Supplementary Data

General. All NMR spectra were recorded on a 400 MHz AMX Bruker NMR spectrometer. ^{1}H, ^{13}C, and ^{19}F chemical shifts are reported in δ values in ppm downfield with the deuterated solvent as the internal reference. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, dt = doublet of triplet, bs = broad singlet, m = multiplet), integration, coupling constant (Hz). Low-resolution mass spectra were obtained on an Agilent 1200 series 6130 mass spectrometer with electrospray ionization. High-resolution mass spectra were recorded on a Waters Q-TOF API-US plus Acquity system with electrospray ionization. Analytical thin layer chromatography (TLC) was performed on EM reagent 0.25 mm silica gel 60-F plates. All samples were of ≥95% purity as analysed by LC-UV/vis-MS. Analytical HPLC was performed on an Agilent 1200 series with UV detection at 214 and 254 nm. Preparative purification was performed on normal-phase silica gel with a CombiFlash RF system (Teledyne), with UV detection at 214 and 254 nm and ELSD detection. All microwave reactions were carried out in a Biotage® Initiator Microwave Synthesizer. Solvents for extraction, washing, and chromatography were HPLC grade. All reagents were purchased from Aldrich Chemical Co. and used without purification.

Synthesis and Characterization of PLX4720 (8a)

***N*-(3,5-Difluorophenyl) propane-1-sulfonamide (3).** Propane-1-sulfonyl chloride (**2**) (1.85 mL, 16.4 mmol) was added dropwise to a solution of 2,4-difluoroaniline (**1**) (2.0 g, 15.5 mmol), pyridine (1.33 mL), and dimethyaminopyridine (DMAP) (70 mg, 0.62 mmol) in anhydrous dichloromethane (15 mL). Upon completion of the addition, the reaction mixture was irradiated at 100 °C for 30 min. The reaction mixture was then dissolved in ethyl acetate (100 mL), washed with water (2 x 20 mL) and brine (20 mL), and dried over $MgSO_4$. The crude mixture was then purified by flash chromatography on silica gel to afford **3** (3.2 g, 81%) as a tan solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.5-7.51 (m, 1H), 6.91-6.86 (m, 1H), 6.83 (bs, 1H), 3.07-3.03 (m, *2*H), 1.89-1.83 (m, 2H), 1.03 (t, J = 7.5 Hz, 3H); ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ -112.2-122.5; LCMS *m/z* calcd. For $C_9H_{12}F_2NO_2S$ ($M+H^+$): 235.25; found: 235.30 (ESI+).

***N*-(3,5-Difluoro-4-formylphenyl) propane-1-sulfonamide (5).** Compound **3** (900 mg, 3.8 mmol) in THF was added to a stirred solution of lithium bis(trimethylsilyl)amide (LHMDS) (8.5 mL) at -78 °C under nitrogen and the reaction mixture was stirred for 3 h at 0 °C. The reaction mixture was cooled to -78 °C and *N*-formylmorpholine (**4**) (0.58 mL, 5.7 mmol) was added. The resulting mixture was stirred for 30 min at 0 °C, followed by microwave irradiation at 110 °C for 1 h, quenched with 1.0 N HCl, and extracted (3 x 20 mL) with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel afford **5** (555 mg, 56%) as a brown solid: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 7.85 (dt, J = 8.9, 5.5 Hz, 1H), 7.05 (dt, J = 9.3, 1.7 Hz, 1H), 6.63 (bs, 1H), 3.10-3.06 (m, 2H), 1.94-1.84 (m, 2H), 1.06 (t, J = 7.5 Hz, 3H); ^{19}F-NMR (282 MHz, $CDCl_3$) δ -116.6, -112.4; LCMS *m/z* calcd. For $C_{10}H_{10}F_2NO_3S$ ($M-H^+$): 262.26; found: 262.30 (ESI-).

***N*-(3-((5-Chloro-1H-pyrrolo[2,3-*b*]pyridine-3-yl)(hydroxyl)methyl)2,4-difluorophenyl)propane-1-sulfonamide (7a).** Potassium carbonate (157 mg, 1.14 mmol) was added to a solution of **5** (47 mg, 0.175 mmol) and 5-chloro-7-azaindole (**6a**) (32 mg, 0.210 mmol) in methanol:water (1:1; 6.0 mL). The reaction mixture was microwaved at 130 °C for 30 min. The reaction mixture pH was then adjusted to 7 with 4.0 N HCl and extracted with ethyl acetate (3 x 10 mL). The combined organics were then dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel afford **7a** (64 mg, 88%) as a light-brown solid: ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.55 (s, 1H), 8.18 (s, 1H), 7.93 (s, 1H), 7.5 (m, 2H), 7.01 (m, 2H), 6.06 (s, 1H), 3.01 (m, 1H), 1.77 (m, 1H), 0.95 (m, 3H); ^{19}F-NMR (282 MHz, DMSO-d_6) δ -114.2, -119.8; LCMS *m/z* calcd. For $C_{17}H_{16}ClF_2N_3O_3S$ ($M+H^+$): 415.84; found 415.90 (ESI+).

***N*-(5-Chloro-1H-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonoamide (8a, PLX4720).** 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (146 mg, 0.64 mmol) in 0.04 mL water was added to a solution of **7a** (130 mg, 0.40 mmol) in 1,4-dioxane (1.0 mL) at room temperature. The reaction mixture was irradiated with microwaves at 100 °C for 10 min, then quenched with saturated sodium bicarbonate (10 mL). The organic volatiles were removed under vacuum and the residue diluted with water and extracted with THF/ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude solid was purified by flash chromatography on silica gel to afford **8a** (113 mg, 87%) as a brown solid: ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.55 (s, 1H), 8.65 (s, 1H), 8.30 (s, 1H), 7.60 (m, 2H), 7.25 (m,

2H), 3.15 (m, 1H), 1.90 (m, 1H), 0.95 (m, 3H); ^{19}F-NMR (282 MHz, DMSO-d_6) δ -117.10, -122.39; LCMS *m/z* calcd. For $C_{17}H_{14}ClF_2N_3O_3S$ ($M+H^+$): 413.83; found 414.10 (ESI+).

Synthesis and Characterization of PLX4032 (8b)

5-(4-Chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (6b). 5-Bromo-7-azaindole (**6e**) (1.0 g, 5.0 mmol) and (4-chlorophenyl)boronic acid (**6f**) (954 mg, 6.2 mmol) were dissolved in 1,2-dimethoxyethane (28 mL). A solution of potassium carbonate (844 mg, 6.2 mmol) in water (8.0 mL) was then added. The resulting mixture was purged with argon for 5 min, followed by addition of bis(triphenylphosphine)dichloropalladium(II) (356 mg, 0.5 mmol). The reaction mixture was then reacted at 130 °C for 30 min under microwave irradiation. The volatiles were then removed under reduced pressure and the crude residue diluted with water (30 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layer was dried over sodium sulphate, filtered, and the resulting filtrate evaporated *in vacuo* to give a crude solid that was purified using flash column chromatography to afford compound **6b** (875 mg, 76%) as a light-brown crystalline solid. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.85 (bs, 1H), 8.54 (d, *J* = 2.0, 1H), 8.12 (d, *J* = 2.0, 1H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.41 (m, 1H), 6.58 (m, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ 148.6, 141.8, 138.4, 132.1, 129.3, 128.9, 127.5, 127.2, 126.5, 120.0, 100.6; LCMS *m/z* calcd. for $C_{13}H_{10}ClN_2$ (MH^+): 229.1; found: 229.0 (ESI+).

***N*-(3-((5-(4-Chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)(hydroxy)methyl)-2,4-difluorophenyl)propane-1-sulfonamide (7b).** To a suspension of 5-(4-chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (**6b**) (100 mg, 0.44 mmol) and *N*-(2,4-difluoro-3-formylphenyl)propane-1-sulfonamide (**5**) (139 mg, 0.53 mmol) in methanol (7.0 mL) was added potassium hydroxide (197 mg, 3.5 mmol). The reaction mixture was stirred at room temperature for 3 d and then evaporated to dryness. The crude reaction mixture was diluted with water (5.0 mL) and the pH adjusted to 7 with 4.0 N hydrochloric acid (10 mL). The resulting mixture was then diluted with water (25 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over sodium sulphate and evaporated *in vacuo* to give a crude solid (as a 2:1 mixture of the -OMe and free-OH **7b**).

The crude solid (~ 0.44 mmol) was next dissolved in acetic acid (3.0 mL), to which 48% (wt) aqueous hydrobromic acid (0.3 mL) was added dropwise. The resulting mixture was stirred overnight at room temperature and evaporated *in vacuo*. The crude residue was diluted with water (25 mL) and ethyl acetate (20 mL) and adjusted to pH 7 with solid potassium carbonate. The layers were separated and the aqueous layer extracted with ethyl acetate (2 x 10 mL). The combined organic layers were then dried over sodium sulphate, filtered, and the resulting filtrate evaporated *in vacuo* to give compound **7b** (96 mg, 44%) as a viscous gum that was used directly in the subsequent step. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.55 (s, 1H), 8.53 (s, 1H), 8.09 (s, 1H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.5 Hz, 2H), 7.38 (m, 2H), 7.08 (m, 1H), 6.41 (s, 1H), 2.98 (m, 2H), 1.65 (m, 2H), 0.85 (m, 3H); ^{19}F-NMR (282 MHz, DMSO-d_6) δ -114.1, -119.7; LCMS *m/z* calcd. for $C_{23}H_{21}ClF_2N_3O_3S$ (MH^+): 492.0; found: 491.9 (ESI+).

***N*-(3-(5-(4-Chlorophenyl)-1*H*-pyrrolo[2,3-*b*]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (8b, PLX4032).** 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (95 mg, 0.42 mmol) in 0.04 mL water was added to a solution of **7b** (130 mg, 0.26 mmol) in 1,4-dioxane (1.0 mL) at room temperature. The reaction mixture was irradiated with microwaves at 100 °C for 10 min, then quenched with saturated sodium bicarbonate (10 mL). The organic volatiles were removed under vacuum and the residue diluted with water and extracted with THF/ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude solid was purified by flash chromatography on silica gel to afford PLX4032 (**8b**) (119 mg, 92%) as an off-white crystalline solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 9.75 (s, 1H), 8.71 (s, 1H), 8.63 (bs, 1H), 8.25 (bs, 1H), 7.78 (d, *J* = 8.5 Hz, 2H), 7.60 (m, 1H), 7.55 (d, *J* = 8.5 Hz, 2H), 7.27 (m, 1H), 3.12 (m, 2H), 1.74 (m, 2 H), 0.95 (m, 3H); ^{19}F-NMR (282 MHz, DMSO-d_6) δ -115.6, -120.6; LCMS *m/z* calcd. for $C_{23}H_{19}ClF_2N_3O_3S$ (MH^+): 490.0; found: 489.9 (ESI+).