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Azaindole Hydroxamic Acids are Potent HIV-1 Integrase Inhibitors

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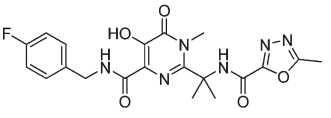
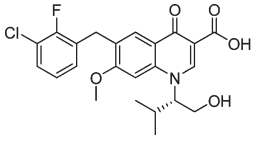
HIV-1 integrase (IN) is one of three enzymes encoded by the HIV genome and is essential for viral replication. Recently, HIV-1 IN inhibitors have emerged as a new promising class of therapeutics. Herein, we report the discovery of azaindole carboxylic acids and azaindole hydroxamic acids as potent inhibitors of the HIV-1 IN enzyme and their structure−activity relationships. Several 4-fluorobenzyl substituted azaindole hydroxamic acids showed potent antiviral activities in cell-based assays and offered a structurally simple scaffold for the development of novel HIV-1 IN inhibitors.

Introduction

Human immunodeficiency virus type 1 (HIV-1[a]), the causative pathogen of AIDS, replicates utilizing three essential enzymes encoded in the HIV pol gene: reverse transcriptase (RT), protease (PR), and integrase (IN). Many anti-HIV agents target either RT[1] or PR.[2] More recently, inhibitors of the host coreceptor chemokine receptor 5 (CCR5)[3,4] and the viral IN enzyme have emerged as two new promising classes of therapeutics for the treatment of AIDS[5,6] Efforts to target HIV-1 IN in particular have yielded the recent approval of raltegravir (MK-0518)[7,8] and encouraging phase II clinical trial with elvitegravir (GS-9137, JTK 303).[9] Several drivers remain however to discover new chemical classes of HIV-1 IN inhibitors that might be developed with complementary or improved properties regarding resistance, dosing, and tolerability.[10] Below, we present results from our own HIV-1 IN program aimed at addressing those needs.



Raltegravir (MK-0518)



Elvitegravir (GS-9137, JTK 303)

The catalytic core domain of IN contains two aspartate (Asp64, Asp116) and one glutamate (Glu152) residues that are critical for the catalytic activity of IN and are believed to bind Mg^{2+} and Mn^{2+} ions.[11] Recent data suggest that Mg^{2+} is the biologically relevant divalent metal critical for IN activity.[12] It is generally believed that IN inhibitors such as diketo acids (DKA, **A**), or the dihydroxy pyrimidines carboxamide class (**B**) bind these two metal ions in the active site while the hydrophobic aryl group participates in a specific interaction with an adjacent hydrophobic pocket or surface (Figure 1).[13,14] Broad screening of our internal compound collection lead to the identification of azaindole carboxylic acids **1a**−**h** with modest activity (IC_{50}: 0.95−7.35 μM) and good ligand efficiencies LE[15,16] (Δg > 0.35 kcal/mol) in the primary enzymatic assay (Table 1). As hydroxamic acids are recognized for their metal binding properties.[17] we reasoned that replacing the bidentate picolinic acid (picA, **C**)[18,19] moiety that only binds one Mg^{2+} by a picoline hydroxamic acid (picHA, **D**) moiety (Figure 1) would greatly facilitate binding of two Mg^{2+} ions, leading to improved inhibitory properties.[20]

Results and Discussion

Replacing the carboxylic acid moiety in compounds **1b** and **1c** by a hydroxamic acid moiety (compounds **2b** and **2c**) lead to a 40-fold increase in potency in the enzymatic assay, providing excellent potencies in our antiviral cell protection assay (EC_{50} < 10 nM) with no observed cytotoxicity up to the highest concentration tested (**2b**: CC_{50} > 320 μM; **2c**: CC_{50} > 1 μM). We explored a number of different aryl groups and concluded that compounds containing at least one (≥1) fluorine atom, with one fluorine required to be in the para position (**2b**: IC_{50} 84 nM, EC_{50} 8 nM; **2c**: IC_{50} 137 nM, EC_{50} 9

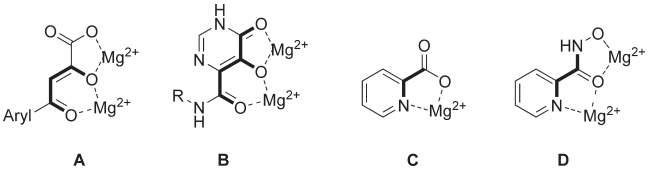


Figure 1. Metal binding of DKA (A), dihydroxypyrimidine carboxamide (B), PicA (C), and PicHA (D).

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[a] Abbreviations: biolum Ames, bioluminescent reverse mutation assay; CCR5, chemokine receptor 5; CC_{50}, 50% cytotoxic concentration; CPE, cytopathic effect; DCM, dichloromethane; DIEA, diisopropyl ethylamine; DKA, diketo acid; DMAP, dimethylamino pyridine; DMF, dimethylformamide; DMF-DMA, dimethylformamide dimethylacetal; DMSO, dimethylsulfoxide; EC_{50}, 50% effective concentration; ER, extraction ratio; HIV, human immunodeficiency virus; HATU, 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HTS, high-throughput screening; hHEP, human hepatocyte; hLM, human liver microsome; HPLC, high-performance liquid chromatography; IC_{50}, 50% inhibitory concentration; IN, integrase; LC-MS, liquid chromatography−mass spectrometry; LE, ligand efficiency; NADPH, reduced nicotineamide adenine dinucleotide phosphate; PicA, picolinic acid; PicHA, picoline hydroxamic acid; PR, protease; RT, reverse transcriptase; SPA, scintillation proximity assay; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TLC, thin-layer chromatography.

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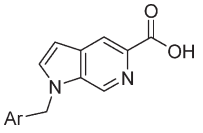
nM) provided the best combination of potency in both biochemical and cell-based assays (Table 2), and the best ligand efficiencies LE (Δg).[10]

Through metabolic activation, hydroxamic acids can undergo a Lossen rearrangement to form potentially mutagenic isocyanates.[21−23] It has been noted that the presence of the NH function is essential for mutagenicity of hydroxamic acids.[24] For the Lossen rearrangement to occur, the OH needs to be converted to a leaving group and then formation of the nitrene and rearrangement leads to the undesired isocyanate.[25] We reasoned that alkylation of either the NH or the OH would circumvent Lossen rearrangement. Methylation of either the NH or OH in compound **2b** provided compounds **3b** (EC_{50}: 32 nM) and **4b** (EC_{50}: 21 nM), leading to a small loss of cell-based antiviral activity. Methylation of both heteroatoms (compound **5b,** $EC_{50} > 10\ \mu M$) resulted in complete loss of enzymatic activity (Table 3). We evaluated compound **3b** in our bioluminescent reverse mutation assay (biolum Ames)[26] using *Salmonella* tester strains TA98 and TA100 and found it to be nonmutagenic in the presence and absence of activating enzymes (S9 fraction), whereas the unsubstituted hydroxamic acid **9** and the *O*-methylated analogue **4b** gave a positive result in both strains with and without metabolic activation by S9 fraction. Both *O*-methylated compounds **4b** (extraction ratio (ER) = 0.68) and **5b** (ER = 1) were rapidly cleared in our human liver P450 microsome (hLM) lability assay in the presence of NADPH. The *N*-methylated compound **3b** (ER < 0.36) showed low turnover in hLM against oxidative metabolism, however it was rapidly cleared in human hepatocytes (hHEP) due to glucuronidation of the free OH, a well-known drug metabolism pathway for hydroxamic acids.[27,28] We investigated if metabolism could be attenuated with bulkier R_1 groups. Increasing the size of R_1 (Table 4) did not modify turnover rate in human hepatocytes and resulted in a rapid drop in both biochemical and cell-based antiviral assays.

Table 1. Enzymatic Activities and Ligand Efficiencies of Azaindole Carboxylic Acids from High-Throughput Screening (HTS)



compd	Ar	IC_{50}[a] (μM)	LE (Δg)[b] (kcal/mol)
1a	2-F-Ph	> 50	< 0.29
1b	2,4-F-Ph	3.50 ± 0.90	0.353
1c	4-F-Ph	7.35 ± 4.45(2)	0.351
1d	2,3,4-F-Ph	3.69 ± 0.41	0.336
1e	2-F, 3-Cl-Ph	0.95 ± 0.36	0.390
1f	2,6-F-3-Cl-Ph	1.19 ± 0.93	0.366
1g	2,3-Cl-Ph	5.42 ± 2.2	0.341
1h	4-Cl-thiophene	3.20 ± 0.14	0.393

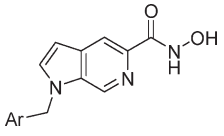
[a] Strand transfer scintillation proximity assay. [b] Ligand efficiency (LE), $\Delta g = \Delta G/N_{\text{non-hydrogenatoms}}$; $\Delta G = -RT \ln(IC_{50})$; $T = 300$ K.

Synthesis

The chemistry used for formation of azaindole esters **19a−b** and final products **2−11** is depicted in Scheme 1. Hydroxypyridine **12** was converted to the corresponding bromide **13** using $POBr_3$. Reaction of **13** with zinc cyanide[29] in the presence of a catalytic amounts of $Pd(PPh_3)_4$ provided nitrile **14**, which was converted to esters **15** (R = Me) and **16** (R = Et) under acidic Pinner conditions. Reaction of **15** and **16** with dimethylformamide dimethyl acetal (DMF-DMA) followed by reduction as described by Leimgruber-Batcho[30] provided azaindole esters **17** and **18**,[31,32] which were alkylated using benzyl halides and sodium hydride to provide esters **19** (R = Me) and **20** (R = Et). Saponification of esters **20a−h** with NaOH provided acids **1a−h**.

Hydroxamic acids **2−11** were prepared either by treatment of esters **19** and **20** with hydroxyl amines in the presence of NaOH,[33] or by coupling acids **1a−h** with hydroxyl amines in the presence of HATU. *N*-Alkylated hydroxylamines **23a−c**

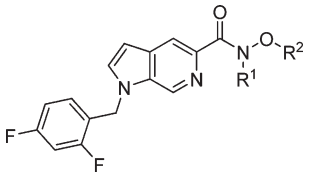
Table 2. Enzymatic and Antiviral Activity of Azaindole Hydroxamic Acids



compd	Ar	IC_{50}[a] (nM)	EC_{50}[b] (nM)	CC_{50}[b] (μM)	LE (Δg)[c] (kcal /mol)
2b	2,4-F-Ph	84 ± 38 (6)	8	> 320	0.440
2c	4-F-Ph	137 ± 31	9	159	0.444
2e	2-F, 3-Cl-Ph	102 ± 1	8	> 320	0.436
2f	2,6-F, 3-Cl-Ph	131 ± 35	7	> 1	0.407
2g	2,3-Cl-Ph	442 ± 175	35	> 320	0.393
2h	4-Cl-thiophene	387 ± 48	20	> 10	0.436
2i	2-pyridyl	779 ± 217 (2)	88	> 10	0.418
2j	3-$HOCH_2$-2-pyridyl	5730 ± 290 (2)	730	> 10	0.324
2k	2-CN, 4-F-Ph	812 ± 680 (2)	120	> 10	0.360
2l	3-CN-Ph	1620 ± 200 (2)	500	> 10	0.358
2m	4-CN-Ph	> 10000	1200	> 10	< 0.29
2n	2-$CONH_2$, 4-F-Ph	1300 ± 40 (2)	55	> 10	0.333
2o	3-$CONH_2$, 4-F-Ph	608 ± 28 (2)	58	> 10	0.352
2p	3-$CONH_2$-Ph	1720 ± 60 (2)	530	> 10	0.341
2q	4-$CONH_2$-Ph	> 10000	> 10,00	> 10	< 0.29

[a] Strand transfer scintillation proximity assay. [b] HIV-1 cytopathic effect (CPE) inhibition assay; EC_{50}, 50% effective concentration; CC_{50}, 50% cytotoxic concentration. [c] Ligand efficiency (LE), $\Delta g = \Delta G/N_{\text{non-hydrogenatoms}}$; $\Delta G = -RT \ln(IC_{50})$; $T = 300$ K.

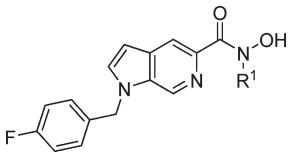
Table 3. Enzymatic and Antiviral Activity, Metabolic Stability, and Mutagenicity of *N*- and *O*-Methyl Hydroxamic Acids



compd	R^1	R^2	IC_{50}[a] (nM)	EC_{50}[b] (nM)	CC_{50}[b] (μM)	ER[c] (hLM)	ER[c] (hHEP)	Biolum Ames[d]
2b	H	H	84 ± 38 (6)	8	> 320	< 0.26	0.9	positive
3b	CH_3	H	250 ± 91 (4)	32	135	< 0.36	1	negative
4b	H	CH_3	356 ± 213 (4)	21	> 320	0.68	1	positive
5b	CH_3	CH_3	> 50000	> 10000	> 10	1.00	1	ND

[a] Strand transfer scintillation proximity assay. [b] HIV-1 cytopathic effect (CPE) inhibition assay; EC_{50}, 50% effective concentration, CC_{50}, 50% cytotoxic concentration. [c] Metabolic stability in human liver microsomes (hLM) + NADPH, and in human hepatocytes (hHEP); ER, extraction ratio after 4 h. [d] Bioluminescent reverse mutation assay (Biolum Ames) in *Salmonella* tester strains TA98 and TA100 ± metabolizing enzymes (S9 fraction); ND, not determined.

Table 4. Enzymatic and Antiviral Activity of *N*-Alkyl-Substituted Hydroxamic Acids



compd	R^1	IC_{50}[a] (nM)	EC_{50}[b] (nM)	CC_{50}[b] (μM)	ER[c] (hHEP)
2c	H	137 ± 31	9	> 320	0.92
6c	methyl	250 ± 14	39	200	1.0
7c	*n*-propyl	618 ± 108	350	26	0.96
8c	3-OH-propyl	804 ± 127	300	77	0.95
9c	*iso*-butyl	1700 ± 200	1400	102	0.95
10c	*iso*-propyl	8000 ± 3700	3500	36	0.93
11c	benzyl	23000 ± 3370	330	> 320	1

[a] Strand transfer scintillation proximity assay. [b] HIV-1 cytopathic effect (CPE) inhibition assay; EC_{50}, 50% effective concentration; CC_{50}, 50% cytotoxic concentration. [c] Metabolic stability in human hepatocytes (hHEP); ER, extraction ratio after 4 h.

(Scheme 2) were prepared by alkylation of the sodium salt of ethyl 3-methyl-4-isoxazolecarboxylate[34] **21** with iodoalkanes, followed by cleavage of **22a**−**c** under acid conditions.

Conclusion

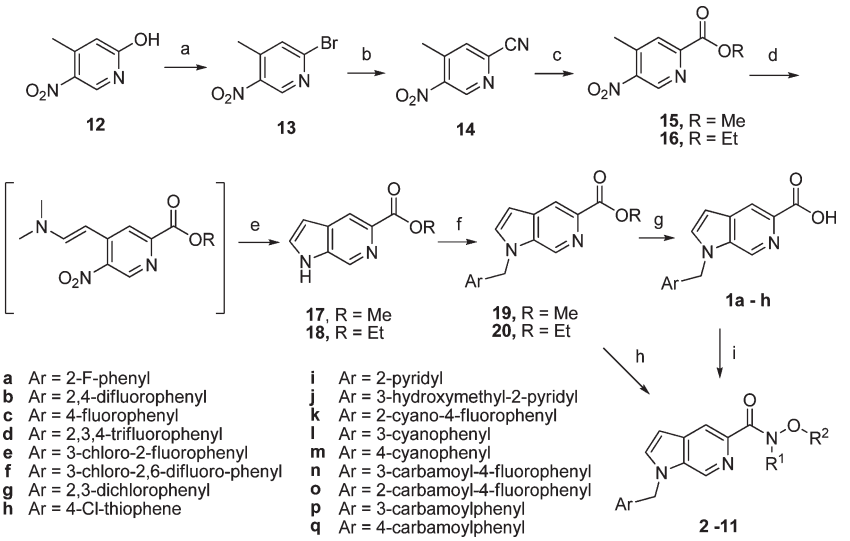
Azaindole hydroxamic acids **9**−**12** are potent HIV integrase inhibitors with antiviral cell-based activities comparable to the currently marketed HIV Integrase inhibitor raltegravir (EC_{50}: 10 nM).[7] Unsubstituted hydroxamic acids are mutagenic, while *N*-methylation leads to analogues (e.g., compound **3b**) that show a negative result in the Ames assay. Both unsubstituted and *N*-alkyl substituted hydroxamic acids are cleared through phase 2 glucuronidation pathways, and further efforts toward attenuating glucuronidation will be reported in a subsequent publication.

Experimental Section

Integrase Strand-Transfer Scintillation Proximity Assay (SPA). A detailed description of the integrase strand-transfer scintillation proximity assay is described[35] and briefly summarized here. Full-length HIV-1 IN constructed with an amino terminal 6-histidine tag, and mutations described by Chen et al.[36] was expressed in *Escherichia coli* and purified following standard methods. Double-stranded donor DNA (ds-DNA) representing preprocessed ds-DNA derived from the LTR U5 sequence of the viral genome was synthesized (TriLink Biotechnologies, San Diego, CA) as a 5′ biotinylated strand and a CA base-pair overhang at the 5′ end of the nonbiotinylated strand. A 3′ dideoxy derivative of the donor DNA was generated as a control ds-DNA to test for nonspecific interactions. Target ds-DNA was prepared as a [^{3}H]-thymidine labeled product (PerkinElmer Life Sciences Inc., Boston, MA) from enzymatic extension of overhanging 3′ ends of poly(dA) DNA. The final product consists of 5′-blunt end ds-DNA with six [^{3}H]-thymidine nucleotides at both 5′ ends and specific activity of > 900 Ci/mmol. Biotinylated donor ds-DNA bound to streptavidin-coated polyvinyltoluene SPA beads (Amersham Pharmacia, Piscataway, NJ) was incubated with enzyme 15 min at 22 °C to form an integrase−donor DNA complex. The strand-transfer reaction was initiated by addition of [^{3}H]-thymidine labeled target DNA. Final assay conditions were 2 pmol donor DNA, 246 nM integrase, and 50 nM target DNA in 22.5 mM MOPS (pH 7.2), 20 mM NaCl, 4 mM CHAPS, 0.05% NP40, 4 mM $MgCl_2$, 1% DMSO, and 10 mM DTT. Reactions were for 50 min at 37 °C, followed by addition of 150 mM EDTA, 90 mM NaOH, and 6 M CsCl to stop the reaction and dissociate integrase/DNA complexes. Compounds solvated and diluted in 100% DMSO were transferred to the assay well in 10% DMSO prior to addition of assay components. Activity was measured in the TopCount plate-based scintillation counter programmed with quench correction to normalize data for potential color absorption of the compounds (PerkinElmer Life Sciences Inc., Boston, MA). Compounds are tested as 2−3 replicates per concentration in 1 or more independent experiments. The corrected percentage inhibition for a compound was fit to a four-parameter logistic equation with variable Hill slope using GraphPad Prism software (GraphPad Software, La Jolla, CA). Acceptable criteria for a curve fit is a percent correlation coefficient (R^2) exceeding 92%. Data is reported as the mean IC_{50} ± standard deviation (SD) and number (N) of independent experiments. All other enzymatic data is IC_{50} ± standard error (SE) of the curve fit parameter from replicate compound doses in a single experiment.

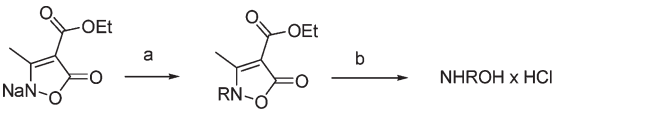
HIV-1 Cytopathic Effect (CPE) Inhibition Assay. The antiviral activities of potential modulator compounds (test compounds) were determined as a function of their ability to protect T-cells from the cytopathic effects of HIV-1 infection using the XTT dye reduction method.[37] CEM-SS cells seeded at 2×10^4 cells per well into 96-well plates were mock infected or infected with HIV-1 RF virus at an MOI resulting in 90% cell

Scheme 1. Synthesis of Hydroxamic Acids **2**−**11**[a]



[a] Reagents and conditions: (a) $POBr_3$/DCM, heat, 34 h (90%); (b) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 80 °C, 3 h (83%); (c) HCl, MeOH, H_2O, or H_2SO_4,EtOH, heat, 3 h (92%); (d) DMF-DMA, DMF, 90 °C, 0.5 h; (e) Pd/C, MeOH, H_2, 50 °C, 3 d (70%, 2 steps); (f) $ArCH_2$(Cl,Br), NaH, DMF or THF (47−100%) (g) NaOH, MeOH, H_2O (18−91%); (h) NaOH, NH_2OH, MeOH (4−28%); (i) HATU, NEt_3 or DIEA or DMAP, NHR_1OR_2 (7−87%).

Scheme 2. Synthesis of *N*-Alkyl Hydroxylamines[a]



[a] Reagents and conditions: (a) RI, DMF, 120 °C, 1 h (13−34%); (b) HCl (quant).

death after 6 days. Test compounds at two or more replicate wells per half-log dilution were added to the cells at the time of seeding and prior to the mock or HIV-1 RF virus infection. On day 6, 50 μL of XTT (1 mg/mL XTT tetrazolium and 0.02 nM phenazine methosulfate) was added to the wells for additional 4 h incubation. Cell viability, as determined by the amount of XTT formazan produced, was quantified spectrophotometrically by absorbance at 450 nm. Data from CPE assays were expressed as the percent of formazan produced in compound-treated cells compared to formazan produced in wells of uninfected, compound-free cells. The 50% effective concentration (EC_{50}) was calculated as the concentration of compound that increased the percentage of formazan production in infected, compound-treated cells to 50% of that produced by uninfected, compound-free cells. The 50% cytotoxic concentration (CC_{50}) was calculated as the concentration of compound that decreased the percentage of formazan produced in uninfected, compound-treated cells compared to uninfected, compound-free cells. Compounds were tested in one or more independent experiments. Variability was typically less than 30% for replicate data.

General Synthetic. Starting materials and other reagents were purchased from commercial suppliers and were used without further purification, unless otherwise indicated. All reactions were performed under a positive pressure of nitrogen, argon, or with a drying tube, at ambient temperature (unless otherwise stated), in anhydrous solvents, unless otherwise indicated. Analytical thin-layer chromatography was performed on glass-backed silica gel 60 °F 254 plates (Analtech (0.25 mm)) and eluted with the appropriate solvent ratios (v/v). The reactions were assayed by high-performance liquid chromotagraphy (HPLC) or thin-layer chromatography (TLC) and terminated as judged by the consumption of starting material. The TLC plates were visualized by UV, phosphomolybdic acid stain, or iodine stain. Microwave assisted reactions were run in a Smith-Creator (Personal Chemistry). ^{1}H NMR spectra were recorded on a Bruker instrument operating at 300 MHz unless otherwise indicated. NMR spectra are obtained as DMSO-d_6 or $CDCl_3$ solutions (reported in ppm), using chloroform as the reference standard (7.25 ppm) or DMSO-d_6 (2.50 ppm). Other NMR solvents were used as needed. When peak multiplicities are reported, the following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, br = broadened, dd = doublet of doublets, dt = doublet of triplets. Coupling constants, when given, are reported in Hz. The mass spectra were obtained using liquid chromatography mass spectrometry (LC-MS) on an Agilent instrument using atmospheric pressure chemical ionization (APCI) or electrospray ionization (ESI). High resultion mass measurement were carrried out on an Agilent TOF 6200 series with ESI. All test compounds showed ≥95% purity as determined by combustion analysis or by high-performance liquid chromatography (HPLC). HPLC conditions were as follows: Eclipse XDB C8, 4.6 mm × 150 mm, 5 μm, 5% → 95% CH_3CN/H_2O/0.1%TFA, 10 min run, flow rate 1.5 mL/min, UV detection (λ = 254, 224 nm), or 5% → 95% CH_3CN/H_2O/0.1%TFA, 9 min run, hold 95% CH_3CN/H_2O/0.1%TFA for 3 min, flow rate 1.5 mL/min. Combustion analyses were performed by Atlantic Microlab, Inc. (Norcross, GA).

Bromo-4-methyl-5-nitropyridine (13). A solution of 4-methyl-5-nitropyridin-2-ol **12** (82 g, 0.53 mol) and $POBr_3$ (229 g, 0.8 mol, 1.5 equiv) in dichloromethane (2 L) was heated under a nitrogen atmosphere in a 3 L three-neck flask with overhead stirrer for 24 h. The mixture cooled to room temperature and then was chilled in an ice−water bath and filtered. The solid consisted of a 1:1 mixture of desired product **13** and unreacted starting material **12**; the filtrate contained the desired product and unreacted $POBr_3$. The solid (46 g) and fresh $POBr_3$ was dissolved in dichloromethane and refluxed for 10 h. The liquid was decanted and combined with the filtrate of the first reaction. The combined solutions were concentrated to a volume of 1.5 L. With stirring in an ice−water bath, ice (500 g) was added to quench excess $POBr_3$. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The

combined organic extracts were dried (magnesium sulfate) and concentrated. The product was recrystallized from hexane. Yield: 104 g (90%). ^{1}H NMR ($CDCl_3$) δ 8.95 (s, 1H), 7.52 (s, 1H), 2.63 (s, 3H). LC-MS (APCI, M − H$^-$) m/z 215 and 217 (bromine isotope pattern).

4-Methyl-5-nitropyridine-2-carbonitrile (14). 2-Bromo-4-methyl-5-nitropyridine **13** (104 g, 0.479 mol), $Zn(CN)_2$ (79 g, 0.673 mol), 1.4 equiv), and $Pd(PPh_3)_4$ (27 g, 0.023 mol, 5 mol %) were added to a round-bottom flask (NOTE: using catalyst purchased from STREM resulted in shorter reaction times and better yields). DMF (900 mL) was degassed for 10 min before adding to the solid mixture. The mixture was heated in an oil bath to an internal temperature of 80 °C. The color changed from light-yellow to light-brown as the internal temperature reached 80 °C. The mixture was stirred at the same temperature for 3 h and monitored by TLC. The solvent was removed in vacuo. The residue was cast into a mixture of dichloromethane: water, and insoluble material was removed by filtration through celite. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried (magnesium sulfate) and concentrated. The residue was purified by column chromatography starting with 100% hexane to hexane/ethyl acetate 4:1. Recrystallization from hexane yielded 65.8 g (83%) of the desired product. ^{1}H NMR ($CDCl_3$) δ 9.20 (s, 1H), 7.73 (s, 1H), 2.71 (s, 1H). LC-MS (APCI, M − H$^-$) m/z 162.

Methyl 4-Methyl-5-nitropyridine-2-carboxylate (15). HCl gas was bubbled into the solution of **14** (30 g, 0.185 mol) in methanol (200 mL) with cooling in a ice−water bath for 5 min. Then 3.3 mL water (1 equiv) was added to the flask. The resulting solution was heated to reflux for 3 h. The desired product precipitated as HCl salt (white crystals). The mixture was cooled to room temperature, and the precipitate was collected by vacuum filtration. The solid was transferred to a 1 L separation funnel, neutralized with satd aq $NaHCO_3$ (400 mL), and extracted with dichloromethane (400 mL). The organic layer was dried over Na_2SO_4, concentrated, and dried in vacuo to give a white solid (33 g, 92% yield). ^{1}H NMR (DMSO-d_6) δ 9.19 (s, 1H), 8.21 (s, 1H), 3.91 (s, 3H), 2.63 (s, 3H). LC-MS (APCI, M + H$^+$) m/z 197.0.

Ethyl 4-Methyl-5-nitropyridine-2-carboxylate (16). Concentrated sulfuric acid (768 mL) was added slowly to ethanol (1.6 L) with cooling. **14** (62.4 g, 0.38 mol) was added to the cold solution, and the solution was then warmed to reflux under nitrogen for 2 h. The majority of the solvent was removed in vacuo, and the remaining thick solution was poured onto ice (1 kg). After stirring for 15 min, the mixture was extracted with ether (2 × 1 L) and multiple times with dichloromethane. (NOTE: the organic layer is the TOP layer due to lower density than water/sulfuric acid 1:1). As the extraction continued, the organic layer changed from top layer to bottom layer due to change in density as less ethanol was extracted. The combined organic extracts were dried (magnesium sulfate) and concentrated. Recrystallization from hexane yielded 44.4 g (56%) of the desired product. ^{1}H NMR ($CDCl_3$) δ 9.22 (s, 1 H), 8.13 (s, 1H), 4.51 (q, J = 7.5 Hz, 2H), 2.71 (s, 3 H), 1.46 (t, J = 7.5 Hz, 3 H). LC-MS: (APCI, M + H$^+$) m/z 209.

Methyl 1*H*-Pyrrolo[2,3-*c*]pyridine-5-carboxylate (17). A mixture of **15** (3.5 g, 17.8 mmol) and dimethylformamide dimethylacetal (DMF-DMA) (3.6 mL, 1.5 equiv) in acetonitrile (35 mL) was heated in a microwave at 140 °C for 20 min. The solvent was removed, and the residue (5.1 g) was carried onto the next step without further purification. To a 500 mL Parr bottle was added crude (*E*)-methyl 4-(2-(dimethylamino)vinyl)-5-nitropicolinate (18.9 g, 75.2 mmol) and anhydrous methanol (200 mL). The mixture was purged with nitrogen gas for 10 min. To this suspension was added Pd/C (1.90 g, 10% w/w), and the suspension was degassed for 5 more min. The hydrogenation began with 43 psi H_2, and an exotherm was noted (about 2−3 °C per min) inside the Parr bottle (monitored internally). As the temperature inside of the reaction reached 45 °C, the hydrogen gas flow into the Parr bottle was stopped and the temperature was allowed to cool down to 25 °C for 30 min. The color of the liquid of the suspension changed from purple−red to light-green and then colorless in the first hour of the reduction, and about 30 psi H_2 was consumed. The hydrogen pressure was brought to 50 psi, and the hydrogenation was continued at 50 °C for 20 h. After cooling the reaction mixture to 20 °C, the solid mixture, which contained Pd(10%)/C and product, was isolated by filtration. The solid mixture was suspended in DMSO (200 mL), and the suspension was heated on a hot plate to 80 °C inside with stirring for 10 min. The hot suspension was filtered and the Pd(10%)/C solid was washed with a small portion of DMSO (50 mL). The DMSO filtrate and washing were combined and poured into water (600 mL) and the mixture was allowed to stir for 1 h. Solids were removed by filtration through a cake of celite to afford a pale-yellow liquid, which was concentrated in vacuo to provide the title compound as an ivory solid (11.3 g, 86%). ^{1}H NMR (DMSO-d_6) δ 11.99 (s, 1H), 8.80 (s, 1H), 8.36 (s, 1H), 7.73 (d, J = 3.0 Hz, 1H), 6.68 (d, J = 2.8 Hz, 1H), 3.84 (s, 3H). LC-MS (APCI, M − H$^-$) m/z 175.

Ethyl 1*H*-Pyrrolo[2,3-*c*]pyridine-5-carboxylate (18). A mixture of **16** (39.5 g, 0.19 mol) and DMF-DMA (30.6 g, 0.26 mol, 1.35 equiv) in DMF (470 mL) was heated to 90 °C for 30 min. The solvent was removed in vacuo. The residue (78 g) was used without further purification in the next step. A solution of crude (*E*)-ethyl 4-(2-(dimethylamino)vinyl)-5-nitropicolinate (78 g) in ethanol (350 mL) was degassed and Pd (10%)/C (12 g, 30 wt %) was added. The mixture was shaken in a Parr shaker under hydrogen (40 psi) for 16 h. The initial reaction was exothermic, the temperature rose to 65 °C within 2 h, the pressure dropped by 30 psi, and the color changed from red to light-green. After the solution reached room temperature, the flask was shaken under hydrogen (50 psi) for 16 h. The reaction was monitored by LC-MS; at this point the solution contained 30% of desired product. After shaking under hydrogen (50 psi, 50 °C) for additional 2.5 days, the LC-MS showed 70% of the desired product. The mixture was filtered through a pad of celite, and the filter cake was extracted twice by refluxing in ethanol (2 × 1 L) and filtration of the hot solution. The combined filtrates were concentrated, and the residue was recrystallized from ethanol to give 20 g of pure product. The mother liquor containing the desired product and the intermediate was concentrated and dissolved in ethanol (300 mL). The mixture was hydrogenated at 50 °C and 50 psi for 3 days using Pd (10%)/C (5 g), and then was worked up as before to provide additional 3 g of desired product for a total yield of 23 g (64%). ^{1}H NMR (DMSO-d_6) δ 11.99 (s, 1H), 8.82 (s, 1H), 8.37 (s, 1H), 7.73 (s, 1H), 6.69 (s, 1H), 4.32 (q, J = 7.5 Hz, 2H), 1.34 (t, J = 7.5 Hz, 3H). LC-MS (APCI, M + H$^+$) m/z 191.

General Procedure A. Methyl 1-(4-Fluorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (19c). To a stirred solution of **17** (15.0 g, 85.1 mmol) in DMF (120 mL) at 10 °C under a nitrogen atmosphere was added sodium hydride (3.75 g, 60% in mineral oil, 93.7 mmol, 1.1 equiv) in three portions over 5 min. The slurry gradually became a homogeneous solution after stirring for 130 min, and then 4-fluorobenzyl bromide (0.60 g, 2.89 mmol) was added at such a rate that the temperature did not exceed 15 °C. The resulting mixture was allowed to warm to room temperature and was stirred for 2.5 h at ambient temperature. The mixture was carefully poured into water (120 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with water (2 × 30 mL), dried over sodium sulfate, and concentrated in vacuo to provide the crude product as a sticky yellow solid. The crude material was purified by flash chromatography (hexane:ethyl acetate 2:1), to provide the title compound as a white solid (21.3 g, 88% yield). ^{1}H NMR (DMSO-d_6) δ 8.97 (s, 1H), 8.30 (s, 1H), 7.87 (d, J = 2.8 Hz, 1H), 7.34 (dd, J = 8.3, 5.7 Hz, 2H), 7.15 (t, J = 8.9 Hz, 2H), 6.73

(d, J = 2.8 Hz, 1H), 5.59 (s, 2H), 3.84 (s, 3H). LC-MS (APCI, M + H$^+$) m/z 285.3.

Methyl 1-(2,4-Difluorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (19b). Prepared from **17** (976 mg, 5.5 mmol) using 2,4-difluorobenzylbromide (1.13 g, 5.5 mmol) as described by general procedure A to provide 1.32 g (82%) colorless needles. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.36 (s, 1H), 7.79 (d, J = 3.03 Hz, 1H), 7.32 (dd, J = 8.97, 6.69 Hz, 2H), 7.32 (m, 1H), 7.07 (td, J = 8.53, 1.89 Hz, 1H), 6.75 (d, J = 3.03 Hz, 1H), 5.65 (s, 2H), 3.85 (s, 3H). LC-MS (APCI, M + H$^+$) m/z 303.0.

Methyl 1-(2-Cyano-4-fluorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (19k). Prepared according to general procedure A using THF as solvent to provide the crude product (750 mg, 82%), which was used in the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.94 (s, 1H), 8.39 (s, 1H), 7.95 (dd, J = 8.5, 2.7 Hz, 1H), 7.79 (d, J = 3.2 Hz, 1H), 7.54 (td, J = 8.9, 2.7 Hz, 1H), 7.08 (dd, J = 8.9, 5.5 Hz, 1H), 6.81 (d, J = 3.0 Hz, 1H), 5.84 (s, 2H), 3.86 (s, 3H). LC-MS (ESI, M + H$^+$) m/z 311.2.

Methyl 1-(3-Cyanobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (19l). Prepared from **17** and 3-cyano-benzylbromide (870 mg) as described by general procedure A using THF as solvent. Yield: 100%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 (s, 1H), 8.37 (s, 1H), 7.92 (d, J = 3.2 Hz, 1H), 7.83 (bs, 1H), 7.78 (m, 1H), 7.57 (s, 1H), 7.56 (m, 1H), 6.77 (d, J = 3.2 Hz, 1H), 5.68 (s, 2H), 3.86 (s, 3H). LC-MS (ESI, M + H$^+$) m/z 292.

Methyl 1-(4-Cyanobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (19m). Prepared from **17** and 4-cyano-benzylbromide (300 mg) as described by general procedure A using THF as solvent. Yield: 73%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (s, 1H), 8.37 (s, 1H), 7.90 (d, J = 3.2 Hz, 1H), 7.81 (d, J = 8.1 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 6.79 (d, J = 3.2 Hz, 1H), 5.74 (s, 2H), 3.85 (s, 3H). LC-MS (ESI, M + H$^+$) m/z 292.

Methyl 1-(Pyridin-2-ylmethyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (19i). Prepared from **17** and 2-(bromomethyl)pyridine hydrobromide salt (340 mg) as described by general procedure A using THF as solvent and an additional equivalent of NaH to free base the aforementioned salt. Yield: 90%. LC-MS (ESI, M + H$^+$) m/z 268. Used as crude material in the next step.

Methyl 1-((6-(Hydroxymethyl)pyridin-2-yl)methyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (19j). Prepared from **17** and (6-(bromomethyl)pyridin-2-yl)methanol (170 mg) as described by general procedure A using THF as solvent. Yield: 40%. LC-MS (ESI, M + H$^+$) m/z 298. Used as crude material in the next step.

Ethyl 1-(2,4-Difluorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (20b). Prepared from **18** and 2,4-difluorobenzyl bromide (0.60 g, 2.89 mmol) as described by general procedure A. Yield: 0.40 g (48%). ^{1}H NMR (DMSO-d_6) δ 8.98 (s, 1H), 8.37 (s, 1H), 7.80 (d, J = 3.0 Hz, 1H), 7.38−7.27 (m, 2H), 7.11 (dd, J = J' = 6.2 Hz, 1H), 6.76 (d, J = 3.2 Hz, 1H), 5.66 (s, 2H), 4.33 (q, 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H). LC-MS (ESI, M + H$^+$) m/z 317.0.

Ethyl 1-(4-Fluorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (20c). Prepared from **18** and 4-fluorobenzyl bromide (220 mg, 1.18 mmol) as described by general procedure A. Yield: 110 mg (47%). ^{1}H NMR (CD$_3$OD) δ 8.91 (s, 1H), 8.62 (s, 1H), 7.90 (d, J = 3.0 Hz, 1H), 7.42 (m, 2H), 7.20 (m, 2H), 6.90 (d, J = 3.0 Hz, 1H), 5.75 (s, 2H), 4.60 (q, J = 7.0 Hz, 2H), 1.60 (t, J = 7.0 Hz, 3H). LC-MS (ESI, M + H$^+$) m/z 299.1.

Ethyl 1-(2,3,4-Trifluorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (20d). Prepared from **18** and 2,3,4-trifluorobenzyl bromide (177 mg, 0.79 mmol) as described by general procedure A. Yield: 101 mg (38%). ^{1}H NMR (CDCl$_3$) δ 8.84 (brs., 1H), 8.50 (brs, 1H), 7.38 (d, J = 2.6 Hz, 1H), 7.26 (s, 1H), 6.89 (t, J = 7.9 Hz, 1H), 6.75 (d, J = 7.9 Hz,1H), 6.71 (d, J = 2.6 Hz, 1H), 5.48 (s, 2H), 4.49 (q, J = 7.1 Hz, 2H), 4.49 (q, J = 7.1 Hz, 2H), 1.46 (t, J = 7.1 Hz, 3H). LC-MS (ESI, M + H$^+$) m/z 335.0.

Ethyl 1-(3-Chloro-2-fluorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (20e). Prepared from **18** and 3-chloro-2-fluorobenzyl bromide (180 mg, 0.81 mmol) as described by general procedure A. Yield: 250 mg (95%). ^{1}H NMR (CDCl$_3$) δ 9.05 (s, 1H), 8.50 (s, 1H), 7.55 (d, J = 3.0 Hz, 1H), 7.40 (m, 1H), 7.00 (m, 2H), 6.80 (d, J = 3.0 Hz, 1H), 5.55 (s, 2H), 4.50 (q, J = 7.0 Hz, 2H), 1.50 (t, J = 7.0 Hz, 3H). LC-MS (ESI, M + H$^+$) m/z 333.0.

Ethyl 1-(3-Chloro-2,6-difluorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (20f). Prepared from **18** and 3-chloro-2,6-difluoro-benzyl bromide (210 mg, 0.87 mmol) as described by general procedure A. Yield: 130 mg (47%). ^{1}H NMR (CD$_3$OD) δ 8.96 (s, 1H), 8.47 (s, 1H), 7.71 (d, J = 3.0 Hz, 1H), 7.55 (m, 1H), 7.05 (m, 1H), 6.75 (d, J = 3.0 Hz, 1H), 5.72 (s, 2H), 4.52 (q, J = 7.3 Hz, 2H), 1.45 (t, J = 7.3 Hz, 3H). LC-MS (ESI, M + H$^+$) m/z 351.0.

Ethyl 1-(2,3-Dichlorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (20g). Prepared from **18** and 2,3-dichlorobenzyl chloride (170 mg, 0.87 mmol) as described by general procedure A. Yield: 240 mg (84%). ^{1}H NMR (DMSO-d_6) δ 9.15 (s, 1H), 8.63 (s, 1H), 8.04 (d, J = 3.0 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.52 (t, J = 7.9 Hz, 1H), 7.04 (d, J = 3.0 Hz, 1H), 6.91 (d, J = 7.9 Hz, 1H), 6.01 (s, 2H), 4.56 (q, J = 7.2 Hz, 2H), 1.57 (t, J = 7.0 Hz, 3H). LC-MS (ESI, M + H$^+$): 349.0, 351.0, 353.0 (10:6:1).

Ethyl 1-(5-Chloro-thiophen-2-ylmethyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylate (20h). Prepared from **19b** and 2-chloro-5-(chloromethyl)thiophene (150 mg, 0.90 mmol) as described by general procedure A. Yield: 280 mg (87%). ^{1}H NMR (CD$_3$OD) δ 8.89 (s, 1H), 8.48 (s, 1H), 7.72 (d, J = 3.2 Hz, 1H), 6.99 (d, J = 3.8 Hz, 1H), 6.87 (d, J = 4.8 Hz, 1H), 6.75(d, J = 3.2 Hz, 1H), 5.73 (s, 2H), 4.46 (q, J = 7.2 Hz, 2H), 1.46 (t, J = 7.2 Hz, 3H). LC-MS (ESI, M + H$^+$) m/z 321.0.

General Procedure B. 1-(2,4-Difluorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylic Acid (1b). To **19b** (0.30 g, 1.58 mmol) in methanol (3 mL) was added sodium hydroxide (0.076 g, 3.16 mmol) in water (0.5 mL). The reaction was heated in a Smith-Creator (microwave reactor from Personal Chemistry) to 100 °C for 5 min. The solution was poured into water (30 mL) and the pH was adjusted to 2−3 by addition of citric acid. The precipitate that formed was collected by filtration and dried in vacuo to provide **1b** as a white powder (0.15 g, 55% yield). ^{1}H NMR (DMSO-d_6) δ 8.97 (s, 1H), 8.35 (s, 1H), 7.82 (d, J = 3.2 Hz, 1H), 7.33 (m, 2H), 7.09 (t, J = 8.4 Hz, 1H), 6.76 (d, J = 3.2 Hz, 1H), 5.67 (s, 2H). LC-MS (ESI, M + H$^+$): 289.1. HRMS calcd for $C_{15}H_{11}F_2N_2O_2$ [M + H$^+$] 289.07831; found 289.077457.

1-(4-Fluorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylic Acid (1c). Prepared from **19c** (110 mg, 0.37 mmol) as described by general procedure B. Yield: 40 mg (40%). ^{1}H NMR (DMSO-d_6) δ 8.97 (s, 1H), 8.35 (s, 1H), 7.90 (d, J = 3.0 Hz, 1H), 7.35 (m, 2H), 7.15 (m, 2H), 6.76 (d, J = 3.0 Hz, 1H), 5.67 (s, 2H). LC-MS (ESI, M + H$^+$) m/z 271.1.

1-(2,3,4-Trifluorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylic Acid (1d). Prepared from **20d** (100 mg, 0.3 mmol) as described by general procedure B. Yield: 87 mg (91%). ^{1}H NMR (DMSO-d_6) δ 8.99 (s, 1H), 8.36 (s, 1H), 7.83 (d, J = 2.64 Hz, 1H), 7.30 (q, J = 7.93 Hz, 1H), 7.08 (m, 1H), 6.77 (d, J = 3.02 Hz, 1H), 5.73 (s, 2H). LC-MS (ESI, M + H$^+$) m/z 307.0. HRMS calcd for $C_{15}H_{19}F_3N_2O_2$ (M + H$^+$) 307.0694; found 307.0705.

1-(3-Chloro-2-fluorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylic Acid (1e). Prepared from **20e** (250 mg, 0.75 mmol) as described by general procedure B. Yield: 40 mg (18%). ^{1}H NMR (DMSO-d_6) δ 8.96 (s, 1H), 8.35 (s, 1H), 7.84 (d, J = 3.0 Hz, 1H), 7.56 (t, J = 7.4 Hz, 1H), 7.19 (t, J = 7.9 Hz, 1H), 7.09 (t, J = 7.3 Hz, 1H), 5.75 (s, 2H). LC-MS (ESI, M + H$^+$) m/z 305.0.

1-(3-Chloro-2,6-difluorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylic Acid (1f). Prepared from **20f** (130 mg, 0.37 mmol) as described by general procedure B. Yield: 86 mg (72%). ^{1}H NMR (DMSO-d_6) δ 8.95 (s, 1H), 8.34 (s, 1H), 7.75 (d, J = 3.2 Hz, 1H), 7.69 (m, 1H), 7.28 (m, 1H), 6.75 (d, J = 3.2 Hz, 1H), 5.75 (s, 2H). LC-MS (ESI, M + H$^+$) m/z 323.0.

1-(2,3-Dichlorobenzyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylic Acid (1g). Prepared from **20g** (240 mg, 0.69 mmol) as described by general procedure B except that the mixture was heated to 60 °C for 16 h. Yield: 160 mg (67%). ^{1}H NMR (DMSO-d_6) δ 8.92 (s, 1H), 8.40 (s, 1H), 7.83 (d, J = 3.0 Hz, 1H), 7.62 (d, J = 7.4 Hz, 1H), 7.30 (t, J = 7.8 Hz, 1H), 6.83 (d, J = 3.0 Hz, 1H), 6.68 (d, J = 7.9 Hz, 1H), 5.79 (s, 2H). LC-MS (ESI, M + H$^+$) m/z 320.9, 323.0, 325.0 (10:6:1). HRMS calcd for $C_{15}H_{11}Cl_2N_2O_2$ [M + H$^+$] 321.0204; found 321.0198.

1-(5-Chloro-thiophen-2-ylmethyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxylic Acid (1h). Prepared from **20h** (240 mg, 0.75 mmol) as described by general procedure B. Yield: 150 mg (68%). ^{1}H NMR (DMSO-d_6) δ 9.05 (s, 1H), 8.34 (s, 1H), 7.88 (d, J = 3.0 Hz, 1H), 7.12 (d, J = 3.8 Hz, 1H), 7.01 (d, J = 4.0 Hz, 1H), 6.75 (d, J = 3.0 Hz, 1H), 5.78 (s, 2H). LC-MS (ESI, M + H$^+$) m/z 293.0.

General Procedure C. (1-(2,4-Difluorobenzyl)-*N*-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide (2b). To a solution of **1b** (0.15 g, 0.52 mmol) in DMF (10 mL) were added HATU (0.20 g, 0.52 mmol), triethylamine (0.15 mL, 1.05 mmol), and hydroxylamine hydrochloride (0.036 g, 0.52 mmol). The resulting mixture was stirred for 16 h at ambient temperature. The mixture was cast into water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with water (2 × 30 mL), dried over sodium sulfate, concentrated in vacuo, and purified by preparative HPLC to provide **1b** as a white powder (0.075 g, 48% yield). ^{1}H NMR (DMSO-d_6) δ 11.14 (s, 1H), 8.92 (s, 1H), 8.85 (s, 1H), 8.21 (s, 1H), 7.78 (s, 1H), 7.26−7.38 (m, 2H), 7.08 (t, J = 8.3 Hz, 1H), 6.71 (d, J = 3.0 Hz, 1H), 5.64 (s, 2H). LC-MS (ESI, M + H$^+$) m/z 304.1. HRMS calcd for $C_{15}H_{12}F_2N_3O_2$ (M + H) 304.0898; found 304.0886. Anal. ($C_{15}H_{11}F_2N_3O_2$) C, H, N.

1-(4-Fluorobenzyl)-*N*-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide (2c). Prepared from **1c** (150 mg, 0.56 mmol) as described by general procedure C. Yield: 60 mg (29%). ^{1}H NMR (DMSO-d_6) δ 11.12 (s, 1H), 8.90 (s, 1H), 8.83 (s, 1H), 8.21 (s, 1H), 7.85 (d, J = 3.0 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 6.71 (d, J = 3.0 Hz, 1H), 5.59 (s, 2H). LC-MS (ESI, M + H$^+$) m/z 286.1. HRMS calcd for $C_{15}H_{13}FN_3O_2$ (M + H) 286.0992; found 286.0978.

1-(3-Chloro-2-fluorobenzyl)-*N*-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide (2e). Prepared from **1e** (190 mg, 0.62 mmol) as described by general procedure C. Yield: 120 mg (60%). ^{1}H NMR (DMSO-d_6) δ 11.16 (s, 1H), 8.95 (s, 1H), 8.85 (s, 1H), 8.23 (s, 1H), 7.79 (d, J = 2.8 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.10 (t, J = 7.5 Hz, 1H), 6.73 (d, J = 3.0 Hz, 1H), 5.74 (s, 2H). LC-MS (ESI, M + H$^+$) m/z 320.0. HRMS calcd for $C_{15}H_{12}ClFN_3O_2$ (M + H$^+$) 320.0602; found 320.06045.

1-(3-Chloro-2,6-difluorobenzyl)-*N*-hydroxy-1*H*-pyrrolo[2,3-*c*]-pyridine-5-carboxamide (2f). Prepared from **1f** (210 mg, 0.65 mmol) as described by general procedure C. Yield: 75 mg (34%). ^{1}H NMR (DMSO-d_6) δ 11.17 (s, 1H), 8.89 (s, 1H), 8.81 (s, 1H), 8.18 (s, 1H), 7.69−7.70 (m, 2H), 7.25 (m, 1H), 6.68 (s, 1H), 5.70 (s, 2H). LC-MS (APCI, M + H$^+$) m/z 338.0. HRMS (M + H$^+$) calcd for $C_{15}H_{11}ClF_2N_3O_2$ (M + H$^+$) 338.0508; found 338.0511.

(1-(2,3-Dichlorobenzyl)-*N*-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide (2g). Prepared from **1g** (160 mg, 0.50 mmol) as described by general procedure C. Yield: 36.4 mg (22%). ^{1}H NMR (DMSO-d_6) δ 11.15 (s, 1H), 8.91 (s, 1H), 8.78 (s, 1H), 8.24 (s, 1H), 7.76 (d, J = 3.2 Hz, 1H), 7.60 (d, J = 8.1 Hz, 1H), 7.28 (t, J = 8.1 Hz, 1H), 6.76 (d, J = 3.2 Hz, 1H), 6.67 (d, J = 8.1 Hz, 1H), 5.75 (s, 2H). LC-MS (ESI, M + H$^+$) m/z 336.0, 338.0, 340.0 (10:6:1). HRMS calcd for $C_{15}H_{12}Cl_2N_3O_2$ (M + H$^+$) 336.0303; found 336.0300.

1-(5-Chloro-thiophen-2-ylmethyl)-*N*-hydroxy-1*H*-pyrrolo[2,3-*c*]-pyridine-5-carboxamide (2h). Prepared from **1h** (150 mg, 0.51 mmol) as described by general procedure C. Yield: 33 mg (21%). ^{1}H NMR (DMSO-d_6) δ 11.15 (s, 1H), 8.93 (s, 2H), 8.21 (s, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.10 (d, J = 3.0 Hz, 1H), 6.99 (d, J = 2.8 Hz, 1H), 6.70 (d, J = 3.0 Hz, 1H), 5.76 (s, 2H). LC-MS (ESI, M + H$^+$) m/z 308.0. HRMS calcd for $C_{13}H_{11}ClN_3O_2S$ (M + H$^+$) 308.0261; found 308.0265. Anal. ($C_{13}H_{10}ClN_3O_2S$) C, H, N

General Procedure D. 1-(2-Carbamoyl-4-fluorobenzyl)-*N*-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide (2n) and 1-(2-Cyano-4-fluorobenzyl)-*N*-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide (2k). To a solution of **19k** (688 mg, 2.22 mmol) in methanol (22 mL) was added hydroxyl amine (50% solution in water, 0.722 mL, 11.1 mmol) and 1 N sodium hydroxide (4.44 mL, 11.1 mmol). The solution was stirred at ambient temperature for 16 h. The reaction mixture was adjusted to pH 7 by addition of 1 N HCl,to provide a white precipitate. The solid was collected by filtration, washed with water and ethyl acetate, and dried in vacuo. Purification by reversed-phase preparative HPLC (acetonitrile:water:TFA) provided **2k** (190 mg, 28%) and the nitrile hydrolysis product **2n** (25 mg, 4%). Data for **2n**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (bs, 1H), 8.91 (bs, 1H), 8.75 (s, 1H), 8.21 (s, 1H), 8.07 (s, 1H), 7.74 (d, J = 3.0 Hz, 1H), 7.70 (s, 1H), 7.36 (dd, J = 9.4, 2.8 Hz, 1H), 7.22 (td, J = 8.5, 2.8 Hz, 1H), 7.00 (dd, J = 8.5, 5.6 Hz, 1H), 6.70 (d, J = 2.8 Hz, 1H), 5.75 (s, 2H). LC-MS (ESI, M + H$^+$) m/z 329.2. Data for **2k**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.16 (bs, 1H), 8.91 (bs, 1H), 8.82 (s, 1H), 8.25 (s, 1H), 7.95 (dd, J = 8.6, 2.5 Hz, 1H), 7.77 (d, J = 3.0 Hz, 1H), 7.55 (td, J = 8.6, 3.0 Hz, 1H), 7.10 (dd, J = 8.6, 5.3 Hz, 1H), 6.77 (d, J = 3.0 Hz, 1H), 5.82 (s, 2H). LC-MS (ESI, M + H$^+$) m/z 311.2.

1-(3-Carbamoyl-4-fluorobenzyl)-*N*-hydroxy-1*H*-pyrrolo[2,3-*c*]-pyridine-5-carboxamide (2o). Prepared from **19o** as described by general procedure D to provide 33 mg (8%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.52 (s, 1H), 9.09 (s, 1H), 8.34 (s, 1H), 8.13 (s, 1H), 7.68 (s, 2H), 7.67 (s, 1H), 7.47 (m, 1H), 7.26 (dd, J = 10.1, 8.8 Hz, 1H), 6.89 (s, 1H), 5.69 (s, 2H). LC-MS (ESI, M + H$^+$) m/z 329.2.

***N*-Hydroxy-1-(pyridin-2-ylmethyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide (2i).** Prepared from crude **19i** as described by general procedure D to provide 63 mg (23%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.12 (s, 1H), 8.90 (s, 1H), 8.80 (s, 1H), 8.52 (d, J = 5.7 Hz, 1H), 8.21 (s, 1H), 7.83 (d, J = 3.0 Hz, 1H), 7.76 (td, J = 7.7, 1.7 Hz, 1H), 7.30 (dd, J = 4.9, 1.1 Hz, 1H), 7.21 (d, J = 7.7 Hz, 1H), 6.71 (d, J = 3.0 Hz, 1H), 5.69 (s, 2H). LC-MS (ESI, M + H$^+$) m/z 269.2.

1-(3-Carbamoylbenzyl)-*N*-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide (2p) and 1-(3-Cyanobenzyl)-*N*-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide (2l). Prepared from **19l** as described by general procedure D to provide **2p** (16 mg, 9%) and **2l** (23 mg, 14%). Data for **2p**: ^{1}H NMR (400 MHz, CD_3OD) δ 11.52 (bs, 1H), 9.06 (s, 1H), 8.36 (s, 1H), 8.13 (s, 1H), 7.97 (s, 1H), 7.84 (s, 1H), 7.79 (m, 1H), 7.42 (d, J = 5.1 Hz, 2H), 7.38 (s, 1H), 6.90 (s, 1H), 5.73 (s, 2H). LC-MS (ESI, M + H$^+$) m/z 311.2. Data for **2l**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.10 (bs, 1H), 8.9 (bs, 1H), 8.86 (s, 1H), 8.22 (s, 1H), 7.89 (d, J = 3.0 Hz, 1H), 7.84 (s, 1H), 7.57 (dt, J = 6.8, 1.8 Hz, 1H), 7.56 (s, 1H), 7.55 (m, 1H), 6.73 (d, J = 3.0 Hz, 1H), 5.66 (s, 2H). LC-MS (ESI, M + H$^+$) m/z 293.2.

***N*-Hydroxy-1-{[6-(hydroxymethyl)pyridin-2-yl]methyl}-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide (2j).** Prepared from **19j** as described by general procedure D to provide 69 mg (51%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.76 (bs, 1H), 9.18 (s, 1H), 8.43 (s, 1H), 8.23 (s, 1H), 7.79 (dd, J = J' = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 6.98 (s, 1H), 5.79 (s, 2H), 4.49 (s, 2H). LC-MS (ESI, M + H$^+$) m/z 299.2.

1-(4-Carbamoylbenzyl)-*N*-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide (2q) and 1-(4-Cyanobenzyl)-*N*-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide (2m). Prepared from **19m** as described by general procedure D to provide **2q** (43 mg, 6%) and **2m** (50 mg, 6%). Data for **2m**: ^{1}H NMR (400 MHz, CD_3OD) δ 11.50 (bs, 1H), 9.02 (s, 1H), 8.35 (s, 1H), 8.12 (s, 1H), 7.93 (s, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.36 (s, 1H), 7.32 (d, J = 8.1 Hz, 1H), 6.90 (s, 1H), 5.74 (s, 2H). LC-MS (ESI,

M + H): 311.2. Data for **2q**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (bs, 1H), 8.91 (bs, 1H), 8.79 (s, 1H), 8.23 (s, 1H), 7.87 (d, J = 3.0 Hz, 1H), 7.81 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.2 Hz, 2H), 6.74 (d, J = 3.0 Hz, 1H), 5.72 (s, 2H). LC-MS (ESI, M + H^+) m/z 293.2.

1-(2,4-Difluorobenzyl)-*N*-hydroxy-*N*-methyl-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide (3b). Prepared from **1b** (200 mg, 0.69 mmol), *N*-methyl hydroxylamine hydrochloride (60 mg, 0.72 mmol), triethylamine (0.20 mL, 1.43 mmol), and HATU (270 mg, 0.71 mmol) as described by general procedure C. Yield: 120 mg (55%). ^{1}H NMR (DMSO-d_6) δ 11.10 (br, 1H), 8.92 (s, 1H), 8.04 (s, 1H), 7.82 (s, 1H), 7.26−7.38 (m, 2H), 7.07−7.08 (m, 1H), 6.72 (s, 1H), 5.64 (s, 2H), 3.33 (s, 3H). LC-MS (ESI, M + H^+) m/z 318.0. HRMS calcd for $C_{16}H_{14}F_2N_3O_2$ (M + H^+) 318.1054; found 318.1037. Anal. ($C_{16}H_{13}F_2N_3O_2$) C, H, N.

1-(2,4-Difluorobenzyl)-*N*-methoxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide (4b). Prepared from **1b**, *O*-methyl hydroxylamine hydrochloride (200 mg, 0.69 mmol), triethylamine (0.20 mL, 1.43 mmol), and HATU (262 mg, 0.69 mmol) as described by general procedure C. Yield: 190 mg (87%). ^{1}H NMR (CD_3OD) δ 8.80 (s, 1H), 8.33 (s, 1H), 7.64 (d, J = 3.0 Hz, 1H), 7.26 (m, 1H), 6.96−7.08 (m, 2H), 6.74 (d, J = 3.0 Hz, 1H), 5.62 (s, 2H) 3.85 (s, 3H). LC-MS (ESI, M + H^+) m/z 318.0. HRMS calcd for $C_{16}H_{14}F_2N_3O_2$ (M + H) 318.1054; found 318.1045.

(2,4-Difluorobenzyl)-*N*-methyl-*N*-methoxy-1*H*-pyrrolo[2,3-*c*]-pyridine-5-carboxamide (5b). Prepared from **1b** (190 mg, 0.66 mmol), *N,O*-dimethyl hydroxylamine hydrochloride (77 mg, 0.79 mmol), diisopropylethylamine (0.46 mL, 2.64 mmol), and HATU (301 mg, 0.79 mmol) as described by general procedure C. Yield: 88 mg (39%). ^{1}H NMR (DMSO-d_6) δ 8.88 (s, 1 H), 7.86 (s, 1 H), 7.75 (d, J = 3.0 Hz, 1H), 7.23−7.40 (m, 2H), 6.66 (d, J = 3.0 Hz, 1 H), 5.62 (s, 2 H), 3.69 (s, 3 H), 3.29 (s, 3 H). LC-MS (APCI, M + H^+) m/z 332.2.

1-(4-Fluorobenzyl)-*N*-hydroxy-*N*-methyl-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide (6c). Prepared from **1c** (87 mg, 0.232 mmol), *N*-methyl hydroxylamine hydrochloride (32 mg, 0.38 mmol), diisopropylethylamine (0.224 mL, 1.29 mmol), and HATU (147 mg, 0.38 mmol as described by general procedure C. Yield: 76.0 mg (79%). ^{1}H NMR (DMSO-d_6) δ 12.00 (bs, 1H), 8.91 (s, 1H), 8.03 (s, 1H), 7.91 (d, J = 2.8 Hz, 1H), 7.38 (dd, J = 5.7 Hz, 8.5 Hz, 2H), 7.12 (d, J = 8.5 Hz, 2H), 6.71 (d, J = 3.0 Hz, 1H), 5.59 (s, 2H), 3.33 (s, 3H). LC-MS (ESI, M + H^+) m/z 301.1. HRMS calcd for $C_{16}H_{15}FN_3O_2$ (M + H^+) 300.1148; found 300.1138. Anal. ($C_{16}H_{14}FN_3O_2$) C, H, N.

1-(4-Fluorobenzyl)-*N*-hydroxy-*N*-propyl-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide (7c). Prepared from **1c** (150 mg, 0.56 mmol), *N*-propyl hydroxylamine hydrochloride **23a** (124 mg, 1.11 mmol), dimethylaminopyridine (DMAP, 270 mg, 2.2 mmol), and HATU (230 mg, 0.60 mmol) as described by general procedure C. Yield: 37 mg (20%). ^{1}H NMR (DMSO-d_6) δ 11.93 (bs, 1H), 8.88 (s, 1H), 7.99 (s, 1H), 7.88 (d, J = 3.0 Hz, 1H), 7.34 (m, 2H), 7.15 (d, J = 8.8 Hz, 2H), 6.69 (d, J = 3.0 Hz, 1H), 5.56 (s, 2H), 3.66 (t, J = 7.1 Hz, 2H), 1.64 (m, 2H), 0.83 (s, 3H). LC-MS (ESI, M + H^+) m/z 328.1. HRMS calcd for $C_{18}H_{19}FN_3O_2$ (M + H^+) 328.1456; found 328.1458.

1-(4-Fluorobenzyl)-*N*-hydroxy-*N*-(3-hydroxypropyl)-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide (8c). Prepared from **1c** (190 mg, 0.70 mmol), **23b** (180 mg, 1.41 mmol), DMAP (350 mg, 2.87 mmol), and HATU (263 mg, 0.69 mmol) as described by general procedure C. Yield: 34.2 mg (14%). ^{1}H NMR (CD_3OD) δ 8.71 (s, 1H), 8.20 (s, 1H), 7.71 (d, J = 3.0 Hz, 1H), 7.26 (m, 2H), 7.05 (d, J = 8.9 Hz, 2H), 6.75 (d, J = 3.0 Hz, 1H), 5.55 (s, 2H), 3.90 (m, 2H), 3.65 (t, J = 6.0 Hz, 2H), 1.94−2.00 (m, 2H). LC-MS (ESI, M + H^+) m/z 344.1. HRMS calcd for $C_{18}H_{19}FN_3O_3$ (M + H^+) 344.1405; found 344.1402. Anal. ($C_{18}H_{18}FN_3O_3$) C, H, N.

1−4-(Fluorobenzyl)-*N*-hydroxy-*N*-isobutyl-1*H*-pyrrolo[2,3-*c*]-pyridine-5-carboxamide (9c). Prepared from **1c** (150 mg, 0.56 mmol), **23c** (140 mg, 1.12 mmol), DMAP (270 mg, 2.21 mmol), and HATU (230 mg, 0.60 mmol) as described by general procedure C. Yield: 67.4 mg (35%). ^{1}H NMR (DMSO-d_6) δ 12.00 (bs, 1H), 8.83 (s, 1H), 7.95 (s, 1H), 7.84 (d, J = 3.0 Hz, 1H), 7.29 (m, 2H), 7.10 (d, J = 8.8 Hz, 2H), 6.64 (d, J = 3.0 Hz, 1H), 5.51 (s, 2H), 3.50 (d, J = 7.2 Hz, 2H), 1.98−2.05 (m, 1H), 0.80 (s, 6H). LC-MS (ESI, M + H^+) m/z 342.1. HRMS calcd for $C_{19}H_{21}FN_3O_2$ (M + H^+) 342.1613; found 342.1608.

1-(4-Fluorobenzyl)-*N*-hydroxy-*N*-isopropyl-1*H*-pyrrolo[2,3-*c*]-pyridine-5-carboxamide (10c). Prepared from **1c** (160 mg, 0.59 mmol), *N*-isopropylhydroxylamine hydrochloride (114 mg, 1.22 mmol), DMAP (290 mg, 2.73 mmol), and HATU (230 mg, 0.60 mmol) as described by general procedure C. Yield: 23 mg (7%). ^{1}H NMR ($CDCl_3$) δ 8.59 (s, 1H), 8.46 (s, 1H), 7.39 (s, 1H), 7.10 (m, 2H), 7.02 (d, J = 8.6 Hz, 2H), 6.73 (s, 1H), 5.41 (s, 2H), 5.08 (m, 1H), 1.33 (d, J = 6.6 Hz, 6H). LC-MS (APCI, M + H^+) m/z 328.1. HRMS calcd for $C_{18}H_{18}FN_3O_2$ (M + H^+) 328.1456; found 328.1456.

***N*-Benzyl-1-(4-fluorobenzyl)-*N*-hydroxy-1*H*-pyrrolo[2,3-*c*]pyridine-5-carboxamide (11c).** Prepared from **1c** (150 mg, 0.56 mmol), *N*-benzylhydroxylamine hydrochloride (90 mg, 0.56 mmol), triethylamine (0.16 mL, 1.15 mmol), and HATU (210 mg, 0.55 mmol) as described by general procedure C. Yield: 60 mg (29%). ^{1}H NMR (DMSO-d_6) δ 8.92 (s, 1H), 8.11 (s, 1H), 7.91 (d, J = 2.8 Hz, 1H), 7.26−7.38 (m, 7H), 7.16 (d, J = 8.5 Hz, 2H), 6.72 (d, J = 2.8 Hz, 1H), 5.58 (s, 2H), 4.97 (s, 2H). LC-MS (ESI, M + H^+) m/z 376.1. HRMS calcd for $C_{22}H_{19}FN_3O_2$ (M + H^+) 376.1461; found 376.1448. Anal. ($C_{22}H_{18}FN_3O_2$) C, H, N.

General Procedure E. Ethyl 3-Methyl-5-oxo-2-propyl-2,5-dihydroisoxazole-4-carboxylate (22a). To a stirred solution of ethyl 3-methyl-5-oxo-2,5-dihydroisoxazole-4-carboxylate sodium salt (**21**)[32] in DMF (20 mL) was added 1-iodopropane (1.70 g, 18.1 mmol). The resulting mixture was heated to 120 °C for 1 h. The cold solution was poured into ice−water (30 mL), and extracted with dichloromethane (2 × 50 mL). The organic layer was washed with water (2 × 50 mL), dried over sodium sulfate, concentrated, and purified by flash chromatography with ethyl acetate/hexane (1/1) to provide a solid product (0.52 g, 13% yield). ^{1}H NMR ($CDCl_3$) δ 4.33 (q, J = 7.1 Hz, 2H), 3.86 (t, J = 6.8 Hz, 2H), 2.57 (s, 3H), 1.81−1.88 (m, 2H), 1.37 (t, J = 7.1 Hz, 3H), 0.98 (t, J = 7.6 Hz, 3H). LC-MS (APCI, M + H^+) m/z 214.1.

Ethyl 3-Methyl-5-oxo-2-[(3-*tert*-butyldimethylsilanoxyl)propyl]-2,5-dihydroisoxazole-4-carboxylate (22b). Prepared by alkylation of **21** (3.08 g, 15.54 mmol) with (3-bromopropoxy)(tert-butyl)dimethylsilane (7.2 mL, 31.08 mmol) as described by general procedure E. Yield: 1.8 g (34%). ^{1}H NMR ($CDCl_3$) δ 4.30 (q, J = 7.2 Hz, 2H), 4.00 (t, J = 6.4 Hz, 2H), 3.58 (t, J = 5.5 Hz, 2H), 2.55 (s, 3H), 1.93−1.96 (m, 2H), 1.34 (t, J = 7.0 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H). LC-MS (APCI, M + H^+) m/z 344.1.

Ethyl 3-Methyl-5-oxo-2-isobutyl-2,5-dihydroisoxazole-4-carboxylate (22c). Prepared by alkylation of **21** (2.0 g, 10.36 mmol) with 1-iodo-3-methylbutane (2.4 mL, 20.73 mmol) as described by general procedure E. Yield: 510 mg (22%). ^{1}H NMR ($CDCl_3$) δ 4.12 (q, J = 7.1 Hz, 2H), 3.47 (t, J = 6.8 Hz, 2H), 2.35 (s, 3H), 2.02 (m, 1H), 1.16 (t, J = 7.1 Hz, 3H), 0.77 (d, J = 6.8 Hz, 6H). LC-MS (APCI, M + H^+) m/z 228.2.

General Procedure F. *N*-Propylhydroxylamine Hydrochloride (23a). To a stirred solution of **22a** (0.52 g, 2.44 mmol) in water (10 mL) were added acetic acid (10 mL) and hydrochloric acid (1 mL, 37%). The resulting solution was heated reflux for 8 h, and solvents were removed in vacuo to provide a glue-like liquid (0.30 g, quant), which was used without further purification. ^{1}H NMR ($CDCl_3$) δ 10.94 (s, 2H), 3.24 (s, 2H), 2.77 (m, 2H), 1.89 (m, 2H), 1.03 (t, J = 7.5 Hz, 3H).

***N*-(3-Hydroxypropyl)hydroxylamine Hydrochloride (43b).** Prepared from **22b** (1.8 g, 5.25 mmol) as described by general procedure F. Yield: 760 mg (quant). ^{1}H NMR (DMSO-d_6) δ 11.32 (s, 3H), 10.80 (s, 1H), 3.47 (d, J = 6.1 Hz, 2H), 3.10−3.17 (m, 2H), 1.17−1.78 (m, 2H).

***N*-Isobutylhydroxylamine Hydrochloride (23c).** Prepared from **22c** (510 mg, 2.25 mmol) as described by general procedure F. Yield: 280 mg (99%). ^{1}H NMR (DMSO-d_6) δ 11.22 (s, 2H),

10.78 (s, 1H), 2.95 (d, J = 7.0 Hz, 2H), 2.01−2.06 (m, 1H), 0.95 (d, J = 6.8 Hz, 6H).

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