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One-pot microwave assisted synthesis and structural elucidation of novel ethyl 3-substituted-7-methylindolizine-1-carboxylates with larvicidal activity against *Anopheles arabiensis*

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ABSTRACT

In the present investigation a series of novel ethyl 3-substituted-7-methylindolizine-1-carboxylates was achieved by microwave assisted one-pot method. The purity of the compounds was ascertained by HPLC and structural elucidation of the title compounds was achieved by FT-IR, NMR (^{1}H and ^{13}C), LC-MS and elemental analysis. One randomly selected compound from the series was further studied by single crystal X-ray method for intra and intermolecular interactions. Larvicidal properties of the characterized compounds were evaluated against *Anopheles arabiensis* and it was found that indolizine pharmacophore influences larvicidal activity as we can see larvicidal activity for all the analogues. The synthesized analogues (**2j**, **2m** and **2f**) were the most potent compounds based on the functional groups on the indolizine pharmacophore for larvicidal assay.

1. Introduction

Indolizine derivatives are one of the major classes of heterocycles. Functionalized indolizines have found wide applications in natural products and synthetic pharmaceuticals, which are associated with a broad spectrum of pharmacological properties such as analgesic [1], anticancer [2,3], antidiabetic [4], antihistaminic [5], anti-inflammatory [6], antileishmanic [7], antimicrobial [8], antimutagenic [9], antioxidant [10], antitubercular [11], antiviral [12], larvicidal [13], in vitro COX-2 inhibition [14] and herbicidal activities [15]. Indolizines nucleus substituted at C-3 positions are very attractive heterocyclic units, as a number of representatives of this class [16,17] and, especially their partially or completely reduced analogues, indolizidine alkaloids [18,19] and related unnatural compounds [20,21], exhibit important biological properties. The development of efficient methods for rapid construction and functionalization of indolizine has gained much attention, especially towards differently substituted indolizines. There is particular interest in elaborating efficient approaches towards C-3 positions and in their biological application. Documented approaches to

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indolizine mainly include the following Schotz reaction [22], Tschitschibabin reaction [23–25], dipolar cycloadditions of pyridinium and related heteroaromatic ylides with electron-deficient alkynes or alkenes [13,26–29], cyclization of pyridines with alkenyldiazoacetates [30], C–H functionalization reaction [31–35], transmetal catalysed cycloisomerizations of alkynylpyridine derivatives [36–39], azaarenes with enals by an amine-NHC relay catalysis [40], 1,3-dipolar cyclocondensation using potassium dichromate as oxidant [41] and trans annulations of pyridotriazoles with alkynes [42,43]. Despite primordial importance in synthetic chemistry these methods often involve multistage synthesis and suffer from limited substrate availability in some cases. Therefore, there is a need for suitable method for the construction of pharmacologically active heterocyclic compounds. In continuation of our efforts to develop novel heterocyclic compounds with larvicidal activity [13,44] and screening of pharmacologically active heterocyclic compounds for polymorphism property [45–47], herewith we undertake a convenient, straightforward, and one-pot synthesis of ethyl 3-substituted-7-methylindolizine-1-carboxylate using microwave method with potential larvicidal activity against *Anopheles arabiensis*.

2. Experimental section

2.1. General

All the commercially available chemicals were purchased from Sigma-Aldrich, India. All the reactions were carried out in hot-air dried glass wares under nitrogen atmosphere using dry solvents. Chemical reactions were monitored on thin layer chromatography (TLC). TLC was performed on Sigma-Aldrich Silica gel on TLC aluminium foils with n-hexane and ethyl acetate (4:6) as solvent system and visualization with UV-light/iodine chamber. Melting points were determined on a Büchi melting point B-545 apparatus. The FT-IR spectra were recorded on a Shimadzu FT-IR spectrometry. NMR (400 MHz) spectra were recorded at ambient temperature using $CDCl_3$ 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 follows; 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 mode, MS range 100–2000. Elemental analysis was performed on Thermo Finnigan FLASH EA 1112 CHN analyzer. Single crystal X-ray diffraction study was accomplished using Bruker APEX II diffractometer equipped with a CCD detector using monochromated Mo K_α radiation ($\lambda = 0.71073$ Å).

2.2. General procedure for the synthesis of ethyl 3-(4-chlorobenzoyl)-2,7-dimethylindolizine-1-carboxylate (**2a**)

To a mixture of 4-methyl pyridine (0.1 g, 1.07 mmol), 4-chlorophenacyl bromide (0.249 g, 1.07 mmol), and ethylbutynoate (0.120 g, 1.07 mmol), triethylamine (0.108 g, 1.07 mmol) in acetonitrile (4 mL) in 8 mL Microwave tube under nitrogen atmosphere. The reaction mixture was irradiated at 100 °C in a microwave initiator for 5 min. The completion of reaction was monitored on TLC. The reaction medium was evaporated under reduced pressure, the crude reaction mass was diluted with water, extracted twice the aqueous layer with ethyl acetate and was washed with brine solution. Organic layer was evaporated under reduced pressure and residue obtained was purified by column chromatography using 60–120 mesh silica gel with hexane and ethylacetate solvent system to afford 0.343 g of ethyl 3-(4-chlorobenzoyl)-2,7-dimethylindolizine-1-carboxylate **2a** at 90% yield.

2.2.1. Ethyl 3-(4-chlorobenzoyl)-2,7-dimethylindolizine-1-carboxylate (**2a**)

IR (KBr, cm^{-1}): 2977.89, 1689.53, 1616.24, 1421.44, 1217.00; ^1H NMR (400 MHz $CDCl_3$) $\delta = 9.44–9.43$ (1H, d, $J = 7.2$ Hz), 8.17 (1H, s), 7.65–7.63 (2H, m), 7.48–7.46 (2H, m), 6.84–6.82 (1H, d, $J = 7.2$ Hz), 4.43–4.38 (2H, q, $J = 7.2$ Hz), 2.49 (3H, s), 2.23 (3H, s), 1.46–1.42 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (100 MHz $CDCl_3$) $\delta = 186.01, 165.09, 140.23, 139.65, 138.89, 138.13, 137.97, 130.27, 128.84, 127.55, 122.17, 118.10, 116.95, 104.54, 59.76, 21.64, 15.19, 14.54$; LC-MS (ESI, Positive): m/z: $(M + H)^+$: 356; Anal. calculated for: $C_{20}H_{18}ClNO_3$; C, 67.51; H, 5.10; N, 3.94; Found: C, 67.49; H, 5.06; N, 3.98.

2.2.2. Ethyl 3-(4-fluorobenzoyl)-2,7-dimethylindolizine-1-carboxylate (**2b**)

IR (KBr, cm^{-1}): 2985.60, 1674.10, 1600.81, 1504.37, 1379.01, 1222.79; ^1H NMR (400 MHz $CDCl_3$) $\delta = 9.40–9.39$ (1H, d, $J = 7.2$ Hz), 8.16 (1H, s), 7.74–7.70 (2H, m), 7.20–7.16 (2H, m), 6.83–6.81 (1H, d, $J = 7.2$ Hz), 4.43–4.38 (2H, q, $J = 7.2$ Hz), 2.48 (3H, s), 2.23 (3H, s), 1.46–1.42 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (100 MHz $CDCl_3$) $\delta = 186.02, 166.25, 165.13, 163.74, 140.14, 138.70, 137.87, 137.45, 137.42, 131.38, 131.29, 127.47, 122.25, 118.09, 116.85, 115.77, 115.55, 104.39, 59.73, 21.63, 15.12, 14.55$; LC-MS (ESI, Positive): m/z: $(M + H)^+$: 340; Anal. calculated for: $C_{20}H_{18}FNO_3$; C, 70.78; H, 5.35; N, 4.13; Found: C, 7.82; H, 5.36; N, 4.08.

2.2.3. Ethyl 3-(4-fluorobenzoyl)-7-methylindolizine-1-carboxylate (**2c**)

IR (KBr, cm^{-1}): 2983.67, 1676.03, 1600.81, 1504.37, 1380.94, 1222.70; ^1H NMR (400 MHz $CDCl_3$) $\delta = 9.85–9.83$ (1H, d, $J = 7.2$ Hz), 8.21 (1H, s), 7.88–7.84 (2H, m), 7.76 (1H, s), 7.24–7.20 (2H, m), 6.97–6.95 (1H, d, $J = 7.2$ Hz), 4.42–4.37 (2H, q, $J = 7.2$ Hz), 2.49 (3H, s), 1.44–1.40 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (100 MHz $CDCl_3$) $\delta = 183.76, 165.98, 164.17, 163.48, 140.50, 139.59, 136.21, 136.18, 131.30, 131.21, 129.05, 128.62, 121.94, 118.32, 117.82, 115.58, 115.37, 105.29, 60.05, 21.66, 14.57$; LC-MS (ESI, Positive): m/z: $(M + H)^+$: 326; Anal. calculated for: $C_{19}H_{16}FNO_3$; C, 70.14; H, 4.96; N, 4.31; Found: C, 70.15; H, 4.92; N, 4.33.

2.2.4. Ethyl 3-(4-cyanobenzoyl)-7-methylindolizine-1-carboxylate (**2d**)

IR (KBr, cm^{-1}): 2989.46, 2231.49, 1699.17, 1623.95, 1525.59, 1350.08, 1218.93; ^1H NMR (400 MHz $CDCl_3$ $\delta = 9.88–9.86$ (1H, d, $J = 7.2$ Hz), 8.24 (1H, s), 7.91–7.89 (2H, d, $J = 8$ Hz), 7.84–7.82 (2H, d, $J = 8$ Hz), 7.70 (1H, s), 7.02–7.00 (1H, d, $J = 7.2$ Hz), 4.42–4.37 (2H, q, $J = 7.2$ Hz), 2.54 (3H, s), 1.43–1.40 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (100 MHz $CDCl_3$) $\delta = 182.82, 163.90, 143.85, 140.84, 140.43, 132.26, 129.43, 129.31, 128.74, 121.51, 118.49, 118.30, 118.20, 114.71, 106.06, 60.21, 21.72, 14.55$; LC-MS (ESI, Positive): m/z: $(M + H)^+$: 333; Anal. calculated for: $C_{20}H_{16}N_2O_3$; C, 72.28; H, 4.85; N, 8.43; Found: C, 72.29; H, 4.79; N, 8.41.

2.2.5. Ethyl 3-(4-chlorobenzoyl)-2-ethyl-7-methylindolizine-1-carboxylate (**2e**)

IR (KBr, cm^{-1}): 2968.24, 1681.81, 1606.59, 1504.59, 1377.08, 1222.79; ^1H NMR (400 MHz $CDCl_3$) $\delta = 9.30–9.28$ (1H, d, $J = 7.2$ Hz), 8.19 (1H, s), 7.66–7.64 (2H, m), 7.48–7.46 (2H, m), 6.81–6.80 (1H, d, $J = 7.2$ Hz), 4.44–4.39 (2H, q, $J = 7.2$ Hz), 2.76–2.70 (2H, q, $J = 7.2$ Hz), 2.48 (3H, s), 1.46–1.42 (3H, t, $J = 7.2$ Hz), 1.03–1.00 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (100 MHz $CDCl_3$) $\delta = 186.36, 164.79, 144.52, 140.53, 139.64, 138.69, 137.86, 129.98, 128.74, 127.61, 121.43, 118.31, 116.85, 103.39, 59.75, 21.62, 20.00, 16.05, 14.45$; LC-MS (ESI, Positive): m/z: $(M + H)^+$: 370; Anal. calculated for: $C_{21}H_{20}ClNO_3$; C, 68.20; H, 5.45; N, 3.79; Found: C, 68.21; H, 5.44; N, 3.76.

*2.2.6. Ethyl 3-(4-bromobenzoyl)-2,7-dimethylindolizine-1-carboxylate (**2f**)*

IR (KBr, cm^{-1}): 2975.96, 1689.24, 1616.24, 1423.37, 1217.00, 1178.43; ^1H NMR (400 MHz $CDCl_3$) δ = 9.36–9.34 (1H, d, J = 7.2 Hz), 8.07 (1H, s), 7.55–7.53 (2H, m), 7.48–7.46 (2H, m), 6.75–6.73 (1H, d, J = 7.2 Hz), 4.34–4.28 (2H, q, J = 7.2 Hz), 2.39 (3H, s), 2.13 (3H, s), 1.36–1.32 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ = 186.09, 165.09, 140.25, 140.11, 138.94, 138.20, 132.40, 131.81, 130.41, 127.51, 126.45, 122.13, 118.10, 116.98, 104.57, 59.77, 21.65, 15.22, 14.55; LC-MS (ESI, Positive): m/z: $(M + H)^+$: 400; Anal. calculated for: $C_{20}H_{18}BrNO_3$; C, 60.01; H, 4.53; N, 3.50; Found: C, 59.98; H, 4.56; N, 3.46.

*2.2.7. Ethyl 3-(4-bromobenzoyl)-7-methylindolizine-1-carboxylate (**2g**)*

IR (KBr, cm^{-1}): 2975.96, 1706.88, 1612.38, 1525.59, 1463.87, 1346.22, 1222.79, 1170.71; ^1H NMR (400 MHz $CDCl_3$) δ = 9.86–9.84 (1H, d, J = 7.2 Hz), 8.22 (1H, s), 7.74–7.70 (5H, m), 6.98–6.96 (1H, d, J = 7.2 Hz), 4.42–4.37 (2H, q, J = 7.2 Hz), 2.53 (3H, s), 1.44–1.40 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ = 183.86, 164.10, 140.59, 139.78, 138.81, 131.63, 130.47, 129.15, 128.68, 126.07, 121.81, 118.35, 117.93, 105.45, 60.08, 21.67, 14.57; LC-MS (ESI, Positive): m/z: $(M + H)^+$: 386; Anal. calculated for: $C_{19}H_{16}BrNO_3$; C, 59.08; H, 4.18; N, 3.63; Found: C, 59.04; H, 4.13; N, 3.67.

*2.2.8. Ethyl 3-benzoyl-7-methylindolizine-1-carboxylate (**2h**)*

IR (KBr, cm^{-1}): 2977.89, 1693.38, 1606.59, 1525.59, 1344.29, 1207.36, 1182.28; ^1H NMR (400 MHz $CDCl_3$) δ = 9.89–9.87 (1H, d, J = 7.2 Hz), 8.21 (1H, s), 7.84–7.79 (3H, m), 7.59–7.51 (3H, m), 6.96–6.95 (1H, d, J = 7.2 Hz), 4.41–4.36 (2H, q, J = 7.2 Hz), 2.52 (3H, s), 1.43–1.39 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ = 185.27, 164.24, 140.45, 140.05, 139.47, 131.32, 129.32, 128.92, 128.67, 128.36, 128.23, 122.16, 118.27, 117.74, 105.18, 60.00, 21.66, 14.57; LC-MS (ESI, Positive): m/z: $(M + H)^+$: 308; Anal. calculated for: $C_{19}H_{17}NO_3$; C, 74.25; H, 5.58; N, 4.56; Found: C, 74.22; H, 5.53; N, 4.54.

*2.2.9. Ethyl 3-(4-cyanobenzoyl)-2,7-dimethylindolizine-1-carboxylate (**2i**)*

IR (KBr, cm^{-1}): 2950.89, 2225.70, 1704.96, 1608.52, 1217.00; ^1H NMR (400 MHz $CDCl_3$) δ = 9.60–9.58 (1H, d, J = 7.2 Hz), 8.19 (1H, s), 7.81–7.79 (2H, d, J = 8 Hz), 7.76–7.74 (2H, d, J = 8 Hz), 6.90–6.88 (1H, d, J = 7.2 Hz), 4.43–4.38 (2H, q, J = 7.2 Hz), 2.50 (3H, s), 2.16 (3H, s), 1.45–1.42 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ = 184.94, 164.87, 145.35, 140.60, 139.76, 139.00, 132.43, 129.05, 127.84, 121.77, 118.23, 118.17, 117.44, 105.22, 59.91, 21.70, 15.20, 14.52; LC-MS (ESI, Positive): m/z: $(M + H)^+$: 347; Anal. calculated for: $C_{21}H_{18}N_2O_3$; C, 72.82; H, 5.24; N, 8.09; Found: C, 72.84; H, 5.21; N, 8.07.

*2.2.10. Ethyl 3-(4-bromobenzoyl)-2-ethyl-7-methylindolizine-1-carboxylate (**2j**)*

IR (KBr, cm^{-1}): 2952.81, 1704.96, 1596.95, 1417.58, 1218.93, 1135.99; ^1H NMR (400 MHz $CDCl_3$) δ = 9.31–9.29 (1H, d, J = 7.2 Hz), 8.18 (1H, s), 7.65–7.63 (2H, m), 7.58–7.56 (2H, m), 6.82–6.80 (1H, d, J = 7.2 Hz), 4.44–4.39 (2H, q, J = 7.2 Hz), 2.73–2.70 (2H, q, J = 7.2 Hz), 2.48 (3H, s), 1.46–1.42 (3H, t, J = 7.2 Hz), 1.03–1.00 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ = 186.43, 164.78, 144.59, 140.54, 140.10, 138.74, 131.70, 130.12, 127.63, 126.31, 121.39, 118.31, 116.88, 103.41, 59.76, 21.62, 20.01, 16.06, 14.45; LC-MS (ESI, Positive): m/z: $(M + H)^+$: 414; Anal. calculated for: $C_{21}H_{20}BrNO_3$; C, 60.88; H, 4.87; N, 3.38; Found: C, 60.87; H, 4.85; N, 3.33.

*2.2.11. Ethyl 3-benzoyl-2-ethyl-7-methylindolizine-1-carboxylate (**2k**)*

IR (KBr, cm^{-1}): 2985.60, 1676.03, 1600.81, 1504.81, 1380.94, 1222.79, 1166.85; ^1H NMR (400 MHz $CDCl_3$) δ = 9.31–9.29 (1H, d, J = 7.2 Hz), 8.18 (1H, s), 7.70–7.68 (2H, m), 7.59–7.47 (3H, m), 6.80–6.78 (1H, d, J = 7.2 Hz), 4.44–4.38 (2H, q, J = 7.2 Hz), 2.74–2.70 (2H, q, J = 7.2 Hz), 2.47 (3H, s), 1.45–1.42 (3H, t, J = 7.2 Hz), 1.02–0.98 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ = 187.87, 164.89, 144.49, 141.32, 140.40, 138.39, 131.57, 128.48, 128.41, 127.64, 121.74, 118.25, 116.68, 103.18, 59.67, 21.61, 19.91, 16.01, 14.45; LC-MS (ESI, Positive): m/z: $(M + H)^+$: 336; Anal. calculated for: $C_{21}H_{21}NO_3$; C, 75.20; H, 6.31; N, 4.18; Found: C, 75.22; H, 6.35; N, 4.21.

*2.2.12. Ethyl 3-(4-cyanobenzoyl)-2-ethyl-7-methylindolizine-1-carboxylate (**2l**)*

IR (KBr, cm^{-1}): 2981.74, 2227.63, 1697.24, 1627.81, 1423.37, 1217.00, 1110.92; ^1H NMR (400 MHz $CDCl_3$) δ = 9.52–9.50 (1H, d, J = 7.2 Hz), 8.22 (1H, s), 7.81–7.79 (2H, d, J = 8 Hz), 7.76–7.74 (2H, d, J = 8 Hz), 6.88–6.87 (1H, d, J = 7.2 Hz), 4.44–4.39 (2H, q, J = 7.2 Hz), 2.64–2.58 (2H, q, J = 7.2 Hz), 2.50 (3H, s), 1.45–1.42 (3H, t, J = 7.2 Hz), 0.99–0.96 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ = 185.24, 164.55, 145.60, 145.46, 140.97, 139.66, 132.29, 128.65, 128.01, 120.92, 118.43, 118.18, 117.38, 114.61, 104.08, 59.90, 21.68, 19.97, 16.00, 14.42; LC-MS (ESI, Positive): m/z: $(M + H)^+$: 361; Anal. calculated for: $C_{22}H_{20}N_2O_3$; C, 73.32; H, 5.59; N, 7.77; Found: C, 73.38; H, 5.58; N, 7.74.

*2.2.13. Ethyl 2-ethyl-3-(4-fluorobenzoyl)-7-methylindolizine-1-carboxylate (**2m**)*

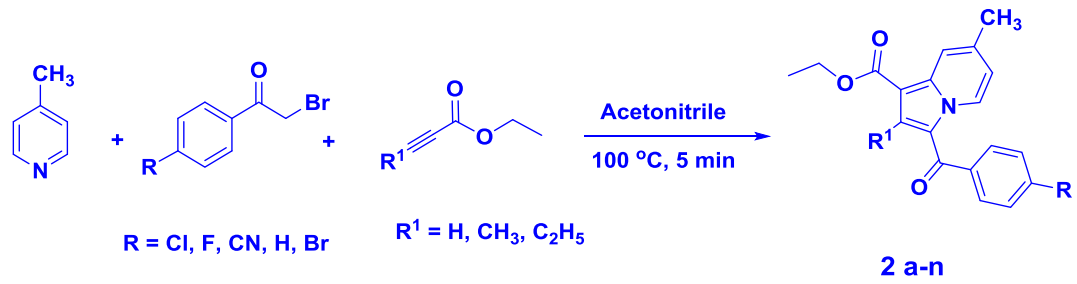
IR (KBr, cm^{-1}): 2977.89, 1689.53, 1616.24, 1423.37, 1217.00, 1178.43, 1178.43, 1108.99; ^1H NMR (400 MHz $CDCl_3$) δ = 9.24–9.22 (1H, d, J = 7.2 Hz), 8.18 (1H, s), 7.74–7.71 (2H, m), 7.20–7.15 (2H, m), 6.80–6.78 (1H, d, J = 7.2 Hz), 4.44–4.39 (2H, q, J = 7.2 Hz), 2.74–2.69 (2H, q, J = 7.2 Hz), 2.47 (3H, s), 1.46–1.42 (3H, t, J = 7.2 Hz), 1.04–1.00 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ = 186.38, 166.18, 164.83, 163.67, 144.19, 140.42, 138.47, 137.43, 137.40, 131.09, 131.00, 127.50, 121.53, 118.29, 116.74, 115.68, 115.46, 103.23, 59.72, 21.61, 19.99, 16.01, 14.45; LC-MS (ESI, Positive): m/z: $(M + H)^+$: 354; Anal. calculated for: $C_{21}H_{20}FNO_3$; C, 71.37; H, 5.70; N, 3.96; Found: C, 71.41; H, 5.69; N, 3.98.

*2.2.14. Ethyl 3-(4-chlorobenzoyl)-7-methylindolizine-1-carboxylate (**2n**)*

IR (KBr, cm^{-1}): 2968.24, 1681.81, 1606.59, 1504.37, 1377.08, 1222.79, 1170.71; ^1H NMR (400 MHz $CDCl_3$) δ = 9.85–9.83, (1H, d, J = 7.2 Hz), 8.22 (1H, s), 7.79–7.75 (3H, m), 7.52–7.50 (7H, m), 6.98–6.96 (1H, m), 4.42–4.37 (2H, q, J = 7.2 Hz), 2.53 (3H, s), 1.43–1.40 (3H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz $CDCl_3$) δ = 183.77, 164.11, 140.57, 139.74, 138.36, 137.61, 130.31, 129.12, 128.67, 128.64, 121.85, 118.34, 117.91, 105.42, 60.07, 21.67, 14.56; LC-MS (ESI, Positive): m/z: $(M + H)^+$: 342; Anal. calculated for: $C_{19}H_{16}ClNO_3$; C, 66.77; H, 4.72; N, 4.10; Found: C, 66.72; H, 4.75; N, 4.09.

2.3. Single crystal X-ray study

Single crystal of compound **2k** was obtained from mixture of acetone and ethanol solvent at 1:1 ratio by slow evaporation method at low temperature in the range of 12–14 °C as block-shape and yellow in colour by slow evaporation method at room temperature. Single-crystal X-ray diffraction data for **2k** were collected on a Bruker KAPPA APEX II DUO diffractometer using graphite-monochromated Mo-K_α radiation (χ = 0.71073 Å). Data collection was carried out at 153 (2) K. Temperature was controlled by an Oxford Cryostream cooling system (Oxford Cryostat). Cell



Scheme 1. Microwave assisted one-pot synthesis of ethyl 3-substituted-7-methylindolizine-1-carboxylate analogues **2a-n**.

refinement and data reduction were performed using the program SAINT [48]. The data were scaled and absorption correction performed using SADABS. The structure was solved by direct methods using SHELXS-97 [49], data were scaled and refined by full-matrix least-squares methods based on F^2 using SHELXL-2014 [49]. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were placed in idealised positions and refined in riding models with U_{iso} assigned 1.2 or 1.5 times U_{eq} of their parent atoms and the C–H bond distances were constrained in the range from 0.95 Å to 0.99 Å. The structure was refined to R factor of 0.0513. The crystallographic details are listed in Table 3. Intermolecular interactions, thermal ellipsoid diagram and packing diagrams are generated using CSD software ORTEP [50] and Mercury 3.8 [51].

2.4. Pharmacology

2.4.1. Larvicidal activity

The *Anopheles arabiensis* used were from a colonized strain from Zimbabwe which had been reared according to the WHO (1975) guidelines [52] in an insectary simulating the temperature (27.5 °C), humidity (70%), and lighting (12/12) of a malaria endemic environment. One mL of test compound (1 mg/mL) was added to distilled water (250 mL) producing a final concentration of 4 μg/mL. Thirty 3rd instar larvae were placed in the container. A negative control used a solvent (acetone) and distilled water and a positive control included an effective emulsifiable organophosphate larvicidal (Temephos; Mostop; Agrivo) used by the malaria control program. Each container was monitored for larval mortality at 24 h intervals for a period of three days and fed specially made cat food with reduced oil/fat content at regular intervals. Bioassays were triplicated. The percentage mortality was calculated relative to the initial number of exposed larvae. The larvicidal results are tabulated in Table 4.

2.4.2. Data analysis

General linear mixed models [53] were used to determine differences between treatments registered in larval mortality (larvicide assays). Dependent variables were *A. arabiensis* mortality, fixed effects were test compound (test compounds **2a-n**, acetone, and Temephos) and observation period (24 and 48 h). Random effects were mosquito groups (i.e., container in larvicide tests). In all cases, a value of $p < 0.05$ was considered statistically significant. Throughout the text, the results are presented as the adjusted mean plus/minus the standard error.

3. Results and discussion

3.1. Chemistry

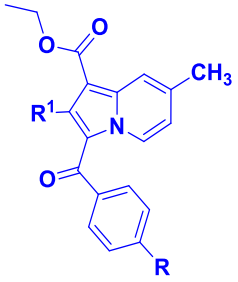
One-pot microwave assisted synthesis of ethyl 3-substituted-7-methylindolizine-1-carboxylate analogues **2a-n** has been achieved by running reaction at 1.07 mmol scale between 4-methyl pyridine, 4-chlorophenacyl bromide, ethylbutynoate, and triethylamine in acetonitrile in 8 mL Microwave tube under nitrogen atmosphere for 5 min Scheme 1. Completion of reaction was monitored by TLC. The reaction medium was diluted with water, the aqueous layer was extracted with ethyl acetate two times and the organic layer was washed with brine solution. Organic layer was evaporated under reduced pressure and the final product left over was purified by column chromatography. The purity was over 99% and the yield obtained was in the range of 86–93%.

In the present investigation we tried to standardise the reaction condition required for the construction of ethyl 3-substituted-7-methylindolizine-1-carboxylate **2a-n** by microwave method using appropriate base and solvent as shown in Table 1. In order to select appropriate base and solvent for better yield of the product by one-pot microwave method, we tried few attempts for compound **2a** and these were as follows. In the first attempt, we tried 1.07 mmol scale reaction for 5 min time having reactants as illustrated in Scheme 1 with bases such as triethylamine, sodium hydroxide, and potassium carbonate in tetrahydrofuran solvent at 100 °C. It was found that, the better yield with triethylamine base and tetrahydrofuran solvent was at 80%. Similarly second attempt was made having acetonitrile as solvent at 100 °C and found better yield with triethylamine and acetonitrile at 90%. In the third attempt ethanol was used as solvent and reaction was extended up to 120 °C and

Table 1
Screening optimum conditions for synthesis of ethyl 3-substituted-7-methylindolizine-1-carboxylate **2a-n**.

Sl No	Base	Reaction Time in minutes	Solvent	Temp (°C)	Yield (Isolated yields)
1	TEA	5	Tetrahydrofuran	100	80
2	NaOH	5	Tetrahydrofuran	100	78
3	K_2CO_3	5	Tetrahydrofuran	100	74
4	TEA	5	Acetonitrile	100	90
5	NaOH	5	Acetonitrile	100	86
6	K_2CO_3	5	Acetonitrile	100	84
7	TEA	5	Ethanol	120	82
8	NaOH	5	Ethanol	120	79
9	K_2CO_3	5	Ethanol	120	77

Table 2
Physicochemical constants of substituted 3-(4-substitutedbenzoyl)-7-methyl-2-substituted indolizine-1-carboxylate **2a-n**.



Comp code	Mol formulae (Mol mass)	R	R^1	Yield (%)[a,b]	m.p (°C)	cLogP[c]
2a	$C_{20}H_{18}ClNO_3$ (355)	Cl	CH_3	90	143–144	6.0702
2b	$C_{20}H_{18}FNO_3$ (339)	F	CH_3	89	117–118	5.5002
2c	$C_{19}H_{16}FNO_3$ (325)	F	H	93	141–142	5.0012
2d	$C_{20}H_{16}N_2O_3$ (332)	CN	H	90	135–136	4.3495
2e	$C_{21}H_{20}ClNO_3$ (369)	Cl	C_2H_5	88	101–102	6.5992
2f	$C_{20}H_{18}BrNO_3$ (399)	Br	CH_3	90	149–150	6.2202
2g	$C_{19}H_{16}BrNO_3$ (385)	Br	H	91	119–120	5.7212
2h	$C_{19}H_{17}NO_3$ (307)	H	H	92	140–141	4.8504
2i	$C_{21}H_{18}N_2O_3$ (346)	CN	CH_3	89	146–147	4.8485
2j	$C_{21}H_{20}BrNO_3$ (413)	Br	C_2H_5	87	114–115	6.7492
2k	$C_{21}H_{21}NO_3$ (335)	H	C_2H_5	86	110–111	5.8784
2l	$C_{22}H_{20}N_2O_3$ (360)	CN	C_2H_5	87	108–109	5.3775
2m	$C_{21}H_{20}FNO_3$ (353)	F	C_2H_5	86	102–103	6.0292
2n	$C_{19}H_{16}ClNO_3$ (341)	Cl	H	93	120–121	5.5712

[a] All of the products were characterized by spectral and physical data.
[b] Yields after purification by column chromatography method.
[c] *cLogP* was calculated using ChemBioDraw Ultra 13.0v.

found the maximum yield with triethylamine and ethanol at 82%. However, it is apparent from the three trials that, triethylamine is an ideal base for the construction of indolizine pharmacophore by this approach using tetrahydrofuran, acetonitrile, and ethanol solvents over sodium hydroxide and potassium carbonate bases. Triethylamine and acetonitrile combination was used for the construction of title compounds **2b-n**. The physicochemical constants of the title compounds **2a-n** are tabulated in Table 2. FT-IR, NMR, LC-MS, and elemental analysis techniques were used to confirm the molecular structure of the compounds. In FT-IR the carbonyl group from the ester functional group and alkyl carbon-hydrogen stretching was observed in the range of 1674–1708, 2952–2989 cm^{-1}, respectively. Carbon-bromine, carbon-chlorine, carbon-fluorine, and carbon-nitrile stretching's are observed at 590–598, 790–798, 1217–1222 and 2227–2231 cm^{-1}, respectively. In proton NMR, methyl group at seventh position of indolizine nucleus

Table 3
Crystal data and measurement details for compound **2k**.

Crystal data	Compound **2k**
Formula	$C_{21}H_{21}NO_3$
CCDC Number	1553592
Formula weight	335.4
Crystal morphology	block
Crystal size (mm)	0.05 × 0.12 × 0.37
Temperature/K	153 (2)
Radiation	Mo K_α
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	*P* -1
a (Å)	4.8210 (7)
B (Å)	11.8102 (19)
c (Å)	15.5400 (24)
α (°)	92.270 (3)
β (°)	95.501 (3)
γ(°)	99.449 (3)
Volume ($Å^3$)	867.39 (6)
Z	2
Density (gm/cm^3)	1.28
μ (1/mm)	0.086
F (000)	356
θ (min, max)	1.3, 27.9
Total number of refl^n	15552
No. Unique refl^n	4165
No. of parameters	229
$R\_$ obs, wR_2_obs	0.051, 0.093
$\Delta\rho_{min}$ ($eÅ^{-3}$), $\Delta\rho_{max}$ ($eÅ^{-3}$)	−0.277, 0.299
GooF	1.023

Table 4
Mortality of *Anopheles arabiensis* larvae exposed to test compounds **2a-n** at 4 μg/mL (1 mg/250 mL) and their negative (acetone) and positive (Temephos) controls.

Compound	Mortality (%)	
	24 h	48 h
2a ^{AB}	61.11	64.44
2b ^{CD}	75.56	77.78
2c ^{CE}	77.78	81.11
2d ^{BF}	58.89	61.11
2e ^{CD}	74.44	76.67
2f ^{EG}	82.22	85.56
2g ^{DH}	70	73.33
2h ^{I}	36.67	41.11
2i ^{AH}	65.56	68.89
2j ^{G}	87.78	90
2k ^{BF}	54.44	58.89
2l ^{CDE}	76.67	80
2m ^{G}	86.67	87.78
2n ^{F}	51.11	55.56
Temephos ^{J}	97.78	98.89
Acetone ^{K}	7.78	10

Adjusted means are shown. Adjusted standard errors were 2.3.
$^{A–K}$ Compounds sharing a letter do not differ significantly ($p > 0.05$).

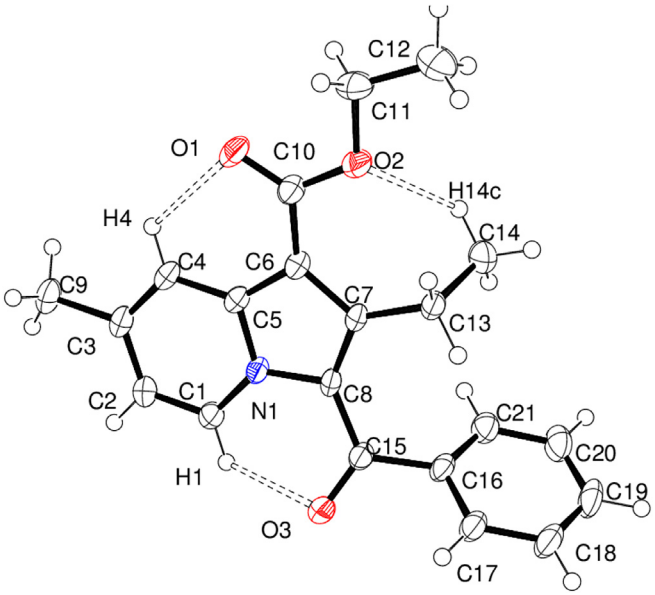


Fig. 1. Thermal ellipsoid of 50% probability plot of **2k** with atom labelling, which adopts the conformation with C–H···O intra-molecular interactions as shown in dotted lines. For clarity the non-participating hydrogen atoms are not labelled.

appeared as singlet peak in the range of $\delta = 2.394–2.549$. In carbon NMR carbonyl carbon peak for title compounds **2a-n** was observed in the range of $\delta = 182.82–187.87$.

3.2. Single crystal structural analysis

Fig. 1 shows the thermal ellipsoid plot of **2k** with atom labelling which adopts the conformation with intra-molecular C–H···O (C1–H1···O3; 2.28 Å, 115°; C4–H4···O1 2.43 Å, 116° and C14–H14C···O2; 2.49 Å, 120°) hydrogen bonds. Crystal structure of **2k** prefers head to head pair manner arrangement through three different type of C–H···O hydrogen bonds (C1–H1···O3; 2.37 Å, 165°; C17–H17···O31; 2.47 Å, 167°; C19–H19···O1; 2.56 Å, 170°) and further, the C–H ··· π (C13–H13 ··· Cg_1 (centroid of five-member ring of N1/C5/C6/C7/C8); 2.73 Å) Band π ··· π (Cg_1 ··· Cg_2 (centroid of six-member ring of N1/C1/C2/C3/C4/C5); 3.64 Å) lead to stabilize the three dimensional zig-zag arrangement as shown along a-axis of the unit cell (Fig. 2). It is noteworthy to mention that, this series of molecules **2a-n**, bear the same skeleton with carbonyl, ester as common functional group as a result these molecules may prefer similar conformation and supramolecular assembly of compound **2k** as evidenced from single crystal X-ray study, however it is also expected in variation of their conformation and supramolecular assembly due to alteration of substituent's with steric or electronic effect. Crystallization of the remaining molecules of these series molecules is still under progress to understand their structural insight.

3.3. Pharmacology

3.3.1. Larvicidal activity

There were significant effects of treatment ($p < 0.0001$) and exposure time ($p < 0.0001$) but not for their interaction ($p = 0.86$). Overall, mortality moderately but significantly increased from 24 h (66.5 ± 0.6%) to 48 h (69.4 ± 0.6%). Mortality of larvae exposed to any of the compounds tested was higher than the negative control acetone (Table 4), indicating toxicity against *A. arabiensis*. The most toxic compounds were **2j**, **2m**, and **2f**, with mortality ranging from 83.89 to 88.9%, however below the positive control temephos (98.3%). The compounds **2k**, **2n**, and **2h** showed the lowest larvicidal activity (lower than 60%).

Results suggest that the larvicidal activity of the test compounds depend both on their relative substituents on the indolizine pharmacophore and their position on the indolizine nucleus. Compounds **2f** and **2j** were significantly more lethal against the mosquito larvae compared to compound **2g**, which may be due to the relative position of the bromine and alkyl functional groups on the indolizine pharmacophore.

4. Conclusions

In summary, we have described herein the one-pot microwave assisted synthesis and larvicidal activity of novel ethyl 3-substituted-7-methylindolizine-1-carboxylates. Out of triethylamine, sodium hydroxide and potassium carbonate in acetonitrile solvent tried for microwave assisted synthesis, trimethylamine, and

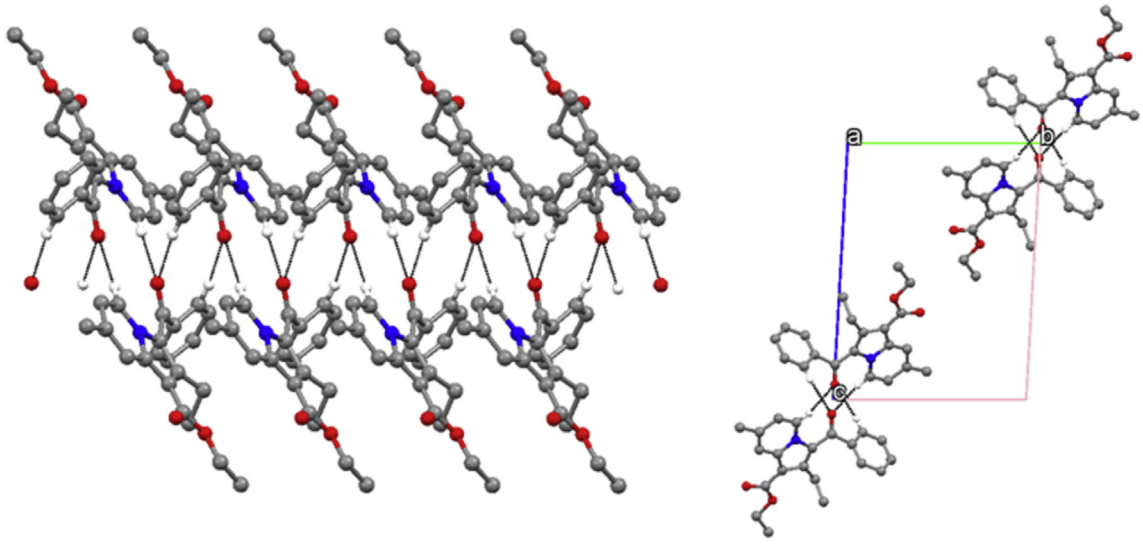


Fig. 2. The molecules form head to head pair-wise arrangement with C–H···O hydrogen bonds and further, the C–H ··· π and π···π interactions lead to stabilize stacking arrangement along a-axis of the unit cell.

acetonitrile emerged as good combination for the construction of ethyl 3-substituted-7-methylindolizine-1-carboxylate scaffolds in less reaction time with good yields. Structure activity relationship of ethyl 3-substituted-7-methylindolizine-1-carboxylates revealed that, different functional groups on para position of phenyl ring and second carbon on indolizine pharmacophore is very essential for potential larvicidal activity.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.molstruc.2017.11.131.

Competing interests

The authors declare that they have no competing interests.

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