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Environmentally Friendly Nafion-Catalyzed Synthesis of Substituted 2-Ethyl-3-Methylquinolines from Aniline and Propionaldehyde under Microwave Irradiation

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Abstract: Herein, we report a facile synthetic methodology for the preparation of 2,3-dialkylquinolines from anilines and propionaldehydes. This cyclization involved environmentally friendly Nafion® NR50 as an acidic catalyst with microwave irradiation as the heating source. A series of substituted 2-ethyl-3-methylquinolines were prepared from various anilines and propionaldehyde derivatives through this protocol with good to excellent yields. Some new chemical structures were confirmed by X-ray single-crystal diffraction analysis and the related data were provided. The plausible reaction mechanism studies are also discussed.

Keywords: nafion; quinoline; microwave irradiation

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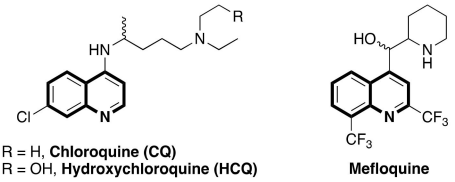
1. Introduction

A quinoline scaffold is a versatile synthetic building block in various natural products [1–5], exceptional pharmaceuticals [6–8], physical materials [9–13], and is an important intermediate for asymmetric synthesis [14–18]. Functionalized quinolines are broadly used in agrochemicals [19,20], dyes [21,22], and some biologically active molecules for antimalarial [23–25], anticancer [26–30], antiviral [31], antifungal [32], anti-bacterial [33], and anti-inflammatory functions [34,35]. In particular, since the 17th century, the quinoline alkaloid quinine has been viewed historically as the first cure for treating or preventing malaria, [36,37]. Recently, some reports indicated that some quinoline-containing compounds are potentially active SARS-CoV-2 inhibitors [38–40], and some quinoline-derived drugs, as shown in Scheme 1, are currently being investigated as a possible cure for COVID-19 infection [41,42]. Numerous classical methodologies for the construction of the quinoline skeleton, such as the Combes reaction, the Conrad–Limpach–Knorr reaction, the Doebner–Von Miller reaction, the Friedlander reaction, the Povaror reaction, the Pfitzinger reaction, and the Skraup reaction have been well documented [43–47].

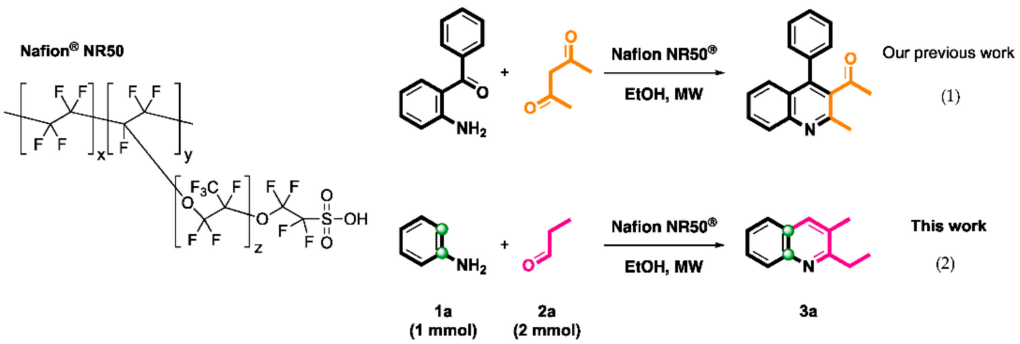


Scheme 1. Some quinoline-based antimalarial drugs.

Alkylated quinolines display some meaningful activity against cancer, inflammation, malaria, and tuberculosis [48–52]. Among them, 2-alkylquinolines show better activities compared to the other alkyl-substituted quinolines. The alkyl groups at the C-2 position are adjacent to the quinoline nitrogen atom, which increases the lipophilicity and promotes cell permeability [53]. Although the synthesis of 2,3-dialkylated quinolines involving readily

available starting materials such as aldehydes, ketones, alkenes, alkynes, cyclobutanes, or allyl alcohols is broadly reported [54–67], the protocol to synthesize alkylated quinolines poses a challenge to medicinal chemists.

In continuation of our investigations toward the synthesis of nitrogen-containing heterocyclic compounds [68–71], we recently provided a synthetic route for the Friedländer quinoline synthesis from 2-aminobenzophenone and acetylacetone catalyzed by Nafion® NR50 particles under microwave irradiation ((1) in Scheme 2) [69]. Nafion® is a commercially available synthetic polymer particle which possesses ionic properties [72]. Its unique ionic properties result from the copolymerization of incorporating perfluorovinyl ether groups terminated with sulfonate groups onto a tetrafluoroethylene (PTFE) skeleton [73]. The chemical structure of Nafion® NR50 is shown in Scheme 2. Considering the importance of alkylated quinolines in medicinal chemistry, the efficiency of microwave irradiation and recyclable features of Nafion® NR50 in green chemistry, the development of a facile synthetic protocol is of great interest. Herein, we provide an efficient synthetic protocol for the preparation of a 2-ethyl-3-methylquinoline skeleton from aniline and propionaldehyde using Nafion® NR50 with good to excellent yields under microwave irradiation ((2) in Scheme 2). Four chemical structures are confirmed by X-ray single-crystal diffraction analysis.



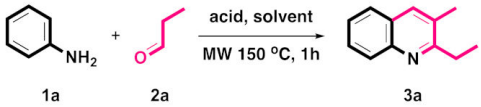
Scheme 2. Nafion® NR50-mediated synthesis of quinolines.

2. Results and Discussion

Initially, we conducted the investigation with the cyclization of readily available aniline **1a** and propionaldehyde **2a** as model substrates in the solvent under microwave irradiation (T = 150 °C), and the related results are summarized in Table 1. By using liquid acids, such as AcOH (acetic acid), TFA (trifluoroacetic acid), and TfOH (triflic acid), quinoline **1a** was obtained at 15% to 40% yield (entries 1–3). The involvement of substituted sulfonic acids, including MsOH (methansulfonic acid), BsOH (benzenesulfonic acid), and *p*-TsOH.H_2O (*p*-toluenesulfonic acid) provided product **3a** in similar yields (entries 4–6). Other metal triflates such as AgOTf, $Bi(OTf)_3$, $Fe(OTf)_2$, $Fe(OTf)_3$, and $Sn(OTf)_2$ were also examined in this reaction, as shown in entries 7–11, and the isolated yields of **3a** were lower than that obtained after using sulfonic acids. Other Lewis acids including $BF_3.OEt_2$, $InCl_3$, and $AlCl_3$ promoted the reactions, and the isolated yields are shown in entries 12–14. Among these entries, $BF_3.OEt_2$ showed the best performance. According to our previous work [69], we further examined the environmentally friendly solid acid Nafion® NR50, and the desired product **3a** was obtained at 93% yield (entry 15). However, only a 30% yield of **3a** was observed when liquid Nafion® NR117 was used as an acid catalyst (entry 16). No better yields were observed by changing the reaction solvents (entries 17–20). Changing the heating source from microwave irradiation to normal hot plate, the yield was decreased to 40% yield. It is possible that the boiling point of propionaldehyde is lower than the reaction temperature, and the reaction was conducted in the open system (entry 21). Considering the green chemistry concept and environmentally friendly nature, we selected Nafion® NR50 as acid and ethanol as a solvent under microwave irradiation as the best reaction condition

for this synthetic protocol. Microwave irradiation has attracted considerable attention in the past decade for increasing reaction efficiency [74,75]. Therefore, we confirmed that the condition of entry 15 is the most suitable condition in this double intermolecular cyclization for the construction of the corresponding 2-ethyl-3-methylquinolines.

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

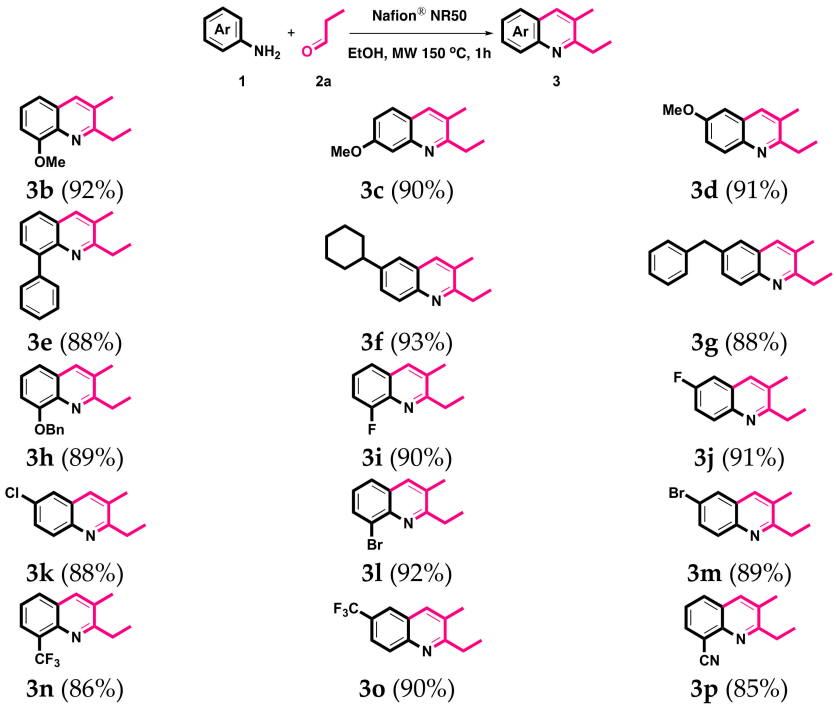


Entry	Acid	Solvent	Yields [b]
entry 1	AcOH	EtOH	25
entry 2	TFA	EtOH	15 [c]
entry 3	TfOH	EtOH	40
entry 4	MsOH	EtOH	35
entry 5	BsOH	EtOH	38
entry 6	*p*-TsOH	EtOH	39
entry 7	AgOTf	EtOH	45
entry 8	$Bi(OTf)_3$	EtOH	30
entry 9	$Fe(OTf)_2$	EtOH	28
entry 10	$Fe(OTf)_3$	EtOH	29
entry 11	$Sn(OTf)_2$	EtOH	32
entry 12	BF_3OEt_2	EtOH	55
entry 13	$InCl_3$	EtOH	23
entry 14	$AlCl_3$	EtOH	33
entry 15	Nafion® NR50	EtOH	93
entry 16	Nafion® NR117	EtOH	30
entry 17	Nafion® NR50	CH_2Cl_2	36
entry 18	Nafion® NR50	toluene	17 [c]
entry 19	Nafion® NR50	1,4-dioxane	77
entry 20	Nafion® NR50	DMF	65
entry 21 [d]	Nafion® NR50	EtOH	40

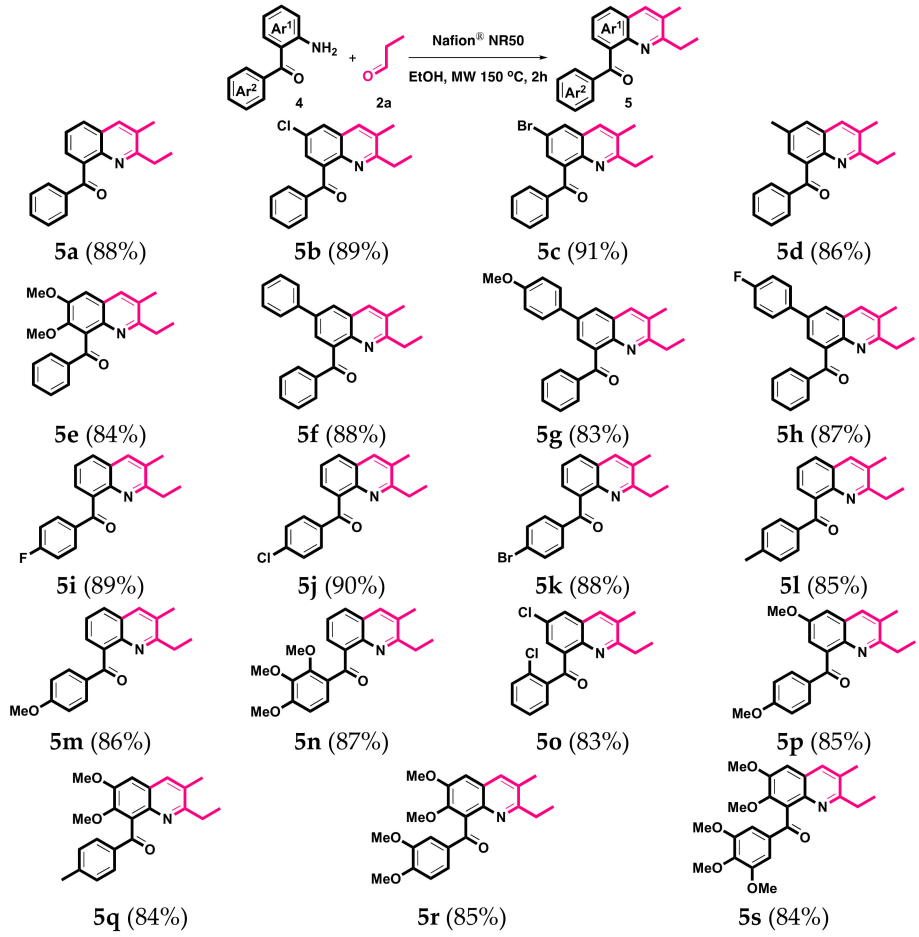
[a] Reaction conditions: **1a** (2.0 mmol), **2a** (4.2 mmol), acid (0.1 mmol), solvent (5 mL). [b] Isolated yields. [c] We obtained 45% of *N*-propylamine. [d] Hot plate as heating source.

After obtaining the optimal reaction conditions, the scope of the reaction with respect to various anilines was evaluated. As shown in Scheme 3, a variety of commercially available anilines, **1b–1p**, were investigated with propionaldehyde **2a** in this intermolecular reaction. The anilines containing both electron-withdrawing groups (EWGs) and electron-donating groups (EDGs) on different positions successfully gave good to excellent yields of the corresponding quinolines **3b–3p**. The structure of **3p** was confirmed by single-crystal X-ray crystallography [76].

Quinolinyl ketones are regarded as a versatile directing group by the cooperation of transition metal catalysts for activating the organic transformation [77–82]. A variety of 2-aminobenzophenone **4** were subjected to react with propionaldehyde **2a** in the optimized reaction condition. As shown in Scheme 4, a wide range of 2-aminobenzophenones could be used in this cyclization. Various substituted groups at different positions of the Ar^1 and Ar^2 rings smoothly delivered good to excellent yields of the desired 8-substituted quinolinyl ketones **5** in 2 h. Not only non-substituted 2-aminobenzophenone **4a**, but some functional groups such as chloro- (**4b**), bromo- (**4c**), methyl- (**4d**), dimethoxy- (**4e**), phenyl- (**4f**), *p*-methoxyphenyl- (**4g**) and *p*-fluorophenyl- (**4h**) on the Ar^1 ring; fluoro- (**4i**), chloro- (**4j**), bromo- (**4k**), methyl- (**4l**), methoxy- (**4m**), trimethoxy- (**4n**) on Ar^2, and both EWGs dichloro- (**4o**) and both EWGs multimethoxy- (**4p-4s**) on the Ar^1 and Ar^2 rings were well tolerated in this transformation. The related 8-substituted quinolinyl ketones **5** are illustrated in Scheme 4. The structures of **5a**, **5b**, and **5d** were also confirmed by single-crystal X-ray crystallography [76].

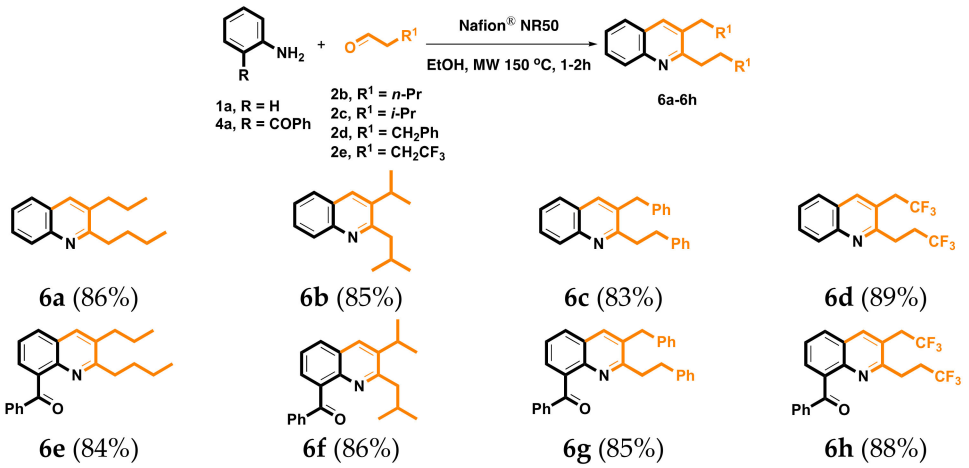


Scheme 3. Synthesis of **3**. Reaction conditions: **1** (1.0 mmol), **2a** (2.1 mmol), Nafion® NR50 (0.1 mmol), EtOH (10 mL). Isolated yields.

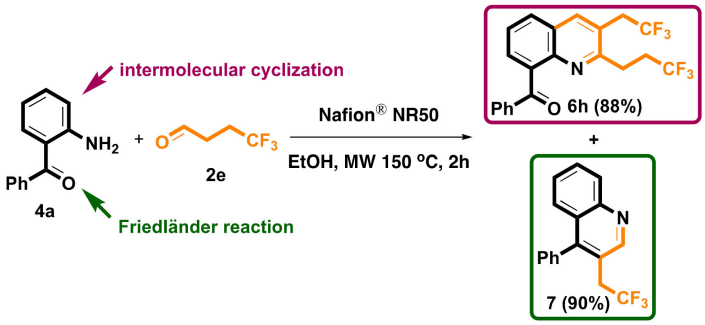


Scheme 4. The synthesis of **5**. Reaction conditions: **4** (1.0 mmol), **2a** (2.1 mmol), Nafion® NR50 (0.1 mmol), and EtOH (10 mL). Isolated yields.

We next investigated the scope of substituents on the terminal of propionaldehyde by using aniline **1a** and 2-aminobenzophenone **4a** as the model aminobenzene substrate. Four propionaldehyde analogues were investigated, including valeraldehyde **2b**, isovaleraldehyde **2c**, 3-phenylpropionaldehyde **2d** and 4,4,4-trifluorobutyraldehyde **2e**. As illustrated in Scheme 5, changing the substituted group on propionaldehydes **2** did not influence the preparation of corresponding quinolines **6a**–**6h** and gave modest to good yields. Based on our previous experience for the synthesis of quinolines by Friedländer reaction from 2-aminobenzophenone **4a** with monocarbonyl synthons [69], it is possible that the electron-withdrawing CF_3 group on **2e** change in α-methylene reactivity could also access the Friedländer-type protocol to prepare the desired quinoline **7** by decreasing to one equivalent (Scheme 6). Friedländer quinoline synthesis is the reaction of 2-aminobenzaldehyde with acetylaldehyde to generate quinoline skeleton. In 2020, we developed a Nafion® NR50-catalyzed Friedländer quinoline synthesis; the related mechanism was also reported [69].

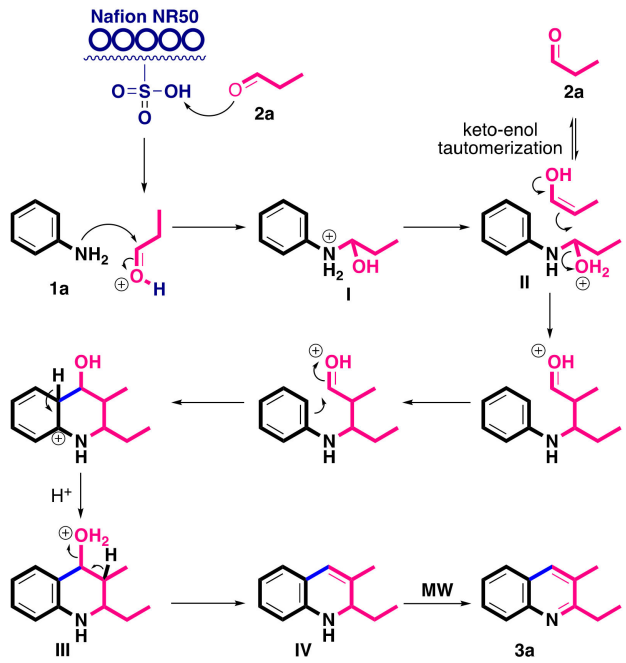


Scheme 5. The synthesis of **6**. Reaction conditions: **1a** or **4a** (1.0 mmol), **2a** (2.1 mmol), Nafion® NR50 (0.1 mmol), and EtOH (10 mL). Reaction time: 1 h for **6a**–**6d** and 2 h for **6e**–**6h**. Isolated yields.



Scheme 6. The Friedländer quinoline synthesis of **7**.

Based on the results of current assays, compounds **1a** and **2a** are selected as model substrates to speculate the possible mechanism for the desired quinoline **3a** synthesis, as shown in Scheme 7. To start with, the first 1.0 equiv. of propionaldehyde **2a** was protonated by Nafion® NR50 and reacted with **1a** to produce intermediate **I**, then proton transfer occurred to form intermediate **II**. The keto-enol tautomerization of the second 1.0 equivalent of **2a** conducted with intermediate **II** to generate intermediate **III** via a consecutive intramolecular cyclization. Dehydration was then performed in acidic conditions to give an intermediate **IV**. The aromatic cyclization of intermediate **IV** was performed under microwave irradiation to produce the desired quinoline **3a**.



Scheme 7. A plausible mechanism for the synthesis of quinoline **3a**.

To observe the efficiency of the environmentally friendly Nafion® NR50 particles, the recycling experiments were conducted at least 10 times, and the corresponding yields are shown in Figure 1. Photos of the physical states for every experiment are provided in Table S1 in the Supporting Information. The recovered Nafion® NR50 particles was reused 10 times in the reaction of **1a** and **2a**. Although the shapes of particles became different, no obvious yield change was observed.

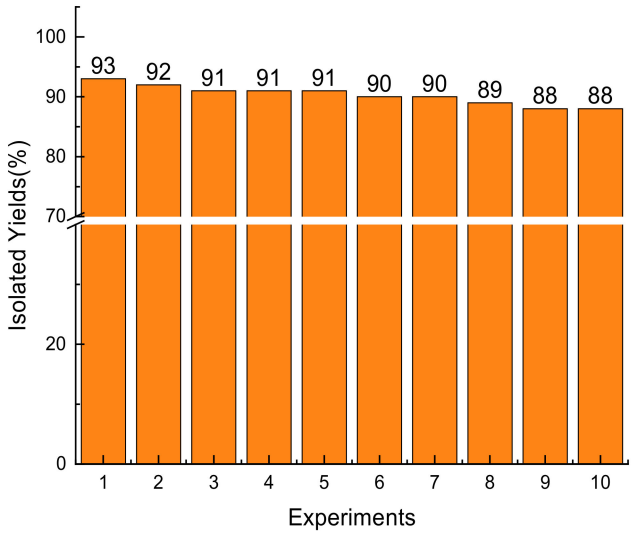
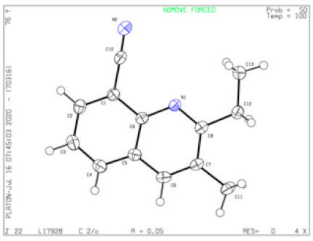
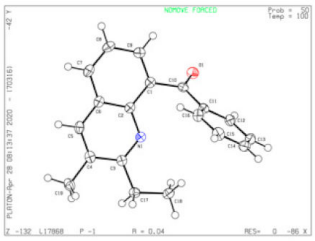
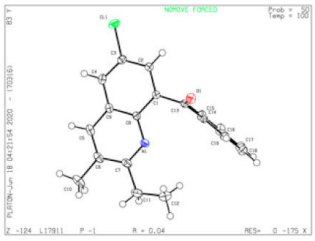
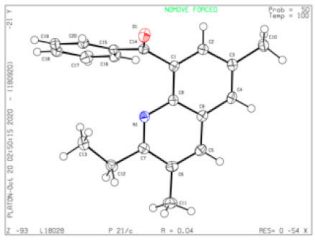


Figure 1. Recycling experiments.

On the basis of the abovementioned results, four new chemical structures are confirmed by single-crystal X-ray crystallography. The corresponding crystal structures of **3p**, **5a**, **5b** and **5d**, and related data are described in Table 2. Furthermore, no alert A and B are presented in the checkcif output, as reported in the Supplementary Materials file.

Table 2. Crystal data for compounds **3p**, **5a**, **5b** and **5d**.

	 Compound **3p**		 Compound **5a**	
	 Compound **5b**		 Compound **5d**	
CCDC number	1940046 (**3p**)	2002378 (**5a**)	2013112 (**5b**)	2039753 (**5d**)
Crystal system	Monoclinic	Triclinic	Triclinic	Monoclinic
Space group	C 2/c	P-1	P-1	P 21/c
a (Å)	20.8096 (12)	8.4108 (3)	7.4420 (3)	13.2934 (5)
b (Å)	8.4535 (5)	8.9126 (3)	10.3406 (3)	14.2302 (5)
c (Å)	15.3108 (16)	10.9019 (4)	10.7949 (4)	8.6189 (3)
α (°)	90	103.454 (2)	103.4120 (10)	90
β (°)	128.6800 (10)	97.603 (2)	100.533 (2)	108.5200 (10)
γ (°)	90	111.8150 (10)	90.7170 (10)	90
Volume ($Å^3$)/Z	2102.6 (3)/8	715.90 (4)/2	793.14 (5)/2	1545.98 (10)/4
Temperature (K)	100.0 (2)	100.0 (2)	100.0 (2)	100.0 (2)
D_{calcd} (Mg/m^3)	1.240	1.277	1.297	1.243
Absorption coefficient (mm^{-1})	0.075	0.079	0.242	0.076
F(000)/GOF	832/1.022	292/1.027	324/1.092	616/1.041
Crystal size (mm)	0.139 × 0.103 × 0.099	0.238 × 0.208 × 0.149	0.365 × 0.351 × 0.319	0.214 × 0.202 × 0.094
Theta range for data collection (°)	2.687 to 28.345	2.586 to 27.103	2.028 to 33.138	2.158 to 27.098
Reflections collected	28,515	31,756	45,950	43,540
Independent reflections	2620 (R = 0.1270)	3168 (R = 0.0684)	6054 (R = 0.0386)	3392 (R = 0.0506)

3. Experimental Section

3.1. General Information

All reagents and solvents were commercially available (Sigma-Aldrich, St. Louis, MO, USA) and used without further purification. Reactions were routinely performed using the Discover SP system (2010 version, CEM Corporation, Matthews, NC, USA) in the sealed reaction vessels in standard mode with the temperature monitored using a vertically focused IR sensor. All reactions were monitored by TLC on silica gel 60 F254 (Merck) with detection by UV light. Column chromatography was performed using silica gel (200–300 mesh). Products in organic solvents were dried with anhydrous magnesium sulfate before concentration in vacuo. Melting points were determined with a MP-2D (Mandarin In Scientific, New Taipei, Taiwan) melting apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVIII 500 MHz instruments operating at 500 and at 125 MHz, respectively. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad), coupling constants (Hz) and integration. HRMS were obtained on a Waters LCT Premier XE (Waters Corp., Manchester, UK) instrument equipped with an electrospray source. The X-ray intensity data were measured at low temperature 100 K using Mo Kα radiation diffractometer equipped with a kappa geometry

goniometer and corrected for absorption effects using the numerical method (SADABS). The yields are provided in mol% and the corresponding product weights are also shown.

3.2. General Procedure for the Synthesis of Skeletons **3**, **5**, **6** *and* **7**

A mixture of anilines 1 or 4 (1.0 mmol), substituted propionaldehydes 2 (2.1 mmol), Nafion® NR50 (0.1 mmol) in ethanol (10 mL), in a dried 35 mL microwave vial at 25 °C. The mixture was subjected to a microwave irradiation instrument and stirred at 150 °C for skeleton between 1 and 2 h. The consumption of the starting materials were confirmed by TLC. The reaction was cooled to 25 °C, the mixture of crude product was transferred to a 100 mL round bottom flask, and the solvent was concentrated to afford crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 4/1–1/1) afforded compounds **3a**–**3p**, **5a**–**5s**, **6a**–**6h** and **7**.

4. Data

*4.1. 2-Ethyl-3-methylquinoline (***3a***)*

Yield = 93% (159 mg); colorless solid; mp = 63–64 °C; HRMS (ESI, M^+ + H) calcd for $C_{12}H_{14}N$ 172.1126, found 172.1125; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.5 Hz, 1H), 7.79 (s, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H), 2.98 (q, *J* = 8.5 Hz, 2H), 2.45 (s, 3H), 1.37 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.20, 146.59, 135.62, 129.30, 128.44, 128.18, 127.24, 126.59, 125.49, 29.42, 19.01, 12.76. The NMR spectroscopic data of this compound are consistent with reported literature [83].

*4.2. 2-Ethyl-8-methoxy-3-methylquinoline (***3b***)*

Yield = 92% (185 mg); colorless solid; mp = 84–85 °C; HRMS (ESI, M^+ + H) calcd for $C_{13}H_{16}NO$ 202.1232, found 202.1229; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.35 (t, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 4.07 (s, 3H), 3.06 (q, *J* = 7.5 Hz, 2H), 2.49 (s, 3H), 1.37 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.39, 154.97, 138.47, 135.90, 129.94, 128.50, 125.64, 118.71, 106.80, 56.04, 29.82, 19.06, 13.13. The NMR spectroscopic data of this compound are consistent with reported literature [84].

*4.3. 2-Ethyl-7-methoxy-3-methylquinoline (***3c***)*

Yield = 90% (181 mg); brown gum; HRMS (ESI, M^+ + H) calcd for $C_{13}H_{16}NO$ 202.1226, found 202.1232; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (s, 1H), 7.57 (d, *J* = 9.0 Hz, 1H), 7.36 (d, *J* = 2.5 Hz, 1H), 7.10 (dd, *J* = 2.5, 9.0 Hz, 1H), 3.93 (s, 3H), 2.96 (q, *J* = 7.5 Hz, 2H), 2.44 (s, 3H), 1.36 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.46, 159.90, 148.15, 135.64, 127.66, 126.90, 122.39, 118.60, 106.73, 55.42, 29.52, 18.83, 12.95. The NMR spectroscopic data of this compound are consistent with reported literature [59].

*4.4. 2-Ethyl-6-methoxy-3-methylquinoline (***3d***)*

Yield = 91% (183 mg); brown gum; HRMS (ESI, M^+ + H) calcd for $C_{13}H_{16}NO$ 202.1226, found 202.1222; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, *J* = 9.5 Hz, 1H), 7.70 (s, 1H), 7.25 (dd, *J* = 2.5, 9.5 Hz, 1H), 6.95 (d, *J* = 3.0 Hz, 1H), 3.88 (s, 3H), 2.94 (q, *J* = 8.0 Hz, 2H), 2.44 (s, 3H), 1.34 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.62, 157.07, 142.60, 134.72, 129.88, 129.58, 128.07, 120.59, 104.43, 55.36, 29.18, 19.04, 12.87. The NMR spectroscopic data of this compound are consistent with reported literature [67].

*4.5. 2-Ethyl-3-methyl-8-phenylquinoline (***3e***)*

Yield = 88% (217 mg); yellow gum; HRMS (ESI, M^+ + H) calcd for $C_{18}H_{18}N$ 248.1434, found 248.1430; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, *J* = 8.0 Hz, 2H), 7.87 (s, 1H), 7.76–7.70 (m, 2H), 7.57–7.51 (m, 3H), 7.44 (t, *J* = 7.0 Hz, 1H), 2.97 (q, *J* = 7.5 Hz, 2H), 2.49 (s, 3H), 1.40 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.09, 143.86, 139.67, 139.63, 135.34, 131.08 (2×), 129.32, 128.90, 127.64, 127.44 (2×), 126.86, 126.37, 125.34, 28.99, 18.90, 11.59.

*4.6. 6-Cyclohexyl-2-ethyl-3-methylquinoline (**3f**)*

Yield = 93% (235 mg); yellow gum; HRMS (ESI, M^+ + H) calcd for $C_{18}H_{24}N$ 254.1903, found 254.1904; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.5 Hz, 1H), 7.74 (s, 1H), 7.49 (dd, *J* = 1.5, 8.5 Hz, 1H), 7.46 (s, 1H), 2.96 (q, *J* = 7.5 Hz, 2H), 2.68–2.59 (m, 1H), 2.43 (s, 3H), 1.94 (d, *J* = 12.5 Hz, 2H), 1.87 (d, *J* = 12.5 Hz, 2H), 1.77 (d, *J* = 12.5 Hz, 1H), 1.55–1.23 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.27, 145.46, 145.22, 135.43, 129.02, 128.43, 128.13, 127.24, 123.11, 44.32, 34.32 (2×), 29.33, 26.79 (2×), 26.08, 18.98, 12.91. The NMR spectroscopic data of this compound are consistent with reported literature [85].

*4.7. 6-Benzyl-2-ethyl-3-methylquinoline (**3g**)*

Yield = 88% (230 mg); brown gum; HRMS (ESI, M^+ + H) calcd for $C_{19}H_{20}N$ 262.1590, found 252.1589; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.01 (d, *J* = 9.0 Hz, 1H), 7.73 (s, 1H), 7.51–7.45 (m, 2H), 7.37–7.30 (m, 2H), 7.28–7.21 (m, 3H), 4.15 (s, 2H), 3.00 (q, *J* = 7.5 Hz, 2H), 2.46 (s, 3H), 1.41 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.55, 145.43, 140.65, 138.29, 135.27, 129.90, 129.27, 128.86 (2×), 128.48, 128.38 (2×), 127.19, 126.06, 125.69, 41.69, 29.29, 18.93, 12.78.

*4.8. 8-(Benzyloxy)-2-ethyl-3-methylquinoline (**3h**)*

Yield = 89% (247 mg); brown gum; HRMS (ESI, M^+ + H) calcd for $C_{19}H_{20}NO$ 278.1539, found 278.1545; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.57 (d, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 8.0 Hz, 2H), 7.33–7.27 (m, 3H), 7.03–6.95 (m, 1H), 5.46 (s, 2H), 3.07 (q, *J* = 7.5 Hz, 2H), 2.48 (s, 3H), 1.44 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.05, 153.97, 138.88, 137.49, 135.56, 129.84, 128.57, 128.37 (2×), 127.46, 126.85 (2×), 125.47, 119.26, 110.07, 70.93, 29.43, 18.99, 12.69.

*4.9. 2-Ethyl-8-fluoro-3-methylquinoline (**3i**)*

Yield = 90% (170 mg); colorless solid; mp = 65–66 °C; HRMS (ESI, M^+ + H) calcd for $C_{12}H_{13}FN$ 190.1027, found 190.1022; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.35–7.19 (m, 2H), 2.99 (q, *J* = 7.5 Hz, 2H), 2.43 (s, 3H), 1.35 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.62, 157.60 (d, *J* = 253.625 Hz), 136.64 (d, *J* = 11.125 Hz), 135.21 (d, *J* = 2.25 Hz), 130.51, 128.94 (d, *J* = 1.375 Hz), 125.12 (d, *J* = 8.0 Hz), 122.19 (d, *J* = 4.25 Hz), 122.22 (d, *J* = 19.125 Hz), 29.45, 18.98, 12.66. The NMR spectroscopic data of this compound are consistent with reported literature [59].

*4.10. 2-Ethyl-6-fluoro-3-methylquinoline (**3j**)*

Yield = 91% (172 mg); brown gum; HRMS (ESI, M^+ + H) calcd for $C_{12}H_{13}FN$ 190.1027, found 190.1022; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02–7.94 (m, 1H), 7.70 (s, 1H), 7.37–7.31 (m, 1H), 7.27–7.23 (m, 1H), 2.94 (q, *J* = 7.5 Hz, 2H), 2.43 (s, 3H), 1.35 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.42 (d, *J* = 2.0 Hz), 159.92 (d, *J* = 244.5 Hz), 143.61, 134.89 (d, *J* = 4.875 Hz), 130.82 (d, *J* = 9.0 Hz), 130.28, 127.69 (d, *J* = 10.0 Hz), 118.10 (d, *J* = 25.375 Hz), 109.54 (d, *J* = 21.5 Hz), 29.21, 18.97, 12.56. The NMR spectroscopic data of this compound are consistent with reported literature [59].

*4.11. 6-Chloro-2-ethyl-3-methylquinoline (**3k**)*

Yield = 88% (180 mg); brown gum; HRMS (ESI, M^+ + H) calcd for $C_{12}H_{13}ClN$ 206.0731, found 206.0726; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (d, *J* = 9.0 Hz, 1H), 7.57 (s, 1H), 7.54 (s, 1H), 7.46 (dd, *J* = 1.5, 8.5 Hz, 1H), 2.90 (q, *J* = 7.5 Hz, 2H), 2.37 (s, 3H), 1.32 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.35, 144.79, 134.41, 130.91, 130.34, 130.02, 128.86, 127.69, 125.16, 29.20, 18.91, 12.40. The NMR spectroscopic data of this compound are consistent with reported literature [59].

*4.12. 8-Bromo-2-ethyl-3-methylquinoline (**3l**)*

Yield = 92% (229 mg); colorless solid; mp = 50–51 °C; HRMS (ESI, M^+ + H) calcd for $C_{12}H_{13}BrN$ 250.0226, found 250.0221; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91 (d, *J* = 7.5 Hz,

1H), 7.74 (s, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.25 (t, *J* = 8.0 Hz, 1H), 3.00 (q, *J* = 7.5 Hz, 2H), 2.44 (s, 3H), 1.46 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.85, 143.34, 135.49, 131.64, 130.48, 128.29, 126.49, 125.80, 124.41, 29.16, 18.74, 11.89.

*4.13. 6-Bromo-2-ethyl-3-methylquinoline (**3m**)*

Yield = 89% (222 mg); colorless solid; mp = 53–54 °C; HRMS (ESI, M^+ + H) calcd for $C_{12}H_{13}BrN$ 250.0226, found 250.0220; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (d, *J* = 9.0 Hz, 1H), 7.75 (s, 1H), 7.62 (s, 1H), 7.60 (s, 1H), 2.91 (q, *J* = 7.5 Hz, 2H), 2.40 (s, 3H), 1.33 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.57, 145.02, 134.36, 131.45, 130.37, 130.20, 128.54, 128.28, 119.08, 29.28, 18.98, 12.42. The NMR spectroscopic data of this compound are consistent with reported literature [84].

*4.14. 2-Ethyl-3-methyl-8-(trifluoromethyl)quinoline (**3n**)*

Yield = 86% (206 mg); white solid; mp = 68–69 °C; HRMS (ESI, M^+ + H) calcd for $C_{13}H_{13}F_3N$ 240.1000, found 240.0997; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, *J* = 7.0 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.84 (s, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 2.90 (q, *J* = 7.0 Hz, 2H), 2.47 (s, 3H), 1.45 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.62, 142.95, 134.90, 131.07, 130.65, 127.57, 127.20 (q, *J* = 28.875 Hz), 126.44 (q, *J* = 5.5 Hz), 124.36 (q, *J* = 271.875 Hz), 124.05, 29.11, 18.98, 11.30.

*4.15. 2-Ethyl-3-methyl-6-(trifluoromethyl)quinoline (**3o**)*

Yield = 90% (215 mg); yellow gum; HRMS (ESI, M^+ + H) calcd for $C_{13}H_{13}F_3N$ 240.0995, found 240.0992; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (d, *J* = 9.0 Hz, 1H), 7.96 (s, 1H), 7.83 (s, 1H), 7.75 (dd, *J* = 1.5, 8.5 Hz, 1H), 2.98 (q, *J* = 7.5 Hz, 2H), 2.46 (s, 3H), 1.37 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.65, 147.53, 136.06, 130.93, 129.61, 127.36 (q, *J* = 32.25 Hz), 126.15, 124.58 (q, *J* = 4.25 Hz), 124.20 (q, *J* = 270.5 Hz), 123.85 (q, *J* = 2.625 Hz), 29.47, 19.00, 12.38. The NMR spectroscopic data of this compound are consistent with reported literature [86].

*4.16. 2-Ethyl-3-methylquinoline-8-carbonitrile (**3p**)*

Yield = 85% (167 mg); colorless solid; mp = 121–122 °C; HRMS (ESI, M^+ + H) calcd for $C_{13}H_{13}N_2$ 197.1073, found 197.1073; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.92 (d, *J* = 7.0 Hz, 1H), 7.87 (d, *J* = 7.0 Hz, 1H), 7.79 (s, 1H), 7.43 (t, *J* = 7.0 Hz, 1H), 2.96 (q, *J* = 7.0 Hz, 2H), 2.44 (s, 3H), 1.41 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.38, 145.62, 135.13, 133.94, 131.58, 126.91, 124.60, 117.58, 112.02, 29.03, 18.90, 11.52. Single-crystal X-ray diagram: crystal of *3p* was grown by slow diffusion of EtOAc into a solution of *3p* in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the monoclinic crystal system, space group C 2/c, *a* = 20.8096(12) Å, α = 90°; *b* = 8.4535(5) Å, β = 128.6800(10)°; *c* = 15.3108(16) Å, γ = 90°. *V* = 2102.6(3) Å^3, *Z* = 8, d_{calcd} = 1.240 Mg/m^3, *F*(000) = 832, 2θ range 2.687–28.345, *R* indices (all data) *R*1 = 0.0971, w*R*2 = 0.1285. CCDC number is 2016728.

*4.17. (2-Ethyl-3-methylquinolin-8-yl)(phenyl)methanone (**5a**)*

Yield = 88% (242 mg); colorless solid; mp = 129–130 °C; HRMS (ESI, M^+ + H) calcd for $C_{19}H_{18}NO$ 276.1383, found 276.1381; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.0 Hz, 1H), 7.83 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.74 (dd, *J* = 1.5, 7.5 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 2H), 2.71 (q, *J* = 7.5 Hz, 2H), 2.41 (s, 3H), 0.90 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.14, 162.68, 144.27, 139.13, 138.62, 134.63, 132.35, 130.21, 129.76 (2×), 128.89, 127.91 (2×), 127.55, 126.98, 125.05, 28.62, 19.01, 10.64. Single-crystal X-ray diagram: crystal of *5a* was grown by slow diffusion of EtOAc into a solution of *5a* in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the triclinic crystal system, space group P -1, *a* = 8.4108(3) Å, α = 103.454(2)°; *b* = 8.9126(3) Å, β = 97.603(2)°; *c* = 10.9019(3) Å, γ = 111.8150(10)°. *V* = 715.90(4) Å^3, *Z* = 2, d_{calcd} = 1.277 Mg/m^3, *F*(000) = 292, 2θ range 2.586–27.103, *R* indices (all data) *R*1 = 0.0607, w*R*2 = 0.1047. CCDC number is 2002378.

*4.18. (6-Chloro-2-ethyl-3-methylquinolin-8-yl)(phenyl)methanone (**5b**)*

Yield = 89% (275 mg); white solid; mp = 117–118 °C; HRMS (ESI, M^+ + H) calcd for $C_{19}H_{17}ClNO$ 310.0993, found 310.0993; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, *J* = 2.5 Hz, 1H), 7.74 (d, *J* = 7.0 Hz, 1H), 7.73 (s, 1H), 7.70 (s, 1H), 7.65 (d, *J* = 2.0 Hz, 1H), 7.51 (t, *J* = 7.0 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 2H), 2.68 (q, *J* = 7.5 Hz, 2H), 2.37 (s, 3H), 0.87 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.30, 162.98, 142.55, 140.17, 138.43, 133.63, 132.67, 131.30, 130.62, 129.66 (2×), 127.98 (2×), 127.87, 127.71, 127.23, 28.50, 18.93, 10.43. Single-crystal X-ray diagram: crystal of *5b* was grown by slow diffusion of EtOAc into a solution of *5b* in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the triclinic crystal system, space group P -1, *a* = 7.4420(3) Å, α = 103.4120(10)°; *b* = 10.3406(3) Å, β = 100.533(2)°; *c* = 10.7949(4) Å, γ = 90.7170(10)°. *V* = 793.14(5) Å^3, *Z* = 2, d_{calcd} = 1.297 Mg/m^3, *F*(000) = 324, 2*θ* range 2.028–33.138, *R* indices (all data) *R*1 = 0.0482, w*R*2 = 0.1123. CCDC number is 2013112.

*4.19. (6-Bromo-2-ethyl-3-methylquinolin-8-yl)(phenyl)methanone (**5c**)*

Yield = 91% (321 mg); yellow solid; mp = 141–142 °C; HRMS (ESI, M^+ + H) calcd for $C_{19}H_{17}BrNO$ 354.0488, found 354.0489; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, *J* = 2.0 Hz, 1H), 7.77 (d, *J* = 2.0 Hz, 1H), 7.75–7.71 (m, 3H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 2H), 2.68 (q, *J* = 7.5 Hz, 2H), 2.39 (s, 3H), 0.88 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.22, 163.18, 142.83, 140.32, 138.47, 133.55, 132.71, 131.32, 130.60, 130.39, 129.72 (2×), 128.25, 128.02 (2×), 118.58, 28.59, 18.99, 10.45.

*4.20. (2-Ethyl-3,6-dimethylquinolin-8-yl)(phenyl)methanone (**5d**)*

Yield = 86% (249 mg); yellow solid; mp = 132–133 °C; HRMS (ESI, M^+ + H) calcd for $C_{20}H_{20}NO$ 290.1539, found 290.1547; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.0 Hz, 2H), 7.72 (s, 1H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 2H), 2.68 (q, *J* = 7.5 Hz, 2H), 2.54 (s, 3H), 2.37 (s, 3H), 0.88 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.23, 161.61, 142.84, 139.12, 138.30, 134.75, 134.03, 132.25, 130.04, 129.71 (2×), 129.57, 127.87, 127.83 (2×), 127.01, 28.43, 21.39, 18.95, 10.62. Single-crystal X-ray diagram: crystal of *5d* was grown by slow diffusion of EtOAc into a solution of *5d* in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the monoclinic crystal system, space group P 21/c, *a* = 13.2934(5) Å, α = 90°; *b* = 14.2302(5) Å, β = 108.5200(10)°; *c* = 8.6189(3) Å, γ = 90°. *V* = 1545.98(10) Å^3, *Z* = 4, d_{calcd} = 1.243 Mg/m^3, *F*(000) = 616, 2*θ* range 2.158–27.098, *R* indices (all data) *R*1 = 0.0479, w*R*2 = 0.0968. CCDC number is 2039753.

*4.21. (2-Ethyl-6,7-dimethoxy-3-methylquinolin-8-yl)(phenyl)methanone (**5e**)*

Yield = 84% (282 mg); white solid; mp = 130–131 °C; HRMS (ESI, M^+ + H) calcd for $C_{21}H_{22}NO_3$ 336.1594, found 336.1596; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.59 (s, 1H), 7.49 (t, *J* = 7.0 Hz, 1H), 7.35 (t, *J* = 8.0 Hz, 2H), 4.05 (s, 3H), 4.01 (s, 3H), 2.65 (q, *J* = 7.5 Hz, 2H), 2.39 (s, 3H), 0.81 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.42, 160.70, 147.30, 143.70, 140.30, 139.45, 134.28, 132.18, 130.11, 129.74 (2×), 128.61, 127.80 (2×), 122.41, 116.58, 61.31, 56.79, 28.30, 19.19, 10.41.

*4.22. (2-Ethyl-3-methyl-6-phenylquinolin-8-yl)(phenyl)methanone (**5f**)*

Yield = 88% (309 mg); yellow solid; mp = 140–141 °C; HRMS (ESI, M^+ + H) calcd for $C_{25}H_{22}NO$ 352.1696, found 352.1694; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (d, *J* = 1.5 Hz, 1H), 8.00 (d, *J* = 2.0 Hz, 1H), 7.87 (s, 1H), 7.82 (d, *J* = 7.5 Hz, 2H), 7.74 (d, *J* = 7.5 Hz, 2H), 7.53–7.47 (m, 3H), 7.42–7.38 (m, 3H), 2.73 (q, *J* = 7.0 Hz, 2H), 2.42 (s, 3H), 0.93 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.94, 162.73, 143.67, 139.99, 139.03, 138.99, 137.82, 134.84, 132.45, 130.57, 129.81 (2×), 128.92 (2×), 127.94 (2×), 127.68, 127.31 (2×), 127.26, 127.10, 126.43, 28.62, 19.03, 10.69.

*4.23. (2-Ethyl-6-(4-methoxyphenyl)-3-methylquinolin-8-yl)(phenyl)methanone (**5g**)*

Yield = 83% (316 mg); yellow solid; mp = 96–97 °C; HRMS (ESI, M^+ + H) calcd for $C_{26}H_{24}NO_2$ 382.1802, found 382.1805; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (dd, *J* = 2.0, 6.0 Hz, 2H), 7.86–7.78 (m, 3H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.54–7.48 (m, 1H), 7.38 (t, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 3.86 (s, 3H), 2.72 (q, *J* = 7.5 Hz, 2H), 2.40 (s, 3H), 0.92 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.03, 162.36, 159.44, 143.38, 139.02, 138.82, 137.40, 134.70, 132.40, 130.47, 129.79 (2×), 128.33 (2×), 127.91 (2×), 127.30, 126.88, 125.62, 114.36 (2×), 55.31, 28.56, 19.00, 10.68.

*4.24. (2-Ethyl-6-(4-fluorophenyl)-3-methylquinolin-8-yl)(phenyl)methanone (**5h**)*

Yield = 87% (321 mg); yellow solid; mp = 146–147 °C; HRMS (ESI, M^+ + H) calcd for $C_{25}H_{21}FNO$ 370.1602, found 370.1602; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96 (d, *J* = 2.0 Hz, 1H), 7.93 (d, *J* = 2.0 Hz, 1H), 7.85 (s, 1H), 7.81 (s, 1H), 7.80 (s, 1H), 7.69–7.66 (m, 2H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.17 (t, *J* = 8.5 Hz, 2H), 2.72 (q, *J* = 7.0 Hz, 2H), 2.41 (s, 3H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.87, 162.82, 162.66 (d, *J* = 245.875 Hz), 143.58, 139.05 (d, *J* = 26.375 Hz), 136.85, 136.14 (d, *J* = 3.125 Hz), 134.76, 132.50, 130.71, 129.79 (2×), 128.92 (d, *J* = 8.125 Hz, 2×), 127.96 (2×), 127.24, 126.89, 126.27, 115.83 (d, *J* = 21.5 Hz, 2×), 28.62, 19.03, 10.65.

*4.25. (2-Ethyl-3-methylquinolin-8-yl)(4-fluorophenyl)methanone (**5i**)*

Yield = 89% (261 mg); yellow solid; mp = 124–125 °C; HRMS (ESI, M^+ + H) calcd for $C_{19}H_{17}FNO$ 294.1289, found 294.1288; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.86–7.81 (m, 2H), 7.80–7.75 (m, 2H), 7.71 (d, *J* = 7.0 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.03 (t, *J* = 8.5 Hz, 2H), 2.72 (q, *J* = 7.0 Hz, 2H), 2.40 (s, 3H), 0.92 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.52, 165.33 (d, *J* = 252.125 Hz), 162.73, 144.09, 138.23, 135.54 (d, *J* = 2.625 Hz), 134.66, 132.30 (d, *J* = 9.25 Hz, 2×, 130.29, 129.05, 127.57, 126.96, 125.08, 114.95 (d, *J* = 21.75 Hz, 2×), 28.58, 18.96, 10.63.

*4.26. (4-Chlorophenyl)(2-ethyl-3-methylquinolin-8-yl)methanone (**5j**)*

Yield = 90% (278 mg); White solid; mp = 127–128 °C; HRMS (ESI, M^+ + H) calcd for $C_{19}H_{17}ClNO$ 310.0993, found 310.0998; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.84 (d, *J* = 8.5 Hz, 1H), 7.82 (s, 1H), 7.72 (d, *J* = 7.0 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 8.5 Hz, 2H), 2.72 (q, *J* = 7.0 Hz, 2H), 2.40 (s, 3H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.90, 162.76, 144.10, 138.58, 137.98, 137.58, 134.66, 131.08 (2×), 130.33, 129.21, 128.18 (2×), 127.71, 126.96, 125.10, 28.59, 18.97, 10.59.

*4.27. (4-Bromophenyl)(2-ethyl-3-methylquinolin-8-yl)methanone (**5k**)*

Yield = 88% (311 mg); yellow solid; mp = 117–118 °C; HRMS (ESI, M^+ + H) calcd for $C_{19}H_{17}BrNO$ 354.0488, found 354.0496; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.5 Hz, 1H), 7.83 (s, 1H), 7.72 (dd, *J* = 1.0, 7.0 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.5 Hz, 2H), 2.72 (q, *J* = 7.0 Hz, 2H), 2.41 (s, 3H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.13, 162.80, 144.12, 138.02, 137.94, 134.67, 131.22 (2×), 131.18 (2×), 130.36, 129.25, 127.76, 127.33, 126.98, 125.12, 28.62, 19.00, 10.60.

*4.28. (2-Ethyl-3-methylquinolin-8-yl)(p-tolyl)methanone (**5l**)*

Yield = 85% (246 mg); yellow solid; mp = 104–105 °C; HRMS (ESI, M^+ + H) calcd for $C_{20}H_{20}BrNO$ 290.1539, found 290.1543; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.83 (s, 1H), 7.82 (d, *J* = 7.5 Hz, 1H), 7.68–7.65 (m, 3H), 7.51 (t, *J* = 7.0 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 2.74 (q, *J* = 7.0 Hz, 2H), 2.41 (s, 3H), 2.39 (s, 3H), 0.95 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.69, 162.72, 144.26, 143.16, 138.91, 136.46, 134.65, 130.15, 130.00 (2×), 128.64 (2×), 128.59, 127.23, 126.99, 124.98, 28.69, 21.65, 19.01, 10.83.

*4.29. (2-Ethyl-3-methylquinolin-8-yl)(4-methoxyphenyl)methanone (**5m**)*

Yield = 86% (262 mg); yellow solid; mp = 95–96 °C; HRMS (ESI, M^+ + H) calcd for $C_{20}H_{20}BrNO_2$ 306.1489, found 306.1485; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 7.0 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 2H), 3.84 (s, 3H), 2.75 (q, *J* = 7.5 Hz, 2H), 2.41 (s, 3H), 0.99 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.54, 163.13, 162.75, 144.19, 139.00, 134.68, 132.22 (2×), 131.97, 130.12, 128.45, 127.11, 126.98, 124.99, 113.15 (2×), 55.37, 28.69, 19.00, 10.96.

*4.30. (2-Ethyl-3-methylquinolin-8-yl)(2,3,4-trimethoxyphenyl)methanone (**5n**)*

Yield = 87% (318 mg); yellow gum; HRMS (ESI, M^+ + H) calcd for $C_{22}H_{24}NO_4$ 366.1700, found 366.1696; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (s, 1H), 7.78 (d, *J* = 7.5 Hz, 2H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 9.0 Hz, 1H), 6.68 (d, *J* = 9.0 Hz, 1H), 3.89 (s, 3H), 3.75 (s, 3H), 3.27 (s, 3H), 2.69 (q, *J* = 7.5 Hz, 2H), 2.37 (s, 3H), 0.90 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.01, 162.14, 156.84, 153.74, 144.06, 141.70, 140.50, 134.72, 129.84, 128.83, 128.79, 127.39, 126.73, 126.19, 125.07, 106.46, 60.98, 60.69, 56.04, 28.49, 18.95, 10.62.

*4.31. (6-Chloro-2-ethyl-3-methylquinolin-8-yl)(2-chlorophenyl)methanone (**5o**)*

Yield = 83% (285 mg); yellow solid; mp = 123–124 °C; HRMS (ESI, M^+ + H) calcd for $C_{19}H_{16}Cl_2NO$ 344.0604, found 344.0606; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.93 (d, *J* = 2.5 Hz, 1H), 7.83 (d, *J* = 2.0 Hz, 1H), 7.70 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.38–7.33 (m, 2H), 7.30–7.25 (m, 1H), 2.62 (q, *J* = 7.5 Hz, 2H), 2.36 (s, 3H), 0.77 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.28, 163.07, 142.55, 140.59, 139.30, 133.78, 132.05, 131.41, 131.25, 130.94, 130.49, 130.15, 130.05, 129.09, 127.82, 126.45, 28.61, 19.01, 10.24.

*4.32. (2-Ethyl-6-methoxy-3-methylquinolin-8-yl)(4-methoxyphenyl)methanone (**5p**)*

Yield = 85% (285 mg); yellow solid; mp = 176–177 °C; HRMS (ESI, M^+ + H) calcd for $C_{21}H_{22}NO_3$ 336.1594, found 336.1591; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.22 (s, 1H), 7.73 (d, *J* = 9.0 Hz, 2H), 7.67 (d, *J* = 8.0 Hz, 1H), 6.84 (d, *J* = 8.5 Hz, 3H), 4.03 (s, 3H), 3.84 (s, 3H), 2.72 (q, *J* = 7.0 Hz, 2H), 2.41 (s, 3H), 0.93 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.19, 162.83, 162.77, 156.42, 145.28, 132.75, 132.19 (2×), 131.40, 129.47, 129.08, 128.71, 118.83, 112.98 (2×), 102.91, 55.79, 55.36, 28.61, 19.09, 10.80.

*4.33. (2-Ethyl-6,7-dimethoxy-3-methylquinolin-8-yl)(p-tolyl)methanone (**5q**)*

Yield = 84% (293 mg); yellow solid; mp = 92–93 °C; HRMS (ESI, M^+ + H) calcd for $C_{22}H_{24}NO_3$ 350.1751, found 350.1749; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.09 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.53 (s, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 4.04 (s, 3H), 4.00 (s, 3H), 2.67 (q, *J* = 7.0 Hz, 2H), 2.40 (s, 3H), 2.38 (s, 3H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.95, 160.71, 147.24, 143.38, 142.99, 140.27, 136.69, 134.68, 130.06, 130.00 (2×), 128.60, 128.52 (2×), 122.41, 116.23, 61.29, 56.77, 28.36, 21.59, 19.18, 10.59.

*4.34. (3,4-Dimethoxyphenyl)(2-ethyl-6,7-dimethoxy-3-methylquinolin-8-yl)methanone (**5r**)*

Yield = 85% (336 mg); yellow solid; mp = 141–142 °C; HRMS (ESI, M^+ + H) calcd for $C_{23}H_{26}NO_5$ 396.1806, found 396.1805; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.59 (d, *J* = 1.5 Hz, 1H), 7.48 (s, 1H), 7.13 (dd, *J* = 1.5, 8.5 Hz, 1H), 6.72 (d, *J* = 8.5 Hz, 1H), 4.03 (s, 3H), 3.98 (s, 3H), 3.89 (s, 3H), 3.88 (s, 3H), 2.70 (q, *J* = 7.5 Hz, 2H), 2.40 (s, 3H), 0.94 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.81, 160.85, 152.85, 148.59, 147.16, 143.15, 140.27, 134.71, 132.12, 130.05, 128.64, 126.07, 122.43, 115.98, 111.14, 109.50, 61.28, 56.76, 55.95, 55.92, 28.42, 19.20, 10.98.

*4.35. (2-Ethyl-6,7-dimethoxy-3-methylquinolin-8-yl)(3,4,5-trimethoxyphenyl)methanone (**5s**)*

Yield = 84% (357 mg); yellow solid; mp = 121–122 °C; HRMS (ESI, M^+ + H) calcd for $C_{24}H_{28}NO_6$ 426.1911, found 426.1912; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.52 (s, 1H), 7.02 (s, 2H), 4.03 (s, 3H), 3.99 (s, 3H), 3.88 (s, 3H), 3.72 (s, 6H), 2.69 (q, *J* = 7.0 Hz, 2H), 2.39 (s, 3H), 0.92 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.95, 160.88, 152.54

(2×), 147.10, 143.52, 142.11, 140.24, 134.43, 134.02, 130.04, 128.69, 122.40, 116.43, 107.69 (2×), 61.25, 60.79, 56.74, 56.17 (2×), 28.31, 19.17, 10.86.

*4.36. 2-Butyl-3-propylquinoline (**6a**)*

Yield = 86% (195 mg); yellow gum; HRMS (ESI, M^+ + H) calcd for $C_{16}H_{22}N$ 228.1747, found 228.1741; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (d, *J* = 8.5 Hz, 1H), 7.83 (s, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 3.01–2.95 (m, 2H), 2.80–2.73 (m, 2H), 1.83–1.68 (m, 4H), 1.55–1.46 (m, 2H), 1.04 (t, *J* = 7.5 Hz, 3H), 0.99 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.23, 146.47, 134.77, 133.79, 128.41, 128.24, 127.15, 126.81, 125.44, 35.59, 34.36, 31.82, 23.53, 23.00, 14.02, 13.99. The NMR spectroscopic data of this compound are consistent with reported literature [60].

*4.37. 2-Isobutyl-3-isopropylquinoline (**6b**)*

Yield = 85% (193 mg); yellow gum; HRMS (ESI, M^+ + H) calcd for $C_{16}H_{22}N$ 228.1747, found 228.1746; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.5 Hz, 1H), 7.94 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.62–7.59 (m, 1H), 7.45–7.42 (m, 1H), 3.36–3.30 (m, 1H), 2.93 (d, *J* = 7.5 Hz, 2H), 2.31–2.25 (m, 1H), 1.33 (d, *J* = 7.0 Hz, 6H), 1.01 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.68, 146.12, 140.67, 131.44, 128.46, 128.25, 127.21, 126.96, 125.42, 44.05, 29.31, 28.73, 23.79 (2×), 22.57 (2×). The NMR spectroscopic data of this compound are consistent with reported literature [87].

*4.38. 3-Benzyl-2-phenethylquinoline (**6c**)*

Yield = 83% (268 mg); white solid; mp = 102–103 °C; HRMS (ESI, M^+ + H) calcd for $C_{24}H_{22}N$ 324.1747, found 324.1749; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, *J* = 8.5 Hz, 1H), 7.77 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.68 (t, *J* = 8.0 Hz, 1H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.34–7.15 (m, 8H), 7.12 (d, *J* = 7.5 Hz, 2H), 4.09 (s, 2H), 3.29–3.19 (m, 2H), 3.16–3.04 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.20, 146.85, 141.93, 139.26, 136.35, 132.43, 128.88 (2×), 128.78, 128.66 (2×), 128.53 (3×), 128.32 (2×), 127.12, 127.10, 126.48, 125.89, 125.86, 38.68, 37.69, 35.28. The NMR spectroscopic data of this compound are consistent with reported literature [85].

*4.39. 3-(2,2,2-Trifluoroethyl)-2-(3,3,3-trifluoropropyl)quinoline (**6d**)*

Yield = 89% (273 mg); white solid; mp = 92–93 °C; HRMS (ESI, M^+ + H) calcd for $C_{14}H_{12}F_6N$ 308.0869, found 308.0870; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (s, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.76–7.70 (m, 1H), 7.57–7.52 (m, 1H), 3.62 (q, *J* = 10.0 Hz, 2H), 3.30–3.22 (m, 2H), 2.94–281 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.16, 147.30, 138.82, 130.09, 128.82, 127.41 (q, *J* = 274.625 Hz), 127.31, 126.73, 126.65, 125.58 (q, *J* = 272.0 Hz), 121.97, 36.47 (q, *J* = 90 Hz), 31.87 (q, *J* = 28.75 Hz), 27.40.

*4.40. (2-Butyl-3-propylquinolin-8-yl)(phenyl)methanone (**6e**)*

Yield = 84% (278 mg); yellow solid; mp = 68–69 °C; HRMS (ESI, M^+ + H) calcd for $C_{23}H_{26}NO$ 332.2009, found 332.2005; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.83 (s, 1H), 7.79–7.74 (m, 2H), 7.71 (dd, *J* = 1.5, 7.0 Hz, 1H), 7.55–7.48 (m, 2H), 7.36 (t, *J* = 7.5 Hz, 2H), 2.71 (q, *J* = 7.0 Hz, 4H), 1.75–1.64 (m, 2H), 1.39–1.31 (m, 2H), 1.17–1.08 (m, 2H), 1.03 (t, *J* = 7.0 Hz, 3H), 0.72 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.18, 161.84, 144.12, 139.06, 138.58, 134.54, 133.84, 132.36, 129.73 (2×), 128.98, 127.93 (2×), 127.42, 126.83, 124.95, 34.46, 34.30, 29.33, 23.08, 22.34, 14.02, 13.94.

*4.41. (2-Isobutyl-3-isopropylquinolin-8-yl)(phenyl)methanone (**6f**)*

Yield = 86% (285 mg); yellow gum; HRMS (ESI, M^+ + H) calcd for $C_{23}H_{26}NO$ 332.2009, found 332.2003; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.87 (dd, *J* = 1.5, 8.5 Hz, 1H), 7.80–7.73 (m, 2H), 7.70 (dd, *J* = 1.5, 7.0 Hz, 1H), 7.54–7.47 (m, 2H), 7.36 (t, *J* = 8.0 Hz, 2H), 3.29–3.20 (m, 1H), 2.66 (d, *J* = 7.0 Hz, 2H), 1.91–1.83 (m, 1H), 1.31 (d, *J* = 6.5 Hz, 6H), 0.68 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.26, 160.62, 143.87, 141.17, 138.96, 138.67,

132.33, 130.74, 129.67 (2×), 129.03, 127.94 (2×), 127.22, 126.92, 124.90, 43.54, 28.56, 27.28, 23.50 (2×), 22.47 (2×).

*4.42. (3-Benzyl-2-phenethylquinolin-8-yl)(phenyl)methanone (**6g**)*

Yield = 85% (363 mg); yellow solid; mp = 137–138 °C; HRMS (ESI, M^+ + H) calcd for $C_{31}H_{26}NO$ 428.2009, found 428.2009; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.90–7.77 (m, 4H), 7.76 (s, 1H), 7.57 (t, *J* = 8.0 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 2H), 7.36–7.30 (m, 2H), 7.29–7.24 (m, 1H), 7.21–7.16 (m, 2H), 7.15–7.09 (m, 3H), 6.94 (d, *J* = 7.5 Hz, 2H), 4.04 (s, 2H), 3.01 (t, *J* = 8.0 Hz, 2H), 2.62 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.93, 160.78, 144.30, 142.26, 139.14, 138.71, 138.49, 135.32, 133.10, 132.49, 129.73 (2×), 129.30, 128.91 (2×), 128.64 (2×), 128.38 (2×), 128.09 (2×), 128.04 (3×), 126.82, 126.49, 125.54, 125.32, 38.44, 36.85, 32.88.

*4.43. Phenyl(3-(2,2,2-trifluoroethyl)-2-(3,3,3-trifluoropropyl)quinolin-8-yl)methanone (**6h**)*

Yield = 88% (362 mg); yellow gum; HRMS (ESI, M^+ + H) calcd for $C_{21}H_{16}F_6NO$ 412.1131, found 412.1123; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.96 (dd, *J* = 2.0, 8.5 Hz, 1H), 7.91 (dd, *J* = 2.0, 8.5 Hz, 1H), 7.75–7.69 (m, 2H), 7.68–7.63 (m, 1H), 7.56–7.52 (m, 1H), 7.40 (t, *J* = 8.0 Hz, 2H), 3.56 (q, *J* = 10.0 Hz, 2H), 3.03–2.97 (m, 2H), 2.11–1.99 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 198.32, 157.04, 144.56, 139.20, 138.53, 138.42, 132.69, 129.95, 129.79, 129.43 (2×), 128.18 (2×), 127.43 (q, *J* = 274.375 Hz), 126.36, 125.44 (q, *J* = 275.75 Hz), 122.65, 122.63, 36.21 (q, *J* = 30.25 Hz), 30.07 (q, *J* = 28.625 Hz), 27.17.

*4.44. 4-Phenyl-3-(2,2,2-trifluoroethyl)quinoline (**7**)*

Yield = 90% (258 mg); yellow gum; HRMS (ESI, M^+ + H) calcd for $C_{17}H_{13}F_3N$ 288.0995, found 288.0992; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.98 (s, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.74–7.68 (m, 1H), 7.57–7.49 (m, 3H), 7.47–7.37 (m, 2H), 7.27 (dd, *J* = 2.0, 8.0 Hz, 2H), 3.42 (q, *J* = 10.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.67, 149.24, 147.58, 135.35, 129.51 (d, *J* = 20.25 Hz), 129.37 (2×), 129.19, 128.76, 128.64 (2×), 128.47, 127.59, 126.82 (d, *J* = 35.5 Hz), 125.45 (q, *J* = 275.875 Hz), 120.97 (d, *J* = 2.125 Hz), 35.23 (q, *J* = 30.25 Hz).

5. Conclusions

In summary, an environmentally friendly and atom-economical synthetic route is reported for the preparation of functionalized 2,3-dialkylquinolines from substituted anilines and functionalized propionaldehydes using Nafion® NR50 as an acidic catalyst. The reaction worked well with various substituted anilines and propionaldehydes and provided the corresponding quinolines in good to excellent yields. A series of quinolinyl ketones were also synthesized, indicating that this reaction features good functional group tolerance. Moreover, the Nafion® NR50 particles could be repeatedly used and exhibit good efficiency, demonstrating their environmentally friendly properties. Four structures were confirmed by single-crystal X-ray crystallography. Further investigations of Nafion® NR50 particles are currently underway in our group.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/catal11080877/s1. Detailed experimental procedures and spectroscopic data for all compounds and X-ray analysis data for **3p**, **5a**, **5b** and **5d** (PDF).

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Data Availability Statement: All required data are presented in this file.

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