An Efficient Synthesis of Pyrimido[4,5-*b*]quinoline Derivatives *via* Three-Component Reaction in Aqueous Media

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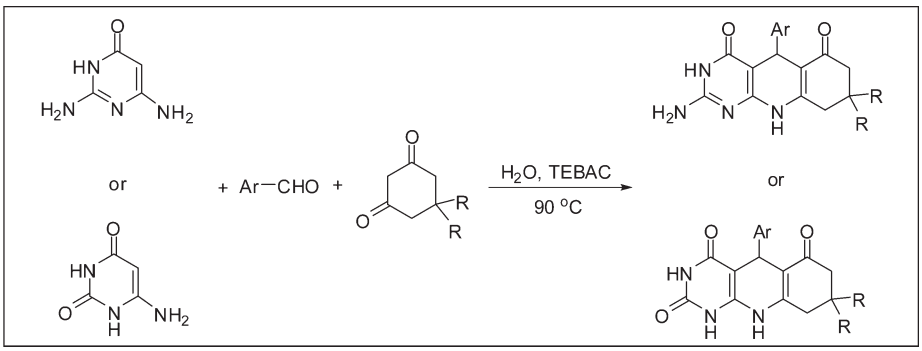
Received February 25, 2008
DOI 10.1002/jhet.57
Published online 13 April 2009 in Wiley InterScience (www.interscience.wiley.com).



A series of pyrimido[4,5-*b*]quinoline derivatives was synthesized by three-component reaction of 6-aminopyrimidine, aromatic aldehydes and 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione in aqueous media in the presence of triethylbenzylammonium chloride. This protocol has the advantages of higher yields, lower lost, easy work-up, and environmentally friendly procedure.

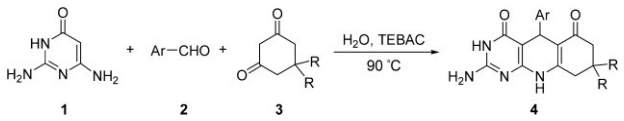
J. Heterocyclic Chem., **46**, 237 (2009).

INTRODUCTION

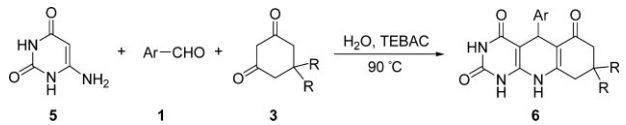
The importance of uracil and its annelated derivatives is well recognized by synthetic [1] as well as biological [2] chemists. With the development of clinically useful anticancer and antiviral drugs [3], there has recently been remarkable interest in the synthetic manipulations of uracils [4]. Uracil derivatives have been reported in the literature to be versatile building blocks for the synthesis of a wide range of heterocyclic motifs, including pyridopyrimidines [5] and pyrazolopyrimidines [6]. Pyrido[2,3-*d*]pyrimidines have received considerable attention over the past years because of their wide range of biological activities, such as antitumor [7], antibacterial [8], anti-inflammatory [9], antifungal [10], antileishmaniasis [11], and also act as cyclin-dependent kinase 4 inhibitors [12]. Recently, Tu *et al*. [13] reported the synthesis of pyrimido[4,5-*b*]quinoline-4,6-dione through one-pot condensation of 2,6-diaminopyrimidine-4-one, aldehyde and cyclic a 1,3-dicarbonyl compound in glycol under microwave irradiation without catalyst. However, they were reacted in organic solvent and needed a special reaction instrument.

Multicomponent reactions (MCRs), in which multiple reactions are combined into one synthetic operation, have been used extensively to form carbon–carbon and carbon-heteroatom bonds in synthetic chemistry [14]. Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedural step, thus avoid complicated purification operations and allow savings of both solvents and reagents. The need to reduce the amount of toxic waste and by-product arising from chemical process requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods. One of the most promising approaches is using water as reaction media. Breslow *et al*. [15], who showed that hydrophobic effects could strongly enhance the rate of several organic reactions, rediscovered the use of water as a solvent in organic chemistry in the 1980s. There has been growing recognition that water is an attractive medium for many organic reactions [16]. Many MCRs in aqueous medium have been reported [17]. As part of our current studies on the development of new routes to heterocyclic systems [18], we now report an efficient and clean synthetic route to pyrimido[4,5-*b*]quinoline derivatives in aqueous media.

Scheme 1



Scheme 2



RESULTS AND DISCUSSION

When the three-component reaction of 2,6-diaminopyrimidine-4-one **1**, aromatic aldehyde **2**, and 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione **3** was performed in water in the presence of TEBAC at 90°C, 2-amino-5-aryl-8,9-dihydropyrimidino[4,5-*b*]quinoline-4,6(1*H*,3*H*,5*H*,10*H*)-dione **4** were obtained in high yields (Scheme 1). The results are summarized in Table 1.

As expected, when the 2,6-diaminopyrimidine-4-one **1** was replaced by 6-aminopyrimdine-1,3-dione **5**, another series of 5-aryl-8,9-dihydropyrimido[4,5-*b*]quinoline-2,4,6(1*H*,3*H*,5*H*,10*H*)-trione **6** were obtained under the same reaction conditions (Scheme 2). The results are summarized in Table 2.

As shown in Tables 1 and 2, this protocol can be applied not only to aromatic aldehydes with either electron-withdrawing groups (such as nitro- or halide-groups) or electron-donating groups (such as alkoxy or alkyl groups), but also to heterocyclic aldehydes with excellent yields under same conditions. Therefore, we concluded that the electronic nature of the substituents has no significant effect on these reactions.

In this study, all the products were characterized by mp, IR, and ^{1}H NMR spectral data as well as elemental analyses.

A reasonable mechanism for the formation of the product **4** is outlined in Scheme 3. The reaction occurs *via* an initial formation of α,β-unsaturated ketone, from the Knoevenagel condensation of aldehyde and 1,3-dicarbonyl compounds, which suffers nucleophilic attack to give the Michael adduct **7**. The intermediate product **7** then cyclizes and subsequently dehydrates to afford the product **4**.

In summary, a series of pyrimido[4,5-*b*]quinoline derivatives were synthesized *via* three-component reaction of aldehydes, 6-amminopyrimidine and 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione in water in the presence of TEBAC. Compared with other methods, this new method has the advantages of high yields, mild reaction conditions, easy work-up, inexpensive reagents, and environmentally friendly procedure.

Table 1

The synthesis of pyrimido[4,5-*b*]quinoline derivatives **4** in aqueous media.

Entry	R	Ar	Reaction time (h)	Isolated yield (%)
4a	H	4-FC_6H_4	12	95
4b	H	4-HOC_6H_4	16	93
4c	H	3-$NO_2C_6H_4$	18	94
4d	H	4-$NO_2C_6H_4$	16	90
4e	H	4-ClC_6H_4	20	92
4f	H	4-BrC_6H_4	20	86
4g	CH_3	4-ClC_6H_4	18	95
4h	CH_3	4-HOC_6H_4	20	86
4i	CH_3	4-$NO_2C_6H_4$	16	86
4j	CH_3	3,4-$(CH_3O)_2C_6H_3$	17	92
4k	CH_3	3,4-$Cl_2C_6H_3$	20	96
4l	CH_3	3-$NO_2C_6H_4$	13	94
4m	CH_3	4-BrC_6H_4	12	94
4n	CH_3	3,4-$OCH_2OC_6H_3$	21	92
4o	CH_3	Pyridine-3-yl	14	88

EXPERIMENTAL

Melting points were determined with a TX-5 microscopic melting-point apparatus and were uncorrected. IR spectra were recorded on a Tensor 27 spectrometer in KBr. ^{1}H NMR spectra were measured on a Bruker DPX-400 MHz spectrometer using TMS standard and DMSO-d_6 as solvent. Elemental analyses were performed on Perkin-Elmer 2400II elemental analyzer.

General Procedure for the Synthesis of Pyrimido[4,5-*b*]quinoline Derivatives. A suspension of a mixture of 6-aminopyrimidine **1** or **5** (2 mmol), aldehyde **2** (2 mmol), 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione **3** (2 mmol) and TEBAC (0.15 g, 0.66 mmol) was stirred in water (10 mL) at 90°C for several hours. After completion monitored by TLC, the reaction mixture was allowed to cool to room temperature. The crystalline powder formed recrystallized from DMF to give pure **4** or **6**.

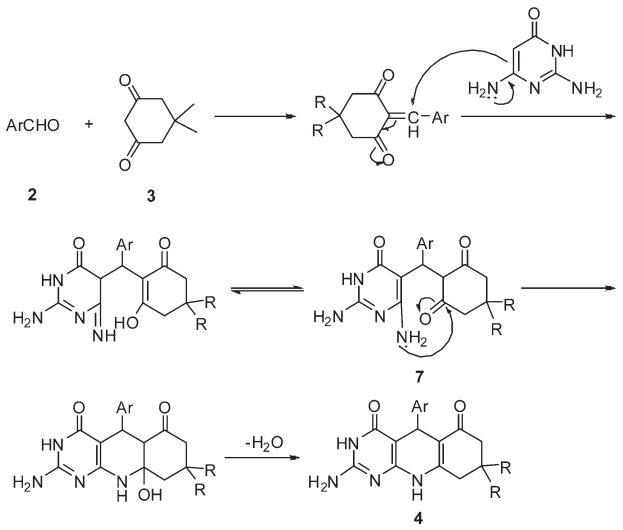
2-Amino-5-(4-fluorophenyl)-8,9-dihydropyrimido[4,5-b]-quinoline-4,6(3H,5H,7H,10H)-dione (4a). This compound was obtained as white needles with mp > 300°C; IR (potassium

Table 2

The synthesis of pyrimido[4,5-*b*]quinoline derivatives **6** in aqueous media.

Entry	R	Ar	Reaction time (h)	Isolated yield (%)
6a	H	3,4- $Cl_2C_6H_3$	8	76
6b	H	3-$NO_2C_6H_4$	20	98
6c	H	2,4-$Cl_2C_6H_3$	16	75
6d	H	2-$NO_2C_6H_4$	12	93
6e	H	4-$NO_2C_6H_4$	13	86
6f	CH_3	3,4-$(CH_3O)_2C_6H_3$	20	91
6g	CH_3	4-HOC_6H_4	22	98

Scheme 3



bromide): 3328, 3148, 2947, 1676, 1644, 1514, 1447, 1362, 1287, 1229, 1149, 1089, 1050, 1014, 994, 897, 839, 816, 770, 750, 735, 700 cm^{-1}; ^1H NMR (DMSO-d_6): 1.70–1.95 (m, 2H, CH_2), 2.13–2.25 (m, 2H, CH_2), 2.45–2.73 (m, 2H, CH_2), 4.85 (s, 1H, CH), 6.34 (br. s, 2H, NH_2), 6.97 (dd, J_1 = 6.0 Hz, J_2 = 8.8 Hz, 2H, ArH), 7.19 (dd, J_1 = 6.0 Hz, J_2 = 8.8 Hz,, 2H, ArH), 9.38 (br. s, 1H, NH), 10.44 (br. s, 1H, NH). *Anal.* Calcd. for $C_{17}H_{15}FN_4O_2$: C, 62.57; H, 4.63; N, 17.17. Found: C, 62.82; H, 4.48; N, 17.36.

2-Amino-5-(4-hydroxyphenyl)-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4b). This compound was obtained as pale yellow prisms with mp > 300°C; IR (potassium bromide): 3556, 3335, 3151, 2955, 1679, 1651, 1519, 1455, 1372, 1267, 1187, 1049, 994, 896, 839, 818, 772, 734, 700 cm^{-1}; ^1H NMR (DMSO-d_6): 1.72–1.95 (m, 2H, CH_2), 2.15–2.24 (m, 2H, CH_2), 2.42–2.60 (m, 2H, CH_2), 4.76 (s, 1H, CH), 6.27 (br. s, 2H, NH_2), 6.54 (d, J = 8.4 Hz, 2H, ArH), 6.96 (d, J = 8.4 Hz, 2H, ArH), 8.98 (s, 1H, OH), 9.28 (br. s, 1H, NH), 10.33 (br. s, 1H, NH). *Anal*. Calcd. for $C_{17}H_{16}N_4O_3$: C, 62.95; H, 4.97; N, 17.27. Found: C, 63.05; H, 5.08; N, 17.13.

2-Amino-5-(3-nitrophenyl)-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4c). This compound was obtained as pale yellow prisms with mp > 300°C (Lit. [13] > 300°C); IR (potassium bromide): 3462, 3249, 2934, 1679, 1647, 1517, 1426, 1345, 1287, 1227, 1191, 1134, 1095, 1050, 994, 913, 824, 802, 772, 759, 705 cm^{-1}; ^1H NMR (DMSO-d_6): 1.73–1.96 (m, 2H, CH_2), 2.12–2.30 (m, 2H, CH_2), 2.50–2.65 (m, 2H, CH_2), 4.96 (s, 1H, CH), 6.40 (br. s, 2H, NH_2), 7.49 (t, J = 8.0 Hz, 1H, ArH), 7.36 (d, J = 8.0 Hz, 1H, ArH), 7.94–7.96 (m, 1H, ArH), 8.02 (s, 1H, ArH), 9.52 (br. s, 1H, NH),10.44 (br. s, 1H, NH). *Anal.* Calcd. for $C_{17}H_{15}N_5O_4$: C, 57.79; H, 4.28; N, 19.82. Found: C, 57.98; H, 4.15; N, 20.05.

2-Amino-5-(4-nitrophenyl)-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4d). This compound was obtained as pale yellow prisms with mp > 300°C (Lit. [13] > 300°C); IR (potassium bromide): 3328, 3149, 3028, 2957, 1681, 1639, 1618, 1522, 1458, 1426, 1367, 1349, 1289, 1268, 1231, 1205, 1183, 1138, 995, 823, 704 cm^{-1}; ^1H NMR (DMSO-d_6): 1.73–1.95 (m, 2H, CH_2), 2.12–2.28 (m, 2H, CH_2), 2.51–2.63 (m, 2H, CH_2), 4.95 (s, 1H, CH), 6.39 (br. s, 2H, NH_2), 7.44 (d, J = 8.8 Hz, 2H, ArH), 8.06 (d, J = 8.8 Hz, 2H, ArH), 9.51 (br. s, 1H, NH), 10.45 (br. s, 1H, NH). *Ana*l. Calcd. for $C_{17}H_{15}N_5O_4$: C, 57.79; H, 4.28; N, 19.82. Found: C, 58.01; H, 4.16; N, 19.69.

2-Amino-5-(4-chlorophenyl)-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4e). This compound was obtained as pale yellow prisms with mp > 300°C (Lit. [13] > 300°C); IR (potassium bromide): 3358, 3151, 2955, 1683, 1647, 1617, 1519, 1488, 1457, 1426, 1370, 1290, 1267, 1230, 1204, 1188, 1137, 1089, 1014, 994, 832, 813 cm^{-1}; ^1H NMR (DMSO-d_6): 1.72–1.95 (m, 2H, CH_2), 2.13–2.27 (m, 2H, CH_2), 2.45–2.59 (m, 2H, CH_2), 4.83 (s, 1H, CH), 6.34 (br. s, 2H, NH_2), 7.17–7.24 (m, 4H, ArH), 9.40 (br. s, 1H, NH), 10.44 (br. s, 1H, NH). *Anal*. Calcd. for $C_{17}H_{15}ClN_4O_2$: C, 59.57; H, 4.41; N, 16.34. Found: C, 59.83; H, 4.26; N, 16.56.

2-Amino-5-(4-bromophenyl)-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4f). This compound was obtained as pale yellow prisms with mp > 300°C (Lit. [13] > 300°C); IR (potassium bromide): 3343, 3152, 2954, 1676, 1652, 1520, 1485, 1457, 1426, 1397, 1369, 1290, 1257, 1230, 1203, 1183, 1137, 1071, 1051, 1010, 994, 898, 831, 811, 777, 733, 706 cm^{-1}; ^1H NMR (DMSO-d_6): 1.71–1.95 (m, 2H, CH_2), 2.11–2.27 (m, 2H, CH_2), 2.45–2.60 (m, 2H, CH_2), 4.82 (s, 1H, CH), 6.33 (br. s, 2H, NH_2), 7.13 (d, J = 8.4 Hz, 2H, ArH), 7.35 (d, J = 8.4 Hz, 2H, ArH), 9.40 (br. s, 1H, NH), 10.40 (br. s, 1H, NH). *Anal*. Calcd. for $C_{17}H_{15}BrN_4O_2$: C, 52.73; H, 3.90; N, 14.47. Found: C, 52.94; H, 3.86; N, 14.63.

2-Amino-5-(4-chlorophenyl)-8,8-dimethyl-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4g). This compound was obtained as yellow needles with mp > 300°C (Lit. [13] > 300°C); IR (potassium bromide): 3397, 3169, 2965, 1679, 1647, 1621, 1515, 1478, 1446, 1363, 1303, 1279, 1246, 1217, 1198, 1155, 1140, 1090, 1014, 860, 805, 778, 690 cm^{-1}; ^1H NMR (DMSO-d_6): 0.89 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.98 (d, J = 16.0 Hz, 1H, CH), 2.17 (d, J = 16.0 Hz, 1H, CH), 2.38 (d, J = 17.2 Hz, 1H, CH), 2.45 (d, J = 17.2 Hz, 1H, CH), 4.79 (s, 1H, CH), 6.34 (br. s, 2H, NH_2), 7.17 (d, J = 8.4 Hz, 2H, ArH), 7.21 (d, J = 8.4 Hz, 2H, ArH), 9.35 (br. s, 1H, NH), 10.41 (br. s, 1H, NH). *Anal*. Calcd. for $C_{19}H_{19}ClN_4O_2$: C, 61.54; H, 5.16; N, 15.11. Found: C, 61.76; H, 5.09; N, 15.28.

2-Amino-5-(4-hydroxyphenyl)-8,8-dimethyl-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4h). This compound was obtained as pale yellow prisms with mp > 300°C; IR (potassium bromide): 3440, 3330, 2955, 1675, 1647, 1615, 1514, 1455, 1372, 1284, 1250, 1226, 1202, 1173, 1168, 1139, 1105, 1057, 1028, 975, 854, 808, 769 cm^{-1}; ^1H NMR (DMSO-d_6): 0.90 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.98 (d, J = 16.0 Hz, 1H, CH), 2.15 (d, J = 16.0 Hz, 1H, CH), 2.36 (d, J = 17.2 Hz, 1H, CH), 2.43 (d, J = 17.2 Hz, 1H, CH), 4.71 (s, 1H, CH), 6.25 (br. s, 2H, NH_2), 6.53 (d, J = 8.0 Hz, 2H, ArH), 6.95 (d, J = 8.0 Hz, 2H, ArH), 8.95 (br. s, 1H, OH), 9.23 (br. s, 1H, NH), 10.31 (br. s, 1H, NH). *Anal*. Calcd. for $C_{19}H_{20}N_4O_3$: C, 64.76; H, 5.72; N, 15.90. Found: C, 64.83; H, 5.84; N, 15.78.

2-Amino-5-(4-nitrophenyl)-8,8-dimethyl-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4i). This compound was obtained as yellow needles with mp > 300°C (Lit. [13] > 300°C); IR (potassium bromide): 3470, 3335, 3256,

3179, 3069, 2958, 1661, 1618, 1594, 1516, 1453, 1419, 1366, 1352, 1285, 1245, 1227, 1204, 1188, 1157, 881, 830, 805, 785, 739, 684 cm^{-1}; ^1H NMR (DMSO-d_6): 0.89 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.98 (d, J = 16.0 Hz, 1H, CH), 2.18 (d, J = 16.0 Hz, 1H, CH), 2.41 (d, J = 17.2 Hz, 1H, CH), 2.48 (d, J = 17.2 Hz, 1H, CH), 4.91 (s, 1H, CH), 6.38 (br. s, 2H, NH_2), 7.43 (dd, J_1 = 6.8 Hz, J_2 = 6.0 Hz, 2H, ArH), 8.08 (dd, J_1 = 6.8 Hz, J_2 = 6.0 Hz 2H, ArH), 9.46 (br. s, 1H, NH), 10.43 (br. s, 1H, NH). *Anal*. Calcd. for $C_{19}H_{19}N_5O_4$: C, 59.84; H, 5.02; N, 18.36. Found: C, 60.05; H, 4.97; N, 18.54.

2-Amino-5-(3,4-dimethoxyphenyl)-8,8-dimethyl-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4j). This compound was obtained as yellow prisms with mp > 300°C (Lit. [13] > 300°C); IR (potassium bromide): 3432, 3263, 3184, 2956, 1669, 1625, 1588, 1513, 1451, 1369, 1283, 1266, 1246, 1224, 1199, 1139, 1025, 803, 766 cm^{-1}; ^1H NMR (DMSO-d_6): 0.94 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.00 (d, J = 15.6 Hz, 1H, CH), 2.18 (d, J = 15.6 Hz, 1H, CH), 2.38 (d, J = 17.2 Hz, 1H, CH), 2.45 (d, J = 17.2 Hz, 1H, CH), 3.65 (s, 3H, CH_3O), 3.67 (s, 3H, CH_3O), 4.77 (s, 1H, CH), 6.28 (br. s, 2H, NH_2), 6.64 (d, J = 8.0 Hz, 1H, ArH), 6.74 (d, J = 8.0 Hz, 1H, ArH), 6.83 (s, 1H, ArH), 9.24 (br. s, 1H, NH), 10.33 (br. s, 1H, NH). *Anal*. Calcd. for $C_{21}H_{24}N_4O_4$: C, 63.62; H, 6.10; N, 14.13. Found: C, 63.74; H, 6.02; N, 14.26.

2-Amino-5-(3,4-dichlorophenyl)-8,8-dimethyl-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4k). This compound was obtained as white needles with mp > 300°C; IR (potassium bromide): 3462, 3252, 3059, 2957, 1677, 1603, 1519, 1461, 1372, 1307, 1284, 1228, 1191, 1173, 1140, 1097, 1028, 878, 842, 818, 791, 748, 703 cm^{-1}; ^1H NMR (DMSO-d_6): 0.90 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 2.00 (d, J = 16.0 Hz, 1H, CH), 2.18 (d, J = 16.0 Hz, 1H, CH), 2.40 (d, J = 17.2 Hz, 1H, CH), 2.46 (d, J = 17.2 Hz, 1H, CH), 4.78 (s, 1H, CH), 6.39 (br. s, 2H, NH_2), 7.12 (dd, J_1 = 2.0 Hz, J_2 = 8.0 Hz, 1H, ArH), 7.33 (d, J = 2.0 Hz, 1H, ArH), 7.44 (d, J = 8.0 Hz, 1H, ArH), 9.42 (br. s, 1H, NH), 10.44 (br. s, 1H, NH). *Anal*. Calcd. for $C_{19}H_{18}Cl_2N_4O_2$: C, 56.31; H, 4.48; N, 13.82. Found: C, 56.48; H, 4.33; N, 13.97.

2-Amino-5-(3-nitrophenyl)-8,8-dimethyl-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4l). This compound was obtained as yellow needles with mp > 300°C (Lit. [13] > 300°C); IR (potassium bromide): 3470, 3350, 3257, 3194, 2958, 1664, 1649, 1509, 1443, 1417, 1364, 1308, 1285, 1242, 1226, 1202, 1188, 1157, 1098, 1025, 881, 830, 806, 785, 738 cm^{-1}; ^1H NMR (DMSO-d_6): 0.90 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.99 (d, J = 16.0 Hz, 1H, CH), 2.19 (d, J = 16.0 Hz, 1H, CH), 2.42 (d, J = 17.6 Hz, 1H, CH), 2.49 (d, J = 17.6 Hz, 1H, CH), 4.92 (s, 1H, CH), 6.39 (br. s, 2H, NH_2), 7.50 (t, J = 8.0 Hz, 1H, 1H, ArH), 7.64 (d, J = 7.6 Hz, 1H, ArH), 7.95 (d, J = 7.6 Hz, 1H, ArH), 7.99 (s, 1H, ArH), 9.45 (br. s, 1H, NH), 10.42 (br. s, 1H, NH). *Anal*. Calcd. for $C_{19}H_{19}N_5O_4$: C, 59.84; H, 5.02; N, 18.36. Found: C, 59.98; H, 5.14; N, 18.19.

2-Amino-5-(4-bromophenyl)-8,8-dimethyl-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4m). This compound was obtained as yellow needles with mp > 300°C; IR (potassium bromide): 3471, 3323, 3250, 3186, 1659, 1621, 1515, 1486, 1451, 1370, 1284, 1238, 1227, 1204, 1155, 1070, 1011, 842, 809, 782 cm^{-1}; ^1H NMR (DMSO-d_6): 0.89 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.98 (d, J = 16.0 Hz, 1H, CH), 2.17 (d, J = 16.0 Hz, 1H, CH), 2.38 (d, J = 17.2 Hz, 1H, CH), 2.45 (d, J = 17.2 Hz, 1H, CH), 4.77 (s, 1H, CH), 6.32 (br. s, 2H, NH_2), 7.12 (d, J = 8.4 Hz, 2H, ArH), 7.35 (d, J =8.4 Hz, 2H, ArH), 9.34 (br. s, 1H, NH), 10.38 (br. s, 1H, NH). *Anal*. Calcd. for $C_{19}H_{19}BrN_4O_2$: C, 54.95; H, 4.61; N, 13.49. Found: C, 55.06; H, 4.53; N, 13.41.

2-Amino-5-(3,4-dimethylenedioxyphenyl)-8,8-dimethyl-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4n). This compound was obtained as yellow needles with mp > 300°C (Lit. [13] > 300°C); IR (potassium bromide): 3216, 3188, 2958, 2902, 1622, 1558, 1540, 1508, 1488, 1455, 1372, 1283, 1232, 1200, 1041, 1029, 931, 882, 784 cm^{-1}; ^1H NMR (DMSO-d_6): 0.91 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 2.00 (d, J = 16.0 Hz, 1H, CH), 2.16 (d, J = 16.0 Hz, 1H, CH), 2.38 (d, J = 17.2 Hz, 1H, CH), 2.44 (d, J = 17.2 Hz, 1H, CH), 4.73 (s, 1H, CH), 5.89 (s, 2H, OCH_2O), 6.35 (br. s, 2H, NH_2), 6.60 (d, J = 8.0 Hz, 1H, ArH), 6.66–6.72 (m, 2H, ArH), 9.32 (br. s, 1H, NH), 10.46 (br. s, 1H, NH). *Anal*. Calcd. for $C_{20}H_{20}N_4O_4$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.07; H, 5.42; N, 14.86.

2-Amino-5-(pyridin-3-yl)-8,8-dimethyl-8,9-dihydropyrimido[4,5-b]quinoline-4,6(3H,5H,7H,10H)-dione (4o). This compound was obtained as yellow needles with mp > 300°C; IR (potassium bromide): 3417, 3373, 3263, 3194, 2960, 1660, 1625, 1544, 1513, 1470, 1453, 1400, 1370, 1277, 1242, 1227, 1197, 1154, 1140, 1044, 843, 804, 783, 752, 711 cm^{-1}; ^1H NMR (DMSO-d_6): 0.89 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.99 (d, J = 16.0 Hz, 1H, CH), 2.18 (d, J = 16.0 Hz, 1H, CH), 2.41 (d, J = 16.8 Hz, 1H, CH), 2.47 (d, J = 16.8 Hz, 1H, CH), 4.79 (s, 1H, CH), 6.36 (br. s, 2H, NH_2), 7.20 (dd, J_1 = 4.8 Hz, J_2 = 8.0 Hz, 1H, ArH), 7.49 (dd, J_1 = 2.0 Hz, J_2 = 4.8 Hz, 1H, ArH), 8.25 (dd, J_1 = 2.0 Hz, J_2 = 4.8 Hz, 1H, ArH), 8.39 (d, J = 2.0 Hz, 1H, ArH), 9.41 (br. s, 1H, NH), 10.42 (br. s, 1H, NH). *Anal*. Calcd. for $C_{18}H_{19}N_5O_2$: C, 64.08; H, 5.68; N, 20.76. Found: C, 64.32; H, 5.54; N, 20.92.

5-(3,4-Dichlorophenyl)-8,9-dihydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,5H,7H,10H)-trione (6a). This compound was obtained as white prisms with mp > 300°C; IR (potassium bromide): 3247, 3207, 3078, 2949, 1714, 1682, 1629, 1609, 1522, 1476, 1439, 1378, 1330, 1303, 1252, 1228, 1182, 1143, 1112, 1029, 994, 955, 901, 820, 778 cm^{-1}; ^1H NMR (DMSO-d_6): 1.71–1.96 (m, 2H, CH_2), 2.10–2.30 (m, 2H, CH_2), 2.54–2.66 (m, 2H, CH_2), 4.76 (s, 1H, CH), 7.16 (dd, J_1 = 2.0 Hz, J_2 = 8.4 Hz, 1H, ArH), 7.38 (d, J = 2.0 Hz, 1H, ArH), 7.47 (d, J = 8.4 Hz, 1H, ArH), 9.00 (br. s, 1H, NH), 10.29 (br. s, 1H, NH), 10.80 (br. s, 1H, NH). *Anal*. Calcd. for $C_{17}H_{13}Cl_2N_3O_3$: C, 53.99; H, 3.46; N, 11.11. Found: C, 54.08; H, 3.56; N, 11.04.

5-(3-Nitrophenyl)-8,9-dihydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,5H,7H,10H)-trione (6b). This compound was obtained as pale yellow prisms with mp > 300°C; IR (potassium bromide): 3279, 3221, 3074, 2970, 1720, 1684, 1632, 1597, 1528, 1470, 1447, 1382, 1358, 1258, 1207, 1186, 1147, 1128, 1089, 994, 914, 845, 822, 772, 740 cm^{-1}; ^1H NMR (DMSO-d_6): 1.75–1.99 (m, 2H, CH_2), 2.18–2.30 (m, 2H, CH_2), 2.53–2.69 (m, 2H, CH_2), 4.91 (s, 1H, CH), 7.52 (t, J = 8.0 Hz, 1H, ArH), 7.66 (d, J = 6.0 Hz, 1H, ArH), 7.98 (t, J = 8.0 Hz, 1H, ArH), 8.03 (s, 1H, ArH), 9.05 (br. s, 1H, NH), 10.32 (br. s, 1H, NH), 10.81 (br. s, 1H, NH). *Anal*. Calcd. for $C_{17}H_{14}N_4O_5$: C, 57.63; H, 3.98; N, 15.81. Found: C, 57.81; H, 4.02; N, 15.69.

5-(2,4-Dichlorophenyl)-8,9-dihydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,5H,10H)-trione (6c). This compound was obtained as white prisms with mp > 300°C; IR (potassium bromide): 3248, 3207, 3079, 2952, 1723, 1670, 1629, 1603, 1537, 1483, 1426, 1418, 1382, 1341, 1267, 1187, 1149, 1110, 1036, 994, 904, 862, 815, 760, 705 cm^{-1}; ^1H NMR (DMSO-d_6): 1.70–1.95 (m, 2H, CH_2), 2.10–2.27 (m, 2H, CH_2), 2.51–2.60 (m, 2H, CH_2), 5.03 (s, 1H, CH), 7.26 (dd, $J_1 = 2.0$ Hz, $J_2 = 8.4$ Hz, 1H, ArH), 7.31 (d, $J = 8.4$ Hz, 1H, ArH), 7.34 (d, $J = 2.0$ Hz, 1H, ArH), 8.97 (br. s, 1H, NH), 10.21 (br. s, 1H, NH), 10.67 (br. s, 1H, NH). *Anal*. Calcd. for $C_{17}H_{13}Cl_2N_3O_3$: C, 53.99; H, 3.46; N, 11.11. Found: C, 54.07; H, 3.28; N, 11.25.

5-(2-Nitrophenyl)-8,9-dihydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,5H,7H,10H)-trione (6d). This compound was obtained as red prisms with mp > 300°C; IR (potassium bromide): 3298, 3246, 3010, 2962, 2829, 1734, 1664, 1644, 1531, 1485, 1429, 1378, 1359, 1304, 1261, 1227, 1188, 1143, 1000, 893, 867, 755, 706, 689 cm^{-1}; ^1H NMR (DMSO-d_6): 1.74–1.96 (m, 2H, CH_2), 2.10–2.28 (m, 2H, CH_2), 2.51–2.62 (m, 2H, CH_2), 5.61 (s, 1H, CH), 7.29–7.34 (m, 1H, ArH), 7.41 (dd, $J_1 = 1.2$ Hz, $J_2 = 7.6$ Hz, 1H, ArH), 7.51–7.57 (m, 1H, ArH), 7.71 (dd, $J_1 = 1.2$ Hz, $J_2 = 8.0$ Hz, 1H, ArH), 8.92 (br. s, 1H, NH), 10.18 (br. s, 1H, NH), 10.68 (br. s, 1H, NH). *Anal*. Calcd. for $C_{17}H_{14}N_4O_5$: C, 57.63; H, 3.98; N, 15.81. Found: C, 57.82; H, 4.06; N, 15.96.

5-(4-Nitrophenyl)-8,9-dihydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,5H,7H,10H)-trione (6e). This compound was obtained as yellow needles with mp > 300°C; IR (potassium bromide): 3360, 3272, 3194, 3052, 2947, 1713, 1669, 1522, 1483, 1438, 1411, 1380, 1348, 1265, 1207, 1188, 1148, 1109, 998, 869, 824, 765, 697 cm^{-1}; ^1H NMR (DMSO-d_6): 1.73–1.98 (m, 2H, CH_2), 2.15–2.30 (m, 2H, CH_2), 2.55–2.70 (m, 2H, CH_2), 4.90 (s, 1H, CH), 7.48 (d, $J = 8.8$ Hz, 2H, ArH), 8.08 (d, $J = 8.8$ Hz, 2H, ArH), 9.04 (br. s, 1H, NH), 10.30 (br. s, 1H, NH), 10.80 (br. s, 1H, NH). *Anal*. Calcd. for $C_{17}H_{14}N_4O_5$: C, 57.63; H, 3.98; N, 15.81. Found: C, 57.88; H, 4.09; N, 15.74.

5-(3,4-Dimethoxyphenyl)-8,9-dihydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,5H,7H,10H)-trione (6f). This compound was obtained as pale yellow needles with mp > 300°C; IR (potassium bromide): 3598, 3179, 2954, 1723, 1653, 1595, 1536, 1470, 1417, 1377, 1335, 1266, 1231, 1202, 1169, 1141, 1087, 1025, 974, 930, 864, 797, 762 cm^{-1}; ^1H NMR (DMSO-d_6): 0.89 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.04 (d, $J = 16.0$ Hz, 1H, CH), 2.22 (d, $J = 16.0$ Hz, 1H, CH), 2.42 (d, $J = 17.2$ Hz, 1H, CH), 2.49 (d, $J = 17.6$ Hz, 1H, CH), 3.67 (s, 6H, 2 × CH_3O), 4.71 (s, 1H, CH), 6.66 (dd, $J_1 = 1.6$ Hz, $J_2 = 8.0$ Hz, 1H, ArH), 6.77 (d, $J = 8.0$ Hz, 1H, ArH), 6.81 (d, $J = 1.6$ Hz, 1H, ArH), 8.73 (br. s, 1H, NH), 10.21 (br. s, 1H, NH), 10.71 (br. s, 1H, NH). *Anal*. Calcd. for $C_{21}H_{23}N_3O_5$: C, 63.46; H, 5.83; N, 10.57. Found: C, 63.72; H, 5.69; N, 10.75.

5-(4-Hydroxyphenyl)-8,9-dihydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,5H,7H,10H)-trione (6g). This compound was obtained as pale yellow needles with mp > 300°C; IR (potassium bromide): 3328, 3201, 3021, 2954, 2933, 2874, 1707, 1679, 1614, 1542, 1512, 1480, 1416, 1376, 1329, 1296, 1252, 1227, 1206, 1177, 1164, 1146, 1050, 1003, 861, 851, 830, 797, 786, 764 cm^{-1}; ^1H NMR (DMSO-d_6): 0.89 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.01 (d, $J = 16.0$ Hz, 1H, CH), 2.19 (d, $J = 16.0$ Hz, 1H, CH), 2.40 (d, $J = 16.8$ Hz, 1H, CH), 2.47 (d, $J = 16.8$ Hz, 1H, CH), 4.64 (s, 1H, CH), 6.56 (d, $J = 8.0$ Hz, 2H, ArH), 6.96 (d, $J = 8.0$ Hz, 2H, ArH), 8.70 (br. s, 1H, OH), 9.09 (br. s, 1H, NH), 10.18 (br. s, 1H, NH), 10.72 (br. s, 1H, NH). *Anal*. Calcd. F or $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found: C, 64.63; H, 5.36; N, 11.97.

Acknowledgment. We are grateful to the Foundation of the Key Laboratory of Biotechnology on Medical Plants of Jiangsu Province for financial support.

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