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Synthesis of Aryl- and Heteroaryl[*a*]pyrrolo[3,4-*c*]carbazoles

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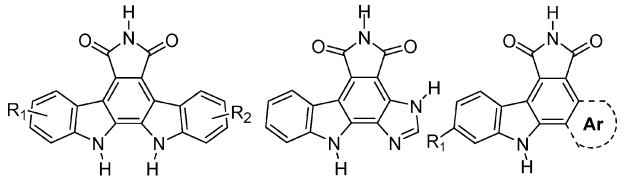
Synthesis of aryl- and hetero[*a*]pyrrolo[3,4-*c*]carbazoles by photochemical oxidation and Heck cyclization are described. Photochemical oxidation of 2-naphthyl indolyl maleimide affords two different carbazole regioisomers, depending on the reaction conditions. The regiochemistry of the cyclization can be controlled using the Heck reaction.

Introduction

The indolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole alkaloids represent an interesting class of compounds that exhibit diverse biological activities.[1−3] For example, arcyriaflavin derivatives **1** have antiviral activity against human citomegalovirus,[4] antimicrobacterial activity against *Bacillus cereus*,[5] antitumor activity against P388 leukemia cells,[5] and inhibit protein kinase A (PKA), protein kinase C (PKC),[5−7] topoisomerases I and II,[5] as well as tyrosine and serine kinases.[5,7,8] Arcyriaflavin analogues are currently being evaluated in human clinical trials as anticancer drugs.[3] More recently, a new class of imidazolo-[4,5-*a*]pyrrolo[3,4-*c*]carbazoles was reported and synthesized (Scheme 1),[9−11] and of this class granulatimide **2**, isolated from *Didemnum granulatum*, acts as a specific G2 cell cycle checkpoint inhibitor.

SCHEME 1



1 **2** **3**

However, despite the vast amount of work in this area, there has been very little research on the synthesis and biological activity of the aryl- and heteroaryl[*a*]pyrrolo-[3,4-*c*]carbazoles **3**.[10−14] Recently, we disclosed our results that identified a novel series of aryl- and heteroaryl[*a*]-pyrrolo[3,4-*c*]carbazoles **3** as cyclin D1-CDK4 inhibitors.[15] This paper will describe our efforts to develop a general synthetic method to prepare this class of compounds via the photochemical oxidation and a novel Heck cyclization strategy.

Results and Discussion

The most direct approach for the synthesis of indolo-[2,3-*a*]pyrrolo[3,4-*c*]carbazoles **1** is by oxidation of the corresponding bisindolylmaleimides, and numerous methods to perform this reaction have been reported (hν with or without I_2 or Pd/C,[16−19] DDQ with or without

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TABLE 1. Photochemical Synthesis of Aryl- and Heteroaryl[*a*]pyrrolo[3,4-*c*]carbazoles

entry	5	Ar	% yield 5	% yield 3	orientation of 3	overall % yield from 4
1	**a**	Ph	99	24	benzo[*a*] (**3a**)	24[a]
2	**b**	1-naphthyl	95	97	naphtho[2,1-*a*] (**3b**)	92[b]
3	**c**	2-naphthyl	49	73	naphtho[1,2-*a*] (**3c**)	38[b]
4	**d**	2-thienyl	89	72	thieno[3,2-*a*] (**3d**)	64[a]
5	**e**	3-benzo[*b*]thienyl	97	11	benzo[*b*]thieno[2,3-*a*] (**3e**)	11[a]

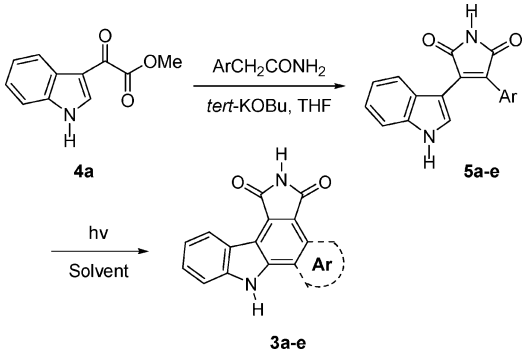
[a] Benzene, reflux, Fisher IR lamp with 15% mol I_2, 20−60 h. [b] Acetone, 35 °C, Osram Hg-HP, lamp 15−20 h.

p-TsOH,[20−22] $Pd(OAc)_2$,[23] $PdCl_2$, $Pd(O_2CCF_3)_2$,[24] $CuCl_2$, and PIFA[25]). However, limited reports have appeared on the application of this chemistry to the synthesis of aryl- and heteroaryl[*a*]pyrrolo[3,4-*c*]carbazoles **3**. Benzo[*a*]pyrrolo[3,4-*c*]carbazole **3a** has been prepared, albeit in 14% yield, by $Pd(OAc)_2$-mediated oxidative cyclization of the corresponding phenyl indolyl maleimide **5a**.[23] The naphtho[2,1-*a*]pyrrolo[3,4-*c*]carbazole **3b** was prepared in four steps and 24% yield by a reaction sequence that employs a key Diels−Alder reaction followed by DDQ oxidation.[13] The 7-methylnaphtho[2,3-*a*]pyrrolo[3,4-*c*]carbazole of **3c′** was prepared by a tandem Suzuki−Heck reaction sequence to prepare the carbazole ring system from 3-(3-indolyl)-4-bromo-*N*-methylmaleimide in four steps and 56% overall yield.[26] Our goal was to develop a general method for the synthesis of aryl- and heteroaryl[*a*]-pyrrolo[3,4-*c*]carbazoles **3** from the corresponding indolyl aryl and heteroaryl maleimides **5a**−**e** and **7a**−**g** using photochemical oxidation and Heck cyclization chemistries, respectively. We will first describe the results of our efforts with the photochemical oxidation reaction.

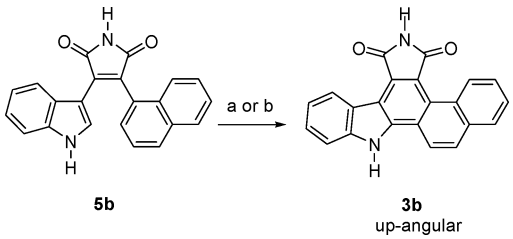
Aryl- and heteroarylindolyl maleimides **5a**−**e** were prepared in 49−99% yield by condensation of the indolyl-3-glyoxylate **4a** with aryl- and heteroaryl acetamides (Table 1, Scheme 2).[27,28] Maleimide **5d** was prepared by condensation of 2-thienyl glyoxylate with indole-3-acetamide and required DMAP/$(Im)_2CO$ in acetonitrile to dehydrate the intermediate hydroxysuccinimide.[29] With an efficient synthesis of **5a**−**e** developed, the photochemical oxidation was examined using benzene or acetone as the solvent and I_2 or acetone as the oxidizing agent to afford carbazoles **3a**−**e** in 11−97% isolated yield (Table 1).

Interesting results were obtained during the photochemical oxidation of 1- and 2-substituted naphthyl indolylmaleimides **5b**[29] and **5c**. Irradiation of 1-naphthyl-3-indolyl maleimide **5b** under a variety of conditions afforded only the naphtho[2,1-*a*]carbazole **3b** (up-angular) in 92−97% yield (Scheme 3, Table 2, entries 1−3). In comparison, photooxidation of 2-naphthyl-3-indolyl maleimide **5c** afforded both the naphtho[1,2-*a*]carbazole **3c** (down angular) and naphtho[2,3-*a*]carbazole **3c′** (linear), depending on the reaction conditions (Scheme 4). In PhH with I_2 at reflux a 4:1 mixture of **3c** and **3c′** was obtained in 74% yield, with the naphtho[1,2-*a*]carbazole **3c** being the major isomer (Table 2, entry 4). Unfortunately, this mixture could not be purified by

SCHEME 2



SCHEME 3[a]



[a] (a) Fisher IR lamp with 15 mol % I_2 for 36 h. (b) Osram Hg-HP lamp for 20 h.

TABLE 2. Photochemical Synthesis of Naphtho[*a*]pyrrolo[3,4-*c*]carbazoles 3

entry	5	solvent	*T*, °C[g]	conditions	% yield
1	**b**	PhH	100	hν, I_2[a]	92 (**3b**)
2	**b**	PhH	35	hν, I_2[b]	96 (**3b**)
3	**b**	acetone	35	hν[c]	97 (**3b**)
4	**c**	PhH	100	hν, I_2[d]	74 (**3c**/**3c′** = 4:1)[e]
5	**c**	acetone	35	hν[c]	73 (**3c**)
6	**c**	HOAc	reflux	$Pd(OAc)_2$	9 (**3c′**)[f]
7	**c**	DMF	reflux	$PdCl_2$	0 (**3c** + **3c′**)

[a] Fisher IR lamp with 15 mol % I_2 for 36 h. [b] Osram Hg-W lamp with 25 mol % I_2. [c] Osram Hg-HP lamp. [d] Fisher IR lamp with 6 mol % I_2. [e] Determined by ^1H NMR (500 MHz). [f] Reaction time 18 h. [g] Reactions run for 15 h unless otherwise indicated.

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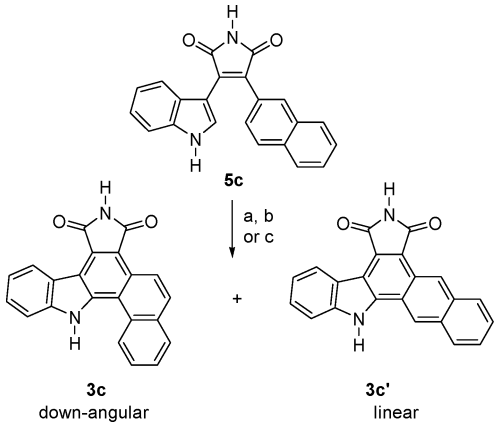
SCHEME 4 [a]



[a] (a) Fisher IR lamp with 15 mol % I_2 for 36 h. (b) Osram Hg-W lamp with 25 mol % I_2. (c) Osram Hg-HP lamp.

crystallization or column chromatography. However, under milder conditions, using acetone as solvent at room temperature, **3c** was the only product isolated in 73% yield (Table 2, entry 5). In contrast to the result of the photochemical reaction, treatment of **5c** with $Pd(OAc)_2$ in refluxing HOAc afforded only carbazole **3c′**, albeit in 9% yield (Table 2, entry 6). Unfortunately, the use of neutral conditions such as $PdCl_2$ in DMF failed to provide either carbazole **3c** or **3c′** (Table 2, entry 7).

The structure of the naphthocarbazole isomers was determined by 1-D and 2-D NMR studies. The ^1H and ^{13}C NMR showed well-resolved resonances for all of the proton and carbon atoms. For carbazole **3b**, the COSY data showed a two-spin system with a doublet at 8.61 ppm (H-13) coupled to the doublet at 8.21 ppm (H-14). The COSY analysis for the mixture **3c/3c′** (Table 2, entry 4) showed three spin systems for the major component (**3c**). A doublet at 9.12 ppm coupled to the doublet at 8.15 ppm is only compatible with the down-angular orientation. The minor component showed two singlets at 9.58 and 9.28 ppm, which is only consistent with the linear carbazole **3c′**. Significant differences in the ^1H NMR data for the three compounds were observed in the chemical shifts of the naphthyl proton resonances, corroborating the different orientation of this ring. The final assignments were completed with pure samples (Table 2, entries 5 and 6). Due to the planar aromatic structure, H-4, H-8, and H-13 in **3b** (δ 9.09, 9.95, and 8.61 ppm), H-2, H-6, and H-11 in **3c** (δ 9.12, 9.09, and 9.25 ppm) and H-5, H-9, and H-14 in **3c′** (δ 8.84, 9.54, and 9.24 ppm) have demonstrated a large chemical shift relative to the corresponding maleimides **5**.[30] This effect is attributed to the neighboring group effect from the maleimide carbonyls and the indole NH in either carbazoles (Figure 1).

The results obtained with **5c** indicate that formation of carbazole **3c** is preferred over formation of carbazole **3c′** both kinetically and thermodynamically. The reaction conditions that generate **3c′** required reflux and in both instances contained an oxidant capable of promoting alternate mechanisms such as thermal electrocyclization (PhH/I_2 reflux) or consecutive addition−elimination ($Pd(OAc)_2$/HOAc). These alternative pathways would not share the same transition states and would not necessarily have the same preference for the angular carbazole. The formation of **3c′** under certain conditions (reflux) is therefore probably not due to kinetic vs thermodynamic effects but to a change of mechanism. These results represent the first application of a photochemical oxidation to prepare this novel class of compounds.

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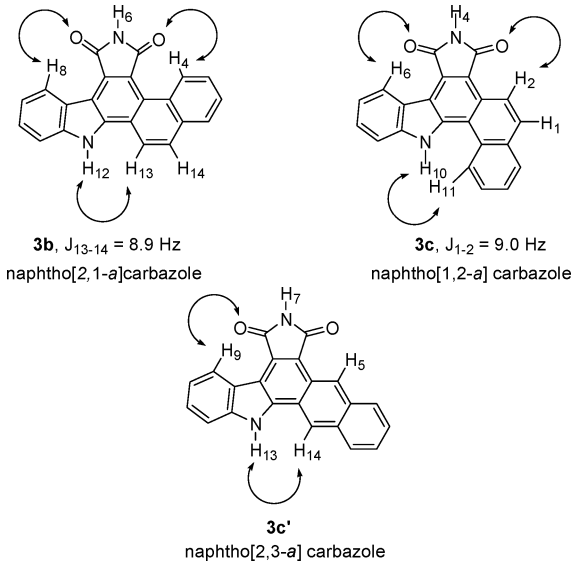
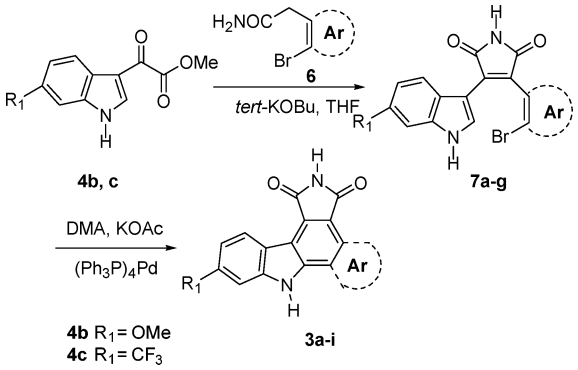


FIGURE 1.

SCHEME 5



Although the photochemical oxidation afforded efficient access to aryl- and heteroaryl[*a*]pyrrolo[3,4-*c*]carbazoles **3a**−**e**, the yields were variable, the reactions needed to be preformed at high dilution, and long reaction times were required. Thus, as a parallel strategy, we evaluated a synthesis of **3** by Heck cyclization from the corresponding 2-bromoaryl and 2-bromoheteroaryl indolylmaleimides **7a**−**g** (Scheme 5). The first step of this approach required synthesis of the 2-bromoaryl and 2-bromoheteroarylindolyl maleimides **7a**−**g**. These compounds have previously not been reported in the literature but were prepared in one step and 18−84% yield using our standard conditions involving condensation of 2-bromoaryl, or 2-bromoheteroaryl acetamides **6** with indolyl-3-glyoxylates **4b** or **c** (Scheme 5).

The initial conditions employed in the Heck reaction ($Pd(OAc)_2$, PPh_3, Na_2CO_3, in DMF at 150 °C) failed to provide the desired carbazoles **3**. However, upon optimization, alternative conditions were identified (($Ph_3P)_4Pd$,

TABLE 3. Heck Cyclization of 2-Bromoaryl and Heteroarylmaleimides (Scheme 5)

Entry	R_1		Yield, % (7)	Yield, % (3)[a]	Overall Yield % from 4
1	H	2-Br Ph	84 (**7a**)	75 (**3a**)	63
2	OMe	2-Br Ph	49 (**7b**)	71 (**3f**)	35
3	CF_3	2-Br Ph	48 (**7c**)	70 (**3g**)	34
4	H	1-Br naphthyl	61 (**7d**)	68 (**3c**)[b]	41
5	H	2-Br naphthyl	66 (**7e**)	75 (**3b**)	49
6	H	2-Br, 5-OMe Ph	65 (**7f**)	61 (**3h**)	40
7	H	2-Br-thiophene	18 (**7g**)	26 (**3i**)	5

[a] Reactions performed in DMA with 1 equiv of KOAc and 5 mol % of $(Ph_3P)_4Pd$ unless otherwise indicated. [b] Reaction with 20 mol % $(Ph_3P)_4Pd$.

KOAc, DMA at 130 °C) that afforded a 75% yield of carbazole **3a**. These conditions proved general for 2-bromo-substituted aryl- and heteroarylmaleimides **7a**−**g** to provide the corresponding carbazoles **3a**−**i** in 26−75% yield (Scheme 5, Table 3). In this case, both the 1-naphthyl and 2-naphthyl derivatives **7d** and **7e** were converted regioselectively into the desired carbazoles **3c** and **3b**, respectively. The Heck cyclization conditions were unsuccessful when the indole nitrogen was alkylated.

Conclusion

We have identified two new methods for the synthesis of a novel class of aryl- and heteroaryl[*a*]pyrrolo[3,4-*c*]-carbazoles **3**. The photooxidation reaction affords carbazoles **3** in two steps and 11−92% yield from indolyl-3-glyoxylyl esters **4**, whereas the corresponding Heck cyclization approach affords **3** in two steps and 5−63% overall yield from **4**, but has the advantage that it minimizes issues with high reaction dilution and long reaction times. Application of this chemistry provides access to a variety of novel compounds that have been shown to be potent inhibitors of cyclin D1-CDK4 in vitro.

Experimental Section

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. TLC was performed on Kiesegel 60 F254 plates (Merck) using reagent grade solvents. Flash chromatography was performed using Merck silica gel 60 (230−400 mesh). ^{1}H NMR spectra were collected at 300 MHz and ^{13}C NMR at 75 MHz in $CDCl_3$ unless otherwise specified. Chemical shifts are in ppm downfield from internal tetramethylsilane. Mass spectral and combustion analysis were performed by the Eli Lilly and Co. Physical Chemistry Department.

3-(3-Indolyl)-4-(2-naphthyl)-1*H*-pyrrole-2,5-dione (5c). To a suspension of the methyl, (1*H*-indol-3-yl) oxoacetate (0.568 g, 3.33 mmol) and 2-naphthylacetamide[31] (0.56 g, 3.0 mmol) in anhydrous THF (13 mL) at 0 °C was added 1.0 M *tert*-KOBu^t in THF (9.1 mL). The ice bath was removed and the reaction mixture was allowed to warm to room temperature for 15 h (overnight). The reaction was quenched with saturated NH_4Cl (30 mL) and extracted with EtOAc (35 × 2 mL). The organic layer was washed with saturated aqueous NaCl, dried (Na_2SO_4), and filtered. The solvent was removed in vacuo to afford an orange solid. The solid was purified by flash chromatography (2:3 hexanes:EtOAc) to afford 0.5 g (49%) of **5c** as an orange solid: mp 272−274 °C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.95 (s, 1H, NH indole), 11.13 (s, 1H, NH maleimide), 8.08 (s, 1H), 8.00 (d, 1H, J = 2.1 Hz), 7.88−7.83 (m, 2H), 7.76 (d, 1H, J = 8.6 Hz), 7.55−7.46 (m, 2H), 7.42−7.38 (m, 2H), 6.98 (t, 1H, J = 7.5 Hz), 6.52 (t, 1H, J = 7.5 Hz), 6.33 (d, 1H, J = 8.0 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 172.8, 172.5, 136.7, 132.9, 132.7, 132.6, 131.3, 129.5, 128.7, 128.5, 128.4, 127.8, 127.5, 127.1, 126.9, 126.6, 124.4, 122.2, 121.2, 119.9, 112.4, 104.4; MS (EI) *m/e* calcd for C_{22} $H_{14}N_2O_2$ 338.10, found 338.0 [M^+, 100.0].

Benzo[*a*]pyrrolo[3,4-*c*]carbazole-1,3(2*H*,8*H*)-dione (3a).[23] **Procedure A.** A mixture of 3-[3-indolyl]-4-(1-phenyl)-1*H*-pyrrole-2,5-dione **5a** (0.16 g, 0.56 mmol) and I_2 (21.1 mg, 0.08 mmol) in dry PhH (45 mL) was irradiated with a Fisher infrared lamp for 20 h. The reaction was cooled to room temperature and the solid was collected by filtration. Trituration with EtOAc afforded 37.5 mg (24%) **3a** as a yellow solid.

Procedure B. Following the General Procedure via the Heck Cyclization. Bromomaleimide **7a (**1.0 mmol), $(Ph_3P)_4Pd$ (59 mg, 0.05 mmol), KOAc (103 mg, 1.05 mmol), and DMA (18 mL) were combined. The solution was heated to reflux for 2 h. The reaction mixture was cooled and diluted with EtOAc (200 mL). The organic phase was washed with 5% LiCl(aq) (2 × 200 mL) and saturated NaCl(aq) (2 × 200 mL). The organic phase was separated, dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo. The resulting orange residue was slurried in EtOAc and the solid was filtered to provide 213 mg (75%) of **3a** as an orange solid: ^{1}H NMR (DMSO-d_6, 200 MHz) δ 12.94 (br s, 1H, NH indole), 11.15 (br s, 1H, NH maleimide), 8.99 (dd, 1H, J = 7.5 Hz, 2.7 Hz), 8.90 (d, 1H, J = 7.8 Hz), 8.68 (dd, 1H, J = 6.9 Hz, 2.1 Hz),7.72−7.86 (m, 3H), 7.55 (dt, 1H, J = 7.2 Hz, 0.9 Hz), 7.37 (t, 1 H, J = 6.9 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 172.2, 171.3, 141.1, 140.5, 129.2, 128.8, 128.4, 127.2, 126.7, 125.6, 124.7, 123.4, 123.3, 122.0, 121.4.

Naphtho[2,1-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*,12*H*)-dione (3b).[13] **Procedure A.** A mixture of 3-[3-indolyl]-4-(1-naphthyl)-1*H*-pyrrole-2,5-dione **5b**[29] (80 mg 0.24 mmol) in dry acetone (60 mL) was irradiated with a Osram Hg HP (HQL 125W) lamp for 20 h. The reaction was cooled to room temperature and the solvent was removed. After trituration with Et_2O, the solid was collected by filtration to afford 77 mg (97%) of **3b** as a yellow solid.

Procedure B. Following the General Procedure via the Heck Cyclization. Bromomaleimide **7e** (0.15 g, 0.359 mmol, 1.0 equiv), KOAc (0.035 g, 0.359 mmol, 1.0 equiv), and $(Ph_3P)_4Pd$ (0.083 g, 0.0719 mmol, 0.2 equiv) in anhydrous DMA (7.5 mL) were combined. The resulting heterogeneous mixture was heated at 130 °C for 32 h, DMA evaporated, and the resulting residue purified by flash chromatography using 75 g of silica gel 60 (230−400 mesh) and a 1:1 solution of hexanes:EtOAc to afford 0.09 g (75% yield) of **3b** as an orange solid: mp >300 °C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.82 (s, 1H, NH indole), 11.31 (1H, NH maleimide), 9.97−9.94 (m, 1H), 9.09 (d, 1H, J = 7.8 Hz), 8.61 (d, 1H, J = 8.9 Hz), 8.21 (d, 1H, J = 8.9 Hz), 8.11−8.08 (m, 1H), 7.71 (m, 1 H), 7.77−7.71 (m, 3H), 7.61 (t, 1H, J = 7.0 Hz), 7.356 (t, 1H, J = 8.0 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 171.1, 169.8, 141.4, 140.9, 132.7, 129.9, 129.6, 129.2, 128.9, 128.1, 127.5, 127.1, 126.1, 125.7, 125.0, 121.8, 120.9, 120.5, 119.9, 113.9, 111.6. Anal. Calcd for C_{22} $H_{12}N_2O_2$: C, 78.84; H, 4.03; N, 8.00. Found: C, 78.74; H, 4.08, N, 8.21.

Naphtho[1,2-*a*]pyrrolo[3,4-*c*]carbazole-3,5(4*H*,10*H*)-dione (3c). Procedure A. A mixture of 3-[3-indolyl]-4-(2-naphthyl)-1*H*-pyrrole-2,5-dione **5c**[29] (0.255 g, 0.75 mmol) in acetone (160 mL) was irradiated with an Osram Hg high-pressure lamp (HQL 125W) for 15 h. The reaction was cooled to room temperature and the solid triturated with Et_2O and collected by filtration to afford 0.185 g (73%) of **3c** as a yellow solid.

(31) Sharifi, A.; Mohsenzadeh, F.; Mojtahedi, M. M.; Saidi, M. R.; Balalaie, S. *Synth. Commun.* **2001**, *31*, 431−434.

Procedure B. Bromomaleimide **7d** (300 mg, 0.719 mmol), KOAc (72 mg, 0.72 mmol), and $(Ph_3P)_4Pd$ [167 mg, 0.145 mmol, 0.20 equiv—attempts to use less catalyst (0.05−0.10 equiv)—were unsuccessful] were combined in anhydrous DMA (15 mL). The reaction was heated at 130 °C for 1−2 h; then the DMA was removed in vacuo and the residue was dissolved in THF (25 mL) and adsorbed onto silica gel 60 (1.2 g). Purification (50 g of silica gel 60, 6:1 THF:toluene as eluent) afforded only a trace of product. The bulk of the product was flushed off of the column using large volumes of THF. All product-containing eluents were combined and concentrated in vacuo to dryness. The resulting residue was triturated with EtOAc (40 mL) to form a homogeneous yellow-orange slurry. The slurry was stirred at 60−65 °C for 20−30 min, allowed to cool to room temperature, and then force-cooled to 0−5 °C. After stirring for 1 h at 0−5 °C, the product was isolated by filtration, rinsed with cold EtOAc, and dried in a vacuum oven at 50 °C to afford 168 mg of **3c**. The yield corrected for 1.6 wt % residual solvents by ^{1}H NMR was 165 mg (68%): ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.54 (s, 1H, NH indole), 11.30 (s, 1H, NH maleimide), 9.25 (d, 1H, J = 8.9 Hz), 9.12 (d, 1H, J = 9.0 Hz), 9.09 (d, 1H, J = 8.1 Hz), 8.19 (d, 1H, J = 7.5 Hz), 8.15 (d, 1H, J = 9.0 Hz), 7.96 (m, 1H)), 7.98−7.94 (m, 2H), 7.84 (t, 1H, J = 7.3 Hz), 7.63 (t, 1H, J = 7.7 Hz), 7.43 (t, 1H, J = 7.5 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 171.6, 170.2, 141.5, 139.8, 132.3, 129.2, 129.1, 128.2, 128.0, 127.4, 127.3, 127.2, 126.6, 125.9, 124.4, 122.2, 121.0, 120.5, 119.2, 118.8, 116.5, 112.7; HRMS (ES) m/z calcd for $C_{22}H_{12}N_2O_2$ 337.0977, found 337.0968;

Naphtho[2,3-*a*]pyrrolo[3,4-*c*]carbazole-6,8(7*H*,13*H*)-dione (3c′). A mixture of 3-[3-indolyl]-4-(2-naphthyl)-1*H*-pyrrole-2,5-dione **5c**[29] (0.11 g, 0.325 mmol) and $Pd(OAc)_2$ (0.073 g, 0.325 mmol) in glacial HOAc (15 mL) was heated at reflux (110 °C) under N_2 for 18 h. The reaction mixture was cooled to room temperature, filtered over Celite, and evaporated. The residue was purified by flash chromatography (6:1 CH_2Cl_2:EtOAc) to afford 10 mg (9%) of **3c′** as an orange solid: ^{1}H NMR (DMSO-d_6, 300 MHz): δ 13.20 (s, 1H, NH indole), 11.17 (s, 1H, NH maleimide), 9.54 (s, 1H), 9.24 (s, 1H,), 8.84 (d, 1H, J = 8.3 Hz), 8.22 (d, 1H, J = 7.8 Hz), 8.13 (d, 1H, J = 7.9 Hz), 7.73 (d, 1H, J = 7.8 Hz), 7.67−7.60 (m, 2H), 7.50 (dt, 1H, J = 1.2 Hz, J = 7.6 Hz), 7.35 (dt, 1H, J = 1.2 Hz, J = 7.6 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 171.8, 171.7, 140.2, 138.3, 132.0, 131.5, 128.8, 128.2, 127.2, 126.9, 125.8, 124.5, 123.9, 123.7, 121.8, 121.5, 121.4, 121.0, 119.0, 112.0, 109.6. MS (ES): m/e calcd for $C_{22}H_{12}N_2O_2$ 336.09, found 690.0 $[2M + NH_4]^+$; 335.1 $[M - H]^-$.

Thieno[3,2-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*,13*H*)-dione (3d). A mixture of 3-[3-indolyl]-4-(2-thienyl)-1*H*-pyrrole-2,5-dione **5d** (0.15 g, 0.51 mmol) and I_2 (19.4 mg, 0.08 mmol) in dry PhH (70 mL) was irradiated with a Fisher Infrared lamp for 60 h. The reaction was cooled to room temperature and the solid collected by filtration. Trituration with EtOAc afforded 107 mg (72%) of **3d** as a yellow solid: ^{1}H NMR (DMSO-d_6, 200 MHz) δ 12.74 (s, 1H, NH-indole), 11.21 (s, 1H, NH-maleimide), 8.87 (d, 1H, J = 7.8 Hz), 8.20 (1H, d, J = 5.5 Hz), 8.07 (d,1H, J = 5.5 Hz), 7.70 (d, 1H, J = 8.4 Hz), 7.56 dt, 1H, J = 1.1 Hz, J = 7.1 Hz), 7.37 (t, 1H, J = 7.7 Hz).

Benzo[*b*]thieno[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-(6*H*,-12*H*)-dione (3e). A mixture of 3-[3-indolyl]-4-(3-benzothienyl)-1*H*-pyrrole-2,5-dione **5e** (0.15 g, 0.43 mmol) and I_2 (16.5 mg in dry PhH (60 mL) was irradiated with a Fisher infrared lamp for 60 h. The reaction was cooled to room temperature and the solid collected by filtration. Trituration with hot EtOAc afforded 16.5 mg (11%) of **3e** as a yellow solid: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.79 (s, 1H, NH indole), 11.36 (s, 1, NH maleimide), 9.80 (m, 1H), 9.02 (d, 1H, J = 7.84 Hz), 8.24 (m, 1H), 7.71−7.57 (m, 4H), 7.38 (t, 1H, J = 7.49 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 170.8, 170.3, 141.4, 138.9, 138.3, 134.3, 129.8, 127.8, 127.2, 126.7, 126.5, 125.4, 125.0, 123.2, 120.8, 119.7, 115.3, 111.8.

General Procedure for Formation of 2-Bromoaryl and Heteroarylmaleimides (7). 3-(1*H*-Indol-3-yl)-4-(2-bromophenyl)-1*H*-pyrrole-2,5-dione (7a). 2-Bromophenylacetamide **6a** (1.00 g, 4.7 mmol) and methyl indole-3-glyoxylate (1.92 g, 9.4 mmol) were slurried in THF (10 mL). The slurry was cooled to 0 °C and 1.0 M *tert*-KOBu in THF (28 mL, 28.0 mmol) added dropwise, the temperature being kept below 5 °C. Upon completion of the addition, the reaction mixture was warmed to 50 °C and reaction progress monitored by LC. After ∼1 h the reaction mixture was cooled to room temperature and quenched with 1.0 M HCl(aq) (100 mL). The mixture was transferred to a separatory funnel and washed with EtOAc (2 × 100 mL). The combined organic phases were washed with saturated $NaHCO_3$(aq) (2 × 100 mL) and saturated NaCl(aq) (1 × 100 mL). The organic phase was separated, dried (Na_2SO_4), and filtered and the solvent removed in vacuo. The resulting residue was slurried in a 2:1 hexanes:EtOAc solution (80 mL), cooled to 0 °C, and filtered to afford 1.45 g (84%) of **7a** as an orange solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 12.30 (br s, 1H, NH indole), 8.21 (d, 1H, J = 3.0 Hz), 7.78−7.80 (m, 1H), 7.40−7.45 (m, 4H), 7.08 (dt, 1H, J = 8.1 Hz, 0.9 Hz), 6.70 (dt, 1H, J = 8.4 Hz, 1.2 Hz), 6.26 (d, 1H, J = 8.4 Hz), 5.74 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 171.8, 170.9, 136.2, 134.9, 132.7, 132.3, 132.0, 131.3, 130.4, 128.4, 127.3, 124.6, 123.7, 122.0, 120.0, 112.0, 104.9; HRMS (ES) m/z calcd for $C_{18}H_{11}BrN_2O_2$ 366.0004, found 366.0005.

3-[2-Bromophenyl]-4-[6-(methoxy)-1*H*-indol-3-yl]-1*H*-pyrrole-2,5-dione (7b). Reagents employed: 2-bromophenylacetamide **6a** (214 mg, 1.0 mmol), 6-methoxy indolyl-3-glyoxylate (255 mg, 1.1 mmol), anhydrous THF (4.2 mL), and 1.0 M *tert*-KOBu in THF (4.0 mL). After workup, the orange solid was adsorbed onto silica gel and purified by silica gel chromatography (2:1 EtOAc:hexanes) to yield 195 mg (49%) of **7b** as an orange solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 11.74 (br s, 1H, NH indole), 11.07 (br s, 1H, NH maleimide), 7.90 (d, 1H, J = 3.6 Hz), 7.71 (dd, 1H, J = 2.8 Hz, 12.0 Hz), 7.28−7.39 (m, 2H), 6.86 (d, 1H, J = 2.8 Hz), 6.28 (dd, 1H, J = 3.2 Hz, 12 Hz), 6.18 (d, 1H, J = 12.0 Hz), 3.68 (s, 3H); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 172.0, 171.2, 155.8, 137.4, 135.0, 132.9, 132.5, 132.2, 130.7, 130.6, 128.0, 127.4, 123.9, 120.9, 118.7, 109.9, 105.2, 95.2, 55.0; HRMS (ES) m/z calcd for $C_{19}H_{13}BrN_2O_3$ 396.0110, found 396.0110.

3-[2-Bromophenyl]-4-[6-(trifluoromethyl)-1*H*-indol-3-yl]-1*H*-pyrrole-2,5-dione (7c). Reagents employed: 2-bromophenyl-acetamide **6a** (300 mg, 1.4 mmol), 6-trifluoromethyl indolyl-3-glyoxylate (750 mg, 2.8 mmol), anhydrous THF (3.0 mL), and 1.0 M *tert*-KOBu in THF (9.0 mL). After workup, the orange solid was purified by column chromatography to afford 582 mg (48%) of **7c** as a yellow solid: ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.27 (br s, 1H, NH indole), 11.23 (br s, 1H, NH maleimide), 8.12 (d, 1H, J = 3.0 Hz), 7.42−7.47 (m, 2H), 7.34−7.31 (m, 3H), 6.97−6.98 (m, 1H), 6.63 (d, 1H, J = 8.5 Hz); ^{13}C NMR (DMSO-d_6, 400 MHz) δ 171.5, 170.7, 135.2, 135.2, 134.3, 133.7, 132.4, 132.1, 131.9, 130.7, 130.2, 127.5, 126.0, 123.4, 123.3, 122.5, 122.1, 120.6, 116.0, 109.5, 104.9; HRMS (ES) m/z calcd for $C_{19}H_{10}BrN_2O_3F_3$ 433.9878, found 433.9877.

3-(1*H*-Indol-3-yl)-4-(1-bromo-2-naphthalenyl)-1*H*-pyrrole-2,5-dione (7d). Reagents used: 1-bromo-2-naphthaleneacetamide (2.75 g, 10.4 mmol), methyl indole-3-glyoxylate (4.24 g, 20.9 mmol, 2.00 equiv), THF (82 mL), and 1.0 M *tert*-KOBu in THF (63 mL, 63 mmol, 6.0 equiv). After workup, 4.29 g of crude product was obtained that was slurried in warm (50 °C) EtOAc (86 mL) for 5−10 min, allowed to cool to room temperature, and then force-cooled to 0−5 °C for 1 h. The product was isolated by filtration and dried in a vacuum oven at 50 °C to afford 2.82 g of **7d**. The yield corrected for 6 wt % EtOAc by ^{1}H NMR was 2.65 g (61%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.94 (bs, 1H, NH indole), 11.18 (bs, 1H, NH maleimide), 8.22 (d, 1H, J = 8.1 Hz), 8.04−7.95 (m, 3H), 7.74−7.64 (dt, 2H, J = 6.6 Hz, 6.22 Hz), 7.40 (t, 2H, J = 8.4 Hz), 6.99−6.93 (m, 1H), 6.51−6.47 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.1, 171.2, 136.4, 135.3, 133.7, 131.5, 131.4, 129.8, 128.4, 128.3, 128.2, 127.8, 127.5, 126.7, 124.9, 124.1,

122.1, 121,1, 120.1, 112.2, 105.1; HRMS (ES) *m/z* calcd for $C_{22}H_{13}BrN_2O_2$ 417.0239, found 417.0249. Anal. Calcd for $C_{22}H_{13}BrN_2O_2$: C, 63.33; H, 3.14; N, 6.71. Found: C, 62.80, H, 3.36, N, 6.40.

3-(1*H*-Indol-3-yl)-4-(2-bromo-1-naphthalenyl)-1*H*-pyrrole-2,5-dione (7e). Reagents used: 2-bromo-1-naphthaleneacetamide (1.07 g, 4.05 mmol, 1.0 equiv), in THF (20 mL) methyl indole-3-glyoxylate (1.65 g, 8.10 mmol. 2.0 equiv), 1 M *tert*-KOBu in THF (24.3 mL, 24.3 mmol, 6.0 equiv), and 3 N HCl (13 mL, 39 mmol, 1.6 equiv based on mmol of *tert*-KOBu). The crude material obtained after workup was purified by flash chromatography using 80 g of silica gel 60 (Merck, 230−400 mesh) and a 1:1 solution of hexanes:EtOAc as eluent to afford 1.12 g (66%) of **7e** as a red-orange solid: ^{1}H NMR ($CDCl_3$) δ 11.87 (d, 1H, J = 1.0 Hz), 11.24 (s, 1H), 8.00 (m, 3H), 7.83 (d, 1H, J = 8.8 Hz), 7.73 (d, 1H, J = 8.1 Hz), 7.42 (ddd, 1H, J = 1.5, 5.5, 6.7 Hz), 7.32 (d, 1H, J = 8.1 Hz), 6.95 (ddd, 1H, J = 1.1, 6.7, 8.1 Hz), 6.53 (ddd, 1H, J = 0.7, 7.3, 8.1 Hz), 6.45 (d, 1H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 172.1, 171.3, 137.0, 136.4, 132.8, 131.6, 130.8, 130.1, 129.4, 128.4, 127.7, 127.2, 126.6, 125.5, 124.9, 122.9, 122.2, 120.3, 120.2, 112.1, 105.5; HRMS (ES) calcd for $C_{22}H_{14}N_2O_2Br$ 417.0239, found 417.0231. Anal. Calcd for $C_{22}H_{14}N_2O_2Br$: C, 63.3; H, 3.15; N, 6.71. Found: C, 63.3; H, 3.31; N, 6.54.

3-(1*H*-Indol-3-yl)-4-(2-bromo-5-methoxyphenyl)-1*H*-pyrrole-2,5-dione (7f). 2-Bromo-5-methoxyphenylacetamide[32] (287 mg, 1.17 mmol) and methyl indolyl-3-glyoxylate (310 mg, 1.53 mmol) were slurried in anhydrous THF (4.7 mL). *tert*-KOBu (4.7 mL, 1.0 M THF) was added in one portion at room temperature. After ∼1 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl (25 mL) and the biphasic solution transferred to a separatory funnel. The aqueous phase was separated, extracted with EtOAc (2 × 15 mL), and discarded. The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. The resulting orange solid was adsorbed onto silica gel and purified by silica gel chromatography (2:1 EtOAc:hexanes) to yield 302 mg (65%) of **7f** as an orange solid: ^{1}H NMR (acetone-d_6, 300 MHz) δ 11.05 (s, 1H), 9.88 (s, 1H), 8.15 (d, 1H, J = 3.0 Hz), 7.58 (d, 1H, J = 8.0 Hz), 7.46 (d, 1H, J = 8.0 Hz), 7.09 (t, 1H, J = 8.0 Hz), 6.95−7.00 (m, 2H), 6.77 (t, 1H, J = 8.0 Hz), 6.68 (d, 1H, J = 8.0 Hz), 3.74 (s, 3H); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 172.8, 171.9, 159.0, 137.2, 135.8, 134.4, 134.0, 132.3, 129.2, 125.6, 123.0, 121.0, 118.5, 117.1, 115.1, 112.9, 105.8, 56.2; HRMS calcd for $C_{19}H_{14}BrN_2O_3$ 397.0188, found 397.0174.

3-(2-Bromothien-3-yl)-4-(1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione (7g). To a mixture of 2-bromo-3-thiopheneacetamide (1.2 g, 5.45 mmol, 1.0 equiv), THF (24 mL), and methyl indole-3-glyoxylate (2.22 g, 10.9 mmol. 2.0 equiv) was added 1 M *tert*-KOBu in THF (32.7 mL, 32.7 mmol, 6.0 equiv). After 18 h, the reaction was quenched by the addition of a 3 N HCl solution (8.75 mL, 26.3 mmol, 1.6 equiv based on mmol of *tert*-KOBu) and then heated to reflux and stirred under nitrogen for 90 min. After workup, the crude material was purified through a pad of silica gel 60 (Merck, 230−400 mesh) to afford 0.36 g (18%) of **7g** as an orange solid: ^{1}H NMR ($CDCl_3$) δ 11.96 (s, 1H, NH indole), 11.09 (s, 1H, NH maleimide), 8.06 (d, 1H, J = 3.1 Hz), 7.69 (d, 1H, J = 5.7 Hz), 7.42 (d, 1H, J = 8.4 Hz), 7.08 (m, 2H), 6.75 (t, 1H, J = 7.5 Hz), 6.41(d, 1H, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 171.7, 171.1, 136.2, 134.7, 132.2, 131.3, 129.8, 127.6, 124.7, 122.7, 122.0, 120.2, 119.6, 113.4, 112.1, 105.3; HRMS (ES) calcd for $C_{16}H_{10}N_2O_2SBr$ 372.9646, found 372.9664.

General Procedure for Carbazole Formation via the Heck Cyclization. To a solution of the corresponding bromomaleimide (1.0 mmol), $(Ph_3P)_4Pd$ (0.05 mmol), and potassium acetate (KOAc, 1.05 mmol) previously purged (3×) with nitrogen was added dimethylacetamide (DMA, 18 mL). The solution was heated to reflux and reaction progress monitored by LC until the starting material had been completely consumed. The reaction mixture was cooled and diluted with EtOAc (200 mL). The organic phase was washed with 5% LiCl(aq) (2 × 200 mL) and saturated NaCl(aq) (2 × 200 mL). The organic phase was separated, dried (Na_2SO_4), and filtered, and the solvent was removed in vacuo. The resulting orange residue was purified by column chromatography.

10-Methoxybenzo[*a*]pyrrolo[3,4-*c*]carbazole-1,3(2*H*,8*H*)-dione (3f). Reagents used: Bromomaleimide **7b** (120 mg, 0.3 mmol), anhydrous DMA (6 mL), KOAc (30 mg, 0.3 mmol). and $(Ph_3P)_4Pd$ (18 mg, 0.015 mmol, 5 mol %). The reaction was heated at 130 °C for ∼2.5 h, then DMA was evaporated, and the resulting residue was adsorbed onto silica gel and purified by chromatography (3:1 toluene:THF) to afford 67 mg (71%) of **3f** as an orange solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 12.80 (br s, 1H, NH indole), 11.10 (br s, 1H, NH maleimide), 8.96 (d, 1H, J = 10.4 Hz), 8.73 (d, 1H, J = 12.0 Hz), 8.61 (d, 1H, J = 11.6 Hz), 7.74−7.82 (m, 2H), 7.16 (d, 1H, J = 2.8 Hz), 7.00 (dd, 1H, J = 12 Hz, 3.2 Hz), 3.90 (s, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 172.3, 171.4, 160.0, 142.1, 140.9, 128.32, 128.26, 126.2, 125.6, 123.14, 123.09, 119.0, 115.8, 112.9, 111.0, 95.5, 56.1; HRMS (ES) calcd for $C_{23}H_{14}N_2O_3$ 316.0848, found 316.0848.

10-Trifluoromethylbenzo[*a*]pyrrolo[3,4-*c*]carbazole-1,3(2*H*,8*H*)-dione (3g). Reagents used: Bromomaleimide **7c** (460 mg, 1.1 mmol), KOAc (120 mg, 1.1 mmol), and $(Ph_3P)_4Pd$ (60 mg, 0.05 mmol, 5 mol %) in anhydrous DMA (23 mL). The reaction was heated at 130 °C for ∼3 h, then DMA was evaporated, and the resulting residue was adsorbed onto silica gel and purified by chromatography (3:1 toluene:THF) to afford 250 mg (70%) of **3g** as a yellow solid: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.20 (br s, 1H, NH indole), 11.20 (br s, 1H, NH maleimide), 8.94−8.99 (m, 2H), 8.63 (d, 1H, J = 8.5 Hz), 7.93 (s, 1H), 7.80−7.86 (m, 2H), 7.66 (d, 1H, J = 7.0 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 171.9, 170.8, 142.1, 139.2, 129.2, 128.6, 126.9, 126.8, 126.6, 125.6, 125.3, 124.5, 123.4, 123.2, 120.1, 117.4, 111.2, 109.3; HRMS (ES) calcd for $C_{19}H_9F_3N_2O_2$ 355.0693, found 355.0694.

5-Methoxybenzo[*a*]pyrrolo[3,4-*c*]carbazole-1,3(2*H*,8*H*)-dione (3h). Reagents used: Bromomaleimide **7f** (135 mg, 0.34 mmol), KOAc (32 mg, 0.34 mmol), $(Ph_3P)_4Pd$ (19.6 mg, 0.017 mmol, 5 mol %) in anhydrous DMA (6 mL). The reacion was heated to ∼120 °C for 24 h, then the DMA was evaporated, and the reaction was partitioned between EtOAc and saturated aqueous $NaHCO_3$. The aqueous layer was extracted with EtOAc (2 × 15 mL), and the combined organic portions were washed with 5% aqueous LiCl (2 × 15 mL). The organic layer was dried and concentrated onto silica gel and purified by chromatography (30% EtOAc hexanes) to afford 66 mg (61%) of **3h** as an orange solid: ^{1}H NMR (DMSO-d_6, 300 MHz) δ 11.53 (s, 1H), 9.89 (s, 1H), 9.01 (d, 1H, J = 8 Hz), 8.52 (s, 1H), 8.28 (d, 1H, J = 8 Hz), 7.53 (d, 1H, J = 8 Hz), 7.42−7.46 (m, 1H), 7.24−7.36 (m, 2H), 3.96 (s, 3H); ^{13}C NMR (DMSO-d_6, 300 MHz) δ 171, 170, 160, 136, 135, 134, 134, 132, 130, 129, 126, 122, 121, 118, 117, 115, 112, 106, 55.0; HRMS calcd for $C_{19}H_{13}N_2O_3$ 317.0926, found 317.0919.

Thieno[2,3-*a*]pyrrolo[3,4-*c*]carbazole-4,6(5*H*,11*H*)-dione (3i). Reagents used: Bromomaleimide **7g** (0.30 g, 0.804 mmol, 1.0 equiv), KOAc (0.079 g, 0.804 mmol, 1.0 equiv), and $(Ph_3P)_4Pd$ (0.186 g, 0.161 mmol, 0.2 equiv) in anhydrous DMA (15 mL). The reaction was heated at 130 °C for 90 min, then DMA was removed in vacuo and the dark residue triturated in hexanes. The resulting mixture was then filtered through a glass frit. The solid collected was rinsed with hexanes and dried under vacuum at 50 °C. The crude product was purified by flash chromatography using 50 g of silica gel 60 (230−400mesh) and a 1:1 solution of hexanes:EtOAc to afford 0.06 g (26% yield) of **3i** as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 12.65 (s, 1H, NH indole), 11.07 (s, 1H, NH maleimide), 8.88 (d, 1H, J = 7.9 Hz), 8.12 (d, 1H, J = 5.3 Hz), 8.02 (d, 1H, J = 5.3 Hz),

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7.64 (d, 1H, $J = 8.4$ Hz), 7.54 (t, 1H, $J = 7.5$ Hz), 7.35 (t, 1H, $J = 7.5$ Hz): ^{13}C NMR ($CDCl_3$) δ 170.4, 170.0, 140.3, 138.0, 132.4, 130.9, 126.9, 126.8, 125.3, 124.1, 121.6, 120.8, 120.3, 117.9, 113.1, 111.4; HRMS (ES) calcd for $C_{16}H_9N_2O_2S$ 293.0385, found 293.0385.

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