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Synthesis of diverse isatins *via* ring contraction of 3-diazoquinoline-2,4-diones†

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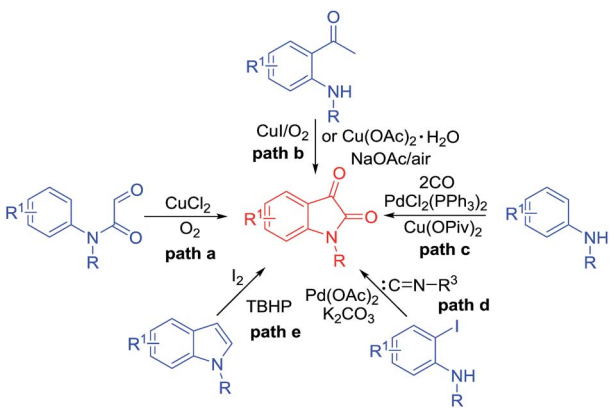
An efficient synthesis of diverse isatin derivatives was accomplished by a copper-mediated reaction of 3-diazoquinoline-2,4-diones *via* ring contraction through domino Wolff rearrangement, decarboxylation, bromination, substitution, and dehydration. This protocol has several advantages as a one-pot procedure, with functional group tolerance, and high yield.

Introduction

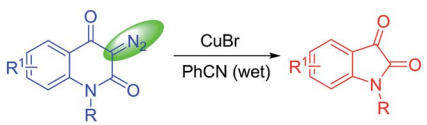
Isatin is a well-known and important compound found in many natural products and bioactive materials.[1] Molecules bearing an isatin moiety possess a broad range of biological properties, such as anticancer,[2] antimalarial,[3] anticonvulsant,[4] antitubercular,[5] anti-inflammatory,[6] antifungal,[7] antiviral,[8] and anti-HIV activities.[9] In addition, they are widely used as building blocks for the synthesis of bioactive natural products[10] and valuable molecules, such as donaxaridine,[11] trikentramides A–D,[12] and ammosamides.[13]

Owing to their potent biological and pharmacological properties, many methods have been reported for the construction of isatins. Among these, Sandmeyer,[14] Gassman,[15] Martinet,[16] and Stollé[17] reported the classical methods for the preparation of isatins. These methods suffer from harsh conditions, expensive reagents, multi-step reactions, and limitation of substrates. To overcome these shortcomings, several effective approaches for the synthesis of isatin derivatives (Scheme 1) have recently been reported, which include the copper-catalyzed intramolecular C–H oxidation/acylation of formyl-*N*-arylformamides (path a),[18] copper-catalyzed or -mediated intramolecular C–H oxidation of 2-aminoacetophenones (path b),[19] palladium-catalyzed double carbonylation of C–H bonds (path c),[20] palladium-catalyzed double hydrolysis to *N*-benzyl-2-iodoanilines (path d),[21] and I_2/TBHP mediated oxidation of indoles (path e).[22] These developed strategies for the construction of isatins have been accomplished by intra- or intermolecular cyclization through the formation of a C–C bond at the *o*-position of aniline with suitable substrates and C–N bond formation of aniline with *o*-substituted functional groups. On the other hand, there is still strong demand for a more convenient synthetic protocol for biologically interesting isatin derivatives. To the best of the authors' knowledge, synthetic approaches to isatins through the ring contraction of 3-diazoquinoline-2,4-diones have not been demonstrated so far.

We have developed simple and facile synthetic methodologies for the preparation of heterocycles and valuable molecules by decompositon of diazo compounds.[23] In particular, Rh(II)-catalyzed reaction of diazo compounds for the synthesis of oxindoles was described.[24] As a part of an ongoing study of diazo compounds, this study examines the copper-mediated reactions of 3-diazoquinoline-2,4-diones to afford diverse isatin derivatives. This paper describes a one-pot protocol for biologically interesting isatin derivatives by copper-mediated reactions of 3-diazoquinoline-2,4-diones in wet benzonitrile (Scheme 2).



Scheme 1 Recently reported approaches for the construction of isatins.



Scheme 2 Copper-mediated reactions of 3-diazoquinoline-2,4-diones for the synthesis isatins.

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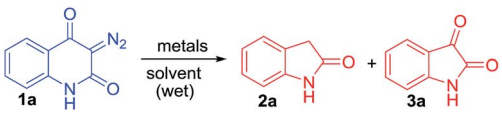
Results and discussion

This study was initiated by the preparation of diazo compounds **1a–1x** by the reported diazo transfer method using mesyl azide with the respective hydroxyl quinolinone,[25] which were obtained from aniline and Meldrum's acid.[26] Subsequently, the reaction of 3-diazoquinoline-2,4-dione (**1a**) for the synthesis of isatin (**3a**) was performed using several catalysts and solvents (Table 1). When **1a** was refluxed in chlorobenzene in the presence of 1 mol% of $Rh_2(OPiv)_4$ for 5 h, oxindole (**2a**) was produced in 78% yield without the formation of isatin (**3a**) (entry 1). With CuO (20 mol%) and $Cu(OAc)_2$ (20 mol%), product **2** was isolated in 15 and 13% yields, respectively whereas product **3** was obtained in trace amount (entry 2 and 3). Interestingly, product **3a** was produced in 19% yield using 20 mol% of $CuCl_2$ in refluxing benzonitrile for 6 h (entry 4). Increasing the amount of $CuCl_2$ to 1 or 2 equiv. increased the yield of **3a** to 33% and 61%, respectively (entry 5 and 6). Upon loading 1 or 2 equiv. of various metal salts, such as $CuBr_2$, CuCl and CuBr, the best yield (84%) was obtained in the presence of 2 equiv. of CuBr in refluxing benzonitrile for 3 h (entries 7–12). In other polar or nonpolar solvents, such as propionitrile, chlorobenzene, and toluene, **3a** was produced in 79, 40, and 46% yields, respectively (entries 13–15). The identity of **3a** was confirmed by an analysis of its spectroscopic data and a comparison with the reported compound.[22] The ^{1}H NMR of **3a** showed NH peak at δ = 11.02 ppm as a singlet and four aromatic protons at δ = 7.75, 7.18, 7.05, and 6.90 ppm.

Under the optimized reaction conditions, the generality of this reaction was explored further using various 3-diazoquinoline-2,4-diones (**1b–1i**) bearing substituents on the benzene ring (Table 2). Reactions of diazo compounds **1b–1e** bearing electron-donating groups such as 6-methyl, 8-methyl, 6-isopropyl, or 6-methoxy on the benzene ring for 4–5 h provided the desired products **3b–3e** in 80–86% yields, whereas those of **1f–1i** bearing the electron-withdrawing groups, 5-chloro, 6-chloro, 7-chloro or 6-bromo, for 3–4 h afforded products **3f–3i** (84–88%) in a slightly increased yield.

Further reactions of other *N*-substituted 3-diazoquinoline-2,4-diones **1j–1r** were successful (Table 3). The treatment of 3-diazoquinoline-2,4-diones **1j–1n** bearing a methyl, ethyl, 3-methylbut-2-en-1-yl, but-3-en-1-yl, or cinnamyl group on the nitrogen atom for 3–5 h produced the desired products **3j–3n** in 81–91% yields. A reaction of 3-diazoquinoline-2,4-dione **1o** bearing a benzyl group on the nitrogen atom afforded product **3o** in 87% yield. Similarly, the diazo compounds **1p–1r** bearing an electron-donating or withdrawing group, such as 3-

Table 1 Optimization of the reaction conditions for the synthesis of **3a**



Entry	Catalysts	Solvent	Conditions	Yield[a] (%) 2a	3a
1	$Rh_2(OPiv)_4$ (0.01 eq.)	PhCl	Reflux, 5 h	78	0
2	CuO (0.2 eq.)	PhCl	Reflux, 8 h	15	Trace
3	$Cu(OAc)_2$ (0.2 eq.)	PhCl	Reflux, 8 h	13	Trace
4	$CuCl_2$ (0.2 eq.)	PhCN	Reflux, 6 h	0	19
5	$CuCl_2$ (1 eq.)	PhCN	Reflux, 4 h	0	33
6	$CuCl_2$ (2 eq.)	PhCN	Reflux, 4 h	0	61
7	$CuBr_2$ (1 eq.)	PhCN	Reflux, 4 h	0	26
8	$CuBr_2$ (2 eq.)	PhCN	Reflux, 3 h	0	53
9	CuCl (1 eq.)	PhCN	Reflux, 3 h	0	58
10	CuCl (2 eq.)	PhCN	Reflux, 3 h	0	64
11	CuBr (1 eq.)	PhCN	Reflux, 4 h	0	74
12	**CuBr (2 eq.)**	**PhCN**	**Reflux, 3 h**	**0**	**84**
13	CuBr (2 eq.)	CH_3CH_2CN	Reflux, 3 h	0	79
14	CuBr (2 eq.)	PhCl	Reflux, 6 h	0	40
15	CuBr (2 eq.)	Toluene	Reflux, 6 h	0	46

[a] Isolated yield after column chromatography.

Table 2 Additional reactions for the synthesis of various isatins **3b–3i** bearing substituents on the benzene ring

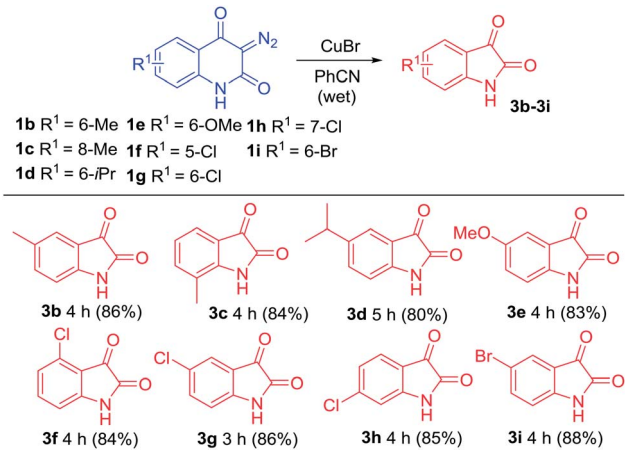


Table 3 Additional reactions for the synthesis of various isatins **3j–3r** bearing substituents on the nitrogen atom

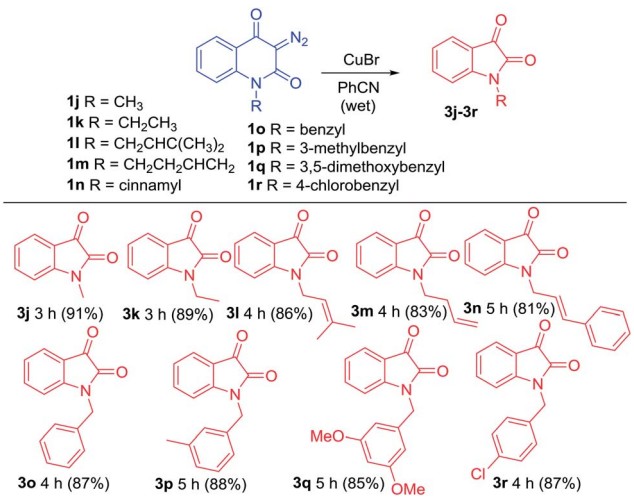
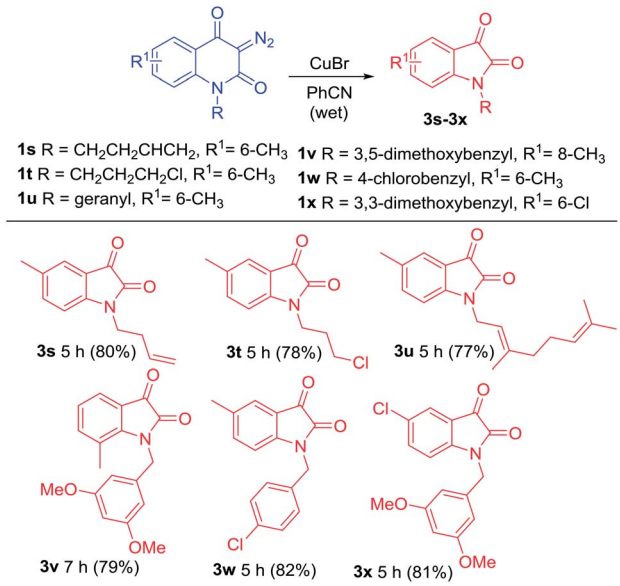


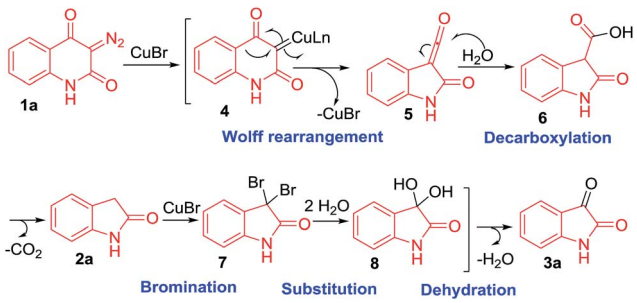
Table 4 Additional reactions for the synthesis of various isatins **3s–3x** bearing substituents on the benzene ring and nitrogen atom



methylbenzyl, 3,5-dimethoxybenzyl, or 4-chlorobenzyl provided the desired products **3p–3r** in 88, 85, or 87% yields respectively.

To further demonstrate the versatility of this protocol, reactions with diazo compounds **1s–1x** bearing substituents on the benzene ring and nitrogen atom were next examined (Table 4). The reactions of **1s–1u** bearing a methyl group on the benzene ring and but-3-en-1-yl, 3-chloropropyl, or geranyl group on the nitrogen atom provided the expected products **3s–3u** in 80, 78, and 77% yields, respectively. With **1v** and **1w** bearing an electron donating methyl group on the benzene and a 3,5-dimethoxy or 4-chlorobenzyl group on the nitrogen atom produced **3v** and **3w** in 79 and 82% yields, respectively. With **1x** bearing an electron-withdrawing chloro group, the desired product **3x** was produced in 81% yield. These reactions provided a rapid synthetic route for the synthesis of diverse and various isatin derivatives.

The formation of **3a** can be explained by the reaction mechanism shown in Scheme 3. In the presence of CuBr, diazo compound **1a** first forms metal carbenoid **4** by the loss of nitrogen. The intermediate **4** would undergo Wolff rearrangement to give ketene **5**, which leads to **2a** *via* the nucleophilic attack of water followed by decarboxylation.[24] The α,α-dibromination of **2a** in the presence of CuBr gives the intermediate **7**, which is reacted with water to furnish **8**. Dehydration of **8** gives final product **3a**.[27]



Scheme 3 Proposed mechanism for the formation of **3a** from **1a**.

Conclusions

An efficient and simple method was developed for the construction of isatin derivatives by ring contraction through domino reaction from readily available 3-diazoquinoline-2,4-diones in high yield. This protocol allows the preparation of diverse and functionalized isatin derivatives, which could be used widely for the synthesis of bioactive natural products and pharmaceuticals. This reaction has several advantages, such as a one-pot procedure, tolerance of various functional groups, and high yield.

Experimental

General information

All experiments were conducted in a nitrogen atmosphere. Merck silica gel plates (Art. 5554) precoated with a fluorescent indicator were used for analytical TLC. Flash column chromatography was performed using silica gel 9385 (Merck). The melting points were determined using micro-cover glasses on a Fisher-Johns apparatus and were uncorrected. The ^{1}H NMR spectra were recorded on a Varian-VNS (300 MHz), DPX (300 MHz) and VNS (600 MHz) spectrometer in DMSO-d_6 using the solvent chemical shift of 2.50 ppm. The ^{13}C NMR spectra were recorded on a Varian-VNS (75 MHz), DPX (75 MHz) and VNS (150 MHz) spectrometer in the DMSO-d_6 using the solvent chemical shift, 39.5 ppm. The Fourier transform infrared (FT-IR) spectra were recorded on PerkinElmer FT-IR spectrometer Spectrum Two™. The high resolution mass (HRMS) were obtained with a JEOL JMS-700 spectrometer at the Korea Basic Science Institute.

General procedure for the synthesis of isatin derivatives (3a–3x)

To a mixture of 3-diazoquinoline-2,4-diones **1a–1x** (0.5 mmol), benzonitrile (3 mL) and water (0.2 mL), CuBr (143 mg, 1.0 mmol) was added and the reaction mixture was vigorously stirred at 140 °C for 3–7 h under N_2 atmosphere. The completion of the reaction was indicated by TLC analysis. The volatiles were removed *in vacuo* and the residue was purified by silica gel column chromatography using hexane/EtOAc (5 : 1) as the eluent to afford the desired products **3a–3x**.

Characterization data of synthesized compounds

Indoline-2,3-dione (3a). Yield 84%; red solid; mp 197–199 °C. IR (ATR): 3470, 3369, 3176, 3102, 1728, 1675, 1614, 1463, 1362, 1326, 1253, 1010, 763, 677, 454, 405 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6): δ 11.02 (1H, s), 7.75 (1H, td, J = 7.2, 1.2 Hz), 7.48 (1H, d, J = 7.8 Hz), 7.05 (1H, t, J = 7.8 Hz), 6.90 (1H, d, J = 8.4 Hz). ^{13}C NMR (150 MHz, DMSO-d_6): δ 184.4, 159.4, 150.7, 138.5, 124.6,

122.8, 117.8, 112.2. HRMS m/z (M^+): calcd for $C_8H_5NO_2$: 147.0320; found: 147.0322.

5-Methylindoline-2,3-dione (3b). Yield 86%; red solid; mp 179–181 °C. IR (ATR): 3183, 2922, 2854, 1732, 1613, 1461, 1379, 1286, 1191, 1122, 1036, 966, 818, 732, 658, 547, 452, 405 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 10.93 (1H, s), 7.38 (1H, d, J = 8.1 Hz), 7.30 (1H, s), 6.79 (1H, d, J = 8.1 Hz), 2.24 (3H, s). ^{13}C NMR (150 MHz, DMSO-d_6): δ 184.6, 159.5, 148.6, 138.8, 132.0, 124.8, 117.8, 112.0, 20.1. HRMS m/z (M^+): calcd for $C_9H_7NO_2$: 161.0477; found: 161.0479.

7-Methylindoline-2,3-dione (3c). Yield 84%; yellow solid; mp 158–160 °C. IR (ATR): 3458, 3160, 3102, 1730, 1592, 1457, 1381, 1319, 1250, 1155, 1034, 928, 790, 737, 686, 547, 474, 405 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 10.99 (1H, s), 7.43 (1H, t, J = 7.8 Hz), 6.85 (1H, d, J = 7.5 Hz), 6.70 (1H, d, J = 7.8 Hz), 2.42 (3H, s). ^{13}C NMR (150 MHz, DMSO-d_6): δ 185.0, 159.2, 150.8, 139.7, 137.9, 124.8, 115.9, 109.5, 17.4. HRMS m/z (M^+): calcd for $C_9H_7NO_2$: 161.0477; found: 161.0475.

5-Isopropylindoline-2,3-dione (3d). Yield 80%; yellow solid; mp 137–137 °C. IR (ATR): 3304, 2921, 2854, 1739, 1622, 1484, 1381, 1262, 1111, 1024, 830, 726, 657, 594, 498, 473, 427, 404 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ 10.93 (1H, s), 7.48 (1H, dd, J = 8.4, 1.8 Hz), 7.37 (1H, d, J = 1.8 Hz), 6.83 (1H, d, J = 7.8 Hz), 2.88–2.85 (1H, m), 1.17 (6H, d, J = 6.6 Hz); ^{13}C NMR (150 MHz, DMSO-d_6): δ 184.6, 159.5, 148.9, 143.1, 136.5, 122.2, 117.8, 112.1, 32.7, 23.7, 23.6. HRMS m/z (M^+): calcd for $C_{11}H_{11}NO_2$: 189.0790; found: 189.0791.

5-Methoxyindoline-2,3-dione (3e). Yield 83%; red solid; mp 194–196 °C. IR (ATR): 3435, 3094, 2842, 1732, 1484, 1630, 1304, 1237, 1195, 1152, 1031, 977, 901, 821, 732, 695, 597, 454, 405 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ 11.02 (1H, s), 7.17 (1H, dd, J = 7.8, 3.0 Hz), 7.06 (1H, d, J = 2.4 Hz), 6.84 (1H, d, J = 9.0 Hz), 3.74 (3H, s). ^{13}C NMR (150 MHz, DMSO-d_6): δ 184.6, 159.5, 155.3, 144.6, 124.9, 118.1, 113.2, 108.8, 55.8. HRMS m/z (M^+): calcd for $C_9H_7NO_3$: 177.0426; found: 177.0424.

4-Chloroindoline-2,3-dione (3f). Yield 84%; yellow solid; mp 253–255 °C. IR (ATR): 3451, 3181, 2989, 1735, 1606, 1471, 1437, 1312, 1273, 1242, 1195, 1154, 912, 782, 660, 546, 452, 405 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ 11.20 (1H, s), 7.54 (1H, t, J = 8.4 Hz), 7.06 (1H, d, J = 8.4 Hz), 6.84 (1H, t, J = 7.8 Hz). ^{13}C NMR (150 MHz, DMSO-d_6): δ 181.2, 158.6, 152.1, 139.0, 131.0, 123.6, 114.8, 111.0. HRMS m/z (M^+): calcd for $C_8H_4ClNO_2$: 180.9931; found: 180.9928.

5-Chloroindoline-2,3-dione (3g). Yield 86%; orange solid; mp 247–249 °C. IR (ATR): 3066, 2846, 1742, 1697, 1613, 1450, 1307, 1264, 1209, 1165, 1116, 1042, 843, 742, 650, 578, 456, 405 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ 11.13 (1H, s), 7.59 (1H, d, J = 9.0 Hz), 7.52 (1H, s), 6.91 (1H, d, J = 7.8 Hz). ^{13}C NMR (150 MHz, DMSO-d_6): δ 183.3, 159.1, 149.2, 137.3, 126.8, 124.1, 119.1, 113.9. HRMS m/z (M^+): calcd for $C_8H_4ClNO_2$: 180.9931; found: 180.9927.

6-Chloroindoline-2,3-dione (3h). Yield 85%; red solid; mp 255–257 °C. IR (ATR): 3482, 3164, 3063, 1741, 1475, 1442, 1324, 1278, 1245, 1097, 1063, 917, 892, 830, 788, 702, 664, 596, 664, 596, 518, 470 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ 11.15 (1H, s), 7.52 (1H, d, J = 8.4 Hz), 7.11 (1H, dd, J = 7.8, 1.2 Hz), 6.93 (1H, d, J = 1.2). ^{13}C NMR (150 MHz, DMSO-d_6): δ 183.0, 159.4, 151.8, 142.3, 126.2, 122.7, 116.7, 112.2. HRMS m/z (M^+): calcd for $C_8H_4ClNO_2$: 180.9931; found: 180.9930.

5-Bromoindoline-2,3-dione (3i). Yield 88%; yellow solid; mp 246–248 °C. IR (ATR): 3196, 2999, 2824, 1746, 1610, 1468, 1290, 1238, 1166, 1122, 843, 716, 658, 574, 461 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ 11.02 (1H, s), 7.44 (1H, t, J = 7.8 Hz), 7.21 (1H, d, J = 7.8 Hz), 6.88 (1H, d, J = 7.8 Hz). ^{13}C NMR (150 MHz, DMSO-d_6): δ 181.7, 158.6, 152.5, 138.9, 126.7, 119.4, 116.4, 111.3. HRMS m/z (M^+): calcd for $C_8H_4BrNO_2$: 224.9425; found: 224.9424.

1-Methylindoline-2,3-dione (3j). Yield 91%; red solid; mp 125–127 °C. IR (ATR): 3447, 2924, 2857, 1718, 1600, 1464, 1366, 1323, 1256, 1191, 1161, 1112, 1088, 1028, 953, 861, 808, 699, 556, 526, 469 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 7.66 (1H, t, J = 7.8 Hz), 7.52 (1H, d, J = 7.5 Hz), 7.14–7.09 (2H, m), 3.13 (3H, s). ^{13}C NMR (75 MHz, DMSO-d_6): δ 183.5, 158.2, 151.4, 138.2, 124.2, 123.2, 117.4, 110.6, 26.0. HRMS m/z (M^+): calcd for $C_9H_7NO_2$: 161.0477; found: 161.0474.

1-Ethylindoline-2,3-dione (3k). Yield 89%; red solid; mp 87–88 °C. IR (ATR): 3439, 2981, 2873, 1725, 1604, 1461, 1349, 1286, 1195, 1158, 1124, 1090, 1049, 964, 934, 867, 814, 754, 699, 678, 563, 469 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ 7.65 (1H, td, J = 8.4, 1.2 Hz), 7.53 (1H, d, J = 7.8 Hz), 7.18 (1H, d, J = 8.4 Hz), 7.11 (1H, t, J = 7.8 Hz), 3.71–3.68 (2H, m), 1.18 (3H, t, J = 7.2 Hz). ^{13}C NMR (150 MHz, DMSO-d_6): δ 183.6, 157.7, 150.4, 138.2, 124.6, 123.0, 117.5, 110.6, 34.3, 12.3. HRMS m/z (M^+): calcd for $C_{10}H_9NO_2$: 175.0633; found: 175.0635.

1-(3-Methylbut-2-en-1-yl)indoline-2,3-dione (3l). Yield 86%; red solid; mp 85–87 °C. IR (ATR): 3462, 2997, 2915, 1727, 1605, 1463, 1348, 1174, 1092, 1030, 937, 757, 611, 553, 466 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ 7.65 (1H, td, J = 7.8, 1.2 Hz), 7.54 (1H, d, J = 6.6 Hz), 7.12 (1H, t, J = 7.2 Hz), 7.01 (1H, d, J = 7.8 Hz), 5.20–5.17 (1H, m), 4.26 (2H, d, J = 7.2 Hz), 1.78 (3H, s), 1.69 (3H, s). ^{13}C NMR (150 MHz, DMSO-d_6): δ 183.5, 157.6, 150.5, 138.16, 136.8, 124.4, 123.2, 117.8, 117.5, 110.9, 37.5, 25.3, 18.0. HRMS m/z (M^+): calcd for $C_{13}H_{13}NO_2$: 215.0946; found: 215.0948.

1-(But-3-en-1-yl)indoline-2,3-dione (3m). Yield 83%; red solid; mp 72–73 °C. IR (ATR): 3456, 3084, 2933, 2856, 1729, 1598, 1466, 1353, 1292, 1179, 1127, 1089, 1042, 999, 921, 869, 705, 637, 589, 552, 471 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ 7.66 (1H, t, 7.8), 7.53 (1H, d, J = 6.6 Hz), 7.21 (1H, d, J = 7.8 Hz), 7.12 (1H, t, J = 7.2 Hz), 5.85–5.78 (1H, m), 5.06 (1H, dd, J = 16.8, 1.2 Hz), 5.00 (1H, d, J = 9.6 Hz), 3.73 (2H, t, J = 6.6 Hz), 2.38 (2H, dd, J = 13.8, 6.6 Hz). ^{13}C NMR (150 MHz, DMSO-d_6): δ 183.6, 158.1, 150.7, 138.4, 135.1, 124.6, 123.3, 117.4, 117.3, 111.0, 39.0, 31.2. HRMS m/z (M^+): calcd for $C_{12}H_{11}NO_2$: 201.0790; found: 201.0787.

1-Cinnamylindoline-2,3-dione (3n). Yield 81%; red solid; mp 88–90 °C. IR (ATR): 3451, 2920, 2852, 1735, 1603, 1465, 1371, 1319, 1142, 1069, 1039, 964, 896, 783, 745, 694, 540, 517 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ 7.63 (1H, t, J = 7.8 Hz), 7.57 (1H, d, J = 7.8 Hz), 7.41 (2H, d, J = 8.4 Hz), 7.31 (2H, t, J = 8.4 Hz), 7.23 (1H, t, J = 7.8 Hz), 7.15–7.11 (2H, m), 6.74 (1H, d, J = 16.2 Hz), 6.30 (1H, dt, J = 16.2, 6.0 Hz), 4.47 (2H, d, J = 6.0 Hz). ^{13}C NMR (150 MHz, DMSO-d_6): δ 183.3, 158.0, 150.5, 138.0, 136.1, 132.0, 128.6, 127.7, 126.3, 124.5, 122.8, 119.1, 117.7,

111.1, 41.3. HRMS m/z (M^+): calcd for $C_{17}H_{13}NO_2$: 263.0946; found: 263.0948.

1-Benzylindoline-2,3-dione (3o). Yield 87%; red solid; mp 126–127 °C. IR (ATR): 3447, 3032, 2970, 1728, 1605, 1463, 1344, 1300, 1174, 1079, 1001, 816, 754, 690, 624, 551, 504, 465 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ 7.58–7.56 (2H, m), 7.42 (2H, d, J = 7.8 Hz), 7.34 (2H, t, J = 7.2 Hz), 7.27 (1H, t, J = 7.8 Hz), 7.11 (1H, t, J = 7.8 Hz), 6.96 (1H, d, J = 8.4 Hz), 4.90 (2H, s). ^{13}C NMR (150 MHz, DMSO-d_6): δ 183.1, 158.3, 150.3, 137.9, 135.5, 128.7, 127.5, 127.4, 124.5, 123.3, 117.7, 111.1, 43.0. HRMS m/z (M^+): calcd for $C_{15}H_{11}NO_2$: 237.0790; found: 237.0791.

1-(3-Methylbenzyl)indoline-2,3-dione (3p). Yield 88%; red solid; mp 130–132 °C. IR (ATR): 3460, 2920, 2853, 1732, 1606, 1466, 1338, 1148, 1092, 1007, 935, 876, 775, 691, 633, 509, 556, 466, 429 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ 7.56 (2H, t, J = 8.4 Hz), 7.24–7.21 (3H, m), 7.12–7.08 (2H, m), 6.95 (1H, d, J = 7.8 Hz), 4.86 (2H, s), 2.26 (3H, s). ^{13}C NMR (150 MHz, DMSO-d_6): δ 183.1, 158.3, 150.4, 138.0, 137.9, 135.4, 128.5, 128.2, 127.8, 124.5, 124.4, 123.3, 117.7, 111.1, 42.9, 21.0. HRMS m/z (M^+): calcd for $C_{16}H_{13}NO_2$: 251.0946; found: 251.0943.

1-(3,5-Dimethoxybenzyl)indoline-2,3-dione (3q). Yield 85%; red solid; mp 183–185 °C. IR (ATR): 2966, 2834, 1734, 1603, 1463, 1347, 1294, 1199, 1156, 1040, 938, 865, 837, 762, 681, 599, 469, 542, 469 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ 7.58–7.55 (2H, m), 7.11 (1H, t, J = 7.8 Hz), 6.94 (1H, d, J = 7.8 Hz), 6.58 (2H, s), 6.40 (1H, s), 4.81 (2H, s), 3.70 (6H, s). ^{13}C NMR (150 MHz, DMSO-d_6): δ 183.1, 160.7, 158.4, 150.4, 137.9, 137.8, 124.4, 123.3, 117.8, 111.1, 105.4, 99.1, 55.2, 43.0. HRMS m/z (M^+): calcd for $C_{17}H_{15}NO_4$: 297.1001; found: 297.1001.

1-(4-Chlorobenzyl)indoline-2,3-dione (3r). Yield 87%; red solid; mp 167–169 °C. IR (ATR): 3443, 2922, 2853, 1731, 1607, 1464, 1343, 1164, 1088, 1010, 928, 846, 796, 755, 599, 546, 464, 419 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ 7.57 (2H, t, J = 7.2 Hz), 7.46 (2H, d, J = 8.4 Hz), 7.39 (2H, d, J = 7.8 Hz), 7.11 (1H, t, J = 7.8 Hz), 6.95 (1H, d, J = 7.8 Hz), 4.90 (2H, s). ^{13}C NMR (150 MHz, DMSO-d_6): δ 183.1, 158.5, 150.2, 138.1, 134.7, 132.3, 129.4, 128.7, 124.7, 124.5, 123.5, 117.9, 111.1, 111.0, 42.4. HRMS m/z (M^+): calcd for $C_{15}H_{10}ClNO_2$: 271.0400; found: 271.0403.

1-(But-3-en-1-yl)-5-methylindoline-2,3-dione (3s). Yield 80%; red solid; mp 73–75 °C. IR (ATR): 3460, 2964, 2922, 2852, 1733, 1617, 1594, 1452, 1345, 1296, 1122, 997, 822, 660, 588, 472 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ 7.45 (1H, d, J = 7.2 Hz), 7.32 (1H, s), 7.08 (1H, d, J = 7.8 Hz), 5.82–5.77 (1H, m), 5.04 (1H, d, J = 17.4 Hz), 4.9 (1H, d, J = 9.6 Hz), 3.69 (2H, t, J = 7.2 Hz), 2.35 (2H, dd, J = 14.4, 7.2 Hz), 2.25 (3H, s). ^{13}C NMR (150 MHz, DMSO-d_6): δ 183.6, 157.9, 148.4, 138.6, 135.0, 132.5, 124.7, 117.2, 117.1, 110.7, 38.9, 31.2, 19.9. HRMS m/z (M^+): calcd for $C_{13}H_{13}NO_2$: 215.0946; found: 215.0949.

1-(3-Chloropropyl)-5-methylindoline-2,3-dione (3t). Yield 78%; red solid; mp 98–100 °C. IR (ATR): 3466, 2935, 2861, 1728, 1619, 1488, 1451, 1346, 1290, 1201, 1165, 1126, 832, 639, 754, 716, 469 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): 7.46 (1H, d, J = 8.4 Hz), 7.34 (1H, s), 7.07 (1H, d, J = 8.4 Hz), 3.75 (2H, t, J = 7.2 Hz), 3.70 (2H, t, J = 7.2 Hz), 2.27 (3H, s), 2.07–2.02 (2H, m). ^{13}C NMR (150 MHz, DMSO-d_6): δ 183.5, 158.3, 148.3, 138.3, 132.5, 124.7, 117.6, 110.3, 42.7, 37.1, 30.0, 20.0. HRMS m/z (M^+): calcd for $C_{12}H_{12}ClNO_2$: 237.0557; found: 237.0555.

(*E*)-5-Methyl-1-(3,6,7-trimethylocta-2,6-dien-1-yl)indoline-2,3-dione (3u). Yield 77%; red solid; mp 55–57 °C; IR (ATR): 3447, 2964, 2916, 1734, 1621, 1489, 1438, 1374, 1334, 1261, 1172, 1021, 888, 822, 764, 657, 580, 467 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ 7.42 (1H, d, J = 8.1 Hz), 7.31 (1H, s), 6.86 (1H, d, J = 8.1 Hz), 5.14 (1H, t, J = 6.0 Hz), 4.97 (1H, m), 4.22 (2H, d, J = 6.3 Hz), 2.24 (3H, s), 2.02–1.97 (4H, m), 1.76 (3H, s), 1.54 (3H, s), 1.49 (3H, s). ^{13}C NMR (75 MHz, DMSO-d_6): δ 183.7, 157.6, 148.3, 140.1, 138.4, 132.6, 131.0, 124.6, 123.7, 117.8, 117.4, 110.7, 38.7, 37.5, 25.7, 25.4, 20.0, 17.5, 16.2. HRMS m/z (M^+): calcd for $C_{19}H_{23}NO_2$: 297.1729; found: 297.1731.

1-(3,5-Dimethoxybenzyl)-7-methylindoline-2,3-dione (3v). Yield 79%: red solid; mp 138–139 °C. IR (ATR): 3001, 2834, 1781, 1730, 1601, 1463, 1369, 1234, 1152, 1027, 927, 779, 734, 684, 593, 514, 427 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ 7.43 (1H, t, J = 8.4 Hz), 6.91 (1H, d, J = 7.2 Hz), 6.77 (1H, d, J = 7.8 Hz), 6.55 (2H, s), 6.39 (1H, s), 4.79 (2H, s), 3.70 (6H, s), 2.47 (3H, s). ^{13}C NMR (150 MHz, DMSO-d_6) 184.0, 161.2, 158.6, 150.9, 139.8, 138.4, 137.7, 125.9, 116.1, 109.0, 105.8, 99.5, 55.6, 43.4, 17.9. HRMS m/z (M^+): calcd for $C_{18}H_{17}NO_4$: 311.1158; found: 311.1157.

1-(4-Chlorobenzyl)-5-methylindoline-2,3-dione (3w). Yield 82%; red solid; mp 167–169 °C. IR (ATR): 3439, 2921, 2854, 1744, 1721, 1614, 1486, 1334, 1263, 1224, 1176, 1092, 1017, 950, 705, 659, 598, 462, 425 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6): δ 7.44 (2H, t, J = 8.4 Hz), 7.39 (4H, d, J = 8.4 Hz), 6.85 (1H, t, J = 9.0 Hz), 4.88 (2H, s), 2.25 (3H, s). ^{13}C NMR (150 MHz, DMSO-d_6): δ 183.1, 158.4, 148.0, 138.2, 134.6, 132.8, 132.1, 129.3, 128.5, 124.7, 117.7, 110.8, 42.2, 20.0. HRMS m/z (M^+): calcd for $C_{16}H_{12}ClNO_2$: 285.0557; found: 285.0558.

5-Chloro-1-(3,5-dimethoxybenzyl)indoline-2,3-dione (3x). Yield 81%; red solid; mp 172–174 °C. IR (ATR) 3458, 2934, 2842, 1734, 1595, 1465, 1433, 1322, 1259, 1211, 1155, 1055, 1021, 933, 851, 810, 733, 666, 595, 526, 459 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6) δ 7.62–7.61 (2H, m), 6.92 (1H, d, J = 9.6 Hz), 6.59 (2H, s), 6.40 (1H, s), 4.8 (2H, s), 3.70 (6H, s). ^{13}C NMR (150 MHz, DMSO-d_6): δ 182.0, 160.7, 158.2, 148.8, 137.6, 136.7, 127.5, 123.9, 119.3, 112.7, 105.4, 99.1, 55.2, 43.1. HRMS m/z (M^+) calcd for $C_{17}H_{14}ClNO_4$: 331.0611; found: 331.0614.

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