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Copper-Catalyzed *N*-Arylation of Pyranoquinolinones with Boronic Acids at Room Temperature without Ligand

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Abstract: Pyranoquinolinones synthesized from citral were used for Cu-catalyzed *N*-arylation with a wide range of arylboric acids. The reaction proceeded well with a broad substrate scope, providing a direct way to access highly functional pyranoquinolinone core structure derivatives in yields of up to 80%. Compared to citral, the compounds we obtained have a much better inhibitory effect on HeLa cervical cancer cells, and compound **3p** has an IC_{50} value of 4.6 μM, lower than cisplatin's 5.9 μM.

Keywords: citral; pyranoquinolinone; *N*-arylation

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1. Introduction

As a naturally occurring monoterpenoid, citral has been commonly considered to be a promising antimicrobial compound due to its strong antibacterial and antifungal activities [1–4]. It is particularly noteworthy that citral treatment (24 h incubation) could significantly decrease the percentage of cell viability in HeLa cells, and a 500 μg/mL (IC_{50}) concentration of citral was required for the good inhibition of HeLa cells [**1d**]. However, compared with many commercially available fungicides, citral still has the disadvantages of low antibacterial activity, strong volatility and low chemical stability. Thus, in recent years, citral has been converted into a series of derivatives in order to afford compounds with better biological activity [5–7].

Pyranoquinolinone alkaloids have a variety of interesting biological activities and are widely distributed in nature [8–16]. These molecules could be used as the synthetic precursors of polyheterocycles and dimeric quinoline alkaloids [17–21]. Thus, a variety of synthetic approaches to afford pyranoquinolinone derivatives have been reported [22–26]. Ytterbium (III)-catalyzed transformations of 4-hydroxy-1*H*-quinolin-2-ones and enals into pyranoquinolinones were previously reported by Lee and coworkers [27]. However, the yields of pyranoquinolinones were unsatisfactory. Again, they developed a methodology for the synthesis of pyranoquinolinones in good yield by the formal [3 + 3] cycloaddition of 2,4-dihydroxyquinoline and varied *α*,*β*-unsaturated aldehydes [28]. It was a convenient and efficient way to produce pyranoquinolinone derivatives with a variety of substituents on the 2*H*-pyranyl rings. However, there are no efficient and general methods for preparing those pyranoquinolinones with various substituents on the quinoline ring.

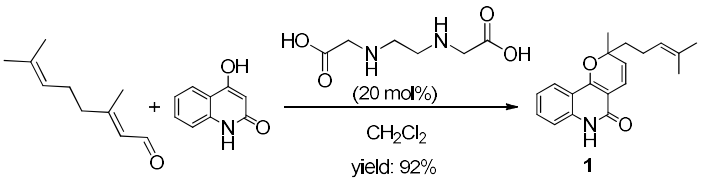
Transition-metal-catalyzed C(aryl)-N bond formation reaction is an important tool in organic synthesis [29–32]. Over the past few years, varied synthetic methods have been developed for the *N*-arylation of heterocycles. Among them, the classic copper-catalyzed Ullmann reaction has the shortcomings of the requirement of stoichiometric amounts of copper reagents, high temperatures, long reaction time and low yields [33–35]. Similarly, Pd-catalyzed Buchwald–Hartwig coupling has the disadvantages of high temperature,

strong base and need for an expensive Pd/ligand combination [36,37]. Notably, copper-promoted Chan–Lam coupling for *O*- and *N*-arylation with boronic acids became a good choice in for carbon–heteroatom transformation [38–42]. This Chan–Lam type of coupling received attention from various organic chemists over the years for its advantages of mild reaction conditions, room temperature, weak base and ambient atmosphere [43–60].

Prompted by the advantages of the importance of pyranoquinolinone alkaloids and inspired by what was mentioned about citral above, we envisioned that the Chan–Lam coupling of *N*-arylation with arylboronic acids could provide the desired pyranoquinolinone derivatives with a variety of substituents on the quinoline ring.

2. Results and Discussion

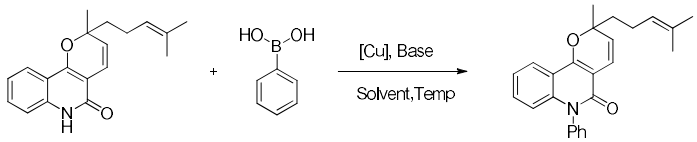
Firstly, we used citral to synthesize pyranoquinolinone compound **1** (Scheme 1).



Scheme 1. Synthesis of pyranoquinolinone compound **1** starting from 2,4-dihydroxyquinoline and citral.

Applying the reaction conditions described in ref. [13] ($Cu(OTf)_2$, 1,10-Phen, DMSO), our investigation started with the reactions of 2-methyl-2-(4-methylpent-3-en-1-yl)-2*H*-pyrano[3,2-c]quinolin-5(6*H*)-one (**1**) and phenylboronic acid (**2a**), and the desired product (**3a**) could only be afforded in trace amounts (entry 1, Table 1). When this reaction was catalyzed by $Cu(OAc)_2$ in DMSO with 1,10-Phen as the ligand, the desired product (**3a**) was isolated only in 5% yield (entry 2, Table 1). Increasing the amount of 1,10-Phen to 200 mol% had a positive impact on the isolated yield, giving the desired product (**3a**) in 10% yield (entry 3, Table 1). Thus, we considered that 1,10-Phen acted as a base rather than a ligand to promote the reaction. When we shifted to using pyridine instead of 1,10-Phen, a better change was observed in the product yield, with 16% (entry 4, Table 1). Encouraged by these results, we performed the transformation with K_2CO_3 and Et_3N (2.0 equiv) as the bases with a catalytic amount of $Cu(OAc)_2$ (20 mol%) in DMSO, and the desired product yields were 19% and 25%, respectively (entries 5–6, Table 1). Therefore, we took Et_3N as the best choice, and other solvents (DCM, DCE, DMF, MeCN, DMAc, MeOH, EtOAc) were surveyed. However, none of them was more efficient than DMSO for this reaction (entries 7–15, Table 1). When Et_3N and 1,10-Phen are used together to promote this reaction [61], the desired product yield will not be improved (entry 8, Table 1). When the amount of $Cu(OAc)_2$ was increased to 100 mol%, the reaction did not occur (entry 9, Table 1). To find a suitable catalytic system for the *N*-arylation of pyranoquinolinones, more Cu catalysts were evaluated in detail (CuCl, CuBr, CuI, CuO, $CuSO_4$, $Cu(acac)_2$, CuF_2), and the use of CuI improved the yield to 76% (entries 16–22, Table 1). We discovered that the reaction worked more efficiently under this open-air condition when Cu^+ was used as a catalyst instead of Cu^{2+}, and the desired product (**3a**) was afforded in yields of 36%, 42%, 76% and 18% (entries 16–19, Table 1). In order to enhance the yield, the reaction was carried out with other solvents such as DCM and MeCN with CuI as the catalyst; however, the product was furnished in trace amounts (entries 23–24, Table 1). Therefore, DMSO was the best choice. Increasing the CuI loading to 50 mol% resulted in a lower 19% yield (entry 25, Table 1). Further increasing the Cu-catalyst loading to 100 mol% had a negative effect on the yield of the product, forming **3a** only in a 9% yield (entry 26, Table 1). Finally, we tried to raise the temperature to increase the yield. However, increasing the temperature to 40 °C reduced the product yield to 19%, and increasing the temperature to above 60 °C afforded the product (**3a**) in trace amounts (entries 27–29, Table 1).

Table 1. Optimization of the reaction conditions [a].



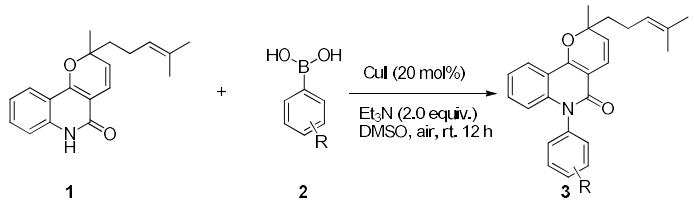
1 **2a** **3a**

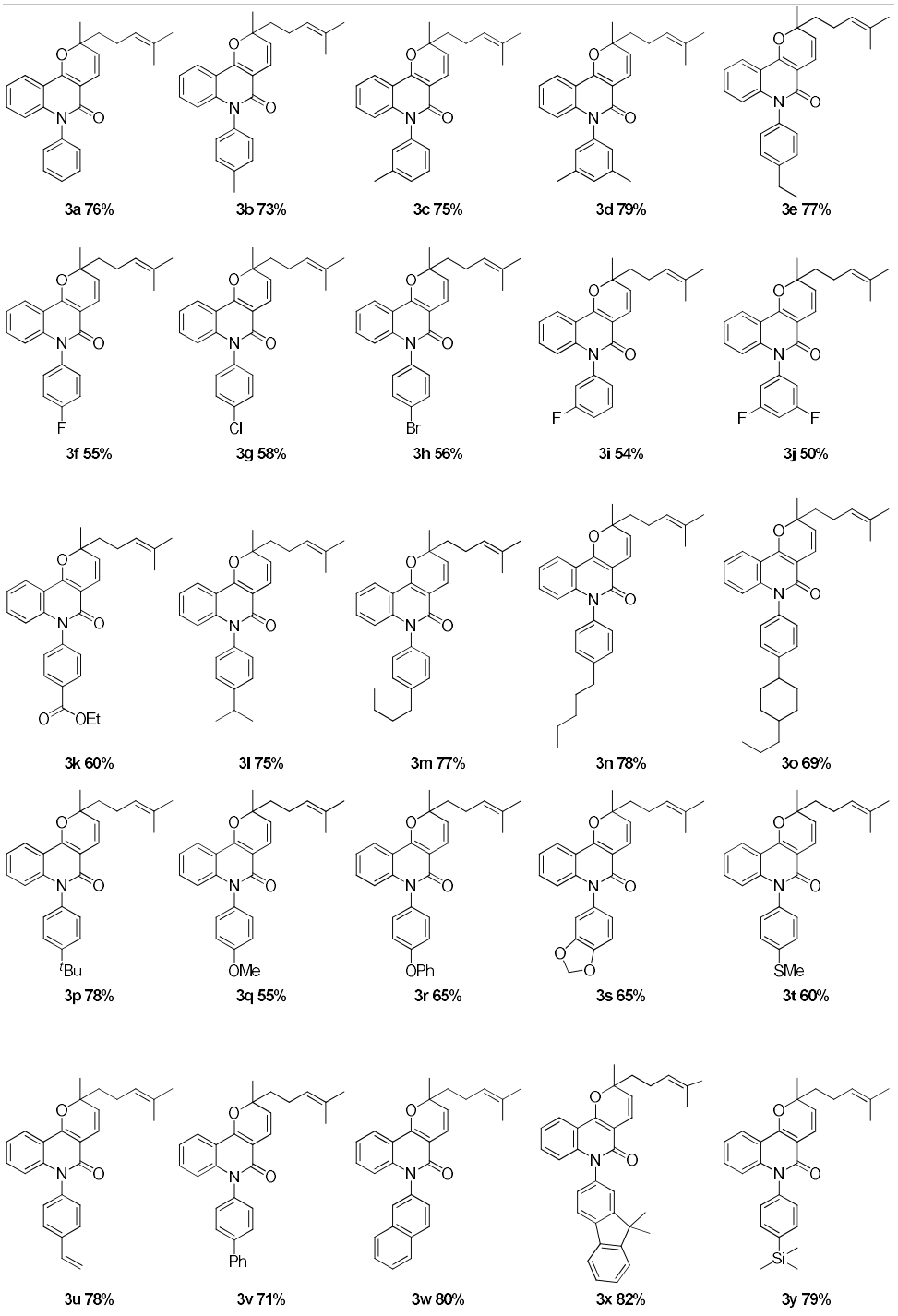
Entry	[Cu]	Base	Solvent	Yield [b]
1	$Cu(OTf)_2$	1,10-Phen	DMSO	trace
2 [c]	$Cu(OAc)_2$	1,10-Phen	DMSO	5%
3	$Cu(OAc)_2$	1,10-Phen	DMSO	10%
4	$Cu(OAc)_2$	Pyridine	DMSO	16%
5	$Cu(OAc)_2$	K_2CO_3	DMSO	19%
6	$Cu(OAc)_2$	Et_3N	DMSO	25%
7	$Cu(OAc)_2$	Et_3N	DCM	11%
8	$Cu(OAc)_2$	Et_3N and 1,10-Phen	DCM	10%
9 [d]	$Cu(OAc)_2$	Et_3N and 1,10-Phen	DCM	trace
10	$Cu(OAc)_2$	Et_3N	DCE	13%
11	$Cu(OAc)_2$	Et_3N	DMF	18%
12	$Cu(OAc)_2$	Et_3N	MeCN	trace
13	$Cu(OAc)_2$	Et_3N	DMAc	15%
14	$Cu(OAc)_2$	Et_3N	MeOH	trace
15	$Cu(OAc)_2$	Et_3N	EtOAc	trace
16	CuCl	Et_3N	DMSO	36%
17	CuBr	Et_3N	DMSO	42%
18	CuI	Et_3N	DMSO	76%
19	CuO	Et_3N	DMSO	18%
20	$CuSO_4$	Et_3N	DMSO	trace
21	$Cu(acac)_2$	Et_3N	DMSO	trace
22	CuF_2	Et_3N	DMSO	20%
23	CuI	Et_3N	DCM	trace
24	CuI	Et_3N	MeCN	trace
25 [e]	CuI	Et_3N	DMSO	19%
26 [f]	CuI	Et_3N	DMSO	9%
27 [g]	CuI	Et_3N	DMSO	19%
28 [h]	CuI	Et_3N	DMSO	trace
29 [i]	CuI	Et_3N	DMSO	trace

[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.6 mmol), [Cu] (0.2 equiv.), base (2.0 equiv.), solvent (5.0 mL), rt under air, 12 h. [b] Isolated yields. [c] 1,10-Phen with 20 mol%. [d] $Cu(OAc)_2$ with 100 mol%. [e] CuI with 50 mol%. [f] CuI with 100 mol%. [g] Reaction temperature of 40 °C. [h] Reaction temperature of 60 °C. [i] Reaction temperature of 80 °C.

With the optimal reaction conditions in hand (**1** (0.5 mmol), **2** (0.6 mmol), CuI (0.2 equiv.), Et_3N (2.0 equiv.), DMSO (5.0 mL), rt under air, 12 h), we started to investigate the scope of this reaction. Various arylboronic acids (**2**) were employed in the Cu-catalyzed reactions (Table 2). For a wide range of arylboronic acids with either electron-rich or electron-poor aryl groups, the corresponding coupling with compound **1** proceeded smoothly, giving the desired *N*-arylation pyranoquinolinone derivatives (**3**) with high efficiency and *regio*-selectivity (*N*-arylation not *O*-arylation). The efficiency of the reaction was sensitive to the substituents on the aromatic rings in different arylboronic acids (**3a**–**3k**, Table 2).

Table 2. Substrate exploration [a].





[a] **1** (0.5 mmol), **2** (0.6 mmol), CuI (0.2 equiv.), Et_3N (2.0 equiv.), DMSO (5.0 mL), rt under air, 12 h.

Arylboronic acids with an electron-donating group on the aromatic ring gave a yield comparable to that of those bearing an electron-withdrawing group on the aromatic ring. For example, arylboronic acids with an electron-donating group, such as CH_3 or CH_3CH_2, on the phenyl ring reacted with compound **1** to afford the corresponding products in 73–77% yields (**3a**–**3e,** Table 2). When arylboronic acids with an electron-withdrawing group (F, Cl, Br or COOEt) on the phenyl ring reacted with compound **1**, yields of about 50–60% of the desired products were obtained (**3f**–**3k**, Table 2). Noteworthily, the reaction tolerates a variety of substituents in the para position. For instance, the compounds **2l**–**2p** could react smoothly to afford the desired compound with 69–78% yields, respectively, which were comparable to those of the products **3a**–**3k** (**3l**–**3p**, Table 2). Oddly enough, when arylboronic acids with a CH_3O on the phenyl ring were reacted with compound **1**, a yield of only 55% of the desired products was afforded (**3q**, Table 2). Other electron-donating groups such as PhO and CH_3S did not affect the reaction yield, giving the desired *N*-arylation derivatives with 60–65% yield (**3r**–**3t**, Table 2). Other arylboronic acids containing the conjugated group substituents were very compatible in the reactions, with 71–82% yields (**3u**–**3x**, Table 2). Si-substituted arylboronic acid was also tolerant in this reaction and showed a good yield of 79% (**3y,** Table 2). We chose *o*-tolylboronic acid and (2-fluorophenyl)boronic acid to test the tolerance of the reaction to steric hindrance. However, the reaction results were not good, giving no desired products. Except for steric hindrance, we do not know how to explain this reaction phenomenon.

The IC_{50} values of 25 citral pyranoquinolinone derivatives on HeLa cervical cancer cells were preliminarily measured using the WST-8 method to evaluate their inhibitory activities against tumor cells (Table 3). The IC_{50} values of these derivatives on HeLa cervical cancer cells ranged from 4.6 μM to 40.5 μM, with compound **3p** having an IC_{50} value of 4.6 μM, lower than cisplatin's 5.9 μM. This compound is expected to be used for further research on tumor inhibition activity.

Table 3. Inhibitory activities of citral pyranoquinolinone derivatives against HeLa cervical cancer cells.

Compound	IC_{50}/μM	Compound	IC_{50}/μM
3a	22.7	**3n**	26.3
3b	17.1	**3o**	30.4
3c	18.2	**3p**	4.6
3d	20.3	**3q**	24.5
3e	29.8	**3r**	10.2
3f	16.3	**3s**	23.3
3g	26.2	**3t**	29.3
3h	14.2	**3u**	18.9
3i	28.7	**3v**	23.2
3j	14.3	**3w**	6.4
3k	10.3	**3x**	18.7
3l	40.5	**3y**	14.6
3m	21.1	cisplatin	5.9

3. Materials and Methods

3.1. General Information

Unless otherwise noted, all of the reagents were purchased from Shanghai Aladdin Bio-Chem Technology Co., Ltd. (Shanghai, China) and used without purification. Purification of products was conducted by flash chromatography on silica gel (200–300 mesh). Nuclear magnetic resonance (NMR) spectra were measured on a Bruker Avance III 400 (Bruker, Billerica, MA, USA). The 1*H*-NMR (400 MHz) chemical shifts were obtained relative to $CDCl_3$ as the internal reference ($CDCl_3$: δ 7.26 ppm). The ^{13}C-NMR (100 MHz) chemical shifts were obtained using $CDCl_3$ as the internal standard ($CDCl_3$: δ 77.16 ppm). Chemical shifts are reported in ppm using tetramethylsilane as the internal standard (s = singlet, d = doublet,

t = triplet, q = quartet, dd = doublet of doublets, m = multiplet). HR-MS data were obtained on a VG ZAB-HS mass spectrometer and a Bruker Apex IV FTMS spectrometer.

3.2. General Procedure for the N-Arylation of Pyranoquinolinones with Boronic Acids

Pyranoquinolinone (0.6 mmol), arylboronic acid 2 (0.6 mmol), CuI (20 mmol%), Et_3N (2.0 equiv) and DMSO (5.0 mL) were added to a sealed tube. Then, the mixture was stirred at room temperature in the air for 12 h. After the disappearance of the substrate as indicated by the TLC, the mixture was concentrated in vacuo, and the resulting crude product was purified by column chromatography to afford the products **3**.

*3.3. Characterization Data for Products **3a**–**3y***

2-methyl-2-(4-methylpent-3-en-1-yl)-6-phenyl-2,6-dihydro-5*H*-pyrano[3,2-c]quinolin-5-one (**3a**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.61–7.54 (m, 2H), 7.53–7.47 (m, 1H), 7.33–7.26 (m, 3H), 7.21–7.15 (m, 1H), 6.78 (d, *J* = 10.0 Hz, 1H), 6.61 (d, *J* = 8.4 Hz, 1H), 5.51 (d, *J* = 10.0 Hz, 1H), 5.13 (ddd, *J* = 7.2, 6.0, 1.2 Hz, 1H), 2.19 (q, *J* = 7.6 Hz, 2H), 1.96–1.85 (m, 1H), 1.83–1.76 (m, 1H), 1.65 (s, 3H), 1.58 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 156.1, 140.4, 137.9, 132.0, 130.4, 130.1, 129.2, 128.7, 125.2, 123.8, 122.8, 121.9, 118.2, 115.9, 115.7, 105.6, 81.7, 41.7, 27.2, 25.7, 22.7, 17.7. HRMS (ESI): *m*/*z* [M + H]$^+$ Calcd for $C_{25}H_{26}NO_2^+$: 372.1958, found: 372.1956. Figure S1 in the Supplementary Materials.

2-methyl-2-(4-methylpent-3-en-1-yl)-6-(p-tolyl)-2,6-dihydro-5*H*-pyrano[3,2-c]quinolin-5-one (**3b**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.32–7.25 (m, 1H), 7.19–7.12 (m, 3H), 6.78 (d, *J* = 10.0 Hz, 1H), 6.65 (d, *J* = 8.5 Hz, 1H), 5.50 (d, *J* = 10.0 Hz, 1H), 5.13 (t, *J* = 7.2 Hz, 1H), 2.45 (s, 3H), 2.19 (q, *J* = 7.6 Hz, 2H), 1.94–1.87 (m, 1H), 1.82–1.76 (m, 1H), 1.64 (s, 3H), 1.58 (s, 3H), 1.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 156.0, 140.6, 138.6, 135.2, 132.0, 130.7, 130.3, 128.8, 125.2, 123.8, 122.7, 121.9, 118.3, 116.0, 115.7, 105.6, 81.6, 41.7, 27.2, 25.6, 22.7, 21.3, 17.7. HRMS (ESI): *m*/*z* [M + H]$^+$ Calcd for $C_{26}H_{28}NO_2^+$: 386.2115, found: 386.2113. Figure S2 in the Supplementary Materials.

2-methyl-2-(4-methylpent-3-en-1-yl)-6-(m-tolyl)-2,6-dihydro-5*H*-pyrano[3,2-c]quinolin-5-one (**3c**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 1H), 7.33–7.27 (m, 2H), 7.21–7.15 (m, 1H), 7.10–7.04 (m, 2H), 6.78 (d, *J* = 10.0 Hz, 1H), 6.63 (d, *J* = 8.4 Hz, 1H), 5.50 (d, *J* = 10.0 Hz, 1H), 5.20–5.05 (m, 1H), 2.41 (s, 3H), 2.19 (q, *J* = 7.6 Hz, 2H), 1.95–1.86 (m, 1H), 1.82–1.74 (m, 1H), 1.65 (s, 3H), 1.58 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 156.0, 140.5, 140.1, 137.8, 132.0, 130.3, 129.8, 129.7, 129.5, 126.1, 125.2, 123.8, 122.7, 121.9, 118.3, 116.0, 115.7, 105.6, 81.6, 41.7, 27.2, 25.6, 22.7, 21.4, 17.7. HRMS (ESI): *m*/*z* [M + H]$^+$ Calcd for $C_{26}H_{28}NO_2^+$: 386.2115, found: 386.2113. Figure S3 in the Supplementary Materials.

6-(3,5-dimethylphenyl)-2-methyl-2-(4-methylpent-3-en-1-yl)-2,6-dihydro-5*H*-pyrano[3,2-c]quinolin-5-one (**3d**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.30 (ddd, *J* = 8.4, 6.8, 1.6 Hz, 1H), 7.17 (ddd, *J* = 8.0, 7.2, 0.8 Hz, 1H), 7.11 (s, 1H), 6.90–6.85 (m, 2H), 6.78 (d, *J* = 10.0 Hz, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 5.49 (d, *J* = 10.0 Hz, 1H), 5.13 (t, *J* = 7.2 Hz, 1H), 2.37 (s, 6H), 2.18 (q, *J* = 7.6 Hz, 2H), 1.93–1.85 (m, 1H), 1.82–1.74 (m, 1H), 1.65 (s, 3H), 1.58 (s, 3H), 1.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 155.9, 140.5, 139.8, 137.7, 132.0, 130.4, 130.3, 126.6, 125.2, 123.8, 122.6, 121.8, 118.3, 116.1, 115.7, 105.7, 81.6, 41.7, 27.2, 25.6, 22.6, 21.3, 17.6. HRMS (ESI): *m*/*z* [M + H]$^+$ Calcd for $C_{27}H_{30}NO_2^+$: 400.2271, found: 400.2273. Figure S4 in the Supplementary Materials.

6-(4-ethylphenyl)-2-methyl-2-(4-methylpent-3-en-1-yl)-2,6-dihydro-5*H*-pyrano[3,2-c]-quinolin-5-one (**3e**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.20–7.14 (m, 2H), 7.11–7.05 (m, 1H), 6.99–6.92 (m, 3H), 6.57 (d, *J* = 10.0 Hz, 1H), 6.44 (d, *J* = 8.4 Hz, 1H), 5.28 (d, *J* = 10.0 Hz, 1H), 4.92 (t, *J* = 7.2 Hz, 1H), 2.54 (q, *J* = 7.6 Hz, 2H), 1.98 (q, *J* = 7.6 Hz, 2H), 1.74–1.64 (m, 1H), 1.62–1.53 (m, 1H), 1.43 (s, 3H), 1.37 (s, 3H), 1.31 (s, 3H), 1.10 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 156.0, 144.7, 140.6, 135.4, 132.0, 130.3, 129.5, 128.9, 125.2, 123.8, 122.7, 121.8, 118.3, 116.0, 115.8, 105.6, 81.6, 41.7, 28.6, 27.2,

25.6, 22.7, 17.6, 15.3. HRMS (ESI): *m*/*z* [M + H]$^+$ Calcd for $C_{27}H_{30}NO_2^+$: 400.2271, found: 400.2273. Figure S5 in the Supplementary Materials.

6-(4-fluorophenyl)-2-methyl-2-(4-methylpent-3-en-1-yl)-2,6-dihydro-5*H*-pyrano[3,2-c]-quinolin-5-one (**3f**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.35–7.29 (m, 1H), 7.27–7.23 (m, 4H), 7.23–7.18 (m, 1H), 6.76 (d, *J* = 10.0 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 5.51 (d, *J* = 10.0 Hz, 1H), 5.16–5.08 (m, 1H), 2.19 (q, *J* = 7.6 Hz, 2H), 1.94–1.86 (m, 1H), 1.83–1.75 (m, 1H), 1.64 (s, 3H), 1.58 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 161.3, 156.3, 140.4, 133.7, 130.9, 130.5, 125.4, 123.7, 122.9, 122.2, 118.0, 117.1, 116.2, 116.1, 115.8, 105.5, 81.8, 41.7, 27.3, 25.6, 22.6, 17.6. HRMS (ESI): *m*/*z* [M + H]$^+$ Calcd for $C_{25}H_{25}FNO_2^+$: 390.1864, found: 390.1869. Figure S6 in the Supplementary Materials.

6-(4-chlorophenyl)-2-methyl-2-(4-methylpent-3-en-1-yl)-2,6-dihydro-5*H*-pyrano[3,2-c]-quinolin-5-one (**3g**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.57–7.50 (m, 2H), 7.35–7.29 (m, 1H), 7.25–7.17 (m, 3H), 6.75 (d, *J* = 10.0 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 5.51 (d, *J* = 10.0 Hz, 1H), 5.17–5.07 (m, 1H), 2.18 (q, *J* = 7.6 Hz, 2H), 1.95–1.86 (m, 1H), 1.83–1.74 (m, 1H), 1.64 (s, 3H), 1.58 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 156.3, 140.1, 136.3, 134.7, 132.1, 130.7, 130.6, 130.3, 125.4, 123.7, 122.9, 122.2, 118.0, 116.7, 115.8, 105.4, 81.9, 41.7, 27.3, 25.6, 22.6, 17.6. HRMS (ESI): *m*/*z* [M + H]$^+$ Calcd for $C_{25}H_{25}ClNO_2^+$: 406.1568, found: 406.1563. Figure S7 in the Supplementary Materials.

6-(4-bromophenyl)-2-methyl-2-(4-methylpent-3-en-1-yl)-2,6-dihydro-5*H*-pyrano[3,2-c]-quinolin-5-one (**3h**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.71–7.67 (m, 2H), 7.33 (ddd, *J* = 8.8, 7.2, 1.6 Hz, 1H), 7.25–7.19 (m, 1H), 7.18–7.14 (m, 2H), 6.75 (d, *J* = 10.0 Hz, 1H), 6.65–6.56 (m, 1H), 5.51 (d, *J* = 10.0 Hz, 1H), 5.16–5.07 (m, 1H), 2.18 (q, *J* = 7.6 Hz, 2H), 1.94–1.86 (m, 1H), 1.83–1.76 (m, 1H), 1.64 (s, 3H), 1.58 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 156.5, 140.0, 136.8, 133.4, 132.1, 131.0, 130.6, 125.5, 123.7, 123.0, 122.9, 122.3, 117.9, 117.3, 115.8, 105.4, 81.9, 41.7, 27.3, 25.6, 22.6, 17.7. HRMS (ESI): *m*/*z* [M + H]$^+$ Calcd for $C_2H_{25}BrNO_2^+$: 450.1063, found: 450.1060. Figure S8 in the Supplementary Materials.

6-(3-fluorophenyl)-2-methyl-2-(4-methylpent-3-en-1-yl)-2H-pyrano[3,2-c]quinolin-5(6*H*)-one (**3i**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.54 (dd, *J* = 14.4, 8.1 Hz, 1H), 7.33 (ddd, *J* = 8.6, 7.2, 1.5 Hz, 1H), 7.27–7.17 (m, 2H), 7.09 (d, *J* = 7.8 Hz, 1H), 7.03 (ddd, *J* = 9.0, 4.3, 2.2 Hz, 1H), 6.76 (d, *J* = 10.1 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 5.51 (d, *J* = 10.1 Hz, 1H), 5.17–5.08 (m, 1H), 2.19 (dd, *J* = 15.6, 7.7 Hz, 2H), 1.96–1.85 (m, 1H), 1.84–1.74 (m, 1H), 1.65 (s, 3H), 1.58 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 162.3, 160.9, 156.3, 140.0, 139.2, 130.5, 125.4, 125.1, 123.7, 122.9, 122.2, 117.9, 116.8, 115.9, 115.7, 113.6, 105.3, 104.8, 82.0, 41.7, 27.3, 25.6, 22.6, 17.6. HRMS (ESI): *m*/*z* [M + H]$^+$ Calcd for $C_{25}H_{25}FNO_2^+$: 390.1864, found: 390.1868. Figure S9 in the Supplementary Materials.

6-(3,5-difluorophenyl)-2-methyl-2-(4-methylpent-3-en-1-yl)-2,6-dihydro-5*H*-pyrano[3,2-c]-quinolin-5-one (**3j**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.36 (ddd, *J* = 8.8, 7.2, 1.6 Hz, 1H), 7.25–7.20 (m, 1H), 6.98 (tt, *J* = 8.8, 2.4 Hz, 1H), 6.90–6.83 (m, 2H), 6.74 (d, *J* = 10.0 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 5.52 (d, *J* = 10.0 Hz, 1H), 5.12 (ddd, *J* = 7.2, 6.0, 1.2 Hz, 1H), 2.18 (q, *J* = 7.6 Hz, 2H), 1.96–1.86 (m, 1H), 1.83–1.74 (m, 1H), 1.64 (s, 3H), 1.59–1.57 (m, 3H), 1.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 163.7, 160.7, 156.4, 139.6, 132.1, 130.7, 125.5, 123.7, 123.1, 122.5, 117.8, 115.8, 115.3, 113.2, 105.3, 104.8, 82.0, 41.7, 27.3, 25.6, 22.6, 17.6. HRMS (ESI): *m*/*z* [M + H]$^+$ Calcd for $C_{25}H_{24}F_2NO_2^+$: 408.1770, found: 408.1779. Figure S10 in the Supplementary Materials.

ethyl4-(2-methyl-2-(4-methylpent-3-en-1-yl)-5-oxo-2H-pyrano[3,2-c]quinolin-6(5*H*)-yl)-benzoate (**3k**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.8 Hz, 2H), 7.98 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.37 (d, *J* = 7.2 Hz, 2H), 7.33–7.28 (m, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 10.0 Hz, 1H), 6.57 (d, *J* = 8.4 Hz, 1H), 5.51 (d, *J* = 10.0 Hz, 1H), 5.13 (t, *J* = 7.2 Hz, 1H), 4.43 (q, *J* = 7.2 Hz, 2H), 2.19 (q, *J* = 7.6 Hz, 2H), 1.96–1.86 (m, 1H), 1.83–1.75 (m, 1H), 1.65 (s, 3H), 1.58 (s, 3H), 1.54 (s, 3H), 1.43 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 160.9, 156.3, 142.1, 139.9, 132.1, 131.4, 130.9, 130.5, 129.5, 125.4, 123.7, 122.9, 122.2, 118.0, 115.8, 115.5, 105.5, 81.8, 61.3, 41.7, 27.2, 25.6, 22.6, 17.6, 14.3. HRMS (ESI): *m*/*z* [M + H]$^+$ Calcd for $C_{28}H_{30}NO_4^+$: 444.2169, found: 444.2168. Figure S11 in the Supplementary Materials.

6-(4-isopropylphenyl)-2-methyl-2-(4-methylpent-3-en-1-yl)-2,6-dihydro-5*H*-pyrano[3,2-c]quinolin-5-one (**3l**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.44–7.38 (m, 2H), 7.30 (ddd, *J* = 8.8, 7.2, 1.6 Hz, 1H), 7.21–7.14 (m, 3H), 6.78 (d, *J* = 10.0 Hz, 1H), 6.65 (d, *J* = 8.0 Hz, 1H), 5.49 (d, *J* = 10.0 Hz, 1H), 5.17–5.09 (m, 1H), 3.06–2.96 (m, 1H), 2.19 (q, *J* = 7.6 Hz, 2H), 1.96–1.85 (m, 1H), 1.84–1.74 (m, 1H), 1.65 (s, 3H), 1.58 (s, 3H), 1.53 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 156.0, 149.3, 140.6, 135.4, 132.0, 130.3, 128.8, 128.1, 125.2, 123.8, 122.7, 121.9, 118.3, 116.0, 115.8, 105.6, 81.6, 41.7, 34.0, 27.2, 25.6, 24.0, 22.7, 17.7. HRMS (ESI): *m*/*z* [M + H]$^+$ Calcd for $C_{28}H_{32}NO_2^+$: 414.2428, found: 414.2425. Figure S12 in the Supplementary Materials.

6-(4-butylphenyl)-2-methyl-2-(4-methylpent-3-en-1-yl)-2,6-dihydro-5*H*-pyrano[3,2-c]-quinolin-5-one (**3m**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.39–7.33 (m, 2H), 7.32–7.26 (m, 1H), 7.19–7.12 (m, 3H), 6.78 (d, *J* = 10.0 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 5.49 (d, *J* = 10.0 Hz, 1H), 5.17–5.09 (m, 1H), 2.75–2.64 (m, 2H), 2.19 (q, *J* = 7.6 Hz, 2H), 1.94–1.86 (m, 1H), 1.83–1.75 (m, 1H), 1.72–1.65 (m, 2H), 1.64 (s, 3H), 1.58 (s, 3H), 1.52 (s, 3H), 1.45–1.39 (m, 2H), 0.97 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 156.0, 143.5, 140.6, 135.4, 132.0, 130.3, 130.0, 128.8, 125.2, 123.8, 122.7, 121.8, 118.3, 116.0, 115.8, 105.6, 81.6, 41.7, 35.4, 33.4, 27.2, 25.6, 22.7, 22.4, 17.6, 14.0. HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{29}H_{34}NO_2^+$: 428.2584, found: 428.2580. Figure S13 in the Supplementary Materials.

2-methyl-2-(4-methylpent-3-en-1-yl)-6-(4-pentylphenyl)-2,6-dihydro-5*H*-pyrano[3,2-c]-quinolin-5-one (**3n**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.39–7.33 (m, 2H), 7.32–7.26 (m, 1H), 7.20–7.13 (m, 3H), 6.78 (d, *J* = 10.0 Hz, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 5.49 (d, *J* = 10.0 Hz, 1H), 5.13 (t, *J* = 7.2 Hz, 1H), 2.75–2.64 (m, 2H), 2.19 (q, *J* = 7.6 Hz, 2H), 1.94–1.85 (m, 1H), 1.83–1.76 (m, 1H), 1.72–1.67 (m, 2H), 1.64 (s, 3H), 1.58 (s, 3H), 1.52 (s, 3H), 1.41–1.34 (m, 4H), 0.92 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 156.0, 143.5, 140.6, 135.4, 132.0, 130.3, 130.0, 128.8, 125.1, 123.8, 122.7, 121.8, 118.3, 116.0, 115.8, 105.6, 81.6, 41.7, 35.7, 31.6, 31.0, 27.2, 25.6, 22.7, 22.6, 17.6, 14.0. HRMS (ESI): *m*/*z* [M + H]$^+$ Calcd for $C_{30}H_{36}NO_2^+$: 442.2741, found: 442.2743. Figure S14 in the Supplementary Materials.

2-methyl-2-(4-methylpent-3-en-1-yl)-6-(4-(4-propylcyclohexyl)phenyl)-2,6-dihydro-5*H*-pyrano[3,2-c]quinolin-5-one (**3o**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.42–7.36 (m, 2H), 7.31–7.26 (m, 1H), 7.19–7.14 (m, 3H), 6.77 (d, *J* = 10.0 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 5.49 (d, *J* = 10.0 Hz, 1H), 5.17–5.05 (m, 1H), 2.56 (tt, *J* = 7.6, 3.2 Hz, 1H), 2.19 (q, *J* = 7.6 Hz, 2H), 2.03–1.95 (m, 2H), 1.93–1.86 (m, 3H), 1.82–1.75 (m, 1H), 1.64 (s, 3H), 1.58 (s, 3H), 1.52 (s, 3H), 1.52–1.44 (m, 2H), 1.40–1.33 (m, 3H), 1.25–1.19 (m, 2H), 1.14–1.03 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 156.0, 148.3, 140.6, 135.4, 132.0, 130.3, 128.8, 128.4, 125.1, 123.8, 122.7, 121.8, 118.3, 116.0, 115.7, 105.6, 81.6, 44.4, 41.7, 39.7, 37.1, 34.4, 33.6, 27.2, 25.6, 22.7, 20.0, 17.7, 14.4. HRMS (ESI): *m*/*z* [M + H]$^+$ Calcd for $C_{34}H_{42}NO_2^+$: 496.3210, found: 496.3216. Figure S15 in the Supplementary Materials.

6-(4-(tert-butyl)phenyl)-2-methyl-2-(4-methylpent-3-en-1-yl)-2,6-dihydro-5*H*-pyrano-[3,2-c]quinolin-5-one (**3p**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.62–7.52 (m, 2H), 7.30 (ddd, *J* = 8.8, 7.2, 1.6 Hz, 1H), 7.21–7.14 (m, 3H), 6.78 (d, *J* = 10.0 Hz, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 5.49 (d, *J* = 10.0 Hz, 1H), 5.13 (ddd, *J* = 7.2, 6.0, 1.2 Hz, 1H), 2.19 (q, *J* = 7.6 Hz, 2H), 1.95–1.85 (m, 1H), 1.83–1.73 (m, 1H), 1.64 (s, 3H), 1.58 (s, 3H), 1.53 (s, 3H), 1.39 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 156.0, 151.6, 140.6, 135.1, 132.0, 130.3, 128.5, 127.0, 125.2, 123.8, 122.7, 121.8, 118.3, 116.0, 115.8, 105.6, 81.6, 41.7, 34.8, 31.4, 27.2, 25.6, 22.7, 17.7. HRMS (ESI): *m*/*z* [M + H]$^+$ Calcd for $C_{29}H_{34}NO_2^+$: 428.2584, found: 428.2589. Figure S16 in the Supplementary Materials.

6-(4-methoxyphenyl)-2-methyl-2-(4-methylpent-3-en-1-yl)-2,6-dihydro-5*H*-pyrano[3,2-c]quinolin-5-one (**3q**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.30 (ddd, *J* = 8.4, 7.2, 1.2 Hz, 1H), 7.21–7.14 (m, 3H), 7.11–7.03 (m, 2H), 6.77 (d, *J* = 10.0 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 5.50 (d, *J* = 10.0 Hz, 1H), 5.13 (ddd, *J* = 7.2, 6.0, 1.2 Hz, 1H), 3.88 (s, 3H), 2.18 (q, *J* = 7.6 Hz, 2H), 1.95–1.85 (m, 1H), 1.83–1.73 (m, 1H), 1.64 (s, 3H), 1.58 (s, 3H), 1.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 159.6, 156.0, 140.8, 132.0, 130.5, 130.3, 130.1, 125.2, 123.8, 122.7, 121.8, 118.3, 115.9, 115.8, 115.3, 105.6, 81.6, 55.5, 41.7, 27.2, 25.6, 22.6, 17.6.

HRMS (ESI): m/z $[M + H]^+$ Calcd for $C_{26}H_{28}NO_3^+$: 402.2064, found: 402.2069. Figure S17 in the Supplementary Materials.

2-methyl-2-(4-methylpent-3-en-1-yl)-6-(4-phenoxyphenyl)-2,6-dihydro-5*H*-pyrano[3,2-c]quinolin-5-one (**3r**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.42–7.36 (m, 2H), 7.36–7.30 (m, 1H), 7.24–7.11 (m, 8H), 6.77 (d, *J* = 10.0 Hz, 1H), 6.70 (d, *J* = 8.4 Hz, 1H), 5.50 (d, *J* = 10.0 Hz, 1H), 5.13 (t, *J* = 7.2 Hz, 1H), 2.19 (q, *J* = 7.6 Hz, 2H), 1.96–1.85 (m, 1H), 1.83–1.74 (m, 1H), 1.64 (s, 3H), 1.58 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 157.7, 156.5, 156.1, 140.6, 132.5, 132.0, 130.5, 130.4, 129.9, 125.2, 123.9, 123.8, 122.8, 122.0, 119.7, 119.6, 118.2, 115.8, 115.8, 105.6, 81.7, 41.7, 27.2, 25.6, 22.7, 17.6. HRMS (ESI): m/z $[M + H]^+$ Calcd for $C_{31}H_{30}NO_3^+$: 464.2220, found: 464.2225. Figure S18 in the Supplementary Materials.

6-(3,5-dimethylphenyl)-2-methyl-2-(4-methylpent-3-en-1-yl)-2,6-dihydro-5*H*-pyrano-[3,2-c]quinolin-5-one (**3s**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.33 (ddd, *J* = 8.6, 7.2, 1.2 Hz, 1H), 7.19 (ddd, *J* = 8.0, 7.2, 0.8 Hz, 1H), 6.99–6.94 (m, 1H), 6.79–6.70 (m, 4H), 6.12–6.01 (m, 2H), 5.50 (d, *J* = 10.4 Hz, 1H), 5.12 (t, *J* = 7.2 Hz, 1H), 2.18 (q, *J* = 7.6 Hz, 2H), 1.94–1.86 (m, 1H), 1.83–1.74 (m, 1H), 1.64 (s, 3H), 1.58 (s, 3H), 1.52 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 156.1, 148.9, 147.9, 140.6, 132.0, 131.4, 130.4, 125.2, 123.8, 122.8, 122.4, 122.0, 118.2, 115.9, 115.8, 110.0, 109.1, 105.5, 101.9, 81.7, 41.7, 27.2, 25.6, 22.6, 17.6. HRMS (ESI): m/z $[M + H]^+$ Calcd for $C_{26}H_{26}NO_4^+$: 416.1856, found: 416.1858. Figure S19 in the Supplementary Materials.

2-methyl-2-(4-methylpent-3-en-1-yl)-6-(4-(methylthio)phenyl)-2,6-dihydro-5*H*-pyrano-[3,2-c]quinolin-5-one (**3t**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.46–7.40 (m, 2H), 7.33–7.28 (m, 1H), 7.21–7.15 (m, 3H), 6.77 (d, *J* = 10.0 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 5.50 (d, *J* = 10.0 Hz, 1H), 5.13 (t, *J* = 7.2 Hz, 1H), 2.55 (s, 3H), 2.18 (q, *J* = 7.6 Hz, 2H), 1.94–1.85 (m, 1H), 1.83–1.74 (m, 1H), 1.65 (s, 3H), 1.58 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 156.1, 140.4, 139.5, 134.8, 132.0, 130.4, 129.5, 127.8, 125.2, 123.8, 122.8, 122.0, 118.2, 115.8, 115.8, 105.6, 81.7, 41.7, 27.2, 25.6, 22.6, 17.6, 15.8. HRMS (ESI): m/z $[M + H]^+$ Calcd for $C_{26}H_{28}NO_2S^+$: 418.1835, found: 418.1839. Figure S20 in the Supplementary Materials.

2-methyl-2-(4-methylpent-3-en-1-yl)-6-(4-vinylphenyl)-2,6-dihydro-5*H*-pyrano[3,2-c]-quinolin-5-one (**3u**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.63–7.56 (m, 2H), 7.32–7.26 (m, 1H), 7.25–7.21 (m, 2H), 7.18 (t, *J* = 7.6 Hz, 1H), 6.84–6.74 (m, 2H), 6.66 (d, *J* = 8.4 Hz, 1H), 5.82 (d, *J* = 17.6 Hz, 1H), 5.50 (d, *J* = 10.0 Hz, 1H), 5.34 (d, *J* = 10.8 Hz, 1H), 5.13 (t, *J* = 7.2 Hz, 1H), 2.19 (q, *J* = 7.6 Hz, 2H), 1.96–1.85 (m, 1H), 1.84–1.77 (m, 1H), 1.64 (s, 3H), 1.58 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 156.1, 140.4, 138.1, 137.3, 136.1, 132.0, 130.4, 129.32 (d, *J* = 2.1 Hz), 127.8, 125.2, 123.8, 122.8, 122.0, 118.2, 115.9, 115.8, 115.1, 105.6, 81.7, 41.7, 27.2, 25.6, 22.7, 17.7. HRMS (ESI): m/z $[M + H]^+$ Calcd for $C_{27}H_{28}NO_2^+$: 398.2115, found: 398.2118. Figure S21 in the Supplementary Materials.

6-([1,1′-biphenyl]-4-yl)-2-methyl-2-(4-methylpent-3-en-1-yl)-2,6-dihydro-5*H*-pyrano-[3,2-c]quinolin-5-one (**3v**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.80–7.75 (m, 2H), 7.68–7.62 (m, 2H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.40–7.36 (m, 1H), 7.36–7.30 (m, 3H), 7.20 (t, *J* = 7.6 Hz, 1H), 6.80 (d, *J* = 10.0 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 5.51 (d, *J* = 10.0 Hz, 1H), 5.14 (t, *J* = 7.2 Hz, 1H), 2.20 (q, *J* = 7.6 Hz, 2H), 1.97–1.86 (m, 1H), 1.85–1.75 (m, 1H), 1.65 (s, 3H), 1.59 (s, 3H), 1.54 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 156.2, 141.7, 140.4, 137.0, 132.0, 130.5, 129.5, 129.4, 128.9, 128.8, 127.7, 127.3, 125.3, 123.8, 122.8, 122.0, 118.2, 115.9, 115.8, 105.6, 81.7, 41.8, 27.2, 25.6, 22.7, 17.7. HRMS (ESI): m/z $[M + H]^+$ Calcd for $C_{31}H_{30}NO_2^+$: 448.2271, found: 448.2273. Figure S22 in the Supplementary Materials.

2-methyl-2-(4-methylpent-3-en-1-yl)-6-(naphthalen-2-yl)-2,6-dihydro-5*H*-pyrano[3,2-c]-quinolin-5-one (**3w**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.6 Hz, 1H), 7.99 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.86 (d, *J* = 7.9 Hz, 1H), 7.80 (s, 1H), 7.55 (pd, *J* = 7.2, 1.2 Hz, 2H), 7.35 (dt, *J* = 8.4, 2.0 Hz, 1H), 7.29–7.24 (m, 1H), 7.22–7.15 (m, 1H), 6.80 (d, *J* = 10.0 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 5.52 (d, *J* = 10.0 Hz, 1H), 5.14 (t, *J* = 7.2 Hz, 1H), 2.21 (q, *J* = 7.6 Hz, 2H), 1.97–1.87 (m, 1H), 1.85–1.75 (m, 1H), 1.66 (s, 3H), 1.60 (s, 3H), 1.55 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 156.2, 140.5, 135.3, 134.0, 133.2, 132.0, 130.4,

130.1, 128.2, 128.1, 127.9, 126.8, 126.7, 126.6, 125.3, 123.8, 122.8, 122.0, 118.2, 116.0, 115.8, 105.7, 81.7, 41.7, 27.2, 25.6, 22.7, 17.7. HRMS (ESI): m/z [M + H]$^+$ Calcd for $C_{29}H_{28}NO_2^+$: 422.2115, found: 422.2118. Figure S23 in the Supplementary Materials.

6-(9,9-dimethyl-9H-fluoren-2-yl)-2-methyl-2-(4-methylpent-3-en-1-yl)-2,6-dihydro-5*H*-pyrano[3,2-c]quinolin-5-one (**3x**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (dd, J = 8.0, 1.2 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.77 (dd, J = 6.0, 2.4 Hz, 1H), 7.48–7.43 (m, 1H), 7.39–7.33 (m, 3H), 7.32–7.27 (m, 1H), 7.23 (dt, J = 8.0, 2.4 Hz, 1H), 7.21–7.16 (m, 1H), 6.81 (d, J = 10.0 Hz, 1H), 6.69 (d, J = 8.4 Hz, 1H), 5.51 (dd, J = 10.0, 1.6 Hz, 1H), 5.20–5.08 (m, 1H), 2.20 (q, J = 7.6 Hz, 2H), 1.96–1.87 (m, 1H), 1.85–1.75 (m, 1H), 1.66 (s, 3H), 1.60 (s, 3H), 1.54 (d, J = 4.0 Hz, 3H), 1.52 (s, 3H), 1.50 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3, 156.1, 155.5, 154.0, 140.8, 139.7, 138.4, 136.9, 132.0, 130.4, 127.9, 127.7, 127.2, 125.3, 123.8, 123.6, 122.8, 122.7, 121.9, 121.3, 120.3, 118.3, 116.0, 115.9, 105.7, 81.7, 47.2, 41.7, 27.2, 27.1, 27.0, 25.7, 22.6, 17.7. HRMS (ESI): m/z [M + H]$^+$ Calcd for $C_{34}H_{34}NO_2^+$: 488.2584, found: 488.2588. Figure S24 in the Supplementary Materials.

2-methyl-2-(4-methylpent-3-en-1-yl)-6-(4-(trimethylsilyl)phenyl)-2,6-dihydro-5*H*-pyrano[3,2-c]quinolin-5-one (**3y**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, J = 8.0, 1.2 Hz, 1H), 7.53–7.45 (m, 2H), 7.10–7.06 (m, 1H), 7.05–7.02 (m, 2H), 7.00–6.93 (m, 1H), 6.56 (d, J = 10.0 Hz, 1H), 6.43 (d, J = 8.4 Hz, 1H), 5.28 (d, J = 10.0 Hz, 1H), 4.91 (t, J = 7.2 Hz, 1H), 1.97 (q, J = 7.6 Hz, 2H), 1.73–1.64 (m, 1H), 1.62–1.52 (m, 1H), 1.43 (s, 3H), 1.37 (s, 3H), 1.31 (s, 3H), 0.11 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 157.2, 142.4, 141.5, 139.4, 136.1, 135.8, 133.1, 131.4, 129.4, 126.3, 124.9, 123.8, 123.0, 119.3, 117.1, 116.8, 116.1, 106.7, 82.8, 42.8, 28.3, 26.7, 23.8, 18.7. HRMS (ESI): m/z [M + H]$^+$ Calcd for $C_{28}H_{34}NO_2Si^+$: 444.2353, found: 444.2358. Figure S25 in the Supplementary Materials.

4. Conclusions

In summary, we have developed an efficient Cu-catalyzed protocol for the *N*-arylation of pyranoquinolinone, which is synthesized from citral. This "open-flask" chemistry can be carried out at room temperature under ligand-free conditions. This chemistry was general, and the reaction conditions were mild compared to Ullmann cross-coupling and Buchwald–Hartwig cross-coupling reactions, thus offering an alternative to these approaches. This article briefly evaluated the inhibitory activity of 25 compounds obtained on tumor cells. Compared to citral, the compounds we obtained have a much better inhibitory effect on HeLa cervical cancer cells. Further studies on the mechanism and synthetic applications are ongoing in our laboratory.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/catal13071060/s1, Figure S1. ^{13}C NMR and ^{1}H NMR ($CDCl_3$) spectrum of compound **3a**; Figure S2. ^{13}C NMR and ^{1}H NMR ($CDCl_3$) spectrum of compound **3b**; Figure S3. ^{13}C NMR and ^{1}H NMR ($CDCl_3$) spectrum of compound **3c**; Figure S4. ^{13}C NMR and ^{1}H NMR ($CDCl_3$) spectrum of compound **3d**; Figure S5. ^{13}C NMR and ^{1}H NMR ($CDCl_3$) spectrum of compound **3e**; Figure S6. ^{13}C NMR and ^{1}H NMR ($CDCl_3$) spectrum of compound **3f**; Figure S7. ^{13}C NMR and ^{1}H NMR ($CDCl_3$) spectrum of compound **3g**; Figure S8. ^{13}C NMR and ^{1}H NMR ($CDCl_3$) spectrum of compound **3h**; Figure S9. ^{13}C NMR and ^{1}H NMR ($CDCl_3$) spectrum of compound **3i**; Figure S10. ^{13}C NMR and ^{1}H NMR ($CDCl_3$) spectrum of compound **3j**; Figure S11. ^{13}C NMR and ^{1}H NMR ($CDCl_3$) spectrum of compound **3k**; Figure S12. ^{13}C NMR and ^{1}H NMR ($CDCl_3$) spectrum of compound **3l**; Figure S13. ^{13}C NMR and ^{1}H NMR ($CDCl_3$) spectrum of compound **3m**; Figure S14. ^{13}C NMR and ^{1}H NMR ($CDCl_3$) spectrum of compound **3n**; Figure S15. ^{13}C NMR and ^{1}H NMR ($CDCl_3$) spectrum of compound **3o**; Figure S16. ^{13}C NMR and ^{1}H NMR ($CDCl_3$) spectrum of compound **3p**; Figure S17. ^{13}C NMR and ^{1}H NMR ($CDCl_3$) spectrum of compound **3q**; Figure S18. ^{13}C NMR and ^{1}H NMR ($CDCl_3$) spectrum of compound **3r**; Figure S19. ^{13}C NMR and ^{1}H NMR ($CDCl_3$) spectrum of compound **3s**; Figure S20. ^{13}C NMR and ^{1}H NMR ($CDCl_3$) spectrum of compound **3t**; Figure S21. ^{13}C NMR and ^{1}H NMR ($CDCl_3$) spectrum of compound **3u**; Figure S22. ^{13}C NMR and ^{1}H NMR ($CDCl_3$) spectrum of compound **3v**; Figure S23. ^{13}C NMR and ^{1}H NMR ($CDCl_3$) spectrum of compound **3w**; Figure S24. ^{13}C NMR and ^{1}H NMR ($CDCl_3$) spectrum of compound **3x**; Figure S25. ^{13}C NMR and ^{1}H NMR ($CDCl_3$) spectrum of compound **3y**.

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