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Synthesis of Kappa Opioid Antagonists Based On Pyrrolo[1,2-α]quinoxalinones Using an *N*-Arylation/Condensation/Oxidation Reaction Sequence

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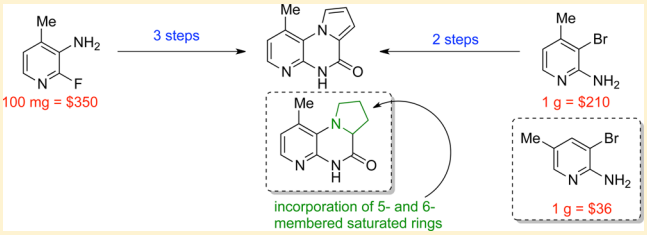
Supporting Information

ABSTRACT: The quinoxaline and quinoxalinone family of nitrogen heterocycles is present in molecules of therapeutic relevance for diverse applications ranging from infectious diseases to neuroscience targets. Here, we describe a general synthetic sequence to afford pyrrolo[1,2-α]quinoxalinones from commercially available starting materials and their use in preparing potential kappa opioid receptor antagonists. The biological data obtained from the latter set of compounds is briefly presented and discussed.



The pyrrolo[1,2-α]quinoxaline and pyrrolo[1,2-α]-quinoxalinone cores are nitrogen-rich heterocycles that are known to appear in bioactive molecules, including serotonin (5-HT_3) receptor agonists,[1] kappa opioid receptor (KOR) antagonists,[2] HCV inhibitors,[3] HIV-1 reverse transcriptase inhibitors,[4] antipsychotic agents,[5] and PARP-1 inhibitors[6] (Figure 1). Despite this, there are surprisingly few synthetic routes leading to the pyrrolo[1,2-α]quinoxalinone core.[7] Even fewer strategies currently exist for the construction of the pyrido[2,3-*e*]pyrrolo[1,2-α]pyrazinone ring system as found in molecules such as ML190.[2]

The most widely utilized and comprehensive methods for pyrrolo[1,2-α]quinoxalinone construction are illustrated in Figure 2. The classical method for the preparation of pyrrolo[1,2-α]quinoxalinone includes pyrrole formation (Clauson−Kaas variant of the Paal−Knorr pyrrole synthesis),[8] nitro group reduction or nucleophilic aromatic substitution with ammonia, and cyclization with triphosgene (Figure 2a).[2,9] Although straightforward, this method depends on the availability of nitroaniline or fluoroaniline substrates and utilizes the toxic reagent triphosgene. Recent alternatives introduced include a palladium-catalyzed intramolecular *N*-arylation (Figure 2b).[10] The limitations to this method are that the amide starting materials are generally noncommercial and that only *N*-alkylated amides work. The reaction of 1,2-dihalobenzenes or 2-halonitroarenes with pyrrole-2-carboxamides allows the direct synthesis of this core, but relatively few of these methods have been applied to heterocycles (one such example is drawn in Figure 2c).[11] As in the previous method, the requirement for *N*-aryl or -alkyl substitution limits utility. In 2009, Yuan and Ma reported a one-pot coupling/hydrolysis/condensation sequence of 2-halotrifluoroacetanilides with pyrrole-2-carboxylate esters (Figure 2d).[12] Although this method offers a convenient approach to access pyrrolo[1,2-α]quinoxalinones, limitations include starting material availability and few reported examples containing heterocycles on the western portion of the tricyclic ring system.

As part of a synthetic program toward KOR antagonists, we identified ML190 (Figure 1) as a lead structure. As we embarked on an analog campaign based on this compound, it became clear that more general ways of making the key ring system were needed. In this paper, we describe (1) the versatile synthesis of pyrrolo[1,2-α]quinoxalinones and novel quinoxalinones containing a pyridine moiety in the western portion of the core and (2) the construction and screening of an analogue library as KOR antagonists.

Unlike previous routes to construct pyrrolo[1,2-α]-quinoxalinones from pyrrole-containing substrates, we considered that the pyrrole could be obtained after the skeletal framework was constructed via oxidation of the saturated system (Figure 3b). This would permit the use of commercially available precursors (aminopyridines) to generate unprotected amide products that are not generally tolerated under the previously reported methodologies. To this end, we noted a one-pot copper-catalyzed protocol reported by Tanimori and colleagues for the synthesis of substituted quinoxalinones utilizing haloanilines and various amino acid precursors (Figure 3a).[13,14] Although the majority of the derivatives investigated

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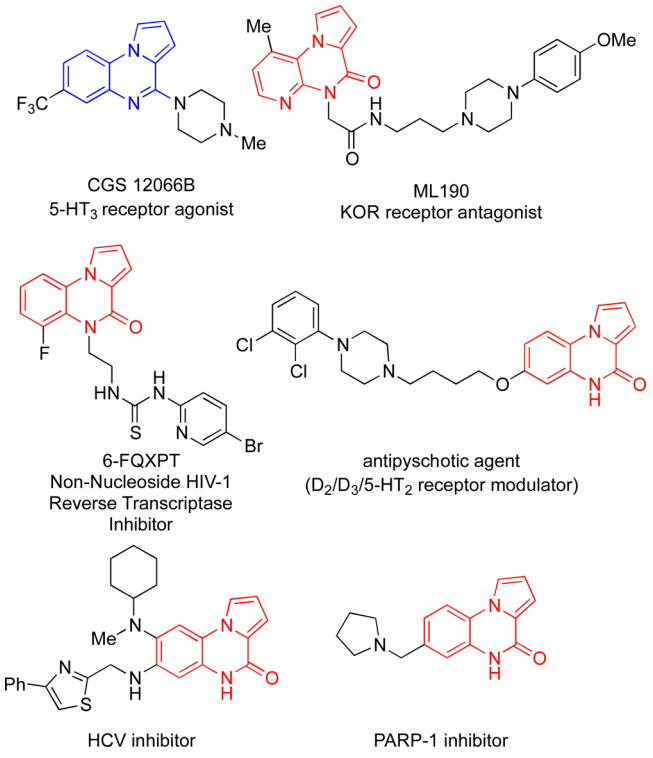

Figure 1. Representative examples of bioactive pyrrolo[1,2-α]-quinoxaline (blue) and pyrrolo[1,2-α]quinoxalinone (red) derivatives.

by Tanimori used a carbocyclic bromoaniline for the electrophile, they also included a few 2-amino-3-bromopyridines.

With this background, we considered a two-step protocol that begins with copper-catalyzed Ullmann *N*-arylation and intramolecular condensation of readily available 2-amino-3-bromopyridines and L-proline followed by oxidation to afford the pyrrole ring. We were particularly encouraged by the commercial availability of a range of substituted 2-amino-3-bromopyridines in contrast to the meager availability of substituted 3-amino-2-fluoropyridines utilized in our prior route (Figure 2a).[2] We note that this route makes it easy to incorporate different amino acids into the sequence, which is useful in analogue synthesis campaigns.

We first determined that a small variation of Tanimori's previously reported conditions allowed us to replace pipecolic acid with L-proline as the substrate. Specifically, we found that potassium phosphate (2 equiv) as the base, the inclusion of substoichiometric TMEDA or DMEDA as chelator, reaction temperature of 130 °C for 24−48 h, and degassing solvent improved the overall yield and reduced side product formation for the two-step process. In this way, three representative pyridines **1**−**3** were converted to **4**−**6** in 55−79% yields (Scheme 1).

We next set out to effect the pyrrolidine to pyrrole oxidation. To that end, we screened a variety of oxidants, including sodium hypochlorite, DDQ,[15] Dess−Martin periodinane, in situ-generated IBX,[16] and Pd/C in cyclohexene.[17] Ultimately, we settled upon MnO_2, which afforded the pyrrole product in higher conversion and with fewer of the uncharacterized side products observed with other dehydrogenation conditions. With a viable oxidant in hand, we next screened several solvents (xylene, EtOH, DCM, and THF) and found that significant product formation occurred only in refluxing THF. After product isolation, it was noted that the desired product was

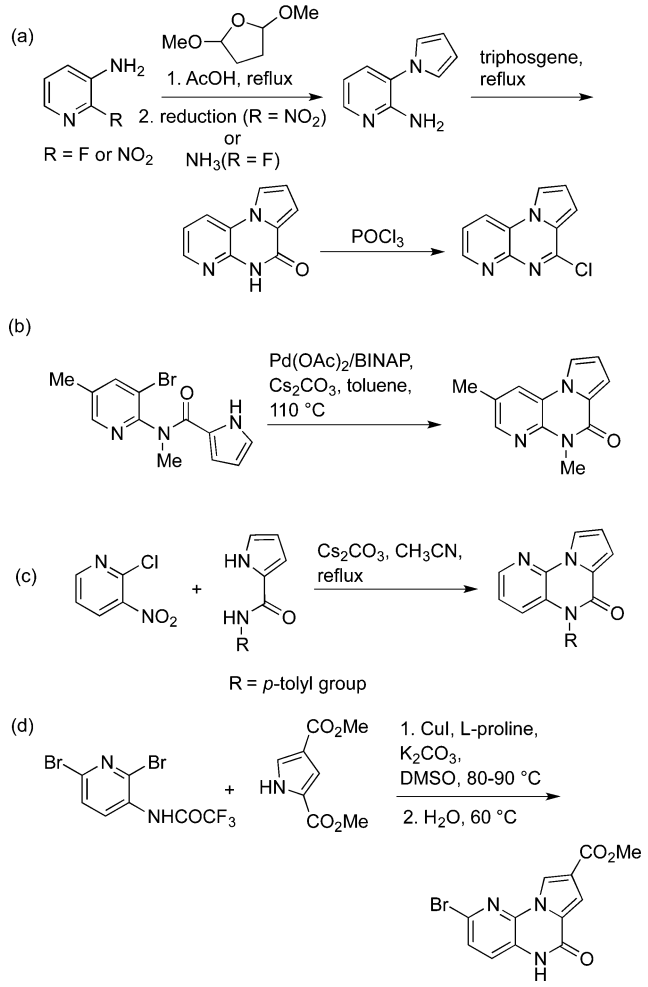

Figure 2. Representative methods for the synthesis of pyrrolo[1,2-α]quinoxalinones with demonstrated applications toward pyrido[2,3-*e*]pyrrolo[1,2-α]pyrazinone analogues.

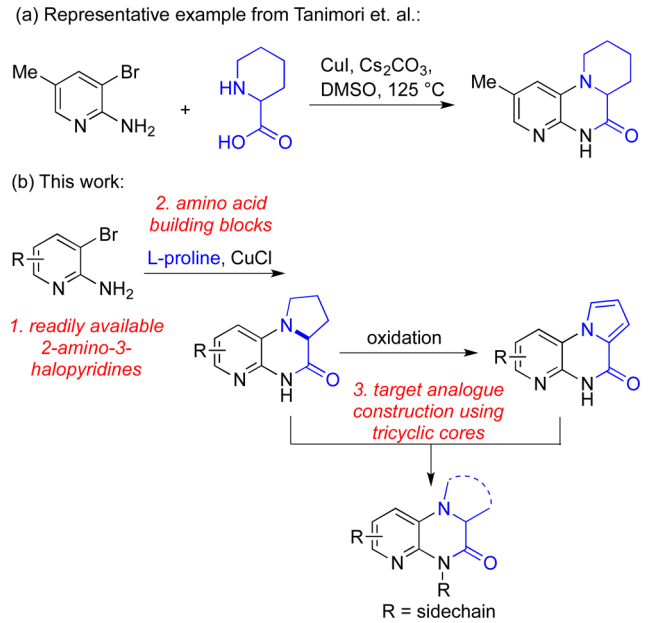

Figure 3. (a) Tanimori's one-pot synthesis of quinoxalinones.[13,14] (b) Our strategy to construct pyrido[2,3-*e*]pyrrolo[1,2-α]pyrazinones including inherent diversity opportunities highlighted in red.

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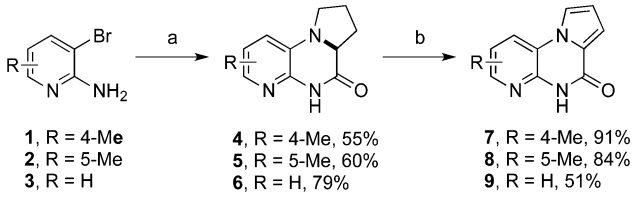
Scheme 1[a]



[a]Reagents and conditions: (a) L-Proline, CuCl, DMEDA, K_3PO_4, DMSO, 115 °C—130 °C; (b) MnO_2, THF, reflux.

insoluble in most organic solvents at room temperature (e.g., THF, EtOAc, DCM, MeOH, and EtOH). Taking this into consideration, the overall reaction yield of **7** was significantly improved (from 41 to 91%) by using hot THF (70 °C) during filtration to remove the solid oxidant upon reaction completion. Applying these conditions to **5** and **6** afforded the corresponding pyrroles **8** and **9** in 84 and 51% yields, respectively (Scheme 1).

The optimized conditions for the synthesis of **4** were applied to a survey of pyridine and amino acid components (Figure 4).

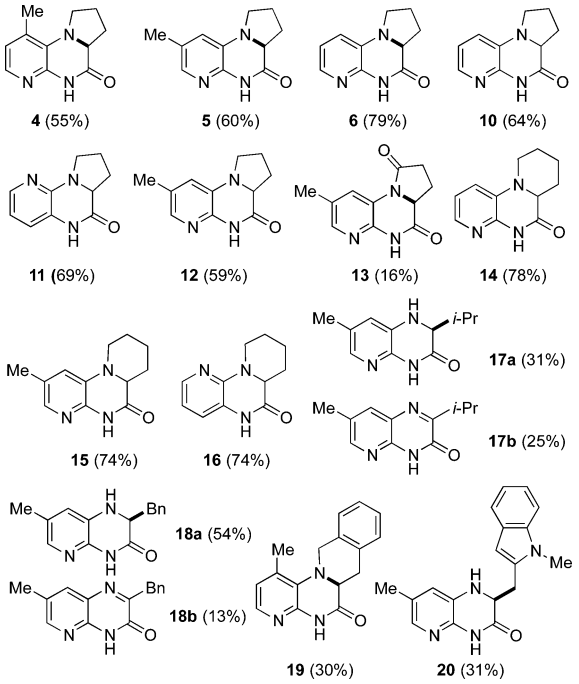
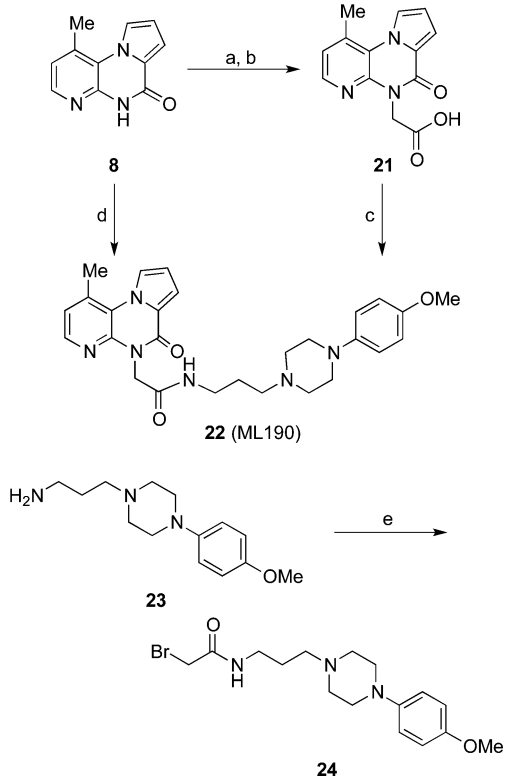


Figure 4. Structures and yields of reaction products obtained for a range of 2-amino-3-bromopyridines and 2-bromo-3-aminopyridines and amino acid components. Yields refer to reactions carried out using CuCl, DMEDA, K_3PO_4, DMSO, 115−130 °C, except for **11**, which was made using Tanimori's conditions (CuI and Cs_2CO_3).[13] Stereochemistry is shown for enantiomerically pure products; others are racemic.

The results show good tolerance to a variety of amino acid substitutions and gave acceptable yields with both substituted and unsubstituted pyridine components. Even though in some cases the overall yield was modest (e.g., **13**, **17**, **19**, and **20**), reaction optimization has not been done for those substrate combinations, and the reaction afforded sufficient material (>25 mg) for derivatization to final analogues. Interestingly, it was observed that for both substrates **17** and **18** two products were isolated from the reaction mixtures. In addition to obtaining the desired products (**17a** and **18a**), the oxidized quinoxalones (**17b** and **18b**) were also isolated, which to our knowledge has not been previously reported using these reaction conditions.

To illustrate the value of these compounds in medicinal chemistry discovery, we used the above building blocks in the syntheses of candidate KOR antagonists using the methods shown in Scheme 2 (specifically illustrated for ML190 (**22**);

Scheme 2[a]



[a]Reagents and conditions: (a) NaH, ethyl 2-bromoacetate, DMF, 73% yield; (b) LiOH, MeOH:H_2O:THF (1:1:4), 73% yield; (c) DIC, DMAP, **23**, 21% yield; (d) NaH, **24**, DMF, 22% yield; (e) 2-bromoacetyl bromide, DCM, 0 °C, 1 h, 57% yield

details and yields for other examples are provided in the Supporting Information). The final analogues synthesized are summarized in Figure 5.

We assessed KOR antagonism using one of two methods (Table 1). In the first, a standard GTPγS assay[18,19] provided IC_{50} values from concentration-response curves (**25**−**30**) with our lead compound ML190 (**22**) provided for comparison. Alternatively, three-point screens using the Cellomics β-arrestin recruitment assay (**31**−**33**) provided values that are expressed as % U69,593 maximum stimulation remaining at given concentrations. We investigated analogues that retained the side chain from ML190 (**22**) as well as side chains inspired by the known KOR antagonist JDTic (**32** and **33**). The results indicate that the pyrrole is crucial for KOR antagonist activity as the unoxidized analogues were significantly less potent than the corresponding pyrroles (cf. **22** (ML190) vs **26** and **27**). Furthermore, analogues that more closely resembled ML190 (**22**) such as **25** were more potent than the exploratory analogues. Disappointingly, none of the exploratory directions resulted in improved KOR antagonism either on the core scaffold (**26**−**31**) or on the side chain (**32**−**33**). Accordingly,

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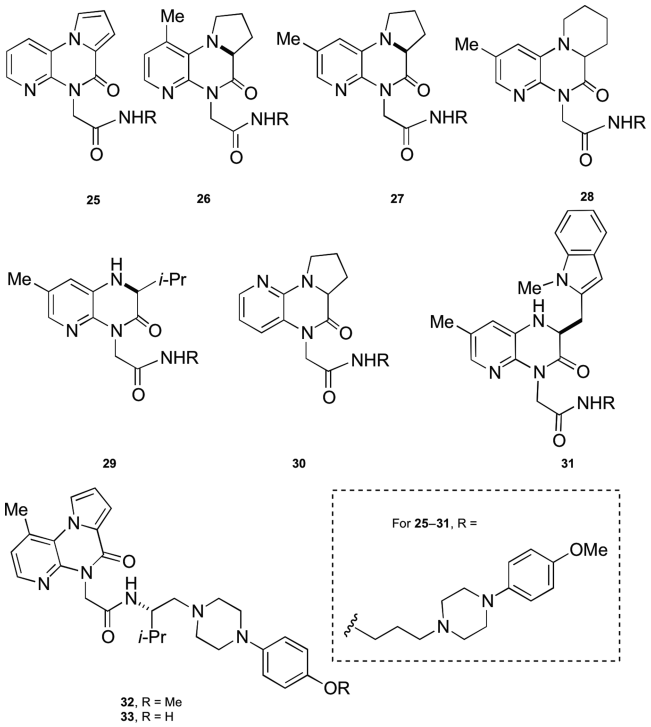

Figure 5. Compounds prepared according to the protocols in Scheme 2 and assayed for KOR antagonist activity (see Supporting Information for synthetic details). Note: compound **25** was prepared as previously described.[2]

Table 1. KOR Antagonist Activity of ML190 Analogues Prepared[a]

	KOR antagonist activity			
		% U69,593 maximum stimulation remaining[f]		
cmpd	IC_{50} (μM)[b]	1 μM cmpd	100 nM cmpd	10 nM cmpd
norBNI	0.0003	0.9	0.6	0.1
22 (ML190)	0.148			
25[c]	0.173			
26	2.82			
27	2.62			
28	0.906			
29	0.433			
30[d]	NC (85.7)[e]			
31[d]		0.5	94.8	85.5
32		65.7	64.9	73.7
33		58.4	90.6	94.3

[a]Each compound was examined by one of two different methods. [b]GTPγS assay, concentration-response curve. [c]Synthesized previously and retested with our new analogues.[2] [d]NC = not converged at 10 μM. [e]Imax % U69,593 remaining. [f]β-arrestin recruitment (Cellomics assay platform), % U69,593 maximum stimulation remaining at concentration of test compound listed. U69,593 KOR EC_{50} = 68 nM.[19]

no attempt was made to compare compound activities prepared by the two different techniques. Nonetheless, the analogues possess interesting architectures and were synthesized in sufficient quantity to allow inclusion in future screening campaigns for nonopioid targets.

CONCLUSIONS

In conclusion, we have reported an efficient synthesis of pyridopyrrolo[1,2-α]quinoxalinones and pyridoquinoxalinones from commercially available fragments. This methodology enabled rapid access to a library of core structures that were further converted to final analogue compounds. A representative set of analogues were assayed for KOR antagonism, which provided additional structure-activity relationships in this chemotype and provided analogues not accessible via prior synthetic routes. Although none of the exploratory directions presented here benefitted the KOR antagonism, the synthetic route enabled construction of analogues with new structural motifs that were synthesized in sufficient quantity to allow inclusion in future screening campaigns for nonopioid targets.

EXPERIMENTAL SECTION

General Information. Reactions were performed under an argon atmosphere in flame-dried glass 2.0−5.0 mL microwave reaction vials, 8 mL (2 dram) or 20 mL reaction vials, or round-bottom flasks sealed with a rubber sleeve-type septa and argon balloon. All chemicals were used as received from a commercial source without further purification except for CuCl, which was purified by precipitation from a concentrated HCl solution by dilution with water and filtration.[20] Thin-layer chromatography (TLC) was performed using commercial silica gel 60 F254-coated aluminum-backed sheets. Visualization was accomplished with UV light (254 nm) and iodine vapor chamber or *p*-anisaldehyde staining by heating. Purification was carried out on an automated flash chromatography/medium-pressure liquid chromatography (MPLC) system using normal-phase silica flash columns (4, 12, or 24 g). Infrared spectra were acquired as films or solids. All nuclear magnetic resonance spectra (^{1}H, ^{13}C, and APT) were recorded on a 400 MHz, a 500 MHz with a dual carbon/proton cryoprobe, or 600 MHz with a dual carbon/proton cryoprobe instrument. NMR samples were recorded in deuterated chloroform ($CDCl_3$) or deuterated dimethyl sulfoxide (DMSO-d_6). Chemical shifts are reported in parts per million (ppm) and are referenced to the center line of the solvent ($CDCl_3$: δ 7.26 ppm for ^{1}H NMR and 77.23 for ^{13}C NMR: δ 5.32 ppm for ^{1}H NMR and 54.00 for ^{13}C NMR; DMSO-d_6: δ 2.50 ppm for ^{1}H NMR and 39.52 for ^{13}C NMR). Coupling constants are given in hertz (Hz). HRMS data were collected with a time-of-flight mass spectrometer and an electrospray ion source (ESI). Melting points were determined in open capillary tubes using an automated melting point apparatus and are uncorrected. Microsyringes were used to deliver volumes between 1.00 and 200.00 μL. Spectroscopic data for the known compounds prepared according to the methodology described in the paper match with those reported in the literature.

General Procedure A for *N*-Arylation/Condensation. Following Tanimori's reaction procedure[14] with modification, this procedure describes reaction conditions for larger scale setups (≥299 mg, 1.601 mmol of aminopyridine substrate). To a flame-dried and argon-purged round-bottom flask was added anhydrous DMSO. The solvent was sparged with argon while vigorously stirring for 2−4 h and used in the following procedure. To a 2-neck flame-dried and argon-purged round-bottom flask fitted with an inlet thermometer was added freshly purified and dried CuCl (0.107 mmol, 0.20 equiv) followed by argon-sparged DMSO (112 mmol, 105 equiv). This CuCl solution was sparged for 15 min while stirring. To the CuCl solution was then added TMEDA or DMEDA (0.214 mmol, 0.20 equiv) via microsyringe followed by anhydrous degassed DMSO (35.2 mmol, 32.9 equiv). This mixture was stirred at rt while degassing for 1 h. To this mixture was then added potassium phosphate (2.14 mmol, 2.0 equiv) followed by aminopyridine (1.07 mmol, 1.0 equiv) and then amino acid (2.14 mmol, 2.0 equiv). The walls of the flask were washed with additional DMSO (28.2 mmol, 26.4 equiv), and the reaction mixture was stirred while sparging for an additional 30 min. Then, the reaction flask was fitted with a dried reflux condenser, purged with argon, and heated to 115 or 125 °C under an argon balloon. The reaction was monitored by TLC (70:30 EtOAc/hexanes and stained with iodine vapors and *p*-anisaldehyde). After stirring for 12−48 h, the reaction mixture was cooled to rt and transferred to a 500 mL Erlenmeyer flask with a large stir bar. To the Erlenmeyer solution was added 250 mL of

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EtOAc, and this solution was stirred for 15 min at rt. After 15 min, the solution was transferred to a 1000 mL separatory funnel, and the organic layer was washed with water (10 × 10 mL) and brine (3 × 10 mL). The organic layer was collected, dried over Na_2SO_4, and concentrated to give the crude product as an oily residue. The crude product was dissolved in a minimal amount of DCM and MeOH and adsorbed onto Celite by removal of solvents. The Celite was loaded into a sample cartridge and used for automated MPLC purification. Purification was carried out using a 24 g normal-phase silica flash column on an automated MPLC system with a gradient elution from 0 to 100% EtOAc/hexanes over 30−50 min. Concentration of appropriate fractions afforded desired products.

General Procedure B for *N*-Arylation/Condensation. Following Tanimori's reaction protocol[14] with modifications, this general procedure describes our most optimized reaction conditions. To a flame-dried and argon-purged round-bottom flask was added anhydrous DMSO. The solvent was sparged with argon while vigorously stirring for 2−4 h and used in the following procedure. A flame-dried and argon-purged glass 2.0−5.0 mL microwave reaction vial was fitted with a rubber sleeve-type septa and argon balloon. To the microwave vial were added CuCl (0.035 mmol, 0.10 equiv) followed by the anhydrous sparged DMSO (36.4 mmol, 105 equiv). The CuCl solution was sparged with argon for 15 min, and then DMEDA (0.069 mmol, 0.20 equiv) was added via microsyringe. This solution was then sparged while vigorously stirring for 2−4 h. It is noted that a color change of solution from pale yellow → green → dark green → dark blue green → bright blue was observed while sparging (Figure S34). After the solution became a bright blue or dark blue green color, potassium phosphate (0.694 mmol, 2 equiv) was added to the catalyst and ligand solution, followed by aminopyridine (0.347 mmol, 1.0 equiv) and then amino acid (0.694 mmol, 2 equiv). The walls of the reaction vial were washed with DMSO (9.02 mmol, 26 equiv), and the reaction mixture with all reagents was sparged for an additional 30 min. The solutions were typically cloudy and blue or lavender in color. After 30 min, the needle was raised out of the solution, and the vial was heated to 130 °C under an argon atmosphere (balloon). The reaction was monitored by TLC (70:30 EtOAc/hexanes and stained with iodine vapors and *p*-anisaldehyde). After stirring for 48 h, the reaction mixture was cooled to rt and transferred to a 250 mL Erlenmeyer flask with a large stir bar. To the Erlenmeyer solution was added 150 mL of EtOAc, and this solution was stirred for 15 min at rt. Then, the solution was transferred to a 250 mL separatory funnel, and the organic layer was washed with water (10 × 5 mL) and brine (3 × 5 mL). The organic layer was collected, dried over Na_2SO_4, and concentrated to give the crude product as an oily residue. The crude product was dissolved in a minimal amount of DCM and MeOH and adsorbed onto Celite by removal of solvents. The Celite was loaded into a sample cartridge and used for automated MPLC purification. Purification was carried out using a 12 g normal phase silica flash column on an automated MPLC system with a gradient elution from 0 to 100% EtOAc/hexanes over 30−50 min. Concentration of appropriate fractions afforded desired products.

General Procedure C for *N*-Arylation/Condensation. Following Tanimori's original reaction procedure,[13] this procedure describes our least optimized reaction conditions. To a flame-dried and argon-purged round-bottom flask was added anhydrous DMSO. The solvent was sparged with argon while vigorously stirring for 2−4 h and used in the following procedure. To a flame-dried and argon-purged glass 20 mL reaction vial fitted with rubber sleeve-type septa and argon balloon were added 2-bromopyridin-3-amine (1.43 mmol, 1.0 equiv), DL-proline (3.01 mmol, 2.1 equiv), cesium carbonate (2.15 mmol, 1.5 equiv), and CuI (0.143 mmol, 0.10 equiv). To this was then added DMSO (4.72 mL), and the reaction mixture was deoxygenated for 40 min by sparging with an argon balloon. The reaction mixture was then heated to 120 °C with vigorous stirring and monitored by TLC (10:90 EtOH/EtOAc; staining with *p*-anisaldehyde). It was observed that after 5 h the 2-bromopyridin-3-amine was completely consumed. The mixture was cooled to rt (mixture was dark black) and treated with saturated aqueous ammonium chloride (25 mL) and then transferred to a 125 mL separatory funnel. The aqueous solution was extracted with EtOAc (3 × 40 mL). The organic layers were combined, washed with brine (3 × 30 mL), dried over Na_2SO_4, and concentrated to dryness. The crude product was dissolved in a minimal amount of DCM and MeOH and adsorbed onto Celite by removal of solvents. The Celite was loaded into a sample cartridge and used for automated MPLC purification. Purification was carried out using a 12 g normal-phase silica flash column on an automated MPLC system with a gradient elution from 0 to 100% EtOAc/hexanes or 0 to 50% MeOH/DCM over 30−50 min. Concentration of appropriate fractions afforded desired products.

General Procedure for MnO_2 Oxidation. To a flame-dried and argon-purged round-bottom flask was added pyrrolidine substrate (2.89 mmol, 1.0 equiv) followed by activated manganese(IV) oxide (10 or 12 equiv). The reaction vessel was slowly purged with argon and to this vessel was then added anhydrous THF (488 mmol, 169 equiv). The round-bottom flask was then fitted with an oven-dried reflux condenser and heated to reflux (80 °C) under argon. The reaction was monitored by TLC (60:40 EtOAc/hexanes) and UPLC (reverse phase; basic mobile phase) for consumption of the starting material. After refluxing overnight, the reaction mixture was filtered hot through a 1 in. pad of Celite. The Celite was washed with fresh hot THF (70 °C; 4 × 50 mL). The filtrate was concentrated to give the crude product as a sand-like solid that was insoluble in THF without heating. The Celite from the filtration was placed into a round-bottom flask and heated to 80 °C to extract any additional compound left on the Celite. After stirring for 15 min, the mixture was then filtered using a Büchner funnel and filter paper. The Celite and filter paper was then washed with additional fresh hot THF (70 °C; 5 × 50 mL). The filtrate was combined to the previous filtrate to obtain the title compound as a sand-like solid, which was used without further purification. If purification was needed, the crude products were purified by MPLC. The crude product was dissolved in a minimal amount of warm THF (50 °C) and adsorbed onto Celite by removal of solvent. The Celite was loaded into a sample cartridge and used for automated MPLC purification. Purification was carried out using a 4 or 12 g normal-phase silica flash column on an automated MPLC system with a gradient elution from 0 to 50% DCM/MeOH over 30−50 min. Concentration of appropriate fractions afforded desired products as sand-like powders.

(S)-1-Methyl-6a,7,8,9-tetrahydropyrido[2,3-e]pyrrolo[1,2-a]-pyrazin-6(5H)-one ***4***. Following *N*-arylation/condensation procedure A, CuCl (5.3 mg, 0.535 mmol, 0.10 equiv), TMEDA (160 μL, 1.069 mmol, 0.20 equiv), 3-bromo-4-methylpyridin-2-amine (1.0 g, 5.35 mmol, 1.0 equiv), L-proline (1.23 g, 10.69 mmol, 2.0 equiv), and potassium phosphate (2.3 g, 10.69 mmol, 2.0 equiv) in DMSO (17.4 mL) were reacted at 115 °C for 12 h. Following column chromatography (0 to 90% EtOAc/hexanes), **4** was isolated in 55% yield (603 mg, 2.96 mmol) as a pale yellow fine powder; dec 210−214 °C. R_f = 0.37 (70% EtOAc/hexanes). IR (neat) 3040, 2920, 1680, 1463, 1384, 1265, 832 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6) δ 10.71 (s, 1H), 7.75 (d, J = 5.0 Hz, 1H), 6.82 (d, J = 5.0 Hz, 1H), 3.85 (dd, J = 8.2, 2.4 Hz, 1H), 3.55 (dt, J = 9.0, 7.1 Hz, 1H), 2.90 (td, J = 8.5, 4.8 Hz, 1H), 2.47 (tt, J = 5.7, 1.9 Hz, 1H), 2.25 (s, 3H), 2.14−2.04 (m, 1H), 1.89 (dt, J = 11.7, 4.0 Hz, 1H), 1.73−1.52 (m, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 169.2, 144.4, 140.6, 138.3, 128.7, 120.8, 59.4, 52.8, 27.0, 24.0, 17.6. HRMS (ESI-TOF) calcd for $C_{11}H_{13}N_3O_1Na$ $[M + Na]^+$: 226.0951, found 226.0951.

(S)-2-Methyl-6a,7,8,9-tetrahydropyrido[2,3-e]pyrrolo[1,2-a]-pyrazin-6(5H)-one ***5***. Following *N*-arylation/condensation procedure B, CuCl (3.2 mg, 0.032 mmol, 0.10 equiv), DMEDA (6.9 μL, 0.064 mmol, 0.2 equiv), 3-bromo-5-methylpyridin-2-amine (60 mg, 0.321 mmol, 1.0 equiv), L-proline (74 mg, 0.642 mmol, 2.0 equiv), and potassium phosphate (112 mg, 0.642 mmol, 2.0 equiv) in DMSO (3 mL) were reacted at 130 °C for 48 h. Following column chromatography (0 to 90% EtOAc/hexanes), **5** was isolated in 60% yield (39 mg, 0.193 mmol) as a pale yellow fluffy powder; dec 199−213 °C. R_f = 0.37 (70% EtOAc/hexanes). IR (neat) 3037, 2980, 2920, 2853, 1672, 1598, 1450, 1385 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6) δ 10.63 (s, 1H), 7.44 (d, J = 1.8 Hz, 1H), 6.73 (d, J = 1.8 Hz, 1H), 3.70 (dd, J = 9.4, 6.6 Hz, 1H), 3.37 (t, J = 4.6 Hz, 1H), 3.22−3.05 (m, 1H),

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2.18 (s, 3H), 2.15−2.07 (m, 1H), 2.03−1.81 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.6, 140.2, 135.5, 130.4, 127.7, 118.2, 59.6, 45.7, 26.6, 21.7, 17.6. HRMS (ESI-TOF) calcd for $C_{11}H_{14}N_3O_1$ $[M + H]^+$: 204.1131, found 204.1131.

(S)-6a,7,8,9-Tetrahydropyrido[2,3-e]pyrrolo[1,2-a]pyrazin-6(5H)-one ***6***. Following *N*-arylation/condensation procedure A, CuCl (46 mg, 0.464 mmol, 0.10 equiv), TMEDA (139 μL, 0.927 mmol, 0.20 equiv), 3-bromopyridin-2-amine (1.0 g, 5.35 mmol, 1.0 equiv), L-proline (1.2 g, 10.69 mmol, 2.0 equiv), and potassium phosphate (1.9 g, 9.27 mmol, 2.0 equiv) in DMSO (14 mL) were reacted at 115 °C for 12 h. Following column chromatography (0 to 100% EtOAc/hexanes), **6** was isolated in 79% yield (692 mg, 3.65 mmol) as a dark gold-yellow fine powder; dec 190−192 °C. R_f = 0.33 (70% EtOAc/hexanes). IR (neat) 3123, 3049, 2916, 2849, 1674, 1589, 1469, 1288, 753 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.74 (s, 1H), 7.61 (dd, J = 4.2, 2.2 Hz, 1H), 6.88 (dd, J = 4.5, 2.1 Hz, 2H), 3.75 (dt, J = 10.6, 3.9 Hz, 1H), 3.38 (ddd, J = 8.8, 5.2, 2.2 Hz, 1H), 3.14 (dt, J = 5.4, 3.2 Hz, 1H), 2.17−2.05 (m, 1H), 2.05−1.83 (m, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.7, 142.2, 135.9, 130.7, 118.7, 117.2, 59.6, 45.7, 26.6, 21.7. HRMS (ESI-TOF) calcd for $C_{10}H_{12}N_3O_1$ $[M + H]^+$: 190.0974, found 190.0975.

1-Methylpyrido[2,3-e]pyrrolo[1,2-a]pyrazin-6(5H)-one ***7***. Following the general MnO_2 reaction procedure, pyrrolidine **4** (159 mg, 0.782 mmol, 1.0 equiv) was reacted with MnO_2 (816 mg, 9.39 mmol, 12.0 equiv) in THF (12 mL) at reflux for 20 h. After filtration over Celite and concentration, **7** was isolated in 91% yield (142 mg, 0.715 mmol) as a pale yellow fine powder; dec 275−300 °C. R_f = 0.29 (70% EtOAc/hexanes). IR (neat) 3040, 2851, 1664, 1609, 1358, 712 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.64 (s, 1H), 8.14 (t, J = 2.0 Hz, 1H), 8.12 (d, J = 4.8 Hz, 1H), 7.13 (t, J = 5.1 Hz, 2H), 6.73 (t, J = 3.4 Hz, 1H), 2.80 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 155.2, 143.8, 135.3, 124.4, 123.5, 122.2, 118.7, 113.0, 111.5, 22.0. HRMS (ESI-TOF) calcd for $C_{11}H_{10}N_3O_1$ $[M + H]^+$: 200.0818, found 200.0818. This data is consistent with that previously reported.[2]

2-Methylpyrido[2,3-e]pyrrolo[1,2-a]pyrazin-6(5H)-one ***8***. Following the general MnO_2 reaction procedure, pyrrolidine **5** (494 mg, 2.431 mmol, 1.0 equiv) was reacted with MnO_2 (2.5 g, 29.2 mmol, 12.0 equiv) in THF (40 mL) at reflux for 22 h. After filtration over Celite and concentration, **8** was isolated in 84% yield (406 mg, 2.038 mmol) as a dark yellow fine powder; dec 172−176 °C. R_f = 0.33 (70% EtOAc/hexanes). IR (neat) 3121, 3049, 2919, 2852, 1667, 1492, 1359, 722 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.65−11.56 (m, 1H), 8.35 (d, J = 9.5 Hz, 1H), 8.19 (d, J = 9.5 Hz, 1H), 8.13 (d, J = 9.5 Hz, 1H), 7.10−6.99 (m, 1H), 6.75−6.68 (m, 1H), 2.37 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 155.5, 144.8, 139.7, 127.8, 123.0, 118.4, 113.4, 111.7, 17.4. HRMS (ESI-TOF) calcd for $C_{11}H_{10}N_3O_1$ $[M + H]^+$: 200.0818, found 200.0818.

Pyrido[2,3-e]pyrrolo[1,2-a]pyrazin-6(5H)-one ***9***. Following the general MnO_2 reaction procedure, pyrrolidine **6** (10 mg, 0.053 mmol, 1.0 equiv) was reacted with MnO_2 (45 mg, 0.528 mmol, 10.0 equiv) in THF (866 μL) at reflux for 20 h. After filtration over Celite and concentration, **9** was isolated in 51% yield (5 mg, 0.053 mmol) as a dark yellow fine powder; dec 164−168 °C. R_f = 0.29 (70% EtOAc/hexanes). IR (neat) 3384, 3126, 2972, 2893, 2849, 1671, 1495, 1361, 755.8 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.70 (s, 1H), 8.46 (dd, J = 8.1, 1.4 Hz, 1H), 8.27 (dd, J = 4.8, 1.4 Hz, 1H), 8.24−8.21 (m, 1H), 7.27 (dd, J = 8.1, 4.8 Hz, 1H), 7.06 (dd, J = 3.8, 1.4 Hz, 1H), 6.72 (t, J = 3.3 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 155.6, 144.8, 141.8, 123.1, 122.7, 118.8, 118.3, 113.4, 111.8. HRMS (ESI-TOF) calcd for $C_{10}H_8N_3O_1$ $[M + H]^+$: 186.0662, found 186.0662. This data is consistent with that previously reported.[2]

6a,7,8,9-Tetrahydropyrido[2,3-e]pyrrolo[1,2-a]pyrazin-6(5H)-one ***10***. Following *N*-arylation/condensation procedure B, CuCl (3.4 mg, 0.035 mmol, 0.10 equiv), DMEDA (7.47 μL, 0.069 mmol, 0.2 equiv), 3-bromopyridin-2-amine (60 mg, 0.347 mmol, 1.0 equiv), DL-proline (80 mg, 0.694 mmol, 2.0 equiv), and potassium phosphate (121 mg, 0.694 mmol, 2.0 equiv) in DMSO (3 mL) were reacted at 130 °C for 48 h to afford **10**. Following column chromatography (0 to 90% EtOAc/hexanes), **10** was isolated in 64% yield (42 mg, 0.222 mmol) as a pale yellow fluffy powder; dec 200−210 °C. R_f = 0.33 (70% EtOAc/hexanes). IR (neat) 3047, 2966, 2915, 2848, 2779, 1675, 1588, 1468, 1373, 1288, 752 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.74 (s, 1H), 7.61 (q, J = 3.2 Hz, 1H), 6.88 (d, J = 3.5 Hz, 2H), 3.75 (ddd, J = 9.5, 6.6, 3.1 Hz, 1H), 3.38 (tt, J = 8.9, 3.9 Hz, 1H), 3.14 (dq, J = 9.4, 5.5, 5.0 Hz, 1H), 2.13 (dp, J = 11.4, 4.2 Hz, 1H), 2.04−1.86 (m, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.8, 142.2, 135.9, 130.7, 118.7, 117.2, 59.6, 45.8, 26.6, 21.7. HRMS (ESI-TOF) calcd for $C_{10}H_{12}N_3O_1$ $[M + H]^+$: 190.0975, found 190.0974.

6a,7,8,9-Tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one ***11***. Following *N*-arylation/condensation procedure C, 2-bromopyridin-3-amine (248 mg, 1.43 mmol, 1.0 equiv), DL-proline (347 mg, 3.01 mmol, 2.1 equiv), cesium carbonate (701 mg, 2.150 mmol, 1.5 equiv), and CuI (27.3 mg, 0.143 mmol, 0.10 equiv) in DMSO (4.72 mL) was heated to 120 °C for 5 h. Following column chromatography (0 to 90% EtOAc/hexanes), **11** was isolated in 69% yield (189 mg, 0.999 mmol) as an off-white fine powder; dec 114−116 °C. R_f = 0.19 (70% EtOAc/hexanes). IR (neat) 3188, 3035, 2920, 2873, 1671, 1610, 1488, 1238, 752 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.42 (s, 1H), 7.70 (dd, J = 5.1, 1.6 Hz, 1H), 6.97 (dd, J = 7.5, 1.6 Hz, 1H), 6.59 (dd, J = 7.5, 5.1 Hz, 1H), 3.97 (dd, J = 8.9, 6.3 Hz, 1H), 3.59 (td, J = 7.8, 4.3 Hz, 1H), 3.39 (ddd, J = 10.9, 8.5, 4.2 Hz, 1H), 2.30−2.12 (m, 1H), 2.05−1.83 (m, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 166.2, 146.1, 141.0, 122.6, 119.6, 113.0, 59.0, 45.1, 27.6, 21.6. HRMS (ESI-TOF) calcd for $C_{10}H_{12}N_3O_1$ $[M + H]^+$: 190.0975, found 190.0974. This data is consistent with that previously reported.[21]

6a,7,8,9-Tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-6(5H)-one ***12***. Following *N*-arylation/condensation procedure B, CuCl (3.2 mg, 0.032 mmol, 0.10 equiv), DMEDA (6.91 μL, 0.064 mmol, 0.2 equiv), 3-bromo-5-methylpyridin-2-amine (60 mg, 0.321 mmol, 1.0 equiv), DL-proline (74 mg, 0.642 mmol, 2.0 equiv), and potassium phosphate (112 mg, 0.642 mmol, 2.0 equiv) in DMSO (3 mL) were reacted at 130 °C for 48 h. Following column chromatography (0 to 90% EtOAc/hexanes), **12** was isolated in 59% yield (39 mg, 0.190 mmol) as an off-white fluffy powder; dec 202−213 °C. R_f = 0.33 (70% EtOAc/hexanes). IR (neat) 3039, 2980, 2921, 2854, 1674, 1385, 1288, 861 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.63 (s, 1H), 7.44 (d, J = 1.8 Hz, 1H), 6.73 (d, J = 1.8 Hz, 1H), 3.70 (dd, J = 9.4, 6.6 Hz, 1H), 3.38 (td, J = 8.7, 5.1 Hz, 1H), 3.18−3.05 (m, 1H), 2.18 (s, 3H), 2.12 (ddt, J = 11.5, 7.4, 4.0 Hz, 1H), 2.02−1.82 (m, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.6, 140.2, 135.5, 130.4, 127.7, 118.2, 59.6, 45.7, 26.6, 21.7, 17.6. HRMS (ESI-TOF) calcd for $C_{11}H_{14}N_3O_1$ $[M + H]^+$: 204.1131, found 204.1131.

(S)-2-Methyl-7,8-dihydropyrido[2,3-e]pyrrolo[1,2-a]pyrazine-6,9-(5H,6aH)-dione ***13***. Following *N*-arylation/condensation procedure A, CuCl (37.0 mg, 0.373 mmol, 0.10 equiv), TMEDA (112 μL, 0.747 mmol, 0.20 equiv), 3-bromo-5-methylpyridin-2-amine (699 mg, 3.73 mmol, 1.0 equiv), L-pyroglutamic acid (964 mg, 7.46 mmol, 4.0 equiv; added in two portions 2 × 2.0 equiv over 1 h), and potassium phosphate (1.97 g, 9.27 mmol, 2.0 equiv) in DMSO (17 mL) were reacted at 115 °C for 30 h. Following column chromatography (0 to 100% EtOAc/hexanes), **13** was isolated in 16% yield (131 mg, 0.603 mmol) as a white fluffy powder; dec 261−269 °C. R_f = 0.15 (70% EtOAc/hexanes). IR (neat) 3051, 2998, 2842, 2768, 1680, 1354, 1243, 823 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6) δ 11.05 (s, 1H), 8.14 (d, J = 2.1 Hz, 1H), 7.90 (d, J = 2.3 Hz, 1H), 4.54 (t, J = 8.4 Hz, 1H), 2.66−2.57 (m, 1H), 2.45−2.31 (m, 2H), 2.26 (s, 3H), 2.24−2.15 (m, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 173.8, 168.2, 143.1, 141.5, 127.3, 127.0, 120.2, 56.6, 30.7, 21.0, 17.4. HRMS (ESI-TOF) calcd for $C_{11}H_{12}N_3O_2$ $[M + H]^+$: 218.0924, found 218.0923.

7,8,9,10-Tetrahydro-5H-dipyrido[1,2-a:2′,3′-e]pyrazin-6(6aH)-one ***14***. Following *N*-arylation/condensation procedure B, CuCl (3.4 mg, 0.035 mmol, 0.10 equiv), DMEDA (7.47 μL, 0.069 mmol, 0.2 equiv), 3-bromopyridin-2-amine (60 mg, 0.347 mmol, 1.0 equiv), DL-pipecolic acid (90 mg, 0.694 mmol, 2.0 equiv), and potassium phosphate (121 mg, 0.694 mmol, 2.0 equiv) in DMSO (3 mL) were reacted at 130 °C for 48 h. Following column chromatography (0 to 90% EtOAc/hexanes), **14** was isolated in 78% yield (55 mg, 0.271 mmol) as a white fluffy powder; dec 185−188 °C. R_f = 0.41 (70% EtOAc/hexanes). IR (neat) 3051, 2909, 2935, 2844, 1684, 1584, 1236, 1138, 782 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.79 (s, 1H),

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7.65 (dd, J = 4.9, 1.4 Hz, 1H), 7.32−7.06 (m, 1H), 6.91 (dd, J = 8.0, 4.9 Hz, 1H), 3.72 (dt, J = 12.7, 2.4 Hz, 1H), 3.54 (dd, J = 11.3, 3.1 Hz, 1H), 2.66 (td, J = 12.4, 3.0 Hz, 1H), 2.14−1.94 (m, 1H), 1.94−1.75 (m, 1H), 1.69 (dq, J = 11.7, 2.6 Hz, 1H), 1.61−1.29 (m, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.5, 141.3, 136.8, 131.2, 118.9, 118.1, 58.7, 45.6, 26.8, 23.0, 22.9. HRMS (ESI-TOF) calcd for $C_{11}H_{14}N_3O_1$ [M + H]$^+$: 204.1131, found 204.1130.

2-Methyl-7,8,9,10-tetrahydro-5H-dipyrido[1,2-a:2′,3′-e]pyrazin-6(6aH)-one ***15***. Following *N*-arylation/condensation procedure B, CuCl (3.2 mg, 0.032 mmol, 0.10 equiv), DMEDA (6.19 μL, 0.064 mmol, 0.2 equiv), 3-bromo-5-methylpyridin-2-amine (60 mg, 0.321 mmol, 1.0 equiv), DL-pipecolic acid (83 mg, 0.642 mmol, 2.0 equiv), and potassium phosphate (112 mg, 0.642 mmol, 2.0 equiv) in DMSO (3 mL) were reacted at 130 °C for 48 h. Following column chromatography (0 to 90% EtOAc/hexanes), **15** was isolated in 74% yield (53 mg, 0.260 mmol) as a white fluffy powder; dec 231−236 °C. R_f = 0.37 (70% EtOAc/hexanes). IR (neat) 3060, 2952, 2933, 2858, 1674, 1516, 1255, 868 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.69 (s, 1H), 7.48 (d, J = 1.7 Hz, 1H), 6.99 (d, J = 1.8 Hz, 1H), 3.84−3.63 (m, 1H), 3.60−3.43 (m, 1H), 2.77−2.58 (m, 1H), 2.19 (s, 3H), 2.09−1.97 (m, 1H), 1.90−1.79 (m, 1H), 1.76−1.58 (m, 1H), 1.53−1.32 (m, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.3, 139.2, 136.3, 130.8, 127.9, 119.1, 58.8, 45.5, 26.8, 23.1, 22.8, 17.7. HRMS (ESI-TOF) calcd for $C_{12}H_{16}N_3O_1$ [M + H]$^+$: 218.1288, found 218.1287. This data is consistent with that previously reported.[13]

7,8,9,10-Tetrahydro-5H-dipyrido[1,2-a:3′,2′-e]pyrazin-6(6aH)-one ***16***. Following *N*-arylation/condensation procedure B, CuCl (3.4 mg, 0.035 mmol, 0.10 equiv), DMEDA (7.47 μL, 0.069 mmol, 0.2 equiv), 2-bromopyridin-3-amine (60 mg, 0.347 mmol, 1.0 equiv), DL-pipecolic acid (90 mg, 0.694 mmol, 2.0 equiv), and potassium phosphate (121 mg, 0.694 mmol, 2.0 equiv) in DMSO (3 mL) were reacted at 130 °C for 48 h. Following column chromatography (0 to 90% EtOAc/hexanes), **15** was isolated in 74% yield (52.7 mg, 0.259 mmol) as a white fluffy powder; dec 202−205 °C. R_f = 0.41 (70% EtOAc/hexanes). IR (neat) 3194, 3141, 3091, 2925, 1652, 1612, 1469, 1255, 759 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.46 (s, 1H), 7.74 (dd, J = 5.0, 1.6 Hz, 1H), 6.96 (dd, J = 7.5, 1.6 Hz, 1H), 6.62 (dd, J = 7.5, 5.0 Hz, 1H), 4.52 (ddt, J = 13.2, 4.1, 1.9 Hz, 1H), 3.84 (dd, J = 11.7, 2.9 Hz, 1H), 2.60 (td, J = 12.8, 2.8 Hz, 1H), 2.10−1.97 (m, 1H), 1.92−1.81 (m, 1H), 1.67−1.59 (m, 1H), 1.56−1.31 (m, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 166.3, 146.0, 140.9, 121.5, 119.9, 113.6, 59.0, 43.5, 27.8, 23.6, 23.2. HRMS (ESI-TOF) calcd for $C_{11}H_{14}N_3O_1$ [M + H]$^+$: 204.1131, found 204.1130. This data is consistent with that previously reported.[22]

(S)-2-Isobutyl-7-methyl-1,4-dihydropyrido[2,3-b]pyrazin-3(2H)-one ***17a***. Following *N*-arylation/condensation procedure A, CuCl (16 mg, 0.160 mmol, 0.10 equiv), TMEDA (48 μL, 0.321 mmol, 0.20 equiv), 3-bromo-5-methylpyridin-2-amine (300 mg, 1.604 mmol, 1.0 equiv), L-leucine (421 mg, 3.21 mmol, 2.0 equiv), and potassium phosphate (681 mg, 3.21 mmol, 2.0 equiv) in DMSO (5.71 mL) were reacted in a flame-dried reaction vial at 115 °C for 10 h. Following column chromatography (0 to 100% EtOAc/hexanes), **17a** was isolated in 31% yield (110 mg, 0.500 mmol) as a pale yellow powder; mp 170−76 °C. R_f = 0.31 (70% EtOAc/hexanes). IR (neat) 3325, 2956, 2868, 1664, 1608, 1363, 1281, 865 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.51 (s, 1H), 7.38 (s, 1H), 6.85 (s, 1H), 6.16 (s, 1H), 3.97−3.60 (m, 1H), 2.14 (s, 3H), 1.98−1.66 (m, 1H), 1.62−1.31 (m, 2H), 0.89 (ddd, J = 6.4, 4.3, 1.7 Hz, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.6, 138.3, 135.7, 129.1, 127.5, 119.9, 53.6, 41.1, 23.4, 21.7, 17.5. HRMS (ESI-TOF) calcd for $C_{12}H_{18}N_3O_1$ [M + H]$^+$: 220.1444, found 220.1444. Although trace amounts of **17b** were observed by TLC and ^{1}H NMR of the crude reaction, only 5.9 mg (8% yield) of **17b** (mixture with residual **17a**) was isolated during purification.

2-Isobutyl-7-methylpyrido[2,3-b]pyrazin-3(4H)-one ***17b***. Following *N*-arylation/condensation procedure B, CuCl (3.2 mg, 0.032 mmol, 0.10 equiv), DMEDA (6.19 μL, 0.064 mmol, 0.2 equiv), 3-bromo-5-methylpyridin-2-amine (60 mg, 0.321 mmol, 1.0 equiv), L-leucine (84 mg, 0.642 mmol, 2.0 equiv), and potassium phosphate (112 mg, 0.642 mmol, 2.0 equiv) in DMSO (3 mL) were reacted at 130 °C for 48 h. Following column chromatography (0 to 90% EtOAc/hexanes), **17b** was isolated in 25% yield (18 mg, 0.081 mmol) as a white fluffy cotton-like powder; dec 185−187 °C. R_f = 0.43 (70% EtOAc/hexanes). IR (neat) 3019, 2924, 2959, 1662, 1595, 1259, 897 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.67 (s, 1H), 8.33 (d, J = 2.1 Hz, 1H), 7.98 (d, J = 2.4 Hz, 1H), 2.67 (d, J = 7.1 Hz, 2H), 2.37 (s, 3H), 2.28−2.17 (m, 1H), 0.93 (d, J = 6.7 Hz, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 162.5, 156.1, 149.7, 141.6, 135.8, 128.9, 126.4, 41.5, 26.1, 22.5, 17.2. HRMS (ESI-TOF) calcd for $C_{12}H_{16}N_3O_1$ [M + H]$^+$: 218.1288, found 218.1287. Although trace amounts of **17a** were observed by TLC and ^{1}H NMR of the crude product, **17a** was not successfully isolated during purification.

(S)-2-Benzyl-7-methyl-1,4-dihydropyrido[2,3-b]pyrazin-3(2H)-one ***18a***. Following *N*-arylation/condensation procedure B, CuCl (3.2 mg, 0.032 mmol, 0.10 equiv), DMEDA (6.19 μL, 0.064 mmol, 0.2 equiv), 3-bromo-5-methylpyridin-2-amine (60 mg, 0.321 mmol, 1.0 equiv), L-phenylalanine (106 mg, 0.321 mmol, 2.0 equiv), and potassium phosphate (112 mg, 0.642 mmol, 2.0 equiv) in DMSO (3 mL) were reacted at 130 °C for 48 h. Following column chromatography (0 to 90% EtOAc/hexanes), **18a** was isolated in 54% yield (44 mg, 0.174 mmol) as a pale yellow crystalline solid; mp 179−182 °C. R_f = 0.28 (70% EtOAc/hexanes). IR (neat) 3395, 3300, 2850, 1669, 1361, 1282, 1220, 854 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.54 (s, 1H), 7.39−7.01 (m, 6H), 6.79 (d, J = 1.9 Hz, 1H), 6.06 (d, J = 2.0 Hz, 1H), 4.11 (s, 1H), 3.05−2.69 (m, 2H), 2.10 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.4, 138.0, 137.1, 135.5, 129.7, 129.0, 128.1, 127.5, 126.3, 119.6, 56.7, 38.1, 17.5. HRMS (ESI-TOF) calcd for $C_{15}H_{16}N_3O_1$ [M + H]$^+$: 254.1288, found 254.1287. The data for **18a** is consistent with that previously reported.[14] Products **18a** and **18b** were isolated from the same reaction mixture.

2-Benzyl-7-methylpyrido[2,3-b]pyrazin-3(4H)-one ***18b***. Following *N*-arylation/condensation procedure B, CuCl (3.2 mg, 0.032 mmol, 0.10 equiv), DMEDA (6.2 μL, 0.064 mmol, 0.2 equiv), 3-bromo-5-methylpyridin-2-amine (60 mg, 0.321 mmol, 1.0 equiv), L-phenylalanine (106 mg, 0.321 mmol, 2.0 equiv), and potassium phosphate (112 mg, 0.642 mmol, 2.0 equiv) in DMSO (3 mL) were reacted at 130 °C for 48 h. Following column chromatography (0 to 90% EtOAc/hexanes), **18b** was isolated in 13% yield (11 mg, 0.042 mmol) as a white crystalline solid; mp 196−201 °C. R_f = 0.34 (70% EtOAc/hexanes). IR (neat) 3030, 2922, 2846, 1674, 1592, 1426, 1258, 751 cm^{-1}. ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.77 (s, 1H), 8.36 (d, J = 2.7 Hz, 1H), 7.99 (d, J = 3.2 Hz, 1H), 7.37−7.28 (m, 4H), 7.22 (t, J = 6.9 Hz, 1H), 4.14 (d, J = 2.9 Hz, 2H), 2.37 (d, J = 2.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 161.6, 155.8, 150.0, 141.7, 137.1, 136.0, 129.2, 129.0, 128.3, 126.4, 126.4, 38.9, 17.2. HRMS (ESI-TOF) calcd for $C_{15}H_{14}N_3O_1$ [M + H]$^+$: 252.1131, found 252.1131. Products **18a** and **18b** were isolated from the same reaction mixture.

(S)-1-Methyl-7,12-dihydro-5H-pyrido[2′,3′:5,6]pyrazino[1,2-b]-isoquinolin-6(6aH)-one ***19***. Following *N*-arylation/condensation procedure B, CuCl (3.2 mg, 0.032 mmol, 0.10 equiv), DMEDA (6.2 μL, 0.064 mmol, 0.2 equiv), 3-bromo-4-methylpyridin-2-amine (60 mg, 0.321 mmol, 1.0 equiv), (*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (114 mg, 0.321 mmol, 2.0 equiv), and potassium phosphate (112 mg, 0.642 mmol, 2.0 equiv) in DMSO (3 mL) were reacted at 130 °C for 48 h. Following column chromatography (0 to 100% EtOAc/hexanes) followed by (0 to 50% MeOH/DCM), **19** was isolated in 30% yield (26 mg, 0.098 mmol) as a bright yellow powder; dec 187−203 °C. R_f = 0.38 (70% EtOAc/hexanes). IR (neat) 3027, 2854, 1681, 1607, 1428, 1351, 1251, 841 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.83 (s, 1H), 7.97 (d, J = 5.1 Hz, 1H), 7.34−7.08 (m, 4H), 7.04 (dd, J = 7.6, 1.3 Hz, 1H), 6.94 (dd, J = 5.1, 0.7 Hz, 1H), 4.12−4.03 (m, 1H), 3.95 (dd, J = 7.1, 1.7 Hz, 1H), 3.67−3.59 (m, 1H), 3.51−3.43 (m, 1H), 3.19−3.08 (m, 1H), 2.33 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.3, 147.1, 144.1, 141.9, 132.7, 131.9, 130.9, 128.5, 126.6, 126.1, 125.7, 120.7, 54.8, 48.4, 25.4, 16.2. HRMS (ESI-TOF) calcd for $C_{16}H_{16}N_3O_1$ [M + H]$^+$: 266.1288, found 266.1288.

(S)-7-Methyl-2-((1-methyl-1H-indol-2-yl)methyl)-1,4-dihydropyrido[2,3-b]pyrazin-3(2H)-one ***20***. Following *N*-arylation/condensation procedure A, CuCl (16 mg, 0.160 mmol, 0.10 equiv),

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TMEDA (48 μL, 0.320 mmol, 0.20 equiv), 3-bromo-5-methylpyridin-2-amine (299 mg, 1.601 mmol, 1.0 equiv), 1-methyl-L-tryptophan (629 mg, 2.88 mmol, 1.8 equiv), and potassium phosphate (612 mg, 2.88 mmol, 1.8 equiv) in DMSO (9.0 mL) were reacted at 115 °C for 30 h. Following column chromatography (0 to 100% EtOAc/hexanes) followed by (0 to 50% MeOH/DCM), **20** was isolated in 31% yield (154.4 mg, 0.504 mmol) as a burnt orange crispy solid; dec 169−176 °C. R_f = 0.27 (70% EtOAc/hexanes). IR (neat) 3358, 2890, 1671, 1607, 1471, 1328, 866 cm^{-1}. ^1H NMR (600 MHz, DMSO-d_6) δ 10.53 (s, 1H), 7.53 (d, J = 7.9 Hz, 1H), 7.40−7.29 (m, 2H), 7.17−7.06 (m, 2H), 7.02 (d, J = 7.5 Hz, 1H), 6.77 (d, J = 1.9 Hz, 1H), 6.01 (d, J = 2.0 Hz, 1H), 4.12−4.07 (m, 1H), 3.72 (s, 3H), 3.13−3.05 (m, 1H), 3.00−2.93 (m, 1H), 2.10 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 168.0, 138.1, 136.5, 135.3, 129.1, 128.6, 127.8, 127.4, 120.9, 119.7, 118.6, 118.4, 109.5, 108.5, 56.2, 32.3, 28.1, 17.5. HRMS (ESI-TOF) calcd for $C_{18}H_{19}N_4O_1$ $[M + H]^+$: 307.1553, found 307.1554.

2-(1-Methyl-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6H)-yl)-acetic Acid ***21***. The preparation of fragment **21** was carried out using our previously reported procedure.[2] To a 20 mL reaction vial containing **34** (68 mg, 0.238 mmol, 1.0 equiv) was added LiOH (8.58 mg, 0.358 mmol, 1.5 equiv) and then 2.0 mL of a 1:1:4 H_2O/MeOH/THF solvent solution. The vial was capped and stirred at rt. The reaction was monitored by TLC (1:10 EtOH/EtOAc) and UPLC analysis for the consumption of starting material. After 15 h, the crude reaction mixture was diluted with H_2O (5 mL) and transferred to a separatory funnel. The aqueous layer was washed with Et_2O (3 × 10 mL), collected, and acidified (pH 2−3) by adding 2 N HCl (aqueous) dropwise. At pH 3, it was observed that a white precipitate started to crash out of the aqueous solution. The mixture was transferred into the separatory funnel and extracted with EtOAc (3 × 20 mL) and brine (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation to give crude product **21** in 73% yield (45 mg, 0.175 mmol) as a pale yellow solid that was used without further purification. ^1H NMR (500 MHz, DMSO-d_6) δ 8.45−7.92 (m, 2H), 7.39−7.08 (m, 2H), 6.79 (dd, J = 3.9, 2.9 Hz, 1H), 5.01 (s, 2H), 2.85 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.8, 154.5, 143.2, 141.5, 136.0, 124.0, 123.3, 122.8, 119.6, 113.4, 112.7, 41.7, 22.3. This data is consistent with that previously reported.[2]

3-(4-(4-Methoxyphenyl)piperazin-1-yl)propan-1-amine ***23***. The preparation of aminopiperazine fragment **23** was prepared as previously reported.[2,23] To a solution of 3-(4-(4-methoxyphenyl)-piperazin-1-yl)propanenitrile **35** (1.33 g, 5.42 mmol; see synthesis below) in ether (20 mL) was slowly added 2.0 M lithium aluminum hydride in THF (2.98 mL, 5.96 mmol) at 0 °C. The reaction was slowly warmed to room temperature and monitored by TLC for disappearance of the starting material (50:50 EtOAc/hexanes and 5:95 MeOH/DCM; starting material stains white and desired product stains dark purple with *p*-anisaldehye). After approximately 16 h stirring at rt, the reaction mixture was cooled to 0 °C, and the reaction was quenched with Glauber's salt (Na_2SO_4·10 H_2O) slowly over approximately 1 h at 0 °C. After the generation of H_2 gas subsided, the reaction was allowed to warm to rt and stirred for 1 h at rt. The mixture was filtered over a pad of Celite, and the filtrate was concentrated by rotary evaporation to give the crude product as a tan solid in 98% yield (1.35 g, 5.41 mmol). ^1H NMR (400 MHz, $CDCl_3$) δ 6.94−6.87 (m, 2H), 6.87−6.80 (m, 2H), 3.76 (s, 3H), 3.15−3.04 (m, 4H), 2.78 (t, J = 6.8 Hz, 2H), 2.66−2.57 (m, 4H), 2.50−2.42 (m, 2H), 1.75−1.61 (m, 2H), 1.52 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8, 145.8, 118.1, 114.4, 56.5, 55.6, 53.5, 50.7, 40.8, 30.6. HRMS (ESI-TOF) calcd for $C_{14}H_{24}N_3O_1$ $[M + H]^+$: 250.1919, found 250.1914. This data is consistent with that previously reported.[2]

2-Bromo-N-(3-(4-(4-methoxyphenyl)piperazin-1-yl)propyl)-acetamide ***24***. The preparation of side chain coupling fragment **24** was carried out with modification of a previously reported procedure for acylation of amines with bromoacetyl bromide.[24] In a 25 mL flame-dried RBF was added 2-bromoacetyl bromide (0.312 mL, 3.58 mmol) in DCM (16 mL), and the solution was cooled to 0 °C in an ice bath. The solution was stirred at 0 °C for 30 min, and then triethylamine (0.499 mL, 3.58 mmol) was added slowly dropwise following addition of 3-(4-(4-methoxyphenyl)piperazin-1-yl)propan-1-amine (446 mg, 1.789 mmol) dissolved in DCM (5 mL). The resulting reaction mixture was stirred at 0 °C for 1 h. The reaction was monitored by TLC (5:95 MeOH/DCM and 10:90 EtOH/EtOAc) and UPLC analysis. After 1 h, the starting material was consumed, and the reaction was quenched with 2 mL of DI H_2O. The crude mixture was transferred into a separatory funnel, and the organic layer was washed with 5 × 3 mL of water and 3 mL of brine. The organic layers were combined, dried over Na_2SO_4, and concentrated by rotary evaporation to give the crude product as a light brown oil residue. The crude product was dissolved in a minimal amount of DCM and MeOH and adsorbed onto silica by removal of solvents. The silica was loaded into a sample cartridge and used for automated MPLC purification. Purification was carried out using a 24 g normal-phase silica flash column on an automated MPLC system with a gradient elution from 100% hexanes to 90% DCM/MeOH over 30 min. Concentration of appropriate fractions afforded **24** in 57% yield (330 mg, 0.893 mmol) as a light tan oil residue that solidified upon drying under high vacuum to a crispy tan solid. Compound **24** was stored under argon in the freezer as the compound decomposes over time (2 weeks in freezer) and especially when exposed to air at rt (~2 days at rt). ^1H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H), 7.00−6.91 (m, 2H), 6.90−6.80 (m, 2H), 3.88 (s, 2H), 3.69 (s, 3H), 3.68−3.62 (m, 3H), 3.60−3.52 (m, 3H), 3.22−3.05 (m, 5H), 2.97−2.84 (m, 1H), 1.92−1.79 (m, 1H), 1.21−1.14 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 166.4, 153.7, 143.7, 118.0, 114.4, 55.2, 53.4, 51.1, 46.9, 45.7, 36.4, 29.5, 23.6, 8.6. HRMS (ESI-TOF) calcd for $C_{16}H_{25}BrN_3O_2$ $[M + H]^+$: 370.1131, found 370.1118.

Method A: General Procedure for the Coupling of the Acid Scaffold to the Amine Fragment.[2] The carboxylic acid component (1.0 equiv), amine fragment (1.3 equiv), and DMAP (0.1 equiv) were dissolved in 1 mL of DCM. Diisopropylcarbodiimide (4.8 equiv) was added to the mixture via syringe in one aliquot. The mixture was stirred at room temperature overnight. After 14−16 h, the solvent was removed, and the reaction mixture was purified using normal-phase automated MPLC purification (DCM/MeOH or EtOAc/hexanes) or mass-directed reverse-phase HPLC to afford coupled product.

Method B: General Procedure for the Coupling of the Amide Core Scaffold to the Side Chain Fragment.[24] The amide component (1.2 equiv) was added to a solution of NaH (1.2 equiv) in DMF (2 mL) at rt and stirred for 30 min at rt. After 30 min, a solution of the bromoacetamide (1.0 equiv) in 1 mL of DMF was added to the reaction mixture at 0 °C. The reaction mixture was warmed to rt and stirred overnight at rt. After 10−16 h, the reaction was quenched with H_2O, and the solvents were removed. The crude mixture was purified using normal-phase automated MPLC purification (DCM/MeOH or EtOAc/hexanes) or mass-directed reverse-phase HPLC to afford coupled product.

N-(3-(4-(4-methoxyphenyl)piperazin-1-yl)propyl)-2-(1-methyl-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6H)-yl)acetamide ***22***. Compound **22** was prepared using both coupling methods described above. Method A: In a flame-dried 15 mL round-bottom flask purged with argon was added 2-(1-methyl-6-oxopyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazin-5(6*H*)-yl)acetic acid **21** (29 mg, 0.113 mmol, 1.0 equiv), 3-(4-(4-methoxyphenyl)piperazin-1-yl)propan-1-amine **23** (38.1 mg, 0.158 mmol, 1.4 equiv), DMAP (1.381 mg, 0.013 mmol, 0.10 equiv), and 3 mL of anhydrous DCM. Diisopropylcarbodiimide (84 μL, 0.542 mmol, 4.8 equiv) was added slowly dropwise at rt. The reaction mixture was stirred overnight (14 h) at rt. Then, the solvents were removed by rotary evaporation, and the sample was purified by mass-directed reverse-phase HPLC purification to give **22** in 21% yield (3.6 mg, 0.007 mmol, 94.3% purity). Method B: To a 2 dram flame-dried reaction vial were added NaH (8.11 mg, 0.203 mmol) followed by anhydrous DMF (2.0 mL). To a separate 2 dram flame-dried reaction vial was added 1-methylpyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazin-6(5*H*)-one **8** (20.2 mg, 0.101 mmol). To this was added 1 mL of anhydrous DMF, and this mixture was stirred for 15 min at rt. After 15 min, the 1-methylpyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazin-6(5*H*)-one substrate mixture was slowly added to the NaH/DMF mixture. To a separate 2 dram flame-dried reaction vial was added 2-bromo-*N*-(3-(4-(4-methoxyphenyl)piperazin-1-yl)propyl)acetamide **24** (48.8 mg, 0.132

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mmol) and 1 mL of anhydrous DMF. After 30 min, the 2-bromo-*N*-(3-(4-(4-methoxyphenyl)piperazin-1-yl)propyl)acetamide solution was added to the substrate mixture. The reaction mixture was stirred overnight at rt (14 h) and then quenched with 2 drops of water. The crude mixture was concentrated by rotary evaporation to give the crude product as a brown residue. The crude product was dissolved in a minimal amount of DCM and MeOH and adsorbed onto silica by removal of solvents. The silica was loaded into a sample cartridge and used for automated MPLC purification. Purification was carried out using a 4 g normal-phase silica flash column on an automated MPLC system with a gradient elution from 100 to 90% DCM/MeOH over 30−50 min. Concentration of appropriate fractions afforded **22** in 22% yield (11.3 mg, 0.023 mmol, 77% purity) as an off-white solid. Spectral data provided for **22** obtained from Method B: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, J = 4.8 Hz, 1H), 7.86 (dd, J = 3.0, 1.5 Hz, 1H), 7.31 (dd, J = 4.0, 1.4 Hz, 1H), 7.22−7.15 (m, 1H), 6.97 (dd, J = 4.9, 0.8 Hz, 1H), 6.82 (s, 4H), 6.66 (dd, J = 4.0, 2.9 Hz, 1H), 5.10 (s, 2H), 3.76 (s, 3H), 3.40 (q, J = 5.9 Hz, 2H), 3.05−2.96 (m, 4H), 2.73 (s, 3H), 2.70−2.59 (m, 4H), 2.55 (t, J = 6.4 Hz, 2H), 1.80−1.70 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 155.9, 154.0, 145.3, 143.3, 142.4, 135.0, 124.2, 122.9, 122.7, 120.6, 118.3, 114.5, 113.6, 57.2, 55.7, 53.4, 50.2, 44.3, 39.1, 29.8, 25.0, 23.0. HRMS (ESI-TOF) calcd for $C_{27}H_{33}N_6O_3$ $[M + H]^+$: 489.2609, found 489.2628. This data is consistent with that previously reported.[2]

(S)-N-(3-(4-(4-Methoxyphenyl)piperazin-1-yl)propyl)-2-(1-methyl-6-oxo-6a,7,8,9-tetrahydropyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6H)-yl)acetamide ***26***. Compound **26** was prepared using general coupling method B as described above. To a solution of NaH (3.8 mg, 0.096 mmol) in DMF (2.0 mL) in a flame-dried and argon-purged 2 dram reaction vial was added **4** (20 mg, 0.096 mmol) at rt. After 30 min, the reaction mixture was cooled to 0 °C, and a solution of **24** (30 mg, 0.080 mmol) in DMF (1 mL) was added dropwise. The reaction was warmed to rt and stirred overnight. After 15 h, the reaction was quenched with 1 mL of H_2O and transferred to a 125 mL separatory funnel; the aqueous layer was diluted with EtOAc (50 mL), and the organic layer was washed with water (5 × 3 mL) and brine (3 × 4 mL). The EtOAc layer was collected, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to the give the crude product as an oily residue. The crude mixture (56 mg) was purified by mass-directed reverse-phase HPLC to afford coupled product **26** in 36% yield (21 mg, 0.043 mmol, 100% purity) as a crystalline yellow solid; mp 140−142 °C. R_f = 0.67 (1% MeOH/DCM). IR (neat) 3297, 2945, 2822, 1660, 1509, 1233, 1031, 820 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.94 (s, 1H), 7.83 (d, J = 4.9 Hz, 1H), 6.93−6.85 (m, 1H), 6.83−6.76 (m, 4H), 4.82−4.60 (m, 1H), 4.57−4.44 (m, 1H), 4.00 (dd, J = 8.1, 2.2 Hz, 1H), 3.67 (s, 3H), 3.62−3.48 (m, 1H), 3.12−3.05 (m, 3H), 2.98 (t, J = 5.0 Hz, 4H), 2.92 (d, J = 5.2 Hz, 1H), 2.54 (s, 0H), 2.46 (t, J = 5.0 Hz, 4H), 2.29 (d, J = 6.0 Hz, 5H), 2.16 (s, 1H), 1.97−1.85 (m, 1H), 1.72−1.61 (m, 1H), 1.60−1.51 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.3, 167.1, 152.8, 145.5, 144.6, 140.3, 139.0, 129.7, 121.2, 117.3, 114.2, 59.4, 55.4, 55.2, 52.9, 52.6, 49.6, 43.0, 37.0, 27.5, 26.4, 23.8, 17.5. HRMS (ESI-TOF) calcd for $C_{27}H_{37}N_6O_3$ $[M + H]^+$: 493.2922, found 493.2938.

(S)-N-(3-(4-(4-Methoxyphenyl)piperazin-1-yl)propyl)-2-(2-methyl-6-oxo-6a,7,8,9-tetrahydropyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6H)-yl)acetamide ***27***. Compound **27** was prepared using general coupling method B as described above. To a solution of NaH (3.8 mg, 0.096 mmol) in DMF (2.0 mL) in a flame-dried and argon-purged 2 dram reaction vial was added **5** (19 mg, 0.096 mmol) at rt. After 30 min, the reaction was cooled to 0 °C, and a solution of **24** (30 mg, 0.080 mmol) in DMF (1 mL) was added dropwise. The reaction was warmed to rt and stirred overnight. After 15 h, the reaction was quenched with 1 mL of H_2O and transferred to a 125 mL separatory funnel; the aqueous layer was diluted with EtOAc (50 mL), and the organic layer was washed with water (5 × 3 mL) and brine (3 × 4 mL). The EtOAc layer was collected, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to give the crude product as an oily residue. The crude mixture (27 mg) was purified by mass-directed reverse-phase HPLC to afford coupled product **27** in 10% yield (4 mg, 0.008 mmol, 97.3% purity) as an off-white solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.95 (s, 1H), 7.49 (dd, J = 1.9, 0.9 Hz, 1H), 6.91−6.77 (m, 5H), 4.67−4.60 (m, 1H), 4.50−4.42 (m, 1H), 3.83 (s, 1H), 3.67 (s, 3H), 3.45−3.37 (m, 1H), 3.15 (td, J = 9.0, 6.0 Hz, 1H), 3.07 (d, J = 6.2 Hz, 2H), 2.98 (t, J = 5.0 Hz, 4H), 2.54 (s, 1H), 2.46 (t, J = 4.9 Hz, 3H), 2.30 (t, J = 7.2 Hz, 2H), 2.20 (s, 3H), 2.19 (s, 1H), 2.06−1.87 (m, 3H), 1.61−1.51 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.4, 166.4, 152.3, 144.9, 139.5, 134.6, 130.8, 127.6, 117.9, 116.7, 113.7, 59.0, 54.8, 54.6, 52.3, 49.1, 45.2, 41.9, 36.4, 26.4, 25.8, 20.9, 16.9. HRMS (ESI-TOF) calcd for $C_{27}H_{37}N_6O_3$ $[M + H]^+$: 493.2922, found 493.2924.

N-(3-(4-(4-Methoxyphenyl)piperazin-1-yl)propyl)-2-(2-methyl-6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:2′,3′-e]pyrazin-5-yl)acetamide ***28***. Compound **28** was prepared using coupling method A: In a flame-dried 15 mL round-bottom flask purged with argon were added 2-(2-methyl-6-oxo-6,6a,7,8,9,10-hexahydro-5*H*-dipyrido[1,2-a:2′,3′-e]pyrazin-5-yl)acetic acid **37** (9 mg, 0.039 mmol, 1.0 equiv), 3-(4-(4-methoxyphenyl)piperazin-1-yl)propan-1-amine **23** (10 mg, 0.039 mmol, 1.0 equiv), DMAP (0.50 mg, 3.92 μmol), and 2.0 mL of anhydrous DCM. Diisopropylcarbodiimide (3 μL, 0.188 mmol, 4.8 equiv) was added slowly dropwise at rt. The reaction mixture was stirred overnight (14 h) at rt. After 14 h, the solvents were removed by rotary evaporation, and the sample was purified by mass-directed reverse-phase HPLC purification to give **28** in 62% yield (12 mg, 0.025 mmol, 100% purity) as a fluffy white powder; mp 154−156 °C. R_f = 0.55 (1% MeOH/DCM). IR (neat) 3316, 2958, 2826, 1682, 1662, 1476, 1257 1010, 821 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.95 (t, J = 5.6 Hz, 1H), 7.52 (dd, J = 1.8, 0.9 Hz, 1H), 7.05 (d, J = 1.8 Hz, 1H), 6.91−6.76 (m, 4H), 4.62−4.48 (m, 2H), 3.78−3.72 (m, 1H), 3.67 (s, 3H), 3.07 (q, J = 6.6 Hz, 2H), 2.99 (t, J = 4.9 Hz, 4H), 2.69 (d, J = 3.1 Hz, 1H), 2.54 (s, 1H), 2.47 (t, J = 4.4 Hz, 4H), 2.30 (t, J = 7.1 Hz, 2H), 2.21 (t, J = 0.7 Hz, 3H), 2.07−2.01 (m, 1H), 1.84 (s, 1H), 1.68 (d, J = 2.7 Hz, 1H), 1.61−1.53 (m, 2H), 1.52−1.40 (m, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.7, 166.9, 152.9, 145.6, 139.4, 136.0, 131.9, 128.5, 119.5, 117.4, 114.4, 58.9, 55.5, 55.3, 53.0, 49.8, 45.8, 42.5, 37.2, 27.2, 26.5, 23.1, 22.9, 17.7. HRMS (ESI-TOF) calcd for $C_{28}H_{39}N_6O_3$ $[M + H]^+$: 507.3078, found 507.3084.

(S)-2-(2-Isobutyl-7-methyl-3-oxo-2,3-dihydropyrido[2,3-b]-pyrazin-4(1H)-yl)-N-(3-(4-(4-methoxyphenyl)piperazin-1-yl)propyl)-acetamide ***29***. Compound **29** was prepared using coupling method B: To a solution of NaH (5.91 mg, 0.148 mmol, 1.2 equiv) in DMF (2.0 mL) in a flame-dried and argon-purged 2 dram reaction vial was added **17a** (27 mg, 0.096 mmol, 1.0 equiv) at rt. After 30 min, the reaction was cooled to 0 °C, and a solution of **24** (54 mg, 0.148 mmol, 1.2 equiv) in DMF (1 mL) was added dropwise. The reaction was warmed to rt and stirred overnight. After 15 h, the reaction was quenched with 1 mL of H_2O and transferred to a 125 mL separatory funnel; the aqueous layer was diluted with EtOAc (50 mL), and the organic layer was washed with water (5 × 3 mL) and brine (3 × 4 mL). The EtOAc layer was collected, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to give the crude product as an oily residue. The crude product was dissolved in a minimal amount of DCM and MeOH and adsorbed onto Celite by removal of solvents. The Celite was loaded into a sample cartridge and used for automated MPLC purification. Purification was carried out using a 4 g normal-phase silica flash column on an automated MPLC system with gradient elution from 0 to 5% MeOH/DCM over 30−50 min. Concentration of appropriate fractions afforded **26** in 21% yield (13 mg, 0.026 mmol, 82% purity) as a crispy tan solid; mp 125−127 °C. R_f = 0.51 (1% MeOH/DCM). IR (neat) 3371, 3274, 2952, 2811, 1666, 1514, 1224, 820 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (dd, J = 1.9, 0.9 Hz, 1H), 6.92−6.86 (m, 2H), 6.86−6.81 (m, 2H), 6.77−6.67 (m, 1H), 4.89−4.61 (m, 2H), 4.08 (s, 1H), 3.91 (d, J = 2.2 Hz, 1H), 3.76 (s, 3H), 3.40 (q, J = 6.1 Hz, 2H), 3.21 (s, 3H), 2.82 (d, J = 7.1 Hz, 5H), 2.61 (s, 3H), 2.20 (d, J = 0.8 Hz, 3H), 1.84 (s, 2H), 1.72 (ddd, J = 11.0, 6.5, 2.9 Hz, 2H), 1.61 (dd, J = 9.5, 8.4 Hz, 1H), 1.04−0.83 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 168.3, 149.3, 139.1, 137.9, 137.2, 129.3, 128.9, 121.8, 118.8, 114.6, 55.7, 54.8, 53.2, 50.1, 43.8, 41.2, 40.8, 24.4, 23.4, 22.9, 21.6, 17.9, 17.9. HRMS (ESI-TOF) calcd for $C_{28}H_{41}N_6O_3$ $[M + H]^+$: 509.3235, found 509.3262.

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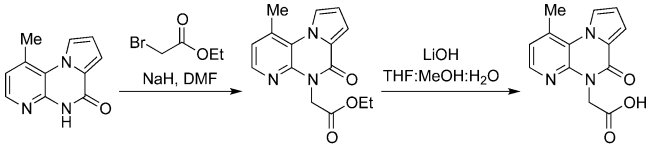
N-(3-(4-(4-Methoxyphenyl)piperazin-1-yl)propyl)-2-(6-oxo-6a,7,8,9-tetrahydropyrido[3,2-e]pyrrolo[1,2-a]pyrazin-5(6H)-yl)-acetamide ***30***. Compound **30** was prepared using coupling method B: To a solution of NaH (7.0 mg, 0.175 mmol, 1.2 equiv) in DMF (2.0 mL) in a flame-dried and argon-purged 2 dram reaction vial was added **11** (33 mg, 0.175 mmol, 1.2 equiv) at rt. After 30 min, the reaction was cooled to 0 °C, and a solution of **24** (54 mg, 0.146 mmol, 1.0 equiv) in DMF (1.0 mL) was added dropwise. The reaction was warmed to rt and stirred overnight. After 15 h, the reaction was quenched with 1 mL of H_2O and transferred to a 125 mL separatory funnel; the aqueous layer was diluted with EtOAc (50 mL), and the organic layer was washed with water (5 × 3 mL) and brine (3 × 4 mL). The EtOAc layer was collected, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to give the crude product (50 mg) as an oily residue. The sample was purified by mass-directed reverse-phase HPLC purification to give **30** in 25% yield (18 mg, 0.0376 mmol, 94% purity) as a fluffy white solid; mp 158−160 °C. R_f = 0.51 (1% MeOH/DCM). IR (neat) 3343, 2948, 2809, 1656, 1493, 1514, 1241, 1030, 820 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 8.12 (d, J = 5.6 Hz, 1H), 7.78 (dd, J = 5.0, 1.4 Hz, 1H), 6.99 (dd, J = 7.8, 1.4 Hz, 1H), 6.92−6.85 (m, 2H), 6.82−6.77 (m, 2H), 6.68 (dd, J = 7.8, 5.0 Hz, 1H), 4.75−4.54 (m, 1H), 4.36−4.19 (m, 1H), 4.14−3.97 (m, 1H), 3.67 (s, 3H), 3.59 (s, 1H), 3.45 (s, 1H), 3.22−3.07 (m, 2H), 2.99 (t, J = 5.0 Hz, 4H), 2.48−2.44 (m, 4H), 2.34−2.26 (m, 2H), 2.24 (d, J = 5.6 Hz, 1H), 2.05−1.87 (m, 3H), 1.65−1.50 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.4, 165.8, 152.8, 146.6, 145.4, 141.1, 124.4, 119.8, 117.2, 114.2, 113.0, 58.7, 55.3, 55.1, 52.8, 49.5, 45.1, 44.0, 37.0, 27.7, 26.3, 21.5. HRMS (ESI-TOF) calcd for $C_{26}H_{35}N_6O_3$ $[M + H]^+$: 479.2765, found 479.2761.

(S)-N-(3-(4-(4-Methoxyphenyl)piperazin-1-yl)propyl)-2-(7-methyl-2-((1-methyl-1H-indol-2-yl)methyl)-3-oxo-2,3-dihydropyrido[2,3-b]-pyrazin-4(1H)-yl)acetamide ***31***. Compound **31** was prepared using coupling method B: To a solution of NaH (6 mg, 0.160 mmol, 2.0 equiv) in DMF (2.0 mL) in a flame-dried and argon-purged 2 dram reaction vial was added **20** (24 mg, 0.080 mmol, 1.0 equiv) at rt. After 30 min, the reaction was cooled to 0 °C, and a solution of **24** (38 mg, 0.104 mmol, 1.3 equiv) in DMF (1 mL) was added dropwise. The reaction was warmed to rt and stirred overnight. After 15 h, the reaction was quenched with 1 mL of H_2O and transferred to a 125 mL separatory funnel; the aqueous layer was diluted with EtOAc (50 mL), and the organic layer was washed with water (5 × 3 mL) and brine (3 × 4 mL). The EtOAc layer was collected, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to give the crude product (26 mg) as an oily residue. The sample was purified by mass-directed reverse-phase HPLC purification to give **31** in 17% yield (8.0 mg, 0.013 mmol, 99% purity) as a bright orange oil residue. R_f = 0.55 (1% MeOH/DCM). IR (neat) 3296, 3051, 2942, 2828, 1660, 1510, 1237, 1033, 826 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6) δ 7.93 (t, J = 5.6 Hz, 1H), 7.48 (dt, J = 7.9, 0.9 Hz, 1H), 7.39−7.32 (m, 2H), 7.16−7.07 (m, 2H), 7.01 (ddd, J = 8.0, 6.9, 1.0 Hz, 1H), 6.90−6.84 (m, 2H), 6.84−6.77 (m, 3H), 6.14 (d, J = 2.0 Hz, 1H), 4.51 (d, J = 1.3 Hz, 2H), 4.20 (ddd, J = 6.9, 4.6, 2.0 Hz, 1H), 3.68 (d, J = 12.9 Hz, 6H), 3.20−3.05 (m, 3H), 3.04−2.92 (m, 5H), 2.47 (t, J = 4.9 Hz, 4H), 2.30 (t, J = 7.2 Hz, 2H), 2.10 (t, J = 0.7 Hz, 3H), 1.58 (q, J = 7.0 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 167.2, 167.0, 152.8, 145.5, 138.0, 136.5, 134.9, 130.0, 128.8, 127.8, 127.8, 121.0, 120.1, 118.4, 117.3, 114.2, 109.5, 108.3, 56.3, 55.4, 55.2, 52.9, 49.6, 42.1, 37.0, 32.3, 28.5, 26.4, 17.3. HRMS (ESI-TOF) calcd for $C_{34}H_{42}N_7O_3$ $[M + H]^+$: 596.3344, found 596.3318.

(S)-N-(1-(4-(4-Methoxyphenyl)piperazin-1-yl)-3-methylbutan-2-yl)-2-(1-methyl-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6H)-yl)-acetamide ***32***. Compound **32** was prepared following a previously reported coupling protocol.[25] In a 10 mL flame-dried round-bottom flask was added **39** (38 mg, 0.136 mmol, 1.0 equiv) and **21** (35 mg, 0.136 mmol, 1.0 equiv) followed by (1*H*-benzo[*d*][1,2,3]triazol-1-yl)oxy)tri(pyrrolidin-1-yl)phosphonium hexafluorophosphate(V) (71 mg, 0.136 mmol, 1.0 equiv). To this mixture were added THF (4.0 mL) and then trimethylamine (57 μL, 0.408 mmol, 3.0 equiv), and the reaction mixture was stirred overnight at rt. After stirring at rt for 24 h, the crude reaction mixture was poured into a 125 mL Erlenmeyer containing DCM (10 mL) and water (5 mL). After this mixture was stirred for 10 min, it was then transferred to a 60 mL separatory funnel. The organic layer was separated from the aqueous layer and washed with saturated $NaHCO_3$(aq) (2 × 20 mL) and brine (3 × 30 mL), dried over Na_2SO_4, and concentrated to dryness to give the crude product as a thick oil. The crude product was dissolved in a minimal amount of DCM and MeOH and adsorbed onto Celite by removal of solvents. The Celite was loaded into a sample cartridge and used for automated MPLC purification. Purification was carried out using a 4 g normal-phase silica flash column on an automated MPLC system with a gradient elution from 100 to 90% DCM/MeOH over 30 min. Concentration of appropriate fractions afforded **32** in 80% yield (56 mg, 0.109 mmol, 91% purity) as a white powder; dec 171−173 °C. R_f = 0.55 (1% MeOH/DCM). IR (neat) 3298, 2952, 2829, 1652, 1511, 1468, 1381, 1216, 1084, 817 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 4.9 Hz, 1H), 7.86 (dd, J = 3.0, 1.5 Hz, 1H), 7.31 (dd, J = 4.1, 1.4 Hz, 1H), 6.99−6.91 (m, 1H), 6.87−6.74 (m, 4H), 6.67 (dd, J = 4.0, 2.9 Hz, 1H), 6.38−6.20 (m, 1H), 5.15 (d, J = 1.4 Hz, 2H), 4.02−3.87 (m, 1H), 3.78 (s, 3H), 3.16 (td, J = 6.7, 3.5 Hz, 4H), 2.68 (s, 3H), 2.55−2.42 (m, 3H), 1.89−1.72 (m, 4H), 0.88 (t, J = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.4, 155.9, 153.9, 145.6, 143.4, 142.2, 135.0, 124.2, 123.0, 122.8, 120.6, 118.2, 114.6, 113.7, 113.6, 58.5, 55.8, 53.5, 51.3, 50.1, 46.5, 46.4, 44.6, 30.3, 26.6, 26.5, 22.9, 18.8, 18.2. HRMS (ESI-TOF) calcd for $C_{29}H_{37}N_6O_3$ $[M + H]^+$: 517.2922, found 517.2936.

(S)-N-(1-(4-(4-Hydroxyphenyl)piperazin-1-yl)-3-methylbutan-2-yl)-2-(1-methyl-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6H)-yl)-acetamide ***33***. Compound **33** was prepared following a previously reported coupling protocol.[25] To a 25 mL flame-dried round-bottom flask were added **40** (20 mg, 0.076 mmol, 1.0 equiv) and **21** (25 mg, 0.084 mmol, 1.1 equiv) followed by ((1*H*-benzo[*d*][1,2,3]triazol-1-yl)oxy)tri(pyrrolidin-1-yl)phosphonium hexafluorophosphate(V) (40 mg, 0.0.076 mmol, 1.0 equiv). To this mixture were added THF (10 mL) and then trimethylamine (22 μL, 0.304 mmol, 4.0 equiv), and the reaction mixture was stirred overnight at rt. After stirring at rt for 24 h, the crude reaction mixture was poured into a 125 mL Erlenmeyer containing DCM (10 mL) and water (5 mL). After this mixture was stirred for 10 min, it was then transferred to a 60 mL separatory funnel. The organic layer was separated from the aqueous layer and washed with saturated $NaHCO_3$(aq) (2 × 20 mL) and brine (3 × 30 mL), dried over Na_2SO_4, and concentrated to dryness to give the crude product as a thick oil. The crude product was dissolved in a minimal amount of DCM and MeOH and adsorbed onto Celite by removal of solvents. The Celite was loaded into a sample cartridge and used for automated MPLC purification. Purification was carried out using a 4 g normal-phase silica flash column on an automated MPLC system with a gradient elution from 100 to 95% DCM/MeOH over 20 min. Concentration of appropriate fractions afforded **33** in 42% yield (16 mg, 0.032 mmol, 96.7% purity) as a light purple solid; dec 190−192 °C. R_f = 0.55 (1% MeOH/DCM). IR (neat) 3254, 2962, 2825, 1641, 1514, 1381, 1234, 1149, 725 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 4.9 Hz, 1H), 7.85 (dd, J = 2.9, 1.5 Hz, 1H), 7.32 (dd, J = 4.0, 1.4 Hz, 1H), 6.98−6.87 (m, 1H), 6.75−6.56 (m, 5H), 6.43−6.31 (m, 1H), 5.18 (s, 2H), 4.07−3.95 (m, 1H), 2.82−2.70 (m, 4H), 2.62 (dd, J = 10.9, 5.1 Hz, 4H), 2.52−2.30 (m, 4H), 1.98−1.86 (m, 1H), 0.93−0.84 (m, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 166.9, 154.8, 154.8, 150.8, 144.3, 144.3, 142.9, 142.0, 135.5, 123.7, 123.6, 122.5, 119.6, 117.6, 115.4, 113.2, 112.4, 59.5, 53.0, 50.8, 50.0, 42.8, 30.3, 22.2, 19.5, 17.5. HRMS (ESI-TOF) calcd for $C_{28}H_{33}N_6O_3$ $[M - H]^-$: 501.2620, found 501.2601.

KOR Analogue Library Synthesis.



Ethyl 2-(1-Methyl-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6H)-yl)acetate ***34***. The preparation of fragment **34** was carried out using

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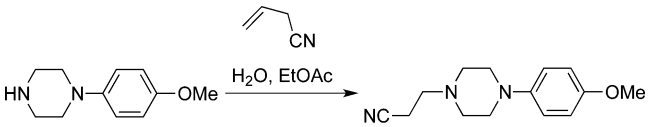
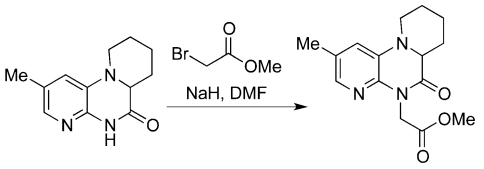
our previously reported procedure.[2] To a 20 mL flame-dried and argon-purged reaction vial were added 1-methylpyrido[2,3-*e*]pyrrolo-[1,2-*a*]pyrazin-6(5*H*)-one **7** (114 mg, 0.572 mmol, 1.0 equiv) followed by DMF (1.0 mL). To a separate 20 mL flame-dried and argon-purged reaction vial were added NaH (46 mg, 1.14 mmol, 2.0 equiv) followed by anhydrous DMF (1 mL). The NaH/DMF solution was cooled to 0 °C for 15 min, and then the substrate solution (**7**) was slowly added via syringe. This mixture was stirred at 0 °C for 2 h. After 2 h, ethyl 2-bromoacetate (82 μL, 0.741 mmol, 1.3 equiv) was added dropwise to the mixture at 0 °C. The reaction was warmed to rt and stirred overnight. After stirring for 15 h, additional NaH (34 mg, 0.855 mmol, 1.5 equiv) and ethyl 2-bromoacetate (82 μL, 0.741 mmol, 1.3 equiv) were added to the reaction. The reaction mixture remained stirring overnight at rt. After a total of 48 h, the starting material was completely consumed, and the reaction was quenched on ice with a few drops of DI H_2O. The solvents were removed by rotary evaporation to give the crude product as a tan residue. The crude product was dissolved in a minimal amount of DCM and MeOH and adsorbed onto silica by removal of solvents. The silica was loaded into a sample cartridge and used for automated MPLC purification. Purification was carried out using a normal-phase silica flash column on an automated MPLC system with a gradient elution from 5 to 100% EtOAc/hexanes over 30 min. Concentration of appropriate fractions afforded **34** in 41% yield (68 mg, 0.238 mmol) as a pale yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.22 (dd, J = 3.0, 1.5 Hz, 1H), 8.20 (d, J = 4.9 Hz, 1H), 7.46−7.01 (m, 2H), 6.79 (dd, J = 3.9, 2.9 Hz, 1H), 5.08 (s, 2H), 4.13 (q, J = 7.1 Hz, 2H), 2.84 (s, 3H), 1.18 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 168.5, 154.5, 143.2, 141.3, 136.1, 124.1, 123.2, 123.0, 119.6, 113.4, 112.9, 60.9, 41.7, 22.2, 14.1. LRMS (ESI-TOF) calcd for $C_{15}H_{16}N_3O_3$ $[M + H]^+$: 286.11, found 286.13. This data is consistent with that previously reported.[2]

*2-(1-Methyl-6-oxopyrido[2,3-e]pyrrolo[1,2-a]pyrazin-5(6H)-yl)-acetic acid **21**.* The preparation of fragment **21** was carried using our previously reported procedure.[2] To a 20 mL reaction vial containing **34** (68 mg, 0.238 mmol, 1.0 equiv) was added LiOH (8.58 mg, 0.358 mmol, 1.5 equiv) and then 2.0 mL of a 1:1:4 H_2O/MeOH/THF solvent solution. The vial was capped and stirred at rt. The reaction was monitored by TLC (1:10 EtOH/EtOAc) and UPLC analysis for the consumption of starting material. After 15 h, the crude reaction mixture was diluted with H_2O (5 mL) and transferred to a separatory funnel. The aqueous layer was washed with Et_2O (3 × 10 mL). The aqueous layer was collected and acidified (pH 2−3) by adding 2 N HCl (aqueous) dropwise. At pH 3, it was observed that a white precipitate started to crash out of the aqueous solution. The mixture was transferred into the separatory funnel and extracted with EtOAc (3 × 20 mL) and brine (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation to give crude product **21** in 73% yield (45 mg, 0.175 mmol) as a pale yellow solid, which was used without further purification. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.45−7.92 (m, 2H), 7.39−7.08 (m, 2H), 6.79 (dd, J = 3.9, 2.9 Hz, 1H), 5.01 (s, 2H), 2.85 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.8, 154.5, 143.2, 141.5, 136.0, 124.0, 123.3, 122.8, 119.6, 113.4, 112.7, 41.7, 22.3. This data is consistent with that previously reported.[2]

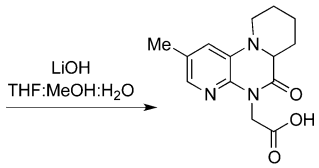


35

*3-(4-(4-Methoxyphenyl)piperazin-1-yl)propanenitrile **35**.* Preparation of 3-(4-(4-methoxyphenyl)piperazin-1-yl)propanenitrile **35** has been previously reported,[2,23] and we have prepared it with modification.[26] To a 50 mL round-bottom flask was added 1-(4-methoxyphenyl)piperazine (2.4 g, 12.69 mmol) and 4.0 mL of DI water, and this mixture was stirred for 5 min at rt. All of the solid was completely dissolved, and the reaction mixture was clear pale yellow in color. To this was added acrylonitrile (1.0 g, 1.247 mL, 19.04 mmol) dropwise. As the acrylonitrile was being added, the reaction mixture solidified after approximately half of the syringe volume was added. The remaining acrylonitrile was added, and 7 mL of EtOAc was added. The white precipitate was dissolved in the organic layer. The reaction vial was stirred for 30 min in aqueous/organic mixture before extracting with EtOAc. The reaction mixture was extracted with 3 × 15 mL of EtOAc. The organic layers were combined, collected over Na_2SO_4, filtered, and concentrated by rotary evaporation to yield **35** in 98% yield (crude) as a white crystalline solid (3.1 g, 12.60 mmol). R_f = 0.39 (8:1 EtOAc/hexanes; stains as a white spot with *p*-anisaldehyde). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.91−6.86 (m, 2H), 6.84−6.78 (m, 2H), 3.68 (s, 3H), 3.06−2.95 (m, 4H), 2.77−2.66 (m, 2H), 2.63−2.53 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.1, 145.6, 118.9, 118.4, 114.6, 55, 53.5, 52.9, 50.7, 16.0. HRMS (ESI-TOF) calcd for $C_{14}H_{20}N_3O_1$ $[M + H]^+$: 246.1601, found 246.1600. This data is consistent with that previously reported.[2]



15 **36**



37

*Methyl 2-(2-Methyl-6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido-[1,2-a:2′,3′-e]pyrazin-5-yl)acetate **36**.* The preparation of fragment **36** was carried using our previously reported procedure.[2] To a 20 mL flame-dried and argon-purged reaction vial were added **15** (60 mg, 0.276 mmol, 1.0 equiv) followed by DMF (2.0 mL). To a separate 20 mL flame-dried and argon-purged reaction vial were added NaH (12 mg, 0.304, 1.1 equiv) followed by anhydrous DMF (1 mL). The NaH/DMF solution was cooled to 0 °C for 15 min, and then the substrate solution (**15**) was slowly added via syringe. This mixture was stirred at 0 °C for 2 h. Then, methyl 2-bromoacetate (28 μL, 0.304 mmol, 1.1 equiv) was added dropwise to the mixture at 0 °C. The reaction was warmed to rt and stirred overnight. After stirring for 12 h, the starting material was completely consumed, and the reaction was quenched on ice with a few drops of DI H_2O. The solvents were removed by rotary evaporation to give the crude product as a tan residue. The crude product was dissolved in a minimal amount of DCM and MeOH and adsorbed onto silica by removal of solvents. The silica was loaded into a sample cartridge and used for automated MPLC purification. Purification was carried out using a normal-phase silica flash column on an automated MPLC system with a gradient elution from 5 to 100% EtOAc/hexanes over 30 min. Concentration of appropriate fractions afforded **36** in 63% yield (50 mg, 0.175 mmol) as a yellow orange sticky residue. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, J = 1.8, 0.9 Hz, 1H), 6.82 (d, J = 1.7 Hz, 1H), 4.92−4.78 (m, 2H), 3.73 (s, 3H), 3.71−3.67 (m, 1H), 3.67−3.61 (m, 1H), 2.79−2.66 (m, 1H), 2.25 (d, J = 0.8 Hz, 3H), 2.03−1.90 (m, 1H), 1.81−1.72 (m, 1H), 1.71−1.39 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.4, 168.5, 139.2, 136.9, 132.1, 129.0, 119.5, 59.9, 52.4, 46.4, 41.8, 27.3, 23.7, 23.2, 18.2. HRMS (ESI-TOF) calcd for $C_{15}H_{20}N_3O_3$ $[M + H]^+$: 290.1505, found 290.1513.

*2-(2-Methyl-6-oxo-6,6a,7,8,9,10-hexahydro-5H-dipyrido[1,2-a:2′,3′-e]pyrazin-5-yl)acetic Acid **37**.* The preparation of fragment **37** was carried using our previously reported procedure.[2] To a 20 mL reaction vial containing **36** (39 mg, 0.138 mmol, 1.0 equiv) were added LiOH (8.66 mg, 0.206 mmol, 1.5 equiv) and then 1.4 mL of a 1:1:4 H_2O/MeOH/THF solvent solution. The vial was capped and stirred at rt. The reaction was monitored by TLC (1:10 EtOH/EtOAc) and UPLC analysis for the consumption of starting material. After 15 h, the crude reaction mixture was diluted with H_2O (5 mL)

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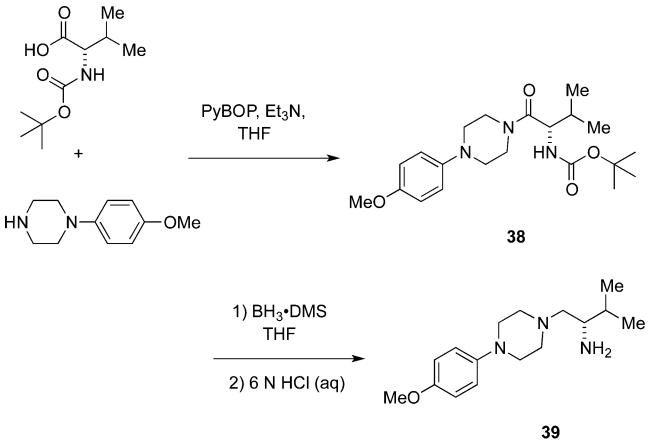
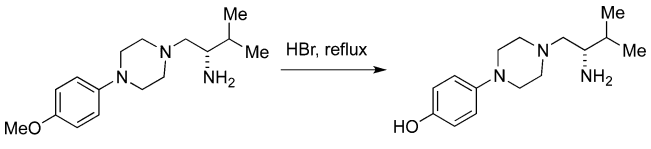
and transferred to a separatory funnel. The aqueous layer was washed with Et_2O (3 × 10 mL). The aqueous layer was collected and acidified (pH 2–3) by adding 2 N HCl (aqueous) dropwise. At pH 3, it was observed that a white precipitate started to crash out of the aqueous solution. The mixture was transferred into the separatory funnel and extracted with EtOAc (3 × 20 mL) and brine (2 × 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation to give crude product **37** in 82% yield (31 mg, 0.112 mmol) as a light green solid, which was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68–7.52 (m, 1H), 6.93–6.76 (m, 1H), 5.00–4.90 (m, 1H), 4.89–4.80 (m, 1H), 3.78–3.52 (m, 2H), 2.84–2.64 (m, 1H), 2.34–2.19 (m, 4H), 2.01–1.92 (m, 1H), 1.82–1.72 (m, 1H), 1.71–1.56 (m, 2H), 1.55–1.43 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 168.2, 139.0, 136.1, 132.2, 129.3, 120.0, 59.7, 46.4, 42.1, 27.1, 23.4, 23.0, 18.1. HRMS (ESI-TOF) calcd for $C_{14}H_{18}N_3O_3$ $[M + H]^+$: 276.1343, found 276.1349.



tert-Butyl (S)-(1-(4-(4-Methoxyphenyl)piperazin-1-yl)-3-methyl-1-oxobutan-2-yl)carbamate ***38***. Compound **38** was prepared following a previously reported coupling protocol.[25] To a 100 mL flame-dried round-bottom flask were added 1-(4-methoxyphenyl)piperazine (1.0 g, 5.20 mmol, 1.0 equiv), followed by THF (50 mL), and *N*-α-*t*-BOC-L-valine (1.1 g, 5.20 mmol, 1.0 equiv), ((1*H*-benzo[*d*][1,2,3]triazol-1-yl)oxy)tri(pyrrolidin-1-yl)phosphonium hexafluorophosphate(V) (2.71 g, 5.20 mmol, 1.0 equiv), and triethylamine (2.18 mL, 15.60 mmol, 3.0 equiv). The reaction was monitored by TLC, and after 4 h, the starting material was consumed. The crude reaction mixture was poured into a 250 mL Erlenmeyer containing Et_2O (100 mL) and water (25 mL). After this mixture was stirred for 10 min, it was then transferred to a 250 mL separatory funnel. The organic layer was separated from the aqueous layer and washed with 10% $NaHCO_3$(aq) and 2 × 20 mL of brine (3 × 30 mL), dried over Na_2SO_4, and concentrated to dryness to give the crude product as a thick oil. The crude product was dissolved in a minimal amount of DCM and MeOH and adsorbed onto Celite by removal of solvents. The silica was loaded into a sample cartridge and used for automated MPLC purification. Purification was carried out using a 4 g normal-phase silica flash column on an automated MPLC system with a gradient elution from 100 to 95% DCM/MeOH over 30 min. Concentration of appropriate fractions afforded **38** in 98% yield (2 g, 5.13 mmol) as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (d, J = 8.2 Hz, 2H), 5.30 (s, 1H), 4.54–4.38 (m, 1H), 3.78 (s, 4H), 3.34–2.90 (m, 5H), 2.17 (s, 1H), 2.00–1.90 (m, 1H), 1.87–1.76 (m, 4H), 1.44 (s, 9H), 0.97 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.8, 156.1, 130.1, 121.3, 119.5, 116.3, 114.9, 113.2, 79.8, 68.1, 55.8, 55.7, 54.9, 54.8, 53.6, 52.2, 51.7, 46.5, 46.4, 46.3, 42.5, 31.8, 31.6, 31.1, 28.5, 26.6, 26.5, 25.8, 19.8, 17.4, 17.2. LRMS (ESI-TOF) calcd for $C_{21}H_{34}N_3O_4$ $[M + H]^+$: 392.19, found 392.50.

tert-Butyl (S)-(1-(4-(4-Methoxyphenyl)piperazin-1-yl)-3-methyl-1-oxobutan-2-yl)carbamate ***39***. Compound **39** was prepared following a previously reported protocol.[25] To a flame-dried and argon-purged 100 mL round-bottom flask were added **38** (460 mg, 1.134 mmol, 1.0 equiv) followed by anhydrous THF (25 mL). The mixture was cooled to 0 °C, and 2 M borane-methyl sulfide complex in THF (2.8 mL, 1.134 mmol, 5.0 equiv) was carefully added dropwise. The reaction mixture was stirred at reflux for 2 h. After 2 h, the reaction mixture was cooled to 0 °C, and to the solution was added 5 mL of 6 N HCl(aq) carefully over approximately 40 min. Then, the mixture was fitted with a reflux condenser and heated to reflux for 2 h. The reaction was then cooled to rt and slowly quenched with water (70 mL) and EtOAc (70 mL), and the mixture was stirred for 15 min at rt. The aqueous layer was then basified with sat. $NaHCO_3$(aq) and extracted with DCM (3 × 100 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated by rotary evaporation to give product **39** in 97% yield (320 mg, 1.098 mmol) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.92–6.84 (m, 2H), 6.84–6.76 (m, 2H), 3.67 (s, 3H), 3.08–2.90 (m, 6H), 2.77–2.67 (m, 1H), 2.64–2.55 (m, 1H), 2.47–2.36 (m, 1H), 2.26–2.11 (m, 2H), 1.82–1.66 (m, 2H), 1.54 (pd, J = 6.8, 4.8 Hz, 1H), 0.93–0.75 (m, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 152.8, 145.5, 117.3, 117.3, 114.2, 62.3, 55.2, 53.3, 53.3, 52.2, 49.7, 45.9, 45.9, 31.2, 26.0, 25.9, 19.3, 17.5. LRMS (ESI-TOF) calcd for $C_{16}H_{28}N_3O_1$ $[M + H]^+$: 278.41, found 278.18.



(S)-4-(4-(2-Amino-3-methylbutyl)piperazin-1-yl)phenol ***40***. Compound **40** was prepared following a previously reported demethylation protocol.[25] To a 2.0—5.0 mL microwave reaction vial were added **39** (50 mg, 0.180 mmol, 1.0 equiv) followed by 1 mL of 48% HBr. The vial was sealed, heated to 110 °C, and left stirring overnight. The reaction was monitored by UPLC, and after 17 h, it was observed that the starting material was consumed. The reaction mixture was concentrated under a stream of nitrogen to dryness. After approximately 6 h, the residue was dissolved in 3 mL of DI H_2O. The mixture was basified to pH 10 with solid Na_2CO_3. The aqueous solution was extracted with DCM (3 × 10 mL), and the organic layers were combined, washed with brine (1 × 15 mL), dried over Na_2SO_4, and concentrated by rotary evaporation to give the crude product as a tan sticky residue. After treatment with Et_2O, evaporation of solvent, and drying overnight, the crude product became a light peach-colored solid in 72% yield (34 mg, 0.131 mmol), which was used without further purification. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.79 (s, 1H), 7.13–5.94 (m, 4H), 2.95 (s, 4H), 2.71–2.54 (m, 4H), 2.43–2.36 (m, 2H), 2.24–2.09 (m, 2H), 1.57–1.46 (m, 1H), 1.09 (t, J = 7.0 Hz, 1H), 0.92–0.79 (m, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 150.8, 144.2, 117.6, 115.4, 62.6, 53.4, 52.2, 50.1, 31.3, 19.3, 17.4. HRMS (ESI-TOF) calcd for $C_{15}H_{26}N_3O_1$ $[M + H]^+$: 264.2070, found 264.2069.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01350.

Copies of ^{1}H and ^{13}C NMR spectra for new and known compounds prepared by the present method (PDF)

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Notes

The authors declare no competing financial interest.

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