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Graphical Abstract

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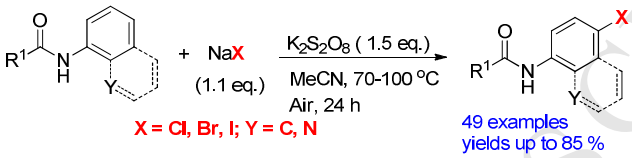
College of chemical and materials engineering, Wenzhou University, Wenzhou 325035, China

Author to whom correspondence should be addressed; E-Mail: kamenzxh@wzu.edu.cn



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College of chemical and materials engineering, Wenzhou University, Wenzhou 325035, China
Author to whom correspondence should be addressed; E-Mail: kamenzxh@wzu.edu.cn

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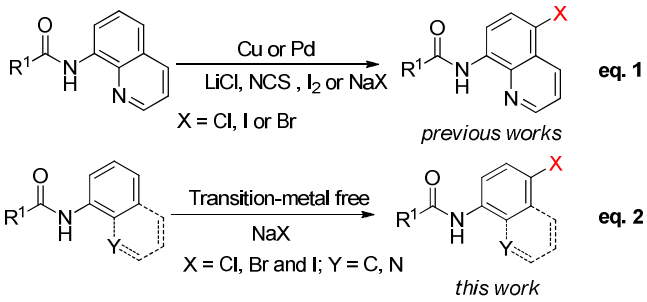
ABSTRACT

An efficient and mild halogenation of 8-acylaminoquinoline at the C5 position was described. The reaction utilized easily available sodium halides as the halogen sources and proceeded smoothly under transition metal-free conditions. Various 8-aminoquinolines with a number of functional groups were compatible in this reaction to afford the corresponding halogenated products in moderate to good yields. Moreover, the reaction conditions also tolerated the substrates without the 8-aminoquinolyl auxiliary, such as *N*-phenyl amide and *N*-naphthyl amide.

1. Introduction

Quinolines had been attracted increasing interest owing to their existence in many naturally occurring and bioactive molecules [1]. Among the various kinds of quinolines derivatives, the halogenated quinolines are one of the most significant scaffolds in a great number of biological and pharmacological natural products and marketed drugs [2]. Hence, the synthesis of halogenated quinolines has aroused much attention. Traditionally, the halogenation reaction can be achieved from the electrophilic aromatic substitution by the halogen or the other halogenation reagents [3], directed *ortho* metalation followed by halogen quenching [4] or the Sandmeyer reaction [5]. However, these methods suffered from the harsh reaction conditions, low yield, over-halogenation as well as the dangerous reaction procedures.

With the great development of transition-metal catalyzed C-H functionalization [6], metal-catalyzed the inert C-H bonds to C-X (X = halogen) has emerged as a powerful strategy for the synthesis of halogenated derivatives instead of the traditional halogenated methods [7]. For example, Stahl and co-workers firstly reported the copper-mediated chlorination of quinolines using 2 equiv LiCl as the chlorine source [8]. The copper and palladium mediated C-H chlorination on 8-acylaminoquinoline scaffolds utilizing *N*-chlorosuccinimide was also reported by Zhang's group [9]. Subsequently, Mu group studied the copper-catalyzed C-H iodination of quinolines with iodine [10]. Recently, Zhang group developed copper-catalyzed halogenation using sodium halides under mild conditions [11]. However, these reactions required copper/palladium as the metal catalyst or were limited to only chlorination/iodination reaction (Scheme 1, eq. 1). Recently, Li group developed a transition-metal-free oxidative halogenation of 8-aminoquinoline amides [12], the excellent work further urged us to seek for some direct and metal-free methods to synthesize halogenated quinolines. Herein, we wish to report the regioselective C5 halogenation of quinolines using sodium halides as the halogen sources. The reaction can proceed smoothly without using any transition metal catalyst, giving the halogenated quinolines in moderate to good yields (Scheme 1, eq. 2). In addition, the halogenation can successfully apply to the substrate amides without the 8-aminoquinolyl auxiliary.

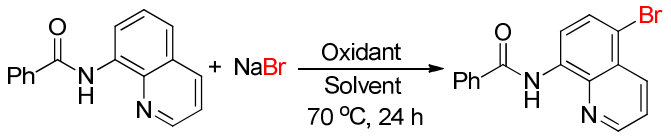


Scheme 1. Synthesis of the halogenated quinolines

We chose the model reaction between *N*-(quinolin-8-yl)benzamide **1a** and NaBr under air atmosphere to optimize the reaction conditions, and the results were listed in **Table 1**. To our delight, the desired brominated product **3ab** was obtained in 59 % yield in the presence of $K_2S_2O_8$ (1.0 equiv) and CH_3CN (2 mL) at 70 °C for 24 h (entry 1). However, when the $K_2S_2O_8$ amount was enhanced to 1.5-2.0 equiv, 85-86 % yield of **3ab** can be obtained (entries 2-3). During the screening of various oxidants, $PhI(OAc)_2$ and $Mn(OAc)_3 \cdot 3H_2O$ were found to provide lower yields while no reaction was observed when utilizing TBHP, O_2 or NMO (4-methylmorpholine *N*-oxide) as the oxidant (entries 4-8). Among the various solvents screened such as DCE, DMSO, dioxane and toluene, the initially employed solvent CH_3CN was found to be more effective (entries 9-12). It was found that the yield was decreased to 62 % when the reaction was carried out at 50 °C, while no obvious yield increasement

was observed at 100 °C (entries 13-14). Shorten the reaction time to 18 h, only 73 % yield of product **3ab** was obtained (entry 15). Thus the optimal condition was finally identified as follows: *N*-(quinolin-8-yl)benzamide **1a** (1.0 equiv), NaBr (1.1 equiv), $K_2S_2O_8$ (1.5 equiv), CH_3CN (2 mL), 70 °C under air atmosphere for 24 h.

Table 1. Screening Conditions [a]



1a **3ab**

Entry	Oxidant (equiv)	Solvent	Yield (%) [b] **3ab**
1	$K_2S_2O_8$ (1.0 eq)	MeCN	59
2	$K_2S_2O_8$ (1.5 eq)	MeCN	85
3	$K_2S_2O_8$ (2.0 eq)	MeCN	86
4	TBHP (1.5 eq)	MeCN	NR
5	$PhI(OAc)_2$ (1.5 eq)	MeCN	57
6	O_2	MeCN	NR
7	$Mn(OAc)_3 \cdot 3H_2O$ (1.5 eq)	MeCN	35
8	NMO (1.5 eq)	MeCN	NR
9	$K_2S_2O_8$ (1.5 eq)	DCE	75
10	$K_2S_2O_8$ (1.5 eq)	DMSO	32
11	$K_2S_2O_8$ (1.5 eq)	Dioxane	51
12	$K_2S_2O_8$ (1.5 eq)	Toluene	44
13 [c]	$K_2S_2O_8$ (1.5 eq)	MeCN	87
14 [d]	$K_2S_2O_8$ (1.5 eq)	MeCN	62
15 [e]	$K_2S_2O_8$ (1.5 eq)	MeCN	73

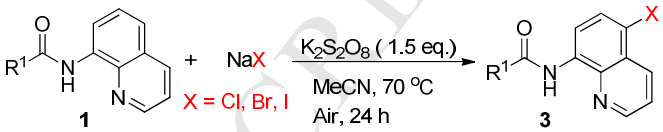
[a] Reaction conditions: **1a** (0.2 mmol), **NaBr** (0.22 mmol), oxidant in solvent (2 mL) under air atmosphere at 70 °C for 24 h; [b] Isolated yield; [c] at 100 °C; [d] at 50 °C; [e] for 12 h; NR = no reaction

With the optimum reaction conditions in hand, we next investigated the substrate scope of various amides with 8-aminoquinoline moiety, and the results were summarized in Table 2. The bromination showed good functional group tolerance. In general, the reactants with electron-donating substituents afforded the desired products in higher yields than those bearing electron-withdrawing moieties. For example, methyl substituted amides afforded their brominated products in 74-79 % yields except the lower yield of methoxyl derivative **3db**. Fluoride, bromide and trifluoromethyl substituted products **3eb**, **3ib** and **3jb** were isolated in 60 %, 75 % and 58 % yields, respectively. While *o*, *m*, *p*-chloro benzamides gave the corresponding products **3fb**, **3gb** and **3hb** in 65-77 % yields. Moreover, the diphenyl and 2-naphthamide equivalents were also compatible with the reaction conditions, affording products **3kb** and **3lb** in 58 % and 70 % yields, respectively. Gratifyingly, alkyl amides such as propionamide, cyclohexanecarboxamide and 2-phenylacetamides underwent the bromination successfully to give products **3mb-3ob** in 56-74 % yields. Unfortunately, the furan-2-carboxamide afforded the brominated product **3pb** only in 24 % yield.

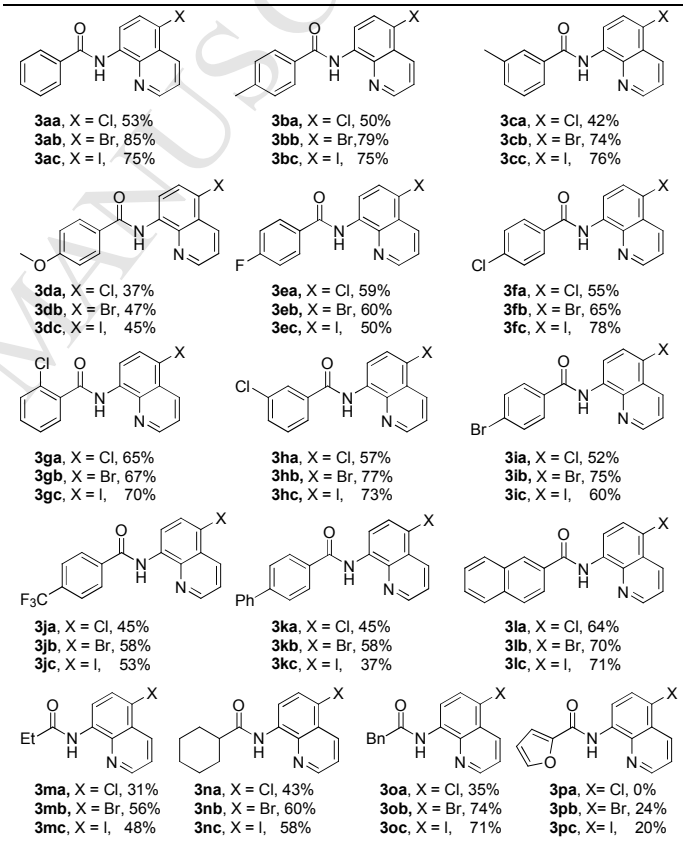
In the further study, we found that chlorination and iodination could also be realized successfully as well as bromination under the optimum reaction conditions. The structure of chlorinated product **3aa** was confirmed by X-ray crystallography, which demonstrated that the halogenation proceed at the C5 position of quinolines (Figure 1). Among the three halogenation reactions, the activity of bromination was the best, followed by iodination, and then chlorination. Accordingly, we investigated the scope and limitation of the chlorination and iodination (Table 2).

Similar to bromination, both the iodination and chlorination showed good functional group tolerance. *N*-(quinolin-8-yl) aryl amides bearing various groups such as methyl, methoxyl, halogen, trifluoromethyl, phenyl and naphthyl underwent the reactions smoothly, providing the corresponding halogenated products in moderate and good yields. In addition, *N*-(quinolin-8-yl) alkyl amides, such as *N*-(quinolin-8-yl)propionamide, *N*-(quinolin-8-yl)cyclohexanecarboxamide were also tolerated, giving **3ma, 3na, 3mc** and **3nc** in acceptable yields. However, the low activity of furan-2-carboxamide resulted in its intact in the chlorination and 20 % yield of the iodinated product **3pc**.

Table 2. The C5 halogenation of quinolines [a,b]



1 **3**



[a] Reaction conditions: **1** (0.2 mmol), **NaX** (0.22 mmol), $K_2S_2O_8$ (1.5 equiv) in CH_3CN (2 mL) under air atmosphere at 70 °C for 24 h; [b] Isolated yield.

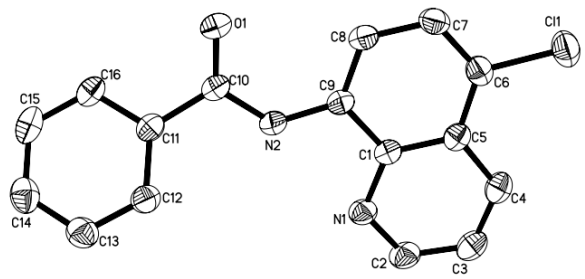
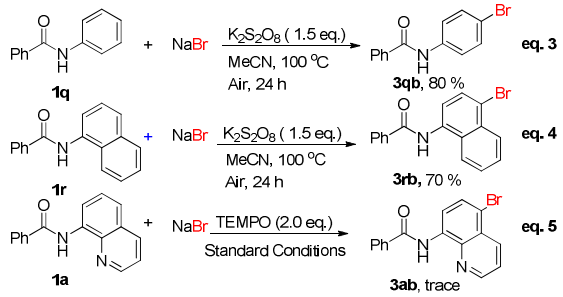


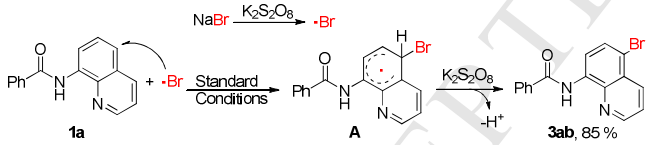
Figure 1. X-ray Structure of Compound **3aa**, Ellipsoids are represented at 30% probability

To further understand this transformation, the reactions of *N*-phenylbenzamide **1q** and *N*-naphthylbenzamide **1r** with NaBr were carried out under the reaction conditions (Scheme 2, eq. 3 and 4). It was glad to find that when the reaction temperature was increased to 100 °C, the brominated products **3qb** and **3rb** were obtained in 80 % and 70 % yields, respectively. Different from the previous reports [11], these results suggested that the reactions were not promoted by any potential trace amount of copper salt in the reaction mixture. Moreover, the bromination of substrate **1a** and NaBr was conducted in the presence of 2.0 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a radical scavenger, but the reaction was completely restrained and most of substrate **1a** was recovered (Scheme 2, eq.5). All of the above results disclosed that this halogenation of quinolines might be involved in a straight-forward radical process.



Scheme 2. Control Experiment

On the basis of the obtained experimental results, a plausible mechanism is proposed for this reaction (Scheme 3). The bromide radical was firstly produced in the presence of $K_2S_2O_8$ and NaBr. Then the radical selectively attacked substrate **1a** at the C5 position to give cyclo radical **A**. Single electron transfer and deprotonation of cyclo radical **A** in the presence of $K_2S_2O_8$ gave the desired product **3ab**.



Scheme 3. Possible Mechanism

3. Conclusions

In conclusion, we have developed an efficient and mild halogenation of 8-acylaminoquinoline at the C5 position. The reaction utilized easily available sodium halides as the halogen sources and proceeded smoothly under transition metal-free conditions, affording the corresponding halogenated products in moderate to good yields. Notably, the halogenation was also successfully applied to the substrate amides without the 8-aminoquinolyl auxiliary. Further study showed that the reaction might involve a single electron transfer mechanism.

4. Experimental Section

4.1 General

Chemicals were either purchased or purified by standard techniques. ^{1}H NMR and ^{13}C NMR spectra were measured on a 500 MHz spectrometer (^{1}H at 500 MHz, ^{13}C at 125 MHz), using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in δ relative to TMS, and the coupling constants *J* are given in hertz. High-resolution mass spectra were recorded on an ESI-Q-TOF mass spectrometer. Melting point data are uncorrected. Column chromatography was performed using EM silica gel 60 (300-400 mesh).

4.2 General Procedure for the Synthesis of 3-sulfenylflavones derivative 3-26

The quinolines **1a** (0.2 mmol), sodium halides (0.22 mmol) and $K_2S_2O_8$ (1.5 equiv) were added to an oven-dried tube, and then CH_3CN (2.0 mL) was added. Then the reaction mixture was stirred at 70 °C for 24 h under air atmosphere. After the reaction was finished, the mixture was concentrated in vacuum, and the resulting crude product was purified by flash chromatography on silica gel using hexane or hexane/ethyl acetate (20:1) as the eluent to give the pure products.

4.3. Characterization data

4.3.1 N-(5-chloroquinolin-8-yl)benzamide (**3aa**) [7e]. White solid, m.p. 130-131 °C, 53% yield (30.0 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.67 (s, 1H), 8.89-8.87 (m, 2H), 8.58 (d, *J* = 8.5 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.61-7.54 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 148.9, 139.5, 135.0, 134.0, 133.6, 132.1, 129.0, 127.5, 127.4, 126.2, 124.6, 122.5, 116.6.

4.3.2 *N-(5-chloroquinolin-8-yl)-4-methylbenzamide* (**3ba**) [11]. White solid, m.p. 131-132 °C, 50% yield (29.7 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.61 (s, 1H), 8.86-8.84 (m, 2H), 8.54 (d, *J* = 8.5 Hz, 1H), 7.95 (d, *J* = 7.5 Hz, 2H), 7.61 (d, *J* = 8.5 Hz , 1H), 7.55 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.33 (d, *J* = 7.5 Hz, 2H), 2.44 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.4, 148.8, 142.6, 139.4, 134.1, 133.5, 132.2, 129.6, 127.42, 127.41, 126.1, 124.4, 122.4, 116.5, 21.6.

4.3.3 N-(5-chloroquinolin-8-yl)-3-methylbenzamide (**3ca**) [11]. White solid, m.p. 85-86 °C, 42% yield (24.9 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.62 (s, 1H), 8.87-8.86 (m, 2H), 8.56 (d, *J* = 8.5, Hz, 1H), 7.86-7.83 (m, 2H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.56 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.44-7.38 (m, 2H), 2.48 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 148.8, 139.4, 138.8, 135.0, 134.1, 133.5, 132.9, 128.8, 128.2, 127.4, 126.1, 124.5, 124.3, 122.5, 116.6, 21.6.

4.3.4 N-(5-chloroquinolin-8-yl)-4-methoxybenzamide (**3da**) [7e]. White solid, m.p. 184-185 °C, 37% yield (23.1 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.61 (s, 1H), 8.89 (dd, *J* = 4.5, 1.5 Hz, 1H), 8.86 (d, *J* = 8.0 Hz, 1H), 8.58 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.04 (d, *J* = 9.0 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.59 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.04 (d, *J* = 9.0 Hz, 2H), 3.90 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 162.9, 148.8, 139.5, 134.3, 133.6, 129.3, 127.5, 127.4, 126.2, 124.3, 122.5, 116.5, 114.2, 55.6.

4.3.5 N-(5-chloroquinolin-8-yl)-4-fluorobenzamide (**3ea**) [7e]. White solid, m.p. 146-147 °C, 59% yield (35.5 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.61 (s, 1H), 8.88 (d, *J* = 2.5 Hz, 1H), 8.84 (d, *J* = 8.0 Hz, 1H), 8.58 (d, *J* = 8.5 Hz, 1H), 8.07 (t, *J* = 6.5 Hz, 2H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.59 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.22 (t, *J* = 8.0 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3 (d, J_{CF} = 251.3 Hz), 164.4, 148.9, 139.5, 133.9, 133.7, 131.3 (d, J_{CF} = 2.5 Hz), 129.8 (d, J_{CF} = 8.8 Hz), 127.5, 126.2, 124.8, 122.6, 116.7, 116.1 (d, J_{CF} = 22.5 Hz).

4.3.6 4-chloro-N-(5-chloroquinolin-8-yl)benzamide (**3fa**) [7e]. White solid, m.p. 158-159 °C, 55% yield (34.9 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.62 (s, 1H), 8.87 (dd, *J* = 4.0, 1.5 Hz,

1H), 8.82 (d, *J* = 8.5 Hz, 1H), 8.57 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.99-7.98 (m, 2H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.58 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.52-7.50 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 148.9, 139.4, 138.5, 133.8, 133.7, 133.4, 129.2, 128.8, 127.4, 126.2, 124.9, 122.6, 116.7.

4.3.7 2-chloro-N-(5-chloroquinolin-8-yl)benzamide (**3ga**). White solid, m.p. 151-152 °C, 65% yield (41.2 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.48 (s, 1H), 8.90 (d, *J* = 8.5 Hz, 1H), 8.83 (d, *J* = 3.0 Hz, 1H), 8.58 (d, *J* = 8.5 Hz, 1H), 7.82 (d, *J* = 7.0 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.57 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.51-7.50 (m, 1H), 7.46-7.39 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 149.0, 139.4, 135.7, 133.9, 133.5, 131.8, 131.3, 130.7, 130.4, 127.4, 127.3, 126.2, 125.1, 122.5, 117.0. HRMS (ESI): calcd for $C_{16}H_{10}NaCl_2N_2O^+$ ([M + Na]$^+$) 339.0062, Found: 339.0062.

4.3.8 3-chloro-N-(5-chloroquinolin-8-yl)benzamide (**3ha**) [7e]. White solid, m.p. 130-131 °C, 57% yield (36.2 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.63 (s, 1H), 8.90 (dd, *J* = 4.0, 1.5 Hz, 1H), 8.84 (d, *J* = 8.5, Hz, 1H), 8.60 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.04 (t, *J* = 1.5 Hz, 1H), 7.94-7.92 (m, 1H), 7.65 (d, *J* = 8.5Hz, 1H), 7.61 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.57-7.55 (m, 1H), 7.50-7.47 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.1, 149.0, 139.3, 136.8, 135.3, 133.8, 133.7, 132.2, 130.3, 127.9, 127.5, 126.2, 125.4, 125.1, 122.6, 116.9.

4.3.9 4-bromo-N-(5-chloroquinolin-8-yl)benzamide **(3ia)**. Yellow solid, m.p. 164-165 °C, 52% yield (37.6 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.62 (s, 1H), 8.87 (dd, *J* = 4.5, 1.5 Hz, 1H), 8.82 (d, *J* = 8.5 Hz, 1H), 8.57 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.92-7.90 (m, 2H), 7.68-7.66 (m, 2H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.58 (dd, *J* = 8.5, 4.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5, 148.9, 139.4, 133.9, 133.73, 133.65, 132.2, 129.0, 127.4, 126.9, 126.2, 124.9, 122.6, 116.7.

4.3.10 N-(5-chloroquinolin-8-yl)-4-(trifluoromethyl)benzamide (**3ja**)**.** White solid, m.p. 139-140 °C, 45% yield (31.6 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.67 (s, 1H), 8.87-8.86 (m,1H), 8.82 (dd, *J* = 8.5, 2.5 Hz, 1H), 8.57-8.55 (m, 1H), 8.14 (d, *J* = 7.5 Hz, 2H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.62 (dd, *J* = 8.5, 3.0 Hz, 1H), 7.60-7.57 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 149.0, 139.3, 138.2, 133.9, 133.7, 133.5, 127.9, 127.4, 126.2, 126.0 (q, J_{CF} = 3.8 Hz), 125.2, 123.8 (q, J_{CF} = 271.3 Hz), 122.6, 116.8. HRMS (ESI): calcd for $C_{17}H_{11}ClF_3N_2O^+$ ([M + H]$^+$) 351.0507, Found: 351.0510.

4.3.11 N-(5-chloroquinolin-8-yl)-[1,1'-biphenyl]-4-carboxamide (**3ka**). White solid, m.p. 173-174 °C, 45% yield (32.3 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.72 (s, 1H), 8.91-8.89 (m, 2H), 8.59 (d, *J* = 8.5 Hz, 1H), 8.14 (d, *J* = 7.5 Hz, 2H), 7.77 (d, *J* = 7.5 Hz, 2H), 7.66 (d, *J* = 7.5 Hz, 3H), 7.59 (dd, *J* = 8.5, 4.5 Hz, 1H), 7.51-7.48 (m, 2H), 7.43-7.40 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 148.9, 145.0, 140.2, 139.5, 134.1, 133.7, 133.6, 129.1, 128.3, 128.0, 127.6, 127.5, 127.4, 126.2, 124.6, 122.5, 116.7. HRMS (ESI): calcd for $C_{22}H_{16}ClN_2O^+$ ([M + H]$^+$) 359.0946, Found: 359.0932.

4.3.12 N-(5-chloroquinolin-8-yl)-2-naphthamide (**3la**). White solid, m.p. 164-165 °C, 64% yield (42.6 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.80 (s, 1H), 8.93-8.91 (m, 2H), 8.59-8.57 (m, 2H), 8.10 (d, *J* = 8.5 Hz, 1H), 8.03 (d, *J* = 7.5 Hz, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.62-7.56 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 148.9, 139.5, 135.2, 134.1, 133.6, 132.9, 132.3, 129.3, 128.9, 128.14, 128.07, 127.9, 127.5, 127.0, 126.2, 124.6, 123.8, 122.5, 116.7. HRMS (ESI): calcd for $C_{20}H_{14}ClN_2O^+$ ([M + H]$^+$) 333.0789, Found: 333.0788.

4.3.13 N-(5-chloroquinolin-8-yl)propionamide (**3ma**) [14]. Yellow solid, m.p. 75-76 °C, 31% yield (14.6 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (s, 1H), 8.81 (d, *J* = 4.0 Hz, 1H), 8.70 (d, *J* = 8.5 Hz, 1H), 8.53 (d, *J* = 8.5 Hz, 1H), 7.57-7.52 (m, 2H), 2.59 (q, *J* = 7.5 Hz, 2H), 1.33 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 148.6, 139.0, 134.0, 133.5, 127.4, 126.0, 124.2, 122.4, 116.5, 31.3, 9.8.

4.3.14 N-(5-chloroquinolin-8-yl)cyclohexanecarboxamide (**3na**) [11]. Yellow solid, m.p. 63-64 °C, 43% yield (24.8 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.84 (s, 1H), 8.85 (dd, *J* = 4.5, 1.5 Hz, 1H), 8.74 (d, *J* = 8.5 Hz, 1H), 8.56 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.59-7.55 (m, 2H), 2.50-2.44 (m, 1H), 2.09-2.06 (m, 2H), 1.90-1.86 (m, 2H), 1.75-1.72 (m, 1H), 1.67-1.59 (m, 2H), 1.43-1.25 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 148.7, 139.2, 134.1, 133.6, 127.5, 126.1, 124.1, 122.4, 116.6, 47.0, 29.9, 25.9, 25.9.

4.3.15 N-(5-chloroquinolin-8-yl)-2-phenylacetamide (**3oa**). Yellow solid, m.p. 107-108 °C, 35% yield (20.8 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.86 (s, 1H), 8.71-8.69 (m, 2H), 8.53-8.51 (m, 1H), 7.58-7.56 (m, 1H), 7.52-7.50 (m, 1H), 7.44-7.40 (m, 4H), 7.35-7.33 (m, 1H), 3.89 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 148.7, 139.1, 134.7, 133.8, 133.5, 129.7, 129.2, 127.6, 127.4, 126.0, 124.5, 122.3, 116.6, 45.5. HRMS (ESI): calcd for $C_{17}H_{14}ClN_2O^+$ ([M + H]$^+$) 297.0789, Found: 297.0790.

4.3.16 N-(5-bromoquinolin-8-yl)benzamide (**3ab**) [7e]. White solid, m.p. 124-125 °C, 85% yield (56.3 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.71 (s, 1H), 8.87 (dd, *J* = 4.0, 1.5 Hz, 1H), 8.83 (d, *J* = 8.5 Hz, 1H), 8.55 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.08-8.06 (m, 2H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.61-7.54 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 148.9, 139.6, 136.2, 135.1, 134.7, 132.2, 131.2, 129.0, 127.5, 122.9, 117.3, 114.6.

4.3.17 N-(5-bromoquinolin-8-yl)-4-methylbenzamide (**3bb**) [11]. White solid, m.p. 120-121 °C, 79% yield (53.9 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.65 (s, 1H), 8.84 (d, *J* = 3.0 Hz, 1H), 8.81 (d, *J* = 8.5 Hz, 1H), 8.51 (d, *J* = 8.5 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.55 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 2H), 2.45 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 148.8, 142.7, 139.6, 136.1, 134.8, 132.2, 131.1, 129.6, 127.43, 127.37, 122.8, 117.1, 114.3, 21.7.

4.3.18 N-(5-bromoquinolin-8-yl)-3-methylbenzamide (**3cb**) [11]. White solid, m.p. 92-93 °C, 74% yield (50.5 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.62 (s, 1H), 8.84-8.80 (m, 2H), 8.51 (d, *J* = 8.5 Hz, 1H), 7.86-7.81 (m, 3H), 7.54 (dd, *J* = 8.5, 4.5 Hz, 1H), 7.43-7.37 (m, 2H), 2.47 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 148.8, 139.6, 138.8, 136.1, 135.0, 134.7, 132.9, 131.1, 128.8, 128.2, 127.4, 124.3, 122.8, 117.2, 114.4, 21.6.

4.3.19 N-(5-bromoquinolin-8-yl)-4-methoxybenzamide (**3db**) [7e]. White solid, m.p. 191-192 °C, 47% yield (33.6 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.62 (s, 1H), 8.85 (dd, *J* = 4.0, 1.5 Hz, 1H), 8.80 (d, *J* = 8.5 Hz, 1H), 8.53 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.04-8.02 (m, 2H), 7.83 (d, J = 8.0 Hz, 1H) 7.57 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.04-7.02 (m, 2H), 3.89 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 162.8, 148.8, 139.6, 136.2, 134.9, 131.2, 129.3, 127.4, 127.3, 122.8, 117.0, 114.2, 55.6.

4.3.20 N-(5-bromoquinolin-8-yl)-4-fluorobenzamide (**3eb**) [7e]. White solid, m.p. 170-171 °C, 60% yield (41.4 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.62 (s, 1H), 8.84 (dd, *J* = 4.5, 1.5 Hz, 1H), 8.78 (d, *J* = 8.5 Hz, 1H), 8.53 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.08-8.05 (m, 2H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.57 (dd, *J* = 8.5, 4.0

Hz, 1H), 7.22 (t, *J* = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2 (d, J_{CF} = 251.3 Hz), 164.4, 148.9, 139.5, 136.2, 134.5, 131.2 (d, J_{CF} = 3.8 Hz), 131.1, 129.8 (d, J_{CF} = 10.0 Hz), 127.4, 122.9, 117.2, 116.0 (d, J_{CF} = 22.5 Hz), 114.7.

4.3.21 N-(5-bromoquinolin-8-yl)-4-chlorobenzamide (**3fb**). Yellow solid, m.p. 156-157 °C, 65% yield (47.0 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.58 (s, 1H), 8.80-8.79 (m, 1H), 8.72 (d, *J* = 8.5 Hz, 1H), 8.46 (d, *J* = 8.5 Hz, 1H), 7.95 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.53 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.47 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2, 148.9, 139.4, 138.4, 136.1, 134.3, 133.2, 131.0, 129.2, 128.7, 127.3, 122.8, 117.1, 114.7.

4.3.22 N-(5-bromoquinolin-8-yl)-2-chlorobenzamide (**3gb**) [7e]. Yellow solid, m.p. 166-167 °C, 67% yield (48.5 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.49 (s, 1H), 8.83 (d, *J* = 8.0 Hz, 1H), 8.79 (dd, *J* = 4.5, 1.5 Hz, 1H), 8.51 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.85-7.81 (m, 2H), 7.55 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.50-7.48 (m, 1H), 7.45-7.38 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 149.0, 139.5, 136.1, 135.6, 134.5, 131.8, 131.3, 131.0, 130.7, 130.3, 127.4, 127.3, 122.9, 117.5, 115.0.

4.3.23 N-(5-bromoquinolin-8-yl)-3-chlorobenzamide (**3hb**) [7e]. Yellow solid, m.p. 132-133 °C, 77% yield (55.7 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.60 (s, 1H), 8.84 (d, *J* = 4.0 Hz, 1H), 8.74 (d, *J* = 8.5 Hz, 1H), 8.50 (d, *J* = 8.5 Hz, 1H), 8.01 (s, 1H), 7.89 (d, *J* = 7.5 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.57-7.53 (m, 2H), 7.46 (t, *J* = 7.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 149.0, 139.5, 136.7, 136.1, 135.2, 134.3, 132.1, 131.0, 130.2, 127.8, 127.4, 125.3, 122.9, 117.3, 114.9.

4.3.24 4-bromo-N-(5-bromoquinolin-8-yl)benzamide (**3ib**). Yellow solid, m.p. 160-161 °C, 75% yield (60.9 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.67 (s, 1H), 8.873-8.866 (m, 1H), 8.80 (d, *J* = 8.5 Hz, 1H), 8.56 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 2H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.60 (dd, *J* = 8.5, 4.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 149.0, 148.4, 144.8, 139.5, 136.1, 134.3, 131.1, 127.4, 122.9, 117.3, 115.5, 114.7, 112.7.

4.3.25 N-(5-bromoquinolin-8-yl)-4-(trifluoromethyl)benzamide (**3jb**). White solid, m.p. 129-130 °C, 58% yield (45.8 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.67 (s, 1H), 8.82 (d, *J* = 2.5 Hz, 1H), 8.74 (d, *J* = 8.5 Hz, 1H), 8.49 (d, *J* = 8.5 Hz, 1H), 8.13 (d, *J* = 8.0 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 3H), 7.55 (dd, *J* = 8.5, 4.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 149.0, 139.4, 138.2, 136.2, 134.1, 133.8 (q, J_{CF} = 32.5 Hz), 131.0, 127.8, 127.4, 126.0 (q, J_{CF} = 3.8 Hz), 123.8 (q, J_{CF} = 271.2 Hz), 122.9, 117.3, 115.1. HRMS (ESI): calcd for $C_{17}H_{11}BrF_3N_2O^+$ ([M + H]$^+$) 395.0001, Found: 394.9996.

4.3.26 N-(5-bromoquinolin-8-yl)-[1,1'-biphenyl]-4-carboxamide (**3kb**). Yellow solid, m.p. 185-186 °C, 58% yield (46.8 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.75 (s, 1H), 8.88 (dd, *J* = 4.0, 1.5 Hz, 1H), 8.85 (d, *J* = 8.5 Hz, 1H), 8.55 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.14 (d, *J* = 8.5 Hz, 2H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.67-7.65 (m, 2H), 7.59 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 2H), 7.43-7.40 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 148.9, 145.0, 140.1, 139.6, 136.2, 134.7, 133.6, 131.2, 129.1, 128.3, 128.0, 127.6, 127.44, 127.38, 122.9, 117.3, 114.6. HRMS (ESI): calcd for $C_{22}H_{16}BrN_2O^+$ ([M + H]$^+$) 403.0441, Found: 403.0428.

4.3.27 N-(5-bromoquinolin-8-yl)-2-naphthamide (**3lb**). White solid, m.p. 175-176 °C, 70% yield (52.8 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.83 (s, 1H), 8.88-8.86 (m, 2H), 8.57-8.53 (m, 2H), 8.10 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 7.0 Hz, 1H), 7.97 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.59-7.57 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 148.9, 139.6, 136.2, 135.1, 134.7, 132.9, 132.2, 131.1, 129.3, 128.9, 128.2, 128.1, 127.9, 127.4, 127.0, 123.7, 122.8, 117.3, 114.6. HRMS (ESI): calcd for $C_{20}H_{14}BrN_2O^+$ ([M + H]$^+$) 377.0284, Found: 377.0288.

4.3.28 N-(5-bromoquinolin-8-yl)propionamide (**3mb**) [13]. Yellow solid, m.p. 104-105 °C, 56% yield (31.3 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.78 (d, *J* = 3.5 Hz, 1H), 8.65 (d, *J* = 8.5 Hz, 1H), 8.47 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.52 (dd, *J* = 8.5, 4.5 Hz, 1H), 2.58 (q, *J* = 7.5 Hz, 2H), 1.32 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.5, 148.7, 139.2, 136.0, 134.6, 131.0, 127.3, 122.7, 117.0, 114.0, 31.4, 9.8.

4.3.29 N-(5-bromoquinolin-8-yl)cyclohexanecarboxamide (**3nb**) [11]. Yellow solid, m.p. 109-110 °C, 60% yield (40.0 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.85 (s, 1H), 8.81-8.80 (m, 1H), 8.68 (d, *J* = 8.5 Hz, 1H), 8.50 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.54 (dd, *J* = 8.5, 4.0 Hz, 1H), 2.50-2.43 (m, 1H), 2.07 (d, *J* = 13.5 Hz, 2H), 1.89-1.86 (m, 2H), 1.73 (d, *J* = 12.5 Hz, 1H), 1.66-1.58 (m, 2H), 1.43-1.33 (m, 2H), 1.31-1.25 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 148.7, 139.3, 136.1, 134.7, 131.1, 127.3, 122.7, 117.1, 114.0, 47.0, 29.8, 25.90, 25.86.

4.3.30 N-(5-bromoquinolin-8-yl)-2-phenylacetamide (**3ob**) [12]. Yellow solid, m.p. 116-117 °C, 74% yield (50.5 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.85 (s, 1H), 8.67 (d, *J* = 4.0 Hz, 1H), 8.64 (d, *J* = 8.0 Hz, 1H), 8.43 (d, *J* = 8.5 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.48-7.40 (m, 5H), 7.36-7.33 (m, 1H), 3.88 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 148.7, 139.2, 135.9, 134.6, 134.4, 130.9, 129.7, 129.1, 127.5, 127.2, 122.6, 116.9, 114.4, 45.5.

4.3.31 N-(5-bromoquinolin-8-yl)furan-2-carboxamide (**3pb**) [11]. Yellow solid, m.p. 189-190 °C, 24% yield (15.2 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.72 (s, 1H), 8.89-8.88 (m, 1H), 8.75 (d, *J* = 8.5 Hz, 1H), 8.53-8.51 (m, 1H), 7.81 (d, *J* = 8.5 Hz, 1H), 7.62 (s, 1H), 7.57 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.30 (d, *J* = 3.0 Hz, 1H), 6.590-6.587 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 149.0, 148.4, 144.8, 139.5, 136.1, 134.3, 131.1, 127.4, 122.9, 117.3, 115.5, 114.7, 112.7.

4.3.32 N-(5-iodoquinolin-8-yl)benzamide (**3ac**) [7e]. White solid, m.p. 153-154 °C, 75% yield (56.1 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.68 (s, 1H), 8.76 (d, *J* = 4.0 Hz, 1H), 8.66 (d, *J* = 8.5 Hz, 1H), 8.32 (d, *J* = 8.5 Hz, 1H), 8.08-8.04 (m, 3H), 7.59-7.48 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 148.9, 140.9, 139.4, 138.4, 135.6, 135.0, 132.1, 129.8, 129.0, 127.4, 123.3, 118.0, 89.6.

4.3.33 N-(5-iodoquinolin-8-yl)-4-methylbenzamide (**3bc**) [11]. White solid, m.p. 175-176 °C, 75% yield (58.2 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.68 (s, 1H), 8.79 (d, *J* = 4.0 Hz, 1H), 8.69 (d, *J* = 8.5 Hz, 1H), 8.35 (d, *J* = 8.5 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 2H), 7.52 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.33 (d, *J* = 7.5 Hz, 2H), 2.44 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 148.9, 142.7, 140.9, 139.5, 138.5, 135.8, 132.2, 129.8, 129.6, 127.4, 123.3, 118.0, 89.4, 21.7.

4.3.34 N-(5-iodoquinolin-8-yl)-3-methylbenzamide (**3cc**) [11]. White solid, m.p. 115-116 °C, 76% yield (59.0 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.63 (s, 1H), 8.77-8.76 (m, 1H), 8.66 (d, *J* = 8.5 Hz, 1H), 8.31 (d, *J* = 8.5 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.85-7.82 (m, 2H), 7.49 (dd, *J* = 8.5, 4.5 Hz, 1H), 7.42-7.36 (m, 2H), 2.47 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 148.9, 140.7, 139.4, 138.8, 138.4, 135.7, 135.0, 132.8, 129.7, 128.8, 128.1, 124.3, 123.2, 118.0, 89.5, 21.6.

4.3.35 N-(5-iodoquinolin-8-yl)-4-methoxybenzamide (**3dc**) [7e]. White solid, m.p. 170-171 °C, 45% yield (36.4 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.67 (s, 1H), 8.82 (dd, *J* = 4.0, 1.0 Hz, 1H), 8.70 (d, *J* = 8.5 Hz, 1H), 8.39 (dd, *J* = 8.5, 1.0 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 8.06-8.03 (m, 2H), 7.56 (dd, *J* = 8.5, 4.0 Hz, 1H), 7.06-7.03 (m, 2H), 3.90 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 162.9, 148.9, 140.9, 139.6, 138.6, 135.9, 129.9, 129.4, 127.4, 123.3, 117.9, 114.2, 89.2, 55.6.

4.3.36 4-fluoro-N-(5-iodoquinolin-8-yl)benzamide (**3ec**) [7e]. White solid, m.p. 169-170 °C, 50% yield (39.2 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.65 (s, 1H), 8.80-8.79 (m, 1H), 8.65 (d, *J* = 8.5 Hz, 1H), 8.37 (d, *J* = 8.5 Hz, 1H), 8.11-8.05 (m, 3H), 7.54 (dd, *J* = 8.5, 3.0 Hz, 1H), 7.23-7.20 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3 (d, J_{CF} = 251.3 Hz), 164.3, 149.0, 140.9, 139.4, 138.5, 135.5, 131.2 (d, J_{CF} = 2.5 Hz), 129.83 (d, J_{CF} = 8.8 Hz), 129.82, 123.4, 118.0, 116.0 (d, J_{CF} = 21.3 Hz), 89.7.

4.3.37 4-chloro-N-(5-iodoquinolin-8-yl)benzamide (**3fc**) [7e]. Yellow solid, m.p. 179-180 °C, 78% yield (63.7 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.64 (s, 1H), 8.77 (d, *J* = 4.0 Hz, 1H), 8.63 (d, *J* = 8.0 Hz, 1H), 8.34 (d, *J* = 8.5 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.5 Hz, 2H), 7.54-7.48 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 149.0, 140.9, 139.4, 138.5, 138.4, 135.4, 133.3, 129.8, 129.2, 128.8, 123.4, 118.1, 89.9.

4.3.38 2-chloro-N-(5-iodoquinolin-8-yl)benzamide (**3gc**). Yellow solid, m.p. 181-182 °C, 70% yield (57.2 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.51 (s, 1H), 8.73 (d, *J* = 4.0, 1H), 8.70 (d, *J* = 8.0, 1H), 8.34 (d, *J* = 8.5 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 7.5 Hz, 1H), 7.51-7.48 (m, 2H), 7.44-7.37 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 149.0, 140.8, 139.3, 138.3, 135.6, 135.5, 131.8, 131.3, 130.7, 130.3, 129.8, 127.3, 123.3, 118.3, 90.2. HRMS (ESI): calcd for $C_{16}H_{11}ClIN_2O^+$ ($[M + H]^+$) 408.9599, Found: 408.9610.

4.3.39 3-chloro-N-(5-iodoquinolin-8-yl)benzamide (**3hc**) [7e]. Yellow solid, m.p. 175-176 °C, 73% yield (59.7 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.65 (s, 1H), 8.80 (dd, *J* = 4.0, 1.5 Hz, 1H), 8.64 (d, *J* = 8.5 Hz, 1H), 8.36 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.09 (d, *J* = 8.5 Hz, 1H), 8.02 (t, *J* = 1.5 Hz, 1H), 7.91-7.90 (m, 1H), 7.55-7.53 (m, 2H), 7.47 (t, *J* = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 149.1, 140.9, 139.3, 138.4, 136.8, 135.3, 135.2, 132.2, 130.2, 129.8, 127.8, 125.4, 123.4, 118.2, 90.1.

4.3.40 4-bromo-N-(5-iodoquinolin-8-yl)benzamide (**3ic**) [10]. Yellow solid, m.p. 169-170 °C, 60% yield (54.4 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.70 (s, 1H), 8.82 (dd, *J* = 4.0, 1.5 Hz, 1H), 8.67 (d, *J* = 8.0 Hz, 1H), 8.40 (dd, *J* = 8.5, 1.0 Hz, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 7.94-7.92 (m, 2H), 7.69-7.68 (m, 2H), 7.57 (dd, *J* = 8.5, 4.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5, 149.1, 141.1, 139.4, 138.5, 135.4, 133.9, 132.3, 129.9, 129.0, 127.0, 123.4, 118.2, 90.0.

4.3.41 N-(5-iodoquinolin-8-yl)-4-(trifluoromethyl)benzamide (**3jc**) [13]. White solid, m.p. 122-123 °C, 53% yield (46.9 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.71 (s, 1H), 8.78 (d, *J* = 4.0 Hz, 1H), 8.63 (d, *J* = 8.0 Hz, 1H), 8.35 (d, *J* = 8.5 Hz, 1H), 8.14 (d, *J* = 8.0 Hz, 2H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 2H), 7.53 (dd, *J* = 8.5, 4.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 149.1, 141.0, 139.3, 138.4, 138.2, 135.2, 133.8 (q, J_{CF} = 32.5 Hz), 129.8, 127.9, 126.0 (q, J_{CF} = 3.8 Hz), 123.4, 123.3 (q, J_{CF} = 271.3 Hz), 118.2, 90.2.

4.3.42 N-(5-iodoquinolin-8-yl)-[1,1'-biphenyl]-4-carboxamide (**3kc**). White solid, m.p. 200-201 °C, 37% yield (33.3mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.80 (s, 1H), 8.85 (dd, *J* = 4.5, 1.5 Hz, 1H), 8.74 (d, *J* = 8.5 Hz, 1H), 8.42 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.15 (d, *J* = 8.5 Hz, 3H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.68-7.66 (m, 2H), 7.58 (dd, *J* = 8.5, 4.5 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.43-7.40 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 149.0, 145.0, 141.0, 140.2, 139.6, 138.6, 135.7, 133.7, 129.9, 129.1, 128.3, 128.0, 127.7, 127.4, 123.4, 118.1, 89.6. HRMS (ESI): calcd for $C_{22}H_{16}IN_2O^+$ ($[M + H]^+$) 451.0302, Found: 451.0304.

4.3.43 N-(5-iodoquinolin-8-yl)-2-naphthamide (**3lc**) [13]. White solid, m.p. 150-151 °C, 71% yield (60.2 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.78 (s, 1H), 8.77 (d, *J* = 3.5 Hz, 1H), 8.69 (d, *J* = 8.0 Hz, 1H), 8.52 (s, 1H), 8.30 (d, *J* = 8.5 Hz, 1H), 8.06 (d, *J* = 8.5 Hz, 2H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.58-7.53 (m, 2H), 7.47 (dd, *J* = 8.5, 4.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 148.9 , 140.7, 139.4, 138.4, 135.6, 135.1, 132.8, 132.1, 129.7, 129.3, 128.8, 128.1, 128.0, 127.9, 126.9, 123.7, 123.2, 118.0, 89.6.

4.3.44 N-(5-iodoquinolin-8-yl)propionamide (**3mc**) [13]. Yellow solid, m.p. 124-125 °C, 48% yield (31.3 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.80 (s, 1H), 8.75 (d, *J* = 4.0 Hz, 1H), 8.54 (d, *J* = 8.0 Hz, 1H), 8.34 (d, *J* = 8.5 Hz, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.51 (dd, *J* = 8.5, 4.0 Hz, 1H), 2.59 (q, *J* = 7.5 Hz, 2H), 1.33 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 148.8, 140.8, 139.1, 138.5, 135.7, 129.7, 123.2, 117.9, 89.1, 31.4, 9.8.

4.3.45 N-(5-iodoquinolin-8-yl)cyclohexanecarboxamide **(3nc)** [11]. Yellow solid, m.p. 112-113 °C, 58% yield (44.1 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.84 (s, 1H), 8.71 (dd, *J* = 4.0, 1.0 Hz, 1H), 8.52 (d, *J* = 8.5 Hz, 1H), 8.27 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 7.45 (dd, *J* = 8.5, 4.0 Hz, 1H), 2.47-2.41 (m, 1H), 2.07-2.04 (m, 2H), 1.87-1.84 (m, 2H), 1.72-1.70 (m, 1H), 1.65-1.57 (m, 2H), 1.40-1.23 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 148.7, 140.7, 139.1, 138.3, 135.6, 129.5, 123.1, 117.8, 89.0, 46.9, 29.8, 25.83, 25.79.

4.3.46 N-(5-iodoquinolin-8-yl)-2-phenylacetamide (**3oc**) [13]. Yellow solid, m.p. 99-100 °C, 71% yield (55.1 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.89 (s, 1H), 8.62 (d, *J* = 4.0 Hz, 1H), 8.52 (d, *J* = 8.5 Hz, 1H), 8.29 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.46-7.40 (m, 5H), 7.35-7.33 (m, 1H), 3.88 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 148.8, 140.7, 139.1, 138.3, 135.4, 134.6, 129.7, 129.6, 129.1, 127.5, 123.2, 117.8, 89.5, 45.5.

4.3.47 N-(5-iodoquinolin-8-yl)furan-2-carboxamide (**3pc**) [11]. Yellow solid, m.p. 177-178 °C, 20% yield (14.6 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.71 (s, 1H), 8.80-8.79 (m, 1H), 8.59 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.33 (d, *J* = 8.5 Hz, 1H), 8.07-8.05 (m, 1H), 7.58 (s, 1H), 7.52-7.50 (m, 1H), 7.21 (d, *J* = 1.5 Hz, 1H), 6.55-6.54 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 149.1, 148.4, 144.8, 140.9, 139.4, 138.4, 135.3, 129.9, 123.4, 118.2, 115.6, 112.7, 89.8.

4.3.48 N-(4-bromophenyl)benzamide (**3qb**) [15]. White solid, m.p. 201-202 °C, 80% yield (44.1 mg). ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 10.37 (s, 1H), 7.95 (d, *J* = 7.0 Hz, 2H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.61-7.58 (m, 1H), 7.55-7.52 (m, 4H). ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 165.6, 138.5, 134.7, 131.6, 131.3, 128.3, 127.6, 122.2, 115.3.

4.3.49 N-(4-bromonaphthalen-1-yl)benzamide (**3rb**) [16]. White solid, m.p. 236-237 °C, 70% yield (45.6 mg). ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 10.52 (s, 1H), 8.19 (d, *J* = 8.5 Hz, 1H), 8.10-8.07 (m, 3H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.74 (t, *J* = 7.5 Hz, 1H), 7.68-7.63 (m, 2H), 7.58 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 166.2, 134.21, 134.19, 131.7, 131.5, 130.4, 129.6, 128.4, 127.9, 127.8, 126.9, 126.6, 124.5, 124.2, 119.2.

Supporting Information:

The crystal data of compound **3aa** and the copies of ^{1}H and ^{13}C NMR spectra for the products can be seen in the Supplementary data.

CCDC 1517307 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ata_request/cif.

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References and notes

[1] (a) Vandekerckhove, S.; Tran, H. G.; Desmet, T.; D'hooghe, M. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 4641. (b) Patel, S. R.; Gangwal, R.; Sangamwar, A. T.; Jain, R. *Eur. J. Med. Chem.* **2015**, *93*, 511. (c) Vandekerckhove, S.; Herreweghe, S. V.; Willems, J.; Danneels, B.; Desmet, T.; Kock, C. D.; Smith, P. J.; Chibale, K.; D'hooghe, M. *Eur. J. Med. Chem.* **2015**, *92*, 91. (d) McDaniel, T. J. Lansdell, T. A.; Dissanayake, A. A.; Azevedo, L. M.; Claes, J.; Odom, A. L.; Tepe, J. J. *Bioorg. Med. Chem*. **2016**, *24*, 2441.

[2] (a) Hughes, C. C.; MacMillan, J. B.; Gaudencio, S. P.; Jensen, P. R.; Fenical, W. *Angew. Chem., Int. Ed.* **2009**, *48*, 725; (b) Pan, E.; Jamison, M.; Yousufuddin, M.; MacMillan, J. B. *Org. Lett.* **2012**, *14*, 2390; (c) Vippagunta, S. R.; Dorn, A.; Matile, H.; Bhattacharjee, A. K.; Karle, J. M.; Ellis, W. Y.; Ridley, R. G.; Vennerstrom, J. L. *J. Med. Chem.* **1999**, *42*, 4630; (d) Madrid, P. B.; Sherrill, J.; Liou, A. P.; Weisman, J. L.; DeRisib, J. L.; Guy, R. K. *Bioorg. Med. Chem. Lett*. **2005**, *15*, 1015. (f) Heidary, D. K.; Howerton, B. S.; Glazer, E. C. *J. Med. Chem*. **2014**, *57*, 8936. (g) Bhat, S.; Shim, J. S.; Zhang, F.; Chong, C. R.; Liu, J. O. *Org. Biomol. Chem*. **2012**, *10*, 2979.

[3] (a) Din, M. K.; Choudhury, A. K. *Chem. Ind.* **1963**, *46*, 1840; (b) Tong, Y. C. *J. Heterocycl. Chem*. **1970**, *7*, 171. (c) Zhou, C-Y.; Li, J.; Peddibhotla, S.; Romo, D. *Org. Lett.* **2010**, *12*, 2104.

[4] (a) Beak, P.; Snieckus, V. *Acc. Chem. Res*. **1982**, *15*, 306. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (c) Gilman, H.; Dietrich, J. J. *J. Am. Chem. Soc.* **1957**, *79*, 1439.

[5] (a) Merkushev, E. B. *Synthesis.* **1988**, 923. (b) Daniel, D. S.; Abdelouahid, S.; Mourad, C.; Maria do Carmo, C.; Jose, M-C. *Synthesis*. **2010**, *16*, 2725.

[6] Selected examples please see: (a) Davies, H. M. L.; Morton, D. *J. Org. Chem.*, **2016**, 81, 343. (b) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879. (c) Noisier, A. F. M.; Brimble, M. A. *Chem. Rev.*, **2014**, *114*, 8775. (d) Guo, X-X.; Gu, D-W.; Wu, Z.; Zhang, W. *Chem. Rev.*, **2015**, *115*, 1622.

[7] Selected examples please see: (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev*. **2010**, *110*, 1147. (b) Zhao, X.; Dimitrijevic, E.; Dong, V. M. *J. Am. Chem. Soc*. **2009**, *131*, 3466. (c) Yang, X.; Sun, Y.; Sun, T-Y.; Rao, Y. *Chem. Commun*. **2016**, *52*, 6423. (d) Moghaddam, F. M.; Tavakoli, G.; Saeednia, B.; Langer, P.; Jafari, B. *J. Org. Chem*. **2016**, *81*, 3868. (e) Liu, X-X.; Wu, Z-Y.; Luo, X-L.; He, Y-Q.; Zhou, X-Q.; Fan, Y-X.; Huang, G-S. *RSC Adv.* **2016**, *6*, 71485.

[8] Suess, A. M.; Ertem, M. Z.; Cramer, C. J.; Stahl, S. S. *J. Am. Chem. Soc.* **2013**, *135*, 9797.

[9] Guo, H.; Chen, M.; Jiang, P.; Chen, J.; Pan, L.; Wang, M.; Xie, C.; Zhang, Y. *Tetrahedron*. **2015**, *71*, 70.

[10] Wu, C.; Zhou, H.; Wu, Q.; He, M.; Li, P.; Su, Q.; Mu, Y. *Synlett*. **2016**, *27*, 868.

[11] Xu, J.; Zhu, X.; Zhou, G.; Ying, B.; Ye, P.; Su, L.; Shen, C.; Zhang, P. *Org*. *Biomol*. *Chem*. **2016**, *14*, 3016.

[12] Wang, Y.; Wang, Y.; Jiang, K.; Zhang, Q.; Li, D. *Org. Biomol. Chem***. 2016,** *14***,** 10180.

[13] Sahoo, H.; Ramakrishna, I.; Baidya, M. *ChemistrySelect.* **2016**, *1*, 1949.

[14] Kubo, T.; Aihara, Y.; Chatani, N. *Chem. Lett.* **2015**, *44*, 1365–1367.

[15] Kuninobu, Y.; Uesugi, T.; Kawata, A.; Takai, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 10406.

[16] Reddy, M. S.; Satyanarayana, P. V. V.; Haribabu, B. *Lett. Org. Chem.* **2012**, *9*, 739-744.