JOC The Journal of Organic Chemistry

Article

Visible Light Promoted Photocatalytic C-5 Carboxylation of 8-Amino Quinoline Amides and Sulfonamides via a Single Electron Transfer Pathway

Chiranjit Sen, Tapan Sahoo, Harshvardhan Singh, Eringathodi Suresh, and Subhash Chandra Ghosh

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b00942 • Publication Date (Web): 16 Jul 2019

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Visible Light Promoted Photocatalytic C-5 Carboxylation of 8-Amino Quinoline Amides and Sulfonamides via a Single Electron Transfer Pathway

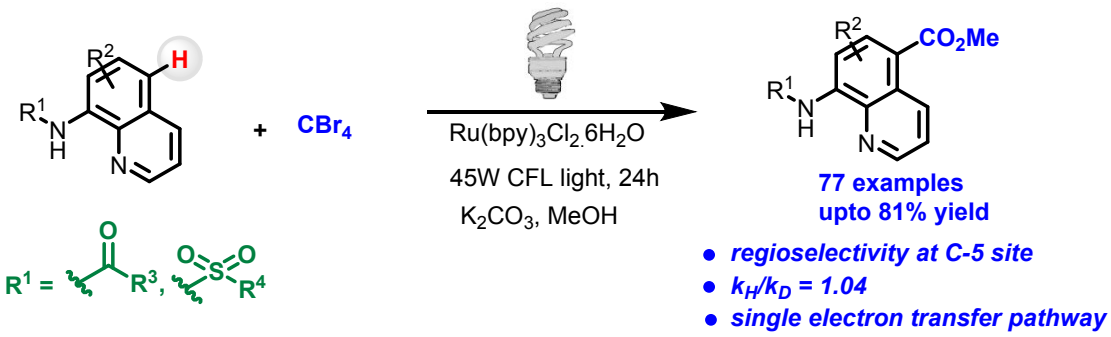
Chiranjit Sen,[a,b] Tapan Sahoo, [a,b] Harshvardhan Singh, [a,b] Eringathodi Suresh, [b,c] and Subhash Chandra Ghosh*, [a,b]

[a] Natural Products and Green Chemistry Division,

[b] Academy of Scientific and Innovative Research (AcSIR)

[c] Analytical and Environmental Science Division and Centralized Instrument Facility

Central Salt and Marine Chemicals Research Institute (CSIR-CSMCRI), G.B. Marg, Bhavnagar-364002, Gujarat, India.

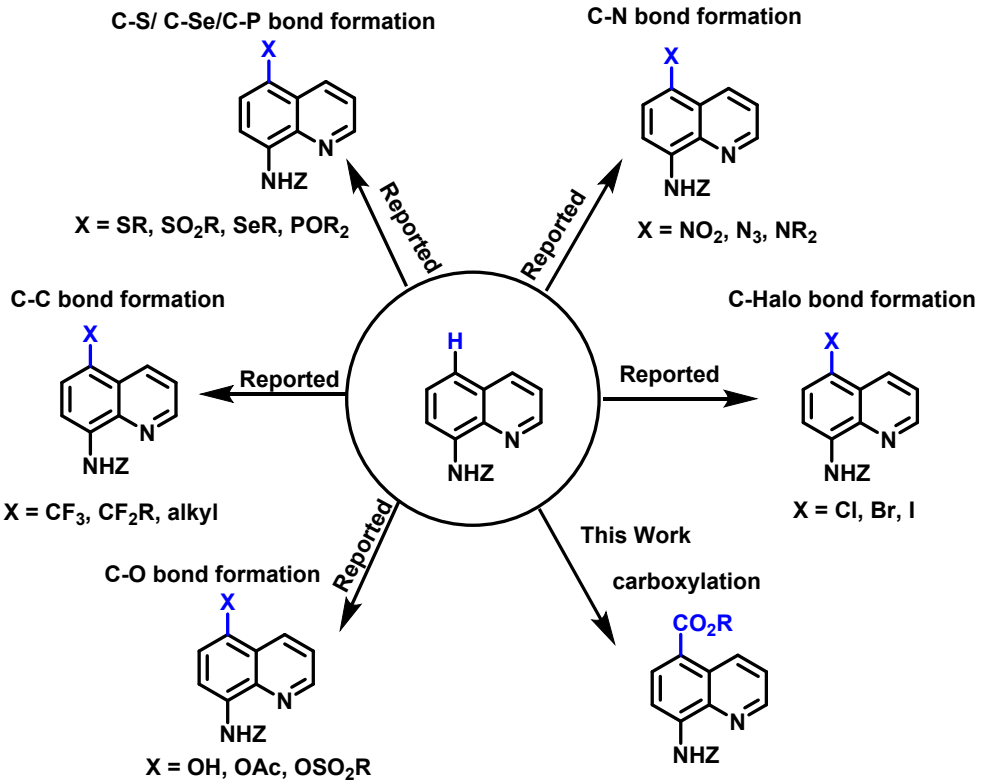


ABSTRACT: An efficient photocatalytic method was developed for the remote C5-H bond carboxylation of 8-amino quinoline amide and sulphonamide derivatives. This methodology uses in situ generated •CBr_3 radical as carboxylation agent with alcohol and further extended to a variety of arenes and heteroarenes to synthesize the desired carboxylated product in moderate to good yields. The reaction proceeds through a single electron transfer (SET)

pathway was established by a control experiment and identifying BHT trapped aryl radical cation intermediate in HRMS.

INTRODUCTION

Quinoline and its derivatives are widely considered as a pivotal structural motif of a diverse array of natural products, pharmaceuticals, and functional materials.[1] Several antimalarial drugs like primaquine, pamaquine, bulaquine, and tafenoquine contain an 8-aminoquinoline scaffold.[2] Commercial drugs like imiquimod, anticancer agents, chloroquine an antimalarial drug, and levofloxacin an antibiotic, contains an amino group and a carboxylic group in the quinoline moiety.[3] Also, 8-sulfonamidoquinoline scaffolds are widely used for the selective turn-on Zn(II) fluorescent sensors.[4] Moreover, quinoline carboxylates are widely recognized as a pivotal structural component and play a predominant role as precursors for a variety of biologically active molecules.[5] Therefore, considerable efforts have been made for the functionalization of quinoline derivatives.[6] Among them, remote C-5 functionalization of 8-aminoquinoline is one of the challenging and interesting topics for the chemist[7-](Scheme 1). Several reports have been described for halogenation,[8] sulfonylation,[9] nitration,[10] azidation,[11] acyloxylation,[12] phosphonation,[13] thiolation,[14] thioesterification,[15] amination,[16] alkylation,[17] difluoroalkylation,[18] hydroxylation[19] trifluoromethylation[20] and selenylation. [21] However, despite the considerable advances no example for C-5 carboxylation are reported in the literature. Therefore, the development of highly efficient methods for direct regioselective carboxylation of quinoline scaffold under the mild and sustainable condition is highly desirable for organic synthesis. In this context, visible light mediated photocatalysis can run under mild conditions and proceed mostly *via* a radical or radical ion intermediate.[22] The simple and efficient generation of such reactive intermediates by visible light and applied them in organic transformations received considerable attention. In this regard, carbon tetra bromide used as a masked carboxylating reagent, initial incorporation of •CBr_3 radical to the aromatic nuclei,



Scheme 1: C-5 functionalization of 8-amino quinoline derivatives

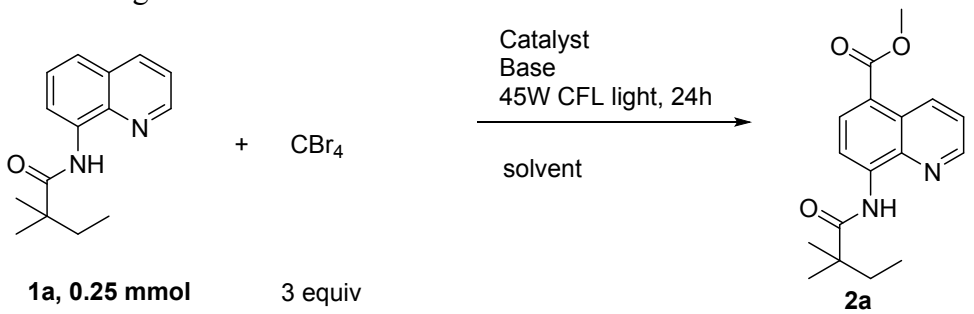
followed by alcoholysis to deliver the desired carboxylate. Mukminov and co-workers[23] first demonstrated the iron-catalyzed carboxylation of the only benzofuran, at 100-140 °C. Greaney and co-workers[24] reported the ruthenium (III) chloride catalyzed *meta*-carboxylation of arenes containing azine type directing group at 85°C, with a moderate yield (44-63%). Very recently we have also reported the copper-catalyzed C-4 carboxylation of 1-naphthylamide derivatives in moderate to good yields.[25] Tang and co-workers[26] reported carboxylation of styrene using cooperative Eosin -Y as photocatalyst and cobalt iodide with CBr_4 and DMSO. Photocatalytic carboxylation of indoles reported by Bandini and co-workers using $[Ru(bpy)_3](PF_6)_2$ as the photocatalyst, iPr_2NH as a base, in 0.05 M methanol, under irradiation with 7 W blue LED light.[27] It is noteworthy that, to achieve the regioselectivity, C(3) substitution of indoles are essential to furnishing desired indole C(2) carboxylate, without any substituents, indole-3-carboxylate was obtained in moderate yield. As part of our ongoing research on regioselective quinoline C-H functionalization,[28] herein, we report the regioselective C-5 carboxylation of 8-

aminoquinoline derivatives with CBr_4 and methanol and other alcohols using economic $Ru(bpy)_3Cl_2.6H_2O$ as a suitable photocatalyst at room temperature under irradiation with visible light (45 W CFL lamp). This mild and practical methodology broadly applicable for the carboxylation of a wide range of 8-amino quinoline amide and sulfonamide derivatives in good yields.

RESULTS AND DISCUSSION

We began our study by choosing 2,2-dimethyl-N-(quinolin-8- yl)butanamide (**1a**) as a model substrate to identify the catalytic system for carboxylation with CBr_4 and methanol as solvent under irradiation with 45W CFL lamp in the presence of a suitable photocatalyst. Initially, $Ru(bpy)_3(PF_6)_2$ was chosen as the photocatalyst, in the presence of K_2CO_3 as a base, as expected the reaction goes well, and 67% of desired carboxylated product was isolated (table 1, entry 1). Altering the photocatalyst's counter anion to chloride i.e., more economic $Ru(bpy)_3Cl_2.6H_2O$ was tested and to our delight improvement in the yield (entry 2, 72%) was observed. Replacement of Ru(II) photocatalyst to the other organo photocatalyst like Eosin-Y, Rose Bengal and 9-Mesityl-10-methylacridinium perchlorate were unsuccessful (entries 3-5).

Table 1: Screening of reaction conditions[a]



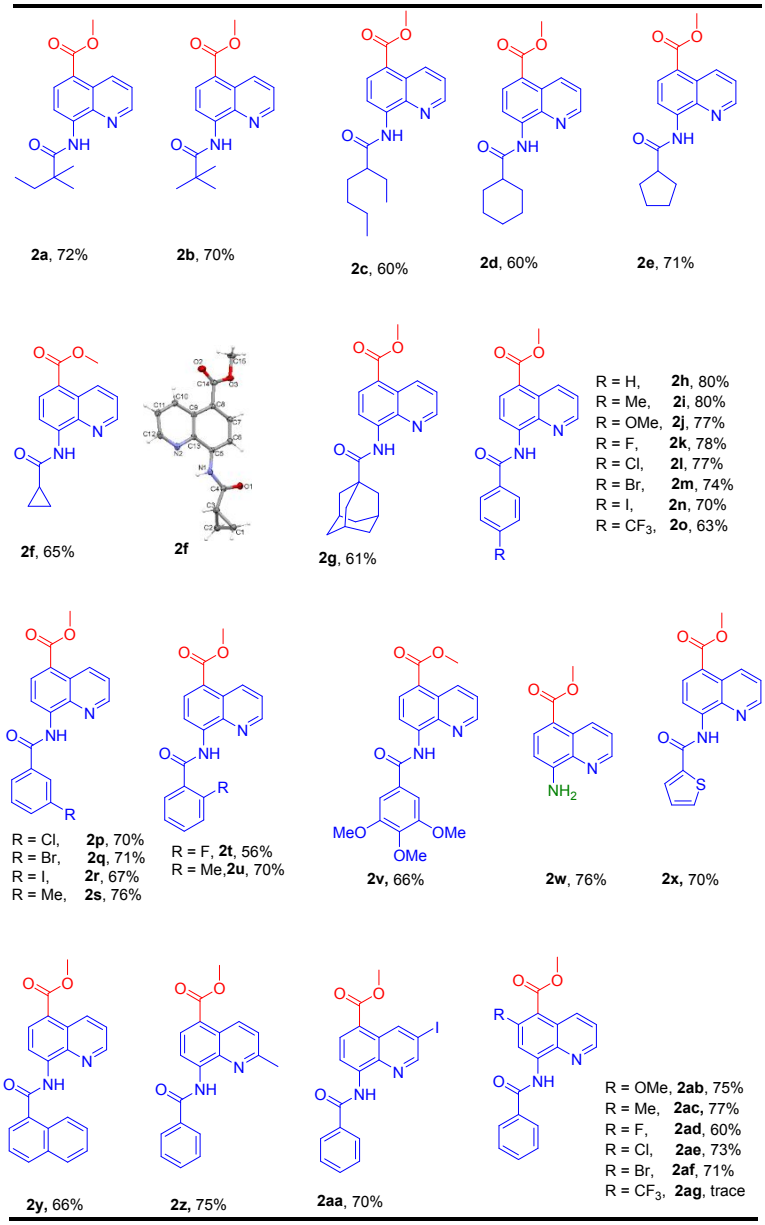
Entry	Photocatalyst	Base	Solvent	Yield %
1	$Ru(bpy)_3(PF_6)_2$	K_2CO_3	MeOH	67
2	$Ru(bpy)_3Cl_2.6H_2O$	K_2CO_3	MeOH	72
3	Eosin-Y	K_2CO_3	MeOH	NR
4	Rose Bengal	K_2CO_3	MeOH	NR

5	9-Mesityl-10-methylacridinium Perchlorate	K_2CO_3	MeOH	NR
6	$Ru(bpy)_3Cl_2.6H_2O$	Na_2CO_3	MeOH	60
7	$Ru(bpy)_3Cl_2.6H_2O$	NaOAc	MeOH	65
8	$Ru(bpy)_3Cl_2.6H_2O$	$NaHCO_3$	MeOH	35
9	$Ru(bpy)_3Cl_2.6H_2O$	K_3PO_4	MeOH	66
10	$Ru(bpy)_3Cl_2.6H_2O$	iPr_2NH	MeOH	33
11	$Ru(bpy)_3Cl_2.6H_2O$	DABCO	MeOH	24
12	$Ru(bpy)_3Cl_2.6H_2O$	Et_3N	MeOH	25
13	$Ru(bpy)_3Cl_2.6H_2O$	DBU	MeOH	30
14	$Ru(bpy)_3Cl_2.6H_2O$	K_2CO_3	MeOH	30[b]
15	$Ru(bpy)_3Cl_2.6H_2O$	K_2CO_3	MeOH	NR[c]
16	$Ru(bpy)_3Cl_2.6H_2O$		MeOH	12
17	$Ru(bpy)_3Cl_2.6H_2O$	K_2CO_3	MeOH	18[d]

[a] under argon atmosphere, [b] 7 W blue LED; [c] without light, [d] under oxygen atmosphere, NR: no reaction

Further, we optimized the reaction by varying the base, inorganic bases like Na_2CO_3, $NaHCO_3$, NaOAc and K_3PO_4 did not improve the yield (entries 6-9), while organic bases such as iPr_2NH, DABCO, Et_3N, DBU showed diminished reactivity (entries 10-13). Subsequently, various mix solvent was screened (SI, Table S2), in methanol acetonitrile (1: 4) mixed solvent similar yield (69 %) was achieved. Altering of the light source to 7W blue LED, was ineffective only 30% of carboxylated was isolated, while, in the absence of light no reaction was observed (entries 14-15).

Table 2: Substrate scope for 8-amido quinoline moiety



Unless otherwise mentioned reactions were carried out in a sealed tube in the presence 1 (0.25 mmol), CBr_4 (0.75 mmol), $Ru(bpy)_3Cl_2.6H_2O$ (2 mol%), K_2CO_3 (0.5 mmol) and MeOH (2 mL) under visible light (45 W CFL lamp) for 24h at room temperature.

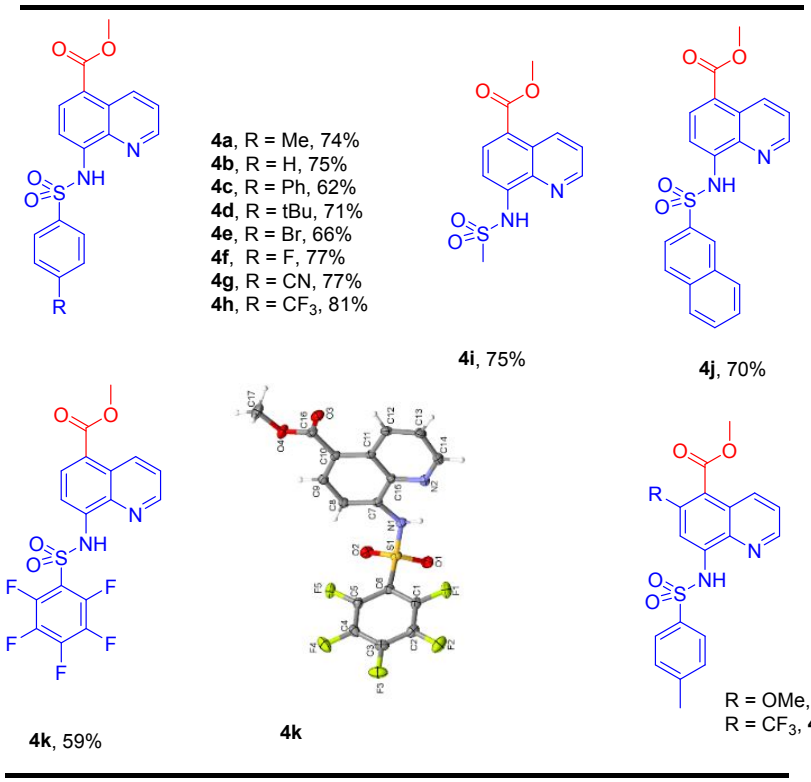
Then the reaction was carried out in the absence of K_2CO_3, afforded12% of the desired product, which indicates that the base is essential for this reaction (entry 16). Performing the reaction

under oxygen atmosphere only 18% of the carboxylated product was obtained (entry 17), indicates that oxygen restrains the reaction thus inert atmosphere is desired.

With the optimization condition in hand, we next explore the substrate scope for the carboxylation of various 8-aminoquinoline amides as shown in **Table 2**. The carboxylation proceeds well with 8-aminoquinoline alkyl amides (entries **2a-2g**) produced the corresponding carboxylated product in 60-72% yield. Regardless of acyclic (**2a-2c**), or cyclic (**2d-2g**), and even sterically hindered like adamantyl carboxamides (**2g**, 61%) showed similar reactivity. In addition, the structure of the **2f** was undoubtedly confirmed by the single crystal X-ray analysis (CCDC- 1888178, see SI for details). Moreover, 8- aminoquinoline aromatic amides with electron donating (2i-2j, 2s, 2u-v), neutral (2h, 80%) or electron withdrawing groups (2k-r, 2t) at the *para*, *meta,* and *ortho*- position works similarly to give C5-carboxylated product. Interestingly, NH-Boc protected amine furnished the C5-carboxylated product but with the deprotection of the Boc group (2w, 76%). Replacement of the aryl with thienyl or naphthyl amides exerted comparable yields (2x, 2y). Next, the substitution on the quinoline moiety was explored, substitution with methyl at C-2 and with iodo at C-3 delivered C-5 carboxylation product in high yields (**2z**, 75%, 2aa, 70%). Moreover, substitution at the C-6 position, sterically hindered for C-5 carboxylation, with variety of electron donating (-OMe, 2ab; -Me, 2ac) and withdrawing functional group (halo) does not have any effect on reactivity and regioselectivity for carboxylation. While, in the presence of a trifluoromethyl group, a strong electron withdrawing group inhibits the reaction, an only a trace amount of desired product was observed (2ag, trace). It was also reported that the presence of strong electron withdrawing group (like nitro and cyano) in the quinoline moiety inhibits the halogenation[8b] and thiocyanation [21b] reaction which proceeds through the SET mechanism, thus electron rich arenes work better in this system. Encouraged by these results for carboxylation of 8-aminoquinoline alkyl/aryl amides with CBr_4/MeOH, we turned our attention for the

carboxylation of other important sulphonamide derivatives, results are summarized in **Table 3**. When N-(quinolin-8-yl)toluenesulfonamide was used as a substrate with CBr_4/MeOH, C5-carboxylated product was obtained in very good yield

Table 3: Substrate scope for 8-amino quinoline sulfonamides

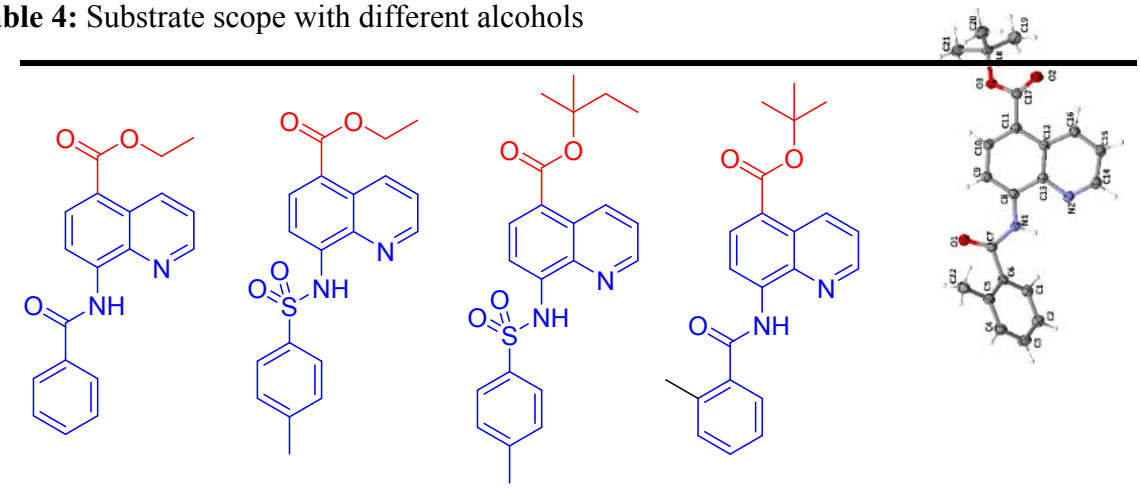


Reaction conditions: substrate 3 (0.25 mmol), CBr_4 (0.75 mmol), $Ru(bpy)_3Cl_2.6H_2O$ (2 mol%), K_2CO_3 (0.5 mmol) and MeOH (2 mL) under visible light (45 W CFL lamp) for 24h at room temp.

(Table 3, **4a**, 74%). N-(quinolin-8-yl)benzenesulfonamide also provided similar yields of the carboxylated product (**4b**, 74%). Several *para*-substituted benzenesulfonamides including electron-donating (**4c, 4d**), and electron-withdrawing group (**4e-4h**) were tested and found compatible for our developed process and delivered carboxylated product in good to excellent yields (up to 81%). Moreover, the alkyl sulfonamides (**4i**, 75%) works well under optimal conditions. In addition, the reaction with naphthalene sulphonamide and pentafluorobenzene sulphonamides afforded exclusively C5-carboxylated product in good yields (**4j,** 70% and **4k**,

59%) respectively, the structure of **4k** was further confirmed by X-ray crystallography (CCDC-1888239). It is important to note that, one of the most efficient membrane-permeable fluorescent probes for zinc (II), 6-methoxy-8-p-toluenesulfonamido-quinoline (TSQ, **3l**),[29] is carboxylated with high yield and excellent regioselectivity (**4l**, 79%), and could be applicable for further sensing studies. As observed in the quinoline amide case, similarly in the presence of strong electron withdrawing group (-CF_3) in the quinoline moiety, carboxylation completely inhibited (**4m**). To further demonstrate the potential application of this methodology, we have performed the carboxylation with different alcohols as demonstrated in **Table 4**. To our delight, when ethanol was used as solvent instead of methanol compound **1a** and **3h** were carboxylated efficiently and afforded ethyl carboxylate products in similar yields (**5a**, 61%, and **5b**, 65%). However, when *tert*-amyl alcohol and *tert*-butanol were used, lower yields (5c, 25% and 5d, 25%) obtained in the carboxylation might be due to the steric factor. In addition, the structure of the *tert*-butyl carboxylated product (5d) was confirmed by X-ray crystallography (CCDC-1888179).

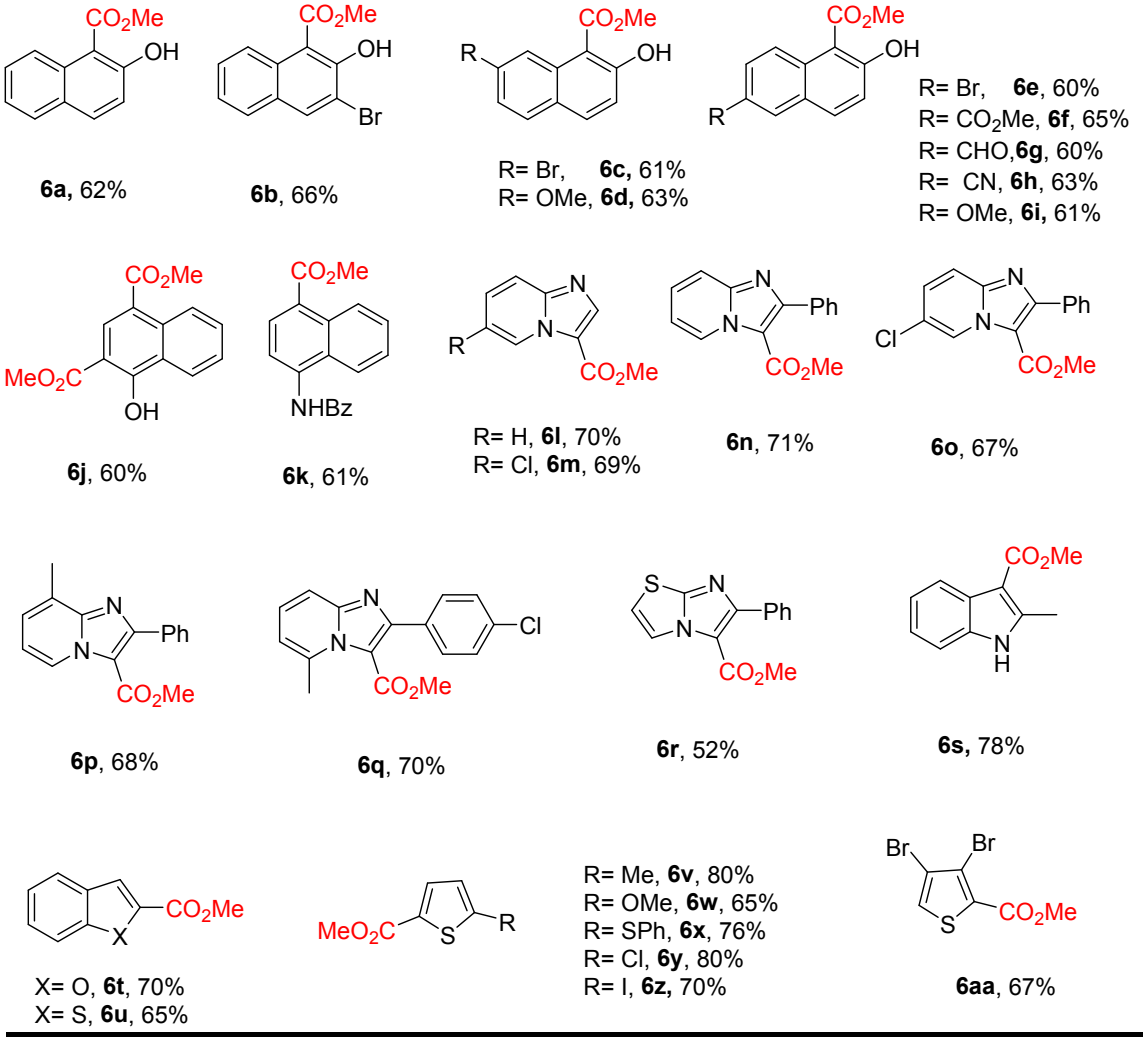
Table 4: Substrate scope with different alcohols



Reaction conditions: Substrate (0.25 mmol) CBr_4 (0.75 mmol), $Ru(bpy)_3Cl_2.6H_2O$ (2 mol%), K_2CO_3 (0.5 mmol), alcohol (250 µL), acetonitrile (1.5 mL) under visible light (45 W CFL lamp) for 24h at room temperature.

Next, we further explored the possibility of extending the reaction to the other arenes and hetarenes. To our delight, the carboxylation worked well with a variety of aromatic and heteroaromatic compounds, providing carboxylated products in good yields (Table 5). The carboxylation proceeds well with β-naphthol (6a, 62%), and several electron donating and withdrawing group substituted β –naphthol (**6b-6i**). It is noteworthy that functional groups like

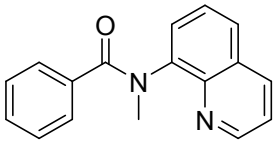
Table 5: Substrate scope with different arenes and hetarenes



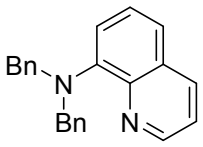
Reaction conditions: Substrate (0.25 mmol) CBr_4 (0.75 mmol), $Ru(bpy)_3Cl_2.6H_2O$ (2 mol%), K_2CO_3 (0.5 mmol), and methanol (2 mL) under visible light (45 W CFL lamp) for 24h at room temperature.

hydroxyl, aldehyde, cyano, and bromo are well tolerated in this transformation. When α-naphthol was used, di carboxylated product was obtained in good yield (6j, 60%). However, 1-benzamidonaphthalene afforded C4-carboxylated product in good yield (6k, 61%). A series of other heteroaromatic compounds including imidazo[1,2-a]pyridine, imidazo[2,1-b]thiazole, indole, benzofuran, benzothiophene and, thiophenes were all compatible with this transformation and afforded very good yields (**6k-6aa,** up to 80%). The regioselectivity of the hetarenes due to the higher reactivity of that position of the corresponding radical cation species and CBr_3 radical would preferentially react at that position to get the desired product.[26, 30] Furthermore, the selective removal of the amide group (2h) with HCl to synthesize corresponding free amine substrates in excellent yield (2w, 98%), showcased the synthetic utility of our method.

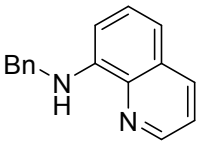
A series of experiments were carried out under the standard reaction condition with several designed substrates (8a-h, Figure 1). When, N-methyl-N-(quinolin-8-yl)benzamide (8a), N, N-dibenzylquinolin-8-amine (8b), N-benzylquinolin-8-amine (8c) and 8-aminoquinolin (8d) were examined under standard condition, no carboxylation product was obtained. These results indicate that the presence of secondary amide or sulphonamide is crucial, they help to stabilize the intermediate radical/ radical cation species and played a key role in the regioselective carboxylation.



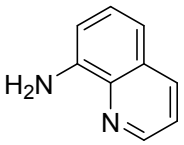
8a



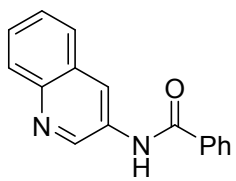
8b



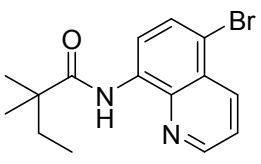
8c



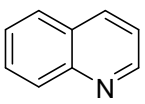
8d



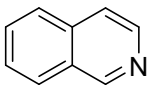
8e



8f



8g



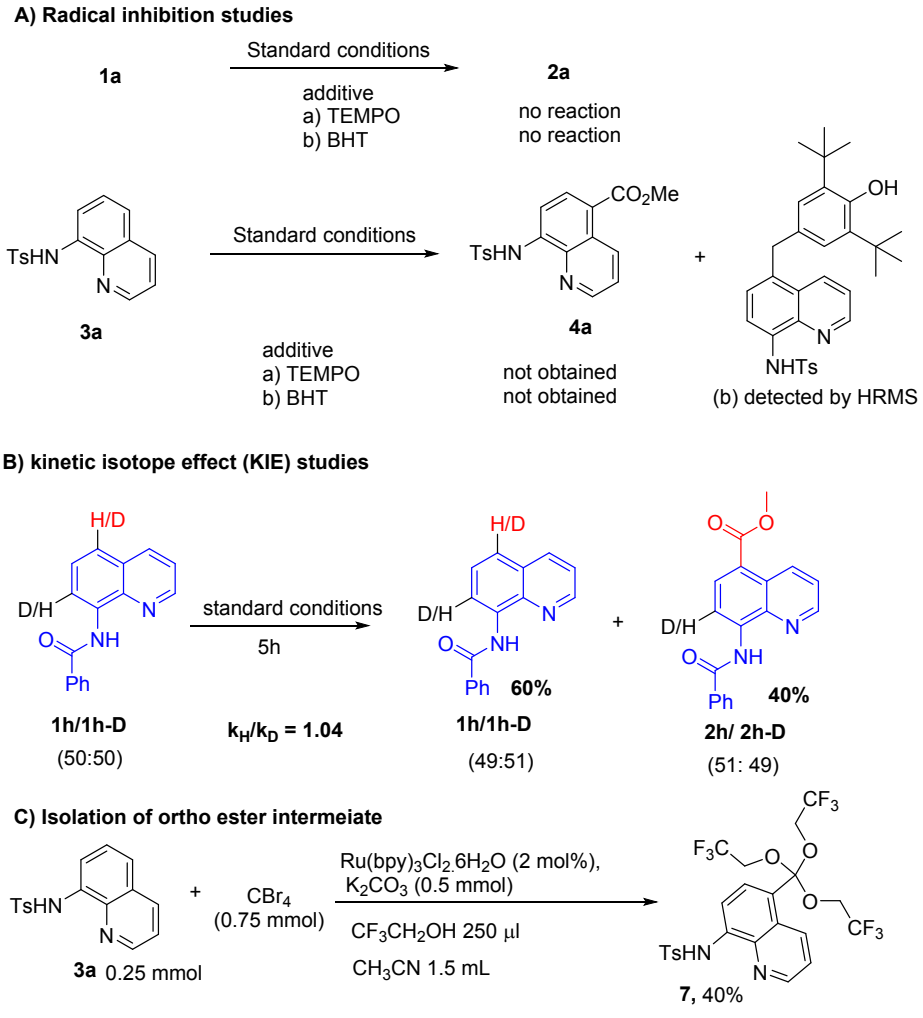
8h

Figure 1: Unreactive substrates

Also, when C-3 amido quinoline (8e) was used no carboxylated product was observed, even when C-5 position is blocked (8f) no carboxylation takes place in any other position. Moreover, simple quinoline or isoquinoline are also found unreactive.

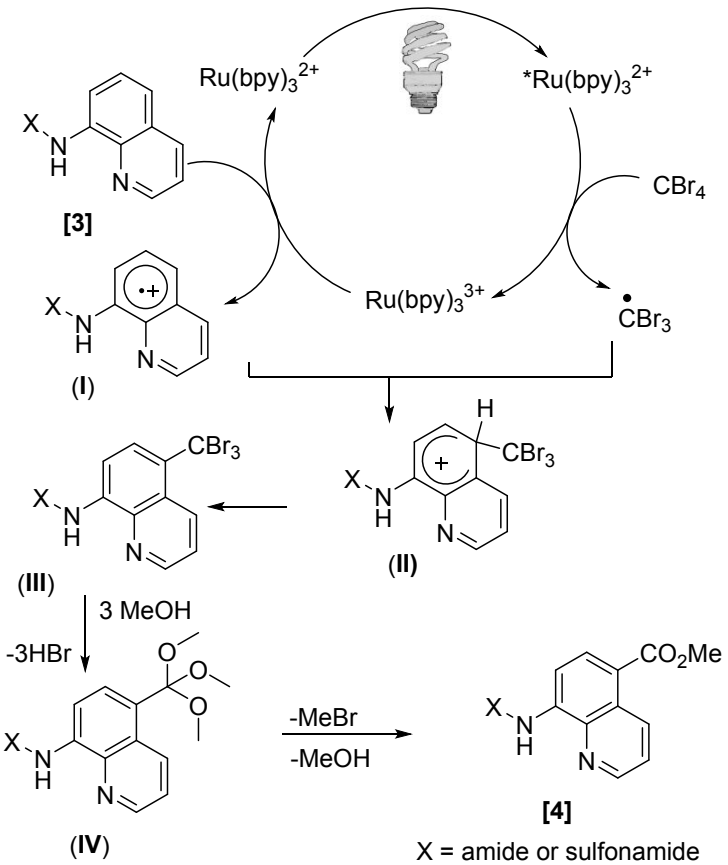
To gain insight into the reaction mechanism, a series of the experiment were carried out. Upon addition of the radical scavenger, TEMPO or BHT the reaction was completely inhibited for both amide (1a) and sulfonamide (3a) substrates (Scheme 2A), we have also identified the BHT trapped sulfonamide compound in HRMS. These results consistent with the literature report in the similar system, [8a, 16a, 16c-d] indicates that the reaction might undergo through a single electron transfer (SET) pathway, and generates aryl radical at C5-position quinoline moiety.

Scheme 2: Control experiments for the mechanistic study



Next, kinetic isotope effect (KIE) for the reaction was determined by the intermolecular competitive reaction of two isotopomeric substrates (**1h** and **1h-D, Scheme 2-B**), and k_H/k_D ratio = 1.04 was obtained. Which indicates that C-H bond cleavage is not involved in the rate determining step.[8a,21b] Next, we used 2,2,2 trifluoroethanol instead of methanol as alcohol source, to our surprise we have found the orthoester (Scheme 2C, 7), which indicates that all three Br in CBr_3 (III) was replaced by an alkoxy group, then converted to the desired ester. Then, the role of light was investigated, the reaction completely stops at dark and restarted once again when the light was on. Also, oxidation potential was measured for compound 1h and 3a and found 1.30 V and 0.78 V vs Fc^+/Fc respectively. (see supporting information for details). On the basis of the above experimental observations and previous literature report [7, 8a, 16a, 16c-d, 21, 22a, 24-26,] a tentative mechanism was proposed in **scheme 3** using N-(quinolin-8-yl)arylsulfonamide (3) as an

Scheme 3: Proposed mechanism



example of this photocatalytic carboxylation. $Ru(bpy)_3^{2+}$ upon irradiation with visible light undergoes lowest energy triplet excited state $*Ru(bpy)_3^{2+}$. This photo-excited species reduced CBr_4 to generate $\bullet CBr_3$ radical species and KBr, and catalyst self-oxidized to intermediate $Ru(bpy)_3^{3+}$ Ru^{III} species. Next, a single electron transfer (SET) process occurred between Ru^{III} and the 8-aminoquinoline moiety and provided quinoline radical cation complex (I) [7, 21] and regenerates the photocatalyst $Ru(bpy)_3^{2+}$, the whole process proceed *via* oxidative quenching cycle of photoexcited state $*Ru(bpy)_3^{2+}$ species.[8a] Next, the tribromomethyl radical may then react with the aromatic radical cation species (I) at the C-5 position of the quinoline moiety, produced an aryl cation (II). Rearomatization of the intermediate (II) *via* deprotonation yielded (III) and followed by methanolysis provided orthoester (IV), which upon hydrolyzed under acidic condition and provided the desired ester (4).

CONCLUSION

In summary, we have developed a visible light promoted remote C-5 carboxylation of 8-amino quinoline amides or sulfonamides *via* direct C-H functionalization using CBr_4 and methanol or other alcohol. This carboxylation method run under mild conditions (RT, 45W white LED) with wide substrate scope and well functional group tolerance. The applicability of the method further showcased by the functionalization of TSQ the most efficient membrane-permeable fluorescent probes for zinc (II) and selective deprotection of amide group to synthesis 8-aminoquinoline-5-carboxylate. Control experiments, with trapping of radical intermediate, reveals that reaction proceeds through a single electron transfer pathway.

EXPERIMENTAL SECTION

General Information:

All reactions were carried out in oven-dried glassware under standard reaction conditions. All chemicals were purchased from TCI and catalysts were purchased from Sigma Aldrich and used without further purifications. All solvents were dried by the standard reported procedures and stored over activated molecular sieves. Purification of compounds done by flash chromatography (200-400 mesh silica gel) was used by gradient elution of ethyl acetate (EA) and n-hexane mixture. ^{1}H/ ^{13}C NMR was recorded on 600/151 MHz NMR spectrometer in $CDCl_3$ unless otherwise mentioned, using TMS as the reference in ppm. ^{19}F-NMR spectra were recorded at 600 MHz. The following abbreviations were used to describe peak splitting patterns when appropriate, s = singlet, Broad singlet (br.s), d = doublet, t = triplet, m = multiplet, dd = doublet of doublet, ddd= doublet of doublet of doublet, td = triplet of doublet, dt = doublet of triplet, qd = quartet of doublet, m= multiplet, Coupling constants *J*, were reported in hertz unit (Hz). Mass spectral data for the new compound were obtained using electro spray ionization time-of-flight (ESI-TOF) mode on the mass spectrometer.

Experimental procedure for carboxylation reaction:

Procedure: A mixture of 2,2-dimethyl-N-(quinolin-8-yl)butanamide **1a** (61 mg, 0.25 mmol, 1 equiv.,), carbon tetrabromide 0.75 mmol (3 equiv., 249 mg), catalyst $Ru(bpy)_3Cl_2.6H_2O$ 2 mol% (3.8 mg) and K_2CO_3 0.5 mmol (2equiv., 69 mg) were taken in a reaction tube under nitrogen atmosphere, then 2mL methanol was added over it. The mixture was stirred and irradiated using a 45W CFL lamp (Havells 45W, 2800 lumen, Cool Daylight 6500K, without any filter) at a distance of about 5 cm for 24h. After completion of the reaction, the reaction mixture was poured into H_2O (10 mL) and extracted with DCM (3×10 mL). The combined organic layer was washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed

under reduced pressure, and the crude reaction mixture was purified by flash chromatography using n-hexane /ethyl acetate (95/5) as an eluent to isolate the desired carboxylated product. All other C-5 carboxylated products were purified by flash chromatography using n-hexane /ethyl acetate (5-10%) as an eluent and prepared following this general procedure.

Removal of the directing group:

Methyl 8-benzamidoquinoline-5-carboxylate (**2h**, 0.25 mmol, 76.5 mg) was taken in a 10 mL reaction tube with 2mL ethanol as solvent. Conc. HCl (0.5 mL) was slowly added over it at room temperature. Then, the reaction mixture was refluxed for 12h and reaction progress was monitored by TLC. Upon completion of the reaction, the solvent was removed under reduced pressure. 10 mL of saturated $NaHCO_3$ solution was added for quenching and extracted with DCM (3 x 25 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the desired product was purified (**2w**, 98%, 43 mg) by flash chromatography using silica gel and EtOAc/n-hexane (10%) as an eluent.

Control experiment in the presence of radical inhibitor TEMPO and BHT

A mixture of 2,2-dimethyl-N-(quinolin-8-yl)butanamide **1a** 0.25 mmol (1 equiv., 61 mg), carbon tetrabromide 0.75 mmol (3 equiv., 249 mg), catalyst $Ru(bpy)_3Cl_2.6H_2O$ 2 mol% (3.8 mg) , base K_2CO_3 0.5 mmol (2equiv., 69 mg) and radical inhibitor TEMPO or BHT were taken in a reaction tube under nitrogen atmosphere at room temperature. Then methanol (2mL) was added and stirred for 24h using a 45W CFL lamp as a light source (Havells 45W, 2800 lumen, Cool Daylight 6500K) at a distance of about 5 cm. Reaction progress was by monitored by TLC. No product was obtained even after 24h, and the reaction is completely inhibited by the radical scavenger.

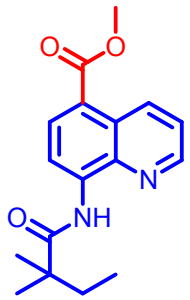
Isolation and detection of intermediate:

Procedure: A mixture of 4-methyl-N-(quinolin-8-yl)benzenesulfonamide (3a), (74.5 mg, 0.25 mmol, 1 equiv.,), carbon tetrabromide 0.75 mmol (3 equiv., 249 mg), catalyst $Ru(bpy)_3Cl_2.6H_2O$ 2 mol% (3.8 mg) and K_2CO_3 0.5 mmol (2equiv., 69 mg) were taken in a reaction tube under nitrogen atmosphere, then 250µl 2,2,2-trifluoroethanol and 1.5 mL acetonitrile was added over it. The mixture was stirred and irradiated using a 45W CFL light source at a distance of about 5 cm for 24h. After completion of the reaction, the reaction mixture was poured into H_2O (15 mL) and extracted with DCM (3×20 mL). The combined organic layer was washed with brine (15 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude reaction mixture was purified by flash chromatography using n-hexane /ethyl acetate (90/10) as an eluent to isolate the desired ortho ester (**7**) product.

Physical Properties and Characterization Data of the Synthesized Compounds

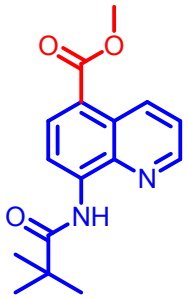
Methyl 8-(2,2-dimethylbutanamido)quinoline-5-carboxylate (2a)

White solid, mp 98 – 100 °C, n-hexane/EtOAc (95/5), 72% (54 mg) ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.53 (s, 1H), 9.51 (d, *J* = 7.2 Hz, 1H), 8.90 – 8.74 (m, 2H), 8.37 (d, *J* = 8.1 Hz, 1H), 7.58 (dd, *J* = 8.7, 4.1 Hz, 1H), 3.98 (s, 3H), 1.78 (q, *J* = 7.5 Hz, 2H), 1.40 (s, 6H), 0.96 (t, *J* = 7.5 Hz, 3H).^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 177.3, 166.9, 148.3, 139.2, 138.5, 135.3, 133.2, 127.4, 123.1, 119.4, 114.4, 52.2, 44.4, 34.2, 25.2, 9.4. HRMS (ESI): *m/z* calcd for $C_{17}H_{20}N_2O_3Na$ $[M+Na]^+$: 323.1372, found 323.1359.



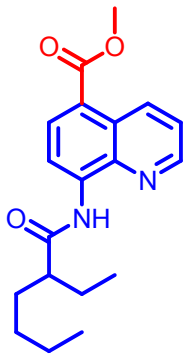
Methyl 8-pivalamidoquinoline-5-carboxylate (2b)

White solid, mp 140 – 142 °C n-hexane/EtOAc (95/5), 70% (50 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 10.56 (s, 1H), 9.55 – 9.44 (m, 1H), 8.86 – 8.74 (m, 2H), 8.36 (d, *J* = 8.4 Hz, 1H), 7.57 (dd, *J* = 8.7, 4.1 Hz, 1H), 3.97 (s, 3H), 1.44 (s, 9H).^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 177.8, 166.9, 148.3, 139.2,



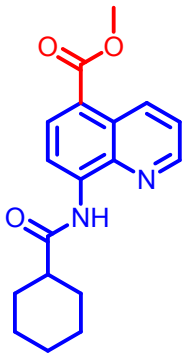
138.5, 135.3, 133.2, 127.3, 123.1, 119.4, 114.4, 52.2, 40.7, 27.8. HRMS (ESI): *m/z* calcd for $C_{16}H_{19}N_2O_3$ $[M+H]^+$: 287.1396, found 287.1404.

Methyl 8-(2-ethylhexanamido)quinoline-5-carboxylate (2c)



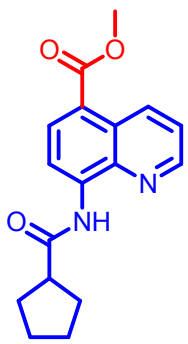
semi solid, n-hexane/EtOAc (95/5), 60% (61 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 10.14 (s, 1H), 9.51 (dd, *J* = 8.7, 1.6 Hz, 1H), 8.86 – 8.78 (m, 2H), 8.36 (d, *J* = 8.3 Hz, 1H), 7.58 (dd, *J* = 8.7, 4.1 Hz, 1H), 3.98 (s, 3H), 2.42 (tt, *J* = 8.9, 5.3 Hz, 1H), 1.88 – 1.75 (m, 2H), 1.69 – 1.58 (m, 2H), 1.42 – 1.32 (m, 4H), 1.01 (t, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 175.5, 166.8, 148.2, 139.0, 138.1, 135.3, 133.1, 127.4, 123.1, 119.5, 114.6, 52.1, 51.2, 32.6, 29.9, 26.3, 22.9, 14.1, 12.2. HRMS (ESI): *m/z* calcd for $C_{19}H_{25}N_2O_3$ $[M+H]$: 329.1865, found 329.1844.

Methyl 8-(cyclohexanecarboxamido)quinoline-5-carboxylate (2d)



White solid, mp 116 – 118 °C, n-hexane/EtOAc (95/5), 60% (47 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 10.19 (s, 1H), 9.51 (d, *J* = 7.4 Hz, 1H), 8.88 – 8.59 (m, 2H), 8.36 (d, *J* = 8.6 Hz, 1H), 7.58 (dd, *J* = 8.7, 4.1 Hz, 1H), 3.98 (s, 3H), 2.50 (tt, *J* = 11.8, 3.5 Hz, 1H), 2.09 (dd, *J* = 13.3, 2.1 Hz, 2H), 1.91 – 1.85 (m, 2H), 1.78 – 1.71 (m, 1H), 1.66 – 1.59 (m, 2H), 1.44 – 1.36 (m, 2H), 1.32 (m, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 175.4, 166.9, 148.2, 139.2, 135.4, 133.2, 127.4, 123.2, 119.4, 114.6, 52.2, 47.1, 29.8, 25.9, 25.8. HRMS (ESI): *m/z* calcd for $C_{18}H_{20}N_2O_3Na$ $[M+Na]^+$: 335.1372, found 335.1363

Methyl 8-(cyclopentanecarboxamido)quinoline-5-carboxylate (2e)

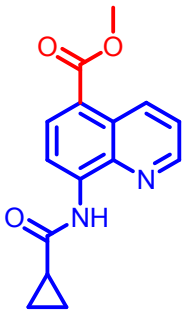


White solid, mp 118 – 120 °C, n-hexane/EtOAc (95/5), 71% (53 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 10.15 (s, 1H), 9.49 (dd, *J* = 8.7, 1.6 Hz, 1H),

8.85 – 8.72 (m, 2H), 8.34 (d, J = 8.3 Hz, 1H), 7.56 (dd, J = 8.7, 4.1 Hz, 1H), 3.97 (s, 3H), 2.98 (p, J = 8.1 Hz, 1H), 2.12 – 1.95 (m, 4H), 1.89 – 1.78 (m, 2H), 1.75 – 1.63 (m, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 175.6, 166.8, 148.1, 139.2, 138.0, 135.3, 133.2, 127.3, 123.1, 119.3, 114.4, 52.1, 47.6, 30.7, 26.1. HRMS (ESI): *m/z* calcd for $C_{17}H_{18}N_2O_3Na$ $[M+Na]^+$: 321.1215, found 321.1210.

Methyl 8-(cyclopropanecarboxamido)quinoline-5-carboxylate (2f)

White solid, mp 164 – 166 °C, n-hexane/EtOAc (95/5), 65% (44 mg).^1H NMR (600 MHz, $CDCl_3$).δ 10.33 (s, 1H), 9.52 (d, J = 9.2 Hz, 1H), 8.84 (d, J = 3.3 Hz, 1H), 8.74 (d, J = 8.2 Hz, 1H), 8.35 (d, J = 8.2 Hz, 1H), 7.59 (dd, J = 8.6, 4.0 Hz, 1H), 3.98 (s, 3H), 1.95 – 1.69 (m, 1H), 1.29 – 1.08 (m, 2H), 1.05 – 0.89 (m, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 172.9, 166.9, 148.2, 139.1, 137.9, 135.4, 133.2, 127.4, 123.2, 119.4, 114.5, 52.2, 16.6,. HRMS (ESI): *m/z* calcd for $C_{15}H_{15}N_2O_3$ $[M+H]^+$: 271.1083, found 271.1070.

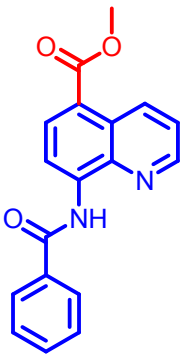


Methyl 8-((3r,5r,7r)-adamantane-1-carboxamido)quinoline-5-carboxylate (2g)

White solid, mp 196 – 198 °C, n-hexane/EtOAc (95/5), 61% (56 mg).^1H NMR (600 MHz, $CDCl_3$).δ 10.53 (s, 1H), 9.57 – 9.39 (m, 1H), 8.86 (d, J = 5.1 Hz, 1H), 8.81 (d, J = 8.4 Hz, 1H), 8.36 (d, J = 8.3 Hz, 1H), 7.58 (dd, J = 9.0, 4.4 Hz, 1H), 3.97 (s, 3H), 2.16 (s, 3H), 2.11 (d, J = 2.7 Hz, 6H), 1.814-1.671 (m, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 177.3, 166.9, 148.3, 139.2, 138.5, 135.3, 133.2, 127.4, 123.1, 119.3, 114.5, 52.2, 42.6, 39.4, 36.6, 28.3. HRMS (ESI): *m/z* calcd for $C_{22}H_{25}N_2O_3$ $[M+H]^+$: 365.1865, found 365.1861.

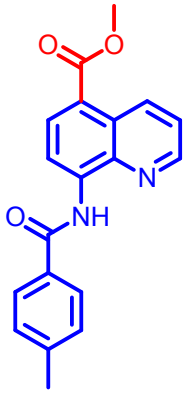
Methyl 8-benzamidoquinoline-5-carboxylate (2h)

White solid, mp 175 – 177 °C, n-hexane/EtOAc (95/5), 80% (61 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 11.05 (s, 1H), 9.58 – 9.47 (m, 1H), 8.90 (dd, J = 36.3, 5.4 Hz, 2H), 8.42 (d, J = 8.1 Hz, 1H), 8.09 (d, J = 7.4 Hz, 2H), 7.66 – 7.53 (m, 4H), 3.99 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.8, 165.8, 148.4, 139.1, 138.5, 135.4, 134.8, 133.1, 132.4, 129.0, 127.5, 127.4, 123.3, 119.9, 114.7, 52.2. HRMS (ESI): *m/z* calcd for $C_{18}H_{15}N_2O_3$ $[M+H]^+$: 307.1083.1603, found 307.1078.



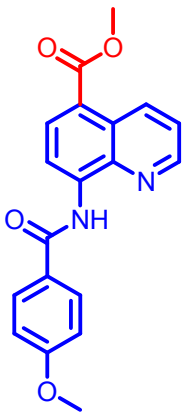
Methyl 8-(4-methylbenzamido)quinoline-5-carboxylate (2i)

White solid, mp 162 – 164 °C, n-hexane/EtOAc (95/5), 80% (64 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 11.01 (s, 1H), 9.55 – 9.48 (m, 1H), 8.89 (dd, J = 31.7, 5.4 Hz, 2H), 8.40 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 8.1 Hz, 2H), 7.59 (dd, J = 8.6, 4.1 Hz, 1H), 7.35 (d, J = 7.9 Hz, 2H), 3.99 (s, 3H), 2.46 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.9, 165.7, 148.3, 143.0, 139.2, 138.5, 135.4, 133.2, 132., 129.7, 127.5, 127.4, 123.3, 119.6, 114.6, 52.2, 21.7. HRMS (ESI): *m/z* calcd for $C_{19}H_{17}N_2O_3$ $[M+H]^+$: 321.1239, found 321.1236.

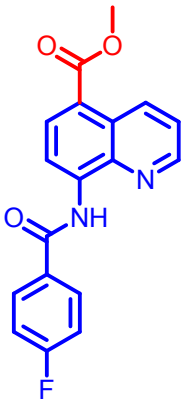


Methyl 8-(4-methoxybenzamido)quinoline-5-carboxylate (2j)

White solid, mp 154 – 156 °C, n-hexane/EtOAc (95/5), 77% (65 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 10.99 (s, 1H), 9.54 (dt, J = 8.7, 1.6 Hz, 1H), 8.92 (dd, J = 8.3, 1.5 Hz, 1H), 8.88 (dt, J = 4.0, 1.5 Hz, 1H), 8.42 (dd, J = 8.3, 1.4 Hz, 1H), 8.07 (dd, J = 8.8, 1.0 Hz, 2H), 7.61 (ddd, J = 8.7, 4.1, 1.5 Hz, 1H), 7.07 – 7.04 (m, 2H), 3.99 (s, 3H), 3.91 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.9, 165.3, 163.0, 148.3, 139.3, 138.5, 135.4, 133.2, 129.5, 127.5, 127.1, 123.3, 119.5, 114.5, 114.3, 55.7, 52.2. HRMS (ESI): *m/z* calcd for $C_{19}H_{16}N_2O_4Na$ $[M+Na]^+$: 359.1008, found 359.1016.

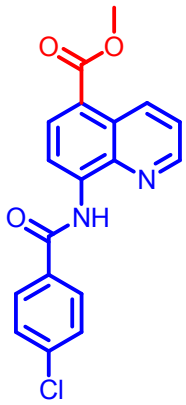


Methyl 8-(4-fluorobenzamido)quinoline-5-carboxylate (2k).



White solid, mp 182 – 184 °C, n-hexane/EtOAc (95/5), 78% (63 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 10.98 (s, 1H), 9.62 – 9.43 (m, 1H), 8.97 – 8.80 (m, 2H), 8.41 (d, J = 8.2 Hz, 1H), 8.18 – 8.04 (m, 2H), 7.61 (dd, J = 8.6, 4.0 Hz, 1H), 7.30 – 7.17 (m, 2H), 3.99 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.8, 165.4 (d, $^{1}J_{C\text{-}F}$ = 252 Hz), 164.6, 148.4, 138.9, 138.4, 135.5, 133.1, 130.0 (d, $^{3}J_{C\text{-}F}$ = 9 Hz), 127.4, 123.3, 120.0, 116.2 (d, $^{2}J_{C\text{-}F}$ = 22.5 Hz), 114.7, 52.2. HRMS (ESI): *m/z* calcd for $C_{18}H_{13}FN_2O_3Na$ $[M+Na]^+$: 347.0808, found 347.0777

Methyl 8-(4-chlorobenzamido)quinoline-5-carboxylate (2l)



White solid, mp 184 – 186 °C, n-hexane/EtOAc (95/5), 77% (66 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 10.98 (s, 1H), 9.52 (d, J = 9.2 Hz, 1H), 8.87 (dd, J = 11.3, 6.4 Hz, 2H), 8.39 (d, J = 8.2 Hz, 1H), 8.01 (d, J = 8.7 Hz, 2H), 7.60 (dd, J = 8.7, 4.1 Hz, 1H), 7.52 (d, J = 8.1 Hz, 2H), 3.99 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.8, 164.6, 148.4, 138.7, 138.7, 138.4, 135.5, 133.1, 133.0, 129.3, 128.9, 127.3, 123.3, 120.0, 114.7, 52.2. HRMS (ESI): *m/z* calcd for $C_{18}H_{14}ClN_2O_3$ $[M+H]^+$: 341.0693, found 341.0684

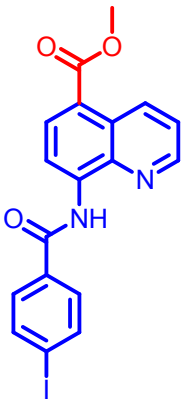
Methyl 8-(4-bromobenzamido)quinoline-5-carboxylate (2m)

White solid, mp 196 – 198 °C, n-hexane/EtOAc (95/5), 74% (71 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 11.02 (s, 1H), 9.54 (d, J = 9.5 Hz, 1H), 8.90 (dd, J = 15.0, 6.5 Hz, 2H), 8.42 (d, J = 8.1 Hz, 1H), 7.96 (d, J = 8.7 Hz, 2H), 7.71 (d, J = 8.1 Hz, 2H), 7.63 (dd, J = 8.6, 4.1 Hz, 1H), 4.00 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.8, 164.8, 148.5, 138.8, 138.4, 135.5, 133.7, 133.1,

132.3, 129.1, 127.4, 127.3, 123.4, 120.2, 114.8, 52.3. HRMS (ESI): *m/z* calcd for $C_{18}H_{14}BrN_2O_3$ $[M+H]^+$: 385.0188, found 385.0190.

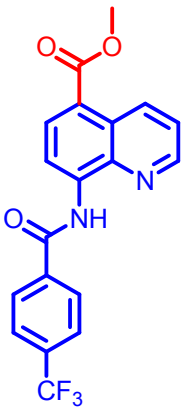
Methyl 8-(4-iodobenzamido)quinoline-5-carboxylate (2n)

White solid, mp 182 – 184 °C, n-hexane/EtOAc (95/5), 70% (76 mg). ^{1}H NMR (600 MHz, $CDCl_3$).δ 11.01 (s, 1H), 9.58 – 9.47 (m, 1H), 8.93 – 8.83 (m, 2H), 8.42 (d, J = 8.2 Hz, 1H), 7.92 (d, J = 8.9 Hz, 2H), 7.81 (t, J = 4.9 Hz, 2H), 7.62 (dd, J = 8.6, 4.0 Hz, 1H), 4.00 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.8, 165.0, 148.4, 138.8, 138.4, 138.3, 135.5, 134.2, 133.1, 129.1, 127.4, 123.4, 120.2, 114.8, 99.6, 52.3. HRMS (ESI): *m/z* calcd for $C_{18}H_{13}IN_2O_3Na$ $[M+Na]^+$: 454.9869, found 454.9864.



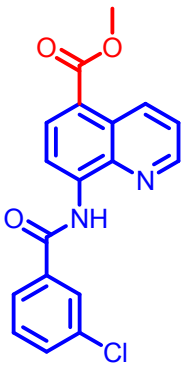
Methyl 8-(4-(trifluoromethyl)benzamido)quinoline-5-carboxylate (2o)

White solid, mp 177 – 179 °C, 63% (59 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 11.07 (s, 1H), 9.53 (d, J = 8.6 Hz, 1H), 8.89 (dd, J = 18.8, 6.0 Hz, 2H), 8.41 (d, J = 8.2 Hz, 1H), 8.19 (d, J = 8.1 Hz, 2H), 7.83 (d, J = 8.1 Hz, 2H), 7.62 (dd, J = 8.7, 4.1 Hz, 1H), 4.00 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.7, 164.4, 148.5, 138.5, 138.3, 138.0, 135.5, 133.9 (q, $^2J_{C\text{-}F}$ = 33 Hz), 133.0, 128.0, 127.4, 126.1 (q, $^3J_{C\text{-}F}$ = 3 Hz), 123.7 (q, $^1J_{C\text{-}F}$ = 272 Hz), 123.3, 120.4, 115.0, 52.3. HRMS (ESI): *m/z* calcd for $C_{19}H_{14}F_3N_2O_3$ $[M+H]^+$: 375.0957, found 375.0985 .



Methyl 8-(3-chlorobenzamido)quinoline-5-carboxylate (2p)

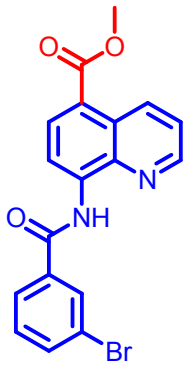
White solid, mp 161 – 163 °C 70% (60 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 10.99 (s, 1H), 9.57 – 9.47 (m, 1H), 8.89 (dd, J = 6.6, 4.7 Hz, 2H), 8.41 (d, J = 8.1 Hz, 1H), 8.06 (d, J = 2.1 Hz,



1H), 7.95 (d, J = 7.9 Hz, 1H), 7.62 (dd, J = 8.6, 4.0 Hz, 1H), 7.58 (d, J = 8.6 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 4.00 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 166.8, 164.4, 148.5, 138.7, 138.4, 136.6, 135.5, 135.3, 133.0, 132.4, 130.3, 128.0, 127.4, 125.5, 123.4, 120.2, 114.9, 52.3. HRMS (ESI): *m/z* calcd for $C_{18}H_{14}ClN_2O_3$ $[M+H]^+$: 341.0693, found 341.0689.

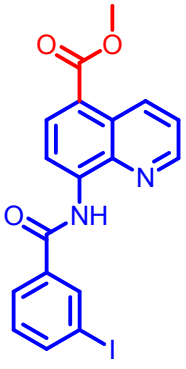
Methyl 8-(3-bromobenzamido)quinoline-5-carboxylate (2q)

White solid, mp 121 – 123 °C (71%, 68 mg).^1H NMR (600 MHz, $CDCl_3$).δ 10.99 (s, 1H), 9.57 – 9.48 (m, 1H), 8.93 – 8.85 (m, 2H), 8.42 (d, J = 8.7 Hz, 1H), 8.22 (d, J = 2.0 Hz, 1H), 8.00 (d, J = 7.6 Hz, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.63 (dd, J = 8.8, 4.2 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 4.00 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 166.8, 164.3, 148.5, 138.7, 138.4, 136.8, 135.5, 135.3, 133.0, 130.9, 130.6, 127.4, 125.9, 123.4, 123.3, 120.6, 114.9, 52.3. HRMS (ESI): *m/z* calcd for $C_{18}H_{14}BrN_2O_3$ $[M+H]^+$: 385.0188, found 385.0190.



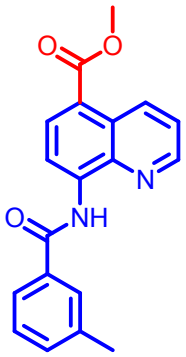
Methyl 8-(3-iodobenzamido)quinoline-5-carboxylate (2r)

White solid, mp 174 – 176 °C, (67%, 72 mg)^1H NMR (600 MHz, $CDCl_3$). δ 10.94 (s, 1H), 9.60 – 9.39 (m, 1H), 8.88 (dd, J = 6.3, 3.7 Hz, 2H), 8.39 (d, J = 8.5 Hz, 2H), 8.01 (d, J = 8.0 Hz, 1H), 7.93 (d, J = 7.5 Hz, 1H), 7.61 (dd, J = 8.9, 4.3 Hz, 1H), 7.36 – 7.20 (m, 1H), 3.99 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 166.8, 164.1, 148.5, 141.2, 138.6, 138.4, 136.7, 135.5, 133.0, 130.6, 127.3, 126.45, 123.3, 120.2, 114.9, 94.8, 52.3. HRMS (ESI): *m/z* calcd for $C_{18}H_{13}IN_2O_3Na$ $[M+Na]^+$: 454.9869, found 454.9859.



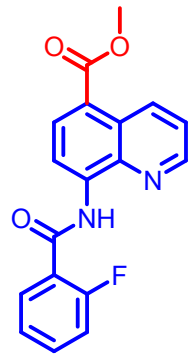
Methyl 8-(3-methylbenzamido)quinoline-5-carboxylate (2s)

White solid, mp 143 – 145 °C, (76%, 61 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 11.02 (s, 1H), 9.58 – 9.46 (m, 1H), 8.92 (dd, *J* = 31.0, 6.7 Hz, 2H), 8.42 (d, *J* = 8.1 Hz, 1H), 7.95 – 7.83 (m, 2H), 7.61 (dd, *J* = 8.7, 4.1 Hz, 1H), 7.48 – 7.40 (m, 2H), 4.00 (s, 3H), 2.49 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.9, 166.1, 148.4, 139.2, 139.0, 138.5, 135.4, 134.8, 133.2, 128.9, 128.3, 127.4, 124.5, 123.3, 119.8, 114.8, 52.2, 21.7. HRMS (ESI): *m/z* calcd for $C_{19}H_{17}N_2O_3$ $[M+H]^+$: 321.1239, found 321.1238



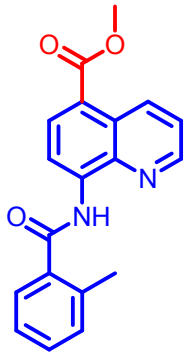
Methyl 8-(2-fluorobenzamido)quinoline-5-carboxylate (2t)

White solid, mp 193 – 195 °C, (56%, 46 mg).^{1}H NMR (600 MHz, $CDCl_3$). δ 11.46 (s, 1H), 9.51 (dd, *J* = 8.7, 1.6 Hz, 1H), 8.97 (d, *J* = 8.3 Hz, 1H), 8.89 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.41 (d, *J* = 8.3 Hz, 1H), 8.22 (td, *J* = 7.8, 1.8 Hz, 1H), 7.68 – 7.51 (m, 2H), 7.35 (td, *J* = 7.8, 1.0 Hz, 1H), 7.26 (m, 1H), 4.00 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.9, 162.1, 160.8 (d, $^{1}J_{C\text{-}F}$ = 249 Hz), 148.5, 139.3, 138.5, 135.25, 134.1 (d, $^{3}J_{C\text{-}F}$ = 10.5 Hz), 133.0, 132.3, 127.4, 125.1, 123.3, 121.8 (d, $^{2}J_{C\text{-}F}$ = 27 Hz), 120.2, 116.6 (d, $^{2}J_{C\text{-}F}$ = 24 Hz), 115.4, 52.2. HRMS (ESI): *m/z* calcd for $C_{18}H_{14}FN_2O_3$ $[M+H]^+$: 325.0988, found 325.0989.



Methyl 8-(2-methylbenzamido)quinoline-5-carboxylate (2u)

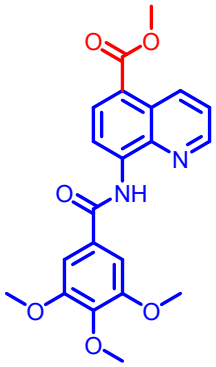
White solid, mp 153 – 155 °C, (70%, 56 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 10.53 (s, 1H), 9.59 – 9.46 (m, 1H), 8.94 (d, *J* = 8.2 Hz, 1H), 8.80 (d, *J* = 5.1 Hz, 1H), 8.42 (d, *J* = 8.1 Hz, 1H), 7.70 (d, *J* = 7.3 Hz, 1H), 7.59 (dd, *J* = 9.0, 4.3 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.40 – 7.29 (m, 2H), 4.00 (s, 3H), 2.61 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.5, 166.9, 148.3, 139.2, 138.3, 137.1, 136.2, 135.4, 133.1, 131.7, 130.8, 127.5, 127.4, 126.3, 123.3, 120.0, 114.7, 52.3,



20.4. HRMS (ESI): *m/z* calcd for $C_{19}H_{17}N_2O_3$ $[M+H]^+$: 321.1239, found 321.1237.

Methyl 8-(3,4,5-trimethoxybenzamido)quinoline-5-carboxylate (2v)

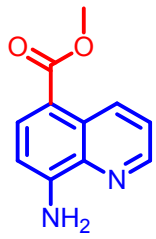
White solid, mp 198 – 200 °C, (66%, 65 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 10.96 (s, 1H),



9.55 (d, *J* = 8.3 Hz, 1H), 8.89 (dd, *J* = 16.2, 6.2 Hz, 2H), 8.44 (d, *J* = 8.2 Hz, 1H), 7.62 (dd, *J* = 8.7, 4.1 Hz, 1H), 7.31 (s, 2H), 4.00 (s, 9H), 3.95 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.9, 165.6, 153.6, 148.4, 139.0, 138.5, 135.5, 133.2, 130.3, 127.5, 123.3, 119.9, 114.7, 105.0, 61.2, 56.6, 52.3. HRMS (ESI): *m/z* calcd for $C_{21}H_{21}N_2O_6$ $[M+H]^+$: 397.1400, found 397.1384.

Methyl 8-aminoquinoline-5-carboxylate (2w)

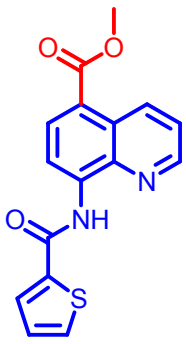
White solid, mp 170 – 172 °C, (76%, 38 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 9.51 (d, *J* = 7.6



Hz, 1H), 8.80 – 8.69 (m, 1H), 8.22 (d, *J* = 8.7 Hz, 1H), 7.51 (dd, *J* = 8.6, 4.0 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 5.56 (s, 2H), 3.93 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, , $CDCl_3$) δ 167.4, 149.0, 147.2, 135.1, 134.0, 128.7, 123.2, 113.2, 107.6, 107.5, 51.7. HRMS (ESI): *m/z* calcd for $C_{11}H_{11}N_2O_2$ $[M+H]^+$: 203.0821, found 203.0815

Methyl 8-(thiophene-2-carboxamido)quinoline-5-carboxylate (2x)

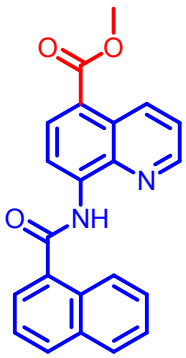
White solid, mp 164 – 166 °C, (70%, 55 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 10.90 (s, 1H),



9.62 – 9.45 (m, 1H), 8.93 – 8.76 (m, 2H), 8.41 (d, *J* = 8.1 Hz, 1H), 7.87 (d, *J* = 3.9 Hz, 1H), 7.69 – 7.58 (m, 2H), 7.24 – 7.16 (m, 1H), 3.99 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.9, 160.3, 148.4, 139.8, 138.8, 138.2, 135.5, 133.1, 131.7, 129.1, 128.2, 127.4, 123.3, 119.9, 114.7, 52.2.

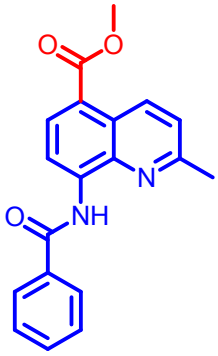
HRMS (ESI): *m/z* calcd for $C_{16}H_{13}N_2O_3S$ [*M*+*H*]: 313.0647, found 313.0625.

Methyl 8-(1-naphthamido)quinoline-5-carboxylate (2y)



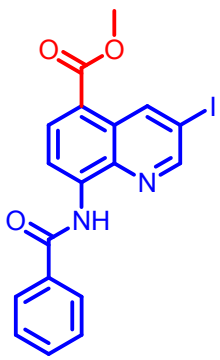
semi solid, (66%, 59 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 10.73 (s, 1H), 9.53 (d, *J* = 8.8 Hz, 1H), 9.05 (d, *J* = 8.3 Hz, 1H), 8.77 (d, *J* = 3.8 Hz, 1H), 8.53 (d, *J* = 8.3 Hz, 1H), 8.47 (d, *J* = 8.2 Hz, 1H), 8.03 (d, *J* = 8.2 Hz, 1H), 7.97 – 7.90 (m, 2H), 7.64 – 7.54 (m, 4H), 4.01 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.1, 166.9, 148.4, 139.3, 138.3, 135.4, 134.2, 134.0, 133.1, 131.7, 130.4, 128.6, 127.6, 127.4, 126.8, 125.9, 125.6, 125.0, 123.3, 120.1, 114.9, 52.3. HRMS (ESI): *m/z* calcd for $C_{22}H_{17}N_2O_3$ [*M*+*H*]$^+$: 357.1239, found 357.1215.

Methyl 8-benzamido-2-methylquinoline-5-carboxylate (2z)



White solid, mp 198 – 200 °C, (75%, 60 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 11.13 (s, 1H), 9.39 (d, *J* = 9.1 Hz, 1H), 8.90 (d, *J* = 8.1 Hz, 1H), 8.35 (d, *J* = 8.1 Hz, 1H), 8.11 – 8.08 (m, 2H), 7.60 (dq, *J* = 15.2, 7.6 Hz, 3H), 7.48 (d, *J* = 8.5 Hz, 1H), 3.99 (s, 3H), 2.79 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 167.0, 165.7, 157.4, 138.4, 138.0, 135.4, 135.0, 132.3, 132.1, 129.1, 127.5, 125.6, 124.1, 119.8, 114.7, 52.2, 25.4. HRMS (ESI): *m/z* calcd for $C_{19}H_{17}N_2O_3$ [*M*+*H*]$^+$: 321.1239, found 321.1236.

Methyl 8-benzamido-3-iodoquinoline-5-carboxylate (2aa)

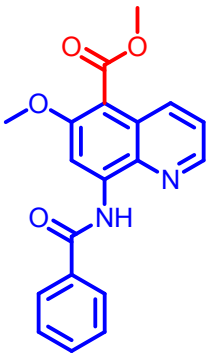


White solid, mp 180 – 182 °C, (71%, 77 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 10.79 (s, 1H), 10.00 – 9.90 (m, 1H), 9.03 – 8.88 (m, 2H), 8.39 (td, *J* = 8.0, 3.5 Hz, 1H), 8.05 (d, *J* = 7.9 Hz, 2H), 7.65 – 7.53 (m, 3H), 3.99 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.4, 165.7, 153.8, 143.3, 139.3, 136.6, 134.6, 134.0, 132.5, 129.1, 128.8, 127.5, 118.7, 115.2, 93.3, 52.3.

HRMS (ESI): *m/z* calcd for $C_{18}H_{13}IN_2O_3Na$ $[M+Na]^+$: 454.9869, found 454.9859.

Methyl 8-benzamido-6-methoxyquinoline-5-carboxylate (2ab)

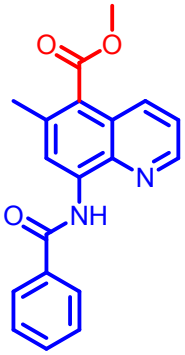
White solid, mp 148 – 150 °C, (76%, 64 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 10.94 (s, 1H),



8.95 (s, 1H), 8.73 – 8.69 (m, 1H), 8.32 (d, J = 8.0 Hz, 1H), 8.09 (d, J = 7.5 Hz, 2H), 7.60 (dt, J = 26.8, 7.5 Hz, 3H), 7.51 – 7.47 (m, 1H), 4.09 (s, 3H), 4.02 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 167.4, 165.9, 157.1, 146.3, 138.2, 134.7, 133.9, 133.3, 132.4, 129.1, 127.5, 126.8, 123.3, 110.0, 103.8, 57.0, 52.5. HRMS (ESI): *m/z* calcd for $C_{19}H_{16}N_2O_4Na$ $[M+Na]^+$: 359.1008, found 359.1016.

Methyl 8-benzamido-6-methylquinoline-5-carboxylate (2ac)

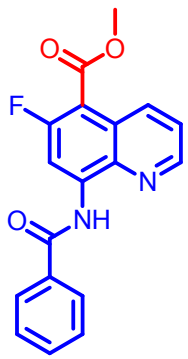
White solid, mp 85 – 87 °C, (77%, 62 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 10.83 (s, 1H), 8.85



(s, 1H), 8.80 (d, J = 4.6 Hz, 1H), 8.38 (d, J = 7.8 Hz, 1H), 8.08 (d, J = 7.5 Hz, 2H), 7.58 (dt, J = 14.9, 7.1 Hz, 3H), 7.51 (dd, J = 8.6, 4.1 Hz, 1H), 4.03 (s, 3H), 2.63 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.8, 165.7, 147.8, 137.9, 137.1, 136.1, 135.0, 134.0, 132.2, 129.0, 127.5, 125.9, 123.1, 122.7, 118.9, 52.3, 21.6. HRMS (ESI): *m/z* calcd for $C_{19}H_{17}N_2O_3$ $[M+H]^+$: 321.1239, found 321.1222

Methyl 8-benzamido-6-fluoroquinoline-5-carboxylate(2ad)

White solid, mp 130 – 132 °C, (60%, 48.6 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 10.90 (s, 1H),

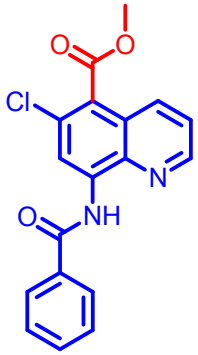


8.81 (d, J = 7.8 Hz, 1H), 8.76 (d, J = 3.0 Hz, 1H), 8.72 (d, J = 12.7 Hz, 1H), 8.01 (d, J = 7.2 Hz, 2H), 7.52 (m, 4H), 3.96 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 165.8, 165.1, 160.7 (d, $^1J_{C\text{-}F}$ = 257 Hz), 147.7, 135.7, 134.8 (d, $^3J_{C\text{-}F}$ = 6 Hz) , 134.4, 132.6, 130.3, 129.1, 128.6, 127.6, 123.8,

107.8 (d, $^{2}J_{C\text{-}F}$ = 15 Hz), 106.8 (d, $^{2}J_{C\text{-}F}$ = 33 Hz), 52.7. HRMS (ESI): *m/z* calcd for $C_{18}H_{13}FN_2O_3Na$ $[M+Na]^+$: 347.0808, found 347.0783

Methyl 8-benzamido-6-chloroquinoline-5-carboxylate (2ae)

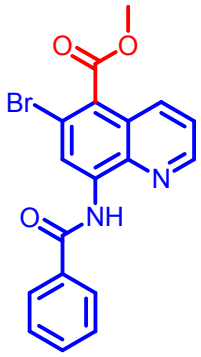
White solid, mp 105 – 107 °C, (73%, 62 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 10.73 (s, 1H),



8.95 (d, *J* = 1.6 Hz, 1H), 8.79 (d, *J* = 4.2 Hz, 1H), 8.19 (d, *J* = 8.3 Hz, 1H), 8.00 (d, *J* = 7.4 Hz, 2H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.50 (t, *J* = 7.3 Hz, 4H), 3.99 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.6, 165.7, 148.7, 137.0, 136.9, 134.5, 133.7, 132.5, 130.3, 129.1, 128.62, 127.5, 126.2, 123.5, 117.5, 53.0. HRMS (ESI): *m/z* calcd for $C_{18}H_{14}ClN_2O_3$ $[M+H]^+$: 341.0693, found 341.0677

Methyl 8-benzamido-6-bromoquinoline-5-carboxylate (2af)

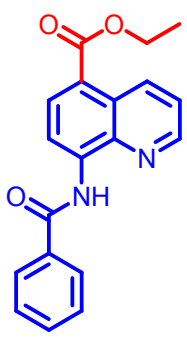
White solid, mp 120 – 122 °C, (71%, 68 mg).^{1}H NMR (600 MHz,) δ 10.78 (s, 1H), 9.19 (s,



1H), 8.88 (d, *J* = 4.9 Hz, 1H), 8.22 (d, *J* = 9.5 Hz, 1H), 8.07 (d, *J* = 7.3 Hz, 2H), 7.62 – 7.60 (m, 1H), 7.59 – 7.55 (m, 3H), 4.07 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz,) δ 167.27, 165.66, 148.80, 137.11, 136.77, 134.50, 133.81, 132.50, 130.33, 129.09, 128.63, 127.51, 126.35, 123.45, 120.17, 53.00. For $C_{18}H_{13}BrN_2O_3Na$ $[M+Na]^+$: 407.0007, found 407.9985

Ethyl 8-benzamidoquinoline-5-carboxylate (5a)

White solid, mp 86 – 88 °C, (32%, 24 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 11.06 (s, 1H), 9.54

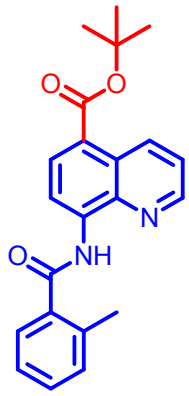


(d, *J* = 9.1 Hz, 1H), 8.95 (d, *J* = 8.1 Hz, 1H), 8.88 (d, *J* = 3.3 Hz, 1H), 8.43 (d, *J* = 8.3 Hz, 1H), 8.10 (d, *J* = 7.2 Hz, 2H), 7.64 – 7.53 (m, 4H), 4.46 (q, *J* = 7.1 Hz, 2H), 1.47 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz,) δ 166.5, 165.8, 148.3, 139.0, 138.5, 135.5, 134.9, 133.0, 132.4, 132.0, 129.0, 127.5,

123.2, 121.8, 120.3, 114.7, 61.2, 14.6. HRMS (ESI): *m/z* calcd for $C_{19}H_{17}N_2O_3$ $[M+H]^+$: 321.1161, found 321.1250.

tert-Butyl 8-(2-methylbenzamido)quinoline-5-carboxylate (5d)

White solid, mp 110 – 112 °C, (25%, 23 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 10.50 (s, 1H),



9.49 (d, J = 8.4 Hz, 1H), 8.92 (d, J = 8.2 Hz, 1H), 8.78 (d, J = 3.4 Hz, 1H), 8.33 (d, J = 8.3 Hz, 1H), 7.70 (d, J = 7.4 Hz, 1H), 7.56 (dd, J = 8.7, 4.0 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.34 (dd, J = 11.5, 7.5 Hz, 2H), 2.61 (s, 3H), 1.68 (s, 9H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.5, 165.9, 148.2, 138.6, 138.4, 137.0, 136.3, 135.5, 132.7, 131.7, 130.8, 127.5, 127.3, 126.2, 123.0, 122.1, 114.7, 81.7, 28.5, 20.4. HRMS (ESI): *m/z* calcd for $C_{22}H_{22}N_2O_3Na$ $[M+Na]^+$: 385.1528, found 385.1539.

Product Spectral characterization data of 8-aminoquinolinyl sulphonamides:

Methyl 8-(4-methylphenylsulfonamido)quinoline-5-carboxylate (4a)

The pure compound 4a was isolated by flash chromatography (n-hexane/EtOAc ,90/10) yielded

white solid, mp 136 – 138 °C, (74%, 66mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 9.61 (s, 1H), 9.42 – 9.36 (m, 1H), 8.82 – 8.74 (m, 1H), 8.24 (d, J = 8.8 Hz, 1H), 7.83 (d, J = 8.6 Hz, 2H), 7.77 (d, J = 8.1 Hz, 1H), 7.54 (dd, J = 8.7, 4.1 Hz, 1H), 7.19 (d, J = 8.4 Hz, 2H), 3.94 (s, 3H), 2.31 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.6, 148.7, 144.4, 138.4, 137.9, 136.3, 135.3, 132.3, 129.8, 127.5, 127.4, 123.5, 120.0, 112.0, 52.2, 21.6. HRMS (ESI): *m/z* calcd for $C_{18}H_{16}N_2O_4SK$ $[M+K]^+$: 395.0468, found 395.0482.

Methyl 8-(phenylsulfonamido)quinoline-5-carboxylate (4b)

The pure compound 4b was isolated by flash chromatography (n-hexane/EtOAc ,90/10) yielded white solid, mp 203 – 205 °C, (75%, 64 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 9.64 (s, 1H), 9.41 (d, *J* = 8.9 Hz, 1H), 8.80 (d, *J* = 3.9 Hz, 1H), 8.25 (d, *J* = 8.2 Hz, 1H), 7.96 (d, *J* = 7.8 Hz, 2H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.56 (dd, *J* = 8.8, 4.2 Hz, 1H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 3.95 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.6, 148.7, 139.3, 138.3, 138.0, 135.4, 133.4, 132.3, 129.3, 127.6, 127.3, 123.6 120.2, 112.2, 52.3. HRMS (ESI): *m/z* calcd for $C_{17}H_{14}N_2O_4SK$ $[M+K]^+$: 381.0311, found 381.0295 and $C_{17}H_{15}N_2O_4S$ $[M+H]^+$: 343.0753, found 343.0737

Methyl 8-([1,1'-biphenyl]-4-ylsulfonamido)quinoline-5-carboxylate (4c)

The pure compound 4c was isolated by flash chromatography (n-hexane/EtOAc ,90/10) yielded semi solid, (62%, 65 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 9.68 (s, 1H), 9.45 – 9.39 (m, 1H), 8.84 – 8.78 (m, 1H), 8.27 (d, *J* = 8.1 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 2H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.61 (d, *J* = 8.1 Hz, 2H), 7.56 (dd, *J* = 8.9, 4.3 Hz, 1H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.39 – 7.35 (m, 2H), 3.95 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 167.1, 149.2, 146.8, 139.76, 138.8, 138.4, 138.3, 135.8, 132.8, 129.6, 129.1, 128.3, 128.0, 127.8, 124.1, 120.7, 112.6, 52.7. HRMS (ESI): *m/z* calcd for $C_{23}H_{18}N_2O_4SNa$ $[M+Na]^+$: 441.0885, found 441.0868.

Methyl 8-(4-(*tert*-butyl)phenylsulfonamido)quinoline-5-carboxylate (4d)

White solid, mp 158 – 160 °C, (71%, 71 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 9.63 (s, 1H), 9.45 – 9.37 (m, 1H), 8.82 – 8.77 (m, 1H), 8.25 (d, *J* = 8.1 Hz, 1H), 7.90 – 7.85 (m, 2H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.55 (dd, *J* = 8.7, 4.1 Hz, 1H), 7.45 – 7.39 (m, 2H), 3.95 (s, 3H), 1.25 (s, 9H). ^{13}C{^{1}H} NMR (151 MHz,) δ

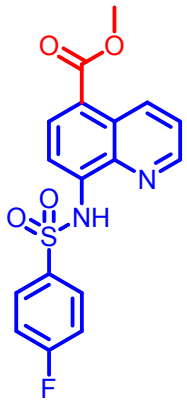
166.7, 157.3, 148.7, 138.5, 137.9, 136.3, 135.3, 132.4, 127.4, 127.2, 126.3, 123.6, 119.9, 111.9, 52.2, 35.3, 31.1. HRMS (ESI): *m/z* calcd for $C_{21}H_{23}N_2O_4S$ $[M+H]^+$: 399.1379, found 399.1372.

Methyl 8-(4-bromophenylsulfonamido)quinoline-5-carboxylate (4e)

White solid, mp 110 – 112 °C, (66%, 69 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 9.63 (s, 1H), 9.42 (d, J = 9.8 Hz, 1H), 8.79 (d, J = 2.7 Hz, 1H), 8.25 (d, J = 8.2 Hz, 1H), 7.79 (dd, J = 12.6, 8.1 Hz, 3H), 7.59 – 7.51 (m, 3H), 3.96 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.5, 148.9, 138.3, 137.9, 135.4, 132.5, 132.3, 132.2, 128.8, 128.5, 127.6, 123.7, 120.6, 112.4, 52.3. HRMS (ESI): *m/z* calcd for $C_{17}H_{14}BrN_2O_4S$ $[M+H]^+$: 420.9858, found 420.9847.

Methyl 8-(4-fluorophenylsulfonamido)quinoline-5-carboxylate (4f)

White solid, mp 148 – 150 °C, (77%, 69 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 9.62 (s, 1H), 9.42 (d, J = 8.6 Hz, 1H), 8.79 (s, 1H), 8.26 (d, J = 8.2 Hz, 1H), 7.96 (dd, J = 7.7, 5.0 Hz, 2H), 7.79 (d, J = 8.1 Hz, 1H), 7.62 – 7.50 (m, 1H), 7.08 (t, J = 8.2 Hz, 2H), 3.95 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.5, 166.3, 164.7, 148.8, 138.1, 138.0, 135.4, 135.3, 132.2, 130.1, 130.1, 127.6, 123.7, 120.5, 116.6, 116.5, 112.4, 52.3. HRMS (ESI): *m/z* calcd for $C_{17}H_{14}FN_2O_4S$ $[M+H]^+$: 361.0658, found 361.0644.

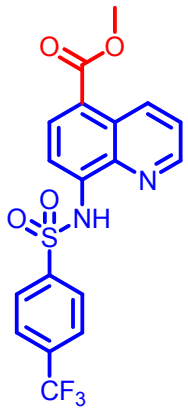


Methyl 8-(4-cyanophenylsulfonamido)quinoline-5-carboxylate (4g)

White solid, mp 168 – 170 °C, (77%, 71 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 9.69 (s, 1H), 9.43 (d, J = 8.8 Hz, 1H), 8.80 (d, J = 4.1 Hz, 1H), 8.27 (d, J = 8.2 Hz, 1H), 8.05 (d, J = 8.2 Hz, 2H), 7.82 (d, J = 8.3 Hz, 1H), 7.70 (d, J = 8.2 Hz, 2H), 7.58 (dd, J = 8.7, 4.1 Hz, 1H), 3.96 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$)

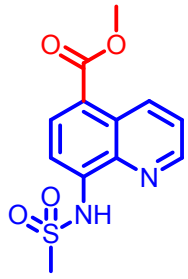
δ 166.4, 149.0, 143.4, 138.0, 137.4, 135.6, 133.1, 132.1, 127.9, 127.6, 123.8, 121.2, 117.1, 112.8, 52.4. For $C_{18}H_{14}N_2O_4S$ $[M+H]^+$: 368.0705, found 368.0691.

Methyl 8-(4-(trifluoromethyl)phenylsulfonamido)quinoline-5-carboxylate (4h)



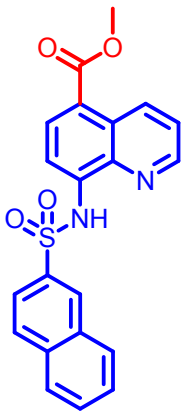
White solid, mp 156 – 158 °C, 81%, (83 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 9.69 (s, 1H), 9.43 (d, J = 8.8 Hz, 1H), 8.80 (s, 1H), 8.27 (d, J = 8.3 Hz, 1H), 8.07 (d, J = 8.1 Hz, 2H), 7.82 (d, J = 8.2 Hz, 1H), 7.68 (d, J = 8.1 Hz, 2H), 7.58 (dd, J = 8.0, 3.5 Hz, 1H), 3.96 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.5, 148.9, 142.8, 138.0, 137.7, 135.5, 134.9 (q, $^2J_{C\text{-}F}$ = 33 Hz), 132.1, 127.8, 127.6, 126.5, 123.8, 123.1 (q, $^1J_{C\text{-}F}$ = 271 Hz), 120.9, 112.5, 52.4. ^{19}F NMR (CDCl3, 600 MHz) δ –63.2 HRMS (ESI): *m/z* calcd for $C_{18}H_{14}F_3N_2O_4S$ $[M+H]^+$: 411.0626, found 411.0610.

Methyl 8-(methylsulfonamido)quinoline-5-carboxylate (4i)



White solid, mp 164 – 166 °C, (75%, 53 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 9.50 (d, J = 9.5 Hz, 1H), 9.36 (s, 1H), 8.85 (d, J = 4.7 Hz, 1H), 8.35 (d, J = 8.1 Hz, 1H), 7.83 (d, J = 8.5 Hz, 1H), 7.62 (dd, J = 8.7, 4.1 Hz, 1H), 4.00 (s, 3H), 3.12 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.61, 148.9, 138.7, 137.9, 135.5, 132.4, 127.8, 123.8, 120.5, 111.9, 52.4, 40.0. HRMS (ESI): *m/z* calcd for $C_{12}H_{12}N_2O_4SNa$ $[M+Na]^+$: 303.0415, found 303.0417.

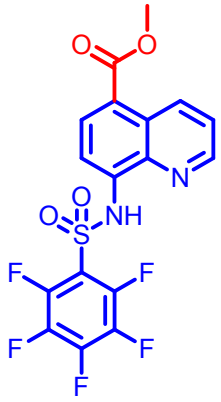
Methyl 8-(naphthalene-2-sulfonamido)quinoline-5-carboxylate (4j)



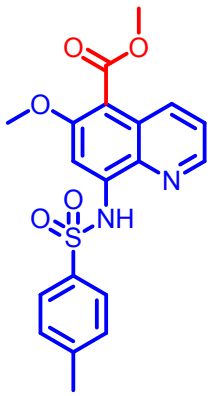
White solid, mp 137 – 139 °C, (70%, 69 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 9.73 (s, 1H), 9.38 (d, J = 8.3 Hz, 1H), 8.80 (s, 1H), 8.57 (s, 1H), 8.23 (d, J = 8.0 Hz, 1H), 7.87 (m, 5H), 7.62 – 7.50 (m, 3H), 3.92 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.6, 148.7, 138.3, 137.9, 136.1, 135.3, 135.2, 132.3, 132.0,

129.8, 129.5, 129.2, 129.2, 128.0, 127.8, 127.6, 123.6, 122.2, 120.2, 112.1, 52.2. HRMS (ESI): *m/z* calcd for $C_{21}H_{17}N_2O_4S$ $[M+H]^+$: 393.0909, found 393.0901.

Methyl 8-(perfluorophenylsulfonamido)quinoline-5-carboxylate (4k)



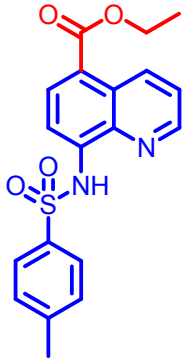
White solid, mp 114 – 116 °C, (59%, 64 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 9.45 (d, *J* = 8.9 Hz, 1H), 8.87 (d, *J* = 4.0 Hz, 1H), 8.29 (d, *J* = 8.3 Hz, 1H), 7.86 (d, *J* = 8.2 Hz, 1H), 7.63 (dd, *J* = 8.7, 4.2 Hz, 1H), 3.97 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.4, 149.3, 137.9, 136.8, 135.5, 132.1, 127.7, 124.0, 121.7, 112.3, 52.4. HRMS (ESI): *m/z* calcd for $C_{17}H_9F_5N_2O_4SNa$ $[M+Na]^+$: 455.0101, found 455.0092.



Methyl 6-methoxy-8-(4-methylphenylsulfonamido)quinoline-5-carboxylate (4l)

White solid, mp 128 – 130 °C, (79%, 76 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 9.35 (s, 1H), 8.54 (d, *J* = 3.9 Hz, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.58 (s, 1H), 7.33 (dd, *J* = 8.5, 4.2 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 2H), 3.89 (s, 6H), 2.24 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 167.0, 156.4, 146.7, 144.5, 137.5, 136.1, 133.4, 133.1, 129.9, 127.3, 127.0, 123.5, 110.3, 101.8, 57.0, 52.5, 21.6. HRMS (ESI): *m/z* calcd for $C_{19}H_{19}N_2O_5S$ $[M+H]^+$: 387.1015, found 387.1001

Ethyl 8-(4-methylphenylsulfonamido)quinoline-5-carboxylate (5b)



White solid, mp 93 – 95 °C, (65%, 60 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 9.60 (s, 1H), 9.41 (d, *J* = 8.7 Hz, 1H), 8.79 (d, *J* = 3.5 Hz, 1H), 8.25 (d, *J* = 8.1 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.55 (dd, *J* = 8.7, 4.1 Hz, 1H),

7.20 (d, J = 8.0 Hz, 2H), 4.41 (q, J = 7.1 Hz, 2H), 2.32 (s, 3H), 1.42 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 166.2, 148.7, 144.3, 138.3, 138.0, 136.3, 135.3, 132.2, 129.9, 127.6, 127.4, 123.5, 120.4, 112.1, 61.2, 21.6, 14.5. HRMS (ESI): *m/z* calcd for $C_{19}H_{19}N_2O_4S$ $[M+H]^+$: 371.1066, found 371.1054.

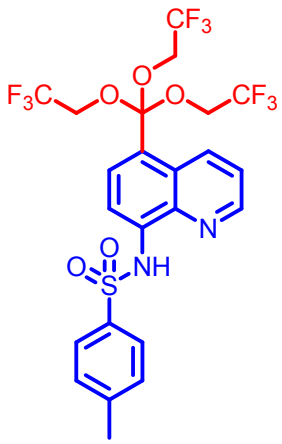
tert-pentyl 8-(4-methylphenylsulfonamido)quinoline-5-carboxylate (5c)

semi solid, (25%, 26 mg).^1H NMR (600 MHz, $CDCl_3$).δ 9.58 (s, 1H), 9.38 (d, J = 8.5 Hz, 1H),

8.78 (d, J = 3.1 Hz, 1H), 8.15 (d, J = 8.3 Hz, 1H), 7.83 (d, J = 8.0 Hz, 2H), 7.76 (d, J = 8.2 Hz, 1H), 7.52 (dd, J = 8.6, 4.0 Hz, 1H), 7.20 (d, J = 7.9 Hz, 2H), 2.32 (s, 3H), 1.95 (q, J = 7.3 Hz, 2H), 1.59 (s, 6H), 0.98 (t, J = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (151 MHz,) δ 165.5, 148.5, 144.3, 138.0, 137.9, 136.4, 135.4, 131.8, 129.9, 127.5, 127.4, 123.3, 122.1, 112.2, 84.4, 33.85, 29.85, 25.94, 21.7. HRMS (ESI): *m/z* calcd for $C_{22}H_{24}N_2NaO_4S$ $[M+Na]^+$: 435.1354, found 435.1344.

4-methyl-N-(5-(tris(2,2,2-trifluoroethoxy)methyl)quinolin-8-yl)benzenesulfonamide (7)

White solid, mp 105 – 107 °C, (40%, 60 mg).^1H NMR (600 MHz, $CDCl_3$).δ 9.49 (s, 1H), 8.89



– 8.79 (m, 2H), 7.93 – 7.86 (m, 3H), 7.77 – 7.68 (m, 1H), 7.56 (dd, J = 7.8, 3.3 Hz, 1H), 7.25 (d, J = 8.0 Hz, 2H), 3.67 (q, J = 7.1 Hz, 6H), 2.35 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz,) δ 149.4, 144.5, 138.5, 137.3, 136.5, 133.6, 129.9, 129.2, 127.5, 124.9, 123.5, 123.3 (q, $^1J_{C\text{-}F}$ = 274 Hz),120.7, 114.4, 111.8, 61.1 (d, $^2J_{C\text{-}F}$ = 36 Hz), 21.6. ^{19}F NMR (565 MHz,) δ -73.53, -73.54, -73.55. HRMS (ESI): *m/z* calcd for $C_{23}H_{20}F_9N_2O_5S$ $[M+H]^+$: 607.0949, found 607.0907 and HRMS (ESI): *m/z* calcd for $C_{23}H_{19}F_9N_2O_5S$ $[M+K]^+$: 645.0508, found 645.0460

Product Spectral characterization data of different arenes and hetarenes:

Methyl 2-hydroxy-1-naphthoate (6a)[31]

Yellowish solid, mp 77 – 79 °C, n-hexane/EtOAc (95/5), 62% (32 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 12.27 (s, 1H), 8.73 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 8.9 Hz, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.55 (dd, J = 9.5, 7.1 Hz, 1H), 7.37 (t, J = 7.4 Hz, 1H), 7.16 (d, J = 9.1 Hz, 1H), 4.10 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 173, 164.5, 137.0, 131.9, 129.2, 128.8, 128.6, 125.5, 123.8, 119.4, 104.8, 52.5. GC-MS: *m/z* 202 (M^+). HRMS (ESI): *m/z* calcd for $C_{12}H_{11}O_3$ $[M+H]^+$: 203.0708, found 203.0695.

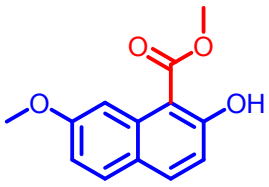
Methyl 3-bromo-2-hydroxy-1-naphthoate (6b)[31]

Yellowish solid, mp 93 – 95 °C, n-hexane/EtOAc (95/5), 66% (46 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 12.97 (s, 1H), 8.68 (d, J = 8.7 Hz, 1H), 8.22 (s, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.57 (t, J = 7.3 Hz, 1H), 7.39 (t, J = 7.5 Hz, 1H), 4.13 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 172.8, 160.5, 139.4, 131.0, 128.9, 128.9, 128.4, 125.5, 124.6, 113.1, 106.0, 53.1. HRMS (ESI): *m/z* calcd for $C_{12}H_{10}BrO_3$ $[M+H]^+$: 280.9813, found 280.9787.

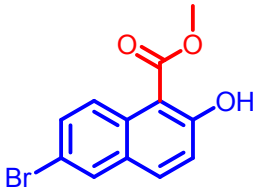
Methyl 7-bromo-2-hydroxy-1-naphthoate (6c)[31]

White solid, mp 123 – 125 °C, n-hexane/EtOAc (95/5), 61% (43.0 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 12.37 (s, 1H), 8.92 (d, J = 20.2 Hz, 1H), 7.87 – 7.80 (m, 1H), 7.63 – 7.55 (m, 1H), 7.47 (d, J = 9.1 Hz, 1H), 7.20 – 7.11 (m, 1H), 4.12 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 172.5, 165.2, 136.74, 133.0, 130.6, 128.0, 127.2, 123.6, 120.0, 119.9, 104.1, 52.8. HRMS (ESI): *m/z* calcd for $C_{12}H_{10}BrO_3$ $[M+H]^+$: 280.9813, found 280.9787.

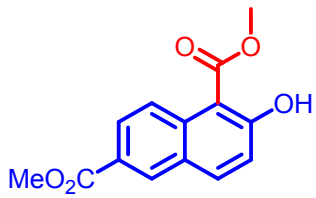
Methyl 2-hydroxy-7-methoxy-1-naphthoate (6d)[31]

White solid, mp 105 – 107 °C, n-hexane/EtOAc (95/5), 63% (37.0 mg).^{1}H NMR (600 MHz,  $CDCl_3$) δ 12.29 (s, 1H), 8.20 (d, J = 2.1 Hz, 1H), 7.82 (d, J = 8.9 Hz, 1H), 7.65 (d, J = 9.0 Hz, 1H), 7.10 – 6.94 (m, 2H), 4.11 (s, 3H), 3.94 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 173.0, 165.3, 160.0, 136.8, 133.6, 130.7, 124.0, 116.8, 114.7, 106.4, 104.1, 55.3, 52.5. HRMS (ESI): *m/z* calcd for $C_{13}H_{13}O_4$ $[M+H]^+$: 233.0814, found 233.0798

Methyl 6-bromo-2-hydroxy-1-naphthoate (6e) [36]

White solid, mp 78 – 80 °C, n-hexane/EtOAc (95/5), 60% (42.0 mg).^{1}H NMR (600 MHz,  $CDCl_3$) δ 12.27 (s, 1H), 8.57 (t, J = 10.7 Hz, 1H), 7.84 (d, J = 8.6 Hz, 1H), 7.74 (t, J = 10.4 Hz, 1H), 7.57 (dd, J = 8.4, 6.5 Hz, 1H), 7.15 (t, J = 8.4 Hz, 1H), 4.09 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 172.5, 164.5, 135.8, 131.5, 130.9, 130.4, 130.0, 127.3, 120.6, 120.6, 117.4, 104.8, 52.7. HRMS (ESI): *m/z* calcd for $C_{12}H_{10}BrO_3$ $[M+H]^+$: 280.9813, found 280.9787.

Dimethyl 2-hydroxynaphthalene-1,6-dicarboxylate (6f)

White solid, mp 138 – 140 °C, n-hexane/EtOAc (95/5), 65% (42.0 mg).^{1}H NMR (600 MHz,  $CDCl_3$) δ 12.47 (s, 1H), 8.75 (d, J = 9.1 Hz, 1H), 8.45 (s, 1H), 8.11 (d, J = 9.2 Hz, 1H), 7.96 (d, J = 9.0 Hz, 1H), 7.21 (d, J = 9.1 Hz, 1H), 4.12 (s, 3H), 3.97 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 172.7, 167.0, 166.2, 138.0, 134.7, 131.8, 131.7, 128.1, 127.9, 125.6, 125.6, 125.3, 120.5, 120.4, 105.0, 52.8, 52.3. HRMS (ESI): *m/z* calcd for $C_{14}H_{13}O_5$ $[M+H]^+$: 261.0763, found 261.0740

Methyl 6-formyl-2-hydroxy-1-naphthoate (6g)

White solid, mp 130 – 132 °C, n-hexane/EtOAc (95/5), 60% (35.0 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 12.51 (s, 1H), 10.09 (s, 1H), 8.83 (d, J = 8.9 Hz, 1H), 8.22 (s, 1H), 8.03 – 7.97 (m, 2H), 7.24 (d, J = 2.1 Hz, 1H), 4.12 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 191.8, 172.6, 166.6, 138.0, 135.9, 134.3, 132.0, 128.0, 126.4, 126.1, 120.9, 105.4, 53.0. HRMS (ESI): *m/z* calcd for $C_{13}H_{11}O_4$ $[M+H]^+$: 231.0657, found 231.0638

Methyl 6-cyano-2-hydroxy-1-naphthoate (6h)[36]

White solid, mp 190 – 192 °C, n-hexane/EtOAc (95/5), 63% (36.0 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 12.51 (s, 1H), 8.82 (d, J = 9.1 Hz, 1H), 8.09 (d, J = 1.5 Hz, 1H), 7.90 (d, J = 9.0 Hz, 1H), 7.67 (d, J = 9.4 Hz, 1H), 7.31 – 7.23 (m, 1H), 4.12 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 172.3, 166.5, 136.9, 134.5, 134.1, 129.4, 127.8, 126.7, 126.7, 121.6, 121.6, 119.1, 107.3, 105.1, 53.0. HRMS (ESI): *m/z* calcd for $C_{13}H_9NO_3Na$ $[M+Na]^+$: 250.0480, found 250.0450.

Methyl 2-hydroxy-6-methoxy-1-naphthoate(6i)

White solid, mp 80 – 82 °C, n-hexane/EtOAc (95/5), 61% (35.0 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 12.02 (s, 1H), 8.66 (d, J = 9.5 Hz, 1H), 7.80 (d, J = 9.0 Hz, 1H), 7.22 (dd, J = 9.3, 2.5 Hz, 1H), 7.15 (d, J = 8.8 Hz, 1H), 7.10 (d, J = 2.3 Hz, 1H), 4.10 (s, 3H), 3.91 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz,) δ 172.8, 162.8, 155.8, 135.8, 130.0, 127.0, 126.7, 120.1, 119.8, 108.1, 105.1, 55.4, 52.5. HRMS (ESI): *m/z* calcd for $C_{13}H_{13}O_4$ $[M+H]^+$: 233.0814, found 233.0798

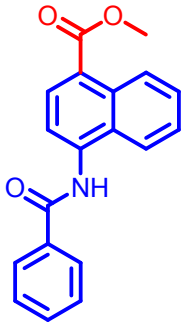
Dimethyl 4-hydroxynaphthalene-1,3-dicarboxylate (6j)

White solid, mp 124 – 126 °C, n-hexane/EtOAc (95/5), 60% (39.0 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 12.32 (s, 1H), 8.95 (d, J = 8.6 Hz, 1H), 8.57 (s, 1H), 8.42 (d,

J = 8.2 Hz, 1H), 7.67 (dd, J = 9.7, 7.0 Hz, 1H), 7.56 – 7.45 (m, 1H), 3.97 (s, 3H), 3.91 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 171.1, 167.2, 164.4, 135.3, 131.3, 130.8, 126.3, 126.1, 125.2, 124.3, 117.8, 104.7, 52.8, 52.2. HRMS (ESI): *m/z* calcd for $C_{14}H_{13}O_5$ $[M+H]^+$: 261.0763, found 261.0740

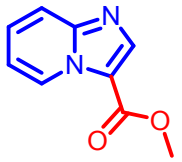
Methyl 4-benzamido-1-naphthoate (6k)

White solid, mp 166 – 168 °C, n-hexane/EtOAc (90/10), 61% (47 mg).^1H NMR (600 MHz, $CDCl_3$) δ 9.09 (d, J = 8.7 Hz, 1H), 8.44 (s, 1H), 8.29 (dd, J = 20.8, 8.1 Hz, 2H), 8.00 (d, J = 7.2 Hz, 2H), 7.95 (d, J = 8.5 Hz, 1H), 7.65 (dd, J = 13.9, 6.4 Hz, 1H), 7.61 (dd, J = 13.2, 6.9 Hz, 2H), 7.56 (t, J = 7.5 Hz, 2H), 4.01 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 167.7, 166.1, 136.9, 134.8, 132.5, 132.5, 131.1, 129.2, 128.0, 127.3, 127.2, 126.8, 126.5, 124.0, 120.2, 118.2, 52.3. HRMS (ESI): *m/z* calcd for $C_{19}H_{15}NO_3Na$ $[M+Na]^+$: 328.0950, found 328.0948. HRMS (ESI): *m/z* calcd for $C_{19}H_{15}NO_3K$ $[M+K]^+$: 344.0689, found 344.0690.



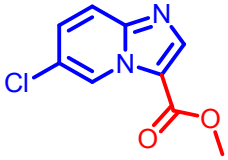
Methyl imidazo[1,2-a]pyridine-3-carboxylate (6l)

Yellowish solid, mp 100 – 102 °C, n-hexane/EtOAc (90/10), 70% (31.0 mg).^1H NMR (600 MHz, $CDCl_3$) δ 9.29 (d, J = 6.9 Hz, 1H), 8.29 (s, 1H), 7.74 (d, J = 9.0 Hz, 1H), 7.46 – 7.35 (m, 1H), 7.04 (t, J = 6.9 Hz, 1H), 3.93 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 161.1, 148.5, 141.7, 141.5, 127.8, 118.0, 115.7, 114.5, 51.6. HRMS (ESI): *m/z* calcd for $C_9H_9N_2O_2$ $[M+H]^+$: 177.0664, found 177.0677.



Methyl 6-chloroimidazo[1,2-a]pyridine-3-carboxylate (6m)

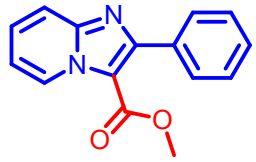
Yellowish solid, mp 150 – 152 °C, n-hexane/EtOAc,(90/10), 69% (36.0 mg). ^1H NMR (600 MHz, $CDCl_3$) δ 9.36 (d, J = 1.7 Hz, 1H), 8.27 (s, 1H), 7.68 (d, J = 9.4 Hz, 1H), 7.39 (dd, J = 9.2, 2.2 Hz, 1H), 3.95 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 160.8,



146.7, 141.7, 129.2, 125.8, 123.0, 118.2, 116.2, 51.9. HRMS (ESI): *m/z* calcd for $C_9H_8ClN_2O_2$ $[M+H]^+$: 211.0274, found 211.0269.

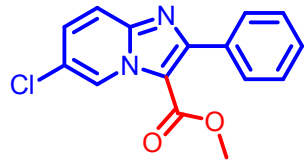
Methyl 2-phenylimidazo[1,2-a]pyridine-3-carboxylate (6n)

Yellowish solid, mp 124 – 126 °C, n-hexane/EtOAc (90/10), 71% (45.0 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 9.41 (d, J = 6.9 Hz, 1H), 7.76 (t, J = 7.5 Hz, 3H), 7.50 – 7.35 (m, 4H), 7.04 (t, J = 6.9 Hz, 1H), 3.81 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 161.6, 153.7, 147.2, 134.4, 130.2, 128.9, 128.5, 128.3, 127.8, 117.6, 114.4, 111.8, 51.4. HRMS (ESI): *m/z* calcd for $C_{15}H_{12}N_2O_2Na$ $[M+Na]^+$: 275.0796, found 275.0780.



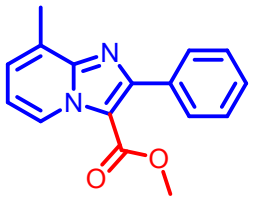
Methyl 6-chloro-2-phenylimidazo[1,2-a]pyridine-3-carboxylate (6o)

Yellow solid, mp 137 – 139 °C, n-hexane/EtOAc (80/20), 67% (48.0 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.75 (dd, J = 6.0, 2.1 Hz, 2H), 7.68 (d, J = 9.5 Hz, 1H), 7.51 – 7.38 (m, 4H), 3.84 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 161.4, 154.2, 145.6, 134.1, 130.2, 129.5, 129.1, 127.9, 126.5, 122.6, 117.9, 112.3, 51.6. GC-MS: *m/z* for $C_{15}H_{11}ClN_2O_2$: 286 (M^+). HRMS (ESI): *m/z* calcd for $C_{15}H_{11}ClN_2O_2K$ $[M+K]^+$: 325.0146, found 325.0126



Methyl 8-methyl-2-phenylimidazo[1,2-a]pyridine-3-carboxylate (6p)

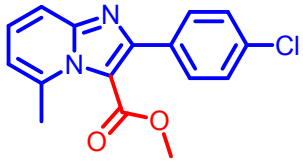
Yellow solid, mp 106 – 108 °C, n-hexane/EtOAc (90/10), 68% (45.0 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 9.17 (d, J = 7.0 Hz, 1H), 7.71 – 7.61 (m, 2H), 7.40 – 7.28 (m, 3H), 7.13 (d, J = 6.9 Hz, 1H), 6.85 (t, J = 7.0 Hz, 1H), 3.71 (s, 3H), 2.59 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 161.8, 153.3, 147.5, 134.8, 130.2, 128.7, 127.8, 127.6, 127.1, 126.2, 114.3, 112.2, 51.3, 17.2. GC-MS: *m/z* for



$C_{16}H_{14}N_2O_2$: 266 (M^+). HRMS (ESI): *m/z* calcd for $C_{16}H_{14}N_2O_2K$ $[M+K]^+$: 305.0692, found 325.0731

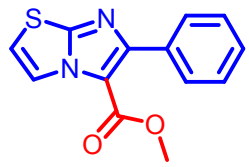
Methyl 2-(4-chlorophenyl)-5-methylimidazo[1,2-a]pyridine-3-carboxylate (6q)

Yellowish solid, mp 147 – 149 °C, n-hexane/EtOAc (90/10), 70% (53.0 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 9.19 (s, 1H), 7.70 (dd, *J* = 6.4, 4.5 Hz, 2H), 7.63 (d, *J* = 9.0 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 9.5 Hz, 1H), 3.82 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 161.4, 152.2, 146.2, 134.8, 133.0, 131.5, 131.3, 128.0, 126.3, 124.4, 116.8, 111.5, 51.3, 18.6. HRMS (ESI): *m/z* calcd for $C_{16}H_{14}ClN_2O_2$ $[M+H]^+$: 301.0744, found 301.0746.



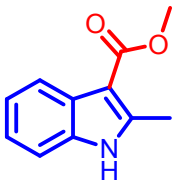
Methyl 6-phenylimidazo[2,1-b]thiazole-5-carboxylate (6r)

Yellowish solid, mp 114 – 116 °C, n-hexane/EtOAc (90/10), 52% (34.0 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (d, *J* = 4.5 Hz, 1H), 7.87 – 7.80 (m, 2H), 7.48 – 7.36 (m, 3H), 6.97 (d, *J* = 4.5 Hz, 1H), 3.86 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 160.6, 154.3, 153.1, 133.8, 129.9, 128.9, 127.9, 121.9, 114.6, 113.6, 51.7, GC-MS: *m/z* for $C_{13}H_{10}N_2O_2S$: 258 (M^+). HRMS (ESI): *m/z* calcd for $C_{13}H_{10}N_2O_2SK[M+K]^+$: 297.0100, found 297.0091

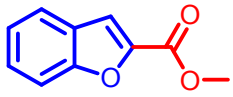


Methyl 2-methyl-1H-indole-3-carboxylate (6s)[27]

White solid, mp 149 – 151 °C, n-hexane/EtOAc (95/5), 78% (37.0 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.01 (d, *J* = 7.7 Hz, 1H), 7.21 (d, *J* = 7.9 Hz, 1H), 7.12 (dt, *J* = 14.8, 7.2 Hz, 2H), 3.86 (s, 3H), 2.64 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.8, 144.3, 134.7, 127.2, 122.5, 121.8, 121.3, 110.7, 104.5, 51.0, 14.3. HRMS (ESI): *m/z* calcd for $C_{11}H_{12}NO_2$ $[M+H]^+$: 190.0868, found 190.0878.

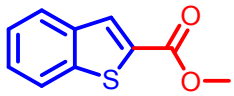


Methyl benzofuran-2-carboxylate (6t)[27]



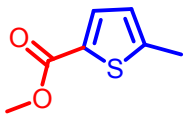
White solid, n-hexane/EtOAc (95/5), 70% (31 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.9 Hz, 1H), 7.59 (d, *J* = 8.3 Hz, 1H), 7.53 (s, 1H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 3.98 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 160.1, 155.8, 145.5, 127.8, 127.0, 123.9, 123.0, 114.1, 112.5, 52.5. GC-MS: *m/z* for $C_{10}H_8O_3$: 176 (M^+).

Methyl benzo[b]thiophene-2-carboxylate (6u)[32]



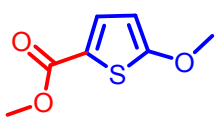
Yellowish solid, mp 62 – 64 °C, n-hexane/EtOAc (95/5), 65% (32.0 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.87 (t, *J* = 8.0 Hz, 2H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 3.95 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 163.4, 142.4, 138.8, 133.5, 130.8, 127.1, 125.7, 125.0, 122.9, 52.7. GC-MS: *m/z* for $C_{10}H_8O_2S$: 192 (M^+).

Methyl 2-methylthiophene-3-carboxylate(6v)[27]



Yellowish liquid, n-hexane/EtOAc (95/5), 80% (31.0 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (d, *J* = 3.2 Hz, 1H), 6.75 (d, *J* = 1.7 Hz, 1H), 3.85 (s, 3H), 2.51 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 162.7, 147.9, 133.9, 130.9, 126.4, 51.9, 15.7. GC-MS: *m/z* for $C_7H_8O_2S$: 156 (M^+).

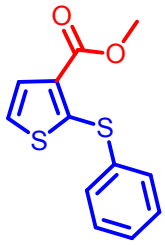
Methyl 5-methoxythiophene-2-carboxylate (6w)[35]



Yellowish liquid, n-hexane/EtOAc (95/5), 65% (28.0 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 (d, *J* = 4.3 Hz, 1H), 6.21 (d, *J* = 4.4 Hz, 1H), 3.93 (s, 3H), 3.82 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 172.5, 163.1, 133.4, 118.7, 105.6, 60.5, 52.1. GC-MS: *m/z* for $C_7H_8O_3S$: 172 (M^+).

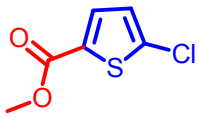
Methyl 5-(phenylthio)thiophene-2-carboxylate (6x)

Yellowish liquid, n-hexane/EtOAc (95/5), 76% (48.0 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, *J* = 4.5 Hz, 1H), 7.53 – 7.35 (m, 5H), 7.25 (d, *J* = 3.4 Hz, 1H), 3.98 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 161.9, 142.3, 136.0, 135.9, 133.9, 133.3, 133.2, 129.8, 129.4, 127.6, 52.3. GC-MS: *m/z* for $C_{12}H_{10}O_2S_2$: 250(M^+). HRMS (ESI): *m/z* calcd for $C_{12}H_{11}O_2S_2$ $[M+H]^+$: 251.0200, found 251.0187.



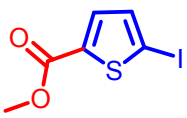
Methyl 5-chlorothiophene-2-carboxylate (6y)[34]

Colourless liquid, n-hexane/EtOAc (95/5), 80% (35.0 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 – 7.63 (m, 1H), 7.04 (d, *J* = 2.9 Hz, 1H), 3.98 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 161.8, 137.5, 133.2, 131.8, 127.4, 52.4. GC-MS: *m/z* for $C_6H_5ClO_2S$: 176(M^+).



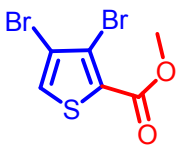
Methyl 5-iodothiophene-2-carboxylate (6z)[31]

Yellow solid, mp 91 – 93 °C, n-hexane/EtOAc (95/5), 70% (47.0 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 – 7.37 (m, 1H), 7.25 (dd, *J* = 6.2, 4.4 Hz, 1H), 3.86 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 161.4, 139.3, 137.9, 134.6, 82.9, 52.5, GC-MS: *m/z* for $C_6H_5IO_2S$: 268 (M^+).



Methyl 3,4-dibromothiophene-2-carboxylate(6aa)[27]

White solid, mp 137 – 139 °C, n-hexane/EtOAc (95/5), 67% (50.0 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (s, 1H), 3.92 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 160.4, 128.7, 120.5, 117.0, 52.7.GC-MS: *m/z* 300 (M^+).



General procedure and Characterization Data of the Synthesized Starting Compounds

<u>General procedure for the synthesis of 8-nitro quinoline substrates</u>:

All the 8-nitro quinolones substrate were prepared by the literature method [20c]

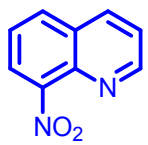
Representing procedure: Glycerol (2.97 mL, 2.7 equiv.) was taken in a 100 mL of oven-dried two-necked RB flask, 2-nitroaniline substance (15 mmol, 1 equiv.) and NaI (45 mg, 0.02 equiv.) were added over it. The mixture was stirred at room temperature for 5 min, then it was placed to an ice bath. Conc. H_2SO_4 (1.95 mL, 2.3 equiv.) was added dropwise with stirring for 10 min. Finally, the reaction mixture was heated at 140 °C for 2h with vigorous stirring. After completion of the reaction, the mixture was cooled to room temperature, diluted with 100 mL water and extracted with DCM (100 mL x4). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4, concentrated in vacuum to furnish yellowish 8-nitroquinoline derivative. The products were purified by flash chromatography using 5-10% ethyl acetate in n-hexane.

Spectral characterization data:

8-nitro quinoline reactant Spectral characterization data:

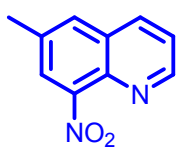
8-nitroquinoline (9a) [CAS Number: 607-35-2]

Yellow solid. 81%, (2.1 g) .^{1}H NMR (600 MHz, $CDCl_3$).δ 9.09 (d, J = 4.3 Hz, 1H), 8.28 (d, J = 8.7 Hz, 1H), 8.06 (dd, J = 6.9, 2.9 Hz, 2H), 7.63 (dd, J = 11.3, 4.8 Hz, 1H), 7.61 – 7.55 (m, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 152.8, 139.7, 136.3, 132.2, 129.2, 127.4, 125.5, 124.0, 123.0.



6-methyl-8-nitroquinoline (9b)[20C]

Yellowish solid. 85%, (2.4 g).^{1}H NMR (200 MHz, $CDCl_3$) δ 9.00 (dd, J = 4.2, 1.6 Hz, 1H), 8.16 (dd, J = 8.4, 1.7 Hz, 1H), 7.89 (d, J = 1.8 Hz, 1H), 7.80 (s, 1H), 7.51 (dd, J = 8.4, 4.2 Hz, 1H), 2.60 (s, 3H). ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ 151.9, 138.3, 135.9, 135.6, 131.0, 129.2, 125.9, 122.9, 21.5.



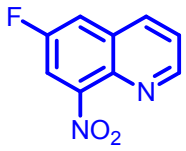
6-methoxy-8-nitroquinoline (9c)[20a]

Yellowish solid. 75%, (2.3 g).^{1}H NMR (600 MHz, $CDCl_3$) δ 8.90 (d, J = 3.4 Hz, 1H), 8.13 (d, J = 8.2 Hz, 1H), 7.69 (d, J = 1.8 Hz, 1H), 7.49 (dd, J = 8.4, 4.2 Hz, 1H),

7.27 (d, J = 2.2 Hz, 1H), 3.98 (s, 3H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 156.3, 150.1, 149.0, 135.6, 135.0, 130.2, 123.1, 116.8, 109.6, 56.3.

6-fluoro-8-nitroquinoline (9d)[37a]

Yellowish solid. 83%, (2.4 g).^{1}H NMR (600 MHz, $CDCl_3$) δ 9.07 – 9.01 (m, 1H), 8.26 – 8.20 (m, 1H), 7.86 (dd, J = 7.3, 2.5 Hz, 1H), 7.70 (dd, J = 8.0, 2.3 Hz, 1H), 7.59 (dd, J = 8.3, 4.3 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 158.1 (d, $^{1}J_{C\text{-}F}$ = 250 Hz) , 152.1, 149.0, 136.9, 135.7 (d, $^{3}J_{C\text{-}F}$ = 6 Hz), 129.7 (d, $^{3}J_{C\text{-}F}$ = 9 Hz), 123.7, 115.2 (d, $^{2}J_{C\text{-}F}$ = 21 Hz), 114.7 (d, $^{2}J_{C\text{-}F}$ = 30 Hz).

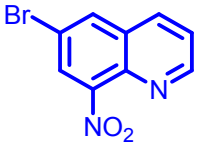


6-chloro-8-nitroquinoline (9e)[37b]

Yellowish solid. 82%, (2.6 g).^{1}H NMR (200 MHz, $CDCl_3$) δ 9.06 (dd, J = 4.2, 1.7 Hz, 1H), 8.19 (dd, J = 8.4, 1.7 Hz, 1H), 8.02 (q, J = 2.2 Hz, 2H), 7.59 (dd, J = 8.4, 4.2 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 152.9, 148.7, 138.2, 135.4, 131.2, 130.6, 129.8, 124.9, 123.8.

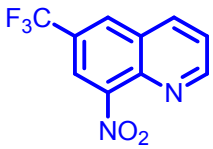
6-bromo-8-nitroquinoline (9f)[37d]

Yellowish solid. 76%, (2.9 g).^{1}H NMR (600 MHz, $CDCl_3$) δ 9.08 (s, 1H), 8.30 – 8.03 (m, 3H), 7.62 (dd, J = 22.8, 15.5 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 153.0, 138.4, 136.3, 135.3, 133.9, 130.2, 127.2, 125.5, 123.8, 118.4.



8-nitro-6-(trifluoromethyl)quinoline (9g)[37e]

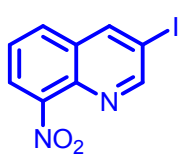
Yellow solid. 46%, (1.7 g).^{1}H NMR (600 MHz, $CDCl_3$) δ 9.19 (s, 1H), 8.47 – 8.33 (m, 2H), 8.21 (s, 1H), 7.71 (dd, J = 7.4, 3.3 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (151 MHz,) δ 154.8, 148.9, 140.6, 137.1, 129.6, 128.6, 127.9 (q, $^{2}J_{C\text{-}F}$ =33 Hz), 124.2, 122.9 (q, $^{1}J_{C\text{-}F}$ = 270 Hz), 119.9.



Iodination reaction of 8-nitro quinoline: 3-iodo-8-nitroquinoline by iodination from 8-nitroquinoline prepared according to the reported literature.[38]

To a mixture of 8-nitro quinoline (**9a**, 3 mmol, 1 equiv.) in MeCN (8 mL) was added in a 20 mL RBF with iodine (1.2 equiv.) and TBHP (8 equiv., 70% aq. solution) at RT. Then, the reaction mixture was heated at 80 ˚C for 24h. After completion of the reaction, the solvent was removed under reduced pressure and to the crude mixture aqueous saturated sodium thiosulfate solution was added. The mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure to produce a yellowish solid product. The pure product was isolated by flash chromatography using 10% EtOAc in n-hexanes (yield 85%).

3-iodo-8-nitroquinoline (9h)[38]



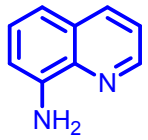
Yellowish solid. 85%, (765 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 9.18 (d, *J* = 2.0 Hz, 1H), 8.66 (s, 1H), 8.07 (d, *J* = 6.9 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.65 (t, *J* = 8.0 Hz, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 158.1, 148.4, 143.9, 137.8, 131.1, 130.5, 126.5, 124.4, 92.2.

General procedure for the synthesis of 8-amino quinoline derivatives:

All the substituted 8-amino quinolones were prepared by the literature method[39, 20a]

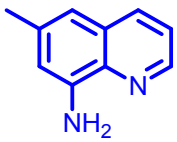
Representing procure: A mixture 8-nitroquinoline (**9a**, 522 mg, 3 mmol, 1.0 equiv.), activated charcoal (300 mg), iron chloride (97.32 mg, 20 mol%), and hydrazine monohydrate (5 equiv.) in methanol (15 mL) was stirred at 80 °C for 12 h. The reaction mixture was filtered through celite and the solvent was removed under reduced pressure to give 8-aminoquinoline. The pure product was isolated by flash chromatography using 10% EtOAc/n-hexanes.

Quinolin-8-amine (10a) [CAS Number: 578-66-5]



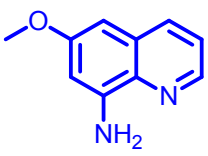
Pale yellow solid. 90%, (389 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 8.76 (d, J = 5.1 Hz, 1H), 8.11 – 8.00 (m, 1H), 7.37 – 7.34 (m, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 4.98 (s, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 147.6, 144.1, 138.6, 136.1, 129.0, 127.5, 121.5, 116.2, 110.2.

6-methylquinolin-8-amine (10b)[20c]



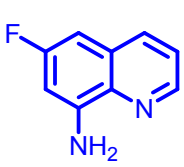
Pale yellow solid. 87%, (412 mg).^{1}H NMR (200 MHz, $CDCl_3$) δ 8.61 (dd, J = 4.2, 1.6 Hz, 1H), 7.88 (dd, J = 8.3, 1.6 Hz, 1H), 7.34 – 7.10 (m, 1H), 6.85 (s, 1H), 6.69 (d, J = 1.6 Hz, 1H), 4.81 (s, 2H), 2.35 (s, 2H). ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ 146.7, 143.7, 137.5, 137.4, 135.4, 129.0, 121.5, 115.4, 112.2, 22.1.

6-methoxyquinolin-8-amine (10c)[20a]



Pale yellow solid. 85%, (444 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 8.64 – 8.53 (m, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.31 (dd, J = 8.1, 4.5 Hz, 1H), 6.58 (d, J = 2.1 Hz, 1H), 6.48 (d, J = 2.1 Hz, 1H), 4.99 (s, 2H), 3.88 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 159.0, 145.2, 135.6, 134.9, 130.0, 122.0, 101.8, 94.7, 55.4.

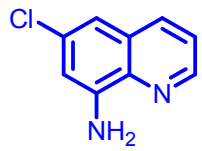
6-fluoroquinolin-8-amine (10d)[37a]



Pale yellow solid. 87%, (423 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 8.67 (d, J = 4.2 Hz, 1H), 8.05 – 7.88 (m, 1H), 7.35 (dd, J = 8.3, 4.0 Hz, 1H), 6.72 (dd, J = 9.2, 2.1 Hz, 1H), 6.65 (dd, J = 10.4, 2.2 Hz, 1H), 5.17 (s, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 161.7 (d, $^{1}J_{C\text{-}F}$ = 242 Hz), 146.5, 146.3 (d, $^{3}J_{C\text{-}F}$ = 13 Hz), 135.8, 135.6 (d, $^{4}J_{C\text{-}F}$ = 4.5 Hz), 129.5 (d, $^{3}J_{C\text{-}F}$ = 12 Hz), 122.3, 99.4 (d, $^{2}J_{C\text{-}F}$ = 30 Hz), 98.7 (d, $^{2}J_{C\text{-}F}$ = 23 Hz),

6-chloroquinolin-8-amine (10e)[37c]

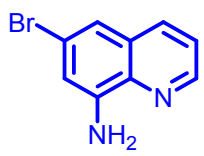
Pale yellow solid. %, (438 mg).^{1}H NMR (200 MHz, $CDCl_3$) δ 8.72 (dd, J = 4.2, 1.6 Hz, 1H),



7.96 (dd, J = 8.3, 1.7 Hz, 1H), 7.37 (dd, J = 8.3, 4.2 Hz, 1H), 7.10 (d, J = 2.1 Hz, 1H), 6.86 (d, J = 2.1 Hz, 1H), 5.09 (s, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 147.5, 145.3, 137.1, 135.3, 133.3, 129.4, 122.4, 114.5, 110.3.

6-bromoquinolin-8-amine (10f)[37d]

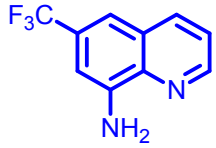
Pale yellow solid. 85%, (566 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 8.73 (d, J = 3.0 Hz, 1H), 7.95



(d, J = 8.3 Hz, 1H), 7.38 (dd, J = 8.1, 3.8 Hz, 1H), 7.27 (d, J = 11.6 Hz, 1H), 7.00 (s, 1H), 5.08 (s, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 147.7, 145.4, 137.3, 135.1, 129.9, 122.4, 121.5, 117.8, 112.9.

6-(trifluoromethyl)quinolin-8-amine (10g)[37e]

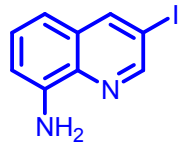
Pale yellow solid. 78%, (496 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 8.83 (s, 1H), 8.11 (d, J = 6.8



Hz, 1H), 7.42 (d, J = 20.1 Hz, 2H), 7.02 (s, 1H), 5.19 (s, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 149.4, 145.0, 139.3, 137.0, 129.4 (q, $^{2}J_{C\text{-}F}$ = 32 Hz), 127.9, 124.3 (q, $^{1}J_{C\text{-}F}$ = 270 Hz), 122.5, 113.3 (q, $^{3}J_{C\text{-}F}$ = 4.5 Hz), 105.0.

3-iodoquinolin-8-amine (10h)

Pale yellow solid. 81%, (656 mg).^{1}H NMR (600 MHz, $CDCl_3$).δ 8.85 (s, 1H), 8.42 (s, 1H), 7.32



(t, J = 7.9 Hz, 1H), 7.01 (d, J = 8.1 Hz, 1H), 6.91 (d, J = 7.5 Hz, 1H), 4.96 (s, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 152.6, 144.3, 143.7, 136.5, 130.7, 128.6, 115.1, 110.7, 90.5.

Preparation of 8-aminoquinolinyl amides:

All 8-aminoquinoline amides from the acid halide (compounds starting material 1a, 1c, 1d, 1e, 1f, 1h, 1i, 1j, 1k, 1l, 1p, 1t, 1u, 1x,1y, 1z) and from the carboxylic acid (compounds starting material 1g, 1m, 1n, 1o, 1q, 1r,1s, 1v,) prepared according to the reported literature.[38-40]

Procedure A: Synthesis of amide from the benzoyl chloride:

A 100 mL round bottom flask was charged with 8-aminoquinoline (**10a**, 865 mg, 6.0 mmol), Et_3N (1.1 ml, 1.2 equiv.), and dichloromethane (CH_2Cl_2, 20 ml) under an inert atmosphere. The corresponding acid chloride in dichloromethane was added slowly at 0ºC. The mixture was stirred for overnight at room temperature. The reaction was quenched with 10 mL of saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the pure product was isolated by flash chromatography using 10% EtOAc/n-hexane.

Procedure B: Synthesis from carboxylic acid:

A 50 mL round bottom flask was charged with the corresponding carboxylic acid (3 mmol), N, N-dimethylformamide (3 drops), and CH_2Cl_2 (12 mL) under an N_2 atmosphere at 0 °C. Oxalyl chloride (6.0 mmol, 2 equiv.) was added dropwise and the reaction mixture was stirred for 4 h at room temperature. The solvent was removed under reduced pressure. The acid chloride was used without further purification. A 100 mL two-neck round bottom flask was charged with 8-aminoquinoline **10a**, 561.6 mg, 1.3 equiv.), Et_3N (6 mmol, 0.850 ml), and dichloromethane (12 mL) under N_2 atmosphere at 0 °C. The corresponding acid chloride in dichloromethane was added dropwise to the reaction mixture stirred for overnight at room temperature. The reaction was quenched with 10 mL of saturated $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The pure product was isolated by flash chromatography using 5-10% EtOAc/n-hexane.

Spectral characterization data of 8-aminoquinolinyl amides:

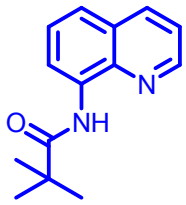
2,2-dimethyl-N-(quinolin-8-yl)butanamide (1a)

White solid. 96%, (1.40 g) .^{1}H NMR (600 MHz, $CDCl_3$).δ 10.24 (s, 1H), 8.86 – 8.76 (m, 2H),

8.15 (d, *J* = 8.2 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.45 (dd, *J* = 8.2, 4.1 Hz, 1H), 1.77 (q, *J* = 7.5 Hz, 2H), 1.39 (s, 6H), 0.96 (t, *J* = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 176.8, 148.4, 138.9, 136.4, 134.8, 128.1, 127.6, 121.7, 121.3, 116.3, 44.2, 34.3, 25.3, 9.5. HRMS (ESI): *m/z* calcd for $C_{15}H_{18}N_2OK$ $[M+K]^+$: 281.1056, found 281.1033

N-(quinolin-8-yl)pivalamide (1b)

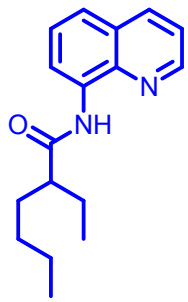
Colourless semisolid. 95%, (1.30 g) .^{1}H NMR (600 MHz, $CDCl_3$).δ 10.28 (s, 1H), 8.80 (d, *J* =



7.2 Hz, 2H), 8.14 (d, *J* = 8.1 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 1.43 (s, 9H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 177.4, 148.3, 138.9, 136.4, 134.8, 128.0, 127.6, 121.6, 121.3, 116.3, 40.5, 27.9. HRMS (ESI): *m/z* calcd for $C_{14}H_{17}N_2O$ $[M+H]^+$: 229.1341, found 229.1332

4-(heptan-3-yl)-N-(quinolin-8-yl)benzamide (1c)

Semi solid. 95%, (1.56 g) .^{1}H NMR (600 MHz, $CDCl_3$) δ 9.86 (s, 1H), 8.85 (d, *J* = 7.6 Hz, 1H),



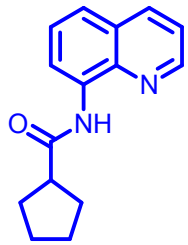
8.81 (s, 1H), 8.14 (t, *J* = 8.1 Hz, 1H), 7.53 (dd, *J* = 13.1, 7.4 Hz, 1H), 7.48 (t, *J* = 7.1 Hz, 1H), 7.44 (dt, *J* = 11.5, 5.8 Hz, 1H), 2.39 (s, 1H), 1.86 – 1.76 (m, 2H), 1.69 – 1.56 (m, 2H), 1.34 (d, *J* = 24.7 Hz, 4H), 1.01 (t, *J* = 7.4 Hz, 3H), 0.88 (t, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 175.1, 148.3, 138.5, 136.4, 134.6, 128.0, 127.5, 121.6, 121.4, 116.6, 51.1, 32.7, 29.9, 26.4, 22.9, 14.1, 12.2. HRMS (ESI): *m/z* calcd for $C_{17}H_{23}N_2O$ $[M+H]^+$: 271.1810, found 271.1799.

N-(quinolin-8-yl)cyclohexanecarboxamide (1d)

Semisolid. 98%, (1.50 g).^{1}H NMR (600 MHz, $CDCl_3$).δ 9.89 (s, 1H), 8.80 (s, 2H), 8.13 (t, *J* = 7.4 Hz, 1H), 7.55 – 7.41 (m, 3H), 2.52 – 2.43 (m, 1H), 2.08 (d, *J* = 12.5 Hz, 2H), 1.87 (d, *J* = 10.7 Hz, 2H), 1.73 (d, *J* = 11.6 Hz, 1H), 1.64 (q, *J* = 12.3 Hz, 2H), 1.34 (ddd, *J* = 25.0, 17.5, 6.7 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 175.0, 148.2, 138.6, 136.5, 134.7, 128.0, 127.5, 121.6, 121.4, 116.6, 47, 42.9, 29.9, 29.0, 25.9, 25.5. HRMS (ESI): *m/z* calcd for $C_{16}H_{19}N_2O$ $[M+H]^+$: 255.1497, found 255.1489.

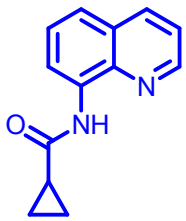
N-(quinolin-8-yl)cyclopentanecarboxamide (1e)

White solid. 97%, (1.40 g) .^{1}H NMR (600 MHz, $CDCl_3$).δ 9.87 (s, 1H), 8.79 (d, *J* = 7.9 Hz, 2H), 8.15 (d, *J* = 7.9 Hz, 1H), 7.53 (t, *J* = 7.9 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.44 (dd, *J* = 8.1, 4.5 Hz, 1H), 2.95 (p, *J* = 8.2 Hz, 1H), 2.10 – 1.94 (m, 4H), 1.89 – 1.79 (m, 2H), 1.72 – 1.63 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 175.2, 148.2, 138.5, 136.5, 134.9, 128.1, 127.6, 121.7, 121., 116.5, 47.5, 30.7, 26.1. HRMS (ESI): *m/z* calcd for $C_{15}H_{17}N_2O$ $[M+H]^+$: 241.1341, found 241.1327.



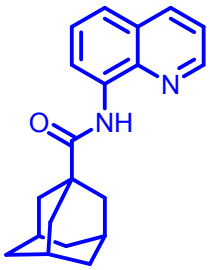
N-(quinolin-8-yl)cyclopropanecarboxamide (1f)

White solid. 95%, (1.20 g) .^{1}H NMR (600 MHz, $CDCl_3$).δ 10.02 (s, 1H), 8.81 (d, *J* = 4.7 Hz, 1H), 8.74 (d, *J* = 7.6 Hz, 1H), 8.18 – 8.13 (m, 1H), 7.52 (td, *J* = 7.9, 2.6 Hz, 1H), 7.50 – 7.43 (m, 2H), 1.81 (tt, *J* = 8.6, 4.4 Hz, 1H), 1.16 (dd, *J* = 6.9, 4.2 Hz, 2H), 0.93 – 0.89 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 172.4, 148.2, 138.4, 136.5, 134.8, 128.1, 127.6, 121.7, 121.3, 116.5, 16.4, 8.3. HRMS (ESI): *m/z* calcd for $C_{13}H_{13}N_2O$ $[M+H]^+$: 213.1028, found 213.1017



(3r,5r,7r)-N-(quinolin-8-yl)adamantane-1-carboxamide (1g)

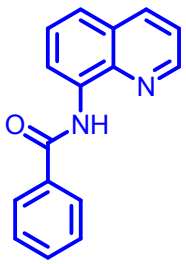
White solid. 90%, (1.1 g) .^{1}H NMR (600 MHz, $CDCl_3$) δ 10.23 (s, 1H), 8.85 – 8.80 (m, 2H),



8.17 – 8.10 (m, 1H), 7.55 – 7.50 (m, 1H), 7.50 – 7.41 (m, 2H), 2.14 (s, 3H), 2.11 (s, 6H), 1.81 (d, J = 1.5 Hz, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 176.9, 148.3, 139.0, 136.4, 134.8, 128.1, 127.6, 121.6, 121.3, 116.5, 42.4, 39.5, 36.7, 28.4. HRMS (ESI): *m/z* calcd for $C_{20}H_{23}N_2O$ $[M+H]^+$: 307.1810, found 307.1803.

N-(quinolin-8-yl)benzamide (1h)

White solid. 95%, (1.40 g) .^{1}H NMR (600 MHz, $CDCl_3$).δ 10.73 (s, 1H), 8.94 (d, J = 7.5 Hz,



1H), 8.82 (d, J = 2.5 Hz, 1H), 8.15 (d, J = 8.2 Hz, 1H), 8.08 (d, J = 7.5 Hz, 2H), 7.62 – 7.50 (m, 5H), 7.44 (dd, J = 7.7, 3.7 Hz, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 165.6, 148.4, 138.9, 136.5, 135.2, 134.7, 131.9, 128.9, 128.1, 127.5, 127.4, 121.8, 121.8, 116.7. HRMS (ESI): *m/z* calcd for $C_{16}H_{13}N_2O$ $[M+H]^+$: 249.1028, found 249.1012

N-(5,7-dideuterio-8-quinolinyl)benzamide (1h-D)

The amide was synthesized from benzoyl chloride and 5,7-dideuterio-8-aminoquinoline **(10a-D)** according to the general amide synthesis procedure.

White solid. 95%, (1.40 g).^{1}H NMR (600 MHz, $CDCl_3$) δ 10.75 (s, 1H), 8.85 (d, J = 3.0 Hz,

1H), 8.18 (dd, J = 7.6, 2.7 Hz, 1H), 8.09 (d, J = 7.0 Hz, 2H), 7.63 – 7.51 (m, 4H), 7.51 – 7.42 (m, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 165.6, 148.4, 138.9, 136.4, 135.3, 134.6, 132.0, 128.9, 128.0, 127.4, 127.3, 121.8, 121.7, 121.5, 121.3, 116.5, 116.4, 116.2. HRMS (ESI): *m/z* calcd for $C_{16}H_{11}D_2N_2O$ $[M+H]^+$: 251.1153, found 251.1140.

4-methyl-N-(quinolin-8-yl)benzamide (1i)

White solid. 94%, (1.49 g) .^{1}H NMR (600 MHz, $CDCl_3$).δ 10.72 (s, 1H), 8.94 (d, J = 7.6 Hz, 1H), 8.85 (s, 1H), 8.18 (d, J = 8.2 Hz, 1H), 7.99 (d, J = 7.6 Hz, 2H), 7.59 (t, J = 7.8 Hz, 1H), 7.53 (d, J = 8.3 Hz, 1H), 7.48 (s, 1H), 7.34 (d, J = 7.6 Hz, 2H), 2.45 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 165.6, 148.4, 142.5, 138.9, 136.5, 134.9, 132.5, 129.6, 128.1, 127.6, 127.5, 121.8, 121.7, 116.6, 21.7. HRMS (ESI): *m/z* calcd for $C_{17}H_{15}N_2O$ $[M+H]^+$: 263.1184, found 263.1165

4-methoxy-N-(quinolin-8-yl)benzamide (1j)

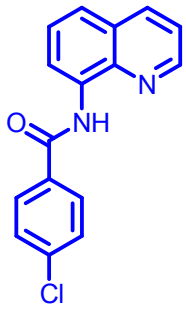
White solid. 95%, (1.58 g) .^{1}H NMR (600 MHz, $CDCl_3$). δ 10.68 (s, 1H), 8.92 (d, J = 7.7 Hz, 1H), 8.85 (d, J = 2.4 Hz, 1H), 8.18 (d, J = 8.6 Hz, 1H), 8.06 (d, J = 8.2 Hz, 2H), 7.59 (t, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.50 – 7.45 (m, 1H), 7.04 (d, J = 7.7 Hz, 2H), 3.89 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$)δ 165.18, 162.7, 148.4, 138.9, 136.5, 134.9, 133.0, 129.3, 128.2, 127.7, 121.8, 121.5, 116.5, 114.1, 55.6. HRMS (ESI): *m/z* calcd for $C_{17}H_{15}N_2O_2$ $[M+H]^+$: 279.1134, found 279.1116

4-fluoro-N-(quinolin-8-yl)benzamide (1k)

White solid. 93%, (1.48 g) .^{1}H NMR (600 MHz, $CDCl_3$)δ 10.70 (s, 1H), 8.91 (d, J = 7.0 Hz, 1H), 8.85 (d, J = 5.0 Hz, 1H), 8.19 (d, J = 8.0 Hz, 1H), 8.10 (dd, J = 8.4, 5.4 Hz, 2H), 7.60 (t, J = 7.8 Hz, 1H), 7.55 (d, J = 8.2 Hz, 1H), 7.48 (dd, J = 8.2, 3.9 Hz, 1H), 7.22 (t, J = 8.4 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$)δ 165.1(d, $^1J_{C\text{-}F}$ = 252 Hz), 164.5, 148.5, 138.9, 136.6, 134.6, 131.5, 129.8 (d, $^3J_{C\text{-}F}$ = 9 Hz), 128.1, 127.6, 122.0, 121.9, 116.7, 116.1 (d, $^2J_{C\text{-}F}$ = 21 Hz)). HRMS (ESI): *m/z* calcd for $C_{16}H_{12}FN_2O$ $[M+H]^+$: 267.0934, found 267.0922

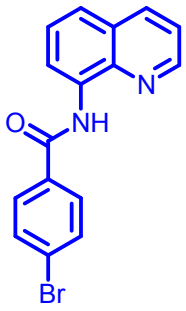
4-chloro-N-(quinolin-8-yl)benzamide (1l)

White solid. 93%, (1.57 g) .^{1}H NMR (600 MHz, $CDCl_3$).δ 10.72 (s, 1H), 8.91 (d, J = 7.6 Hz, 1H), 8.85 (d, J = 3.0 Hz, 1H), 8.20 (d, J = 8.1 Hz, 1H), 8.03 (d, J = 8.6 Hz, 2H), 7.60 (t, J = 7.9 Hz, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.52 (d, J = 8.6 Hz, 2H), 7.49 (dd, J = 8.1, 4.4 Hz, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 164.5, 148.5, 138.9, 138.3, 136.6, 134.5, 133.7, 129.2, 128.9, 128.2, 127.6, 122.1, 121.9, 116.8. HRMS (ESI): *m/z* calcd for $C_{16}H_{12}ClN_2O$ $[M+H]^+$: 283.0638, found 283.0624



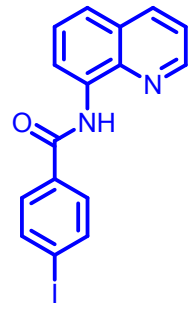
4-bromo-N-(quinolin-8-yl)benzamide (1m)

White solid. 91%, (1.16 g) .^{1}H NMR (600 MHz, $CDCl_3$).δ 10.72 (s, 1H), 8.91 (d, J = 7.5 Hz, 1H), 8.85 (d, J = 4.3 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 8.3 Hz, 2H), 7.69 (d, J = 7.8 Hz, 2H), 7.60 (t, J = 7.9 Hz, 1H), 7.56 (d, J = 8.1 Hz, 1H), 7.49 (dd, J = 8.0, 4.5 Hz, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 164.6, 148.5, 138.9, 136.6, 134.5, 134.2, 132.2, 129.1, 128.2, 127.6, 126.8, 122.1, 121.9, 116.8. HRMS (ESI): *m/z* calcd for $C_{16}H_{12}BrN_2O$ $[M+H]^+$: 327.0133, found 327.0140.

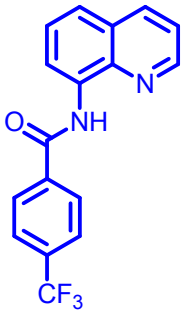


4-iodo-N-(quinolin-8-yl)benzamide (1n)

White solid. 90%, (1.31 g) .^{1}H NMR (600 MHz, $CDCl_3$). δ 10.72 (s, 1H), 8.90 (d, J = 6.9 Hz, 1H), 8.86 – 8.84 (m, 1H), 8.21 – 8.18 (m, 1H), 7.90 (d, J = 8.8 Hz, 2H), 7.80 (d, J = 8.3 Hz, 2H), 7.60 (t, J = 8.0 Hz, 1H), 7.56 (d, J = 7.7 Hz, 1H), 7.49 (dd, J = 8.1, 4.5 Hz, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 164.8, 148.5, 138.9, 138.2, 136.6, 134.8, 134.5, 129.0, 128.2, 127.6, 122.1, 121.9, 116.8, 99.1. HRMS (ESI): *m/z* calcd for $C_{16}H_{1a}IN_2OK$ $[M+K]^+$: 412.9553, found 412.9562.



N-(quinolin-8-yl)-4-(trifluoromethyl)benzamide (1o)

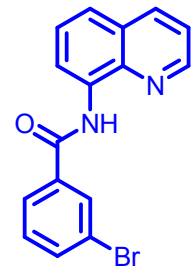


White solid. 91%, (1.72 g) .^{1}H NMR (600 MHz, $CDCl_3$).δ 10.78 (s, 1H), 8.91 (d, J = 7.1 Hz, 1H), 8.85 (s, 1H), 8.18 (d, J = 7.5 Hz, 3H), 7.81 (d, J = 7.7 Hz, 2H), 7.63 – 7.55 (m, 2H), 7.51 – 7.46 (m, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 164.2, 148.6, 138.8, 138.5, 136.6, 134.3, 133.6 (q, $^{2}J_{C\text{-}F}$ =31.5 Hz), 128.1, 127.9, 127.6, 126.0, 123.9 (q, $^{1}J_{C\text{-}F}$ = 271.5 Hz), 122.3, 122.0, 116.9. HRMS (ESI): *m/z* calcd for $C_{17}H_{12}F_3N_2O$ $[M+H]^+$: 317.0902, found 317.0908.

3-chloro-N-(quinolin-8-yl)benzamide (1p)

White solid. 89%, (979 mg) .^{1}H NMR (600 MHz, $CDCl_3$).δ 10.66 (s, 1H), 8.92 – 8.82 (m, 2H), 8.17 (dd, J = 21.9, 8.1 Hz, 1H), 8.05 (d, J = 10.1 Hz, 1H), 7.93 (dd, J = 13.6, 7.8 Hz, 1H), 7.62 – 7.42 (m, 5H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.1, 148.5, 138.8, 137.0, 136.5, 135.1, 134.4, 132.0, 130.2, 128.1, 127.8, 127.5, 127.5, 125.4, 122.1, 121.9, 116.8, 116.8. HRMS (ESI): *m/z* calcd for $C_{16}H_{12}ClN_2O$ $[M+H]^+$: 283.0638, found 283.0624

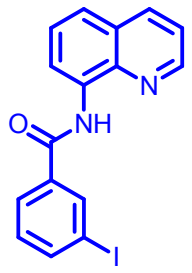
3-bromo-N-(quinolin-8-yl)benzamide (1q)



White solid. 90%, (1.14 g) .^{1}H NMR (600 MHz, $CDCl_3$).δ 10.68 (s, 1H), 8.92 – 8.83 (m, 2H), 8.23 – 8.16 (m, 2H), 7.99 (d, J = 8.0 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.62 – 7.54 (m, 2H), 7.49 (dd, J = 8.1, 4.5 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 164.0, 148.6, 138.9, 137.3, 136.6, 134.9, 134.4, 130.8, 130.5, 128.1, 127.6, 125.8, 123.2, 122.2, 121.9, 116.9.

3-iodo-N-(quinolin-8-yl)benzamide (1r)

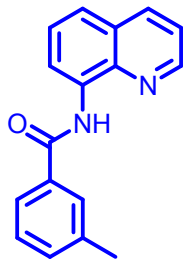
White solid. 94%, (1.37 g) .^{1}H NMR (600 MHz, $CDCl_3$). δ 10.66 (s, 1H), 8.91 – 8.82 (m, 2H),



8.40 (d, *J* = 7.8 Hz, 1H), 8.21 – 8.14 (m, 1H), 8.01 (t, *J* = 9.3 Hz, 1H), 7.90 (dd, *J* = 11.4, 8.0 Hz, 1H), 7.57 (dt, *J* = 25.3, 8.0 Hz, 2H), 7.51 – 7.44 (m, 1H), 7.28 (dd, *J* = 14.6, 6.7 Hz, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 163.9, 148.5, 140.8, 138.8, 137.3, 136.6, 136.6, 134.4, 130.5, 128.1, 127.5, 126.4, 122.1, 121.9, 116.8, 94.7. HRMS (ESI): *m/z* calcd for $C_{16}H_{11}IN_2OK$ $[M+K]^+$: 412.9553, found 412.9560

3-methyl-N-(quinolin-8-yl)benzamide (1s)

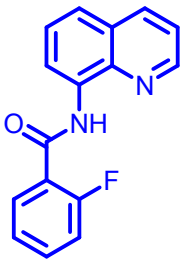
White solid. 95%, (1.49 g).^{1}H NMR (600 MHz, $CDCl_3$).δ 10.71 (s, 1H), 8.94 (d, *J* = 6.5 Hz, 1H), 8.86 (s, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.94 – 7.83 (m, 2H), 7.60 (t, *J* = 7.9 Hz, 1H), 7.54



(d, *J* = 8.1 Hz, 1H), 7.50 – 7.46 (m, 1H), 7.43 (t, *J* = 7.1 Hz, 1H), 7.39 (d, *J* = 7.3 Hz, 1H), 2.48 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 165.9, 148.4, 138.9, 138.8, 136.5, 135.3, 134.8, 132.7, 128.8, 128.2, 128.2, 127.6, 124.4, 121.8, 121.8, 116.7, 21.6 HRMS (ESI): *m/z* calcd for $C_{17}H_{15}N_2O$ $[M+H]^+$: 263.1184, found 263.1165

2-fluoro-N-(quinolin-8-yl)benzamide (1t)

Brownies solid. 92%, (1.46 g) .^{1}H NMR (600 MHz, $CDCl_3$).δ 11.16 (s, 1H), 8.98 (d, *J* = 7.3



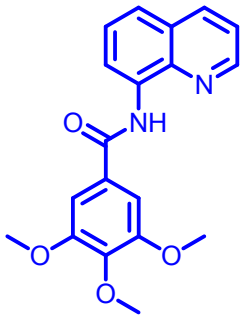
Hz, 1H), 8.87 (d, *J* = 3.2 Hz, 1H), 8.22 (t, *J* = 8.1 Hz, 1H), 8.17 (d, *J* = 8.1 Hz, 1H), 7.56 (tt, *J* = 14.5, 7.5 Hz, 3H), 7.46 (dd, *J* = 8.2, 3.9 Hz, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.24 (dd, *J* = 11.6, 8.3 Hz, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 161.8, 160.7 (d, $^{1}J_{C\text{-}F}$ = 248 Hz) 148.6, 138.9, 136.4, 135.0, 133.7 (d, $^{3}J_{C\text{-}F}$ = 9 Hz), 132.2, 128.1, 127.5, 125.0, 122.3, 122.2, 121.8, 117.4, 116.6 (d, $^{2}J_{C\text{-}F}$ = 24 Hz). HRMS (ESI): *m/z* calcd for $C_{16}H_{12}FN_2O$ $[M+H]^+$: 267.0934, found 267.0922

2-methyl-N-(quinolin-8-yl)benzamide(1u)

White solid. 93%, (1.46 g) .^{1}H NMR (600 MHz, $CDCl_3$). δ 10.21 (s, 1H), 8.95 (d, *J* = 7.5 Hz, 1H), 8.77 (d, *J* = 4.9 Hz, 1H), 8.18 (d, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 7.4 Hz, 1H), 7.60 (t, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.45 (dd, *J* = 8.3, 4.1 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.32 (dd, *J* = 9.7, 8.0 Hz, 2H), 2.61 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 168.3, 148.4, 138.8, 136.8, 136.8, 136.5, 134.9, 131.5, 130.5, 128.1, 127.6, 127.4, 126.2, 121.9, 121.8, 116.6, 20.3. HRMS (ESI): *m/z* calcd for $C_{17}H_{14}N_2OK$ $[M+K]^+$: 301.0743, found 301.0710

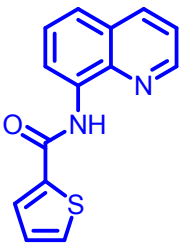
3,4,5-trimethoxy-N-(quinolin-8-yl)benzamide (1v)

White solid. 85%, (1.12 g) .^{1}H NMR (600 MHz, $CDCl_3$) δ 10.66 (s, 1H), 8.90 (d, *J* = 7.4 Hz, 1H), 8.85 (d, *J* = 4.2 Hz, 1H), 8.21 (d, *J* = 8.1 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.56 (d, *J* = 8.2 Hz, 1H), 7.49 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.31 (s, 2H), 4.00 (s, 6H), 3.94 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 165.4, 157.2, 153.5, 148.5, 141.49, 138.9, 136.6, 134.7, 130.9, 128.2, 127.7, 121.9, 116.7, 104.9, 61.1, 56.6. HRMS (ESI): *m/z* calcd for $C_{19}H_{18}N_2O_4K$ $[M+K]^+$: 377.0904, found 377.0880 and . HRMS (ESI): *m/z* calcd for $C_{19}H_{19}N_2O_4K$ $[M+H]^+$: 339.1345, found 339.1307

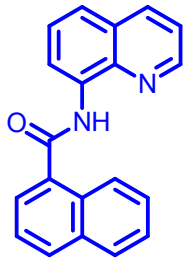


N-(quinolin-8-yl)thiophene-2-carboxamide (1x)

White solid. 98%, (1.49 g) .^{1}H NMR (600 MHz, $CDCl_3$)δ 10.60 (s, 1H), 8.87 – 8.81 (m, 2H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 3.6 Hz, 1H), 7.60 – 7.55 (m, 2H), 7.53 (d, *J* = 8.1 Hz, 1H), 7.47 (dd, *J* = 8.2, 4.3 Hz, 1H), 7.20 – 7.16 (m, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 160.2, 148.5, 140.2, 138.7, 136.5, 134.5, 131.1, 128.6, 128.1, 128.0, 127.6, 121.9, 121.8, 116.7. HRMS (ESI): *m/z* calcd for $C_{14}H_{11}N_2OS$ $[M+H]^+$: 255.0592, found 255.0577.

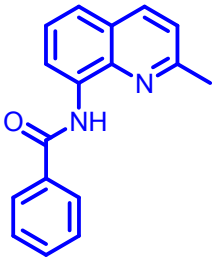


N-(quinolin-8-yl)-1-naphthamide (1y)



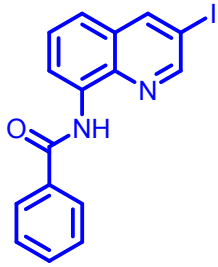
White solid. 90%, (1.60 g).^{1}H NMR (600 MHz, $CDCl_3$) δ 10.42 (s, 1H), 9.06 (d, *J* = 7.5 Hz, 1H), 8.73 (d, *J* = 2.9 Hz, 1H), 8.54 (d, *J* = 8.4 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.99 (d, *J* = 8.2 Hz, 1H), 7.91 (dd, *J* = 7.1, 4.8 Hz, 2H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.56 (dq, *J* = 14.8, 7.3 Hz, 4H), 7.42 (dd, *J* = 8.4, 4.1 Hz, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 167.8, 148.4, 138.8, 136.5, 135.0, 134.8, 134.0, 131.2, 130.5, 128.5, 128.1, 127.6, 127.4, 126.6, 125.7, 125.6, 125.0, 122.1, 121.8, 116.8. HRMS (ESI): *m/z* calcd for $C_{20}H_{14}N_2ONa$ [*M*+*Na*]$^{+}$: 321.1004, found 321.1011.

N-(2-methylquinolin-8-yl)benzamide (1z)



White solid. 95%, (1.49 g) .^{1}H NMR (600 MHz, $CDCl_3$).δ 10.81 (s, 1H), 8.89 (d, *J* = 7.5 Hz, 1H), 8.08 (d, *J* = 7.2 Hz, 2H), 8.03 (t, *J* = 8.6 Hz, 1H), 7.59 – 7.54 (m, 3H), 7.51 – 7.45 (m, 2H), 7.32 (dd, *J* = 10.8, 5.6 Hz, 1H), 7.22 – 2.76 (d, *J* = 4.7 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 165.5, 157.3, 138.2, 136.6, 135.4, 134.0, 131.9, 130.3, 128.9, 128.6, 127.4, 126.5, 126.2, 122.6, 121.6, 116.6, 25.5. HRMS (ESI): *m/z* calcd for $C_{17}H_{14}N_2OK$ [*M*+*K*]$^{+}$: 301.0743, found 301.0753.

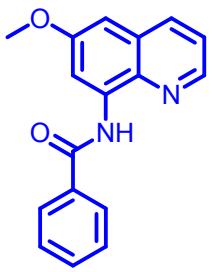
N-(3-iodoquinolin-8-yl)benzamide (1aa)



White solid. 90%, (2.01 g).^{1}H NMR (600 MHz, $CDCl_3$). δ 10.52 (s, 1H), 8.95 (d, *J* = 8.4 Hz, 2H), 8.55 (s, 1H), 8.06 (d, *J* = 7.9 Hz, 2H), 7.58 (dt, *J* = 14.9, 8.0 Hz, 4H), 7.42 (d, *J* = 8.2 Hz, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 165.6, 153.7, 144.2, 137.1, 135.1, 135.0, 132.1, 129.8, 129.0, 128.8, 127.4, 120.8, 117.3, 90.6. HRMS (ESI): *m/z* calcd for $C_{16}H_{11}IN_2OK$ [*M*+*K*]$^{+}$: 412.9553, found 412.9552. 6l

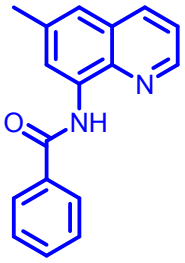
N-(6-methoxyquinolin-8-yl)benzamide (1ab)

White solid. 93%, (1.55 g).^{1}H NMR (600 MHz, $CDCl_3$). δ 10.71 (s, 1H), 8.68 (t, *J* = 4.3 Hz, 2H), 8.07 (dd, *J* = 14.9, 7.9 Hz, 3H), 7.60 – 7.54 (m, 3H), 7.42 (dd, *J* = 8.4, 4.0 Hz, 1H), 6.84 (d, *J* = 1.8 Hz, 1H), 3.96 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 165.6, 158.7, 145.8, 135.6, 135.5, 135.2, 132.1, 129.1, 129.0, 127.5, 122.3, 109.1, 100.2, 55.8. For $C_{17}H_{15}N_2O_2$ $[M+H]^+$: 279.1134, found 279.1116



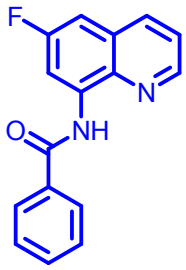
N-(6-methylquinolin-8-yl)benzamide (1ac)

White solid. 93%, (1.46 g) .^{1}H NMR (600 MHz, $CDCl_3$). δ 10.71 (s, 1H), 8.82 (s, 1H), 8.77 (d, *J* = 3.7 Hz, 1H), 8.12 – 8.05 (m, 3H), 7.59 – 7.54 (m, 3H), 7.46 – 7.41 (m, 1H), 7.32 (s, 1H), 2.58 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 165.6, 147.5, 137.8, 137.7, 135.8, 135.3, 134.3, 132.0, 129.0, 128.2, 127.4, 121.9, 120.8, 118.8, 22.5. HRMS (ESI): *m/z* calcd for $C_{17}H_{15}N_2O$ $[M+H]^+$: 263.1184, found 263.1165



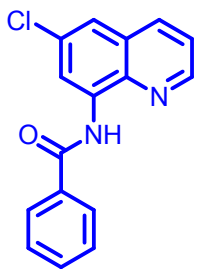
N-(6-fluoroquinolin-8-yl)benzamide (1ad)

White solid. 88%, (1.40 g) .^{1}H NMR (600 MHz, $CDCl_3$). δ 10.76 (s, 1H), 8.83 – 8.70 (m, 1H), 8.14 – 8.03 (m, 3H), 7.58 (dt, *J* = 26.1, 7.2 Hz, 3H), 7.52 – 7.44 (m, 1H), 7.18 – 7.09 (m, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 165.6, 161.1 (d, $^{1}J_{C\text{-}F}$ = 245 Hz), 147.5, 136.5 (d, $^{3}J_{C\text{-}F}$ = 13.5 Hz), 136.2, 135.9 (d, $^{4}J_{C\text{-}F}$ = 6 Hz), 134.7, 132.3, 129.0, 128.6 (d, $^{3}J_{C\text{-}F}$ = 10.5 Hz), 127.5, 122.8, 107.5 (d, $^{2}J_{C\text{-}F}$ =33 Hz), 104.5 (d, $^{2}J_{C\text{-}F}$ = 22.5 Hz). HRMS (ESI): *m/z* calcd for $C_{16}H_{12}FN_2O$ $[M+H]^+$: 267.0934, found 267.0922



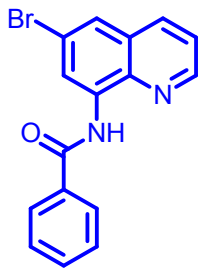
N-(6-chloroquinolin-8-yl)benzamide (1ae)

White solid. 90%, (1.52 g) .^{1}H NMR (600 MHz, $CDCl_3$). δ 10.71 (s, 1H), 8.98 (s, 1H), 8.90 – 8.79 (m, 1H), 8.14 – 8.04 (m, 3H), 7.61 (dd, *J* = 8.7, 5.6 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 2H), 7.54 (d, *J* = 1.8 Hz, 1H), 7.52 – 7.48 (m, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 165.6, 148.5, 137.5, 135.7, 134.8, 133.7, 132.3, 130.3, 129.0, 128.6, 127.5, 122.8, 120.3, 117.6. HRMS (ESI): *m/z* calcd for $C_{16}H_{12}ClN_2O$ $[M+H]^+$: 283.0638, found 283.0624



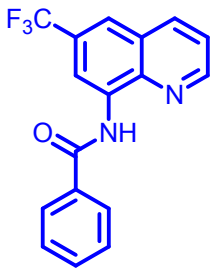
N-(6-bromoquinolin-8-yl)benzamide (1af)

White solid. 91%, (1.78 g) .^{1}H NMR (600 MHz, $CDCl_3$).δ 10.58 (s, 1H), 8.99 (s, 1H), 8.79 – 8.70 (m, 1H), 7.98 (d, *J* = 7.8 Hz, 3H), 7.60 (s, 1H), 7.49 (dt, *J* = 26.6, 7.5 Hz, 3H), 7.40 (dd, *J* = 8.3, 3.6 Hz, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 165.5, 148.6, 137.5, 135.6, 135.5, 134.8, 132.3, 129.0, 129.0, 127.4, 123.6, 122.8, 121.8, 120.0. HRMS (ESI): *m/z* calcd for $C_{16}H_{12}BrN_2O$ $[M+H]^+$: 327.0133, found 327.0140.



N-(6-(trifluoromethyl)quinolin-8-yl)benzamide (1ag)

White solid. 81%, (1.54 g) .^{1}H NMR (600 MHz, $CDCl_3$). δ 10.77 (s, 1H), 9.20 (d, *J* = 1.9 Hz, 1H), 8.97 (d, *J* = 2.4 Hz, 1H), 8.29 (dd, *J* = 8.0, 2.7 Hz, 1H), 8.09 (d, *J* = 7.4 Hz, 2H), 7.86 (s, 1H), 7.65 – 7.53 (m, 4H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 165.6, 150.4, 139.6, 137.5, 135.7, 134.4, 132.3, 129.5 (q, $^2J_{C\text{-}F}$ = 33 Hz), 129.0, 127.4, 127.0, 124.0 (q, $^1J_{C\text{-}F}$ = 271 Hz), 123.0, 119.2, 112.2. HRMS (ESI): *m/z* calcd for $C_{17}H_{12}F_3N_2O$ $[M+H]^+$: 317.0902, found 317.0908



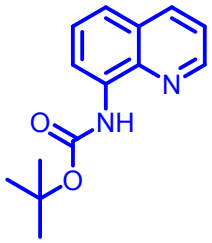
Synthesis of *tert*-butyl quinolin-8-ylcarbamate:[43]

Procedure: A mixture of 8-aminoquinoline (**10a**, 0.72 g, 5.00 mmol, 1.0 equiv), di-*tert*-butyl dicarbonate (2.2 g, 10.0 mmol, 2.0 equiv), and dioxane (14 mL) was stirred at 80 °C for 2 d.

The solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel to give **1w** (1.20, 98% yield).

***tert*-Butyl quinolin-8-ylcarbamate (1w)**

White solid. 98%, (1.20 g).^{1}H NMR (600 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.79 (s, 1H), 8.42 (d, J = 6.5 Hz, 1H), 8.13 (d, J = 8.2 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.42 (d, J = 7.6 Hz, 2H), 1.58 (s, 9H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 153.0, 148.1, 138.4, 136.4, 135.3, 128.2, 127.5, 121.7, 120.3, 114.6, 28.6, 27.6. HRMS (ESI): *m/z* calcd for $C_{14}H_{16}N_2O_2$ $[M+H]^+$: 245.1290, found 245.1286.



<u>Preparation of amides from the sulfonyl chloride</u>:

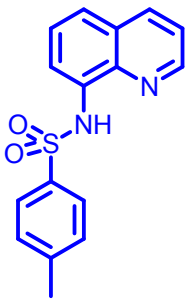
All sulfonamides were prepared according to the reported literature.[44-45]

Procedure: To a 100 mL round bottom flask was charged with 8-aminoquinoline (**10a**, 865 mg, 6.0 mmol), Et_3N (1.1 ml, 1.2 equiv.), and CH_2Cl_2 (12 ml) under an N_2 atmosphere. The corresponding sulfonyl chloride (1.2 equiv.) in dichloromethane was added slowly at 0 °C and further stirred at room temperature for overnight. The completion of the reaction was monitored by TLC. The reaction was quenched with 20 mL of saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude mixture was purified flash chromatography using silica gel and EtOAc/n-hexane (10-20%) as an eluent.

Spectral characterization data of quinolinyl sulphonamide:

4-methyl-N-(quinolin-8-yl)benzenesulfonamide (3a)

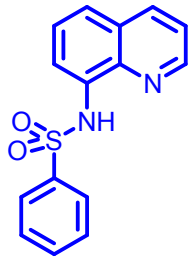
Brownies solid. 85%, (1.52 g) .^{1}H NMR (600 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.76 (d, J = 4.6 Hz, 1H), 8.09 (d, J = 7.9 Hz, 1H), 7.81 (dd, J = 10.4, 4.9 Hz, 3H), 7.46 – 7.38



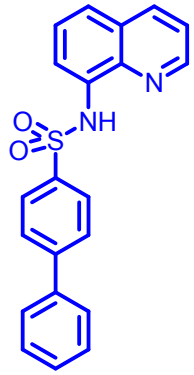
(m, 3H), 7.15 (d, J = 8.2 Hz, 2H), 2.29 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 148.8, 143.9, 138.6, 136.6, 136.3, 134.0, 129.7, 128.3, 127.4, 127.0, 122.1, 122.1, 115.0, 21.6. HRMS (ESI): *m/z* calcd for $C_{16}H_{15}N_2O_2S$ $[M+H]^+$: 299.0854, found 299.0833

N-(quinolin-8-yl)benzenesulfonamide (3b)

White solid. 83%, (1.41 g).^1H NMR (600 MHz, $CDCl_3$).δ 9.24 (s, 1H), 8.75 (d, J = 4.1 Hz,



1H), 8.09 (d, J = 8.1 Hz, 1H), 7.91 (d, J = 7.6 Hz, 2H), 7.83 (d, J = 6.9 Hz, 1H), 7.47 – 7.40 (m, 4H), 7.36 (t, J = 7.5 Hz, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 148.9, 139.5, 138.7, 136.4, 133.9, 133.0, 129.0, 128.3, 127.3, 127.0, 122.3, 122.1, 115.2. HRMS (ESI): *m/z* calcd for $C_{15}H_{13}N_2O_2S$ $[M+H]^+$: 285.0698, found 285.0698.

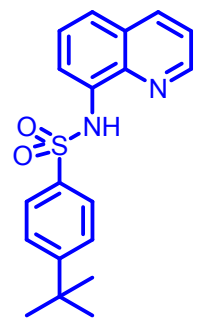


N-(quinolin-8-yl)-[1,1'-biphenyl]-4-sulfonamide (3c)

White solid. 77%, (1.66 g) .^1H NMR (600 MHz, $CDCl_3$).δ 9.28 (s, 1H), 8.77 (d, J = 3.0 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.97 (d, J = 8.1 Hz, 2H), 7.87 (dd, J = 6.1, 2.6 Hz, 1H), 7.59 – 7.53 (m, 2H), 7.47 (t, J = 8.4 Hz, 4H), 7.41 (dd, J = 13.9, 7.7 Hz, 3H), 7.36 (t, J = 7.1 Hz, 1H). $^{13}C\{^1H\}$ NMR (151 MHz $CDCl_3$,) δ 148.9, 145.9, 139.3, 138.7, 138.1, 136.4, 133.9, 129.1, 128.6, 128.4, 127.9, 127.6, 127.4, 127.0, 122.3, 122.1, 115.2. HRMS (ESI): *m/z* calcd for $C_{21}H_{17}N_2O_2S$ $[M+H]^+$: 361.1011, found 361.0993.

4-(*tert*-butyl)-N-(quinolin-8-yl)benzenesulfonamide (3d)

Brownies solid. 80%, (1.63 g).^1H NMR (600 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.76 (d, J = 3.7 Hz,

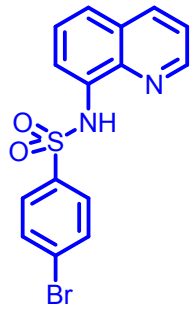


1H), 8.10 (d, J = 8.2 Hz, 1H), 7.83 (dd, J = 10.9, 5.1 Hz, 3H), 7.45 (d, J = 5.7 Hz, 2H), 7.42 (dd, J = 8.1, 4.3 Hz, 1H), 7.38 (d, J = 8.4 Hz, 2H), 1.23

(s, 9H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 156.8, 148.8, 138.6, 136.6, 136.4, 134.1, 128.3, 127.2, 127.1, 126.1, 122.1, 122.0, 114.80 35.2, 31.1. HRMS (ESI): *m/z* calcd for $C_{19}H_{21}N_2O_2S$ $[M+H]^+$: 341.1324, found 341.1307

4-bromo-N-(quinolin-8-yl)benzenesulfonamide (3e)

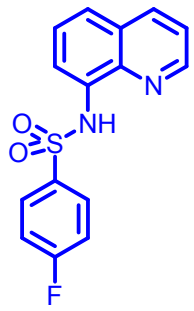
Brownies solid. 78%, (1.69 g).^{1}H NMR (600 MHz, $CDCl_3$).δ 9.25 (s, 1H), 8.77 – 8.74 (m, 1H),



8.11 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.51 – 7.41 (m, 5H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 149.0, 138.6, 138.5, 136.5, 133.5, 132.3, 128.9, 128.4, 128.1, 127.00, 122.7, 122.2, 115.6. HRMS (ESI): *m/z* calcd for $C_{15}H_{12}BrN_2O_2S$ $[M+H]^+$: 362.9803, found 362.9791

4-fluoro-N-(quinolin-8-yl)benzenesulfonamide (3f)

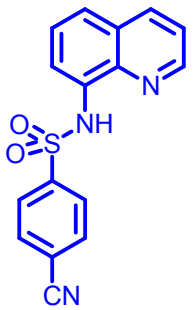
Brownies solid. 75%, (1.36 g) .^{1}H NMR (600 MHz, $CDCl_3$).δ 9.21 (s, 1H), 8.75 (d, *J* = 3.8 Hz,



1H), 8.10 (d, *J* = 8.2 Hz, 1H), 7.94 – 7.88 (m, 2H), 7.83 (d, *J* = 7.5 Hz, 1H), 7.47 (dd, *J* = 17.0, 7.9 Hz, 2H), 7.42 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.02 (t, *J* = 8.3 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 165.3 (d, $^{1}J_{C\text{-}F}$ = 254 Hz) , 149.0, 138.7, 136.5, 135.5, 133.7, 132.3 (d, $^{3}J_{C\text{-}F}$ = 9 Hz), 130.1, 128.4, 127.0, 122.7, 122.2, 116.3 (d, $^{2}J_{C\text{-}F}$ = 22.5 Hz), 115.6. HRMS (ESI): *m/z* calcd for $C_{15}H_{11}FN_2O_2SK$ $[M+K]^+$: 341.0162, found 341.0144

4-cyano-N-(quinolin-8-yl)benzenesulfonamide (3g)

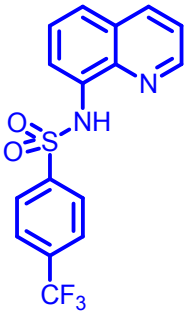
White solid. 85%, (1.58 g).^{1}H NMR (600 MHz, $CDCl_3$).δ 9.27 (s, 1H), 8.75 (d, *J* = 3.7 Hz,



1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 8.1 Hz, 2H), 7.86 (d, *J* = 7.4 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.44 (dd, *J* = 8.3, 4.5 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 149.2, 143.6, 138.7, 136.5, 133.0, 132.8, 128.4, 127.9, 126.9, 123.3, 122.4,

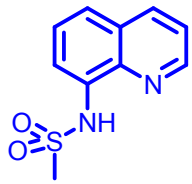
117.3, 116.7, 116.1. HRMS (ESI): *m/z* calcd for $C_{16}H_{12}N_3O_2S$ $[M+H]^+$: 310.0650, found 310.0644

N-(quinolin-8-yl)-4-(trifluoromethyl)benzenesulfonamide (3h)



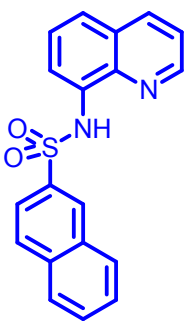
White solid. 88%, (1.86 g).^{1}H NMR (600 MHz, $CDCl_3$).δ 9.29 (s, 1H), 8.76 (d, *J* = 4.3 Hz, 1H), 8.12 (d, *J* = 8.1 Hz, 1H), 8.03 (d, *J* = 8.2 Hz, 2H), 7.86 (d, *J* = 7.2 Hz, 1H), 7.62 (d, *J* = 8.3 Hz, 2H), 7.51 (d, *J* = 8.1 Hz, 1H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.44 (dd, *J* = 8.3, 4.3 Hz, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 149.1, 143.0, 138.7, 136.5, 134.6 (q, $^2J_{C\text{-}F}$ = 33 Hz) 133.3, 128.4, 127.8, 127.0, 126.2 (q, $^3J_{C\text{-}F}$ = 3 Hz), 123.2 (q, $^1J_{C\text{-}F}$ = 270 Hz), 123.0, 122.3, 115.6. HRMS (ESI): *m/z* calcd for $C_{16}H_{12}F_3N_2O_2S$ $[M+H]^+$: 353.0572, found 353.0556.

N-(quinolin-8-yl)methanesulfonamide (3i)



White solid. 80%, (1.07 g) .^{1}H NMR (600 MHz, $CDCl_3$) δ 8.93 (s, 1H), 8.83 (d, J = 3.1 Hz, 1H), 8.21 – 8.18 (m, 1H), 7.86 (d, J = 7.5 Hz, 1H), 7.58 (d, J = 8.3 Hz, 1H), 7.54 (t, J = 7.9 Hz, 1H), 7.50 (dd, J = 8.3, 4.2 Hz, 1H), 3.03 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 149.1, 138.8, 136.5, 134.3, 128.6, 127.2, 122.6, 122.3, 115.3, 39.4. HRMS (ESI): *m/z* calcd for $C_{10}H_{11}N_2O_2S$ $[M+H]^+$: 223.0541, found 223.0535

N-(quinolin-8-yl)naphthalene-2-sulfonamide (3j)

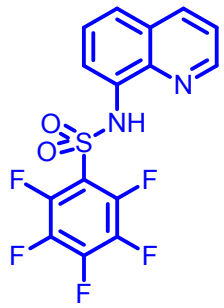


Brownies solid. 72%, (1.44 g) .^{1}H NMR (600 MHz, $CDCl_3$).δ 9.38 (s, 1H), 8.75 (d, *J* = 4.6 Hz, 1H), 8.52 (s, 1H), 8.06 (d, *J* = 9.2 Hz, 1H), 7.91 – 7.85 (m, 3H), 7.80 – 7.74 (m, 2H), 7.57 – 7.50 (m, 2H), 7.41 (t, *J* = 4.1 Hz, 2H), 7.38 (dd, *J* = 8.2, 4.3 Hz, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 148.7, 138.5, 136.6, 136.4, 135.0, 133.8, 132.0, 129.4, 129.4, 129.0, 128.9, 128.3, 127.9, 127.5, 127.0,

122.4, 122.33, 122.1, 115.4. HRMS (ESI): *m/z* calcd for $C_{19}H_{14}N_2O_2SNa$ $[M+Na]^+$: 357.0674, found 357.0669

2,3,4,5,6-pentafluoro-N-(quinolin-8-yl)benzenesulfonamide (3k)

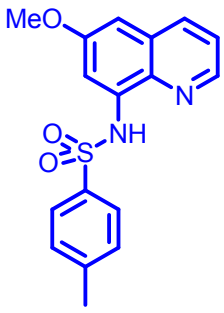
White solid. 70%, (1.57 g).^{1}H NMR (600 MHz, $CDCl_3$).δ 8.82 (d, *J* = 4.7 Hz, 1H), 8.16 (d, *J* = 7.9 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.52 – 7.46 (m, 2H).^{13}C NMR



(151 MHz, $CDCl_3$) ^{13}C{^{1}H} NMR (151 MHz,) δ 149.4, 138.5, 136.5, 132.4, 128.5, 127.0, 123.6, 122.6, 115.1. ^{19}F NMR (565 MHz,) δ -135.29, -135.31, -135.32, -135.32, -135.34, -135.35, -135.36, -135.38, -144.72, -144.73, -144.74, -144.75, -144.77, -144.78, -144.79, -144.80, -144.81, -158.39, -158.40, -158.41, -158.43, -158.44, -158.45, -158.46, -158.48, -158.50. HRMS (ESI): *m/z* calcd for $C_{15}H_8F_5N_2O_2S$ $[M+H]^+$: 375.0227, found 375.0217

N-(6-methoxyquinolin-8-yl)-4-methylbenzenesulfonamide (3l)

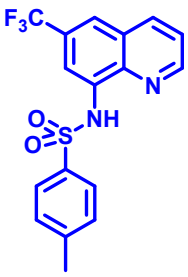
White solid. 79%, (1.56 g).^{1}H NMR (600 MHz, $CDCl_3$)·δ 9.20 (s, 1H), 8.58 (d, *J* = 4.2 Hz,



1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.0 Hz, 2H), 7.47 (s, 1H), 7.35 (dd, *J* = 8.3, 4.1 Hz, 1H), 7.18 (d, *J* = 7.9 Hz, 2H), 6.69 (s, 1H), 3.87 (s, 3H), 2.31 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 158.2, 146.2, 143.9, 136.5, 135.0, 129.7, 129.3, 127.4, 122.5, 107.4, 99.7, 55.7, 21.6. HRMS (ESI): *m/z* calcd for $C_{17}H_{16}N_2O_3SNa$ $[M+Na]^+$: 351.0779, found 351.0782 .

4-Methyl-N-(6-(trifluoromethyl)quinolin-8-yl)benzenesulfonamide (3m)

White solid. 62%, (113 mg for 0.5 mmol).^{1}H NMR (200 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.92



(dd, *J* = 4.3, 1.6 Hz, 1H), 8.23 (dd, *J* = 8.3, 1.6 Hz, 1H), 8.04 (d, *J* = 1.7 Hz, 1H), 7.94 – 7.84 (m, 2H), 7.80 (s, 1H), 7.59 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 2.36 (s, 3H). ^{13}C{^{1}H} NMR (50 MHz, $CDCl_3$) δ 150.8,

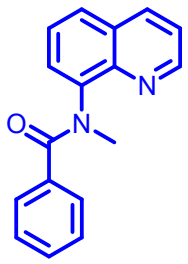
144.4, 139.3, 137.3, 136.0, 135.1, 129.8, 128.9 (q, $^{2}J_{C\text{-}F}$ = 33 Hz), 127.4, 127.2, 123.8 (q, $^{1}J_{C\text{-}F}$ = 271 Hz), 123.3, 119.5 (q, $^{3}J_{C\text{-}F}$ = 5 Hz), 110.0, (q, $^{3}J_{C\text{-}F}$ = 6 Hz), 21.5. HRMS (ESI): *m/z* calcd for $C_{17}H_{12}F_3N_2O_2S$ $[M+H]^+$: 367.0728, found 367.0748.

Synthesis of N-methyl-N-(quinolin-8-yl)benzamide:[46]

Procedure: To a suspension of sodium hydride (2.05 equiv, 50 mg, 1.24 mmol) in dry DMF (3 mL), was added to a solution of *N*-(quinolin-8-yl)benzamide (**1h**,1 equiv, 150 mg, 0.604 mmol) in dry DMF (3 mL) at 0 °C. The reaction mixture was allowed to room temperature and stirred for 3 h. Then methyl iodide (1.3 equiv, 49 µL, 0.785 mmol) was added dropwise and again stirred at room temperature for 1 h. After completion, the reaction mixture was diluted with DCM, the organic layer was washed with brine solution, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography. The *N*-methyl amide was isolated as a white solid **8a** (145.6 mg, 92% yield).

N-methyl-N-(quinolin-8-yl)benzamide (8a)

White solid. 92%, (145.6 mg).^{1}H NMR (600 MHz, $CDCl_3$)δ 8.99 (s, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.44 – 7.33 (m, 3H), 7.31 – 7.26 (m, 2H), 7.07 (s, 1H), 6.98 (s, 2H), 3.61 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 172.3, 150.7, 144.0, 142.6, 136.8, 136.3, 129.4, 129.3, 129.3, 128.1, 127.7, 127.5, 126.3, 121.8, 38.6.



Synthesis of N,N-dibenzylquinolin-8-amine:[43]

Procedure: To a solution of 8-aminoquinoline (**10a**, 144 mg, 1mmol, 1.0 equiv) in acetonitrile (3mL), benzyl bromide (152 µL, 1.2 mmol, 1.2 equiv), K_2CO_3 (414 mg, 3.0 mmol, 3.0 equiv), was added then stirred at 120 °C for 7 h. After completion of the reaction, the solvent was evaporated in vacuum and 100 mL ethyl acetate was added. The organic layer was washed with water and brine solution, dried over Na_2SO_4 and the organic portion was concentrated under

reduced pressure. The residue was purified by flash chromatography on silica gel (ethyl acetate/n-hexane) to give **8b** (291.7 mg, 90% yield)

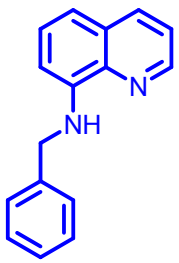
N,N-dibenzylquinolin-8-amine (8b)

Yellow colour solid. 90%, (291.7 mg) .^{1}H NMR (600 MHz, $CDCl_3$)δ 8.93 (d, *J* = 3.2 Hz, 1H), 8.08 (d, *J* = 8.1 Hz, 1H), 7.37 (dd, *J* = 8.1, 3.7 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 7.4 Hz, 4H), 7.23 (dd, *J* = 14.6, 7.2 Hz, 5H), 7.17 (t, *J* = 7.2 Hz, 2H), 6.90 (d, *J* = 7.7 Hz, 1H), 4.70 (s, 4H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 147.8, 147.1, 143.2, 138.9, 136.6, 129.9, 128.6, 128.2, 126.9, 126.5, 120.9, 120.7, 119.0, 56.8. HRMS (ESI): *m/z* calcd for $C_{23}H_{21}N_2$ $[M+H]^+$: 325.1705, found 325.1731

Synthesis of N-benzyl aminoquinoline: [43]

Procedure: To a solution of 8-aminoquinoline (**10a**, 432 mg, 3.00 mmol, 1.0 equiv) in pyridine (0.24 mL, 3.00 mmol, 1.0 equiv), benzyl chloride (0.52 mL, 4.50 mmol, 1.5 equiv) was slowly added, then the mixture was heated at 140 °C for 12 h. Pyridine was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (n-hexane/ ethyl acetate) to give desired product (**8c**, 561.9 mg, 80% yield)

N-benzylquinolin-8-amine (8c)



Yellow solid. 80%, (561.9 mg).^{1}H NMR (600 MHz, $CDCl_3$)δ 8.70 (s, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.43 (d, *J* = 6.2 Hz, 2H), 7.36 – 7.29 (m, 4H), 7.26 (d, *J* = 6.5 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.66 – 6.58 (m, 2H), 4.54 (s, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 147.0, 144.7, 139.4, 138.3, 136.1, 128.7, 127.9, 127.5, 127.2, 121.5, 114.3, 105.2, 47.8. HRMS (ESI): *m/z* calcd for $C_{16}H_{15}N_2$ $[M+H]^+$: 235.1235, found 235.1204.

Synthesis of N-(5-bromoquinolin-8-yl)-2,2-dimethylbutanamide:[47]

In a 10 mL reaction tube, were charged with 1 mmol (**1a**, 1 equiv) 2,2-dimethyl-N-(quinolin-8-yl)butanamide, 1.1 mmol NBS, 4 mmol potassium persulphate (4 equiv, $K_2S_2O_8$) in 4 mL methanol. Then the reaction tube is placed in a 50 °C in open to air condition for 2h. After completion of the reaction, the solvent was evaporated in vacuum and 25 mL ethyl acetate was added, the organic layer is washed with water and brine solution. After drying over Na_2SO_4, the organic portion was concentrated under reduced pressure. The brominated product (**8f**) was isolated by flash chromatography using Ethylacetate/n-hexane solvent system.

N-(5-bromoquinolin-8-yl)-2,2-dimethylbutanamide (8f)

White solid. 92%, (294.4 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 10.20 (s, 1H), 8.83 (d, *J* = 3.2 Hz, 1H), 8.71 (d, *J* = 8.3 Hz, 1H), 8.52 (d, *J* = 8.2 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.56 (dd, *J* = 8.6, 3.5 Hz, 1H), 1.76 (q, *J* = 7.4 Hz, 2H), 1.38 (s, 6H), 0.95 (t, *J* = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 176.9, 148.8, 139.6, 136.1, 134.7, 131.1, 127.3, 122.7, 116.9, 114.0, 44.3, 34.2, 25.2, 9.4. HRMS (ESI): *m/z* calcd for $C_{15}H_{17}BrN_2ONa$ [M+Na]+: 343.0422, found 343.0413

Synthesis of deuterated aminoquinoline: [48]

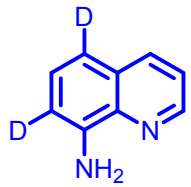
The deuterated 8-aminoquinoline was synthesized from 8-aminoquinoline with DCl/D_2O method by modified the literature reported procedure and the spectral characterization was confirmed with literature report.

Procedure: In a reaction tube with a magnetic stir bar, 8-amino quinoline **10a** (1 equiv, 1 mmol, 144 mg), Deuterium oxide (D_2O, 2 mL) and 35% DCl (120 µl) were added. The reaction mixture was heated at 170 °C for 1 h. After completion, the reaction mixture was cooled to room temperature and neutralized using a saturated aqueous solution of Na_2HCO_3. The aqueous part was extracted with dichloromethane (20 mL x 3). The combined organic part was dried over Na_2SO_4 and concentrated under reduced pressure. The pure bisdeuterated product (**10a-**

D, 98%, pale yellow solid) was isolated by flash chromatography using EA/ n-hexane solvent system.

5,7-dideuterio-8-aminoquinoline (10a-D)

Pale yellow solid. 98%, (143.2 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 8.68 (d, *J* = 3.7 Hz, 1H), 7.98 (d, *J* = 8.3 Hz, 1H), 7.27 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.25 (s, 1H), 4.90 (s, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 147.6, 144.0, 138.5, 136.1, 128.9, 127.3, 121.4, 116.0, 115.9, 115.7, 110.0, 109.9, 109.7.



ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

A copy of ^{1}H, ^{13}C and ^{19}F NMR spectra, KIE experimental data, CV data and the crystallographic data of this work are available in the SI file (PDF).

AUTHOR INFORMATION

Corresponding Author

* E-mail: scghosh@csmcri.res.in

ORCID

Subhash Chandra Ghosh: 0000-0002-6528-1582

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We are thankful to the SERB, DST, India (EMR/2016/002427), for financial support for this work. The authors also acknowledge AESD&CIF of CSIR-CSMCRI for constant analytical support. CS, TS, and HS thanks to CSIR, DST, and UGC for their fellowship respectively. CSIR-CSMCRI Communication No. 010/2019.

REFERENCES:

1. (a) Hughes, C .C; MacMillan, B. J.; GaudÞncio, P. S.; Fenical, W; La Clair, J. J. Ammosamides A and B target myosin. *Angew. Chem. Int. Ed*. **2009**, *48*, 728 -732. (b) Hughes, C. C; MacMillan, B. J.; GaudÞncio, P. S.; Jensen, R. P.; Fenical, W. the ammosamides: structures of cell cycle modulators from a marine-derived streptomyces species. *Angew. Chem. Int. Ed*. **2009**, *48*, 725 -727. (c) Vale, N.; Moreira, R.; Gomes, P. Primaquine revisited six decades after its discovery. *E. J. Med. Chem.* **2009**, *44,* 937–953. (d) Abouelhassan, Y.; Garrison, T. A; Burch, M. G.; Wong, W.; Norwood, M. V.; Huigens, W. R. Discovery of quinoline small molecules with potent dispersal activity against methicillin-resistant Staphylococcus aureus and Staphylococcus epidermidis biofilms using a scaffold hopping strategy. *Bioorg. Med. Chem. Lett*. **2014**, *24*, 5076-5080. (e) Zhong, F.; Geng, G.; Chen, B.; Pan, T.; Li, Q.; Zhang, H.; Bai, C. Identification of benzenesulfonamide quinoline derivatives as potent HIV-1 replication inhibitors targeting Rev protein**.** *Org. Biomol. Chem***.,** **2015**, *13*, 1792-1799. (f) Tran, C.; Gallavardin, T.; Petit, M.; Slimi, R.; Dhimane, H.; Blanchard-Desce, M.; Acher, C. F.; Ogden, D.; Dalko, I. P. Two-Photon "Caging" Groups: Effect of Position Isomery on the Photorelease Properties of Aminoquinoline-Derived Photolabile Protecting Groups. *Org. Lett.*,**2015**,*17*, 402–405.

2. (a) Kaur, K.; Jain, M.; Reddy, P. R.; Jain, R. Quinolines and structurally related heterocycles as antimalarials. *E. J. Med. Chem*. **2010**, *45*, 3245-3264. (b) Colomb, J.; Becker, G.; Fieux, S.; Zimmer, Luc.; Billard, T. Syntheses, Radiolabelings, and in Vitro Evaluations of Fluorinated PET Radioligands of 5-HT6 Serotoninergic Receptors. *J. Med. Chem.* **2014**, *57*, 3884-3890.

3. Foroumadi, A.; Emami, S.; Mansouri, S.; Javidnia, A.; Adeli, S. N.; Shirazi, H. F.; Shafiee, Abbas. Synthesis and antibacterial activity of levofloxacin derivatives with certain bulky residues on piperazine ring. *E. J. Med. Chem*. **2007**, *42*, 985-992.

4. (a) Rouffet, M..; Oliveira, F. de .C. A.; Udi, Y.; Agrawal, A.; Sagi, I.; McCammon, Andrew. J.; Cohen, M. S. From Sensors to Silencers: Quinoline- and Benzimidazole-Sulfonamides as Inhibitors for Zinc Proteases. *J. Am. Chem. Soc.,* **2010**, *132* ,8232–8233. (b) Rouffet, M.; Cohen, M. S. Emerging trends in metalloprotein inhibition. *Dalton Trans.*, **2011**, *40*, 3445–3454. (c) Major Jourden, L. J.; Daniel, B. K.; Cohen.; M. S. Investigation of self-immolative linkers in the design of hydrogen peroxide activated metalloprotein inhibitors. *Chem. Commun.,* **2011**, *47*, 7968–7970 (d) Xia, S.; Liu, G.; Pu, S.; A highly selective fluorescence sensor for Zn2+ and Cu2+ based on diarylethene with a piperazine-linked amidoquinoline unit. *J. Mater. Chem.C,* **2015**, *3*, 4023-4029.

5. (a) Horchler, C. L.; McCauley, J. P.; Hall, Jr. J. E.; Snyder, D. H.; Moore, W. C.; Hudzik, T. J.; Chapdelaine, M. Synthesis of novel quinolone and quinoline-2-carboxylic acid (4-morpholin-4-yl-phenyl)amides: A late-stage diversification approach to potent 5HT1B antagonists. J. *Bioorg. Med. Chem*. **2007**, *15*, 939–950; (b) Musiol, R.; Jampilek, J.; Kralova, K.; Richardson, D. R.; Kalinowski, D.; Podeszwa, B.; Finster, J.; Niedbala, H.; Palka, A.; Polanski, Investigating biological activity spectrum for novel quinoline analogues. J. *Bioorg. Med. Chem*. **2007**, *15*, 1280–1288.

6. For selected examples, see (a) Kwak, J.; Kim, M.; Chang, S. Rh(NHC)-Catalyzed Direct and Selective Arylation of Quinolines at the 8-Position. *J. Am. Chem. Soc.* **2011**, *133*, 3780-3783. (b) Tobisu, M.; Hyodo, I.; Chatani, N. Nickel-Catalyzed Reaction of Arylzinc Reagents with N-Aromatic Heterocycles: A Straightforward Approach to C−H Bond Arylation of Electron-Deficient Heteroaromatic Compounds. *J. Am. Chem. Soc*. **2009**, *131*, 12070-12071. (c) Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. Direct

C−H Arylation of Electron-Deficient Heterocycles with Arylboronic Acids. *J. Am. Chem. Soc.* **2010**, *132*, 13194-13196. (d) Chen, Q.; du Jourdin, X. M.; Knochel, P. Transition-Metal-Free BF3-Mediated Regioselective Direct Alkylation and Arylation of Functionalized Pyridines Using Grignard or Organozinc Reagents. *J. Am. Chem. Soc*. **2013**, 135, 4958-4961 (e) Hwang, H.; Kim, J.; Jeong, J.; Chang, S. Regioselective Introduction of Heteroatoms at the C-8 Position of Quinoline N-Oxides: Remote C–H Activation Using N-Oxide as a Stepping Stone. *J. Am. Chem. Soc.* **2014**, *136*, 10770-.10776 (f) Yamamoto, S.; Saga, Y.; Andou, T.; Matsunaga, S.; Kanai, M. Cobalt-Catalyzed C-4 Selective Alkylation of Quinolines. *Adv. Synth. Catal,* **2014**, *356*, 401-405. (g) Iwai, T.; Sawamura, M. Transition-Metal-Catalyzed Site-Selective C–H Functionalization of Quinolines beyond C_2 Selectivity. *ACS Catal,* **2015**, *5*, 5031-5040 and references cited therein.

7. Khan, B.; Dutta, H. S.; Koley, D. Remote C-H Functionalizationof 8-Aminoquinolinamides. *Asian. J. Org. Chem* **2018**, *7*, 1270-1297.

8. (a) Suess, M. A.; Ertem, Z. M.; Cramer, J. C.; Stahl, S. S. Divergence between Organometallic and Single-Electron-Transfer Mechanisms in Copper(II)-Mediated Aerobic C–H Oxidation. *J. Am. Chem. Soc.* **2013**, *135*, 9797−9804. (b) Qiao, H.; Sun, S.; Yang, F.; Zhu, Y.; Kang, J.; Wu, Yusheng; Wu, Y. Merging Photoredox Catalysis with Iron(III) Catalysis: C5-H Bromination and Iodination of 8-Aminoquinoline Amides in Water. *Adv. Synth. Catl.* **2017**, *359*, 1976-1980. (c) Dua,Y.; Liu, Y.; Wan, J-P.; Copper-Catalyzed One-Pot N-Acylation and C5–H Halogenation of 8-Aminoquinolines: The Dual Role of Acyl Halides. *J. Org. Chem.* **2018**, *83*, 3403−3408 (d) Motati, D.R.; Uredi, D.; Watkins, E. B. A general method for the metal-free, regioselective, remote C–H halogenation of 8-substituted quinolines. *Chem. Sci.,* **2018**, *9*, 1782–1788 and references cited therein.

9. (a) Qiao, H.; Sun, S.; Yang, F.; Zhu, Y.; Zhu, W.; Dong, Y.; Wu, Y.; Kong, X.; Jiang, L.; Wu, Y. Copper(I)-Catalyzed Sulfonylation of 8-Aminoquinoline Amides with Sulfonyl

Chlorides in Air. *Org. Lett.* **2015**, *17*, 6086−6089. (b) Wang, K., Wang, G., Duan, G., Xia, C. Cobalt(II)-Catalyzed Remote C5-Selective C–H Sulfonylation of Quinolines *via* Insertion of Sulfur dioxide. *RSC Adv.,* **2017**, *7,* 51313–51317. (c) Xia, H., An, Y., Zeng, X., Wu, J. A copper-Catalyzed Sulfonylative C–H bond Functionalization from Sulfur dioxide and Aryldiazonium tetrafluoroborates. *Org. Chem. Front.,* **2018,** *5*, 366–370 and references cited therein.

10. (a) He, Y., Zhao, N., Qiu, L., Zhang, X., & Fan, X . Regio- and Chemoselective Mono- and Bisnitration of 8-Amino quinoline Amides with $Fe(NO_3)_3 \cdot 9H_2O$ as Promoter and Nitro Source. *Org. Lett.,* **2016,** *18,* 6054–6057. (b) Zhu, X., Qiao, L., Ye, P., Ying, B., Xu, J., Shen, C., & Zhang, P. Copper-Catalyzed Rapid C–H Nitration of 8-Aminoquinolines by Using Sodium Nitrite as the Nitro Source Under Mild Conditions. *RSC Adv.,* **2016,** 6, 89979–89983. (c) Whiteoak, C. J., Planas, O., Company, A., & Ribas, X. AFirst Example of Cobalt-Catalyzed Remote C-H Functionalization of 8-Aminoquinolines Operating through a Single Electron Transfer Mechanism. *Adv. Synth. Catal.,* **2016**, 358, 1679 – 1688.

11. Dou, Y., Xie, Z., Sun, Z., Fang, H., Shen, C., Zhang, P., & Zhu, Q. Copper(II)-Catalyzed Direct Azidation of N-Acylated 8-Aminoquinolines by Remote C-H Activation. *ChemCatChem,* **2016,** *8,* 3570–3574.

12. Xia, C., Wang, K., Xu, J., Shen, C., Sun, D., Li, H., Wang.; Zhang, P. Selective Remote Esterification of 8-Aminoquinoline Amides via copper(II)-Catalyzed C(sp2)–O Cross-Coupling Reaction. *Org. Biomol. Chem.,* **2017,** *15*, 531–535.

13. (a) Sun, M., Sun, S., Qiao, H., Yang, F., Zhu, Y., Kang, J., Wu, Y.; Wu, Y. Silver(I)-promoted C5–H Phosphonation of 8-Aminoquinoline Amides with H-phosphonates. *Org. Chem. Front.*, **2016**, *3*, 1646–1650. (b) Qiao, H., Sun, S., Zhang, Y., Zhu, H., Yu, X., Yang, F., Wu, Y.; Li, Z.; Wu, Y. Merging Photoredox Catalysis with transition metal catalysis: site-

Selective C4 or C5-H Phosphonation of 8-Aminoquinoline Amides. *Org. Chem. Front.* **2017,** *4,* 1981–1986.

14. (a) Zhu, L., Qiu, R., Cao, X., Xiao, S., Xu, X., Au, C.-T., & Yin, S.-F.; Copper-Mediated Remote C–H Bond Chalcogenation of Quinolines on the C5 Position. *Org. Lett*. **2015**, *17*, 5528−553 (b) Yu, Q., Yang, Y., Wan, J.-P., & Liu, Y. Copper-Catalyzed C5−H Sulfenylation of Unprotected 8-Aminoquinolines Using Sulfonyl Hydrazides. *J. Org. Chem.* **2018**, *83*, 11385−11391

15. Shen, C., Yang, M., Xu, J., Chen, C., Zheng, K., Shen, J., Zhang, P. Iodobenzene Catalyzed Synthesis of Aryl Sulfonate Esters from Aminoquinolines via Remote radical C–O Cross-coupling. RSC Adv., **2017**, *7*, 49436-49439.

16. (a) Ji, D., He, X., Xu, Y., Xu, Z., Bian, Y., Liu, W., Zhu, Q., Xu, Y. Metal-Free Remote C–H Bond Amidation of 8-Amidoquinolines on the C5 Position under Mild Conditions. *Org. Lett*. **2016**, *18*, 4478−4481 (b) Sahoo, H., Reddy, M. K., Ramakrishna, I., & Baidya, M. Copper-Catalyzed 8-Amido Chelation-Induced Remote C-H Aminationof Quinolines. *Chem. Eur. J.* **2016**, *22*, 1592 – 1596. (c) Yi, H., Chen, H., Bian, C., Tang, Z., Singh, A. K., Qi, X., Yue, X.; Lan, Y.; Lee, J-F.; Lei, A. Coordination strategy-induced selective C–H amination of 8-aminoquinolines. *Chem. Commun.,* **2017**, *53*, 6736—6739.

17. (a) Cong, X., & Zeng, X. Iron-Catalyzed, Chelation-Induced Remote C–H Allylation of Quinolines via 8-Amido Assistance. *Org. Lett.* **2014**, *16*, 3716−3719 (b) Reddy, M. D., Fronczek, F. R., & Watkins, E. B. Rh-Catalyzed, Regioselective, C–H Bond Functionalization: Access to Quinoline-Branched Amines and Dimers. *Org. Lett***., 2016***, 18,* 5620–5623.

18. (a) Chen, H., Li, P., Wang, M., & Wang, L. Nickel-Catalyzed Site-Selective C–H Bond Difluoroalkylation of 8-Aminoquinolines on the C5-Position. *Org. Lett.*, **2016**, *18* (19), 4794–4797. (b) Chen, C., Zeng, R., Zhang, J., & Zhao, Y. Ruthenium Catalyzed Difluoroalkylation of 8-Aminoquinoline Amides at the C5 Position. *Eur. J. Org. Chem.* **2017**, 6947–6950. (c)

Han, S., Liang, A., Ren, X., Gao, X., Li, J., Zou, D., Wu, Y., Wu, Y. Copper-catalyzed remote C-H Ethoxycarbonyl Difluoromethylation of 8-Aminoquinolines with Bis(pinacolato)diboron as Reductant. *Tetrahedron Letters*, **2017**, *58*, 4859–4863

19. Mondal, S.; Hajra, A. Metal-Free C-5 Hydroxylation of 8-Aminoquinoline Amide. *J. Org. Chem*. **2018**, *83*, 11392-11398.

20. (a) Kuninobu, Y., Nishi, M., Kanai, M. 5-Position-selective C–H trifluoromethylation of 8-aminoquinoline Derivatives. *Org. Biomol. Chem.,* **2016**, *14*, 8092–8100. (b) Jin, L.-K., Lu, G.-P., Cai, C. Copper-Catalyzed 8-amido Chelation-induced Regioselective C–H Fluoroalkylation of Quinolones. *Org. Chem. Front.,* **2016**, *3*, 1309–1313.. (c) Xu, J., Qiao, L., Ying, B., Zhu, X., Shen, C., Zhang, P. Transition-metal-free direct Perfluoroalkylation of Quinoline amides at C5 Position Through Radical Cross-Coupling Under Mild Conditions. *Org. Chem. Front.,* **2017**, *4*, 1116–1120 and references cited therein.

21. (a) Sahoo, H., Mandal, A., Selvakumar, J., Baidya, M. Remote C–H Selenylation of 8-Amidoquinolines via Copper-Catalyzed Radical Cross-Coupling. *Eur. J. Org. Chem*.**2016**, 4321-4327; (b) Chen, J., Wang, T., Wang, T., Lin, A., Yao, H., Xu, J. Copper-catalyzed C5-selective thio/selenocyanation of 8-aminoquinolines *Org. Chem. Front.*, **2017**, *4*, 130–134.

22. for selected reviews on visible light induced photocatalysis (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis., *Chem. Rev*. **2013**, *113*, 5322-5363. (b) Skubi, K. L.; Blum, T. R.; Yoon, T. P. Dual Catalysis Strategies in Photochemical Synthesis. *Chem. Rev*. **2016**, *116,* 10035-10074 (c) Xuan, J.; Zhang, Z. G.; Xiao, W. J. Visible Light Induced Decarboxylative Functionalization of Carboxylic Acids and Their Derivatives. *Angew. Chem., Int. Ed*. **2015**, *54*, 15632 – 15641. (d) Konig, B. Photocatalysis in Organic Synthesis – Past, Present, and Future. *Eur. J. Org. Chem*. **2017**, 1979-1981; (e) I. Ghosh, L. Marzo, A. Das, R. Shaikh, B. König, Visible Light Mediated Photoredox Catalytic Arylation Reactions. *Acc.*

Chem. Res. **2016**, *49*, 1566–1577 (f) Boubertakh, O.; Goddard, J.-P. Construction and Functionalization of Heteroarenes by Use of Photoredox Catalysis. *Eur. J. Org. Chem*.**2017**, 2072–2084; (g) *Visible Light Photocatalysis in Organic Chemistry* (Ed: Stephenson, C. R. J., Yoon, T. P.; MacMillan, D. W. C.) Wiley-VCH, Weinheim. **2018**.

23. Khusnutdinov, R. I., Baiguzina, A. R., & Mukminov, R. R. Synthesis of 1-benzofuran-2-carboxylates by Reaction of 1-benzofuran with Halomethanes and Alcohols in the Presence of Iron Compounds., *Russian Journal of Organic Chemistry,* **2011**, *47*, 437–441.

24. Barlow, H. L., Teskey, C. J., & Greaney, M. F. Ruthenium-Catalyzed meta-Carboxylation., *Org. Lett.*,**2017**,*19*, 6662–6665.

25. Sahoo, T.; Sen, C.; Singh, H.; Suresh, E.; Ghosh, S. C. Copper-Catalyzed C-4 Carboxylation of 1-NaphthylamideDerivatives with CBr4/MeOH, Adv. Synth. Catal. 10.1002/adsc.201900482

26. Song, C., Chen, P., Tang, Y. Carboxylation of Styrenes with CBr_4 and DMSO via Cooperative Photoredox and Cobalt catalysis., *RSC Adv*., **2017**, *7*, 11233-11243.

27. Yang, Q-Q., Marchini, M., Xiao, W-J., Ceroni, P., and Bandini, M., Visible-Light-Induced Direct Photocatalytic Carboxylation of Indoles with CBr_4/MeOH. *Chem. Eur. J.* **2015**, *21*, 18052 – 18056.

28. (a) Sen, C.; Ghosh, S. C. Transition Metal Free Regioselective Alkylation of Quinoline N-Oxides via Oxidative Alkyl Migration and C−C Bond Cleavage of *tert/sec* Alcohols., *Adv. Synth. Catal*. **2018**, *360*, 905 –910. (b) Singh, H.; Sen, C.; Sahoo. T. Ghosh. S. C. A Visible Light Mediated Regioselective Halogenation of Anilides and Quinolines by Using a Heterogeneous Cu-MnO Catalyst., *Eur. J. Org. Chem*. **2018**, 4748-4753. (c) Sen, C.; Sahoo, T.; Ghosh, S. C. Regio Selective C-H Halogenation of 8-Amido Quinolines under Transition Metal Free Conditions. *ChemistrySelect*. **2017**, *2*, 2745-2749.

29. (a) Meeusen, J. W.; Tomasiewicz, H.; Nowakowski, A.; Petering, D. H. TSQ (6-Methoxy-8-p-Toluenesulfonamido-Quinoline), a Common Fluorescent Sensor for Cellular Zinc, Images Zinc Proteins., *Inorg. Chem*. **2011**, *50*, 7563-7573; (b) Fahrni, C. J.; O'Halloran, T. V. Aqueous Coordination Chemistry of Quinoline-Based Fluorescence Probes for the Biological Chemistry of Zinc. *J. Am. Chem. Soc*. **1999**,*121*, 11448–11458.

30. Zhu, S. Q.; Liu, Y. L.; Li, H.; Xu, X.; H. Qing F. L. Direct and Regioselective C−H Oxidative Difluoromethylation of Heteroarenes *J. Am. Chem. Soc*. **2018**, *140*, 11613−11617.

31. Yin, Q., Wang, S-G., Liang, X-W., Gao, D-W., Zheng, J., You, S-L., Organocatalytic Asymmetric Chlorinative Dearomatization of Naphthols. *Chem. Sci*., **2015**, *6*, 4179-4183.

32. Cheng, J., Zhu, M., Wang, C., Li, J., Jiang, X., Wei, Y., Xiao, J. Chemoselective Dehydrogenative Esterification of Aldehydes and Alcohols with a Dimeric Rhodium(ii) Catalyst. *Chemical Science*,**2016***, 7,* 4428–4434.

33. D'Auria, M., & Mauriello, G. Bis-(trifluoroacetoxy)iodobenzene iodine system: An Efficient and Selective Reagent for Iodination of Thiophene Derivatives. *Tetrahedron Letters*,**1995**, *36,*4883–4884.

34. Marzo, L., Wang, S., & König, B. Visible-Light-Mediated Radical Arylation of Anilines with Acceptor-Substituted (Hetero)aryl Halides. *Organic Letters*, **2017**, *19*, 5976–5979.

35. Satonaka, H. The Substituent Effects in Thiophene Compounds. .1H NMR and IR Studies in Methyl (Substituted 2-Thiophenecarboxylate). *Bulletin of the Chemical Society of Japan*, **1983**, *56*, 2463–2468.

36. Aoyama, T., Okutome, T., Nakayama, T., Yaegashi, T., Matsui, R., Nunomura, Sfujii, S. Synthesis and structure-activity study of protease inhibitors. IV. Amidinonaphthols and related acyl derivatives. *Chemical & Pharmaceutical Bulletin*.**1985**, *33*, 1458-1471

37. (a) Gershon, H., Clarke, D. D., & Gershon, M., Preparation of 6-Fluoro-8-quinolinol and

related 6-Fluoroquinolines. *Monatshefte Fur Chemie*, **2002**, *133*, 1437–1442. (b) Kassem, S., Lee, A. T. L., Leigh, D. A., Markevicius, A., & Solà, J. Pick-up, transport and release of a molecular cargo using a small-molecule robotic arm. *Nature Chemistry*, **2015**, *8*, 138–143. (c) Pratt, T. Y., & Drake, L. N. *Quinolinequinones. V. 6-Chloro- and 7-Chloro-5,8-quinolinequinones. J. Am. Chem. Soc,* **1960** *,82,* 1155–1161. (d) Stanek, J., Konrad, M., Mannsperger, J., Hoffmann, A., & Herres-Pawlis, S. Influence of functionalized substituents on the electron-transfer abilities of copper guanidinoquinoline complexes. *Eur. J. Inorg. Chem*. **2018**, 4997–5006. (e) Lüdtke, C., Haupt, A., Wozniak, M., & Kulak, N. Synthesis of fluorine-containing 1,10-phenanthrolines using mild versions of skraup and doebner-von miller reactions. *Journal of Fluorine Chemistry*, **201**7, *193*, 98–105

38. Sharma, K. K.; Patel, D. I.; Jain, R. Metal-Free Synthesis of N-Fused Heterocyclic Iodides via C-H Functionalization Mediated by Tert-Butylhydroperoxide. *Chem. Commun.* **2015**, *51*, 15129–15132.

39. Petit, M.; Tran, C.; Roger, T.; Gallavardin, T.; Dhimane, H.; Palma-Cerda, F.; Blanchard-Desce, M.; Acher, F. C.; Ogden, D.; Dalko, P. I. Substitution Effect on the One- and Two-Photon Sensitivity of DMAQ "Caging" Groups. *Org. Lett.* **2012**, *14*, 6366–6369.

40. Zhang, S. Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. Pd-Catalyzed Monoselective Ortho - C–H Alkylation of N -Quinolyl Benzamides: Evidence for Stereoretentive Coupling of Secondary Alkyl Iodides. *J. Am. Chem. Soc.* **2015**, *137*, 531–539.

41. Wang, Z.; Ni, J.; Kuninobu, Y.; Kanai, M. Copper-Catalyzed Intramolecular C(Sp 3)-H and C(Sp 2)-H Amidation by Oxidative Cyclization. *Angew. Chemie Int. Ed.* **2014**, *53*, 3496–3499.

42. He, Z.; Huang, Y. Diverting C−H Annulation Pathways: Nickel-Catalyzed Dehydrogenative Homologation of Aromatic Amides. *ACS Catal.* **2016**, *6*, 7814–7823.

43. Kuninobu, Y.; Nishi, M.; Kanai, M. 5-Position-Selective C-H Trifluoromethylation of 8-Aminoquinoline Derivatives. *Org. Biomol. Chem.* **2016**, *14*, 8092–8100.

44. Kalsi, D.; Sundararaju, B. Cobalt Catalyzed C-H and N-H Bond Annulation of Sulfonamide with Terminal and Internal Alkynes. *Org. Lett.* **2015**, *17*, 6118–6121.

45. Thrimurtulu, N.; Nallagonda, R.; Volla, C. M. R. Cobalt-Catalyzed Aryl C-H Activation and Highly Regioselective Intermolecular Annulation of Sulfonamides with Allenes. *Chem. Commun.* **2017**, *53*, 1872–1875.

46. Whiteoak, C. J.; Planas, O.; Company, A.; Ribas, X. A First Example of Cobalt-Catalyzed Remote C-H Functionalization of 8-Aminoquinolines Operating through a Single Electron Transfer Mechanism. *Adv. Synth. Catal.* **2016**, *358*, 1679–1688.

47. Sen, C.; Sahoo, T.; Ghosh, S. C. Regio-Selective C−H Halogenation of 8-Amido-Quinolines under Transition Metal-Free Conditions. *ChemistrySelect* **2017**, *2*, 2745–2749.

48. Martins, A., & Lautens, M. A Simple, Cost-Effective Method for the Regioselective Deuteration of Anilines. *Org. Lett.*, **2008**, *10*, 4351–4353.