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Synthesis of Indolo- and Benzothieno[2,3-*b*]quinolines by a Cascade Cyclization of *o*-Alkynylisocyanobenzene Derivatives

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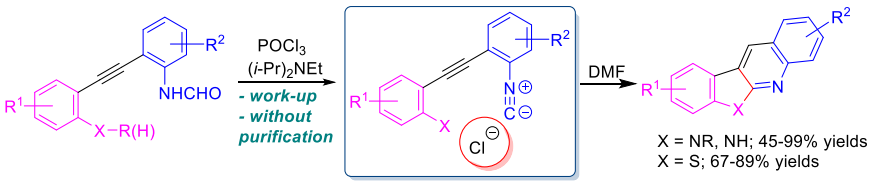


ABSTRACT: A new synthetic approach for the synthesis of indolo[2,3-*b*]quinolines and benzothieno[2,3-*b*]quinolines has been developed by employing the freshly prepared *o*-alkynylisocyanobenzenes derived from *o*-alkynylformamide derivatives as substrates. The synthetic transformations involved chloride ion triggered 6-*endo* cyclization of *o*-alkynylisocyanobenzenes to generate 2-chloroquinolines *in situ*, which further cyclized intramolecularly with nitrogen or sulfur atom via a cascade process to provide the corresponding indolo[2,3-*b*]quinolines and benzothieno[2,3-*b*]quinolines, respectively, in moderate to excellent yields.

1. INTRODUCTION

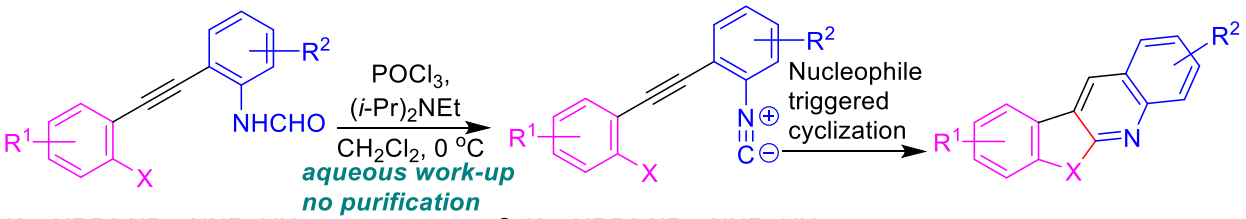
As important intermediates in organic synthesis, isocyanides are the versatile building blocks being employed in multicomponent reactions (MCRs), and have been widely applied to access *N*-heterocycles with delicate molecular complexity.[1] Isocyanides can also react with various radical and anion species to generate the respective imidoyl radical and anion intermediates for further transformations.[2] Synthetic applications have been widely demonstrated on the synthesis of *N*-containing heterocycles through the intramolecular addition to alkene,[3] alkyne,[4] or arene[5] moieties to access various substituted indole, quinoline, isoquinoline, and phenanthridine derivatives.

Heteroaryl[*b*]quinolines are important scaffolds found in naturally occurring compounds,[6] and organic materials.[7] In particular, indoloquinolines bearing an indole ring fused to the [*b*] side of a quinoline ring are privileged structural motifs and explicitly exhibit a broad spectrum of biological activities as anticancer, antimalarial, antiplasmodial, and antibacterial agents.[8] Given their significant properties in various fields, numerous synthetic approaches have been continually reported for the preparation of such the indoloquinoline skeletons.[9]

In recent years, we and others studied nucleophile triggered cyclization of *o*-alkynylisocyanobenzenes.[10] Widely used by several research groups including us, 2-alkynyl-*N*,*N*-dialkylanilines are synthetically useful substrates employed for preparation nitrogen-containing heterocycles.[11] As a part of our program on the construction on *N*-heterocycles, we envisioned that *o*-alkynylisocyanobenzenes **2** and **5** could undergo a cascade cyclization mediated by a nucleophile and would provide an access to highly functionalized indolo[2,3-

b]quinolines and benzothieno[2,3-*b*]quinolines[12] in a single step, involving the formation of C−C, and C−X (X = N, S) bonds via a cascade strategy (Scheme 1).

Scheme 1. Design Synthetic Approach to Indolo[2,3-*b*]quinolines and Benzothieno[2,3-*b*]quinolines



1: X = NRR′, NR_2, NHR, NH_2
4: X = SMe

2: X = NRR′, NR_2, NHR, NH_2
5: X = SMe

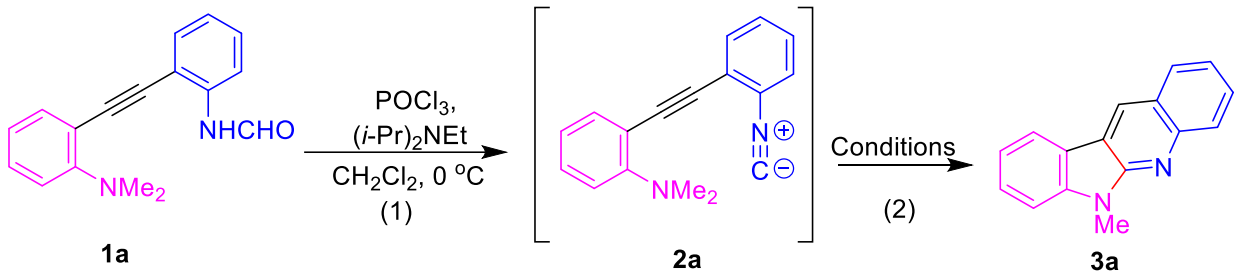
3: X = NR, NH
6: X = S

2. RESULTS AND DISCUSSION

We employed *o*-alkynylisocyanobenzene **2a** as a model substrate to screen for the optimized reaction conditions. Compound **2a** was readily obtained from its corresponding formamide **1a** upon treatment with $POCl_3$, *i*-Pr_2NEt in CH_2Cl_2 at 0 °C.[10a,b] Compound **2a** is inherently unstable therefore, after aqueous work-up, it was employed in the next step without purification. It is worth mentioning that in contrast to our recently published articles,[10a,b] in this work, prior filtration of the freshly prepared isocyanides through alumina column was not performed. Several reaction parameters including solvents, temperature and time were screened and the results are summarized in Table 1. On the basis of our previous works on isocyanide chemistry, we first exposed **2a** [prepared from **1a** (0.5 mmol)] in DMF (2 mL, 0.25 M) at room temperature for overnight (16 h).[10b] Gratifyingly, the reaction readily took place and the desired indolo[2,3-*b*]quinoline **3a** was obtained in moderate yield (62% yield) (Table 1, entry 1). Slightly lower yield was observed when the reaction was shortened from 16 h to 1 h (Table 1, entry 2).

The reaction proceeded more efficiently and gave 90% yield of **3a** when the reaction was carried out in DMF at 80 °C for 1 h (Table 1, entry 3). Next, a variety of solvents were evaluated (Table 1, entries 3−10). Among the organic solvents (DMSO, EtOAc, toluene, CH_3CN, THF, and MeOH) and water screened, DMF gave optimum results. It is worth to emphasize that, after aqueous work-up, if **2a** was filtered through a short-path column packed with Aluminium oxide, Type E[10a,b] or Florisil prior to the reaction in step (2), the desired product **3a** was obtained in lower yields (Table 1, entries 11−12).

Table 1. Optimization of the Reaction Conditions[a]



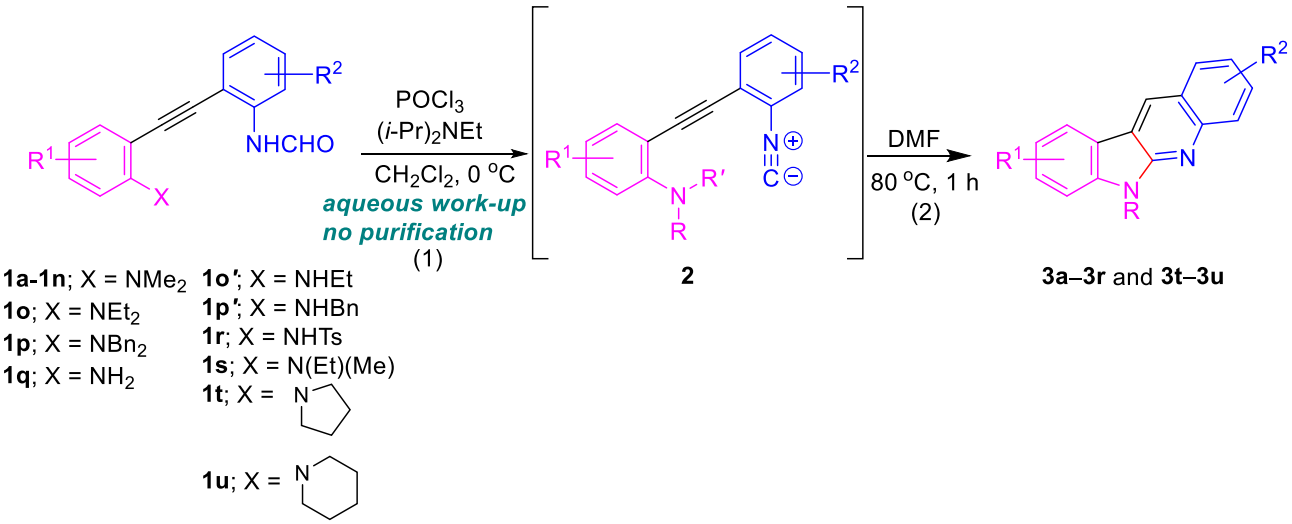
entry	solvent	temp[b] (°C)	time (h)	yield[c] (%)
1	DMF	rt	16	62
2	DMF	rt	1	50
3	**DMF**	**80**	**1**	**90**
4	DMSO	80	1	80
5	EtOAc	80	1	78
6	Toluene	80	1	79
7	CH_3CN	80	1	70
8	THF	80	1	68
9	MeOH	80	1	46
10	H_2O	80	1	48
11[d]	DMF	80	1	80
12[e]	DMF	80	1	76

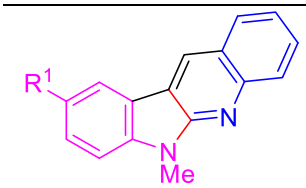
[a]Reaction conditions: Step (1): **1a** (0.5 mmol, 1.0 equiv), $POCl_3$ (0.07 mL, 0.75 mmol, 1.5 equiv), $(i\text{-Pr})_2NEt$ (0.70 mL, 4.0 mmol, 8.0 equiv), CH_2Cl_2 (4 mL, 0.125 M), 0 °C, 1 h, followed by aqueous work-up. Step (2): The crude mixture of **2a** from Step (1) was diluted in the solvent (2 mL, 0.25 M) under various reaction conditions. [b]Oil-bath temperature. [c]Isolated yields after column chromatography (SiO_2). [d]**2a** was filtered through a short-path Aluminium oxide-Type E column and was eluted with EtOAc. [e]**2a** was filtered through a short-path Florisil column and was eluted with EtOAc.

After the optimal reaction conditions were identified (Table 1, entry 3), the substrate scope and limitation of the reaction were evaluated. Substrates **2b**–**2n** with different substituted patterns and electronic properties on the aniline moiety (R^1) and the isocyanoaryl moiety (R^2) toward the indolo[2,3-*b*]quinoline formation were investigated and the results are summarized in Scheme 2. Compounds **2b**–**2g** bearing different substituent groups on the aniline moiety (R^1), including 4-Me, 4-CF_3, 4-F, 4-Cl, 4-Br and 5-Cl, smoothly provided the corresponding products **3b**–**3g** in good to excellent yields (71−78% yields). Next, substrates **2h**–**2n** with different substituted patterns and electronic properties on the isocyanoaryl moiety (R^2), including 4-Me, 4-CF_3, 4-F, 4-Cl, 4-Br, 4-NO_2 and 5-Cl, were well accommodated and yielded products **3h**–**3n** in good yields (70−88% yields). Using substrates **2o** and **2p** bearing diethyl and dibenzyl moieties on the aniline nitrogen provided the respective *N*-ethyl and *N*-benzyl products **3o** and **3p** in good yields (85–99% yields). The free NH_2 substrate **2q** gave product **3q** in low yield (45% yield). Noteworthy, the monoethyl and monobenzyl aniline substrates **2o′** and **2p′** also delivered, after deprotonation, products **3o** and **3p** in moderate yields (64–77% yields). Compound **2r** bearing NHTs at the aniline moiety gave **3r** in 89% yield. The steric effect in the dealkylation step was also briefly evaluated. Substrate **1s** bearing ethyl and methyl groups at the nitrogen atom was employed as a substrate to study the influence of the alkyl groups on product distribution after dealkylation. Under the standard reaction conditions, **1s** provided a mixture of **3b** and **3o** which can be readily separated. After chromatographic purification, compounds **3b** and **3o** were isolated in 21% and 57% yields, respectively. This observation emphasized that the dealkylation preferably took place at the less steric methyl group. Finally, when cyclic aniline derivatives **1t** and **1u** were employed as starting compounds, products **3t** and **3u** were obtained in 53% and 78% yields, respectively. The yields of **3t** and **3u** can be slightly improved to 66% and 84%

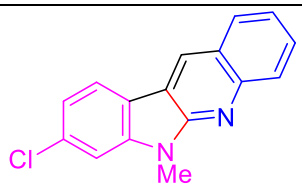
yields, respectively, when the reactions were carried out in the presence of *n*-Bu_4NCl (0.5 mmol, 1.0 equiv). These implied the role of the chloride ion (Cl^-) in assisting the dealkylation in the mechanistic pathway.

Scheme 2. Scopes of Compounds 2[a]

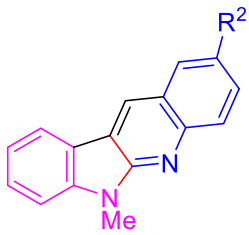




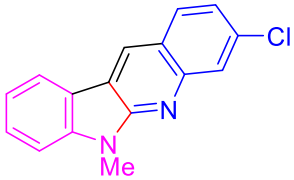
3a, R^1 = H (90%)
3b, R^1 = Me (72%)
3c, R^1 = CF_3 (78%)
3d, R^1 = F (74%)
3e, R^1 = Cl (76%)
3f, R^1 = Br (71%)

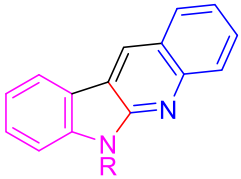


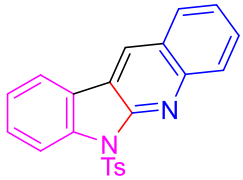
3g (71%)



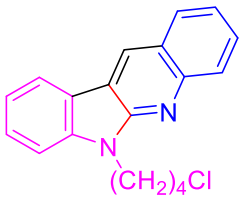
3h, R^2 = Me (84%)
3i, R^2 = CF_3 (77%)
3j, R^2 = F (79%)
3k, R^2 = Cl (85%)
3l, R^2 = Br (82%)
3m, R^2 = NO_2 (88%)



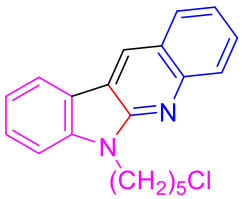




3n (70%)



3o, R = Et (85%)[b] (77%)[c]
3p, R = Bn (99%)[d] (64%)[e]
3q, R = H (45%)



3r (89%)

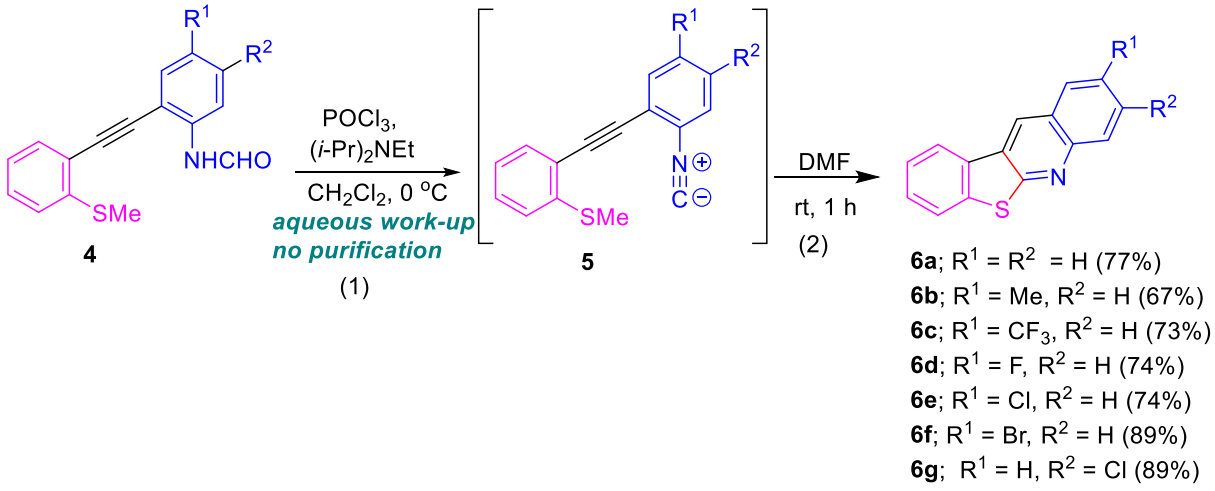
3t (53%) (66%)[f]

3u (78%) (84%)[f]

[a]Reaction conditions: Step (1): **1** (0.5 mmol, 1.0 equiv), $POCl_3$ (0.07 mL, 0.75 mmol, 1.5 equiv), (*i*-Pr)$_2$NEt (0.70 mL, 4.0 mmol, 8.0 equiv), CH_2Cl_2 (4 mL, 0.125 M), 0 °C, 1 h, followed by aqueous work-up. Step (2): The crude mixture of **2** from step (1) was diluted in DMF (2 mL, 0.25 M), 80 °C, 1 h. In parenthesis: isolated yields after column chromatography (SiO_2). [b]From **1o**. [c]From **1o´**. [d]From **1p**. [e]From **1p´**. [f]In the presence of *n*-Bu_4NCl (0.1390 g, 0.5 mmol, 1 equiv).

The synthetic utility of the current protocol was further extended to the synthesis of benzothieno[2,3-*b*]quinolines **6**.[12] Pleasingly, the established protocol can also be applied to access **6** and the results are shown in Scheme 3.[13] The reaction of **5**, prepared from the corresponding formamide substrates **4**, readily proceeded in DMF at room temperature to yield the products **6** in good yields (67−89% yields). Ultimately, efforts were also extended to the substrate of oxygen analogs in order to access benzofurano[2,3-*b*]quinolines, unfortunately without success.

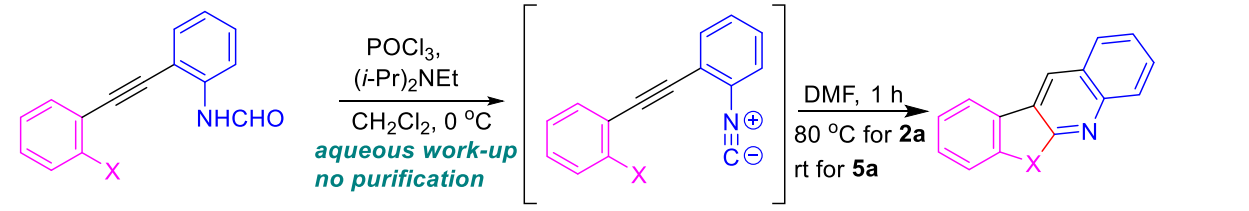
Scheme 3. Scopes of Compounds 5[a]



[a]Reaction conditions: Step (1): **4** (0.5 mmol, 1.0 equiv), $POCl_3$ (0.07 mL, 0.75 mmol, 1.5 equiv), $(i\text{-Pr})_2NEt$ (0.70 mL, 4.0 mmol, 8.0 equiv), CH_2Cl_2 (4 mL, 0.125 M), 0 °C, 1 h, followed by aqueous work-up. Step (2): The crude mixture of **5** from Step (1) was diluted in DMF (2 mL, 0.25 M), room temperature, 1 h. In parenthesis: isolated yields after column chromatography (SiO_2).

To demonstrate the synthetic utility of the present reaction, a gram-scale reaction was evaluated. Under standard reaction conditions, **1a** (1.32 g, 5 mmol) and **4a** (1.34 g, 5 mmol) were efficiently converted into **3a** (0.9832 g, 85% yield) and **6a** (0.8552 g, 73% yield), respectively (Scheme 4).

Scheme 4. Gram-Scale Synthesis of 3a and 6a



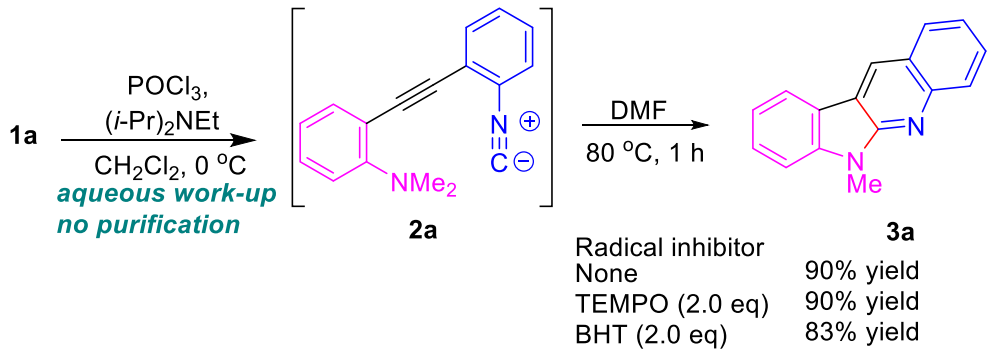
To gain a better understanding on the reaction mechanism, a series of control experiments were carried out as shown in Scheme 5. Neither TEMPO nor BHT affected the reactions of **2a**

[Scheme 5, (a)]. These results implied that the reaction should proceed through a non-radical pathway. As previously mentioned, filtration of the prepared isocyanide **2a** through aluminium oxide, Type E or Florisil column deteriorated the reaction efficiency (Table 1, entries 11−12). However, when the reaction of **2a**, pre-filtered with Florisil column, was carried out in the presence of *n*-Bu_4NCl (0.1390 g, 0.5 mmol, 1.0 equiv), the product yield of **3a** improved considerably (from 76% yield to 93% yield) [Scheme 5, (b)]. These results suggested that chloride ion might facilitate the present transformation. While substrates **2** bearing *N*,*N*-dialkylaniline moiety smoothly underwent the reaction to give the corresponding indolo[2,3-*b*]quinolines **3**, the reaction of -NHBn analog **2p′**, in the presence of *n*-Bu_4NCl (0.1390 g, 0.5 mmol, 1.0 equiv) gave the desired product **3p** (33% yield) along with the 2-chloroquinoline **7** (34% yield) [Scheme 5, (c)]. Exposure of **7** to the standard reaction conditions (DMF, 80 ^oC, 1 h) yielded **3p** in quantitative yield [Scheme 5, (d)], suggesting that 2-chloroquinoline adduct might be an intermediate in the present reaction. Worthily to emphasize, when cyclic anilines, for example, **2t** was employed as a substrate, **3t** was isolated in 53% yield [Scheme 5, (e)]. This observation emphasized the role of chloride ion (Cl^-) in the mechanistic pathway. Additionally, the reaction of isocyanide **9** was also evaluated. Thus, compound **8** was treated with $POCl_3$, *i*-Pr_2NEt in CH_2Cl_2 at 0 ^oC for 1 h. After aqueous work up followed by evaporation to dryness, **9** was diluted with DMF and the solution was stirred at room temperature for 4 h. After chromatographic purification, 2-chloro-3-phenylquinoline (**10**) and 3-phenylquinolin-2(1*H*)-one (**11**) were obtained in 71% and 10% yields, respectively [Scheme 5, (f)]. This observation implied that there were chloride ion and water, possibly in the crude isocyanide substance and moisture in DMF, serving as nucleophiles. Finally, when D_2O (0.018 mL, 1.0 mmol, 2.0 equiv) was introduced into the reaction, a mixture of products **[*d*$_1$]-3a** and **3a** (**[*d*$_1$]-3a**:**3a** = 9:1, ^1H

NMR analysis; see Supporting Information) was obtained [Scheme 5(g)]. The results obtained implied that the proton source from water served as a proton donor in the mechanistic pathway during quinoline ring formation.

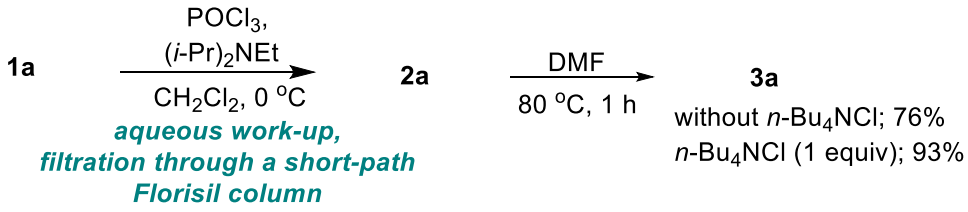
Scheme 5. Control Experiments

(a)

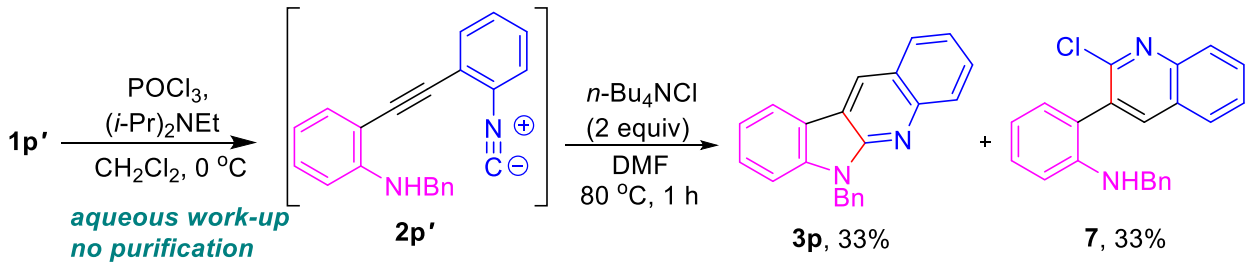


Radical inhibitor	
None	90% yield
TEMPO (2.0 eq)	90% yield
BHT (2.0 eq)	83% yield

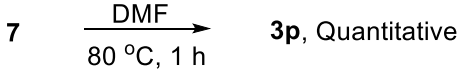
(b)



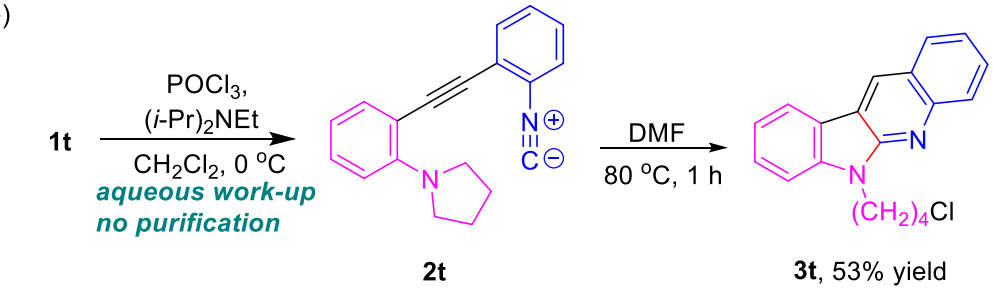
(c)



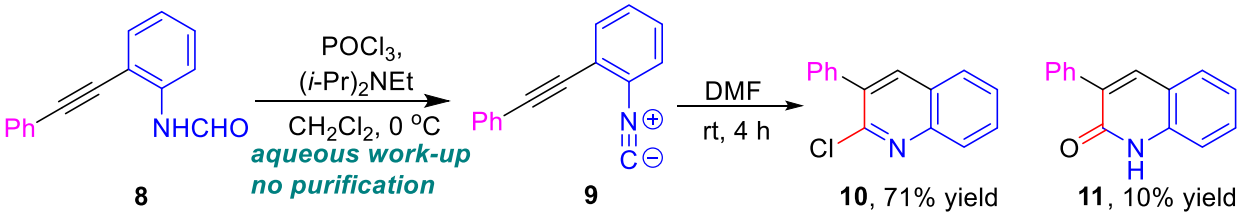
(d)



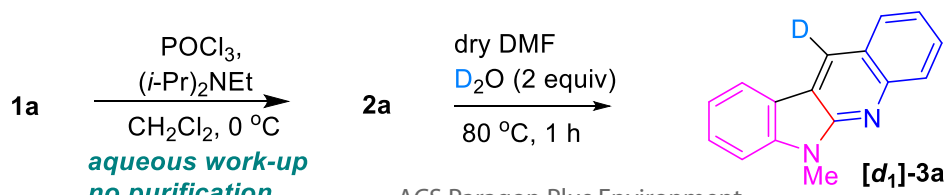
(e)



(f)



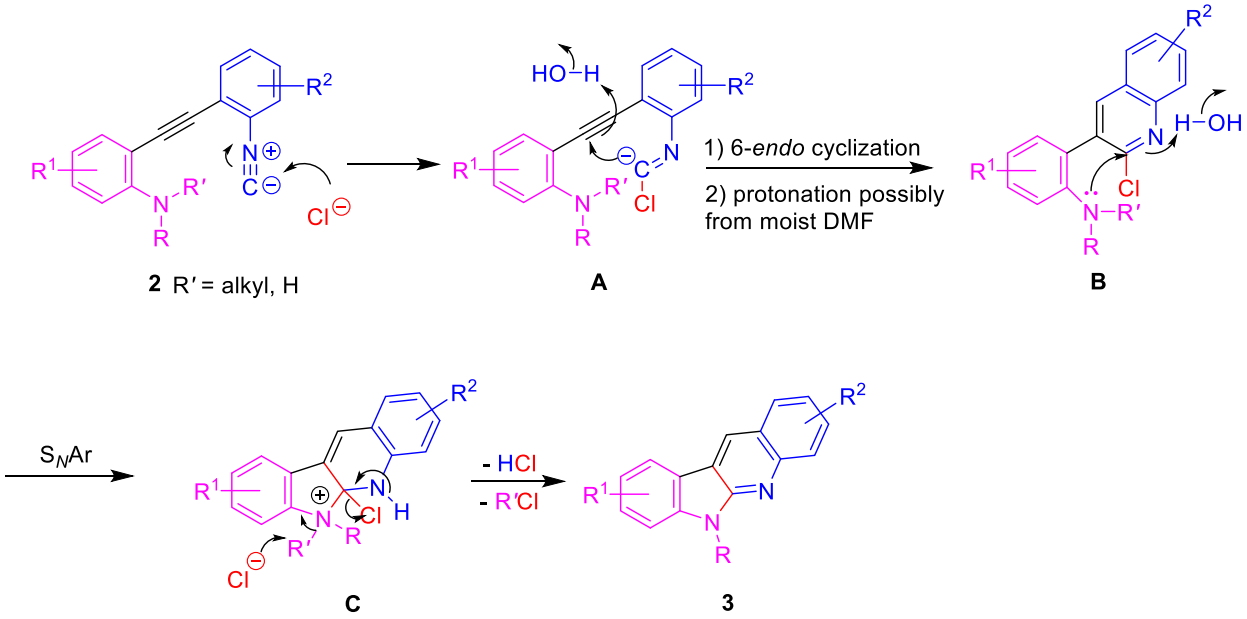
(g)



[d_1]-**3a** : **3a** = 9 :1 (^{1}H NMR analysis)

On the basis of the experimental results (Table 1 and Schemes 2−3), control evidences (Scheme 5) as well as the previously reported literature, a plausible reaction mechanism is outlined as shown in Scheme 6. Explanation of the reaction mechanism was described employing **2** as the model substrates. Initially, chloride ion (Cl^-) which most possibly stems from the step of isocyanide preparation, acts as a nucleophile and adds to the isocyano carbon leading to the corresponding imidoyl anion intermediate **A**. Next, **A** undergoes 6-*endo* cyclization followed by protonation, possibly from moisture in DMF or water in the crude isocyanide substance, leading to 2-chloroquinoline adduct **B**. Subsequent intramolecular nucleophilic aromatic substitution (S_NAr) readily take place to provide cationic intermediate **C**. Dealkylation (dialkylanilines and methyl sulfides) or the loss of HCl (monosubstituted anilines) with the aid of chloride ion and aromatization finally leads to the observed products **3**. The reaction mechanism for the conversion of **5** to **6** should also follow a similar pathway.

Scheme 6. Plausible Reaction Mechanism



3. CONCLUSIONS

In summary, we have developed metal-free, rapid, and convenient synthetic route to access indolo[2,3-*b*]quinolines and benzothieno[2,3-*b*]quinolines via cascade reactions of the respective 2-[(2-isocyanoaryl)ethynyl]anilines **2** and {2-[(2-isocyanoaryl)ethynyl]aryl}(methyl)sulfanes **5**. The reaction involves chloride ion triggered 6-*endo* cyclization followed by intramolecular nucleophilic aromatic substitution (S_NAr). The established reaction offers ease of experimentation without the need to perform the reaction under air- and moisture-free conditions and can accommodate a wide range of substrate scopes to provide the products in moderate to excellent yields. Further investigation on optical properties and pharmacological evaluation of new indolo- and benzothieno[2,3-*b*]quinoline analogs are currently on going and will soon be reported. We are at the moment expanding this protocol to access other nitrogen- and sulfur-containing polycycles.

4. EXPERIMENTAL SECTION

General Procedure: The nuclear magnetic resonance (NMR) spectra were recorded in deuterochloroform ($CDCl_3$) with 400 MHz spectrometer. Chemical shifts for ^1H and $^{13}C\{^1H\}$ NMR spectra were reported in parts per million (ppm, δ). The chemical shift of ^1H NMR spectra is reported with reference to tetramethylsilane (δ = 0.00 ppm) as the internal reference, while the chemical shift of $^{13}C\{^1H\}$ NMR is reported with reference to $CDCl_3$ at 77.0 ppm. Coupling constants (*J*) were reported in hertz. Infrared spectra were recorded using an FT-IR spectrometer and only partial data were reported in cm^{-1}. High-Resolution Mass Spectra (HRMS) were recorded using time-of-flight (TOF) and electrospray ionization (ESI). Unless otherwise noted, the commercial grade chemicals were used without prior purification. Column chromatography

was performed using silica gel 60 (particle size 0.06−0.2 mm; 70−230 mesh ASTM). Analytical TLC was performed with silica gel 60 F_{254} aluminum sheets.

*General Procedure for the Synthesis of Compounds **1***. To a two-neck flask containing 2-iodoaniline derivatives (10 mmol, 1.0 equiv), $PdCl_2(PPh_3)_2$ (91.2 mg, 0.13 mmol, 0.013 equiv), and CuI (19 mg, 0.1 mmol, 0.01 equiv) was added Et_3N (1 mL/mmol) under argon atmosphere. Next, the reaction was added dropwise with a solution of *N*-(2-ethynylphenyl)formamide derivatives (11 mmol, 1.1 equiv) in THF (1 mL/mmol) at room temperature under argon atmosphere. The reaction mixture was stirred at room temperature under argon atmosphere for 16 h, then quenched with saturated aqueous NH_4Cl (20 mL) and the resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (anh. $MgSO_4$), filtered, and concentrated under reduced pressure (aspirator). The crude product was purified by column chromatography on silica gel (EtOAc/hexane) to provide the corresponding compounds **1**. The peaks of ^1H and ^{13}C NMR spectral data of compounds **1** were observed as the mixture of amide rotamers.[4a,c]

*N-(2-((2-(Dimethylamino)phenyl)ethynyl)phenyl)formamide (**1a**)*. Purification by column chromatography (EtOAc/hexane, 1:19 v/v) afforded **1a** (0.9912 g, 75%); pale brown viscous liquid; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.86 (br s, 0.66H), 8.73 (br d, J = 10.8 Hz, 0.34H), 8.73 (d, J = 10.8 Hz, 0.34H), 8.49−8.47 (m, 1.32H), 7.51−7.46 (m, 2H), 7.35−7.21 (m, 2.34H), 7.12−7.05 (m, 2H), 7.01−6.95 (m, 1H), 2.92 & 2.88 (each s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 161.1, 158.8, 155.9, 155.3, 132.2, 138.1, 132.7, 132.7, 131.6, 130.5, 129.7, 129.4, 129.2, 123.9, 123.6, 122.1, 121.8, 119.7, 118.2, 118.0, 116.2, 115.0, 113.3, 112.4, 96.0, 95.9, 89.3, 88.8, 44.4, 43.9 ppm; IR (neat): 3293, 2203, 1683, 1263 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{17}H_{16}N_2ONa$ 287.1155, found 287.1151.

N-(2-((2-(Dimethylamino)-5-methylphenyl)ethynyl)phenyl)formamide ***(1b)***. Purification by column chromatography (EtOAc/hexane, 1:9 v/v) afforded **1b** (0.9325 g, 67%); pale brown viscous liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.07 (br s, 0.68H), 8.95 (d, J = 11.2 Hz, 0.32H), 8.78 (br d, J = 8.0 Hz, 0.32H), 8.51−8.49 (m, 1.35H), 7.52−7.46 (m, 1H), 7.37−7.30 (m, 2.32H), 7.15−7.08 (m, 2H), 7.01 (d, J = 8.4 Hz, 1H), 2.89 & 2.86 (each s, 6H), 2.31 & 2.30 (each s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.2, 158.9, 154.7, 153.4, 138.5, 132.9, 131.7, 130.6, 130.4, 129.5, 129.3, 124.0, 123.7, 119.8, 118.4, 118.3, 116.7, 114.8, 113.2, 112.5, 96.4, 92.6, 45.0, 44.3, 20.4 ppm; IR (neat): 3247, 2223, 1693, 1265 cm^{-1}; HRMS (ESI-TOF) *m/z* [M + Na]$^{+}$ calcd for $C_{18}H_{18}N_2ONa$ 301.1311, found 301.1312.

N-(2-((2-(Dimethylamino)-5-(trifluoromethyl)phenyl)ethynyl)phenyl)formamide ***(1c)***. Purification by column chromatography EtOAc/hexane, 1:4 v/v) afforded **1c** (1.3625 g,82%); pale yellow solid; mp = 125.4−127.0 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.89 (d, J = 11.6 Hz, 0.34H), 8.50 (s, 0.66H), 8.46 (d, J = 8.4 Hz, 0.66H), 8.42 (br s, 1H), 7.72 (s, 1H), 7.55−7.49 (m, 2H), 7.39−7.32 (m, 1H), 7.28 (d, J = 8.0 Hz, 0.34H), 7.17−7.10 (m, 1H), 7.03 (d, J = 8.8 Hz, 1H), 3.023 & 3.016 (each s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.2, 158.8, 157.7, 157.2, 138.0, 137.9, 132.2, 131.1, 130.7 (q, $J_{C,F}$ = 3.7 Hz), 130.6 (q, $J_{C,F}$ = 3.6 Hz), 130.0, 129.8, 126.6 (q, $J_{C,F}$ = 3.8 Hz), 125.37, 125.34, 124.3, 123.99 (q, $J_{C,F}$ = 269.7 Hz), 123.95, 123.0, 122.83 (q, $J_{C,F}$ = 33.0 Hz), 122.6, 120.0, 117.5, 117.3, 115.6, 114.5, 113.7 (q, $J_{C,F}$ = 118.6 Hz), 112.0, 94.93, 94.89, 90.2, 89.9, 43.6, 43.3 ppm; IR (neat): 3248, 2203, 1661, 1273 cm^{-1}; HRMS (ESI-TOF) *m/z* [M + Na]$^{+}$ calcd for $C_{18}H_{15}F_3N_2ONa$ 355.1029, found 355.1033.

N-(2-((2-(Dimethylamino)-5-fluorophenyl)ethynyl)phenyl)formamide ***(1d)***. Purification by column chromatography (EtOAc/hexane, 1:9 v/v) afforded **1d** (0.8893 g, 63%); pale brown viscous liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.03 (br s, 0.61H), 8.96 (d, J = 11.2 Hz, 0.39H),

8.83 (br d, J = 9.2 Hz, 0.39H), 8.52−8.49 (m, 1.22H), 7.52 (d, J = 7.6 Hz, 0.39H), 7.48 (d, J = 7.6 Hz, 0.61H), 7.39−7.29 (m, 1.39H), 7.20−7.16 (m, 1H), 7.13−7.01 (m, 3H), 2.88 & 2.85 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 161.1, 158.0 (d, $J_{C,F}$ = 241.4 Hz), 158.9, 157.8 (d, $J_{C,F}$ = 240.8 Hz), 138.6, 138.5, 131.7, 130.5, 129.9, 129.7, 123.9, 123.7, 120.0 (d, $J_{C,F}$ = 8.4 Hz), 119.8, 119.7 (d, $J_{C,F}$ = 8.4 Hz), 118.7, 118.48, 118.45 (d, $J_{C,F}$ = 11.6 Hz), 118.6 (d, $J_{C,F}$ = 23.6 Hz), 118.40, 118.39 (d, $J_{C,F}$ = 23.7 Hz), 118.37, 116.52 (d, $J_{C,F}$ = 22.0 Hz), 116.50 (d, $J_{C,F}$ = 22.0 Hz), 114.8, 112.7, 111.8, 94.8, 94.6, 90.1, 89.5, 45.0, 44.4 ppm; IR (neat): 3271, 2329, 1697, 1264 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{17}H_{15}FN_2ONa$ 305.1061, found 305.1062.

N-(2-((5-Chloro-2-(dimethylamino)phenyl)ethynyl)phenyl)formamide ***(1e)***. Purification by column chromatography (EtOAc/hexane, 1:9 v/v) afforded **1e** (0.9411 g, 63%); pale brown viscous liquid; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.92 (d, J = 11.2 Hz, 1H), 8.65 (br d, J = 8.0 Hz, 0.42H), 8.52 (s, 0.58H), 8.47 (d, J = 8.0 Hz, 0.58H), 7.50−7.45 (m, 2H), 7.37−7.34 (m, 1H), 7.30−7.25 (m, 1.42H), 7.14−7.09 (m, 1H), 7.07−7.00 (m, 1H), 2.93 (s, 6H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 161.1, 158.8, 154.6, 153.9, 138.3, 132.2, 132.0, 131.9, 130.8, 129.9, 129.8, 129.69, 129.68, 127.0, 126.8, 124.1, 123.8, 119.9, 119.5, 119.3, 117.7, 117.6, 115.1, 112.9, 111.9, 94.7, 94.6, 90.3, 89.8, 44.5, 43.9 ppm; IR (neat): 3270, 2209, 1688, 1260 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{17}H_{15}ClN_2ONa$ 321.0765, found 321.0768.

N-(2-((5-Bromo-2-(dimethylamino)phenyl)ethynyl)phenyl)formamide ***(1f)***. Purification by column chromatography (EtOAc/hexane, 1:9 v/v) afforded **1f** (1.0297 g, 60%); pale brown viscous liquid; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.93 (d, J = 11.2 Hz, 0.37H), 8.70 (br s, 0.63H), 8.57 (br d, J = 11.2 Hz, 0.37H), 8.51−8.47 (m, 1.26H), 7.60−7.58 (m, 1H), 7.52−7.47 (m, 1H), 7.42−7.28 (m, 2.37H), 7.16−7.09 (m, 1H), 6.93 (d, J = 8.8 Hz, 1H), 2.92 & 2.89 (each s, 6H);

$^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 161.1, 158.7, 155.0, 154.4, 138.3, 135.1, 135.0, 131.9, 130.8, 130.0, 129.8, 124.1, 123.9, 119.9, 119.7, 119.2, 118.0, 115.1, 114.2, 114.0, 112.0, 94.7, 94.6, 90.5, 89.9, 44.4, 43.9 ppm; IR (neat): 3367, 2204, 1694, 1263 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{17}H_{15}BrN_2ONa$ 365.0260, found 365.0258.

*N-(2-((4-Chloro-2-(dimethylamino)phenyl)ethynyl)phenyl)formamide (**1g**)*. Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **1g** (1.1204 g, 75%); pale brown viscous liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.84 (d, J = 11.2 Hz, 0.37H), 8.68 (br s, 0.63H), 8.52 (br d, J = 10.8 Hz, 0.37H), 8.46−8.42 (m, 1.26H), 7.47−7.43 (m, 1H), 7.36−7.25 (m, 2H), 7.19 (d, J = 8.4 Hz, 0.37H), 7.10−7.04 (m, 1H), 6.95 (d, J =2.4 Hz, 1H), 6.91−6.87 (m, 1H), 2.90 & 2.87 (each s, 6H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 161.1, 158.8, 156.5, 156.0, 138.0, 137.9, 135.4, 133.9, 133.8, 131.8, 130.8, 129.6, 129.5, 124.1, 123.8, 121.8, 121.6, 119.9, 118.5, 118.3, 115.4, 113.9, 113.2, 112.2, 95.1, 94.9, 90.1, 89.6, 44.0, 43.5 ppm; IR (neat): 3295, 2206, 1688, 1267 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{17}H_{15}ClN_2ONa$ 321.0765, found 321.0766.

*N-(2-((2-(Dimethylamino)phenyl)ethynyl)-4-methylphenyl)formamide (**1h**)*. Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **1h** (0.9742 g, 70%); pale brown viscous liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.86 (d, J = 11.2 Hz, 1H), 8.59 (br d, J = 10.4 Hz, 0.31H), 8.48 (s, 0.69H), 8.35 (d, J = 8.4 Hz, 0.69H), 7.50−7.46 (m, 1H), 7.35−7.31 (m, 2.31H), 7.18−6.97 (m, 3H), 2.94 & 2.92 (each s, 6H), 2.32 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 161.3, 158.8, 144.7, 136.0, 135.8, 133.8, 133.4, 132.93, 132.91, 132.1, 130.9, 130.3, 130.1, 129.8, 129.0, 124.8, 122.0, 119.9, 118.3, 118.2, 116.5, 116.3, 115.36, 115.35, 113.5, 112.3, 95.4, 94.3, 89.3, 89.2, 44.6, 44.0, 20.7, 20.6 ppm; IR (neat): 3270, 2199, 1686, 1265 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{18}H_{18}N_2ONa$ 301.1311, found 301.1315.

N-(2-((2-(Dimethylamino)phenyl)ethynyl)-4-(trifluoromethyl)phenyl)formamide ***(1i)***. Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **1i** (0.7311 g, 44%); pale brown viscous liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.14 (br s, 0.72H), 9.03 (d, J = 10.8 Hz, 0.28H), 8.95 (br d, J = 9.6 Hz, 0.28H), 8.64 (d, J = 8.8 Hz, 0.72H), 8.55 (d, J = 1.2 Hz, 0.72H), 7.77−7.74 (m, 1H), 7.59−7.54 (m, 1H), 7.51−7.48 (m, 1H), 7.41−7.34 (m, 1.28H), 7.12 (d, J = 8.4 Hz, 1H), 7.07−7.01 (m, 1H), 2.93 & 2.90 (each s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.7, 159.1, 156.4, 155.7, 141.1, 140.8, 135.1, 132.9, 132.7, 130.4, 128.6, 127.5 (q, $J_{C,F}$ = 3.6 Hz), 126.3 (q, $J_{C,F}$ = 269.8 Hz), 126.3 (q, $J_{C,F}$ = 3.5 Hz), 125.8 (q, $J_{C,F}$ = 33.8 Hz), 126.09, 126.05, 122.5, 122.3, 119.7, 118.6, 118.3, 116.0, 114.3, 113.4, 112.9, 97.8, 97.4, 88.0, 87.4, 44.7, 44.1 ppm; IR (neat): 3270, 2210, 1703, 1267 cm^{-1}; HRMS (ESI-TOF) *m/z* [M + Na]$^{+}$ calcd for $C_{18}H_{15}F_3N_2ONa$ 355.1029, found 355.1029.

N-(2-((2-(Dimethylamino)phenyl)ethynyl)-4-fluorophenyl)formamide ***(1j)***. Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **1j** (0.5786 g, 41%); pale brown viscous liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.89 (br s, 0.75H), 8.80 (d, J = 11.2 Hz, 0.25H), 8.60 (br d, J = 10.8 Hz, 0.25H), 8.48− 8.44 (m, 1.50H), 7.49−7.46 (m, 1H), 7.36−7.31 (m, 1H), 7.21 (dd, J = 8.4 Hz, J = 3.2 Hz, 0.25H), 7.17 (dd, J = 8.6 Hz, J = 3.0 Hz, 1H), 7.09−6.97 (m, 3H), 2.92 & 2.89 (each s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.3, 159.0 (d, $J_{C,F}$ = 243.0 Hz), 158.7, 158.2 (d, $J_{C,F}$ = 242.7 Hz), 156.2, 155.6, 134.7 (d, $J_{C,F}$ = 2.7 Hz), 134.5 (d, $J_{C,F}$ = 2.7 Hz), 133.0, 132.9, 130.2, 122.4, 121.9, 121.4 (d, $J_{C,F}$ =8.2 Hz), 118.3, 118.2, 118.0 (d, $J_{C,F}$ = 24.0 Hz), 117.0, 116.8 (d, $J_{C,F}$ = 54.8 Hz), 116.7, 116.3 (d, $J_{C,F}$ = 22.1 Hz), 116.0 (d, $J_{C,F}$ = 59.5 Hz), 115.9, 115.3 (d, $J_{C,F}$ = 9.7 Hz), 114.0 (d, $J_{C,F}$ = 9.6 Hz), 97.1, 96.9, 88.4, 88.0, 44.6, 44.0 ppm; IR (neat): 3272, 2203, 1690, 1259 cm^{-1}; HRMS (ESI-TOF) *m/z* [M + Na]$^{+}$ calcd for $C_{17}H_{15}FN_2ONa$ 305.1061, found 305.1060.

N-(4-Chloro-2-((2-(dimethylamino)phenyl)ethynyl)phenyl)formamide ***(1k)***. Purification by column chromatography (EtOAc/hexane, 1:19 v/v) afforded **1k** (0.5975 g, 40%); brown viscous liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.93 (br s, 0.71H), 8.88 (d, J = 11.2 Hz, 0.29H), 8.68 (br d, J = 8.8 Hz, 0.29H), 8.49 (d, J = 1.6 Hz, 0.71H), 8.45 (d, J = 8.8 Hz, 0.71H), 7.49−7.45 (m, 2H), 7.37−7.31 (m, 1H), 7.29 (dd, J = 9.2 Hz, J = 2.4 Hz, 1H), 7.20 (d, J = 8.8 Hz, 0.29H), 7.09 (d, J = 8.4 Hz, 1H), 7.05−6.98 (m, 1H), 2.92 & 2.89 (each s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.0, 158.9, 156.3, 155.7, 136.9, 133.0, 132.9, 131.2, 130.3, 130.1, 129.5, 129.3, 129.2, 128.7, 125.1, 122.5, 122.1, 121.0, 118.5, 118.3, 116.2, 115.9, 115.1, 114.1, 97.5, 97.2, 88.2, 87.7, 44.7, 44.1 ppm; IR (neat): 3256, 2196, 1689, 1258 cm^{-1}; HRMS (ESI-TOF) *m/z* [M + Na]$^{+}$ calcd for $C_{17}H_{15}ClN_2ONa$ 321.0765, found 321.0763.

N-(4-Bromo-2-((2-(dimethylamino)phenyl)ethynyl)phenyl)formamide ***(1l)***. Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **1l** (0.9268 g, 54%); brown viscous liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.95 (br s, 0.76H), 8.84 (d, J = 10.8 Hz, 0.24H), 8.72 (br d, J = 10.8 Hz, 0.24H), 8.47 (d, J = 1.6 Hz, 0.76H), 8.37 (d, J = 8.8 Hz, 0.76H), 7.61 (d, J = 2.0 Hz, 0.24H), 7.58 (d, J = 2.4 Hz, 0.76H), 7.48−7.44 (m, 1H), 7.41 (dd, J = 8.8 Hz, J = 2.4 Hz, 0.76H), 7.37 (dd, J = 8.8 Hz, J = 2.4 Hz, 0.24H), 7.35−7.30 (m, 1H), 7.10−7.06 (m, 1.24H), 7.02−6.96 (m, 1H), 2.90 & 2.87 (each s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.8, 158.8, 156.3, 155.6, 137.3, 134.3, 134.0, 132.94, 132.91, 132.86, 132.3, 132.2, 130.34, 130.28, 124.0,122.4, 122.1, 121.2, 119.6, 118.4, 118.2, 116.4, 116.3, 116.0, 115.9, 115.8, 115.3, 114.4, 97.6, 97.3, 88.0, 87.5, 44.7, 44.1 ppm; IR (neat): 3269, 2196, 1689, 1258 cm^{-1}; HRMS (ESI-TOF) *m/z* [M + Na]$^{+}$ calcd for $C_{17}H_{15}BrN_2ONa$ 365.0260, found 365.0264.

N-(2-((2-(Dimethylamino)phenyl)ethynyl)-4-nitrophenyl)formamide ***(1m)***. Purification by column chromatography (EtOAc/hexane, 2:3 v/v) afforded **1m** (0.6032 g, 39%); orange solid; mp

= 102.12−103.1 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.92 (br s, 0.75H), 9.09 (br d, J = 10.4 Hz, 0.25H), 8.70 (d, J = 9.2 Hz, 0.75H), 8.58 (s, 0.75H), 8.38−8.35 (m, 1.25H), 8.20 (d, J = 9.2 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.39 (t, J = 8.4 Hz, 1.25H), 7.14 (d, J = 8.0 Hz, 1H), 7.07 (t, J = 7.4 Hz, 1H), 2.91 (s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.3, 159.0, 156.8, 155.9, 143.2, 143.1, 132.9, 132.7, 130.8, 126.9, 125.8, 124.9, 124.7, 122.8, 122.6, 119.5, 118.9, 118.5, 115.6, 113.5, 113.3, 99.3, 98.4, 87.2, 86.6, 44.9, 44.3 ppm; IR (neat): 3256, 2187, 1671, 1267 cm^{-1}; HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{17}H_{15}N_3O_3Na$ 332.1006, found 332.1004.

*N-(5-Chloro-2-((2-(dimethylamino)phenyl)ethynyl)phenyl)formamide (**1n**)*. Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **1n** (0.8216 g, 55%); pale brown viscous liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.01 (br s, 0.74H), 8.19 (d, J = 10.8 Hz, 0.26H), 8.76 (br d, J = 11.6 Hz, 0.26H), 8.58 (d, J = 2.4 Hz, 0.74H), 8.50 (d, J = 1.6 Hz, 0.74H), 7.49−7.45 (m, 1H), 7.58 (d, J = 8.4 Hz, 0.26H), 7.39 (d, J = 8.4 Hz, 0.74H), 7.36−7.31 (m, 1H), 7.28 (d, J = 1.6 Hz, 0.26H), 7.11−7.07 (m, 2H), 7.05−6.98 (m, 1H), 2.91 & 2.89 (each s, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 160.7, 158.9, 156.2, 155.2, 139.3, 139.1, 135.2, 135.0, 132.7, 132.6, 132.4, 131.2, 130.1, 124.1, 124.0, 122.5, 122.2, 120.0, 118.5, 118.3, 116.3, 115.1, 111.7, 110.8, 97.1, 96.9, 88.5, 87.9, 44.7, 44.1 ppm; IR (neat): 3256, 2207, 1690, 1260 cm^{-1}; HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{17}H_{15}ClN_2ONa$ 321.0765, found 321.0765.

*N-(2-((2-(Diethylamino)phenyl)ethynyl)phenyl)formamide (**1o**)*. Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **1o** (0.7748 g, 53%); pale brown viscous liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.22 (br s, 0.70H), 8.95 (br s, 0.60H), 8.55 (s, 0.70H), 8.53−8.52 (m, 0.70H), 7.52−7.47 (m, 2H), 7.36−7.26 (m, 2.30H), 7.16−7.02 (m, 3H), 3.32 (q, J = 7.2 Hz, 1.20H), 3.22 (q, J = 7.2 Hz, 2.80H), 1.05−0.99 (m, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ

161.0, 158.8, 152.7, 152.1, 138.5, 132.3, 132.3, 131.5, 130.3, 129.32, 129.27, 129.22, 129.15, 123.7, 123.6, 123.2, 122.8, 122.1, 121.8, 119.8, 119.8, 119.6, 114.5, 113.1, 112.4, 96.6, 96.4, 88.5, 88.0, 48.3, 47.8, 12.1, 12.0 ppm; IR (neat): 3248, 2206, 1694, 1252 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{19}H_{20}N_2ONa$ 315.1468, found 315.1469.

*N-(2-((2-(Ethylamino)phenyl)ethynyl)phenyl)formamide (**1o′**).* Purification by column chromatography (EtOAc/hexane, 1:9 v/v) afforded **1o′** (1.0177 g, 77%); pale brown viscous liquid; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.79 (d, J = 11.6 Hz, 0.27H), 8.53 (d, J = 8.0 Hz, 0.73H), 8.23 (d, J = 1.6 Hz, 0.73H), 7.69 (d, J = 8.0 Hz, 0.73H), 7.66 (d, J = 8.0 Hz, 0.27H), 7.51−7.41 (m, 3H), 7.39−7.28 (m, 3H), 7.26−7.52 (m, 1.27H), 6.56 (s, 0.73H), 6.52 (s, 0.27H), 3.99 (q, J = 6.8 Hz, 2H), 1.20 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 161.1, 158.8, 136.7, 136.1, 134.6, 134.0, 132.2, 131.0, 130.1, 130.0, 128.12, 128.06, 124.5, 124.1, 122.7, 122.29, 122.26, 121.9, 120.9, 120.86, 120.84, 120.2, 116.4, 110.1, 110.0, 103.5, 103.1, 38.6, 15.3 ppm; IR (neat): 3182, 2115, 1666, 1252 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{17}H_{16}N_2ONa$ 287.1155, found 287.1155.

*N-(2-((2-(Dibenzylamino)phenyl)ethynyl)phenyl)formamide (**1p**).* Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **1p** (1.1454 g, 55%); pale brown viscous liquid; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.46 (d, J = 11.2 Hz, 0.28H), 8.41 (d, J = 8.0 Hz, 0.72H), 8.14 (br d, J = 11.2 Hz, 0.28H), 8.08 (br s, 0.72H), 7.99 (d, J = 1.2 Hz, 0.72H), 7.58−7.53 (m, 1H), 7.34−7.12 (m, 11H), 7.06 (t, J = 7.6 Hz, 1H), 6.99 (t, J = 7.4 Hz, 0.72H), 6.93 (t, J = 7.4 Hz, 0.28H), 6.84−6.79 (m, 1.28H), 4.50 (s, 1.12H), 4.42 (s, 2.88H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 161.1, 158.9, 152.6, 152,3, 137.9, 137.7, 137.6, 134.0, 133.9, 132.4, 131.5, 129.6, 129.5, 129.3, 128.4, 128.24, 128.22, 127.3, 126.9, 124.3, 123.8, 122.1, 121.7, 121.5, 121.2, 119.9, 116.4, 116.1, 115.6, 113.8, 112.5, 96.2, 96.1, 89.1, 88.6, 56.3, 56.1 ppm; IR (neat): 3164,

2111, 1685, 1290 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{29}H_{24}N_2ONa$ 439.1781, found 439.1782.

*N-(2-((2-(Benzylamino)phenyl)ethynyl)phenyl)formamide (**1p′**).* Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **1p′** (1.2730 g, 78%); pale brown viscous liquid; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.82 (d, J = 11.2 Hz, 0.36H), 8.40 (d, J = 8.0 Hz, 0.64H), 8.29 (s, 0.64H), 7.90 (br s, 1H), 7.51−7.47 (m, 1H), 7.43−7.27 (m, 7.36H), 7.24−7.15 (m, 1H), 7.15 (t, J = 7.6 Hz, 0.36H), 7.10 (t, J = 7.6 Hz, 0.64H), 6.74−6.96 (m, 1H), 6.66 (d, J = 8.4 Hz, 0.64H), 6.61 (d, J = 8.4 Hz, 0.36H), 5.00 (br s, 1H), 4.47 & 4.44 (each s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 161.3, 158.8, 148.8, 138.7, 137.6, 132.9, 132.4, 132.3, 131.2, 130.8, 129.7, 129.6, 128.8, 128.7, 127.5, 127.23, 127.18, 127.1, 124.6, 124.0, 120.2, 116.9, 116.8, 116.4, 112.2, 110.3, 110.2, 106.6, 93.3, 93.2, 89.6, 89.3, 47.8, 47.6 ppm; IR (neat): 3368, 2205, 1685, 1292 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{22}H_{18}N_2ONa$ 349.1311, found 349.1313.

*N-(2-((2-Aminophenyl)ethynyl)phenyl)formamide (**1q**).*[14] Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **1q** (1.0404 g, 88%); white solid; mp = 99.4−100.6 °C (CH_2Cl_2/hexane) (lit.[13b] mp 101.0−103.0 °C); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.81 (d, J = 11.2 Hz, 0.34H), 8.49 (s, 0.66H), 8.43 (d, J = 8.4 Hz, 0.66H), 8.05 (br s, 1H), 7.56−7.50 (m, 1H), 7.38−7.32 (m, 2H), 7.26−7.10 (m, 2.34H), 6.77−6.75 (m, 2H), 4.26 (br s, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 161.5, 159.0, 147.9, 137.7, 137.3, 132.8, 132.3, 132.2, 131.8, 130.53, 130.50, 129.8, 129.6, 124.7, 124.0, 120.2, 118.2, 118.1, 116.6, 114.7, 114.6, 114.0, 112.2, 106.9, 106.8, 93.2, 93.1, 89.0, 88.9 ppm; IR (neat): 3409, 2206, 1643, 1250 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{15}H_{12}N_2ONa$ 259.0842, found 259.0841.

*N-(2-((2-((4-Methylphenyl)sulfonamido)phenyl)ethynyl)phenyl)formamide (**1r**).* Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **1r** (1.2690 g, 65%); pale brown solid;

mp = 136.7−138.4 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.53 (d, J = 11.2 Hz, 0.45H), 8.39 (d, J = 8.4 Hz, 0.55H), 8.35 (d, J = 8.4 Hz, 0.45H), 8.26 (d, J = 8.0 Hz, 0.55H), 8.20 (d, J = 1.6 Hz, 0.55H), 7.55−7.38 (m, 4H), 7.36−7.28 (m, 3H), 7.23 (d, J = 7.6 Hz, 0.45H), 7.18−7.13 (m, 1H), 7.11−7.04 (m, 3H), 6.57 (d, J = 8.8 Hz, 1H), 2.33 & 2.32 (each s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.8, 159.9, 158.9, 145.3, 136.4, 135.7, 132.6, 131.6, 130.5, 130.4, 129.9, 129.8, 129.5, 127.0, 126.8, 125.6, 125.5, 124.5, 124.4, 123.9, 122.14, 121.08, 121.0, 118.8, 116.1, 116.0, 114.3, 114.2, 100.0, 94.3, 21.6 ppm; IR (neat): 3305, 2073, 1683, 1256, 1173 (SO_2) cm^{-1}; HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{22}H_{18}N_2O_3SNa$ 413.0930, found 413.0936.

*N-(2-((2-(ethyl(methyl)amino)phenyl)ethynyl)phenyl)formamide (**1s**)*. Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **1s** (0.7098 g, 51%); brown viscous liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.80 (d, J = 11.2 Hz, 0.78H) 8.56 (br d, J = 10.0 Hz, 0.22H), 8.41−8.39 (m, 1.22H), 7.42−7.37 (m, 2H), 7.25−7.13 (m, 2.78H), 7.03−6.98 (m, 2H), 6.97−6.86 (m, 1H), 3.24 (q, J = 6.8 Hz, 0.78H), 3.16 (q, J = 6.8 Hz, 1.22H), 2.77 & 2.73 (each s, 3H), 1.02−0.97 (m, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 161.1, 158.9, 154.7, 154.4, 138.3, 133.0, 131.9, 130.7, 129.7, 129.5, 129.3, 124.0, 123.7, 122.3, 121.9, 119.8, 119.7, 119.6, 115.1, 113.5, 112.5, 96.4, 96.2, 88.9, 88.4, 50.6, 50.0, 41.3, 40.8, 12.3, 12.0 ppm; IR (neat): 3250, 2207, 1690, 1260 cm^{-1}; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{18}H_{19}N_2O$ 279.1492, found 279.1494.

*N-(2-((2-(Pyrrolidin-1-yl)phenyl)ethynyl)phenyl)formamide (**1t**)*. Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **1t** (0.8130 g, 56%); brown viscous liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.82 (d, J = 11.6 Hz, 0.36H), 8.46 (s, 0.64H), 8.43 (d, J = 8.4 Hz, 0.64H), 8.10 (br s, 0.64H), 7.99 (br d, J = 10.4 Hz, 0.36H), 7.50−7.43 (m, 2H), 7.35−7.29 (m,

1H), 7.27−7.21 (m, 1H), 7.15 (d, J = 7.6 Hz, 0.36H), 7.12−7.08 (m, 1H), 6.75−6.69 (m, 2H), 3.60−3.56 (m, 4H), 1.97−1.84 (m, 4H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 161.3, 158.9, 150.5, 150.4, 137.6, 135.4, 135.1, 132.2, 131.1, 130.10, 130.08, 129.2, 129.0, 124.5, 123.9, 119.9, 117.3, 117.1, 116.1, 114.6, 114.4, 114.2, 113.1, 107.9, 98.2, 86.8, 50.6, 50.5, 25.64, 25.59 ppm; IR (neat): 3306, 2202, 1685, 1263 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{19}H_{18}N_2ONa$ 313.1311, found 313.1313.

*N-(2-((2-(piperidin-1-yl)phenyl)ethynyl)phenyl)formamide (**1u**)*. Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **1u** (0.8827 g, 58%); yellow viscous liquid; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.87 (d, J = 11.6 Hz, 0.27H), 8.53 (s, 0.73H), 8.47 (d, J = 8.4 Hz, 0.73H), 8.43 (br s, 0.73H), 8.25 (br d, J = 10.4 Hz, 0.27H), 7.55−7.49 (m, 3H), 7.36−7.24 (m, 2.27H), 7.15−7.08 (m, 1H), 7.03−6.64 (m, 2H), 3.13−3.10 (m, 4H), 1.76−1.70 (m, 4H), 1.61−1.56 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 161.0, 158.8, 155.7, 150.4, 137.6, 133.6, 133.5, 132.5, 131.3, 130.0, 129.4, 129.3, 124.2, 123.8, 121.9, 121.6, 119.8, 118.4, 118.3, 116.5, 115.5 112.6, 95.9, 95.8, 88.5, 88.2, 53.3, 53.0, 26.4, 26.2, 24.2, 24.0 ppm; IR (neat): 3325, 2206, 1688, 1229 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{20}H_{21}N_2O$ 305.1648, found 305.1649.

*General Procedure for the Synthesis of Compounds **4***. To a two-neck flask containing (2-iodophenyl)(methyl)sulfane (10 mmol, 1.0 equiv), $PdCl_2(PPh_3)_2$ (91.2 mg, 0.13 mmol, 0.013 equiv), and CuI (19 mg, 0.1 mmol, 0.01 equiv) was added Et_3N (1 mL/mmol) under argon atmosphere. Next, the reaction was added dropwise with a solution of *N*-(2-ethynylphenyl)formamide derivatives (11 mmol, 1.1 equiv) in THF (1 mL/mmol) at room temperature under argon atmosphere. The reaction mixture was stirred at room temperature under argon atmosphere for 16 h, then quenched with saturated aqueous NH_4Cl (20 mL) and the

resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (anh. $MgSO_4$), filtered, and concentrated under reduced pressure (aspirator). The crude product was purified by column chromatography on silica gel (EtOAc/hexane) to provide the corresponding compounds **4**. The peaks of ^1H and ^{13}C NMR spectral data of compounds **4** were observed as the mixture of amide rotamers.

*N-(2-((2-(Methylthio)phenyl)ethynyl)phenyl)formamide (**4a**)*. Purification by column chromatography (EtOAc/hexane, 3:7 v/v) afforded **4a** (1.0024 g, 75%); white solid; mp = 89.6−91.5 °C (CH_2Cl_2/hexane); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.89 (d, J = 11.2 Hz, 0.23H), 8.74 (br s, 0.77H), 8.57 (br d, J = 10.0 Hz, 0.23H), 8.58 (d, J = 1.6 Hz, 0.77H), 8.48 (d, J = 8.4 Hz, 0.77H), 7.56−7.48 (m, 2H), 7.38−7.31 (m, 2H), 7.28 (d, J = 8.0 Hz, 1.23H), 7.20−7.15 (m, 1H), 7.13−7.08 (m, 1H), 2.563 & 2.558 (each s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 161.8, 159.0, 140.4, 138.4, 132.5, 132.0, 131.9, 131.2, 139.9, 129.8, 129.4, 125.4, 125.2, 125.1, 124.7, 124.2, 123.8, 121.2, 119.8, 115.5, 112.0, 94.4, 90.7, 90.3, 15.8, 15.5 ppm; IR (neat): 3353, 1683, 1277 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{16}H_{13}NOSNa$ 290.0610, found 290.0618.

*N-(2-((2-(Methylthio)phenyl)ethynyl)-4-methylphenyl)formamide (**4b**)*. Purification by column chromatography (EtOAc/hexane, 3:7 v/v) afforded **4b** (1.3082 g, 93%); pale yellow solid; mp = 75.6−77.3 °C (CH_2Cl_2/hexane); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.82 (d, J = 11.0 Hz, 0.26H), 8.64 (br s, 0.74H), 8.48 (s, 0.74H), 8.45 (br d, J = 9.6 Hz, 0.26H), 8.34 (d, J = 8.4 Hz, 0.74H), 7.50−7.46 (m, 1H), 7.36−7.30 (m, 2H), 7.27−7.22 (m, 1H), 7.19−7.11 (m, 2.26H), 2.54 (s, 3H), 2.31 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 161.3, 158.7, 141.6, 140.3, 136.0, 135.8, 134.0, 133.3, 132.7, 131.8, 131.4, 130.6, 130.5, 129.2, 125.4, 125.1, 124.9, 124.6, 121.3, 120.9, 119.7, 115.7, 113.0, 111.8, 93.9, 93.8, 90.8, 90.5, 20.6, 20.5, 15.7, 15.4 ppm; IR (neat): 3349,

1706, 1232 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{17}H_{15}NOSNa$ 304.0767, found 304.0770.

*N-(2-((2-(Methylthio)phenyl)ethynyl)-4-trifluoromethylphenyl)formamide (**4c**).* Purification by column chromatography (EtOAc/hexane, 3:7 v/v) afforded **4c** (0.8553 g, 51%); pale yellow solid; mp = 100.9−102.8 °C (CH_2Cl_2/hexane); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.97 (d, J = 11.2 Hz, 0.18H), 8.89 (br s, 0.82H), 8.78 (br d, J = 8.0 Hz, 0.18H), 8.61 (d, J = 8.8 Hz, 0.82H), 8.55 (s, 0.82H), 7.79−7.76 (m, 1H), 7.59−7.48 (m, 2H), 7.37 (t, J = 7.6 Hz, 1H), 7.29−7.25 (m, 1.18H), 7.19 (d, J = 7.6 Hz, 1H), 2.56 & 2.56 (each s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 160.6, 159.0, 141.8, 141.0, 140.8, 140.5, 132.1, 131.9, 129.7, 129.3, 128.1 (q, $J_{C,F}$ = 3.9 Hz), 126.5 (q, $J_{C,F}$ = 3.5 Hz), 125.7 (q, $J_{C,F}$ = 35.6 Hz), 125.4, 125.2, 124.8, 123.6 (q, $J_{C,F}$ = 267.9 Hz), 120.5, 120.2, 119.6, 114.5, 112.9, 112.2, 95.7, 95.6, 89.1, 88.7, 15.7, 15.4 ppm; IR (neat): 3325, 1705, 1149 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{17}H_{12}F_3NOSNa$ 358.0484, found 358.0481.

*N-(2-((2-(Methylthio)phenyl)ethynyl)-4-fluorophenyl)formamide (**4d**).* Purification by column chromatography (EtOAc/hexane, 3:7 v/v) afforded **4d** (0.9134 g, 64%); white solid; mp = 117.6−119.0 °C (CH_2Cl_2/hexane); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.75 (d, J = 10.8 Hz, 0.29H), 8.65 (br s, 0.71H), 8.47 (s, 0.71H), 8.44 (dd, J = 8.8 Hz, J = 5.4 Hz, 1H), 7.50−7.45 (m, 1H), 7.37−7.33 (m, 1H), 7.26−7.21 (m, 1.29H), 7.19−7.13 (m, 2H), 7.04 (td, J = 8.6 Hz, J = 2.7 Hz, 1H), 2.54 & 2.53 (each s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 161.3, 159.0 (d, $J_{C,F}$ = 243.3 Hz), 158.7, 158.1 (d, $J_{C,F}$ = 242.9 Hz), 141.9, 140.5, 134.7 (d, $J_{C,F}$ = 2.8 Hz), 134.5 (d, $J_{C,F}$ = 3.2 Hz), 132.0, 131.9, 129.6, 125.3 (d, $J_{C,F}$ = 24.3 Hz), 125.0, 124.6, 121.3 (d, $J_{C,F}$ = 8.1 Hz), 120.6, 120.2, 118.6 (d, $J_{C,F}$ = 24.0 Hz), 117.4, 117.3 (d, $J_{C,F}$ = 24.1 Hz), 116.9, 116.8 (d, $J_{C,F}$ = 22.9 Hz), 116.7 (d, $J_{C,F}$ = 22.1), 114.9 (d, $J_{C,F}$ = 9.8 Hz), 113.4 (d, $J_{C,F}$ = 9.5 Hz), 95.0, 89.5, 89.4,

15.7, 15.4 ppm; IR (neat): 3262, 1662, 1260 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{16}H_{12}FNOSNa$ 308.0516, found 308.0519.

*N-(2-((2-(Methylthio)phenyl)ethynyl)-4-chlorophenyl)formamide (**4e**)*. Purification by column chromatography (EtOAc/hexane, 3:7 v/v) afforded **4e** (0.7998 g, 53%); pale yellow solid; mp = 108.8−109.6 °C (CH_2Cl_2/hexane); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.86 (d, J = 10.8 Hz, 0.16H), 8.71 (br s, 0.84H), 8.53 (br d, J = 8.0 Hz, 0.16H), 8.50 (d, J = 2.0 Hz, 0.84H), 8.44 (d, J = 8.8 Hz, 0.84H), 7.52−7.48 (m, 2H), 7.37 (td, J = 7.8 Hz, J = 1.2 Hz, 1H), 7.32−7.27 (m, 2H), 7.19−7.13 (m, 1.16H), 2.56 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 160.9, 158.8, 140.5, 136.9, 132.1, 132.0, 131.8, 130.5, 129.8, 129.7, 128.6, 125.5, 125.2, 125.1, 124.7, 120.9, 120.7, 116.5, 113.5, 95.3, 89.3, 88.9, 15.8, 15.5 ppm; IR (neat): 3342, 1697, 1255 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{16}H_{12}ClNOSNa$ 324.0220, found 324.0224.

*N-(2-((2-(Methylthio)phenyl)ethynyl)-4-bromophenyl)formamide (**4f**)*. Purification by column chromatography (EtOAc/hexane, 3:7 v/v) afforded **4f** (1.6112 g, 93%); white solid; mp = 97.5−98.8 °C (CH_2Cl_2/hexane); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.83 (d, J = 10.8 Hz, 0.20H), 8.69 (br s, 0.80H), 8.53 (br d, J = 11.2 Hz, 0.20H), 8.49 (d, J = 1.2 Hz, 0.80H), 8.37 (d, J = 8.8 Hz, 0.80H), 7.65−7.61 (m, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.43 (dd, J = 4.6 Hz, J = 2.4 Hz, 1H), 7.37−7.34 (m, 1H), 7.26 (d, J = 7.2 Hz, 1H), 7.19−7.10 (m, 1.20H), 2.54 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 160.8, 158.8, 141.9, 140.5, 137.4, 137.3, 134.7, 133.4, 132.6, 132.5, 132.1, 132.1, 131.9, 129.7, 129.7, 125.4, 125.2, 125.1, 124.7, 121.1, 120.7, 116.6, 116.0, 114.8, 113.8, 95.5, 95.4, 89.1, 88.8, 15.8, 15.5 ppm; IR (neat): 3342, 1694, 1256 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{16}H_{12}BrNOSNa$ 367.9715, found 367.9725.

*N-(2-((2-(Methylthio)phenyl)ethynyl)-5-chlorophenyl)formamide (**4g**)*. Purification by column chromatography (EtOAc/hexane, 3:7 v/v) afforded **4g** (0.7850 g, 52%); pale yellow solid; mp =

155.2−156.0 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.88 (d, J = 10.8 Hz, 0.16H), 8.78 (br s, 0.84H), 8.62 (br d, J = 9.2 Hz, 0.16H), 8.58 (d, J = 2.0 Hz, 0.84H), 8.52 (d, J = 1.6 Hz, 0.84H), 7.52−7.46 (m, 1.16H), 7.43 (d, J = 8.0 Hz, 1H), 7.38 (dd, J = 7.6 Hz, J = 1.4 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 7.20 (td, J = 7.6 Hz, J = 0.8 Hz, 1H), 7.09 (dd, J = 8.4 Hz, J = 2.0 Hz, 1H), 2.57 (s,3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 158.8, 140.3, 139.1, 135.7, 131.9, 131.8, 129.5, 125.6, 125.3, 124.0, 121.0, 119.9, 110.3, 95.2, 89.7, 15.9 ppm; IR (neat): 3331, 1685, 1260 cm^{-1}; HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{16}H_{12}ClNOSNa$ 324.0220, found 324.0223.

*General Procedure for Preparation of Compounds **2**, **5** and **9**.* To a solution of *N*-(2-((2-(dimethylamino)phenyl)ethynyl)phenyl)formamides **1**, or *N*-(2-((2-(methylthio)phenyl)ethynyl)phenyl)formamides **4**, or *N*-(2-(phenylethynyl)phenyl)formamide **8** (0.5 mmol, 1.0 equiv) and diisopropylethylamine (0.70 mL, 4.0 mmol, 8.0 equiv) in CH_2Cl_2 (4 mL, 0.125 M) was added dropwise $POCl_3$ (0.07 mL, 0.75 mmol, 1.5 equiv) at 0 ^{o}C under argon atmosphere. The reaction mixture was stirred at 0 ^{o}C for 1 h. The reaction was quenched with $NaHCO_3$ (5 mL) and the resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (anh. $MgSO_4$), filtered, and concentrated under reduced pressure (aspirator). The crude product was subsequently used in the next step without prior purification.

*General Procedure for the Synthesis of Compounds **3**.* To a round-bottomed flask filled with compound **2** {freshly prepared from the corresponding compound **1** (0.5 mmol)} was diluted with DMF (2 mL, 0.25 M). The reaction mixture was stirred at 80 ^{o}C for 1 h, then diluted with H_2O (5 mL) and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (anh. $MgSO_4$), filtered, and concentrated

under reduced pressure (aspirator). The crude product was purified by column chromatography on silica gel (EtOAc/hexane) to yield the corresponding indolo[2,3-*b*]quinolines **3**.

*6-Methyl-6H-indolo[2,3-b]quinoline (**3a**).*[9m] Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **3a** (105 mg, 90%); pale yellow solid. mp = 73.2−74.5 °C (CH_2Cl_2/hexane) (lit.[9m] mp 83.0−87.0 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.62 (s, 1H), 8.17 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 7.6 Hz, 1H), 7.96 (d, J = 8.0 Hz, 1H), 7.73 (t, J = 8.2 Hz, 1H), 7.57 (t, J = 7.6 Hz, 1H), 7.45 (t, J = 7.4 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.30 (t, J = 7.4 Hz, 1H), 3.95 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 152.5, 146.3, 142.7, 128.9, 128.5, 128.1, 127.5, 127.1, 123.9, 122.9, 121.4, 120.3, 120.0, 118.2, 108.7, 27.8 ppm; IR (neat): 3050, 2921, 1635, 1604, 1490, 1428 cm^{-1}; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{16}H_{13}N_2$ 233.1073, found 233.1074.

*6,9-Dimethyl-6H-indolo[2,3-b]quinoline (**3b**).* Purification by column chromatography (EtOAc/hexane, 1:9 v/v) afforded **3b** (89 mg, 72%); pale yellow solid; mp = 77.9−78.9 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.60 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.90 (s, 1H), 7.69 (t, J = 8.4 Hz, 1H), 7.42 (t, J = 7.8 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.26 (d, J = 8.0 Hz, 1H), 3.92 (s, 1H), 2.53 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 152.9, 146.7, 140.9, 129.3, 129.1, 128.7, 128.4, 127.3, 127.1, 124.0, 122.7, 121.5, 120.4, 118.2, 108.3, 27.7, 21.3 ppm; IR (neat): 3050, 2917, 1636, 1609, 1483, 1447 cm^{-1}; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{17}H_{15}N_2$ 247.1230, found 247.1231.

*6-Methyl-9-(trifluoromethyl)-6H-indolo[2,3-b]quinoline (**3c**).* Purification by column chromatography (EtOAc/hexane, 1:9 v/v) afforded **3c** (117 mg, 78%); pale yellow solid; mp = 117.5−118.3 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.45 (s, 1H), 8.15 (s, 1H), 8.11 (d, J = 8.8 Hz, 1H), 8.01 (d, J = 8.0 Hz, 1H), 7.82 (dd, J = 8.8 Hz, J = 2.0 Hz, 1H), 7.56 (t, J =

8.2 Hz, 1H), 7.29 (t, J = 7.0 Hz, 2H), 3.82 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 153.3, 147.5, 142.7, 128.6, 128.2, 127.4, 126.3 (q, $J_{C,F}$ = 4.4 Hz), 125.9, 124.5 (q, $J_{C,F}$ = 269.5 Hz), 124.4 (q, $J_{C,F}$ = 32.7 Hz), 124.1 (q, $J_{C,F}$ = 3.0 Hz), 123.2, 121.5, 120.8 (q, $J_{C,F}$ = 119.2 Hz), 120.3, 119.7, 108.8, 27.5 ppm; IR (neat): 3061, 2926, 1606, 1574, 1472, 1420 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{17}H_{12}F_3N_2$ 301.0947, found 301.0948.

*9-Fluoro-6-methyl-6H-indolo[2,3-b]quinoline (**3d**)*. Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **3d** (93 mg, 74%); yellow solid; mp = 113.9−115.7 °C (CH_2Cl_2/hexane); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.63 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.73 (t, J = 7.8 Hz, 1H), 7.46 (t, J = 7.4 Hz, 1H), 7.30 (d, J = 6.0 Hz, 2H), 3.95 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 157.6 (d, $J_{C,F}$ = 235.7 Hz), 153.0, 154.7 (d, $J_{C,F}$ = 346.2 Hz), 147.0, 139.0, 129.2, 128.6, 127.9, 127.4, 123.8, 123.0, 120.8 (d, $J_{C,F}$ = 9.3 Hz), 117.6 (d, $J_{C,F}$ = 4.0 Hz), 115.3 (d, $J_{C,F}$ = 24.8 Hz), 109.1 (d, $J_{C,F}$ = 8.7 Hz), 107.7 (d, $J_{C,F}$ = 24.2 Hz), 27.8 ppm; IR (neat): 3050, 2918, 1612, 1571, 1477, 1426 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{16}H_{12}FN_2$ 251.0979, found 251.0980.

*9-Chloro-6-methyl-6H-indolo[2,3-b]quinoline (**3e**)*. Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **3e** (102 mg, 76%); yellow solid; mp = 139.5−140.9 °C (CH_2Cl_2/hexane); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.49 (s, 1H), 8.10 (d, J = 8.8 Hz, 1H), 7.96 (s, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.72 (t, J = 7.6 Hz, 1H), 7.48-7.42 (m, 2H), 7.20 (d, J = 8.8 Hz, 1H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 152.6, 147.0, 141.0, 129.3, 128.6, 128.0, 127.9, 127.5, 125.4, 124.0, 123.2, 121.4, 121.2, 117.1, 109.6, 27.8 ppm; IR (neat): 3065, 2929, 1603, 1569, 1478, 1420 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{16}H_{12}ClN_2$ 267.0684, found 267.0686.

*9-Bromo-6-methyl-6H-indolo[2,3-b]quinoline (**3f**).*[9m] Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **3f** (110 mg, 71%); yellow solid; mp = 157.7−159.3 °C (CH_2Cl_2/hexane) (lit.[9m] mp 132.0−134.0 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.54 (s, 1H), 8.15 (d, J = 2.0 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.72 (t, J = 7.6 Hz, 1H), 7.62 (dd, J = 8.4 Hz, J = 1.6 Hz, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 3.88 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 152.5, 147.0, 141.3, 130.5, 129.3, 128.6, 127.8, 127.5, 124.1, 124.0, 123.1, 122.0, 116.9, 112.5, 110.0, 27.7 ppm; IR (neat): 3064, 2927, 1600, 1570, 1476, 1418 cm^{-1}; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{16}H_{12}BrN_2$ 311.0178, found 311.0178.

*8-Chloro-6-methyl-6H-indolo[2,3-b]quinoline (**3g**).* Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **3g** (95 mg, 71%); pale brown solid; mp = 174.1−175.5 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.57 (s, 1H), 8.11 (d, J = 8.8 Hz, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.72 (t, J = 8.4 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.32 (s, 1H), 7.23 (dd, J = 8.2 Hz, J = 1.8 Hz, 1H), 3.89 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 152.8, 146.7, 143.4, 133.8, 129.0, 128.5, 127.5, 127.4, 124.1, 123.2, 122.1, 120.2, 118.8, 117.3, 109.0, 27.7 ppm; IR (neat): 3050, 2926, 1600, 1570, 1491, 1417 cm^{-1}; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{16}H_{12}ClN_2$ 267.0684, found 267.0682.

*2,6-Dimethyl-6H-indolo[2,3-b]quinoline (**3h**).*[9t] Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **3h** 103 mg, 84%); pale orange solid; mp = 102.9−104.0 °C (CH_2Cl_2/hexane) (lit.[9t] mp 201.0 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.63 (s, 1H), 8.15 (d, J = 8.0 Hz, 1H), 8.05 (d, J = 8.8 Hz, 1H), 7.76 (s, 1H), 7.60-7.55 (m, 2H), 7.41 (d, J = 8.0 Hz, 1H), 7.30 (t, J = 7.4 Hz, 1H), 3.99 (s, 3H), 2.58 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 142.8, 132.4, 131.2, 128.0, 127.39, 127.36, 127.1, 126.8, 124.1, 121.4, 120.4, 119.8, 118.2, 108.7, 27.8,

21.4 ppm; IR (neat): 3024, 2917, 1632, 1572, 1473, 1392 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{17}H_{15}N_2$ 247.1230, found 247.1233.

*6-Methyl-2-(trifluoromethyl)-6H-indolo[2,3-b]quinoline (**3i**).* Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **3i** (115 mg, 77%); pale brown solid; mp = 112.6−114.6 °C (CH_2Cl_2/hexane); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.68 (s, 1H), 8.26 (s, 1H), 8.19 (d, J = 8.8 Hz, 1H), 8.14 (d, J = 7.6 Hz, 1H), 7.86 (dd, J = 8.6 Hz, J = 2.0 Hz, 1H), 7.62 (t, J = 8.2 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.34 (t, J = 7.4 Hz, 1H), 3.96 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 153.5, 147.6, 142.9, 128.7, 128.3, 127.8, 125.6 (q, $J_{C,F}$ = 4.4 Hz), 125.9, 124.6 (q, $J_{C,F}$ = 32.3 Hz), 124.5 (q, $J_{C,F}$ = 270.2 Hz), 124.4 (q, $J_{C,F}$ = 3.1 Hz), 122.7, 121.7, 121.2 (q, $J_{C,F}$ = 132.3 Hz), 120.5, 119.9, 109.0, 27.8 ppm; IR (neat): 3060, 2924, 1606, 1574, 1472, 1420 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{17}H_{12}F_3N_2$ 301.0947, found 301.0950.

*2-Fluoro-6-methyl-6H-indolo[2,3-b]quinoline (**3j**).* Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **3j** (99 mg, 79%); pale yellow solid; mp = 126.0−127.0 °C (CH_2Cl_2/hexane); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.47 (s, 1H), 8.06 (d, J = 9.2 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.57−7.50 (m, 2H), 7.45 (dt, J = 8.8 Hz, J = 2.9 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.26 (t, J = 7.4 Hz, 1H), 3.87 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 158.2 (d, $J_{C,F}$ = 241.3 Hz), 152.3, 143.2 (d, $J_{C,F}$ = 65.5 Hz), 129.3 (d, $J_{C,F}$ = 8.8 Hz), 128.3, 126.2 (d, $J_{C,F}$ = 5.1 Hz), 124.0 (d, $J_{C,F}$ = 9.4 Hz), 121.5, 119.9, 119.9, 119.8, 118.6 (d, $J_{C,F}$ = 25.4 Hz), 118.7, 111.1 (d, $J_{C,F}$ = 21.5 Hz), 108.6, 27.5 ppm; IR (neat): 3055, 2928, 1605, 1577, 1473, 1423 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{16}H_{12}FN_2$ 251.0979, found 251.0989.

*2-Chloro-6-methyl-6H-indolo[2,3-b]quinoline (**3k**).* Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **3k** (113 mg, 85%); pale yellow solid; mp = 132.2−133.7 °C (CH_2Cl_2/hexane); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.61 (s, 1H), 8.15 (d, J = 7.6 Hz, 1H), 8.06 (d,

J = 9.2 Hz, 1H), 7.97 (d, *J* = 2.0 Hz, 1H), 7.65-7.59 (m, 2H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 4.0 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 145.1, 143.0, 140.9, 129.5, 129.0, 128.5, 128.1, 126.9, 126.2, 124.6, 121.7, 120.2, 120.1, 118.9, 108.9, 27.7 ppm; IR (neat): 3050, 2928, 1600, 1577, 1474, 1417 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{16}H_{12}ClN_2$ 267.0684, found 267.0685.

*2-Bromo-6-methyl-6H-indolo[2,3-b]quinoline (**3l**).* Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **3l** (128 mg, 82%); pale yellow solid; mp = 160.0−162.0 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.50 (s, 1H), 8.10 (d, *J* = 7.6 Hz, 1H), 8.07 (d, *J* = 2.4 Hz, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.73 (dd, *J* = 9.2 Hz, *J* = 2.4 Hz, 1H), 7.59 (t, *J* = 8.2 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 1H), 3.92 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 152.7, 145.2, 142.9, 131.9, 130.2, 129.1, 128.5, 126.1, 125.1, 121.6, 120.2, 120.0, 118.7, 115.8, 108.8, 27.7 ppm; IR (neat): 3052, 2926, 1602, 1567, 1471, 1416 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{16}H_{12}BrN_2$ 311.0178, found 311.0174.

*6-Methyl-2-nitro-6H-indolo[2,3-b]quinoline (**3m**).* Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **3m** (122 mg, 88%); yellow solid; decomposition at 160.0 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.92 (d, *J* = 2.8 Hz, 1H), 8.75 (s, 1H), 8.43 (dd, *J* = 9.2 Hz, *J* = 2.4 Hz, 1H), 8.16 (d, *J* = 7.6 Hz, 1H), 8.13 (d, *J* = 9.2 Hz, 1H), 7.65 (t, *J* = 8.2 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 3.99 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 154.2, 149.1, 142.9, 142.5, 129.2, 128.6, 128.5, 125.5, 122.2, 122.1, 121.9, 121.0, 119.9, 119.6, 109.2, 27.8 ppm; IR (neat): 3079, 2923, 1604, 1576, 1468, 1398 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{16}H_{11}N_3O_2Na$ 300.0743, found 300.0748.

*3-Chloro-6-methyl-6H-indolo[2,3-b]quinoline (**3n**).*[9t] Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **3n** (93 mg, 70%); pale yellow solid; mp = 160.7−161.9 °C

(CH_2Cl_2/hexane) (lit.[9t] mp 206.0 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.62 (s, 1H), 8.12-8.10 (m, 2H), 7.89 (d, J = 8.8 Hz, 1H), 7.59 (t, J = 8.2 Hz, 1H), 7.41−7.38 (m, 2H), 7.31 (dd, J = 7.6 Hz, J = 0.8 Hz, 1H), 3.95 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 153.0, 147.0, 142.8, 134.6, 129.5, 128.3, 127.1, 126.4, 123.8, 122.3, 121.4, 120.23, 120.16, 118.3, 108.8, 27.7 ppm; IR (neat): 3051, 2928, 1600, 1566, 1470, 1389 cm^{-1}; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{16}H_{12}ClN_2$ 267.0684, found 267.0686.

*6-Ethyl-6H-indolo[2,3-b]quinoline (**3o**).*[9m] Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **3o** (105 mg, 85%) as a white solid; mp = 89.9−91.0 °C (from CH_2Cl_2/hexanes) (lit.[9m] mp 93.0−95.0 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.70 (s, 1H), 8.16 (d, J = 8.0 Hz, 2H), 8.00 (d, J = 8.0 Hz, 1H), 7.73 (t, J = 8.4 Hz, 1H), 7.58 (t, J = 8.2 Hz, 1H), 7.48−7.43 (m, 2H), 7.30 (t, J = 7.4 Hz, 1H), 4.60 (q, J = 7.2 Hz, 2H), 1.52 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 152.1, 146.8, 141.8, 128.7, 128.5, 127.9, 127.5, 127.2, 124.1, 122.8, 121.5, 120.5, 119.7, 118.2, 108.8, 36.1, 13.7 ppm; IR (neat): 3064, 2930, 1602, 1569, 1487, 1407 cm^{-1}; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{17}H_{15}N_2$ 247.1230, found 247.1224.

*6-Benzyl-6H-indolo[2,3-b]quinoline (**3p**).*[9r] Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **3p** (119 mg, 99%); pale yellow solid; mp = 170.8−171.5 °C (CH_2Cl_2/hexane) (lit.[9r] mp 160.0−163.0 °C); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.72 (s, 1H), 8.16 (t, J = 8.4 Hz, 2H), 8.02 (d, J = 7.6 Hz, 1H), 7.74 (t, J = 8.2 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 7.35−7.22 (m, 7H), 5.76 (s, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 152.6, 146.8, 142.0, 137.2, 128.8, 128.6, 128.4, 128.0, 127.7, 127.34, 127.30, 127.1, 124.3, 123.0, 121.4, 120.6, 120.1, 118.1, 109.6, 44.9 ppm; IR (neat): 3051, 2914, 1602, 1568, 1485, 1407 cm^{-1}; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{22}H_{17}N_2$ 309.1386, found 309.1387.

*6H-Indolo[2,3-b]quinoline (**3q**)*.[9b] Purification by column chromatography (EtOAc/hexane, 2:3 v/v) afforded **3q** (49 mg, 45%); yellow solid; mp > 300 °C (CH_2Cl_2/hexane) (lit.[9b] mp 346.0−348.0 °C); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.69 (s, 1H), 9.05 (s, 1H), 8.26 (d, J = 7.6 Hz, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 8.8 Hz, 1H), 7.72 (t, J = 7.6 Hz, 1H), 7.55−7.46 (m, 3H), 7.26 (t, J = 7.4 Hz, 1H); ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): δ 152.9, 146.3, 141.5, 128.7, 128.2, 127.4, 127.0, 123.7, 122.7, 121.8, 120.3, 119.7, 117.9, 110.9 ppm; IR (neat): 3141, 3084, 2921, 1610, 1577, 1458, 1403 cm^{-1}; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{15}H_{11}N_2$ 219.0917, found 219.0920.

*6-Tosyl-6H-indolo[2,3-b]quinoline (**3r**)*.[9c] Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **3r** (166 mg, 89%); brown viscous liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.29 (dd, J = 8.4 Hz, J = 0.4 Hz, 1H), 7.56−7.46 (m, 5H), 7.42−7.34 (m, 3H), 7.31−7.27 (m, 1H), 7.10 (d, J = 8.4 Hz, 2H), 2.30 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 167.3, 145.0, 137.8, 135.2, 134.5, 132.8, 129.9, 129.8, 129.6, 129.5, 128.3, 127.0, 126.7, 126.7, 125.5, 124.3, 121.3, 116.1, 115.3, 21.5 ppm; IR (neat): 3065, 2924, 1596, 1446, 1368, 1172 (SO_2) cm^{-1}; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{22}H_{16}N_2O_2SNa$ 395.0825, found 395.0824.

*6-(4-Chlorobutyl)-6H-indolo[2,3-b]quinoline (**3t**)*. Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **3t** (82 mg, 53%); pale yellow viscous liquid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.70 (s, 1H), 8.14 (t, J = 8.4 Hz, 2H), 8.00 (d, J = 8.0 Hz, 1H), 7.73 (t, J = 8.4 Hz, 1H), 7.58 (t, J = 8.2 Hz, 1H), 7.48−7.42 (m, 2H), 7.31 (t, J = 7.8 Hz, 1H), 4.57 (t, J = 6.8 Hz, 2H), 3.65 (t, J = 6.6 Hz, 2H), 2.18−2.11 (m, 2H), 1.91−1.84 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 152.5, 146.7, 142.0, 128.8, 128.4, 128.0, 127.6 127.3, 124.1, 122.9, 121.5, 120.5,

119.9, 118.0, 108.9, 44.6, 40.3, 29.7, 25.8 ppm; IR (neat): 3052, 2929, 1603, 1570, 1469, 1407 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{19}H_{18}ClN_2$ 309.1153, found 309.1154.

*6-(5-chloropentyl)-6H-indolo[2,3-b]quinoline (**3u**).* Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **3u** (126 mg, 78%); pale yellow viscous liquid; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.68 (s, 1H), 8.15 (t, *J* = 7.6 Hz, 2H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.74 (t, *J* = 7.2 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 7.4 Hz, 1H), 2.02−1.95 (m, 2H), 1.93−1.86 (m, 2H), 1.61−1.53 (m, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 152.4, 146.8, 142.1, 128.6, 128.4, 127.9, 127.6, 127.1, 124.1, 122.8, 121.4, 120.4, 119.7, 118.0, 108.8, 44.7, 40.9, 32.2, 27.7, 24.2 ppm; IR (neat): 3053, 2932, 1603, 1570, 1468, 1408 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{20}H_{20}ClN_2$ 323.1310, found 323.1312.

*General Procedure for the Synthesis of Compounds **6**.* To a round-bottomed flask filled with compound **5** {freshly prepared from the corresponding compound **4** (0.5 mmol)} was diluted with DMF (2 mL, 0.25 M). The reaction mixture was stirred at room temperature (32 ^oC) for 1 h, then diluted with H_2O (5 mL) and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (anh. $MgSO_4$), filtered, and concentrated under reduced pressure (aspirator). The crude product was purified by column chromatography on silica gel (EtOAc/hexane or CH_2Cl_2/EtOAc/hexane or CH_2Cl_2/hexane) to yield the corresponding benzothieno[2,3-*b*]quinolines **6**.

*Benzo[4,5]thieno[2,3-b]quinoline (**6a**).*[12a] Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **6a** (95 mg, 77%); white solid; mp = 143.3−144.6 °C (CH_2Cl_2/hexane) (lit.[12a] mp 140.0−142.0 °C); ^1H NMR ($CDCl_3$, 400 MHz): δ 8.69 (s, 1H), 8.14−8.12 (m, 2H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.74 (t, *J* = 7.8 Hz, 1H),

7.56−7.44 (m, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 163.2, 147.7, 138.4, 132.4, 129.7, 128.7, 128.4, 128.3, 128.1, 127.8, 125.6, 125.4, 125.0, 123.1, 122.1 ppm; IR (neat): 3049, 2926, 1585, 1555, 1493, 1450 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{15}H_{10}NS$ 236.0534, found 236.0533.

*9-Methylbenzo[4,5]thieno[2,3-b]quinoline (**6b**).* Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **6b** (86 mg, 67%); white solid; mp = 177.0−178.6 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.67 (s, 1H), 8.19−8.17 (m, 1H), 8.04 (d, J = 8.8 Hz, 1H), 7.85−7.83 (m, 1H), 7.76 (s, 1H), 7.60 (dd, J = 8.8 Hz, J = 2.0 Hz, 1H), 7.54−7.47 (m, 2H), 2.58 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 162.3, 146.5, 138.4, 135.5, 132.6, 132.2, 128.7, 128.3, 127.8, 127.2, 127.0, 125.5, 124.9, 123.1, 122.2, 21.58 ppm; IR (neat): 3031, 1583, 1492, 1467, 1453, 1416 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{16}H_{12}NS$ 250.0685, found 250.0685.

*9-(Trifluoromethyl)benzo[4,5]thieno[2,3-b]quinoline (**6c**).* Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **6c** (112 mg, 73%); white solid; mp = 206.3−207.5 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.77 (s, 1H), 8.29 (s, 1H), 8.21 (d, J = 8.8 Hz, 1H), 8.17 (d, J = 7.6 Hz, 1H), 7.89 (dd, J = 8.8 Hz, J = 1.8 Hz, 1H), 7.83 (d, J = 7.2 Hz, 1H), 7.57−7.48 (m, 2H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 165.6, 148.2, 138.5, 131.8, 129.8, 129.3, 129.1, 128.3, 127.5 (q, $J_{C,F}$ = 32.6 Hz), 126.3 (q, $J_{C,F}$ = 4.6 Hz), 125.4, 125.2 (q, $J_{C,F}$ = 2.9 Hz), 124.2, 124.1 (q, $J_{C,F}$ = 270.8 Hz), 123.2, 122.7, 122.5 ppm; IR (neat): 1630, 1588, 1557, 1470, 1456, 1434 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{16}H_9F_3NS$ 304.0402, found 304.0407.

*9-Fluorobenzo[4,5]thieno[2,3-b]quinoline (**6d**).* Purification by column chromatography (CH_2Cl_2/EtOAc/hexane, 2:1:7 v/v) afforded **6d** (103 mg, 75%); pale yellow solid; mp =

206.9−208.8 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.67 (s, 1H), 8.17 (d, J = 7.6 Hz, 1H), 8.12 (dd, J = 9.2 Hz, J = 5.2 Hz, 1H), 7.84 (d, J = 7.2 Hz, 1H), 7.59 (dd, J = 9.2 Hz, J = 2.8 Hz, 1H), 7.56−7.47 (m, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 162.6, 159.8 (d, $J_{C,F}$ = 246.1 Hz), 144.8, 138.7, 132.0, 130.5 (d, $J_{C,F}$ = 9.1 Hz), 129.3, 128.8, 127.0 (d, $J_{C,F}$ = 5.7 Hz), 125.9 (d, $J_{C,F}$ = 10.1 Hz), 125.1, 123.2, 122.4, 120.0 (d, $J_{C,F}$ = 26.1 Hz), 111.0 (d, $J_{C,F}$ = 21.8 Hz) ppm; IR (neat): 3038, 1625, 1587, 1556, 1493, 1454 cm^{-1}; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{15}H_9FNS$ 254.0434, found 254.0432.

9-Chlorobenzo[4,5]thieno[2,3-b]quinoline ***(6e)***. Purification by column chromatography (CH_2Cl_2/hexane, 2:3 v/v) afforded **6e** (100 mg, 74%); white solid; mp = 230.0−231.9 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.65 (s, 1H), 8.18 (d, J = 7.6 Hz, 1H), 8.07 (d, J = 8.8 Hz, 1H), 7.97 (d, J = 2.4 Hz, 1H), 7.84 (d, J = 6.8 Hz, 1H), 7.68 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H), 7.57−7.48 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 163.5, 146.0, 138.6, 132.1, 131.1, 130.6, 129.7, 129.4, 128.8, 126.8, 126.7, 126.0, 125.2, 123.2, 122.4 ppm; IR (neat): 3043, 1598, 1582, 1550, 1479, 1450 cm^{-1}; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{15}H_9ClNS$ 270.0139, found 270.0139.

9-Bromobenzo[4,5]thieno[2,3-b]quinoline ***(6f)***. Purification by column chromatography (CH_2Cl_2/hexane, 2:3 v/v) afforded **6f** (137 mg, 89%) as a white solid; mp = 234.3−235.8 °C (from CH_2Cl_2/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.67 (s, 1H), 8.20 (d, J = 7.6 Hz, 1H), 8.17 (d, J = 2 Hz, 1H), 8.01 (d, J = 8.8 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.82 (dd, J = 8.8 Hz, J = 2.2 Hz, 1H), 7.58−7.50 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 163.6, 146.1, 138.6, 133.1, 132.1, 130.2, 129.8, 129.4, 128.9, 126.6, 126.5, 125.2, 123.2, 122.4, 119.3 ppm; IR (neat): 3034, 1600, 1583, 1549, 1479, 1448 cm^{-1}; HRMS (ESI-TOF) *m/z* [M + H]$^+$ calcd for $C_{15}H_9BrNS$ 313.9634, found 313.9631.

*8-Chlorobenzo[4,5]thieno[2,3-b]quinoline (**6g**).* Purification by column chromatography (CH_2Cl_2/hexane, 2:3 v/v) afforded **6g** (120 mg, 89%); pale white solid; mp = 199.3−200.2 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.66 (s, 1H), 8.14 (d, J = 3.6 Hz, 1H), 8.10 (s, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.55−7.47 (m, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 164.2, 147.7, 138.3, 135.5, 132.1, 129.4, 128.8, 128.6, 127.4, 127.1, 126.7, 125.1, 123.7, 123.1, 122.2 ppm; IR (neat): 3033, 1599, 1586, 1551, 1483, 1446 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + H]^+$ calcd for $C_{15}H_9ClNS$ 270.0139, found 270.0141.

*Synthesis of N-Benzyl-2-(2-chloroquinolin-3-yl)aniline (**7**).* To a round-bottomed flask filled with **2p′** {freshly prepared from **1p′** (326 mg, 1 mmol)} was diluted with DMF (4 mL, 0.25 M). To this mixture was added *n*-Bu_4NCl (556 mg, 2 mmol). The reaction mixture was stirred at 80 ^{o}C for 2 h, then diluted with H_2O (10 mL) and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (anh. $MgSO_4$), filtered, and concentrated under reduced pressure (aspirator). Purification by column chromatography (EtOAc/hexane, 1:9 v/v) afforded **3p** (101 mg, 33%) and *N*-benzyl-2-(2-chloroquinolin-3-yl)aniline (**7**) (117 mg, 33%); pale yellow solid; mp = 167.6–168.1 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.71 (s, 1H), 8.13 (d, J = 7.6 Hz, 2H), 7.99 (d, J = 8.0 Hz, 1H), 7.70 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.4 Hz, 2H), 7.31–7.20 (m, 7H), 5.73 (s, 2H), 2.34 (br s, 0.45H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 152.7, 146.9, 142.1, 137.3, 128.8, 128.6, 128.4, 128.0, 127.7, 127.33, 127.31, 127.2, 124.4, 123.0, 121.4, 120.7, 120.1, 118.1, 109.7, 45.0 ppm; IR (neat): 3288, 1569, 1453 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M - H]^+$ calcd for $C_{22}H_{16}ClN_2$ 343.0997, found 343.0992.

*Synthesis of 6-Benzyl-6H-indolo[2,3-b]quinoline (**3p**) from **7**.* A solution of **7** (86.2 mg, 0.25 mmol) in DMF (2 mL, 0.125 M) was stirred at 80 ^{o}C for 1 h, then diluted with H_2O (5 mL) and

the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (anh. $MgSO_4$), filtered, and concentrated under reduced pressure (aspirator). The crude product was purified by column chromatography on silica gel (EtOAc/hexane, 1:4 v/v) to yield **3p** in quantitative yield.

*Synthesis of N-(2-(Phenylethynyl)phenyl)formamide (**8**).*[10a−f] To a two-neck flask containing *N*-(2-iodophenyl)formamide (2.4695 g, 10 mmol), $PdCl_2(PPh_3)_2$ (91.2 mg, 0.13 mmol), and CuI (19 mg, 0.1 mmol) was added THF (1 mL/mmol) and Et_3N (1 mL/mmol) under argon atmosphere. Next, the reaction was added dropwise ethynylbenzene (1.21 mL, 11 mmol) at room temperature under argon atmosphere. The reaction mixture was stirred at room temperature under argon atmosphere for 16 h. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and the resulting mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried (anh. $MgSO_4$), filtered, and concentrated under reduced pressure (aspirator). Crude product was purified by column chromatography on silica gel (ethyl acetate/hexanes) to provide the corresponding *N*-(2-(phenylethynyl)phenyl)formamide (**8**). Purification by column chromatography (EtOAc/hexane, 1:4 v/v) afforded **8** (2.0577 g, 95%); white solid; mp 91.0−92.5 °C (CH_2Cl_2/hexane); The peaks of ^1H and ^{13}C NMR spectral data of **8** were observed as the mixture of amide rotamers; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.86 (d, J = 11.3 Hz, 0.35H), 8.54 (s, 0.65H), 8.47 (d, J = 8.3 Hz, 0.64H), 8.02 (br s, 1H), 7.58−7.53 (m, 3H), 7.42−7.34 (m, 4H), 7.28−7.26 (m, 0.36H), 7.20−7.12 (m, 1H); $^{13}C\{^1H\}$ NMR (126 Hz, $CDCl_3$) δ 161.3, 158.9, 137.8, 137.5, 132.9, 131.9, 131.6, 129.7, 129.6, 129.0, 128.5, 128.5, 124.5, 123.9, 122.1, 122.0, 120.0, 116.1, 113.5, 112.0, 96.5, 83.8, 83.6 ppm; IR (neat) 3137, 1686, 1269 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{15}H_{11}NONa$ 244.0738, found: 244.0736.

*Synthesis of 2-Chloro-3-phenylquinoline (**10**) and 3-Phenylquinolin-2(1H)-one (**11**).* To a round-bottomed flask filled with **9** {freshly prepared from **8** (111 mg, 0.5 mmol)} was diluted with DMF (2 mL, 0.25 M). The reaction mixture was stirred at room temperature for 4 h, then diluted with H_2O (5 mL) and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (anh. $MgSO_4$), filtered, and concentrated under reduced pressure (aspirator). Crude product was purified by column chromatography on silica gel (EtOAc/hexane) to yield the corresponding 2-chloro-3-phenylquinoline (**10**) and 3-phenylquinolin-2(1*H*)-one (**11**).

*2-Chloro-3-phenylquinoline (**10**).*[10d, 10e] Purification by column chromatography (EtOAc/hexane, 1:9 v/v) afforded **10** (85 mg, 71%); pale yellow solid; mp = 52.6–54.7 °C (CH_2Cl_2/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.09 (s, 1H), 8.07 (d, J = 8.8 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.74 (t, J = 7.6 Hz, 1H), 7.57 (t, J = 7.4 Hz, 1H), 7.54–7.43 (m, 5H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 149.5, 146.8, 138.7, 137.5, 134.7, 130.3, 129.5, 128.2, 127.4, 127.2, 127.1 ppm; IR (neat): 1560, 1396, 1134 cm^{-1}; HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{15}H_{10}ClNNa$ 262.0394, found: 262.0396.

*3-Phenylquinolin-2(1H)-one (**11**).*[10a–b] Purification by column chromatography (EtOAc/hexane, 2:3 v/v) afforded **11** (11 mg, 10%); white solid; mp = 231.1–231.8 °C (CH_2Cl_2/hexanes); ^{1}H NMR (400 MHz; DMSO-d_6) δ 11.98 (s, 1H), 8.09 (s, 1H), 7.77–7.72 (m, 3H), 7.50 (td, J = 7.7, 1.2 Hz, 1H), 7.45–7.41 (m, 2H), 7.39–7.34 (m, 2H), 7.21–7.17 (m, 1H) ppm.; ^{13}C{^{1}H} NMR (100 MHz; DMSO-d_6) δ 161.5, 138.8, 138.1, 136.7, 132.0, 130.6, 129.1, 128.6, 128.4, 128.3, 122.3, 120.0, 115.1 ppm.; IR (neat) ν 2945, 1650 cm^{-1}; HRMS (ESI-TOF) *m/z* [M + Na]$^+$ calcd for $C_{15}H_{11}NONa$ 244.0738, found 244.0732.

Synthesis of ***[d$_1$]-3a***. To a two-neck flask filled with **2a** {freshly prepared from **1a** (110.6 mg, 0.5 mmol)} was dried by vacuum pump and argon flowing for 15 min. Then, dry DMF (2 mL, 0.25 M) and D_2O (1.0 mmol, 2.0 equiv, 0.018 mL) were added into the reaction at room temperature under Ar atmosphere. The reaction mixture was stirred at 80 ^oC for 1 , then diluted with H_2O (5 mL) and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (20 mL), dried (anh. $MgSO_4$), filtered, and concentrated under reduced pressure (aspirator). Crude product was purified by column chromatography on silica gel (EtOAc/hexane, 1: 4 v/v) to yield a mixture of **3a** and **[*d$_1$*]-3a** in a ratio of 1 : 9 (^{1}H NMR analysis).

A Mixture of 6-Methyl-6H-indolo[2,3-b]quinoline ***(3a)*** and *6-Methyl-6H-indolo[2,3-b]quinoline-11-d* ***([d$_1$]-3a)*** *(1 : 9 mole/mole)*; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.67 (s, 0.13H), 8.15 (d, J = 8.8 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.73 (t, J = 8.4 Hz, 1H), 7.58 (t, J = 7.2 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.30 (t, J = 7.4 Hz, 1H), 3.96 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 152.8, 146.8, 142.8, 128.8, 128.4, 128.0, 127.5, 127.3, 124.0, 122.8, 121.4, 120.4, 119.9, 118.1, 108.7, 27.7 ppm; IR (neat): 3050, 2919, 1636, 1607, 1487, 1430 cm^{-1}; HRMS (ESI-TOF) *m/z* $[M]^+$ calcd for $C_{16}H_{11}DN_2$ 233.1058, found 233.1061; HRMS (ESI-TOF) *m/z* $[M + Na]^+$ calcd for $C_{16}H_{12}N_2Na$ 255.0893, found 255.0887.

Supporting Information

This material is available free of charge on the ACS Publications website at http://pub.acs.org.

Optimization of reaction conditions for the synthesis of **6**, copies of ^{1}H- and ^{13}C-NMR spectra for compounds **1**, **3**, **4**, **6**, **7**, **8**, **10**, **11** (pdf).

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