I_2-Catalyzed Reactions of Schiff Base and Alkyl Aldehyde towards Benzo[*f*]quinoline Derivatives

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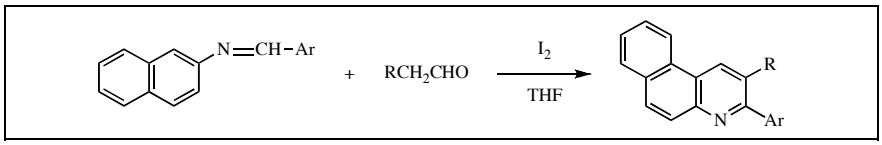

A mild, efficient, and general method for the synthesis of benzo[*f*]quinoline derivatives *via* a molecular iodine-catalyzed reaction of Schiff base with alkyl aldehydes has been described. The structure of **3o** was confirmed by X-ray diffraction study.

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INTRODUCTION

Quinoline and its derivatives represent an important class of nitrogen-containing heterocycles as they constitute useful intermediates in organic synthesis and are useful dyes [1]. And they are well known in the pharmaceutical industry and have been shown to possess a broad spectrum of biological activities including such as antiasthmatic, antiinflammatory and antimalarial activity [2]. In addition, quinoline derivatives have been evaluated as anticancer and antihelmintic agents [3]. A number of synthetic strategies have been developed for the preparation of substituted quinolines [4], except for the classic methods for the synthesis of quinoline derivatives include Skraup, Doebner–Von Miller, Conrad–Limbach, Combes and Pfitzinger quinoline syntheses [5].

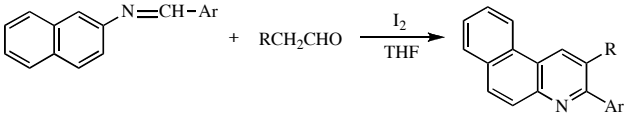
In recent years, the use of molecular iodine in organic synthesis has received considerable attention as an inexpensive, non-toxic, readily available mild Lewis acid catalyst for organic transformations such as dehydration of tertiary alcohols to alkenes [6], synthesis of benzyl alkyl ethers [7], synthesis of mixed ethers under hydrogen pressure [8], bis-indoles [9], deprotection of acetals [10], esterification [11], transesterification [12] and Michael addition [13]. Herein we would like to report 2-aryl-benzo[*f*]quinoline derivatives in THF catalyzed by iodine by the reaction of Schiff base and alkyl aldehydes.

RESULTS AND DISCUSSION

When the reaction of *N*-arylidenenaphthalen-2-amine **1** and alkyl aldehyde **2** was carried out in THF at refluxing temperature in the presence of iodine (Scheme 1), the 2-arylbenzo[*f*]quinoline derivatives were obtained as expected in good yields.

In our initial study, the reaction of *N*-(4-chloro-phenyl-idene)naphthalen-2-amine **1a** and propylaldehyde **2** was used as a model reaction to optimize the conditions. The reaction was first carried out in THF in the absence of I_2. No reaction occurred at room temperature and reflux

Scheme 1



1 **2** **3**

condition (Table 1, entries 1 and 2). Similar reactions were then attempted in the presence of 10, 20 and 30 mol% of I_2. The results from Table 1 (entries 5, 6 and 7) showed that 10 mol% I_2 at reflux in THF was sufficient to push the reaction forward. Higher loading of the catalyst did not improve the reaction yield to a great extent. To find the optimum reaction temperature, the reaction was carried out with 10 mol% of I_2 at room temperature, 50° and reflux temperature, resulting in the isolation of **3a** in trace amount, 52 % and 73 % yields (Table 1, entries 3-6), respectively. Thus, 10 mol% of I_2 and a reaction temperature at reflux were optimal conditions. In addition, CH_3CN, benzene, DMF and $ClCH_2CH_2Cl$ (Table 1, entries 8~11) were also tested as the solvents. In these cases, product **3a** was formed in slightly lower yield (Table 1, entries 8-11).

Table 1

Synthesis of **3a** in THF under different reaction conditions [a].

Entry	Temp. / °C	I_2/ mol %	Solvent	Yields [b]/%
1	r.t.	0	THF	0
2	Reflux	0	THF	0
3	r.t.	10	THF	trace
4	50	10	THF	52
5	Reflux	10	THF	73
6	Reflux	20	THF	72
7	Reflux	30	THF	73
8	Reflux	10	CH_3CN	72
9	Reflux	30	Benzene	70
10	80	20	DMF	70
11	Reflux	20	$ClCH_2CH_2Cl$	69

[a] Reagents and conditions: **1** (2 mmol), **2** (2 mmol), I_2 (10 mol%), solvent (10 mL). [b] Isolated yields.

Under the optimized reaction conditions, a variety of Schiff bases **1** and alkyl aldehydes **2** were tested. They all gave the corresponding 3-arylbenzo[*f*]quinolines in moderate to good yields (Table 2).

Table 2

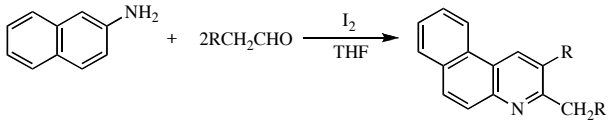
I_2 catalyzed reaction of N-arylidenenaphthalen-2-amine and alkyl aldehyde in THF [a].

Entry	Ar	R	Products	Time / h	Yields [b]/ %
1	4-ClC_6H_4	CH_3	**3a**	3	73
2	4-FC_6H_4	CH_3	**3b**	3	72
3	4-BrC_6H_4	CH_3	**3c**	4	78
4	2,4-$Cl_2C_6H_3$	CH_3	**3d**	3	70
5	2-Thiophenyl	CH_3	**3e**	5	68
6	4-$NO_2C_6H_4$	CH_3	**3f**	3	77
7	4-$NO_2C_6H_4$	CH_2CH_3	**3g**	3	79
8	2-Thiophenyl	CH_2CH_3	**3h**	4	72
9	4-BrC_6H_4	CH_2CH_3	**3i**	3	72
10	4-FC_6H_4	CH_2CH_3	**3j**	3	66
11	4-ClC_6H_4	CH_2CH_3	**3k**	3	80
12	3,4-$Cl_2C_6H_3$	CH_2CH_3	**3l**	3	74
13	3-BrC_6H_4	CH_2CH_3	**3m**	5	68
14	4-$NO_2C_6H_4$	Ph	**3n**	5	70
15	4-BrC_6H_4	Ph	**3o**	5	72
16	4-ClC_6H_4	Ph	**3p**	5	75
17	4-FC_6H_4	Ph	**3q**	5	75
18	3-BrC_6H_4	Ph	**3r**	5	78
19	2-Thiophenyl	Ph	**3s**	5	74
20	4-BrC_6H_4	$(CH_2)_4CH_3$	**3t**	4	76
21	3-BrC_6H_4	$(CH_2)_4CH_3$	**3u**	4	69

[a]Reagents and conditions: **1** (2 mmol), **2** (2.1 mmol), I_2 (10 mol%), THF (10 mL). [b]Isolated yields.

We also try to examine the alkylimines, which are difficult to purify by distillation, recrystallization, or column chromatography. However, one-pot reactions of naphthalen-2-amine (1.0 equiv) and alkyl aldehyde **2** (2.1 equiv) in the presence of iodine (1 mol %) in THF under reflux and an air atmosphere were performed, the resulting alkylimine further reacted with excess alkyl aldehyde **2** to give the corresponding 2,3-dialkylbenzo-[*f*]quinoline **4** in generate yields (Scheme 3, Table 3).

Scheme 2



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According to the literatures [14], we think that iodine catalyzes the reaction as a mild Lewis acid. The mechanism was proposed as shown in Scheme 2. In the presence of iodine, alkyl aldehyde is in equilibrium with the enol form **I**. The enol immediately reacts with the iodine-activated Schiff base to form intermediate **II**, followed by an intramolecular Friedel–Crafts cyclization to give **III**. The subsequent dehydration of **III** results in dihydroquinoline **IV**, which is further oxidized by air to give an aromatized benzo[*f*]quinoline **3**.

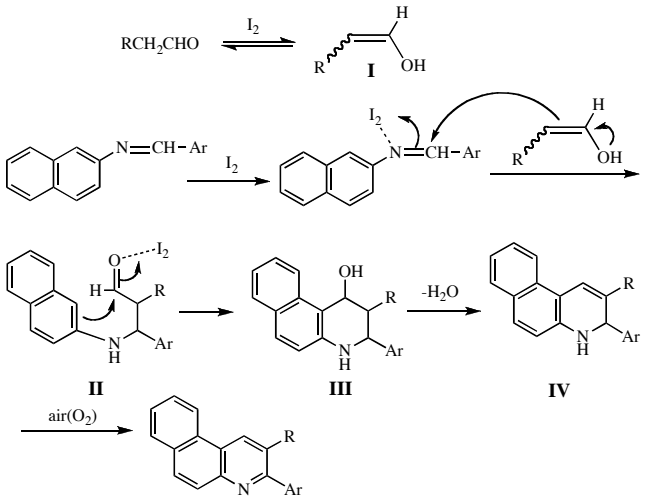
Table 3

I_2 catalyzed reaction of naphthalen-2-amine and alkyl aldehyde in THF

Entry	R	Products	Time / h	Yields [b]/ %
1	CH_3	**4a**	4	59
2	CH_2CH_3	**4b**	4	68
3	$(CH_2)_4CH_3$	**4c**	4	73

[a] Reagents and conditions: naphthalen-2-amine (2 mmol), **2** (4.2 mmol), I_2 (10 mol%), THF (10 mL). [b]Isolated yields.

Scheme 3



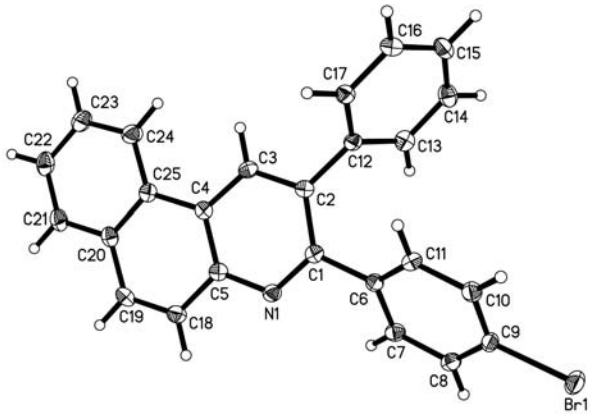


Figure 1. Crystal structure of product **3o**.

The products **3** and **4** were completely characterized by IR, ^{1}H NMR and elemental analyses, and the data was in agreement with their structures. In order to further confirm the structure, the X-ray diffraction analysis [15] of the product **3o** was carried out. The crystal structure of **3o** was shown in Figure 1.

In summary, we have developed a general route to benzo[*f*]quinolines from Schiff bases and alkyl aldehydes catalyzed by iodine. The procedure offers several advantages of mild and metal-free reaction conditions, operational simplicity, and inexpensive reagents.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a TENSOR 27 spectrometer in KBr pellet. ^{1}H NMR spectra were obtained in DMSO-d_6 solution with Me_4Si as internal standard using a Bruker-400 spectrometer. Elemental analyses were carried out using Perkin-Elmer 240 II analyzer. X-ray diffraction was measured on a Rigaku Mercury diffractometer.

Typical procedure for 3-arylbenzo[*f*]quinoline derivatives 3. A mixture of *N*-arylidenenaphthalen-2-amine (**1**, 2.0 mmol), alkyl aldehyde (**2**, 2.1 mmol), iodine (0.051 g, 0.2 mmol) and THF (10 mL) was stirred under reflux for several hours to complete the reaction (monitored by TLC). The reaction mixture was directly evaporated and 3-arylbenzo[*f*]quinoline derivatives **3** were obtained by silica gel column chromatography with petroleum ether–acetone (10:1, v/v).

3-(4-Chlorophenyl)-2-methylbenzo[*f*]quinoline (**3a**). This compound was obtained as pale yellow crystals, mp 168~170 °C; ir (KBr): ν_{max} 3048, 2969, 2929, 1594, 1561, 1478, 1449, 1401, 1373, 1276, 1236, 1219, 1168, 1108, 1086, 1035, 1012, 1003, 894, 830, 769, 757, 746, 727; ^{1}H nmr (DMSO-d_6): δ 2.57 (s, 3H, CH_3), 7.59 (d, J = 8.4 Hz, 2H, ArH), 7.72-7.79 (m, 4H, ArH), 7.90 (d, J = 9.2 Hz, 1H, ArH), 8.05-8.08 (m, 2H, ArH), 8.88 (d, J = 8.0 Hz, 1H, ArH), 9.17 (s, 1H, ArH).*Anal*. Calcd for $C_{20}H_{14}ClN$: C, 79.07; H, 4.65; N, 4.61. Found: C, 79.21; H, 4.59; N, 4.70.

3-(4-Fluorophenyl)-2-methylbenzo[*f*]quinoline (**3b**). This compound was obtained as pale yellow crystals, mp 157~158 °C; ir (KBr): ν_{max} 3065, 2984, 2966, 1599, 1562, 1506, 1477, 1450, 1440, 1397, 1384, 1299, 1276, 1157, 1094, 1038, 951, 903, 853, 837, 818, 796, 756, 702, 676; ^{1}H nmr (DMSO-d_6): δ 2.56 (s, 3H, CH_3), 7.35 (t, J = 8.8 Hz, 2H, ArH), 7.70-7.78 (m, 4H, ArH), 7.89 (d, J = 9.2 Hz, 1H, ArH), 8.04-8.07 (m, 2H, ArH), 8.87 (d, J = 8.0 Hz, 1H, ArH), 9.14 (s, 1H, ArH).*Anal*. Calcd for $C_{20}H_{14}FN$: C, 83.60; H, 4.91; N, 4.87. Found: C, 83.52; H, 4.90; N, 4.59.

3-(4-Bromophenyl)-2-methylbenzo[*f*]quinoline (**3c**). This compound was obtained as pale yellow crystals, mp 167~169 °C; ir (KBr): ν_{max} 3051, 2981, 2957, 1602, 1585, 1559, 1477, 1453, 1440, 1393, 1381, 1282, 1219, 1167, 1101, 1072, 1003, 904, 831, 795, 763, 784, 717; ^{1}H nmr (DMSO-d_6): δ 2.58 (s, 3H, CH_3), 7.66 (d, J = 8.4 Hz, 2H, ArH), 7.70-7.79 (m, 4H, ArH), 7.91 (d, J = 8.8 Hz, 1H, ArH), 8.05-8.09 (m, 2H, ArH), 8.89 (d, J = 8.4 Hz, 1H, ArH), 9.18 (s, 1H, ArH). *Anal*. Calcd for $C_{20}H_{14}BrN$: C, 68.98; H, 4.05; N, 4.02. Found: C, 68.77; H, 4.20; N, 4.08.

3-(2,4-Dichlorophenyl)-2-methylbenzo[*f*]quinoline (**3d**). This compound was obtained as pale yellow crystals, mp 157~158 °C; ir (KBr): ν_{max} 3058, 2959, 2920, 1604, 1586, 1552, 1474, 1449, 1401, 1376, 1277, 1034, 1168, 1140, 1098, 1074, 1039, 1031, 1004, 889, 869, 854, 829, 809, 755, 744, 704, 669; ^{1}H nmr (DMSO-d_6): δ 2.37 (s, 3H, CH_3), 7.58 (d, J = 8.0 Hz, 1H, ArH), 7.59 (d, J = 8.4 Hz, 1H, ArH), 7.71-7.81 (m, 3H, ArH), 7.88 (d, J = 9.2 Hz, 1H, ArH), 8.05-8.09 (m, 2H, ArH), 8.89 (d, J = 8.0 Hz, 1H, ArH), 9.20 (s, 1H, ArH). *Anal*. Calcd for $C_{20}H_{13}Cl_2N$: C, 71.02; H, 3.87; N, 4.14. Found: C, 71.20; H, 3.89; N, 4.05.

2-Methyl-3-(2-thiophenyl)-benzo[*f*]quinoline (**3e**). This compound was obtained as pale yellow crystals, mp 125~126 °C. ir (KBr): ν_{max} 3080, 3062, 2962, 2925, 1006, 1589, 1562, 1531, 1478, 1438, 1423, 1393, 1384, 1308, 1269, 1242, 1220, 1200, 1159, 1039, 989, 949, 902, 851, 830, 752, 743, 722, 703, 676; ^{1}H nmr (DMSO-d_6): δ 2.81 (s, 3H, CH_3), 7.23-7.25 (m, 1H, ArH), 7.66-7.77 (m, 4H, ArH), 7.84 (d, J = 8.8 Hz, 1H, ArH), 8.01-8.05 (m, 2H, ArH), 8.82 (d, J = 8.0 Hz, 1H, ArH), 9.11 (s, 1H, ArH). *Anal*. Calcd for $C_{18}H_{13}NS$: C, 78.51; H, 4.76; N, 5.09. Found: C, 78.66; H, 4.63; N, 4.97.

2-Methyl-3-(4-nitrophenyl)-benzo[*f*]quinoline (**3f**). This compound was obtained as pale yellow crystals, mp 187~188 °C; ir (KBr): ν_{max} 3046, 2965, 1597, 1566, 1518, 1512, 1481, 1451, 1399, 1385, 1344, 1321, 1284, 1200, 1101, 1054, 1034, 1008, 898, 864, 854, 825, 746, 731, 714, 696; ^{1}H nmr (DMSO-d_6): δ 2.59 (s, 3H, CH_3), 7.71-7.80 (m, 2H, ArH), 7.92 (d, J = 9.2 Hz, 1H, ArH), 7.99 (d, J = 8.4 Hz, 2H, ArH), 8.06-8.10 (m, 2H, ArH), 8.38 (d, J = 8.0 Hz, 2H, ArH), 8.90 (d, J = 8.0 Hz, 1H, ArH), 9.29 (s, 1H, ArH). *Anal*. Calcd for $C_{20}H_{14}N_2O_2$: C, 76.42; H, 4.49; N, 8.91. Found: C, 76.46; H, 4.55; N, 8.77.

2-Ethyl-3-(4-nitrophenyl)-benzo[*f*]quinoline (**3g**). This compound was obtained as pale yellow crystals, mp 152~153 °C; ir (KBr): ν_{max} 3080, 2961, 2920, 1603, 1597, 1568, 1517, 1477, 1444, 1347, 1319, 1281, 1103, 1034, 1013, 905, 864, 854, 836, 828, 748, 732, 718, 694; ^{1}H nmr (DMSO-d_6): δ 1.22 (t, J = 7.2 Hz, 3H, CH_3), 2.89 (q, J = 7.2 Hz, 2H, CH_2), 7.74-7.79 (m, 2H, ArH), 7.91 (d, J = 8.4 Hz, 3H, ArH), 8.06-8.11 (m, 2H, ArH), 8.38 (d, J = 8.0 Hz, 2H, ArH), 8.97 (d, J = 8.0 Hz, 1H, ArH), 9.23 (s, 1H, ArH). *Anal*. Calcd for $C_{21}H_{16}N_2O_2$: C, 76.81; H, 4.91; N, 8.53. Found: C, 76.70; H, 4.99; N, 8.50.

2-Ethyl-3-(2-thiophenyl)-benzo[*f*]quinoline (**3h**). This compound was obtained as pale yellow crystals, mp 104~106 °C; ir (KBr): ν_{max} 3054, 2967, 2934, 2908, 2979, 1603, 1586, 1563, 1529, 1475, 1442, 1423, 1400, 1382, 1329, 1309, 1265, 1240, 1224, 1201, 1134, 1083, 1068, 998, 905, 850, 827, 748, 735, 709, 673; ^{1}H nmr (DMSO-d_6): δ 1.40 (t, J = 7.2 Hz, 3H, CH_3), 3.18 (q, J = 7.2 Hz, 2H, CH_2), 7.23-7.26 (m, 1H, ArH), 7.70-7.76 (m, 4H, ArH), 7.86 (d, J = 8.4 Hz, 1H, ArH), 8.03-8.07 (m, 2H, ArH), 8.88 (d, J = 8.4 Hz, 1H, ArH), 9.11 (s, 1H, ArH).*Anal*. Calcd for $C_{19}H_{15}NS$: C, 78.86; H, 5.22; N, 4.84. Found: C, 78.67; H, 5.35; N, 4.98.

3-(4-Bromophenyl)-2-ethylbenzo[*f*]quinoline (**3i**). This compound was obtained as pale yellow crystals, mp 140~142 °C; ir (KBr): ν_{max} 3050, 2974, 2932, 2910, 2829, 1603, 1586, 1473, 1440, 1405, 1393, 1373, 1331, 1316, 1293, 1274, 1220, 1131, 1099, 1071, 1008, 1031, 903, 827, 791, 751, 739, 723; ^{1}H nmr (DMSO-d_6): δ 1.22 (t, J = 7.6 Hz, 3H, CH_3), 2.89 (q, J = 7.6 Hz, 2H, CH_2), 7.59 (d, J = 8.4 Hz, 2H, ArH), 7.71-7.78 (m, 4H, ArH), 7.90 (d, J = 8.8 Hz, 1H, ArH), 8.05-8.09 (m, 2H, ArH), 8.95 (d, J = 8.0 Hz, 1H, ArH), 9.17 (s, 1H, ArH). *Anal*. Calcd for $C_{21}H_{16}BrN$: C, 69.62; H, 4.45; N, 3.87. Found: C, 69.77; H, 4.40; N, 3.90.

2-Ethyl-3-(4-fluorophenyl)-benzo[*f*]quinoline (**3j**). This compound was obtained as pale yellow crystals, mp 124~126 °C; ir (KBr): ν_{max} 3054, 2972, 1600, 1058, 1474, 1441, 1403, 1377, 1333, 1318, 1275, 1222, 1160, 1097, 1031, 903, 861, 827, 792, 750; ^{1}H nmr (DMSO-d_6): δ 1.22 (t, J = 7.2 Hz, 3H, CH_3), 2.90 (q, J = 7.2 Hz, 2H, CH_2), 7.34-7.38 (m, 2H, ArH), 7.68-7.78 (m, 4H, ArH), 7.90 (d, J = 9.2 Hz, 1H, ArH), 8.06-8.09 (m,

2H, ArH), 8.95 (d, J = 8.0 Hz, 1H, ArH), 9.17 (s, 1H, ArH).*Anal*. Calcd for $C_{21}H_{16}FN$: C, 83.70; H, 5.35; N, 4.65. Found: C, 68.77; H, 4.20; N, 4.08.

3-(4-Chlorophenyl)-2-ethylbenzo[*f*]quinoline (**3k**). This compound was obtained as white powder, mp 142~143 °C, ir (KBr): ν_{max} 3051, 2974, 2939, 1600, 1055, 1484, 1441, 1275, 1133, 1092, 1032, 1013, 903, 872, 827, 768, 751; ^{1}H nmr (DMSO-d_6): δ 1.23 (t, J = 7.6 Hz, 3H, CH_3), 2.90 (q, J = 7.6 Hz, 2H, CH_2), 7.60 (d, J = 8.4 Hz, 2H, ArH), 7.67 (d, J = 8.4 Hz, 2H, ArH), 7.71-7.80 (m, 2H, ArH), 7.91 (d, J = 8.8 Hz, 1H, ArH), 8.06-8.10 (m, 2H, ArH), 8.96 (d, J = 8.0 Hz, 1H, ArH), 9.18 (s, 1H, ArH). *Anal*. Calcd for $C_{21}H_{16}ClN$: C, 79.36; H, 5.07; N, 4.41. Found: C, 79.50; H, 5.00; N, 4.48.

3-(3,4-Dichlorophenyl)-2-ethylbenzo[*f*]quinoline (**3l**). This compound was obtained as pale yellow crystals, mp 105~107 °C; ir (KBr): ν_{max} 3059, 2957, 2932, 2877, 1584, 1553, 1466, 1444, 1406, 1388, 1373, 1337, 1311, 1281, 1248, 1219, 1134, 1069, 1028, 905, 880, 870, 837, 806, 750, 700; ^{1}H nmr (DMSO-d_6): δ 1.23 (t, J = 7.6 Hz, 3H, CH_3), 2.89 (q, J = 7.6 Hz, 2H, CH_2), 7.63 (d, J = 8.4 Hz, 1H, ArH), 7.71-7.80 (m, 3H, ArH), 7.91 (d, J = 9.2 Hz, 2H, ArH), 8.05-8.10 (m, 2H, ArH), 8.95 (d, J = 8.0 Hz, 1H, ArH), 9.18 (s, 1H, ArH). *Anal*. Calcd for $C_{21}H_{15}Cl_2N$: C, 71.60; H, 4.29; N, 3.98. Found: C, 68.77; H, 4.20; N, 4.08.

3-(3-Bromophenyl)-2-ethylbenzo[*f*]quinoline (**3m**). This compound was obtained as white powder, mp 88~90 °C; ir (KBr): ν_{max} 3059, 2970, 2926, 2869, 1589, 1558, 1474, 1445, 1407, 1379, 1294, 1276, 1195, 1164, 1061, 908, 875, 830, 793, 769, 750, 719, 690; ^{1}H nmr (DMSO-d_6): δ 1.23 (t, J = 7.2 Hz, 3H, CH_3), 2.90 (q, J = 7.2 Hz, 2H, CH_2), 7.49~7.52 (m, 1H, ArH), 7.64 (d, J = 8.4 Hz, 1H, ArH), 7.70-7.81 (m, 4H, ArH), 7.91 (d, J = 9.2 Hz, 1H, ArH), 8.06-8.10 (m, 2H, ArH), 8.96 (d, J = 8.4 Hz, 1H, ArH), 9.18 (s, 1H, ArH). *Anal*. Calcd for $C_{21}H_{16}BrN$: C, 69.62; H, 4.45; N, 3.87. Found: C, 69.51; H, 4.62; N, 3.98.

3-(4-Nitrophenyl)-2-phenylbenzo[*f*]quinoline (**3n**). This compound was obtained as Pale yellow crystals, mp 224~226 °C; ir (KBr): ν_{max} 3050, 1668, 1596, 1562, 1512, 1473, 1432, 1396, 1382, 1342, 1311, 1277, 1246, 1179, 1138, 1105, 1063, 1011, 909, 864, 852, 837, 759, 747, 701; ^{1}H nmr (DMSO-d_6): δ 7.40 (s, 5H, ArH), 7.69 (d, J = 8.4 Hz, 2H, ArH), 7.76-7.78 (m, 2H, ArH), 8.02 (d, J = 8.8 Hz, 1H, ArH), 8.18 (d, J = 8.4 Hz, 2H, ArH), 8.20 (d, J = 8.0 Hz, 2H, ArH), 9.03 (d, J = 7.6 Hz, 1H, ArH), 9.29 (s, 1H, ArH). *Anal*. Calcd for $C_{25}H_{16}N_2O_2$: C, 79.77; H, 4.28; N, 7.44. Found: C, 79.85; H, 4.13; N, 7.54.

3-(4-Bromophenyl)-2-phenylbenzo[*f*]quinoline (**3o**). This compound was obtained as pale yellow crystals, mp 205~207 °C; ir (KBr): ν_{max} 3056, 1678, 1603, 1584, 1566, 1487, 1472, 1431, 1402, 1393, 1277, 1247, 1178, 1104, 1072, 1008, 947, 910, 864, 833, 776, 760, 748, 716, 700; ^{1}H nmr (DMSO-d_6): δ 7.38 (d, J = 8.4 Hz, 2H, ArH), 7.39 (s, 5H, ArH), 7.52 (d, J = 8.4 Hz, 2H, ArH), 7.74-7.76 (m, 2H, ArH), 7.99 (d, J = 8.8 Hz, 1H, ArH), 8.09-8.11 (m, 1H, ArH), 8.17 (d, J = 8.8 Hz, 1H, ArH), 9.19 (d, J = 7.6 Hz, 1H, ArH), 9.21 (s, 1H, ArH). *Anal*. Calcd for $C_{25}H_{16}BrN$: C, 73.18; H, 3.93; N, 3.41. Found: C, 73.25; H, 3.88; N, 3.20.

3-(4-Chlorophenyl)-2-phenylbenzo[*f*]quinoline (**3p**). This compound was obtained as pale yellow crystals, mp 186~188 °C; ir (KBr): ν_{max} 3083, 3048, 1603, 1588, 1568, 1493, 1472, 1431, 1395, 1383, 1277, 1246, 1177, 1086, 1012, 948, 910, 864, 833, 776, 764, 749, 723, 700, 676; ^{1}H nmr (DMSO-d_6): δ 7.36-7.44 (m, 9H, ArH), 7.73-7.76 (m, 2H, ArH), 7.98 (d, J = 9.2 Hz, 1H, ArH), 8.08 (d, J = 6.8 Hz, 1H, ArH), 8.15 (d, J = 9.2 Hz, 1H, ArH), 8.97 (d, J = 7.6 Hz, 1H, ArH), 9.19 (s, 1H, ArH). *Anal*. Calcd for $C_{25}H_{16}ClN$: C, 82.07; H, 4.41; N, 3.83. Found: C, 82.30; H, 4.19; N, 4.01.

3-(4-Fluorophenyl)-2-phenylbenzo[*f*]quinoline (**3q**). This compound was obtained as pale yellow crystals, mp 145~147 °C; ir (KBr): ν_{max} 3045, 1602, 1559, 1518, 1508, 1475, 1454, 1432, 1401, 1383, 1276, 1234, 1156, 1081, 1005, 909, 830, 814, 779, 753, 705; ^{1}H nmr (DMSO-d_6): δ 7.15 (d, J = 8.8 Hz, 2H, ArH), 7.36-7.42 (m, 5H, ArH), 7.45-7.49 (m, 2H, ArH), 7.72-7.78 (m, 2H, ArH), 7.99 (d, J = 8.8 Hz, 1H, ArH), 8.08-8.10 (m, 1H, ArH), 8.17 (d, J = 8.8 Hz, 1H, ArH), 8.98 (d, J = 7.6 Hz, 1H, ArH), 9.19 (s, 1H, ArH). *Anal*. Calcd for $C_{25}H_{16}FN$: C, 85.94; H, 4.62; N, 4.01. Found: C, 85.90; H, 4.55; N, 4.13.

3-(3-Bromophenyl)-2-phenylbenzo[*f*]quinoline (**3r**). This compound was obtained as pale yellow crystals, mp 144~145 °C; ir (KBr): ν_{max} 3054, 3027, 1599, 1558, 1471, 1451, 1440, 1431, 1415, 1392, 1309, 1278, 1246, 1222, 1075, 1062, 1004, 925, 908, 879, 830, 796, 767, 754, 703, 686; ^{1}H nmr (DMSO-d_6): δ 7.23-7.27 (m, 1H, ArH), 7.33-7.40 (m, 6H, ArH), 7.53 (d, J = 8.0 Hz, 1H, ArH), 7.67 (s, 1H, ArH), 7.72-7.78 (m, 2H, ArH), 8.01 (d, J = 9.2 Hz, 1H, ArH), 8.10 (d, J = 8.0 Hz, 1H, ArH), 8.18 (d, J = 9.2 Hz, 1H, ArH), 8.99 (d, J = 7.2 Hz, 1H, ArH), 9.20 (s, 1H, ArH). *Anal*. Calcd for $C_{25}H_{16}BrN$: C, 73.18; H, 3.93; N, 3.41. Found: C, 73.27; H, 3.89; N, 3.29.

2-Phenyl-3-(2-thiophenyl)-benzo[*f*]quinoline (**3s**). This compound was obtained as yellow crystals, mp 184~186 °C; ir (KBr): ν_{max} 3050, 1604, 1580, 1561, 1526, 1473, 1437, 1422, 1392, 1305, 1273, 1248, 1228, 1097, 1058, 1003, 912, 866, 848, 829, 756, 710; ^{1}H nmr (DMSO-d_6): δ 6.51-6.52 (m, 1H, ArH), 6.83-6.91 (m, 1H, ArH), 7.52-7.54 (m, 5H, ArH), 7.62 (d, J = 9.2 Hz, 1H, ArH), 7.70-7.72 (m, 2H, ArH), 7.93 (d, J = 8.8 Hz, 1H, ArH), 8.06-8.07 (m, 1H, ArH), 8.14 (d, J = 9.2 Hz, 1H, ArH), 8.87~8.89 (m, 1H, ArH), 9.02 (s, 1H, ArH). *Anal*. Calcd for $C_{23}H_{15}NS$: C, 81.87; H, 4.48; N, 4.15. Found: C, 81.80; H, 4.59; N, 4.07.

2-(*n*-Amyl)-3-(4-bromophenyl)-benzo[*f*]quinoline (**3t**). This compound was obtained as yellow crystals, mp 93~95 °C; ir (KBr): ν_{max} 3054, 2955, 2926, 2854, 1624, 1592, 1516, 1476, 1446, 1407, 1307, 1237, 1102, 1072, 1032, 1010, 905, 869, 838, 812, 765, 750, 741, 727; ^{1}H nmr (DMSO-d_6): δ 0.78 (t, J = 6.8 Hz, 3H, CH_3), 1.20~1.23 (m, 4H, $2CH_2$), 1.55~1.58 (m, 2H, CH_2), 2.89 (t, J = 7.2 Hz, 2H, CH_2), 7.58 (d, J = 8.4 Hz, 2H, ArH), 7.72-7.78 (m, 4H, ArH), 7.90 (d, J = 8.8 Hz, 1H, ArH), 8.06-8.09 (m, 2H, ArH), 8.95 (d, J = 8.0 Hz, 1H, ArH), 9.18 (s, 1H, ArH). *Anal*. Calcd for $C_{24}H_{22}BrN$: C, 71.29; H, 5.48; N, 3.46. Found: C, 71.25; H, 5.58; N, 3.27.

2-(*n*-Amyl)-3-(3-bromophenyl)-benzo[*f*]quinoline (**3u**). This compound was obtained as yellow crystals, mp 79~81 °C; ir (KBr): ν_{max} 3052, 2953, 2924, 2857, 1624, 1591, 1560, 1478, 1448, 1405, 1377, 1273, 1056, 906, 887, 836, 810, 782, 752, 695; ^{1}H nmr (DMSO-d_6): δ 0.80 (t, J = 6.8 Hz, 3H, CH_3), 1.20~1.24 (m, 4H, $2CH_2$), 1.57~1.60 (m, 2H, CH_2), 2.87 (t, J = 7.6 Hz, 2H, CH_2), 7.48-7.52 (m, 1H, ArH), 7.62 (d, J = 7.6 Hz, 1H, ArH), 7.69-7.79 (m, 4H, ArH), 7.90 (d, J = 9.2 Hz, 1H, ArH), 8.06-8.09 (m, 2H, ArH), 8.95 (d, J = 8.0 Hz, 1H, ArH), 9.18 (s, 1H, ArH). *Anal*. Calcd for $C_{24}H_{22}BrN$: C, 71.29; H, 5.48; N, 3.46. Found: C, 71.33; H, 5.56; N, 3.40.

Typical procedure for 2,3-dialkylbenzo[*f*]quinoline derivatives 4. A mixture of naphthalen-2-amine (2.0 mmol), alkyl aldehyde (2, 4.2 mmol), iodine (0.051 g, 0.2 mmol) and THF (10 mL) was stirred under reflux for several hours to

complete the reaction (monitored by TLC). The reaction mixture was directly evaporated and 2,3-dialkylbenzo[*f*]quinoline derivatives **4** were obtained by silica gel column chromatography with petroleum ether–acetone (10:1, v/v).

3-Ethyl-2-methylbenzo[*f*]quinoline (**4a**). This compound was obtained as pale yellow crystals, mp 215-217 °C; ir (KBr): ν_{max} 3030, 2979, 2920, 2846, 2822, 1584, 1570, 1560, 1516, 1473, 1459, 1391, 1355, 1304, 1271, 1229, 1060, 1035, 894, 881, 818, 763, 714; ^{1}H nmr (DMSO-d_6): δ 1.38 (t, J = 7.6 Hz, 3H, CH_3), 2.71 (s, 3H, CH_3), 3.19 (q, J = 7.0 Hz, 2H, CH_3), 7.85-7.95 (m, 2H, ArH), 8.05 (d, J = 9.2 Hz, 1H, ArH), 8.21 (d, J = 8.0 Hz, 1H, ArH), 8.41 (d, J = 8.8 Hz, 1H, ArH), 8.99 (d, J = 8.0 Hz, 1H, ArH), 9.73 (s, 1H, ArH). *Anal*. Calcd for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33. Found: C, 86.97; H, 6.68; N, 6.30.

2-Ethyl-3-(*n*-proyl)-benzo[*f*]quinoline (**4b**). This compound was obtained as Pale yellow crystals, mp 208~210 °C; ir (KBr): ν_{max} 2960, 2928, 2869, 1634, 1602, 1582, 1514, 1468, 1453, 1430, 1360, 1318, 1287, 1258, 1223, 1205, 1081, 934, 895, 825, 755, 713; ^{1}H nmr (DMSO-d_6): δ 0.87 (t, J = 7.2 Hz, 3H, CH_3), 1.07 (t, J = 7.2 Hz, 3H, CH_3), 1.39-1.43 (m, 2H, CH_3), 3.05 (q, J = 7.2 Hz, 2H, CH_3), 3.19 (t, J = 7.8 Hz, 2H, CH_3), 7.87-7.96 (m, 2H, ArH), 8.07 (d, J = 9.2 Hz, 1H, ArH), 8.23 (d, J = 8.8 Hz, 1H, ArH), 8.45 (d, J = 9.2 Hz, 1H, ArH), 9.10 (d, J = 8.0 Hz, 1H, ArH), 9.75 (s, 1H, ArH). *Anal*. Calcd for $C_{18}H_{19}N$: C, 86.70; H, 7.68; N, 5.62. Found: C, 86.79; H, 7.60; N, 5.55.

2-(*n*-Amyl)-3-(*n*-hexyl)-benzo[*f*]quinoline (**4c**). This compound was obtained as pale yellow crystals, mp 51~52 °C. ir (KBr): ν_{max} 3051, 2952, 2923, 2857, 1610, 1569, 1479, 1467, 1432, 1406, 1381, 1353, 1305, 1231, 1207, 1185, 1126, 1031, 906, 897, 830, 749, 728; ^{1}H nmr (DMSO-d_6): δ 0.84~0.90(m, 6H, $2CH_3$), 1.30~1.38 (m, 10H, $5CH_2$), 1.66~1.78 (m, 4H, $2CH_2$), 2.84 (t, J = 7.6 Hz, 2H, CH_2), 2.92 (t, J = 7.6 Hz, 2H, CH_2), 7.63-7.73 (m, 2H, ArH), 7.83 (d, J = 9.2 Hz, 1H, ArH), 7.98-8.01 (m, 2H, ArH), 8.82 (d, J = 8.0 Hz, 1H, ArH), 8.90 (s, 1H, ArH). *Anal*. Calcd for $C_{24}H_{31}N$: C, 86.43; H, 9.37; N, 4.20. Found: C, 86.30; H, 9.52; N, 4.11.

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REFERENCES AND NOTES

[1] Brock, E. D.; Lewis, D. M.; Yousaf, T. I.; Harper, H. H. (The Procter and Gamble Company USA) WO9951688, **1999**.

[2a] Beagley, P.; Blackie, M. A. L.; Chibale, K.; Clarkson, C.; Meijboom, R.; Moss, J. R.; Smith, P.; Su, H. *Dalton Trans*. **2003**, 3046-3051. [b] Sawada, Y.; Kayakiri, H.; Abe, Y.; Mizutani, T.; Inamura, N.; Asano, M.; Hatori, C.; Aramori, I.; Oku, T.; Tanaka, H. *J. Med. Chem*. **2004**, *47*, 2853-2863. [c] Ma, Z.; Hano, Y.; Nomura, T.; Chen, Y. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 1193-1196. [d] Denton, T. T.; Zhang, X.; Cashman, J. R. *J. Med. Chem*. **2005**, *48*, 224-239. [e] Fokialakis, N.; Magiatis, P.; Chinou, L.; Mitaku, S.; Tillequin, F. *Chem. Pharm. Bull*. **2002**, *50*, 413-414. [f] Fossa, P.; Mosti, L.; Menozzi, G.; marzano, C.; Baccichetti, F.; Bordin, F. *Bioorg. Med. Chem*. **2002**, *10*, 743-751. [g] Ryckebusch, A.; Derprez-Poulain, R.; Maes, L.; Debreu-Fontaine, M. A.; Mouray, E.; Grellier, P.; Sergheraert, C.; *J. Med. Chem*. **2003**, *46*, 542-557. [h] Morgan, L. R.; Jursic, B. S.; Hooper, C. L.; Neumann, D. M.; Thangaraj, K.; Leblanc, B. *Bioorg. Med. Chem. Lett*. **2002**, *12*, 3407-3411.

[3] Sakata, G.; Makino, K.; Karasawa, Y. *Heterocycles* **1988**, 27, 2481–2515,

[4a] Demeunynck, M.; Moucheron, C.; Mesmaeker, A. K.-D. *Tetrahedron Lett*. **2002**, *43*, 261–264; [b] Baraznenok, I. L.; Nenajdenko, V. G.; Balenkova, E. S. *Eur. J. Org. Chem*. **1999**, 937–941; [c] Ali, M. M.; Tasneem, K. C.; Rajanna, P. K.; Prakash, S. *Synlett* **2001**, 251–253; [d] Palacios, F.; Ochoa de Retana, A. M.; Oyarzabal, J. *Tetrahedron* **1999**, *55*, 5947–5964; [e] Charpentier, P.; Lobregat, V.; Levacher, V.; Dupas, G.; Queguiner, G.; Bourguignon, J. *Tetrahedron Lett*. **1998**, *39*, 4013–4016; [f] Cho, C. S.; Kim, B. T.; Kim, T. J.; Shim, S. C. *Chem. Commun*. **2001**, 2576–2577; [g] Uchiyama, K.; Hayashi, Y.; Narasaka, K. *Synlett* **1997**, 445–447; [h] Crousse, B.; Begue, J.-P.; Bonnet-Delpon, D. *J. Org. Chem*. **2000**, *65*, 5009–5013; [i] Lin, X. F.; Cui, S. L.; Wang, Y. G. *Tetrahedron Lett*. **2006**, *47*, 4509-4512. [j] Lin, X. F.; Cui, S. L.; Wang, Y. G. *Tetrahedron Lett*. **2006**, *47*, 3127-3130.

[5a] Skraup, H. *Chem. Ber*. **1880**, *13*, 2086–2087; [b] Mansake, R. H.; Kulka, M. *Org. React*. **1953**, *7*, 59–61; [c] Doebner, O.; Miller, V. W. *Chem. Ber*. **1881**, *14*, 2812–2813; [d] Conrad, M.; Limbach, L. *Chem. Ber*. **1887**, *20*, 944–945; [e] Combes, A. *Compt. Rend*. **1888**, *106*, 142–143; [f] Pfitzinger, W. *J. Prakt. Chem*. **1886**, *33*, 100.

[6] Whitmore, F. C.; Rothrock, H. S. *J. Am. Chem. Soc*. **1933**, *55*, 1106–1109.

[7] Rutherford, K. G.; Mamer, O. A.; Prokipcak, J. M.; Jobin, R. A. *Can. J. Chem*. **1966**, *44*, 2337–2339.

[8] Jenner, G. *Tetrahedron Lett*. **1988**, *29*, 2445–2448. 15. Hessian, K. O.; Flynn, B. L. *Org. Lett*. **2003**, *5*, 4377–4380.

[9] Bandgar, B. P.; Shaikh, K. A. *Tetrahedron Lett*. **2003**, *44*, 1959–1961.

[10] Sun, J.; Dong, Y.; Cao, L.; Wang, X.; Wang, S.; Hu, Y. *J. Org. Chem*. **2004**, *69*, 8932–8934.

[11] Ramalinga, K.; Vijayalakshimi, P.; Kaimal, T. N. B. *Tetrahedron Lett*. **2002**, *43*, 879–882.

[12] Chavan, S. P.; Kale, R. R.; Shivasankar, K.; Chandake, S. I.; Benjamin, S. B. *Synthesis* **2003**, 2695–2698.

[13a] Yadav, J. S.; Reddy, B. V. S.; Sadasiv, K.; Satheesh, G. *Tetrahedron Lett*. **2002**, *43*, 9695–9697; [b] Wang, S. Y.; Ji, S. J.; Loh, T. P. *Synlett* **2003**, 2377–2379.

[14a] Ji, S. J.; Wang, S. Y.; Zhang, Y.; Loh, T. P. *Tetrahedron* **2004**, *60*, 2051–2055; [b] Ke, B. W.; Qin, Y.; He, Q. F.; Huang, Z. Y.; Wang, F. P. *Tetrahedron Lett*. **2005**, *46*, 1751–1753.

[15] Crystal data for **3o**: $C_{25}H_{16}BrN$; M = 410.30, Pale yellow block crystals, 0.78 × 0.55 × 0.17 mm, Monoclinic, space group P 21/c, a = 12.704 (2), b = 9.4917 (14), c = 15.142 (3) Å, β = 94.612 (4) °, V = 1819.9 (5) ^{3}, Z = 4, D_c = 1.497 g.cm^{-3}. F(000) = 832, μ(Mo$K\alpha$) = 2.268 mm^{-1}. Intensity data were collected on Rigaku Mercury diffractometer with graphite monochromated Mo$K\alpha$ radiation (λ = 0.71070 Å) using ω scan mode with 3.03 ° < θ < 25.35 °. 3336 unique reflections were measured and 3034 reflections with I>2σ(I) were used in the refinement. Structure solved by direct methods and expanded using Fourier techniques. The final cycle of full-matrix least squares technique to R = 0.0423 and wR = 0.0814.