Supporting Information

Synthesis and SAR studies of 1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamides as phosphodiesterase 4B (PDE4B) inhibitors

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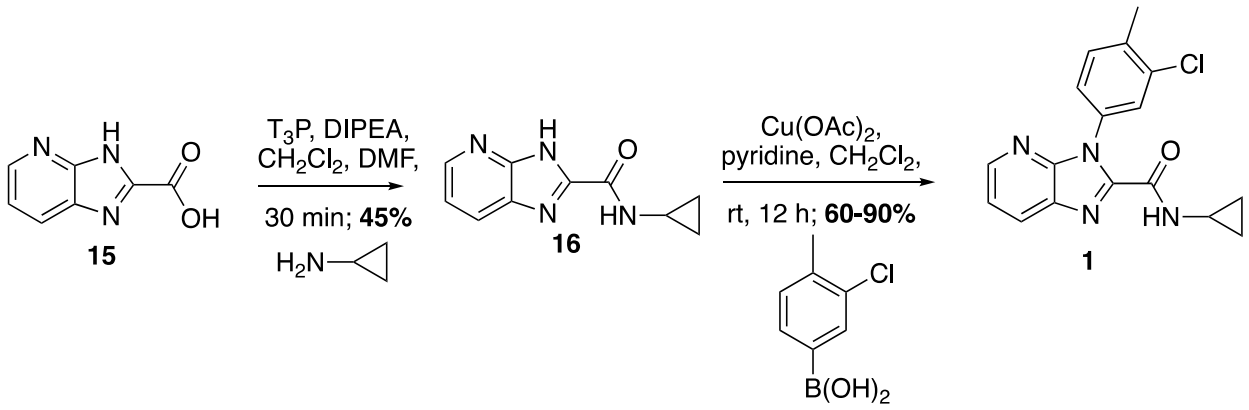
General Procedures:

All ^{1}H & ^{13}C NMR spectra were recorded on Bruker AV-400 (500 MHz) instrument. Chemical shifts are reported in ppm relative to residual solvent peaks as an internal standard set to δH 7.26 or δC 77.0 ($CDCl_3$). Data are reported as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), and integration. Low resolution mass spectra were obtained on an Agilent 1260 LCMS with electrospray ionization, with a gradient of 5-95% MeCN in 0.1% formic acid water over 4 min. High-resolution mass spectra were obtained on a Shimadzu IT-TOF mass spectrometer with electrospray ionization. Analytical thin layer chromatography was performed on LuxPlate silica gel 60 F254 plates. Visualization was accomplished with UV light, and/or the use of ninhydrin, anisaldehyde and ceric ammonium molybdate solutions followed by charring on a hot-plate. Chromatography on silica gel was performed using Silica Gel 60Å (230-400 mesh) from Sorbent Technologies. Solvents for extraction, washing, and chromatography were HPLC grade. All reagents were purchased from Aldrich Chemical Co. (or similar) and were used without purification. All reagents and solvents were commercial grade and purified prior to use when necessary. Microwave synthesis was performed on an Anton Paar Monowave 400 equipped with an autosampler. Compounds were purified on a Gilson preparative reversed-phase HPLC system comprised of a 322 aqueous pump with solvent-selection valve, 334 organic pump, GX-271 liquid hander, two column switching valves, and a 159 UV detector. UV wavelength for fraction collection was user-defined, with absorbance at 254 nm always monitored. Column: Phenomenex Axia-packed Luna C18, 50 x 21.2 mm, 5 μm. For Acidic Method: Mobile phase: CH_3CN in H_2O (0.1% formic acid). Gradient conditions: 2.0 min equilibration, followed by user-defined gradient

(starting organic percentage, ending organic percentage, duration, typically 15 mins), hold at 95% CH_3CN in H_2O (0.1% TFA) for 2 min, 20 mL/min, 23° C.

Chemical Synthesis:

Scheme I:

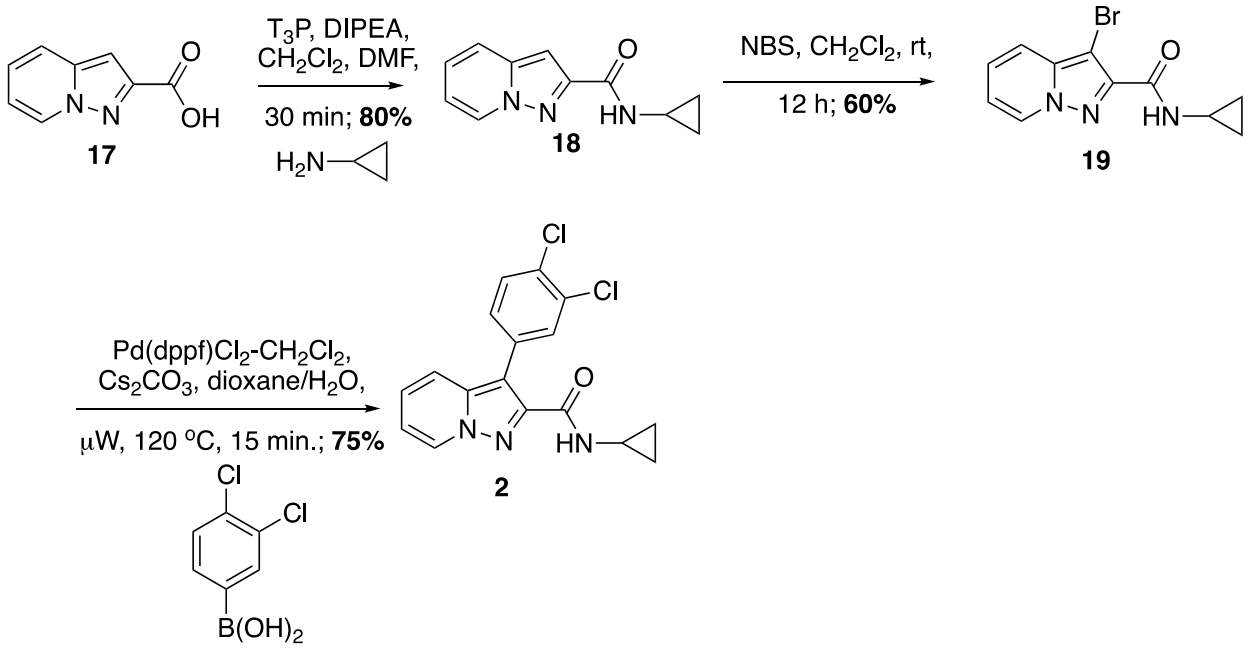


***N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide (16).** A one-dram vial equipped with magnetic stir bar and screw cap vial was charged with **15** (0.10 g; 0.60 mmol), cyclopropyl amine (0.44 mL; 3.1 mmol), diisopropyl ethylamine (0.047 mL; 0.67 mmol), CH_2Cl_2 (10 mL) and was stirred for approximately 5 minutes. Propylphoshonic anhydride (T_3P, 50 wt. % in ethyl acetate) (0.55 mL; 9.6 mmol), was added and the reaction stirred until LCMS analysis indicated significant consumption of the starting materials (30 min). The crude reaction mixture was diluted with water (15 mL) and the mixture extracted with dichloromethane (4 x 15 mL). The combined organic layers were dried over Na_2SO_4 and were evaporated under reduced pressure to give the crude product that was purified by flash column chromatography on silica gel (dry loaded using silica/DCM) with a gradient of 0 – 100% ethyl acetate in hexanes to give the corresponding amide product **16** (55 mg; 45% yield). LCMS: R_T = 1.579 min., >98% @ 215 and 254 nm, *m/z* = 203.0 $[M + H]^+$. ^1H NMR (499 MHz, DMSO-d_6) δ 8.71 (d, *J* = 7.0 Hz, 1H), 8.55 (d, *J* = 4.6 Hz, 1H),

7.66 (d, *J* = 8.9 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.13 (t, *J* = 6.9 Hz, 1H), 2.88 (dq, *J* = 7.3, 3.9 Hz, 1H), 0.75 – 0.67 (m, 2H), 0.63 (dd, *J* = 5.0, 2.5 Hz, 2H).

3-(3-chloro-4-methylphenyl)-*N*-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridine-2-carboxamide (1). A reaction flask was charged with **16** (0.055 g; 0.27 mmol), 3-chloro-4-methylphenyl boronic acid (0.093 g; 0.54 mmol), cupric acetate (0.074 g; 0.41 mmol), CH_2Cl_2 (5.0 mL) or CH_3CN (5.0 mL) and then pyridine (0.088 mL; 1.1 mmol), along with 4 Å MS. The reaction mixture was stirred at room temperature overnight. The mixture was filtered through a short pad of Celite. The filtrate was concentrated and purified on silica gel (eluting with 0-50% EtOAc/hexane followed by 0-5% MeOH/dichloromethane) to give the desired product (**1**) (60 mg; 70% yield). LCMS: R_T = 2.534 min, >98% @ 215 and 254 nm, m/z = 327.0 $[M + H]^+$. ^{1}H NMR (499 MHz, Chloroform-*d*) δ 8.69 (d, *J* = 2.2 Hz, 1H), 8.61 (d, *J* = 2.2 Hz, 1H), 7.52 (d, *J* = 1.8 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.33 (dd, *J* = 7.7, 1.8 Hz, 1H), 5.89 (s, 1H), 2.80 (dq, *J* = 7.3, 3.7 Hz, 1H), 2.50 (s, 3H), 0.79 (dd, *J* = 7.2, 1.7 Hz, 2H), 0.41 – 0.29 (m, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 162.78, 155.78, 148.38, 142.78, 142.42, 139.99, 137.76, 135.18, 133.07, 131.60, 130.65, 130.63, 128.35, 29.71, 23.11, 20.09, 6.84.

Scheme II:



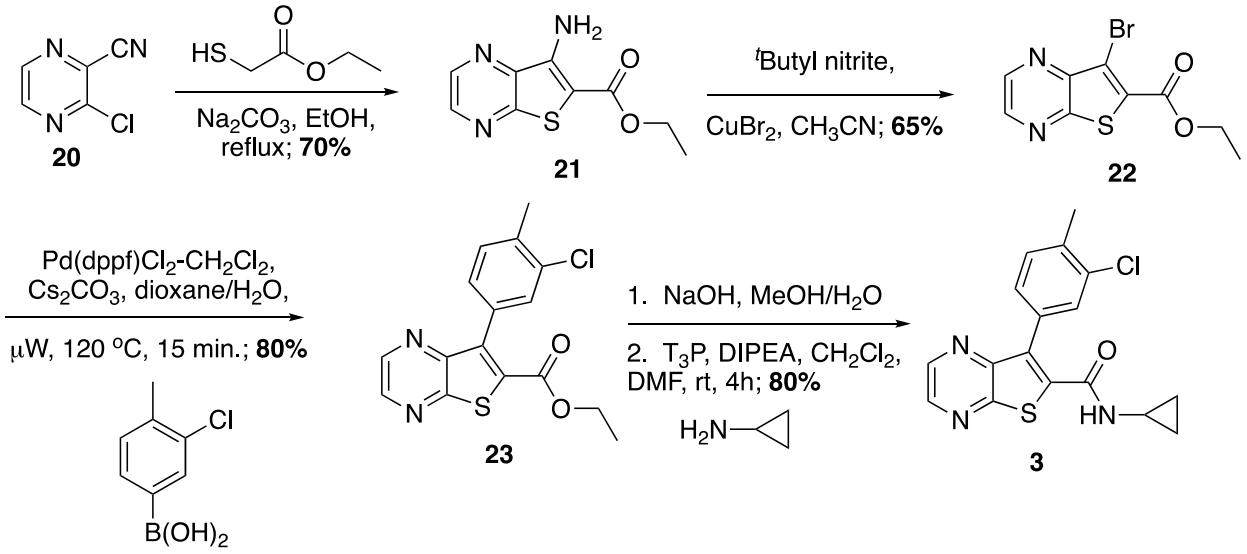
***N*-cyclopropylpyrazolo[1,5-*a*]pyridine-2-carboxamide (18).** Following the amide coupling procedure outlined in Scheme I gave the corresponding amide product **18** (1.4 g; 80% yield). LCMS: R_T = 1.579 min, >98% @ 215 and 254 nm, *m/z* = 202.0 $[M + H]^+$. ^1H NMR (499 MHz, DMSO-d_6) δ 8.71 (d, *J* = 7.0 Hz, 1H), 8.55 (d, *J* = 4.6 Hz, 1H), 7.66 (d, *J* = 8.9 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.13 (t, *J* = 6.9 Hz, 1H), 2.88 (dq, *J* = 7.3, 3.9 Hz, 1H), 0.75 – 0.67 (m, 2H), 0.63 (dd, *J* = 5.0, 2.5 Hz, 2H).

3-bromo-*N*-cyclopropylpyrazolo[1,5-*a*]pyridine-2-carboxamide (19). To a solution of **18** (0.45 g; 2.2 mmol) in CH_2Cl_2 (5.0 mL) was added NBS (0.48 g; 2.7 mmol) and catalytic amount of acetic acid (75 μL). The reaction mixture was stirred at rt for 20 h. The crude reaction mixture was diluted with water (5.0 mL) and the mixture extracted with CH_2Cl_2 (3 x 5.0 mL). The combined organic layers were dried over Na_2SO_4 and were evaporated under reduced pressure to give the crude product that was purified by flash column chromatography on silica gel (dry loaded using silica/DCM) with a gradient of 0 – 80% ethyl acetate in hexanes to give compound **19** (0.37 g; 60% yield). LCMS: R_T = 2.181 min, >98% @ 215 and 254 nm, *m/z* = 280.4 $[M + H]^+$. ^1H NMR

(499 MHz, DMSO-d_6) δ 8.71 (d, *J* = 7.0 Hz, 1H), 8.55 (d, *J* = 4.6 Hz, 1H), 7.66 (d, *J* = 8.9 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 2.88 (dq, *J* = 7.3, 3.9 Hz, 1H), 0.75 – 0.67 (m, 2H), 0.63 (dd, *J* = 5.0, 2.5 Hz, 2H).

***N*-cyclopropyl-3-(3,4-dichlorophenyl)pyrazolo[1,5-*a*]pyridine-2-carboxamide (2).** To a solution of **19** (0.050 g; 0.10 mmol) in 9:1 Dioxane/H_2O, was added 3,4-dichlrophenyl boronic acid (0.090 g; 0.50 mmol), Cs_2CO_3 (0.11 g; 0.34 mmol), and Pd(dppf)Cl_2-CH_2Cl_2 (0.010 g; 0.020 mmol) and the mixture was heated in a microwave reactor at 120 °C for 15 min. Upon cooling, the solution was partitioned between EtOAc and sat. aq. NaCl. The org layer was separated, dried ($MgSO_4$), concentrated, and purified by flash chromatography on silica gel (dry loaded using silica/DCM) with a gradient of 0 – 80% ethyl acetate in hexanes to give the target compound **2** (27 mg; 78% yield). LCMS: R_T = 2.637 min, >98% @ 215 and 254 nm, *m/z* = 344.0 $[M + H]^+$. ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.69 (d, *J* = 2.2 Hz, 1H), 8.61 (d, *J* = 2.2 Hz, 1H), 7.52 (d, *J* = 1.8 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.33 (dd, *J* = 7.7, 1.8 Hz, 1H), 5.89 (s, 1H), 2.80 (dq, *J* = 7.3, 3.7 Hz, 1H), 2.50 (s, 3H), 0.79 (dd, *J* = 7.2, 1.7 Hz, 2H), 0.41 – 0.29 (m, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 162.78, 155.78, 148.38, 142.78, 142.42, 139.99, 137.76, 135.18, 133.07, 131.60, 130.65, 130.63, 128.35, 29.71, 23.11, 20.09, 6.84.

Scheme III:



Ethyl 7-aminothieno[2,3-*b*]pyrazine-6-carboxylate (21). A mixture of 3-chloropyrazine-2-carbonitrile, **20**, (2.0 g; 14 mmol), sodium carbonate (1.9 g; 19 mmol) and ethyl-2-mercaptoacetate (1.9 mL; 19 mmol) in ethanol (20 mL) was heated to reflux for 6 h. The reaction was quenched with water (1.5 L) and stirred for additional 30 min. The resulting precipitate was collected and washed with water. The residue was dissolved in diethyl ether and a black precipitate was filtrated off. Ether was evaporated to give ethyl 7-aminothieno[2,3-*b*]pyrazine-6-carboxylate (**21**) (2.2 g; 70% yield). LCMS: R_T = 2.637 min, >95% @ 215 and 254 nm, *m/z* = 224.0 $[M + H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$) 8.63 (d, *J* = 2.2 Hz, 1H), 8.58 (d, *J* = 2.2 Hz, 1H), 6.19 (br s, 2H), 4.40 (q, *J* = 7.2 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H).

Ethyl 7-bromothieno[2,3-*b*]pyrazine-6-carboxylate (22). To a solution of copper (II) bromide (2.19 g; 8.96 mmol) and *tert*-butylnitrite (1.17 g; 11.7 mmol) in acetonitrile (20 mL) was added **21** (2.0 g; 9.0 mmol) in portions over 2 h and stirred at rt for an additional 3 h. The reaction mixture was poured in aq. NH_3 (20 mL). The resulting solution was extracted with EtOAc (3 x 15 mL), dried ($MgSO_4$), concentrated, and purified by flash chromatography on silica gel (dry loaded using silica/DCM) 0 – 100% ethyl acetate in hexanes to give the corresponding ethyl 7-bromothieno[2,3-

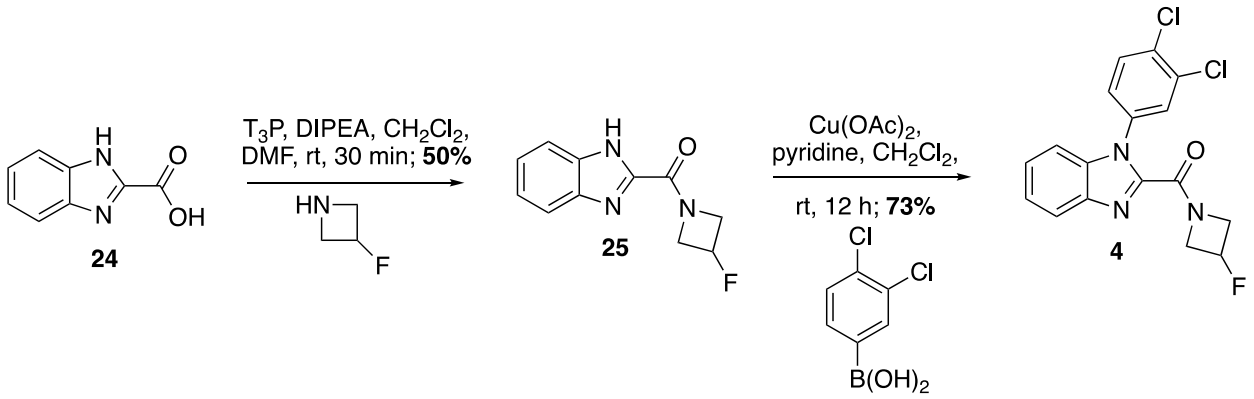
b]pyrazine-6-carboxylate (**22**) (1.5 g; 60% yield). LCMS: R_T = 3.723 min, >95% @ 215 and 254 nm, *m/z* = 286.9 $[M + H]^+$; ^{1}H-NMR (400 MHz, $CDCl_3$) 8.84 (d, *J* = 2.3 Hz, 1H), 8.70 (d, *J* = 2.3 Hz, 1H), 4.51 (q, *J* = 14.0 and 7.0 Hz, 2H), 1.48 (t, *J* = 7.0 Hz, 3H).

Ethyl 7-(3-chloro-4-methylphenyl)thieno[2,3-*b*]pyrazine-6-carboxylate (23). Following the cross-coupling procedure outlined in Scheme II gave the corresponding compound **23** (0.12 g; 80% yield). LCMS: R_T = 3.112 min, >98% @ 215 and 254 nm, *m/z* = 333.0 $[M + H]^+$; ^{1}H NMR (499 MHz, DMSO-d_6) δ 8.86 (dt, *J* = 20.2, 1.8 Hz, 2H), 7.61 (s, 1H), 7.47 (d, *J* = 7.9 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 2.43 (s, 3H), 1.19 (dd, *J* = 8.0, 6.3 Hz, 3H).

7-(3-Chloro-4-methylphenyl)-*N*-cyclopropylthieno[2,3-*b*]pyrazine-6-carboxamide (3). To a solution of the **23** (0.12 g; 0.36 mmol) in MeOH (6.0 mL) was added a predissolved solution of NaOH (0.36 mL; 0.72 mmol) in H_2O (1.0 mL). The reaction mixture was stirred at rt overnight. The reaction mixture was then concentrated *in vacuo* and acidified with 1N HCl (pH≈4). The aq mixture was extracted with EtOAc, dried ($MgSO_4$) and concentrated to give the corresponding acid derivative which was used without further purification. LCMS: R_T = 2.581 min, >98% @ 215 and 254 nm, *m/z* = 304.9 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.82 (dd, *J* = 18.2, 2.6 Hz, 2H), 7.57 (s, 1H), 7.51 – 7.33 (m, 2H), 2.41 (s, 3H).

Following the amide coupling procedure outlined in Scheme I gave the corresponding product (**3**) (20 mg; 78% yield). LCMS: R_T = 2.637 min, >98% @ 215 and 254 nm, *m/z* = 344.0 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.69 (d, *J* = 2.2 Hz, 1H), 8.61 (d, *J* = 2.2 Hz, 1H), 7.52 (d, *J* = 1.8 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.33 (dd, *J* = 7.7, 1.8 Hz, 1H), 5.89 (s, 1H), 2.80 (dq, *J* = 7.3, 3.7 Hz, 1H), 2.50 (s, 3H), 0.79 (dd, *J* = 7.2, 1.7 Hz, 2H), 0.41 – 0.29 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.78, 155.78, 148.38, 142.78, 142.42, 139.99, 137.76, 135.18, 133.07, 131.60, 130.65, 130.63, 128.35, 29.71, 23.11, 20.09, 6.84.

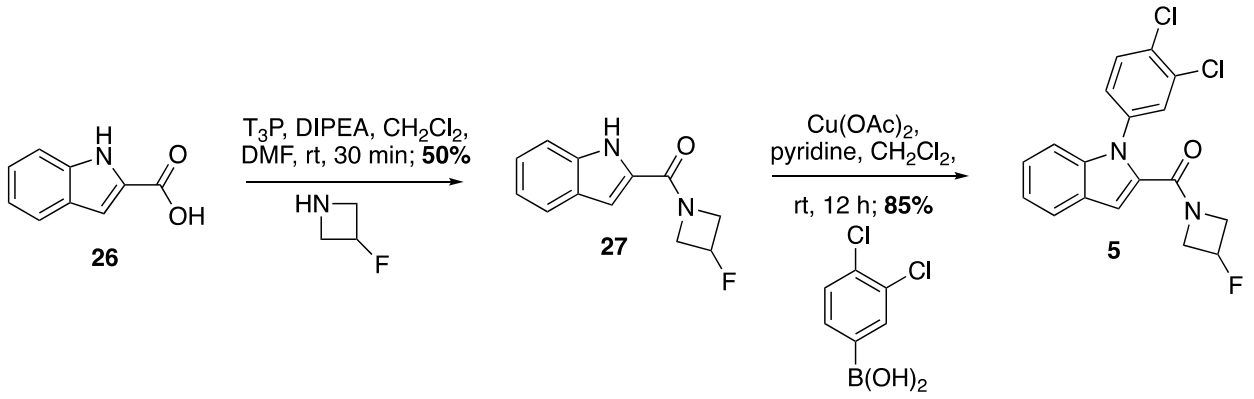
Scheme IV:



(1*H*-Benzo[*d*]imidazol-2-yl)(3-fluoroazetidin-1-yl)methanone (25). Following the amide coupling procedure outlined in Scheme I gave the corresponding amide product (**25**) (34 mg; 50% yield). LCMS: R_T = 2.032 min, >98% @ 215 and 254 nm, *m/z* = 220.0 $[M + H]^+$; ^{1}H NMR (499 MHz, DMSO-d_6) δ 13.27 (s, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.30 (dt, *J* = 31.6, 7.5 Hz, 2H), 5.57 (t, *J* = 4.4 Hz, 1H), 5.51 – 5.39 (m, 1H), 5.06 (ddd, *J* = 21.9, 12.3, 5.8 Hz, 1H), 4.73 (dd, *J* = 24.3, 12.2 Hz, 1H), 4.49 (ddd, *J* = 19.9, 11.9, 6.0 Hz, 1H), 4.19 (dd, *J* = 24.8, 12.0 Hz, 1H).

(1-(3,4-Dichlorophenyl)-1*H*-benzo[*d*]imidazol-2-yl)(3-fluoroazetidin-1-yl)methanone (4). Following the cross-coupling procedure outlined in Scheme I gave the desired product **4** (60 mg; 73% yield). LCMS: R_T = 2.884 min, >98% @ 215 and 254 nm, *m/z* = 364.0 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.52 (d, *J* = 2.6 Hz, 1H), 7.40 (dt, *J* = 8.9, 5.7 Hz, 2H), 7.28 (d, *J* = 2.8 Hz, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 5.42 (ddt, *J* = 56.8, 6.2, 3.0 Hz, 1H), 5.17 (ddd, *J* = 21.4, 12.5, 6.0 Hz, 1H), 4.94 (ddd, *J* = 23.9, 13.0, 3.4 Hz, 1H), 4.44 (ddd, *J* = 19.4, 12.4, 6.1 Hz, 1H), 4.35 – 4.19 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.24, 158.21, 142.53, 141.75, 136.57, 136.10, 133.29, 133.18, 130.89, 129.25, 126.95, 125.84, 124.08, 121.34, 110.97, 83.36, 81.73, 62.17, 61.96, 56.48, 56.27.

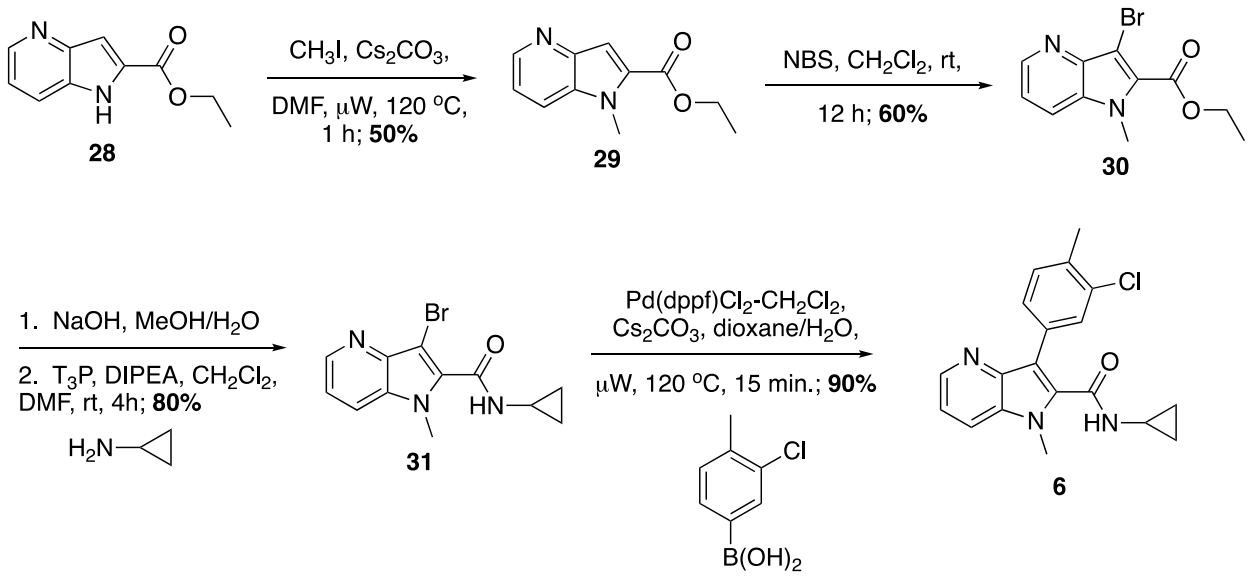
Scheme V:



(3-fluoroazetidin-1-yl)(1*H*-indol-2-yl)methanone (27). Following the amide coupling procedure as outlined in Scheme I gave the desired compound **27** (0.12 g; 50% yield). LCMS: R_T = 2.266 min, >98% @ 215 and 254 nm, *m/z* = 219.0 $[M + H]^+$; ^{1}H NMR (499 MHz, DMSO-d_6) δ 11.66 (s, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.06 (t, *J* = 7.4 Hz, 1H), 6.86 (s, 1H), 5.52 (ddt, *J* = 57.6, 5.9, 3.2 Hz, 1H), 4.82 (d, *J* = 21.2 Hz, 1H), 4.62 (d, *J* = 23.4 Hz, 1H), 4.45 (s, 1H), 4.15 (d, *J* = 22.9 Hz, 1H).

(1-(3,4-dichlorophenyl)-1*H*-indol-2-yl)(3-fluoroazetidin-1-yl)methanone (5). Following the cross-coupling procedure as outlined in Scheme I gave the desired compound **5** (70 mg; 85% yield). LCMS: R_T = 2.962 min, >98% @ 215 and 254 nm, *m/z* = 363.0 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.9 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.50 (d, *J* = 2.4 Hz, 1H), 7.33 (ddd, *J* = 8.4, 6.8, 1.3 Hz, 1H), 7.30 – 7.22 (m, 2H), 7.16 (d, *J* = 8.3 Hz, 1H), 6.96 (s, 1H), 5.41 (dtt, *J* = 56.6, 6.4, 3.4 Hz, 1H), 4.51 (s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.24, 162.22, 139.20, 137.95, 132.91, 132.21, 130.72, 129.62, 129.60, 127.33, 126.52, 125.44, 122.16, 121.77, 110.99, 108.46, 83.00, 81.37.

Scheme VI:



Ethyl 1-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-2-carboxylate (29). To a solution of **28** (0.25 g; 1.3 mmol) in DMF (10 mL), was added the methyl iodide (0.10 mL; 1.6 mmol), Cs_2CO_3 (0.64 g; 1.9 mmol), and the resulting mixture was heated in a microwave reactor at 120 °C for 1 h. Upon cooling, the solution was partitioned between EtOAc and sat. aq. NaCl. The organic layer was separated, dried ($MgSO_4$), concentrated, and purified by flash chromatography on silica gel (dry loaded using silica/DCM) with a gradient of 0 – 20% MeOH:DCM to give the corresponding intermediate (**29**) (0.13 g; 50% yield). LCMS: R_T = 1.631 min, >98% @ 215 and 254 nm, *m/z* = 205.1 $[M + H]^+$; ^1H NMR (499 MHz, DMSO-d_6) δ 8.50 (d, *J* = 4.3 Hz, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), 7.40 – 7.32 (m, 1H), 7.30 (s, 1H), 4.36 (qd, *J* = 7.1, 1.5 Hz, 2H), 4.05 (d, *J* = 1.8 Hz, 3H), 1.36 (td, *J* = 7.2, 1.7 Hz, 3H).

Ethyl 3-bromo-1-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-2-carboxylate (30). To a solution of **29** (0.58 g; 2.8 mmol) in CH_2Cl_2 (15 mL) was added NBS (0.56 g; 3.1 mmol) and catalytic amount of acetic acid (0.10 mL). The reaction mixture was stirred at rt for 20 h. The crude reaction mixture was diluted with water (5.0 mL) and the mixture extracted with CH_2Cl_2 (3 x 5.0 mL). The combined organic layers were dried over Na_2SO_4 and were evaporated under reduced pressure to

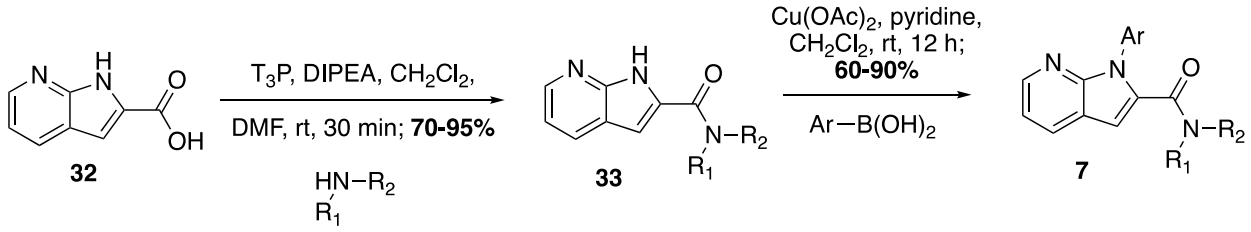
give the crude product (**30**) which was used without further purification. LCMS: R_T = 2.265 min, >95% @ 215 and 254 nm, *m/z* = 282.9 $[M + H]^+$; ^{1}H NMR (499 MHz, DMSO-d_6) δ 8.56 (d, *J* = 4.3 Hz, 1H), 8.16 (d, *J* = 8.7 Hz, 1H), 7.44 (dd, *J* = 8.6, 4.3 Hz, 1H), 4.42 (q, *J* = 7.1 Hz, 2H), 4.01 (s, 3H), 1.40 (t, *J* = 7.1 Hz, 3H).

3-bromo-*N*-cyclopropyl-1-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-2-carboxamide (31). Following the saponification procedure outlined in Scheme II, gave the intermediate acid. LCMS: R_T = 0.523 min, >95% @ 215 and 254 nm, *m/z* = 254.9 $[M + H]^+$; ^{1}H NMR (499 MHz, DMSO-d_6) δ 13.86 (s, 1H), 8.55 (d, *J* = 4.4 Hz, 1H), 8.13 (d, *J* = 8.6 Hz, 1H), 7.42 (dd, *J* = 8.6, 4.4 Hz, 1H), 4.02 (s, 3H).

Following the amide coupling procedure as outlined in Scheme I gave corresponding amide product (**31**) (0.18 g; 80% yield). LCMS: R_T = 1.628 min, >98% @ 215 and 254 nm, *m/z* = 293.9 $[M + H]^+$; ^{1}H NMR (499 MHz, DMSO-d_6) δ 8.90 – 8.73 (m, 1H), 8.48 (d, *J* = 4.4 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.34 (dd, *J* = 8.8, 4.5 Hz, 1H), 3.81 (s, 3H), 2.94 (dt, *J* = 8.1, 3.8 Hz, 1H), 0.78 (d, *J* = 6.8 Hz, 2H), 0.70 – 0.55 (m, 2H).

3-(3-chloro-4-methylphenyl)-*N*-cyclopropyl-1-methyl-1*H*-pyrrolo[3,2-*b*]pyridine-2-carboxamide (6). Following the cross-coupling procedure as outlined in Scheme II gave the desired compound, **6** (31 mg; 90% yield). LCMS: R_T = 2.073, >98% @ 215 and 254 nm, m/z = 340.1 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.4 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 1H), 7.57 (s, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.38 – 7.15 (m, 2H), 5.88 (s, 1H), 4.02 (s, 3H), 2.87 – 2.71 (m, 1H), 2.44 (s, 3H), 0.78 (d, *J* = 7.2 Hz, 2H), 0.47 – 0.29 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.33, 145.00, 142.91, 135.23, 134.53, 132.03, 131.20, 131.16, 130.88, 130.56, 128.47, 118.87, 117.49, 116.45, 31.43, 22.71, 19.87, 6.55.

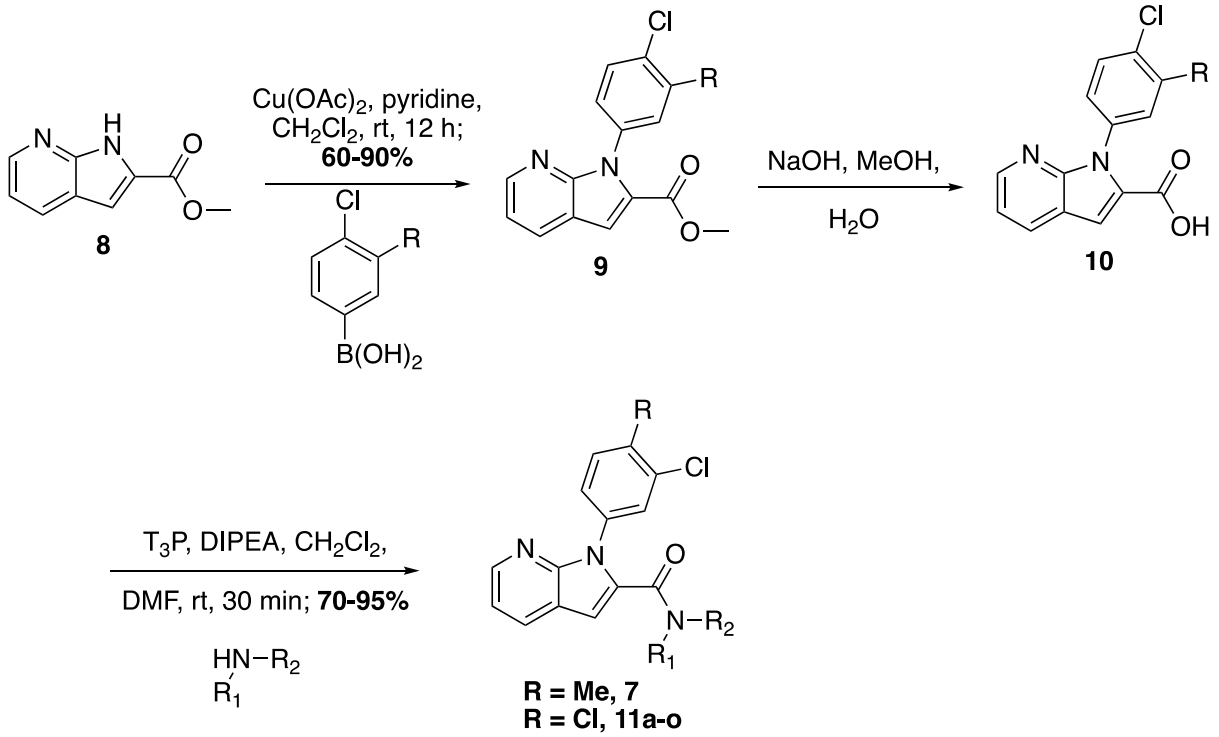
Scheme VII:



***N*-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (33).** The amide coupling procedure as outlined in Scheme VI gave the desired product **33**.

1-(3-chloro-4-methylphenyl)-*N*-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (7). The cross-coupling procedure as outlined in Scheme V gave the desired product **7** (0.12 g; 43% yield). LCMS: R_T = 2.570 min., >98% @ 215 and 254 nm, *m/z* = 326.0 $[M + H]^+$. ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.43 (dd, J= 4.8, 1.6 Hz, 1H), 8.01 (dd, J= 8.0, 1.6 Hz, 1H), 7.43 (d, J= 2.1 Hz, 1H), 7.40 (d, J= 8.0 Hz, 1H), 7.29 (s, 1H), 7.19 (dd, J= 7.9, 4.6 Hz, 1H), 7.02 (s, 1H), 6.07 (s, 1H), 2.80 (dd, J= 7.0, 3.6 Hz, 1H), 2.46 (s, 3H), 0.87 –0.77 (m, 2H), 0.53 –0.44 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.24, 149.74, 146.51, 136.44, 135.35, 134.66, 133.39, 131.24, 130.44, 128.42, 126.15, 119.02, 117.78, 104.75, 22.78, 19.92, 6.90. HRMS: calc'd for $C_{18}H_{17}ClN_3O$ $[M + H]^+$ 326.1060, found 326.1035.

Scheme VIII:

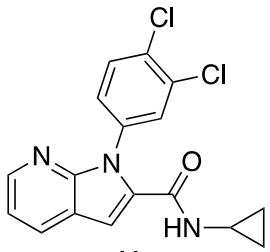


Methyl 1-(3,4-dichlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylate (9). The cross-coupling procedure as outlined in Scheme I gave the desired product **9** (0.68 g; 75% yield). LCMS: R_T = 2.92 min, >98% @ 215 and 254 nm, *m/z* = 321.0 $[M + H]^+$; ^{1}H NMR (499 MHz, DMSO-d_6) δ 8.43 (d, *J* = 4.3 Hz, 1H), 8.26 (d, *J* = 7.8 Hz, 1H), 7.83 (s, 1H), 7.78 (d, *J* = 8.5 Hz, 1H), 7.51 (s, 1H), 7.46 (d, *J* = 8.9 Hz, 1H), 7.37 – 7.29 (m, 1H), 3.77 (s, 3H).

1-(3,4-dichlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylic acid (10). The saponification procedure as outlined in Scheme III gave the desired acid, **10**, which was used without further purification. LCMS: R_T = 2.560 min, >98% @ 215 and 254 nm, *m/z* = 306.9 $[M + H]^+$; ^{1}H NMR (499 MHz, DMSO-d_6) δ 13.19 (s, 1H), 8.41 (d, *J* = 4.5 Hz, 1H), 8.24 (d, *J* = 7.9 Hz, 1H), 7.81 (d, *J* = 2.5 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.45 (q, *J* = 3.3, 2.0 Hz, 2H), 7.30 (dd, *J* = 8.0, 4.6 Hz, 1H).

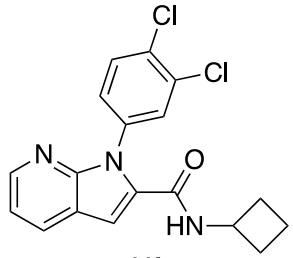
General Procedure for compounds **11a-o.**

The amide coupling procedure as outlined in Scheme I gave the desired compounds, **11a-o**.



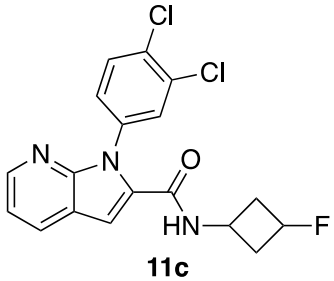
11a

***N*-cyclopropyl-1-(3,4-dichlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (11a).** (43 mg; 78% yield). LCMS: R_T = 2.597 min, >98% @ 215 and 254 nm, *m/z* = 346.0 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.44 (d, *J* = 4.7 Hz, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.67 – 7.48 (m, 2H), 7.33 (d, *J* = 8.5 Hz, 1H), 7.21 (dd, *J* = 7.8, 4.3 Hz, 1H), 6.97 (s, 1H), 6.25 (s, 1H), 2.82 (dq, *J* = 7.4, 4.0 Hz, 1H), 0.86 (d, *J* = 6.8 Hz, 2H), 0.62 – 0.51 (m, 2H).^{13}C NMR (126 MHz, $CDCl_3$) δ 162.16, 149.59, 146.62, 136.16, 133.04, 132.85, 132.42, 130.58, 129.80, 127.28, 119.07, 118.10, 104.54, 22.85, 6.93.



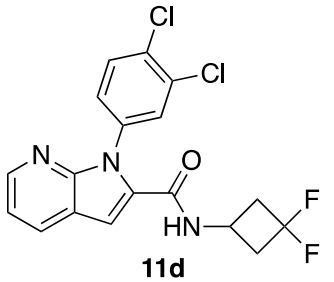
11b

***N*-cyclobutyl-1-(3,4-dichlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (11b).** (46 mg; 82% yield). LCMS: R_T = 2.771, >98% @ 215 and 254 nm, m/z = 360.0 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.40 (t, *J* = 12.9 Hz, 1H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.52 (d, *J* = 14.7 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.20 (dd, *J* = 7.5, 4.7 Hz, 1H), 7.05 (d, *J* = 23.5 Hz, 1H), 4.46 – 4.38 (m, 1H), 2.35 (d, *J* = 8.0 Hz, 2H), 1.94 – 1.84 (m, 2H), 1.74 (dd, *J* = 11.1, 5.2 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.98, 149.12, 146.04, 136.05, 133.42, 132.78, 132.36, 130.96, 130.57, 129.67, 127.20, 118.01, 104.66, 44.84, 30.89, 15.13.



11c

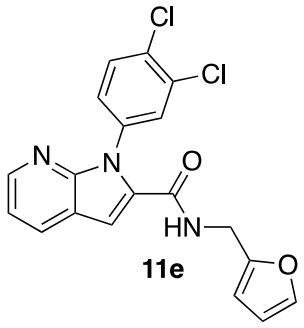
1-(3,4-Dichlorophenyl)-*N*-(3-fluorocyclobutyl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (11c). (51 mg; 84% yield). LCMS: R_T = 2.696 min, >98% @ 215 and 254 nm, *m/z* = 378.0 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.51 – 8.37 (m, 1H), 8.05 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.56 (d, *J* = 2.4 Hz, 1H), 7.34 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.23 (dd, *J* = 7.9, 4.6 Hz, 1H), 7.03 (s, 1H), 6.19 (s, 1H), 5.22 (ddt, *J* = 55.9, 6.5, 3.1 Hz, 1H), 4.64 (dt, *J* = 8.6, 6.0 Hz, 1H), 2.72 (dddt, *J* = 17.8, 12.0, 8.2, 3.7 Hz, 2H), 2.39 (ddt, *J* = 20.4, 13.4, 6.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.55, 149.64, 146.82, 136.06, 132.95, 132.54, 130.64, 130.62, 129.75, 127.21, 118.99, 118.20, 104.82, 87.23, 85.63, 41.77, 38.30, 38.12.



11d

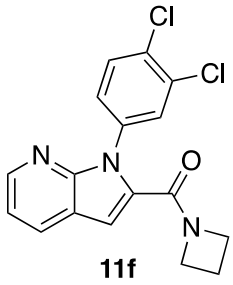
1-(3,4-dichlorophenyl)-*N*-(3,3-difluorocyclobutyl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (11d). (48 mg; 75% yield). LCMS: R_T = 2.777 min, >98% @ 215 and 254 nm, *m/z* = 396.0 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 4.5, 1.6 Hz, 1H), 8.06 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.55 (d, *J* = 2.3 Hz, 1H), 7.33 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.24 (dd, *J* = 7.9, 4.6 Hz, 1H), 7.07 (s, 1H), 6.40 – 6.24 (m, 1H), 4.40 (td, *J* = 7.6, 6.7, 3.7 Hz, 1H), 3.09 (ddt, *J* = 11.7, 8.5, 2.9 Hz, 2H), 2.63 – 2.44 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.70,

149.68, 146.98, 135.98, 133.00, 132.68, 132.30, 130.78, 130.78, 130.67, 129.81, 127.27, 118.95, 118.27, 105.09, 53.43, 43.33, 43.14, 42.96, 35.36, 35.29, 35.24, 35.17.



11e

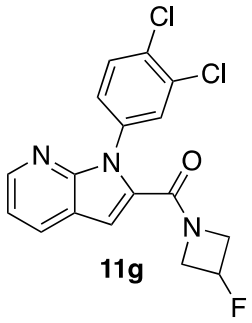
1-(3,4-dichlorophenyl)-*N*-(furan-2-ylmethyl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (11e). (56 mg; 90% yield). LCMS: R_T = 2.744 min, >98% @ 215 and 254 nm, *m/z* = 386.0 $[M + H]^+$; ^1H NMR (499 MHz, $CDCl_3$) δ 8.43 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.00 (dt, *J* = 8.1, 1.3 Hz, 1H), 7.64 – 7.49 (m, 2H), 7.29 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.20 (dd, *J* = 7.9, 4.7 Hz, 1H), 7.02 (s, 1H), 6.60 (d, *J* = 5.6 Hz, 1H), 6.38 – 6.28 (m, 1H), 6.24 (d, *J* = 3.2 Hz, 1H), 4.54 (d, *J* = 5.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.62, 150.54, 149.65, 146.71, 142.42, 136.12, 132.86, 132.81, 132.33, 130.63, 130.55, 129.72, 127.19, 119.06, 118.13, 110.57, 107.88, 105.09, 36.61.



11f

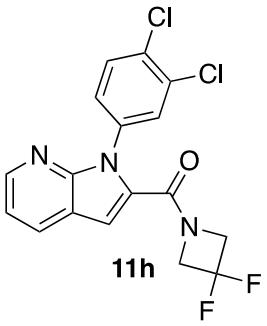
Azetidin-1-yl(1-(3,4-dichlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)methanone (11f). (28 mg; 50% yield). LCMS: R_T = 2.631 min, >98% @ 215 and 254 nm, *m/z* = 346.0 $[M + H]^+$; ^1H NMR (499 MHz, $CDCl_3$) δ 8.44 (dd, *J* = 4.6, 1.5 Hz, 1H), 8.04 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.67 – 7.52 (m, 2H), 7.34 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.22 (dd, *J* = 7.9, 4.7 Hz, 1H), 6.89 (s, 1H), 4.50 –

4.10 (m, 5H), 2.39 (p, *J* = 7.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.83, 149.11, 146.36, 136.42, 132.71, 132.08, 130.94, 130.46, 130.44, 129.47, 126.99, 119.32, 117.93, 105.51, 16.05.



11g

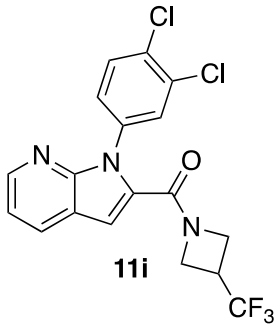
(1-(3,4-dichlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)(3-fluoroazetidin-1-yl)methanone (11g). (38 mg; 65% yield). LCMS: R_T = 2.636, >98% @ 215 and 254 nm, m/z = 364.0 $[M+H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.46 (d, *J* = 4.6 Hz, 1H), 8.06 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.71 – 7.53 (m, 2H), 7.32 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.23 (dd, *J* = 7.9, 4.7 Hz, 1H), 6.91 (s, 1H), 5.40 (ddq, *J* = 56.6, 6.7, 3.4 Hz, 1H), 4.52 (d, *J* = 37.9 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.08, 149.34, 146.91, 136.23, 132.79, 132.31, 130.62, 130.51, 130.16, 129.60, 127.09, 119.09, 118.15, 106.18, 82.84, 81.21, 29.72. HRMS: calc'd for $C_{17}H_{13}Cl_2FN_3O$, 364.0420; found, 364.0280.



11h

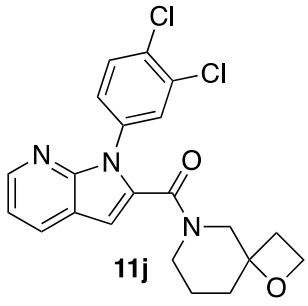
(1-(3,4-dichlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)(3,3-difluoroazetidin-1-yl)methanone (11h). (37 mg; 60% yield). LCMS: R_T = 2.764 min, >98% @ 215 and 254 nm, *m/z* = 382.0 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.07 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.67 – 7.52 (m, 2H), 7.36 – 7.21 (m, 2H), 6.93 (s, 1H), 4.58 (s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$)

δ 162.13, 162.10, 162.07, 149.48, 147.34, 136.08, 132.85, 132.49, 130.81, 130.55, 129.73, 129.51, 127.17, 118.94, 118.33, 117.35, 115.17, 112.98, 106.75. HRMS: calc'd for $C_{17}H_{12}Cl_2F_2N_3O$, 382.0325 $[M + H]^+$; found, 382.0200.



11i

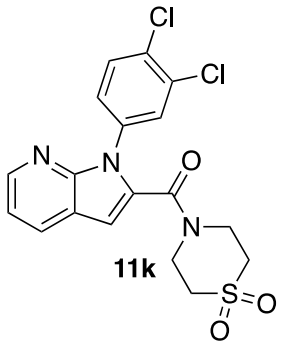
(1-(3,4-dichlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)(3,3-difluoroazetidin-1-yl)methanone (11i). (41 mg; 62% yield). LCMS: R_T = 2.830 min, >98% @ 215 and 254 nm, *m/z* = 414.0 $[M + H]^+$; ^1H NMR (499 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 4.6, 1.7 Hz, 1H), 8.05 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.64 – 7.54 (m, 2H), 7.38 – 7.27 (m, 1H), 7.23 (dd, *J* = 7.9, 4.7 Hz, 1H), 6.92 (s, 1H), 4.61 – 4.14 (m, 4H), 3.37 (dtd, *J* = 14.1, 8.7, 5.3 Hz, 1H).^{13}C NMR (126 MHz, $CDCl_3$) δ 162.11, 149.31, 146.98, 136.14, 132.81, 132.29, 130.70, 130.53, 129.64, 129.52, 127.00, 119.10, 118.23, 106.25, 51.89, 48.00, 32.98, 32.73, 32.47, 32.21. HRMS: calc'd for $C_{18}H_{13}Cl_2F_3N_3O$, 414.0388 $[M + H]^+$; found, 414.0105.



11j

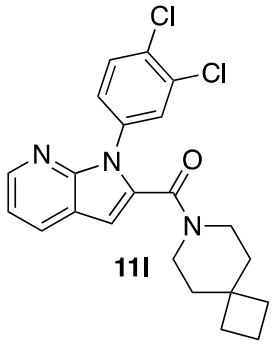
(1-(3,4-dichlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)(1-oxa-6-azaspiro[3.5]nonan-6-yl)methanone (11j). (54 mg; 80% yield). LCMS: R_T = 2.685 min, >98% @ 215 and 254 nm, *m/z*

= 416.0 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.52 – 8.36 (m, 1H), 8.03 (d, *J* = 7.7 Hz, 1H), 7.75 (d, *J* = 90.1 Hz, 1H), 7.64 – 7.40 (m, 2H), 7.22 (dd, *J* = 7.9, 4.7 Hz, 1H), 6.80 (dd, *J* = 30.8, 9.8 Hz, 1H), 4.79 – 4.44 (m, 2H), 4.45 – 4.06 (m, 2H), 3.42 (ddd, *J* = 60.5, 22.2, 10.6 Hz, 2H), 3.26 – 2.95 (m, 1H), 2.50 – 2.20 (m, 2H), 2.07 – 1.53 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.47, 145.52, 135.72, 132.96, 131.63, 130.72, 130.10, 128.47, 126.00, 119.63, 117.94, 104.13, 103.45, 82.26, 65.27, 64.56, 56.68, 36.48, 30.20, 20.67.



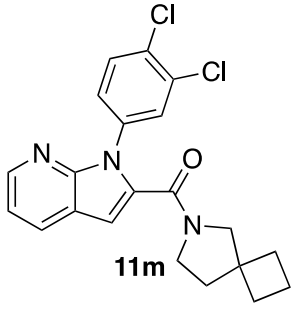
11k

(1-(3,4-dichlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)(1,1-dioxidothiomorpholino) methanone (11k). (54 mg; 78% yield). LCMS: R_T = 2.505 min, >98% @ 215 and 254 nm, *m/z* = 424.0 $[M + H]^+$; ^{1}H NMR (499 MHz, DMSO-d_6) δ 8.40 (dd, *J* = 4.6, 1.6 Hz, 1H), 8.20 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.89 (d, *J* = 2.4 Hz, 1H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.43 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.32 (dd, *J* = 7.9, 4.6 Hz, 1H), 4.04 (s, 4H), 3.27 (t, *J* = 5.3 Hz, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 161.73, 148.39, 145.99, 136.52, 131.99, 131.51, 131.33, 131.10, 130.37, 129.17, 127.52, 119.46, 118.66, 105.00, 51.33, 40.59, 40.42, 40.26, 40.09.



11l

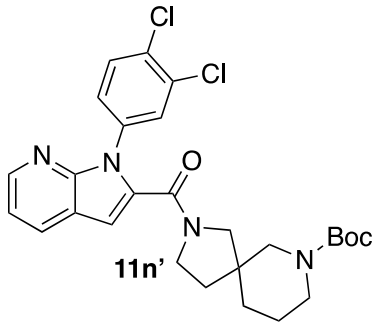
(1-(3,4-dichlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)(7-azaspiro[3.5]nonan-7-yl) methanone (11l). (46 mg; 69% yield). LCMS: R_T = 3.208 min, >98% @ 215 and 254 nm, *m/z* = 414.1 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.40 (d, *J* = 5.3 Hz, 1H), 8.00 (d, *J* = 7.9 Hz, 1H), 7.69 (d, *J* = 2.4 Hz, 1H), 7.58 (d, *J* = 8.6 Hz, 1H), 7.44 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.20 (dd, *J* = 7.9, 4.7 Hz, 1H), 6.74 (s, 1H), 3.46 (d, *J* = 127.2 Hz, 4H), 1.91 (q, *J* = 7.9, 6.9 Hz, 2H), 1.78 (dt, *J* = 16.7, 7.9 Hz, 4H), 1.59 (s, 2H), 1.37 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.84, 148.02, 145.31, 135.79, 133.52, 132.97, 131.63, 130.75, 130.04, 129.96, 128.38, 125.86, 119.76, 117.94, 103.15, 44.32, 39.18, 37.83, 36.85, 31.35, 15.01.



11m

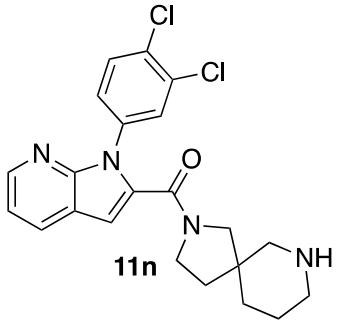
(1-(3,4-dichlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)(6-azaspiro[3.4]octan-6-yl) methanone (11m). (48 mg; 75% yield). LCMS: R_T = 3.024 min, >98% @ 215 and 254 nm, *m/z* = 400.0 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.42 (t, *J* = 4.9 Hz, 1H), 8.02 (t, *J* = 7.9 Hz, 1H), 7.66 (d, *J* = 2.4 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.43 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.22 (dd, *J* = 8.1, 4.5 Hz, 1H), 6.84 (d, *J* = 9.3 Hz, 1H), 3.57 (t, *J* = 7.1 Hz, 1H), 3.41 (d, *J* = 2.6 Hz, 2H), 2.06 –

1.79 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.55, 145.66, 136.11, 134.13, 132.90, 131.62, 130.67, 130.15, 128.42, 125.92, 119.67, 117.95, 103.77, 103.71, 59.79, 57.23, 47.19, 45.12, 44.73, 43.56, 37.62, 36.02, 30.92, 30.56, 15.93.



11n'

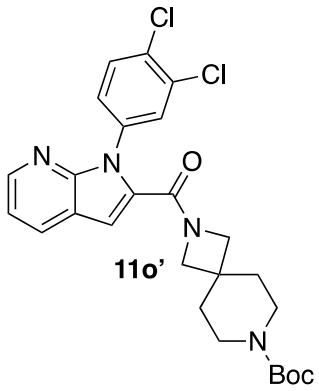
***tert*-butyl 2-(1-(3,4-dichlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carbonyl)-2,7-diazaspiro [4.5]decane-7-carboxylate (11n')** (35 mg, 44% yield). LCMS: R_T = 3.047 min, >98% @ 215 and 254 nm, *m/z* = 529.1 $[M + H]^+$.



11n

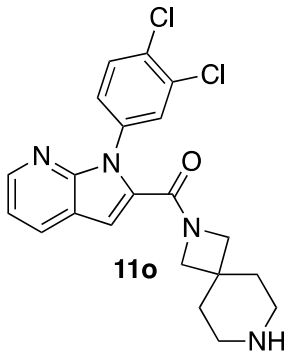
(1-(3,4-dichlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)(6-azaspiro[3.4]octan-6-yl) methanone (11n). A solution of *tert*-butyl 2-(1-(3,4-dichlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carbonyl)-2,7-diazaspiro[4.5]decane-7-carboxylate (0.035 g, 0.066 mmol) in CH_2Cl_2 (5.0 mL) was treated with TFA (0.65 mL) for 12 h. The solvent was removed *in vacuo* and the crude was dissolved in 10% MeOH/CH_2Cl_2, washed with sat. aq. $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated. The crude product was purified on silica gel (eluting with 0-15% MeOH/DCM) to

give the desired product **11n** (20 mg; 71% yield). LCMS: R_T = 1.996 min, >98% @ 215 and 254 nm, *m/z* = 429.1 $[M + H]^+$; ^1H NMR (499 MHz, $CDCl_3$) δ 8.40 (dd, *J* = 11.1, 4.7 Hz, 1H), 8.00 (d, *J* = 7.9 Hz, 1H), 7.70 – 7.52 (m, 2H), 7.40 (ddd, *J* = 25.0, 8.5, 2.5 Hz, 1H), 7.19 (td, *J* = 8.7, 4.7 Hz, 1H), 6.88 (d, *J* = 21.0 Hz, 1H), 4.38 (s, 3H), 3.61 (dtt, *J* = 24.3, 15.2, 8.8 Hz, 3H), 3.40 (dd, *J* = 33.6, 12.2 Hz, 1H), 3.14 – 2.64 (m, 4H), 1.95 (ddt, *J* = 52.3, 13.5, 6.9 Hz, 1H), 1.85 – 1.60 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.30, 145.77, 136.21, 133.70, 132.75, 131.55, 130.70, 130.28, 128.52, 126.16, 119.51, 117.92, 104.21, 57.15, 54.89, 46.86, 44.17, 35.18, 33.79, 32.82.



11o'

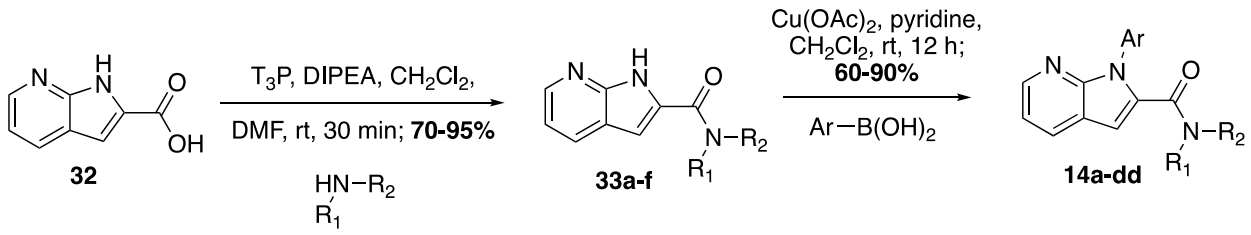
***tert*-butyl 2-(1-(3,4-dichlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carbonyl)-2,7-diazaspiro [3.5] nonane-7-carboxylate (11o').** (45 mg, 54% yield). LCMS: R_T = 2.965 min, >98% @ 215 and 254 nm, *m/z* = 515.1 $[M + H]^+$.



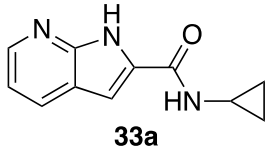
11o

(1-(3,4-dichlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)(2,7-diazaspiro[3.5]nonan-2-yl) methanone (11o). A solution of *tert*-butyl 2-(1-(3,4-dichlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carbonyl)-2,7-diazaspiro[3.5]nonane-7-carboxylate (0.055 g, 0.087 mmol) in CH_2Cl_2 (5.0 mL) was treated with TFA (0.65 mL) for 12 h. The solvent was removed *in vacuo* and the crude was dissolved in 10% MeOH/CH_2Cl_2, washed with sat. aq. $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated. The crude product was purified on silica gel (eluting with 0-15% MeOH/DCM) to give the desired product **11o** (27 mg; 74% yield). LCMS: R_T = 1.939 min, >98% @ 215 and 254 nm, *m/z* = 415.0 $[M + H]^+$; ^1H NMR (499 MHz, $CDCl_3$) δ 8.43 (d, *J* = 4.6 Hz, 1H), 8.02 (d, *J* = 7.9 Hz, 1H), 7.67 – 7.51 (m, 2H), 7.33 (dd, *J* = 8.5, 2.4 Hz, 1H), 7.20 (dd, *J* = 8.0, 4.6 Hz, 1H), 6.90 (s, 1H), 4.01 (s, 2H), 3.84 (s, 3H), 2.88 (d, *J* = 8.0 Hz, 4H), 1.90 – 1.70 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.20, 149.14, 146.62, 136.45, 132.65, 132.02, 130.63, 130.49, 130.47, 129.45, 127.00, 119.22, 118.08, 105.85, 62.70, 58.40, 50.55, 48.65, 42.61, 34.91, 34.30.

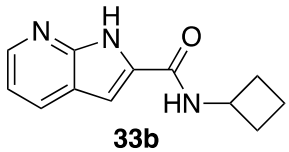
Scheme IX:



The amide coupling procedure as outlined in Scheme I gave the corresponding amide products (**33a-e**).

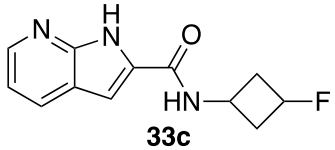


***N*-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (33a).** (0.65 g; 50% yield). LCMS: R_T = 1.699 min., >95% @ 215 and 254 nm, *m/z* = 202.1 $[M + H]^+$ ^{1}H NMR (499 MHz, DMSO) δ 12.06 (s, 1H), 8.52 (d, *J* = 3.7 Hz, 1H), 8.35 (d, *J* = 3.5 Hz, 1H), 8.08 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.14 (dd, *J* = 7.9, 4.6 Hz, 1H), 7.11 (d, *J* = 2.0 Hz, 1H), 2.89 (tq, *J* = 7.7, 3.9 Hz, 1H), 0.84 – 0.71 (m, 2H), 0.65 – 0.56 (m, 2H).^{13}C NMR (126 MHz, DMSO) δ 162.62, 149.18, 146.07, 133.08, 130.80, 120.16, 117.25, 102.56, 23.58, 6.73.



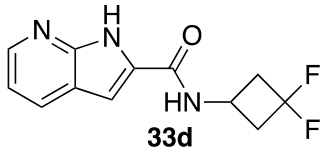
33b

***N*-cyclobutyl-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (33b).** (0.51 g; 45% yield). LCMS: R_T = 1.708 min, >98% @ 215 and 254 nm, *m/z* = 216.0 $[M + H]^+$; ^{1}H NMR (499 MHz, DMSO) δ 12.05 (s, 1H), 8.67 (d, *J* = 7.5 Hz, 1H), 8.34 – 8.30 (m, 1H), 8.09 – 8.03 (m, 1H), 7.13 (s, 1H), 7.11 (dd, *J* = 7.9, 4.6 Hz, 1H), 4.53 – 4.34 (m, 1H), 2.29 – 2.21 (m, 2H), 2.08 (qd, *J* = 9.4, 2.4 Hz, 2H), 1.76 – 1.66 (m, 2H).



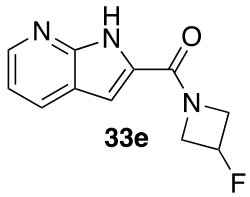
33c

***N*-(3-fluorocyclobutyl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (33c).** (0.58 g; 55% yield). LCMS: R_T = 1.847 min, >98% @ 215 and 254 nm, *m/z* = 234.0 $[M + H]^+$; ^{1}H NMR (499 MHz, DMSO-d_6) δ 12.08 (s, 1H), 8.74 (d, *J* = 6.9 Hz, 1H), 8.33 (d, *J* = 4.5 Hz, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.13 (s, 1H), 5.31 (dt, *J* = 56.9, 5.0 Hz, 1H), 4.58 (q, *J* = 7.2 Hz, 1H), 2.57 (dd, *J* = 15.3, 6.8 Hz, 2H), 2.48 (s, 2H).



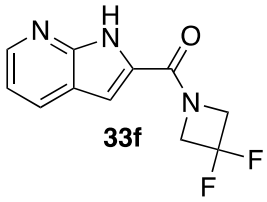
33d

***N*-(3,3-difluorocyclobutyl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (33d).** (0.51 g; 65% yield). LCMS: R_T = 2.001 min, >98% @ 215 and 254 nm, *m/z* = 252.0 $[M + H]^+$; ^{1}H NMR (499 MHz, DMSO-d_6) δ 12.15 (s, 1H), 8.94 (d, *J* = 6.8 Hz, 1H), 8.40 – 8.27 (m, 1H), 8.09 (d, *J* = 7.9 Hz, 1H), 7.19 – 7.06 (m, 2H), 4.31 (p, *J* = 7.5 Hz, 1H), 2.99 (q, *J* = 6.7 Hz, 2H), 2.79 (dt, *J* = 18.4, 7.0 Hz, 2H), 0.94 (t, *J* = 7.0 Hz, 1H).



33e

(3-Fluoroazetidin-1-yl)(1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)methanone (33e). (0.40 g; 45% yield). LCMS: R_T = 1.764 min, >98% @ 215 and 254 nm, *m/z* = 220.0 $[M + H]^+$; ^{1}H NMR (499 MHz, DMSO-d_6) δ 12.15 (s, 1H), 8.94 (d, *J* = 6.8 Hz, 1H), 8.40 – 8.27 (m, 1H), 8.09 (d, *J* = 7.9 Hz, 1H), 7.19 – 7.06 (m, 2H), 4.31 (p, *J* = 7.5 Hz, 1H), 2.99 (q, *J* = 6.7 Hz, 2H), 2.79 (dt, *J* = 18.4, 7.0 Hz, 2H), 0.94 (t, *J* = 7.0 Hz, 1H).



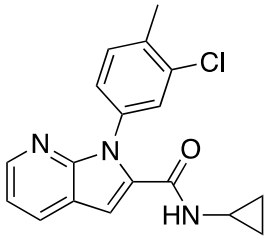
33f

(3,3-difluoroazetidin-1-yl)(1H-pyrrolo[2,3-b]pyridin-2-yl)methanone (33f). To a round bottom flask was added 1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylic acid (0.500 g, 3.09 mmol), HATU (1.60 g, 4.62 mmol), dimethylformamide (12.5 mL), and N,N-diisopropylethylamine (3.88 mL, 22.2 mmol) at room temperature and stirred for 30 minutes. To that was added 3,3-

difluoroazetidine hydrochloride (0.480 g, 3.70 mmol) after stirring at room temperature for 48 h, the reaction was diluted with ice cold water and product was filtered, washed with more ice-cold water and hexane. Precipitated thus obtained were dried under vacuum to afford desired product. 0.35 g (47%). LCMS: R_T = 1.96 min., >98% @ 215 and 254 nm, *m/z* = 238.0 $[M + H]^+$. ^{1}H NMR (499 MHz, DMSO) δ 12.25 – 12.12 (m, 1H), 8.38 (dd, *J* = 4.6, 1.5 Hz, 1H), 8.08 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.15 (dd, *J* = 7.9, 4.6 Hz, 1H), 6.95 (d, *J* = 1.5 Hz, 1H), 4.99 (s, 2H), 4.56 (s, 2H).

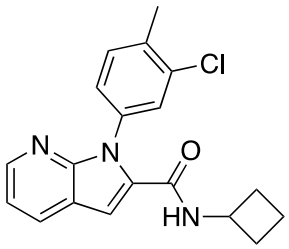
Synthesis of compounds **14a-cc**:

The cross-coupling procedure as outlined in Scheme I gave the desired products **14a-cc**.



14a

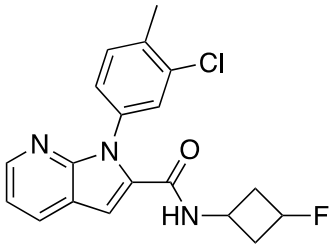
1-(3-chloro-4-methylphenyl)-*N*-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (14a). (75 mg; 74% yield). LCMS: R_T = 1.939 min, >98% @ 215 and 254 nm, *m/z* = 415.0 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.46 (d, *J* = 4.0 Hz, 1H), 8.06 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.55 (t, *J* = 8.2 Hz, 1H), 7.33 (dd, *J* = 9.4, 2.4 Hz, 1H), 7.22 (ddd, *J* = 11.3, 8.4, 3.8 Hz, 2H), 6.92 (s, 1H), 5.39 (ddq, *J* = 56.6, 6.4, 3.2 Hz, 1H), 4.68 – 4.16 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.12, 162.10, 158.77, 156.77, 149.26, 146.86, 136.60, 136.53, 130.64, 130.56, 130.23, 124.07, 124.04, 120.91, 120.77, 119.15, 118.17, 116.45, 116.27, 106.22, 99.98, 82.82, 81.18, 29.72.



14b

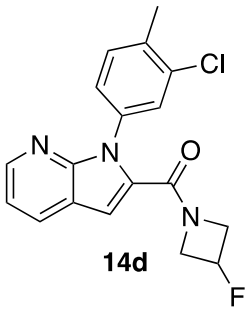
1-(3-chloro-4-methylphenyl)-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide

(14b). (68 mg; 76% yield). LCMS: R_T = 2.723 min, >98% @ 215 and 254 nm, *m/z* = 340.0 [M + H]$^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.39 (d, *J* = 4.2 Hz, 1H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.43 (s, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.29 – 7.24 (m, 2H), 7.18 (dd, *J* = 7.7, 4.8 Hz, 1H), 7.06 (s, 1H), 4.46 – 4.39 (m, 1H), 2.32 (m, 2H), 2.21 (s, 3H), 1.83 – 1.75 (m, 2H), 1.70 (dt, *J* = 11.3, 4.6 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.99, 149.28, 145.99, 136.51, 135.19, 134.67, 133.67, 131.27, 130.83, 128.35, 126.13, 119.32, 117.74, 104.91, 44.77, 30.92, 19.85, 15.11.



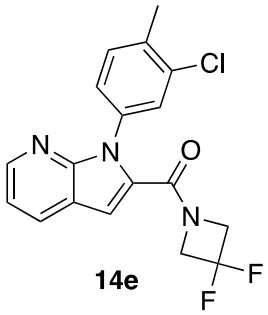
14c

1-(4-chloro-3-methylphenyl)-*N*-(3-fluorocyclobutyl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (14c). (67 mg; 88% yield). LCMS: R_T = 2.644 min, >98% @ 215 and 254 nm, *m/z* = 358.0 [M + H]$^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.49 – 8.40 (m, 1H), 8.08 – 7.98 (m, 1H), 7.49 – 7.38 (m, 2H), 7.29 (d, *J* = 2.2 Hz, 1H), 7.24 – 7.14 (m, 1H), 7.07 (s, 1H), 6.08 (d, *J* = 6.2 Hz, 1H), 5.13 (dq, *J* = 56.1, 4.0, 2.5 Hz, 1H), 4.65 – 4.53 (m, 1H), 2.75 – 2.58 (m, 2H), 2.47 (s, 3H), 2.28 (td, *J* = 14.0, 7.0 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.58, 146.51, 141.19, 136.62, 135.93, 135.21, 134.83, 133.81, 131.39, 130.73, 128.45, 126.18, 117.90, 105.27, 41.50, 38.27, 38.09, 20.60, 19.94.



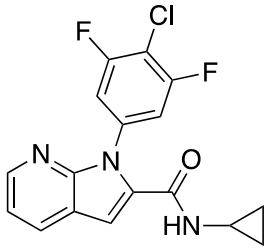
14d

(1-(3-chloro-4-methylphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)(3-fluoroazetidin-1-yl) methanone (14d). (45 mg; 74% yield). LCMS: R_T = 2.588 min, >98% @ 215 and 254 nm, *m/z* = 344.0 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.46 (s, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.47 (s, 1H), 7.39 (d, *J* = 7.9 Hz, 1H), 7.27 (s, 1H), 7.22 (d, *J* = 7.1 Hz, 1H), 6.90 (s, 1H), 5.37 (dtt, *J* = 56.5, 6.4, 3.5 Hz, 1H), 4.40 (d, *J* = 89.2 Hz, 5H), 2.46 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.43, 146.71, 136.08, 135.47, 134.44, 131.07, 130.57, 130.42, 128.02, 125.80, 119.07, 117.83, 105.63, 82.85, 81.21, 29.71, 19.93.



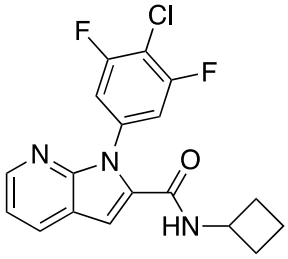
14e

(1-(3-chloro-4-methylphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)(3,3-difluoroazetidin-1-yl)methanone (14e). (7 mg; 5%). LCMS: R_T = 2.750 min., >95% @ 215 and 254 nm, *m/z* = 362.0 $[M + H]^+$. ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 4.6, 1.5 Hz, 1H), 8.04 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.44 (d, *J* = 2.1 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.24 (dd, *J* = 8.0, 2.1 Hz, 1H), 7.20 (dd, *J* = 7.9, 4.6 Hz, 1H), 6.90 (s, 1H), 4.51 (t, *J* = 11.0 Hz, 4H), 2.44 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.81, 149.76, 147.35, 136.67, 135.60, 134.88, 131.46, 131.05, 130.32, 128.47, 126.18, 119.33, 118.34, 117.72, 115.54, 113.36, 106.54, 20.27.



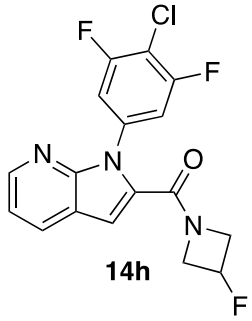
14f

1-(4-chloro-3,5-difluorophenyl)-*N*-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (14f). (56 mg; 66% yield). LCMS: R_T = 2.572 min, >98% @ 215 and 254 nm, *m/z* = 348.0 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.50 – 8.38 (m, 1H), 8.02 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.23 (dd, *J* = 7.9, 4.6 Hz, 1H), 7.17 – 7.07 (m, 2H), 6.95 (s, 1H), 6.33 (s, 1H), 2.84 (dq, *J* = 7.2, 3.6 Hz, 1H), 0.88 (d, *J* = 6.8 Hz, 2H), 0.66 – 0.57 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.02, 159.60, 159.57, 157.61, 157.57, 149.54, 146.80, 136.31, 132.84, 130.65, 119.06, 118.32, 112.40, 112.21, 104.65, 22.88, 6.91.



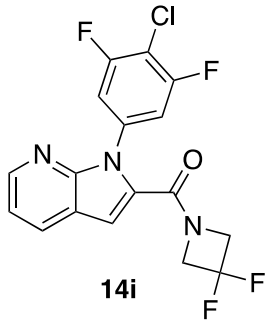
14g

1-(4-chloro-3,5-difluorophenyl)-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (14g). (45 mg; 69% yield). LCMS: R_T = 2.742 min, >98% @ 215 and 254 nm, *m/z* = 362.0 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.24 (dd, *J* = 7.6, 4.6 Hz, 1H), 7.14 (d, *J* = 7.4 Hz, 2H), 7.00 (s, 1H), 6.28 (d, *J* = 6.3 Hz, 1H), 4.56 – 4.45 (m, 1H), 2.47 – 2.39 (m, 2H), 2.00 – 1.91 (m, 3H), 1.83 – 1.76 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.67, 159.61, 159.57, 157.61, 157.57, 149.37, 146.54, 136.25, 133.18, 130.72, 118.31, 112.33, 112.12, 104.59, 45.05, 31.18, 15.18.



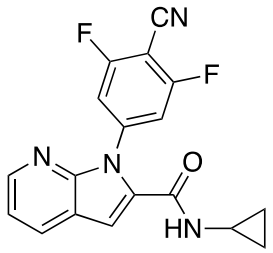
14h

(1-(4-chloro-3,5-difluorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)(3-fluoroazetidin-1-yl) methanone (14h). (47 mg; 71% yield). LCMS: R_T = 2.611 min, >98% @ 215 and 254 nm, *m/z* = 366.0 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.47 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.06 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.25 (dd, *J* = 8.0, 4.7 Hz, 1H), 7.20 – 7.08 (m, 2H), 6.92 (s, 1H), 5.43 (dtt, *J* = 56.4, 6.3, 3.4 Hz, 1H), 4.50 (s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.74, 159.58, 159.54, 157.58, 157.54, 149.22, 147.04, 136.42, 136.32, 130.78, 129.97, 119.15, 118.39, 112.24, 112.22, 112.19, 112.07, 112.04, 112.02, 106.63, 82.82, 81.18, 29.71. HRMS: calc'd for $C_{17}H_{12}ClF_3N_3O$, 366.0621 $[M + H]^+$; found, 366.0484.



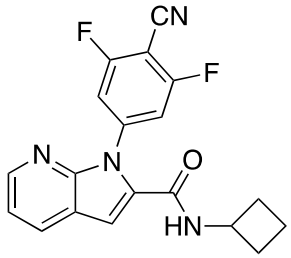
14i

(1-(4-chloro-3,5-difluorophenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)(3,3-difluoroazetidin-1-yl)methanone (14i). (21 mg; 26%). LCMS: R_T = 2.75 min., >98% @ 215 and 254 nm, *m/z* = 384.0 $[M + H]^+$. ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.49 (dd, *J* = 4.6, 1.4 Hz, 1H), 8.08 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.27 (dd, *J* = 8.0, 4.7 Hz, 1H), 7.16 – 7.09 (m, 2H), 6.94 (s, 1H), 4.61 (s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.76, 159.61, 159.57, 157.61, 157.58, 149.31, 147.41, 136.12, 131.00, 129.38, 119.02, 118.55, 117.28, 115.09, 112.91, 112.38, 112.16, 110.24.



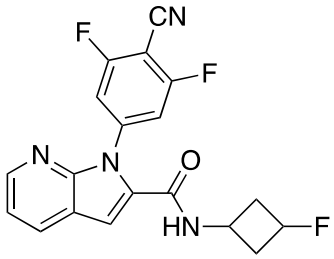
14j

1-(4-cyano-3,5-difluorophenyl)-*N*-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (14j). (54 mg; 65% yield). LCMS: R_T = 2.444 min, >98% @ 215 and 254 nm, *m/z* = 339.0 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.52 – 8.40 (m, 1H), 8.06 (d, *J* = 7.6 Hz, 1H), 7.28 (s, 3H), 7.23 (d, *J* = 9.0 Hz, 2H), 7.00 (s, 1H), 6.41 (s, 1H), 2.87 (s, 1H), 0.92 (d, *J* = 6.8 Hz, 2H), 0.75 – 0.59 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.89, 161.88, 149.27, 147.02, 132.49, 130.94, 119.34, 118.93, 112.10, 111.92, 109.02, 105.95, 22.99, 6.97.



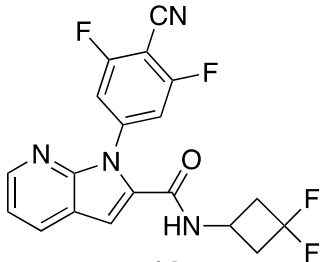
14k

1-(4-cyano-3,5-difluorophenyl)-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (14k). (42 mg; 67% yield). LCMS: R_T = 2.612 min, >98% @ 215 and 254 nm, *m/z* = 353.0 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.45 (d, *J* = 4.1 Hz, 1H), 8.08 (dd, *J* = 19.3, 7.8 Hz, 1H), 7.30 – 7.26 (m, 1H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.04 (s, 1H), 6.41 (s, 1H), 4.50 (dt, *J* = 15.8, 7.9 Hz, 1H), 2.54 – 2.38 (m, 2H), 2.08 – 1.97 (m, 2H), 1.81 (dt, *J* = 18.2, 8.9 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.88, 161.80, 159.52, 149.11, 146.78, 143.29, 132.86, 130.99, 119.47, 118.90, 111.95, 111.80, 109.05, 105.85, 45.18, 31.14, 15.21.



14l

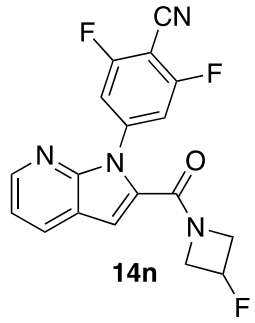
1-(4-cyano-3,5-difluorophenyl)-*N*-(3-fluorocyclobutyl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (14l). (58 mg; 74% yield). LCMS: R_T = 2.542 min, >98% @ 215 and 254 nm, *m/z* = 371.1 $[M + H]^+$; ^{1}H NMR (499 MHz, DMSO-d_6) δ 9.08 (d, *J* = 6.9 Hz, 1H), 8.41 (d, *J* = 4.5 Hz, 1H), 8.26 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 9.6 Hz, 2H), 7.41 (s, 1H), 7.34 (dd, *J* = 7.9, 4.7 Hz, 1H), 5.29 (dddd, *J* = 56.7, 10.3, 6.4, 4.0 Hz, 1H), 4.44 (dtd, *J* = 11.4, 7.2, 5.7, 2.9 Hz, 1H), 4.05 (s, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.25, 163.20, 161.22, 161.16, 160.16, 160.07, 149.13, 146.67, 144.69, 133.35, 131.61, 119.61, 119.21, 113.05, 112.85, 109.91, 107.09, 89.88, 88.12, 86.54, 48.19, 48.02, 47.85, 40.99, 37.77, 37.60, 31.11.



14m

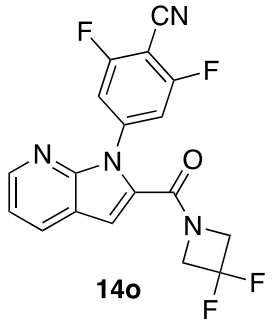
1-(4-cyano-3,5-difluorophenyl)-*N*-(3,3-difluorocyclobutyl)-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (14m). (47 mg; 61% yield). LCMS: R_T = 2.623 min, >98% @ 215 and 254 nm, *m/z* = 389.0 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.09 (d, *J* = 7.8 Hz, 1H), 7.36 – 7.29 (m, 1H), 7.22 (d, *J* = 8.7 Hz, 2H), 7.11 (s, 1H), 6.59 – 6.38 (m, 1H), 4.42 (d, *J* = 9.8 Hz, 1H), 3.24 – 3.00 (m, 2H), 2.63 (td, *J* = 13.7, 5.9 Hz, 2H). 163.94, 161.86, 160.42, 149.37, 143.20,

131.81, 131.12, 119.14, 112.11, 111.93, 108.98, 106.57, 43.29, 43.11, 42.92, 35.58, 35.51, 35.46, 35.39.



14n

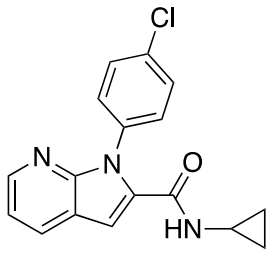
2,6-difluoro-4-(2-(3-fluoroazetidine-1-carbonyl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)benzonitrile (14n). (39 mg; 61% yield). LCMS: R_T = 2.490 min, >98% @ 215 and 254 nm, *m/z* = 357.0 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.47 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.08 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.36 – 7.26 (m, 1H), 7.26 – 7.20 (m, 2H), 6.97 (s, 1H), 5.46 (ddt, *J* = 56.3, 6.1, 2.9 Hz, 1H), 4.82 – 4.20 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.90, 163.85, 161.82, 161.77, 161.29, 161.27, 148.97, 147.25, 143.35, 131.07, 129.65, 119.43, 118.97, 112.00, 111.97, 111.83, 111.80, 109.00, 107.94, 91.41, 82.80, 81.16, 29.72.



14o

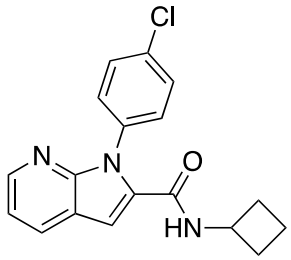
4-(2-(3,3-difluoroazetidine-1-carbonyl)-1H-pyrrolo[2,3-b]pyridin-1-yl)-2,6-difluorobenzonitrile (14o). (15 mg; 19%). LCMS: R_T = 2.64 min., >98% @ 215 and 254 nm, *m/z* = 375.0 $[M + H]^+$. ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.49 (dd, *J* = 4.5, 1.0 Hz, 1H), 8.10 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.31 (dd, *J* = 7.9, 4.6 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.99 (s, 1H), 4.65 (br, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.92,

163.87, 161.84, 161.79, 161.33, 149.09, 147.66, 143.16, 131.25, 129.05, 119.27, 119.12, 117.20, 115.01, 112.83, 112.19, 112.02, 108.91, 108.43, 91.67.



14p

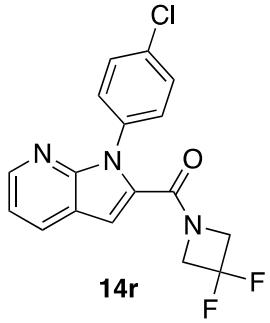
1-(4-chlorophenyl)-*N*-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (14p). (54 mg; 70% yield). LCMS: R_T = 2.404 min, >98% @ 215 and 254 nm, *m/z* = 312.0 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.44 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.02 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.40 (d, *J* = 8.3 Hz, 2H), 7.20 (dd, *J* = 7.9, 4.7 Hz, 1H), 7.02 (s, 1H), 6.09 (s, 1H), 2.80 (dq, *J* = 7.4, 3.7 Hz, 1H), 0.89 – 0.78 (m, 2H), 0.56 – 0.44 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.26, 149.70, 146.53, 135.28, 134.13, 133.26, 130.47, 129.37, 129.08, 119.07, 117.87, 104.75, 77.29, 77.23, 77.03, 76.78, 22.81, 6.90.



14q

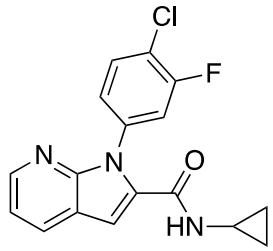
1-(4-chlorophenyl)-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (14q). (38 mg; 65% yield). LCMS: R_T = 2.582 min, >98% @ 215 and 254 nm, *m/z* = 326.0 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.44 (d, *J* = 4.2 Hz, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 13.4 Hz, 1H), 7.20 (dd, *J* = 7.7, 4.7 Hz, 1H), 7.06 (s, 1H), 6.06 (d, *J* = 6.1 Hz, 1H),

4.57 – 4.42 (m, 1H), 2.37 (d, *J* = 6.5 Hz, 2H), 1.88 – 1.78 (m, 3H), 1.78 – 1.70 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.88, 149.57, 146.32, 135.26, 134.17, 133.56, 130.54, 129.41, 129.09, 119.19, 117.84, 104.77, 44.88, 31.17, 15.14.



14r

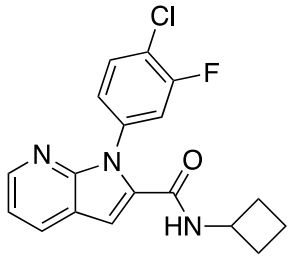
(1-(4-chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)(3,3-difluoroazetidin-1-yl)methanone (14r). (11 mg; 7%). LCMS: R_T = 2.633 min., >95% @ 215 and 254 nm, *m/z* = 348.0 $[M + H]^+$. ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.45 (dd, *J* = 4.6, 1.5 Hz, 1H), 8.05 (d, *J* = 7.9 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.41 – 7.33 (m, 2H), 7.21 (dd, *J* = 7.9, 4.6 Hz, 1H), 6.92 (s, 1H), 4.50 (t, *J* = 11.3 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.87, 149.75, 147.40, 135.51, 134.36, 131.05, 130.23, 129.63, 129.07, 119.38, 118.43, 117.66, 115.48, 113.30, 106.77.



14s

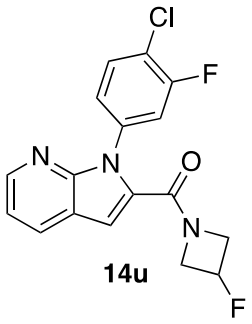
1-(4-chloro-3-fluorophenyl)-*N*-cyclopropyl-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (14s). (39 mg; 69% yield). LCMS: R_T = 2.482 min, >98% @ 215 and 254 nm, *m/z* = 330.0 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.03 (d, *J* = 7.8 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.37 – 7.13 (m, 3H), 6.98 (s, 1H), 6.25 (s, 1H), 2.82 (s, 1H), 0.86 (d, *J* = 7.1 Hz, 2H), 0.58 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$)

δ 162.18, 158.82, 156.84, 149.52, 146.56, 136.50, 136.43, 133.05, 130.64, 124.34, 119.10, 118.12, 116.72, 116.54, 104.62, 22.86, 6.92.



14t

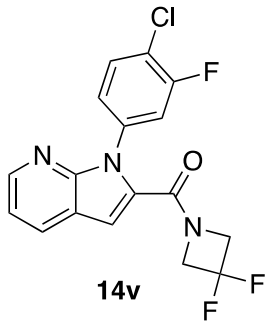
1-(4-chloro-3-fluorophenyl)-*N*-cyclobutyl-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxamide (14t). (40 mg; 64% yield). LCMS: R_T = 2.643 min, >98% @ 215 and 254 nm, *m/z* = 344.0 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.45 (d, *J* = 3.3 Hz, 1H), 8.06 (t, *J* = 12.3 Hz, 1H), 7.55 (t, *J* = 8.2 Hz, 1H), 7.31 (d, *J* = 9.2 Hz, 1H), 7.23 (t, *J* = 6.4 Hz, 2H), 6.19 (d, *J* = 5.8 Hz, 1H), 4.49 (dq, *J* = 16.0, 8.0 Hz, 1H), 2.45 – 2.35 (m, 2H), 1.96 – 1.86 (m, 2H), 1.82 – 1.71 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.79, 156.84, 149.41, 146.39, 133.39, 130.66, 130.66, 124.29, 118.08, 116.68, 116.50, 116.41, 104.55, 77.28, 77.02, 76.77, 44.97, 31.19, 15.27.



14u

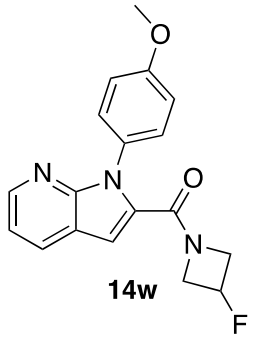
(1-(4-chloro-3-fluorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)(3-fluoroazetidin-1-yl) methanone (14u). (42 mg; 67% yield). LCMS: R_T = 2.521 min, >98% @ 215 and 254 nm, *m/z* = 348.0 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.46 (d, *J* = 4.0 Hz, 1H), 8.06 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.55 (t, *J* = 8.2 Hz, 1H), 7.33 (dd, *J* = 9.4, 2.4 Hz, 1H), 7.22 (ddd, *J* = 11.3, 8.4, 3.8 Hz,

2H), 6.92 (s, 1H), 5.39 (ddq, *J* = 56.6, 6.4, 3.2 Hz, 1H), 4.68 – 4.16 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.12, 162.10, 158.77, 156.77, 149.26, 146.86, 136.60, 136.53, 130.64, 130.56, 130.23, 124.07, 124.04, 120.91, 120.77, 119.15, 118.17, 116.45, 116.27, 106.22, 99.98, 82.82, 81.18, 29.72. HRMS: calc'd for $C_{17}H_{13}ClF_2N_3O$, 348.0715 $[M + H]^+$; found, 348.0620.



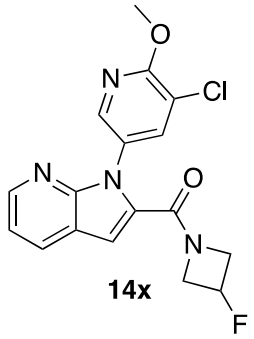
14v

(1-(4-chloro-3-fluorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)(3,3-difluoroazetidin-1-yl)methanone (14v). (10 mg; 6%). LCMS: R_T = 2.684 min., >95% @ 215 and 254 nm, *m/z* = 366.0 $[M + H]^+$. ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 4.6, 1.5 Hz, 1H), 8.05 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.53 (t, *J* = 8.2 Hz, 1H), 7.29 (dd, *J* = 9.3, 2.3 Hz, 1H), 7.23 (dd, *J* = 7.9, 4.6 Hz, 1H), 7.17 (ddd, *J* = 8.5, 2.1, 1.1 Hz, 1H), 6.92 (s, 1H), 4.55 (s, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.48, 159.15, 157.15, 149.68, 147.55, 136.73, 136.66, 131.21, 130.97, 129.99, 124.50, 124.47, 121.51, 121.37, 119.37, 118.67, 117.65, 116.92, 116.74, 115.47, 113.29, 107.10.



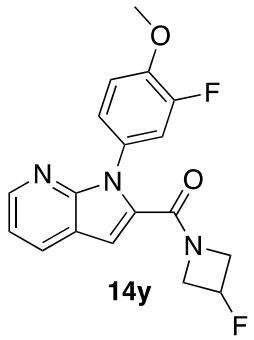
14w

(3-fluoroazetidin-1-yl)(1-(4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)methanone (14w). (38 mg; 65% yield). LCMS: R_T = 2.274 min, >98% @ 215 and 254 nm, *m/z* = 326.0 $[M + H]^+$; ^1H NMR (499 MHz, $CDCl_3$) δ 8.46 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.04 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.45 – 7.35 (m, 2H), 7.19 (dd, *J* = 7.9, 4.7 Hz, 1H), 7.10 – 7.02 (m, 2H), 6.90 (s, 1H), 5.32 (dtd, *J* = 56.5, 6.2, 3.2 Hz, 1H), 4.42 (ddd, *J* = 18.9, 12.0, 6.7 Hz, 2H), 4.35 – 4.16 (m, 2H), 3.89 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.95, 159.06, 149.45, 146.40, 131.08, 130.30, 129.49, 128.39, 119.10, 117.55, 114.35, 105.02, 82.81, 81.18, 55.47.



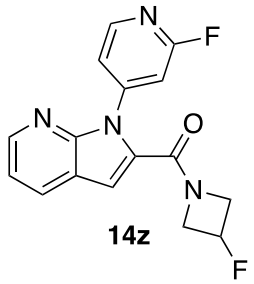
14x

(1-(5-chloro-6-methoxypyridin-3-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)(3-fluoroazetidin-1-yl) methanone (14x). (46 mg; 71% yield). LCMS: R_T = 2.460 min, >98% @ 215 and 254 nm, *m/z* = 361.0 $[M + H]^+$; ^1H NMR (499 MHz, $CDCl_3$) δ 8.46 (d, *J* = 5.0 Hz, 1H), 8.11 (d, *J* = 2.3 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 2.3 Hz, 1H), 7.23 (dd, *J* = 7.9, 4.5 Hz, 1H), 6.90 (s, 1H), 5.41 (ddt, *J* = 56.4, 6.1, 3.0 Hz, 1H), 4.37 (d, *J* = 133.2 Hz, 6H), 4.10 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.98, 161.96, 158.79, 149.74, 146.98, 143.25, 137.97, 130.61, 130.08, 127.68, 118.98, 118.13, 117.80, 105.98, 82.85, 81.22, 77.30, 77.05, 76.79, 54.69. HRMS: calc'd for $C_{17}H_{15}ClFN_4O_2$ 361.0868 $[M + H]^+$; found, 361.0705.



14y

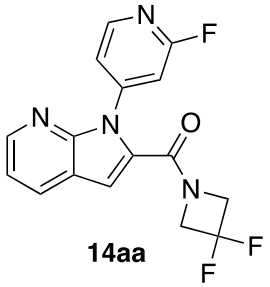
(1-(3-fluoro-4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)(3-fluoroazetidin-1-yl) methanone (14y). (50 mg; 80% yield). LCMS: R_T = 2.330 min, >98% @ 215 and 254 nm, *m/z* = 344.1 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.46 (d, *J* = 4.3 Hz, 1H), 8.04 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.26 – 7.15 (m, 3H), 7.10 (t, *J* = 8.9 Hz, 1H), 6.89 (s, 1H), 5.36 (ddt, *J* = 56.6, 6.2, 3.0 Hz, 1H), 4.47 (s, 3H), 4.32 (s, 3H), 3.96 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.49, 152.80, 150.83, 149.52, 147.55, 147.46, 146.67, 130.41, 129.54, 123.51, 119.01, 117.81, 116.04, 113.08, 105.43, 82.83, 81.20, 56.33.



14z

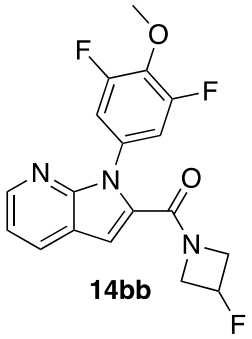
(3-fluoroazetidin-1-yl)(1-(2-fluoropyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)methanone (14z). (34 mg; 60% yield). LCMS: R_T = 2.157 min, >98% @ 215 and 254 nm, *m/z* = 315.0 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.45 (d, *J* = 33.8 Hz, 2H), 8.07 (d, *J* = 7.9 Hz, 1H), 7.47 – 7.34 (m, 1H), 7.28 (q, *J* = 15.8, 10.9 Hz, 2H), 6.99 (s, 1H), 5.41 (dtt, *J* = 56.3, 6.3, 3.4 Hz, 1H), 4.67 – 4.20 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.12, 162.10, 158.77, 156.77, 149.26, 146.86, 136.60, 136.53, 130.64, 130.56, 130.23, 124.07, 124.04, 120.91, 120.77, 119.15, 118.17, 116.45,

116.27, 106.22, 99.98, 82.82, 81.18, 29.72. HRMS: calc'd for $C_{16}H_{13}F_2N_4O$, 315.1057 $[M + H]^+$; found, 315.1047.



14aa

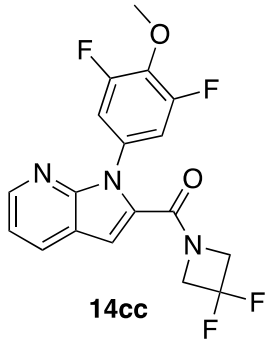
(3,3-difluoroazetidin-1-yl)(1-(2-fluoropyridin-4-yl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)methanone (14aa). (6 mg; 4%). LCMS: R_T = 2.328 min., >95% @ 215 and 254 nm, *m/z* = 333.0 $[M + H]^+$. ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.48 (dd, *J* = 4.6, 1.5 Hz, 1H), 8.36 (d, *J* = 5.4 Hz, 1H), 8.06 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.31 (d, *J* = 5.4 Hz, 1H), 7.28 (dd, *J* = 8.0, 4.7 Hz, 1H), 7.15 (s, 1H), 6.99 (s, 1H), 4.56 (t, *J* = 10.1 Hz, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.35, 163.45, 162.27, 149.25, 148.49, 148.38, 148.25, 147.67, 131.38, 129.75, 119.92, 119.88, 119.82, 119.30, 117.55, 115.37, 113.18, 108.72, 108.34, 108.02.



14bb

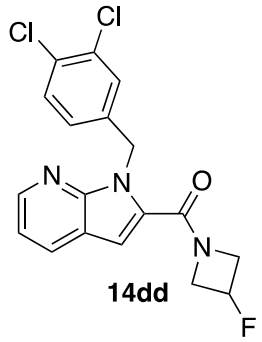
(1-(3,5-difluoro-4-methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)(3-fluoroazetidin-1-yl) methanone (14bb). (54 mg; 82% yield). LCMS: R_T = 2.456 min, >98% @ 215 and 254 nm, *m/z* = 362.0 $[M + H]^+$; ^{1}H NMR (499 MHz, $CDCl_3$) δ 8.47 (dd, *J* = 4.7, 1.5 Hz, 1H), 8.05 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.23 (dd, *J* = 7.9, 4.6 Hz, 1H), 7.05 (d, *J* = 8.2 Hz, 2H), 6.89 (s, 1H), 5.41 (ddt, *J* = 56.4, 6.1, 2.9 Hz, 1H), 4.69 – 4.21 (m, 5H), 4.08 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.04, 162.02, 156.27, 156.21, 154.29, 154.23, 149.32, 146.86, 136.40, 131.18, 130.62, 130.27, 119.07,

118.12, 112.43, 112.38, 112.28, 112.23, 106.05, 82.81, 81.17, 61.89, 61.86, 61.84. HRMS: $C_{18}H_{15}F_3N_3O_2$, 362.1116 $[M + H]^+$; found, 362.0960.



14cc

(1-(3,5-difluoro-4-methoxyphenyl)-1H-pyrrolo[2,3-b]pyridin-2-yl)(3,3-difluoroazetidin-1-yl)methanone (14cc). (20 mg; 25%). LCMS: R_T = 2.62 min., >98% @ 215 and 254 nm, *m/z* = 380.0 $[M + H]^+$. ^1H NMR (499 MHz, $CDCl_3$) δ 8.49 (dd, *J* = 4.6, 1.5 Hz, 1H), 8.06 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.25 (dd, *J* = 7.9, 4.7 Hz, 1H), 7.08 – 7.01 (m, 2H), 6.92 (s, 1H), 4.57 (br s., 4H), 4.09 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.07, 156.25, 154.28 149.42, 147.24, 136.59, 130.90, 129.69, 118.96, 118.29, 117.31, 115.13, 112.53, 112.39, 106.61, 61.86.



14dd

(1-(3,4-dichlorobenzyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl)(3-fluoroazetidin-1-yl)methanone (14dd). To a solution of **33e** (0.015 g; 0.068 mmol) in DMF (2.0 mL), was added 4-(bromomethyl)-1,2-dichlorobenzene (0.017 g; 0.082 mmol), Cs_2CO_3 (0.044 g; 0.14 mmol), and was heated in a microwave reactor at 120 ˚C for 1h. Upon cooling, the solution was partitioned

between EtOAc and sat NaCl. The org layer was separated, dried ($MgSO_4$), concentrated, and purified by flash chromatography chromatography on silica gel (dry loaded using silica/DCM) with a gradient of 0 – 70% EtOAc:Hexanes to give the corresponding target compound **14dd** (23 mg; 90% yield). LCMS: R_T = 2.853 min, >98% @ 215 and 254 nm, *m/z* = 378.0 $[M + H]^+$; ^1H NMR (499 MHz, $CDCl_3$) δ 8.51 (dd, *J* = 4.7, 1.6 Hz, 1H), 8.02 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.33 (dd, *J* = 5.2, 3.1 Hz, 2H), 7.20 (dd, *J* = 7.9, 4.7 Hz, 1H), 7.11 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.74 (s, 1H), 5.90 (s, 2H), 5.34 (ddq, *J* = 56.6, 6.3, 3.2 Hz, 1H), 4.59 – 4.22 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.13, 148.44, 146.29, 139.06, 132.34, 131.24, 130.51, 130.33, 129.47, 128.42, 127.08, 118.73, 117.46, 105.05, 82.82, 81.19, 45.12.

Preparation of mouse bone marrow-derived macrophages and evaluation of PDE4 inhibitors on macrophage pro-inflammatory activity.

Macrophages were expanded from the bone marrow of C57BL/6 mice as previously described.[1] Briefly, bone marrow was flushed from femurs with sterile RPMI-1640 serum-free medium and cultured in RPMI-1640 containing 10% FBS (Atlanta Biologicals, Atlanta, GA), penicillin/streptomycin/fungizone, and 5% conditioned medium from L929 fibroblasts as a source of macrophage-colony stimulating factor (M-CSF). After a 6 day expansion period, macrophages were harvested and plated in a 96-well plate at $5x10^4$ cells/well. The following day, macrophages were pre-treated with various concentrations of rolipram or the novel PDE4 inhibitors described in this report (1 or 10 μM) for 30 min prior to stimulation with LPS (100 ng/ml) or Pam3Cys (10 μg/ml)(both from Invivogen, San Diego, CA). After a 24 h treatment period, conditioned medium was assessed for TNF-α release by enzyme-linked immunosorbent assay (ELISA; BD OptEIA, San Jose CA). Controls included unstimulated macrophages or cells exposed to PDE4 inhibitors alone.

References.

(1) Hanke, M. L., Heim, C. E., Angle, A., Sanderson, S. D., Kielian, T. Targeting macrophage activation for the prevention and treatment of Stapylococcus aureus biofilm infections. *J. Immunol.* **2013**, *190*, 2159-2168.

Table 1. Selectivity for Compound **11h**.

PDE Selectivity (BPS Biosciences):

PDE Isoform	**% Inhibition at 10 μM**	**IC_{50} (nM)**
PDE1A1	23	
PDE1B	18	
PDE1C	15	
PDE2A1	4	
PDE2A1	7	
PDE3A	7	
PDE3B	87	
PDE4A1A	23	
PDE4B2	93	140
PDE4C1	54	
PDE4D3	79	880
PDE5A1	13	
PDE6C	3	
PDE7A1	1	
PDE7B	1	
PDE8A1	10	
PDE9A2	2	
PDE10A1	23	
PDE10A2	29	
PDE11A4	15	

Table 2. PDSP Selectivity for **11h [2]:**

Receptor	**% Inhibition (nM)**		**Receptor**	**% Inhibition (nM)**
5-HT_{1A}	8		BZP rat brain	24.4
5-HT_{1B}	0.9		D1	4.1
5-HT_{1D}	0		D2	7.2
5-HT_{1E}	5.9		D3	22.8
5-HT_{2A}	0.03		D4	9.8
5-HT_{2B}	10.4		D5	-5.9
5-HT_{2C}	59 (>10,000)		DAT	20.1
5-HT_{3}			DOR	30.4
5-HT_{5A}	6.4		H1	-16
5-HT_{6}	6.4		H2	-2.3
5-HT_{7A}	7.1		H3	4.6
α_{1A}	-1.7		KOR	14.7
α_{1B}	-10.9		M1	-4.4
α_{1D}	2.5		M2	-6.9
α_{2A}	4.6		M3	14.2
α_{2B}	4.5		M4	-15.2
α_{2C}	6.8		M5	19.8
β2	-1.9		MOR	-7
PBR	34.5			

σ1	23.1		σ2	70 (7,822)

References:

[2] Besnard J.; Ruda G. F.; Setola, V.; Abecassis, K.; Rodriguiz, R. M.; Huang, X. P.; Norval, S.; Sassano, M. F.; Shin, A. I.; Webster, L. A.; Simeons, F. R.; Stojanovski, L.; Prat, A.; Seidah, N. G.; Constam, D. B.; Bickerton, G. R.; Read, K. D.; Wetsel, W. C.; Gilbert, I. H.; Roth, B. L.; Hopkins, A. L., "Automated design of ligands to polypharmacological profiles", *Nature* **2012**, *492*, 215-220.