Donor-Acceptor-Donor NIR II Emissive Rhodindolizine Dye Synthesized by C-H Bond Functionalization

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Supporting Information Placeholder

ABSTRACT: A NIR II emissive dye was synthesized by the C-H bond functionalization of 1-methyl-2-phenylindolizine with 3,6-dibromoxanthene. The rhodindolizine (**RhIndz**) spirolactone product was non-fluorescent; however, upon opening of the lactone ring by the formation of the ethyl ester derivative, the fluorophore absorbs at 920 nm and emits at 1092 nm, which are both in the NIR II region. In addition, 4-cyanophenyl- (**CNRhIndz**) and 4-methoxyphenyl-substituted rhodindolizine (**MeORhIndz**) could also be prepared by the C-H activation reaction.

Photoluminescent materials in the near-infrared I (NIR I) (~ 0.7 μm – 0.9 μm) and near-infrared II (NIR II) (~ 0.9 μm – 1.7 μm) region of the electromagnetic spectrum have applications in many areas such as optical recording, laser filters, thermal writing displays, bioimaging, NIR photography, photodynamic therapy, and solar cells.[1-11] Among these applications, NIR I and NIR II materials are desirable for tissue imaging due to the deeper penetration of light, minimal tissue damage, and high spatial resolution as a result of low autofluorescence in the NIR I and NIR II regions.[12-17] There are several examples of NIR I dyes derived from common fluorescent dye scaffolds such as cyanine,[18-23] phthalocyanine and porphyrin,[11, 24-25] squaraine,[26-29] BODIPY analogs,[30-32] benzo[c]heterocycle,[33] and xanthene derivatives.[11, 34-37] Among these common scaffolds, xanthene-based dyes are widely explored due to their outstanding photophysical properties and stimuli responses. Consequently, they have been modified to achieve absorption and emission wavelengths in the NIR I region. For example, replacing the bridged oxygen atom of the xanthene scaffold to phosphorous[38] or silicon[39] leads to a reduced optical energy gap into the NIR I region. Subsequently, there are a number of examples from our group,[40] and others,[41-42] that have demonstrated strong atom substitution effects with various xanthene-based dyes. In addition, Yuan and coworkers have developed several NIR I dyes with moderate to high quantum yields by extending the π-conjugation of the xanthene scaffold.[43-44] In contrast, while there are several examples of NIR I emissive dyes, there are only a few NIR II fluorophores available.[2, 14-17, 45-49] Nanoparticles and quantum dots have shown interesting photophysical properties as NIR II fluorophores with very high quantum efficiencies;[50-51] however, these nanoparticles tend to be insoluble, slow to excrete from the body, and accumulate in the spleen and liver, making them non-ideal therapeutic agents in many cases.[52-53] In this regard, small molecule organic dyes are attractive for clinical applications because of their tendency to metabolize in the cells and low toxicity.[16, 18-19] Recently, researchers have sought different strategies to develop NIR II organic emissive dyes such as combining donor and acceptor groups.[54-57] This approach is well-developed for organic electronic devices, and this strategy has been successful in producing low bandgap molecules. The choice of a good donor - acceptor pair can significantly lower the optical bandgap of a dye due to the promotion of charge transfer events.[8, 58] Indolizines are gaining use in dye-sensitized solar cells as the donor due to a good donor strength compared to ubiquitous triphenylamine donors and other alkyl amine-based donor groups.[46, 59-61] The excellent donor strength of indolizines is a result of several factors such as, having a nitrogen atom with three separate single bonds creating a fully planar geometry, a fully conjugated π-scaffold with

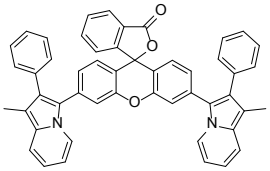


Figure 1. Rhodindolizine structure

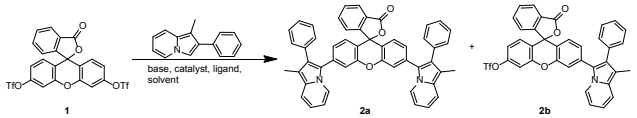
the nitrogen lone pair, low stabilization energy, and a pro-aromatic nature.[46, 60, 62] Owing to the excellent photophysical properties of xanthene-based dyes and their electron accepting ability, we have designed a donor-acceptor-donor NIR II fluorescent dye by coupling the 3-position of the electron rich indolizine to the 3 and 6 positions of the electron poor xanthene using the C-H bond functionalization reaction (Figure 1).

C-H bond functionalization/activation has emerged as a very useful method for the formation of sp^2 – hybridized C-C bonds. C-H activation synthetic routes have an advantage over the classical cross-coupling approaches in that additional synthetic steps to activate the carbon site and the production of toxic by-products are avoided.[63-65] C-H functionalization can be highly tolerant of many functional groups, which makes it desirable for the preparation of drugs and natural products. However, since there are usually many C-H bonds on the substrates, selectivity can be challenging. While C-H functionalization on sp^2 – hybridized carbon centers has been widely developed for the preparation of conjugated compounds for applications in organic devices, only a few examples have been reported for the synthesis of photoluminescent dyes.[56] For instance, Verbelen et al. have developed several BODIPY dyes by radical C-H arylation and alkylation.[66-67] They have also reported the direct palladium catalyzed C-H activation at the 3- and 3,5-positions of a BODIPY derivative that resulted in high fluorescence quantum yields ($\phi > 0.85$).[68] Perumal and coworkers have reported tetrasubstituted olefinic xanthene dyes with aggregation induced emission (AIE) properties, which were synthesized by a tandem Pd-catalyzed 6-exo-dig cyclization followed by a C-H activation reaction.[69] Gryko and coworkers have prepared indolizine-based dyes by a double C-H activation of electron deficient indolizines with the electron rich dibromoarenes, fluorene and thiophene.[70] They obtained the desired bis-indolizine products in 58% and 47% yield respectively.

Herein, we reported the first NIR II xanthene-based dye, which was prepared by the C-H bond functionalization reaction of 1-methyl-2-phenylindolizine with 3′,6′-dibromofluoran (a xanthene derivative). The specific methyl/phenyl substitution pattern on the indolizine was selected as these groups allow for a simple synthesis of an electron rich indolizine with prolonged ambient stability. The target dye is inspired by the popular rhodamine dyes; however, the xanthene core is attached to carbon atoms of indolizine (Figure 1), instead of nitrogen atoms, which is common to the rhodamine structure. Interestingly, 3',6'-bis(1-methyl-2-phenylindolizin-3-yl)-3*H*-spiro[2-benzofuran-1,9'-xanthen]-3-one (Figure 1), which is referred to as rhodindolizine (**RhIndz**) from here on, undergoes the typical molecular optical switching between the closed spirocyclic ring structure and the open-form that is commonly observed for rhodamine dyes. **RhIndz** shows intense absorption and emission in the NIR II region of the spectrum, which is desirable for biological imaging. To analyze the substituent effects on the C-H activation reaction, substituted indolizines containing both electron withdrawing and electron donating groups on the phenyl ring were investigated.

The C-H bond functionalization is an attractive method for preparing 3-substituted indolizine since preparing/isolating 3-haloindolizines, which are common precursors to other classical cross coupling reagents such as organoboron and organotin reagents is challenging. Furthermore, the direct borylation at the 3-position of the indolizine is also challenging, while the C-H bond functionalization at the 3-position of indolizine has been reported.[70,71] The synthesis of **RhIndz** begins with the known 3,6-ditriflated fluorescein (1) reported by Lavis and coworkers.[72] The intermolecular C-H bond functionalization of 1-methyl-2-phenylindolizine with the 3,6-ditriflated xanthene derivative was explored by varying the catalyst, ligand, base, additive, solvent, temperature and time according to Table 1 and SI Table 1 (Supporting Information). We began our study with $PdCl_2(PPh_3)_2$ (10 mol %) as the catalyst, potassium acetate (KOAc) (5.2 equiv.) as the base, and N-methyl-2-pyrrolidone (NMP) as the solvent at 80 ºC for 6.5 h (Table 1, Entry 1). For these conditions, 5% of the desired disubstituted product (**2a**) and 10% of undesired monosubstituted product (**2b**) were isolated. Increasing the time to 17 h only slightly increased the yield of the desired product (Table 1, Entry 2). Notably, changing the base to cesium carbonate (Cs_2CO_3), potassium *tert*-butoxide (KO^{t}Bu), or sodium *tert*- butoxide (NaO^{t}Bu) yielded

Table 1. Optimization of reaction conditions for xanthene ditriflate



1 2a 2b

entry	catalyst	ligand	KOAc (equiv)	temp (°C)	time (h)	(%)[a] 2a:2b
1	$PdCl_2(PPh_3)_2$	None	(5.2)	80	6.5	5:10
2	$PdCl_2(PPh_3)_2$	None	(5.2)	80	18	8:17
3	$Pd(OAc)_2$	PPh_3	(3.0)	150	20	14:0
4	$Pd(OAc)_2$	XPhos	(6.0)	100	20	22:20
5[b]	$Pd(OAc)_2$	XPhos	(6.0)	100	20	5:6

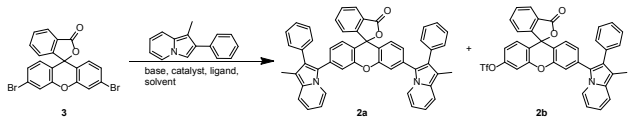
Reactions are carried out in a sealed tube under nitrogen atmosphere in the presence of **1** (0.083 mmol), 1-methyl-2-phenylindolizine (0.167 mmol), NMP (entries 1 and 2) or DMF as solvent (0.34 – 2.0 mL), catalyst (10 mol %), ligand (20 mol %when added), and KOAc. [a]Isolated yields (%) were reported for **2a** and **2b**.[b]Pivalic acid added (30 mol %).

trace or no product (Supporting Information SI Table 1, Entries 1-3). In fact, the ditriflated xanthene precursor was converted to fluorescein by a de-triflation process that was previously observed by Rogers et al.,[73] with the recovery of the indolizine starting material. When the catalyst was changed to $Pd(OAc)_2$ (10 mol %) with triphenylphosphine (PPh_3) (20 mol %) as the ligand, KOAc (3 equiv) as the base in DMF at 150 °C for 18 h – 20 h, only the desired product **2a** was obtained in 14% isolated yield (Table 1, Entry 3). The yield of the desired product increased to 22% when XPhos (20 mol %) was used as the ligand in place of PPh_3 at 100 °C (Table 1, Entry 4). The work of Fagnou and coworkers has shown the direct arylation of electron rich indolizines with trialkylphosphines;[72] however, with (^{t}Bu)$_2$PMeHBF$_4$ added as the ligand, no product was obtained (Supporting Information SI Table 1, Entry 4). In fact, the addition of pivalic acid (30 mol %) or any condition that requires strong bases such as K_2CO_3, Cs_2CO_3 and KO^{t}Bu, including the conditions reported by Ozawa and coworkers that use $Pd(dba)_3{\cdot}CHCl_3$ adduct (10 mol %) as the catalyst,[74] resulted in only trace or no product at all (Supporting Information , SI Table 1, Entries 5 – 10). In all cases, mostly unreacted starting materials were recovered.

While the target dye is accessible from the xanthene ditriflate precursor with yields high enough for photophysical stud-

ies, the C-H bond functionalization of 1-methyl-2-phenylindolizine with 3′,6′-dibromofluoran[75] was investigated to determine if the reaction yield could be improved (Table 2). Beginning with one of the highest yielding conditions from the ditriflate study in Table 1, 3′,6′-dibromofluoran (**3**) and 1-methyl-2-phenylindolizine were subjected to $PdCl_2(PPh_3)_2$ (10 mol %) as the catalyst, KOAc (5.2 equiv) as the base, and NMP as the solvent at 80 °C for 18 h. From these reaction conditions, the desired product was isolated in 23% yield (Table 2, Entry 1). Changing the base to Cs_2CO_3 did not affect the yield (Table 2, Entry 2), and there was no observable conversion with NaO′Bu (SI Table 2, Entry 1). However, by increasing the reaction temperature and time to 110 °C and 24 h respectively, the desired product could be isolated in 35% yield (Table 2, Entry 3). Further increase in the temperature to 150 °C did not improve the yield (Table 2, Entry 4). Again, Fagnou's conditions or the use of XPhos only lowered the percent conversion after 18 h (SI Table 2, Entries 2 & 3). To the best of our knowledge, this is the first known case of a xanthene-based $C(sp^2)$-$C(sp^2)$ bond C-H activation cross-coupling reaction, and this route sets a precedent for the rapid access of aryl-xanthene derivatives. Furthermore, our yields were comparable to the literature where bis-indolizine products were prepared by C-H bond functionalization.[70]

Table 2. Optimization of reaction conditions with 3′,6′-dibromofluoran (3)



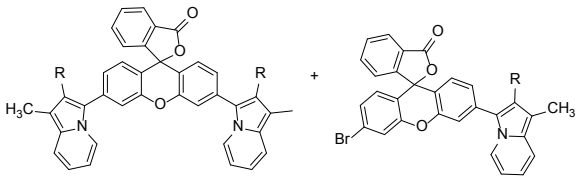
entry	catalyst	base (equiv)	temp (°C)	time (h)	yield (%)[a]
1	$PdCl_2(PPh_3)_2$	KOAc (5.2)	80	18	23
2	$PdCl_2(PPh_3)_2$	Cs_2CO_3 (5.2)	80	18	23
3	$PdCl_2(PPh_3)_2$	KOAc (5.2)	110	24	35
4	$PdCl_2(PPh_3)_2$	KOAc (5.2)	150	24	35

Unless otherwise specified, the reaction was carried out in a sealed tube under nitrogen atmosphere in the presence of **3** (0.11 mmol), 1-methyl-2-phenylindolizine (0.24 mmol), NMP solvent (0.34 – 2 mL), $PdCl_2(PPh_3)_2$ (10 mol %), and base, for 18 – 24 h at 80 °C - 150 °C. [a]Isolated yields (%) reported for **2a**.

In order to probe the substrate scope with respect to the C-H bond functionalization of the indolizine coupling partner, the electronic effects on the reaction was investigated. As such, the C-H bond functionalization of six phenyl-substituted 1-methyl-2-phenylindolizine containing electron donating and withdrawing groups were investigated in comparison with the parent 1-methyl-2-phenylindolizine using the optimized conditions from Table 3. 4-Cyanophenyl-substituted rhodindolizine (**CN RhIndz**) was obtained in comparative yield relative to **RhIndz** (30% versus 35% respectively) indicating that the resonance withdrawing CN group is tolerated in this reaction. However, 4-trifluoromethylphenyl-substituted (**CF_3RhIndz**), 4-nitrophenyl-substituted rhodindolizine (**NO_2RhIndz**) and 3,5-ditrifluoromethylphenyl-substituted (**diCF_3RhIndz**), led to low or trace amounts of the corresponding products. The origin of the low yields is not obvious, but it is notable that the starting materials, compound **3** and indolizine precursors were not consumed during the reaction. Modifying the phenyl group with the electron donating phenol substituent led to only trace product, presumably due to the reaction not tolerating acidic functionality (Table 3, Entry 5.) On the other hand, the methoxy derivative gave a reasonable yield (20%) of the desired product (Table 3, Entry 6).

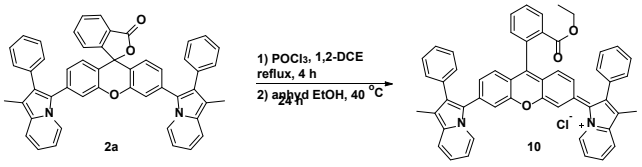
With **RhIndz** in hand, the reactivity of the spirolactone functionality was explored. Interestingly, upon exposure to strong Bronsted acids the lactone ring resisted ring opening. However, the ring opened acid chloride derivative could be prepared directly from the lactone using $POCl_3$ in refluxing 1,2-dichloroethane (Scheme 1),[76] which was reacted with anhydrous ethanol to form the ethyl ester (**10**). Having accessed both the ring closed (**2a**) and ring open (**10**) forms, the photophysical properties of these derivatives were investigated.

Table 3. Substrate Scope with Substituted Indolizines



compound	R group	yield (%) di : mono
CNRhIndz **4**	4-CNPh	30 : 14
CF_3RhIndz **5**	4-CF_3Ph	11 : 6
NO_2RhIndz **6**	4-NO_2Ph	trace
diCF_3RhIndz **7**	3,5-bisCF_3Ph	trace
HORhIndz **8**	4-OHPh	trace
MeORhIndz **9**	4-OMePh	20:0

The absorption maximum for **RhIndz** is 375 nm (SI Figure 1). However, upon the formation of the ethyl ester, a large bathochromic shift of 550 nm occurs shifting the maximum absorption to 920 nm, which is within the NIR II region. The dye also displays a high molar absorptivity of 97,500 $M^{-1}cm^{-1}$, which is critical for a practical molecular brightness (MB). Excitingly, dye **10** also exhibits an emission peak at ~1092 nm in the NIR II region, which is almost 200 nm Stokes shift (Figure 2). This observed emission is broad extending from 950 nm to just beyond 1400 nm in dichloromethane with a quantum yield (Φ) of ~0.03% when using a cyanine references dye (C5).[20] While this Φ appears low, we stress that very few molecular emissive materials exist in this region.[2] Additionally, a range of solvent polarities were evaluated to access the polarity of **RhIndz** in the ground-state via absorption spectroscopy and in the excited-state via fluorescence spectroscopy (SI Figure 2). Both the absorption and emission maxima varied by < 0.04 eV in energy for solvents ranging in dipole from 3.96 debye to 0.36 debye and with dielectric constants ranging from 46.7 to 3.96. These very large ranges of solvent properties show very small changes in the absorption maxima, which indicates minimal conformational or localized charge density changes occurring in the ground or excited state of **10** due to the solvent properties.



Scheme 1. Synthesis of RhIndz ethyl ester **10** from RhIndz **2a**

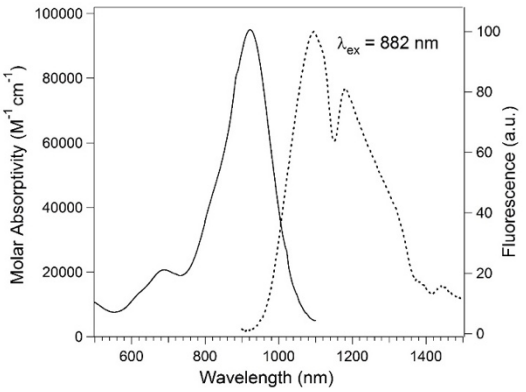


Figure 2. Molar absorptivity and emission of RhIndz ethyl ester in dichloromethane. Note: the drop in the emission spectrum at ~1150 nm is a possible spectrometer artifact (see SI Figure 3).

In conclusion, we have demonstrated the use of C-H bond functionalization reaction to prepare NIR II emissive dyes by the combination of the electron rich indolizine donor with the electron poor xanthene core. The best condition found was $PdCl_2(PPh_3)_2$ catalyst with KOAc base and NMP as solvent at 110 °C. CNRhIndz and MeORhIndz were also prepared by the C- bond activation reaction; while CF_3RhIndz, (diCF_3)RhIndz and OHRhIndz only gave trace amounts of the product, with recovery of the starting materials. The RhIndz dye, while not a typical rhodamine structure with N-xanthene bonds, was non-fluorescent in the closed spirocyclic structure; however, with the formation of the opened ethyl ester derivative, the fluorophore possessed absorption and emission within the NIR II region with high molar absorptivity and a Φ of ~0.03%. To the best of our knowledge, this is the first xanthene-based emissive dye with photophysical properties in the NIR II region.

EXPERIMENTAL SECTION

General Methods.

All chemicals and solvents were purchased from commercial suppliers and used without further purification unless otherwise specified. ^{1}H NMR (500 MHz) and ^{13}C NMR (500 MHz) spectra were recorded in deuterated solvents on a Bruker AVANCE 500 NMR Spectrometer. J values are expressed in Hz and quoted chemical shifts are in ppm downfield from tetramethylsilane (TMS) reference using the residual protonated solvents as an internal standard. The signals have been designated as follows: s (singlet), d (doublet), t (triplet), m (multiplets). High resolution mass spectra (HRMS) were determined on Bruker-micrOTOF-Q II Mass Spectrometer. Melting point was recorded on a Thermal Analysis (TA) Differential Scanning Calorimeter (Q200) under nitrogen flow. Absorption spectra were acquired using a Cary 5000 UV-Vis-NIR spectrophotometer in a 1-cm quartz cell. Fluorescence spectra were acquired using a Horiba QuantaMaster 8075-21 spectrofluorometer with xenon lamp excitation and liquid nitrogen cooled indium gallium arsenide solid state detector. The choice of 882 nm excitation was chosen to coincide with a Xe emission peak. The relative quantum yield of the rhodindolizine dye was calculated using a technique previously outlined by Miller et al.[77]A cyanine dye was chosen as the standard due to the similar absorption and emissive regions. The dye, C5, has a known quantum yield of 2.2%.[19] The absorbance point for the quantum yield was chosen because of similar overlap in the absorption spectra between the standard and the rhodindolizine dye. An excitation wavelength of 870 nm was used for both the C5 and rhodindolizine dyes. Both samples were solvated in DCM to a 10 μM concentration.

3-oxo-3H-spiro[isobenzofuran-1,9'-xanthene]-3',6'-diylbis(trifluoromethanesulfonate) (**1**) was prepared according to literature procedure.[72]

3',6'-dibromofluoran (**3**) was prepared according to literature procedure. [75]

Representative procedure for the preparation of **RhIndz** (**2a**) (Table 1)

Compound **1** (50 mg, 0.083 mmol), 1-methyl-2-phenylindolizine (35 mg, 0.167 mmol), solvent (0.34 – 2.0 mL), catalyst (5 – 10 mol %), base, and additives (pivalic acid) were placed in a microwave sealed tube, flushed with nitrogen and heated for 12 – 24 h at 80 – 150 °C according to Table 1. The reactions were monitored by TLC and NMR. Once it was determined that the reaction conversion has plateaued, the crude was diluted with 30 mL of dichloromethane and washed with water (5 x 10 mL). The crude product was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure.

*3',6'-bis(1-methyl-2-phenylindolizin-3-yl)-3H-spiro[2-benzofuran-1,9'-xanthen]-3-one (**2a**)*

The crude product was purified by column chromatography on silica gel (hexane: ethyl acetate, 70:30) to give the product (**2a**) as a light-yellow solid in 20% yield (12 mg). mp: 331.4 °C – 348.4 °C ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.11 (d, *J* = 7.2 Hz, 2H), 8.00 (d, *J* = 7.6 Hz, 1H), 7.73 (td, *J* = 7.6, 1.1 Hz, 1H), 7.68 – 7.63 (m, 1H), 7.40 (d, *J* = 9.0 Hz, 2H), 7.33 – 7.20 (m, 13H), 6.97 (dd, *J* = 8.2, 1.7 Hz, 2H), 6.78 (d, *J* = 8.2 Hz, 2H), 6.73 – 6.68 (m, 2H), 6.46 (t, *J* = 6.7 Hz, 2H), 2.31 (d, *J* = 4.5 Hz, 6H). ^{13}C{1H}NMR (126 MHz, CD_2Cl_2) δ 169.6, 153.3, 152.0, 135.82, 135.79, 135.1, 131.4, 131.2, 130.6, 129.3, 128.8, 128.6, 127.1, 126.9, 126.3, 126.2, 125.6, 124.6, 124.5, 124.3, 122.5, 120.4, 119.6, 118.7, 118.1, 117.9, 117.7, 117.2, 111.2, 108.2, 82.8, 9.5. HRMS-ESI-TOF (*m/z*): $[M+H]^+$ calcd for $C_{50}H_{34}N_2O_3H$ 711.2642 found 711.2642.

*3'-(1-methyl-2-phenylindolizin-3-yl)-3-oxo-3H-spiro[2-benzofuran-1,9'-xanthen]-6'-yl trifluoromethanesulfonate (**2b**)*

The crude product was purified by column chromatography on silica gel (hexane: ethyl acetate, 70:30) to give the product (**2b**) as a light-yellow solid in 22% yield (12 mg). mp: 234.6 °C – 256.8 °C ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.14 (s, 1H), 8.03 (d, *J* = 6.6 Hz, 1H), 7.73 – 7.67 (m, 2H), 7.54 (s, 1H), 7.41 (d, *J* = 7.7 Hz, 1H), 7.32 - 7.24 (m, 8H), 7.00 – 7.01 (m, 1H), 6.92 (br, s, 1H), 6.81 – 6.82 (m, 1H), 6.71 (br, s, 1H), 6.47 (br, s, 1H), 2.32 (s, 3H). ^{13}C{1H} NMR (126 MHz, CD_2Cl_2) δ 169.4, 153.2, 152.8, 152.3, 151.9, 135.86, 135.85, 135.8, 135.14, 135.12, 131.47 131.45, 131.2, 130.6, 129.5, 129.3, 128.8, 128.7, 126.9, 126.4, 125.6, 124.6, 122.5, 120.3, 118.8, 118.2, 118.1, 117.9 (q,

J_{C-F} = 320 Hz), 117.2, 111.3, 111.0, 108.2, 82.4, 9.5. HRMS-ESI-TOF (*m/z*): $[M+K]^+$ calcd for $C_{36}H_{22}F_3NO_6SK$ 692.0752 found 692.0751.

Representative procedure for the preparation RhIndz and phenyl-substituted RhIndz (Table 2 and Table 3)

The reaction was carried out in a sealed tube under nitrogen atmosphere in the presence of 3′,6′-dibromofluoran (**3**) (0.458 g, 1 mmol), 1-methyl-2-phenylindolizine (0.456 g, 2.2 mmol), solvent (3 mL), catalyst 10 mol %), base, and additives (PivOH) for 18 – 24 h at 110 °C. The reactions were monitored by TLC and ^{1}H NMR. Once it was determined that the reaction conversion had plateaued, the crude was diluted with 30 mL of dichloromethane and washed with water (5 x 10 mL). The crude product was dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (hexane: ethyl acetate, 70:30) to give the product (**2a**) as a light-yellow solid in 35% yield (244 mg).

4-(3-{3′-[2-(4-cyanophenyl)-1-methylindolizin-3-yl]-3-oxo-3H-spiro[2-benzofuran-1,9′-xanthen]-6′-yl}-1-methylindolizin-2-yl)benzonitrile (**4a**)

Yellow solid, 30 % yield, (25 mg). mp: 238.9 °C – 259.1 °C ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.09 (d, *J* = 7.1 Hz, 2H), 8.03 (d, *J* = 7.6 Hz, 1H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 4H), 7.42 (d, *J* = 9.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 4H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.22 (s, 2H), 6.93 (d, *J* = 8.2 Hz, 2H), 6.82 (d, *J* = 8.2 Hz, 2H), 6.76 – 6.71 (m, 2H), 6.50 (t, *J* = 6.8 Hz, 2H), 2.32 (s, 6H). ^{13}C{1H} NMR (126 MHz, CD_2Cl_2) δ 169.5, 153.2, 152.0, 141.1, 135.9, 134.5, 132.5, 131.8, 131.7, 130.7, 129.2, 127.3, 127.0, 126.5, 125.7, 124.5, 122.5, 120.6, 119.6, 118.9, 118.4, 118.3, 117.7, 111.9, 110.5, 108.1, 82.5, 9.5. . HRMS-ESI-TOF (*m/z*): $[M+K]^+$ calcd for $C_{52}H_{32}N_4O_3K$ 799.2106 found 799.2106

3′-(2-(4-cyanophenyl)-1-methylindolizin-3-yl)-3-oxo-3H-spiro[2-benzofuran-1,9′-xanthen]-6′-yltrifluormethanesufonate (**4b**)

Yellow solid, 14 % yield, (9 mg). mp: 239.4 °C – 255.3 °C ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.11 (d, *J* = 7.2 Hz, 1H), 8.04 (d, *J* = 7.4 Hz, 1H), 7.79 – 7.72 (m, 1H), 7.72 – 7.65 (m, 1H), 7.61 (s, 1H), 7.59 (s, 1H), 7.57 – 7.54 (m, 1H), 7.43 (d, *J* = 9.0 Hz, 1H), 7.38 – 7.30 (m, 3H), 7.26 (d, *J* = 5.6 Hz, 2H), 7.00 – 6.91 (m, 2H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.74 (dd, *J* = 8.7, 6.5 Hz, 1H), 6.50 (t, *J* = 6.8 Hz, 1H), 2.33 (d, *J* = 2.8 Hz, 3H). ^{13}C{1H} NMR (126 MHz, CD_2Cl_2) δ 169.6, 153.4, 152.1, 152.0, 142.8, 141.1, 135.9, 134.4, 132.5, 131.8, 131.8, 130.7, 129.21, 129.16, 127.3, 126.8, 126.4, 125.7, 124.5, 123.3, 122.5, 120.7, 119.6, 119.3, 119.0, 118.4, 118.3, 117.7, 116.2, 111.9, 110.5, 108.1, 82.4, 9.6. HRMS-ESI-TOF (*m/z*): $[M+K]^+$ calcd for $C_{36}H_{21}BrN_2O_3K$ 609.0808 found 609.0877

3′,6′-bis(2-(3,5-bis(trifluoromethyl)phenyl)-1-methylindolizin-3-yl)-3H-spiro[2-benzofuran-1,9′-xanthen]-3-one (**5a**)

Brown solid, 11% yield (10 mg). mp: 200.5 °C – 230.4 °C ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.09 (d, *J* = 7.2 Hz, 2H), 8.02 (d, *J* = 7.5 Hz, 1H), 7.78 – 7.72 (m, 1H), 7.70 – 7.64 (m, 1H), 7.57 (d, *J* = 8.1 Hz, 4H), 7.42 (d, *J* = 9.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 4H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 1.5 Hz, 2H), 6.96 (dd, *J* = 8.2, 1.6 Hz, 2H), 6.82 (d, *J* = 8.2 Hz, 2H), 6.73 (dd, *J* = 8.9, 6.5 Hz, 2H), 6.52 – 6.45 (m, 2H), 2.32 (s, 6H). ^{13}C{1H} NMR (126 MHz, CD_2Cl_2) δ 169.5, 153.2, 152.1, 140.0, 135.9, 134.7, 131.6, 131.5, 130.7 (q, $^2J_{C-F}$ = 32 Hz), 129.1, 128.8, 128.5 (q, $^3J_{C-F}$ = 4 Hz), 127.6, 127.0, 126.4, 126.2, 125.7, 125.6, 125.5, 124.5 (q, $^1J_{C-F}$ = 272 Hz), 124.0, 122.5, 120.6, 118.9, 118.3, 118.2, 117.6, 111.7, 108.2, 82.6, 9.5. . HRMS-ESI-TOF (*m/z*): $[M+H]^+$ calcd for $C_{52}H_{32}F_6N_2O_3H$ 847.2389 found 847.2389

3′-(1-methyl-2-(4-(trifluoromethyl)phenyl)indolizin-3-yl)-3-oxo-3H-spiro[2-benzofuran-1,9′-xanthen]-6′-yltrifluoromethanesulfonate (**5b**)

Brown solid, 6% yield (5 mg). mp: 205.9 °C – 255.9 °C ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.11 (d, *J* = 7.2 Hz, 1H), 8.04 (d, *J* = 7.3 Hz, 1H), 7.71 (dt, *J* = 20.2, 7.2 Hz, 2H), 7.62 – 7.51 (m, 3H), 7.47 – 7.23 (m, 6H), 6.99 (d, *J* = 8.1 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.78 – 6.69 (m, 1H), 6.49 (t, *J* = 6.7 Hz, 1H), 2.33 (s, 3H). ^{13}C{1H} NMR (126 MHz, CD_2Cl_2) δ 169.6, 153.4, 152.11, 152.06, 142.8, 140.0, 135.9, 134.7, 131.6, 131.5, 130.7 (q, $^2J_{C-F}$ = 32 Hz), 129.2, 129.1, 128.5 (q, $^3J_{C-F}$ = 4 Hz), 127.6, 126.9, 126.4, 125.7, 125.57, 125.55, 124.5 (q, $^1J_{C-F}$ = 272 Hz), 123.2, 122.5, 120.6, 119.3, 119.0, 118.3, 118.2, 117.5, 116.2, 111.7, 108.2, 82.4, 9.6. HRMS-ESI-TOF (*m/z*): $[M+K]^+$ calcd for $C_{36}H_{21}BrF_3NO_3K$ 690.0288 found 690.0284

3′,6′-bis(2-(4-methoxyphenyl)-1-methylindolizin-3-yl)-3H-spiro[2-benzofuran-1,9′-xanthen]-3-one (**9a**)

Pale Green solid, 20 % yield (17 mg). mp: 236.2 °C – 255.2 °C ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.11 (d, *J* = 7.1 Hz, 2H), 8.01 (d, *J* = 7.6 Hz, 1H), 7.74 (t, *J* = 7.4 Hz, 1H), 7.66 (t, *J* = 7.3 Hz, 1H), 7.39 (d, *J* = 8.9 Hz, 2H), 7.31 – 7.23 (m, 3H), 7.13 (t, *J* = 9.3 Hz, 4H), 6.96 (d, *J* = 8.2 Hz, 2H), 6.85 (d, *J* = 7.1 Hz, 4H), 6.78 (d, *J* = 8.1 Hz, 2H), 6.68 (dd, *J* = 15.7, 7.7 Hz, 2H), 6.44 (t, *J* = 6.7 Hz, 2H), 3.79 (s, 6H), 2.29 (s, 6H). ^{13}C NMR (126 MHz, CD_2Cl_2) δ 169.6, 158.9, 153.3, 152.0, 135.8, 135.3, 132.2, 131.5, 130.6, 128.9, 128.8, 127.9, 127.1, 126.3, 125.6, 124.6, 122.4, 120.3, 118.7, 118.0, 117.8, 117.1, 114.1, 111.1, 108.2, 82.8, 55.7, 9.5. HRMS-ESI-TOF (*m/z*): $[M+K]^+$ calcd for $C_{52}H_{38}N_2O_5K$ 809.2412 found 809.2411

(Z)-3-(9-(2-(ethoxycarbonyl)phenyl)-6-(1-methyl-2-phenylindolizin-3-yl)-3H-xanthen-3-ylidene)-1-methyl-2-phenyl-3H-indolizin-4-ium (**10**)

Compound **2a** (80 mg, 0.112 mmol) was transferred to a 150 mL two neck round bottom flask and flushed with nitrogen thoroughly for 10 minutes. 1,2-Dichloroethane (4.8 mL) and $POCl_3$ (0.03 mL) were added to the flask and the reaction was refluxed for 4 h. The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure to give a green solid, which was used in the next step without further purification. The reaction mixture was thoroughly flushed with nitrogen for 10 min, followed by the addition of dry ethanol (3.0 mL), and stirring at 50 ºC for 24 h. The reaction mixture was concentrated under reduced pressure and the solid was dissolved in chloroform (20 mL). The organic layer was washed with water (8 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a green solid. The solid was then washed with hot hexane (20 x 5 mL), and recrystallize from hexane: ethyl acetate mixture to give 28 mg of a green solid in 34% yield. mp: 303.7 °C – 329.1 °C ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.32 (s, 1H), 8.11 (d, *J* = 5.9 Hz, 1H), 8.01 (d, 1H), 7.79 (s, 2H), 7.73 (s, 1H), 7.66 (t, 1H), 7.57 (s, 1H), 7.41 (s, 4H), 7.27 (dd, *J* = 29.1, 13.4 Hz, 10H), 6.93 (d, *J* = 26.1 Hz, 2H), 6.83 (d, *J* = 6.4 Hz, 1H), 6.78 (d, *J* = 7.4 Hz, 1H), 6.70 (t, 1H), 6.46 (t, 1H), 4.09 (q, 2H), 2.35 – 2.23 (m, 6H), 1.31 (t, 3H). ^{13}C{1H} NMR (126 MHz, $CDCl_3$) δ 165.4, 161.2, 157.1, 142.7, 137.5, 135.3, 134.7, 134.6, 134.4, 133.9, 133.3, 131.3, 131.2, 131.1, 130.9, 130.8, 130.7, 130.2, 129.3, 129.1, 129.0, 128.8, 128.5, 128.4, 127.8, 126.6, 126.0, 125.4, 124.9,

124.0, 122.2, 122.14, 122.09, 118.34, 118.30, 117.9, 117.4, 116.9, 115.1, 114.3, 113.1, 111.0, 107.9, 61.9, 14.3, 9.4. HRMS-ESI-TOF (*m/z*): $[M]^+$ calcd for $C_{52}H_{39}N_2O_3^+$ 739.2955 found 739.2924

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Further optimization of Tables 1 and 2 (PDF); Absorption Spectrum of compound 2a (PDF); Proton and Carbon NMR (PDF)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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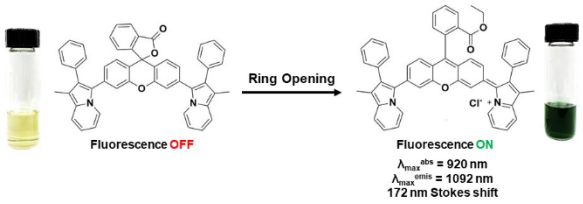

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