Very Important Publication

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Copper(II)/Silver(I)-Catalyzed Sequential Alkynylation and Annulation of Aliphatic Amides with Alkynyl Carboxylic Acids: Efficient Synthesis of Pyrrolidones

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Abstract: A highly efficient protocol for the synthesis of pyrrolidones by the copper-catalyzed alkynylation/annulation of aliphatic amides with alkynyl carboxylic acids is discussed in this paper. A broad range of easily accessible alkynyl carboxylic acids were introduced at the β-methyl group of aliphatic amides with the assistance of an 8-aminoquinolyl auxiliary group via decarboxylation to achieve the subsequent cyclic C–N bond formation within one hour. High selectivity of *β*-methyl groups over methylene groups was observed, and the extension of this catalytic system to the activation of methylene C–H bonds failed. The substrates with two different groups at the α-position of the aliphatic amides lead to the formation of diastereoisomers which is determined by ^{1}H NMR spectroscopy. The initially produced products with *Z*-configurations can be easily transformed to the corresponding products with *E*-configurations by the treatment with dilute *p*-toluenesulfonic acid after the reaction. This catalytic tandem decarboxylative cyclization provides a new opportunity for the direct functionalization of sp^3 C–H bonds.

Keywords: alkynylation/annulations; C–H activation; copper; decarboxylation; pyrrolidones

Introduction

The transition metal-catalyzed direct functionalization of C–H bonds has proven to be an economical and straightforward alternative to traditional synthetic methods which rely on the use of reactive functional groups. The advantages of C–H activation have enabled the construction of carbon–carbon and carbon–heteroatom bonds with great efficiency and selectivity. However, transition metal-catalyzed direct functionalization of unactivated C(sp^3)–H bonds[1] is especially challenging due to its inertness and competing β-hydride elimination. In recent years, the strategy of chelation-assisted C–H activation has significantly improved the selective C(sp^3)–H functionalization, and important transformations of sp^3 C–H bonds have been achieved.[2,3] In particular, the bidentate strategy, which was first introduced by the Daugulis group,[4] presents a powerful capability to increase the reactivity of sp^3 C–H bonds through the formation of stable metallacycle intermediates,[5,6a] which allowed a number of new approaches for C(sp^3)–H bond functionalization including arylation, alkynylation, alkoxylation, alkylation, cyclization, and amination.[6] Despite these significant achievements, the direct functionalization of sp^3 C–H bonds is still in its early stage. The coupling partners are very limited, and the exploration of new active coupling partners for the smooth functionalization of C(sp^3)–H bonds is highly desired.

Catalytic decarboxylative coupling is considered to be one of the most promising atom-economical organic processes for C–C bond formation, because the use of a stoichiometric amount of organometallic or organic halide reagents can be avoided.[7] Since Meyers' original reports of the palladium-mediated decarboxylative coupling of olefins and benzoic acids,[8] extensive studies on catalytic decarboxylation have been carried out throughout the past few decades.[9] For example, biaryls were successfully prepared by palladium-catalyzed decarboxylative coupling of aryl carboxylic acid salts with aryl halides/tosylates by Gooßen

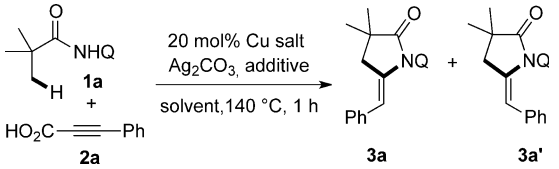
and coworkers.[10] The key point of this chemistry is the formation of organometallic species from the low cost, diverse, and ready availability carboxylate salts via metal-mediated extrusion of CO_2 to undergo the subsequent coupling reactions. Depending on the catalytic system and the reaction conditions employed, diverse organometallic species, such as acyl and aryl metallic intermediates, can be generated in situ, leading to the establishment of a range of useful cross-coupling reactions.[11] In recent years, the development of new decarboxylation reactions capable of catalytically transforming the inert C(sp^2)–H bonds of organic molecules into useful functional groups has opened up attractive new strategies for C–C bond formation, which has rapidly emerged as a very active area of research.[12] However, the catalytic decarboxylative coupling reaction with the use of an unactivated alkyl C–H bond as the reaction partner has not yet been achieved.

Results and Discussion

Recently, we developed nickel-catalyzed thioetherification[13] and copper-mediated aryloxylation[14] of unactivated C(sp^3)–H bonds by employing a bidentate directing group. We envisioned that the difficult but highly desirable decarboxylative cross-coupling of alkynyl carboxylic acids with unactivated aliphatic C(sp^3)–H bonds might be achieved by applying bidentate strategy to form the alkynylated products. Although great efforts have been made towards C(sp^2)–H bond alkynylation,[15,16] only few catalytic systems for the alkynylation of C(sp^3)–H bonds have been reported.[17] We began by screening reaction conditions for the decarboxylative coupling of propionamide (**1a**) with phenylpropiolic acid (**2a**) under copper catalysis with the assistance of an 8-aminoquinoline auxiliary, which was first introduced by the Daugulis research group[4] (Table 1).

To our delight, a trace of new compound **3a'** was observed using 20 mol% $Cu(OAc)_2$ in the presence of Ag_2CO_3 in DMF at 140 °C for 1 h (Table 1, entry 1). After extensive screening of a large array of reaction parameters, we found that the addition of tetrabutylammonium iodide (TBAI) significantly improved the reaction and **3a'** was observed as the main product. However, after flash column chromatography separation, a mixture of **3a** and **3a'** was obtained. This result illustrates that the transformation of compound **3a'** to **3a** was easily achieved. To obtain a pure compound, the reaction solution was treated with dilute *p*-toluenesulfonic acid for half an hour after the reaction at room temperature (see Experimental Section for details). Fortunately, a thorough transformation of compound **3a'** to **3a** took place, and pure **3a** was isolated in 92% yield (Table 1, entry 2; see Supporting Information). To understand the role of the TBAI, various additives were tested. The replacement of TBAI with tetrabutylammonium bromide (TBAB) gave a yield of 78% (Table 1, entry 9). Other ammonium salts, such as tetrabutylammonium chloride (TBACl), tetraethylammonium bromide (TEAB), and tetraethylammonium iodide (TEAI) proved less effective for the reaction (see Supporting Information). It was observed that the addition of TBAI resulted in the better solubility of the catalyst and metal oxidant (see Supporting Information). These results indicate that the main role of TBAI in this reaction might be as a phase transfer catalyst to promote the reaction.[18] The use of $Cu(OAc)_2{\cdot}H_2O$ as the catalyst gave a comparable result (Table 1, entry 3). After careful characterization, it was concluded that **3a** was not the expected simple alkynylated product but a five-membered ring lactam, which is a derivative of pyrrolidone. Pyrrolidones are important structural motifs of natural products and pharmaceutical agents,[19] and much effort is focused on their synthesis.[20] The single crystal X-ray analysis further confirmed the structure of the product[21] (see Supporting Information). Thus, a new set of reaction conditions for the synthesis of pyrrolidones by copper-catalyzed tandem decarboxylative cross-coupling/cyclization of aliphatic amides and alkynyl carboxylic acids was developed.

Table 1. Optimization of reaction conditions.[a]



Entry	[Cu]	Additive	Yield [%][b]
1	$Cu(OAc)_2{\cdot}H_2O$		trace
2	$Cu(OAc)_2$	TBAI	92 (<1:99)
3	$Cu(OAc)_2{\cdot}H_2O$	TBAI	92 (<1:99)
4	$Cu(OTFA)_2$	TBAI	70 (<1:99)
5	$Cu(OTf)_2$	TBAI	66 (<1:99)
6	CuI	TBAI	72 (<1:99)
7	CuBr	TBAI	69 (<1:99)
8	CuCl	TBAI	51 (<1:99)
9	$Cu(OAc)_2{\cdot}H_2O$	TBAB	78 (<1:99)
10	$Cu(OAc)_2{\cdot}H_2O$	NaI	16 (<1:99)

[a] *Reaction conditions*: **1a** (0.1 mmol), **2a** (0.2 mmol), [Cu] (0.02 mmol), Ag_2CO_3 (0.4 mmol), additive (0.3 mmol), DMF (1.5 mL), 1 h at 140 °C. The reaction solution was treated with *p*-toluenesulfonic acid for half an hour after the reaction. The ratio of **3a** to **3a'** before the treatment with *p*-toluenesulfonic acid is presented in the parentheses.

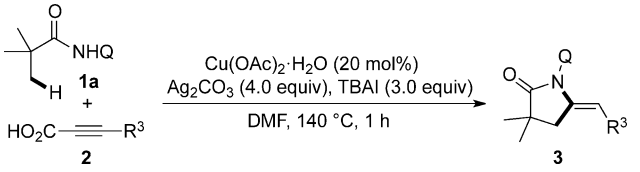
[b] Isolated yield of **3a** based on **1a** by flash column chromatography. Q = Quinolin-8-yl, TBAI = Tetrabutylammonium Iodide.

Other copper salts, including $Cu(OTFA)_2$, $Cu(OTf)_2$, CuI, CuBr, and CuCl, also showed reactivity (Table 1, entries 4–8). The reaction can be performed in many common solvents, such as DMSO, toluene, and *N*,*N*-dimethylacetamide (DMA), albeit DMF afforded the best result (see Supporting Information).

With this efficient catalytic system in hand, we studied the generality of this new tandem decarboxylative cross-coupling/cyclization reaction with diverse alkynyl carboxylic acids as summarized in Table 2. Notably, most of the products presented excellent stereoselectivity to give the products with an *E*-configuration. Both electron-rich and electron-deficient alkynyl carboxylic acids displayed excellent reactivity to give the corresponding five-membered ring lactams in high yields (Table 2, **3a**–**3k**), but 3-(4-methoxyphenyl)propiolic acid presented a slightly lower reactivity (Table 2, **3g**). Various functionalities, such as $-CH_3$, $-OCH_3$, -F, -Cl, -Br, and -CN (Table 2, **3h**–**3k**), were tolerated, showing the good generality of this catalytic process. 3-(Naphthalen-1-yl)propiolic acid participated smoothly in the reaction, which resulted in 63% yield (Table 2, **3l**). The employment of heterocyclic alkynyl carboxylic acids, such as 3-(thiophen-3-yl)propiolic acid and 3-(thiophen-2-yl)propiolic acid, resulted in the successful generation of the desired lactam products (Table 2, **3m** and **3n**). It should be noted that the relatively less reactive alkylpropiolic acids, such as 3-cyclohexylpropiolic acid and 3-cyclopropylpropiolic acid, showed comparable reactivity to afford the corresponding lactams in good yields (Table 1, **3o** and **3p**). However, the transformation and isolation of the stereoisomer was quite difficult and a mixture of *Z*- and *E*-isomers was obtained.

Under similar reaction conditions, various aliphatic amides reacted smoothly with **2a** to produce the corresponding substituted pyrrolidones (Table 3). When the two substituent groups at the α-position of the aliphatic amides were different, a mixture of two isomers was obtained, and the control experiments implied that the mixture consisted of two diastereoisomers whose ratio was determined by ^{1}H NMR (see Supporting Information for details). For instance, substrate amides **1b**–**1m**, which bear two different substituent groups at their α-position, generated the corresponding products as a mixture of two isomers while substrate amides **1n**–**1r** with two of the same substituent groups at the α-position afforded the desired products as a single isomer. Excellent site selectivity of the *β*-methyl groups over the methylene and benzyl groups was presented, and the coupling of *γ*- or *δ*-methyl group C–H bonds was not observed (Table 3, **4a**–**4j**). In the case of 2-phenyl-substituted substrates, the reaction showed an excellent selectivity for the sp^3 C–H bonds of the *β*-methyl group over the aromatic C–H bonds of the phenyl group (Table 3,

Table 2. Substrate scope of alkynyl carboxylic acids.[a,b]



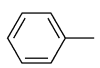
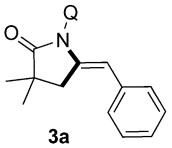
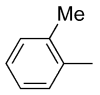
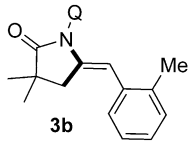
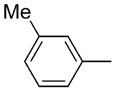
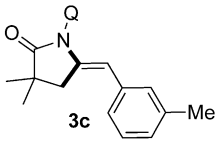
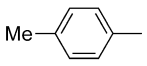
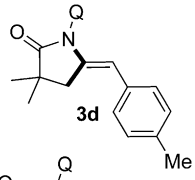
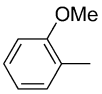
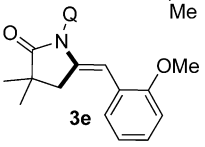
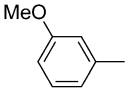
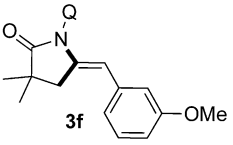
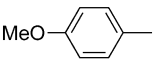
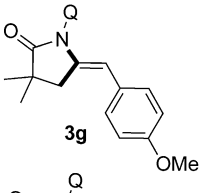
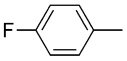
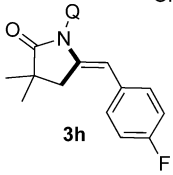
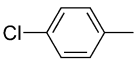
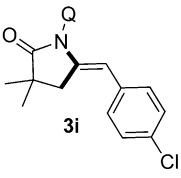
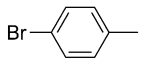
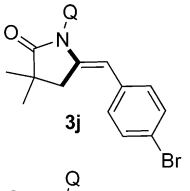
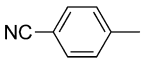
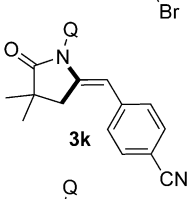
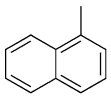
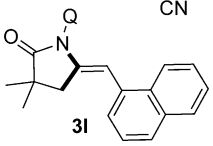
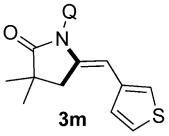
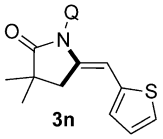
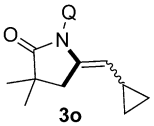
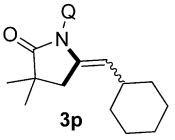
Entry	R^3	3	Yield
1		 **3a**	92
2		 **3b**	85
3		 **3c**	91
4		 **3d**	90
5		 **3e**	78
6		 **3f**	81
7		 **3g**	61
8		 **3h**	88
9		 **3i**	89

Table 2. (Continued)

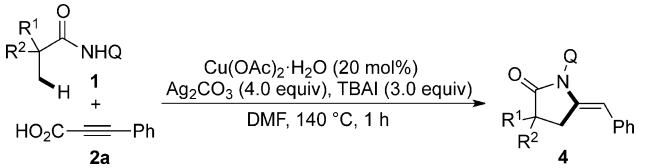
Entry	R^3	3	Yield
10		 **3j**	91
11		 **3k**	74
12		 **3l**	63
13		 **3m**	63
14		 **3n**	71
15		 **3o**	81 *Z*/*E* = 1:1.5
16		 **3p**	70 *Z*/*E* = 1:2

[a] *Reaction conditions*: **1a** (0.1 mmol), **2** (0.2 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.02 mmol), Ag_2CO_3 (0.4 mmol), TBAI (0.3 mmol), DMF (1.5 mL), 1 h at 140 °C. The reaction solution was treated with dilute *p*-toluenesulfonic acid for half an hour after the reaction at room temperature.

[b] Isolated yield of **3** based on **1a** by flash column chromatography. Q = Quinolin-8-yl, TBAI = Tetrabutylammonium Iodide.

4k–**4m**), indicating the preferential formation of a five-membered ring aliphatic copper intermediate as opposed to a six membered ring aromatic copper intermediate in the metalation step.[6p] It was worthwhile to note that the cyclic substrates, including cyclopropanecarboxamide, cyclobutanecarboxamide, cyclopentanecarboxamide, and cyclohexanecarboxamide, could participate in the reaction to produce valuable spiro-γ-lactams (**4n**–**4q**), which are impor-

Table 3. Substrate scope of aliphatic amides.



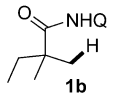
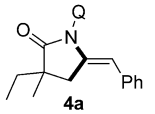
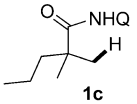
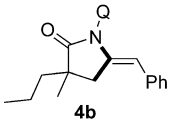
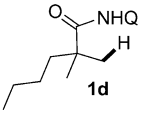
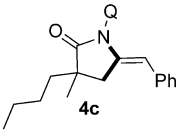
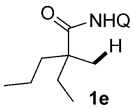
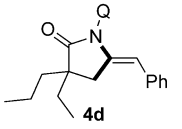
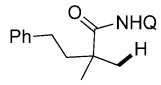
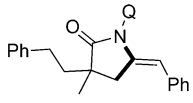
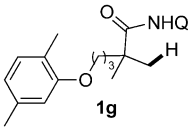
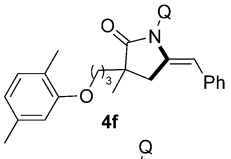
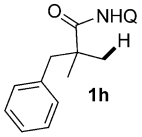
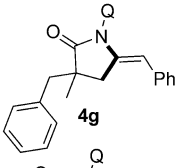
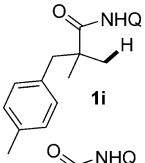
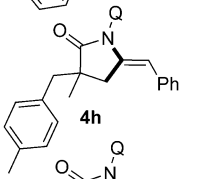
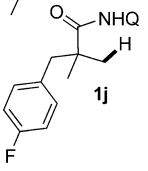
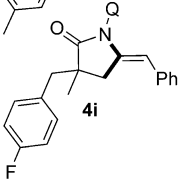
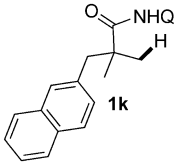
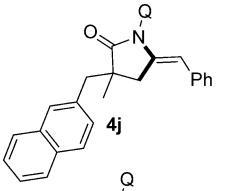
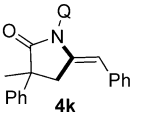
Entry	1	4	Yield
1	 **1b**	 **4a**	73 d.r. = 1:1.1
2	 **1c**	 **4b**	76 d.r. = 1:1.3
3	 **1d**	 **4c**	71 d.r. = 1:1.1
4	 **1e**	 **4d**	74 d.r. = 1:1
5	 **1f**	 **4e**	70 d.r. = 1:1.3
6	 **1g**	 **4f**	64 d.r. = 1:1.1
7	 **1h**	 **4g**	80 d.r. = 1:2
8	 **1i**	 **4h**	86 d.r. = 1:2
9	 **1j**	 **4i**	72 d.r. = 1:1.4
10	 **1k**	 **4j**	85 d.r. = 1:1.5
11	 **1l**	 **4k**	65 d.r. = 1:1.1

Table 3. (Continued)

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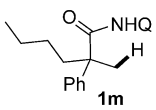
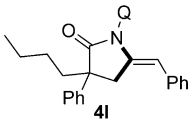
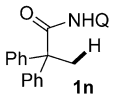
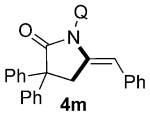
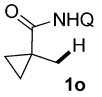
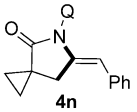
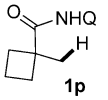
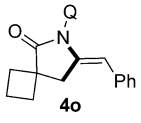
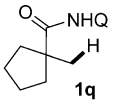
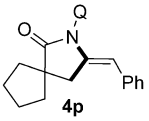
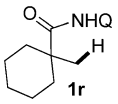
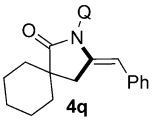
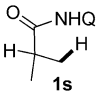
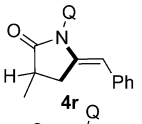
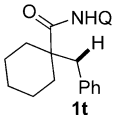
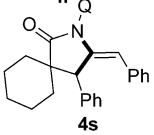
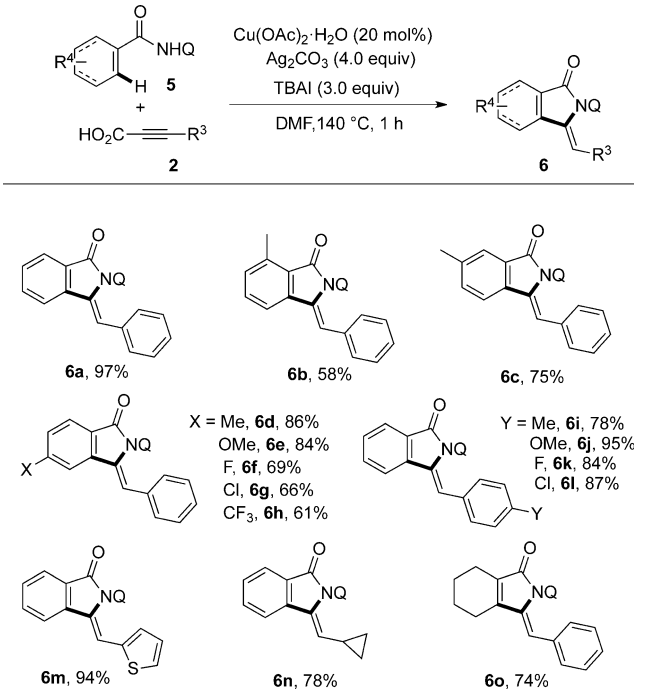
12	 **1m**	 **4l**	71 d.r. = 1:1.1
13	 **1n**	 **4m**	78
14	 **1o**	 **4n**	39
15	 **1p**	 **4o**	68
16	 **1q**	 **4p**	52
17	 **1r**	 **4q**	90
18	 **1s**	 **4r**	0
19	 **1t**	 **4s**	0

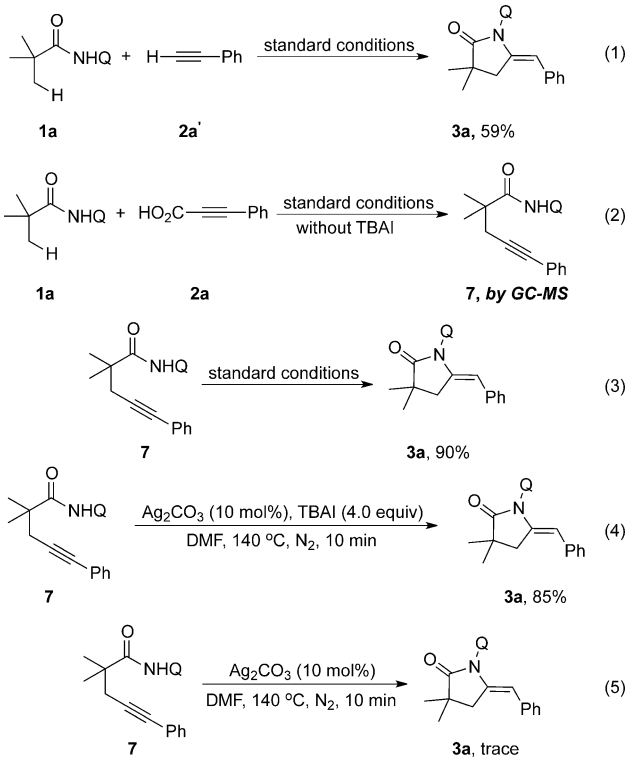
tant drug intermediates that are difficult to synthesize by the known methods.[22] Interestingly, along with the enlargement of the ring at the α-position of the amides, the enhanced reactivity was obtained by producing diverse spiro-γ-lactam products in higher yields, which is due in part to the more suitable angle for the formation of metallacycle intermediate.[6h] Unfortunately, the substrate amide bearing hydrogen at the α-position could not be tolerated in this reaction and the C–H bonds of methylene were not reactive as well (**4r** and **4s**).

The presented copper-catalyzed decarboxylative cyclic-coupling reaction can be successfully extended to various substituted aromatic amides as shown in Table 4. A variety of aromatic amides bearing either electron-withdrawing groups or electron-donating groups were applicable to the transformation to produce diverse isoindolin-1-ones.[16j] However, electron-deficient benzamides showed the relatively lower reactivity (Table 4, **6a**–**6h**). The cleavage of C(sp^2)–H bonds in *meta*-methyl substituted benzamide occurred predominantly at the sterically less congested site and the yield of *ortho*-substituted benzamides was obviously decreased due to the steric factor (Table 4, **6b** and **6c**). The generality of alkynyl carboxylic acids is superior. A range of functionalities, such as methyl, methoxyl, fluorine, and chlorine, could be tolerated under the reaction conditions, which allowed for the highly diverse synthesis of functionalized isoindolin-1-ones (Table 4, **6i-6l**). 3-(Thiophen-2-yl)propiolic acid gave the thiophene containing isoindolinone in 94% yield (Table 4 < xtabr4, **6m**). Cyclopropylpropiolic acid was compatible with the standard reaction conditions to deliver **6n** in 78% yield. Importantly, acrylamide substrate showed comparable reactivity to afford the fused pyrrolidone in good yield (Table 4, **6o**).

Table 4. Reactions of aromatic amides with alkynyl carboxylic acids.



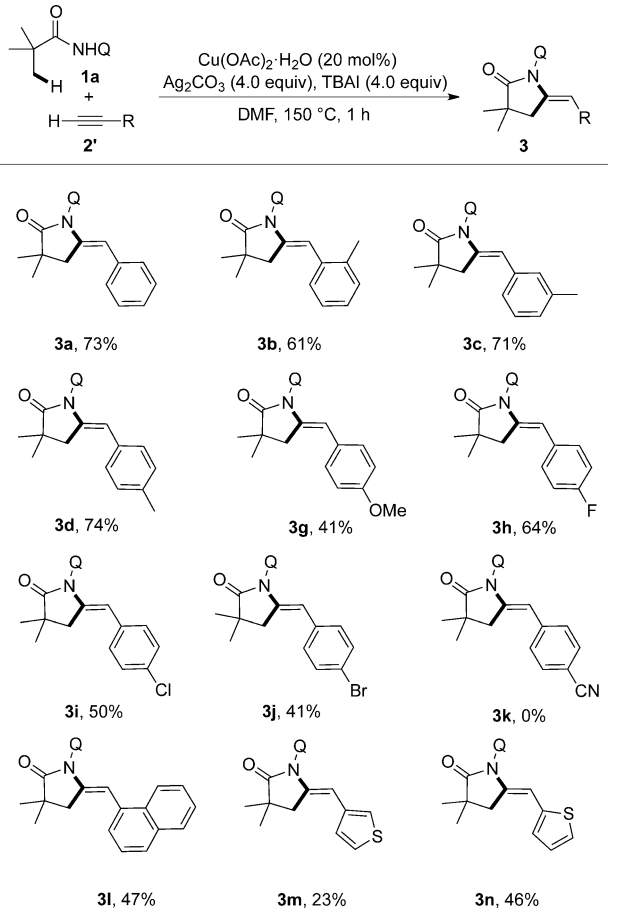
The exact mechanism of this tandem decarboxylative cross-coupling/cyclization is not clear at the moment. The decarboxylation may be promoted by either copper or silver salts to form phenylacetylide species.[7a] Alternatively, a protodecarboxylation process might be involved to generate ethynylbenzene which transforms to phenylacetylide species in the presence of silver and copper salts. This possibility is proven by the reaction of **1a** and ethynylbenzene under the standard reaction conditions, which produced pyrrolidone **3a** in a low yield (Scheme 1, eq. 1). Furthermore, we optimized the reaction conditions



Scheme 1. The control experiments.

for terminal alkynes in this transformation and the scope of substrates is summarized in Table 5. These results indicate that terminal alkynes were less effective than alkynyl carboxylic acids in this copper catalytic system. Further investigation proved that the alkynylated product **7** existed in the reaction (Scheme 1, eq. 2; see Supporting Information). The intramolecular cyclization process occurred with the combination of catalytic Ag_2CO_3 and TBAI in the absence of copper catalysis but a trace of **3a** was observed in the absence of TBAI (Scheme 1, eq. 3–5). Because the silver(I) catalyzed intramolecular hydroamination of alkynes has been reported by Looper and Bi,[23] we proposed that the TBAI might promote the dissolution of Ag_2CO_3 in the organic solvent so that the silver(I)-catalyzed cyclization of **7** could proceed smoothly. Based on the previous study[6p,24] and our experiment results, a tentative reaction pathway is hypothesized as shown in Scheme 2. First, intermediate **A** forms through a C–H cyclocupration process and the oxidation of **A** by another copper(II) species gives rise to the alkyl/Cu^{III} complex **B**, which undergoes the ligand exchange with metal phenylacetylide to give alkynyl copper intermediate **C**. MALDI-TOF mass analysis of the reaction mixture of benzamide **5a** and alkynyl carboxylic acid **2a** indeed presented the signal of the exact mass of alkynyl copper intermediate **D** (Scheme 3; see Supporting Information), which partially supports the mechanism. The subsequent reductive elimination of intermediate **C** generates the alkynylated product **7**, which undergoes the intramolecular cyclization to give the pyrrolidone derivative.

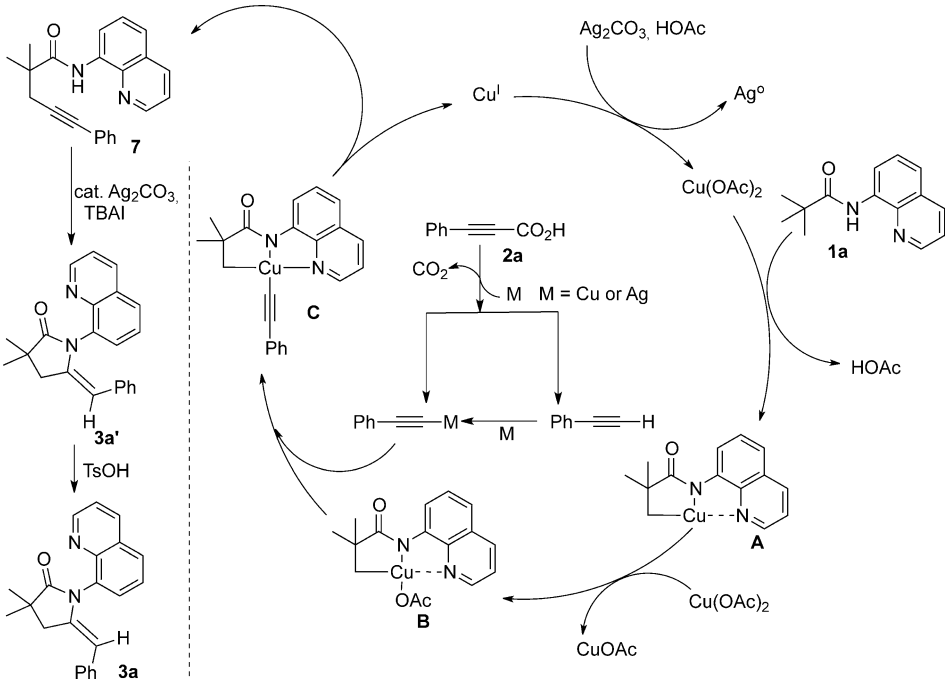
Table 5. Reactions of **1a** with terminal alkynes[a]



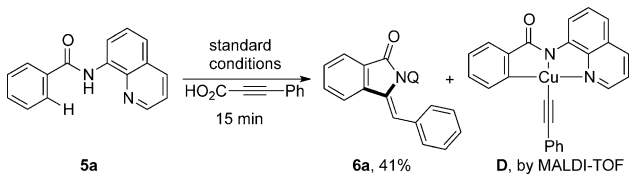
[a] *Reaction conditions*: **1a** (0.1 mmol), **2** (0.2 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.02 mmol), Ag_2CO_3 (0.4 mmol), TBAI (0.4 mmol), DMF (1.5 mL), 1 h at 150 °C. The reaction solution was treated with *p*-toluenesulfonic acid for half an hour after the reaction. Isolated yield of **3** based on **1a** by flash column chromatography. Q = Quinolin-8-yl, TBAI = tetrabutylammonium iodide.

Conclusions

In summary, we have developed a highly efficient method for the synthesis of pyrrolidones via the copper-catalyzed tandem decarboxylative cross-coupling/cyclization of aliphatic amides and alkynyl carboxylic acids. For the first time, the catalytic decarboxylative process is extended to the direct functionalization of unactivated sp^3 C–H bonds. The reaction features short reaction time (1 h), a broad substrate scope, and readily available reagents. The detailed mechanistic study of the reaction and exploration of



Scheme 2. The plausible mechanism.



Scheme 3. Matrix-assisted Laser Desorption Ionization Time-of-flight Mass Spectroscopy (MALDI-TOF-MS) of **D** obtained from the reaction of **5a** and **2a** under standard conditions for 15 min.

decarboxylative coupling of other carboxylic acids with sp^3 C–H bonds are currently underway in our laboratory.

Experimental Section

General Information

All commercial materials were used as received unless otherwise noted. ^{1}H NMR spectra were recorded at 400 MHz and 500 MHz using TMS as internal standard. ^{13}C NMR spectra were recorded at 100 MHz and 125 MHz using TMS as internal standard. The multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), multiplet (m), and triplet (t). Mass spectroscopy data of the products were collected on an HRMS-TOF instrument.

Copper(II)/Silver(I)-Catalyzed Sequential Alkynylation and Annulation of Aliphatic Amides with Alkynyl Carboxylic Acids

A mixture of *N*-(quinolin-8-yl)pivalamide (**1a**, 22.8 mg, 0.1 mmol), $Cu(OAc)_2{\cdot}H_2O$ (3.9 mg, 0.02 mmol), Ag_2CO_3 (110.3 mg, 0.4 mmol), TBAI (110.8 mg, 0.3 mmol), phenylpropiolic acid (**2a**, 29.2 mg, 0.2 mmol) and DMF (1.5 mL) was added to a 25 mL sealed tube. The tube was stirred at 140 °C for 1 h. Then, the reaction mixture was cooled to room temperature, and dilute *p*-toluenesulfonic acid (1.0 mL, 0.2 M in CH_2Cl_2) was added in the reaction system, by stirring for half an hour at room temperature. A saturated solution of potassium carbonate (10.0 mL) was added to the reaction tube. The mixture was extracted with ethyl acetate (3×15 mL), and the organic phase was dried over Na_2SO_4 and was concentrated in vacuo. Then the mixture was subjected to column chromatography on silica gel (hexane/ethyl acetate = 2:1) to give the desired product (**3a**, 30.2 mg, 92 %).

(*Z*)-5-Benzylidene-3,3-dimethyl-1-(quinolin-8-yl)pyrrolidin-2-one (3a′): R_f 0.53 (hexane/EtOAc = 2:1). Yellow oil. Isolated yield: 28.9 mg, 89 %. ^{1}H NMR ([D$_6$]DMSO, 400 MHz) δ 8.86 (dd, J_1 = 1.6 Hz, J_2 = 4.0 Hz, 1H), 8.17 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 7.92 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H), 7.44–7.47 (m, 1H), 7.37–7.39 (m, 1H), 7.27–7.31 (m, 1H), 6.56–6.60 (m, 1H), 6.44 (t, J = 7.6 Hz, 2H), 6.35 (d, J = 7.6 Hz, 2H), 5.69 (s, 1H), 2.88–2.96 (m, 2H), 1.39 (s, 3H), 1.33 (s, 3H). ^{13}C NMR ([D$_6$]DMSO, 100 MHz) δ 181.1, 150.1, 143.2, 138.5, 135.9, 134.6, 134.2, 129.2, 128.3, 128.0, 127.7, 125.9, 125.5, 124.7, 121.4, 102.7, 42.7, 39.9, 25.0, 24.5. HRMS (EI-TOF) calcd for $C_{22}H_{20}N_2O$ (M^+): 328.1576, found: 328.1578.

(*E*)-5-Benzylidene-3,3-dimethyl-1-(quinolin-8-yl)pyrrolidin-2-one (3a): R_f 0.51 (hexane/EtOAc = 2:1). White solid.

Isolated yield: 30.2 mg, 92%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.87 (dd, J_1=1.6 Hz, J_2=4.4 Hz, 1H), 8.20 (dd, J_1=1.6 Hz, J_2=8.0 Hz, 1H), 7.92 (dd, J_1=2.0 Hz, J_2=7.6 Hz, 1H), 7.63–7.70 (m, 2H), 7.40–7.43 (m, 1H), 7.21–7.25 (m, 2H), 7.06 −7.10 (m, 3H), 5.28 (t, J=2.0 Hz, 1H), 3.10–3.28 (m, 2H), 1.53 (s, 3H), 1.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.1, 151.1, 144.3, 143.0, 137.0, 136.2, 133.3, 130.4, 129.6, 129.3, 128.3, 127.6, 126.4, 125.2, 121.9, 104.4, 41.2, 40.9, 26.1, 25.7. HRMS (EI-TOF) calcd for $C_{22}H_{20}N_2O$ (M^+): 328.1576, found: 328.1578.

(*E*)-3,3-Dimethyl-5-(2-methylbenzylidene)-1-(quinolin-8-yl)pyrrolidin-2-one (3b): R_f 0.50 (hexane/EtOAc=2:1). White solid. Isolated yield: 29.0 mg, 85%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.88 (dd, J_1=1.6 Hz, J_2=4.4 Hz, 1H), 8.19 (dd, J_1=1.6 Hz, J_2=8.4 Hz, 1H), 7.90 (dd, J_1=1.2 Hz, J_2=8.0 Hz, 1H), 7.63–7.72 (m, 2H), 7.40–7.43 (m, 1H), 7.24–7.26 (m, 1H), 7.11–7.15 (m, 1H), 7.04–7.07 (m, 2H), 5.26 (s, 1H), 2.95–3.10 (m, 2H), 1.90 (s, 3H), 1.50 (s, 3H), 1.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.3, 151.0, 144.3, 142.6, 136.2, 136.1, 135.6, 133.5, 130.3, 129.9, 129.5, 129.2, 127.6, 126.4, 125.9, 125.5, 121.8, 102.7, 40.9, 40.5, 25.8, 25.4, 19.8. HRMS (EI-TOF) calcd for $C_{23}H_{22}N_2O$ (M^+): 342.1732, found: 342.1734.

(*E*)-3,3-Dimethyl-5-(3-methylbenzylidene)-1-(quinolin-8-yl)pyrrolidin-2-one (3c): R_f 0.52 (hexane/EtOAc=2:1). White solid. Isolated yield: 31.1 mg, 91%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.87 (dd, J_1=1.6 Hz, J_2=4.4 Hz, 1H), 8.19 (dd, J_1=1.6 Hz, J_2=8.4 Hz, 1H), 7.91 (dd, J_1=2.0 Hz, J_2=7.6 Hz, 1H), 7.63–7.69 (m, 2H), 7.39–7.42 (m, 1H), 7.13 (t, J=7.6 Hz, 1H), 6.89–6.94 (m, 3H), 5.24 (d, J=1.6 Hz, 1H), 3.10–3.28 (m, 2H), 2.26 (s, 3H), 1.53 (s, 3H), 1.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.1, 151.1, 144.3, 142.8, 137.8, 136.9, 136.1, 133.4, 130.4, 129.6, 129.2, 128.5, 128.2, 126.4, 126.0, 124.5, 121.8, 104.5, 41.2, 40.9, 26.1, 25.7, 21.5. HRMS (EI-TOF) calcd for $C_{23}H_{22}N_2O$ (M^+): 342.1732, found: 342.1735.

(*E*)-3,3-Dimethyl-5-(4-methylbenzylidene)-1-(quinolin-8-yl)pyrrolidin-2-one (3d): R_f 0.51 (hexane/EtOAc=2:1). White solid. Isolated yield: 30.7 mg, 90%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.85 (s, 1H), 8.15 (d, J=8.0 Hz, 1H), 7.92 (d, J=7.6 Hz, 1H), 7.60–7.67 (m, 2H), 7.40–7.43 (d, J=3.6 Hz, 1H), 7.00–7.02 (m, 4H), 5.25 (s, 12H), 3.08–3.25 (m, 2H), 3.26 (3, 1H), 1.52 (s, 3H), 1.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.1, 151.1, 144.4, 144.2, 136.2, 134.9, 134.1, 133.5, 130.4, 129.6, 129.2, 129.0, 127.5, 126.4, 121.9, 104.3, 41.2, 40.9, 26.1, 25.7, 21.1. HRMS (EI-TOF) calcd for $C_{23}H_{22}N_2O$ (M^+): 342.1732, found: 342.1736.

(*E*)-5-(2-Methoxybenzylidene)-3,3-dimethyl-1-(quinolin-8-yl)pyrrolidin-2-one (3e): R_f 0.43 (hexane/EtOAc=2:1). White solid. Isolated yield: 27.9 mg, 78%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.85 (dd, J_1=1.6 Hz, J_2=4.4 Hz, 1H), 8.13 (dd, J_1=1.2 Hz, J_2=8.4 Hz, 1H), 7.85–7.87 (m, 1H), 7.71 (dd, J_1=1.2 Hz, J_2=7.2 Hz, 1H), 7.60–7.64 (m, 1H), 7.34–7.37 (m, 1H), 7.28–7.30 (m, 1H), 7.07–7.11 (m, 1H), 6.87–6.91 (m, 1H), 6.72–6,74 (m, 1H), 5.53 (s, 1H), 3.57 (s, 3H), 3.02–3.24 (m, 2H), 1.51 (s, 3H), 1.40 (s, 3H). **^{13}C** NMR ($CDCl_3$, 100 MHz) δ 181.2, 156.4, 151.0, 144.3, 142.6, 136.1, 133.5, 130.4, 129.6, 129.1, 128.0, 126.8, 126.4, 125.9, 121.7, 120.3, 110.6, 99.3, 55.4, 41.1, 40.9, 25.8, 25.7. HRMS (EI-TOF) calcd for $C_{23}H_{22}N_2O_2$ (M^+): 358.1681, found: 358.1683.

(*E*)-5-(3-Methoxybenzylidene)-3,3-dimethyl-1-(quinolin-8-yl)pyrrolidin-2-one (3f): R_f 0.42 (hexane/EtOAc=2:1). White solid. Isolated yield: 28.9 mg, 81%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.86 (dd, J_1=2.0 Hz, J_2=4.0 Hz, 1H), 8.18 (dd, J_1=1.6 Hz, J_2=8.4 Hz, 1H), 7.91 (dd, J_1=1.6 Hz, J_2=8.0 Hz, 1H), 7.62–7.69 (m, 2H), 7.39–7.42 (m, 1H), 7.12–7.17 (m, 1H), 6.70 (d, J=7.6 Hz, 1H), 6.63–6.65 (m, 2H), 5.25 (t, J=1.6 Hz, 1H), 3.73 (s, 3H), 3.11–3.28 (m, 2H), 1.53 (s, 3H), 1.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.2, 159.5, 151.2, 144.3, 143.3, 138.4, 136.2, 133.3, 130.4, 129.6, 129.3, 129.2, 126.4, 121.9, 120.2, 113.3, 110.6, 104.3, 55.2, 41.3, 40.9, 26.1, 25.7. HRMS (EI-TOF) calcd for $C_{23}H_{22}N_2O_2$ (M^+): 358.1681, found: 358.1682.

(*E*)-5-(4-Methoxybenzylidene)-3,3-dimethyl-1-(quinolin-8-yl)pyrrolidin-2-one (3g): R_f 0.42 (hexane/EtOAc=2:1). White solid. Isolated yield: 21.8 mg, 61%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.87 (dd, J_1=2.0 Hz, J_2=4.0 Hz, 1H), 8.19 (dd, J_1=1.6 Hz, J_2=8.4 Hz, 1H), 7.90 (dd, J_1=1.6 Hz, J_2=8.0 Hz, 1H), 7.64–7.67 (m, 2H), 7.39–7.42 (m, 1H), 7.02–7.04 (m, 2H), 6.77–6.79 (m, 2H), 5.23 (s, 1H), 3.75 (s, 3H), 3.10–3.20 (m, 2H), 1.53 (s, 3H), 1.42 (s, 3H). **^{13}C** NMR ($CDCl_3$, 100 MHz) δ 181.0, 157.3, 151.1, 144.3, 141.3, 136.2, 133.4, 130.4, 129.6, 129.6, 129.2, 128.7, 126.4, 121.9, 113.8, 103.9, 55.3, 41.1, 40.9, 26.1, 25.7. HRMS (EI-TOF) calcd for $C_{23}H_{22}N_2O_2$ (M^+): 358.1681, found: 358.168.

(*E*)-5-(4-Fluorobenzylidene)-3,3-dimethyl-1-(quinolin-8-yl)pyrrolidin-2-one (3h): R_f 0.50 (hexane/EtOAc=2:1). White solid. Isolated yield: 30.4 mg, 88%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.88 (dd, J_1=2.0 Hz, J_2=4.4 Hz, 1H), 8.20 (dd, J_1=1.6 Hz, J_2=8.4 Hz, 1H), 7.92 (dd, J_1=2.4 Hz, J_2=7.6 Hz, 1H), 7.63–7.68 (m, 2H), 7.40–7.43 (m, 1H), 7.03–7.06 (m, 2H), 6.90–6.94 (m, 2H), 5.23 (s, 1H), 3.05–3.23 (m, 2H), 1.53 (s, 3H), 1.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.1, 160.6 (J_{C-F}=243.1 Hz), 151.2, 144.3, 142.6 (J_{C-F}=2.1 Hz), 136.2, 133.2, 130.0 (J_{C-F}=3.6 Hz), 130.4, 129.6, 129.3, 128.9 (J_{C-F}=7.5 Hz), 126.4, 121.9, 115.1 (J_{C-F}=21.4 Hz), 103.3, 41.0, 40.8, 26.1, 25.7. HRMS (EI-TOF) calcd for $C_{22}H_{19}FN_2O$ (M^+): 346.1481, found: 346.1481.

(*E*)-5-(4-Chlorobenzylidene)-3,3-dimethyl-1-(quinolin-8-yl)pyrrolidin-2-one (3i): R_f 0.49 (hexane/EtOAc=2:1). White solid. Isolated yield: 32.2 mg, 89%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.88 (dd, J_1=1.6 Hz, J_2=4.0 Hz, 1H), 8.21 (dd, J_1=1.6 Hz, J_2=8.4 Hz, 1H), 7.93 (dd, J_1=2.4 Hz, J_2=7.2 Hz, 1H), 7.65–7.68 (m, 2H), 7.41–7.44 (m, 1H), 7.17–7.19 (m, 2H), 7.00 −7.12 (m, 2H), 5.22 (s, 1H), 3.05–3.24 (m, 2H), 1.53 (s, 3H), 1.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.1, 151.1, 144.1, 143.5, 136.3, 135.5, 133.1, 130.6, 130.5, 129.6, 129.4, 128.7, 128.4, 126.4, 121.9, 103.3, 41.1, 40.8, 26.1, 25.7. HRMS (EI-TOF) calcd for $C_{22}H_{19}ClN_2O$ (M^+): 362.1186, found: 362.1187.

(*E*)-5-(4-Bromobenzylidene)-3,3-dimethyl-1-(quinolin-8-yl)pyrrolidin-2-one (3j): R_f 0.47 (hexane/EtOAc=2:1). Yellow solid. Isolated yield: 36.9 mg, 91%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.88 (dd, J_1=1.6 Hz, J_2=4.4 Hz, 1H), 8.20 (dd, J_1=1.6 Hz, J_2=8.4 Hz, 1H), 7.92 (dd, J_1=2.4 Hz, J_2=7.2 Hz, 1H), 7.63–7.68 (m, 2H), 7.40–7.43 (m, 1H), 7.32–7.34 (m, 2H), 6.94–6.956 (m, 2H), 5.20 (s, 1H), 3.04–3.23 (m, 2H), 1.53 (s, 3H), 1.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.9, 146.0, 139.0, 138.4, 131.0, 130.8, 127.9, 126.1, 125.2, 124.4, 124.2, 123.9, 121.2, 116.7, 113.4, 98.1, 35.9, 35.6, 20.9, 20.5. HRMS (EI-TOF) calcd for $C_{22}H_{19}BrN_2O$ (M^+): 406.0681, found: 406.0684.

(*E*)-4-((4,4-Dimethyl-5-oxo-1-(quinolin-8-yl)pyrrolidin-2-ylidene)methyl)benzonitrile (3k): R_f 0.44 (hexane/EtOAc=

2:1). White solid. Isolated yield: 26.1 mg, 74%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.86 (dd, J_1=1.6 Hz, J_2=4.4 Hz, 1H), 8.21 (dd, J_1=1.6 Hz, J_2=8.4 Hz, 1H), 7.95 (dd, J_1=3.6 Hz, J_2=5.6 Hz, 1H), 7.66–7.68 (m, 2H), 7.42–7.49 (m, 3H), 7.13–7.16 (m, 2H), 5.26 (s, 1H), 3.11–3.28 (m, 2H), 1.55 (s, 3H), 1.45 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.1, 151.3, 146.5, 144.1, 142.1, 136.2, 132.8, 132.1, 130.3, 129.6, 127.7, 126.4, 122.0, 119.4, 107.8, 103.1, 41.5, 40.8, 26.2, 25.7. HRMS (EI-TOF) calcd for $C_{23}H_{19}N_3O$ (M^+): 353.1528, found: 353.1530.

(*E*)-3,3-Dimethyl-5-(naphthalen-1-ylmethylene)-1-(quinolin-8-yl)pyrrolidin-2-one (3l): R_f 0.52 (hexane/EtOAc=2:1). White solid. Isolated yield: 23.8 mg, 63%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.96 (dd, J_1=1.6 Hz, J_2=4.4 Hz, 1H), 8.22 (dd, J_1=1.6 Hz, J_2=8.4 Hz, 1H), 7.93 (dd, J_1=1.6 Hz, J_2=8.4 Hz, 1H), 7.77–7.82 (m, 2H), 7.63–7.71 (m, 3H), 7.44–7.47 (m, 1H), 7.38–7.43 (m, 3H), 7.30–7.34 (m, 1H), 5.75 (d, J=2.0 Hz, 1H), 2.92–3.08 (m, 2H), 1.48 (s, 3H), 1.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.5, 151.1, 144.3, 143.9, 136.3, 133.8, 133.7, 133.5, 132.1, 130.4, 129.7, 129.3, 128.4, 126.5, 125.7, 125.6, 125.5, 125.4, 124.6, 121.9, 101.5, 40.9, 40.4, 25.7, 25.4. HRMS (EI-TOF) calcd for $C_{26}H_{22}N_2O$ (M^+): 378.1732, found: 378.1734.

(*E*)-3,3-Dimethyl-1-(quinolin-8-yl)-5-(thiophen-3-ylmethylene)pyrrolidin-2-one (3m): R_f 0.48 (hexane/EtOAc=2:1). Yellow solid. Isolated yield: 21.0 mg, 63%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.88 (dd, J_1=1.6 Hz, J_2=4.0 Hz, 1H), 8.21 (dd, J_1=1.6 Hz, J_2=8.0 Hz, 1H), 7.93 (dd, J_1=2.8 Hz, J_2=6.4 Hz, 1H), 7.65–7.67 (m, 2H), 7.41–7.44 (m, 1H), 7.20 (dd, J_1=2.8 Hz, J_2=3.2 Hz, 1H), 6.90 (dd, J_1=1.2 Hz, J_2=5.2 Hz, 1H), 6.86 (d, J=2.4 Hz, 1H), 5.31 (t, J=1.6 Hz, 1H), 3.09–3.20 (m, 2H), 1.55 (s, 3H), 1.44 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.2, 151.2, 144.3, 142.4, 137.7, 136.2, 133.2, 130.4, 129.6, 129.3, 127.8, 126.4, 125.0, 121.9, 119.3, 98.9, 41.1, 40.8, 26.3, 25.9. HRMS (EI-TOF) calcd for $C_{20}H_{18}N_2OS$ (M^+): 334.1140, found: 334.1140.

(*E*)-3,3-Dimethyl-1-(quinolin-8-yl)-5-(thiophen-2-ylmethylene)pyrrolidin-2-one (3n): R_f 0.48 (hexane/EtOAc=2:1). Yellow solid. Isolated yield: 23.7 mg, 71%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.86 (dd, J_1=1.6 Hz, J_2=4.0 Hz, 1H), 8.19 (dd, J_1=1.6 Hz, J_2=8.4 Hz, 1H), 7.92 (dd, J_1=2.8 Hz, J_2=6.8 Hz, 1H), 7.62–7.67 (m, 2H), 7.39–7.42 (m, 1H), 7.09 (d, J=5.2 Hz, 1H), 6.88–6.90 (m, 1H), 6.62 (d, J=3.6 Hz, 1H), 5.50 (s, 1H), 3.05–3.25 (m, 2H), 1.56 (s, 3H), 1.46 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.3, 151.3, 144.3, 142.1, 140.4, 136.2, 133.1, 130.4, 129.6, 129.4, 127.0, 126.4, 124.2, 122.7, 121.9, 98.2, 41.0, 40.9, 26.5, 26.0. HRMS (EI-TOF) calcd for $C_{20}H_{18}N_2OS$ (M^+): 334.1140, found: 334.1140.

5-(Cyclopropylmethylene)-3,3-dimethyl-1-(quinolin-8-yl)-pyrrolidin-2-one (3o): *Z*-R_f 0.41, E-R_f 0.41, (hexane/EtOAc=2:1). Yellow oil. Isolated yield: 12.7 mg, 39%. The ratio of *Z*/*E* was 1:1.5 as determined by ^{1}H NMR. ^{1}H NMR ($CDCl_3$, 400 MHz, a mixture of two isomers) δ 9.16 (dd, J_1=1.6 Hz, J_2=4.0 Hz, 1H, *E*-isomer), 9.09 (dd, J_1=1.6 Hz, J_2=4.0 Hz, 1H, *Z*-isomer), 8.55 (dd, J_1=1.6 Hz, J_2=8.4 Hz, 1H, *Z*-isomer), 8.43 (dd, J_1=1.6 Hz, J_2=8.4 Hz, 1H, *E*-isomer), 8.07–8.13 (m, 2H, *Z*- and *E*-isomers), 7.84–7.95 (m, 4H, *Z*- and *E*-isomers), 7.73–7.76 (m, 1H, *Z*-isomer), 7.65–7.68 (m, 1H, *E*-isomer), 3.96–3.99 (m, 2H, *Z*- and *E*-isomers), 3.11–3.31 (m, 2H, *E*-isomer), 2.54–2.68 (m, 2H, *Z*-isomer), 1.87 (s, 3H, *Z*-isomer), 1.79 (s, 3H, *E*-isomer), 1.68 (s, 3H, *E*-isomer), 1.63 (s, 3H, *Z*-isomer), 1.00–1,04 (m, 1H, *E*-isomer), 0.85–0.92 (m, 3H, *Z*- and *E*-isomers), 0.65–0.70 (m, 2H, *Z*-isomer), 0.34–0.38 (m, 1H, *E*-isomer), 0.28–0.32 (m, 1H, *E*-isomer), 0.18–0.24 (m, 2H, *Z*-isomer). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.9, 181.0, 151.0, 149.2, 144.3, 143.6, 139.4, 137.9, 136.1, 134.5, 133.5, 132.1, 130.2, 129.7, 129.5, 128.9, 127.6, 127.0, 126.3, 121.7, 121.4, 105.8, 91.4, 47.3, 45.3, 40.9, 40.6, 38.8, 26.9, 26.2, 25.8, 9.3, 6.7, 6.6, 6.2, 4.6, 4.5. HRMS (EI-TOF) calcd for $C_{19}H_{20}N_2O$ (M^+): 292.1576, found: 292.1576.

5-(Cyclohexylmethylene)-3,3-dimethyl-1-(quinolin-8-yl) pyrrolidin-2-one (3p): *Z*-R_f 0.55, *E*-R_f 0.55, (hexane/EtOAc=2:1). Yellow oil. Isolated yield: 12.7 mg, 39%. The ratio of *Z*/*E* was 1:2 as determined by ^{1}H NMR. ^{1}H NMR ($CDCl_3$, 400 MHz, a mixture of two isomers) δ 8.86 (dd, J_1=1.6 Hz, J_2=4.0 Hz, 1H, *E*-isomer), 8.81 (dd, J_1=1.6 Hz, J_2=4.4 Hz, 1H, *Z*-isomer), 8.28 (d, J=8.4 Hz, 1H, *Z*-isomer), 8.16 (d, J=8.4 Hz, 1H, *E*-isomer), 7.84–7.87 (m, 1H, *E*-isomer), 7.81–7.83 (m, H, *Z*-isomer), 7.58–7.66 (m, 3H, *Z*- and *E*-isomers), 7.46–7.49 (m, 1H, *Z*-isomer), 7.37–7.40 (m, 1H, *E*-isomer), 4.03–4.06 (m, 2H, *Z*- and *E*-isomers), 2.71–2.91 (m, 2H, *E*-isomer), 2.00–2.41 (m, 2H, *Z*- and *E*-isomers), 1.80–1.84 (m, 1H, *Z*-isomer), 1.51–1.65 (m, 9H, *Z*- and *E*-isomers), 1.48 (s, 3H, *E*-isomer), 1.38 (s, 3H, *E*-isomer), 1.38 (s, 3H, *Z*-isomer), 1.14–1.27 (m, 3H, *Z*- and *E*-isomers), 0.97–1.06 (m, 2H, *Z*- and *E*-isomers), 0.84–0.94 (m, 1H, *Z*-isomer), 0.71–0.82 (m, 2H, *E*-isomer). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.5, 181.1, 150.8, 149.1, 144.3, 143.6, 138.5, 137.9, 136.0, 134.7, 133.8, 132.2, 130.2, 129.7, 129.5, 128.7, 127.5, 127.1, 126.2, 121.6, 121.4, 108.7, 91.3, 48.6, 48.3, 40.9, 40.6, 38.7, 36.3, 35.0, 34.8, 33.8, 33.7, 26.9, 26.9, 26.5, 26.3, 26.2, 26.2, 26.1, 26.0, 25.9, 25.6. HRMS (EI-TOF) calcd for $C_{22}H_{26}N_2O$ (M^+): 334.2045, found: 334.2050.

(*E*)-5-Benzylidene-3-ethyl-3-methyl-1-(quinolin-8-yl) pyrrolidin-2-one (4a): R_{f1} 0.55, R_{f2} 0.53 (hexane/EtOAc=2:1). Yellow oil. Isolated yield: 24.9 mg, 73%. The ratio of two isomers was 1:1.1 as determined by ^{1}H NMR. ^{1}H NMR ($CDCl_3$, 400 MHz, a mixture of two isomers) δ 8.84–8.87 (m, 2H), 8.18 (s, 1H), 8.16 (s, 1H), 7.90 (s, 1H), 7.88 (s, 1H), 7.61–7.69 (m, 4H), 7.37–7.40 (m, 2H), 7.21–7.24 (m, 4H), 7.05–7.12 (m, 6H), 5.27 (s, 1H), 5.25 (s, 1H), 2.97–3.35 (m, 4H), 1.69–2.00 (m, 4H), 1.51 (s, 3H), 1.39 (s, 3H), 1.15 (t, J=7.2 Hz), 1.05 (t, J=7.6 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.7, 180.6, 151.2, 151.1, 144.3, 144.3, 143.4, 143.3, 137.1, 136.2, 136.1, 133.5, 133.4, 130.5, 130.4, 129.6, 129.3, 129.2, 128.3, 127.6, 126.4, 126.4, 125.2, 121.89, 104.2, 104.0, 44.6, 39.2, 38.1, 31.7, 31.5, 24.6, 24.0, 9.1, 9.0. HRMS (EI-TOF) calcd for $C_{23}H_{22}N_2O$ (M^+): 342.1732, found: 342.1732.

(*E*)-5-Benzylidene-3-methyl-3-propyl-1-(quinolin-8-yl) pyrrolidin-2-one (4b): R_{f1} 0.55, R_{f2} 0.52 (hexane/EtOAc=2:1). Yellow oil. Isolated yield: 27.1 mg, 76%. The ratio of two isomers was 1:1.3 as determined by ^{1}H NMR. ^{1}H NMR ($CDCl_3$, 400 MHz, a mixture of two isomers) δ 8.86–8.88 (m, 2H), 8.21 (t, J=1.6 Hz, 1H), 8.18 (t, J=1.6 Hz, 1H), 7.90–7.93 (m, 2H), 7.63–7.69 (m, 4H), 7.39–7.42 (m, 2H), 7.21–7.25 (m, 4H), 7.06–7.12 (m, 6H), 5.27 (s, 1H), 5.24 (s, 1H), 3.14–3.24 (m, 4H), 1.73–1.90 (m, 4H), 1.60–1.70 (m, 4H), 1.51 (s, 3H), 1.40 (s, 3H), 0.95–1.02 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.8, 180.7, 151.2, 151.2, 144.3, 143.4, 143.3, 137.1, 136.2, 136.1, 133.5, 133.3, 130.5, 130.4, 129.6, 129.6, 129.3, 129.2, 128.3, 127.6, 126.4, 126.4, 125.1, 121.9, 104.2, 104.0, 44.3, 44.3, 41.4, 41.0, 38.8, 38.6, 24.9, 24.3, 17.9,

17.8, 14.7, 14.6. HRMS (EI-TOF) calcd for $C_{24}H_{24}N_2O$ (M^+): 356.1889, found: 356.1884.

(*E*)-5-Benzylidene-3-butyl-3-methyl-1-(quinolin-8-yl) pyrrolidin-2-one (4c): R_{f1} 0.56, R_{f2} 0.54 (hexane/EtOAc = 2:1). Yellow oil. Isolated yield: 26.2 mg, 71%. The ratio of two isomers was 1:1.1 as determined by ^{1}H NMR. ^{1}H NMR ($CDCl_3$, 400 MHz, a mixture of two isomers) δ 8.85–8.88 (m, 2H), 8.21 (t, J = 1.6 Hz, 1H), 8.18 (t, J = 1.6 Hz, 1H), 7.90–7.93 (m, 2H), 7.63–7.69 (m, 4H), 7.39–7.43 (m, 2H), 7.16–7.25 (m, 4H), 7.06–7.12 (m, 6H), 5.27 (s, 1H), 5.24 (s, 1H), 2.99–3.36 (m, 4H), 1.75–1.86 (m, 4H), 1.54–1.71 (m, 4H), 1.52 (s, 3H), 1.36–1.42 (s, 7H), 0.92–0.98 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.8, 180.8, 151.2, 151.0, 144.3, 143.4, 143.3, 137.1, 136.2, 136.1, 133.5, 133.3, 130.5, 130.4, 129.6, 129.6, 129.3, 129.2, 128.3, 127.6, 127.5, 126.4, 126.4, 125.1, 121.9, 104.1, 104.0, 44.3, 44.2, 38.8, 38.7, 38.6, 38.5, 26.8, 26.7, 24.9, 24.4, 23.3, 23.2, 14.2, 14.1. HRMS (EI-TOF) calcd for $C_{25}H_{26}N_2O$ (M^+): 370.2045, found: 370.2048.

(*E*)-5-Benzylidene-3-ethyl-3-propyl-1-(quinolin-8-yl) pyrrolidin-2-one (4d): R_{f1} 0.49, R_{f2} 0.49 (hexane/EtOAc = 5:1). Yellow oil. Isolated yield: 27.4 mg, 74%. The ratio of two isomers was 1:1 as determined by ^{1}H NMR. ^{1}H NMR ($CDCl_3$, 400 MHz, a mixture of two isomers) δ 8.85–8.88 (m, 2H), 8.21 (t, J = 1.6 Hz, 1H), 8.18 (t, J = 1.6 Hz, 1H), 7.90–7.94 (m, 2H), 7.65–7.66 (m, 4H), 7.39–7.43 (m, 2H), 7.22–7.25 (m, 4H), 7.06–7.14 (m, 6H), 5.23 (d, 2H), 3.07–3.29 (m, 4H), 1.57–1.2.00 (m, 10H), 1.43–1.54 (m, 2H), 1.17 (t, J = 7.2 Hz, 3H), 1.05 (t, J = 7.2 Hz, 3H), 0.95–1.02 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.9, 179.9, 151.1, 151.1, 144.3, 144.3, 143.8 137.2, 136.1, 133.6, 130.4, 129.5, 129.2, 128.3, 127.5, 126.4, 126.3, 125.0, 121.8, 103.6, 48.3, 40.2, 39.9, 35.5, 30.7, 17.7, 17.6, 14.8, 14.6, 8.8, 8.8. HRMS (EI-TOF) calcd for $C_{25}H_{26}N_2O$ (M^+): 370.2045, found: 370.2043.

(*E*)-5-Benzylidene-3-methyl-3-phenethyl-1-(quinolin-8-yl)-pyrrolidin-2-one (4e): R_{f1} 0.53, R_{f2} 0.51 (hexane/EtOAc = 2:1). Yellow oil. Isolated yield: 29.2 mg, 70%. The ratio of two isomers was 1.3:1 as determined by ^{1}H NMR. ^{1}H NMR ($CDCl_3$, 400 MHz, a mixture of two isomers) δ 8.86 (dd, J_1 = 1.6 Hz, J_2 = 4.0 Hz), 8.81 (dd, J_1 = 1.6 Hz, J_2 = 4.0 Hz), 8.17 (s, 1H), 8.15 (s, 1H), 7.90 (s, 1H), 7.88 (s, 1H), 7.61–7.71 (m, 4H), 7.05–7.10 (m, 4H), 7.35–7.39 (m, 2H), 7.15–7.30 (m, 14H), 7.05–7.10 (m, 6H), 5.29–5.30 (m, 2H), 2.71–3.40 (m, 8H), 1.97–2.18 (m, 4H), 1.59 (s, 3H), 1.48 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.3, 180.2, 151.2, 151.1, 144.3, 143.1, 142.7, 141.9, 137.0, 136.2, 133.5, 133.3, 130.5, 130.4, 129.6, 129.4, 129.3, 128.6, 128.5, 128.4, 128.4, 127.7, 126.4, 126.4, 126.0, 125.8, 125.3, 122.0, 104.4, 104.3, 44.4, 44.4, 41.2, 40.8, 39.0, 38.7, 31.2, 31.1, 24.9, 24.6. HRMS (EI-TOF) calcd for $C_{29}H_{26}N_2O$ (M^+): 418.2045, found: 418.2006.

(*E*)-5-Benzylidene-3-(3-(2,5-dimethylphenoxy)propyl)-3-methyl-1-(quinolin-8-yl)pyrrolidin-2-one (4f): R_{f1} 0.52, R_{f2} 0.50 (hexane/EtOAc = 2:1). Yellow oil. Isolated yield: 30.4 mg, 64%. The ratio of two isomers was 1.1:1 as determined by ^{1}H NMR. ^{1}H NMR ($CDCl_3$, 400 MHz, a mixture of two isomers) δ 8.87 (d, J = 3.2 Hz), 8.79 (d, J = 3.2 Hz, 1H), 8.17–8.20 (m, 2H), 7.90–7.92 (m, 2H), 7.62–7.70 (m, 4H), 7.37–7.42 (m, 2H), 7.21–7.24 (m, 4H), 7.06–7.11 (m, 6H), 6.99–7.01 (m, 2H), 6.63–6.67 (m, 4H), 5.26–5.29 (m, 2H), 3.99–4.06 (m, 2H), 3.05–3.39 (m, 4H), 2.30 (s, 3H), 2.28 (s, 3H), 2.19–2.20 (m, 6H), 1.91–2.16 (m, 8H), 1.57 (s, 3H), 1.46 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.5, 181.4, 157.2, 157.0, 150.1, 150.0, 143.8, 143.7, 136.7, 136.6, 136.5, 135.7, 135.6, 135.1, 135.0, 134.5, 134.4, 130.4, 130.4, 130.4, 129.4, 129.1, 128.8, 128.1, 128.0, 126.2, 126.1, 125.6, 125.0, 124.9, 123.7, 123.7, 121.2, 121.2, 120.9, 120.7, 112.1, 112.1, 103.5, 103.4, 43.9, 43.8, 41.4, 41.1, 35.2, 35.0, 24.9, 23.8, 23.6, 21.5, 16.0. HRMS (EI-TOF) calcd for $C_{32}H_{32}N_2O_2$ (M^+): 476.2464, found: 476.247.

(*E*)-3-Benzyl-5-benzylidene-3-methyl-1-(quinolin-8-yl)pyrrolidin-2-one (4g): R_{f1} 0.52, R_{f2} 0.50 (hexane/EtOAc = 2:1). Yellow oil. Isolated yield: 32.3 mg, 80%. The ratio of two isomers was 1:2 as determined by ^{1}H NMR. ^{1}H NMR ($CDCl_3$, 400 MHz, a mixture of two isomers) δ 8.84–8.87 (m, 2H), 8.15–8.20 (m, 2H), 7.92 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz), 7.87 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz), 7.65–7.70 (m, 1H), 7.56–7.60 (m, 1H), 7.37–7.42 (m, 2H), 7.26–7.35 (m, 9H), 7.18–7.23 (m, 3H), 7.04–7.07 (m, 3H), 6.99–7.01 (m, 2H), 5.30 (s, 1H), 5.05 (s, 1H), 2.81–3.46 (m, 7H), 1.61 (s, 3H), 1.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.3, 179.7, 151.2, 151.1, 144.3, 144.3, 142.8, 142.8, 137.6, 137.6, 137.0, 136.9, 136.2, 133.3, 133.2, 130.8, 130.4, 130.4, 130.3, 129.6, 129.5, 129.4, 129.3, 128.4, 128.3, 127.6, 126.9, 126.6, 126.4, 125.3, 125.2, 122.0, 121.9, 104.9, 104.1, 46.0, 45.6, 44.3, 43.2, 37.7, 37.3, 25.7, 24.0. HRMS (EI-TOF) calcd for $C_{28}H_{24}N_2O$ (M^+): 404.1889, found: 404.1892.

(*E*)-5-Benzylidene-3-methyl-3-(4-methylbenzyl)-1-(quinolin-8-yl)pyrrolidin-2-one (4h): R_{f1} 0.52, R_{f2} 0.50 (hexane/EtOAc = 2:1). Yellow oil. Isolated yield: 35.9 mg, 85%. The ratio of two isomers was 1:2 as determined by ^{1}H NMR. ^{1}H NMR ($CDCl_3$, 400 MHz, a mixture of two isomers) δ 8.85–8.88 (m, 2H), 8.17–8.22 (m, 2H), 7.89–7.94 (m, 2H), 7.68–7.70 (m, 1H), 7.58–7.62 (m, 1H), 7.39–7.44 (m, 2H), 7.34–7.36 (m, 1H), 7.16–7.23 (m, 6H), 7.11–7.13 (m, 3H), 7.04–7.08 (m, 3H), 7.00–7.02 (m, 2H), 5.30 (s, 1H), 5.07 (s, 1H), 2.78–3.46 (m, 6H), 2.36 (s, 5H), 1.59 (s, 3H), 1.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.4, 179.8, 151.2, 151.1, 144.3, 144.3, 142.9, 137.0, 136.9, 136.3, 136.1, 136.0, 134.4, 133.2, 130.7, 130.4, 130.3, 129.6, 129.5, 129.3, 129.2, 129.0, 128.9, 128.3, 128.2, 127.6, 127.5, 126.4, 125.2, 125.1, 121.9, 121.8, 104.8, 104.1, 45.9, 45.5, 43.7, 42.8, 37.7, 37.2, 25.6, 23.9, 21.2. HRMS (EI-TOF) calcd for $C_{29}H_{26}N_2O$ (M^+): 418.2045, found: 418.2045.

(*E*)-5-Benzylidene-3-(4-fluorobenzyl)-3-methyl-1-(quinolin-8-yl)pyrrolidin-2-one (4i): R_{f1} 0.52, R_{f2} 0.51 (hexane/EtOAc = 2:1). Yellow oil. Isolated yield: 30.4 mg, 72%. The ratio of two isomers was 1:1.4 as determined by ^{1}H NMR. ^{1}H NMR ($CDCl_3$, 400 MHz, a mixture of two isomers) δ 8.81 (s, 2H), 7.86–7.92 (m, 2H), 7.42–7.47 (m, 2H), 7.24–7.35 (m, 6H), 7.12–7.19 (m, 2H), 7.00–7.06 (m, 6H), 6.51–6.57 (m, 2H), 6.32–6.45 (m, 6H), 6.12–6.13 (m, 2H), 5.67 (s, 1H), 5.54 (s, 1H), 2.65–3.26 (m, 8H), 1.56 (s, 3H), 1.39 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.0, 180.7, 163.0, 161.1, 150.0, 149.9, 143.7, 143.6, 138.4, 138.2, 135.7, 135.6, 134.9, 134.8, 134.3, 134.1, 133.3, 132.2, 132.1, 131.9, 131.9, 129.2, 128.8, 128.7, 128.0, 127.9, 126.1, 126.0, 125.6, 125.5, 125.0, 124.8, 121.2, 121.1, 115.2, 115.0, 114.8, 104.0, 103.3, 45.4, 45.3, 43.4, 42.4, 40.5, 39.7, 25.0, 23.3. HRMS (EI-TOF) calcd for $C_{28}H_{23}FN_2O$ (M^+): 422.1794, found: 422.1798.

(*E*)-5-Benzylidene-3-methyl-3-(naphthalen-2-ylmethyl)-1-(quinolin-8-yl)pyrrolidin-2-one (4j): R_{f1} 0.50, R_{f2} 0.48 (hexane/EtOAc = 2:1). Yellow oil. Isolated yield: 38.5 mg, 85%. The ratio of two isomers was 1:1.5 as determined by ^{1}H NMR. ^{1}H NMR ($CDCl_3$, 400 MHz, a mixture of two isomers) δ 8.85 (s, 2H), 8.13–8.23 (m, 4H), 7.93 (d, J = 8.0 Hz),

7.72–7.85 (m, 5H), 7.64–7.68 (m, 1H), 7.33–7.55 (m, 10H), 7.09–7.17 (m, 4H), 6.94–7.02 (m, 4H), 6.78–6.80 (m, 2H), 5.34 (s, 1H), 5.00 (s, 1H), 3.67–4.03 (m, 2H), 3.32–3.52 (m, 4H), 2.78–3.04 (m, 2H), 1.68 (s, 3H), 1.47 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.6, 179.8, 151.1, 144.4, 144.2, 143.1, 142.7, 136.8, 136.7, 136.2, 136.1, 134.0, 133.9, 133.5, 133.1, 133.0, 130.4, 130.2, 129.7, 129.5, 129.3, 129.2, 129.1, 128.8, 128.7, 128.6, 128.2, 128.1, 127.6, 127.5, 127.4, 126.4, 126.3, 126.0, 126.0, 125.5, 125.4, 125.3, 125.2, 125.1, 124.4, 124.3, 122.0, 121.8, 105.0, 104.1, 46.5, 46.4, 39.3, 38.3, 37.7, 37.5, 25.7, 23.8. HRMS (EI-TOF) calcd for $C_{32}H_{26}N_2O$ (M^+): 454.2045, found: 454.2048.

(*E*)-5-Benzylidene-3-methyl-3-phenyl-1-(quinolin-8-yl) pyrrolidin-2-one (4k): R_{f1} 0.60, R_{f2} 0.57 (hexane/EtOAc = 2:1). Yellow oil. Isolated yield: 25.3 mg, 65%. The ratio of two isomers was 1:1.1 as determined by ^{1}H NMR. ^{1}H NMR ($CDCl_3$, 400 MHz, a mixture of two isomers) δ 8.90 (s, 2H), 8.20–8.21 (m, 2H), 7.93–7.94 (m, 2H), 7.81–7.83 (m, 2H), 7.58–7.77 (m, 6H), 7.37–7.43 (m, 6H), 7.21–7.29 (m, 6H), 7.06–7.11 (m, 6H), 5.36 (s, 1H), 5.31 (s, 1H), 3.42–3.73 (m, 4H), 1.95 (s, 3H), 1.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.2, 178.9, 151.2, 151.1, 144.3, 144.1, 142.5, 142.4, 136.8, 136.7, 136.3, 136.2, 133.4, 133.2, 130.6, 130.4, 129.6, 129.6, 129.4, 129.4, 128.7, 128.6, 128.4, 127.7, 127.6, 127.0, 126.9, 126.7, 126.4, 126.4, 126.1, 125.4, 122.0, 122.0, 104.7, 104.6, 48.5, 48.5, 43.6, 42.6, 25.8, 25.2. HRMS (EI-TOF) calcd for $C_{27}H_{22}N_2O$ (M^+): 390.1732, found: 390.1736.

(*E*)-5-Benzylidene-3-butyl-3-phenyl-1-(quinolin-8-yl) pyrrolidin-2-one (4l): R_{f1} 0.51, R_{f2} 0.51 (hexane/EtOAc = 5:1). Yellow oil. Isolated yield: 30.6 mg, 71%. The ratio of two isomers was 1:1.1 as determined by ^{1}H NMR. ^{1}H NMR ($CDCl_3$, 400 MHz, a mixture of two isomers) δ 8.89 (dd, J_1 = 1.2 Hz, J_2 = 3.2 Hz, 1H), 8.85 (dd, J_1 = 1.2 Hz, J_2 = 3.2 Hz, 1H), 8.21 (s, 1H), 8.19 (s, 1H), 7.91–7.94 (m, 2H), 7.78–7.80 (m, 2H), 7.73–7.74 (m, 1H), 7.67–7.70 (m, 1H), 7.61–7.65 (m, 4H), 7.35–7.44 (m, 6H), 7.21–7.28 (m, 6H), 7.06–7.15 (m, 6H), 5.31 (s, 1H), 5.29 (s, 1H), 3.50–3.72 (m, 4H), 2.15–2.37 (m, 4H), 1.50–1.59 (m, 4H), 1.37–1.48 (m, 4H), 0.92–0.95 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 178.1, 177.9, 151.1, 151.0, 144.3, 144.1, 142.8, 142.8, 142.8, 137.0, 136.9, 136.1, 136.1, 133.4, 130.5, 130.4, 129.6, 129.6, 129.3, 129.3, 128.6, 128.5, 128.4, 128.4, 127.7, 127.7, 126.9, 126.8, 126.7, 126.5, 126.4, 125.3, 125.3, 122.0, 121.9, 104.3, 104.0, 52.1, 52.0, 40.5, 39.2, 38.9, 26.9, 26.8, 23.3, 23.2, 14.2, 14.1. HRMS (EI-TOF) calcd for $C_{30}H_{28}N_2O$ (M^+): 432.2202, found: 432.2204.

(*E*)-5-Benzylidene-3,3-diphenyl-1-(quinolin-8-yl) pyrrolidin-2-one (4m): R_f 0.47 (hexane/EtOAc = 5:1). Yellow solid. Isolated yield: 35.2 mg, 78%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.86 (dd, J_1 = 1.6 Hz, J_2 = 4.0 Hz, 1H), 8.19 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 7.92 (dd, J_1 = 4.0 Hz, J_2 = 6.0 Hz, 1H), 7.59–7.63 (m, 4H), 7.54–7.57 (m, 2H), 7.40–7.44 (m, 1H), 7.33–7.39 (m, 4H), 7.26–7.32 (m, 3H), 7.23–7.25 (m, 2H), 7.15–7.17 (m, 2H), 7.08–7.12 (m, 1H), 5.37 (s, 1H), 4.00–4.16 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.3, 151.1, 144.6, 144.2, 142.7, 141.9, 136.6, 136.2, 133.3, 130.4, 129.5, 129.4, 128.6, 128.4, 128.4, 128.4, 128.0, 127.8, 127.3, 126.9, 126.4, 125.5, 122.0, 104.5, 57.4, 42.5. HRMS (EI-TOF) calcd for $C_{32}H_{24}N_2O$ (M^+): 452.1889, found: 452.1881.

(*E*)-6-Benzylidene-5-(quinolin-8-yl)-5-azaspiro[2.4] heptan-4-one (4n): R_f 0.48 (hexane/EtOAc = 2:1). Yellow oil. Isolated yield: 12.7 mg, 39%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.87 (dd, J_1 = 1.6 Hz, J_2 = 4.4 Hz, 1H), 7.90 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 7.48 (dd, J_1 = 1.2 Hz, J_2 = 8.4 Hz, 1H), 7.37 (dd, J_1 = 1.2 Hz, J_2 = 7.6 Hz, 1H), 7.27–7.30 (m, 1H), 7.19 −7.23 (m, 1H), 7.54–6.57 (m, 1H), 6.42–6.45 (m, 2H), 6.35 (J = 7.2 Hz, 2H), 5.69 (s, 1H), 3.11–3.39 (m, 2H), 1.48–1.53 (m, 1H), 1.39–1.43 (m, 1H), 1.02–1.08 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.1, 150.1, 143.7, 138.8, 135.8, 135.0, 134.7, 129.5, 128.8, 128.2, 128.0, 126.0, 125.6, 124.8, 121.1, 103.1, 35.2, 21.8, 15.8, 15.4. HRMS (EI-TOF) calcd for $C_{22}H_{18}N_2O$ (M^+): 326.1419, found: 326.1423.

(*E*)-7-Benzylidene-6-(quinolin-8-yl)-6-azaspiro[3.4] octan-5-one (4o): R_f 0.50 (hexane/EtOAc = 2:1). White solid. Isolated yield: 23.1 mg, 68%. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.88 (d, J = 3.0 Hz, 1H), 8.21 (d, J = 8.5 Hz, 1H), 7.93 (dd, J_1 = 1.5 Hz, J_2 = 7.0 Hz, 1H), 7.64–7.69 (m, 2H), 7.41–7.44 (m, 1H), 7.22–7.26 (m, 2H), 7.07–7.12 (m, 3H), 5.25 (s, 1H), 3.39–3.57 (m, 2H), 2.81–2.85 (m, 1H), 2.67–2.71 (m, 1H), 2.14–2.25 (m, 3H), 2.04–2.08 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.8, 151.2, 144.2, 143.2, 137.0, 136.3, 133.4, 130.5, 129.6, 129.2, 128.3, 127.6, 126.4, 125.2, 121.9, 104.0, 45.5, 40.2, 32.3, 31.8, 16.4. HRMS (EI-TOF) calcd for $C_{23}H_{20}N_2O$ (M^+): 340.1576, found: 340.1579.

(*E*)-3-Benzylidene-2-(quinolin-8-yl)-2-azaspiro[4.4] nonan-1-one (4p): R_f 0.51 (hexane/EtOAc = 2:1). White solid. Isolated yield: 18.3 mg, 52%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.88 (dd, J_1 = 1.6 Hz, J_2 = 4.4 Hz, 1H), 8.21 (dd, J_1 = 1.6 Hz, J_2 = 8.4 Hz, 1H), 7.93 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H), 7.64–7.71 (m, 2H), 7.41–7.44 (m, 1H), 7.21–7.26 (m, 2H), 7.06–7.11 (m, 3H), 5.27 (s, 1H), 3.14–3.32 (m, 2H), 2.33–2.37 (m, 1H), 2.22–2.25 (m, 1H), 1.86–1.93 (m, 3H), 1.78–1.84 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 181.1, 151.2, 144.3, 143.5, 137.1, 136.2, 133.5, 130.4, 129.6, 129.2, 128.3, 127.6, 126.4, 125.2, 121.9, 104.1, 51.2, 41.1, 38.4, 38.0, 25.6, 25.5. HRMS (EI-TOF) calcd for $C_{24}H_{22}N_2O$ (M^+): 354.1732, found: 354.1734.

(*E*)-3-Benzylidene-2-(quinolin-8-yl)-2-azaspiro[4.5] decan-1-one (4q): R_f 0.55 (hexane/EtOAc = 2:1). White solid. Isolated yield: 33.0 mg, 90%. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.86 (d, J = 2.5 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H), 7.92 (dd, J_1 = 1.5 Hz, J_2 = 7.0 Hz, 1H), 7.64–7.68 (m, 2H), 7.40–7.43 (m, 1H), 7.23–7.26 (m, 2H), 7.07–7.14 (m, 3H), 5.25 (s, 1H), 3.10–3.31 (m, 2H), 1.89–1.95 (m, 3H), 1.82–1.84 (m, 2H), 1.69–1.72 (m, 2H), 1.38–1.52 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.9, 151.1, 144.3, 143.4, 137.1, 136.2, 133.3, 130.5, 129.6, 129.2, 128.3, 127.6, 126.4, 125.1, 121.9, 104.1, 45.3, 37.1, 33.6, 33.6, 25.4, 22.4, 22.2. HRMS (EI-TOF) calcd for $C_{25}H_{24}N_2O$ (M^+): 368.1889, found: 368.1890.

(*Z*)-3-Benzylidene-2-(quinolin-8-yl)isoindolin-1-one (6a): R_f 0.23 (hexane/EtOAc = 2:1). White solid. Isolated yield: 33.7 mg, 97%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.83 (d, J = 2.4 Hz, 1H), 7.94–7.99 (m, 2H), 7.87 (d, J = 7.6 Hz, 1H), 7.65–7.68 (m, 1H), 7.52–7.57 (m, 2H), 7.46 (d, J = 7.2 Hz, 1H), 7.25–7.29 (m, 2H), 6.79 (s, 1H), 6.65–6.68 (m, 1H), 6.50–6.54 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.2, 150.4, 144.4, 138.7, 136.1, 135.9, 134.2, 133.6, 132.3, 130.1, 129.1, 128.9, 128.4, 128.3, 128.2, 126.3, 126.1, 125.7, 124.0, 121.2, 119.7, 107.4. HRMS (EI-TOF) calcd for $C_{24}H_{16}N_2O$ (M^+): 348.1263, found: 348.126.

(*Z*)-3-Benzylidene-5-methyl-2-(quinolin-8-yl)isoindolin-1-one (6b): R_f 0.25 (hexane/EtOAc = 2:1). White solid. Isolated yield: 30.7 mg, 85%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.87 (dd, J_1 = 1.6 Hz, J_2 = 3.6 Hz, 1H), 7.97 (dd, J_1 = 1.6 Hz, J_2 =

3.6 Hz, 1H), 7.87 (d, J=7.6 Hz, 1H), 7.67 (s, 1H), 7.57 (dd, J_1=1.2 Hz, J_2=4.0 Hz, 1H), 7.47 (dd, J_1=1.2 Hz, J_2=7.6 Hz, 1H), 7.36–7.38 (m, 1H), 7.27–7.32 (m, 2H), 6.77 (s, 1H), 6.64–6.68 (m, 1H), 6.50–6.56 (m, 4H), 2.54 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.3, 150.3, 144.3, 143.0, 139.1, 136.2, 136.0, 134.2, 133.6, 130.3, 130.2, 128.9, 128.3, 128.1, 126.3, 126.0, 125.7, 123.8, 121.2, 120.0, 107.0, 22.2. HRMS (EI-TOF) calcd for $C_{25}H_{18}N_2$ (M^+): 362.1419, found: 362.1423.

(*Z*)-3-Benzylidene-6-methyl-2-(quinolin-8-yl)isoindolin-1-one (6c): R_f 0.34 (hexane/EtOAc=2:1). White solid. Isolated yield: 27.1 mg, 75%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.84 (dd, J_1=1.6 Hz, J_2=4.0 Hz, 1H), 7.95 (dd, J_1=2.0 Hz, J_2=8.4 Hz, 1H), 7.74–7.78 (m, 2H), 7.56 (dd, J_1=1.2 Hz, J_2=8.4 Hz, 1H), 7.44–7.49 (m, 2H), 7.25–7.30 (m, 2H), 6.73 (s, 1H), 6.64–6.68 (m, 1H), 6.50–6.55 (m, 4H), 2.51 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.3, 150.4, 144.5, 139.4, 136.3, 136.2, 135.8, 134.4, 133.7, 133.3, 130.1, 128.9, 128.5, 128.3, 128.2, 126.3, 125.9, 125.7, 124.0, 121.2, 119.5, 106.7, 21.6. HRMS (EI-TOF) calcd for $C_{25}H_{18}N_2O$ (M^+): 362.1419, found: 362.1418.

(*Z*)-3-Benzylidene-7-methyl-2-(quinolin-8-yl)isoindolin-1-one (6d): R_f 0.46 (hexane/EtOAc=2:1). White solid. Isolated yield: 21.0 mg, 58%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.87 (dd, J_1=1.2 Hz, J_2=3.2 Hz, 1H), 7.97 (dd, J_1=1.2 Hz, J_2=7.8 Hz, 1H), 7.70 (d, J=6.0 Hz, 1H), 7.51–7.58 (m, 2H), 7.44 (dd, J_1=1.2 Hz, J_2=6.0 Hz, 1H), 7.27–7.31 (m, 3H), 6.76 (s, 1H), 6.66 (t, J=5.6 Hz, 1H), 6.50–6.57 (m, 4H), 2.77 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.9, 150.5, 144.5, 139.3, 138.1, 136.1, 135.8, 134.4, 133.8, 131.8, 131.1, 130.1, 128.9, 128.3, 128.2, 126.3, 125.9, 125.7, 125.6, 121.2, 117.1, 106.5, 17.6. HRMS (EI-TOF) calcd for $C_{25}H_{18}N_2O$ (M^+): 362.1419, found: 362.1419.

(*Z*)-3-Benzylidene-5-methoxy-2-(quinolin-8-yl)isoindolin-1-one (6e): R_f 0.13 (hexane/EtOAc=2:1). White solid. Isolated yield: 31.7 mg, 84%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.85 (dd, J_1=1.6 Hz, J_2=4.0 Hz, 1H), 7.96 (dd, J_1=1.6 Hz, J_2=8.4 Hz, 1H), 7.89 (d, J=8.4 Hz, 1H), 7.56 (dd, J_1=1.2 Hz, J_2=8.4 Hz, 1H), 7.47 (dd, J_1=1.2 Hz, J_2=7.6 Hz, 1H), 7.32 (d, J=2.0 Hz, 1H), 7.26–7.30 (m, 2H), 7.09 (dd, J_1=2.0 Hz, J_2=8.4 Hz, 1H), 6.74 (s, 1H), 6.65–6.68 (m, 1H), 6.50–6.56 (m, 4H), 3.96 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.9, 162.5, 149.2, 143.4, 139.9, 135.0, 134.8, 133.2, 132.5, 129.0, 127.8, 127.2, 127.1, 125.2, 124.9, 124.6, 124.4, 120.2, 120.1, 115.4, 106.0, 102.7, 54.8. HRMS (EI-TOF) calcd for $C_{25}H_{18}N_2O_2$ (M^+): 378.1368, found: 378.1367.

(*Z*)-3-Benzylidene-5-fluoro-2-(quinolin-8-yl)isoindolin-1-one (6f): R_f 0.13 (hexane/EtOAc=2:1). White solid. Isolated yield: 25.3 mg, 69%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.84 (dd, J_1=1.6 Hz, J_2=4.0 Hz, 1H), 7.95–7.98 (m, 2H), 7.58 (dd, J_1=1.2 Hz, J_2=8.4 Hz, 1H), 7.53 (dd, J_1=2.0 Hz, J_2=8.4 Hz, 1H), 7.47 (dd, J_1=1.2 Hz, J_2=7.2 Hz, 1H), 7.23–7.32 (m, 3H), 6.75 (s, 1H), 6.66–6.71 (m, 1H), 6.51–6.54(m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.1, 165.8 (d, J_{C-F}=249.6 Hz), 150.4, 144.2, 141.1 (d, J_{C-F}=11.4 Hz), 135.9, 135.3 (d, J_{C-F}=3.6 Hz), 133.9, 133.1, 130.1, 128.9, 128.5, 128.1, 126.4, 126.3, 126.2 (d, J_{C-F}=10.0 Hz), 125.7, 124.4 (d, J_{C-F}=1.7 Hz), 121.3, 116.9 (d, J_{C-F}=22.9 Hz), 108.4, 106.8 (d, J_{C-F}=24.9 Hz). HRMS (EI-TOF) calcd for $C_{24}H_{15}FN_2O$ (M^+): 366.1168, found: 366.1167.

(*Z*)-3-Benzylidene-5-chloro-2-(quinolin-8-yl)isoindolin-1-one (6g): R_f 0.39 (hexane/EtOAc=2:1). White solid. Isolated yield: 25.2 mg, 66%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.83 (dd, J_1=1.6 Hz, J_2=4.0 Hz, 1H), 7.96(dd, J_1=1.6 Hz, J_2=8.4 Hz, 1H), 7.91 (d, J=8.0 Hz, 1H), 7.86 (d, J=1.6 Hz, 1H), 7.58 (dd, J_1=1.2 Hz, J_2=7.2 Hz, 1H), 7.52 (dd, J_1=1.6 Hz, J_2=6.4 Hz, 1H), 7.47 (dd, J_1=1.6 Hz, J_2=6.0 Hz, 1H), 7.27–7.31 (m, 2H), 6.77 (s, 1H), 6.66–6.71 (m, 1H), 6.53(d, J=4.8 Hz, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.2, 150.4, 144.2, 140.2, 138.7, 135.9, 135.1, 133.9, 133.1, 130.0, 129.5, 128.9, 128.6, 128.1, 126.7, 126.4, 126.3, 125.7, 125.2, 121.3, 120.1, 108.6. HRMS (EI-TOF) calcd for $C_{24}H_{15}ClN_2O$ (M^+): 382.0873, found: 382.0869.

(*Z*)-3-Benzylidene-2-(quinolin-8-yl)-5-(trifluoromethyl)-isoindolin-1-one (6h): R_f 0.29 (hexane/EtOAc=2:1). Yellow solid. Isolated yield: 25.4 mg, 61%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.82 (dd, J_1=1.6 Hz, J_2=4.0 Hz, 1H), 8.10–8.15 (m, 2H), 7.97 (dd, J_1=1.6 Hz, J_2=8.4 Hz, 1H), 7.82 (d, J=7.6 Hz, 1H), 7.60 (dd, J_1=1.2 Hz, J_2=8.4 Hz, 1H), 7.49–7.51 (m, 1H), 7.29–7.33 (m, 2H), 6.89 (s, 1H), 6.67–6.72 (m, 1H), 6.54–6.57 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.8, 150.5, 144.1, 138.9, 135.9, 135.1, 134.3 (q, J_{C-F}=32.0 Hz), 133.7, 132.9, 131.0, 130.0, 128.9, 128.7, 128.1, 126.8 (q, J_{C-F}=304.4 Hz), 126.4, 126.4, 125.9 (q, J_{C-F}=3.4 Hz), 125.7, 124.6, 121.4, 117.1 (q, J_{C-F}=4.7 Hz), 109.3. HRMS (EI-TOF) calcd for $C_{25}H_{15}F_3N_2O$ (M^+): 416.1136, found: 416.1139.

(*Z*)-3-(4-Methylbenzylidene)-2-(quinolin-8-yl)isoindolin-1-one (6i): R_f 0.29 (hexane/EtOAc=2:1). White solid. Isolated yield: 28.2 mg, 78%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.84 (dd, J_1=1.6 Hz, J_2=4.4 Hz, 1H), 7.97–7.99 (m, 2H), 7.87 (d, J=8.0 Hz, 1H), 7.65–7.69 (m, 1H), 7.53–7.61 (m, 2H), 7.46 (dd, J_1=1.2 Hz, J_2=7.2 Hz, 1H), 7.27–7.32 (m, 2H), 6.79 (s, 1H), 6.42 (d, J=7.6 Hz, 2H), 6.32 (d, J=8.0 Hz, 2H), 2.00 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.1, 150.4, 144.5, 138.8, 135.8, 135.7, 135.7, 134.4, 132.2, 130.5, 130.1, 129.0, 128.9, 128.3, 128.1, 128.0, 127.0, 125.7, 123.9, 121.2, 119.6, 107.6, 21.9. HRMS (EI-TOF) calcd for $C_{25}H_{18}N_2O$ (M^+): 362.1419, found: 362.1424.

(*Z*)-3-(4-Methoxybenzylidene)-2-(quinolin-8-yl)isoindolin-1-one (6j): R_f 0.16 (hexane/EtOAc=2:1). Pale yellow solid. Isolated yield: 35.9 mg, 95%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.86 (dd, J_1=1.6 Hz, J_2=4.0 Hz, 1H), 7.97–8.02 (m, 2H), 7.87 (d, J=7.6 Hz, 1H), 7.61–7.69 (m, 2H), 7.54 (t, J=7.6 Hz, 1H), 7.47 (dd, J_1=1.2 Hz, J_2=7.2 Hz, 1H), 7.30–7.34 (m, 2H), 6.77 (s, 1H), 6.48 (d, J=8.8 Hz, 2H), 6.07 (d, J=8.8 Hz, 2H), 3.55 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.2, 157.8, 150.3, 144.4, 138.8, 135.9, 135.5, 134.3, 132.2, 130.1, 129.4, 128.9, 128.9, 128.3, 128.2, 126.0, 125.8, 123.9, 121.3, 119.6, 111.9, 107.4, 55.1. HRMS (EI-TOF) calcd for $C_{25}H_{18}N_2O_2$ (M^+): 378.1368, found: 378.1369.

(*Z*)-3-(4-Fluorobenzylidene)-2-(quinolin-8-yl)isoindolin-1-one (6k): R_f 0.23 (hexane/EtOAc=2:1). White solid. Isolated yield: 30.7 mg, 84%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.83 (dd, J_1=1.6 Hz, J_2=4.0 Hz, 1H), 7.98–8.01 (m, 2H), 7.86 (d, J=7.6 Hz, 1H), 7.66–7.70 (m, 1H), 7.63 (dd, J_1=1.2 Hz, J_2=8.4 Hz, 1H), 7.54–7.58 (m, 1H), 7.49 (dd, J_1=1.6 Hz, J_2=7.2 Hz, 1H), 7.29–7.35 (m, 2H), 6.72 (s, 1H), 6.49–6.53 (m, 2H), 6.19–6.23 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.1, 160.9 (d, J_{C-F}=244.5 Hz), 159.7, 150.4, 144.4, 138.5, 136.5, 135.9, 134.1, 132.3, 130.1, 129.7 (d, J_{C-F}=8.4 Hz), 129.5 (d, J_{C-F}=3.2 Hz), 129.2, 128.9, 128.5, 128.3, 125.7, 124.0, 121.4, 119.7, 113.1 (d, J_{C-F}=21.2 Hz), 106.1. HRMS (EI-TOF) calcd for $C_{24}H_{15}FN_2O$ (M^+): 366.1168, found: 366.1169.

(*Z*)-3-(4-Chlorobenzylidene)-2-(quinolin-8-yl)isoindolin-1-one (6l): R_f 0.26 (hexane/EtOAc = 2:1). White solid. Isolated yield: 33.2 mg, 87%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ8.80 (d, J = 3.2 Hz, 1H), 7.97–7.99 (m, 2H), 7.83 (d, J = 7.6 Hz, 1H), 7.62–7.67 (m, 2H), 7.55 (t, J = 7.2 Hz, 1H), 7.48 (d, J = 7.2 Hz, 1H), 7.27–7.35 (m, 2H), 6.68 (s, 1H), 6.42–6.47 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.0, 150.4, 144.3, 138.4, 136.8, 135.9, 134.1, 132.4, 132.0, 131.8, 130.2, 129.3, 129.3, 128.9, 128.5, 128.3, 126.3, 125.8, 124.0, 121.4, 119.7, 105.8. HRMS (EI-TOF) calcd for $C_{24}H_{15}ClN_2O$ (M^+): 382.0873, found: 382.0878.

(*Z*)-2-(Quinolin-8-yl)-3-(thiophen-2-ylmethylene)isoindolin-1-one (6m): R_f 0.26 (hexane/EtOAc = 2:1). Yellow solid. Isolated yield: 33.2 mg, 94%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.86 (dd, J_1 = 1.6 Hz, J_2 = 4.0 Hz, 1H), 8.10 (dd, J_1 = 1.2 Hz, J_2 = 8.0 Hz, 1H), 7.98 (d, J = 7.2 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.77 (dd, J_1 = 1.2 Hz, J_2 = 8.4 Hz, 1H), 7.62–7.70 (m, 2H), 7.54–7.57 (m, 1H), 7.44–7.48 (m, 1H), 7.36 (q, J = 4.0 Hz, 1H), 6.75–6.76 (m, 2H), 6.25–6.28 (m, 1H), 5.97–5.98 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.1, 150.7, 144.9, 138.7, 136.0, 135.9, 135.7, 134.1, 132.3, 130.2, 129.2, 129.0, 128.8, 128.3, 128.0, 126.0, 125.8, 124.1, 121.5, 119.6, 99.8. HRMS (EI-TOF) calcd for $C_{22}H_{14}N_2OS$ (M^+): 354.0827, found: 354.0823.

(*Z*)-3-(Cyclopropylmethylene)-2-(quinolin-8-yl)isoindolin-1-one (6n): R_f 0.15 (hexane/EtOAc = 2:1). White solid. Isolated yield: 24.3 mg, 78%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.19 (dd, J_1 = 1.6 Hz, J_2 = 4.4 Hz, 1H), 8.47 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 8.17–8.22 (m, 2H), 8.12 (dd, J_1 = 1.2 Hz, J_2 = 7.2 Hz, 1H), 7.90–7.94 (m, 2H), 7.83–7.87 (m, 1H), 7.72–7.76 (m, 1H), 7.67–7.71 (m, 1H), 5.37–5.39 (m, 1H), 0.60–0.67 (m, 2H), 0.53–0.59 (m, 1H), 0.36–0.42 (m, 1H), 0.21–0.27 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.0, 151.2, 145.4, 138.1, 136.1, 135.4, 135.2, 131.8, 130.6, 139.2, 129.1, 128.1, 127.8, 126.2, 123.7, 121.8, 118.9, 113.9, 8.7, 8.6. HRMS (EI-TOF) calcd for $C_{21}H_{16}N_2O$ (M^+): 312.1263, found: 312.1266.

(*Z*)-3-Benzylidene-2-(quinolin-8-yl)-2,3,4,5,6,7-hexahydro-1*H*-isoindol-1-one (6o): R_f 0.16 (hexane/EtOAc = 2:1). Yellow oil. Isolated yield: 26.0 mg, 74%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.90 (dd, J_1 = 1.2 Hz, J_2 = 4.0 Hz, 1H), 7.97 (dd, J_1 = 1.6 Hz, J_2 = 4.0 Hz, 1H), 7.53 (dd, J_1 = 0.8 Hz, J_2 = 4.0 Hz, 1H), 7.35 (dd, J_1 = 1.2 Hz, J_2 = 7.2 Hz, 1H), 7.28–7.31 (m, 1H), 7.21–7.26 (m, 1H), 6.63–6.67 (m, 1H), 6.48–6.55 (m, 4H), 6.22 (s, 1H), 2.56–2.64 (m, 2H), 2.45–2.46 (m, 2H), 1.80–1.93 (m, 4H). **^{13}C** NMR ($CDCl_3$, 100 MHz) δ 171.3, 150.2, 146.3, 144.6, 140.0, 136.0, 134.5, 133.8, 130.2, 129.8, 128.9, 128.2, 127.8, 126.3, 126.1, 125.8, 121.1, 109.3, 22.3, 22.0, 21.5, 20.6. HRMS (EI-TOF) calcd for $C_{24}H_{20}N_2O$ (M^+): 352.1576, found: 352.1575.

Synthesis of 2,2-Dimethyl-5-phenyl-*N*-(quinolin-8-yl)pent-4-ynamide (7)

Preparation of ethyl 2,2-dimethylpentynoate: To a solution of freshly prepared LDA (39.3 mmol) in THF (35 mL) cooled to −78 °C was added a solution of ethyl isobutyrate (5.0 mL, 37.4 mmol) in THF (42 mL) by addition funnel over 1 h with stirring. After addition was completed, the reaction mixture stirred for 20 min at −78 °C and then warmed to 0 °C and stirred for 10 min before cooling back to −78 °C. A solution of propargyl bromide (5.0 mL, 80 wt% in toluene, 44.88 mmol) in THF (21 mL) was then added drop wise. The mixture was stirred overnight and warm to room temperature. After quenching with NH_4Cl (aq. ~60 mL) the organic layer was separated and the aqueous layer extracted with Et_2O (2×20 mL). The organic layers were combined and washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated to brown oil. This oil was purified by flash column chromatography on silica gel, eluting with hexane, to afford 2, 2-dimethyl-ethyl pentynoate.

Preparation of ethyl 2,2-dimethyl-5-phenylpentynoate: ethyl 2,2-dimethylpentynoate (4.63 g, 30 mmol) was added to a solution of dry, degassed triethylamine/acetonitrile (100 mL, 1:4, 0.3 M) and iodobenzene (6.71 mL, 60 mmol). After stirring at room temperature for 10 min, $Pd(PPh_3)_4$ (243 mg, 0.21 mmol, 0.7 mol%) and CuI (286 mg, 1.5 mmol, 5 mol%) were added. The reaction mixture was stirred at room temperature in the dark for 22 h. The crude mixture was then filtered through a plug of celite and concentrated to yellow oil. The oil was purified by flash chromatography, eluting with hexane, to afford the product as colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.37–7.39 (s, 2H), 7.25–7.28 (s, 3H), 4.16 (m, J = 3.6 Hz, 2H), 2.65 (s, 2H), 1.33 (s, 6H), 1.26 (t, J = 3.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 176.7, 131.6, 128.2, 127.7, 123.7, 86.8, 82.7, 60.7, 42.5, 30.6, 24.7, 14.3.

Preparation of 2,2-dimethyl-5-phenyl-4-pentynoic acid: To a solution of NaOH (1.77 g, 44.4 mmol) in methanol/H_2O (2:1, 205 mL, 0.1 M) was added the 2,2-dimethyl-5-phenyl ethyl pentynoate (5.11 g, 22.2 mmol). The mixture was heated at reflux (80 °C) for 4 h. After cooling back to room temperature, the crude mixture was concentrated and then diluted with H_2O (15 mL). The aqueous mixture was extracted with Et_2O (3×10 mL). The aqueous layer was acidified to pH 2 with concentrated HCl and extracted with ethyl acetate (3×20 mL). These extracts were washed with brine (~10 mL), dried over $MgSO_4$ and concentrated to white solid.

Oxalyl chloride (1.75 mL, 20 mmol) was added slowly to a stirred solution of the 2, 2-dimethyl-5-phenyl-4-pentynoic acid in CH_2Cl_2 (20 mL) and DMF (0.1 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C and another 4 h at room temperature, and evaporated in vacuo. The residue was then dissolved in toluene (5 mL), evaporated in vacuo twice, to give the crude acid chloride, which was used directly for the next step without further purification.

The acid chloride was added dropwise to a solution of 8-aminoquinoline (1.01 g, 7.0 mmol) and Et_3N (1.7 mL, 12 mmol) in CH_2Cl_2 (12 mL). The mixture was stirred overnight at room temperature. Then the mixture was diluted with CH_2Cl_2 (10 mL), washed successively with water, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/hexane (1:20, v/v), to afford 2, 2-dimethyl-5-phenyl-*N*-(quinolin-8-yl)pent-4-ynamide (**7**) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.45 (s, 1H), 8.83 (d, J = 7.6 Hz, 1H), 8.66 (dd, J_1 = 1.6 Hz, J_2 = 2.8 Hz, 1H), 8.12 (d, J = 7.6 Hz, 1H), 7.47–7.55 (m, 2H), 7.37–7.41 (m, 1H), 7.32–7.34 (m, 2H), 7.17–7.23 (m, 3H), 2.85 (s, 2H), 1.59 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3, 148.3, 138.8, 136.3, 134.6, 131.7, 128.1, 127.9, 127.7,

127.4, 123.7, 121.6, 121.5, 116.4, 86.8, 83.5, 43.8, 31.1, 25.2. HRMS (EI-TOF) calcd for $C_{22}H_{20}N_2O$ (M^+): 328.1576, found 328.1576.

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