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Synthesis of Pyrazolo[1,5-*c*]quinazoline Derivatives through Copper-Catalyzed Tandem Reaction of 5-(2-Bromoaryl)-1*H*-pyrazoles with Carbonyl Compounds and Aqueous Ammonia

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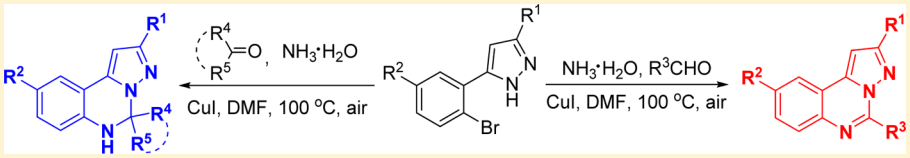
Supporting Information



ABSTRACT: A practical and efficient synthesis of pyrazolo[1,5-*c*]quinazolines and 5,6-dihydropyrazolo[1,5-*c*]quinazolines, including several spiro compounds, through copper-catalyzed tandem reaction of 5-(2-bromoaryl)-1*H*-pyrazoles with carbonyl compounds and aqueous ammonia under air has been developed. Compared with literature methods toward pyrazolo[1,5-*c*]quinazoline derivatives, the synthetic method reported in this paper has the advantages of readily available and inexpensive starting materials and reagents, broad scope of substrates, and mild reaction conditions.

INTRODUCTION

N-Fused heterocycles have attracted considerable interest since they are widely present in naturally occurring alkaloids with a broad range of biological activities.[1] In addition, they are also valuable building blocks of potential drug molecules such as Belotecan hydrochloride (CKD-602), Sitagliptin phosphate (MK-0431), and FK-453.[2] Among those N-fused heterocycles, pyrazolo[1,5-*c*]quinazoline derivatives have been used as Gly/NMDA receptor and excitatory amino acid antagonists,[3] potent phosphodiesterase 10A and Eg5 ATPase, and potential vaccinia virus inhibitors.[4] To date, the most frequently used synthetic routes toward pyrazolo[1,5-*c*]quinazoline derivatives involve the condensation of 5-(*o*-aminophenyl) pyrazoles with acyl chlorides, aldehydes, or ketones under the promotion of strong acid or base.[3−5] While these synthetic methods are generally efficient, they usually suffer from difficult to obtain starting materials, harsh reaction conditions, or multistep processes. Therefore, a more practical and general pathway toward pyrazolo[1,5-*c*]quinazoline skeleton starting from simple and easy to obtain starting materials is highly desirable.

Meanwhile, the development of novel copper-catalyzed coupling reactions to construct complex organic molecules has been one of the hottest research fields in organic synthesis. This is mainly due to the fact that, compared with other transition-metal catalysts, copper catalysts are efficient, inexpensive, less toxic, and easy to handle. Recently, copper-catalyzed coupling reactions have been extensively utilized in carbon−carbon and carbon−heteroatom bond formation reactions.[6] Through this kind of reaction, various N-fused heterocyclic compounds have been prepared.[7] On the basis of the above facts and as a continuation of our recent studies with regard to pyrazole derivatives,[8] we found that copper-catalyzed tandem reaction of 5-(2-bromoaryl)-1*H*-pyrazoles with carbonyl compounds and aqueous ammonia provided a straightforward route to pyrazolo[1,5-*c*]quinazolines as well as 5,6-dihydropyrazolo[1,5-*c*]quinazolines. Herein, we would like to disclose the details of our research work.

RESULTS AND DISCUSSION

Initially, we chose 5-(2-bromophenyl)-3-methyl-1*H*-pyrazole (**1a**), benzaldehyde (**2a**), and aqueous ammonia as model substrates to optimize the reaction conditions with regard to copper catalysts, solvents, and reaction temperature. After some trials, we were able to find that treatment of a mixture of **1a**, **2a**, and aqueous ammonia with CuCl (10 mol %) in DMSO at 100 °C in a sealed tube under air for 24 h could afford 2-methyl-5-phenylpyrazolo[1,5-*c*]quinazoline (**3a**) in 58% yield (Table 1, entry 1). It is noted that this Cu(I)-catalyzed tandem reaction could be realized in the absence of additional ligand and base. In this process, aqueous ammonia served not only as a reactant but also as a base to neutralize the in situ formed hydrobromic acid. Subsequently, several copper catalysts, including copper(I) and copper(II) salts, were screened by employing DMSO as the solvent. Among them, CuI emerged as the most efficient (compare entries 1−5). Then, the effect of solvent on this tandem reaction was also investigated by using CuI as the catalyst (compare entries 3 and 6−8), and a highest yield of 88% was obtained with DMF as the reaction medium (entry 6). It was also observed that reaction temperatures higher or lower

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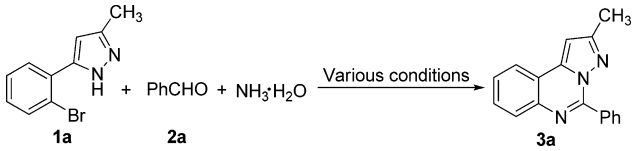
Table 1. Optimization of Reaction Conditions for the Synthesis of 3a[a]



1a 2a 3a

entry	catalyst	solvent	T (°C)	yield (%)[b]
1	CuCl	DMSO	100	58
2	CuBr	DMSO	100	65
3	CuI	DMSO	100	84
4	$Cu(OAc)_2$	DMSO	100	81
5	$CuCl_2$	DMSO	100	75
6	**CuI**	**DMF**	**100**	**88**
7	CuI	^{i}PrOH	100	27
8	CuI	toluene	100	0
9	CuI	DMF	120	70
10	CuI	DMF	80	47
11[c]	CuI	DMF	100	61

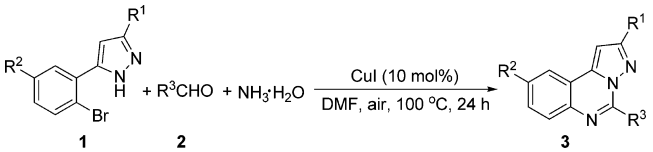
[a]Unless otherwise noted, the reactions were run with 0.4 mmol of **1a**, 0.48 mmol of **2a**, 0.04 mmol of catalyst, and 0.4 mL of 26% aqueous ammonia in 1.5 mL of solvent in a sealed tube under air for 24 h. [b]Isolated yield. [c]CH_3COONH_4 (6 mmol) was used to replace aqueous ammonia.

than 100 °C resulted in decreased yields of **3a** (entries 9 and 10). When ammonium acetate was used to replace aqueous ammonia as the source of ammonia, lower yield of **3a** was observed (entry 11).

With the optimized reaction conditions (Table 1, entry 6) in hand, the scope and generality of this copper-catalyzed tandem reaction leading to pyrazolo[1,5-*c*]quinazolines was studied. First, it was observed that while aryl-, heteroaryl-, alkenyl-, and alkyl-substituted aldehydes were all compatible with the reaction conditions to provide the desired products in moderate to good yields, aromatic aldehydes generally gave the corresponding products in yields higher than those of aliphatic aldehydes (Table 2, entries 14, 15, 20, and 25). It was also found that aryl-substituted aldehydes with various substituents on the aryl ring underwent this tandem reaction smoothly, and various functional groups, from the electron-rich methoxy to the electron-deficient trifluoromethyl, were well tolerated with the reaction conditions. With 1-naphthaldehyde and heteroaryl aldehydes, the corresponding products **3j**−**3l** were obtained in 58−71% yields (entries 10−12). Moreover, the reaction of cinnamaldehyde with **1a** and aqueous ammonia proceeded smoothly to give **3m** in 54% yield (entry 13). The effect of different R^1 and R^2 groups in 5-(2-bromoaryl)-1*H*-pyrazoles (**1**) on this reaction was also studied. It turned out that the electronic effect and steric hindrance of R^1 and R^2 did not show obvious effect on the output of the reactions.

To elucidate the mechanism of the copper-catalyzed tandem reaction, several control experiments were carried out. First, we found that, although copper-catalyzed direct amination of aryl halides with aqueous ammonia has been previously reported,[9] treatment of **1a** with aqueous ammonia in the presence of CuI (10 mol %) at 100 °C for 24 h resulted in a complex mixture, and the expected 5-(2-aminophenyl)-3-methyl-1*H*-pyrazole (**4**) was not observed by LCMS analysis (Scheme 1). This result might rule out the possibility of compound **4** as an intermediate for the formation of **3a**.

Table 2. Scope of the Synthesis of Pyrazolo[1,5-*c*]quinazolines (3)[a]

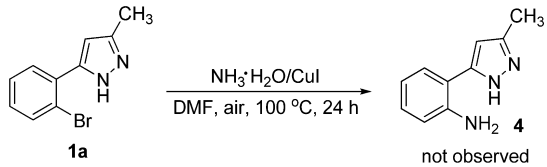


1 2 3

entry	R^1	R^2	R^3	product	yield (%)[b]
1	CH_3	H	Ph	**3a**	88
2	CH_3	H	4-$CH_3C_6H_4$	**3b**	80
3	CH_3	H	4-FC_6H_4	**3c**	61
4	CH_3	H	4-BrC_6H_4	**3d**	65
5	CH_3	H	4-ClC_6H_4	**3e**	75
6	CH_3	H	3-ClC_6H_4	**3f**	73
7	CH_3	H	2-ClC_6H_4	**3g**	40
8	CH_3	H	4-$CF_3C_6H_4$	**3h**	60
9	CH_3	H	3,4-$(CH_3O)_2C_6H_3$	**3i**	63
10	CH_3	H	1-naphthyl	**3j**	64
11	CH_3	H	4-pyridyl	**3k**	58
12	CH_3	H	2-thienyl	**3l**	71
13	CH_3	H	styryl	**3m**	54
14	CH_3	H	*n*-propyl	**3n**	35
15	CH_3	H	H[c]	**3o**	40
16	Ph	H	Ph	**3p**	82
17	Ph	H	4-$CH_3C_6H_4$	**3q**	75
18	Ph	H	4-ClC_6H_4	**3r**	72
19	Ph	H	1-naphthyl	**3s**	65
20	Ph	H	*n*-propyl	**3t**	57
21	4-ClC_6H_4	H	Ph	**3u**	79
22	4-$CH_3C_6H_4$	H	Ph	**3v**	73
23	Ph	Cl	Ph	**3w**	81
24	Ph	Cl	4-$CH_3C_6H_4$	**3x**	82
25	Ph	Cl	*n*-propyl	**3y**	48
26	Ph	CH_3O	Ph	**3z**	78

[a]The reactions were performed with **1** (0.4 mmol), **2** (0.48 mmol), CuI (0.04 mmol), 26% aqueous ammonia (0.4 mL), and DMF (1.5 mL) at 100 °C in a sealed tube under air for 24 h. [b]Isolated yield. [c]$(CHO)_n$ (2.0 equiv) was used.

Scheme 1. Attempted Amination of 1a with Aqueous Ammonia



1a 4 not observed

Second, it was observed that treating a mixture of **1a**, **2a**, and aqueous ammonia with CuI at 100 °C for 12 h under nitrogen atmosphere could afford 2-methyl-5-phenyl-5,6-dihydropyrazolo[1,5-*c*]quinazoline (**5a**) in a yield of 77%. Subsequently, stirring the solution of **5a** in DMF in the presence of CuI (10 mol %) at 100 °C under air for 5 h could afford **3a** in 96% yield (Scheme 2). These results suggested that **5a** should be a key intermediate of the above-described tandem process leading to **3a**.

Based on the above observations, a plausible mechanism for the formation of **3a** is illustrated in Scheme 3. Initially, condensation of benzaldehyde (**2a**) with aqueous ammonia affords phenylmethanimine (**I**). N-Arylation of **I** with 5-(2-bromophenyl)-3-methyl-1*H*-pyrazole (**1a**) under the catalysis

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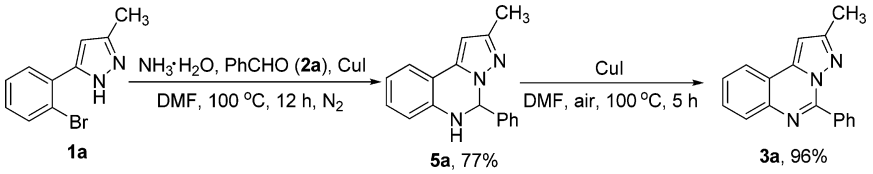
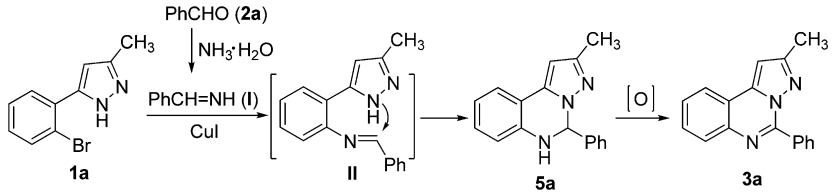
Scheme 2. Formation of 5a under Nitrogen and Its Transformation into 3a under Air



Scheme 3. Plausible Mechanism for the Formation of 3a



of CuI[10] gives rise to intermediate **II**. Intramolecular nucleophilic cyclization of **II** affords the key intermediate **5a**. Subsequent oxidative aromatization of **5a** by air in the presence of CuI gives **3a** as the final product.

Having established an efficient protocol for the preparation of pyrazolo[1,5-*c*]quinazolines via the tandem reaction of 5-(2-bromoaryl)-1*H*-pyrazoles with aldehydes and aqueous ammonia, we were then interested in whether this protocol was also compatible with ketones as the carbonyl component. Thus, **1a** (0.4 mmol) was treated with acetone (0.8 mmol) and aqueous ammonia under the optimized conditions for the preparation of **3** (Table 1, entry 6). We were pleased to find that the envisioned tandem reaction proceeded smoothly with acetone to generate the desired 2,5,5-trimethyl-5,6-dihydropyrazolo-[1,5-*c*]quinazoline (**7a**) in 44% yield. Furthermore, increasing the amount of acetone from 2 to 4 equiv could improve the yield of **7a** to 54% (Table 3, entry 1). Interestingly, with cyclopentanone (2 equiv) as the carbonyl component, 2′-methyl-6′*H*-spiro[cyclopentane-1,5′-pyrazolo[1,5-*c*]-quinazoline] (**7d**) could be obtained in a yield of 51% (Table 3, entry 4). Increasing the amount of cyclopentanone from 2 to 4 equiv did not improve the yield. Based on the above results, the scope of the reaction leading to 5,6-dihydropyrazolo[1,5-*c*]quinazolines **7** was explored by using 5-(2-bromoaryl)-1*H*-pyrazoles **1** (0.4 mmol), aqueous ammonia (0.4 mL), and acyclic ketones (1.6 mmol) or cyclic ketones (0.8 mmol) as reactants and CuI (0.04 mmol) as catalyst in DMF under air atmosphere (Table 3). It was found that various aliphatic ketones, including acyclic and cyclic ketones, were suitable substrates for this reaction and afforded the corresponding products in modest to good yields. Moreover, acetophenone, an aryl-substituted ketone, was also tried for this copper-catalyzed tandem reaction, but it failed to provide the desired product.

It is noted that, during our studies on this work, Fu and co-workers described an efficient copper-catalyzed one-pot, two-step synthesis of pyrazolo[1,5-*c*]quinazolines starting from 1-(2-halophenyl)-3-alkylprop-2-yn-1-ones, hydrazine, and amidines under the promotion of Cs_2CO_3.[11] Compared with Fu's synthesis of pyrazolo[1,5-*c*]quinazolines, our method has the following notable features. First, both pyrazolo[1,5-*c*]-quinazolines and 5,6-dihydropyrazolo[1,5-*c*]quinazolines, including the synthetically attractive spiro scaffolds, can be prepared with our method, while Fu's method is limited to the preparation of pyrazolo[1,5-*c*]quinazolines. Second, inert atmosphere is required in Fu's protocol, while our procedure is accomplished under air.

To further simplify the operation, we have tried a four-component protocol for the synthesis of pyrazolo[1,5-*c*]-quinazoline derivatives by using 1-(2-bromophenyl)-1,3-diones **8**, hydrazine hydrate, carbonyl compounds, and aqueous ammonia as the starting materials. Thus, 1-(2-bromophenyl)-butane-1,3-dione (**8a**) was treated with hydrazine hydrate (1.1 equiv) in DMF at room temperature for 2 h. Then, benzaldehyde (1.5 equiv), CuI (10 mol %), and aqueous ammonia were added. The mixture was then stirred at 100 °C for 24 h. To our delight, **3a** could be isolated from the resulting mixture in a total yield of 74% (Scheme 4).

The substrate scope of the above-described one-pot, two-step, four-component reaction was then studied. It showed that different combinations of 1-(2-bromophenyl)-1,3-diones with hydrazine hydrate, carbonyl compounds, and aqueous ammonia were proved to be suitable for this tandem process to provide the corresponding pyrazolo[1,5-*c*]quinazoline derivatives in reasonably good yields (Table 4, entries 1−6).

■ CONCLUSION

In summary, we have developed a facile methodology for the synthesis of pyrazolo[1,5-*c*]quinazolines or 5,6-dihydro-pyrazolo[1,5-*c*]quinazolines via copper-catalyzed tandem reaction of 5-(2-bromoaryl)-1*H*-pyrazoles with carbonyl compounds and aqueous ammonia under air atmosphere. Interestingly, with cyclic ketones, the corresponding spiro-5,6-dihydropyrazolo[1,5-*c*]quinazolines were successfully synthesized in modest yields. Moreover, we found that the tandem reaction could also be carried out in a one-pot, four-component manner by starting with 1-(2-bromophenyl)-1,3-diones, hydrazine hydrate, carbonyl compounds, and aqueous ammonia. Compared with literature procedures, advantages of the present protocol include readily available starting materials, diversity of products, good functional group tolerance, and simple operation process. Further application of this catalytic system to the synthesis of other N-fused heterocycles is currently underway in our laboratory.

■ EXPERIMENTAL SECTION

General Methods. Unless noted, all commercial reagents and solvents were used without further purification. 1-(2-Bromoaryl)-1,3-diones **8** were prepared according to the published methods.[12] 5-(2-Bromoaryl)-1*H*-pyrazoles **1** were prepared though the condensation of

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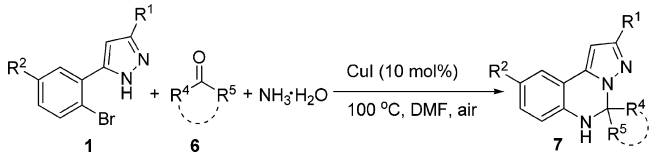
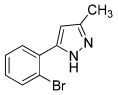
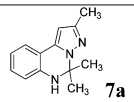
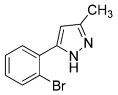
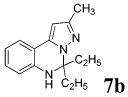
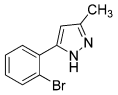
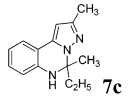
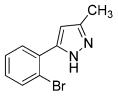
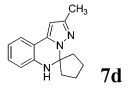
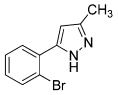
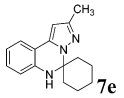
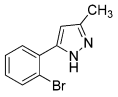
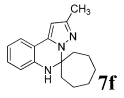
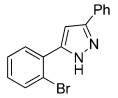
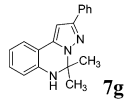
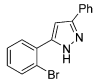
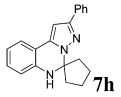
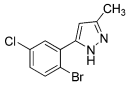
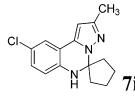
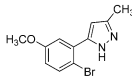
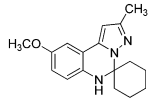
Table 3. Synthesis of 5,6-Dihydropyrazolo[1,5-*c*]quinazolines 7[a]

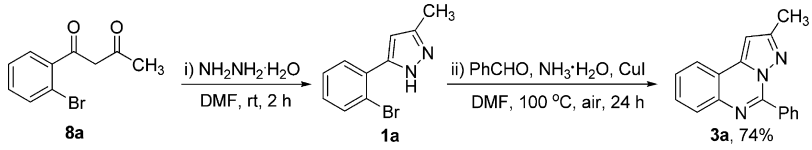


1 6 7

entry	1	6	time (h)	product	yield (%)[b]
1			4	 **7a**	54
2			6	 **7b**	33
3			6	 **7c**	54
4			6	 **7d**	51
5			4	 **7e**	69
6			5	 **7f**	32
7			12	 **7g**	55
8			12	 **7h**	44
9			4	 **7i**	54
10			5	 **7j**	60

[a]The reactions were carried out with **1** (0.4 mmol), acyclic ketone (1.6 mmol) or cyclic ketone (0.8 mmol), CuI (0.04 mmol), 26% aqueous ammonia (0.4 mL), and DMF (1.5 mL) at 100 °C in a sealed tube under air for the indicated time. [b]Isolated yield.

Scheme 4. One-Pot, Four-Component Reaction Leading to 3a



8a **1a** **3a**, 74%

1-(2-bromoaryl)-1,3-diones **8** with hydrazine hydrate according to the literature procedures.[13] Melting points were recorded with a micro melting point apparatus and uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. High-resolution mass spectra (HRMS) were obtained by using a MicrOTOF mass spectrometer. 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).

General Procedure for the Preparation of Pyrazolo[1,5-*c*]quinazolines 3. To a tube containing 5-(2-bromoaryl)-1*H*-pyrazole **1** (0.4 mmol), aldehyde **2** (0.48 mmol), and CuI (0.04 mmol) in DMF (1.5 mL) was added 26% aqueous ammonia (0.4 mL). Then, the tube was sealed, and the mixture was stirred at 100 °C under air atmosphere for 12 h. After being cooled to room temperature, the tube was open to air for 1 min and then sealed again. Upon being stirred at 100 °C for another 12 h, the reaction was quenched with NH_4Cl solution and extracted with ethyl acetate two times. The combined organic layer

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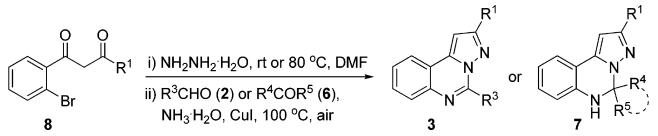
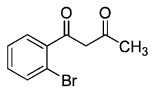
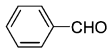
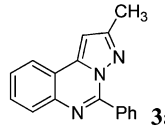
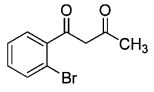
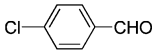
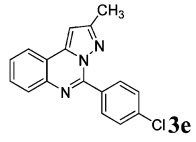
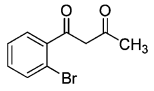
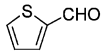
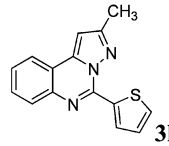
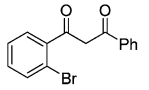
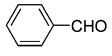
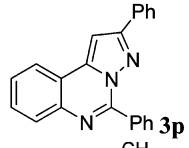
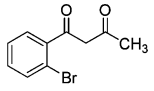
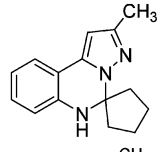
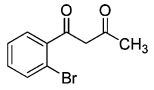
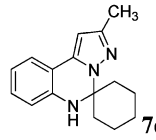
Table 4. One-Pot, Four-Component Synthesis of Pyrazolo[1,5-*c*]quinazoline Derivatives[a]



entry	8	2 or 6	product	yield (%)[b]
1			 **3a**	74
2			 **3e**	70
3			 **3l**	55
4			 **3p**	44
5			 **7d**	36
6			 **7e**	38

[a]Reaction conditions: **8** (0.5 mmol), hydrazine hydrate (0.55 mmol), DMF (2 mL), 2 h, room temperature for R^1 = Me; 80 °C for R^1 = Ph, and then CuI (0.05 mmol), aqueous ammonia (0.5 mL), aldehyde (0.75 mmol) or ketone (1.0 mmol), 100 °C, air, 24 h for aldehyde, 5 h for ketone. [b]Isolated yield.

was washed with H_2O and brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the crude product was purified by chromatography on silica gel to afford the desired pyrazolo[1,5-*c*]quinazoline **3**.

2-Methyl-5-phenylpyrazolo[1,5-*c*]quinazoline (3a): Petroleum ether/ethyl acetate (8:1) as eluent; white solid (91 mg, 88%), mp 68−70 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.55 (s, 3H), 6.83 (s, 1H), 7.54−7.65 (m, 5H), 7.96−8.00 (m, 2H), 8.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 98.2, 119.3, 122.9, 127.3, 128.2, 128.5, 129.5, 130.3, 130.9, 132.9, 140.0, 141.3, 147.5, 153.4; HRMS (ESI) calcd for $C_{17}H_{14}N_3$ $[M + H]^+$ 260.1182, found 260.1166.

2-Methyl-5-*p*-tolylpyrazolo[1,5-*c*]quinazoline (3b): Petroleum ether/ethyl acetate (8:1) as eluent; white solid (87 mg, 80%), mp 76−78 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.46 (s, 3H), 2.55 (s, 3H), 6.81 (s, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.51 (t, J = 7.6 Hz, 1H), 7.59−7.64 (m, 1H), 7.96 (t, J = 8.0 Hz, 2H), 8.31 (d, J = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 21.6, 98.1, 119.3, 122.9, 127.1, 128.5, 128.9, 129.5, 130.1, 130.3, 140.1, 141.2, 141.3, 147.6, 153.3; HRMS (ESI) calcd for $C_{18}H_{16}N_3$ $[M + H]^+$ 274.1339, found 274.1326.

5-(4-Fluorophenyl)-2-methylpyrazolo[1,5-*c*]quinazoline (3c): Petroleum ether/ethyl acetate (8:1) as eluent; white solid (68 mg, 61%), mp 119−121 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.55 (s, 3H), 6.84 (s, 1H), 7.24 (t, J = 8.4 Hz, 2H), 7.52−7.56 (m, 1H), 7.61−7.65 (m, 1H), 7.96−7.98 (m, 2H), 8.48 (t, J = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 98.3, 115.2 (d, J = 22.1 Hz, 2C), 119.3, 122.9, 127.4, 128.5, 129.0 (d, J = 3.1 Hz, 1C), 129.6, 132.7 (d, J = 8.3 Hz, 2C), 139.9, 141.4. 146.3, 153.5, 164.4 (d, J = 250.0 Hz, 1C); HRMS (ESI) calcd for $C_{17}H_{13}FN_3$ $[M + H]^+$ 278.1088, found 278.1108.

5-(4-Bromophenyl)-2-methylpyrazolo[1,5-*c*]quinazoline (3d): Petroleum ether/ethyl acetate (8:1) as eluent; white solid (88 mg, 65%), mp 176−178 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.54 (s, 3H), 6.82 (s, 1H), 7.54 (t, J = 7.6 Hz, 1H), 7.63 (t, J = 7.2 Hz, 1H), 7.69 (d, J = 8.4 Hz, 2H), 7.96 (d, J = 8.0 Hz, 2H), 8.33 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 98.4, 119.4, 123.0, 125.6, 127.6, 128.6, 129.7, 131.4, 131.8, 132.0, 139.8, 141.4, 146.3, 153.6; HRMS (ESI) calcd for $C_{17}H_{13}BrN_3$ $[M + H]^+$ 338.0287, found 338.0315.

5-(4-Chlorophenyl)-2-methylpyrazolo[1,5-*c*]quinazoline (3e): Petroleum ether/ethyl acetate (8:1) as eluent; white solid (88 mg, 75%), mp 174−176 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.55 (s, 3H), 6.83 (s, 1H), 7.52−7.56 (m, 3H), 7.63 (t, J = 7.6 Hz, 1H), 7.96 (d, J = 8.0 Hz, 2H), 8.41 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 98.3, 119.3, 122.9, 127.5, 128.4, 128.6, 129.6, 131.3, 131.8, 137.0, 139.9, 141.4, 146.2, 153.5; HRMS (ESI) calcd for $C_{17}H_{13}ClN_3$ $[M + H]^+$ 294.0793, found 294.0819.

5-(3-Chlorophenyl)-2-methylpyrazolo[1,5-*c*]quinazoline (3f): Petroleum ether/ethyl acetate (8:1) as eluent; white solid (86 mg,

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73%), mp 140−142 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.54 (s, 3H), 6.79 (s, 1H), 7.46−7.54 (m, 3H), 7.59−7.63 (m, 1H), 7.92−7.96 (m, 2H), 8.34−8.35 (m, 1H), 8.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 98.4, 119.3, 122.9, 127.6, 128.58, 128.62, 129.4, 129.7, 130.4, 130.9, 134.1, 134.5, 139.7, 141.3, 145.8, 153.6; HRMS (ESI) calcd for $C_{17}H_{13}ClN_3$ $[M + H]^+$ 294.0793, found 294.0811.

5-(2-Chlorophenyl)-2-methylpyrazolo[1,5-*c*]quinazoline (3g): Petroleum ether/ethyl acetate (8:1) as eluent; white solid (47 mg, 40%), mp 139−141 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.49 (s, 3H), 6.84 (s, 1H), 7.45−7.52 (m, 2H), 7.55−7.61 (m, 2H), 7.64−7.68 (m, 2H), 8.01 (t, J = 8.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.5, 98.7, 119.7, 123.2, 127.1, 127.9, 128.7, 129.7, 130.0, 130.8, 131.3, 133.1, 133.6, 139.7, 140.4, 146.5, 154.1; HRMS (ESI) calcd for $C_{17}H_{13}ClN_3$ $[M + H]^+$ 294.0793, found 294.0783.

2-Methyl-5-(4-(trifluoromethyl)phenyl)pyrazolo[1,5-*c*]-quinazoline (3h). Petroleum ether/ethyl acetate (8:1) as eluent; white solid (79 mg, 60%), mp 104−106 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.55 (s, 3H), 6.83 (s, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.62−7.66 (m, 1H), 7.82 (d, J = 8.8 Hz, 2H), 7.97 (d, J = 8.0 Hz, 2H), 8.54 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 98.4, 119.4, 123.0, 123.9 (q, J = 270.5 Hz, CF_3), 125.1 (q, J = 3.8 Hz, 2C), 127.8, 128.7, 129.7, 130.8, 132.4 (q, J = 32.0 Hz, 1C), 136.2, 139.7, 141.3, 145.9, 153.7; HRMS (ESI) calcd for $C_{18}H_{13}F_3N_3$ $[M + H]^+$ 328.1056, found 328.1086.

5-(3,4-Dimethoxyphenyl)-2-methylpyrazolo[1,5-*c*]-quinazoline (3i): Petroleum ether/ethyl acetate (5:1) as eluent; white solid (80 mg, 63%), mp 106−107 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.54 (s, 3H), 3.97 (s, 3H), 4.01 (s, 3H), 6.81 (s, 1H), 7.03 (d, J = 8.8 Hz, 1H), 7.50 (t, J = 7.2 Hz, 1H), 7.61 (t, J = 8.0 Hz, 1H), 7.94−7.97 (m, 2H), 8.02 (d, J = 1.6 Hz, 1H), 8.17 (dd, J = 2.0, 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 56.0, 56.1, 98.2, 110.4, 113.4, 119.2, 122.9, 124.2, 125.3, 127.1, 128.4, 129.6, 140.0, 141.5, 147.0, 148.5, 151.4, 153.3; HRMS (ESI) calcd for $C_{19}H_{18}N_3O_2$ $[M + H]^+$ 320.1394, found 320.1416.

2-Methyl-5-(naphthalen-1-yl)pyrazolo[1,5-*c*]quinazoline (3j): Petroleum ether/ethyl acetate (8:1) as eluent; white solid (79 mg, 64%), mp 163−165 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.44 (s, 3H), 6.88 (s, 1H), 7.41−7.45 (m, 1H), 7.50−7.54 (m, 1H), 7.59−7.73 (m, 4H), 7.94−7.96 (m, 2H), 8.06 (t, J = 8.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 98.6, 119.6, 123.1, 125.1, 125.3, 126.2, 126.8, 127.7, 128.1, 128.5, 128.7, 129.7, 130.7, 131.3, 133.8, 139.9, 140.8, 148.0, 153.9 (one ^{13}C signal was not observed); HRMS (ESI) calcd for $C_{21}H_{16}N_3$ $[M + H]^+$ 310.1339, found 310.1330.

2-Methyl-5-(pyridin-4-yl)pyrazolo[1,5-*c*]quinazoline (3k): Petroleum ether/ethyl acetate (5:1) as eluent; white solid (60 mg, 58%), mp 149−150 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.56 (s, 3H), 6.87 (s, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.64−7.68 (m, 1H), 7.98−8.01 (m, 2H), 8.39 (d, J = 3.6 Hz, 2H), 8.86 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 98.5, 119.6, 123.0, 124.3, 128.2, 128.9, 129.9, 139.6, 140.5, 141.3, 144.7, 149.7, 153.9; HRMS (ESI) calcd for $C_{16}H_{13}N_4$ $[M + H]^+$ 261.1135, found 261.1119.

2-Methyl-5-(thiophen-2-yl)pyrazolo[1,5-*c*]quinazoline (3l): Petroleum ether/ethyl acetate (8:1) as eluent; white solid (75 mg, 71%), mp 105−107 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.60 (s, 3H), 6.79 (s, 1H), 7.25−7.27 (m, 1H), 7.48 (t, J = 8.0 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.65 (d, J = 4.8 Hz, 1H), 7.93 (t, J = 8.0 Hz, 2H), 8.88 (d, J = 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.4, 98.1, 118.8, 122.9, 126.9, 127.8, 128.1, 129.6, 131.7, 133.7, 135.6, 139.9, 141.2, 141.8, 153.3; HRMS (ESI) calcd for $C_{15}H_{12}N_3S$ $[M + H]^+$ 266.0746, found 266.0770.

(*E*)-2-Methyl-5-styrylpyrazolo[1,5-*c*]quinazoline (3m): Petroleum ether/ethyl acetate (8:1) as eluent; yellow solid (62 mg, 54%), mp 113−115 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.57 (s, 3H), 6.74 (s, 1H), 7.38−7.48 (m, 4H), 7.60 (t, J = 7.6 Hz, 1H), 7.77 (d, J = 7.2 Hz, 2H), 7.91 (t, J = 8.8 Hz, 2H), 8.10 (d, J = 15.6 Hz, 1H), 8.28 (d, J = 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.3, 98.3, 117.5, 119.3, 123.1, 126.8, 128.1, 128.3, 128.8, 129.6, 129.7, 135.8, 140.0, 140.3, 140.4, 145.4, 153.1; HRMS (ESI) calcd for $C_{19}H_{16}N_3$ $[M + H]^+$ 286.1339, found 286.1352.

2-Methyl-5-propylpyrazolo[1,5-*c*]quinazoline (3n): Petroleum ether/ethyl acetate (5:1) as eluent; white solid (32 mg, 35%), mp 84−86 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.11 (t, J = 7.2 Hz, 3H), 1.98−2.08 (m, 2H), 2.54 (s, 3H), 3.30 (t, J = 8.0 Hz, 2H), 6.74 (s, 1H), 7.48 (t, J = 7.2 Hz, 1H), 7.59 (t, J = 7.2 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 14.3, 19.7, 34.7, 98.2, 119.3, 123.0, 126.8, 127.9, 129.4, 139.7, 140.1, 151.1, 153.1; HRMS (ESI) calcd for $C_{14}H_{16}N_3$ $[M + H]^+$ 226.1339, found 226.1334.

2-Methylpyrazolo[1,5-*c*]quinazoline (3o): Petroleum ether/ethyl acetate (5:1) as eluent; white solid (29 mg, 40%), mp 71−73 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.55 (s,3H), 6.77 (s, 1H), 7.57 (t, J = 8.0 Hz, 1H), 7.62−7.66 (m, 1H), 7.93 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 7.6 Hz, 1H), 9.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 98.2, 119.8, 123.2, 127.9, 128.5, 129.6, 139.0, 139.5, 139.7, 154.4; HRMS (ESI) calcd for $C_{11}H_{10}N_3$ $[M + H]^+$ 184.0869, found 184.0858.

2,5-Diphenylpyrazolo[1,5-*c*]quinazoline (3p) (ref 11): Petroleum ether/ethyl acetate (5:1) as eluent; white solid (105 mg, 82%), mp 107−109 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (s, 1H), 7.40−7.50 (m, 3H), 7.54−7.67 (m, 5H), 8.01−8.06 (m, 4H), 8.53−8.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 95.2, 119.5, 123.0, 126.8, 127.5, 128.1, 128.7, 128.8, 129.1, 129.8, 130.6, 131.0, 132.4, 132.7, 140.0, 141.8, 147.5, 154.7; MS (ESI) m/z 322.4 $[M + H]^+$.

2-Phenyl-5-*p*-tolylpyrazolo[1,5-*c*]quinazoline (3q) (ref 11): Petroleum ether/ethyl acetate (5:1) as eluent; white solid (101 mg, 75%), mp 132−134 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.51 (s, 3H), 7.29 (s, 1H), 7.41−7.43 (m, 3H), 7.46−7.54 (m, 3H), 7.63 (t, J = 8.0 Hz, 1H), 8.00 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 7.2 Hz, 2H), 8.49 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7, 95.1, 119.4, 122.9, 126.8, 127.3, 128.6, 128.75, 128.82, 129.0, 129.7, 129.9, 130.6, 132.5, 140.1, 141.3, 141.8, 147.5, 154.5; MS (ESI) m/z 336.4 $[M + H]^+$.

5-(4-Chlorophenyl)-2-phenylpyrazolo[1,5-*c*]quinazoline (3r): Petroleum ether/ethyl acetate (8:1) as eluent; white solid (103 mg, 72%), mp 170−172 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (s, 1H), 7.42−7.50 (m, 3H), 7.57 (t, J = 8.8 Hz, 3H), 7.66 (t, J = 7.2 Hz, 1H), 7.99−8.06 (m, 4H), 8.54 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 95.3, 119.4, 123.0, 126.8, 127.7, 128.3, 128.7, 128.8, 129.2, 129.9, 131.0, 132.1, 132.2, 137.2, 139.8, 141.9, 146.3, 154.8; HRMS (ESI) calcd for $C_{22}H_{15}ClN_3$ $[M + H]^+$ 356.0949, found 356.0974.

5-(Naphthalen-1-yl)-2-phenylpyrazolo[1,5-*c*]quinazoline (3s): Petroleum ether/ethyl acetate (8:1) as eluent; white solid (97 mg, 65%), mp 220−222 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.45 (m, 5H), 7.53 (t, J = 7.6 Hz, 1H), 7.64−7.74 (m, 3H), 7.80−7.86 (m, 3H), 7.97 (d, J = 8.4 Hz, 1H), 8.03−8.10 (m, 3H), 8.16 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 95.6, 119.8, 123.2, 125.0, 125.5, 126.1, 126.7, 126.8, 127.9, 128.4, 128.57, 128.65, 128.8, 129.0, 129.9, 130.4, 130.8, 131.4, 132.3, 133.8, 139.9, 141.4, 148.2, 155.1; HRMS (ESI) calcd for $C_{26}H_{18}N_3$ $[M + H]^+$ 372.1495, found 372.1486.

2-Phenyl-5-propylpyrazolo[1,5-*c*]quinazoline (3t) (ref 11): Petroleum ether/ethyl acetate (8:1) as eluent; white solid (65 mg, 57%), mp 76−78 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16 (t, J = 7.2 Hz, 3H), 2.10 (m, 2H), 3.40 (t, J = 7.6 Hz, 2H), 7.22 (s, 1H), 7.40−7.44 (m, 1H), 7.48−7.53 (m, 3H), 7.59−7.64 (m, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 8.0 Hz, 1H), 8.04−8.06 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 19.8, 34.8, 95.3, 119.4, 123.0, 126.8, 127.0, 128.1, 128.8, 129.0, 129.6, 132.7, 139.8, 140.5, 151.5, 154.5; MS (ESI) m/z 288.4 $[M + H]^+$.

2-(4-Chlorophenyl)-5-phenylpyrazolo[1,5-*c*]quinazoline (3u): Petroleum ether/ethyl acetate (8:1) as eluent; white solid (113 mg, 79%), mp 166−168 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25 (s, 1H), 7.42 (d, J = 8.0 Hz, 2H), 7.54−7.67 (m, 5H), 7.93 (d, J = 8.4 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 8.48−8.51 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 95.2, 119.4, 123.0, 127.7, 128.0, 128.2, 128.8, 129.0, 129.9, 130.6, 130.9, 131.1, 132.6, 135.0, 140.0, 142.0, 147.4, 153.5; HRMS (ESI) calcd for $C_{22}H_{15}ClN_3$ $[M + H]^+$ 356.0949, found 356.0975.

5-Phenyl-2-*p*-tolylpyrazolo[1,5-*c*]quinazoline (3v): Petroleum ether/ethyl acetate (8:1) as eluent; white solid (98 mg, 73%), mp 140−142 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.42 (s, 3H), 7.27−7.29

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(m, 3H), 7.54−7.67 (m, 5H), 7.93 (d, J = 7.6 Hz, 2H), 8.03 (t, J = 7.6 Hz, 2H), 8.54−8.56 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 95.1, 119.5, 123.0, 126.7, 127.5, 128.1, 128.7, 129.5, 129.6, 129.7, 130.7, 131.0, 132.8, 139.1, 140.0, 141.8, 147.5, 154.8; HRMS (ESI) calcd for $C_{23}H_{18}N_3$ $[M + H]^+$ 336.1495, found 336.1488.

9-Chloro-2,5-diphenylpyrazolo[1,5-*c*]quinazoline (3w) (ref 11): Petroleum ether/ethyl acetate (8:1) as eluent; white solid (115 mg, 81%), mp 148−150 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21 (s, 1H), 7.40−7.48 (m, 3H), 7.52−7.60 (m, 4H), 7.87 (d, J = 8.8 Hz, 1H), 7.93 (d, J = 2.4 Hz, 1H), 7.98 (d, J = 7.2 Hz, 2H), 8.50−8.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 95.6, 120.4, 122.3, 126.7, 128.1, 128.8, 129.2, 130.09, 130.14, 130.6, 131.1, 132.1, 132.4, 133.0, 138.3, 140.7, 147.4, 154.7; MS (ESI) m/z 356.8 $[M + H]^+$.

9-Chloro-2-phenyl-5-*p*-tolylpyrazolo[1,5-*c*]quinazoline (3x): Petroleum ether/ethyl acetate (8:1) as eluent; white solid (121 mg, 82%), mp 178−180 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.49 (s, 3H), 7.29 (s, 1H), 7.38−7.49 (m, 5H), 7.56 (dd, J = 2.0, 8.8 Hz, 1H), 7.91 (d, J = 8.8 Hz, 1H), 8.00−8.03 (m, 3H), 8.44−8.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7, 95.7, 120.4, 122.4, 126.8, 128.8, 128.9, 129.2, 129.6, 130.1, 130.7, 132.2, 132.9, 138.5, 140.8, 141.6, 147.7, 154.8 (one ^{13}C signal was not observed); HRMS (ESI) calcd for $C_{23}H_{17}ClN_3$ $[M + H]^+$ 370.1106, found 370.1093.

9-Chloro-2-phenyl-5-propylpyrazolo[1,5-*c*]quinazoline (3y): Petroleum ether/ethyl acetate (8:1) as eluent; white solid (62 mg, 48%), mp 98−100 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14 (t, J = 7.6 Hz, 3H), 2.06 (m, 2H), 3.35 (t, J = 7.6 Hz, 2H), 7.17 (s, 1H), 7.40−7.53 (m, 4H), 7.79 (d, J = 8.8 Hz, 1H), 7.91−7.92 (m, 1H), 8.00−8.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 19.7, 34.6, 95.7, 120.4, 122.4, 126.7, 128.9, 129.2, 129.6, 129.9, 132.3, 132.5, 138.2, 139.4, 151.7, 154.6; HRMS (ESI) calcd for $C_{19}H_{17}ClN_3$ $[M + H]^+$ 322.1106, found 322.1098.

9-Methoxy-2,5-diphenylpyrazolo[1,5-*c*]quinazoline (3z) (ref 11): Petroleum ether/ethyl acetate (8:1) as eluent; white solid (110 mg, 78%), mp 141−143 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.93 (s, 3H), 7.21−7.24 (m, 2H), 7.33 (m, 1H), 7.41−7.49 (m, 3H), 7.59−7.60 (m, 3H), 7.91 (d, J = 8.8 Hz, 1H), 8.03 (d, J = 7.2 Hz, 2H), 8.52−8.53 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 55.7, 95.0, 103.9, 119.1, 120.3, 126.7, 128.1, 128.7, 129.0, 130.2, 130.5, 130.6, 132.5, 132.9, 134.6, 141.6, 145.4, 154.2, 158.7; MS (ESI) m/z 352.4 $[M + H]^+$.

Typical Procedure for the Preparation of Compound 5a. To a mixture of pyrazole **1a** (94.8 mg, 0.4 mmol), benzaldehyde **2a** (48.7 μL, 0.48 mmol), and CuI (7.6 mg, 0.04 mmol) in DMF (1.5 mL) was added 26% aqueous ammonia (0.4 mL) in a sealed tube (15 mL) under nitrogen atmosphere, and the mixture was stirred at 100 °C for 12 h. The reaction was quenched with NH_4Cl solution and extracted with ethyl acetate two times. The combined organic layer was washed with H_2O and brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the crude product was purified by chromatography on silica gel, eluting with petroleum ether/ethyl acetate (3:1), to afford **5a** (80 mg) as white solid in 77% isolated yield (mp 158−160 °C): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.27 (s, 3H), 4.82 (br s, 1H), 6.37 (s, 1H), 6.44 (s, 1H), 6.62 (d, J = 7.6 Hz, 1H), 6.85−6.88 (m, 1H), 7.09−7.13 (m, 1H), 7.24−7.26 (m, 2H), 7.30−7.31 (m, 3H), 7.46−7.48 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 72.1, 99.3, 113.9, 114.8, 119.4, 123.8, 126.4, 128.7, 129.0, 129.1, 138.0, 139.1, 139.9, 149.5; HRMS (ESI) calcd for $C_{17}H_{16}N_3$ $[M + H]^+$ 262.1339, found 262.1364.

Typical Procedure for the Preparation of 3a via Copper-Catalyzed Aerobic Oxidation of 5a. To a solution of compound **5a** (64.3 mg, 0.246 mmol) in DMF (2 mL) was added CuI (4.7 mg, 0.0246 mmol), and then the mixture was stirred at 100 °C for 5 h under air atmosphere. The resultant mixture was poured into water and extracted with ethyl acetate two times. The combined organic layer was washed with H_2O and brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum and the crude product was purified by chromatography on silica gel to afford compound **3a** (62 mg) as white solid in 96% isolated yield.

General Procedure for the Preparation of 5,6-Dihydropyrazolo[1,5-*c*]quinazolines 7. To a mixture of pyrazole **1** (0.4 mmol), acyclic ketone (1.6 mmol) or cyclic ketone (0.8 mmol), and CuI (0.04 mmol) in DMF (1.5 mL) was added 26% aqueous ammonia (0.4 mL) in a sealed tube (15 mL) under air atmosphere, and the mixture was stirred at 100 °C for the time indicated in Table 3. Upon completion as monitored by TLC, the reaction was quenched with NH_4Cl solution and extracted with ethyl acetate two times. The combined organic layer was washed with H_2O and brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the crude product was purified by chromatography on silica gel to afford the desired 5,6-dihydropyrazolo[1,5-*c*]quinazoline **7**.

2,5,5-Trimethyl-5,6-dihydropyrazolo[1,5-*c*]quinazoline (7a): Petroleum ether/ethyl acetate (5:1) as eluent; white solid (46 mg, 54%), mp 105−106 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.72 (s, 6H), 2.34 (s, 3H), 4.20 (br s, 1H), 6.28 (s, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.85 (t, J = 7.6 Hz, 1H), 7.11−7.15 (m, 1H), 7.39−7.41 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 28.0, 71.9, 99.5, 114.8, 115.3, 119.7, 123.9, 129.1, 137.3, 139.2, 148.6; HRMS (ESI) calcd for $C_{13}H_{16}N_3$ $[M + H]^+$ 214.1339, found 214.1319.

5,5-Diethyl-2-methyl-5,6-dihydropyrazolo[1,5-*c*]quinazoline (7b). Petroleum ether/ethyl acetate (5:1) as eluent; white solid (32 mg, 33%), mp 73−75 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, J = 7.2 Hz, 6H), 1.75−1.84 (m, 2H), 2.29−2.38 (m, 2H), 2.32 (s, 3H), 3.91 (br s, 1H), 6.23 (s, 1H), 6.63 (d, J = 8.0 Hz, 1H), 6.74 (t, J = 7.6 Hz, 1H), 7.06−7.10 (m, 1H), 7.33 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 7.8, 13.9, 33.7, 77.7, 98.4, 112.9, 113.7, 118.3, 123.7, 129.2, 138.4, 140.2, 148.7; HRMS (ESI) calcd for $C_{15}H_{20}N_3$ $[M + H]^+$ 242.1652, found 242.1637.

5-Ethyl-2,5-dimethyl-5,6-dihydropyrazolo[1,5-*c*]quinazoline (7c): Petroleum ether/ethyl acetate (5:1) as eluent; white solid (49 mg, 54%), mp 67−69 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, J = 7.6 Hz, 3H), 1.74 (s, 3H), 1.80−1.86 (m, 1H), 2.14−2.20 (m, 1H), 2.32 (s, 3H), 4.13 (br s, 1H), 6.26 (s, 1H), 6.68 (d, J = 8.4 Hz, 1H), 6.81 (t, J = 8.0 Hz, 1H), 7.09−7.13 (m, 1H), 7.36−7.38 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.2, 13.8, 26.3, 33.7, 74.6, 99.1, 114.3, 114.8, 119.2, 123.8, 129.1, 137.5, 139.5, 148.6; HRMS (ESI) calcd for $C_{14}H_{18}N_3$ $[M + H]^+$ 228.1495, found 228.1501.

2′-Methyl-6′*H*-spiro[cyclopentane-1,5′-pyrazolo[1,5-*c*]-quinazoline] (7d): Petroleum ether/ethyl acetate (8:1) as eluent; white solid (49 mg, 51%), mp 131−133 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.78−1.81 (m, 2H), 1.92−1.95 (m, 4H), 2.33 (s, 3H), 2.44−2.49 (m, 2H), 4.32 (br s, 1H), 6.30 (s, 1H), 6.72 (d, J = 8.4 Hz, 1H), 6.87 (t, J = 7.6 Hz, 1H), 7.10−7.14 (m, 1H), 7.40 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 23.7, 38.0, 82.0, 99.8, 115.6, 115.7, 119.9, 123.9, 128.9, 138.0, 139.5, 148.5; HRMS (ESI) calcd for $C_{15}H_{18}N_3$ $[M + H]^+$ 240.1495, found 240.1506.

2′-Methyl-6′*H*-spiro[cyclohexane-1,5′-pyrazolo[1,5-*c*]-quinazoline] (7e): Petroleum ether/ethyl acetate (8:1) as eluent; white solid (70 mg, 69%), mp 110−112 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27−1.37 (m, 2H), 1.43−1.53 (m, 2H), 1.70−1.81 (m, 2H), 2.00−2.03 (m, 2H), 2.19 (dt, J = 4.0, 13,2 Hz, 2H), 2.34 (s, 3H), 4.60 (br s, 1H), 6.28 (s, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.85 (t, J = 7.2 Hz, 1H), 7.10−7.14 (m, 1H), 7.39 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 22.3, 24.6, 34.6, 72.9, 99.5, 115.4, 115.8, 119.7, 123.8, 129.0, 137.4, 138.7, 148.4; HRMS (ESI) calcd for $C_{16}H_{20}N_3$ $[M + H]^+$ 254.1652, found 254.1636.

2′-Methyl-6′*H*-spiro[cycloheptane-1,5′-pyrazolo[1,5-*c*]-quinazoline] (7f): Petroleum ether/ethyl acetate (5:1) as eluent; white solid (34 mg, 32%), mp 116−118 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.57−1.65 (m, 6H), 1.80 (s, 2H), 1.96−2.01 (m, 2H), 2.33 (s, 3H), 2.37−2.43 (m, 2H), 4.41 (br s, 1H), 6.27 (s, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.85 (t, J = 7.6 Hz, 1H), 7.13 (t, J = 8.0 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 22.6, 29.7, 39.5, 76.9, 99.3, 115.4, 115.7, 119.7, 123.7, 128.9, 137.1, 139.0, 148.4; HRMS (ESI) calcd for $C_{17}H_{22}N_3$ $[M + H]^+$ 268.1808, found 268.1826.

5,5-Dimethyl-2-phenyl-5,6-dihydropyrazolo[1,5-*c*]-quinazoline (7g): Petroleum ether/ethyl acetate (8:1) as eluent; white solid (61 mg, 55%), mp 172−174 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.80 (s, 6H), 4.13 (br s, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.80 (s, 1H), 6.91 (t, J = 8.0 Hz, 1H), 7.17 (t, J = 8.0 Hz, 1H), 7.31 (t, J = 7.2 Hz, 1H), 7.42 (t, J = 7.6 Hz, 2H), 7.51 (d, J = 7.2 Hz, 1H), 7.88 (d, J =

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7.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 28.0, 72.3, 96.9, 114.8, 115.5, 119.9, 124.0, 125.8, 127.6, 128.6, 129.2, 133.7, 137.6, 139.2, 151.3; HRMS (ESI) calcd for $C_{18}H_{18}N_3$ $[M + H]^+$ 276.1495, found 276.1506.

2′-Phenyl-6′*H*-spiro[cyclopentane-1,5′-pyrazolo[1,5-*c*]quinazoline] (7h): Petroleum ether/ethyl acetate (8:1) as eluent; white solid (53 mg, 44%), mp 150−152 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.83 (s, 2H), 1.99 (s, 4H), 2.61 (s, 2H), 4.23 (br s, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.83 (s, 1H), 6.93 (t, J = 8.0 Hz, 1H), 7.15−7.19 (m, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.44 (t, J = 8.0 Hz, 2H), 7.51−7.53 (m, 1H), 7.91 (d, J = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.9, 38.4, 82.4, 97.1, 115.6, 115.8, 120.1, 124.0, 125.7, 127.6, 128.6, 129.1, 133.8, 138.3, 139.6, 151.0; HRMS (ESI) calcd for $C_{20}H_{20}N_3$ $[M + H]^+$ 302.1652, found 302.1661.

9′-Chloro-2′-methyl-6′*H*-spiro[cyclopentane-1,5′-pyrazolo-[1,5-*c*]quinazoline] (7i): Petroleum ether/ethyl acetate (8:1) as eluent; white solid (59 mg, 54%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.75−1.78 (m, 2H), 1.88−1.95 (m, 4H), 2.31 (s, 3H), 2.41−2.46 (m, 2H), 4.34 (br s, 1H), 6.27(s, 1H), 6.65 (d, J = 8.0 Hz, 1H), 7.05 (dd, J = 2.4, 8.8 Hz, 1H), 7.35 (d, J = 2.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 23.7, 38.1, 82.0, 100.3, 117.0, 123.5, 124.7, 128.5, 136.9, 138.0, 148.7 (one ^{13}C signal was not observed); HRMS (ESI) calcd for $C_{15}H_{17}ClN_3$ $[M + H]^+$ 274.1106, found 274.1126.

9′-Methoxy-2′-methyl-6′*H*-spiro[cyclohexane-1,5′-pyrazolo-[1,5-*c*]quinazoline] (7j): Petroleum ether/ethyl acetate (8:1) as eluent; white solid (68 mg, 60%), mp 104−106 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.28−1.35 (m, 2H), 1.47−1.57 (m, 2H), 1.70−1.77 (m, 2H), 1.95−1.98 (m, 2H), 2.10−2.17 (m, 2H), 2.33 (s, 3H), 3.79 (s, 3H), 4.17 (br s, 1H), 6.27 (s, 1H), 6.73−6.79 (m, 2H), 6.95 (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.8, 22.3, 24.8, 34.3, 55.7, 73.0, 99.8, 108.5, 115.2, 117.7, 118.6, 132.1, 137.2, 148.2, 154.1; HRMS (ESI) calcd for $C_{17}H_{22}N_3O$ $[M + H]^+$ 284.1757, found 284.1744.

General Procedure for the Preparation of Pyrazolo[1,5-*c*]quinazoline Derivatives 3 or 7 via Copper-Catalyzed One-Pot, Four-Component Reaction. A mixture of compound **8** (0.5 mmol) and hydrazine hydrate (0.55 mmol) in DMF (2 mL) was stirred at room temperature or 80 °C for 2 h in a sealed tube. Then CuI (0.05 mmol), aldehyde (0.75 mmol) or aliphatic ketone (1.0 mmol), and 26% aqueous ammonia (0.5 mL) were successively added into the reaction system at room temperature, and the mixture was stirred at 100 °C for 24 h (for aldehyde) or 5 h (for ketone) in the same sealed tube under air atmosphere. The reaction was quenched with NH_4Cl solution and extracted with ethyl acetate two times. The combined organic layer was washed with H_2O and brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the crude product was purified by chromatography on silica gel to afford the desired product **3** or **7**.

Compounds **3a**, **3e**, **3l**, **3p**, **7d**, and **7e** were prepared through the above procedure, and the structure of these compounds was confirmed by ^{1}H NMR and TLC analysis.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra of **3a−3z**, **5a**, and **7a−7j**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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