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Synthesis of 2',3',4'-triaryl-5,6-dihydro-8*H*-spiro[indolizine-7,5'-isoxazolidin]-8-ones *via* 1,3-dipolar cycloaddition reaction involving (*Z*)-*C*-aryl-*N*-phenylnitrones

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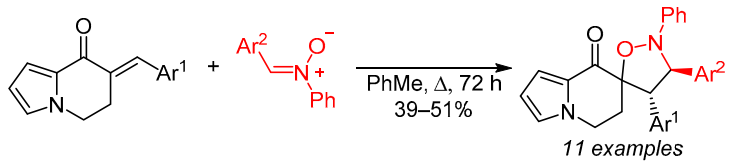


The 1,3-dipolar cycloaddition of *C*-aryl-*N*-phenylnitrones to 7-arylmethylidene-6,7-dihydroindolizin-8(5*H*)-ones afforded novel 2',3',4'-triaryl-5,6-dihydro-8*H*-spiro[indolizine-7,5'-isoxazolidin]-8-ones in moderate yields. The structures of all the products were proved by NMR and IR spectroscopy, HRMS, and X-ray analysis.

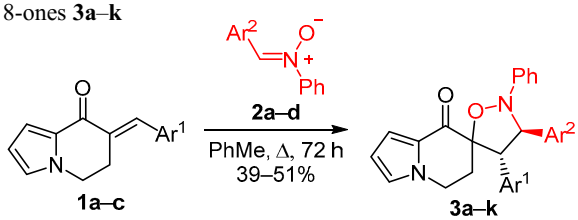
Keywords: indolizine, isoxazolidine, nitrone, 1,3-dipolar cycloaddition.

Isoxazolidines are presented in many known pharmacological alkaloids such as pyrinodemin A,[1] lycojaponicumin B,[2] flueggine A,[3] setigerumine I,[4] and dactylicapnosinine.[5] The derivatives of isoxazolidine possess an extensive spectrum of biological activities such as antiviral, antifungal, and antimicrobial,[6] and are also used as hypoglycemic agents[7] and reductase inhibitors.[8] The isoxazolidines are important intermediates for the concise synthesis of pharmaceutically important building blocks such as 1,3-aminocarbonyls, 1,3-amino alcohols, β-lactams and a variety of natural products.[8] The 1,3-dipolar cycloaddition reaction of nitrones with electrophilic olefins is one of the most convenient methods to construct isoxazolidines.[9]

Indolizine cycle is a ubiquitous fragment of many biologically significant alkaloids: kinganone,[10] (+)-monomorine,[11] indolizidine 209D,[12] and polygonatines A, B.[13] Indolizine derivatives have been widely studied due to their biological activities (antiHIV,[14] hypoglycemic,[15] antitumor,[16] and antimicrobial[17]), ability to act as glycogen synthase kinase-3β inhibitors[18] and 5-hydroxytryptamine receptor antagonists.[19]

Herein, we report the synthesis of 2',3',4'-triaryl-5,6-dihydro-8*H*-spiro[indolizine-7,5'-isoxazolidin]-8-ones by the cycloaddition of *C*-aryl-*N*-phenylnitrones with 7-arylmethylidene-6,7-dihydroindolizin-8(5*H*)-ones in continuation of our work regarding 1,3-dipolar cycloaddition reactions[20] and synthesis of indolizine derivatives.[21] 1,3-Dipolar cycloaddition of compounds **1a**–**c** with nitrones **2a**–**d** in refluxing PhMe yielded the corresponding spiroisooxazolines **3a**–**k** in satisfactory yields with high regioselectivity (Scheme 1) .

Scheme 1. Synthesis of spiro[indolizine-7,5'-isoxazolidin]-8-ones **3a**–**k**



1 a Ar^1 = 4-BrC_6H_4, **b** Ar^1 = 4-ClC_6H_4, **c** Ar^1 = 4-FC_6H_4
2 a Ar^2 = Ph, **b** Ar^2 = 4-BrC_6H_4, **c** Ar^2 = 4-ClC_6H_4, **d** Ar^2 = 4-MeC_6H_4
3 a Ar^1 = 4-BrC_6H_4, Ar^2 = Ph; **b** Ar^1 = Ar^2 = 4-ClC_6H_4;
c Ar^1 = 4-FC_6H_4, Ar^2 = 4-BrC_6H_4;
d Ar^1 = 4-BrC_6H_4, Ar^2 = 4-ClC_6H_4;
e Ar^1 = 4-ClC_6H_4, Ar^2 = 4-MeC_6H_4; **f** Ar^1 = 4-FC_6H_4, Ar^2 = Ph;
g Ar^1 = 4-ClC_6H_4, Ar^2 = 4-BrC_6H_4; **h** Ar^1 = Ar^2 = 4-BrC_6H_4;
i Ar^1 = 4-ClC_6H_4, Ar^2 = Ph; **j** Ar^1 = 4-FC_6H_4, Ar^2 = 4-ClC_6H_4;
k Ar^1 = 4-BrC_6H_4, Ar^2 = 4-MeC_6H_4

The structures of products **3a**–**k** were established by IR and ^{1}H, ^{13}C NMR spectroscopy and HRMS. The high-resolution mass spectrum of product **3a** contained a signal of protonated molecular ion with *m*/*z* 499.1018. The IR spectrum of the product **3a** displayed a characteristic absorption of carbonyl group at 1650 cm^{-1}, isoxazolidine ring (C–N) at 1176 cm^{-1}, as well as N–O fragment at 945 cm^{-1}. The ^{1}H NMR spectrum of compound **3a** revealed a doublet of doublets of doublets at 1.84 ppm (J = 14.0, J = 12.5, J = 5.0 Hz) and a doublet of triplets at 2.14 ppm (J = 14.0, J = 2.5 Hz) assigned to the 6-CH_2 protons; a doublet of doublets of doublets at 3.98 ppm (J = 12.5, J = 5.0, J = 2.0 Hz) and a triplet of doublets at 4.43 ppm (J = 12.5, J = 3.0 Hz) corresponding to the 5-CH_2 protons; a doublet at 4.84 ppm and a doublet at 5.08 ppm assigned to the 3'-CH and 4'-CH protons, respectively; a doublet of doublets at 6.29 (J = 4.0, J = 2.0 Hz) and a triplet at 6.84 ppm assigned to the H-2 and H-3 protons of the pyrrole cycle, respectively.

The ^{13}C NMR spectrum of product **3a** exhibited the presence of carbonyl group at 180.2 ppm. Signals at 30.8 and 41.4 ppm were assigned to the C-6 and C-5 atoms, respectively. The signal at 83.1 corresponded to the spiro carbon atom C-7. In addition, signals at 73.9 and 59.2 ppm represented C-3' and C-4' atoms, respectively. The ^{1}H–^{13}C HMBC spectrum of compound **3a** confirmed the correlation between carbonyl group and 6-CH_2 and 4'-CH protons, the cross peak of C-5 carbon and H-3 proton was also detected, the C-7 carbon atom with the signal at 83.1 ppm correlated with 3'-CH and 5-CH_2 protons. Some significant 2D NMR correlations for the assignment of H and C atoms and confirmation of the structure of compound **3a** are shown in Figure 1. Further, the X-ray analysis of compound **3e** allowed to make the final assignment of the structure of cycloaddition reaction product and identify it as product **3** in contrast to products **3'**, **3''**, or **3'''** (Fig. 2, Scheme 2).

The possible pathways of the cycloaddition reaction between dipolarophile **1** and nitrone **2** is shown in Scheme 2. Thus, there are four different variations of nitrone **2** attack to the double bond of dipolarophile **1**. Addition of the O atom of nitrone **2** to the the most substituted carbon of dipolarophiles should lead to the formation of products **3** and/or **3'** which could be distinguished and proved by NMR data. Thus, possessing two characteristic signals of protons of isoxazolidine cycle at 4.84 and 5.08 ppm assigned to 3'-CH and 4'-CH atoms gave coupling constant J = 10.0 Hz which confirmed the *trans* location of 3'-CH and 4'-CH hydrogen atoms in the cycle.[22] The O atom attack to the less substituted carbon atom of dipolarophile **1** should provide products **3''** and **3'''** which were not detected. In our point of view, the regioselectivity was determined by the attack of the most nucleophilic center of diarylnitrone **2** on the most activated atom of the C=C moiety of dipolarophile **1**.[23] On the other hand, the stereoselectivity was influenced by steric effects which favored 3,4-*trans* configuration in the transition state.[24]

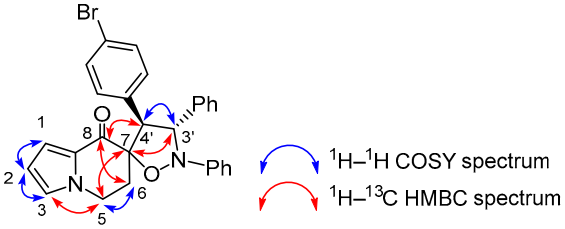


Figure 1. The main correlations in the ^{1}H–^{1}H COSY and ^{1}H–^{13}C HMBC spectra of compound **3a**.

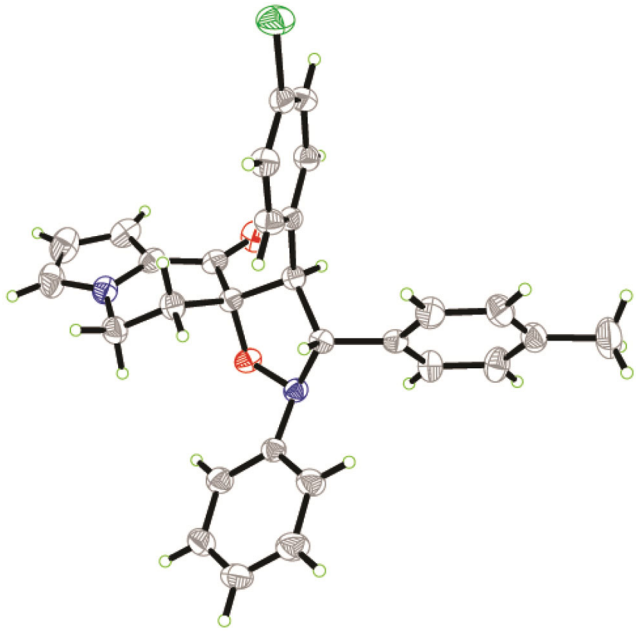
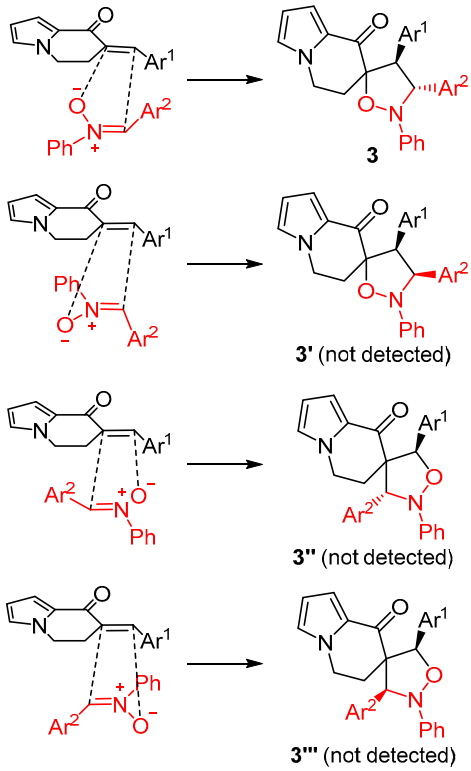


Figure 2. The molecular structure of compound **3e** with atom represented by thermal vibration ellipsoids of 50% probability.

Scheme 2. Possible reaction pathways for the formation of compound **3**



In conclusion, we have developed an efficient [3+2]-regioselective cycloaddition reaction of 7-arylmethylidene-6,7-dihydroindolizin-8(5*H*)-ones to arylnitrones, affording a variety of 2',3',4'-triaryl-5,6-dihydro-8*H*-spiro[indolizine-7,5'-isoxazolidin]-8-ones in moderate yields.

Experimental

IR spectra were recorded on a PerkinElmer Spectrum One spectrometer using KBr pellets. ^{1}H, ^{13}C NMR spectra (500 and 125 MHz, respectively) and ^{1}H–^{13}C HMQC, ^{1}H–^{13}C HMBC, and ^{1}H–^{1}H COSY spectra were acquired on a Bruker Avance II 500 spectrometer in $CDCl_3$ solution using TMS as internal standard. HRMS analyses were conducted on a Finnigan LCQ Advantage MAX mass spectrometer (ESI). Melting points were determined on a Yanaco MP-500 melting point apparatus and are uncorrected. TLC analyses were performed on Merck TLC Silica gel 60 F_{254} plates using petroleum ether – EtOAc, 4:1. Crude products were purified by column chromatography using silica gel (100–200 mesh, Beijing Innochem Company).

Starting compounds **1a**–**c** were synthesized according to literature method,[25] *C*-aryl-*N*-phenylnitrones **2a**–**d** were synthesized by the reaction of nitrobenzene and arylaldehyde in the presence of zinc as previously reported.[26] All other chemicals were obtained from commercial suppliers and were used without additional purification.

Synthesis of 2',3',4'-triaryl-5,6-dihydro-8*H*-spiro[indolizine-7,5'-isoxazolidin]-8-ones 3a–k (General method). A mixture of the corresponding 7-arylmethylidene-6,7-dihydroindolizin-8(5*H*)-one **1a**–**c** (1 mmol) and *C*-aryl-*N*-phenylnitrones **2a**–**d** (1.5 mmol) in PhMe (20 ml) was refluxed for 72 h. The solvent was removed under reduced pressure, and the reaction mixture was purified by flash column chromatography, eluent petroleum ether – EtOAc, 4:1.

4'-(4-Bromophenyl)-2',3'-diphenyl-5,6-dihydro-8*H*-spiro[indolizine-7,5'-isoxazolidin]-8-one (3a). Yield 214 mg (43%), white solid, mp 215–217°C. IR spectrum, ν, cm^{-1}: 1650, 1592, 1525, 1485, 1391, 1176, 1066, 945, 754, 693. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.84 (1H, ddd, *J* = 14.0, *J* = 12.5, *J* = 5.0, CH_2); 2.14 (1H, dt, *J* = 14.0, *J* = 2.5, CH_2); 3.98 (1H, ddd, *J* = 12.5, *J* = 5.0, *J* = 2.0, CH_2); 4.43 (1H, td, *J* = 12.5, *J* = 3.0, CH_2); 4.84 (1H, d, *J* = 10.0, CH); 5.08 (1H, d, *J* = 10.0, CH); 6.29 (1H, dd, *J* = 4.0, *J* = 2.0, H pyrrole); 6.84 (1H, t, *J* = 1.5, H pyrrole); 6.93–6.96 (3H, m, H pyrrole, H Ar); 7.14–7.16 (1H, m, H Ar); 7.18–7.22 (4H, m, H Ar); 7.25–7.31 (3H, m, H Ar); 7.40–7.42 (2H, m, H Ar); 7.48–7.50 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 30.8; 41.4; 59.2; 73.9; 83.1; 111.5; 116.1; 116.7; 121.8; 122.6; 126.7; 127.4; 128.2; 128.7; 128.9; 129.7; 131.3; 131.8; 133.9; 138.9; 150.5; 180.2. Found, *m*/*z*: 499.1018 $[M+H]^+$. $C_{28}H_{24}BrN_2O_2$. Calculated, *m*/*z*: 499.1016.

3',4'-Bis(4-chlorophenyl)-2'-phenyl-5,6-dihydro-8*H*-spiro[indolizine-7,5'-isoxazolidin]-8-one (3b). Yield 229 mg (47%), white solid, mp 240–242°C. IR spectrum, ν, cm^{-1}: 1654, 1595, 1528, 1487, 1395, 1183, 1068, 941, 752, 698. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.84 (1H, ddd, *J* = 14.0, *J* = 12.5, *J* = 5.0, CH_2); 2.12 (1H, dt, *J* = 14.0, *J* = 2.5, CH_2); 4.00 (1H, ddd, *J* = 12.5, *J* = 5.0, *J* = 2.0, CH_2); 4.44 (1H, td, *J* = 12.5, *J* = 3.0, CH_2); 4.79 (1H, d, *J* = 10.0, CH); 5.01 (1H, d, *J* = 10.0, CH); 6.29 (1H, dd, *J* = 4.0, *J* = 2.0, H pyrrole); 6.85 (1H, t, *J* = 1.5, H pyrrole); 6.92–6.99 (3H, m, H pyrrole, H Ar); 7.15–7.16 (1H, m, H Ar); 7.18–7.21 (2H, m, H Ar); 7.27–7.29 (6H, m, H Ar); 7.42–7.43 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 30.9; 41.4; 59.0; 73.9; 83.0; 111.5; 116.3; 116.7; 122.9; 126.6; 128.7; 129.0; 129.1; 129.5; 130.7; 133.3; 133.8; 133.9; 137.5; 149.9; 180.2. Found, *m*/*z*: 489.1134 $[M+H]^+$. $C_{28}H_{23}Cl_2N_2O_2$. Calculated, *m*/*z*: 489.1131.

3'-(4-Bromophenyl)-4'-(4-fluorophenyl)-2'-phenyl-5,6-dihydro-8*H*-spiro[indolizine-7,5'-isoxazolidin]-8-one (3c). Yield 237 mg (46%), white solid, mp 223–225°C. IR spectrum, ν, cm^{-1}: 1655, 1598, 1509, 1485, 1395, 1184, 1070, 940, 752, 699. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.84 (1H, ddd, *J* = 14.0, *J* = 12.5, *J* = 5.0, CH_2); 2.13 (1H, dt, *J* = 14.0, *J* = 2.5, CH_2); 4.00 (1H, ddd, *J* = 12.5, *J* = 5.0, *J* = 2.0, CH_2); 4.43 (1H, td, *J* = 12.5, *J* = 3.0, CH_2); 4.77 (1H, d, *J* = 10.0, CH); 5.01 (1H, d, *J* = 10.0, CH); 6.29 (1H, dd, *J* = 4.0, *J* = 2.5, H pyrrole); 6.84 (1H, t, *J* = 1.5, H pyrrole); 6.92–6.94 (2H, m, H pyrrole, H Ar); 6.97–7.02 (3H, m, H Ar); 7.14–7.16 (1H, m, H Ar); 7.18–7.21 (2H, m, H Ar); 7.27–7.30 (2H, m, H Ar); 7.35–7.37 (2H, m, H Ar); 7.41–7.43 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 30.8; 41.4; 59.0; 74.0; 83.0; 111.5; 115.8 (d, *J* = 21.0); 116.2; 116.7; 122.0; 122.8; 126.6; 128.7; 128.8; 129.0; 129.6; 130.4; 130.9 (d, *J* = 8.0); 132.0; 138.2; 150.1; 163.3 (d, *J* = 246.0); 180.3. Found, *m*/*z*: 517.0916 $[M+H]^+$. $C_{28}H_{23}BrFN_2O_2$. Calculated, *m*/*z*: 517.0921.

4'-(4-Bromophenyl)-3'-(4-chlorophenyl)-2'-phenyl-5,6-dihydro-8*H*-spiro[indolizine-7,5'-isoxazolidin]-8-one (3d). Yield 271 mg (51%), white solid, mp 233–235°C. IR spectrum, ν, cm^{-1}: 1653, 1594, 1528, 1486, 1395, 1185, 1070, 942, 752, 697. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.84 (1H, ddd, *J* = 14.0, *J* = 12.5, *J* = 5.0, CH_2); 2.14 (1H, dt, *J* = 14.0, *J* = 2.5, CH_2); 4.01 (1H, ddd, *J* = 12.5, *J* = 5.0, *J* = 2.0, CH_2); 4.43 (1H, td, *J* = 12.5, *J* = 3.0, CH_2); 4.79 (1H, d, *J* = 10.0, CH); 5.08 (1H, d, *J* = 10.0, CH); 6.30 (1H, dd, *J* = 4.0, *J* = 2.0, H pyrrole); 6.85 (1H, t, *J* = 2.0, H pyrrole); 6.93–6.97 (3H, m, H pyrrole, H Ar); 7.15–7.16 (1H, m, H Ar); 7.18–7.21 (4H, m, H Ar); 7.27–7.28 (2H, m, H Ar); 7.41–7.44 (4H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 30.9; 41.4; 59.1; 73.8; 82.9; 111.5; 116.4; 116.8; 122.0; 122.9; 126.6; 128.7; 129.1; 129.5; 131.1; 131.9; 133.9; 137.5; 149.9; 180.2. Found, *m*/*z*: 533.0624 $[M+H]^+$. $C_{28}H_{23}BrClN_2O_2$. Calculated, *m*/*z*: 533.0626.

4'-(4-Chlorophenyl)-2'-phenyl-3'-(*p*-tolyl)-5,6-dihydro-8*H*-spiro[indolizine-7,5'-isoxazolidin]-8-one (3e). Yield 192 mg (41%), white solid, mp 226–228°C. IR spectrum, ν, cm^{-1}: 1656, 1598, 1527, 1488, 1396, 1186, 1067, 956, 760, 697. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.83 (1H, ddd, *J* = 14.0, *J* = 12.5, *J* = 5.0, CH_2); 2.13 (1H, dt, *J* = 14.0, *J* = 2.5, CH_2); 2.29 (3H, s, CH_3); 3.97 (1H, ddd, *J* = 12.5, *J* = 5.0, *J* = 2.0, CH_2); 4.43 (1H, td, *J* = 12.5, *J* = 3.0, CH_2); 4.81 (1H, d, *J* = 10.0, CH); 5.09 (1H, d, *J* = 10.0, CH); 6.28 (1H, dd, *J* = 4.0, *J* = 2.5, H pyrrole); 6.84 (1H, t, *J* = 2.0, H pyrrole); 6.93–6.95 (3H, m, H pyrrole, H Ar); 7.08–7.09 (2H, m, H Ar); 7.14–7.16 (1H, m, H Ar); 7.17–7.19 (2H, m, H Ar); 7.24–7.28 (4H, m, H Ar); 7.37 (2H, d, *J* = 8.0, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.2; 30.8; 41.4; 59.0;

73.8; 83.0; 111.4; 116.2; 116.7; 122.5; 126.5; 127.3; 128.6; 128.8; 129.5; 129.7; 130.7; 133.5; 133.6; 135.7; 137.8; 150.6; 180.3. Found, *m/z*: 469.1675 $[M+H]^+$. $C_{29}H_{26}ClN_2O_2$. Calculated, *m/z*: 469.1677.

4'-(4-Fluorophenyl)-2',3'-diphenyl-5,6-dihydro-8*H*-spiro[indolizine-7,5'-isoxazolidin]-8-one (3f). Yield 171 mg (39%), white solid, mp 202–204°C. IR spectrum, ν, cm^{-1}: 1657, 1598, 1510, 1486, 1396, 1183, 1068, 941, 755, 698. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.84 (1H, ddd, *J* = 14.0, *J* = 12.5, *J* = 5.0, CH_2); 2.15 (1H, dt, *J* = 14.0, *J* = 2.5, CH_2); 3.98 (1H, ddd, *J* = 12.5, *J* = 5.0, *J* = 2.0, CH_2); 4.43 (1H, td, *J* = 12.5, *J* = 3.0, CH_2); 4.86 (1H, d, *J* = 10.0, CH); 5.10 (1H, d, *J* = 10.0, CH); 6.29 (1H, dd, *J* = 4.0, *J* = 2.0, H pyrrole); 6.84 (1H, t, *J* = 2.0, H pyrrole); 6.93–6.99 (5H, m, H pyrrole, H Ar); 7.15–7.16 (1H, m, H Ar); 7.17–7.20 (2H, m, H Ar); 7.27–7.32 (5H, m, H Ar); 7.49–7.50 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 30.8; 41.4; 59.0; 74.1; 83.1; 111.4; 115.6 (q, *J* = 21.0); 116.0; 116.7; 122.5; 126.5; 127.3; 128.1; 128.6; 128.8; 129.7; 130.5 (d, *J* = 3.0); 131.0 (d, *J* = 7.5); 139.0; 150.6; 163.2 (d, *J* = 245.0); 180.3. Found, *m/z*: 439.1819 $[M+H]^+$. $C_{28}H_{24}FN_2O_2$. Calculated, *m/z*: 439.1816.

3'-(4-Bromophenyl)-4'-(4-chlorophenyl)-2'-phenyl-5,6-dihydro-8*H*-spiro[indolizine-7,5'-isoxazolidin]-8-one (3g). Yield 239 mg (45%), white solid, mp 253–255°C. IR spectrum, ν, cm^{-1}: 1653, 1596, 1527, 1488, 1395, 1183, 1068, 941, 759, 697. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.84 (1H, ddd, *J* = 14.0, *J* = 12.5, *J* = 5.0, CH_2); 2.13 (1H, dt, *J* = 14.0, *J* = 3.0, CH_2); 3.99 (1H, ddd, *J* = 12.5, *J* = 5.0, *J* = 2.0, CH_2); 4.43 (1H, td, *J* = 12.5, *J* = 3.0, CH_2); 4.77 (1H, d, *J* = 10.0, CH); 5.01 (1H, d, *J* = 10.0, CH); 6.29 (1H, dd, *J* = 4.0, *J* = 2.5, H pyrrole); 6.85 (1H, t, *J* = 1.5, H pyrrole); 6.92–6.93 (2H, m, H pyrrole, H Ar); 6.95–6.98 (1H, m, H Ar); 7.14–7.16 (1H, m, H Ar); 7.18–7.21 (2H, m, H Ar); 7.26–7.28 (4H, m, H Ar); 7.35–7.37 (2H, m, H Ar); 7.42–7.44 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 30.9; 41.4; 59.1; 73.9; 83.0; 111.5; 115.2; 116.3; 116.8; 122.1; 122.9; 126.6; 128.0; 128.6; 128.7; 128.8; 129.0; 129.1; 129.2; 129.5; 130.7; 131.6; 132.0; 133.3; 133.8; 138.1; 150.0; 180.2. Found, *m/z*: 533.0624 $[M+H]^+$. $C_{28}H_{23}BrClN_2O_2$. Calculated, *m/z*: 533.0626.

3',4'-Bis(4-bromophenyl)-2'-phenyl-5,6-dihydro-8*H*-spiro[indolizine-7,5'-isoxazolidin]-8-one (3h). Yield 277 mg (48%), white solid, mp 230–232°C. IR spectrum, ν, cm^{-1}: 1654, 1594, 1528, 1488, 1395, 1185, 1068, 943, 759, 695. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.84 (1H, ddd, *J* = 14.0, *J* = 12.5, *J* = 5.0, CH_2); 2.12 (1H, dt, *J* = 14.0, *J* = 2.5, CH_2); 4.00 (1H, ddd, *J* = 12.5, *J* = 5.0, *J* = 2.0, CH_2); 4.43 (1H, td, *J* = 12.5, *J* = 3.0, CH_2); 4.77 (1H, d, *J* = 10.0, CH); 5.00 (1H, d, *J* = 10.0, CH); 6.29 (1H, dd, *J* = 4.0, *J* = 2.5, H pyrrole); 6.85 (1H, t, *J* = 1.5, H pyrrole); 6.92–6.93 (2H, m, H pyrrole, H Ar); 6.95–6.98 (1H, m, H Ar); 7.14–7.15 (1H, m, H Ar); 7.18–7.21 (4H, m, H Ar); 7.35–7.37 (2H, m, H Ar); 7.41–7.44 (4H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 30.9; 41.4; 59.1; 73.8; 82.9; 111.5; 116.3; 116.8; 122.9; 126.6; 128.3; 128.7; 129.0; 129.5; 131.1; 131.5; 131.9; 132.0; 133.8; 138.0; 149.9; 180.2. Found, *m/z*: 577.0121 $[M+H]^+$. $C_{28}H_{23}Br_2N_2O_2$. Calculated, *m/z*: 577.0121.

4'-(4-Chlorophenyl)-2',3'-diphenyl-5,6-dihydro-8*H*-spiro[indolizine-7,5'-isoxazolidin]-8-one (3i). Yield 181 mg (40%), white solid, mp 191–192°C. IR spectrum, ν, cm^{-1}: 1655, 1595, 1527, 1487, 1395, 1182, 1067, 942, 755, 696. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.83 (1H, ddd, *J* = 18.0, *J* = 12.5, *J* = 5.0, CH_2); 2.12 (1H, dt, *J* = 14.0, *J* = 3.0, CH_2); 3.98 (1H, ddd, *J* = 12.5, *J* = 5.0, *J* = 2.0, CH_2); 4.43 (1H, td, *J* = 12.5, *J* = 3.0, CH_2); 4.85 (1H, d, *J* = 10.0, CH); 5.10 (1H, d, *J* = 10.0, CH); 6.28 (1H, dd, *J* = 4.0, *J* = 2.0, H pyrrole); 6.83 (1H, t, *J* = 1.5, H pyrrole); 6.93–6.95 (3H, m, H pyrrole, H Ar); 7.14–7.19 (3H, m, H Ar); 7.27–7.31 (7H, m, H Ar); 7.48–7.49 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 30.8; 41.4; 59.1; 74.0; 83.1; 111.5; 116.0; 116.7; 122.5; 126.6; 127.3; 128.2; 128.6; 128.8; 128.9; 129.7; 130.8; 133.3; 133.6; 138.9; 150.5; 180.2. Found, *m/z*: 455.1522 $[M+H]^+$. $C_{28}H_{24}ClN_2O_2$. Calculated, *m/z*: 455.1521.

3'-(4-Chlorophenyl)-4'-(4-fluorophenyl)-2'-phenyl-5,6-dihydro-8*H*-spiro[indolizine-7,5'-isoxazolidin]-8-one (3j). Yield 208 mg (44%), white solid, mp 229–231°C. IR spectrum, ν, cm^{-1}: 1658, 1598, 1527, 1488, 1396, 1187, 1069, 941, 759, 700. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.84 (1H, ddd, *J* = 14.0, *J* = 12.5, *J* = 5.0, CH_2); 2.13 (1H, dt, *J* = 14.0, *J* = 3.0, CH_2); 4.00 (1H, ddd, *J* = 12.5, *J* = 5.0, *J* = 2.0, CH_2); 4.43 (1H, td, *J* = 12.5, *J* = 3.0, CH_2); 4.79 (1H, d, *J* = 10.0, CH); 5.01 (1H, d, *J* = 10.0, CH); 6.29 (1H, dd, *J* = 4.0, *J* = 2.5, H pyrrole); 6.85 (1H, t, *J* = 1.5, H pyrrole); 6.92–6.94 (2H, m, H pyrrole, H Ar); 6.95–7.02 (3H, m, H Ar); 7.15–7.16 (1H, m, H Ar); 7.18–7.22 (2H, m, H Ar); 7.27–7.31 (4H, m, H Ar); 7.42–7.44 (2H, m, H Ar). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 30.9; 41.4; 59.0; 73.9; 83.0; 111.5; 115.7 (d, *J* = 21.0); 116.2; 116.7; 122.8; 126.5; 128.6; 128.7; 129.0; 129.6; 130.4 (d, *J* = 3.0); 131.0 (d, *J* = 8.0); 133.8; 137.6; 150.1; 163.3 (d, *J* = 246.0); 180.3. Found, *m/z*: 473.1424 $[M+H]^+$. $C_{28}H_{23}ClFN_2O_2$. Calculated, *m/z*: 473.1427.

4'-(4-Bromophenyl)-2'-phenyl-3'-(*p*-tolyl)-5,6-dihydro-8*H*-spiro[indolizine-7,5'-isoxazolidin]-8-one (3k). Yield 251 mg (49%), white solid, mp 229–231°C. IR spectrum, ν, cm^{-1}: 1655, 1596, 1527, 1488, 1396, 1186, 1067, 943, 760, 696. ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.83 (1H, ddd, *J* = 14.0, *J* = 12.5, *J* = 5.0, CH_2); 2.13 (1H, dt, *J* = 14.0, *J* = 2.5, CH_2); 2.29 (3H, s, CH_3); 3.98 (1H, ddd, *J* = 12.5, *J* = 5.0, *J* = 2.0, CH_2); 4.43 (1H, td, *J* = 12.5, *J* = 3.0, CH_2); 4.81 (1H, d, *J* = 10.0, CH); 5.08 (1H, d, *J* = 10.0, CH); 6.28 (1H, dd, *J* = 4.0, *J* = 2.0, H pyrrole); 6.84 (1H, t, *J* = 1.5, H pyrrole); 6.92–6.94 (3H, m, H pyrrole, H Ar); 7.09–7.10 (2H, m, H Ar); 7.14–7.21 (5H, m, H Ar); 7.36–7.41 (4H, m, H Ar). ^{13}C NMR spectrum, δ, ppm: 21.1; 30.9; 41.4; 59.0; 73.7; 82.9; 111.4; 116.1; 116.7; 121.7; 122.5; 126.6; 127.3; 128.6; 129.5; 129.7; 131.1; 131.8; 134.0; 135.7; 137.8; 150.5; 180.3. Found, *m/z*: 513.1176 $[M+H]^+$. $C_{29}H_{26}BrN_2O_2$. Calculated, *m/z*: 513.1172.

X-ray structural analysis of compound 3e. A suitable crystal was obtained by slow diffusion of hexane into a solution of compound **3e** in EtOAc. Single crystal X-ray crystallographic data were collected on a Bruker Apex II CCD diffractometer with monochromatic MoKα radiation (λ 0.71073 Å) at 296(2) K. The data set was integrated and reduced applying the SAINT program with absorption and

scaling correction being undertaken with the SADABS program. The structure was resolved by the direct method, all non-hydrogen atoms were refined by the full-matrix least-square procedure on F^2 using the SHELXL-2014 program set in conjunction with the Olex2 program.[27] Crystal data for compound **3e**: $C_{29}H_{25}ClN_2O_2$, M_r 468.96, monoclinic space group *P*2*yn*; *a* 13.2609(15), *b* 11.7853(14), *c* 15.4849(18) Å; β 94.116(2)°; *V* 2413.8(5) Å^3; *T* 296 (2) K; *Z* 4; d_{calc} 1.290 g·cm^{-3}; μ 0.187 mm^{-1}; *F*(000) 984; R_{int} 0.0394, 4247 reflections, 2991 with $I > 2\sigma(I)$ for 308 parameters, *GOF* 1.024, R_1 0.0406, wR_2 0.0987 ($I > 2\sigma(I)$) and R_1 0.0648, wR_2 0.1133 (all data). The complete crystallogrpahic dataset was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1983953).

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