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Electrophilic acetylation and formylation of pyrrolo[1,2-*a*]pyrazines: substituent effects on regioselectivity

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Dedicated to Professor George A. Kraus in celebration of his many outstanding contributions to organic synthesis

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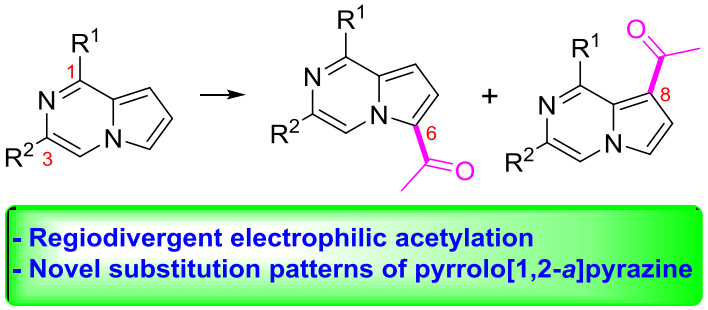
Abstract

Described herein is electrophilic acetylation and formylation of pyrrolo[1,2-*a*]pyrazines with substituent(s) at C1 and/or C3 position(s) where substituents around the core skeleton allowed regiodivergent access to C6- or C8-acetylpyrrolo[1,2-*a*]pyrazines. While acetylation of pyrrolo[1,2-*a*]pyrazines (R(1) = H and R(3) = aryl or methyl) mainly gave rise to C8-acetylated products, acetylation with pyrrolo[1,2-*a*]pyrazines (R(1) = methyl and R(2) = aryl or methyl) provided C6-acetylated compounds as major products. In contrast, Vilsmeier-Haack formylation of pyrrolo[1,2-*a*]pyrazines took place at C6 position irrespective of the substituents at C1 and/or C3 site(s).



Keywords: Electrophilic acylation, pyrrolo[1,2-*a*]pyrazines, Vilsmeier-Haack formylation, Friedel-Crafts acylation; regioselectivity

Introduction

Generation of novel heterocyclic chemical scaffolds, with unprecedented substitution patterns via regio-selective installation of various functional groups around heterocyclic core skeletons, is highly important in the search for new effective pharmacophores in drug discovery programs. As illustrated in Figure 1, the bicyclic aza-heterocyclic pyrrolo[1,2-*a*]pyrazine system has been employed as a core chemical structure in a variety of medicinal chemistry efforts to discover an array of biological activities, including anticancer and antitubercular activities, depending on the substituents with different orientation.[1-6]

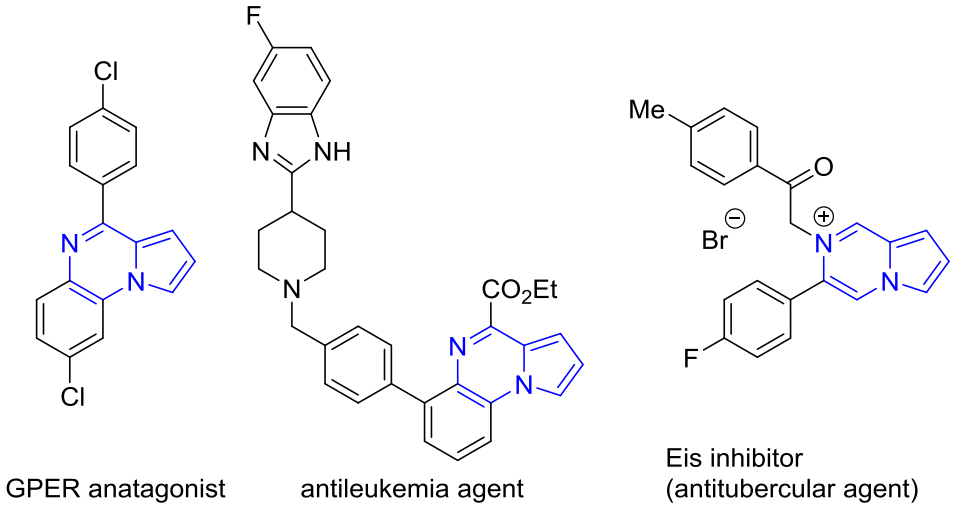
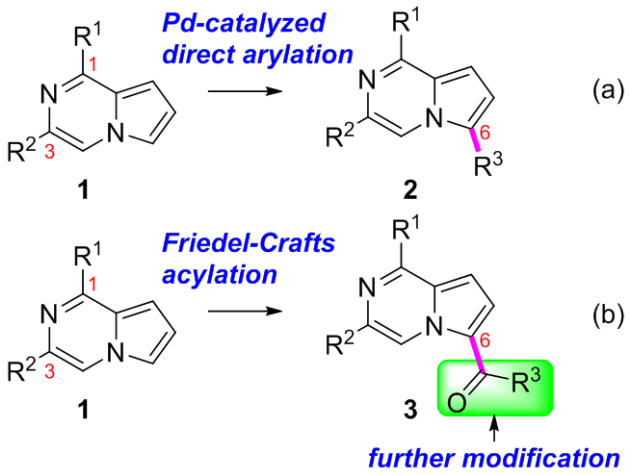


Figure 1. Some bioactive pyrrolo[1,2-*a*]pyrazine derivatives

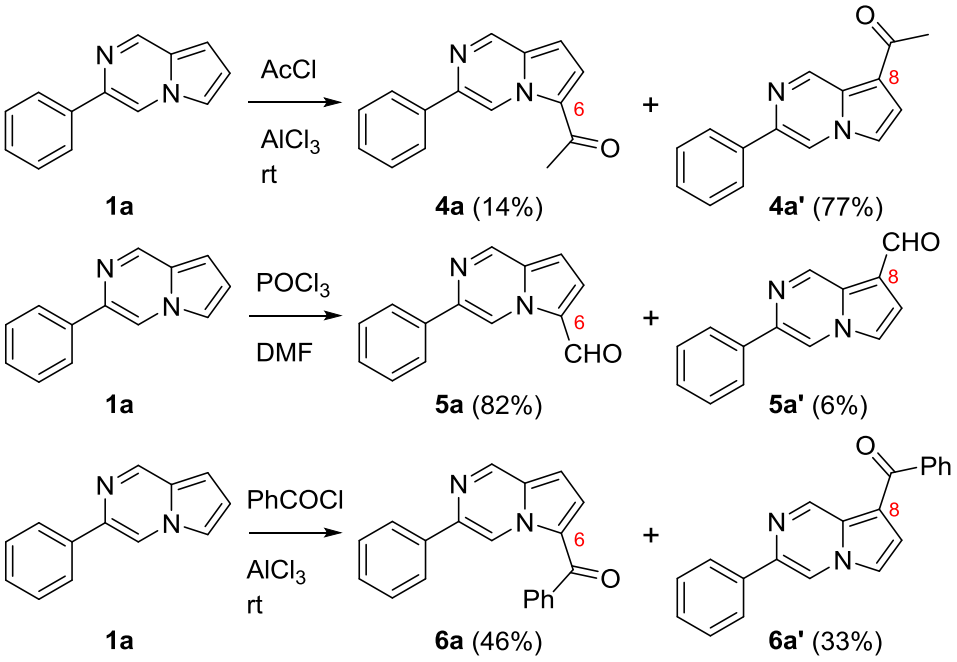
Clearly, these medicinal studies were made possible by synthetic strategies and technologies that enable a variety of functional groups to be arranged around the basic template at will. With the intention to construct a novel pyrrolo[1,2-*a*]pyrazine-based chemical library, we have reported on a diversity-oriented synthesis of pyrrolo[1,2-*a*]pyrazines with a (hetero)aryl moiety at the C6 position by way of Pd-catalyzed direct arylation (Scheme 1a).[7] The resulting 6-arylpyrrolo[1,2-*a*]pyrazines were found to have anti-osteoporotic activity.[8] To explore new territory based on pyrrolo[1,2-*a*]pyrazine, we investigated electrophilic acylation to install an acyl unit which could be further elaborated. From several literature precedents,[9-15] we reasoned that Friedel-Crafts type acylation of **1** would mainly provide **3** having an acyl group at the C6 site (Scheme 1b).
Contrary to our expectation, we found that regioselectivity (C6 *vs*. C8) of acylation with **1** is highly dependent on the substituent(s) of **1** and the acylating agent, which is described herein.



Scheme 1. Synthetic-investigation plans: direct arylation using organometallic chemistry (1a) vs. acylation (1b).

Results and Discussion

As mentioned in the Introduction, we wished to introduce either an acetyl or a formyl group at the C6 position of **1**[16] as a functional handle for further derivatization. For this purpose, we reacted the C3-phenyl compound **1a** with acetyl chloride in the presence of $AlCl_3$ as shown in Scheme 2. Two monoacetyl compounds were observed. NMR analysis revealed that the major product is the C8-acetyl pyrrolo[1,2-*a*]pyrazine (**4a'**) (77%) and the minor product is the C6-acetylated compound **4a** (14%). The structure of **4a'** was further confirmed by X-ray crystallographic analysis (Figure 2).[17]



Scheme 2. Electrophilic acylation of **1a.**

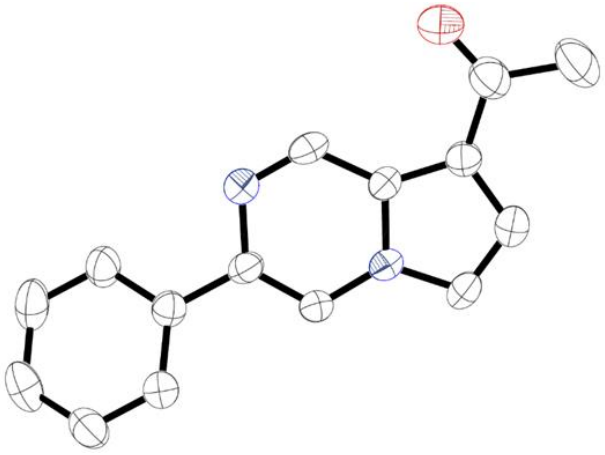
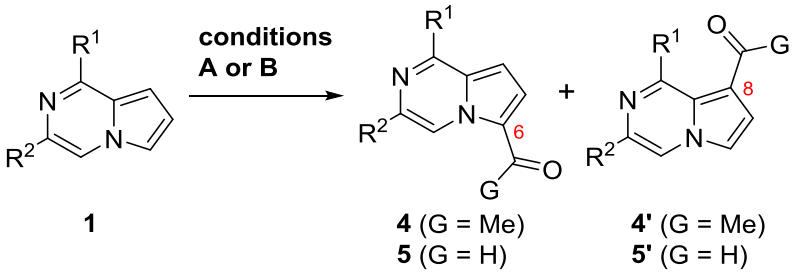


Figure 2. Crystal structure of **4a'.**

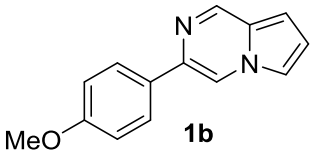
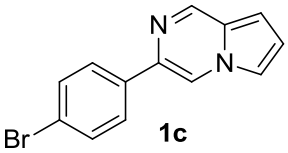
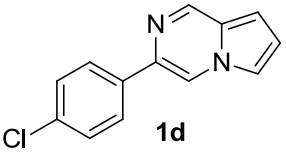
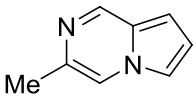
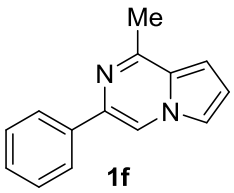
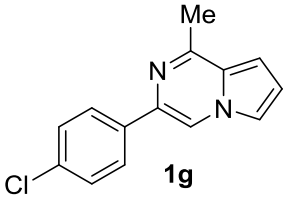
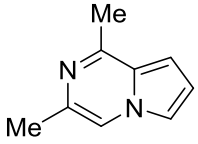
This was quite surprising to us because several previous studies had indicated preferential acetylation at the C6 site of pyrrolo[1,2-*a*]pyrazines under similar conditions. On the other hand, Vilsmeier-Haack formylation[18] of **1a** produced the C6-formylated product (**5a**) as the major product. These two results led us to conclude that the steric effect of a phenyl moiety at C3 plays a crucial role in controlling the regioselectivity of acetylation. With our expectation that a bulkier group than acetyl would afford better C8 regioselectivity, we conducted benzoylation of **1a** with PhCOCl and $AlCl_3$, however, no selectivity was observed in this case. Rather, the C6-benzoylated compound (**6a**) was obtained slightly preferentially (46% yield) to **6a'** (33%). These alterations of reaction sites in Friedel-Crafts type acylations, as well as a lack of systematic study with respect to substituent effects of pyrrolo[1,2-*a*]pyrazines on site-selective acylations, led us to investigate the roles of substituents in determining the regioselectivity of acylation.

To examine the general pattern of electrophilic acetylation and formylation, several pyrrolo[1,2-*a*]-pyrazines were submitted to the identical conditions (Scheme 3 and Table 1). As expected, C8-acetylation occurred to afford **4'** as the major products, irrespective of the electronic nature (electron-rich or poor) of the R^2 moiety, whereas, products having a formyl group at C6 site were formed under Vilsmeier-Haack formylation conditions (entries 1-6). When R^2 is methyl, a regioselective ratio of acetylation (C6 *vs* C8) decreases a little bit probably due to a smaller steric effect (entry 7). In cases of pyrrolo[1,2-*a*]pyrazines bearing a methyl at R^1 site (**1f-h**), C6-acetylation became a major pathway, indicating that the R^1 substituent plays a bigger role than R^2 in regioselection control (entries 9, 11, and 12).



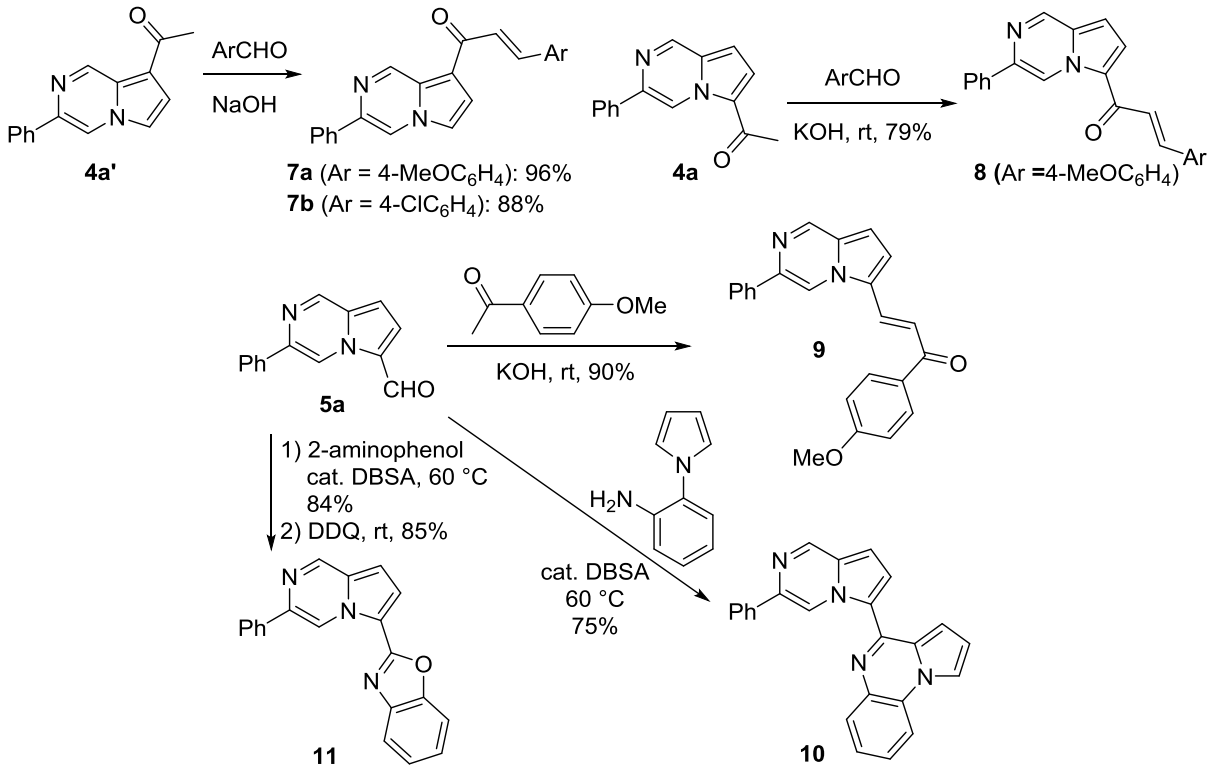
Scheme 3. Electrophilic acetylation and formylation reactions of pyrrolo[1,2-*a*]pyrazine (**1**).

Table 1. Products of electrophilic acetylation and formylation reactions of **1**

Entry	**1**	Conditions[a]	Products[b]	
1	 **1b**	**A**	**4b** (8)	**4b'** (73)
2		**B**	**5b** (86)	**5b'** (9)
3	 **1c**	**A**	**4c** (12)	**4c'** (84)
4		**B**	**5c** (83)	**5c'** (0)
5	 **1d**	**A**	**4d** (6)	**4d'** (87)
6		**B**	**5d** (95)	**5d'** (0)
7	 **1e**	**A**	**4e** (13)	**4e'** (66)
8		**B**	**5e** (80)	**5e'** (14)
9	 **1f**	**A**	**4f** (67)	**4f'** (6)
10		**B**	**5f** (65)	**5f'** (0)
11	 **1g**	**A**	**4g** (77)	**4g'** (0)
12	 **1h**	**A**	**4h** (73)	**4h'** (6)

[a] *Conditions A*: A mixture of **1** (30 mg), acetyl chloride (10 equiv), and $AlCl_3$ (10 equiv) in CH_2Cl_2 (2.5 mL) was stirred at rt. *Conditions B*: To a mixture of $POCl_3$ (5 equiv) in DMF (1 mL) was added **1** (30 mg, dissolved in 0.5 mL of DMF) at rt. [b] Isolated yield (%).

Further elaboration of the resulting acetyl- or formyl-containing pyrrolo[1,2-*a*]pyrazines was conducted (Scheme 4).



Scheme 4. Further functionalization.

Base-mediated aldol condensation of **4a'**, **4a**, and **5a** proceeded well to give the corresponding chalcones[19-26] **7-9** in good yields. Notably, easy access to regioisomeric chalcones (**7a**, **8**, and **9**) was allowed by these acetylation/formylation-aldol procedures, enabling us to compare biological effects of these constitutional isomers bearing a chalcone moiety with different orientation.[27] The formyl group in **5a** was also employed to install additional aromatic systems such as pyrrolo[1,2-*a*]quinoxaline[28] and benzoxazole[29] as shown in **10** and **11**.

Conclusions

In summary, we have investigated substituent effect on regioselectivity in electrophilic acetylation and formylation of pyrrolo[1,2-*a*]pyrazines. While Vilsmeier-Haack formylation proceeded mainly at the C6 position to give the corresponding C6-formyl products, Friedel-Crafts type acetylation occurred at the C6 or C8 positions as a major pathway depending on the pre-existing substituents of the substrates. New substitution patterns of pyrrolo[1,2-*a*]pyrazines were realized by these regiodivergent acylations. Further functionalization of this basic skeleton and biological tests of the synthesized compounds are currently in progress.

Experimental Section

General. Unless specified, all reagents and starting materials were purchased from commercial sources and used as received without purification. “Concentrated” refers to the removal of volatile solvents via distillation

using a rotary evaporator. "Dried" refers to pouring onto, or passing through, anhydrous magnesium sulfate followed by filtration. Flash chromatography was performed using silica gel (230−400 mesh) with hexanes, ethyl acetate, and dichloromethane as the eluents. All reactions were monitored by thin-layer chromatography on 0.25 mm silica plates (F-254) visualized with UV light. Melting points were measured using a capillary melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz NMR spectrometer and were described as chemical shifts, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant in hertz (Hz), and number of protons. HRMS was measured with an electrospray ionization (ESI) and Q-TOF mass analyzer.

General procedure A. To a stirred solution of the different pyrrolo[1,2-a]pyrazines (30 mg) were added $AlCl_3$ (10 equiv) and acetyl chloride (10 equiv) in CH_2Cl_2 (2.5 mL) at room temperature. After being stirred at room temperature for 1-6 h, the reaction mixture was poured into ice-cold water, neutralized with aqueous $NaHCO_3$, and extracted with CH_2Cl_2 (5 mL × 2). The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel (various hexanes:ethyl-acetate ratios) gave the corresponding products.

1-(3-Phenylpyrrolo[1,2-*a*]pyrazin-6-yl)ethanone (**4a**) **and 1-(3-phenylpyrrolo[1,2-*a*]pyrazin-8-yl)ethanone** (**4a'**). Prepared from 3-phenylpyrrolo[1,2-*a*]pyrazine (30 mg, 0.15 mmol), $AlCl_3$ (200 mg, 1.50 mmol), and acetyl chloride (107 µL, 1.50 mmol) using general procedure **A** for 3 h. Purification by flash chromatography on silica gel (hexanes:EtOAc, 9:1) afforded **4a** (5 mg, 14%) as a brown solid, mp 112.5-114.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 9.10 (s, 1H), 8.01 (d, *J* 7.2 Hz, 2H), 7.48-7.53 (m, 3H), 7.40 (t, *J* 7.2 Hz, 1H), 6.82 (d, *J* 4.4 Hz, 1H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 144.2, 141.2, 137.1, 131.1, 128.9, 128.7, 126.5, 124.4, 123.2, 116.8, 104.4, 27.8; HRMS (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{15}H_{13}N_2O$ 237.1022, found 237.1020. Purification by flash chromatography on silica gel (hexanes:EtOAc, 4:1) afforded **4a'** (28 mg, 77%) as a pale yellow solid; mp 172.5-174.2 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.77 (s, 1H), 8.28 (s, 1H), 7.93 (d, *J* 7.6 Hz, 2H), 7.46-7.50 (m, 2H), 7.40-7.43 (m, 2H), 7.26 (s, 1H), 2.59 (s, 3H); **^{13}C** NMR (100 MHz, $CDCl_3$) δ 193.2, 146.1, 140.5, 136.7, 129.1, 128.9, 127.7, 126.3, 117.9, 116.9, 115.5, 114.8, 28.2; HRMS (ESI-QTOF) *m/z* $[M+Na]^+$ calcd for $C_{15}H_{12}N_2ONa$ 259.0842, found 259.0841.

1-(3-(4-Methoxyphenyl)pyrrolo[1,2-*a*]pyrazin-6-yl)ethanone (**4b**) **and 1-(3-(4-methoxyphenyl)-pyrrolo[1,2-*a*]pyrazin-8-yl)ethanone** (**4b'**)**.** Prepared from 3-(4-methoxyphenyl)pyrrolo[1,2-*a*]pyrazine (30 mg, 0.13 mmol), $AlCl_3$ (173 mg, 1.30 mmol), and acetyl chloride (92.4 µL, 1.30 mmol) using general procedure **A** for 1 h. Purification by flash chromatography on silica gel (hexanes:EtOAc, 9:1) afforded **4b** (3 mg, 8%) as a yellow solid, mp 144.4-146.2 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 9.06 (s, 1H), 7.95 (d, *J* 8.4 Hz, 2H), 7.50 (d, *J* 4.4 Hz, 1H), 7.02 (d, *J* 8.4 Hz, 2H), 6.79 (d, *J* 4.0 Hz, 1H), 3.87 (s, 3H), 2.62 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 188.7, 160.3, 144.1, 141.2, 130.9, 129.7, 127.8, 124.3, 123.1, 115.9, 114.4, 104.3, 55.5, 27.9; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}N_2O_2$ 267.1128, found 267.1123. Purification by flash chromatography on silica gel (hexanes:EtOAc, 4:1) afforded **4b'** (26 mg, 73%) as a brown solid, mp 206.2-208.1 °C; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 8.18 (s, 1H), 7.85 (d, *J* 8.0 Hz, 2H), 7.35 (d, *J* 2.4 Hz, 1H), 7.22 (d, *J* 2.4 Hz, 1H), 7.99 (d, *J* 8.0 Hz, 2H), 3.85 (s, 3H), 2.57 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 193.1, 160.3, 145.9, 140.4, 129.2, 127.6, 127.5, 117.8, 116.8, 115.3, 114.5, 113.8, 55.5, 28.1; **HRMS** (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}N_2O_2$ 267.1128, found 267.1125.

1-(3-(4-Bromophenyl)pyrrolo[1,2-*a*]pyrazin-6-yl)ethanone (**4c**) **and 1-(3-(4-bromophenyl)pyrrolo[1,2-*a*]-pyrazin-8-yl)ethanone** (**4c'**). Prepared from 3-(4-bromophenyl)pyrrolo[1,2-*a*]pyrazine (30 mg, 0.11 mmol), $AlCl_3$ (147 mg, 1.10 mmol), and acetyl chloride (78.2 µL, 1.10 mmol) using general procedure **A** for 1.5 h. Purification by flash chromatography on silica gel (hexanes:EtOAc, 4:1) afforded **4c** (4 mg, 12%) as a pale

yellow solid, mp 186.1-188.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 9.06 (s, 1H), 7.88 (d, *J* 8.4 Hz, 2H), 7.60 (d, *J* 8.4 Hz, 2H), 7.52 (d, *J* 4.4 Hz, 1H), 6.82 (d, *J* 4.4 Hz, 1H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9, 144.3, 139.9, 136.0, 132.1, 131.0, 127.9, 124.5, 123.4, 123.0, 116.8, 104.6, 27.9; HRMS (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{15}H_{12}BrN_2O$ 315.0128, found 315.0123. Purification by flash chromatography on silica gel (CH_2Cl_2:MeOH, 40:1) afforded **4c'** (29 mg, 84%) as an off-white solid, mp 226.6-228.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 8.28 (s, 1H), 7.81 (d, *J* 8.4 Hz, 2H), 7.60 (d, *J* 8.4 Hz, 2H), 7.40 (s, 1H), 7.26 (s, 1H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 146.3, 139.4, 135.6, 132.2, 127.8, 123.1, 118.0, 117.2, 115.6, 114.8, 28.2; HRMS (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{15}H_{12}BrN_2O$ 315.0128, found 315.0125.

1-(3-(4-Chlorophenyl)pyrrolo[1,2-*a*]pyrazin-6-yl)ethanone (**4d**) **and 1-(3-(4-chlorophenyl)pyrrolo[1,2-*a*]pyrazin-8-yl)ethanone** (**4d'**)**.** Prepared from 3-(4-chlorophenyl)pyrrolo[1,2-*a*]pyrazine (30 mg, 0.13 mmol), $AlCl_3$ (173 mg, 1.30 mmol), and acetyl chloride (92.4 µL, 1.30 mmol) using general procedure **A** for 2 h. Purification by flash chromatography on silica gel (hexanes:EtOAc, 9:1) afforded **4d** (2 mg, 6%) as a brown solid, mp 177.3-179.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 9.08 (s, 1H), 7.95 (d, *J* 8.4 Hz, 2H), 7.53 (d, *J* 4.4 Hz, 1H), 7.45 (d, *J* 8.4 Hz, 2H), 6.83 (d, *J* 4.4 Hz, 1H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.9, 144.3, 140.0, 135.6, 134.8, 131.0, 129.2, 127.7, 124.5, 123.4, 116.8, 104.6, 27.9; HRMS (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{15}H_{12}ClN_2O$ 271.0633, found 271.0638. Purification by flash chromatography on silica gel (hexanes:EtOAc, 7:3) afforded **4d'** (31 mg, 87%) as a yellow solid, mp 214.2-216.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (d, *J* 0.8 Hz, 1H), 8.26 (d, *J* 1.2 Hz, 1H), 7.86 (d, *J* 8.4 Hz, 2H), 7.43 (d, *J* 8.4 Hz, 2H), 7.39 (d, *J* 2.8 Hz, 1H), 7.25-7.26 (m, 1H), 2.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.2, 146.2, 139.3, 135.2, 134.9, 129.2, 127.7, 127.5, 118.0, 117.1, 115.6, 114.8, 28.2; HRMS (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{15}H_{12}ClN_2O$ 271.0633, found 271.0631.

1-(3-Methylpyrrolo[1,2-*a*]pyrazin-6-yl)ethanone (**4e**) **and 1-(3-methylpyrrolo[1,2-*a*]pyrazin-8-yl)ethanone** (**4e'**). Prepared from 3-methylpyrrolo[1,2-*a*]pyrazine (30 mg, 0.23 mmol), $AlCl_3$ (307 mg, 2.30 mmol), and acetyl chloride (163.5 µL, 2.30 mmol) using general procedure **A** for 3 h. Purification by flash chromatography on silica gel (hexanes:EtOAc, 9:1) afforded **4e** (5.2 mg, 13%) as a yellow solid, mp 86.3-89.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 8.94 (s, 1H), 7.44 (d, *J* 3.2 Hz, 1H), 6.74 (d, *J* 4.0 Hz, 1H), 2.58 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.6, 143.9, 139.9, 130.9, 123.7, 122.5, 117.5, 104.1, 27.8, 21.4; HRMS (ESI-QTOF) *m/z* $[M+Na]^+$ calcd for $C_{10}H_{10}N_2ONa$ 197.0685, found 197.0681. Purification by flash chromatography on silica gel (hexanes:EtOAc, 7:3) afforded **4e'** (26 mg, 66%) as a pale yellow solid, mp 166.2-168.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (s, 1H), 7.73 (s, 1H), 7.24 (br s, 1H), 7.17 (br s, 1H), 2.54 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.1, 145.8, 139.1, 127.4, 117.3, 116.6, 115.5, 114.5, 27.9, 21.0; HRMS (ESI-QTOF) *m/z* $[M+Na]^+$ calcd for $C_{10}H_{10}N_2ONa$ 197.0685, found 197.0685.

1-(1-Methyl-3-phenylpyrrolo[1,2-*a*]pyrazin-6-yl)ethanone (**4f**) **and 1-(1-methyl-3-phenylpyrrolo[1,2-*a*]pyrazin-8-yl)ethanone** (**4f'**)**.** Prepared from 1-methyl-3-phenylpyrrolo[1,2-*a*]pyrazine (30 mg, 0.14 mmol), $AlCl_3$ (187 mg, 1.40 mmol), and acetyl chloride (99.5 µL, 1.40 mmol) using general procedure **A** for 6 h. Purification by flash chromatography on silica gel (hexanes:EtOAc, 19:1) afforded **4f** (24 mg, 67%) as an orange solid, mp 157.6-159.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 8.01 (d, *J* 7.2 Hz, 2H), 7.46-7.50 (m, 3H), 7.37-7.41 (m, 1H), 6.78 (d, *J* 4.0 Hz, 1H), 2.83 (s, 3H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.7, 152.5, 140.7, 137.4, 130.7, 128.9, 128.5, 126.6, 124.8, 122.8, 115.2, 103.8, 27.9, 22.2; HRMS (ESI-QTOF) *m/z* $[M+Na]^+$ calcd for $C_{16}H_{14}N_2ONa$ 273.0998, found 273.0995. Purification by flash chromatography on silica gel (hexanes:EtOAc, 17:3) afforded **4f'** (2.3 mg, 6%) as an off-white solid, mp 123.6-125.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.94 (d, *J* 7.2 Hz, 2H), 7.45-7.49 (m, 2H), 7.38-7.41 (m, 2H), 7.26 (s, 1H), 3.06 (s, 3H), 2.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3, 169.3, 160.6, 155.2, 139.3, 136.8, 129.0, 128.7, 126.2, 118.9, 115.3, 112.9, 297, 26.5; HRMS (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}N_2O$ 251.1179, found 251.1177.

1-[3-(4-Chlorophenyl)-1-methylpyrrolo[1,2-*a*]pyrazin-6-yl]ethanone (**4g**)**.** Prepared from 3-(4-chlorophenyl)-1-methylpyrrolo[1,2-*a*]pyrazine (30 mg, 0.12 mmol), $AlCl_3$ (160 mg, 1.20 mmol), and acetyl chloride (85.3 µL, 1.20 mmol) using general procedure **A** for 2 h. Purification by flash chromatography on silica gel (hexanes:EtOAc, 9:1) afforded **4g** (27 mg, 77%) as a pale orange solid, mp 146.5-148.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.96 (d, *J* 8.4 Hz, 2H), 7.49 (d, *J* 4.8 Hz, 1H), 7.43 (d, *J* 8.8 Hz, 2H), 6.78 (d, *J* 4.4 Hz, 1H), 2.81 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.8, 152.6, 139.5, 135.9, 134.5, 130.7, 129.1, 127.7, 124.8, 122.9, 115.1, 103.9, 27.9, 22.1; HRMS (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{16}H_{14}ClN_2O$ 285.0789, found 285.0788.

1-(1,3-Dimethylpyrrolo[1,2-*a*]pyrazin-6-yl)ethanone (**4h**) **and 1-(1,3-dimethylpyrrolo[1,2-*a*]pyrazin-8-yl)ethanone** (**4h'**)**.** Prepared from 1,3-dimethylpyrrolo[1,2-*a*]pyrazine (30 mg, 0.21 mmol), $AlCl_3$ (280 mg, 2.10 mmol), and acetyl chloride (149.3 µL, 2.10 mmol) using general procedure **A** for 1 h. Purification by flash chromatography on silica gel (hexanes:EtOAc, 7:3) afforded **4h** (28.2 mg, 73%) as a white solid, mp 120.2-122.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.30 (s, 1H), 7.42 (d, *J* 4.4 Hz, 1H), 6.72 (d, *J* 4.4 Hz, 1H), 2.73 (s, 3H), 2.58 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.5, 152.1, 139.2, 130.4, 124.1, 122.0, 115.7, 103.6, 27.8, 21.9, 21.4; HRMS (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{11}H_{13}N_2O$ 189.1022, found 189.1023. Purification by flash chromatography on silica gel (hexanes:EtOAc, 3:2) afforded **4h'** (2.4 mg, 6%) as a white solid, mp 157.4-159.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.23 (d, *J* 2.8 Hz, 1H), 7.18 (d, *J* 2.8 Hz, 1H), 2.96 (s, 3H), 2.60 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.3, 154.9, 137.8, 127.5, 125.7, 118.4, 114.3, 113.7, 29.6, 26.1, 20.9; HRMS (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{11}H_{13}N_2O$ 189.1022, found 189.1021.

General procedure B. In a vial charged with DMF (1.5 mL) at 0 °C was added POCl3 (5 equiv) and the reaction mixture was stirred for 20 min. To this mixture was added, dropwise, pyrrolo[1,2-a]pyrazine (30 mg, dissolved in 0.5 ml DMF) at 0 °C. After being stirred at room temperature for 1-3 h, the reaction mixture was poured into ice-cold water and neutralized with aqueous NaHCO3 solution. The reaction mixture was extracted with ethyl acetate (5 mL× 2), washed with aqueous NaCl (5 mL × 2). The organic layers were dried over MgSO4 and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel (hexanes:ethyl acetate) afforded the corresponding products.

3-Phenylpyrrolo[1,2-*a*]pyrazine-6-carbaldehyde (**5a**) **and 3-phenylpyrrolo[1,2-*a*]pyrazine-8-carbaldehyde** (**5a'**). Prepared from 3-phenylpyrrolo[1,2-*a*]pyrazine (30 mg, 0.15 mmol), and $POCl_3$ (70 µL, 0.75 mmol) using general procedure **B** for 3 h. Purification by flash chromatography on silica gel (hexanes:EtOAc, 9:1) afforded **5a** (28.3 mg, 82%) as a pale yellow solid, mp 95.6-97.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 9.85 (s, 1H), 9.14 (s, 1H), 8.01 (d, *J* 8.0 Hz, 2H), 7.48-7.52 (m, 3H), 7.42 (t, *J* 6.8 Hz, 1H), 6.86 (d, *J* 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.8, 144.3, 141.7, 136.6, 131.8, 129.1, 128.9, 126.5, 126.0, 125.3, 116.7, 105.3; HRMS (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{14}H_{11}N_2O$ 223.0866, found 223.0870. Purification by flash chromatography on silica gel (hexanes:EtOAc, 4:1) afforded **5a'** (2 mg, 6%) as a brown solid, mp 144.4-146.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.13 (s, 1H), 9.65 (s, 1H), 8.34 (d, *J* 1.2 Hz, 1H), 7.94 (d, *J* 7.6 Hz, 2H), 7.41-7.52 (m, 4H), 7.35 (d, *J* 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.5, 144.8, 141.4, 129.6, 129.2, 129.1, 127.4, 126.4, 118.6, 117.1, 116.7, 115.2; HRMS (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{14}H_{11}N_2O$ 223.0866, found 223.0864.

3-(4-Methoxyphenyl)pyrrolo[1,2-*a*]pyrazine-6-carbaldehyde (**5b**) **and 3-(4-Methoxyphenyl)pyrrolo[1,2-*a*]pyrazine-8-carbaldehyde** (**5b'**)**.** Prepared from 3-(4-methoxyphenyl)pyrrolo[1,2-*a*]pyrazine (30 mg, 0.13 mmol) and $POCl_3$ (60.7 µL, 0.65 mmol) using general procedure **B** for 2 h. Purification by flash chromatography on silica gel (hexanes:EtOAc, 9:1) afforded **5b** (29 mg, 86%) as a yellow solid, mp 132.5-134.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 9.79 (s, 1H), 9.11 (s, 1H), 7.95 (d, *J* 8.8 Hz, 2H), 7.48 (d, *J* 4.8 Hz, 1H), 7.02 (d, *J* 8.8 Hz, 2H), 6.84 (d, *J* 4.4 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.7, 160.4, 144.2, 141.6, 131.7,

129.2, 127.8, 125.8, 125.1, 115.7, 114.5, 105.1, 55.5; HRMS (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{15}H_{13}N_2O_2$ 253.0972, found 253.0979. Purification by flash chromatography on silica gel (hexanes:EtOAc, 7:3) afforded **5b'** (3 mg, 9%) as a brown solid, mp 170.2-172.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (s, 1H), 9.62 (s, 1H), 8.26 (s, 1H), 7.88 (d, *J* 8.8 Hz, 2H), 7.43 (d, *J* 2.0 Hz, 1H), 7.33 (d, *J* 2.4 Hz, 1H), 7.02 (d, *J* 8.4 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.4, 164.2, 160.5, 144.6, 141.3, 129.0, 127.6, 118.5, 117.0, 116.5, 114.5, 114.1, 55.6; HRMS (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{15}H_{13}N_2O_2$ 253.0972, found 253.0974.

3-(4-Bromophenyl)pyrrolo[1,2-*a*]pyrazine-6-carbaldehyde (**5c**)**.** Prepared from 3-(4-bromophenyl)pyrrolo[1,2-*a*]pyrazine (30 mg, 0.11 mmol) and $POCl_3$ (51.4 µL, 0.55 mmol) using general procedure **B** for 1 h. Purification by flash chromatography on silica gel (hexanes:EtOAc, 19:1) afforded **5c** (27.6 mg, 83%) as a pale yellow solid, mp 132.6-135.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 9.85 (s, 1H), 9.12 (s, 1H), 7.89 (d, *J* 8.4 Hz, 2H), 7.61 (d, *J* 8.4 Hz, 2H), 7.51 (d, *J* 4.8 Hz, 1H), 6.87 (d, *J* 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 144.5, 140.5, 135.6, 132.2, 131.8, 127.9, 126.2, 125.4, 123.3, 116.6, 105.5; HRMS (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{14}H_{10}BrN_2O$ 300.9971, found 300.9967.

3-(4-Chlorophenyl)pyrrolo[1,2-*a*]pyrazine-6-carbaldehyde (**5d**)**.** Prepared from 3-(4-chlorophenyl)pyrrolo[1,2-*a*]pyrazine (30 mg, 0.13 mmol) and $POCl_3$ (60.7 µL, 0.65 mmol) using general procedure **B** for 1 h. Purification by flash chromatography on silica gel (hexanes:EtOAc, 9:1) afforded **5d** (32 mg, 95%) as a pale yellow solid, mp 123.9-125.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 9.83 (s, 1H), 9.11 (s, 1H), 7.95 (d, *J* 8.4 Hz, 2H), 7.51 (d, *J* 4.8 Hz, 1H), 7.46 (d, *J* 8.4 Hz, 2H), 6.86 (d, *J* 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 144.4, 140.5, 135.1, 135.0, 131.7, 129.2, 127.7, 126.1, 125.3, 116.6, 105.5; HRMS (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{14}H_{10}ClN_2O$ 257.0476, found 257.0480.

3-Methylpyrrolo[1,2-*a*]pyrazine-6-carbaldehyde (**5e**) **and 3-methylpyrrolo[1,2-*a*]pyrazine-8-carbaldehyde** (**5e'**). Prepared from 3-methylpyrrolo[1,2-*a*]pyrazine (30 mg, 0.23 mmol) and $POCl_3$ (107.5 µL, 1.15 mmol) using general procedure **B** for 2 h. Purification by flash chromatography on silica gel (hexanes:EtOAc, 9:1) afforded **5e** (29 mg, 80%) as a pale yellow solid, mp 105.8-107.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.85 (s, 1H), 9.25 (s, 1H), 8.97 (s, 1H), 7.42 (d, *J* 4.8 Hz, 1H), 6.78 (d, *J* 4.8 Hz, 1H), 2.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.6, 144.1, 140.6, 131.6, 125.3, 124.5, 117.5, 105.0, 21.2; HRMS (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_9H_9N_2O$ 161.0709, found 161.0715. Purification by flash chromatography on silica gel (hexanes:EtOAc, 4:1) afforded **5e'** (5 mg, 14%) as a yellow solid, mp 114.2-116.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 9.50 (s, 1H), 7.79 (s, 1H), 7.32 (d, *J* 2.0 Hz, 1H), 7.28 (d, *J* 2.0 Hz, 1H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.5, 144.6, 140.1, 127.7, 118.2, 116.9, 115.9, 115.8, 21.2; HRMS (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_9H_9N_2O$ 161.0709, found 161.0710.

1-Methyl-3-phenylpyrrolo[1,2-*a*]pyrazine-6-carbaldehyde (**5f**). Prepared from 1-methyl-3-phenylpyrrolo[1,2-*a*]pyrazine (30 mg, 0.14 mmol) and $POCl_3$ (65.4 µL, 0.70 mmol) using general procedure **B** for 2 h. Purification by flash chromatography on silica gel (hexanes:EtOAc, 9:1) afforded **5f** (22 mg, 65%) as a yellow solid, mp 137.4-139.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90 (s, 1H), 9.73 (s, 1H), 8.01 (d, *J* 8.0 Hz, 2H), 7.46-7.51 (m, 3H) 7.40 (t, *J* 7.2 Hz, 1H), 6.82 (d, *J* 4.0 Hz, 1H), 2.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.8, 152.7, 141.2, 136.9, 131.5, 128.9, 128.8, 126.5, 125.6, 115.0, 104.7, 22.2; HRMS (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{15}H_{13}N_2O$ 237.1022, found 237.1025.

Phenyl-(3-phenylpyrrolo[1,2-*a*]pyrazin-6-yl)methanone (**6a**) **and phenyl-(3-phenylpyrrolo[1,2-*a*]pyrazin-8-yl)methanone** (**6a'**). Prepared from 3-phenylpyrrolo[1,2-*a*]pyrazine (30 mg, 0.15 mmol), $AlCl_3$ (200 mg, 1.50 mmol), and benzoyl chloride (69.7 µL, 0.60 mmol) using general procedure **A** for 5 h. Purification by flash chromatography on silica gel (hexanes:EtOAc, 19:1) afforded **6a** (21.2 mg, 46%) as a yellow solid, mp 120.6-122.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.13 (s, 1H), 9.14 (s, 1H), 8.05 (d, *J* 8.0 Hz, 2H), 7.86 (d, *J* 8.4 Hz, 2H), 7.60 (t, *J* 7.2 Hz, 1H), 7.49-7.55 (m, 4H), 7.40-7.44 (m, 2H), 6.85 (d, *J* 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

186.2, 144.3, 141.3, 139.8, 137.1, 131.9, 131.7, 129.2, 129.0, 128.8, 128.6, 126.5, 126.0, 124.12, 117.0, 104.6; HRMS (ESI-QTOF) *m/z* $[M+Na]^+$ calcd for $C_{20}H_{14}N_2ONa$ 321.0998, found 321.0995. Purification by flash chromatography on silica gel (hexanes:EtOAc, 9:1) afforded **6a'** (15.3 mg, 33%) as a yellow solid, mp 183.6-185.2 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 8.32 (s, 1H), 7.94 (d, *J* 7.6 Hz, 2H), 7.88 (d, *J* 6.8 Hz, 2H), 7.58 (t, *J* 7.2 Hz, 1H), 7.47-7.53 (m, 4H), 7.39-7.44 (m, 2H), 7.21 (d, *J* 2.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.3, 146.1, 140.7, 139.9, 136.7, 131.8, 129.2, 129.1, 128.9, 128.5, 126.3, 119.7, 115.8, 115.6, 114.9; HRMS (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{15}N_2O$ 299.1179, found 299.1174.

(*E*)-3-(4-Methoxyphenyl)-1-(3-phenylpyrrolo[1,2-*a*]pyrazin-8-yl)prop-2-en-1-one (**7a**)**.** To a stirred mixture of 1-(3-phenylpyrrolo[1,2-*a*]pyrazin-8-yl)ethan-1-one (**4a**) (50 mg, 0.21 mmol) and 4-methoxybenzaldehyde (26 µL, 0.21 mmol) in ethanol (2 mL) was added NaOH (42 mg, 1.05 mmol) in water (2 mL) at room temperature. After being stirred at 60 °C for 16 h, the reaction mixture was cooled to rt and the precipitated product was suction-filtered to give **7a** as a yellow solid (72 mg, 96%). mp 192.2-193.6 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.92 (s, 1H), 8.30 (s, 1H), 7.94 (d, *J* 7.2 Hz, 2H), 7.84 (d, *J* 15.6 Hz, 1H), 7.62 (d, *J* 8.8 Hz, 2H), 7.49 (t, *J* 7.2 Hz, 2H), 7.44-7.36 (m, 4H), 6.94 (d, *J* 8.4 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.2, 161.5, 146.6, 142.4, 140.7, 136.7, 130.2, 129.1, 128.9, 128.7, 128.0, 126.3, 121.2, 117.9, 117.1, 115.6, 115.0, 114.5, 55.5; HRMS (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{19}N_2O_2$ 335.1441, found 335.1445.

(*E*)-3-(4-Chlorophenyl)-1-(3-phenylpyrrolo[1,2-*a*]pyrazin-8-yl)prop-2-en-1-one (**7b**). Prepared from 1-(3-phenylpyrrolo[1,2-*a*]pyrazin-8-yl)ethan-1-one (**4a**) (50 mg, 0.21 mmol), 4-chlorobenzaldehyde (30 mg, 0.21 mmol), and NaOH (42 mg, 1.05 mmol) in EtOH/water (1:1, 4 mL) using the same procedure as that for the synthesis of **7a**. Suction-filtration afforded **7b** as a yellow solid (66 mg, 88%). mp 218.3-218.8 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 8.32 (d, *J* 1.6 Hz, 1H), 7.94 (d, *J* 7.2 Hz, 2H), 7.81 (d, *J* 15.6 Hz, 1H), 7.59 (d, *J* 8.4 Hz, 2H), 7.50-7.38 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.6, 161.1, 146.3, 140.9, 136.5, 136.0, 133.6, 129.5, 129.2, 128.9, 128.8, 128.6, 126.2, 123.7, 117.3, 117.0, 115.6, 114.9; HRMS (ESI-QTOF) *m/z* $[M+Na]^+$ calcd for $C_{22}H_{15}ClN_2NaO$ 381.0765, found 381.0767.

(*E*)-3-(4-Methoxyphenyl)-1-(3-phenylpyrrolo[1,2-*a*]pyrazin-6-yl)prop-2-en-1-one (**8**)**.** To a stirred solution of 1-(3-phenylpyrrolo[1,2-*a*]pyrazin-6-yl)ethanone (**4a**) (50 mg, 0.21 mmol) in ethanol (3 mL) was added KOH (71 mg, 1.26 mmol) in water (0.5 mL) at room temperature. After 10 min, 4-methoxybenzaldehyde (28 µL, 0.23 mmol) was added to the reaction mixture. After being stirred at room temperature for 16 h, the reaction mixture was poured into ice-cold water, neutralized with 1M HCl, and extracted with ethyl acetate (5 mL × 2). The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel (hexanes:ethyl acetate, 4:1) gave **8** as a yellow solid (59 mg, 79%). mp 188.2-190.6 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.27 (s, 1H), 9.11 (s, 1H), 8.05 (d, *J* 7.6 Hz, 2H), 7.86 (d, *J* 15.6 Hz, 1H), 7.69 (d, *J* 4.4 Hz, 1H), 7.63 (d, *J* 8.4 Hz, 2H), 7.50 (t, *J* 7.6 Hz, 2H), 7.39-7.43 (m, 2H), 6.96 (d, *J* 8.4 Hz, 2H), 6.88 (d, *J* 4.0 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 161.7, 144.1, 142.6, 141.1, 137.1, 131.4, 130.3, 129.0, 128.7, 127.7, 126.5, 125.7, 122.3, 120.8, 117.3, 114.5, 104.8, 55.6; HRMS (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{23}H_{19}N_2O_2$ 355.1441, found 355.1442.

(*E*)-1-(4-Methoxyphenyl)-3-(3-phenylpyrrolo[1,2-*a*]pyrazin-6-yl)prop-2-en-1-one (**9**). Prepared from 3-phenylpyrrolo[1,2-*a*]pyrazine-6-carbaldehyde (**5a**) (50 mg, 0.22 mmol), KOH (74 mg, 1.32 mmol) in water (0.5 mL), and 4-methoxyacetophenone (36.3 mg, 0.24 mmol) using the same procedure as that for the synthesis of **8**. Purification by flash chromatography on silica gel (hexanes:EtOAc, 9:1) afforded **9** as a yellow solid (72 mg, 90%). mp 193.4-195.8 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, *J* 0.8 Hz, 1H), 8.49 (s, 1H), 8.22 (d, *J* 15.2 Hz, 1H), 8.08 (d, *J* 8.8 Hz, 2H), 7.96 (d, *J* 7.2 Hz, 2H), 7.57 (d, *J* 15.2 Hz, 1H), 7.50 (t, *J* 7.2 Hz, 2H), 7.41-7.44 (m, 2H), 7.00 (d, *J* 8.8 Hz, 2H), 6.91 (d, *J* 4.4 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.7, 163.6, 144.7,

139.9, 137.1, 131.3, 130.8, 130.6, 129.1, 128.8, 128.0, 126.3, 124.9, 118.6, 116.7, 114.0, 112.3, 106.3, 55.7; HRMS (ESI-QTOF) *m/z* $[M+Na]^+$ calcd for $C_{23}H_{18}N_2O_2Na$ 377.1260, found 377.1263.

4-(3-Phenylpyrrolo[1,2-*a*]pyrazin-6-yl)pyrrolo[1,2-*a*]quinoxaline (**10**). To a stirred solution of **5a** (50 mg, 0.22 mmol) in THF (2 mL) were added 2-(1*H*-pyrrol-1-yl)aniline (41.76 mg, 0.26 mmol) and *p*-dodecylbenezenesulfonic acid (DBSA) (14.36 mg, 0.04 mmol). After being stirred at 60 °C for 16 h, the reaction mixture was cooled to rt, diluted with ethyl acetate (5 mL), and washed with aqueous $NaHCO_3$ (5 ml × 2) and water (5 mL). The aqueous layer was extracted with ethyl acetate (5 mL) one more time. The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel (hexanes:ethyl acetate, 9:1) gave **10** as a yellow solid (61 mg, 75%). mp 170.7-173.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.12 (s, 1H), 9.06 (s, 1H), 8.00-8.03 (m, 4H), 7.91 (d, *J* 8.0 Hz, 1H), 7.74 (d, *J* 4.4 Hz, 1H), 7.48-7.57(m, 4H), 7.39 (t, *J* 7.2 Hz, 1H), 7.24 (d, *J* 4.0 Hz, 1H), 6.96-6.99 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 144.5, 138.8, 138.0, 135.6, 130.2, 129.7, 128.9, 128.2, 127.6, 126.9, 126.3, 125.6, 124.7, 123.1, 119.8, 116.2, 115.0, 114.3, 113.9, 108.2, 104.5; HRMS (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{24}H_{17}N_4$ 361.1448, found 361.1443.

2-(3-Phenylpyrrolo[1,2-*a*]pyrazin-6-yl)benzoxazole (**11**)**.** To a stirred solution of **5a** (50 mg, 0.22 mmol) in ethanol (3 mL) were added 2-aminophenol (48 mg, 0.44 mmol) and *p*-dodecylbenezenesulfonic acid (7.18 mg, 0.02 mmol). After being stirred at 60 °C for 16 h, the reaction mixture was cooled to rt, diluted with ethyl acetate (5 mL), and washed with aqueous $NaHCO_3$ (5 ml × 2) and water (5 mL). The aqueous layer was extracted with ethyl acetate (5 mL) one more time. The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel (hexanes:ethyl acetate, 19:1) furnished the Schiff base product as a yellow solid (59 mg, 84%). To this Schiff base product (59 mg, 0.19 mmol) in CH_2Cl_2 (3 mL) was added DDQ (65 mg, 0.29 mmol). After being stirred at room temperature for 2 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and washed with aqueous Na_2CO_3 (5 mL × 3) and water (5 mL × 2). The aqueous layer was extracted with ethyl acetate (5 mL) one more time. The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give the crude product. Purification by flash chromatography on silica gel (hexanes:ethyl acetate, 49:1) afforded **11** as a pale yellow solid (50 mg, 85%). mp 206.2-208.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 9.08 (s, 1H), 8.09 (d, *J* 8.0 Hz, 2H), 7.82 (d, *J* 7.2 Hz, 1H), 7.70 (d, *J* 4.4 Hz, 1H), 7.53-7.60 (m, 3H), 7.36-7.46 (m, 3H), 6.96 (d, *J* 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 149.5, 144.3, 142.3, 140.1, 137.5, 130.7, 129.0, 128.6, 126.6, 125.0, 124.8, 119.8, 119.2, 116.1, 114.8, 110.4, 105.0; HRMS (ESI-QTOF) *m/z* $[M+H]^+$ calcd for $C_{20}H_{14}N_3O$ 312.1131, found 312.1136.

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Supplementary Material

^{1}H and ^{13}C NMR spectra of synthesized compounds, and a CIF file for **4a'.** Readers will be able to access supporting information using the link "Supplementary Material" in the journal issue contents page.

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