

## 3-Haloquinolines by Friedländer Reaction of $\alpha$ -Haloketones

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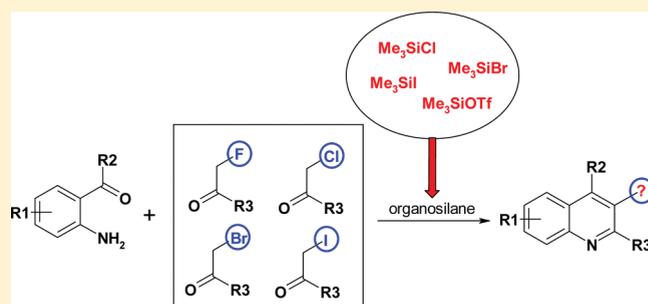
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**S** Supporting Information

**ABSTRACT:** A general approach to 3-fluoro-, 3-chloro-, and 3-bromoquinolines which relies on organosilane-promoted Friedländer reaction of  $\alpha$ -haloketones is described. The scope of the methylene component as well as influence of the organosilane component on the outcome of the reaction is studied. The method can be used under parallel synthesis conditions.



### INTRODUCTION

Quinoline derivatives fairly take a leading position among other aromatic heterocycles in organic chemistry and related areas. The quinoline scaffold has been identified among privileged ones in drug discovery.<sup>1</sup> In particular, quinoline derivatives can be found among antimalarial, antibacterial, antiasthmatic, antihypertensive, and anti-inflammatory agents.<sup>2–4</sup> Aryl-substituted quinolines act as ligands for 5-lipoxygenase,<sup>5</sup> tyrosine kinase (PDGF-RTK),<sup>6</sup> leukotriene,<sup>7</sup> LTD<sub>4</sub>,<sup>8</sup> and other receptors. Furthermore, polyquinolines were shown to undergo hierarchical self-assembly into nanostructures with promising electronic and photonic properties.<sup>9</sup>

3-Haloquinolines **1** are valuable building blocks for the preparation of otherwise hardly accessible 3-substituted quinolines, in particular, using palladium-catalyzed couplings. On the other hand, 3-fluoroquinolines are of especial interest to medicinal chemistry: introduction of a fluorine atom into organic molecules is widely considered to improve their physicochemical parameters related to ADME properties.<sup>10</sup>

Most of the methods used for the preparation of 3-haloquinolines<sup>11</sup> **1** included either direct or indirect introduction of halogen (e.g., by Sandmeyer reaction) into the quinoline core.<sup>12</sup> Alternative approaches included dichlorocarbene-promoted indole ring expansion,<sup>13</sup> iodine-induced cyclization of *N*-propargylanilines,<sup>14</sup> cyclization of *ortho*-substituted difluorostyrenes,<sup>15</sup> and other methods.<sup>16</sup> Noteworthy, classical condensations such as Doebner–Miller, Combes,<sup>17</sup> Pfitzinger,<sup>12c</sup> or Friedländer reactions were rarely used for the synthesis of 3-haloquinolines.

In this work, we wish to report a general method for the synthesis of 3-haloquinolines **1** and their heteroanalogues using

Friedländer reaction of *ortho*-aminocarbonyl compounds and  $\alpha$ -haloketones.

### RESULTS AND DISCUSSION

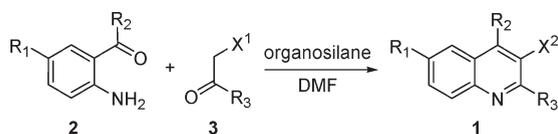
It has been shown previously that organosilanes can be used as promoters for various reactions of carbonyl compounds.<sup>18</sup> In particular, we have reported that chlorotrimethylsilane is an effective promoter for the Friedländer reaction of *ortho*-amino-carbonyl compounds and classical methylene components (i.e.,  $\beta$ -dicarbonyl compounds, acetophenones, and their analogues, cyclic ketones). The scope of the reaction was demonstrated by variation of both carbonyl and methylene components of the reaction.<sup>19,20</sup>

$\alpha$ -Haloketones are rarely encountered among methylene components of the classical condensation reactions<sup>21</sup> as the presence of an additional electrophilic center results in further transformations (e.g., formation of epoxides in Darzens reaction<sup>22</sup>). In particular, apart from two isolated examples described by our group (i.e., 4-chloroacetoacetate<sup>19</sup> and 1,3-dichloroacetone<sup>23</sup>), there have been no reports using  $\alpha$ -haloketones as substrates for the organosilane-promoted Friedländer reactions (Scheme 1).

To address the problem of selectivity in the latter transformations, first we studied condensation of 2'-aminobenzophenone **2a** and  $\alpha$ -haloacetophenones **3a–d** in the presence of various organosilanes (Table 1, entries 1–16). It was found that, in the case of  $\alpha$ -fluoroacetophenone **3a**, 3-fluoro-2,4-diarylquinoline **1aa** is formed in 93–95% yields irrelevant to the organosilane used as the reaction promoter. Analogously, 2,4-diarylquinoline **4**

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**Scheme 1. Organosilane-Promoted Friedländer Reaction of *ortho*-Aminocarbonyl Compounds **2** and  $\alpha$ -Haloketones **3****



was the main product (80–93% yield) obtained in the reaction of **2a** and  $\alpha$ -iodoacetophenone **3d** in all of the cases studied. As for **3b** and **3c**, the outcome of the reaction depended critically on the organosilane used. In particular, quinolines **1ab** and **1ac** were obtained from both these substrates in the case of Me<sub>3</sub>SiCl and Me<sub>3</sub>SiBr, respectively. Hence the halogen atom in the final 3-haloquinoline arrived from the reaction promoter not from the  $\alpha$ -haloketone **3b** or **3c**. Moreover, the 3-unsubstituted product **4** was obtained from **3b** or **3c** in the presence of Me<sub>3</sub>SiI. Finally, the use of Me<sub>3</sub>SiOTf allowed the halogen atom from the starting  $\alpha$ -haloketone **3b** or **3c** to be retained in the corresponding products **1ab** and **1ac**.

The tendencies described in the above paragraph were confirmed on a wide scope of the substrates. In particular, 3-chloroquinolines **1ae**–**1cb** were obtained by the reaction of *ortho*-aminoketones **2a**–**2c** and  $\alpha$ -chloroketones **3** (Table 1, entries 17–24, 29–33). While in the case of **2a** and **2c** the corresponding 3-chloroquinolines **1** were formed in good yields (56–87%), the yields of the products prepared from **2b** were moderate to good (47–76%), presumably due to the self-condensation of **2b**.

The method was successfully applied to the synthesis of 3-chlorothieno[2,3-*b*]pyridines. Hence thienopyridines **5a**–**5c** were obtained in 79–83% yields starting from the thiophene **6** and  $\alpha$ -chloroketones **3** (Table 1, entries 36–38).

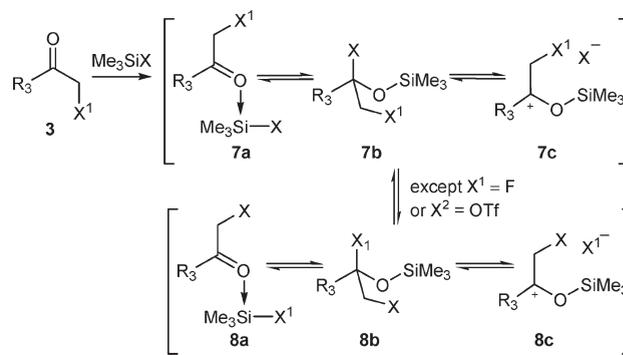
$\alpha$ -Bromoketones **3n** and **3o** smoothly reacted with ketone **2a** in the presence of bromotrimethylsilane, leading to the formation of 3-bromoquinolines **1an** and **1ao** in good yields (73–88%) (Table 1, entries 25 and 26).

Finally, 3-fluoroquinolines **1ap**, **1ba**, **1cp**, and **1dp** and thienopyridines **5d** and **5e** were isolated in good yields (75–89%, except **1ba**) as the products of the Friedländer reactions involving  $\alpha$ -fluoroketones **3a** and **3p** (Table 1, entries 27, 28, 34, 35, 39, and 40). Again, the yield was moderate (39%) in the case of **1ba** obtained from *o*-aminoacetophenone **2b**.

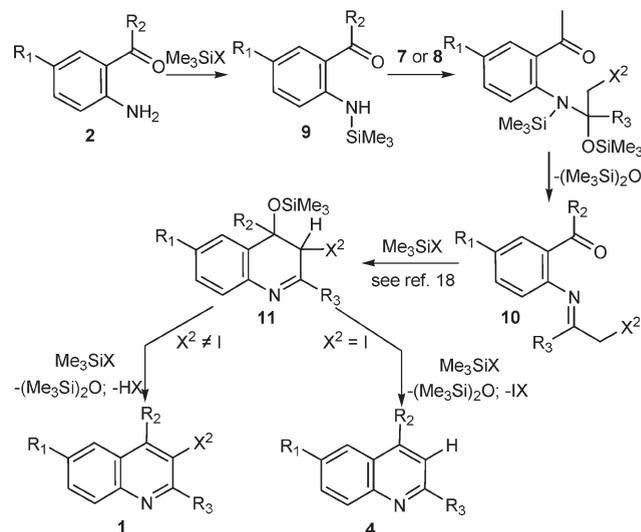
The results obtained on the organosilane-promoted Friedländer reaction can be explained by the transformations shown in the Schemes 2 and 3. The reaction starts with activation of  $\alpha$ -haloketone **3** upon action of the organosilane Me<sub>3</sub>SiX giving adducts **7a**–**7c**.<sup>18</sup> **7** can equilibrate with intermediates **8** via the halogen exchange.<sup>24</sup> Provided that 5-fold excess of the organosilane is used, these equilibria are shifted toward the formation of **8**. The formation of **8** is disfavored in the case of X<sup>1</sup> = F due to the resistance to substitution of the C–F bond and in the case of X = OTf due to the low nucleophilicity of this counterion. Hence for X<sup>1</sup> = F or X = OTf, X<sup>2</sup> in the Scheme 3 is the same as X<sup>1</sup>, otherwise X<sup>2</sup> = X.

Either **7** or **8** can react with *N*-silyl derivatives **9** of the aminocarbonyl compounds **2**, yielding imines **10**. The latter undergo an intramolecular aldol-type reaction, whose mechanism is well-documented in the literature.<sup>18</sup> Intermediate **11** then can react with organosilane by two means. If X<sup>2</sup>  $\neq$  I, then HX is

**Scheme 2. Reaction of  $\alpha$ -Haloketones **3** and Organosilanes**



**Scheme 3. Reaction of Aminoketones **2** and Intermediates **7** or **8** in the Presence of Organosilane (for X<sup>1</sup> = F or X = OTf, X<sup>2</sup> = X<sup>1</sup>, Otherwise X<sup>2</sup> = X)**



eliminated to give the 3-haloquinolines **1**; otherwise, IX is eliminated instead to yield **4**.

## CONCLUSIONS

Organosilane-promoted Friedländer reaction of  $\alpha$ -haloketones and *ortho*-aminocarbonyl compounds is a general and efficient method for the synthesis of 3-fluoro-, 3-chloro-, and 3-bromoquinolines.

The combination of organosilane and  $\alpha$ -haloketone used critically influences the reaction outcome. In the case of  $\alpha$ -fluoroketones, 3-fluoroquinolines are formed regardless the organosilane used. If an  $\alpha$ -iodoketone is introduced into the reaction, 3-unsubstituted quinoline is obtained. In the case of  $\alpha$ -chloro- and  $\alpha$ -bromoketones, the outcome of the reaction depends on the organosilane used. If Me<sub>3</sub>SiCl or Me<sub>3</sub>SiBr are the reaction promoters, 3-haloquinoline formed contains the halogen atom from the organosilane used. On the contrary, the halogen atom from  $\alpha$ -haloketone is retained in the case of Me<sub>3</sub>SiOTf. Finally, the use of Me<sub>3</sub>SiI resulted in the formation of 3-unsubstituted quinolines.

As the operating procedure of the organosilane-promoted Friedländer reaction is technically simple, the method can be used under parallel synthesis conditions.

Table 1. Friedländer Reaction of Aminoketones 2, 6, and  $\alpha$ -Haloketones 3

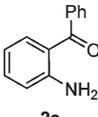
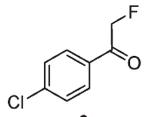
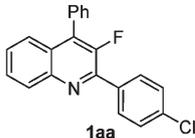
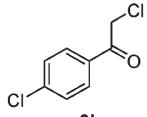
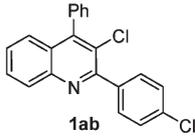
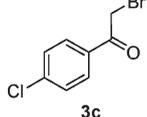
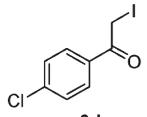
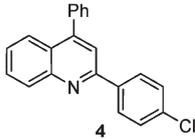
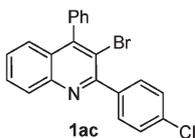
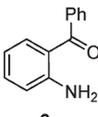
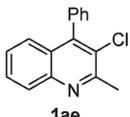
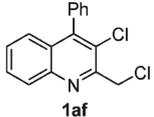
Entry No.	Organosilane	Aminoketone	$\alpha$ -Haloketone	Product	Yield, %
1	Me <sub>3</sub> SiCl	 <b>2a</b>	 <b>3a</b>	 <b>1aa</b>	93
2	Me <sub>3</sub> SiCl	<b>2a</b>	 <b>3b</b>	 <b>1ab</b>	91
3	Me <sub>3</sub> SiCl	<b>2a</b>	 <b>3c</b>	<b>1ab</b>	80
4	Me <sub>3</sub> SiCl	<b>2a</b>	 <b>3d</b>	 <b>4</b>	90
5	Me <sub>3</sub> SiBr	<b>2a</b>	<b>3a</b>	<b>1aa</b>	95
6	Me <sub>3</sub> SiBr	<b>2a</b>	<b>3b</b>	 <b>1ac</b>	90
7	Me <sub>3</sub> SiBr	<b>2a</b>	<b>3c</b>	<b>1ac</b>	90
8	Me <sub>3</sub> SiBr	<b>2a</b>	<b>3d</b>	<b>4</b>	92
9	Me <sub>3</sub> SiI	<b>2a</b>	<b>3a</b>	<b>1aa</b>	93
10	Me <sub>3</sub> SiI	<b>2a</b>	<b>3b</b>	<b>4</b>	90
11	Me <sub>3</sub> SiI	<b>2a</b>	<b>3c</b>	<b>4</b>	70
12	Me <sub>3</sub> SiI	<b>2a</b>	<b>3d</b>	<b>4</b>	80
13	Me <sub>3</sub> SiOTf	<b>2a</b>	<b>3a</b>	<b>1aa</b>	94
14	Me <sub>3</sub> SiOTf	<b>2a</b>	<b>3b</b>	<b>1ab</b>	90
15	Me <sub>3</sub> SiOTf	<b>2a</b>	<b>3c</b>	<b>1ac</b>	48
16	Me <sub>3</sub> SiOTf	<b>2a</b>	<b>3d</b>	<b>4</b>	93
17	Me <sub>3</sub> SiCl	 <b>2a</b>	 <b>3e</b>	 <b>1ae</b>	73
18	Me <sub>3</sub> SiCl	<b>2a</b>	 <b>3f</b>	 <b>1af</b>	87

Table 1. Continued

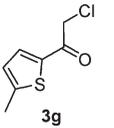
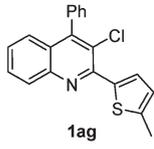
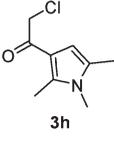
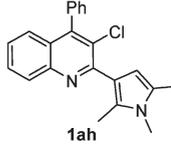
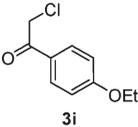
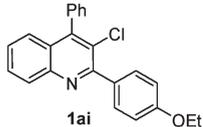
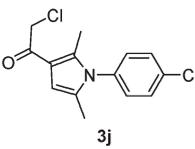
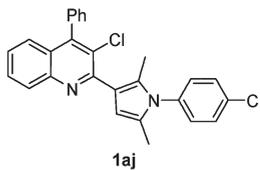
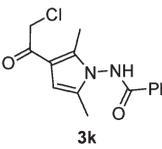
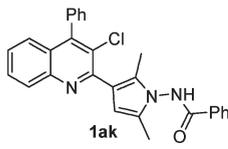
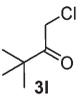
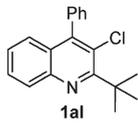
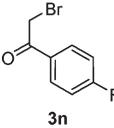
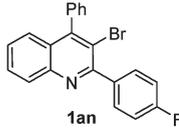
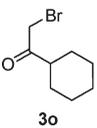
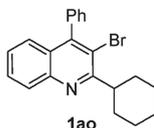
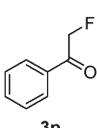
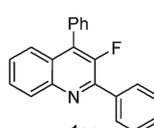
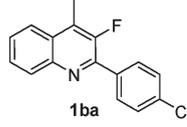
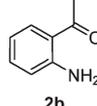
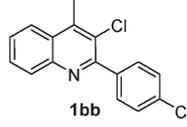
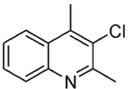
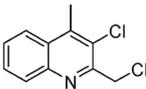
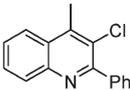
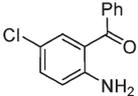
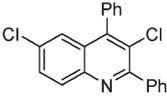
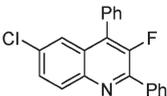
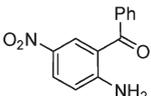
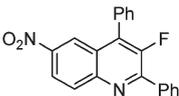
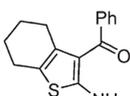
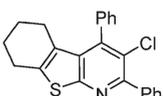
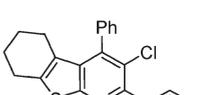
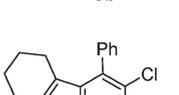
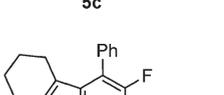
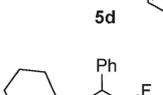
Entry No.	Organosilane	Aminoketone	$\alpha$ -Haloketone	Product	Yield, %
19	Me <sub>3</sub> SiCl	<b>2a</b>	 <b>3g</b>	 <b>1ag</b>	67
20	Me <sub>3</sub> SiCl	<b>2a</b>	 <b>3h</b>	 <b>1ah</b>	85
21	Me <sub>3</sub> SiCl	<b>2a</b>	 <b>3i</b>	 <b>1ai</b>	81
22	Me <sub>3</sub> SiCl	<b>2a</b>	 <b>3j</b>	 <b>1aj</b>	76
23	Me <sub>3</sub> SiCl	<b>2a</b>	 <b>3k</b>	 <b>1ak</b>	73
24	Me <sub>3</sub> SiCl	<b>2a</b>	 <b>3l</b>	 <b>1al</b>	56
25	Me <sub>3</sub> SiBr	<b>2a</b>	 <b>3n</b>	 <b>1an</b>	88
26	Me <sub>3</sub> SiBr	<b>2a</b>	 <b>3o</b>	 <b>1ao</b>	73
27	Me <sub>3</sub> SiCl	<b>2a</b>	 <b>3p</b>	 <b>1ap</b>	87
28	Me <sub>3</sub> SiCl	<b>2b</b>	<b>3a</b>	 <b>1ba</b>	39
29	Me <sub>3</sub> SiCl	 <b>2b</b>	<b>3b</b>	 <b>1bb</b>	69

Table 1. Continued

Entry No.	Organosilane	Aminoketone	$\alpha$ -Haloketone	Product	Yield, %
30	Me <sub>3</sub> SiCl	<b>2b</b>	<b>3e</b>	 <b>1be</b>	47
31	Me <sub>3</sub> SiCl	<b>2b</b>	<b>3f</b>	 <b>1bf</b>	76
32	Me <sub>3</sub> SiCl	<b>2b</b>	 <b>3m</b>	 <b>1bm</b>	63
33	Me <sub>3</sub> SiCl	 <b>2c</b>	<b>3m</b>	 <b>1cm</b>	89
34	Me <sub>3</sub> SiCl	<b>2c</b>	<b>3p</b>	 <b>1cp</b>	83
35	Me <sub>3</sub> SiCl	 <b>2d</b>	<b>3p</b>	 <b>1dp</b>	80
36	Me <sub>3</sub> SiCl	 <b>6</b>	<b>3m</b>	 <b>5a</b>	79
37	Me <sub>3</sub> SiCl	<b>6</b>	<b>3e</b>	 <b>5b</b>	83
38	Me <sub>3</sub> SiCl	<b>6</b>	<b>3g</b>	 <b>5c</b>	83
39	Me <sub>3</sub> SiCl	<b>6</b>	<b>3a</b>	 <b>5d</b>	79
40	Me <sub>3</sub> SiCl	<b>6</b>	<b>3p</b>	 <b>5e</b>	75

## EXPERIMENTAL SECTION

**General Comments.** All starting materials were commercially available and were used without additional purification. All solvents were purified by standard methods. All procedures were carried out under open atmosphere with no precautions taken to exclude ambient moisture. Melting points are uncorrected.  $^1\text{H}$  NMR spectra were recorded on 400 and 500 MHz spectrometers with TMS as an internal standard.  $^{13}\text{C}$  NMR (125 MHz) and NMR experiments were recorded on a 500 MHz with TMS as internal standard. LC/MS spectra were recorded using a chromatography/mass spectrometric system that consists of high-performance liquid chromatograph equipped with a diode-matrix and mass-selective detector. Ionization method, chemical ionization under atmospheric pressure (APCI). Ionization mode, simultaneous scanning of positive and negative ions in the mass range of 80–1000  $m/z$ . According to HPLC MS and  $^1\text{H}$  NMR spectra data, all synthesized compounds have purity >95%.

**General Procedure for Organosilane-Promoted Friedländer Reaction.** *ortho*-Aminocarbonyl compounds **2a–d** or **6** (1 mmol) and  $\alpha$ -haloketones **3a–p** (1 mmol) were placed in an 8 mL pressure tube and dissolved in DMF (2 mL). Organosilane (5 mmol) was added dropwise to the solution at 0 °C. The tube was thoroughly sealed and heated on a steam bath for 4–10 h ( $\text{Me}_3\text{SiCl}$ ) or allowed to stand for 24–48 h (other organosilanes). After cooling, the tube was opened (CAUTION! Excessive pressure inside), and the reaction mixture was poured into water (5 mL) and then sonicated at 20 °C for 1 h. The precipitate formed was filtered and washed with small amount of  $\text{CH}_3\text{CN}$ . The crude product was recrystallized from 2-propanol or  $\text{CH}_3\text{CN}$  or purified by flash chromatography (hexanes–ether (95:5 or 9:1) as an eluent) to yield the compounds **1**, **4**, or **5** (Table 1).

**2-(4-Chlorophenyl)-3-fluoro-4-phenylquinoline (1aa):** Yield 89%; mp 113 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 7.58–7.67 (m, 9H), 7.82 (t, 1H,  $^3J_{\text{H,H}} = 7.5$  Hz), 8.09 (d, 2H,  $^3J_{\text{H,H}} = 8.0$  Hz), 8.19 (d, 1H,  $^3J_{\text{H,H}} = 8.5$  Hz);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  = 125.6 (d,  $^3J_{\text{C,F}} = 5.0$  Hz), 127.7, 128.5, 129.1, 129.2, 129.50, 129.54, 129.9, 130.5, 131.0, 131.40, 131.44, 133.0 (d,  $^2J_{\text{C,F}} = 14.5$  Hz), 134.7 (d,  $^3J_{\text{C,F}} = 5.0$  Hz), 135.2, 145.1 (d,  $^3J_{\text{C,F}} = 3.5$  Hz), 147.3 (d,  $^2J_{\text{C,F}} = 15.9$  Hz), 151.2 (d,  $^1J_{\text{C,F}} = 257.8$  Hz);  $^{19}\text{F}$  NMR (DMSO- $d_6$ )  $\delta$  = –123.1; APCI MS ( $M^+ + 1$ ) = 334. Anal. Calcd for  $\text{C}_{21}\text{H}_{13}\text{ClFN}$ : C, 75.57; H, 3.93; N, 4.20. Found: C, 75.54; H, 3.92; N, 4.22.

**3-Chloro-2-(4-chlorophenyl)-4-phenylquinoline (1ab):** Yield 84%; mp 154 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 7.35 (d, 1H,  $^3J_{\text{H,H}} = 8.3$  Hz), 7.42 (d, 2H,  $^3J_{\text{H,H}} = 7.5$  Hz), 7.54–7.62 (m, 6H), 7.77–7.84 (m, 3H), 8.12 (d, 1H,  $^3J_{\text{H,H}} = 8.3$  Hz);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  = 125.9, 126.2, 127.6, 128.4, 128.5, 129.2, 129.7, 130.6, 131.8, 134.3, 135.6, 138.1, 146.1, 147.2, 156.0; APCI MS ( $M^+ + 1$ ) = 350. Anal. Calcd for  $\text{C}_{21}\text{H}_{13}\text{Cl}_2\text{N}$ : C, 72.02; H, 3.74; N, 4.00. Found: C, 72.04; H, 3.75; N, 4.03.

**3-Bromo-2-(4-chlorophenyl)-4-phenylquinoline (1ac):** Yield 83%; mp 142 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 7.33 (d, 1H,  $^3J_{\text{H,H}} = 8.3$  Hz), 7.39 (d, 2H,  $^3J_{\text{H,H}} = 7.8$  Hz), 7.55–7.62 (m, 6H), 7.72 (d, 2H,  $^3J_{\text{H,H}} = 8.5$  Hz), 7.83 (t, 1H,  $^3J_{\text{H,H}} = 7.8$  Hz), 8.10 (d, 1H,  $^3J_{\text{H,H}} = 8.8$  Hz);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  = 118.2, 126.5, 127.8, 128.4, 128.5, 129.1, 129.2, 129.5, 129.7, 130.8, 131.8, 134.1, 137.9, 139.8, 146.3, 149.9, 157.5; APCI MS ( $M^+ + 1$ ) = 395. Anal. Calcd for  $\text{C}_{21}\text{H}_{13}\text{BrClN}$ : C, 63.91; H, 3.32; N, 3.55. Found: C, 63.85; H, 3.35; N, 3.52.

**3-Chloro-2-methyl-4-phenylquinoline (1ae):** Yield 73%; mp 108 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 2.79 (s, 3H), 7.29 (d, 1H,  $^3J_{\text{H,H}} = 8.4$  Hz), 7.36 (d, 2H,  $^3J_{\text{H,H}} = 7.4$  Hz), 7.51 (t, 1H,  $^3J_{\text{H,H}} = 7.6$  Hz), 7.56–7.61 (m, 3H), 7.76 (t, 1H,  $^3J_{\text{H,H}} = 7.6$  Hz), 8.03 (d, 1H,  $^3J_{\text{H,H}} = 8.4$  Hz);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  = 24.7, 126.0, 127.17, 127.24, 127.3, 128.97, 129.04, 129.6, 129.9, 135.5, 145.4, 145.8, 156.4; APCI MS ( $M^+ + 1$ ) = 254. Anal. Calcd for  $\text{C}_{16}\text{H}_{12}\text{ClN}$ : C, 75.74; H, 4.77; N, 5.52. Found: C, 75.71; H, 4.79; N, 5.54.

**3-Chloro-2-(chloromethyl)-4-phenylquinoline (1af):** Yield 87%; mp 152 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 5.10 (s, 2H), 7.35–7.40 (m, 3H), 7.58–7.64 (m, 4H), 7.84 (t, 1H,  $^3J_{\text{H,H}} = 7.55$  Hz), 8.13 (d, 1H,  $^3J_{\text{H,H}} = 8.5$  Hz);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  = 46.5, 126.2, 126.6, 128.0, 128.8, 129.2, 129.3, 129.5, 129.6, 130.7, 135.0, 145.6, 147.2, 153.8; APCI MS ( $M^+ + 1$ ) = 288. Anal. Calcd for  $\text{C}_{16}\text{H}_{11}\text{Cl}_2\text{N}$ : C, 66.69; H, 3.85; N, 4.86. Found: C, 66.72; H, 3.82; N, 4.81.

**3-Chloro-2-(5-methyl-2-thienyl)-4-phenylquinoline (1ag):** Yield 67%; mp 124 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 2.53 (s, 3H), 6.92 (br s, 1H), 7.24 (d, 1H,  $^3J_{\text{H,H}} = 8.4$  Hz), 7.39 (d, 2H,  $^3J_{\text{H,H}} = 7.6$  Hz), 7.50 (t, 1H,  $^3J_{\text{H,H}} = 7.6$  Hz), 7.56–7.62 (m, 3H), 7.77 (t, 1H,  $^3J_{\text{H,H}} = 7.6$  Hz), 8.00 (m, 2H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  = 15.6, 124.1, 126.2, 126.9, 127.1, 127.8, 129.1, 129.2, 129.6, 130.7, 131.0, 135.7, 140.5, 144.8, 145.7, 147.9, 149.2; APCI MS ( $M^+ + 1$ ) = 336. Anal. Calcd for  $\text{C}_{20}\text{H}_{14}\text{ClNS}$ : C, 71.53; H, 4.20; N, 4.17. Found: C, 71.51; H, 4.23; N, 4.19.

**3-Chloro-4-phenyl-2-(1,2,5-trimethyl-1H-pyrrol-3-yl)quinoline (1ah):** Yield 85%; mp 136 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 2.22 (s, 3H), 2.36 (s, 3H), 3.46 (s, 3H), 6.21 (s, 1H), 7.25 (d, 1H,  $^3J_{\text{H,H}} = 8.3$  Hz), 7.40 (d, 2H,  $^3J_{\text{H,H}} = 7.1$  Hz), 7.47 (t, 1H,  $^3J_{\text{H,H}} = 7.5$  Hz), 7.53–7.61 (m, 3H), 7.73 (t, 1H,  $^3J_{\text{H,H}} = 7.4$  Hz), 7.98 (d, 1H,  $^3J_{\text{H,H}} = 8.3$  Hz);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  = 12.0, 12.9, 30.5, 107.8, 117.8, 126.0, 126.6, 126.7, 126.9, 127.0, 128.8, 129.07, 129.11, 129.3, 129.7, 129.9, 136.3, 146.1, 146.3, 154.7; APCI MS ( $M^+ + 1$ ) = 347. Anal. Calcd for  $\text{C}_{22}\text{H}_{19}\text{ClN}_2$ : C, 76.18; H, 5.52; N, 8.08. Found: C, 76.20; H, 5.49; N, 8.16.

**3-Chloro-2-(4-ethoxyphenyl)-4-phenylquinoline (1ai):** Yield 81%; mp 106 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 1.37 (t, 3H,  $^3J_{\text{H,H}} = 7.1$  Hz), 4.12 (q, 2H,  $^3J_{\text{H,H}} = 7.1$  Hz), 7.07 (d, 2H,  $^3J_{\text{H,H}} = 8.8$  Hz), 7.33 (d, 1H,  $^3J_{\text{H,H}} = 8.3$  Hz), 7.43 (d, 2H,  $^3J_{\text{H,H}} = 7.4$  Hz), 7.56–7.63 (m, 4H), 7.73 (d, 2H,  $^3J_{\text{H,H}} = 8.8$  Hz), 7.81 (t, 1H,  $^3J_{\text{H,H}} = 7.4$  Hz), 8.11 (d, 1H,  $^3J_{\text{H,H}} = 8.3$  Hz);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  = 15.2, 63.7, 114.3, 126.15, 126.23, 127.4, 128.1, 129.1, 129.2, 129.5, 129.7, 130.6, 131.4, 131.6, 135.8, 145.9, 147.3, 156.8, 159.6; APCI MS ( $M^+ + 1$ ) = 360. Anal. Calcd for  $\text{C}_{23}\text{H}_{18}\text{ClNO}$ : C, 76.77; H, 5.04; N, 3.89. Found: C, 76.75; H, 5.06; N, 3.86.

**3-Chloro-2-[1-(4-chlorophenyl)-2,5-dimethyl-1H-pyrrol-3-yl]-4-phenylquinoline (1aj):** Yield 76%; mp 168 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 2.05 (s, 3H), 2.17 (s, 3H), 6.42 (s, 1H), 7.28 (m, 1H), 7.41–7.50 (m, 5H), 7.55–7.66 (m, 5H), 7.75 (m, 1H), 8.01 (m, 1H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  = 11.1, 11.3, 106.3, 116.5, 126.1, 126.7, 126.8, 127.1, 127.3, 128.1, 129.0, 129.14, 129.16, 129.25, 129.29, 129.6, 129.7, 130.1, 132.2, 133.0, 136.2, 146.1, 146.6, 154.1, 166.4; APCI MS ( $M^+ + 1$ ) = 443. Anal. Calcd for  $\text{C}_{27}\text{H}_{20}\text{Cl}_2\text{N}_2$ : C, 73.14; H, 4.55; N, 6.32. Found: C, 73.16; H, 4.58; N, 6.33.

**N-[3-(3-Chloro-4-phenylquinolin-2-yl)-2,5-dimethyl-1H-pyrrol-1-yl]benzamide (1ak):** Yield 73%; mp >300 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 2.14 (s, 3H), 2.27 (s, 3H), 6.33 (s, 1H), 7.28 (d, 1H,  $^3J_{\text{H,H}} = 8.3$  Hz), 7.42 (d, 2H,  $^3J_{\text{H,H}} = 8.0$  Hz), 7.50 (t, 1H,  $^3J_{\text{H,H}} = 7.7$  Hz), 7.55–7.62 (m, 5H), 7.67 (m, 1H), 7.76 (t, 1H,  $^3J_{\text{H,H}} = 7.7$  Hz), 8.03 (m, 3H), 11.50 (s, 1H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  = 12.7, 13.1, 109.2, 119.1, 126.1, 126.7, 127.0, 127.3, 127.4, 128.9, 129.16, 129.21, 129.7, 130.0, 130.1, 130.6, 133.3, 136.2, 137.2, 146.1, 146.5, 154.2; APCI MS ( $M^+ + 1$ ) = 452. Anal. Calcd for  $\text{C}_{28}\text{H}_{22}\text{ClN}_3\text{O}$ : C, 74.41; H, 4.91; N, 9.30. Found: C, 74.44; H, 4.89; N, 9.32.

**2-tert-Butyl-3-chloro-4-phenylquinoline (1al):** Yield 56%; mp 115 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 1.61 (s, 9H), 7.21 (d, 1H,  $^3J_{\text{H,H}} = 8.5$  Hz), 7.36 (d, 2H,  $^3J_{\text{H,H}} = 7.1$  Hz), 7.50–7.60 (m, 4H), 7.76 (t, 1H,  $^3J_{\text{H,H}} = 7.6$  Hz), 8.04 (d, 1H,  $^3J_{\text{H,H}} = 8.3$  Hz);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  = 29.4, 40.5, 125.9, 126.5, 127.24, 127.7, 128.8, 129.1, 129.63, 129.65, 130.0, 136.2, 144.6, 147.8, 163.3; APCI MS ( $M^+ + 1$ ) = 296. Anal. Calcd for  $\text{C}_{19}\text{H}_{18}\text{ClN}$ : C, 77.15; H, 6.13; N, 4.73. Found: C, 77.18; H, 6.11; N, 4.76.

**3-Bromo-2-(4-fluorophenyl)-4-phenylquinoline (1an):** Yield 88%; mp 140 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 7.33–7.38 (m, 3H),

7.40 (d, 2H,  $^3J_{\text{H,H}} = 7.1$  Hz), 7.56–7.63 (m, 4H), 7.77 (m, 2H), 7.84 (t, 1H,  $^3J_{\text{H,H}} = 7.7$  Hz), 8.12 (d, 1H,  $^3J_{\text{H,H}} = 8.5$  Hz);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta = 115.2$  (d,  $^2J_{\text{C,F}} = 21.9$  Hz), 118.4, 126.5, 127.8, 128.4, 129.1, 129.2, 129.5, 129.6, 130.8, 132.1 (d,  $^3J_{\text{C,F}} = 8.5$  Hz), 137.5 (d,  $^4J_{\text{C,F}} = 3.0$  Hz), 137.9, 146.3, 149.8, 157.7, 162.7 (d,  $^1J_{\text{C,F}} = 245.9$  Hz); APCI MS ( $M^+ + 1$ ) = 379. Anal. Calcd for  $\text{C}_{21}\text{H}_{13}\text{BrFN}$ : C, 66.69; H, 3.46; N, 3.70. Found: C, 66.63; H, 3.48; N, 3.73.

**3-Bromo-2-cyclohexyl-4-phenylquinoline (1ao):** Yield 73%; mp 120 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta = 1.33$  (m, 1H), 1.43 (m, 2H), 1.73 (m, 3H), 1.87 (m, 2H), 1.97 (m, 2H), 3.42 (m, 1H), 7.24 (d, 1H,  $^3J_{\text{H,H}} = 8.0$  Hz), 7.32 (d, 2H,  $^3J_{\text{H,H}} = 7.4$  Hz), 7.48 (t, 1H,  $^3J_{\text{H,H}} = 8.0$  Hz), 7.53–7.60 (m, 3H), 7.77 (t, 1H,  $^3J_{\text{H,H}} = 7.6$  Hz), 8.03 (d, 1H,  $^3J_{\text{H,H}} = 8.3$  Hz);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta = 26.2$ , 26.6, 32.0, 45.3, 120.1, 126.3, 127.44, 127.47, 128.9, 129.1, 129.3, 129.5, 130.2, 138.2, 146.2, 148.7, 163.2; APCI MS ( $M^+ + 1$ ) = 367. Anal. Calcd for  $\text{C}_{21}\text{H}_{20}\text{BrN}$ : C, 68.86; H, 5.50; N, 3.82. Found: C, 68.88; H, 5.53; N, 3.85.

**3-Fluoro-2,4-diphenylquinoline (1ap):** Yield 87%; mp 123 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta = 7.53$ –7.62 (m, 10H), 7.78 (t, 1H,  $^3J_{\text{H,H}} = 7.5$  Hz), 8.02 (d, 2H,  $^3J_{\text{H,H}} = 7.7$  Hz), 8.16 (d, 1H,  $^3J_{\text{H,H}} = 8.5$  Hz);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta = 125.5$  (d,  $^3J_{\text{C,F}} = 5.5$  Hz), 127.5, 128.2, 129.0, 129.2, 129.4, 129.6, 129.7, 129.9, 130.2, 130.5, 131.1, 132.8 (d,  $^2J_{\text{C,F}} = 15.0$  Hz), 135.9 (d,  $^3J_{\text{C,F}} = 5.0$  Hz), 145.2 (d,  $^3J_{\text{C,F}} = 4.0$  Hz), 148.7 (d,  $^2J_{\text{C,F}} = 15.9$  Hz), 151.2 (d,  $^1J_{\text{C,F}} = 257.8$  Hz);  $^{19}\text{F}$  NMR (DMSO- $d_6$ )  $\delta = -128.0$ ; APCI MS ( $M^+ + 1$ ) = 300. Anal. Calcd for  $\text{C}_{21}\text{H}_{14}\text{FN}$ : C, 84.26; H, 4.71; N, 4.68. Found: C, 84.24; H, 4.74; N, 4.64.

**2-(4-Chlorophenyl)-3-fluoro-4-methylquinoline (1ba):** Yield 39%; mp 116 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta = 2.64$  (s, 3H), 7.63 (d, 2H,  $^3J_{\text{H,H}} = 8.6$  Hz), 7.69 (t, 1H,  $^3J_{\text{H,H}} = 7.5$  Hz), 7.77 (t, 1H,  $^3J_{\text{H,H}} = 7.3$  Hz), 8.02 (d, 2H,  $^3J_{\text{H,H}} = 8.6$  Hz), 8.08 (d, 1H,  $^3J_{\text{H,H}} = 8.6$  Hz), 8.10 (d, 1H,  $^3J_{\text{H,H}} = 8.3$  Hz);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta = 10.2$  (d,  $^3J_{\text{C,F}} = 6.0$  Hz), 124.6 (d,  $^3J_{\text{C,F}} = 5.0$  Hz), 127.9, 128.55 (d,  $^4J_{\text{C,F}} = 3.0$  Hz), 129.0, 129.1 (d,  $^2J_{\text{C,F}} = 15.0$  Hz), 129.4 (d,  $^4J_{\text{C,F}} = 2.0$  Hz), 130.0, 131.30 (d,  $^4J_{\text{C,F}} = 5.5$  Hz), 134.8 (d,  $^3J_{\text{C,F}} = 5.0$  Hz), 135.0, 144.6 (d,  $^4J_{\text{C,F}} = 3.0$  Hz), 146.6 (d,  $^2J_{\text{C,F}} = 15.9$  Hz), 152.9 (d,  $^1J_{\text{C,F}} = 255.3$  Hz);  $^{19}\text{F}$  NMR (DMSO- $d_6$ )  $\delta = -128.0$ ; APCI MS ( $M^+ + 1$ ) = 272. Anal. Calcd for  $\text{C}_{16}\text{H}_{11}\text{ClFN}$ : C, 70.73; H, 4.08; N, 5.15. Found: C, 70.75; H, 4.11; N, 5.18.

**3-Chloro-2-(4-chlorophenyl)-4-methylquinoline (1bb):** Yield 69%; mp 158 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta = 2.81$  (s, 3H), 7.58 (d, 2H,  $^3J_{\text{H,H}} = 8.5$  Hz), 7.71 (m, 3H), 7.81 (t, 1H,  $^3J_{\text{H,H}} = 7.5$  Hz), 8.03 (d, 1H,  $^3J_{\text{H,H}} = 8.3$  Hz), 8.20 (d, 1H,  $^3J_{\text{H,H}} = 8.5$  Hz);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta = 16.2$ , 125.0, 126.9, 127.8, 128.2, 128.5, 130.0, 130.4, 131.7, 134.1, 138.5, 143.3, 145.5, 155.7; APCI MS ( $M^+ + 1$ ) = 288. Anal. Calcd for  $\text{C}_{16}\text{H}_{11}\text{Cl}_2\text{N}$ : C, 66.69; H, 3.85; N, 4.86. Found: C, 66.72; H, 3.81; N, 4.89.

**3-Chloro-2,4-dimethylquinoline (1be):** Yield 47%; mp 102 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta = 2.74$  (s, 3H), 2.76 (s, 3H), 7.64 (t, 1H,  $^3J_{\text{H,H}} = 7.6$  Hz), 7.76 (t, 1H,  $^3J_{\text{H,H}} = 7.2$  Hz), 7.96 (d, 1H,  $^3J_{\text{H,H}} = 8.4$  Hz), 8.13 (d, 1H,  $^3J_{\text{H,H}} = 8.8$  Hz);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta = 15.8$ , 24.8, 124.9, 127.1, 127.4, 128.5, 129.2, 129.8, 141.4, 145.3, 156.0; APCI MS ( $M^+ + 1$ ) = 192. Anal. Calcd for  $\text{C}_{11}\text{H}_{10}\text{ClN}$ : C, 68.94; H, 5.26; N, 7.31. Found: C, 68.96; H, 5.29; N, 7.28.

**3-Chloro-2-(chloromethyl)-4-methylquinoline (1bf):** Yield 76%; mp 98 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta = 2.79$  (s, 3H), 5.03 (s, 2H), 7.73 (t, 1H,  $^3J_{\text{H,H}} = 7.2$  Hz), 7.83 (t, 1H,  $^3J_{\text{H,H}} = 7.4$  Hz), 8.04 (d, 1H,  $^3J_{\text{H,H}} = 8.3$  Hz), 8.18 (d, 1H,  $^3J_{\text{H,H}} = 8.6$  Hz);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta = 15.8$ , 46.6, 124.8, 127.4, 128.0, 128.4, 129.7, 130.4, 143.2, 145.0, 153.2; APCI MS ( $M^+ + 1$ ) = 226. Anal. Calcd for  $\text{C}_{11}\text{H}_9\text{Cl}_2\text{N}$ : C, 58.43; H, 4.01; N, 6.19. Found: C, 58.46; H, 4.03; N, 6.16.

**3-Chloro-4-methyl-2-phenylquinoline (1bm):** Yield 63%; mp 108 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta = 2.82$  (s, 3H), 7.51 (m, 3H), 7.65–7.72 (m, 3H), 7.80 (t, 1H,  $^3J_{\text{H,H}} = 7.7$  Hz), 8.03 (d, 1H,  $^3J_{\text{H,H}} = 8.3$  Hz), 8.20 (d, 1H,  $^3J_{\text{H,H}} = 8.6$  Hz);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta = 16.3$ , 125.0, 127.1, 127.7, 128.0, 128.4, 129.2, 129.7, 130.0, 130.4, 139.7, 143.1, 145.5, 156.9; APCI MS ( $M^+ + 1$ ) = 254. Anal. Calcd for

$\text{C}_{16}\text{H}_{12}\text{ClN}$ : C, 75.74; H, 4.77; N, 5.52. Found: C, 75.76; H, 4.79; N, 5.54.

**3,6-Dichloro-2,4-diphenylquinoline (1cm):** Yield 89%; mp 122 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta = 7.24$  (br s, 1H), 7.44 (m, 2H), 7.51 (m, 3H), 7.60 (m, 3H), 7.72 (m, 2H), 7.82 (d, 1H,  $^3J_{\text{H,H}} = 8.4$  Hz), 8.13 (d, 1H,  $^3J_{\text{H,H}} = 8.6$  Hz);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta = 124.6$ , 127.3, 128.2, 128.4, 129.3, 129.4, 129.4, 129.6, 129.9, 130.9, 131.9, 132.9, 135.0, 139.0, 144.5, 146.3, 157.6; APCI MS ( $M^+ + 1$ ) = 350. Anal. Calcd for  $\text{C}_{21}\text{H}_{13}\text{Cl}_2\text{N}$ : C, 72.02; H, 3.74; N, 4.00. Found: C, 72.05; H, 3.71; N, 4.03.

**6-Chloro-3-fluoro-2,4-diphenylquinoline (1cp):** Yield 83%; mp 137 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta = 7.49$  (m, 1H), 7.56–7.65 (m, 8H), 7.80 (dd, 1H,  $^3J_{\text{H,H}} = 9.0$  Hz,  $^4J_{\text{H,H}} = 2.2$  Hz), 8.02 (m, 2H), 8.18 (d, 1H,  $^3J_{\text{H,H}} = 9.0$  Hz);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta = 124.1$  (d,  $^3J_{\text{C,F}} = 5.4$  Hz), 128.5, 129.0, 129.4, 129.67, 129.71, 129.8, 130.0, 130.4, 130.5, 132.1, 132.2 (d,  $^2J_{\text{C,F}} = 15.2$  Hz), 132.9, 135.5 (d,  $^3J_{\text{C,F}} = 4.6$  Hz), 143.6 (d,  $^3J_{\text{C,F}} = 3.9$  Hz), 149.3 (d,  $^2J_{\text{C,F}} = 15.8$  Hz), 151.8 (d,  $^1J_{\text{C,F}} = 259.4$  Hz);  $^{19}\text{F}$  NMR (DMSO- $d_6$ )  $\delta = -126.2$ ; APCI MS ( $M^+ + 1$ ) = 334. Anal. Calcd for  $\text{C}_{21}\text{H}_{13}\text{ClFN}$ : C, 75.57; H, 3.93; N, 4.20. Found: C, 75.59; H, 3.96; N, 4.23.

**3-Fluoro-6-nitro-2,4-diphenylquinolinequinoline (1dp):** Yield 80%; mp 205 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta = 7.53$ –7.70 (m, 8H), 8.09 (m, 2H), 8.36 (m, 1H), 8.41 (m, 1H), 8.48 (m, 1H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta = 122.4$  (d,  $^3J_{\text{C,F}} = 5.3$  Hz), 122.8, 126.8, 128.5, 129.1, 129.5, 129.91, 129.95, 130.2, 130.7, 131.1, 131.9, 134.7 (d,  $^2J_{\text{C,F}} = 16.0$  Hz), 135.1 (d,  $^3J_{\text{C,F}} = 4.6$  Hz), 146.1, 147.0 (d,  $^3J_{\text{C,F}} = 3.8$  Hz), 152.1 (d,  $^1J_{\text{C,F}} = 260.9$  Hz), 152.3 (d,  $^2J_{\text{C,F}} = 16.0$  Hz);  $^{19}\text{F}$  NMR (DMSO- $d_6$ )  $\delta = -124.6$ ; APCI MS ( $M^+ + 1$ ) = 345. Anal. Calcd for  $\text{C}_{21}\text{H}_{13}\text{FN}_2\text{O}_2$ : C, 73.25; H, 3.81; N, 8.14. Found: C, 73.27; H, 3.84; N, 8.17.

**3-Chloro-2-(4-chlorophenyl)-4-phenyl-5,6,7,8-tetrahydro-[1]benzothieno[2,3-b]pyridine (5a):** Yield 83%; mp 164 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta = 1.51$  (m, 2H), 1.75 (m, 4H), 2.85 (m, 2H), 7.38 (m, 2H), 7.53 (m, 3H), 7.57 (d, 2H,  $^3J_{\text{H,H}} = 8.3$  Hz), 7.74 (d, 2H,  $^3J_{\text{H,H}} = 8.3$  Hz);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta = 22.4$ , 25.7, 26.2, 34.6, 126.0, 128.1, 128.5, 128.6, 129.1, 129.5, 131.7, 131.9, 134.0, 136.3, 137.7, 140.8, 144.1, 150.8, 158.4; APCI MS ( $M^+ + 1$ ) = 410. Anal. Calcd for  $\text{C}_{23}\text{H}_{17}\text{Cl}_2\text{NS}$ : C, 67.32; H, 4.18; N, 3.41. Found: C, 67.35; H, 4.16; N, 3.44.

**3-Chloro-5,6,7,8-tetrahydro-2,4-diphenyl[1]benzothieno[2,3-b]pyridine (5b):** Yield 79%; mp 158 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta = 1.51$  (m, 2H), 1.74 (m, 4H), 2.84 (m, 2H), 7.38 (m, 2H), 7.48–7.53 (m, 6H), 7.70 (d, 2H,  $^3J_{\text{H,H}} = 7.6$  Hz);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta = 22.4$ , 25.8, 26.2, 34.6, 126.0, 128.0, 128.4, 128.6, 129.0, 129.5, 129.9, 131.4, 136.5, 139.0, 140.4, 144.0, 152.1, 158.4; APCI MS ( $M^+ + 1$ ) = 376. Anal. Calcd for  $\text{C}_{23}\text{H}_{18}\text{ClNS}$ : C, 73.49; H, 4.83; N, 3.73. Found: C, 73.47; H, 4.86; N, 3.76.

**3-Chloro-2-(chloromethyl)-5,6,7,8-tetrahydro-4-phenyl-1]benzothieno[2,3-b]pyridine (5c):** Yield 83%; mp 124 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta = 1.49$  (m, 2H), 1.74 (m, 4H), 2.84 (m, 2H), 5.01 (s, 1H), 7.33 (m, 2H), 7.53 (m, 3H);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta = 22.3$ , 22.4, 25.8, 26.3, 46.3, 127.4, 128.2, 128.6, 129.2, 129.4, 132.5, 135.8, 141.4, 144.0, 148.8, 157.9; APCI MS ( $M^+ + 1$ ) = 348. Anal. Calcd for  $\text{C}_{18}\text{H}_{15}\text{Cl}_2\text{NS}$ : C, 62.07; H, 4.34; N, 4.02. Found: C, 62.09; H, 4.37; N, 4.06.

**2-(4-Chlorophenyl)-3-fluoro-5,6,7,8-tetrahydro-4-phenyl-1]benzothieno[2,3-b]pyridine (5d):** Yield 79%; mp 143 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta = 1.54$  (m, 2H), 1.76 (m, 2H), 1.88 (m, 2H), 2.86 (m, 2H), 7.48 (m, 2H), 7.55 (m, 3H), 7.59 (d, 2H,  $^3J_{\text{H,H}} = 8.6$  Hz), 7.99 (d, 2H,  $^3J_{\text{H,H}} = 7.8$  Hz);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta = 22.4$ , 22.5, 26.0, 26.3, 128.3 (d,  $^3J_{\text{C,F}} = 3.5$  Hz), 128.5, 129.0, 129.3, 130.1, 130.8 (d,  $^3J_{\text{C,F}} = 6.4$  Hz), 131.8, 132.6 (d,  $^2J_{\text{C,F}} = 19.4$  Hz), 134.3 (d,  $^3J_{\text{C,F}} = 5.0$  Hz), 134.5, 140.2 (d,  $^2J_{\text{C,F}} = 16.4$  Hz), 141.5, 152.9 (d,  $^1J_{\text{C,F}} = 250.3$  Hz), 155.8 (d,  $^4J_{\text{C,F}} = 3$  Hz);  $^{19}\text{F}$  NMR (DMSO- $d_6$ )  $\delta = -129.8$ ; APCI MS ( $M^+ + 1$ ) = 394. Anal. Calcd for  $\text{C}_{23}\text{H}_{17}\text{ClFNS}$ : C, 70.13; H, 4.35; N, 3.56. Found: C, 70.16; H, 4.38; N, 3.58.

**3-Fluoro-5,6,7,8-tetrahydro-2,4-diphenyl[1]benzothieno[2,3-b]pyridine (5e):** Yield 75%; mp 118 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  = 1.51 (m, 2H), 1.73 (m, 2H), 1.85 (m, 2H), 2.83 (m, 2H), 7.46–7.51 (m, 8H), 7.93 (d, 2H,  $^3J_{\text{H,H}} = 7.1$  Hz);  $^{13}\text{C}$  NMR (DMSO- $d_6$ )  $\delta$  = 22.4, 22.5, 26.1, 26.3, 128.4 (d,  $^3J_{\text{C,F}} = 3.5$  Hz), 128.5, 129.0, 129.2 (d,  $^3J_{\text{C,F}} = 6$  Hz), 129.3, 129.6, 130.1, 131.5, 132.0, 132.6 (d,  $^2J_{\text{C,F}} = 18.9$  Hz), 135.5 (d,  $^3J_{\text{C,F}} = 5$  Hz), 141.2, 141.7 (d,  $^2J_{\text{C,F}} = 16.5$  Hz), 152.5 (d,  $^1J_{\text{C,F}} = 249.3$  Hz), 155.7 (d,  $^4J_{\text{C,F}} = 3$  Hz);  $^{19}\text{F}$  NMR (DMSO- $d_6$ )  $\delta$  = -134.9; APCI MS ( $M^+ + 1$ ) = 360. Anal. Calcd for  $\text{C}_{23}\text{H}_{18}\text{FN}$ : C, 76.78; H, 5.04; N, 3.90. Found: C, 76.23, H, 5.05; N, 3.86.

## ASSOCIATED CONTENT

**S Supporting Information.** Characterization data of products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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