

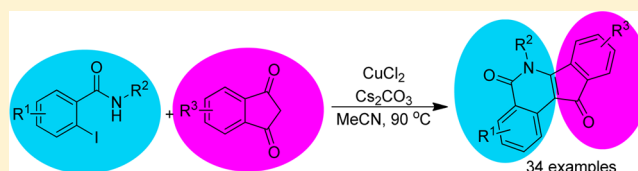
# Synthesis of Biologically Active Indenoisoquinoline Derivatives via a One-Pot Copper(II)-Catalyzed Tandem Reaction

Chia-Yu Huang,<sup>†</sup> Veerababurao Kavala,<sup>†</sup> Chun-Wei Kuo, Ashok Konala, Tang-Hao Yang, and Ching-Fa Yao<sup>\*†</sup>

Department of Chemistry, National Taiwan Normal University, 88, Sec. 4, Ting-Chow Road, Taipei 116, Taiwan R.O.C

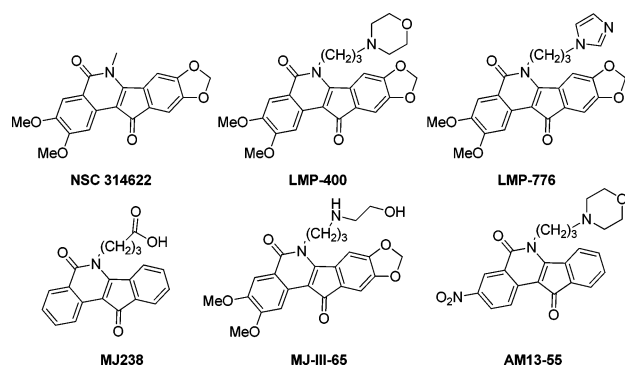
**S** Supporting Information

**ABSTRACT:** A concise route for the synthesis of indenoisoquinoline derivatives from 2-iodobenzamide and 1,3-indanedione derivatives in the presence of copper(II) chloride and cesium carbonate in acetonitrile solvent is reported. A wide variety of 2-iodobenzamide derivatives and indandiones could be used to synthesize indenoisoquinoline derivatives and other fused indenoisoquinoline in moderate to good yields. This methodology was adapted for the one-step synthesis of a series of clinically active topoisomerase I inhibitors such as NSC 314622, LMP-400, LMP-776.



## INTRODUCTION

Indeno[1,2-*c*]isoquinoline derivatives have been reported to have potential inhibition activities against topoisomerase I (Top1).<sup>1</sup> In fact, camptothecin (CPT) derivatives appear to be best Top1 inhibitors that are currently available.<sup>2</sup> However, extensive research by Cushman and co-workers from the NIH revealed that indenoisoquinoline derivatives are novel Top1 inhibitors with better pharmacokinetic features than CPT and that they have good chemical stability and resistance to reversal after the drug is removed.<sup>3</sup> Some of the indeno[1,2-*c*]isoquinoline derivatives that are reported to have anticancer activities are shown in Figure 1.



**Figure 1.** Some important indenoisoquinoline derivatives having Top1 inhibitors activity.

In addition, indenoisoquinoline derivatives showed potential activity for treating visceral leishmaniasis.<sup>4</sup> Indeno[1,2-*c*]isoquinoline derivatives such as LMP-400 and LMP-776 have also been used as multitumor treatment drugs.<sup>5</sup> The first indenoisoquinoline derivative was synthesized accidentally by Cushman et al. as a byproduct that was produced during the

synthesis of nitidine chloride.<sup>6</sup> Later, the same group developed efficient procedures for the synthesis of indeno[1,2-*c*]isoquinoline derivatives, such as by the condensation of indeno[1,2-*c*]isochromene-5,11-diones<sup>7</sup> and amines, homophthalic anhydrides, and arylmethanimines.<sup>8</sup> Other groups have also used Cushman group strategies for the construction of indenoisoquinoline derivatives.<sup>9</sup>

Other alternative procedures developed in recent years include the intramolecular cyclization reaction of 2-((4-methoxybenzyl)oxy)benzamide and *N*,2-dimethylbenzamide, the ring-closing metathesis reaction of polyenic benzamides.<sup>10</sup> Very recently, Hsieh and co-workers reported on the cobalt-catalyzed annulation of 2-halobenzaldimines with terminal alkynes followed by oxidation to furnish indenoisoquinolines.<sup>11</sup> Some other methods have also been developed for the synthesis of indeno[1,2-*c*]isoquinoline derivatives.<sup>12</sup> Known synthetic strategies for accessing indeno[1,2-*c*]isoquinoline derivatives are summarized in Figure 2.

Most of the reported methods have one or more shortcomings such as the need for multiple steps, limited substrate scope, unavailable starting materials, and other stereochemistry problems. Hence, the concise synthesis of bioactive indeno[1,2-*c*]isoquinoline derivatives from readily available starting materials would be useful, given the present status of the process. In 2012, we published the copper-catalyzed synthesis of isocoumarin derivatives from acyclic 1,3-diketones and 2-halobenzamide derivatives.<sup>13</sup> Further, when the acyclic 1,3-diketones were replaced with 1,3-hexadione in this reaction, the isoquinoline derivative was produced in poor yield. On the other hand, Liang et al. also showed similar results when similar materials were reacted in the absence of a metal catalyst.<sup>14</sup> Based on previous reports<sup>15</sup> and our prior experience with 2-

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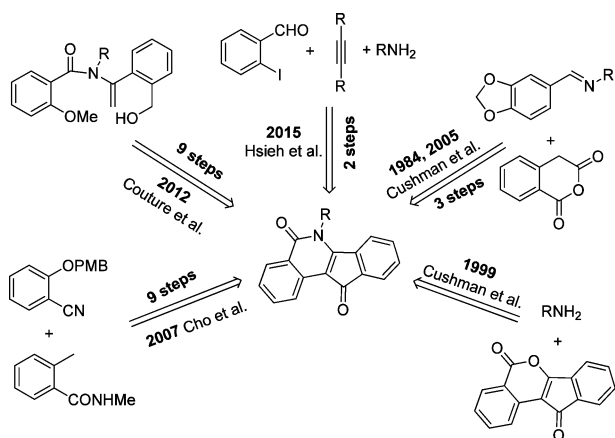
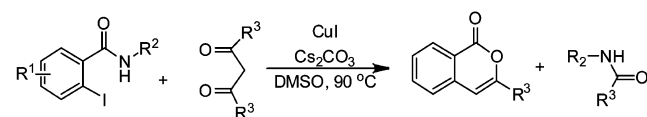


Figure 2. Synthetic strategies of indenoisoquinolines.

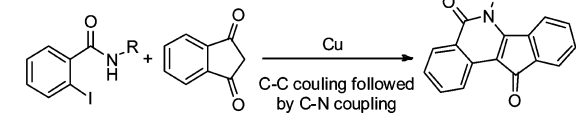
iodobenzamide derivatives under conditions of copper catalysis,<sup>16</sup> we envisioned that indeno[1,2-*c*]isoquinoline derivatives could be synthesized in a concise manner from 2-iodobenzamide derivatives and 1,3-indandiones as starting materials, which are commercially available materials (Scheme 1).

### Scheme 1. Copper-Catalyzed Tandem Reactions

Previous work:



This work:



## RESULTS AND DISCUSSION

To execute our plan, we used 2-iodo-*N*-methylbenzamide **1a** and indandione **2a** as model substrates. To initiate the reaction, we treated 2-iodo-*N*-methylbenzamide **1a** with 1,3-indandione in the presence of 2 equiv of  $K_2CO_3$  in acetonitrile at 90 °C (Table 1, entry 1). No indenoisoquinoline derivative was produced in the reaction. Even when the reaction was conducted in DMSO in the presence of cesium carbonate, the desired product was not produced. Next, the reaction was conducted in the presence of CuI and  $K_2CO_3$  in acetonitrile at 90 °C. In this case, the desired indeno[1,2-*c*]isoquinoline derivative was produced in 51% yield.

Encouraged by this finding, we next optimized the reaction conditions. We examined the use of a variety of solvents. An inseparable mixture of products was produced in polar aprotic solvents such as DMSO and DMF (entries 3 and 4), while a moderate yield of the product was obtained when dioxane was used as the solvent (entry 5). Moreover, no reaction occurred when toluene was used (entry 6). We also examined different copper catalysts such as  $CuSO_4$ , CuCl, and  $CuCl_2$  (entries 7–9). Among the copper salts used for our transformation, CuCl and  $CuCl_2$  seemed to be equally efficient, however, the yield dropped as the reaction was conducted with CuCl under argon (entry 10), meaning that copper(II) did play an important

Table 1. Optimization of Reaction Conditions

entry <sup>a</sup>	additive	base (equiv)	solvent	temp. (°C)	time (h)	yield (%) <sup>b</sup>
1	–	$K_2CO_3$ (2)	MeCN	90	2	NR
2	CuI	$K_2CO_3$ (2)	MeCN	90	4	51
3	CuI	$K_2CO_3$ (2)	DMF	80	5	mixture
4	CuI	$K_2CO_3$ (2)	DMSO	80	2	mixture
5	CuI	$K_2CO_3$ (2)	dioxane	100	2.5	48
6	CuI	$K_2CO_3$ (2)	toluene	110	2	NR
7	$CuSO_4$	$K_2CO_3$ (2)	MeCN	90	4	35
8	CuCl	$K_2CO_3$ (2)	MeCN	90	4	64
9	$CuCl_2$	$K_2CO_3$ (2)	MeCN	90	2.5	61
10 <sup>c</sup>	CuCl	$K_2CO_3$ (2)	MeCN	90	4	53
11	$CuCl_2$	$Cs_2CO_3$ (2)	MeCN	90	3	67
12	$CuCl_2$	$Cs_2CO_3$ (1.2)	MeCN	90	3	72
13 <sup>d</sup>	CuCl <sub>2</sub>	$Cs_2CO_3$ (1.2)	MeCN	90	4	56

<sup>a</sup>Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), additive (5 mmol %), base, solvent (0.5 mL). <sup>b</sup>Isolated yields. <sup>c</sup>Under Ar. <sup>d</sup>Microwave.

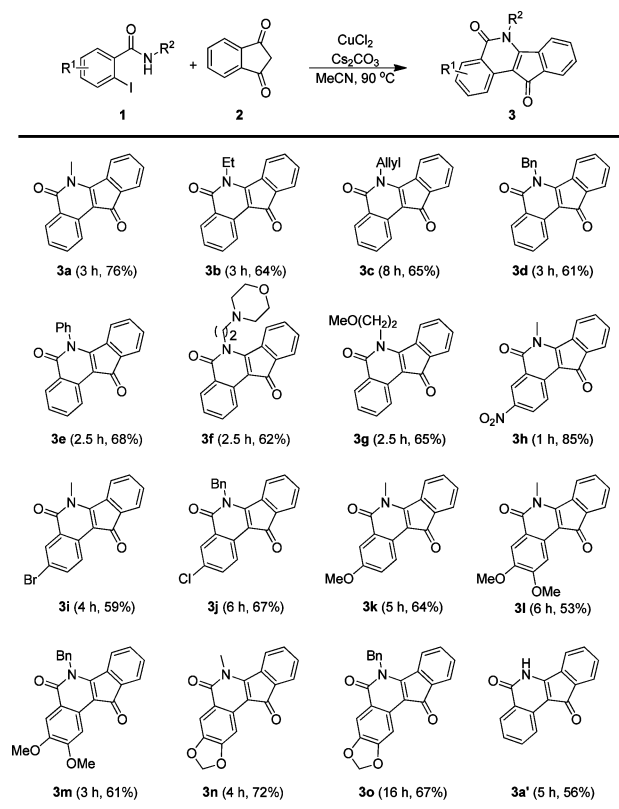
catalytic role in our reactions. Moreover, when the base  $K_2CO_3$  was replaced with  $Cs_2CO_3$ , the yield of the desired product was slightly higher (entry 11). It is notable that the reaction furnished good yields of the desired product when the amount of base was decreased from 2 equiv to 1.2 equiv (entry 12). Finally, when the reaction was performed under microwave conditions, it took a longer time to reach completion (entry 13).

After establishing the optimized reaction conditions, we explored the substrate scope and limitations of the methodology. We initially examined the reaction of various *N*-substituted 2-iodobenzamides and indane-1,3-dione (Table 2). When 2-iodobenzamide substrates having different *N*-substitutions such as methyl, ethyl, allyl, benzyl, phenyl, 3-morphinoethyl, and methoxyethyl groups were used, the reaction proceeded smoothly to afford the corresponding indenoisoquinoline derivatives in good yields (**3a–3g**). Even the reaction of *N*-unprotected 2-iodobenzamide and indandione worked well to afford the desired indenoisoquinoline (**3a'**). Further, compounds with electron-withdrawing substituents such as nitro, chloro, and bromo groups on the iodobenzamide moiety also worked well in affording the desired products (**3h–3j**). The X-ray structure of **3j** is presented as Figure 3. It is noteworthy that the yield of the desired product obtained in the case of a nitro substituent was superior to any other substituent. On the other hand, electron-donating groups such as methoxy, methylenedioxy furnished the desired indeno[1,2-*c*]isoquinoline derivatives in good to moderate yields (**3k–3o**).

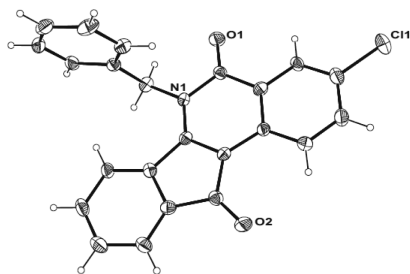
A literature survey indicated that most of the bioactive compounds possess a dimethoxy or a methylenedioxy group on the indenone moiety. Hence, we examined the reactions of dimethoxy and methylenedioxy-substituted indandiones with various 2-iodobenzamide derivatives (Table 3).

When 2-iodobenzamides bearing electron-withdrawing substrates such as nitro or bromo groups (**3r**, **3s**, and **3z**) were

Table 2. Scope of the Reaction of Various Indenoisoquinoline Derivatives

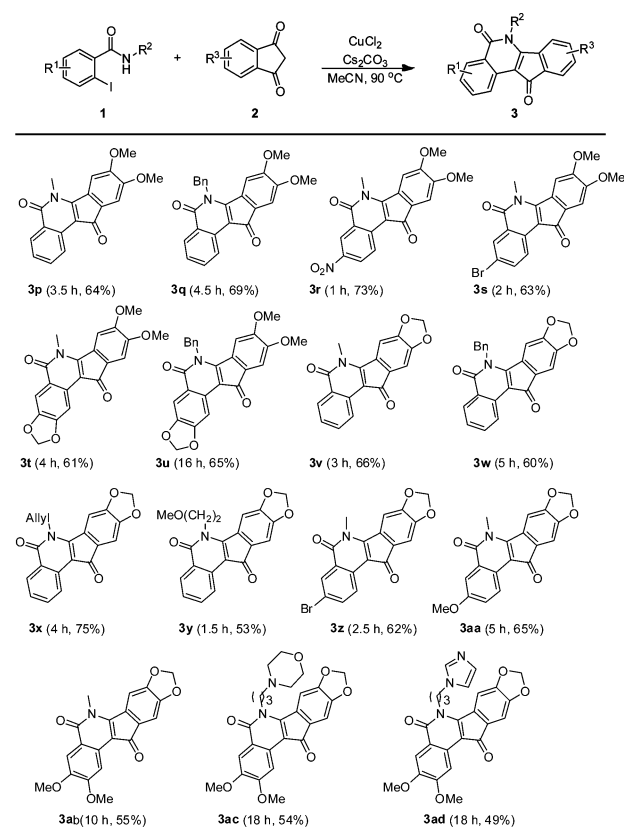


<sup>a</sup>Reaction conditions: **1** (1 mmol), **2** (1.5 mmol), CuCl<sub>2</sub> (5 mol %), Cs<sub>2</sub>CO<sub>3</sub> (1.2 mmol), MeCN (10–15 mL), 90 °C. <sup>b</sup>Isolated yields.

Figure 3. X-ray structure of **3j**.

used, the reactions proceeded faster than when unsubstituted benzamides (**3p**, **3q**, **3v**, and **3w**) were used, but longer reaction times were needed for benzamides with electron-donating groups like methoxy, dimethoxy, and methylenedioxy groups (**3t**, **3u**, and **3aa–3ad**). Moreover, the yields of the desired products were more or less similar in almost all substrates containing *N*-methyl and *N*-benzyl substitutions, irrespective of the electronic effect on benzamide rings. However, when benzamide substrates having an *N*-morphinopropyl or *N*-imidazopropyl group were used, the desired product was produced in 54% and 49% yields, respectively (**3ac** and **3ad**). Using the above developed methodology, we were able to synthesize a series of clinically tested anticancer agents such as NSC 314622 (**3ab**), LMP-400 (**3ac**), and LMP-776 (**3ad**) in moderate yields. The solubility of some compounds (**3h**, **3r**, **3s**, **3y**, **3z**, **3aa**, **3ac**, and **3ad**) were extremely poor in deuterated solvents such as CDCl<sub>3</sub>, D<sub>2</sub>O, acetonitrile-*d*<sub>3</sub>, acetone-*d*<sub>6</sub>, acetic acid-*d*<sub>4</sub>, MeOD, and DMSO-*d*<sub>6</sub>, which made it difficult to

Table 3. Synthesis of Various Indenoisoquinolines from Various 2-Iodobenzamide Derivatives and 3,4-Dimethoxyindan-1,3-diones/3,4-methylenedioxy-1,3-diones

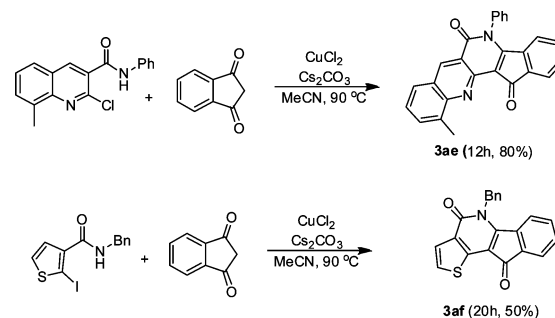


<sup>a</sup>Reaction conditions: **1** (1 mmol), **2a** (1.5 mmol), CuCl<sub>2</sub> (5 mol %), Cs<sub>2</sub>CO<sub>3</sub> (1.2 mmol), MeCN (10–15 mL), 90 °C. <sup>b</sup>Isolated yields.

obtain high-quality <sup>1</sup>H spectra. However, the solubility could be greatly improved by adding few drops of trifluoroacetic acid-*d* in the tube sample, making it a convenient way for recording <sup>13</sup>C spectra of these compounds.

As shown in Scheme 2, we introduced a heterocycle containing ortho halo amide derivatives such as 2-chloro-8-

Scheme 2. Synthesis of Heterocyclic Fused Indenopyridone Derivatives



methyl-*N*-phenylquinoline-3-carboxamide and *N*-benzyl-2-iodothiophene-3-carboxamide in the present protocol instead of an benzamide component. It is interesting that under optimized reaction conditions, the former substrate provided the corresponding pentacyclic multi heterocyclic compound 11-methyl-5-phenyl-5*H*-benzo[*b*]indeno[1,2-*h*][1,6]naphthyrid-

ine-6,13-dione (**3ae**) in high yield. The latter substrate *N*-benzyl-2-iodothiophene-3-carboxamide afforded the tetracyclic compound 5-benzyl-4*H*-indeno[1,2-*b*]thieno[2,3-*d*]pyridine-4,10(5*H*)-dione (**3af**) in moderate yield.

To further extend the scope of this methodology for the synthesis of fused indenoisoquinoline derivatives, we examined the reaction of 2-iodo-*N*-(2-iodobenzyl)benzamide and 1,3-indandione using the developed reaction conditions, with 6-(2-iodobenzyl)-5*H*-indeno[1,2-*c*]isoquinoline-5,11(6*H*)-dione (**3ag**) being produced, which was further converted into the corresponding azepine-fused indenoisoquinoline derivative 1*H*-6*a*-azabenz[*a*]benzo[5,6]-cyclohepta[1,2,3,4-*def*]fluorene-1,6(7*H*)-dione (**4a**) through a Heck reaction, as shown in Scheme 3 (the X-ray structure is shown as Figure 4). Finally,

### Scheme 3. Synthesis of Fused Indenoisoquinoline Derivatives

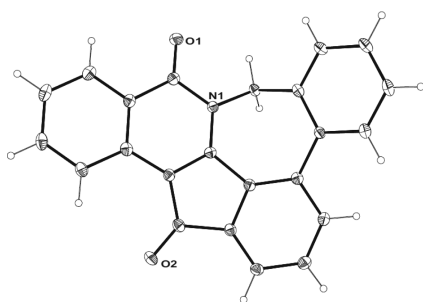
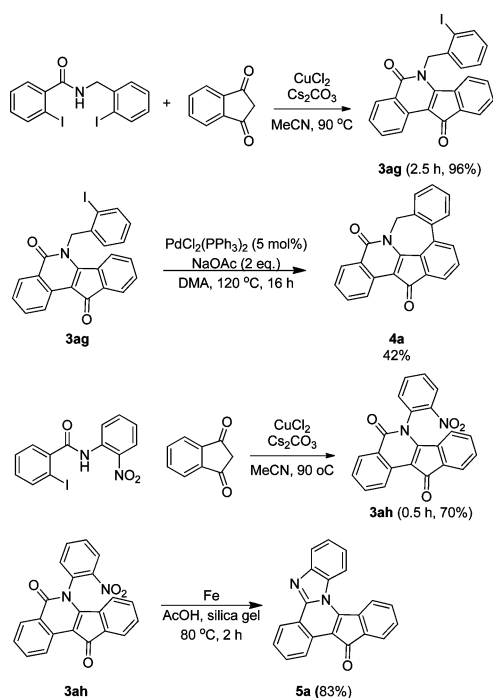


Figure 4. X-ray structure of **4a**.

we carried out the reaction of the 2-iodobenzamide substrate derived from 2-nitroaniline and 1,3-indandione under optimized reaction conditions, with 6-(2-nitrophenyl)-5*H*-indeno[1,2-*c*]isoquinoline-5,11(6*H*)-dione (**3ah**) being obtained in good yield. Further, this compound was subjected to the reductive cyclization in the presence of iron/acetic acid to afford 10*H*-benzo[4,5]imidazo[2,1-*a*]indeno[1,2-*c*]isoquinolin-10-one (**5a**) in high yield.

## CONCLUSION

In summary, we report the successful development of a short and efficient route for the synthesis of bioactive indenoisoquinoline derivatives by using a copper(II)-catalyzed tandem reaction under mild conditions. A wide variety of benzamide derivatives and indandiones were used to furnish indenoisoquinoline derivatives in moderate to good yields. In addition, using the developed procedures, we were able to synthesize clinically active Top1 inhibitors such as NSC 314622, LMP-400 and LMP-776 in a single step. Further, the current protocol was successfully extended to the synthesis of other fused indenoisoquinoline cores, thus making them available for use in additional SAR studies.

## EXPERIMENTAL SECTION

**General Information.** Reagents and solvents were purchased from various commercial sources and were used directly without any further purification, unless otherwise stated. Column chromatography was performed using 63–200 mesh silica gel. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded at 400/500/600 and 100/125/150 MHz, respectively. Chemical shifts are reported in parts per million ( $\delta$ ) using TMS and chloroform as internal standards, and coupling constants are expressed in hertz. Melting points were recorded using an electrothermal capillary melting point apparatus and are uncorrected. HRMS spectra were recorded using ESI-TOF or EI<sup>+</sup> mode. The starting 2-iodobenzamide derivatives **1** and indandione derivatives **2** were all synthesized following previously reported methods from 2-iodobenzoyl chlorides<sup>17</sup> and benzaldehydes,<sup>18</sup> respectively.

**General Procedure for Indenoisoquinoline 3.** 2-Iodobenzamide **1** (1 mmol), indandione **2** (1.5 mmol), and Cs<sub>2</sub>CO<sub>3</sub> (0.39 g, 1.2 mmol) were added to a 50 mL round-bottom flask equipped with a magnetic stir bar, and 10–15 mL of acetonitrile was added. The mixture was heated to 90 °C for 5 min, and then CuCl<sub>2</sub> (0.0085 g, 0.05 mmol) was added and reacted for the time indicated. The progress of the reaction was monitored by TLC for disappearance of **1**. After the reaction was completed, it was brought back to r.t., 1–2 mL of brine was added, and the acetonitrile was removed under reduced pressure. More iced brine was added, and the indenoisoquinoline was solidified. If the crude was sticky oil, adding a moderate amount of acetone or EA was acceptable to assist solidification. The precipitation (fine power) was then filtered by gravity filtration, and the resulting solid was washed thoroughly with iced water and then dried in 60–100 °C ovens to yield the desired product. In a few cases, the solids were mixtures of the products and unconsumed amides. In such cases, the crude products were washed with EA/hexane or acetone to yield the pure products.

**General Procedure for 1*H*-6*a*-Azabenz[*a*]benzo[5,6]-cyclohepta[1,2,3,4-*def*]fluorene-1,6(7*H*)-dione 4a.** Indenoisoquinoline **3ag** (0.116 g, 0.25 mmol), PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> (0.009 g, 0.0125  $\mu$ mol), and NaOAc (0.041 g, 0.5 mmol) were added to a 10 mL round-bottom flask under N<sub>2</sub> atmosphere, and then 4 mL of DMA was added and heated to 120 °C for 16 h. After the reaction was completed, the mixture was purified by column chromatography using EA/hexane as the eluent to yield the pure product **4a** as a red solid (0.035 g, 42%).

**General Procedure for 10*H*-Benzo[4,5]imidazo[2,1-*a*]indeno[1,2-*c*]isoquinolin-10-one 5a.** A mixture of indenoisoquinoline **3ah** (0.092 g, 0.25 mmol), Fe powder (0.07 g, 1.25 mmol), and AcOH (4 mL) were heated to 80 °C for 2 h. After the reaction was completed, the mixture was filtered through a Celite pad and washed with EA. The eluent was evaporated, and the solid collected was then washed with EA to yield the desired product **5a** as a red solid (0.066 g, 83%).

**Spectral Data.** 6-Methyl-5*H*-indeno[1,2-*c*]isoquinoline-5,11(6*H*)-dione (**3a**).<sup>11</sup> Yield: 199 mg, 76%. Red solid. Mp: 240–242 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  8.69 (d, *J* = 8.0 Hz, 1H), 8.36 (d, *J* = 8.2 Hz, 1H), 7.75–7.71 (m, 1H), 7.68–7.63 (m, 2H), 7.49–7.41 (m, 3H), 4.08 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  190.7, 163.7, 156.3, 137.9, 135.4, 134.1, 133.3, 132.4, 131.3, 128.8, 127.4, 123.7, 123.6, 123.5, 123.0, 108.6, 32.5; HRMS (ESI) *m/z* calcd for C<sub>17</sub>H<sub>12</sub>NO<sub>2</sub> (M<sup>+</sup> + H) 262.0868, found 262.0869.

**5H-Indeno[1,2-*c*]isoquinoline-5,11(6H)-dione (3a').** Yield: 138 mg, 56%. Orange solid. Mp: >350 °C. <sup>1</sup>H NMR (400 MHz, (CD<sub>3</sub>)<sub>2</sub>SO) δ 8.39 (d, *J* = 8.0 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.87–7.73 (m, 2H), 7.54–7.41 (m, 4H); <sup>13</sup>C NMR (100 MHz, (CD<sub>3</sub>)<sub>2</sub>SO) δ 190.2, 164.6, 157.7, 137.6, 135.1, 134.1, 133.6, 131.8, 128.3, 126.7, 124.5, 122.9, 122.5, 121.2, 105.9; HRMS (ESI) *m/z* calcd for C<sub>16</sub>H<sub>10</sub>NO<sub>2</sub> (M<sup>+</sup> + H) 248.0706, found 248.0705.

**6-Ethyl-5H-indeno[1,2-*c*]isoquinoline-5,11(6H)-dione (3b).<sup>1b</sup>** Yield: 177 mg, 64%. Brown solid. Mp: 184–186 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.70 (d, *J* = 8.1 Hz, 1H), 8.34 (d, *J* = 8.1 Hz, 1H), 7.74–7.70 (m, 1H), 7.63 (d, *J* = 6.7 Hz, 1H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.48–7.38 (m, 3H), 4.60 (q, *J* = 7.1 Hz, 2H), 1.55 (t, *J* = 7.1 Hz, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 190.7, 163.5, 155.7, 137.3, 135.5, 134.0, 133.4, 132.5, 131.2, 128.6, 127.4, 123.8, 123.7, 123.5, 122.7, 108.8, 40.2, 14.7; HRMS (ESI) *m/z* calcd for C<sub>18</sub>H<sub>14</sub>NO<sub>2</sub> (M<sup>+</sup> + H) 276.1025, found 276.1026.

**6-Allyl-5H-indeno[1,2-*c*]isoquinoline-5,11(6H)-dione (3c).<sup>8d</sup>** Yield: 187 mg, 65%. Red solid. Mp: 160–162 °C. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 8.68 (d, *J* = 8.0 Hz, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 7.73–7.70 (m, 1H), 7.58 (d, *J* = 6.2 Hz, 1H), 7.47–7.44 (m, 2H), 7.40–7.33 (m, 2H), 6.14–6.08 (m, 1H), 5.30 (d, *J* = 10.4 Hz, 1H), 5.20–5.16 (m, 3H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 190.7, 163.3, 156.0, 137.1, 135.3, 134.1, 133.3, 132.5, 131.6, 131.1, 128.8, 127.4, 123.7, 123.6, 123.3, 123.1, 117.6, 108.8, 46.6; HRMS (ESI) *m/z* calcd for C<sub>19</sub>H<sub>14</sub>NO<sub>2</sub> (M<sup>+</sup> + H) 288.1025, found 288.1024.

**6-Benzyl-5H-indeno[1,2-*c*]isoquinoline-5,11(6H)-dione (3d).<sup>12b</sup>** Yield: 202 mg, 61%. Orange solid. Mp: 208–210 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.76 (d, *J* = 8.1 Hz, 1H), 8.38 (d, *J* = 8.2 Hz, 1H), 7.79–7.75 (m, 1H), 7.62–7.60 (d, *J* = 6.8 Hz, 1H), 7.51–7.48 (m, 1H), 7.37–7.23 (m, 8H), 5.80 (s, 2H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub> + CF<sub>3</sub>CO<sub>2</sub>D) δ 191.5, 164.7, 156.3, 137.0, 135.0, 134.9, 133.9, 132.8, 131.5, 129.4, 128.9, 128.1, 125.9, 123.9, 123.4, 109.9, 48.9; HRMS (ESI) *m/z* calcd for C<sub>23</sub>H<sub>16</sub>NO<sub>2</sub> (M<sup>+</sup> + H) 338.1181, found 338.1183.

**6-Phenyl-5H-indeno[1,2-*c*]isoquinoline-5,11(6H)-dione (3e).** Yield: 220 mg, 68%. Red solid. Mp: 242–244 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.74 (d, *J* = 7.9 Hz, 1H), 8.37 (d, *J* = 8.1 Hz, 1H), 7.80 (m, 1H), 7.65–7.64 (m, 3H), 7.56–7.44 (m, 4H), 7.26–7.21 (m, 1H), 7.01–6.98 (m, 1H), 5.49 (d, *J* = 7.5 Hz, 1H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 190.8, 163.8, 155.5, 137.7, 137.3, 135.0, 134.4, 132.9, 132.9, 130.9, 130.3, 128.9, 128.9, 127.5, 124.2, 123.9, 123.0, 122.6, 108.4; HRMS (ESI) *m/z* calcd for C<sub>22</sub>H<sub>14</sub>NO<sub>2</sub> (M<sup>+</sup> + H) 324.1025, found 324.1027.

**6-(2-Morpholinoethyl)-5H-indeno[1,2-*c*]isoquinoline-5,11(6H)-dione (3f).<sup>19</sup>** Yield: 224 mg, 62%. Pale brown solid. Mp: 192–194 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.71 (d, *J* = 8.2 Hz, 1H), 8.33 (d, *J* = 8.0 Hz, 1H), 7.75–7.68 (m, 2H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.49–7.44 (m, 2H), 7.42–7.39 (m, 1H), 4.69 (t, *J* = 7.6 Hz, 2H), 3.74 (t, *J* = 4.6 Hz, 4H), 2.82 (t, *J* = 7.6 Hz, 2H), 2.62 (t, *J* = 4.6 Hz, 4H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 190.6, 163.5, 155.8, 137.4, 135.4, 134.1, 133.5, 132.5, 131.2, 128.6, 127.5, 123.7, 123.6, 123.5, 122.6, 108.9, 67.2, 56.9, 54.2, 42.6; HRMS (ESI) *m/z* calcd for C<sub>22</sub>H<sub>21</sub>N<sub>2</sub>O<sub>3</sub> (M<sup>+</sup> + H) 361.1552, found 361.1553.

**6-(2-Methoxyethyl)-5H-indeno[1,2-*c*]isoquinoline-5,11(6H)-dione (3g).<sup>8d</sup>** Yield: 199 mg, 65%. Red solid. Mp: 184–186 °C. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 8.70 (d, *J* = 8.0 Hz, 1H), 8.33 (d, *J* = 8.3 Hz, 1H), 7.73–7.70 (m, 2H), 7.61 (d, *J* = 7.0 Hz, 1H), 7.47–7.42 (m, 2H), 7.38–7.36 (m, 1H), 4.71 (t, *J* = 6.4 Hz, 2H), 3.85 (t, *J* = 6.4 Hz, 2H), 3.38 (s, 3H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 190.8, 163.8, 156.4, 137.7, 135.3, 134.1, 133.3, 132.6, 131.1, 128.6, 127.4, 123.8, 123.6, 123.5, 123.3, 108.9, 70.1, 59.5, 44.8; HRMS (ESI) *m/z* calcd for C<sub>19</sub>H<sub>16</sub>NO<sub>3</sub> (M<sup>+</sup> + H) 306.1130, found 306.1130.

**6-Methyl-3-nitro-5H-indeno[1,2-*c*]isoquinoline-5,11(6H)-dione (3h).<sup>20</sup>** Yield: 261 mg, 85%. Red solid. Mp: >350 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub> + CF<sub>3</sub>CO<sub>2</sub>D) δ 9.21 (s, 1H), 8.86 (d, *J* = 8.9 Hz, 1H), 8.58 (d, *J* = 8.9 Hz, 1H), 7.80 (d, *J* = 7.1 Hz, 1H), 7.76 (d, *J* = 7.1 Hz, 1H), 7.62–7.54 (m, 2H), 4.19 (s, 3H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub> + CF<sub>3</sub>CO<sub>2</sub>D) δ 191.2, 163.9, 146.3, 137.0, 136.8, 135.0, 134.5, 133.0, 128.6, 125.3, 125.2, 124.8, 124.5, 123.0, 108.5, 33.5; HRMS (ESI) *m/z* calcd for C<sub>17</sub>H<sub>11</sub>N<sub>2</sub>O<sub>4</sub> (M<sup>+</sup> + H) 307.0719, found 307.0716.

**3-Bromo-6-methyl-5H-indeno[1,2-*c*]isoquinoline-5,11(6H)-dione (3i).<sup>20</sup>** Yield: 201 mg, 59%. Orange solid. Mp: 272–274 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.56 (d, *J* = 8.7 Hz, 1H), 8.50 (s, 1H), 7.80 (d, *J* = 8.6 Hz, 1H), 7.68–7.64 (m, 2H), 7.46–7.40 (m, 2H), 4.07 (s, 3H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub> + CF<sub>3</sub>CO<sub>2</sub>D) δ 191.7, 163.7, 156.4, 138.1, 137.3, 134.7, 134.3, 132.1, 131.3, 131.1, 125.4, 124.5, 124.4, 123.7, 122.0, 109.4, 33.4; HRMS (ESI) *m/z* calcd for C<sub>17</sub>H<sub>11</sub>BrNO<sub>2</sub> (M<sup>+</sup> + H) 339.9973, found 339.9970.

**6-Benzyl-3-chloro-5H-indeno[1,2-*c*]isoquinoline-5,11(6H)-dione (3j).** Yield: 249 mg, 67%. Orange solid. Mp: 261–263 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.70 (d, *J* = 8.5 Hz, 1H), 8.34 (s, 1H), 7.69 (d, *J* = 8.3 Hz, 1H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.37–7.21 (m, 8H), 5.79 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 190.5, 162.7, 156.3, 137.1, 135.3, 135.1, 134.8, 133.6, 131.3, 131.0, 129.4, 128.4, 128.0, 125.9, 125.5, 124.9, 123.6, 123.2, 108.6, 48.5; HRMS (ESI) *m/z* calcd for C<sub>23</sub>H<sub>15</sub>ClNO<sub>2</sub> (M<sup>+</sup> + H) 372.0791, found 372.0789.

**3-Methoxy-6-methyl-5H-indeno[1,2-*c*]isoquinoline-5,11(6H)-dione (3k).** Yield: 187 mg, 64%. Brown solid. Mp: 228–230 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.59 (d, *J* = 8.4 Hz, 1H), 7.74 (s, 1H), 7.64–7.55 (m, 2H), 7.41–7.33 (m, 3H), 4.06 (s, 3H), 3.93 (s, 3H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 190.8, 163.4, 159.2, 154.0, 138.3, 135.3, 133.3, 130.8, 126.5, 125.4, 125.1, 124.4, 123.5, 122.5, 109.0, 108.8, 55.8, 32.6; HRMS (ESI) *m/z* calcd for C<sub>18</sub>H<sub>14</sub>NO<sub>3</sub> (M<sup>+</sup> + H) 292.0974, found 292.0973.

**2,3-Dimethoxy-6-methyl-5H-indeno[1,2-*c*]isoquinoline-5,11(6H)-dione (3l).<sup>10</sup>** Yield: 171 mg, 53%. Red solid. Mp: 281–283 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.10 (s, 1H), 7.70 (s, 1H), 7.62–7.58 (m, 2H), 7.43–7.34 (m, 2H), 4.07 (s, 3H), 4.05 (s, 3H), 4.00 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 190.9, 162.8, 155.1, 154.8, 149.7, 138.2, 135.4, 133.3, 130.9, 128.1, 123.4, 122.7, 117.9, 108.5, 103.7, 56.5, 56.3, 32.5; HRMS (ESI) *m/z* calcd for C<sub>19</sub>H<sub>16</sub>NO<sub>4</sub> (M<sup>+</sup> + H) 322.1079, found 322.1079.

**6-Benzyl-2,3-dimethoxy-5H-indeno[1,2-*c*]isoquinoline-5,11(6H)-dione (3m).<sup>12b</sup>** Yield: 243 mg, 61%. Brown solid. Mp: 289–290 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.18 (s, 1H), 7.73 (s, 1H), 7.56 (d, *J* = 6.6 Hz, 1H), 7.37–7.33 (m, 2H), 7.28–7.22 (m, 6H), 5.79 (s, 2H), 4.09 (s, 3H), 3.99 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 191.1, 162.9, 155.3, 154.9, 149.8, 137.6, 135.8, 135.3, 133.4, 130.7, 129.3, 128.4, 127.8, 126.0, 123.2, 122.7, 118.0, 108.9, 108.7, 103.8, 56.6, 56.3, 48.3; HRMS (ESI) *m/z* calcd for C<sub>25</sub>H<sub>20</sub>NO<sub>4</sub> (M<sup>+</sup> + H) 398.1392, found 398.1390.

**6-Methyl-5H-[1,3]dioxolo[4,5-*g*]indeno[1,2-*c*]isoquinoline-5,11(6H)-dione (3n).** Yield: 220 mg, 72%. Red solid. Mp: 327–329 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.11 (s, 1H), 7.69 (s, 1H), 7.63–7.60 (m, 2H), 7.44–7.35 (m, 2H), 6.10 (s, 2H), 4.04 (s, 3H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub> + CF<sub>3</sub>CO<sub>2</sub>D) δ 192.1, 165.4, 154.6, 154.5, 149.0, 137.5, 134.7, 134.2, 131.6, 130.7, 124.4, 123.3, 118.9, 110.3, 106.1, 102.6, 101.6, 33.4; HRMS (ESI) *m/z* calcd for C<sub>18</sub>H<sub>12</sub>NO<sub>4</sub> (M<sup>+</sup> + H) 306.0766, found 306.0765.

**6-Benzyl-5H-[1,3]dioxolo[4,5-*g*]indeno[1,2-*c*]isoquinoline-5,11(6H)-dione (3o).** Yield: 256 mg, 67%. Brown solid. Mp: 302–304 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.17 (s, 1H), 7.70 (s, 1H), 7.57 (d, *J* = 6.4 Hz, 1H), 7.35–7.33 (m, 2H), 7.26–7.21 (m, 6H), 6.11 (s, 2H), 5.76 (s, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 190.8, 162.8, 154.9, 153.7, 148.3, 137.3, 135.7, 135.2, 133.5, 130.8, 130.2, 129.3, 128.3, 127.9, 125.9, 123.4, 122.8, 119.6, 109.1, 106.8, 102.2, 102.0, 48.3; HRMS (ESI) *m/z* calcd for C<sub>24</sub>H<sub>16</sub>NO<sub>4</sub> (M<sup>+</sup> + H) 382.1079, found 382.1079.

**8,9-Dimethoxy-6-methyl-5H-indeno[1,2-*c*]isoquinoline-5,11(6H)-dione (3p).** Yield: 206 mg, 64%. Brown solid. Mp: 326–328 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.59 (d, *J* = 8.0 Hz, 1H), 8.31 (d, *J* = 8.4 Hz, 1H), 7.70–7.66 (m, 1H), 7.42–7.39 (m, 1H), 7.22 (s, 1H), 7.18 (s, 1H), 4.03 (s, 3H), 4.00 (s, 3H), 3.97 (s, 3H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub> + CF<sub>3</sub>CO<sub>2</sub>D) δ 192.7, 156.1, 152.6, 151.2, 135.2, 132.8, 131.4, 128.6, 128.4, 127.8, 123.3, 122.5, 108.9, 108.8, 57.0, 56.7, 33.2; HRMS (ESI) *m/z* calcd for C<sub>19</sub>H<sub>16</sub>NO<sub>4</sub> (M<sup>+</sup> + H) 322.1079, found 322.1078.

**6-Benzyl-8,9-dimethoxy-5H-indeno[1,2-*c*]isoquinoline-5,11(6H)-dione (3q).<sup>12b</sup>** Yield: 274 mg, 69%. Brown solid. Mp: 272–274 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.68 (d, *J* = 8.1 Hz, 1H), 8.38 (d, *J* = 8.1 Hz, 1H), 7.77–7.73 (m, 1H), 7.49–7.45 (m, 1H), 7.40–7.36 (m, 2H),

7.31 (d,  $J = 7.1$  Hz, 1H), 7.25 (d,  $J = 7.5$  Hz, 2H), 7.17 (s, 1H), 6.78 (s, 1H), 5.81 (s, 1H), 3.93 (s, 3H), 3.61 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  190.6, 163.8, 156.3, 151.9, 150.6, 135.9, 134.1, 132.9, 130.3, 129.4, 128.9, 128.5, 127.9, 126.8, 125.5, 123.2, 123.0, 108.4, 108.0, 107.4, 56.5, 56.4, 48.2; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{25}\text{H}_{20}\text{NO}_4$  ( $\text{M}^+ + \text{H}$ ) 398.1392, found 398.1391.

**8,9-Dimethoxy-6-methyl-3-nitro-5H-indeno[1,2-*c*]isoquinoline-5,11(6*H*)-dione (3r).** Yield: 268 mg, 73%. Brown solid. Mp: 345–347 °C (decompose).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3 + \text{CF}_3\text{CO}_2\text{D}$ )  $\delta$  9.11 (s, 1H), 8.69 (d,  $J = 9.0$  Hz, 1H), 8.46 (d,  $J = 9.0$  Hz, 1H), 7.33 (s, 1H), 7.24 (s, 1H), 4.09 (s, 3H), 4.03 (s, 3H), 4.00 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3 + \text{CF}_3\text{CO}_2\text{D}$ )  $\delta$  190.7, 163.7, 159.5, 152.8, 152.3, 145.7, 137.0, 130.1, 129.0, 128.5, 125.4, 124.6, 122.0, 109.2, 108.6, 107.6, 57.0, 56.8, 33.2; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{15}\text{N}_2\text{O}_6$  ( $\text{M}^+ + \text{H}$ ) 367.0930, found 367.0926.

**3-Bromo-8,9-dimethoxy-6-methyl-5H-indeno[1,2-*c*]isoquinoline-5,11(6*H*)-dione (3s).** Yield: 251 mg, 63%. Brown solid. Mp: >350 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.47–8.44 (m, 2H), 7.75 (d,  $J = 8.3$  Hz, 1H), 7.22 (s, 1H), 7.17 (s, 1H), 4.02 (s, 3H), 4.00 (s, 3H), 3.97 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3 + \text{CF}_3\text{CO}_2\text{D}$ )  $\delta$  190.7, 163.0, 156.2, 152.4, 151.3, 137.5, 131.1, 128.4, 124.8, 123.7, 120.8, 108.5, 108.1, 107.8, 56.9, 56.6, 32.8; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{14}\text{BrNO}_4$  ( $\text{M}^+ + \text{H}$ ) 399.0106, found 399.0109.

**8,9-Dimethoxy-6-methyl-5H-[1,3]dioxolo[4,5-*g*]indeno[1,2-*c*]isoquinoline-5,11(6*H*)-dione (3t).** Yield: 223 mg, 61%. Brown solid. Mp: 321–323 °C.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.03 (s, 1H), 7.66 (s, 1H), 7.21 (s, 1H), 7.15 (s, 1H), 6.08 (s, 2H), 4.01 (s, 3H), 3.99 (s, 3H), 3.96 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3 + \text{CF}_3\text{CO}_2\text{D}$ )  $\delta$  193.1, 155.2, 153.8, 152.8, 150.8, 149.2, 131.8, 131.4, 128.2, 125.2, 109.4, 108.9, 105.6, 102.8, 101.2, 56.9, 56.7, 33.5; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{20}\text{H}_{16}\text{NO}_6$  ( $\text{M}^+ + \text{H}$ ) 366.0978, found 366.0976.

**6-Benzyl-8,9-dimethoxy-5H-[1,3]dioxolo[4,5-*g*]indeno[1,2-*c*]isoquinoline-5,11(6*H*)-dione (3u).** Yield: 287 mg, 65%. Brown solid. Mp: 315–317 °C. (500 MHz,  $\text{CDCl}_3 + \text{CF}_3\text{CO}_2\text{D}$ )  $\delta$  8.03 (s, 1H), 7.63 (s, 1H), 7.39–7.36 (m, 2H), 7.33–7.30 (m, 1H), 7.24 (s, 1H), 7.17 (d,  $J = 7.4$  Hz, 2H), 6.73 (s, 1H), 6.15 (s, 2H), 5.82 (s, 2H), 3.91 (s, 3H), 3.59 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3 + \text{CF}_3\text{CO}_2\text{D}$ )  $\delta$  192.9, 164.4, 155.1, 154.7, 152.7, 150.5, 149.0, 134.6, 131.5, 130.8, 129.7, 128.5, 127.9, 125.3, 118.3, 110.3, 108.9, 106.2, 102.7, 101.3, 56.6, 56.5, 49.3; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{26}\text{H}_{20}\text{NO}_6$  ( $\text{M}^+ + \text{H}$ ) 442.1291, found 442.1292.

**6-Methyl-5H-[1,3]dioxolo[4',5':5,6]indeno[1,2-*c*]isoquinoline-5,11(6*H*)-dione (3v).** Yield: 202 mg, 66%. Brown solid. Mp: 308–310 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.59 (d,  $J = 7.8$  Hz, 1H), 8.32 (d,  $J = 8.2$  Hz, 1H), 7.71–7.67 (m, 1H), 7.43–7.39 (m, 1H), 7.19 (s, 1H), 7.13 (s, 1H), 6.10 (s, 2H), 4.00 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3 + \text{CF}_3\text{CO}_2\text{D}$ )  $\delta$  191.1, 155.5, 152.3, 149.9, 135.1, 132.9, 132.6, 129.9, 128.6, 127.8, 123.3, 122.3, 109.5, 106.5, 106.2, 103.3, 33.1; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{12}\text{NO}_4$  ( $\text{M}^+ + \text{H}$ ) 306.0766, found 306.0763.

**6-Benzyl-5H-[1,3]dioxolo[4',5':5,6]indeno[1,2-*c*]isoquinoline-5,12(6*H*)-dione (3w).** Yield: 229 mg, 60%. Brown solid. Mp: 297–299 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.66 (d,  $J = 8.5$  Hz, 1H), 8.34 (d,  $J = 8.0$  Hz, 1H), 7.75–7.71 (m, 1H), 7.46–7.42 (m, 1H), 7.38–7.34 (m, 2H), 7.30–7.20 (m, 3H), 7.09 (s, 1H), 6.80 (s, 1H), 6.00 (s, 2H), 5.73 (s, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3 + \text{CF}_3\text{CO}_2\text{D}$ )  $\delta$  191.0, 155.3, 152.3, 149.8, 135.2, 132.8, 132.3, 130.7, 130.0, 128.7, 127.8, 123.4, 122.5, 118.1, 109.6, 106.3, 106.2, 103.1, 47.2; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{24}\text{H}_{16}\text{NO}_4$  ( $\text{M}^+ + \text{H}$ ) 382.1079, found 382.1079.

**6-Allyl-5H-[1,3]dioxolo[4',5':5,6]indeno[1,2-*c*]isoquinoline-5,12(6*H*)-dione (3x).** Yield: 249 mg, 75%. Brown solid. Mp: 242–244 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.62 (d,  $J = 8.5$  Hz, 1H), 8.32 (d,  $J = 8.0$  Hz, 1H), 7.72–7.69 (m, 1H), 7.44–7.41 (m, 1H), 7.11 (s, 1H), 7.00 (s, 1H), 6.18–6.03 (m, 3H), 5.33 (d,  $J = 10.4$  Hz, 1H), 5.20–5.11 (m, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  189.5, 163.3, 151.5, 149.3, 134.1, 132.7, 132.3, 131.5, 130.7, 128.8, 126.9, 123.3, 123.0, 117.6, 105.8, 105.6, 103.9, 102.8, 46.3; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{20}\text{H}_{14}\text{NO}_4$  ( $\text{M}^+ + \text{H}$ ) 322.0923, found 322.0923.

**6-(2-Methoxyethyl)-5H-[1,3]dioxolo[4',5':5,6]indeno[1,2-*c*]isoquinoline-5,12(6*H*)-dione (3y).** Yield: 186 mg, 53%. Brown solid. Mp: 205–207 °C (decompose).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.66 (d,  $J = 8.4$  Hz, 1H), 8.32 (d,  $J = 7.7$  Hz, 1H), 7.73–7.70 (m, 1H),

7.46–7.42 (m, 1H), 7.35 (s, 1H), 7.14 (s, 1H), 6.13 (s, 2H), 4.66 (t,  $J = 5.9$  Hz, 2H), 3.87 (t,  $J = 6.2$  Hz, 2H), 3.40 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3 + \text{CF}_3\text{CO}_2\text{D}$ )  $\delta$  190.9, 155.4, 152.3, 149.7, 135.2, 132.8, 132.8, 130.1, 128.4, 127.7, 123.4, 109.8, 106.4, 106.1, 103.2, 70.0, 60.0, 45.0; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{20}\text{H}_{16}\text{NO}_5$  ( $\text{M}^+ + \text{H}$ ) 350.1028, found 350.1026.

**3-Bromo-6-methyl-5H-[1,3]dioxolo[4',5':5,6]indeno[1,2-*c*]isoquinoline-5,12(6*H*)-dione (3z).** Yield: 238 mg, 62%. Brown solid. Mp: 322–324 °C (decompose).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.48–8.45 (m, 2H), 7.76 (d,  $J = 9.8$  Hz, 1H); 7.19 (s, 1H), 7.13 (s, 1H), 6.11 (s, 2H), 4.00 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3 + \text{CF}_3\text{CO}_2\text{D}$ )  $\delta$  190.6, 163.9, 155.7, 152.4, 150.0, 138.1, 132.8, 131.2, 131.1, 130.0, 124.9, 123.7, 121.4, 108.8, 106.6, 106.2, 103.3, 33.2; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{11}\text{BrNO}_4$  ( $\text{M}^+ + \text{H}$ ) 383.9871, found 383.9866.

**3-Methoxy-6-methyl-5H-[1,3]dioxolo[4',5':5,6]indeno[1,2-*c*]isoquinoline-5,12(6*H*)-dione (3aa).** Yield: 218 mg, 65%. Brown solid. Mp: 286–288 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.51 (d,  $J = 8.8$  Hz, 1H); 7.7 (s, 1H), 7.31–7.26 (m, 2H), 7.13 (s, 1H), 7.09 (s, 1H), 6.08 (s, 2H), 3.99 (s, 3H), 3.91 (s, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3 + \text{CF}_3\text{CO}_2\text{D}$ )  $\delta$  192.2, 159.3, 153.2, 152.7, 149.6, 133.6, 129.4, 127.3, 126.4, 125.1, 108.2, 106.9, 106.1, 103.3, 55.9, 33.4; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{14}\text{NO}_5$  ( $\text{M}^+ + \text{H}$ ) 336.0872, found 336.0868.

**2,3-Dimethoxy-6-methyl-5H-[1,3]dioxolo[4',5':5,6]indeno[1,2-*c*]isoquinoline-5,12(6*H*)-dione (3ab).** Yield: 201 mg, 55%. Brown solid. Mp: 298–300 °C (decompose).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.00 (s, 1H), 7.66 (s, 1H), 7.14 (s, 1H), 7.08 (s, 1H), 6.09 (s, 2H), 4.05 (s, 3H), 3.99 (s, 3H), 3.99 (s, 3H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3 + \text{CF}_3\text{CO}_2\text{D}$ )  $\delta$  191.2, 156.0, 153.8, 152.4, 149.8, 149.6, 133.3, 129.8, 129.2, 116.8, 109.6, 108.0, 106.5, 105.9, 103.2, 103.0, 56.6, 56.3, 33.2; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{20}\text{H}_{16}\text{NO}_6$  ( $\text{M}^+ + \text{H}$ ) 366.0978, found 366.0978.

**2,3-Dimethoxy-6-(3-morpholinopropyl)-5H-[1,3]dioxolo[4',5':5,6]indeno[1,2-*c*]isoquinoline-5,12(6*H*)-dione (3ac).** Yield: 259 mg, 54%. Brown solid. Mp: 293–295 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.05 (s, 1H), 7.65 (s, 1H), 7.43 (s, 1H), 7.09 (s, 1H), 6.10 (s, 1H), 4.55–4.48 (m, 2H), 4.05 (s, 3H), 3.99 (s, 3H), 3.79–3.92 (m, 4H), 2.60–2.48 (m, 6H), 2.06–1.97 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3 + \text{CF}_3\text{CO}_2\text{D}$ )  $\delta$  191.2, 152.9, 152.5, 150.1, 150.0, 131.9, 129.6, 129.4, 116.3, 110.4, 107.5, 106.7, 104.8, 103.5, 103.2, 64.2, 56.7, 56.2, 55.5, 52.9, 42.0, 24.3; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{26}\text{H}_{27}\text{N}_2\text{O}_7$  ( $\text{M}^+ + \text{H}$ ) 479.1818, found 479.1820.

**6-(3-(1*H*-imidazol-1-yl)propyl)-2,3-dimethoxy-5H-[1,3]dioxolo[4',5':5,6]indeno[1,2-*c*]isoquinoline-5,12(6*H*)-dione (3ad).** Yield: 225 mg, 49%. Brown solid. Mp: 320–322 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.05 (s, 1H), 7.66 (s, 1H), 7.64–7.59 (m, 1H), 7.19–7.13 (m, 1H), 7.08 (s, 1H), 7.07–7.03 (m, 1H), 6.43 (s, 1H), 6.09 (s, 2H), 4.47 (t,  $J = 6.8$  Hz, 2H), 4.22 (t,  $J = 6.8$  Hz, 2H), 4.05 (s, 3H), 4.00 (s, 3H), 2.39–2.32 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3 + \text{CF}_3\text{CO}_2\text{D}$ )  $\delta$  191.8, 156.5, 153.1, 152.8, 150.1, 135.3, 132.2, 129.8, 129.6, 121.9, 121.0, 116.4, 110.5, 107.7, 107.1, 104.9, 103.6, 103.3, 56.7, 56.3, 47.5, 42.1, 30.3; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{25}\text{H}_{22}\text{N}_3\text{O}_6$  ( $\text{M}^+ + \text{H}$ ) 460.1509, found 460.1507.

**11-Methyl-5-phenyl-5H-benzo[*b*]indeno[1,2-*h*][1,6]-naphthyridine-6,13-dione (3ae).** Yield: 311 mg, 80%. Pale brown solid. Mp: >350 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  9.16 (s, 1H), 7.82 (d,  $J = 8.0$  Hz, 1H), 7.75 (d,  $J = 7.3$  Hz, 1H), 7.69–7.64 (m, 4H), 7.53–7.47 (m, 3H), 7.32–7.28 (m, 1H), 7.06–7.02 (m, 1H), 5.56 (d,  $J = 7.6$  Hz, 1H), 3.01 (s, 3H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3 + \text{CF}_3\text{CO}_2\text{D}$ )  $\delta$  189.8, 166.0, 160.7, 151.3, 143.0, 141.0, 138.1, 135.8, 135.6, 135.2, 135.1, 134.8, 132.1, 131.3, 130.5, 129.9, 128.0, 127.7, 127.0, 126.2, 125.3, 118.2, 99.7, 16.0; HRMS (ESI)  $m/z$  calcd for  $\text{C}_{26}\text{H}_{17}\text{N}_2\text{O}_2$  ( $\text{M}^+ + \text{H}$ ) 389.1290, found 389.1288.

**5-Benzyl-4*H*-indeno[1,2-*b*]thieno[2,3-*d*]pyridine-4,10(5*H*)-dione (3af).** Yield: 172 mg, 50%. Orange solid. Mp: 232–234 °C.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.94 (d,  $J = 5.2$  Hz, 1H), 7.86 (d,  $J = 5.2$  Hz, 1H), 7.37–7.22 (m, 7H), 5.81 (s, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  189.1, 159.5, 156.6, 140.3, 137.7, 136.8, 135.4, 134.9, 133.6, 131.1, 129.4, 128.8, 128.0, 126.0, 123.8, 123.2, 123.0, 110.2, 47.9; HRMS

(ESI)  $m/z$  calcd for  $C_{21}H_{14}NO_2S$  ( $M^+ + H$ ) 344.0745, found 344.0745.

**6-(2-Iodobenzyl)-5H-indeno[1,2-c]isoquinoline-5,11(6H)-dione (3ag).** Yield: 445 mg, 96%. Orange solid. Mp: 236–238 °C.  $^1H$  NMR (500 MHz,  $CDCl_3 + CF_3CO_2D$ )  $\delta$  8.74 (d,  $J = 8.1$  Hz, 1H), 8.37 (d,  $J = 8.1$  Hz, 1H), 7.97 (d,  $J = 7.9$  Hz, 1H), 7.83–7.80 (m, 1H), 7.59–7.53 (m, 2H), 7.32–7.21 (m, 3H), 7.03–7.00 (m, 1H), 6.96 (d,  $J = 7.4$  Hz, 1H), 6.74 (d,  $J = 7.8$  Hz, 1H), 5.65 (s, 2H);  $^{13}C$  NMR (125 MHz,  $CDCl_3 + CF_3CO_2D$ )  $\delta$  191.5, 164.4, 156.0, 140.2, 136.6, 135.1, 134.7, 134.1, 132.8, 131.5, 129.8, 129.3, 129.0, 128.2, 125.9, 124.0, 123.3, 123.0, 116.0, 113.7, 110.0, 96.7, 54.4; HRMS (ESI)  $m/z$  calcd for  $C_{23}H_{15}INO_2$  ( $M^+ + H$ ) 464.0147, found 464.0151.

**6-(2-Nitrophenyl)-5H-indeno[1,2-c]isoquinoline-5,11(6H)-dione (3ah).** Yield: 258 mg, 70%. Pale brown solid. Mp: 286–288 °C.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.75 (d,  $J = 8.1$  Hz, 1H), 8.40 (d,  $J = 7.8$  Hz, 1H), 8.32 (d,  $J = 8.2$  Hz, 1H), 7.94–7.86 (m, 3H), 7.82–7.79 (m, 1H), 7.61–7.58 (m, 2H), 7.53–7.49 (m, 1H), 7.04–7.00 (m, 1H), 5.57 (d,  $J = 7.1$  Hz, 1H);  $^{13}C$  NMR (125 MHz,  $CDCl_3 + CF_3CO_2D$ )  $\delta$  191.5, 154.6, 146.4, 137.7, 136.7, 135.6, 135.4, 134.4, 133.6, 133.1, 132.1, 131.8, 131.6, 131.2, 129.1, 128.3, 126.8, 124.5, 124.1, 124.0, 123.5, 121.2, 110.2; HRMS (ESI)  $m/z$  calcd for  $C_{22}H_{13}N_2O_4$  ( $M^+ + H$ ) 369.0875, found 369.0876.

**1H-6a-Azabenz[a]benzo[5,6]cyclohepta[1,2,3,4-def]fluorene-1,6(7H)-dione (4a).** Yield: 141 mg, 42%. Red solid. Mp: 276–278 °C.  $^1H$  NMR (400 MHz,  $CDCl_3 + (CD_3)_2SO$ )  $\delta$  8.46 (d,  $J = 8.1$  Hz, 1H), 8.13 (d,  $J = 7.9$  Hz, 1H), 7.57–7.53 (m, 1H), 7.30–7.27 (m, 2H), 7.08–7.00 (m, 4H), 6.88–6.85 (m, 2H), 5.55 (d,  $J = 7.4$  Hz, 1H);  $^{13}C$  NMR (100 MHz,  $CDCl_3 + (CD_3)_2SO$ )  $\delta$  190.4, 162.6, 155.9, 141.0, 136.6, 134.1, 133.8, 132.9, 132.5, 130.9, 130.5, 129.0, 128.3, 126.8, 124.2, 123.8, 123.1, 122.2, 121.9, 120.7, 118.7, 108.2; HRMS (ESI)  $m/z$  calcd for  $C_{23}H_{14}NO_2$  ( $M^+$ ) 336.1025, found 336.1026.

**10H-Benzo[4,5]imidazo[2,1-a]indeno[1,2-c]isoquinolin-10-one (5a).** Yield: 267 mg, 83%. Red solid. Mp: 286–288 °C.  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$  8.56 (d,  $J = 8.0$  Hz, 1H), 8.41 (d,  $J = 7.5$  Hz, 1H), 7.86 (d,  $J = 8.1$  Hz, 1H), 7.76–7.71 (m, 3H), 7.64 (d,  $J = 7.0$  Hz, 1H), 7.56–7.52 (m, 2H), 7.50–7.46 (m, 2H), 5.46 (s, 2H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$  189.5, 163.0, 137.2, 136.3, 135.7, 135.5, 134.1, 134.0, 132.9, 132.6, 132.2, 131.7, 131.6, 129.9, 129.5, 129.2, 128.6, 127.1, 124.7, 123.8, 122.8, 107.5, 47.9; HRMS (ESI)  $m/z$  calcd for  $C_{22}H_{13}N_2O$  ( $M^+$ ) 321.1028, found 321.1028.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02814.

$^1H$  and  $^{13}C$  NMR spectra for all products (PDF)

X-ray crystallography data for 3j (CIF)

X-ray crystallography data for 4a (CIF)

## ■ AUTHOR INFORMATION

### Corresponding Author

\*E-mail: cheyaocf@ntnu.edu.tw.

### ORCID

Ching-Fa Yao: 0000-0002-8692-5156

### Author Contributions

†These authors contributed equally.

### Notes

The authors declare no competing financial interest.

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