Synthesis F.-P. Liu et al. Paper

Preparation of 2-(3-Methyleneindolin-2-yl)phenols via Sodium Hydride Promoted C–C/C–O Bond Cleavage

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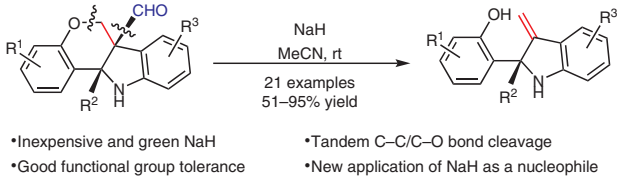

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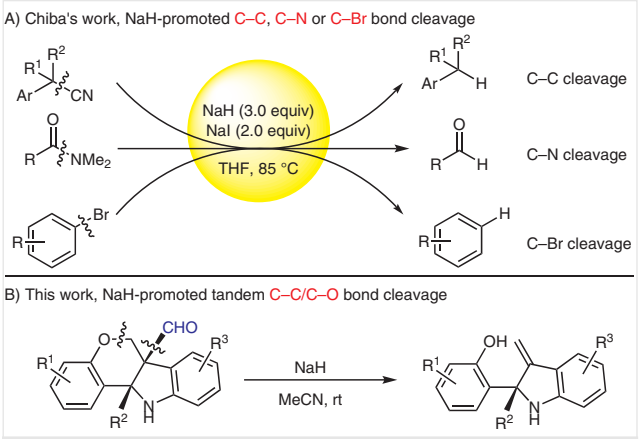
Abstract A variety of 2-(3-methyleneindolin-2-yl)phenols were prepared in good to excellent yields through a NaH-promoted C–C/C–O bond cleavage of fused indolines under mild and simple conditions. Mechanistic studies showed that NaH serves as a nucleophile, attacking the aldehyde group of indoline, which is followed by tandem C–C/C–O bond cleavage to afford the desired products. A representative 2-(3-methyleneindolin-2-yl)phenol was easily prepared on a gram scale.

Key words cascade reaction, C–C/C–O bond cleavage, indolines, phenols, sodium hydride

Sodium hydride (NaH) is a structurally simple, inexpensive, and environmentally benign reagent in organic synthesis because hydrogen is usually produced as byproduct in the reaction.[1] It is usually used as a mixture of 60% NaH (w/w) in mineral oil, available from many suppliers, which is safer to handle and weigh than pure NaH.[2] Typically, NaH is one of the most widely used reagents as a base for the deprotonation of alcohols, amides, or esters to promote their substitution and related cascade reactions.[3] However, NaH is rarely used as a reductant or a nucleophile to promote an organic transformation.[4] Chiba and co-workers developed a unique NaH–LiI or NaI composite system to promote C–C, C–N, or C–Br bond cleavage of nitriles, amides, and aryl halides (Scheme 1-A).[5] In this context, it is evident that NaH possesses a highly important utility in organic reactions, greener and more environmentally friendly than transition-metal catalysis in modern organic chemistry, and thus a good complement to transition-metal catalysis for purity requirements in biological and medicinal research.[6] Therefore, the development of novel and efficient applications of NaH in green organic transformations is desirable, especially for the synthesis of indoline alkaloids because of their importance in pharmaceuticals.



Scheme 1 NaH-promoted C–C or carbon–heteroatom bond cleavage

Recently, we reported that fused indolines containing C2/C3 quaternary carbons can be easily prepared in good yields from oximes and diaryliodonium salts through a selective *N*-arylation and cycloaddition cascade strategy.[7] During the continuing research on these indoline scaffolds, we found that the fused indolines containing C2/C3 quaternary carbons could be easily converted into 2-(3-methyleneindolin-2-yl)phenols via NaH-promoted C–C/C–O bond cleavage under mild and simple conditions. However, the role of NaH was unclear and the substrate scope to access the 2-(3-methyleneindolin-2-yl)phenols remained unexplored. On the other hand, indoline scaffolds are important cores, existing in a variety of indole alkaloids, such as kopsanone, scholarisine A, preakuammicine, and phalarine.[8] To

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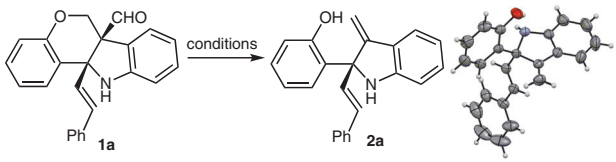
date, many strategies to construct these scaffolds have been developed and successfully used to synthesize complex natural products.[9] To establish the role of NaH and the reaction scope, herein we report a NaH-promoted C–C/C–O bond cleavage of easily accessed fused indolines to prepare 2-(3-methyleneindolin-2-yl)phenols under mild and simple conditions (Scheme 1-B).

Initially, we found that when fused indoline **1a** was treated with 3.0 equivalents of NaH in DMSO at room temperature for 2 hours, the 2-(3-methyleneindolin-2-yl)phenol product **2a** was obtained in 89% yield (Table 1, entry 1). The structure of compound **2a** was confirmed by X-ray diffraction analysis,[10] showing that the NaH-promoted C–C bond and C–O bond cleavage had occurred in a one-pot manner. It is noteworthy that the NaH we used was a mixture of 60% NaH (w/w) in mineral oil. Next, solvent screening showed that low yields of product **2a** were obtained in DMF, DCE, or toluene, while the reaction in THF failed to afford **2a** (entries 2–5). However, a 38% yield of **2a** was obtained in THF when 3.0 equivalents of NaI were added (entry 6). Pleasingly, a 90% yield of **2a** was obtained when MeCN was used as solvent (entry 7). We surmised that NaH might play a role as a base. Consequently, the influence of base was also investigated. Both KOH and NaOH promoted the reaction and afforded product **2a** in 46% yield (entries 8, 9). However, K_2CO_3 did not participate in the reaction and no conversion was observed after 24 hours (entry 10). To our surprise, when NaH was replaced by other hydrides, such as $NaBH_4$ and $LiAlH_4$, desired product **2a** was not observed and only the aldehyde reduction product was obtained in a quantitative yield (entries 11, 12). The use of 4.0 or 2.0 equivalents of NaH delivered **2a** in 53% and 74% yield, respectively (entries 13, 14). When the reaction temperature was increased to 60 °C, the yield of **2a** dropped to 65% (entry 15). No reaction occurred in the absence of NaH (entry 16). Hence, the optimal conditions for preparing product **2a** were 3.0 equivalents of NaH in MeCN at room temperature.

With the optimal reaction conditions in hand, we next explored the substrate scope with a variety of fused indolines **1** to prepare 2-(3-methyleneindolin-2-yl)phenols **2** (Scheme 2). Various R^2 styrenyl groups bearing an electron-donating or electron-withdrawing group at the *para*-, *meta*-, or *ortho*-position of the aryl ring were well tolerated, affording the corresponding products **2a**–**2g** in good to excellent yields. It can be seen that the styrenyl groups with an electron-donating group gave better yields than those with an electron-withdrawing group (**2a**, **2b** vs **2c**, **2d**). The R^3 group on the aryl ring was compatible with various substituents, including electron-donating and electron-withdrawing groups at the *para*-, *meta*-, or *ortho*-positions, to result in products **2h**–**2q** in moderate to good yields. Some R^3 electron-withdrawing groups resulted in lower yields because of the recovery of starting materials (**2k** and **2m**).

Table 1 Optimization of the Reaction Conditions[a]

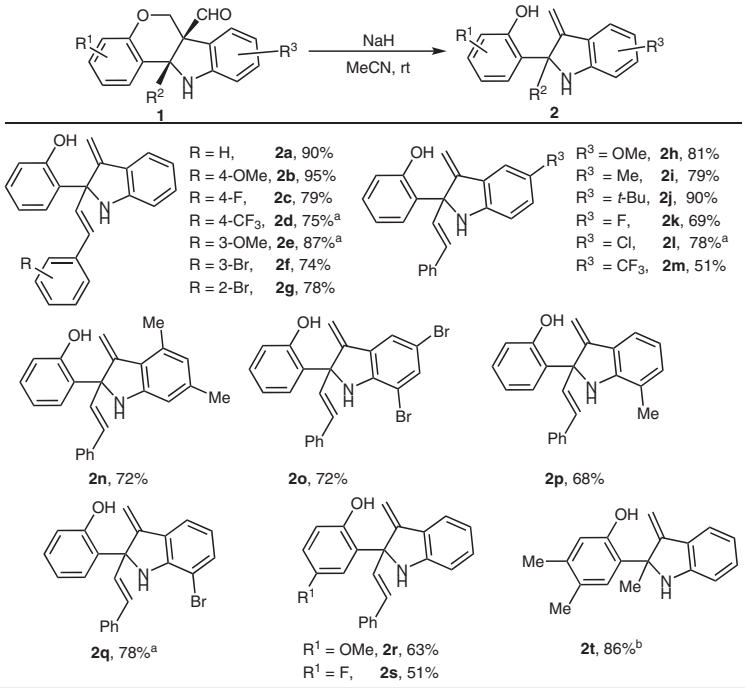


Entry	Base	Solvent	Yield (%) of **2a**[b]
1	NaH	DMSO	89
2	NaH	DMF	31
3	NaH	DCE	52
4	NaH	toluene	21
5	NaH	THF	<5, 25[c]
6	NaH	THF	38[d]
7	NaH	MeCN	90
8	KOH	MeCN	46
9	NaOH	MeCN	46
10	K_2CO_3	MeCN	<5
11	$NaBH_4$	MeCN	–
12	$LiAlH_4$	MeCN	–
13	NaH	MeCN	53[e]
14	NaH	MeCN	74[f]
15	NaH	MeCN	65[g]
16	–	MeCN	–

[a] Reaction conditions: **1a** (0.2 mmol), base (0.6 mmol, 3.0 equiv), solvent (2.0 mL), rt, 1–24 h.
[b] Isolated yield.
[c] Run for 48 h.
[d] NaI (3.0 equiv) added.
[e] NaH (4.0 equiv).
[f] NaH (2.0 equiv).
[g] Run at 60 °C.

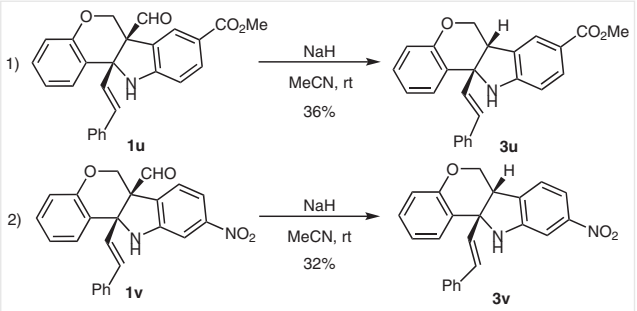
Product **2r** bearing a methoxy group as R^1 was obtained in better yield than **2s** with a fluoro group. To our surprise, when the reaction of substrate **1t** with a methyl group as the R^2 group was conducted under the optimized conditions, no desired product **2t** was observed. However, lowering the temperature to 0 °C afforded the desired **2t** in 86% yield.

Interestingly, when the R^3 group was an ester at the *para*-position of the aryl ring, namely **1u**, the desired 2-(3-methyleneindolin-2-yl)phenol was not observed. However, decarbonylation product **3u** was obtained in 36% yield (Scheme 3-1). Similarly, **1v** with R^3 as a nitro group at the *meta*-position of the aryl ring also afforded decarbonylation product, in this case **3v** in 32% yield (Scheme 3-2). The yields of compound **3u** and **3v** were low because the reaction did not run to completion even after a long reaction time (48 h), and recovered starting material **1u**/**1v** was isolated. Moreover, compound **2u** or **2v** cannot be observed in these two examples. In comparison, the reaction of **1k** and



Scheme 2 Reaction scope of C–C/C–O bond cleavage to prepare 2-(3-methyleneindolin-2-yl)phenols **2**. *Reagents and conditions*: **1** (0.2 mmol), NaH (0.6 mmol, 3.0 equiv, 60% NaH (w/w) in mineral oil), MeCN (2.0 mL), rt, 1–12 h; isolated yields. [a] Run for 4–6 h. [b] Run at 0 °C.

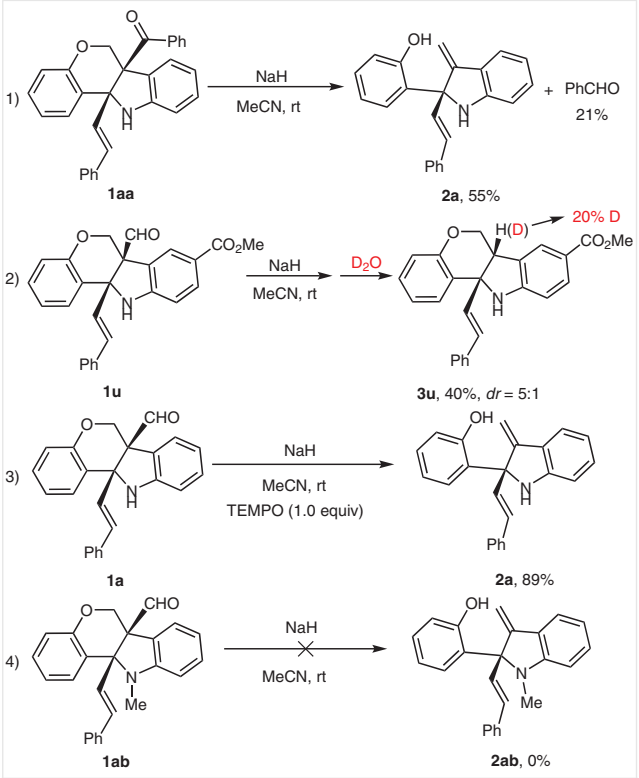
1m with F and CF_3 at the *para*-position of the aryl ring (Scheme 2) afforded **2k** and **2m**, and not **3k** and **3m**, under the standard conditions. These results indicated that strong electron-withdrawing groups at the aryl ring of the indoline moiety inhibit the sequential C–O bond cleavage. The formation of compound **3** might require a strong electron-withdrawing group, such as NO_2 or CO_2Me, to stabilize the intermediate of C–C bond cleavage.



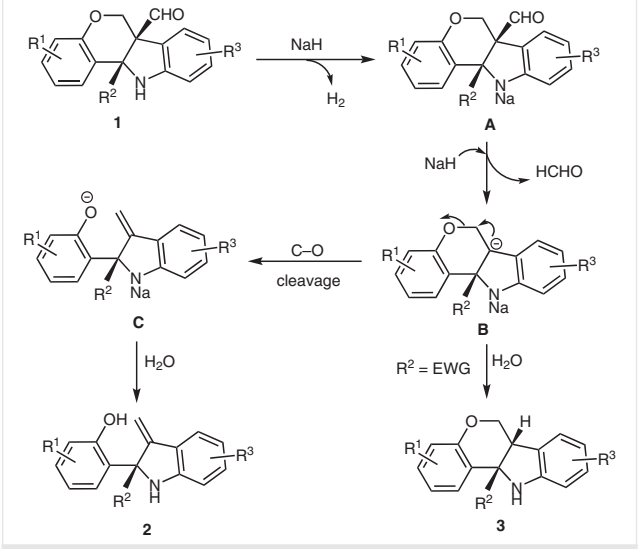
Scheme 3 Substituent effect on the formation of fused indolines **3**

To better understand the mechanism for the formation of compounds **2** and **3**, control experiments were performed (Scheme 4). When compound **1aa** was subjected to the optimized conditions, desired **2a** was obtained in 55% yield accompanied by a 21% yield of benzaldehyde (Scheme 4-1). This result revealed that the reaction should release one equivalent of aldehyde through C–C bond cleavage by NaH. Compound **1u** was reacted with NaH; then, the reaction was quenched with D_2O. Expected product **3u** was obtained in 40% yield with a 5:1 *dr*, and 20% deuteration at the indoline C3-position was observed (Scheme 4-2). This result indicates that the formation of compound **3** involved an intermolecular protonation step. When **1a** was subjected to the standard conditions with the addition of TEMPO (1.0 equiv), product **2a** was still obtained in 89% yield, which suggests that the reaction might not involve a radical process (Scheme 4-3). No reaction occurred with *N*-methyl-protected substrate **1ab** under the standard conditions, with the recovery of starting material **1ab** (Scheme 4-4).

Based on the experimental results, a plausible mechanism for the formation of compounds **2** and **3** is proposed. As shown in Scheme 5, deprotonation of compound **1** forms intermediate **A** and releases hydrogen. Then, NaH might serve as a nucleophile to attack the aldehyde group of **A**, which then undergoes C–C bond cleavage to provide carbanion intermediate **B** with release of HCHO. C–O bond cleavage of **B** provides intermediate **C**. Intermediate **C** is quenched with water affording compound **2**. Alternatively, R^3 as a strong electron-withdrawing group stabilizes the carbanion of **B**. Finally, intermediate **B** undergoes protonation to afford compound **3**. It is noteworthy that the substituent effect of the aryl ring of indoline controls the selectivity for formation of compounds **2** and **3**.

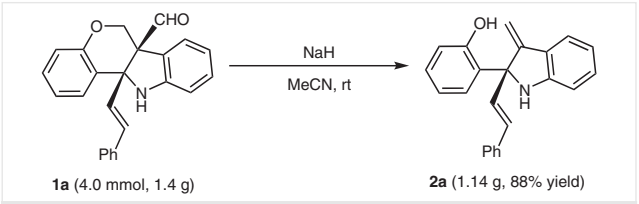


Scheme 4 Mechanistic studies



Scheme 5 Proposed mechanism

To show the efficiency of this protocol for preparing 2-(3-methyleneindolin-2-yl)phenols, a gram-scale preparation of **2a** was performed (Scheme 6). When compound **1a** (1.4 g) was subjected to the optimal NaH conditions for 4 hours, phenol **2a** was obtained in 88% yield (1.14 g). The gram-scale preparation of 2-(3-methyleneindolin-2-yl)phenols by this simple procedure allows further potential applications of these compounds in pharmaceuticals.



Scheme 6 Gram-scale preparation of 2-(3-methyleneindolin-2-yl)phenol **2a**

In summary, we have developed a novel NaH-promoted tandem C–C/C–O bond cleavage of fused indolines to prepare a variety of 2-(3-methyleneindolin-2-yl)phenols. Preliminary results show that NaH serves as a nucleophile in the reaction. The present method features mild and simple conditions, gram-scale preparation, tandem C–C/C–O bond cleavage, and a new application of NaH in organic transformations.

All reactions were performed under a N_2 atmosphere except noted. Commercially available reagents were used without further purification. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a 400 or 500 MHz Bruker Avance instrument with TMS as the internal standard. NMR data are represented as follows: chemical shift (ppm), multiplicity (standard abbreviations), coupling constant(s) in hertz (Hz), and integration. IR spectra were recorded on a PerkinElmer/Spectrum Two FT-IR spectrophotometer, and only major peaks are reported (in cm^{-1}). HRMS were measured on a Thermo Fisher Scientific/Exactive spectrometer in ESI mode with a TOF mass analyzer. Flash column chromatography was performed on silica gel (300–400 mesh). The fused indolines **1a**–**1q**, **1s**–**1v**, **1aa**, and **1ab**[7] were prepared according to literature methods and their spectroscopic data matched literature values.

Fused Indolines 1; General Procedure[7]

A Teflon-sealed reaction flask was charged with an alkynyl-tethered oxime (0.2 mmol), a diaryliodonium salt (0.4 mmol, 2.0 equiv), and KOH (0.24 mmol, 1.2 equiv) under an air atmosphere, and CCl_4 (2.0 mL) was added. The reaction vessel was sealed with a Teflon cap and stirred vigorously at 25 °C for 3–12 h until the starting material disappeared (monitored by TLC). Then, the reaction mixture was stirred vigorously at 80 °C for 3–6 h (monitored by TLC). After this time, the solvent was removed under reduced pressure and the crude product was purified by flash chromatography (the crude residue was dry-loaded with silica gel; EtOAc/petroleum ether, 1:50 to 1:10) to provide the fused indoline **1**.

(*E*)-2-Methoxy-11a-styryl-6,6a,11,11a-tetrahydrochromeno[4,3-*b*]indole-6a-carbaldehyde (1r)

Yield: 0.054 g (70%); yellow solid; mp 119–120 °C.

IR (thin film): 3454, 2834, 1605, 1496, 1210, 1055, 813, 749 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.57 (s, 1 H), 7.37–7.36 (m, 2 H), 7.32–7.24 (m, 3 H), 7.15–7.11 (m, 2 H), 7.00 (d, *J* = 16.0 Hz, 1 H), 6.84–6.77 (m, 2 H), 6.73–6.68 (m, 3 H), 6.46 (d, *J* = 15.6 Hz, 1 H), 4.70 (d, *J* = 12.4 Hz, 1 H), 4.38 (s, 1 H), 4.34 (d, *J* = 12.0 Hz, 1 H), 3.70 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.0, 154.6, 149.9, 148.3, 135.7, 132.6, 130.1, 129.0, 128.6, 128.2, 127.6, 126.8, 124.7, 122.8, 120.3, 118.5, 115.0, 111.9, 110.8, 70.1, 63.3, 61.7, 55.7.

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{22}NO_3$ [M + H]$^+$: 384.1594; found: 384.1617.

2-(3-Methyleneindolin-2-yl)phenols 2 and Fused Indolines 3; General Procedure

A Teflon-sealed flask was charged with a fused indoline **1** (0.2 mmol) and NaH (0.6 mmol, 3.0 equiv, 60% NaH (w/w) in mineral oil) under N_2 atmosphere. Then, MeCN (2.0 mL) was added. The reaction vessel was sealed with a Teflon cap and stirred vigorously at rt (about 30 °C) for 1–12 h until the substrate **1** disappeared (monitored by TLC). After this time, the reaction was quenched with H_2O (5 mL) and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and filtered. The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (the crude residue was dry-loaded with silica gel; EtOAc/petroleum ether, 1:50 to 1:10) to provide compounds **2** and **3**.

(*E*)-2-(3-Methylene-2-styrylindolin-2-yl)phenol (2a)

Yield: 0.059 g (90%); white solid; mp 178–179 °C.

IR (thin film): 3324, 2926, 1502, 1459, 1251, 1124, 875, 751 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.98 (s, 1 H), 7.50 (d, *J* = 7.6 Hz, 1 H), 7.37 (d, *J* = 7.2 Hz, 2 H), 7.31–7.27 (m, 2 H), 7.24–7.17 (m, 4 H), 6.97 (t, *J* = 7.6 Hz, 1 H), 6.90–6.85 (m, 3 H), 6.60 (d, *J* = 15.6 Hz, 1 H), 6.47 (d, *J* = 15.6 Hz, 1 H), 5.71 (s, 1 H), 4.71 (s, 1 H), 4.44 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.8, 148.2, 147.1, 136.0, 131.3, 130.4, 130.2, 129.5, 129.1, 128.8, 128.6, 128.1, 126.8, 126.4, 122.0, 121.4, 119.2, 117.9, 113.6, 106.7, 74.5.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{20}NO$ [M + H]$^+$: 326.1539; found: 326.1534.

(*E*)-2-(2-(4-Methoxystyryl)-3-methyleneindolin-2-yl)phenol (2b)

Yield: 0.067 g (95%); white solid; mp 153–154 °C.

IR (thin film): 2927, 1604, 1460, 1257, 1100, 807 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.98 (s, 1 H), 7.44 (d, *J* = 7.2 Hz, 1 H), 7.33–7.29 (m, 3 H), 7.14–7.06 (m, 2 H), 6.87–6.85 (m, 2 H), 6.82 (d, *J* = 8.8 Hz, 1 H), 6.78 (d, *J* = 7.6 Hz, 1 H), 6.74 (d, *J* = 9.6 Hz, 1 H), 6.68–6.64 (m, 1 H), 6.50 (d, *J* = 16.0 Hz, 1 H), 6.33 (d, *J* = 16.0 Hz, 1 H), 5.70 (s, 1 H), 4.81 (s, 1 H), 3.72 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.6, 156.8, 148.2, 147.1, 130.7, 130.1, 129.4, 129.1, 128.9, 128.6, 128.3, 128.0, 126.6, 121.9, 121.4, 119.1, 117.9, 114.0, 113.7, 106.7, 74.7, 55.3.

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{22}NO_2$ [M + H]$^+$: 356.1645; found: 356.1640.

(*E*)-2-(2-(4-Fluorostyryl)-3-methyleneindolin-2-yl)phenol (2c)

Yield: 0.054 g (79%); white solid; mp 156–157 °C.

IR (thin film): 3316, 2926, 1600, 1459, 1251, 1232, 816, 756 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.94 (s, 1 H), 7.45–7.42 (m, 3 H), 7.31 (d, *J* = 7.6 Hz, 1 H), 7.14–7.11 (m, 2 H), 7.09–7.05 (m, 1 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 6.78–6.73 (m, 2 H), 6.69–6.57 (m, 3 H), 6.38 (d, *J* = 16.0 Hz, 1 H), 5.71 (s, 1 H), 4.85 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.6 (d, *J* = 246.9 Hz), 156.8, 148.0, 147.0, 132.1 (d, *J* = 2.8 Hz), 130.2, 130.1, 129.6, 129.0, 128.8, 128.4, 128.3, 126.3, 122.0, 121.4, 119.2, 118.0, 115.6 (d, *J* = 21.0 Hz), 113.7, 106.8, 74.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –113.5.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{19}FNO$ [M + H]$^+$: 344.1445; found: 344.1440.

(*E*)-2-(3-Methylene-2-(4-(trifluoromethyl)styryl)indolin-2-yl)phenol (2d)

Yield: 0.059 g (75%); white solid; mp 181–182 °C.

IR (thin film): 2963, 1616, 1461, 1327, 1106, 804 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.93 (s, 1 H), 7.62 (s, 3 H), 7.43 (d, *J* = 7.6 Hz, 1 H), 7.33 (d, *J* = 7.6 Hz, 1 H), 7.15–7.11 (m, 1 H), 7.09–7.05 (m, 1 H), 6.85–6.70 (m, 5 H), 6.66–6.62 (m, 1 H), 6.49 (d, *J* = 15.6 Hz, 1 H), 5.74 (s, 1 H), 4.91 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.3, 151.5, 150.7, 141.5, 137.8, 130.7, 129.3, 129.0, 128.9, 128.5, 128.4, 128.1 (q, *J* = 31.3 Hz), 127.5, 126.3 (q, *J* = 3.8 Hz), 123.6 (q, *J* = 245.8 Hz), 121.7, 119.1, 118.3, 117.1, 110.7, 105.1, 72.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –62.6.

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{19}F_3NO$ [M + H]$^+$: 394.1413; found: 394.1408.

(*E*)-2-(2-(3-Methoxystyryl)-3-methyleneindolin-2-yl)phenol (2e)

Yield: 0.061 g (87%); white solid; mp 158–159 °C.

IR (thin film): 3321, 2932, 1577, 1459, 1250, 1156, 883, 762 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.96 (s, 1 H), 7.44 (d, *J* = 7.2 Hz, 1 H), 7.33 (d, *J* = 7.2 Hz, 1 H), 7.23–7.19 (m, 1 H), 7.15–7.06 (m, 2 H), 6.98–6.95 (m, 2 H), 6.85–6.81 (m, 1 H), 6.79–6.77 (m, 2 H), 6.75–6.72 (m, 1 H), 6.69–6.66 (m, 2 H), 6.39 (d, *J* = 16.0 Hz, 1 H), 5.73 (s, 1 H), 4.88 (s, 1 H), 3.73 (s, 3 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 160.1, 156.4, 151.3, 150.8, 138.7, 134.7, 130.6, 130.2, 129.1, 129.0, 128.6, 127.6, 126.2, 121.7, 119.4, 119.0, 118.3, 117.1, 113.9, 111.8, 110.8, 105.0, 73.0, 55.6.

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{22}NO_2$ [M + H]$^+$: 356.1645; found: 356.1640.

(*E*)-2-(2-(3-Bromostyryl)-3-methyleneindolin-2-yl)phenol (2f)

Yield: 0.060 g (74%); white solid; mp 185–186 °C.

IR (thin film): 3325, 2962, 1602, 1457, 1248, 1101, 805, 760 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.91 (s, 1 H), 7.62 (s, 1 H), 7.42–7.38 (m, 3 H), 7.31 (d, *J* = 7.6 Hz, 1 H), 7.27–7.23 (m, 1 H), 7.14–7.05 (m, 2 H), 6.82 (d, *J* = 8.4 Hz, 1 H), 6.78–6.70 (m, 2 H), 6.66–6.62 (m, 2 H), 6.39 (d, *J* = 16.0 Hz, 1 H), 5.72 (s, 1 H), 4.89 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 158.3, 151.4, 150.7, 136.4, 134.0, 131.4, 130.7, 130.5, 129.2, 129.0, 128.6, 126.1, 126.0, 122.8, 121.7, 119.1, 118.3, 117.1, 110.8, 105.1, 72.8.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{19}BrNO$ [M + H]$^+$: 404.0645; found: 404.0638.

(*E*)-2-(2-(2-Bromostyryl)-3-methyleneindolin-2-yl)phenol (2g)

Yield: 0.063 g (78%); white solid; mp 149–150 °C.

IR (thin film): 3431, 1606, 1461, 1246, 747 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.93 (s, 1 H), 7.52–7.47 (m, 3 H), 7.27–7.19 (m, 4 H), 7.11–7.07 (m, 1 H), 6.99–6.96 (m, 2 H), 6.91–6.87 (m, 3 H), 6.37 (d, *J* = 15.6 Hz, 1 H), 5.74 (s, 1 H), 4.75 (s, 1 H), 4.48 (br s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.7, 148.1, 146.9, 136.2, 133.1, 132.9, 130.6, 130.2, 129.6, 129.2, 129.0, 128.7, 127.5, 127.2, 126.0, 124.1, 122.0, 121.5, 119.2, 118.0, 113.5, 106.8, 74.5.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{19}BrNO$ $[M + H]^+$: 404.0645; found: 404.0638.

(*E*)-2-(5-Methoxy-3-methylene-2-styrylindolin-2-yl)phenol (2h)

Yield: 0.058 g (81%); white solid; mp 165–166 °C.

IR (thin film): 3433, 2924, 1640, 1459, 1116, 761 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.45 (s, 1 H), 7.38–7.37 (m, 2 H), 7.32–7.28 (m, 2 H), 7.25–7.20 (m, 3 H), 7.04 (s, 1 H), 6.90–6.80 (m, 4 H), 6.60 (d, *J* = 15.6 Hz, 1 H), 6.49 (d, *J* = 15.6 Hz, 1 H), 5.69 (s, 1 H), 4.72 (s, 1 H), 4.28 (br s, 1 H), 3.81 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.0, 155.6, 148.5, 140.6, 136.0, 131.3, 130.5, 130.1, 129.5, 129.0, 128.6, 128.1, 126.8, 126.3, 119.0, 117.9, 117.1, 114.7, 106.9, 105.9, 75.2, 55.8.

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{22}NO_2$ $[M + H]^+$: 356.1645; found: 356.1638.

(*E*)-2-(5-Methyl-3-methylene-2-styrylindolin-2-yl)phenol (2i)

Yield: 0.054 g (79%); white solid; mp 153–154 °C.

IR (thin film): 3432, 1638, 1384, 749 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 10.25 (s, 1 H), 7.38–7.37 (m, 2 H), 7.32–7.29 (m, 2 H), 7.24–7.21 (m, 4 H), 7.03 (d, *J* = 8.0 Hz, 1 H), 6.90 (d, *J* = 8.0 Hz, 1 H), 6.87 (d, *J* = 8.0 Hz, 1 H), 6.81 (d, *J* = 8.0 Hz, 1 H), 6.61 (d, *J* = 15.5 Hz, 1 H), 6.48 (d, *J* = 15.5 Hz, 1 H), 5.69 (s, 1 H), 4.69 (s, 1 H), 4.36 (br s, 1 H), 2.33 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.9, 148.2, 144.7, 136.0, 131.6, 131.3, 131.0, 130.5, 129.5, 129.1, 129.0, 128.6, 128.5, 128.1, 126.8, 126.7, 126.4, 121.8, 119.0, 117.9, 113.6, 106.4, 74.9, 20.6.

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{22}NO$ $[M + H]^+$: 340.1696; found: 340.1691.

(*E*)-2-(5-*tert*-Butyl-3-methylene-2-styrylindolin-2-yl)phenol (2j)

Yield: 0.069 g (90%); white solid; mp 150–151 °C.

IR (thin film): 3318, 2961, 1609, 1490, 1257, 1108, 815, 748 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.26 (s, 1 H), 7.51 (s, 1 H), 7.39–7.37 (m, 2 H), 7.32–7.28 (m, 3 H), 7.24–7.20 (m, 3 H), 6.89–6.81 (m, 3 H), 6.62 (d, *J* = 16.0 Hz, 1 H), 6.48 (d, *J* = 16.0 Hz, 1 H), 5.72 (s, 1 H), 4.69 (s, 1 H), 4.35 (br s, 1 H), 1.32 (s, 9 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.9, 148.7, 145.2, 144.7, 136.1, 131.3, 130.5, 129.4, 129.0, 128.6, 128.5, 128.1, 127.6, 126.8, 126.6, 119.0, 118.0, 117.9, 113.3, 106.1, 74.9, 34.5, 31.6.

HRMS (ESI): *m*/*z* calcd for $C_{27}H_{28}NO$ $[M + H]^+$: 382.2165; found: 382.2156.

(*E*)-2-(5-Fluoro-3-methylene-2-styrylindolin-2-yl)phenol (2k)

Yield: 0.047 g (69%); white solid; mp 162–163 °C.

IR (thin film): 3327, 2924, 1580, 1484, 1254, 1114, 805, 750 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.96 (s, 1 H), 7.40–7.38 (m, 2 H), 7.32–7.28 (m, 4 H), 7.22–7.19 (m, 1 H), 7.15–7.11 (m, 1 H), 6.94–6.89 (m, 1 H), 6.83–6.77 (m, 1 H), 6.74–6.71 (m, 1 H), 6.65–6.62 (m, 2 H), 6.41 (d, *J* = 15.6 Hz, 1 H), 5.78 (s, 1 H), 4.91 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 157.7 (d, *J* = 231.1 Hz), 156.4, 150.5 (d, *J* = 2.9 Hz), 147.8, 137.2, 134.2, 129.3, 129.2, 128.9, 128.6, 128.0 (d, *J* = 23.3 Hz), 127.7, 127.6, 127.0, 119.1, 117.1, 116.9, 111.5 (d, *J* = 8.0 Hz), 108.5 (d, *J* = 23.3 Hz), 106.6, 73.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –121.7.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{19}FNO$ $[M + H]^+$: 344.1445; found: 344.1441.

(*E*)-2-(5-Chloro-3-methylene-2-styrylindolin-2-yl)phenol (2l)

Yield: 0.056 g (78%); white solid; mp 165–166 °C.

IR (thin film): 3337, 1462, 1261, 1105, 822, 755 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.79 (s, 1 H), 7.47 (s, 1 H), 7.40–7.38 (m, 2 H), 7.31–7.28 (m, 3 H), 7.22–7.19 (m, 1 H), 7.15–7.11 (m, 1 H), 7.07 (d, *J* = 8.4 Hz, 1 H), 6.84 (d, *J* = 7.6 Hz, 1 H), 6.80–6.76 (m, 1 H), 6.71 (d, *J* = 8.0 Hz, 1 H), 6.66 (d, *J* = 16.0 Hz, 1 H), 6.40 (d, *J* = 15.6 Hz, 1 H), 5.79 (s, 1 H), 4.93 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.6, 147.1, 145.6, 135.7, 131.5, 130.4, 130.0, 129.9, 129.7, 129.0, 128.7, 128.3, 127.2, 126.8, 126.0, 121.5, 119.3, 118.0, 114.6, 108.2, 75.2.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{19}ClNO$ $[M + H]^+$: 360.1150; found: 360.1145.

(*E*)-2-(3-Methylene-2-styryl-5-(trifluoromethyl)indolin-2-yl)phenol (2m)

Yield: 0.040 g (51%); white solid; mp 168–169 °C.

IR (thin film): 3331, 2962, 2925, 1513, 1451, 1262, 1102, 803, 748 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.67 (s, 1 H), 7.69 (s, 1 H), 7.43–7.41 (m, 2 H), 7.38 (s, 1 H), 7.35–7.29 (m, 4 H), 7.23–7.20 (m, 1 H), 7.15–7.11 (m, 1 H), 6.82 (d, *J* = 8.0 Hz, 1 H), 6.78–6.74 (m, 1 H), 6.69 (d, *J* = 16.0 Hz, 1 H), 6.42 (d, *J* = 16.0 Hz, 1 H), 5.84 (s, 1 H), 4.99 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.2, 150.1, 146.8, 135.7, 131.4, 129.9, 129.8, 129.0, 128.7, 128.5, 128.4, 127.5 (q, *J* = 3.6 Hz), 126.8, 126.1, 119.6, 118.8 (q, *J* = 3.6 Hz), 118.1, 112.9, 108.6, 74.9.

^{19}F NMR (470 MHz, $CDCl_3$): δ = –61.4.

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{19}F_3NO$ $[M + H]^+$: 394.1413; found: 394.1408.

(*E*)-2-(4,6-Dimethyl-3-methylene-2-styrylindolin-2-yl)phenol (2n)

Yield: 0.051 g (72%); white solid; mp 180–181 °C.

IR (thin film): 3433, 2963, 1533, 1383, 1261, 1097, 803 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.98 (s, 1 H), 7.38–7.36 (m, 2 H), 7.32–7.28 (m, 2 H), 7.26–7.21 (m, 3 H), 6.91 (d, *J* = 7.6 Hz, 1 H), 6.83–6.82 (m, 1 H), 6.58–6.53 (m, 3 H), 6.47 (d, *J* = 16.0 Hz, 1 H), 5.62 (s, 1 H), 4.71 (s, 1 H), 4.39 (br s, 1 H), 2.48 (s, 3 H), 2.27 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.9, 148.7, 148.0, 140.0, 136.1, 135.0, 131.0, 130.9, 129.5, 129.3, 128.6, 128.0, 126.8, 126.7, 125.3, 123.9, 119.0, 118.0, 111.7, 109.2, 74.9, 21.5, 20.7.

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{24}NO$ $[M + H]^+$: 354.1852; found: 354.1848.

(*E*)-2-(5,7-Dibromo-3-methylene-2-styrylindolin-2-yl)phenol (2o)

Yield: 0.069 g (72%); white solid; mp 101–102 °C.

IR (thin film): 3406, 2926, 1580, 1444, 1241, 1108, 752, 692 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.96 (s, 1 H), 7.66 (s, 1 H), 7.44–7.40 (m, 3 H), 7.32–7.28 (m, 3 H), 7.23–7.20 (m, 1 H), 7.17–7.13 (m, 1 H), 6.85–6.82 (m, 1 H), 6.80–6.76 (m, 1 H), 6.67 (d, *J* = 15.6 Hz, 1 H), 6.34 (d, *J* = 16.0 Hz, 1 H), 5.91 (s, 1 H), 5.04 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 156.0, 149.4, 149.1, 137.0, 133.8, 133.6, 129.5, 129.4, 129.2, 128.5, 128.4, 128.2, 128.1, 127.0, 123.8, 119.2, 117.1, 108.8, 103.0, 73.1.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{18}Br_2NO$ $[M + H]^+$: 481.9750; found: 481.9746.

(*E*)-2-(7-Methyl-3-methylene-2-styrylindolin-2-yl)phenol (2p)

Yield: 0.046 g (68%); white solid; mp 140–141 °C.

IR (thin film): 3431, 2963, 1614, 1383, 1262, 1096, 803 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 10.08 (s, 1 H), 7.39–7.36 (m, 3 H), 7.32–7.29 (m, 2 H), 7.26–7.21 (m, 3 H), 7.05 (d, *J* = 7.0 Hz, 1 H), 6.92–6.84 (m, 3 H), 6.61 (d, *J* = 15.5 Hz, 1 H), 6.50 (d, *J* = 16.0 Hz, 1 H), 5.71 (s, 1 H), 4.72 (s, 1 H), 4.29 (br s, 1 H), 2.21 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.8, 148.6, 145.7, 136.0, 131.3, 131.0, 130.6, 129.5, 129.0, 128.6, 128.4, 128.2, 126.8, 126.5, 122.9, 122.2, 119.2, 118.9, 117.9, 106.7, 74.5, 16.5.

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{22}NO$ $[M + H]^+$: 340.1696; found: 340.1726.

(*E*)-2-(7-Bromo-3-methylene-2-styrylindolin-2-yl)phenol (2q)

Yield: 0.064 g (78%); white solid; mp 143–144 °C.

IR (thin film): 3330, 2925, 1639, 1441, 1244, 1102, 813, 750 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 10.02 (s, 1 H), 7.47 (d, *J* = 7.6 Hz, 1 H), 7.41–7.39 (m, 2 H), 7.36 (d, *J* = 7.6 Hz, 1 H), 7.31–7.27 (m, 3 H), 7.23–7.19 (m, 1 H), 7.17–7.13 (m, 1 H), 6.88 (d, *J* = 7.6 Hz, 1 H), 6.83–6.80 (m, 1 H), 6.67–6.58 (m, 2 H), 6.31 (d, *J* = 16.0 Hz, 1 H), 5.86 (s, 1 H), 5.03 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.9, 150.1, 149.5, 137.0, 133.8, 132.5, 129.4, 129.1, 128.3, 128.2, 128.1, 128.0, 127.7, 126.9, 121.0, 119.7, 119.2, 117.1, 107.7, 102.9, 73.1.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{19}BrNO$ $[M + H]^+$: 404.0645; found: 404.0638.

(*E*)-4-Methoxy-2-(3-methylene-2-styrylindolin-2-yl)phenol (2r)

Yield: 0.045 g (63%); yellow solid; mp 160–161 °C.

IR (thin film): 3453, 2926, 1640, 1488, 1248, 1041, 879, 750 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.42 (s, 1 H), 7.48 (d, *J* = 7.6 Hz, 1 H), 7.34–7.15 (m, 6 H), 6.94–6.91 (m, 1 H), 6.87–6.76 (m, 4 H), 6.59 (d, *J* = 15.6 Hz, 1 H), 6.43 (d, *J* = 15.6 Hz, 1 H), 5.71 (s, 1 H), 4.76 (s, 1 H), 4.47 (s, 1 H), 3.72 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.3, 150.4, 148.0, 147.3, 135.9, 131.3, 130.2, 130.1, 128.6, 128.5, 128.0, 127.4, 126.8, 121.7, 121.3, 118.1, 115.6, 113.6, 113.4, 106.6, 74.4, 55.7.

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{22}NO_2$ $[M + H]^+$: 356.1645; found: 356.1664.

(*E*)-4-Fluoro-2-(3-methylene-2-styrylindolin-2-yl)phenol (2s)

Yield: 0.035 g (51%); white solid; mp 158–159 °C.

IR (thin film): 3434, 2963, 1605, 1480, 1261, 1097, 800, 749 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.74 (s, 1 H), 7.52 (d, *J* = 7.6 Hz, 1 H), 7.38–7.36 (m, 2 H), 7.32–7.27 (m, 3 H), 7.23–7.19 (m, 1 H), 7.00–6.95 (m, 2 H), 6.94–6.88 (m, 2 H), 6.83–6.80 (m, 1 H), 6.62 (d, *J* = 15.6 Hz, 1 H), 6.43 (d, *J* = 15.6 Hz, 1 H), 5.74 (s, 1 H), 4.75 (s, 1 H), 4.46 (br s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.1 (d, *J* = 235.5 Hz), 152.7 (d, *J* = 2.2 Hz), 147.8, 147.0, 135.7, 131.9, 130.3, 129.5, 128.7, 128.6, 128.3, 126.8, 122.1, 121.4, 118.6, 118.5, 115.9 (d, *J* = 22.6 Hz), 115.5 (d, *J* = 24.1 Hz), 113.7, 106.9, 74.3.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –124.7.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{19}FNO$ $[M + H]^+$: 344.1445; found: 344.1439.

4,5-Dimethyl-2-(2-methyl-3-methyleneindolin-2-yl)phenol (2t)

Yield: 0.046 g (86%); white solid; mp 138–139 °C.

IR (thin film): 3432, 3328, 2925, 2857, 1615, 1463, 1261, 1103, 801, 749 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.45 (s, 1 H), 7.45 (d, *J* = 7.2 Hz, 1 H), 7.25–7.20 (m, 1 H), 7.08 (s, 1 H), 6.97–6.89 (m, 2 H), 6.67 (s, 1 H), 5.39 (s, 1 H), 4.65 (s, 1 H), 4.16 (br s, 1 H), 2.24 (s, 3 H), 2.20 (s, 3 H), 1.74 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.1, 152.8, 147.6, 137.6, 130.0, 128.1, 127.9, 126.8, 125.0, 121.7, 121.6, 118.9, 113.5, 102.8, 69.4, 29.1, 19.4, 19.1.

HRMS (ESI): *m*/*z* calcd for $C_{18}H_{20}NO$ $[M + H]^+$: 266.1539; found: 266.1535.

Methyl (*E*)-11a-Styryl-6,6a,11,11a-tetrahydrochromeno[4,3-*b*]indole-8-carboxylate (3u)

Yield: 0.028 g (36%); white solid; mp 109–110 °C.

IR (thin film): 3482, 1712, 1602, 1436, 1263, 804, 752 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.04–8.02 (m, 2 H), 7.82 (d, *J* = 16.0 Hz, 1 H), 7.51–7.50 (m, 3 H), 7.42 (d, *J* = 7.0 Hz, 1 H), 7.36–7.34 (m, 5 H), 7.19–7.13 (m, 2 H), 6.66 (d, *J* = 16.0 Hz, 1 H), 4.72 (s, 2 H), 3.40 (s, 3 H), 2.45 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.9, 163.0, 159.2, 155.7, 141.1, 135.9, 131.7, 131.4, 130.8, 129.5, 128.7, 127.8, 123.8, 123.5, 121.7, 116.9, 114.4, 114.3, 113.1, 78.3, 75.7, 56.0, 51.9.

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{22}NO_3$ $[M + H]^+$: 384.1594; found: 384.1591.

(*E*)-9-Nitro-11a-styryl-6,6a,11,11a-tetrahydrochromeno[4,3-*b*]indole (3v)

Yield: 0.024 g (32%); white solid; mp 107–108 °C.

IR (thin film): 3386, 1616, 1525, 802 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 8.0 Hz, 1 H), 7.30–7.27 (m, 5 H), 7.24–7.21 (m, 3 H), 7.01–7.00 (m, 3 H), 6.54 (d, *J* =16.0 Hz, 1 H), 6.25 (d, *J* = 16.0 Hz, 1 H), 4.82 (s, 1 H), 4.64 (dd, *J* = 10.5, 5.0 Hz, 1 H), 4.25 (dd, *J* = 10.5, 4.5 Hz, 1 H), 3.84 (t, *J* = 11.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.5, 151.9, 146.7, 135.8, 133.3, 129.8, 129.2, 129.1, 128.6, 128.5, 127.9, 126.6, 124.2, 122.3, 121.9, 117.9, 114.4, 114.1, 65.3, 64.7, 48.2.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{19}N_2O_3$ $[M + H]^+$: 371.1390; found: 371.1385.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611850.

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(10) CCDC 1855985 (**2a**) contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.