Diversity-Oriented Synthesis of Functionalized Quinolin-2(1*H*)-ones via Pd-Catalyzed Site-Selective Cross-Coupling Reactions

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Biologically active 3-amino-4-arylquinolin-2(1*H*)-ones and 3-alkenyl-4-arylquinolin-2(1*H*)-ones were synthesized in an efficient and concise manner, utilizing readily available 4-hydroxyquinolin-2(1*H*)-one as starting material. The key steps, which introduced selectivity and diversity in the synthesis, were the palladium-catalyzed site-selective Suzuki−Miyaura/Buchwald−Hartwig amination and Suzuki−Miyaura/Heck coupling reactions of 3-bromo-4-trifloxy-quinolin-2(*1H*)-one.

Introduction

The prominence of quinolin-2(1*H*)-one in natural products and biologically active molecules has promoted considerable efforts toward their synthesis.[1] As a "privileged" scaffold, quinolin-2(1*H*)-one shows interesting biological properties.[1,2] (Figure 1) For instance, compound **A** and the related reduced allylic alcohols have been found as a novel and potent maxi-K channel openers useful for the treatment of male erectile dysfunction.[1a−c] 3-Amino-4-arylquinolin-2(1*H*)-ones **B** were discovered to possess neuroprotective properties.[1e] A class of potent KDR kinase inhibitors containing the 1*H*-indole-2-yl-quinolin-2(1*H*)-one core structure was reported by Merck, such as compound **C** which has been utilized for clinical development for cancer therapy.[2a−f] 6-Functionalized 4-arylquinolin-2(1*H*)-one **D** has been identified as a novel, selective, nonpeptide farnesyl protein inhibitor and is currently in human clinical trials as an orally active antitumor agent.[1f,1g] In connection with a chemical genetic approach of analyzing biological systems by using interfacing libraries of natural productlike molecules with biological assays,[3] we became interested in developing new approaches for synthesis of functionalized quinolin-2(1*H*)-ones, such as 3-alkenyl-4-arylquinolin-2(1*H*)-ones **A** and 3-amino-4-arylquinolin-2(1*H*)-one **B**, with a hope of finding more active hits or leads for our particular biological assays.[4]

Although there are reported methods for the synthesis of 3-alkenyl-4-arylquinolin-2(1*H*)-ones **A**[1d] or 3-amino-4-arylquinolin-2(1*H*)-one **B**[1e] which allows the chemists to synthesize the intriguing molecules individually via multiple steps, it is highly desired to develop even more effective and general synthetic methodologies for these heterocycle formations in order to build up complex natural productlike molecules in a combinatorial format.

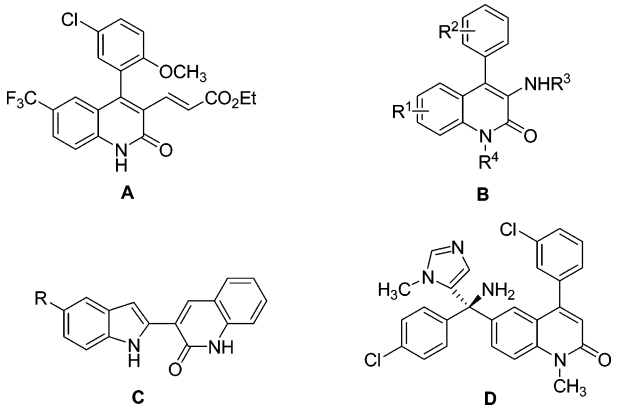
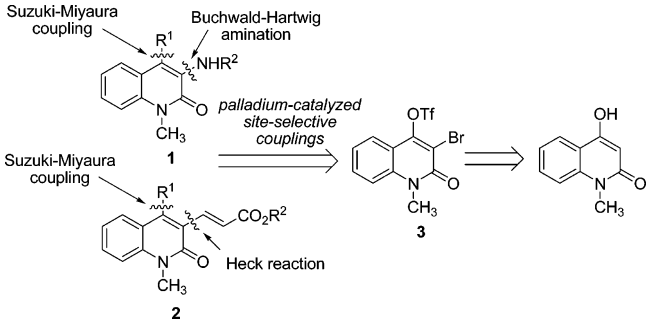


Figure 1. Biologically active molecules. (A) For the treatment of male eretile dysfunction. (B) With neuroprotective properties. (C) Merck KDR inhibitor. (D) Antitumor.

Scheme 1



Results and Discussion

Retrosynthetically, the key compound in our overall synthetic route was identified as 3-bromo-4-trifloxy-quinolin-2(1*H*)-one **3** (Scheme 1). Prompted by the recent advances of halogenation of 1,3-dicarbonyl compounds,[5] we envisioned that this compound could be generated by treatment of 4-hydroxyquinolin-2(1*H*)-one with NBS/$Mg(ClO_4)_2$ and trifluoromethanesulfonic anhydride, subsequently. It is well-known that 4-hydroxyquinolin-2(1*H*)-ones are useful intermediates for many industrial products, and several methods for their preparation have been reported.[6] To verify the

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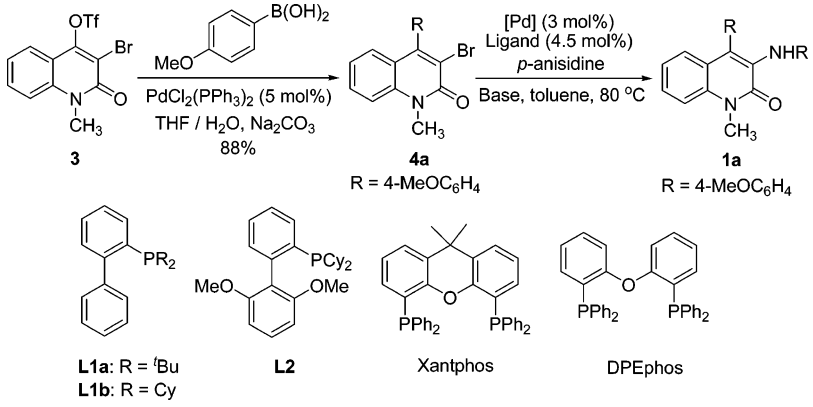
Table 1. Conditions Screening for Palladium-Catalyzed Reaction of 4-Aryl-3-bromoquinolin-2(1*H*)-one **4a** with *p*-Anisidine



entry	[Pd]	ligand	base	yield (%)[a]
1	$Pd_2(dba)_3$	/	Cs_2CO_3	11
2	$Pd_2(dba)_3$	Xantphos	Cs_2CO_3	78
3	$Pd_2(dba)_3$	DPEphos	Cs_2CO_3	73
4	$Pd_2(dba)_3$	**L1a**	Cs_2CO_3	trace
5	$Pd_2(dba)_3$	**L1b**	Cs_2CO_3	trace
6	$Pd_2(dba)_3$	**L2**	Cs_2CO_3	88
7	$Pd_2(dba)_3$	DPPF	Cs_2CO_3	65
8	$Pd_2(dba)_3$	(*R*)−BINAP	Cs_2CO_3	92
9	$Pd_2(dba)_3$	(*R*)−BINAP	K_2CO_3	52
10	$Pd_2(dba)_3$	(*R*)−BINAP	*t*-BuOK	68
11	$Pd(OAc)_2$	(*R*)−BINAP	Cs_2CO_3	91

[a] Isolated yield based on 4-aryl-3-bromoquinolin-2(1*H*)-one **4a**.

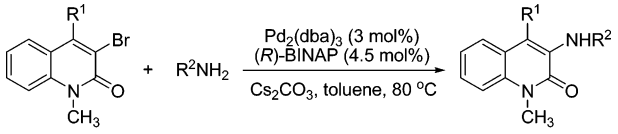
practicability of the projected route as shown in Scheme 1, an initial model study was performed using the commercially available 4-hydroxyquinolin-2(1*H*)-one as the starting material (Scheme 1).

As described above, 3-bromo-4-trifloxy-quinolin-2(1*H*)-one **3** could be easily synthesized in high yield (92%) in two steps from 4-hydroxy-quinolin-2(1*H*)-one. We conceived that the 4-trifloxy group attached to the electron-withdrawing α,β-unsaturated double bond in compound **3** may increase its capability to oxidatively add to the transition metals. Therefore, the regioselective cross-couplings of **3** catalyzed by a transition metal are possible. Due to their easy handling and long shelf life, arylboronic acid derivatives would be the starting materials of choice. Thus, we started to explore the possibility of using **3** as an electrophile for the Suzuki−Miyaura reaction.[7] To our delight, we found that the corresponding product **4a** could be afforded in 88% yield under standard conditions [$PdCl_2(PPh_3)_2$, THF/H_2O, Na_2CO_3] for the reaction of 3-bromo-4-trifloxy-quinolin-2(1*H*)-one **3** with 4-methoxyphenylboronic acid. With this compound in hand, we started to investigate the further elaboration by installing amino groups on the 3-position of quinolin-2(1*H*)-one (Table 1).

Our studies commenced with the reaction of 3-bromo-4-(4-methoxyphenyl)quinolin-2(1*H*)-one **4a** with *p*-anisidine in toluene at 80 °C catalyzed by $Pd_2(dba)_3$, in the presence of Cs_2CO_3 as the base. To our delight, we observed the formation of desired product **1a** although the yield was low (11%; Table 1, entry 1). The result was dramatically improved when Xantphos was added as the ligand (78% yield; Table 1, entry 2). Similar yield (73%) was obtained when Xantphos was replaced by DPEphos (Table 1, entry 3). Surprisingly, only a trace amount of product **1a** was detected when ligand **L1a** or **L1b** was utilized in the reaction (Table 1, entries 4 and 5). Treatment of 3-bromo-4-(4-methoxyphenyl)quinolin-2(1*H*)-one **4a** and *p*-anisidine in the presence of phosphine ligand **L2** gave the product in 88% yield (Table 1, entry 6). Further studies revealed that the yield could be increased to 92% when (*R*)-BINAP was employed in the reaction in combination with Cs_2CO_3 (Table 1, entry 8). Inferior results were generated when the base was changed to K_2CO_3 or *t*-BuOK (Table 1, entries 9 and 10). Similar yield was afforded when $Pd(OAc)_2$ was used instead of $Pd_2(dba)_3$ (91% yield; Table 1, entry 11).

With this promising result in hand, we started to investigate the scope of this reaction under the optimized reaction conditions [$Pd_2(dba)_3$ (3 mol %), (*R*)-BINAP (4.5 mol %), Cs_2CO_3, toluene, 80 °C], and the results are shown in Table 2. From Table 2, it was found that, for most of cases, reactions of 3-bromo-4-arylquinolin-2(1*H*)-one **4** with various amines catalyzed by $Pd_2(dba)_3$/(*R*)-BINAP furnished the corresponding 3-amino products **1** in good to excellent yields. The reactions were very clean and usually completed in several hours. No big difference was observed for the electron-donating or electron-withdrawing groups attached on the aromatic ring of substrates. For example, reaction of 3-bromo-4-(4-methoxyphenyl)quinolin-2(1*H*)-one **4a** with *p*-anisidine afforded the desired product **1a** in 92% yield (Table 2, entry 1). 3-Bromo-4-(4-cyanophenyl)quinolin-2(1*H*)-one **4b** reacted with *p*-anisidine, leading to the corresponding product **1f** in 90% yield (Table 2, entry 8). A 93% yield of product **1g** was generated when 4-fluoroaniline was used instead of *p*-anisidine in the reaction of 3-bromo-4-(4-cyanophenyl)quinolin-2(1*H*)-one **4b** (Table 2, entry 9). No reaction occurred when bulky amines, such as 2,6-diisopropylbenzenamine and 2,4,6-trimethylbenzenamine,

Table 2. Palladium-Catalyzed Reactions of 4-Aryl-3-bromoquinolin-2(1*H*)-one **4** with Various Amines



4 **1**

entry	R^1	R^2	product	yield (%)[a]
1	4-$MeOC_6H_4$ (**4a**)	4-$MeOC_6H_4$	**1a**	92
2	4-$MeOC_6H_4$ (**4a**)	4-FC_6H_4	**1b**	75
3	4-$MeOC_6H_4$ (**4a**)	C_6H_5	**1c**	90
4	4-$MeOC_6H_4$ (**4a**)	$C_6H_5CH_2$	**1d**	79
5	4-$MeOC_6H_4$ (**4a**)	$CH_3(CH_2)_4$	**1e**	91
6	4-$MeOC_6H_4$ (**4a**)	2,6-diisopropyl-phenyl		NR
7	4-$MeOC_6H_4$ (**4a**)	2,4,6-trimethyl-phenyl		NR
8	4-NCC_6H_4 (**4b**)	4-$MeOC_6H_4$	**1f**	90
9	4-NCC_6H_4 (**4b**)	4-FC_6H_4	**1g**	93
10	4-NCC_6H_4 (**4b**)	C_6H_5	**1h**	95
11	C_6H_5 (**4c**)	4-$MeOC_6H_4$	**1i**	84
12	C_6H_5 (**4c**)	4-FC_6H_4	**1j**	72
13	C_6H_5 (**4c**)	C_6H_5	**1k**	85
14	2-$MeOC_6H_4$ (**4d**)	4-$MeOC_6H_4$	**1l**	83
15	3-AcC_6H_4 (**4e**)	4-$MeOC_6H_4$	**1m**	76
16	3-NCC_6H_4 (**4f**)	4-$MeOC_6H_4$	**1n**	87

[a] Isolated yield based on 4-aryl-3-bromoquinolin-2(1*H*)-one **4**.

were employed in the reaction of 3-bromo-4-(4-methoxyphenyl)quinolin-2(1*H*)-one **4a** (Table 2, entries 6 and 7). Moreover, aliphatic amines were also good partners in this kind of transformation. For instance, reaction of 3-bromo-4-(4-methoxyphenyl)quinolin-2(1*H*)-one **4a** with benzyl amine or *n*-pentylamine proceeded smoothly to afford the desired product in 79% or 91% yield, respectively (Table 2, entries 4 and 5).

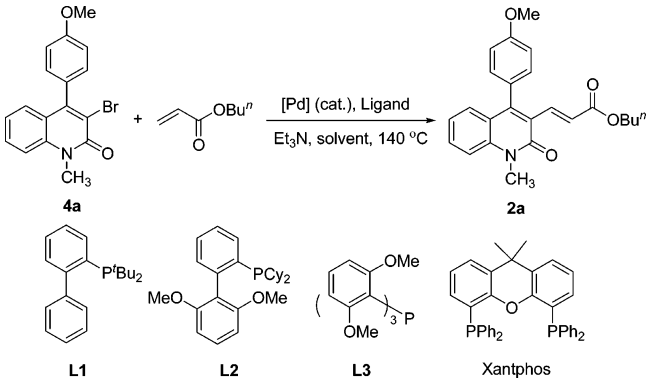
After installing amino groups in the 3-position of quinolin-2(1*H*)-one via palladium-catalyzed amination reaction, we shifted our focus for introducing an alkenyl group on the 3-position. Initial studies were performed for the reaction of 4-aryl-3-bromoquinolin-2(1*H*)-one **4a** with *n*-butyl acrylate. The results of condition screening are shown in Table 3. In the presence of $Pd(PPh_3)_4$ and Et_3N in DMF, a 27% yield of product **2a** was obtained (Table 3, entry 1). The result could be improved by adding different phosphine ligands. For example, 67% yield of compound **2a** was generated in the presence of **L3** (Table 3, entry 3). Finally, it was found that the yield could be increased to 80% when tetrabutylammonium bromide was added as an additive (Table 3, entry 10).

The scope of this Heck reaction was also investigated, and the results are shown in Table 4. It was found that all reactions proceeded smoothly to afford the desired products **2** in good yield, despite different aryl groups being attached on the 4-position of substrate **4**.

Conclusion

In summary, we have described an efficient and general route for the synthesis of biologically active 3-amino-4-arylquinolin-2(1*H*)-ones and 3-alkenyl-4-arylquinolin-2(1*H*)-ones via palladium-catalyzed site-selective cross-coupling reaction, starting from 4-hydroxyquinolin-2(1*H*)-one. The diversity could be easily introduced when the selectivity occurred. Construction of a small library and screening for biological activity of these small molecules are under investigation in our laboratory.

Table 3. Conditions Screening for Palladium-Catalyzed Reaction of 4-Aryl-3-bromoquinolin-2(1*H*)-one **4a** with *n*-Butyl Acrylate



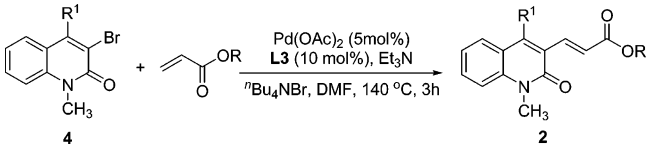
4a **2a**

L1 **L2** **L3** Xantphos

entry	[Pd]	ligand	solvent	yield (%)[a]
1	$Pd(PPh_3)_4$	/	DMF	27
2	$Pd(OAc)_2$	tri-*o*-tolylphosphine	DMF	59
3	$Pd(OAc)_2$	**L3**	DMF	67
4	$Pd(OAc)_2$	**L3**	DMAc	44
5	$Pd(OAc)_2$	PCy_3	DMF	trace
6	$Pd(OAc)_2$	DPPF	DMF	NR
7	$Pd(OAc)_2$	**L1**	DMF	trace
8	$Pd(OAc)_2$	**L2**	DMF	51
9	$Pd(OAc)_2$	Xantphos	DMF	NR
10	$Pd(OAc)_2$	**L3**/^{n}Bu_4NBr	DMF	80
11	$Pd(OAc)_2$	**L3**	DMAc	44

[a] Isolated yield based on 4-aryl-3-bromoquinolin-2(1*H*)-one **4a**.

Table 4. Palladium-Catalyzed Reaction of 4-Aryl-3-bromoquinolin-2(1*H*)-one **4** with *n*-Butyl or Ethyl Acrylate



4 **2**

entry	R^1	R	product	yield (%)[a]
1	4-$MeOC_6H_4$ (**4a**)	^{n}Bu	**2a**	80
2	4-CNC_6H_4 (**4b**)	^{n}Bu	**2b**	65
3	C_6H_5 (**4c**)	^{n}Bu	**2c**	70
4	2-$MeOC_6H_4$ (**4d**)	^{n}Bu	**2d**	68
5	3-AcC_6H_4 (**4e**)	^{n}Bu	**2e**	67
6	3-NCC_6H_4 (**4f**)	^{n}Bu	**2f**	60
7	C_6H_5 (**4c**)	Et	**2g**	81

[a] Isolated yield based on 4-aryl-3-bromoquinolin-2(1*H*)-one **4**.

Experimental Section

All reactions were performed in test tubes under nitrogen atmosphere. Flash column chromatography was performed using silica gel (60-Å pore size, 32−63 μm, standard grade). Analytical thin−layer chromatography was performed using glass plates precoated with 0.25 mm 230−400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin-layer chromatography plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on

rotary evaporators at ~20 Torr (house vacuum) at 25−35 °C. Commercial reagents and solvents were used as received.

General Procedure for the Preparation of Compounds 4 through Cross-Coupling Reaction between 3-Bromo-4-trifloxy-quinolin-2(1H)-one and Arylboronic Acids. Potassium carbonate (2.0 M in water, 0.75 mL) was added to a solution of 3-bromo-4-trifloxy-quinolin-2(1*H*)-one (192.5 mg, 0.50 mmol) **3**, $PdCl_2(PPh_3)_2$ (17.5 mg, 0.025 mmol), and boronic acid (1.1 equiv) in THF (4.0 mL) under nitrogen atmosphere. The reaction mixture was stirred overnight at room temperature. Following completion of the reaction as indicated by TLC, the reaction mixture was diluted with ethyl acetate (20 mL) and separated. The organic phase was dried and filtered, and the filtrate was concentrated to a residue that was purified by flash chromatography (silica gel, 2/1 (v/v) petroleum ether/ethyl acetate) to give the corresponding product **4**.

3-Bromo-4-(4-methoxyphenyl)-1-methylquinolin-2(1H)-one (4a):[7] 88% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.60 (t, J = 7.5 Hz, 1H), 7.43 (d, J = 8.5 Hz, 1H), 7.20−7.28 (m, 3H), 7.14 (t, J = 7.5 Hz, 1H), 7.07 (d, J = 8.0 Hz, 2H), 3.91 (s, 3H), 3.89 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 159.9, 158.7, 150.6, 139.1, 131.0, 130.2, 129.8, 128.8, 122.7, 121.9, 119.8, 114.5, 114.3, 55.6, 31.5. MS (ESI): m/z 344.0 ($M^+ + 1$).

4-(3-Bromo-1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)-benzonitrile (4b): 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.86 (d, J = 7.8 Hz, 2H), 7.64 (t, J = 7.8 Hz, 1H), 7.46 (d, J = 8.3 Hz, 1H), 7.42 (d, J = 8.2 Hz, 2H), 7.16 (t, J = 8.2 Hz, 1H), 7.02 (d, J = 8.2 Hz, 1H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 157.9, 148.4, 141.8, 138.9, 132.6, 131.2, 129.6, 127.6, 122.8, 120.4, 119.0, 118.3, 114.6, 112.7, 31.3. MS (ESI): m/z 361.0 ($M^+ + Na$). Anal. calcd for $C_{17}H_{11}BrN_2O$: C, 60.20; H, 3.27; N, 8.26. Found: C, 60.04; H, 3.45; N, 8.01.

3-Bromo-1-methyl-4-phenylquinolin-2(1H)-one (4c):[7] 87% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.58−7.63 (m, 1H), 7.49−7.58 (m, 3H), 7.44 (d, J = 8.5 Hz, 1H), 7.26−7.30 (m, 2H), 7.10−7.20 (m, 2H), 3.90 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 158.6, 150.8, 139.1, 137.6, 131.0, 130.1, 128.8, 128.2, 127.7, 122.7, 121.6, 119.4, 114.5, 31.5. MS (ESI): m/z 314.0 ($M^+ + 1$).

3-Bromo-4-(2-methoxyphenyl)-1-methylquinolin-2(1H)-one (4d):[7] 85% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.56−7.61 (m, 1H), 7.48−7.52 (m, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.07−7.17 (m, 5H), 3.89 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 159.6, 156.4, 148.4, 139.1, 131.1, 130.8, 130.6, 130.1, 128.2, 126.5, 122.7, 121.1, 120.2, 114.5, 111.7, 56.0, 31.4. MS (ESI): m/z 344.0 ($M^+ + 1$).

4-(3-Acetylphenyl)-3-bromo-1-methylquinolin-2(1H)-one (4e): 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.11−8.09 (m, 1H), 7.89−7.88 (m, 1H), 7.69−7.51 (m, 2H), 7.50−7.45 (m, 2H), 7.14−7.10 (m, 2H), 3.89 (s, 3H), 2.65 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 197.2, 157.9, 149.2, 138.7, 137.6, 137.3, 133.1, 130.9, 129.0, 128.3, 127.8, 123.1, 120.7, 119.1, 114.3, 31.1, 26.6. MS (ESI): m/z 375.0 ($M^+ + Na$). Anal. calcd for $C_{18}H_{14}BrNO_2$: C, 60.69; H, 3.96: N, 3.93. Found: C, 60.92; H, 3.99: N, 3.72.

3-(3-Bromo-1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)-benzonitrile (4f):[7] 73% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.82 (d, J = 7.5 Hz, 1H), 7.59−7.71 (m, 3H), 7.53 (d, J = 7.5 Hz, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 158.2, 148.2, 139.2, 138.8, 133.5, 132.6, 132.5, 131.5, 130.1, 127.9, 123.1, 120.9, 119.9, 118.4, 114.9, 113.5, 31.6. MS (ESI): m/z 339.0 ($M^+ + 1$).

General Procedure for Palladium-Catalyzed Reactions of 4-Aryl-3-bromoquinolin-2(1H)-one 4 with Amines. A Schlenk flask was charged with **4** (0.2 mmol), amine (0.24 mmol), Cs_2CO_3 (0.28 mmol), tris-(dibenzylideneacetone)-dipalladium(0) (0.006 mmol, 3.0 mol % Pd), (*R*)-BINAP (0.009 mmol), and toluene (1 mL) under nitrogen atmosphere. The reaction mixture was stirred at 80 °C overnight. Following completion of the reaction as indicated by TLC, the solution was then allowed to cool to room temperature, taken up in ether (10 mL), filtered, and concentrated. The crude product was then purified by flash chromatography (silica gel, 2/1 (v/v) petroleum ether/ethyl acetate) to give the corresponding products **1**.

4-(4-Methoxyphenyl)-3-(4-methoxyphenylamino)-1-methylquinolin-2(1H)-one (1a): 92% yield. ^{1}H NMR (400 MHz, CDCl3) δ (ppm) 7.39−7.38 (m, 2H), 7.32 (d, J = 7.7 Hz, 1H), 7.12−7.09 (m, 1H), 7.03 (d, J = 8.2 Hz, 2H), 6.73 (d, J = 8.2 Hz, 2H), 6.63 (s, 1H), 6.60 (d, J = 8.7 Hz, 2H), 6.49 (d, J = 8.7 Hz, 2H), 3.89 (s, 3H), 3.75 (s, 3H), 3.67 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ (ppm) 159.5, 158.7, 155.1, 135.4, 134.9, 132.1, 131.3, 127.2, 126.4, 125.4, 125.2, 123.6, 122.8, 122.3, 113.8, 113.6, 113.3, 55.4, 55.2, 30.4. MS (ESI): m/z 387.1 ($M^+ + 1$). Anal. calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25. Found: C, 74.18; H, 5.96; N, 7.06.

3-(4-Fluorophenylamino)-4-(4-methoxyphenyl)-1-methylquinolin-2(1H)-one (1b): 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.42−7.41 (m, 2H), 7.38 (d, J = 8.2 Hz, 1H), 7.15−7.10 (m, 1H), 7.08 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 8.2 Hz, 2H), 6.66−6.58 (m, 5H), 3.89 (s, 3H), 3.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.6, 158.9, 138.1, 135.3, 131.3, 131.2, 127.1, 127.0, 126.9, 125.7, 122.7, 122.6, 122.4, 114.5, 114.3, 114.0, 113.8, 55.2, 30.4. MS (ESI): m/z 375.0 ($M^+ + 1$). Anal. calcd for $C_{23}H_{19}FN_2O_2$: C, 73.78; H, 5.11: N, 7.48. Found: C, 73.59; H, 4.96: N, 7.31.

4-(4-Methoxyphenyl)-1-methyl-3-(phenylamino)quinolin-2(1H)-one (1c): 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.43−7.40 (m, 3H), 7.15−7.13 (m, 3H), 6.95 (t, J = 7.8 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 6.74 (t, J = 7.7 Hz, 1H), 6.64 (d, J = 7.7 Hz, 2H), 6.56 (bs, 1H), 3.88 (s, 3H), 3.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.7, 158.9, 142.1, 135.7, 131.1, 130.5, 128.7, 127.9, 127.2, 127.0, 125.9, 122.4, 122.3, 121.3, 120.0, 114.0, 113.8, 55.2, 30.4. MS (ESI): m/z 357.1 ($M^+ + 1$). Anal. calcd for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86. Found: C, 77.88; H, 5.28; N, 7.59.

3-(Benzylamino)-4-(4-methoxyphenyl)-1-methylquinolin-2(1H)-one (1d): 79% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.34−7.28 (m, 2H), 7.23−7.14 (m, 5H), 7.10−7.02

(m, 4H), 6.96 (d, $J = 8.2$ Hz, 2H), 5.64 (bs, 1H), 3.86 (s, 3H), 3.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.4, 159.0, 139.8, 134.5, 133.5, 131.8, 128.2, 128.0, 127.2, 126.8, 125.4, 124.7, 123.8, 122.3, 120.6, 113.8, 113.6, 55.2, 49.4, 30.5. MS (ESI): *m*/*z* 371.1 ($M^+ + 1$). Anal. calcd for $C_{24}H_{22}N_2O_2$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.93; H, 6.04; N, 7.12.

4-(4-Methoxyphenyl)-1-methyl-3-(pentylamino)quinolin-2(1H)-one (1e): 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.31−7.25 (m, 4H), 7.11 (d, $J = 6.4$ Hz, 1H), 7.05 (t, $J = 7.8$ Hz, 1H), 7.00 (d, $J = 8.8$ Hz, 2H), 5.28 (bs, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 2.49 (t, $J = 6.8$ Hz, 2H), 1.31−1.29 (m, 2H), 1.16−1.08 (m, 4H), 0.81 (t, $J = 7.3$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.4, 158.9, 135.0, 133.2, 131.8, 128.6, 125.0, 124.5, 124.1, 122.2, 119.1, 113.7, 113.6, 55.2, 45.4, 30.4, 29.9, 28.8, 22.3, 13.9. MS (ESI): *m*/*z* 351.1 ($M^+ + 1$). Anal. calcd for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.53; H, 7.47; N, 7.55.

4-(3-(4-Methoxyphenylamino)-1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)benzonitrile (1f): 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.44−7.40 (m, 4H), 7.18 (d, $J = 8.2$ Hz, 1H), 7.11−7.09 (m, 2H), 6.96 (bs, 1H), 6.57 (d, $J = 8.2$ Hz, 2H), 6.45 (d, $J = 8.7$ Hz, 2H), 3.92 (s, 3H), 3.69 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.2, 156.1, 140.6, 134.3, 134.2, 132.9, 131.6, 131.3, 126.5, 125.6, 124.2, 122.7, 121.9, 120.4, 118.6, 114.2, 113.4, 110.6, 55.4, 30.6. MS (ESI): *m*/*z* 382.0 ($M^+ + 1$). Anal. calcd for $C_{24}H_{19}N_3O_2$: C, 75.57; H, 5.02; N, 11.02. Found: C, 75.69; H, 5.31; N, 10.94.

4-(3-(4-Fluorophenylamino)-1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)benzonitrile (1g): 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.49 (d, $J = 6.8$ Hz, 2H), 7.45−7.44 (m, 2H), 7.27 (d, $J = 6.8$ Hz, 2H), 7.18−7.12 (m, 2H), 6.92 (bs, 1H), 6.65−6.58 (m, 4H), 3.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.9, 159.2, 157.5, 140.3, 137.4, 137.3, 134.8, 131.9, 131.8, 131.1, 127.1, 124.4, 124.3, 124.2, 122.8, 122.6, 121.3, 118.4, 114.9, 114.6, 114.3, 111.0, 30.6. MS (ESI): *m*/*z* 370.0 ($M^+ + 1$). Anal. calcd for $C_{23}H_{16}FN_3O$: C, 74.78; H, 4.37; N, 11.38. Found: C, 74.30; H, 4.19; N, 10.91.

4-(1-Methyl-2-oxo-3-(phenylamino)-1,2-dihydroquinolin-4-yl)benzonitrile (1h): 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.45−7.43 (m, 4H), 7.29 (d, $J = 7.8$ Hz, 2H), 7.23 (d, $J = 8.2$ Hz, 1H), 7.16−7.12 (m, 1H), 7.01 (bs, 1H), 6.90 (t, $J = 8.2$ Hz, 2H), 6.77 (t, $J = 7.3$ Hz, 1H), 6.60 (d, $J = 7.7$ Hz, 2H), 3.91 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.3, 140.9, 140.3, 134.9, 131.8, 131.3, 131.1, 128.1, 127.1, 124.5, 122.8, 122.7, 121.9, 121.2, 118.6, 114.3, 114.6, 110.9, 30.6. MS (ESI): *m*/*z* 352.1 ($M^+ + 1$). Anal. calcd for $C_{23}H_{17}N_3O$: C, 78.61; H, 4.88; N, 11.96. Found: C, 78.16; H, 5.17; N, 11.70.

3-(4-Methoxyphenylamino)-1-methyl-4-phenylquinolin-2(1H)-one (1i): 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.41−7.38 (m, 2H), 7.28−7.08 (m, 7H), 6.66 (bs, 1H), 6.60 (d, $J = 8.7$ Hz, 2H), 6.46 (d, $J = 8.7$ Hz, 2H), 3.90 (s, 3H), 3.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.6, 155.2, 135.2, 135.1, 134.8, 132.0, 130.2, 128.1, 127.2, 126.4, 125.3, 125.1, 124.0, 122.6, 122.3, 114.0, 113.9, 113.3, 55.4, 30.5. MS (ESI): *m*/*z* 357.1 ($M^+ + 1$). Anal. calcd for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86. Found: C, 77.05; H, 5.97; N, 7.46.

3-(4-Fluorophenylamino)-1-methyl-4-phenylquinolin-2(1H)-one (1j): 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.42−7.41 (m, 2H), 7.33 (d, $J = 8.7$ Hz, 1H), 7.22−7.11 (m, 6H), 6.66 (bs, 1H), 6.61−6.57 (m, 4H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.6, 159.5, 157.1, 138.1, 138.0, 135.2, 134.9, 131.3, 130.1, 128.2, 127.5, 127.0, 126.6, 125.6, 123.1, 123.0, 122.5, 122.2, 114.6, 114.3, 114.0, 30.5. MS (ESI): *m*/*z* 345.0 ($M^+ + 1$). Anal. calcd for $C_{22}H_{17}FN_2O$: C, 76.73; H, 4.98; N, 8.13. Found: C, 76.54; H, 5.02; N, 7.70.

1-Methyl-4-phenyl-3-(phenylamino)quinolin-2(1H)-one (1k): 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.43−7.37 (m, 3H), 7.24−7.11 (m, 6H), 6.93 (t, $J = 7.8$ Hz, 2H), 6.73 (t, $J = 7.3$ Hz, 1H), 6.64 (t, $J = 7.8$ Hz, 2H), 6.62 (bs, 1H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.6, 135.6, 134.9, 130.5, 130.0, 128.3, 128.2, 127.9, 127.5, 127.2, 125.7, 122.4, 122.0, 121.5, 120.3, 114.0, 30.4. MS (ESI): *m*/*z* 327.0 ($M^+ + 1$). Anal. calcd for $C_{22}H_{18}N_2O$: C, 80.96; H, 5.56; N, 8.58. Found: C, 80.86; H, 5.27; N, 8.42.

4-(2-Methoxyphenyl)-3-(4-methoxyphenylamino)-1-methylquinolin-2(1H)-one (1l): 83% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.36−7.34 (m, 2H), 7.13−7.00 (m, 4H), 6.81 (d, $J = 7.3$ Hz, 1H), 6.77 (bs, 1H), 6.66−6.62 (m, 3H), 6.46−6.43 (m, 2H), 3.89 (s, 3H), 3.66 (s, 3H), 3.60 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.5, 156.3, 155.3, 134.8, 134.3, 132.5, 131.4, 129.2, 126.0, 125.3, 124.5, 123.9, 122.4, 122.3, 121.0, 120.4, 113.7, 112.8, 110.2, 55.4, 54.8, 30.4. MS (ESI): *m*/*z* 387.1 ($M^+ + 1$). Anal. calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25. Found: C, 74.22; H, 5.41; N, 7.09.

4-(3-Acetylphenyl)-3-(4-methoxyphenylamino)-1-methylquinolin-2(1H)-one (1m): 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.71 (d, $J = 7.3$ Hz, 1H), 7.57 (s, 1H), 7.41−7.29 (m, 4H), 7.16 (d, $J = 7.3$ Hz, 1H), 7.09 (t, $J = 8.2$ Hz, 1H), 6.89 (bs, 1H), 6.58 (d, $J = 8.7$ Hz, 2H), 6.40 (d, $J = 8.7$ Hz, 2H), 3.93 (s, 3H), 3.63 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 197.6, 159.4, 155.7, 136.7, 135.8, 134.9, 134.6, 134.4, 132.9, 130.7, 128.3, 126.8, 126.4, 125.4, 124.7, 122.6, 122.5, 122.0, 114.0, 113.3, 55.3, 30.6, 26.4. MS (ESI): *m*/*z* 399.0 ($M^+ + 1$). Anal. calcd for $C_{25}H_{22}N_2O_3$: C, 75.36; H, 5.57; N, 7.03. Found: C, 75.00; H, 5.77; N, 6.75.

3-(3-(4-Methoxyphenylamino)-1-methyl-2-oxo-1,2-dihydroquinolin-4-yl)benzonitrile (1n): 87% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.41−7.23 (m, 6H), 7.11−7.06 (m, 2H), 6.99 (bs, 1H), 6.59 (d, $J = 9.1$ Hz, 2H), 6.47 (d, $J = 9.1$ Hz, 2H), 3.92 (s, 3H), 3.70 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 159.2, 156.1, 136.7, 134.9, 134.3, 134.2, 134.0, 133.1, 130.5, 128.8, 126.4, 125.8, 124.1, 122.7, 122.1, 119.5, 118.4, 114.1, 113.4, 112.0, 55.4, 30.6. MS (ESI): *m*/*z* 382.1 ($M^+ + 1$). Anal. calcd for $C_{24}H_{19}N_3O_2$: C, 75.57; H, 5.02; N, 11.02. Found: C, 75.85; H, 5.45; N, 10.69.

General Procedure for Palladium-Catalyzed Reaction of 3-Bromo-4-arylquinolin-2(1H)-one 4 with *n*-Butyl Acrylate or Ethyl Acrylate. A Schlenk flask was charged

with **4** (0.2 mmol), *n*-butyl acrylate, or ethyl acrylate (0.4 mmol), Et_3N (0.6 mmol), $Pd(OAc)_2$ (0.01 mmol, 5.0 mol % Pd), tris(2,6-dimethoxyphenyl)-phosphine (0.02 mmol), *n*-Bu_4NBr (0.02 mmol), and DMF (1 mL) under nitrogen atmosphere. The reaction mixture was stirred at 140 °C for 3 h. The solution was then allowed to cool to room temperature, taken up in DCM (5 mL), washed with water and brine, and then separated. The solution was dried and filtered, and the filtrate was concentrated to a residue that was purified by flash chromatography (silica gel, 2/1 (v/v) petroleum ether/ethyl acetate) to give the corresponding products **2**.

(*E*)-Butyl 3-(4-(4-methoxyphenyl)-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)acrylate (2a): 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.61−7.56 (m, 1H), 7.41 (d, J = 8.2 Hz, 1H), 7.38 (s, 2H), 7.27−7.25 (m, 1H), 7.17−7.03 (m, 5H), 4.08 (t, J = 6.8 Hz, 2H), 3.90 (s, 3H), 3.83 (s, 3H), 1.60−1.55 (m, 2H), 1.37−1.31 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.0, 160.8, 159.7, 152.1, 139.4, 138.6, 131.4, 130.6, 129.2, 127.3, 123.6, 123.5, 122.0, 121.4, 114.1, 114.0, 63.9, 55.2, 30.6, 29.8, 19.1, 13.6. MS (ESI): *m*/*z* 392.1 ($M^+ + 1$). Anal. calcd for $C_{24}H_{25}NO_4$: C, 73.64; H, 6.44; N, 3.58. Found: C, 73.26; H, 6.40; N, 3.25.

(*E*)-Butyl 3-(4-(4-cyanophenyl)-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)acrylate (2b): 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.86 (d, J = 7.8 Hz, 2H), 7.64−7.60 (m, 1H), 7.46−7.37 (m, 4H), 7.17−7.12 (m, 2H), 7.02 (d, J = 8.2 Hz, 1H), 4.08 (t, J = 6.4 Hz, 2H), 3.84 (s, 3H), 1.60−1.54 (m, 2H), 1.36−1.28 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.6, 160.2, 149.4, 140.3, 139.4, 137.1, 132.5, 131.9, 130.2, 128.3, 125.0, 123.4, 122.4, 120.1, 118.1, 114.4, 112.9, 64.2, 30.5, 29.9, 19.0, 13.6. MS (ESI): *m*/*z* 387.1 ($M^+ + 1$). Anal. calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25. Found: C, 74.95; H, 5.95; N, 6.92.

(*E*)-Butyl 3-(1-methyl-2-oxo-4-phenyl-1,2-dihydroquinolin-3-yl)acrylate (2c): 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.61−7.50 (m, 4H), 7.42−7.33 (m, 3H), 7.25−7.17 (m, 3H), 7.13−7.09 (m, 1H), 4.07 (t, J = 6.4 Hz, 2H), 3.83 (s, 3H), 1.58−1.54 (m, 2H), 1.34−1.29 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.9, 160.7, 152.1, 139.4, 138.3, 135.3, 131.5, 129.2, 128.7, 128.6, 123.8, 123.3, 122.1, 121.1, 114.0, 63.9, 30.6, 29.8, 19.0, 13.6. MS (ESI): *m*/*z* 362.1 ($M^+ + 1$). Anal. calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.47; H, 6.59; N, 3.46.

(*E*)-Butyl 3-(4-(2-methoxyphenyl)-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)acrylate (2d): 68% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.58−7.46 (m, 2H), 7.41−7.28 (m, 3H), 7.16−7.05 (m, 5H), 4.07 (t, J = 6.4 Hz, 2H), 3.82 (s, 3H), 3.69 (s, 3H), 1.59−1.53 (m, 2H), 1.35−1.30 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 168.0, 160.8, 156.4, 149.5, 139.4, 138.7, 131.3, 130.6, 130.4, 128.7, 124.0, 123.8, 123.5, 122.0, 120.9, 120.8, 114.0, 111.3, 63.9, 55.6, 30.6, 29.7, 19.1, 13.6. MS (ESI): *m*/*z* 392.1 ($M^+ + 1$). Anal. calcd for $C_{24}H_{25}NO_4$: C, 73.64; H, 6.44; N, 3.58. Found: C, 73.19; H, 6.46; N, 3.26.

(*E*)-Butyl 3-(4-(3-acetylphenyl)-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)acrylate (2e): 67% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.11 (d, J = 7.8 Hz, 1H), 7.84 (s, 1H), 7.66 (t, J = 7.3 Hz, 1H), 7.62−7.58 (m, 1H), 7.45 (t, J = 8.7 Hz, 2H), 7.40 (d, J = 16.0 Hz, 1H), 7.23 (d, J = 15.6 Hz, 1H), 7.14−7.06 (m, 2H), 4.06 (t, J = 6.4 Hz, 2H), 3.85 (s, 3H), 2.64 (s, 3H), 1.58−1.53 (m, 2H), 1.34−1.28 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 197.3, 167.8, 160.5, 150.7, 139.4, 137.7, 137.3, 136.0, 133.8, 131.7, 129.2, 128.9, 128.8, 128.6, 124.4, 123.5, 122.3, 120.7, 114.2, 64.1, 30.6, 29.9, 26.7, 19.1, 13.6. MS (ESI): *m*/*z* 404.1 ($M^+ + 1$). Anal. calcd for $C_{25}H_{25}NO_4$: C, 74.42; H, 6.25; N, 3.47. Found: C, 74.15; H, 6.17; N, 3.20.

(*E*)-Butyl 3-(4-(4-cyanophenyl)-1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)acrylate (2f): 60% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.84−7.82 (m, 1H), 7.71−7.61 (m, 2H), 7.56−7.37 (m, 4H), 7.16−7.12 (m, 2H), 7.02−7.00 (m, 1H), 4.08 (t, J = 6.8 Hz, 2H), 3.84 (s, 3H), 3.69 (s, 3H), 1.60−1.56 (m, 2H), 1.36−1.30 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.5, 160.2, 148.9, 139.4, 137.0, 136.9, 133.7, 132.6, 132.3, 131.9, 129.8, 128.3, 125.1, 123.8, 122.4, 120.3, 118.0, 114.4, 113.3, 64.2, 30.6, 29.9, 19.1, 13.6. MS (ESI): *m*/*z* 387.1 ($M^+ + 1$). Anal. calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25. Found: C, 74.93; H, 6.03; N, 6.97.

(*E*)-Ethyl 3-(1-methyl-2-oxo-4-phenyl-1,2-dihydroquinolin-3-yl)acrylate (2g):[1d] 81% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.60−7.50 (m, 4H), 7.41(d, J = 8.2 Hz, 1H), 7.33 (s, 2H), 7.25−7.17 (m, 3H), 7.12−7.09 (m, 1H), 4.13 (q, J = 7.3 Hz, 2H), 3.83 (s, 3H), 1.22 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 167.9, 160.7, 152.0, 139.4, 138.3, 135.3, 131.5, 129.2, 129.1, 128.7, 128.6, 123.8, 123.3, 122.1, 121.1, 114.0, 60.1, 29.8, 14.1.

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Supporting Information Available. Copies of ^{1}H and ^{13}C NMR spectra of unknown compounds. This information is available free of charge via the Internet at http: //pubs.acs.org.

References and Notes

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