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C5-regioselective C-H fluorination of 8-aminoquinoline amides and sulfonamides with selectfluor under metal-free conditions

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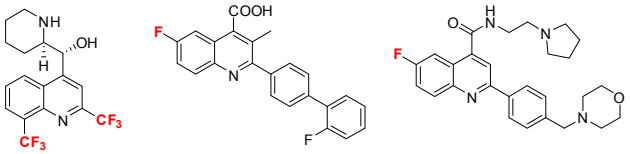
A novel and efficient regioselective C-H fluorination of 8-aminoquinoline amides and sulfonamides at C5 position was achieved. Using selectfluor as "F" reagent and HOAc as additive, the reaction proceeds smoothly via radical pathway. This method features metal-free conditions, broad substrate scope and operational simplicity.

Introduction

Fluoro or fluoro-containing groups substituted quinoline moieties are of great importance as these structures usually existed in advanced functional materials and pharmaceuticals.[1] For example, Mefloquine[2] and Brequinar[3] are marketed antimalaria and anticancer drugs respectively, whereas PfEF2 (translation elongation factor 2) inhibitor[4] is potential drug candidate in preclinical development (**Figure 1**). The incorporation of fluoro or fluoro-containing groups into bioactive organic molecules will remarkably modulate the physicochemical and biological properties.[5a-5c] As a result, the direct and efficient construction of C-F or C-CF_3 etc chemical bonds has gained considerable attention and is a continuous issue in organic synthesis.[5d, 5e]

In view of atom economic point, the direct C-H functionalization catalyzed by TM (transition metal) has been demonstrated and developed to be a powerful tool in organic synthesis.[6] Except for the ortho C-H transformation which has been developed well and usually be controlled via σ-chelation assistance, the remote C-H activation research is still a big challenge nowadays.[7] Since stahl group firstly reported that the remote C5 chlorination of quinolines catalyzed by CuCl in acidic conditions through SET (single electron transfer) process,[8] diverse TM catalyzed regioselective C5 functionalization has succeeded continuelly.[9] Among them, as shown in **scheme 1**, several groups have independently achieved C-CF_3 coupling at the C5 position of quinolines catalyzed by Cu species (**eq 1**).[10] Later on, Wang and co-workers reported a simple and novel protocol for nickel-catalyzed C5 difluoroalkylation of 8-aminoquinoline scaffolds with functionalized difluoromethyl bromides (**eq 2**).[11] We also successfully achieved C5 selective fluorination of 8-aminoquinoline derivatives for the first time catalyzed by cheap TM $NiSO_4$ (**eq 3**).[12] Interestingly, the more attractive metal-free strategies about C5 highly selective functionalization on quinolines were also reported recently.[13a-13h] In the absence of any TM catalysts, Zhang group established an eco-friendly, convenient and practical method for C5 perfluoroalkylation of quinolines (**eq 4**).[13k] Wu and co-workers provided an oxidative trifluoromethylation of 8-aminoquinoline scaffolds on the C5 position with $NaSO_2CF_3$ as "CF_3" source and PIDA as oxidant (**eq 5**).[13d]



Mefloquine Brequinar Pf EF2 inhibitor

Figure 1 Selected examples of bioactive fluoro and fluoro-containing groups substituted quinolines.

Transition-metal-free conditions have the advantages of being atom economical, inexpensive, operational simplicity, and avoidance of the metal pollution to environment.[13a,13i,13j] Undoubtedly, metal-free reactions can meet well the requirement of green chemistry in modern organic synthesis area. Thus, the above successful metal-free reactions (**eq 4** and **5**) inspired us to investigate the regioselective C-F bond formation on quinolines again. Meanwhile, we also noted that other C5-H selective functionalization such as halogenation (Cl, Br, I)[13a,13c,13e], sulfonylation[13b] and amidation[14] were also developed without any TM catalysts. In view of the reaction mechanism in detail, we found that these reactions occurred mostly under oxidative additives. Additionally, whether via SET process or not,[13b,13h] the N-cation radicals derived from NH-pyridine moiety, or their resonance delocalization structures,[13e,15] are the key intermediates, which induced other radical groups to attack the C5 position on quinolines. We suspected that some "F" reagents acting as "F" donor and oxidant, could facilitate the metal-free C5 fluorination on quinolines under suitable conditions. For instance, the electrophilic N-F reagents, selectfluor (1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo

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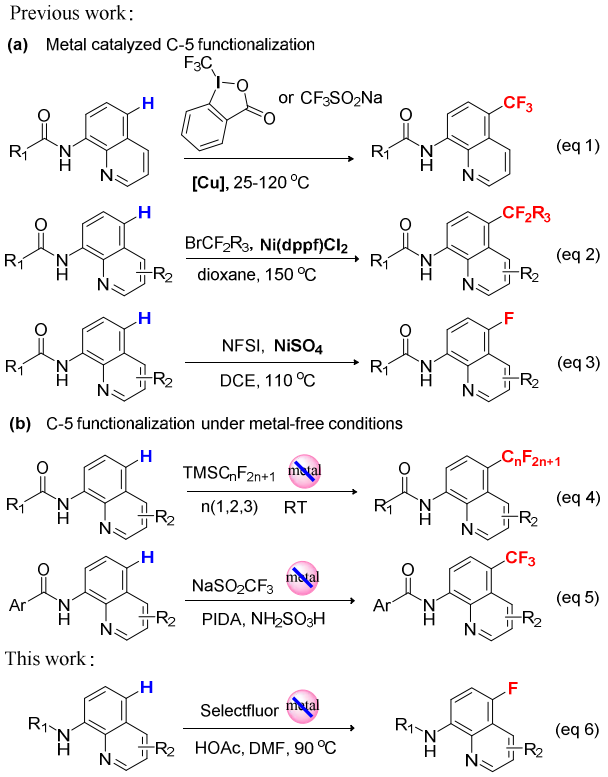
[2.2.2] octane bis (tetrafluoroborate))[15,16,17] and NFSI (N-Fluorobenzenesulfonimide) [12,14b,18], which have dual functions and have been applied successfully in many reported F radical addition reactions. Especially selectfluor, without any initiator, could be produced F anion and N cation radicals, the latter has been proved with the strong ability to capture the proton H from the N-H bond of anilide.[15] Herein, we report our research results (**eq 6**).

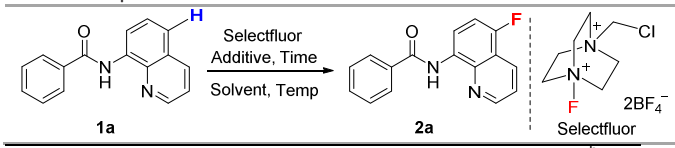


Scheme 1 Methods for preparation of C-5 selective fluoro and fluoro-containing groups substituted quinolines.

Results and discussion

To test this transition metal-free hypothesis, N-(quinolin-8-yl)-benzamide **1a** was chosen as model substrate (**Table 1**). Firstly, 1.5 equiv selectfluor was used as "F" source in green solvent, water, without any additive, no reaction was observed after 10 hours at 25°C. We suggested that N-(quinolin-8-yl)-benzamide molecules' energy at around room temperature was not high enough to initiate the reaction. Then, the temperature was increased to 80 °C and 100 °C (entries **2-3**), while **1a** smoothly conversed to C-5 mono-fluorinated product **2a** with very low yield and good yield respectively. Inspired by these results, we increased the reaction temperature to 120 °C and 140 °C, respectively for entries **4** and **5**. But, no additional benefit was gained at above 100 °C, as yields decreased. Subsequently, solvent screening proved that DMF was the best suitable solvent affording product in isolated yield 49% (entries **6-9**). Then, a range of additives including $Cu(OAc)_2$, PIDA, KHS_2O_8, NH_4OAc, and PivOH were examined in DMF, but none of them improved the yields (entries **10-14**). Whereas, HOAc was a good additive to the reaction system with increased yield of 59% (entry **15** *vs* **9**). Next, we explored the optimal reaction time to reveal 4 h as the suitable reaction time (entries **16-18**). Remarkably, when NFSI was used instead of selectfluor as "F" source, there was almost no target fluorination generated (entries **17**). After further exploration of the stoichiometry of selectfluor and the temperature (entries **19-21**), it was found that selectfluor, 2.0 equiv and temperature 90 °C were favorable condition for the reaction. Thus, selectfluor 2.0 equiv, HOAc 1.2 equiv, reaction time 4 h and temperature 90 °C in DMF was chosen as the best reaction conditions (entry **20**).

Table 1 Optimization of the reaction conditions[a]



Entry	Additive	Solvent	Time (h)	Temp (°C)	Yield[b] (%)
1	—	H_2O	10	25	n.r.
2	—	H_2O	10	80	trace
3	—	H_2O	10	100	38
4	—	H_2O	10	120	34
5	—	H_2O	10	140	10
6	—	Toluene	10	100	trace
7	—	DCE	10	100	23
8	—	THF	10	100	trace
9	—	DMF	10	100	49
10	$Cu(OAc)_2$	DMF	10	100	45
11[c]	PIDA	DMF	10	100	40
12	KHS_2O_8	DMF	10	100	33
13	NH_4OAc	DMF	10	100	40
14	PivOH	DMF	10	100	38
15	HOAc	DMF	10	100	58
16	HOAc	DMF	15	100	51
17	HOAc	DMF	4	100	67 (n.r.[c])
18	HOAc	DMF	2	100	57
19[d]	HOAc	DMF	4	100	50
20[e]	**HOAc**	**DMF**	**4**	**90**	**70**
21[e]	HOAc	DMF	4	100	66

[a] Reaction conditions: **1a** (0.2 mmol), Selectfluor (0.3 mmol), additive (0.24 mmol), solvent (1.5 mL), in air. [b] Isolated yield. [c] Selectfluor was replaced with NFSI. [d] Selectfluor (1.0 equiv). [e] Selecftluor (2.0 equiv). n.r. = no reaction.

With the optimized reaction conditions in hand, the limitation and scope was investigated for diverse 8-amino-quinoline scaffolds. The results were illustrated in **Table 2**. Apparently, N-(8-quinolinyl) amides, regardless arylcarboxamides or alkylcarboxamides were all converted into corresponding products (**2a-2j**, **2k-2q**) in good yields 43%-74%. For aryl amides substrates, different substituents on the benzene ring, including electron-donating group CH_3 (**2c**, **2g**, **2h**) and electron-withdrawing group such as halides chloride and bromine (**2b**, **2d-2f**), had no obvious electronic effect on the selective fluorination reaction.

Notably, Cl and CH_3 groups on the *ortho*- or *para*- position of benzene ring, reactions exhibited similar activity and good yields of 63% and 71% (**2b**, **2e**), 67% and 59% (**2c**, **2g**), suggesting that the

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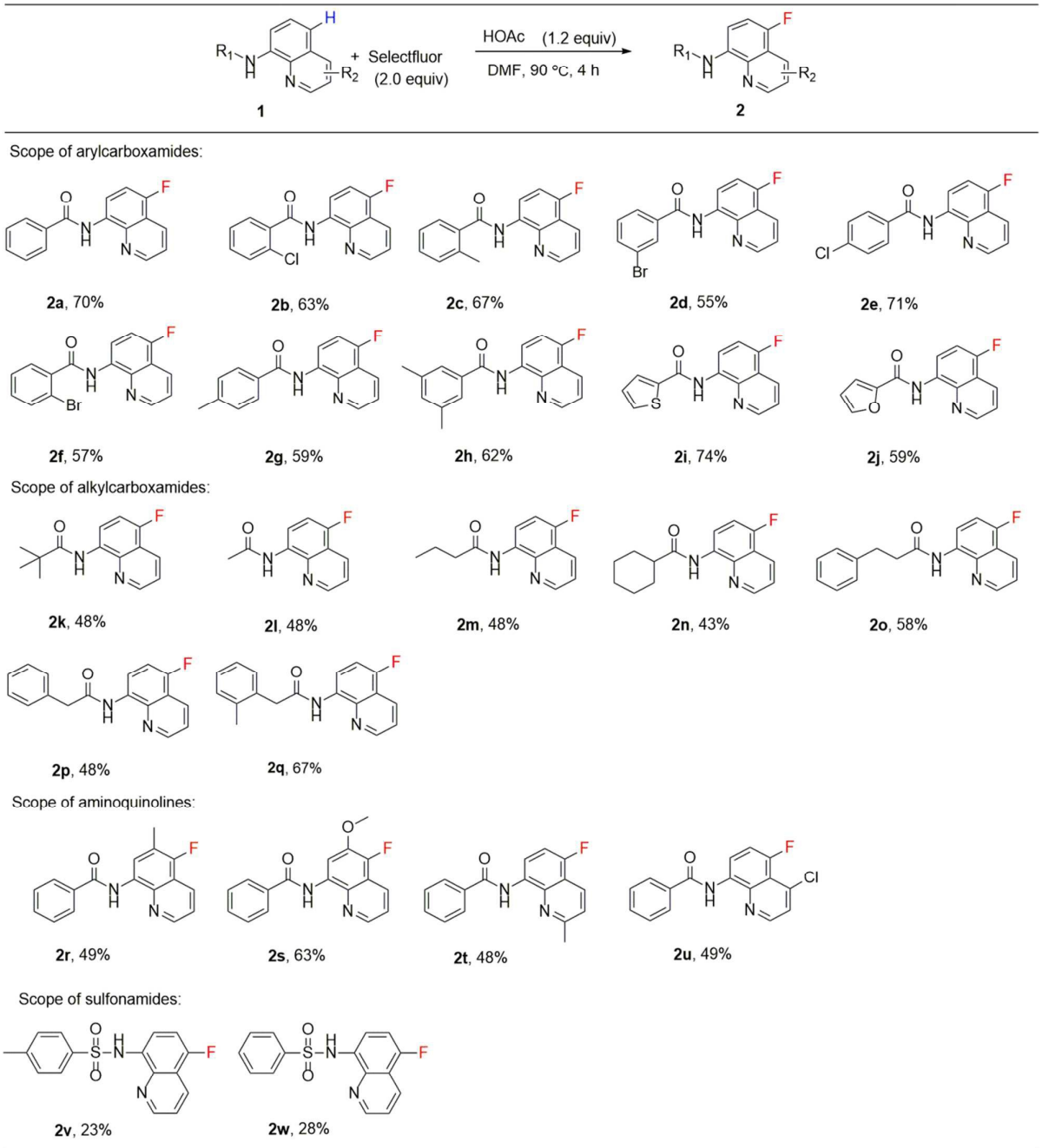
steric hindrance effect was minimal in this protocol. Moreover, the heterocyclic amides also worked well and afforded the fluorinated products in yields of 74% and 59% respectively (**2i**, **2j**), which revealed the functional groups good tolerance. Substrates with diverse aliphatic substituents, had lower activity and provided products **2k-2p** in yields 43-58%, **2q** 67%, and no obvious steric hindrance.

Then, we set out to explore the scope of the aminoquinoline moiety. The introduction of methyl, methoxy or chloride groups into different positions (C-2, C-6 and C-4) of quinoline ring was tolerated, and the corresponding C-5 fluorinated products were obtained in preferable yields 49%, 63%, 48% and 49% (**2r**, **2s**, **2t**, **2u**).

Table 2 Substrates scope of 8-aminoquinolines[a]



[a]Standard reaction conditions: **1** (0.2 mmol), Selectfluor (0.4 mmol) and HOAc (0.24mmol) were added into DMF (1.5 ml) and the mixture was stirred for 4 h at 90 °C. Isolated yields.

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Finally, we were delighted to find that substrates sulfamides achieved the regioselective C-F bond formation successfully in yield 23% and 28% (**2v**, **2w**). Even the yields are low, but the methodology provided direct remote C-H fluorination of quinolines with low activated sulfonyl substituent for the first time, which has ever failed using the reported Ni-catalyzed fluorination method.[12] Therefore, it was concluded that various substrates were tolerated well in the metal-free catalyzed remote fluorination procedure of quinolineamides and quinolinesulfamides.

In addition, X-ray analysis of **2e** crystal unambiguously confirmed the regioselective C-5 fluorination of the quinolines (see Supporting Information for details).[19] The single-crystal structure of **2e** from X-ray diffraction was shown here in **Figure 2**.

It is deserved to be mentioned that other quinolines (**3-10**) were detected under the standard conditions (**Figure 3**). However, no any desired product was observed. Due to the strong electron-withdrawing effect of NO_2 group in the

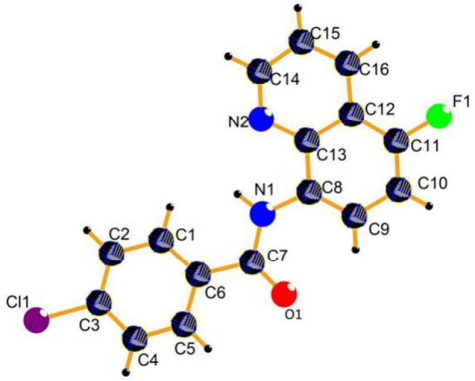


Figure 2 Single-crystal X-ray structure of **2e**.

benzene ring, quinoline derivatives **3** and **4** did not success in the fluorinated transformation. The naphthylamide derivative **5** and **10** were ineffective which attributed to the intrinsic low activity of naphthalene ring, also suggesting that the reaction may not proceed through an aromatic electrophilic substitution pathway. It should be noted that both quinoline analogues without amido bond (**6**, **8**) or without free NH moiety (**7**) failed in this remote regioselective C-H activation. The results indicated that the presence of both of an amide or sulfamide free NH moiety and carbonyl or sulfonyl group were required in the fluorination protocol.[20] Additionally, when we adopted N-(8-quinolinyl) amides, of which C-5 position was blocked by chlorine atom, no any desired C-5 or other C-4, C-7 fluorination occurred (**9**). It was concluded that the C-5 selectivity of the reaction was quite excellent.

In order to explore the reaction mechanism, control experiments were performed (**Scheme 2**). Under the standard reaction conditions, when radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyoxy) (2.0 equiv) was added into the **1d** reaction system, the fluorination process was inhibited and only trace of terminal product **2d** (< 5% yield) was obtained. This result demonstrated that free radical pathway was involved in the regioselective C-H fluorination. The fluorine radical adduct **TEMPO-F** could be detected by LC-MS (HRMS: 176.0219) and in 46% F-NMR yield.

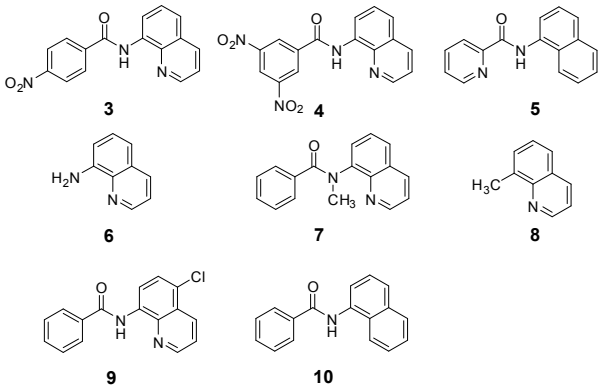
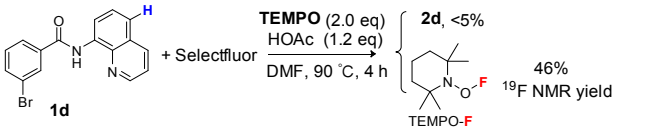


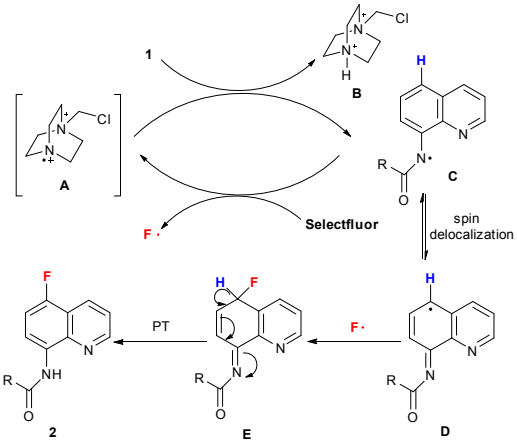
Figure 3 Ineffective metal-free catalyzed C5-fluorination of substrates.



Detected by **HRLC-MS**! ([M+H]$^+$ found: 176.0219)

Scheme 2 Control experiments.

So, on the basis of above experimental results and literatures reported by others,[13a,15,17b] a plausible mechanism was illustrated in **Scheme 3**. Firstly, the interaction between the N-F reagent selectfluor and quinolineamides **1** facilitated the generation of F radical and key cationic N-radical A.[15] Then, the latter captured the proton H in NH moiety of N-(8-quinolinyl) amides **1** to generate compound **B** and N-radical intermediate **C**. **C** was easily transformed to intermediate **D** via spin delocalization. Finally, the F radical attacked the C-5 position of **D** through coupling reaction to give intermediate **E**. A PT (proton transfer) process took place automatically to afford the desired product **2**.



Scheme 3 Plausible reaction mechanism.

To validate the synthetic utility of the metal-free protocol, the reaction on a 4.03 mmol (1.00 g) gram-scale of **1a** was conducted

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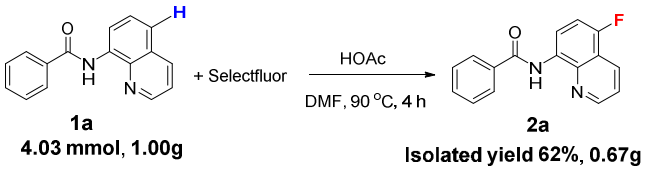
under the standard conditions. As shown in **Scheme 4**, the desired product **2a** was obtained in 62% isolated yield. The result indicated that the present strategy was possible for the synthesis of C-5 fluorinated quinolines in large quantities. The hydrolysis of the amide **2a** was easily achieved through treatment with NaOH in EtOH to obtain 5-fluoro-8-aminoquinoline without damaging the C-F bond reported by our group previously.[12]



Scheme 4 Gram-scale reaction of the C5-selective fluorination of quinolines.

Conclusions

In summary, we have developed a novel non metal-catalyzed regioselective fluorination of 8-aminoquinoline derivations on C-5 position. Using selectfluor as fluorinated reagent, and no additional oxidants, the protocol provides a useful methodology for the efficient construction of C-F bond on quinoline scaffolds with broad functional groups compatibility. The plausible radical mechanism was also demonstrated. The application of fluorinated modification on bioactive compounds for drug discovery using this method was underway in our lab.

Experimental section

General

All reagents, starting materials, and solvents were purchased from commercial sources and used without treatment, unless otherwise indicated. All the solvents were dried and newly distilled. NMR spectra were obtained on a Bruker AMX 400 system using chloroform-d as deuterated solvents and TMS as internal standard. The ^{1}H-NMR spectra were recorded at 400 MHz, the ^{13}C-NMR spectra were recorded at 100 MHz, and the ^{19}F-NMR spectra were recorded at 376 MHz. All shifts were given in ppm. All coupling constants (*J* values) were reported in Hertz (Hz). Single crystal X-ray diffraction data were collected using a Bruker-AXS SMART APEX2 CCD diffractometer (Mo Kα, λ = 0.71073 Å). High-Resolution Liquid Chromatography-Mass Spectrometry was recorded on the Bruker MicrOTOF QⅡ. Column chromatography was performed on silica gel 100-200 mesh or 200-300 mesh. Ethyl acetate and petroleum ether were used for column chromatography.

Procedure for the synthesis of substituted amides 1a-1w

Preparation of amides **1a-1w** according to literature procedures reported previously from 8-aminoquinoline and corresponding acyl chloride: A solution of 8-aminoquinoline (1.44 g, 10.0 mmol) and NEt_3 (1.01 g, 11.0 mmol) in dichloromethane (10 mL) was added dropwise to a stirring solution of an acid chloride (11.0 mmol) in dichloromethane (40 mL) under the ice bath conditions. The resulting mixture was stirred at 25 °C for 10 hours. Then, the mixture was quenched with saturated aq. $NaHCO_3$ (50 mL), and was extracted with dichloromethane for three times (3 x 50 mL). The organic layer was dried over Na_2SO_4. After filtration and evaporation, the amides were purified by column chromatography (hexane: ethyl acetate 10:1-4:1) through silica gel.

Procedure for the synthesis of regioselective C5 fluorinated N-(8-quinolinyl) amides and sulfonamides (2a-2w)

N-(8-quinolinyl) amide or sulfonamide 1 (0.2 mmol, 1.0 equiv), Selecfluor (0.4 mmol, 2.0 equiv), HOAc (0.24 mmol, 1.2 equiv) were mixed in DMF (1.5 mL) and stirred for 4 h in a sealed tube at 90 °C. The organic layer was washed with H_2O, and was extracted with dichloromethane for three times (3 x 10 mL). Then, the organic layer was dried over anhydrous Na_2SO_4, and resulting organic solution was concentrated under reduced pressure and further purified by flash chromatography (SiO_2, petroleum ether/ethyl acetate gradient 30:1-10:1), yielding the target product **2a-2w**.

N-(5-fluoroquinolin-8-yl)benzamide (2a). White solid, isolated yield: 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.55 (s, 1H), 8.91 (t, *J* = 6.6 Hz, 2H), 8.47 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 7.0 Hz, 2H), 7.65-7.52 (m, 4H), 7.29 (d, *J* = 9.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.34 (s), 153.01 (d, *J* = 251.2 Hz), 149.14 (s), 138.97 (d, *J* = 3.0 Hz), 134.99 (s), 131.91 (s), 131.12 (d, *J* = 4.0 Hz), 129.86 (d, *J* = 3.6 Hz), 128.83 (s), 127.24 (s), 121.77 (d, *J* = 2.6 Hz), 118.82 (d, *J* = 18.3 Hz), 116.04 (d, *J* = 7.7 Hz), 110.52 (d, *J* = 19.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -129.01 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{16}H_{11}FN_2O$: 267.0928, found: 267.0927.

2-chloro-N-(5-fluoroquinolin-8-yl)benzamide (2b). White solid, isolated yield: 63%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.35 (s, 1H), 8.92 (dd, *J* = 8.6, 5.5 Hz, 1H), 8.86 (d, *J* = 3.1 Hz, 1H), 8.48 (d, *J* = 8.4 Hz, 1H), 7.82 (dd, *J* = 7.2, 1.5 Hz, 1H), 7.58-7.49 (m, 2H), 7.48-7.39 (m, 2H), 7.30 (d, *J* = 9.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.72 (s), 153.26 (d, *J* = 251.7 Hz), 149.23 (s), 138.92 (d, *J* = 3.2 Hz), 135.63 (s), 131.60 (s), 131.15 (s), 130.97 (d, *J* = 4.2 Hz), 130.55 (s), 130.14 (s), 129.79 (d, *J* = 3.7 Hz), 127.19 (s), 121.79 (d, *J* = 2.7 Hz), 118.81 (d, *J* = 18.1 Hz), 116.47 (d, *J* = 7.8 Hz), 110.46 (d, *J* = 19.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -128.39 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{16}H_{10}ClFN_2O$: 301.0538, found: 301.0542.

2-methyl-N-(5-fluoroquinolin-8-yl)benzamide (2c). White solid, isolated yield: 67%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.03 (s, 1H), 8.90 (dd, *J* = 8.5, 5.5 Hz, 1H), 8.84 (d, *J* = 4.1 Hz, 1H), 8.48 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.55 (dd, *J* = 8.4, 4.3 Hz, 1H), 7.46-7.27 (m, 4H), 2.60 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.06 (s), 153.05 (d, *J* = 251.3 Hz), 149.12 (s), 138.82 (d, *J* = 3.1 Hz), 136.71 (s), 136.46 (s), 131.42 (s), 131.26 (d, *J* = 4.0 Hz), 130.41 (s), 129.81 (d, *J* = 3.6 Hz), 127.23 (s), 126.05 (s), 121.75 (d, *J* = 2.5 Hz), 118.80 (d, *J* = 18.1 Hz), 116.01 (d, *J* = 7.7 Hz), 110.46 (d, *J* = 19.6 Hz), 20.24 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -128.93 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{17}H_{13}FN_2O$: 281.1085, found: 281.1092.

3-bromo-N-(5-fluoroquinolin-8-yl)benzamide (2d). White solid, isolated yield: 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.49 (s, 1H), 8.93 (d, *J* = 3.0 Hz, 1H), 8.87 (dd, *J* = 8.6, 5.4 Hz, 1H), 8.48 (d, *J* = 8.5 Hz, 1H), 8.20 (s, 1H), 7.98 (d, *J* = 7.5 Hz, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.58 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 9.3 Hz,

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1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.76 (s), 153.21 (d, *J* = 251.8 Hz), 149.26 (s), 138.95 (s), 136.99 (s), 134.85 (s), 130.78 (d, *J* = 4.0 Hz), 130.57 (s), 130.34 (s), 129.92 (d, *J* = 3.6 Hz), 125.66 (s), 123.08 (s), 121.85 (d, *J* = 2.5 Hz), 118.84 (d, *J* = 18.3 Hz), 116.27 (d, *J* = 7.8 Hz), 110.50 (d, *J* = 19.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -128.39 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{16}H_{10}BrFN_2O$: 345.0033, 347.0013, found: 345.0039, 347.0019.

4-chloro-N-(5-fluoroquinolin-8-yl)benzamide (2e). White solid, isolated yield: 71%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.51 (s, 1H), δ 8.91 (d, *J* = 4.1 Hz, 1H), 8.87 (dd, *J* = 8.6, 5.4 Hz, 1H), 8.48 (d, *J* = 8.4 Hz, 1H), 8.01 (d, *J* = 8.4 Hz, 2H), 7.60-7.51 (m, 3H), 7.29 (d, *J* = 9.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.20 (s), 153.14 (d, *J* = 251.6 Hz), 149.20 (s), 138.93 (d, *J* = 3.1 Hz), 138.19 (s), 133.38 (s), 130.88 (d, *J* = 4.0 Hz), 129.94 (d, *J* = 3.6 Hz), 129.10 (s), 128.67 (s), 121.83 (d, *J* = 2.5 Hz), 118.85 (d, *J* = 18.3 Hz), 116.15 (d, *J* = 7.7 Hz), 110.53 (d, *J* = 19.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -128.57 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{16}H_{10}ClFN_2O$: 301.0538, found: 301.0532.

2-bromo-N-(5-fluoroquinolin-8-yl)benzamide (2f). White solid, isolated yield: 57%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.11 (s, 1H), 8.99-8.81 (m, 2H), 8.46 (d, *J* = 8.4 Hz, 1H), 7.70 (t, *J* = 7.8 Hz, 2H), 7.53 (dd, *J* = 8.2, 4.1 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 9.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.74 (s), 153.28 (d, *J* = 251.7 Hz), 149.20 (s), 138.88 (s), 138.17 (s), 133.70 (s), 131.55 (s), 130.88 (s), 129.84 (s), 129.71 (d, *J* = 23.0 Hz), 127.67 (s), 121.78 (s), 119.68 (s), 118.82 (d, *J* = 18.3 Hz), 116.46 (d, *J* = 7.5 Hz), 110.45 (d, *J* = 19.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -128.27 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{16}H_{10}BrFN_2O$: 345.0033, 347.0013, found: 345.0037, 347.0019.

4-methyl-N-(5-fluoroquinolin-8-yl)benzamide (2g). White solid, isolated yield: 59%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.52 (s, 1H), 8.96-8.86 (m, 2H), 8.47 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 7.7 Hz, 2H), 7.56 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.35 (d, *J* = 7.7 Hz, 2H), 7.29 (t, *J* = 9.2 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.32 (s), 152.92 (d, *J* = 251.1 Hz), 149.08 (s), 142.40 (s), 138.97 (d, *J* = 2.8 Hz), 132.19 (s), 131.24 (d, *J* = 4.0 Hz), 129.83 (d, *J* = 3.8 Hz), 129.48 (s), 127.25 (s), 121.71 (d, *J* = 2.4 Hz), 118.82 (d, *J* = 18.1 Hz), 115.94 (d, *J* = 7.6 Hz), 110.53 (d, *J* = 19.6 Hz), 21.56 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -129.27 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{17}H_{13}FN_2O$: 281.1085, found: 281.1089.

3,5-dimethyl-N-(5-fluoroquinolin-8-yl)benzamide (2h). White solid, isolated yield: 62%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.46 (s, 1H), 8.98-8.86 (m, 2H), 8.47 (d, *J* = 8.4 Hz, 1H), 7.65 (s, 2H), 7.56 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.28 (d, *J* = 9.2 Hz, 1H), 7.23 (d, *J* = 12.4 Hz, 1H), 2.44 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.80 (s), 152.94 (d, *J* = 251.0 Hz), 149.11 (s), 138.99 (d, *J* = 3.1 Hz), 138.51 (s), 135.05 (s), 133.53 (s), 131.25 (d, *J* = 4.2 Hz), 129.82 (d, *J* = 3.7 Hz), 124.98 (s), 121.70 (d, *J* = 2.6 Hz), 118.81 (d, *J* = 18.2 Hz), 116.04 (d, *J* = 7.7 Hz), 110.52 (d, *J* = 19.6 Hz), 21.39 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -129.26 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{18}H_{15}FN_2O$: 295.1241, found: 295.1238.

N-(5-fluoroquinolin-8-yl)thiophene-2-carboxamide (2i). White solid, isolated yield: 74%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.33 (s, 1H), 8.94-8.88 (m, 1H), 8.84 (dd, *J* = 8.6, 5.4 Hz, 1H), 8.46 (d, *J* = 8.4 Hz, 1H), 8.19-8.13 (m, 1H), 7.68 (d, *J* = 5.0 Hz, 1H), 7.55 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.44 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.28 (t, *J* = 9.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.90 (s), 152.96 (d, *J* = 251.2 Hz), 149.11 (s), 138.79 (d, *J* = 3.0 Hz), 138.19 (s), 131.02 (d, *J* = 4.0 Hz), 129.85 (d, *J* = 3.6 Hz), 128.93 (s), 126.78 (s), 126.27 (s), 121.74 (d, *J* = 2.5 Hz), 118.82 (d, *J* = 18.2 Hz), 115.99 (d, *J* = 7.6 Hz), 110.53 (d, *J* = 19.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -129.10 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{14}H_9FN_2OS$: 273.0492, found:273.0495.

N-(5-fluoroquinolin-8-yl)furan-2-carboxamide (2J). White solid, isolated yield: 59%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.59 (s, 1H), 8.95 (d, *J* = 3.8 Hz, 1H), 8.83 (dd, *J* = 8.6, 5.4 Hz, 1H), 8.47 (d, *J* = 8.4 Hz, 1H), 7.63 (s, 1H), 7.57 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.33-7.26 (m, 2H), 6.60 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.29 (s), 153.14 (d, *J* = 251.4 Hz), 149.24 (s), 148.27 (s), 144.53 (s), 138.90 (d, *J* = 3.2 Hz), 130.75 (d, *J* = 3.9 Hz), 129.83 (d, *J* = 3.8 Hz), 121.76 (d, *J* = 2.6 Hz), 118.87 (d, *J* = 18.2 Hz), 116.23 (d, *J* = 7.8 Hz), 115.15 (s), 112.46 (s), 110.51 (d, *J* = 19.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -128.74 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{14}H_9FN_2O_2$: 257.0721, found: 257.0726.

N-(5-fluoroquinolin-8-yl)pivalamide (2k). White solid, isolated yield: 48%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.07 (s, 1H), 8.87 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.75 (dd, *J* = 8.6, 5.5 Hz, 1H), 8.43 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.52 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.24 -7.13 (m, 1H), 1.42 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.10 (s), 152.71 (d, *J* = 250.5 Hz), 149.04 (s), 138.94 (d, *J* = 3.0 Hz), 131.22 (d, *J* = 4.1 Hz), 129.76 (d, *J* = 3.6 Hz), 121.59 (d, *J* = 2.5 Hz), 118.72 (d, *J* = 18.1 Hz), 115.65 (d, *J* = 7.6 Hz), 110.42 (d, *J* = 19.4 Hz), 40.27 (s), 27.73 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -129.81 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{14}H_{15}FN_2O$: 247.1241, found: 247.1245.

N-(5-fluoroquinolin-8-yl)acetamide (2l). White solid, isolated yield: 48%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.59 (s, 1H), 8.86 (d, *J* = 4.1 Hz, 1H), 8.72 (dd, *J* = 8.6, 5.5 Hz, 1H), 8.44 (d, *J* = 8.4 Hz, 1H), 7.53 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.21 (t, *J* = 9.2 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.61 (s), 152.80 (d, *J* = 250.8 Hz), 148.94 (s), 138.44 (d, *J* = 2.1 Hz), 131.04 (d, *J* = 4.1 Hz), 129.82 (d, *J* = 3.7 Hz), 121.64 (d, *J* = 2.5 Hz), 118.71 (d, *J* = 18.1 Hz), 115.94 (d, *J* = 7.6 Hz), 110.42 (d, *J* = 19.6 Hz), 25.03 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -129.40 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{11}H_9FN_2O$: 205.0772, found: 205.0774.

N-(5-fluoroquinolin-8-yl)butyramide (2m). White solid, isolated yield: 48%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.62 (s, 1H), 8.86 (d, *J* = 3.5 Hz, 1H), 8.74 (dd, *J* = 8.2, 5.8 Hz, 1H), 8.44 (d, *J* = 8.4 Hz, 1H), 7.53 (dd, *J* = 8.3, 4.1 Hz, 1H), 7.21 (t, *J* = 9.2 Hz, 1H), 2.53 (t, *J* = 7.5 Hz, 2H), 1.90-1.80 (m, 2H), 1.06 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.58 (s), 152.74 (d, *J* = 250.6 Hz), 148.93 (s), 138.54 (d, *J* = 2.9 Hz), 131.10 (d, *J* = 3.9 Hz), 129.78 (d, *J* = 3.6 Hz), 121.60 (d, *J* = 2.6 Hz), 118.72 (d, *J* = 18.0 Hz), 115.86 (d, *J* = 7.6 Hz), 110.43 (d, *J* = 19.6 Hz), 40.09 (s), 19.13 (s), 13.82 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -129.55 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{13}H_{13}FN_2O$: 233.1085, found: 233.1089.

N-(5-fluoroquinolin-8-yl)cyclohexanecarboxamide (2n). White solid, isolated yield: 43%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.76 (s, 1H), 8.88 (dd, *J* = 4.3, 1.6 Hz, 1H), 8.77 (dd, *J* = 8.7, 5.5 Hz, 1H), 8.47 (dd, *J* = 8.4, 1.5 Hz, 1H), 7.55 (dd, *J* = 8.4, 4.3 Hz, 1H), 7.26- 7.19 (m, 1H), 2.49 (m, 1H), 2.17-2.01 (m, 2H), 1.96-1.82 (m, 2H), 1.78-1.57 (m, 3H), 1.45-1.24 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.71 (s), 152.68 (d, *J* = 250.7 Hz), 148.89 (s), 138.61 (d, *J* = 2.6 Hz), 131.16 (d, *J* = 4.0 Hz), 129.81 (d, *J* = 3.7 Hz), 121.58 (d, *J* = 2.5 Hz), 118.71 (d, *J* = 18.0 Hz), 115.90 (d, *J* = 7.6 Hz), 110.45 (d, *J* = 19.5 Hz), 46.82 (s), 29.75 (s), 25.77 (s), 25.75 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -129.73

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(s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{16}H_{17}FN_2O$: 273.1398, found: 273.1395.

N-(5-fluoroquinolin-8-yl)-3-phenylpropanamide (2o). White solid, isolated yield: 58%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.59 (s, 1H), 8.82 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.74 (dd, *J* = 8.6, 5.4 Hz, 1H), 8.43 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.52 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.35-7.28 (m, 4H), 7.25-7.17 (m, 2H), 3.20-3.10 (t, *J* = 7.8 Hz, 2H), 2.93-2.83 (t, *J* = 7.8 Hz, 2H). ^{13}C NMR (100MHz, $CDCl_3$) δ: 170.57 (s), 152.82 (d, *J* = 250.9 Hz), 148.92 (s), 140.71 (s), 138.51 (d, *J* = 3.0 Hz), 130.96 (d, *J* = 4.1 Hz), 129.78 (d, *J* = 3.7 Hz), 128.57 (s), 128.39 (s), 126.27 (s), 121.63 (d, *J* = 2.5 Hz), 118.71 (d, *J* = 18.1 Hz), 115.96 (d, *J* = 7.7 Hz), 110.43 (d, *J* = 19.6 Hz), 39.66 (s), 31.48 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -129.34 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{18}H_{15}FN_2O$: 295.1241, found: 295.1238.

N-(5-fluoroquinolin-8-yl)-2-phenylacetamide (2p). White solid, isolated yield: 48%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.82 (d, *J* = 90.9 Hz, 1H), 8.88-8.60 (m, 2H), 8.26 (dd, *J* = 8.3, *J* =1.3 Hz, 1H), 7.51-7.39 (m, 4H), 7.33 (dd, *J* = 13.1, 6.1 Hz, 2H), 7.18 (t, *J* = 9.2 Hz, 1H), 3.88 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.47 (s), 153.06 (d, *J* = 251.1 Hz), 138.81 (s), 134.75 (s), 131.07 (d, *J* = 4.1 Hz), 129.84 (d, *J* = 3.6 Hz), 129.68 (s), 129.14 (s), 127.52 (s), 121.70 (d, *J* = 2.6 Hz), 118.80 (d, *J* = 18.1 Hz), 116.02 (d, *J* = 7.7 Hz), 110.50 (d, *J* = 19.6 Hz), 45.43 (s), 29.84 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -129.08 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{17}H_{13}FN_2O$: 281.1085, found: 281.1087.

N-(5-fluoroquinolin-8-yl)-2-(o-tolyl)acetamide (2q). White solid, isolated yield: 67%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.64 (s, 1H), 8.73-8.66 (m, 2H), 8.38 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.45 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.39-7.26 (m, 5H), 7.21-7.15 (t, *J* = 9.2 Hz, 1H), 3.89 (s, 2H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.21 (s), 152.90 (d, *J* = 250.9 Hz), 149.00 (s), 138.71 (d, *J* = 2.7 Hz), 137.25 (s), 133.09 (s), 130.91 (d, *J* = 4.0 Hz), 130.81 (s), 130.59 (s), 129.59 (d, *J* = 3.6 Hz), 127.83 (s), 126.64 (s), 121.54 (d, *J* = 2.6 Hz), 118.62 (d, *J* = 18.2 Hz), 115.75 (d, *J* = 7.8 Hz), 110.32 (d, *J* = 19.6 Hz), 43.21 (s), 19.71 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -129.20 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{18}H_{15}FN_2O$: 295.1241, found: 295.1237.

N-(5-fluoro-6-methylquinolin-8-yl)benzamide (2r). White solid, isolated yield: 49%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.52 (s, 1H), 8.83 (dd, *J* = 4.4, 2.9 Hz, 2H), 8.41 (dd, *J* = 8.4, 1.4 Hz, 1H), 8.07 (dd, *J* = 7.8, 1.4 Hz, 2H), 7.60-7.50 (m, 4H), 2.51 (d, *J* = 2.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.30 (s), 150.44 (d, *J* = 248.1 Hz), 148.09 (s), 137.79 (d, *J* = 2.8 Hz), 135.05 (s), 131.86 (s), 130.46 (d, *J* = 4.1 Hz), 129.31 (d, *J* = 4.2 Hz), 128.83 (s), 127.23 (s), 121.72 (d, *J* = 2.6 Hz), 118.82 (d, *J* = 18.2 Hz), 115.99 (d, *J* = 7.6 Hz), 110.53 (d, *J* = 19.7 Hz). 14.82 (d, *J* = 3.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -133.73 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{17}H_{13}FN_2O$: 281.1085, found: 281.1086.

N-(5-fluoro-6-methoxyquinolin-8-yl)benzamide (2s). White solid, isolated yield: 63%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.65 (s, 1H), 9.02 (d, *J* = 8.5 Hz, 1H), 8.77 (dd, *J* = 4.2, 1.4 Hz, 1H), 8.43 (dd, *J* = 8.5, 1.4 Hz, 1H), 8.10 (d, *J* = 7.0 Hz, 2H), 7.63-7.49 (m, 4H), 4.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.45 (s), 146.67 (s), 143.56 (d, *J* = 9.2 Hz), 140.62 (d, *J* = 247.4 Hz), 134.76 (s), 133.48 (d, *J* = 35.8 Hz), 132.04 (s), 131.52 (s), 130.16 (s), 128.68 (dd, *J* = 22.7, 19.7 Hz), 127.23 (s), 122.11 (s), 119.41 (d, *J* = 15.1 Hz), 106.32 (s), 57.29 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -153.44 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{17}H_{13}FN_2O_2$: 297.1034, found: 297.1036.

N-(5-fluoro-2-methylquinolin-8-yl)benzamide (2t). White solid, isolated yield: 48%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.60 (s, 1H), 8.85 (dd, *J* = 8.6, 5.5 Hz, 1H), 8.33 (d, *J* = 8.5 Hz, 1H), 8.07 (d, *J* = 6.9 Hz, 2H), 7.63-7.54 (m, 3H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.19 (t, *J* = 9.2 Hz, 1H), 2.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.17 (s), 158.32 (s), 153.28 (d, *J* = 250.7 Hz), 138.52 (s), 135.19 (s), 131.79 (s), 130.46 (d, *J* = 4.2 Hz), 129.88 (d, *J* = 3.4 Hz), 128.83 (s), 127.19 (s), 122.55 (d, *J* = 2.4 Hz), 116.87 (d, *J* = 18.2 Hz), 116.03 (d, *J* = 7.8 Hz), 109.52 (d, *J* = 19.7 Hz), 25.50 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -129.19 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{17}H_{13}FN_2O$: 281.1085, found: 281.1088.

N-(4-chloro-5-fluoroquinolin-8-yl)benzamide (2u). White solid, isolated yield: 49%. ^{1}H NMR (400 MHz, $CDCl_3$) δ： 10.59 (s, 1H), 9.17-8.93 (m, 1H), 8.73 (dd, *J* = 6.5, 4.9 Hz, 1H), 8.07 (dd, *J* = 6.6, 4.9 Hz, 2H), 7.66-7.55 (m, 4H), 7.37 (dd, *J* = 12.1, 8.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.24 (s), 158.39 (s), 153.34 (d, *J* = 251.4 Hz), 138.59 (s), 135.26 (s), 131.86 (s), 130.53 (d, *J* = 4.8 Hz), 129.94 (d, *J* = 3.9 Hz), 128.89 (s), 127.26 (s), 122.61 (d, *J* = 3.1 Hz), 116.93 (d, *J* = 17.9 Hz), 116.10 (d, *J* = 7.7 Hz), 109.59 (d, *J* = 18.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -119.89 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{16}H_{10}ClFN_2O$: 301.0538, found: 301.0538.

4-methyl-N-(5-fluoroquinolin-8-yl)benzenesulfonamide (2v). White solid, isolated yield: 23%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.06 (d, *J* = 87.3 Hz, 1H), 8.80 (d, *J* = 3.9, 1.6 Hz, 1H), 8.51-8.33 (m, 1H), 7.81-7.71 (m, 3H), 7.55-7.46 (m, 1H), 7.20-7.11 (m, 3H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.53 (d, *J* = 251.7 Hz), 149.37 (d, *J* = 39.5 Hz), 143.88 (d, *J* = 16.7 Hz), 139.01 (s), 136.18 (s), 133.25 (d, *J* = 22.4 Hz), 129.66 (dd, *J* = 21.7, 7.3 Hz), 127.23 (s), 126.73 (s), 122.67 (s), 121.96 (d, *J* = 2.7 Hz), 115.16 (d, *J* = 8.2 Hz), 110.18 (d, *J* = 20.4 Hz), 21.46 (s). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -128.34 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{16}H_{13}FN_2O_2S$: 317.0755, found: 317.0758.

N-(5-fluoroquinolin-8-yl)benzenesulfonamide (2w). White solid, isolated yield: 28%. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.19 (s, 1H), 8.79 (dd, *J* = 6.7, 2.7 Hz, 1H), 8.49-8.33 (m, 1H), 7.88 (dd, *J* = 15.2, 7.4 Hz, 2H), 7.83-7.74 (m, 1H), 7.54-7.32 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.69 (d, *J* = 252.5 Hz), 149.43 (d, *J* = 39.7 Hz), 139.08 (d, *J* = 9.9 Hz), 133.10 (dd, *J* = 28.0, 17.8 Hz), 129.81 (d, *J* = 3.6 Hz), 128.93 (d, *J* = 11.9 Hz), 127.17 (s), 126.72 (s), 126.23 (s), 125.26 (s), 122.37 (d, *J* = 70.5 Hz), 116.04-114.25 (m), 110.20 (d, *J* = 20.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -127.95 (s). HRMS (ESI): m/z: calcd for $[M+H]^+$ $C_{15}H_{11}FN_2O_2S$: 303.0598, found: 303.0600.

Conflicts of interest

There are no conflicts to declare.

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