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Domino Oxidative Cyclization of 2-Aminoacetophenones for the One-Pot Synthesis of Tryptanthrin Derivatives

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A new CuI/DMSO-mediated oxidative domino process has been developed for the synthesis of tryptanthrin derivatives. This is the first example of the synthesis of tryptanthrin derivatives directly from 2-aminoaryl methyl ketones and isatoic anhydrides through copper-promoted oxidative functionalization.

Introduction

The direct C–H-bond functionalization of sp^3-CH_3 groups is a versatile synthetic strategy for the construction of C–C and C–N bonds.[1] It proceeds through the activation of sp^3- or sp^2-C–H bonds by a metal species, followed by oxidative addition.[2] Recently, much effort has been directed towards the development of sp^3-C–H-bond amidation through oxidative C–H/N–H cross-coupling reactions.[3] Recently, the use of Cu^I salts for oxidative C–H-bond functionalization has received much attention due to the low cost, negligible toxicity, ready availability, and broad substrate tolerance of these salts.[4]

The indolo[2,1-*b*]quinazoline core is found in many biologically active natural products, including the asperlicins, the benzomalvins, the circumdatins, tryptanthrin, phaitanthrins A–E, methylisatoid, candidine, etc. (Figure 1).[5] Compounds containing this moiety have been found to have a broad spectrum of biological activities.[5–7] Tryptanthrin, a naturally occurring indolo[2,1-*b*]quinazoline alkaloid, was isolated from the indigo plant *Strobilanthes cusia* (Acanthaceae).[8] It shows remarkable cytotoxicity against various cancer cell lines, including human breast carcinoma (MCF-7), lung carcinoma (NCI-H460), and central nervous system carcinoma (SF-268).[5] It also shows potent antimicrobial and antileishmanial activity.[9] Recently, tryptanthrin derivatives have been reported to act as potent antitubercular agents.[10]

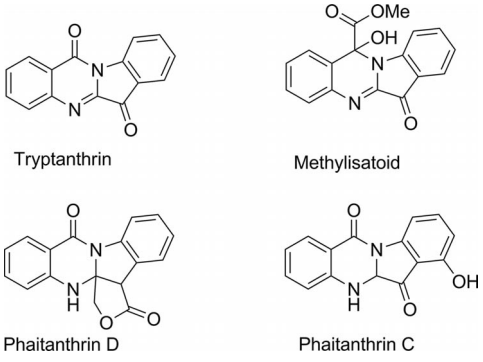
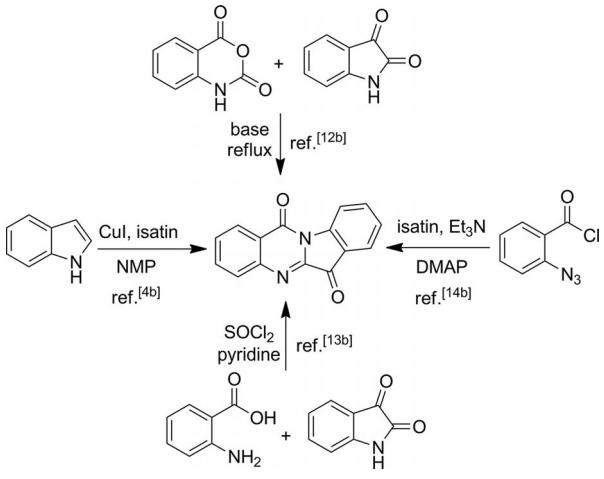


Figure 1. Biologically active quinazolinone natural products.

Due to the scarcity of natural tryptanthrin, and to its unique biological activity, several synthetic methods have been developed for the synthesis of tryptanthrin derivatives (Scheme 1).[11] The condensation of isatoic anhydride with



Scheme 1. Previous approaches. NMP = *N*-methylpyrrolidine; DMAP = 4-(dimethylamino)pyridine.

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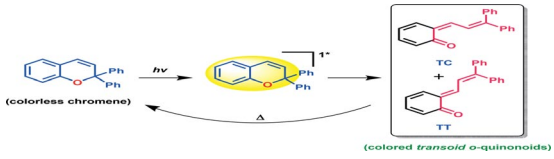
isatin in the presence of base under heating conditions is one of the more direct of these methods.[12] An alternative approach involves the coupling of *ortho*-aminobenzoic acid with isatin using $SOCl_2$.[13] Eguchi et al. reported the synthesis of tryptanthrin from 2-azidobenzoyl chloride through an intramolecular aza-Wittig reaction using triethylamine.[14] Bergman et al. reported the formation of tryptanthrin from isatin using $POCl_3$.[15] However, many of these methods involve step-by-step synthetic strategies. Therefore, the development of a one-pot strategy for the synthesis of tryptanthrin derivatives would be desirable, especially for the generation of diversified scaffolds.

Results and Discussion

Following on from our interest in quinazolinone alkaloids,[16] in this paper, we report a new strategy for the synthesis of tryptanthrin derivatives from acetophenone and isatoic anhydride using CuI/DMSO under aerobic conditions. We first prepared *N*-(2-acetylphenyl)-2-aminobenzamide (**A**) from isatoic anhydride (**1**) and 2-aminoacetophenone (**2**) in a single step (see Supporting Information). Substrate (**A**) was then heated at 100 °C in the presence of CuI (10 mol-%) in DMSO under pure oxygen (Scheme 2).



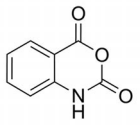
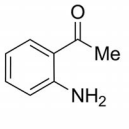
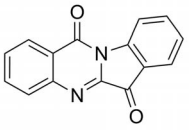
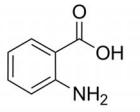
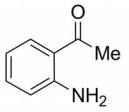
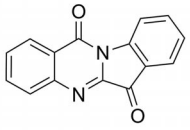
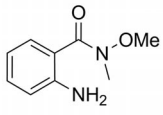
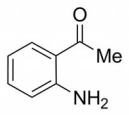
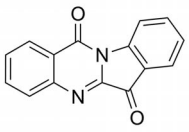
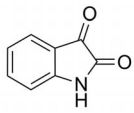
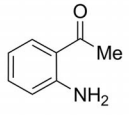
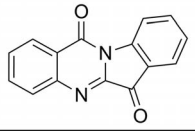
Scheme 2. Oxidative cyclization of **A** to give tryptanthrin.

The expected product, tryptanthrin (**3a**), was obtained in only 40% yield after 12 h. It was purified by flash column chromatography on silica gel, and characterized by NMR and IR spectroscopy and mass spectrometry.

Encouraged by this result, we next tried to develop a one-step synthesis of tryptanthrin from commercially available precursors. Accordingly, we carried out the condensation of 2-aminoacetophenone (**2**) with different substrates, including isatoic anhydride, 2-aminobenzoic acid, 2-amino-*N*-methoxy-*N*-methylbenzamide, and isatin, under similar conditions (Table 1).

The condensation of 2-aminoacetophenone (**2**) with isatoic anhydride gave the desired product (i.e., **3a**) in 40% yield (Table 1, Entry a). To optimize the conditions, various catalysts were then screened, and the results are presented in Table 2. None of the catalysts tested gave the desired product except for copper salts and iodine (Table 2, Entries a–d). Of the various copper salts tested, CuI was found to be superior in terms of yield. Therefore, the reaction was tested with different amounts of CuI (Table 2, Entries h–j). Indeed, the yield was improved from 50 to 75% by increasing the amount of CuI to 1.5 equiv. (Table 2, Entry j). In the absence of a catalyst, the reaction did not give the desired product. To our surprise, an I_2/DMSO system also gave the product (i.e., **3a**), albeit in low yield (Table 2, Entry k).

Table 1. Screening of substrates for the formation of **3a**.

Entry	Substrate	2-Aminoacetophenone (**2**)[a]	Product **3**	Time [h]	Yield [%]
a				10	40
b				16	20
c				12	30
d				12	35

[a] Reaction was carried out using CuI (10 mol-%) in DMSO at 100 °C.

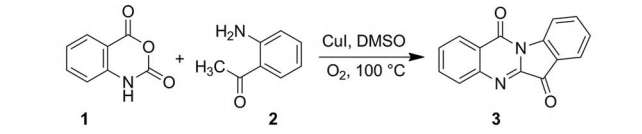
Table 2. Optimizing the conditions for the formation of **3a**.[a]

Entry	Catalyst	Amount [mol-%]	Time [h]	Yield [%]
a	$AlCl_3$	10	10	0
b	$ZnCl_2$	10	12	0
c	$FeCl_3$	10	10	0
d	$InCl_3$	10	12	0
e	$Cu(OAc)_2$	10	12	25
f	CuOTf	10	10	20
g	$Cu(OTf)_2$	10	12	30
h	CuI	10	12	40
i	CuI	30	12	50
j	CuI	150	10	75
k	I_2	150	12	45

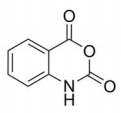
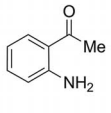
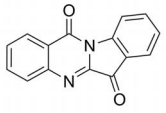
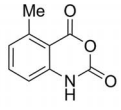
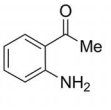
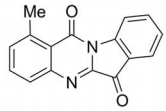
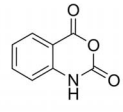
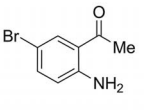
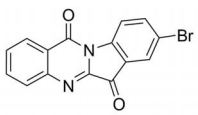
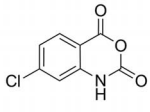
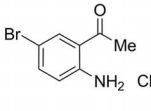
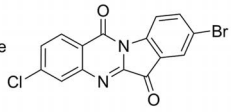
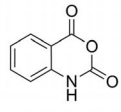
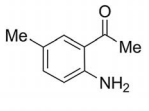
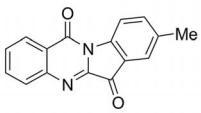
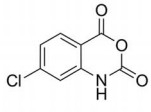
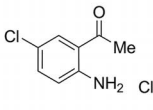
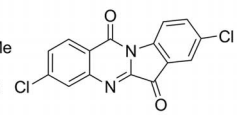
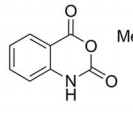
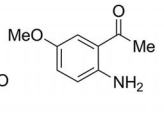
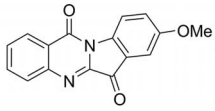
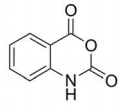
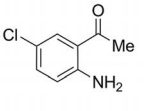
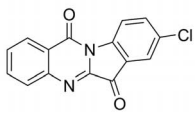
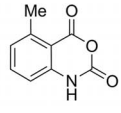
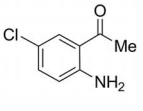
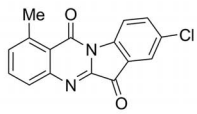
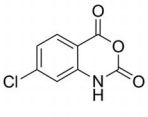
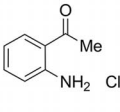
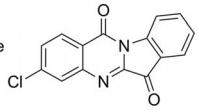
[a] A mixture of isatoic anhydride (**1**) (0.5 mmol), 2-aminoacetophenone (**2**) (0.6 mmol) and CuI (1.5 equiv.) in DMSO (5 mL) was stirred at 100 °C under oxygen.

To try to further improve the yield of **3a**, the reaction was carried out at different temperatures. The maximum conversion was achieved using 1.5 equiv. of CuI at 100 °C in DMSO (Table 2, Entry j). It is noteworthy that the product was obtained in low yield (35%) when the reaction was run under nitrogen. The scope of this process was further evaluated with respect to substituted isatoic anhydrides such as 6-methyl and 4-chloro derivatives, which were prepared according to a reported procedure.[17] In all cases, the corresponding tryptanthrin derivatives were obtained in good yields (Table 3). The method was also found to work well with 2-aminoaryl methyl ketones bearing different substituents on the aromatic ring (Table 3).

Table 3. Domino cyclization of isatoic anhydride (**1**) (0.5 mmol), 2-aminoacetophenone (**2**) (0.6 mmol) and CuI (1.5 equiv.) in DMSO (5 mL) at 100 °C under oxygen.

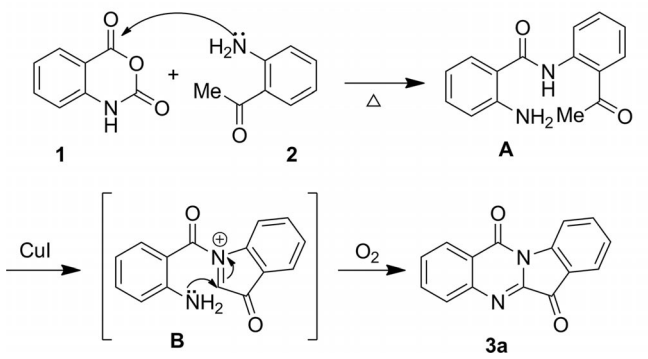


1 2 3

Entry	Isatoic anhydride	2-Aminoaceto-phenone	Product 3[a]	Time [h]	Yield [%][b]
a				10	75
b				10	65
c				14	70
d				14	68
e				10	62
f				12	62
g				10	60
h				12	63
i				12	60
j				12	62

[a] All the products were characterized by NMR spectroscopy and mass spectrometry. [b] Yield refers to pure products after chromatography.

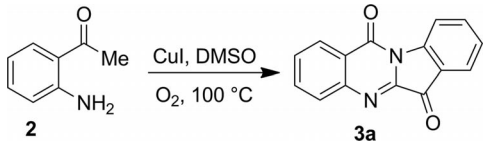
Based on the above results, we propose a possible mechanism for this reaction, as shown in Scheme 3. The reaction is proposed to proceed through the formation of amide **A**. Copper-mediated aerobic oxidation of **A** can generate acyliminium ion **B**.[4b] Subsequent cyclization of **B** followed by oxidative aromatization would give tryptanthrin **3** (Scheme 3).



1 2 A B 3a

Scheme 3. Possible reaction mechanism.

Finally, we attempted the synthesis of tryptanthrin from 2-aminoacetophenone (**2**) without the use of isatoic anhydride. To our delight, the desired product, tryptanthrin (**3a**), was isolated in 70% yield when 2-aminoacetophenone (**2**) was heated in DMSO at 100 °C in the presence of CuI (1.5 equiv.) under oxygen (Scheme 4).

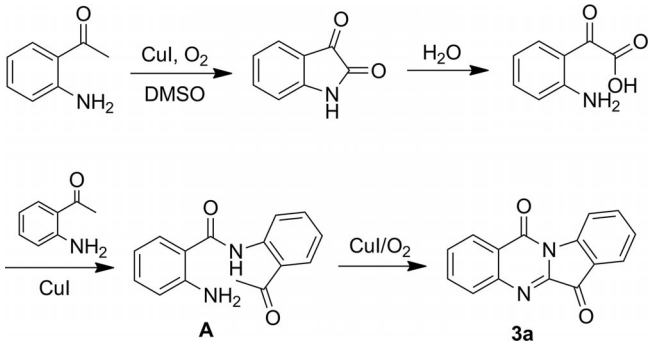


2 3a

Scheme 4. Formation of **3a** from 2-aminoacetophenone (**2**).

We examined the substrate scope, by testing the method with 5-chloro- and 5-bromo-2-aminoacetophenones. However, these substrates failed to undergo self-condensation to give the expected tryptanthrin derivatives under similar conditions. Instead, the corresponding isatins were isolated in low yields (20–30%). This is due to the intrinsic low reactivity of these substrates compared to 2-aminoacetophenone.

Based on previous observations,[18] we also propose a similar mechanism for this transformation (Scheme 5). To study the reaction pathway, 2-aminoacetophenone (**2**) was treated with CuI (1.5 equiv.) in the presence of pivalic acid (1.0 equiv.) under oxygen at 100 °C for 12 h.[18e] To our surprise, no tryptanthrin was formed, and instead isatin was isolated in 60% yield. These results indicate that the reaction proceeds through the formation of isatin from 2-aminoacetophenone (**2**).[18] Subsequent hydrolysis of isatin generates the α-oxocarboxylic acid, which can then undergo copper-catalysed decarboxylative coupling with another molecule of 2-aminoacetophenone (**2**) to give amide **A**.[4b] As shown in Scheme 3, **A** can undergo a series of transformations to give the desired tryptanthrin (**3a**).



Scheme 5. Possible reaction mechanism.

Recently, the formation of isatin from 2-aminoacetophenone (**2**) has been reported through an oxidative functionalization.[18] However, the formation of tryptanthrin from 2-aminoacetophenone (**2**) is an entirely new and attractive strategy.

Conclusions

We developed a new one-pot strategy for the synthesis of tryptanthrin derivatives from 2-aminoaryl methyl ketones and isatoic anhydrides. This domino process proceeds through copper-mediated aerobic oxidation, imine formation, nucleophilic addition, and oxidative aromatization. This method is applicable to a wide range of substrates, and has a high functional-group tolerance. The method uses readily available reagents, and is quite simple, convenient, and practical.

Experimental Section

General Remarks: All solvents were dried according to standard literature procedures. Reactions were carried out in oven-dried round-bottomed flasks under oxygen. Crude products were purified by column chromatography on silica gel (60–120 or 100–200 mesh). Spots on hin-layer chromatography plates were visualized by exposure to ultraviolet light and/or by exposure to iodine vapours and/or by exposure to a methanolic acidic solution of *p*-anisaldehyde followed by heating (< 1 min) on a hot plate (ca. 250 °C). Organic solutions were concentrated using a rotary evaporator at 35–40 °C. ^{1}H and ^{13}C (proton-decoupled) NMR spectra were recorded in $CDCl_3$ with a 200, 300, 400, or 500 MHz NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane, which was used as an internal standard. Coupling constants (J) are quoted in Hertz (Hz). Mass spectra were recorded with a mass spectrometer using the electrospray ionization (ESI) or the atmospheric-pressure chemical ionization (APCI) technique.

***N*-(2-Acetylphenyl)-2-aminobenzamide (A):** Isatoic anhydride (0.5 mmol) and 2-aminoacetophenone (**2**) (0.6 mmol) were dissolved in DMF (5 mL) at 25 °C. The resulting mixture was stirred under reflux for 1 h. After TLC indicated that the reaction was complete, the mixture was quenched with saturated $NaHCO_3$ solution (1.0 mL) and extracted with ethyl acetate (2–5 mL). The combined organic layers were washed with brine (3–5 mL), dried with anhydrous Na_2SO_4, and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography (100–200 mesh) with ethyl acetate/hexane as eluent to give pure *N*-(2-acetylphenyl)-2-aminobenzamide (**A**). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 12.5 (br. s, 1 H), 8.89 (d, J = 7.9 Hz, 1 H), 7.96 (d, J = 6.5 Hz, 1 H), 7.79 (d, J = 8.0 Hz, 1 H), 7.61 (t, J = 7.1 Hz, 1 H), 7.29–7.26 (m, 1 H), 7.15 (t, J = 7.1 Hz, 1 H), 6.81–6.71 (m, 1 H), 5.79 (br. s, 2 H), 2.72 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.9, 168.6, 149.9, 141.5, 135.1, 132.9, 131.8, 130.9, 128.8, 127.8, 122.2, 120.7, 117.5, 116.9, 23.7 ppm. MS (ESI): *m*/*z* = 255 $[M + H]^+$. HRMS (ESI): calcd. for $C_{15}H_{15}N_2O_2$ 255.1133; found 255.1128.

Procedure for the Synthesis of Tryptanthrin from 2-Aminoacetophenone (2): CuI (1.5 equiv.) was added to a stirred solution of 2-aminoacetophenone (**2**) (0.6 mmol) in DMSO (5 mL) at 25 °C. The resulting mixture was stirred at 100 °C under oxygen for the specified time (Table 2). After TLC indicated that the reaction was complete, the mixture was quenched with saturated $NaHCO_3$ solution (1.0 mL) and extracted with dichloromethane (2× 5 mL). The combined organic layers were washed with brine (3–5 mL), dried with anhydrous Na_2SO_4, and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography (100–200 mesh) with ethyl acetate/hexane as eluent to give the pure tryptanthrin.

Indolo[2,1-*b*]quinazoline-6,12-dione (Tryptanthrin) (3a): Solid; m.p. 260–262 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.66 (d, J = 7.7 Hz, 1 H), 8.43 (d, J = 7.9 Hz, 1 H), 8.02 (d, J = 8.0 Hz, 1 H), 7.92 (d, J = 7.5 Hz, 1 H), 7.85 (dt, J = 1.3, 7.4 Hz, 1 H), 7.79 (t, J = 7.7 Hz, 1 H), 7.67 (t, J = 7.7 Hz, 1 H), 7.43 (d, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 181.8, 157.0, 145.7, 145.4, 137.4, 134.3, 130.0, 129.5, 126.8, 126.5, 124.7, 123.1, 121.3, 117.4 ppm. MS (EI): *m*/*z* = 248 $[M]^+$. HRMS (EI): calcd. for $C_{15}H_8N_2O_2$ 248.0586; found 248.0586.

1-Methylindolo[2,1-*b*]quinazoline-6,12-dione (3b): Solid; m.p.195–197 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.65 (d, J = 7.8 Hz, 1 H), 7.93 (t, J = 7.2 Hz, 2 H), 7.80–7.75 (m, 2 H), 7.60–7.43 (m, 3 H), 2.5 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 180.9, 164.3, 156.8, 142.6, 138.1, 134.1, 133.2, 129.1, 126.8, 125.2, 121.9, 117.9, 23.0 ppm. MS (EI): *m*/*z* = 262 $[M]^+$. HRMS (EI): calcd. for $C_{16}H_{10}N_2O_2$ 262.0742; found 262.0738.

8-Bromoindolo[2,1-*b*]quinazoline-6,12-dione (3c): Solid; m.p. 290–292 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.6–8.43 (m, 3 H), 7.76–7.68 (m, 2 H), 7.40 (t, J = 7.7 Hz, 1 H), 7.15 (s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 189.5, 155.5, 154.3, 137.5, 135.9, 134.9, 134.8, 131.0, 129.7, 125.5, 124.7, 113.9, 113.0, 112.7 ppm. MS (EI): *m*/*z* = 325 $[M]^+$. HRMS (EI): calcd. for $C_{15}H_7BrN_2O_2$ 325.9691; found 325.9697.

8-Bromo-3-chloroindolo[2,1-*b*]quinazoline-6,12-dione (3d): Solid; m.p. 256–258 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.12 (d, J = 8.4 Hz, 1 H), 7.91 (d, J = 8.7 Hz, 1 H), 7.61–7.55 (m, 2 H), 7.45 (m, 1 H), 6.86 (s, 1 H), 6.62 (dd, J = 1.7, 8.7 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 180.0, 146.4, 138.5, 136.3, 129.9, 128.7, 127.1, 124.9, 124.5, 115.1, 115.0, 113.8 ppm. MS (EI): *m*/*z* = 359 $[M]^+$. HRMS (EI): calcd. for $C_{15}H_6BrClN_2O_2$ 359.9302; found 359.9305.

8-Methylindolo[2,1-*b*]quinazoline-6,12-dione (3e): Solid; m.p. 281–283 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.93 (dd, J = 8.2, 13.9 Hz, 1 H), 8.64–8.51 (m, 1 H), 8.30–8.11 (m, 1 H), 7.88–7.37 (m, 2 H), 7.34–7.28 (m, 1 H), 3.02 (s, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 181.8, 167.7, 147.9, 146.0, 143.7, 138.3, 134.5, 131.5, 129.6, 127.0, 126.5, 117.3, 116.8, 116.1, 25.2 ppm. MS (EI): *m*/*z* = 262 $[M]^+$. HRMS (EI): calcd. for $C_{16}H_{10}N_2O_2$ 262.0742; found 262.0746.

3,8-Dichloroindolo[2,1-*b*]quinazoline-6,12-dione (3f): Solid; m.p. 288–290 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.23 (d, J = 8.4 Hz, 1 H), 7.97 (d, J = 8.7 Hz, 1 H), 7.71–7.67 (m, 1 H), 7.56 (s, 1 H), 7.52–7.50 (m, 1 H), 7.43 (dd, J = 1.9, 8.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.1, 157.5, 157.0, 149.6, 146.6, 131.7, 130.4, 130.1, 129.3, 128.1, 127.7, 125.4, 116.7, 115.6 ppm. MS (EI): m/z = 315 $[M]^+$. HRMS (EI): calcd. for $C_{15}H_6Cl_2N_2O_2$ 315.9806; found 315.9815.

8-Methoxyindolo[2,1-*b*]quinazoline-6,12-dione (3g): Solid; m.p. 278–280 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.53 (d, J = 8.7 Hz, 1 H), 8.43 (dd, J = 1.4, 8.1 Hz, 1 H), 8.03 (d, J = 8.0 Hz, 1 H), 7.85 (dt, J = 1.8, 8.5 Hz, 1 H), 7.73–7.66 (m, 1 H), 7.39 (d, J = 3.9 Hz, 1 H), 7.32 (dd, J = 2.8, 8.8 Hz, 1 H), 3.90 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.8, 158.1, 156.1, 146.1, 144.9, 139.9, 134.4, 130.2, 129.8, 127.0, 124.6, 123.5, 122.5, 118.8, 108.1, 56.1 ppm. MS (EI): m/z = 278 $[M]^+$. HRMS (EI): calcd. for $C_{16}H_{10}N_2O_3$ 278.0691; found 278.0695.

8-Chloroindolo[2,1-*b*]quinazoline-6,12-dione (3h): Solid; m.p. 290–292 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.53 (d, J = 8.7 Hz, 1 H), 8.37 (d, J = 7.7 Hz, 1 H), 7.97 (d, J = 8.0 Hz, 1 H), 7.84–7.79 (m, 2 H), 7.71–7.60 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 181.1, 158.0, 157.0, 146.8, 144.6, 140.0, 134.9, 130.6, 130.3, 127.4, 125.1, 123.7, 122.8, 119.1, 108.3 ppm. MS (EI): m/z = 282 $[M]^+$. HRMS (EI): calcd. for $C_{15}H_7ClN_2O_2$ 282.0196; found 282.0197.

8-Chloro-1-methylindolo[2,1-*b*]quinazoline-6,12-dione (3i): Solid; m.p. 265–267 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.62 (d, J = 8.6 Hz, 1 H), 7.89–7.85 (m, 1 H), 7.76–7.68 (m, 2 H), 7.57–7.54 (m, 1 H), 7.45 (d, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.8, 169.8, 147.9, 145.7, 142.7, 137.5, 134.3, 133.5, 130.8, 130.1, 129.3, 128.7, 125.0, 122.8, 119.1, 23.6 ppm. MS (EI): m/z = 296 $[M]^+$. HRMS (EI): calcd. for $C_{16}H_9ClN_2O_2$ 296.0353; found 296.0355.

3-Chloroindolo[2,1-*b*]quinazoline-6,12-dione (3j): Solid; m.p. 282–284 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.59 (d, J = 8.0 Hz, 1 H), 8.36 (d, J = 8.4 Hz, 1 H), 8.15 (d, J = 8.4 Hz, 1 H), 8.03–8.00 (m, 1 H), 7.92 (d, J = 7.5 Hz, 1 H), 7.80 (dt, J = 1.3, 8.0 Hz, 1 H), 7.64–7.58 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.6, 166.2, 145.2, 143.6, 139.2, 131.1, 129.8, 128.9, 128.8, 127.5, 126.8, 126.7, 122.5, 119.4 ppm. MS (EI): m/z = 282 $[M]^+$. HRMS (EI): calcd. for $C_{15}H_7ClN_2O_2$ 282.0196; found 282.0194.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H and ^{13}C NMR spectra.

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