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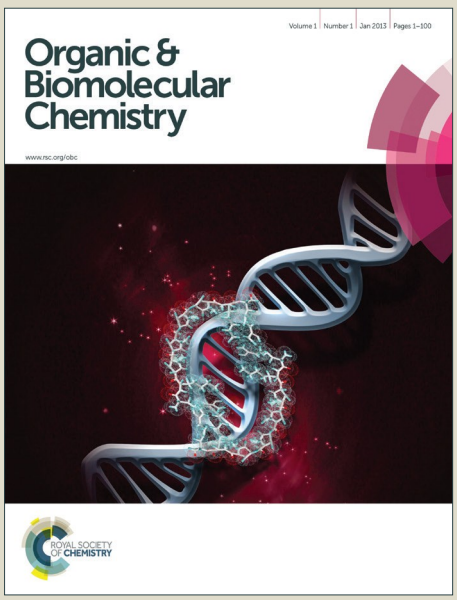

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ARTICLE

Divergent Copper-mediated dimerization and hydroxylation of benzamides involving C-H bond functionalization

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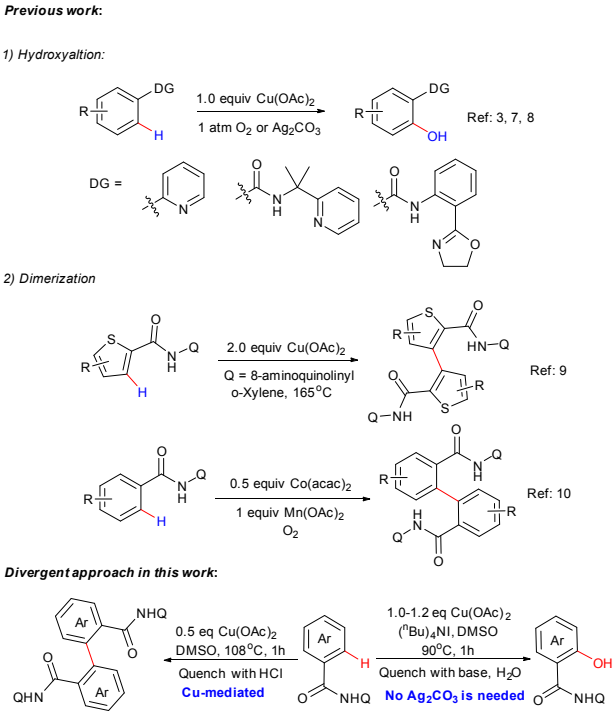
Convenient methods were developed for copper-mediated oxidative C-H activation of aminoquinoline benzamides. The reaction conditions can be tuned to give either hydroxylation or dimerization compounds as the major products effiecntly. Preliminary mechanistic studies suggested that different coordination states of copper may lead to different reaction outcomes.

Introduction

Directed C-H bond functionalizations mediated by transition metals have attracted extensive research interests recently and have led to practical applications in natural product synthesis and pharmaceutical research.[1] Copper-mediated oxidative C–H functionalization is an important research direction,[2] as copper salts are generally inexpensive and abundant. Such transformations can be facilitated by either monodentate (represented by the C-H functionalization of 2-arylpyridines reported independently by Yu[3] and Chatani[4] in 2006) or bidentate ligands (showcased by the 8-aminoquinoline-derived auxiliary[5] first developed by Daugulis). A variety of other directing groups have been developed since then, including the the 2-(pyridine-2-yl)isopropyl (PIP) group reported by Shi[6] and co-workers. The PIP group can promote ortho-selective hydroxylation and methoxylation using Ag_2CO_3 as the oxidant.[7] During the preparation of our manuscript, a simple method of copper-mediated ortho-selective hydroxylation of arenes using molecular oxygen as the oxidant was reported by Yu and co-workers with oxazol-2-yl as the directing group[8]. Besides copper-mediated hydroxylation, there were only limited reports exploring dimerization of arenes through a directed C-H functionalization. In 2014, Miura *et al.* reported aminoquinoline-directed homocoupling of thiophenes mediated by copper.[9] Very recently, the Daugulis group reported a novel Co- and Mn-promoted dimerization of aminoquinoline benzamides.[10] Herein we report a divergent approach for both dimerization and hydroxylation of arenes through aerobic copper-mediated C-H functionalization. We found that small variations of additives could direct the reaction toward different pathways. These easy-to-operate and robust protocols may facilitate the preparation of important building blocks in medicinal chemistry.



Scheme 1 Cu-mediated dimerization and hydroxylation of benzamides

Results and discussion

In our efforts for the hydroxylation of 4-fluoro benzamide, following a slightly modified procedure from the report by Shi and co-workers,[7] with aminoquinoline instead of PIP as the directing group,

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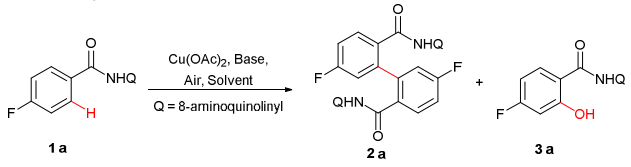
we found that hydroxylation product (**3a**) could be obtained in 56% yield, with a 19% isolated yield of the dimerization product (**2a**). To our surprise, applying similar condition without Ag_2CO_3 afforded a 60% yield of the dimerization product **2a**, along with a 30% yield of the hydroxylation product **3a** (Table 1, entry 1-2). The different preference toward either reaction pathway spurred our further interest in investigating the detail and identifying a divergent approach to either dimerization or hydroxylation. In the presence of 1 equivalent of K_2CO_3 at 100 °C with reaction mixture simply opened to air, the yield of dimerization product **2a** was improved to 76% (Table 1, entry 3). The loading of $Cu(OAc)_2$ could be lowered to 0.5 equivalent without affecting the outcome of the reaction. Further reduction of $Cu(OAc)_2$ loading reduced the reaction conversion significantly (Table 1, entry 4-6). Thus we used 0.5 equivalent $Cu(OAc)_2$ in our standard condition for dimerization. It should be noted that in the report by Miura *et al*,[9] the dimerization reaction proceeded at a higher temperature (165 °C) and longer time (3 hr), which is likely due to the use of non-polar solvents such as o-xylene, and the absence of a base. In contrast, we postulated that basic conditions and a polar solvent such as DMSO may promote a more facile formation of copper complex via deprotonation of the amide, which was reflected in our screening of different solvents (Table 1, entry 7-9). These combined factors may account for generally higher yields and milder conditions with our procedures.

Hydroxylation was favored when TBAI was added as an additive (Table 1, entry 10). After optimization of reaction temperature, and the loading of $Cu(OAc)_2$ and TBAI, a 66% yield of the hydroxylation product (**3a**) was obtained using 1.1 equivalents of $Cu(OAc)_2$ and 2 equivalents of TBAI. The reaction proceeded at 90 °C for 1 h with the reaction mixture open to air (Table 1, entry 16). More detailed reaction discovery and optimization process can be found in the supporting information.

Table 1 Optimization of the reaction conditions[a]

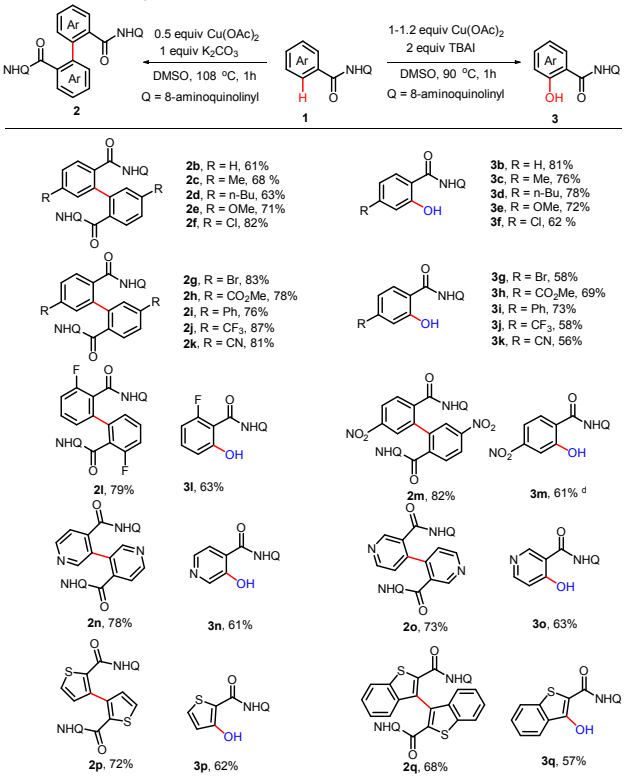


Entry	$Cu(OAc)_2$ (equiv)	Base/Additive (equiv)	Solvent	Yield [b] (**2a**/**3a** %)
1	1.0	Ag_2CO_3 (1.0)	DMSO	19 / 56
2	1.0	None	DMSO	58 / 21
3	1.0	K_2CO_3 (1.0)	DMSO	76 / 8
4	0.5	K_2CO_3 (1.0)	DMSO	78 / <5
5[c]	**0.5**	**K_2CO_3 (1.0)**	**DMSO**	**84 / <5**
6	0.2	K_2CO_3 (1.0)	DMSO	34 / <5
7	0.5	K_2CO_3 (1.0)	Toluene	9 / <5
8	0.5	K_2CO_3 (1.0)	dioxane	11 / <5
9	0.5	K_2CO_3 (1.0)	DMF	72 / 12
10	1.0	TBAI (2.0)	DMSO	9 / 73
11	1.0	TBAI (1.0)	DMSO	11 / 68
12	0.5	TBAI (2.0)	DMSO	<5 / 48
13	1.1	TBAI (2.0)	DMSO	<5 / 75
14	2.0	TBAI (2.0)	DMSO	9 / 75
15[d]	1.1	TBAI (2.0)	DMSO	<5 / 42
16[e]	**1.1**	**TBAI (2.0)**	**DMSO**	**<5 / 78**
17[d]	1.0	K_2CO_3 (1.0)	DMSO	8/32
18[d]	2.0	K_2CO_3 (1.0)	DMSO	38/41
19[d]	2.0	TBAI(2.0)	DMSO	<5/63

[a] Reaction conditions: **1a** (0.2 mmol), Cu salt, base (0.2 mmol), solvent (2 mL), 100 °C, air, 1h. [b] Isolated yield. [c] 108 °C for 1hr [d] under Ar atmosphere. [e] 90 °C for 1hr;

With the optimized conditions in hand, we then examined the scope of benzamide substrates for both dimerization and hydroxylation (Table 2).

Table 2 The scope of substrates[a, b, c]



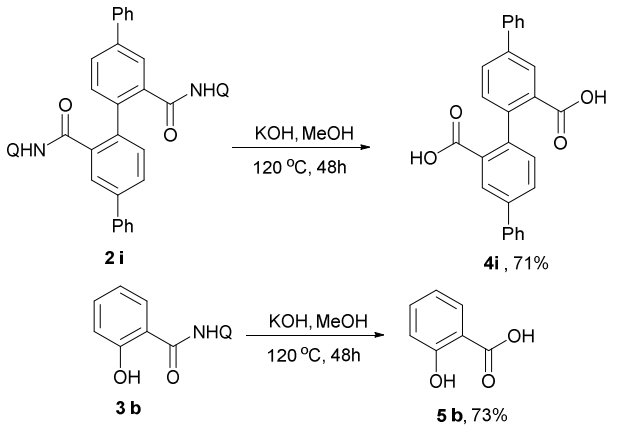
[a]Dimerization reaction conditions: Amide (1 mmol), $Cu(OAc)_2$ (0.5 mmol), K_2CO_3 (1 mmol), DMSO (5 mL), 108 °C, air, 1 h. [b]Hydroxylation reaction conditions: Amide (1 mmol), $Cu(OAc)_2$ (0.5 mmol), TBAI (1 mmol), DMSO (10 mL), 90 °C, air, 1 h. [c]Yield of isolated product. [d] Reaction was performed at 65 °C.

As shown in Table 2, both electron-rich and -deficient substituents such as alkyl, methoxy, trifluoromethyl, fluoro, and bromo are well-tolerated under the reaction conditions, thus generating the corresponding dimerization and hydroxylation products in moderate to excellent yields. Nitro group, a strong electron withdrawing substituent (**1m**), and hetero arenes, such as pyridines (**1n** and **1o**) and thiophenes (**1p** and **1q**), were tolerated as well, demonstrating a wide range of-functional group compatibility of our robust protocols for both reaction pathways. No significant difference was observed between 3- and 4-pyridylcarboxyamides (**1o** and **1n**). In the case of **1o**, the reaction favored the formation of the C-C bond *para* to the nitrogen atom of the pyridyl group.

To demonstrate the utility of this hydroxylation reaction, we conducted deprotection of the directing group with dimerization and hydroxylation products. The aminoquinoline directing group was smoothly removed bytreating product **2i** and **3b** with

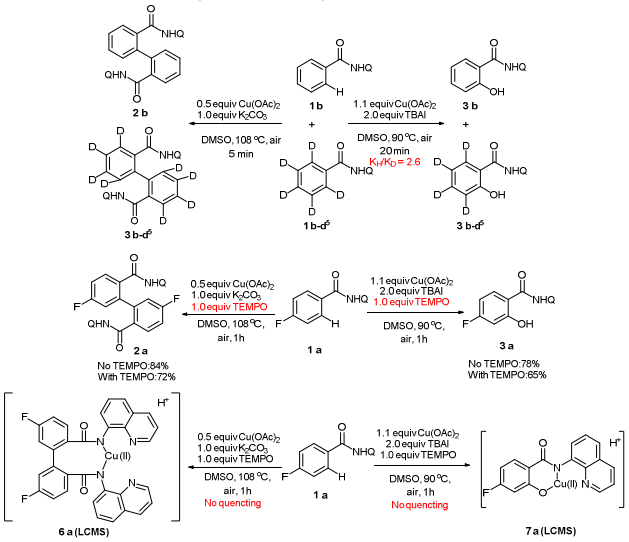
KOH/EtOH at 120 °C for 48 h, and the corresponding acids were obtained in 71% and 73% yield, respectively (Scheme 2).

Scheme 2. Removal of the Directing Group



To probe the mechanism of this reaction, we performed a series of experiments as shown in Table 1. Under inert atmosphere, the reaction of benzamide **1a** stopped at around 50% conversion with 1 equivalent of $Cu(OAc)_2$ (Table 1, Entry 17). Applying similar conditions with 2 equivalents of $Cu(OAc)_2$ gave almost full conversion with about 1:1 ratio of dimerization (**2a**) and hydroxyaltion (**3a**) products (Table 1, Entry 18) . Such observation suggests that oxygen helps the turnover of copper with less than 2 equivalents of $Cu(OAc)_2$ under the dimerization conditions. In addition, excess $Cu(OAc)_2$ favored the formation of hydroxylation product **3a**. Under hydroxylation conditions in the presence of TBAI and 2 equivelents of $Cu(OAc)_2$, the reaction gave almost full conversion with similar yield of **3a** isolated as under our standard condition for hydroxylation in table 1, entry 19.

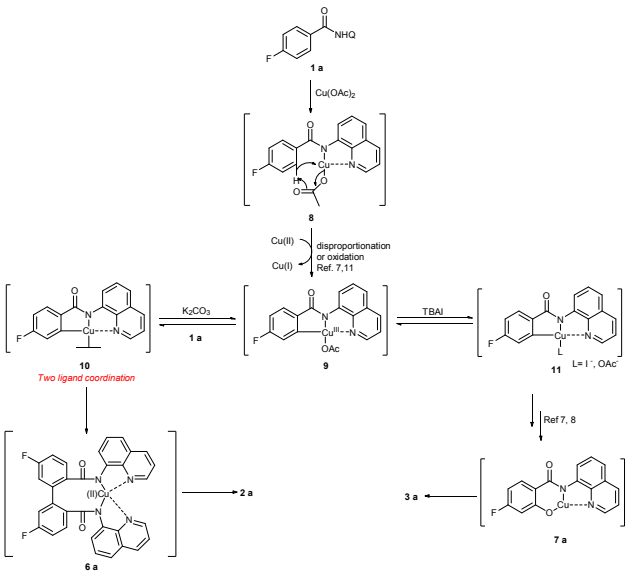
Scheme 3. Further experiments to probe reaction mechanism



In the subsequent mechanistic studies (Scheme 3), significant kinetic isotope effects were observed for the hydroxlation of **1b**. However, Kinetic isotope experiment for the dimmerization is not conclusive due to very fast reaction under standard conditions. Next, it was found that the addition of the commonly used radical quencher 2,2,6,6-tetramethylpiperidine-N-oxyl (TEMPO) had negligible effect on the yield, indicating that the reaction did not significantly involve a radical reaction pathway. Thirdly, LC/MS analysis of the reaction mixture suggested that major intermediates before quenching were **6a** and **7a**, corresponding to the molarity requirements of $Cu(OAc)_2$ in earlier optimization efforts for dimerization and hydroxylation, respectively (0.5 equivalent of $Cu(OAc)_2$ was needed for dimerization and 1.0 equivalent was needed for hydroxylation (see supporting information for details).

Combining the above results, we proposed that the hydroxylation reaction involved a copper-mediated C–H cleavage step rather than an electrophilic aromatic substitution (SEAr) or a radical pathway, which is consistent with previous reports.[7, 8] The reaction may start from the complexation of **1a** with copper to give Cu(II)-complex **8**. An acetate ligand-enabled C–H activation affords the Cu(III)-aryl species **9**. The C-H activation step from **8** to **9** could go through either a one step disproportionative C–H activation directly[11] or a two step process, which is acetate-enabled, concerted-metalation-deprotonation C–H activation to a Cu(II)-aryl species, followed by disproportionation or oxidation to afford Cu(III)-aryl intermediate **9**.[7] Subsequently, additional base (K_2CO_3) could deprotonate excess benzamide **1a** and promote two ligand coordination on the copper to give intermediate **10**. Following reductive elimination gives intermediate **6a**, which leads to the formation of dimerization product **2a** after work-up. In the case of reactions using TBAI as an additive, presumably iodide serves as a ligand for copper and prevents dimerization, , which leads to the C-O bond formation pathway and form intermediate **7a**, as suggested previously.[7] The final work-up of intermediate **7a** then gives hydroxylation product **3a**.

Scheme 4. Plausible reaction mechanism.



Conclusions

In conclusion, we developed a divergent approach for the copper-mediated dimerization and hydroxylation of bezamides through C-H bond functionalization, directed by a removable bidentate auxiliary. The reaction conditions tolerated various functional groups and thus can be applied to heterocycles such as pyridines and thiophenes. Preliminary mechanistic studies revealed more details in this copper-mediated C-H bond functionalization process and may guide future efforts to improve the process.

Experimental

All reagents and metal catalysts were obtained from commercial sources and used without further purification. NMR spectra were obtained on a Bruker AV II-400 MHz spectrometer (^{1}H NMR at 400 MHz, ^{13}C NMR at 100 MHz, and ^{19}F NMR at 375 MHz). The ^{1}H NMR chemical shifts were measured relative to $CDCl_3$ or DMSO-d_6 as the internal reference ($CDCl_3$: δ= 7.26 ppm; DMSO-d_6: δ= 2.50 ppm). The ^{13}C NMR chemical shifts were given using $CDCl_3$ or DMSO-d_6 as the internal standard ($CDCl_3$: δ= 77.16 ppm; DMSO-d_6: δ= 39.52 ppm). Mass spectroscopy data were collected on an HRMS-ESI instrument.

General Procedure for the Dimerization

A solution of amide **1** (1 mmol, 1.0 equiv), K_2CO_3 (138 mg, 1 mmol, 1.0 equiv), $Cu(OAc)_2$ (91 mg, 0.5 mmol, 0.5 equiv) in DMSO (5 mL) was stirred at room temperature for 5 min and the mixture was then heated at 108 ^{o}C for 1h under air. After completion of the reaction as detected by TLC, the reaction mixture was cooled to room temperature. Then $Na_2S{\cdot}xH2O$ (500 mg), CH_2Cl_2 (50 mL) and H_2O (50 mL) were added, resulting biphasic solution was stirred 10 min at room temperature and filtered through a pad of celite, organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). Combined organic phase was dried with anhydrous magnesium sulfate. After concentration, product was purified using column chromatography on silica gel with DCM-MeOH (100: 1 to 10:1) as the eluent togive the desired product **2**.

5, 5'-Difluoro-N2, N2'-di (quinolin-8-yl)-[1, 1'-biphenyl]-2, 2'-dicarboxamide (2a). White solid, 83% yield, mp 247-249 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.27 (s, 2H), 8.63 (dd, *J* = 6.8, 2.1 Hz, 2H), 8.48 (dd, *J* = 4.2, 1.6 Hz, 2H), 7.94 (dd, *J* = 8.3, 1.6 Hz, 2H), 7.84 (dd, *J* = 8.5, 5.6 Hz, 2H), 7.29-7.11 (m, 10H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.14, 163.59 (d, *J* = 250.8 Hz), 147.87, 141.56 (d, *J* = 7.2 Hz), 138.29, 135.91, 134.49, 132.74 (d, *J* = 3.3 Hz), 130.31 (d, *J* = 9.1 Hz), 127.54, 127.11, 121.65, 121.46, 117.90 (d, *J* = 22.4 Hz), 116.69 (s), 115.37 (d, *J* = 21.2 Hz); ^{19}F NMR(375 MHz, $CDCl_3$) δ −109.73 to −109.80 (m, 2F); HRMS (ESI-TOF) calcd for $C_{32}H_{21}F_2N_4O_2$ $[M + H]^+$: 531.1627, found: 531.1633.

N2, N2'-Di (quinolin-8-yl)-[1, 1'-biphenyl]-2, 2'-dicarboxamide (2b). White solid, 61% yield, mp 215-217 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.36 (s, 2H), 8.69 (d, *J* = 7.3 Hz, 2H), 8.46 (dd, *J* = 4.0, 1.2 Hz, 2H), 7.94 (d, *J* = 8.2 Hz, 2H), 7.86 (d, *J* = 7.4 Hz, 2H), 7.50 – 7.37 (m, 6H), 7.32 – 7.22 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.55, 147.79, 139.83, 138.42, 136.52, 135.86, 134.76, 130.97, 130.55, 128.08, 127.99, 127.58, 127.13, 121.47, 121.36, 116.72; HRMS (ESI-TOF) calcd for $C_{32}H_{23}N_4O_2$ $[M + H]^+$: 495.1816, found: 495.1818.

5, 5'-Dimethyl-N2, N2'-di(quinolin-8-yl)-[1,1'-biphenyl]-2,2'-dicarboxamide (2c). White solid, 68% yield, mp 227-229 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.27 (s, 2H), 8.65 (dd, *J* = 7.4, 1.4 Hz, 2H), 8.44 (dd, *J* = 4.2, 1.6 Hz, 2H), 7.90 (dd, *J* = 8.3, 1.6 Hz, 2H), 7.74 (d, *J* = 7.8 Hz, 2H), 7.27-7.14 (m, 10H), 2.38 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.59, 147.67, 140.79, 140.20, 138.27, 135.76, 134.87, 133.72, 131.71, 128.59, 128.05, 127.45, 127.06, 121.27, 121.14, 116.52, 21.57; HRMS (ESI-TOF) calcd for $C_{34}H_{27}N_4O_2$ $[M + H]^+$: 523.2129, found: 523.2133.

5, 5'-Dibutyl-N2, N2'-di(quinolin-8-yl)-[1,1'-biphenyl]-2,2'-dicarboxamide (2d). White solid, 63% yield, mp 147-148 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 2H), 8.73 (d, *J* = 6.7 Hz, 2H), 8.45 (dd, *J* = 4.1, 1.4 Hz, 2H), 7.96 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.81 (d, *J* = 7.9 Hz, 2H), 7.35-7.15 (m, 10H), 2.54 (t, *J* = 7.6 Hz, 4H), 1.46 – 1.30 (m, 4H), 1.17 – 1.03 (m, 4H), 0.71 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.74, 147.75, 145.61, 139.66, 138.50, 135.85, 134.93, 134.07, 131.13, 128.52, 127.98, 127.63, 127.20, 121.31, 121.29, 116.59, 35.49, 33.32, 22.13, 13.92; HRMS (ESI-TOF) calcd for $C_{40}H_{39}N_4O_2$ $[M + H]^+$: 607.3068, found: 607.3077.

5, 5'-Dimethoxy-N2, N2'-di (quinolin-8-yl)-[1, 1'-biphenyl]-2, 2'-dicarboxamide (2e). White solid, 71% yield, mp 184-185 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.26 (s, 1H), 8.70 (dd, *J* = 7.4, 1.4 Hz, 1H), 8.48 (dd, *J* = 4.2, 1.6 Hz, 1H), 7.96 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.32 – 7.23 (m, 4H), 6.96 (d, *J* = 2.5 Hz, 1H), 6.92 (dd, *J* = 8.5, 2.6 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.03, 161.10, 147.65, 141.82, 138.38, 135.99, 134.98, 130.26, 128.99, 127.64, 127.25, 121.33, 121.24, 116.70, 115.93, 113.73, 55.60; HRMS (ESI-TOF) calcd for $C_{34}H_{27}N_4O_4$ $[M + H]^+$: 555.2027, found: 555.2025.

5, 5'-Dichloro-N2, N2'-di (quinolin-8-yl)-[1, 1'-biphenyl]-2, 2'-dicarboxamide (2f). White solid, 82% yield, mp 246-248 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.24 (s, 2H), 8.59 (dd, *J* = 5.9, 2.9 Hz, 2H), 8.49 (d, *J* = 2.8 Hz, 2H), 7.93 (d, *J* = 7.2 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.49 (d, *J* = 1.8 Hz, 2H), 7.43 (dd, *J* = 8.2, 1.9 Hz, 2H), 7.32 – 7.25 (m, 4H), 7.22-7.17 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.04, 147.80, 140.58, 138.05, 136.85, 136.08, 134.81, 134.28, 130.84, 129.41, 128.60, 127.51, 127.12, 121.70, 121.44, 116.90; HRMS (ESI-TOF) calcd for $C_{32}H_{21}Cl_2N_4O_2$ $[M + H]^+$: 563.1036, found: 563.1035.

5,5'-Dibromo-N2,N2'-di(quinolin-8-yl)-[1,1'-biphenyl]-2,2'-dicarboxamide （2g）. White solid, 83% yield, mp 246-248 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 2H), 8.59 (dd, *J* = 5.7, 3.2 Hz, 2H), 8.50 (dd, *J* = 4.1, 1.4 Hz, 2H), 7.95 (d, *J* = 8.2 Hz, 2H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 1.8 Hz, 2H), 7.59 (dd, *J* = 8.2, 1.9 Hz, 2H), 7.30 (dd, *J* = 8.2, 4.3 Hz, 2H), 7.23 – 7.18 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.14, 147.73, 140.59, 137.90, 136.29, 135.23, 134.12, 133.70, 131.58, 129.54, 127.55, 127.20, 125.21, 121.76, 121.43, 117.13; HRMS (ESI-TOF) calcd for $C_{32}H_{21}Br_2N_4O_2$ $[M + H]^+$: 651.0026, found: 651.0025.

Dimethyl 6, 6'-bis (quinolin-8-ylcarbamoyl)-[1, 1'-biphenyl]-3, 3'-dicarboxylate (2h). White solid, 78% yield, mp 252-254 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.36 (s, 2H), 8.58 (dd, *J* = 4.9, 4.1 Hz, 2H), 8.46 (dd, *J* = 4.2, 1.6 Hz, 2H), 8.19 – 8.09 (m, 4H), 7.95 – 7.86 (m, 4H), 7.29-7.25 (m, 2H), 7.19-7.14 (m, 4H), 3.92 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.21, 147.88, 140.08, 139.65, 138.15, 135.84, 134.25, 132.11, 132.03, 129.58, 128.00, 127.42, 126.94, 121.75, 121.45, 116.72, 52.51; HRMS (ESI-TOF) calcd for $C_{36}H_{27}N_4O_6$ $[M + H]^+$: 611.1925, found: 611.1915.

N4', N6''-di (quinolin-8-yl)-[1, 1':3', 1'':3'', 1'''-quaterphenyl]-4', 6''-dicarboxamide (2i). White solid in 76% yield, mp 201-203 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.37 (s, 2H), 8.70 (dd, *J* = 7.0, 1.8 Hz, 2H), 8.45 (dd, *J* = 4.1, 1.4 Hz, 2H), 7.95 (dd, *J* = 8.2, 1.8 Hz, 4H), 7.79 (d, *J* = 1.7 Hz, 2H), 7.66 (dd, *J* = 8.0, 1.8 Hz, 2H), 7.64 – 7.57 (m, 4H), 7.41 (t, *J* = 7.3 Hz, 4H), 7.38 – 7.32 (m, 2H), 7.29 – 7.20 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.19, 147.81, 143.46, 140.32, 140.01, 138.36, 135.93, 135.31, 134.72, 129.88, 128.95, 128.86, 128.03 (s), 127.58, 127.46, 127.14, 126.68, 121.44, 121.36, 116.73 (s); HRMS (ESI-TOF) calcd for $C_{44}H_{31}N_4O_2$ [M + H] $^+$: 647.2442, found: 647.2434.

N2, N2'-di (quinolin-8-yl)-5, 5'-bis (trifluoromethyl)-[1, 1'-biphenyl]-2, 2'-dicarboxamide (2j). White solid in 87% yield, mp 231-233 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.30 (s, 2H), 8.56 (dd, *J* = 5.8, 3.1 Hz, 2H), 8.50 (dd, *J* = 4.2, 1.6 Hz, 2H), 7.97 – 7.91 (m, 4H), 7.83 – 7.75 (m, 4H), 7.31 (dd, *J* = 8.3, 4.2 Hz, 2H), 7.19 – 7.13 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.65, 147.97, 139.65, 138.05, 135.90, 132.82 (q, J_{C-F} = 32.8 Hz), 128.37, 127.92, 127.88, 127.40, 126.92, 126.60 (q, J_{C-F} = 3.7 Hz), 123.65 (q, J_{C-F} = 271.2 Hz), 121.89, 121.52, 116.70; ^{19}F NMR (375MHz, $CDCl_3$, ppm) δ -61.29; HRMS (ESI-TOF) calcd for $C_{34}H_{21}F_6N_4O_2$ [M + H] $^+$: 631.1563, found: 631.1567.

5, 5'-Dicyano-N2,N2'-di(quinolin-8-yl)-[1,1'-biphenyl]-2,2'-dicarboxamide (2k). White solid, 81% yield, mp 212-214 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 2H), 8.51 (ddd, *J* = 5.8, 5.3, 2.1 Hz, 4H), 7.97 – 7.89 (m, 4H), 7.82 – 7.75 (m, 4H), 7.31 (dd, *J* = 8.3, 4.2 Hz, 2H), 7.24 – 7.16 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.97, 148.07, 140.15, 139.32, 138.05, 136.07, 134.03, 133.75, 132.53, 128.61, 127.50, 126.98, 122.31, 121.65, 117.71, 116.97, 114.88; HRMS (ESI-TOF) calcd for $C_{34}H_{21}N_6O_2$ [M + H] $^+$: 545.1721, found: 545.1723.

3, 3'-Difluoro-N2, N2'-di(quinolin-8-yl)-[1,1'-biphenyl]-2,2'-dicarboxamide (2l). White solid in 79% yield, mp 215-217 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.90 (s, 2H), 8.65 (dd, *J* = 7.3, 1.4 Hz, 2H), 8.50 (dd, *J* = 4.2, 1.5 Hz, 2H), 7.98 (dd, *J* = 8.3, 1.5 Hz, 2H), 7.45 – 7.35 (m, 4H), 7.31 – 7.20 (m, 6H), 7.05 – 6.97 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.07, 159.61 (d, *J* = 247.7 Hz), 148.07, 140.12, 138.93, 136.14, 134.13, 131.03 (d, *J* = 9.1 Hz), 127.88, 127.13, 126.08 (d, *J* = 3.1 Hz), 125.38 (d, *J* = 17.5 Hz), 122.58, 121.47, 118.77, 115.58(d, *J* = 22.1 Hz); ^{19}F NMR(375 MHz, $CDCl_3$) δ−115.25 to−115.29 (m, 2F); HRMS (ESI-TOF) calcd for $C_{32}H_{21}F_2N_4O_2$ [M + H] $^+$: 531.1627, found: 531.1632.

5, 5'-Dinitro-N2,N2'-di(quinolin-8-yl)-[1,1'-biphenyl]-2,2'-dicarboxamide (2m). White solid in 82% yield, mp 153-155 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.42 (s, 2H), 8.54 – 8.46 (m, 4H), 8.38 (dt, *J* = 8.3, 2.1 Hz, 4H), 8.00 (d, *J* = 8.3 Hz, 2H), 7.94 (dd, *J* = 8.3, 1.4 Hz, 2H), 7.31 (dd, *J* = 8.3, 4.2 Hz, 2H), 7.20 – 7.12 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.77, 148.90, 147.97, 141.63, 139.93, 137.80, 136.23, 133.58, 129.00, 127.46, 126.97, 125.74, 123.94, 122.37, 121.66, 117.13; ^{19}F NMR(375 MHz, $CDCl_3$) δ−115.25 to−125.29 (m, 1F); HRMS (ESI-TOF) calcd for $C_{32}H_{21}N_6O_6$ [M + H] $^+$: 585.1517, found: 585.1512.

N4, N4'-di (quinolin-8-yl)-[3, 3'-bipyridine]-4, 4'-dicarboxamide (2n). White yellow solid, 78% yield, mp 252-254 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.35 (s, 2H), 8.81 (d, *J* = 5.0 Hz, 2H), 8.77 (s, 2H), 8.63 (dd, *J* = 4.1, 1.4 Hz, 2H), 8.37 (d, *J* = 7.5 Hz, 2H), 8.25 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.89 (d, *J* = 5.0 Hz, 2H), 7.52 (dd, *J* = 8.3, 4.2 Hz, 2H), 7.45 (d, *J* = 7.9 Hz, 2H), 7.27 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO): δ 164.24, 150.86, 150.37, 148.63, 142.70, 137.54, 136.34, 133.26, 130.30, 127.30, 126.42, 122.57, 122.09, 121.24, 116.43; HRMS (ESI-TOF) calcd for $C_{30}H_{21}N_6O_2$ [M + H] $^+$: 497.1721, found: 497.1720.

N3,N3'-di(quinolin-8-yl)-[4,4'-bipyridine]-3,3'-dicarboxamide (2o). White solid, 73% yield, mp 205-207 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (s, 2H), 9.13 (s, 2H), 8.78 (d, *J* = 4.9 Hz, 2H), 8.57 (dd, *J* = 6.9, 2.0 Hz, 2H), 8.52 (dd, *J* = 4.2, 1.6 Hz, 2H), 7.95 (dd, *J* = 8.3, 1.6 Hz, 2H), 7.39 (d, *J* = 5.0 Hz, 2H), 7.30 (dd, *J* = 8.3, 4.2 Hz, 2H), 7.24 – 7.17 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.45, 151.72, 148.58, 148.11, 145.80, 138.21, 136.05, 133.93, 131.62, 127.55, 126.92, 124.37, 122.21, 121.66, 116.96; HRMS (ESI-TOF) calcd for $C_{30}H_{21}N_6O_2$ [M + H] $^+$: 497.1721, found: 497.1717.

N2, N2'-di (quinolin-8-yl)-[3, 3'-bithiophene]-2, 2'-dicarboxamide (2p). White yellow solid, 72% yield, mp 196-198 °C. ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 10.33 (s, 2H), 8.77 (dd, *J* = 7.4, 1.5 Hz, 2H), 8.68 (dd, *J* = 4.2, 1.7 Hz, 2H), 8.01 (dd, *J* = 8.3, 1.6 Hz, 2H), 7.65 (d, *J* = 5.0 Hz, 2H), 7.47 – 7.38 (m, 4H), 7.33 (dd, *J* = 8.3, 4.2 Hz, 2H), 7.16 (d, *J* = 5.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.89, 148.34, 139.90, 138.74, 136.04, 134.46, 134.38, 131.44, 131.05, 127.85, 127.24, 121.86, 121.64, 116.80; HRMS (ESI-TOF) calcd for $C_{28}H_{19}N_4O_2S_2$ [M + H] $^+$: 507.0944, found: 507.0937.

N2, N2'-di(quinolin-8-yl)-[3,3'-bibenzo[b]thiophene]-2,2'-dicarboxamide (2q). White yellow solid, 68% yield, mp 273-275 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.54 (s, 2H), 8.73 (dd, *J* = 7.4, 1.6 Hz, 2H), 8.58 (dd, *J* = 4.3, 1.6 Hz, 2H), 8.02 (d, *J* = 8.1 Hz, 2H), 7.95 (dd, *J* = 8.3, 1.6 Hz, 2H), 7.47 – 7.42 (m, 2H), 7.41 – 7.32 (m, 6H), 7.31 – 7.24 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.04, 148.38, 141.98, 141.06, 140.56, 138.63, 135.93, 134.20, 127.79, 127.74, 127.34, 127.07, 125.57, 124.66, 122.54, 122.06, 121.68, 116.89; HRMS (ESI-TOF) calcd for $C_{36}H_{23}N_4O_2S_2$ [M + H] $^+$: 607.1257, found: 607.1250.

General Procedure for the Hydroxylation

To a 25 mL Schlenk tube were added amide **1** (1 mmol, 1.0 equiv), TBAI (738 mg, 2 mmol, 2.0 equiv), Cu $(OAc)_2$(200 mg, 1.1 mmol, 1.1 equiv), DMSO (10 mL). The reaction tube was stirred at room temperature for 5 min and the mixture was then heated at 90 ^{o}C for 1h under air. LCMS show the reaction was completed, the reaction mixture was cooled to room temperature, Na_2S·xH2O (500 mg), CH_2Cl_2 (50 mL) and H_2O (50 mL) were added. Resulting biphasic solution was stirred 10 min at room temperature and filtered through a pad of celite. Organic layer was separated and aqueous layer was extracted with CH_2Cl_2 (2 x 50 mL). Combined organic phase was dried with anhydrous $MgSO_4$. After concentration, product was purified using column chromatography on silica gel using appropriate eluent.

4-Fluoro-2-hydroxy-N-(quinolin-8-yl)benzamide （3a）. White solid, 78.5% yield, mp 163-164 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.64 (s, 1H), 10.87 (s, 1H), 8.87 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.78 (dd, *J* = 5.2, 3.8 Hz, 1H), 8.20 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.83 (dd, *J* = 8.7, 6.1 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.51 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.77 – 6.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.94, 166.60 (d, *J* = 252.0 Hz), 164.49 (d, *J* = 13.8 Hz), 148.67, 138.89, 136.66, 133.57, 128.18, 128.07, 127.48, 122.51, 122.05, 117.12, 112.01, 107.16 (d, *J* = 22.8 Hz), 105.57 (d, *J* = 23.5 Hz); ^{19}F NMR(375 MHz, $CDCl_3$) δ −103.04 to

−103.11 (m, 1F); HRMS (ESI-TOF) calcd for $C_{16}H_{12}FN_2O_2$ $[M + H]^+$: 283.0877, found: 283.0881.

2-Hydroxy-N-(quinolin-8-yl)benzamide (3b). White solid in 81% yield, mp 131-132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.31 (s, 1H), 10.98 (s, 1H), 8.88 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.83 (dd, *J* = 6.3, 2.6 Hz, 1H), 8.20 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.86 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.60 – 7.57 (m, 2H), 7.52-7.46 (m, 2H), 7.06 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.03 – 6.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.63, 162.27, 148.65, 138.98, 136.62, 134.75, 133.76, 128.16, 127.50, 126.22, 122.42, 122.02, 119.18, 118.96, 117.11, 115.36; HRMS (ESI-TOF) calcd for $C_{16}H_{13}N_2O_2$ $[M + H]^+$: 265.0972, found: 265.0973.

2-Hydroxy-4-methyl-N-(quinolin-8-yl)benzamide (3c). White solid in 76% yield, mp 158-160 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.29 (s, 1H), 10.89 (s, 1H), 8.87 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.81 (dd, *J* = 6.8, 2.1 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.61 – 7.54 (m, 2H), 7.49 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.87 (s, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.66, 162.26, 148.58, 145.90, 138.94, 136.57, 133.86, 128.14, 127.49, 126.03, 122.21, 121.95, 120.36, 119.05, 116.98, 112.72, 21.87; HRMS (ESI-TOF) calcd for $C_{17}H_{15}N_2O_2$ $[M + H]^+$: 279.1128, found: 279.1127.

4-Butyl-2-hydroxy-N-(quinolin-8-yl)benzamide (3d). White solid, 78% yield, mp 91-93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.29 (s, 1H), 10.90 (s, 1H), 8.87 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.81 (dd, *J* = 6.8, 2.1 Hz, 1H), 8.19 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.61 – 7.54 (m, 2H), 7.49 (dd, *J* = 8.4, 4.2 Hz, 1H), 6.88 (d, *J* = 1.6 Hz, 1H), 6.82 (dd, *J* = 8.0, 1.6 Hz, 1H), 2.64 (t, *J* = 7.6 Hz, 2H), 1.68 – 1.59 (m, 2H), 1.43 – 1.34 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.67, 162.28, 150.83, 148.58, 138.96, 136.58, 133.89, 128.15, 127.49, 126.05, 122.20, 121.95, 119.74, 118.39, 116.98, 112.91, 35.82, 33.03, 22.44, 14.06; HRMS (ESI-TOF) calcd for $C_{20}H_{21}N_2O_2$ $[M + H]^+$: 321.1598, found: 321.1597.

2-Hydroxy-4-methoxy-N-(quinolin-8-yl)benzamide (3e). White solid, 72% yield, mp 145-147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.66 (s, 1H), 10.80 (s, 1H), 8.87 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.79 (dd, *J* = 7.1, 1.7 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.49 (dd, *J* = 8.3, 4.2 Hz, 1H), 6.59 – 6.50 (m, 2H), 3.86 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.53, 164.83, 164.58, 148.55, 138.93, 136.59, 133.96, 128.16, 127.54, 127.52, 122.05, 121.94, 116.87, 108.32, 107.59, 101.82, 55.63; HRMS (ESI-TOF) calcd for $C_{17}H_{15}N_2O_3$ $[M + H]^+$: 295.1077, found: 295.1076.

4-Chloro-2-hydroxy-N-(quinolin-8-yl) benzamide (3f). White solid, 62% yield, mp 179-181 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.49 (s, 1H), 10.92 (s, 1H), 8.91 – 8.85 (m, 1H), 8.83 – 8.76 (m, 1H), 8.21 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.77 (d, *J* = 8.6 Hz, 1H), 7.62 – 7.57 (m, 2H), 7.52 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.07 (d, *J* = 2.0 Hz, 1H), 6.98 (dd, *J* = 8.5, 2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.85, 162.94, 148.69, 140.28, 138.85, 136.65, 133.45, 128.12, 127.45, 127.14, 122.62, 122.07, 119.65, 118.98, 117.17, 113.87; HRMS (ESI-TOF) calcd for $C_{16}H_{12}ClN_2O_2$ $[M + H]^+$: 299.0582, found: 299.0586.

4-Bromo-2-hydroxy-N-(quinolin-8-yl)benzamide (3g). White solid, 58% yield, mp 182-184 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.46 (s, 1H), 10.94 (s, 1H), 8.89 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.83 – 8.77 (m, 1H), 8.22 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.73 – 7.68 (m, 1H), 7.63 – 7.56 (m, 2H), 7.52 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.25 (d, *J* = 1.9 Hz, 1H), 7.14 (dd, *J* = 8.5, 1.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.01, 162.86, 148.74, 138.91, 136.70, 133.49, 128.68, 128.17, 127.50, 127.21, 122.67, 122.55, 122.11, 122.04, 117.24, 114.31; HRMS (ESI-TOF) calcd for $C_{16}H_{12}BrN_2O_2$ $[M + H]^+$: 343.0077, found: 343.0080.

Methyl 3-hydroxy-4-(quinolin-8-ylcarbamoyl)benzoate (3h). White solid in 69% yield, mp 181-183 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.29 (s, 1H), 11.01 (s, 1H), 8.88 (dt, *J* = 6.7, 3.4 Hz, 1H), 8.83 – 8.76 (m, 1H), 8.22 – 8.18 (m, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.69 (d, *J* = 1.6 Hz, 1H), 7.63 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.60 – 7.56 (m, 2H), 7.50 (dt, *J* = 7.6, 3.8 Hz, 1H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.69, 166.17, 161.97, 148.76, 138.88, 136.64, 135.51, 133.39, 128.11, 127.43, 126.26, 122.79, 122.10, 120.20, 119.75, 118.67, 117.28, 52.62; HRMS (ESI-TOF) calcd for $C_{18}H_{15}N_2O_4$ $[M + H]^+$: 323.1026, found: 323.1028.

3-Hydroxy-N-(quinolin-8-yl)-[1,1'-biphenyl]-4-carboxamide (3i). White solid, 73% yield, mp 167-169 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.40 (s, 2H), 11.00 (s, 2H), 8.90 (dd, *J* = 4.2, 1.6 Hz, 2H), 8.84 (dd, *J* = 6.6, 2.3 Hz, 2H), 8.21 (dd, *J* = 8.3, 1.6 Hz, 2H), 7.92 (d, *J* = 8.3 Hz, 2H), 7.69 – 7.64 (m, 4H), 7.63 – 7.57 (m, 4H), 7.54 – 7.46 (m, 6H), 7.44 – 7.39 (m, 2H), 7.30 (d, *J* = 1.7 Hz, 2H), 7.27 – 7.23 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.47, 162.52, 148.62, 147.53, 139.78, 138.92, 136.70, 133.76, 129.06, 128.49, 128.18, 127.53, 127.30, 126.69, 122.42, 122.01, 118.09, 117.20, 117.04, 114.10; HRMS (ESI-TOF) calcd for $C_{22}H_{17}N_2O_2$ $[M + H]^+$: 341.1285, found: 341.1284.

2-Hydroxy-N-(quinolin-8-yl)-4-(trifluoromethyl)benzamide (3j). White solid in 58% yield, mp 150-152 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.45 (s, 1H), 11.05 (s, 1H), 8.89 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.84 – 8.78 (m, 1H), 8.22 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.95 (d, *J* = 8.3 Hz, 1H), 7.64 – 7.56 (m, 2H), 7.53 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.31 (s, 1H), 7.23 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.46, 162.23, 148.82, 138.90, 136.72, 136.04 (q, $J_{C\text{-}F}$ = 32.5 Hz), 133.29, 128.16, 127.47, 126.95, 123.40 (q, $J_{C\text{-}F}$ = 271.3 Hz), 122.95, 122.17, 118.02, 117.36, 116.30 (q, $J_{C\text{-}F}$ = 4.0 Hz), 115.51 (q, $J_{C\text{-}F}$ = 3.7 Hz); ^{19}F NMR(375 MHz, $CDCl_3$) δ −63.63; HRMS (ESI-TOF) calcd for $C_{17}H_{12}F_3N_2O_2$ $[M + H]^+$: 333.0845, found: 333.0849.

4-Cyano-2-hydroxy-N-(quinolin-8-yl)benzamide (3k), White solid in 56% yield, mp 247-248 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.52 (s, 1H), 11.07 (s, 1H), 8.90 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.81 (dd, *J* = 6.8, 2.2 Hz, 1H), 8.24 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.67 – 7.58 (m, 2H), 7.54 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.34 (d, *J* = 1.5 Hz, 1H), 7.27 (q, *J* = 1.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.06, 162.09, 148.89, 138.87, 136.79, 133.09, 128.17, 127.48, 127.09, 123.20, 122.89, 122.25, 122.07, 119.03, 117.86, 117.55, 117.51;HRMS (ESI-TOF) calcd for $C_{17}H_{12}N_3O_2$ $[M + H]^+$: 290.0924, found: 290.0922.

2-Fluoro-N-(quinolin-8-yl)benzamide (3l). White solid, 63% yield, mp 171-173 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.19 (s, 1H), 11.53 (d, *J* = 19.3 Hz, 1H), 8.92 – 8.83 (m, 2H), 8.18 (d, *J* = 8.3 Hz, 1H), 7.61 – 7.55 (m, 2H), 7.48 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.37 (dd, *J* = 15.1, 8.3 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 6.72 (dd, *J* = 12.6, 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.63 (d, *J* = 3.6 Hz), 164.15 (d, *J* = 4.4 Hz), 161.39 (d, *J* = 246.8 Hz), 160.15, 148.87, 139.07, 136.43, 134.13 (d, *J* = 13.3 Hz), 128.13, 127.37, 122.91, 121.97, 118.16, 114.86 (d, *J* = 2.9 Hz), 106.07(d, *J* = 25.5 Hz), 104.73 (d, *J* = 12.1 Hz); ^{19}F NMR(375 MHz, $CDCl_3$) δ−109.88 to−109.99 (m, 1F); HRMS (ESI-TOF) calcd for $C_{16}H_{12}FN_2O_2$ $[M + H]^+$: 283.0877, found: 283.0878.

2-Hydroxy-4-nitro-N-(quinolin-8-yl)benzamide (3m). The reaction temperature was at 65°C. White solid, 61% yield, mp 251-253 °C. ^{1}H NMR (400 MHz, DMSO): δ 12.82 (s, 1H), 12.36 (s, 1H), 8.94 (dd, *J* = 6.1, 4.1 Hz, 2H), 8.44 (dd, *J* = 8.3, 1.4 Hz, 1H), 8.30 (d, *J*

= 8.7 Hz, 1H), 7.85 (d, *J* = 2.2 Hz, 1H), 7.80 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.65 (dt, *J* = 11.3, 6.1 Hz, 2H); ^{13}C NMR (100 MHz, DMSO): δ 161.62, 156.44, 149.89, 149.15, 138.31, 136.69, 134.85, 132.82, 127.92, 127.15, 124.98, 122.48, 122.26, 117.05, 113.95, 111.51; HRMS (ESI-TOF) calcd for $C_{16}H_{12}N_3O_4$ [M+H] $^+$: 310.0822, found: 310.0821.

3-Hydroxy-N-(quinolin-8-yl)isonicotinamide (3n). White solid, 61% yield, mp 263-265 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.31 (s, 2H), 8.95 (dd, *J* = 4.5, 1.7 Hz, 2H), 8.45 (dd, *J* = 8.2, 1.4 Hz, 2H), 8.24 (s, 1H), 7.93 (d, *J* = 5.0 Hz, 1H), 7.74 (d, *J* = 7.4 Hz, 1H), 7.66 (dt, *J* = 10.7, 6.1 Hz, 2H); ^{13}C NMR (100 MHz, DMSO): δ 161.90, 149.19, 140.15, 138.36, 138.31, 136.78, 136.68, 134.86, 127.93, 127.15, 123.51, 122.51, 122.29, 121.07, 117.05; HRMS (ESI-TOF) calcd for $C_{15}H_{12}N_3O_2$ [M + H] $^+$: 266.0924, found: 266.0922.

4-Hydroxy-N-(quinolin-8-yl)nicotinamide (3o). White solid, 63% yield, mp 262-264 °C. ^{1}H NMR (400 MHz, DMSO) δ 13.86 (s, 1H), 12.21 (s, 1H), 8.97 – 8.90 (m, 2H), 8.62 (d, *J* = 4.0 Hz, 1H), 8.38 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.89 – 7.83 (m, 1H), 7.69 – 7.55 (m, 3H), 6.50 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO): δ 177.27, 163.06, 149.00, 142.30, 138.76, 138.08, 136.29, 135.73, 127.95, 126.99, 122.00, 121.90, 119.64, 118.55, 117.42; HRMS (ESI-TOF) calcd for $C_{15}H_{12}N_3O_2$ [M + H] $^+$: 266.0924, found: 266.0927.

3-Hydroxy-N-(quinolin-8-yl)thiophene-2-carboxamide (3p). White solid, 62% yield, mp 174-175 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.17 (s, 1H), 10.12 (s, 1H), 8.87 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.76 (dd, *J* = 6.8, 2.1 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.49 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.37 (d, *J* = 5.4 Hz, 1H), 6.84 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.01, 164.77, 148.64, 138.60, 136.52, 134.02, 128.14, 128.09, 127.45, 122.05, 121.97, 120.46, 116.86, 106.00; HRMS (ESI-TOF) calcd for $C_{15}H_{10}N_2O_2S$ [M + H] $^+$:271.0536, found: 271.0533.

3-hydroxy-N-(quinolin-8-yl)benzo[b]thiophene-2-carboxamide (3q). White solid, 57% yield, mp 208-210 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.77 (s, 1H), 10.25 (s, 1H), 8.91 (dd, *J* = 4.3, 1.6 Hz, 1H), 8.79 (dd, *J* = 6.7, 2.2 Hz, 1H), 8.24 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.66 – 7.57 (m, 2H), 7.55 – 7.49 (m, 2H), 7.43 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.54, 159.83, 148.58, 138.43, 137.01, 136.79, 133.83, 131.46, 128.85, 128.19, 127.52, 124.82, 123.21, 123.13, 122.35, 121.99, 117.38, 103.77; HRMS (ESI-TOF) calcd for $C_{19}H_{12}N_2O_2S$ [M + H] $^+$:321.0692, found: 321.0694.

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