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MICROWAVE-ASSISTED AND SOLVENT-FREE SYNTHESIS OF QUINOLINE DERIVATIVES AND THEIR FLUORESCENCE PROPERTIES

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Abstract – A protocol for the microwave-assisted Friedländer synthesis of quinoline derivatives under solvent-free conditions has been developed. According to this modified method, quinoline derivatives were synthesized by condensation of 2-aminobenzophenone with the corresponding carbonyl compounds in the presence of phosphomolybdic acid for 8 min in a 320 W microwave with yields ranging from 61% to 90%. The fluorescence properties of the synthesized compounds were studied, and all compounds showed good fluorescence properties. The substituted groups and the concentrations of quinolines and solvents had significant effects on the compounds' fluorescence properties. This method provides a convenient way to obtain quinolines, and is beneficial to the application of these compounds.

INTRODUCTION

Quinolines have been found to be very useful compounds that not only possess anticancer,¹ antimalarial,² antibacterial,³ and other bioactivities,⁴ but whose fluorescent properties of high quantum yield are also attracting increasing attention. Quinolines have been used in organic light-emitting diodes (OLEDs) as a blue light-emitting material in the solid state.⁵ Fluorescent quinoline molecular systems, which undergo signal changes upon addition of external substances, are called fluorescent sensors. Such systems can be used to detect metal ions, such as sodium, potassium, magnesium, or calcium,⁶ and nitric oxide etc.

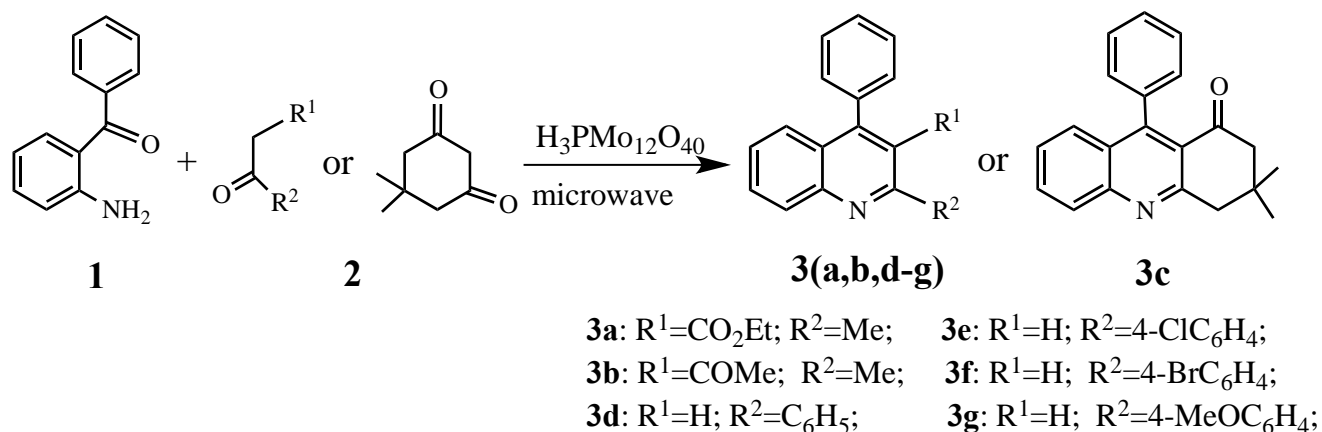
A number of established protocols are available for the synthesis of a quinoline nucleus, and can be modified to prepare a number of quinoline derivatives. The classical protocols include the Friedländer,

Skraup, Doebner-von Miller, Pfitzinger, Conrad–Limpach, and Combes protocols.⁷ Among them, Friedländer annulation is the most simple and straightforward method for the synthesis of polysubstituted quinolines.⁸ This method involves the condensation of 2-aminoaryl ketones with carbonyl compounds that possess a reactive methylene group followed by cyclodehydration in the presence of a Lewis acid or base at a high temperature (150–220 °C). However, many of these procedures have significant drawbacks, such as harsh reaction conditions, low yields, expensive catalysts, and longer reaction times. Thus, researchers have been trying to find a simple and environmentally friendly protocol that uses inexpensive and readily available reagents.⁹ Recently, microwave irradiation, as a heating method in organic synthesis, has caused a revolution in green chemistry and has become widely accepted on a laboratory scale.¹⁰ As a result, the synthesis of quinolines requires significantly less energy and time, and is more environmentally friendly.¹¹

Here, we designed a microwave-assisted, solid-phase synthesis method for the solvent-free synthesis of quinolines by the Friedländer protocol. According to this modified method, 2-aminobenzophenone was condensed with acetylacetone, ethyl acetoacetate, phenyl methyl ketone, or substituted acetophenone in the presence of phosphomolybdic acid for 8 min in a 320 W microwave to synthesize the corresponding quinoline derivatives with yields ranging from 61% to 90%. The fluorescence properties of the target compounds were studied.

RESULTS AND DISCUSSION

In general, a microwave-assisted synthesis was used in the construction of nitrogen-containing heterocyclic compounds to reduce reaction times and increase yields. The quinoline derivatives were prepared by reacting 2-aminobenzophenone with α -methylene ketones under microwave irradiation without a solvent (Scheme 1). As shown in Table 1, the yields of quinolines were closely related to the reactive abilities of the methylene groups on the carbonyl compounds. The two neighboring carbonyl groups made the methylene groups of acetylacetone and ethyl acetoacetate more reactive and had a positive effect on the yields of the corresponding quinolines. The activity of the methyl group of the acetophenone molecule was significantly affected by *para*-substitution on the benzene ring of the acetophenone. In addition, its activity can be increased by an electron-withdrawing group. Therefore, the yield of quinoline prepared by acetophenone with a Cl or Br substituent on the *para*-position of the benzene ring was higher than that with *p*-methoxyacetophenone.



Scheme 1. A schematic of the procedure for synthesizing quinoline derivatives

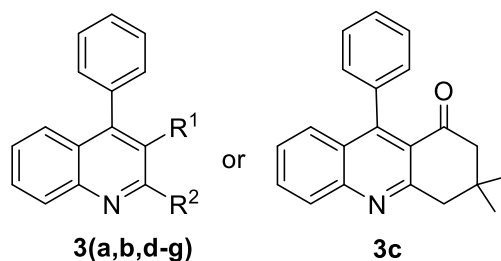


Table 1. The structures and yields of quinoline derivatives

Entry	R ¹	R ²	Products	Yield (%)
3a	CO ₂ Et	Me		90
3b	COMe	Me		89
3c				82
3d	H	C ₆ H ₅		68
3e	H	4-ClC ₆ H ₄		71
3f	H	4-BrC ₆ H ₄		76
3g	H	4-MeOC ₆ H ₄		61

For the synthesis of quinoline derivatives via Friedländer annulation, the catalyst is an important factor that affects the yield of quinoline. Generally, the Friedländer synthesis of quinoline involves an acid- or a base-catalyzed condensation between a 2-aminoaryl ketone and ketones or keto esters containing a reactive α -methylene group followed by a cyclodehydration. To determine the effect of catalysts on the quinolone yield, a reaction of 2-aminobenzophenone (0.01 mol) with acetylacetone (0.012 mol) was conducted using various catalysts (0.5 mmol) by irradiation for 8 minutes at 320 W (microwave power) (Table 2). The reactions were carried out using ZnCl_2 , AlCl_3 , *p*-toluenesulfonic acid (TsOH), NaOH, H_2SO_4 , K_2CO_3 , and phosphomolybdic acid ($\text{H}_3\text{PMO}_{12}\text{O}_{40}$) as a catalyst, respectively. The best yield was obtained with phosphomolybdic acid. Further, the reaction time, the radiation power, and the stoichiometric ratio of 2-aminobenzophenone to α -methylene ketones, etc. were found to have a moderate effect on the reaction. In addition, it is worth noting that an excess of both irradiation power and time can cause side reactions that reduce the yield and purity of the final product.

Table 2. The effects of catalysts on the yields of quinolines

Entry	Catalyst (mol%)	Radiation power (w)	Radiation time (min)	Yield (%)
1	H_2SO_4 (5)	320	8	78
2	HCl(5)	320	8	70
3	NaOH(5)	320	8	57
4	TsOH (5)	320	8	76
5	ZnCl_2 (5)	320	8	81
6	AlCl_3 (5)	320	8	79
7	K_2CO_3 (5)	320	8	36
8	$\text{H}_3\text{PMO}_{12}\text{O}_{40}$ (5)	320	8	89

The fluorescence excitation and emission data of compounds **3a–3g** were recorded at the concentration of 10^{-6} M in different solvents (Table 3). The results show that the maximum excitation wavelengths of all compounds were at 263–339 nm, and the maximum emission wavelengths at 308–407 nm. Solvents have modest effects on the excitation and emission wavelengths of the quinolines. The λ_{exc} and λ_{em} of **3a–3g** were at their maximum in acetone. The substituted groups on the quinolines did not cause significant differences in the excitation and emission wavelengths of the recorded quinoline derivatives.

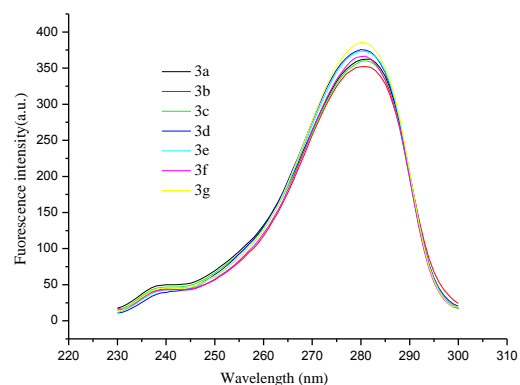
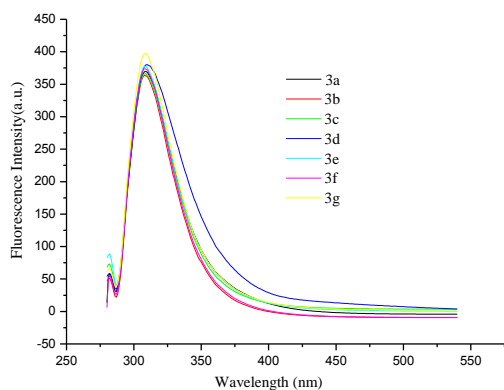
Table 3. The fluorescence spectroscopy data of compounds **3a–3g**

Entry		3a	3b	3c	3d	3e	3f	3g
CH ₂ Cl ₂	λ_{ex}^a	270.0	271.4	264.4	264.2	264.0	263.0	277.8
	λ_{em}^a	359.4	358.4	359.0	359.2	359.0	359.4	387.8
	$\epsilon \times 10^6{}^b$	1.46	1.37	1.38	1.37	1.43	1.42	1.41
EtOH	λ_{ex}^a	276.0	276.0	275.4	275.6	275.8	276.0	275.6
	λ_{em}^a	337.0	337.0	336.8	337.2	337.0	337.2	337.0
	$\epsilon \times 10^6{}^b$	1.85	1.90	1.92	1.88	1.74	1.70	1.82
THF	λ_{ex}^a	280.4	280.2	281.0	280.8	280.6	281.0	280.8
	λ_{em}^a	308.6	308.0	308.6	309.6	308.0	308.0	308.0
	$\epsilon \times 10^6{}^b$	1.01	0.85	0.85	0.93	0.83	0.82	0.92
Me ₂ CO	λ_{ex}^a	328.0	328.6	328.6	328.0	328.6	329.0	339.4
	λ_{em}^a	403.4	406.8	402.4	407.0	406.0	404.2	395.2
	$\epsilon \times 10^6{}^b$	0.69	0.69	0.84	0.78	0.46	0.96	0.81

^a (nm) ^b (dm³•mol⁻¹•cm⁻¹)

The overall results on the excitation and emission spectra of **3a–3g** (as shown in Figures 1 and 2) showed no significant differences. However, there were some noticeable regularities. Despite the fact that **3d–3g** share the same conjugated system, i.e., they all have two benzene rings on the parent structure of the quinolines, their fluorescence intensities were different. The effect was caused by the different substituted groups on the *para*-position of the benzene ring attached to the 2-position of the quinolines. The electron-donating group -OMe of **3g** brought about a *p*-conjugate function to enhance the conjugation degree of the electron, which resulted in a higher transition probability between the lowest excited singlet state and the ground state. As a result, the fluorescent intensity of **3g** was higher. For **3e** and **3f** with Cl or Br electron-withdrawing substituents on the *para*-position of the benzene ring attached to the 2-position of quinoline, according to the "heavy atom effect", the molecular weight of halogen atoms increased as the strength of the spin-orbit interaction was increased. This increased the probability of the singlet state and, as a result, the fluorescence intensities of the compounds were gradually weakened. The observed fluorescence intensity of **3e** (higher than that of **3f**) confirmed the principle. In addition, if the conjugate system of the benzene ring is larger, then its fluorescence intensity is higher. This was in agreement with the observed higher overall fluorescence intensities of **3d–3g** compared to those of **3a–3c**. The larger electron-donating effect of -CO₂Et (compared to that of -COMe) caused the higher fluorescence intensity

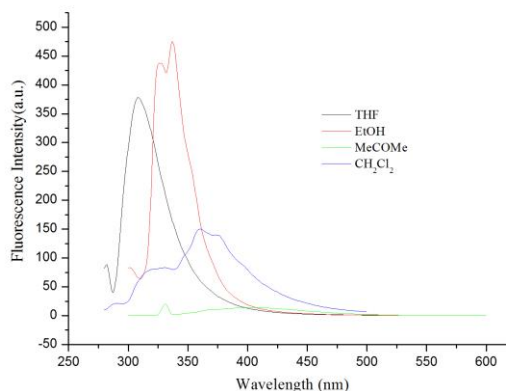
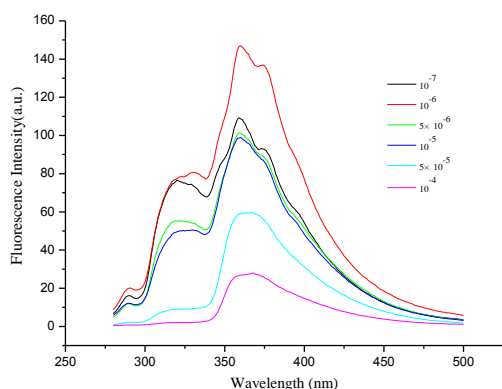
of **3a** (compared to that of **3b**), and the fluorescence intensity of **3c** was intermediate because of the electron-donating effect of the ring alkyl group.



(Left) Figure 1. The emission spectra of compounds **3a–3g** in dilute (1×10^{-6} M) THF solution

(Right) Figure 2. The excitation spectra of compounds **3a–3g** in dilute (1×10^{-6} M) THF solution

The fluorescence intensity of compound **3e** regularly varied with its concentration in CH_2Cl_2 solution (Figure 3). When the concentration of **3e** increased from 10^{-7} M to 10^{-4} M, its fluorescence intensity rapidly decreased. This was caused by the solvation effect. As the concentration of the compound became higher, the intermolecular interaction also increased. Before the occurrence of fluorescence, the molecularly excited singlet state collided with an unexcited fluorescent molecule, leading to self-quenching, which eventually leads to a decrease in fluorescence intensity and even complete quenching. The fluorescence intensity of **3e** was maximal at the concentration of 10^{-6} M; and, by continuously lowering the concentration of **3e**, the fluorescence intensity was decreased accordingly.



(Left) Figure 3. The emission spectra of compound **3e** at different concentrations in CH_2Cl_2 solution

(Right) Figure 4. The emission spectra of compound **3e** at a concentration of 10^{-6} M

The different solvents had a great effect on the fluorescence intensity emission spectrum of compound **3e** at a concentration of 10^{-6} M (Figure 4). In a polar solvent, such as ethanol or tetrahydrofuran, **3e** had a strong fluorescence intensity. By increasing the polarity of the solvent, the energy of the $\pi \rightarrow \pi^*$ transition decreased, resulting in the enhancement of fluorescence and a significant red shift of the fluorescence peak. In other solvents, the Stokes effect of **3e** showed an obvious difference; in CH_2Cl_2 , the Stokes shift was much higher (95 nm) than in THF (only 27.4 nm).

A simple, convenient, and efficient protocol for the microwave-assisted Friedländer synthesis of quinoline derivatives under solvent-free conditions was developed. The high yields of products, the easy-to-perform work-up procedure, and phosphomolybdic acid as a heteropolyacid catalyst should make it the preferred procedure for the preparation of quinoline derivatives. Since the new method uses phosphomolybdic acid as catalyst and avoids hazardous organic solvents, it is more environmentally friendly.

The reaction reagents in this experiment are α -methylene ketones and 2-aminobenzophenone. The selection of α -methylene ketones is based on the influence of adjacent functional groups on the reaction of α -methylene. Electron-withdrawing group is beneficial to the activation of methylene, while electron-repelling group reduces the reactivity. Compounds **3a–3c** (Table 1) are representative quinoline derivatives generated from 2-aminobenzophenone and α -methylene ketones containing two carbonyl groups. The *ortho*-substituents of one carbonyl group of α -methylene ketones affects activity of α -methylene group and the whole reaction. So, higher yield (90%) was obtained for compound **3a** due to strong electron attraction of ethoxycarbonyl. In addition, compounds **3d–3g** are the representative quinolines derived from 2-aminobenzophenone and α -methylene ketones containing a benzoyl group with *para*-substituent group. The *para*-substituents of benzene affect carbonyl group, further influencing the reaction. The lower yield (61%) of **3g** is due to the electron donation of *para*-methoxy group on benzene ring.

Several quinoline derivatives showed good fluorescence properties during the experiments. The substituted groups on the *para*-position of the benzene ring attached to the 2-position of quinolines have significant effects on the fluorescence intensities of the quinolines. The fluorescence intensity is closely related to the concentration of quinolines in the solvent, and higher concentrations may cause the fluorescence intensity to decrease rapidly, even to complete quenching. The fluorescence intensity of quinolines is also very sensitive to the polarity of solvents; polar solvents will improve the fluorescence intensity. The quinoline derivatives showed higher fluorescence intensities in ethanol and tetrahydrofuran. In conclusion, this method provides a convenient way to obtain quinolines and is beneficial to the application of these compounds.

EXPERIMENTAL

Materials and Apparatus: Elemental analyses were performed on an Elementar Vario EL III. IR spectra were recorded on a Specode 75 model (Carl Zeiss, Jena, Germany) using KBr as the sample holder. ^1H NMR spectra were recorded on a Varian Inova 400 and 600 MHz instrument with chemical shifts reported relative to tetramethylsilane (TMS). ^{13}C NMR spectra were recorded on a Varian Inova 151 MHz instrument with chemical shifts reported relative to tetramethylsilane (TMS). GC-MS spectra were determined on a Varian 3800 spectrometer. All materials were weighed in the air. Flash column chromatography was performed with silica gel (100–200 mesh). Fluorescence spectra were recorded using a Hitachi F-7000 spectrofluorophotometer. Fluorescence scans were recorded from 200 nm to 700 nm. Kitchen microwave oven (MI-231A, Wmax : 800W, Midea Group, China). All measurements were carried out at room temperature. All reagents were commercially available, and were used without further purification.

The general procedure for the synthesis of compounds **3a–3g** was as follows: 2-aminobenzophenone (0.01 mol), α -methyleneketones (0.012 mol), and $\text{H}_3\text{PMo}_{12}\text{O}_{40}$ (0.91 g, 0.5 mmol) were added to a mortar, ground (homogenized), and then transferred to a sealed glass tube with rubber stopper, and were then irradiated for 8 min in a microwave oven with wattage power set at 320 W. After being cooled to room temperature in a water bath, water (10 mL) was added to the reaction mixture, and the suspension was treated with 10% NaOH and extracted with EtOAc (3 \times 10 mL). The organic phase was dried over anhydrous magnesium sulfate, concentrated under reduced pressure to yield the crude product, and then purified by (silica gel) column chromatography (petroleum ether:EtOAc = 3:1 as an eluent) to yield pure products.

Ethyl 2-methyl-4-phenylquinoline-3-carboxylate (3a): a pale yellow granular crystals (2.63 g, 90%); mp 99.1–101.7 °C; IR(KBr) ν 3057, 2985, 1728, 1580, 1502, 1406, 1286, 1235, 1065, 769 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 1.02 (t, J = 7.8 Hz, 3H), 2.85 (s, 3H), 4.15 (m, 2H), 7.26–7.47 (m, 6H), 7.58 (d, 1H), 7.78 (t, 1H), 8.23 (d, J = 7.6 Hz, 1H); ^{13}C NMR (151 MHz, CDCl_3) δ 168.55, 154.76, 147.76, 146.46, 135.86, 130.61, 130.21, 129.31, 129.04, 128.84, 128.30, 127.56, 126.70, 126.45, 125.30, 61.47, 23.93, 13.90, 13.64; MS (70 eV) m/z (%): 292.2 (M+1, 100), 293.2 (25), 264.1 (18). Anal. Calcd for $\text{C}_{19}\text{H}_{17}\text{NO}_2$: C, 78.33; H, 5.88; N 4.81. Found: C, 78.31; H, 5.87; N, 4.82.

1-(2-Methyl-4-phenylquinolin-3-yl)ethanone (3b): a yellow flaky crystals (2.33 g, 89%); mp 104–106 °C; IR(KBr) ν 3057, 2959, 1697, 1572, 1445, 1405, 1217, 756, 701 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 2.13 (s, 3H), 2.85 (s, 3H), 7.22–7.49 (m, 6H), 7.56 (d, J = 8.3 Hz, 1H), 7.73 (t, J = 7.3 Hz, 1H), 8.23 (d, J = 8.6 Hz, 1H); ^{13}C NMR (151 MHz, CDCl_3) δ 199.19, 151.02, 140.22, 134.09, 131.15, 129.38, 129.06, 128.28, 128.11, 118.28, 117.32, 116.90, 116.63, 116.06, 115.18; MS (70 eV) m/z (%): 262.1

(M+1, 100), 218.1 (76), 204 (7). Anal. Calcd for C₁₈H₁₅NO: C, 82.73; H, 5.79; N, 5.36. Found C, 82.75; H, 5.78; N, 5.34.

3,3-Dimethyl-9-phenyl-3,4-dihydroacridin-1(2H)-one (3c): a yellow powder (2.48 g, 82%); mp 190.3–192.2 °C; IR(KBr) ν 3057, 2959, 1715, 1600, 1565, 1210, 736 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.12 (s, 6H), 2.37 (s, 2H), 3.26 (s, 2H), 7.18–7.26 (m, 2H), 7.46–7.62 (m, 4H), 7.76 (m, 2H), 8.16 (d, *J* = 8 Hz, 1H); ¹³C NMR (151 MHz, CDCl₃) δ 198.09, 161.28, 151.14, 149.14, 137.73, 131.97, 131.55, 128.78, 128.55, 128.25, 127.86, 127.55, 122.84, 54.36, 48.55, 32.39, 28.57, 28.39; MS (70 eV) *m/z* (%) 302.2 (M+1, 100), 303.2 (23), 324.2 (18). Anal. Calcd for C₂₁H₁₉NO: C, 83.69; H, 6.35; N, 4.65. Found C, 83.68; H, 6.34; N 4.66.

2,4-Diphenylquinoline (3d): a yellow granular crystals (1.91 g, 68%); mp 106.1–107.4 °C; IR(KBr) ν 3052, 1586, 1551, 1447 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.41–7.44 (m, 2H), 7.46–7.53 (m, 7H), 7.69 (t, *J* = 7.5 Hz, 1H), 7.78 (s, 1H), 7.830 (d, *J* = 3.0 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 2H), 8.12 (d, *J* = 9.0 Hz, 1H); ¹³C NMR (151 MHz, CDCl₃) δ 150.89, 140.08, 134.63, 134.46, 133.95, 131.00, 129.24, 128.92, 128.14, 127.99, 127.47, 118.14, 117.45, 117.19, 116.75, 115.93, 115.48, 115.04; MS (70 eV) *m/z* (%) 282.1 (M+1, 100), 283.1 (3), 202 (15). Anal. Calcd for C₂₁H₁₅N: C, 89.65; H, 5.37; N, 4.98. Found C, 89.68; H, 5.36; N, 4.87.

2-(4-Chlorophenyl)-4-phenylquinoline (3e): a pale yellow needle-like crystals (2.23 g, 71%); mp 97.7–100.8 °C; IR(KBr) ν 3054, 1591, 1545, 1487, 1416, 1094, 769, 699 cm⁻¹; ¹H NMR(400 MHz, CDCl₃) δ 7.38–7.49 (m, 8H), 7.69–7.76 (m, 2H), 7.89 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 2H), 8.12 (d, *J* = 8.4 Hz, 1H); ¹³C NMR (151 MHz, CDCl₃) δ 155.43, 149.32, 148.68, 138.17, 137.95, 135.48, 130.01, 129.52, 129.38, 128.90, 128.80, 128.69, 128.61, 128.44, 126.43, 125.74, 125.40, 119.02, 118.59; MS (70 eV) *m/z* (%) 316.2 (M+1, 100), 317.2 (22), 318.2 (33). Anal. Calcd for C₂₁H₁₄ClN: C, 79.87; H, 4.47; N, 4.44. Found C, 79.85; H, 4.45; N, 4.46.

2-(4-Bromophenyl)-4-phenylquinoline (3f): a pale yellow needle-like crystals (2.72 g, 76%); mp 126.5–128.3 °C; IR(KBr) ν 3051, 1590, 1544, 1486, 1416, 1356, 1072, 1008, 829, 768, 701 cm⁻¹; ¹H NMR(400 MHz, CDCl₃) δ 7.34–7.71 (m, 10H), 7.79 (d, *J* = 8.1 Hz, 1H), 8.01 (d, *J* = 8.7 Hz, 2H), 8.14 (d, *J* = 8.4 Hz, 1H); ¹³C NMR (151 MHz, CDCl₃) δ 155.69, 149.56, 148.91, 138.62, 138.38, 132.27, 131.92, 130.24, 129.74, 129.61, 129.33, 129.14, 128.83, 128.62, 126.67, 126.00, 125.62, 124.09, 119.18, 118.75; MS (70 eV) *m/z* (%) 360 (M+1, 100), 361 (24), 362 (98). Anal. Calcd for C₂₁H₁₄BrN: C, 70.01; H, 3.92; N, 3.92. Found: C, 69.78; H, 3.96; N, 3.93.

2-(4-Methoxyphenyl)-4-phenylquinoline (3g): a colorless needle-like crystals (1.89 g, 61%); mp 83.4–84.2 °C; IR(KBr) ν 3052, 1587, 1551, 1480, 1448, 743, 701, 643 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 8.25 (d, *J* = 8.4 Hz, 1H), 8.20–8.19 (dd, *J* = 2.1 Hz, 2H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.79 (s, 1H), 7.72 (t, *J* = 8.3 Hz, 1H), 7.59–7.51 (m, 5H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.08–7.04 (m, 2H), 3.88 (s, 3H); ¹³C NMR

(151 MHz, CDCl₃) δ 160.95, 156.52, 149.09, 148.94, 138.62, 138.62, 132.31, 129.63, 129.02, 128.70 (s, 5H), 125.62, 119.00, 114.53, 114.13, 55.49; MS (70 eV) m/z (%) 312.2 (M+1, 100), 313.2 (23). Anal. Calcd for C₂₂H₁₇NO: C, 84.86; H, 5.50; N, 4.50. Found: C, 84.92; H, 5.52; N, 4.48.

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