7], CNS depressant activity [8],estrogen receptor binding [9] anti-oxidant property [10,11],antimicrobial and analgesic activity [12,13],many amino acid derivatives with an active indolizine nucleus have been utilized in cancer therapy [14-15].

MATERIALS AND METHODS

All reactions were carried out in hot-air dried glass wares under nitrogen atmosphere using dry solvents.^{1}H-NMR (400 MHz) spectra were recorded at ambient temperature using $CDCl_3$, DMSO-D_6 as a solvent using Bruker-400 spectrometer. Chemical shift values are measured in δ ppm and were referenced with TMS. The peak multiplicities were given as followed; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. LC-MS analysis was performed on Agilent LC-1200 series coupled with 6140 single quad mass spectrometer with ESI +ve and –ve mode, MS range 100-2000. IR spectra were recorded on Brucker alpha FT-IR spectrometer using a KBr pellets. Elemental analyses were recorded using Perkin Elmer CHNS analyzer.

Preparation of Compounds

Preparation of 3-acetyl-1-(2-(4-cyanophenyl)-2-oxoethyl)pyridinium bromide 1d: To a stirred solution of 3-acetyl pyridine 1 g (0.0082 mol) in dry acetone (5 mL), was added 1.75 g (0.0082 mol) of 4-cyano phenacylbromide, stirred at room temperature for five hours. Solids were separated out, filtered and dried under vacuum to afford 2.82 g (98.9 % yield) of 3-acetyl-1-(2-(4-cyanophenyl)-2-oxoethyl)pyridiniumbromide. Similarly, other compounds of the series 1a-f were prepared.

Preparation of ethyl 6-acetyl-3-(4-cyanobenzoyl)-2-methylindolizine-1-carboxylate 2g: To a stirred solution of 3-acetyl-1-(2-(4-cyanophenyl)-2-oxoethyl)pyridiniumbromide, 0.5 g (0.0014 mol), in dry DMF(5 mL) was added ethylbut-2-ynoate 0.179 g (0.0015 mol) and K_2CO_3 0.441 g (0.0031 mol). Stirring was continues for 30 min at room temperature. Completion of reaction was monitored by TLC. The reaction mass was evaporated under reduced pressure and diluted with ethyl acetate. Organic layer was washed with water, brine and dried with sodium sulphate. The crude compound was purified by column chromatography to afford 0.25 g (46 % yield) of ethyl 6-acetyl-3-(4-cyanobenzoyl)-2-methylindolizine-1-carboxylate 2g and the 0.05 g (9% yield) ethyl 8-acetyl-3-(4-cyanobenzoyl)-2-methylindolizine-1-carboxylate3g as by-product other isomer. Similarly, other compounds of the series 2a-l were prepared along with the by-products other isomer 3a-l.

3-Acetyl-1-(2-oxo-2-phenylethyl)pyridiniumbromide 1a: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 240.2; ^{1}H NMR (400 MHz, DMSO-D_6): δ 9.68 (s, 1H), 9.25-9.23(d, J=6.8 Hz, 1H), 9.18-9.16 (d, J=8 Hz, 1H), 8.47-8.43 (m, 1H), 8.10-8.08 (d, J=7.2 Hz, 2H), 7.83-7.79 (m, 1H), 7.70-7.66 (m, 2H), 6.65 (s, 2H), 2.75 (s, 3H).

3-Acetyl-1-(2-(4-chlorophenyl)-2-oxoethyl)pyridiniumbromide 1b: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 274.2; ^{1}H NMR (400 MHz, DMSO-D_6): δ 9.60 (s, 1H), 9.18-9.16 (m, 2H), 8.45-8.42 (m, 1H), 8.11-8.09 (d, J=7.2 Hz, 2H), 7.797.77 (d, J=7.2 Hz, 2H), 6.56 (s, 2H), 2.74 (s, 3H).

3-Acetyl-1-(2-(4-bromophenyl)-2-oxoethyl)pyridiniumbromide 1c: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 318.2; ^{1}H NMR (400 MHz, DMSO-D_6): δ 9.63 (s, 1H), 9.20-9.15 (m, 2H), 8.46-8.42 (m, 1H), 8.02-8.00 (d, J=7.2 Hz, 2H), 7.93-7.91 (d, J=7.2 Hz, 2H), 6.59 (s, 2H), 2.74 (s, 3H).

3-Acetyl-1-(2-(4-cyanophenyl)-2-oxoethyl)pyridiniumbromide 1d: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 265.2; ^{1}H NMR (400 MHz, DMSO-D_6): δ 9.60 (s, 1H), 9.20-9.17 (m, 2H), 8.47-8.44 (m, 1H), 8.25-8.23 (d, J=7.2 Hz, 2H), 8.19-8.17 (d, J=7.2 Hz, 2H), 6.60 (s, 2H), 2.75 (s, 3H).

3-Acetyl-1-(2-(2-chlorophenyl)-2-oxoethyl)pyridiniumbromide 1e: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 274.2; ^{1}H NMR (400 MHz, DMSO-D_6): δ 9.63 (s, 1H), 9.21-9.17 (m, 2H), 8.46-8.43 (m, 1H), 8.15-8.13 (d, J=6.8 Hz, 1H), 7.74-7.62 (m, 3H), 6.52 (s, 2H) 2.75 (s, 3H).

3-Acetyl-1-(2-(2-nitrophenyl)-2-oxoethyl)pyridiniumbromide 1f: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 285.2; ^{1}H NMR (400 MHz, DMSO-D_6): δ 9.65 (s, 1H), 9.22-9.19 (m, 2H), 8.52-8.48 (m, 1H), 8.29-8.27 (d, J=7.2 Hz, 1H), 8.18-8.16 (d, J=7.2 Hz, 1H), 8.08-7.94 (m, 2H), 6.57 (s, 2H), 2.78 (s, 3H).

Ethyl-6-acetyl-3-benzoyl-2-methylindolizine-1-carboxylate 2a: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 350.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.13 (s, 1H), 8.35-8.33 (d, J=7.2 Hz, 1H), 7.89-7.87 (m, 1H), 7.72-7.70 (m, 2H), 7.62-7.50 (m, 3H), 4.43-4.38 (q, J=7.2 Hz, 2H) , 2.68 (s, 3H), 2.25 (s, 3H), 1.44-1.41 (t, J=7.2 Hz, 3H); Anal. Calcd. For $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01; Found : C, 71.1; H, 5.21; N, 3.99.

Ethyl-6-acetyl-3-benzoyl-2-ethylindolizine-1-carboxylate 2b: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 364.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.97 (s, 1H), 8.37-8.36 (d, J=7.2 Hz, 1H), 7.87-7.85 (d, J=7.2 Hz, 1H), 7.74-7.71 (m, 2H), 7.61-7.43 (m, 3H), 4.44-4.38 (q, J=7.2 Hz, 2H), 2.75-2.68 (q, J=7.2 Hz, 2H), 2.60 (s, 3H), 1.45-1.41 (t, J=7.2 Hz, 3H), 1.03-0.99 (t, J=7.2 Hz, 3H); IR (neat cm^{-1}); 1686, 1626, 1602, 1573; Anal. Calcd. For $C_{22}H_{21}NO_4$: C, 72.71; H, 5.82; N, 3.85; Found : C, 72.52; H, 5.62; N, 3.49.

Ethyl-6-acetyl-3-(4-chlorobenzoyl)-2-methylindolizine-1-carboxylate 2c: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 384.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.42 (s, 1H), 8.36-8.34 (d, J=8.0Hz, 1H), 7.90-7.88 (d, J=8.0 Hz, 1H), 7.68-7.66 (d, J=8 Hz, 2H), 7.37-7.35 (d, J=8 Hz, 2H), 4.43-4.38 (q, J=7.2 Hz, 2H) , 2.68 (s, 3H), 2.27 (s, 3H), 1.45-1.41 (t, J=7.2 Hz, 3H) . IR (neat cm^{-1}): 1705, 1686, 1626, 1599; Anal. Calcd. For $C_{21}H_{18}ClNO_4$: C, 65.71; H, 4.73; N, 3.65; Found: C, 65.39; H, 4.51; N, 3.29.

Ethyl-6-acetyl-3-(4-chlorobenzoyl)-2-ethylindolizine-1-carboxylate 2d: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 398.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.96 (s, 1H), 8.37-8.35 (d, J=8.0 Hz, 1H), 7.88-7.85 (d, J=8.0 Hz, 1H), 7.69-7.67 (d, J=8.0 Hz, 2H), 7.37-7.35 (d, J=8.0 Hz, 2H), 4.44-4.39 (q, J=7.2 Hz, 2H), 2.78-2.72 (q, J=7.2 Hz, 2H), 2.62 (s, 3H), 1.45-1.41 (t, J=7.2 Hz, 3H) ,1.04-1.00 (t, J=7.2 Hz, 3H); IR (neat cm^{-1}): 1686, 1626, 1588; Anal. Calcd. For $C_{22}H_{20}ClNO_4$: C, 66.42; H, 5.07; N, 3.52; Found: C, 65.22; H, 4.92; N, 3.13.

Ethyl-6-acetyl-3-(4-bromobenzoyl)-2-methylindolizine-1-carboxylate 2e: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 428.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.12 (s, 1H), 8.36-8.34 (d, J=7.2 Hz, 1H), 7.90-7.88 (d, J=7.2 Hz, 1H), 7.67-7.65 (d, J=8 Hz, 2H), 7.60-7.58 (d, J=8 Hz, 2H), 4.42-4.38 (q, J=7.2 Hz, 2H), 2.68 (s, 3H), 2.27 (s, 3H), 1.45-1.41 (t, J=7.2 Hz, 3H); IR (neat cm^{-1}): 1704, 1686, 1584; Anal. Calcd. For $C_{21}H_{18}BrNO_4$: C, 58.89; H, 4.24; N, 3.27; Found: C, 58.10; H, 4.11; N, 3.09.

Ethyl-6-acetyl-3-(4-bromobenzoyl)-2-ethylindolizine-1-carboxylate 2f: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 442.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.98 (s, 1H), 8.37-8.35 (d, J=8.0 Hz, 1H), 7.88-7.86 (d, J=8.0 Hz, 1H), 7.75-7.73 (d, J=8.0 Hz, 2H), 7.65-7.63 (d, J=8.0 Hz, 2H), 4.42-4.39 (q, J=7.2 Hz, 2H), 2.76-2.72 (q, J=7.2 Hz, 2H), 2.68 (s, 3H), 1.45-1.41 (t, J=7.2 Hz, 3H),1.04-1.00 (t, J=7.2 Hz, 3H); IR (neat cm^{-1}): 1686, 1626, 1584; Anal. Calcd. For $C_{22}H_{20}BrNO_4$: C, 59.74; H, 4.56; N, 3.17; Found: C, 58.52; H, 4.42; N, 3.02.

Ethyl-6-acetyl-3-(4-cyanobenzoyl)-2-methylindolizine-1-carboxylate 2g: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 375.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.27 (s, 1H), 8.40-8.38 (d, J=9.6 Hz, 1H), 7.97-7.94 (d, J=9.2 Hz, 1H), 7.84-7.78 (m, 4H), 4.45-4.39 (q, J=7.2 Hz, 2H) , 2.67 (s, 3H), 2.23 (s, 3H), 1.46-1.48 (t, J=7.2 Hz, 3H); IR (neat cm^{-1}): 2231, 1707,1684, 1624; Anal. Calcd. For $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48; Found: C, 69.99; H, 4.61; N, 7.39.

Ethyl-6-acetyl-3-(4-cyanobenzoyl)-2-ethylindolizine-1-carboxylate 2h: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 389.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.22 (s, 1H), 8.33-8.31 (d, J=9.6 Hz, 1H), 7.87-7.85 (d, J=9.2 Hz, 1H), 7.80-7.74 (m, 4H), 4.49-4.43 (q, J=7.2 Hz, 2H) , 2.65 (s, 3H),2.57-2.51 (q, J=7.2 Hz, 2H), 1.37-1.33 (t, J=7.2 Hz, 3H), 0.97-0.93 (t, J=7.2 Hz, 3H); Anal. Calcd. For $C_{23}H_{20}N_2O_4$; C, 71.12; H, 5.19; N, 7.21; Found; C, 70.82; H, 5.09; N, 7.01.

Ethyl-6-acetyl-3-(2-chlorobenzoyl)-2-methylindolizine-1-carboxylate 2i: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 384.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.83 (s, 1H), 8.40-8.38 (d, J=8.0 Hz, 1H), 8.00-7.98 (d, J=8.0 Hz, 1H), 8.04-8.02 (d, J=9.2 Hz, 1H), 7.62-7.59 (m, 2H), 7.54-7.53 (d, J=8.2 Hz, 1H), 4.40-4.37 (q, J=8.0 Hz, 2H), 2.73 (s, 3H), 2.14 (s, 3H), 1.43-1.39 (t, J=7.2 Hz, 3H); IR (neat cm^{-1}): 1699, 1679, 1594; Anal. Calcd. For $C_{21}H_{18}ClNO_4$: C, 65.71; H, 4.73; N, 3.65; Found: C, 64.99; H, 4.51; N, 3.59.

Ethyl-6-acetyl-3-(2-chlorobenzoyl)-2-ethylindolizine-1-carboxylate 2j: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 398.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.70 (s, 1H), 8.43-8.41 (d, J=8.0 Hz, 1H), 7.99-7.97 (d, J=8.0 Hz, 1H), 7.57-7.51 (m, 3H), 7.42-7.40 (m, 1H), 4.42-4.37 (q, J=8.0 Hz, 2H), 2.73 (s, 3H), 2.62-2.60 (q, J=7.2 Hz, 2H), 1.43-1.40 (t, J=7.2 Hz, 3H), 0.97-0.93 (t, J=7.2 Hz, 3H); IR (neat cm^{-1}): 1694, 1682, 1625, 1595; Anal. Calcd. For $C_{22}H_{20}ClNO_4$: C, 66.42; H, 5.07; N, 3.52; Found: C, 65.52; H, 4.92; N, 3.33.

Ethyl-6-acetyl-2-methyl-3-(2-nitrobenzoyl)indolizine-1-carboxylate 2k: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 395.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.72 (s, 1H), 8.42-8.40 (d, J=8.0 Hz, 1H), 8.28-8.26 (d, J=8 Hz, 1H), 8.04-8.02 (d, J=9.2 Hz, 1H), 7.81-7.73 (m, 2H), 7.54-7.53 (d, J=8.2 Hz, 1H), 4.39-4.37 (q,

J=8 Hz, 2H), 2.74 (s, 3H), 2.64 (s, 3H), 1.42-1.39 (t, J=7.2 Hz, 3H); Anal. Calcd. For $C_{21}H_{18}N_2O_6$: C, 63.96; H, 4.60; N, 7.10; Found: C, 63.31; H, 4.41; N, 7.03.

Ethyl-6-acetyl-2-ethyl-3-(2-nitrobenzoyl)indolizine-1-carboxylate 2l: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 409.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.69 (s, 1H), 8.40-8.38 (d, J=8.0 Hz, 1H), 8.26-8.24 (d, J=8 Hz, 1H), 8.02-8.00 (d, J=9.2 Hz, 1H), 7.79-7.71 (m, 2H), 7.52-7.50 (d, J=8.2 Hz, 1H), 4.40-4.38 (q, J=8Hz, 2H), 2.74 (s, 3H), 2.42-2.40 (q, J=7.2 Hz, 2H), 1.42-1.39 (t, J=7.2 Hz, 3H), 1.01-0.99 (t, J=7.2 Hz, 3H); Anal. Calcd. For $C_{22}H_{20}N_2O_6$; C, 64.70; H, 4.94; N, 6.86; Found : C, 63.52; H, 4.32; N, 6.03.

Ethyl-8-acetyl-3-benzoyl-2-methylindolizine-1-carboxylate 3a: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 350.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.53-9.50 (d, J=7.6 Hz, 1H), 7.71-7.69 (d, J=7.2 Hz, 2H), 7.60-7.56 (m, 1H), 7.50-7.43 (m, 3H), 6.97-6.93 (m, 1H), 4.35-4.30 (q, J=7.2 Hz, 2H), 2.58 (s, 3H), 2.12 (s, 3H), 1.35-1.31 (t, J=7.2 Hz, 3H); Anal. Calcd. For $C_{21}H_{19}NO_4$; C, 72.19; H, 5.48; N, 4.01; Found; C, 71.79; H, 5.28; N, 3.91.

Ethyl-8-acetyl-3-benzoyl-2-ethylindolizine-1-carboxylate 3b: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 364.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.34-9.32 (d, J=7.6 Hz, 1H), 7.73-7.70 (d, J=7.2 Hz, 2H), 7.58-7.57 (m, 1H), 7.50-7.43 (m, 3H), 6.93-6.89 (m, 1H), 4.36-4.30 (q, J=7.2 Hz, 2H) , 2.62-2.59 (q, J=7.2 Hz, 2H), 2.58 (s, 3H), 1.36-1.32 (t, J=7.2 Hz, 3H) , 0.98-0.94 (t, J=7.2 Hz, 3H). Anal. Calcd. For $C_{22}H_{21}NO_4$; C, 72.71; H; 5.82, N, 3.85; Found; C, 71.91; H, 5.52; N, 3.65.

Ethyl-8-acetyl-3-(4-chlorobenzoyl)-2-methylindolizine-1-carboxylate 3c: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 384.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.50-9.48 (d, J=7.6 Hz, 1H), 7.65-7.63 (d, J=7.2 Hz, 2H), 7.49-7.44 (m, 3H), 6.98-6.95 (m, 1H), 4.35-4.30 (q, J=7.2 Hz, 2H) , 2.59 (s, 3H), 2.15 (s, 3H), 1.35-1.32 (t, J=7.2 Hz, 3H); Anal. Calcd. For $C_{21}H_{18}ClNO_4$; C, 65.71; H, 4.73; N, 3.65; Found; C, 65.01; H, 4.23; N, 3.35.

Ethyl-8-acetyl-3-(2-chlorobenzoyl)-2-ethylindolizine-1-carboxylate 3d: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 398.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.35-9.33 (d, J=7.6 Hz, 1H), 7.66-7.59 (m, 2H), 7.42-7.36 (m, 3H), 6.96-6.92 (m, 1H), 4.33-4.27 (q, J=7.2 Hz, 2H) , 2.66-2.62 (q, J=7.2 Hz, 2H), 2.57 (s, 3H), 1.40-1.35 (t, J=7.2 Hz, 3H), 0.98-0.94 (t, J=7.2 Hz, 3H); Anal. Calcd. For $C_{22}H_{20}ClNO_4$; C, 66.42; H, 5.07; N, 3.52; Found; C, 65.82; H, 4.89; N, 3.22.

Ethyl-8-acetyl-3-(4-bromobenzoyl)-2-methylindolizine-1-carboxylate 3e: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 428.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.51-9.49 (d, J=7.6 Hz, 1H), 7.65-7.63 (d, J=7.2 Hz, 2H), 7.62-7.60 (d, J=7.2 Hz, 2H), 7.46-7.44 (d, J=7.2 Hz, 1H), 6.98-6.95 (m, 1H), 4.35-4.30 (q, J=7.2 Hz, 2H) , 2.59 (s, 3H), 2.15 (s, 3H), 1.35-1.32 (t, J=7.2 Hz, 3H); Anal. Calcd. For $C_{21}H_{18}BrNO_4$; C, 58.89; H, 4.24; N, 3.27; Found; C, 58.09; H, 4.14; N, 3.07.

Ethyl-8-acetyl-3-(4-bromobenzoyl)-2-ethylindolizine-1-carboxylate 3f: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 442.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.35-9.33 (d, J=7.6 Hz, 1H), 7.66-7.59 (m, 4H), 7.46-7.44 (d, J=7.2 Hz, 1H), 6.96-6.92 (m, 1H), 4.33-4.27 (q, J=7.2 Hz, 2H) , 2.66-2.62 (q, J=7.2 Hz, 2H), 2.57 (s, 3H), 1.40-1.35 (t, J=7.2 Hz, 3H), 0.98-0.94 (t, J=7.2 Hz, 3H); Anal. Calcd. For $C_{22}H_{20}BrNO_4$; C, 59.74; H, 4.56; N, 3.17; Found; C, 59.09; H, 4.42; N, 3.07.

Ethyl-8-acetyl-3-(4-cyanobenzoyl)-2-methylindolizine-1-carboxylate 3g: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 375.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.68-9.66 (d, J=7.2 Hz, 1H), 7.84-7.66 (m, 4H), 7.54-7.52 (d, J=7.2 Hz, 1H), 7.05-7.02 (t, J=7.2 Hz, 1H), 4.36-4.31 (q, J=7.2 Hz, 2H) , 2.67 (s, 3H), 2.11 (s, 3H), 1.29-1.26 (t, J=7.2 Hz, 3H); IR (neat cm^{-1}): 2229, 1703, 1681, 1620; Anal. Calcd. For $C_{22}H_{18}N_2O_4$; C, 70.58; H, 4.85; N, 7.48, Found; C, 69.98; H, 4.53; N, 7.08.

Ethyl-8-acetyl-3-(4-cyanobenzoyl)-2-ethylindolizine-1-carboxylate 3h: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 389.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.56-9.54 (d, J=7.2 Hz, 1H), 7.84-7.66 (m, 4H), 7.53-7.51 (d, J=7.2 Hz, 1H), 7.03-7.01 (t, J=7.2 Hz, 1H), 4.37-4.32 (q, J=7.2 Hz, 2H) , 2.57-2.51 (q, J=7.2 Hz, 2H), 2.15 (s, 3H), 1.37-1.33 (t, J=7.2 Hz, 3H), 0.97-0.93 (t, J=7.2 Hz, 3H); Anal. Calcd. For $C_{23}H_{20}N_2O_4$; C, 71.12; H ,5.19; N, 7.21; Found; C, 70.74; H, 5.04; N, 7.08.

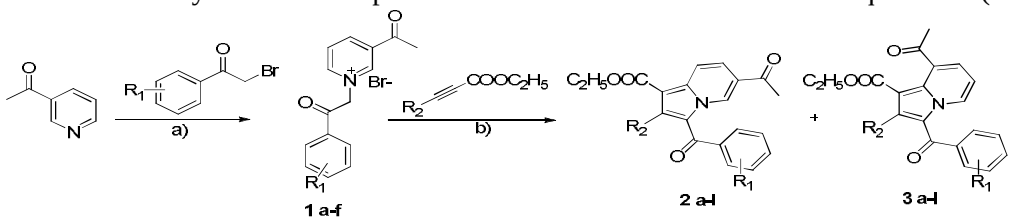
Ethyl-8-acetyl-3-(2-chlorobenzoyl)-2-methylindolizine-1-carboxylate 3i: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 384.2; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.20-10.18 (d, J=7.2 Hz, 1H), 7.85-7.83 (d, J=8.0 Hz, 1H), 7.69-7.67 (d, J=8 Hz, 1H), 7.04-7.02 (m, 1H), 6.79-6.73 (m, 2H), 6.54-6.53 (m, 1H), 4.25-4.21 (q,

J=8 Hz, 2H), 2.64 (s, 3H), 2.10 (s, 3H), 0.99-0.96 (t, J=7.2 Hz, 3H); Anal. Calcd. For $C_{21}H_{18}ClNO_4$; C, 65.71; H, 4.73; N, 3.65; Found; C, 65.19; H, 4.34; N, 3.25.

Ethyl-8-acetyl-3-(2-chlorobenzoyl)-2-ethylindolizine-1-carboxylate 3j: LC-MS (ESI, Positive): m/z: $[M+H]^+$: 398.2; ^1H NMR (400 MHz, $CDCl_3$): δ 10.13-10.11 (d, J=7.2 Hz, 1H), 7.93-7.91 (d, J=8.0 Hz, 1H), 7.61-7.63 (d, J=8 Hz, 1H), 7.50-7.47 (m, 3H), 7.03-7.01 (m, 1H), 4.21-4.18 (q, J=8 Hz, 2H), 2.63 (s, 3H), 2.35-2.32 (q, J=7.2 Hz, 2H), 1.30-1.27 (t, J=7.2 Hz, 3H), 0.93-0.90 (t, J=7.2 Hz, 3H); Anal. Calcd. For $C_{22}H_{20}ClNO_4$; C, 66.42; H, 5.07; N, 3.52; Found; C, 66.02; H, 4.89; N, 3.22.

RESULTS AND DISCUSSION

N-Heterocyclic ylides (1a-f) were prepared by stirring substituted pyridines with substituted phenacyl bromides separately in the presence of acetone at room temperature. The solids were filtered and dried under vacuum and used as such. The ylides obtained were up to 96-99% yield. Anticipated indolizines have been prepared by the 1,3-dipolar cycloaddition reaction of N-heterocyclic ylides with electron deficient alkynes in the presence of anhydrous K_2CO_3 and DMF as a solvent. The reaction time has been drastically reduced to just 30 minutes with constant stirring. The completion of reaction was monitored by TLC. The solvent was removed by distillation under reduced pressure and the reaction mixture was diluted with ethyl acetate. The organic layer was washed with water, brine and dried with anhydrous sodium sulphate purified by column chromatography using 60-120 mesh silica gel and hexane-ethylacetate as a solvent. In the present investigation. Acetylenes bearing one electron withdrawing group and one electron donating group is an additional factor. As expected, 3-acetyl-1-(2-(4-cyanophenyl)-2-oxoethyl)pyridiniumbromides 1a-f on addition to alkynes yield a Isomeric mixture of ethyl-6-acetyl-3-(4-cyanobenzoyl)-2-methylindolizine-1-carboxylate 2a-l and ethyl 8-acetyl-3-(4-cyanobenzoyl)-2-methylindolizine-1-carboxylate 3a-l**.** Compounds 3a-l have been obtained in minor quantities (5-9%).



Scheme 1. a) Acetone, rt; b) K_2CO_3, DMF, rt, 30 mins**.**

Table 1

Comp	R_1	Yield(%)	Comp	R_1	R_2	Yield (%)	Comp	R_1	R_2	Yield (%)
1a	4-H	99.2	2a	4-H	CH_3	46	3a	4-H	CH_3	7
1b	4-Cl	98	2b	4-H	C_2H_5	43	3b	4-H	C_2H_5	6
1c	4-Br	98.5	2c	4-Cl	CH_3	52	3c	4-Cl	CH_3	7
1d	4-CN	98.9	2d	4-Cl	C_2H_5	50	3d	4-Cl	C_2H_5	5
1e	2-Cl	97.3	2e	4-Br	CH_3	50	3e	4-Br	CH_3	6
1f	2-NO_2	97.6	2f	4-Br	C_2H_5	47	3f	4-Br	C_2H_5	5
			2g	4-CN	CH_3	46	3g	4-CN	CH_3	9
			2h	4-CN	C_2H_5	44	3h	4-CN	C_2H_5	7
			2i	2-Cl	CH_3	50	3i	2-Cl	CH_3	8
			2j	2-Cl	C_2H_5	48	3j	2-Cl	C_2H_5	6
			2k	2-NO_2	CH_3	51	3k	2-NO_2	CH_3	9
			2l	2-NO_2	C_2H_5	49	3l	2-NO_2	C_2H_5	7

All the synthesized compounds have been purified by column chromatography and recrystallized with ethyl acetate. The structures have been confirmed by spectroscopic techniques like IR, ^{1}H-NMR, LC-MS, elemental analysis. Synthesized compounds have been tested for Antimicrobial Activity.

APPLICATIONS

These synthesized compounds are used in biological application. In this we are tested antimicrobial activity of newly synthesized compounds, activity details are in below.

Antimicrobial Activity

Antibacterial Assay: The agar well diffusion method was followed for the screening of antibacterial activities of the synthesized chemical compounds. All the Bacterial strains were incubated at 37^{o}C for about 48 h by inoculation in to nutrient broth (Difco).The molten nutrient agar was inoculated with 100µl of the inoculum and poured into the Petri plate. After medium was solidified, a well was made in the plates with the help of cup-borer (0.85 cm). The synthesized test compound was introduced in to the well and Petri plates were incubated at 37^{0}C ±0.1^{0}C for 48 h. The synthesized compounds were dissolved in DMSO to get stock solutions. Commercial bactericide Ciprofloxacin was used as standard (100 µg per 100µl of sterilized distilled water) conmitantly with the test samples. The diameter of inhibition zones (in mm) was determined and data was statistically evaluated by Turkey's fair wise comparison test.

Antifungal Assay: The agar well diffusion method was followed for the screening of antifungal activities of the synthesized chemical compounds. All the fungal strains were incubated at 37^{o}C for about 72 hrs by inoculation in to potatodectrose broth (Himedia). The molten PDA media was inoculated with 100µl of the inoculum and poured into the Petri plate. After medium was solidified, a well was made in the plates with the help of cup-borer (0.85 cm). The synthesized test compound was introduced in to the well and Petri plates were incubated at 37^{0}C ±0.1^{0}C for 72 h. The synthesized compounds were dissolved in DMSO to get stock solutions. Commercial antifungal Nystatin was used as standard (100 µg per 100µl of sterilized distilled water) conmitantly with the test samples. The diameter of inhibition zones (in mm) was determined and data was statistically evaluated by Turkey's fair wise comparison test.

All compounds showed comparable antimicrobial activity. Results are reported in table 2. Some compounds showed both antibacterial and antifungal activity against *Bacillus flexus* (gram positive bacteria) and *Scopulariopsis* spp. respectively. The compound 2a showed maximum antifungal activity against *Scopulariopsis* spp. whereas compound 2g showed maximum antibacterial activity against *Bacillus flexus*. The compound 2b, 2j, 2c, 3b, 3j, 3c showed minimal antibacterial activity and 2g, 2k, 3e, 3h showed minimal antifungal activity. The compounds 2a, 2b, 2g, 2h, 3a, 3b, 3g, 3h, have both antibacterial and antifungal activity. The compounds 2c, 2d, 2i, 2j, 3c, 3i, have only antibacterial activity and no antifungal activity. The compounds 2e, 2f, 2k, 3e, 3f, 3k have antifungal activity and no antibacterial activity. The compounds 2l, 3d, 3l have no antibacterial (Gram positive) and antifungal activity(*Scopulariopsis* spp.).

Table 2. Antibacterial and antifungal activity of compounds **2a-l** and **3a-l**.

Sl NO	COMP	Antimicrobial activity			
		Bacteria		Fungus	
		Gram positive *(Bacillus flexus)*	Gram negative *(Pseudomonas* Spp.)	*(Scopulariopsis* spp.	(*Aspergillus tereus)*
	Standard	-	-	-	-
1	**2a**	+++	-	++++	-
2	**2b**	+	-	++	-
3	**2c**	+	-	-	-

4	**2d**	++	-	-	-
5	**2e**	-	-	++	-
6	**2f**	-	-	+++	-
7	**2g**	++++	-	+	-
8	**2h**	++	-	++	-
9	**2i**	+++	-	-	-
10	**2j**	+	-	-	-
11	**2k**	-	-	+	-
12	**2l**	-	-	-	-
13	**3a**	+++	-	+++	-
14	**3b**	+	-	++	-
15	**3c**	+	-	-	-
16	**3d**	-	-	-	-
17	**3e**	-	-	+	-
18	**3f**	-	-	++	-
19	**3g**	+++	-	++	-
20	**3h**	++	-	+	-
21	**3i**	++	-	-	-
22	**3j**	+	-	-	-
23	**3k**	-	-	++	-
24	**3l**	-	-	-	-

++++ = 15mm, +++ = 11mm, ++ = 8mm, + = 4mm

The compounds did not show any antibacterial and antifungal activity with respect to *Pseudomonas Spp* (Gram negative bacteria) and *Aspergillus tereus* respectively.

CONCLUSIONS

The research work is focused on the efficient synthesis of indolizines with drastically reduced time of reaction. The reactions performed are eco-friendly as they are carried out at room temperature. The publication of these facts would be of significant use for the scientific community.

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