Efficient Copper-Catalyzed Synthesis of 2-Amino-4(*3H*)-quinazolinone and 2-Aminoquinazoline Derivatives

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Abstract: We have developed a versatile and efficient method for copper-catalyzed synthesis of both 2-amino-4(*3H*)-quinazolinone and 2-aminoquinazoline derivatives. The protocol uses readily available substituted 2-halobenzoic acids, 2-bromobenzaldehyde, 2-bromophenyl ketones and guanidines as the starting materials, inexpensive copper(I) iodide as the catalyst, and the method has important application values for construction of N-heterocycles in organic chemistry and medicinal chemistry.

Key words: copper-catalyzed, cross-coupling, 2-amino-4(*3H*)-quinazolinone, 2-aminoquinazoline, synthetic method

The quinazoline skeleton is found to be an important class of molecules with physiological significance and pharmaceutical utility.[1] The quinazoline derivatives with different substituent groups show different biological and medicinal activity. 2-Amino-4(3*H*)-quinazolinone derivatives display a large range of biological properties such as antitumor (thymidylate synthase inhibition), antibacterial and antifungal activities,[2] antihypertensive effects,[3] or dopamine agonist activity.[4] They have also been shown to interfere with insulin secretion and smooth muscle contractile activity by targeting KATP channel activity,[5] and such molecules were used as analgesic and anti-inflammatory agents.[6]

For example, 2-(arylamino)-4(3*H*)-quinazolinone **A** is an inhibitor of the enzyme aldose reductase,[6] which prevents the onset of diabetic complications, and compound **B** shows antihypertensive activity (Figure 1).[7] Compound **C** displays potent inhibitors of tRNA-guanine transglycosylase,[8] and compound **D** was used as a 2′-deoxynucleotide analogue.[9] The 2-aminoquinazolines have been shown to be potential histamine H2 antagonists,[10] thymidylate synthase inhibitors,[11] cognition enhancement agents,[12] and inhibitors of tumor necrosis factor.[13] For example, it is reported that **E** is used as potent H4R (the human histamine H4 receptor) ligands,[14] arylaminoquinazoline pyridones **F** as potent, selective, and orally efficacious inhibitors of receptor tyrosine kinase c-Kit,[15] and **G** as a 2′-deoxynucleotide analogue (Figure 1).[16] Although some methods have been reported for the synthesis of 2-amino-4(3*H*)-quinazolinone[17] and 2-aminoquinazoline derivatives,[15,16] the routes used are often troublesome and some starting materials are not readily available or are difficult to prepare, so it is highly desirable to develop a more convenient and efficient method. Recently, great progress for copper-catalyzed N-arylations have been made,[18] and we have also developed some copper-catalyst systems that were used in N-arylations.[19] Some N-heterocycles have been constructed via the Ullmann coupling by us[20] and other research groups.[21] Herein, we report a simple, practical and efficient strategy for copper-catalyzed synthesis of 2-amino-4(3*H*)-quinazolinone and 2-aminoquinazoline derivatives.

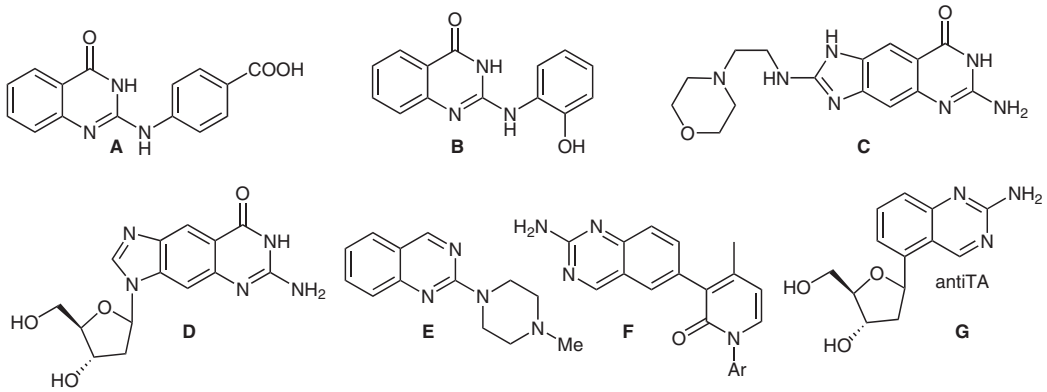

Figure 1 Several examples of 2-amino-4(3*H*)-quinazolinone and 2-aminoquinazoline derivatives with biological and medicinal activity

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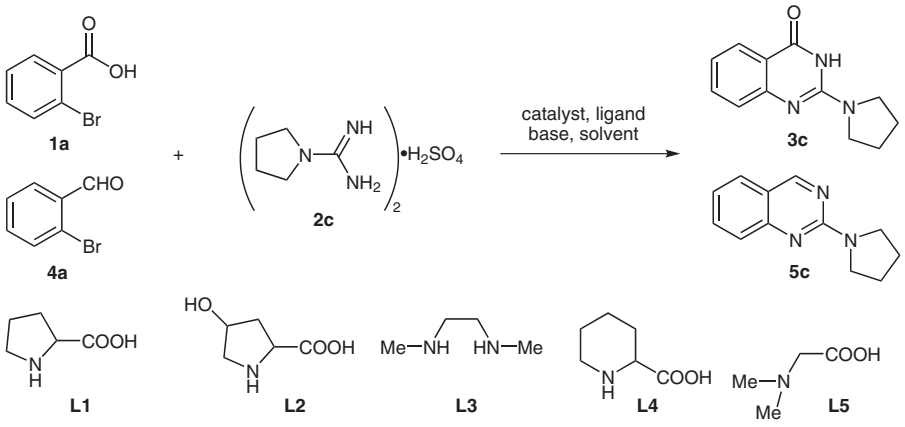
Initially, 2-bromobenzoic acid and pyrrolidine-1-carboxamidine sulfate were chosen as the model substrates to optimize reaction conditions including optimization of catalysts, solvents and bases. As shown in Table 1, several copper catalysts were tested using cesium carbonate as the base and *N*,*N*-dimethylformamide as the solvent under nitrogen atmosphere at 110 °C (entries 1–6), and copper iodide showed the best activity (entry 1). The effect of solvents was investigated (compare entries 1, 7 and 8), and *N*,*N*-dimethylformamide was the best choice (entry 1). Other bases, potassium carbonate and tripotassium phosphate, were also screened, and cesium carbonate

Table 1 Copper-Catalyzed Coupling of Pyrrolidine-1-carboxamidine Sulfate with 2-Bromobenzoic Acid or 2-Bromobenzaldehyde: Optimization of Conditions[a]

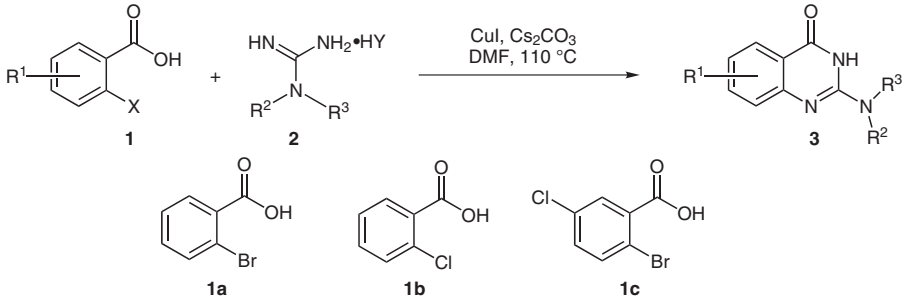


Entry	Catalyst	Ligand	Base	Solvent	Yield (%)[b]
1	CuI	–	Cs_2CO_3	DMF	85
2	Cu	–	Cs_2CO_3	DMF	67
3	$CuSO_4$	–	Cs_2CO_3	DMF	80
4	CuBr	–	Cs_2CO_3	DMF	75
5	Cu_2O	–	Cs_2CO_3	DMF	83
6	$Cu(OAc)_2·H_2O$	–	Cs_2CO_3	DMF	77
7	CuI	–	Cs_2CO_3	DMSO	78
8	CuI	–	Cs_2CO_3	toluene	trace
9	CuI	–	K_2CO_3	DMF	70
10	CuI	–	K_3PO_4	DMF	73
11	–	–	Cs_2CO_3	DMF	0
12	CuI	**L1**	Cs_2CO_3	DMF	78
13	CuI	–	Cs_2CO_3	DMF	21[c]
14	CuI	**L1**	Cs_2CO_3	DMF	67[c]
15	CuI	**L2**	Cs_2CO_3	DMF	41[c]
16	CuI	**L3**	Cs_2CO_3	DMF	65[c]
17	CuI	**L4**	Cs_2CO_3	DMF	32[c]
18	CuI	**L5**	Cs_2CO_3	DMF	38[c]
19	CuI	**L1**	Cs_2CO_3	DMF	53

[a] Reaction conditions: using **1a** as the substrate for entries 1–12; using **4a** as the substrate for entries 13–19. 2-Bromobenzoic acid or 2-bromobenzaldehyde (0.5 mmol), pyrrolidine-1-carboxamidine sulfate (**2c**) (1 mmol), catalyst (0.1 mmol), ligand (0.2 mmol), base (2 mmol), solvent (3 mL for entries 1–12, 5 mL for entries 13–19) under N_2. Reaction temperature (110 °C for entries 1–12, 120 °C for entries 13–19).
[b] Isolated yield.
[c] In the presence of 200 mg of 4 Å MS.

proved to be the most effective base (compare entries 1, 9 and 10). No target product was observed in the absence of catalyst (entry 11). Reaction yield decreased when L-proline was used as the ligand (entry 12). Reaction temperature was also investigated, the yield of the target product reached a maximum when temperature was gradually raised to 110 °C. However, reaction of 2-bromobenzaldehyde with pyrrolidine-1-carboxamidine sulfate did not perform well (entry 13) under the optimized conditions in entry 1. Various ligands **L1–L5** were screened in the presence of 200 mg of 4 Å MS (entries 14–18), and L-proline showed highest efficiency (entry 14). The coupling provided lower yield in the absence of 4 Å MS (entry 19). After the optimization process for catalysts, ligands, solvents and bases, the various 2-amino-4(3*H*)-quinazolinone and 2-aminoquinazoline derivatives were synthesized under our standard conditions: 20 mol% copper(I) iodide as the catalyst, 4 equivalents cesium carbonate as the base (relative to 2-halobenzoic acids, 2-bromobenzaldehydes or 2-bromophenyl ketones) and *N*,*N*-dimethylformamide as the solvent at 110 °C or 120 °C under a nitrogen atmosphere. 40 mol% L-proline as the ligand was required using 2-bromobenzaldehyde or 2-bromophenyl ketones as the substrates, and 4 Å MS was added for 2-bromobenzaldehyde.

Table 2 Copper-Catalyzed Synthesis of 2-Amino-4(*3H*)-quinazolinoe Derivatives[a]



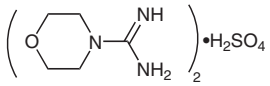
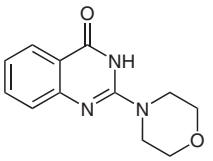
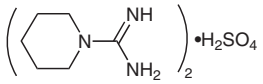
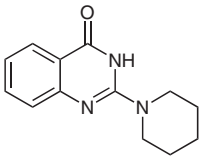
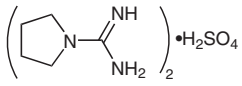
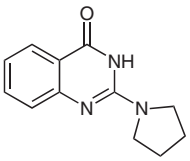
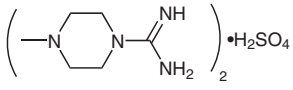
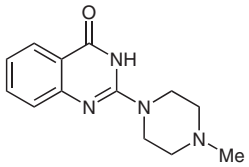
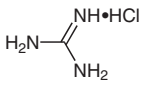
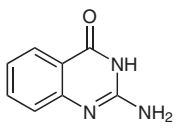
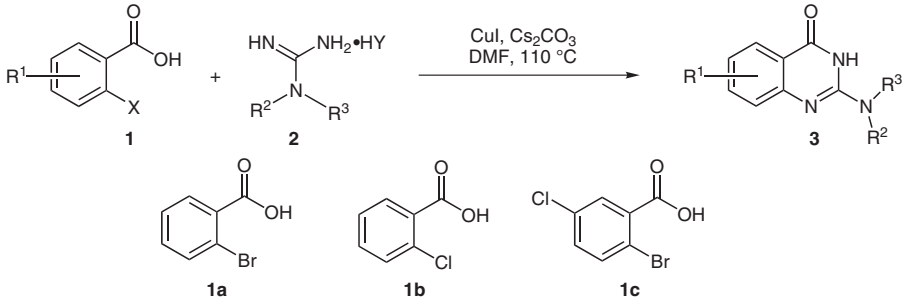
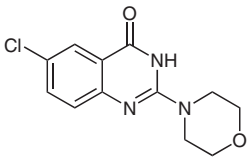
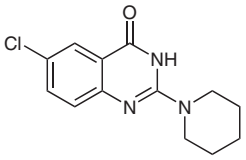
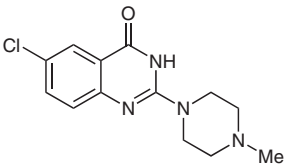
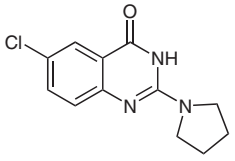
Entry	1	2	Product, Yield[b]
1	**1a**	 **2a**	 **3a** (81%)
2	**1a**	 **2b**	 **3b** (80%)
3	**1a**	 **2c**	 **3c** (85%)
4	**1a**	 **2d**	 **3d** (84%)
5	**1a**	 **2e**	 **3e** (64%)

Table 2 Copper-Catalyzed Synthesis of 2-Amino-4(*3H*)-quinazolinoe Derivatives[a] (continued)



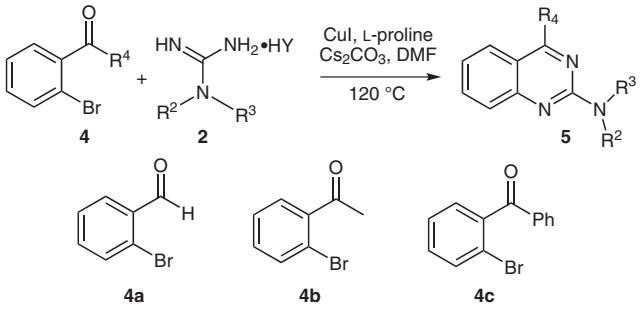
Entry	1	2	Product, Yield[b]
6	**1b**	**2a**	**3a** (74%)
7	**1b**	**2b**	**3b** (77%)
8	**1b**	**2c**	**3c** (78%)
9	**1b**	**2d**	**3d** (75%)
10	**1b**	**2e**	**3e** (50%)
11	**1c**	**2a**	 **3f** (90%)
12	**1c**	**2b**	 **3g** (94%)
13	**1c**	**2d**	 **3h** (93%)
14	**1c**	**2c**	 **3i** (95%)

[a] Reaction conditions: under N_2, substituted 2-halobenzoic acid (0.5 mmol), guanidine sulfate (1 mmol) or guanidine hydrochloride (1 mmol), CuI (0.1 mmol), Cs_2CO_3 (2 mmol), DMF (3 mL), reaction temperature (110 °C), reaction time (20 h for entries 1–4; 40 h for others).
[b] Isolated yield.

The scope of copper-catalyzed couplings of the substituted 2-halobenzoic acids with guanidine salt derivatives was investigated under our optimized conditions. As shown in Table 2, all the examined substrates gave the corresponding 2-amino-4(3*H*)-quinazolinone derivatives in good to excellent yields. The substituted guanidines displayed higher reactivity than free guanidine. Interestingly, 2-chlorobenzoic acid (**1b**) also provided good yields (entries 6–10). Aryl chlorides are weak substrates in the previous copper-catalyzed N-arylations,[18,19] and the results showed the *ortho*-effect of carboxyl during N-arylations (see the reaction mechanism). In addition, N-arylation for 2-bromo-5-chlorobenzoic acid selectively occurred at the *ortho*-site C–Br bond of carboxyl **1c**, and C–Cl bond at the 5-site remained which also exhibited the *ortho*-effect of carboxyl (entries 11–14). 2-Bromo-5-

chlorobenzoic acid (entries 11–14) provided higher yields than the other 2-halobenzoic acids. We also attempted cascade reactions of 2-bromobenzaldehyde or 2-bromophenyl ketones with guanidine salt derivatives to synthesize various 2-aminoquinazoline derivatives under our optimized conditions. As shown in Table 3, the tested substrates provided moderate to good yields. In general, the order of reactivity is 1-(2-bromophenyl)ethanone > 2-bromobenzaldehyde > (2-bromophenyl)(phenyl)methanone, and the substituted guanidines showed higher reactivity than free guanidine which are similar to the results shown in Table 2.

Table 3 Copper-Catalyzed Synthesis of 2-Aminoquinazoline Derivatives[a]



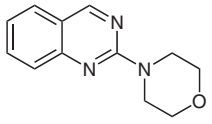
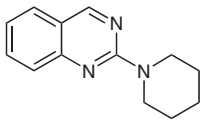
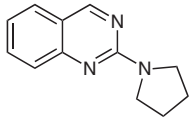
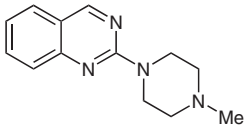
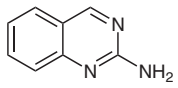
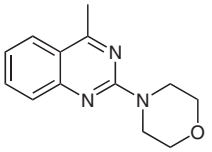
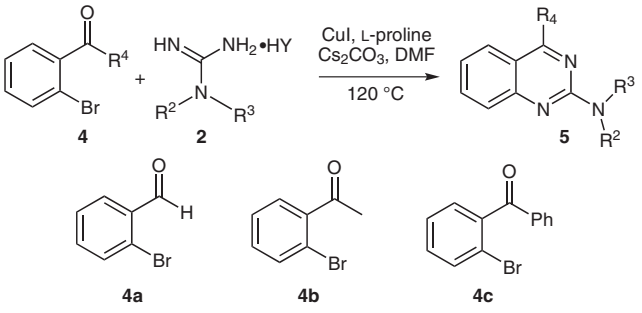
Entry	4	2	Product/Yield[b]
1	**4a**	**2a**	 **5a** (64%)
2	**4a**	**2b**	 **5b** (60%)
3	**4a**	**2c**	 **5c** (67%)
4	**4a**	**2d**	 **5d** (48%)
5	**4a**	**2e**	 **5e** (51%)
6	**4b**	**2a**	 **5f** (67%)

Table 3 Copper-Catalyzed Synthesis of 2-Aminoquinazoline Derivatives[a] (continued)



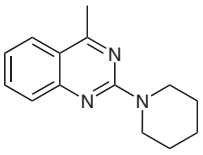
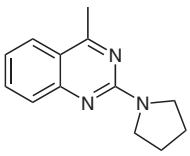
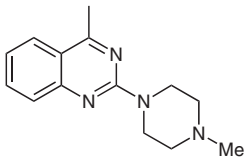
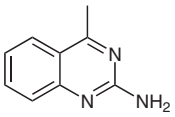
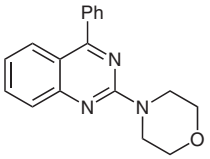
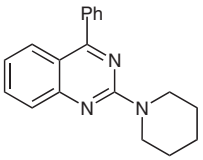
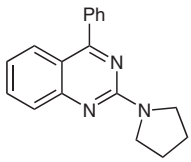
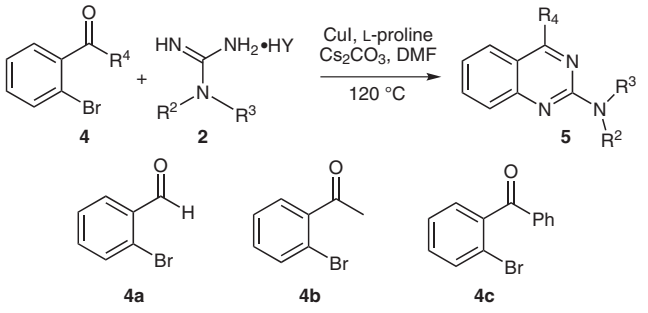
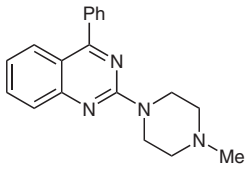
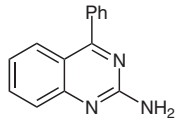
Entry	4	2	Product/Yield[b]
7	**4b**	**2b**	 **5g** (81%)
8	**4b**	**2c**	 **5h** (83%)
9	**4b**	**2d**	 **5i** (81%)
10	**4b**	**2e**	 **5j** (48%)
11	**4c**	**2a**	 **5k** (55%)
12	**4c**	**2b**	 **5l** (50%)
13	**4c**	**2c**	 **5m** (56%)

Table 3 Copper-Catalyzed Synthesis of 2-Aminoquinazoline Derivatives[a] (continued)



Entry	4	2	Product/Yield[b]
14	**4c**	**2d**	 **5n** (48%)
15	**4c**	**2e**	 **5o** (45%)

[a] Reaction conditions: under N_2, reaction temperature (120 °C), reaction time (40 h), aldehyde or ketone (0.5 mmol), guanidine sulfate (1 mmol) or guanidine hydrochloride (1 mmol), CuI (0.1 mmol), L-proline (0.2 mmol), Cs_2CO_3 (2 mmol), DMF (5 mL). 200 mg of 4 Å MS was added for aldehyde.
[b] Isolated yield.

A possible formation mechanism of 2-amino-4(3*H*)-quinazolinone derivatives was proposed in Scheme 1 according to the results shown in Table 2 and the *ortho*-substituent effect.[22] Coordination of substituted 2-halobenzoic acid with copper(I) iodide first forms **6** in the presence of base (Cs_2CO_3). Oxidative addition of **6** and a complex of copper with guanidine provides coordinate **7**, reductive elimination of **7** gives the N-arylation product (**8**) of guanidine, releasing copper catalyst, and coupling of the carboxyl and amino groups in **8** affords the target product **3** leaving water.

In summary, we have developed a versatile and efficient method for the copper-catalyzed synthesis of both 2-amino-4(3*H*)-quinazolinone and 2-aminoquinazoline derivatives. The couplings were performed using readily available starting materials (substituted 2-halobenzoic acids, 2-bromobenzaldehyde, 2-bromophenyl ketones and guanidines) and inexpensive catalyst (CuI). The present method shows simple, economical and practical advantages over the previous methods, so it will provide an opportunity for construction of diverse and useful molecules in biological chemistry and medicinal chemistry.

All reactions were carried out under N_2. NMR spectra were recorded on a Jeol JNM-ECA 300 spectrometer in $CDCl_3$ using TMS as the internal standard (^{1}H NMR: TMS at 0.00 ppm, $CDCl_3$ at 7.24 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm) or in DMSO-d_6 using TMS as the internal standard (^{1}H NMR: TMS at 0.00 ppm, DMSO at 2.50 ppm; ^{13}C NMR: DMSO at 40.0 ppm). Low-resolution ESI-MS were carried out on a Bruker ESQYIRE-LC spectrometer, and high-resolution mass spectra were recorded on a Waters Q-TOF Premier spectrometer. PE = petroleum ether (bp 60–90 °C).

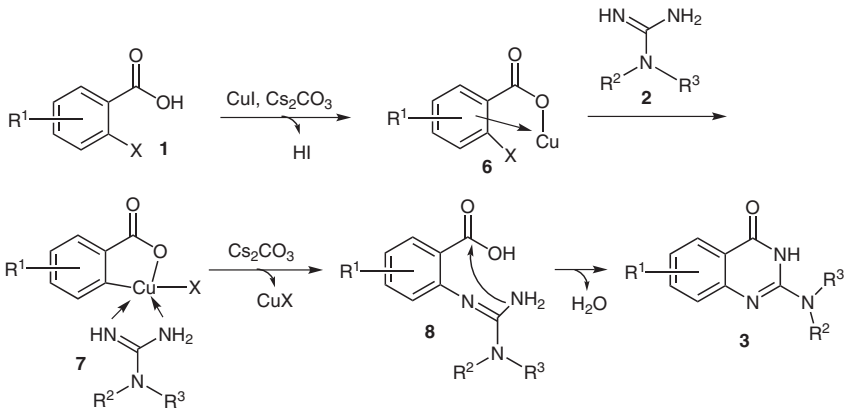
Compounds 3a–i; General Procedure

A two-neck round bottom flask was charged with a magnetic stirrer, evacuated and backfilled with N_2. Substituted 2-halobenzoic acid (0.5 mmol), guanidine sulfate (1 mmol) or guanidine hydrochloride (1 mmol), Cs_2CO_3 (2 mmol, 652 mg) and DMF (3 mL) were added. After stirring for 20 min under N_2, CuI (0.1 mmol) was added to the flask. The reaction temperature was raised to 110 °C. After 20 h (for entries 1–4 in Table 2) or 40 h (for entries 5–14 in Table 2), the resulting solution was cooled to r.t. and filtered, and the solid was washed with DMF (3 mL). The combined filtrate was concentrated with the aid of a rotary evaporator, and the residue was purified by column chromatography on silica gel to provide the desired product.

2-(Morpholin-1-yl)quinazolin-4(3*H*)-one (3a)[23]

Eluent: PE–EtOAc (2:1). Yield: 93 mg (81% using 2-bromobenzoic acid as the substrate); 85 mg (74% using 2-chlorobenzoic acid as the substrate). White solid; mp > 250 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.83 (br s, 1 H), 8.02 (d, *J* = 7.9 Hz, 1 H), 7.62 (t, *J* = 8.2 Hz, 1 H), 7.41 (d, *J* = 8.2 Hz, 1 H), 7.19 (t, *J* = 7.2 Hz, 1 H), 7.81–7.87 (m, 8 H).



Scheme 1 Possible formation mechanism of 2-amino-4(3*H*)-quinazolinone derivatives

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 165.6, 151.1, 150.4, 135.1, 126.2, 125.5, 123.0, 116.9, 66.7, 45.6.

MS: *m*/*z* $[M + H]^+$ = 232.2.

2-(Piperidin-1-yl)quinazolin-4(3*H*)-one (3b)[24]
Eluent: PE–EtOAc (2:1). Yield: 92 mg (80% using 2-bromobenzoic acid as the substrate); 89 mg (77% using 2-chlorobenzoic acid as the substrate). White solid; mp 225–228 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.55 (br s, 1 H), 8.04 (dd, *J* = 7.9, 1.4 Hz, 1 H), 7.57 (dt, *J* = 7.6, 1.4 Hz, 1 H), 7.37 (d, *J* = 8.2 Hz, 1 H), 7.12 (t, *J* = 7.9 Hz, 1 H), 3.77 (m, 4 H), 1.72 (m, 6 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 165.7, 151.6, 150.5, 134.8, 126.3, 125.2, 122.2, 116.6, 46.4, 25.8, 24.6.

MS: *m*/*z* $[M + H]^+$ = 230.3.

2-(Pyrrolidin-1-yl)quinazolin-4(3*H*)-one (3c)
Eluent: PE–EtOAc (2:1). Yield: 91 mg (85% using 2-bromobenzoic acid as the substrate); 84 mg (78% using 2-chlorobenzoic acid as the substrate). White solid; mp 232–235 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.00 (br s, 1 H), 8.05 (d, *J* = 7.6 Hz, 1 H), 7.57 (t, *J* = 8.3 Hz, 1 H), 7.38 (d, *J* = 8.3 Hz, 1 H), 7.10 (t, *J* = 7.2 Hz, 1 H), 3.71 (t, *J* = 6.2 Hz, 4 H), 2.06 (t, *J* = 6.5 Hz, 4 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 165.0, 151.7, 148.9, 134.6, 126.3, 124.6, 121.5, 116.2, 46.7, 25.4.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{14}N_3O$: 216.1137; found: 216.1141.

2-(4-Methylpiperazin-1-yl)quinazolin-4(3*H*)-one (3d)[23a]
Eluent: $CHCl_3$–MeOH (30:1). Yield: 103 mg (84% using 2-bromobenzoic acid as the substrate); 91 mg (75% using 2-chlorobenzoic acid as the substrate). White solid; mp 225–228 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 11.78 (br s, 1 H), 8.04 (d, *J* = 7.6 Hz, 1 H), 7.60 (t, *J* = 6.9 Hz, 1 H), 7.39 (d, *J* = 7.9 Hz, 1 H) 7.17 (t, *J* = 7.6 Hz, 1 H), 3.85 (t, *J* = 4.5 Hz, 4 H), 2.59 (t, *J* = 4.5 Hz, 4 H), 2.38 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75MHz): δ = 165.5, 151.3, 150.3, 134.9, 126.1, 125.3, 122.6, 116.7, 54.7, 46.1, 45.0.

MS: *m*/*z* $[M + H]^+$ = 245.2.

2-Aminoquinazolin-4(3*H*)-one (3e)[25]
Eluent: $CHCl_3$–MeOH (from 100:1 to 20:1). Yield: 52 mg (64% using 2-bromobenzoic acid as the substrate); 41 mg (50% using 2-chlorobenzoic acid as the substrate). White solid; mp > 250 °C.

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 11.18 (br s, 1 H), 7.87 (dd, *J* = 7.9, 1.4 Hz, 1 H), 7.55 (dt, *J* = 7.4, 1.7 Hz, 1 H), 7.19 (d, *J* = 8.3 Hz, 1 H), 7.09 (t, *J* = 7.6 Hz, 1 H), 6.50 (br s, 2 H).

^{13}C NMR (DMSO-d_6, 75 MHz): δ = 163.5, 152.7, 134.6, 126.5, 123.7, 122.1, 117.6.

MS: *m*/*z* $[M + H]^+$ = 162.2.

6-Chloro-2-(morpholin-1-yl)quinazolin-4(3*H*)-one (3f)
Eluent: $CHCl_3$–MeOH (from 100:1 to 60:1). Yield: 119 mg (90%). White solid; mp > 250 °C.

^{1}H NMR (DMSO-d_6, 600 MHz): δ = 11.58 (br s, 1 H), 7.84 (s, 1 H) 7.62 (dd, *J* = 8.4, 2.8 Hz, 1 H), 7.29 (d, *J* = 9.0 Hz, 1 H), 3.69–3.59 (m, 8 H),

^{13}C NMR (DMSO-d_6, 150 MHz): δ = 162.6, 151.6, 149.6, 134.9, 127.6, 126.6, 125.3, 118.7, 66.2, 45.9.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{13}ClN_3O_2$: 266.0696; found: 266.0702.

6-Chloro-2-(piperidin-1-yl)quinazolin-4(3*H*)-one (3g)[17c]
Eluent: $CHCl_3$–MeOH (from 100:1 to 60:1). Yield: 124 mg (94%). White solid; mp > 250 °C.

^{1}H NMR (DMSO-d_6, 600 MHz): δ = 11.44 (br s, 1 H), 7.81 (s, 1 H), 7.58 (dd, *J* = 8.5, 2.8 Hz, 1 H), 7.25 (d, *J* = 9.0 Hz, 1 H), 3.61 (t, *J* = 5.5 Hz, 4 H), 1.53–1.59 (m, 6 H).

^{13}C NMR (DMSO-d_6, 150 MHz): δ = 162.7, 151.2, 150.1, 134.8, 127.4, 126.0, 125.2, 118.2, 46.2, 25.6, 24.5.

MS: *m*/*z* $[M + H]^+$ = 264.1.

6-Chloro-(4-methylpiperazin-1-yl)quinazolin-4(3*H*)-one (3h)[26]
Eluent: $CHCl_3$–MeOH (from 100:1 to 30:1). Yield: 129 mg (93%). White solid; mp > 250 °C (Lit.[26] > 250 °C).

^{1}H NMR (DMSO-d_6, 600 MHz): δ = 11.50 (br s, 1 H), 7.82 (s, 1 H), 7.60 (dd, *J* = 8.6, 2.1 Hz, 1 H), 7.30 (d, *J* = 7.6 Hz, 1 H), 3.62 (t, *J* = 4.8 Hz, 4 H), 2.37 (t, *J* = 4.8 Hz, 4 H), 2.20 (s, 3 H).

^{13}C NMR (DMSO-d_6, 150 MHz) (small amount of D_2SO_4 was added to promote dissolving power of sample in DMSO-d_6): δ = 162.7, 157.6, 151.1, 146.0, 135.3, 128.1, 125.5, 118.5, 52.2, 43.0, 42.7.

MS: *m*/*z* $[M + H]^+$ = 279.1.

6-Chloro-2-(pyrrolidin-1-yl)quinazolin-4(3*H*)-one (3i)[26]
Eluent: $CHCl_3$–MeOH (from 100:1 to 60:1). Yield: 118 mg (95%). White solid; mp > 250 °C (Lit.[26] >250 °C).

^{1}H NMR (DMSO-d_6, 600 MHz): δ = 11.28 (br s, 1 H), 7.81 (s, 1 H), 7.54 (dd, *J* = 8.6, 2.8 Hz, 1 H), 7.23 (d, *J* = 8.9 Hz, 1 H), 3.49 (t, *J* = 6.2 Hz, 4 H), 1.90 (t, *J* = 6.2 Hz, 4 H).

^{13}C NMR (DMSO-d_6, 150 MHz) (small amount of D_2SO_4 was added to promote dissolving power of sample in DMSO-d_6): δ = 159.7, 147.2, 138.2, 136.5, 129.7, 126.3, 119.9, 116.6, 49.6, 25.1.

MS: *m*/*z* $[M + H]^+$ = 250.1.

Compounds 5a–o; General Procedure
A two-neck round bottom flask was charged with a magnetic stirrer, evacuated and backfilled with N_2. 2-Bromobenzaldehyde or 2-bromophenyl ketone (0.5 mmol), guanidine sulfate (1 mmol) or guanidine hydrochloride (1 mmol), L-proline (0.2 mmol), Cs_2CO_3 (2 mmol, 652 mg) and DMF (5 mL) were added (200 mg of 4 Å MS was added for 2-bromobenzaldehyde). After stirring for 20 min under N_2, CuI (0.1 mmol) was added to the flask, and then the reaction temperature was raised to 120 °C. After 40 h, the resulting solution was cooled to r.t. and filtered, and the solid was washed with DMF (3 mL). The combined filtrate was concentrated with the aid of a rotary evaporator, and the residue was purified by column chromatography on silica gel to provide the desired product.

2-(Morpholin-1-yl)quinazoline (5a)
Eluent: PE–EtOAc (40:1). Yield: 68 mg (64%). Yellow solid; mp 112–115 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 9.00 (s, 1 H), 7.68–7.63 (m, 2 H), 7.58 (d, *J* = 8.6 Hz, 1 H), 7.22 (t, *J* = 7.9 Hz, 1 H), 3.95 (t, *J* = 4.5 Hz, 4 H), 3.81 (t, *J* = 5.4 Hz, 4 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 161.5, 159.3, 152.2, 134.2, 127.5, 125.8, 122.8, 119.8, 67.0, 44.6.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{14}N_3O$: 216.1137; found: 216.1142.

2-(Piperidin-1-yl)quinazoline (5b)[27]
Eluent: PE–EtOAc (40:1). Yield: 63 mg (60%). Yellow solid; mp 148–150 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.96 (s, 1 H), 7.64–7.52 (m, 3 H), 7.17–7.12 (m, 1 H), 3.92 (t, *J* = 6.0 Hz, 4 H), 1.64 (m, 6 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 161.4, 159.4, 152.6, 133.9, 127.4, 125.6, 122.1, 119.4, 45.2, 26.0, 25.1.

MS: *m*/*z* $[M + H]^+$ = 214.4.

2-(Pyrrolidin-1-yl)quinazoline (5c)
Eluent: PE–EtOAc (40:1). Yield: 67 mg (67%). Yellow solid; mp 90–93 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.98 (s, 1 H), 7.66–7.57 (m, 3 H), 7.15 (td, *J* = 6.3, 1.5 Hz, 1 H), 3.70 (t, *J* = 6.6 Hz, 4 H), 2.03 (m, 4 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 161.2, 158.1, 152.7, 134.1, 127.6, 125.5, 121.8, 119.4, 47.0, 25.7.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{14}N_3$: 200.1188; found: 200.1185.

2-(4-methylpiperazin-1-yl)quinazoline (5d)[14]
Eluent: $CHCl_3$–MeOH (from 100:1 to 30:1). Yield 55 mg (48%). Yellow solid; mp 55–58 °C (Lit.[14] 74–76 °C).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.99 (s, 1 H), 7.65 (m, 2 H), 7.56 (d, *J* = 8.4 Hz, 1 H), 7.21 (t, *J* = 6.9 Hz, 1 H), 4.03 (m, 4 H), 2.57 (m, 4 H), 2.39 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 161.5, 159.2, 152.3, 134.2, 127.5, 125.7, 122.6, 119.7, 55.1, 46.2, 43.9.

MS: *m*/*z* $[M + H]^+$ = 229.2.

2-Aminoquinazoline (5e)[27b,28]
Eluent: $CHCl_3$–MeOH (from 100:1 to 50:1). Yield: 37 mg (51%). Yellow solid; mp 196–199 °C (Lit.[28] 204 °C).

^{1}H NMR (DMSO-d_6, 300 MHz): δ = 9.10 (s, 1 H), 7.77 (d, *J* = 7.9 Hz, 1 H), 7.66 (t, *J* = 6.8 Hz, 1 H), 7.42 (d, *J* = 8.2 Hz, 1 H), 7.20 (t, *J* = 6.9 Hz, 1 H), 6.91 (br s, 2 H).

^{13}C NMR (DMSO-d_6, 75 MHz): δ = 162.8, 161.4, 152.3, 134.5, 128.4, 125.0, 122.4, 120.0.

MS: *m*/*z* $[M + H]^+$ = 146.2.

4-Methyl-2-(morpholin-1-yl)quinazoline (5f)[29]
Eluent: PE–EtOAc (40:1). Yield: 77 mg (67%). Yellow solid; mp 62–64 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.84 (d, *J* = 8.3 Hz, 1 H), 7.64–7.59 (m, 2 H), 7.20 (td, *J* = 7.5, 1.8 Hz, 1 H), 3.96 (t, *J* = 4.5 Hz, 4 H), 3.81 (t, *J* = 4.6 Hz, 4 H), 2.78 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 169.1, 158.5, 151.9, 133.6, 126.4, 125.3, 122.4, 119.3, 67.1, 44.6, 21.9.

MS: *m*/*z* $[M + H]^+$ = 230.2.

4-Methyl-2-(piperidin-1-yl)quinazoline (5g)
Eluent: PE–EtOAc (40:1). Yield 92 mg (81%). Yellow solid, mp 69–71 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.70 (d, *J* = 8.3 Hz, 1 H), 7.60–7.52 (m, 2 H), 7.12 (m, 1 H), 3.93 (m, 4 H), 2.74 (s, 3 H), 1.63 (m, 6 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 168.7, 158.7, 152.3, 133.4, 126.2, 125.2, 121.7, 118.8, 45.0, 26.0, 25.1, 21.9.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{18}N_3$: 228.1501; found: 228.1504.

4-Methyl-2-(pyrrolidin-1-yl)quinazoline (5h)
Eluent: PE–EtOAc (40:1). Yield: 89 mg (83%). Yellow solid; mp 69–72 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.79 (d, *J* = 7.9 Hz, 1 H), 7.58–7.69 (m, 2 H), 7.11 (m, 1 H), 3.70 (t, *J* = 6.8 Hz, 4 H), 2.76 (s, 3 H), 2.00 (m, 4 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 168.7, 157.6, 152.4, 133.4, 126.0, 125.4, 121.4, 118.8, 46.8, 25.7, 21.9.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{16}N_3$: 214.1344; found: 214.1351.

4-Methyl-2-(4-methylpiperazin-1-yl)quinazoline (5i)
Eluent: $CHCl_3$–MeOH (30:1). Yield: 99 mg (81%). Yellow solid; mp 38–39 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.76 (d, *J* = 7.9 Hz, 1 H), 7.61–7.53 (m, 2 H), 7.14 (m, 1 H), 4.00 (t, *J* = 4.8 Hz, 4 H), 2.73 (s, 3 H), 2.50 (t, *J* = 4.8 Hz, 4 H), 2.33 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 168.8, 158.5, 152.0, 133.5, 126.3, 125.2, 122.1, 119.0, 55.2, 46.3, 43.9, 21.9.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{19}N_4$: 243.1610. found: 243.1612.

4-Methyl-2-aminoquinazoline (5j)
Eluent: $CHCl_3$–MeOH (100:1). Yield: 38 mg (48%). Yellow solid; mp 137–139 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.85 (d, *J* = 8.2 Hz, 1 H), 7.64 (t, *J* = 6.9 Hz, 1 H), 7.54 (d, *J* = 8.6 Hz, 1 H), 7.23 (t, *J* = 7.5 Hz, 1 H), 5.85 (br s, 2 H), 2, 77 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.3, 159.7, 151.6, 133.9, 125.7, 125.4, 122.8, 119.6, 21.6.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_9H_{11}N_3$: 160.0875; found: 160.0873.

4-Phenyl-2-(morpholin-1-yl)quinazoline (5k)[29]
Eluent: PE–EtOAc (50:1). Yield: 80 mg (55%). Yellow solid; mp 118–120 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.84 (d, *J* = 8.3 Hz, 1 H), 7.76–7.73 (m, 2 H), 7.66–7.65 (m, 2 H), 7.54–7.52 (m, 3 H), 7.19–7.14 (m, 1 H), 4.00 (t, *J* = 4.5 Hz, 4 H), 3.82 (t, *J* = 5.2 Hz, 4 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 169.4, 158.7, 153.5, 137.9, 133.7, 129.9, 129.8, 128.5, 127.4, 126.4, 122.6, 118.0, 67.1, 44.6.

MS: *m*/*z* $[M + H]^+$ = 292.1.

4-Phenyl-2-(piperidin-1-yl)quinazoline (5l)[29]
Eluent: PE–EtOAc (50:1). Yield: 72 mg (50%). Yellow solid; mp 96–98 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.77 (d, *J* = 8.6 Hz, 1 H), 7.74–7.69 (m, 2 H), 7.63–7.53 (m, 2 H), 7.49–7.45 (m, 3 H), 7.06 (dt, *J* = 7.2, 1.4 Hz, 1 H), 3.97 (t, *J* = 5.5 Hz, 4 H), 1.65 (m, 6 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 169.1, 158.8, 154.0, 138.2, 133.5, 130.0, 129.6, 128.4, 127.4, 126.3, 121.9, 117.6, 45.1, 26.2, 25.2.

MS: *m*/*z* $[M + H]^+$ = 290.2.

4-Phenyl-2-(pyrrolidin-1-yl)quinazoline (5m)
Eluent: PE–EtOAc (50:1). Yield: 77 mg (56%). Yellow solid; mp 146–149 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.81–7.72 (m, 3 H), 7.68–7.58 (m, 2 H), 7.52–7.50 (m, 3 H), 7.08 (dt, *J* = 7.4, 1.7 Hz, 1 H), 3.76 (t, *J* = 6.9 Hz, 4 H), 2.02 (m, 4 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 169.2, 157.7, 153.9, 138.2, 133.5, 129.9, 129.6, 128.4, 127.5, 126.0, 121.5, 117.6, 46.9, 25.7.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{18}N_3$: 276.1501; found: 276.1504.

4-Phenyl-2-(4-methylpiperazin-1-yl)quinazoline (5n)[29]
Eluent: $CHCl_3$–MeOH (30:1). Yield: 71 mg (48%). Yellow solid; mp 96–98 °C (Lit.[29] 97–98 °C).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.82 (d, *J* = 8.2 Hz, 1 H), 7.75–7.72 (m, 2 H), 7.64–7.62 (m, 2 H), 7.52–7.50 (m, 3 H), 7.12 (dt, *J* = 6.8, 2.7 Hz, 1 H), 4.06 (m, 4 H), 2.54 (m, 4 H), 2.37 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 169.2, 158.7, 153.7, 138.0, 133.6, 129.9, 129.7, 128.4, 127.4, 126.3, 122.3, 117.8, 55.2, 46.3, 44.0.

MS: *m*/*z* $[M + H]^+$ = 305.2.

2-Amino-4-phenylquinazoline (5o)[30]
Eluent: PE–EtOAc (from 20:1 to 2:1). Yield: 50 mg (45%). Yellow solid; mp 125–128 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.82 (d, *J* = 8.6 Hz, 1 H), 7.69–7.60 (m, 4 H), 7.54–7.51 (m, 3 H), 7.19 (t, *J* = 7.9 Hz, 1 H), 5.94 (br s, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.8, 159.8, 153.1, 137.2, 134.1, 129.9, 129.5, 128.6, 127.6, 125.7, 123.0, 118.5.

MS: *m*/*z* $[M + H]^+$ = 222.2.

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