

# Facile One-Pot Synthesis of Quinazoline-2,4-dione Derivatives and Application to Naturally Occurring Alkaloids from *Zanthoxylum Arborescens*

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## Introduction

Quinazoline-2,4-diones are one of the important heterocycles<sup>1</sup> and have been shown to possess pharmacologically interesting properties such as anti-hypertensive,<sup>2</sup> anti-diabetic,<sup>3</sup> and immunosuppressive activities.<sup>4</sup> Among these, synthetic pelanserine (TR2515) (**1**)<sup>5</sup> is a well established potent anti-hypertensive, having activity comparable to ketanserin,<sup>6</sup> which is an anti-hypertensive agent used clinically. As alkaloids containing the quinazoline-2,4-dione moiety, compounds **2** and **3** were isolated from *Zanthoxylum arborescens* (Figure 1).<sup>7</sup> This wide range of biological activities has stimulated interest in new approaches for the synthesis of quinazoline-2,4-dione derivatives.

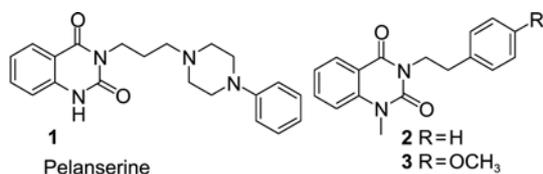
Several synthetic approaches to quinazoline-2,4-dione derivatives have been reported.<sup>8</sup> The general methods include a four-step reaction starting from phthalate monomethyl ester<sup>9</sup> and one-step palladium-catalyzed urea arylation-intramolecular ester amidation.<sup>10</sup> There is still a demand for a more convenient and efficient synthetic method that can efficiently provide quinazoline-2,4-dione derivatives. We report herein a convenient one-pot synthesis of quinazoline-2,4-dione derivatives. We also report on the synthesis of the naturally occurring alkaloids **2** and **3**.

## Results and Discussion

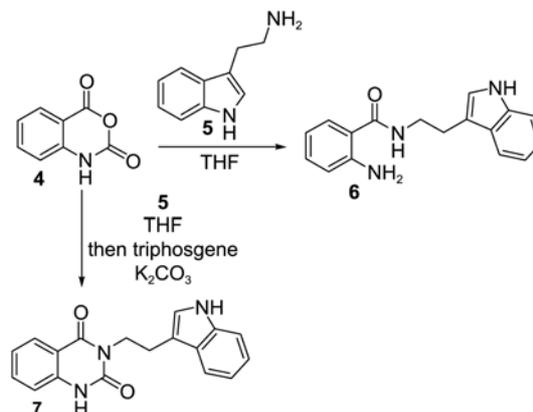
A two-step reaction for the synthesis of quinazoline-2,4-dione derivatives starting from isatoic anhydride and amines has already been described.<sup>11</sup> However, a one-pot approach for the synthesis of quinazoline-2,4-dione derivatives from commercially available isatoic anhydride has not been reported. Direct reaction of isatoic anhydride (**4**) with tryptamine (**5**) in THF at room temperature for 5 h afforded aminobenzamide **6** in 80% yield (Scheme 1) without any formation of quinazoline-2,4-dione **7**. The nucleophilic

attack of primary amine of **5** to carbonyl group on the oxazine ring of isatoic anhydride (**4**) followed by loss of carbon dioxide produced compound **6**. The structural assignment of **6** was confirmed by <sup>13</sup>C NMR, which clearly showed a carbonyl peak of amide group at 168.9 ppm. To give the quinazoline-2,4-dione moiety, reaction of isatoic anhydride (**4**) and tryptamine (**5**) with triphosgene was next attempted. Treatment of isatoic anhydride (**4**) with both tryptamine (**5**) and triphosgene in the presence of K<sub>2</sub>CO<sub>3</sub> in THF at room temperature for 20 h gave the product **7** in only 20% yield. However, treatment of **4** with **5** in THF at room temperature for 5 h followed by further reaction by addition of triphosgene and K<sub>2</sub>CO<sub>3</sub> at room temperature for 15 h provided **7** in increased yield (73%). The structure of **7** was easily confirmed by <sup>1</sup>H NMR analysis and direct comparison with reported data.<sup>12</sup>

In order to extend the utility of this methodology, further reactions of isatoic anhydride (**4**) and several primary amines with triphosgene in the presence of K<sub>2</sub>CO<sub>3</sub> using conditions described above were next attempted to synthesize a variety of quinazoline-2,4-dione derivatives. The results are summarized in Table 1. First, the reaction of isatoic anhydride and aliphatic amines with a long chain or cyclic ring was examined. The reaction of **4** with butylamine afforded **8** in 50% yield, whereas that with 1-hexylamine gave **9** in 71% yield (entries 1 and 2). Similarly, the reaction of 4-phenylbutylamine, 2-piperidinoethylamine, 2-morpholinoethylamine, and cyclohexylmethylamine having a ring provided the desired products **10-13** in 55, 44, 52, and 53% yield (entries



**Figure 1.** Synthesized and naturally occurring representative quinazoline-2,4-diones.



**Scheme 1**

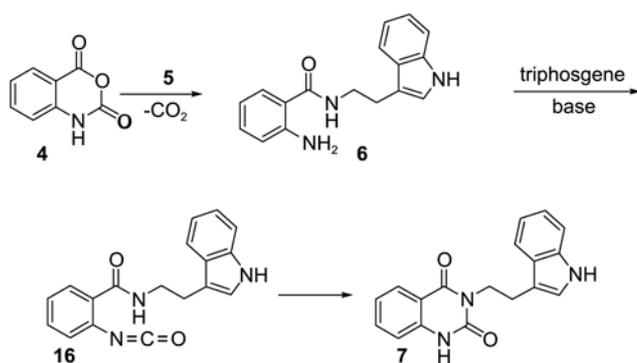
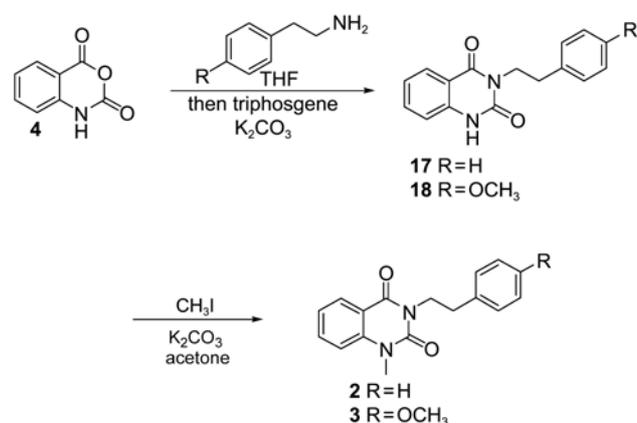
**Table 1.** Synthesis of a variety of quinazoline-2,4-diones starting from isatoic anhydride (**4**)

Entry	Starting material	Amine	Product	Yield (%)
1				50
2				71
3				55
4				44
5				52
6				53
7				65
8				58

3-6), respectively. Reactions with benzylamine and 4-methoxybenzylamine gave compounds **14** and **15** in 65 and 58% yield, respectively (entries 7 and 8). These reactions provided a rapid synthetic route to quinazoline-2,4-dione derivatives with a variety of substituents at the 3-position of the quinazolinone moiety.

The formation of **7** may be explained as shown in Scheme 2. Amine **5** was first reacted with isatoic anhydride (**4**) to give the aminobenzamide **6**. The ring opening of **4** with amines has already been described by another group.<sup>13</sup> The aminobenzamide **6** was cyclized using triphosgene in the presence of a base through the intermediate **16** to give product **7**. The existence of the isocyanate intermediate formed from the reaction of aminobenzamide and triphosgene has also been proven by Eckert.<sup>14</sup>

As an application of this methodology, the concise synthesis of naturally occurring alkaloids **2** and **3** was attempted (Scheme 3). Reaction of **4** with phenethylamine in THF at room temperature for 5 h followed by further reaction with triphosgene in the presence of 5 equivalents of  $K_2CO_3$  at room temperature for 15 h afforded **17** in 78% yield, whereas that with 4-methoxyphenethylamine gave **18** in 81% yield. Treatment of **17** and **18** with methyl iodide in the presence of  $K_2CO_3$  in refluxing acetone for 5 h gave the

**Scheme 2****Scheme 3**

expected products **2** and **3** in 95 and 83% yield, respectively. The spectroscopic data for synthetic materials **2** and **3** are in good agreement with the data reported for the natural products.<sup>7</sup>

In conclusion, we have described a one-pot synthesis of biologically interesting quinazoline-2,4-dione derivatives starting from isatoic anhydride with primary amines and subsequent addition of triphosgene under a base. As an application of this methodology, naturally occurring alkaloids **2** and **3** were synthesized starting from isatoic anhydride in 2-step.

## Experimental Section

All the experiments were carried out in a nitrogen atmosphere. Merck precoated silica gel plates (Art. 5554) with a fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). The  $^1H$  NMR and  $^{13}C$  NMR spectra were recorded on a Bruker Model ARX (300 and 75 MHz, respectively) spectrometer in  $CDCl_3$  or  $DMSO-d_6$ . The IR spectra were recorded on a Jasco FTIR 5300 spectrophotometer.

**2-Amino-N-[2-(1H-indol-3-yl)ethyl]benzamide (6).** To a solution of isatoic anhydride (163 mg, 1.0 mmol) in THF (15 mL) was added tryptamine (1.1 mmol). The mixture was stirred at room temperature for 5 h. The reaction mixture

was quenched by the addition of saturated  $\text{NH}_4\text{Cl}$  solution (50 mL) and extracted with ethyl acetate (50 mL  $\times$  3). The organic layer was washed with water (40 mL), dried ( $\text{MgSO}_4$ ), and evaporated under reduced pressure to give yellow solids. The solids were recrystallized by ethanol to give **6** (223 mg, 80%) as a solid; mp 159-160 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$  10.82 (1H, s), 8.35 (1H, t,  $J = 5.5$  Hz), 7.59 (1H, d,  $J = 7.8$  Hz), 7.46 (1H, d,  $J = 7.8$  Hz), 7.35 (1H, d,  $J = 8.1$  Hz), 7.19-6.97 (4H, m), 6.70 (1H, d,  $J = 7.5$  Hz), 6.50 (1H, dd,  $J = 7.5, 7.0$  Hz), 6.42 (2H, s), 3.54 (2H, t,  $J = 7.5$  Hz), 2.94 (2H, t,  $J = 7.5$  Hz);  $^{13}\text{C}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$  168.9, 149.7, 136.3, 131.6, 128.1, 127.4, 122.7, 121.0, 118.4, 118.3, 116.4, 115.0, 114.7, 112.1, 111.5, 39.9, 25.3; IR (KBr) 3409, 3056, 2927, 1630, 1581, 1518, 1426, 1276, 1245, 1171, 1096, 746  $\text{cm}^{-1}$ .

**Typical Procedures for the Synthesis of Quinazoline-2,4-diones 7-15 and 17-18.** To a solution of isatoic anhydride (163 mg, 1.0 mmol) in THF (15 mL) was added amines (1.1 mmol). The mixture was stirred at room temperature for 5 h. Then triphosgene (296 mg, 1.0 mmol) and  $\text{K}_2\text{CO}_3$  (690 mg, 5.0 mmol) was added and the resulting mixture was further stirred for 15 h to complete the reactions. The reaction mixture was quenched by the addition of saturated  $\text{NH}_4\text{Cl}$  solution (50 mL) and extracted with ethyl acetate (50 mL  $\times$  3). The organic layer was washed with water (40 mL), dried ( $\text{MgSO}_4$ ), and evaporated under reduced pressure to give yellow solids. The solids were recrystallized by ethanol to give pure products **7-15** and **17-18**.

**3-[2-(1H-Indol-3-yl)ethyl]-1H,3H-quinazoline-2,4-dione (7):** Yield 73%; mp 306-307 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$  11.3 (1H, s), 10.80 (1H, s), 7.98 (1H, d,  $J = 7.5$  Hz), 7.69 (1H, d,  $J = 7.5$  Hz), 7.66 (1H, dd,  $J = 7.8, 7.0$  Hz), 7.35 (1H, d,  $J = 7.8$  Hz), 7.24-7.19 (3H, m), 7.08 (1H, dd,  $J = 7.5, 7.0$  Hz), 7.00 (1H, dd,  $J = 7.5, 7.0$  Hz), 4.17 (2H, t,  $J = 8.1$  Hz), 2.99 (2H, t,  $J = 8.1$  Hz);  $^{13}\text{C}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$  161.8, 150.0, 139.2, 136.2, 134.6, 127.0, 122.5, 122.1, 120.7, 118.1, 114.9, 113.7, 111.1, 111.0, 40.5, 23.3; IR (KBr) 3366, 3063, 1706, 1645, 1448, 1349, 1281, 1104, 1003, 740  $\text{cm}^{-1}$ .

**3-Butyl-1H,3H-quinazoline-2,4-dione (8):** Yield 50%; mp 156-156 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  10.82 (1H, s), 8.10 (1H, d,  $J = 7.8$  Hz), 7.57 (1H, t,  $J = 7.8$  Hz), 7.21-7.12 (2H, m), 4.08 (2H, t,  $J = 7.5$  Hz), 1.74-1.59 (2H, m), 1.47-1.35 (2H, m), 0.95 (3H, t,  $J = 7.2$  Hz);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  162.4, 152.4, 138.7, 134.8, 128.2, 123.2, 115.1, 114.6, 40.8, 30.0, 20.2, 13.8; IR (KBr) 3194, 3065, 2955, 1715, 1639, 1493, 1450, 1410, 1345, 1274, 1078, 950, 760  $\text{cm}^{-1}$ .

**3-Hexyl-1H,3H-quinazoline-2,4-dione (9):** Yield 71%; mp 152-154 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  9.97 (1H, s), 8.12 (1H, d,  $J = 7.8$  Hz), 7.59 (1H, dd,  $J = 8.1, 7.8$  Hz), 7.21 (1H, dd,  $J = 8.1, 7.8$  Hz), 7.08 (1H, d,  $J = 8.1$  Hz), 4.06 (2H, t,  $J = 7.5$  Hz), 1.75-1.65 (2H, m), 1.42-1.30 (6H, m), 0.87 (3H, t,  $J = 7.2$  Hz);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  162.3, 151.9, 138.5, 134.9, 128.4, 123.3, 114.9, 114.4, 41.1, 31.5, 27.8, 26.6, 22.5, 14.1; IR (KBr) 3440, 3062, 2933, 2359, 1714, 1660, 1454, 1282, 1081, 837, 756  $\text{cm}^{-1}$ .

**3-(4-Phenylbutyl)-1H,3H-quinazoline-2,4-dione (10):** Yield 55%; mp 97-98 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  10.61 (1H, s), 8.13 (1H, d,  $J = 7.8$  Hz), 7.58 (1H, dd,  $J = 8.1, 7.2$  Hz), 7.27-7.10 (7H, m), 4.14 (2H, t,  $J = 6.9$  Hz), 2.69 (2H, t,  $J = 6.9$  Hz), 1.79-1.73 (4H, m);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  162.3, 152.4, 142.2, 138.7, 134.9, 128.4, 128.3, 128.2, 125.7, 123.3, 115.0, 114.7, 40.8, 35.6, 28.7, 27.6; IR (KBr) 3195, 2941, 1720, 1635, 1448, 1358, 1269, 1111, 1056, 755  $\text{cm}^{-1}$ .

**3-[2-(Piperidin-1-yl) ethyl]-1H,3H-quinazoline-2,4-dione (11):** Yield 44%; mp 187-189 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  10.46 (1H, s), 8.02 (1H, d,  $J = 8.1$  Hz), 7.53 (1H, dd,  $J = 8.1, 7.5$  Hz), 7.14 (1H, dd,  $J = 8.1, 7.5$  Hz), 7.04 (1H, d,  $J = 8.1$  Hz), 4.24 (2H, t,  $J = 7.2$  Hz), 2.69 (2H, t,  $J = 7.2$  Hz), 2.64-2.52 (4H, m), 1.66-1.54 (4H, m), 1.47-1.38 (2H, m);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  162.3, 151.8, 138.7, 134.8, 128.3, 123.2, 114.8, 114.5, 56.2, 54.7, 38.0, 25.8, 24.3; IR (KBr) 3442, 3062, 2931, 1720, 1658, 1449, 1294, 1112, 1044, 832, 755  $\text{cm}^{-1}$ .

**3-[2-(Morpholin-4-yl)ethyl]-1H,3H-quinazoline-2,4-dione (12):** Yield 52%; mp 198-203 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  10.04 (1H, s), 8.08 (1H, d,  $J = 7.8$  Hz), 7.57 (1H, dd,  $J = 7.8, 7.2$  Hz), 7.20 (1H, dd,  $J = 8.0, 7.2$  Hz), 7.04 (1H, d,  $J = 8.1$  Hz), 4.23 (2H, t,  $J = 6.6$  Hz), 3.68 (4H, t,  $J = 4.5$  Hz), 2.70 (2H, t,  $J = 6.6$  Hz), 2.64-2.54 (4H, m);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  162.3, 151.8, 138.5, 135.0, 128.4, 123.4, 114.8, 114.6, 67.0, 56.0, 53.8, 37.7; IR (KBr) 3439, 3065, 2931, 1718, 1647, 1451, 1283, 1116, 862, 759  $\text{cm}^{-1}$ .

**3-(Cyclohexylmethyl)-1H,3H-quinazoline-2,4-dione (13):** Yield 53%; mp 209-212 °C;  $^1\text{H}$ -NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  10.40 (1H, s), 8.12 (1H, d,  $J = 7.8$  Hz), 7.59 (1H, dd,  $J = 7.8, 7.2$  Hz), 7.02 (1H, dd,  $J = 8.1, 7.2$  Hz), 7.11 (1H, d,  $J = 8.1$  Hz), 3.96 (2H, d,  $J = 7.2$  Hz), 1.95-1.82 (1H, m), 1.76-1.63 (5H, m), 1.28-1.10 (5H, m);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  162.7, 162.3, 152.5, 138.7, 134.9, 128.5, 123.3, 115.0, 114.7, 46.8, 36.6, 30.9, 26.4, 25.9; IR (KBr) 3440, 3195, 2919, 1719, 1638, 1445, 1269, 1111, 952, 758  $\text{cm}^{-1}$ .

**3-Benzyl-1H,3H-quinazoline-2,4-dione (14):** Yield 65%; mp 214-236 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  10.07 (1H, s), 8.13 (1H, d,  $J = 7.8$  Hz), 7.59-7.49 (3H, m), 7.30-7.17 (4H, m), 7.03 (1H, d,  $J = 8.1$  Hz), 5.27 (2H, s);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  162.4, 151.0, 139.2, 137.0, 134.5, 128.4, 128.1, 127.9, 127.1, 122.5, 115.1, 114.2, 43.7; IR (KBr) 3205, 3074, 2943, 1313, 1662, 1491, 1449, 1406, 1350, 963, 760  $\text{cm}^{-1}$ .

**3-(4-Methoxybenzyl)-1H,3H-quinazoline-2,4-dione (15):** Yield 58%; mp 210-216 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  10.29 (1H, s), 8.12 (1H, d,  $J = 7.5$  Hz), 7.56 (1H, t,  $J = 7.5, 7.0$  Hz), 7.48 (2H, d,  $J = 7.8$  Hz), 7.19 (1H, dd,  $J = 7.8, 7.0$  Hz), 7.05 (1H, d,  $J = 7.8$  Hz), 6.86 (2H, d,  $J = 7.8$  Hz), 5.21 (2H, s), 3.74 (3H, s);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  162.4, 159.2, 152.3, 138.6, 135.0, 130.5, 129.2, 128.5, 123.4, 115.0, 114.8, 113.8, 55.2, 43.7; IR (KBr) 3440, 3070, 2929, 1713, 1654, 1509, 1448, 1251, 1170, 1107, 1036, 823, 760  $\text{cm}^{-1}$ .

**3-Phenethyl-1H,3H-quinazoline-2,4-dione (17):** Yield 78%; mp 174-175 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  10.45

(1H, s), 8.14 (1H, d,  $J = 7.8$  Hz), 7.61 (1H, dd,  $J = 8.1, 7.8$  Hz), 7.35-7.17 (6H, m), 7.12 (1H, d,  $J = 8.1$  Hz), 4.35-4.30 (2H, m), 3.10-3.00 (2H, m);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  162.2, 152.0, 138.7, 138.6, 135.0, 128.9, 128.5, 128.4, 126.5, 123.4, 115.1, 114.7, 42.3, 34.1; IR (KBr) 3063, 2937, 1716, 1658, 1493, 1451, 1411, 1352, 1282, 1168, 1114, 1004, 824, 760  $\text{cm}^{-1}$ .

**3-(4-Methoxyphenethyl)-1H,3H-quinazoline-2,4-dione (18):** Yield 81%; mp 224-228 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  10.73 (1H, s), 7.87 (1H, d,  $J = 8.1$  Hz), 7.34 (1H, t,  $J = 8.4$  Hz), 7.04-6.94 (4H, m), 6.63 (2H, d,  $J = 8.7$  Hz), 4.05-3.99 (2H, m), 3.58 (3H, s), 2.75-2.70 (2H, m);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  162.1, 157.7, 150.4, 139.1, 134.2, 130.4, 129.4, 127.4, 122.1, 114.8, 113.9, 113.4, 54.7, 41.7, 32.6; IR (KBr) 3459, 2927, 1723, 1655, 1512, 1452, 1410, 1289, 1246, 1177, 1122, 1032, 826, 754  $\text{cm}^{-1}$ .

**General Procedure for Synthesis of 2 and 3.** Methyl iodide (85 mg, 0.6 mmol) in acetone (1.0 mL) was added to a solution of compound 17 (133 mg, 0.5 mmol) or 18 (148 mg, 0.5 mmol) and potassium carbonate (345 mg, 2.5 mmol) in acetone (10 mL). The reaction mixture was stirred in refluxing acetone for 5 h. The solvent was evaporated under reduced pressure. The residue was treated with water, acidified with a saturated aqueous  $\text{NH}_4\text{Cl}$  solution (50 mL), and extracted with ethyl acetate (50 mL  $\times$  3). The combined organic layer were washed with brine (50 mL), dried over  $\text{MgSO}_4$ , filtered, and evaporated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel to give 2 or 3.

**1-Methyl-3-phenethyl-1H,3H-quinazoline-2,4-dione (2):** Yield 95%; mp 101-102 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.21 (1H, dd,  $J = 7.8, 1.5$  Hz), 7.67-7.62 (1H, m), 7.34-7.15 (7H, m), 4.32-4.26 (2H, m), 3.58 (3H, m), 3.00-2.94 (2H, m);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  161.5, 150.8, 140.5, 138.6, 134.9, 128.9, 128.8, 128.4, 126.4, 122.9, 115.6, 113.4, 43.2, 34.0, 30.6; IR (KBr) 3029, 2942, 1700, 1654, 1608, 1484, 1427, 1397, 1351, 1317, 1257, 1142, 1031, 759  $\text{cm}^{-1}$ .

**1-Methyl-3-(4-Methoxyphenethyl)-1H,3H-quinazoline-2,4-dione (3):** Yield 83%; mp 135-136 °C;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  8.20 (1H, dd,  $J = 7.8, 1.2$  Hz), 7.64 (1H, ddd,  $J = 8.4, 7.2, 1.2$  Hz), 7.26-7.20 (3H, m), 7.17 (1H, d,  $J = 8.4$  Hz), 6.82 (2H, d,  $J = 8.7$  Hz), 4.27-4.22 (2H, m), 3.79

(3H, s), 3.57 (3H, s), 2.93-2.89 (2H, m);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  161.5, 158.3, 150.9, 140.5, 135.0, 130.7, 129.9, 128.9, 122.9, 115.6, 113.9, 113.4, 55.2, 43.4, 33.1, 30.6; IR (KBr) 3442, 3032, 2966, 2930, 1696, 1653, 1612, 1508, 1483, 1428, 1350, 1243, 1175, 1127, 1031, 834, 755  $\text{cm}^{-1}$ .

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