One-Pot Approach to *N*-Quinolyl 3′/4′-Biaryl Carboxamides by Microwave-Assisted Suzuki−Miyaura Coupling and *N*-Boc Deprotection

Zhi-You Huang,[†] Jing-Fang Yang,[†] Ke Song,[†] Qian Chen,[†] Shao-Lin Zhou,[†] Ge-Fei Hao,*[,†] and Guang-Fu Yang*[,†,‡]

[†]Key Laboratory of Pesticide & Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Wuhan 430079, P. R. China

[‡]Collaborative Innovation Center of Chemical Science and Engineering, Tianjing 300072, P. R. China

S *Supporting Information*

ABSTRACT: *N*-Quinolyl biaryl carboxamides have received tremendous attention for their notable biological properties. Here we have described a general protocol for the preparation of *N*-quinolyl 3′/4′-biaryl carboxamides by microwave-assisted Suzuki−Miyaura cross-coupling reaction and *N*-Boc deprotection in one pot. This method, which did not require acids, was used to produce a series of *N*-quinolyl 3′/4′-biaryl carboxamides with excellent functional group tolerance and high yields (70% to 95%).
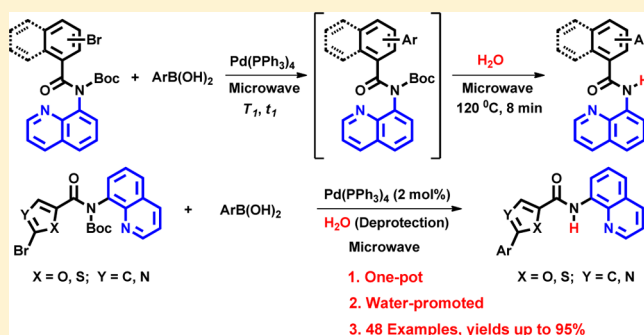
INTRODUCTION

The biaryl carboxamides play important roles as vital building blocks in the synthesis of a diversity of drugs such as anticancer,[1−4] anti-inflammatory,[5,6] anxiolytic,[7] Alzheimer's,[8] and anemia therapeutic agents.[9] Among these biaryl carboxamides, *N*-quinolyl (Q) 3′/4′-biaryl carboxamide is a unique substructure in medicinal chemistry that has shown the potential to antagonize bacteria,[10] promote weight loss,[11] promote differentiation of adult human cardiac progenitor cells,[12] and activate TRPV1 (transient receptor potential vanilloid type 1) ion channel.[13,14]

Although a variety of procedures are available for preparing *N*-Q 2′-biaryl carboxamides, methods available for the synthesis of *N*-Q 3′/4′-biaryl carboxamides are still limited. *N*-Q 3′/4′-biaryl carboxamides are often synthesized starting from halogen-substituted aromatic esters and aromatic boronic acids via three steps including Suzuki−Miyaura coupling, ester hydrolysis, and amide formation (Scheme 1, b).[13−15] However, these multistep processes are usually time-consuming and tedious procedures. Recently, Jana and Singh have reported an elegant example of preparing 2′,4′-difluoro-*N*-(quinolin-8-yl)[1,1′-biphenyl]-4-carboxamide via the direct Suzuki−Miyaura cross-coupling reaction of 4-bromo-*N*-(quinolin-8-yl)benzamide and (2,4-difluorophenyl)boronic acid.[16] However, this method requires a large amount of aromatic boronic acids (2.0 equiv). More importantly, the amide bearing a 8-amioquinolinyl moiety can strongly chelate the palladium catalyst, which may poison the catalyst and result in the high loading of catalyst. Thus, it is still desirable to develop low cost protocols for the synthesis of *N*-Q

Scheme 1. Selected Methods To Synthesize N-Q 3′/4′-Biaryl Carboxamides
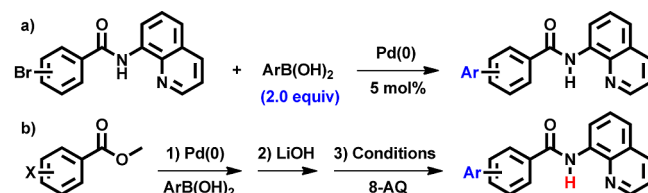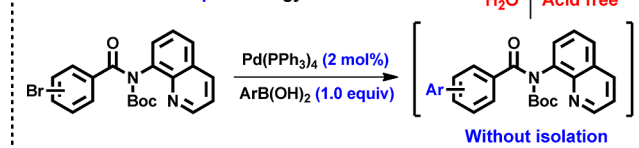
3′/4′-biaryl carboxamides. Moreover, during the course of our study on preparing *N*-(pyridin-2-ylmethyl)biphenyl-4-sulfonamides,[17] we found that the *N*-Boc protection material could be easily prepared in higher yields. Further, the one-pot method is less time-consuming and gives a higher yield than the stepwise approach. Hence, the one-pot method has drawn the attention of chemists.[18] Herein, we report a one-pot, microwave-assisted Suzuki−Miyaura cross-coupling and *N*-Boc-deprotection ap-

Table 1. Optimization of Pd(PPh$_3$)$_4$-Catalyzed Suzuki−Miyaura Coupling and Water-Promoted N-Boc-Deprotecting One-Pot Reaction[a,b]
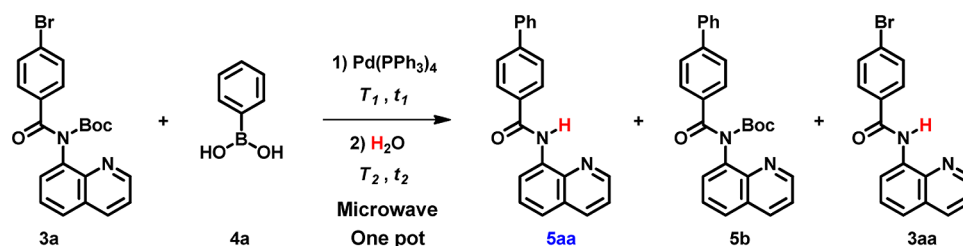
entry	organic solvent	base	catalyst (x mol %)	T$_1$ (°C), t$_1$ (min)	T$_2$(°C), t$_2$(min)	yield (5aa, %)	yield (5b, %)	yield (3aa, %)
1	dioxane	NaOAc	2	80, 6	120, 8	78	0	18
2	**dioxane**	**NaOAc**	**2**	**80, 8**	**120, 8**	**94**	**<1**	**<1**
3	dioxane	NaOAc	2	80, 10	120, 8	94	<1	<1
4	dioxane	NaOAc	2	85, 8	120, 8	84	0	14
5	DME	NaOAc	2	80, 8	120, 8	91	0	<5
6	DMF	NaOAc	2	80, 8	120, 8	86	0	<5
7	2-Me THF	NaOAc	2	80, 8	120, 8	35	41	21
8	2-propanol	NaOAc	2	80, 8	120, 8	51	0	46
9	dioxane	Na$_2$CO$_3$	2	80, 8	120, 8	86	0	11
10	dioxane	K$_3$PO$_3$	2	80, 8	120, 8	81	0	15
11	dioxane	Cs$_2$CO$_3$	2	80, 8	120, 8	77	0	18
12	dioxane		2	80, 8	120, 8	0	0	95
13	dioxane	NaOAc	1.5	80, 8	120, 8	89	0	<5
14	dioxane	NaOAc	1.0	80, 8	120, 8	81	0	14
15	dioxane	NaOAc		80, 8	120, 8	0	0	95
16[c]	dioxane	NaOAc	2	80, 8	120, 8	<5	0	94
17[c]	dioxane	NaOAc	10	80, 8	120, 8	9	0	88
18[d]	dioxane	NaOAc	2	80, 120	reflux, 600	22	71	<5

[a]Reactions conditions: (1) 3a (0.2 mmol), 4a (0.2 mmol), catalyst was Pd(PPh$_3$)$_4$, base (0.4 mmol), solvent 4 mL (3 mL of organic solvent and 1 mL of H$_2$O); (2) under N$_2$. [b]Isolated yield. [c]Catalyst was Pd/C (10%) [d]Conventional heating.
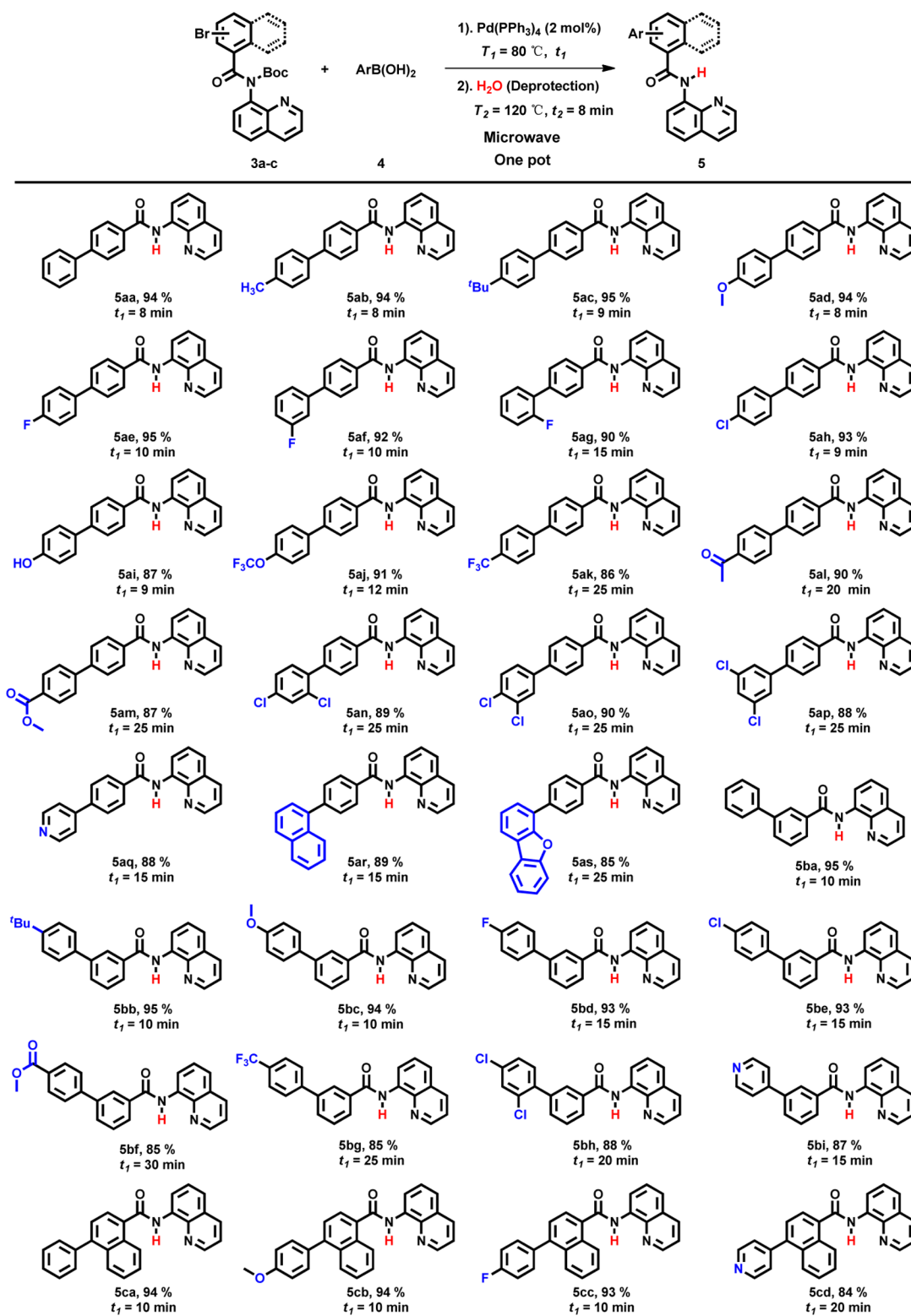
proach to prepare a variety of N-Q 3′/4′-biaryl carboxamides with excellent functional group tolerance and high yields.

Although the palladium-catalyzed Suzuki−Miyaura reactions were found to be the best approaches to synthesize biaryl carboxamides,[19] the direct Suzuki−Miyaura coupling to N-8-quinolyl 3′/4′-biaryl carboxamides took more time and wasted 1.0 equiv of boronic acid. Thus, it is obvious that the catalyst could be inactivated by the N-8-quinolyl to some extent.[15,19e,20] Thus, it is beneficial to prevent the N-8-quinolyl group from chelating the catalyst in order to facilitate the economic conversion of starting materials. Even more important, in our continuous efforts on the application of microwave irradiation in the target-oriented synthesis,[21] our present aim is to develop a one-pot strategy toward N-Q 3′/4′-biaryl carboxamides via sequential Pd(PPh$_3$)$_4$-catalyzed Suzuki−Miyaura coupling and water-promoted N-Boc deprotection under microwave irradiation.

RESULTS AND DISCUSSION

Although the conditions of coupling and the deprotection of amide N-Boc are known separately,[22] it is still a big challenge to find the optimum conditions to perform Suzuki−Miyaura coupling and amide N-Boc deprotection sequentially in a one-pot manner under microwave irradiation. For our initial studies, the reaction of bromide 3a with 1.0 equiv of phenylboronic aicd 4a in the presence of Pd(PPh$_3$)$_4$ and NaOAc under microwave irradiation was chosen as a benchmark reaction (Table 1; for the optimization of amide N-Boc deprotection see Table S1). To our delight, 78% of coupling and deprotecting product (5aa) was

obtained at a temperature of 80 °C in 6 min (Table 1, entry 1). Process monitoring indicated that 3a could not be completely converted into the Suzuki−Miyaura coupling product 5b, but the deprotection of 5b and the remaining 3a was smooth. Therefore, in order to improve the yield of 5aa, the reaction time was prolonged to promote the first-step Suzuki−Miyaura coupling. Thus, the desired product 5aa was obtained in the same yield of 94% in 8 and 10 min (entries 2 and 3). However, the yield of 5aa was reduced to 84% with a temperature of 85 °C (entry 4). In addition, different solvents were screened, such as water mixed with dioxane, DME, DMF, 2-Me-THF, and 2-propanol (entries 2 and 5−8). The mixture of water and dioxane (v/v = 1:3) was shown to produce the best results. Subsequently, the effect of base on this reaction was explored, and among these bases (NaOAc, Na$_2$CO$_3$, K$_3$PO$_4$, and Cs$_2$CO$_3$), NaOAc was identified as the best one (entries 2 and 9−11). In addition, we noted that in the absence of base (entry 12) or catalyst (entry 15) the coupling reaction would not take place, but the deprotection was not affected. Finally, the effect of palladium loading was invested. We found that decreasing the loading of catalyst to 1.5 mol % (entry 13) and 1.0 mol % (entry 14) gave an 87% and 81% yield of 5aa, respectively, while, a small amount of 5aa was obtained when 2.0 and 10 mol % of Pd/C was used (entries 16 and 17). Compared with conventional heating (entry 18), microwave irradiation could significantly accelerate the reaction and notably improve the yield of the product. As a result, the combination of 2.0 mol % of Pd(PPh$_3$)$_4$, 1.0 equiv of phenylboronic acid, and 2.0 equiv of NaOAc in dioxane mixed water with a temperature of 80 °C for 8 min for the first step followed by increasing the reaction

Table 2. Scope of 3a−c and (Hetero)arylboronic Acid (4)[a,b]

5aa, 94 % t_1 = 8 min	**5ab, 94 %** t_1 = 8 min	**5ac, 95 %** t_1 = 9 min	**5ad, 94 %** t_1 = 8 min
5ae, 95 % t_1 = 10 min	**5af, 92 %** t_1 = 10 min	**5ag, 90 %** t_1 = 15 min	**5ah, 93 %** t_1 = 9 min
5ai, 87 % t_1 = 9 min	**5aj, 91 %** t_1 = 12 min	**5ak, 86 %** t_1 = 25 min	**5al, 90 %** t_1 = 20 min
5am, 87 % t_1 = 25 min	**5an, 89 %** t_1 = 25 min	**5ao, 90 %** t_1 = 25 min	**5ap, 88 %** t_1 = 25 min
5aq, 88 % t_1 = 15 min	**5ar, 89 %** t_1 = 15 min	**5as, 85 %** t_1 = 25 min	**5ba, 95 %** t_1 = 10 min
5bb, 95 % t_1 = 10 min	**5bc, 94 %** t_1 = 10 min	**5bd, 93 %** t_1 = 15 min	**5be, 93 %** t_1 = 15 min
5bf, 85 % t_1 = 30 min	**5bg, 85 %** t_1 = 25 min	**5bh, 88 %** t_1 = 20 min	**5bi, 87 %** t_1 = 15 min
5ca, 94 % t_1 = 10 min	**5cb, 94 %** t_1 = 10 min	**5cc, 93 %** t_1 = 10 min	**5cd, 84 %** t_1 = 20 min

[a]Reactions conditions:**3a−c** (0.2 mmol), **4** (0.2 mmol), Pd(PPh$_3$)$_4$ (2 mol %), NaOAc (0.4 mmol), dioxane/H$_2$O = 3 mL:1 mL, T_2 = 120 °C, t_2 = 8 min, protected by N$_2$. [b]Isolated yield.

temperature to 120 °C over 8 min for the second step were chosen as the optimal conditions.

Once the optimized reaction conditions were identified, the scope and limitations of this one-pot process were explored. A variety of aromatic boronic acids and bromine-substituted *N*-Q

arylamides were applied. Various substituted (hetero)-arylboronic acids were examined, the results are shown in Table 2. The reactions between **3a** and (hetero)arylboronic acids (**4**) always proceeded smoothly. Both electron-withdrawing and electron-donating groups, such as methoxycarbonyl (**5am**),

trifluoromethyl (**5ak**) and methyl (**5ab**), *tert*-butyl (**5ac**), methoxy (**5ad**), halogen (**5ae–ah**), and trifluoromethoxy (**5aj**) afforded the desired products in good to excellent yields. More importantly, the reaction was proven to be well tolerant of valuable but unstable groups, such as hydroxyl (**5ai**) and acetyl (**5al**). In addition, disubstituted and heteroarylboronic acids were also investigated and afforded the corresponding products (**5an–as**). To increase the scope of our one-pot reaction, the **3b** and (hetero)arylboronic acids (**4**) were tested. Very similar results were obtained in the presence of the meta substituent *N*-Q benzamide (**3b**). The reaction of phenylboronic aid gave **5ba** in 95% yields. The reaction of electron-rich phenylboronic acids with 4-*tert*-butyl and 4-methoxy substituents led to **5bb** and **5bc** in 95% and 94% yield, respectively. The halogen-substituted phenylboronic acids (**5bd–be**) could also give excellent yields. Even the electron-deficient phenylboronic acids, with methoxycarbonyl and trifluoromethyl groups, were found to be suitable partners for the one-pot reaction and gave **5bf** and **5bg** in good yields. Of note, the 2,4-dichloro-substituted phenylboronic and 4-pyridinylboronic acids could be successfully converted to the products **5bh–bi**. Next, several reactions using **3c** as the starting materials were performed. The target products **5ca–cd** were obtained in 84–94% yields using 2.0 mol % of Pd(PPh$_3$)$_4$ as the catalyst under microwave irradiation. Furthermore, the structure of **5ba** was confirmed by X-ray data, and it showed that the phenyl group was at the meta position (Figure 1).
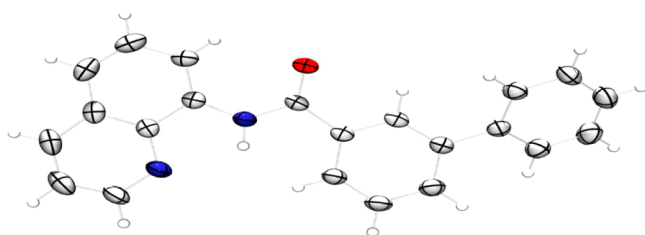

Figure 1. ORTEP diagrams of **5ba** (the thermal ellipsoids are drawn at the 50% probability level).

Notably, the one-pot reaction was not limited to the use of *N*-Q five-membered heteroaryl carboxamides. The reaction of (hetero)arylboronic acids (**4**) with **3d–f** (containing furanyl, thiophenyl, and thiazolyl, respectively) also produced the desired products **6** in good to excellent yield (Table 3). It was obvious that **3d** could produce more products than only **3e** and **3f**.

To further examine the one-pot reaction and rapidly expand our unique compound collection, we also carried out the reaction between **3g** and (hetero)arylboronic acids (**4**). Accordingly, the target-oriented products, biaryl carboxamide pyrabactin (Py) analogues as abscisic acid (ABA) agonists (**7aa–ag**), were obtained in 86–95% yield (Table 4). The analogue **7aa** has been found to be active on the ABA receptor PYR1 via a subsequent molecular simulation study (Figure 2). The pyridine ring can form conservative π–π stacking interactions with residue Y126 (Figure 2B). The amide group can not only form a hydrogen bond with residue E100 but also form another hydrogen bond with residue K65 to stabilize the binding mode. However, the biphenyl group makes **7aa** bind with P94 much more closely than bromine atom. As shown in Table 5, the estimated binding free energy of **7aa** is −4.42 kcal/mol, which is nearly equal to that of ABA (−4.34 kcal/mol) but higher than that of pyrabactin (−7.12 kcal/mol).

Table 3. Scope of 3d–f and (Hetero)arylboronic Acid (4)^{a,b}
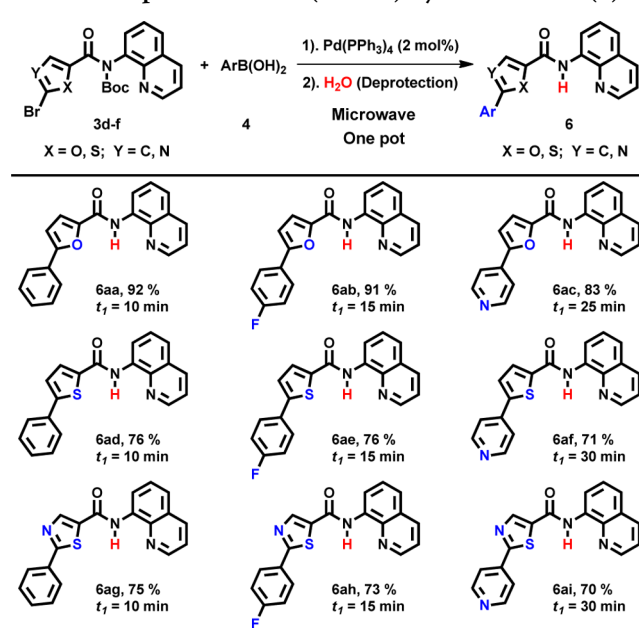
^{a}Reactions conditions:**3d–f** (0.2 mmol), **4** (0.2 mmol), Pd(PPh$_3$)$_4$ (2 mol %), NaOAc (0.4 mmol), dioxane/H$_2$O = 3 mL:1 mL, T_2 = 120 °C, t_2 = 8 min, protected by N$_2$. ^{b}Isolated yield.

The molecular mechanics Poisson−Boltzmann surface area (MM-PBSA) method in the AMBER12 package was employed to perform the free energy analyses. The overall objective of the MM-PBSA method is to calculate the free energy difference between two states that most often represent the bound and unbound states of two solvated molecules. The free energy of the ligand binding with the receptor, ΔG_{bind}, is calculated from the difference between the free energy of the receptor−ligand complex ($G_{complex}$) and the sum of the free energies of the unbound receptor ($G_{receptor}$) and ligand (G_{ligand}) as shown in eq 1.

$$\Delta G_{bind} = G_{complex} - (G_{ligand} + G_{receptor}) \quad (1)$$

The binding free energy ΔG_{bind} includes three items: MM gas-phase binding energy (ΔE_{MM}), solvation free energy (ΔG_{sol}), and entropy contribution ($-T\Delta S$). The sum of molecular mechanical gas-phase binding energy (ΔE_{MM}) and solvation free energy (ΔG_{sol}) is denoted by the binding energy (ΔE_{bind}). The ΔG_{bind} was estimated from ΔE_{bind} and $-T\Delta S$ in eq 2. The ΔE_{bind} is calculated from ΔE_{MM} and ΔG_{sol} in eq 3.

$$\Delta G_{bind} = \Delta E_{bind} - T\Delta S \quad (2)$$
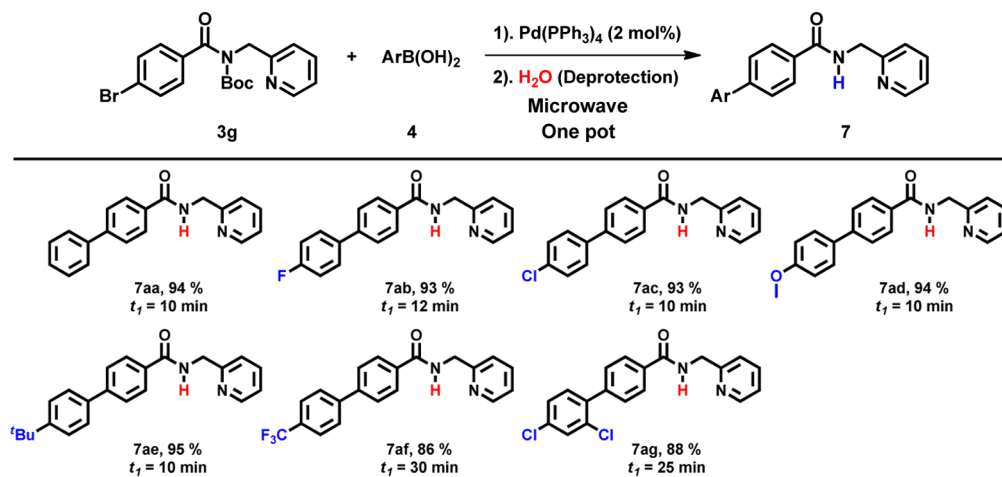
$$\Delta E_{bind} = \Delta E_{MM} + \Delta G_{sol} \quad (3)$$

The ΔE_{MM} is calculated by eq 4 where ΔE_{ele} and ΔE_{VDW} represent the electrostatic and van der Waals interactions. The solvation free energy ΔG_{sol} consists of two parts: the electrostatic contribution to the solvation free energy (ΔG_{PB}) and non-electrostatic contribution to the solvation free energy (ΔG_{np}) as described in eq 5.

$$\Delta E_{MM} = \Delta E_{ele} + \Delta E_{VDW} \quad (4)$$

$$\Delta G_{sol} = \Delta G_{PB} + \Delta G_{np} \quad (5)$$

$$\Delta S = \Delta S_{conf} + \Delta S_{sol} \quad (6)$$

Table 4. Scope of 3g and (Hetero)arylboronic Acid (4)[a,b]

7aa, 94 %
t_1 = 10 min

7ab, 93 %
t_1 = 12 min

7ac, 93 %
t_1 = 10 min

7ad, 94 %
t_1 = 10 min

7ae, 95 %
t_1 = 10 min

7af, 86 %
t_1 = 30 min

7ag, 88 %
t_1 = 25 min

[a]Reactions conditions:**3g** (0.2 mmol), **4** (0.2 mmol), Pd(PPh$_3$)$_4$ (2 mol %), NaOAc (0.4 mmol), dioxane/H$_2$O = 3 mL:1 mL, T_2 = 120 °C, t_2 = 8 min, protected by N$_2$. [b]Isolated yield.
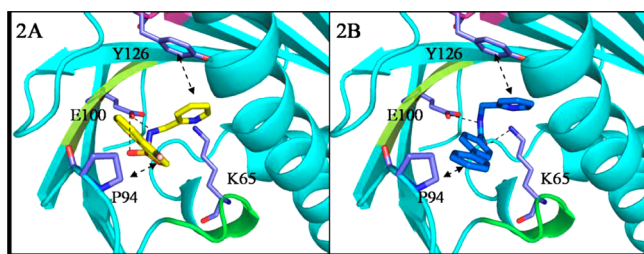

Figure 2. Computational modeling of **Py** (A) and **7aa** (B) in PYR1 (PDB code: 3QN1).

The ΔS_{sol} and ΔS_{conf} are the solvation entropy and the conformational entropy change in eq 6. In the binding process, the conformational entropy change is related to the change of the number of rotatable bonds during the binding process, and the solvation entropy is related to the tendency of water molecules to minimize their contacts with hydrophobic groups in protein. When an empirical solvation model is developed, one calculates the parameters against the available experimental data without accounting for the detailed structural information, which means to average the overall solvation contributions from both solvent and solute. Therefore, the computational procedure that was used to evaluate the entropic contribution ($-T\Delta S$) to the binding free energy was the same as in our previous publication.[23]

$$-T\Delta S_{conf} = w(\Delta N_{rot}) \qquad (7)$$

The contribution to the binding free energy from the conformational entropy change is proportional to the number (ΔN_{rot}) of the lost rotatable bonds during the binding in which w is the scaling factor (eq 7). This adjustable parameter (w) was calibrated to be 1 kcal/mol for the PYR1 proteins. We note that the w value of 1 kcal/mol used in the present study is the same as that used previously by other researchers.[24] The adjustment of

the w value usually does not change the qualitative order of the calculated binding free energies calculated for a series of compounds binding with a given type of protein.[25]

CONCLUSION

In summary, a one-pot microwave-assisted Suzuki−Miyaura cross-coupling reaction and *N*-Boc deprotection for preparing a variety of *N*-Q 3′/4′-biaryl carboxamides was developed. A series of *N*-Q biaryl carboxamides was obtained in good to excellent yields. In addition, the broad substrate scopes and excellent reactivity make the strategy operationally concise and facilitate rapid library construction of potential pyrabactin analogues as abscisic acid analogues.

EXPERIMENTAL SECTION

General Information. All reagents and solvents were obtained commercially except when otherwise noted. Thin-layer chromatography (TLC) analysis was used to monitor the reaction, which was carried out on silica plates. Flash column chromatography was performed using silica gel (200−300 mesh). ^{1}H spectra were recorded in CDCl$_3$ or DMSO-d_6 on 400 or 600 MHz NMR spectrometers and resonances (δ) are given in parts per million relative to tetramethylsilane. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, q = quarternary), coupling constants (Hz), and integration. ^{13}C spectra were recorded in CDCl$_3$ or DMSO-d_6 on 100 or 150 MHz NMR spectrometers and resonances (δ) are given in ppm. High-resolution mass spectra (HRMS) were analyzed by a TOF analyzer. Microwave irradiation reactions were carried out on a Smith synthesizer instrument (the temperature of reaction system was controlled by the wall infrared sensor, while the pressure was regulated by a noninvasive pressure sensor). All products reported showed ^{1}H and ^{13}C NMR spectra in agreement with the assigned structures.

General Procedure for the Synthesis of Compounds 3a−g. The synthesis of **3aa−ag** is representative: compound **2** (amino, 10 mmol) and DMAP (3 mmol) were placed in a 100 mL, two-necked reaction flask, and the flask was flushed with nitrogen. Dichloromethane

Table 5. Binding Free Energies (kcal/mol) Calculated for the PYR1 with ABA, Py, and 7aa

	ΔE_{ele}	ΔE_{VDW}	ΔE_{MM}	ΔG_{sol}	ΔE_{bind}	$-T\Delta S$	ΔG_{bind}
ABA	−38.14	−40.45	−78.59	58.03	−20.56	16.22	−4.34
Py	−34.96	−45.13	−80.09	57.53	−22.56	15.44	−7.12
7aa	−54.59	−40.35	−94.94	70.42	−24.53	20.11	−4.42

(40 mL), triethylamine (12 mmol), and **1** (acid, 11 mmol) were added, and the mixture was stirred at room temperature for 18 h. The resulting mixture was then quenched with water. The mixture was extracted with dichloromethane, and the combined organic layer was dried over sodium sulfate. Concentration in vacuum followed by silica gel column purification (petroleum ether/acetone = 20:2) gave **3aa–ag**.[26−28]

The synthesis of **3a–g** is representative: Boc anhydride (6 mmol) was added to a solution of **3aa–ag** (3 mmol) and DMAP (4.5 mmol) in CH$_2$Cl$_2$ (40 mL), and the reaction mixture was stirred overnight. The reaction mixture was quenched with satd aq NH$_4$Cl (40 mL) and extracted with CH$_2$Cl$_2$ (3 × 40 mL). The combined organic extracts were dried (Na$_2$SO$_4$), concentrated under reduced pressure, and purified by column chromatography (petroleum ether/acetone = 20:2, R_f = 0.15) to give **3a–g**.[29−31]

Typical Pd(PPh$_3$)$_4$-Catalyzed and Water-Promoted One-Pot Strategy to N-Q Biaryl Carboxamides 5−7. Compound **3** (0.2 mmol) and arylboronic acids (**4**, 0.2 mmol) were dissolved in dioxane (3 mL) and H$_2$O (1 mL) in a microwave tube under a nitrogen atmosphere. Pd(PPh$_3$)$_4$ (2 mol %, 4.6 mg) and sodium acetate (0.4 mmol) were added, and the reaction mixture was irradiated in a microwave apparatus at 80 °C for 8−30 min. Then the temperature was increased to 120 °C for another 8 min. After the reaction mixture was cooled to ambient temperature, the product was concentrated, and the crude mixture was purified by column chromatography on silica gel (petroleum ether/acetone = 20:1.5) to the desired product.

4-Bromo-1-(quinolin-8-yl)benzamide (3aa): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 3.043g, yield 93%; mp 128−129 °C;[32] ^{1}H NMR (600 MHz, DMSO) δ 10.67 (s, 1H), 8.99 (dd, J = 4.2, 1.2 Hz, 1H), 8.71 (d, J = 7.8 Hz, 1H), 8.47 (dd, J = 8.4, 1.2 Hz, 1H), 7.99 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 8.4 Hz, 2H), 7.77 (d, J = 8.2 Hz, 1H), 7.71−7.65 (m, 2H); ^{13}C NMR (150 MHz, DMSO) δ 163.5, 149.1, 138.2, 136.6, 133.8, 133.4, 131.9, 129.1, 127.7, 126.9, 125.9, 122.4, 122.2, 116.7; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{16}$H$_{12}$BrN$_2$O 327.0133, found 327.0121.

3-Bromo-1-(quinolin-8-yl)benzamide (3ab): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 3.01 g, yield 92%; mp 99−100 °C;[33] ^{1}H NMR (600 MHz, DMSO) δ 10.71 (s, 1H), 9.04 (s, 1H), 8.72 (d, J = 7.8 Hz, 1H), 8.52 (d, J = 8.4 Hz, 1H), 8.24 (s, 1H), 8.09 (d, J = 7.2 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.76−7.70 (m, 2H), 7.65 (t, J = 7.8 Hz, 1H); ^{13}C NMR (150 MHz, DMSO) δ 163.0, 149.1, 138.4, 136.7, 136.6, 134.7, 133.7, 131.0, 130.0, 127.8, 126.9, 125.9, 122.7, 122.3, 122.2, 117.2; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{16}$H$_{12}$BrN$_2$O 327.0133, found 327.0123.

4-bromo-1-(quinolin-8-yl)-1-naphthamide (3ac): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 3.395 g, yield 90%; mp 198−199 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 10.41 (s, 1H), 9.04 (s, 1H), 8.76 (s, 1H), 8.54 (s, 1H), 8.36 (d, J = 7.8 Hz, 1H), 8.23 (s, 1H), 7.91 (s, 1H), 7.78 (s, 1H), 7.65 (m, 4H), 7.49 (s, 1H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 166.9, 148.3, 138.3, 136.4, 134.4, 134.3, 132.1, 131.2, 129.0, 128.0, 127.8, 127.4, 127.3, 126.0, 125.9, 125.5, 122.2, 121.7, 116.9; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{20}$H$_{14}$BrN$_2$O 377.0290, found 377.0278.

5-Bromo-1-(quinolin-8-yl)furan-2-carboxamide (3ad): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 2.601 g, yield 82%; mp 109−110 °C;[34] ^{1}H NMR (600 MHz, DMSO) δ 10.54 (s, 1H), 9.02 (dd, J = 4.2, 1.2 Hz, 1H), 8.68 (d, J = 7.8 Hz, 1H), 8.48 (dd, J = 8.4, 1.2 Hz, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.70 (dd, J = 8.4, 4.2 Hz, 1H), 7.65 (t, J = 7.8 Hz, 1H), 7.43 (d, J = 3.6 Hz, 1H), 6.94 (d, J = 3.6 Hz, 1H); ^{13}C NMR (150 MHz, DMSO) δ 154.3, 149.3, 149.1, 137.8, 136.8, 133.3, 127.8, 127.0, 125.6, 122.5, 122.4, 118.0, 116.4, 115.1; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{14}$H$_{10}$BrN$_2$O$_2$ 316.9926, found 316.9915.

5-Bromo-N-(quinolin-8-yl)thiophene-2-carboxamide (3ae): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 2.699 g, yield 81%; mp 156−157 °C;[35] ^{1}H NMR (600 MHz, DMSO) δ 10.58 (s, 1H), 9.00 (d, J = 4.2 Hz, 1H), 8.50 (d, J = 7.8 Hz, 2H), 7.90 (d, J = 4.2 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.70 (dd, J = 8.4, 4.2 Hz, 1H), 7.66 (t, J = 7.8 Hz, 1H), 7.43 (d, J = 4.2 Hz, 1H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 159.0, 147.7, 141.2, 137.6, 137.4, 133.4, 130.9, 128.8, 128.1, 127.7, 122.2, 121.6, 119.0, 118.0; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{14}$H$_{10}$BrN$_2$OS 332.9697, found 332.9665.

5-Bromo-N-(quinolin-8-yl)thiazole-2-carboxamide (3af): white solid (petroleum ether/acetone = 20:3, R_f = 0.15); 2.707 g, yield 81%; mp 137−138 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 10.55 (s, 1H), 8.87 (d, J = 4.2. Hz, 1H), 8.79−8.72 (m, 1H), 8.22 (d, J = 8.4 Hz, 2H), 7.61−7.56 (m, 2H), 7.52 (dd, J = 8.4, 4.2 Hz, 1H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 157.2, 156.0, 148.5, 141.3, 138.1, 137.9, 136.4, 133.4, 127.8, 127.2, 122.4, 121.9, 116.7; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{13}$H$_9$BrN$_3$OS 333.9650, found 333.9641.

4-Bromo-N-(pyridin-2-ylmethyl)benzamide (3ag): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 2.737 g, yield 94%; mp 112−113 °C;[36] ^{1}H NMR (600 MHz, CDCl$_3$) δ 8.57 (d, J = 4.2 Hz, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.72 (m, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 7.8 Hz, 1H), 7.25 (s, 1H), 4.76 (d, J = 4.8 Hz, 2H); ^{13}C NMR (150 MHz, DMSO) δ 165.5, 158.6, 148.9, 136.7, 133.3, 131.4, 129.4, 125.1, 122.1, 121.0, 44.8; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{13}$H$_{12}$BrN$_2$O 291.0133, found 291.0146.

tert-Butyl (4-bromobenzoyl)(quinolin-8-yl)carbamate (3a): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 1.180 g, yield 92%; mp 159−160 °C; ^{1}H NMR (600 MHz, DMSO) δ 8.90 (d, J = 4.2 Hz, 1H), 8.47 (d, J = 8.4 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.82 (d, J = 7.2 Hz, 1H), 7.76 (s, 4H), 7.68 (t, J = 7.8 Hz, 1H), 7.61 (dd, J = 8.4, 4.2 Hz, 1H), 1.14 (s, 9H); ^{13}C NMR (150 MHz, DMSO) δ 171.7, 152.4, 150.7, 143.3, 136.5, 136.2, 131.3, 130.0, 129.3, 128.6, 128.5, 126.4, 125.0, 122.0, 82.7, 27.0; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{21}$H$_{20}$BrN$_2$O$_3$ 427.0657, found 427.0630.

tert-Butyl (3-bromobenzoyl)(quinolin-8-yl)carbamate(3b): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 1.154 g, yield 90%; mp 125−126 °C; ^{1}H NMR (600 MHz, DMSO) δ 8.91 (d, J = 3.0 Hz, 1H), 8.48 (d, J = 7.8 Hz, 1H), 8.07 (d, J = 7.8 Hz, 1H), 8.00 (s, 1H), 7.86 (d, J = 7.2 Hz, 1H), 7.80 (m, 2H), 7.69 (t, J = 7.8 Hz, 1H), 7.61 (dd, J = 8.4, 4.2 Hz, 1H), 7.51 (t, J = 7.8 Hz, 1H), 1.14 (s, 9H); ^{13}C NMR (150 MHz, DMSO) δ 171.1, 152.3, 150.8, 143.3, 139.3, 136.5, 136.3, 134.0, 130.6, 130.4, 129.5, 128.7, 128.6, 126.8, 126.4, 122.1, 121.3, 82.9, 27.0; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{21}$H$_{20}$BrN$_2$O$_3$ 427.0657, found 427.0635.

tert-Butyl (4-bromo-1-naphthoyl)(quinolin-8-yl)carbamate (3c): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 1.289 g, yield 90%; mp 159−160 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 9.00 (s, 1H), 8.65 (s, 1H), 8.33 (s, 1H), 8.24 (d, J = 7.8 Hz, 1H), 7.95 (s, 1H), 7.91 (d, J = 7.8 Hz, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.80 (d, J = 7.2 Hz, 1H), 7.65 (d, J = 6.6 Hz, 4H), 7.48 (s, 1H), 0.90 (s, 9H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 171.8, 152.6, 150.5, 136.3, 131.8, 131.6, 129.3, 129.2, 128.9, 128.6, 127.8, 127.7, 127.4, 126.3, 126.2, 125.4, 125.0, 121.7, 83.5, 27.1; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{25}$H$_{22}$BrN$_2$O$_3$ 477.0814, found 477.0800.

tert-Butyl (5-bromofuran-2-carbonyl) (quinolin-8-yl)carbamate (3d): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 1.089 g, yield 87%; mp 111−112 °C; ^{1}H NMR (600 MHz, DMSO) δ 8.88 (s, 1H), 8.47 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 7.2 Hz, 1H), 7.66 (t, J = 7.8 Hz, 1H), 7.60 (dd, J = 8.4, 4.2 Hz, 1H), 7.25 (d, J = 3.0 Hz, 1H), 6.90 (d, J = 3.0 Hz, 1H), 1.32 (s, 9H); ^{13}C NMR (150 MHz, DMSO) δ 162.4, 155.0, 151.9, 150.9, 145.8, 143.2, 136.5, 135.8, 135.7, 129.4, 129.1, 128.6, 126.4, 122.2, 83.4, 27.2; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{19}$H$_{18}$BrN$_2$O$_4$ 417.0450, found 417.0461.

tert-Butyl (5-bromothiophene-2-carbonyl)(quinolin-8-yl)-carbamate (3e): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 1.118 g, yield 86%; mp 92−93 °C; ^{1}H NMR (600 MHz, DMSO) δ 8.91 (d, J = 4.2 Hz, 1H), 8.47 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 7.2 Hz, 1H), 7.66 (t, J = 7.8 Hz, 1H), 7.61 (dd, J = 8.4, 4.2 Hz, 1H), 7.39 (d, J = 4.2 Hz, 1H), 7.28 (d, J = 4.2 Hz, 1H), 1.26 (s, 9H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 164.4, 153.0, 150.4, 143.9, 140.4, 136.8, 136.1, 133.1, 130.0, 129.0, 128.9, 128.4, 126.2, 121.7, 119.9, 83.4, 27.6; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{19}$H$_{18}$BrN$_2$O$_3$S 433.0222, found 433.0211.

tert-Butyl (5-bromothiazole-2-carbonyl)(quinolin-8-yl)carbamate (3f): white solid (petroleum ether/acetone =20:3, R_f = 0.15); 1.081 g, yield 83%; mp 111−112 °C; ^{1}H NMR (600 MHz, DMSO) δ 8.92 (d, J = 4.2 Hz, 1H), 8.49 (d, J = 8.4 Hz, 1H), 8.15 (s, 1H), 8.09 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 7.2 Hz, 1H), 7.69 (t, J = 7.8 Hz, 1H), 7.63 (dd, J = 8.4, 4.2 Hz, 1H), 1.26 (s, 9H); ^{13}C NMR (150 MHz, DMSO) δ 162.3, 155.0,

151.9, 150.9, 145.8, 143.2, 136.5, 135.8, 135.7, 129.4, 129.1, 128.6, 126.4, 122.2, 83.3, 27.2; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₁₈H₁₇BrN₃O₃S 434.0174, found 434.0135.

tert-Butyl (4-bromobenzoyl)(pyridin-2-ylmethyl)carbamate (3g): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 1.080 g, yield 92%; mp 82−83 °C; ¹H NMR (600 MHz, DMSO) δ 8.50 (d, *J* = 4.8 Hz, 1H), 7.79 (t, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.30−7.25 (m, 1H), 5.01 (s, 2H), 1.10 (s, 9H); ¹³C NMR (150 MHz, CDCl₃) δ 172.2, 156.8, 153.0, 149.2, 136.4, 136.3, 131.1, 129.3, 125.4, 122.0, 120.8, 83.3, 50.1, 27.4; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₁₈H₂₀BrN₂O₃ 391.0657, found 391.0659.

tert-Butyl [1,1'-biphenyl]-4-carbonyl(quinolin-8-yl)carbamate (5a): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 75.6 mg, yield 89%; mp 155−156 °C; ¹H NMR (600 MHz, DMSO) δ 8.93 (d, *J* = 4.2 Hz, 1H), 8.48 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 7.2 Hz, 2H), 7.85 (d, *J* = 7.2 Hz, 2H), 7.82 (d, *J* = 7.2 Hz, 1H), 7.77 (d, *J* = 7.2 Hz, 2H), 7.69 (t, *J* = 7.8 Hz, 1H), 7.65−7.59 (m, 1H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.44 (t, *J* = 7.2 Hz, 1H), 1.15 (s, 9H); ¹³C NMR (150 MHz, DMSO) δ 172.3, 152.7, 150.7, 143.5, 143.1, 139.1, 136.8, 136.4, 135.8, 129.3, 129.1, 128.8, 128.7, 128.4, 128.2, 126.9, 126.4, 122.0, 82.5, 27.0; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₂₇H₂₅N₂O₃ 425.1865, found 425.1867.

N-(Quinolin-8-yl)[1,1'-biphenyl]-4-carboxamide (5aa): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 61.0 mg, yield 94%; mp 153−154 °C;[37] ¹H NMR (600 MHz, DMSO) δ 10.74 (s, 1H), 9.02 (s, 1H), 8.77 (d, *J* = 7.8 Hz, 1H), 8.49 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 7.2 Hz, 2H), 7.94 (d, *J* = 7.2 Hz, 2H), 7.78 (m, 3H), 7.74−7.65 (m, 2H), 7.54 (t, *J* = 7.2 Hz, 2H), 7.46 (t, *J* = 7.2 Hz, 1H); ¹³C NMR (150 MHz, DMSO) δ 164.1, 149.2, 143.6, 138.9, 138.3, 136.8, 134.0, 133.1, 129.1, 128.3, 127.9, 127.7, 127.2, 127.1, 127.0, 122.4, 116.6; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₂₂H₁₇N₂O 325.1341, found 325.1335.

4'-Methyl-1-(quinolin-8-yl)[1,1'-biphenyl]-4-carboxamide (5ab): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 63.6 mg, yield 94%; mp 154−155 °C; ¹H NMR (600 MHz, CDCl₃) (δ ppm): 10.73 (s, 1H), 9.01 (s, 1H), 8.77 (d, *J* = 7.8 Hz, 1H), 8.49 (d, *J* = 8.4 Hz, 1H), 8.12 (d, *J* = 7.8 Hz, 2H), 7.91 (d, *J* = 7.8 Hz, 2H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.68 (t, *J* = 8.4 Hz, 4H), 7.34 (d, *J* = 7.8 Hz, 2H), 2.38 (s, 3H); ¹³C NMR (150 MHz, DMSO) δ 164.1, 149.2, 143.5, 138.2, 137.8, 136.8, 136.0, 134.0, 132.8, 129.7, 127.8, 127.7, 127.1, 126.9, 126.8, 122.4, 122.3, 116.5, 20.7; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₂₃H₁₉N₂O 339.1497, found 339.1488.

4'-tert-Butyl-1-(quinolin-8-yl)[1,1'-biphenyl]-4-carboxamide (5ac): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 72.3 mg, yield 95%; mp 148−149 °C; ¹H NMR (600 MHz, DMSO) δ 10.73 (s, 1H), 9.01 (s, 1H), 8.77 (d, *J* = 7.2 Hz, 1H), 8.49 (d, *J* = 7.8 Hz, 1H), 8.12 (d, *J* = 7.2 Hz, 2H), 7.91 (d, *J* = 7.2 Hz, 2H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.70 (m, 4H), 7.54 (d, *J* = 7.2 Hz, 2H), 1.33 (s, 9H); ¹³C NMR (151 MHz, cdcl₃) δ 165.12, 151.14, 148.19, 144.36, 138.68, 136.99, 136.34, 134.55, 133.41, 127.93, 127.74, 127.42, 127.15, 126.82, 125.87, 121.62, 121.58, 116.50, 34.57, 31.28; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₂₆H₂₅N₂O 381.1967, found 381.1961.

4'-Methoxy-1-(quinolin-8-yl)[1,1'-biphenyl]-4-carboxamide (5ad): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 66.6 mg, yield 94%; mp 178−179 °C; ¹H NMR (600 MHz, DMSO) δ 10.72 (s, 1H), 9.01 (s, 1H), 8.77 (d, *J* = 7.2 Hz, 1H), 8.49 (d, *J* = 7.8 Hz, 1H), 8.10 (d, *J* = 7.8 Hz, 2H), 7.89 (d, *J* = 7.8 Hz, 2H), 7.75 (d, *J* = 7.8 Hz, 3H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 7.8 Hz, 2H), 3.83 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 165.11, 159.69, 148.21, 144.11, 138.71, 136.31, 134.57, 133.02, 132.33, 128.22, 127.93, 127.75, 127.40, 126.78, 121.61, 121.56, 116.45, 114.33, 55.35; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₂₃H₁₉N₂O₂ 355.1447, found 355.1441.

4'-Fluoro-1-(quinolin-8-yl)[1,1'-biphenyl]-4-carboxamide (5ae): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 65.1 mg, yield 95%; mp 152−153 °C; ¹H NMR (600 MHz, DMSO) δ 10.73 (s, 1H), 9.01 (s, 1H), 8.77 (d, *J* = 7.2 Hz, 1H), 8.48 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 7.8 Hz, 2H), 7.92 (d, *J* = 7.8 Hz, 2H), 7.87−7.81 (m, 2H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.74−7.65 (m, 2H), 7.37 (t, *J* = 8.4 Hz, 2H); ¹³C NMR (150 MHz, DMSO) δ 164.04, 162.33 (d, *J* = 244.2 Hz), 149.17, 142.52, 138.23, 136.77, 135.37, 134.00, 133.10, 129.02 (d, *J* = 8.4 Hz), 127.83, 127.71, 127.12, 127.04, 122.34, 122.31, 116.52, 115.91 (d, *J* = 21.2 Hz);

HRMS (ESI) *m/z* [M + H]⁺ calcd for C₂₂H₁₆FN₂O 343.1247, found 343.1261

3'-Fluoro-1-(quinolin-8-yl)[1,1'-biphenyl]-4-carboxamide (5af): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 63.0 mg, yield 92%; mp 93−94 °C; ¹H NMR (600 MHz, DMSO) δ 10.74 (s, 1H), 9.02 (s, 1H), 8.76 (d, *J* = 7.2 Hz, 1H), 8.49 (d, *J* = 7.8 Hz, 1H), 8.14 (d, *J* = 7.8 Hz, 2H), 7.98 (d, *J* = 7.8 Hz, 2H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.68 (m, 4H), 7.63−7.54 (m, 1H), 7.29 (t, *J* = 7.8 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 164.84, 163.14 (d, *J* = 245.0 Hz), 148.21, 143.10, 142.15 (d, *J* = 7.7 Hz), 138.64, 136.38, 134.42, 134.26, 130.39 (d, *J* = 8.1 Hz), 127.93, 127.86, 127.40, 127.33, 122.79, 121.71, 121.64, 116.58, 114.78 (d, *J* = 20.9 Hz), 114.05 (d, *J* = 22.2 Hz); HRMS (ESI) *m/z* [M + H]⁺ calcd for C₂₂H₁₆FN₂O 343.1247, found 343.1257.

2'-Fluoro-1-(quinolin-8-yl)[1,1'-biphenyl]-4-carboxamide (5ag): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 61.6 mg, yield 90%; mp 139−140 °C; ¹H NMR (600 MHz, DMSO) δ 10.75 (s, 1H), 9.01 (s, 1H), 8.77 (d, *J* = 7.2 Hz, 1H), 8.49 (d, *J* = 7.8 Hz, 1H), 8.16 (d, *J* = 7.8 Hz, 2H), 7.82 (d, *J* = 7.8 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.73−7.62 (m, 3H), 7.51 (d, *J* = 6.0 Hz, 1H), 7.44−7.34 (m, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 164.97, 159.72 (d, *J* = 247.5 Hz), 148.23, 139.26, 138.68, 136.34, 134.50, 134.13, 130.59, 129.67 (d, *J* = 8.1 Hz), 129.33 (d, *J* = 2.7 Hz), 127.94, 127.39, 124.50 (d, *J* = 3.5 Hz), 121.67, 121.64, 116.54, 116.22 (d, *J* = 22.7 Hz); HRMS (ESI) *m/z* [M + H]⁺ calcd for C₂₂H₁₆FN₂O 343.1247, found 343.1260.

4'-Chloro-1-(quinolin-8-yl)[1,1'-biphenyl]-4-carboxamide (5ah): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 66.7 mg, yield 93%; mp 153−154 °C; ¹H NMR (600 MHz, DMSO) δ 10.73 (s, 1H), 9.01 (s, 1H), 8.76 (d, *J* = 7.2 Hz, 1H), 8.49 (d, *J* = 8.4 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 2H), 7.95 (d, *J* = 8.4 Hz, 2H), 7.83 (d, *J* = 8.4 Hz, 2H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 7.2 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H); ¹³C NMR (150 MHz, DMSO) δ 164.02, 149.20, 142.21, 138.26, 137.70, 136.78, 133.98, 133.44, 133.21, 129.04, 128.71, 127.84, 127.78, 127.17, 127.05, 122.37, 116.60; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₂₂H₁₆ClN₂O 359.0951, found 359.0945.

4'-Hydroxy-1-(quinolin-8-yl)[1,1'-biphenyl]-4-carboxamide (5ai): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 59.2 mg, yield 87%; mp 218−219 °C; ¹H NMR (600 MHz, DMSO) δ 10.71 (s, 1H), 9.75 (s, 1H), 9.01 (s, 1H), 8.77 (d, *J* = 7.2 Hz, 1H), 8.48 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 7.8 Hz, 2H), 7.85 (d, *J* = 7.8 Hz, 2H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.70 (m, 2H), 7.64 (m, 2H), 6.91 (d, *J* = 7.8 Hz, 2H); ¹³C NMR (150 MHz, DMSO) δ 164.2, 158.0, 149.2, 143.7, 138.2, 136.8, 134.1, 132.0, 129.6, 128.2, 127.9, 127.7, 127.1, 126.3, 122.4, 122.2, 116.5, 116.0; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₂₂H₁₇N₂O₂ 341.1290, found 341.1281.

N-(Quinolin-8-yl)-4'-(trifluoromethoxy)[1,1'-biphenyl]-4-carboxamide (5aj): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 74.3 mg, yield 91%; mp 150−151 °C; ¹H NMR (600 MHz, DMSO) δ 10.74 (s, 1H), 9.01 (s, 1H), 8.76 (d, *J* = 7.2 Hz, 1H), 8.49 (d, *J* = 7.8 Hz, 1H), 8.15 (d, *J* = 7.2 Hz, 2H), 7.96 (d, *J* = 7.2 Hz, 2H), 7.92 (d, *J* = 7.8 Hz, 2H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.74−7.65 (m, 2H), 7.53 (d, *J* = 7.8 Hz, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 164.85, 149.12, 148.25, 143.04, 138.70, 138.65, 136.37, 134.46, 134.13, 128.55, 127.96, 127.89, 127.42, 127.34, 121.73, 121.66, 121.29, 119.61, 116.56 (OCF₃ carbons are merging with other peaks); HRMS (ESI) *m/z* [M + H]⁺ calcd for C₂₃H₁₆F₃N₂O₂ 409.1164, found 409.1173.

N-(Quinolin-8-yl)-4'-(trifluoromethyl)[1,1'-biphenyl]-4-carboxamide (5ak): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 67.5 mg, yield 86%; mp 157−158 °C; ¹H NMR (600 MHz, DMSO) δ 10.74 (s, 1H), 9.01 (s, 1H), 8.76 (s, 1H), 8.48 (s, 1H), 8.17 (s, 2H), 8.01 (s, 4H), 7.88 (s, 2H), 7.77 (s, 1H), 7.70 (s, 2H); ¹³C NMR (150 MHz, CDCl₃) δ 164.78, 148.26, 143.45, 142.94, 138.68, 136.44, 134.64, 134.42, 127.97, 127.58, 127.49, 127.44, 126.85, 125.82 (q, *J* = 3.0 Hz), 125.04, 124.14 (q, *J* = 270.8 Hz), 123.24, 121.80, 121.69, 116.63; HRMS (ESI) *m/z* [M + H]⁺ calcd for C₂₃H₁₆F₃N₂O 393.1215, found 393.1221.

4'-Acetyl-1-(quinolin-8-yl)[1,1'-biphenyl]-4-carboxamide (5al): yellow solid (petroleum ether/acetone = 20:1, R_f = 0.15); 66.0 mg, yield 90%; mp 159−160 °C; ¹H NMR (600 MHz, DMSO) δ 10.75 (s, 1H), 9.02 (s, 1H), 8.77 (d, *J* = 7.2 Hz, 1H), 8.49 (d, *J* = 7.8 Hz, 1H), 8.17 (d, *J* = 7.8 Hz, 2H), 8.10 (d, *J* = 7.8 Hz, 2H), 8.02 (d, *J* = 7.8 Hz, 2H), 7.96 (d, *J* = 7.8 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.74−7.67 (m, 2H),

2.65 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 197.53, 164.75, 148.26, 144.35, 143.05, 138.67, 136.36, 136.33, 134.57, 134.40, 128.94, 127.93, 127.89, 127.53, 127.39, 127.28, 121.75, 121.68, 116.52, 26.63; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{24}$H$_{19}$N$_2$O$_2$ 367.1447, found 367.1445.

Methyl 4′-(quinolin-8-ylcarbamoyl)[1,1′-biphenyl]-4-carboxylate (5am): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 66.5 mg, yield 87%; mp 151−152 °C; ^{1}H NMR (600 MHz, DMSO) δ 10.74 (s, 1H), 9.01 (s, 1H), 8.76 (s, 1H), 8.48 (s, 1H), 8.16 (s, 2H), 8.09 (s, 2H), 8.00 (s, 2H), 7.95 (s, 2H), 7.77 (s, 1H), 7.70 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 166.7, 164.7, 148.2, 144.2, 143.1, 138.6, 136.3, 134.5, 134.4, 130.1, 129.5, 127.9, 127.8, 127.5, 127.4, 127.1, 121.7, 121.6, 116.5, 52.1; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{24}$H$_{19}$N$_2$O$_3$ 383.1396, found 383.1389.

2′,4′-Dichloro-1-(quinolin-8-yl)[1,1′-biphenyl]-4-carboxamide (5an): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 70.0 mg, yield 89%; mp 189−190 °C; ^{1}H NMR (600 MHz, DMSO) δ 10.74 (s, 1H), 9.00 (s, 1H), 8.76 (d, J = 7.8 Hz, 1H), 8.49 (d, J = 7.8 Hz, 1H), 8.14 (d, J = 7.8 Hz, 2H), 7.82 (s, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.69 (m, 3H), 7.64−7.52 (m, 2H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 165.0, 148.3, 141.7, 138.8, 138.0, 136.4, 134.6, 134.5, 134.3, 133.2, 131.9, 129.9, 129.8, 128.0, 127.5, 127.3, 127.2, 121.8, 121.7 116.6; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{22}$H$_{15}$Cl$_2$N$_2$O 393.0561, found 393.0555.

3′,4′-Dichloro-1-(quinolin-8-yl)[1,1′-biphenyl]-4-carboxamide (5ao): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 70.8 mg, yield 90%; mp 158−159 °C; ^{1}H NMR (600 MHz, DMSO) δ 10.73 (s, 1H), 9.01 (s, 1H), 8.75 (d, J = 7.2 Hz, 1H), 8.49 (d, J = 7.8 Hz, 1H), 8.14 (d, J = 7.8 Hz, 2H), 8.09 (s, 1H), 8.00 (d, J = 7.2 Hz, 2H), 7.85−7.75 (m, 3H), 7.69 (d, J = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 164.7, 148.3, 141.9, 139.9, 138.7, 136.4, 134.5, 134.4, 133.0, 132.2, 130.8, 128.9, 128.0, 127.4, 127.2, 126.3, 121.8, 121.7, 116.6; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{22}$H$_{15}$Cl$_2$N$_2$O 393.0561, found 393.0558.

3′,5′-Dichloro-1-(quinolin-8-yl)[1,1′-biphenyl]-4-carboxamide (5ap): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 69.2 mg, yield 88%; mp 158−159 °C; ^{1}H NMR (600 MHz, CDCl$_3$) (δ ppm): 10.73 (s, 1H), 9.01 (d, J = 3.6 Hz, 1H), 8.75 (d, J = 7.2 Hz, 1H), 8.49 (d, J = 7.2 Hz, 1H), 8.14 (m, 3H), 8.02 (d, J = 8.4 Hz, 2H), 7.87 (s, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.73−7.66 (m, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 164.68, 148.29, 142.93, 141.70, 138.69, 136.44, 135.47, 134.91, 134.38, 128.02, 127.85, 127.50, 127.46, 127.40, 125.70, 121.84, 121.71, 116.65; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{22}$H$_{15}$Cl$_2$N$_2$O 393.0561, found 393.0553.

4-(Pyridin-4-yl)-1-(quinolin-8-yl)benzamide (5aq): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 57.3 mg, yield 88%; mp 201−202 °C; ^{1}H NMR (600 MHz, DMSO) δ 10.76 (s, 1H), 9.01 (s, 1H), 8.76 (d, J = 6.0 Hz, 1H), 8.72 (s, 2H), 8.49 (d, J = 6.6 Hz, 1H), 8.19 (d, J = 6.0 Hz, 2H), 8.08 (s, 2H), 7.83 (s, 2H), 7.78 (d, J = 6.6 Hz, 1H), 7.70 (s, 2H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 164.5, 150.3, 148.3, 147.1, 141.3, 138.6, 136.4, 135.4, 134.3, 128.0, 127.9, 127.4, 127.3, 121.8, 121.7, 121.6, 116.5; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{21}$H$_{16}$N$_3$O 326.1293, found 326.1289.

4-(Naphthalen-1-yl)-1-(quinolin-8-yl)benzamide (5ar): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 66.6 mg, yield 89%; mp 151−152 °C; ^{1}H NMR (600 MHz, DMSO) δ 10.76 (s, 1H), 9.03 (s, 1H), 8.78 (d, J = 7.2 Hz, 1H), 8.49 (d, J = 7.8 Hz, 1H), 8.38 (s, 1H), 8.19 (d, J = 7.8 Hz, 2H), 8.08 (m, 4H), 7.98 (m, 2H), 7.78 (d, J = 7.8 Hz, 1H), 7.74−7.67 (m, 2H), 7.59 (d, J = 6.0 Hz, 2H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 165.05, 148.20, 144.39, 138.66, 137.19, 136.38, 134.51, 133.71, 133.51, 132.86, 128.62, 128.28, 127.94, 127.84, 127.62, 127.58, 127.43, 126.45, 126.31, 126.17, 125.16, 121.64, 116.55; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{26}$H$_{19}$N$_2$O 375.1497, found 375.1487.

4-(Dibenzo[b,d]furan-4-yl)-1-(quinolin-8-yl)benzamide (5as): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 70.5 mg, yield 85%; mp 189−190 °C; ^{1}H NMR (600 MHz, DMSO) δ 10.80 (s, 1H), 9.03 (s, 1H), 8.80 (d, J = 6.6 Hz, 1H), 8.50 (d, J = 7.8 Hz, 1H), 8.25 (m, 4H), 8.20 (s, 2H), 7.84 (d, J = 6.6 Hz, 1H), 7.79 (t, J = 8.4 Hz, 2H), 7.72 (s, 2H), 7.60 (m, 3H), 7.47 (s, 1H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 165.1, 156.2, 153.3, 148.3, 139.9, 138.8, 136.4, 134.6, 134.2, 129.1, 128.0, 127.7, 127.5, 127.4, 126.8, 125.1, 124.7, 124.0, 123.3, 122.9, 121.7, 120.7, 120.4, 116.7, 111.9; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{28}$H$_{19}$N$_2$O$_2$ 415.1447, found 415.1435.

N-(Quinolin-8-yl)[1,1′-biphenyl]-3-carboxamide (5ba): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 61.6 mg, yield 95%; mp 82−83 °C;[38] ^{1}H NMR (600 MHz, DMSO) δ 10.74 (s, 1H), 8.99 (d, J = 3.0 Hz, 1H), 8.74 (d, J = 7.8 Hz, 1H), 8.48 (d, J = 7.8 Hz, 1H), 8.29 (s, 1H), 8.03 (d, J = 7.2 Hz, 1H), 7.97 (d, J = 7.2 Hz, 1H), 7.79 (t, J = 8.4 Hz, 3H), 7.73 (t, J = 7.8 Hz, 1H), 7.71−7.67 (m, 2H), 7.54 (t, J = 7.8 Hz, 2H), 7.45 (t, J = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, DMSO) δ 164.5, 149.2, 140.9, 139.3, 138.4, 136.7, 135.3, 134.0, 130.3, 129.6, 129.1, 128.0, 127.8, 127.0, 126.9, 125.9, 125.5, 122.5, 122.3, 117.0; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{22}$H$_{17}$N$_2$O 325.1341, found 325.1336.

4′-tert-Butyl)-1-(quinolin-8-yl)[1,1′-biphenyl]-3-carboxamide (5bb): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 72.3 mg, yield 95%; mp 116−117 °C; ^{1}H NMR (600 MHz, DMSO) δ 10.73 (s, 1H), 8.99 (d, J = 3.0 Hz, 1H), 8.75 (d, J = 7.8 Hz, 1H), 8.48 (d, J = 8.4 Hz, 1H), 8.27 (s, 1H), 8.01 (d, J = 7.8 Hz, 1H), 7.94 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.70 (m, 5H), 7.55 (d, J = 7.8 Hz, 2H), 1.34 (s, 9H); ^{13}C NMR (150 MHz, DMSO) δ 164.5, 150.4, 149.1, 140.8, 138.3, 136.7, 136.4, 135.2, 134.0, 130.1, 129.6, 127.8, 127.0, 126.5, 125.8, 125.6, 125.2, 122.4, 122.3, 116.8, 34.23, 31.02; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{26}$H$_{25}$N$_2$O 381.1967, found 381.1960.

4′-Methoxy-1-(quinolin-8-yl)[1,1′-biphenyl]-3-carboxamide (5bc): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 66.6 mg, yield 94%; mp 74−75 °C; ^{1}H NMR (600 MHz, DMSO) δ 10.72 (s, 1H), 8.99 (s, 1H), 8.74 (d, J = 7.2 Hz, 1H), 8.48 (d, J = 7.2 Hz, 1H), 8.24 (s, 1H), 7.97 (d, J = 6.0 Hz, 1H), 7.92 (d, J = 6.6 Hz, 1H), 7.82−7.64 (m, 6H), 7.10 (d, J = 7.2 Hz, 2H), 3.83 (s, 3H); ^{13}C NMR (150 MHz, DMSO) δ 164.6, 159.3, 149.2, 140.6, 138.4, 136.7, 135.2, 134.1, 131.6, 129.8, 129.6, 128.1, 127.9, 127.0, 125.1, 124.9, 122.4, 122.3, 116.9, 114.5, 55.2; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{23}$H$_{19}$N$_2$O$_2$ 355.1447, found 355.1440.

4′-Fluoro-1-(quinolin-8-yl)[1,1′-biphenyl]-3-carboxamide (5bd): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 63.7 mg, yield 93%; mp 141−142 °C; ^{1}H NMR (600 MHz, DMSO) δ 10.73 (s, 1H), 8.99 (d, J = 4.2 Hz, 1H), 8.72 (d, J = 7.8 Hz, 1H), 8.48 (d, J = 8.4 Hz, 1H), 8.27 (s, 1H), 8.03 (d, J = 7.8 Hz, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.85 (dd, J = 8.4, 5.4 Hz, 2H), 7.78 (d, J = 8.4 Hz, 1H), 7.74−7.67 (m, 3H), 7.37 (t, J = 9.0 Hz, 2H); ^{13}C NMR (150 MHz, DMSO) δ 164.53, 162.17 (d, J = 243.5 Hz), 149.21, 139.85, 138.47, 136.73, 135.81, 135.32, 134.04, 130.27, 129.65, 129.01 (d, J = 8.0 Hz),, 127.86, 126.99, 125.87, 125.46, 122.53, 122.31, 117.08, 115.90 (d, J = 21.1 Hz); HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{22}$H$_{16}$FN$_2$O 343.1247, found 343.1251.

4′-Chloro-1-(quinolin-8-yl)[1,1′-biphenyl]-3-carboxamide (5be): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 66.7 mg, yield 93%; mp 156−157 °C; ^{1}H NMR (600 MHz, DMSO) δ 10.73 (s, 1H), 8.99 (d, J = 4.2 Hz, 1H), 8.72 (d, J = 7.8 Hz, 1H), 8.48 (d, J = 8.4 Hz, 1H), 8.30 (s, 1H), 8.05 (d, J = 7.8 Hz, 1H), 7.97 (d, J = 7.8 Hz, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.4 Hz, 1H), 7.73 (t, J = 7.8 Hz, 1H), 7.71−7.67 (m, 2H), 7.60 (d, J = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 165.16, 148.28, 140.57, 138.64, 138.56, 136.34, 135.77, 134.36, 133.87, 130.20, 129.25, 129.01, 128.40, 127.90, 127.36, 126.09, 125.92, 121.79, 121.66, 116.55; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{22}$H$_{16}$ClN$_2$O 359.0951, found 359.0944.

Methyl 3′-(quinolin-8-ylcarbamoyl)[1,1′-biphenyl]-4-carboxylate (5bf): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 65.0 mg, yield 85%; mp 166−167 °C; ^{1}H NMR (600 MHz, DMSO) δ 10.74 (s, 1H), 8.99 (d, J = 3.6 Hz, 1H), 8.72 (d, J = 7.8 Hz, 1H), 8.48 (d, J = 8.4 Hz, 1H), 8.36 (s, 1H), 8.10 (t, J = 9.0 Hz, 3H), 8.04 (d, J = 7.8 Hz, 1H), 7.97 (d, J = 7.8 Hz, 2H), 7.77 (dd, J = 15.6, 7.8 Hz, 2H), 7.69 (t, J = 6.6 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 166.79, 165.08, 148.27, 144.49, 140.60, 138.60, 136.40, 135.81, 134.32, 130.49, 130.16, 129.31, 129.27, 127.91, 127.38, 127.11, 126.45, 126.42, 121.82, 121.67, 116.62, 52.15. HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{24}$H$_{19}$N$_2$O$_3$ 383.1396, found 383.1395.

N-(Quinolin-8-yl)-4′-(trifluoromethyl)[1,1′-biphenyl]-3-carboxamide (5bg): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 66.7 mg, yield 85%; mp 151−152 °C; ^{1}H NMR (600 MHz, DMSO) δ 10.74 (s, 1H), 8.98 (s, 1H), 8.72 (d, J = 7.5 Hz, 1H), 8.48 (d, J = 8.3 Hz, 1H), 8.36 (s, 1H), 8.10 (d, J = 7.4 Hz, 1H), 8.04 (d, J = 7.9 Hz, 3H), 7.89 (d, J = 7.8 Hz, 2H), 7.78 (t, J = 8.0 Hz, 2H), 7.69 (t, J = 7.0 Hz, 2H); ^{13}C NMR (150 MHz, DMSO) δ 164.53, 162.98, 161.35, 149.21, 139.84,

138.46, 136.72, 135.79, 135.32, 134.03, 130.26, 129.64, 129.02, 128.97, 127.85, 126.98, 125.85, 125.44, 122.52, 122.29, 117.08, 115.96, 115.82 (CF$_3$ carbons are merging with other peaks); HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{23}$H$_{16}$F$_3$N$_2$O 393.1215, found 393.1223.

2′,4′-Dichloro-1-(quinolin-8-yl)[1,1′-biphenyl]-3-carboxamide **(5bh):** white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 69.2 mg, yield 88%; mp 139−140 °C; ^{1}H NMR (600 MHz, DMSO) δ 10.72 (s, 1H), 8.98 (d, J = 3.6 Hz, 1H), 8.72 (d, J = 7.8 Hz, 1H), 8.48 (d, J = 8.4 Hz, 1H), 8.17 (s, 1H), 8.08 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H), 7.75 (m, 3H), 7.68 (t, J = 7.8 Hz, 2H), 7.46 (t, J = 9.6 Hz, 1H), 7.28 (t, J = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, DMSO) δ 164.27, 149.19, 138.40, 136.73, 134.99, 134.91, 133.98, 132.34, 132.11, 132.08, 132.05, 132.02, 129.39, 127.84, 127.56, 126.99, 126.36, 123.97, 122.52, 122.32, 116.97, 112.33, 112.19, 104.82, 104.65, 104.48; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{22}$H$_{15}$Cl$_2$N$_2$O 393.0561, found 393.0553.

3-(Pyridin-4-yl)-1-(quinolin-8-yl)benzamide **(5bi):** white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 56.6 mg, yield 87%; mp 151−152 °C; ^{1}H NMR (600 MHz, DMSO) δ 10.74 (s, 1H), 8.99 (d, J = 3.0 Hz, 1H), 8.72 (d, J = 6.0 Hz, 2H), 8.48 (d, J = 7.2 Hz, 1H), 8.42 (s, 1H), 8.13 (d, J = 7.8 Hz, 1H), 8.10 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 6.0 Hz, 2H), 7.81−7.77 (m, 2H), 7.72−7.66 (m, 2H), 7.66−7.60 (m, 1H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 164.7, 150.2, 148.3, 147.3, 138.7, 138.6, 136.3, 136.0, 134.2, 132.0, 130.1, 129.5, 127.8, 127.3, 127.2, 126.2, 121.9, 121.6, 116.5; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{21}$H$_{16}$N$_3$O 326.1293, found 326.1295.

4-Phenyl-1-(quinolin-8-yl)-1-naphthamide **(5ca):** white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 70.4 mg, yield 94%; mp 72−73 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 10.48 (s, 1H), 9.08 (d, J = 7.2 Hz, 1H), 8.77 (s, 1H), 8.59 (d, J = 8.4 Hz, 1H), 8.21 (d, J = 7.8 Hz, 1H), 7.96 (d, J = 7.8 Hz, 2H), 7.67 (t, J = 7.8 Hz, 1H), 7.62−7.56 (m, 2H), 7.54−7.44 (m, 8H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 167.8, 148.3, 143.3, 140.2, 138.5, 136.4, 134.8, 134.1, 132.1, 130.7, 129.9, 128.3, 128.0, 127.6, 127.4, 127.1, 126.5, 125.9, 125.8, 124.9, 121.9, 121.7, 116.7; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{26}$H$_{19}$N$_2$O 375.1497, found 375.1486.

4-(4-Methoxyphenyl)-1-(quinolin-8-yl)-1-naphthamide **(5cb):** white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 76.0 mg, yield 94%; mp 136−137 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 10.47 (s, 1H), 9.08 (d, J = 7.2 Hz, 1H), 8.76 (s, 1H), 8.59 (d, J = 9.0 Hz, 1H), 8.20 (d, J = 7.8 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 7.2 Hz, 1H), 7.68−7.64 (m, 1H), 7.62−7.56 (m, 2H), 7.50 (t, J = 6.6 Hz, 2H), 7.46 (d, J = 8.4 Hz, 3H), 3.92 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 167.8, 159.2, 148.2, 143.0, 138.5, 136.3, 134.8, 133.8, 132.5, 132.3, 131.0, 130.7, 127.9, 127.4, 127.0, 126.6, 126.4, 125.9, 125.8, 125.0, 121.9, 121.7, 116.7, 113.8, 55.3; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{27}$H$_{21}$N$_2$O$_2$ 405.1603, found 405.1597.

4-(4-Fluorophenyl)-1-(quinolin-8-yl)-1-naphthamide **(5cc):** white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 73.0 mg, yield 93%; mp 143−144 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 10.48 (s, 1H), 9.08 (d, J = 7.2 Hz, 1H), 8.77 (s, 1H), 8.59 (d, J = 8.4 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 7.2 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.67 (t, J = 7.8 Hz, 1H), 7.63−7.57 (m, 2H), 7.53−7.46 (m, 5H), 7.22 (t, J = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 167.7, 162.4 (d, J = 245.7 Hz), 148.3, 142.1, 138.5, 136.4, 136.1, 134.7, 134.3, 132.1, 131.5 (d, J = 8.0 Hz), 130.6, 128.0, 127.4, 127.1, 126.7, 126.2, 126.0, 125.8, 124.8, 122.0, 121.7, 116.8, 115.3 (d, J = 21.2 Hz); HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{26}$H$_{18}$FN$_2$O 393.1403, found 393.1397.

4-(Pyridin-4-yl)-1-(quinolin-8-yl)-1-naphthamide **(5cd):** white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 63.1 mg, yield 84%; mp 193−194 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 10.48 (s, 1H), 9.07 (d, J = 7.2 Hz, 1H), 8.79 (s, 2H), 8.77 (s, 1H), 8.60 (d, J = 8.4 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 7.2 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.67 (t, J = 7.8 Hz, 1H), 7.63 (m, 2H), 7.56 (t, J = 7.8 Hz, 1H), 7.54−7.50 (m, 3H), 7.48 (dd, J = 7.8, 3.6 Hz, 1H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 167.33, 149.76, 148.30, 148.22, 140.10, 138.50, 136.38, 135.32, 134.59, 131.24, 130.60, 127.96, 127.45, 127.39, 127.16, 126.05, 125.83, 125.64, 124.86, 124.70, 122.10, 121.72, 116.75; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{25}$H$_{18}$N$_3$O 376.1450, found 376.1445.

5-Phenyl-N-(quinolin-8-yl)furan-2-carboxamide **(6aa):** white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 57.8 mg, yield 92%; mp 159−160 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 10.92 (s, 1H), 8.95 (d, J =

3.0 Hz, 1H), 8.89 (d, J = 7.2 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 7.8 Hz, 2H), 7.60 (d, J = 7.8 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.54−7.47 (m, 3H), 7.39 (t, J = 5.4 Hz, 2H), 6.84 (d, J = 3.6 Hz, 1H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 156.23, 155.70, 148.39, 147.19, 138.52, 136.20, 134.14, 129.56, 128.82, 128.65, 127.89, 127.28, 124.49, 121.64, 121.59, 117.05, 116.48, 107.47; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{20}$H$_{15}$N$_2$O$_2$ 315.1134, found 315.1140.

5-(4-Fluorophenyl)-N-(quinolin-8-yl)furan-2-carboxamide **(6ab):** white solid (petroleum ether/acetone =20:2, R_f = 0.15); 60.5 mg, yield 92%; mp 157−158 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 10.88 (s, 1H), 8.94 (d, J = 3.6 Hz, 1H), 8.89 (d, J = 7.2 Hz, 1H), 8.23 (d, J = 8.4 Hz, 1H), 7.90−7.82 (m, 2H), 7.61 (t, J = 7.8 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.52 (dd, J = 8.4, 4.2 Hz, 1H), 7.39 (d, J = 3.6 Hz, 1H), 7.19 (t, J = 8.4 Hz, 2H), 6.78 (d, J = 3.6 Hz, 1H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 162.8 (d, J = 248.0 Hz), 156.1, 154.8, 148.4, 147.2, 138.5, 136.2, 134.1, 127.9, 127.3, 126.40 (d, J = 8.3 Hz), 126.0, 121.7, 121.6, 117.1, 116.5, 116.0 (d, J = 21.0 Hz), 107.2; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{20}$H$_{14}$FN$_2$O$_2$ 333.1039, found 333.1040.

5-(Pyridin-4-yl)-N-(quinolin-8-yl)furan-2-carboxamide **(6ac):** white solid (petroleum ether/acetone =20:3, R_f = 0.15); 52.4 mg, yield 83%; mp 187−188 °C; ^{1}H NMR (600 MHz, DMSO) δ 10.96 (s, 1H), 8.96 (d, J = 3.0 Hz, 1H), 8.88 (d, J = 7.2 Hz, 1H), 8.75 (d, J = 5.4 Hz, 2H), 8.23 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 5.4 Hz, 2H), 7.60 (q, J = 8.4 Hz, 2H), 7.54 (dd, J = 8.4, 4.2 Hz, 1H), 7.42 (d, J = 3.6 Hz, 1H), 7.08 (d, J = 3.6 Hz, 1H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 155.61, 152.59, 150.34, 148.60, 148.49, 138.44, 136.23, 136.21, 133.79, 127.86, 127.22, 121.95, 121.69, 118.18, 116.76, 116.56, 110.75; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{19}$H$_{14}$N$_3$O$_2$ 316.1086, found 316.1089.

5-Phenyl-N-(quinolin-8-yl)thiophene-2-carboxamide **(6ad):** white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 50.2 mg, yield 76%; mp 135−136 °C; ^{1}H NMR (600 MHz, DMSO) δ 10.59 (s, 1H), 9.01 (s, 1H), 8.60 (d, J = 7.8 Hz, 1H), 8.48 (d, J = 7.8 Hz, 1H), 8.03 (s, 1H), 7.81 (d, J = 7.8 Hz, 2H), 7.77 (d, J = 8.4 Hz, 1H), 7.70 (s, 2H), 7.67 (t, J = 7.8 Hz, 1H), 7.49 (t, J = 7.8 Hz, 2H), 7.42 (t, J = 7.2 Hz, 1H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 159.82, 149.77, 148.24, 138.36, 136.32, 134.19, 133.38, 129.38, 129.00, 128.55, 127.88, 127.36, 126.07, 123.59, 121.66, 121.59, 116.39; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{20}$H$_{15}$N$_2$OS 331.0905, found 331.0910.

5-(4-Fluorophenyl)-N-(quinolin-8-yl)thiophene-2-carboxamide **(6ae):** white solid (petroleum ether/acetone =20:2, R_f = 0.15); 53.0 mg, yield 76%; mp 169−170 °C; ^{1}H NMR (600 MHz, DMSO) δ 10.58 (s, 1H), 9.00 (s, 1H), 8.59 (d, J = 7.8 Hz, 1H), 8.48 (d, J = 7.8 Hz, 1H), 8.02 (s, 1H), 7.85 (d, J = 6.0 Hz, 2H), 7.77 (d, J = 8.4 Hz, 1H), 7.71−7.62 (m, 3H), 7.34 (t, J = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 162.80 (d, J = 247.7 Hz), 159.66, 148.54, 148.22, 138.43, 138.34, 136.28, 134.14, 129.69, 129.67, 129.33, 127.86, 127.79 (d, J = 8.1 Hz), 127.32, 123.54, 121.62 (d, J = 5.3 Hz), 116.37, 115.97 (d, J = 21.9 Hz); HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{20}$H$_{14}$FN$_2$OS 349.0811, found 349.0817.

5-(Pyridin-4-yl)-N-(quinolin-8-yl)thiophene-2-carboxamide **(6af):** white solid (petroleum ether/acetone = 20:3, R_f = 0.15); 47.1 mg, yield 71%; mp 194−195 °C; ^{1}H NMR (600 MHz, DMSO) δ 10.64 (s, 1H), 9.01 (s, 1H), 8.66 (s, 2H), 8.59 (d, J = 7.2 Hz, 1H), 8.48 (d, J = 8.4 Hz, 1H), 8.10 (s, 1H), 7.96 (s, 1H), 7.79 (s, 3H), 7.70 (s, 1H), 7.57 (s, 1H); ^{13}C NMR (150 MHz, DMSO) δ 159.3, 150.5, 148.4, 146.0, 141.0, 140.5, 138.4, 136.4, 134.0, 129.2, 127.9, 127.4, 125.7, 121.9, 121.8, 120.0, 116.6; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{19}$H$_{14}$N$_3$OS 332.0858, found 332.0852.

5-Phenyl-N-(quinolin-8-yl)thiazole-2-carboxamide **(6ag):** white solid (petroleum ether/acetone = 20:3, R_f = 0.15); 49.7 mg, yield 75%; mp 157−158 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 10.92 (s, 1H), 8.95 (d, J = 3.6 Hz, 1H), 8.90 (d, J = 7.8 Hz, 1H), 8.21 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 7.8 Hz, 2H), 7.60 (t, J = 7.8 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.51 (m, 3H), 7.40 (t, J = 6.0 Hz, 2H), 6.84 (d, J = 3.6 Hz, 1H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 156.3, 155.7, 148.4, 147.2, 138.5, 136.3, 134.1, 129.6, 128.8, 128.7, 127.9, 127.3, 124.5, 121.7, 121.6, 117.1, 116.6, 107.5; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{19}$H$_{14}$N$_3$OS 332.0858, found 332.0861.

5-(4-Fluorophenyl)-N-(quinolin-8-yl)thiazole-2-carboxamide **(6ah):** white solid (petroleum ether/acetone = 20:4, R_f = 0.15); 51.0 mg, yield 73%; mp 157−158 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 10.88 (s,

1H), 8.93 (d, J = 3.0 Hz, 1H), 8.89 (d, J = 7.2 Hz, 1H), 8.21 (d, J = 7.8 Hz, 1H), 7.85 (dd, J = 8.4, 5.4 Hz, 2H), 7.60 (t, J = 7.8 Hz, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.51 (dd, J = 8.4, 4.2 Hz, 1H), 7.37 (d, J = 3.6 Hz, 1H), 7.19 (t, J = 8.4 Hz, 2H), 6.77 (d, J = 3.6 Hz, 1H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 162.8 (d, J = 247.8 Hz), 156.1, 154.8, 148.3, 147.2, 138.4, 136.3, 134.0, 127.9, 127.3, 126.4 (d, J = 8.3 Hz), 125.9, 121.7, 121.6, 117.1, 116.6, 116.0 (d, J = 21.9 Hz), 107.2; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{19}$H$_{13}$FN$_3$OS 350.0763, found 350.0780.

5-(Pyridin-4-yl)-N-(quinolin-8-yl)thiazole-2-carboxamide (6ai): white solid (petroleum ether/acetone =20:4, R_f = 0.15); 46.5 mg, yield 70%; mp 186−187 °C; ^{1}H NMR (600 MHz, CDCl$_3$) δ 10.96 (s, 1H), 8.96 (s, 1H), 8.88 (d, J = 7.2 Hz, 1H), 8.75 (d, J = 4.8 Hz, 2H), 8.23 (d, J = 8.4 Hz, 1H), 7.75 (d, J = 4.8 Hz, 2H), 7.64−7.56 (m, 2H), 7.54 (dd, J = 8.4, 4.2 Hz, 1H), 7.42 (d, J = 3.6 Hz, 1H), 7.08 (d, J = 3.6 Hz, 1H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 155.6, 152.6, 150.3, 148.6, 148.5, 138.5, 136.3, 133.8, 127.9, 127.2, 122.0, 121.7, 118.2, 116.8, 116.6, 110.8; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{18}$H$_{13}$N$_4$OS 333.0810, found 333.0813.

N-(Pyridin-2-ylmethyl)[1,1'-biphenyl]-4-carboxamide (7aa): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 54.2 mg, yield 94%; mp 124−125 °C;[39] ^{1}H NMR (600 MHz, DMSO) δ 9.20 (s, 1H), 8.52 (d, J = 4.8 Hz, 1H), 8.03 (d, J = 7.8 Hz, 2H), 7.81 (d, J = 7.8 Hz, 2H), 7.76 (m, 3H), 7.50 (t, J = 7.2 Hz, 2H), 7.43 (d, J = 7.2 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.31−7.24 (m, 1H), 4.60 (d, J = 6.0 Hz, 2H); ^{13}C NMR (150 MHz, DMSO) δ 166.0, 158.8, 148.9, 142.9, 139.2, 136.7, 133.0, 129.0, 128.1, 128.0, 126.9, 126.6, 122.1, 120.9, 44.8; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{19}$H$_{17}$N$_2$O 289.1341, found 289.1365.

4'-Fluoro-N-(pyridin-2-ylmethyl)[1,1'-biphenyl]-4-carboxamide (7ab): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 57.0 mg, yield 93%; mp 171−172 °C; ^{1}H NMR (600 MHz, DMSO) δ 9.20 (t, J = 5.4 Hz, 1H), 8.52 (d, J = 4.2 Hz, 1H), 8.02 (d, J = 7.8 Hz, 2H), 7.84−7.73 (m, 5H), 7.33 (t, J = 7.2 Hz, 3H), 7.30−7.26 (m, 1H), 4.60 (d, J = 6.0 Hz, 2H).^{13}C NMR (150 MHz, DMSO) δ 166.0, 162.3 (d, J = 243.6 Hz), 158.9, 148.9, 141.8, 136.7, 135.6, 132.9, 129.0 (d, J = 8.1 Hz), 128.0, 126.6, 122.1, 120.9, 115.9 (d, J = 21.3 Hz), 44.8; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{19}$H$_{16}$FN$_2$O 307.1247, found 307.1239.

4'-Chloro-N-(pyridin-2-ylmethyl)[1,1'-biphenyl]-4-carboxamide (7ac): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 60.1 mg, yield 93%; mp 193−194 °C; ^{1}H NMR (600 MHz, DMSO) δ 9.21 (s, 1H), 8.52 (s, 1H), 8.02 (d, J = 6.6 Hz, 2H), 7.84−7.73 (m, 5H), 7.55 (d, J = 3.6 Hz, 2H), 7.33 (d, J = 8.4 Hz, 1H), 7.28 (s, 1H), 4.59 (d, J = 5.4 Hz, 2H); ^{13}C NMR (150 MHz, DMSO) δ 165.9, 158.8, 148.9, 141.5, 138.0, 136.8, 133.3, 133.0, 129.0, 128.7, 128.1, 126.6, 122.1, 120.9, 44.8; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{19}$H$_{16}$ClN$_2$O 323.0951, found 323.0942.

4'-Methoxy-N-(pyridin-2-ylmethyl)[1,1'-biphenyl]-4-carboxamide (7ad): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 59.9 mg, yield 94%; mp 139−140 °C; ^{1}H NMR (600 MHz, DMSO) δ 9.18 (t, J = 6.0 Hz, 1H), 8.52 (d, J = 4.2 Hz, 1H), 7.99 (d, J = 8.4 Hz, 2H), 7.77 (m, 3H), 7.71 (d, J = 9.0 Hz, 2H), 7.33 (d, J = 7.8 Hz, 1H), 7.30−7.25 (m, 1H), 7.06 (d, J = 9.0 Hz, 2H), 4.59 (d, J = 6.0 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (150 MHz, DMSO) δ 166.1, 159.4, 158.9, 148.9, 142.6, 136.8, 132.2, 131.4, 128.1, 128.0, 126.0, 122.1, 120.9, 114.5, 55.2, 44.8; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{20}$H$_{19}$N$_2$O$_2$ 319.1447, found 319.1438.

4'-tert-Butyl-N-(pyridin-2-ylmethyl)[1,1'-biphenyl]-4-carboxamide (7ae): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 65.4 mg, yield 95%; mp 102−103 °C; ^{1}H NMR (600 MHz, DMSO) δ 9.18 (t, J = 6.0 Hz, 1H), 8.52 (d, J = 4.8 Hz, 1H), 8.01 (d, J = 8.4 Hz, 2H), 7.80−7.73 (m, 3H), 7.67 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 7.8 Hz, 1H), 7.31−7.23 (m, 1H), 4.60 (d, J = 6.0 Hz, 2H), 1.32 (s, 9H); ^{13}C NMR (150 MHz, DMSO) δ 166.1, 158.9, 150.6, 148.9, 142.8, 136.7, 136.3, 132.7, 128.0, 126.6, 126.4, 125.8, 122.1, 120.9, 44.7, 34.3, 31.1; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{23}$H$_{25}$N$_2$O 345.1967, found 345.1958.

N-(Pyridin-2-ylmethyl)-4'-(trifluoromethyl)[1,1'-biphenyl]-4-carboxamide (7af): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 61.3 mg, yield 86%; mp 187−188 °C; ^{1}H NMR (600 MHz, DMSO) δ 9.27 (t, J = 6.0 Hz, 1H), 8.53 (d, J = 4.8 Hz, 1H), 8.07 (d, J = 8.4 Hz, 2H), 7.98 (d, J = 8.4 Hz, 2H), 7.88 (m, 4H), 7.77 (t, J = 7.2 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.30−7.25 (m, 1H), 4.61 (d, J = 6.0 Hz, 2H); ^{13}C NMR (150 MHz, DMSO) δ 165.9, 158.8, 148.9, 143.2, 141.2,

136.7, 133.9, 131.4, 129.5, 128.2, 127.7, 127.1, 125.9, 125.2, 123.4, 122.1, 120.9, 44.8 (CF$_3$ carbons are merging with other peaks); HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{20}$H$_{16}$F$_3$N$_2$O 357.1215, found 357.1207.

2',4'-Dichloro-N-(pyridin-2-ylmethyl)[1,1'-biphenyl]-4-carboxamide (7ag): white solid (petroleum ether/acetone = 20:1, R_f = 0.15); 62.9 mg, yield 88%; mp 106−107 °C; ^{1}H NMR (600 MHz, DMSO) δ 9.26 (s, 1H), 8.52 (d, J = 4.1 Hz, 1H), 8.02 (d, J = 8.0 Hz, 2H), 7.84−7.68 (m, 2H), 7.56 (d, J = 8.0 Hz, 3H), 7.49 (d, J = 8.3 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.31−7.25 (m, 1H), 4.60 (d, J = 5.7 Hz, 2H); ^{13}C NMR (150 MHz, CDCl$_3$) δ 165.93, 158.73, 148.86, 140.40, 137.99, 136.71, 133.71, 133.34, 132.65, 132.27, 129.33, 129.26, 127.74, 127.31, 122.08, 120.87, 44.73; HRMS (ESI) m/z [M + H]$^+$ calcd for C$_{19}$H$_{15}$Cl$_2$N$_2$O 357.0561, found 357.0551.

PYR1 Computational Modeling. Molecular docking studies were performed to simulate the binding of compound to PYR1. Conformational optimizations were performed on A, which was used as the starting structure for docking. The PYR1 crystal structure (PDB: 3QN1) was prepared as follows: (1) water and ligand were removed; (2) polar hydrogen atoms were added; (3) a grid box for the binding site was created (center x = 0.943, center y = 22.758, center z = 33.926/size x = 18, size y = 18, size z = 18). Docking calculations were performed on it with AutoDock4.0.2. The protein and ligand structures were prepared with AutoDock Tools.3. The atomic Gasteiger−Huckel charges were assigned to the ligand and receptor. A total of 256 runs were launched for each compound. Most of the parameters for the docking calculation were set to the default values recommended by the software. Each docked structure was scored by the built-in scoring function and was clustered according to RMSD < 2 Å.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01725.

> X-ray data of compound **5ba** (CIF)
> ^{1}H and ^{13}C NMR spectra and X-ray crystallographic data (PDF)

AUTHOR INFORMATION

Corresponding Authors
*E-mail: gfhao@mail.ccnu.edu.cn.
*E-mail: gfyang@mail.ccnu.edu.cn.

Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENTS

REFERENCES

(1) Senger, J.; Melesina, J.; Marek, M.; Romier, C.; Oehme, I.; Witt, O.; Sippl, W.; Jung, M. *J. Med. Chem.* **2016**, *59*, 1545−1555.

(2) Zhao, H.; Garg, G.; Zhao, J.; Moroni, E.; Girgis, A.; Franco, L. S.; Singh, S.; Colombo, G.; Blagg, B. S. *J. Eur. J. Med. Chem.* **2015**, *89*, 442−466.

(3) Ohashi, M.; Oyama, T.; Putranto, E. W.; Waku, T.; Nobusada, H.; Kataoka, K.; Matsuno, K.; Yashiro, M.; Morikawa, K.; Huh, N. H.; Miyachi, H. *Bioorg. Med. Chem.* **2013**, *21*, 2319−2332.

(4) Ravu, V. R.; Leung, G. Y. C.; Lim, C. S.; Ng, S. Y.; Sum, R. J.; Chen, D. Y. K. *Eur. J. Org. Chem.* **2011**, *2011*, 463−468.

(5) Liang, J.; van Abbema, A.; Balazs, M.; Barrett, K.; Berezhkovsky, L.; Blair, W.; Chang, C.; Delarosa, D.; DeVoss, J.; Driscoll, J.; Eigenbrot, C.; Ghilardi, N.; Gibbons, P.; Halladay, J.; Johnson, A.; Kohli, P. B.; Lai, Y.; Liu, Y.; Lyssikatos, J.; Mantik, P.; Menghrajani, K.; Murray, J.; Peng, I.;

Sambrone, A.; Shia, S.; Shin, Y.; Smith, J.; Sohn, S.; Tsui, V.; Ultsch, M.; Wu, L. C.; Xiao, Y.; Yang, W.; Young, J.; Zhang, B.; Zhu, B. Y.; Magnuson, S. *J. Med. Chem.* **2013**, *56*, 4521−4536.

(6) Shimizu, H.; Tanaka, S.; Toki, T.; Yasumatsu, I.; Akimoto, T.; Morishita, K.; Yamasaki, T.; Yasukochi, T.; Iimura, S. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5113−5118.

(7) Mor, M.; Rivara, S.; Lodola, A.; Plazzi, P. V.; Tarzia, G.; Duranti, A.; Tontini, A.; Piersanti, G.; Kathuria, S.; Piomelli, D. *J. Med. Chem.* **2004**, *47*, 4998−5008.

(8) Mach, U. R.; Lewin, N. E.; Blumberg, P. M.; Kozikowski, A. P. *ChemMedChem* **2006**, *1*, 307−314.

(9) Vachal, P.; Miao, S.; Pierce, J. M.; Guiadeen, D.; Colandrea, V. J.; Wyvratt, M. J.; Salowe, S. P.; Sonatore, L. M.; Milligan, J. A.; Hajdu, R.; Gollapudi, A.; Keohane, C. A.; Lingham, R. B.; Mandala, S. M.; DeMartino, J. A.; Tong, X.; Wolff, M.; Steinhuebel, D.; Kieczykowski, G. R.; Fleitz, F. J.; Chapman, K.; Athanasopoulos, J.; Adam, G.; Akyuz, C. D.; Jena, D. K.; Lusen, J. W.; Meng, J.; Stein, B. D.; Xia, L.; Sherer, E. C.; Hale, J. J. *J. Med. Chem.* **2012**, *55*, 2945−2959.

(10) Kasai, S.; Kamata, M.; Masada, S.; Kunitomo, J.; Kamaura, M.; Okawa, T.; Takami, K.; Ogino, H.; Nakano, Y.; Ashina, S.; Watanabe, K.; Kaisho, T.; Imai, Y. N.; Ryu, S.; Nakayama, M.; Nagisa, Y.; Takekawa, S.; Kato, K.; Murata, T.; Suzuki, N.; Ishihara, Y. *J. Med. Chem.* **2012**, *55*, 4336−4351.

(11) Lanier, M.; Schade, D.; Willems, E.; Tsuda, M.; Spiering, S.; Kalisiak, J.; Mercola, M.; Cashman, J. R. *J. Med. Chem.* **2012**, *55*, 697−708.

(12) Williams, J. D.; Khan, A. R.; Cardinale, S. C.; Butler, M. M.; Bowlin, T. L.; Peet, N. P. *Bioorg. Med. Chem.* **2014**, *22*, 419−434.

(13) Westaway, S. M.; Thompson, M.; Rami, H. K.; Stemp, G.; Trouw, L. S.; Mitchell, D. J.; Seal, J. T.; Medhurst, S. J.; Lappin, S. C.; Biggs, J.; Wright, J.; Arpino, S.; Jerman, J. C.; Cryan, J. E.; Holland, V.; Winborn, K. Y.; Coleman, T.; Stevens, A. J.; Davis, J. B.; Gunthorpe, M. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5609−5613.

(14) Westaway, S. M.; Chung, Y. K.; Davis, J. B.; Holland, V.; Jerman, J. C.; Medhurst, S. J.; Rami, H. K.; Stemp, G.; Stevens, A. J.; Thompson, M.; Winborn, K. Y.; Wright, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4533−4536.

(15) For selected recent examples of condensation between acid and 8-aminoquinoline, see: (a) Yan, Q.; Chen, Z.; Yu, W.; Yin, H.; Liu, Z.; Zhang, Y. *Org. Lett.* **2015**, *17*, 2482−2485. (b) Shibata, K.; Chatani, N. *Chem. Sci.* **2016**, *7*, 240−245. (c) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2013**, *135*, 5308−5311.

(16) Singh, B. K.; Jana, R. *J. Org. Chem.* **2016**, *81*, 831−841.

(17) Huang, Z. Y.; Yang, J. F.; Chen, Q.; Cao, R. J.; Huang, W.; Hao, G. F.; Yang, G. F. *RSC Adv.* **2015**, *5*, 75182−75186.

(18) (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (c) Broadwater, S. J.; Roth, S. L.; Price, K. E.; Kobašlija, M.; McQuade, D. T. *Org. Biomol. Chem.* **2005**, *3*, 2899. (d) Sydnes, M. *Curr. Green Chem.* **2014**, *1*, 216.

(19) For selected recent examples of palladium-catalyzed reactions to biaryl carboxamides, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Stanforth, S. P. *Tetrahedron* **1998**, *54*, 263−303. (c) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174−238. (d) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792−9826. (e) Aihara, Y.; Chatani, N. *Chem. Sci.* **2013**, *4*, 664−670. (f) Stibingerova, I.; Voltrova, S.; Kocova, S.; Lindale, M.; Srogl, J. *Org. Lett.* **2016**, *18*, 312−315. (g) Kleeb, S.; Pang, L.; Mayer, K.; Eris, D.; Sigl, A.; Preston, R. C.; Zihlmann, P.; Sharpe, T.; Jakob, R. P.; Abgottspon, D.; et al. *J. Med. Chem.* **2015**, *58*, 2221−2239. (h) Barrett, K. T.; Miller, S. *Org. Lett.* **2015**, *17*, 580−583.

(20) For selected recent examples of the *N*-8-quinolyl group chelating the catalyst, see: (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154−13155. (b) Aihara, Y.; Chatani, N. *Chem. Sci.* **2013**, *4*, 664−670. (c) Shibata, K.; Chatani, N. *Org. Lett.* **2014**, *16*, 5148−5151. (d) Yokota, A.; Aihara, Y.; Chatani, N. *J. Org. Chem.* **2014**, *79*, 11922−11932.

(21) (a) Liu, Y. C.; Huang, Z. Y.; Chen, Q.; Yang, G. F. *Tetrahedron* **2013**, *69*, 9025−9032. (b) Qu, R. Y.; Liu, Y. C.; Wu, Q. Y.; Chen, Q.; Yang, G. F. *Tetrahedron* **2015**, *71*, 8123−8130. (c) Liu, Y. C.; Ye, C. J.;

Chen, Q.; Yang, G. F. *Tetrahedron Lett.* **2013**, *54*, 949−955. (d) Liu, Y. C.; Qu, R. Y.; Chen, Q.; Wu, Q. Y.; Yang, G. F. *Tetrahedron* **2014**, *70*, 2746−2752. (e) Zhou, Z.; Zhao, P.; Huang, W.; Yang, G. *Adv. Synth. Catal.* **2006**, *348*, 63−67. (f) Zhou, Z. Z.; Yang, G. F. *Bioorg. Med. Chem.* **2006**, *14*, 8666−8674. (g) Zhou, Z. Z.; Ji, F. Q.; Cao, M.; Yang, G. F. *Adv. Synth. Catal.* **2006**, *348*, 1826−1830.

(22) For selected recent examples of the deprotection of amide *N*-Boc, see: (a) El Kazzouli, S.; Koubachi, J.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. *Tetrahedron Lett.* **2006**, *47*, 8575. (b) Wang, J.; Liang, Y. L.; Qu, J. *Chem. Commun.* **2009**, 5144.

(23) Hao, G. F.; Zhu, X. L.; Ji, F. Q.; Zhang, L.; Yang, G. F.; Zhan, C. G. *J. Phys. Chem. B* **2009**, *113*, 4865−4875.

(24) Raha, K.; Merz, K. M. *J. Med. Chem.* **2005**, *48*, 4558.

(25) Pan, Y.; Gao, D.; Zhan, C. G. *J. Am. Chem. Soc.* **2008**, *130*, 5140.

(26) Grigorjeva, L.; Daugulis, O. *Org. Lett.* **2014**, *16*, 4684−4687.

(27) Katayev, D.; Pfister, K. F.; Wendling, T.; Gooßen, L. J. *Chem. - Eur. J.* **2014**, *20*, 9902−9905.

(28) Zhang, S. Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2015**, *137*, 531−539.

(29) Takamatsu, K.; Hirano, K.; Miura, M. *Org. Lett.* **2015**, *17*, 4066−4069.

(30) Talbot, E. P.; Fernandes, T. d. A.; McKenna, J. M.; Toste, F. D. *J. Am. Chem. Soc.* **2014**, *136*, 4101−4104.

(31) Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem.* **2013**, *125*, 4553−4557.

(32) Tran, L. D.; Popov, I.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 18237.

(33) Ano, Y.; Tobisu, M.; Chatani, N. *Org. Lett.* **2012**, *14*, 354.

(34) Goldfarb, S. D. (The University of Rochester) Patent US20090163545, 2016; p 18.

(35) Dahl, R. (Eiger biopharmaceutical, Inc.) Patent WO2016032569 A1, 2016; p 132.

(36) Inoue, S.; Shiota, H.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 6898.

(37) Gui, Q.; Chen, X.; Hu, L.; Wang, D.; Liu, J.; Tan, Z. *Adv. Synth. Catal.* **2016**, *358*, 509.

(38) Kubo, T.; Chatani, N. *Org. Lett.* **2016**, *18*, 1698.

(39) Shiota, H.; Ano, Y.; Aihara, Y.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 14952.