A Concise One-Pot Approach to the Synthesis of 4-(1*H*-Indol-3-yl)quinolines

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Abstract: An operationally simple procedure, involving conjugate addition of NaI to β-(2-aminophenyl)-α,β-ynones/cyclization/Pd-catalyzed reaction with 2-alkynyl-trifluoroacetanilides, afforded 4-(1*H*-indol-3-yl)quinolines. The whole process was carried out in the same flask, without any intermediate work-up and using ethanol as solvent.

Key words: annulation, palladium, quinolines, indoles, heterocycles, one-pot reaction

The quinoline nucleus[1] is present in many biologically active compounds as well as in naturally occurring products. Quinoline-containing molecules are widely studied as antimalarial drugs[2] and new quinoline derivatives are currently being investigated for their pharmacological properties.[3] Such compounds are active, for example, as antidepressants,[4] NK3 receptor antagonists,[5] antifungals,[6] antimicrobials,[7] antioxidants,[8] kinase inhibitors,[9] and liver X receptor agonists.[10] In particular, quinolines bearing an indolyl substituent, namely 4-(1*H*-indol-3-yl)quinolines **4**, show potent and selective pharmacological activity as antagonists of D_2 prostaglandin receptor CRTh2, and are thus potentially useful in treatments of asthma and other allergic disorders.[11]

Compounds **4** are generally obtained by reaction of 3-unsubstituted indoles with 4-chloroquinolines at 100–140 °C.[11] A related reaction between indole and 4-chloro-2,8-bis(trifluoromethyl)quinoline in the presence of $AlCl_3$ has been reported more recently.[12] Moreover, Pd-catalyzed coupling of 1-tosyl-3-tributylstannyl-indole with 2,8-bis(trifluoromethyl)quinolin-4-yl triflate[13] and 3-indolylboronic acid with 4-bromo-6-methoxyquinoline were also described.[14]

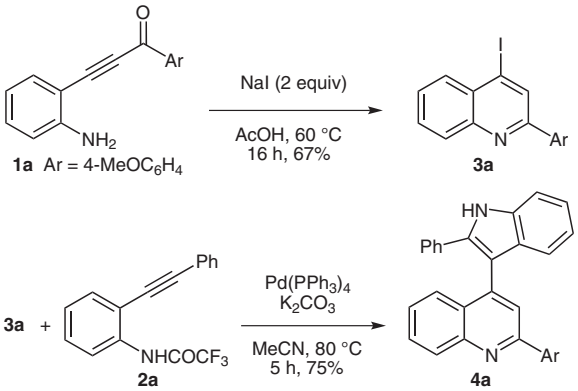
All these procedures rely on the coupling of a suitable indole with a functionalized quinoline ring; direct assembly of **4** from acyclic precursors has not been accomplished. Therefore, it seemed desirable to develop a general and effective route to heterocycles **4** starting from alkynes **1** and **2**.

We have previously investigated the use of β-(2-aminophenyl)-α,β-ynones **1** in a variety of sequential addition/annulation reactions leading to quinolines and fused polycyclic quinolines.[15]

On the other hand, Pd-catalyzed reaction of 2-alkynyltrifluoroacetanilides **2** with organic electrophiles constitutes an efficient tool for the synthesis of 3-substituted indoles through an aminopalladation/reductive elimination sequence. This procedure allows the use of a wide range of organic electrophiles, such as aryl/heteroaryl,[16] alkyl[17] and alkynyl halides,[18] arenediazonium tetrafluoroborates,[19] α-iodoenones,[20] aryl[16b] or vinyl[16c] triflates and allyl esters.[21]

Our aim was therefore to explore a combination of these two methodologies, leading to quinolines and indoles respectively, and to develop a new, one-pot approach to 4-(1*H*-indol-3-yl)quinolines **4**. Herein, we report the results of this investigation.

We previously reported that the conjugate addition of NaI to **1** in acetic acid as solvent, followed by cyclization/dehydration in situ, affords 4-iodoquinolines **3** that (after an extractive work-up of the reaction mixture) can be used in subsequent Pd-catalyzed functionalization reactions (Scheme 1).[15f] However, the use of **3** as an organic electrophile in an aminopalladation/reductive elimination process leading to indoles has not been investigated.



Scheme 1

We started our study by reacting iodoquinoline **3a** (obtained by the methodology mentioned above) with 2-phenylethynyltrifluoroacetanilide **2a** in the presence of K_2CO_3 and $[Pd(PPh_3)_4]$; 4-(1*H*-indol-3-yl)quinoline derivative **4a** was isolated in satisfactory yield in this experiment (Scheme 1). With this result in hand, we tried to

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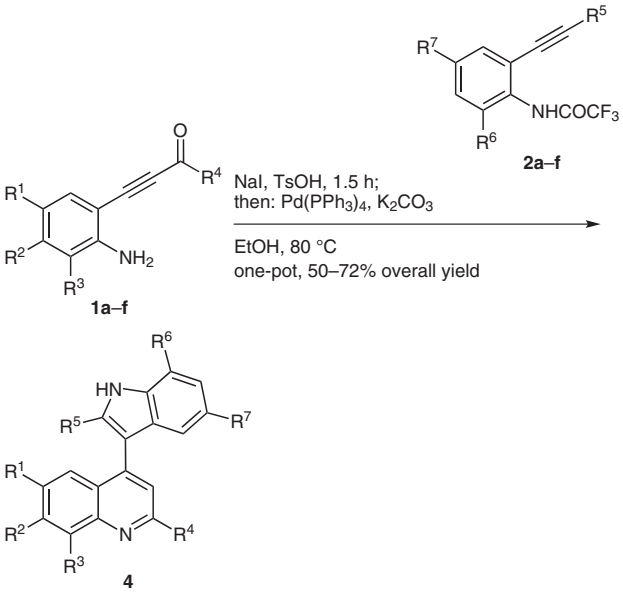
develop a more convenient one-pot procedure for the synthesis of target derivatives **4**. According to our previous results, the conjugate addition reaction of an iodide anion to α,β-ynones **1** occurs under acidic conditions (no reaction was observed by reacting **1a** with NaI in neat MeCN or EtOH at 80 °C), whereas the subsequent Pd-catalyzed process requires a basic reaction medium, i.e., the presence of a carbonate base was required to generate an anionic nitrogen nucleophile.[22]

Taking into account this difference, we attempted to carry out a two-step, one-pot protocol by adding **2a**, the base, and the catalyst to the reaction mixture just after the conversion of **1a** into **3a**. This approach clearly requires a reduction in the amount of acid used in the first step in order to limit the excess of base needed for subsequent indole formation. The reaction between **1a** and NaI (2 equiv) was then tested in acetonitrile at 80 °C in the presence of 1.1 equivalents of acetic acid, but GC-MS analysis of the reaction mixture showed the formation of only negligible amounts of **3a** after 20 hours. In contrast, when the reaction was carried out in the presence of 1 equivalent of *p*-toluene sulfonic acid in ethanol at 80 °C, complete conversion into **3a** was observed in 1.5 hours; subsequent addition of **2a** (1.2 equiv), K_2CO_3 (4 equiv) and $[Pd(PPh_3)_4]$ (0.03 equiv) to the reaction mixture, gave **4a**, which was isolated in 70% overall yield after 4.5 hours.

When the whole process was carried out in acetonitrile, similar results were achieved (71% overall yield); however, the more environmentally benign solvent, ethanol, was chosen as the reaction medium in further experiments. The reaction was then extended to include a range of α,β-ynones **1a–f** and alkynyl-trifluoroacetanilides **2a–f** (Scheme 2).

As reported in Table 1, this two-step, one-pot reaction afforded the target indoloquinolines in moderate to good overall yields, and various functional groups were tolerated in both the quinoline and indole moieties of **4**. Moreover, substituents could also be introduced in the benzenic rings of both indole (entry 7) and quinoline (entries 10–12) systems. When **2c** was reacted with **1e** in ethanol, the product **4ec** was isolated as the ethyl ester, likely through transesterification in situ (entry 11). According to this hypothesis, the reaction of **2c** with **1a** in acetonitrile afforded the expected methyl ester **4ac** (entry 3).



R^1	R^2	R^3	R^4	1	R^5	R^6	R^7	2
H	H	H	4-$MeOC_6H_4$	**1a**	Ph	H	H	**2a**
H	H	H	3-MeC_6H_4	**1b**	2-thienyl	H	H	**2b**
H	H	H	4-$EtOCOC_6H_4$	**1c**	3-$MeOCOC_6H_4$	H	H	**2c**
H	H	H	4-$MeCOC_6H_4$	**1d**	4-NCC_6H_4	H	H	**2d**
F	H	F	2-$MeOC_6H_4$	**1e**	4-$MeCOC_6H_4$	F	F	**2e**
H	H	H	4-NCC_6H_4	**1f**	cycloocten-1-yl	H	H	**2f**

Scheme 2

Table 1 Synthesis of Indoloquinolines **4** from α,β-Ynones **1** and Alkynyltrifluoroacetanilides **2**[a]

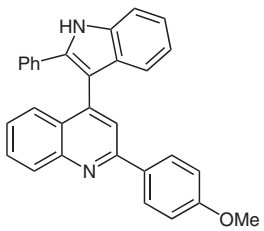
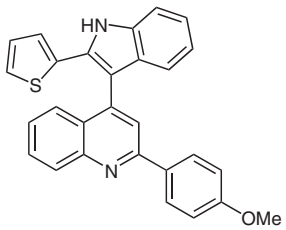
Entry	**1**, **2**	4-(1*H*-Indol-3-yl)quinoline **4**	Time (h)[b]	Yield (%)[c]
1	**1a** **2a**	**4aa** 	4.5	70
2	**1a** **2b**	**4ab** 	4	51

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Table 1 Synthesis of Indoloquinolines **4** from α,β-Ynones **1** and Alkynyltrifluoroacetanilides **2**[a] (continued)

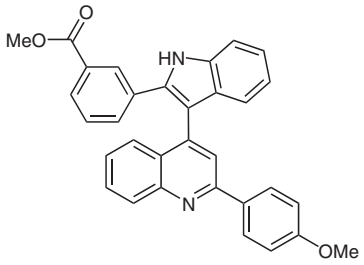
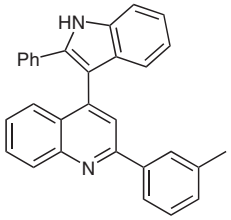
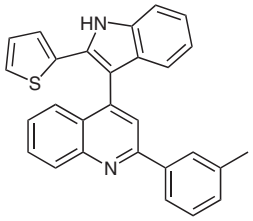
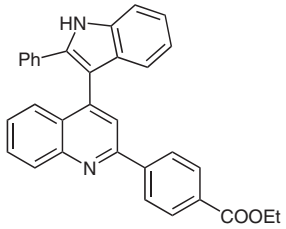
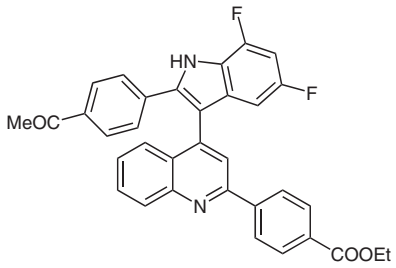
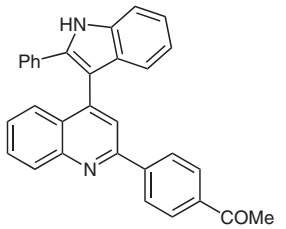
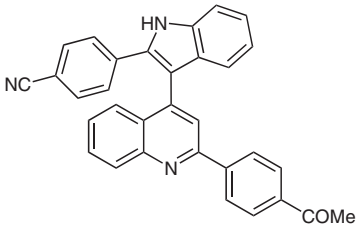
Entry	**1**, **2**	4-(1*H*-Indol-3-yl)quinoline **4**	Time (h)[b]	Yield (%)[c]
3	**1a** **2c**	**4ac** 	5	72[d]
4	**1b** **2a**	**4ba** 	3	70
5	**1b** **2b**	**4bb** 	2.5	70
6	**1c** **2a**	**4ca** 	2.5	50[e]
7	**1c** **2e**	**4ce** 	7	55
8	**1d** **2a**	**4da** 	6.5	51
9	**1c** **2d**	**4dd** 	6	60

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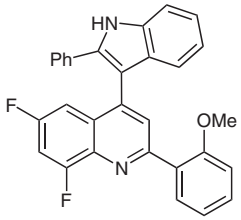
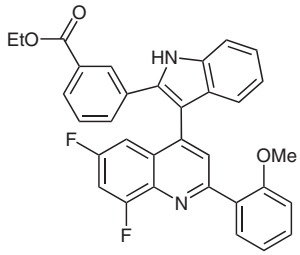
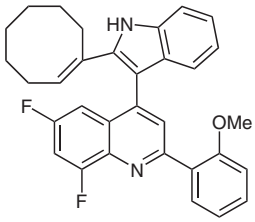
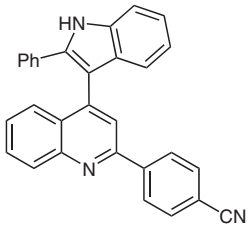
Table 1 Synthesis of Indoloquinolines **4** from α,β-Ynones **1** and Alkynyltrifluoroacetanilides **2**[a] (continued)

Entry	**1**, **2**	4-(1*H*-Indol-3-yl)quinoline **4**	Time (h)[b]	Yield (%)[c]
10	**1e** **2a**	**4ea** 	5	69
11	**1e** **2c**	**4ec** 	6	50
12	**1e** **2f**	**4ef** 	6	56
13	**1f** **2a**	**4fa** 	2.5	51[e]

[a] Unless otherwise stated, reactions were carried out in EtOH at 80 °C using the following molar ratios: **1**/NaI/TsOH = 1:2:1; then after 1.5 h: **2**/K_2CO_3/[$Pd(PPh_3)_4$] = 1.2:4:0.03 (under N_2).
[b] Reaction times refer to the second step.
[c] Overall yield of pure isolated products based on **1**.
[d] Reaction carried out in MeCN.
[e] [$Pd_2(dba)_3$] (0.02 equiv) and $P(Cy)_3$ (0.04 equiv) were used as catalyst.

In conclusion, we have developed a straightforward methodology for the synthesis of 4-(1*H*-indol-3-yl)quinolines **4** through a two-step, one-pot double cyclization, without any intermediate work-up. The results obtained widen significantly the scope of both previously reported methodologies, leading to indoles from 2-alkynyltrifluoroacetanilides **2** and to quinolines from β-(2-aminophenyl)-α,β-ynones **1**. Moreover, while Pd-catalyzed aminopalladation and reductive elimination procedures reported so far were carried out in acetonitrile or tetrahydrofuran, environmentally benign ethanol was used as reaction medium in the present work.

Melting points are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR (75.49 MHz) spectra were recorded with a Varian Mercury 300 spectrometer. ESI mass spectra were recorded with a ThermoFinnigan LCQ Deca XP Plus. IR spectra were recorded in KBr pellets with a Perkin-Elmer 683 or a Varian 100 FT-IR spectrometer.

β-(2-Aminophenyl)-α,β-ynones **1a/1b**,[15f] **1c**[15a] and **1e/1f**[15b] are known compounds. Compound **1d** was obtained in 75% yield by using the procedure reported previously.[15b] 2-Alkynyltrifluoroacetanilides **2a/2b/2f**[23] and **2c/2e**[20] are known compounds; **2d** was obtained in 67% yield by using the procedure reported previously.[20]

1-(4-Acetylphenyl)-3-(2-aminophenyl)prop-2-yn-1-one (1d)
Yield: 75%; mp 138–140 °C.

IR (KBr): 3437, 2180, 1684, 1637, 1567, 1385 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.68 (s, 3 H, CH_3), 4.52 (br s, 2 H, NH_2), 7.78–7.74 (m, 2 H), 7.32–7.24 (m, 1 H), 7.50 (dd, *J* = 8.0, 1.5 Hz, 1 H), 8.10–8.08 (m, 2 H), 8.31–8.28 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 26.7 (CH_3), 92.6 and 93.3 (*C*≡C), 103.3 (C), 114.8 (CH), 117.9 (CH), 128.3 (2 CH), 129.4 (2 CH), 132.9 (CH), 133.7 (CH), 140.0 (C), 140.7 (C), 150.7 (CNH_2), 176.7 (C≡C *C*O), 197.2 (MeCO).

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N-{2-[(4-Cyanophenyl)ethynyl]phenyl}-2,2,2-trifluoroacetamide (2d)
Yield: 67%; mp 137–139 °C.

IR (KBr): 3294, 2222, 1709, 1600, 1580, 1547 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.25 (td, *J* = 7.7, 1.1 Hz, 1 H), 7.46 (td, *J* = 8.0, 1.5 Hz, 1 H), 7.59 (ddd, *J* = 7.7, 1.5, 0.4 Hz, 1 H), 7.61–7.59 (m, 2 H), 7.69–7.66 (m, 2 H), 8.32 (dd, *J* = 8.0, 0.6 Hz, 1 H), 8.76 (br s, 1 H, NH)

^{13}C NMR ($CDCl_3$): δ = 87.1 and 95.7 (*C*≡C), 112.6 (*C*CN), 113.0 (C), 115.8 (q, *J* = 289.2 Hz, CF_3), 117.9 (CN), 120.3 (CH), 125.7 (CH), 126.5 (C), 130.6 (CH), 131.8 (2 CH), 132.0 (CH), 132.2 (2 CH), 136.25 (C), 154.3 (q, *J* = 37.5 Hz, CO).

4-(1*H*-Indol-3-yl)quinolines 4: Typical Procedure
To a solution of 3-(2-amino-3,5-difluorophenyl)-1-(2-methoxyphenyl)prop-2-yn-1-one (**1e**; 0.194 g, 0.68 mmol) in EtOH (5 mL) were added NaI (0.202 g, 1.35 mmol) and *p*-toluenesulfonic acid (0.117 g, 0.68 mmol). The mixture was stirred at 80 °C for 1.5 h and briefly cooled for 5 min. Then, 2-(phenylethynyl)trifluoroacetanilide (**2a**; 0.234 g, 0.81 mmol), K_2CO_3 (0.376 g, 2.72 mmol) and $[Pd(PPh_3)_4]$ (0.023 g, 0.02 mmol) were added. The resulting mixture was stirred under N_2 at 80 °C for 5 h, then extracted with 0.5 M NH_4Cl (100 mL) and EtOAc (3 × 50 mL). The organic layer was dried (Na_2SO_4) and evaporated. Column chromatographic purification on silica gel (hexane–EtOAc, 90:10 v/v) afforded 6,8-difluoro-2-(2-methoxyphenyl)-4-(2-phenyl-1*H*-indol-3-yl)quinoline (**4ea**).

Yield: 0.214 g (69%); mp 237–238 °C.

IR (KBr): 3300, 3050, 2981, 2910, 2809, 1628, 1550, 1492, 1481, 1435, 1418, 1247, 1227, 1100 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.63 (s, 3 H, OCH_3), 6.93 (d, *J* = 8.3 Hz, 1 H), 7.19–7.10 (m, 3 H), 7.28–7.21 (m, 4 H), 7.40–7.30 (m, 5 H), 7.51 (d, *J* = 8.0 Hz, 1 H), 7.98 (dd, *J* = 7.5, 1.6 Hz, 1 H), 8.06 (s, 1 H), 8.70 (br s, NH, 1 H).

^{13}C NMR ($CDCl_3$): δ = 55.4 (OCH_3), 104.7 (dd, *J* = 29.6, 22.9 Hz, CH), 105.7 (dd, *J* = 22.7, 4.7 Hz, CH), 111.2 (CH), 111.4 (CH), 119.8 (CH), 120.6 (C), 120.9 (CH), 121.3 (CH), 123.2 (CH), 127.4 (C), 127.6 (2CH), 127.9 (CH), 128.2 (CH), 128.4 (C), 128.9 (2CH), 129.3 (C), 130.6 (CH), 131.9 (C), 136.0 (C), 140.1 (C), 140.2 (C), 156.2 (C), 157.4 (C), 158.1 (dd, *J* = 247.6, 11.3 Hz, CF), 158.8 (dd, *J* = 259.1, 12.9 Hz, CF).

MS (ESI): *m*/*z* (%) = 463 (100) $[M + H]^+$.

2-(4-Methoxyphenyl)-4-(2-phenyl-1*H*-indol-3-yl)quinoline (4aa)
Yield: 70%; mp 138–139 °C.

IR (KBr): 3410, 1620, 1597, 1520, 1258 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 3.78 (s, 3 H, OCH_3), 7.04–6.97 (m, 3 H), 7.31–7.40 (m, 6 H), 7.43 (d, *J* = 6.9 Hz, 2 H), 7.68–7.58 (m, 3 H), 7.99 (s, 1 H), 8.10 (d, *J* = 8.3 Hz, 1 H), 8.17 (d, *J* = 8.7 Hz, 2 H), 12.01 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 55.2 (OCH_3), 109.22 (C), 111.7 (CH), 114.2 (2 CH), 118.8 (CH), 120.0 (CH), 120.2 (CH), 122.4 (CH), 125.7 (CH), 126.0 (CH), 126.1 (C), 127.5 (2 CH), 127.7 (CH), 128.6 (4 CH), 128.9 (C), 129.5 (CH), 129.6 (CH), 131.1 (C), 131.9 (C), 135.8 (C), 136.3 (C), 143.3 (C), 148.4 (C), 155.6 (C), 160.6 (C).

MS (ESI): *m*/*z* (%) = 427 (100) $[M + H]^+$.

2-(4-Methoxyphenyl)-4-[2-(2-thienyl)-1*H*-indol-3-yl]quinoline (4ab)
Yield: 51%; mp 218–219 °C.

IR (KBr): 3322, 3015, 1654, 1583, 1532, 1443, 1348, 1255 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 3.83 (s, 3 H, OCH_3), 7.11–6.95 (m, 3 H), 7.28–7.18 (m, 2 H), 7.42–7.38 (m, 2 H), 7.56 (d, *J* = 8.1 Hz, 1 H), 7.65 (d, *J* = 8.0 Hz, 1 H), 7.76 (t, *J* = 7.5 Hz, 1 H), 8.10 (d, *J* = 8.2 Hz, 2 H), 8.22 (d, *J* = 8.2 Hz, 2 H), 8.43 (d, *J* = 8.0 Hz, 2 H), 12.00 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 55.2 (OCH_3), 109.0 (C), 111.3 (CH), 114.2 (2CH), 118.6 (CH), 120.0 (CH), 120.8 (CH), 122.5 (CH), 125.4 (CH), 125.7 (CH), 125.9 (CH), 126.4 (C), 126.6 (CH), 127.2 (CH), 128.6 (2CH), 129.4 (CH), 129.7 (CH), 130.1 (C), 131.0 (C), 133.6 (C), 136.0 (C), 142.4 (C), 148.3 (C), 155.5 (C), 160.6 (C), 163.2 (C).

MS (ESI): *m*/*z* (%) = 433 (100) $[M + H]^+$.

Methyl 3-{3-[2-(4-Methoxyphenyl)quinolin-4-yl]-1*H*-indol-2-yl}benzoate (4ac)
Yield: 50%; mp 165–166 °C.

IR (KBr): 3367, 3055, 2969, 1712, 1598, 1587, 1505, 1272, 1236 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.85 (s, 3 H, OCH_3), 3.87 (s, 3 H, $COOCH_3$), 6.98–6.93 (m, 2 H), 7.14–7.06 (m, 2 H), 7.34–7.23 (m, 4 H), 7.48 (d, *J* = 7.1 Hz, 1 H), 7.64 (td, *J* = 7.0, 1.4 Hz, 1 H), 7.72 (d, *J* = 8.2 Hz, 1 H), 7.84–7.81 (m, 2 H), 8.07–8.02 (m, 2 H), 8.23–8.19 (m, 2 H), 9.51 (s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 52.3 (OCH_3), 55.4 ($COOCH_3$), 111.3 (CH), 111.5 (C), 114.1 (2CH), 119.9 (CH), 120.8 (CH), 121.0 (CH), 123.3 (CH), 125.8 (CH), 126.3 (CH), 126.5 (C), 127.9 (CH), 128.70 (CH), 128.74 (CH), 128.9 (2CH), 129.5 (C), 129.6 (CH), 129.7 (CH), 130.9 (C), 132.0 (CH), 132.19 (C), 132.24 (C), 134.6 (C), 136.2 (C), 142.9 (C), 149.0 (C), 156.8 (C), 160.7 (C), 166.2 (CO).

MS (ESI): *m*/*z* (%) = 485 (100) $[M + H]^+$.

2-(3-Methylphenyl)-4-(2-phenyl-1*H*-indol-3-yl)quinoline (4ba)
Yield: 70%; mp 198–200 °C.

IR (KBr): 3413, 3100, 2960, 1750, 1615, 1600, 1470 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 3.37 (s, 3 H, CH_3), 7.02 (t, *J* = 7.2 Hz, 1 H), 7.40–7.13 (m, 11 H), 7.57 (d, *J* = 8.1 Hz, 1 H), 7.70–7.62 (m, 2 H), 7.98–7.90 (m, 2 H), 8.14 (d, *J* = 8.2 Hz, 1 H), 11.99 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 21.0 (CH_3), 109.1 (C), 111.7 (CH), 118.7 (CH), 120.1 (CH), 120.9 (CH), 122.4 (CH), 124.4 (CH), 126.0 (CH), 126.2 (CH), 126.4 (C), 127.5 (2 CH), 127.8 (CH), 128.6 (2 CH), 128.7 (CH), 128.9 (C), 129.7 (CH), 129.8 (CH), 130.2 (CH), 131.2 (C), 132.1 (CH), 135.8 (C), 136.3 (C), 138.0 (C), 138.9 (C), 143.5 (C), 148.4 (C), 156.1 (C).

MS (ESI): *m*/*z* (%) = 411 (100) $[M + H]^+$.

2-(3-Methylphenyl)-4-[2-(2-thienyl)-1*H*-indol-3-yl]quinoline (4bb)
Yield: 70%; mp 205–206 °C.

IR (KBr): 3421, 3100, 3061, 3030, 2919, 2850, 1722, 1651, 1616, 1588, 1450, 1424, 1341, 1188, 1159 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.46 (s, 3 H, CH_3), 6.71 (dd, *J* = 3.6, 0.8 Hz, 1 H), 7.01 (dd, *J* = 5.0, 3.6 Hz, 1 H), 7.12–7.05 (m, 3 H), 7.17 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.26–7.24 (m, 3 H), 7.39–7.41 (m, 3 H), 7.62–7.57 (m, 2 H), 7.76–7.72 (m, 1 H), 8.10 (d, *J* = 8.2 Hz, 1 H), 8.3 (br s, 1 H, NH)

^{13}C NMR ($CDCl_3$): δ = 21.5 (CH_3), 110.3 (C), 110.8 (CH), 119.9 (CH), 120.4 (CH), 120.5 (CH), 121.2 (CH), 122.5 (CH), 122.9 (CH), 124.5 (CH), 125.4 (CH), 126.3 (C), 126.8 (CH), 127.9 (CH), 128.4 (2CH), 128.9 (2CH), 130.5 (CH), 130.8 (C), 132.3 (C), 134.8 (C), 135.7 (C), 136.6 (C), 141.8 (C),145.4 (C), 148.5 (C), 157.1 (C).

MS (ESI): *m*/*z* (%) = 417 (100) $[M + H]^+$.

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Ethyl 4-[4-(2-Phenyl-1*H*-indol-3-yl)quinolin-2-yl]benzoate (4ca)
Yield: 50%; mp 193–194 °C.

IR (KBr): 3369, 3059, 2925, 2853, 1719, 1604, 1594, 1579, 1542, 1447, 1273, 1100 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.42 (t, *J* = 7.0 Hz, 3 H, $COOCH_2CH_3$), 4.40 (q, *J* = 7.0 Hz, 2 H, $COOCH_2CH_3$), 7.11–7.03 (m, 1 H), 7.30–7.24 (m, 5 H), 7.40 (d, *J* = 7.4 Hz, 1 H), 7.51–7.46 (m, 2 H), 7.66 (d, *J* = 8.3 Hz, 1 H), 7.79–7.75 (m, 2 H), 8.17–8.13 (m, 3 H), 8.18 (d, *J* = 8.8 Hz, 1 H), 8.33 (d, *J* = 8.1 Hz, 2 H), 12.05 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 14.1 ($COOCH_2CH_3$), 60.7 ($COOCH_2CH_3$), 109.0 (C), 111.7 (CH), 118.7 (CH), 1120.0 (CH), 120.8 (CH), 122.3 (CH), 126.1 (CH), 126.4 (CH), 126.7 (C), 127.3 (2CH), 127.51 (2CH), 127.53 (CH), 128.5 (2CH), 128.9 (C), 129.5 (2CH), 129.8 (2CH), 130.5 (C), 131.9 (C), 136.0 (C), 136.3 (C), 143.0 (C), 143.9 (C), 148.5 (C), 154.7 (C), 165.4 (CO).

MS (ESI): *m*/*z* (%) = 469 (100) $[M + H]^+$.

Ethyl 4-{4-[2-(4-Acetylphenyl)-5,7-difluoro-1*H*-indol-3-yl]quinolin-2-yl}benzoate (4ce)
Yield: 55%; mp 270 °C (dec.).

IR (KBr): 3437, 3295, 3070, 2990, 2964, 2925, 1714, 1684, 1648, 1607, 1595 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.32 (t, *J* = 6.94 Hz, 3 H, OCH_2CH_3), 2.43 (s, 3 H, CH_3), 4.32 (q, *J* = 6.94 Hz, 2 H, OCH_2CH_3), 6.78 (d, *J* = 6.78 Hz, 1 H), 7.15 (t, *J* = 9.83 Hz, 1 H), 7.38 (t, *J* = 7.37 Hz, 1 H), 7.57–7.52 (m, 3 H), 7.79–7.70 (m, 3 H), 8.03 (d, *J* = 8.1 Hz, 2 H, A part of AB system), 8.17–8.14 (m, 2 H), 8.36 (d, *J* = 8.1 Hz, 2 H, B part of AB system), 12.64 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 14.2 (OCH_2CH_3), 26.6 (CH_3CO), 60.9 (OCH_2CH_3), 98.2 (t, *J* = 20 Hz, CH), 99.9 (d, *J* = 20 Hz, CH), 111.4 (C), 121.0 (CH), 121.5 (d, *J* = 14 Hz, *C*), 125.5 (CH), 126.3 (C),127.1 (CH), 127.5 (2 CH), 127.9 (2 CH), 128.4 (2 CH), 129.6 (2 CH), 129.9 (CH), 130.2 (CH), 130.5 (C), 131.2 (dd, *J* = 11, 7 Hz, C), 135.3 (C), 135.9 (C), 137.6 (C), 142.3 (C), 142.6 (C), 148.3 (C), 148.4 (dd, *J* = 248, 14 Hz, CF), 154.8 (C), 156.5 (dd, *J* = 237, 10 Hz, CF), 165.5 (*C*OOEt), 197.2 (CH_3CO).

MS (ESI): *m*/*z* (%) = 547 (100) $[M + H]^+$.

1-{4-[4-(2-Phenyl-1*H*-indol-3-yl)quinolin-2-yl]phenyl}ethanone (4da)
Yield: 51%; mp 219–220 °C.

IR (KBr): 3219, 3062, 3040, 2919, 1686, 1595, 1579, 1540, 1504, 1450, 1356 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.59 (s, 3 H, CH_3), 7.34–7.07 (m, 9 H), 7.49 (d, *J* = 8.1 Hz, 1 H), 7.67 (t, *J* = 7.5 Hz, 1 H), 7.81 (d, *J* = 8.2 Hz, 1 H), 7.87 (s, 1 H), 8.01 (d, *J* = 8.2 Hz, 2 H, A part of AB system), 8.16 (d, *J* = 8.2 Hz, 2 H, B part of AB system), 8.25 (d, *J* = 8.4 Hz, 1 H), 8.77 (br s, 1 H, NH).

^{13}C NMR ($CDCl_3$): δ = 26.6 (CH_3CO), 111.0 (C), 111.2 (CH), 119.9 (CH), 120.9 (CH), 121.4 (CH), 123.2 (CH), 126.4 (CH), 126.6 (CH), 127.3 (C), 127.6 (2 CH), 127.7 (2 CH), 128.1 (CH), 128.7 (2 CH), 128.8 (2 CH), 129.6 (C), 129.7 (CH), 130.2 (CH), 132.0 (C), 136.1 (C), 136.2 (C), 137.5 (C), 143.6 (C), 144.1 (C), 149.2 (C), 155.7 (C), 197.7 (CO).

MS (ESI): *m*/*z* (%) = 439 (100) $[M + H]^+$.

4-{3-[2-(4-Acetylphenyl)quinolin-4-yl]-1*H*-indol-2-yl}benzonitrile (4dd)
Yield: 60%; mp 290 °C (dec.).

IR (KBr): 3366, 3058, 2926, 2866, 2226, 1679, 1605, 1267, 1239 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.60 (s, 3 H, CH_3), 7.02 (t, *J* = 7.5 Hz, 1 H), 7.18 (d, *J* = 7.8 Hz, 1 H), 7.27 (t, *J* = 7.6 Hz, 1 H), 7.37 (t, *J* = 7.6 Hz, 1 H), 7.64–7.55 (m, 4 H), 7.76–7.67 (m, 3 H), 8.07 (d, *J* = 8.4 Hz, 2 H), 8.15 (s, 1 H), 8.19 (d, *J* = 8.4 Hz, 1 H), 8.37 (d, *J* = 8.2 Hz, 2 H), 12.15 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 26.6 (CH_3), 109.7 (C), 111.0 (C), 111.8 (CH), 118.4 (CN), 119.0 (CH), 120.3 (CH), 120.8 (CH), 123.2 (CH), 125.6 (CH), 126.3 (C), 126.7 (CH), 127.3 (2CH), 127.7 (2CH), 128.5 (2CH), 128.7 (C), 129.8 (CH), 129.9 (CH), 132.3 (2CH), 133.6 (C), 136.2 (C), 136.6 (C), 137.2 (C), 142.5 (C), 143.0 (C), 148.3 (C), 154.7 (C), 197.3 (CO).

MS (ESI): *m*/*z* (%) = 464 (50) $[M + H]^+$.

Ethyl 3-{3-[6,8-Difluoro-2-(2-methoxyphenyl) quinolin-4-yl]-1*H*-indol-2-yl}benzoate (4ec)
Yield: 50%; mp 188–190 °C.

IR (KBr): 3320, 3038, 2905, 2830, 1715, 1587, 1572, 1260, 1085 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.21 (t, *J* = 7.0 Hz, 3 H, CH_2CH_3), 3.70 (s, 3 H, OCH_3), 4.22 (q, *J* = 7.0 Hz, 2 H, CH_2CH_3), 7.21–7.09 (m, 5 H), 7.33 (t, *J* = 7.4 Hz, 2 H), 7.48 (t, *J* = 7.6 Hz, 2 H), 7.76–7.63 (m, 2 H), 7.87 (d, *J* = 7.5 Hz, 1 H), 7.94 (dd, *J* = 7.5, 1.7 Hz, 1 H), 8.06 (d, *J* = 9.1 Hz, 2 H), 12.28 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 13.8 (CH_2CH_3), 55.5 (OCH_3), 60.7 (CH_2CH_3), 105.1 (m, 2CH), 109.1 (C), 112.0 (2CH), 118.6 (CH), 120.4 (CH), 120.8 (CH), 122.9 (CH), 127.1 (CH), 127.3 (C), 127.9 (C), 128.21 (CH), 128.26 (C), 128.32 (CH), 129.2 (CH), 130.2 (CH), 131.0 (2CH), 131.9 (C), 132.0 (C), 134.8 (C), 136.2 (t, *J* = 7 Hz, C), 136.5 (C), 140.8 (t, *J* = 3 Hz, C), 155.7 (C), 157.1 (C), 157.1 (dd, *J* = 245.3, 10.3 Hz, CF), 158.9 (dd, *J* = 260.2, 11.7 Hz, CF), 165.1 (CO).

MS (ESI): *m*/*z* (%) = 535 (100) $[M + H]^+$.

4-(2-Cyclooct-1-en-1-yl-1*H*-indol-3-yl)-6,8-difluoro-2-(2-methoxyphenyl)quinoline (4ef)
Yield: 56%; mp 217–218 °C.

IR (KBr): 3450, 2940, 2900, 2820, 1628, 1595, 1550, 1485, 1249 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.38–1.33 (m, CH_2, 8 H), 2.27–2.15 (m, 4 H), 3.82 (s, CH_2, 3 H), 6.01 (t, *J* = 8.3 Hz, 1 H), 7.32–7.00 (m, 7 H), 7.45–7.37 (m, 2 H), 7.99 (dd, *J* = 7.5, 1.7 Hz, 1 H), 8.10 (s, 1 H), 8.46 (br s, NH, 1 H).

^{13}C NMR ($CDCl_3$): δ = 25.9 (CH_2), 26.6 (CH_2), 27.0 (CH_2), 27.9 (CH_2), 29.1 (CH_2), 29.6 (CH_2), 55.6 (CH_3), 104.7 (dd, *J* = 29.6, 23.0 Hz, CH), 105.8 (dd, *J* = 22.5, 4.7 Hz, CH), 109.2 (C), 110.7 (CH), 111.4 (CH), 119.2 (CH), 120.5 (CH), 121.3 (CH), 122.7 (CH), 123.9 (C), 127.1 (C), 127.5 (CH),130.6 (CH), 130.8 (C), 131.2 (C), 131.7 (CH), 131.9 (CH), 133.1 (C), 135.1 (C), 138.0 (C), 141.7 (C), 156.2 (C), 157.5 (C), 158.0 (dd, *J* = 247.5, 11.3 Hz, CF), 158.7 (dd, *J* = 259.0, 13.0 Hz, CF).

MS (ESI): *m*/*z* (%) = 495 (100) $[M + H]^+$.

4-[4-(2-Phenyl-1*H*-indol-3-yl)quinolin-2-yl]benzonitrile (4fa)
Yield: 51%; mp 275 °C (dec.).

IR (KBr): 3318, 3940, 2900, 2822, 2200, 1720, 1590, 1572, 1438, 1223 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 7.01 (d, *J* = 7.5 Hz, 1 H), 7.22–7.16 (m, 5 H), 7.41–7.35 (m, 3 H), 7.57 (d, *J* = 8.0 Hz, 1 H), 7.71 (d, *J* = 8.0 Hz, 2 H), 7.91 (d, *J* = 8.3 Hz, 2 H), 8.09 (s, 1 H), 8.16 (d, *J* = 8.6 Hz, 1 H), 8.39 (d, *J* = 8.3 Hz, 2 H), 11.94 (s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 108.6 (C), 111.6 (CH), 111.9 (C), 118.6 (C), 118.7 (CH), 120.0 (CH), 120.7 (CH), 122.2 (CH), 126.1 (CH),

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126.61 (CH), 126.63 (CH), 127.5 (2CH), 127.9 (2CH), 128.1 (C), 128.4 (2CH), 128.8 (C), 129.8 (2CH), 131.8 (C), 132.5 (2CH), 136.0 (C), 136.3 (C), 142.9 (C), 144.1 (C), 148.4 (C), 153.9 (CN).

MS (ESI): *m/z* (%) = 422 (100) $[M + H]^+$.

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