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ARTICLE

Rapid assembly of quinazolinone scaffold via copper-catalyzed tandem reaction of 2-bromobenzamides with aldehydes and aqueous ammonia: application to the synthesis of alkaloid tryptanthrin

Cite this: DOI: 10.1039/xoxxoooooox

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

www.rsc.org/

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An efficient and practical procedure for the preparation of 2-substituted and 2,3-disubstituted quinazolinones was achieved through copper-catalyzed tandem reaction of 2-bromobenzamides with aldehydes and aqueous ammonia under air. Control experimental results indicated that this tandem reaction is triggered by a copper-catalyzed direct amination of 2-bromobenzamides with aqueous ammonia, followed by cyclocondensation and oxidative aromatization. As an application, this novel methodology provides a concise and practical one-pot route to the synthesis of alkaloid tryptanthrin.

1. Introduction

Quinazolinone derivatives, as an important class of six-membered nitrogen-containing heterocyclic skeletons, have been extensively studied since they are present in many naturally occurring alkaloids and synthetic drug candidates (Figure 1),[1] and also exhibit significant antitumor,[2] anticonvulsant,[3] antifungal,[4] antitubercular,[5] and antimicrobial[6] activities.

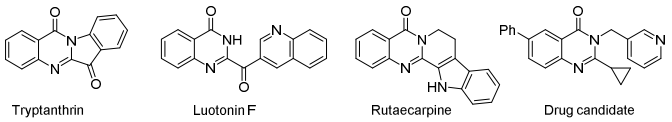


Figure 1. Selected naturally occurring alkaloids and drug candidate with quinazolinone skeleton.

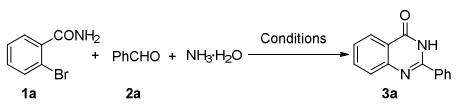
In view of their importance, many approaches have been developed for the preparation of quinazolinone derivatives. Among them, typical synthetic approaches mostly involve the acid- or base-promoted condensation of carboxylic acid derivatives with 2-aminobenzoic acids or their derivatives[7] and the cascade condensation/oxidation sequence of aldehydes with 2-aminobenzamides.[8] While these approaches are efficient, they usually suffer from difficult-to-prepare starting materials, use of stoichiometric or large excess oxidants, low yields, or harsh reaction conditions. Therefore, the development of more practical and efficient approaches toward quinazolinone derivatives remains an attractive task for organic chemists.

Recently, transition-metal-catalyzed reactions have emerged as versatile tools for the construction of quinazolinones. For example, palladium-catalyzed carbonylation/cyclization cascades turned out to be an efficient approach toward quinazolinone derivatives.[9] Moreover, these compounds can also be conveniently prepared through copper-catalyzed tandem reactions of 2-halobenzoic acid derivatives with amidines, α-amino acids, benzylamines, or amides.[10] As a continuation of our recent studies on the synthesis of *N*-heterocycles,[11] we found that copper-catalyzed tandem reaction of 2-bromobenzamides with aldehydes and aqueous ammonia, being more readily available and less expensive, offers a more practical and efficient route toward quinazolinone derivatives. Herein, we wish to disclose the details of our research work.

2. Results and discussion

Initially, 2-bromobenzamide (**1a**), benzaldehyde (**2a**), and aqueous ammonia were employed as model substrates to optimize the reaction parameters such as catalysts, bases, ligands, solvents, and temperature. As listed in Table 1, five copper salts were screened by using DMSO as solvent and K_2CO_3 as base at 100 °C under air atmosphere (entries 1-5). Among them, CuBr exhibited slightly higher catalytic activity (entry 5). We next examined different bases (entries 5-8), and Cs_2CO_3 provided the highest yield (entry 6). When DMF and dioxane were used to replace DMSO as the reaction medium, the yields of **3a** decreased significantly (entries 6 vs 9-10). The effect of ligands on this reaction was also investigated (entries 6 and 11-13), and L-proline proved to be optimal (entry 11). Increasing the amount of **2a** from 1.5 to 2.0 equiv (relative to **1a**) gave **3a** in a higher yield (72%) (entry 11 vs 14). In addition, the reaction temperatures higher or lower than 100 °C resulted in decreased yields of **3a** (entries 14-16).

Table 1. Optimization for the synthesis of 2-phenylquinazolin-4(3*H*)-one (**3a**)[a]



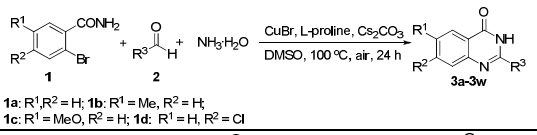
Entry	Catalyst	Base	Ligand	Solvent	T (°C)	Yield (%)[b]
1	$Cu(OAc)_2$	K_2CO_3	—	DMSO	100	53
2	$CuCl_2$	K_2CO_3	—	DMSO	100	52
3	CuCl	K_2CO_3	—	DMSO	100	52
4	CuI	K_2CO_3	—	DMSO	100	50
5	CuBr	K_2CO_3	—	DMSO	100	56
6	CuBr	Cs_2CO_3	—	DMSO	100	60
7	CuBr	K_3PO_4	—	DMSO	100	52
8	CuBr	NaOAc	—	DMSO	100	14
9	CuBr	Cs_2CO_3	—	DMF	100	23
10	CuBr	Cs_2CO_3	—	dioxane	100	0
11	CuBr	Cs_2CO_3	L-proline	DMSO	100	64
12	CuBr	Cs_2CO_3	DMEDA	DMSO	100	58
13	CuBr	Cs_2CO_3	1,10-phen	DMSO	100	48
14[c]	**CuBr**	**Cs_2CO_3**	**L-proline**	**DMSO**	**100**	**72**
15[c]	CuBr	Cs_2CO_3	L-proline	DMSO	120	65
16[c]	CuBr	Cs_2CO_3	L-proline	DMSO	80	66

[a]Unless otherwise noted, the reactions were carried out with **1a** (0.4 mmol), **2a** (0.6 mmol), aqueous ammonia (0.5 mL), base (0.8 mmol), catalyst (0.04 mmol), ligand (0.08 mmol), and solvent (1.5 mL) at 100 °C in a sealed tube under air for 24 h. [b]Isolated yield of **3a**. [c]**2a** (0.8 mmol) was used.

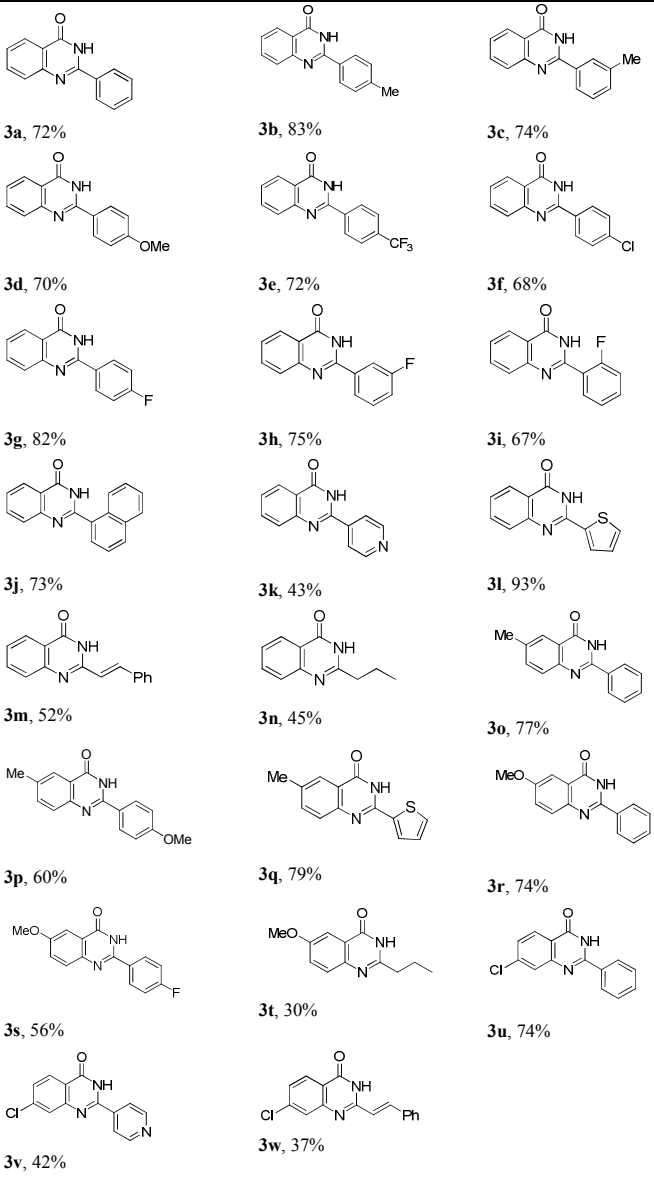
With the optimized conditions (Table 1, entry 14) in hand, the scope and limitation of this copper-catalyzed tandem reaction leading to 2-substituted quinazolinones were investigated and the results are shown in Table 2. First, aryl-substituted aldehydes bearing either electron-donating or electron-withdrawing groups on the aromatic ring (including: Me, MeO, CF_3, Cl, F) reacted very well with **1a** and aqueous ammonia to provide the desired products **3a**-**3i** in 67-83% yields (entries 1-9). And it was found that the steric hindrance of aromatic aldehydes has slightly influence on the outcome of the reactions (entries 7-9). With 1-naphthaldehyde, quinazolinone **3j** was formed in 73% yield (entry 10). Heteroaryl aldehydes also underwent this tandem reaction smoothly, and it was observed that electron-rich thiophene-2-carbaldehyde provided the corresponding product in yield higher than that of electron-poor pyridine-4-carbaldehyde (entries 11-12). In addition, both alkenyl- and alkyl-substituted aldehydes were well compatible with the reaction conditions to generate the desired products **3m** and **3n** in moderate yields (entries 13-14). Next, 2-bromobenzamides **1** with different substitution patterns were investigated under our optimized reaction conditions, and it was observed that the tandem reactions of amides **1b**-**1d** with different aldehydes **2** and aqueous ammonia proceeded smoothly to afford 2-substituted quinazolinones **3o**-**3w** in yields ranging from 30-79% (entries 15-23).

Having accomplished an efficient protocol for the synthesis of 2-substituted quinazolinones through the tandem reaction of 2-bromobenzamides with aldehydes and aqueous ammonia, we were then interested in whether this protocol could be

Table 2. Synthesis of 2-substituted quinazolinones **3a**-**3w**[a,b]



1a: R^1,R^2 = H; **1b**: R^1 = Me, R^2 = H; **1c**: R^1 = MeO, R^2 = H; **1d**: R^1 = H, R^2 = Cl

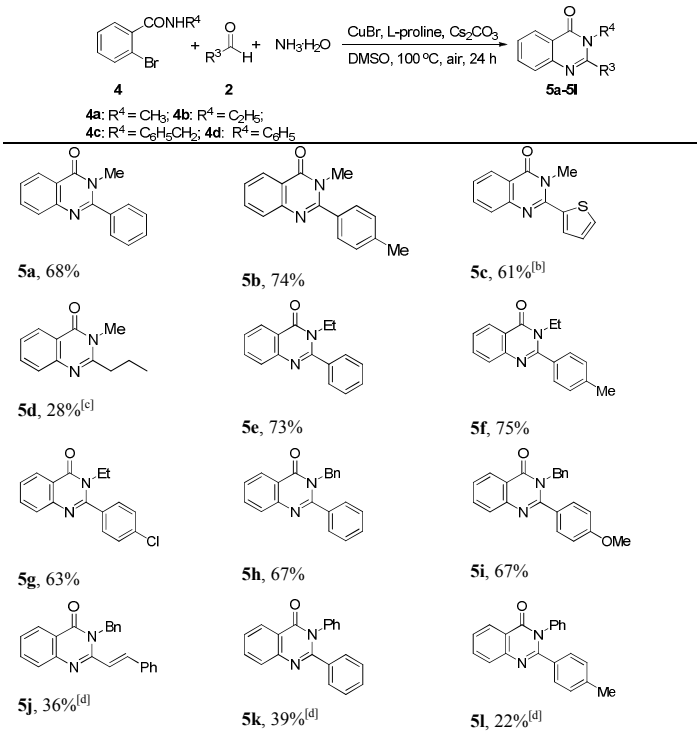


[a]Reaction conditions: **1** (0.4 mmol), **2** (0.8 mmol), aqueous ammonia (0.5 mL), CuBr (0.04 mmol), Cs_2CO_3 (0.8 mmol), L-proline (0.08 mmol), DMSO (1.5 mL), 100 °C, under air, 24 h. [b]Isolated yields are shown.

successfully applied in the preparation of 2,3-disubstituted quinazolinones by using *N*-substituted 2-bromobenzamides as starting materials. Thus, *N*-methyl 2-bromobenzamide (**4a**) was then treated with benzaldehyde (**2a**) and aqueous ammonia under the optimized conditions for the synthesis of **3a** (Table 1, entry 14). To our delight, the expected tandem reaction proceeded smoothly to afford 3-methyl-2-phenylquinazolin-4(3*H*)-one (**5a**) in 68% yield (Table 3, entry 1). Due to the good efficiency of the above catalytic process, no further

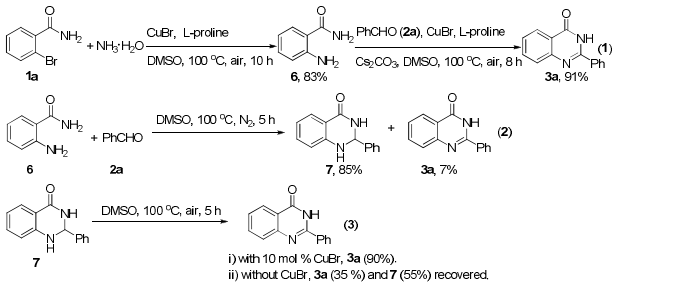
optimization of the reaction conditions was tried. Next, the generality of this reaction was examined. As shown in Table 3, aryl-, heteroaryl-, alkyl-, and alkenyl-substituted aldehydes were compatible with the reaction conditions to afford the corresponding 2,3-disubstituted quinazolinones **5** in modest to good yields, and aryl-substituted aldehydes generally showed higher reactivity than alkyl- and alkenyl-substituted aldehydes (entries 4 and 10). In addition, with thiophene-2-carbaldehyde, the corresponding product **5c** was obtained in 39% yield under standard conditions, whereas elevating reaction temperature to 140 °C gave **5c** in a higher yield (61%) (entry 3). Then, the scope of N-substituted amides **4** was also investigated by employing benzaldehyde (**2a**) and aqueous ammonia as reaction partners, and it turned out that *N*-alkyl substituted amides **4a**-**4c** generally provided the corresponding products in yields higher than *N*-aryl substituted amide **4d** (entries 1, 5, 8 vs 11).

Table 3. Synthesis of 2,3-disubstituted quinazolinones **5a-5l**[a]



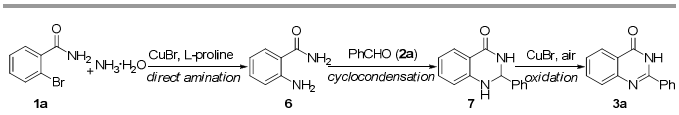
[a]Reaction conditions: **4** (0.4 mmol), **2** (0.8 mmol), aqueous ammonia (0.5 mL), CuBr (0.04 mmol), Cs_2CO_3 (0.8 mmol), L-proline (0.08 mmol), DMSO (1.5 mL), 100 °C, under air, 24 h. [b]The reaction was performed at 140 °C for 30 h. [c]Butyraldehyde (1.2 mmol) was used. [d]Some unknown by-products were formed.

To explore the reaction mechanism, several control experiments were carried out and the results are illustrated in Scheme 1. First, treatment of **1a** with aqueous ammonia by using CuBr as catalyst and L-proline as ligand under air afforded 2-aminobenzamide (**6**) in 83% yield; subsequent cyclocondensation of **6** with benzaldehyde (**2a**) followed by oxidation gave rise to quinazolinone **3a** in a yield of 91% (Scheme 1, eq. 1). Next, treating a mixture of **6** and **2a** under nitrogen atmosphere could afford intermediate **7** (85%) along with **3a** (7%) (Scheme 1, eq. 2); then, the oxidation of **7** in the presence of CuBr under air provided the final product **3a** in 90% yield (Scheme 1, eq. 3).



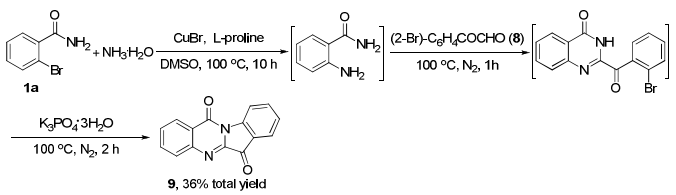
Scheme 1. Control experiments

Based on the above results, a plausible mechanism for the formation of quinazolinone **3a** is depicted in Scheme 2. Initially, copper-catalyzed direct amination of **1a** with aqueous ammonia by using L-proline as ligand affords intermediate **6**. Cyclocondensation of **6** with benzaldehyde (**2a**) gives rise to intermediate **7**, which is subsequently oxidized by air under the catalysis of CuBr to generate the final product **3a**.



Scheme 2. Plausible mechanism for the formation of **3a**

To showcase the usefulness of this novel methodology, we designed and developed a practical three-step one-pot procedure for the construction of alkaloid tryptanthrin, which is frequently found in a number of plants and exhibits potent cytotoxicity against human cell lines (MCF-7, NCI-H460, and SF-268).[12] As shown in Scheme 3, tryptanthrin (**9**) could be conveniently prepared in 36% total yield through copper-catalyzed amination of **1a** with aqueous ammonia followed by condensation/oxidation[13] cascade of the in situ formed 2-aminobenzamide with aldehyde (**8**) and base-promoted intramolecular cross-coupling reaction. It should be noted that the present protocol is a concise and practical alternative toward tryptanthrin derivatives.[14]



Scheme 3. Copper-catalyzed one-pot synthesis of alkaloid tryptanthrin (**9**)

3. Conclusions

In summary, we have developed a convenient and rapid synthetic route to 2-substituted and 2,3-disubstituted quinazolinones *via* copper-catalyzed tandem reaction of 2-bromobenzamides with aldehydes and aqueous ammonia under air. The present protocol exhibits good functional group tolerance, readily available and inexpensive starting materials, and operational simplicity. Moreover, this novel methodology has been successfully applied in the construction of alkaloid tryptanthrin. To further explore novel synthetic approaches toward other nitrogen-containing heterocyclic compounds is underway in our laboratory.

4. Experimental

General Methods. Unless noted, all commercial reagents and solvents were used without further purification. High-resolution mass spectra (HRMS) were obtained by using a MicrOTOF mass spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. All reactions were monitored by thin-layer chromatography (TLC) using silica gel plates (silica gel 60 F254 0.25 mm) and components were visualized by observation under UV light (254 and 365 nm).

Typical Procedure for the Preparation of Quinazolinone 3a. To a mixture of 2-bromobenzamide **1a** (80 mg, 0.4 mmol), benzaldehyde **2a** (82 μL, 0.8 mmol), CuBr (5.8 mg, 0.04 mmol), Cs_2CO_3 (261 mg, 0.8 mmol), and L-proline (9.2 mg, 0.08 mmol) in DMSO (1.5 mL) was added 26% aqueous ammonia (0.5 mL) in a tube under air atmosphere. Then the tube was sealed, and the mixture was stirred at 100 °C for 12 h. Next, the tube was opened to air and the mixture was stirred at 100 °C for another 12 h. After being cooled to room temperature, the resulting mixture was quenched with NH_4Cl solution and extracted with ethyl acetate. The combined organic layer was washed with H_2O and brine, and then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by chromatography on silica-gel to afford quinazolinone **3a** in 72% isolated yield.

2-Phenylquinazolin-4(3*H*)-one (3a)[10e]: Petroleum ether/ethyl acetate (3:1) as eluent; white solid; yield: 64 mg (72%); mp 231-233 °C (lit.[10e] 234-235 °C). ^{1}H NMR (DMSO-*d*6, 400 MHz) δ 7.49-7.59 (m, 4H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.80-7.84 (m, 1H), 8.13-8.18 (m, 3H), 12.55 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 121.4, 126.3, 127.1, 128.0, 128.2, 129.1, 131.9, 133.2, 135.1, 149.2, 152.8, 162.7. MS (ESI) *m*/*z* 223.2 [M + H]$^+$.

2-*p*-Tolylquinazolin-4(3*H*)-one (3b)[10e]: Petroleum ether/ethyl acetate (3:1) as eluent; light yellow solid; yield: 78 mg (83%); mp 238-240 °C (lit.[10e] 261-263 °C). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.34 (s, 3H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.45-7.49 (m, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.77-7.81 (m, 1H), 8.08 (d, *J* = 8.4 Hz, 2H), 8.13 (d, *J* = 7.2 Hz, 1H), 12.42 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.4, 121.4, 126.3, 126.8, 127.9, 128.1, 129.6, 130.4, 134.9, 141.9, 149.4, 152.7, 162.7. MS (ESI) *m*/*z* 237.2 [M + H]$^+$.

2-*m*-Tolylquinazolin-4(3*H*)-one (3c)[9i]: Petroleum ether/ethyl acetate (3:1) as eluent; white solid; yield: 70 mg (74%); mp 217-218 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.39 (s, 3H), 7.36-7.43 (m, 2H), 7.47-7.51 (m, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.79-7.83 (m, 1H), 7.96 (d, *J* = 7.2 Hz, 1H), 8.01 (s, 1H), 8.14 (d, *J* = 7.2 Hz, 1H), 12.44 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.4, 121.5, 125.4, 126.3, 127.0, 128.0, 128.8, 128.9, 132.5, 133.1, 135.0, 138.4, 149.3, 152.8, 162.7. MS (ESI) *m*/*z* 237.3 [M + H]$^+$.

2-(4-Methoxyphenyl)quinazolin-4(3*H*)-one (3d)[10e]: Petroleum ether/ethyl acetate (3:1) as eluent; light yellow solid; yield: 71 mg (70%); mp 238-240 °C (lit.[10e] 247-248 °C). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.82 (s, 3H), 7.06 (d, *J* = 8.8 Hz, 2H), 7.45 (t, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.78 (t, *J* = 7.6 Hz, 1H), 8.11 (d, *J* = 7.6 Hz, 1H), 8.17 (d, *J* = 8.4 Hz, 2H), 12.37 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 55.9, 114.5, 121.2, 125.3, 126.3, 126.5, 127.8, 129.9, 134.9, 149.5, 152.3, 162.4, 162.7. MS (ESI) *m*/*z* 253.4 [M + H]$^+$.

2-(4-(Trifluoromethyl)phenyl)quinazolin-4(3*H*)-one (3e)[9b]: Petroleum ether/ethyl acetate (4:1) as eluent; white solid; yield: 84 mg (72%); mp 260-262 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.54 (t, *J* = 7.2 Hz, 1H), 7.76 (d, *J* = 7.6 Hz, 1H), 7.83-7.86 (m, 1H), 7.90 (d, *J* = 7.6 Hz, 2H), 8.15 (d, *J* = 7.2 Hz, 1H), 8.36 (d, *J* = 8.0 Hz, 2H), 12.76 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 121.7, 124.4 (q, *J* = 270.5 Hz, CF_3), 125.9 (q, *J* = 3.8 Hz, 2C), 126.4, 127.5, 128.1, 129.2, 131.6 (q, *J* = 32.0 Hz, 1C), 135.2, 137.1, 148.9, 151.7, 162.7. HRMS (ESI) calcd for $C_{15}H_{10}F_3N_2O$ [M + H]$^+$ 291.0740, found 291.0737.

2-(4-Chlorophenyl)quinazolin-4(3*H*)-one (3f)[15]: Purified by washing crude product with CH_2Cl_2 (3 mL); light yellow solid; yield: 70 mg (68%); mp 281-283 °C (lit.[15] 298-300 °C). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.52 (t, *J* = 7.2 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.83 (t, *J* = 8.0 Hz, 1H), 8.14 (d, *J* = 8.0 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 2H), 12.58 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 121.5, 126.4, 127.3, 128.0, 129.2, 130.1, 132.0, 135.2, 136.8, 149.0, 151.9, 162.6. MS (ESI) *m*/*z* 257.8 [M + H]$^+$.

2-(4-Fluorophenyl)quinazolin-4(3*H*)-one (3g)[9b]: Petroleum ether/ethyl acetate (3:1) as eluent; yellow solid; yield: 79 mg (82%); mp 254-256 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.36-7.40 (m, 2H), 7.49-7.53 (m, 1H), 7.72 (d, *J* = 7.2 Hz, 1H), 7.80-7.84 (m, 1H), 8.12-8.15 (m, 1H), 8.22-8.25 (m, 2H), 12.55 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 116.1 (d, *J* = 21.8 Hz, 2C), 121.3, 126.3, 127.1, 127.9, 129.7 (d, *J* = 2.9 Hz, 1C), 130.8 (d, *J* = 9.5 Hz, 2C), 135.1, 149.1, 151.9, 162.7, 164.5 (d, *J* = 248.0 Hz, 1C). MS (ESI) *m*/*z* 241.1 [M + H]$^+$.

2-(3-Fluorophenyl)quinazolin-4(3*H*)-one (3h)[16]: Petroleum ether/ethyl acetate (3:1) as eluent; light yellow solid; yield: 72 mg (75%); mp 229-231 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.40-7.44 (m, 1H), 7.50-7.61 (m, 2H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.83 (t, *J* = 7.2 Hz, 1H), 7.97-8.05 (m, 2H), 8.14 (d, *J* = 7.2 Hz, 1H), 12.58 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 115.0 (d, *J* = 23.6 Hz, 1C), 118.7 (d, *J* = 21.3 Hz, 1C), 121.6, 124.4 (d, *J* = 3.0 Hz, 1C), 126.3, 127.3, 128.1, 131.2 (d, *J* = 8.4 Hz, 1C), 135.1, 135.5 (d, *J* = 7.6 Hz, 1C), 148.9, 151.5, 162.57 (d, *J* = 242.4 Hz, 1C), 162.58. MS (ESI) *m*/*z* 241.2 [M + H]$^+$.

2-(2-Fluorophenyl)quinazolin-4(3*H*)-one (3i): Petroleum ether/ethyl acetate (3:1) as eluent; light yellow solid; yield: 64

mg (67%); mp 153-155 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.34-7.40 (m, 2H), 7.53-7.64 (m, 2H), 7.70-7.86 (m, 3H), 8.16 (dd, J = 1.2, 8.0 Hz, 1H), 12.56 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 116.6 (d, J = 21.3 Hz, 1C), 121.6, 122.8 (d, J = 13.0 Hz, 1C), 125.1 (d, J = 3.8 Hz, 1C), 126.3, 127.5, 128.0, 131.5 (d, J = 2.3 Hz, 1C), 133.3 (d, J = 8.4 Hz, 1C), 135.1, 149.2, 150.4, 160.1 (d, J = 248.4 Hz, 1C), 162.0. HRMS (ESI) calcd for $C_{14}H_{10}FN_2O$ $[M + H]^+$ 241.0772, found 241.0768.

2-(Naphthalen-1-yl)quinazolin-4(3*H*)-one (3j)[10e]: Petroleum ether/ethyl acetate (2:1) as eluent; light yellow solid; yield: 79 mg (73%); mp 251-253 °C (lit.[10e] 278-281 °C). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.55-7.65 (m, 4H), 7.72 (d, J = 7.6 Hz, 1H), 7.78 (d, J = 6.8 Hz, 1H), 7.85 (t, J = 6.8 Hz, 1H), 8.02-8.05 (m, 1H), 8.11 (d, J = 8.4 Hz, 1H), 8.15-8.17 (m, 1H), 8.21 (d, J = 7.6 Hz, 1H), 12.66 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 121.7, 125.6, 125.7, 126.3, 126.8, 127.3, 127.6, 128.0, 128.2, 128.8, 130.7, 130.9, 132.2, 133.6, 135.0, 149.2, 154.2, 162.4. MS (ESI) m/z 273.5 $[M + H]^+$.

2-(Pyridin-4-yl)quinazolin-4(3*H*)-one (3k)[15]: Petroleum ether/ethyl acetate (3:1) as eluent; light yellow solid; yield: 38 mg (43%); mp 270-272 °C (lit.[15] 281-283 °C). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.53-7.57 (m, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.82-7.86 (m, 1H), 8.08-8.09 (m, 2H), 8.15 (d, J = 7.6 Hz, 1H), 8.76-8.77 (m, 2H), 12.72 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 121.9, 122.0, 126.4, 127.9, 128.2, 135.2, 140.4, 148.7, 150.7, 151.0, 162.5. MS (ESI) m/z 224.2 $[M + H]^+$.

2-(Thiophen-2-yl)quinazolin-4(3*H*)-one (3l)[10e]: Petroleum ether/ethyl acetate (3:1) as eluent; light yellow solid; yield: 85 mg (93%); mp 256-258 °C (lit.[10e] 275-276 °C). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.20-7.22 (m, 1H), 7.44-7.48 (m, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.75-7.78 (m, 1H), 7.83-7.85 (m, 1H), 8.10 (d, J = 8.0 Hz, 1H), 8.21-8.22 (m, 1H), 12.63 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 121.3, 126.5, 126.8, 127.4, 129.0, 129.9, 132.6, 135.2, 137.8, 148.3, 149.1, 162.3. MS (ESI) m/z 229.3 $[M + H]^+$.

(*E*)-2-Styrylquinazolin-4(3*H*)-one (3m): Petroleum ether/ethyl acetate (4:1) as eluent; light yellow solid; 52 mg (52%); mp 226-228 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.00 (d, J = 16.0, 1H), 7.39-7.49 (m, 4H), 7.64-7.67 (m, 3H), 7.77-7.82 (m, 1H), 7.94 (d, J = 16.0 Hz, 1H), 8.09-8.11 (m, 1H), 12.33 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 121.6, 126.3, 126.7, 127.6, 128.1, 129.6, 130.3, 135.0, 135.5, 138.7, 149.5, 151.9, 162.2 (one ^{13}C signal was not observed). HRMS (ESI) calcd for $C_{16}H_{13}N_2O$ $[M + H]^+$ 249.1022, found 249.1021.

2-Propylquinazolin-4(3*H*)-one (3n)[10d]: Petroleum ether/ethyl acetate (3:1) as eluent; light yellow solid; yield: 34 mg (45%); mp 180-183 °C (lit.[10d] 200-202 °C). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.91 (t, J = 7.2 Hz, 3H), 1.68-1.77 (m, 2H), 2.55 (t, J = 7.6 Hz, 2H), 7.43 (t, J = 7.2 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.73-7.76 (m, 1H), 8.06 (d, J = 7.2 Hz, 1H), 12.15 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 13.9, 20.6, 36.8, 121.2, 126.1, 126.3, 127.2, 134.7, 149.4, 157.7, 162.2. MS (ESI) m/z 189.2 $[M + H]^+$.

6-Methyl-2-phenylquinazolin-4(3*H*)-one (3o)[15]: Petroleum ether/ethyl acetate (3:1) as eluent; light yellow solid; yield: 73 mg (77%); mp 220-222 °C (lit.[15] 238-240 °C). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.43 (s, 3H), 7.52-7.62 (m, 5H), 7.93 (s, 1H), 8.15-8.16 (m, 2H), 12.42 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.3, 121.2, 125.7, 127.9, 128.1, 129.0, 131.7, 133.3, 136.3, 136.7, 147.2, 151.9, 162.6. MS (ESI) m/z 237.3 $[M + H]^+$.

2-(4-Methoxyphenyl)-6-methylquinazolin-4(3*H*)-one (3p): Petroleum ether/ethyl acetate (2:1) as eluent; light yellow solid; yield: 64 mg (60%); mp 258-260 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.42 (s, 3H), 3.82 (s, 3H), 7.05 (d, J = 8.8 Hz, 2H), 7.56-7.61 (m, 2H), 7.90 (s, 1H), 8.15 (d, J = 8.8 Hz, 2H), 12.29 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.3, 55.9, 114.4, 120.9, 125.4, 125.7, 127.6, 129.8, 136.21, 136.25, 147.4, 151.5, 162.2, 162.7. HRMS (ESI) calcd for $C_{16}H_{15}N_2O_2$ $[M + H]^+$ 267.1128, found 267.1125.

6-Methyl-2-(thiophen-2-yl)quinazolin-4(3*H*)-one (3q): Petroleum ether/ethyl acetate (3:1) as eluent; yellow solid; yield: 77 mg (79%); mp 244-247 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.39 (s, 3H), 7.18-7.20 (m, 1H), 7.49-7.57 (m, 2H), 7.80 (d, J = 4.4 Hz, 1H), 7.88 (s, 1H), 8.18 (d, J = 2.4 Hz, 1H), 12.53 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.3, 121.1, 125.9, 127.3, 128.9, 129.5, 132.2, 136.3, 136.5, 138.0, 147.1, 147.5, 162.2. HRMS (ESI) calcd for $C_{13}H_{11}N_2OS$ $[M + H]^+$ 243.0587, found 243.0583.

6-Methoxy-2-phenylquinazolin-4(3*H*)-one (3r)[9i]: Petroleum ether/ethyl acetate (3:1) as eluent; light yellow solid; yield: 75 mg (74%); mp 246-247. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.87 (s, 3H), 7.42 (dd, J = 3.2, 8.8 Hz, 1H), 7.49-7.55 (m, 4H), 7.68 (d, J = 8.8 Hz, 1H), 8.14 (dd, J = 1.6, 8.0 Hz, 2H), 12.49 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 56.1, 106.3, 122.3, 124.6, 128.0, 129.0, 129.7, 131.5, 133.3, 143.7, 150.6, 158.2, 162.5. MS (ESI) m/z 253.1 $[M + H]^+$.

2-(4-Fluorophenyl)-6-methoxyquinazolin-4(3*H*)-one (3s): CH_2Cl_2/MeOH (50:1) as eluent; white solid; yield: 60 mg (56%); mp 265-266 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.88 (s, 3H), 7.36 (t, J = 8.8 Hz, 2H), 7.42-7.44 (m, 1H), 7.53 (s, 1H), 7.68 (d, J = 8.8 Hz, 1H), 8.19-8.22 (m, 2H), 12.52 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 56.1, 106.3, 116.1 (d, J = 22.3 Hz, 2C), 122.2, 124.6, 129.7, 129.8 (d, J = 2.4 Hz, 1C), 130.5 (d, J = 9.0 Hz, 2C), 143.6, 149.7, 158.3, 162.5, 164.3 (d, J = 248.1 Hz, 1C). HRMS (ESI) calcd for $C_{15}H_{12}FN_2O_2$ $[M + H]^+$ 271.0877, found 271.0877.

6-Methoxy-2-propylquinazolin-4(3*H*)-one (3t): Petroleum ether/ethyl acetate (2:1) as eluent; white solid; yield: 26 mg (30%); mp 227-229. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 0.89 (t, J = 7.2 Hz, 3H), 1.65-1.75 (m, 2H), 2.52 (t, J = 7.6 Hz, 2H), 3.82 (s, 3H), 7.34 (dd, J = 3.2, 8.8 Hz, 1H), 7.44 (d, J = 3.2 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 12.16 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 13.9, 20.7, 36.6, 56.0, 106.2, 121.9, 124.2, 128.8, 143.7, 155.5, 157.7, 162.1. HRMS (ESI) calcd for $C_{12}H_{15}N_2O_2$ $[M + H]^+$ 219.1128, found 219.1124.

7-Chloro-2-phenylquinazolin-4(3*H*)-one (3u)[15]: Petroleum ether/ethyl acetate (3:1) as eluent; light yellow solid; yield: 76 mg (74%); mp 267-269 °C (lit.[15] 286-288 °C). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.50-7.61 (m, 4H), 7.75 (d, J = 2.0 Hz, 1H), 8.10-8.16 (m, 3H), 12.65 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 120.3, 127.0, 127.2, 128.4, 129.1, 132.2, 132.8,

139.6, 150.3, 154.2, 162.1 (one ^{13}C signal was not observed). MS (ESI) *m/z* 257.6 $[M + H]^+$.

7-Chloro-2-(pyridin-4-yl)quinazolin-4(3*H*)-one (3v): Petroleum ether/ethyl acetate (3:2) as eluent; light yellow solid; yield: 43 mg (42%); mp 235-237 °C. ^1H NMR (DMSO-d_6, 400 MHz) δ 7.58 (d, *J* = 8.8 Hz, 1H), 7.81 (s, 1H), 8.07 (d, *J* = 4.8 Hz, 2H), 8.14 (d, *J* = 8.4 Hz, 1H), 8.78 (d, *J* = 4.4 Hz, 2H), 12.88 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 120.8, 122.1, 127.3, 128.0, 128.5, 139.8, 140.1, 149.9, 150.8, 152.5, 161.9. HRMS (ESI) calcd for $C_{13}H_9ClN_3O$ $[M + H]^+$ 258.0429, found 258.0425.

(*E*)-7-Chloro-2-styrylquinazolin-4(3*H*)-one (3w): Petroleum ether/ethyl acetate (2:1) as eluent; light yellow solid; yield: 42 mg (37%); mp 267-269 °C. ^1H NMR (DMSO-d_6, 400 MHz) δ 6.97 (d, *J* = 16.0 Hz, 1H), 7.40-7.48 (m, 4H), 7.62-7.67 (m, 3H), 7.93 (d, *J* = 16.4 Hz, 1H), 8.06 (d, *J* = 8.4 Hz, 1H), 12.44 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 120.4, 121.2, 126.6, 126.9, 128.2, 128.4, 129.6, 130.5, 135.3, 139.56, 139.60, 150.6, 153.3, 161.6. HRMS (ESI) calcd for $C_{16}H_{12}ClN_2O$ $[M + H]^+$ 283.0633, found 283.0630.

3-Methyl-2-phenylquinazolin-4(3*H*)-one (5a)[17]: Petroleum ether/ethyl acetate (4:1) as eluent; white solid; yield: 64 mg (68%); mp 122-124 °C (lit.[17] 130-132 °C). ^1H NMR ($CDCl_3$, 400 MHz) δ 3.48 (s, 3H), 7.46-7.56 (m, 6H), 7.73 (m, 2H), 8.31 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.2, 120.5, 126.7, 127.0, 127.5, 128.0, 128.9, 130.1, 134.3, 135.4, 147.3, 156.1, 162.7. HRMS (ESI) calcd for $C_{15}H_{13}N_2O$ $[M + H]^+$ 237.1022, found 237.1020.

3-Methyl-2-*p*-tolylquinazolin-4(3*H*)-one (5b)[17]: Petroleum ether/ethyl acetate (4:1) as eluent; white solid; yield: 74mg (74%); mp 131-133 °C (lit.[17] 139-140 °C). ^1H NMR ($CDCl_3$, 400 MHz) δ 2.41 (s, 3H), 3.48 (s, 3H), 7.30 (d, *J* = 7.6 Hz, 2H), 7.44-7.48 (m, 3H), 7.71 (m, 2H), 8.29 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.4, 34.3, 120.5, 126.6, 126.9, 127.4, 128.0, 129.5, 132.5, 134.3, 140.3, 147.3, 156.3, 162.8. HRMS (ESI) calcd for $C_{16}H_{15}N_2O$ $[M + H]^+$ 251.1179, found 251.1197.

3-Methyl-2-(thiophen-2-yl)quinazolin-4(3*H*)-one (5c): Petroleum ether/ethyl acetate (3:1) as eluent; light yellow solid; yield: 59 mg (61%); mp 64-66 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.74 (s, 3H), 7.13-7.15 (m, 1H), 7.43-7.54 (m, 3H), 7.68-7.74 (m, 2H), 8.27 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 34.1, 120.1, 126.8, 127.0, 127.4, 129.4, 129.8, 134.3, 137.1, 147.2, 150.1, 162.7 (one ^{13}C signal was not observed). HRMS (ESI) calcd for $C_{13}H_{11}N_2OS$ $[M + H]^+$ 243.0587, found 243.0588.

3-Methyl-2-propylquinazolin-4(3*H*)-one (5d): Petroleum ether/ethyl acetate (5:1) as eluent; light yellow solid; yield: 23 mg (28%); mp 66-69 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.08 (t, *J* = 7.2 Hz, 3H), 1.81-1.91 (m, 2H), 2.80 (t, *J* = 8.0 Hz, 2H), 3.62 (s, 3H), 7.39-7.43 (m, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.69 (dt, *J* = 1.6, 8.4 Hz, 1H), 8.24 (dd, *J* = 1.6, 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 20.3, 30.5, 37.5, 120.1, 126.3, 126.7, 126.8, 134.0, 147.2, 157.1, 162.6. HRMS (ESI) calcd for $C_{12}H_{15}N_2O$ $[M + H]^+$ 203.1179, found 203.1182.

3-Ethyl-2-phenylquinazolin-4(3*H*)-one (5e): Petroleum ether/ethyl acetate (8:1) as eluent; white solid; yield: 73 mg (73%); mp 127-129 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20 (t, *J* = 6.8 Hz, 3H), 4.02 (q, *J* = 6.8 Hz, 2H), 7.46-7.51 (m, 6H), 7.72-7.73 (m, 2H), 8.32 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 41.2, 121.0, 126.7, 127.0, 127.4, 127.7, 128.8, 129.8, 134.3, 135.5, 147.1, 156.2, 162.0. HRMS (ESI) calcd for $C_{16}H_{15}N_2O$ $[M + H]^+$ 251.1179, found 251.1180.

3-Ethyl-2-*p*-tolylquinazolin-4(3*H*)-one (5f): Petroleum ether/ethyl acetate (6:1) as eluent; white solid; yield: 79 mg (75%); mp 100-103 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20 (t, *J* = 6.8 Hz, 3H), 2.42 (s, 3H), 4.04 (q, *J* = 6.8 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 7.6 Hz, 2H), 7.45-7.49 (m, 1H), 7.70-7.73 (m, 2H), 8.31 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 21.4, 41.2, 120.9, 126.7, 126.9. 127.4, 127.6, 129.4, 132.7, 134.3, 139.9, 147.2, 156.4, 162.1. HRMS (ESI) calcd for $C_{17}H_{17}N_2O$ $[M + H]^+$ 265.1335, found 265.1333.

2-(4-Chlorophenyl)-3-ethylquinazolin-4(3*H*)-one (5g): Petroleum ether/ethyl acetate (6:1) as eluent; white solid; yield: 72mg (63%); mp 110-113 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20 (t, *J* = 6.8 Hz, 3H), 4.01 (q, *J* = 6.8 Hz, 2H), 7.47-7.51 (m, 5H), 7.68-7.76 (m, 2H), 8.30 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 41.2, 121.0, 126.8, 127.2, 127.4, 129.1, 129.2, 133.9, 134.4, 136.1, 147.0, 155.1, 161.9. HRMS (ESI) calcd for $C_{16}H_{14}ClN_2O$ $[M + H]^+$ 285.0789, found 285.0790.

3-Benzyl-2-phenylquinazolin-4(3*H*)-one (5h)[18]: Petroleum ether/ethyl acetate (6:1) as eluent; white solid; yield: 84 mg (67%); mp 126-128 °C (lit.[18] 140-142 °C). ^1H NMR ($CDCl_3$, 400 MHz) δ 5.28 (s, 2H), 6.92-6.94 (m, 2H), 7.19-7.21 (m, 3H), 7.33-7.36 (m, 2H), 7.38-7.42 (m, 2H), 7.45-7.49 (m, 1H), 7.51-7.55 (m, 1H), 7.77-7.78 (m, 2H), 8.38 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 48.8, 120.9, 127.0, 127.1, 127.2, 127.5, 127.6, 128.0, 128.56, 128.63, 130.0, 134.6, 135.2, 136.6, 147.2, 156.5, 162.5. MS (ESI) *m/z* 313.4 $[M + H]^+$.

3-Benzyl-2-(4-methoxyphenyl)quinazolin-4(3*H*)-one (5i)[19]: Petroleum ether/ethyl acetate (6:1) as eluent; white solid; yield: 92 mg (67%); mp 101-103 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.83 (s, 3H), 5.30 (s, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.96-6.98 (m, 2H), 7.19-7.24 (m, 3H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.48-7.52 (m, 1H), 7.76 (d, *J* = 4.0 Hz, 2H), 8.35 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 49.0, 55.5, 114.0, 120.7, 126.9, 127.0, 127.1, 127.4, 127.5, 127.7, 128.6, 129.7, 134.6, 136.7, 147.3, 156.4, 160.8, 162.6. HRMS (ESI) calcd for $C_{22}H_{19}N_2O_2$ $[M + H]^+$ 343.1441, found 343.1430.

(*E*)-3-Benzyl-2-styrylquinazolin-4(3*H*)-one (5j): Petroleum ether/ethyl acetate (8:1) as eluent; light yellow solid; yield: 49 mg (36%); mp 132-134 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 5.52 (s, 2H), 7.03 (d, *J* = 15.2 Hz, 1H), 7.29-7.39 (m, 8H), 7.45-7.49 (m, 3H), 7.76 (m, 2H), 7.94 (d, *J* = 15.2 Hz, 1H), 8.35 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 46.9, 119.4, 120.5, 126.6, 127.2, 127.3, 127.8, 128.9, 129.1, 129.8, 134.5, 135.3, 136.3, 141.1, 147.6, 152.5, 162.5 (two ^{13}C signals were not observed). HRMS (ESI) calcd for $C_{23}H_{19}N_2O$ $[M + H]^+$ 339.1492, found 339.1483.

2,3-Diphenylquinazolin-4(3*H*)-one (5k)[9f]: Petroleum ether/ethyl acetate (8:1) as eluent; light yellow solid; yield: 46 mg (39%); mp 150-152 °C (lit.[9f] 158-159 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.15 (d, *J* = 8.0 Hz, 2H), 7.19-7.34 (m, 8H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.79-7.85 (m, 2H), 8.36 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 121.0, 127.2, 127.4, 127.7, 128.0, 128.5, 129.0, 129.1, 129.4, 134.8, 135.4, 137.6, 147.4, 155.3, 162.3 (one ^{13}C signal was not observed). MS (ESI) *m*/*z* 299.2 $[M + H]^+$.

3-Phenyl-2-*p*-tolylquinazolin-4(3*H*)-one (5l)[9f]: Petroleum ether/ethyl acetate (5:1) as eluent; white solid; yield: 28mg (22%); mp 169-171 °C (lit.[9f] 171-172 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.27 (s, 3H), 7.01 (d, *J* = 8.0 Hz, 2H), 7.15-7.17 (m, 2H), 7.22-7.35 (m, 5H), 7.51-7.55 (m, 1H), 7.78-7.85 (m, 2H), 8.34-8.36 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3, 120.9, 127.20, 127.22, 127.6, 128.4, 128.7, 129.00, 129.02, 129.1, 132.4, 134.8, 137.8, 139.6, 147.5, 155.4, 162.4. MS (ESI) *m*/*z* 313.4 $[M + H]^+$.

Preparation of 2-Aminobenzamide 6. To a tube containing 2-bromobenzamide **1a** (80 mg, 0.4 mmol), CuBr (5.8 mg, 0.04 mmol), and L-proline (9.2 mg, 0.08 mmol) in DMSO (1.5 mL) was added 26% aqueous ammonia (0.5 mL). Then, the tube was sealed, and the mixture was stirred at 100 °C for 10 h under air atmosphere. After being cooled to room temperature, the resulting mixture was quenched with NH_4Cl solution and extracted with ethyl acetate. The combined organic layer was washed with H_2O and brine, and then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by chromatography on silica-gel, eluting with CH_2Cl_2/ethyl acetate (1:1), to afford 2-aminobenzamide **6** (45 mg) as white solid in 83% isolated yield. Mp 98-100 °C (lit.[20] 110 °C). ^{1}H NMR (DMSO-d_6, 400 MHz)[20] δ 6.44 (t, *J* = 7.2 Hz, 1H), 6.52 (s, 2H), 6.64 (d, *J* = 8.0 Hz, 1H), 7.02 (br s, 1H), 7.07-7.11 (m, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.68 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 114.2, 114.8, 116.9, 129.2, 132.3, 150.7, 171.8. MS (ESI) *m*/*z* 137.2 $[M + H]^+$.

Preparation of Compound 7. A mixture of compound **6** (54.4 mg, 0.4 mmol) and benzaldehyde **2a** (82 μL, 0.8 mmol) in DMSO (1.5 mL) was stirred at 100 °C for 5 h under nitrogen atmosphere, and then the reaction was quenched with NH_4Cl solution and extracted with ethyl acetate. The combined organic layer was washed with H_2O and brine, and then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by chromatography on silica-gel, eluting with CH_2Cl_2/ethyl acetate (6:1), to afford 2-phenyl-2,3-dihydroquinazolin-4(1*H*)-one **7** (76 mg) as white solid in 85% isolated yield. Mp 220-223 °C (lit.[17] 222-225 °C). ^{1}H NMR (DMSO-d_6, 400 MHz)[17] δ 5.68 (s, 1H), 6.59 (t, *J* = 7.6 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 7.05 (s, 1H), 7.15 (t, *J* = 8.0 Hz, 1H), 7.23-7.31 (m, 3H), 7.42 (d, *J* = 6.8 Hz, 2H), 7.54 (d, *J* = 7.6 Hz, 1H), 8.25 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 67.0, 114.9, 115.4, 117.6, 127.3, 127.8, 128.8, 128.9, 133.8, 142.1, 148.3, 164.1. MS (ESI) *m*/*z* 225.2 $[M + H]^+$.

Preparation of Alkaloid Tryptanthrin (9). To a mixture of 2-bromobenzamide **1a** (80 mg, 0.4 mmol), CuBr (5.8 mg, 0.04 mmol), and L-proline (9.2 mg, 0.08 mmol) in DMSO (1.5 mL) was added 26% aqueous ammonia (0.5 mL) in a tube under air atmosphere. Then the tube was sealed, and the mixture was stirred at 100 °C for 10 h. After the excess ammonia was removed from the reaction mixture under reduced pressure, a solution of 2-(2-bromophenyl)-2-oxoacetaldehyde **8** (0.8 mmol) in DMSO (1.6 mL) was added into the same tube. When the resulting mixture was stirred at 100 °C for 1 h under nitrogen atmosphere, $K_3PO_4 \cdot 3H_2O$ (213 mg, 0.8 mmol) was added and the mixture was stirred at 100 °C for another 2 h under nitrogen atmosphere. At last, the reaction was quenched with NH_4Cl solution and extracted with CH_2Cl_2. The combined organic layer was washed with H_2O and brine, and then dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was purified by chromatography on silica-gel, eluting with CH_2Cl_2/ethyl acetate (100:1), to afford tryptanthrin **9** (36 mg) as yellow solid in 36% total yield. Mp 257-259 °C (lit.[14a] 268.2-270.1 °C). ^{1}H NMR ($CDCl_3$, 400 MHz)[14a] δ 7.40 (t, *J* = 7.6 Hz, 1H), 7.62-7.66 (m, 1H), 7.73-7.77 (m, 1H), 7.82 (dt, *J* = 1.2, 8.0 Hz, 1H), 7.88 (d, *J* = 7.2 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 8.38 (dd, *J* = 1.2, 8.0 Hz, 1H), 8.57 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 117.9, 121.9, 123.7, 125.4, 127.2, 127.5, 130.2, 130.7, 135.1, 138.2, 144.3, 146.3, 146.5, 158.0, 182.5. HRMS (ESI) calcd for $C_{15}H_9N_2O_2$ $[M + H]^+$ 249.0659, found 249.0658.

Acknowledgements

This work was financially supported by the National Natural Science Foundation of China (Grants 21202040 and 21272058), Project funded by China Postdoctoral Science Foundation (2014M552007), and PCSIRT (IRT1061).

Notes and references

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† Electronic Supplementary Information (ESI) available: The copies of ^{1}H NMR and ^{13}C NMR spectra of **3a-3w**, **5a-5l**, **6**, **7**, and **9**. See DOI: 10.1039/b000000x/

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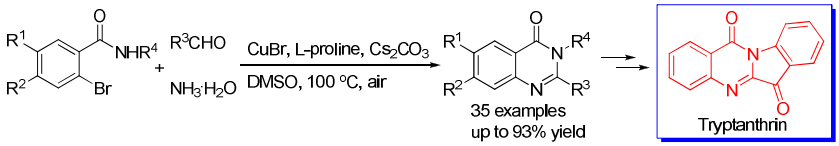
Graphical Abstract



An efficient synthesis of quinazolinones via copper-catalyzed tandem reaction of 2-bromobenzamides with aldehydes and aqueous ammonia has been developed.