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Green Method for the Synthesis of Benzo[*f*]pyrimido[4,5-*b*]quinoline Derivatives Catalyzed by Iodine in Aqueous Media

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Abstract: A convenient one-pot synthesis of benzo[*f*]pyrimido[4,5-*b*]quinoline derivatives is described via three-component reaction of benzaldehydes, naphthalen-2-amine, and barbituric acid at room temperature in aqueous media catalyzed by iodine. Compared with other methods, this three-component reaction used a green solvent, gave good yields, and was operationally simple.

Keywords: Aqueous media, benzo[*f*]pyrimido[4,5-*b*]quinoline, iodine, three-component reaction

INTRODUCTION

The development of multicomponent reactions (MCRs) has attracted much attention from the vantage point of combinatorial and medicinal chemistry.[1] Generally, the MCR strategy affords savings in time and effort and has significant advantages over conventional two-component reactions in several aspects, such as variability and high-bond-forming efficiency. With a small set of starting materials, very large libraries

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can be developed within a short time, which can be applied to research on medicinal chemistry.

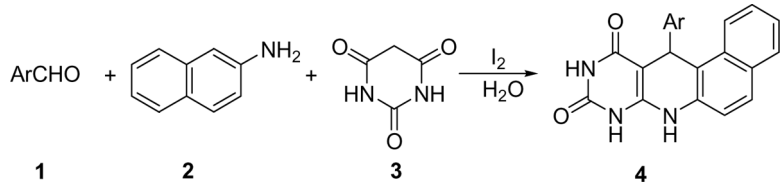
Compounds bearing pyrimidoquinoline are common in a variety of biologically important natural products and potent drugs. It is noteworthy that pyrimidoquinoline derivatives manifest a number of important and therapeutically useful biological activities such as antibacterial,[2] antifungal,[3] antimalarial,[4] and antifolate[5] activities and inhibitory activity of lytic KSHV DNA synthesis.[6] Despite this broad range of applications, only a few members of this family of compounds have been reported.[7] The development of new methods for their assembly is therefore of considerable synthetic importance.

Recently, Kozlov and Basalaeva[7a] reported in 2007 that benzo[*f*]-pyrimido[4,5-*b*]quinoline-9,11-diones could be obtained by a three-component reaction of benzaldehyde, naphthalen-2-amine, and barbituric acid in boiling butanol. However, this reaction suffers from the drawbacks of poor yields (14–70%), use of organic solvent (butanol), and harsh reaction condition. To obtain the desired products in an experimentally friendly procedure and in better yields, we performed the reaction of Schiff base with barbituric acid in water at 100°C, with benzo[*f*]quinolin-3-cabonyl urea being obtained in good yields.[8] In the designed reaction, the ring of barbituric acid was unexpectedly opened. Perhaps the reason the ring opened was the high reaction temperature. So in our continuing study, we performed the three-component reaction in water at room temperature. To our disappointment, the reaction stayed at the stage of Knoevenagel reaction of benzaldehydes and barbituric acid; the naphthalen-2-amine did not attend the reaction at all. Subsequently, a little iodine was added to the reaction system, the desired reaction took place smoothly, and the product of benzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-diones was isolated in good yields.

RESULTS AND DISCUSSION

The three-component reaction of substituted benzaldehydes **1**, naphthalen-2-amine **2,** and barbituric acid **3** was performed at room temperature in aqueous media catalyzed by 5 mol% iodine. The 12-aryl-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*] quinoline-9,11-diones **4** were obtained in good yields (Scheme 1).

In our initial study, the reaction of 2,3-dichlorobenzaldehyde **1a**, naphthalen-2-amine **2,** and barbituric acid **3** was used as a model reaction to optimize the conditions. A summary of the optimization experiment is provided in Table 1. The reaction was first carried out in water at room temperature to avoid a ring-opening reaction. It turned out that no



Scheme 1. Reaction of **1**, **2**, and **3** catalyzed by iodine in water.

reaction occurred without the catalyst (Table 1, entry 1). Similar reactions were then attempted in the presence of 5, 10 and 20 mol% of I_2. The results from Table 1 (entries 2–4) showed that 5 mol% I_2 at room temperature in water was sufficient to push the reaction forward. Great loading of the catalyst did not improve the yield to a great extent. In addition, CH_3CN, benzene, tetrahydrofuran (THF), and $ClCH_2CH_2Cl$ (Table 1, entries 5–8) were also tested as the solvents. In these cases, product **4a** was formed in slightly lesser yields (Table 1, entries 5–8).

To apply this reaction to a library synthesis, various kinds of benzaldehydes were reacted with **2** and **3** to give the corresponding benzo[*f*]-pyrimido[4,5-*b*]quinoline derivatives **4**, and representative examples are shown in Table 2. All of the benzaldehydes gave the expected products in good yields, either bearing electron-withdrawing groups (such as halide, nitro) or electron-donating groups (such as alkyl group, alkoxyl group) under the same reaction conditions. Therefore, we concluded that the electronic nature of the substituents has no significant effects on this reaction. The structure of the products **4c** was confirmed by x-ray diffraction analysis, as shown in Fig. 1.

In conclusion, an efficient and green method for the synthesis of 12-aryl-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione

Table 1. Synthesis of **4a** in water under different reaction conditions[a]

Entry	Solvent	Amount (mol%)	Time (h)	Yields[b] (%)
1	H_2O	0	10	0
2	**H_2O**	**5**	**8**	**92**
3	H_2O	10	8	91
4	H_2O	20	8	92
5	CH_3CN	5	8	80
6	Benzene	5	8	76
7	THF	5	8	90
8	$ClCH_2CH_2Cl$	5	8	78

[a]Reagents and conditions: **1** (2 mmol), **2** (2 mmol), **3** (2 mmol), and solvent (10 mL).
[b]Isolated yields.

Table 2. Synthesis of **4** in water at room temperature catalyzed by iodine

Entry	Ar	Products	Time (h)	Yields (%)
1	2,3-$Cl_2C_6H_3$	**4a**	6	92
2	3-BrC_6H_4	**4b**	6	91
3	2,4-$Cl_2C_6H_3$	**4c**	6	89
4	2-ClC_6H_4	**4d**	6	89
5	2-$NO_2C_6H_4$	**4e**	6	91
6	4-$CH_3OC_6H_4$	**4f**	7	88
7	2,3-$(CH_3O)_2C_6H_3$	**4g**	8	92
8	3-$NO_2C_6H_4$	**4h**	6	82
9	3,4-$(CH_3)_2C_6H_3$	**4i**	6	86
10	C_6H_5	**4j**	6	92
11	2-$CH_3OC_6H_4$	**4k**	6	84
12	3,5-$(CH_3O)_2C_6H_3$	**4l**	6	91
13	2-BrC_6H_4	**4m**	6	89
14	4-FC_6H_4	**4n**	7	92
15	2-FC_6H_4	**4o**	6	86
16	4-HOC_6H_4	**4p**	6	89
17	4-$NO_2C_6H_4$	**4q**	7	92

derivatives by a three-component reaction of benzaldehyde, naphthalen-2-amine, and barbituric acid was successfully developed in water catalyzed by iodine. This new method has the advantages of good yields, mild

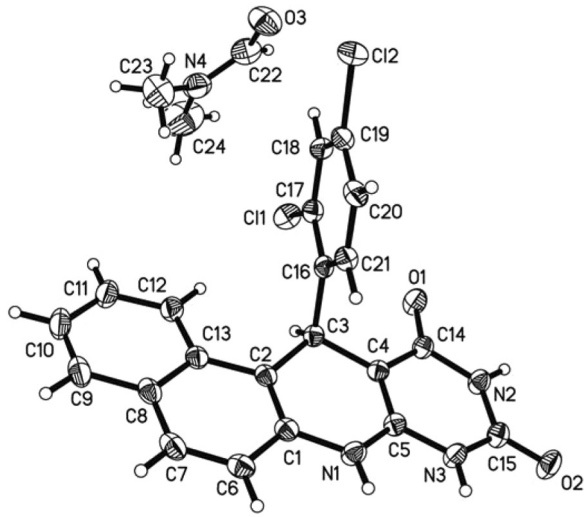


Figure 1. Crystal structure of **4c** with a molecule of DMF solvent.

reaction conditions, easy workup, inexpensive reagents, and environmentally friendly procedure. In addition, water was chosen as a green solvent.

EXPERIMENTAL

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

General Procedure for the Synthesis of 12-Aryl-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-diones 4

A suspension of the mixture of benzaldehyde **1** (2.0 mmol), naphthalen-2-amine **2** (2.0 mmol, 0.286 g), barbituric acid **3** (2.0 mmol, 0.256 g), and iodine (0.1 mmol, 0.025 g) was stirred in water (10 mL) at room temperature for 6–8 h. The powder formed was collected by filtration, washed with water and recrystallized from dimethyiformamide (DMF) and water, and kept at 80°C for 5 h under vacuum to give pure 12-aryl-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-diones **4**.

Data

12-(2,3-Dichlorophenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione **4a**

Pale yellow crystals, mp > 300°C. IR (KBr): 3196, 3074, 3014, 1710, 1644, 1588, 1544, 1470, 1446, 1420, 1399, 1347, 1308, 1236, 1180, 1153, 1045, 862, 811, 775, 747.^{1}H NMR (DMSO-d_6) δ: 6.06 (s, 1H, CH), 7.14–7.18 (m, 1H, ArH), 7.31–7.38 (m, 4H, ArH), 7.45 (t, J = 7.6 Hz, 1H, ArH), 7.83 (d, J = 8.8 Hz, 2H, ArH), 7.99 (d, J = 8.41 Hz, 1H, ArH), 9.31 (s, 1H, NH), 10.48 (s, 1H, NH), 10.63 (s, 1H, NH). Anal. calcd. for $C_{21}H_{13}Cl_2N_3O_2$: C, 61.48; H, 3.19; N, 10.24. Found: C, 61.40; H, 3.35; N, 10.30.

12-(3-Bromophenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione **4b**

Pale yellow crystals, mp > 300°C. IR (KBr): 3202, 3072, 1725, 1682, 1638, 1589, 1541, 1470, 1426, 1387, 1304, 1231, 1195, 1160, 1180, 1118, 1073, 1038, 967, 818, 765, 743, 694. ^{1}H NMR (DMSO-d_6) δ: 5.74 (s, 1H, CH), 7.12–7.15 (m, 1H, ArH), 7.21–7.27 (m, 2H, ArH), 7.33–7.46 (m, 4H, ArH), 7.84–7.90 (m, 3H, ArH), 9.19 (s, 1H, NH), 10.48 (s, 1H, NH), 10.70 (s, 1H, NH). Anal. calcd. for $C_{21}H_{14}BrN_3O_2$: C, 60.02; H, 3.36; N, 10.00. Found: C, 59.93; H, 3.50; N, 9.97.

12-(2,4-Dichlorophenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione **4c**

Pale yellow crystals, mp > 300°C. IR (KBr): 3158, 1618, 1319, 1288, 1253, 1223, 1181, 1144, 1103, 1045, 975, 882, 835, 802, 763, 736.^{1}H NMR (DMSO-d_6) δ: 5.98 (s, 1H, CH), 7.23 (dd, $J_1 = 8.4$ Hz, $J_2 = 1.6$ Hz, 1H, ArH), 7.32–7.37 (m, 3H, ArH), 7.42–7.45 (m, 2H, ArH), 7.83 (d, $J = 8.8$ Hz, 2H, ArH), 8.01 (d, $J = 8.4$ Hz, 1H, ArH), 9.23 (s, 1H, NH), 10.43 (s, 1H, NH), 10.62 (s, 1H, NH). Anal. calcd. for $C_{21}H_{13}Cl_2N_3O_2$: C, 61.48; H, 3.19; N, 10.24. Found: C, 61.56; H, 3.10; N, 10.38.

X-ray crystallography for **4c**: Empirical formula $C_{24}H_{18}Cl_2N_4O_3$, $F_W = 481.32$, $T = 293(2)$ K, Monoclinic, space group P 21/n, $a = 6.4798(16)$ Å, $b = 20.595(5)$ Å, $c = 16.723(4)$ Å, $\beta = 95.267(7)°$, $V = 2222.3(9)$ Å^3, $Z = 4$, $Dc = 1.439$ Mg/m^3, $\lambda(MoK\alpha) = 0.71070$ Å, $\mu = 0.327$ mm^{-1}, $F(000) = 992$. $3.15° < \theta < 25.35°$, $R = 0.0580$, $wR = 0.1456$. $S = 1.147$, Largest diff. Peak and hole: 0.541 and -0.270 e · Å^{-3}.

12-(2-Chlorophenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione **4d**

Pale yellow crystals, mp > 300°C. IR (KBr): 3179, 3067, 3015, 1713, 1651, 1587, 1539, 1469, 1419, 1396, 1298, 1235, 1041, 830, 814, 768, 739. ^{1}H NMR (DMSO-d_6) δ: 6.00 (s, 1H, CH), 7.05–7.09 (m, 1H, ArH), 7.12–7.16 (m, 1H, ArH), 7.28 (d, $J = 8.0$ Hz, 1H, ArH), 7.31–7.36 (m, 3H, ArH), 7.42–7.46 (m, 1H, ArH), 7.82 (d, $J = 8.4$ Hz, 2H, ArH), 8.08 (d, $J = 8.8$ Hz, 1H, ArH), 9.19 (s, 1H, NH), 10.38 (s, 1H, NH), 10.56 (s, 1H, NH). Anal. calcd. for $C_{21}H_{14}ClN_3O_2$: C, 67.12; H, 3.75; N, 11.18. Found: C, 67.25; H, 3.71; N, 11.10.

12-(2-Nitrophenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione **4e**

Pale yellow crystals, mp > 300°C. IR (KBr): 3279, 3086, 1704, 1553, 1436, 1348, 1288, 1250, 1228, 1280, 1175, 1106, 1041, 810, 825, 807, 790, 768, 748, 701. ^{1}H NMR (DMSO-d_6) δ: 6.07 (s, 1H, CH), 7.06 (dd, $J_1 = 8.0$ Hz, $J_2 = 1.2$ Hz, 1H, ArH), 7.27–7.37 (m, 2H, ArH), 7.40–7.45 (m, 3H, ArH), 7.82–7.92 (m, 2H, ArH), 7.90 (d, $J = 8.8$ Hz, 1H, ArH), 8.38 (d, $J = 8.4$ Hz, 2H, ArH), 9.27 (s, 1H, NH), 10.45 (s, 1H, NH), 10.64 (s, 1H, NH). Anal. calcd. for $C_{21}H_{14}N_4O_4$: C, 65.28; H, 3.65; N, 14.50. Found: C, 65.20; H, 3.77; N, 14.34.

12-(4-Methoxyphenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione **4f**

Pale yellow crystals, mp > 300°C. IR (KBr): 3195, 3073, 1700, 1647, 1554, 1470, 1399, 1301, 1254, 1234, 1180, 1108, 1038, 972, 822, 769, 748.^{1}H NMR (DMSO-d_6) δ: 5.66 (s, 1H, CH), 6.72 (d, $J = 8.4$ Hz, 2H, ArH), 7.6 (d, $J = 8.4$ Hz, 2H, ArH), 7.31–7.44 (m, 3H, ArH), 7.81–7.83 (m, 2H, ArH), 7.91 (d, $J = 8.0$ Hz, 1H, ArH), 9.09 (s, 1H, NH), 10.38 (s, 1H, NH), 10.63 (s, 1H, NH). Anal. calcd. for $C_{22}H_{17}N_3O_3$: C, 71.15; H, 4.61; N, 11.31. Found: C, 71.10; H, 4.71; N, 11.28.

12-(2,3-Dimethoxyphenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione **4g**

Pale yellow crystals, mp > 300°C. IR (KBr): 3264, 3208, 3307, 2936, 2837, 1701, 1641, 1608, 1544, 1463, 1418, 1298, 1275, 1233, 1166, 1126, 1062, 1044, 897, 773, 748.^{1}H NMR (DMSO-d_6) δ: 3.72 (s, 3H, CH_3O), 3.95 (s, 3H, CH_3O), 5.97 (s, 1H, CH), 6.71 (dd, $J_1 = 2.8$ Hz, $J_2 = 6.8$ Hz, 1H, ArH), 6.80–6.85 (m, 2H, ArH), 7.29–7.33 (m, 2H, ArH), 7.43 (t, $J = 7.6$ Hz, 1H, ArH), 7.75 (d, $J = 9.6$ Hz, 2H, ArH), 8.29 (d, $J = 8.8$ Hz, 1H, ArH), 9.07 (s, 1H, NH), 10.38 (s, 1H, NH), 10.59 (s, 1H, NH). Anal. calcd. for $C_{23}H_{19}N_3O_4$: C, 68.82; H, 4.77; N, 10.47. Found: C, 68.96; H, 4.82; N, 10.37.

12-(3-Nitrophenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione **4h**

Pale yellow crystals, mp > 300°C. IR (KBr): 3402, 3077, 1730, 1471, 1409, 1346, 1294, 1253, 1206, 1187, 1097, 1041, 971, 906, 826, 815, 770, 743.

^{1}H NMR (DMSO-d_6) δ: 5.91 (s, 1H, CH), 7.32–7.36 (m, 1H, ArH), 7.41 – 7.51 (m, 3H, ArH), 7.73 (d, $J = 8.0$ Hz, 1H, ArH), 7.84–7.93 (m, 4H, ArH), 8.10 (dd, $J_1 = 3.6$ Hz, $J_2 = 1.6$ Hz, 1H, ArH), 9.29 (s, 1H, NH), 10.55 (s, 1H, NH), 10.72 (s, 1H, NH). Anal. calcd. for $C_{21}H_{14}N_4O_4$: C, 65.28; H, 3.65; N, 14.50. Found: C, 65.33; H, 3.57; N, 14.47.

12-(3,4-Dimethylphenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione **4i**

Pale yellow crystals, mp > 300°C. IR (KBr): 3199, 3075, 1706, 1645, 1509, 1542, 1470, 1450, 1398, 1296, 1234, 1122, 1038, 819, 772, 750, 714.^{1}H NMR (DMSO-d_6) δ: 2.04 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 5.62 (s, 1H, CH), 6.89 (d, $J = 8.0$ Hz, 1H, ArH), 6.94 (d, $J = 8.0$ Hz, 1H, ArH), 7.04 (s, 1H, ArH), 7.30–7.44 (m, 3H, ArH), 7.82 (d, $J = 8.8$ Hz, 2H, ArH), 7.90 (d, $J = 8.4$ Hz, 1H, ArH), 9.10 (s, 1H, NH), 10.41 (s, 1H, NH), 10.62 (s, 1H, NH). Anal. calcd. for $C_{23}H_{19}N_3O_2$: C, 74.78; H, 5.18; N, 11.37. Found: C, 74.59; H, 5.29; N, 11.40.

12-Phenyl-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione **4j**

Pale yellow crystals, mp > 300°C. IR (KBr): 3196, 3074, 1743, 1642, 1589, 1472, 1396, 1345, 1303, 1234, 1197, 1121, 1097, 1075, 1040, 1030, 969, 828, 813, 775, 746, 696.^{1}H NMR (DMSO-d_6) δ: 5.71 (s, 1H, CH), 7.03–7.06 (m, 1H, ArH), 7.16 (t, $J = 7.6$ Hz, 2H, ArH), 7.26–7.44 (m, 5H, ArH), 7.83 (d, $J = 8.8$ Hz, 2H, ArH), 7.92 (d, $J = 8.4$ Hz, 1H, ArH), 9.11 (s, 1H, NH), 10.40 (s, 1H, NH), 10.65 (s, 1H, NH). Anal. calcd. for $C_{21}H_{15}N_3O_2$: C, 73.89; H, 4.43; N, 12.31. Found: C, 73.87; H, 4.26; N, 12.44.

12-(2-Methoxyphenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione **4k**

Pale yellow crystals, mp > 300°C. IR (KBr): 3178, 3133, 3065, 3012, 2955, 2812, 1710, 1043, 1584, 1539, 1490, 1463, 1417, 1392, 1326, 1300, 1250, 1234, 1182, 1098, 1026, 840, 815, 751.^{1}H NMR (DMSO-d_6) δ: 3.88 (s, 3H, CH_3O), 5.98 (s, 1H, CH), 6.74–6.77 (m, 1H, ArH), 6.91 (d, $J = 8.0$ Hz, 1H, ArH), 7.00–7.04 (m, 1H, ArH), 7.21 (dd, $J_1 = 7.6$ Hz, $J_2 = 1.2$ Hz, 1H, ArH), 7.28–7.32 (m, 2H, ArH), 7.40–7.43 (m, 1H, ArH), 7.75 (d, $J = 8.8$ Hz, 1H, ArH), 7.78 (d, $J = 8.4$ Hz, 1H, ArH), 8.18 (d, $J = 8.4$ Hz, 1H, ArH), 9.05 (s, 1H, NH), 10.33 (s, 1H, NH), 10.50 (s, 1H, NH). Anal. calcd. for $C_{22}H_{17}N_3O_3$: C, 71.15; H, 4.61; N, 11.31. Found: C, 71.27; H, 4.57; N, 11.39.

12-(3,5-Dimethoxyphenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione **4l**

Pale yellow crystals, mp > 300°C. IR (KBr): 3270, 3203, 2936, 2837, 1704, 1647, 1610, 1590, 1542, 1463, 1397, 1327, 1315, 1233, 1201, 1161, 1071, 1055, 889, 865, 850, 821, 772, 745.^{1}H NMR (DMSO-d_6) δ: 3.62 (s, 6H, 2∗CH_3O), 5.68 (s, 1H, CH), 6.23–6.24 (m, 1H, ArH), 6.39 (d, $J = 2.0$ Hz, Hz, 2H, ArH), 7.33–7.39 (m, 2H, ArH), 7.42–7.47 (m, 1H, ArH), 7.82–7.85 (m, 2H, ArH), 7.92 (d, $J = 8.4$ Hz, 1H, ArH), 9.11 (s, 1H, NH), 10.66 (s, 1H, NH). Anal. calcd. for $C_{23}H_{19}N_3O_4$: C, 68.82; H, 4.77; N, 10.47. Found: C, 68.99; H, 4.69; N, 10.53.

12-(2-Bromophenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione **4m**

Pale yellow crystals, mp > 300°C. IR (KBr): 3311, 3171, 3052, 1702, 1587, 1462, 1327, 1310, 1283, 1248, 1230, 1175, 1105, 1043, 1020, 827, 803, 769, 745, 713.^{1}H NMR (DMSO-d_6) δ: 5.95 (s, 1H, CH), 6.96–6.99 (m, 1H, ArH), 7.14–7.18 (m, 1H, ArH), 7.28–7.36 (m, 3H, ArH), 7.42–7.47 (m, 2H, ArH), 7.82 (d, $J = 8.4$ Hz, 2H, ArH), 8.17 (d, $J = 8.8$ Hz, 1H, ArH), 9.20 (s, 1H, NH), 10.40 (s, 1H, NH), 10.58 (s, 1H, NH). Anal. calcd. for $C_{21}H_{14}BrN_3O_2$: C, 60.02; H, 3.36; N, 10.00. Found: C, 59.90; H, 3.38; N, 10.18.

12-(4-Fluorophenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione **4n**

Pale yellow crystals, mp > 300°C. IR (KBr): 3191, 3071, 1721, 1638, 1603, 1544, 1504, 1472, 1450, 1397, 1351, 1300, 1224, 1199, 1156, 1121, 1095, 1035, 833, 821, 801, 747, 714. ^{1}H NMR (DMSO-d_6) δ: 5.74 (s, 1H, CH), 6.96–7.00 (m, 2H, ArH), 7.27–7.35 (m, 3H, ArH), 7.37–7.44 (m, 2H, ArH), 7.71–7.76 (m, 2H, ArH), 7.83 (d, $J = 8.8$ Hz, 1H, ArH), 9.13 (s, 1H, NH), 10.41 (s, 1H, NH), 10.67 (s, 1H, NH). Anal. calcd. for $C_{21}H_{14}FN_3O_2$: C, 70.19; H, 3.93; N, 11.69. Found: C, 70.10; H, 3.85; N, 11.77.

12-(2-Fluorophenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione **4o**

Pale yellow crystals, mp > 300°C. IR (KBr): 3172, 3086, 1708, 1634, 1608, 1559, 1486, 1474, 1399, 1277, 1236, 1203, 1126, 1086, 1036, 824, 773, 751,

733.^{1}H NMR (DMSO-d_6) δ: 5.74 (s, 1H, CH), 6.96–7.00 (m, 2H, ArH), 7.27–7.35 (m, 3H, ArH), 7.37–7.44 (m, 2H, ArH), 7.71–7.76 (m, 2H, ArH), 7.83 (d, $J = 8.8$ Hz, 1H, ArH), 9.13 (s, 1H, NH), 10.41 (s, 1H, NH), 10.67 (s, 1H, NH). Anal. calcd. for $C_{21}H_{14}FN_3O_2$: C, 70.19; H, 3.93; N, 11.69. Found: C, 70.29; H, 3.90; N, 11.70.

12-(4-Hydroxyphenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione **4p**

Pale yellow crystals, mp > 300°C. IR (KBr): 3552, 3197, 1707, 1646, 1544, 1510, 1470, 1395, 1343, 1299, 1234, 1180, 1122, 1103, 1075, 1041, 970, 818, 772, 747.^{1}H NMR (DMSO-d_6) δ: 5.61 (s, 1H, CH), 6.54 (d, $J = 8.4$ Hz, 2H, ArH), 7.05 (d, $J = 8.4$ Hz, 2H, ArH), 7.31–7.40 (m, 2H, ArH), 7.42–7.44 (m, 1H, ArH), 7.80–7.83 (m, 2H, ArH), 7.91 (d, $J = 8.4$ Hz, 1H, ArH), 9.03 (s, 1H, OH), 9.10 (s, 1H, NH), 10.33 (s, 1H, NH), 10.61 (s, 1H, NH). Anal. calcd. for $C_{21}H_{15}N_3O_3$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.67; H, 4.30; N, 11.82.

12-(4-Nitrophenyl)-7,8,9,10,11,12-hexahydrobenzo[*f*]pyrimido[4,5-*b*]quinoline-9,11-dione **4q**

Pale yellow crystals, mp > 300°C. IR (KBr): 3200, 3075, 1704, 1642, 1590, 1515, 1468, 1395, 1347, 1300, 1235, 1185, 1109, 1050, 972, 892, 862, 823, 770, 750.^{1}H NMR (DMSO-d_6) δ: 5.88 (s, 1H, CH), 7.32–7.36 (m, 1H, ArH), 7.40–7.44 (m, 2H, ArH), 7.54 (d, $J = 8.8$ Hz, 2H, ArH), 7.83–7.88 (m, 3H, ArH), 8.06 (d, $J = 8.0$ Hz, 2H, ArH), 9.26 (s, 1H, NH), 10.51 (s, 1H, NH), 10.72 (s, 1H, NH). Anal. calcd. for $C_{21}H_{14}N_4O_4$: C, 65.28; H, 3.65; N, 14.50. Found: C, 65.43; H, 3.40; N, 14.39.

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