Supporting Information

Discovery of PF-06463922, a macrocyclic inhibitor of ALK/ROS1 with pre-clinical brain exposure and broad spectrum potency against ALK-resistant mutations

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Contents

Single Crystal X-Ray of HCl salt of PF-06463922 (8k)

Experimental Summary

CCDC 986729 contains the supplementary crystallographic data for structure, **8k**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

The single crystal X-ray diffraction studies were carried out on a Bruker Kappa Photon CMOS CCD diffractometer equipped with Mo K_α radiation (λ = 0.71073 Å). Crystals of the subject compound were grown by vapor diffusion of pentane into a MeCN/EtOH solution. A 0.37 x 0.15 x 0.11 mm colorless block was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100 (2) K using ϕ and ϖ scans. Crystal-to-detector distance was 40 mm and exposure time was 10 seconds per frame using a scan width of 0.5°. Data collection was 99.8% complete to 25.00° in θ. A total of 28909 reflections were collected covering the indices, -15<=h<=16, -22<=k<=22, -25<=l<=22. 4946 reflections were found to be symmetry independent, with a R_{int} of 0.0362. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be $P2_12_12_1$. The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by direct methods (SHELXS) produced a complete phasing model consistent with the proposed structure.

All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-97). All hydrogen atoms were placed using a riding model. Their positions were

constrained relative to their parent atom using the appropriate HFIX command in SHELXL-97. Crystallographic data are summarized in Table 1.

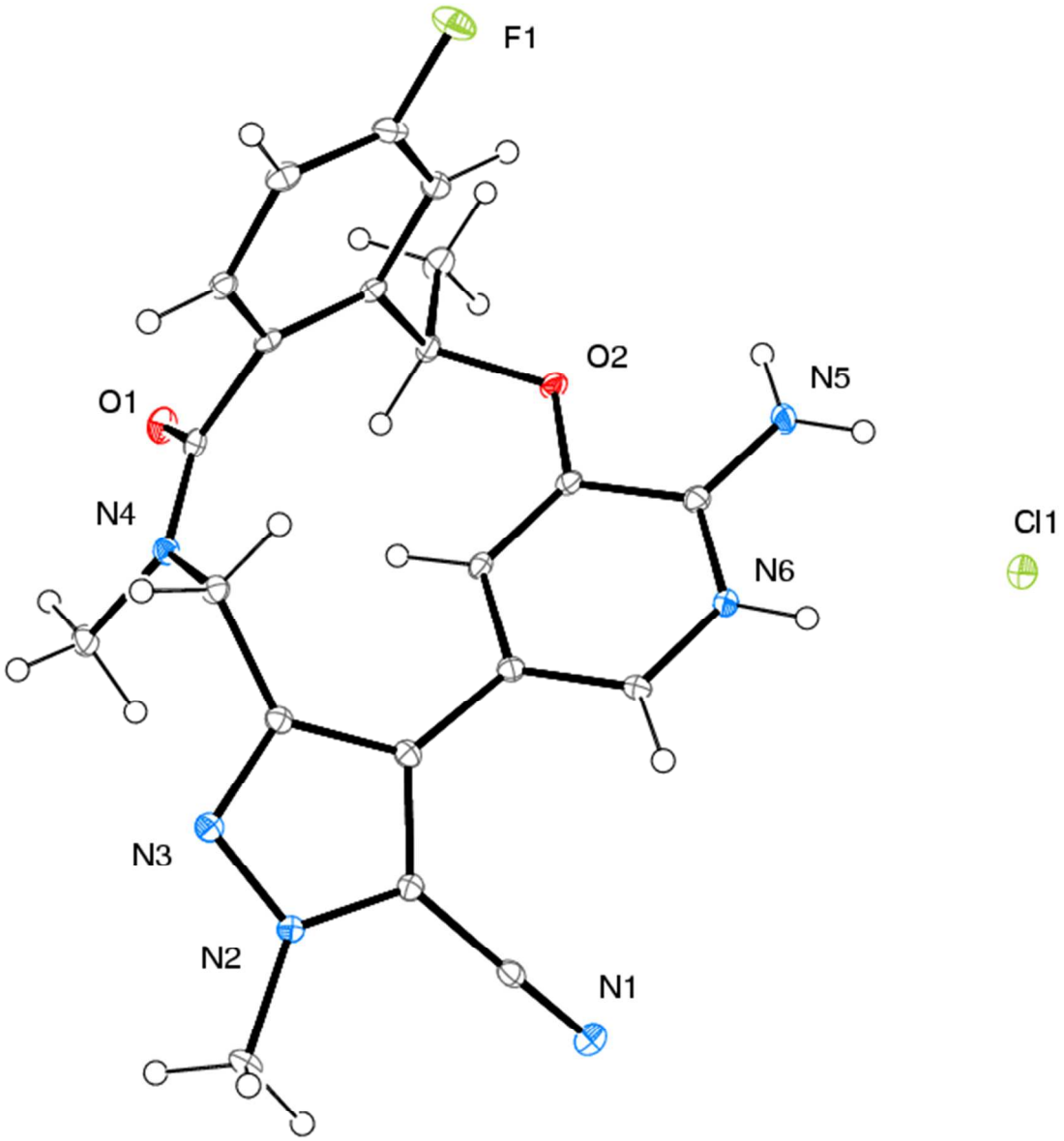


Table 1. Crystal data and structure refinement for **8k**.

Empirical formula	C23 H27.50 Cl F N6.50 O4
Molecular formula	C21 H20 F N6 O2, 0.5(C2 H6 O), 0.5(C2 H3 N), Cl, 1.5(H2 O)

Formula weight	513.47	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 13.5237(5) Å	$\alpha = 90°$.
	b = 17.6508(6) Å	$\beta = 90°$.
	c = 20.4826(6) Å	$\gamma = 90°$.
Volume	4889.3(3) $Å^3$	
Z	8	
Density (calculated)	1.395 Mg/m^3	
Absorption coefficient	0.208 mm^{-1}	
F(000)	2152	
Crystal size	0.37 x 0.15 x 0.11 mm^3	
Crystal color, habit	Colorless Block	
Theta range for data collection	2.30 to 26.40°.	
Index ranges	-15<=h<=16, -22<=k<=22, -25<=l<=22	
Reflections collected	28909	
Independent reflections	9818 [R(int) = 0.0362]	
Completeness to theta = 25.00°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9775 and 0.9272	
Refinement method	Full-matrix least-squares on F^2	

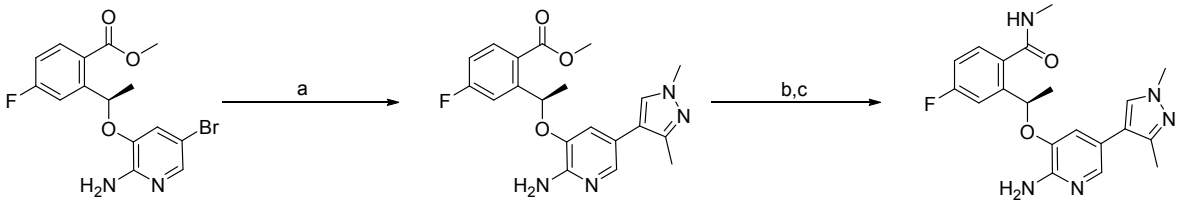
Data / restraints / parameters	9818 / 0 / 669
Goodness-of-fit on F^2	1.044
Final R indices [I>2sigma(I)]	R1 = 0.0335, wR2 = 0.0741
R indices (all data)	R1 = 0.0437, wR2 = 0.0795
Absolute structure parameter	-0.01(4)
Extinction coefficient	not measured
Largest diff. peak and hole	0.370 and -0.232 e.$Å^{-3}$

Experimentals and Schemes for Intermediates

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 chromatography (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 Biotage Initiator. ^{1}H NMR spectra were recorded on a Bruker instrument operating at 400 MHz unless otherwise indicated. ^{1}H NMR spectra are obtained as DMSO-d_6 or $CDCl_3$ solutions as indicated (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 hertz. 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 resolution mass measurements were carried 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: XBridge C18 column @ 80 °C, 4.6 mm x 150 mm, 5 μm, 5%-95% MeOH/H_2O buffered with 0.2% formic acid/0.4% ammonium formate, 3 min run, flow rate 1.2 mL/min, UV detection (λ = 254, 224 nm). Combustion analyses were performed by Atlantic Microlab, Inc. (Norcross, Georgia).

Scheme S1. Synthesis of 2-[(1*R*)-1-{[2-amino-5-(1,3-dimethyl-1*H*-pyrazol-4-yl)pyridin-3-yl]oxy}ethyl]-4-fluoro-*N*-methylbenzamide **6e**



Reagents and conditions: (a) 5 mol% $Pd(PPh_3)_4$, 1.4 eq 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole, 3 eq K_2CO_3, dioxane/H_2O (1:1), reflux, 2 h; (b) 5 eq KOH, MeOH/H_2O (1:1), rt, 5 h, 41% over 2 steps; (c) 1 eq CDI, 5 eq $MeNH_2$ (2 M in THF), THF, rt, 30 min, 38%.

2-[(1R)-1-{[2-amino-5-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-3-yl]oxy}ethyl]-4-fluoro-N-methylbenzamide (**6e**) $Pd(PPh_3)_4$ (60 mg, 0.05 mmol) was added to a degassed mixture of **44** (380 mg, 1.03 mmol), 1,3-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (320 mg, 1.44 mmol), potassium carbonate (427 mg, 3.09 mmol) in dioxane (15 mL) and water

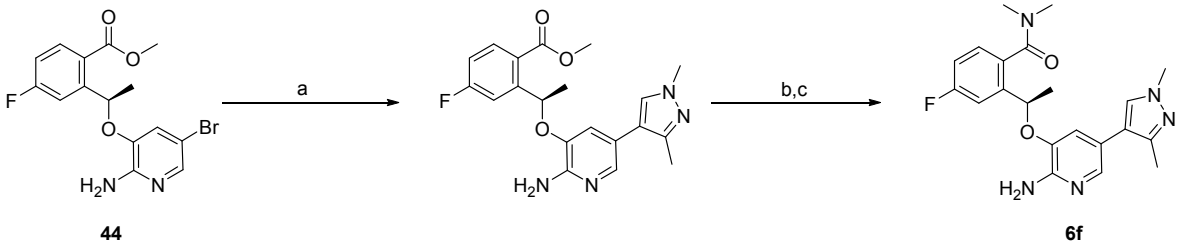
(15 mL). The resulting mixture was heated to 80 °C for 2 h, then allowed to cool to room temperature. The reaction was diluted with EtOAc (20 mL) then washed with water (2 x 20 mL). The organics were combined, dried ($MgSO_4$), the solvents removed *in vacuo,* and the residue purified by column chromatography eluting with MeOH/CH_2Cl_2 (1 – 10%) to give (*R*)-methyl 2-(1-((2-amino-5-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-3-yl)oxy)ethyl)-4-fluorobenzoate (581 mg, contains pinacol residues) as a dark oil, which was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, *J* = 8.8, 5.7 Hz, 1 H), 7.58 (d, *J* = 1.8 Hz, 1 H), 7.22 (s, 1 H), 7.01 (ddd, *J* = 8.8, 7.6, 2.7 Hz, 1 H), 6.66 (d, *J* = 1.8 Hz, 1 H), 6.43 – 6.34 (m, 1 H), 4.95 (s, 2 H), 3.92 (s, 3 H), 3.80 (s, 3 H), 2.02 (s, 3 H), 1.68 (d, *J* = 6.2 Hz, 3 H).

A solution of KOH (238 mg, 4.25 mmol) in water (5 ml) was added to a solution of (*R*)-methyl-2-(1-((2-amino-5-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-3-yl)oxy)ethyl)-4-fluorobenzoate (480 mg, 0.85 mmol) in MeOH (5 mL) at room temperature. The resulting mixture was stirred for 5 h (TLC analysis indicated completion). 2M HCl (2 mL) was added and the solvents removed *in vacuo*. The residue was purified by reverse phase column chromatography (eluent: 0 - 100% MeCN in H_2O containing 0.1% formic acid) to give (*R*)-2-(1-((2-amino-5-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-3-yl)oxy)ethyl)-4-fluorobenzoic acid (125 mg, 41% yield over 2 steps) as a colorless solid. LC-MS (ESI) *m/z* 371.2 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.99 – 7.86 (m, 1 H), 7.59 (s, 1 H), 7.52 – 7.40 (m, 2 H), 7.16 (t, *J* = 8.6 Hz, 1 H), 6.76 (s, 1 H), 6.43 (d, *J* = 6.5 Hz, 1 H), 5.84 (s, 2 H), 3.70 (s, 3 H), 1.96 (s, 3 H), 1.59 (d, *J* = 6.2 Hz, 3 H).

CDI (83 mg, 0.34 mmol) was added to a stirred suspension of (*R*)-2-(1-((2-amino-5-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-3-yl)oxy)ethyl)-4-fluorobenzoic acid (125 mg, 0.34 mmol) in

THF (5 mL) at room temperature. The reaction was then heated to 70 °C for 1 h, then allowed to cool to room temperature. The resulting solution was poured into a solution of methyl amine (2M in THF, 0.85 mL, 1.7 mmol) in THF (2 mL) cooled in an ice bath. After stirring at room temperature for 30 min, the solvents were removed *in vacuo* and the residue purified by reverse phase chromatography (eluent: 0 - 100% MeCN in H_2O containing 0.1% formic acid) to give (2-[(1*R*)-1-{[2-amino-5-(1,3-dimethyl-1*H*-pyrazol-4-yl)pyridin-3-yl]oxy}ethyl]-4-fluoro-*N*-methylbenzamide **(6e)** (71 mg, 54% yield). In order to remove aliphatic impurities present in the ^{1}H NMR of the sample, further purification was carried out by normal phase chromatography on silica gel (eluent: MeOH/CH_2Cl_2 1 – 5%) to give 2-[(1*R*)-1-{[2-amino-5-(1,3-dimethyl-1*H*-pyrazol-4-yl)pyridin-3-yl]oxy}ethyl]-4-fluoro-*N*-methylbenzamide (**6e**) (50 mg, 38% yield) as a white solid. LC-MS (ESI) *m/z* 384.1 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (q, *J* = 4.7 Hz, 1 H), 7.59 (s, 1 H), 7.52 – 7.35 (m, 3 H), 7.16 (td, *J* = 8.5, 2.7 Hz, 1 H), 6.91 (d, *J* = 1.9 Hz, 1 H), 6.01 - 5.88 (m, 1 H), 5.80 (s, 2H), 3.71 (s, 3 H), 2.78 (d, *J* = 4.5 Hz, 3 H), 2.03 (s, 3 H), 1.57 (d, *J* = 6.3 Hz, 3 H).

Scheme S2. Synthesis of 2-[(1*R*)-1-{[2-amino-5-(1,3-dimethyl-1*H*-pyrazol-4-yl)pyridin-3-yl]oxy}ethyl]-4-fluoro-*N*,*N*-dimethylbenzamide **6f**



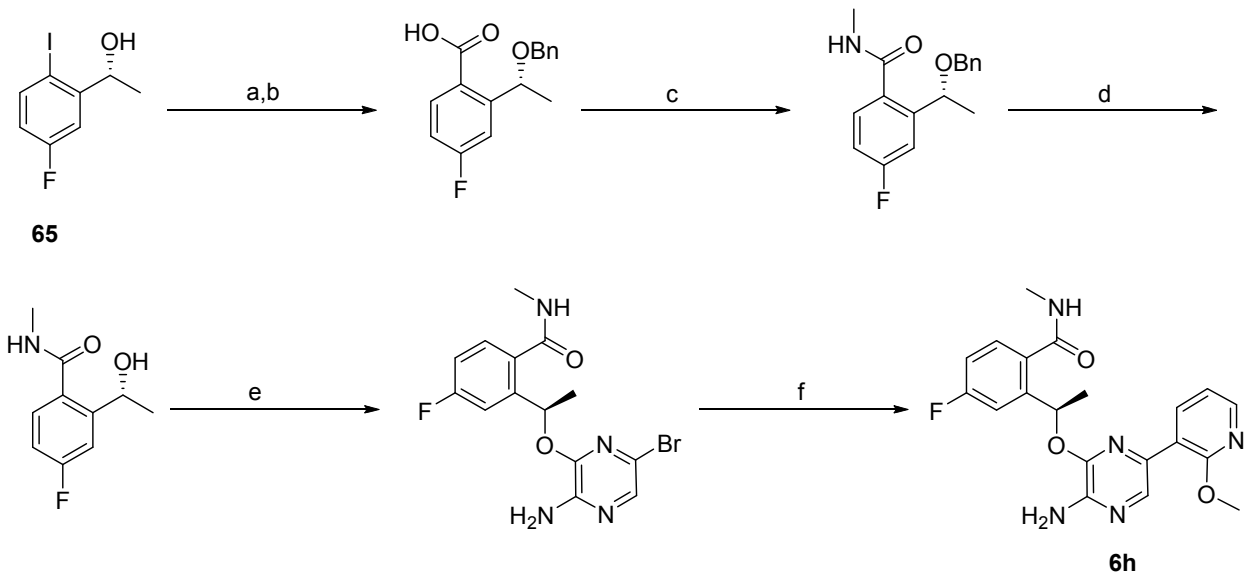
Reagents and conditions: (a) 5 mol% $Pd(PPh_3)_4$, 1.1 eq 4-bromo-1,3-dimethyl-1*H*-pyrazole, 1.5 eq B_2pin_2, 3 eq K_2CO_3, DME/H_2O (1:1), reflux, 1.5 h, quant.; (b) 10 eq LiOH, THF/MeOH/H_2O (2:2:1), rt, 16 h, 46%; (c) 1.2 eq CDI, 2 eq Me_2NH (2 M in THF), THF, rt, 1h, 16%.

2-[(1R)-1-{[2-amino-5-(1,3-dimethyl-1H-pyrazol-4-yl)pyridin-3-yl]oxy}ethyl]-4-fluoro-N,N-dimethylbenzamide (**6f)** A mixture containing **44** (130 mg, 0.35 mmol), 4-bromo-1,3-dimethyl-1*H*-pyrazole (73 mg, 0.42 mmol), B_2pin_2 (117 mg, 0.52 mmol), potassium carbonate (146 mg, 1.06 mmol), $Pd(Ph_3)_4$ (20 mg, 5 mol%), DME (2 mL) and water (2 mL) was degassed (N_2) then heated at 105 °C in a sealed vial for 1.5 h. The reaction was then cooled to room temperature, partitioned between water (30 mL) and EtOAc (50 mL). The layers were separated and the aqueous extracted with EtOAc (3 x 50 mL). The combined organics were dried ($MgSO_4$), the solvents removed, and the residue purified by column chromatography on silica gel eluting with EtOAc : cyclohexane (20 – 100%), and then 20% MeOH/EtOAc. Methyl 2-[(1*R*)-1-{[2-amino-5-(1,3-dimethyl-1*H*-pyrazol-4-yl)pyridin-3-yl]oxy}ethyl]-4-fluorobenzoate (422 mg, contains residual EtOAc) was isolated as a yellow gum. LC-MS (ESI) *m/z* 385.4 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 8.04 (m, 1 H), 7.60 (s, 1 H), 7.31 – 7.30 (m, 1 H), 7.20 (s, 1 H), 7.02 – 7.00 (m, 1 H), 6.65 (s, 1 H), 6.35 (q, 1 H), 4.75 (br s, 2 H), 3.90 (s, 3 H), 3.80 (s, 3 H), 2.05 (s, 3 H), 1.70 (d, 3 H).

$LiOH.H_2O$ (168 mg, 4.0 mmol) was added in a single portion to a stirred solution of methyl 2-[(1*R*)-1-{[2-amino-5-(1,3-dimethyl-1*H*-pyrazol-4-yl)pyridin-3-yl]oxy}ethyl]-4-fluorobenzoate (384 mg, 1 mmol) in THF/MeOH/H_2O (10:10:5 mL). The reaction was stirred at room temperature for 16 h, and then concentrated *in vacuo* (to ~5 mL). The mixture was acidified with HCl (6M) until pH~5 (pH paper), then extracted with EtOAc (2 x 30 mL). The combined organics were dried ($MgSO_4$) and the solvents removed *in vacuo* to give **2**-[(1*R*)-1-{[2-amino-5-(1,3-dimethyl-1*H*-pyrazol-4-yl)pyridin-3-yl]oxy}ethyl]-4-fluorobenzoic acid (171 mg, 46% yield) as a colorless oil, which was used without further purification. LC-MS (ESI) *m/z* 371.3 $[M+H]^+$.

CDI (90 mg, 0.55 mmol) was added in a single portion to a stirred solution of 2-[(1*R*)-1-{[2-amino-5-(1,3-dimethyl-1*H*-pyrazol-4-yl)pyridin-3-yl]oxy}ethyl]-4-fluorobenzoic acid (171 mg, 0.46 mmol) in THF (5 mL) at room temperature. The reaction was heated to 50 °C for 1 h, then cooled to room temperature. This mixture was added *via* pipette to a stirred solution of dimethylamine (2M in THF, 0.46 mL, 0.92 mmol) in THF (3 mL). After stirring for 1 h at room temperature, the reaction was diluted with EtOAc (20 mL) and washed with aq. $NaHCO_3$ (2 x 20 mL) then with 1M HCl (2 x 20 mL). The desired product remained in the acidic aqueous phase. The pH was adjusted to ~7 with 1M NaOH aqueous solution and the solution concentrated *in vacuo*. The solids were filtered, and washed with MeOH. The solvent was removed *in vacuo* and the residue purified by reverse phase chromatography (eluting with H_2O/MeCN/0.1% formic acid – 0 -100%) to give 66 mg of a 1:1 mixture of the starting material and the desired amide, which were observed to co-run on LC-MS under acidic conditions. This material was re-dissolved in EtOAc (20 mL) then washed with aq. $NaHCO_3$ (6 x 20 mL), and then brine (20 mL). The organics were dried (MgSO4), the solvents removed *in vacuo* and the residue purified by SCX-2 cartridge to give 2-[(1*R*)-1-{[2-amino-5-(1,3-dimethyl-1*H*-pyrazol-4-yl)pyridin-3-yl]oxy}ethyl]-4-fluoro-*N*,*N*-dimethylbenzamide (**6f)** (30 mg, 16% yield) as a pale yellow gum. LC-MS (ESI) *m/z* 398.2 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 7.57 (s, 1 H), 7.50 (d, 1 H), 7.37 - 7.34 (m, 1 H), 7.31-7.27 (m, 1 H), 7.12 - 7.07 (m, 2 H), 5.62 - 5.59 (m, 1 H), 3.80 (s, 3 H), 3.09 (s, 3 H), 2.72 (s, 3 H), 2.09 (s, 3 H), 1.68 (d, J = 6.4 Hz, 3 H).

Scheme S3. Synthesis of 2-[(1*R*)-1-{[3-amino-6-(2-methoxypyridin-3-yl)pyrazin-2-yl]oxy}ethyl]-4-fluoro-*N*-methylbenzamide **6h**



Reagents and conditions: (a) 1.1 eq NaH (60% in mineral oil), 1 eq BnBr, THF, rt, 14 h, 51%; (b) 1.5 eq *n*-BuLi (2.5 M in hexane), CO_2 gas, THF, - 78 °C to rt, 16 h, 59%; (c) 1.2 eq EDCI, 0.5 eq HOBt, 3 eq $MeNH_2$ (2 M in THF), THF, rt, 14 h, 78%; (d) 10 mol% Pd/C (10 %), 50 psi H_2 gas, EtOH, 50 °C, 14 h, 54%; (e) 1.2 eq 2-amino-3,5-dibromopyrazine, 3 eq Cs_2CO_3, acetone, 80 °C, 16 h, 58%; (f) 10 mol% $Pd(PPh_3)_4$, 2 eq (2-methoxypyridin-3-yl)boronic acid, 3 eq Na_2CO_3, MeOH/CH_2Cl_2 (3:1), 120 °C, 1 h, 35%.

2-[(1R)-1-{[3-amino-6-(2-methoxypyridin-3-yl)pyrazin-2-yl]oxy}ethyl]-4-fluoro-N-methylbenzamide (**6h**) To a solution of **65** (12.1 g, 45.47 mmol) in dry THF (150 mL) was added NaH (60% in mineral oil, 2.0 g, 50.0 mmol) in small portions over 5 min whilst cooling the reaction mixture in an ice bath. The reaction mixture was stirred for 30 min at 5 °C before adding benzyl bromide (5.4 mL, 45.47 mmol). The reaction was allowed to stir at room temperature overnight, then the solvent was evaporated and the resulting residue taken up in EtOAc (200 mL) and washed with water (20 mL) followed by brine (20 mL). The organic phase was dried over Na_2SO_4 and evaporated to give the crude product, which was purified by silica gel column chromatography eluting with 0 – 2% acetone/heptanes to give 2-[(1*R*)-1-(benzyloxy)ethyl]-4-fluoro-1-iodobenzene (8.1 g, 51% yield) as clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 - 7.73

(m, 1 H), 7.41 - 7.25 (m, 6 H), 6.79 - 6.74 (m, 1 H), 4.71 - 4.66 (m, 1 H), 4.47 (d, 1 H), 4.44 (d, 1 H), 1.41 (d, 3 H).

To a solution of 2-[(1*R*)-1-(benzyloxy)ethyl]-4-fluoro-1-iodobenzene (4.7 g, 12.9 mmol) in dry THF (60 mL) was added slowly *n*-BuLi (2.5M solution in hexane, 7.7 mL, 19.35 mmol) while keeping the reaction temperature at -78 °C. The reaction was stirred for 30 min at -78 °C before CO_2 gas (generated from Cardice) was bubbled through the reaction mixture for 10 min. The reaction was allowed to warm to room temperature, and stirred overnight. The majority of the solvent was then evaporated and the residue treated with 10% $NaHCO_3$ (50 mL), followed by extraction of the aqueous mixture with EtOAc (15 mL). The bicarbonate extract was separated, and carefully acidified with solid $KHSO_4$ to pH~4, and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with water (5 mL), followed by brine (5 mL), dried over Na_2SO_4, and concentrated. The yellow solid was triturated with heptanes (25 mL), filtered, then washed with additional heptanes (5 mL) to give 2-[(1*R*)-1-(benzyloxy)ethyl]-4-fluorobenzoic acid (2.2 g, 59% yield) as an off-white solid. LC-MS (ESI) *m/z* 280.4 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, 1 H), 7.47 (dd, 1 H), 7.20 - 7.18 (m, 5 H), 7.01 - 6.96 (m, 1 H), 5.44 - 5.34 (m, 1 H), 4.40 (d, 1 H), 4.32 (d, 1 H), 1.45 (d, 3 H).

To a solution of 2-[(1*R*)-1-(benzyloxy)ethyl]-4-fluorobenzoic acid (2.8 g, 10.2 mmol) in THF (25 mL) was added EDCI (2.41 g, 12.2 mmol) and HOBt (0.78 g, 5.1 mmol), and the mixture stirred for 40 min before adding methyl amine (2 M solution in THF, 15.5 mL, 30.6 mmol). The reaction was stirred overnight at room temperature. The reaction mixture was concentrated and the residue was taken up in EtOAc (75 mL), and washed with water (10 mL) and brine (10 mL). The EtOAc phase was dried over Na_2SO_4, and concentrated. The crude product was purified by silica gel column chromatography using 2% MeOH in CH_2Cl_2 to furnish 2-[(1*R*)-1-

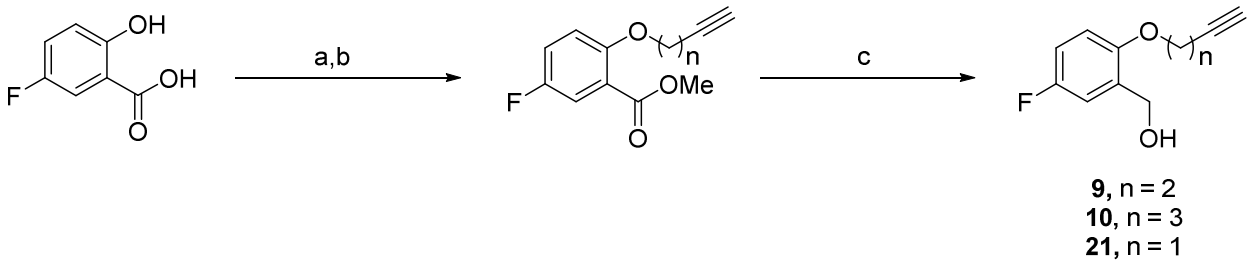
(benzyloxy)ethyl]-4-fluoro-*N*-methylbenzamide (2.3 g, 78% yield) as a white solid. LC-MS (ESI) *m/z* 310.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, 1 H), 7.34 - 7.25 (m, 6 H), 7.00 - 6.95 (m, 1 H), 6.03 (br s, 1 H), 4.97 - 4.92 (m, 1 H), 4.45 (d, 1 H), 4.37(d, 1 H), 2.90 (d, 3 H), 1.51 (d, 3 H).

To a solution of 2-[(1*R*)-1-(benzyloxy)ethyl]-4-fluoro-*N*-methylbenzamide (2.2 g, 4.17 mmol) in ethanol (50 mL) was added Pd/C (10%, 220 mg) ,and the mixture hydrogenated at 50 psi at 50 °C for 16 h. The reaction mixture was filtered through Celite, eluting with additional MeOH (5 mL) and the combined filtrate evaporated. Purification of the crude product by silica gel column chromatography using 6% MeOH in CH_2Cl_2 provided 4-fluoro-2-[(1*R*)-1-hydroxyethyl]-*N*-methylbenzamide (0.81 g, 54% yield) as white solid. LC-MS (ESI) *m/z* 180.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, 1 H), 7.11 (dd, 1 H), 6.90 - 6.85 (m, 1 H), 6.39 (br s, 1 H), 4.89 - 4.84 (m, 1 H), 4.56 (br s, 1 H), 2.94 (d, 3 H), 1.47 (d, 3 H).

To a solution of 4-fluoro-2-[(1*R*)-1-hydroxyethyl]-*N*-methylbenzamide (0.81 g, 4.1 mmol) in acetone (40 mL), was added 2-amino-3,5-dibromopyrazine (1,25 g, 4.92 mmol) and Cs_2CO_3 (4.0 g, 12.3 mmol) and the reaction mixture heated at 80 °C overnight. The solvent was removed, and the residue was taken up in EtOAc (50 mL), washed with water (5 mL) and brine (5 mL). The organic phase was dried over Na_2SO_4, and evaporated. Purification of the crude product by silica gel column chromatography using 3% MeOH in CH_2Cl_2 provided 2-{(1*R*)-1-[(3-amino-6-bromopyrazin-2-yl)oxy]ethyl}-4-fluoro-*N*-methylbenzamide (0.88 g, 58% yield) as an off-white solid. LC-MS (ESI) *m/z* 367.5/369.5 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1 H), 7.48 (dd, 1 H), 7.35 (s, 1 H), 7.10 (dd, 1 H), 7.25 (s, 1 H), 7.10 (dd, 1 H), 7.01 - 6.96 (m 1 H), 6.22 - 6.16 (m, 1 H), 4.93 (br s, 2 H), 3.08 (d, 3 H), 1.67 (d, 3 H).

To a microwave vial was added 2-{(1*R*)-1-[(3-amino-6-bromopyrazin-2-yl)oxy]ethyl}-4-fluoro-*N*-methylbenzamide (75 mg, 0.20 mmol), (2-methoxypyridin-3-yl)boronic acid (62.0 mg, 0.40 mmol) and Na_2CO_3 (63.5 mg, 0.60 mmol) followed by a mixture of CH_2Cl_2 (0.5 mL) and MeOH (1.5 mL). The reaction mixture was degassed by bubbling with nitrogen for 2 min before the addition of $Pd(PPh_3)_4$ (23.0 mg, 0.02 mmol). The reaction mixture was irradiated in the microwave at 120 °C for 1 h. After cooling, the reaction mixture was diluted with EtOAc (20 mL) and washed with water (3 mL) and brine (3 mL). The organic phase was dried over Na_2SO_4 and concentrated. The crude material was purified by chromatography on silica gel eluting with 2.5% MeOH in CH_2Cl_2 to give 2-[(1*R*)-1-{[3-amino-6-(2-methoxypyridin-3-yl)pyrazin-2-yl]oxy}ethyl]-4-fluoro-*N*-methylbenzamide (**6h)** (28.0 mg, 35% yield) as an off-white solid. LC-MS (ESI) *m/z* 398.1 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 – 8.09 (m, 1 H), 8.07 (s, 1 H), 7.59 – 7.57 (m, 1 H), 7.48 – 7.46 (m, 1H), 7.20 – 7.19 (m, 1 H), 7.01 – 6.99 (m, 1 H), 6.36 – 6.29 (m, 1 H), 5.03 (s, 2 H), 3.10 (s, 3 H), 2.67 (d, *J* = 5 Hz, 3 H), 1.68 (d, *J* = 5.6 Hz, 3 H).

Scheme S4. Synthesis of **9**, **10** and **21**



9, n = 2
10, n = 3
21, n = 1

Reagents and conditions (yields for n = 2) : (a) H_2SO_4, MeOH, reflux, 14 h, 76%; (b) 1.1 eq but-3-yn-1-ol, 2 eq Ph_3P, 2 eq DIAD, 1 eq TEA, THF, rt, 20 h, 45%; (c) 2.7 eq $LiBH_4$, THF, 52%.

(2-(But-3-yn-1-yloxy)-5-fluorophenyl)methanol **(9)**. To a solution of 5-fluoro-2-hydroxybenzoic acid (2.5 g, 16 mmol) in MeOH (32 mL) was added sulfuric acid (2.0 mL, 21 mmol). The solution was heated at reflux overnight, cooled to room temperature and concentrated. The residue was dissolved in EtOAc (100 mL), washed with saturated $NaHCO_3$ (3 x 50 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated to give methyl 5-fluoro-2-hydroxybenzoate (2.1 g, 76% yield) as a cream solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 7.54 - 7.45 (m, 1 H), 7.40 (td, J = 8.6, 3.2 Hz, 1 H), 7.01 (dd, J = 9.1, 4.5 Hz, 1 H), 3.89 (s, 3 H).

To a solution of methyl 5-fluoro-2-hydroxybenzoate (22.0 g, 129 mmol), but-3-yn-1-ol (10.0 g, 142.8 mmol), and Ph_3P (68.0 g, 260 mmol) in THF (160 mL) was added TEA (18.0 mL, 129 mmol) followed by the dropwise addition at 0 °C of a solution of DIAD (53.4 mL, 260 mmol) in THF (40 mL). The solution was stirred at room temperature for 20 h and concentrated. TBME (200 mL) was added, and the mixture stirred at room temperature for 30 min. The mixture was filtered, and the filtrate concentrated to a residue, which was purified by flash chromatography on silica gel eluting with EtOAc/heptanes (5 - 20%) to give methyl 2-(but-3-yn-1-yloxy)-5-fluorobenzoate (13.0 g, 45% yield) as a white solid.

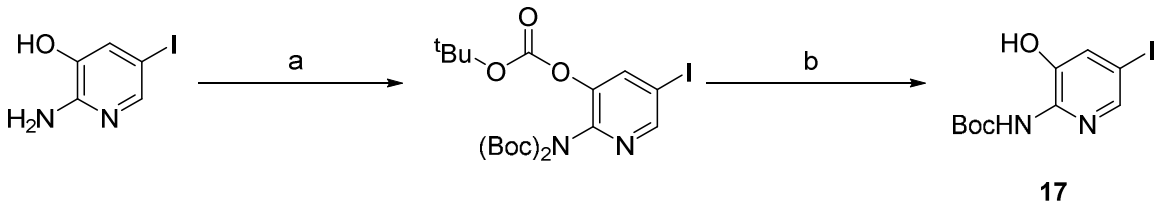
To a stirred solution of methyl 2-(but-3-yn-1-yloxy)-5-fluorobenzoate (18.0 g, 76.2 mmol) in THF (360 mL) was added in a portion-wise manner $LiBH_4$ (4.4 g, 202.6 mmol) at 0 °C under nitrogen. After the addition, the mixture was stirred at 50 °C for 5 h. TLC (petroleum ether/EtOAc = 6 : 1) indicated the reaction was complete. The mixture was cooled to 0 °C, and water (50 mL) was added in a dropwise manner. The aqueous layer was extracted with EtOAc (2 x 200 mL). The combined organic extracts were washed with brine (2 x 150 mL), dried over Na_2SO_4 and concentrated to give a residue, which was purified by column chromatography on

silica gel (petroleum ether / EtOAc = 10 : 1) to give **9** (8.2 g, 52% yield) as a white solid**.** LC-MS (APCI), *m/z* 176 $[M - OH]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.20 - 7.17 (m, 1 H), 7.05 - 6.96 (m, 2 H), 5.20 (t, 1 H), 4.54 (t, 2 H), 4.08 (t, 2 H), 2.90 (t, 1 H), 2.66 - 2.62 (m, 2 H).

(5-Fluoro-2-(pent-4-yn-1-yloxy)phenyl)methanol **(10)**. Compound **10** was prepared in a similar manner to **9** with but-3-yn-1-ol being used in step 2**.** LC-MS (APCI), *m/z* 191 $[M - OH]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.22 - 7.19 (m, 1 H), 7.08 - 6.98 (m, 2 H), 5.23 (t, 1 H), 4.55 (t, 2 H), 4.08 (t, 2 H), 2.88 (t, 1 H), 2.40 - 2.38 (m, 2 H), 1.97 - 1.91 (m, 2 H).

(5-Fluoro-2-(prop-2-yn-1-yloxy)phenyl)methanol **(21)**. Compound **21** was prepared in a similar manner to **9** with prop-2-yn-1-ol being used in step 2**.** ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21 - 7.13 (m, 1 H), 7.03 (dd, J = 6.2, 1.6 Hz, 2 H), 5.20 (t, J = 5.7 Hz, 1 H), 4.79 (d, J = 2.3 Hz, 2 H), 4.48 (d, J = 5.8 Hz, 2 H), 3.55 (t, J = 2.4 Hz, 1 H).

Scheme S5. Synthesis of (3-Hydroxy-5-iodo-pyridin-2-yl)-carbamic acid *tert*-butyl ester (**17**)



17

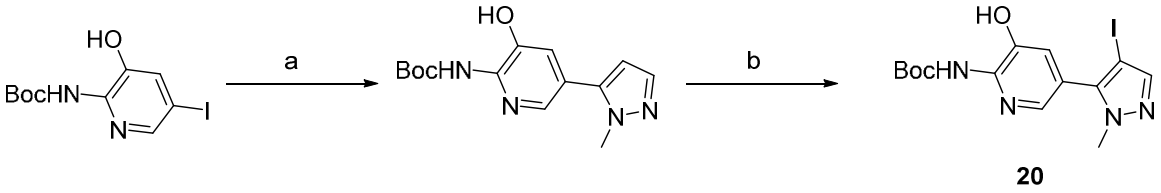
Reagents and conditions: (a) 3 eq $(Boc)_2O$, 20 mol% DMAP, DMF, rt, 16 h, 26%; (b) 40 mol% *N*,*N*-diethylenediamine, MeCN, rt, 6 h, 59%.

tert-Butyl (3-hydroxy-5-iodopyridin-2-yl)carbamate **(17)**. A mixture of 2-amino-5-iodopyridin-3-ol (623 mg, 2.64 mmol), DMAP (64.5 mg, 0.528 mmol), and $(Boc)_2O$ (1.73g, 7.92 mmol) in DMF (7.5 mL) was stirred at room temperature overnight. The mixture was diluted

with EtOAc (100 mL), washed with saturated aq. $NaHCO_3$ (2 x 50 mL), brine (50 mL), dried over $MgSO_4$, filtered and concentrated to dryness. The residue was purified by flash chromatography on silica gel using a gradient of 0 - 35% EtOAc/heptanes as eluent to give the exhaustively protected di-*tert*-butyl {3-[(*tert*-butoxycarbonyl)oxy]-5-iodopyridin-2-yl}imidodicarbonate (372 mg, 26% yield) as a gum. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (d, J = 1.77 Hz, 1 H), 8.36 (d, J = 1.77 Hz, 1 H), 1.48 (2, 9H), 1.39 (s, 18 H).

A mixture of di-*tert*-butyl {3-[(*tert*-butoxycarbonyl)oxy]-5-iodopyridin-2-yl}imidodicarbonate (106 mg, 0.98 mmol) and *N,N*-diethylenediamine (30.6 µL, 0.218 mmol) in MeCN (1 mL) was stirred at room temperature for 5 h. After this time, the starting material was still evident by LC-MS. More *N,N*-diethylenediamine (28 µL, 0.198 mmol) was added. After stirring at room temperature for a further 1 h, LC-MS indicated that the reaction was complete. The mixture was concentrated to dryness and the residue purified by flash chromatography on silica gel using a gradient of 0 - 50% CH_2Cl_2/heptanes as eluent to obtain tert-Butyl (3-hydroxy-5-iodopyridin-2-yl)carbamate **17** (37 mg, 59% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (br s, 1 H), 8.83 (s, 1 H), 8.00 (d, J = 1.52 Hz, 1 H), 7.48 (d, J = 1.77 Hz, 1 H), 1.43 (s, 9 H).

Scheme S6. Synthesis of *tert*-butyl (3-hydroxy-5-(4-iodo-1-methyl-1H-pyrazol-5-yl)pyridin-2-yl)carbamate **(20)**



20

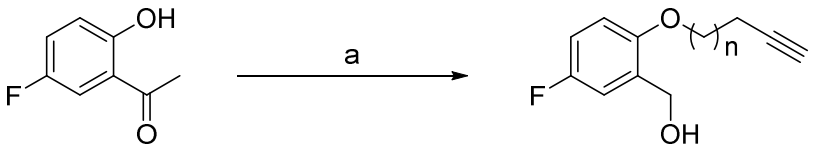
Reagents and conditions: (a) 1.5 eq 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole, 10 mol% $PdCl_2$(dppf), 3 eq CsF, MeOH, 60 °C, 12 h, 67%; (b) 1.5 eq AgOTf, 1.5 eq I_2 (0.25 M in EtOH), EtOH, rt, 4 h, 58%.

tert-Butyl (3-hydroxy-5-(4-iodo-1-methyl-1H-pyrazol-5-yl)pyridin-2-yl)carbamate **(20)**. To a mixture of *tert*-butyl (3-hydroxy-5-iodopyridin-2-yl)carbamate (500 mg, 1.49 mmol) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (464 mg, 2.23 mmol) in MeOH (9.9 mL) was added CsF (678 mg, 4.46 mmol) in water (1 mL). The mixture was bubbled with nitrogen for 5 min, and then $PdCl_2$.dppf (1:1 with CH_2Cl_2, 122 mg, 0.15 mmol) was added. The reaction was heated at 60 °C overnight then diluted with EtOAc (50 mL), washed with water (10 mL), brine (25 mL), dried ($MgSO_4$), filtered and concentrated. The crude product was purified by flash chromatography on silica gel eluting with EtOAc/heptanes (0 - 75%). The fractions containing the desired product were concentrated and the product was crashed out using CH_2Cl_2/Et_2O to give *tert*-butyl [3-hydroxy-5-(1-methyl-1*H*-pyrazol-5-yl)pyridin-2-yl]carbamate (290 mg, 67% yield) as a colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (s, 1 H), 9.02 (s, 1 H), 7.99 (s, 1 H), 7.48 (s, 1 H), 7.31 (s, 1 H), 6.44 (s, 1 H), 3.85 (s, 3 H), 1.46 (s, 9 H).

To a mixture of *tert*-butyl [3-hydroxy-5-(1-methyl-1*H*-pyrazol-5-yl)pyridin-2-yl]carbamate (960 mg, 3.3 mmol) and AgOTf (850 mg, 3.3 mmol) in EtOH (30 mL) was added a solution of I_2 (0.25 M in EtOH, 13 mL, 3.31 mmol). After 1 h, additional AgOTf (425 mg, 1.66 mmol) and I_2 (0.25 M in EtOH, 6.6 mL, 1.66 mmol) were added. Once LC-MS showed the reaction was completed (4 h), the mixture was filtered and the mother liquor was diluted with EtOAc (100 mL), washed with 1 N Na_2CO_3 (50 mL), saturated $Na_2S_2O_3$/water (50 mL), and brine (50 mL). The combined aqueous layers were neutralized with 4 N HCl and extracted with CH_2Cl_2 (2 x 150 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated. The crude product was purified by flash chromatography on silica gel eluting with EtOAc/heptanes (0 - 100%) to give tert-Butyl (3-hydroxy-5-(4-iodo-1-methyl-1H-pyrazol-5-yl)pyridin-2-

yl)carbamate **20** (800 mg, 58% yield) as a cream solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (br s, 1 H), 9.02 (s, 1 H), 7.89 (d, J = 2.0 Hz, 1 H), 7.63 (s, 1 H), 7.25 (d, J = 2.0 Hz, 1 H), 3.80 (s, 3 H), 1.47 (s, 9 H).

Scheme S7. Synthesis of **30** and **31**



30, n = 1
31, n = 2

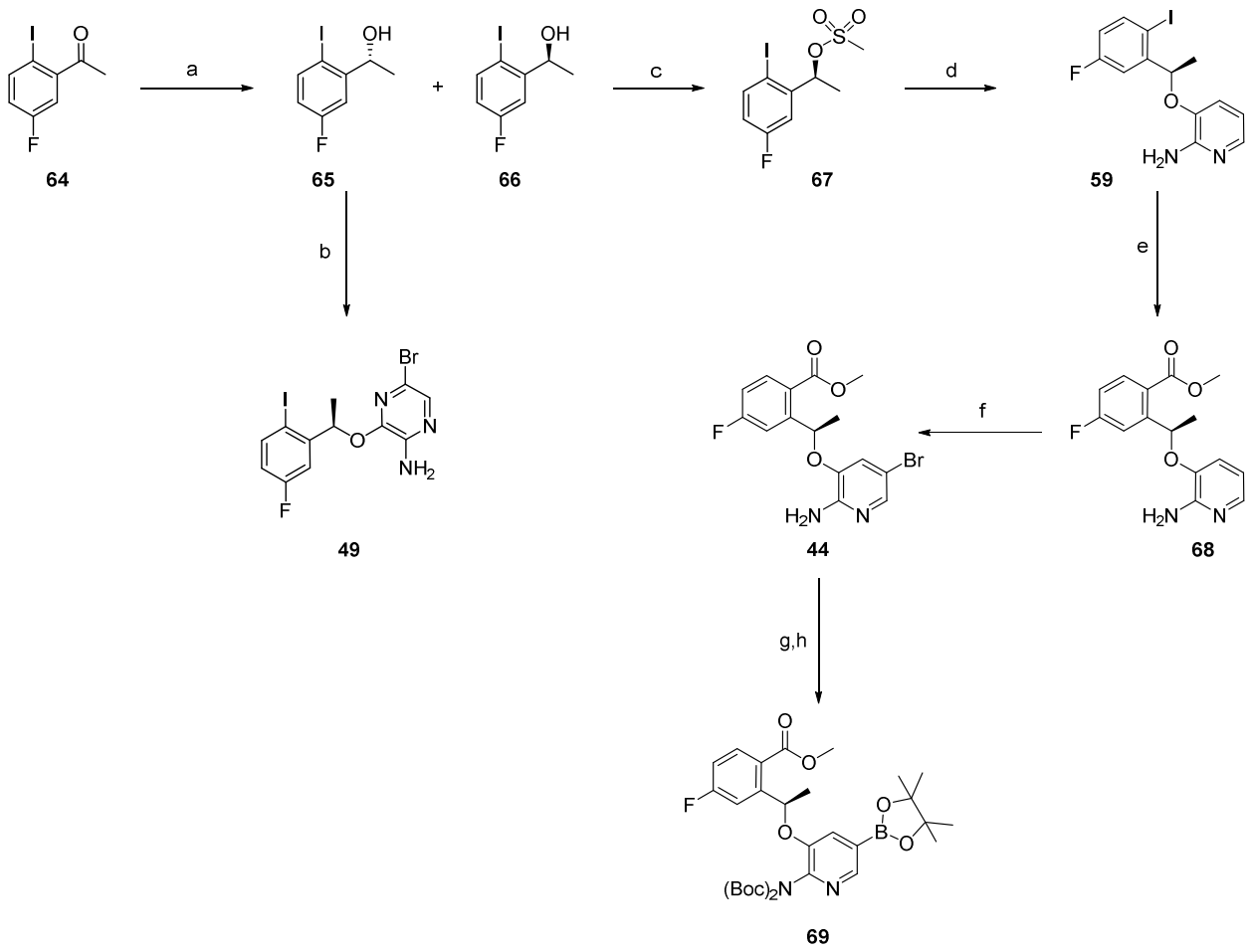
Reagents and conditions (yields for n = 1) : (a) 1.5 eq but-3-yn-1-ol, 1.5 eq Ph_3P, 1.5 eq DIAD, THF, rt, 20 h, 36%.

1-[2-(But-3-yn-1-yloxy)-5-fluorophenyl]ethanone **(30)**. To a ice-cooled solution of 1-(5-fluoro-2-hydroxyphenyl)ethanone (3 g, 19.5 mmol), but-3-yn-1-ol (2.21 mL, 29.2 mmol) and Ph_3P (7.66 g, 29.2 mmol) in THF (97.3 mL) was added in a drop-wise manner DIAD (5.79 mL, 29.2 mmol). Upon addition, the reaction turned yellow. The ice bath was removed, and the reaction allowed to warm to room temperature, and stirred for 14 h. The reaction was concentrated, and purified by chromatography on silica gel eluting with 0 - 25% EtOAc/heptanes to provide **30** (1.43 g, 36% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.42 - 7.37 (m, 1 H), 7.34 (dd, J = 9.1, 3.3 Hz, 1 H), 7.21 (dd, J = 9.1, 4.3 Hz, 1 H), 4.19 (t, J = 6.2 Hz, 2 H), 2.89 (t, J = 2.6 Hz, 1 H), 2.71 (dt, J = 6.2, 2.6 Hz, 2 H), 2.60 (s, 3 H).

1-[2-(Pent-4-yn-1-yloxy)-5-fluorophenyl]ethanone **(31)**. Compound **31** was prepared in a similar manner to **30** with pent-4-yn-1-ol being used in place of but-3-yn-1-ol in the reaction. LC-MS (APCI) *m/z* 221.1 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.46 - 7.28 (m, 2 H), 7.20

(dd, J = 8.9, 4.2 Hz, 1 H), 4.15 (t, J = 6.2 Hz, 2 H), 2.55 (s, 3 H), 2.37 (dt, J = 7.1, 2.6 Hz, 2 H), 2.00 - 1.91 (m, 2 H).

Scheme S8. Synthesis of Pyridine and Pyrazine headpieces, **44, 49, 59,** and **69**



Reagents and conditions: (a) 1.1 eq $NaBH_4$, MeOH, 0 °C, 1 h, 99% then SFC separation; (b) 1 eq 2-amino-3,5-dibromopyrazine, 1 eq NaH (60 wt%), THF, reflux, 18 h, 39%; (c) 1.5 eq MsCl, 2 eq TEA, TBME, 0 °C, 3 h; (d) 1.5 eq 2-amino-3-hydroxypyridine, 2.5 eq Cs_2CO_3, 2-MeTHF, acetone, 80 °C, 24 h, 39% over 2 steps; (e) 10 mol% Pd(dppf)Cl_2, 2 eq TEA, MeOH, 100 °C, 6 bar of CO, 16 h, 79%; (f) 1 eq NBS, MeCN, <10 °C, 15 min, 73%; (g) 3 eq $(Boc)_2O$, 3 eq DIPEA, 5 mol% DMAP, CH_2Cl_2, 16 h, 88%; (h) 10 mol% cataCXium A, 5 mol% Pd$(OAc)_2$, 1.1 eq B_2pin_2, 3 eq KOAc, toluene, 16 h, quant.

(1R)-1-(5-Fluoro-2-iodophenyl)ethanol **(65)** *and (1S)-1-(5-fluoro-2-iodophenyl)ethanol* **(66)**. To an ice-cooled solution of 1-(5-fluoro-2-iodophenyl)ethanone[1] (5 g, 18.94 mmol) in MeOH (70 mL) was added sodium borohydride (788 mg, 20.83 mmol). Upon completion of the addition, the reaction was allowed to warm to room temperature and stirred for 1 h. Water (50 mL) and EtOAc (50 mL) were added to the mixture, and the organic phase separated. The aqueous mixture was further extracted with EtOAc (2 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford the racemic alcohol (5.3 g, 99% yield) as a colorless oil, which was used without further purification. A 260 g batch of racemic alcohol was subjected to chiral separation by SFC using an Chiralcel AD-H 5 μm column (4.6 x 250 mm) eluting with 5 - 40 % MeOH (w. 0.05% DEA) @ 100 bar with a flow rate of 2.35 mL/min. (1R)-1-(5-Fluoro-2-iodophenyl)ethanol **65** (124 g) was obtained as a white solid as peak 1 (R_t = 4.32 min) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 5.6, 2.8 Hz, 1 H), 7.32 (dd, *J* = 6.8 Hz, 3.2 Hz, 1 H), 6.76 – 6.71 (m, 1 H), 5.04 - 4.99 (m, 1 H), 2.01 (br s, 1 H), 1.44 (d, *J* = 11.6 Hz, 3 H). (1S)-1-(5-fluoro-2-iodophenyl)ethanol **66** (120 g) was obtained as a white solid as peak 2 (R_t = 5.17 min); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 5.6, 2.8 Hz, 1 H), 7.32 (dd, *J* = 6.8 Hz, 3.2 Hz, 1 H), 6.76 – 6.71 (m, 1 H), 5.04 - 4.99 (m, 1 H), 2.01 (br s, 1 H), 1.44 (d, *J* = 11.6 Hz, 3 H).

(1S)-1-(5-Fluoro-2-iodophenyl)ethanol **(66)**. A solution of (–)-DIP-Cl[2] (57.1 g, 178 mmol) in THF (100 ml) was cooled to -20 ° to -30 °C. A solution of **64** (31.3 g, 119 mmol) in THF (100 ml) was then added drop-wise over 30 min *via* addition funnel. The reaction was warmed to room temperature. After 2 h, the reaction was cooled to -30 °C and another portion of (–)-DIP-Cl (38.0 g, 119 mmol) was added. After 30 min, the reaction was allowed to warm to room temperature and after 1 h, the solvents were removed *in vacuo* and the residue re-dissolved in

TBME (200 mL). A solution of diethanolamine (31 g, 296 mmol) in EtOH/THF (15 mL/30 mL) was added *via* addition funnel to the reaction mixture cooled in an ice bath. A white precipitate formed. The suspension was heated at reflux for 2 h and then cooled to room temperature, filtered and the mother liquids concentrated *in vacuo*. The residue was suspended in heptanes/EtOAc (7 : 3, 200 mL) and again filtered. This procedure was repeated until no more solids could be observed and the combined liquids were concentrated. The final yellow oil was purified by column chromatography on silica gel (eluent: cyclohexane/EtOAc – 99 : 1 to 96 : 4). The resulting colorless oil was further purified by recrystallization from heptanes, to give alcohol **66** (25 g, 80% yield, 99% purity and 96% ee) as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, *J* = 5.6, 2.8 Hz, 1 H), 7.32 (dd, *J* = 6.8 Hz, 3.2 Hz, 1 H), 6.76 – 6.71 (m, 1 H), 5.04 - 4.99 (m, 1 H), 2.01 (br s, 1 H), 1.44 (d, *J* = 11.6 Hz, 3 H). Chiral GC (column CP-Chirasil-DexnCB): 96% ee; minor peak (Rt = 17.7 min) and major peak (Rt = 19.4 min). Absolute stereochemistry was confirmed by VCD analysis.

(1S)-1-(5-Fluoro-2-iodophenyl)ethyl methanesulfonate **(67)**. A solution of **66** (22 g, 83 mmol) in TBME (350 mL) was cooled in an ice bath and TEA (23 mL, 166 mmol) followed by MsCl (9.6 mL, 124 mmol) were added sequentially in a drop-wise manner. The reaction was then warmed to room temperature and stirred for 3 h. The reaction mixture was filtered and the solids washed with EtOAc. The mother liquids were concentrated *in vacuo* to give **67** (35 g, 80% yield) as a pale yellow oil. This material was taken into the following step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, 1 H), 7.24 (dd, 1 H), 6.82 (ddd, 1 H), 2.92 (s, 3 H), 1.64 (d, 3 H).

3-[(1R)-1-(5-Fluoro-2-iodophenyl)ethoxy]pyridin-2-amine **(59)**. A suspension of Cs_2CO_3 (65 g, 201 mmol) and 2-amino-3-hydroxypyridine (13.3 g, 121 mmol) in 2-MeTHF (600 mL) and

acetone (300 mL) was stirred at room temperature for 30 min then heated at 40 °C before drop-wise addition of a solution of **67** (34.4 g, 80 mmol) in 2-MeTHF (300 mL) *via* addition funnel. The resulting mixture was left stirring at 75 - 80 °C for 24 h. The reaction was then filtered through Celite washing with TBME, the solvents removed *in vacuo* and the residue purified by column chromatography over silica gel eluting with cyclohexane/EtOAc (9 : 1 to 1 : 1) to give **59** (14.3 g, 39 % yield, 90% ee) as a white solid. The solids were then recrystallized from heptane/EtOAc to give compound **59** (10.8 g, 37% yield, 95% ee). LC-MS (ESI) *m/z* 359 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, 1 H), 7.38 (dd, 1 H), 7.10 (dd, 1 H), 6.75 (ddd, 1 H), 6.51 - 6.44 (m, 2 H), 5.39 - 5.34 (m, 1 H), 4.73 (br s, 2 H), 1.61 (d, 3 H). HPLC (Chiralpak IC 4.6 x 250 mm): 95% ee; (Rt (minor) = 10.4 min; Rt (major) = 14.7 min); eluent : 20% IPA in heptanes with 0.2% DEA, 0.7 mL/min.

Methyl 2-{(1R)-1-[(2-aminopyridin-3-yl)oxy]ethyl}-4-fluorobenzoate **(68)**. Compound **59** (20 g, 57 mmol) was dissolved in MeOH (300 mL), and sequentially treated with TEA (15.4 mL, 113 mmol) and $PdCl_2$(dppf) (4.1 g, 5.7 mmol). This mixture was heated at 100 °C for 16 h under 7 bar CO pressure. LC-MS indicated consumption of starting material. The reaction mixture was filtered through a pad of Celite, and the filtrate evaporated to a brown oil. The crude product was purified by flash chromatography over silica gel, which was eluted with 50% to 75% EtOAc in cyclohexane, affording pure **68** (13.0 g, 79% yield) as a brick-red solid. LC-MS (ESI), *m/z* 291$[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, 1 H), 7.60 (dd, 1 H), 7.28 (dd, 1 H), 7.00 (ddd, 1 H), 6.61 (dd, 1 H), 6.42 (dd, 1 H), 6.32 (q, 1 H), 4.75 (br s, 2 H), 3.94 (s, 3 H), 1.65 (d, 3 H).

(R)-Methyl 2-(1-((2-amino-5-bromopyridin-3-yl)oxy)ethyl)-4-fluorobenzoate **(44)**. Compound **68** (13.0 g, 45 mmol) was dissolved in MeCN (195 mL), and cooled to <10 °C in an ice water

bath. NBS (7.9 g, 45 mmol) was added drop-wise to the cooled reaction mixture as a solution in MeCN (195 mL), monitoring the internal temperature to ensure it did not rise above 10 °C. After addition was complete, the mixture was stirred for 15 min. TLC (1 : 1 cyclohexane/EtOAc) showed consumption of starting material. The reaction mixture was evaporated, and the residue re-dissolved in EtOAc (400 mL), and washed with 2 M aqueous NaOH (2 x 300 mL), and 10% aqueous sodium thiosulfate solution (300 mL). The organic extracts were dried over $MgSO_4$, and evaporated to a red oil (17.6 g). The crude product was purified over silica gel, which was eluted with 10% to 50% EtOAc in cyclohexane, which gave **44** (12.0 g, 73% yield). LC-MS (ESI), *m/z* 369/371 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (dd, 1 H), 7.66 (d, 1 H), 7.25 (dd, 1 H), 7.03 (ddd, 1 H), 6.75 (d, 1 H), 6.33 (q, 1 H), 4.81 – 4.74 (br s, 2 H), 3.96 (s, 3 H), 1.65 (d, 3 H). A Chiralpak AD-H 5 μm column (4.6 x 100 mm) was eluted with 10% MeOH (0.1% DEA) in CO_2 at 120 bar. A flow rate of 5.0 mL/min gave the minor isomer (Rt = 0.6 min) and the major isomer (Rt = 0.8 min) (99% ee). Optical rotation: $[\alpha]^{20}_D$ = -92.4 ° (c = 1.5, MeOH).

In several preparations, the racemic compound **rac-(44)** was utilized, and the final enantiomers separated. **Rac-(44)** was prepared by the same sequence though starting from the racemic alcohol prepared by the borohydride reduction described above.

Methyl 2-[(1R)-1-({2-[bis(tert-butoxycarbonyl)amino]-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-3-yl}oxy)ethyl]-4-fluorobenzoate **(69)**. To a solution of **44** (5 g, 13.5 mmol), DIPEA (7.08 mL, 40.6 mmol), DMAP (331 mg, 2.71 mmol) in CH_2Cl_2 (55 mL) was added $(Boc)_2O$ (8.87 g, 40.6 mmol), and the reaction allowed to stir at room temperature for 16 h. The reaction was concentrated, and the residue purified by column chromatography on silica gel eluting with 0 - 25% EtOAc/heptanes to afford methyl 2-[(1*R*)-1-({2-[bis(*tert*-

butoxycarbonyl)amino]-5-bromopyridin-3-yl}oxy)ethyl]-4-fluorobenzoate (6.8 g, 88% yield) as a clear, viscous gum, which was used without further purification.

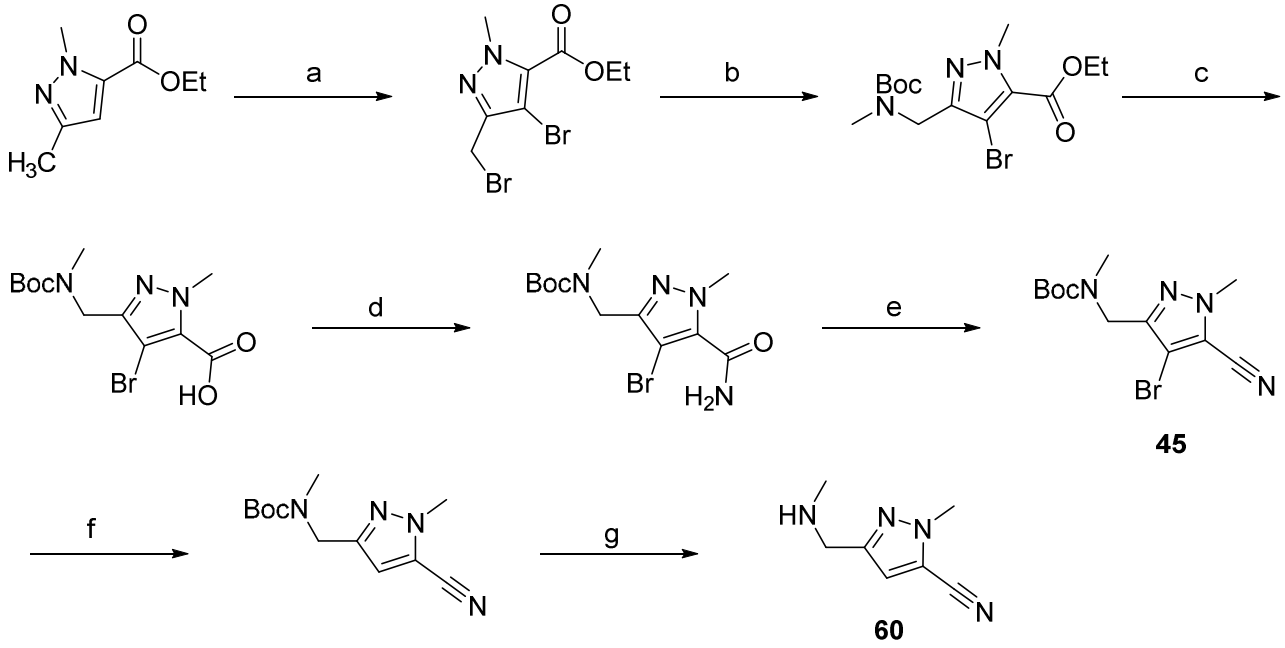
Methyl 2-[(1*R*)-1-({2-[bis(*tert*-butoxycarbonyl)amino]-5-bromopyridin-3-yl}oxy)ethyl]-4-fluorobenzoate (6.8 g, 12 mmol)), B_2pin_2 (3.34 g, 13.1 mmol), KOAc (3.52 g, 35.8 mmol) were suspended in toluene (80 mL), and nitrogen bubbled through the mixture for 10 min. To this was added cataCXium A (441 mg, 1.19 mmol) and $Pd(OAc)_2$ (134 mg, 0.6 mmol), and the reaction was heated at 100 °C for 16 h. The reaction was diluted with EtOAc (250 mL), washed with water (2 x 100 mL), and brine (100 mL), and dried over $MgSO_4$. The organic solution was filtered, concentrated *in vacuo*, and the residue purified by column chromatography over silica gel eluting with 0 – 100 % EtOAc/heptanes to afford **69** (7.4 g, 100% yield) as a viscous gum, which was used without further purification (~ 85% pure, contains dimer and aliphatic impurities).

5-Bromo-3-[(1R)-1-(5-fluoro-2-iodophenyl)ethoxy]pyrazin-2-amine **(49)**. To a solution of **65** (17.8 g, 67.9 mmol) in THF (350 mL) was added NaH (2.7 g, 60% in mineral oil, 67.9 mmol) at 0 °C under nitrogen. The mixture was stirred for a further 30 min. A solution of 2-amino-3,5-dibromopyrazine (17.1 g, 67.9 mmol) in anhydrous THF (150 mL) was added to the above mixture at 0 °C, and the mixture was refluxed for 18 h. LC-MS indicated that 90% of the starting alcohol had been consumed. The volatiles were removed under reduced pressure, and the residue was diluted with a mixture of H_2O (100 mL) and EtOAc (100 mL). The mixture was filtered, the organic layer removed, and the aqueous layer further extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and concentrated to give a residue, which was purified by silica gel column eluting with petroleum ether:EtOAc (30 : 1 to 20 : 1) to give **49** (11.5 g, 39% yield) as a yellow solid. LC-MS *m/z* 438/440 $[M+H]^+$;

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 - 7.69 (m, 1 H), 7.55 (s, 1 H), 7.04 (d, *J* = 6.8 Hz, 1 H), 6.71 - 6.65 (m, 1 H), 6.10 (q, *J* = 6.4 Hz, 1 H), 4.81 (br s, 2 H), 1.55 (d, *J* = 6.4 Hz, 3 H).

In several preparations, the racemic compound **rac-(49)** was utilized, and the final enantiomers separated. **Rac-(49)** was prepared by the same sequence though starting from the racemic alcohol prepared by the borohydride reduction described above.

Scheme S9. Synthesis of **45** and **60**



Reagents and conditions: (a) 2.1 eq NBS, 15 mol% dibenzoyl peroxide, 1,2-dichloroethane, reflux, 16 h, 58%; (b) 1.5 eq NaH (60 % in mineral oil), 1.5 eq *tert*-butyl methylcarbamate, DMF, 0 °C - rt, 13 h, 33%; (c) 2 eq NaOH, EtOH/H_2O (1 : 1), reflux, 2 h, 85%; (d) 2 eq NH_4Cl, 1.5 eq EDCI, 1 eq HOBt, 2 eq TEA, DMF, rt, 18 h, 94%; (e) 2 eq TFAA, 3 eq TEA, CH_2Cl_2, -5 °C - 0 °C, 90 min, 71%; (f) 5 mol% $Pd(OAc)_2$, 20 mol% PPh_3, 2 eq K_2CO_3, *n*-BuOH, reflux, 4 h, 88%; (g) 5 eq HCl in dioxane (4 M), CH_2Cl_2, 0 °C - rt, 4 h, 96%.

tert-Butyl ((4-bromo-5-cyano-1-methyl-1H-pyrazol-3-yl)methyl)-(methyl)carbamate **(45)**. Ethyl 1,3-dimethyl-1*H*-pyrazole-5-carboxylate (158 g, 0.94 mol) was dissolved in 1,2-dichloroethane (2500 mL). NBS (351.4 g, 1.97 mol) was then added, followed by the radical initiator, dibenzoylperoxide (29.6 g, 122 mmol). The reaction mixture was stirred at reflux overnight. TLC (petroleum ether/EtOAc 10 : 1) showed the reaction was completed. The solvent was removed under vacuum to give a wet yellow solid. Water was added (200 mL) and the aqueous phase was extracted with TBME (3 x 600 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to give a yellow oil. This material was purified by column chromatography over silica gel eluting with petroleum ether/EtOAc (100 : 1 to 30 : 1) to yield ethyl 4-bromo-3-(bromomethyl)-1-methyl-1*H*-pyrazole-5-carboxylate (180 g, 58% yield) as a pale yellow solid. LC-MS (ESI) *m/z* 324/326/328 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.58 (s, 2 H), 4.38 - 4.31 (m, 2 H), 4.12 (s, 3 H), 1.36 - 1.31 (m, 3 H).

To a solution of NaH (10 g, 60% in mineral oil, 251.5 mmol) in THF (750 mL) was added drop-wise a solution of *tert*-butyl methylcarbamate (32.9 g, 251.5 mmol) in DMF (150 mL) at 0 °C. After addition, the reaction mixture was stirred at room temperature for 1 h. Ethyl 4-bromo-3-(bromomethyl)-1-methyl-1*H*-pyrazole-5-carboxylate (55 g, 167.68 mmol) in THF (200 mL) was then added drop-wise to the above mixture at 0 °C. After completion of the addition, the resulting mixture was stirred at room temperature for 12 h. TLC (petroleum ether/EtOAc 10 : 1) showed the reaction was completed. To the reaction mixture was added brine (20 mL) at 0 °C. The mixture was then extracted with EtOAc (3 x 300 mL). The combined extracts were washed with brine (2 x 200 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was purified *via* column chromatography over silica gel, petroleum ether/EtOAc (100 : 1 to 10 : 1) to give ethyl 4-bromo-3-{[(*tert*-butoxycarbonyl)(methyl)amino]methyl}-1-methyl-1*H*-

pyrazole-5-carboxylate (23 g, 33% yield) as a yellow oil, which was used without further purification.

A mixture of ethyl 4-bromo-3-{[(*tert*-butoxycarbonyl)(methyl)amino]methyl}-1-methyl-1*H*-pyrazole-5-carboxylate (29.5 g, 78 mmol) and NaOH (6.2 g, 156 mmol) in EtOH (400 mL) and H_2O (400 mL) was heated at reflux for 2 h. TLC (petroleum ether/EtOAc 10:1) showed the reaction mixture was completed. The solvent was removed under reduced pressure to give a white solid. The solid was suspended in EtOAc (100 mL) and washed with 5% HCl solution (200 mL). The organic phase was separated and washed with brine (250 mL), dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to give 4-bromo-3-{[(*tert*-butoxycarbonyl)(methyl)amino]methyl}-1-methyl-1*H*-pyrazole-5-carboxylic acid (23 g, 85% yield) as a yellow gum. LC-MS (ESI) *m/z* 348/350 $[M+H]^+$ and 248/250 $[M\text{-}Boc]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ 4.27 (s, 2 H), 3.92 (s, 3 H), 2.70 (s, 3 H), 1.40 (s, 9 H).

4-Bromo-3-{[(*tert*-butoxycarbonyl)(methyl)amino]methyl}-1-methyl-1*H*-pyrazole-5-carboxylic acid (39 g, 112.06 mmol) was dissolved in DMF (600 mL). HOBt (15 g, 112.06 mmol) was added, followed by ammonium chloride (11.87 g, 224.1 mmol). EDCI (32.4 g, 168.1 mmol) was then added, followed by TEA (31.2 mL, 221 mmol). The reaction mixture was stirred at room temperature. After 18 h, the solvent was removed under reduced pressure to give a yellow oil. The residue was dissolved in EtOAc (300 mL). The organic phase was washed with aq. HCl (1 N, 100 mL), $NaHCO_3$ (sat. solution, 150 mL) and then brine (100 mL). The combined organic layers were dried over Na_2SO_4 and the solvent removed *in vacuo* to give *tert*-butyl [(4-bromo-5-carbamoyl-1-methyl-1*H*-pyrazol-3-yl)methyl]methylcarbamate (37 g, 94% yield) as a dark yellow oil. This material was used directly in the next step without further purification. LC-

MS (ESI), *m/z* 347/349 $[M+H]^+$ and 247/249 $[M\text{-}Boc]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 6.74 (br s, 1 H), 5.95 (br s, 1 H), 4.49 (br s, 2 H), 4.16 (s, 3 H), 2.81 (br s, 3 H), 1.47 (s, 9 H).

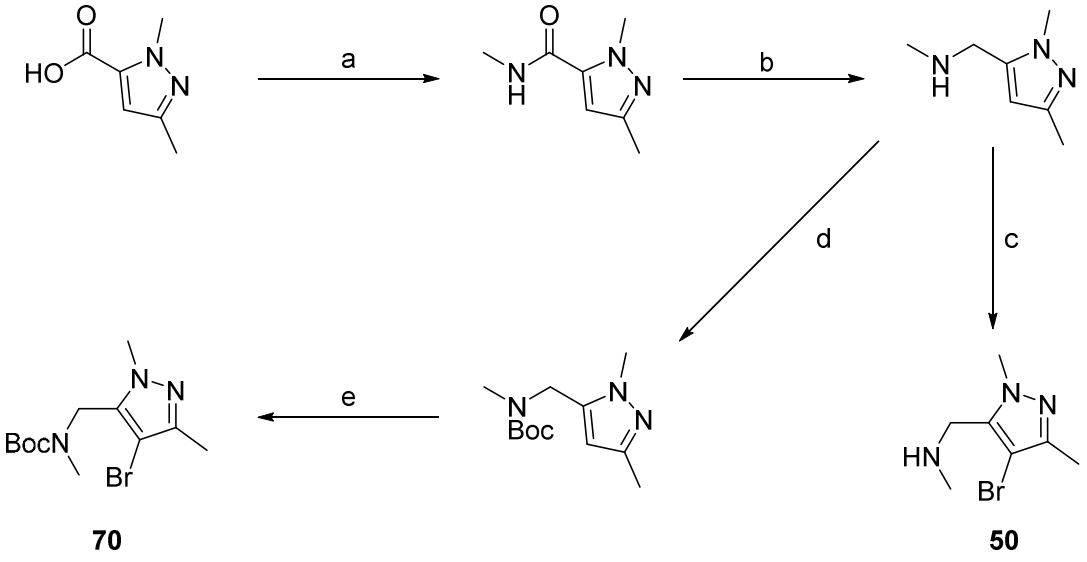
tert-Butyl [(4-bromo-5-carbamoyl-1-methyl-1*H*-pyrazol-3-yl)methyl]methylcarbamate (37 g, 106.3 mmol) was dissolved in CH_2Cl_2 (1 L). TEA (45 mL, 323 mmol) was then added, and the reaction mixture cooled down to -5 °C. TFAA (30 mL, 215.5 mmol) in CH_2Cl_2 (200 mL) was added drop-wise over 30 min. After addition, the reaction mixture was stirred at 0 °C for 1 h. After this time, the solvents were removed under reduced pressure to give a dark yellow oil. This residue was diluted in CH_2Cl_2 (500 mL), washed with 5% citric acid (200 mL), sat. $NaHCO_3$ (300 mL) and brine (200 mL), dried over $MgSO_4$, filtered and the solvents removed *in vacuo* to give a dark yellow oil. The crude product was purified by column chromatography on silica gel eluting with petroleum ether/EtOAc (50 : 1 to 10 : 1) to give **45** (24.8 g, 71% yield) as a yellow solid. LC-MS (ESI), *m/z* 329/331 $[M+H]^+$ and 229/231 $[M\text{-}Boc]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 4.46 (br s, 2 H), 4.01 (s, 3 H), 2.83 (br s, 3 H), 1.47 (s, 9 H).

1-Methyl-3-[(methylamino)methyl]-1H-pyrazole-5-carbonitrile **(60)**. A suspension of **45** (118 g, 358 mmol) in *n*-butanol (1.20 L) was degassed and placed under nitrogen. K_2CO_3 (99.0 g, 716 mmol), PPh_3 (18.7 g, 71.3 mmol) and $Pd(OAc)_2$ (4.00 g, 17.8 mmol) were then added and the mixture was heated for 4 h, reaching 80 °C after 1 h, and achieving reflux after 3 h. The mixture was allowed to cool to room temperature then diluted with EtOAc (1 L) and washed with water (1 L) and brine (1 L). The organic layer was dried ($MgSO_4$) and filtered. On standing overnight a small amount of precipitate had formed, and so the mixture was filtered and then concentrated *in vacuo* to give 117.4 g of a brown oil. Purification by column chromatography over silica gel (10 - 30% EtOAc/heptanes) gave Boc-protected intermediate *tert*-butyl [(5-cyano-1-methyl-1*H*-pyrazol-3-yl)methyl]methylcarbamate (74.8 g, 84% yield) as a yellow oil. Impure fractions were

combined to give 5.98 g of yellow oil that were purified further by column chromatography over silica gel eluting with 10% -100% EtOAc in heptanes. This gave a further 3.92 g of *tert*-butyl [(5-cyano-1-methyl-1*H*-pyrazol-3-yl)methyl]methyl carbamate as a yellow oil (4% yield). LC-MS (ESI), *m/z* 251 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (s, 1H), 4.38 (s, 2H), 4.01 (s, 3H), 2.84 (s, 3H), 1.47 (s, 9H).

A solution of *tert*-butyl [(5-cyano-1-methyl-1*H*-pyrazol-3-yl)methyl]methylcarbamate (78.7 g, 314 mmol) in CH_2Cl_2 (400 mL) was cooled to 0 °C under nitrogen and a 4 M solution of HCl in dioxane (400 mL, 1.6 mol) was added over 5 min. After stirring at 0 °C for 30 min the mixture was allowed to warm to room temperature and stirred for a further 3 h. The reaction mixture was concentrated to approximately 150 mL, cooled and filtered, washing with 100 mL of TBME. The solids were air dried to give **60** (56.12 g, 96% yield) as a colorless crystalline solid. LC-MS (ESI), *m/z* 151$[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.50 (s, 2 H), 7.31 (s, 1 H), 4.13 (s, 2 H), 4.03 (s, 3 H), 2.52 (s, 3 H).

Scheme S10. Synthesis of **50** and **70**



70 **50**

Reagents and conditions: (a) 1.2 eq CDI, THF, 50 °C, 30 min, then 2.9 eq $MeNH_2$ (2 M in THF), rt, 1 h, 91%; (b) 8 eq BH_3.DMS, THF, 50 °C, 3 h, 83%; (c) 1.05 eq NBS, AcOH/CH_2Cl_2 (4 : 3), 0 °C – rt, 2 h, quant. (~ 90% pure); (d) 1.5 eq $(Boc)_2O$, CH_2Cl_2, rt, 14 h, 78%; (e) 1.05 eq NBS, 1.15 eq $NaHCO_3$, MeCN, -5 °C – rt, 4 h, 95%.

1-(4-Bromo-1,3-dimethyl-1H-pyrazol-5-yl)-N-methylmethanamine **(50)**. CDI (2.8 g, 17 mmol) was added to a suspension of 1,3-dimethyl-1*H*-pyrazole-5-carboxylic acid (2.0 g, 14 mmol) in THF (25 mL) at 20 °C. The mixture was then warmed to 50 °C with stirring for 30 min (gas evolution was observed). The mixture was then cooled to -10 °C and methylamine (2 M in THF, 20 mL, 40.0 mmol) was added in one portion. The ice bath was removed and the reaction was stirred at room temperature for 1 h. The mixture was then concentrated and purified by column chromatography over silica gel, which was eluted with 100% EtOAc, giving *N*-1,3-trimethyl-1*H*-pyrazole-5-carboxamide (2.0 g, 91% yield) as a clear oil. TLC: R_f = 0.60 (100% EtOAc). LC-MS (ESI), *m/z* 154 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (s, 1 H), 6.00 (br s, 1 H), 4.09 (s, 3 H), 2.93 (d, 3 H), 2.23 (s, 3 H).

BH_3·DMS (8.0 g, 105 mmol) was added slowly to a solution of *N*-1,3-trimethyl-1*H*-pyrazole-5-carboxamide (2.0 g, 13.0 mmol) in THF at -5 °C. After complete addition, the mixture was stirred at 50 °C for 3 h, before being cooled and allowed to stir at room temperature overnight. The reaction was then cooled to 0 °C and 6 M HCl (30 mL) was added slowly (frothing occurred). After complete addition, the mixture was stirred at 70 °C for 30 min, before cooling to 0 °C and being basified with NaOH (30% aq solution) to pH 13 (pH paper). The mixture was concentrated under reduced pressure to remove THF and then extracted into CH_2Cl_2 (5 x 40 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to give 1-(1,3-dimethyl-1*H*-pyrazol-5-yl)-*N*-methylmethanamine (1.5 g, 83% yield). TLC: R_f = 0.20 (98% EtOAc and

2% 7 M NH_3 in MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (s, 1 H), 3.78 (s, 3 H), 3.68 (s, 2 H), 2.40 (s, 3 H), 2.20 (s, 3 H).

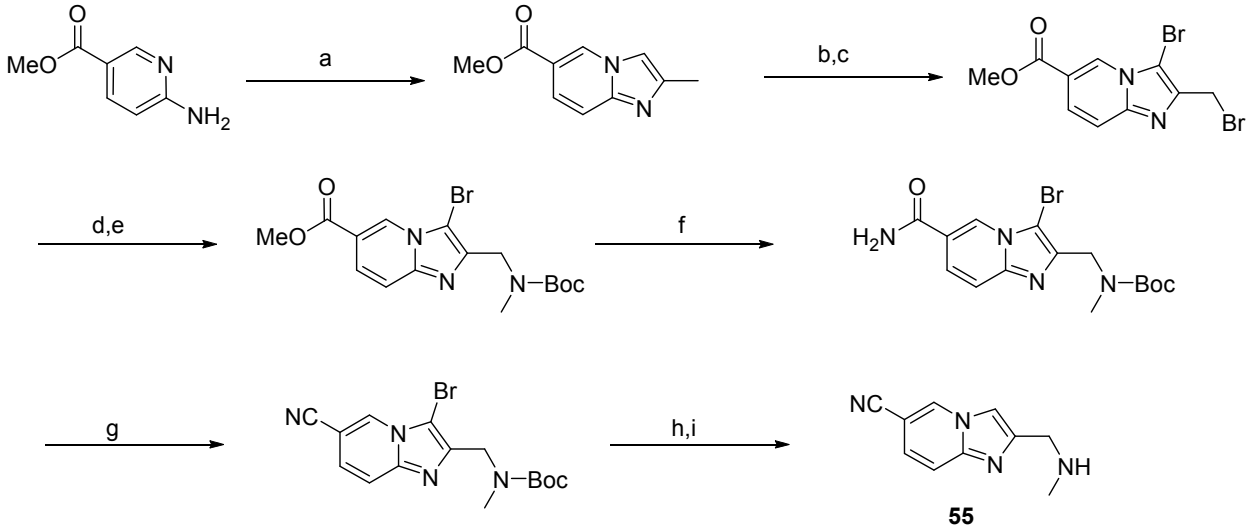
To an ice-cooled solution of 1-(1,3-dimethyl-1*H*-pyrazol-5-yl)-*N*-methylmethanamine (4 g, 28.74 mmol) in acetic acid (80 mL) and CH_2Cl_2 (60 mL) was added in a portion-wise manner NBS (5.37 g, 30.2 mmol). On completion of the addition, the ice-bath was removed, and the reaction allowed to stir at room temperature for 2 h. The reaction was added in a drop-wise manner to an ice-cooled solution of 50% aqueous NaOH (50 mL), and stirred for 2 h. The mixture was diluted with CH_2Cl_2 (100 mL), and the organic extract separated. The aqueous mixture was further extracted with EtOAc (2 x 200 mL), and the combined organic extracts were dried over K_2CO_3, filtered and concentrated to afford **50** (7 g) as a white solid, which was used without further purification (*ca*. 90% pure – contaminated with succinimide residues). LC-MS (ESI) *m/z* 218.0 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.68 (s, 3 H), 3.55 (s, 2 H), 2.13 (s, 3 H), 2.00 (s, 3 H).

tert-Butyl [(4-bromo-1,3-dimethyl-1H-pyrazol-5-yl)methyl]methylcarbamate **(70)**. To a solution of 1-(1,3-dimethyl-1*H*-pyrazol-5-yl)-*N*-methylmethanamine (1.5 g, 10.7 mmol) in CH_2Cl_2 (30 mL) was added $(Boc)_2O$ (3.27 g, 15 mmol). The mixture was stirred overnight, concentrated under reduced pressure and the residue purified by flash chromatography over silica gel, eluting with 30 - 50% EtOAc in cyclohexane, to give *tert*-butyl [(1,3-dimethyl-1*H*-pyrazol-5-yl)methyl]methylcarbamate (2.0 g, 78% yield) as a colorless oil. TLC: R_f = 0.50 (1 : 1 EtOAc/cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (s, 1 H), 4.61 (s, 2 H), 3.78 (s, 3 H), 2.78 (s, 3 H), 2.20 (s, 3 H), 1.48 (s, 9 H).

tert-Butyl [(1,3-dimethyl-1*H*-pyrazol-5-yl)methyl]methylcarbamate (2.1 g, 8.8 mmol) was dissolved in MeCN (31 mL), $NaHCO_3$ (0.88 g, 10 mmol) was added, and the mixture was cooled

to 0 °C. NBS (1.6 g, 9.2 mmol) was added and the reaction mixture was stirred for 1 h at ~ 5 °C. LC-MS showed consumption of *tert*-butyl [(1,3-dimethyl-1*H*-pyrazol-5-yl)methyl] methylcarbamate. The reaction mixture was warmed to room temperature, filtered and concentrated under vacuum to give a yellow oil. TBME (100 mL) was added and a white solid was observed and filtered. The mother liquors were concentrated and TBME (150 mL) was added again. The white solid formed was filtered and the mother liquors were washed with a diluted aqueous solution of sodium thiosulfate (50 mL), water (75 mL) then brine (75 mL). The solution was dried over $MgSO_4$, filtered and concentrated under vacuum to give *tert*-butyl [(4-bromo-1,3-dimethyl-1*H*-pyrazol-5-yl)methyl]methylcarbamate **(70)** (2.7 g, 95% yield) as a white solid. LC-MS (ESI), *m/z* 318/320 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 4.50 (s, 2 H), 3.79 (s, 3 H), 2.70 (s, 3 H), 2.20 (s, 3 H), 1.45 (s, 9 H).

Scheme S11. Synthesis of 2-((methylamino)methyl)imidazo[1,2-*a*]pyridine-6-carbonitrile **(55)**



Reagents and conditions: (a) 15 eq 1-chloropropane-2-one, EtOH, reflux, 36 h, 44%; (b) 1.1 eq Br_2, MeCN, rt, 1 h, 66%; (c) 0.9 eq NBS, 10 mol% AIBN, 1,2-dichloroethane, reflux, 2 h, 67%; (d) 25 eq $MeNH_2$ (2 M in THF), THF, 0 °C – rt, 2 h, 67%; (e) 2 eq $(Boc)_2O$, 1 eq DMAP,

CH_2Cl_2, rt, 12 h, 67%; (f) NH_3 (7N in MeOH), 80 °C, 12 h, 83%; (g) 2 eq TFAA, 3 eq TEA, CH_2Cl_2, 0 °C, 2 h, 92%; (h) Pd/C, MeOH, 1 bar H_2, rt, 2 h, 51%; (i) HCl (7 N in EtOAc), CH_2Cl_2, rt, 12 h, 100%.

2-[(Methylamino)methyl]imidazo[1,2-a]pyridine-6-carbonitrile **(55)**. A mixture of methyl 6-aminopyridine-3-carboxylate (50 g, 0.329 mmol) and 1-chloropropane-2-one (448.4 g, 4.87 mol) in EtOH (150 mL) was heated at reflux for 24 h. TLC (petroleum ether/EtOAc 1:1) showed that approximately half of the methyl 6-aminopyridine-3-carboxylate remained. No change was observed after reflux for a further 12 h. The mixture was concentrated *in vacuo* to give the residue, which was dissolved in CH_2Cl_2 (200 mL), washed with aqueous $NaHCO_3$ solution (2 N, 50 mL) and brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product, which was purified by column chromatography over silica gel (petroleum ether/EtOAc 2 : 1 to 1 : 1) to obtain methyl 2-methylimidazo[1,2-*a*]pyridine-6-carboxylate (18 g, 44% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1 H), 7.81 - 7.48 (m, 2 H), 7.41 (s, 1 H), 3.94 (s, 1 H), 2.47 (s, 1 H).

To a solution of methyl 2-methylimidazo[1,2-*a*]pyridine-6-carboxylate (16 g, 0.089 mol) in MeCN (400 mL) was added Br_2 (15.62 g, 0.098 mol) at room temperature. The resulting mixture was stirred at room temperature for 1 h. TLC (EtOAc) showed the reaction was complete. The mixture was diluted with CH_2Cl_2 (500 mL) and then washed with saturated aqueous $NaHCO_3$ solution (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product, which was purified by column chromatography over silica gel (petroleum ether/CH_2Cl_2 2 : 1 to 1 : 1) to give methyl 3-bromo-2-methylimidazo[1,2-*a*]pyridine-6-carboxylate (15 g, 66% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1 H), 8.44 - 8.42 (m, 1 H), 8.37 - 8.34 (m, 1 H), 4.07 (s, 3 H), 2.74 (s, 3 H).

To a mixture of methyl 3-bromo-2-methylimidazo[1,2-*a*]pyridine-6-carboxylate (16 g, 0.063 mol) and NBS (9.95 g, 0.056 mol) in 1,2-dichloroethane (375 mL) was added AIBN (1.025 g, 0.0063 mol) at room temperature under a nitrogen atmosphere. The resulting mixture was heated at reflux for 2 h. TLC (petroleum ether/EtOAc 3 : 1) showed that most of the methyl 3-bromo-2-methylimidazo[1,2-*a*]pyridine-6-carboxylate had been consumed. The mixture was cooled to room temperature and washed with saturated aqueous $NaHCO_3$ solution (50 mL), brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product, which was purified by column chromatography over silica gel (petroleum ether/EtOAc 4 : 1 to 1 : 1) and then re-crystallized from petroleum ether/EtOAc (5 : 1, 30 mL) to afford methyl 3-bromo-2-(bromomethyl)imidazo[1,2-*a*]pyridine-6-carboxylate (14 g, 67% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 - 8.75 (m, 1 H), 7.88 - 7.80 (m, 1 H), 7.62 - 7.55 (m, 1 H), 4.67 (s, 2 H), 4.00 (s, 3 H).

To a solution of methyl 3-bromo-2-(bromomethyl)imidazo[1,2-*a*]pyridine-6-carboxylate (14 g, 41.92 mmol) in THF (200 mL) was added methylamine (520 mL, 1.048 mol, 2 M in THF) over 1 min. The resulting mixture was stirred at 0 °C for 1 h and then at room temperature for 1 h. TLC (petroleum ether/EtOAc 3 : 1) showed most of methyl 3-bromo-2-(bromomethyl)imidazo[1,2-*a*]pyridine-6-carboxylate had been consumed. The mixture was concentrated *in vacuo* at 25 °C for 20 min, and then at 40 °C to give the crude product, which was purified by column chromatography over silica gel, (petroleum ether/EtOAc 1 : 1 to CH_2Cl_2/MeOH 50 : 1) to obtain methyl 3-bromo-2-[(methylamino)methyl]imidazo[1,2-*a*]pyridine-6-carboxylate (8.4 g, 67% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (m, 1 H), 7.84 - 7.81 (m, 1 H), 7.60 - 7.52 (m, 1 H), 4.18 - 4.15 (s, 2 H), 4.00 (s, 3 H), 2.65 (s, 3 H).

To a suspension of methyl 3-bromo-2-[(methylamino)methyl]imidazo[1,2-*a*]pyridine-6-carboxylate (8.4 g, 28.28 mmol) in CH_2Cl_2 (250 mL) was added Boc_2O (12.5 g, 56.56 mmol) and DMAP (3.47 g, 28.28 mmol) at room temperature. The resulting mixture was stirred at room temperature for 12 h. TLC (CH_2Cl_2/MeOH 20 : 1) showed the reaction was complete. The mixture was concentrated *in vacuo* to give the crude product, which was purified by column chromatography over silica gel (petroleum ether/EtOAc 10 : 1 to 5 : 1) to obtain methyl 3-bromo-2-{[(*tert*-butoxycarbonyl)(methyl)amino]methyl}imidazo[1,2-*a*]pyridine-6-carboxylate (7.5 g, 67% yield) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1 H), 7.80 - 7.78 (m, 1 H), 7.59 - 7.56 (m, 1 H), 4.68 (s, 2 H), 4.00 (s, 3 H), 3.95 (s, 3 H), 1.50 (s, 9 H).

The reaction was run in 3 x 1 g batches: A solution of methyl 3-bromo-2-{[(*tert*-butoxycarbonyl)(methyl)amino]methyl}imidazo[1,2-*a*]pyridine-6-carboxylate (1 g, 2.519 mmol) in NH_3/MeOH (7 N, 70 mL) was sealed and heated at 80 °C for 12 h. TLC (petroleum ether/EtOAc 1 : 1) showed the reaction was complete. The reactions were combined, and concentrated *in vacuo* to give the crude product, which was purified by column chromatography over silica gel (petroleum ether/EtOAc 5 : 1 to 1 : 1) to obtain *tert*-butyl [(3-bromo-6-carbamoylimidazo[1,2-*a*]pyridin-2-yl)methyl]methylcarbamate (2.4 g, 83% yield) as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD) δ 8.90 (s, 1 H), 7.90 - 7.82 (m, 1 H), 7.65 - 7.55 (m, 1 H), 4.65 (s, 2 H), 2.95 - 2.84 (m, 3 H), 1.45 (s, 9 H).

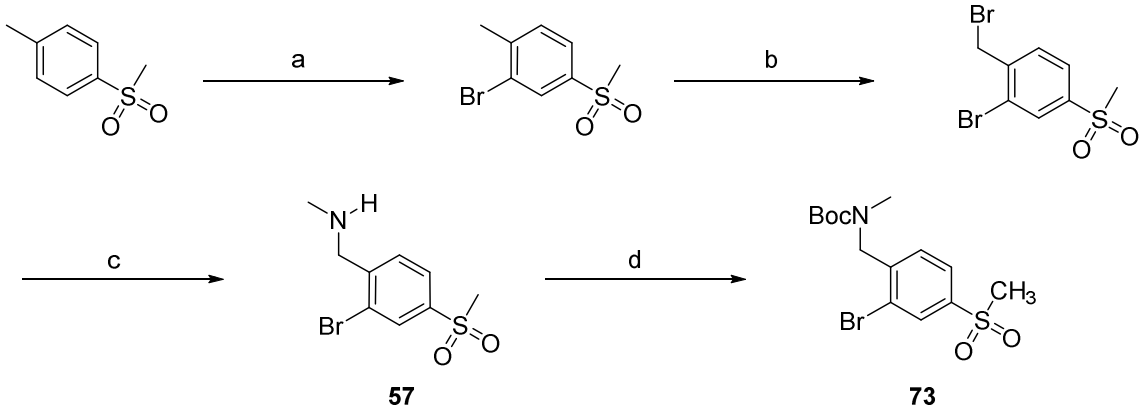
To a solution of *tert*-butyl [(3-bromo-6-carbamoylimidazo[1,2-*a*]pyridin-2-yl)methyl]methylcarbamate (2.4 g, 6.28 mmol) in anhydrous CH_2Cl_2 (50 mL) was added TEA (2.6 mL, 18.85 mmol) and then in a drop-wise manner TFAA (1.73 mL, 12.57 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 2 h. TLC (petroleum ether/EtOAc 1 : 1) showed the reaction was complete. The mixture was concentrated *in vacuo* to give the residue, which was

partitioned between CH_2Cl_2 (100 mL) and brine (20 mL). The organic layer was separated, washed with critic acid (1 N, 10 mL), saturated aqueous $NaHCO_3$ solution (10 mL) and brine (10 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give the crude product, which was purified by column chromatography over silica gel (petroleum ether/EtOAc 5 : 1 to 1 : 1) to obtain *tert*-butyl [(3-bromo-6-cyanoimidazo[1,2-*a*]pyridin-2-yl)methyl]methylcarbamate (2.1 g, 92% yield) as a yellow solid. LC-MS (ESI), *m/z* 308 $[M-55]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1 H), 7.68 - 7.65 (m, 1 H), 7.35 - 7.26 (m, 1 H), 4.66 (s, 2 H), 2.93 (s, 3 H), 1.47 (s, 9 H).

To a solution of *tert*-butyl [(3-bromo-6-cyanoimidazo[1,2-*a*]pyridin-2-yl)methyl]methylcarbamate (0.45 g, 1.23 mmol) in MeOH (80 mL) was added Pd/C (150 mg, 10 % wet Degussa grade) at room temperature. The resulting mixture was purged with H_2 three times and stirred under a pressure of H_2 (15 psi) at room temperature for 2 h. TLC (petroleum ether/EtOAc 3 : 1) showed the reaction was complete. The mixture was filtered and washed with MeOH (30 mL). The filtrate was concentrated *in vacuo* to give the crude product, which was purified by column chromatography over silica gel, (petroleum ether/EtOAc 5 : 1) to give *tert*-butyl [(6-cyanoimidazo[1,2-*a*]pyridin-2-yl)methyl]methylcarbamate (0.18 g, 51% yield) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 8.52 (s, 1 H), 7.64 - 7.50 (m, 2 H), 7.27 (s, 1 H), 4.59 (s, 2 H), 2.98 (s, 3 H), 1.50 (s, 9 H).

To a solution of *tert*-butyl [(6-cyanoimidazo[1,2-*a*]pyridin-2-yl)methyl]methylcarbamate (0.18 g, 0.627 mmol) in CH_2Cl_2 (10 mL) was added HCl (7 N in EtOAc, 20 mL) at room temperature. The resulting mixture was stirred at room temperature for 12 h. The mixture was concentrated *in vacuo* to give 2-[(methylamino)methyl]imidazo[1,2-*a*]pyridine-6-carbonitrile **(55)** (0.15 g, 100% yield) as a white solid. ^1H NMR (400 MHz, CD_3OD) δ 9.48 (s, 1 H), 8.48 (s, 1 H), 8.15 - 8.05 (m, 2 H), 4.58 (s, 2 H), 2.85 (s, 3 H).

Scheme S12. Synthesis of **57** and **73**



Reagents and conditions: (a) 1.2 eq NBS, c. H_2SO_4, rt, 16 h, 100%; (b) 1 eq NBS, 10 mol% dibenzoyl peroxide, 1,2-dichloroethane, 85 °C, 2 h, 33%; (c) $MeNH_2$ (33 % in EtOH), rt, 16 h, 100%; (d) 1.25 eq $(Boc)_2O$, CH_2Cl_2, 0 °C – rt, 18 h, 48%.

1-[2-Bromo-4-(methylsulfonyl)phenyl]-N-methylmethanamine **(57)**. To a stirred mixture of NBS (12.0 g, 68 mmol), and methyl 4-methylphenyl sulfone (10.0 g, 58 mmol) was added concentrated sulfuric acid (50 mL). The solution initially turned green, after which a pale yellow color persisted. The solution was stirred for 16 h at room temperature. The mixture was carefully poured onto ice (400 mL), and then extracted with EtOAc (500 mL). The organic layer was washed with 2 M aqueous NaOH (2 x 300 mL), then dried over $MgSO_4$, and evaporated to give 2-bromo-1-methyl-4-(methylsulfonyl)benzene (14.7 g, 100% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, 1 H), 7.77 (dd, 1 H), 7.43 (d, 1 H), 3.05 (s, 3 H), 2.48 (s, 3 H).

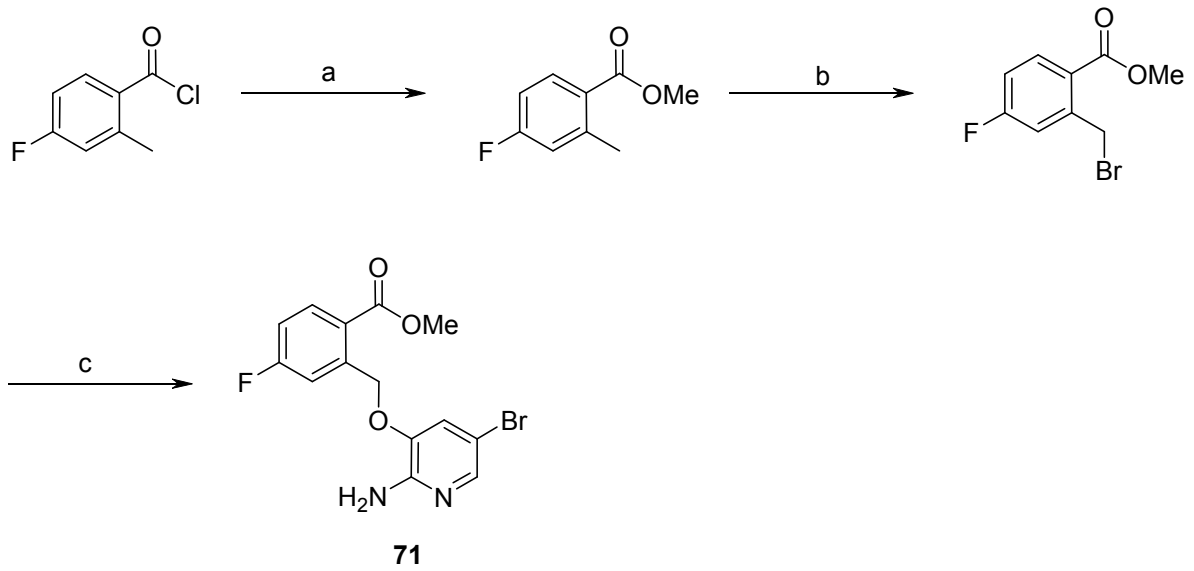
2-Bromo-4-methyl-1-(methylsulfonyl)benzene (10.0 g, 40 mmol) was dissolved in 1,2-dichloroethane (250 mL), followed by addition of NBS (7.1 g, 40 mmol) and dibenzoyl peroxide (970 mg, 4.0 mmol), in small portions. After stirring at 85 °C for 2 h, TLC (4 : 1 cyclohexane/EtOAc) indicated near-consumption of the starting material, and the emergence of a minor spot for di-brominated material. The mixture was allowed to cool, diluted to 500 mL with CH_2Cl_2, and washed with water (2 x 250 mL). The organic layer was dried over $MgSO_4$ and

evaporated to a yellow oil. The viscous oil was cooled in an ice bath to give a solid. Trituration of the solid with Et_2O gave 2-bromo-1-(bromomethyl)-4-(methylsulfonyl)benzene (4.4 g, 33% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, 1 H), 7.87 (dd, 1 H), 7.66 (d, 1 H), 4.60 (s, 2 H), 3.05 (s, 3 H).

2-Bromo-4-(bromomethyl)-1-(methylsulfonyl)benzene (4.3 g, 13 mmol) was dissolved in methylamine solution (33% solution in EtOH, 100 mL), and stirred at room temperature for 16 h. TLC (EtOAc) and LC-MS indicated consumption of starting material, and the major peak for the product. The mixture was evaporated to give 1-[2-bromo-4-(methylsulfonyl)phenyl]-*N*-methylmethanamine **(57)** (3.7 g, 100% yield) as a white solid. LC-MS (ESI), *m/z* 278/280 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 8.16 (d, 1 H), 7.94 (dd, 1 H), 7.71 (d, 1 H), 3.97 (s, 2 H), 3.15 (s, 3 H), 2.49 (s, 3 H).

tert-Butyl [2-bromo-4-(methylsulfonyl)benzyl]methylcarbamate **(73)**. 1-[2-Bromo-4-(methylsulfonyl)phenyl]-*N*-methylmethanamine **(57)** (3.7 g, 13 mmol) was dissolved in CH_2Cl_2 (40 mL), and the mixture cooled to 0 °C. A solution of di(*tert*-butyl) dicarbonate (3.5 g, 16 mmol) in CH_2Cl_2 (35 mL) was added in a drop-wise manner. The ice bath was removed and the mixture stirred for 18 h at room temperature. LC-MS and TLC (1 : 1 cyclohexane/EtOAc) showed consumption of compound **57**, so the reaction was diluted to 150 mL with CH_2Cl_2, and washed with water (2 x 100 mL). The organic extracts were dried over $MgSO_4$, and evaporated to a pale yellow oil. The crude product was purified over silica gel which was eluted with a gradient of 10% to 20% EtOAc in cyclohexane to give *tert*-butyl [2-bromo-4-(methylsulfonyl)benzyl]methylcarbamate **(73)** (2.4 g, 48% yield). LC-MS (ESI), *m/z* 378/380 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 8.15 (d, 1 H), 7.95 (d, 1 H), 7.40 (d, 1 H), 4.58 (s, 2 H), 3.15 (s, 3 H), 2.95 (s, 3 H), 1.52 - 1.36 (br, 9 H, *t*-Bu rotamers).

Scheme S13. Synthesis of Methyl 2-{[(2-amino-5-bromopyridin-3-yl)oxy]methyl}-4-fluorobenzoate **(71)**



71

Reagents and conditions: (a) MeOH/CH_2Cl_2, 0 °C – rt, 2 h, 91%; (b) 1.1 eq NBS, 2 mol% dibenzoyl peroxide, 1,2-dichloroethane, 80 °C, 8 h, 87%; (c) 0.95 eq 2-amino-5-bromopyridin-3-ol, 1.1 eq Cs_2CO_3, MeCN, 50 °C, 5 h, 44%.

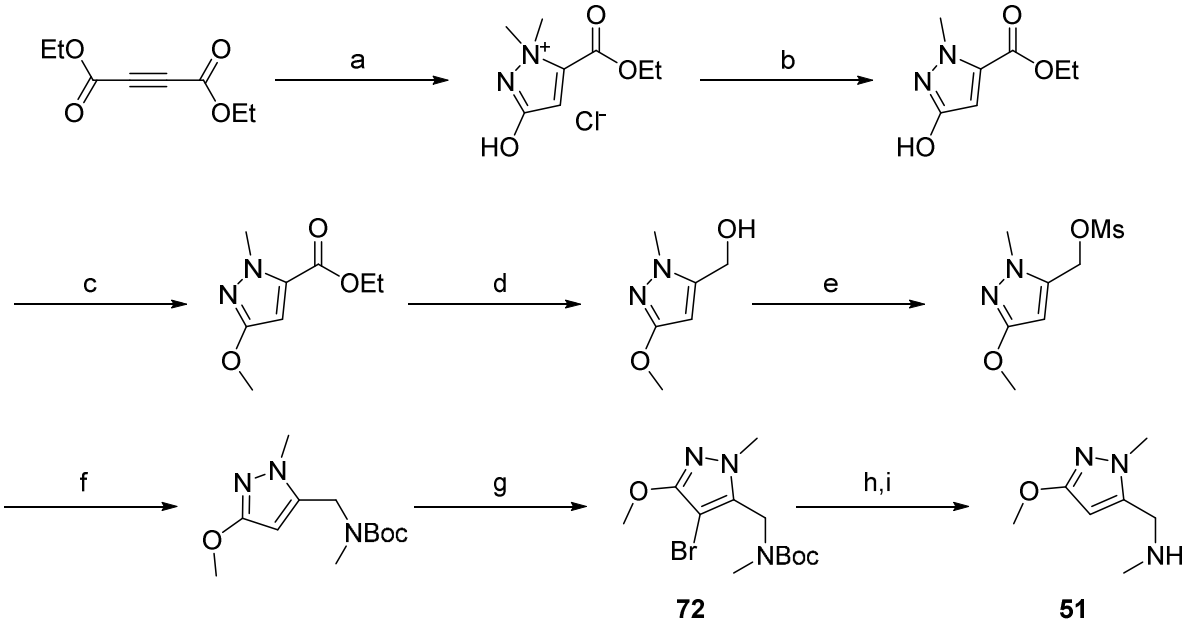
Methyl 2-{[(2-amino-5-bromopyridin-3-yl)oxy]methyl}-4-fluorobenzoate **(71)**. To an ice-cooled solution of 4-fluoro-2-methylbenzoyl chloride (24.3 g, 141 mmol) in CH_2Cl_2 (300 mL) was added MeOH (100 mL) drop-wise over 20 min. The reaction mixture was then allowed to warm to room temperature and stirred for 2 h. The reaction was then concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (200 mL) and then washed with saturated aqueous $NaHCO_3$ (150 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated *in vacuo* to give methyl 4-fluoro-2-methylbenzoate (19.5 g, 91% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.92 (m, 1 H), 6.95 - 6.85 (m, 2 H), 3.90 (s , 3 H), 2.60 (s , 3 H).

To a solution of methyl 4-fluoro-2-methylbenzoate (6.3 g, 41.4 mmol) in 1,2-dichloroethane (100 mL) was added NBS (8.1 g, 46 mmol) followed by a catalytic amount of dibenzoyl peroxide (200 mg, 0.82 mmol). The reaction was then heated at 80 °C for 8 h. The reaction was cooled to room temperature, and the precipitated solid was removed by filtration and washed with TBME (200 mL). The filtrate was concentrated *in vacuo* and the residue was partitioned between 2 N NaOH (150 mL) and TBME (150 mL). The organic layer was separated, dried over $MgSO_4$, filtered and concentrated to give methyl 2-(bromomethyl)-4-fluorobenzoate (8.9 g, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 8.02 (m, 1 H), 7.20 – 7.16 (m, 1 H), 7.10 – 7.08 (m, 1 H), 4.90 (s, 2 H), 3.95 (s, 3 H).

To methyl 2-(bromomethyl)-4-fluorobenzoate (15.0 g, 61 mmol) in MeCN (150 mL) at room temperature was added 2-amino-5-bromopyridin-3-ol (10.9 g, 58 mmol) followed by cesium carbonate (23 g, 69 mmol). The mixture was then heated at 50 °C for 5 h before cooling to room temperature. The mixture was then concentrated *in vacuo* to remove ~ 80% of the MeCN before the residue was partitioned between water (400 mL) and EtOAc (400 mL). The two layers were separated and the aqueous layer was re-extracted with EtOAc (400 mL). The combined organics were then concentrated *in vacuo* to give a dark brown solid. (Note that the aqueous layer was still very dark and contained insoluble solids, and as such the yield is likely to be compromised by the lack of solubility of the product in organic solvents). The solid residue was then slurried in TBME (300 mL) for 20 min and methyl 2-{[(2-amino-5-bromopyridin-3-yl)oxy]methyl}-4-fluorobenzoate **(71)** (11.5 g, 52%) was collected as a dark grey solid. This product was purified further by column chromatography on silica gel eluting with EtOAc/cyclohexane (3 : 1 to neat EtOAc) to give methyl 2-{[(2-amino-5-bromopyridin-3-yl)oxy]methyl}-4-fluorobenzoate **(71)** (9.5 g, 44% yield) as an off-white solid. LC-MS (ESI), *m/z* 355/357 $[M+H]^+$; ^{1}H NMR (400

MHz, $CDCl_3$) δ 8.10 – 8.08 (m, 1 H), 7.75 (s ,1 H), 7.35 – 7.32 (m, 1 H), 7.10 – 7.06 (m, 1 H), 7.05 (s, 1 H), 5.50 (s, 2 H), 4.75 (br s, 1 H), 3.90 (s, 3 H).

Scheme S14. Synthesis of **51** and **72**



Reagents and conditions: (a) 1.2 eq 1,1-dimethylhydrazine, EtOH/H_2O (1 : 1), 0 °C – rt, 90 min; (b) 1 N HCl, rt, 90 min, 25% over 2 steps; (c) 4.5 eq MeI, 3 eq K_2CO_3, reflux, 7 h, 74%; (d) 1.3 eq $LiAlH_4$, THF, 0 °C – rt, 16 h, 83%; (e) 1.5 eq MsCl, 1.5 eq TEA, CH_2Cl_2, 0 °C – rt, 16 h; (f) 1.8 eq NaH (60 % in mineral oil), 1.8 eq *tert*-butyl methylcarbamate, DMF, 0 °C - rt, 12 h, 65% over 2 steps; (g) 1.1 eq NBS, CH_2Cl_2, 0 °C – rt, 2 h, 76%; (h) 10 mol% $Pd(P^tBu_3)_2$, 3 eq KOAc, MeOH, 120 °C, microwave, 1 h ; (i) 4 M HCl in dioxane, CH_2Cl_2, rt, 12 h, 92% over 2 steps.

tert-Butyl [(4-bromo-3-methoxy-1-methyl-1H-pyrazol-5-yl)methyl]methylcarbamate **(72)**. A mixture of diethyl but-2-ynedioate (110 mL, 0.69 mol) in 1 : 1 EtOH/ H_2O (1.2 L) was slowly added at 0 °C to a solution of 1,1-dimethylhydrazine (50 g, 0.83 mol) in 1 : 1 EtOH/ H_2O (400 mL). The solution was stirred at 0 °C for 30 min, then allowed to warm to room temperature for 1 h. The mixture was concentrated and the residue was partitioned between water (500 mL) and EtOAc (500 mL). The aqueous layer was concentrated to give the intermediate, which was taken

up directly in 1 N HCl (600 mL), and stirred at room temperature for 1.5 h. The mixture was extracted with CH_2Cl_2 (500 mL), and the aqueous layer was concentrated to give the residue, which was purified by column chromatography on silica gel (petroleum ether/EtOAc 6 : 1) to yield ethyl 3-hydroxy-1-methyl-1*H*-pyrazole-5-carboxylate (28.8 g, 25% yield) as a white solid, which was used without further purification.

A mixture of ethyl 3-hydroxy-1-methyl-1*H*-pyrazole-5-carboxylate (35 g, 0.2 mol), K_2CO_3 (82 g, 0.6 mol) and MeI (129.7 g, 0.9 mol) were heated at reflux for 7 h. TLC (petroleum ether/EtOAc 6 : 1) showed the reaction was complete. The mixture was filtered and the filtrate was concentrated to give a residue, which was purified by column chromatography on silica gel (petroleum ether/EtOAc 20 : 1) to yield ethyl 3-methoxy-1-methyl-1*H*-pyrazole-5-carboxylate (27.3 g, 74%) as a yellow oil, which was used directly in the next step.

To a mixture of $LiAlH_4$ (8.5 g, 220 mmol) in THF (400 mL) was added a solution of ethyl 3-methoxy-1-methyl-1*H*-pyrazole-5-carboxylate (29.4 g, 0.17 mol) in THF (200 mL) in a drop-wise manner at 0 °C. After the addition was complete, the reaction mixture was stirred at room temperature for 16 h. TLC (petroleum ether/EtOAc 1 : 1) indicated the reaction was complete. The reaction mixture was quenched by slow addition of 20% aq. NaOH (30 mL). The mixture was filtered, and the filtrate was concentrated *in vacuo* to give (3-methoxy-1-methyl-1*H*-pyrazol-5-yl)methanol (20 g, 83% yield) as a colorless oil, which was used without further purification.

To a solution of (3-methoxy-1-methyl-1*H*-pyrazol-5-yl)methanol (20 g, 140 mmol) and TEA (21.3 g, 210 mmol) in CH_2Cl_2 (300 mL) was added MsCl (23.63 g, 210 mmol) in a drop-wise manner at 0 °C. After addition, the reaction mixture was stirred at room temperature for 16 h. TLC (petroleum ether/EtOAc 1 : 1) indicated that the reaction was complete. The reaction mixture was washed with 1 N HCl (200 mL), sat. $NaHCO_3$ (200 mL) and brine (200 mL), dried

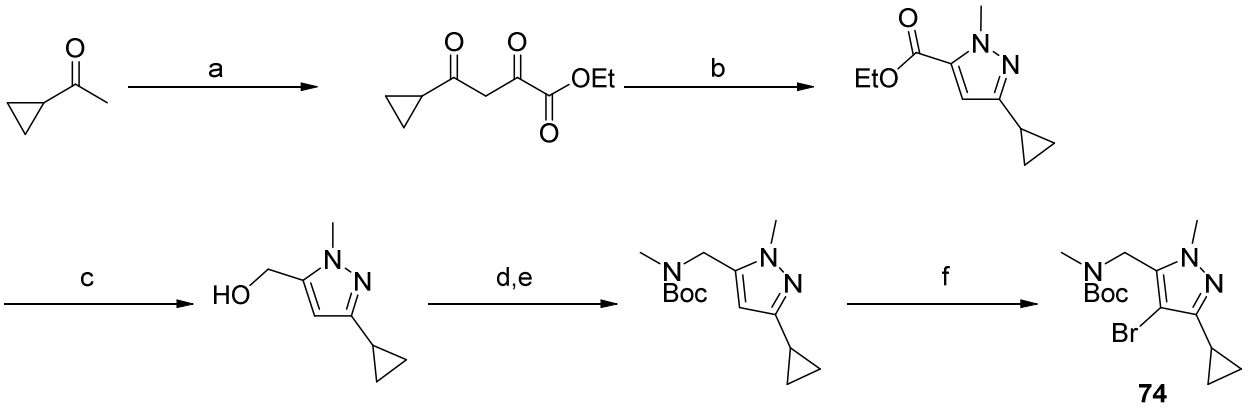
over Na_2SO_4, and concentrated *in vacuo* to give crude (3-methoxy-1-methyl-1*H*-pyrazol-5-yl)methyl methanesulfonate, which was used directly in the next step.

To a solution of *tert*-butyl methylcarbamate (32 g, 250 mmol) in DMF (200 mL) was added NaH (10 g, 60% in mineral oil, 250 mmol) in portions at 0 °C. After the addition was completed, the reaction mixture was stirred at room temperature for 1 h. A solution of (3-methoxy-1-methyl-1*H*-pyrazol-5-yl)methyl methanesulfonate (140 mmol) in DMF (50 mL) was then added in a drop-wise manner to the reaction solution at 0 °C. After the addition was complete, the resulting mixture was then stirred at room temperature for 12 h. TLC (petroleum ether/EtOAc 3 : 1) indicated that the reaction was complete. The reaction mixture was poured into ice-water (300 mL), then extracted with EtOAc (3 x 300 mL). The combined extracts were washed with brine (3 x 100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was purified by column chromatography (silica gel, petroleum ether/EtOAc 20 : 1) to give *tert*-butyl [(3-methoxy-1-methyl-1*H*-pyrazol-5-yl)methyl] methylcarbamate (23 g, 65% yield) as a yellow oil.

To a solution of *tert*-butyl [(3-methoxy-1-methyl-1*H*-pyrazol-5-yl)methyl]methylcarbamate (12 g, 46.8 mmol) in CH_2Cl_2 (300 mL) was added NBS (9.18 g, 51.3 mmol) in a portion-wise manner at 0 °C. After the addition was completed, the reaction mixture was stirred at room temperature for 2 h. TLC (petroleum ether/EtOAc 3:1) indicated that the reaction was complete. The reaction mixture was washed with sat. $NaHCO_3$ (3 x 100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give *tert*-butyl [(4-bromo-3-methoxy-1-methyl-1*H*-pyrazol-5-yl)methyl]methylcarbamate **(72)** (12 g, 76% yield) as a yellow solid. LC-MS (ESI), *m/z* 335.9 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 4.47 (s, 2 H), 3.92 - 3.89 (m, 3 H), 3.72 - 3.70 (m, 3 H), 2.75 - 2.71 (m, 3 H), 1.44 (s, 9 H).

1-(3-Methoxy-1-methyl-1H-pyrazol-5-yl)-N-methylmethanamine **(51)**. To a solution of *tert*-butyl [(4-bromo-3-methoxy-1-methyl-1*H*-pyrazol-5-yl)methyl]methylcarbamate **(72)** (300 mg, 0.90 mmol) in MeOH (4.49 mL) in a microwave vial was added KOAc (264 mg, 2.69 mmol), and $Pd(P^tBu_3)_2$ (46.9 mg, 0.09 mmol). The reaction was heated in the microwave to 120 °C for 45 min. LC-MS indicated that the reaction was not complete, and so a further portion of $Pd(^tBu_3)_2$ (46.9 mg, 0.09 mmol) was added, and the reaction heated at 120 °C for 3 h. The reaction was diluted with EtOAc (25 mL), washed with water (10 mL), brine (10 mL), dried over $MgSO_4$, and concentrated. The residue was taken up in CH_2Cl_2 (2.24 mL), and 4 M HCl in dioxane (2.24 mL) added. The reaction was stirred for 12 h, then concentrated to afford **51** (159 mg, 92% yield) as an orange gum, which was used without further purification. LC-MS (ESI) *m/z* 156.2 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (br s, 2 H), 5.92 (s, 1 H), 4.14 (t, J = 5.5 Hz, 2 H), 3.74 (s, 3 H), 3.72 (s, 3 H), 2.57 - 2.52 (m, 3 H).

Scheme S15. Synthesis of *tert*-butyl ((4-bromo-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)methyl)(methyl)carbamate **(74)**



Reagents and conditions: (a) 1.1 eq Na, 1 eq diethyl diethanedioate, EtOH, 0 °C – rt, 3 h, 51%; (b) 1.5 eq $MeNHNH_2$ (40 % in H_2O), EtOH, 0 °C, 1 h, 25%; (c) 1.2 eq $LiAlH_4$, THF, 0 °C – rt, 2 h, 92% ; (d) 1.1 eq MsCl, 1.5 eq TEA, CH_2Cl_2, 0 C – rt, 3 h, 66%; (e) 1.3 eq NaH (60 % in

mineral oil), 1.3 eq *tert*-butyl methylcarbamate, DMF, 0 °C – rt, 16 h, 94%; (f) 1 eq NBS, CH_2Cl_2, 0 °C – rt, 2 h, 85%.

tert-Butyl [(4-bromo-3-cyclopropyl-1-methyl-1H-pyrazol-5-yl)methyl]methylcarbamate **(74)**. Sodium (16.1 g, 0.7 mol) was added in portions to EtOH (1500 mL) at ambient temperature and then the mixture was stirred at ambient temperature until all of the solids had dissolved. Diethyl ethanedioate (93 g, 0.636 mol) was added, and the solution was cooled to 0 °C. 1-Cyclopropylethanone (53.5 g, 0.636 mol) was then added in a drop-wise manner at 0 °C. After the addition was completed, the resulting mixture was stirred at room temperature for 3 h. TLC (petroleum ether/EtOAc 5 : 1) indicated that the reaction was complete. Ice-water (200 mL) was added, and the mixture was neutralized with concentrated HCl. The neutralized solution was concentrated *in vacuo* to remove EtOH and the residue was extracted with EtOAc (3 x 400 mL). The combined extracts were washed with brine (500 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give ethyl 4-cyclopropyl-2,4-dioxobutanoate (60 g, 51%) as pale yellow oil, which was used without further purification.

To a solution of ethyl 4-cyclopropyl-2,4-dioxobutanoate (65 g, 0.353 mol) in EtOH (1000 mL) was added in a drop-wise manner to a solution of methylhydrazine (61.94 g, 0.530 mol, 40% in H_2O) at 0 °C over 1 h. After the addition was completed, the reaction mixture was stirred at 0 °C for 1 h, and then at room temperature for 1 h. TLC (petroleum ether/EtOAc 5 : 1) indicated that the reaction was complete. The reaction mixture was concentrated *in vacuo*, and the residue was extracted with EtOAc (3 x 400 mL). The combined organic layers were washed with brine (300 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give a residue which was purified *via* column chromatography on silica gel (petroleum ether/EtOAc 15 : 1) to give ethyl 3-cyclopropyl-1-methyl-1*H*-pyrazole-5-carboxylate (17 g, 25%) as a pale yellow oil. (Note the

regioisomer is more polar and can be obtained as an off-white solid (33 g, 48% yield) by further elution of the column with petroleum ether/EtOAc 3 : 1).

To a mixture of $LiAlH_4$ (4.2 g, 111.2 mmol) in THF (200 mL) was added in a drop-wise manner a solution of ethyl 3-cyclopropyl-1-methyl-1*H*-pyrazole-5-carboxylate (18 g, 92.6 mmol) in THF (50 mL) at -10 to 0 °C. Upon completion of the addition, the reaction mixture was stirred at room temperature for 2 h. TLC (petroleum ether/EtOAc 1 : 1) indicated that the reaction was complete. The reaction mixture was carefully quenched with 20% aq. NaOH (20 mL). The mixture was filtered and the filtrate was concentrated *in vacuo* to give a residue, which was purified *via* column chromatography on silica gel (petroleum ether/EtOAc 3 : 1) to give (3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)methanol (13 g, 92% yield) as a white solid, which was used without further purification.

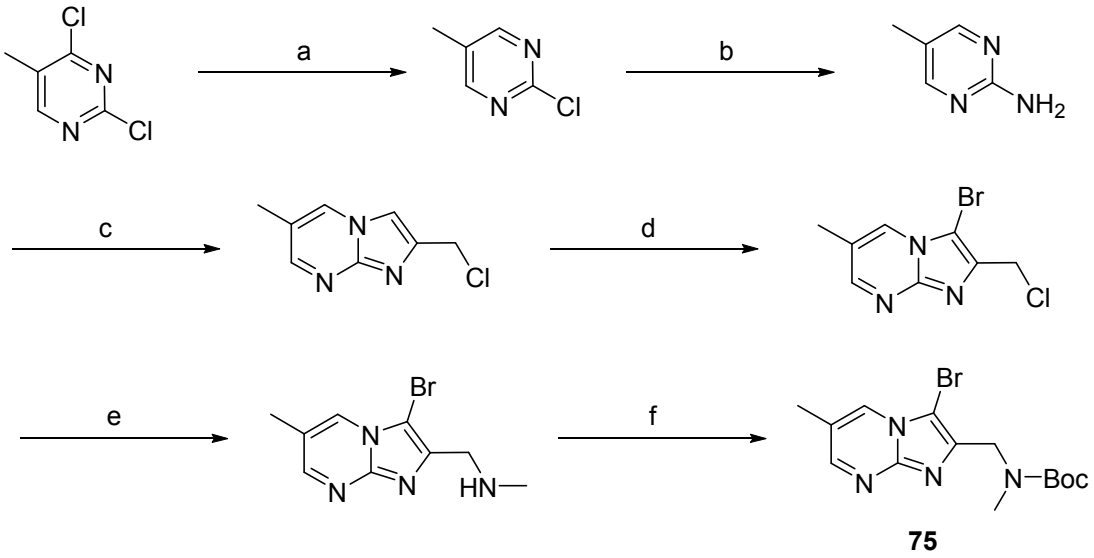
To a solution of (3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)methanol (13 g, 85.5 mmol) and TEA (13 g, 128 mmol) in CH_2Cl_2 (200 mL) was added in a drop-wise manner MsCl (10.7 g, 94 mmol) at 0 °C. After addition was completed, the reaction mixture was stirred at room temperature for 3 h. TLC (petroleum ether/EtOAc 3 : 1) indicated that the reaction was complete. The reaction mixture was washed with water (3 x 100 mL), sat. $NaHCO_3$ (3 x 100 mL) and brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give (3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)methyl methanesulfonate (13 g, 66% yield) as a red oil, which was used directly in the next step.

To a solution of *tert*-butyl methylcarbamate (9.6 g, 73.3 mmol) in DMF (100 mL) was added in portions NaH (2.9 g, 60% in mineral oil, 73.3 mmol) at 0 °C. After addition, the reaction mixture was stirred at room temperature for 1 h. A solution of (3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)methyl methanesulfonate (13 g, 56.4 mmol) in DMF (20 mL) was then added drop-

wise at 0 °C. After completion of the addition, the reaction mixture was stirred at room temperature for 16 h. TLC (petroleum ether/EtOAc 3 : 1) indicated that the reaction was complete. The reaction mixture was poured into ice-water (200 mL) and the mixture was extracted with EtOAc (3 x 150 mL). The combined extracts were washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was purified *via* column chromatography on silica gel (petroleum ether/EtOAc 3 : 1) to give *tert*-butyl [(3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)methyl]methylcarbamate (14.1 g, 94% yield) as an off-white solid, which was used directly in the next step.

To a solution of *tert*-butyl [(3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)methyl]methylcarbamate (14.1 g, 53.1 mmol) in CH_2Cl_2 (100 mL) was added in portions NBS (9.4 g, 53.1 mmol) at 0 °C. After addition was completed, the reaction was stirred at room temperature for 2 h. TLC (petroleum ether/EtOAc 3 : 1) indicated that the reaction was complete. The reaction mixture was washed with sat. $NaHCO_3$ (3 x 100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give a residue, which was purified *via* column chromatography on silica gel (petroleum ether/EtOAc 6 : 1) to give *tert*-butyl [(4-bromo-3-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)methyl]methylcarbamate **(74)** (15.5 g, 85% yield) as a white solid. LC-MS (ESI) *m/z* 344 $[M+H]^+$; ^1H NMR (400 MHz, $CDCl_3$) δ 4.49 (s, 2 H), 3.70 (s, 3 H), 2.66 (s, 3 H), 1.80 -1.75 (m, 1 H), 1.38 (s, 9 H), 0.86 - 0.79 (m, 4 H).

Scheme S16. Synthesis of *N*-methyl-1-(6-methylimidazo[1,2-*a*]pyrimidin-2-yl)methanamine **(75)**



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Reagents and conditions: (a) 3 eq Zn, H_2O, reflux, 3 h, 78%; (b) Aq. NH_3 (35%)/IMS (1 : 1), 200 °C, 4 h, 92% (c) 2 eq, 1,3-dichloroacetone, THF, 90 °C, 3 days, 24%; (d) 1.1 eq NBS, MeCN, rt, 14 h, 32%; (e) 15 eq $MeNH_2$ (2 M in THF), THF, 60 °C, 4 h, 15%; (f) 4 eq $(Boc)_2O$, 3.2 eq DIPEA, 20 mol% DMAP, CH_2Cl_2, 0 °C- rt, 14 h, 69%.

tert-Butyl [(3-bromo-6-methylimidazo[1,2-a]pyrimidin-2-yl)methyl]methylcarbamate **(75)**. A suspension of 2,4-dichloro-5-methylpyrimidine (50.0 g, 307 mmol) and freshly activated (acid washed) Zn (59.8 g, 920 mmol) in water (500 mL) was heated at reflux for 3 h. TLC showed consumption of the starting material. The reaction mixture was cooled to room temperature, filtered through a pad of Celite, and rinsed with CH_2Cl_2 (500 mL). The phases of the filtrate were separated and the organic phase was washed with brine (300 mL), dried over $MgSO_4$, filtered and concentrated under vacuum carefully to give 2-chloro-5-methylpyrimidine as a beige powder (30.6 g, 78% yield, 95% purity by ^{1}H NMR).^{1}H NMR (400 MHz, DMSO-d_6) δ 8.63 (d, J = 0.9 Hz, 2 H), 2.27 (t, J = 0.8 Hz, 3 H).

To a solution of 2-chloro-5-methylpyrimidine (10.0 g, 77.79 mmol) in IMS (100 mL) was added aqueous ammonia (35%, 100 mL). The reaction mixture was transferred to a sealed bomb and heated at 200 °C for 4 h. The mixture was allowed to cool to room temperature and

concentrated to remove most of the solvent. Water (25 mL) was added and the solid obtained was filtered and dried under vacuum to give the desired 2-amino-5-methylpyrimidine (7.85 g, 92% yield) as an off-white solid. LC-MS (ESI), *m/z* 110 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.06 (s, 2 H), 6.30 (s, 2 H), 2.03 (s, 3 H).

To a slurry of 2-amino-5-methylpyrimidine (10.36 g, 94.98 mmol) in THF (250 mL) was added 1,3-dichloroacetone (23.84 g, 187.00 mmol) and 4 Å molecular sieves (28 g). The reaction mixture was heated at 90 °C for 3 days, then the reaction mixture was concentrated and the resulting residue dissolved in water (200 mL). The solution was treated with solid K_2CO_3 (10 g) and stirred for 10 min before extraction with EtOAc (3 x 400 mL). The combined EtOAc extracts were washed with brine (500 mL) and concentrated to give the crude product as a thick brown oil. The aqueous phase was subjected to liquid-liquid extraction with CH_2Cl_2 (500 mL) and the resulting product obtained was combined with the crude oil obtained from the EtOAc extractions for purification. Purification by silica gel column chromatography using 0.5% - 1% MeOH in CH_2Cl_2 furnished 2-(chloromethyl)-6-methylimidazo[1,2-*a*]pyrimidine (4.2 g, 24% yield) as off-white solid. LC-MS (ESI), *m/z* 182 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 2.4 Hz, 1 H), 8.23 (dd, *J* = 2.4, 1.2 Hz, 1 H), 7.56 (d, *J* = 0.8 Hz, 1 H), 4.79 (d, *J* = 0.8 Hz, 2 H), 2.37 (d, *J* = 1.1 Hz, 3 H).

To a solution of 2-(chloromethyl)-6-methylimidazo[1,2-*a*]pyrimidine (4.2 g, 23.12 mmol) in MeCN (65 mL) was added NBS (4.49 g, 25.2 mmol) and the reaction stirred at room temperature overnight. The solvent was removed under vacuum and the crude product was dissolved in EtOAc (200 mL). The solid precipitate was removed by filtration, and the filtrate was evaporated to give the crude product as a light yellow gum. Purification of the crude product by silica gel column chromatography using 0.5% MeOH in CH_2Cl_2 furnished the pure 3-bromo-2-

(chloromethyl)-6-methylimidazo[1,2-*a*]pyrimidine (1.9 g, 32% yield) as an off-white solid. LC-MS (ESI), *m/z* 260/262 $[M+H]^+$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 2.4 Hz, 1 H), 8.14 (dd, *J* = 2.4, 1.2 Hz, 1 H), 4.78 (s, 2 H), 2.44 (s, 3 H).

To a suspension of 3-bromo-2-(chloromethyl)-6-methylimidazo[1,2-*a*]pyrimidine (1.68 g, 6.45 mmol) in THF (20 mL) being heated at 60 °C, was slowly added a solution of methylamine (2 M in THF, 53.2 mL, 96.75 mmol) over a period of 30 min using a syringe pump. Once the addition was complete, the reaction was heated at 60 °C for 4 h. The mixture was cooled and concentrated. The resulting residue was purified by silica gel flash column chromatography using 10% MeOH in CH_2Cl_2 along with 0.1% of 35% aqueous ammonia. The product obtained was found to contain a small amount of undesired dimer and so was further purified by reverse phase chromatography using a MeCN/H_2O solvent gradient. The product thus obtained was contaminated with a trace of impurity and was purified again by flash silica gel column chromatography using 4% MeOH in CH_2Cl_2 (containing 7 N ammonia) to furnish 1-(3-bromo-6-methylimidazo[1,2-*a*]pyrimidin-2-yl)-*N*-methylmethanamine (254 mg, 15% yield) as a yellow solid. LC-MS (ESI), *m/z* 255/257 $[M+H]^+$; ^{1}H NMR (400 MHz, CD_3OD) δ 8.89 – 8.22 (m, 2 H), 3.88 (s, 2 H), 2.45 (d, *J* = 1.1 Hz, 3 H), 2.42 (s, 3 H).

To a solution of 1-(3-bromo-6-methylimidazo[1,2-*a*]pyrimidin-2-yl)-*N*-methylmethanamine (250 mg, 0.980 mmol), DIPEA (0.512 mL, 2.94 mmol) and DMAP (23.9 mg, 0.196 mmol) in CH_2Cl_2 (4 mL) was added $(Boc)_2O$ (856 mg, 3.92 mmol) at 0 °C. The mixture was stirred at room temperature overnight, concentrated and purified by silica gel chromatography using 0 - 75% EtOAc/heptanes to give *tert*-butyl [(3-bromo-6-methylimidazo[1,2-*a*]pyrimidin-2-yl)methyl]methylcarbamate (**75**) (241 mg, 69% yield) as a gum. LC-MS (ESI), *m/z* 355/357

$[M+H]^+$; ^1H NMR (400MHz, DMSO-d_6) δ 8.59 (s, 1 H), 8.48 (d, J = 2.3 Hz, 1 H), 4.52 (s, 2 H), 2.85 (br s, 3 H), 2.37 (s, 3 H), 1.39 (d, J = 15.9 Hz, 9 H).

Table 2. Selectivity of compound **8k** in an extended kinase panel

Kinase	% Inhibition at 1μM[a]	Assay technology	IC_{50}[a] (Ki[b]), nM
ROS1	102	Z'-LYTE™	<0.005[b]
ALK	Not in panel		<0.07[b]
ALK L1196M	Not in panel		0.7[b]
LTK (TYK1)	111	Z'-LYTE™	2.7
FER	104	Z'-LYTE™	3.3
FES (FPS)	97	Z'-LYTE™	6.0
PTK2B (FAK2)	101	Z'-LYTE™	14
TNK2 (ACK)	99	LanthaScreen™	17[c]
PTK2 (FAK)	99	Z'-LYTE™	17
NTRK2 (TRKB)	103	Z'-LYTE™	23[b]
NTRK1 (TRKA)	87	Z'-LYTE™	24
NTRK3 (TRKC)	95	Z'-LYTE™	46
FRK (PTK5)	94	Z'-LYTE™	53
EGFR (ErbB1) T790M L858R	85	Z'-LYTE™	245
IGF1R	72	Z'-LYTE™	296
STK22B (TSSK2)	75	LanthaScreen™	302[c]
EGFR (ErbB1) T790M	76	Z'-LYTE™	319
EPHA1	74	Z'-LYTE™	375
DCAMKL2 (DCK2)	73	Z'-LYTE™	370
JAK2	79	Z'-LYTE™	529
EPHA7	69	LanthaScreen™	
SRMS (Srm)	65	Z'-LYTE™	
EPHB1	62	Z'-LYTE™	
LRRK2	60	Z'-LYTE™	
MAP2K6 (MKK6)	56	LanthaScreen™	
EPHA4	56	Z'-LYTE™	
JAK2 JH1 JH2	52	Z'-LYTE™	
INSRR (IRR)	52	Z'-LYTE™	
MUSK	51	Z'-LYTE™	
PTK6 (Brk)	47	Z'-LYTE™	
JAK2 JH1 JH2 V617F	45	Z'-LYTE™	
EPHA2	44	Z'-LYTE™	
CAMK2D (CaMKII delta)	42	Z'-LYTE™	

HCK	40	Z'-LYTE™	
EPHB4	39	Z'-LYTE™	
IRAK1	38	Adapta™	
MAP2K3 (MEK3)	36	LanthaScreen™	
INSR	35	Z'-LYTE™	1200
RAF1 (cRAF) Y340D Y341D	33	Z'-LYTE™	
BRSK1 (SAD1)	33	Z'-LYTE™	
FGR	32	Z'-LYTE™	
EPHA5	30	Z'-LYTE™	
AURKA (AURA)	29	Z'-LYTE™	
LYN B	28	Z'-LYTE™	
LYN A	27	Z'-LYTE™	
EPHB2	26	Z'-LYTE™	
MAP3K2 (MEKK2)	26	LanthaScreen™	
SYK	26	Z'-LYTE™	
SRC N1	23	Z'-LYTE™	
CSF1R (FMS)	19	Z'-LYTE™	
CAMK1D (CaMKI delta)	18	Z'-LYTE™	
GRK4	18	Z'-LYTE™	
SRC	17	Z'-LYTE™	
CAMK4 (CaMKIV)	16	Z'-LYTE™	
TEK (Tie2)	15	Z'-LYTE™	
KIT V654A	15	LanthaScreen™	
MERTK (cMER)	14	Z'-LYTE™	
EPHB3	14	Z'-LYTE™	
MET (cMet)	14	Z'-LYTE™	>8700
EGFR (ErbB1) L861Q	13	Z'-LYTE™	
YES1	12	Z'-LYTE™	
LCK	12	Z'-LYTE™	
PRKCG (PKC gamma)	12	Z'-LYTE™	
ABL1 T315I	12	Z'-LYTE™	
KIT T670I	12	Z'-LYTE™	
BLK	12	Z'-LYTE™	
EGFR (ErbB1)	11	Z'-LYTE™	
MAP3K3 (MEKK3)	11	LanthaScreen™	
TXK	11	Z'-LYTE™	
PLK3	11	Z'-LYTE™	
MET M1250T	11	Z'-LYTE™	
EPHA8	11	Z'-LYTE™	
CAMK2A (CaMKIIa)	11	Z'-LYTE™	
PKN1 (PRK1)	11	Z'-LYTE™	
PKN1 (PRK1)	11	Z'-LYTE™	
DNA-PK	10	Z'-LYTE™	

BMX	9	Z'-LYTE™	
STK33	9	LanthaScreen™	
MAPK10 (JNK3)	9	Z'-LYTE™	
BRAF V599E	8	LanthaScreen™	
PRKD1 (PKC mu)	8	Z'-LYTE™	
PDGFRB (PDGFR beta)	8	Z'-LYTE™	
PDGFRA T674I	8	Z'-LYTE™	
FGFR3	8	Z'-LYTE™	
MYLK2 (MLCK_sk)	8	Z'-LYTE™	
DDR1	8	LanthaScreen™	
CHEK2 (CHK2)	7	Z'-LYTE™	
CDC42 BPB (MRCKB)	7	Z'-LYTE™	
ABL1 Y253F	7	Z'-LYTE™	
HIPK4	7	Z'-LYTE™	
CAMK2B (CaMKII beta)	7	Z'-LYTE™	
DAPK1	7	Adapta™	
MST1R (RON)	7	Z'-LYTE™	
BTK	7	Z'-LYTE™	
EGFR (ErbB1) L858R	7	Z'-LYTE™	
PRKG1	7	Z'-LYTE™	
LIMK1	7	LanthaScreen™	
MARK2	6	Z'-LYTE™	
TYRO3 (RSE)	6	Z'-LYTE™	
MAP3K8 (COT)	6	Z'-LYTE™	
ERBB4 (HER4)	6	Z'-LYTE™	
RPS6KA3 (RSK2)	6	Z'-LYTE™	
ROCK1 (ROCKI)	6	Z'-LYTE™	
CDK8/cyclin C	5	LanthaScreen™	
MAP2K2 (MEK2)	5	LanthaScreen™	
CAMKK1 (CAMKKA)	5	LanthaScreen™	
PLK2	5	Z'-LYTE™	
WEE1	5	LanthaScreen™	
EPHA3	5	LanthaScreen™	
PRKD2 (PKD2)	5	Z'-LYTE™	
MAPK3 (ERK1)	4	Z'-LYTE™	
PASK	4	Z'-LYTE™	
MARK1	4	Z'-LYTE™	
TEC	4	LanthaScreen™	
PAK1	4	Z'-LYTE™	
ABL2 (Arg)	4	Z'-LYTE™	
CDK9/cyclin T1	4	Adapta™	
CDK5/p35	4	Z'-LYTE™	
PDGFRA (PDGFR alpha)	4	Z'-LYTE™	

STK3 (MST2)	4	Z'-LYTE™	
IKBKB (IKKb)	3	Z'-LYTE™	
SGKL (SGK3)	3	Z'-LYTE™	
BRAF	3	LanthaScreen™	
MAPK1 (ERK2)	3	Z'-LYTE™	
CHEK1 (CHK1)	3	Z'-LYTE™	
ITK	2	Z'-LYTE™	
DMPK	2	LanthaScreen™	
RPS6KA1 (RSK1)	2	Z'-LYTE™	
FGFR4	2	Z'-LYTE™	
TYK2	2	Z'-LYTE™	>10,000
CSK	2	Z'-LYTE™	
JAK3	2	Z'-LYTE™	>10,000
CDK1/cyclin B	2	Z'-LYTE™	
EEF2K	2	Z'-LYTE™	
TBK1	2	Z'-LYTE™	
NEK2	1	Z'-LYTE™	
PRKCB1 (PKC beta I)	1	Z'-LYTE™	
RPS6KA4 (MSK2)	1	Z'-LYTE™	
RPS6KA4 (MSK2)	1	Z'-LYTE™	
ABL1	1	Z'-LYTE™	
DAPK3 (ZIPK)	1	Z'-LYTE™	
RET	1	Z'-LYTE™	
RET V804L	1	Z'-LYTE™	
TAOK2 (TAO2)	1	Z'-LYTE™	
AKT3 (PKB gamma)	1	Z'-LYTE™	
PDGFRA V561D	1	Z'-LYTE™	
ABL1 G250E	1	Z'-LYTE™	
WNK2	0	LanthaScreen™	
RIPK2	0	LanthaScreen™	
MST4	0	Z'-LYTE™	
PRKCE (PKC epsilon)	0	Z'-LYTE™	
MAP3K14 (NIK)	0	LanthaScreen™	
PRKCZ (PKC zeta)	0	Z'-LYTE™	
MAP3K10 (MLK2)	-1	LanthaScreen™	
FGFR1	-1	Z'-LYTE™	
ABL1 E255K	-1	Z'-LYTE™	
DYRK3	-1	Z'-LYTE™	
PRKCQ (PKC theta)	-1	Z'-LYTE™	
ZAK	-1	LanthaScreen™	
NEK7	-1	Z'-LYTE™	
FYN	-2	Z'-LYTE™	
CLK1	-2	Z'-LYTE™	

CSNK1A1 (CKIa)	-2	Z'-LYTE™	
CDK7/cyclin H/MNAT1	-2	Adapta™	
KIT	-2	Z'-LYTE™	
MAPKAPK3	-2	Z'-LYTE™	
PAK4	-2	Z'-LYTE™	
DDR2	-2	LanthaScreen™	
FLT3 D835Y	-2	Z'-LYTE™	
PDGFRA D842V	-2	Z'-LYTE™	
RET Y791F	-3	Z'-LYTE™	
DYRK1B	-3	Z'-LYTE™	
CDK2 /CyclinA	-3	Z'-LYTE™	
PAK6	-3	Z'-LYTE™	
AKT1 (AKT)	-3	Z'-LYTE™	
AXL	-3	Z'-LYTE™	
PIM2	-3	Z'-LYTE™	
PRKACA (PKACa)	-4	Z'-LYTE™	
CSNK2A2 (CKIIa prime)	-4	Z'-LYTE™	
STK17A (DRAK1)	-4	LanthaScreen™	
FLT3	-4	Z'-LYTE™	
ERBB2 (HER2)	-5	Z'-LYTE™	
PDPK1 (PDK1) (direct)	-5	Z'-LYTE™	
CSNK1E (CK1 epsilon)	-5	Z'-LYTE™	
MAPKAPK2 (MK2)	-5	Z'-LYTE™	
AMPK A2/B1/G1	-5	Z'-LYTE™	
PAK2 (PAK65)	-5	Z'-LYTE™	
SGK1 (SGK)	-5	Z'-LYTE™	
MATK (HYL)	-6	Z'-LYTE™	
KDR (VEGFR2)	-6	Z'-LYTE™	
GSG2 (Haspin)	-6	Adapta™	
MAP4K4 (ZC1)	-7	Z'-LYTE™	
MAPK14 (p38) direct	-7	Z'-LYTE™	
JAK1	-7	Z'-LYTE™	>10,000
GSK3A (GSK3 alpha)	-7	Z'-LYTE™	
CHUK (IKK alpha)	-8	Adapta™	
MAP3K7/MAP3K7IP1 (TAK1-TAB1)	-8	LanthaScreen™	
FGFR3 K650E	-8	Z'-LYTE™	
ZAP70	-8	Z'-LYTE™	
ACVR1B (ALK4)	-9	Z'-LYTE™	
PRKCD (PKC delta)	-9	Z'-LYTE™	
TGFBR1 (ALK5)	-9	LanthaScreen™	
STK16 (PKL12)	-9	LanthaScreen™	
FGFR2	-11	Z'-LYTE™	
FLT4 (VEGFR3)	-11	Z'-LYTE™	

FLT1 (VEGFR1)	-12	Z'-LYTE™	
FRAP1 (mTOR)	-13	Z'-LYTE™	
MAP3K5 (ASK1)	-16	LanthaScreen™	

[a] % Inhibition or IC_{50} from Invitrogen assays using ATP concentrations near the ATP K_M, except where noted differently. MAP3K8 (COT), MAPK10 (JNK3) and RAF1 (cRAF) Y340D Y341D were tested by cascade assays with 100 μM ATP. LanthaScreen™ binding assays did not use ATP.
[b] Ki values calculated using tight-binding (Morrison) equation for competitive inhibitors tested in Caliper off-chip mobility shift assays conducted at Pfizer.
[c] IC_{50} from Invitrogen LanthaScreen™ binding assays.

References

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