Received Date : 26-Mar-2016

Revised Date : 19-May-2016

Accepted Date : 06-Jul-2016

Article type : Research Article

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

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/cbdd.12823

ABSTRACT

Greener synthesis of a series of novel indolizine analogues have been achieved by the cyclization of aromatic cycloimmoniumylides with electron deficient alkynes in 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 Temephos as standard at 4 μ g/mL. Title compounds **2e**, **2f** and **2g** emerged as promising larvicidal agents.

Keywords:

Indolizine analogues, synthesis, characterization, larvicidal activity.

Introduction

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 tubersonine (14), (-)-strychnine (15), (+)vinblastine (16), (-)-monomorine (17), (-)-gephyrotoxin (18), etc. On the other hand,

synthetic indolizine derivatives have been reported as calcium channel blockers (19), phospholipase A_2 inhibitors (20), histamine H_3 -receptors antagonist (21), 5-HT³-receptors antagonists (22), anti-inflammatory (23, 24), anti-tumour agents (25-27), oral hypoglycaemic (28) and CNS activity (29-31). In continuation of our studies on synthesis of promising heterocyclic compounds for anti-TB (32), anticancer (33, 34) and anti-mosquito properties (35, 36) and screening them for polymorphism behavior (37-39) 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 (40).

Materials and Methods

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 CDCl₃, 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; 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. Elemental analyses were recorded using Perkin Elmer CHNS analyser. All the commercially available chemicals were purchased from Sigma-Aldrich Chemicals Company.

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 phenacylbromide (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.

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

To a stirred solution of 1-(2-(substituted phenyl)-2-oxoethyl)pyridiniumbromide (0.0016 mol), in water (10 mL), was added ethyl propiolate / ethyl 2-butynoate (0.0016 mol), stirred at 80 °C for 3h. 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 sulphate. 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 3.

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

FTIR (KBr) (cm⁻¹): 1679, 1620, 1595; ¹H NMR (400 MHz, CDCl₃) $\delta = 9.99-9.97$ (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 = 7.2Hz, 2H), 1.42-1.37 (t, J = 7.2, 3H); ¹³C NMR (300 MHz, CDCl₃) = 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: C₁₈H₁₄N₂O₅; C, 63.90; H, 4.17; N, 8.28; Found: C, 63.87; H, 4.10; N, 8.22.

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

FTIR (KBr) (cm⁻¹): 1681, 1618, 1595; ¹H NMR(400 MHz, CDCl₃) 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* = 7.2Hz, 2H), 2.18 (s, 3H), 1.44-1.40 (t, *J* = 8Hz, 3H); ¹³C 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; LC-MS (ESI, Positive): *m/z*: (M+H)⁺: 353.2; Anal. calculated for: C₁₉H₁₆N₂O₅; C, 64.77; H, 4.58; N, 7.95; Found: C, 64.70; H, 4.48; N, 7.88.

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

FTIR (KBr) (cm⁻¹): 1699, 1614, 1523; ¹H NMR (400 MHz, CDCl₃) 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 = 7.2Hz, 2H), 1.42-1.38 (t, J = 7.2Hz, 3H); ¹³C 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: C₁₈H₁₄ClNO₃; C, 65.96; H, 4.31; N, 4.27; Found: C, 65.91; H, 4.30; N, 4.31.

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

FTIR (KBr) (cm⁻¹): 1687, 1620, 1510; ¹H NMR (400 MHz, CDCl₃) $\delta = \delta$ 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* = 7.2Hz, 2H), 2.23 (s, 3H), 1.44-1.40 (t, *J* = 7.2Hz, 3H); ¹³C NMR (400 MHz, CDCl₃) $\delta = 186.3$, 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: C₁₉H₁₆ClNO₃; C, 66.77; H, 4.72; N, 4.10; Found: C, 66.83; H, 4.71; N, 3.99.

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

FTIR (KBr) (cm⁻¹): 1699, 1612, 1521; ¹H NMR (400 MHz, CDCl₃) 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* = 7.2Hz, 2H), 1.42-1.38 (t, *J* = 7.2Hz, 3H); ¹³C 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: C₁₈H₁₄BrNO₃; C, 58.08; H, 3.79; N, 3.76; Found; C, 57.98; H, 3.83; N, 3.68.

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

FTIR (KBr) (cm⁻¹): 1687, 1622, 1618; ¹H NMR (400 MHz, CDCl₃) δ = 9.51-9.49 (m, 1H), 8.36-8.33 (m, 1H), 7.63-7.61 (d, *J* = 10.4Hz, 2H), 7.57-7.55 (d, *J* = 9Hz, 2H), 7.38-7.36 (m, 1H), 6.98-6.96 (m, 1H), 4.42-4.36 (q, *J* = 7.2Hz, 2H) , 2.23 (s, 3H), 1.44-1.40 (t, *J* = 7.2Hz, 3H). LC-MS (ESI, Positive): *m/z*: (M+H)⁺: 386.2; Anal. calculated for: C₁₉H₁₆BrNO₃; C, 59.08; H, 4.18; N, 3.63; Found; C, 59.13; H, 4.06; N, 3.65.

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

FTIR (KBr) (cm⁻¹): 1699, 1618, 1522; ¹H NMR (400 MHz, CDCl₃) 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* = 7.2Hz, 2H), 1.42-1.38 (t, *J* = 7.2Hz, 3H). LC-MS (ESI, Positive): *m/z*: (M+H)⁺: 312.2: Anal. calculated for: C₁₈H₁₄FNO₃; C, 69.45; H, 4.53; N, 4.50; Found; C, 69.41; H, 4.50; N, 4.55.

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

FTIR (KBr) (cm⁻¹): 1681, 1600, 1510; ¹H NMR (400 MHz, CDCl₃) $\delta = 9.43-9.42$ (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 = 8.4Hz, 2H), 6.96-6.93 (m, 1H), 4.42-4.36 (q, J = 7.2Hz, 2H), 2.23 (s, 3H), 1.44-1.40 (t, J = 7.2Hz, 3H); ¹³C NMR (400 MHz, CDCl₃) $\delta = 186.28$, 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: C₁₉H₁₆FNO₃; C, 70.14; H, 4.96; N, 4.31; Found; C, 70.15; H, 4.91; N, 4.33.

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

FTIR (KBr) (cm⁻¹): 1685, 1604, 1521; ¹H NMR (400 MHz, CDCl₃) 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* = 8Hz, 2H), 7.09-7.07 (m, 1H), 4.40-4.35 (q, *J* = 7.2Hz, 2H), 2.46 (s, 3H), 1.41-1.38 (t, *J* = 7.2Hz, 3H); ¹³C NMR (400 MHz, CDCl₃) 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: C₁₉H₁₇NO₃; 74.25; H, 5.58; N, 4.56; Found; 74.28; H, 5.57; N, 4.51.

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

FTIR (KBr) (cm⁻¹): 2227, 1683, 1616; ¹H NMR (400 MHz, CDCl₃) 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* = 8.4Hz, 2H), 7.73 (s, 1H), 7.54-7.52 (m, 1H), 7.17-7.14 (m, 1H), 4.41-4.36 (q, *J* = 7.2Hz, 2H), 1.42-1.38 (t, *J* = 7.2Hz, 3H); ¹³C NMR (300 MHz, CDCl₃) 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: C₁₉H₁₄N₂O₃; C, 71.69; H, 4.43; N, 8.80; Found; C, 71.58; H, 4.47; N, 8.76.

Larvicidal Activity

The Anopheles arabiensis used were from a colonized strain from Zimbabwe which had been reared according to the WHO (1975) guidelines (40) 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 μ g/mL. Thirty 3rd 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 Temephos (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 4.

Data analysis

General linear mixed models (41) 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-j**, acetone, and Temephos) and observation period (24 and 48 h). Random effects were mosquito groups (i.e., container in larvicide tests). Bonferroni-Hom 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.

Results and Discussion

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*-quarterisation and intramolecular cyclocondensation reactions (47) or the cycloaddition reaction (48, 49) of *N*-acyl/alkyl pyridinium salts. Another stereo selective 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*-heterocyclicylides (**1a-f**) were prepared by stirring substituted 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 sulphate 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 K₂CO₃, TEA, NaHCO₃ and water at different temperatures as tabulated in Table 1. 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 compare to other solvents such as DMF, MeCN, and THF (Table 2).

Entry	Base	Solvent	Temp (°C)	Yield (%)
1	K ₂ CO 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

 Table 1: Reaction condition for product 2a with different bases and solvents at various temperatures

RT = room temperature

Table 2: 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



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, 3h.

Table 3: Physicochemical constants of ethyl 3-(substituted benzoyl)-2-substituted indolizine

 1-carboxylate analogues 2a-j

		Ó		∕−R ¹		
Compound	Mol formulae	R^1	R ²	Yield	m.p (°C)	<i>c</i> LogP ^c
Compound	(Mol mass)			$(\%)^{\mathrm{a},\mathrm{b}}$		
2a	C ₁₈ H ₁₄ N ₂ O ₅ (338)	NO ₂	Н	83	158-159	4.1470
2b	$C_{19}H_{16}N_{2}O_{5}\left(352\right)$	NO_2	CH ₃	76	134-135	4.6460
2c	C ₁₈ H ₁₄ ClNO ₃ (327)	Cl	Н	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	Н	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	Н	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	Н	77	145-146	4.8504
2ј	$C_{19}H_{14}N_2O_3$ (318)	CN	Н	79	151-152	3.8505

 $H_{2} O$ $H_{3}C^{-C} O$ N R^{2} O

^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.

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, ¹H-NMR, ¹³C-NMR, FTIR and elemental analysis. In the ¹H-NMR of title compounds **2b**, **2d**, **2f** and **2h** methyl protons as R² on indolazine nucleus are observed as singlet in the range of $\delta 2.18-2.23$. In ¹³C-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.

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 4 summarises 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 Temephos (98 % mortality), followed by compound 2f (81 %). The remaining compounds exerted moderate mortalities, ranging from 42 to 64 %. Compound 2e having election withdrawing bromine at fourth positon of phenyl ring exhibited 93% larvicidal activity whereas compound 2g having election withdrawing fluorine atom at fourth positon 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 Temephos. Compound 2f with election withdrawing bromine at para positon of phenyl ring and methyl as R^2 on indolazine 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.

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	Ν	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
Temephos ^D	97.8	98.9

Table 4: Mortality of *Anopheles arabiensis* larvae exposed to test compounds **2a-j** indolizines at $4 \mu g/mL$ (1 mg/250 mL) and their negative (acetone) and positive (Temephos) controls. Adjusted means are shown. Adjusted standard errors were 2.7.

^{A-E} Compounds not sharing a letter differ significantly (p < 0.05).

Conclusions

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

Acknowledgement

Authors are thankful to Sahyadri Science College, Shimoga, National Research Foundation (96807), South Africa and Durban University of Technology for support and facilities. Medical Research council for facilities to screen the compounds for larvicidal activity.

Supplementary data

Supplementary data related to this article can be found as attachment.

Competing interests

The authors declare that they have no competing interests.

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