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A convenient synthetic approach to 11*H*-indolo[3,2-*c*]quinoline framework via Friedlander condensation and Cadogan cyclization

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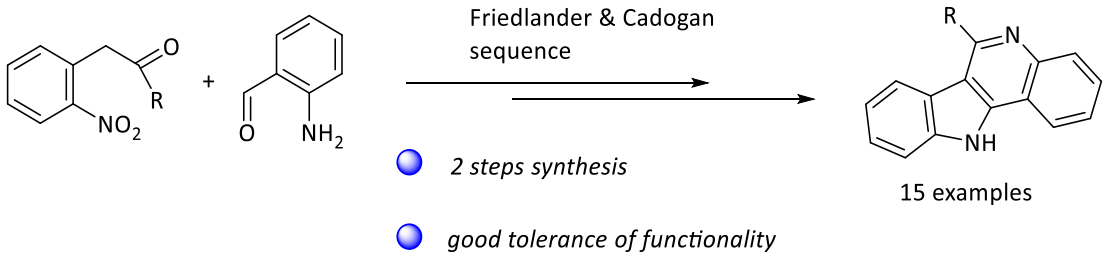
Abstract

Indolo[3,2-*c*]quinolines bearing various substituents have been prepared from o-aminobenzaldehydes and 2-nitrophenyl substituted ketones through a two-step sequence involving Friedlander condensation and Cadogan cyclization.



Keywords: Indolo[3,2-*c*]quinoline, Friedlander reaction; Cadogan synthesis; cyclization

Introduction

Natural indolo[3,2-*c*]quinolines and their synthetic analogs exhibit a wide range of physiological activities, such as antimicrobial,[1] antimalarial,[2,3] anti-tumor,[4] anti-tuberculosis[5] as well as DYRK1A kinase inhibitory properties.[6]

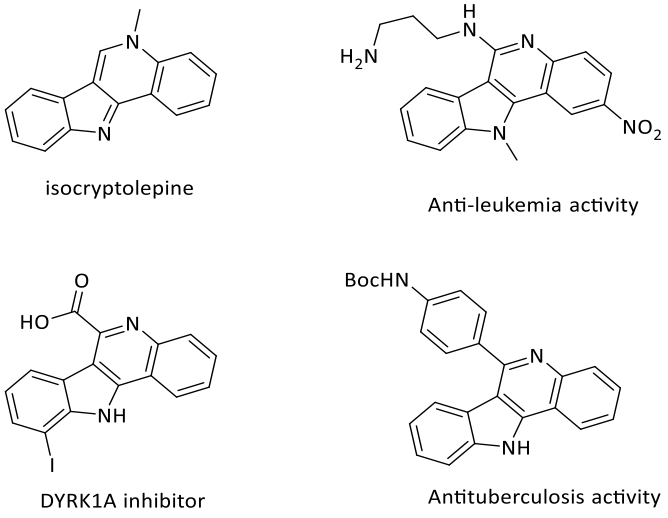
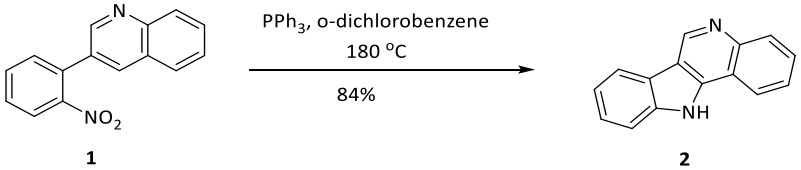


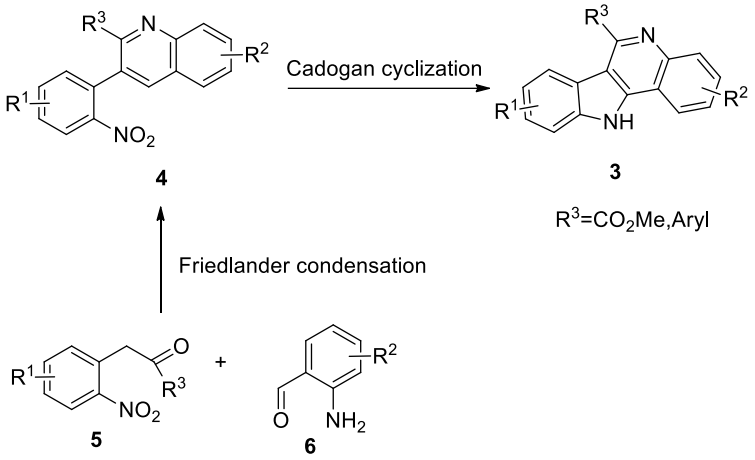
Figure 1. Naturally occurring and pharmaceutically interesting indolo[3,2-*c*]quinolines.

A number of elegant methods have been developed to construct indolo[3,2-*c*]quinolines,[7] involving Graebe-Ullmann reaction,[8,9] Fischer indolization,[10-13] Vilsmeier reaction,[14] electrocyclization,[15-17] aza-[4+2]-cycloaddition[18-19] and Pd-catalyzed coulping reactions.[20-23] While being generally effective and reliable, some of these literature methods still suffer from using extravagantly functionalized substrates, generation of halide wastes and harsh reaction conditions.

Cadogan cyclization reaction is considered as one of the best methods for the preparation of various aza-heterocycles as carbazoles, indoles, carbolines, starting from the appropriate nitro substrates and a series of tetravalent phosphorus reagents.[24] According to our knowledge, there were no reports to achieve a Cadogan-type C-N bond formation at the C4-position of quinoline to construct indolo[3,2-*c*]quinolines.[25] However, we found that quinoline **1** could be converted to **2** smoothly in a usual Cadogan condition (Scheme 1). Since medicinal derivatives bearing the indolo[3,2-*c*]quinoline framework is interesting to be prepared, we further considered that indolo[3,2-*c*]quinoline derivatives **3** with functional groups such as ester and phenyl could be produced through a Friedlander condensation[26,27]/Cadogan cyclization sequence from 2-nitrophenyl ketones **5** and 2-aminobenzaldehydes **6** (Scheme 2). Herein, we report a concise synthesis of indolo[3,2-*c*]quinoline derivatives **3a-o** which involves sequential assemblies of the quinoline and indole cores.



Scheme 1. Initial attempt synthesis of indolo[3,2-*c*]quinoline **2.**

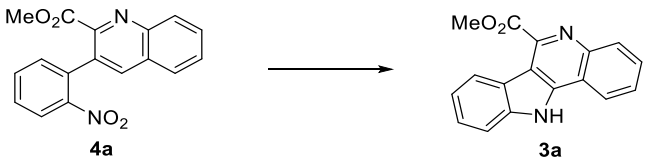


Scheme 2. Synthesis of indolo[3,2-*c*]quinoline derivatives.

Results and Discussion

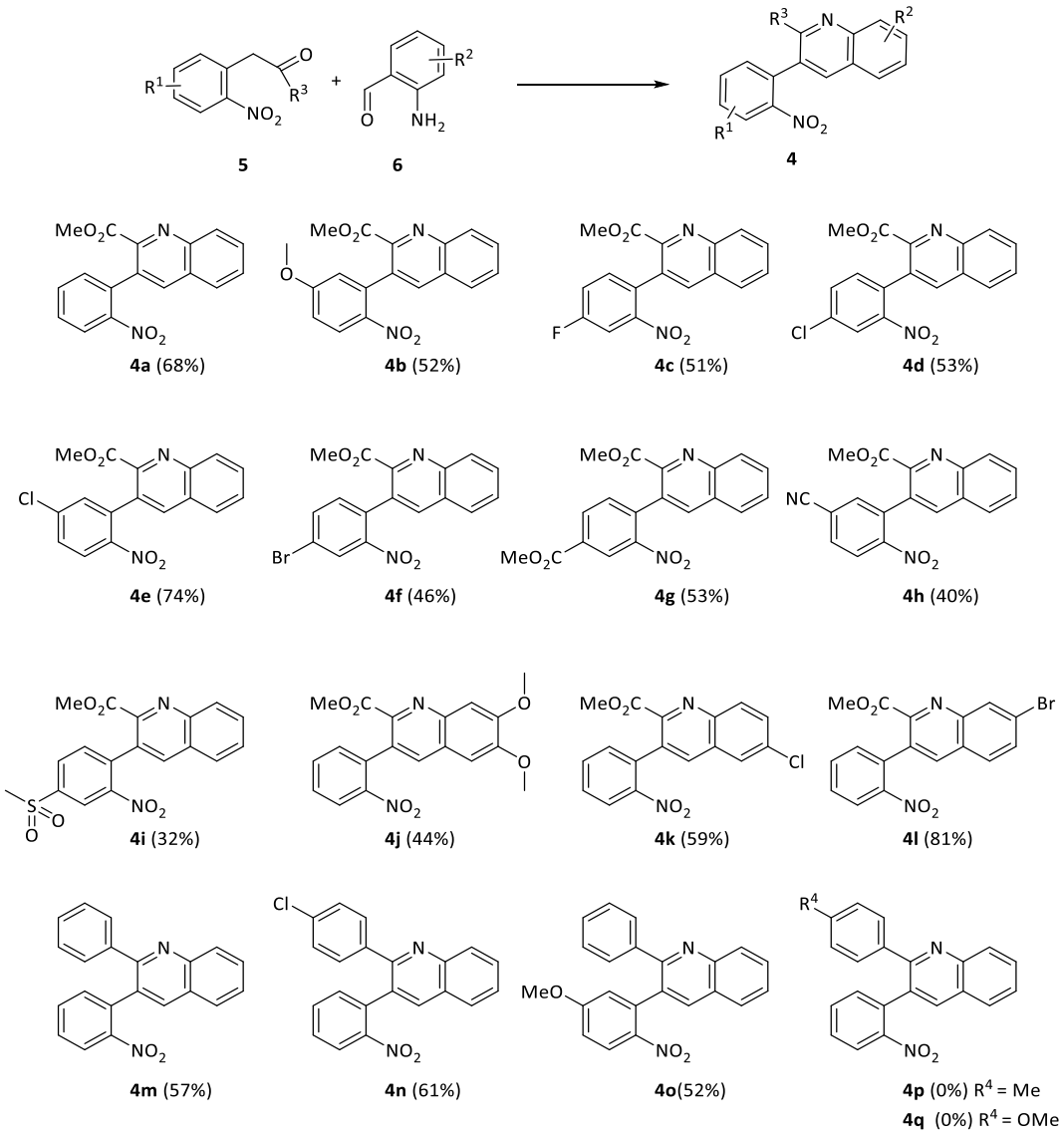
Initially, the starting 2-nitrophenyl substituted ketones **5** required for the Friedlander condensation were prepared through 1 or 2 steps from commecially available 2-nitrotoluene and dimethyl oxalate or 2-nitrobenzaldehyde according the known procedures.[28,29] The Friedlander condensation of methyl 3-(2-nitrophenyl)-2-oxopropanoates **5** with 2-aminobenzaldehyde **6** in the presence of piperidine as the catalyst was proceeded smoothly to produce quinolines **4a-l** in moderate to good yield (Scheme 3). However, these conditions were proved to be unsuitable for the syntheses of **4m-o**. Instead, when piperidine and AcOH were used as co-catalyst in toluene, compounds **4m-o** could be obtained in 52-57% yields. However, the quinolines **4p** and **4q** were yet exceptions and could not be formed under these conditions, a result that was attributed to the introduction of electron-donating groups to nitro-benzene ring of **5**.

Table 1. Optimization studies for Cadogan cyclization



Entry[a]	Condition	Yield[b]
1	1.5 eq PPh_3 in *o*-DCB, 180 °C, 24 h	69%
2	1.5 eq $P(OEt)_3$ in diglyme, 130 °C, 16 h	55%
3	1.5 eq DPPE, neat, 150 °C, 2 h	26%
4	$P(OEt)_3$, 130 °C, 16 h	74%

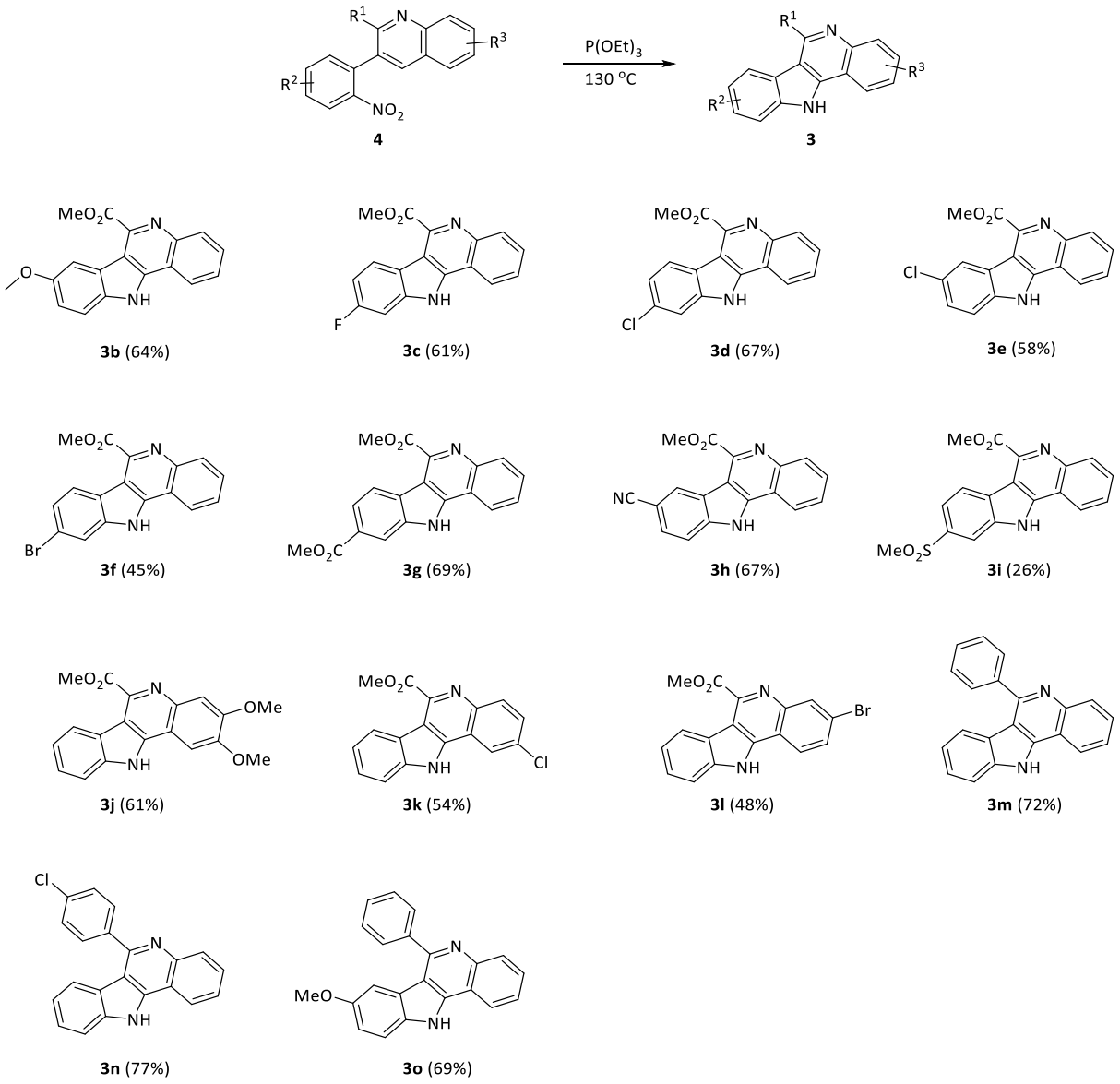
[a]Entry 1-2: compound **4a** (308 mg, 1 mmol) with the additive in 1.0 mL of solvent;
Entry 3: compound **4a** (308 mg, 1 mmol), without solvent.
Entry 4: compound **4a** (308 mg, 1 mmol) in 1.0 mL of $P(OEt)_3$.
[b]Isolated yield.



Conditions for **4a-l**: **5** (3.0 mmol), **6** (3.3 mmol) and piperidine (3.6 mmol, 0.11 mL) in 10.0 mL DMF, 40 °C
Conditions for **4m-p**: **5** (3.0 mmol), **6** (6.0 mmol) and piperidine (0.6 mmol, 57 mL) and AcOH (0.6 mmol, 36 mL) in toluene, 110 °C
(%) : isolated yield.

Scheme 3. Substrates **3** for Friedlander condensation.

The second step in the synthesis of indolo[3,2-*c*]quinolines was the reductive cyclization of nitro compounds **4**. We decided to briefly study the specific conditions for this Cadogan transformation and quinoline **4a** was chosen as standard substrate to investigate suitable reaction conditions. Triphenylphosphine, triethyl phosphite and DPPE were used as reducing agents and diglyme or o-DCB was adopted as the solvent in these screenings (Table 1). To our delight, all these conditions could promote the desired ransformation, and it was found that indolo[3,2-*c*]quinoline **3a** was formed in a highest yield (74%) at 130 °C in $P(OEt)_3$(Table 1, entry 4). The structure of cyclized derivative **3a** was confirmed by the ^1H, ^{13}C NMR spectral data and HRMS.



[a]**4** (1.0 mmol) in 1.0 mL $P(OEt)_3$, 130 °C, for 16-24 h; isolated yield.

Scheme 4. Substrate scope for Cadogan cyclization.[a]

Next, the optimized condition for the preparation of **3a** was used for the synthesis of other indolo[3,2-*c*]quinolines **3b-o** (Scheme 4). Generally, ester substrates **4b-l** bearing electron-donating group (OMe) or electron-withdrawing substituents (F, Cl, Br, CO_2Me, CN and $MeSO_2$) on the nitrobenzene or quinoline fragment did not significantly influence the efficiency, by this protocol, except **3i** which was generated in a relative low yield, other products (**3b-h**, **3j-l**) were produced in moderate to good yields (45-69%). Meanwhile, the transformation of substrates **4m-o** with phenyl groups at the C2-position of quinoline fragment proceeded smoothly to afford **3m-o** in 69-77% yields.

Conclusions

In summary, we have developed a convenient and 2-steps synthesis of indolo[3,2-*c*]quinoline structures from o-aminobenzaldehydes and specific 2-nitrophenyl substituted ketones by means of Friedlander condensation, followed by Cadogan cyclization. The method proceeded well with wide functional group tolerance, the easiness of the procedures for assembling precursors combined with the fact that the moderate to good yields could be achieved facilitated the preparation of a variety of functionalized indolo[3,2-*c*]quinoline derivatives. We envision extension of this protocol in medicinal chemistry.

Experimental Section

General. All reagents used were of analytical purity. Column chromatography was carried out on silica gel. ^{1}H NMR spectra were recorded at 600 MHz and ^{13}C NMR spectra were recorded at 150 MHz and ^{19}F NMR spectra were recorded at 565 MHz. All new products were further characterized by HRMS; copies of their ^{1}H NMR and ^{13}C NMR and ^{19}F NMR spectra are provided in the Supporting Information. Unless otherwise stated, all reagents and solvents were purchased from commercial suppliers and used without further purification.

Synthesis of compound 2. Compound **1** (250 mg, 1.0 mmol) and PPh_3 (394 mg, 1.5 mmol) were dissolved in o-DCB (3.0 mL), the solution was stirred at 180 °C under Ar for 24 h. The mixture was concentrated under reduced pressure and purified by flash column chromatography (DCM/MeOH = 100:1-50:1) to obtain compound **2** (183 mg, 84%) as a white solid.

11*H*-indolo[3,2-*c*]quinoline (2). ^{1}H NMR (600 MHz, $CDCl_3$) δ 12.79 (s, 1H), 9.60 (s, 1H), 8.52 (d, *J* 7.4 Hz, 1H), 8.32 (d,.*J*.7.6 Hz, 1H), 8.15 (d,.*J*.8.3 Hz, 1H), 7.79 - 7.65 (m, 3H), 7.50 (t,.*J*.7.4 Hz, 1H), 7.34 (t,.*J*.7.4 Hz, 1H). The NMR data is consistent with literature values.[30]

Synthesis of compounds 4a-o. For compounds **4a-l**: nitro-compound **5** (3.0 mmol), amino-compound **6** (3.3 mmol) and piperidine (330 μL, 3.6 mmol) were dissolved in DMF (10 mL). The reaction mixture was stirred at 40 °C for 6-12 h (TLC monitoring). The mixture was diluted with ethyl acetate and the organic fraction was washed with water, brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by column chromatography (PE:EA=5:1-1:1) to yield compound **4a-l**.

For compounds **4m-o**: nitro-compound **5** (3.0 mmol) and amino-compound **6** (6.0 mmol), piperidine (57 μL, 0.6 mmol) and AcOH (36 μL, 0.6 mmol) were dissolved in toluene (10 mL). The reaction mixture was stirred at 110 °C for 6-12 h (TLC monitoring). The mixture was concentrated under reduced pressure, and diluted with ethyl acetate and the organic fraction was washed with water, brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (PE:DCM=1:2-1:1) to yield compounds **4m-o**.

Methyl 3-(2-nitrophenyl)quinoline-2-carboxylate (4a). 666 mg, yield 68%, yellow solid. mp 112.8-113.3 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 (d,.*J*.8.53 Hz, 1H), 8.22 (dd,.*J*.8.30, 0.90 Hz, 1H), 8.09 (s, 1H), 7.80 - 7.90 (m, 2H), 7.67 - 7.76 (m, 2H), 7.58 - 7.65 (m, 1H), 7.40 (dd, *J* 7.40, 1.12 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.4, 147.4, 146.2, 146.1, 137.1, 134.7, 133.0, 132.1, 131.7, 130.4, 130.1, 128.9, 128.7, 128.1, 127.2, 124.3, 76.8, 76.6, 52.9. HRMS (ESI) *m/z* calcd for $C_{17}H_{12}O_4N_2Na[M+Na]^+$: 331.0689, found: 331.0687 .

Methyl 3-(5-methoxy-2-nitrophenyl)quinoline-2-carboxylate (4b). 528 mg, yield 52%, yellow solid. mp 177.2-178.6 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.33 (d,.*J*.8.5 Hz, 1H), 8.27 (d,.*J*.9.2 Hz, 1H), 8.06 (s, 1H), 7.90 - 7.79 (m, 2H), 7.68 (s, 1H), 7.03 (dd,.*J*.2.7, 9.2 Hz, 1H), 6.82 (d,.*J*.2.9 Hz, 1H), 3.91 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (150 MHz,

$CDCl_3$) δ 165.6, 163.1, 146.3, 146.3, 140.7, 137.8, 136.9, 132.8, 130.6, 130.3, 129.0, 128.3, 127.4, 127.2, 117.1, 113.2, 56.0, 53.1. HRMS (ESI) *m/z* calcd for $C_{18}H_{14}O_5N_2Na[M+Na]^+$: 361.0795, found: 361.0791 .

Methyl 3-(4-fluoro-2-nitrophenyl)quinoline-2-carboxylate (4c). 499 mg, yield 51%, yellow solid. mp 142.0-143.1 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 (d,.*J*.8.5 Hz, 1H), 8.07 (s, 1 H), 7.96 (dd,.*J*.2.7, 8.3 Hz, 1H), 7.91 - 7.82 (m, 2H), 7.76 - 7.66 (m, 1H), 7.45 (dd,.*J*.2.6, 7.5 Hz, 1H), 7.42 - 7.35 (m, 1H), 3.88 (s, 3H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.8, 161.9 (d, J_{C-F} = 251.8 Hz), 148.4 (d, J_{C-F} = 8.7 Hz), 146.7, 146.3, 137.8, 133.5 (d, J_{C-F} = 7.4 Hz), 131.6, 131.2 (d, J_{C-F} = 5.0 Hz), 131.0, 130.5, 129.5, 128.5, 127.6, 120.8 (d, J_{C-F} = 21.09 Hz), 112.5(d, J_{C-F} = 27.3 Hz), 53.4; ^{19}F NMR (565 MHz, $CDCl_3$) δ -109.83. HRMS (ESI) *m/z* calcd for $C_{17}H_{11}O_4N_2FNa[M+Na]^+$: 349.0595, found: 349.0592 .

Methyl 3-(4-chloro-2-nitrophenyl)quinoline-2-carboxylate (4d). 545 mg, yield 53%, yellow solid. mp 180.3-181.4 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 (d,.*J*.8.5 Hz, 1H), 8.22 (d,.*J*.2.0 Hz, 1H), 8.06 (s, 1H), 7.91 - 7.81 (m, 2H), 7.75 - 7.65 (m, 2H), 7.35 (d,.*J*.8.1 Hz, 1 H), 3.89 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.4, 147.7, 146.3, 145.7, 137.2, 134.5, 133.3, 133.1, 132.7, 131.1, 130.7, 130.1, 129.1, 128.0, 127.2, 124.5, 53.0. HRMS (ESI) *m/z* calcd for $C_{17}H_{11}O_4N_2ClNa[M+Na]^+$: 365.0300, found: 365.0299.

Methyl 3-(5-chloro-2-nitrophenyl)quinoline-2-carboxylate (4e). 759 mg, yield 74%, yellow solid. mp 158.7-159.4 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.34 (d,.*J*.8.5 Hz, 1H), 8.19 (d,.*J*.9.0 Hz, 1H), 8.08 (s, 1H), 7.90 - 7.82 (m, 2H), 7.74 - 7.67 (m, 1H), 7.56 (dd,.*J*.2.2, 9.0 Hz, 1H), 7.40 (d,.*J*.2.0 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.5, 146.4, 145.9, 145.7, 139.6, 137.3, 136.9, 131.7, 131.3, 130.9, 130.3, 129.3, 128.9, 128.1, 127.4, 125.9, 53.2. HRMS (ESI) *m/z* calcd for $C_{17}H_{11}O_4N_2ClNa[M+Na]^+$: 365.0300, found: 365.0294.

Methyl 3-(4-bromo-2-nitrophenyl)quinoline-2-carboxylate (4f). 534 mg, yield 46%, yellow solid. mp 184.6-185.3 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.37 (d,.*J*.2.0 Hz, 1H), 8.34 (d,.*J*.8.5 Hz, 1H), 8.06 (s, 1H), 7.90 - 7.83 (m, 3H), 7.75 - 7.69(m, 1H), 7.28 (d,.*J*.8.3 Hz, 1 H), 3.89 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.4, 147.8, 146.3, 145.6, 137.1, 136.0, 133.7, 132.9, 131.2, 130.7, 130.1, 129.1, 128.0, 127.4, 127.2, 122.0, 53.0. HRMS (ESI) *m/z* calcd for $C_{17}H_{12}O_4N_2Br[M+H]^+$: 386.9975, found: 386.9968.

Methyl 3-(4-(methoxycarbonyl)-2-nitrophenyl)quinoline-2-carboxylate (4g). 582 mg, yield 53%, yellow solid. mp 180.0-181.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.85 (s, 1 H), 8.39 - 8.32 (m, 2H), 8.09 (s, 1 H), 7.90 - 7.82 (m, 2H), 7.74 - 7.68 (m, 1 H), 7.50 (d,.*J* 7.9 Hz, 1 H), 4.02 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.3, 164.5, 147.4, 146.3, 145.4, 139.1, 136.9, 133.6, 132.0, 131.4, 130.9, 130.7, 130.1, 129.2, 127.9, 127.3, 125.4, 53.0, 52.6. HRMS (ESI) *m/z* calcd for $C_{19}H_{14}O_6N_2Na[M+Na]^+$: 389.0744, found: 389.0741 .

Methyl 3-(5-cyano-2-nitrophenyl)quinoline-2-carboxylate (4h). 400 mg, yield 40%, yellow solid. mp 209.0-210.3 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.35 (d,.J.8.5 Hz, 1H), 8.29 (d,.J.8.5 Hz, 1H), 8.10 (s, 1H), 7.93 - 7.86 (m, 3H), 7.77 - 7.70 (m, 2H), 3.90 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.5, 149.7, 146.7, 145.2, 137.6, 136.4, 135.4, 132.5, 131.3, 130.4, 130.1, 129.7, 128.1, 127.5, 125.2, 117.0, 116.5, 53.3. HRMS (ESI) *m/z* calcd for $C_{18}H_{11}O_4N_3Na[M+Na]^+$: 356.0642, found: 356.0634.

Methyl 3-(4-(methylsulfonyl)-2-nitrophenyl)quinoline-2-carboxylate (4i). 371 mg, yield 32%, yellow solid. mp 176.8-177.6 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.76 (d,.*J*.1.8 Hz, 1H), 8.35 (d,.J.8.5 Hz, 1H), 8.27 (dd,.*J*.1.8, 7.9 Hz, 1H), 8.08 (s, 1H), 7.94 - 7.85 (m, 2H), 7.78 - 7.70 (m, 1H), 7.64 (d,.*J*.8.1 Hz, 1H), 3.90 (s, 3H), 3.22 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.6, 147.8, 146.6, 145.1, 141.4, 140.6, 137.4, 133.2, 131.5, 131.3, 130.9, 130.4, 129.7, 128.0, 127.5, 123.9, 53.3, 44.4. HRMS (ESI) *m/z* calcd for $C_{18}H_{15}O_6N_2S[M+H]^+$: 387.0645, found: 387.0638.

Methyl 6,7-dimethoxy-3-(2-nitrophenyl)quinoline-2-carboxylate (4j). 486 mg, yield 44%, yellow solid. mp 205.8-206.6 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.21 - 8.16 (m, 2H), 7.83 (t,.*J*.7.4 Hz, 1H), 7.71 (t,.*J*.7.4 Hz, 1H), 7.56 (s, 1H), 7.53 (d,.*J*.7.2 Hz, 1H), 7.45 (s, 1H), 3.99 (s, 3H), 3.94 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 166.1, 153.8, 152.0, 148.2, 143.7, 143.4, 136.0, 134.9, 134.2, 132.7, 130.2, 129.6, 124.7, 124.7,

108.1, 105.6, 56.5, 56.4, 52.6. HRMS (ESI) *m/z* calcd for $C_{19}H_{16}O_6N_2Na[M+Na]^+$: 391.0901, found: 391.0893.

Methyl 6-chloro-3-(2-nitrophenyl)quinoline-2-carboxylate (4k). 607 mg, yield 59%, yellow solid. mp 181.8-183.0 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.27 (d,*J*.9.2 Hz, 1H), 8.24 (dd,*J*.1.1, 8.3 Hz, 1H), 8.00 (s, 1H), 7.85 (d,*J*.2.2 Hz, 1H), 7.77 (dd,*J*.2.4, 9.1 Hz, 1H), 7.75 - 7.71(m, 1H), 7.66 - 7.60 (m, 1H), 7.38 (dd,*J*.1.3, 7.6 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.4, 147.6, 146.5, 144.7, 136.3, 135.1, 134.5, 133.4, 133.4, 131.9, 131.8, 131.7, 129.2, 128.9, 126.1, 124.6, 53.2. HRMS (ESI) *m/z* calcd for $C_{17}H_{11}O_4N_2ClNa[M+Na]^+$: 365.0300, found: 365.0297.

Methyl 7-bromo-3-(2-nitrophenyl)quinoline-2-carboxylate (4l). 927 mg, yield 81%, yellow solid. mp 143.8-146.4 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.23 (d,*J*.8.1 Hz, 1H), 8.06 (s, 1H), 7.80 - 7.68 (m, 3H), 7.63 (t,*J*.7.9 Hz, 1 H), 7.39 (d,*J*.7.6 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.4, 147.6, 147.3, 146.9, 137.2, 134.5, 133.4, 132.7, 132.6, 132.5, 131.8, 129.1, 128.6, 126.9, 124.9, 124.6, 53.2. HRMS (ESI) *m/z* calcd for $C_{17}H_{12}O_4N_2Br[M+H]^+$: 386.9975, found: 386.9967.

3-(2-Nitrophenyl)-2-phenylquinoline (4m). 555 mg, yield 57%, white solid. mp 173.1-174.0 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.41 (s, 1H), 8.11 (d,*J*.8.3 Hz, 1H), 8.07 (d,*J*.7.6 Hz, 1H), 7.98 - 7.93 (m, 1H), 7.86 - 7.82 (m, 1H), 7.82 - 7.78 (m, 1H), 7.70 - 7.60 (m, 3H), 7.32 - 7.21 (m, 5H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 157.1, 148.1, 146.9, 139.2, 136.8, 134.5, 134.0, 133.4, 130.9, 130.5, 129.5, 129.4, 128.9, 128.4, 128.0, 128.0, 127.2, 126.6, 124.6. HRMS (ESI) *m/z* calcd for $C_{21}H_{15}O_2N_2[M+H]^+$: 327.1128, found: 327.1126.

2-(4-Chlorophenyl)-3-(2-nitrophenyl)quinoline (4n). 664 mg, yield 61%, white solid. mp 147.0-147.4 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.21 (d,.J.8.5 Hz, 1 H), 8.10 (s, 1 H), 7.95 (d,.J.8.1 Hz, 1 H), 7.87 (d,.J.8.1 Hz, 1 H), 7.80 (t,*J*.7.7 Hz, 1 H), 7.67 - 7.59 (m, 2 H), 7.55 - 7.50 (m, 1 H), 7.41 (d,*J*.7.4 Hz, 1 H), 7.35 (d,*J*.8.3 Hz, 2 H), 7.23 (d,*J*.8.3 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.4, 148.6, 147.5, 137.9, 136.5, 134.9, 134.6, 133.1, 133.0, 130.9, 130.8, 130.3, 129.5, 128.9, 128.3, 127.5, 127.2, 126.8, 124.7. HRMS (ESI) *m/z* calcd for $C_{21}H_{14}O_2N_2Cl[M+H]^+$: 361.0738, found: 361.0735.

3-(5-Methoxy-2-nitrophenyl)-2-phenylquinoline (4o). 550 mg, yield 52%, white solid. mp 174.5-174.8 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.25 (d,*J*.8.5 Hz, 1H), 8.12 (s, 1H), 7.97 (d,*J*.8.5 Hz, 1H), 7.88 (d,*J*.8.1 Hz, 1H), 7.79 (t,*J*.7.6 Hz, 1H), 7.63 - 7.58 (m, 1H), 7.40 (d,*J*.7.9 Hz, 2H), 7.33 - 7.24 (m, 3H), 6.97 - 6.87 (m, 2H), 3.88 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.7, 162.7, 157.4, 147.2, 141.4, 139.2, 137.8, 135.7, 131.5, 129.8, 129.3, 129.2, 129.1, 128.1, 127.8, 127.2, 127.1, 126.7, 126.5, 117.8, 113.2, 55.8. HRMS (ESI) *m/z* calcd for $C_{22}H_{17}O_3N_2[M+H]^+$: 357.1234, found: 357.1231.

Synthesis of compounds 3a-o. Compound **4a-o** (1.0 mmol) was dissolved in $P(OEt)_3$ (1.0 mL), the solution was stirred at 130 °C under Ar for 16-24 h. The mixture was concentrated under reduced pressure, and purified by flash column chromatography (PE/EA = 4:1-1:1) to obtain the compounds **3a-o**.

Methyl 11*H*-indolo[3,2-*c*]quinoline-6-carboxylate (3a). 205 mg, yield 74%, white solid. mp 201.1-201.9 °C. ^{1}H NMR (600 MHz, $CDCl_3$+three drops of CD_3OD) δ 13.07 (s, 1H), 8.61 (d,*J*.7.6 Hz, 1H), 8.42 (d,*J*.8.1 Hz, 1H), 8.22 (d,*J*.7.6 Hz, 2H), 7.86 - 7.79 (m, 1H), 7.76 (d,*J*.8.1 Hz, 1H), 7.55 (t,*J*.7.5 Hz, 1H), 7.36 (t,*J*.7.5 Hz, 1 H), 4.11 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$+three drops of CD_3OD) δ 167.2, 144.3, 143.8, 141.7, 139.3, 129.9, 129.1, 127.5, 126.3, 123.0, 122.1, 120.9, 120.5, 117.4, 112.0, 111.8, 52.8. HRMS (ESI) *m/z* calcd for $C_{17}H_{13}O_2N_2[M+H]^+$: 277.0972, found: 277.0968.

Methyl 8-methoxy-11*H*-indolo[3,2-*c*]quinoline-6-carboxylate (3b). 196 mg, yield 64%, white solid. mp 222.0-223.7 °C. ^{1}H NMR (600 MHz, $CDCl_3$+three drops of CD_3OD) δ 8.29 (d,*J*.8.1 Hz, 1H), 8.19 (d,*J*.8.5 Hz, 1H), 8.03 (s, 1H), 7.74 - 7.66 (m, 1H), 7.65 - 7.57 (m, 1H), 7.48 (d,*J*.8.8 Hz, 1H), 7.09 (d,*J*.8.8 Hz, 1H), 4.15 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$+three drops of CD_3OD) δ 166.7, 154.1, 143.2, 143.0, 142.2, 134.1, 128.5, 128.1, 126.5, 121.0, 120.8, 117.2, 115.2, 112.3, 111.3, 105.5, 54.8, 52.0. HRMS (ESI) *m/z* calcd for $C_{18}H_{15}O_3N_2[M+H]^+$: 307.1077, found: 307.1076.

Methyl 9-fluoro-11*H*-indolo[3,2-*c*]quinoline-6-carboxylate (3c). 180 mg, yield 61%, white solid. mp 223.1-224.0 °C. ^{1}H NMR (600 MHz, $CDCl_3$+three drops of CD_3OD) δ 8.41 (dd,.*J*.5.5, 8.4 Hz, 1H), 8.17 (dd,.*J*.8.1, 18.2 Hz, 2H), 7.66 (t,.J.7.3 Hz, 1H), 7.61 - 7.55 (m, 1H), 7.17 (d,.*J*.8.5 Hz, 1H), 7.03 - 6.87 (m, 1H), 4.11 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$+three drops of CD_3OD) δ 166.9, 161.9 (d, J_{C-F} = 243.2 Hz), 143.4, 142.9, 140.4 (d, J_{C-F} = 12.4 Hz), 129.0, 128.7, 127.3, 125.2 (d, J_{C-F} = 9.9 Hz), 121.2, 117.5 (d, J_{C-F} = 22.3 Hz), 112.7, 108.9 (d, J_{C-F} = 24.8 Hz), 97.6 (d, J_{C-F} = 26.1 Hz), 52.4; ^{19}FNMR (565 MHz, $CDCl_3$+three drops of CD_3OD) -111.70. HRMS (ESI) *m/z* calcd for $C_{17}H_{12}O_2N_2F[M+H]^+$: 295.0877, found: 295.0876.

Methyl 9-chloro-11*H*-indolo[3,2-*c*]quinoline-6-carboxylate (3d). 208 mg, yield 67%, white solid. mp 229.2-230.7 °C. ^{1}H NMR (600 MHz, $CDCl_3$+three drops of CD_3OD) δ 8.52 - 8.42 (m, 1H), 8.16 (d,.*J*.6.7 Hz, 2H), 7.63 - 7.56 (m, 1H), 7.52 (dd,.*J*.7.0, 7.9 Hz, 1H), 7.42 - 7.36 (m, 1H), 7.31 (dd,.*J*.2.0, 8.5 Hz, 1H), 4.11 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$+three drops of CD_3OD) δ 166.8, 143.7, 143.4, 142.8, 137.8, 129.5, 128.9, 127.3, 126.4, 126.2, 123.5, 122.1, 121.2, 117.4, 112.3, 112.1, 52.9. HRMS (ESI) *m/z* calcd for $C_{17}H_{12}O_2N_2Cl[M+H]^+$: 311.0582, found: 311.0581.

Methyl 8-chloro-11*H*-indolo[3,2-*c*]quinoline-6-carboxylate (3e). 180 mg, yield 58%, white solid. mp 227.1-228.3 ℃. ^{1}H NMR (600 MHz, $CDCl_3$+three drops of CD_3OD) δ 8.14 (d,.*J*.8.5 Hz, 1H), 7.94 (dd,.*J*.8.3, 15.0 Hz, 2H), 7.45 - 7.38 (m, 1H), 7.36 - 7.30 (m, 1H), 7.23 (d,.*J*.1.8 Hz, 1H), 6.92 (dd,.*J*.1.9, 8.6 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$+three drops of CD_3OD) δ 166.2, 143.0, 142.6, 142.2, 139.5, 131.1, 128.5, 128.3, 126.7, 124.2, 120.6, 120.6, 119.0, 116.8, 111.9, 110.5, 52.0. HRMS (ESI) *m/z* calcd for $C_{17}H_{12}O_2N_2Cl[M+H]^+$: 311.0582, found: 311.0580.

Methyl 9-bromo-11*H*-indolo[3,2-*c*]quinoline-6-carboxylate (3f). 160 mg, yield 45%, white solid. mp 223.8-225.5 °C. ^{1}H NMR (600 MHz, $CDCl_3$+three drops of CD_3OD) δ 8.37 (d,.*J*.8.5 Hz, 1H), 8.22 - 8.03 (m, 2H), 7.67 - 7.54 (m, 2H), 7.51 (d,.*J*.7.0 Hz, 1H), 7.36 - 7.19 (m, 1H), 4.08 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$+three drops of CD_3OD) δ 166.9, 143.7, 143.3, 142.6, 140.3, 129.4, 128.9, 127.3, 125.2, 124.0, 121.1, 120.0, 119.6, 117.4, 114.1, 112.6, 52.8. HRMS (ESI) *m/z* calcd for $C_{17}H_{12}O_2N_2Br[M+H]^+$: 355.0077, found: 355.0075.

Dimethyl 11*H*-indolo[3,2-*c*]quinoline-6,9-dicarboxylate (3g). 230 mg, yield 69%, white solid. mp 243.3-244.0 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.16 (br. s., 1H), 8.50 (d,.*J*.7.9 Hz, 1H), 8.43 (d,.*J*.8.3 Hz, 1H), 8.22 - 8.15 (m, 2H), 7.87 - 7.74 (m, 3H), 4.08 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 166.8, 166.6, 144.4, 144.0, 143.2, 138.6, 130.0, 129.7, 127.8, 126.7, 124.2, 123.2, 122.3, 121.1, 117.2, 113.0, 111.4, 52.8, 52.3. HRMS (ESI) *m/z* calcd for $C_{19}H_{15}O_4N_2[M+Na]^+$: 335.1026, found: 335.1024 .

Methyl 8-cyano-11*H*-indolo[3,2-*c*]quinoline-6-carboxylate (3h). 202 mg, yield 67%, white solid. mp 240.2-240.5 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.38 (br. s., 1H), 8.83 (s, 1H), 8.49 (d,.*J*.7.9 Hz, 1H), 8.18 (d,.*J*.8.1 Hz, 1H), 7.87 - 7.72 (m, 4H), 4.08 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 166.6, 144.0, 143.4, 142.9, 141.2, 130.0, 129.8, 128.9, 128.8, 128.1, 122.1, 120.6, 120.3, 117.2, 113.1, 111.6, 102.8, 52.9. HRMS (ESI) *m/z* calcd for $C_{18}H_{12}O_2N_3[M+Na]^+$: 302.0924, found: 302.0922.

Methyl 9-(methylsulfonyl)-11*H*-indolo[3,2-*c*]quinoline-6-carboxylate (3i). 92 mg, yield 26%, white solid. mp 238.2-239.8 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.49 (s, 1H), 8.65 (d,.*J*.8.5 Hz, 1H), 8.58 (d,.*J*.7.9 Hz, 1H), 8.27 - 8.19 (m, 2H), 7.93 - 7.82 (m, 3H), 4.11 (s, 3H), 3.32 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 166.8, 144.6, 144.1, 143.7, 138.3, 137.8, 130.1, 130.1, 128.2, 124.2, 124.2, 122.4, 118.9, 117.3, 111.2, 111.1, 53.0, 44.2. HRMS (ESI) *m/z* calcd for $C_{18}H_{15}O_4N_2S[M+Na]^+$: 355.0747, found: 355.0743.

Methyl 2,3-dimethoxy-11*H*-indolo[3,2-*c*]quinoline-6-carboxylate (3j). 205 mg, yield 61%, white solid. mp 135.2-137.0 °C. 1H NMR (600 MHz, DMSO-d_6) δ 12.69 (s, 1H), 8.48 (d,.*J*.7.9 Hz, 1H), 7.98 (s, 1H), 7.71 (d,.*J*.8.1 Hz, 1H), 7.60 (s, 1H), 7.54 - 7.44 (m, 1H), 7.35 - 7.25 (m, 1H), 4.06 (s, 3H), 4.02 (s, 3H), 3.96 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 167.4, 151.6, 150.3, 141.5, 141.4, 140.3, 139.4, 126.1, 123.4, 120.8, 120.5, 112.1, 111.7, 111.6, 109.2, 100.9, 56.0, 55.9, 52.5. HRMS (ESI) *m/z* calcd for $C_{19}H_{17}O_4N_2[M+H]^+$: 337.1183, found: 337.1180 .

Methyl 2-chloro-11*H*-indolo[3,2-*c*]quinoline-6-carboxylate (3k). 168 mg, yield 54%, white solid. mp 232.0-234.2 °C. ^{1}H NMR (600 MHz, $CDCl_3$+three drops of CD_3OD) δ 8.55 - 8.45 (m, 1H), 8.21 - 8.10 (m, 1H), 8.05 (dd,*J*.3.8, 9.0 Hz, 1H), 7.51 (d,*J*.8.1 Hz, 1H), 7.42 (s, 2H), 7.31 - 7.25 (m, 1H), 4.13 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$+three drops of CD_3OD) δ 167.0, 143.8, 141.8, 141.3, 139.6, 132.8, 131.0, 129.3, 126.5, 123.9, 121.2, 120.9, 120.5, 118.1, 113.5, 111.4, 53.0. HRMS (ESI) *m/z* calcd for $C_{17}H_{12}O_2N_2Cl[M+H]^+$: 311.0582, found: 311.0580.

Methyl 3-bromo-11*H*-indolo[3,2-*c*]quinoline-6-carboxylate (3l). 171 mg, yield 48%, white solid. mp 203.5-213.3 °C. ^{1}H NMR (600 MHz, $CDCl_3$+three drops of CD_3OD) δ 8.42 (dd,*J*.3.8, 8.1 Hz, 1H), 8.32 (d,*J*.2.7 Hz, 1H), 8.02 (dd,*J*.4.6, 8.6 Hz, 1H), 7.58 - 7.53 (m, 1H), 7.50 (dd,*J*.4.0, 7.9 Hz, 1H), 7.45 - 7.37 (m, 1H), 7.30 - 7.22 (m, 1H), 4.12 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$+three drops of CD_3OD) δ 166.9, 144.4, 144.2, 141.9, 139.5, 131.6, 130.1, 126.3, 123.6, 122.6, 122.4, 121.1, 120.8, 116.0, 113.2, 111.3, 52.9. HRMS (ESI) *m/z* calcd for $C_{17}H_{12}O_2N_2Br[M+H]^+$: 355.0077, found: 355.0075.

6-Phenyl-11*H*-indolo[3,2-*c*]quinoline (3m). 212 mg, yield 72%, white solid. mp 238.1-240.1 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.93 (s, 1H), 8.58 (d,*J*.7.9 Hz, 1H), 8.14 (d,*J*.8.3 Hz, 1H), 7.83 (d,*J*.6.7 Hz, 2H), 7.80 - 7.67 (m, 3H), 7.67 - 7.58 (m, 3H), 7.50 (d,*J*.8.1 Hz, 1H), 7.44 (t,*J*.7.5 Hz, 1H), 7.13 (t,*J*.7.6 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 155.6, 145.0, 141.1, 140.8, 139.1, 129.4, 129.0, 128.9, 128.6, 128.5, 125.7, 125.5, 122.0, 121.7, 121.1, 120.3, 116.3, 112.0. HRMS (ESI) *m/z* calcd for $C_{21}H_{15}N_2[M+H]^+$: 295.1230, found: 295.1228.

6-(4-Chlorophenyl)-11*H*-indolo[3,2-*c*]quinoline (3n). 253 mg, yield 77%, white solid. mp 312.3-313.8 °C. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.94 (s, 1H), 8.60 - 8.55 (m, 1H), 8.13 (d,J.7.9 Hz, 1H), 7.89 - 7.84 (m, 2H), 7.80 - 7.67 (m, 5H), 7.53 (d,*J*.8.1 Hz, 1H), 7.49 - 7.43 (m, 1H), 7.17 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 154.2, 144.9, 141.1, 139.5, 139.1, 133.7, 130.8, 129.4, 128.6, 128.6, 125.9, 125.5, 122.0, 121.5, 121.0, 120.5, 116.3, 112.1, 111.8. HRMS (ESI) *m/z* calcd for $C_{21}H_{14}N_2Cl[M+ H]^+$: 329.0840, found: 329.0839.

8-Methoxy-6-phenyl-11*H*-indolo[3,2-*c*]quinoline (3o). 224 mg, yield 69%, white solid. mp 264.1-266.7 °C. ^{1}H NMR (600 MHz, $CDCl_3$+three drops of CD_3OD) δ 8.18 (dd,*J*.8.2, 13.6 Hz, 2H), 7.86 - 7.76 (m, 2H), 7.62 - 7.49 (m, 3H), 7.42 (t,*J*.8.0 Hz, 2H), 6.98 (dd,*J*.2.5, 8.8 Hz, 1H), 6.87 (d,*J*.2.2 Hz, 1H), 3.60 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$+three drops of CD_3OD) δ 156.0, 153.8, 144.4, 141.5, 139.9, 133.8, 128.7, 128.6, 128.2, 128.0, 125.0, 122.7, 120.9, 116.3, 114.4, 112.6, 111.8, 103.8, 55.2. HRMS (ESI) *m/z* calcd for $C_{22}H_{17}N_2[M+H]^+$: 325.1335, found: 325.1331.

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Supplementary Material

Copies of ^{1}H and ^{13}C NMR spectra of compounds **2**, **4a-o** and **3a-o** are given in the Supplementary Material file associated with this manuscript.

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