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Molecular Iodine: A Versatile Catalyst for the Synthesis of 4-Aryl-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,10-diones in Water

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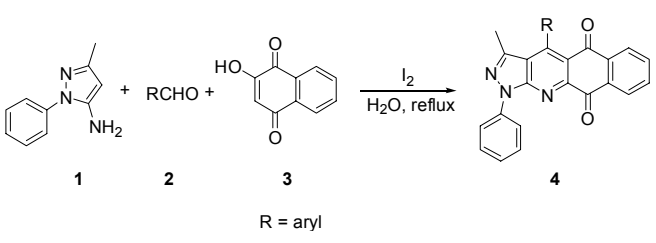
Multicomponent reactions (MCRs) have attracted considerable attention since they are performed without need to isolate any intermediate during their processes; may reduce time and save both energy and raw materials.[1] They have merits over two-component reactions in several aspects including the simplicity of a one-pot procedure, possible structural variations and building up complex molecules.

Pyrazolo[3,4-*b*]quinoline derivatives are used as pharmaceutical agents,[2] as inhibitors of oncogenic Ras,[3] and as a dopant in the multiplayer OLED fabrication.[4] In the past several decades, three general strategies for the synthesis of pyrazolo [3,4-*b*]quinolines have been developed: 1) by the Friedlander condensation reaction of 2-aminobenzophenones and pyrazolin-5-ones.[5] Availability of 2-aminobenzophenones limits the range of applicability of this reaction; 2) by cyclization of 4-arylidenepyrazolin-5-ones with anilines[6] or 5-*N*-arylpyrazoles with aromatic aldehydes.[7] The method is complicated and has a lower yield; 3) by a three-component one-pot reaction of aromatic aldehydes, 5-amino-3-methyl-1-phenylpyrazole and dimedone under thermal[8] or microwave condition.[9]

Organic reactions in water have become an important research area. Many reactions have been accomplished in aqueous medium.[10] Water has therefore become an attractive medium for many organic reactions, not only for the advantages concerning the avoidance of expensive, catalysts and solvents, but also for some unique reactivity and selectivity. In recent years, the use of molecular iodine in organic synthesis has received considerable attention due to powerful catalytic activity for various organic transformations.[11] We now report a highly efficient procedure for the preparation of 4-aryl-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,10-diones using I_2 as an efficient catalyst in water (Scheme 1).

Initial study was performed by the one-pot reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (1 mmol), benzaldehyde (1 mmol) and 2-hydroxynaphthalene-1,4-dione (1 mmol) in water in the presence of 10 mol % I_2 at reflux temperature. To our delight, we observed the formation of 4-phenyl-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,10-dione. Complete conversion and 92% isolated yield was obtained after 5 hours.



Scheme 1

To optimize the amount of catalyst and the reaction temperature, the reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (1 mmol), benzaldehyde (1 mmol) and 2-hydroxynaphthalene-1,4-dione (1 mmol) in water was selected as a model. The best result was obtained by carrying out the reaction using 10 mol % I_2 at reflux temperature.

Based on the optimized reaction conditions, a range of 4-aryl-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,10-diones (**4**) was synthesized by the reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (**1**, 1 mmol) with arylaldehydes (**2**, 1 mmol) and 2-hydroxynaphthalene-1,4-dione (**3**, 1 mmol) in H_2O. The reaction proceeded at reflux temperature within 7 h in excellent yields after the addition of the cataylst I_2 (10 mol %) (Table 2). In addition, we noticed also that when this reaction was carried out with aliphatic aldehyde such as butanal or pentanal, TLC and ^{1}H NMR spectra of the reaction mixture showed a combination of starting materials and numerous products, the yield of the expected product was very poor.

Table 1. Optimization of catalyst loading and reaction temperature of one-pot synthesis of 4-phenyl-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,10-dione[a]

Entry	I_2 (mol %)	Time (h)	Temp. (°C)	Yield (%)[b]
1	0	10	reflux	26
2	5	8	80	62
3	5	8	90	67
4	5	8	reflux	72
5	10	10	r.t.	56
6	10	5	50	62
7	10	5	80	75
8	10	5	90	86
9	10	5	reflux	92
10	15	5	90	86
11	15	5	reflux	90
12	20	5	reflux	91

[a]Reaction conditions: 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (1 mmol); benzaldehyde (1 mmol); 2-hydroxynaphthalene-1,4-dione (1 mmol); H_2O (10 mL). [b]Isolated yield.

In general, iodine is reaction with water to afford strong acid. Therefore the following reaction mechanism is suggested. First, the condensation of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine **1** and 2-hydroxynaphthalene-1,4-dione **3** gave the intermediate product **5**. The addition of **5** to aldehyde **2** then furnished the intermediate product **6**, which on intermolecular cyclization and dehydration gave rise to **7**. In the last step, the intermediate-product **7** aromatized by air-oxidation to product **4**.

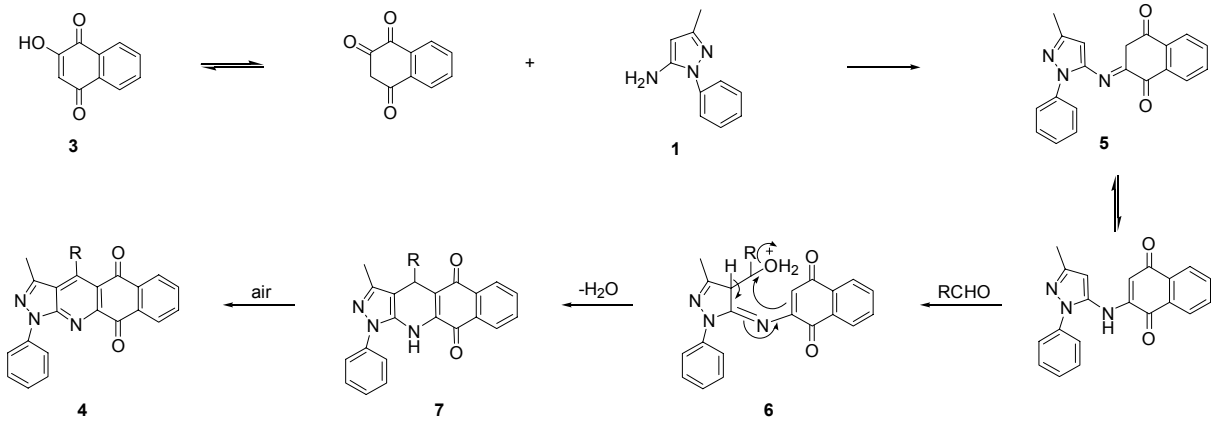
Table 2. Synthesis of 4-aryl-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,10-diones[a]

Entry	R	Time (h)	Product	Yield (%)[b]
1	C_6H_5	5	**4a**	92
2	4-Cl-C_6H_4	6	**4b**	93
3	4-MeO-C_6H_4	5	**4c**	90
4	4-Me-C_6H_4	5	**4d**	88
5	4-NO_2-C_6H_4	6	**4e**	91
6	4-F-C_6H_4	6	**4f**	94
7	3-NO_2-C_6H_4	7	**4g**	87
8	2-Cl-C_6H_4	5	**4h**	85
9	3,4-Cl_2-C_6H_3	7	**4i**	89

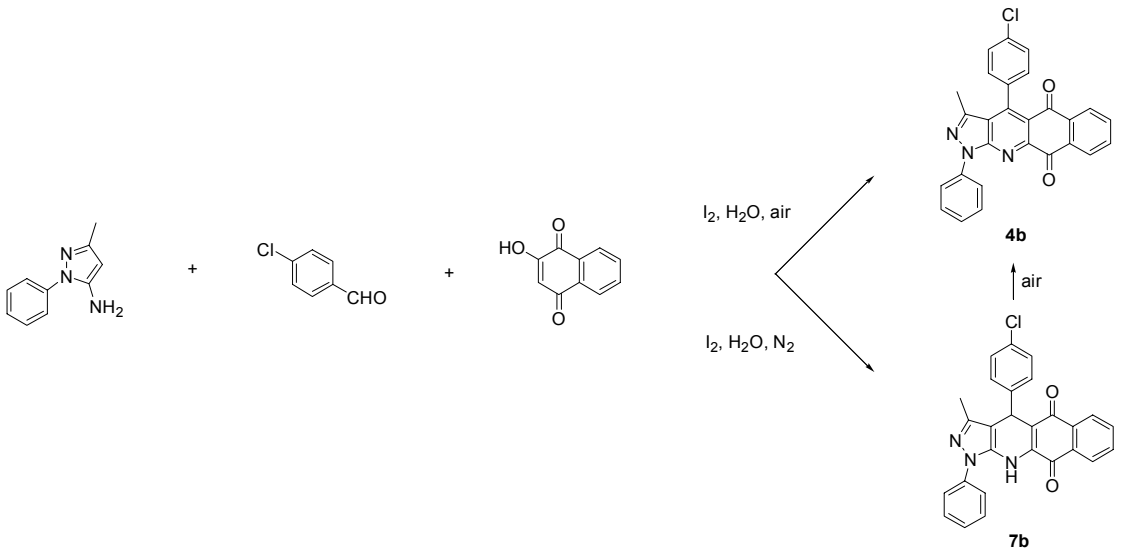
[a]Reaction conditions: 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (1 mmol); arylaldehyde (1 mmol); 2-hydroxynaphthalene-1,4-dione (1 mmol); I_2 (10 mol %); H_2O (10 mL); reflux. [b]Isolated yield.

In order to determine air-oxidation proceeded in the reaction**,** multicomponent condensation reaction of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, 4-chorobenzaldehyde and 2-hydroxynaphthalene-1,4-dione in the presence of molecular iodine was selected as a model. Compound **7b** was a principal product in nitrogen atmosphere. The compound **7b** was easily oxidized by air bubbling, forming the fully aromatic product **4b** (Scheme 3).

In summary, an efficient methodology for the synthesis of 4-aryl-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,10-diones has been developed. To our best knowledge, this is the first report for the synthesis of these compounds by multicomponent condensation of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine, aldehydes and 2-hydroxynaphthalene-1,4-dione in the presence of molecular iodine as a catalyst in water. The simple experimental procedure, utilization of an inexpensive and readily available catalyst, and excellent yields are the advantages of the present method.



Scheme 2



Scheme 3

Experimental Section

4-Aryl-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,10-diones (4a-4i). A mixture of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (1 mmol), aldehyde (1 mmol), 2-hydroxynaphthalene-1,4-dione (1 mmol) and I_2 (0.1 mmol) in H_2O (10 mL) was heated at reflux temperature for the appropriate time. The reaction was monitored by TLC. After completion, the mixture was treated with aqueous $Na_2S_2O_3$ solution, extracted with CH_2Cl_2 (2 × 10 mL). The extract was dried over sodium sulfate, filtered and solvent was evaporated in vacuo. Products **4** were purified by recrystallizing from ethanol.

4-Phenyl-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,10-dione (4a): Yellow crystals, mp 266 ~ 267 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.82 (d, 1H, *J* = 8.0 Hz), 8.31 (d, 2H, *J* = 7.6 Hz), 8.16 (d, 1H, *J* = 7.6 Hz), 7.88-7.84 (m, 1H), 7.64-7.52 (m, 6H), 7.43-7.39 (m, 1H), 7.32-7.30 (m, 2H), 1.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.5, 179.9, 153.7, 152.2, 150.5, 146.5, 138.6, 137.3, 136.0, 135.9, 131.7, 131.3, 129.2, 129.1, 128.4, 127.2, 127.0, 126.5, 121.3, 119.8, 117.0, 14.3; Anal. calcd for $C_{27}H_{17}N_3O_2$: C 78.06, H 4.12, N 10.11; found: C 78.19, H 4.06, N10.08.

4-(*p*-Chloro-phenyl)-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,10-dione (4b): Yellow crystals, mp 243 ~ 245 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.80 (d, 1H, *J* = 8.0 Hz), 8.30 (d, 2H, *J* = 8.0 Hz), 8.15 (d, 1H, *J* = 7.6 Hz), 7.87-7.83 (m, 1H), 7.64-7.51 (m, 5H), 7.43-7.40 (m, 1H), 7.28-7.24 (m, 2H), 2.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.3, 179.9, 153.8, 150.8, 150.5, 146.2, 138.5, 137.1, 136.0, 134.6, 134.3, 131.6, 131.4, 129.3, 129.2, 129.1, 128.7, 128.5, 127.2, 126.7, 121.4, 121.0, 119.7, 116.8, 14.5; Anal. calcd for $C_{27}H_{16}ClN_3O_2$: C 72.08, H 3.58, N 9.34; found: C 72.35, H 3.39, N 9.50.

4-(*p*-Methoxyl-phenyl)-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,10-dione (4c): Yellow crystals, mp 274 ~ 275 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.82 (d, 1H, *J* = 8.0 Hz), 8.32 (d, 2H, *J* = 8.0 Hz), 8.16 (d, 1H, *J* = 8 Hz), 7.88-7.84 (m, 1H), 7.64-7.60 (m, 3H), 7.43-7.39 (m, 1H), 7.23 (d, 2H, *J* = 8.4 Hz), 7.06 (d, 2H, *J* = 8.4 Hz), 3.93 (s, 3H), 2.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.8, 180.3, 159.8, 153.8, 152.4, 150.5, 146.6, 138.6, 137.4, 136.0, 131.6, 131.3, 129.2, 129.0, 128.6, 127.7, 127.2, 126.5, 121.4, 120.2, 117.3, 113.9, 55.3, 14.6; Anal. calcd for $C_{28}H_{19}N_3O_3$: C 75.49, H 4.30, N 9.43; found: C 75.41, H 4.33, N 9.51.

4-(*p*-Methyl-phenyl)-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,10-dione (4d): Yellow crystals, mp 276 ~ 277 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.82 (d, 1H, *J* = 8.0 Hz), 8.31 (d, 2H, *J* = 8.0 Hz), 8.15 (d, 1H, *J* = 7.6 Hz), 7.85 (t, 1H, *J* = 7.8 Hz), 7.63-7.60 (m, 3H), 7.41 (t, 1H, *J* = 7.2 Hz), 7.33 (d, 2H, *J* = 7.6 Hz), 7.18 (d, 2H, *J* = 7.6 Hz), 2.49 (s, 3H), 1.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.7, 180.1, 153.7, 152.6, 150.5, 146.7, 138.6, 138.2, 137.4, 135.9, 132.8, 131.6, 131.3, 129.2, 129.1, 129.0, 127.2, 126.9, 126.5, 121.4, 120.0, 117.1, 21.5, 14.4; Anal. calcd for $C_{28}H_{19}N_3O_2$: C 78.31, H 4.46, N 9.78; found: C 78.50, H 4.42, N 9.82.

4-(*p*-Nitro-phenyl)-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,10-dione (4e): Yellow crystals, mp 326 ~ 328 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.82 (d, 1H, *J* = 8.0 Hz), 8.42 (d, 2H, *J* = 8.4 Hz), 8.30 (d, 2H, *J* = 8.0 Hz), 8.18 (d, 1H, *J* = 7.6 Hz), 7.88 (t, 1H, *J* = 7.8 Hz), 7.67-7.62 (m, 3H), 7.51 (d, 2H, *J* = 8.8 Hz), 7.44 (t, 1H, *J* = 7.4 Hz), 1.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.8, 179.6, 153.9, 150.5, 149.2, 147.9, 145.7, 143.1, 138.4, 136.9, 136.2, 131.7, 131.6, 129.4, 129.3, 128.2, 127.3, 126.9, 123.8, 121.5, 119.2, 116.1, 14.5; Anal. calcd for $C_{27}H_{16}N_4O_4$: C 70.43, H 3.50, N 12.17; found: C 70.48, H 3.38, N 12.25.

4-(*p*-Fluoro-phenyl)-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,10-dione (4f): Yellow crystals, mp 282 ~ 283 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.77 (d, 1H, *J* = 8.0 Hz), 8.30 (d, 2H, *J* = 7.6 Hz), 8.05 (d, 1H, *J* = 7.2 Hz), 7.98-7.94 (m, 1H), 7.74-7.66 (m, 3H), 7.44-7.36 (m, 5H), 1.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.5, 180.0, 164.1, 161.6, 153.8, 151.1, 150.2, 146.3, 138.6, 137.2, 136.0, 131.7, 131.6, 131.4, 129.3, 129.2, 129.1, 129.0, 128.9, 127.2, 126.7, 121.4, 119.9, 117.0, 115.7, 115.5, 14.4; Anal. calcd for $C_{27}H_{16}FN_3O_2$: C 74.82, H 3.72, N 9.69; found: C 75.02, H 3.68, N 9.76.

4-(*m*-Nitro-phenyl)-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,10-dione (4g): Yellow crystals, mp 288 ~ 289 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.83 (d, 1H, *J* = 8.0 Hz), 8.41 (d, 1H, *J* = 8.4 Hz), 8.30 (d, 2H, *J* = 8.0 Hz), 8.24 (s, 1H), 8.18 (d, 1H, *J* = 7.6 Hz), 7.89 (t, 1H, *J* = 7.2 Hz), 7.75 (t, 1H, *J* = 7.8 Hz), 7.69-7.61 (m, 4H), 7.44 (t, 1H, *J* = 14.8 Hz), 1.97 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.9, 179.7, 153.9, 150.6, 148.7, 148.2, 145.6, 138.4, 137.7, 136.9, 136.2, 133.3, 131.7, 131.6, 129.6, 129.3, 129.2, 127.3, 126.9, 123.4, 122.4, 121.5, 119.4, 116.5, 14.6; Anal. calcd for $C_{27}H_{16}N_4O_4$: C 70.43, H 3.50, N 12.17; found: C 70.54, H 3.32, N 12.21.

4-(*o*-Chloro-phenyl)-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,10-dione (4h): Yellow crystals, mp 229 ~ 230 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.84 (d, 1H, *J* = 8.0 Hz), 8.33 (d, 2H, *J* = 8.0 Hz), 8.19 (d, 1H, *J* = 7.6 Hz), 7.89-7.85 (m, 1H), 7.65-7.40 (m, 7H), 7.25-7.23 (m, 1H), 2.00 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.9, 179.3, 153.8, 150.8, 148.5, 146.2, 138.6, 137.2, 136.0, 135.1, 131.7, 131.6, 131.4, 129.9, 129.5, 129.3, 129.2, 128.3, 127.2, 127.0, 126.6, 121.4, 119.6, 116.5, 13.6; Anal. calcd for $C_{27}H_{16}ClN_3O_2$: C 72.08, H 3.58, N 9.34; found: C 72.19, H 3.70, N 9.28.

4-(3,4-Dichloro-phenyl)-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,10-dione (4i): Yellow crystals, mp 269 ~ 270 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.78 (d, 1H, *J* = 8.0 Hz), 8.28 (d, 2H, *J* = 8.0 Hz), 8.15 (d, 1H, *J* = 7.6 Hz), 7.87-7.83 (m, 1H), 7.63-7.59 (m, 4H), 7.43-7.40 (m, 2H), 7.16 (d, 1H, *J* = 8.0 Hz), 2.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.9, 179.5, 153.7, 150.4, 148.9, 145.9, 138.4, 136.9, 136.1, 135.7, 132.8, 131.5, 130.5, 129.2, 129.0, 127.2, 126.8, 126.6, 121.3, 119.4, 116.5, 14.7; Anal. calcd for $C_{27}H_{15}Cl_2N_3O_2$: C 66.96, H 3.12, N 8.68; found: C 67.03, H 3.20, N 8.58.

1,4-Dihydrogen-4-(*p*-chloro-phenyl)-3-methyl-1-phenyl-1*H*-benzo[*h*]pyrazolo[3,4-*b*]quinoline-5,10-dione (7b). In nitrogen atmosphere, a mixture of 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (1 mmol), 4-chorobenzaldehyde (140 mg, 1 mmol), 2-hydroxynaphthalene-1,4-dione (1 mmol) and I_2 (0.1 mmol) in H_2O (10 mL) was stirred at room temperature for 5 h. The reaction was monitored by TLC. After completion, the mixture was treated with aqueous $Na_2S_2O_3$ solution, extracted with CH_2Cl_2 (2 × 10 mL). The extract was dried over sodium sulfate, filtered and solvent was evaporated in vacuo. The residue was

purified by silica gel column chromatography using $CHCl_3$ as eluent to give **7b** as a brownish red solid (360 mg, 80%); mp 252 ~ 253 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.12 (t, 2H, J = 9.4 Hz), 7.80-7.32 (m, 10H), 7.06 (t, 2H, J = 8.4 Hz), 5.45 (s, 1H), 2.03 (s, 3H); Anal. calcd for $C_{27}H_{18}ClN_3O_2$: C 71.76, H 4.01, N 9.30; found: C 71.84, H 3.96, N 9.35.

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