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Copper-Catalyzed Tandem Reactions for Synthesis of Pyrazolo[5,1-*a*]isoquinolines with Heterocyclic Ketene Aminals as Ligands

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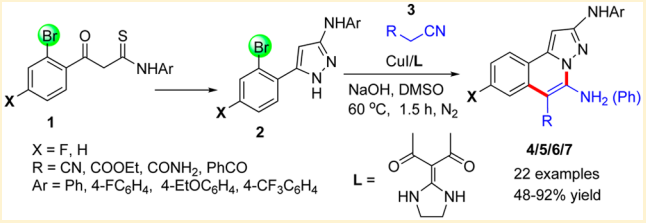
Supporting Information

ABSTRACT: A CuI-catalyzed tandem reaction of 5-(2-bromoaryl)-*N*-aryl-1*H*-pyrazol-3-amines with active acetonitrile derivatives to prepare pyrazolo[5,1-*a*]isoquinolines in good to excellent yields has been successfully developed under mild conditions with heterocyclic ketene aminals (HKAs) as new ligands. This is the first time HKAs have been used as ligands for copper-catalyzed coupling reactions.



INTRODUCTION

The exploration of privileged structures in drug discovery is a rapidly emerging theme in medicinal chemistry. The isoquinoline structural framework and heterofused analogues appear in a plethora of natural products and in a variety of known inhibitors for a broad range of receptors, such as the inhibitor of human topoisomerase I (lamellarin D)[1] and anticancer agents.[2] Additionally, functionalized pyrazolo[1,5-*a*]pyridines are important pharmacophores and str widely found in many biologically active compounds. Some of them were found to be novel cytokine-suppressive anti-inflammatory agents (an inhibitor of potent p38 kinase),[3] novel antiherpetic compounds possessing antiviral activity against HSV-1 and HSV-2,[4] and potential agents for melatonin receptor (MT1/MT2) ligands.[5]

The pyrazolo[5,1-*a*]isoquinoline motif, which incorporates both isoquinoline and pyrazolo[1,5-*a*]pyridine skeletons, was discovered to display promising activities, such as CDC25B inhibition, TC-PTP and PTP1B (protein tyrosine phosphatase) inhibition (compound **I**),[6] dopamine D4 receptor antagonism (compound **II**),[7] and CB1 cannabinoid receptor antagonism (compound **III**)[8] (Figure 1). Hence, the synthesis of pyrazoloisoquinoline incorporating two privileged heterocycles could be a valuable strategy to discover new bioactive compounds.

However, the synthesis of pyrazolo[5,1-*a*]isoquinolines has received little attention. The Wu group[9] has demonstrated that *N*′-(2-alkynylbenzylidene)hydrazide was the key species in tandem reactions for construction of the pyrazolo[5,1-*a*]-isoquinoline framework. Recently, they reported a reaction of 2-alkynylbenzaldehydes with 1*H*-pyrazole catalyzed by CuI to generate pyrazolo[5,1-*a*]isoquinolines.[10] Ackermann[11a] and Li[11b] also reported the synthesis of pyrazoloisoquinolines by Rh-catalyzed oxidative coupling. Despite some progresses being achieved in the synthesis of pyrazolo[5,1-*a*]isoquinolines, the construction of some specific substituted patterns remains difficult.

In the past few decades, research on copper-catalyzed coupling reactions of aryl halides with nucleophiles has gained a lot of attention and led to efficient C−C bond formation (Hurtley reactions) and C−heteroatom cross-coupling reactions (Ullmann condensation reactions and halide-exchange processes).[2c,12] Researchers from the groups of Buchwald,[13] Ma,[14] Taillefer,[15] Fu,[16] and Xi[17] elaborated convenient protocols for aryl halide amination, and an avalanche of publications have followed their pioneering works. During the development of these processes, ligand identification has played an important role in improving both the efficiencies and scope of the methodology. Although various well-known ligands have been reported, such as diamine derivatives,[18a,b] amino acids,[18c] *N*-hydroxyimides,[18d] diketones or diphenols,[18e] D-glucosamine,[18f,g] pyridine *N*-oxides,[18e,h] 2-pyridinyl *β*-ketones,[18f] and so on, room for exploration of a novel efficient ligand-assisted system still remains.

Heterocyclic ketene aminals (HKAs) have proven to be important synthons in the construction of heterocyclic systems.[19] *β*-Ketothioamides (KTAs) have emerged as powerful synthons in the construction of heterocycles.[20] In continuation of our ongoing research interest in the synthesis of heterocycles,[21] we became intrigued in exploring the use of HKAs as new ligands and KTAs as building blocks to develop a concise copper-catalyzed tandem reaction for the synthesis of pyrazolo[5,1-*a*]isoquinolines. To the best of our knowledge, no report on the use of HKAs as ligands for the copper-catalyzed coupling reactions has been disclosed.

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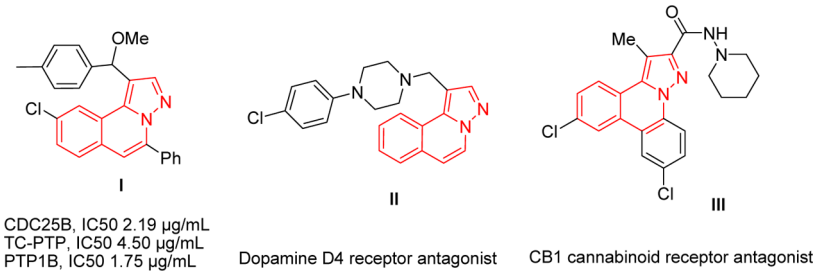
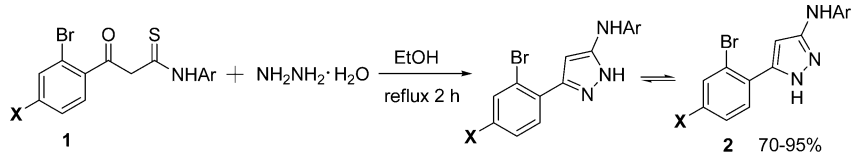


Figure 1. Representative examples of pyrazolo[5,1-*a*]isoquinolines with bioactivities.

Scheme 1. Synthesis of 5-(2-Bromoaryl)-*N*-aryl-1*H*-pyrazol-3-amines 2



RESULTS AND DISCUSSION

5-(2-Bromophenyl)-*N*-aryl-1*H*-pyrazol-3-amines **2**, required as the key cyclization precursors for the copper-catalyzed coupling reactions, were readily obtained by a modified method of earlier reported procedures,[20b,22] in which *β*-(2-bromoaroyl)-thioacetanilides **1** were utilized to react with hydrazine hydrate in EtOH (Scheme 1).

Since the conditions of copper-catalyzed coupling reactions, including catalysts, ligands, bases, solvents, and temperature, are crucial to the reaction outcome, a survey on these influential factors was carried out by using the reaction of 5-(2-bromophenyl)-*N*-phenyl-1*H*-pyrazol-3-amine (**2a**) and malononitrile (**3a**) as the model reaction (Table 1).

Initially, the presence of Na_2CO_3 as the base and a catalytic amount of CuI (10 mol %) as the copper source in DMSO at room temperature only led to recovered starting materials and very low conversion to the corresponding 5-amino-2-(phenylamino)pyrazolo[5,1-*a*]isoquinoline-6-carbonitrile (**4a**) (Table 1, entry 1). Then increasing the reaction temperature to 60 °C greatly improved the yield of **4a** (Table 1, entry 2), but a disappointing result was obtained with a further increase of the reaction temperature (Table 1, entry 3). Omission of the copper catalyst or base shut down the reactivity, and omission of the nitrogen atmosphere led to low conversion (Table 1, entries 1, 4, and 5). Next other bases such as NaOH and Cs_2CO_3 were screened, and the results showed that NaOH provided the highest yield of 60% (Table 1, entries 6 and 7). Also, the examination of various solvents showed that dioxane, DMF, and CH_3CN were not favored for this reaction (Table 1, entries 8−10).

With the optimum conditions above, we placed our focus on exploring ligands for CuI. Initially, common ligands were tested, and the results revealed they were not suitable for this reaction. For example, L-proline (**L1**), though being suitable for numerous copper-catalyzed reactions, is not very effective for this reaction and only gave 65% yield (Table 1, entry 11). Ethane-1,2-diamine (**L2**) performed worse (Table 1, entry 12). 1,10-Phenanthroline (**L3**) performed better, but also gave only 70% yield (Table 1, entry 13). Next we sought to evaluate the use of new ligands such as HKAs for this reaction. Gratifyingly, all five designed HKAs (**L4**−**L8**) afforded higher yields under the same reaction conditions (Table 1, entries 14−18). Even a catalytic amount of 3-(imidazolidin-2-ylidene)pentane-2,4-dione (**L4**; 10 mol %) gave an excellent yield of 90% (Table 1, entry 14).

As control subjects, pentane-2,4-dione (**L9**) and 1*H*-imidazole (**L10**) were also screened (Table 1, entries 19 and 20). As expected, **L9** also promoted this reaction, but its ability was inferior to that of **L4**, which might be due to the fact that **L9** is itself an activated methylene compound and is able to react with substrate **2a**, whereas few of the byproducts were observed for **L10**, which was subjected to the NH group participating in the nucleophilic attack on the cyano group. Finally, the ratio of ligand **L4** and CuI was tested, and the results suggested that the best ratio is 1:1 (Table 1, entries 21−23). Several other copper salts such as CuBr, CuCl, and $CuSO_4$ were also investigated, and CuI was proven to be most effective (Table 1, entries 24−26).

The scope of copper-catalyzed coupling reactions of 5-(2-bromoaryl)-*N*-aryl-1*H*-pyrazol-3-amines **2** with malononitrile (**3a**) or ethyl 2-cyanoacetate (**3b**) or 2-cyanoacetamide (**3c**) was investigated under optimized conditions (10 mol % CuI as the catalyst, 10 mol % **L4** as the ligand, 2 equiv of NaOH as the base in DMSO (2 mL) at 60 °C under a nitrogen atmosphere) (Table 2). The coupling reactions proceeded smoothly in all cases, giving rise to the corresponding pyrazolo[5,1-*a*]-isoquinolines **4**−**6**.

It is found from the reactions of various substituted 5-(2-bromoaryl)-*N*-aryl-1*H*-pyrazol-3-amines **2** with **3a** that the substituents on the *N*-aryl group have little effect on the nucleophilicity of the NH of pyrazole. Substrates **2** with an electron-withdrawing substituent on the *N*-aryl group gave higher yields than those with an electron-donating substituent. In addition, the substitution of a fluorine atom on the phenyl ring attached directly to the pyrazole ring also improved the reactivity of **2**.

Comparing the coupling reactions of **2** with **3a**, **3b**, and **3c**, it is found that the reaction yields of products **4**, **5**, and **6** are significantly different, which reveals the following order of reactivity: malononitrile (**3a**) > ethyl 2-cyanoacetate (**3b**) > 2-cyanoacetamide (**3c**).

Considering the lower price of aryl chlorides than the corresponding bromides, the coupling reaction of 5-(2-chlorophenyl)-*N*-phenyl-1*H*-pyrazol-3-amine with **3a** was investigated. As expected, a relatively low yield of 75% for **4a** was obtained because of the low activity of aryl chloride in the CuI-

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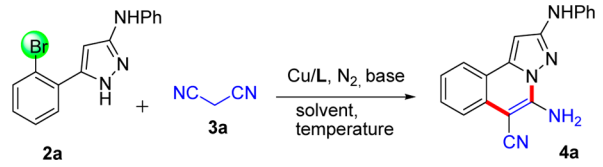
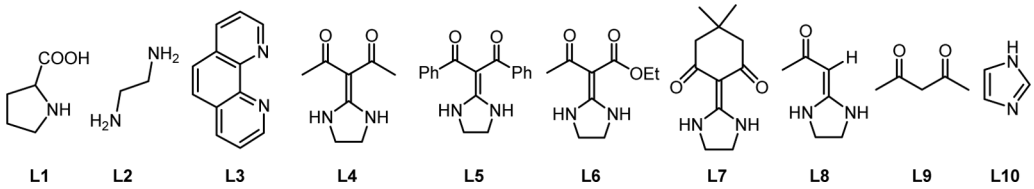
Table 1. Optimization of Reaction Conditions for the Copper-Catalyzed Synthesis of 4a[a]



entry	base	solvent	catalyst (amt/equiv)	L[b] (amt/equiv)	*T* /°C	time/h	yield[c] /%
1	Na_2CO_3	DMSO	CuI (0.1)		rt	3	30 or 15[d]
2	Na_2CO_3	DMSO	CuI (0.1)		60	3	50
3	Na_2CO_3	DMSO	CuI (0.1)		80	3	47
4	Na_2CO_3	DMSO			rt	6	NR[e]
5		DMSO	CuI (0.1)		rt	6	NR[e]
6	Cs_2CO_3	DMSO	CuI (0.1)		60	3	55
7	NaOH	DMSO	CuI (0.1)		60	3	60
8	NaOH	DMF	CuI (0.1)		60	3	45
9	NaOH	dioxane	CuI (0.1)		60	3	30
10	NaOH	CH_3CN	CuI (0.1)		60	3	32
11	NaOH	DMSO	CuI (0.1)	**L1** (0.1)	60	1	65
12	NaOH	DMSO	CuI (0.1)	**L2** (0.1)	60	1	50
13	NaOH	DMSO	CuI (0.1)	**L3** (0.1)	60	1	70
14	NaOH	DMSO	CuI (0.1)	**L4** (0.1)	60	1	90
15	NaOH	DMSO	CuI (0.1)	**L5** (0.1)	60	1	80
16	NaOH	DMSO	CuI (0.1)	**L6** (0.1)	60	1	85
17	NaOH	DMSO	CuI (0.1)	**L7** (0.1)	60	1	70
18	NaOH	DMSO	CuI (0.1)	**L8** (0.1)	60	1	72
19	NaOH	DMSO	CuI (0.1)	**L9** (0.1)	60	1	80
20	NaOH	DMSO	CuI (0.1)	**L10** (0.1)	60	1	61
21	NaOH	DMSO	CuI (0.05)	**L4** (0.05)	60	1	45
22	NaOH	DMSO	CuI (0.1)	**L4** (0.05)	60	1	75
23	NaOH	DMSO	CuI (0.1)	**L4** (0.2)	60	1	85
24	NaOH	DMSO	CuBr (0.1)	**L4** (0.1)	60	1	80
25	NaOH	DMSO	CuCl (0.1)	**L4** (0.1)	60	1	76
26	NaOH	DMSO	$CuSO_4$ (0.1)	**L4** (0.1)	60	1	50

[a]Reaction conditions: **2a** (0.5 mmol), malononitrile (**3a**) (0.6 mmol), base (1.0 mmol), solvent (2.0 mL), N_2. [b]The structures of the ligands are as follows:



[c]Isolated yield. [d]No nitrogen. [e]No reaction.

catalyzed tandem reaction (Table 2, entry 1). Moreover, increasing the reaction temperature failed to promote the coupling efficiency.

The new catalytic system was also found to be applicable to cross-coupling reactions of 5-(2-bromoaryl)-*N*-aryl-1*H*-pyrazol-3-amines **2a−c** with 3-oxo-3-phenylpropanenitrile (**3d**) (Scheme 2). However, it is worthwhile to note that these coupling reactions occurred in a different way: nucleophilic attack of the nitrogen atom of the pyrazole ring occurred on the carbonyl group rather than on the cyano group as previously reported.[23] Three examples were presented; all of them afforded the corresponding products **7a−c** in moderate yields under the same reaction conditions.

With respect to the reaction mechanism, it is currently believed that the reaction occurs via the formation of an intermediate, [L*n*Cu^{I}Nu][24] (where L is the ligand and Nu is the nucleophile), prior to aryl halide activation, which is also in agreement with the ESI-MS experiments in several recent studies.[25] Moreover, arylcopper(III) complexes have been identified recently through an oxidative addition to form a Cu(III) intermediate in terms of halide activation.[12(h),26] On the bsais of the above results, we formulated a possible mechanism for the copper-catalyzed tandem cyclization in Scheme 3. The Hurtley reaction constitutes the first step of this domino sequence. First, the chelating of CuI with **L4** forms a reactive species I. Then, in the presence of a base, intermediate II (LCu^{I}Nu) is formed (where L is the ligand **L4** and Nu is the nucleophile carbanion from active acetonitrile derivatives **3**), and the subsequent oxidative addition of II with aryl halides **2** leads to the intermediate III (arylcopper(III)). Then the intermediate II (LCu^{I}Nu) is regenerated by a putative reductive elimination followed by attack of the above carbanion on the arylcopper(III) species, giving IV simultaneously, which

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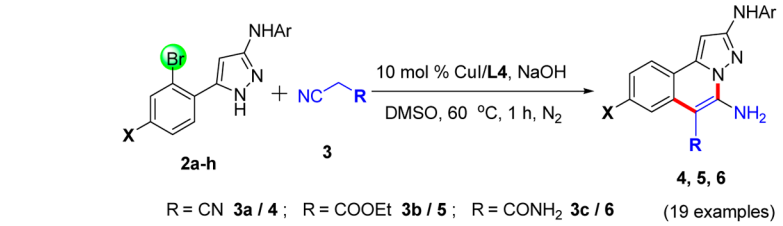
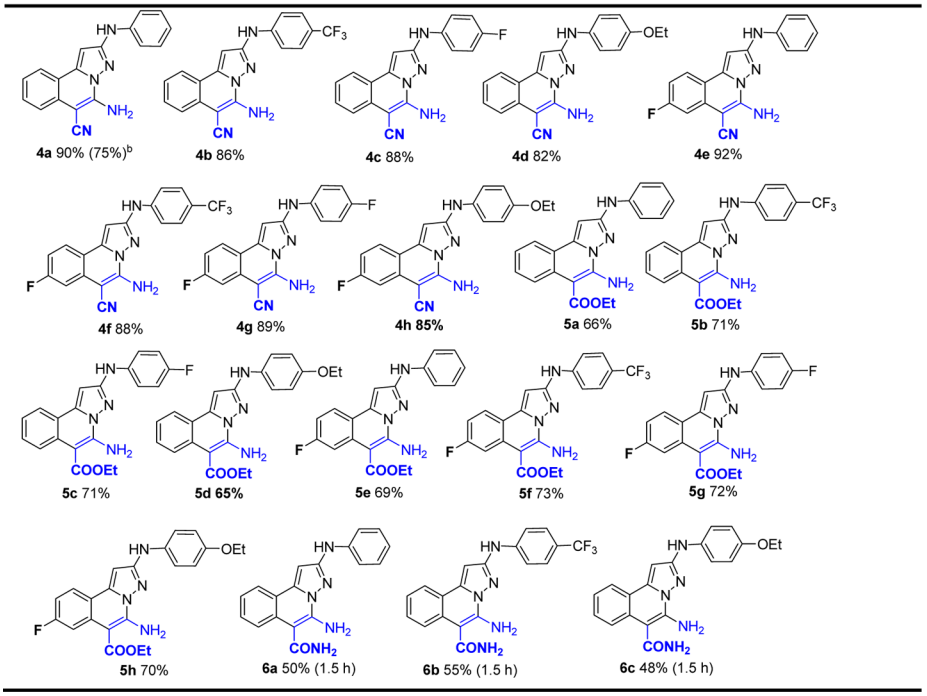
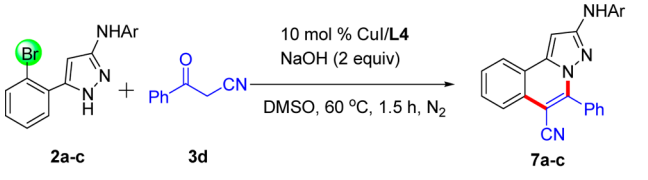
Table 2. Investigation on the Scope of 2 with 3a−c for Pyrazolo[5,1-*a*]isoquinolines 4−6[a]





[a]Reaction conditions: **2** (0.5 mmol), **3** (0.6 mmol), NaOH (1.0 mmol), CuI (0.05 mmol, 10 mmol %), and **L4** (0.05 mmol, 10 mmol %) in 2.0 mL of DMSO at 60 °C under a nitrogen atmosphere. Isolated yield. [b]Product from the chloride.

Scheme 2. Investigation on the Reaction of 2 with 3d



7a: Ar = C_6H_5, 52%
7b: Ar = 4-$CF_3C_6H_4$, 50%
7c: Ar = 4-$EtOC_6H_4$, 60%

undergoes intramolecular nucleophic addition and tautormerization to provide the desired products **4**.

CONCLUSION

We have demonstrated for the first time that medicinally useful pyrazolo[5,1-*a*]isoquinolines can be easily prepared in good to excellent yields by the coupling reactions of 5-(2-bromoaryl)-*N*-aryl-1*H*-pyrazol-3-amines with active acetonitrile derivatives using a combination of CuI and a HKA-type ligand. This approach complements the more commonly used strategies for construction of diverse pyrazolo[5,1-*a*]isoquinolines. Most importantly, these pyrazoloisoquinolines containing amino and cyano groups or carboxylate and acetamide groups are not only useful, biologically active molecules but also interesting intermediates, which should be significant for drug discovery. Investigations on the potential application of these ligands in other types of copper-catalyzed coupling reactions are under way and will be reported in due course.

EXPERIMENTAL SECTION

General Methods. All the reagents were purchased as commercially available sources unless noted otherwise, and solvents for extraction and chromatography were distilled before use. DMSO was used without any purification. Chromatography refers to open column chromatography on silica gel (100−200 mesh) or neutral Al_2O_3 (101.96 mesh). Melting points were recorded on a microscopic melting apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a 500 MHz instrument and ^{13}C NMR spectra on a 125 MHz instrument in DMSO-d_6 or $CDCl_3$. Chemical shifts are reported in δ (ppm) relative to TMS. IR spectra were recorded on an FT-IR spectrometer, and only major peaks are reported in inverse centimeters. HRMS spectra were obtained on a spectrometer with an ESI source.

General Experimental Procedures for Compounds 2 (2a for Example). A mixture of 3-(2-bromophenyl)-3-oxo-*N*-phenylpropanethioamide (**1a**) (334 mg, 1 mmol) and hydrazine hydrate (60 mg, 1.2 mmol) in 5 mL of ethanol was stirred under reflux for 2 h. After completion of the reaction as monitored by TLC, the cooled mixture was concentrated in vacuo and separated by column chromatography (eluting with 4:1 (v/v) petroleum ether/ethyl acetate) to afford 5-(2-bromophenyl)-*N*-phenyl-1*H*-pyrazol-3-amine (**2a**), 282.6 mg, 90% yield.

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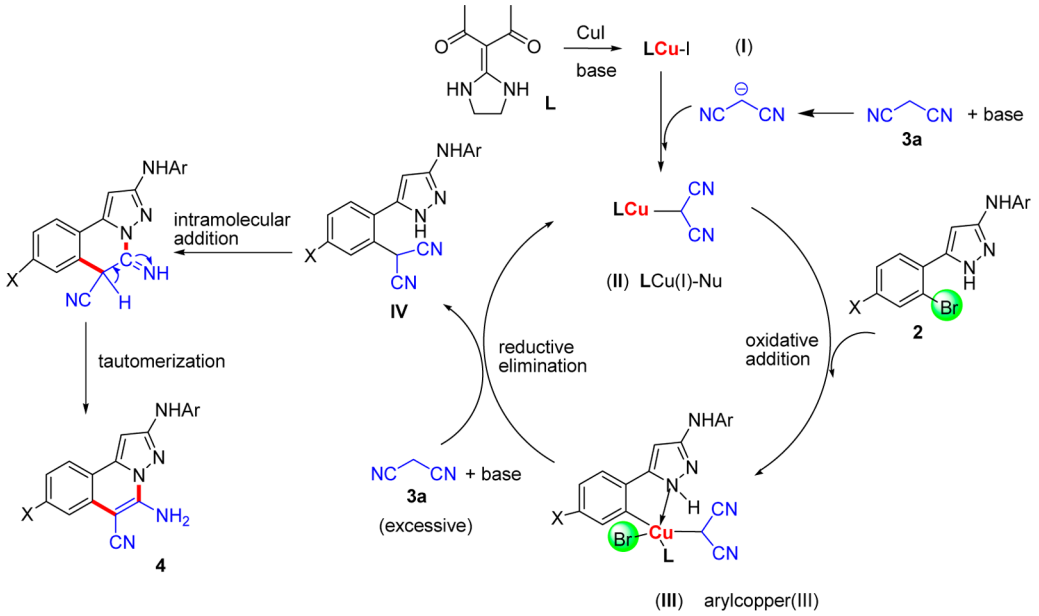
Scheme 3. Possible Copper-Catalyzed Tandem Cyclization Mechanism



General Experimental Procedures for Compounds 4–7. A flask was charged with NaOH (40 mg, 1 mmol) in 2 mL of DMSO, and 5-(2-bromoaryl)-*N*-aryl-1*H*-pyrazol-3-amines **2** (0.5 mmol) and **3** (0.6 mmol) were added to the flask. The mixture was stirred at 60 °C under a nitrogen atmosphere for 15 min, and then CuI (9.5 mg, 0.05 mmol) and **L4** (8.4 mg, 0.05 mmol) were added. Until **2** was consumed as monitored by TLC, the reaction system was cooled to room temperature. The cooled mixture was partitioned between water and ethyl acetate. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (10 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (for products **4**–**6**) or neutral Al_2O_3 (for products **7**) with eluent 2:1 (v/v) petroleum ether/ethyl acetate to afford the products.

5-(2-Bromophenyl)-*N*-phenyl-1*H*-pyrazol-3-amine (2a). White solid (297.3 mg, 95%). Mp: 86–89 °C. IR (KBr, cm^{-1}): ν 3400, 3269, 3041, 1597, 1570, 1542, 1500, 764, 749, 696. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.12 (s, 1H), 6.36 (s, 1H), 6.90 (t, J = 7.28 Hz, 1H), 7.17 (d, J = 8.00 Hz, 2H), 7.21–7.26 (m, 2H), 7.28 (d, J = 8.05 Hz, 1H), 7.37 (t, J = 7.58 Hz, 1H), 7.52 (d, J = 7.60 Hz, 1H), 7.68 (d, J = 8.05 Hz, 1H), 9.91 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 95.6, 115.8, 120.1, 121.4, 127.7, 129.3, 129.9, 130.7, 130.9, 133.9, 143.1, 151.0. HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{15}H_{13}BrN_3$, 314.0285; found, 314.0293.

5-(2-Bromophenyl)-*N*-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-3-amine (2b). White solid (350.5 mg, 92%). Mp: 134–136 °C. IR (KBr, cm^{-1}): ν 3397, 3286, 2933, 1620, 1556, 1334, 1111, 838, 758. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.37 (s, 1H), 6.38 (s, 1H), 7.22 (d, J = 8.45 Hz, 2H), 7.27 (s, 1H), 7.39 (t, J = 7.43 Hz, 1H), 7.48–7.52 (m, 3H), 7.69 (d, J = 8.00 Hz, 1H), 10.14 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 96.5, 114.7, 121.6, 124.6 ($^1J_{C-F}$ = 273.9 Hz), 126.6, 127.8, 130.2, 130.7, 134.0, 142.7, 146.0, 150.2. HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{16}H_{12}BrF_3N_3$, 382.0175; found, 382.0167.

5-(2-Bromophenyl)-*N*-(4-fluorophenyl)-1*H*-pyrazol-3-amine (2c). White solid (301.21 mg, 91%). Mp: 118–120 °C. IR (KBr, cm^{-1}): ν 3428, 3405, 2929, 1600, 1560, 1547, 1220, 830, 750, 669. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.02 (s, 1H), 6.26 (s, 1H), 6.96 (t, J = 8.65 Hz, 2H), 7.12–7.16 (m, 2H), 7.22–7.23 (m, 1H), 7.37 (t, J = 7.58 Hz, 1H), 7.49 (t, J = 7.75 Hz, 1H), 7.67 (d, J = 8.00 Hz, 1H), 10.01 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 95.1, 115.7 ($^2J_{C-F}$ = 22.4 Hz), 117.5, 121.3, 127.7, 129.9, 130.7, 133.9, 139.2, 142.7, 151.8, 157.2 ($^1J_{C-F}$ = 238.9 Hz). HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{15}H_{12}BrFN_3$, 332.0195; found, 332.0199.

5-(2-Bromophenyl)-*N*-(4-ethoxyphenyl)-1*H*-pyrazol-3-amine (2d). White solid (314.2 mg, 88%). Mp: 91–94 °C. IR (KBr, cm^{-1}): ν 3415, 3258, 2896, 1547, 1501, 1239, 1051, 819, 756, 712. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.40 (t, J = 7.03 Hz, 3H), 3.50 (s, 1H), 4.00 (q, J = 6.95 Hz, 2H), 5.91 (s, 1H), 6.24 (s, 1H), 6.85 (d, J = 8.80 Hz, 2H), 7.13 (d, J = 8.75 Hz, 2H), 7.22 (t, J = 7.65 Hz, 1H), 7.36 (t, J = 7.48 Hz, 1H), 7.50 (d, J = 7.35 Hz, 1H), 7.66 (d, J = 8.00 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.9, 63.9, 94.5, 115.4, 118.4, 121.3 127.6, 129.8, 130.7, 130.9, 133.9, 136.4, 142.9, 152.4, 153.4. HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{17}H_{17}BrN_3O$, 358.0562; found, 358.0555.

5-(2-Bromo-4-fluorophenyl)-*N*-phenyl-1*H*-pyrazol-3-amine (2e). White solid (297.9 mg, 90%). Mp: 136–138 °C. IR (KBr, cm^{-1}): ν 3403, 3257, 2859, 1601, 1512, 1506, 1206, 869, 753, 698. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.07 (s, 1H), 6.30 (s, 1H), 6.89 (t, J = 7.33 Hz, 1H), 7.06–7.10 (m, 1H), 7.14 (d, J = 7.95 Hz, 2H), 7.25 (s, 1H), 7.27 (d, J = 8.00 Hz, 1H), 7.41 (dd, J = 2.52 Hz, J = 8.23 Hz, 1H), 7.48 (dd, J = 5.98 Hz, J = 8.58 Hz, 1H), 10.15 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 95.8, 115.0 ($^2J_{C-F}$ = 21.0 Hz), 115.8, 120.3, 121.0 ($^2J_{C-F}$ = 24.4 Hz), 121.9, 127.5, 129.3, 131.8, 142.9, 150.7, 162.1 ($^1J_{C-F}$ = 253.4 Hz). HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{15}H_{12}BrFN_3$, 332.0190; found, 332.0199.

5-(2-Bromo-4-fluorophenyl)-*N*-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-3-amine (2f). White solid (342.3 mg, 86%). Mp: 148–150 °C. IR (KBr, cm^{-1}): ν 3451, 3313, 2860, 1618, 1598, 1329, 1207, 1106, 863, 791, 671. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.30 (s, 1H), 6.31 (s, 1H), 7.09–7.13 (m, 1H), 7.22 (d, J = 8.30 Hz, 2H), 7.44 (dd, J = 2.30 Hz, J = 8.10 Hz, 1H), 7.47–7.50 (m, 3H), 10.06 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 96.6, 113.7, 115.2 ($^2J_{C-F}$ = 21.2 Hz), 121.2 ($^2J_{C-F}$ = 24.6 Hz), 121.9, 124.6 ($^1J_{C-F}$ = 267.8 Hz), 126.6, 131.9, 145.8, 162.3 ($^1J_{C-F}$ = 253.9 Hz). HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{16}H_{11}BrF_4N_3$, 400.0078; found, 400.0072.

5-(2-Bromo-4-fluorophenyl)-*N*-(4-fluorophenyl)-1*H*-pyrazol-3-amine (2g). White solid (289.7 mg, 83%). Mp: 130–132 °C. IR (KBr, cm^{-1}): ν 3412, 3363, 2860, 1603, 1603, 1557, 1212, 1003, 870, 778. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.99 (s, 1H), 6.21 (s, 1H), 6.96 (t, J = 8.62 Hz, 2H), 7.07–7.14 (m, 3H), 7.42 (dd, J = 2.48 Hz, J = 8.13 Hz, 1H), 7.46 (dd, J = 5.98 Hz, J = 8.58 Hz, 1H), 9.28 (s, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 95.3, 115.0 ($^2J_{C-F}$ = 20.9 Hz), 115.6, 115.8, 117.5, 121.0 ($^2J_{C-F}$ = 24.5 Hz), 127.3, 131.8, 139.1, 142.4, 151.4, 157.3 ($^1J_{C-F}$ = 238.6 Hz), 162.1 ($^1J_{C-F}$ = 253.4 Hz). HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{15}H_{11}BrF_2N_3$, 350.0109; found, 350.0104.

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5-(2-Bromo-4-fluorophenyl)-*N*-(4-ethoxyphenyl)-1*H*-pyrazol-3-amine (2h). White solid (301.2 mg, 80%). Mp: 135−137 °C. IR (KBr, cm^{-1}): ν 3401, 3262, 2896, 1548, 1505, 1237, 1050, 920, 822, 775. ^1H NMR ($CDCl_3$, 500 MHz): δ 1.40 (t, J = 6.95 Hz, 3H), 4.00 (q, J = 6.95 Hz, 2H), 6.00 (s, 1H), 6.18 (s, 1H), 6.84 (d, J = 8.80 Hz, 2H), 7.06−7.11 (m, 3H), 7.41 (dd, J = 2.55 Hz, J = 8.25 Hz, 1H), 7.47 (dd, J = 5.95 Hz, J = 8.60 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.9, 63.9, 94.5, 114.9 ($^2J_{C-F}$ = 21.4 Hz), 115.4, 118.4, 120.9 ($^2J_{C-F}$ = 24.4 Hz), 121.8, 127.7, 131.8, 136.3, 142.8, 151.8, 153.5, 162.0. ($^1J_{C-F}$ = 253.4 Hz). HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{17}H_{16}BrFN_3O$, 376.0469; found, 376.0461.

5-Amino-2-(phenylamino)pyrazolo[5,1-*a*]isoquinoline-6-carbonitrile (4a). Brown solid (134.5 mg, 90%). Mp: 197−199 °C. IR (KBr, cm^{-1}): ν 3451, 3376, 3326, 2195, 1629, 1592, 1557, 1499, 752, 692. ^1H NMR (DMSO-d_6, 500 MHz): δ 6.75 (s, 1H), 6.87 (t, J = 7.28 Hz, 1H), 7.27−7.34 (m, 3H), 7.58 (d, J = 3.80 Hz, 2H), 7.74 (d, J = 7.80 Hz, 2H), 7.79 (s, 2H), 8.11 (d, J = 7.90 Hz, 1H), 9.31 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 66.1, 89.8, 116.4, 117.1, 118.1, 120.2, 121.8, 123.9, 125.1, 129.4, 129.7, 130.1, 139.6, 142.3, 147.2, 155.5. HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{18}H_{14}N_5$, 300.1249; found, 300.1250.

5-Amino-2-((4-(trifluoromethyl)phenyl)amino)pyrazolo[5,1-*a*]isoquinoline-6-carbonitrile (4b). White solid (157.8 mg, 86%). Mp: 288−290 °C. IR (KBr, cm^{-1}): ν 3450, 3354, 3154, 2194, 1623, 1594, 1553, 1508, 1449, 1326, 833. ^1H NMR (DMSO-d_6, 500 MHz): δ 6.81 (s, 1H), 7.32−7.36 (m, 1H), 7.58−7.60 (m, 4H), 7.90 (s, 2H), 7.95 (d, J = 8.60 Hz, 2H), 8.14 (d, J = 7.90 Hz, 1H), 9.80 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 66.3, 90.0, 116.3, 116.9, 118.0, 119.7, 120.0, 122.8 ($^1J_{C-F}$ = 267.8 Hz), 124.3, 125.1, 126.5, 129.7, 130.1, 139.7, 145.5, 147.2, 154.5. HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{19}H_{13}F_3N_5$, 368.1123; found, 368.1135.

5-Amino-2-((4-fluorophenyl)amino)pyrazolo[5,1-*a*]-isoquinoline-6-carbonitrile (4c). Gray solid (139.5 mg, 88%). Mp: 252−254 °C. IR (KBr, cm^{-1}): ν 3459, 3399, 3308, 2199, 1610, 1598, 1569, 1511, 1490, 1331, 837. ^1H NMR (DMSO-d_6, 500 MHz): δ 6.72 (s, 1H), 7.09 (t, J = 8.80 Hz, 2H), 7.31−7.34 (m, 1H), 7.57 (d, J = 3.85 Hz, 2H), 7.78 (q, J = 4.55 Hz, 2H), 7.82 (s, 2H), 8.12 (d, J = 7.95 Hz, 1H), 9.33 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 65.9, 89.5, 115.7 ($^2J_{C-F}$ = 21.6 Hz), 116.3, 118.2, 118.4 ($^3J_{C-F}$ = 8.4 Hz), 121.7, 123.8, 125.1, 129.8, 130.1, 138.8, 139.6, 147.2, 154.4 ($^1J_{C-F}$ = 271.2 Hz). HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{18}H_{13}FN_5$, 318.1155; found, 318.1165.

5-Amino-2-((4-ethoxyphenyl)amino)pyrazolo[5,1-*a*]-isoquinoline-6-carbonitrile (4d). Black solid (140.6 mg, 82%). Mp: 236−238 °C. IR (KBr, cm^{-1}): ν 3467, 3396, 3354, 2978, 2927, 2200, 1630, 1596, 1559, 1509, 1241, 823. ^1H NMR (DMSO-d_6, 500 MHz): δ 1.30 (t, J = 6.95 Hz, 3H), 3.96 (q, J = 6.92 Hz, 2H), 6.67 (s, 1H), 6.85 (d, J = 8.90 Hz, 2H), 7.28−7.32 (m, 1H), 7.55 (d, J = 2.80 Hz, 2H), 7.65 (d, J = 8.95 Hz, 2H), 7.73 (s, 2H), 8.08 (d, J = 7.90 Hz, 1H), 9.06 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 15.3, 63.5, 65.7, 89.3, 115.2, 115.3, 116.3, 118.3, 121.7, 123.7, 125.0, 129.7, 129.9, 135.8, 139.5, 147.1, 152.6, 155.7. HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{20}H_{18}N_5O$, 344.1511; found, 344.1520.

5-Amino-8-fluoro-2-(phenylamino)pyrazolo[5,1-*a*]-isoquinoline-6-carbonitrile (4e). Gray solid (145.8 mg, 92%). Mp: 228.5−230 °C. IR (KBr, cm^{-1}): ν 3449, 3385, 3344, 2197, 1625, 1596, 1511, 1454, 1330, 1250, 751, 690. ^1H NMR (DMSO-d_6, 500 MHz): δ 6.72 (s, 1H), 6.86 (t, J = 7.20 Hz, 1H), 7.14−7.20 (m, 2H), 7.27 (t, J = 7.85 Hz, 2H), 7.74 (d, J = 7.85 Hz, 2H), 7.96 (s, 2H), 8.19 (dd, J = 5.75, 8.70 Hz, 1H), 9.31 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 65.8, 89.9, 106.6 ($^2J_{C-F}$ = 23.9 Hz), 111.9 ($^2J_{C-F}$ = 23.7 Hz), 113.2, 117.1, 117.8, 120.2, 128.1 ($^3J_{C-F}$ = 8.8 Hz), 129.3, 132.2 ($^3J_{C-F}$ = 7.7 Hz), 139.1, 142.2, 147.5, 155.5, 163.2 ($^1J_{C-F}$ = 244.2 Hz). HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{18}H_{13}FN_5$, 318.1155; found, 318.1165.

5-Amino-8-fluoro-2-((4-(trifluoromethyl)phenyl)amino)-pyrazolo[5,1-*a*]isoquinoline-6-carbonitrile (4f). Brown solid (169.4 mg, 88%). Mp: 319−321 °C. IR (KBr, cm^{-1}): ν 3454, 3379, 3345, 2190, 1623, 1598, 1553, 1372, 1326, 820. ^1H NMR (DMSO-d_6, 500 MHz): δ 6.79 (s, 1H), 7.19−7.22 (m, 2H), 7.57 (d, J = 8.70 Hz, 2H), 7.95 (d, J = 8.60 Hz, 2H), 8.08 (s, 2H), 8.23 (dd, J = 5.75, 8.50 Hz, 1H), 9.82 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 66.1, 90.2, 106.7 ($^2J_{C-F}$ = 25.7 Hz), 112.1 ($^2J_{C-F}$ = 23.9 Hz), 113.2, 116.9, 118.8 ($^1J_{C-F}$ = 260.7 Hz), 126.5, 128.3 ($^3J_{C-F}$ = 9.2 Hz), 132.2 ($^3J_{C-F}$ = 9.3 Hz), 139.3, 145.5, 147.6, 154.7, 163.3 ($^1J_{C-F}$ = 242.4 Hz). HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{19}H_{12}F_4N_5$, 386.1029; found, 386.1035.

5-Amino-8-fluoro-2-((4-fluorophenyl)amino)pyrazolo[5,1-*a*]-isoquinoline-6-carbonitrile (4g). Yellow solid (149.1 mg, 89%). Mp: 283−285 °C. IR (KBr, cm^{-1}): ν 3461, 3362, 3303, 2194, 1622, 1565, 1512, 1492, 1326, 816. ^1H NMR (DMSO-d_6, 500 MHz): δ 6.69 (s, 1H), 7.07 (t, J = 8.78 Hz, 2H), 7.14−7.19 (m, 2H), 7.77 (q, J = 4.52 Hz, 2H), 7.98 (s, 2H), 8.19 (dd, J = 5.82, 8.48 Hz, 1H), 9.34 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 65.7, 89.7, 106.7 ($^2J_{C-F}$ = 25.7 Hz), 112.0 ($^2J_{C-F}$ = 23.9 Hz), 113.2, 115.8 ($^2J_{C-F}$ = 20.2 Hz), 117.9, 118.5, 128.0, 128.2, 132.2, 138.7, 139.2, 147.6, 156.6 ($^1J_{C-F}$ = 262.5 Hz), 163.3 ($^1J_{C-F}$ = 242.4 Hz). HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{18}H_{12}F_2N_5$, 336.1061; found, 336.1072.

5-Amino-2-((4-ethoxyphenyl)amino)-8-fluoropyrazolo[5,1-*a*]isoquinoline-6-carbonitrile (4h). Gray solid (153.4 mg, 85%). Mp: 268−270 °C. IR (KBr, cm^{-1}): ν 3440, 3365, 3305, 2982, 2929, 2193, 1625, 1598, 1560, 1512, 1353, 1242, 816. ^1H NMR (DMSO-d_6, 500 MHz): δ 1.30 (t, J = 6.90 Hz, 3H), 3.96 (q, J = 6.90 Hz, 2H), 6.66 (s, 1H), 6.85 (d, J = 8.80 Hz, 2H), 7.13−7.19 (m, 2H), 7.65 (d, J = 8.90 Hz, 2H), 7.90 (s, 2H), 8.17 (t, J = 7.08 Hz, 1H), 9.08 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 15.3, 63.5, 65.5, 89.5, 106.6 ($^2J_{C-F}$ = 23.2 Hz), 111.9 ($^2J_{C-F}$ = 23.2 Hz), 113.1, 115.2, 117.9, 118.4, 128.1 ($^3J_{C-F}$ = 9.3 Hz), 132.2 ($^3J_{C-F}$ = 9.3 Hz), 135.7, 139.1, 147.5, 152.7, 155.9, 163.2 ($^1J_{C-F}$ = 243.2 Hz). HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{20}H_{17}FN_5O$, 362.1417; found, 362.1412.

Ethyl 5-Amino-2-(phenylamino)pyrazolo[5,1-*a*]isoquinoline-6-carboxylate (5a). Red solid (114.2 mg, 66%). Mp: 167−169 °C. IR (KBr, cm^{-1}): ν 3472, 3394, 3311, 2981, 2924, 1663, 1621, 1605, 1577, 1555, 1495, 1449, 1205, 746, 691. ^1H NMR (DMSO-d_6, 500 MHz): δ 1.39 (t, J = 7.10 Hz, 3H), 4.40 (q, J = 7.10 Hz, 2H), 6.70 (s, 1H), 6.86 (t, J = 7.30 Hz, 1H), 7.26−7.30 (m, 3H), 7.46−7.50 (m, 1H), 7.68 (d, J = 7.70 Hz, 2H), 8.07−8.08 (m, 3H), 8.60 (d, J = 8.60 Hz, 1H), 9.28 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 14.9, 60.4, 84.1, 88.9, 116.9, 120.1, 123.3, 124.8, 125.1, 129.3, 129.7, 139.7, 142.5, 146.9, 155.3, 168.7. HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{20}H_{19}N_4O_2$, 347.1508; found, 347.1512.

Ethyl 5-Amino-2-((4-(trifluoromethyl)phenyl)amino)-pyrazolo[5,1-*a*]isoquinoline-6-carboxylate (5b). White solid (146.9 mg, 71%). Mp: 195−197 °C. IR (KBr, cm^{-1}): ν 3475, 3388, 3314, 2954, 2918, 2849, 1662, 1620, 1600, 1579, 1554, 1494, 1333, 1210, 837. ^1H NMR (DMSO-d_6, 500 MHz): δ 1.41 (t, J = 7.08 Hz, 3H), 4.42 (q, J = 7.10 Hz, 2H), 6.79 (s, 1H), 7.31 (t, J = 7.56 Hz, 1H), 7.51 (t, J = 7.85 Hz, 1H), 7.61 (d, J = 8.70 Hz, 2H), 7.89 (d, J = 8.60 Hz, 2H), 8.13 (t, J = 8.40 Hz, 3H), 8.61 (d, J = 8.60 Hz, 1H), 9.80 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 14.8, 60.6, 84.4, 89.3, 116.6, 116.8, 123.3, 124.2 ($^1J_{C-F}$ = 218.5 Hz), 126.6, 129.4, 129.7, 139.8, 145.7, 146.9, 154.4, 168.7. HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{21}H_{18}F_3N_4O_2$, 415.1382; found, 415.1395.

Ethyl 5-Amino-2-((4-fluorophenyl)amino)pyrazolo[5,1-*a*]-isoquinoline-6-carboxylate (5c). Gray solid (129.2 mg, 71%). Mp: 230−232 °C. IR (KBr, cm^{-1}): ν 3474, 3403, 3306, 2980, 2927, 1664, 1622, 1580, 1557, 1507, 1494, 1369, 1205, 833. ^1H NMR (DMSO-d_6, 500 MHz): δ 1.39 (t, J = 7.10 Hz, 3H), 4.39 (q, J = 7.07 Hz, 2H), 6.67 (s, 1H), 7.10 (t, J = 8.76 Hz, 2H), 7.26 (t, J = 7.45 Hz, 1H), 7.47 (t, J = 7.80 Hz, 1H), 7.70−7.72 (m, 2H), 8.06 (t, J = 9.80 Hz, 1H), 8.10 (s, 2H), 8.59 (d, J = 8.65 Hz, 1H), 9.31 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 14.9, 60.2, 84.0, 88.7, 115.8 ($^2J_{C-F}$ = 22.0 Hz), 116.8, 118.3 ($^3J_{C-F}$ = 7.3 Hz), 123.3, 124.9, 125.1, 129.4, 129.8, 139.0, 139.7, 147.0, 155.3, 156.7 ($^1J_{C-F}$ = 285.5 Hz), 168.8. HRMS (ESI-TOF, $[M + H]^+$): calcd for $C_{20}H_{18}FN_4O_2$, 365.1414; found, 365.1425.

Ethyl 5-Amino-2-((4-ethoxyphenyl)amino)pyrazolo[5,1-*a*]-isoquinoline-6-carboxylate (5d). Gray solid (126.7 mg, 65%). Mp: 204−206 °C. IR (KBr, cm^{-1}): ν 3467, 3409, 3304, 2981, 2926, 1665, 1620, 1598, 1580, 1552, 1204, 827. ^1H NMR (DMSO-d_6, 500

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MHz): δ 1.30 (t, J = 6.98 Hz, 3H), 1.39 (t, J = 7.08 Hz, 3H), 3.97 (q, J = 6.98 Hz, 2H), 4.39 (q, J = 7.10 Hz, 2H), 6.63 (s, 1H), 6.85−6.88(m, 2H), 7.26 (t, J = 7.60 Hz, 1H), 7.45−7.48(m, 1H), 7.58−7.60 (m, 2H), 8.04−8.06 (m, 3H), 8.59 (d, J = 8.65 Hz, 1H), 9.04 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 14.8, 15.2, 60.4, 63.6, 83.9, 88.5, 115.3, 116.8, 118.3, 123.2, 124.8, 125.1, 129.2, 129.8, 136.0, 139.7, 146.9, 152.8, 155.7, 168.7. HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{22}H_{23}N_4O_3$, 391.1770; found, 391.1785.

Ethyl 5-Amino-8-fluoro-2-(phenylamino)pyrazolo[5,1-*a*]-isoquinoline-6-carboxylate (5e). Gray solid (125.6 mg, 69%). Mp: 166.5−168.5 °C. IR (KBr, cm^{-1}): ν 3471, 3389, 3317, 2980, 2922, 2851, 1665, 1623, 1605, 1579, 1556, 1370, 1213, 750, 692. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.39 (t, J = 7.13 Hz, 3H), 4.39 (q, J = 7.08 Hz, 2H), 6.69 (s, 1H), 6.87 (t, J = 7.30 Hz, 1H), 7.12−7.15 (m, 1H), 7.27−7.31 (m, 2H), 7.68 (d, J = 8.05 Hz, 2H), 8.15 (dd, J = 6.53, 8.68 Hz, 1H), 8.21 (s, 2H), 8.35 (dd, J = 2.55 Hz, J = 13.95 Hz, 1H), 9.31 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 14.8, 60.6, 83.6, 89.1, 110.3 ($^2J_{C-F}$ = 26.1 Hz), 111.3 ($^2J_{C-F}$ = 23.7 Hz), 113.7, 116.9, 120.2, 127.5 ($^3J_{C-F}$ = 9.5 Hz), 129.3, 132.0 ($^3J_{C-F}$ = 10.9 Hz), 139.2, 142.3, 147.5, 155.4, 162.9 ($^1J_{C-F}$ = 240.2 Hz), 168.3. HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{20}H_{18}FN_4O_2$, 365.1414; found, 365.1409.

Ethyl 5-Amino-8-fluoro-2-((4-(trifluoromethyl)phenyl)-amino)pyrazolo[5,1-*a*]isoquinoline-6-carboxylate (5f). White solid (157.7 mg, 73%). Mp: 155−157 °C. IR (KBr, cm^{-1}): ν 3457, 3313, 3312, 2981, 2952, 1654, 1620, 1605, 1584, 1557, 1328, 1217, 835. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.40 (t, J = 7.05 Hz, 3H), 4.40 (q, J = 7.03 Hz, 2H), 6.76 (s, 1H), 7.15 (t, J = 7.03 Hz, 3H), 7.59 (d, J = 8.55 Hz, 2H), 7.88 (d, J = 8.45 Hz, 2H), 8.19 (t, J = 7.15 Hz, 1H), 8.28 (s, 2H), 8.35 (d, J = 13.95 Hz, 1H), 9.81 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 14.7, 60.7, 83.9, 89.5, 110.4 ($^2J_{C-F}$ = 27.5 Hz), 111.5 ($^2J_{C-F}$ = 24.1 Hz), 113.7, 116.7, 119.8, 120.0, 124.3, 126.6, 127.6 ($^3J_{C-F}$ = 10.3 Hz), 131.9 ($^3J_{C-F}$ = 8.6 Hz), 139.3, 145.6, 147.5, 154.5, 162.9 ($^1J_{C-F}$ = 239.3 Hz), 168.3. HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{21}H_{17}F_4N_4O_2$, 433.1288; found, 433.1296.

Ethyl 5-Amino-8-fluoro-2-((4-fluorophenyl)amino)pyrazolo-[5,1-*a*]isoquinoline-6-carboxylate (5g). Yellow solid (137.5 mg, 72%). Mp: 229−231 °C. IR (KBr, cm^{-1}): ν 3472, 3390, 3302, 2981, 2930, 1666, 1621, 1581, 1557, 1507, 1369, 1327, 1214, 823. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.38 (t, J = 7.05 Hz 3H), 4.39 (q, J = 7.05 Hz, 2H), 6.65 (s, 1H), 7.08−7.13 (m, 3H), 7.71 (q, J = 4.55 Hz, 2H), 8.14 (t, J = 7.55 Hz, 1H), 8.23 (s, 2H), 8.34 (dd, J = 1.75, 13.95 Hz, 1H), 9.33 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 14.8, 60.7, 83.6, 88.9, 110.4 ($^2J_{C-F}$ = 26.2 Hz), 111.4 ($^2J_{C-F}$ = 23.7 Hz), 113.7, 115.8 ($^2J_{C-F}$ = 22.1 Hz), 118.4 ($^3J_{C-F}$ = 6.6 Hz), 127.6 ($^3J_{C-F}$ = 9.8 Hz), 132.0 ($^3J_{C-F}$ = 10.6 Hz), 138.9, 139.3, 147.6, 156.5 ($^1J_{C-F}$ = 270.6 Hz), 162.9 ($^1J_{C-F}$ = 241.2 Hz), 168.4. HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{20}H_{17}F_2N_4O_2$, 383.1320; found, 383.1325.

Ethyl 5-Amino-2-((4-ethoxyphenyl)amino)-8-fluoro-pyrazolo[5,1-*a*]isoquinoline-6- carboxylate (5h). White solid (142.8 mg, 70%). Mp: 203−205 °C. IR (KBr, cm^{-1}): ν 3464, 3395, 3365, 2981, 2929, 1664, 1622, 1581, 1557, 1511, 1370, 1325, 1215, 817. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.30 (t, J = 6.93 Hz, 3H), 1.39 (t, J = 7.03 Hz, 3H), 3.96 (q, J = 6.83 Hz, 2H), 4.39 (q, J = 6.95 Hz, 2H), 6.62 (s, 1H), 6.86 (d, J = 8.95 Hz, 2H), 7.11 (s, 1H), 7.59 (d, J = 8.95 Hz, 2H), 8.13 (t, J = 6.13 Hz, 1H), 8.17 (s, 2H), 8.34 (d, J = 13.90 Hz, 1H), 9.06 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 14.8, 15.3, 60.6, 63.6, 83.5, 88.7, 110.3 ($^2J_{C-F}$ = 26.2 Hz), 111.3 ($^2J_{C-F}$ = 23.0 Hz), 113.7, 115.3, 118.4, 127.4, 132.0 ($^3J_{C-F}$ = 10.1 Hz), 135.8, 139.2, 147.5, 152.8, 155.9, 162.8 ($^1J_{C-F}$ = 242.4 Hz), 168.3. HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{22}H_{22}FN_4O_3$, 409.1676; found, 409.1669.

5-Amino-2-(phenylamino)pyrazolo[5,1-*a*]isoquinoline-6-carboxamide (6a). Yellow solid (79.2 mg, 50%). Mp: 224.5−225.5 °C. IR (KBr, cm^{-1}): ν 3426, 3364, 3326, 3183, 1638, 1598, 1578, 1484, 742, 701. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.67 (s, 1H), 6.83 (t, J = 7.28 Hz, 1H), 6.91 (s, 2H), 7.23−7.28 (m, 3H), 7.45 (t, J = 7.58 Hz, 1H), 7.59 (s, 2H), 7.63 (d, J = 8.00 Hz, 2H), 7.92 (d, J = 8.40 Hz, 1H), 8.06 (d, J = 7.85 Hz, 1H), 9.14 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 87.3, 91.7, 116.6, 119.8, 122.7, 123.8, 124.8, 128.8, 129.5, 129.7, 139.0, 141.6, 142.9, 154.5, 169.9. HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{18}H_{16}N_5O$, 318.1355; found, 318.1349.

5-Amino-2-((4-(trifluoromethyl)phenyl)amino)pyrazolo[5,1-*a*]isoquinoline-6-carboxamide (6b). Yellow solid (105.9 mg, 55%). Mp: 316-317 °C. IR (KBr, cm^{-1}): ν 3454, 3374, 3325, 3193, 1640, 1618, 1577, 1486, 1328, 829. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 6.75 (s, 1H), 6.98 (s, 2H), 7.26 (t, J = 7.18 Hz, 1H), 7.47 (t, J = 7.38 Hz, 1H), 7.59 (d, J = 8.10 Hz, 2H), 7.64 (s, 2H), 7.84 (d, J = 7.95 Hz, 2H), 7.93 (d, J = 8.55 Hz, 1H), 8.10 (d, J = 7.90 Hz, 1H), 9.68 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 87.8, 92.3, 116.3, 116.7, 119.4, 119.6, 119.9, 123.9 ($^1J_{C-F}$ = 247.6 Hz), 126.7, 129.0, 129.7, 139.1, 141.4, 146.3, 153.5, 169.8. HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{19}H_{15}F_3N_5O$, 386.1229; found, 386.1235.

5-Amino-2-((4-ethoxyphenyl)amino)pyrazolo[5,1-*a*]-isoquinoline-6-carboxamide (6c). Yellow solid (86.6 mg, 48%). Mp: 260−262 °C. IR (KBr, cm^{-1}): ν 3430, 3361, 3326, 3181, 1637, 1622, 1580, 1512, 1484, 1243, 825. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.29 (t, J = 6.90 Hz, 3H), 3.95 (q, J = 6.92 Hz, 2H), 6.59 (s, 1H), 6.85 (t, J = 8.80 Hz, 2H), 6.90 (s, 2H), 7.22 (t, J = 7.43 Hz, 1H), 7.44 (t, J = 7.62 Hz, 1H), 7.55 (d, J = 8.80 Hz, 4H), 7.92 (d, J = 8.35 Hz, 1H), 8.04 (d, J = 7.85 Hz, 1H), 8.89 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 15.4, 63.7, 86.8, 91.4, 115.4, 116.6, 118.0, 122.7, 123.8, 124.8, 128.8, 129.8, 136.5, 139.0, 141.7, 152.5, 155.80, 170.0. HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{20}H_{20}N_5O_2$, 362.1617; found, 362.1620.

5-Phenyl-2-(phenylamino)pyrazolo[5,1-*a*]isoquinoline-6-carbonitrile (7a). Red solid (93.6 mg, 52%). Mp: 210−212 °C. IR (KBr, cm^{-1}): ν 3403, 2216, 1618, 1595, 1550, 1499, 756, 705, 691. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.49 (s, 1H), 6.84 (s, 1H), 6.99−7.02 (m, 1H), 7.26 (s, 1H), 7.28 (d, J = 1.10 Hz, 1H), 7.30−7.33 (m, 2H), 7.61−7.63 (m, 3H), 7.65−7.71 (m, 2H), 7.82−7.85 (m, 2H), 8.06−8.13 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 87.6, 116.6, 117.3, 121.6, 123.8, 125.3, 127.3, 128.3, 128.4, 129.3, 130.2, 130.6, 130.8, 140.8, 141.2, 155.5. HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{24}H_{17}N_4$, 361.1453; found, 361.1462.

5-Phenyl-2-((4-(trifluoromethyl)phenyl)amino)pyrazolo[5,1-*a*]isoquinoline-6-carbonitrile (7b). Gray solid (107 mg, 50%). Mp: 301−303 °C. IR (KBr, cm^{-1}): ν 3399, 2224, 1617, 1597, 1558, 1482, 1327, 838, 753, 704. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.12 (s, 1H), 7.49 (d, J = 8.60 Hz, 2H), 7.53 (d, J = 8.85 Hz, 2H), 7.66 (t, J = 3.05 Hz, 3H), 7.72−7.79 (m, 2H), 7.85−7.87 (m, 2H), 7.93 (d, J = 7.85 Hz, 1H), 8.41 (d, J = 7.80 Hz, 1H), 9.85 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 90.0, 93.1, 116.2, 117.1, 123.1 ($^1J_{C-F}$ = 275.4 Hz), 124.8, 125.3, 126.4, 126.7, 128.8, 129.2, 130.5, 130.8, 131.2, 131.7, 140.3, 145.6, 145.7, 154.9. HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{25}H_{16}F_3N_4$, 429.1327; found, 429.1320.

2-((4-Ethoxyphenyl)amino)-5-phenylpyrazolo[5,1-*a*]-isoquinoline-6-carbonitrile (7c). Red solid (121.2 mg, 60%). Mp: 249−251 °C. IR (KBr, cm^{-1}): ν 3397, 2208, 1615, 1594, 1581, 1551, 1476, 1232, 826, 759, 705. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 1.26 (t, J = 6.95 Hz, 3H), 3.92 (q, J = 6.93 Hz, 2H), 6.76 (d, J = 8.90 Hz, 2H), 6.96 (s, 1H), 7.29 (d, J = 8.90 Hz, 2H), 7.63−7.76 (m, 5H), 7.82−7.84 (m, 2H), 7.90 (d, J = 7.95 Hz, 1H), 8.35 (d, J = 7.80 Hz, 1H), 9.09 (s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 15.2, 63.7, 89.0, 91.8, 115.3, 117.2, 118.3, 121.8, 124.6, 125.1, 127.0, 128.7, 128.8, 130.1, 130.6, 131.0, 131.4, 135.2, 140.2, 145.4, 152.9, 156.5. HRMS (ESI-TOF, [M + H]$^+$): calcd for $C_{26}H_{21}N_4O$, 405.1715; found, 405.1709.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR and ^{13}C NMR spectra of all new compounds. 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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