One-Pot Friedländer Quinoline Synthesis: Scope and Limitations

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Abstract: A highly effective one-pot Friedländer quinoline synthesis from *o*-nitroarylcarbaldehydes and ketones or aldehydes was developed and the scope and limitations of the method were examined. The *o*-nitroarylcarbaldehydes were reduced to *o*-aminoarylcarbaldehydes with iron in the presence of a catalytic amount of aqueous hydrochloric acid; the amino compounds were then condensed in situ with ketones or aldehydes to form mono- or disubstituted quinolines, respectively, in good-to-excellent yields (58–100%).

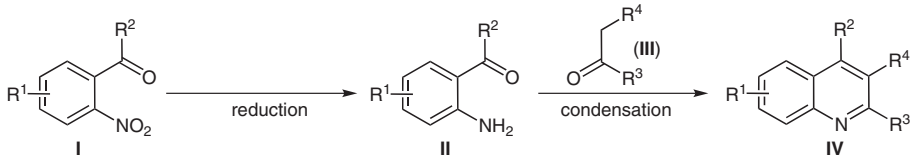
Key words: quinolines, condensation, heterocycles, aldehydes, ketones

Quinolines are an important class of heterocycles that have long been used antimalarial agents,[1] and more recently have been used as protein kinase inhibitors for the treatment of cancer.[2] These beneficial biological activities continue to make quinolines attractive targets for both synthetic and medicinal chemists. Among the many methods available for constructing the quinoline ring, the Friedländer quinoline synthesis has proven to be a very powerful tool.[3] This reaction typically requires two steps: reduction of an *o*-nitro aldehyde or ketone **I** into an *o*-amino aldehyde or ketone **II** followed by condensation of this intermediate with a ketone or aldehyde **III** (Scheme 1).

Often the amino carbonyl intermediate **II** is unstable, especially when R^2 = H, and it may undergo self-condensation. To overcome this potential problem and make this century-old reaction more practical, several laboratories have attempted to develop one-pot procedures involving the use of **II** generated in situ.[4,5] Of particular interest is the one-pot method developed by Miller and McNaughton,[4a] which uses a tin(II) chloride/zinc chloride system to convert *o*-nitro aldehydes or ketones into 2-monosubstituted or 2,3-disubstituted quinolines. This method works well with a range of aliphatic ketones but, unfortunately, it is not applicable to aromatic ketones such as acetophenone.[5] We therefore attempted to develop a method that would permit the preparation of 2-aryl-substituted quinolines. As reported in our previous preliminary communication,[5] we have discovered a practical one-pot Friedländer quinoline synthesis that uses inexpensive and readily available reagents such as iron powder, aqueous hydrochloric acid, and solid potassium hydroxide. Our method successfully condensed a variety of *o*-nitro aldehydes (or ketones) with various carbonyl co-reactants. Herein, we report a study of the scope and limitations of the one-pot Friedländer quinoline synthesis.

In a typical operation, 2-nitrobenzaldehyde was reduced with 4.0 equivalents of iron powder in the presence of 5 mol% of aqueous hydrochloric acid in refluxing ethanol. The reduction was usually complete within 30–40 minutes (as monitored by thin-layer chromatography). After this time, 1.0 equivalents of a carbonyl compound and 1.2 equivalents of powdered potassium hydroxide were added. The mixture was then stirred at reflux for a further 40–60 minutes to complete the condensation reaction. A classical aqueous workup followed by chromatography over silica gel or by recrystallization afforded the desired quinoline products. The results from the reactions of 2-nitrobenzaldehyde with various carbonyl compounds are summarized in Table 1.

Our one-pot procedure worked not only with aliphatic ketones (entries 10–14), but also with a wide variety of other ketones, including aromatic (entries 1–5), heteroaromatic (entries 6–8), and α,β-unsaturated (entry 9) ketones, giving good-to-excellent yields of the corresponding quinolines. In the case of methyl pyruvate, the ester group was hydrolyzed under the basic conditions present during the condensation step, and the corresponding quinoline-2-carboxylic acid was isolated as its hydrochloride salt after



Scheme 1

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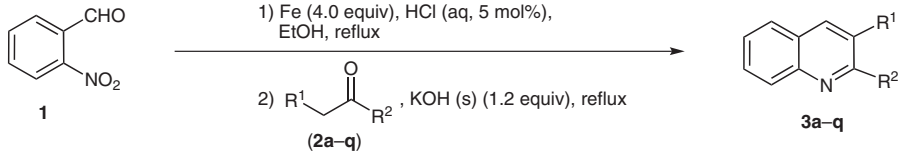
acidification of the reaction mixture (entry 15). Note that an acetal group (entry 16) and an α,β-unsaturated ketone (entry 9) were unaffected by the reaction conditions, and that an aldehyde can be used as the carbonyl component of **III** without observable self-condensation (entry 17), thereby allowing the introduction of an aryl group at the 3-position of the quinoline instead of the typical substitutions at the 2-position.

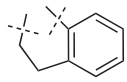
Because a wide range of carbonyl components are compatible with this one-pot procedure, we prepared 2-(cyclo)alkyl, 2-(het)aryl-, 2-styryl-, 2-carboxy-, 2,3-dialkyl-, 2-phenyl-3-methoxy-, 2-(dimethoxymethyl)-, and 3-arylquinolines in generally good-to-excellent yields. When indan-1-one was used as the carbonyl component, the tetracyclic product **3e** was obtained in 63% yield (entry 5).

Our investigations next turned to the nature of the *o*-nitrocarboxaldehyde component, and the results are listed in Table 2.

In general, *o*-nitro carbaldehydes with electron-withdrawing groups (entries 1, 4, 7–15) or with electron-donating groups (entries 2–3) both performed well under the reaction conditions, affording good-to-excellent yields (58–95%) in all cases. A lower yield (58%) was obtained with 5-bromo-2-nitrobenzaldehyde (entry 1), because debromination occurred during the iron reduction stage. However, as expected, the chloro group was well tolerated (entries 7–15), and this can provide a handle for further palladium-mediated derivatization reactions of the quinoline products. For example, we were able to convert 7-chloroquinolines into 7-boronatoquinolines in high yields

Table 1 Reactions of 2-Nitrobenzaldehyde with Various Carbonyl Compounds



Entry[a]	R^1	R^2	Product	Isolated yield (%)
1	H	Ph	**3a**	99
2	OMe	Ph	**3b**	66[b]
3	Me	Ph	**3c**	92[c]
4	H	1,3-benzodioxol-5-yl	**3d**	70
5			**3e**	63
6	H	2-pyridyl	**3f**	92
7	H	1-methylpyrrol-2-yl	**3g**	88
8	H	2-thienyl	**3h**	80
9	H	(*E*)-2-phenylvinyl	**3i**	77
10	H	Me	**3j**	64
11	$(CH_2)_5$		**3k**	95
12	Et	Pr	**3l**	85
13	H	*t*-Bu	**3m**	90[d]
14	H	cyclopropyl	**3n**	91
15	H	CO_2Me (CO_2H)[e]	**3o**	95
16	H	$CH(OMe)_2$	**3p**	90
17	Ph	H	**3q**	87[f]

[a] All reactions were carried out on a 1.0-mmol scale. The reaction times for the reduction and condensation stages were 40 min and 30 min, respectively, unless otherwise noted.
[b] 2 h for the reduction and 3 h for the condensation.
[c] 60 min for the reduction.
[d] 2 h for the condensation.
[e] Isolated as the HCl salt of the acid.
[f] 1 h for the reduction and 5 h for the condensation.

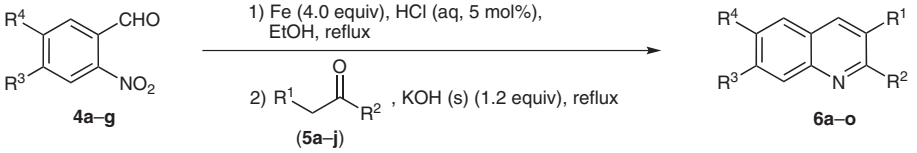
under palladium-catalyzed conditions[6] (results not shown).

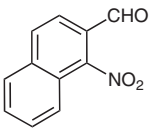
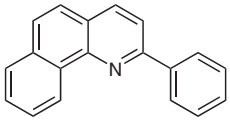
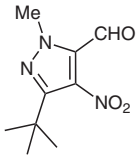
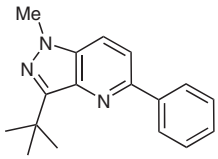
When a strongly electron-donating group, such as a dimethylamino group, was present on the phenyl ring, both reduction and condensation stages took significantly longer (5 h and 48 h compared with the usual 40 min and 30 min, respectively; entry 3). This is attributed to the reduced electrophilicity of the aldehyde group as a result of the electron-rich nature of the phenyl ring to which the aldehyde is attached.[7] A longer condensation time was also required for the naphthyl system (entry 5), possibly because of steric effects.[8]

Heteroaryl *o*-nitro carbaldehydes can also be smoothly converted into the corresponding fused quinolinoid systems. This is exemplified by entry 6, in which a pyrazolo[4,3-*b*]pyridine derivative was prepared in high yield (82%). These results further demonstrate the broad applicability of our one-pot method, which permits the preparation of quinoline derivatives functionalized on both the phenyl and the pyridyl rings. Furthermore, the relatively mild reaction conditions permit the introduction of functional groups that can act as handles for further elaboration of the quinoline products.

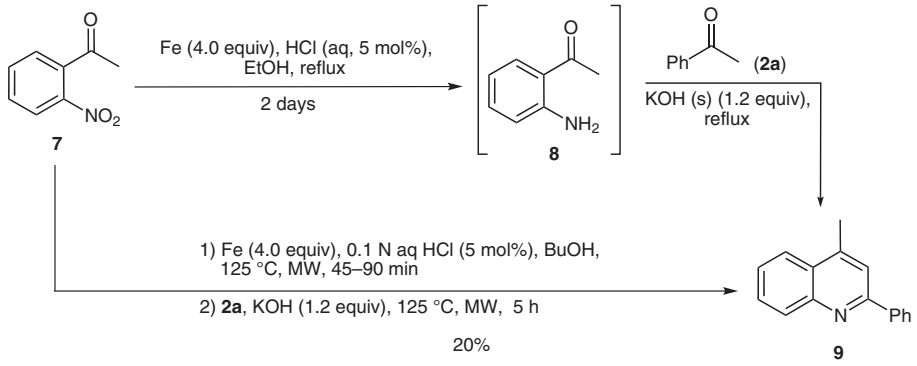
To extend the scope of our methodology, we attempted to apply the usual reaction conditions to *o*-nitro ketone **7** to

Table 2 Reactions of Ketones with Various *o*-Nitrocarbaldehydes



Entry[a]	R^3/R^4 or nitro aldehyde	R^2/R^1	Product	Isolated yield (%)
1	Br/H	Ph/H	**6a**	58
2	OCH_2O	Ph/H	**6b**	82
3	Me_2N/H	Ph/H	**6c**	67[b]
4	CO_2Me (CO_2H)/H	Ph/H	**6d**	91[c]
5		Ph/H	 **6e**	95[d]
6		Ph/H	 **6f**	82
7	Cl/H	2-FC_6H_4/H	**6g**	87
8	Cl/H	2-ClC_6H_4/H	**6h**	68
9	Cl/H	2-MeC_6H_4/H	**6i**	76
10	Cl/H	Ph/Me	**6j**	75
11	Cl/H	*i*-Pr/H	**6k**	84
12	Cl/H	*t*-Bu/H	**6l**	81
13	Cl/H	cyclopropyl/H	**6m**	71
14	Cl/H	cyclobutyl/H	**6n**	65
15	Cl/H	cyclohexyl/H	**6o**	78

[a] All reactions were carried out on a 1.0-mmol scale. The reaction times for the reduction and condensation stages were 40 min and 30 min, respectively, unless otherwise noted.
[b] 5 h for the reduction and 48 h for the condensation.
[c] The product was isolated as the HCl salt of the acid.
[d] 8 equiv of iron and 16 mol% HCl(aq) [0.1 N] were used; 5 h for the reduction and 15 h for the condensation.

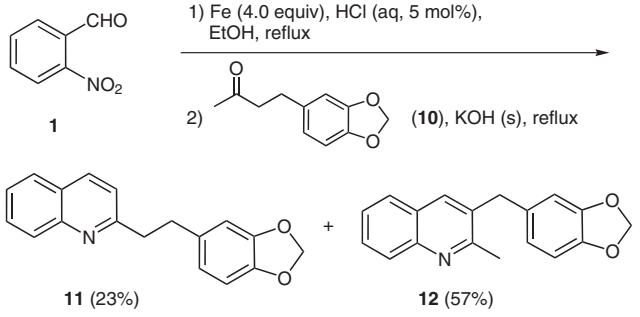


Scheme 2

introduce functionality at the 4-position of the quinoline ring (Scheme 2). In this case, the reduction stage took considerably longer (2 days compared with the usual 40 min) to provide the amino ketone intermediate (**8**), and after the addition of acetophenone (**2a**), an additional two days were required for the condensation stage to reach a conversion of about 40% (as judged by LC/MS). However, microwave conditions and the use of higher-boiling butan-1-ol as the solvent significantly reduced the reaction times to 45–90 minutes for the reduction stage and to five hours for the condensation stage. Unfortunately, the reaction again stalled at about 40% conversion, and the desired product **9** was obtained in only 20% isolated yield.

As an application of our method, we attempted to synthesize the 2-alkyl-substituted quinoline alkaloid **11**, a natural product isolated from the stem, root, bark, and leaves of *Galipea longiflora* by Fournet and co-workers.[9] The first synthesis of this compounds was reported by Burnell and co-workers[10] in 1993 (Scheme 3).

Application of the conditions that we used for *o*-nitro carboxaldehydes to the commercially available starting materials **1** and **10** gave the desired natural product **11** together with undesired 2,3-disubstituted quinoline **12** in a ratio of approximately a 1:2.5. The preference for the formation of compound **12** over compound **11**, the former being obtained by reaction at the sterically more-hindered methylene group of ketone **10**, is not currently understood.[11]

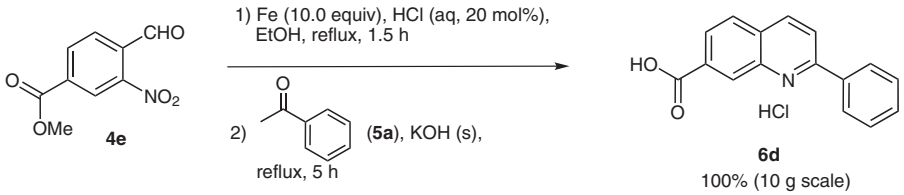


Scheme 3

To illustrate the scalability of our one-pot procedure, we prepared 2-phenylquinoline-7-carboxylic acid (**6d**; Table 2, entry 4) on a 10-gram scale. The desired product was isolated in quantitative yield as the hydrochloride salt (Scheme 4). On this larger scale, 10 equivalents of iron powder and 20 mol% of hydrochloric acid were used, and the reaction times for both the reduction (1.5 h) and the condensation (5 h) stages were markedly longer than for reactions on the smaller scale.

The above examples demonstrate that our one-pot Friedländer quinoline synthesis is an effective, practical, and scalable procedure. A wide variety of (het)aryl *o*-nitro carboxaldehydes with electron-withdrawing or electron-donating substituents react smoothly with various carbonyl compounds, including aliphatic, (het)aromatic, or α,β-unsaturated ketones, and even an aldehyde. A wide range of functional groups, such as methoxy, chloro, fluoro, cyclopropyl, ester (hydrolyzed to acid), Michael acceptors, and acetals are tolerated, enabling the preparation of a variety of quinolines in good-to-excellent yields. However, *o*-nitro ketones and other substrates with functional groups that are sensitive to reduction, such as bromo, performed poorly under these conditions, giving lower isolated yields of products.

In summary, we have developed a highly versatile one-pot Friedländer quinoline synthesis from *o*-nitro carbaldehydes and ketones/aldehydes and have tested its scope and limitations. The method, which uses inexpensive, readily available, and common reagents, is scalable and requires



Scheme 4

no moisture- or oxygen-free operations or complex workups. The reaction conditions are sufficiently mild to tolerate a variety of functional groups that can serve as handles for further elaboration of the quinoline products.

Commercially available reagents, anhyd solvents, and HPLC-grade solvents were used without further purification. Reactions were monitored by TLC on silica gel 60 F254 (0.2 mm)-precoated aluminum foil/plastic. Flash chromatography was performed with silica gel (400–230 mesh). IR spectra were recorded on a Perkin-Elmer Spectrum 1000 FT-IR spectrometer as thin films using diffuse reflectance. ^{1}H NMR and ^{13}C NMR spectra were recorded with Varian or Bruker instruments (400 MHz for ^{1}H; 100 MHz for ^{13}C) at r.t. with TMS or the residual solvent peak as the internal standard. The positions of lines or multiplets are given in ppm (δ), and the coupling constants (*J*) are given as absolute values in Hz. LC/MS analysis was performed using Hewlett Packard HP1100 (OpenLynx LC-MS: detection: UV at 254 nM; column: XTerra MS C_{18}, 5- particle size, 4.6 × 50 mm; mobile phase: 5-min gradient of MeCN and 0.01% HCO_2H in H_2O; flow rate: 1.3 mL/min). Mass spectra were recorded on Micromass_ZQ200 (OpenLynx LC-MS) mass spectrometers by electrospray ionization (ESI). Melting points were determined with a Mel-Temp II apparatus and are uncorrected. Elemental analyses were carried out by Atlantic Microlab, Inc., Norcross, GA, USA.

Quinolines; General Procedure

Fe powder (<10 μm, Aldrich; 223 mg, 4.0 mmol) and 0.1 M aq HCl (0.5 mL, 0.05 mmol) were added sequentially to a solution of an *o*-nitroarylcarbaldehyde **1** or **4a**–**g** (1.0 mmol) in EtOH (3 mL), and the resulting mixture was stirred vigorously at 95 °C (oil bath) while the reaction was monitored (TLC). On completion of the reaction (40 min–5 h), the carbonyl compound **2a**–**q**, **5a**–**j**, or **10** (1.0 mmol) and powdered KOH (67.3 mg, 1.2 mmol) were added sequentially in portions. (***CAUTION!*** Potential exotherm; add the KOH slowly.) The mixture was stirred at 95 °C while the reaction was monitored (TLC). Upon completion of the reaction (30 min–48 h), the mixture was cooled to r.t., diluted with CH_2Cl_2 (50 mL) and filtered through a Celite pad. The filtrate was washed with H_2O (10 mL) and the aqueous phase was back-extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude material was purified by chromatography (silica gel, EtOAc–hexane or MeOH–CH_2Cl_2) to give the desired quinoline products **3a**–**q**, **6a**–**o**, **11**, or **12**.

For the carboxylic acid products (entry 15 in Table 1 and entry 4 in Table 2), the workup was modified as follows. The inorganic solids were removed by filtration of the warm mixture and the filtrate was acidified to pH 1.0 with 4 M aq HCl. The solvents were removed on a Rotovap, and H_2O (10 mL) was added. The product was extracted into THF (3 × 15 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the desired acids as their HCl salts.

2-Phenylquinoline (3a)

Yield: 99%; mp 84–85 °C.

IR (thin film, KBr): 3057, 1615, 1596, 1582, 1153, 1508, 1490, 1319, 1074 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15–8.28 (m, 4 H), 7.85 (d, *J* = 8.1 Hz, 1 H), 7.70–7.78 (m, 1 H), 7.53–7.57 (m, 3 H), 7.46–7.51 (m, 1 H), 7.43 (d, *J* = 8.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.4, 136.8, 129.8, 129.7, 129.4, 128.9, 127.6, 127.5, 127.2, 127.2, 126.3, 119.0.

MS (ESI): *m/z* = 206.20 [M + H]$^+$.

HPLC: t_R = 3.68 min (OpenLynx).

3-Methoxy-2-phenylquinoline (3b)

Yield: 66%; R_f = 0.39 (EtOAc–hexanes, 1:4).

IR (thin film, KBr): 3056, 2924, 2852, 1686 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15–8.21 (m, 1 H), 8.00–8.06 (m, 2 H), 7.76 (dd, *J* = 1.3 Hz, 1 H), 7.57–7.64 (m, 1 H), 7.55 (t, *J* = 2.0, 1.5 Hz, 1 H), 7.53–7.55 (m, 1 H), 7.52 (d, *J* = 1.0 Hz, 1 H), 7.50 (t, *J* = 1.5 Hz, 1 H), 7.47–7.49 (m, 1 H), 3.91–3.98 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.0, 151.7, 143.1, 137.9, 129.8, 129.4, 128.9, 128.7, 128.1, 126.9, 126.8, 126.3, 112.9, 55.5.

MS (ESI): *m/z* = 236.18 [M + H]$^+$.

HPLC: t_R = 1.86 min (OpenLynx).

3-Methyl-2-phenylquinoline (3c)

Yield: 92%; R_f = 0.57 (EtOAc–hexanes, 1:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, *J* = 8.6 Hz, 1 H), 8.03 (s, 1 H), 7.79 (d, *J* = 8.1 Hz, 1 H), 7.65–7.71 (m, 1 H), 7.58–7.64 (m, 2 H), 7.42–7.56 (m, 4 H), 2.48 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.0, 147.0, 141.0, 137.0, 129.2, 129.2, 128.8, 128.7, 128.3, 128.2, 127.6, 126.7, 126.4, 26.0.

MS (ESI): *m/z* = 220.20 [M + H]$^+$.

HPLC: t_R = 2.46 min (OpenLynx).

2-(1,3-Benzodioxol-5-yl)quinoline (3d)

Yield: 70%; mp 87–89 °C; R_f = 0.62 (EtOAc–hexanes, 1:4).

IR (thin film, KBr): 3056, 2893, 2778, 1596, 1487, 1444, 1247, 1038, 809, 512 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 8.6 Hz, 1 H), 8.11 (d, *J* = 8.6 Hz, 1 H), 8.04 (d, *J* = 8.1 Hz, 1 H), 7.98 (d, *J* = 7.8 Hz 1 H), 7.82–7.90 (m, 2 H), 7.72–7.81 (m, 1 H), 7.53–7.62 (m, 1 H), 7.09 (d, *J* = 8.08 Hz, 1 H), 6.13 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.4, 148.6, 148.0, 147.3, 136.9, 132.9, 129.8, 128.9, 127.6, 126.7, 126.1, 121.6, 118.3, 108.4, 107.0, 101.4.

MS (ESI): *m/z* = 250.17 [M + H]$^+$.

HPLC: t_R = 2.87 min (OpenLynx).

11*H*-Indeno[1,2-*b*]quinoline (3e)

Yield: 63%; mp 164–166 °C; R_f = 0.5 (EtOAc–hexanes, 1:4).

IR (thin film, KBr): 2924, 1623, 1562, 1498, 1463, 1394, 1318, 905, 770, 732 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 7.1 Hz, 1 H), 8.21 (d, *J* = 8.3 Hz, 1 H), 7.99 (s, 1 H), 7.64–7.74 (m, 2 H), 7.50 (m, 2 H), 7.45 (m, 2 H), 3.86 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.3, 147.7, 144.9, 140.1, 134.3, 130.8, 129.7, 128.8, 128.5, 127.6, 125.2, 121.8, 33.7.

MS (ESI): *m/z* = 218.20 [M + H]$^+$.

HPLC: t_R = 3.32 min (OpenLynx).

2-Pyridin-2-ylquinoline (3f)

Yield: 92%; mp 95.5–97.0 °C.

IR (thin film, KBr): 3054, 1595, 1555, 1502, 1419, 1237, 1123, 1088, 993, 957, 944, 741, 713, 623 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.74–8.76 (m, 1 H), 8.68 (d, *J* = 8.4 Hz, 1 H), 8.58 (d, *J* = 8.8 Hz, 1 H), 8.30 (d, *J* = 8.4 Hz, 1 H), 8.21 (d, *J* = 8.4 Hz, 1 H), 7.86–7.90 (m, 2 H), 7.74–7.76 (m, 1 H), 7.56–7.59 (m, 1 H), 7.37–7.38 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.3, 156.2, 149.2, 147.9, 136.9, 136.8, 129.8, 129.6, 128.3, 127.6, 126.7, 124.0, 121.8, 118.9.

MS (ESI): *m/z* = 207.14 $[M + H]^+$.

HPLC: t_R = 3.28 min (OpenLynx).

2-(1-Methyl-1*H*-pyrrol-2-yl)quinoline (3g)
Yield: 88%; mp 51–52 °C; R_f = 0.52 (EtOAc–hexanes, 1:4).

IR (thin film, KBr): 1615, 1600, 1235 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 8.8 Hz, 1 H), 8.02 (dd, *J* = 8.5, 1.14 Hz, 1 H), 7.76 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.71 (d, *J* = 8.6 Hz, 1 H), 7.67 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1 H), 7.46 (ddd, *J* = 8.0, 6.9, 1.3 Hz, 1 H), 6.80–6.83 (m, 1 H), 6.79 (dd, *J* = 3.9, 1.9 Hz, 1 H), 6.23 (dd, *J* = 3.9, 2.7 Hz, 1 H), 4.22 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.3, 147.7, 135.9, 132.3, 129.4, 129.1, 127.7, 127.5, 126.1, 125.5, 120.2, 112.4, 107.9, 37.7.

MS (ESI): *m/z* = 209.25 $[M + H]^+$.

HPLC: t_R = 2.70 min (OpenLynx).

2-(2-Thienyl)quinoline (3h)
Yield: 80%; mp 130–132 °C; R_f = 0.44 (EtOAc–hexanes, 1:4).

IR (thin film, KBr): 3100, 3059, 1613, 1592, 1551, 1526, 1498, 1426, 1316, 1242, 1227, 1143, 1121, 1057, 905, 820, 719 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 8.0 Hz, 1 H), 8.09 (d, *J* = 7.6 Hz, 1 H), 7.77 (d, *J* = 8.8 Hz, 1 H), 7.70–7.77 (m, 2 H), 7.68 (ddd, *J* = 8.4, 6.8, 1.6 Hz, 1 H), 7.47 (ddd, *J* = 8.0, 6.8, 1.2 Hz, 1 H), 7.46 (dd, *J* = 5.2, 1.2 Hz, 1 H), 7.15 (dd, *J* = 5.2, 4.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.4, 148.2, 145.5, 136.8, 129.9, 129.4, 128.7, 128.2, 127.6, 127.3, 126.2, 126.1, 117.8.

MS (ESI): *m/z* = 212.14 $[M + H]^+$.

HPLC: t_R = 3.74 min (OpenLynx).

2-[(*E*)-2-Phenylvinyl]quinoline (3i)
Yield: 77%; R_f = 0.43 (EtOAc–hexanes, 1:4).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 8.4 Hz, 1 H), 8.01 (d, *J* = 8.8 Hz, 1 H), 7.72–7.62 (m, 5 H), 7.57 (d, *J* = 8.8 Hz, 1 H), 7.47–7.37 (m, 4 H), 7.34–7.30 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.0, 148.3, 136.6, 136.3, 134.5, 129.8, 129.3, 129.1, 128.8, 128.7, 127.6, 127.4, 127.3, 126.2, 119.3.

2-Methylquinoline (3j)
Yield: 64%; R_f = 0.43 (EtOAc–hexanes, 1:4).

IR (thin film, KBr): 1601, 1506, 1423, 1312, 1221, 813, 782, 741, 616 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.01–8.04 (m, 2 H), 7.75 (d, *J* = 8.0 Hz, 1 H), 7.67 (m, 1 H), 7.64 (m, 1 H), 7.26 (d, *J* = 8.4 Hz, 1 H), 2.74 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 147.8, 136.1, 129.4, 128.6, 127.5, 126.4, 125.6, 121.9, 25.3.

MS (ESI): *m/z* = 144.22 $[M + H]^+$.

HPLC: t_R = 0.89 min (OpenLynx).

1,2,3,4-Tetrahydroacridine (3k)
Yield: 95%; R_f = 0.43 (EtOAc–hexanes, 1:4).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.4 Hz, 1 H), 7.70 (s, 1 H), 7.63 (d, *J* = 8.0 Hz, 1 H), 7.57 (dt, *J* = 2.4, 7.2 Hz, 1 H), 7.39 (dt, *J* = 1.2, 7.2 Hz, 1 H), 3.10 (t, *J* = 5.8 Hz, 2 H), 2.92 (t, *J* = 6.4 Hz, 2 H), 1.99–1.92 (m, 2 H), 1.87–1.82 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 146.7, 134.9, 130.9, 128.5, 128.3, 127.2, 126.9, 125.5, 33.6, 29.3, 23.3, 22.9.

MS (ESI): *m/z* = 184.21 $[M + H]^+$.

HPLC: t_R = 1.86 min (OpenLynx).

3-Ethyl-2-propylquinoline (3l)
Yield: 85%; R_f = 0.68 (EtOAc–hexanes, 3:7).

IR (thin film, KBr): 3058, 2962, 1490, 1420, 1209, 1148, 908, 747, 616 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.3 Hz, 1 H), 7.86 (s, 1 H), 7.72 (d, *J* = 8.1 Hz, 1 H), 7.55–7.65 (m, 1 H), 7.44 (t, *J* = 7.6 Hz, 1 H), 2.91–3.04 (m, 2 H), 2.84 (q, *J* = 7.3 Hz, 2 H), 1.76–1.94 (m, 2 H), 1.34 (t, *J* = 7.6 Hz, 3 H), 1.08 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.0, 146.2, 135.4, 134.1, 128.5, 128.3, 127.4, 126.9, 125.6, 37.7, 25.2, 22.9, 14.4, 14.4.

MS (ESI): *m/z* = 200.21 $[M + H]^+$.

HPLC: t_R = 2.34 min (OpenLynx).

2-*tert*-Butylquinoline (3m)
Yield: 90%; R_f = 0.73 (EtOAc–hexanes, 1:4).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 8.8 Hz, 2 H), 7.77 (d, *J* = 8 Hz, 1 H), 7.67 (m, 1 H), 7.53 (d, *J* = 8.8 Hz, 1 H), 7.48 (m, 1 H), 1.49 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3, 147.5, 135.9, 129.5, 129.0, 127.3, 126.5, 125.7, 118.2, 77.4, 76.8, 38.2, 30.2.

MS (ESI): *m/z* = 186.24 $[M + H]^+$.

HPLC: t_R = 2.18 min (OpenLynx).

2-Cyclopropylquinoline (3n)
Yield: 91%; R_f = 0.47 (EtOAc–hexanes, 1:4).

IR (thin film, KBr): 3056, 3006, 1616, 1600, 1504, 1425, 1302, 1213, 1204, 1166, 1082, 1022, 951, 909, 819, 751, 619 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.6 Hz, 1 H), 7.96 (d, *J* = 8.4 Hz, 1 H), 7.73 (dd, *J* = 1.2, 8.0 Hz, 1 H), 7.64 (ddd, *J* = 1.2, 7.0, 8.8 Hz, 1 H), 7.42 (ddd, *J* = 1.2, 7.0, 8.0 Hz, 1 H), 7.16 (d, *J* = 8.4 Hz, 1 H), 2.28–2.20 (m, 1 H), 1.18–1.12 (m, 2 H), 1.12–1.05 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.4, 148.0, 135.8, 129.2, 128.6, 127.4, 126.7, 125.1, 119.3, 18.1, 10.2.

MS (ESI): *m/z* = 170.14 $[M + H]^+$.

HPLC: t_R = 1.79 min (OpenLynx).

Quinoline-2-carboxylic Acid Hydrochloride (3o)
Yield: 95%; mp 150–153 °C (dec.).

^1H NMR (400 MHz, MeOH-d_4): δ = 8.53 (d, *J* = 8.3 Hz, 1 H), 8.21–8.25 (m, 2 H), 8.03 (d, *J* = 8.3 Hz, 1 H), 7.85–7.89 (m, 1 H), 7.72–7.76 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 149.6, 148.1, 139.8, 132.1, 131.1, 130.3, 130.1, 129.2, 121.9.

MS (ESI): *m/z* = 174.06 $[M + H]^+$.

HPLC: t_R = 1.80 min (OpenLynx).

2-(Dimethoxymethyl)quinoline (3p)
Yield: 90%; R_f = 0.37 (EtOAc–$CHCl_3$, 1:5).

IR (thin film, KBr): 2932, 2830, 1601, 1504, 1102, 1067 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8.3 Hz, 1 H), 8.16 (d, *J* = 8.3 Hz, 1 H), 7.84 (d, *J* = 8.1 Hz, 1 H), 7.70–7.77 (m, 1 H), 7.68 (d, *J* = 8.3 Hz, 1 H), 7.53–7.60 (m, 1 H), 5.50 (s, 1 H), 3.48 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.7, 137.0, 129.5, 128.1, 127.6, 126.8, 124.8, 118.7, 105.1, 54.2.

MS (ESI): *m/z* = 204.21 $[M + H]^+$.

HPLC: t_R = 2.84 min (OpenLynx).

3-Phenylquinoline (3q)
Yield: 87%; mp 177–180 °C (HCl salt); R_f = 0.16 (CH_2Cl_2–hexanes, 1:1).

IR (thin film, KBr): 3058, 3031, 1597, 1568, 1493, 1460, 1448, 1363, 1341, 1126, 1026, 954, 903, 786, 762, 696 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.19 (d, *J* = 2.2 Hz, 1 H), 8.31 (d, *J* = 2.2 Hz, 1 H), 8.15 (d, *J* = 8.6 Hz, 1 H), 7.89 (dd, *J* = 1.8, 8.2 Hz, 1 H), 7.75–7.69 (m, 3 H), 7.58 (ddd, *J* = 1.2, 6.8, 8.2 Hz, 1 H), 7.56–7.51 (m, 2 H), 7.47–7.42 (m_c, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.9, 147.3, 137.8, 133.8, 133.2, 129.3, 129.2, 129.1, 128.1, 128.0, 128.0, 127.4, 126.9.

MS (ESI): *m/z* = 206.14 $[M + H]^+$.

HPLC: t_R = 2.78 min (OpenLynx).

7-Bromo-2-phenylquinoline (6a)
Yield: 58%; mp 122.0–123.5 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.37 (s, 1 H), 8.15–8.21 (m, 5 H), 7.90 (d, *J* = 8.4 Hz, 1 H), 7.70 (d, *J* = 8.8 Hz, 1 H), 7.62 (dd, *J* = 10.4, 1.6 Hz, 1 H), 7.46–7.56 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2, 148.9, 139.1, 136.9, 132.1, 129.9, 129.8, 129.0, 128.8, 127.8, 125.9, 123.9, 119.4.

MS (ESI): *m/z* = 284 ($[M + H]^+$, ^{79}Br), 286 ($[M + H]^+$, ^{81}Br).

HPLC: t_R = 4.20 min (OpenLynx).

Anal. Calcd for $C_{15}H_{10}BrN$: C, 63.40; H, 3.55; N, 4.93; Br 28.12. Found: C, 63.41; H, 3.41; N, 4.84; Br, 28.31.

6-Phenyl[1,3]dioxolo[4,5-*g*]quinoline (6b)
Yield: 82%; mp 110–112 °C; R_f = 0.25 (CH_2Cl_2–hexanes, 1:1).

IR (thin film, KBr): 1792, 1772, 1683, 1652, 1616, 1230, 1171, 1037 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.11–8.04 (m, 2 H), 7.90 (d, *J* = 8.6 Hz, 1 H), 7.63 (d, *J* = 8.3 Hz, 1 H), 7.51–7.44 (m, 2 H), 7.43–7.36 (m, 2 H), 6.96 (s, 1 H), 6.01 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.2, 150.7, 147.6, 146.5, 139.7, 135.4, 128.85, 128.71, 127.2, 124.0, 117.1, 106.1, 102.5, 101.6.

MS (ESI): *m/z* = 250.17 $[M + H]^+$.

HPLC: t_R = 2.63 min (OpenLynx).

***N*,*N*-Dimethyl-2-phenylquinolin-7-amine (6c)**
Yield: 67%; R_f = 0.49 (EtOAc–$CHCl_3$, 1:5).

IR (thin film, KBr): 3058, 3030, 1617, 1595 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, *J* = 7.3 Hz, 2 H), 8.07 (d, *J* = 8.3 Hz, 1 H), 7.68 (d, *J* = 9.1 Hz, 1 H), 7.58 (d, *J* = 8.3 Hz, 1 H), 7.49–7.56 (m, 3 H), 7.42–7.49 (m, 1 H), 7.18 (dd, *J* = 9.1, 2.53 Hz, 1 H), 3.14 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.8, 107.7, 115.5, 116.4, 120.2, 127.8, 128.2, 128.9, 129.1, 136.4, 151.8, 157.9.

MS (ESI): *m/z* = 249.16 $[M + H]^+$.

HPLC: t_R = 1.97 min (OpenLynx).

2-Phenylquinoline-7-carboxylic Acid Hydrochloride (6d)
Yield: 91%; mp 255 °C.

IR (thin film, KBr): 2924, 1682, 975, 760 cm^{-1}.

^1H NMR (400 MHz, MeOH-d_4): δ = 8.79-8.80 (m, 1 H), 8.45 (dd, *J* = 0.8, 8.8 Hz, 1 H), 8.16-8.19 (m, 2 H), 8.14 (dd, *J* = 1.6, 8.4 Hz, 1 H), 8.10 (d, *J* = 8.8 Hz, 1 H), 8.02 (d, *J* = 8.4 Hz, 1 H), 7.50-7.59 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.7, 149.3, 141.0, 139.2, 134.5, 133.0, 131.7, 131.6, 130.7, 129.8, 129.5, 127.8, 122.9.

MS (ESI): *m/z* = 250.15 $[M + H]^+$.

HPLC: t_R = 3.20 min (OpenLynx).

2-Phenylbenzo[*h*]quinoline (6e)
Yield: 95%; mp 66–67 °C; R_f = 0.76 (EtOAc–hexanes, 1:4).

IR (thin film, KBr): 3050, 2360 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.37 (d, *J* = 7.2 Hz, 1 H), 8.51 (d, *J* = 8.4 Hz, 1 H), 8.44 (d, *J* = 7.6 Hz, 2 H), 8.31 (d, *J* = 8.4 Hz, 1 H), 8.06 (d, *J* = 8.0 Hz, 1 H), 7.90–7.97 (m, 2 H), 7.76–7.83 (m, 2 H), 7.61 (t, *J* = 7.4 Hz, 2 H), 7.53 (t, *J* = 7.2 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 137.2, 133.5, 130.9, 129.5, 128.9, 128.4, 128.0, 127.3, 127.1, 127.0, 125.3, 125.0, 123.9, 119.1.

MS (ESI): *m/z* = 256.11 $[M + H]^+$.

HPLC: t_R = 4.52 min (OpenLynx).

3-*tert*-Butyl-1-methyl-5-phenyl-1*H*-pyrazolo[4,3-*b*]pyridine (6f)
Yield: 82%; mp 103–104 °C; R_f = 0.76 (EtOAc–hexanes, 5:95).

^1H NMR (400 MHz, DMSO-d_6): δ = 8.09 (dt, *J* = 1.2, 7.4 Hz, 2 H), 7.73 (d, *J* = 7.3 Hz, 1 H), 7.63 (d, *J* = 7.3 Hz, 1 H), 7.46 (dt, *J* = 1.8, 7.4 Hz, 2 H), 7.37 (tt, *J* = 1.2, 7.4 Hz, 1 H), 3.99 (s, 3 H), 1.62 (s, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.3, 150.4, 139.6, 139.3, 132.8, 128.3, 128.0, 126.6, 117.3, 116.5, 35.1, 33.2, 29.3.

MS (ESI): *m/z* = 266.23 $[M + H]^+$.

HPLC: t_R = 3.98 min (OpenLynx).

Anal. Calcd for $C_{17}H_{19}N_3$: C, 76.95; H, 7.22; N, 15.84. Found: C, 76.75; H, 7.17; N, 16.11.

7-Chloro-2-(2-fluorophenyl)quinoline (6g)
Yield: 87%; mp 123.5 °C.

IR (thin film, KBr): 2957, 2931, 2866, 1610, 1598, 1497 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.24 (s, 1 H), 8.21 (d, *J* = 8.4 Hz, 1 H), 8.12 (dt, *J* = 1.6, 7.6 Hz, 1 H), 7.92 (dd, *J* = 8.6, 2.8 Hz, 1 H), 7.81 (d, *J* = 8.8 Hz, 1 H), 7.53 (dd, *J* = 8.8, 2.0 Hz, 1 H), 7.44–7.50 (m, 1 H), 7.34 (dt, *J* = 1.2, 7.6 Hz, 1 H), 7.19–7.25 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.1, 159.6, 154.98, 154.96, 148.6, 136.0, 135.5, 131.5, 131.5, 131.2, 131.2, 128.7, 128.7, 127.7, 127.5, 127.3, 125.6, 124.8, 124.7, 122.7, 122.6, 116.4, 116.2.

MS (ESI): *m/z* = 258.12 ($[M + H]^+$, ^{35}Cl), 261.06 ($[M + H]^+$, ^{37}Cl).

HPLC: t_R = 3.69 min (OpenLynx).

7-Chloro-2-(2-chlorophenyl)quinoline (6h)
Yield: 68%; mp 128 °C.

IR (thin film, KBr): 1611, 1598, 1499 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.21–8.29 (m, 2 H), 7.81 (dd, *J* = 20.0, 8.6 Hz, 2 H), 7.68–7.74 (m, 1 H), 7.50–7.60 (m, 2 H), 7.38–7.47 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.3, 135.6, 135.6, 132.3, 131.7, 130.2, 130.1, 128.8, 128.6, 127.9,127.2, 125.5, 123.0.

MS (ESI): *m/z* = 274.11 ($[M + H]^+$, ^{35}Cl), 276.10 ($[M + H]^+$, ^{37}Cl).

HPLC: t_R = 3.63 min (OpenLynx).

7-Chloro-2-(2-methylphenyl)quinoline (6i)
Yield: 76%; mp 79 °C.

IR (thin film, KBr): 2961, 2927, 2862, 1611, 1598, 1497 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 8.1 Hz, 2 H), 7.82 (d, *J* = 8.6 Hz, 1 H), 7.48–7.59 (m, 3 H), 7.31–7.38 (m, 3 H), 2.43 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.9, 147.8, 139.8, 135.7, 135.6, 135.2, 130.6, 129.3, 128.4, 128.4, 128.2, 127.1, 125.7, 124.7, 122.2, 20.0.

MS (ESI): *m/z* = 254.14 ([M + H]$^+$, ^{35}Cl), 256.10 ([M + H]$^+$, ^{37}Cl).

HPLC: t_R = 3.64 min (OpenLynx).

7-Chloro-3-methyl-2-phenylquinoline (6j)
Yield: 75%; mp 106 °C.

IR (thin film, KBr): 2961, 2931, 2866, 1613, 1598, 1497 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.16 (br s, 1 H), 8.02 (s, 1 H), 7.73 (d, *J* = 8.6 Hz, 1 H), 7.54–7.64 (m, 2 H), 7.40–7.56 (m, 4 H), 2.48 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.5, 146.9, 140.4, 136.7, 134.5, 129.6, 128.8, 128.5, 128.4, 128.3, 128.0, 127.5, 125.9, 20.4.

MS (ESI): *m/z* = 253.86 ([M + H]$^+$, ^{35}Cl), 255.68 ([M + H]$^+$, ^{37}Cl).

HPLC: t_R = 4.00 min (OpenLynx).

7-Chloro-2-isopropylquinoline (6k)
Yield: 84%; mp 81–82 °C.

IR (thin film, KBr): 2959, 2928, 2866, 1613, 1598, 1496, 1410 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03–8.07 (m, 2 H), 7.70 (d, *J* = 8.6 Hz, 1 H), 7.43 (dd, *J* = 8.6, 2.0 Hz, 1 H), 7.33 (d, *J* = 8.6 Hz, 1 H), 3.20–3.29 (m, 1 H), 1.39 (d, *J* = 7.1 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.3, 168.8, 148.1, 136.1, 135.0, 128.6, 128.1, 126.7, 125.3, 119.6, 37.2, 22.4.

MS (ESI): *m/z* = 206.12 ([M + H]$^+$, ^{35}Cl), 208.10 ([M + H]$^+$, ^{37}Cl).

HPLC: t_R = 3.84 min (OpenLynx).

2-*tert*-Butyl-7-chloroquinoline (6l)
Yield: 81%; mp 155–157 °C.

IR (thin film, KBr): 2959, 2924, 2859, 2358, 2332, 1116 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01–8.12 (m, 2 H), 7.70 (d, *J* = 8.6 Hz, 1 H), 7.52 (d, *J* = 8.6 Hz, 1 H), 7.43 (dd, *J* = 8.6, 2.0 Hz, 1 H), 1.47 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 147.8, 135.7, 134.8, 128.5, 128.4, 126.6, 124.8, 118.4, 38.3, 30.1.

MS (ESI): *m/z* = 220.15 ([M + H]$^+$, ^{35}Cl), 222.18 ([M + H]$^+$, ^{37}Cl).

HPLC: t_R = 4.35 min (OpenLynx).

7-Chloro-2-cyclopropylquinoline (6m)
Yield: 71%; mp 37 °C.

IR (thin film, KBr): 1611, 1600, 1499 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93–8.03 (m, 2 H), 7.67 (d, *J* = 8.6 Hz, 1 H), 7.39 (dd, *J* = 8.7, 1.9 Hz, 1 H), 7.20 (d, *J* = 8.3 Hz, 1 H), 2.23 (br s, 1 H), 1.06–1.23 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.7, 148.4, 135.5, 135.0, 128.6, 127.7, 126.1, 125.1, 120.0, 18.0, 10.7.

MS (ESI): *m/z* = 203.95 ([M + H]$^+$, ^{35}Cl), 205.95 ([M + H]$^+$, ^{37}Cl).

HPLC: t_R = 3.62 min (OpenLynx).

7-Chloro-2-cyclobutylquinoline (6n)
Yield: 65%; mp 45 °C.

IR (thin film, KBr): 2959, 2871, 1615, 1600, 1497 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (br s, 2 H), 7.71 (d, *J* = 8.6 Hz, 1 H), 7.45 (d, *J* = 8.1 Hz, 1 H), 7.34 (d, *J* = 7.3 Hz, 1 H), 3.87 (br s, 1 H), 2.40–2.53 (m, 4 H), 2.07–2.21 (m, 1 H), 1.92–2.03 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 148.1, 136.0, 135.1, 128.6, 128.1, 126.7, 125.1, 119.9, 42.6, 28.2, 18.3.

MS (ESI): *m/z* = 218.12 ([M + H]$^+$, ^{35}Cl), 220.08 ([M + H]$^+$, ^{37}Cl).

HPLC: t_R = 3.36 min (OpenLynx).

7-Chloro-2-cyclohexylquinoline (6o)
Yield: 78%; mp 79 °C.

IR (thin film, KBr): 2961, 2931, 2862, 1613, 1600, 1497 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (br s, 2 H), 7.71 (d, *J* = 8.1 Hz, 1 H), 7.45 (br s, 1 H), 7.33 (br s, 1 H), 2.91 (br s, 1 H), 2.03 (d, *J* = 11.1 Hz, 2 H), 1.91 (dd, *J* = 9.6, 3.0 Hz, 2 H), 1.81 (d, *J* = 12.4 Hz, 1 H), 1.58–1.70 (m, 2 H), 1.48 (q, *J* = 12.6 Hz, 2 H), 1.28–1.40 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.9, 148.2, 136.1, 135.2, 128.6, 128.2, 126.6, 125.2, 120.0, 47.5, 32.7, 32.7, 26.5, 26.1.

MS (ESI): *m/z* = 246.18 ([M + H]$^+$, ^{35}Cl), 248.14 ([M + H]$^+$, ^{37}Cl).

HPLC: t_R = 3.91 min (OpenLynx).

2-[2-(1,3-Benzodioxol-5-yl)ethyl]quinoline (11)
Yield: 23%; mp 60–63 °C; R_f = 0.39 (EtOAc–hexanes, 1:4).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95–8.24 (m, 2 H), 7.82 (d, *J* = 6.8 Hz, 1 H), 7.75 (br s, 1 H), 7.53 (br s, 1 H), 7.25 (br s, 1 H, obscured), 6.77 (s, 1 H), 6.66–6.74 (m, 2 H), 3.24–3.37 (m, 2 H), 5.93 (s, 2 H), 3.08–3.16 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.7, 147.9, 147.5, 145.7, 136.2, 135.3, 129.4, 128.8, 127.5, 126.8, 125.8, 121.6, 121.3, 109.0, 108.1, 100.7, 41.2, 35.6.

MS (ESI): *m/z* = 277.88 [M + H]$^+$.

HPLC: t_R = 1.97 min (OpenLynx).

3-(1,3-Benzodioxol-5-ylmethyl)-2-methylquinoline (12)
Yield: 57%; mp 126 °C; R_f = 0.24 (EtOAc–hexanes, 1:4).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97–8.24 (m, 1 H), 7.83 (br s, 1 H), 7.75 (d, *J* = 8.1 Hz, 1 H), 7.69 (t, *J* = 7.1 Hz, 1 H), 7.47–7.55 (m, 1 H), 6.78 (d, *J* = 7.8 Hz, 1 H), 6.58–6.67 (m, 2 H), 5.96 (s, 2 H), 4.08 (s, 2 H), 2.71 (br s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8, 147.9, 146.7, 135.7, 132.8, 132.6, 128.8, 128.8, 128.3, 127.2, 127.1, 125.8, 121.8, 109.3, 108.3, 101.0, 38.9, 23.5.

MS (ESI): *m/z* = 277.97 [M + H]$^+$.

HPLC: t_R = 1.47 min (OpenLynx).

4-Methyl-2-phenylquinoline (9)
A tube containing a small stirring bar was charged with Fe powder (<10 μm, Aldrich; 220 mg, 4.0 mmol), 1-(2-nitrophenyl)ethanone (**7**; 160 mg. 1.0 mmol), *n*-BuOH (3 mL), and 0.1 M aq HCl (0.5 mL, 0.05 mmol). The mixture was heated with stirring in a microwave reactor (CEM, 300 W, POWERMAX) at 125 °C for 1.5 h, then cooled to r.t. A 6.7 M aq soln of KOH (0.18 mL, 1.2 mmol) was added, followed by acetophenone (**2a**, 0.12 mL, 1.0 mmol). The mixture was again heated with stirring in the microwave reactor at 125 °C for 5 h then cooled to r.t. and filtered. The metallic residue was rinsed with MeOH, and the filtrate was concentrated in vacuo and purified by preparative TLC [silica gel, EtOAc–hexanes (1:5)] to give a pale yellow oil; yield: 44 mg (20%); R_f = 0.40 (EtOAc–hexanes, 1:5).

IR (thin film, KBr): 3059, 2920, 1683, 1597, 1508, 1409, 1348 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.13–8.31 (m, 3 H), 8.02 (d, *J* = 8.1 Hz, 1 H), 7.70–7.79 (m, 2 H), 7.41–7.64 (m, 4 H), 2.79 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.9, 147.8, 145.0, 139.5, 133.0, 129.4, 129.2, 128.7, 127.6, 126.1, 123.6, 119.8, 19.0.

MS (ESI): *m/z* = 220.18 $[M + H]^+$.

HPLC: t_R = 3.53 min (OpenLynx).

2-Phenylquinoline-7-carboxylic Acid Hydrochloride (6d); Scaled-Up Method

Fe powder (<10 μm, Aldrich; 21.05 g, 377 mmol), H_2O (8 mL), and concd HCl (0.63 mL, 7.5 mmol) were added consecutively to a solution of methyl 4-formyl-3-nitrobenzoate (**4e**; 8.04 g, 38.4 mmol) in EtOH (100 mL). The mixture was stirred at 95 °C for 1.5 h. PhCOMe (**5a**, 4.4 mL, 37.7 mmol) and solid KOH (6.34 g, 113 mmol) were cautiously added, and the mixture was stirred at 95 °C for another 5 h. The inorganic solids were removed by filtration of the warm mixture, and the filtrate was acidified to pH 1.0 with 4 M aq HCl. The solvents were removed on a Rotovap, and H_2O (10 mL) was added. The product was extracted with THF (3 × 100 mL) and the extracts were dried ($MgSO_4$), filtered and concentrated in vacuo to afford the acid **6d** as its HCl salt; yield: 10.9 g (quant). The analytical data were identical with those of the product from the small-scale reaction.

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References

(1) For recent reviews, see: (a) Stocks, P. A.; Raynes, K. J.; Ward, S. A. In *Antimalarial Chemotherapy: Mechanisms of Action, Resistance, and New Directions in Drug Discovery (Infectious Disease)*; Rosenthal, P. J., Ed.; Humana: Totawa / NJ, **2001**, Chap. 13, 235. (b) Waters, N. C.; Dow, G. S.; Kozar, M. P. *Expert Opin. Ther. Pat.* **2004**, *14*, 1125. (c) Fitch, C. D. *Life Sci.* **2004**, *74*, 1957. (d) Olliaro, P. L.; Taylor, W. R. J. *J. Exp. Biol.* **2003**, *206*, 3753. (e) Michael, J. P. *Nat. Prod. Rep.* **2004**, *21*, 650.

(2) (a) Tsou, H.-R.; Overbeek-Klumpers, E. G.; Hallett, W. A.; Reich, M. F.; Floyd, M. B.; Johnson, B. D.; Michalak, R. S.; Nilakantan, R.; Discafani, C.; Golas, J.; Rabindran, S. K.; Shen, R.; Shi, X.; Wang, Y.-F.; Upeslacis, J.; Wissner, A. *J. Med. Chem.* **2005**, *48*, 1107. For a review, see: (b) Boschelli, D. H. *Curr. Top. Med. Chem. (Sharjah, United Arab Emirates)* **2002**, *2*, 1051. (c) Kubo, K.; Ohyama, S.-i.; Shimizu, T.; Takami, A.; Murooka, H.; Nishitoba, T.; Kato, S.; Yagi, M.; Kobayashi, Y.; Iinuma, N.; Isoe, T.; Nakamura, K.; Iijima, H.; Osawa, T.; Izawa, T. *Bioorg. Med. Chem.* **2003**, *11*, 5117. (d) Golas, J. M.; Arndt, K.; Etienne, C.; Lucas, J.; Nardin, D.; Gibbons, J.; Frost, P.; Ye, F.; Boschelli, D. H.; Boschelli, F. *Cancer Res.* **2003**, *63*, 375. (e) Wu, J.; Li, W.; Craddock, B. P.; Foreman, K. W.; Mulvihill, M. J.; Ji, Q.-s.; Miller, W. T.; Hubbard, S. R. *EMBO J.* **2008**, *27*, 1985. (f) Mulvihill, M. J.; Ji, Q.-S.; Coate, H. R.; Cooke, A.; Dong, H.; Feng, L.; Foreman, K.; Rosenfeld-Franklin, M.; Honda, A.; Mak, G.; Mulvihill, K. M.; Nigro, A. I.; O'Connor, M.; Pirrit, C.; Steinig, A. G.; Siu, K.; Stolz, K. M.; Sun, Y.; Tavares, P. A. R.; Yao, Y.; Gibson, N. W. *Bioorg. Med. Chem.* **2008**, *16*, 1359. (g) Ji, Q.-s.; Mulvihill, M. J.; Rosenfeld-Franklin, M.; Cooke, A.; Feng, L.; Mak, G.; O'Connor, M.; Yao, Y.; Pirritt, C.; Buck, E.; Eyzaguirre, A.; Arnold, L. D.; Gibson, N. W.; Pachter, J. A. *Mol. Cancer Ther.* **2007**, *6*, 2158. (h) Mulvihill, M. J.; Cooke, A.; Rosenfeld-Franklin, M.; Buck, E.; Foreman, K.; Landfair, D.; O'Connor, M.; Pirritt, C.; Sun, Y.; Yao, Y.; Arnold, L. D.; Gibson, N. W.; Ji, Q.-s. *Future Med. Chem.* **2009**, *1*, 1153.

(3) (a) For a review, see: Cheng, C.-C.; Yan, S.-J. *Org. React. (N. Y.)* **1982**, *28*, 37. For a recent paper on the mechanism, see: (b) Muchowski, J. M.; Maddox, M. L. *Can. J. Chem.* **2004**, *82*, 461.

(4) (a) McNaughton, B. R.; Miller, B. L. *Org. Lett.* **2003**, *5*, 4257. (b) Eckert, H. *Angew. Chem.* **1981**, *93*, 216. (c) Motokura, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Tetrahedron Lett.* **2004**, *45*, 6029. (d) Cho, C. S.; Kim, B. T.; Choi, H.-J.; Kim, T.-J.; Shim, S. C. *Tetrahedron* **2003**, *59*, 7997. (e) Martinez, R.; Ramon, D. J.; Yus, M. *Eur. J. Org. Chem.* **2007**, 1599. (f) Cho, C. S.; Ren, W. X.; Shim, S. C. *Tetrahedron Lett.* **2006**, *47*, 6781. (g) Cho, C. S.; Ren, W. X.; Shim, S. C. *Bull. Korean Chem. Soc.* **2005**, *26*, 1286.

(5) Li, A.-H.; Ahmed, E.; Chen, X.; Cox, M.; Crew, A. P.; Dong, H.-Q.; Jin, M.; Ma, L.; Panicker, B.; Siu, K. W.; Steinig, A. G.; Stolz, K. M.; Tavares, P. A. R.; Volk, B.; Weng, Q.; Werner, D.; Mulvihill, M. J. *Org. Biomol. Chem.* **2007**, *5*, 61.

(6) Arnold, L. D.; Cesario, C.; Coate, H.; Crew, A. P.; Dong, H.; Foreman, K.; Honda, A.; Laufer, R.; Li, A.-H.; Mulvihill, K. M.; Mulvihill, M. J.; Nigro, A.; Panicker, B.; Steinig, A. G.; Sun, Y.; Weng, Q.; Werner, D. S.; Wyle, M. J.; Zhang, T. WO 2005097800, **2005**; *Chem. Abstr.* **2005**, *142*, 405928.

(7) The Hammett substituent constant (σ value) for the *para*-Me_2N group is –0.205, suggesting that it has an electron-donating effect. See: Hammett, L. P. *J. Am. Chem. Soc.* **1937**, *59*, 96.

(8) Longer condensation times have also been reported for the reaction of the intermediate 1-aminonaphthalene-2-carboxaldehyde with 1,3-diacetylbenzene (31 h) and 2,6-diacetylpyridine (17 h) under essentially the same reaction conditions (KOH in refluxing EtOH); see: Riesgo, E. C.; Jin, X.; Thummel, R. P. *J. Org. Chem.* **1996**, *61* , 3017.

(9) (a) Fournet, A.; Vagneur, B.; Richomme, P.; Bruneton, J. *Can. J. Chem.* **1989**, *67*, 2116. (b) Fournet, A.; Hocquemiller, R.; Roblot, F.; Cavé, A.; Richomme, P.; Bruneton, J. *J. Nat. Prod.* **1993**, *56*, 1547.

(10) Caron, S.; Desfossés, S.; Dionne, R.; Théberge, N.; Burnell, R. H. *J. Nat. Prod.* **1993**, *56*, 138.

(11) The same results were obtained in the 1,8-naphthyridine system when NaOH was used as the base. See: Dormer, P. G.; Eng, K. K.; Farr, R. N.; Humphrey, G. R.; McWilliams, G. C.; Reider, P. J.; Sager, J. W.; Volante, R. P. *J. Org. Chem.* **2003**, *68*, 467.