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

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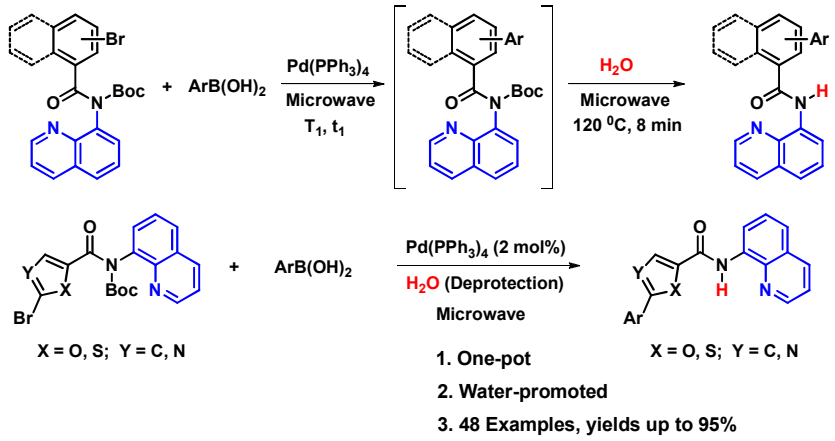
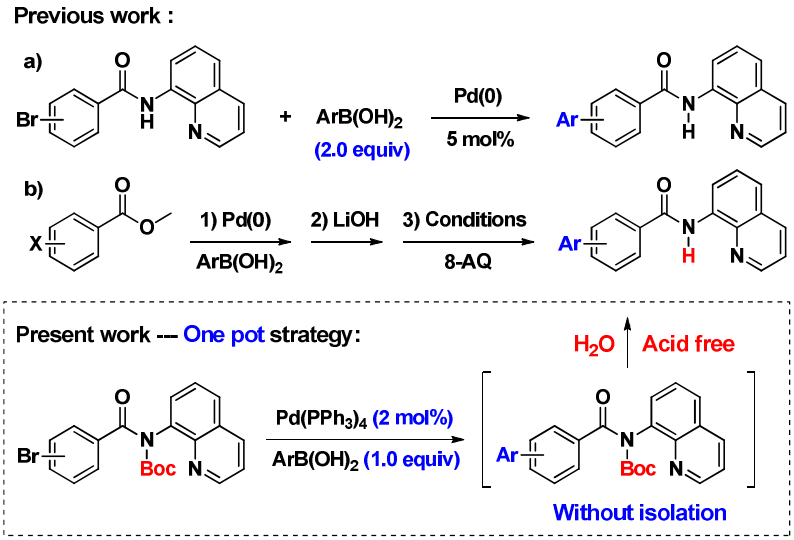


ABSTRACT: *N*-quinolyl biaryl carboxylamides have received tremendous attention for their notable biological properties. Here we have described a general protocol for the preparation of *N*-quinolyl 3'/4'-biaryl carboxylamides by microwave-assisted Suzuki-Miyaura cross-coupling reaction and *N*-Boc deprotection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

Key words: Biaryl carboxylamides; Microwave irradiation; *N*-Boc deprotection; One pot; Suzuki-Miyaura coupling

Introduction

The biaryl carboxylamides 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[8] and anemia therapeutic agents.[9] Among these biaryl carboxylamides, *N*-quinolyl(Q) 3′/4′-biaryl carboxylamide is a unique substructure in medicinal chemistry, which have shown the potential to antagonize bacterium,[10] lose weight,[11] promote differentiation of adult human cardiac progenitor cells[12] and activate TRPV1 (Transient Receptor Potential Vanilloid type 1) ion channel.[13,14]



Scheme 1. Selected methods to synthesize *N*-Q 3′/4′-biaryl carboxylamides

Although a variety of procedures are available for preparing *N*-quinolyl(Q) 2′-biaryl carboxylamides, methods available for the synthesis of *N*-Q 3′/4′-biaryl carboxylamides are still limited. *N*-Q 3′/4′-biaryl carboxylamides 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 multi-step 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-carboxylamide via the direct Suzuki-Miyaura cross-coupling reaction of 4-Bromo-*N*-(quinolin-8-yl) benzamide and (2,4-difluorophenyl) boronic acid.[16] But, this method requires a large amount of aromatic boronic acids (2.0 equivalents). 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 3'/4'-biaryl carboxylamides. 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 step-wise approach. Hence, one pot method draws much attention of chemists.[18] Herein, we reported one-pot microwave-assisted Suzuki-Miyaura cross-coupling and *N*-Boc deprotection approach to prepare a variety of *N*-Q 3'/4'-biaryl carboxylamides with excellent functional group tolerance and high yields.

Although, the palladium-catalyzed Suzuki-Miyaura reactions were found to be the most approaches to synthesize biaryl carboxylamides,[19] the direct Suzuki-Miyaura coupling to *N*-8-quinoly 3'/4'-biaryl carboxylamides consumes more time and wasted 1.0 equivalent boronic acid. So, it is obvious that the catalyst could be inactivated by the *N*-8-quinoly at some extent.[15, 19e, 20] Thus, it is benificial to prevent the *N*-8-quinoly 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 towards *N*-Q 3'/4'-biaryl carboxylamides via sequential $Pd(PPh_3)_4$-catalyzed Suzuki-Miyaura coupling and water-promoted *N*-Boc deprotection under

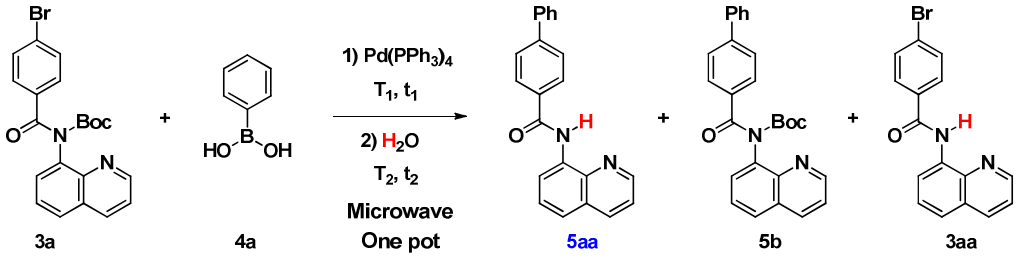
microwave irradiation.

RESULTS AND DISSCUSSION

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 able to perform Suzuki-Miyaura coupling and amide *N*-Boc deprotection sequentially in a one-pot manner under the microwave irradiation. For our initial studies, the reaction of bromide **3a** with 1.0 equivalent phenyl boronic aicd **4a** in the presence of $Pd(PPh_3)_4$ and NaOAc under microwave irradiation was chosen as a benchmark reaction (Table 1. The optimization of amide *N*-Boc deprotecting see Support Information Table S1). To our delight, 78 % of coupling and deprotecting product (**5aa**) was obtained with a temperature of 80 °C in 6 minutes (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 the **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 overwhelmingly. So, the desired product **5aa** was obtained in the same yield of 94% in 8 minutes and 10 minutes (entry 2, 3). However, the yield of **5aa** was reduced to 84% with a temperature of 85 °C (entry 4). Also, the different solvents were screened, such as water mixed with dioxane, DME, DMF, 2-Me THF and isopropanol (entry 2, 5–8). The mixture of water and dioxane (v/v = 1 : 3) was proved to produce the best results. Subsequently, the effect of bases on this reaction was explored, and among these bases (NaOAc, Na_2CO_3, K_3PO_4 and Cs_2CO_3), NaOAc was identified as the best one (entry 2, 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 a 87% and 81%

Table 1. Optimization of $Pd(PPh_3)_4$-Catalyzed Suzuki-Miyaura Coupling and Water-Promoted *N*-Boc Deprotecting One-pot reaction[a,b]

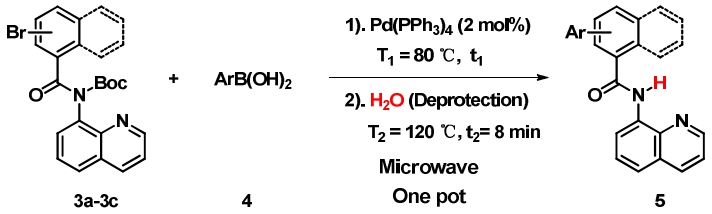


3a 4a 5aa 5b 3aa

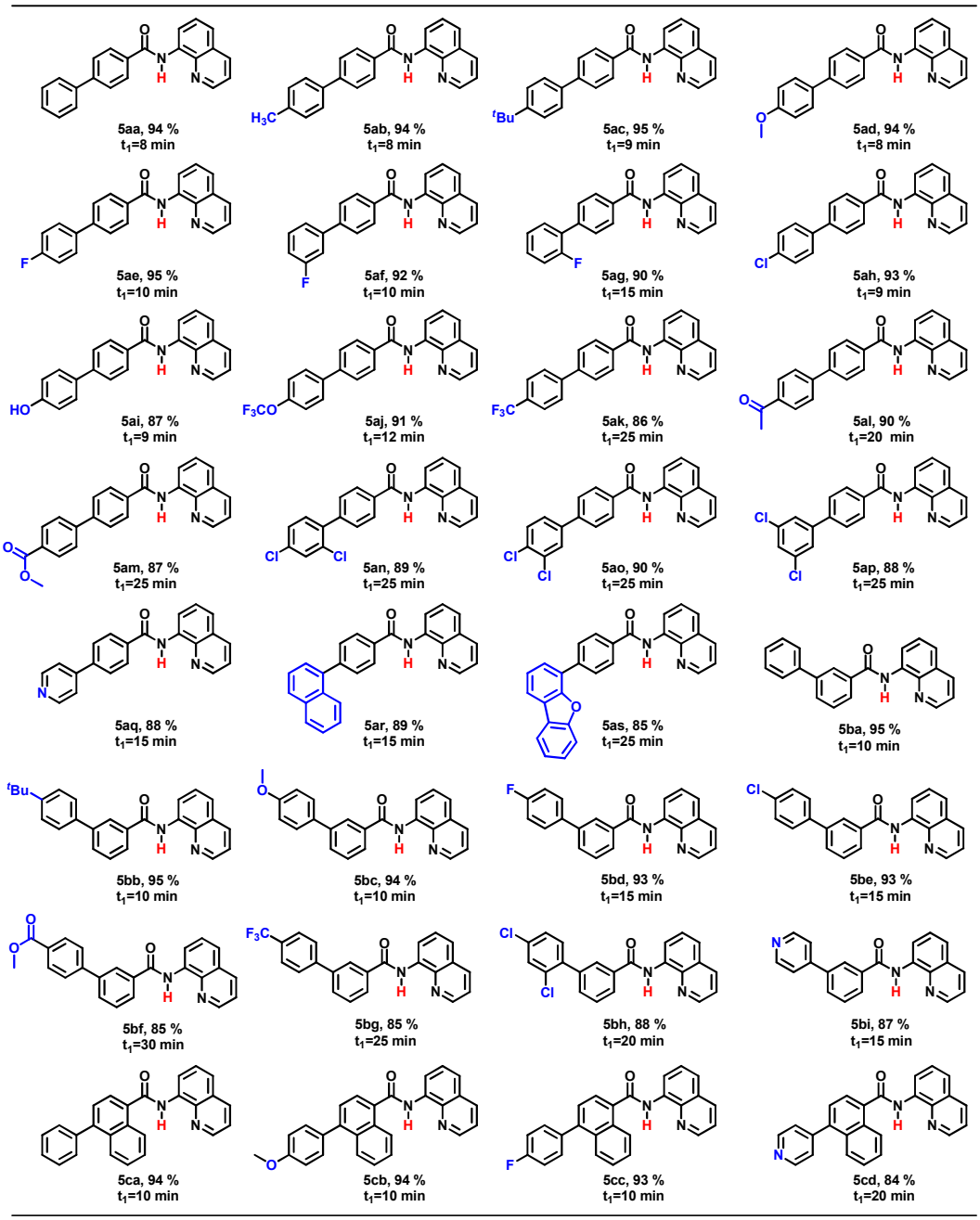
Entry	Organic Solvent	Base	Catalyst (x mol %)	T_1 (℃), t_1 (min)	T_2(℃), t_2(min)	Yield (5aa %)	Yield (5b %)	Yield (3aa %)
1	Dioxane	NaOAc	2	80, 6	120, 8	78	0	18
2	**Dioxane**	**NaOAc**	**2**	**80, 8**	**120, 8**	**94**	<1	<1
3	Dioxane	NaOAc	2	80, 10	120, 8	94	<1	<1
4	Dioxane	NaOAc	2	85, 8	120, 8	84	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	isopropanol	NaOAc	2	80, 8	120, 8	51	0	46
9	Dioxane	Na_2CO_3	2	80, 8	120, 8	86	0	11
10	Dioxane	K_3PO_3	2	80, 8	120, 8	81	0	15
11	Dioxane	Cs_2CO_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 conditons: 1) **3a** (0.2 mmol), **4a** (0.2 mmol), catalyst was $Pd(PPh_3)_4$, base (0.4 mmol), solvent 4 mL (3 mL organic solvent and 1 mL H_2O); 2) under N_2. [b] Isolated yield. [c] Catalyst was Pd/C (10%) [d] Conventional heating.

Table 2. Scope of 3a-3c and (hetero)arylboronic acid (4)[a,b]



3a-3c 4 5



[a] Reactions conditons:**3a-3c** (0.2 mmol), **4** (0.2 mmol), $Pd(PPh_3)_4$ (2 mol%), NaOAc (0.4 mmol), Dioxane:H_2O = 3 mL:1 mL , T_2=120 °C, t_2=8 min, protected by N_2. [b] Isolated yield.

yield of **5aa**, respectively. While, a little bit of **5aa** was obtained when used 2.0 mol % and 10 mol % of Pd/C (entry 16-17). 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 % $Pd(PPh_3)_4$, 1.0 equivalent phenylboronic acid

and 2.0 equivalents NaOAc in dioxane mixed water with a temperature of 80 °C in 8 minutes for the first step and then enhancing the reaction temperature to 120 °C in 8 minutes for the second step was fixed, as 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-sustituted *N*-Q arylamides were applied. Various substituted (hetero)arylboronic acids were determined, the results were shown in Table 2. The reactions between **3a** and (hetero)arylboronic acids (**4**) always went smoothly. Both electron-withdrawing and electron-donating groups, such as methoxycarbonyl (**5am**), trifluoromethyl (**5ak**) and methyl (**5ab**), tert-butyl (**5ac**), methoxy (**5ad**), halogen (**5ae-5ah**), trifluoromethoxy (**5aj**) afforded the desired products in good to excellent yields. More importantly, the reaction was proved to be well tolerant of valuable but unstable groups, such as hydroxyl (**5ai**) and acetyl (**5al**). In addition, disubstituted and hetero-arylboronic acids were also investigated and afforded the corresponding products (**5an-5as**). To increase the scope of our one-pot reaction, the **3b** and (hetero)arylboronic acids (**4**) was tested. Very similar results were obtained in the presence of meta-substituent *N*-Q benzamide (**3b**). The reaction of phenylboronic aid gave **5ba** in 95% yields. The reaction of electron-rich phenylboronic acid, 4-tert-butyl and 4-methoxy, led to **5bb** and **5bc** in 95% and 94% yield, respectively. The halogen substituted phenylboronic acids (**5bd-5be**) could also give excellent yield. Even the electron-

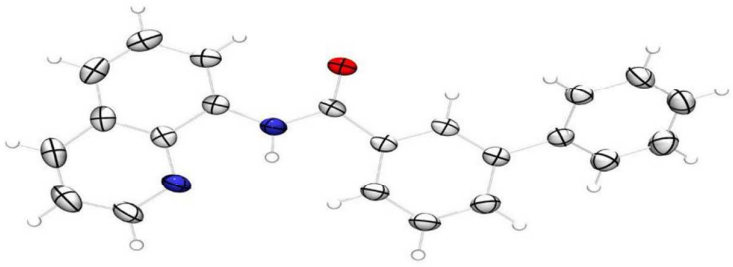
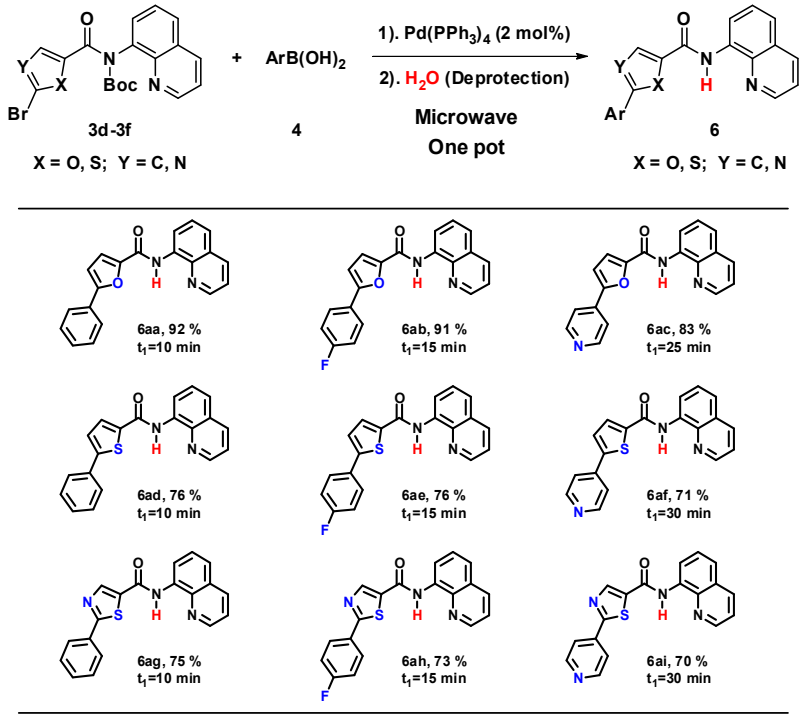


Figure 1. Ortep diagrams of **5ba** (the thermal ellipsoids are drawn at the 50% probability level).

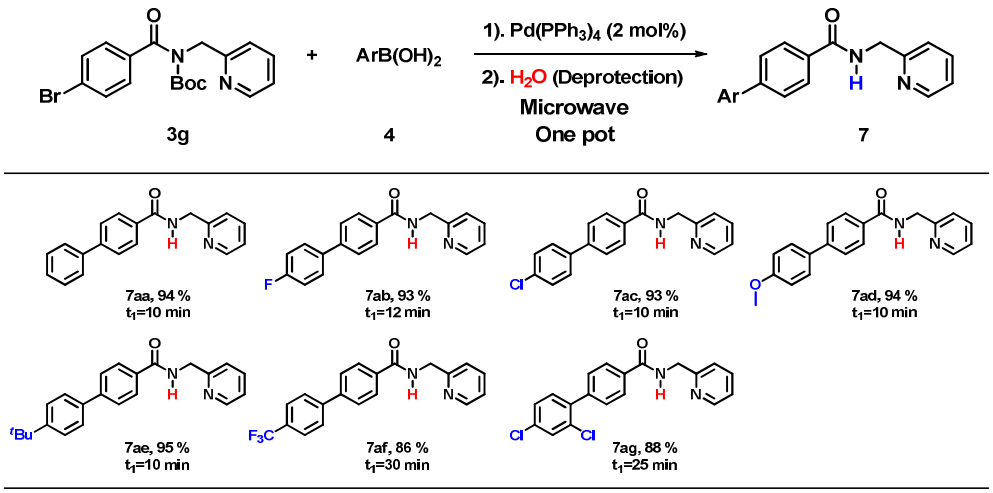
deficient phenylboronic acid, such as methoxycarbonyl and trifluoromethyl groups were found to be suitable partner of one-pot reaction and gave **5bf** and **5bg** in a good yields. Of note, the 2,4-dichloro substituted phenylboronic and 4-pyridinylboronic acid could be successfully converted to the product (**5bh-5bi**). Then, several reactions using **3c** as the starting materials were performed. The target products **5ca-5cd** were obtained in 84-94% yields using 2.0 mol % of

Table 3. Scope of 3d-3f and (hetero) arylboronic acid (4)[a,b]



[a] Reactions conditons:**3d-3f** (0.2 mmol), **4** (0.2 mmol), $Pd(PPh_3)_4$ (2 mol %), NaOAc (0.4 mmol), Dioxane:H_2O = 3 mL:1 mL , T_2=120 °C, t_2=8 min, protected by N_2. [b] Isolated yield.

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



[a] Reactions conditons:**3g** (0.2 mmol), **4** (0.2 mmol), $Pd(PPh_3)_4$ (2 mol %), NaOAc (0.4 mmol), Dioxane:H_2O = 3 mL:1 mL , T_2=120 °C, t_2=8 min, protected by N_2. [b] Isolated yield.

$Pd(PPh_3)_4$ as the catalyst under the 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).

Notably, the one-pot reaction was not limitation to the use of *N*-Q five-membered heteroaryl carboxylamides. The reaction of (hetero)arylboronic acids(**4**) with **3d-3f** (Containing furanyl, thiophenyl, thiazolyl, respectively) were also produced the desired products **6** in good to excellent yield (Table 3). It was obvious that the **3d** could give more corresponding products than **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 carboxylamide pyrabactin (Py) analogues as abscisic acid (ABA) agonists (**7aa-7ag**) were obtained in 86-95% yield (Table 4). The analogue **7aa** has been found to be active on the ABA receptor PYR1 via a further molecular simulation

study (Figure 2). The pyridine ring can form conservative π-π stacking interaction with residue Y126 (Fig. 2B). The amide group can not only form hydrogen bond with residue E100, but also form another hydrogen

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

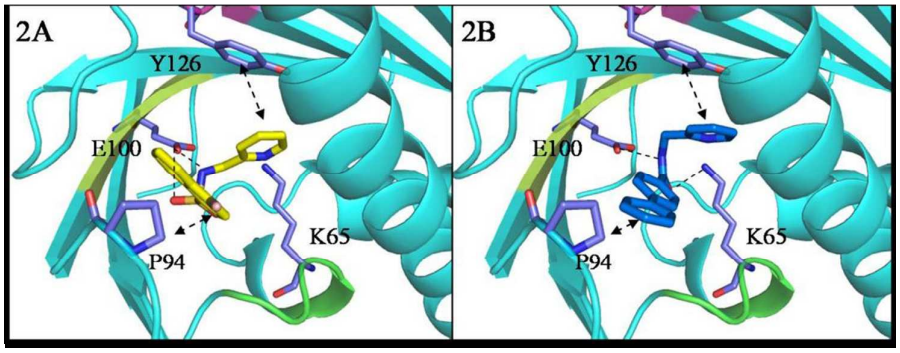


Figure 2. Computational modeling of **Py** (A) and **7aa** (B) in PYR1 (PDB code: **3QN1**)

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 lower than that of pyrabactin (-7.12 kcal/mol).

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 which most often represent the bound and unbound state 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 the following Equation 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 binding energy (ΔE_{bind}). The ΔG_{bind} was estimated from ΔE_{bind} and $-T\Delta S$ in Equation 2. The ΔE_{bind} is calculated from ΔE_{MM} and ΔG_{sol} in Equation 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 Equation 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 ($\Delta G_{\mathbf{PB}}$) and nonelectrostatic contribution to the solvation free energy ($\Delta G_{\mathbf{np}}$) as described in Equation 5 .

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

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

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

The ΔS_{sol} and ΔS_{conf} are the solvation entropy and the conformational entropy change in the Equation 6. In the binding process, the conformational entropy change is related with the change of the number of rotatable bonds during the binding process, 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 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 is used to evaluate the entropic contribution (-TΔS) to the binding free energy was the same as our previous publication.[23]

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

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(Equation 7). This adjustable parameter(*w*) was calibrated to be 1 kcal/mol here 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 carboxylamides was developed. A series of *N*-Q biaryl carboxylamides 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 analogs.

EXPERIMENTAL SECTION

General Information. All reagents and solvents were obtained commercially except when

otherwise noted. Thin-layer chromatography (TLC) analysis was used to monitor 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 (•) 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 (•) 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^{TM} instrument (The temperature of reaction system was controlled by the wall infrared sensor. While, the pressure was regulated by the non-invasive 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-3g. The synthesis of **3aa-3ag** is representative: **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 (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-3ag**.[26-28]

The synthesis of **3a-3g** is representative: Boc-anhydride (6 mmol) was added to a solution of **3aa-3ag** (3 mmol) and DMAP (4.5 mmol) in CH_2Cl_2 (40 mL) and the reaction mixture was

stirred overnight. The reaction mixture was quenched with sat. aq NH_4Cl (40 mL) and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic extracts were dried (Na_2SO_4), concentrated under reduced pressure and purified by column chromatography (petroleum ether / acetone = 20:2, R_f = 0.15) to give the **3a-3g**.[29-31]

Typical $Pd(PPh_3)_4$-Catalyzed and Water-Promoted One-Pot Strategy to *N*-Q Biaryl Carboxamides (5-7). **3** (0.2 mmol) and arylboronic acids (**4**, 0.2 mmol) were dissolved in dioxane (3 mL) and H_2O (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, the reaction mixture was irradiated in a microwave apparatus at 80 ℃ for 8-30 min. Then, the temperature was increased to 120 ℃ 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 $C_{16}H_{12}BrN_2O$ 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 $C_{16}H_{12}BrN_2O$ 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 $C_{20}H_{14}BrN_2O$ 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.[33] ^{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 $C_{14}H_{10}BrN_2O_2$ 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 $C_{14}H_{10}BrN_2OS$

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 $C_{13}H_9BrN_3OS$ 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 $C_{13}H_{12}BrN_2O$ 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 $C_{21}H_{20}BrN_2O_3$ 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 $C_{21}H_{20}BrN_2O_3$ 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 $C_{25}H_{22}BrN_2O_3$ 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 $C_{19}H_{18}BrN_2O_4$ 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 $C_{19}H_{18}BrN_2O_3S$ 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 $C_{18}H_{17}BrN_3O_3S$ 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. ^{1}H 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). ^{13}C NMR (150 MHz, $CDCl_3$) 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 $C_{18}H_{20}BrN_2O_3$ 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. ^{1}H 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). ^{13}C 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 $C_{27}H_{25}N_2O_3$ 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] ^{1}H 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). ^{13}C 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 $C_{22}H_{17}N_2O$ 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. ^{1}H NMR (600 MHz, $CDCl_3$) (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). ^{13}C 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 $C_{23}H_{19}N_2O$ 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. ^{1}H 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). ^{13}C NMR (151 MHz, cdcl$_3$) 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 $C_{26}H_{25}N_2O$ 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. ^{1}H 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). ^{13}C NMR (150 MHz, $CDCl_3$) 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 $C_{23}H_{19}N_2O_2$ 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. ^{1}H 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). ^{13}C 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 $C_{22}H_{16}FN_2O$ 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. ^{1}H 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). ^{13}C NMR (150 MHz, $CDCl_3$) 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 $C_{22}H_{16}FN_2O$ 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. ^{1}H 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). ^{13}C NMR (150 MHz, $CDCl_3$) 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 $C_{22}H_{16}FN_2O$ 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. ^{1}H 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). ^{13}C 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 $C_{22}H_{16}ClN_2O$ 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. ^{1}H 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). ^{13}C 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 $C_{22}H_{17}N_2O_2$ 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. ^{1}H 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). ^{13}C NMR (150 MHz, $CDCl_3$) 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 (OCF_3 carbons are merging with other peaks). HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{23}H_{16}F_3N_2O_2$ 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. ^{1}H 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). ^{13}C NMR (150 MHz, $CDCl_3$) 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 $C_{23}H_{16}F_3N_2O$ 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. ^{1}H 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 $C_{24}H_{19}N_2O_2$ 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 $C_{24}H_{19}N_2O_3$ 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 $C_{22}H_{15}Cl_2N_2O$ 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 $C_{22}H_{15}Cl_2N_2O$ 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 $C_{22}H_{15}Cl_2N_2O$ 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 $C_{21}H_{16}N_3O$ 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 $C_{26}H_{19}N_2O$ 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 $C_{28}H_{19}N_2O_2$ 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 $C_{22}H_{17}N_2O$ 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 $C_{26}H_{25}N_2O$ 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 $C_{23}H_{19}N_2O_2$ 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 $C_{22}H_{16}FN_2O$ 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 $C_{22}H_{16}ClN_2O$ 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 $C_{24}H_{19}N_2O_3$ 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 $C_{23}H_{16}F_3N_2O$ 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 $C_{22}H_{15}Cl_2N_2O$ 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 $C_{21}H_{16}N_3O$ 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 $C_{26}H_{19}N_2O$ 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 $C_{27}H_{21}N_2O_2$ 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 $C_{26}H_{18}FN_2O$ 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 $C_{25}H_{18}N_3O$ 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 $C_{20}H_{15}N_2O_2$ 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 $C_{20}H_{14}FN_2O_2$ 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 $C_{19}H_{14}N_3O_2$ 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 $C_{20}H_{15}N_2OS$ 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 $C_{20}H_{14}FN_2OS$ 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, $CDCl_3$) 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 $C_{19}H_{14}N_3OS$ 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 $C_{19}H_{14}N_3OS$ 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 $C_{19}H_{13}FN_3OS$ 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 $C_{18}H_{13}N_4OS$ 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 $C_{19}H_{17}N_2O$ 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 $C_{19}H_{16}FN_2O$ 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 $C_{19}H_{16}ClN_2O$ 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 $C_{20}H_{19}N_2O_2$ 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 $C_{23}H_{25}N_2O$ 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 $C_{20}H_{16}F_3N_2O$ 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 $C_{19}H_{15}Cl_2N_2O$ 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 to A, which was used as starting structures for docking. The PYR1 crystal structure (PDB: **3QN1**) was prepared as follows: 1) All waters and ligand were removed; 2) The 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

Copies of ^{1}H and ^{13}C NMR spectra, X-ray crystallographicdata (CIF). This material is available free of charge via the internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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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. Edit*. **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) O Sydnes, M. *Curr. Green Chem.* **2014,** *1*, 216.

(19) For selected recent examples of palladium-catalyzed reactions to biaryl carboxylamides, 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.* **2015**, *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. *J. Med. Chem*. **2015**, *58*, 2221-2239. (h) Barrett, K. T.; Miller, S. *J. Org. Lett.* **2015**, *17*, 580-583.

(20) For selected recent examples of *N*-8-quinoly 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.

(34) 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**.

(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.