Note

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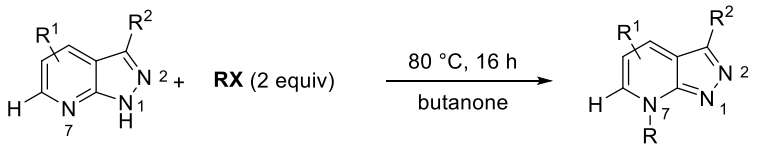
Supporting Information Placeholder



45 - 91% yield for 1° and 2° **RX**

ABSTRACT: A general and mild procedure for alkylation of 7-azaindazole at the N7 position using alkyl halides in butanone is reported, which requires no additives such as acids or bases. The scope of the reaction regarding substituents on 7-azaindazoles and the alkyl electrophiles is presented.

7-Azaindazoles are important building blocks for pharmaceuticals and bioactive agents (Figure 1). Examples of unsubstituted 7-azaindazoles include non-nucleoside reverse transcriptase inhibitors (NNTRIs, **1a**),[1,2] c-Met inhibitors (**1b**),[3] and fibroblast growth factor receptor (FGFR) kinase inhibitors (**1c**).[4] There are also multiple examples of N1 substituted agents, including the dual orexin receptor antagonists (DORAs, **1d**) and the approved pulmonary hypertension drug riociguat (**1e)**, which is a stimulator of soluble guanylate cyclase (sGC).[5,6] Much less common, however are examples of N7 substituted species, which includes the γ-secretase modulator (**1f**) for potential treatment of Alzheimer's disease.[7]

Recently, we became interested in synthesizing structures with N7 alkylated azaindazoles due to their potentially favorable physicochemical properties as compared to the corresponding N1 substituted azaindazoles. As shown in Figure 2, regioisomers **A** and **B** share the same molecular weight and similar topography, but isomer **B** has lower cLogP and is more basic than **A**. We believe that N7 alkylated azaindazoles offer a potentially useful alternative scaffold to modulate the pharmacologic properties of compounds of medicinal interest.

There is an abundance of reports detailing the synthesis of N1 substituted 7-azaindazoles. Indeed, using CAS SciFinder, we identified over 2,000 publications for the preparation of over 30,000 such derivatives. However, there are significantly fewer methods focusing on the synthesis of N7 alkylated 7-azaindazoles. Qin and coworkers reported the synthesis of compound **1f** (Figure 1) and provided a general method for the syntheses of this regioisomer.[7] All compounds in that study were synthesized from a pyridone precursor **2** via a multi-step synthetic route in which the 7-azaindazole core was constructed through hydrazone formation and subsequent ring closure using $POCl_3$ from a ketone intermediate **3** in < 30% total yield (**2** to **1f**, Figure 3). A plausible reason for the scarcity of N7 substituted azaindazoles in literature could be the lack of efficient methods for the synthesis of these compounds. We surmised that a methodology for direct alkylation of 7-azaindazoles at the N7 position would be of great synthetic utility for medicinal chemistry.

Baelen et al. reported that direct N7 alkylation of 7-azaindole **4** with iodomethane in THF upon heating afforded nearly quantitative yield of the N7 methylated product **5** (Figure 3).[8] However, the additional N2 nitrogen in the 7-azaindazole core significantly alters this reactivity. There is limited precedent for direct alkylation of 7-azaindazoles at the N7 position. Wu and coworkers reported, as the only example of direct N7 alkylation of 7-azaindazole, that reaction of **6** with iodomethane under similar conditions gave **7** in only 15% yield (Figure 3).[9] Herein, we report a mild, general, and selective method for the direct alkylation of readily available 7-azaindazoles at the N7 position.

FIGURE 1. 7-Azaindazoles in Compounds of Medicinal Interest

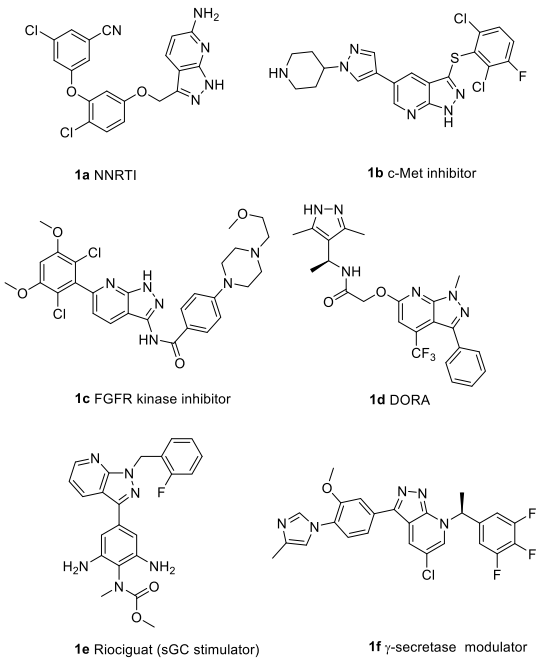
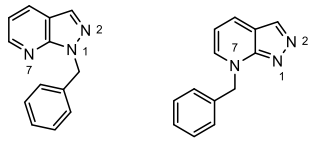


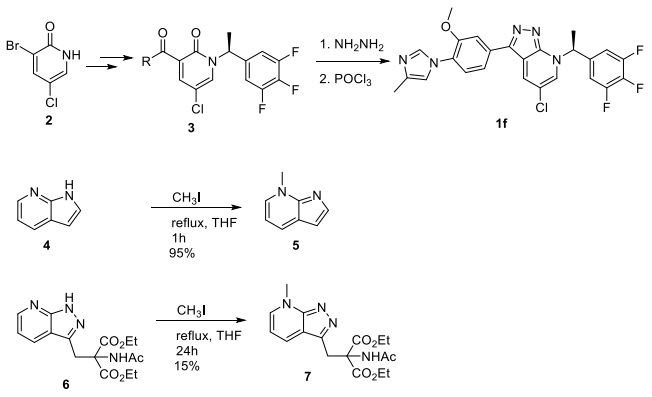
FIGURE 2. Calculated LogP and pKa of N1 and N7 Benzylated 7-Azaindazoles[a]



	A	B
ACD LogP:	2.27	1.26
ACD pKa:	3.7 (N7)	5.5 (N1)

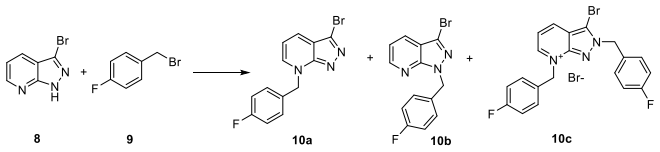
[a]Calculated using ACD/Percepta. pKa refers to the pKa of the most acidic N.

FIGURE 3. Reported Methods for the Synthesis of 7-Azaind(az)oles



We used 3-bromo-1H-pyrazolo[3,4-b]pyridine **8** and 4-fluorobenzyl bromide **9** as model substrates due to the specific need of a medicinal chemistry project. The parameters explored during the optimization included solvent, acid or base additive, and temperature (Table 1). In THF at 80 °C for 16 h (conditions reported by Wu and co-workers),[8] the reaction of **8** and **9** (2 equiv) gave 16% isolated yield of **10a** (N7) and 15% isolated yield of dialkylated product **10c** with 20% of unreacted starting material **9** (entry 1).[10] The dialkylated product **10c** was also formed from **10a** by treating isolated **10a** with **9** under the same reaction conditions, suggesting that **10c** may be formed sequentially from **10a**. In dioxane, the selectivity for **10a** over **10c** (1:1) was higher than reaction in THF (entry 2). Using inorganic bases such as K_2CO_3 or $NaHCO_3$ as an additive, the reaction afforded exclusively the N1 product **10b** (entries 3 & 4). With addition of 1 equivalent of trifluoroacetic acid (TFA), good regioselectivity for **10a** (N7 alkylation) was achieved, although the conversion was low (entry 5). Additional solvents were screened to optimize the yield of **10a** (entry 6–15). We were pleased to find that the reaction in butanone gave 54% yield of **10a** with only negligible amount of **10b** and a small amount (~5%, not isolated) **10c** (entry 15). The yield of **10a** was improved to 78% yield by extending the reaction time to 3 days (entry 16). The addition of TFA (1 equiv) in butanone did not increase the rate of reaction and gave **10a** in 61% yield in 64 h (entry 17). The yield of **10a** was lower at 60 °C in butanone compared with that of at 80 °C (60%, entry 18). Finally, the reaction was conducted with other benzyl halides. Whereas reaction with 4-fluorobenzyl chloride did not give any desired product (entry 20), reaction with 4-fluorobenzyl iodide gave **10a** in a low yield (13%) due to significant bis-alkylation (**10c**, entry 21).

TABLE 1. Optimization of Reaction Conditions for N7 Alkylation of 8[a]



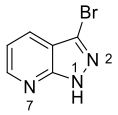
entry	additive (equiv)	solvent	yield of **10a** (%)[b]	yield of **10b** (%)[b]	ratio of **10a**:**10b**:**10c**[c]
1	none	THF	16	n.i.	37:0:63
2	none	dioxane	14	n.i.	49:0:51
3	K_2CO_3 (2)	dioxane	n.i.	39	0:100:0
4	$NaHCO_3$ (2)	dioxane	n.i.	33	0:100:0
5	TFA (1)	dioxane	8	n.i.	n.d.
6	none	toluene	24	n.i.	90:0:10
7	none	DCE	29	n.i.	65:0:35
8	none	ACN	37	n.i.	63:0:37
9	none	DMF	6	n.i.	29:0:71
10	none	DMF:THF (1:1)	20	n.i.	32:6:62
11	none	EtOH	31	n.i.	96:0:4
12	none	^{t}BuOMe	14	n.i.	63:0:37
13	none	DME	24	n.i.	61:0:39
14	none	^{i}PrOAc	27	n.i.	92:0:8
15	none	butanone	54	n.i.	89:0:11
16[d]	none	butanone	78	n.i.	85:0:15
17[d]	TFA (1)	butanone	61	n.i.	79:0:21
18[d,e]	none	butanone	60	n.i.	87:0:13
19[d,f]	none	butanone	75	n.i.	n.d.
20[g]	none	butanone	0	n.i.	n.d.
21[h]	none	butanone	13	n.i.	23:0:77

[a]Reaction conditions: All reactions were performed with **8** (0.5 mmol), **9** (1.0 mmol), and the additive in 2.0 mL of solvent at 80 °C for 16 h unless otherwise noted. [b]Yields of products isolated by NH_4OH workup followed up either prep. TLC or silica gel flash chromatography to a purity of ≥ 95%. n.i.: not isolated and estimated to be <5% by crude LCMS. [c]Determined on crude samples by LCMS using UV area at 220 nM. n.d.: not determined. [d]The reaction time was 64 h. [e]The reaction temperature was 60 °C. [f]Reaction conducted with 1.0 mmol of **8** and 2.0 mmol of **9** in 4 mL of

butanone. [g]Reaction conducted with 4-fluorobenzyl chloride as the electrophile. [h]Reaction conducted with 4-fluorobenzyl iodide as the electrophile.

We hypothesized that the distribution of alkylation products depends on the nucleophilicity of each N atom: with inorganic bases as additive in dioxane, the nucleophile is the anionic form of **8,** with the negative charge mainly localized on N1, whereas with TFA or without additive (the alkylation generates 1 equivalent of acid) in butanone, the nucleophile is the neutral form of **8** with N7 atom being the most nucleophilic N atom. The above rationale is supported by electron density calculation on **8** (Table 2), which indicates that N1 is the most electron-rich N-atom in the anion form and N7 is the most electron-rich N-atom in the neutral form.

TABLE 2. Calculated Electron Densities of N atoms of 8 in Neutral and Anion Forms[a]



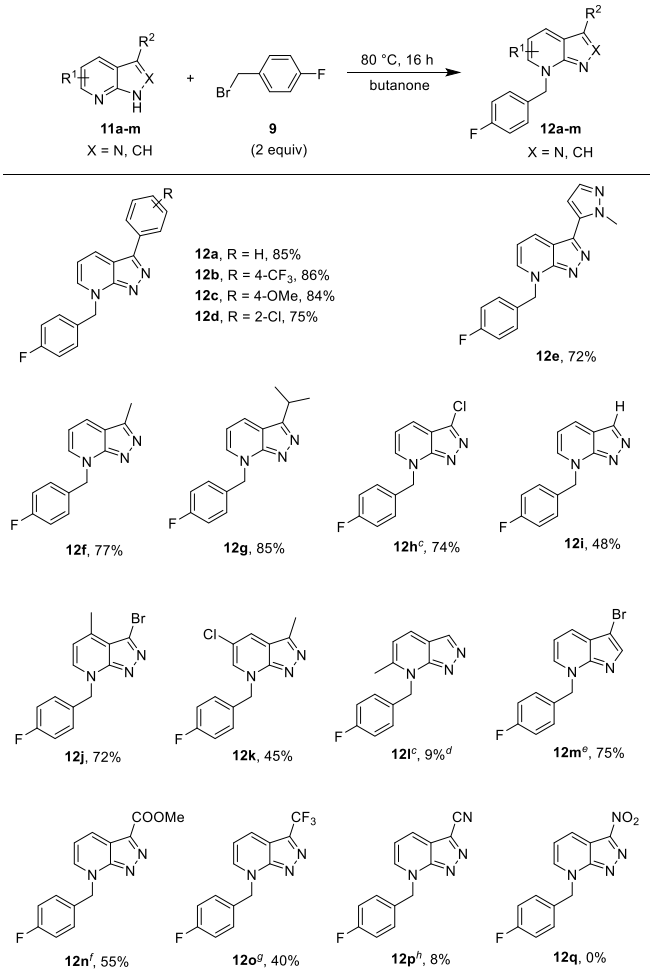
8

Natural bond orbital (NBO) charges			
	N1	N2	N7
Neutral	-0.358	-0.271	-0.466
Anion	-0.498	-0.277	-0.383

[a]Electron density of the nitrogen atoms of **8** are computed with b3lyp/6-311+G** basis set for the neutral form and anion with -1 charge. The electron density at N2 position is almost identical in the two forms. N7 has the largest electron density in the neutral form while in the anion form, deprotonated N1 is the most negatively charged.

With the optimal reaction conditions in hand, we next examined the scope of the N7 selective alkylation reaction with respect to various substituted 7-azaindazoles. As summarized in Figure 4, N7 alkylated products were obtained in excellent yields from a diverse set of substituted 7-azaindazoles under the optimized reaction conditions. For 3-aryl-7-azaindazoles (substrates **11a**–**11d**), neither electronic nature of the substituents (electron-donating or electron-withdrawing groups) nor steric hindrance (Cl group at the 2-position of the phenyl ring, **11d**) impacted the reaction yields (compounds **12a**–**12d**). With Me, *i*Pr and Cl as substituents at the C3 position, the alkylation reaction produced **12f**, **12g**, and **12h** in 77%, 85%, and 74% yields, respectively. A lower yield (**12i**, 48%) was obtained for C3 unsubstituted 7-azaindazole due to formation of the dialkylated byproduct. Whereas reaction of a 4-substituted substrate (**11j**) gave the desired regioisomer in a good yield (72%), reaction of a 5-substitued substrate (**11k**) proceeded more slowly with the starting material remaining after 16 h (presumably due to the electron-withdrawing effect of Cl). Reaction of a 6-substituted azaindazole (**11l**) proceeded with poor selectivity, with the major product being the N2 alkylated product, presumably due to the steric effect of the methyl group at the C6 position. Interestingly, alkylation of 7-azaindole under the standard conditions was faster than alkylation of 7-azaindazole and completed in 3 h with 75% yield (compound **12m**), which is most likely due to the stronger nucleophilicity of the N7 atom in 7-azaindole compared to 7-azaindazole (7-azaindole is more electron-rich than 7-azaindazole). In contrast, reactions of substrates with strongly electron-withdrawing groups were slower and gave the desired products in lower yields (**12n**-**12q**), presumably because of the reduced nucleophilicity of the N7.

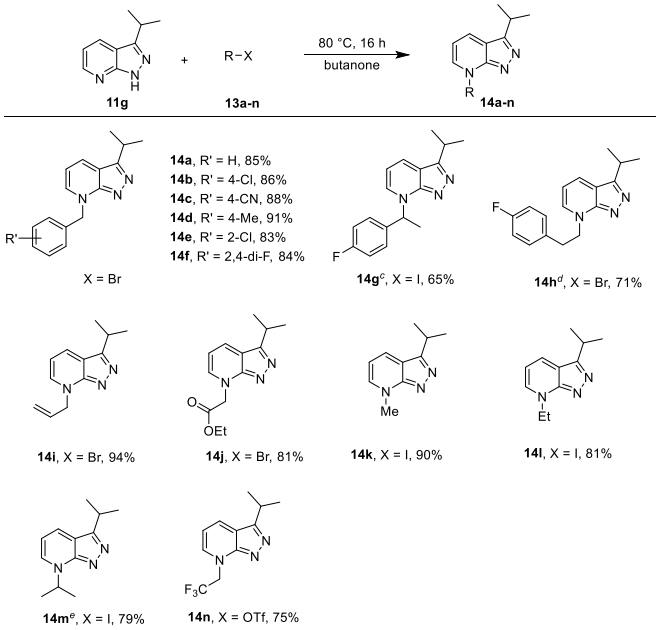
FIGURE 4. Alkylation of 7-Azaindazoles by 4-Fluorobenzyl Bromide - Scope of Substitutions on 7-Azaindazole Core[a,b]



[a]Reaction conditions: All reactions were performed with **11a-m** (0.25 mmol) and **9** (0.5 mmol) in 1.0 mL of butanone at 80 °C for 16 h unless otherwise noted. [b]Yields of products isolated by NH_4OH workup followed by column chromatography to ≥ 95% purity, as illustrated in the SI. [c]The reaction time was 32 h. [d]The major product (40%) was the N2 alkylation product. [e]The reaction time was 3 h. [f]The reaction time was 24 h. [g]The reaction time was 60 h. [h]The reaction time was 120 h.

Next, we examined the N7 alkylation with respect to different types of electrophiles (R-X) as depicted in Figure 5. For substituted benzyl bromides, the reactions gave N7 alkylated products in >80% yields regardless of the substitution pattern of the electrophiles (**14a**–**14f**). For other reactive electrophiles (MeI, allyl bromide, ethyl bromoacetate and CF_3CH_2OTf), the yields were >70%. For less reactive alkyl halides, the rate of reactions decreased substantially, but synthetically useful yields (>60%) were obtained with increased amounts of electrophiles and extended reaction time (**14g**, **14h**, and **14m**).

FIGURE 5. Scope of Electrophiles for N7 Alkylation[a,b]



[a]Reaction conditions: All reactions were performed with **11g** (0.25 mmol) and **13a-n** (0.5 mmol) in 1.0 mL of butanone at 80 °C for 16 h unless otherwise noted. [b]Yields of products isolated by NH_4OH workup followed by column chromatography to ≥ 95% purity, as illustrated in the SI. [c]3 Equiv of alkyl iodide was used and the reaction was stirred at 80 °C for 48 h. [d]6 equiv of alkyl bromide was used and the reaction was stirred at 80 °C for 72 h. [e]10 equiv of alkyl iodide was used and the reaction was stirred at 80 °C for 96 h.

CONCLUSIONS

In conclusion, we developed a general and operationally simple protocol for the synthesis of N7 substituted 7-azaindazoles through direct alkylation of 7-azaindazoles with various electrophiles in butanone. Compared to the previously reported ring forming strategy, the current method offers direct access to this structural motif, allowing rapid SAR exploration at the N7 position of 7-azaindazoles. The method affords products in high yields for 1° and 2° alkyl electrophiles irrespective of the substitutions at C3, C4, and C5 on the 7-azaindazole core (except when C3 is unsubstituted).

EXPERIMENTAL SECTION

General Information: All reagents and solvents were obtained from commercial suppliers and used without further purification unless stated otherwise. All experiments were carried out under N_2, and oven-dried glassware was used in all cases. For thin layer chromatography (TLC), Liang Chen Gui Yuan precoated TLC plates were used, and compounds were visualized with a UV light at 254 nm. Column chromatography separations were performed on silica gel (200−300 mesh). ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on a Varian spectrometer at 400 MHz for ^1H and 100 MHz for ^{13}C or a Bruker Avance III spectrometer at 500 MHz for ^1H and 125 MHz for ^{13}C. High-resolution mass spectra (HRMS) were recorded with an Agilent G6230B instrument and were performed in positive mode with an ESI source on a TOF mass spectrometer.

General Procedure for Azaindazoles Synthesis 11a-11e: To a solution of 3-bromo-1H-pyrazolo[3,4-b]pyridine (1.5 mmol, 1 eq) and Ar-$B(OH)_2$ (1.5 eq) in Dioxane (3 mL)/Water (0.6 mL) was added K_2CO_3 (2 eq) and $Pd(dppf)Cl_2$ (0.1 eq). The mixture was stirred in an oil bath at 90 °C under N_2 for 16 h. After finished, the mixture was diluted with EtOAc (15 mL), the organic layer was washed with water (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography with petroleum ether /ethyl acetate (PE/EA) as the eluent to afford the desired product.

3-phenyl-1H-pyrazolo[3,4-b]pyridine (11a) Colorless solid, PE/EA (1/1), 58% (171 mg). ^1H NMR (400 MHz, DMSO-d_6) δ 13.82 (s, 1H), 8.58 - 8.56 (m, 2H), 8.03 - 8.02 (m, 2H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.28 (dd, *J* = 4.8, 7.6 Hz, 1H). The NMR data agree with the literature data.[11]

3-(4-(trifluoromethyl)phenyl)-1H-pyrazolo[3,4-b]pyridine (11b) Colorless solid, PE/EA (2/1), 39% (105 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 12.51 (br s, 1H), 8.73 (dd, *J* = 1.6, 4.4 Hz, 1H), 8.44 (dd, *J* = 1.6, 8.0 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 7.6 Hz, 2H), 7.33 (dd, *J* = 4.8, 8.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.3, 148.4, 143.3, 133.6, 131.2, 130.4 (q, *J* = 32 Hz), 127.3, 126.0 (q, *J* = 3.7 Hz), 124.1 (q, *J* = 271 Hz), 117.7, 113.8. ^{19}F NMR (470 MHz, $CDCl_3$) δ -62.57. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{13}H_9F_3N_3^+$ 264.0743; Found 264.0741.

3-(4-methoxyphenyl)-1H-pyrazolo[3,4-b]pyridine (11c) Colorless solid, PE/EA (1/1), 50% (173 mg). ^1H NMR (400 MHz, DMSO-d_6) δ 13.68 (br s, 1H), 8.55 - 8.51 (m, 2H), 7.95 (d, *J* = 8.8 Hz, 2H), 7.25 (dd, *J* = 4.4, 8.0 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 159.2, 152.8, 148.7, 142.5, 130.3, 127.8, 125. 8, 117.0, 114.4, 111.8, 55.2. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{13}H_{12}N_3O^+$ 226.0975; Found 226.0975.

3-(2-chlorophenyl)-1H-pyrazolo[3,4-b]pyridine (11d) Colorless solid, PE/EA (1/1), 41% (143 mg). ^1H NMR (400 MHz, DMSO-d_6) δ 13.96 (br s, 1H), 8.58 (dd, *J* = 1.6, 4.4 Hz, 1H), 8.12 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.67 - 7.63 (m, 2H), 7.52 - 7.49 (m, 2H), 7.25 (dd, *J* = 4.4, 8.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 152.1, 149.0, 141.7, 132.2, 132.2, 131.8, 130.4, 130.3, 130.0, 127.5, 117.1, 113.2. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{12}H_9ClN_3^+$ 230.0480 found: 230.0480.

3-(1-methyl-1H-pyrazol-5-yl)-1H-pyrazolo[3,4-b]pyridine (11e) Colorless solid, PE/EA (3/1), 22% (66 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 12.50 (br s, 1H), 8.72 (d, *J* = 4.8 Hz, 1H), 8.28 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.65 (d, *J* = 1.6 Hz, 1H), 7.31 (dd, *J* = 4.8, 8.4 Hz, 1H), 6.76 (d, *J* = 1.6 Hz, 1H), 4.28 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.3, 149.2, 138.6, 136.0, 134.2, 130.5, 117.6, 114.2, 106.4, 39.0. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{10}H_{10}N_5^+$ 200.0931; Found 200.0932.

Procedure for 3-isopropyl-1H-pyrazolo[3,4-b]pyridine (11g): Step 1: To a solution of 2-fluoropyridine (5 g, 51.5 mmol) in THF (60 mL) was added LDA (25.7 mL, 51.5 mmol) at 0 °C under N_2. The mixture was stirred at 0°C for 30 min. Then isobutyraldehyde (7.43 g, 103 mmol) was added by dropwise. The mixture was stirred at 0°C for 2 hours. TLC showed the starting material was consumed. The mixture was quenched with water (50 mL), extracted with EtOAc (50 mL×3). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography with (PE/EA 5:1) to give 1-(2-fluoropyridin-3-yl)-2-methylpropan-1-ol (2.5 g, 29% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, *J* = 4.8 Hz, 1H), 7.92-7.89 (m, 1H), 7.20 - 7.17 (m, 1H), 4.71 (d, *J* = 5.6 Hz, 1H), 2.32 (br s, 1H), 2.01 - 1.96 (m, 1H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H).

Step 2: To a solution of 1-(2-fluoropyridin-3-yl)-2-methylpropan-1-ol (2.5 g, 14.78 mmol) in DCM (50 mL) was added 4Å MS (500 mg) and NMO (2.60 g, 22.16 mmol), the mixture was stirred at 20 °C for 15 min, then TPAP (0.104 g, 0.296 mmol) was added. The resulting mixture was stirred at 20 °C for 3h. Then filtered and the filtrate was concentrated, the residue was purified by silica gel chromatography (PE/EA 2:1) to give 1-(2-fluoropyridin-3-yl)-2-methylpropan-1-one (2 g, 81% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 - 8.35 (m, 1H), 8.28 - 8.23 (m, 1H), 7.33 - 7.29 (m, 1H), 3.48 - 3.41 (m, 1H), 1.20 (d, *J* = 6.8 Hz, 6H).

Step 3: To a solution of 1-(2-fluoropyridin-3-yl)-2-methylpropan-1-one (2 g, 11.96 mmol) in EtOH (20 mL) was added hydrazine hydrate (5 mL, 98 mmol). The mixture was stirred in an oil bath at 80 °C for 16 h. TLC showed starting material was consumed. The mixture was concentrated in vacuum. The residue was diluted with EtOAc (30 mL), washed with water (10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by silica gel chromatography (PE/EA 3:1) to give 3-isopropyl-1H-pyrazolo[3,4-b]pyridine (1.5 g, 78% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.00 (br s, 1H), 8.59 (dd, *J* = 1.2, 4.4 Hz, 1H), 8.15 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.13 (dd, *J* = 4.4, 8.0 Hz, 1H), 3.46 - 3.40 (m, 1H), 1.49 (d, *J* = 6.8 Hz, 6H). The NMR data agree with the literature data.[12]

General Procedure for Alkylation: A solution of azaindazole (0.25 mmol) and halogenoalkane **2** (0.5 mmol) in butanone (1 mL) in a sealed tube was stirred in an oil bath at 80 °C for 16 h. Then NH_3H_2O (28–30% ammonia in water, 1 mL) was added and the mixture was stirred at room temperature for 15 min. The resulting mixture was diluted with EtOAc (10 mL) and water (5 mL). The organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by preparative TLC (with EA/MeOH 10/1 as eluent unless otherwise stated) to give the desired product.

3-Bromo-7-(4-fluorobenzyl)-7H-pyrazolo[3,4-b]pyridine (10a) Synthesized according to the general procedure on a 1-mmol scale and the reaction time was 64 h. Yellow solid, mp 221-223 °C, EA/MeOH (10/1), 75% (231 mg). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.58 (d, *J* = 6.0 Hz, 1H), 8.51 (d, *J* = 7.6 Hz, 1H), 7.55 (dd, *J* = 5.2, 8.0 Hz, 2H), 7.27 (t, *J* = 6.8 Hz, 1H), 7.10 (t, *J* = 8.8 Hz, 2H), 5.91 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 164.6 (d, *J* = 245.9 Hz), 151.5, 141.1, 138.8, 132.2 (d, *J* = 8.4 Hz), 131.9 (d, *J* = 2.9 Hz), 123.4, 122.6, 117.1 (d, *J* = 22.1 Hz), 113.8, 56.8. ^{19}F NMR (470 MHz, MeOH-d_4) δ -114.68. HRMS (ESI) m/z: Calcd for $C_{13}H_{10}{}^{79}BrFN_3^+$ $[M + H]^+$ = 306.0037; Found 306.0040; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{13}H_{10}{}^{81}BrFN_3^+$ 308.0016; Found 308.0020.

7-(4-Fluorobenzyl)-3-phenyl-7H-pyrazolo[3,4-b]pyridine (12a) Yellow solid, EA/MeOH (10/1), 85% (64 mg). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.79 (d, *J* = 7.6 Hz, 1H), 8.43 (d, *J* = 5.6 Hz, 1H), 7.92 (d, *J* = 7.2 Hz, 2H), 7.55 (dd, *J* = 5.2, 8.4 Hz, 2H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.42 - 7.35 (m, 1H), 7.20 (dd, *J* = 6.0, 7.2 Hz, 1H), 7.08 (t, *J* = 8.8 Hz, 2H), 5.91 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 164.5 (d, *J* = 245.9 Hz), 152.1, 149.3, 139.6, 139.5, 134.7, 132.27 (d, *J* = 3.1 Hz), 132.0 (d, *J* = 8.4 Hz), 130.2, 129.4, 128.3, 122.3, 117.0 (d, *J* = 22.0 Hz), 113.5, 57.0. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{15}FN_3^+$ 304.1245; Found 304.1245.

7-(4-Fluorobenzyl)-3-(4-(trifluoromethyl)phenyl)-7H-pyrazolo[3,4-b]pyridine (12b) Yellow solid, mp 332-334 °C, EA/MeOH (10/1), 86% (80 mg). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.89 (d, *J* = 7.6 Hz, 1H), 8.51 (d, *J* = 6.4 Hz, 1H), 8.14 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.57 (dd, *J* = 5.2, 8.4 Hz, 2H), 7.28 (dd, *J* = 6.0, 7.6 Hz, 1H), 7.09 (t, *J* = 8.8 Hz, 2H), 5.95 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 164.6 (d, *J* = 245.9 Hz), 152.3, 147.6, 139.7, 139.6, 138.6, 132.2 (d, *J* = 3.8 Hz), 132.1 (d, *J* = 8.3 Hz), 130.8 (q, *J* = 33 Hz), 128.5, 127.1 (q, *J* = 3.8 Hz), 125.9 (q, *J* = 269.4 Hz), 122.2, 117.0 (d, *J* = 22 Hz), 114.1, 57.2. ^{19}F NMR (470 MHz, $CDCl_3$) δ -62.42, -111.48. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{14}F_4N_3^+$ 372.1118; Found 372.1122.

7-(4-Fluorobenzyl)-3-(4-methoxyphenyl)-7H-pyrazolo[3,4-b]pyridine (12c) Yellow solid, EA/MeOH (10/1), 84% (70 mg). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.77 (d, *J* = 7.6 Hz, 1H), 8.42 (d, *J* = 5.6 Hz, 1H), 7.86 (d, *J* = 9.2 Hz, 2H), 7.55 (dd, *J* = 5.2, 8.4 Hz, 2H), 7.19 (dd, *J* = 6.4, 7.6 Hz, 1H), 7.11 - 7.04 (m, 4H), 5.91 (s, 2H), 3.84 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 164.5 (d, *J* = 245.0 Hz), 161.5, 152.0, 149.4, 139.6, 139.4, 132.3 (d, *J* = 3.6 Hz), 132.0 (d, *J* = 8.1 Hz), 129.6, 127.3, 122.5, 117.0 (d, *J* = 21.8 Hz), 115.7, 113.1, 56.9, 56.0. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{17}FN_3O^+$ 334.1350; Found 334.1355.

3-(2-Chlorophenyl)-7-(4-fluorobenzyl)-7H-pyrazolo[3,4-b]pyridine (12d) Yellow solid, EA/MeOH (10/1), 75% (63 mg). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.54 (d, *J* = 7.6 Hz, 1H), 8.51 (d, *J* = 6.4 Hz, 1H), 7.61 - 7.57 (m, 4H), 7.46 - 7.43 (m, 2H), 7.24 (dd, *J* = 6.4, 7.6 Hz, 1H), 7.12 (t, *J* = 8.8 Hz, 2H), 5.97 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 164.5 (d, *J* = 245.2 Hz), 151.7, 147.8, 140.1, 139.6, 134.3, 133.7, 133.6, 132.2, 132.2 (d, *J* = 8.4 Hz), 131.3, 128.4, 123.0, 117.1 (d, *J* = 22.0 Hz), 116.2, 113.4, 57.2. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{14}ClFN_3^+$ 338.0855; Found 338.0859.

7-(4-Fluorobenzyl)-3-(1-methyl-1H-pyrazol-5-yl)-7H-pyrazolo[3,4-b]pyridine (12e) Yellow solid, EA/MeOH (10/1), 72% (55 mg). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.67 (d, *J* = 7.6 Hz, 1H), 8.53 (d, *J* = 5.6 Hz, 1H), 7.59 - 7.55 (m, 3H), 7.27 (dd, *J* = 6.0, 7.6 Hz, 1H), 7.08 (t, *J* = 8.8 Hz, 2H), 6.70 (d, *J* = 2.0 Hz, 1H), 5.95 (s, 2H), 4.14 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 164.5 (d, *J* = 245.5 Hz), 151.6, 140.1, 139.9, 139.8, 139.0, 136.8, 132.1 (d, *J* = 3.0 Hz), 132.1 (d, *J* = 9.0 Hz), 123.3, 117.0 (d, *J* = 22.4 Hz), 114.0, 107.2, 57.3, 38.9. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{15}FN_5^+$ 308.1306; Found 308.1310.

7-(4-Fluorobenzyl)-3-methyl-7H-pyrazolo[3,4-b]pyridine (12f) Yellow solid, EA/MeOH (10/1), 77% (46 mg). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.54 (dd, *J* = 1.2, 7.6 Hz, 1H), 8.36 (d, *J* = 5.6 Hz, 1H), 7.50 (dd, *J* = 5.2, 8.8 Hz, 2H), 7.11 - 7.05 (m, 3H), 5.83 (s, 2H), 2.63 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 164.5 (d, *J* = 245.2 Hz), 151.4, 146.7, 139.3, 138.4, 132.4, 131.9 (d, *J* = 8.4 Hz), 124.2, 117.0 (d, *J* = 21.3 Hz), 111.9, 56.7, 12.3. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{14}H_{13}FN_3^+$ 242.1088; Found 242.1092.

7-(4-Fluorobenzyl)-3-isopropyl-7H-pyrazolo[3,4-b]pyridine (12g) Yellow solid, EA/MeOH (10/1), 85% (57 mg). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.63 (d, *J* = 7.2 Hz, 1H), 8.35 (d, *J* = 6.0 Hz, 1H), 7.51 (dd, *J* = 5.2, 7.6 Hz, 2H), 7.10 - 7.04 (m, 3H), 5.84 (s, 2H), 3.51 - 3.44 (m, 1H), 1.45 (d, *J* = 7.2 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 164.3 (d, *J* = 244.7 Hz), 156.0, 151.3, 138.9, 138.6, 132.2 (d, *J* = 3 Hz), 131.7 (d, *J* = 8.9 Hz), 122.3, 116.7 (d, *J* = 22.3 Hz), 111.6, 56.5, 29.7, 23.0. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{16}H_{17}FN_3^+$ 270.1401; Found 270.1403.

3-Chloro-7-(4-fluorobenzyl)-7H-pyrazolo[3,4-b]pyridine (12h) Synthesized according to the general procedure and the reaction

time was 32 h. Yellow solid, mp 282-284 °C, EA/MeOH (10/1), 74% (48 mg). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (d, *J* = 6.0 Hz, 1H), 8.53 (d, *J* = 7.6 Hz, 1H), 7.63 (dd, *J* = 5.6, 7.6 Hz, 2H), 7.22 - 7.17 (m, 3H), 5.88 (s, 2H). ^{13}C{^{1}H} NMR (125 MHz, DMSO-d_6) δ 161.6 (d, *J* = 243.7 Hz), 148.7, 138.6, 135.4, 132.1, 130.9 (d, *J* = 3.7 Hz), 130.6 (d, *J* = 8.1 Hz), 118.2, 115.1 (d, *J* = 20.7 Hz), 110.9, 54.1. ^{19}F NMR (470 MHz, $CDCl_3$) δ -111.35. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{13}H_{10}ClFN_3^+$ 262.0542; Found 262.0545.

7-(4-Fluorobenzyl)-7H-pyrazolo[3,4-b]pyridine (12i) Yellow solid, EA/MeOH (8/1), 48% (27 mg). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.66 (d, *J* = 7.6 Hz, 1H), 8.49 (s, 1H), 8.45 (d, *J* = 6.0 Hz, 1H), 7.53 (dd, *J* = 5.2, 8.4 Hz, 2H), 7.19 (dd, *J* = 6.0, 7.6 Hz, 1H), 7.08 (t, *J* = 8.8 Hz, 2H), 5.91 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 164.5 (d, *J* = 244 Hz), 151.0, 139.5, 139.3, 137.8, 132.3 (d, *J* = 3.6 Hz), 132.0 (d, *J* = 8.0 Hz), 124.7, 117.0 (d, *J* = 21.8 Hz), 113.2, 57.2. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{13}H_{11}FN_3^+$ = 228.0932; Found 228.0936.

3-Bromo-7-(4-fluorobenzyl)-4-methyl-7H-pyrazolo[3,4-b]pyridine (12j) Yellow solid, mp 241-243 °C, EA/MeOH (10/1), 72% (57 mg). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.34 (d, *J* = 6.0 Hz, 1H), 7.51 (dd, *J* = 5.2, 8.8 Hz, 2H), 7.09 (t, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 6.4 Hz, 1H), 5.80 (s, 2H), 2.93 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, MeOH-d_4) δ 164.6 (d, *J* = 145.5 Hz), 155.0, 151.1, 140.5, 132.1 (d, *J* = 3.6 Hz), 132.0 (d, *J* = 9.0 Hz), 121.6, 120.6, 117.0 (d, *J* = 21.8 Hz), 115.9, 56.3, 19.1. ^{19}F NMR (470 MHz, MeOH-d_4) δ -114.89. HRMS (ESI) m/z: Calcd for $[M+H]^+$ $C_{14}H_{12}{}^{79}BrFN_3^+$ 322.0193; Found 320.0189; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{14}H_{12}{}^{81}BrFN_3^+$ 322.0173; Found 322.0170.

5-Chloro-7-(4-fluorobenzyl)-3-methyl-7H-pyrazolo[3,4-b]pyridine (12k) Yellow solid, EA/MeOH (10/1), 45% (31 mg). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.65 (d, *J* = 2.0 Hz, 1H), 8.61 (d, *J* = 1.4 Hz, 1H), 7.55 (dd, *J* = 5.2, 8.8 Hz, 2H), 7.10 (t, *J* = 8.8 Hz, 2H), 5.83 (s, 2H), 2.62 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 164.6 (d, *J* = 245.5 Hz), 150.2, 146.9, 138.1, 137.7, 132.1 (d, *J* = 8.2 Hz), 131.9 (d, *J* = 3.0 Hz), 124.6, 118.4, 117.0 (d, *J* = 22.4 Hz), 57.2, 12.2. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{14}H_{12}ClFN_3^+$ 276.0698; Found 276.0699.

7-(4-Fluorobenzyl)-6-methyl-7H-pyrazolo[3,4-b]pyridine (12l) Synthesized according to the general procedure except that the reaction time was 32 h. Yellow solid, EA/MeOH (10/1), 9% (5.5 mg). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.56 (s, 1H), 8.28 (d, *J* = 7.6 Hz, 1H), 7.31 – 7.25 (m, 2H), 6.99 (t, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.08 (s, 2H), 2.67 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, Chloroform-*d*) δ 162.8 (d, *J* = 247.9 Hz), 152.1, 146.3, 137.1, 136.2, 130.0, 129.6 (d, *J* = 8.3 Hz), 121.8, 116.3 (d, *J* = 21.8 Hz), 113.0, 52.0, 20.0. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{14}H_{13}FN_3^+$ 242.1093; Found 242.1101.

3-Bromo-7-(4-fluorobenzyl)-7H-pyrrolo[2,3-b]pyridine (12m) Synthesized according to the general procedure and the reaction time was 3 h. Yellow solid, PE/EA (1/1), 75% (57 mg). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.08 (d, *J* = 7.2 Hz, 2H), 7.64 (s, 1H), 7.39 (dd, *J* = 5.2, 8.4 Hz, 2H), 7.07 - 7.00 (m, 3H), 5.81 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 164.3 (d, *J* = 244.7 Hz), 148.1, 143.4, 133.4, 132.8 (d, *J* = 3.0 Hz), 132.3, 131.5 (d, *J* = 8.2 Hz), 129.6, 116.9 (d, *J* = 21.6 Hz), 112.2, 89.0, 57.8. HRMS (ESI) m/z: Calcd for $C_{14}H_{11}{}^{79}BrFN_2^+$ $[M+H]^+$ = 305.0084; Found 305.0082; HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{14}H_{11}{}^{81}BrFN_2^+$ 307.0064; Found 307.0063.

Methyl 7-(4-fluorobenzyl)-7H-pyrazolo[3,4-b]pyridine-3-carboxylate (12n) Synthesized according to the general procedure and the reaction time was 24 h. Yellow solid, mp 199−201 °C, EA/MeOH (10/1), 55% (39 mg). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.94 (d, *J* = 7.6 Hz, 1H), 8.62 (d, *J* = 6.0 Hz, 1H), 7.58 (dd, *J* = 8.4, 5.6 Hz, 2H), 7.44 (dd, *J* = 7.6, 6.0 Hz, 1H), 7.10 (t, *J* = 8.4 Hz, 2H), 6.03 (s, 2H), 4.00 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 164.6 (d, *J* = 245.9 Hz), 164.3, 151.8, 140.4, 140.1, 139.9, 132.2 (d, *J* = 8.3 Hz), 131.9 (d, *J* = 3.0 Hz), 123.6, 117.1 (d, *J* = 22.0 Hz), 116.3, 57.6, 52.4. ^{19}F NMR (376 MHz, MeOH-d_4) δ -114.5. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{13}FN_3O_2^+$ 286.0986; Found 286.0985.

7-(4-Fluorobenzyl)-3-(trifluoromethyl)-7H-pyrazolo[3,4-b]pyridine (12o) Synthesized according to the general procedure and the reaction time was 60 h. Yellow solid, mp 266−268 °C, EA/MeOH (10/1), 40% (30 mg). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.74 (d, *J* = 7.6 Hz, 1H), 8.68 (d, *J* = 5.2 Hz, 1H), 7.58 - 7.60 (m, 2H), 7.42-7.45 (m, 1H), 7.11 (t, *J* = 8.0 Hz, 2H), 6.04 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 164.7 (d, *J* = 245.5 Hz), 151.4, 140.8, 138.7, 138.5 (q, *J* = 36.4 Hz), 132.3 (d, *J* = 7.4 Hz), 131.8 (d, *J* = 3.0 Hz), 123.8 (q, *J* = 265.6 Hz), 120.4, 117.1 (d, *J* = 21.5 Hz), 115.7, 57.7. ^{19}F NMR (376 MHz, MeOH-d_4) δ -61.2, -114.5. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{14}H_{10}F_4N_3^+$ 296.0805; Found 296.0813.

7-(4-Fluorobenzyl)-7H-pyrazolo[3,4-b]pyridine-3-carbonitrile (12p) Synthesized according to the general procedure and the reaction time was 120 h. Yellow solid, mp 275−276 °C, EA/MeOH (10/1), 8% (5 mg). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.62 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 6.0 Hz, 1H), 7.58 - 7.55 (m, 2H), 7.28 (dd, *J* = 8.0, 6.0 Hz, 1H), 7.10 (t , *J* = 8.5, 2H), 6.06 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, Chloroform-*d*) δ 163.4 (d, *J* = 248.4 Hz), 149.4, 135.8, 135.7, 131.4 (d, *J* = 9.0 Hz), 128.7 (d, *J* = 3.0 Hz), 124.7, 121.9, 116.6 (d, *J* = 21.5 Hz), 114.4, 113.6, 56.8. ^{19}F NMR (471 MHz, Chloroform-*d*) δ -110.5. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{14}H_{10}FN_4^+$ 253.0884; Found 253.0897.

7-Benzyl-3-isopropyl-7H-pyrazolo[3,4-b]pyridine (14a) Yellow solid, EA/MeOH (10/1), 85% (53 mg). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.62 (d, *J* = 7.2 Hz, 1H), 8.32 (d, *J* = 6.4 Hz, 1H), 7.42 (d, *J* = 6.0 Hz, 2H), 7.31 (d, *J* = 6.8 Hz, 3H), 7.07 (t, *J* = 6.8 Hz, 1H), 5.85 (s, 2H), 3.51 - 3.44 (m, 1H), 1.44 (d, *J* = 6.8 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 156.1, 151.6, 139.3, 138.8, 136.3, 130.2, 130.0, 129.7, 122.4, 111.8, 57.5, 29.7, 23.3. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{16}H_{18}N_3^+$ 252.1495; Found 252.1496.

7-(4-Chlorobenzyl)-3-isopropyl-7H-pyrazolo[3,4-b]pyridine (14b) Yellow solid, EA/MeOH (10/1), 86% (61 mg). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.62 (d, *J* = 7.6 Hz, 1H), 8.35 (d, *J* = 6.0 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.08 (t, *J* = 6.8 Hz, 1H), 5.83 (s, 2H), 3.49 - 3.42 (m, 1H), 1.43 (d, *J* = 7.2 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 156.2, 151.5, 139.3, 138.9, 135.8, 135.1, 131.2, 130.2, 122.5, 111.8, 56.8, 29.7, 23.3. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{16}H_{17}ClN_3^+$ 286.1106; Found 286.1109.

4-((3-Isopropyl-7H-pyrazolo[3,4-b]pyridin-7-yl)methyl)benzonitrile (14c) Yellow solid, EA/MeOH (10/1), 88% (61 mg). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.70 (d, *J* = 7.6 Hz, 1H), 8.45 (d, *J* = 5.6 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.15 (dd, *J* = 6.0, 7.2 Hz, 1H), 5.95 (s, 2H), 3.52 - 3.45 (m, 1H), 1.44 (d, *J* = 7.2 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 156.3, 151.4, 141.7, 139.9, 139.5, 134.0, 130.1, 122.6, 119.4, 113.6, 112.04, 57.1, 29.6, 23.2. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{17}N_4^+$ 277.1448; Found 277.1449.

3-Isopropyl-7-(4-methylbenzyl)-7H-pyrazolo[3,4-b]pyridine (14d) Yellow solid, EA/MeOH (10/1), 91% (60 mg). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.59 (d, *J* = 7.2 Hz, 1H), 8.27 (d, *J* = 6.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 7.04 (t, *J* = 6.8 Hz, 1H), 5.78 (s, 2H), 3.50 - 3.43 (m, 1H), 2.24 (s, 3H), 1.43 (d, *J* = 7.2 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 156.1, 151.6, 140.2, 139.1, 138.6, 133.2, 130.8, 129.8, 122.4, 111.8, 57.2, 29.7, 23.3, 21.3. HRMS (ESI) m/z: [M+H]$^+$ Calcd for $C_{17}H_{20}N_3^+$ 266.1652; Found 266.1650.

7-(2-Chlorobenzyl)-3-isopropyl-7H-pyrazolo[3,4-b]pyridine (14e) Yellow solid, EA/MeOH (10/1), 83% (59 mg). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.68 (dd, *J* = 0.8, 7.6 Hz, 1H), 8.14 (d, *J* = 6.0 Hz, 1H), 7.50 (dd, *J* = 0.8, 8.0 Hz, 1H), 7.37 (dt, *J* = 1.6, 8.4 Hz, 1H), 7.28 (dt, *J* = 1.2, 7.6 Hz, 1H), 7.18 - 7.16 (m, 1H), 7.09 (dd, *J* = 6.4, 7.6 Hz, 1H), 5.98 (s, 2H), 3.55 - 3.45 (m, 1H), 1.46 (d, *J* = 6.8 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 156.3, 151.7, 139.2, 138.9, 135.2, 133.1, 131.8, 131.8, 131.3, 128.9, 122.5, 111.7, 55.2, 29.7, 23.3. HRMS (ESI) m/z: [M+H]$^+$ Calcd for $C_{16}H_{17}ClN_3^+$ 286.1106; Found 286.1110.

7-(2,4-Difluorobenzyl)-3-isopropyl-7H-pyrazolo[3,4-b]pyridine (14f) Yellow solid, EA/MeOH (10/1), 84% (60 mg). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.64 (d, *J* = 7.6 Hz, 1H), 8.29 (d, *J* = 6.0 Hz, 1H), 7.56 - 7.53 (m, 1H), 7.11-7.09 (m, 1H), 7.05 - 6.99 (m, 1H), 7.02 - 6.94 (m, 1H), 5.89 (s, 2H), 3.52 - 3.41 (m, 1H), 1.44 (d, *J* = 7.2 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 165.0 (dd, *J* = 248.5, 11.9 Hz), 162.8 (dd, *J* = 248.4, 11.9 Hz), 156.3, 151.5, 139.3, 139.1, 133.9, 122.6, 119.2 (dd, *J* = 14.6, 4.1 Hz), 113.0 (dd, *J* = 21.7, 3.7 Hz), 111.7, 105.4 (t, *J* = 25.6 Hz), 51.4, 29.7, 23.2. HRMS (ESI) m/z: [M+H]$^+$ Calcd for $C_{16}H_{16}F_2N_3^+$ 288.1307; Found 288.1305.

7-(1-(4-Fluorophenyl)ethyl)-3-isopropyl-7H-pyrazolo[3,4-b]pyridine (14g) Three equivalents of 1-fluoro-4-(1-iodoethyl)benzene was used and the reaction was stirred at 60 °C for 48 h. Yellow solid, EA/MeOH (10/1), 65% (46 mg). ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.65 (dd, *J* = 1.0, 7.5 Hz, 1H), 8.33 - 8.32 (m, 1H), 7.55 - 7.53 (m, 2H), 7.14 - 7.12 (m, 3H), 6.73 (q, *J* = 7.0 Hz, 1H), 3.55 - 3.46 (m, 1H), 2.05 (d, *J* = 7.0 Hz, 3H), 1.47 (d, *J* = 7.0 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 164.4 (d, *J* = 245.5 Hz), 156.0, 151.4, 138.8, 138.7, 136.6, 136.0 (d, *J* = 2.9 Hz), 130.9 (t, *J* = 7.8 Hz), 122.2, 117.1 (d, *J* = 22.4 Hz), 117.0 (d, *J* = 21.6 Hz), 112.3 (d, *J* = 6.0 Hz), 61.1, 29.6, 23.2, 20.1. HRMS (ESI) m/z: [M+H]$^+$ Calcd for $C_{17}H_{19}FN_3$ 284.1558; Found 284.1559.

7-(4-Fluorophenethyl)-3-isopropyl-7H-pyrazolo[3,4-b]pyridine (14h) Six equivalents of 1-(2-bromoethyl)-4-fluorobenzene was used and the reaction was stirred at 80 °C for 72 h. Yellow solid, EA/MeOH (10/1), 71% (50 mg). ^{1}H NMR (500 MHz, MeOH-d_4) δ 8.62 (d, *J* = 7.5 Hz, 1H), 7.99 (d, *J* = 6.0 Hz, 1H), 7.13 - 7.10 (m, 2H), 6.98 - 6.94 (m, 3H), 4.89 (t, *J* = 7.5 Hz, 2H), 3.54 - 3.48 (m, 1H), 3.36 - 3.28 (m, 2H), 1.48 (d, *J* = 7.0 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 163.4 (d, *J* = 242.5 Hz), 156.0, 151.0, 139.7, 138.7, 134.4 (d, *J* = 3.7 Hz), 131.9 (d, *J* = 7.4 Hz), 122.1, 116.5 (d, *J* = 21.5 Hz), 111.2, 59.8, 35.1, 29.7, 29.6, 23.3. HRMS (ESI) m/z: [M+H]$^+$ Calcd for $C_{17}H_{19}FN_3^+$ 284.1558; Found 284.1558.

7-Allyl-3-isopropyl-7H-pyrazolo[3,4-b]pyridine (14i) Yellow solid, EA/MeOH (10/1), 94% (47 mg). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.67 (d, *J* = 7.6 Hz, 1H), 8.33 (d, *J* = 6.4 Hz, 1H), 7.13 (dd, *J* = 6.4, 7.6 Hz, 1H), 6.24 - 6.17 (m, 1H), 5.38 - 5.29 (m, 4H), 3.55 - 3.42 (m, 1H), 1.47 (d, *J* = 6.8 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 156.0, 151.3, 139.3, 138.8, 132.3, 122.2, 121.0, 111.8 (d, *J* = 9.7 Hz), 56.6, 29.7, 29.6, 23.3. HRMS (ESI) m/z: [M+H]$^+$ Calcd for $C_{12}H_{16}N_3^+$ 202.1339; Found 202.1337.

Ethyl 2-(3-isopropyl-7H-pyrazolo[3,4-b]pyridin-7-yl)acetate (14j) Yellow solid, EA/MeOH (10/1), 81% (50 mg). ^{1}H NMR (500 MHz, CHLOROFORM-d) δ 8.34 (d, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 6.0 Hz, 1H), 6.86 (dd, *J* = 6.5, 7.5 Hz, 1H), 5.44 (s, 2H), 4.22 (q, *J* = 7.0 Hz, 2H), 3.51 - 3.44 (m, 1H), 1.45 (d, *J* = 7.0 Hz, 6H), 1.26 (t, *J* = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, MeOH-d_4) δ 166.5, 155.6, 150.3, 136.2, 136.0, 122.3, 108.4, 62.5, 52.7, 28.6, 22.7, 14.0. HRMS (ESI) m/z: [M+H]$^+$ Calcd for $C_{13}H_{18}N_3O_2^+$ 248.1394; Found 248.1396.

3-Isopropyl-7-methyl-7H-pyrazolo[3,4-b]pyridine (14k) Yellow solid, EA/MeOH (10/1), 90% (39 mg). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.86 (d, *J* = 7.6 Hz, 1H), 8.58 (d, *J* = 5.6 Hz, 1H), 7.30 (dd, *J* = 6.0, 7.6 Hz, 1H), 4.37 (s, 3H), 3.63 - 3.54 (m, 1H), 1.49 (d, *J* = 7.2 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 154.5, 150.9, 143.6, 140.7, 120.5, 113.8, 41.9, 29.2, 22.9. HRMS (ESI) m/z: [M+H]$^+$ Calcd for $C_{10}H_{14}N_3^+$ 176.1182; Found 176.1182.

7-Ethyl-3-isopropyl-7H-pyrazolo[3,4-b]pyridine (14l) Yellow solid, EA/MeOH (10/1), 81% (38 mg). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.64 (d, *J* = 8.0 Hz, 1H), 8.38 (d, *J* = 6.4 Hz, 1H), 7.11 (dd, *J* = 6.0, 7.2 Hz, 1H), 4.73 (q, *J* = 7.2 Hz, 2H), 3.54 - 3.45 (m, 1H), 1.62 (t, *J* = 7.2 Hz, 3H), 1.45 (d, *J* = 7.2 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 155.7, 151.0, 139.1, 138.4, 121.9, 111.8, 50.5, 29.5, 23.2, 15.2. HRMS (ESI) m/z: [M+H]$^+$ Calcd for $C_{11}H_{16}N_3^+$ 190.1339; Found 190.1337.

3,7-Diisopropyl-7H-pyrazolo[3,4-b]pyridine (14m) Ten equiv 2-iodopropane was used and the reaction was stirred at 80 °C for 96 h. Yellow solid, EA/MeOH (10/1), 79% (40 mg). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.78 (d, *J* = 7.6 Hz, 1H), 8.70 (d, *J* = 6.0 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 5.64 - 5.53 (m, 1H), 3.61 - 3.48 (m, 1H), 1.72 (d, *J* = 6.4 Hz, 6H), 1.48 (d, *J* = 7.2 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 154.7, 150.4, 139.7 (d, *J* = 7.5 Hz), 138.0 (d, *J* = 8.2 Hz), 121.1, 113.6 (d, *J* = 10.4 Hz), 56.7, 29.3, 29.2, 23.1, 23.1, 22.2. HRMS (ESI) m/z: [M+H]$^+$ Calcd for $C_{12}H_{18}N_3^+$ 204.1495; Found 204.1495.

3-Isopropyl-7-(2,2,2-trifluoroethyl)-7H-pyrazolo[3,4-b]pyridine (14n) Yellow solid, EA/MeOH (10/1), 75% (46 mg). ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.75 (d, *J* = 7.6 Hz, 1H), 8.36 (d, *J* = 6.4 Hz, 1H), 7.16 (dd, *J* = 6.4, 7.6 Hz, 1H), 5.52 (q, *J* = 8.8 Hz, 2H), 3.52 - 3.45 (m, 1H), 1.46 (d, *J* = 7.2 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, MeOH-d_4) δ 157.0, 151.7, 140.5, 140.2, 125.0 (q, *J* = 278.2 Hz), 123.3, 111.6, 53.3 (q, *J* = 35.0 Hz), 29.7, 23.2. HRMS (ESI) m/z: [M+H]$^+$ Calcd for $C_{11}H_{13}F_3N_3^+$ 244.1056; Found 244.1060.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

NMR spectra for all products (PDF)

AUTHOR INFORMATION

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