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Regioselective C−H Bond Fluorination of 8-Amidoquinolines with Selectfluor on the C5-Position under Transition-Metal-Free Conditions

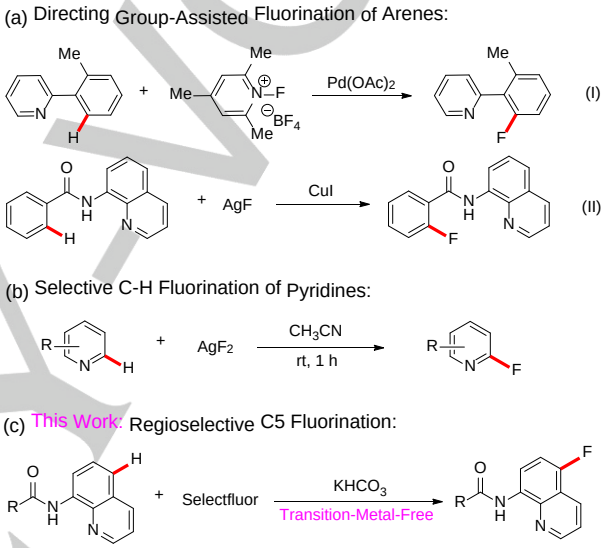
Hao Chen,[a] Pinhua Li,*[a] Min Wang,[a] and Lei Wang*[a,b]

Abstract: A simple and efficient protocol for the regioselective C−H bond fluorination of 8-aminoquinoline scaffolds with Selectfluor under transition-metal-free conditions was developed. The reaction has a broad substrate scope and provides a facile and useful access to the corresponding C5-fluorinated quinolines in good yields.

Introduction

Fluorinated organic molecules are prevalent in pharmaceuticals, agrochemicals and imaging materials.[1] In recent years, the selective introduction of fluorine atoms into small organic molecules has emerged as a new strategy for modulating the properties of chemical leads in drug discovery.[2] Although a variety of methods for the C−F bond formation have been developed in the past few decades, the fact that C−F bond construction remains a challenging project, particularly for the synthesis of aryl fluorides.[3] Classical methods for preparation of fluoroaromatics framework include the conversion of amines via the aryldiazonium salt with HBF_4,[4] the fluorination of Grignard reagents with electrophilic *N*-fluorinated reagents,[5] palladium-mediated fluorination of arylboronic acids,[6] copper-mediated fluorination of aryl iodides and arylboronate esters,[7] as well as the transformation of aryl triflates with simple fluoride salts.[8] However, most of the existing methods require either harsh reaction conditions or highly specialized reagents, which is a great disadvantage in the preparation of complex fluoroarenes.

Transition-metal-catalyzed C−H bond fluorination has emerged as a highly efficient strategy for the rapid construction of fluorinated organic molecules.[9] In 2006, Sanford and co-workers reported a pioneering study on the Pd(II)-catalyzed *ortho*-C−H fluorination directed by pyridyl groups using electrophilic fluorinating reagents (Scheme 1a-I).[10] Subsequently, Yu et al developed the Pd(II)-catalyzed fluorination of aromatic C(sp^2)−H bonds of triflamide-protected benzylamines and *N*-perfluoroaryl benzamides.[11] In 2013, Hartwig's group presented an applicable and safe method for thesite-selective fluorination of a single C−H bond in pyridines and diazines using commercially available silver(II) fluoride (Scheme 1b).[12] Meanwhile, Daugulis demonstrated the copper-catalyzed fluorination of C(sp^2)–H bonds assisted by 8-aminoquinoline and picolinic acid auxiliaries (Scheme 1a-II).[13] Despite these remarkable advances in the directed fluorination of aromatic C(sp^2)−H bonds, developing new routes to C(sp^2)–F formation from readily available precursors under mild and environmentally friendly reaction conditions is highly desirable.



Scheme 1. Approaches for aryl C(sp^2)−H bond fluorination.

In the past few years, the C5-functionalization of quinolines has been achieved considerable attention via transition-metal-catalyzed remote C−H functionalizations, and their halogenation,[14] allylation,[15] chalcogenation,[16] sulfonylation,[17] amination,[18] nitration[19] and phosphonation[20] on the C5-positions of quinolines have been developed. Most recently, a Ni-catalyzed C5-fluorination of 8-aminoquinolines with NFSI was realized.[21] It is worth to note that the remote oxidative C–H functionalization of 8-acylaminoquinolines on the C5-position under metal-free conditions has also received much attention in the past two years.[22] In view of the synthetic utility for the functionalization of quinolines, the development of the new synthetic methodology on their frameworks is essential. As a part of ongoing efforts on C−H functionalization of 8-acylaminoquinolines on the C5-position,[23] herein we demonstrate the fluorination of 8-aminoquinoline scaffolds on their C5-positions with Selectfluor via the direct C−H functionalization under transition-metal-free conditions (Scheme 1c).[24] This method proceeded under simple reaction conditions and showed good air and moisture tolerance and functional group compatibility.

Results and Discussion

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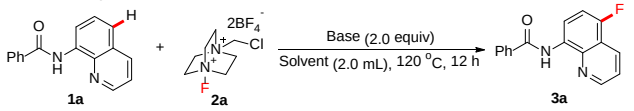
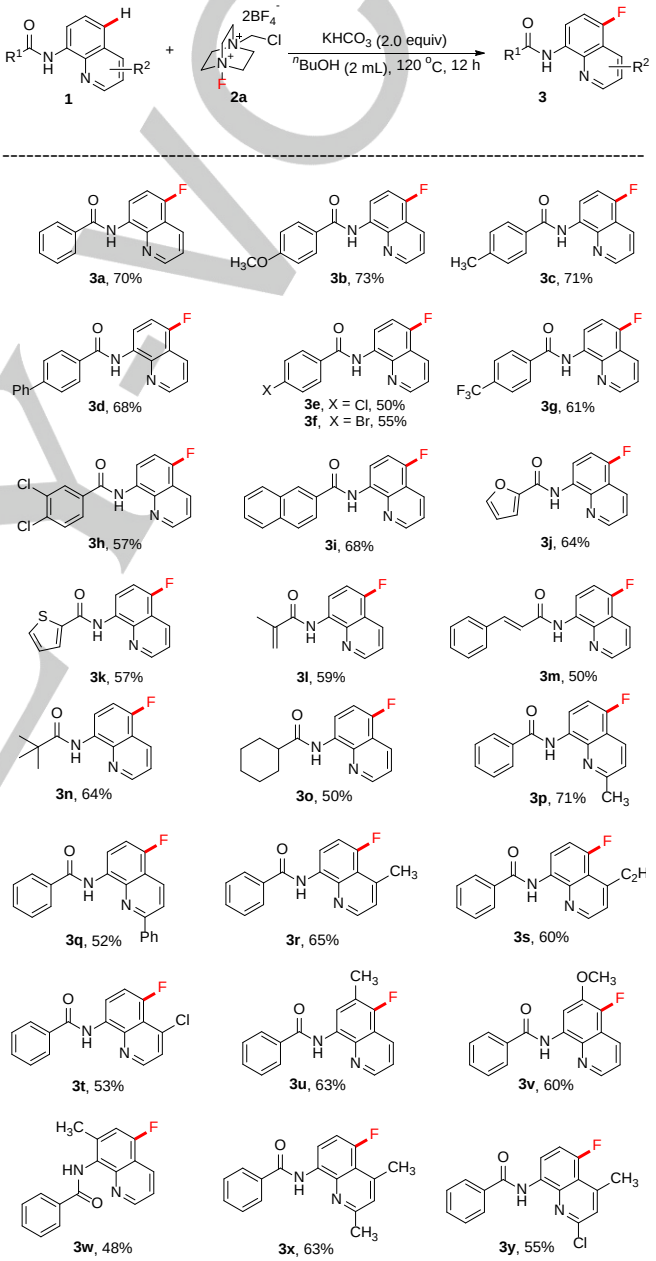
Initially, *N*-(quinolin-8-yl)benzamide (**1a**) and *N*-chloromethyl-*N*′-fluorotriethylenediammoniumbis(tetrafluoroborate) (Selectfluor, **2a**) were chosen as model substrates for optimization of the reaction conditions, and the results are outlined in Table 1. When the reaction was carried out in ethyl alcohol at 120 °C for 12 h in the presence of K_2CO_3 as a base, the remote C5-fluorination proceeded and delivered a sole product **3a** in 5% yield (Table 1, entry 1).The structure of 3a was characterized by ^1H and ^{13}C NMR. An improved yield (33%) of **3a** was obtained when $KHCO_3$ was used as a base, while $NaHCO_3$ was found to be less effective. However, other bases, such as Na_2CO_3, Cs_2CO_3, K_3PO_4, K_2HPO_4, KF, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), DMAP (4-dimethyl aminopyridine) failed in this reaction (Table 1, entries 2−10). Further screening showed that Ni(dppf)Cl_2, Cu(OAc)$_2$ and Fe(OTf)$_2$ were no longer the effective catalyst for the reaction (Table 1, entry 11). Among the examined solvents, ^{n}BuOH was the best of choice (Table 1, entries 12−20). Other fluorinating reagents, including NSFI, Selectfluor II were also examined, both of them failed in this transformation (Table 1, entries 21 and

Table 1. Optimized reaction conditions.[a]



Entry	Base	Solvent	Yield (%)[b]
1	K_2CO_3	EtOH	5
2	$KHCO_3$	EtOH	33
3	Na_2CO_3	EtOH	Trace
4	$NaHCO_3$	EtOH	14
5	Cs_2CO_3	EtOH	Trace
6	K_3PO_4	EtOH	Trace
7	K_2HPO_4	EtOH	Trace
8	KF	EtOH	Trace
9	DBU	EtOH	N. R.
10	DMAP	EtOH	N. R.
11	$KHCO_3$	EtOH	38[c], 37[d], 31[e]
12	$KHCO_3$	^{n}PrOH	45
13	$KHCO_3$	^{n}BuOH	70
14	$KHCO_3$	^{t}BuOH	36
15	$KHCO_3$	1-Pentanol	41
16	$KHCO_3$	1-Hexanol	25
17	$KHCO_3$	DMF	N. R.
18	$KHCO_3$	DMSO	N. R.
19	$KHCO_3$	DCE	N. R.
20	$KHCO_3$	Toluene	15
21	$KHCO_3$	^{n}BuOH	N. R.[f]
22	$KHCO_3$	^{n}BuOH	Trace[g]
23	$KHCO_3$	^{n}BuOH	45[h], 68[i]
24	$KHCO_3$	^{n}BuOH	48[j], 70[k]

[a] Reaction Conditions: **1a** (0.25 mmol), **2a** (0.50 mmol), base (0.50 mmol, 2.0 equiv), solvent (2.0 mL), 120 °C, 12 h. [b] Isolated yield. [c] Ni(dppf)Cl_2 (5 mol%) was added. [d] Cu(OAc)$_2$ (5 mol%) was added. [e] Fe(OTf)$_2$ (5 mol%) was added. [f] NFSI (N-Fluorobenzenesulfonimide) was instead of Selectfluor. [g] Selectfluor II {1-Fluoro-4-methyl-1,4-diazoniabicyclo[2.2.2]octanebis-(tetrafluoroborate)} was instead of Selectfluor. [h] 110 °C. [i] 130 °C. [j] 8h. [k] 16 h. N. R. = No Reaction.

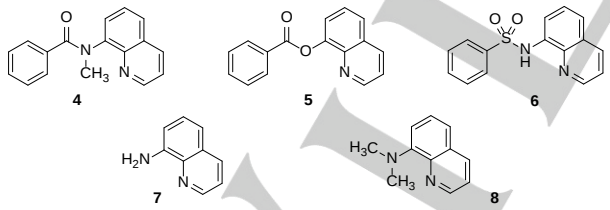


Scheme 2. Substrate scope of amides [Reaction conditions: **1** (0.25 mmol), **2a** (0.50 mmol), $KHCO_3$ (0.50 mmol, 2.0 equiv), *n*-butyl alcohol (2.0 mL), 120 °C, 12 h; isolated yield of the product].

22). The reaction temperature and the reaction time were optimized, also shown in Table 1 (entries 23−24).

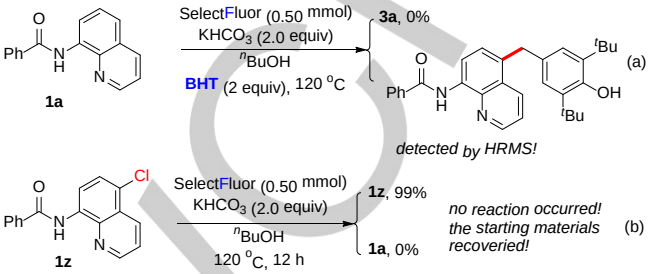
With the optimized reaction conditions in hand, we subsequently explored the substrate scope with respect to 8-aminoquinoline amides, and the results are illustrated in Scheme 2. It can be seen from Scheme 2 that the protecting groups on amino moiety have no obvious influence on the reaction. Aromatic amides with a variety of substituted groups including electron-donating groups (Me, MeO) and electron-withdrawing groups (Ph, Cl, Br, CF_3) on the benzene rings exhibited high reactivity to Selectfluor (**2a**), and the desired products (**3a−g**) were obtained in high yields. In addition, the structure of **3c** was further confirmed by X-ray single crystal analysis.[25] It should be noted that disubstituted (3,4-dichloro)benzamide, 2-naphthamide and heterocyclic amides (furan-2-carboxamide and thiophene-2-carboxamide) could also afford the corresponding C5-fluorinated products (**3h−k**) in moderate to good yields. Furthermore, the reaction scope is beyond aromatic amides, aliphatic amides including methacrylamide, cinnamamide, pivalamide and cyclohexanecarboxamide have a good suitability for the reaction with **2a**, providing the desired products (**3l−o**) in moderate yields. We next explored the applicability of the present protocol for diverse 8-aminoquinoline scaffolds. The results indicated that this reaction is not sensitive to the electron density on the quinoline rings. The quinoline scaffolds bearing both electron-donating groups and electron-withdrawing groups were well tolerated under the standard reaction conditions and the desired products (**3p−w**) were generated in moderate to good yields. The reaction of disubstituted 8-aminoquinoline could also undergo to give the desired products (**3x−y**) in moderate yields.

To further explore the scope of substrate, a series of analogous of quinolones was investigated, which are listed in Scheme 3. Under the optimized reaction conditions, the reaction of *N*-methyl-*N*-(quinolin-8-yl)benzamide (**4**) with **2a** failed to generate the C5-fluorinated product and the starting materials were recovered. Moreover, quinolin-8-ylbenzoate (**5**), *N*-(quinolin-8-yl)benzenesulfon-amide (**6**), 8-aminoquinoline (**7**) and its derivative *N*,*N*-dimethyl-8-aminoquinoline (**8**) were all ineffective in the reaction.



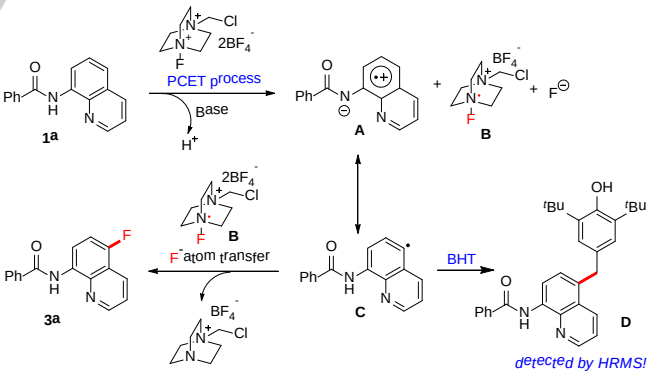
Scheme 3. Ineffective C5-fluorination of substrates (**4−8**).

In order to gain insight into the reaction mechanism, some control experiments, including free radical inhibition and trapping experiments were performed. It was found that the remote C−H fluorination was completely inhibited in the presence of 2,6-di-*tert*-butyl-4-methylphenol (BHT) as a free radical scavenger. Meanwhile, the 8-aminoquinoline C5 radical (**C**, shown in Scheme 5) generated in situ from **1a** through a single electron oxidation was captured, and the corresponding adduct **D** was detected by HRMS (Scheme 4a and Supporting Information). It is indicated that the radical process might be involved in the reaction. Moreover, when C5-position hydrogen of **1a** was substituted by a chlorine atom, no desired product was obtained and the starting materials were recovered (Scheme 4b).



Scheme 4. Control experiments.

Although the exact mechanism remains unclear up till now, on the basis of our experimental results and the literature,[26] a mechanistic hypothesis for the transition-metal free regioselective C−H fluorination of 8-aminoquinoline amide is proposed, as shown in Scheme 5. The initial step involves a proton-coupled electron transfer (PCET)[27] process via the transfer of a single electron (single-electron transfer, SET) and a single proton (deprotonation step) in the presence of a base ($KHCO_3$), converting 8-aminoquinoline amide (**1a**) into an intermediate **A**, along with the generation of free radical intermediate **B**. Then 8-aminoquinoline radical **C** is generated in situ from **A** through a resonance. The subsequent step is a fluorine atom transfer between the radical **C** and intermediate **B** to generate the desired product **3a**. Further investigation is being conducted to afford evidence for the proposed mechanism.



Scheme 5. Plausible mechanism.

Conclusions

In summary, we have established a green and convenient method for C5-fluorination of 8-aminoquinoline scaffolds under transition-metal-free conditions. The reaction system shows tolerance toward numerous 8-aminoquinoline amides, giving the corresponding products in good yields. On the basis of

experimental investigations, a free radical cross-coupling pathway underlying the reaction mechanism is proposed. Further explorations for fluorination of other heteroarene systems under transition-metal free conditions are currently underway in our laboratory.

Experimental Section

General remarks

All ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz Bruker FT-NMR spectrometers (400 MHz or 100 MHz, respectively). All chemical shifts are given as δ value (ppm) with reference to tetramethylsilane (TMS) as an internal standard. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet. The coupling constants, *J*, are reported in Hertz (Hz). High resolution mass spectroscopy data of the product were collected on a Waters Micromass GCT instrument. High resolution mass spectroscopy data of the product were collected on an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS (ESI).

The chemicals and solvents were purchased from commercial suppliers either from Aldrich (USA) or Shanghai Chemical Company (China) without further purification. All the solvents were dried and freshly distilled prior to use. All the reactions were carried out under air atmosphere. Products were purified by flash chromatography on 100–200 mesh silica gels, SiO_2.

General procedure for the C5-fluorination of 8-aminoquinolines

8-Aminoquinoline amide (**1a**, 0.25 mmol), Selectfluor (**2a**, 0.50 mmol), $KHCO_3$ (0.50 mmol) and ^{n}BuOH (2.0 mL) was added to a 15 mL Schlenk tube, and the reaction mixture was stirred in an oil bath at 120 °C for 12 h. Then the reaction mixture was cooled down to room temperature and the reaction solution was concentrated under reduced pressure to yield crude product, which was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 15:1) to give the desired product **3a** in 70 % yield as a white solid.

Characterization data for all products

***N*-(5-Fluoroquinolin-8-yl)benzamide (3a).** White solid (46.6 mg, 70% yield), m.p. 133–134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.53 (s, 1H), 8.91–8.88 (m, 2H), 8.45 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 8.09–8.06 (m, 2H), 7.60–7.53 (m, 4H), 7.27 (t, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.26, 152.97 (d, *J* = 249.6 Hz), 149.08, 138.94 (d, *J* = 3.0 Hz), 134.98, 131.84, 131.10 (d, *J* = 4.1 Hz), 129.78 (d, *J* = 3.6 Hz), 128.78, 127.19, 121.70 (d, *J* = 2.6 Hz), 118.78 (d, *J* = 17.9 Hz), 116.00 (d, *J* = 7.5 Hz), 110.46 (d, *J* = 19.6 Hz). HRMS (ESI) ([M+H]$^+$) Calcd. For $C_{16}H_{12}FN_2O$: 267.0928, Found: 267.0927.

***N*-(5-Fluoroquinolin-8-yl)-4-methoxybenzamide (3b).** White solid (54.0 mg, 73% yield), m.p. 137–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.45 (s, 1H), 8.89–8.85 (m, 2H), 8.43 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz,1H), 8.05–8.02 (m, 2H), 7.53 (dd, J_1 = 4.2 Hz, J_2 = 8.4 Hz,1H), 7.25 (t, *J* = 9.3 Hz, 1H), 7.05–7.01 (m, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.80, 162.51, 152.79 (d, *J* = 249.4 Hz), 148.98, 138.90 (d, *J* = 2.9 Hz), 131.27 (d, *J* = 4.0 Hz), 129.74 (d, *J* = 3.6 Hz), 129.05, 127.25, 121.62 (d, *J* = 2.5 Hz), 118.75 (d, *J* = 18.2 Hz), 115.77 (d, *J* = 7.5 Hz), 113.97, 110.46 (d, *J* = 19.4 Hz), 55.41. HRMS (ESI) ([M+H]$^+$) Calcd. For $C_{17}H_{14}FN_2O_2$: 297.1034, Found: 297.1032.

***N*-(5-Fluoroquinolin-8-yl)-4-methylbenzamide (3c).** White solid (49.7 mg, 71% yield), m.p. 135–137 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.50 (s, 1H), 8.91–8.88 (m, 2H), 8.45 (dd, J_1 = 1.4 Hz, J_2 = 8.4 Hz,1H), 7.97 (d, *J* = 8.1 Hz, 2H), 7.54 (dd, J_1 = 4.3 Hz, J_2 = 8.4 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.27 (t, *J* = 8.8 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.29, 152.92 (d, *J* = 249.5 Hz), 149.05, 142.35, 139.00 (d, *J* = 3.1 Hz), 132.24, 131.27 (d, *J* = 4.1 Hz), 129.79 (d, *J* = 3.7 Hz), 129.45, 127.24, 121.66 (d, *J* = 2.6 Hz), 118.82 (d, *J* = 18.1 Hz), 115.96 (d, *J* = 7.6 Hz), 110.50 (d, *J* = 19.5 Hz), 21.50. HRMS (ESI) ([M+H]$^+$) Calcd. For $C_{17}H_{14}FN_2O$: 281.1085, Found: 281.1084.

***N*-(5-Fluoroquinolin-8-yl)-[1,1'-biphenyl]-4-carboxamide (3d).** White solid (58.2 mg, 68% yield), m.p. 222–224 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.60 (s, 1H), 8.95–8.91 (m, 2H), 8.48 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 8.17–8.15 (m, 2H), 7.80–7.78 (m, 2H), 7.69–7.67 (m, 2H), 7.57 (dd, J_1 = 4.3 Hz, J_2 = 8.4 Hz, 1H), 7.53–7.49 (m, 2H), 7.44–7.41 (m, 1H), 7.29 (t, *J* = 9.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.01, 153.02 (d, *J* = 249.8 Hz), 149.12, 144.68, 140.00, 139.01 (d, *J* = 3.0 Hz), 133.66, 131.17 (d, *J* = 4.2 Hz), 129.84 (d, *J* = 3.6 Hz), 128.95, 128.06, 127.76, 127.46, 127.23, 121.73 (d, *J* = 2.3 Hz), 118.84 (d, *J* = 17.9 Hz), 116.07 (d, *J* = 7.5 Hz), 110.52 (d, *J* = 19.6 Hz). HRMS (ESI) ([M+H]$^+$) Calcd. For $C_{22}H_{16}FN_2O$: 343.1241, Found: 343.1244.

4-Chloro-*N*-(5-fluoroquinolin-8-yl)benzamide (3e). White solid (37.5 mg, 50% yield), m.p. 145–146 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.45 (s, 1H), 8.87 (dd, J_1 = 1.6 Hz, J_2 = 4.2 Hz, 1H), 8.83 (dd, J_1 = 5.4 Hz, J_2 = 8.6 Hz, 1H), 8.43 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 7.99–7.96 (m, 2H), 7.53 (dd, J_1 = 4.2 Hz, J_2 = 8.4 Hz, 1H), 7.51–7.49 (m, 2H), 7.23 (t, *J* = 9.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.02, 153.05 (d, *J* = 250.0 Hz), 149.10, 138.83 (d, *J* = 3.0 Hz), 138.12, 133.28, 130.80 (d, *J* = 4.1 Hz), 129.80 (d, *J* = 3.4 Hz), 129.00, 128.58, 121.72 (d, *J* = 2.4 Hz), 118.74 (d, *J* = 18.0 Hz), 116.05 (d, *J* = 7.6 Hz), 110.41 (d, *J* = 19.6 Hz). HRMS (ESI) ([M+H]$^+$) Calcd. For $C_{16}H_{11}ClFN_2O$: 301.0538, Found: 301.0542.

4-Bromo-*N*-(5-fluoroquinolin-8-yl)benzamide (3f). White solid (47.3 mg, 55% yield), m.p. 193–194 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.46 (s, 1H), 8.88 (dd, J_1 = 1.6 Hz, J_2 = 4.2 Hz, 1H), 8.84 (dd, J_1 = 5.4 Hz, J_2 = 8.6 Hz, 1H), 8.44 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 7.93–7.90 (m, 2H), 7.68–7.66 (m, 2H), 7.54 (dd, J_1 = 4.2 Hz, J_2 = 8.4 Hz, 1H), 7.25 (t, *J* = 9.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.17, 153.08 (d, *J* = 250.1 Hz), 149.13, 138.87 (d, *J* = 3.2 Hz), 133.78, 132.00, 130.81 (d, *J* = 3.9 Hz), 129.83 (d, *J* = 3.6 Hz), 128.77, 126.61, 121.75 (d, *J* = 2.5 Hz), 118.78 (d, *J* = 17.9 Hz), 116.10 (d, *J* = 7.6 Hz), 110.44 (d, *J* = 19.5 Hz). HRMS (ESI) ([M+H]$^+$) Calcd. For $C_{16}H_{11}BrFN_2O$: 345.0033, Found: 345.0031.

***N*-(5-Fluoroquinolin-8-yl)-4-(trifluoromethyl)benzamide (3g).** White solid (50.9 mg, 61% yield), m.p. 140–141 °C. ^{1}H NMR (400

MHz, $CDCl_3$) δ: 10.51 (s, 1H), 8.87 (dd, J_1 = 1.6 Hz, J_2 = 4.2 Hz,1H), 8.83 (dd, J_1 = 5.4 Hz, J_2 = 8.6 Hz,1H), 8.42 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 8.14 (d, *J* = 8.1 Hz, 2H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.53 (dd, J_1= 4.3 Hz, J_2 = 8.4 Hz, 1H), 7.23 (t, *J* = 8.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.70, 153.20 (d, *J* = 250.3 Hz), 149.19, 138.84 (d, *J* = 3.0 Hz), 138.15, 133.45 (q, J_1 = 32.4 Hz, J_2 = 65.1 Hz), 130.61 (d, *J* = 4.1 Hz), 129.82 (d, *J* = 3.6 Hz), 127.61, 125.79 (q, J_1 = 3.6 Hz, J_2 = 7.3 Hz), 123.66 (q, J_1 = 270.8 Hz, J_2 = 541.8 Hz), 121.79 (d, *J* = 2.4 Hz), 118.75 (d, *J* = 18.2 Hz),116.22 (d, *J* = 7.8 Hz), 110.38 (d, *J* = 19.7 Hz). HRMS (ESI) ($[M+H]^+$) Calcd. For $C_{17}H_{11}F_4N_2O$: 335.0802, Found: 335.0799.

3,4-Dichloro-*N*-(5-fluoroquinolin-8-yl)benzamide (3h). White solid (47.6 mg, 57% yield), m.p. 181–183 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.45 (s, 1H), 8.91 (d, *J* = 2.9 Hz, 1H), 8.82 (dd, J_1 = 5.4 Hz, J_2 = 8.6 Hz, 1H), 8.47 (d, *J* = 8.3 Hz, 1H), 8.14 (d, *J* = 1.7 Hz, 1H), 7.88–7.85 (m, 1H), 7.61 (d, *J* = 8.3 Hz, 1H), 7.57 (dd, J_1 = 4.2 Hz, J_2 = 8.4 Hz, 1H), 7.26 (t, *J* = 9.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.88, 153.26 (d, *J* = 250.5 Hz), 149.27, 138.87 (d, *J* = 3.2 Hz), 136.35, 134.76, 133.39, 130.80, 130.57 (d, *J* = 3.9 Hz), 129.92 (d, *J* = 3.6 Hz), 129.49, 126.18, 121.86 (d, *J* = 2.5 Hz), 118.82 (d, *J* = 18.2 Hz), 116.29 (d, *J* = 7.6 Hz), 110.46 (d, *J* = 19.7 Hz). HRMS (ESI) ($[M+H]^+$) Calcd. For $C_{16}H_{10}Cl_2FN_2O$: 335.0149, Found: 335.0151.

***N*-(5-Fluoroquinolin-8-yl)-2-naphthamide (3i).** White solid (53.7 mg, 68% yield), m.p. 158–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.64 (s, 1H), 8.94–8.90 (m, 2H), 8.55 (s, 1H), 8.43 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 8.10–8.08 (m, 1H), 8.03–8.00 (m, 1H), 7.98–7.96 (m, 1H), 7.91–7.89 (m, 1H), 7.61–7.56 (m, 2H), 7.53 (dd, J_1 = 4.3 Hz, J_2 = 8.5 Hz, 1H), 7.26 (t, *J* = 9.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.28, 152.99 (d, *J* = 249.6 Hz), 149.11, 138.97 (d, *J* = 2.9 Hz), 134.91, 132.72, 132.17, 131.16 (d, *J* = 4.0 Hz), 129.79 (d, *J* = 3.5 Hz), 129.15, 128.67, 127.87, 127.84, 127.76, 126.79, 123.58, 121.70 (d, *J* = 2.2 Hz), 118.80 (d, *J* = 18.0 Hz), 116.07 (t, *J* = 7.6 Hz), 110.49 (d, *J* = 19.5 Hz). HRMS (ESI) ($[M+H]^+$) Calcd. For $C_{20}H_{14}FN_2O$: 317.1085, Found: 317.1087.

***N*-(5-Fluoroquinolin-8-yl)furan-2-carboxamide (3j).** White solid (41.0 mg, 64% yield), m.p. 200–201 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.57 (s, 1H), 8.93 (dd, J_1 = 1.6 Hz, J_2 = 4.2 Hz, 1H), 8.82 (dd, J_1 = 5.4 Hz, J_2 = 8.6 Hz, 1H), 8.44 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 7.63–7.62 (m, 1H), 7.55 (dd, J_1 = 4.3 Hz, J_2 = 8.4 Hz, 1H), 7.31–7.30 (m, 1H), 7.24 (t, *J* = 9.4 Hz, 1H), 6.59 (dd, J_1 = 1.8 Hz, J_2 = 3.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.21, 153.06 (d, *J* = 250.0 Hz), 149.20, 148.18, 144.49, 138.80, 130.67 (d, *J* = 4.1 Hz), 129.71 (d, *J* = 3.6 Hz), 121.72 (d, *J* = 2.2 Hz), 118.77 (d, *J* = 18.1 Hz), 116.08 (t, *J* = 7.8 Hz), 115.10, 112.43, 110.42 (d, *J* = 19.6 Hz). HRMS (ESI) ($[M+H]^+$) Calcd. For $C_{14}H_{10}FN_2O_2$: 257.0721, Found: 257.0723.

***N*-(5-Fluoroquinolin-8-yl)thiophene-2-carboxamide (3k).** White solid (38.8 mg, 57% yield), m.p. 167–169 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.39 (s, 1H), 8.91 (dd, J_1 = 1.6 Hz, J_2 = 4.2 Hz, 1H), 8.80 (dd, J_1 = 5.4 Hz, J_2 = 8.6 Hz, 1H), 8.46 (dd, J_1 = 1.5 Hz, J_2 = 8.4 Hz, 1H), 7.83 (dd, J_1 = 1.0 Hz, J_2 = 3.7 Hz, 1H), 7.60 (dd, J_1 = 1.0 Hz, J_2 = 5.0 Hz, 1H), 7.56 (dd, J_1 = 4.2 Hz, J_2 = 8.4 Hz, 1H), 7.26 (t, *J* = 9.4 Hz, 1H), 7.20 (dd, J_1 = 3.8 Hz, J_2 = 4.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.86, 152.99 (d, *J* = 249.5 Hz), 149.14, 139.84, 138.67, 130.92, 130.81 (d, *J* = 4.0 Hz), 129.83 (d, *J* = 3.6 Hz), 128.38, 127.85, 121.76 (d, *J* = 2.5 Hz), 118.78 (d, *J* = 18.1 Hz), 115.98 (t, *J* = 7.7 Hz), 110.51 (d, *J* = 19.6 Hz). HRMS (ESI) ($[M+H]^+$) Calcd. For $C_{14}H_{10}FN_2OS$: 273.0492, Found: 273.0490.

***N*-(5-Fluoroquinolin-8-yl)methacrylamide (3l).** White solid (33.9 mg, 59% yield), m.p. 115–116 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.15 (s, 1H), 8.86 (dd, J_1 = 1.6 Hz, J_2 = 4.2 Hz,1H), 8.78 (dd, J_1 = 5.4 Hz, J_2 = 8.6 Hz, 1H), 8.43 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 7.52 (dd, J_1 = 4.2 Hz, J_2 = 8.4 Hz, 1H), 7.22 (t, *J* = 8.9 Hz, 1H), 6.04 (s, 1H), 5.56 (s, 1H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.26, 152.91 (d, *J* = 249.7 Hz), 149.04, 140.60, 138.86, 130.98 (d, *J* = 3.7 Hz), 129.72 (d, *J* = 3.7 Hz), 121.63, 120.56, 118.73 (d, *J* = 18.1 Hz), 115.91 (d, *J* = 7.5 Hz), 110.40 (d, *J* = 19.6 Hz), 18.62. HRMS (ESI) ($[M+H]^+$) Calcd. For $C_{13}H_{12}FN_2O$: 231.0928, Found: 231.0927.

***N*-(5-Fluoroquinolin-8-yl)cinnamamide (3m).** White solid (36.5 mg, 50% yield), m.p. 156–158 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.80 (s, 1H), 8.88–8.85 (m, 2H), 8.43 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 7.82 (d, *J* =15.5 Hz, 1H), 7.62–7.59 (m, 2H), 7.53 (dd, J_1 = 4.2 Hz, J_2 = 8.4 Hz, 1H), 7.44–7.38 (m, 3H), 7.23 (t, *J* = 9.4 Hz, 1H), 6.77 (d, *J* = 15.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.93, 152.93 (d, *J* = 249.6 Hz), 148.93, 142.09, 138.61 (d, *J* = 2.8 Hz), 134.72, 131.14 (d, *J* = 4.1 Hz), 129.89, 129.77 (d, *J* = 3.7 Hz), 128.82, 127.98, 121.65 (d, *J* = 2.2 Hz), 121.33, 118.71 (d, *J* = 18.1 Hz), 116.28 (d, *J* = 7.6 Hz), 110.49 (d, *J* = 19.6 Hz). HRMS (ESI) ($[M+H]^+$) Calcd. For $C_{18}H_{14}FN_2O$: 293.1085, Found: 293.1082.

***N*-(5-Fluoroquinolin-8-yl)pivalamide (3n).** White solid (39.4 mg, 64% yield), m.p. 71–72 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.07 (s, 1H), 8.87 (dd, J_1 = 1.6 Hz, J_2 = 4.2 Hz, 1H), 8.75 (dd, J_1 = 5.5 Hz, J_2 = 8.7 Hz, 1H), 8.43 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 7.52 (dd, J_1 = 4.3 Hz, J_2 = 8.5 Hz, 1H), 7.21 (t, *J* = 9.0 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.05, 152.70 (d, *J* = 248.8 Hz), 149.01, 138.95 (d, *J* = 2.8 Hz), 131.23 (d, *J* = 3.9 Hz), 129.69 (d, *J* = 3.6 Hz), 121.54 (d, *J* = 2.3 Hz), 118.70 (d, *J* = 18.1 Hz), 115.63 (d, *J* = 7.6 Hz), 110.37 (d, *J* = 19.4 Hz), 40.23, 27.68. HRMS (ESI) ($[M+H]^+$) Calcd. For $C_{14}H_{16}FN_2O$: 247.1241, Found: 247.1244.

***N*-(5-Fluoroquinolin-8-yl)cyclohexanecarboxamide (3o).** White solid (34.0 mg, 50% yield), m.p. 112–114 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.69 (s, 1H), 8.86 (dd, J_1 = 1.6 Hz, J_2 = 4.2 Hz, 1H), 8.75 (dd, J_1 = 5.5 Hz, J_2 = 8.6 Hz, 1H), 8.42 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 7.51 (dd, J_1 = 4.2 Hz, J_2 = 8.4 Hz, 1H), 7.20 (t, *J* = 9.0 Hz, 1H), 2.50–2.42 (m, 1H), 2.10–2.07 (m, 2H), 2.50–2.42 (m, 1H), 1.91–1.87 (m, 2H), 1.78–1.72 (m, 1H), 1.69–1.59 (m, 2H), 1.42–1.34 (m, 2H), 1.33–1.26 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.62, 152.67 (d, *J* = 248.9 Hz), 148.88, 138.68 (d, *J* = 2.9 Hz), 131.19 (d, *J* = 4.0 Hz), 129.71 (d, *J* = 3.7 Hz), 121.53 (d, *J* = 2.4 Hz), 118.69 (d, *J* = 18.0 Hz), 115.84 (d, *J* = 7.4 Hz), 110.38 (d, *J* = 19.5 Hz), 46.79, 29.73, 25.75, 25.72. HRMS (ESI) ($[M+H]^+$) Calcd. For $C_{16}H_{18}FN_2O$: 273.1398, Found: 273.1402.

***N*-(5-Fluoro-2-methylquinolin-8-yl)benzamide (3p).** White solid (49.7 mg, 71% yield), m.p. 115–116 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ:

10.58 (s, 1H), 8.85 (dd, J_1 = 5.5 Hz, J_2 = 8.6 Hz, 1H), 8.32 (d, J = 8.5 Hz, 1H), 8.08–8.06 (m, 2H), 7.60–7.54 (m, 3H), 7.40 (d, J = 8.6 Hz, 1H), 7.18 (t, J = 9.4 Hz, 1H), 2.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.12, 158.29, 153.25 (d, J = 249.2 Hz), 138.52, 135.16, 131.75, 130.43 (d, J = 3.8 Hz), 129.82 (d, J = 3.3 Hz), 128.79, 127.16, 122.50 (d, J = 2.4 Hz), 116.83 (d, J = 18.1 Hz), 116.00 (d, J = 7.8 Hz), 109.48 (d, J = 19.5 Hz), 25.45. HRMS (ESI) ([M+H]$^+$) Calcd. For $C_{17}H_{14}FN_2O$: 281.1085, Found: 281.1083.

***N*-(5-Fluoro-2-phenylquinolin-8-yl)benzamide (3q).** Yellow solid (44.5 mg, 52% yield), m.p. 164–166 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.68 (s, 1H), 8.87 (dd, J_1 = 5.4 Hz, J_2 = 8.6 Hz, 1H), 8.46 (d, J = 8.7 Hz, 1H), 8.17–8.14 (m, 2H), 8.10–8.08 (m, 2H), 7.97 (d, J = 8.7 Hz, 1H), 7.62–7.57 (m, 4H), 7.55–7.53 (m, 2H), 7.22 (t, J = 9.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.93, 155.88, 153.13 (d, J = 249.6 Hz), 138.66 (d, J = 3.0 Hz), 138.52, 135.09, 131.84, 131.08 (d, J = 3.8 Hz), 130.73 (d, J = 3.2 Hz), 129.97, 129.00, 128.86, 127.33, 127.06, 119.30 (d, J = 2.4 Hz), 117.49 (d, J = 18.1 Hz), 116.26 (d, J = 7.7 Hz), 110.25 (d, J = 19.6 Hz). HRMS (ESI) ([M+H]$^+$) Calcd. For $C_{22}H_{16}FN_2O$: 343.1241, Found: 343.1237.

***N*-(5-Fluoro-4-methylquinolin-8-yl)benzamide (3r).** White solid (45.5 mg, 65% yield), m.p. 178–179 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.67 (s, 1H), 8.86 (dd, J_1 = 5.0 Hz, J_2 = 8.7 Hz, 1H), 8.66 (d, J = 4.4 Hz, 1H), 8.08–8.05 (m, 2H), 7.60–7.52 (m, 3H), 7.25–7.19 (m, 2H), 2.85 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.15, 154.67 (d, J = 251.1 Hz), 148.52, 144.32 (d, J = 4.1 Hz), 139.51, 135.09, 131.72, 131.37 (d, J = 4.0 Hz), 128.72, 127.17, 123.91, 118.83 (d, J = 13.5 Hz), 115.88 (d, J = 8.3 Hz), 111.36 (d, J = 22.7 Hz), 22.50 (d, J = 11.0 Hz). HRMS (ESI) ([M+H]$^+$) Calcd. For $C_{17}H_{14}FN_2O$: 281.1085, Found: 281.1088.

***N*-(4-Ethyl-5-fluoroquinolin-8-yl)benzamide (3s).** White solid (44.1 mg, 60% yield), m.p. 112–115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.73 (s, 1H), 8.88 (dd, J_1 = 5.0 Hz, J_2 = 8.6 Hz, 1H), 8.72 (d, J = 4.5 Hz, 1H), 8.09–8.06 (m, 2H), 7.59–7.52 (m, 3H), 7.30 (d, J = 4.5 Hz, 1H), 7.24 (dd, J_1 = 8.7 Hz, J_2 = 12.8 Hz, 1H), 3.27–3.21 (m, 2H), 1.39–1.35 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.17, 154.31 (d, J = 251.2 Hz), 150.26 (d, J = 5.0 Hz), 148.66 (d, J = 1.2 Hz), 139.72 (d, J = 3.0 Hz), 135.14, 131.72, 131.56 (d, J = 4.1 Hz), 128.72, 127.19, 122.14, 118.12 (d, J = 13.3 Hz), 115.82 (d, J = 8.7 Hz), 111.57 (d, J = 23.4 Hz), 28.61 (d, J = 10.9 Hz), 14.93 (d, J = 4.1 Hz). HRMS (ESI) ([M+H]$^+$) Calcd. For $C_{18}H_{16}FN_2O$: 295.1241, Found: 295.1242.

***N*-(4-Chloro-5-fluoroquinolin-8-yl)benzamide (3t).** White solid (39.8 mg, 53% yield), m.p. 168–169 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.52 (s, 1H), 8.92 (dd, J_1 = 4.7 Hz, J_2 = 8.7 Hz, 1H), 8.66 (d, J = 4.7 Hz, 1H), 8.04 (d, J = 7.1 Hz, 2H), 7.59–7.53 (m, 4H), 7.32–7.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.19, 152.53 (d, J = 255.5 Hz), 148.06 (d, J = 1.8 Hz), 140.32, 140.14 (d, J = 2.0 Hz), 134.78, 131.92, 131.51 (d, J = 4.5 Hz), 128.78, 127.16, 123.95, 117.07, 116.99, 113.13 (d, J = 22.1 Hz). HRMS (ESI) ([M+H]$^+$) Calcd. For $C_{16}H_{11}ClFN_2O$: 301.0538, Found: 301.0540.

***N*-(5-Fluoro-6-methylquinolin-8-yl)benzamide (3u).** White solid (44.1 mg, 63% yield), m.p. 221–223 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.45 (s, 1H), 8.79–8.77 (m, 2H), 8.35 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 8.07–8.05 (m, 2H), 7.58–7.52 (m, 3H), 7.46 (dd, J_1 = 4.2 Hz, J_2 = 8.4 Hz, 1H), 2.48 (d, J = 2.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.08, 150.31 (d, J = 246.7 Hz), 147.96, 137.63, 134.95, 131.75, 130.35 (d, J = 3.6 Hz), 129.11 (d, J = 4.2 Hz), 128.72, 127.13, 121.58, 120.27 (d, J = 15.9 Hz), 119.13 (d, J = 4.4 Hz), 118.55 (d, J = 18.8 Hz), 14.69 (d, J = 3.3 Hz). HRMS (ESI) ([M+H]$^+$) Calcd. For $C_{17}H_{14}FN_2O$: 281.1085, Found: 281.1083.

***N*-(5-Fluoro-6-methoxyquinolin-8-yl)benzamide (3v).** White solid (44.4 mg, 60% yield), m.p. 125–126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.57 (s, 1H), 8.96 (d, J = 8.5 Hz, 1H), 8.71 (dd, J_1 = 1.6 Hz, J_2 = 4.2 Hz, 1H), 8.35 (dd, J_1 = 1.5 Hz, J_2 = 8.5 Hz, 1H), 8.07–8.05 (m, 2H), 7.60–7.53 (m, 3H), 7.47 (dd, J_1 = 4.2 Hz, J_2 = 8.5 Hz, 1H), 4.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.26, 146.63, 143.45 (d, J = 9.4 Hz), 140.53 (d, J = 248.5 Hz),134.74, 133.31, 131.96, 131.51 (d, J = 3.9 Hz), 128.82, 128.45 (d, J = 4.2 Hz), 127.15, 122.03 (d, J = 2.7 Hz), 119.30 (d, J = 14.9 Hz), 106.08, 57.20. HRMS (ESI) ([M+H]$^+$) Calcd. For $C_{17}H_{14}FN_2O_2$: 297.1034, Found: 297.1038.

***N*-(5-Fluoro-7-methylquinolin-8-yl)benzamide (3w).** White solid (33.6 mg, 48% yield), m.p. 149–152 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.39 (s, 1H), 8.81 (dd, J_1 = 1.6 Hz, J_2 = 4.2 Hz, 1H), 8.37 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 8.09–8.07 (m, 2H), 7.59–7.56 (m, 1H), 7.52–7.49 (m, 2H), 7.41 (dd, J_1 = 4.2 Hz, J_2 = 8.4 Hz, 1H), 7.18 (d, J = 10.6 Hz, 1H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.96, 154.91 (d, J = 252.0 Hz), 149.95, 142.91 (d, J = 3.8 Hz), 134.52, 134.32 (d, J = 8.1 Hz), 131.82, 129.39 (d, J = 3.6 Hz), 128.62, 128.07 (d, J = 4.2 Hz), 127.72, 120.66 (d, J = 2.4 Hz), 117.34 (d, J = 17.8 Hz), 113.39 (d, J = 19.5 Hz), 20.37 (d, J = 1.1 Hz). HRMS (ESI) ([M+H]$^+$) Calcd. For $C_{17}H_{14}FN_2O$: 281.1085, Found: 281.1087.

***N*-(5-Fluoro-2,4-dimethylquinolin-8-yl)benzamide (3x).** Yellow solid (46.3 mg, 63% yield), m.p. 157–159 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.73 (s, 1H), 8.81 (dd, J_1 = 5.1 Hz, J_2 = 8.6 Hz, 1H), 8.07–8.04 (m, 2H), 7.59–7.53 (m, 3H), 7.16–7.11 (m, 2H), 2.78 (d, J = 6.3 Hz, 3H), 2.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.97, 157.59, 154.91 (d, J = 250.5 Hz), 144.08 (d, J = 4.1 Hz), 139.19 (d, J = 2.8 Hz), 135.25, 131.64, 130.67 (d, J = 4.0 Hz), 128.73, 127.12, 124.56, 116.94 (d, J = 13.4 Hz), 115.85 (d, J = 8.6 Hz), 110.37 (d, J = 22.7 Hz), 25.01, 22.31 (d, J = 10.5 Hz). HRMS (ESI) ([M+H]$^+$) Calcd. For $C_{18}H_{16}FN_2O$: 295.1241, Found: 295.1240.

***N*-(2-Chloro-5-fluoro-4-methylquinolin-8-yl)benzamide (3y).** White solid (43.2 mg, 55% yield), m.p. 222–223 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.22 (s, 1H), 8.90 (dd, J_1 = 5.0 Hz, J_2 = 8.8 Hz, 1H), 8.06–8.03 (m, 2H), 7.61–7.54 (m, 3H), 7.27–7.21 (m, 2H), 2.84–2.82 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.23, 154.66 (d, J = 251.6 Hz), 150.01, 147.92 (d, J = 4.2 Hz), 138.93 (d, J = 3.0 Hz), 134.81, 131.94, 130.70 (d, J = 3.9 Hz), 128.85, 127.19, 124.31, 117.50 (d, J = 8.6 Hz), 112.13 (d, J = 22.6 Hz), 22.39 (d, J = 11.1 Hz). HRMS (ESI) ([M+H]$^+$) Calcd. For $C_{17}H_{13}ClFN_2O$: 315.0695, Found: 315.0699.

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Conflict of Interest

The authors declare no conflict of interest.

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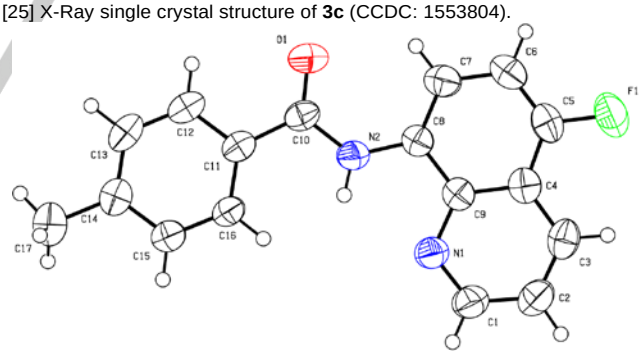

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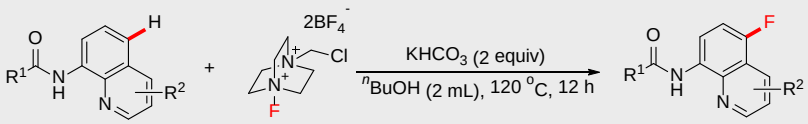

A simple and efficient protocol for the C5-selective fluorination of 8-aminoquinoline scaffolds with Selectfluor under transition-metal free conditions was developed.

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Regioselective C−H Bond Fluorination of 8-Amidoquinolines with Selectfluor on the C5 Position under Transition-Metal-Free Conditions