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ARTICLE

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Amino Acids as the Nitrogen-Containing Motifs in Copper-Catalyzed Domino Synthesis of *N*-Heterocycles

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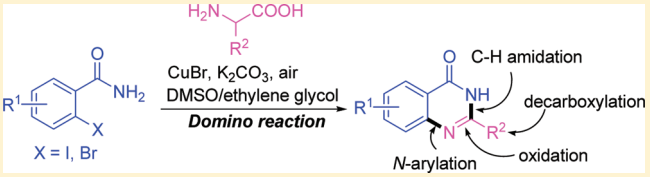
Supporting Information

ABSTRACT: A copper-catalyzed domino method for synthesis of quinazolinones has been developed using readily available α-amino acids as the nitrogen-containing motifs. The domino process underwent Ullmann-type *N*-arylation, decarboxylation, aerobic oxidation, and intramolecular addition. This method should provide a new and useful strategy for construction of *N*-heterocycles.



INTRODUCTION

Nitrogen-containing heterocycles are ubiquitous subunits of a variety of biologically active substances,[1] and they have been assigned as privileged structures in drug development because N-heterocyclic moieties often exhibit improved solubilities and can facilitate salt formation properties, both of which are important for oral absorption and bioavailability.[2] For example, quinazolinone derivatives that widely occur in natural products show various biological and pharmacological activities.[3] They exhibit many central nervous system effects, cardiovascular and antiinflammatory activity, and act as psychotropic, hypnotic, cardiotonic, and antihistamine agents.[3] They are potent antibacterial, antifungal, antiviral, antimycobacterial, and antimalarial substances.[4] Quinazolinone derivatives are also used as inhibitors of various enzymes including monoamine oxidase, aldose reductase, tumor necrosis factor α, and thymidylate synthase.[4,5] Although some methods for syntheses of quinazolinone derivatives have been developed,[3,6] the common starting materials, *o*-amino or *o*-nitro benzoic acid derivatives, often are not readily available or are difficult to prepare. In addition, the traditional single-step procedure affording only one new chemical bond needs time-consuming and costly syntheses, tedious workup, and purification of precursors as well as protection/deprotection of functional groups. Efficient assembly of complex molecules from readily available building blocks is an important task for organic chemists.[7] The domino reaction has thus emerged as a powerful tool for this purpose in which a series of chemical processes can be controlled in a one-pot operation, which potentially minimizes requisite reagents, separation processes, waste, energy, time, and cost.[8] However, the domino process terminates when some unactivated C−H bond appears on the road of cascade reactions. Recently, the direct functionalization of C−H bonds has made great progress,[9] but the domino synthesis of complex molecules combined with C−H activation still is very limited. Herein, we report an efficient domino strategy for synthesis of quinazolinone derivatives through C−H amidation.

Recently, copper-catalyzed Ullmann-type couplings have made great achievement,[10] and some *N*-heterocycles were synthesized through the couplings by other groups[11] and us[12] (including synthesis of quinazolinones by using 2-halobenzoic acid derivatives and amidines as the substrates[12a]). However, the reactions above were performed under conditions of air extrusion, and the precursors required possession of the corresponding functional groups before domino synthesis of *N*-heterocycles, so the scopes of the substrates are limited. To the best of our knowledge, there is no previous report of preparation of *N*-heterocycles through copper-catalyzed Ullmann-type coupling under air together with aerobic oxidative C−H activation. α-Amino acids are more readily available than other compounds in nature and are among the most attractive nitrogen-containing motifs.[13] Herein, a copper-catalyzed domino protocol is designed for synthesis of quinazolinones as shown in Figure 1. We hope that the domino reactions work in the following pathways under air: N-arylation, decarboxylation, aerobic oxidation, and intramolecular addition in reactions of substituted 2-halobenzamides and α-amino acids.

RESULTS AND DISCUSSION

At first, 2-bromobenzamide (**1a**) and L-valine (**2d**) were used as the model substrates to optimize reaction conditions including catalysts, bases, solvents, and reaction temperatures under air (1 atm). As shown in Table 1, four solvents were tested in the presence of 0.1 equiv of CuI and 3 equiv of K_2CO_3 (relative to amount of 2-bromobenzamide) at 120 °C under air (entries 1−4), and DMSO provided the highest yield (entry 2). We screened various copper catalysts (entries 5−10), and CuBr showed the best activity (entry 5). Effect of bases were also investigated (compare entries 5, 11−14), and K_2CO_3 provided the best result (entry 5). Interestingly, addition of small amount

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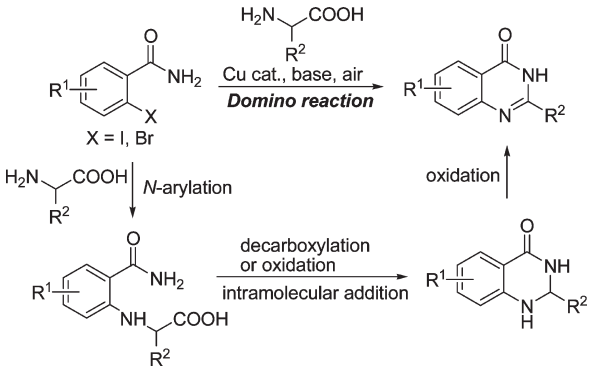


Figure 1. Our copper-catalyzed domino strategy for synthesis of quinazolinones using amino acids as nitrogen-containing motifs.

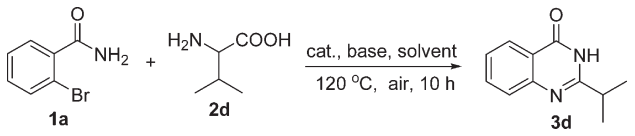
of ethylene glycol improved the reactivity of the substrates (compare entries 5, 15, and 16), and one possible reason is that ethylene glycol could promote the dissolving power of α-amino acids and act as the ligand in the Ullman-type *N*-arylation.

We investigated the scope of copper-catalyzed domino reactions of substituted 2-halobenzamides with α-amino acids under the optimized conditions (using 10 mol % of CuBr as the catalyst, 3 equiv of K_2CO_3 as the base (relative to amount of 2-halobenzamides), and DMSO/ethylene glycol as the solvent). As shown in Table 2, the corresponding quinazolinones were obtained in moderate to good yields for various examined substrates at 110−120 °C. For substituted 2-halobenzamides, the aryl iodides and bromides almost exhibited similar yields (compare entries 6 and 20), but aryl chloride did not work. The 2-halobenzamides containing electron-withdrawing groups provided lower yields than ones containing electron-donating groups. For α-amino acids, their differences of reactivity depended on the chains of α-amino acids, and the α-amino acids containing the bulky chains afforded higher yields. One possible reason is that the imine intermediates (see **II** and **IV** in Scheme 2) containing the bulky chains (stronger electron-donating power) are of higher stability during domino reactions. Unexpectedly, the domino reaction for glycine needed using ethylene glycol as the solvent (entry 1). The copper-catalyzed domino reactions of substituted 2-halobenzamides with α-amino acids showed the good tolerance of the functional groups in the substrates including the amide, nitro, C−Cl, and ether bond.

We explored the copper-catalyzed domino reaction mechanism by performing the following control experiments as shown in Scheme 1. Copper-catalyzed Ullmann-type coupling of 2-bromobenzamide with α-aminobutanoic acid (**2b**) provided *N*-arylation product (**4**) in 79% yield under nitrogen atmosphere (extrusion of air) (Scheme 1A), and only a small amount of quinazoline was observed (6% yield). Compound **4** transformed into 2-ethylquinazolin-4(3*H*)-one (**3b**) in 52% yield under our standard conditions (Scheme 1B).

A possible mechanism for domino reactions of substituted 2-halobenzamides with α-amino acids is suggested in Scheme 2. The Ullmann-type coupling of 2-halobenzamide (**1**) with α-amino acid (**2**) first provides **I**. Then, intermediate **I** can undergo two pathways (pathways A and B). For pathway A, aerobic oxidation of **I** gives **II**, intramolecular cycloaddition of **II** provides **III**,[14] and decarboxylation of **III** affords the target product (**3**). For pathway B, decarboxylation of **I** first occurs to lead to **IV**, and intramolecular cycloaddition of **IV** yields **V**.[14] Finally, aerobic oxidation of **V** provides **3**.

Table 1. Copper-Catalyzed Domino Reaction of 2-Bromobenzamide (1a) with L-Valine (2d) Leading to 2-Isopropylquinazolin-4(3*H*)-one under Air: Optimization of Conditions[a]

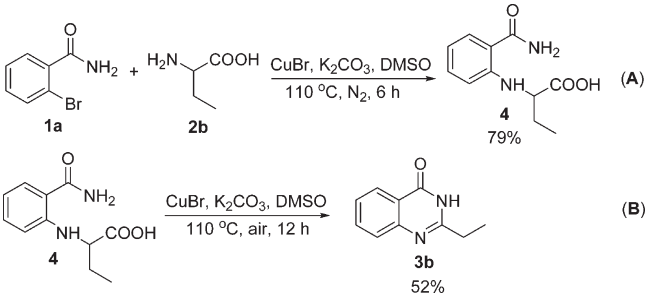


1a 2d 3d

entry	cat.	base	solvent	yield (%)[b]
1	CuI	K_2CO_3	DMF	40
2	CuI	K_2CO_3	DMSO	44
3	CuI	K_2CO_3	ethylene glycol	trace
4	CuI	K_2CO_3	DMA	0
5	CuBr	K_2CO_3	DMSO	60
6	$CuCl_2$	K_2CO_3	DMSO	48
7	Cu_2O	K_2CO_3	DMSO	38
8	CuO	K_2CO_3	DMSO	45
9	$Cu(OAc)_2$	K_2CO_3	DMSO	37
10	CuCl	K_2CO_3	DMSO	51
11	CuBr	Cs_2CO_3	DMSO	42
12	CuBr	K_3PO_4	DMSO	trace
13	CuBr	KOH	DMSO	10
14	CuBr	Na_2CO_3	DMSO	trace
15	CuBr	K_2CO_3	DMSO/ethylene glycol (20:1)	64
16	**CuBr**	**K_2CO_3**	**DMSO/ethylene glycol (75:1)**	**72**

[a] Reaction conditions: 2-bromobenzamide (**1a**) (0.3 mmol), L-valine (**2d**) (0.9 mmol), catalyst (0.03 mmol), base (0.9 mmol), solvent (3 mL) under air. [b] Isolated yield.

Scheme 1. (A) Copper-Catalyzed Ullmann-Type Coupling of 2-Bromobenzamide (1a) with α-Aminobutanoic Acid (2b) To Form *N*-Arylation Product (4) under Nitrogen Atmosphere. (B) Aerobic Oxidation and Addition of 4 To Yield 2-Ethylquinazolin-4(3*H*)-one (3b) under Our Standard Conditions



CONCLUSION

We have developed a simple and efficient copper-catalyzed domino method for construction of quinazolinones. The protocol uses cheap and readily available CuBr as the catalyst, substituted 2-halobenzamides and α-amino acids as the starting materials, and economical and environmentally friendly air as the oxidant, and the corresponding quinazolinones were obtained in moderate to good yields. The domino reactions underwent copper-catalyzed Ullmann-type coupling, aerobic oxidation, C−H amidation, and decarboxylation process. To the best of our knowledge, this is the first example of constructing *N*-heterocycles via Ullmann-type

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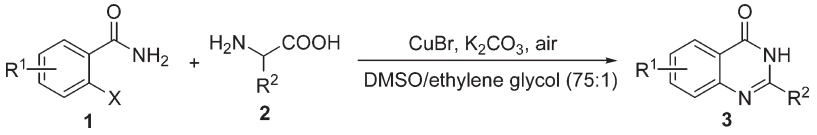
Table 2. Copper-Catalyzed Domino Synthesis of Quinazolinones[a]



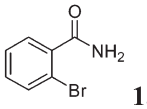
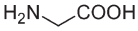
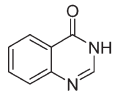
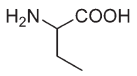
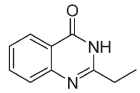
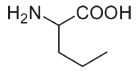
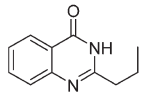
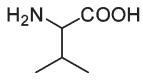
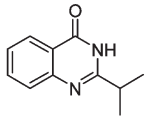
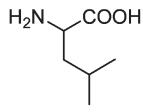
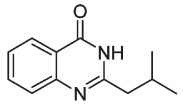
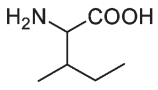
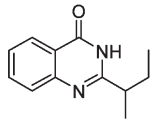
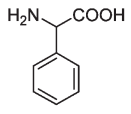
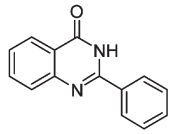
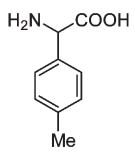
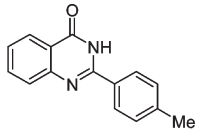
entry	1	2	3 (temp, time)[b]
1	 **1a**	 **2a**	 49% (120 °C, 12 h) **3a**[c]
2	**1a**	 **2b**	 40% (120 °C, 10 h) **3b**
3	**1a**	 **2c**	 50% (120 °C, 8 h) **3c**
4	**1a**	 **2d**	 72% (120 °C, 10 h) **3d**
5	**1a**	 **2e**	 70% (120 °C, 6 h) **3e**
6	**1a**	 **2f**	 66% (120 °C, 8 h) **3f**
7	**1a**	 **2g**	 72% (110 °C, 14 h) **3g**
8	**1a**	 **2h**	 70% (110 °C, 14 h) **3h**

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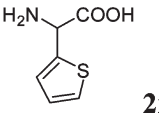
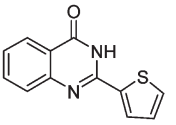
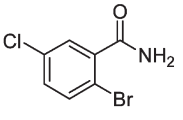
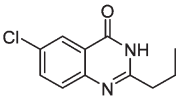
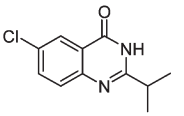
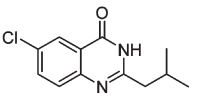
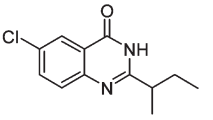
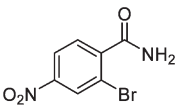
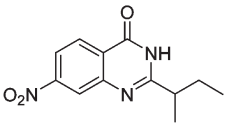
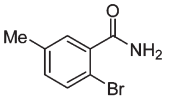
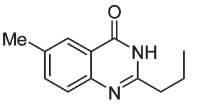
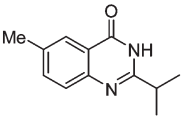
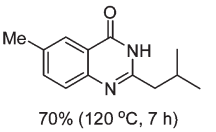
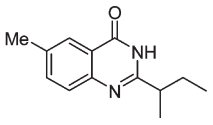
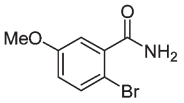
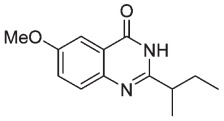
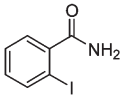
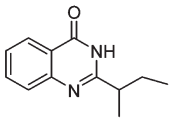
Table 2. Continued

entry	1	2	3 (temp, time)[b]
9	**1a**	 **2i**	 70% (110 °C, 14 h) **3i**
10	 **1b**	**2c**	 52% (120 °C, 7 h) **3j**
11	**1b**	**2d**	 61% (120 °C, 7 h) **3k**
12	**1b**	**2e**	 56% (120 °C, 7 h) **3l**
13	**1b**	**2f**	 60% (120 °C, 7 h) **3m**
14	 **1c**	**2f**	 52% (120 °C, 9 h) **3n**
15	 **1d**	**2c**	 40% (120 °C, 7 h) **3o**
16	**1d**	**2d**	 51% (120 °C, 7 h) **3p**
17	**1d**	**2e**	 70% (120 °C, 7 h) **3q**

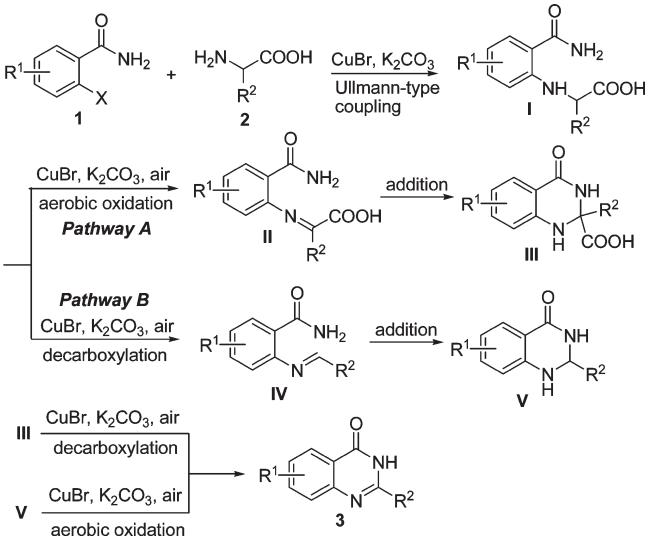
dx.doi.org/10.1021/jo2002227 |*J. Org. Chem.* 2011, 76, 3846–3852

Table 2. Continued

entry	1	2	3 (temp, time)[b]
18	**1d**	**2f**	 70% (120 °C, 7 h) **3r**
19	 **1e**	**2f**	 52% (110 °C, 15 h) **3s**
20	 **1f**	**2f**	 67% (120 °C, 8 h) **3f**

[a] Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), CuBr (0.03 mmol), K_2CO_3 (0.9 mmol), DMSO (2.96 mL), ethylene glycol (0.04 mL) under air. [b] Isolated yield (reaction temperature and time in parentheses). [c] Using ethylene glycol as the solvent.

Scheme 2. Possible Mechanism for Synthesis of Quinazolinone Derivatives



coupling under air and aerobic oxidative C−H functionalization. This method should provide a new and useful strategy for construct of *N*-heterocycles.

EXPERIMENTAL SECTION

General Procedure for Domino Reactions of Substituted 2-Halobenzamides with α-Amino Acids Leading to Quinazolinones. A 25 mL flask equipped with a magnetic stirring bar was charged with substituted 2-halobenzamide (**1**) (0.3 mmol), α-amino acid (**2**) (0.6 mmol), K_2CO_3 (0.9 mmol, 124 mg), and CuBr (0.03 mmol, 4.3 mg) in DMSO (2.96 mL) and ethylene glycol (0.04 mL). The mixture was allowed to stir under air (1 atm) at 110−120 °C for 6−15 h (see Table 2 for details). After completion of the reaction, the resulting solution was cooled to room temperature and filtered, and the solvent of filtrate was removed with the aid of a rotary evaporator. The residue was purified by column chromatography on silica gel using petroleum ether/ethyl acetate (3:1 to 1:1) as eluent to provide the desired product (**3**).

Quinazolinone-4(3H)-one (***3a***)[15]. Eluent: petroleum ether/ethyl acetate (1:2). Yield: 21 mg (49%). White solid. ^{1}H NMR (DMSO-d_6, 600 Mz): δ 12.23 (s, br, 1H), 8.13 (d, 1H, J = 8.3 Hz), 8.1 (s, 1H), 7.82 (t, 1H, J = 7.6 Hz), 7.67 (d, 1H, J = 8.3 Hz), 7.53 (t, 1H, J = 7.6 Hz). ^{13}C NMR (DMSO-d_6, 150 MHz): δ 161.2, 149.3, 145.9, 134.8, 127.8, 127.3, 126.3, 123.2. ESIMS: $[M - H]^-$ m/z 145.3.

2-Ethylquinazolinone-4(3H)-one (***3b***)[16]. Eluent: petroleum ether/ethyl acetate (1:2). Yield: 21 mg (40%). White solid. Mp: 229−231 °C (lit.[16] mp 231−233 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 11.96 (s, br, 1H), 8.29 (d, 1H, J = 7.4 Hz), 7.80−7.70 (m, 2H), 7.46 (t, 1H, J = 8.3 Hz), 2.85 (q, 2H, J = 5.7 Hz), 1.46 (t, 3H, J = 7.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.7, 158.0, 149.9, 135.1, 127.6, 126.7, 126.6, 120.9, 29.5, 11.9. ESIMS: $[M + H]^+$ m/z 175.1, $[M + Na]^+$ m/z 197.1.

2-Propylquinazolinone-4(3H)-one (***3c***)[12a]. Eluent: petroleum ether/ethyl acetate (1:1). Yield: 28 mg (50%). White solid. Mp: 200−202 °C (lit.[12a] mp 198−200 °C). ^{1}H NMR (DMSO-d_6, 600 Mz): δ 12.18 (s, br, 1H), 8.11 (d, 1H, J = 7.9 Hz), 7.78 (t, 1H, J = 7.2 Hz), 7.62 (d, 1H, J = 7.9 Hz), 7.47 (d, 1H, J = 7.2 Hz), 2.60 (t, 2H, J = 7.9 Hz), 1.83−1.74 (m, 2H), 0.96 (t, 3H, J = 7.2 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 161.8, 157.3, 148.9, 134.2, 126.8, 125.8, 125.6, 120.8, 36.3, 20.2, 13.5. ESIMS: $[M + H]^+$ m/z 189.0, $[M + Na]^+$ m/z 211.0.

2-(1-Methylethyl)quinazolinone-4(3H)-one (***3d***)[17]. Eluent: petroleum ether/ethyl acetate (1:1). Yield: 41 mg (72%). White solid. Mp: 225−228 °C (lit.[17] mp 212−214 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 11.85 (s, br, 1H), 8.30 (d, 1H, J = 7.6 Hz), 7.79−7.70 (m, 2H), 7.46 (t, 1H, J = 6.9 Hz), 3.11−3.02 (m, 1H), 1.46 (d, 6H, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.7, 161.3, 149.9, 135.0, 127.7, 126.6, 121.1, 35.3, 20.7. ESIMS: $[M + H]^+$ m/z 189.1

2-(2-Methylpropyl)quinazolinone-4(3H)-one (***3e***)[18]. Eluent: petroleum ether/ethyl acetate (1:1). Yield: 42 mg (70%). White solid. Mp:

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194−196 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 12.24 (s, br, 1H), 8.29 (d, 1H, J = 7.9 Hz), 7.79−7.70 (m, 2H), 7.46 (t, 1H, J = 7.9 Hz), 2.68 (d, 2H, J = 7.6 Hz), 2.42−2.28 (m, 1H), 1.07 (d, 6H, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.8 156.7, 149.8, 135.1, 127.6, 126.6, 126.5, 120.8, 45.1, 28.3, 22.7. ESIMS: $[M + H]^+$ m/z 203.1, $[M + Na]^+$ m/z 225.0.

2-(1-Methylpropyl)quinazolinone-4(3H)-one (**3f**)[19]. Eluent: petroleum ether/ethyl acetate (1:1). Yield: 40 mg (66%) using 2-bromobenzamide as the substrate; 41 mg (67%) using 2-iodobenzamide as the substrate. White solid. Mp: 171−173 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.15 (s, br, 1H), 8.11 (d, 1H, J = 7.9 Hz), 7.78 (t, 1H, J = 6.9 Hz), 7.63 (d, 1H, J = 8.3 Hz), 7.47 (t, 1H, J = 8.3 Hz), 2.75−2.63 (m, 1H), 1.89−1.75 (m, 1H), 1.65−1.51 (m, 1H), 1.26 (d, 3H, J = 6.9 Hz), 0.86 (t, 3H, J = 7.6 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 162.0, 161.0, 148.9, 134.2, 127.0, 126.0, 125.7, 121.0, 40.4, 27.5, 18.2, 11.7. ESIMS: $[M + H]^+$ m/z 203.1.

2-Phenylquinazolin-4(3H)-one (**3g**)[12a]. Eluent: petroleum ether/ethyl acetate (3:1). Yield: 48 mg (72%). White solid. Mp: 235−237 °C (lit.[12a] mp 236−237 °C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.54 (s, br, 1H), 8.21−8.16 (m, 3H), 7.85 (t, 1H, J = 7.6 Hz), 7.75(d, 1H, J = 8.3 Hz), 7.63−7.50 (m, 4H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 162.2, 152.3, 148.7, 134.6, 132.7, 131.3, 128.6, 127.7, 127.5, 126.5, 125.8, 121.0. ESIMS: $[M + H]^+$ m/z 223.2.

2-p-Tolylquinazolin-4(3H)-one (**3h**)[20]. Eluent: petroleum ether/ethyl acetate (3:1). Yield: 50 mg (70%). White solid. Mp: 261−263 °C (lit.[20] mp 261−263 °C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.48 (s, br, 1H), 8.18−8.10 (m, 3H), 7.83 (t, 1H, J = 7.9 Hz),.7.74 (d, 1H, J = 7.2 Hz), 7.51 (t, 1H, J = 6.5 Hz), 7.35 (d, 2H, J = 6.5 Hz), 2.40 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 162.3, 152.2, 148.8, 141.4, 134.5, 129.9, 129.2, 127.7, 127.3, 126.4, 125.9, 120.1, 21.0. ESIMS: $[M - H]^-$ m/z 237.6.

2-(2-Thienyl)quinazolinone-4(3H)-one (**3i**)[21]. Eluent: petroleum ether/ethyl acetate (3:1). Yield: 48 mg (70%). White solid. Mp: 275−276 °C (lit.[21] mp 275−276 °C). ^{1}H NMR (DMSO-d_6, 300 Mz): δ 12.70 (s, br, 1H), 8.28 (d, 1H, J = 3.4 Hz), 8.17 (d, 1H, J = 7.9 Hz), 7.92 (d, 1H, J = 4.8 Hz), 7.85 (t, 1H, 7.2 Hz), 7.70 (d, 1H, J = 8.3 Hz), 7.53 (t, 1H, 7.2 Hz), 7.29 (t, 1H, J = 3.8 Hz), ^{13}C NMR (DMSO-d_6, 75 MHz): δ 161.8, 148.6, 147.8, 137.4, 134.7, 132.2, 129.4, 128.5, 126.9, 126.3, 126.3, 12.9. ESIMS: $[M + H]^+$ m/z 229.2.

6-Chloro-2-(2-methylpropyl)quinazolinone-4(3H)-one (**3j**)[12a]. Eluent: petroleum ether/ethyl acetate (1:1). Yield: 35 mg (52%). White solid. Mp: 248−250 °C (lit.[12a] mp 248−250 °C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.34 (s, br, 1H), 8.01 (d, 1H, J = 2.4 Hz), 7.79 (dd, 1H, J = 2.8, 2.4 Hz), 7.62 (d, 1H, J = 8.6 Hz), 2.61−2.50 (m, 2H), 1.81−1.68 (m, 2H), 0.94 (t, 3H, J = 7.8 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 160.8 158.0, 147.5, 134.3, 130.1, 129.0, 124.6, 122.0, 36.3, 20.1, 13.4. ESIMS: $[M + H]^+$ m/z 223.1.

6-Chloro-2-(1-methylethyl)quinazolinone-4(3H)-one (**3k**). Eluent: petroleum ether/ethyl acetate (1:1). Yield: 41 mg (61%). White solid. Mp: 245−247 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.33 (s, br, 1H), 8.02 (d, 1H, J = 2.4 Hz), 7.80 (dd, 1H, J = 2.4, 2.8 Hz), 7.64 (d, 1H, J = 8.6 Hz), 2.89 (m, 1H), 1.26 (d, 6H, J = 6.9 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 162.2, 161.0, 147.6, 134.4, 130.2, 129.3, 124.7, 122.2, 33.3, 20.3. HR-MS: $[M + H]^+$ m/z calcd for $C_{11}H_{12}ClN_2O$ 223.0638, found 223.0639.

6-Chloro-2-(2-methylpropyl)quinazolinone-4(3H)-one (**3l**). Eluent: petroleum ether/ethyl acetate (1:2). Yield: 40 mg (56%). Yellow solid. Mp: 228−230 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.36 (s, br, 1H), 8.02 (d, 1H, J = 2.4 Hz), 7.80 (dd, 1H, J = 2.4, 2.4 Hz), 7.63 (d, 1H, J = 8.6 Hz), 2.48 (d, 2H, J = 7.2 Hz), 2.25−2.11 (m, 1H), 0.93 (d, 6H, J = 6.5 Hz). ^{13}C (DMSO-d_6, 75 MHz): δ 160.9, 157.4, 147.6, 134.4, 130.1, 129.1, 124.7, 122.0, 43.3, 27.0, 22.1. HR-MS: $[M + H]^+$ m/z calcd for $C_{12}H_{14}ClN_2O$ 237.0795, found 237.0800.

6-Chloro-2-(1-methylpropyl)quinazolinone-4(3H)-one (**3m**). Eluent: petroleum ether/ethyl acetate (1:1). Yield: 43 mg (60%). Yellow solid. Mp: 201−203 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.33 (s, br, 1H), 8.02 (d, 1H, J = 2.4 Hz), 7.80 (dd, 1H, J = 2.8, 2.4 Hz), 7.64 (d, 1H, J = 8.9 Hz), 2.74−2.63 (m, 1H), 1.87−1.73 (m, 1H), 1.64−1.50 (m, 1H), 1.25 (d, 3H, J = 6.9 Hz), 0.85 (t, 3H, J = 7.6 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 161.6, 161.0, 147.6, 134.4, 130.2, 129.2, 40.4, 27.5, 18.1, 11.6. HR-MS: $[M + H]^+$ m/z calcd for $C_{12}H_{14}ClN_2O$ 237.0795, found 237.0796.

2-sec-Butyl-7-nitroquinazolin-4(3H)-one (**3n**). Eluent: petroleum ether/ethyl acetate (1:1). Yield: 38 mg (52%). Light yellow solid. Mp: 208−210 °C. ^{1}H NMR (DMSO-d_6, 600 Mz): δ 12.60 (s, br, 1H), 8.35 (d, 2H, J = 8.6 Hz), 8.22 (dd, 1H, J = 2.1, 2.1 Hz), 2.82−2.70 (m, 1H), 1.93−1.80 (m, 1H), 1.70−1.56 (m, 1H), 1.31 (d, 3H, J = 6.5 Hz), 0.91 (t, 3H, J = 6.9 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 163.6, 161.0, 151.2, 149.3, 128.1, 125.3, 121.9, 119.6, 40.4, 27.5, 18.1, 11.6. ESIMS: $[M + H]^+$ m/z 248.0.

6-Methyl-2-propylquinazolinone-4(3H)-one (**3o**)[22]. Eluent: petroleum ether/ethyl acetate (1:1). Yield: 24 mg (40%). White solid. Mp: 225−227 °C (lit.[22] mp 244.3−244.8 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 11.90 (s, br, 1H), 8.07 (d, 1H, J = 1.7 Hz), 7.60 (dd, 2H, J = 0.7, 1.7 Hz), 2.77 (t, 2H, J = 7.9 Hz), 2.50 (s, 3H), 1.98−1.86 (m, 2H), 1.08 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 164.6, 156.2, 147.8, 136.8, 136.6, 127.3, 125.9, 120.5, 38.0, 21.6, 21.3, 14.1. ESIMS: $[M + H]^+$ m/z 203.2.

6-Methyl-2-(1-methylethyl)quinazolinone-4(3H)-one (**3p**)[22]. Eluent: petroleum ether/ethyl acetate (1:1). Yield: 31 mg (51%). White solid. Mp: 237−239 °C (lit.[22] mp 244.3−244.8 °C). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.05 (s, br, 1H), 7.88 (s, 1H), 7.59 (dd, 1H, J = 1.7, 2.1 Hz), 7.51 (d, 1H, J = 8.3 Hz), 2.94−2.80 (m, 1H), 2.43 (s, 3H), 1.25 (d, 6H, J = 6.9 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 161.9, 160.6, 146.9, 135.5, 126.8, 125.0, 120.7, 33.2, 20.8, 20.4. ESIMS: $[M + H]^+$ m/z 203.2.

6-Methyl-2-(2-methylpropyl)quinazolinone-4(3H)-one (**3q**). Eluent: petroleum ether/ethyl acetate (1:1). Yield: 45 mg (70%). White solid. Mp: 225−227 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.07 (s, br, 1H), 7.87 (s, 1H), 7.60 (dd, 1H, J = 2.1, 2.1 Hz), 7.50 (d, 1H, J = 8.3 Hz), 2.46 (d, 2H, J = 7.2 Hz), 2.42 (s, 3H), 2.24−2.11 (m, 1H), 0.93 (d, 6H, J = 6.5 Hz). ^{13}C (DMSO-d_6, 75 MHz): δ 161.8, 155.8, 146.9, 135.5, 135.4, 126.7, 125.0, 120.5, 43.3, 27.0, 22.1, 20.8. HR-MS $[M + H]^+$ m/z calcd for $C_{13}H_{17}N_2O$ 217.1341, found 217.1343.

6-Methyl-2-(1-methylpropyl)quinazolinone-4(3H)-one (**3r**). Eluent: petroleum ether/ethyl acetate (1:1). Yield: 45 mg (70%). White solid. Mp: 209−211 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.04 (s, br, 1H), 7.90 (s, 1H), 7.60 (d, 1H, J = 8.3 Hz), 7.51 (d, 1H, J = 8.3 Hz), 2.71−2.60 (m, 1H), 2.43 (s, 3H), 1.86−1.72 (m, 1H), 1.63−1.49 (m, 1H), 1.24 (d, 3H, J = 6.9 Hz), 0.84 (t, 3H, J = 7.2 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 161.9, 161.0, 146.9, 135.5, 135.4, 126.8, 125.0, 126.0, 40.3, 27.5, 20.7, 18.2, 11.7. HR-MS: $[M + H]^+$ m/z calcd for $C_{13}H_{17}N_2O$ 217.1341, found 217.1341.

2-sec-Butyl-6-methoxyquinazolin-4(3H)-one (**3s**). Eluent: petroleum ether/ethyl acetate (1:1). Yield: 36 mg (52%). White solid. Mp: 197−199 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 12.09 (s, br, 1H), 7.57 (d, 1H, J = 8.9 Hz), 7.48 (d, 1H, J = 2.4 Hz), 7.37 (dd, 1H, J = 2.1, 2.1 Hz), 3.86 (s, 3H), 2.71−2.59 (m, 1H), 1.86−1.71 (m, 1H), 1.63−1.49 (m, 1H), 1.23 (d, 3H, J = 6.6 Hz), 0.84 (t, 3H, J = 7.2 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 161.8, 158.5, 157.2, 143.4, 128.6, 123.7, 121.6, 105.6, 55.5, 40.2, 27.5, 18.2, 11.7. ESIMS: $[M + H]^+$ m/z 233.1.

■ ASSOCIATED CONTENT

Supporting Information. General experimental procedures, characterization data, and ^{1}H and ^{13}C NMR spectra of these synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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