Synthesis of functionalized *H*-pyrazolo[5,1-*a*]isoquinolines *via* sequential reactions of *N*′-(2-alkynylbenzylidene)hydrazides†

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Diversity-oriented synthesis of functionalized *H*-pyrazolo[5,1-*a*]isoquinolines *via* sequential reactions of *N*′-(2-alkynylbenzylidene)hydrazide is described. Bromine-mediated electrophilic cyclization, Ag-catalyzed alkyne nucleophilic addition, and palladium-catalyzed cross-coupling reaction were involved in the transformation.

Introduction

The use of methodology development and library approaches for the discovery of small-molecule enzyme inhibitors or receptor ligands is well-established.[1] Among the strategies utilized in combinatorial chemistry, the development of cascade or sequential reactions for the efficient construction of small molecules is attractive from the viewpoint of assembly efficiency.[2,3] In connection with our continuing research toward the development of new methods for the expeditious synthesis of privileged organic architectures,[4] we recently reported an efficient synthesis of fused 1,2-dihydroisoquinolines *via* Ag(I)-catalyzed tandem reactions of *N*′-(2-alkynylbenzylidene)hydrazides with various alkynes.[5] Subsequently, a promising result was obtained in the preliminary screening of a HCT-116 inhibition assay. Thus, the discovery of promising lead antitumor compounds and their moderate activity warranted the evaluations of analogous structures in the search for better inhibitors. Therefore, we initiated a program to develop efficient methods for the synthesis of diverse *H*-pyrazolo[5,1-*a*]isoquinoline molecules (Fig. 1), with the hope of finding more active hits for our particular biological assays.

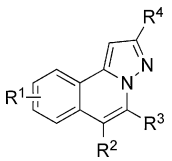
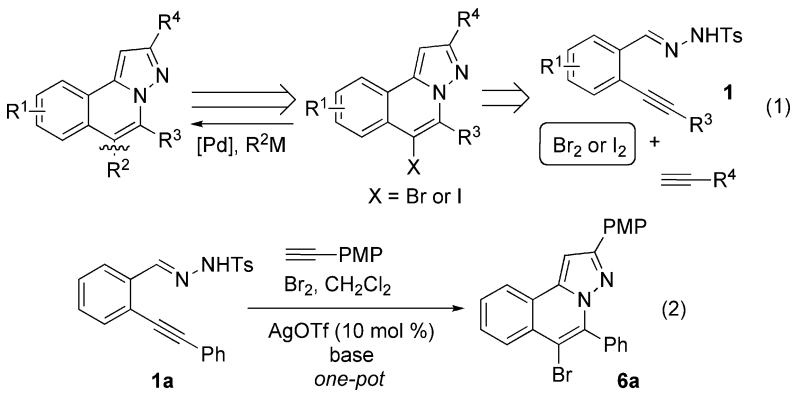


Fig. 1 *H*-Pyrazolo[5,1-*a*]isoquinoline.

Our proposed synthetic route was shown in Scheme 1, eqn (1). Prompted by the recent results for electrophilic cyclization of *N*′-(2-alkynylbenzylidene)hydrazides,[6] we envisioned that in the presence of electrophiles such as iodine or bromine, *N*′-(2-alkynylbenzylidene)hydrazide would undergo electrophilic cyclization, leading to halo-containing isoquinolinium-2-yl amides. Followed by nucleophilic addition of alkyne, the halo-containing *H*-pyrazolo[5,1-*a*]isoquinolines would be generated, which then underwent the palladium-catalyzed cross-coupling reaction to afford the desired functionalized *H*-pyrazolo[5,1-*a*]isoquinolines. Thus, we started to investigate the possibility of this projected synthetic route.

Results and discussion

As described above, in this approach, treatment of *N*′-(2-alkynylbenzylidene)hydrazide **1** with an electrophile should afford isoquinolinium-2-yl amide which may undergo nucleopilic



Scheme 1 Proposed synthetic route.

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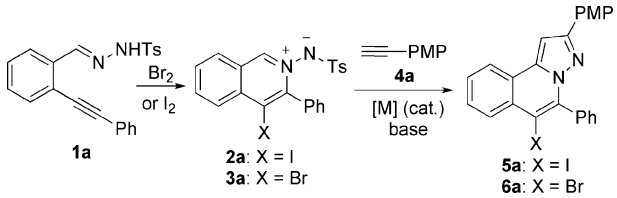
addition in the presence of alkyne. Subsequent aromatization may lead to the formation of *H*-pyrazolo[5,1-*a*]isoquinoline frameworks (Scheme 1, eqn (1)). To identify suitable conditions for the proposed electrophile-mediated domino process, reaction screening involving *N′*-(2-alkynylbenzylidene)hydrazide **1a**, bromine, and 4-methoxyphenylacetylene was carried out in the presence of silver triflate as catalyst (Scheme 1, eqn (2)). Various bases and solvents were examined, however, no desired product was detected. The reaction failed as well when other Lewis acids were employed as catalysts in the transformation. To improve the efficiency of the cascade process, further optimization was carried out using iodo-containing isoquinolinium-2-yl amide **2a** and 4-methoxyphenylacetylene **4a** as substrates (Table 1).

The results of this preliminary survey are shown in Table 1. In an initial experiment, complicated mixture was generated when AgOTf (10 mol%) was employed in the reaction as catalyst at room temperature in CCl_4 in the presence of DBU as base. Parameters including solvents, bases, and other Lewis acids were investigated. Similar results were observed when other solvents such as DCE and DCM were utilized (Table 1, entries 2–3). The results could not be improved when other Lewis acids [CuI, CuBr, $Cu(OTf)_2$, $Zn(OTf)_2$) were used as replacement (Table 1, entries 4–7). To our delight, we observed the formation of the desired product **5a** (31% yield) when the reaction was catalyzed by Ag_2O (10 mol%) (Table 1, entry 8). Under the same conditions, reaction of bromo-containing isoquinolinium-2-yl amide **3a** and 4-methoxyphenylacetylene **4a** afforded the expected product **6a** in 78% yield (Table 1, entry 9). Inferior results were displayed when other bases were used (Table 1, entries 10–12). When the catalytic amount of Ag_2O was decreased to 5 mol%, the desired product **6a** was afforded in 74% yield (Table 1, entry 13). Subsequent examination revealed that the yield increased to 91% when AgOTf was employed as the catalyst in CH_2Cl_2 (Table 1, entry 15). As described previously,[5] the alkyne would act as a nucleophile to attack the isoquinolinium compound **3a** in the presence of base and silver salt, which gave rise to the intermediate **A**. Subsequent intramolecular 5-*endo* cyclization of intermediate **A** and aromatization of intermediate **B** would generate the desired product **6a** (Scheme 2). However, the possible concerted 1,3-dipolar cycloaddition pathway could not be excluded meanwhile.

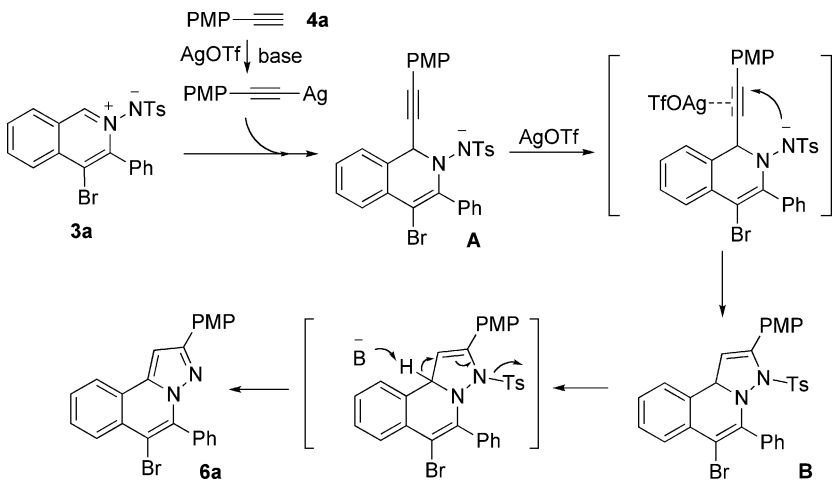
Table 1 Initial studies for reaction of halo-containing isoquinolinium-2-yl amide and alkyne **4a**[a]



Entry	Substrate	Lewis acid	Base	Solvent	Product yield (%)[b]
1	**2a**	AgOTf	DBU	CCl_4	Complicated
2	**2a**	AgOTf	DBU	DCE	Complicated
3	**2a**	AgOTf	DBU	DCM	Complicated
4	**2a**	CuI	DBU	CCl_4	Complicated
5	**2a**	CuBr	DBU	CCl_4	Complicated
6	**2a**	$Zn(OTf)_2$	DBU	CCl_4	Complicated
7	**2a**	$Cu(OTf)_2$	DBU	CCl_4	Complicated
8	**2a**	Ag_2O	DBU	CCl_4	31 (**5a**)
9	**3a**	Ag_2O	DBU	CCl_4	78 (**6a**)
10	**3a**	Ag_2O	K_3PO_4	CCl_4	53 (**6a**)
11	**3a**	Ag_2O	K_2CO_3	CCl_4	51 (**6a**)
12	**3a**	Ag_2O	NaOAc	CCl_4	40 (**6a**)
13[c]	**3a**	Ag_2O	DBU	CCl_4	74 (**6a**)
14	**3a**	AgOTf	DBU	CCl_4	86 (**6a**)
15	**3a**	AgOTf	DBU	DCM	91 (**6a**)

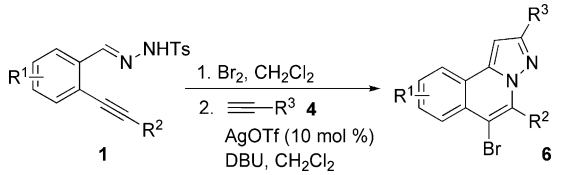
[a] Reaction conditions: Substrate **2a** or **3a** (0.1 mmol), alkyne **4a** (1.5 equiv.), Lewis acid (10 mol%), base (2.5 equiv.), solvent (1.0 mL), room temperature. [b] Isolated yield based on substrate **2a** or **3a**. [c] In the presence of 5 mol% of Ag_2O.

With this promising result in hands, we started to investigate the scope of this reaction. Thus, various *N′*-(2-alkynylbenzylidene)hydrazides **1** were employed in the reactions of bromine and alkynes under the AgOTf-catalyzed conditions [AgOTf (10 mol%), DBU (2.5 equiv.), CH_2Cl_2, room temperature] (Table 2). For most cases, the desired 6-bromo-*H*-pyrazolo[5,1-*a*]isoquinolines were generated in good yields. This silver-catalyzed *H*-pyrazolo[5,1-*a*]isoquinoline formation was found to be workable with teminal acetylenes **4a–4e** bearing aryl, cyclopropyl, butyl, and hydroxy functionality, as well as *N′*-(2-alkynylbenzylidene)hydrazide substrates with electron



Scheme 2 Possible mechanism.

Table 2 Reactions of *N′*-(2-alkynylbenzylidene)hydrazides with bromine and alkynes[a]



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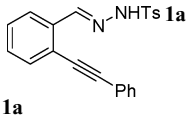
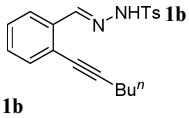
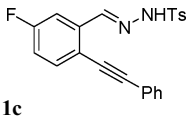
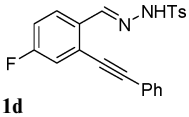
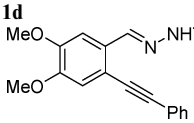
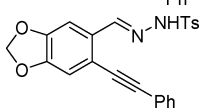
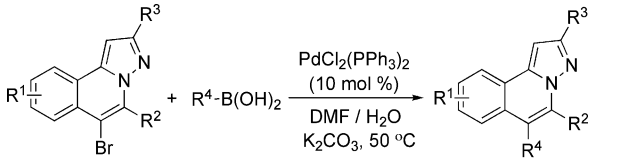
Entry	R^1/R^2	Alkyne **4**	Yield (%)[b]
1		PMP **4a**	91 (**6a**)
2	**1a**	Ph **4b**	70 (**6b**)
3	**1a**	Bu^n **4c**	71 (**6c**)
4	**1a**	 **4d**	80 (**6d**)
5	**1a**	 **4e**	82 (**6e**)
6		PMP **4a**	72 (**6f**)
7	**1b**	 **4d**	61 (**6g**)
8		PMP **4a**	50 (**6h**)
9	**1c**	Ph **4b**	60 (**6i**)
10		PMP **4a**	65 (**6j**)
11	**1d**	 **4d**	65 (**6k**)
12	**1d**	Bu^n **4c**	60 (**6l**)
13		PMP **4a**	—
14		PMP **4a**	—

[a] Reaction conditions: *N′*-(2-alkynylbenzylidene)hydrazide **1** (0.50 mmol), bromine (1.0 equiv.), alkyne **1** (0.75 mmol, 1.5 equiv.), AgOTf (10 mol%), DBU (2.5 equiv.), CH_2Cl_2, room temperature. [b] Isolated yield based on *N′*-(2-alkynylbenzylidene)hydrazide **1**.

withdrawing substituents on the aromatic backbone. For instance, *N′*-(2-alkynylbenzylidene)hydrazide **1a** reacted with bromine and prop-2-yn-1-ol **4e** gave rise to the desired 6-bromo-*H*-pyrazolo[5,1-*a*]isoquinoline **6e** in 82% yield (Table 2, entry 5) In addition to *N′*-(2-alkynylbenzylidene)hydrazide with phenyl group attached to the triple bond, the substrate with *n*-butyl group attached to the triple bond was a good partner as well (Table 2, entries 6 and 7). However, the *N′*-(2-alkynylbenzylidene)hydrazides with electron-donating group attached on the aromatic ring were not good substrates in the reactions, which might be due to their lower electrophilicity toward nucleophilic attack (Table 2, entries 13 and 14). Thus far, compounds **1e** and **1f** have not been workable as substrates in the transformation.

The 6-bromo-*H*-pyrazolo[5,1-*a*]isoquinoline **6** could be further elaborated *via* palladium-catalyzed cross-coupling reactions. All the reactions proceeded smoothly to generate the desired products

Table 3 Palladium-catalyzed Suzuki couplings of 6-bromo-*H*-pyrazolo[5,1-*a*]isoquinoline **6**



6 7

Entry	Compound **6**	$R^4B(OH)_2$	Yield (%)[a]
1	**6a**	4-$MeC_6H_4B(OH)_2$	80 (**7a**)
2	**6b**	4-$MeC_6H_4B(OH)_2$	83 (**7b**)
3	**6c**	4-$MeOC_6H_4B(OH)_2$	84 (**7c**)
4	**6d**	4-$MeC_6H_4B(OH)_2$	86 (**7d**)
5	**6e**	4-$MeC_6H_4B(OH)_2$	50 (**7e**)
6	**6f**	4-$MeC_6H_4B(OH)_2$	88 (**7f**)
7	**6g**	4-$MeOC_6H_4B(OH)_2$	86 (**7g**)
8	**6k**	4-$MeOC_6H_4B(OH)_2$	80 (**7h**)
9	**6l**	$C_6H_5B(OH)_2$	94 (**7i**)

[a] Isolated yield based on 6-bromo-*H*-pyrazolo[5,1-*a*]isoquinoline **6**.

in moderate to good yields. For example, as expected, compound **6a** reacted with 4-methylphenylboronic acid leading to the corresponding *H*-pyrazolo[5,1-*a*]isoquinoline **7a** in 80% yield (Table 3, entry 1). It is noteworthy that the hydroxy group in the transformation could be tolerated. Reaction of substrate **6e** with 4-methylphenylboronic acid afforded the expected coupling product **7e** in 50% yield (Table 3, entry 5).

Conclusions

In summary, we have described an efficient and facile route for the synthesis of functionalized *H*-pyrazolo[5,1-*a*]isoquinolines *via* sequential electrophilic cyclization, nucleophilic addition, and palladium-catalyzed cross-coupling reactions of *N′*-(2-alkynylbenzylidene)hydrazides, bromine with alkynes. The substituents diversity could be easily introduced in the transformations. Construction of small library and biological screening of these small molecules are under investigation in our laboratory, and the results will be reported in due course.

Experimental

All reactions were performed in test tubes under nitrogen atmosphere. Flash column chromatography was performed using silica gel (60-Å pore size, 32–63 μm, standard grade). Analytical thin-layer chromatography was performed using glass plates precoated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporators at ~20 Torr (house vacuum) at 25–35 °C. Commercial reagents and solvents were used as received.

General procedure for reaction of *N′*-(2-alkynylbenzylidene)hydrazide **1** with bromine and alkyne **4**: bromine (0.3 mmol, 1.0 equiv.) in 2.0 mL of CH_2Cl_2 was added dropwisely to a mixture of *N′*-(2-alkynylbenzylidene)hydrazide **1** (0.30 mmol) in CH_2Cl_2 (4.0 mL). The reaction was stirred at room temperature. After completion of reaction as indicated by TLC, the reaction

mixture was then diluted with CH_2Cl_2 (25 mL), washed with saturated aqueous $Na_2S_2O_3$ (25 mL), dried (Na_2SO_4) and filtered. The solvent was then evaporated and the residue was dissolved in 2.0 mL of CH_2Cl_2. Then DBU (2.5 equiv.) and AgOTf (10 mol%) were added. Subsequently, alkyne **4** (1.5 equiv.) in 1.0 mL of CH_2Cl_2 was added dropwise at room temperature under air atmosphere. The reaction mixture was stirred at room temperature for about 5 h. After completion of reaction as indicated by TLC, the mixture was diluted with CH_2Cl_2, washed by water. The organic layer was combined, dried over Na_2SO_4, and purified by column chromatography on silica gel to afford the desired product **6**.

6-Bromo-2-(4-methoxyphenyl)-5-phenylpyrazolo[5,1-*a*]isoquinoline **6a**. Yield: 91%; ^{1}H NMR (400 MHz, $CDCl_3$): 3.81 (s, 3H), 6.89–6.91 (m, 2H), 7.28 (s, 1H), 7.54–7.65 (m, 7H), 7.76–7.79 (m, 2H), 8.12–8.15 (m, 1H), 8.21–8.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.4, 94.6, 108.5, 114.1, 123.8, 123.9, 125.8, 127.8, 127.9, 128.2, 128.3, 128.6, 128.7, 129.3, 130.7, 134.2, 137.9, 139.7, 152.6, 159.9; IR (cm^{-1}): 2965, 2904, 2832, 1618, 1521, 1459, 1434, 1378, 1251, 1173, 1024; *m/z* (ESI): 429 (M^++H); HRMS calcd for $C_{24}H_{18}BrN_2O$ (M+H) 429.0603, found 429.0621.

6-Bromo-2,5-diphenylpyrazolo[5,1-*a*]isoquinoline **6b**. Yield: 70%; ^{1}H NMR (400 MHz, $CDCl_3$): 7.27–7.31 (m, 1H), 7.34–7.38 (m, 3H), 7.52–7.64 (m, 7H), 7.84–7.86 (m, 2H), 8.12–8.14 (m, 1H), 8.20–8.22 (m, 1H);^{13}C NMR (100 MHz, $CDCl_3$): δ 95.1, 108.9, 123.7, 123.9, 126.5, 127.9, 128.3, 128.4, 128.5, 128.6, 128.7, 129.3, 130.7, 133.0, 134.1, 137.9, 139.7, 152.7. IR (cm^{-1}): 3052, 2945, 2919, 2842, 1618, 1598, 1540, 1492, 1470, 1456, 1381, 1319, 1173, 1079; *m/z* (ESI): 399 (M^++H); HRMS calcd for $C_{23}H_{16}BrN_2$ (M+H) 399.0497, found 399.0513.

6-Bromo-2-butyl-5-phenylpyrazolo[5,1-*a*]isoquinoline **6c**. Yield: 71%; ^{1}H NMR (400 MHz, $CDCl_3$): 0.92 (t, J = 7.3 Hz, 3H), 1.36–1.41 (m, 2H), 1.64–1.71 (m, 2H), 2.75 (t, J = 7.80 Hz, 2H), 6.86 (s, 1H), 7.51–7.62 (m, 7H), 8.05–8.07 (m, 1H), 8.16–8.19 (m, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.6, 28.4, 31.9, 96.7, 107.9, 123.6, 123.8, 127.7, 128.1, 128.4, 128.5, 129.3, 130.5, 134.4, 137.7, 139.0, 155.9. IR (cm^{-1}): 3057, 2955, 2928, 2852, 1588, 1541, 1493, 1481, 1465, 1383, 1322; *m/z* (ESI): 379 (M^++H); HRMS calcd for $C_{21}H_{20}BrN_2$ (M+H) 379.0810, found 379.0828.

6-Bromo-2-cyclopropyl-5-phenylpyrazolo[5,1-*a*]isoquinoline **6d**. Yield: 80%; ^{1}H NMR (400 MHz, $CDCl_3$): 0.74–0.78 (m, 2H), 0.93–0.99 (m, 2H), 2.04–2.12 (m, 1H), 6.61 (s, 1H), 7.51–7.61 (m, 7H), 8.00–8.02 (m, 1H), 8.16–8.18 (m, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ 9.31, 9.84, 93.2, 107.8, 123.5, 123.6, 127.7, 128.1, 128.4, 128.5, 129.3, 130.5, 134.3, 137.6, 139.1, 157.9. IR (cm^{-1}): 2955, 2924, 2854, 1618, 1588, 1543, 1492, 1444, 1383, 1337, 1045; *m/z* (ESI): 363 (M^++H); HRMS calcd for $C_{20}H_{16}BrN_2$ (M+H) 363.0497, found 363.0510.

(6-Bromo-5-phenylpyrazolo[5,1-*a*]isoquinolin-2-yl)methanol **6e**. Yield: 82%; ^{1}H NMR (400 MHz, $CDCl_3$)): 4.70 (s, 2H), 7.00 (s, 1H), 7.45–7.62 (m, 7H), 8.01–8.04 (m, 1H), 8.15–8.18 (m, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ 59.0, 96.6, 109.1, 123.6, 123.7, 127.8, 128.3, 128.4, 128.6, 128.8, 129.5, 130.3, 134.0, 137.5, 139.2, 154.3. IR (cm^{-1}): 3401, 3052, 2925, 2847, 1613, 1588, 1540, 1492, 1444, 1411, 1381, 1319, 1032; *m/z* (ESI): 353 (M^++H); HRMS calcd for $C_{18}H_{14}BrN_2O$ (M+H) 353.0290, found 353.0304.

6-Bromo-5-butyl-2-(4-methoxyphenyl)pyrazolo[5,1-*a*]isoquinoline **6f**. Yield: 72%; ^{1}H NMR (400 MHz, $CDCl_3$): 1.03 (t, J = 7.32 Hz, 3H), 1.54–1.58 (m, 2H), 1.83–1.87 (m, 2H), 3.56 (t, J = 7.80 Hz, 2H), 3.86 (s, 3H), 6.99–7.01 (m, 2H), 7.21 (s, 1H), 7.50–7.59 (m, 2H), 7.92–7.98 (m, 2H), 8.04–8.06 (m, 1H), 8.08–8.12(m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.9, 28.8, 31.3, 55.4, 94.4, 107.4, 114.2, 123.2, 123.6, 126.1, 127.1, 127.4, 127.7, 128.3, 128.4, 139.1, 139.5, 152.1, 159.9. IR (cm^{-1}): 2960, 2919, 2852, 1613, 1525, 1460, 1437, 1316, 1250, 1174, 1029; *m/z* (ESI): 409 (M^++H); HRMS calcd for $C_{22}H_{22}BrN_2O$ (M+H) 409.0916, found 409.0913.

6-Bromo-5-butyl-2-cyclopropylpyrazolo[5,1-*a*]isoquinoline **6g**. Yield: 61%; ^{1}H NMR (400 MHz, $CDCl_3$): 0.89–0.94 (m, 2H), 0.99 (t, J = 7.36 Hz, 3H), 1.03–1.07 (m, 2H), 1.47–1.56 (m, 2H), 1.74–1.81 (m, 2H), 2.14–2.19 (m, 1H), 3.48 (t, J = 7.36 Hz, 2H), 6.64 (s, 1H), 7.46–7.57 (m, 2H), 7.94–7.97 (m, 1H), 8.06–8.08 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.15, 9.77, 14.0, 22.8, 28.9, 31.3, 94.1, 106.7, 122.9, 123.5, 127.0, 127.2, 128.3, 128.4, 138.6, 139.3, 157.1. IR (cm^{-1}): 2956, 2926, 2847, 1618, 1598, 1541, 1496, 1449, 1392, 1316, 1070; *m/z* (ESI): 343 (M^++H); HRMS calcd for $C_{18}H_{20}BrN_2$ (M+H) 343.0810, found 343.0819.

6-Bromo-9-fluoro-2-(4-methoxyphenyl)-5-phenylpyrazolo[5,1-*a*]isoquinoline **6h**. Yield: 50%; ^{1}H NMR (400 MHz, $CDCl_3$): 3.82 (s, 3H), 6.89–6.92 (m, 2H), 7.24 (s, 1H), 7.33–7.37 (m, 1H), 7.54–7.60 (m, 5H), 7.75–7.81 (m, 3H), 8.20–8.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.4, 95.2, 107.8, 108.9 (d, $^2J_{CF}$ = 22.9 Hz), 114.1, 117.1 (d, $^2J_{CF}$ = 22.9 Hz), 125.1, 125.2, 125.5, 127.8, 128.4, 129.4, 130.6, 130.7, 133.9, 137.3, 138.9, 152.7, 160.0, 162.2 (d, $^1J_{CF}$ = 248.9 Hz). IR (cm^{-1}): 2960, 2924, 2842, 1603, 1516, 1485, 1458, 1434, 1372, 1250, 1178, 1034; *m/z* (ESI): 447 (M^++H); HRMS calcd for $C_{24}H_{17}BrFN_2O$ (M+H) 447.0508, found 447.0512.

6-Bromo-9-fluoro-2,5-diphenylpyrazolo[5,1-*a*]isoquinoline **6i**. Yield: 60%; ^{1}H NMR (400 MHz, $CDCl_3$): 7.35–7.54 (m, 7H), 7.59–7.65 (m, 1H), 7.70–7.73 (m, 4H), 8.14–8.17 (m, 1H), 8.38–8.41 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.1, 95.5, 110.9(d, $^2J_{CF}$ = 21.9 Hz), 118.1, 119.2, 121.8, 122.4(d, $^2J_{CF}$ = 25.7 Hz), 124.4, 128.1, 128.6, 129.7, 129.9, 132.3, 133.6, 140.3, 142.6, 147.2, 152.5, 161.9 (d, ^{1} J_{CF} = 250.8 Hz). IR (cm^{-1}): 3057, 2960, 2919, 2842, 1618, 1546, 1493, 1439, 1419, 1393, 1301, 1170; *m/z* (ESI): 317 (M^++H); HRMS calcd for $C_{23}H_{15}BrFN_2$ (M+H) 417.0403, found 417.0413.

6-Bromo-8-fluoro-2-(4-methoxyphenyl)-5-phenylpyrazolo[5,1-*a*]isoquinoline **6j**. Yield: 65%; ^{1}H NMR (400 MHz, $CDCl_3$): 3.80 (s, 3H), 6.87–6.89 (m, 2H), 7.18 (s, 1H), 7.29–7.34 (m, 1H), 7.54–7.58 (m, 5H), 7.73–7.76 (m, 2H), 7.85–7.89(m, 1H), 8.06–8.10(m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 94.3, 107.2, 113.4 (d, $^2J_{CF}$ = 24.8 Hz), 114.0, 116.8 (d, $^2J_{CF}$ = 23.8 Hz), 120.4, 125.5, 126.1, 127.7, 128.3, 129.4, 130.6, 130.7, 133.9, 138.9, 139.3, 152.8, 159.9, 162.6 (d, $^1J_{CF}$ = 246.9 Hz). IR (cm^{-1}): 3057, 2924, 2831, 1614, 1518, 1477, 1451, 1437, 1380, 1250, 1171, 1026; *m/z* (ESI): 447 (M^++H); HRMS calcd for $C_{24}H_{17}BrFN_2O$ (M+H) 447.0508, found 447.0515.

6-Bromo-2-cyclopropyl-8-fluoro-5-phenylpyrazolo[5,1-*a*]isoquinoline **6k**. Yield: 65%; ^{1}H NMR (400 MHz, $CDCl_3$): 0.74–0.79 (m, 2H), 0.96–0.99 (m, 2H), 2.04–2.08 (m, 1H), 6.56 (s, 1H), 7.27–7.32 (m, 1H), 7.51–7.59 (m, 5H), 7.84–7.87 (m, 1H), 7.99–8.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.33, 9.83, 93.1, 113.3 (d, $^2J_{CF}$ = 24.8 Hz), 116.7 (d, $^2J_{CF}$ = 23.8 Hz), 120.2, 125.9, 126.1, 128.5, 129.5, 130.3, 130.6, 134.0, 138.7, 138.8, 158.3, 162.5 (d, $^1J_{CF}$ = 246.0 Hz). IR (cm^{-1}): 3052, 2961, 2909, 2852, 1621, 1544, 1499, 1445, 1398, 1378, 1268, 1166; *m/z* (ESI): 381 (M^++H); HRMS calcd for $C_{20}H_{15}BrFN_2$ (M+H) 381.0403, found 381.0412.

6-Bromo-2-butyl-8-fluoro-5-phenylpyrazolo[5,1-*a*]isoquinoline **6l**. Yield: 60%; ^{1}H NMR (400 MHz, $CDCl_3$): 0.92 (t, $J = 7.32$ Hz, 3H), 1.34–1.41 (m, 2H), 1.64–1.68 (m, 2H), 2.74 (t, $J = 7.80$ Hz, 2H), 6.81 (s, 1H), 7.29–7.34 (m, 1H), 7.50–7.56 (m, 5H), 7.85–7.88 (m, 1H), 8.03–8.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.6, 28.3, 31.9, 96.5, 106.7, 113.3 (d, $^2J_{CF} = 24.8$ Hz), 116.7(d, $^2J_{CF} = 23.8$ Hz), 120.4, 126.1, 128.5, 129.5, 130.4, 130.5, 130.6, 134.1, 138.7, 156.3, 162.5 (d, $^1J_{CF} = 246.9$ Hz). IR (cm^{-1}): 3057, 2955, 2927, 2858, 1621, 1541, 1484, 1444, 1398, 1378, 1311, 1269, 1166; *m/z* (ESI): 397 (M^++H); HRMS calcd for $C_{21}H_{19}BrFN_2$ (M+H) 397.0716, found 397.0715.

General procedure for palladium-catalyzed Suzuki couplings of 6-bromo-*H*-pyrazolo[5,1-*a*]isoquinoline **6**. A mixture of 6-bromo-*H*-pyrazolo[5,1-*a*]isoquinoline **6** (0.12 mmol), arylboronic acid (1.2 equiv.), $PdCl_2(PPh_3)_2$ (10 mol%) and K_2CO_3 (2.0 equiv.) in 1.0 mL of DMF–H_2O (5 : 1, v/v) was stirred under N_2 atmosphere at 50–60 °C. After completion of reaction as indicated by TLC, the mixture was cooled to room temperature and water (10 mL) was added. The mixture was extracted with ethyl acetate (5.0 mL × 3) and the organic layer was combined, which was then washed with brine, dried over Na_2SO_4, and purified by column chromatography on silica gel to afford the desired product **7**.

2-(4-Methoxyphenyl)-5-phenyl-6-*p*-tolylpyrazolo[5,1-*a*]isoquinoline **7a**. Yield: 80%; ^{1}H NMR (400 MHz, $CDCl_3$): 2.32 (s, 3H), 3.81 (s, 3H), 6.88–6.92 (m, 2H), 7.05–7.09 (m, 4H), 7.26–7.29 (m, 3H), 7.32 (s, 1H), 7.38–7.44 (m, 4H), 7.52–7.55 (m, 1H), 7.82–7.85 (m, 2H), 8.18 (d $J = 8.24$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 55.4, 94.1, 114.0, 123.5, 123.6, 123.9, 126.3, 126.9, 127.2, 127.5, 127.6, 127.7, 128.0, 128.8, 130.3, 131.5, 131.6, 133.3, 133.4, 136.4, 136.7, 139.9, 152.1, 159.7. IR (cm^{-1}): 2945, 2914, 2837, 1608, 1526, 1458, 1429, 1248, 1163, 1024; *m/z* (ESI): 441 (M^++H); HRMS calcd for $C_{31}H_{25}N_2O$ (M+H) 441.1967, found 441.1980.

2,5-Diphenyl-6-*p*-tolylpyrazolo[5,1-*a*]isoquinoline **7b**. Yield: 83%; ^{1}H NMR (400 MHz, $CDCl_3$): 2.33 (s, 3H), 7.06–7.11 (m, 4H), 7.24–7.32 (m, 4H), 7.36–7.44 (m, 7H), 7.53–7.59 (m, 1H), 7.90–7.93 (m, 2H), 8.20–8.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 94.6, 123.6, 123.9, 124.0, 126.5, 126.9, 127.3, 127.6, 127.7, 128.0, 128.1, 128.6, 128.8, 130.3, 131.5, 131.6, 133.3, 133.5, 136.5, 136.8, 139.9, 152.2. IR (cm^{-1}): 3052, 3016, 2914, 2858, 1588, 1536, 1506, 1456, 1378, 1342, 1178, 1081, 1014; *m/z* (ESI): 411 (M^++H); HRMS calcd for $C_{30}H_{23}N_2$ (M+H) 411.1861, found 411.1873.

2-Butyl-6-(4-methoxyphenyl)-5-phenylpyrazolo[5,1-*a*]isoquinoline **7c**. Yield: 84%; ^{1}H NMR (400 MHz, $CDCl_3$): 0.94 (t, $J = 7.32$ Hz, 3H), 1.39–1.45 (m, 2H), 1.68–1.74 (m, 2H), 2.80 (t, $J = 7.80$ Hz, 2H), 3.78 (s, 3H), 6.77–6.81 (m, 2H), 6.91 (s, 1H), 7.04–7.08 (m, 2H), 7.24–7.29 (m, 3H), 7.31–7.34 (m, 2H), 7.38–7.41 (m, 2H), 7.48–7.54 (m, 1H), 8.13 (d, $J = 7.76$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.7, 28.5, 32.1, 55.2, 96.1, 113.5, 122.6, 123.5, 123.8, 126.7, 127.0, 127.4, 127.8, 128.1, 128.7, 130.3, 131.2, 132.8, 133.5, 136.4, 139.2, 155.4, 158.5. IR (cm^{-1}): 3052, 2955, 2929, 2858, 1603, 1512, 1475, 1460, 1337, 1245, 1168, 1034; *m/z* (ESI): 407 (M^++H); HRMS calcd for $C_{28}H_{27}N_2O$ (M+H) 407.2123, found 407.2141.

2-Cyclopropyl-5-phenyl-6-*p*-tolylpyrazolo[5,1-*a*]isoquinoline **7d**. Yield: 86%; ^{1}H NMR (400 MHz, $CDCl_3$): 0.80–0.84 (m, 2H), 0.96–1.04 (m, 2H), 2.10–2.14 (m, 1H), 2.31 (s, 3H), 6.65 (s, 1H), 7.02–7.07 (m, 4H), 7.25–7.28 (m, 3H), 7.31–7.36 (m, 2H), 7.37–7.40 (m, 2H), 7.48–7.51 (m, 1H), 8.07 (d, $J = 8.28$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.28, 9.96, 21.3, 92.6, 122.8, 123.4, 123.7, 126.7, 127.0, 127.5, 127.7, 128.1, 128.7, 130.2, 131.3, 131.6, 133.3, 133.4, 136.1, 136.6, 139.4, 157.4. IR (cm^{-1}): 3042, 2955, 2923, 2852, 1536, 1513, 1493, 1449, 1398, 1342, 1301, 1178, 1075; *m/z* (ESI): 375 (M^++H); HRMS calcd for $C_{27}H_{23}N_2$ (M+H) 375.1861, found 375.1878.

(5-Phenyl-6-*p*-tolylpyrazolo[5,1-*a*]isoquinolin-2-yl)methanol **7e**. Yield: 50%; ^{1}H NMR (400 MHz, $CDCl_3$)): 2.32 (s, 3H), 4.84 (s, 2H), 7.04–7.09 (m, 5H), 7.27–7.33 (m, 5H), 7.41–7.43 (m, 2H), 7.54–7.57 (m, 1H), 8.15 (d, $J = 8.24$ Hz, 1H);^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 59.6, 95.9, 123.6, 123.9, 124.0, 126.9, 127.4, 127.9, 128.3, 128.8, 130.2, 131.2, 131.5, 133.1, 133.2, 136.2, 136.8, 139.6, 153.7. IR (cm^{-1}): 3354, 3052, 2920, 2847, 1593, 1536, 1513, 1490, 1454, 1388, 1332, 1033; *m/z* (ESI): 365 (M^++H); HRMS calcd for $C_{25}H_{21}N_2O$ (M+H) 365.1654, found 365.1665.

5-Butyl-2-(4-methoxyphenyl)-6-*p*-tolylpyrazolo[5,1-*a*]isoquinoline **7f**. Yield: 88%; ^{1}H NMR (400 MHz, $CDCl_3$): 0.86 (t, $J = 7.32$ Hz, 3H), 1.31–1.38 (m, 2H), 1.74–1.79 (m, 2H), 2.48 (s, 3H), 3.03 (t, $J = 7.80$ Hz, 2H), 3.87 (s, 3H), 6.98–7.03 (m, 2H), 7.18–7.25 (m, 4H), 7.31–7.38 (m, 3H), 7.45–7.49 (m, 1H), 7.97–8.02 (m, 2H), 8.13 (d, $J = 7.80$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 21.4, 22.9, 28.9, 30.3, 55.4, 93.9, 114.2, 121.9, 123.2, 123.4, 126.3, 126.4, 126.7, 127.4, 127.7, 129.3, 130.4, 130.9, 134.0, 137.3, 137.8, 139.6, 151.8, 159.8; IR (cm^{-1}): 2957, 2929, 2868, 1612, 1527, 1510, 1482, 1460, 1438, 1248, 1173, 1106, 1034; *m/z* (ESI): 421 (M^++H); HRMS calcd for $C_{29}H_{29}N_2O$ (M+H) 421.2280, found 421.2296.

5-Butyl-2-cyclopropyl-6-(4-methoxyphenyl)pyrazolo[5,1-*a*]isoquinoline **7g**. Yield: 86%; ^{1}H NMR (400 MHz, $CDCl_3$): 0.81 (t, $J = 7.32$ Hz, 3H), 0.92–0.95 (m, 2H), 1.04–1.09 (m, 2H), 1.28–1.30 (m, 2H), 1.67–1.71 (m, 2H), 2.17–2.22 (m, 1H), 2.95 (t, $J = 7.80$ Hz, 2H), 3.90 (s, 3H), 6.68 (s, 1H), 7.02–7.05 (m, 2H), 7.17–7.23 (m, 3H), 7.41–7.48 (m, 2H), 8.02 (d, $J = 7.80$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.10, 9.86, 13.9, 22.8, 28.9, 30.2, 55.4, 93.3, 113.9, 114.2, 122.9, 123.3, 126.1, 126.2, 127.3, 127.8, 129.3, 130.6, 132.2, 137.9, 156.6, 159.0; IR (cm^{-1}): 2956, 2927, 2852, 1607, 1510, 1456, 1342, 1276, 1245, 1173, 1106, 1040; *m/z* (ESI): 371 (M^++H); HRMS calcd for $C_{25}H_{27}N_2O$ (M+H) 371.2123, found 371.2135.

2-Cyclopropyl-8-fluoro-6-(4-methoxyphenyl)-5-phenylpyrazolo[5,1-*a*]isoquinoline **7h**. Yield: 80%; ^{1}H NMR (400 MHz, $CDCl_3$): 0.79–0.82 (m, 2H), 0.98–1.02 (m, 2H), 2.09–2.14 (m, 1H), 3.79 (s, 3H), 6.60 (s, 1H), 6.77–6.82 (m, 2H), 7.02–7.07 (m, 3H), 7.21–7.35 (m, 6H), 8.04–8.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.29, 9.95, 55.2, 92.4, 111.8 (d, $^2J_{CF} = 22.9$ Hz), 113.7, 115.7 (d, $^2J_{CF} = 23.8$ Hz), 120.3, 121.8, 125.7, 127.8, 128.1, 128.3, 131.1, 132.4, 132.7, 133.2, 137.3, 139.1, 157.8, 158.7, 161.9 (d, $^1J_{CF} = 245.0$ Hz); IR (cm^{-1}): 2924, 2852, 1608, 1512, 1500, 1449, 1403, 1342, 1285, 1246, 1175, 1024; *m/z* (ESI): 409 (M^++H); HRMS calcd for $C_{27}H_{22}FN_2O$ (M+H) 409.1716, found 409.1710.

2-Butyl-8-fluoro-5,6-diphenylpyrazolo[5,1-*a*]isoquinoline **7i**. Yield: 94%; ^{1}H NMR (400 MHz, $CDCl_3$): 0.94 (t, $J = 7.32$ Hz, 3H), 1.37–1.45 (m, 2H), 1.67–1.75 (m, 2H), 2.79 (t, $J = 7.80$ Hz, 2H), 6.86 (s, 1H), 6.97–7.08 (m, 1H), 7.15–7.20 (m, 2H), 7.24–7.31 (m, 9H), 8.09–8.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.7, 28.5, 32.0, 95.9, 111.7 (d, $^2J_{CF} = 22.9$ Hz), 115.7 (d, $^2J_{CF} = 23.8$ Hz), 120.5, 122.3, 125.7, 127.3, 127.8, 128.2, 128.4, 131.1, 131.7, 132.0, 133.0, 136.1, 137.3, 138.9, 155.9, 161.9 (d, $^1J_{CF} = 245.0$ Hz); IR (cm^{-1}): 3062, 2955, 2921, 2847, 1620, 1540, 1486, 1464, 1443, 1400, 1342, 1321, 1265, 1191; *m/z* (ESI): 395 (M^++H); HRMS calcd for $C_{27}H_{24}FN_2$ (M+H) 395.1924, found 395.1945.

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