Synthesis of novel spiro[cyclopropane-indolizine] derivatives via magnesium-mediated conjugate addition of bromoform

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The reaction of 6,7-dihydroindolizin-8(5*H*)-one and an aromatic aldehyde yielded (*E*)-7-(arylmethylene)-6,7-dihydroindolizin-8(5*H*)-ones which underwent addition of bromoform in the presence of magnesium under N_2 to give a novel series of 3-aryl-2,2-dibromo-5'*H*-spiro[cyclopropane-1,7'-indolizin]-8'(6'*H*)-one derivatives. The structures of the products were established by ^{1}H NMR, ^{13}C NMR, IR spectroscopy and mass spectra.

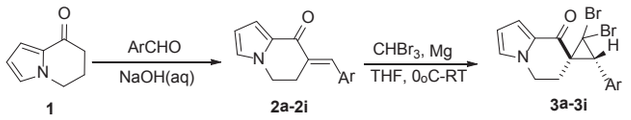
Keywords: cyclopropane, indolizine, spiroheterocyclic, magnesium-mediated conjugate addition, bromoform

The indolizine building block[1–3] is found in biologically active alkaloids such as (+)-monomorine[4], indolizidine 209D[5], polygonatines[6] and kinganone.[7] Related natural products such as rhazinilam possesses intriguing anti-mitotic properties[8] whilst the vincamine alkaloid also has interesting cardiovascular properties[9].

There are some interesting natural products which contain the cyclopropane ring.[10–12] Heterocyclic compounds containing a cyclopropane ring and an indolizine unit could be a useful framework with potential biological activity. We now report the synthesis of a new series of 3-aryl-2,2-dibromo-5′*H*-spiro[cyclopropane-1,7′-indolizin]-8′(6′*H*)-one **3a–j** *via* the addition of bromoform in the presence of Mg (Scheme 1) to (*E*)-7-(arylmethylene)-6,7-dihydroindolizin-8(5*H*)-one **2a–j**.

Results and discussion

The reaction of 6,7-dihydroindolizin-8(5*H*)-one **1** and an aromatic aldehyde to yield (*E*)-7-(arylmethylene)-6,7-dihydroindolizin-8(5*H*)-ones **2** in moderate yields was based on literature methods.[14] The conjugate addition reaction of bromoform (20 equiv.) to (*E*)-7-(arylmethylene)-6,7-dihydroindolizin-8(5*H*)-ones **2** (1 equiv.) obtained 3-aryl-2,2-dibromo-5′*H*-spiro[cyclopropane-1,7′-indolizin]-8′(6′*H*)-one **3** in the presence of Mg (10 equiv.) in dry THF at room temperature under N_2 in moderate yields (Table 1). The progress of this reaction was monitored by TLC and the target products were purified by flash column chromatography on silica gel. As shown in Table 1, the effect of different substituent groups containing electron-donating and electron-withdrawing groups on the phenyl ring of the (*E*)-7-(arylmethylene)-6,7-dihydroindolizin-8(5*H*)-ones were investigated in this reaction (entries 2–9). In general, the conjugate addition and cyclopropanation was completed in less than 3 h, and the products were isolated in moderate to good yield (56–92%). Substrates with an electron-withdrawing group located on the phenyl ring reacted with bromoform to afford the desired products in moderate yield (entries 2, 3). The target products



1 **2a-2i** **3a-3i**

Ar: **a**, C_6H_5; **b**, 4-ClC_6H_4; **c**, 4-FC_6H_4; **d**, 4-$CH_3SC_6H_4$; **e**, 4-$CH_3C_6H_4$; **f**, 4-$CH_3OC_6H_4$; **g**, 3,4-$(OCH_3)_2C_6H_3$; **h**, 3,5-$(OCH_3)C_6H_3$; **i**, 3,4,5-$(OCH_3)_3C_6H_2$;

Scheme 1

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Table 1 Synthesis of spiro[cyclopropane-indolizin] derivatives

Entry	Ar	Product	Time/h	Yield/%
1	C_6H_5	**3a**	2.0	82
2	4Cl-C_6H_4	**3b**	3.0	56
3	4-FC_6H_4	**3c**	3.0	58
4	4-$CH_3SC_6H_4$	**3d**	1.5	68
5	4-$CH_3C_6H_4$	**3e**	1.5	72
6	4–$CH_3OC_6H_4$	**3f**	1.5	78
7	3,4-$(OCH_3)_2C_6H_3$	**3g**	1.0	84
8	3,5-$(OCH_3)_2C_6H_3$	**3h**	1.0	86
9	3,4,5-$(OCH_3)_3C_6H_2$	**3i**	1.0	92

were isolated in good yield when the substituents on the phenyl ring were single and multiple electron-donating groups (entries 4–9).

The structures of all compounds **3a–i** were established by different spectroscopic techniques (NMR, infrared spectrum and mass spectrum). The IR spectrum of **3f** revealed the presence of a carbonyl stretching vibration bands at 1663 cm^{-1}. The ^{1}H NMR spectrum of **3f** revealed one doublet of triplets at δ 2.06 (dt, J_1 = 17.0 Hz, J_2 = 2.5 Hz) and one doublet of doublet of doublets at 2.75 (ddd, J_1 = 14.5 Hz, J_2 = 13.5 Hz, J_3 = 4.5 Hz) corresponding to the protons of methylene (H_2C-3′). Another doublet of doublet of doublets at 4.21 (ddd, J_1 = 7.0 Hz, J_2 = 4.5 Hz, J_3 = 2.0 Hz) and one triplet of doublets at 4.45 (td, J_1 = 12.5 Hz, J_2 = 2.5 Hz) correspond to the protons of methylene (H_2C-4′). A singlet at δ 3.94 was assigned to the proton of CH (HC-3) in cyclopropane ring. The other singlet at δ 3.81 was assigned to the proton of the –OCH_3 on the phenyl ring. There was a doublet of doublet at δ 6.33 (dd, J_1 = 4.0 Hz, J_2 = 2.5 Hz) which was assigned to the protons of HC-7′ on the indolizinone ring. The doublet at δ 7.16 (d, J = 4.5 Hz) and the triplet at 6.93 (t, J = 2.0 Hz) were assigned to the protons of HC-6′ and HC-8′ on the indolizinone ring.

The ^{13}C NMR spectrum of the product **3f** exhibited the presence of carbonyl carbon at δ 179.7 (C-1′). The signal at δ 30.2 and 43.3 were assigned to the carbons of CH_2 (H_2C-3′) and CH_2 (H_2C-4′) respectively on the indolizinone ring (based on the HSQC spectrum). The signal at δ 37.7 was assigned to the carbons of CH (HC-3), of the cyclopropane ring (based on the HSQC spectrum). The signals at δ 111.3, 115.9 and 126.8 represent the carbons of HC-7′, HC-6′ and HC-8′ respectively. The signal at δ 40.6 was in accord with the spiro carbon of C-1.

In the ^{1}H–^{13}C HMBC map of **3f** (Fig. 1), protons of H_2C-3′ and H_2C-4′ on the indolizinone ring and HC-3 in cyclopropane ring were correlated with the spiro carbon C-1 (40.6 ppm), whilst the protons of HC-6′ correlated with the carbon of C-4′ (43.3 ppm). The proton of H_2C-3′ correlated with the carbon of C-3 (30.2 ppm). The correlation between H_2C-3′ and HC-3

with C-1′ revealed the carbon atom of carbonyl carbon (C-1′) at 179.7 ppm. The stereochemistry of the products was determined by a NOESY spectrum. There was no correlation between protons of HC-3 and protons of H_2C-3′ in the NOESY spectrum of **3f**, which showed that the proton of HC-3 and the proton of H_2C-3′ were on the different sides of the cyclopropane ring.

A possible mechanism of the reaction from **2** to **3** is that of a dibromocarbene addition.

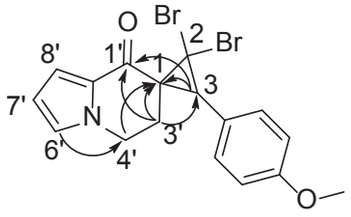

Fig. 1 Partial HMBC diagram of **3f**.

Experimental

Compound **1** was prepared according to the reported procedures.[13] All NMR spectra were recorded on a Bruker AV-II 500 MHz NMR spectrometer, operating at 500 MHz for ^{1}H, and 125 MHz for ^{13}C. TMS was used as an internal reference for ^{1}H and ^{13}C chemical shifts and $CDCl_3$ was used as solvent. The MS were obtained with a Finnigan LCQ Advantage MAX mass spectrometer. IR spectra were recorded on a PE-2000 spectrometer in KBr pellets and are reported in cm^{-1}. Melting points were measured with a Yanaco MP500 melting point apparatus and are uncorrected. Mg turnings were activated by washing with 1% dilute HCl, water, and acetone followed by drying in an oven overnight. The solvents were all distilled prior to use. THF was distilled from Sodium. Other commercially available materials were purchased from Aladdin-Reagent, and were used without further purification.

Synthesis of (E)-7-(arylmethylene)-6,7-dihydroindolizin-8(5H)-ones; general procedure

A mixture of 6,7-dihydroindolizin-8(5*H*)-one 1 (10 mmol) in ethanol (10 mL) and sodium hydroxide (20 mmol) in water (10 mL) was treated with the aromatic aldehyde (10 mmol) with stirring. The reaction mixture was heated to at 45 °C for 2 h (the reaction was followed by TLC). After the reaction, the mixture was cooled to room temperature and the crude product was isolated by filtration through a Buchner funnel. The residue so obtained was washed with water and purified by crystallisation using ethanol to give pure product 2.

*(*E*)-7-Benzylidene-6,7-dihydroindolizin-8(5*H*)-one* **(2a):** Pale yellow solid, yield 55%; m.p. 114–115 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.21–3.23 (m, 2H), 4.08 (t, *J*=6.5 Hz, 2H), 6.29 (dd, J_1=3.5 Hz, J_2=2.5 Hz, 1H), 6.85 (d, *J*=1.5 Hz, 1H), 7.13 (dd, J_1=4.0 Hz, J_2=1.0 Hz, 1H), 7.32–7.35 (m, 1H), 7.37–7.42 (m, 4H), 7.85 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.3, 44.3, 111.1, 115.5, 125.8, 128.5, 128.6, 129.7, 131.4, 132.3, 135.6, 136.5, 177.7; IR (KBr) *v* 1656 cm^{-1}; HRMS (ESI) *m/z* 224.1066 [M+H]$^+$, calcd for $C_{15}H_{14}NO$ 224.1070.

*(*E*)-7-(4-Chlorobenzylidene)-6,7-dihydroindolizin-8(5*H*)-one* **(2b)**: Pale yellow solid, yield 60%; m.p. 185–186 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.20–3.21 (m, 2H), 4.11 (t, *J*=6.0 Hz, 2H), 6.31 (dd, J_1=4.0 Hz, J_2=2.0 Hz, 1H), 6.87 (s, 1H), 7.14–7.15 (m, 1H), 7.31–7.33 (m, 2H), 7.37–7.39 (m, 2H), 7.79 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.3, 44.2, 111.2, 115.7, 125.9, 128.8, 130.9, 131.3, 132.7, 134.1, 134.5, 135.2, 177.4; IR (KBr) *v* 1650 cm^{-1}; HRMS (ESI) *m/z* 258.0671 [M+H]$^+$, calcd for $C_{15}H_{13}ClNO$ 258.0680.

*(*E*)-7-(4-Fluorobenzylidene)-6,7-dihydroindolizin-8(5*H*)-one* **(2c)**: Pale yellow solid, yield 58%; m.p. 145–146 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.21 (t, *J*=5.0 Hz, 2H), 4.09 (dd, J_1=6.5 Hz, J_2=1.5 Hz, 2H), 6.30 (dd, J_1=4.0 Hz, J_2=2.5 Hz, 1H), 6.86–6.87 (m, 1H), 7.08–7.14 (m, 3H), 7.37 (t, *J*=6.5 Hz, 2H), 7.80 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.2, 44.2, 111.1, 115.5, 115.7, 125.9, 131.3, 131.56, 131.63, 131.69, 131.72, 132.1, 135.4, 161.7, 163.6, 177.5; IR (KBr) *v* 1644 cm^{-1}; HRMS (ESI) *m/z* 242.0689 [M+H]$^+$, calcd for $C_{15}H_{13}FNO$ 242.0697.

*(*E*)-7-(4-(Methylthio)benzylidene)-6,7-dihydroindolizin-8(5*H*)-one* **(2d)**: Pale yellow solid, yield 52%; m.p. 152–153 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.51 (s, 3H, -SCH_3), 3.23–3.25 (m, 2H), 4.11 (t, *J*=6.5 Hz, 2H), 6.30 (dd, J_1=4.0 Hz, J_2=2.5 Hz, 1H), 6.86 (t, *J*=2.0 Hz, 1H), 7.14 (dd, J_1=4.0 Hz, J_2=1.5 Hz, 1H), 7.27 (d, *J*=8.0 Hz, 2H), 7.33 (d, *J*=8.0 Hz, 2H), 7.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.3, 27.4, 44.2, 111.1, 115.5, 125.7, 126.0, 130.3, 131.4, 131.6, 132.1, 136.1, 140.0, 177.6; IR (KBr) *v* 1647 cm^{-1}; HRMS (ESI) *m/z* 270.0937 [M+H]$^+$, calcd for $C_{16}H_{16}NOS$ 270.0947.

*(*E*)-7-(4-Methylbenzylidene)-6,7-dihydroindolizin-8(5*H*)-one* **(2e)**: Pale yellow solid, yield 62%; m.p. 134–135 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.38 (s, 3H, –CH_3), 3.24 (ddd, J_1=7.5 Hz, J_2=6.0 Hz, J_3=1.5 Hz, 2H), 4.10 (t, *J*=6.5 Hz, 2H), 6.29 (dd, J_1=4.0 Hz, J_2=2.0 Hz, 1H), 6.85 (t, *J*=2.0 Hz, 1H), 7.13 (dd, J_1=4.0 Hz, J_2=1.5 Hz, 1H), 7.22 (d, *J*=8.0 Hz, 2H), 7.30 (d, *J*=8.0 Hz, 2H), 7.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.4, 27.3, 44.3, 111.0, 115.4, 125.6, 129.3, 129.8, 131.44, 131.48, 132.8, 136.7, 138.9, 177.9; IR (KBr) *v* 1645 cm^{-1}; HRMS (ESI) *m/z* 238.1223 [M+H]$^+$, calcd for $C_{16}H_{16}NO$ 238.1226.

*(*E*)-7-(4-Methoxybenzylidene)-6,7-dihydroindolizin-8(5*H*)-one* **(2f)**: Pale yellow solid, yield 54%; m.p. 150–151 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.25 (t, *J*=6.5 Hz, 2H), 3.84 (s, 3H, –OCH_3), 4.10 (t, *J*=6.5 Hz, 2H), 6.29 (dd, J_1=3.0 Hz, J_2=2.5 Hz, 1H), 6.85 (t, *J*=1.5 Hz, 1H), 6.93–6.95 (m, 2H), 7.11–7.12 (m, 1H), 7.37 (d, *J*=8.5 Hz, 2H), 7.82 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.3, 44.2, 55.4, 110.9, 114.0, 115.3, 125.5, 128.1, 130.3, 131.5, 131.6, 136.5, 160.0, 177.9; IR (KBr) *v* 1656 cm^{-1}; HRMS (ESI) *m/z* 254.1181 [M+H]$^+$, calcd for $C_{16}H_{16}NO_2$ 254.1176.

*(*E*)-7-(3,4-Dimethoxybenzylidene)-6,7-dihydroindolizin-8(5*H*)-one* **(2g)**: Pale yellow solid, yield 64%; m.p. 130–131 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.27 (t, *J*=6.0 Hz, 2H), 3.90 (s, 3H, –OCH_3), 3.91 (s, 3H, –OCH_3), 4.11 (t, *J*=6.0 Hz, 2H), 6.29 (m, 1H), 6.85–6.86 (m, 1H), 6.91 (d, *J*=8.0 Hz, 1H), 6.94 (d, *J*=1.5 Hz, 1H), 7.02 (d, *J*=8.5 Hz, 1H), 7.11–7.12 (m, 1H), 7.81 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.4, 44.2, 55.97, 55.98, 110.9, 111.0, 113.2, 115.3, 123.0, 125.6, 128.4, 130.5, 131.5, 136.7, 148.9, 149.6, 177.7; IR (KBr) *v* 1650 cm^{-1}; HRMS (ESI) *m/z* 284.1266 [M+H]$^+$, calcd for $C_{17}H_{18}NO_3$ 284.1281.

*(*E*)-7-(3,5-Dimethoxybenzylidene)-6,7-dihydroindolizin-8(5*H*)-one* **(2h)**: Pale yellow solid, yield 62%; m.p. 120–121 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.23–3.24 (m, 2H), 3.80 (s, 3H, –OCH_3), 3.81 (s, 3H, –OCH_3), 4.09–4.10 (m, 2H), 6.29 (d, J_1=2.0 Hz, 1H), 6.46 (t, *J*=1.5 Hz, 1H), 6.51–6.52 (m, 2H), 6.86–6.87 (m, 1H), 7.13–7.14 (m, 1H), 7.77 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.5, 44.3, 55.4, 100.5, 107.7, 111.1, 115.5, 125.8, 131.4, 132.7, 136.5, 137.5, 160.8, 177.6; IR (KBr) *v* 1653 cm^{-1}; HRMS (ESI) *m/z* 284.1261 [M+H]$^+$, calcd for $C_{17}H_{18}NO_3$ 284.1281.

*(*E*)-7-(3,4,5-Trimethoxybenzylidene)-6,7-dihydroindolizin-8(5*H*)-one* **(2i)**: Pale yellow solid, yield 61%; m.p. 155–156 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.27 (t, *J*=6.5 Hz, 2H), 3.88 (s, 3H, –OCH_3), 3.89 (s, 6H, –OCH_3), 4.13 (t, *J*=6.5 Hz, 2H), 6.30–6.31 (m, 1H), 6.63 (s, 2H), 6.87 (s, 1H), 7.13–7.14 (m, 1H), 7.79 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.4, 44.2, 56.3, 61.0, 107.2, 111.1, 115.5, 125.7, 131.1, 131.4, 131.6, 136.7, 153.2, 177.5; IR (KBr) *v* 1658 cm^{-1}; HRMS (ESI) *m/z* 314.1375 [M+H]$^+$, calcd for $C_{18}H_{20}NO_4$ 314.1387.

Synthesis of 3-aryl-2,2-dibromo-5'H-spiro[cyclopropane-1,7'-indolizin]-8'(6'H)-one; general procedure

(*E*)-7-(Arylmethylene)-6,7-dihydroindolizin-8(5*H*)-ones 2 (1 mmol) and magnesium (240 mg, 10 mmol) were weighed and added to dry THF (20 mL) in a round-bottomed flask at 0 °C under N_2. Bromoform (4.9 g, 2 mL, 20 mmol) was added dropwise into the stirred mixture over a period of 10 min. The reaction mixture was brought to room temperature for 1–3 hours. The reaction was carried out until TLC analysis showed that no reactant was left in the reaction mixture. The reaction mixture was subsequently quenched with saturated aqueous NH_4Cl (10 mL). The water layer was separated and the organic layer was dried (Na_2SO_4), and the solvent evaporated under vacuum to give the crude product. The crude product was subjected to column chromatography using petroleum/ethyl acetate (*V*:*V*=5:1) as eluent to afford the corresponding compound **3**.

2,2-Dibromo-3-phenyl-5′H-spiro[cyclopropane-1,7′-indolizin]-8′(6′H)-one (**3a**): White solid, yield 82%; m.p. 166–167 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.06 (dt, J_1 = 14.0 Hz, J_2 = 2.5 Hz, 1H, H_2C-3′), 2.76 (ddd, J_1 = 14.5 Hz, J_2 = 13.5 Hz, J_3 = 4.5 Hz, 1H, H_2C-3′), 4.01 (s, 1H, HC-3), 4.21 (ddd, J_1 = 6.5 Hz, J_2 = 4.5 Hz, J_3 = 2.0 Hz, 1H, H_2C-4′), 4.44 (td, J_1 = 13.0 Hz, J_2 = 3.0 Hz, 1H, H_2C-4′), 6.33 (dd, J_1 = 4.0 Hz, J_2 = 2.0 Hz, 1H), 6.94 (s, 1H), 7.17 (dd, J_1 = 4.0 Hz, J_2 = 1.0 Hz, 1H), 7.33–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.3, 35.8, 38.2, 40.6, 43.3, 111.4, 115.9, 126.9, 127.7, 128.6, 129.7, 129.9, 132.9, 179.5; IR (KBr) *v* 1652 cm^{-1}; HRMS (ESI) *m/z* 314.0169 [M–Br]$^+$, calcd for $C_{16}H_{13}BrNO$ 314.0181. Anal. Calcd for $C_{16}H_{13}Br_2NO$: C, 48.64; H, 3.32; N, 3.55. Found: C, 48.62; H, 3.36; N, 3.49%.

2,2-Dibromo-3-(4-chlorophenyl)-5′H-spiro[cyclopropane-1,7′-indolizin]-8′(6′H)-one (**3b**): White solid, yield 56%; m.p. 202–203 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.03 (dt, J_1 = 14.5 Hz, J_2 = 2.5 Hz, 1H, H_2C-3′), 2.75 (ddd, J_1 = 14.0 Hz, J_2 = 13.0 Hz, J_3 = 4.5 Hz, 1H, H_2C-3′), 3.96 (s, 1H, HC-3), 4.22 (ddd, J_1 = 6.5 Hz, J_2 = 4.5 Hz, J_3 = 2.0 Hz, 1H, H_2C-4′), 4.46 (td, J_1 = 13.0 Hz, J_2 = 3.0 Hz, 1H, H_2C-4′), 6.34 (dd, J_1 = 4.0 Hz, J_2 = 2.5 Hz, 1H), 6.95 (t, J = 1.5 Hz, 1H), 7.17 (dd, J_1 = 4.0 Hz, J_2 = 1.5 Hz, 1H), 7.21–7.22 (m, 2H), 7.33–7.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.2, 35.2, 37.5, 40.6,43.2, 111.5, 116.2, 127.0, 128.9, 129.6, 131.3, 131.4, 133.8, 179.2; IR (KBr) *v* 1661 cm^{-1}; HRMS (ESI) *m/z* 347.9768 [M–Br]$^+$, calcd for $C_{16}H_{12}BrClNO$ 347.9791. Anal. Calcd for $C_{16}H_{12}Br_2ClNO$: C, 44.74; H, 2.82; N, 3.26. Found: C, 44.68; H, 2.75; N, 3.28%.

2*,2-Dibromo-3-(4-fluorophenyl)-5′H-spiro[cyclopropane-1,7′-indolizin]-8′(6′H)-one* (**3c**): White solid, yield 58%; m.p. 155–157 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.04 (dt, J_1 = 14.0 Hz, J_2 = 2.5 Hz, 1H, H_2C-3′), 2.75 (ddd, J_1 = 14.0 Hz, J_2 = 13.0 Hz, J_3 = 4.5 Hz, 1H, H_2C-3′), 3.95 (s, 1H, HC-3), 4.22 (ddd, J_1 = 6.5 Hz, J_2 = 4.5 Hz, J_3 = 2.0 Hz, 1H, H_2C-4′), 4.44 (td, J_1 = 13.0 Hz, J_2 = 3.0 Hz, 1H, H_2C-4′), 6.34 (dd, J_1 = 4.0 Hz, J_2 = 2.5 Hz, 1H), 6.95 (t, J = 2.0 Hz, 1H), 7.05–7.08 (m, 2H), 7.16 (dd, J_1 = 4.0 Hz, J_2 = 1.5 Hz, 1H), 7.17–7.24 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.2, 35.5, 37.5, 40.6, 43.2, 111.4, 115.6, 115.8, 116.1, 128.71, 128.73, 129.6, 131.5, 131.6, 161.2, 163.2, 179.3; IR (KBr) *v* 1651 cm^{-1}; HRMS (ESI) *m/z* 332.0073 [M–Br]$^+$, calcd for $C_{16}H_{12}BrFNO$ 332.0086. Anal. Calcd for $C_{16}H_{12}Br_2FNO$: C, 46.52; H, 2.93; N, 3.39. Found: C, 46.54; H, 2.91; N, 3.46%.

2,2-Dibromo-3-(4-(methylthio)phenyl)-5′H-spiro[cyclopropane-1,7′-indolizin]-8′(6′H)-one (**3d**): White solid, yield 68%; m.p. 172–173 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.05 (dt, J_1 = 14.0 Hz, J_2 = 2.5 Hz, 1H, H_2C-3′), 2.45(s, 3H, –SCH_3), 2.74 (ddd, J_1 = 14.0 Hz, J_2 = 12.5 Hz, J_3 = 4.5 Hz, 1H, H_2C-3′), 3.95 (s, 1H, HC-3), 4.21 (ddd, J_1 = 7.0 Hz, J_2 = 4.5 Hz, J_3 = 2.0 Hz, 1H, H_2C-4′), 4.45 (td, J_1 = 12.5 Hz, J_2 = 3.0 Hz, 1H, H_2C-4′), 6.33 (dd, J_1 = 4.0 Hz, J_2 = 2.5 Hz, 1H), 6.94 (t, J = 2.0 Hz, 1H), 7.15–7.19 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.6, 30.2, 35.8, 37.8, 40.6, 43.2, 111.4, 116.0, 126.3, 126.9, 129.5, 129.7, 130.3, 138.3, 179.5; IR (KBr) *v* 1651 cm^{-1}; HRMS (ESI) *m/z* 360.0057 [M–Br]$^+$, calcd for $C_{17}H_{15}BrNOS$ 360.0058.

2,2-Dibromo-3-p-tolyl-5′H-spiro[cyclopropane-1,7′-indolizin]-8′(6′H)-one (**3e**): White solid, yield 72%; m.p. 183–184 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.06 (dt, J_1 = 14.5 Hz, J_2 = 3.0 Hz, 1H, H_2C-3′), 2.35(s, 3H, –CH_3), 2.75 (ddd, J_1 = 14.5 Hz, J_2 = 13.0 Hz, J_3 = 5.0 Hz, 1H, H_2C-3′), 3.96 (s, 1H, HC-3), 4.20 (ddd, J_1 = 6.5 Hz, J_2 = 4.5 Hz, J_3 = 2.0 Hz, 1H, H_2C-4′), 4.44 (td, J_1 = 12.5 Hz, J_2 = 3.0 Hz, 1H, H_2C-4′), 6.33 (dd, J_1 = 4.0 Hz, J_2 = 2.5 Hz, 1H), 6.94 (t, J = 2.0 Hz, 1H), 7.16–7.19 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.3, 30.3, 36.1, 38.0, 40.5, 43.3, 111.3, 115.9, 126.8, 129.3, 129.8, 129.9, 137.5, 179.7; IR (KBr) *v* 1651 cm^{-1}; HRMS (ESI) *m/z* 328.0342 [M–Br]$^+$, calcd for $C_{17}H_{15}BrNO$ 328.0337.

2,2-Dibromo-3-(4-methoxyphenyl)-5′H-spiro[cyclopropane-1,7′-indolizin]-8′(6′H)-one (**3f**): White solid, yield 78%; m.p. 174–176 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.06 (dt, J_1 = 17.0 Hz, J_2 = 2.5 Hz, 1H, H_2C-3′), 2.75 (ddd, J_1 = 14.5 Hz, J_2 = 13.5 Hz, J_3 = 4.5 Hz, 1H, H_2C-3′), 3.81(s, 3H, –OCH_3), 3.94 (s, 1H, HC-3), 4.21 (ddd, J_1 = 7.0 Hz, J_2 = 4.5 Hz, J_3 = 2.0 Hz, 1H, H_2C-4′), 4.45 (td, J_1 = 12.5 Hz, J_2 = 2.5 Hz, 1H, H_2C-4′), 6.33 (dd, J_1 = 4.0 Hz, J_2 = 2.5 Hz, 1H), 6.88–6.91(m, 2H), 6.93 (t, J = 2.0 Hz, 1H), 7.16 (d, J = 4.5 Hz, 1H), 7.16–7.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.2, 36.4, 37.7, 40.6, 43.3, 55.3, 111.3, 114.0, 115.9, 124.9, 126.8, 129.8, 131.0, 159.0, 179.7; IR (KBr) *v* 1663 cm^{-1}; HRMS (ESI) *m/z* 344.0273 [M–Br]$^+$, calcd for $C_{17}H_{15}BrNO_2$ 344.0286. Anal. Calcd for $C_{17}H_{15}Br_2NO_2$: C, 48.03; H, 3.56; N, 3.29. Found: C, 47.81; H, 3.59; N, 3.37%.

2,2-Dibromo-3-(3,4-dimethoxyphenyl)-5′H-spiro[cyclopropane-1,7′-indolizin]-8′(6′H)-one (**3g**): White solid, yield 84%; m.p. 177–178 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.09 (dt, J_1 = 14.5 Hz, J_2 = 2.5 Hz, 1H, H_2C-3′), 2.75 (ddd, J_1 = 14.0 Hz, J_2 = 13.0 Hz, J_3 = 4.5 Hz, 1H, H_2C-3′), 3.88(s, 3H, –OCH_3), 3.89(s, 3H, –OCH_3), 3.96 (s, 1H, HC-3), 4.22 (ddd, J_1 = 6.5 Hz, J_2 = 4.0 Hz, J_3 = 2.0 Hz, 1H, H_2C-4′), 4.46 (td, J_1 = 12.5 Hz, J_2 = 3.0 Hz, 1H, H_2C-4′), 6.34 (dd, J_1 = 4.0 Hz, J_2 = 2.5 Hz, 1H), 6.79–6.86(m, 3H), 6.93 (t, J = 2.0 Hz, 1H), 7.16–7.17 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.4, 36.2, 38.0, 43.3, 55.9, 56.0, 111.0, 111.4, 113.1, 116.0, 122.0, 125.2, 126.9, 129.8, 148.5, 148.9, 179.6; IR (KBr) *v* 1668 cm^{-1}; HRMS (ESI) *m/z* 374.0391 [M–Br]$^+$, calcd for $C_{18}H_{17}BrNO_3$ 374.0392.

2,2-Dibromo-3-(3,5-dimethoxyphenyl)-5′H-spiro[cyclopropane-1,7′-indolizin]-8′(6′H)-one (**3h**): White solid, yield 86%; m.p. 174–175 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.12 (dt, J_1 = 14.5 Hz, J_2 = 3.0 Hz, 1H, H_2C-3′), 2.75 (ddd, J_1 = 14.5 Hz, J_2 = 13.0 Hz, J_3 = 4.5 Hz, 1H, H_2C-3′), 3.78(s, 6H, –OCH_3), 3.96 (s, 1H, HC-3), 4.22 (ddd, J_1 = 9.0 Hz, J_2 = 4.5 Hz, J_3 = 2.5 Hz, 1H, H_2C-4′), 4.45 (td, J_1 = 13.0 Hz, J_2 = 3.0 Hz, 1H, H_2C-4′), 6.33 (dd, J_1 = 4.0 Hz, J_2 = 2.5 Hz, 1H), 6.41(s, 3H), 6.94 (t, J = 2.0 Hz, 1H), 7.15 (dd, J_1 = 4.0 Hz, J_2 = 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.4, 35.6, 38.4, 40.6, 43.3, 55.4, 99.7, 107.8, 111.4, 115.9, 127.0, 129.7, 134.9, 160.8, 179.5; IR (KBr) *v* 1646 cm^{-1}; HRMS (ESI) *m/z* 374.0365 [M–Br]$^+$, calcd for $C_{18}H_{17}BrNO_3$ 374.0392.

2,2-Dibromo-3-(3,4,5-trimethoxyphenyl)-5′H-spiro[cyclopropane-1,7′-indolizin]-8′(6′H)-one (**3i**): White solid, yield 92%; m.p. 178–179 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.09 (dt, J_1 = 12.0 Hz, J_2 = 2.5 Hz, 1H, H_2C-3′), 2.75 (ddd, J_1 = 14.5 Hz, J_2 = 13.0 Hz, J_3 = 4.5 Hz, 1H, H_2C-3′), 3.78(s, 9H, –OCH_3), 3.97 (s, 1H, HC-3), 4.26 (ddd, J_1 = 6.5 Hz, J_2 = 4.5 Hz, J_3 = 2.0 Hz, 1H, H_2C-4′), 4.48 (td, J_1 = 12.5 Hz, J_2 = 3.0 Hz, 1H, H_2C-4′), 6.35 (dd, J_1 = 4.5 Hz, J_2 = 2.5 Hz, 1H), 6.48(s, 2H), 6.96 (t, J = 2.0 Hz, 1H), 7.17 (dd, J_1 = 4.0 Hz, J_2 = 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 30.5, 35.7, 38.4, 40.7, 43.4, 56.2, 60.9, 106.8, 111.4, 116.0, 127.0, 128.2, 129.7, 137.5, 153.3, 179.5; IR (KBr) *v* 1650 cm^{-1}; HRMS (ESI) *m/z* 404.0497 [M–Br]$^+$, calcd for $C_{19}H_{19}BrNO_4$ 404.0497.

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