Synthesis K. Umei et al. Paper

Synthesis of 2-Arylpyrazolo[1,5-*a*]pyridines by Suzuki–Miyaura Cross-Coupling Reaction

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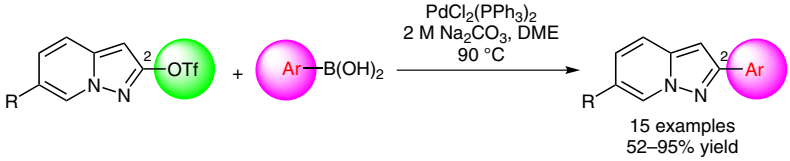

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Abstract Convenient access to a variety of 2-arylated pyrazolo[1,5-*a*]pyridine via pyrazolo[1,5-*a*]pyridine-2-yl triflate using the Suzuki–Miyaura cross-coupling reaction is described. Fifteen 2-arylpyrazolo[1,5-*a*]pyridine derivatives were synthesized in 52–95% yields.

Key words Suzuki–Miyaura cross-coupling reaction, 2-arylpyrazolo[1,5-*a*]pyridine, triflate, regioselectivity, medicinal chemistry

The 2-arylpyrazolo[1,5-*a*]pyridine moiety is an important pharmacophore in medicinal chemistry with respect to drug discovery. For instance, several biologically active compounds contain this moiety, such as poly(ADP-ribose)polymerase (PARP) inhibitor,[1] RNA polymerase inhibitor,[2] AKT inhibitor,[3] adenosine A_1 antagonist,[4] and EP_1 antagonist (Figure 1).[5]

As part of our drug discovery program on EP_1 antagonists for the treatment of overactive bladder syndrome,[5,6] we searched for a rapid and efficient synthetic access to a variety of 2-arylated pyrazolo[1,5-*a*]pyridines, especially 6-substituted 2-arylpyrazolo[1,5-*a*]pyridines such as those with the structure **1** (Figure 1). Several synthetic approaches to the 2-arylpyrazolo[1,5-*a*]pyridine scaffold have been reported. Predominant among these, particularly for 3-substituted 2-arylpyrazolo[1,5-*a*]pyridines, is the construction of the pyrazolopyridine ring via 1,3-dipolar cycloaddition of a 1-aminopyridinium salt with an arylpropynoate (Scheme 1,A).[1,7] However, these reactions typically afforded a regioisomeric mixture of 6-substituted and 4-substituted 2-arylpyrazolo[1,5-*a*]pyridines, thus necessitating a chromatographic separation step. In addition, the removal of the alkoxycarbonyl group at the 3-position on the pyrazolo[1,5-*a*]pyridine ring under acidic and thermal conditions is required for the synthesis of **1**. Other common approaches include intramolecular cycloaddition methods using any of several intermediates, such as phenacylpyridines[8] or ethynylpyridines (Scheme 1,B).[9] Along these lines, Charette and co-workers recently reported an alkenylation/cyclization reaction between *N*-iminopyridinium ylides and alkenyl iodides.[8c] However, these approaches usually require multiple steps for the introduction of the C2 aryl moiety, including complicated steps to construct the pyrazole ring. These drawbacks in synthesis have limited the versatility of the 2-arylpyrazolo[1,5-*a*]pyridine scaffold, especially 6-substituted ones such as **1**, and also limited their medicinal potential.

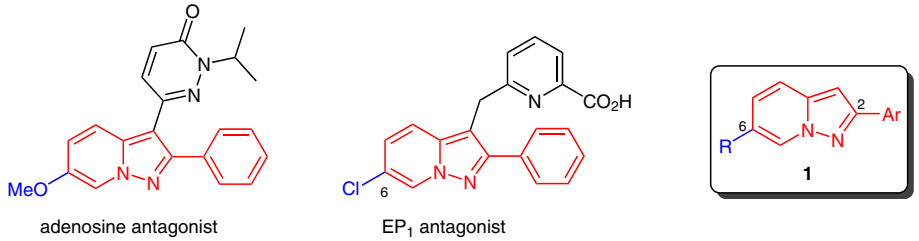
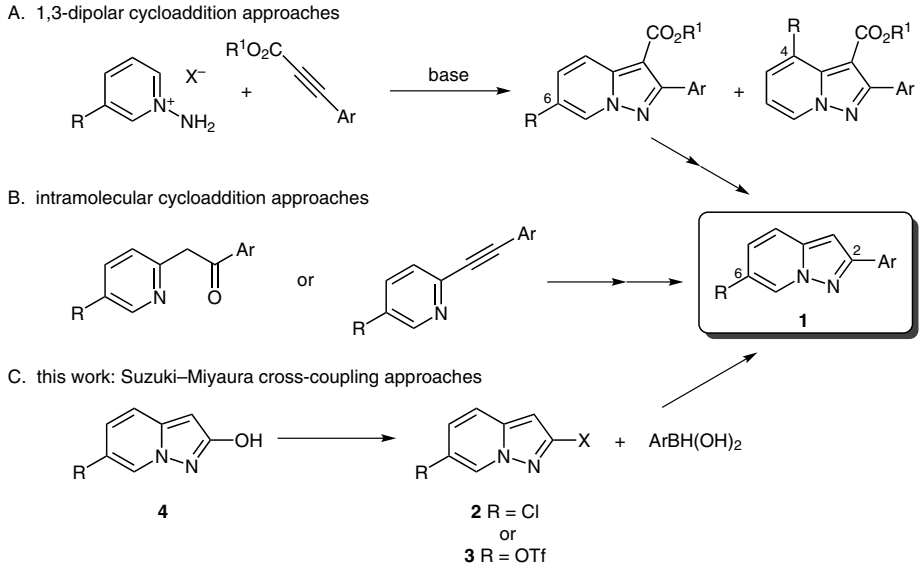


Figure 1 Structures of bioactive molecules and 6-substituted 2-arylpyrazolo[1,5-*a*]pyridine **1**

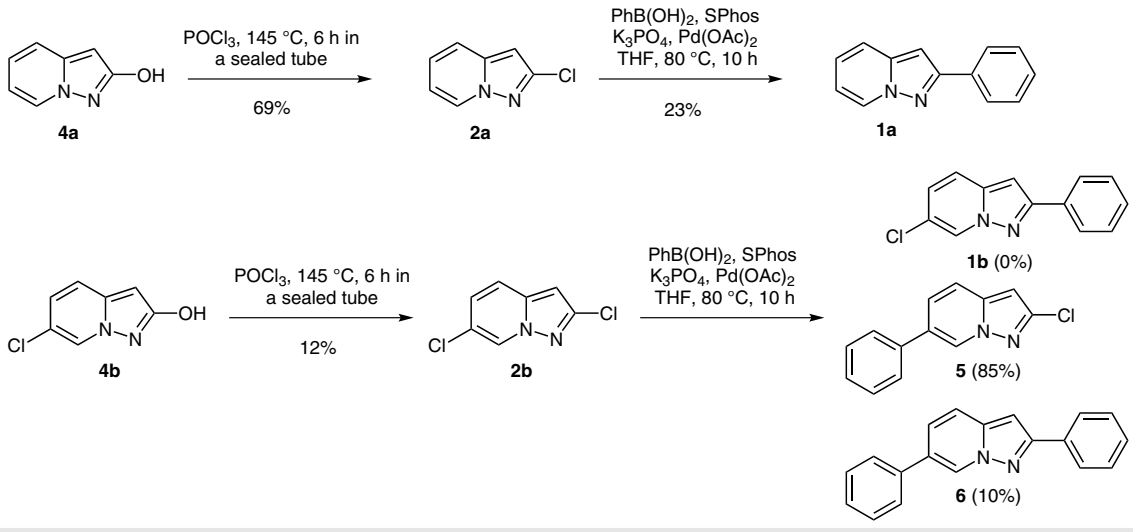


Scheme 1 Synthetic strategies for **1**

In this context, we were interested in developing a rapid and efficient method for the synthesis of 6-substituted 2-arylpyrazolo[1,5-*a*]pyridines **1** to install diverse aryl groups at the C2 position on the pyrazolo[1,5-*a*]pyridine core by using the Suzuki–Miyaura cross-coupling reaction[10] (Scheme 1,C). To the best of our knowledge, only one example of the Suzuki–Miyaura cross-coupling reaction between ethyl 2-(trifluoromethylsulfonyloxy)pyrazolo[1,5-*a*]quinoline-3-carboxylate and phenylboronic acid has been reported, but without a description of the substrate generality of this transformation.[11] However, the reaction afforded the coupling product in a low yield of 46%, which contained an unwanted carboxylate group at C3 that must be remove in two steps for the synthesis of **1**. Thus, a need remains for the development of a new facile procedure for the construction of **1** by the Suzuki–Miyaura cross-coupling reaction.

Herein, we report the synthesis of **1** by the Suzuki–Miyaura cross-coupling reaction under mild conditions in good to moderate yields. The reaction begins with either 2-chloride **2** or 2-triflate **3**, which could be accessed from 2-hydroxide **4**[12] (Scheme 1,C).

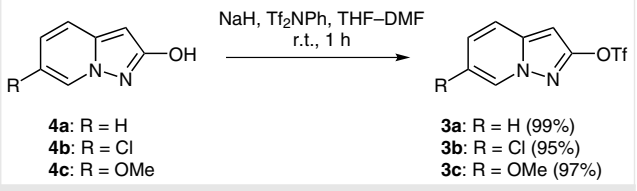
First, the reaction of 2-chloropyrazolo[1,5-*a*]pyridine (**2a**) with phenylboronic acid was chosen as a model reaction to confirm the feasibility of our concept, since the synthesis of **2a** from the hydroxide **4a** has already been reported[13] (Scheme 2). When we carried out the Suzuki–Miyaura



Scheme 2 Suzuki coupling reaction of 2-chloropyrazolo[1,5-*a*]pyridines

coupling reaction of **2a** and phenylboronic acid in the presence of palladium(II) acetate (20 mmol%), 2-(dicyclohexylphosphino)-2′,6′-dimethoxybiphenyl (SPhos, 20 mmol%), and tripotassium phosphate (3 equiv) in tetrahydrofuran at 80 °C, the expected coupling product **1a** was only obtained in 23% yield, although the reaction did not proceed at all under the standard Suzuki–Miyaura coupling reaction conditions, which include the presence of dichlorobis(triphenylphosphine)palladium(II) (10 mmol%) and sodium carbonate (3 equiv) in 1,2-dimethoxyethane–water at 90 °C. This result prompted us to synthesize 6-chloro-2-phenylpyrazolo[1,5-*a*]pyridine (**1b**), which was obtained from 6-chloro-2-hydroxypyrazolo[1,5-*a*]pyridine (**4b**) by the same strategy. However, the chlorination reaction of **4b** with phosphoryl chloride at 145 °C in a sealed tube provided **2b** in only 12% yield. Furthermore, the Suzuki coupling reaction between **2b** and phenylboronic acid did not provide the desired product, **1b**, but proceeded to provide undesired 2-chloro-6-phenylpyrazolo[1,5-*a*]pyridine (**5**) in 85% yield and the double-coupling product **6** in 10% yield. To improve the reactivity of the Suzuki coupling reaction, we attempted to synthesize 2-bromopyrazolo[1,5-*a*]pyridine by the treatment of **4a** with phosphoryl bromide in toluene at reflux temperature for five hours; unfortunately, only starting material was recovered.

We next studied the synthesis of triflates **3** as an alternative to chlorides **2**, since (hetero)aryl triflates are valuable substrates for a number of metal-catalyzed cross-coupling reactions[10] (Scheme 3). Triflation of the alcohol **4a** with *N*-phenyltrifluoromethanesulfonimide[14] provided the corresponding triflate **3a** in quantitative yield. Fortunately, this reaction was compatible with electron-withdrawing and electron-donating substituents such as chloro and methoxy at C6, and afforded the desired products **3b** and **3c** in good yields.



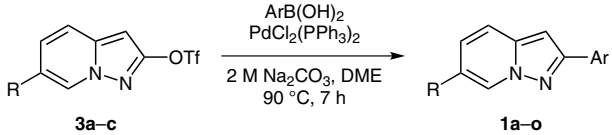
4a: R = H
4b: R = Cl
4c: R = OMe

3a: R = H (99%)
3b: R = Cl (95%)
3c: R = OMe (97%)

Scheme 3 Preparation of triflates **3a**–**c**

Having a facile route to triflates **3** in hand, we next directed our attention to the palladium-catalyzed Suzuki–Miyaura cross-coupling reactions of triflates **3a**–**c** with a variety of arylboronic acids (Table 1). Fortunately, the reaction proceeded very well under the standard Suzuki–Miyaura coupling reaction conditions; that is, the reaction of **3a** with phenylboronic acid (1.5 equiv) in the presence of dichlorobis(triphenylphosphine)palladium(II) (10 mol%) and sodium carbonate (3 equiv) in 1,2-dimethoxyethane at 90 °C afforded the desired coupled product **1a** in 93% yield (entry 1). Both electron-withdrawing and electron-donating groups on the triflate part at C6 position, **3b** and **3c**, respectively, are tolerated in this reaction (entries 2 and 3). To our delight, the reaction of **3b** provided the desired 6-chloro-2-phenylpyrazolo[1,5-*a*]pyridine (**1b**) in 90% yield in a regioselective manner without producing the undesired 6-phenyl coupling product. We next investigated the reactions with a variety of arylboronic acids and found that the reactions provided the corresponding coupled products in good to moderate yields (entries 4–15). Sterically hindered arylboronic acids with *ortho* substituents (Cl, CF_3, OMe) do not limit this reaction (entries 5, 9, and 11). Notably, heteroarylboronic acids are also good substrates for this reaction (entries 12–15).

Table 1 Suzuki Coupling Reactions of Triflates



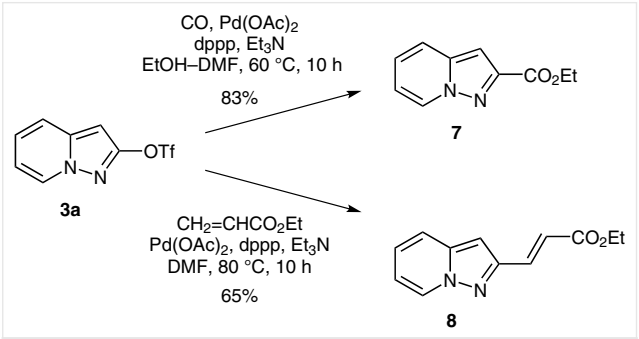
3a–c **1a–o**

Entry	Substrate	R	Ar	Product	Yield (%)
1	**3a**	H	Ph	**1a**	93
2	**3b**	Cl	Ph	**1b**	90
3	**3c**	OMe	Ph	**1c**	92
4	**3a**	H	4-ClC_6H_4	**1d**	88
5	**3a**	H	2-ClC_6H_4	**1e**	87
6	**3b**	Cl	4-FC_6H_4	**1f**	90
7	**3b**	Cl	2-FC_6H_4	**1g**	89
8	**3b**	Cl	4-$F_3CC_6H_4$	**1h**	95
9	**3b**	Cl	2-$F_3CC_6H_4$	**1i**	83
10	**3b**	Cl	4-$MeOC_6H_4$	**1j**	93
11	**3b**	Cl	2-$MeOC_6H_4$	**1k**	92
12	**3b**	Cl	2-furyl	**1l**	80[a]
13	**3b**	Cl	3-furyl	**1m**	52[a]
14	**3b**	Cl	2-thienyl	**1n**	54[a]
15	**3b**	Cl	3-thienyl	**1o**	55[a]

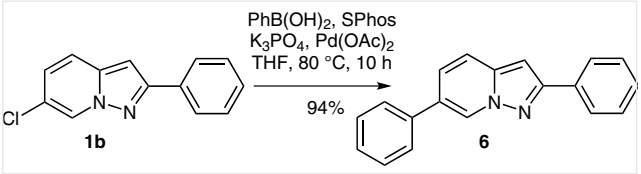
[a] 80 °C, 1 h.

Accomplishing the synthesis of our target, 2-arylpyrazolo[1,5-*a*]pyridines **1**, by the Suzuki–Miyaura cross-coupling reaction prompted us to attempt other palladium coupling reactions. Hence we attempted the reaction of triflate **3a** with carbon monoxide in the presence of palladium(II) acetate (10 mol%), 1,3-bis(diphenylphosphino)propane (dppp) (10 mol%), and triethylamine (3 equiv) in ethanol–*N*,*N*-dimethylformamide at 60 °C, and afforded the desired coupled product **7** in 83% yield (Scheme 4). Additionally, the reaction of **3a** with ethyl acrylate in the presence of palladi-

um(II) acetate (10 mol%) and triethylamine (3 equiv) in *N*,*N*-dimethylformamide at 80 °C provided the desired coupling product **8** in 65% yield.



Scheme 4 Palladium-catalyzed cross-coupling reactions



Scheme 5 Arylation of C6

With the regioselective C2 Suzuki–Miyaura cross-coupling conditions to **1b** obtained (Table 1, entry 2), we next examined the introduction of a phenyl group at the C6 position of **1b** by the Suzuki–Miyaura cross-coupling reaction. Although the double-coupling product **6** can be synthesized from **2b** or **3b** in one pot, stepwise introduction of aryl groups at C2 and C6 positions could be more useful method for the generation of structurally diverse compounds. This reaction afforded desired coupling product **6** in 94% yield by the reaction of **1b** with phenylboronic acid in the presence of palladium(II) acetate (20 mmol%), SPhos (20 mmol%), and tripotassium phosphate (3 equiv), in tetrahydrofuran at 80 °C (Scheme 5).

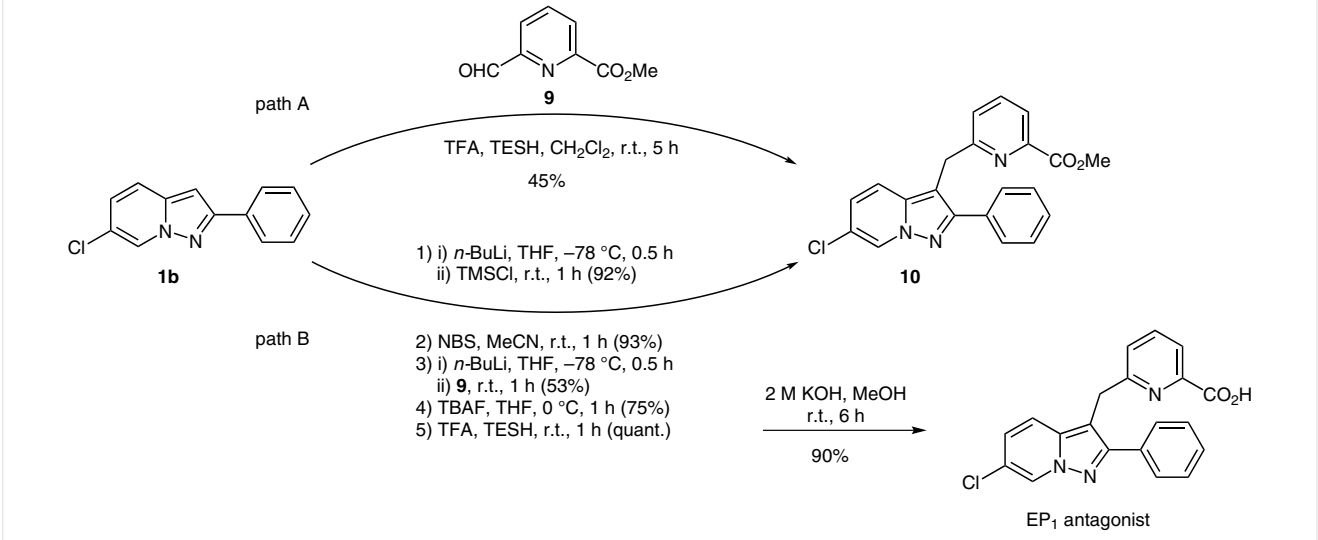
Finally, we examined the synthesis of the EP_1 antagonist as an example of further transformations of 6-substituted 2-arylpyrazolo[1,5-*a*]pyridines **1** (Scheme 6). One- (path A) or five-step (path B) C3-alkylation of **1b** to **10**, followed by hydrolysis afforded the desired EP_1 antagonist.

In summary, we have accomplished a concise and versatile approach to the synthesis of 2-arylpyrazolo[1,5-*a*]pyridines **1** using the Suzuki–Miyaura cross-coupling reaction between the triflates **3** and arylboronic acids. This new method allows new substitution patterns on the C2 aryl unit and can be applied to diversity-oriented synthesis in drug discovery programs.

Melting points were determined with a OptiMelt and are uncorrected. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ or DMSO-d_6 with TMS and the solvent peak as internal standards, on a Jeol ECA-400 (400 MHz) spectrometer. Mass spectra (MS) were obtained on a Hitachi M-2000 mass spectrometer. Column chromatography was carried out on Merck silica gel 60. Analytical TLC was performed on Merck precoated silica gel $60F_{254}$ plates, and the compounds were visualized by UV illumination (254 nm) or by heating after spraying with phosphomolybdic acid in EtOH.

2,6-Dichloropyrazolo[1,5-*a*]pyridine (2b)

A solution of 6-chloropyrazolo[1,5-*a*]pyridin-2-ol (**4a**, 169 mg, 1.00 mmol) in $POCl_3$ (4 mL) was heated at 145 °C for 6 h in a sealed tube. The mixture was cooled to r.t., then it was poured into ice-water and stirred at r.t. for 1 h. The mixture was extracted with CH_2Cl_2 and the organic layer was dried (Na_2SO_4), and then concentrated in vacuo. The crude material was purified by flash column chromatography (silica gel, hexane–EtOAc, 20:1) to give **2b** as a colorless solid; yield: 22.9 mg (12%); mp 72.0–75.0 °C.



Scheme 6 Synthesis of the EP_1 antagonist

IR (ATR): 3144, 3078, 1901, 1744, 1633, 1572, 1527, 1510, 1438, 1365, 1315, 1247, 1110, 1072 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.47 (s, 1 H), 7.14 (dd, *J* = 9.7, 1.8 Hz, 1 H), 7.39 (d, *J* = 9.7 Hz, 1 H), 8.40 (d, *J* = 1.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 96.6, 117.4, 120.3, 126.2, 126.5, 139.8, 144.1.

LRMS (FI): *m*/*z* = 185 $[M]^+$.

HRMS (FI): *m*/*z* $[M]^+$ calcd for $C_7H_4Cl_2N_2$: 185.97515; found: 185.97558.

2-Chloro-6-phenylpyrazolo[1,5-*a*]pyridine (5) and 2,6-Diphenylpyrazolo[1,5-*a*]pyridine (6)

To a solution of 2,6-dichloropyrazolo[1,5-*a*]pyridine (**2b**, 16.8 mg, 89.8 µmol) in THF (1 mL) was added phenylboronic acid (24.0 mg, 0.197 mmol), $Pd(OAc)_2$ (4.1 mg, 18 µmol), SPhos (7.5 mg, 18 µmol), and K_3PO_4 (57.2 mg, 0.269 mmol) at r.t. The mixture was stirred under argon at 80 °C for 10 h. The mixture was cooled to r.t., and then passed through a Celite pad and concentrated in vacuo. The crude material was purified by flash column chromatography (silica gel, hexane–EtOAc, 10:1) to give 2-chloro-6-phenylpyrazolo[1,5-*a*]pyridine (**5**) (17.5 mg, 85%) and 2,6-diphenylpyrazolo[1,5-*a*]pyridine (**6**) (2.5 mg, 10%).

2-Chloro-6-phenylpyrazolo[1,5-*a*]pyridine (5)

Colorless solid; mp 56.0–58.0 °C.

IR (ATR): 3142, 3060, 3032, 2924, 1638, 1538, 1519, 1489, 1454, 1428, 1400, 1365, 1321, 1255, 1104 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.45 (s, 1 H), 7.36–7.59 (m, 7 H), 8.55 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 95.6, 117.0, 125.1, 125.6, 126.5, 126.8, 128.1, 129.2, 136.8, 140.4, 143.8.

LRMS (ESI): *m*/*z* = 229 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{10}ClN_2$: 229.05325; found: 229.05360.

2,6-Diphenylpyrazolo[1,5-*a*]pyridine (6)

Colorless solid; mp 134–137 °C.

IR (ATR): 3056, 2924, 1635, 1598, 1545, 1462, 1442, 1387, 1319, 1246, 1108, 1079, 1027 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.83 (s, 1 H), 7.35–7.43 (m, 3 H), 7.43–7.53 (m, 4 H), 7.53–7.65 (m, 3 H), 7.98 (d, *J* = 8.5 Hz, 2 H), 8.72 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 93.7, 117.8, 124.1, 125.9, 126.2, 126.5, 126.7, 127.8, 128.5, 128.8, 129.2, 133.1, 137.3, 140.6, 154.0.

LRMS (ESI): *m*/*z* = 271 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{15}N_2$: 271.12352; found: 271.12395.

6-Chloro-2-hydroxypyrazolo[1,5-*a*]pyridine (4b); Typical Procedure

A mixture of 2-amino-6-chloropyrazolo[1,5-*a*]pyridine (250 mg, 1.49 mmol) and 50% aq H_2SO_4 (7.5 mL) was stirred at 100 °C for 2 h. The mixture was cooled to r.t., then it was poured into sat. aq $NaHCO_3$ to adjust to pH 11. The mixture was extracted with EtOAc and the combined extracts were dried (Na_2SO_4). The mixture was concentrated in vacuo to give **4b** as a yellow solid; yield: 196 mg (78%); mp 193–198 °C.

IR (ATR): 2984, 2659, 1639, 1544, 1519, 1368, 1303, 1247, 1150, 1068, 1032 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 7.13 (dd, *J* = 9.1, 1.8 Hz, 1 H), 7.40 (d, *J* = 9.1 Hz, 1 H), 8.65 (d, *J* = 1.8 Hz, 1 H), 10.62 (br s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 81.0, 115.8, 116.5, 124.6, 126.3, 139.5, 164.4.

LRMS (EI): *m*/*z* = 168 $[M]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_7H_5ClN_2O$: 168.00904; found: 168.00930.

6-Methoxy-2-hydroxypyrazolo[1,5-*a*]pyridine (4c)

Following the typical procedure for **4b** using 2-amino-6-methoxypyrazolo[1,5-*a*]pyridine (300 mg, 1.84 mmol) and 50% aq H_2SO_4 (10 mL) gave **4c** as a pale yellow solid; yield: 190 mg (63%); mp 166–168 °C.

IR (ATR): 1524, 1355, 1312, 1289, 1234, 1161, 1037, 1020 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.74 (s, 3 H), 5.64 (s, 1 H), 6.90 (td, *J* = 7.9, 2.4 Hz, 1 H), 7.28 (d, *J* = 9.7 Hz, 1 H), 8.05 (d, *J* = 2.4 Hz, 1 H), 10.15 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 56.1, 79.2, 111.5, 115.9, 118.2, 137.1, 146.9, 163.1.

LRMS (EI): *m*/*z* = 164 $[M]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_8H_8N_2O_2$: 164.05858; found: 164.05925.

Pyrazolo[1,5-*a*]pyridin-2-yl Trifluoromethanesulfonate (3a); Typical Procedure

To a solution of **4a** (3.10 g, 23.1 mmol) in THF (17 mL) and DMF (17 mL) was added NaH (1.0 g, 25.4 mmol, 60% dispersion in oil) and Tf_2NPh (9.90 g, 27.7 mmol) at 0 °C. The mixture was stirred for 1 h, then it was added to ice-water and extracted with EtOAc. The organic layer was washed with brine and dried (Na_2SO_4). The mixture was concentrated in vacuo. The crude material was purified by flash column chromatography (silica gel, hexane–EtOAc, 10:1) to give **3a** as a colorless solid; yield: 6.10 g, 99%); mp 37–38 °C.

IR (ATR): 1639, 1520, 1481, 1428, 1340, 1243, 1208, 1127, 1026.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.37 (s, 1 H), 6.89 (td, *J* = 7.3, 1.2 Hz, 1 H), 7.22–7.25 (m, 1 H), 7.51 (d, *J* = 8.5 Hz, 1 H), 8.37 (dt, *J* = 7.3, 1.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 86.6, 113.2, 118.2, 118.7 (d, *J* = 321.4 Hz), 125.2, 128.8, 141.3, 154.6.

LRMS (FI): *m*/*z* = 266 $[M]^+$.

HRMS (FI): *m*/*z* $[M]^+$ calcd for $C_8H_5F_3N_2O_3S$: 265.99730; found: 265.99738.

6-Chloropyrazolo[1,5-*a*]pyridin-2-yl Trifluoromethanesulfonate (3b)

Following the typical procedure for **3a** using **4b** (1.59 g, 9.43 mmol) in THF (10 mL) and DMF (10 mL), NaH (414 mg, 10.4 mmol, 60% dispersion in oil), and Tf_2NPh (3.89 g, 10.4 mmol) gave **3b** as a pale yellow oil; yield: 2.68 g (95%).

IR (ATR): 1640, 1520, 1464, 1426, 1392, 1338, 1206, 1128, 1018 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.42 (s, 1 H), 7.24 (dd, *J* = 9.7, 1.8 Hz, 1 H), 7.47 (d, *J* = 9.7 Hz, 1 H), 8.43 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 87.6, 118.4, 118.7 (d, *J* = 321.4 Hz), 121.5, 127.0, 129.6, 139.6, 154.8.

LRMS (EI): *m*/*z* = 300 $[M + H]^+$.

HRMS (EI): m/z [M]$^+$ calcd for $C_8H_4ClF_3N_2O_3S$: 299.95832; found: 299.95784.

6-Methoxypyrazolo[1,5-*a*]pyridin-2-yl Trifluoromethanesulfonate (3c)

Following the typical procedure for **3a** using **4c** (175 mg, 1.07 mmol) in THF (0.8 mL) and DMF (0.8 mL), NaH (52 mg, 1.3 mmol, 60% dispersion in oil), and Tf_2NPh (460 mg, 1.29 mmol) gave **3c** as a pale yellow oil; yield: 308 mg (97%).

IR (ATR): 1533, 1475, 1424, 1291, 1201, 1134, 1018 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.83 (s, 3 H), 6.31 (s, 1 H), 7.05 (dd, J = 9.7, 2.4 Hz, 1 H), 7.38 (d, J = 9.7 Hz, 1 H), 7.95 (d, J = 2.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.1, 86.5, 111.2, 118.0, 118.8 (d, J = 322.4 Hz), 120.8, 137.3, 149.9, 153.5.

LRMS (ESI): m/z = 297 [M + H]$^+$.

HRMS (ESI): m/z [M + H]$^+$ calcd for $C_9H_8F_3N_2O_4S$: 297.01569; found: 297.01604.

2-Phenylpyrazolo[1,5-*a*]pyridine (1a); Typical Procedure

To a solution of **3a** (50.0 mg, 0.188 mmol) in DME (1 mL) was added phenylboronic acid (35.0 mg, 0.287 mmol), 2 M aq Na_2CO_3 (0.3 mL, 0.6 mmol), and $PdCl_2(PPh_3)_2$ (14.0 mg, 19.9 μmol) at r.t. The mixture was stirred at 90 °C for 4 h, then it was cooled to r.t., diluted with EtOAc, and washed with water and brine. The organic layer was dried (Na_2SO_4), and then concentrated in vacuo. The crude material was purified by flash column chromatography (silica gel, hexane–EtOAc, 10:1) to give **1a** as a colorless solid; yield: 34.0 mg (93%); mp 99–104 °C.

IR (ATR): 3123, 3076, 3034, 1891, 1767, 1634, 1514, 1471, 1456, 1421, 1333, 1257, 1191, 1146, 1082, 1011, 947, 910, 838, 782, 759, 736, 683, 564, 506, 430 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.72 (td, J = 7.3, 1.2 Hz, 1 H), 6.79 (s, 1 H), 7.05–7.11 (m, 1 H), 7.18–7.21 (m, 2 H), 7.34–7.39 (m, 1 H), 7.44–7.49 (m, 1 H), 7.97 (d, J = 7.3 Hz, 2 H), 8.47 (d, J = 7.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 93.7, 111.7, 117.9, 123.4, 126.5, 128.4, 128.5, 128.7, 133.2, 141.6, 153.5.

LRMS (EI): m/z = 194 [M]$^+$.

HRMS (EI): m/z [M]$^+$ calcd for $C_{13}H_{10}N_2$: 194.0844; found: 194.0883.

6-Chloro-2-phenylpyrazolo[1,5-*a*]pyridine (1b)

Following the typical procedure for **1a** using **3b** (50.0 mg, 0.166 mmol) in DME (1 mL), phenylboronic acid (30.5 mg, 0.250 mmol), 2 M aq Na_2CO_3 (0.25 mL, 0.5 mmol), and $PdCl_2(PPh_3)_2$ (11.7 mg, 16.7 μmol) gave **1b** as a yellow solid; yield: 34.0 mg (90%); mp 117–120 °C. ^{1}H NMR spectroscopic data are identical to those reported in the literature.[8c]

IR (ATR): 3068, 2557, 2164, 1947, 1898, 1756, 1697, 1634, 1534, 1506, 1461, 1379, 1309, 1194, 1131, 1060, 949, 854, 806, 755, 682, 576, 505, 423 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.82 (s, 1 H), 7.08 (dd, J = 9.1, 1.8 Hz, 1 H), 7.38 (t, J = 7.3 Hz, 1 H), 7.46 (t, J = 7.3 Hz, 3 H), 7.94 (d, J = 7.3 Hz, 2 H), 8.52 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 94.5, 118.1, 119.7, 125.0, 126.5, 126.6, 128.6, 128.8, 132.8, 140.0, 154.2.

LRMS (EI): m/z = 228 [M]$^+$.

HRMS (EI): m/z [M]$^+$ calcd for $C_{13}H_9ClN_2$: 228.0454; found: 228.0461.

6-Methoxy-2-phenylpyrazolo[1,5-*a*]pyridine (1c)

Following the typical procedure for **1a** using **3c** (50.0 mg, 0.169 mmol) in DME (0.8 mL), phenylboronic acid (30.5 mg, 0.250 mmol), 2 M aq Na_2CO_3 (0.25 mL, 0.5 mmol), and $PdCl_2(PPh_3)_2$ (11.7 mg, 16.7 μmol) gave **1c** as a pale red solid; yield: 35.0 mg (92%); mp 84–85 °C.

IR (ATR): 3048, 2929, 2837, 1713, 1645, 1517, 1466, 1379, 1323, 1280, 1198, 1157, 1128, 1025, 941, 852, 818, 756, 694, 603, 508, 421 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (s, 3 H), 6.74 (s, 1 H), 6.92 (dd, J = 9.7, 1.8 Hz, 1 H), 7.34 (tt, J = 7.3, 1.8 Hz, 1 H), 7.40 (d, J = 9.7 Hz, 1 H), 7.44 (t, J = 7.3 Hz, 2 H), 7.91–7.94 (m, 2 H), 8.09 (d, J = 1.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 56.0, 93.6, 110.9, 117.8, 118.9, 126.1, 128.1, 128.7, 133.4, 137.9, 149.2, 152.7.

LRMS (EI): m/z = 224 [M]$^+$.

HRMS (EI): m/z [M]$^+$ calcd for $C_{14}H_{12}N_2O$: 224.0950; found: 224.0933.

2-(4-Chlorophenyl)pyrazolo[1,5-*a*]pyridine (1d)

Following the typical procedure for **1a** using **3a** (50.0 mg, 0.188 mmol) in DME (1 mL), 4-chlorophenylboronic acid (44.9 mg, 0.287 mmol), 2 M aq Na_2CO_3 (0.3 mL, 0.6 mmol), and $PdCl_2(PPh_3)_2$ (14.0 mg, 19.9 μmol) gave **1d** as a colorless solid; yield: 37.9 mg (88%); mp 103–105 °C. ^{1}H NMR spectroscopic data are identical to those reported in the literature.[15]

IR (ATR): 3073, 3032, 2160, 1899, 1776, 1634, 1599, 1508, 1423, 1333, 1255, 1185, 1089, 1012, 946, 833, 772, 727, 636, 599, 509, 470 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.74 (d, J = 6.7 Hz, 1 H), 6.76 (s, 1 H), 7.10 (t, J = 8.5 Hz, 1 H), 7.42 (d, J = 8.5 Hz, 2 H), 7.51 (d, J = 8.5 Hz, 1 H), 7.90 (d, J = 8.5 Hz, 2 H), 8.46 (d, J = 6.7 Hz, 1 H).

LRMS (EI): m/z = 228 [M]$^+$.

HRMS (EI): m/z [M]$^+$ calcd for $C_{13}H_9ClN_2$: 228.0454; found: 228.0453.

2-(2-Chlorophenyl)pyrazolo[1,5-*a*]pyridine (1e)

Following the typical procedure for **1a** using **3a** (500 mg, 1.88 mmol) in DME (6.3 mL), 2-chlorophenylboronic acid (441 mg, 2.82 mmol), 2 M aq Na_2CO_3 (2.8 mL, 5.63 mmol), and $PdCl_2(PPh_3)_2$ (132 mg, 0.19 mmol) gave **1e** as a yellow oil; yield: 371 mg (87%). ^{1}H NMR spectroscopic data are identical to those reported in the literature.[8c,16]

IR (ATR): 2958, 1713, 1636, 1519, 1460, 1413, 1331, 1249, 1163, 1048, 949, 850, 758, 731, 653, 564, 516, 463 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.77 (td, J = 6.7, 1.2 Hz, 1 H), 7.03 (s, 1 H), 7.10–7.14 (m, 1 H), 7.28–7.39 (m, 2 H), 7.50 (dd, J = 7.9, 1.2 Hz, 1 H), 7.56 (d, J = 9.1 Hz, 1 H), 7.91 (dd, J = 7.9, 1.8 Hz, 1 H), 8.49 (d, J = 6.7 Hz, 1 H).

LRMS (EI): m/z = 228 [M]$^+$.

HRMS (EI): m/z [M]$^+$ calcd for $C_{13}H_9ClN_2$: 228.0454; found: 228.0440.

6-Chloro-2-(4-fluorophenyl)pyrazolo[1,5-*a*]pyridine (1f)

Following the typical procedure for **1a** using **3b** (50.0 mg, 0.166 mmol) in DME (1 mL), 4-fluorophenylboronic acid (35.0 mg, 0.250 mmol), 2 M aq Na_2CO_3 (0.25 mL, 0.5 mmol), and $PdCl_2(PPh_3)_2$ (11.7 mg, 16.7 μmol) gave **1f** as a colorless solid; yield: 37.0 mg (90%); mp 96–102 °C.

IR (ATR): 3085, 1632, 1600, 1508, 1456, 1222, 1156, 1092, 1014, 949, 940, 803, 764, 642, 576, 518 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.76 (s, 1 H), 7.08 (dd, J = 9.4, 1.5 Hz, 1 H), 7.14 (t, J = 8.5 Hz, 2 H), 7.46 (d, J = 9.1 Hz, 1 H), 7.91 (dd, J = 8.5, 5.4 Hz, 2 H), 8.50 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 115.7 (d, *J* = 21.9 Hz), 118.0, 119.8, 125.2, 126.6, 128.2 (d, *J* = 8.6 Hz), 129.0 (d, *J* =3.8 Hz), 140.1, 153.3, 163.1 (d, *J* = 248.0 Hz).

LRMS (FI): *m*/*z* = 246 [M]$^+$.

HRMS (FI): *m*/*z* [M]$^+$ calcd for $C_{13}H_8ClFN_2$: 246.0360; found: 246.0363.

6-Chloro-2-(2-fluorophenyl)pyrazolo[1,5-*a*]pyridine (1g)

Following the typical procedure for **1a** using **3b** (50.0 mg, 0.166 mmol) in DME (1 mL), 2-fluorophenylboronic acid (35.0 mg, 0.250 mmol), 2 M aq Na_2CO_3 (0.25 mL, 0.5 mmol), and $PdCl_2(PPh_3)_2$ (11.7 mg, 16.7 μmol) gave **1g** as a colorless solid; yield: 36.5 mg (89%); mp 142–146 °C.

IR (ATR): 3094, 1892, 1669, 1582, 1507, 1466, 1443, 1380, 1310, 1215 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (d, *J* = 3.6 Hz, 1 H), 7.09 (dd, *J* = 9.4, 1.5 Hz, 1 H), 7.18 (dd, *J* = 11.2, 8.2 Hz, 1 H), 7.24 (t, *J* = 7.7 Hz, 1 H), 7.32–7.38 (m, 1 H), 7.50 (d, *J* = 9.4 Hz, 1 H), 8.14 (td, *J* = 7.7, 1.5 Hz, 1 H), 8.54 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 98.3 (d, *J* = 10.6 Hz), 116.2 (d, *J* = 22.0 Hz), 118.4, 120.1, 120.7 (d, *J* = 11.4 Hz), 124.4 (d, *J* = 2.9 Hz), 124.9, 126.5, 129.0 (d, *J* = 2.9 Hz), 130.0 (d, *J* = 8.6 Hz), 139.7 (d, *J* = 2.9 Hz), 148.6, 160.6 (d, *J* = 250.8 Hz).

LRMS (FI): *m*/*z* = 246 [M]$^+$.

HRMS (FI): *m*/*z* [M]$^+$ calcd for $C_{13}H_8ClFN_2$: 246.0360; found: 246.0366.

6-Chloro-2-[4-(trifluoromethyl)phenyl]pyrazolo[1,5-*a*]pyridine (1h)

Following the typical procedure for **1a** using **3b** (50.0 mg, 0.166 mmol) in DME (1 mL), 4-(trifluoromethyl)phenylboronic acid (47.5 mg, 0.250 mmol), 2 M aq Na_2CO_3 (0.25 mL, 0.5 mmol), and $PdCl_2(PPh_3)_2$ (11.7 mg, 16.7 μmol) gave **1h** as a colorless solid; yield: 46.6 mg (95%); mp 128–133 °C.

IR (ATR): 3079, 1617, 1426, 1322 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.87 (s, 1 H), 7.12 (dd, *J* = 9.1, 1.8 Hz, 1 H), 7.50 (d, *J* = 9.1 Hz, 1 H), 7.71 (d, *J* = 7.9 Hz, 2 H), 8.05 (d, *J* = 7.9 Hz, 2 H), 8.53 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 95.0, 118.3, 120.4, 125.3, 124.2 (d, *J* = 271.8 Hz), 125.7 (d, *J* = 3.8 Hz), 126.6, 126.7, 130.3 (d, *J* = 32.4 Hz), 136.2, 140.1, 152.5.

LRMS (ESI): *m*/*z* = 297 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_9ClF_3N_2$: 297.0406; found: 297.0405.

6-Chloro-2-[2-(trifluoromethyl)phenyl]pyrazolo[1,5-*a*]pyridine (1i)

Following the typical procedure for **1a** using **3b** (50.0 mg, 0.166 mmol) in DME (1 mL), 2-(trifluoromethyl)phenylboronic acid (47.5 mg, 0.250 mmol), 2 M aq Na_2CO_3 (0.25 mL, 0.5 mmol), and $PdCl_2(PPh_3)_2$ (11.7 mg, 16.7 μmol) gave **1i** as a yellow solid; yield: 40.8 mg (83%); mp 71.0–74.0 °C.

IR (ATR): 3141, 3080, 3014, 1837, 1633, 1582, 1535, 1509, 1445 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.75 (s, 1 H), 7.13 (dd, *J* = 9.7, 1.8 Hz, 1 H), 7.49–7.55 (m, 2 H), 7.62 (t, *J* = 7.3 Hz, 1 H), 7.72 (d, *J* = 7.3 Hz, 1 H), 7.80 (d, *J* = 7.3 Hz, 1 H), 8.53 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 98.6 (d, *J* = 2.9 Hz), 118.3, 120.2, 124.0 (d, *J* = 273.7 Hz), 125.1, 126.3 (d, *J* = 5.7 Hz), 126.5, 128.2, 128.7 (d, *J* = 30.5 Hz), 131.6, 132.4, 132.5 (d, *J* = 13.4 Hz), 139.1, 152.3.

LRMS (ESI): *m*/*z* = 297 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_9ClF_3N_2$: 297.0406; found: 297.0407.

6-Chloro-2-(4-methoxyphenyl)pyrazolo[1,5-*a*]pyridine (1j)

Following the typical procedure for **1a** using **3b** (50.0 mg, 0.166 mmol) in DME (1 mL), 4-methoxyphenylboronic acid (38.0 mg, 0.250 mmol), 2 M aq Na_2CO_3 (0.25 mL, 0.5 mmol), and $PdCl_2(PPh_3)_2$ (11.7 mg, 16.7 μmol) gave **1j** as a colorless solid; yield: 40.0 mg (93%); mp 132–137 °C.

IR (ATR): 3089, 2933, 2836, 2552, 1901, 1610, 1521, 1464, 1436 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.85 (s, 3 H), 6.72 (s, 1 H), 6.98 (d, *J* = 9.1 Hz, 2 H), 7.04 (dd, *J* = 9.7, 1.8 Hz, 1 H), 7.41 (d, *J* = 9.7 Hz, 1 H), 7.86 (d, *J* = 9.1 Hz, 2 H), 8.49 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.3, 93.8, 114.2, 117.8, 119.3, 124.9, 125.5, 126.5, 127.7, 140.0, 154.1, 160.1.

LRMS (ESI): *m*/*z* = 259 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{12}ClFN_2O$: 259.0638; found: 259.0639.

6-Chloro-2-(2-methoxyphenyl)pyrazolo[1,5-*a*]pyridine (1k)

Following the typical procedure for **1a** using **3b** (50.0 mg, 0.166 mmol) in DME (1 mL), 2-methoxyphenylboronic acid (38.0 mg, 0.250 mmol), 2 M aq Na_2CO_3 (0.25 mL, 0.5 mmol), and $PdCl_2(PPh_3)_2$ (11.7 mg, 16.7 μmol) gave **1k** as a colorless solid; yield: 39.5 mg (92%); mp 85–88 °C.

IR (ATR): 3167, 3053, 2963, 2833, 1912, 1634, 1581, 1510, 1474, 1445, 1379 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.95 (s, 3 H), 7.04–7.08 (m, 4 H), 7.34–7.38 (m, 1 H), 7.46 (d, *J* = 9.1 Hz, 1 H), 8.07 (dd, *J* = 7.9, 1.8 Hz, 1 H), 8.53 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.6, 98.9, 111.4, 118.2, 119.5, 121.0, 121.6, 124.4, 126.4, 129.4, 129.7, 139.4, 151.0, 157.3.

LRMS (FI): *m*/*z* = 258 [M]$^+$.

HRMS (FI): *m*/*z* [M]$^+$ calcd for $C_{14}H_{11}ClN_2O$: 258.0560; found: 258.0562.

6-Chloro-2-(furan-2-yl)pyrazolo[1,5-*a*]pyridine (1l)

Following the typical procedure for **1a** using **3b** (400 mg, 1.33 mmol) in DME (2.7 mL), (furan-2-yl)boronic acid (194 mg, 1.73 mmol), 2 M aq Na_2CO_3 (2.0 mL, 4.00 mmol), and $PdCl_2(PPh_3)_2$ (187 mg, 0.266 mmol) at 80 °C for 1 h gave **1l** as a colorless solid; yield: 230 mg (80%); mp 99.0–102 °C.

IR (ATR): 3135, 3095, 1616, 1526, 1510, 1447, 1378, 1306, 1222, 1189, 1086, 1016, 927, 894, 800, 749, 700, 596, 572, 436 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.51 (dd, *J* = 3.6, 1.8 Hz, 1 H), 6.72 (s, 1 H), 6.84 (d, *J* = 3.6 Hz, 1 H), 7.06 (dd, *J* = 9.7, 1.8 Hz, 1 H), 7.42 (d, *J* = 9.7 Hz, 1 H), 7.52 (d, *J* = 1.8 Hz, 1 H), 8.47 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 94.7, 117.9, 119.6, 122.3, 125.1, 126.2, 126.3, 126.5, 134.6, 139.8, 150.3.

LRMS (EI): *m*/*z* = 218 [M]$^+$.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{11}H_7ClN_2O$: 218.02469; found: 218.02399.

6-Chloro-2-(furan-3-yl)pyrazolo[1,5-*a*]pyridine (1m)

Following the typical procedure for **1a** using **3b** (400 mg, 1.33 mmol) in DME (2.7 mL), (furan-3-yl)boronic acid (194 mg, 1.73 mmol), 2 M aq Na_2CO_3 (2.0 mL, 4.00 mmol), and $PdCl_2(PPh_3)_2$ (187 mg, 0.266 mmol) at 80 °C for 1 h gave **1m** as a colorless solid; yield: 152 mg (52%); mp 86.0–89.0 °C.

IR (ATR): 3152, 3083, 1616, 1562, 1507, 1402, 1308, 1154, 1068, 1014, 989, 873, 808, 795, 765, 702, 597, 574, 493 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.60 (s, 1 H), 6.84 (s, 1 H), 7.07 (dd, *J* = 9.1, 1.8 Hz, 1 H), 7.42 (d, *J* = 9.1 Hz, 1 H), 7.50 (t, *J* = 1.8 Hz, 1 H), 7.93 (s, 1 H), 8.48 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 94.7, 109.1, 117.7, 119.4, 119.5, 125.1, 126.5, 139.7, 140.3, 143.6, 147.6.

LRMS (EI): *m*/*z* = 218 $[M]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_7ClN_2O$: 218.02469; found: 218.02495.

6-Chloro-2-(thiophen-2-yl)pyrazolo[1,5-*a*]pyridine (1n)

Following the typical procedure for **1a** using **3b** (400 mg, 1.33 mmol) in DME (2.7 mL), (thiophen-2-yl)boronic acid (187 mg, 1.46 mmol), 2 M aq Na_2CO_3 (2.0 mL, 4.00 mmol), and $PdCl_2(PPh_3)_2$ (187 mg, 0.270 mmol) at 80 °C for 1 h gave **1n** as a colorless solid; yield: 170 mg (54%); mp 85.0–88.0 °C.

IR (ATR): 3087, 1630, 1560, 1506, 1475, 1389, 1303, 1215, 1130, 1066, 927, 850, 799, 758, 686, 569 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.71 (s, 1 H), 7.07 (dd, *J* = 9.7, 1.8 Hz, 1 H), 7.11 (d, *J* = 4.8, 3.6 Hz, 1 H), 7.34 (dd, *J* = 4.8, 1.2 Hz, 1 H), 7.41 (d, *J* = 9.7 Hz, 1 H), 7.50 (d, *J* = 3.6, 1.2 Hz, 1 H), 8.48 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 94.3, 117.8, 119.7, 125.2, 125.3, 125.9, 126.5, 127.7, 135.8, 139.9, 149.3.

LRMS (EI): *m*/*z* = 234 $[M]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_7ClN_2S$: 234.00185; found: 234.00124.

6-Chloro-2-(thiophen-3-yl)pyrazolo[1,5-*a*]pyridine (1o)

Following the typical procedure for **1a** using **3b** (800 mg, 2.66 mmol) in DMF (4.0 mL), (thiophen-3-yl)boronic acid (375 mg, 2.93 mmol), 2 M aq Na_2CO_3 (4.0 mL, 8.00 mmol), and $PdCl_2(PPh_3)_2$ (373 mg, 0.530 mmol) at 80 °C for 1 h gave **1o** as a colorless solid; yield: 312 mg (55%); mp 120–123 °C.

IR (ATR): 3082, 1631, 1562, 1508, 1478, 1341, 1307, 1071, 853, 790, 762, 701, 573 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.70 (s, 1 H), 7.07 (dd, *J* = 9.7, 1.5 Hz, 1 H), 7.24 (dd, *J* = 4.8, 3.0 Hz, 1 H), 7.44 (d, *J* = 9.7 Hz, 1 H), 7.57 (dd, *J* = 4.8, 1.2 Hz, 1 H), 7.76 (dd, *J* =3.0, 1.2 Hz, 1 H), 8.49 (d, *J* = 1.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 94.1, 107.7, 111.6, 118.0, 119.9, 125.3, 126.6, 139.6, 142.8, 146.3, 148.2.

LRMS (EI): *m*/*z* = 234 $[M]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_7ClN_2S$: 234.00185; found: 234.00147.

Ethyl Pyrazolo[1,5-*a*]pyridine-2-carboxylate (7)

To a solution of **3a** (53.3 mg, 0.200 mmol) in DMF (0.5 mL) and EtOH (0.5 mL) was added $Pd(OAc)_2$ (22.5 mg, 0.100 mmol), dppp (45.5 mg, 0.110 mmol), and Et_3N (56 µL, 0.40 mmol) at r.t. The mixture was stirred under a CO atmosphere at 60 °C for 10 h. The mixture was cooled to r.t., and then passed through a Celite pad and concentrated in vacuo. The crude material was purified by flash column chromatography (silica gel, hexane–EtOAc, 1:1) to give **7** as a pale yellow solid; yield: 31.6 mg (83%); mp 43.0–46.0 °C.

IR (ATR): 3089, 2981, 1717, 1636, 1516, 1498, 1486, 1404, 1329, 1241, 1197, 1100, 1025 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.45 (t, *J* = 7.3 Hz, 3 H), 4.48 (q, *J* = 7.3 Hz, 2 H), 6.88 (dd, *J* = 7.9, 7.3 Hz, 1 H), 7.08 (s, 1 H), 7.17 (dd, *J* = 9.1, 7.9 Hz, 1 H), 7.59 (d, *J* = 9.1 Hz, 1 H), 8.53 (d, *J* = 7.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4, 61.4, 100.2, 114.1, 119.2, 124.0, 129.0, 140.9, 145.0, 162.8.

LRMS (ESI): *m*/*z* = 191 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{10}H_{11}N_2O_2$: 191.08205; found: 191.08183.

Ethyl (*E*)-3-(Pyrazolo[1,5-*a*]pyridin-2-yl)acrylate (8)

To a solution of **3a** (53.3 mg, 0.200 mmol) in DMF (1 mL) was added ethyl acrylate (0.22 mL, 2.0 mmol), $Pd(OAc)_2$ (22.5 mg, 0.100 mmol), dppp (45.5 mg, 0.110 mmol), and Et_3N (56 µL, 0.40 mmol) at r.t. The mixture was stirred under argon at 80 °C for 10 h. The mixture was cooled to r.t., and then passed through a Celite pad and then concentrated in vacuo. The crude material was purified by flash column chromatography (silica gel, hexane–EtOAc, 3:1) to give **8** as a pale yellow solid; yield: 28.0 mg (65%); mp 56.0–59.0 °C.

IR (ATR): 2984, 2931, 1712, 1646, 1633, 1609, 1514, 1475, 1402, 1348, 1298, 1271, 1243, 1172, 1163, 1033 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (t, *J* = 7.3 Hz, 3 H), 4.27 (q, *J* = 7.3 Hz, 2 H), 6.67 (d, *J* = 15.8 Hz, 1 H), 6.70 (s, 1 H), 6.78 (t, *J* = 7.9 Hz, 1 H), 7.11 (t, *J* = 7.9 Hz, 1 H), 7.50 (d, *J* = 7.9 Hz, 1 H), 7.79 (d, *J* = 15.8 Hz, 1 H), 8.41 (d, *J* = 7.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 60.6, 96.6, 112.8, 118.4, 121.3, 123.8, 128.5, 136.4, 141.3, 149.5, 166.7.

LRMS (ESI): *m*/*z* = 217 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{13}N_2O_2$: 217.09770; found: 217.09813.

2,6-Diphenylpyrazolo[1,5-*a*]pyridine (6)

To a solution of **1b** (68.7 mg, 0.300 mmol) in THF (3 mL) was added phenylboronic acid (55.0 mg, 0.451 mmol), $Pd(OAc)_2$ (13.7 mg, 61.0 µmol), SPhos (25.0 mg, 60.9 µmol), and K_3PO_4 (191 mg, 0.900 mmol) at r.t. The mixture was stirred under argon at 80 °C for 10 h. The mixture was cooled to r.t., and then passed through a Celite pad and then concentrated in vacuo. The crude material was purified by flash column chromatography (silica gel, hexane–EtOAc, 10:1) to give **6** as a colorless solid; yield: 76.5 mg (94%); mp 134–137 °C.

IR (ATR): 3056, 2924, 1635, 1598, 1545, 1462, 1442, 1387, 1319, 1246, 1108, 1079, 1027 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.83 (s, 1 H), 7.35–7.43 (m, 3 H), 7.43–7.53 (m, 4 H), 7.53–7.65 (m, 3 H), 7.98 (d, *J* = 8.5 Hz, 2 H), 8.72 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 93.7, 117.8, 124.1, 125.9, 126.2, 126.5, 126.7, 127.8, 128.5, 128.8, 129.2, 133.1, 137.3, 140.6, 154.0.

LRMS (ESI): *m*/*z* = 271 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{15}N_2$: 271.12352; found: 271.12395.

Methyl 6-[(6-Chloro-2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)methyl]picolinate (10) by Path A

To a stirred solution of **1b** (229 mg, 1.00 mmol) and methyl 6-formylpyridine-2-carboxylate (248 mg, 1.50 mmol) in CH_2Cl_2 (10 mL) was added TFA (0.16 mL, 2.09 mmol) and TESH (0.48 mL, 3.01 mmol), and the mixture was stirred at r.t. for 5 h. The mixture was quenched by the addition of sat. aq $NaHCO_3$ to adjust to pH 11, then it was extracted with EtOAc and the combined extracts were dried (Na_2SO_4). The crude material was purified by flash column chromatography (silica gel, hexane–EtOAc, 4:1) to give **10** as yellow oil; yield: 170 mg (45%).

IR (ATR): 3448, 3065, 2950, 1721, 1630, 1586, 1533, 1460, 1435, 1317, 1289, 1242, 1136, 1075, 993, 918, 835, 754, 699, 674, 576, 498, 417 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.03 (s, 3 H), 4.54 (s, 2 H), 7.04 (dd, *J* = 9.7, 1.8 Hz, 1 H), 7.09 (d, *J* = 7.9 Hz, 1 H), 7.37 (d, *J* = 9.7 Hz, 1 H), 7.38–7.46 (m, 3 H), 7.65 (t, *J* = 7.9 Hz, 1 H), 7.68–7.72 (m, 2 H), 7.96 (d, *J* = 7.9 Hz, 1 H), 8.52 (d, *J* = 1.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 32.5, 52.9, 105.3, 117.4, 120.1, 123.0, 124.6, 125.4, 126.5, 128.4, 128.5, 128.7, 132.7, 137.7, 138.8, 147.5, 153.2, 160.8, 165.8.

LRMS (EI): *m*/*z* = 377 $[M]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{21}H_{16}ClN_3O_2$: 377.0931; found: 377.0932.

Methyl 6-[(6-Chloro-2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)methyl]picolinate (10) by Path B

6-Chloro-2-phenyl-7-(trimethylsilyl)pyrazolo[1,5-*a*]pyridine

To a stirred solution of **1b** (689 mg, 3.01 mmol) in THF (15 mL) was added 2.6 M BuLi in hexane (1.4 mL, 3.62 mmol) at –78 °C, and the mixture was stirred at –78 °C for 0.5 h. TMSCl (1.9 mL, 15.1 mmol) was added to the mixture at –78 °C, and then then it was warmed to r.t. and stirred for 1 h. The mixture was quenched by the addition of sat. aq NH_4Cl, then it was extracted with EtOAc, and the combined extracts were dried (Na_2SO_4). The crude material was purified by flash column chromatography (silica gel, hexane–EtOAc, 4:1) to give the title compound as a yellow solid; yield: 830 mg (92%); mp 91–92 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.63 (s, 9 H), 6.78 (s, 1 H), 7.00 (d, *J* = 9.1 Hz, 1 H), 7.36 (tt, *J* = 7.3, 1.2 Hz, 1 H), 7.40–7.47 (m, 3 H), 7.94–7.97 (m, 2 H).

IR (ATR): 3067, 2954, 2896, 1612, 1535, 1457, 1379, 1279, 1245, 1182, 1108, 1081, 969, 878, 848, 777, 697, 637, 555, 482, 421 cm^{-1}.

LRMS (EI): *m*/*z* = 300 $[M]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{17}ClN_2Si$: 300.0850; found: 300.0841.

3-Bromo-6-chloro-2-phenyl-7-(trimethylsilyl)pyrazolo[1,5-*a*]pyridine

To a stirred solution of 6-chloro-2-phenyl-7-(trimethylsilyl)pyrazolo[1,5-*a*]pyridine (830 mg, 2.76 mmol) in MeCN (14 mL) was added NBS (589 mg, 3.31 mmol) at r.t., and the mixture was stirred at r.t. for 1 h. The mixture was quenched by the addition of sat. aq $NaHCO_3$, then it was extracted with EtOAc and the combined extracts were dried (Na_2SO_4). The crude material was purified by flash column chromatography (silica gel, hexane–EtOAc, 4:1) to give the title compound as a yellow solid; yield: 970 mg (93%); mp 96–97 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.61 (s, 9 H), 7.11 (d, *J* = 9.1 Hz, 1 H), 7.42 (d, *J* = 7.3 Hz, 1 H), 7.44 (d, *J* = 9.1 Hz, 1 H), 7.49 (t, *J* = 7.3 Hz, 2 H), 8.11 (d, *J* = 7.3 Hz, 2 H).

IR (ATR): 3060, 2960, 2903, 1938, 1887, 1792, 1733, 1607, 1527, 1480, 1454, 1382, 1302, 1237, 1146, 1105, 1014, 955, 842, 763, 679, 642, 594, 519, 470, 434 cm^{-1}.

LRMS (ESI): *m*/*z* = 379 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{17}BrClN_2Si$: 379.00329; found: 379.00418.

Methyl 6-[(6-Chloro-2-phenyl-7-(trimethylsilyl)pyrazolo[1,5-*a*]pyridin-3-yl)(hydroxy)methyl]picolinate

To a stirred solution of 3-bromo-6-chloro-2-phenyl-7-(trimethylsilyl)pyrazolo[1,5-*a*]pyridine (530 mg, 1.40 mmol) in THF (3.5 mL) was added 2.6 M BuLi in hexane (0.60 mL, 1.67 mmol) at –78 °C, and the mixture was stirred at –78 °C for 0.5 h. A solution of methyl 6-formylpyridine-2-carboxylate (461 mg, 2.79 mmol) in THF (3.5 mL) was added to the mixture at –78 °C, and then then it was warmed to r.t. and stirred for 1 h. The mixture was quenched by the addition of sat. aq NH_4Cl, then it was extracted with EtOAc, and the combined extracts were dried (Na_2SO_4). The crude material was purified by flash column chromatography (silica gel, hexane–EtOAc, 2:1) to give the title compound as a yellow oil; yield: 345 mg (53%).

IR (ATR): 3421, 2953, 2899, 1721, 1586, 1490, 1457, 1438, 1356, 1314, 1246, 1217, 1137, 1043, 961, 892, 839, 761, 701, 635, 605, 487, 420 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.59 (s, 9 H), 4.05 (s, 3 H), 5.34 (d, *J* = 3.0 Hz, 1 H), 6.28 (d, *J* = 3.0 Hz, 1 H), 6.87 (d, *J* = 9.7 Hz, 1 H), 6.99 (d, *J* = 9.7 Hz, 1 H), 7.22 (d, *J* = 7.9 Hz, 1 H), 7.37–7.48 (m, 3 H), 7.71 (t, *J* = 7.9 Hz, 1 H), 7.83–7.87 (m, 2 H), 8.07 (d, *J* = 7.9 Hz, 1 H).

LRMS (EI): *m*/*z* = 465 $[M]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{24}H_{24}ClN_3O_3Si$: 465.1275; found: 465.1251.

Methyl 6-[(6-Chloro-2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)(hydroxy)methyl]picolinate

To a stirred solution of methyl 6-[(6-chloro-2-phenyl-7-(trimethylsilyl)pyrazolo[1,5-*a*]pyridin-3-yl)(hydroxy)methyl]picolinate (216 mg, 0.55 mmol) in THF (5.5 mL) was added 1 M TBAF in THF (1.10 mL, 1.10 mmol) at 0 °C, and the mixture was stirred at 0 °C for 1 h. The mixture was quenched by the addition of sat. aq NH_4Cl, then it was extracted with EtOAc and the combined extracts were dried (Na_2SO_4). The crude material was purified by flash column chromatography (silica gel, hexane–EtOAc, 2:1) to give the title compound as a yellow oil; yield: 162 mg (75%).

IR (ATR): 3386, 3062, 2951, 2245, 1723, 1632, 1587, 1515, 1460, 1437, 1317, 1294, 1215, 1137, 1076, 1029, 890, 836, 755, 730, 701, 669, 573, 492, 407 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.03 (s, 3 H), 5.37 (br s, 1 H), 6.23 (s, 1 H), 6.95 (dd, *J* = 9.7, 1.8 Hz, 1 H), 7.12 (d, *J* = 9.7 Hz, 1 H), 7.20 (d, *J* = 7.9 Hz, 1 H), 7.39–7.49 (m, 3 H), 7.71 (t, *J* = 7.9 Hz, 1 H), 7.79–7.83 (m, 2 H), 8.02 (d, *J* = 7.9 Hz, 1 H), 8.50 (d, *J* = 1.8 Hz, 1 H).

LRMS (EI): *m*/*z* = 393 $[M]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{21}H_{16}ClN_3O_3$: 393.0880; found: 393.0869.

Methyl 6-[(6-Chloro-2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)methyl]picolinate (10)

To a stirred solution of methyl 6-[(6-chloro-2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)(hydroxy)methyl]picolinate (100 mg, 0.254 mmol) in CH_2Cl_2 (1.3 mL) was added TFA (0.20 mL, 3.05 mmol) and TESH (0.20 mL, 1.52 mmol), and the mixture was stirred at r.t. for 1 h. The mixture was quenched by the addition of sat. aq $NaHCO_3$ to adjust to pH 11. The mixture was extracted with EtOAc and the combined extracts were dried (Na_2SO_4). The crude material was purified by flash column chromatography (silica gel, hexane–EtOAc, 4:1) to give **10** as yellow oil; yield: 97.0 mg (quant.). ^{1}H NMR spectroscopic data are identical with those of **10** prepared using path A.

6-[(6-Chloro-2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)methyl]picolic Acid (EP_1 Antagonist)

To a ice-cooled solution of **10** (90.0 mg, 0.24 mmol) in MeOH (1.2 mL) was added 2 M aq KOH (0.60 mL, 1.19 mmol) and the mixture was stirred at r.t. for 6 h. The reaction was quenched by the addition of 1 M HCl. A precipitate formed and it was collected by filtration and then dried to give the title compound as a colorless solid; yield: 79.0 mg (90%); mp 173–174 °C.

IR (ATR): 3071, 2927, 2528, 1948, 1759, 1703, 1591, 1518, 1463, 1432, 1331, 1248, 1226, 1144, 1079, 995, 927, 829, 810, 752, 694, 661, 570, 482, 414 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.44 (s, 2 H), 7.26 (dd, *J* = 9.1, 1.8 Hz, 1 H), 7.31 (dd, *J* = 7.3, 1.8 Hz, 1 H), 7.37–7.47 (m, 3 H), 7.75 (d, *J* = 9.1 Hz, 1 H), 7.81–7.86 (m, 4 H), 9.03 (d, *J* = 1.8 Hz, 1 H), 13.08 (br s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 31.4, 105.7, 117.9, 119.3, 122.4, 124.3, 125.4, 126.6, 128.3, 128.3, 128.6, 132.6, 138.1, 138.5, 147.9, 151.9, 160.1, 166.1.

LRMS (ESI): *m*/*z* = 364 $[M + H]^+$

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{15}ClN_3O_2$: 364.08528; found: 364.08547.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1381025.

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