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Graphical Abstract

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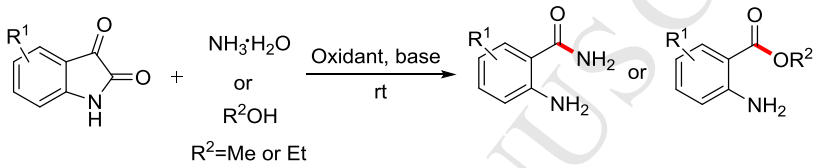

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Oxidative ring-opening of isatins for the synthesis of 2-aminobenzamides and 2-aminobenzoates

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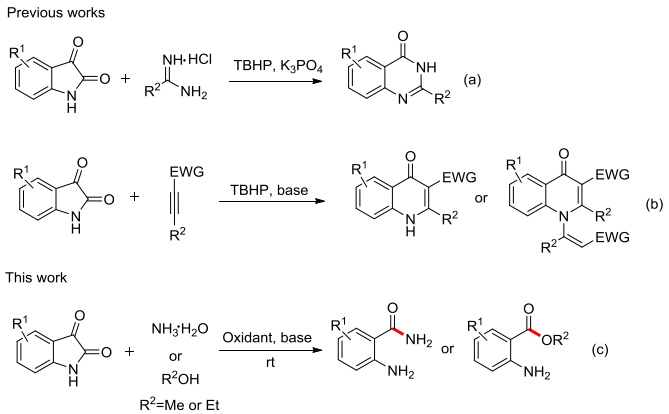
ABSTRACT

An efficient and practical isatin-based oxidative domino protocol has been developed for the facile synthesis of 2-aminobenzamides and 2-aminobenzoates. The robust nature of this reaction system is reflected by accessible starting materials, room temperature and high-yield gram-scale synthesis.

1. Introduction

Anthranilic acid derivatives represent a kind of important and fundamental organic compounds which have been widely applied in many fields such as pharmacochemistry, biochemistry and synthetic chemistry.[1-6] In particular, as one of the anthranilic acid derivatives, 2-aminobenzamide is exemplified as a privileged structure that exists in many pharmaceutical molecules and biologically active compounds such as anticancer drug,[1] anti-inflammatory analgesic[2] and hypolipidemic drug.[3] In addition, 2-aminobenzamide derivatives are often used as synthetic intermediates for the direct synthesis of biologically active molecules.[6] Accordingly, extensive synthetic methods have been developed to access 2-aminobenzamide derivatives.[7-10] Among them, nucleophilic substitution reaction of organic amine with anthranilic acid derivatives were regarded as the prevalent methods. Besides, some groups develop transition-metal-catalyzed sp^2 C-H amination to afford 2-aminobenzamide derivatives from benzoyl amide and appropriate amine source.[10] Despite these advances, the development of new methodologies for constructing diverse 2-aminobenzamides is still in demand.

Isatin is a unique structure possessing a γ-lactam and a ketone. On account of its distinct potential to serve as both an electrophile and a nucleophile, various reactions involving isatins have been established for the construction of useful compounds.[11] Recently, we have reported two robust synthetic methods of quinazolines and 4-quinolones via an innovative isatin-based oxidative cyclization strategy (Scheme 1a and 1b).[12] In conjunction with our ongoing research into developing isatin-based oxidative domino methodologies for the preparation of valuable compounds, Herein we report an efficient transition-metal-free domino strategy for the facile synthesis of 2-aminobenzamide derivatives from commercially available isatins and ammonium hydroxide. To our delight, this proposal is also appropriate for the synthesis of 2-aminobenzoate derivatives (Scheme 1c).

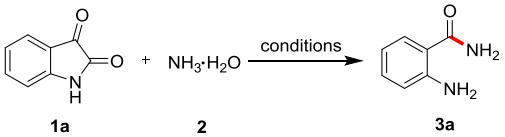


Scheme 1. isatin-based oxidative domino strategy for the synthesis valuable compounds.

2. Results and discussion

Our study commenced with the reaction of isatin **1a** (1.0 mmol) and ammonia hydrate **2a** (3.0 mmol) in the presence of K_3PO_4 and TBHP in DMSO at room temperature (25–30 °C) in a sealed vessel under air for 4 h (Table 1, entry 1). Gratifyingly, the desired 2-aminobenzamide (**3a**) identified by NMR spectra was obtained in 56% yield. However, we found that in the absence of K_3PO_4, the reaction can reach a higher yield of 78% (Table 1, entry 2). In light of the importance of the oxidant,[12] a series of oxidants was subsequently inspected (Table 1, entries 4–8), and H_2O_2 showed the highest efficiency (Table 1, entry 3). Next, several solvents were tested (Table 1, entries 9–12), and DMSO was proved to be the most effective solvent (Table 1, compare entries 3 and 9–12). Overall, the optimized reaction conditions were identified as **1a** (1.0 mmol), 3.0 equiv of **2**, 2.0 equiv of H_2O_2 in 4 mL of DMSO at room temperature in a sealed vessel under air (Table 1, entry 3).

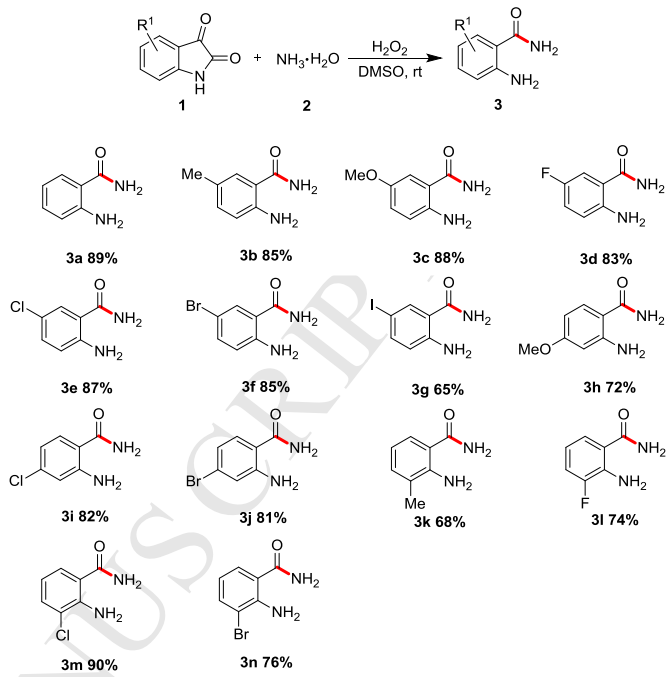
Table 1. Optimization of the reaction conditions[a].



entry	base	oxidant	solvent	yield[b]
1	K_3PO_4	TBHP	DMSO	56%
2	none	TBHP	DMSO	78%
3	**none**	**H_2O_2**	**DMSO**	**89%**
4	none	$K_2S_2O_8$	DMSO	trace
5	none	t-BuONO	DMSO	trace
6	none	m-CPBA	DMSO	trace
7	none	DTBP	DMSO	trace
8	none	BPO	DMSO	82%
9	none	H_2O_2	DMF	51%
10	none	H_2O_2	CH_3CN	trace
11	none	H_2O_2	CH_3CH_2OH	trace
12	none	H_2O_2	H_2O	trace

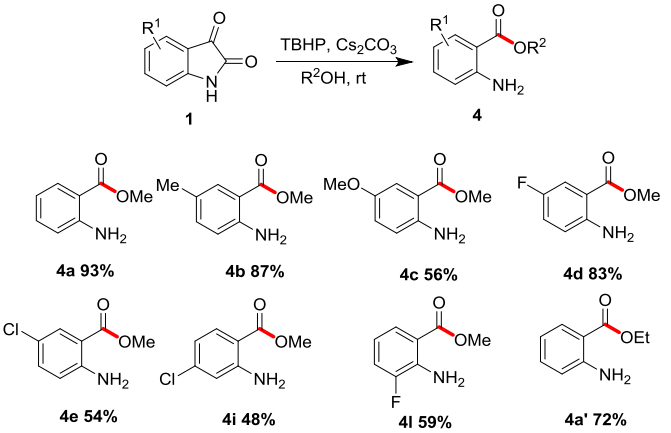
[a]Reaction conditions: **1a** (1.0 mmol), **2** (3.0 mmol), and oxidant (2.0 mmol) were added at room temperature (25–30 °C) in 4 mL of solvent in a sealed vessel under air for 4 h. [b]Isolated yield.

After identifying the optimized conditions, we further evaluated the substrate generality for this reaction (Scheme 2). To our delight, the reaction demonstrated good compatibility and proved to be a general method to build diverse 2-aminobenzamides. Reactions with isatins bearing electron-neutral (H, 5-Me, 7-Me) and electron-donating (5-OMe, 6-OMe) groups all underwent the desired transformation to deliver the corresponding products in moderate to good yields (**3a**–**3c**, 85%–89%; **3k**, 68%; **3h**, 72%). An array of halogen-substituted isatins (5-F, 5-Cl, 5-Br, 5-I, 6-Cl, 6-Br, 7-F, 7-Cl, 7-Br) were all found to be compatible with the reaction (**3d**–**3g**, 65%–87%, **3i**–**3j**, 81%–82%, **3l**–**3n**, 74%–90%), which provided opportunities for further synthetic elaboration.



Scheme 2. Substrates scope of 2-aminobenzamide

In consideration of the importance of 2-aminobenzoate derivatives,[14] we also attempted to apply this oxidative domino strategy to synthesize 2-aminobenzoates. After investigating various reaction parameters including bases and oxidants, the optimized reaction conditions were eventually identified as **1a** (1.0 mmol), 2.0 equiv of TBHP, and 2 equiv of Cs_2CO_3 in 4 mL of CH_3OH or CH_3CH_2OH at room temperature for 4 h (SI, Table 1). Several representative isatins were selected to construct 2-aminobenzoate derivatives. Isatins containing electron-neutral (5-Me), electron-rich (5-OMe), and halogenated substituents (5-F, 5-Cl, 6-Cl, 7-F) were converted to the corresponding products in moderate to good yields (Scheme 3, **4a**–**e**, 54%–93%; **4i**, 48%; **4l**, 59%; **4a′**, 72%).

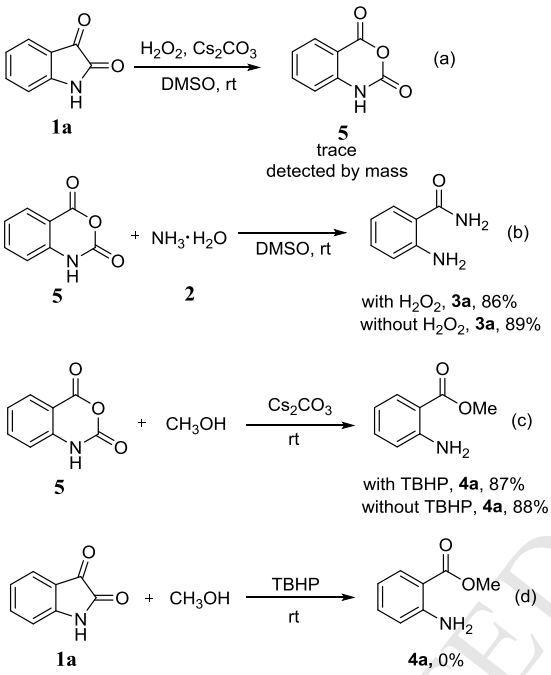


[a]Reaction conditions: **1** (1.0 mmol), TBHP (70%, 2.0 mmol), and Cs_2CO_3 (2.0 mmol) in CH_3OH or CH_3CH_2OH (4 mL) at room temperature (25-30 °C) in a sealed vessel under air for 4 h. [b]Isolated yields.

Scheme 3. Direct synthesis of 2-aminobenzoates from isatins, methanol and ethanol.[a,b]

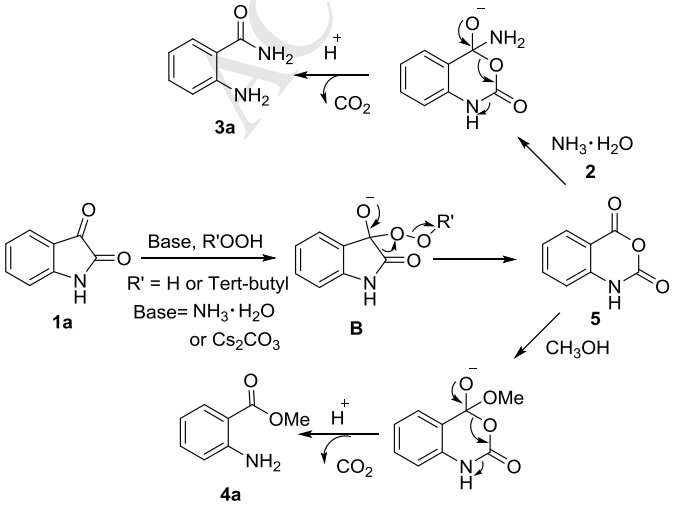
To shed light on the mechanism of this oxidative domino reaction, a series of control experiments were performed (Scheme 4). Only a trace of the oxidative product isatoic anhydride (**5**)

was detected by mass spectroscopy when isatin (**1a**) was conducted under the optimized conditions (Scheme 4a). Next, reaction of isatoic anhydride (**5**) with ammonia (**2**) or methanol under standard conditions yielded the desired product **3a** or **4a** in 86% and 87% yield, respectively. These results indicated that the isatoic anhydride might act as the key intermediate involved in these processes (Scheme 4b and 4c). In the absence of H_2O_2, these reactions still reacted smoothly to give the target products, indicating that H_2O_2 or TBHP is mainly responsible for the transformation of isatin to isatoic anhydride (Scheme 4b and 4c). Moreover, we attempted to react isatin (**1a**) with methanol for this oxidative domino protocol without Cs_2CO_3. Unfortunately, the desired product **4a** was not detected (Scheme 4d).



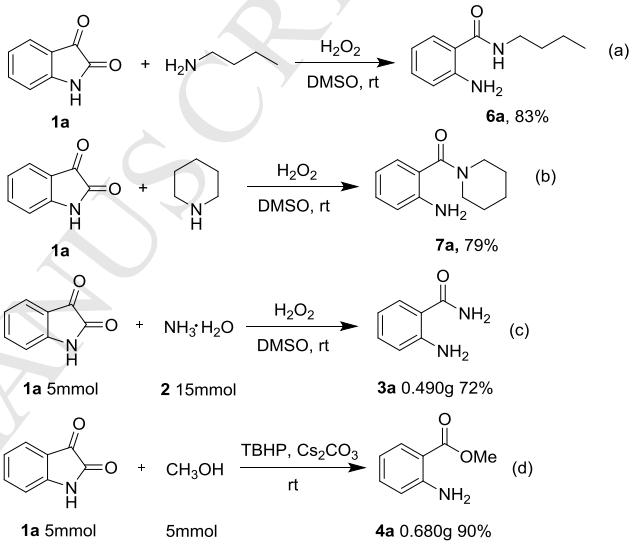
Scheme4. Control experiments

On the basis of the above observations and precedent literature[12-13], a tentative reaction mechanism shown in Scheme 5 was proposed. Initially, intermolecular nucleophilic attack of H_2O_2 or TBHP to isatin (**1a**) affords intermediate **B** with the assistance of base, and intramolecular cyclization followed by rearrangement leads to the formation of the intermediate isatoic anhydride (**5**). Finally, ammonia (**2**) underwent a further nucleophilic attack to the intermediate isatoic anhydride (**5**) to afford the desired product **3a**. Similarly, the target product **4a** could be obtained through an analogous nucleophilic attack.



Scheme 5. Possible mechanism.

To show the generality of this isatin-based oxidative domino protocol for the synthesis of anthranilic acid derivatives, butylamine and piperidine were selected to construct 2-aminobenzamide derivatives, which gave the desired products in good yields under standard conditions (Scheme 6a and 6b). To further indicate the synthetic practicality of the reaction, gram-scale syntheses of 2-aminobenzamide (**3a**) and methyl 2-aminobenzoate (**4a**) were performed, and the desired products **3a** and **4a** were obtained in 72% and 90% yield respectively (Scheme 6c and 6d).



Scheme 6. Gram-Scale experiments

3. Conclusions

In summary, we have developed an efficient transition-metal-free oxidative domino reaction for the facile synthesis of 2-aminobenzamide and 2-aminobenzoates from commercially available isatins, ammonium hydroxide, methanol and ethanol. The easily accessible starting materials, mild reaction conditions, and simple manipulation render this methodology attractive. Further applications of this isatin-based oxidative domino strategy for the synthesis of other valuable compounds are currently underway in our laboratory.

4. Experimental

General Synthesis Information: All isatins (**1a**-**1n**), ammonia and other reagents were obtained from commercial suppliers and used without further purification. TLC analysis was performed using pre-coated glass plates. Column chromatography was performed using silica gel (200–300 mesh). ^1H spectra were recorded in $CDCl_3$ on a Varian Mercury 600 MHz spectrometers. ^{13}C spectra were recorded in $CDCl_3$ or DMSO-d_6 on 150 MHz NMR spectrometers. Chemical shifts are reported in ppm, relative to the internal standard of tetramethylsilane (TMS). The high resolution mass spectra (HRMS) were measured on a Bruker Apex IV FTMS spectrometer by ESI. MS equipped with an electrospray source. Trace MS spectrometer (EI, 70 eV).

Representative procedure for the synthesis of 3 (A): A sealed tube was charged with isatin **1** (**1a** 147 mg, 1.0 mmol), ammonia hydrate **2** (25%, 421mg, 3.0mmol) and H_2O_2 (30%, 227mg, 2.0 mmol) at room temperature, and then solvent DMSO (4 mL) was

added. The resulting mixture was stirred at 30 °C in a sealed vessel under air after 4 hours, then added 50mL water to the mixture, extracted with $CH_3COOC_2H_5$ 3 times (3 × 50 mL). The extract was washed with 30% NaCl solution (V/V), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (Petroleum ether /Ethyl acetate = 3:1) to yield the desired product **3a** as a yellow solid (89% yield).

Representative procedure for the synthesis of 4 (B): A sealed tube was charged with isatin **1** (**1a** 147 mg, 1.0 mmol), TBHP (70%, 257mg, 2.0 mmol), and Cs_2CO_3 (652mg, 2.0 mmol) at room temperature, and then solvent CH_3OH (4 mL) was added. The resulting mixture was stirred at 30 °C in a sealed vessel under air after 4 hours, then added 50mL water to the mixture, extracted with $CH_3COOC_2H_5$ 3 times (3 × 50 mL). The extract was washed with 30% NaCl solution (V/V), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (Petroleum ether /Ethyl acetate = 10:1) to yield the desired product **4a** as a yellow liquid (93% yield).

2-aminobenzamide ***(3a)*****:** Following general procedure A using indoline-2,3-dione (**1a**, 147 mg, 1.0 mmol), ammonia hydrate (**2**, 421 mg, 3.0 mmol) and purified by silicagel column chromatography, afforded the compound as yellow solid (121.1 mg, Yield 89%); ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.74 (s, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.11-7.14 (m, 2H), 6.68 (d, J = 7.8 Hz, 1H), 6.56 (br, 2H), 6.48 (d, J = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 171.4, 150.2, 132.0, 128.8, 116.5, 114.5, 113.7; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_7H_9ON_2$: 137.0709; found: 137.0709. the overall spectroscopic data are in complete agreement with assigned structures and consistent with literature[15]

2-amino-5-methylbenzamide ***(3b)*****:** Following general procedure A using 5-methylindoline-2,3-dione (**1b**, 161 mg, 1.0 mmol), ammonia hydrate (**2**, 421 mg, 3.0 mmol) and purified by silicagel column chromatography, afforded the compound as yellow solid (127.6 mg, yield 85%); ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.68 (s, 1H), 7.35 (s, 1H), 6.95-7.01 (m, 2H), 6.59 (d, J = 8.4 Hz, 1H), 6.31 (d, J = 12.6 Hz, 2H), 2.14 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 171.4, 147.9, 132.8, 128.7, 122.7, 116.6, 113.7, 20.1; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_8H_{11}ON_2$: 151.0866; found: 151.0861. the overall spectroscopic data are in complete agreement with assigned structures and consistent with literature[16]

2-amino-5-methoxybenzamide ***(3c)*****:** Following general procedure A using 5-methoxyindoline-2,3-dione (**1c**, 177 mg, 1.0 mmol), ammonia hydrate (**2**, 421 mg, 3.0 mmol) and purified by silicagel column chromatography, afforded the compound as yellow solid (146 mg, Yield 88%); ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.57 (s, 1H), 7.48 (d, J = 8.4 Hz, 1H), 6.86 (s, 1H), 6.75 (s, 2H), 6.19 (s, 1H), 6.06 (d, J = 8.4 Hz, 1H), 3.68 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 171.2, 162.3, 152.5, 130.6, 106.9, 102.3, 99.3, 54.9; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_8H_{11}O_2N_2$: 167.0815; found: 167.0813. the overall spectroscopic data are in complete agreement with assigned structures and consistent with literature[17]

2-amino-5-fluorobenzamide ***(3d)*****:** Following general procedure A using 5-fluoroindoline-2,3-dione (**1d**, 165 mg, 1.0 mmol), ammonia hydrate (**2**, 421 mg, 3.0 mmol) and purified by silicagel column chromatography, afforded the compound as white solid; (128 mg, Yield 83%); ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.81 (s, 1H), 7.39 (d, J = 10.2 Hz, 1H), 7.22 (s, 1H), 7.04 (s, 1H), 6.69 (d, J = 4.8 Hz, 1H), 6.45 (s, 2H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 170.4, 153.4, 151.9, 147.1, 119.6, 117.8, 114.2, 113.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_7H_8ON_2F$: 155.0615; found: 155.0610. the overall spectroscopic data are in complete agreement with assigned structures and consistent with literature[18]

2-amino-5-chlorobenzamide ***(3e)*****:** Following general procedure A using 5-chloroindoline-2,3-dione (**1e**, 181 mg, 1.0 mmol), ammonia hydrate (**2**, 421 mg, 3.0 mmol) and purified by silicagel column chromatography, afforded the compound as yellow solid (148 mg, Yield 87%); ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.85 (s, 1H), 7.59 (s, 1H), 7.17 (m, 2H), 6.70 (d, J = 8.4 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 170.1, 149.1, 131.7, 128.0, 118.1, 117.5, 114.5; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_7H_8ON_2Cl$: 171.0321; found: 171.0318. the overall spectroscopic data are in complete agreement with assigned structures and consistent with literature[19]

2-amino-5-bromobenzamide ***(3f)*****:** Following general procedure A using 5-bromoindoline-2,3-dione (**1f**, 226 mg, 1.0 mmol), ammonia hydrate (**2**, 421 mg, 3.0 mmol) and purified by silicagel column chromatography, afforded the compound as white solid (183 mg, Yield 85%); ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.87 (s, 1H), 7.69 (s, 1H), 7.24 (m, 2H), 6.72 (d, J = 9.6 Hz, 2H), 6.65 (d, J = 9.0 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 170.0, 149.5, 134.4, 130.8, 118.6, 115.1, 104.8; MS (EI): *m/z* 213.95 the overall spectroscopic data are in complete agreement with assigned structures and consistent with literature[19]

2-amino-5-iodobenzamide ***(3g)*****:** Following general procedure A using 5-iodoindoline-2,3-dione (**1g**, 273 mg, 1.0 mmol), ammonia hydrate (**2**, 421 mg, 3.0 mmol) and purified by silicagel column chromatography, afforded the compound as yellow solid (170 mg, Yield 65%); ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.88 (s, 1H), 7.82 (s, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.18 (s, 1H), 6.71 (s, 2H), 6.55 (d, J = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 170.1, 149.8, 140.0, 136.6, 119.1, 116.1, 74.6; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_7H_8ON_2I$: 262.9676; found: 262.9666. the overall spectroscopic data are in complete agreement with assigned structures and consistent with literature[16]

2-amino-4-methoxybenzamide ***(3h)*****:** Following general procedure A using 6-methoxyindoline-2,3-dione (**1h**, 177 mg, 1.0 mmol), ammonia hydrate (**2**, 421 mg, 3.0 mmol) and purified by silicagel column chromatography, afforded the compound as yellow solid (119 mg, Yield 72%); ^{1}H NMR (600MHz, DMSO-d_6): δ (ppm) 7.58 (s, 1H), 7.49 (d, J = 9.0 Hz, 1H), 6.87 (s, 1H), 6.75 (s, 2H), 6.19 (s, 1H), 6.07 (d, J = 9.0 Hz, 1H), 3.68 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 171.2, 162.3, 152.5, 130.6, 106.9, 102.3, 99.3, 54.9; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_8H_{11}O_2N_2$: 167.0815; found: 167.0808 the overall spectroscopic data are in complete agreement with assigned structures and consistent with literature[20]

2-amino-4-chlorobenzamide ***(3i)*****:** Following general procedure A using 6-chloroindoline-2,3-dione (**1i**, 181 mg, 1.0 mmol), ammonia hydrate (**2**, 421 mg, 3.0 mmol) and purified by silicagel column chromatography, afforded the compound as white solid (140 mg, Yield 82%); ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.80 (s, 1H), 7.53 (d, J = 8.4 Hz, 1H), 7.18 (s, 1H), 6.83 (s, 2H), 6.73 (s, 1H), 6.48 (d, J = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 170.5, 151.6, 136.4, 130.7, 115.2, 114.1, 112.4; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_7H_8ON_2Cl$: 171.0320; found: 171.0312 the overall spectroscopic data are in complete agreement with assigned structures and consistent with literature[19]

2-amino-4-bromobenzamide ***(3j):*** Following general procedure A using 6-bromoindoline-2,3-dione (**1j**, 226 mg, 1.0 mmol), ammonia hydrate (**2**, 421 mg, 3.0 mmol) and purified by silicagel column chromatography, afforded the compound as white solid (174 mg, Yield 81%); ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.84 (s, 1H), 7.48 (d, J = 8.4 Hz, 1H), 7.21 (s, 1H), 6.92 (s, 1H), 6.80 (s, 2H), 6.62 (d, J = 8.4 Hz, 1H). ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 170.9, 151.7, 130.8, 125.7, 118.4, 117.1, 112.8.; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_7H_8ON_2Br$: 214.9815; found: 214.9806. the overall spectroscopic data are in complete agreement with assigned structures and consistent with literature[20]

2-amino-3-methylbenzamide ***(3k)*****:** Following general procedure A using 7-methylindoline-2,3-dione (**1k**, 161 mg, 1.0 mmol), ammonia hydrate (**2**, 421 mg, 3.0 mmol) and purified by silicagel column chromatography, afforded the compound as yellow solid (102 mg, Yield 68%); ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.74 (s, 1H), 7.42 (d, J = 7.8 Hz, 1H), 7.06 (d, J = 7.2 Hz, 2H), 6.37–6.45 (m, 3H), 2.06 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 171.9, 148.3, 132.9, 126.8, 123.2, 114.4, 113.6, 17.8; MS (EI): *m/z* 150.10 the overall spectroscopic data are in complete agreement with assigned structures and consistent with literature[19]

2-amino-3-fluorobenzamide ***(3l)*****:** Following general procedure A using 7-fluoroindoline-2,3-dione (**1l**, 165 mg, 1.0 mmol), ammonia hydrate (**2**, 421 mg, 3.0 mmol) and purified by silicagel column chromatography, afforded the compound as white solid (114 mg, Yield 74%); ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.91 (s, 1H), 7.42 (d, J = 7.8 Hz, 1H), 7.31 (s, 1H), 7.12–7.15 (m, 1H), 6.50 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 170.7, 152.1, 150.5, 138.9, 124.4, 117.1, 116.2, 113.8; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_7H_8ON_2F$: 155.0615; found: 155.0609. the overall spectroscopic data are in complete agreement with assigned structures and consistent with literature[21]

2-amino-3-chlorobenzamide ***(3m)*****:** Following general procedure A using 7-chloroindoline-2,3-dione (**1m**, 181.5 mg, 1.0 mmol), ammonia hydrate (**2**, 421 mg, 3.0 mmol) and purified by silicagel column chromatography, afforded the compound as yellow solid (153.5 mg, Yield 90%); ^{1}H NMR (600 MHz, DMSO-d_6): δ (ppm) 7.95 (s, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.37 (d, J = 7.2 Hz, 2H), 6.71 (d, J = 18.0 Hz, 2H), 6.55 (t, J = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6): δ (ppm) 170.6, 145.7, 132.0, 127.9, 119.1, 115.7, 115.0; HRMS (ESI): *m/z* $[M+H]^+$ calcd for $C_7H_8ON_2Cl$: 171.0320; found: 171.0311. the overall spectroscopic data are in complete agreement with assigned structures and consistent with literature[22]

2-amino-3-bromobenzamide ***(3n)*****:** Following general procedure A using 7-bromoindoline-2,3-dione (**1n**, 226 mg, 1.0 mmol), ammonia hydrate (**2**, 421 mg, 3.0 mmol) and purified by silicagel column chromatography, afforded the compound as white solid (163 mg, Yield 76%); ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 7.95 (s, 1H), 7.59 (d, J = 7.8 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.38 (s, 1H), 6.67 (d, J = 21.6 Hz, 2H), 6.50 (t, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 170.6, 151.6, 136.5, 130.7, 115.2, 114.1, 112.4; MS (EI): *m/z* 213.95 $[M]^+$ the overall spectroscopic data are in complete agreement with assigned structures and consistent with literature[20]

methyl 2-aminobenzoate ***(4a)*****:** Following general procedure B using indoline-2,3-dione (**1a**, 147 mg, 1.0 mmol), methanol (4ml) and purified by silicagel column chromatography, afforded the compound as light yellow oil (140.5 mg, Yield 93%); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.69 (d, J = 8.1 Hz, 1H), 7.08 (t, J = 7.8 Hz, 1H), 6.47 (t, J = 7.2 Hz, 2H), 5.60 (s, 2H), 3.68 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 168.4, 150.3, 133.9, 131.0, 116.5, 116.0, 110.4, 51.3; MS (EI): *m/z* 151.10 the overall spectroscopic data are in complete agreement with assigned structures and consistent with literature[23]

methyl 2-amino-5-methylbenzoate ***(4b)*****:** Following general procedure A using 5-methylindoline-2,3-dione (**1b**, 161 mg, 1.0 mmol), methanol (4ml) and purified by silicagel column chromatography, afforded the compound as yellow solid (143.7 mg, Yield 87%); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.66 (s, 1H), 7.09 (d, J = 8.4 Hz, 1H), 6.59 (d, J = 8.4 Hz, 1H), 5.53 (s, 2H), 3.86 (d, J = 72.0 Hz, 3H), 2.23 (d, J = 61.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 168.5, 148.2, 135.2, 130.7, 125.3, 116.8, 110.5, 51.4, 20.2; MS (EI): *m/z* 165.10 the overall spectroscopic data are in complete agreement with assigned structures and consistent with literature[24]

methyl 2-amino-5-methoxybenzoate ***(4c)*****:** Following general procedure A using 5-methoxyindoline-2,3-dione (**1c**, 177 mg, 1.0 mmol), methanol (4ml) and purified by silicagel column chromatography, afforded the compound as yellow solid (101.4 mg, Yield 56%); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.30 (s, 1H), 6.89-6.90 (m, 1H), 6.57 (d, J = 9.0 Hz, 1H), 5.47 (s, 2H), 3.81 (s, 3H). 3.70 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 168.0, 150.1, 145.0, 123.0, 118.0, 112.6, 110.1, 55.4, 51.3; MS (EI): *m/z* 181.10 the overall spectroscopic data are in complete agreement with assigned structures and consistent with literature[25]

methyl 2-amino-5-fluorobenzoate ***(4d)*****:** Following general procedure A using 5-fluoroindoline-2,3-dione (**1d**, 165 mg, 1.0 mmol), methanol (4ml) and purified by silicagel column chromatography, afforded the compound as yellow oil (140.4 mg, Yield 83%); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.53 (d, J = 9.6 Hz, 1H), 7.02 (d, J = 7.2 Hz, 1H), 6.61–6.62 (m, 1H), 5.59 (s, 2H), 3.88 (d, J = 21.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 167.8, 154.8, 153.2, 147.1, 122.2, 117.9, 116.2, 110.7, 51.9; MS (EI): *m/z* 169.05 the overall spectroscopic data are in complete agreement with assigned structures and consistent with literature[26]

methyl 2-amino-5-chlorobenzoate ***(4e)*****:** Following general procedure A using 5-chloroindoline-2,3-dione (**1e**, 181.5 mg, 1.0 mmol), methanol (4ml) and purified by silicagel column chromatography, afforded the compound as white solid (100.2 mg, Yield 54%); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.81 (s, 1H), 7.19 (d, J = 8.4 Hz, 1H), 6.60 (d, J = 8.4 Hz, 1H), 5.74 (s, 2H), 3.86 (s, 3H).; ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 167.6, 148.9, 134.0, 130.3, 120.5, 118.0, 111.3, 51.8; MS (EI): *m/z* 185.00 the overall spectroscopic data are in complete agreement with assigned structures and consistent with literature[27]

methyl 2-amino-4-chlorobenzoate ***(4i)*****:** Following general procedure A using 6-chloroindoline-2,3-dione (**1i**, 181.5 mg, 1.0 mmol), methanol (4ml) and purified by silicagel column chromatography, afforded the compound as light yellow solid (89 mg, Yield 48%); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.53 (d, J = 8.4 Hz, 1H), 6.42 (s, 1H), 6.36–6.37 (m, 1H), 5.64 (s, 2H), 3.63 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 167.8, 151.1, 139.8, 132.4, 116.4, 115.7, 108.9, 51.5; MS (EI): *m/z* 185.05 the overall spectroscopic data are in complete agreement with assigned structures and consistent with literature[28]

methyl 2-amino-3-fluorobenzoate ***(4l)*****:** Following general procedure A using 7-fluoroindoline-2,3-dione (**1l**, 165 mg, 1.0 mmol), methanol (4ml) and purified by silicagel column chromatography, afforded the compound as yellow solid (99.8 mg, Yield 59%); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.63 (d, J

= 7.8 Hz, 1H), 7.09–7.12 (m, 1H), 6.55 (d, *J* = 6.6 Hz, 1H), 5.80 (s, 2H), 3.88 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 167.9, 152.2, 150.6, 139.6, 126.2, 118.4, 114.6, 112.5, 51.7; MS (EI): *m/z* 169.10 the overall spectroscopic data are in complete agreement with assigned structures and consistent with literature[29]

ethyl 2-aminobenzoate ***(4a')*****:** Following general procedure B using indoline-2,3-dione (**1a**, 147 mg, 1.0 mmol), ethanol (4ml) and purified by silicagel column chromatography, afforded the compound as red oil (118.9 mg, Yield 72 %); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 8.01 (d, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 1H), 6.78 (t, *J* = 8.1 Hz, 2H), 5.87 (s, 2H), 4.46 (dd, *J* = 13.2, 6.6 Hz, 2H), 1.52 (t, *J* = 6.6 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 168.1, 150.4, 133.9, 131.1, 116.6, 116.1, 110.9, 60.2, 14.3; MS (EI): *m/z* 165.10 the overall spectroscopic data are in complete agreement with assigned structures and consistent with literature[30]

2-amino-N-butylbenzamide **(*6a*)**: Following general procedure A using indoline-2,3-dione (1a, 147 mg, 1.0 mmol), butylamine (219 mg, 3.0 mmol) and purified by silicagel column chromatography, afforded the compound as white solid (160 mg, Yield 83%); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.29 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.18 – 7.12 (m, 1H), 6.72 – 6.54 (m, 2H), 6.27 (s, 1H), 5.33 (s, 2H), 3.35 (dd, *J* = 13.0, 7.1 Hz, 2H), 1.60 – 1.47 (m, 2H), 1.41-1.32 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 169.2, 148.3, 131.9, 127.0, 117.1, 116.5, 116.4, 39.3, 31.6, 20.0, 13.7. the overall spectroscopic data are in complete agreement with assigned structures and consistent with literature[31]

(2-aminophenyl)(piperidin-1-yl)methanone **(*7a*):** Following general procedure A using indoline-2,3-dione (1a, 147 mg, 1.0 mmol), piperidine (255 mg, 3.0 mmol) and purified by silicagel column chromatography, afforded the compound as white solid (161 mg, Yield 79%); ^{1}H NMR (600 MHz, $CDCl_3$): δ (ppm) 7.14 (t, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 6.77 – 6.66 (m, 2H), 4.21 (s, 2H), 3.55 (s, 4H), 1.67 (d, *J* = 4.2 Hz, 2H), 1.59 (s, 4H). ^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 169.3, 145.1, 130.0, 127.4, 120.2, 117.2, 116.4, 29.7, 26.3, 24.7. the overall spectroscopic data are in complete agreement with assigned structures and consistent with literature[32]

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