

# Green synthesis of polysubstituted quinoline and benzoquinoline derivatives in ionic liquid via a three-component reaction

Yong Sun · Pei-Jun Cai · Xiang-Shan Wang

Received: 30 March 2014 / Accepted: 20 September 2014  
© Springer Science+Business Media Dordrecht 2014

**Abstract** A three-component reaction of aldehyde, (*E*)-3-aminobut-2-enenitrile and dimedone in ionic liquids, gave 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-arylquinoline-3-carbonitrile derivatives at 50 °C. Using 2-hydroxynaphthalene-1,4-dione to replace dimedone at the same reaction conditions resulted in another series of polysubstituted benzo[*h*]quinoline derivatives in high yields. This method involves the advantages of mild conditions, high yields, one-pot synthesis, and an environmentally benign procedure.

**Keywords** Quinoline · Three-component reaction · Ionic liquids · Synthesis

## Introduction

Quinolines are a very important class of alkaloids with a wide range of pharmacological and biological activities, such as antimicrobial [1], antiproliferative [2], and antituberculosis activities [3]. It has been reported that some of them were used as DNA methylation modulators for the treatment of cancer and hematological disorders [4], and as antimalarial agents in the treatment of malarial infections [5]. Quinidine is a well-known example of quinoline alkaloids (Fig. 1, left) [6], a pharmaceutical agent that acts as a class I antiarrhythmic agent (Ia) in the

---

Y. Sun · P.-J. Cai (✉)

School of Chemical Engineering and Technology, China University of Mining and Technology, Xuzhou 221116, Jiangsu, People's Republic of China  
e-mail: pjcai@cumt.edu.cn

X.-S. Wang (✉)

School of Chemistry and Chemical Engineering, Jiangsu Key Laboratory of Green Synthesis for Functional Materials, Jiangsu Normal University, Xuzhou 221116, Jiangsu, People's Republic of China  
e-mail: xswang1974@yahoo.com

heart. It is widely used for treatment of life-threatening *Plasmodium falciparum* malaria and ventricular arrhythmias. Another important drug is Chloroquine (Fig. 1, right) [7]; it was discovered in 1934 by Hans Andersag and coworkers at the laboratories of Bayer. The United States government-sponsored clinical trials for antimalarial drug development showed unequivocally that chloroquine has a significant therapeutic value as an antimalarial drug. Accordingly, novel strategies for the synthesis of quinolines continued to receive considerable attention in the field of organic synthetics chemistry [8–13].

Ionic liquids have attracted increasing interest in the context of green chemistry in the past few years. They were initially introduced as alternative green reaction media because of their unique chemical and physical properties of nonvolatility, nonflammability, thermal stability, and controlled miscibility [14, 15]. The possibility of recycling them also ensured their utility in organic synthesis as green solvents for a large number of organic transformations [16].

As a continuation of our research devoted to the development of new methods for the preparation of heterocycles in ionic liquids [17–21], we would like to report the synthesis of 4-arylquinoline-3-carbonitrile and 4-arylbenzo[*h*]quinoline-3-carbonitrile derivatives under catalyst-free conditions. The method involved a three-component reaction of aldehyde, (*E*)-3-aminobut-2-enenitrile and dimedone or 2-hydroxynaphthalene-1,4-dione in ionic liquids.

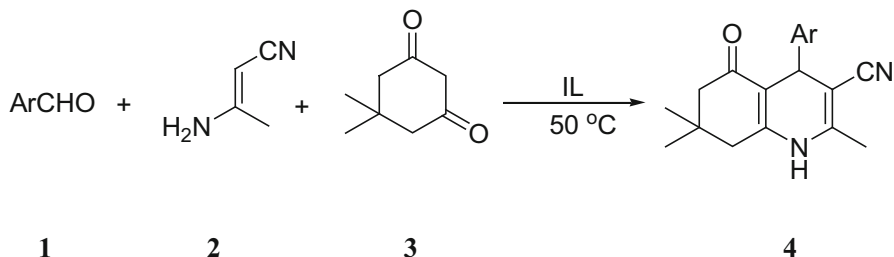
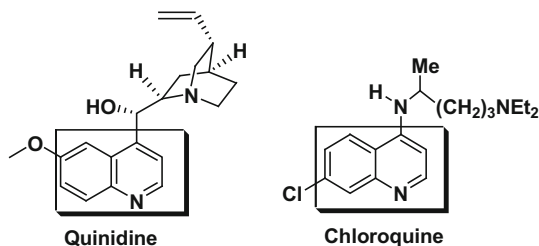
## Results and discussion

Treatment of aldehyde **1**, (*E*)-3-aminobut-2-enenitrile **2**, and 5,5-dimethyl-1,3-cyclohex-2-ene (dimedone) **3** in ionic liquid [BMIm]Br at 50 °C, resulted in the corresponding 1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxo-4-arylquinoline-3-carbonitrile derivatives **4a–k** in high yields (Scheme 1).

Using the conversion of benzaldehyde **1a**, (*E*)-3-aminobut-2-enenitrile **2** and **3** as a model reaction, different temperatures and ionic liquids were explored to obtain an optimal condition, as shown in Table 1. The product **4a** was not detected in ionic liquids at room temperature (Table 1, Entry 1), and was obtained successfully in higher reaction temperature, reaching a maximum of 92 % yield at 50°C (Table 1, entries 2–4). Different imidazolium ionic liquids were also tested, and [BMIm]Br appeared to be the best solvent for this transformation (entry 3 vs. 5–9). Acidic ionic liquids, such as [BMIm][HSO<sub>4</sub>], or acidic catalysts, for example, TsOH and AgOTf, were used to further improve the yields of the product **4a**, to our disappointed, the results are not good (Table 1, entries 10–12).

After reaction completion as monitored by TLC, products were isolated by simple filtration after the addition of a small amount of water to the cooled reaction mixture. Water in the filtrate was removed by distillation under reduced pressure, and the [BMIm]Br in the residue could be reused after being evaporated at 80°C for 4 h in vacuum. Successive reuse of the recycled ionic liquid of [BMIm]Br in the model reaction gave high yields of **4a** (90 %) even after the fourth cycle.

Subsequently, the optimized conditions were applied for the conversion of various kinds of aldehydes into the corresponding 4-arylquinoline-3-carbonitrile

**Fig. 1** The interesting drugs containing quinoline analogues**Scheme 1** The reaction of **1**, **2**, and **3****Table 1** Synthetic results of **4a** under different reaction conditions

Entry	Temp./°C	Ionic liquid <sup>a</sup>	Yield/% <sup>b</sup>
1	r.t.	[BMIm]Br	trace
2	50	[BMIm]Br	92
3	80	[BMIm]Br	87
4	100	[BMIm]Br	85
5	50	[EMIm]Br	84
6	50	[PMIm]Br	82
7	50	[EMIm][BF <sub>4</sub> ]	86
8	50	[PMIm][BF <sub>4</sub> ]	86
9	50	[BMIm][BF <sub>4</sub> ]	88
10	50	[BMIm][HSO <sub>4</sub> ]	72
11	50	[BMIm]Br/TsOH <sup>c</sup>	68
12	50	[BMIm]Br/AgOTf <sup>c</sup>	82

Reaction condition: 2 ml solvent, **1a** (102 mg, 1.0 mmol), **2** (84 mg, 1.0 mmol) and **3** (144 mg, 1.0 mmol)

<sup>a</sup> BMIm = 1-butyl-3-methylimidazolium; EMIm = 1-ethyl-3-methylimidazolium; PMIm = 1-propyl-3-methylimidazolium

<sup>b</sup> Isolated yields

<sup>c</sup> TsOH or AgOTf 0.05 mmol

analogues **4a–k** in high yields (Table 2, entries 1–11). The results are summarized in Table 2. It is observed that the process can tolerate both electron-donating (alkyl and alkoxy) and electron-withdrawing (halogen) substituents in the benzaldehydes. In all cases, the reactions proceeded efficiently at 50°C under mild conditions to afford the corresponding products in high yields.

In our continued study, it was found that 2-hydroxynaphthalene-1,4-dione **5** also gave the satisfied results, if it was used as an 1,3-dicarbonyl compound to react with **1** and **2** under the same reaction conditions (Scheme 2), and resulted another series

**Table 2** Synthetic results of **4a–k** in ionic liquids

Entry	Ar	Time (h)	Products	Yields (%) <sup>a</sup>
1	C <sub>6</sub> H <sub>5</sub>	8	<b>4a</b>	92
2	2-ClC <sub>6</sub> H <sub>4</sub>	6	<b>4b</b>	90
3	4-ClC <sub>6</sub> H <sub>4</sub>	8	<b>4c</b>	89
4	4-BrC <sub>6</sub> H <sub>4</sub>	9	<b>4d</b>	89
5	4-CNC <sub>6</sub> H <sub>4</sub>	6	<b>4e</b>	93
6	4-MeC <sub>6</sub> H <sub>4</sub>	10	<b>4f</b>	87
7	2-MeOC <sub>6</sub> H <sub>4</sub>	12	<b>4g</b>	86
8	2,3-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	6	<b>4h</b>	90
9	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	8	<b>4i</b>	90
10	3,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	8	<b>4j</b>	86
11	3,5-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	10	<b>4k</b>	88

Reaction condition: 2 ml [BMIm]Br, **1** (1.0 mmol), **2** (82 mg, 1.0 mmol), **3** (144 mg, 1.0 mmol) and 50 °C

<sup>a</sup> Isolated yields

of novel 1,4,5,6-tetrahydro-2-methyl-5,6-dioxo-4-arylbenzo[*h*]quinoline-3-carbonitriles **6** in high yields (Table 3). All the products of **4a–k** and **6a–k** were characterized by <sup>1</sup>H NMR, IR and HRMS, and the data were in good agreement with the preconceived structures.

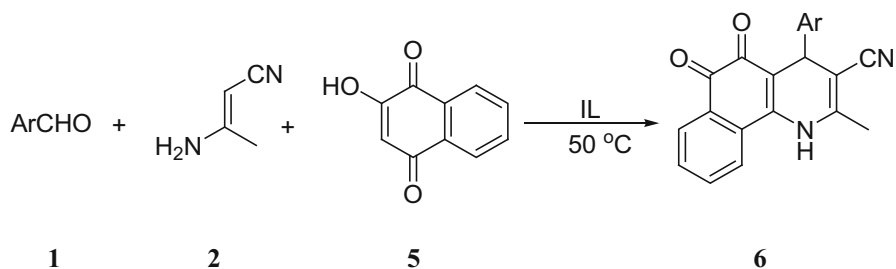
According to the product structures of **4** and **6**, we think that subsequent Knoevenagel condensation, Michael addition, intra-molecular cyclization, and dehydration reaction may take place; the possible reaction mechanism is outlined in Scheme 3.

## Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Tensor 27 spectrometer in KBr pellet. NMR spectra were obtained from a solution in DMSO-*d*<sub>6</sub> or CDCl<sub>3</sub> with Me<sub>4</sub>Si as internal standard using a Bruker-400 spectrometer. HRMS analyses were carried out using a Bruker-micro-TOF-Q-MS analyzer.

General procedure for the synthesis of quinoline and benzo[*h*]quinoline derivatives **4** and **6**

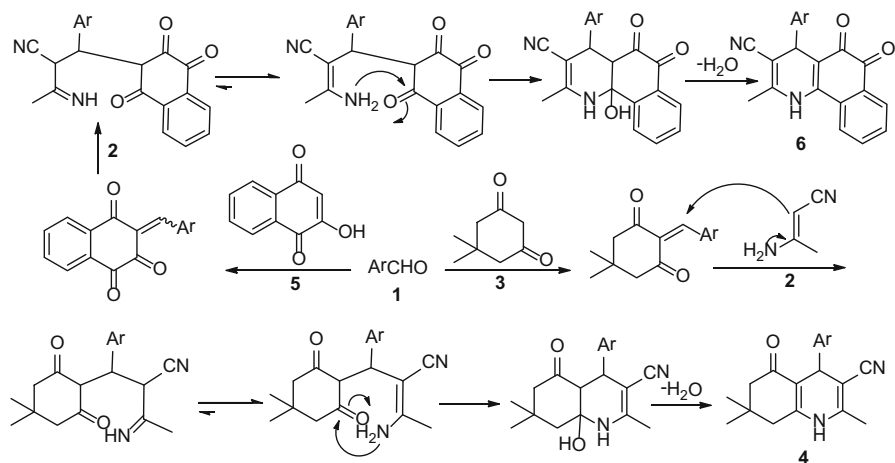
A dry 50-ml flask was charged with aldehyde **1** (1.0 mmol), (*E*)-3-aminobut-2-enenitrile **2** (82 mg, 1.0 mmol), dimedone (144 mg, 1.0 mmol) **3** or 2-hydroxy-naphthalene-1,4-dione **5** (174 mg, 1.0 mmol) and ionic liquid [BMIm]Br (2 ml). The reaction mixture was stirred at 50 °C for 6–14 h, and then a small amount of water (5 ml) was added to the mixture, and the generated yellow solid was filtered off. The water in the filtrate was removed by distillation under reduced pressure, and the ionic liquid in the residue could be reusable by being evaporated at 80 °C for 4 h at vacuum. The crude yellow products were washed with water and purified by

**Scheme 2** Reaction of **1**, **3**, and **5****Table 3** Synthetic results of **6a–k** in ionic liquids

Entry	Ar	Time (h)	Products	Yields (%) <sup>a</sup>
1	C <sub>6</sub> H <sub>5</sub>	10	<b>6a</b>	86
2	4-ClC <sub>6</sub> H <sub>4</sub>	12	<b>6b</b>	90
3	4-FC <sub>6</sub> H <sub>4</sub>	10	<b>6c</b>	84
4	4-BrC <sub>6</sub> H <sub>4</sub>	14	<b>6d</b>	89
5	4-CNC <sub>6</sub> H <sub>4</sub>	8	<b>6e</b>	86
6	4-MeC <sub>6</sub> H <sub>4</sub>	9	<b>6f</b>	90
7	4-MeOC <sub>6</sub> H <sub>4</sub>	9	<b>6g</b>	85
8	2,3-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	8	<b>6h</b>	86
9	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	8	<b>6i</b>	82
10	3,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	8	<b>6j</b>	85
11	3,5-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	12	<b>6k</b>	90

Reaction condition: 2 ml [BMIm]Br, **1** (1.0 mmol), **2** (82 mg, 1.0 mmol), **5** (174 mg, 1.0 mmol) and 50 °C

<sup>a</sup> Isolated yields

**Scheme 3** The possible reaction mechanism

recrystallization from 95 % EtOH, then dried at 80 °C for 2 h under vacuum to give **4** or **6**.

1,4,5,6,7,8-Hexahydro-2,7,7-trimethyl-5-oxo-4-phenylquinoline-3-carbonitrile **4a**: M. p. 236–238 °C, (Lit [22]: 232–234 °C);  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta_{\text{H}}$  0.92 (s, 3H, CH<sub>3</sub>), 1.02 (s, 3H, CH<sub>3</sub>), 1.99 (d,  $J$  = 16.4 Hz, 1H, CH), 2.06 (s, 3H, CH<sub>3</sub>), 2.18 (d,  $J$  = 16.4 Hz, 1H, CH), 2.34 (d,  $J$  = 17.2 Hz, 1H, CH), 2.43 (d,  $J$  = 17.2 Hz, 1H, CH), 4.41 (s, 1H, CH), 7.17–7.20 (m, 3H, ArH), 7.27–7.31 (m, 2H, ArH), 9.44 (s, 1H, NH).  $^{13}\text{C}$  NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta_{\text{C}}$  18.4, 27.5, 29.3, 32.6, 38.4, 41.1, 50.6, 89.0, 109.7, 119.2, 127.1, 127.5, 128.6, 144.4, 144.7, 148.4, 195.4. IR (KBr):  $\nu$  3,288, 3,072, 2,962, 2,930, 2,885, 2,811, 2,751, 2,204, 1,659, 1,608, 1,490, 1,469, 1,382, 1,341, 1,319, 1,260, 1,148  $\text{cm}^{-1}$ . HRMS (ESI,  $m/z$ ): Calcd for C<sub>19</sub>H<sub>19</sub>N<sub>2</sub>O [M–H]<sup>–</sup> 291.1498, found 291.1499.

4-(2-chlorophenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carbonitrile **4b**: M. p. 245–247 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta_{\text{H}}$  0.94 (s, 3H, CH<sub>3</sub>), 1.03 (s, 3H, CH<sub>3</sub>), 1.99 (d,  $J$  = 16.0 Hz, 1H, CH), 2.03 (s, 3H, CH<sub>3</sub>), 2.17 (d,  $J$  = 16.0 Hz, 1H, CH), 2.33 (d,  $J$  = 17.2 Hz, 1H, CH), 2.44 (d,  $J$  = 17.2 Hz, 1H, CH), 4.74 (s, 1H, CH), 7.09–7.24 (m, 4H, ArH), 9.50 (s, 1H, NH). IR (KBr):  $\nu$  3,240, 3,189, 3,077, 2,962, 2,931, 2,895, 2,880, 2,203, 1,660, 1,607, 1,489, 1,471, 1,457, 1,435, 1,383, 1,261, 1,222, 1,149, 751  $\text{cm}^{-1}$ . HRMS (ESI,  $m/z$ ): Calcd for C<sub>19</sub>H<sub>18</sub>ClN<sub>2</sub>O [M–H]<sup>–</sup> 325.1108, found 325.1098.

4-(4-Chlorophenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carbonitrile **4c**: M. p. 253–255 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta_{\text{H}}$  0.91 (s, 3H, CH<sub>3</sub>), 1.02 (s, 3H, CH<sub>3</sub>), 2.01 (d,  $J$  = 16.4 Hz, 1H, CH), 2.07 (s, 3H, CH<sub>3</sub>), 2.18 (d,  $J$  = 16.4 Hz, 1H, CH), 2.33 (d,  $J$  = 17.2 Hz, 1H, CH), 2.42 (d,  $J$  = 17.2 Hz, 1H, CH), 4.44 (s, 1H, CH), 7.20 (d,  $J$  = 8.4 Hz, 2H, ArH), 7.36 (d,  $J$  = 8.4 Hz, 2H, ArH), 9.50 (s, 1H, NH).  $^{13}\text{C}$  NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta_{\text{C}}$  18.5, 27.4, 29.2, 32.6, 38.0, 41.2, 50.5, 88.7, 109.6, 118.9, 128.7, 129.0, 132.8, 143.2, 144.5, 147.9, 195.1. IR (KBr):  $\nu$  3,242, 3,190, 3,078, 2,961, 2,881, 2,810, 2,749, 2,360, 2,200, 1,658, 1,610, 1,491, 1,435, 1,391, 1,317, 1,258, 1,147, 1,126, 1,089, 1,015, 972, 847  $\text{cm}^{-1}$ . HRMS (ESI,  $m/z$ ): Calcd for C<sub>19</sub>H<sub>18</sub>ClN<sub>2</sub>O [M–H]<sup>–</sup> 325.1108, found 325.1095.

4-(4-Bromophenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carbonitrile **4d**: M. p. 204–206 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta_{\text{H}}$  0.91 (s, 3H, CH<sub>3</sub>), 1.02 (s, 3H, CH<sub>3</sub>), 2.01 (d,  $J$  = 16.4 Hz, 1H, CH), 2.06 (s, 3H, CH<sub>3</sub>), 2.18 (d,  $J$  = 16.4 Hz, 1H, CH), 2.33 (d,  $J$  = 17.2 Hz, 1H, CH), 2.42 (d,  $J$  = 17.2 Hz, 1H, CH), 4.42 (s, 1H, CH), 7.14 (d,  $J$  = 8.4 Hz, 2H, ArH), 7.49 (d,  $J$  = 8.4 Hz, 2H, ArH), 9.50 (s, 1H, NH).  $^{13}\text{C}$  NMR (CDCl<sub>3</sub>, 100 MHz):  $\delta_{\text{C}}$  18.3, 27.4, 29.2, 32.6, 38.1, 40.8, 50.6, 88.2, 109.1, 119.2, 121.0, 129.3, 131.7, 143.9, 145.2, 149.1, 195.7. IR (KBr):  $\nu$  3,306, 3,226, 3,096, 2,960, 2,880, 2,811, 2,197, 1,657, 1,638, 1,496, 1,434, 1,394, 1,365, 1,316, 1,258, 1,198, 1,166, 1,144, 1,129, 1,067, 1,010, 975, 843  $\text{cm}^{-1}$ . HRMS (ESI,  $m/z$ ): Calcd for C<sub>19</sub>H<sub>20</sub>BrN<sub>2</sub>O [M + H]<sup>+</sup> 371.0759, found 371.0593.

4-(4-Cyanophenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carbonitrile **4e**: M. p. 251–253 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta_{\text{H}}$  0.91 (s, 3H, CH<sub>3</sub>), 1.02 (s, 3H, CH<sub>3</sub>), 2.02 (d,  $J$  = 16.4 Hz, 1H, CH), 2.08 (s, 3H, CH<sub>3</sub>), 2.18 (d,  $J$  = 16.4 Hz, 1H, CH), 2.35 (d,  $J$  = 17.2 Hz, 1H, CH), 2.43 (d,  $J$  = 17.2 Hz, 1H, CH), 4.55 (s, 1H, CH), 7.39 (d,  $J$  = 8.0 Hz, 2H, ArH), 7.78 (d,  $J$  = 8.0 Hz, 2H,

ArH), 9.57 (s, 1H, NH). IR (KBr):  $\nu$  3,249, 3,158, 3,073, 2,959, 2,931, 2,884, 2,809, 2,749, 2,229, 2,198, 1,656, 1,617, 1,492, 1,433, 1,422, 1,394, 1,380, 1,317, 1,260, 1,146, 1,124, 1,019, 854  $\text{cm}^{-1}$ . HRMS (ESI,  $m/z$ ): Calcd for  $\text{C}_{20}\text{H}_{18}\text{N}_3\text{O}$   $[\text{M}-\text{H}]^-$  316.145, found 316.1457.

1,4,5,6,7,8-Hexahydro-2,7,7-trimethyl-5-oxo-4-*p*-tolylquinoline-3-carbonitrile **4f**: M. p. 234–236 °C;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz):  $\delta_{\text{H}}$  0.91 (s, 3H,  $\text{CH}_3$ ), 1.02 (s, 3H,  $\text{CH}_3$ ), 1.99 (d,  $J = 16.0$  Hz, 1H, CH), 2.05 (s, 3H,  $\text{CH}_3$ ), 2.17 (d,  $J = 16.0$  Hz, 1H, CH), 2.25 (s, 3H,  $\text{CH}_3$ ), 2.32 (d,  $J = 16.8$  Hz, 1H, CH), 2.42 (d,  $J = 16.8$  Hz, 1H, CH), 4.36 (s, 1H, CH), 7.05 (d,  $J = 8.0$  Hz, 2H, ArH), 7.08 (d,  $J = 8.0$  Hz, 2H, ArH), 9.42 (s, 1H, NH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta_{\text{C}}$  18.2, 21.1, 27.4, 29.3, 32.6, 38.0, 40.8, 50.7, 88.8, 109.4, 119.5, 127.3, 129.3, 136.6, 142.0, 144.7, 149.1, 195.8. IR (KBr):  $\nu$  3,241, 3,193, 3,079, 2,963, 2,930, 2,881, 2,199, 1,660, 1,607, 1,491, 1,470, 1,435, 1,381, 1,316, 1,258, 1,147, 1,020, 839, 731  $\text{cm}^{-1}$ . HRMS (ESI,  $m/z$ ): Calcd for  $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}$   $[\text{M}-\text{H}]^-$  305.1654, found 305.1654.

1,4,5,6,7,8-Hexahydro-4-(2-methoxyphenyl)-2,7,7-trimethyl-5-oxoquinoline-3-carbonitrile **4g**: M. p. 255–257 °C;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz):  $\delta_{\text{H}}$  0.98 (s, 3H,  $\text{CH}_3$ ), 1.03 (s, 3H,  $\text{CH}_3$ ), 1.99 (s, 3H,  $\text{CH}_3$ ), 1.98 (d,  $J = 16.0$  Hz, 1H, CH), 2.17 (d,  $J = 16.0$  Hz, 1H, CH), 2.34 (d,  $J = 17.2$  Hz, 1H, CH), 2.44 (d,  $J = 17.2$  Hz, 1H, CH), 3.78 (s, 3H,  $\text{CH}_3\text{O}$ ), 4.84 (s, 1H, CH), 6.84–6.87 (m, 1H, ArH), 6.96 (d,  $J = 8.0$  Hz, 1H, ArH), 7.00 (dd,  $J = 8.0$  Hz,  $J' = 1.6$  Hz, 1H, ArH), 7.13–7.17 (m, 1H, ArH), 9.33 (s, 1H, NH). IR (KBr):  $\nu$  3,299, 3,262, 3,230, 3,097, 2,970, 2,955, 2,938, 2,899, 2,198, 1,657, 1,609, 1,499, 1,460, 1,434, 1,382, 1,316, 1,257, 1,163, 1,147, 1,138, 1,100, 1,014, 764  $\text{cm}^{-1}$ . HRMS (ESI,  $m/z$ ): Calcd for  $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_2$   $[\text{M}-\text{H}]^-$  321.1602, found 321.1614.

4-(2,3-Dichlorophenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carbonitrile **4g**: M. p. >300 °C;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz):  $\delta_{\text{H}}$  0.95 (s, 3H,  $\text{CH}_3$ ), 1.03 (s, 3H,  $\text{CH}_3$ ), 1.98 (d,  $J = 16.0$  Hz, 1H, CH), 2.04 (s, 3H,  $\text{CH}_3$ ), 2.17 (d,  $J = 16.0$  Hz, 1H, CH), 2.35 (d,  $J = 16.8$  Hz, 1H, CH), 2.44 (d,  $J = 16.8$  Hz, 1H, CH), 5.05 (s, 1H, CH), 7.22 (dd,  $J = 8.0$  Hz,  $J' = 1.2$  Hz, 1H, ArH), 7.32 (t,  $J = 8.0$  Hz, 1H, ArH), 7.48 (dd,  $J = 8.0$  Hz,  $J' = 1.2$  Hz, 1H, ArH), 9.87 (s, 1H, NH). IR (KBr):  $\nu$  3,284, 3,236, 3,104, 2,962, 2,957, 2,914, 2,868, 2,193, 1,650, 1,502, 1,447, 1,421, 1,377, 1,321, 1,305, 1,258, 1,153, 1,137, 1,041, 766, 713  $\text{cm}^{-1}$ . HRMS (ESI,  $m/z$ ): Calcd for  $\text{C}_{19}\text{H}_{17}\text{Cl}_2\text{N}_2\text{O}$   $[\text{M} - \text{H}]^-$  359.0718, found 359.0718.

4-(2,4-Dichlorophenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carbonitrile **4i**: M. p. 253–255 °C;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz):  $\delta_{\text{H}}$  0.95 (s, 3H,  $\text{CH}_3$ ), 1.02 (s, 3H,  $\text{CH}_3$ ), 1.98 (d,  $J = 16.4$  Hz, 1H, CH), 2.03 (s, 3H,  $\text{CH}_3$ ), 2.17 (d,  $J = 16.4$  Hz, 1H, CH), 2.34 (d,  $J = 17.2$  Hz, 1H, CH), 2.44 (d,  $J = 17.2$  Hz, 1H, CH), 4.95 (s, 1H, CH), 7.25 (d,  $J = 8.4$  Hz, 1H, ArH), 7.39 (dd,  $J = 8.4$  Hz,  $J' = 2.0$  Hz, 1H, ArH), 7.53 (d,  $J = 2.0$  Hz, 1H, ArH), 9.55 (s, 1H, NH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta_{\text{C}}$  18.4, 27.5, 29.2, 32.5, 36.4, 41.0, 50.4, 87.3, 108.8, 118.6, 127.4, 129.8, 131.6, 133.3, 133.7, 140.3, 145.1, 149.0, 195.1. IR (KBr):  $\nu$  3,185, 3,075, 2,960, 2,936, 2,888, 2,870, 2,810, 2,204, 1,658, 1,604, 1,501, 1,470, 1,435, 1,381, 1,316, 1,259, 1,148, 1,131, 1,100, 1,045, 848, 839  $\text{cm}^{-1}$ . HRMS (ESI,  $m/z$ ): Calcd for  $\text{C}_{19}\text{H}_{17}\text{Cl}_2\text{N}_2\text{O}$   $[\text{M}-\text{H}]^-$  359.0718, found 359.0716.

4-(3,4-Dichlorophenyl)-1,4,5,6,7,8-hexahydro-2,7,7-trimethyl-5-oxoquinoline-3-carbonitrile **4j**: M. p. 231–233 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta_{\text{H}}$  0.92 (s, 3H,  $\text{CH}_3$ ), 1.02 (s, 3H,  $\text{CH}_3$ ), 2.03 (d,  $J = 16.0$  Hz, 1H, CH), 2.08 (s, 3H,  $\text{CH}_3$ ), 2.18 (d,  $J = 16.0$  Hz, 1H, CH), 2.35 (d,  $J = 16.8$  Hz, 1H, CH), 2.42 (d,  $J = 16.8$  Hz, 1H, CH), 4.49 (s, 1H, CH), 7.19 (dd,  $J = 8.4$  Hz,  $J' = 2.0$  Hz, 1H, CH), 7.39 (d,  $J = 2.0$  Hz, 1H, ArH), 7.58 (d,  $J = 8.4$  Hz, 1H, ArH), 9.56 (s, 1H, NH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz):  $\delta_{\text{C}}$  18.6, 27.5, 29.1, 32.7, 38.0, 41.2, 50.5, 88.3, 109.3, 118.7, 127.2, 129.5, 130.5, 131.1, 132.7, 144.7, 144.8, 148.1, 195.1. IR (KBr):  $\nu$  3,190, 3,079, 2,963, 2,936, 2,885, 2,810, 2,750, 2,360, 2,341, 2,207, 1,659, 1,609, 1,490, 1,437, 1,392, 1,351, 1,319, 1,259, 1,147, 1,129, 1,032, 876, 829  $\text{cm}^{-1}$ . HRMS (ESI,  $m/z$ ): Calcd for  $\text{C}_{19}\text{H}_{17}\text{Cl}_2\text{N}_2\text{O}$   $[\text{M}-\text{H}]^+$  359.0718, found 359.0704.

1,4,5,6,7,8-Hexahydro-4-(3,5-dimethoxyphenyl)-2,7,7-trimethyl-5-oxoquinoline-3-carbonitrile **4k**: M. p. 241–243 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta_{\text{H}}$  0.96 (s, 3H,  $\text{CH}_3$ ), 1.03 (s, 3H,  $\text{CH}_3$ ), 2.02–2.06 (m, 4H, CH +  $\text{CH}_3$ ), 2.19 (d,  $J = 16.4$  Hz, 1H, CH), 2.34 (d,  $J = 16.8$  Hz, 1H, CH), 2.44 (d,  $J = 16.8$  Hz, 1H, CH), 3.70 (s, 6H,  $2\text{CH}_3\text{O}$ ), 4.34 (s, 1H, CH), 6.29 (d,  $J = 2.0$  Hz, 2H, ArH), 6.35 (d,  $J = 2.0$  Hz, 1H, ArH), 9.43 (s, 1H, NH). IR (KBr):  $\nu$  3,291, 3,265, 3,233, 3,097, 2,954, 2,840, 2,196, 1,657, 1,610, 1,496, 1,469, 1,431, 1,379, 1,315, 1,257, 1,199, 1,157, 1,065, 858, 709  $\text{cm}^{-1}$ . HRMS (ESI,  $m/z$ ): Calcd for  $\text{C}_{21}\text{H}_{23}\text{N}_2\text{O}_3$   $[\text{M} - \text{H}]^+$  351.1709, found 351.1712.

1,4,5,6-Tetrahydro-2-methyl-5,6-dioxo-4-phenylbenzo[*h*]quinoline-3-carbonitrile **6a**: M. p. 256–258 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta_{\text{H}}$  2.21 (s, 3H,  $\text{CH}_3$ ), 4.81 (s, 1H, CH), 7.21–7.25 (m, 1H, ArH), 7.30–7.35 (m, 4H, ArH), 7.78–7.88 (m, 3H, ArH), 8.03–8.05 (m, 1H, ArH), 10.00 (s, 1H, NH). IR (KBr):  $\nu$  3,127, 3,043, 2,928, 2,839, 2,360, 2,341, 2,197, 1,678, 1,653, 1,637, 1,592, 1,493, 1,367, 1,344, 1,299, 1,244, 1,206, 1,103, 953, 727, 714  $\text{cm}^{-1}$ . HRMS (ESI,  $m/z$ ): Calcd for  $\text{C}_{21}\text{H}_{13}\text{N}_2\text{O}_2$   $[\text{M}-\text{H}]^-$  325.0976, found 325.0969.

4-(4-Chlorophenyl)-1,4,5,6-tetrahydro-2-methyl-5,6-dioxobenzo[*h*]quinoline-3-carbonitrile **6b**: M. p. 263–265 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta_{\text{H}}$  2.21 (s, 3H,  $\text{CH}_3$ ), 4.84 (s, 1H, CH), 7.35 (d,  $J = 8.4$  Hz, 2H, ArH), 7.37 (d,  $J = 8.4$  Hz, 2H, ArH), 7.79–7.88 (m, 3H, ArH), 8.03–8.05 (m, 1H, ArH), 10.03 (s, 1H, NH).  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 100 MHz):  $\delta_{\text{C}}$  18.3, 38.5, 86.2, 115.1, 119.7, 126.0, 126.5, 129.0, 130.1, 130.8, 132.2, 132.3, 133.8, 135.3, 139.0, 144.0, 147.5, 179.6, 182.4. IR (KBr):  $\nu$  3,286, 3,047, 2,985, 2,875, 2,360, 2,341, 2,202, 1,684, 1,650, 1,612, 1,592, 1,490, 1,434, 1,393, 1,364, 1,340, 1,298, 1,252, 1,163, 1,100, 1,087, 1,012, 951  $\text{cm}^{-1}$ . HRMS (ESI,  $m/z$ ): Calcd for  $\text{C}_{21}\text{H}_{12}\text{ClN}_2\text{O}_2$   $[\text{M}-\text{H}]^-$  359.0588, found 359.0586.

4-(4-Fluorophenyl)-1,4,5,6-tetrahydro-2-methyl-5,6-dioxobenzo[*h*]quinoline-3-carbonitrile **6c**: M. p. 273–275 °C;  $^1\text{H}$  NMR (DMSO- $d_6$ , 400 MHz):  $\delta_{\text{H}}$  2.21 (s, 3H,  $\text{CH}_3$ ), 4.82 (s, 1H, CH), 7.14 (t,  $J = 8.8$  Hz, 2H, ArH), 7.34–7.38 (m, 2H, ArH), 7.79–7.88 (m, 3H, ArH), 8.03–8.05 (m, 1H, ArH), 10.01 (s, 1H, NH).  $^{13}\text{C}$  NMR (DMSO- $d_6$ , 100 MHz):  $\delta_{\text{C}}$  18.3, 38.3, 86.4, 115.3, 115.8 (d,  $J_{\text{F-C}} = 21.2$  Hz), 119.7, 126.0, 126.4, 130.1 (d,  $J_{\text{F-C}} = 8.2$  Hz), 130.8, 132.2, 133.8, 135.3, 138.8, 141.3 (d,  $J_{\text{F-C}} = 2.9$  Hz), 147.3, 161.7 (d,  $J_{\text{F-C}} = 241.8$  Hz), 179.7, 182.4. IR (KBr):  $\nu$  3,128, 3,043, 2,929, 2,882, 2,799, 2,357, 2,204, 1,675, 1,652, 1,614, 1,595,



1,504, 1,434, 1,368, 1,344, 1,298, 1,251, 1,219, 1,157, 1,097, 955, 842, 722  $\text{cm}^{-1}$ . HRMS (ESI,  $m/z$ ): Calcd for  $\text{C}_{21}\text{H}_{12}\text{FN}_2\text{O}_2$   $[\text{M}-\text{H}]^-$  343.0883, found 343.0885.

4-(4-Bromophenyl)-1,4,5,6-tetrahydro-2-methyl-5,6-dioxobenzo[*h*]quinoline-3-carbonitrile **6d**: M. p. 267–269  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz):  $\delta_{\text{H}}$  2.20 (s, 3H,  $\text{CH}_3$ ), 4.82 (s, 1H, CH), 7.29 (d,  $J = 8.4$  Hz, 2H, ArH), 7.51 (d,  $J = 8.4$  Hz, 2H, ArH), 7.79–7.87 (m, 3H, ArH), 8.02–8.04 (m, 1H, ArH), 10.03 (s, 1H, NH).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ , 100 MHz):  $\delta_{\text{C}}$  18.3, 38.6, 86.1, 115.0, 119.7, 120.9, 126.0, 126.4, 130.5, 130.8, 132.0, 132.2, 133.8, 135.3, 139.0, 144.4, 147.5, 179.6, 182.3. IR (KBr):  $\nu$  3,234, 3,213, 3,093, 3,062, 2,983, 2,750, 2,359, 2,340, 2,208, 1,678, 1,650, 1,610, 1,595, 1,488, 1,428, 1,339, 1,298, 1,252, 1,069, 1,009, 952, 938, 722  $\text{cm}^{-1}$ . HRMS (ESI,  $m/z$ ): Calcd for  $\text{C}_{21}\text{H}_{12}\text{BrN}_2\text{O}_2$   $[\text{M}-\text{H}]^-$  403.0081, found 403.0097.

4-(4-Cyanophenyl)-1,4,5,6-tetrahydro-2-methyl-5,6-dioxobenzo[*h*]quinoline-3-carbonitrile **6e**: M. p. 267–269  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz):  $\delta_{\text{H}}$  2.21 (s, 3H,  $\text{CH}_3$ ), 4.96 (s, 1H, CH), 7.56 (d,  $J = 8.4$  Hz, 2H, ArH), 7.80–7.86 (m, 5H, ArH), 8.04–8.06 (m, 1H, ArH), 10.09 (s, 1H, NH).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ , 100 MHz):  $\delta_{\text{C}}$  18.3, 39.2, 85.7, 110.5, 114.5, 119.1, 119.5, 126.0, 126.5, 129.3, 130.8, 132.1, 133.1, 133.8, 135.3, 139.4, 148.0, 150.0, 179.5, 182.3. IR (KBr):  $\nu$  3,300, 3,140, 3,035, 2,910, 2,870, 2,798, 2,420, 2,360, 2,224, 2,201, 1,674, 1,650, 1,614, 1,503, 1,435, 1,344, 1,301, 1,252, 1,159, 1,101, 949, 833, 751, 723  $\text{cm}^{-1}$ . HRMS (ESI,  $m/z$ ): Calcd for  $\text{C}_{22}\text{H}_{12}\text{N}_3\text{O}_2$   $[\text{M}-\text{H}]^-$  350.093, found 350.0938.

1,4,5,6-Tetrahydro-2-methyl-5,6-dioxo-4-*p*-tolylbenzo[*h*]quinoline-3-carbonitrile **6f**: M. p. 263–265  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz):  $\delta_{\text{H}}$  2.20 (s, 3H,  $\text{CH}_3$ ), 2.24 (s, 3H,  $\text{CH}_3$ ), 4.76 (s, 1H, CH), 7.12 (d,  $J = 8.0$  Hz, 2H, ArH), 7.19 (d,  $J = 8.0$  Hz, 2H, ArH), 7.79–7.87 (m, 3H, ArH), 8.02–8.05 (m, 1H, ArH), 9.97 (s, 1H, NH).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ , 100 MHz):  $\delta_{\text{C}}$  18.3, 21.1, 38.5, 86.7, 115.7, 119.8, 125.9, 126.4, 128.0, 129.6, 130.7, 132.2, 133.8, 135.3, 136.8, 138.6, 142.2, 147.0, 179.7, 182.4. IR (KBr):  $\nu$  3,245, 3,120, 3,031, 2,925, 2,881, 2,359, 2,310, 2,209, 1,678, 1,666, 1,612, 1,487, 1,430, 1,364, 1,339, 1,297, 1,251, 1,208, 1,161, 1,092, 1,050, 950, 721  $\text{cm}^{-1}$ . HRMS (ESI,  $m/z$ ): Calcd for  $\text{C}_{22}\text{H}_{15}\text{N}_2\text{O}_2$   $[\text{M}-\text{H}]^-$  339.1134, found 339.1141.

1,4,5,6-Tetrahydro-4-(4-methoxyphenyl)-2-methyl-5,6-dioxobenzo[*h*]quinoline-3-carbonitrile **6g**: M. p. 260–262  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz):  $\delta_{\text{H}}$  2.21 (s, 3H,  $\text{CH}_3$ ), 3.71 (s, 3H,  $\text{CH}_3\text{O}$ ), 4.75 (s, 1H, CH), 6.87 (d,  $J = 8.4$  Hz, 2H, ArH), 7.22 (d,  $J = 8.4$  Hz, 2H, ArH), 7.79–7.88 (m, 3H, ArH), 8.03 (d,  $J = 7.2$  Hz, 1H, ArH), 9.96 (s, 1H, NH). IR (KBr):  $\nu$  3,350, 3,085, 2,901, 2,810, 2,359, 2,339, 2,205, 1,675, 1,650, 1,611, 1,595, 1,489, 1,434, 1,343, 1,298, 1,253, 1,176, 1,098, 1,033, 951  $\text{cm}^{-1}$ . HRMS (ESI,  $m/z$ ): Calcd for  $\text{C}_{22}\text{H}_{15}\text{N}_2\text{O}_3$   $[\text{M}-\text{H}]^-$  355.1083, found 355.1089.

4-(2,3-Dichlorophenyl)-1,4,5,6-tetrahydro-2-methyl-5,6-dioxobenzo[*h*]quinoline-3-carbonitrile **6h**: M. p. 280–282  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 400 MHz):  $\delta_{\text{H}}$  2.18 (s, 3H,  $\text{CH}_3$ ), 5.46 (s, 1H, CH), 7.29–7.33 (m, 1H, ArH), 7.46 (dd,  $J = 7.6$  Hz,  $J' = 1.2$  Hz, 1H, ArH), 7.52 (dd,  $J = 7.6$  Hz,  $J' = 1.2$  Hz, 1H, ArH), 7.80–7.84 (m, 3H, ArH), 8.04–8.07 (m, 1H, ArH), 10.07 (s, 1H, NH). IR (KBr):  $\nu$  3,131, 3,042, 2,929, 2,881, 2,800, 2,360, 2,341, 2,205, 1,669, 1,640, 1,614, 1,593, 1,503, 1,474, 1,420, 1,367, 1,346, 1,304, 1,254, 1,158, 1,095, 955, 745  $\text{cm}^{-1}$ . HRMS (ESI,  $m/z$ ): Calcd for  $\text{C}_{21}\text{H}_{11}\text{Cl}_2\text{N}_2\text{O}_2$   $[\text{M} - \text{H}]^-$  393.0198, found 393.0196.

4-(2,4-Dichlorophenyl)-1,4,5,6-tetrahydro-2-methyl-5,6-dioxobenzo[*h*] quinoline-3-carbonitrile **6i**: M. p. 257–259 °C;  $^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>, 400 MHz):  $\delta_{\text{H}}$  2.18 (s, 3H, CH<sub>3</sub>), 5.35 (s, 1H, CH), 7.36 (dd, *J* = 8.4 Hz, *J'* = 2.0 Hz, 1H, ArH), 7.49 (d, *J* = 8.4 Hz, 1H, ArH), 7.60 (d, *J* = 2.0 Hz, 1H, ArH), 7.81–7.84 (m, 3H, ArH), 8.06 (dd, *J* = 6.4 Hz, *J'* = 1.6 Hz, 1H, ArH), 10.04 (s, 1H, NH).  $^{13}\text{C}$  NMR (DMSO-*d*<sub>6</sub>, 100 MHz):  $\delta_{\text{C}}$  18.2, 35.8, 85.3, 114.9, 119.2, 126.0, 126.5, 128.6, 129.0, 130.7, 132.1, 132.7, 132.87, 132.88, 133.9, 135.4, 139.7, 142.0, 147.7, 179.6, 182.2. IR (KBr):  $\nu$  3,250, 3,066, 2,927, 2,850, 2,359, 2,340, 2,204, 1,671, 1,650, 1,614, 1,592, 1,497, 1,473, 1,434, 1,344, 1,296, 1,253, 1,158, 1,096, 1,046, 951 846, 723 cm<sup>-1</sup>. HRMS (ESI, *m/z*): Calcd for C<sub>21</sub>H<sub>11</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub> [M-H]<sup>-</sup> 393.0198, found 393.0198.

4-(3,4-Dichlorophenyl)-1,4,5,6-tetrahydro-2-methyl-5,6-dioxobenzo[*h*] quinoline-3-carbonitrile **6j**: M. p. 231–233 °C;  $^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>, 400 MHz):  $\delta_{\text{H}}$  2.21 (s, 3H, CH<sub>3</sub>), 4.90 (s, 1H, CH), 7.35 (dd, *J* = 8.0 Hz, *J'* = 2.0 Hz, 1H, ArH), 7.59 (d, *J* = 8.0 Hz, 1H, ArH), 7.62 (d, *J* = 2.0 Hz, 1H, ArH), 7.79–7.86 (m, 3H, ArH), 8.03–8.05 (m, 1H, ArH), 10.05 (s, 1H, NH). IR (KBr):  $\nu$  3,140, 3,061, 2,928, 2,796, 2,359, 2,340, 2,203, 1,668, 1,650, 1,614, 1,593, 1,496, 1,474, 1,344, 1,300, 1,252, 1,156, 1,130, 1,096, 1,030, 953 cm<sup>-1</sup>. HRMS (ESI, *m/z*): Calcd for C<sub>21</sub>H<sub>11</sub>Cl<sub>2</sub>N<sub>2</sub>O<sub>2</sub> [M-H]<sup>-</sup> 393.0198, found 393.0199.

1,4,5,6-Tetrahydro-4-(3,5-dimethoxyphenyl)-2-methyl-5,6-dioxobenzo[*h*] quinoline-3-carbonitrile **6k**: M. p. 260–262 °C;  $^1\text{H}$  NMR (DMSO-*d*<sub>6</sub>, 400 MHz):  $\delta_{\text{H}}$  2.21 (s, 3H, CH<sub>3</sub>), 3.71 (s, 6H, 2CH<sub>3</sub>O), 4.74 (s, 1H, CH), 6.40 (d, *J* = 2.0 Hz, 1H, ArH), 6.42 (d, *J* = 2.0 Hz, 2H, ArH), 7.78–7.90 (m, 3H, ArH), 8.03–8.05 (m, 1H, ArH), 9.96 (s, 1H, NH). IR (KBr):  $\nu$  3,210, 3,094, 2,927, 2,839, 2,810, 2,420, 2,390, 2,201, 1,667, 1,610, 1,595, 1,500, 1,475, 1,431, 1,346, 1,318, 1,256, 1,198, 1,157, 1,097, 1,058, 923, 817, 743, 720 cm<sup>-1</sup>. HRMS (ESI, *m/z*): Calcd for C<sub>23</sub>H<sub>17</sub>N<sub>2</sub>O<sub>4</sub> [M-H]<sup>-</sup> 385.1189, found 385.1181.

## Conclusions

In summary, a mild, facile, and environmentally benign method was developed for the synthesis of polysubstituted quinoline and benzo[*h*]quinoline derivatives in high yields in ionic liquids. The advantages of this procedure include mild reaction conditions, good to high yields, one-pot synthesis, operational simplicity, and being environmentally benign.

**Acknowledgments** We are grateful to the National Natural Science Foundation of China (No.51174201), the Open Foundation of Southwest University of Science and Technology (No.11zxjk10), a Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions, and College Industrialization Project (JHB2012-31) of Jiangsu Province for financial support.

## References

1. S. Eswaran, A.V. Adhikari, N.S. Shetty, Eur. J. Med. Chem. **44**, 4637 (2009)
2. M. Mor, F. Bordini, C. Carmi, S. Vezzosi, A. Lodola, P.G. Petronini, R. Alfieri, A. Cavazzoni, PCT International Application No. WO 2010076764 A1, 8 Jul 2010, Chem. Abstr. **153**, 145526, 2010

3. S. Eswaran, A.V. Adhikari, I.H. Chowdhury, N.K. Pal, K.D. Thomas, *Eur. J. Med. Chem.* **45**, 3374 (2010)
4. P. Phiasivongsa, S.G. Redkar, S. Gamage, D. Brooke, W. Denny, D.J. Bearss, H. Vankayalapati, Y. Xu, K. Swierczek, U.S. Patent Applications Publication No. US 20090285772 A1, 19 Nov 2009. *Chem. Abstr.* **152**, 12160, 2009
5. C. Wolf, P.D. Roepe, A.C. De Dios, PCT International Application No. WO 2009148659 A2, 10 Dec 2009. *Chem. Abstr.* **152**, 37412, 2009
6. A.J. Sadeque, C. Wandel, H. He, S. Shah, A.J. Wood, *Clin. Pharmacol. Ther.* **68**, 231 (2000)
7. E. Hempelmann, *Parasitol. Res.* **100**, 671 (2007)
8. M. Hatano, K. Mikami, *J. Am. Chem. Soc.* **125**, 4704 (2003)
9. H. Venkatesan, F.M. Hocutt, T.K. Jones, M.H. Rabinowitz, *J. Org. Chem.* **75**, 3488 (2010)
10. R.P. Korivi, C.H. Cheng, *J. Org. Chem.* **71**, 7079 (2006)
11. G. Sundararajan, N. Prabakaran, B. Varghese, *Org. Lett.* **3**, 1973 (2001)
12. Y. Luo, X. Pan, J. Wu, *Org. Lett.* **13**, 1150 (2011)
13. J. Akbari, A. Heydari, H.R. Kalhor, S.A. Kohan, *J. Comb. Chem.* **12**, 137 (2010)
14. T. Welton, *Chem. Rev.* **99**, 2071 (1999)
15. J. Dupont, R.F. de Souza, P.A.Z. Suarez, *Chem. Rev.* **102**, 3667 (2002)
16. M.A.P. Martins, C.P. Frizzo, D.N. Moreira, N. Zanatta, H.G. Bonacorso, *Chem. Rev.* **108**, 2015 (2008)
17. X.S. Wang, J.R. Wu, J. Zhou, S.J. Tu, *J. Comb. Chem.* **11**, 1011 (2009)
18. X.S. Wang, K. Yang, J. Zhou, S.J. Tu, *J. Comb. Chem.* **12**, 417 (2010)
19. J. Sheng, M.M. Zhang, H. Jiang, X.S. Wang, *J. Chin. Chem. Soc.* **59**, 650 (2012)
20. X.S. Wang, J.R. Wu, J. Zhou, M.M. Zhang, *J. Heterocycl. Chem.* **48**, 1056 (2011)
21. J. Xu, Y.S. Cao, L.Y. Li, Y. Liu, X.S. Wang, *Res. Chem. Intermed.* **40** (2014). doi: [10.1007/s11164-013-1496-2](https://doi.org/10.1007/s11164-013-1496-2)
22. A. Dreimane, *Khimiya Geterotsiklicheskikh Soedinenii* **6**, 791 (1980)