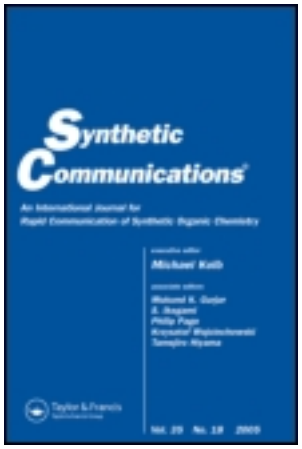

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$AlCl_3$/PCC-SiO_2-PROMOTED OXIDATION OF AZAINDOLES AND INDOLES

Rekulapally Sriram,[1,2] Chebolu Naga Sesha Sai Pavan Kumar,[1] Nerella Raghunandan,[2] Vadla Ramesh,[1] Manda Sarangapani,[2] and Vaidya Jayathirtha Rao[1]

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[2]*University College of Pharmaceutical Sciences, Kakatiya University, Warangal, India*

GRAPHICAL ABSTRACT

Where R = H, Bn, alkyl; R' = H, Cl, NO_2; X = N (2a – 2j); C (2k – 2o)

Abstract *A simple and efficient method is described for the oxidation of 7-azaindoles and indoles to 7-azaisatins and isatins using pyridinium chlorochromate–silica gel (PCC-SiO_2) with the aid of Lewis acid catalyst aluminium chloride ($AlCl_3$) in dichloroethane. Simplicity of the reaction conditions, easy workup procedure, and good yields are the key features of this protocol.*

Keywords Aluminium chloride ($AlCl_3$); azaindoles; azaisatins; indoles; isatins; oxidation; pyridinium chlorochromate (PCC)

INTRODUCTION

Isatins and its derivatives display diverse biological properties, including antimalarial,[1] anticancer,[2] anticonvulsant,[3] anti-inflammatory,[4] antiviral,[5] and antineoplastic[6] activities. In recent years, 7-azaisatins have received considerable interest in view of their potential relationship to pharmacologically important indoles and the purine nucleus and also because of their interesting biological activities. In contrast to isatins, only a few 7-azaisatins are known (viz., 7-azaisatin, 5-bromo-7-azaisatin, and N-alkyl-7-azaisatins).[7] Various 7-azaisatins are synthesized

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for the development of pharmaceuticals such as 7-azaindirubin-3-oxime[8] and 3-arylidene-7-azaoxindoles (Figure 1).[9] The first one showed significant antiproliferative activity against 57 cancer cell lines and also inhibitory activity against a series of kinases,[8] and the other one exhibited TrkA kinase inhibitory activity in pancreatic ductal adenocarcinoma.[9]

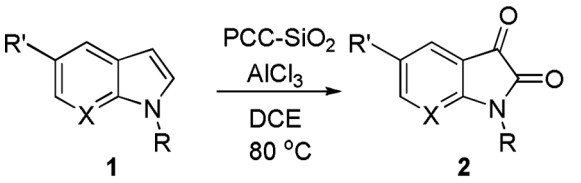
RESULTS AND DISCUSSION

On the basis of the activity of isatin and its derivatives, we envisaged the synthesis of new 7-azaisatins and their derivatives bearing a heterocyclic nitrogen atom at position 7. Kagi first synthesized 7-azaisatin from 7-azaoxindole with nitrous acid and subsequent hydrolysis of the intermediate oxime.[10] Another route for the preparation of 7-azaisatin from 7-azaindole in five steps was reported by Parrick et al.[11] in 1989. Marfat and Carta[12] reported the synthesis of 7-azaoxindoles by the oxidation of indoles with pyridinium bromide perbromide. 5-Bromo-7-azaisatin, an intermediate of 5-bromo-7-azaoxindole derivative, which was the first nonpeptide antagonist of bombesin, was synthesized by oxidation of 7-azaindole with CrO_3 as oxidant in the presence of bromine.[13] Tatsugi et al.[14] reported a one-pot synthesis of 1-alkyl-7-azaisatins via 1-alkyl-7-azaindoles using N-bromosuccinimide (NBS) in dimethylsulfoxide (DMSO) solvent. Yadav et al.[15] used an IBX-$InCl_3$ combination for the oxidation of azaindole to azaisatin, but much importance was given to indoles rather than azaindoles. Unfortunately, many

Table 1. Oxidation of 7-azaindole (0.1 mol) to 7-azaisatin with PCC-SiO_2 using different acid catalysts

S. no.	Catalyst[a]	Time (h)	Isolated yield (%)
1	$AlCl_3$	3	76
2	BF_3	4	45
3	$FeCl_3$	7	30
4	$lnCl_3$	10	20
5	$CeCl_3$	12	Trace

[a]Catalyst 1.3 mol%.



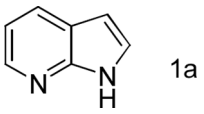
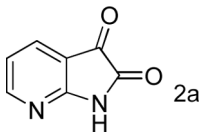
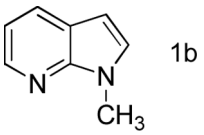
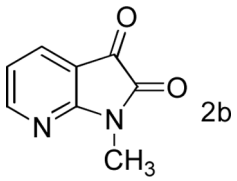
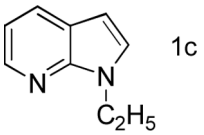
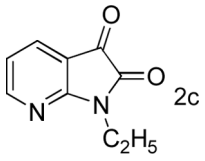
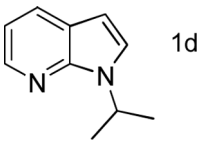
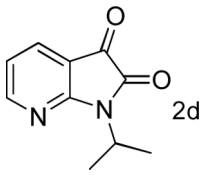
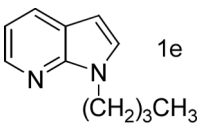
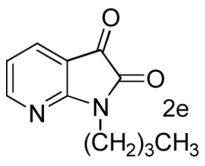
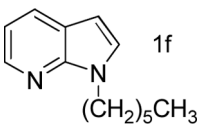
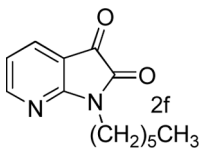
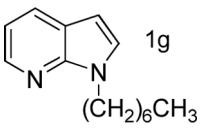
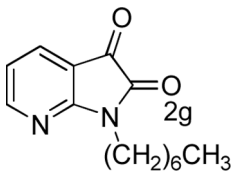
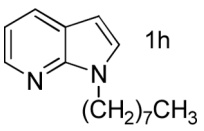
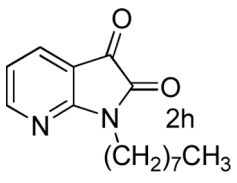
Where R = H, Bn, alkyl

R' = H, Cl, NO_2

X = N (2a – 2j); C (2k – 2o)

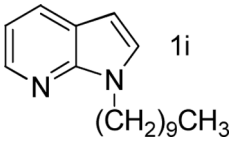
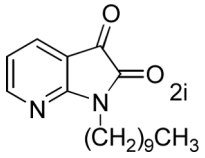
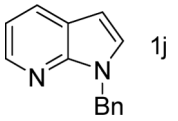
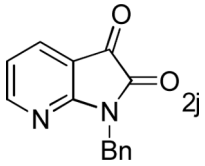
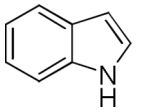
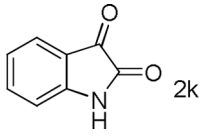
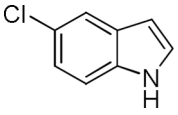
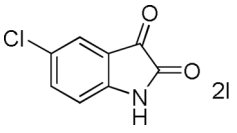
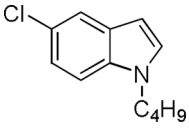
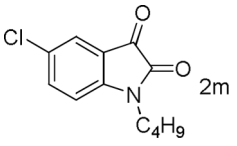
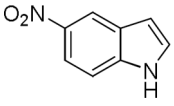
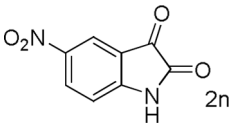
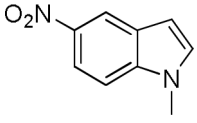
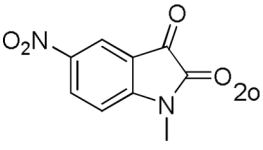
Scheme 1. Oxidation of 7-azaindole to 7-azaisatin with PCC-SiO_2 and $AlCl_3$.

Table 2. Oxidation of 7-azaindoles and indoles using PCC-SiO_2 and $AlCl_3$

S. no.	Substrate	Product	Time (h)	Isolated yield (%)
1	 1a	 2a	3	76
2	 1b	 2b	2.5	80
3	 1c	 2c	2.5	80
4	 1d	 2d	2	81
5	 1e	 2e	2	83
6	 1f	 2f	1.5	83
7	 1g	 2g	1	84
8	 1h	 2h	1	85

(*Continued*)

Table 2. Continued

S. no.	Substrate	Product	Time (h)	Isolated yield (%)
9	 1i	 2i	0.5	87
10	 1j	 2j	1.5	83
11	 1k	 2k	1.5	88
12	 1l	 2l	2	84
13	 1m	 2m	2.5	85
14	 1n	 2n	2.5	85
15	 1o	 2o	2	81

of these methods suffer from limitations such as harsh reaction conditions, poor to moderate yields, long reaction times, tedious workup procedures and co-occurrence of several side products. Zong et al.[16] recently reported all the attempts to prepare 7-azaisatin by the oxidation of commercially available 7-azaindole under a variety of conditions were unsuccessful. All the attempts have taken into consideration, and we developed a convenient method for the efficient oxidation of 7-azaindoles.

Herein, we report for the first time pyridium chlorochromate (PCC)–SiO_2 as oxidizing agent for the oxidation of various 7-azaindoles to 7-azaisatins. To enhance the yield and shorten the reaction times, we have catalyzed the reaction with $AlCl_3$ as

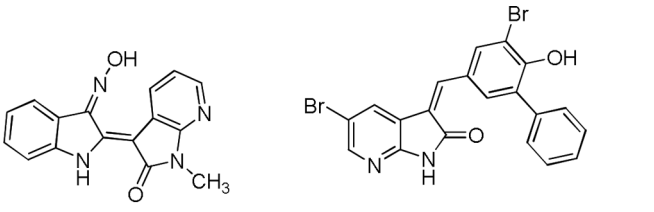


Figure 1. Biologically important azaisatin derivatives.

a Lewis acid catalyst. PCC is milder and less acidic and promotes fewer side reactions that are due to overoxidation. PCC is easier to prepare, shelf stable, and more efficient, but PCC oxidations are characterized by the formation of tarry reduced chromium by-products, which will entrain the desired products and complicate the purification procedure. In PCC-SiO_2-promoted oxidation, the chromium by-products obtained are adsorbed on the silica gel, forming a microgranular solid that can be easily removed by filtration. PCC-SiO_2 is a well-known oxidizing agent for the oxidation of alcohols to aldehydes or ketones with high efficiency.[17]

Recently, our group reported polyaniline catalyst (PANI)/PCC combination for the oxidation of indoles to isatins.[18] Presently we need azaisatins for the preparation and bioevaluation studies of new heterocylces. In continuation of our research work, in this study we have used PCC–silica gel with $AlCl_3$ combination for the synthesis of various 7-azaisatins from 7-azaindoles in an efficient manner. We have effectively utilized this protocol not only for the milligram level but also on a gram-scale level for the preparation of 7-azaisatins, which was difficult in all other procedures. To evaluate the efficiency of the method, oxidation of 7-azaindole was carried out with PCC-SiO_2 using different acid catalysts BF_3, $FeCl_3$, $InCl_3$, $CeCl_3$, and $AlCl_3$ at 80 °C in dichloroethane (DCE). Greater yield and short reaction times were obtained with the use of $AlCl_3$ as the catalyst compared to other catalysts (Table 1).

To determine the versatility of the PCC-SiO_2 and $AlCl_3$ system, 7-azaindole (0.1 mol) and N-alkylated-7-azaindoles[14] (0.1 mol) (prepared from alkylation with different alkyl halides using sodium hydride in THF) were subjected to oxidation by PCC (0.25 mol)–SiO_2 with $AlCl_3$(15 wt%/1.3 mol% with respect to the indole derivative) in dichloroethane (DCE) at 80 °C, and the reactions occurred smoothly without formation of any side products (Scheme 1). We observed that as the alkyl chain increases, the yield of the product increases (Table 2). To study the scope of the method, the reaction was extended to oxidation of simple indoles. Indoles and its derivatives (**1k–1o**) underwent smooth oxidation to their corresponding isatins (**2k–2o**) in excellent yields (Table 2), comparable to the PANI/PCC procedure.

CONCLUSION

In conclusion, we have described an efficient protocol for the preparation of 7-azaisatins by the oxidation of 7-azaindoles using PCC-SiO_2 catalyzed by $AlCl_3$ for the first time. The advantages of the PCC-SiO_2 and $AlCl_3$ system are greater

efficiency, low cost, versatility, gram-level preparative scale, and simple workup procedure. Application of this strategy to the preparation of 7-azaisatins and its derivatives toward investigation for biological activity is currently being pursued.

EXPERIMENTAL

All the chemicals used were of reagent grade and obtained from local suppliers, Aldrich, and Fluka. PCC was freshly prepared from chromium trioxide according to the earlier reported procedure.[19] All reactions were performed in oven-dried glassware under an inert atmosphere. Analytical thin-layer chromatography (TLC) was performed on silica-gel plates, and TLC visualization was carried out with ultraviolet (UV) light. Melting points were determined on a Mettlers-Temp instrument and are uncorrected. Infrared (IR) spectra were recorded using a Perkin-Elmer-1600 Fourier transform (FT)–IR spectrometer; ν in cm^{-1}. ^1H and ^{13}C NMR spectra [$CDCl_3$/dimethylsulfoxide (DMSO-d_6)] were recorded with Gemini-200 and Bruker-Avance-300 instruments; chemical shifts δ are in parts per million (ppm) relative to $SiMe_4$ as an internal standard, and couplings are in hertz (Hz). High-resolution mass spectrometry (HRMS, ESI) data were recorded on a QSTAR XL high-resolution mass spectrometer in m/z (rel. %).

General Experimental Procedure for the Preparation of Compounds 2a–2o

PCC (53.7 g, 0.25 mol) was ground with silica gel (53.7 g, 70–230 mesh) and transferred to a 1-L round-bottom flask containing DCE (400 mL). To the resulting orange suspension was added a solution of N-butyl-7-azaindole (17.4 g, 0.1 mol) in DCE (50 mL) while stirring at room temperature. To this, $AlCl_3$ (15 wt%/1.3 mol% with respect to the N-butyl-7-azaindole) was added, and the reaction mixture was stirred at 80 °C. Completion of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure and the black solid was diluted with 500 ml of *n*-hexane–ethyl acetate (4:1) and filtered under suction through a sintered funnel layered with silica gel (5 cm, 70–230 mesh). The filtrate was evaporated to furnish N-butyl-7-azaisatin as yellow solid (16.93 g, 83%). A similar procedure was adopted for the preparation of other isatins, and the authenticity of the products was confirmed by ^1H NMR, ^{13}C NMR, IR, mass, and HRMS spectral data.[18,20]

Spectral Data of Synthesized Compounds

1H-Pyrrolo[2,3-*b*]pyridine-2,3-dione (2a)[10]. Yellow solid; yield 76%; mp 168–170. ^1H NMR (300 MHz, $CDCl_3$): δ 11.61 (s, 1H), 8.38 (d, 1H, $J = 4.5$ Hz), 7.86 (d, 1H, $J = 7.1$ Hz), 7.10 (t, 1H, $J = 5.2$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 182.9, 163.9, 159.9, 155.2, 132.5, 118.9, 112.8. IR (KBr): 3291, 1743, 1604, 1592, 1458. ESI-MS: m/z 171 $[M + Na]^+$. HRMS calcd. for $C_7H_4N_2O_2Na$ 171.0168; found 171.0170.

1-Methyl-1H-pyrrolo[2,3-*b*]pyridine-2,3-dione (2b)[14]. Yellow solid; yield 80%; mp 160–161. ^1H NMR (300 MHz, $CDCl_3$): δ 8.42 (d, 1H, $J = 4.5$ Hz), 7.79

(d, 1H, $J = 6.7$ Hz), 7.06 (t, 1H, $J = 6.7$ Hz), 3.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 181.9, 163.8, 158.3, 155.8, 132.8, 119.6, 112.0, 25.0. IR (KBr): 1750, 1607, 1594, 1458. ESI-MS: m/z 163 $[M + H]^+$. HRMS calcd. for $C_8H_6N_2O_2$ 162.0428; found 162.049.

1-Ethyl-1H-pyrrolo[2,3-*b*]pyridine-2,3-dione (2c)[14]. Yellow solid; yield 80%; mp 127–128. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.40 (d, 1H, $J = 5.8$ Hz), 7.79 (d, 1H, $J = 6.6$ Hz), 7.07 (t, 1H, $J = 5.8$ Hz), 3.89 (dd, 2H, $J = 7.5$, 6.7 Hz), 1.35 (t, 3H, $J = 7.5$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 182.1, 163.6, 157.9, 155.6, 132.8, 119.4, 112.0, 34.1, 12.8. IR (KBr): 1742, 1607, 1593, 1358. ESI-MS: m/z 176 $[M + H]^+$. HRMS calcd. for $C_9H_8N_2O_2$ 176.0585; found 176.0561.

1-Isopropyl-1H-pyrrolo[2,3-*b*]pyridine-2,3-dione (2d). Yellow solid; yield 81%; mp 152–154. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39 (d, 1H, $J = 5.2$ Hz), 7.79 (d, 1H, $J = 4.5$ Hz), 7.02 (t, 1H, $J = 4.5$ Hz), 4.66–4.78 (m, 1H), 1.52–1.56 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): 182.3, 163.2, 158.1, 154.3, 132.2, 118.7, 112.5, 43.1, 18.9. IR (KBr): 1742, 1603, 1592, 1443. ESI-MS: m/z 191 $[M + H]^+$. HRMS calcd. for $C_{10}H_{11}N_2O_2$ 191.0816; found 191.0820.

1-Butyl-1H-pyrrolo[2,3-*b*]pyridine-2,3-dione (2e). Yellow solid; yield 83%; mp 104–105. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41 (d, 1H, $J = 7.1$ Hz), 7.78 (d, 1H, $J = 6.6$ Hz), 7.05 (t, 1H, $J = 6.7$ Hz), 3.82 (t, 2H, $J = 6.4$ Hz), 1.73 (dd, 2H, $J = 7.9$, 6.7 Hz), 1.43 (dd, 2H, $J = 7.1$, 6.6 Hz), 0.99 (t, 3H, $J = 6.4$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 181.8, 163.0, 158.6, 154.6, 132.2, 119.1, 112.6, 38.0, 29.0, 19.4, 13.4. IR (KBr): 1743, 1621, 1590, 1489. ESI-MS: m/z 227 $[M + Na]^+$. HRMS calcd. for $C_7H_4N_2O_2Na$ 227.0789; found 227.0796.

1-Hexyl-1H-pyrrolo[2,3-*b*]pyridine-2,3-dione (2f). Yellow solid; yield 83%; mp 102–104. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.40 (d, 1H, $J = 6.7$ Hz), 7.78 (d, 1H, $J = 5.2$ Hz), 7.04 (t, 1H, $J = 5.2$ Hz), 3.81 (t, 2H, $J = 7.5$ Hz), 1.73 (dd, 2H, $J = 7.5$, 6.7 Hz), 1.31–1.41 (m, 6H), 0.89 (t, 3H, $J = 6.7$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 181.9, 163.0, 158.6, 154.6, 132.3, 119.1, 112.6, 38.4, 30.8, 26.9, 25.8, 21.9, 13.8. IR (KBr): 1745, 1619, 1589, 1483. ESI-MS: 233 $[M + H]^+$. HRMS calcd. for $C_{13}H_{17}N_2O_2$ 233.1293; found 233.1290.

1-Heptyl-1H-pyrrolo[2,3-*b*]pyridine-2,3-dione (2g). Orange solid; yield 84%; mp 95–97. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41 (d, 1H, $J = 5.2$ Hz), 7.76 (d, 1H, $J = 6.7$ Hz), 7.03 (t, 1H, $J = 5.2$ Hz), 3.81 (t, 2H, $J = 7.5$ Hz), 1.72 (dd, 2H, $J = 7.5$, 6.7 Hz), 1.29–1.42 (m, 8H), 0.88 (t, 3H, $J = 6.7$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 181.4, 163.0, 158.5, 154.6, 132.1, 119.1, 112.6, 38.3, 31.3, 28.8, 26.9, 26.2, 22.0, 13.9. IR (KBr): 1742, 1619, 1589, 1483. ESI-MS: 247 $[M + H]^+$. HRMS calcd. for $C_{14}H_{18}N_2O_2$ 247.1510; found 247.1504.

1-Octyl-1H-pyrrolo[2,3-*b*]pyridine-2,3-dione (2h). Yellow solid; yield 85%; mp 87–88. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39 (d, 1H, $J = 5.2$ Hz), 7.79 (d, 1H, $J = 6.7$ Hz), 7.03 (t, 1H, $J = 5.2$ Hz), 3.81 (t, 2H, $J = 7.5$ Hz), 1.73 (dd, 2H, $J = 7.5$, 6.7 Hz), 1.26–1.37 (m, 10H), 0.88 (t, 3H, $J = 6.7$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 181.8, 163.0, 158.6, 154.6, 132.2, 119.1, 112.6, 38.3, 37.8, 31.1, 28.5, 26.9, 26.2, 22.0, 13.8. IR (KBr): 1741, 1609, 1591, 1451. ESI-MS: 261 $[M + H]^+$. HRMS calcd. for $C_{15}H_{21}N_2O_2$ 261.1610; found 261.1603.

1-Decyl-1H-pyrrolo[2,3-*b*]pyridine-2,3-dione (2i). Yellow solid; yield 87%; mp 88–90. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39 (d, 1H, $J = 5.2$ Hz), 7.78 (d, 1H, $J = 6.7$ Hz), 7.03 (t, 1H, $J = 5.2$ Hz), 3.81 (t, 2H, $J = 7.5$ Hz), 1.73 (dd, 2H, $J = 7.5$ Hz), 1.25–1.38 (m, 14H), 0.88 (t, 3H, $J = 6.7$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 181.8, 163.0, 158.6, 154.6, 132.2, 119.1, 112.6, 38.3, 31.2, 28.8, 28.6, 26.9, 26.2, 22.0, 13.9. IR (KBr): 1744, 1609, 1598, 1449. ESI-MS: 289 $[M + H]^+$. HRMS calcd. for $C_{17}H_{25}N_2O_2$ 289.1929; found 289.1916.

1-Benzyl-1H-pyrrolo[2,3-*b*]pyridine-2,3-dione (2j)[14]. Yellow solid; yield 83%; mp 187–189. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.41 (d, 1H, $J = 5.2$ Hz), 7.77 (d, 1H, $J = 7.7$ Hz), 7.46 (d, 2H, $J = 6.9$ Hz), 7.27–7.31 (m, 3H), 7.04 (dd, 1H, $J = 5.2$, 1.8 Hz), 4.98 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 181.8, 163.5, 158.1, 155.7, 135.4, 132.9, 128.8, 128.7, 128.1, 119.6, 112.1, 42.7. IR (KBr): 1742, 1603, 1592, 1443. ESI-MS: 239 $[M + H]^+$. HRMS calcd. for $C_{14}H_{11}N_2O_2$ 239.0865; found 239.0820.

1H-Indole-2,3-dione (2k)[18]. Orange-red solid; yield 88%; mp 192–194. ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 10.92 (s, 1H), 7.42–7.53 (m, 2H), 7.05 (t, 1H, $J = 8.1$ Hz), 6.90 (d, 1H, $J = 8.1$ Hz). IR (KBr): 2923, 2855, 1732, 1608, 1462, 1343, 1081, 1002, 857. GC-MS: (m/z) 147 $[M^+]$.

5-Chloroindoline2,3-dione (2l)[18]. Yellow-brownish solid; yield 84%; mp 249–251. ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 11.02 (s, 1H), 7.55–7.48 (m, 2H), 6.95 (d, 1H, $J = 9.1$ Hz). GC-MS: (m/z) 181 $[M^+]$.

1-Butyl-5-chloroindoline-2,3-dione (2m)[18]. Orange solid; yield 85%; mp 62–63. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49 (m, 2H, $J = 8.0$ Hz), 6.80 (d, 1H, $J = 8.0$ Hz), 3.7 (t, 2H, $J = 7.3$ Hz), 1.67 (q, 2H, $J = 7.3$ Hz), 1.43 (m, 2H, $J = 7.3$ Hz),), 0.98 (t, 3H, $J = 7.3$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): 182.5, 157.6, 149.4, 137.5, 129.3, 125.1, 118.3, 111.8, 40.07, 29.08, 20.0, 13.5. IR (KBr): 3089, 2953, 1737, 1606, 1448, 1339, 1185, 1116, 844, 720. ESI-MS: 238 $[M + H^+]$. HRMS calcd. for $C_{12}H_{13}NClO_2$ 238.0634; found 238.0630.

5-Nitroindoline-2,3-dione (2n)[18]. Pale-yellow solid; yield 85%; mp 251–253. ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO-d_6): δ 11.65 (s, 1H), 8.58 (dd, 1H, $J = 8.8$, 2.2 Hz), 8.38 (d, 1H, $J = 2.2$ Hz), 7.10 (d, 1H, $J = 8.8$ Hz). GC-MS: (m/z) 192 $[M^+]$.

1-Methyl-5-nitroindoline-2,3-dione (2o)[18]. Yellowish-orange solid; yield 81%; mp 203–204. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.47 (dd, 1H, $J = 8.8$, 2.9 Hz), 8.34 (d, 1H, $J = 2.9$ Hz), 7.06 (d, 1H, $J = 8.8$ Hz), 3.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 182.1, 157.3, 150.3, 140.5, 128.0, 118.3, 116.7, 111.5, 26.2. IR (KBr): 2924, 1743, 1610, 1465, 1331, 1289, 1109, 1074, 845, 747, 710, 600. GC-MS: m/z 206 $[M^+]$. Anal. calc. for $C_9H_6N_2O_4$; C, 52.44; H, 2.93; N, 13.59; Found: C, 52.40; H, 2.78; N, 13.42.

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