An Improved Procedure for the Three-Component Synthesis of Benzo[*g*]chromene Derivatives Using Basic Ionic Liquid

Yi Yu, Hongyun Guo,* and Xiaojun Li

College of Chemical Engineering and Materials, Zhejiang University of Technology, Hangzhou 310014, People's Republic of China
*E-mail: guohy63@163.com

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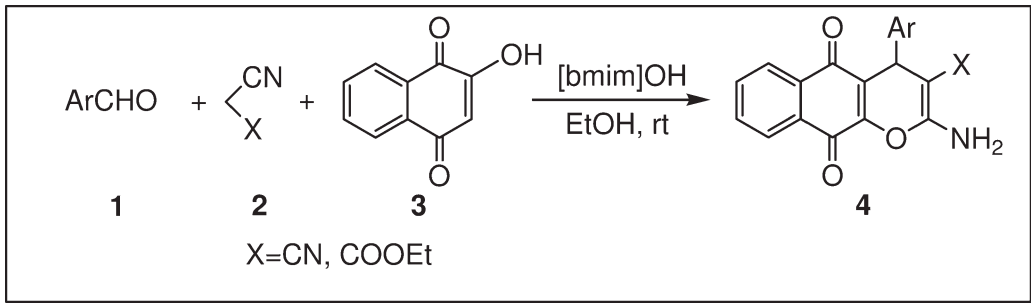

A basic ionic liquid, 1-butyl-3-methyl imidazolium hydroxide ([bmim]OH), efficiently promotes a one-pot, three-component condensation of aromatic aldehydes, malononitrile or ethyl cyanoacetate, and 2-hydroxy-1,4-naphthoquinone to produce 4-aryl-5,10-dihydro-4*H*-benzo[*g*]chromene-5,10-dione derivatives in high yields at room temperature. This reaction does not involve any hazardous organic solvent and toxic catalyst. The ionic liquid is recovered and recycled for subsequent reactions. Moreover, this protocol has the advantages of easy work-up, short reaction time, high yields, and environmentally benign procedure compared with the reported methods.

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INTRODUCTION

Naturally occurring naphthoquinones comprise an important class of natural products with a wide range of biological activity [1] arising from their capability to cause DNA modification. Among the structurally diverse naphthoquinone natural products, lapachol (**a**, Fig. 1) and several 1,4- and 1,2-naphthoquinones are associated with diverse biological activities [2] and are components of antibacterial, fungicidal [3], antimalarial [4], trypanocidal, antiparasitic [5], and antitumoral [6] agents.

One of the most important lapachol derivatives with antitumoral activity is α-lapachone (**b**, Fig. 1). Structure–activity relationship studies in lapachones have shown that the modification to the C-ring [7] leads to significant changes in bioactivities, which are important in searching for possible lead compounds with more potent pharmaceutical activity and less toxicity. On the basis of biological properties, 1,4- and 1,2-naphthoquinones are considered privileged structures in medicinal chemistry [8], with the 1,4-naphthoquinones having great cancer-preventing potential [9]. In addition, more recent investigations have shown that α-lapachone is an effective DNA topoisomerase II inhibitor and is a potential lead compound for the development of drugs for the treatment of multidrug resistant cell lines with low expressions of topoisomerase II [10].

To the best of our knowledge, only few methods are available for the preparation of 4-aryl-5,10-dihydro-4*H*-benzo[*g*]chromene-5,10-dione derivatives [11–14], however, these methods have various drawbacks: reactions require a long time, cannot be carried out one-step operation, harsh reaction conditions, high temperature, and nonrecyclability. Therefore, it is desirable to develop a more efficient and a general method for the synthesis of 4*H*-benzo[*g*]chromene derivatives.

Multicomponent reactions (MCRs) are a powerful method for the synthesis of organic compounds, as the products are formed in a single step, and diversity can be achieved by simply varying each component [15]. Because of their easy operations and good results, MCRs have attracted much attention [16,17].

Our recent interest has been in the development of new synthetic methods on using ionic liquids as reaction media and catalyst [18]. Herein, we would like to report a highly efficient, convenient, and facile method for the synthesis of 4-aryl-5,10-dihydro-4*H*-benzo[*g*]chromene-5,10-dione derivatives in the presence of basic ionic liquid [bmim]OH as catalyst at room temperature.

RESULTS AND DISCUSSION

Initially, the three-component reaction of benzaldehyde (**1a**, 1 mmol), malononitrile (**2**, 1 mmol), and 2-

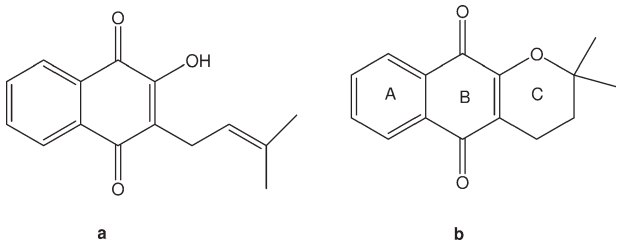


Figure 1. Examples of lapachol derivatives.

hydroxy-1,4-naphthoquinone (**3**, 1 mmol) was carried out in different solvents in the presence of [bmim]OH (10 mol%) at room temperature. As illustrated in Table 1, ethanol was preferred as the optimal solvent. Moreover, we found that the yield of this reaction was affected by the temperature. When the temperature was increased from 40 to 80°C, the yield of product **4a** was decreased from 88 to 52% (Table 1, entries 7–9). We believe that low reaction temperature in this reaction suppress the formation of these side products, hence, yield of the product increases. Therefore, the best temperature for the reaction was room temperature.

Based on the optimized reaction conditions, a series of 4-aryl-5,10-dihydro-4*H*-benzo[*g*]chromene-5,10-dione derivatives were synthesized. The results were summarized in Table 2, show that the three-component reaction in the presence of 10 mol% [bmim]OH at room temperature gave the corresponding products in moderate to good yields. It is obvious that this protocol could be applied to various aromatic aldehydes with electron-withdrawing groups or electron-donating groups. Besides, the results suggest that the substrates bearing electron-withdrawing groups have higher reactivity (higher yields and shorter reaction time) than those bearing electron-donating groups. So, it is concluded that the electronic nature of the substituents on aldehydes has some effect on this reaction. These three-component condensation reactions also proceeded with ethyl caynoacetate (Table 2, entries 13–14), in these cases, the reaction times are longer. It may be due to the less activity of ethyl caynoacetate than malononitrile. However, when the aliphatic aldehyde was applied to this reaction, no expected product was obtained, we attribute this to the slow formation and unstable nature of the alkylidenemalonitrile formed from the aliphatic aldehydes examined. In a further study, alkylidenemalonitrile and 2-hydroxy-1,4-naphthoquinone was used in the same conditions, no desired product was obtained, it may be due to electronic effect. In this study, all the products were characterized by mp, IR, ^{1}H NMR, ^{13}C NMR, and elemental analyses.

As a green solvent or catalyst, the recovery and reuse of ionic liquid are very important in green synthetic process. Therefore, we studied on the reuse of [bmim]OH through model reaction. As shown in Table 3, the ionic liquid [bmim]OH could be successively recovered and reused for four times without remarkable loss in the catalytic activity.

A reasonable mechanism for the formation of the product **4** is outlined in Scheme 2. The reaction occurs via initial formation of benzylidenemalononitrile in quantitative yield by the Knoevenagel addition of malononitrile **2** to the aldehyde **1** and followed by loss of water molecules. Subsequently, presumably involving the *ortho* C-alkylation of 2-hydroxy-1,4-naphthoquinone by reaction with the electrophilic C=C double bond and the nucleophilic addition of the OH group the CN moiety producing the final benzo[*g*]chromene **4**.

Table 1

Reaction conditions optimization for the synthesis of **4a**.

Entry	Solvent	Temperature (°C)	Time (h)	Yield (%)
1	$CHCl_3$	r.t.	2	56
2	CH_3CN	r.t.	2	90
3	DMF	r.t.	2	85
4	CH_3OH	r.t.	2	77
5	H_2O	r.t.	2	Trace
6	C_2H_5OH	r.t.	2	91
7	C_2H_5OH	40	6	88
8	C_2H_5OH	60	6	79
9	C_2H_5OH	80	6	52

Table 2

Synthesis of 4*H*-benzo[g]chromene derivatives **4** using [bmim]OH as catalyst in ethanol.

Entry	Ar	X	Products	Time (h)	Yield (%)
1	C_6H_5—	CN	**4a**	1.0	91
2	4-Cl—C_6H_4—	CN	**4b**	0.8	92
3	4-MeO—C_6H_4—	CN	**4c**	2.0	80
4	4-F—C_6H_4—	CN	**4d**	0.8	88
5	4-OH—C_6H_4—	CN	**4e**	1.5	79
6	4-CH_3—C_6H_4—	CN	**4f**	2.0	81
7	4-NO_2—C_6H_4—	CN	**4g**	0.6	93
8	3-Br—C_6H_4—	CN	**4h**	0.9	89
9	4-OH—3-OCH_3—C_6H_3—	CN	**4i**	2.0	78
10	2-Cl—C_6H_4—	CN	**4j**	1.0	85
11	2,4-Cl_2—C_6H_3—	CN	**4k**	0.7	88
12	2-NO_2—C_6H_4—	CN	**4l**	1.0	82
13	4-Cl—C_6H_4—	COOEt	**4m**	2.0	78
14	4-CH_3—C_6H_4—	COOEt	**4n**	3.0	70

CONCLUSIONS

In summary, the highly functionalized 4*H*-benzo[*g*]-chromene derivatives are of intense attention because of their potential for biological activities, and thus an efficient procedure for their synthesis is of high importance. The present procedure using a basic ionic liquid,

Table 3
Studies on the reuse of [bmim]OH in the preparation of **4a**.

Round	1	2	3	4	5
Yield (%)	91	89	90	87	75

[bmim]OH, in place of conventional bases provides a selective, high yielding one-pot synthesis of highly functionalized 4*H*-benzo[*g*]chromene through a three-component condensation process. The other advantages of this procedure are the use of no hazardous organic solvent in the reaction and the reusability of ionic liquids.

EXPERIMENTAL

Melting points were determined with a X-4 microscopic melting-point apparatus and were uncorrected. IR spectra were recorded on a NEXUS 670 spectrometer in KBr. ^{1}H NMR and ^{13}C NMR spectra were measured on a BRUKER AVANCE-II 500-MHz spectrometer using TMS as an internal standard and DMSO-d_6 as solvent. Elemental analyses were performed on FLASH EA 1112 elemental analyzer.

The synthesis of this task-specific ionic liquid has been carried out from a similar method in the literature [19]. The ionic liquid was formed quantitatively and in high purity as assessed by ^{1}H NMR. All other chemicals (AR grade) were commercially available and used without further purification.

General procedure for the synthesis of 4*H*-benzo[*g*]chromene derivatives 4. The mixture of the aromatic aldehyde **1** (1 mmol), malononitrile or ethyl cyanoacetate **2** (1 mmol), 2-hydroxy-1,4-naphthoquinone **3** (1 mmol), [bmim]OH (0.1 mmol) in EtOH (5 mL) was stirred at room temperature for the appropriate time (monitored by thin-layer chromatography). After completion of the reaction, the result mixture was cooled to room temperature and poured into 10 mL of water. The solid product was collected by filtration and recrystallized from ethanol to give the pure compound **4**. The filtrate was extracted with diethyl ether several times to remove unreacted starting materials and other organic contaminations. Then, the water was evaporated under reduced pressure and dried to recover the ionic liquid for subsequent use.

2-Amino-5,10-dioxo-4-phenyl-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile (4a). This compound was obtained as orange powder with mp 260−261°C (Lit. [11] 261−262°C); IR ν_{max} (KBr): 3401, 3325, 3193, 2199, 1670, 1601, 1405, 1365, 1245, 1205 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 4.61 (1H, s, CH), 7.22−8.07 (11H, m, ArH, and NH_2); ^{13}C NMR (DMSO-d_6): δ 36.5, 57.5, 119.3, 122.1, 125.8, 126.0, 127.1, 127.8, 128.9, 130.7, 131.0, 134.2, 134.5, 143.8, 149.1, 158.6, 177.0, 182.8. *Anal*. calcd. For $C_{20}H_{12}N_2O_3$: C, 73.16; H, 3.68; N, 8.53. Found: C, 73.08; H, 3.62; N, 8.60.

2-Amino-4-(4-chlorophenyl)-5,10-dioxo-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile (4b). This compound was obtained as orange powder with mp 250−252°C (Lit. [11] 249−252°C); IR ν_{max} (KBr): 3410, 3331, 3194, 2203, 1668, 1595, 1411, 1363, 1244, 1205 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 4.65 (1H, s, CH), 7.37−8.07 (10H, m, ArH and NH_2); ^{13}C NMR (DMSO-d_6): δ 36.0, 57.1, 119.5, 121.2, 125.8, 126.1, 128.5, 130.0, 130.9, 131.1, 131.8, 134.1, 134.5, 143.1, 149.0, 158.4, 177.1, 182.5. *Anal*. calcd. For $C_{20}H_{11}ClN_2O_3$: C, 66.22; H, 3.06; N, 7.72. Found: C, 66.15; H, 3.01; N, 7.84.

2-Amino-4-(4-methoxyphenyl)-5,10-dioxo-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile (4c). This compound was obtained as orange powder with mp 244−246°C (Lit. [11] 247−248°C); IR ν_{max} (KBr): 3406, 3333, 2199, 1668, 1596, 1462, 1331, 1244, 1204 cm^{-1}; ^{1}H NMR (DMSO-d_6):δ 3.71 (3H, s, OCH_3), 4.56 (1H, s, CH), 6.84−8.05 (10H, m, ArH and NH_2); ^{13}C NMR (DMSO-d_6): δ 35.8, 55.8, 58.0, 114.1, 119.5, 122.2, 125.8, 126.1, 128.9, 130.7, 131.2, 134.1, 134.5, 136.0, 148.6, 158.3, 177.0, 182.7. *Anal*. Calcd for $C_{21}H_{14}N_2O_4$: C, 70.39; H, 3.94; N, 7.82; Found: C, 70.31; H, 3.98; N, 7.90.

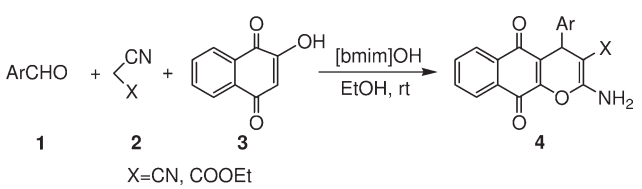
2-Amino-4-(4-fluorophenyl)-5,10-dioxo-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile (4d). This compound was obtained as orange powder with mp 290−292°C (Lit. [12] 286−288°C); IR ν_{max} (KBr): 3420, 3189, 2205, 1668, 1600, 1509, 1411, 1363, 1245, 1205 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 4.64 (1H, s, CH), 7.11−8.06 (10H, m, ArH and NH_2); ^{13}C NMR (DMSO-d_6): δ 35.8, 57.3, 115.1, 119.2, 121.6, 125.7, 126.0, 129.6, 129.7, 130.6, 131.0, 134.1, 134.5, 139.7, 148.9, 158.3, 176.8, 182.5. *Anal*. Calcd for $C_{20}H_{11}FN_2O_3$: C, 69.36; H, 3.20; N, 8.09; Found: C, 69.28; H, 3.25; N, 8.12.

2-Amino-4-(4-hydroxyphenyl)-5,10-dioxo-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile (4e). This compound was obtained as orange powder with mp 255−257°C (Lit. [11] 258−260°C); IR ν_{max} (KBr): 3403, 3195, 2203, 1670, 1610, 1594, 1513, 1404, 1364, 1244, 1207 cm^{-1}; ^{1}H NMR (DMSO-d_6):δ 4.50 (1H, s, CH), 6.66−8.05 (10H, m, ArH and NH_2), 9.35 (1H, s, OH); ^{13}C NMR (DMSO-d_6): δ 35.8, 57.9, 115.2, 119.5, 122.4, 125.8, 126.2, 128.4, 129.0, 130.5, 131.1, 134.1, 134.6, 148.5, 156.4, 158.3, 177.0, 182.8. *Anal*. Calcd for $C_{20}H_{12}N_2O_4$: C, 69.76; H, 3.51; N, 8.14; Found: C, 69.82; H, 3.55; N, 8.16.

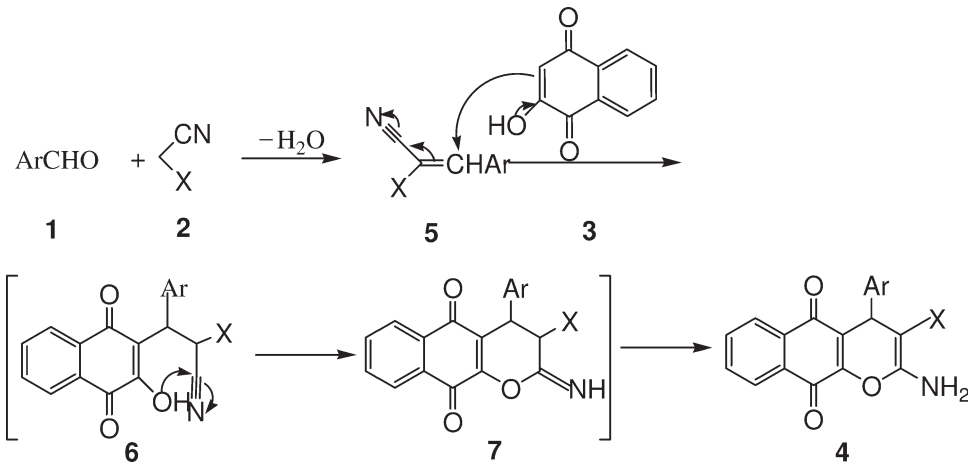
2-Amino-5,10-dioxo-4-p-tolyl-5,10-dihydro-4H-benzo[g]-chromene-3-carbonitrile (4f). This compound was obtained as orange powder with mp 246−248°C (Lit. [11] 242−244°C); IR ν_{max} (KBr): 3411, 3325, 3188, 2204, 1669, 1634, 1595, 1514, 1407, 1362, 1242, 1201 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.24 (3H, s, CH_3), 4.56 (1H, s, CH), 7.09−8.05 (10H, m, ArH and NH_2); ^{13}C NMR (DMSO-d_6): δ 20.5, 36.0, 57.5, 119.2, 122.1, 125.7, 126.0, 127.5, 129.0, 130.5, 131.0, 134.0, 134.5, 136.2, 140.6, 148.7, 158.2, 176.8, 182.5. *Anal*. Calcd for $C_{21}H_{14}N_2O_3$: C, 73.68; H, 4.12; N, 8.18; Found: C, 73.59; H, 4.17; N, 8.12.

2-Amino-4-(4-nitrophenyl)-5,10-dioxo-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile (4g). This compound was obtained as orange powder with mp 236−238°C (Lit. [11] 234−235°C); IR ν_{max} (KBr): 3439, 3401, 3332, 2202, 1668, 1634, 1593, 1520, 1407, 1350, 1245, 1206 cm^{-1}; ^{1}H NMR (DMSO-d_6):δ 4.82 (1H, s, CH), 7.48−8.18 (10H, m, ArH and NH_2); ^{13}C NMR (DMSO-d_6): δ 36.2, 56.4, 118.9, 120.3,

Scheme 1



Scheme 2



122.0, 122.3, 125.6, 126.0, 130.0, 130.6, 130.8, 134.0, 134.3, 134.7, 145.7, 148.0, 149.2, 158.3, 176.7, 182.6. *Anal*. Calcd for $C_{20}H_{11}N_3O_5$: C, 64.35; H, 2.97; N, 11.26; Found: C, 64.28; H, 2.95; N, 11.32.

2-Amino-4-(3-bromophenyl)-5,10-dioxo-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile (4h). This compound was obtained as orange powder with mp 257−258°C (Lit. [11] 259−260°C); IR ν_{max} (KBr): 3408, 3332, 3192, 2200, 1654, 1634, 1593, 1406, 1364, 1246, 1206 cm^{-1}; ^1H NMR (DMSO-d_6): δ 4.64 (1H, s, CH), 7.26−8.06 (10H, m, ArH and NH_2); ^{13}C NMR (DMSO-d_6): δ 36.2, 57.0, 119.1, 120.8, 121.8, 125.7, 126.1, 127.0, 130.0, 130.3, 130.6, 130.9, 134.1, 134.4, 146.3, 149.2, 158.3, 176.7, 182.6. *Anal*. Calcd for $C_{20}H_{11}BrN_2O_3$: C, 58.99; H, 2.72; N, 6.88; Found: C, 58.88; H, 2.76; N, 6.80.

2-Amino-4-(4-hydroxy-3-methoxyphenyl)-5,10-dioxo-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile (4i). This compound was obtained as orange powder with mp 243−245°C; IR ν_{max} (KBr): 3515, 3398, 3334, 3199, 2202, 1668, 1594, 1514, 1363, 1245, 1205 cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.73 (3H, s, OCH_3), 4.51 (1H, s, CH), 6.65−8.05 (9H, m, ArH and NH_2), 8.91 (1H, s, OH); ^{13}C NMR (DMSO-d_6): δ 35.9, 55.7, 57.8, 112.0, 115.4, 119.4, 120.1, 122.2, 125.7, 125.9, 130.5, 131.0, 134.0, 134.4, 134.5, 145.7, 147.4, 148.4, 158.2, 176.9, 182.6. *Anal*. Calcd for $C_{21}H_{14}N_2O_5$: C, 67.38; H, 3.77; N, 7.48; Found: C, 67.28; H, 3.79; N, 7.53.

2-Amino-4-(2-chlorophenyl)-5,10-dioxo-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile (4j). This compound was obtained as orange powder with mp 240−242°C (Lit. [11] 236−239°C); IR ν_{max} (KBr): 3434, 3329, 3215, 2192, 1664, 1636, 1595, 1365, 1246, 1202 cm^{-1}; ^1H NMR (DMSO-d_6): δ 5.15 (1H, s, CH), 7.23−8.07 (10H, m, ArH and NH_2); ^{13}C NMR (DMSO-d_6): δ 33.5, 56.3, 118.8, 121.3, 125.8, 126.1, 127.8, 128.7, 129.4, 130.5, 130.6, 130.9, 132.0, 134.1, 134.6, 140.9, 149.5, 158.4, 176.8, 182.4. *Anal*. Calcd for $C_{20}H_{11}ClN_2O_3$: C, 66.22; H, 3.06; N, 7.72; Found: C, 66.15; H, 3.01; N, 7.78.

2-Amino-4-(2,4-dichlorophenyl)-5,10-dioxo-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile (4k). This compound was obtained as orange powder with mp 286−288°C; IR ν_{max} (KBr): 3467, 3341, 3168, 2201, 1664, 1631, 1591, 1364, 1247, 1200 cm^{-1}; ^1H NMR (DMSO-d_6): δ 5.13 (1H, s, CH), 7.32−8.07 (9H, m, ArH and NH_2); ^{13}C NMR (DMSO-d_6): δ 33.1, 55.8, 118.6, 120.7, 125.7, 126.0, 127.9, 128.6, 130.5, 130.8, 131.9, 132.2, 132.9, 134.1, 134.5, 140.1, 149.5, 158.3, 176.6, 182.3. *Anal*. Calcd for $C_{20}H_{10}Cl_2N_2O_3$: C, 60.48; H, 2.54; N, 7.05; Found: C, 60.37; H, 2.59; N, 7.09.

2-Amino-4-(2-nitrophenyl)-5,10-dioxo-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile (4l). This compound was obtained as orange powder with mp 242−244°C; IR ν_{max} (KBr): 3431, 3338, 3218, 2205, 1667, 1634, 1592, 1361, 1248, 1199 cm^{-1}; ^1H NMR (DMSO-d_6): δ 5.39 (1H, s, CH), 7.46−8.05 (10H, m, ArH and NH_2); ^{13}C NMR (DMSO-d_6): δ 31.0, 55.8, 118.6, 121.2, 124.0, 125.8, 126.0, 128.4, 130.6, 130.7, 131.3, 133.7, 134.2, 134.6, 137.8, 148.5, 149.0, 158.8, 176.7, 182.6. *Anal*. Calcd for $C_{20}H_{11}N_3O_5$: C, 64.35; H, 2.97; N, 11.26; Found: C, 64.25; H, 2.91; N, 11.30.

Ethyl2-Amino-4-(4-chlorophenyl)-5,10-dioxo-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile (4m). This compound was obtained as orange powder with mp 189−191°C; IR ν_{max} (KBr): 3463, 3419, 3307, 2983, 1681, 1657, 1612, 1519, 1275, 1196 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.11 (3H, t, J = 7.0 Hz, CH_3), 3.98 (2H, q, J = 7.0 Hz, CH_2), 4.88 (1H, s, CH), 7.29−8.05 (10H, m, ArH and NH_2); ^{13}C NMR (DMSO-d_6): δ 13.5, 34.1, 59.0, 76.1, 124.4, 125.8, 127.9, 128.3, 129.4, 130.0, 130.3, 130.6, 131.0, 132.4, 134.0, 134.4, 143.9, 148.6, 158.9, 167.5, 176.9, 182.7. *Anal*. Calcd for $C_{22}H_{16}ClNO_5$: C, 64.48; H, 3.94; N, 3.42; Found: C, 64.35; H, 3.89; N, 3.46.

Ethyl 2-Amino-5,10-dioxo-4-p-tolyl-5,10-dihydro-4H-benzo[g]chromene-3-carbonitrile (4n). This compound was obtained as orange powder with mp 211−214°C; IR ν_{max} (KBr): 3465, 3315, 2991, 2923, 1679, 1661, 1612, 1507, 1273, 1194 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.12 (3H, t, J = 7.0 Hz, CH_3), 2.21 (3H, s, CH_3), 3.99 (2H, q, J = 7.0 Hz, CH_2), 4.87 (1H, s, CH), 7.03−8.05 (10H, m, ArH and NH_2); ^{13}C NMR (DMSO-d_6): δ 13.5, 20.5, 34.0, 59.0, 76.6, 125.3, 125.8, 126.0, 127.9, 128.6, 129.0, 130.1, 130.5, 131.0, 134.0, 134.5, 135.5, 141.9, 148.4, 158.9, 167.7, 177.0, 182.7. *Anal*. Calcd for $C_{23}H_{19}NO_5$: C, 70.94; H, 4.92; N, 3.60; Found: C, 70.80; H, 4.89; N, 3.54.

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