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When Indolizine Meets Quinoline: Diversity-Oriented Synthesis of New Polyheterocycles and Their Optical Properties

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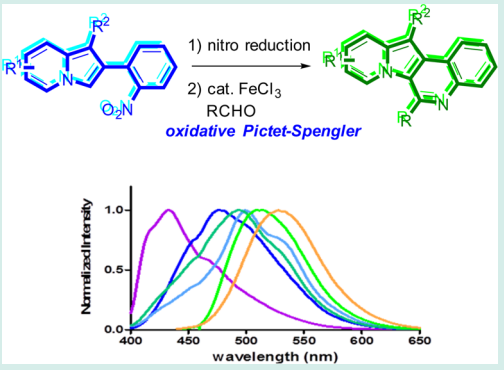
Supporting Information

ABSTRACT: Fluorescence-based technologies play a pivotal role in various biomedical applications. Here we report an efficient route to a new class of fluorophores, indolizino[3,2-*c*]quinolines, via the oxidative Pictet–Spengler cyclization strategy. The condensation of several 2-methylpyridines with 2-bromo-2′-nitroacetophenone allowed for the rapid assembly of indolizines with a 2-nitrophenyl group at the C2 position. The subsequent reduction of the nitro group under mild conditions followed by oxidative Pictet–Spengler cyclization with various aryl aldehydes in the presence of a catalytic amount of $FeCl_3$ furnished the indolizino[3,2-*c*]quinolines in good overall yields. We also examined the photophysical properties of this new series of polyheterocyclic compounds. Several indolizino[3,2-*c*]quinolines were found to have unique and desirable optical properties, suggesting that these compounds may be suitable for use as prospective fluorescent probes in aqueous systems.



KEYWORDS: *Pictet–Spengler cyclization, fluorescence-based technologies, indolizine, quinoline, polyheterocycles*

INTRODUCTION

Indolizines[1] and quinolines[2] are two privileged structures commonly employed in various small molecule drug discovery programs. Figure 1 shows some examples of compounds containing either indolizine or quinoline as their basic core structure; these compounds have been reported to exhibit a wide range of pharmacologically intriguing properties depending on the substitution patterns on these rings.[3]

As part of our ongoing efforts to design and develop efficient methods for synthesizing new chemical scaffolds with distinctive substitution patterns,[4] we became interested in a hybrid structure[5,6] of indolizines and quinolines (Scheme 1). More specifically, these hybrid molecules can be viewed as a merger of 3-acylindolizines[7] and 2-arylquinolines. Since 3-acylindolizines and 2-arylquinolines are known to exhibit anticancer activity, we expected that the new heteroaromatic compounds containing both entities might exhibit not only anticancer activity but also other interesting properties to be utilized as fluorescence sensors.[8] Fused heterocyclic systems with strong fluorescence are intriguing since they can be used as molecular probes in biochemical research,[9] particularly for monitoring interactions with target molecules.[10] Because of the tremendous demands for new fluorophores with unique photophysical properties, considerable efforts have been devoted to develop novel synthetic scaffolds containing new heterocyclic ring systems.[11] Of particular importance in monitoring ligand–target interactions are environment-sensitive fluorophores, the optical properties of which are dependent on the physicochemical properties of the environment surrounding the molecule.[12]

Here, we report a facile route to synthesize highly functionalized indolizino[3,2-*c*]quinolines using an $FeCl_3$-catalyzed oxidative Pictet–Spengler reaction as the key step. In addition, the spectroscopic properties of the indolizino[3,2-*c*]quinoline-containing fluorophores were investigated. The synthesis described herein allows for the efficient preparation of novel fluorophores using a combinatorial strategy, which provides a new synthetic platform for the development of indolizino[3,2-*c*]-quinolines-based fluorescence sensors.

RESULTS AND DISCUSSION

Synthesis. As outlined in Scheme 2, we envisioned that 2-(2-aminophenyl)indolizines **2** would react with aryl aldehydes **3** in the presence of a certain catalyst to afford the desired product, indolizino[3,2-*c*]quinolines (**1**), by oxidative Pictet–Spengler-type cyclization.[13] The substrate **2** would, in turn, be easily prepared by the base-mediated condensation of the 2-picolines **5** and 2-bromo-2′-nitroacetophenone, leading to the formation of the 2-(2-nitrophenyl)indolizines **4** and the subsequent reduction of a nitro group to an amino group.

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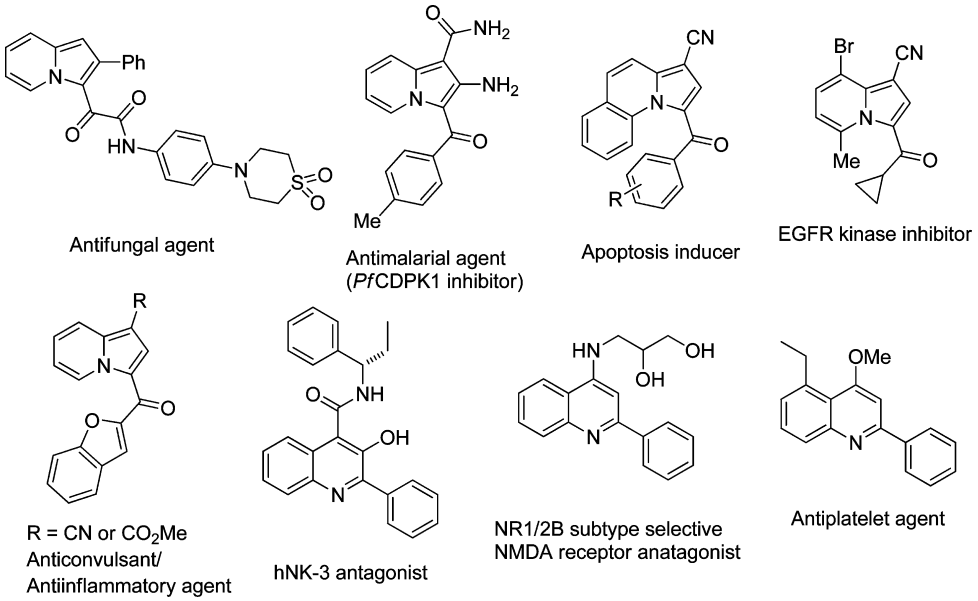
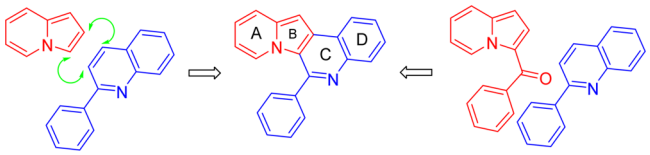
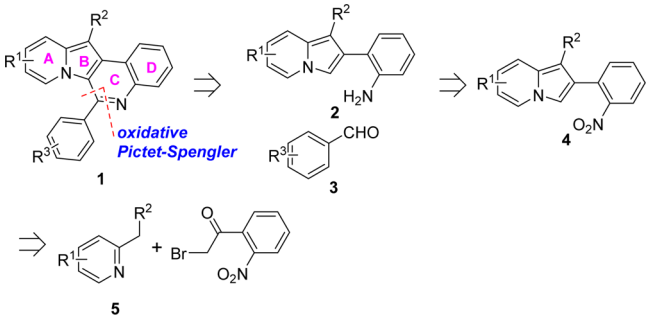


Figure 1. Representative biological modulators containing an indolizine or quinoline nucleus.

Scheme 1. Design of New Hybrid Compounds from Indolizines and Quinolines



Scheme 2. Synthetic Strategy for the Synthesis of Indolizino[3,2-*c*]quinolines



We began this study by preparing several indolizines containing a 2-nitrophenyl group at the C2 position. As shown in Scheme 3, two different methods were employed for the synthesis of **4**. A two-step sequence involving salt formation and base-mediated cyclization was used in case of **4**{*1*}−**4**{*3*},[14] whereas the direct one-pot assembly of indolizines was utilized for **4**{*4*} and **4**{*5*}.[15]

To reduce nitroarenes to the corresponding amines,[16] sodium dithionite[17] was used as a reducing agent (Scheme 4). Thus, indolizines **4**{*1*}−**4**{*5*} were converted to their corresponding amine congeners **2**{*1*}−**2**{*5*}, respectively, in good yields under very mild reaction conditions. An optimization study for oxidative Pictet−Spengler cyclization was conducted with **2**{*1*} and 4-bromobenzaldehyde (**3**{*1*}) in the presence of various catalysts, as shown in Table 1. When either PTSA or PPTS (entries 1 and 3, respectively) was used as catalyst, the desired product **1**{*1*} was isolated along with byproduct **1**{*1*}′, although **1**{*1*} was obtained in higher yield with PTSA. The structure of **1**{*1*} was unambiguously established by an X-ray crystallographic analysis as shown in Figure 2. Elevating the temperature slightly led to an increased yield of **1**{*1*} with the use of PTSA, while no improvement was observed with PPTS (entries 1−4). Using either $InCl_3$ or $BiCl_3$ led to the formation of **1**{*1*}′ as a major product even at 60 °C in modest yield (entries 5−7). Although $AlCl_3$ furnished **1**{*1*} in 64% yield at room temperature, no significant change was observed at 60 °C (entries 8 and 9, respectively). In contrast, **1**{*1*} was obtained as the only isolable compound in the presence of a catalytic amount of $FeCl_3$ (entry 10).[18] The isolated yield was improved in this case by increasing the reaction temperature (entries 11 and 12). With respect to the amount of catalyst, the use of 0.2 equiv of $FeCl_3$ was found to exhibit the best chemical yield (entries 13−15).

Having optimized the conditions for the oxidative Pictet−Spengler cyclization, we reacted **2** with various aryl aldehydes **3** (Figure 3) in the presence of $FeCl_3$. The results are shown in Table 2. In general, both electron-rich and electron-poor aryl aldehydes furnished the corresponding indolizino[3,2-*c*]-quinolines **1** in good to excellent yields. In the case of pyridine-2-carboxaldehyde, the yield was low even in the presence of 0.5 equiv of $FeCl_3$ (entry 14). However, reactions with other heterocyclic aldehydes, such as **3**{*16*}−**3**{*19*}, provided the corresponding products in good yields (entries 15, 23, 28, 29, and 33). Indolizines with electron-withdrawing groups at the C1 position, **2**{*4*} and **2**{*5*}, underwent oxidative cyclization more easily than the other compounds, **2**{*1*}−**2**{*3*}, resulting in better isolated yields.

Finally, additional functional groups were added onto these polycyclic compounds for further diversification (Scheme 5). The Suzuki−Miyaura cross−coupling of **1**{*24*} and **1**{*27*} with several boronic acids afforded the corresponding products **6**−**9** in good yields.[19] Moreover, a bromo group was introduced onto this tetracyclic compound by exposing **1**{*7*} to *N*-bromosuccinimide at room temperature to afford **10**, providing a functional handle for subsequent cross-coupling reactions.[20]

Optical Properties of Indolizino[3,2-*c*]quinolines. With a series of indolizino[3,2-*c*]quinoline analogs in hand, their photophysical properties were examined by spectroscopic

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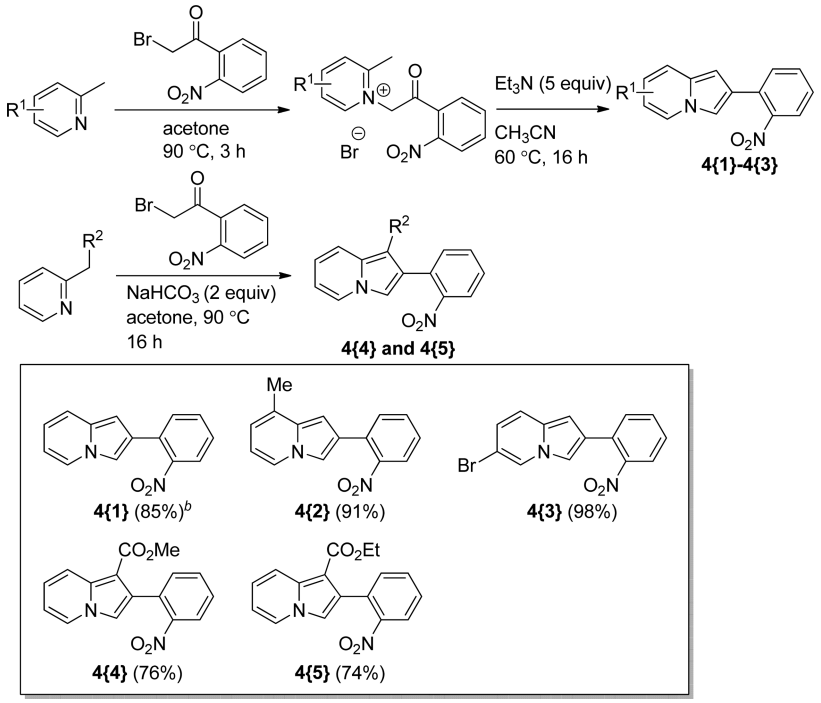
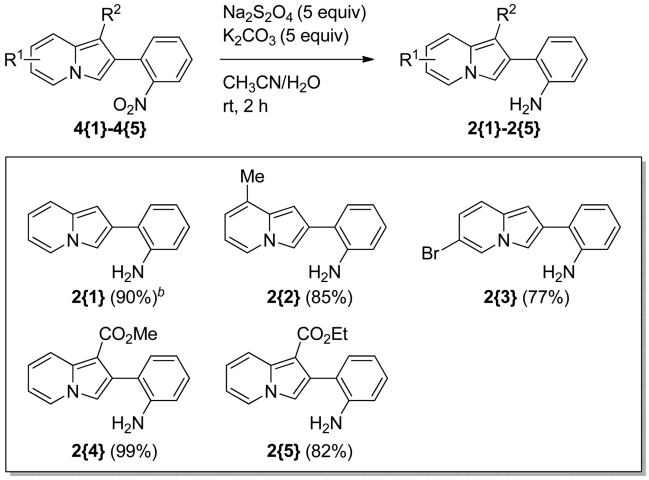
Scheme 3. Synthesis of 2-(2-Nitrophenyl)indolizines[a,b]



[a]For **4**{*1*}−**4**{*3*}: A mixture of 2-bromo-2′-nitroacetophenone (4.1 mmol) and picoline (1.3 equiv) in acetone (12 mL) was heated at 90 °C for 3 h. A mixture of indolizinium salt (4.1 mmol) and Et_3N (5 equiv) in CH_3CN (20 mL) was heated at 60 °C for 16 h. For **4**{**4**} and **4**{**5**}: A mixture of 2-bromo-2′-nitroacetophenone (2.2 mmol), methyl (or ethyl) 2-pyridylacetate (1.5 equiv), and $NaHCO_3$ (2 equiv) in acetone (10 mL) was heated at 90 °C for 16 h. [b]Isolated yields (%)

Scheme 4. Synthesis of 2-(2-Aminophenyl)indolizines[a,b]



[a]A mixture of **4** (1 mmol), sodium dithionite (5 equiv), and K_2CO_3 (5 equiv) in CH_3CN/H_2O (1:1, 10 mL) was stirred at rt for 2 h. [b]Isolated yields (%)

methods. To characterize a new class of fluorophores for biological applications, the desired properties are high emission intensity in water, and large Stokes shift to prevent self-quenching (to minimize homotransfer of energy). In addition, good solubility to minimize aggregations with proteins is necessary for both medicinal chemistry and fluorophore development. In particular, compounds with these properties are highly demanded for protein labeling dyes. Table 3 summarizes the absorption and emission maxima along with the relative fluorescence intensities. In general, the absorption maxima of indolizino[3,2-*c*]quinolines were observed at around 380−430 nm, allowing for excitation with visible light. Emission maxima were observed at around 480−540 nm in aqueous solution. The most notable feature was the large Stokes shifts (90−110 nm) observed in most indolizino[3,2-*c*]quinoline analogs, demonstrating clear separation between the excitation and emission wavelengths. The emission spectra were found to be in a range similar to those of Alexa Fluor 488 or Fluorescein;[21] however, their excitation wavelengths were significantly distant from the emission wavelengths. These characteristics suggest that the compounds may be suitable for biological applications such as cell imaging with multi-fluorescence technology.

Among these series, **1**{*7*} containing the *p*-methoxyphenyl group attached to the C ring exhibited high fluorescence with a maximum emission at 514 nm (Figure 4). The methoxy group at the para position was found to be critical for enhanced fluorescence intensity, which can be rationalized by the opposite location of the electron-donating methoxy group with the electron-deficient quinoline nitrogen. Significant dipole moment changes are expected upon excitation in this molecule. Overall, electronic effects appeared to be well correlated with the spectral properties of indolizino[3,2-*c*]quinolines: the bromo or nitro group attached at the para position of the aromatic ring did not induce fluorescence (**1**{*5*}, **1**{*18*}, and **1**{*36*}), while the electron-rich methoxy group at the para position induced strong fluorescence (**1**{*7*}). The naphthalene substituent at the C6 position of **1**{*12*} also resulted in high fluorescence, but the 2-naphthalene moiety shown in **1**{*13*} led to a decrease in emission intensity. The carboxylic ester group at the C12 position of the B ring led to increased fluorescence, except for the substituent with the nitro group at the para

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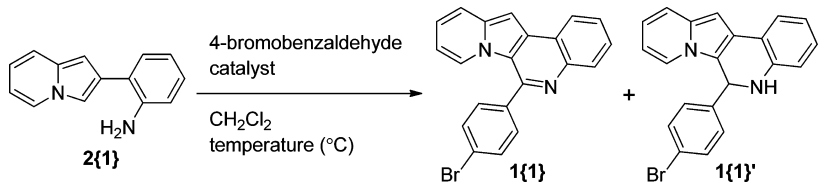
Table 1. Reaction Optimization[a]



entry	catalyst (equiv)	temperature (°C)	yield (%)[b] 1{*1*}	yield (%)[b] 1{*1*}′
1	PTSA (0.1)	rt	36	33
2	PTSA (0.1)	60	46	25
3	PPTS (0.1)	rt	18	62
4	PPTS (0.1)	60	16	56
5	$InCl_3$ (0.1)	rt	5	55
6	$InCl_3$ (0.1)	60	27	34
7	$BiCl_3$ (0.1)	60	10	41
8	$AlCl_3$ (0.1)	rt	64	23
9	$AlCl_3$ (0.1)	60	56	28
10	$FeCl_3$ (0.1)	rt	41	
11	$FeCl_3$ (0.1)	40	71	
12	$FeCl_3$ (0.1)	60	72	
13	$FeCl_3$ (0.2)	60	83	
14	$FeCl_3$ (0.3)	60	77	
15	$FeCl_3$ (0.5)	60	41	

[a]A mixture of 2{*1*} (0.1 mmol), 4-bromobenzaldehyde (1.2 equiv), and catalyst in CH_2Cl_2 (2 mL) was stirred at the indicated temperature for 16 h unless otherwise noted. [b]Isolated yield (%).

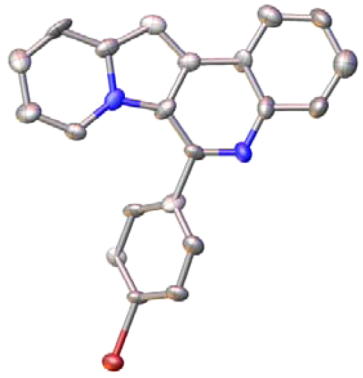


Figure 2. Crystal structure of 1{*1*}.

position of the aromatic ring (1{*36*}). The electron-withdrawing nitro group consistently quenched fluorescence even in the presence of a carboxylic ester (1{*36*}). Meanwhile, the methyl substituent at the C11 position of 1{*22*} led to diminished fluorescence compared with that of 1{*11*}. Substitutions at the R^3 position on the phenyl group exhibited strong correlations of fluorescence with their electronic effects (Figure 5), while no direct relationship was observed with respect to the substituent at R^1 with the optical properties.

Having screened several indolizino[3,2-*c*]quinoline compounds as potential fluorescent probes (Figure 4), we further determined their spectroscopic properties in various solvents. As shown in Table 5, the emission spectra of these indolizino[3,2-*c*]quinoline compounds were dependent on solvent polarity. Among the compounds with strong fluorescence, 1{*7*}, 1{*12*}, 1{*34*}, and 1{*38*} exhibited positive solvatochromic effects,[22] inducing a bathochromic shift of the peak emission in aqueous solution (Table 5). The emission maxima of 1{*7*} and 1{*12*} were notably red-shifted in H_2O (λ_{max}= 511 and 516 nm, respectively) compared to those measured in ethanol (λ_{max}= 465 nm for both molecules). The quantum yields of 1{*7*} and 1{*12*} increased significantly when measured in ethanol using Coumarin 153 as the standard (0.816 and 0.402, respectively). These molecules are thought to have large dipole moment changes upon excitation. In contrast, 1{*33*} exhibited an opposite trend, with a blue-shifted emission maximum in water (λ_{max}= 433 nm). It is noteworthy that solvent-dependent spectroscopic features can be tuned by the addition of different substituents onto indolizino[3,2-*c*]quinolines. Table 5 and Figure 6 present the emission maxima obtained in various solvents. The strong correlation between solvent polarity and fluorescence emissions was not clearly observed. However, because of the environment-sensitive features of indolizino[3,2-*c*]quinolines demonstrated herein, these are expected to be suitable for use as fluorescence probes to monitor biological processes such as drug-target binding or protein dynamics.[10b,12a]

In this study, we report the design, synthesis, and optical characterization of indolizino[3,2-*c*]quinolines as a new class of hybrid heterocycles. By using a diversity-oriented approach, we developed a facile synthetic method for a series of indolizino-[3,2-*c*]quinolines with unique optical properties that are well suited to fluorescence probe applications. The rapid construction of 2-aminophenyl-substituted indolizines and facile oxidative Pictet–Spengler-type cyclization with aryl aldehydes in the presence of $FeCl_3$ allow for diverse indolizino[3,2-*c*]-quinolines in good overall yields. The additional introduction of several functional groups to this scaffold was also demonstrated with a bromo group of several indolizino[3,2-*c*]quinolines by using Pd-catalyzed Suzuki–Miyaura cross-coupling reactions. We are currently investigating an extension of this method for the synthesis of other heterocycles as well as biological applications of the synthesized compounds under various conditions.

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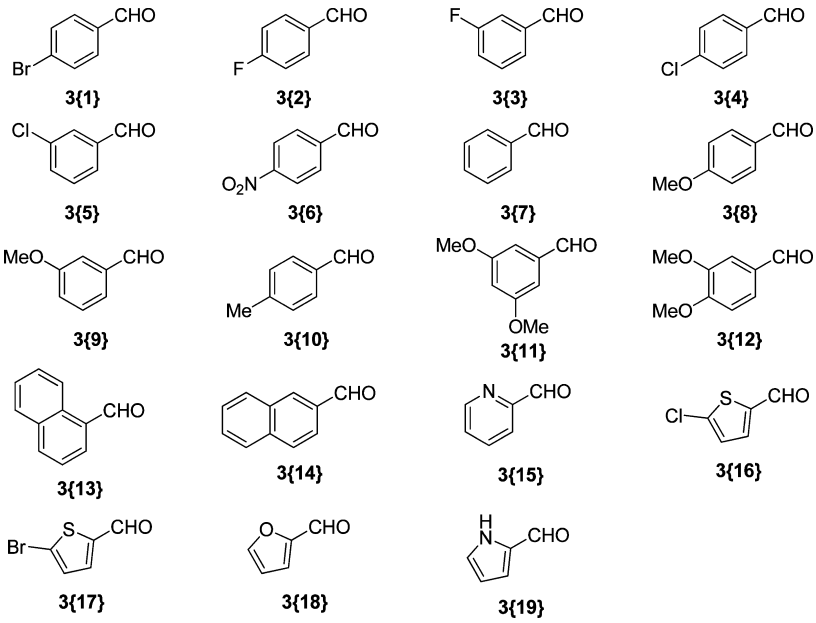


Figure 3. Various aldehydes used in oxidative Pictet–Spengler cyclization.

Although practical issues regarding excitation near UV range and autofluorescence originated from endogenous fluorophores (such as aromatic amino acids and flavin coenzymes in cells) need to be addressed, the knowledge obtained in the present work provides solid foundations for the development of novel environment-sensitive fluorophores.

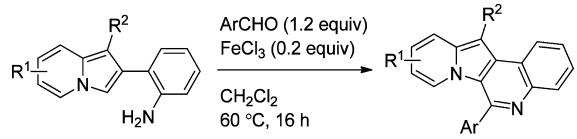
EXPERIMENTAL PROCEDURES

General Methods. Unless specified, all reagents and starting materials were purchased from commercial sources and used as received without purification. "Concentrated" refers to the removal of volatile solvents via distillation using a rotary evaporator. "Dried" refers to pouring onto, or passing through anhydrous magnesium sulfate followed by filtration. Flash chromatography was performed using silica gel (230–400 mesh) with hexanes, ethyl acetate, and dichloromethane as eluent. All reactions were monitored by thin-layer chromatography on 0.25 mm silica plates (F-254) visualizing with UV light. ^{1}H and ^{13}C NMR spectra were recorded on 400 MHz NMR spectrometer and were described as chemical shifts, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant in hertz (Hz), and number of protons. HRMS were measured with electrospray ionization (ESI) and Q-TOF mass analyzer.

Representative Procedure for the Synthesis of 4. *4{1}–4{3}.* A mixture of 2-bromo-2′-nitroacetophenone (4.1 mmol) and picoline (1.3 equiv) in acetone (12 mL) was heated at 90 °C for 3 h. After it was cooled down to room temperature, the reaction mixture was suction-filtered and washed with CH_2Cl_2 (5 mL). The solid was used directly for the next step without further purification. A mixture of indolizinium salt (4.1 mmol) and Et_3N (5 equiv) in CH_3CN (20 mL) was heated at 60 °C for 16 h. After concentration of the reaction mixture under reduced pressure, the resulting residue was purified by silica gel column chromatography (hexanes/ethyl acetate/dichloromethane = 30:1:2) to give **4**{*1*}–**4**{*3*}.

*2-(2-Nitrophenyl)indolizine (**4**{1}):* orange solid, mp 104.6–105.3 °C (891.0 mg, 85%); IR (ATR) ν = 3065, 2922, 1604, 1517, 1454, 1357 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86

Table 2. Oxidative Pictet–Spengler Cyclization of 2 with Various Aldehydes 3[a]



2{1}-2{5} 1{1}-1{39}

entry	2	3	1	yield (%)[b]
1	2{*1*}	3{*1*}	1{*1*}	83
2	2{*1*}	3{*2*}	1{*2*}	56
3	2{*1*}	3{*4*}	1{*3*}	55
4	2{*1*}	3{*5*}	1{*4*}	45
5	2{*1*}	3{*6*}	1{*5*}	55
6	2{*1*}	3{*7*}	1{*6*}	62
7	2{*1*}	3{*8*}	1{*7*}	65
8	2{*1*}	3{*9*}	1{*8*}	52
9	2{*1*}	3{*10*}	1{*9*}	53
10	2{*1*}	3{*11*}	1{*10*}	71
11	2{*1*}	3{*12*}	1{*11*}	68
12	2{*1*}	3{*13*}	1{*12*}	83
13	2{*1*}	3{*14*}	1{*13*}	47
14	2{*1*}	3{*15*}	1{*14*}	28[c]
15	2{*1*}	3{*16*}	1{*15*}	78
16	2{*2*}	3{*1*}	1{*16*}	83
17	2{*2*}	3{*3*}	1{*17*}	80
18	2{*2*}	3{*6*}	1{*18*}	71
19	2{*2*}	3{*9*}	1{*19*}	91
20	2{*2*}	3{*10*}	1{*20*}	79
21	2{*2*}	3{*11*}	1{*21*}	77
22	2{*2*}	3{*12*}	1{*22*}	68
23	2{*2*}	3{*18*}	1{*23*}	79
24	2{*3*}	3{*8*}	1{*24*}	89
25	2{*3*}	3{*10*}	1{*25*}	44
26	2{*3*}	3{*12*}	1{*26*}	75
27	2{*3*}	3{*13*}	1{*27*}	83
28	2{*3*}	3{*17*}	1{*28*}	58
29	2{*3*}	3{*18*}	1{*29*}	93
30	2{*4*}	3{*1*}	1{*30*}	77

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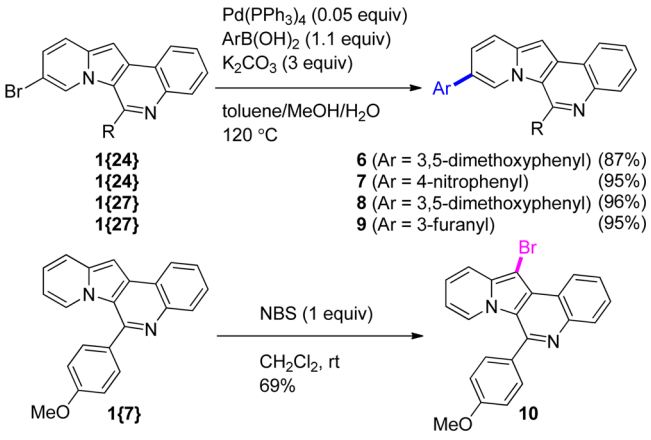
Table 2. continued

entry	2	3	1	yield (%)[b]
31	2{4}	3{11}	1{31}	93
32	2{4}	3{13}	1{32}	99
33	2{4}	3{19}	1{33}	88
34	2{5}	3{3}	1{34}	100
35	2{5}	3{5}	1{35}	95
36	2{5}	3{6}	1{36}	75
37	2{5}	3{9}	1{37}	93
38	2{5}	3{12}	1{38}	98
39	2{5}	3{14}	1{39}	100

[a]A mixture of **2** (0.14 mmol), ArCHO (1.2 equiv), and $FeCl_3$ (0.2 equiv) in CH_2Cl_2 (3 mL) was heated at 60 °C for 16 h unless otherwise noted. [b]Isolated yields (%). [c]$FeCl_3$ (0.5 equiv) was used.

Scheme 5. Further Functionalization of 1 for Additional Diversity[a]



[a]A mixture of **1**{*24*} or **1**{*27*} (0.07 mmol), $Pd(PPh_3)_4$ (0.05 equiv), arylboronic acid (1.1 equiv), and K_2CO_3 (3 equiv) in toluene/MeOH/H_2O (1:1:1, 1.5 mL) was heated at 120 °C for 4 h. A mixture of **1**{*7*} (0.1 mmol) and N-bromosuccinimide (1 equiv) in CH_2Cl_2 (2 mL) was stirred at rt for 1 h.

(d, J = 6.8 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.61−7.49 (m, 2H), 7.43−7.35 (m, 2H), 7.33 (d, J = 8.8 Hz, 1H), 6.67 (t, J = 6.8 Hz, 1H), 6.53−6.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.3, 131.9, 131.7, 129.7, 127.4, 125.2, 123.8, 123.5, 119.4, 117.9, 111.2, 110.9, 98.7; HRMS (ESI) calcd for $C_{14}H_{11}N_2O_2$ 239.0815 ([M + H]$^+$), found 239.0813.

4{4} and 4{5}. A mixture of 2-bromo-2′-nitroacetophenone (2.2 mmol), methyl (or ethyl) 2-pyridylacetate (1.5 equiv), and $NaHCO_3$ (2 equiv) in acetone (10 mL) was heated at 90 °C for 16 h. After concentration of the reaction mixture under reduced pressure, the resulting residue was diluted with CH_2Cl_2 (10 mL) and washed with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL) one more time. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography (hexanes/ethyl acetate/dichloromethane = 10:1:2) to give **4**{*4*} and **4**{*5*}.

*Methyl 2-(2-Nitrophenyl)indolizine-1-carboxylate (**4**{4}):* yellow solid, mp 147.2−148.2 °C (495.4 mg, 76%); IR (ATR) ν = 3081, 2982, 1685, 1504, 1346, 1220 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 9.2 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 6.8 Hz, 1H), 7.59 (t, J = 7.2 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.41 (d, J = 7.2 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 6.72 (t, J = 6.8 Hz, 1H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 149.8, 136.6, 133.0, 132.3, 130.6, 128.4, 125.9, 124.2, 123.2, 120.5, 113.4, 113.0, 101.4, 50.8; HRMS (ESI) calcd for $C_{16}H_{13}N_2O_4$ 297.0870 ([M + H]$^+$), found 297.0872.

Table 3. Fluorescence Intensities and Emission Wavelengths of Indolizino[3,2-*c*]quinolines

	λ_{abs} (nm)	$\lambda_{max\ em}$ (nm)[a]	emission intensity[b]	emission intensity$_{norm}$[c]
1{*1*}	400	522	32.7	0.14
1{*5*}	371, 402	–	–	0.00
1{*6*}	380, 400	519	55.0	0.24
1{*7*}	430	514.5	231.3	0.99
1{*9*}	380, 400	519	59.7	0.26
1{*10*}	399, 421	527.5	60.8	0.26
1{*11*}	399, 421	513	171.3	0.74
1{*12*}	399, 421	514	232.9	1.00
1{*13*}	399, 421	532	39.6	0.17
1{*14*}	400	532	4.7	0.02
1{*15*}	407	536	7.5	0.03
1{*16*}	395	531.5	11.8	0.05
1{*17*}	375, 395	535.5	9.4	0.04
1{*18*}	375, 395	–	–	0.00
1{*20*}	375, 395	527.5	25.5	0.11
1{*21*}	373, 391	535	11.7	0.05
1{*22*}	391	524.5	31.7	0.14
1{*23*}	400	523.5	15.0	0.06
1{*24*}	386, 406, 430	512	89.5	0.38
1{*25*}	386, 406, 430	518	82.4	0.35
1{*26*}	386, 406, 430	513	75.1	0.32
1{*29*}	391, 411	505.5	13.4	0.06
1{*31*}	362, 383	478	80.5	0.35
1{*32*}	362, 380	493	143.5	0.62
1{*33*}	362, 383	432.5	226.5	0.97
1{*34*}	362, 383	476	211.7	0.91
1{*35*}	362, 383	474	98.9	0.42
1{*36*}	384	–	–	0.00
1{*37*}	362, 383	482	186.2	0.80
1{*38*}	362, 383	480.5	210.7	0.90
1{*39*}	362, 383	515	106.5	0.46

[a]Excited at the longest absorption maxima. [b]Fluorescence spectra recorded in H_2O at 2 μM. [c]Normalized fluorescence intensity.

Representative Procedure for the Synthesis of 2. A mixture of **4** (1 mmol), sodium dithionite (5 equiv), and K_2CO_3 (5 equiv) in CH_3CN/H_2O (1:1, 10 mL) was stirred at room temperature for 2 h. After concentration of the reaction mixture under reduced pressure, the resulting residue was diluted with CH_2Cl_2 (10 mL) and washed with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL) one more time. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give **2**.

*2-(Indolizin-2-yl)aniline (**2**{1}):* pale yellow solid, mp 141.8−142.6 °C (188.1 mg, 90%); IR (ATR) ν = 3446, 3360, 3064, 2921, 1610, 1452, 1290 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 6.8 Hz, 1H), 7.47 (s, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 6.82 (t, J = 7.6 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.68 (dd, J = 6.8, 8.8 Hz, 1H), 6.60 (s, 1H), 6.47 (t, J = 6.8 Hz, 1H), 4.04 (br s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 133.2, 130.6, 128.0, 127.1,

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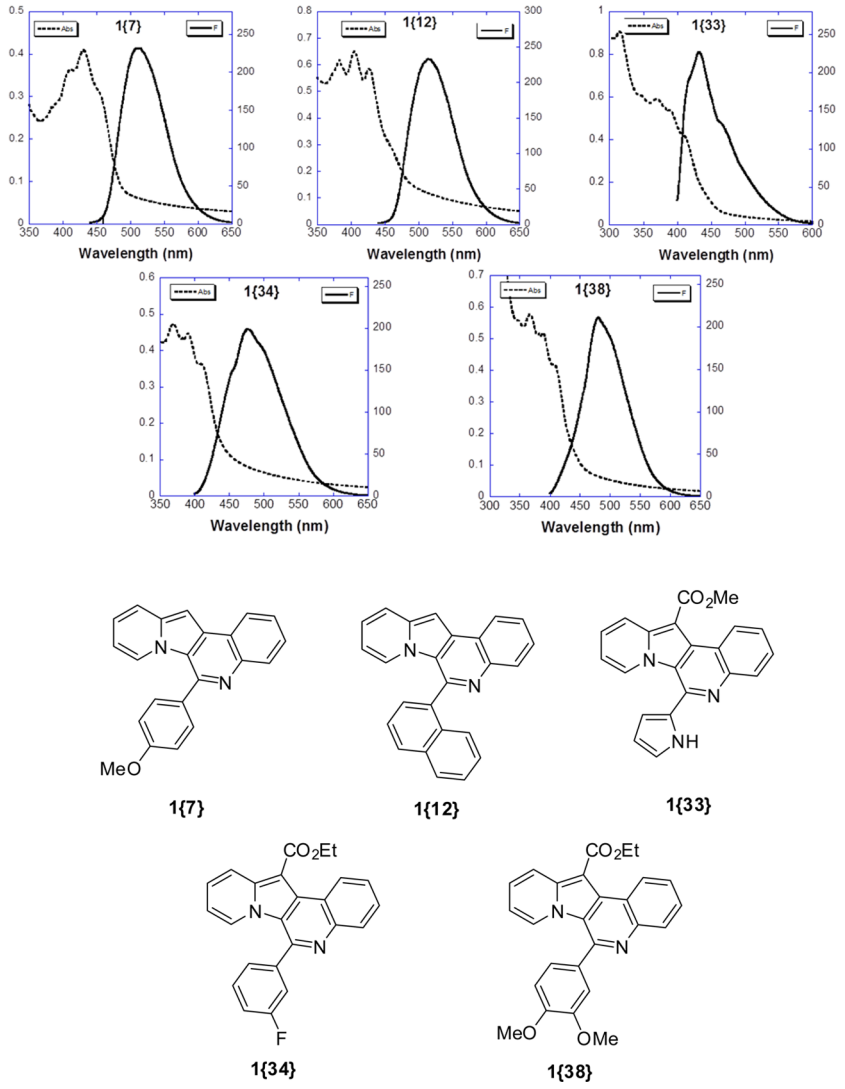

Figure 4. Absorption and emission spectra of **1**{*7*}, **1**{*12*}, **1**{*33*}, **1**{*34*}, and **1**{*38*} measured in water.

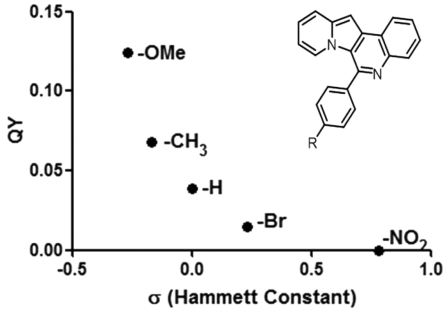

Figure 5. Substituent effect at the R^3 position on the fluorescence quantum yield.

125.1, 121.7, 119.0, 118.7, 117.5, 115.7, 111.1, 110.6, 99.0; HRMS (ESI) calcd for $C_{14}H_{13}N_2$ 209.1073 ($[M + H]^+$), found 209.1066.

Representative Procedure for the Synthesis of 1. A mixture of **2** (0.14 mmol), ArCHO (1.2 equiv), and $FeCl_3$ (0.2 equiv) in CH_2Cl_2 (3 mL) was heated at 60 °C for 16 h. The reaction mixture was washed with H_2O (3 mL). The aqueous layer was extracted with CH_2Cl_2 (3 mL) one more time. The organic layer was dried over $MgSO_4$ and concentrated in vacuo.

Table 4. Optical Properties of Screened Fluorophores with Strong Fluorescence

	extinction coefficient (cm^{-1} M^{-1})	λ_{abs} (nm)	λ_{em} (nm)	Stokes shift (cm^{-1})	Φ^a
1{*7*}	6547	430	515	38383	0.121
1{*12*}	11656	405	515	52739	0.053
1{*33*}	9012	383	433	30150	0.033
1{*34*}	10780	369	476	60919	0.061
1{*38*}	10580	369	481	63103	0.084

[a]Quantum yields were determined using rhodamine 6G as the standard (Φ = 0.86 in water). The excitation/emission wavelengths for rhodamine 6G are 425−575/505−750 nm.

The residue was purified by silica gel column chromatography (hexanes/ethyl acetate/dichloromethane) to give **1**.

*6-(4-Bromophenyl)indolizino[3,2-c]quinoline (**1**{1}):* yellow solid, mp 205.5−205.8 °C (43.4 mg, 83%); IR (ATR) ν = 2921, 2852, 1630, 1480, 1354 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, J = 7.6 Hz, 1H), 8.23 (d, J = 8.0 Hz, 1H), 7.89 (d, J = 6.8 Hz, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.73−7.68 (m, 1H), 7.69−7.62 (m, 2H), 7.58 (d, J = 8.0 Hz, 2H), 7.31 (s, 1H), 7.07 (t, J = 7.6 Hz, 1H), 6.48 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 143.1, 139.1, 138.9, 132.6, 131.9,

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Table 5. Emission Maxima of Screened Fluorophores Measured in Various Solvents at Room Temperature

entry	H_2O λ_{em} (nm)	DMSO λ_{em} (nm)	DMF λ_{em} (nm)	EtOH λ_{em} (nm)	EtOH/$CHCl_3$ = 1:5 λ_{em} (nm)	MC λ_{em} (nm)
1{*7*}	511	512	469	465	466	467
1{*12*}	516	514	478	465.5	467.5	469
1{*33*}	431	453	453	447.5	453.5	453.5
1{*34*}	476	472.5	470	449.5	450	451.5
1{*38*}	478.5	452.5	450	444	447.5	448

130.6, 129.7, 127.8, 126.8, 126.0, 123.7, 123.6, 122.5, 121.0, 119.5, 110.1, 92.4; HRMS (ESI) calcd for $C_{21}H_{14}BrN_2$ 373.0335 ($[M + H]^+$), found 373.0336.

*6-(4-Bromophenyl)-5,6-dihydroindolizino[3,2-c]quinoline (**1**{**1**}′):* pale yellow solid, mp 179.3−180.0 °C; IR (ATR) ν = 3356, 2921, 2851, 1608, 1481 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 7.6 Hz, 1H), 7.40 (d, J = 8.2 Hz, 2H), 7.37 (d, J = 8.8 Hz, 1H), 7.24 (d, J = 7.2 Hz, 1H), 7.11 (d, J = 8.2 Hz, 2H), 6.99 (t, J = 7.2 Hz, 1H), 6.78 (t, J = 7.6 Hz, 1H), 6.74 (s, 1H), 6.62 (dd, J = 6.8, 8.8 Hz, 1H), 6.50 (d, J = 7.6 Hz, 1H), 6.34 (t, J = 6.8 Hz, 1H), 6.04 (s, 1H), 4.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 140.6, 132.4, 128.6, 127.7, 123.7, 122.4, 121.3, 119.1, 118.4, 117.4, 117.1, 113.6, 110.6, 108.1, 107.8, 92.3, 55.8; HRMS (ESI) calcd for $C_{21}H_{16}BrN_2$ 375.0491 ($[M + H]^+$), found 375.0494.

Representative Procedure for the Synthesis of 6−9. A mixture of **1**{*24*} or **1**{*27*} (0.07 mmol), $Pd(PPh_3)_4$ (0.05 equiv), arylboronic acid (1.1 equiv), and K_2CO_3 (3 equiv) in toluene/MeOH/H_2O (1:1:1, 1.5 mL) was heated at 120 °C for 4 h. After concentration of the reaction mixture under reduced pressure, the resulting residue was diluted with CH_2Cl_2 (3 mL) and washed with H_2O (3 mL). The aqueous layer was extracted with CH_2Cl_2 (3 mL) one more time. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give the crude mixture, which was purified by silica gel column chromatography (hexanes/ethyl acetate/dichloromethane = 5:1:2) to give **6**−**9**.

*9-(3,5-Dimethoxyphenyl)-6-(4-methoxyphenyl)indolizino-[3,2-c]quinoline (**6**):* yellow solid, mp 177.5−177.8 °C (28.0 mg, 87%); IR (ATR) ν = 2996, 2920, 1582, 1404, 1438, 1377, 1150, 1024 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 8.0 Hz, 1H), 8.25 (d, J = 8.0 Hz, 1H), 8.19 (s, 1H), 7.74−7.52 (m, 5H), 7.33 (d, J = 9.6 Hz, 1H), 7.25 (s, 1H), 7.14 (d, J = 8.4 Hz, 2H), 6.43 (s, 1H), 6.40 (s, 1H), 3.90 (s, 3H), 3.79 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 160.5, 148.5, 143.2, 139.4, 138.1, 132.1, 130.3, 129.5, 127.7, 125.8, 124.6, 123.7, 123.6, 123.1, 122.5, 121.7, 119.2, 114.9, 104.1, 99.8, 92.4, 55.6, 55.5; HRMS (ESI) calcd for $C_{30}H_{25}N_2O_3$ 461.1860 ($[M + H]^+$), found 461.1859.

Synthesis of 10. A mixture of **1**{*7*} (0.1 mmol) and *N*-bromosuccinimide (1 equiv) in CH_2Cl_2 (2 mL) was stirred at room temperature for 1 h. After concentration of the reaction mixture under reduced pressure, the resulting residue was purified by silica gel column chromatography (hexanes/ethyl acetate/dichloromethane = 10:1:2) to give **10**.

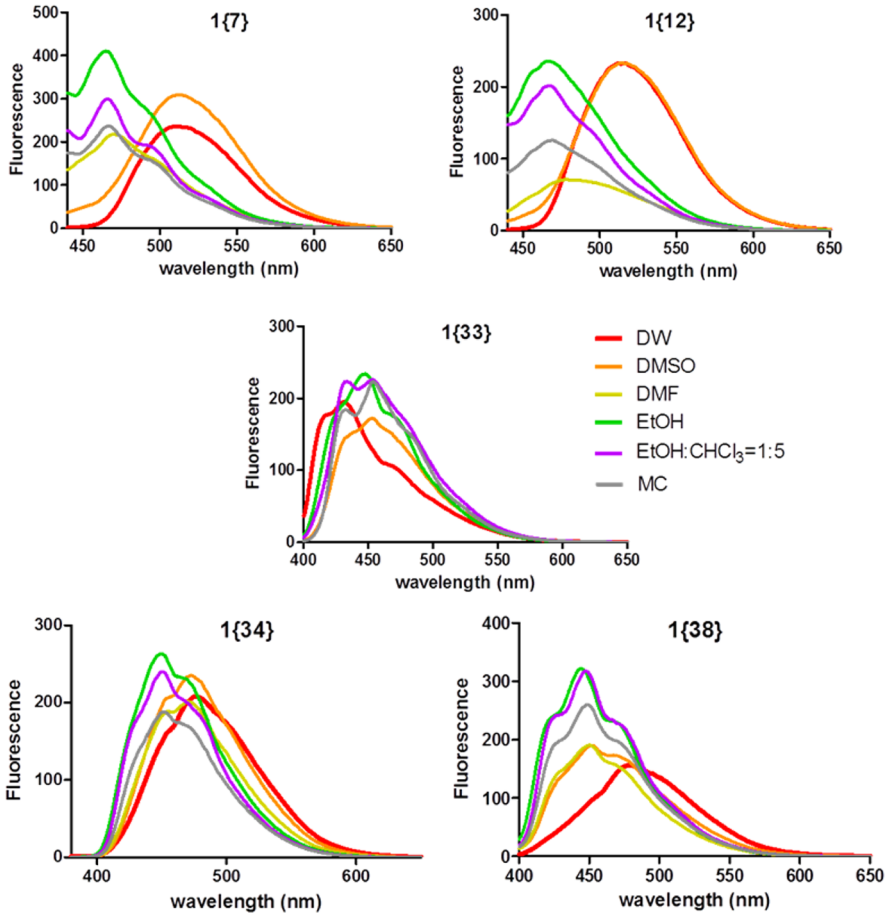

Figure 6. Emission spectra of screened fluorophores in various solvents.

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*12-Bromo-6-(4-methoxyphenyl)indolizino[3,2-c]quinoline (**10**):* yellow solid, mp 221.6−221.9 °C (27.8 mg, 69%); IR (ATR) ν = 2921, 1609, 1493, 1438, 1356, 1248, 1024 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.36 (d, J = 7.6 Hz, 1H), 8.26 (d, J = 8.0 Hz, 1H), 7.90 (d, J = 7.2 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.67 (t, J = 8.0 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.22−7.06 (m, 3H), 6.50 (t, J = 6.8 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 148.2, 143.7, 136.1, 132.0, 130.1, 129.6, 128.0, 127.2, 126.9, 125.6, 124.5, 123.4, 122.1, 120.8, 117.7, 115.0, 110.7, 55.7; HRMS (ESI) calcd for $C_{22}H_{16}BrN_2O$ 403.0441 ($[M + H]^+$), found 403.0435.

Optical Characterization. Fluorescence emission spectra were obtained at 20 °C using JASCO FP-6500 Spectrofluorometer. Ten millimolar stock solutions of indolizino[3,2-*c*]-quinolines compounds dissolved in DMSO were diluted with corresponding solvents. Fluorescence quantum yield was determined as previously describe using rhodamine 6G as a standard (Φ = 0.86 in water).[21] The slit widths used for fluorescence measurement were 3 nm for excitation and 5 nm for emission. Absorption spectra were recorded on PerkinElmer Lamda 20 UV/vis spectrometer at room temperature.

■ ASSOCIATED CONTENT

Supporting Information

Compound characterization data and copies of ^1H and ^{13}C NMR spectra of compounds (**1**, **2**, **4**, **6**−**10**), a CIF file of **1**{*1*} (CCDC 1060165), copies of fluorescence spectra of **1**, and copies of fluorescence spectra of screened fluorophores in organic solvents. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.5b00031.

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Notes

The authors declare no competing financial interest.

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