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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[1] and have been shown to possess pharmacologically interesting properties such as anti-hypertensive,[2] anti-diabetic,[3] and immunosuppressive activities.[4] Among these, synthetic pelanserine (TR2515) (**1**)[5] is a well established potent anti-hypertensive, having activity comparable to ketanserin,[6] 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).[7] 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.[8] The general methods include a four-step reaction starting from phthalate monomethyl ester[9] and one-step palladium-catalyzed urea arylation-intramolecular ester amidation.[10] 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.[11] 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 ^{13}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_2CO_3 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_2CO_3 at room temperature for 15 h provided **7** in increased yield (73%). The structure of **7** was easily confirmed by ^1H NMR analysis and direct comparison with reported data.[12]

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_2CO_3 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

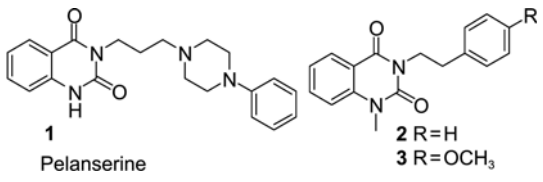
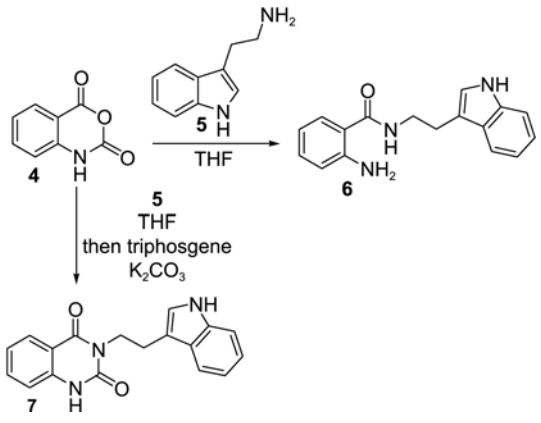
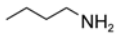
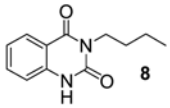
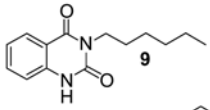
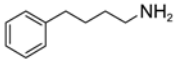
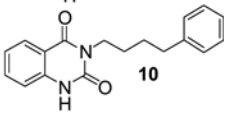
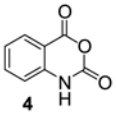
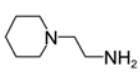
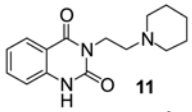
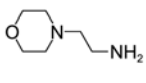
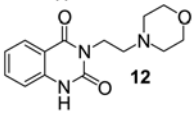
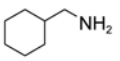
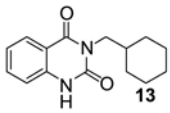
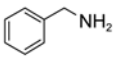
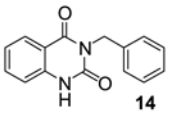
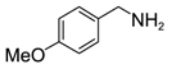
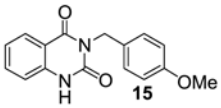


Figure 1. Synthesized and naturally occurring representative quinazoline-2,4-diones.



Scheme 1

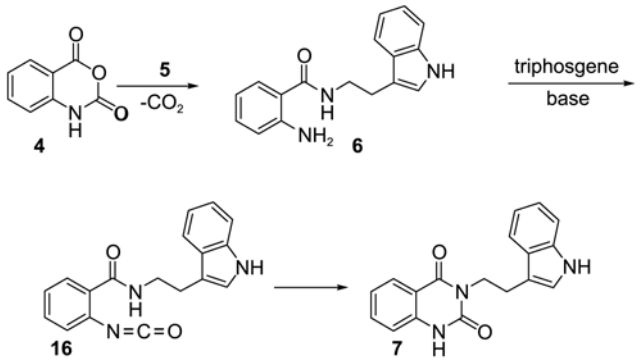
Table 1. Synthesis of a variety of quinazoline-2,4-diones starting from isatoic anhydride (**4**)

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

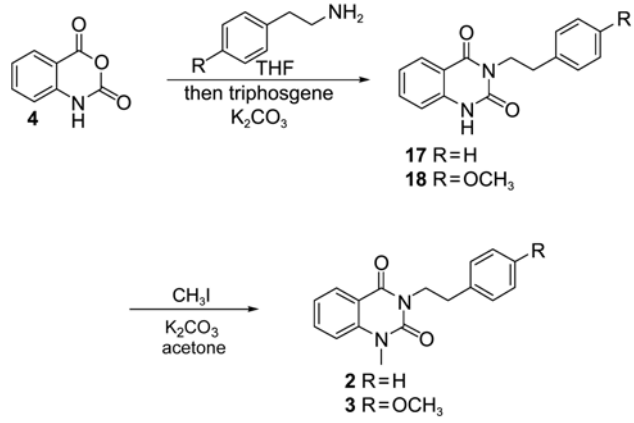
3-6), respectively. Reactions with benzylamine and 4-methoxybenzylamine gave compounds **14** and **15** in 65 and 58% yield, respectively (entries 7 and 8). These reactions provided a rapid synthetic route to quinazoline-2,4-dione derivatives with a variety of substituents at the 3-position of the quinazolinedione 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.[13] 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.[14]

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.[7]

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 ^{1}H 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-(1*H*-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 NH_4Cl solution (50 mL) and extracted with ethyl acetate (50 mL × 3). The organic layer was washed with water (40 mL), dried ($MgSO_4$), 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}H NMR (300 MHz, DMSO-d_6) δ 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}C NMR (300 MHz, DMSO-d_6) δ 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 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 K_2CO_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 NH_4Cl solution (50 mL) and extracted with ethyl acetate (50 mL × 3). The organic layer was washed with water (40 mL), dried ($MgSO_4$), 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-(1*H*-Indol-3-yl)ethyl]-1*H*,3*H*-quinazoline-2,4-dione (7): Yield 73%; mp 306-307 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 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}C NMR (300 MHz, DMSO-d_6) δ 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 cm^{-1}.

3-Butyl-1*H*,3*H*-quinazoline-2,4-dione (8): Yield 50%; mp 156-156 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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}C NMR (75 MHz, $CDCl_3$) δ 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 cm^{-1}.

3-Hexyl-1*H*,3*H*-quinazoline-2,4-dione (9): Yield 71%; mp 152-154 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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}C NMR (75MHz, $CDCl_3$) δ 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 cm^{-1}.

3-(4-Phenylbutyl)-1*H*,3*H*-quinazoline-2,4-dione (10): Yield 55%; mp 97-98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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}C NMR (75 MHz, $CDCl_3$) δ 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 cm^{-1}.

3-[2-(Piperidin-1-yl) ethyl]-1*H*,3*H*-quinazoline-2,4-dione (11): Yield 44%; mp 187-189 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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}C NMR (75 MHz, $CDCl_3$) δ 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 cm^{-1}.

3-[2-(Morpholin-4-yl)ethyl]-1*H*,3*H*-quinazoline-2,4-dione (12): Yield 52%; mp 198-203 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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}C NMR (75 MHz, $CDCl_3$) δ 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 cm^{-1}.

3-(Cyclohexylmethyl)-1*H*,3*H*-quinazoline-2,4-dione (13): Yield 53%; mp 209-212 °C; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 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}C NMR (75 MHz, $CDCl_3$) δ 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 cm^{-1}.

3-Benzyl-1*H*,3*H*-quinazoline-2,4-dione (14): Yield 65%; mp 214-236 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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}C NMR (75 MHz, $CDCl_3$) δ 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 cm^{-1}.

3-(4-Methoxybenzyl)-1*H*,3*H*-quinazoline-2,4-dione (15): Yield 58%; mp 210-216 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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}C NMR (75 MHz, $CDCl_3$) δ 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 cm^{-1}.

3-Phenethyl-1*H*,3*H*-quinazoline-2,4-dione (17): Yield 78%; mp 174-175 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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}C NMR (75 MHz, $CDCl_3$) δ 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 cm^{-1}.

3-(4-Methoxyphenethyl)-1*H*,3*H*-quinazoline-2,4-dione (18): Yield 81%; mp 224-228 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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}C NMR (75 MHz, $CDCl_3$) δ 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 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 NH_4Cl solution (50 mL), and extracted with ethyl acetate (50 mL × 3). The combined organic layer were washed with brine (50 mL), dried over $MgSO_4$, 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-phenethy-1*H*,3*H*-quinazoline-2,4-dione (2): Yield 95%; mp 101-102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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}C NMR (75 MHz, $CDCl_3$) δ 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 cm^{-1}.

1-Methyl-3-(4-Methoxyphenethyl)-1*H*,3*H*-quinazoline-2,4-dione (3): Yield 83%; mp 135-136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 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}C NMR (75 MHz, $CDCl_3$) δ 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 cm^{-1}.

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