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RESEARCH ARTICLE

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Greener synthesis of indolizine analogues using water as a base and solvent: study for larvicidal activity against *Anopheles arabiensis*

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Greener synthesis of a series of novel indolizine analogues have been achieved by the cyclization of aromatic cycloimmonium ylides with electron-deficient alkynes in the presence of water as the base and solvent at 80 °C. Yield of the title compounds was good and reactions performed were eco-friendly. The structures of these newly synthesized compounds have been confirmed by spectroscopic techniques such as FTIR, NMR, LC-MS, and elemental analysis. Characterized title compounds were evaluated for larvicidal activity against *Anopheles arabiensis* by standard WHO larvicidal assay using Temefos as standard at 4 μg/mL. Title compounds **2e**, **2f**, and **2g** emerged as promising larvicidal agents.

KEYWORDS
characterization, indolizine analogues, larvicidal activity, synthesis

Indolizines are bicyclic heterocyclic compounds containing condensed five- and six-membered rings with bridging nitrogen. They are isoelectronic with indole and represent a group of heterocyclic compounds structurally related to purines. Indolizine skeletons with different degrees of unsaturation are present in a wide variety of natural and unnatural azacyclic compounds. Most of the naturally occurring indolizines have been isolated from species of genus *Dendrobates* (Anura: Dendrobatidae) poison-arrow frogs,[1,2] *Monomorium* (Hymenoptera: Formicidae) ants,[3] *Dendrobium* (Asparagales: Orchidaceae) orchids,[4] *Tylophora* (Gentianales: Apocynaceae) vines,[5] and plants of Leguminosae (Fabaceae) family.[6] Indolizine alkaloids display broad spectrum of biological activities.[4–7] Polyhydroxylated indolizine alkaloids are excellent inhibitors of biologically important pathways. These include the binding and processing of glycoproteins,[8] potent glycosidase inhibitor activities,[6,9,10] activity against HIV[11,12] as well as against other

important pathogens.[13] The 1-azabicyclo[4,3,0]nonane (indolizine) framework occupies a special place in heterocyclic systems due to the presence of this structural assembly in a number of natural products of biological importance such as tabersonine,[14,15] (−)-strychnine,[16] (+)-vinblastine,[17] (−)-monomorine,[18] and (−)-gephyrotoxin.[19] On the other hand, synthetic indolizine derivatives have been reported as calcium channel blockers,[20] phospholipase A_2 inhibitors,[21] histamine H_3-receptors antagonist,[22] 5-HT^3-receptors antagonists,[23] anti-inflammatory,[24,25] antitumor agents,[26–28] and oral hypoglycemic[29] and CNS activity.[30–32] In continuation of our studies on synthesis of promising heterocyclic compounds for anti-TB,[33] anticancer,[34,35] and antimosquito properties[36,37] and screening them for polymorphism behavior,[38–40] herewith, we undertake design and synthesis of novel indolizine scaffolds (Scheme 1) to be screened for larvicidal activity against *Anopheles arabiensis* by standard WHO larvicidal assay using standard substance.[41]

1 | MATERIALS AND METHODS

1.1 | Chemistry

All the reactions were carried out in hot-air-dried glass wares under nitrogen atmosphere using dry solvents. 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 follows; s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. LC-MS analysis was performed on Agilent LC-1200 series coupled with 6140 single quad mass spectrometer with ESI-positive and ESI-negative mode, MS range 100–2000. Elemental analyses were recorded using PerkinElmer (Sheffield, UK) CHNS analyzer. All the commercially available chemicals were purchased from Sigma-Aldrich Chemicals Company (Saint Louis, MO, USA).

1.1.1 | General procedure for the preparation of 1-(2-(substituted phenyl)-2-oxoethyl)pyridin-1-ium bromide (1a–f)

To a stirred solution of pyridine (0.012 mol) in dry acetone (10 mL) was added substituted phenacyl bromide (0.012 mol). Stirring was continued for 5 h at room temperature. Solid product separated was filtered and dried under vacuum to afford intermediates 1-(2-(substituted phenyl)-2-oxoethyl)pyridin-1-ium bromide (**1a–f**) at 96%–99% yield.

1.1.2 | General procedure for the preparation of ethyl 3-(substituted benzoyl)-2-methylindolizine-1-carboxylate (2a–j)

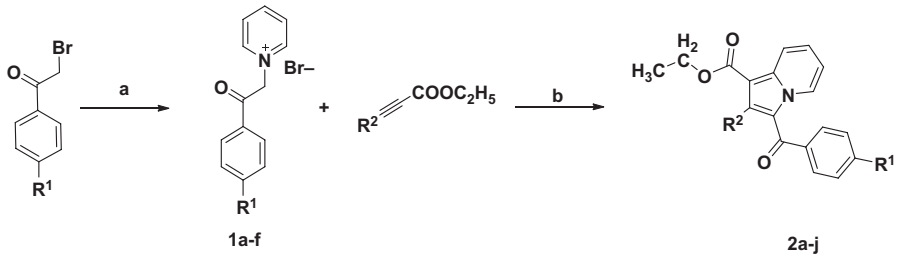
To a stirred solution of 1-(2-(substituted phenyl)-2-oxoethyl) pyridinium bromide (0.0016 mol), in water (10 mL) was added ethyl propiolate/ethyl 2-butynoate (0.0016 mol) and stirred at 80 °C for 3 h. Completion of reaction was monitored on TLC. The reaction mixture was diluted with ethyl acetate. Organic layer was separated, washed with brine, and dried under sodium sulfate. The crude compound was purified by recrystallization method using hexane and ethyl acetate to afford 69%–83% yield of ethyl 3-(substituted benzoyl)-2-methylindolizine-1-carboxylates. The physicochemical constants of the title compounds **2a–j** are tabulated in Table 1.

1.1.3 | Ethyl 3-(4-nitrobenzoyl)indolizine-1-carboxylate (2a)

FTIR (KBr) (cm^{-1}): 1679, 1620, 1595; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.99–9.97 (m, 1H), 8.45–8.36 (m, 3H), 7.97–7.93 (m, 2H), 7.74 (s, 1H), 7.56–7.51 (m, 1H), 7.19–7.15 (m, 1H), 4.42–4.35 (q, J = 7.2 Hz, 2H), 1.42–1.37 (t, J = 7.2, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) = δ 182.86, 163.66, 149.37, 145.34, 140.38, 129.70, 129.31, 129.16, 128.56, 123.66, 121.85, 119.70, 115.94, 107.24, 60.30, 14.49; LC-MS (ESI, Positive): *m/z*: $(M + H)^+$: 339.2; Anal. calculated for: $C_{18}H_{14}N_2O_5$; C, 63.90; H, 4.17; N, 8.28; Found: C, 63.87; H, 4.10; N, 8.22.

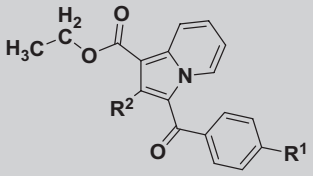
1.1.4 | Ethyl 2-methyl-3-(4-nitrobenzoyl) indolizine-1-carboxylate (2b)

FTIR (KBr) (cm^{-1}): 1681, 1618, 1595; ^{1}H NMR(400 MHz, $CDCl_3$) δ = 9.78–9.76 (m, 1H), 8.40–8.32 (m, 3H), 7.83–7.79 (m, 2H), 7.47–7.41 (m, 1H), 7.07–7.06 (m, 1H), 4.43–4.36 (q, J = 7.2 Hz, 2H), 2.18 (s, 3H), 1.44–1.40 (t, J = 8 Hz, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ = 184.67, 163.74, 148.96, 146.17, 138.89, 137.45, 129.68, 128.55, 128.12, 123.87, 121.81, 118.66, 115.34, 104.88, 59.55, 14.38, 14.24;



SCHEME 1 Synthesis of indolizine analogues **2a–j:** Reagents and conditions (a) pyridine, dry acetone, stir at room temperature, 5 h; (b) water, stir, 80 °C, 3 h

TABLE 1 Physicochemical constants of ethyl 3-(substituted benzoyl)-2-substituted indolizine-1-carboxylate analogues **2a–j**



Compound	Mol formulae (Mol mass)	R^1	R^2	Yield (%)[a,b]	m.p (°C)	*c*LogP[c]
2a	$C_{18}H_{14}N_2O_5$ (338)	NO_2	H	83	158–159	4.1470
2b	$C_{19}H_{16}N_2O_5$ (352)	NO_2	CH_3	76	134–135	4.6460
2c	$C_{18}H_{14}ClNO_3$ (327)	Cl	H	73	122–123	5.0722
2d	$C_{19}H_{16}ClNO_3$ (341)	Cl	CH_3	69	127–128	5.5712
2e	$C_{18}H_{14}BrNO_3$ (371)	Br	H	79	126–127	5.2222
2f	$C_{19}H_{16}BrNO_3$ (385)	Br	CH_3	75	130–131	5.7212
2g	$C_{18}H_{14}FNO_3$ (311)	F	H	80	121–122	4.5022
2h	$C_{19}H_{16}FNO_3$ (325)	F	CH_3	77	124–125	5.0012
2i	$C_{19}H_{17}NO_3$ (307)	CH_3	H	77	145–146	4.8504
2j	$C_{19}H_{14}N_2O_3$ (318)	CN	H	79	151–152	3.8505

[a]All of the products were characterized by spectral and physical data.

[b]Yields after purification by recrystallization method.

[c]*c*Log*P* was calculated using ChemBioDraw Ultra 13.0v.

LC-MS (ESI, Positive): *m/z*: $(M + H)^+$: 353.2; Anal. calculated for: $C_{19}H_{16}N_2O_5$; C, 64.77; H, 4.58; N, 7.95; Found: C, 64.70; H, 4.48; N, 7.88.

1.1.5 | Ethyl 3-(4-chlorobenzoyl)indolizine-1-carboxylate (2c)

FTIR (KBr) (cm^{-1}): 1699, 1614, 1523; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.93–9.91 (m, 1H), 8.42–8.39 (m, 1H), 7.78–7.75 (m, 3H), 7.51–7.45 (m, 3H), 7.12–7.08 (m, 1H), 4.41–4.35 (q, *J* = 7.2 Hz, 2H), 1.42–1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (300 MHz, DMSO-d_6) δ = 183.16, 162.89, 139.06, 137.95, 136.43, 130.47, 128.81, 128.73, 128.59, 127.72, 121.71, 118.77, 116.09, 105.39, 59.73, 14.27; LC-MS (ESI, Positive): *m/z*: $(M + H)^+$: 328.2; Anal. calculated for: $C_{18}H_{14}ClNO_3$; C, 65.96; H, 4.31; N, 4.27; Found: C, 65.91; H, 4.30; N, 4.31.

1.1.6 | Ethyl 3-(4-chlorobenzoyl)-2-methylindolizine-1-carboxylate (2d)

FTIR (KBr) (cm^{-1}): 1687, 1620, 1510; ^{1}H NMR (400 MHz, $CDCl_3$) δ = δ 9.53–9.50 (m, 1H), 8.36–8.33 (m, 1H), 7.65–7.63 (d, J=8.0 Hz, 2H), 7.47–7.45 (d, *J* = 8.0 Hz, 2H), 7.38–7.34 (m, 1H), 6.98–6.94 (m, 1H), 4.42–4.36 (q, *J* = 7.2 Hz, 2H), 2.23 (s, 3H), 1.44–1.40 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ = 186.3, 164.8, 139.6, 139.4, 138.21, 137.75, 130.33, 128.88, 127.96, 127.20, 122.51, 119.3, 114.4, 105.4, 59.84, 15.07, 14.52; LC-MS (ESI, Positive): *m/z*: $(M + H)^+$: 342.2; Anal. calculated for: $C_{19}H_{16}ClNO_3$; C, 66.77; H, 4.72; N, 4.10; Found: C, 66.83; H, 4.71; N, 3.99.

1.1.7 | Ethyl 3-(4-bromobenzoyl)indolizine-1-carboxylate (2e)

FTIR (KBr) (cm^{-1}): 1699, 1612, 1521; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.97–9.87 (m, 1H), 8.41–8.39 (m, 1H), 7.77 (s, 1H), 7.71–7.64 (m, 4H), 7.49–7.46 (m, 1H), 7.12–7.08 (m, 1H), 4.40–4.35 (q, *J* = 7.2 Hz, 2H), 1.42–1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ = 183.27, 162.86, 139.05, 138.28, 131.50, 130.61, 128.82, 128.72, 127.72, 125.34, 121.66, 118.76, 116.09, 105.39, 59.71, 14.25; LC-MS (ESI, Positive): *m/z*: $(M + H)^+$: 372.2; Anal. calculated for: $C_{18}H_{14}BrNO_3$; C, 58.08; H, 3.79; N, 3.76; Found; C, 57.98; H, 3.83; N, 3.68.

1.1.8 | Ethyl 3-(4-bromobenzoyl)-2-methylindolizine-1-carboxylate (2f)

FTIR (KBr) (cm^{-1}): 1687, 1622, 1618; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.51–9.49 (m, 1H), 8.36–8.33 (m, 1H), 7.63–7.61 (d, *J* = 10.4 Hz, 2H), 7.57–7.55 (d, *J* = 9 Hz, 2H), 7.38–7.36 (m, 1H), 6.98–6.96 (m, 1H), 4.42–4.36 (q, *J* = 7.2 Hz, 2H), 2.23 (s, 3H), 1.44–1.40 (t, *J* = 7.2 Hz, 3H). LC-MS (ESI, Positive): *m/z*: $(M + H)^+$: 386.2; Anal. calculated for: $C_{19}H_{16}BrNO_3$; C, 59.08; H, 4.18; N, 3.63; Found; C, 59.13; H, 4.06; N, 3.65.

1.1.9 | Ethyl 3-(4-fluorobenzoyl)indolizine-1-carboxylate (2g)

FTIR (KBr) (cm^{-1}): 1699, 1618, 1522; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.97–9.55 (m, 1H), 8.38–8.37 (m, 1H), 7.87–7.82 (m, 2H), 7.78 (s, 1H), 7.47–7.43 (m, 1H), 7.25–7.21 (t, *J* = 8.4 Hz, 2H), 7.19–7.16 (m, 1H), 4.40–4.35 (q, *J* = 7.2 Hz, 2H), 1.42–1.38 (t, *J* = 7.2 Hz, 3H). LC-MS (ESI, Positive): *m/z*: $(M + H)^+$: 312.2: Anal. calculated for: $C_{18}H_{14}FNO_3$; C, 69.45; H, 4.53; N, 4.50; Found; C, 69.41; H, 4.50; N, 4.55.

1.1.10 | Ethyl 3-(4-fluorobenzoyl)-2-methylindolizine-1-carboxylate (2h)

FTIR (KBr) (cm^{-1}): 1681, 1600, 1510; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.43–9.42 (m, 1H), 8.35–8.33 (m, 1H), 7.74–7.70 (m, 2H), 7.36–7.33 (m, 1H), 7.18–7.15 (t, *J* = 8.4 Hz, 2H), 6.96–6.93 (m, 1H), 4.42–4.36 (q, *J* = 7.2 Hz, 2H), 2.23 (s, 3H), 1.44–1.40 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ = 186.28, 166.38, 164.94, 163.87, 139.53, 137.48, 137.25, 137.22, 131.48, 131.39, 127.90, 127.02, 122.61, 119.36, 115.83, 115.62, 114.35, 105.36, 59.82, 14.99, 14.54; LC-MS (ESI, Positive): *m/z*: $(M + H)^+$: 326.2: Anal. calculated for: $C_{19}H_{16}FNO_3$; C, 70.14; H, 4.96; N, 4.31; Found; C, 70.15; H, 4.91; N, 4.33.

1.1.11 | Ethyl 3-(4-methylbenzoyl)indolizine-1-carboxylate (2i)

FTIR (KBr) (cm^{-1}): 1685, 1604, 1521; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.96–9.94 (m, 1H), 8.40–8.38 (m, 1H), 7.83 (s, 1H), 7.75–7.73 (d, *J* = 8 Hz, 2H), 7.46–7.43 (m, 1H), 7.33–7.31 (d, *J* = 8 Hz, 2H), 7.09–7.07 (m, 1H), 4.40–4.35 (q, *J* = 7.2 Hz, 2H), 2.46 (s, 3H), 1.41–1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ = 185.48, 164.15, 142.10, 139.81, 137.18, 129.16, 129.08, 128.75, 127.50, 122.66, 119.49, 115.15, 106.11, 60.07, 21.58, 14.56; LC-MS (ESI, Positive): *m/z*: $(M + H)^+$: 308.2: Anal. calculated for: $C_{19}H_{17}NO_3$; 74.25; H, 5.58; N, 4.56; Found; 74.28; H, 5.57; N, 4.51.

1.1.12 | Ethyl 3-(4-cyanobenzoyl)indolizine-1-carboxylate (2j)

FTIR (KBr) (cm^{-1}): 2227, 1683, 1616; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.96–9.95 (m, 1H), 8.44–8.42 (m, 1H), 7.90–7.88 (d, *J* = 8.4 Hz, 2H), 7.83–7.81 (d, *J* = 8.4 Hz, 2H), 7.73 (s, 1H), 7.54–7.52 (m, 1H), 7.17–7.14 (m, 1H), 4.41–4.36 (q, *J* = 7.2 Hz, 2H), 1.42–1.38 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ = 183.13, 163.66, 143.61, 140.24, 132.22, 129.27, 129.22, 129.04, 128.41, 121.78, 119.62, 118.06, 115.81, 114.79, 107.06, 60.25, 14.45; LC-MS (ESI, Positive): *m/z*: $(M + H)^+$: 319.2; Anal. calculated for: $C_{19}H_{14}N_2O_3$; C, 71.69; H, 4.43; N, 8.80; Found; C, 71.58; H, 4.47; N, 8.76.

1.2 | Larvicidal activity

The *Anopheles arabiensis* used were from a colonized strain from Zimbabwe which had been reared according to the WHO (1975) guidelines[41] in an insectary simulating the temperature (27.5 °C), humidity (70%), and lighting (12/12) of a malaria-endemic environment. One milliliter of test compound (1 mg/mL) was added to distilled water (250 mL) producing a final concentration of 4 μg/mL. Thirty third-instar larvae were placed in the container. A negative control was set up using a solvent (acetone) and distilled water, and a positive control included Temefos (Mostop; Agrivo), an effective emulsifiable organophosphate larvicidal 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 2.

1.3 | Data analysis

General linear mixed models[a] were used to determine differences between treatments registered in larval mortality (larvicide assays). Dependent variables were *A. arabiensis* mortality, and fixed effects were test compound (test compounds **2a–j**, acetone, and Temefos) and observation period (24 and 48 h). Random effects were mosquito groups (i.e., container in larvicide tests). Bonferroni–Holm test was used for post hoc analyses. 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.

TABLE 2 Mortality of *Anopheles arabiensis* larvae exposed to test compounds **2a–j** indolizines at 4 μg/mL (1 mg/250 mL) and their negative (acetone) and positive (Temefos) controls

	Mortality	
Compound	**24 h**	**48 h**
2a[a]	18.9	20.0
2b[b]	61.1	64.4
2c[b]	55.6	58.9
2d[b]	58.9	61.0
2e[de]	92.2	93.0
2f[e]	77.8	81.1
2g[d]	94.4	95.6
2h[c]	40.0	42.2
2i[b]	60.0	62.2
2j[c]	41.1	43.3
Acetone[a]	7.8	10.0
Temefos[d]	97.8	98.9

Adjusted means are shown. Adjusted standard errors were 2.7.
[a–e]Compounds not sharing a letter differ significantly ($p < 0.05$).

2 | RESULTS AND DISCUSSION

2.1 | Chemistry

The synthesis of biologically active indolizines[42] continues to attract the attention of organic chemists.[43–46] The indolizines are most commonly synthesized by sequential *N*-quarterization and intramolecular cyclocondensation reactions[47] or the cycloaddition reaction[48,49] of *N*-acyl/alkyl pyridinium salts. Another stereoselective route is based on the iron-catalyzed cyclization of *N*-substituted pyrrolotrienes.[50] A similar strategy was reported for the synthesis of indolizines via intramolecular 1,5-dipolar cyclization of 2-vinyl pyridiniumylide in the presence of tetrakis[pyrido] cobalt(II)-dichromate.[51] A new pathway to chiral indolizines was accomplished from proline via the Pauson–Khand reaction[52] involving an intramolecular cyclization reaction.

In the present research, synthesis of intermediates *N*-heterocyclic ylides (**1a–f**) were prepared by stirring pyridines with substituted phenacyl bromides separately in the presence of acetone at room temperature. The products obtained were filtered, dried under vacuum, and recrystallized using ethanol solvent. The yields of ylides (**1a–f**) obtained were 96%–99%. Anticipated indolizines have been prepared by the 1,3-dipolar cycloaddition reaction of *N*-heterocyclic ylides with electron-deficient alkynes in the presence of water as a base and solvent at 80 °C in good yields. The completion of reaction was monitored on TLC. The reaction mixture was diluted with ethyl acetate, the organic layer was separated and washed with brine and dried with anhydrous sodium sulfate, and recrystallized with mixture of hexane-ethyl acetate as a solvent to obtain title compounds at 69%–83% yield.

Synthesis of title compound **2a** was attempted using different solvents (DMF, MeCN, DMF, THF, water) and bases such as K_2CO_3, TEA, $NaHCO_3$, and water at different temperatures as tabulated in Table 3. However, the synthesis of compound **2a** was achieved with water as base and solvent with remarkable increase in yield as well as reduced reaction time compared to other solvents such as DMF, MeCN, and THF (Table 4).

All the compounds have been purified by recrystallization method using appropriate solvents. The structures of all the synthesized compounds have been confirmed by various spectroscopic techniques such as LC-MS, ^{1}H NMR, ^{13}C NMR, FTIR and elemental analysis. In the ^{1}H NMR of title compounds **2b**, **2d**, **2f,** and **2h,** methyl protons as R^2 on indolizine nucleus are observed as singlet in the range of δ 2.18–2.23. In ^{13}C NMR carbonyl carbon is observed in the range of δ 182.86–186.3 for compounds **2a–e** and **2h–j**. Molecular mass of the compounds was in compliance with the molecular ion peak.

TABLE 3 Reaction condition for product **2a** with different bases and solvents at various temperatures

Entry	Base	Solvent	Temp (°C)	Yield (%)
1	K_2CO_3	DMF	RT	68
2	K_2CO_3	MeCN	70	43
3	TEA	DMF	RT	62
4	TEA	THF	60	45
5	$NaHCO_3$	DMF	RT	56
6	Water	Water	80	83

RT, room temperature

2.2 | Pharmacology

Even though indolizines have potent inhibitor activities of biologically important pathways, as was illustrated in the introduction section, their potential as insecticide sources against mosquitoes, to the best of our knowledge, has not been published. Table 2 summarizes results of larvicidal activity assessments. There were significant effects of treatment ($p < 0.0001$) and exposure time ($p < 0.0001$) but not their interaction ($p = 0.88$) on larval mortality. Overall mortality was slightly but significantly higher at 48 h (60.9 ± 0.8) compared to 24 h (58.8 ± 0.8). All compounds tested except indolizine **2a** resulted in mortalities higher than the negative control. Compounds **2e** and **2g** were as effective (93% and 95% mortality, respectively) as the positive control Temefos (98% mortality), followed by compound **2f** (81%). The remaining compounds exerted moderate mortalities, ranging from 42% to 64%. Compound **2e** having electron-withdrawing bromine at fourth position of phenyl ring exhibited 93% larvicidal activity whereas compound **2g** having electron-withdrawing fluorine atom at fourth position of phenyl ring exhibited larvicidal activity at 95%. However, analogous **2a**, **2i,** and **2j** with nitro, methyl, nitrile group, respectively, did not show much promising activity when compared to positive control Temefos. Compound **2f** with electron-withdrawing bromine at para position of phenyl ring and methyl as R^2 on indolizine nucleus exhibited activity at 81%.

These results indicate that indolizine **2e** and **2g** emerged as promising larvicidal agents that merit further research and development for mosquito control.

3 | CONCLUSIONS

The research work is focused on the efficient synthesis of indolizine analogous (**2a–j**) with greener chemistry, which

TABLE 4 Reaction condition for product **2a** with different solvents at various temperatures

Entry	Solvent/base ratio	Temperature (°C)	Yield (%)
1	Water:MeCN (1:1)	70	74
2	Water:THF (1:1)	70	78
3	Water:DMF (1:1)	80	77
4	Water:DMF (2:1)	80	79
5	Water	80	83

provides new method for the synthesis of indolizines. The reactions performed were eco-friendly, and yield of the products were very good at less reaction time with least formation of by-product. All the indolizine analogous were toxic for *A. arabiensis* larvae, and out of the title compounds tested for larvicidal activity, compounds **2e**, **2f,** and **2g** emerged as potent agents comparable to standard compound Temefos.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

NOTE

[a] Di Rienzo JA, Casanoves F, Balzarini MG, Gonzalez L, Tablada M, Robledo CW (2014) InfoStat versión 2014. Grupo InfoStat, FCA, Universidad Nacional de Córdoba, Argentina; Available online at http://www.infostat.com.ar/(visited March 12, 2016) .

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