Synthesis of Coumarin- and Quinolone-Annulated Benzazocinone Frameworks by a Palladium-Catalyzed Intramolecular Heck Reaction

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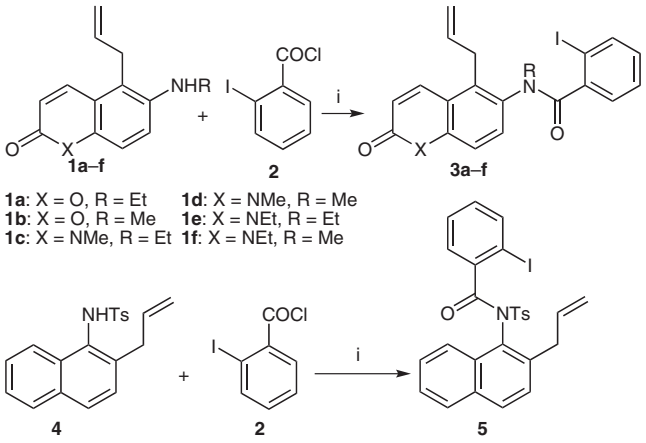
Abstract: A synthetic strategy based on the sequential application of an aromatic aza-Claisen rearrangement and an intramolecular Heck reaction as the key steps has been developed for the synthesis of various new coumarin- and quinolone-annulated benzazocinone derivatives in 60–70% yields.

Key words: heterocycles, annulations, ring closure, rearrangements, catalysis, Heck reactions

Bicyclic and tricyclic fused N-heterocycles form the core structures of many medicinally and clinically important substances.[1] Nitrogen-rich medium-size heterocycles are found in many drugs, preclinical lead substances, and bioactive natural products. Eight-membered nitrogen-containing frameworks are found in several alkaloids such as manzamine A[2,3] and keramamine A.[4] Peesapati et al.[5] synthesized several benzazocinone derivatives that show analgesic, anti-inflammatory, or antimicrobial activities. Furthermore, azocinone derivatives are attractive building blocks for peptides, as they mimic the dipeptide β-turn.[6] Despite the wide range of applications of benzazocinones, there are few reports of efficient syntheses of these compounds. Rings with seven or more members are generally difficult to prepare because of the presence of torsional, transannular, and large-angle strain and of enthalpic and entropic constraints on ring closure.[7] Such compounds therefore pose a major synthetic challenge, and the construction of their basic skeletons by using conventional methods such as lactamization and reduction is relatively difficult.[8–10]

Palladium-catalyzed cyclization is a very powerful and useful tool for the construction of C–C or carbon–heteroatom bonds.[11–17] Generally, palladium-catalyzed coupling reaction of nitrogen-containing compounds[18] require harsh conditions. Donets and Eycken[19] recently developed a microwave-assisted cyclization procedure for the synthesis of extended alkyl chains containing a dibenzazocinone framework; unfortunately, this procedure gave low yields and was applicable only to two-electron-donating substrates. Our continuing efforts in palladium-mediated synthesis of heterocycles[20,21] encouraged us to accept the challenge of synthesizing a dibenzazocinone framework by means of a palladium-catalyzed intramolecular Heck reaction. Here, we report the synthesis of chromeno[6,5-*c*][2]benzazocine and quino[6,5-*c*][2]benzazocine derivatives by means of an aza-Claisen rearrangement and a palladium-catalyzed intramolecular Heck reaction.

The substrates **1a**–**f**[20k,m,21] and **4**[22] were prepared according to published procedures. Treatment of chromenone **1a** with 2-iodobenzoyl chloride (prepared by refluxing 2-iodobenzoic acid with a slight excess of thionyl chloride) in the presence of potassium carbonate as a base and tetrabutylammonium hydrogen sulfate as a phase-transfer catalyst in a mixture of dichloromethane and water at room temperature for six hours gave the Heck precursor **3a** (Scheme 1). The other Heck precursors **3b**–**f** and **5** were prepared similarly.



Scheme 1 Preparation of Heck precursors. *Reagents and conditions*: (i) K_2CO_3 (2 equiv), Bu_4NHSO_4 (10 mol%), CH_2Cl_2/H_2O, r.t.

We then performed an intramolecular Heck reaction with substrate **3a** by adopting Jeffery's two-phase protocol[23] by using palladium(II) acetate as the catalyst, anhydrous *N*,*N*-dimethylformamide as the solvent, potassium acetate as the base, and tetrabutylammonium iodide (TBAI) as the additive. The reaction was allowed to proceed for six hours under a nitrogen atmosphere. We selected palladium(II) acetate as the catalyst because it is widely used in this type of intramolecular Heck reaction. Compound **6a**, the eight-membered 8-*exo*-Heck product, was obtained in 39% yield without any contamination from the 9-*endo*-Heck product **5a** or from the 8-*exo*-isomerized product **4a** (Scheme 2).

Increasing the reaction time did not improve the yield of the reaction. The *exo*-Heck product **6a** was easily characterized from its ^{1}H NMR spectrum, which indicated the

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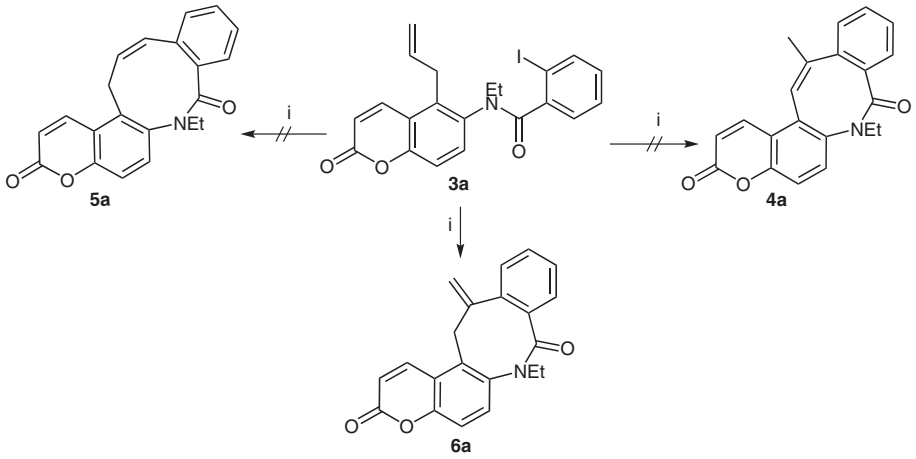

Scheme 2 Probable cyclization scope of the palladium-catalyzed Heck reaction. *Reagents and conditions*: i) $Pd(OAc)_2$ (10 mol%), TBAI (1.2 equiv), KOAc (2.5 equiv), DMF, 90 °C, N_2.

presence of two *exo*-methylene protons belonging to the azocinone ring at $\delta_H = 5.44$ (d, $J = 2.4$ Hz, 2 H). The ^{13}C NMR and mass spectra also supported the structural assignment.

The Heck product **6a** was obtained as a sole product and has not been reported in the literature, so the method is quite important. However, the product was obtained in a low yield (39%). We therefore concentrated on improving the yield of the reaction by carrying out a series of experiments to optimize the catalyst, base, additive, and solvent. The results are summarized in Table 1.

The optimization study showed that the catalyst, base, additive, and solvent all have considerable effects on the reaction yield. TBAB, which plays an important role in the Heck cyclization, was a more effective additive than TBAI. Among the various palladium catalysts tested, palladium tetrakis(triphenylphosphine) was found to be the best choice. The optimal solvent was *N*,*N*-dimethylformamide, and potassium acetate was the optimal base. Therefore, the optimal reaction conditions were identified as palladium tetrakis(triphenylphosphine) as the catalyst, *N*,*N*-dimethylformamide as the solvent, potassium acetate as the base, tributylammonium bromide as the additive, and temperature of 90 °C; under these conditions the reaction took eight hours to reach completion and gave the Heck product **6a** in a yield of 67%.

To examine the tolerance of this intramolecular palladium-catalyzed arylation reaction toward substituents, we

Table 1 Optimization of the Conditions for the Heck Reaction

Entry[a]	Catalyst	Solvent	Base	Additive	Yield (%)
1	$Pd(OAc)_2$	DMF	KOAc	TBAI	39
2	$Pd(OAc)_2$	DMA	KOAc	TBAI	30
3	$PdCl_2$	DMF	KOAc	TBAI	26
4	$PdCl_2(PPh_3)_2$	DMF	KOAc	TBAI	35
5	$Pd(PPh_3)_4$	DMF	KOAc	TBAI	60
6[b]	**$Pd(PPh_3)_4$**	**DMF**	**KOAc**	**TBAB**	**67**
7	$Pd(PPh_3)_4$	DMF	NaOAc	TBAB	58
8	$Pd(PPh_3)_4$	MeCN	KOAc	TBAB	41
9	$Pd(PPh_3)_4$	1,4-dioxane	KOAc	TBAB	43
10	$Pd(PPh_3)_4$	THF	KOAc	TBAB	37
11	$Pd(PPh_3)_4$	DMF	Cs_2CO_3	TBAB	19
12	$Pd(PPh_3)_4$	DMF	KOAc	–	–[c]

[a] All the reactions were carried out at 90 °C.
[b] Optimal reaction conditions.
[c] No reaction.

treated a number of iodobenzamides **3b–f** under optimized reaction condition and we obtained the corresponding tetracyclic azocinone derivatives **6b–f** in 60–70% yield (Table 2). The 1-naphthylamine-derived Heck precursor **5** similarly gave the corresponding benzazocinone derivative **7** in 61% yield.

The formation of the 8-*exo*-Heck product is favored because of the lower steric and transannular interactions.[24] Coumarin and quinolone moieties are found in many natural products with a broad spectrum of biological activities.[25–28] Because benzazocinone moieties are also known to display pharmaceutical and medicinal activities, our

Table 2 Synthesis of Benzazocinone Derivatives by a Heck Reaction

Entry	Substrate	Product	Time (h)	Yield (%)
1	**3a**	**6a**	8	67
2	**3b**	**6b**	8	70
3	**3c**	**6c**	7.25	70
4	**3d**	**6d**	7.5	68
5	**3e**	**6e**	10.5	60
6	**3f**	**6f**	10	62
7	**5**	**7**	8	61

newly formed coumarin- and quinolone-annulated benzazocinones are also expected to show bioactivities.

In conclusion, we have developed an efficient method for the construction of coumarin- and quinolone-fused benzazocinone derivatives by a palladium-catalyzed, ligand-free, Heck coupling reaction. The method is relatively simple, straightforward, and highly regioselective.

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded by using KBr disks or neat liquid samples on a Perkin-Elmer 120–000A spectrometer. NMR spectra were recorded for solns in $CDCl_3$ with TMS as the internal standard on a Bruker Ultrashield-400 spectrometer. ^{13}C-NMR spectra were recorded for solns in $CDCl_3$ on Bruker Ultrashield-400 and Bruker Ultrashield-500 spectrometers. Mass spectra were recorded on a Qtof Micro instrument. CHN analyses were performed on a Perkin-Elmer 2400 series II CHN-analyzer. Silica gel (60–120 mesh) was used for chromatographic separation. Silica gel-G (E-Mark, India) was used for TLC. The PE fraction that we used boiled at 60–80 °C.

Substrates **1a**–**f** [20k,m,21] and **4**[22] were prepared according to the published procedures.

N-(5-Allyl-2-oxo-2*H*-chromen-6-yl)-*N*-ethyl-2-iodobenzamide (3a); Typical Procedure

A mixture of 2-iodobenzoic acid (251 mg, 0.87 mmol) and $SOCl_2$ was refluxed for 3 h. Excess $SOCl_2$ was removed and the residue was dissolved in CH_2Cl_2 (10 mL). A soln of amine **1a** (200 mg, 0.87 mmol) in CH_2Cl_2 (20 mL) and Bu_4NHSO_4 (cat.) was added to the stirred soln of the acid chloride. Aq K_2CO_3 (241.4 mg, 1.74 mmol) was then added slowly and the mixture was stirred for 6 h at r.t. The soln was then washed sequentially with 5% aq HCl (2 × 20 mL) and 5% aq NaOH (2 × 20 mL). The organic layer was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography [silica gel, PE–EtOAc (7:3)] to give a pale yellow gummy liquid; yield: 336.6 mg (84%).

Compounds **3b**–**f** and **5** were similarly prepared. All the amidation reactions were performed by using 200 mg of the appropriate amine.

IR (KBr): 1596, 1652, 1731, 2934 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03 (t, *J* = 6.8 Hz, 3 H), 3.16–3.25 (m, 1 H), 3.65 (dt, *J* = 2.4, 17.2 Hz, 1 H), 3.85 (dt, *J* = 2.4, 16.8 Hz, 1 H), 4.51–4.60 (m, 1 H), 4.83 (d, *J* = 17.2 Hz, 1 H), 5.19 (dd, *J* = 10.8, 15.2 Hz, 1 H), 5.96–6.06 (m, 1 H), 6.39 (d, *J* = 10.0 Hz, 1 H), 6.86 (d, *J* = 8.0 Hz, 1 H), 7.01–7.06 (m, 2 H), 7.43–7.51 (m, 2 H), 7.71 (d, *J* = 7.6 Hz, 1 H), 7.79 (d, *J* = 10.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.4, 31.8, 44.2, 94.1, 116.4, 116.7, 117.8, 118.6, 126.7, 127.4, 128.4, 130.5, 133.5, 135.0, 136.9, 139.6, 140.9, 141.5, 153.8, 159.8, 169.9.

MS (ESI): *m/z* = 460 [M + H]$^+$.

Anal. Calcd for $C_{21}H_{18}INO_3$: C, 54.92; H, 3.95; N, 3.05. Found: C, 54.93; H, 3.91; N, 3.01.

N-(5-Allyl-2-oxo-2*H*-chromen-6-yl)-2-iodo-*N*-methylbenzamide (3b)

Yellow gummy liquid; yield: 351.7 mg (85%).

IR (KBr): 1598, 1668, 1724, 2931 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.40 (s, 3 H), 3.68 (dt, *J* = 2.4, 17.2 Hz, 1 H), 3.89 (dt, *J* = 2.4, 16.8 Hz, 1 H), 4.90 (d, *J* = 17.2 Hz, 1 H), 5.18 (dd, *J* = 10.4, 15.6 Hz, 1 H), 5.97–6.10 (m, 1 H), 6.46 (d, *J* = 9.6 Hz, 1 H), 6.84–6.95 (m, 1 H), 7.06 (t, *J* = 8.0 Hz, 1 H), 7.15 (td, *J* = 1.2, 8.0 Hz, 1 H), 7.36 (d, *J* = 8.8 Hz, 1 H), 7.47–7.58 (m, 1 H), 7.78 (d, *J* = 9.6 Hz, 1 H), 7.94 (d, *J* = 10.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.8, 37.7, 93.8, 116.4, 116.7, 117.7, 118.4, 127.2, 128.6, 130.1, 131.2, 132.1, 134.9, 138.5, 139.6, 140.4, 141.4, 153.7, 160.0, 170.3.

MS (ESI): *m/z* = 468 [M + Na]$^+$.

Anal. Calcd for $C_{20}H_{16}INO_3$: C, 53.95; H, 3.62; N, 3.15. Found: C, 53.97; H, 3.60; N, 3.14.

N-(5-Allyl-1-methyl-2-oxo-1,2-dihydroquinolin-6-yl)-*N*-ethyl-2-iodobenzamide (3c)

Yellow gummy liquid; yield: 339.2 mg (87%).

IR (KBr): 1612, 1645, 1658, 2929 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.37 (t, *J* = 7.2 Hz, 3 H), 3.17–3.23 (m, 2 H), 3.77 (s, 3 H), 4.19 (q, *J* = 7.2 Hz, 2 H), 4.84 (d, *J* = 17.2 Hz, 2 H), 5.97–6.06 (m, 1 H), 6.69 (d, *J* = 10.0 Hz, 1 H), 6.82 (td, *J* = 1.6, 7.6 Hz, 1 H), 6.87 (dd, *J* = 1.6, 7.6 Hz, 1 H), 7.00 (t, *J* = 7.2 Hz, 1 H), 7.10 (d, *J* = 9.2 Hz, 1 H), 7.52 (d, *J* = 8.8 Hz, 1 H), 7.79 (d, *J* = 10.0 Hz, 1 H), 7.95 (d, *J* = 10.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.7, 31.9, 37.6, 44.2, 94.0, 113.2, 117.6, 121.9, 126.6, 127.3, 129.8, 130.3, 132.1, 134.4, 134.7, 135.2, 135.8, 139.0, 139.4, 141.8, 161.1, 170.0.

MS (ESI): *m/z* = 473 [M + H]$^+$.

Anal. Calcd for $C_{22}H_{21}IN_2O_2$: C, 55.94; H, 4.48; N, 5.93. Found: C, 55.90; H, 4.49; N, 5.91.

N-(5-Allyl-1-methyl-2-oxo-1,2-dihydroquinolin-6-yl)-2-iodo-*N*-methylbenzamide (3d)

Yellow solid; yield: 361.2 mg (86%); mp 149–150 °C (MeCN).

IR (KBr): 1610, 1642, 1657, 2929 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.41 (s, 3 H), 3.78 (s, 3 H), 4.10 (q, *J* = 6.8 Hz, 2 H), 4.84 (d, *J* = 17.2 Hz, 1 H), 5.16 (dd, *J* = 10.4, 17.6 Hz, 1 H), 5.99–6.07 (m, 1 H), 6.69 (d, *J* = 10.0 Hz, 1 H), 6.83 (td, *J* = 1.6, 7.6 Hz, 1 H), 6.92 (dd, *J* = 1.2, 7.6 Hz, 1 H), 7.03 (t, *J* = 7.6 Hz, 1 H), 7.12 (d, *J* = 9.2 Hz, 1 H), 7.56 (d, *J* = 9.2 Hz, 1 H), 7.78 (d, *J* = 9.6 Hz, 1 H), 7.93 (d, *J* = 10.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.5, 31.8, 37.6, 93.7, 113.8, 117.4, 121.8, 126.9, 127.1, 129.9, 130.3, 130.6, 135.1, 135.6, 136.5, 139.3, 139.8, 140.0, 141.5, 161.4, 170.3.

MS (ESI): *m/z* = 481 [M + Na]$^+$.

Anal. Calcd for $C_{21}H_{19}IN_2O_2$: C, 55.04; H, 4.18; N, 6.11. Found: C, 55.08; H, 4.17; N, 6.14.

N-(5-Allyl-1-ethyl-2-oxo-1,2-dihydroquinolin-6-yl)-*N*-ethyl-2-iodobenzamide (3e)

Pale yellow solid; yield: 318.9 mg (84%); mp 161–162 °C (MeCN–hexane).

IR (KBr): 1599, 1648, 1662, 2930 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.04 (t, *J* = 7.2 Hz, 3 H), 1.40 (t, *J* = 7.2 Hz, 3 H), 3.17–3.26 (m, 1 H), 3.72 (dt, *J* = 2.4, 16.8 Hz, 1 H), 3.89 (dt, *J* = 2.4, 16.8 Hz, 1 H), 4.10- 4.19 (m, 2 H), 4.54–4.63 (m, 1 H), 4.87 (d, *J* = 16.8 Hz, 1 H), 5.17 (dd, *J* = 10.4, 15.2 Hz, 1 H), 5.96–6.06 (m, 1 H), 6.68 (d, *J* = 10.0 Hz, 1 H), 6.82 (td, *J* = 1.6, 7.6 Hz, 1 H), 6.87 (dd, *J* = 1.6, 7.6 Hz, 1 H), 7.00 (t, *J* = 7.2 Hz, 1 H), 7.10 (d, *J* = 9.2 Hz, 1 H), 7.51 (d, *J* = 9.2 Hz, 1 H), 7.70 (d, *J* = 8.0 Hz, 1 H), 7.79 (d, *J* = 10.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.4, 12.8, 32.0, 37.6, 44.3, 94.1, 113.2, 117.6, 120.3, 121.8, 122.0, 127.3, 129.8, 130.4, 132.1, 134.4, 134.8, 135.2, 135.8, 139.4, 141.8, 161.1, 170.0.

MS (ESI): *m/z* = 487 [M + H]$^+$.

Anal. Calcd for $C_{23}H_{23}IN_2O_2$: C, 56.80; H, 4.77; N, 5.76. Found: C, 56.82; H, 4.74; N, 5.71.

N-(5-Allyl-1-ethyl-2-oxo-1,2-dihydroquinolin-6-yl)-2-iodo-*N*-methylbenzamide (3f)

Yellow gummy liquid; yield: 319.8 mg (82%).

IR (KBr): 1611, 1645, 1659, 2929 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38 (t, *J* = 7.2 Hz, 3 H), 3.17–3.23 (m, 2 H), 3.78 (s, 3 H), 4.19 (q, *J* = 7.2 Hz, 2 H), 4.85 (d, *J* = 17.2 Hz, 2 H), 5.97–6.06 (m, 1 H), 6.69 (d, *J* = 10.0 Hz, 1 H), 6.82 (td, *J* = 1.6, 7.6 Hz, 1 H), 6.87 (dd, *J* = 1.6, 7.6 Hz, 1 H), 7.00 (t, *J* = 7.2 Hz, 1 H), 7.10 (d, *J* = 9.2 Hz, 1 H), 7.52 (d, *J* = 8.8 Hz, 1 H), 7.79 (d, *J* = 10.0 Hz, 1 H), 7.95 (d, *J* = 10.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 12.7, 31.9, 37.6, 44.3, 93.9, 113.3, 117.6, 121.9, 126.7, 127.3, 129.9, 130.4, 132.1, 134.4, 134.8, 135.2, 135.8, 139.1, 139.4, 141.8, 161.1, 170.0.

MS (ESI): *m/z* = 473 [M + H]$^+$.

Anal. Calcd for $C_{22}H_{21}IN_2O_2$: C, 55.94; H, 4.48; N, 5.93. Found: C, 55.90; H, 4.48; N, 5.92.

(5):

***N*-(2-Allyl-1-naphthyl)-2-iodo-*N*-tosylbenzamide (5)**
Off-white gummy liquid; yield: 282.8 mg (84%).

IR (KBr): 1598, 1645, 2858, 2929 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (s, 3 H), 3.64–3.81 (m, 1 H), 4.96 (dd, *J* = 1.6, 17.2 Hz, 1 H), 5.08 (dd, *J* = 1.2, 11.2 Hz, 1 H), 5.20 (d, *J* = 13.6 Hz, 1 H), 5.75–5.91 (m, 1 H), 6.39 (s, 1 H), 6.78 (s, 1 H), 7.01 (d, *J* = 8.0 Hz, 1 H), 7.29–7.37 (m, 3 H), 7.39–7.51 (m, 2 H), 7.52 (d, *J* = 8.0 Hz, 2 H), 7.70 (t, *J* = 8.8 Hz, 2 H), 7.89 (d, *J* = 8.8 Hz, 1 H), 7.96 (d, *J* = 8.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 37.0, 93.5, 117.7, 124.2, 126.0, 126.4, 127.4, 127.5, 128.0, 128.2, 129.1, 129.7, 129.8, 130.7, 130.9, 132.9, 135.1, 135.6, 140.0, 145.5, 168.7.

MS (ESI): *m/z* = 568 [M + H]$^+$.

Anal. Calcd for $C_{27}H_{22}INO_3S$: C, 57.15; H, 3.91; N, 2.47. Found: C, 57.10; H, 3.93; N, 2.46.

7-Ethyl-13-methylene-13,14-dihydro-3*H*-chromeno[6,5-*c*][2]benzazocine-3,8(7*H*)-dione (6a); Typical Procedure
N_2 was bubbled through a mixture of amide **3a** (150 mg, 0.33 mmol), TBAB (126 mg, 0.39 mmol), and fused KOAc (80 mg, 0.82 mmol) in anhyd DMF (10 mL). $Pd(PPh_3)_4$ (37.6 mg, 10 mol%) was then added and the mixture was stirred at 90 °C for 8 h. The mixture was cooled, mixed with H_2O (20 mL), and extracted with EtOAc (3 × 20 mL). The organic extracts were washed successively with H_2O (4 × 10 mL) and brine (10 mL) then dried (Na_2SO_4) and concentrated under reduced pressure to give a viscous mass that was purified by column chromatography [silica gel, PE–EtOAc (7:3)] to give an orange solid; yield: 72.5 mg (67%); mp 161–162 °C (MeCN–hexane).

Products **6b–f** and **7** were similarly prepared from the corresponding Heck precursors (150 mg).

IR (KBr): 1597, 1648, 1734, 2931 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 6.8 Hz, 3 H), 3.66–3.75 (m, 1 H), 4.03 (d, *J* = 16.4 Hz, 1 H), 4.16 (dt, *J* = 2.4, 16.0 Hz, 1 H), 4.26–4.35 (m, 1 H), 5.44 (d, *J* = 2.4 Hz, 2 H), 6.45 (d, *J* = 10.0 Hz, 1 H), 7.11–7.18 (m, 4 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 7.89 (d, *J* = 9.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.5, 34.3, 44.3, 115.4, 116.7, 117.3, 119.9, 127.5, 128.2, 129.1, 129.3, 134.7, 134.9, 135.7, 137.6, 139.4, 140.7, 145.2, 153.4, 159.9, 171.6.

MS (ESI): *m/z* = 332 [M + H]$^+$.

Anal. Calcd for $C_{21}H_{17}NO_3$: C, 76.12; H, 5.17; N, 4.23. Found: C, 76.14; H, 5.16; N, 4.20.

7-Methyl-13-methylene-13,14-dihydro-3*H*-chromeno[6,5-*c*][2]benzazocine-3,8(7*H*)-dione (6b)
Orange solid; yield: 74.8 mg (70%); mp 126–127 °C (MeCN–hexane).

IR (KBr): 1589, 1639, 1730, 2932 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.45 (m, 3 H), 4.05–4.15 (m, 2 H), 5.45 (s, 2 H), 6.45 (d, *J* = 10.0 Hz, 1 H), 7.12–7.25 (m, 4 H), 7.44–7.49 (m, 2 H), 7.88 (d, *J* = 10.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 34.2, 45.8, 115.6, 116.6, 117.3, 119.8, 127.5, 128.2, 129.1, 130.0, 134.8, 134.9, 135.8, 137.6, 139.4, 140.8, 145.2, 153.4, 160.0, 171.6.

MS (ESI): *m/z* = 340 [M + Na]$^+$.

Anal. Calcd for $C_{20}H_{15}NO_3$: C, 75.70; H, 4.76; N, 4.41. Found: C, 75.74; H, 4.74; N, 4.40.

7-Ethyl-4-methyl-13-methylene-4,7,13,14-tetrahydroquino[6,5-*c*][2]benzazocine-3,8-dione (6c)
Brown gummy liquid; yield: 76.5 mg (70%).

IR (KBr): 1568, 1645, 1662, 2922 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.2 Hz, 3 H), 3.22 (d, *J* = 12.0 Hz, 1 H), 3.24 (d, *J* = 12.0 Hz, 1 H), 3.28–3.48 (m, 1 H), 3.77 (s, 3 H), 4.37–4.45 (m, 1 H), 5.45 (d, *J* = 2.4 Hz, 2 H), 6.82 (d, *J* = 10.0 Hz, 1 H), 7.38 (d, *J* = 10.4 Hz, 2 H), 7.69 (t, *J* = 8.8 Hz, 1 H), 7.82–7.84 (m, 2 H), 8.34 (d, *J* = 10.0 Hz, 1 H), 8.51 (d, *J* = 10.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8, 29.7, 34.5, 44.2, 115.2, 119.1, 119.8, 122.5, 125.2, 127.5, 127.8, 128.6, 134.6, 134.8, 135.0, 135.4, 135.9, 137.8, 139.6, 145.5, 161.6, 171.8.

MS (ESI): *m/z* = 345 [M + H]$^+$.

Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.77; H, 5.84; N, 8.05.

4,7-Dimethyl-13-methylene-4,7,13,14-tetrahydroquino[6,5-*c*][2]benzazocine-3,8-dione (6d)
Brown gummy liquid; yield: 70.3 mg (68%).

IR (KBr): 1570, 1641, 1668, 2923 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.30 (d, *J* = 13.6 Hz, 1 H), 3.31 (d, *J* = 13.6 Hz, 1 H), 3.63 (s, 3 H), 3.64 (s, 3 H), 5.44 (d, *J* = 2.4 Hz, 2 H), 6.80 (d, *J* = 8.8 Hz, 1 H), 7.67 (t, *J* = 6.8 Hz, 1 H), 7.82 (d, *J* = 9.6 Hz, 2 H), 7.84 (d, *J* = 10.0 Hz, 2 H), 8.32 (d, *J* = 10.0 Hz, 1 H), 8.56 (d, *J* = 8.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.9, 39.9, 45.1, 116.6, 116.9, 117.9, 118.4, 126.2, 126.9, 127.6, 128.1, 129.8, 131.4, 132.4, 137.8, 140.0, 141.3, 146.8, 155.1, 160.2, 171.9.

MS (ESI): *m/z* = 353 [M + Na]$^+$.

Anal. Calcd for $C_{21}H_{18}N_2O_2$: C, 76.34; H, 5.49; N, 8.48. Found: C, 76.35; H, 5.47; N, 8.44.

4,7-Diethyl-13-methylene-4,7,13,14-tetrahydroquino[6,5-*c*][2]benzazocine-3,8-dione (6e)
Light brown solid; yield: 66.3 mg (60%); mp 154–155 °C (MeCN–hexane).

IR (KBr): 1561, 1651, 1662, 2926 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.2 Hz, 6 H), 3.67–3.76 (m, 1 H), 4.14–4.17 (m, 2 H), 4.24–4.38 (m, 2 H), 4.49–4.57 (m, 1 H), 5.44 (d, *J* = 2.0 Hz, 2 H), 6.73 (d, *J* = 10.0 Hz, 1 H), 7.11 (d, *J* = 7.2 Hz, 2 H), 7.44–7.49 (m, 2 H), 7.64–7.69 (m, 2 H), 7.89 (d, *J* = 10.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8, 29.7, 34.6, 44.3, 114.0, 115.2, 119.4, 121.1, 122.5, 127.3, 127.5, 128.0, 128.6, 128.7, 132.0, 133.9, 135.6, 137.9, 138.6, 145.5, 161.2, 171.8.

MS (ESI): *m/z* = 359 [M + H]$^+$.

Anal. Calcd for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.82. Found: C, 77.11; H, 6.19; N, 7.80.

4-Ethyl-7-methyl-13-methylene-4,7,13,14-tetrahydroquino[6,5-*c*][2]benzazocine-3,8-dione (6f)
Brown gummy liquid; yield: 67.8 mg (62%).

IR (KBr): 1565, 1645, 1664, 2922 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.25 (t, *J* = 7.2 Hz, 3 H), 3.23 (d, *J* = 12.0 Hz, 1 H), 3.24 (d, *J* = 12.0 Hz, 1 H), 3.28–3.48 (m, 1 H), 3.77 (s, 3 H), 4.37–4.44 (m, 1 H), 5.45 (d, *J* = 2.4 Hz, 2 H), 6.82 (d, *J* = 10.0 Hz, 1 H), 7.38 (d, *J* = 10.4 Hz, 2 H), 7.69 (t, *J* = 8.8 Hz, 1 H), 7.82–7.85 (m, 2 H), 8.34 (d, *J* = 10.0 Hz, 1 H), 8.51 (d, *J* = 10.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8, 29.7, 34.5, 44.3, 115.2, 119.1, 119.8, 122.5, 125.2, 127.5, 127.8, 128.6, 134.6, 134.8, 135.0, 135.4, 135.9, 137.8, 139.6, 145.6, 161.6, 171.8.

MS (ESI): *m/z* = 367 $[M + Na]^+$.

Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.75; H, 5.86; N, 8.12.

8-Methylene-14-tosyl-7,14-dihydrobenzo[*f*]naphtho[1,2-*b*]azocin-13(8*H*)-one (7)
Orange gummy liquid; yield: 70.8 mg (61%).

IR (KBr): 1596, 1622, 1695, 2923 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 3 H), 3.74 (d, *J* = 16.8 Hz, 1 H), 4.11 (d, *J* = 16.4 Hz, 1 H), 5.15 (s, 1 H), 5.26 (s, 1 H), 6.98 (d, *J* = 7.2 Hz, 1 H), 7.15 (d, *J* = 6.8 Hz, 1 H), 7.22 (d, *J* = 8.4 Hz, 2 H), 7.37–7.47 (m, 4 H), 7.57 (d, *J* = 8.0 Hz, 1 H), 7.69–7.74 (m, 3 H), 7.88 (d, *J* = 8.0 Hz, 1 H), 8.06 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.8, 39.8, 116.5, 123.7, 125.9, 126.1, 126.3, 126.7, 127.5, 127.7, 128.0, 128.5, 129.0, 129.2, 129.4, 129.6, 130.2, 130.5, 131.9, 134.0, 135.2, 137.4, 144.8, 145.5, 171.3.

MS (ESI): *m/z* = 440 $[M + H]^+$.

Anal. Calcd for $C_{27}H_{21}NO_3S$: C, 73.78; H, 4.82; N, 3.19. Found: C, 73.79; H, 4.76; N, 3.22.

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