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Synthesis, photophysical, and electrochemical properties of 2,5-diaryl-indolizines

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ABSTRACT

A variety of novel 2,5-diaryl-indolizines have been prepared through the palladium-catalyzed cross-coupling reactions of organozinc reagents prepared from 2-aryl-indolizines with aromatic halides. The photophysical properties of representative compounds indicate that the 2,5-diaryl-indolizines are promising candidates to be used in optoelectronic devices and biomolecular labeling. In addition, cyclic voltammetry studies of some nitrophenyl-substituted indolizines have shown evidences of an oxidation process without the correspondent reduction peak suggesting a dimerization reaction.

1. Introduction

The synthesis of fluorescent π-conjugated molecules has received considerable attention since these molecules can be used as electroluminescent material for optoelectronic devices,[1] dyes,[2] sensors,[3] and biomarkers.[4] Indolizines are 10 π-electron aromatic *N*-heterocyclic compounds, which are π-isoelectronic with azulene and naphthalene.[5] Furthermore, they present interesting pharmacological effects.[6] For example, they can function as anti-inflammatory agents,[6b,c] calcium entry blockers,[6d,e] antileishmania,[6f] antiviral,[6g] and anti-tuberculosis agents.[6h,i] Due to their strong fluorescence in the UV–visible region, the photophysical properties of some indolizines have already been reported.[3b,4a,7] In contrast, only a few electrochemical properties of indolizines have been described so far. For example, Troll and co-workers[8] have studied the electrochemical synthesis of substituted indolizines. They have found that, from cyclic voltammetry data in acetonitrile media, oxidation peak is only reversible if there is a substituent at C-1, indicating that the dimerization of the cation radical occurs at this position. It is also known that there is an oxidative dimerization on C-3.[9]

Despite the fact that the aromatic ring of indolizines has a high electron density, some of them can also be reduced electrochemically. Some derivatives have shown a reduction peak around −2.5 V (vs SCE) and a return peak suggesting a reversible charge transfer.[8] The electrochemical studies of biological active indolizines suggested that some of them may inhibit lipid peroxidation by an electron transfer mechanism.[10] Henry and co-workers have proposed a mechanism of electro oxidation of indolizine combining electrochemical, spectroscopic, and computational studies characterizing the plausible products from the oxidation process.[11]

As a consequence of their importance in many research fields, there is a growing interest on the synthesis of indolizine derivatives. Although many synthetic methods being available in the literature,[12] a frequently employed approach is the 1,3-dipolar cycloaddition of pyridinium ylides with electron-deficient alkenes and alkynes.[12h,i] The electrophilic aromatic substitution of indolizines has been widely investigated and it was established that the position C-3 is the most reactive of the indolizinyl ring.[13] Moreover, application of metal-mediated C–H bond functionalization strategies also afforded C-3 substituted indolizines as main products.[14] On the other hand, pioneering studies on the lithiation of 2-phenyl-indolizine performed by Rernard and Gubin have shown that the hydrogen at C-5 is the most acidic of the ring.[15] Further reactions of the lithiated indolizine with different electrophiles led to the preparation of the functionalized derivatives in good yields. Babaev and co-workers have improved the lithiation protocol[16] and applied this strategy for the synthesis of haloindolizines that were

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further submitted to palladium-catalyzed cross-coupling reactions with boronic acids.[17]

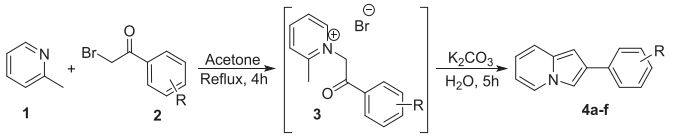
Following our interest in the functionalization of aromatic and heterocyclic compounds using organometallic reagents, herein we report the application of the Negishi cross-coupling approach in the preparation of 2,5-diaryl-indolizines. In addition, the photophysical and electrochemical properties of representative new compounds are discussed. In view of the wide application in biological and technological areas, studies that relate the structure of the fluorophore with their photophysical and electrochemical properties are relevant and justify the efforts to modify molecules by introducing different substituents on the skeleton of the fluorophore.

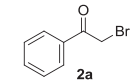
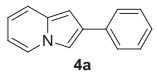
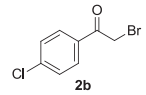
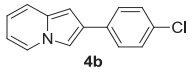
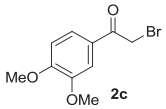
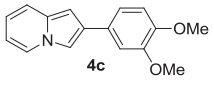
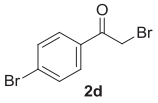
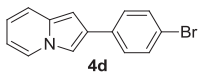
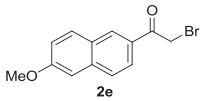
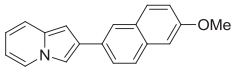
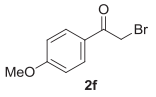
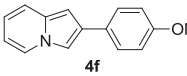
2. Results and discussion

2.1. Synthesis of 2,5-diaryl-indolizines

We initiated our study by applying the Tschitschibabin approach to the synthesis of 2-aryl-indolizines of type **4**. Thus, the reaction of 2-picoline with a number of α-bromo-ketones (**2a**–**f**)[18] led to the expected quaternary pyridinium halides **3**. An intramolecular condensation of **3** mediated by potassium carbonate followed by crystallization afforded indolizines **4a**–**f** from moderate to good yields and with high purity (Table 1).

Table 1
Preparation of 2-aryl-indolizines **4a**–**f**.



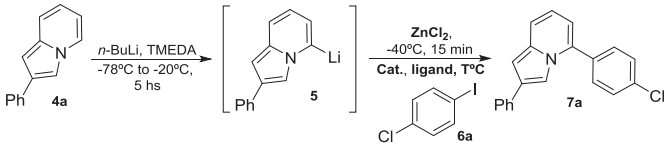
Entry	α-Bromo-ketone (**2**)	Product (**4**)	Yield[a] (%)
1	 **2a**	 **4a**	65
2	 **2b**	 **4b**	89
3	 **2c**	 **4c**	70
4	 **2d**	 **4d**	90
5	 **2e**	 **4e**	60
6	 **2f**	 **4f**	85

[a] Isolated yield.

Palladium-catalyzed coupling reactions are among the most important reactions for the functionalization of aromatics and heterocyclic substrates and have already been successfully used for the functionalization of haloindolizines.[14a,16,19] In our approach to 2,5-diaryl-indolizines, we have investigated the application of Negishi cross-coupling reaction for the arylation and heteroarylation of the position C-5 of the indolizinyl ring.

Aiming to find the best reaction conditions for the Negishi reaction, we have chosen the 2-phenyl-indolizine (**4a**) as a model substrate. Lithiation of **4a** was performed with *n*-BuLi/TMEDA at −20 °C for 5 h. After that, some catalysts and reaction conditions were screened for the cross-coupling reaction. Thus, in the first experiment, after a transmetallation with zinc chloride, a mixture of $Pd_2(dba)_3$ (0.8 mol %) and P(*o*-furyl)$_3$ (1.6 mol %) in THF was added, followed by the addition of 1-chloro-4-iodobenzene (**6a**). The reaction temperature was increased to 25 °C and the mixture was allowed under stirring for 12 h, affording indolizine **7a** in only 17% conversion (Table 2, entry 1). When the cross-coupling reaction was performed at 60 °C, the conversion increased to 92% (Table 2, entry 2). In contrast, when the amounts of the catalyst and the ligand were increased to 2 and 4 mol %, respectively, the yield of **7a** decreased to 50% and the homocoupling product from **6a** (4,4′-dichloro-1,1′-biphenyl) was observed to a large extent (Table 2, entry 3). On the other hand, using reaction conditions as presented in entry 2, the cross-coupling reaction catalyzed by $Pd(PPh_3)_4$ (0.8 mol %) yielded compound **7a** with 94% conversion (Table 2, entry 4). Other palladium catalyst such as $PdCl_2(PPh_3)_2$, $PdCl_2$, and $Pd(OAc)_2$ were also evaluated but the reactions did not present better results than $Pd(PPh_3)_4$ (Table 2, entries 5–8).

Table 2
Screening for the preparation of indolizine **7a**



Entry	Catalyst/mol (%)	Ligand/mol (%)	*T* (°C)	**7a**[a] (%)
1	$Pd_2(dba)_3$/0.8	P(*o*-furyl)$_3$/1.6	25	17
2	$Pd_2(dba)_3$/0.8	P(*o*-furyl)$_3$/1.6	60	92
3	$Pd_2(dba)_3$/2	P(*o*-furyl)$_3$/4.0	60	50
4	$Pd(PPh_3)_4$/0.8	—	60	94
5	$PdCl_2(PPh_3)_2$/0.8	P(*o*-furyl)$_3$/1.6	60	90
6	$PdCl_2$/0.8	P(*o*-furyl)$_3$/1.6	60	65
7	$Pd(OAc)_2$/0.8	P(*o*-furyl)$_3$/1.6	60	71
8	$Pd_2(dba)_3$/0.8	PPh_3/1.6	60	85

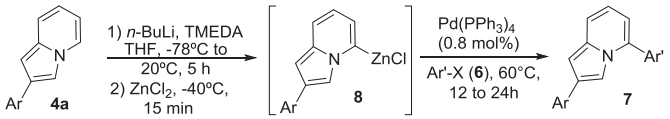
[a] Conversions determined by GC analysis.

As observed in Table 2, conditions used in entry 4 appeared to be the best for this reaction. After the purification step, the desired 5-(4-chlorophenyl)-2-phenyl-indolizine (**7a**) was obtained in 79% yield. Thus, a number of 2,5-diaryl-indolizines were synthesized in good yields through the cross-coupling reaction of organozinc reagents of type **8** with different halides catalyzed by $Pd(PPh_3)_4$ (Table 3).

Aromatic halides containing other withdrawing groups such as fluoro, trifluoromethyl, and nitro were also suitable substrates leading to the desired 5-aryl-2-phenyl-indolizines **7b**–**d** with yields ranging from 75% to 80% (Table 3, entries 2–4). The cross-coupling of **8** with iodobenzene (**6e**) also occurred in good yield as well as with aromatic halides substituted with electron-donating groups such as methyl and methoxy (Table 3, entries 5–8). Due to the steric hindrance, reactions of **8** with *ortho*-substituted iodines such as 1-iodo-2-methylbenzene (**6i**) and 1-iodo-2-methoxybenzene (**6j**) were slow and gave the desired products **7i** and **7j** in only moderate yields (Table 3, entries 9 and 10). Moreover, due to a competitive formation of homocoupling products from the corresponding heterocyclic halides,[20] the cross-coupling of **8** with heterocyclic substrates such as 2-bromothiophene (**6k**) and 2-bromopyridine (**6l**) gave the expected products **7k** and **7l** in 45% and 65% yields, respectively (Table 3, entries 11 and 12).

Additionally, using the same reaction conditions, we have synthesized 2,5-diaryl-indolizines through the cross-coupling of aromatic halides with organozinc reagents prepared from the 2-aryl-indolizines **4b**–**f**. As observed in Table 4, most of the desired

Table 3
Synthesis of 5-aryl-2-phenyl-indolizines



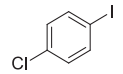
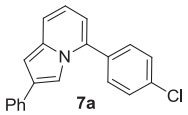
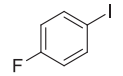
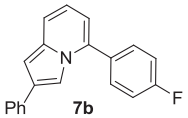
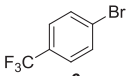
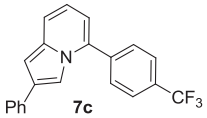
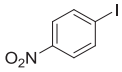
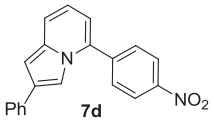
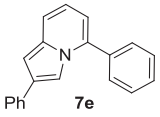
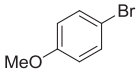
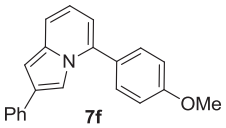
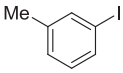
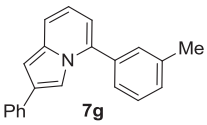
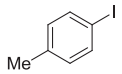
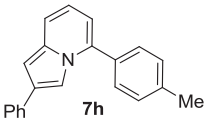
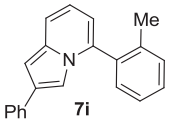
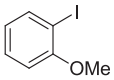
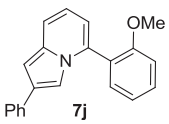
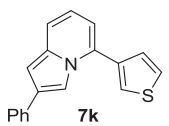
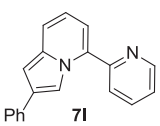
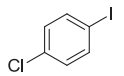
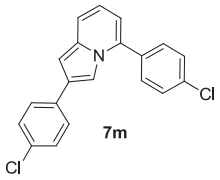
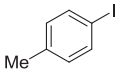
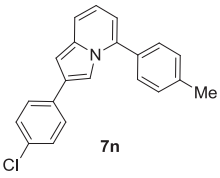
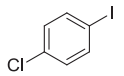
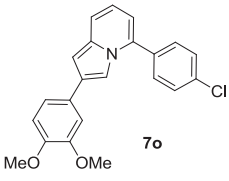
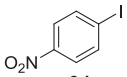
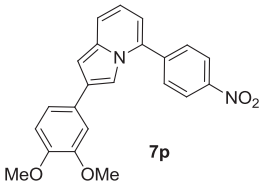
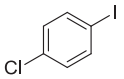
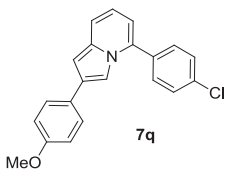
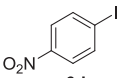
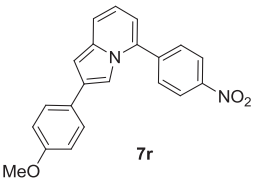
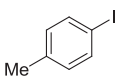
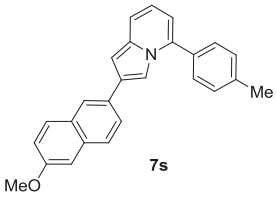
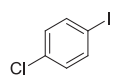
Entry	Halide (**6**)	Time (h)	Product (**7**)	Yield (%)
1	 **6a**	12	 **7a**	79
2	 **6b**	12	 **7b**	79
3	 **6c**	24	 **7c**	80
4	 **6d**	12	 **7d**	75
5	 **6e**	12	 **7e**	82
6	 **6f**	12	 **7f**	78
7	 **6g**	12	 **7g**	86
8	 **6h**	12	 **7h**	86
9	 **6i**	24	 **7i**	64
10	 **6j**	24	 **7j**	60
11	 **6k**	24	 **7k**	45
12	 **6l**	12	 **7l**	65

Table 4
Synthesis of 2,5-diaryl-indolizines

Entry	Halide (**6**)	Substituent (**4**)	Product (**7**)	Yield (%)
1	 **6a**	**4b**	 **7m**	68
2	 **6h**	**4b**	 **7n**	71
3	 **6a**	**4c**	 **7o**	70
4	 **6d**	**4c**	 **7p**	71
5	 **6a**	**4f**	 **7q**	79
6	 **6d**	**4f**	 **7r**	69
7	 **6h**	**4e**	 **7s**	65
8	 **6a**	**4d**	**7a**	35
9	**6h**	**4d**	**7h**	40

compounds were obtained in moderate to good yields. Interestingly, when the 2-(4-bromophenyl)indolizine (**4d**) was used as starting material in cross-coupling reactions with **6a** and **6h**, the 2,5-diaryl-indolizines **7a** and **7h** were isolated in poor yields due to a lithium–bromine exchange side reaction (Table 4, entries 8 and 9).

2.2. Photophysical properties

The photophysical properties of 17 representative compounds (**7a**–**k**, **7m**, **7n**, **7p**–**r**) were investigated by measuring absorption and emission spectra in DMSO, seeing as this solvent is largely used in biological protocols. In addition, some of the highest fluorescent compounds (**7a**, **7f**, **7k**, and **7m**) were also studied in other solvents of different polarities, such as chloroform and 1,4-dioxane, in order to evaluate their promising applications as optoelectronic devices. The 2,5-diaryl-indolizines have similar UV/vis spectral data, as summarized in Table 5, with the longest wavelength absorption changing from 350 to 382 nm (see Fig. S1—Supplementary data). Compounds **7d**, **7p**–**7r**, which sustain 4-nitrophenyl substituents on the C-5 of the indolizine skeleton, have their longest wavelength absorption maxima red-shifted to the 438–442 nm region of the spectrum. This bathochromic effect is attributed to the strong withdrawing character of the nitro group, which reduces considerably the LUMO energy of aromatic compounds.[21] The two lowest energy absorption bands for the most molecules are consistent with π–π* transition (λ_{Abs}∼325 nm) and n→π* transitions (λ_{Abs}∼375 nm), the last one with molar extinction coefficient values (ε) smaller than 10,000 $M^{-1}\,cm^{-1}$. All indolizines investigated are colored since they present maximum absorption in the visible region of the spectra (Table 5). Most of them show intense fluorescence at 450–500 nm when irradiated at the low energy absorption band (see Fig. 1 for representative compounds), as previously reported for other indolizine derivatives.[5a,8] The inset in Fig. 2 shows the normalized absorption, excitation, and emission spectra for one representative compound (**7a**). The similarity between absorption and excitation spectra suggests that only one species is populating the ground state and can be excited to emit fluorescence. Similar behavior was observed for all studied compounds (data not shown).

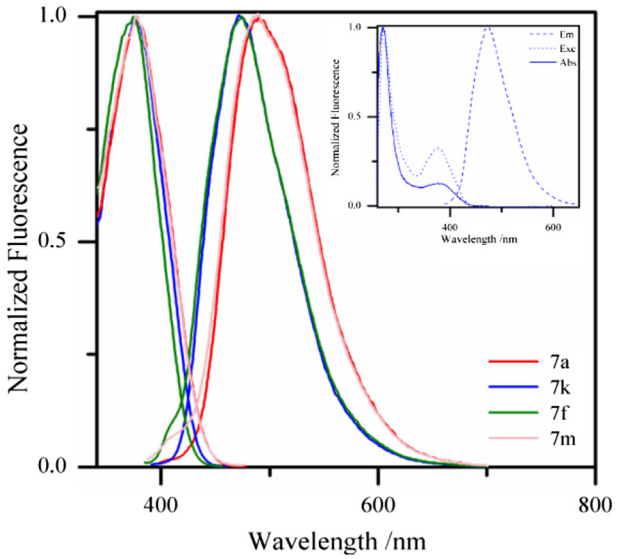


Fig. 1. Normalized fluorescence and excitation spectra of the representative compounds 2,5-diaryl-indolizines measured in DMSO. Excitation and emission slits were 10 nm and 3 nm, respectively. The samples (2.2 μM) were excited at the low energy wavelength of each compound (λ_{exc} changing from 320 nm to 442 nm). Inset: Absorption, excitation, and fluorescence of the compound **7a** in DMSO. A sample of 10 μM was used for the absorption spectrum.

red-shifted (Table S1—Supplementary data) as the solvent polarity increases (chloroform<1,4-dioxane<DMSO). Therefore, the emission color changes were not evident.

Fig. 2 shows the normalized fluorescence spectra, in solution, for some representative compounds, which show blue and green emission. It is evident that the wavelength emission is highly dependent on the substituents at the C-2 and C-5 position of the fluorophore core skeleton of the indolizines.

In addition, the electronic character (donor or withdrawing) of the substituents and the different position assumed on both phenyl rings of the 2,5-diaryl-indolizines **7** series, are crucial to define the fluorescence properties of these molecules. As seen in Table 5, for example, a strong bathochromic effect is observed when OCH_3 (electron donor), in **7f**, is substituted by CF_3 (electron-withdrawing) in **7c**.

Compounds **7a** and **7b**, 5-benzoyl-*p*-substituted with chloro and fluoro, respectively, showed small effect on the fluorescence

Table 5
Photophysical properties of 2,5-diaryl-indolizines **7** series measured in DMSO

Compound	λ_{Abs}/nm ($\varepsilon\times10^{-4}$/$M^{-1}\,cm^{-1}$)	λ_{em}/nm	$\Delta_{\lambda St}$/nm	Φ_F	τ_1/ns	τ_2/ns
7a	262 (2.16), 379 (0.21)	489	110	0.31	0.43±0.0.04 (2%)	12.56±0.02 (98%)
7b	263 (2.63), 321 (0.59), 375 (0.34)	480	105	0.48	—	—
7c	261 (1.69), 324 (0.74), 382 (0.18)	515	133	0.10	—	—
7d	263 (5.25), 347 (0.54), 442 (0.46)	510	68	—	—	—
7e	259 (1.83), 377 (0.22)	483	106	0.59		—
7f	264 (4.20), 376 (0.42)	474	107	0.85	1.22±0.04 (1%)	16.20±0.20 (99%)
7g	270 (2.23), 376 (0.26)	482	106	0.71	—	—
7h	259 (1.61), 327 (0.69), 375 (0.16)	475	100	0.084	—	—
7i	262 (2.20), 308 (0.22), 364 (0.33)	471	107	0.26	—	—
7j	263 (2.73), 356 (0.35)	474	118	0.78	—	—
7k	265 (1.84), 377 (0.20)	472	101	0.79	3.10±0.1 (3%)	14.9±0.02 (97%)
7l	278 (2.01), 326 (1.34), 395 (0.04)	517	122	0.58	—	—
7m	265 (4.00), 377 (0.50)	487	117	0.63	0.6±0.09 (1%)	12.44±0.02 (99%)
7n	264 (2.68), 350 (0.48)	477	127	0.090	—	—
7p	264 (3.17), 349 (0.49), 375 (0.34)	501	63	—	—	—
7q	267 (3.07), 335 (0.96), 400 (0.36)	491	91	0.18	—	—
7r	264 (2.99), 346 (0.52), 438 (0.31)	510	68	—	—	—

The Stokes shift for all of the compounds is high (∼90–133 nm), which suggests these compounds experience geometry changes in the excited state.

It is worth mentioning that the wavelength of maximum fluorescence emission of compounds **7a**, **7f**, **7k**, and **7m** are slightly

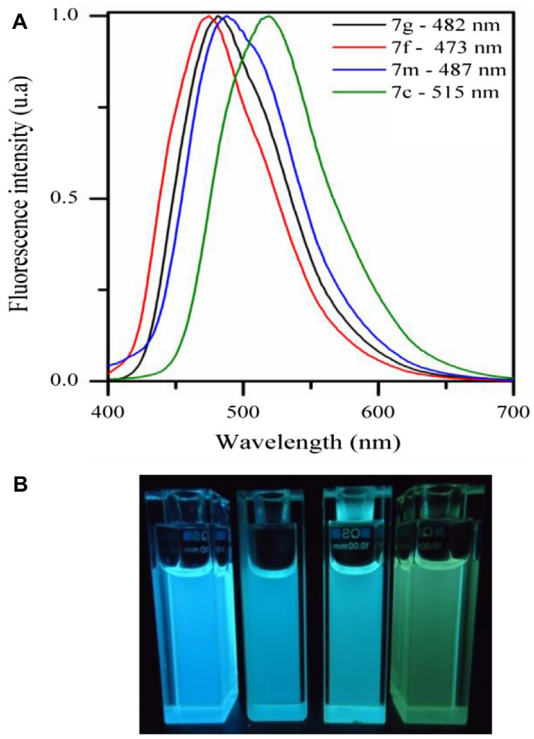


Fig. 2. (A) Normalized fluorescence emission of selected indolizines in DMSO. Excitation and emission slits were 10 nm and 3 nm, respectively. (B) Photoluminescence of indolizines in DMSO excited at 366 nm. From left to right: **7f**, **7g**, **7m**, and **7c**.

quantum yield (Φ_f=0.31–0.48, respectively) compared to compound **7e** (Φ_F=0.59) and similar fluorescence emission wavelength (480–489 nm). However, *p*-CF_3 substitution in **7c** compared to **7e** resulted in a marked reduction of the fluorescence quantum yield (Φ_F=0.1) and maximum emission shifted to longer wavelength (510 nm) due to the strong electron-withdrawing effect of the CF_3. Similar behavior was obtained for all analogs with nitro substituents, such as compounds **7d**, **7p**, and **7r**, which showed no fluorescence, consistent with other studies that also observed fluorescence quenching arising from the nitro group.[21,22] In contrast compound **7f**, carrying the electron-donating group, methoxy, at the *para*-position of the 5-phenyl ring of the indolizine resulted in higher quantum yield (Φ_F=0.85) compared to **7e** (Φ_F=0.59). Changing the OMe substituent from *para* to *ortho* position, no significant effect was observed in fluorescence (Φ_F=0.78) or in wavelength emission (λ_{em}=474 nm). Surprisingly, compounds **7g**, **7h**, and **7i** with methyl substituents at *ortho*, *para*, or *meta* position, respectively, showed different behaviors with stronger fluorescence for the *meta*-methyl-substituted compound (**7g**, Φ_F=0.71) followed by the *ortho* (**7i**) and *para* (**7h**) with Φ_F=0.26 and 0.084, respectively.

The insertion of a second electron-withdrawing substituent, such as chloride, at the *para*-position of the 2-phenyl ring of the indolizine (compound **7m**) resulted in fluorescence improvement compared to **7a**. In contrast, fluorescence quenching was observed when **7e** was, simultaneously, substituted by electron-donating and withdrawing substituents at the *para*-position of both aryl substituents of the indolizine (compounds **7n** and **7q**).

Finally, the substituent pyridine, on the C-5 of the indolizine (compound **7l**) caused no influence on the fluorescence quantum yield compared to **7e**, but its emission was bathochromically shifted to 517 nm. The increased π-conjugation extension arising from pyridine, associated with its planarity in relation to the indolizine skeleton, provides high electronic distribution through the orbitals and explain the substantial bathochromic shift.[23] On the other hand, when thiophenyl was used as substituent (compound **7k**), in spite of the π-conjugated system, an opposite behavior was observed in relation to **7e**, i.e., a higher quantum yield was obtained without significant deviation in the wavelength emission.

The fluorescence lifetime decays measured for compounds **7a**, **7f**, **7k**, and **7m**, (ϕ_f ranging from 0.3 to 0.85), were bi-exponential with lifetimes (τ_f) around 12–16 ns for the largest population (97–99%) (Table 5), which contributes mostly to the static fluorescence emission of the compounds (See also Fig. S4—Supplementary data). A small population (smaller than 3%) with lifetime between 1 and 3 ns was determined. This could be ascribed to a possible oxidation reaction, producing a dimer derivative similar to the other indolizines, which have shown an oxidation process followed by a dimerization reaction from electrochemical data. It is worth pointing out that the electrochemical results from the indolizines in this work have shown similar electrochemical profile. Moreover, this small population is not significant for the total static fluorescence emission observed for all indolizines. The lifetime results for the higher population (12–16 ns) are in the same range of magnitude as those found for other π-conjugated molecules, which were indicated as potential candidates for applications in electroluminescent devices.[23c]

2.3. Electrochemical properties

Cyclic voltammograms of the nitrophenyl-substituted indolizines **7d**, **7r**, and **7p** are shown in Fig. 3B–D, respectively. All of indolizines studied in this work have presented oxidation peak around 1.0 V (vs Ag/AgCl/KCl(sat)). The oxidations are irreversible

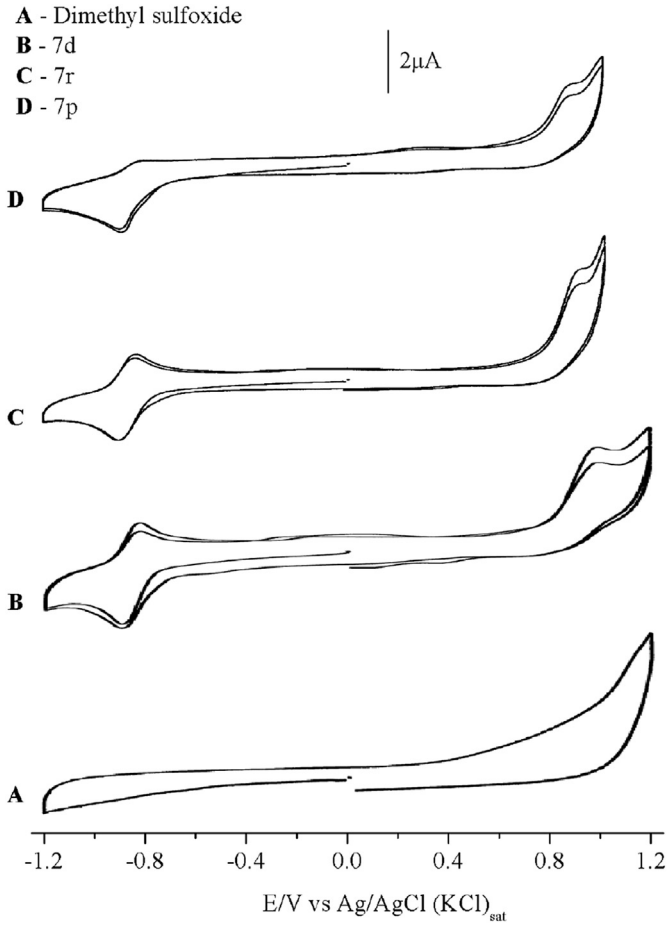


Fig. 3. Cyclic voltammograms of DMSO/TBAH 0.1 M solution (A) in presence of 0.5 mM of **7d** (B), 0.5 mM of **7r** (C), and 0.5 mM of **7p** (D). The scan rate was 100 mV/s, using a glassy carbon (area 0.0314 cm^2) as working electrode.

without the corresponding radical-cation reduction peaks being observed during the cathodic scan, suggesting an EC process. This behavior is similar to the electrochemical oxidations of the indolizine derivatives in which the irreversible oxidation of the 1-unsubstituted indolizines was caused by the dimerization of the cation radicals to afford the 1,1-bisindolizines.[8,10]

The electrochemical reduction behavior of these nitro derivative indolizines can be seen in Fig. 5. The effect of introducing methoxy as substituent in the 5-phenyl substituent group was not valuable and it has not produced a change in energy requirements of the nitro group reduction. On the other hand, the oxidation peak of the anion radical decreased with one methoxy (**7r**) (red line) and more significantly with two methoxy substituents (**7p**) (blue line). Possibly, this fact can be explained by the electron donation character of the methoxy substituent that acts increasing the electronic density on the nitro group. There was an interesting study about substituted nitroimidazole in aprotic medium. In this study, Yanez and co-workers[24] have stated that for new substituted 4-nitroimidazole derivatives the corresponding nitro radical anion decays faster than the nonsubstituted nitro radical. Following another studies from the same group, they have suggested that there are several possibilities for the chemical decay of the radical anion, which are: protonation, dimerization, dismutation, or father–son reactions.[25] Thus, the results in Fig. 4 would be in agreement with the results from the anion radical of nitroimidazoles. For the case of these indolizines, it is necessary further studies to suggest the electrochemical mechanism.

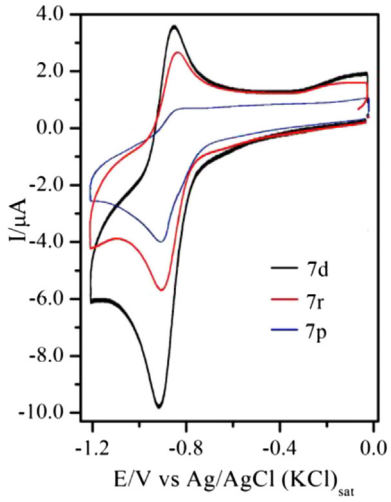


Fig. 4. Cyclic voltammograms of DMSO/TBAH 0.1 M solution in presence of 0.5 mM of **7d** (black line), 0.5 mM of **7r** (red line), and 0.5 mM of **7p** (blue line). The scan rate was 100 mV/s, using a glassy carbon (area 0.0314 cm^2) as working electrode.

Fig. 5 shows a cyclic voltammogram of a solution of TBAH/DMSO 0.1 M saturated with oxygen. The potentiodynamic profile (blue line) is in accordance with earlier work published,[26] which can be represented by Eq. 1:

$$O_2 + e^- \rightleftharpoons O_2^{-\cdot} \quad (1)$$

Cyclic voltammogram from the same solution after the addition of an aliquot of **7d** (red line) has shown that the presence of substrate slightly decreases the oxidation peak of superoxide and keeps the redox process almost the same compared with its behavior without $O_{2(g)}$ (black line). This behavior suggests that this indolizine is not so active with reactive species of oxygen such as superoxide.

On the other hand, introduction of a methoxy group into indolizine (**7d**), to give **7r**, does not change significantly the peak

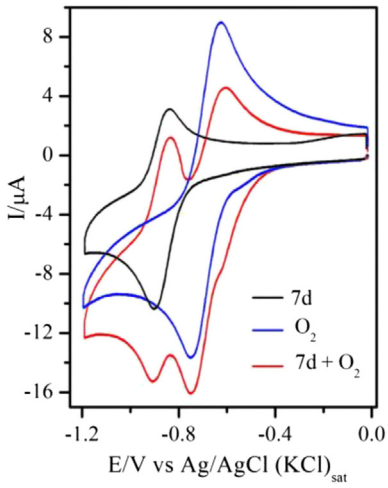


Fig. 5. Cyclic voltammograms of saturated O_2 in DMSO/TBAH 0.1 M solution in absence of indolizine (blue line), presence of 0.5 mM of **7d** and **7d** in absence of $O_{2(g)}$ at scan rate 100 mV/s, using a glassy carbon (area 0.0314 cm^2) as working electrode.

corresponding to the oxidation of superoxide to oxygen. However, the presence of a second methoxy group in **7p** diminishes the oxidation current markedly. It seems that the investigated indolizines in solution decrease the concentration of oxygen as attested by the lower current intensity (Figures in Supplementary data).

3. Conclusions

A variety of novel 2,5-diaryl-indolizines have been successfully prepared using palladium-catalyzed cross-coupling reactions of organozinc reagents prepared from 2-aryl-indolizines with aromatic halides. The photophysical properties of representative compounds of the 2,5-diaryl-indolizines **7** series indicate they are promising candidates to be used as optoelectronic devices and biomolecule labeling. These new compounds show strong blue-light fluorescence in the wavelength range of 471–490 nm with high quantum yields. Exception was observed for compound **7l**, bearing a pyridine substituent, responsible for the green-shifted to 517 nm. In general, electron-withdrawing substituents shifted the emission to higher wavelength, closer to the green region of the spectra. The simultaneous insertion of both electron donor and withdrawing substituents in the molecule decreases significantly the emission quantum yield. As expected, electrochemical results have shown that the oxidation process leads to a radical cation with a subsequent dimerization reaction. The nitrophenyl-substituted indolizines investigated have the stability of their anion radicals, generated by the reduction in aprotic medium, affected by the substituent of the indolizinyl ring. The experiments performed in the presence of oxygen have shown that these compounds are relatively nonsensitive to reactive oxygen species (ROS). Further studies will be conducted in order to investigate additional fluorescence and electrochemical properties of these new compounds. In addition, biological applications such as antiallergic potential, cytotoxicity, calcium influx inhibition, and cell imaging will also be investigated.

4. Experimental section

4.1. General

The solvents were purified according to standard procedures.[27] The starting materials were purchased from Sigma–Aldrich. All air-sensitive and/or water-sensitive reactions were carried out with dry solvents under anhydrous conditions and nitrogen atmosphere. Standard syringe techniques were applied for the

transfer of dry solvents and air-sensitive reagents. The reactions were monitored by TLC on Merck silica gel (60 F 254) by using UV light as a visualizing agent and 5% vanillin in 10% H_2SO_4 with heating as a developing agent. Sigma–Aldrich silica gel (particle size 0.040–0.063 nm) was used for flash chromatography. NMR spectra were recorded with a Bruker DPX 300, 400, and 500 (at 300, 400, and 500 MHz for protons and 75, 100, and 125 MHz for carbon-13, respectively) instrument while using $CDCl_3$, DMSO-d_6, or pyr-d_5 as solvent. The chemical shifts are reported as δ units in parts per million (ppm) relative to the solvent residual peak as the internal reference. Infrared (IR) spectra of all synthesized compounds were recorded on Perkin–Elmer mod.1420 in KBr pellets, the frequencies are given in cm^{-1}. Mass spectra (MS) were measured with Shimadzu GC–MS-QP2010 mass spectrometer. HRMS spectra were measured with a Bruker Daltonics micrOTOF QII/ESI-TOF.

4.2. Procedures

*4.2.1. General procedure for the preparation of **4a**–**f**.* A solution of 2-picoline (**1**) (20 mmol; 1.86 g; 2 mL) and α-bromo-ketone (**2**) (20 mmol) in acetone (100 mL) was heated at reflux for 4 h. The quaternary salt was isolated via filtration and re-dissolved in hot (60–80 °C) water (100 mL). K_2CO_3 (2.76 g; 20 mmol) was added and the mixture heated at 80 °C for 8 h. After filtration and drying in vacuum, the products of type **4** were obtained.

*4.2.1.1. 2-Phenyl-indolizine (**4a**).* From α-bromo-ketone (**2a**) (3.98 g, 20 mmol); yield: 2.51 g (65%); white solid; mp 218–220 °C (lit.[28] mp 214–215 °C); IR (cm^{-1}): 3101, 3072, 3028, 1514, 1454, 759, 690. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, J_1=6.9 Hz, J_2=1.2 Hz, 1H), 7.58–7.55 (m, 2H), 7.49 (d, J=12 Hz, 1H), 7.32–7.27 (m, 3H), 7.19–7.13 (m, 1H), 6.6 (s, 1H), 6.56 (ddd, J_1=9.0 Hz, J_2=6.3 Hz, J_3=0.9 Hz, 1H), 6.36 (dt, J_1=6.6 Hz, J_2=12 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.37, 133.6, 129.4, 128.7 (2C), 126.5, 126.2 (2C), 125.0, 119.0, 117.3, 110.5, 109.2, 96.6; MS (ESI, 70 eV) m/z 193 (M^+, 100%), 165 (15%), 115 (20%), 83 (10%), 77 (5%), 52 (2%). HRMS (ESI) m/z 194.0966 ($[M+H]^+$ calcd for $C_{14}H_{11}N$: 194.0964).

*4.2.1.2. 2-(4-Chlorophenyl)indolizine (**4b**).* From α-bromo-ketone (**2b**) (4.66 g, 20 mmol); yield: 4.05 g (89%); white solid; mp 220 °C (dec) (lit.[29] mp 240–242 °C); IR (KBr): 3079, 3028, 1598, 1467, 1090, 780, 690; ^{1}H NMR (400 MHz, pyr-d_5) δ 8.0 (dd, J_1=6.8 Hz, J_2=0.8 Hz, 1H), 7.79 (s, 1H), 7.72 (d, J=8.4 Hz, 2H), 7.43–7.38 (m, 3H), 6.82 (s, 1H), 6.63 (t, J=6.8 Hz, 1H), 6.41 (t, J=6.4 Hz, 1H). ^{13}C NMR (100 MHz, pyr-d_5) δ 134.0, 133.4, 132.3, 129.4, 128.9 (2C), 127.4 (2C), 125.2, 119.1, 117.8, 110.8, 109.0, 96.8. MS (ESI, 70 eV) m/z 229 (32%), 227 (M^+, 100%), 192 (15%), 165 (10%), 95 (17%), 63 (6%). HRMS (ESI) m/z 228.0593 ($[M+H]^+$ calcd for $C_{14}H_{10}ClN$: 228.0575).

*4.2.1.3. 2-(3,4-Dimethoxyphenyl)indolizine (**4c**).* From α-bromo-ketone (**2c**) (5.18 g, 20 mmol); yield: 3.54 g (70%); white solid; mp 165–167 °C (lit.[30] mp 179 °C); IR (KBr): 3099, 2954, 2837, 1516, 1450, 1259, 1024, 775; ^{1}H NMR (400 MHz, pyr-d_5) δ 7.90 (d, J=6.8 Hz, 1H), 7.43 (s, 1H), 7.36–7.29 (m, 3H), 6.9 (d, J=8 Hz, 1H), 6.78 (s, 1H), 6.52 (t, J=6.4 Hz, 1H), 6.29 (t, J=6.8 Hz, 1H), 3.71 (s, 3H), 3.64 (s, 3H). ^{13}C NMR (100 MHz, pyr-d_5) δ 150.2, 149.0, 133.9, 129.9, 129.1, 125.6, 119.1, 118.9, 117.6, 113.0, 110.8, 110.6, 109.8, 97.0, 55.95, 55.90. MS (ESI, 70 eV) m/z 253 (M^+, 100%), 238 (32%), 210 (32%), 192 (20%), 180 (15%), 167 (33%), 117 (12%). HRMS (ESI) m/z 254.1176 ($[M+H]^+$ calcd for $C_{16}H_{15}NO_2$: 254.1176).

*4.2.1.4. 2-(4-Bromophenyl)indolizine (**4d**).* From α-bromo-ketone (**2d**) (5.55 g, 20 mmol); yield: 4.89 g (90%); white solid; mp 221–223 °C (lit.[1] mp 233–236 °C). IR (KBr): 3107, 3080, 1508, 1456, 1298, 775, 729. ^{1}H NMR (400 MHz, pyr-d_5) δ 7.96 (d, J=6.6 Hz, 1H), 7.75 (s, 1H), 7.62–7.60 (m, 2H), 7.52–7.50 (m, 2H), 7.34 (d, J=8.4 Hz, 1H), 6.76 (s, 1H), 6.57 (t, J=7.6 Hz, 1H), 6.36 (t, J=6.6 Hz, 1H). ^{13}C NMR (pyr-d_5, 100 MHz) δ 135.1, 134.04, 132.1 (2C), 128.2, 128.1 (2C), 125.7, 120.3, 119.3, 118.0, 111.0, 110.3, 97.0. MS (ESI, 70 eV) m/z 273 (95%), 271 (M^+, 100%), 191 (77%), 164 (12%), 136 (10%), 95 (65%), 77 (3%). HRMS (ESI) m/z 272.0069 ($[M+H]^+$ calcd for $C_{14}H_{10}BrN$: 272.0069).

*4.2.1.5. 2-(6-Methoxynaphthalen-2-yl)indolizine (**4e**).* From α-bromo-ketone (**2e**) (5.58 g, 20 mmol); yield: 3.27 g (60%); yellow solid; mp 225 °C (dec); IR (KBr): 3078, 3002, 1599, 1511, 1246, 1036, 790, 726. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.80–7.74 (m, 1H), 7.69–7.67 (m, 2H), 7.31 (t, J=5.9 Hz, 1H), 7.20–7.17 (m, 3H), 7.08–7.05 (m, 2H), 6.72–6.65 (m, 1H), 6.48–6.43 (m, 1H), 3.85 (s, 3H); HRMS (ESI) m/z 274.1221 ($[M+H]^+$ calcd for $C_{19}H_{15}NO$: 274.1232).

*4.2.1.6. 2-(4-Methoxyphenyl)indolizine (**4f**).* From α-bromo-ketone (**2f**) (4.58 g, 20 mmol); yield: 3.79 (85%); white solid; mp 187 °C (dec) (lit.[31] mp 184 °C); IR (KBr): 3090, 3007, 1608, 1521, 1244, 1031, 781, 731; ^{1}H NMR (400 MHz, pyr-d_5) δ 7.90 (d, J=6.4 Hz, 1H), 7.28 (d, J=8.8 Hz, 1H), 6.94 (d, J=8.4 Hz, 2H), 6.74 (s, 1H), 6.50 (t, J=6.4 Hz, 1H), 6.27 (t, J=6.8 Hz, 1H), 3.56 (s, 3H). ^{13}C NMR (100 MHz, pyr-d_5) δ 159.0, 133.9, 129.6, 128.5, 127.6 (2C), 125.6, 119.0, 117.6, 114.7 (2C), 110.5, 109.5, 96.8, 55.1. MS (ESI, 70 eV) m/z 223 (M^+, 100%), 208 (54%), 180 (32%), 152 (17%), 89 (5%), 77 (10%). HRMS (ESI) m/z 224.1075 ($[M+H]^+$ calcd for $C_{15}H_{13}NO$: 224.1070).

*4.2.2. General procedure for the preparation of (**7a**–**7s**).* To a 25-mL round-bottom flask equipped with a magnetic stirring bar and a septum under a nitrogen atmosphere was added a solution of the corresponding 2-aryl-indolizine (0.5 mmol) and TMEDA (1 mmol) in THF (6 mL). This solution was cooled to −78 °C and *n*-BuLi (1.0 mmol; 2 equiv; C=2.47 mol/L) was added dropwisely. After the addition was complete, the reaction mixture was warmed to −20 °C and stirred at this temperature for 5 h. Then, this solution was cooled to −40 °C and a solution of $ZnCl_2$ in THF was added (1 M, 0.5 mmol, 0.5 mL). After 15 min, a solution of $Pd(PPh_3)_4$ (0.8 mol %, 4.5 mg) in THF (1 mL) and a solution of corresponding aryl halide RX (1 mmol, 2 equiv) were added and stirred at 60 °C overnight. The reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with AcOEt (3×40 mL). The solvent was evaporated under vacuum. The crude product was purified by means of chemically active extraction. Firstly the crude product was solubilized with 50 mL of AcOEt and extracted with an aqueous solution of 5 M HCl (50 mL). The aqueous phase was neutralized with a solution of $NaHCO_3$ until pH 7 and extracted with AcOEt (3×30 mL). Then, the organic phase was extracted with aqueous solution of HCl 10% (50 mL). Finally, the combined organic phases were collected and washed with saturated aqueous $NaHCO_3$ and dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under vacuum to give the product.

*4.2.2.1. 5-(4-Chlorophenyl)-2-phenyl-indolizine (**7a**).* From 2-aryl-indolizine (**4a**) (96.5 mg, 0.5 mmol) and 1-chloro-4-iodobenzene (**6a**) (238.45 mg, 1 mmol); yield: 120 mg (79%); dark green solid; mp 101–103 °C; IR (KBr): 3066, 2962, 1597, 1487, 1091, 786, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.55 (m, 5H), 7.51–7.48 (m, 2H), 7.38–7.32 (m, 3H), 7.24–7.20 (m, 1H), 6.80 (d, J=1.48 Hz, 1H), 6.74 (dd, J_1=9.0 Hz, J_2=6.6 Hz, 1H), 6.37 (dd, J_1=6.6 Hz, J_2=1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 135.2, 135.1, 134.8, 133.8, 129.9 (2C), 129.5 (2C), 129.4, 128.7 (2C), 118.5, 117.8, 111.6, 107.7, 97.6. MS (ESI, 70 eV) m/z 303 (M^+, 100%), 236 (3%),

267 (63%), 191 (10%), 115 (3%), 77 (3%). HRMS (ESI) *m*/*z* 304.0884 ([M+H]$^+$ calcd for $C_{20}H_{14}ClN$: 304.0888).

*4.2.2.2. 5-(4-Fluorophenyl)-2-phenyl-indolizine (**7b**).* From 2-aryl-indolizine (**4a**) (96.5 mg, 0.5 mmol) and 4-fluoroiodobenzene (**6b**) (222 mg, 1 mmol); yield: 113 mg (79%); dark green solid; mp 101–103 °C; IR (KBr): 3070, 3030, 1602, 1502, 1222, 767, 692; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63–7.58 (m, 4H), 7.54 (s, 1H), 7.38–7.33 (m, 3H), 7.23–7.20 (m, 3H), 6.80 (s, 1H), 6.75 (t, J=8.0 Hz, 1H), 6.38 (d, J=6.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9 (d, J_1=247.6 Hz, C–F), 135.7, 135.1, 134.8, 131.4 (d, J_4=3.3 Hz, C–F), 130.4 (d, J_3=8.1 Hz, C–F), 129.2, 129.0, 128.6 (2C), 128.0, 126.5, 126.1 (2C), 118.2, 117.8, 116.1 (d, J_2=21.5 Hz, C–F), 111.4, 107.6, 97; MS (ESI, 70 eV) *m*/*z* 287 (M$^+$, 100%), 268 (1%), 209 (16%), 142 (5%), 77 (3%); HRMS (ESI) *m*/*z* 288.1179 ([M+H]$^+$ calcd for $C_{20}H_{14}FN$: 288.1183).

*4.2.2.3. 2-Phenyl-5-(4-(trifluoromethyl)phenyl)indolizine (**7c**).* From 2-aryl-indolizine (**4a**) (96.5 mg, 0.5 mmol) and 4-bromobenzotrifluoride (**6c**) (225 mg, 1 mmol); yield: 134 mg (80%); dark green solid; mp 124–126 °C (lit.[4] mp 129–131 °C); IR (cm^{-1}): 3072, 3032, 1616, 1429, 1327, 771, 696. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84–7.80 (m, 4H), 7.64–7.61 (m, 3H), 7.44–7.37 (m, 3H), 7.28–7.25 (m, 1H), 6.86 (s, 1H), 6.80 (t, J=7.5 Hz, 1H), 6.45 (d, J=6.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9, 135.1, 134.9, 134.8, 131.1 (q, J=32.8, C–F), 129.5, 128.8 (2C), 128.0, 127.8, 126.6, 126.16 (2C), 126.1, 118.8, 117.7, 111.9, 107.6, 97.8. MS (ESI, 70 eV) *m*/*z* 337 (M$^+$, 100%), 260 (15%), 192 (7%), 145 (3%), 115 (2%), 77 (35%). HRMS (ESI) *m*/*z* 338.1159 ([M+H]$^+$ calcd for $C_{21}H_{14}F_3N$: 338.115).

*4.2.2.4. 5-(4-Nitrophenyl)-2-phenyl-indolizine (**7d**).* From 2-aryl-indolizine (**4a**) (96.5 mg, 0.5 mmol) and 1-iodo-4-nitrobenzene (**6d**) (249 mg, 1 mmol); yield: 117 mg (75%); dark red solid; mp 154–156 °C; IR (KBr): 3078, 3037, 2985, 1597, 1510, 1348, 860, 773, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J=8.8 Hz, 2H), 7.77 (d, J=8.8 Hz, 2H), 7.52–7.50 (m, 3H), 7.35 (d, J=8.9 Hz, 1H), 7.27 (t, J=7.4 Hz, 2H), 7.17–7.13 (m, 1H), 6.76 (d, J=1.6 Hz, 1H), 6.70 (dd, J_1=8.9 Hz, J_2=6.72 Hz, 1H), 6.38 (dd, J_1=6.7 Hz, J_2=1.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.9, 141.6, 134.8, 134.7, 134.2, 129.8, 129.2 (2C), 128.7 (2C), 126.7, 126.1 (2C), 124.4 (2C), 119.4, 117.6, 112.6, 107.5, 96.2. MS (ESI, 70 eV) *m*/*z* 314 (M$^+$, 100%), 284 (9%), 267 (50%), 241 (10%), 191 (25%), 132 (16%), 77 (5%). HRMS (ESI) *m*/*z* 315.1123 ([M+H]$^+$ calcd for $C_{20}H_{14}N_2O_2$: 315.1128).

*4.2.2.5. 2,5-Diphenyl-indolizine (**7e**).* From 2-aryl-indolizine (**4a**) (96.5 mg, 0.5 mmol) and iodobenzene (**6e**) (204 mg, 1 mmol); yield: 80 mg (60%); dark green solid; mp 96–98 °C (lit.[4] mp 92–94 °C); IR (KBr): 3057, 3028, 2990, 1600, 1487, 1446, 761, 698. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.59 (m, 5H), 7.54–7.48 (m, 3H), 7.38–7.32 (m, 2H), 7.23–7.19 (m, 1H), 6.79 (d, J=0.8 Hz, 1H), 6.75 (dd, J_1=9.0 Hz, J_2=6.8 Hz, 1H), 6.40 (dd, J_1=6.8 Hz, J_2=1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.7, 135.3, 135.2, 134.7, 129.1, 129.07, 129.03 (2C), 128.6 (2C), 128.4 (2C), 126.4, 126.1 (2C), 118.0, 117.9, 111.3, 107.8, 97.3. MS (ESI, 70 eV) *m*/*z* 269 (M$^+$, 100%), 191 (15%), 133 (6%), 127 (5%), 115 (3%), 77 (3%), 63 (3%). HRMS (ESI) *m*/*z* 270.1280 ([M+H]$^+$ calcd for $C_{20}H_{15}N$: 270.1277).

*4.2.2.6. 5-(4-Methoxyphenyl)-2-phenyl-indolizine (**7f**).* From 2-aryl-indolizine (**4a**) (96.5 mg, 0.5 mmol) and 4-bromoanisole (**6f**) (187 mg, 1 mmol); yield: 116 mg (78%); dark green solid; mp 139–141 °C (lit.[4] mp 146–148 °C); IR (KBr): 3076, 3008, 2933, 1606, 1502, 1247, 1026, 773, 698. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53–7.48 (m, 5H), 7.28–7.24 (m, 3H), 7.15–7.11 (m, 1H), 6.96 (d, J=8.7 Hz, 2H), 6.7 (s, 1H), 6.67 (dd, J_1=8.7 Hz, J_2=6.8 Hz, 1H), 6.29 (d, J=6.7 Hz, 1H), 3.8 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 136.6, 135.3, 132.1, 132.0, 129.8 (2C), 128.6 (2C), 127.7, 126.4, 126.1 (2C), 117.9, 117.7, 114.3 (2C), 111.1, 107.8, 97.2, 55.3. MS (ESI, 70 eV) *m*/*z* 299 (M$^+$, 100%), 284 (8%), 267 (5%), 254 (18%), 178 (8%), 77 (3%). HRMS (ESI) *m*/*z* 300.1384 ([M+H]$^+$ calcd for $C_{21}H_{17}NO$: 300.1383).

*4.2.2.7. 2-Phenyl-5-(m-tolyl)indolizine (**7g**).* From 2-aryl-indolizine (**4a**) (96.5 mg, 0.5 mmol) and 3-iodotoluene (**6g**) (218 mg, 1 mmol); yield: 121 mg (86%); dark green solid; mp 101–103 °C; IR (KBr): 3064, 3068, 2962, 2922, 1602, 1483, 781, 767, 698; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.6 (dd, J_1=10.5 Hz, J_2=1.5 Hz, 2H), 7.46–7.29 (m, 8H), 7.23–7.19 (m, 1H), 6.79–6.74 (m, 2H), 6.4 (d, J=8.0 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 136.3, 135.3, 134.6, 134.2, 130.5, 129.9, 129.3, 129.2, 128.6 (2C), 126.43, 126.41 (2C), 117.8, 117.6, 111.1, 108.0, 97.0, 19.0. MS (ESI, 70 eV) *m*/*z* 283 (M$^+$, 100%), 267 (31%), 206 (35), 191 (5%), 91 (15%), 77 (2%). HRMS (ESI) *m*/*z* 284.1437 ([M+H]$^+$ calcd for $C_{21}H_{17}N$: 284.1434).

*4.2.2.8. 2-Phenyl-5-(p-tolyl)indolizine (**7h**).* From 2-aryl-indolizine (**4a**) (96.5 mg, 0.5 mmol) and 4-iodotoluene (**6h**) (218 mg, 1 mmol); yield: 121 mg (86%); dark green solid; mp 100–102 °C; IR (KBr): 3062, 3030, 2947, 2920, 1560, 1452, 798, 698; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63–7.59 (m, 3H), 7.54 (d, J=8 Hz, 2H), 7.36–7.33 (m, 5H), 6.78 (d, J=1.5 Hz, 1H), 6.75 (dd, J_1=9.0 Hz, J_2=6.5 Hz, 1H), 6.38 (dd, J_1=7.0 Hz, J_2=1.0 Hz, 1H), 2.45 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 136.9, 135.3, 134.7, 132.5, 129.6 (2C), 128.9, 128.6 (2C), 128.3 (2C), 126.4, 126.1 (2C), 117.9, 117.8, 111.1, 107.9, 97.2, 21.4. MS (ESI, 70 eV) *m*/*z* 283 (M$^+$, 100%), 268 (27%), 206 (4%), 191 (9%), 91 (3%), 77 (2%). HRMS (ESI) *m*/*z* 284.1436 ([M+H]$^+$ calcd for $C_{21}H_{17}N$: 284.1434).

*4.2.2.9. 2-Phenyl-5-(o-tolyl)indolizine (**7i**).* From 2-aryl-indolizine (**4a**) (96.5 mg, 0.5 mmol) and 2-iodotoluene (**6i**) (218 mg, 1 mmol); yield: 90 mg (64%); dark green solid; mp 86–88 °C; IR (KBr): 3064, 2947, 2927, 1604, 1481, 761, 694; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.57 (d, J=7.5 Hz, 2H), 7.43–7.31 (m, 8H), 7.04 (s, 1H), 6.80 (d, J=1 Hz, 1H), 6.78 (dd, J_1=9.0 Hz, J_2=6.75 Hz, 1H), 6.38 (d, J=7 Hz, 1H), 2.15 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.2, 136.3, 135.3, 134.6, 134.2, 130.5, 129.9, 129.3, 129.2, 128.6 (2C), 126.43, 126.41, 126.1 (2C), 117.8, 117.6, 111.1, 108.05, 97.0, 19.0. MS (ESI, 70 eV) *m*/*z* 283 (M$^+$, 100%), 268 (25%), 206 (5%), 191 (7%), 91 (2%), 77 (4%). HRMS (ESI) *m*/*z* 284.1442 ([M+H]$^+$ calcd for $C_{21}H_{17}N$: 284.1434).

*4.2.2.10. 5-(2-Methoxyphenyl)-2-phenyl-indolizine (**7j**).* From 2-aryl-indolizine (**4a**) (96.5 mg, 0.5 mmol) and 2-iodoanisole (**6j**) (234 mg, 1 mmol); yield: 89 mg (60%); dark green solid; mp 98–100 °C; IR (KBr): 3074, 2999, 2935, 1598, 1487, 1269, 1024, 775, 694. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.57 (m, 2H), 7.48 (ddd, J_1=8.2 Hz, J_2=7.6 Hz, J_3=1.6 Hz, 1H), 7.39 (dd, J_1=7.6 Hz, J_2=1.6 Hz, 1H), 7.39–7.37 (m, 1H), 7.34–7.30 (m, 2H), 7.21–7.17 (m, 2H), 7.09 (td, J_1=7.6 Hz, J_2=1.2 Hz, 1H), 7.06–7.04 (m, 1H), 6.78 (d, J=2.0 Hz, 1H), 6.74 (dd, J_1=9.0 Hz, J_2=6.6 Hz, 1H), 6.43 (dd, J_1=6.8 Hz, J_2=1.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 135.6, 134.4, 134.1, 131.3, 128.6, 128.5 (2C), 126.2, 126.1 (2C), 124.9, 120.0, 117.9, 117.3, 111.7, 111.07, 108.7, 96.8, 55.4. MS (ESI, 70 eV) *m*/*z* 299 (M$^+$, 100%), 191 (13%), 284 (5%), 268 (84%), 222 (4%), 77 (4%). HRMS (ESI) *m*/*z* 300.1383 ([M+H]$^+$ calcd for $C_{21}H_{17}NO$: 300.1383).

*4.2.2.11. 2-Phenyl-5-(thiophen-3-yl)indolizine (**7k**).* From 2-aryl-indolizine (**4a**) (96.5 mg, 0.5 mmol) and 3-bromothiophene (**6k**) (163 mg, 1 mmol); yield: 61 mg (45%); dark green solid; mp 102–104 °C. IR (KBr): 3058, 3010, 2996, 1598, 1486, 1440, 761, 755, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.58–7.53 (m, 3H), 7.43–7.37 (m, 2H), 7.30–7.26 (m, 3H), 7.17–7.13 (m, 1H), 6.71 (s, 1H), 6.65 (dd, J_1=9.2 Hz, J_2=6.8 Hz, 1H), 6.42 (dd, J_1=6.4 Hz, J_2=1.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.8, 135.2, 134.8, 132.2, 129.2, 128.6 (2C), 127.1, 126.56, 126.51, 126.1 (2C), 124.9, 118.1, 117.6, 111.4,

108.1, 97.4; MS (ESI, 70 eV) *m/z* 275 (M^+, 100%), 237 (17%), 160 (22%), 116 (7%), 89 (10%), 77 (56%); HRMS (ESI) *m/z* 276.0840 ($[M+H]^+$ calcd for $C_{18}H_{13}NS$: 276.0841).

*4.2.2.12. 2-Phenyl-5-(pyridin-2-yl)indolizine (**7l**).* From 2-aryl-indolizine (**4a**) (96.5 mg, 0.5 mmol) and 2-bromopyridine (**6l**) (163 mg, 1 mmol); yield: 61 mg (45%); dark green solid; mp 80 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77–8.76 (m, 1H), 8.2 (s, 1H), 7.86 (td, J_1=8 Hz, J_2=2 Hz, 1H), 7.73 (d, J=8 Hz, 1H), 7.58 (dd, J_1=8.4 Hz, J_2=1.2 Hz, 2H), 7.40–7.35 (m, 2H), 7.31–7.27 (m, 2H), 7.18–7.14 (m, 1H), 6.77 (s, 1H), 6.74–6.70 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 149.4, 140.2, 138.1, 137.3, 133.3, 130.1, 128.8 (2C), 128.1 (2C), 127.8, 124.9, 122.1, 119.6, 117.0, 112.9, 109.2, 97.8. MS (ESI, 70 eV) *m/z* 270 (M^+, 5%), 193 (18%), 192 (12%), 115 (5%), 78 (9%), 77 (2%); HRMS (ESI) *m/z* 271.1239 ($[M+H]^+$ calcd for $C_{19}H_{14}N_2$: 271.1230).

*4.2.2.13. 2,5-Bis(4-chlorophenyl)indolizine (**7m**).* From 2-aryl-indolizine (**4b**) (114 mg, 0.5 mmol) and 1-chloro-4-iodobenzene (**6a**) (238.45 mg, 1 mmol); yield: 115 mg (68%); dark green solid; mp 80 °C (dec); IR (KBr): 3066, 2980, 1485, 1089, 785, 727; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J=8.4 Hz, 2H), 7.46–7.42 (m, 4H), 7.33–7.28 (m, 2H), 7.23 (d, J=8.8 Hz, 2H), 6.71–6.67 (m, 2H), 6.32 (d, J=6.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 135.2, 133.7, 132.2, 132.0, 129.9 (2C), 129.5 (2C), 129.0, 128.8 (2C), 128.2, 127.3 (2C), 118.5, 118.2, 111.8, 107.6, 97.6. MS (ESI, 70 eV) *m/z* 341 (11%), 339 (65%), 337 (M^+, 100%), 302 (20%), 265 (16%), 239 (5%), 191 (10%), 150 (7%), 77 (2%); HRMS (ESI) *m/z* 338.0507 ($[M+H]^+$ calcd for $C_{20}H_{13}Cl_2N$: 338.0498).

*4.2.2.14. 2-(4-Chlorophenyl)-5-(p-tolyl)indolizine (**7n**).* From 2-aryl-indolizine (**4b**) (114 mg, 0.5 mmol) and 4-iodotoluene (**6h**) (218 mg, 1 mmol); yield: 112 mg (71%); dark green solid; mp 92–94 °C; IR (KBr): 3057, 2927, 2866, 1608, 1502, 1091, 785, 729; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.37 (m, 5H), 7.25–7.19 (m, 5H), 7.14–7.13 (m, 1H), 6.69–6.65 (m, 2H), 6.31 (d, J=6.4 Hz, 1H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 136.9, 134.8, 133.8, 132.3, 131.9, 129.7 (2C), 128.6 (2C), 129.3 (2C), 127.7, 127.2 (2C), 118.1, 117.8, 111.3, 107.8, 97.0, 21.3. MS (ESI, 70 eV) *m/z* 319 (32%), 317 (M^+, 100%), 301 (17%), 281 (18%), 204 (6%), 139 (15%), 132 (37%), 77 (3%). HRMS (ESI) *m/z* 318.1067 ($[M+H]^+$ calcd for $C_{21}H_{16}ClN$: 318.1044).

*4.2.2.15. 5-(4-Chlorophenyl)-2-(3,4-dimethoxyphenyl)-indolizine (**7o**).* From 2-aryl-indolizine (**4c**) (126 mg, 0.5 mmol) and 1-chloro-4-iodobenzene (**6a**) (238.45 mg, 1 mmol); yield: 127 mg (70%); dark green solid; mp 93 °C (dec); IR (KBr): 3086, 2956, 2929, 1624, 1514, 1255, 1024, 732; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.55 (m, 3H), 7.46–7.32 (m, 4H), 7.09–7.03 (m, 2H), 6.80–6.71 (m, 2H), 6.36 (m, 1H), 3.85 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 148.1, 141.7, 134.9, 134.1, 132.0, 129.9, 129.7 (2C), 129.2 (2C), 128.3, 119.2, 118.6, 117.5, 112.5, 111.4, 109.6, 107.0, 98.0, 55.98, 55.90; MS (ESI, 70 eV) *m/z* 363 (M^+, 100%), 348 (10%), 320 (22%), 241 (12%), 181 (8%), 164 (7%), 120 (17%), 77 (2%). HRMS (ESI) *m/z* 364.1115 ($[M+H]^+$ calcd for $C_{22}H_{18}ClNO_2$: 364.1099).

*4.2.2.16. 2-(3,4-Dimethoxyphenyl)-5-(4-nitrophenyl)indolizine (**7p**).* From 2-aryl-indolizine (**4c**) (126 mg, 0.5 mmol) and 1-iodo-4-nitrobenzene (**6d**) (249 mg, 1 mmol); yield: 129 mg (69%); dark red solid; mp 97 °C (dec); IR (KBr): 3072, 2958, 2835, 1593, 1516, 1342, 1255, 1026, 856, 794; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J=8.8 Hz, 2H), 7.84–7.79 (m, 2H), 7.43 (s, 1H), 7.35 (d, J=8.8 Hz, 1H), 7.07 (dd, J_1=8 Hz, J_2=2 Hz, 1H), 7.01 (d, J=2 Hz, 1H), 6.8 (d, J=8.8 Hz, 1H), 6.71 (m, 2H), 6.39 (dd, J_1=6.4 Hz, J_2=0.8 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 148.1, 141.7, 138.5, 134.8, 134.1, 129.9, 129.2 (2C), 127.8, 124.4 (2C), 119.2, 118.6, 117.5, 112.5, 111.4, 109.6, 107.0, 98.0, 55.91, 55.90; MS (ESI, 70 eV) *m/z* 374 (M^+, 100%), 343 (21%), 312 (12%), 237 (10%), 122 (19%), 77 (45%). HRMS (ESI) *m/z* 375.1341 ($[M+H]^+$ calcd for $C_{22}H_{18}N_2O_4$: 375.1339).

*4.2.2.17. 5-(4-Chlorophenyl)-2-(4-methoxyphenyl)indolizine (**7q**).* From 2-aryl-indolizine (**4f**) (112 mg, 0.5 mmol) and 1-chloro-4-iodobenzene (**6a**) (238.45 mg, 1 mmol); yield: 131 mg (79%); dark green solid; mp 108 °C; IR (KBr): 3086, 2937, 2833, 1600, 1427, 1251, 1089, 1028, 790, 725; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J=8.4 Hz, 2H), 7.43–7.36 (m, 5H), 7.26 (d, J=8.8 Hz, 1H), 6.83–6.79 (m, 2H), 6.66–6.63 (m, 2H), 6.28 (d, J=6.8 Hz, 1H), 3.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 140.1, 134.9, 133.8, 131.9, 130.1, 129.8 (2C), 129.3 (2C), 128.7, 127.2 (2C), 118.1, 114.0 (2C), 113.4, 111.3, 107.0, 97.2, 55.2; MS (ESI, 70 eV) *m/z* 335 (33%), 333 (M^+, 100%), 318 (22%), 290 (155), 254 (135), 166 (4%), 149 (17%), 127 (23%), 77 (2%). HRMS (ESI) *m/z* 334.0999 ($[M+H]^+$ calcd for $C_{21}H_{16}ClNO$: 334.0993).

*4.2.2.18. 2-(4-Methoxyphenyl)-5-(4-nitrophenyl)indolizine (**7r**).* From 2-aryl-indolizine (**4f**) (112 mg, 0.5 mmol) and 1-iodo-4-nitrobenzene (**6d**) (249 mg, 1 mmol); yield: 120 mg (70%); dark red solid; mp 100–102 °C; IR (KBr): 3078, 3001, 2954, 1600, 1514, 1431, 1344, 1253, 1031, 856, 790; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J=8.8 Hz, 2H), 7.79 (d, J=8.4 Hz, 2H), 7.44–7.42 (m, 3H), 7.34 (d, J=9.2 Hz, 1H), 6.82 (d, J=8.8 Hz, 2H), 6.74–6.70 (m, 2H), 6.39 (d, J=6.4 Hz, 1H), 3.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.7, 147.9, 141.6, 132.0, 131.99, 131.97, 129.3 (2C), 128.5, 128.4, 127.3 (2C), 124.4 (2C), 119.3, 117.9, 114.1 (2C), 112.6, 98.2, 55.2; MS (ESI, 70 eV) *m/z* 344 (M^+, 100%), 298 (16%), 255 (18%), 228 (8%), 172 (4%), 148 (12%), 127 (15%), 77 (2%). HRMS (ESI) *m/z* 345.1241 ($[M+H]^+$ calcd for $C_{21}H_{16}N_2O_3$: 345.1234).

*4.2.2.19. 2-(6-Methoxynaphthalen-2-yl)-5-(p-tolyl)indolizine (**7s**).* From 2-aryl-indolizine (**4e**) (136 mg, 0.5 mmol) and 4-iodotoluene (**6h**) (218 mg, 1 mmol); yield: 117 mg (65%); dark green solid; mp 90–93 °C; IR (KBr): 3026, 2953, 2916, 2868, 1604, 1502, 1255, 1033, 783; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94–7.90 (m, 1H), 7.64 (m, 3H), 7.50 (d, J=8.0 Hz, 2H), 7.43 (d, J=8.0 Hz, 1H), 7.31–7.27 (m, 3H), 7.22–7.17 (m, 2H), 6.81 (s, 1H), 6.69 (m, 1H), 6.33 (d, J=6.47 Hz, 1H), 3.83 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 155.0, 153.4, 139.1, 136.8, 134.9, 132.4, 130.7, 129.7 (2C), 129.5, 128.6, 128.3 (2C), 126.9, 125.5, 123.9, 118.8, 117.7, 113.9, 111.1, 107.9, 105.6, 97.1, 55.2, 21.3. HRMS (ESI) *m/z* 364.1694 ($[M+H]^+$ calcd for $C_{26}H_{21}NO$: 364.1696).

4.3. Photophysical measurements

Absorption spectra were determined in DMSO, using a Shimadzu-2550 UV–vis spectrophotometer. The fluorescence spectra were recorded in a Perkin–Elmer LS-55 by excitation of the samples in its lower energy wavelengths (320–395 nm). The excitation and emission slit were 10 nm and 3 nm, respectively. The emission quantum yields (Φ_F) were determined from corrected fluorescence spectra using quinine sulfate solution in 0.1 N H_2SO_4 as a standard (Φ_F=0.55). All spectrophotometric measurements were carried out in 1 cm path length quartz cuvettes. Fluorescence decays were based on the Stroboscopic technique (Strobe). The excitation source was a pulsed light source (LED), which measures fluorescence intensity at different time delays after pulse. Fluorescence lifetimes were determined from the decays by using the Software from Easy Life V™ and corrected fits for mono- and bi-exponential decay.

4.4. Electrochemical measurements

Electrochemical assays were carried out with a BAS CV-27 potentiostat. Data were recorded on an Omnigraphic XY recorder. Conventional electrochemical cells with three electrodes were employed. A glassy carbon electrode with geometric area of

0.0314 cm^2 was used as working electrode. It was polished prior to use with 1 μ alumina water suspension and rinsed thoroughly with water and acetone. A platinum wire was used as counter electrode and all potentials are referenced to a sodium saturated silver/silver chloride electrode (Ag/AgCl/KCl(sat)) without regard for the liquid junction potential. Cyclic voltammetric studies were carried out at 100 mV/s sweep rate in 5 mL of 0.1 M of TBAH in DMSO solution as supporting electrolyte, where aliquots of 100 mM of the indolizine derivatives in DMSO solution were added. Since the cyclic voltammograms were recorded at a window potential including negative ranges, oxygen-free solution was obtained by bubbling argon through it. When the potential was scanned, the inert gas was kept in the solution to ensure that any oxidation reaction was not begun by oxygen. For the electrochemical process of indolizine in presence of molecular oxygen, the supporting electrolyte was previously saturated with $O_{2(g)}$, and the oxygen redox process was studied in absence and presence of the indolizine. Since the window potential in this study was between +1.2 V and −1.2 V (vs Ag/AgCl(s)/KCl(sat)), three nitro indolizines were chosen. Reduction of nitro group in nonaqueous medium is well known from the literature[32] and the potential is much less negative than −2.5 V (vs SCE) for the indolizine ring.[8] The solutions were stirred for 30 s and allowed to rest for 30 s for equilibration.

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Supplementary data

Absorption and fluorescence emission spectra for all indolizine compounds in DMSO, fluorescence emission for **7a**, **7f**, **7m**, and **7k** in solvents with different polarities, fluorescence lifetime fitting curves for **7a**, **7f**, **7m**, and **7k** in DMSO, and a table containing maximum wavelength absorption and fluorescence emission in different solvents. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.11.105.

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