Supplementary data

Structure-activity relationship study of bone morphogenetic protein (BMP) signaling inhibitors

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Chemistry Material and Methods. Unless otherwise noted, all reagents and solvents were purchased from commercial sources and used without further purification. Compound **1** was purchased from Calbiochem. All palladium reactions were conducted under an argon atmosphere. The ^{1}H NMR spectra were obtained using a Bruker 400 MHz, Varian 400 MHz or 500 MHz spectrometer. All ^{1}H NMR spectra are reported in δ units ppm and are reference to tetramethylsilane (TMS) if conducted in $CDCl_3$ or to the central line of the quintet at 2.49 ppm for samples in DMSO-d_6. Coupling constants (J values) are reported in Hz. Column chromatography was performed on silica gel (Merck, grade 60, 230-400 mesh) or utilizing a CombiFlash Sg 100c separation system (ISCO) with Luknova disposable silica gel columns (ISCO). High-resolution mass spectra were obtained by using a IonSpec 4.7 Tesla FTMS. All melting points were taken in glass capillary tubes on a Mel-Temp® apparatus and are uncorrected.

General Procedure for the synthesis of substituted pyrazolo[1,5-a]pyrimidine derivatives (Method A). Exemplified for the synthesis of 6-(4-Methoxyphenyl)-3-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine (38) and 6-[4-(2-morpholin-4-ylethoxy)phenyl]-3-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine (39): To a solution of 4-pyridylacetonitrile hydrochloride (155 mg, 1 mmol) in DMF (0.5 mL) was added dimethylformamide dimethylacetal (2 mL) and triethylamine (0.15 mL, 1.1 eq). The mixture was heated at 110 ºC for 9 hours and then concentrated to give 3-

dimethylamino-2-pyridin-4-ylacrylonitrile (**3**, Ar = 4-Py) as dark brown crystals and used for the next step without further purification.

Hydrazine hydrobromide (452 mg) was added to **3** (Ar = 4-Py, 1 mmol) in mixture of EtOH (2 mL) and H_2O (0.3 mL). The mixture was heated at 110 ºC for 5 h. The reaction mixture was diluted with H_2O (0.5 mL) and then Na_2CO_3 was added to until the mixture was basic. The mixture was extracted with EtOAc/EtOH (3:1, 3 x 2 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated to get 143 mg (89% yield) of 4-pyridin-4-yl-1H-pyrazol-3-ylamine (**4a**, Ar = 4-Py) as a red solid.

A solution of **4a** (Ar = 4-Py) (143 mg, 0.89 mmol) and 2-(4-methoxyphenyl)malondialdehyde (159 mg, 0.89 mmol) in EtOH (1.5 mL) and acetic acid (1.0 mL) was heated at 110 ºC for 6 h. Upon cooling the reaction mixture, **38** was obtained as light tan crystals (106 mg, 40%). ^{1}H NMR (DMSO-d_6) δ 9.72 (d, *J* = 2.2 Hz, 1H), 9.31 (d, *J* = 2.2 Hz, 1H), 9.29 (s, 1H), 8.86 (d, *J* = 6.6 Hz, 2H), 8.73 (d, *J* = 6.6 Hz, 2H), 7.90 (d, *J* = 8.8 Hz, 2H), 7.15 (d, *J* = 8.8 Hz, 2H), 3.85 (s, 3H); HRMS *m/z* 303.1240 (calc for $C_{18}H_{15}N_4O$, MH^+, 303.1241).

A mixture of **38** (197 mg, 0.65 mmol) in acetic acid containing HBr (45% w/w, 2 mL) was heated in a reaction microwave at 130 ºC for 10 min. The reaction mixture was titurated with EtOAc and then filtrated to give **6** (R_1 = 4-Py, R_2 = 4-OH-Ph, 212 mg, 88%) as a yellow solid.

A mixture of **6** (R_1 = 4-Py, R_2 = 4-OH-Ph, 100 mg, 0.35 mmol), 4-(2-chloroethyl)morpholine hydrogen chloride (116 mg, 0.525 mmol), Cs_2CO_3 (570 mg, 1.75 mmol) and a catalytic amount of NaI in DMF (2 mL) was heated at 60 ºC for 24 h. The reaction mixture was concentrated and the resulting residue was purified by column chromatography using initially dichloromethane/MeOH as eluent and then dichloromethane/MeOH/Et_3N to give 70 mg, (50% yield) of **39** as yellow solid. ^{1}H NMR (DMSO-d6) δ 9.73 (d, *J* = 2.2 Hz, 1H), 9.31 (d, *J* = 2.2 Hz, 1H), 9.27 (s, 1H), 8.85 (d, *J* = 6.8 Hz, 2H), 8.69 (d, *J* = 6.8 Hz, 2H), 7.95 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 2H), 4.47 (t, *J* = 4.6 Hz, 2H), 3.8 – 3.9 (m, 4H), 3.5 – 3.6 (m, 6H); HRMS *m/z* 402.1925 (calc for $C_{23}H_{24}N_5O_2$, MH^+, 402.1919).

Alternative phenol alkylation procedure: Exemplified for the synthesis of 6-{4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-3-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine (41): A reaction microwave vessel was charged with **6** (R_1 = 4-Py, R_2 = 4-OH-Ph, 100 mg, 0.35 mmol), dichloroethane (0.2 mL), K_2CO_3 (240 mg) and DMF (2 mL). The mixture was heated in the microwave reactor at 140 ºC for 5 min and then the reaction mixture was filtered. The filtrate was concentrated and then introduced into a reaction microwave vessel along with N-methylpiperazine (0.03 mL), a catalytic amount of NaI and DMF (1 mL). The mixture was heated in the microwave reactor at 150 ºC for 15 min and then concentrated. The resulting residue was purified by column chromatography initially using dichloromethane/MeOH as eluent and then dichloromethane/MeOH/Et_3N to give 50 mg (34% yield) of **41** as yellow crystals. ^{1}H NMR (DMSO-d_6) δ 9.55 (d, *J* = 2.2 Hz, 1H), 9.15 (d, *J* = 2.2 Hz, 1H), 8.99 (s, 1H), 8.61 (dd, *J* = 4.6, 1.6 Hz, 2H), 8.18 (dd, *J* = 4.6, 1.6 Hz, 2H), 7.85 (d, *J* = 8.8 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 2H), 4.17 (t, *J* = 5.8 Hz, 2H), 2.74 (t, *J* = 5.8 Hz, 2H), 2.28 – 2.52 (m, 8H), 2.22 (s, 3H); HRMS *m/z* 415.2241 (calc for $C_{24}H_{27}N_6O$, MH^+, 415.2243).

The following are other compounds prepared using Method A:

6-[4-(N, N-diethylethoxy)phenyl]-3-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine (40): ^{1}H NMR (DMSO-d_6) δ 9.71 (d, *J* = 2.2 Hz, 1H), 9.30 (d, *J* = 2.2 Hz, 1H), 9.24 (s, 1H), 8.82 (d, *J* = 5.9 Hz, 2H), 8.63 (d, *J* = 5.9 Hz, 2H), 7.94 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 4.42 (t, *J* = 4.5 Hz , 2H), 3.29 – 3.58 (m, 6H), 1.27 (t, *J* = 7.1 Hz, 6H); HRMS *m/z* 388.2132 (calc for $C_{23}H_{26}N_5O$, MH^+, 388.2131).

6-{3-[2-(4-Methylpiperazin-1-yl)ethoxy]phenyl}-3-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine (42): ^{1}H NMR (DMSO-d_6) δ 9.66 (d, *J* = 2.2 Hz, 1H), 9.19 (d, *J* = 2.2 Hz, 1H), 9.03 (s, 1H), 8.62 (d, *J* = 6.2 Hz, 2H), 8.19 (d, *J* = 6.2 Hz, 2H), 7.45 – 7.50 (m, 3H), 7.05 (dt, *J* = 6.6, 2.4 Hz, 1H), 4.22 (t, *J* = 5.8 Hz, 2H), 2.74 (t, *J* = 5.8 Hz, 2H), 2.29 – 2.52 (m, 8H), 2.17 (s, 3H); HRMS *m/z* 415.2241 (calc for $C_{24}H_{27}N_6O$, MH^+, 415.2243).

6-[4-(2-Piperidin-1-ylethoxy)phenyl]pyrazolo[1,5-a]pyrimidine (44): ^{1}H NMR (DMSO-d_6) δ 9.45 (d, *J* = 2.2 Hz, 1H), 9.00 (d, *J* = 2.2 Hz, 1H), 8.32 (d, *J* = 2.2 Hz, 1H), 7.87 (d, *J* = 7.0 Hz, 2H), 7.19 (d, *J* = 7.0 Hz, 2H), 6.85 (d, *J* = 2.2 Hz, 1H), 4.24 (t, *J* = 5.9 Hz, 2H), 2.79 (t, *J* = 5.9 Hz, 2H), 2.50 – 2.58 (m, 4H), 1.55 – 1.65 (m, 4H), 1.42 – 1.54 (m, 2H).

6-[4-(2-Piperidin-1-ylethoxy)phenyl]-3-pyridin-3-yl-pyrazolo[1,5-a]pyrimidine (45): ^{1}H NMR (DMSO-d_6) δ 9.51 (d, *J* = 2.2 Hz, 1H), 9.38 (d, *J* = 1.5 Hz, 1H), 9.10 (d, *J* = 2.2 Hz, 1H), 8.90 (s, 1H), 8.54 (dt, *J* =8.4, 1.5 Hz, 1H), 8.48 (dd, *J* =4.7, 1.5 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 2H), 7.50 (dd, *J* =8.2, 5.0 Hz, 1H), 7.11 (d, *J* = 8.8 Hz, 2H), 4.16 (t, *J* = 6.0 Hz, 2H), 2.70 (t, *J* = 5.9 Hz, 2H), 2.46 – 2.48 (m, 4H), 1.52 – 1.56 (m, 4H), 1.35 – 1.45 (m, 2H).

3-Phenyl-6-[4-(2-piperidin-1-ylethoxy)phenyl]pyrazolo[1,5-a]pyrimidine (46): ^{1}H NMR (DMSO-d_6) δ 9.64 (d, *J* = 2.2 Hz, 1H), 9.23 (d, *J* = 2.2 Hz, 1H), 8.80 (s, 1H), 8.39 (d, *J* = 8.8 Hz, 2H), 7.87 (d, *J* = 8.8 Hz, 2H), 7.65 (t, *J* = 7.8 Hz, 2H), 7.48 (t, *J* = 6.8 Hz, 1H), 7.30 (d, *J* = 8.8 Hz, 2H), 4.35 (t, *J* = 5.9 Hz, 2H), 2.90 (t, *J* = 5.9 Hz, 2H), 2.64 – 2.69 (m, 4H), 1.70 – 1.78 (m, 4H), 1.58 – 1.66 (m, 2H).

4-(6-{4-[2-(4-Methylpiperazin-1-yl)ethoxy]phenyl}pyrazolo[1,5-a]pyrimidin-3-yl)quinoline (53): ^{1}H NMR (DMSO-d_6) δ 9.60 (d, *J* = 2.1 Hz, 1H), 9.07 (d, *J* = 2.1 Hz, 1H), 8.98 (d, *J* = 4.6 Hz, 1H), 8.74 (s, 1H), 8.22 (d, *J* = 8.3 Hz, 1H), 8.12 (d, *J* = 8.3 Hz, 1H), 7.81 – 7.87 (m, 4H), 7.64 (t, *J* = 7.0 Hz, 1H), 7.12 (d, *J* = 8.7 Hz, 2H), 4.17 (t, *J* = 5.7 Hz, 2H), 2.73 (t, *J* = 5.7 Hz, 2H), 2.50 – 2.52 (m, 4H), 2.29 – 2.35 (m, 4H), 2.17 (s, 3H); HRMS *m/z* 465.2397 (calc for $C_{28}H_{29}N_6O$, MH^+, 465.2401).

4-{6-[4-(2-Piperidin-1-ylethoxy)phenyl]pyrazolo[1,5-a]pyrimidin-3-yl}quinoline (54): ^{1}H NMR ($CDCl_3$) δ 9.03 (d, *J* = 4.5 Hz, 1H), 8.93 (d, *J* = 2.2 Hz, 1H), 8.87 (d, *J* = 2.2 Hz, 1H), 8.51 (s, 1H), 8.21 (dd, *J* = 8.5, 2.2 Hz, 2H), 7.81 (dd, *J* = 7.0, 1.3 Hz, 1H), 7.77 (d, *J* = 4.5 Hz, 1H), 7.63 (dd, *J* = 7.0, 1.3 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.12 (d, *J* = 8.8 Hz, 1H), 4.23 (t, *J* = 6.0 Hz, 2H), 2.87 (t, *J* = 6.0 Hz, 2H), 2.56 – 2.59 (m, 4H), 1.63 – 1.87 (m, 4H), 1.48 – 1.54 (m, 2H); HRMS *m/z* 450.2288 (calc for $C_{28}H_{28}N_5O$, MH^+, 450.2292).

4-Pyrazolo[1,5-a]pyrimidin-3-ylquinoline (55): ^{1}H NMR (DMSO-d_6) δ 9.45 (dd, *J* = 7.0, 1.7 Hz, 1H), 9.26 (d, *J* = 5.7 Hz, 1H), 9.01 (s, 1H), 8.87 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.58 (d, *J* = 8.4 Hz, 1H), 8.38 (d, *J* = 5.7 Hz, 1H), 8.28 (d, *J* = 8.4 Hz, 1H), 8.14 (dd, *J* = 8.4, 7.2 Hz, 1H), 7.92 (dd, *J* = 8.4, 7.2 Hz, 1H), 7.40 (dd, *J* = 87.0, 4.2 Hz, 1H); HRMS *m/z* 247.0978 (calc for $C_{15}H_{11}N_4$, MH^+, 247.0978).

4-(6-Phenylpyrazolo[1,5-a]pyrimidin-3-yl)quinoline (56): ^{1}H NMR (DMSO-d_6) δ 9.73 (d, *J* = 2.2 Hz, 1H), 9.16 (d, *J* = 2.2 Hz, 1H), 9.08 (d, *J* = 4.8 Hz, 1H), 8.85 (s, 1H), 8.34 (d, *J* = 8.3 Hz, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 8.00 (d, *J* = 4.8 Hz, 1H), 7.90 – 9.96 (m, 3H), 7.74 (t, *J* = 7.2 Hz, 1H), 7.48 – 7.61 (m, 3H); HRMS *m/z* 323.1291 (calc for $C_{21}H_{15}N_4$, MH^+, 323.1291).

4-[6-(4-Hydroxyphenyl)pyrazolo[1,5-a]pyrimidin-3-yl]quinoline (57): ^{1}H NMR (DMSO-d_6) δ 9.82 (s, 1H), 9.54 (d, *J* = 2.2 Hz, 1H), 9.04 (d, *J* = 2.2 Hz, 1H), 8.98 (d, *J* = 4.5 Hz, 1H), 8.72 (s, 1H), 8.22 (d, *J* = 8.5 Hz, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 7.73 – 7.82 (m, 4H), 7.64 (td, *J* = 8.2, 1.2 Hz, 1H), 6.95 (d, *J* = 8.6 Hz, 2H); HRMS *m/z* 339.1240 (calc for $C_{21}H_{15}N_4O$, MH^+, 339.1242).

General Procedure for the synthesis of substituted pyrazolo[1,5-a]pyrimidine derivatives (Method B). Synthesis of 4-[6-(4-Piperazin-1-ylphenyl)pyrazolo[1,5-a]pyrimidin-3-yl]quinoline (13): 4-Quinolin-4-yl-1H-pyrazol-3-ylamine (**10**, 210 mg, 1.0 mmol), prepared utilizing Method A, and 2-(4-bromophenyl)malondialdehyde (230 mg, 1.0 mmol) in a mixture of EtOH (1.5 mL) and acetic acid (1 mL) was heated in a microwave reactor at 170 ºC for 5 min. The reaction mixture was allowed to cool and then **11** (220 mg, 54% yield) was obtained by filtration as yellow crystals.

N-Cbz-piperazine, (0.15 mL), **11** (100 mg, 0.25 mmol), $Pd_2(dba)_3$ (10 mg), (2-biphenylyl)di-*tert*-butylphosphine (6 mg), and KO-*t*-Bu (42 mg) in dichloroethane (2 mL) was heated at 100 ºC under a nitrogen atmosphere for 20 h. The reaction was purified by column chromatography using CH_2Cl_2/EtOAc to give **12** (20 mg, 15%). Next, 5% Pd/C and **12** (20 mg, 0.37 mmol) in a mixture of MeOH (3 mL) and CH_2Cl_2 (2 mL) was de-gassed and then replaced under an atmosphere of hydrogen at rt for 4 h. The reaction mixture was filtrated and concentrated to give **13** (13 mg, 86%). ^{1}H NMR (DMSO-d_6) δ 9.75 (d, *J* = 2.2 Hz, 1H), 9.40 (br.s, 1H), 9.29 (d, *J* = 5.9 Hz, 1H), 9.28 (d, *J* = 2.2 Hz, 1H), 9.07 (s, 1H), 8.70 (d, *J* = 8.4 Hz, 1H), 8.51 (d, *J* = 5.9 Hz, 1H), 8.47 (d, *J* = 8.4 Hz, 1H), 8.21 (t, *J* = 7.6 Hz, 1H), 7.99 (t, *J* = 7.6 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 3.51 – 3.58 (m, 4H), 3.20 – 3.30 (m, 4H).

General Procedure for the synthesis of substituted pyrazolo[1,5-a]pyrimidine derivatives (Method C). Synthesis of 4-[6-(4-Piperazin-1-ylphenyl)pyrazolo[1,5-a]pyrimidin-3-yl]quinoline hydrochloride salt (13·HCl): A mixture of 2-bromomalondialdehyde (1.5 g, 10 mmol) and 1H-pyrazol-3-ylamine (**4b**, 0.83 g, 10 mmol) in a mixture of EtOH (15 mL) and acetic acid (5 mL) was heated at 80 ºC for 1.5 h. The reaction mixture was concentrated and the resulting residue purified by column chromatography using hexane/EtOAc (5:1) to give **15a** (1.15 g, 58% yield) as light yellow crystals.

The mixture of **15a** (0.87 g, 4.39 mmol), 4-[4-(*tert*-butoxycarbonyl)piperazin-1-yl]phenylboronic acid pinacol ester (1.7 g, 4.39 mmol), $Pd(Ph_3P)_4$ (0.5 g, 0.439 mmol), K_2CO_3 (1.82 g, 13.17), 1,4-dioxane (15 mL) and H_2O (5 mL) was heated at 110 ºC under a nitrogen atmosphere for 5 h in a sealed vial. The reaction mixture was concentrated and the residue was purified by column chromatography using CH_2Cl_2/EtOAc to give **16** (1.4 g, 86% yield). ^{1}H NMR ($CDCl_3$) δ 8.82 (dd, *J* = 2.2, 0.7 Hz, 1H), 8.77 (d, *J* = 2.2 Hz, 1H), 8.16 (d, *J* = 2.2 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.75 (dd, *J* = 2.2, 0.7 Hz, 1H), 3.63 – 3.67 (m, 4H), 3.25 – 3.28 (m, 4H), 1.53 (s, 9H).

To a solution of **16** (1.95 g, 1.2 mmol) in CH_2Cl_2 (20 mL) at 0 ºC was drop-wise added NBS (225 mg, 1.05 eq) in CH_2Cl_2 (10 mL). The resulting mixture was then stirred at 0 ºC for 5h and then washed with H_2O (6 mL x 2). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated to **17a** (1.36 g, 79% yield) as off-white crystals. ^{1}H NMR ($CDCl_3$) δ 8.72 (d, *J* = 2.2 Hz, 1H), 8.66 (d, *J* = 2.2 Hz, 1H), 8.05 (s, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 3.52 – 3.58 (m, 4H), 3.15 – 3.20 (m, 4H), 1.43 (s, 9H).

A microwave reaction vial was charged with **17a** (240 mg, 0.52 mmol), 4-quinoline boronic acid (135 mg, 0.78 mmol), $Pd_2(dba)_3$ (18 mg), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (18 mg), K_3PO_4 (240 mg), and *n*-BuOH (4 mL). The mixture was de-gassed, placed under an atmosphere of nitrogen and heated in a microwave reactor at 150 ºC for 15 min. The reaction mixture was filtrated and washed with CH_2Cl_2. The filtrate was concentrated and the resulting residue purified by column chromatography to give **18a** (141 mg, 46% yield) as light yellow crystals. ^{1}H NMR ($CDCl_3$) δ 9.17 (d, *J* = 4.5 Hz, 1H), 9.07 (d, *J* = 2.2 Hz, 1H), 9.02 (d, *J* = 2.2 Hz, 1H), 8.68 (s, 1H), 8.30 – 8.36 (m, 2H), 7.95 (dd, *J* = 7.0, 1.3 Hz, 1H), 7.92 (d, *J* = 4.5 Hz, 1H), 7.68 – 7.76 (m, 3H), 7.24 (d, *J* = 8.8 Hz, 2H), 3.74 – 3.82 (m, 4H), 3.40 – 3.48 (m, 4H), 1.66 (s, 9H).

A mixture of **18a** (640 mg, 1.26 mmol) in MeOH (10 mL) and HCl in 1,4-dioxane (4M, 6.3 mL) was stirred at rt for 24 h before being concentrated to dryness. The residue was washed with a small amount of MeOH to give **13·HCl** (550 mg, 98% yield) as a yellow solid. ^{1}H NMR (DMSO-d_6) δ 9.75 (d, *J* = 2.2 Hz, 1H), 9.40 (br.s, 1H), 9.29 (d, *J* = 5.9 Hz, 1H), 9.28 (d, *J* = 2.2 Hz, 1H), 9.07 (s, 1H), 8.70 (d, *J* = 8.4 Hz, 1H), 8.51 (d, *J* = 5.9 Hz, 1H), 8.47 (d, *J* = 8.4 Hz, 1H), 8.21 (t, *J* = 7.6 Hz, 1H), 7.99 (t, *J* = 7.6 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 8.8 Hz, 2H), 3.51 – 3.58 (m, 4H), 3.20 – 3.30 (m, 4H); HRMS *m/z* 407.1979 (calc for $C_{25}H_{23}N_6$, MH^+, 407.1979).

The following are other compounds prepared using Method C:

2-Methyl-6-{4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-3-pyridin-4-yl-pyrazolo[1,5-a]pyrimidine (43): ^{1}H NMR ($CDCl_3$) δ 8.82 (d, *J* = 2.2 Hz, 1H), 8.76 (d, *J* = 2.2 Hz, 1H), 8.72 (dd, *J* = 4.6, 1.5 Hz, 2H), 7.83 (dd, *J* = 4.6, 1.5 Hz, 2H), 7.55 (d, *J* = 8.7 Hz, 2H), 7.10 (d, *J* = 8.7 Hz, 2H), 4.21 (t, *J* = 5.8 Hz, 2H), 2.90 (t, *J* = 5.8 Hz, 2H), 2.76 (s, 3H), 2.60 – 2.69 (m, 2H), 2.40 – 2.53 (m, 2H), 2.34 (s, 3H).

6-{4-[2-(4-methylpiperazin-1-yl)ethoxy]phenyl}-3-(3-fluoropyridin-4-yl)-pyrazolo[1,5-a]pyrimidine (47): ^{1}H NMR (DMSO-d_6) δ 9.61 (d, *J* = 2.2 Hz, 1H), 9.20 (d, *J* = 2.2 Hz, 1H), 8.76 (d, *J* = 3.3 Hz, 1H), 8.66 (d, *J* = 3.3 Hz, 1H), 8.61 (dd, *J* = 6.8, 5.2 Hz, 2H), 8.53 (dd, *J* = 5.2, 1.1 Hz, 1H), 7.87 (d, *J* = 8.7 Hz, 2H), 7.13 (d, *J* = 8.7 Hz, 2H), 4.17 (t, *J* = 5.8 Hz, 2H), 2.72 (t, *J* = 5.8 Hz, 2H), 2.51 – 2.52 (m, 4H), 2.29 – 2.34 (m, 4H), 2.16 (s, 3H); HRMS *m/z* 433.2147 (calc for $C_{24}H_{26}N_6OF$, MH^+, 433.2151).

6-[6-(4-Methoxyphenyl)pyrazolo[1,5-a]pyrimidin-3-yl]quinoline (48): Yield: 86%; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.89-8.88 (m, 2H), 8.83 (d, *J* = 2.5 Hz, 1H), 8.59 (m, 2H), 8.44 (dd, *J* = 2.0, 9.0 Hz, 1H), 8.26 (d, *J* = 8.0 Hz, 1H), 8.20 (d, *J* = 9.0 Hz, 1H), 7.57 (d, *J* = 9.0 Hz, 2H), 7.42 (dd, *J* = 3.5, 8.5 Hz, 1H), 7.09 (d, *J* = 9.0 Hz, 2H), 3.90 (s, 3H); mp 254-255 ºC.

8-[6-(4-Methoxyphenyl)pyrazolo[1,5-a]pyrimidin-3-yl]quinoline (49): Yield: 19%; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.22 (s, 1H), 9.00 (dd, *J* = 2.0, 4.5 Hz, 1H), 8.87 (d, *J* =

2.0 Hz, 1H), 8.83 (d, *J* = 2.5 Hz, 1H), 8.60 (dd, *J* = 2.0, 8.5 Hz, 1H), 8.23 (dd, *J* = 2.0, 8.5 Hz, 1H), 7.79 (dd, *J* = 1.5, 7.5 Hz, 1H), 7.70 (t, *J* = 2.5 Hz, 1H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.46 (dd, *J* = 4.0, 8.5 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 2H), 3.89 (s, 3H); mp 184-185 ºC.

5-[6-(4-Methoxyphenyl)pyrazolo[1,5-a]pyrimidin-3-yl]quinoline (50): Yield: 70%; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.96 (dd, *J* = 2.0, 4.0 Hz, 1H), 8.89 (d, *J* = 2.0 Hz, 1H), 8.78 (d, *J* = 2.5 Hz, 1H), 8.40-8.38 (m, 1H), 8.36 (s, 1H), 8.16 (dd, *J* = 1.5, 8.5 Hz, 1H), 7.85-7.78 (m, 2H), 7.56 (d, *J* = 9.0 Hz, 2H), 7.41 (dd, *J* = 4.0, 8.5 Hz, 1H), 7.08 (d, *J* = 9.0 Hz, 2H), 3.89 (s, 3H); mp 209-210 ºC; HRMS *m/z* 353.1397 (calc for $C_{22}H_{17}N_4O$, MH^+, 353.1396).

3-[6-(4-Methoxyphenyl)pyrazolo[1,5-a]pyrimidin-3-yl]quinoline (51): Yield: 92%; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.58 (d, *J*= 2.0 Hz, 1H), 8.92 (d, *J*= 2.0 Hz, 1H), 8.90 (d, *J*= 2.0 Hz, 1H), 8.85 (d, *J*= 2.5 Hz, 1H), 8.63 (s, 1H), 8.13 (d, *J*= 8.5 Hz, 1H), 7.93 (dd, *J*= 1.0, 8.0 Hz, 1H), 7.71-7.67 (m, 1H), 7.59-7.57 (m, 3H), 7.09 (d, *J*= 9.0 Hz, 2H), 3.90 (s, 3H); mp 218-220 ºC.

4-[6-(4-Methoxyphenyl)pyrazolo[1,5-a]pyrimidin-3-yl]quinoline (52): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.02 (d, *J* = 4.4 Hz, 1H), 8.92 (d, *J* = 2.0 Hz, 1H), 8.86 (d, *J* = 2.0 Hz, 1H), 8.51 (s, 1H), 8.23-8.19 (m, 2H), 7.78-7.75 (m, 2H), 7.61-7.57 (m, 3H), 7.10 (d, *J* = 8.8 Hz, 2H), 3.91 (s, 3H); mp 213-214 ºC; HRMS *m/z* 353.1397 (calc for $C_{22}H_{17}N_4O$, MH^+, 353.1394).

4-[6-(3-Piperazin-1-ylphenyl)pyrazolo[1,5-a]pyrimidin-3-yl]quinoline (58): ^{1}H NMR ($CDCl_3$) δ 9.14 (d, *J* = 5.7 Hz, 1H), 9.00 (d, *J* = 1.7 Hz, 1H), 8.33 (d, *J* = 2.0 Hz, 1H), 8.27 (d, *J* = 8.6 Hz, 1H), 8.10 – 8.19 (m, 3H), 8.05 (d, *J* = 5.7 Hz, 1H), 7.89 (td, *J* = 7.8, 1.0 Hz, 1H), 7.65 (d, *J* = 8.6 Hz, 1H), 7.46 – 7.52 (m, 2H), 6.33 (d, *J* = 2.0 Hz, 1H), 3.77 – 3.84 (m, 4H), 3.50 – 3.53 (m, 4H); HRMS *m/z* 407.1979 (calc for $C_{25}H_{23}N_6$, MH^+, 407.1979).

7-Chloro-4-[6-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidin-3-yl]quinoline (59): Yield: 25%; ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.60 (d, *J* = 2.0 Hz, 1H), 9.07 (d, *J* = 2.5 Hz, 1H), 9.00 (d, *J* = 5.0 Hz, 1H), 8.73 (s, 1H), 8.24 (d, *J* = 9.0 Hz, 1H), 8.16 (d, *J* = 2.0 Hz, 1H), 7.86 (d, *J* = 9.0 Hz, 2H), 7.84 (d, *J* = 4.5 Hz, 1H), 7.65 (dd, *J* = 3.0, 9.0 Hz, 1H), 7.12 (d, *J* = 9.0 Hz, 2H), 3.83 (s, 3H); mp > 255 ºC; HRMS *m/z* 387.1007 (calc for $C_{22}H_{16}N_4OCl$, MH^+, 387.1011).

7-Chloro-4-[6-(4-piperazin-1-ylphenyl)pyrazolo[1,5-a]pyrimidin-3-yl]quinoline (60): ^{1}H NMR (DMSO-d_6) δ 9.70 (d, *J* = 2.2 Hz, 1H), 9.12 – 9.20 (m, 3H), 8.90 (s, 1H), 8.47 (d, *J* = 9.2 Hz, 1H), 8.31 (s, 1H), 8.16 – 8.17 (m, 1H), 7.81 – 7.88 (m, 3H), 7.19 (d, *J* = 8.9 Hz, 2H), 3.5 – 3.58 (m, 4H), 3.2 – 3.3 (m, 4H); HRMS *m/z* 441.1589 (calc for $C_{25}H_{22}N_6Cl$, MH^+, 441.1592).

Synthesis of substituted pyrrolo[1,2-a]pyrimidine derivatives (Method D).

4-Bromo-2-trichloroacetylpyrrole (20): Bromine (2.12 g, 10 mmol) was added dropwise to a stirred solution of 2-trichloroacetylpyrrole (**19**, 1.71 g, 10.7 mmol) in $CHCl_3$ (15 mL) at 0 ºC. The mixture was then stirred at 0 ºC for 20 min and at rt for 5 min before quenched with water. The organic layer was washed with sat. $NaHCO_3$ and water, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on silica gel using hexane/ethyl acetate (90:10 to 75:25) to give **20** as a white solid (1.65 g, 57%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.21 (br. s, 1H), 7.35 (dd, *J* =1.5, 2.5 Hz, 1H), 7.15 (dd, *J* =1.5, 2.5 Hz, 1H); mp 135-137 ºC (lit.,[16] 136-138 ºC).

4-Bromo-5-nitro-2-trichloroacetylpyrrole (**21**): A solution of 4-bromo-2-trichloroacetylpyrrole (**20**, 873 mg, 3.0 mmol) in Ac_2O (7 mL) was cooled to 40 ºC and treated dropwise with 70% nitric acid (0.24 mL, 3.0 mmol). The mixture was allowed to warm up to rt over 2 h before quenched with ice-water, and then extracted with ethyl acetate. The organic layer was washed with sat. $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel using CH_2Cl_2/MeOH (95:5) to give **21** as a pale yellow solid (404 mg, 40%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38 (s, 1H); mp 125-126 ºC.

Methyl 4-bromo-5-nitro-1*H*-pyrrole-2-carboxylate (22): 4-Bromo-5-nitro-2-trichloroacetylpyrrole (**21**, 80 mg, 0.24 mmol) was added to 0.5 M MeONa in MeOH (1 mL) at rt. The reaction mixture was stirred at rt for 2 h, then quenched with H_2SO_4 at 0 ºC, followed by addition of ice-water, and extracted with ethyl acetate. The organic layer was washed with water, dried (Na_2SO_4) and concentrated to give **22** as a yellow solid (60 mg, 99%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 6.66 (s, 1H), 3.67 (s, 3H); mp >255 ºC.

Methyl 5-nitro-4-quinolin-4-yl-1*H*-pyrrole-2-carboxylate (23): A mixture of methyl 4-bromo-5-nitro-1*H*-pyrrole-2-carboxylate (**22**, 124 mg, 0.5 mmol), quinoline-4-boronic acid (174 mg, 1.0 mmol), Pd (PPh_3)$_4$ (116 mg, 0.1 mmol), 2.0 M Na_2CO_3 (0.5 mL), and 1,4-dioxane (6 mL) was stirred overnight at 101 ºC, then cooled to rt, diluted with water, and extracted with ethyl acetate. The organic phase was washed with water, dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel using CH_2Cl_2/MeOH (95:5) to give **23** as a yellow solid (90 mg, 60%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 14.5 (br.s, 1H), 8.95 (d, J = 4.5 Hz, 1H), 8.10 (d, J = 3.5 Hz, 1H), 7.79 (m, 1H), 7.68 (d, J = 3.5 Hz, 1H), 7.56 (m, 1H), 7.53 (d, J = 4.5 Hz, 1H), 7.07 (s, 1H), 3.89 (s, 3H); mp 204-205 ºC.

Methyl 3-(4-methoxyphenyl)-8-quinolin-4-yl-pyrrolo[1,2-a]pyrimidine-6-carboxylate (25): A mixture of methyl 5-nitro-4-quinolin-4-yl-1*H*-pyrrole-2-carboxylate (**23**, 90 mg, 0.3 mmol), Pd/C (5%, 45 mg), and MeOH (15 ML) was stirred under argon for 5 min, then under hydrogen for 40 min before removal of the catalyst by filtration through celite. To the orange color filtrate was added 2-(4-methoxyphenyl)malondialdehyde (54 mg, 0.3 mmol) followed by AcOH (2 mL). The resulting reaction mixture was stirred overnight at 82 ºC, then cooled to rt, quenched with sat. $NaHCO_3$, and extracted with ethyl acetate and CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by column chromatography on silica gel using CH_2Cl_2/MeOH (90:10) to give **25** as a yellow solid (90 mg, 73%). ^{1}H NMR (DMSO-d_6, 500 MHz) δ 9.80 (d, J = 3.0 Hz, 1H), 8.97 (d, J = 5.0 Hz, 1H), 8.87 (d, J = 3.0 Hz, 1H), 8.10 (m, 1H), 8.04 (s, 1H), 7.80 (m, 1H), 7.75 (d, J = 5.0 Hz, 1H), 7.75 (d, J = 8.5 Hz, 2H), 7.61 (m, 1H), 7.15 (d, J = 8.5 Hz, 2H), 3.94 (s, 3H), 3.84 (s, 3H); mp 230-231 ºC.

4-[3-(4-Methoxyphenyl)pyrrolo[1,2-a]pyrimidin-8-yl]quinoline (26): Conc. H_2SO_4 (1 mL) was added slowly to 1.5 mL of H_2O at 0 ºC and the resulting solution was added to **25** (10 mg, 0.025 mmol). The mixture was heated to 110 ºC and stirred for 4 h before cooled down to rt, then quenched slowly with saturated $NaHCO_3$, and extracted with ethyl acetate/MeOH (95:5). The combined organic layers were concentrated and the residue was purified by column chromatography on silica gel using CH_2Cl_2/MeOH (95:5) as eluant to give **26** as a brown solid (8 mg, 91%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.98 (d, J = 4.4 Hz, 1H), 8.48 (d, J = 2.0 Hz, 1H), 8.40 (d, J = 2.8 Hz, 1H), 8.27 (d, J = 8.4 Hz,

1H), 8.19 (d, *J* = 8.4 Hz, 1H), 7.77-7.74 (m, 2H), 7.72-7.52 (m, 3H), 7.45 (d, *J* = 3.2 Hz, 1H), 7.34 (d, *J* = 2.8 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 2H), 3.90 (s, 3H); mp 144-145 ºC.

4-(8-Quinolin-4-yl-pyrrolo[1,2-*a*]pyrimidin-3-yl)-phenol (27): Conc. H_2SO_4 (2 mL) was added slowly to 3 mL of H_2O at 0 ºC and the resulting solution was added to **25** (41 mg, 0.1 mmol). The mixture was heated to 110 ºC and stirred for 2 days before cooled down to rt, then quenched slowly with sat. $NaHCO_3$, and extracted with ethyl acetate/MeOH (95:5). The combined organic layers were concentrated and the residue was purified by column chromatography on silica gel using CH_2Cl_2/MeOH (95:5) as eluant to give **27** as a yellow solid (24 mg, 71%). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 9.75 (br.s, 1H), 9.05 (d, *J* = 2.4 Hz, 1H), 8.89 (d, *J* = 4.8 Hz, 1H), 8.53 (d, *J* = 2.4 Hz, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.77-7.71 (m, 3H), 7.59-7.55 (m, 3H), 7.36 (d, *J* = 2.8 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 2H); mp > 255 ºC.

4-{3-[4-(2-Piperidin-1-ylethoxy)phenyl]pyrrolo[1,2-a]pyrimidin-8-yl}quinoline (28): To a solution of **27** (20 mg, 0.06 mmol) under an argon atmosphere in 3 mL of DMF was added NaH (60%, 8 mg, 0.2 mmol) followed by *N*-(2-chloroethyl)piperidine hydrochloride (18 mg, 0.1 mmol). The mixture was stirred at rt for 1 day, then quenched with H_2O, and extracted with ethyl acetate. The organic layer was separated and concentrated. The residue was purified by column chromatography on silica gel using CH_2Cl_2/MeOH (88:12) to give **28** as a brown oil (15 mg, 80%) and 7 mg of recovered starting material. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.97 (d, *J* = 4.5 Hz, 1H), 8.46 (d, *J* = 2.0 Hz, 1H), 8.38 (d, *J* = 2.5 Hz, 1H), 8.25 (d, *J* = 8.5 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 7.75-7.71 (m, 2H), 7.54-7.50 (m, 3H), 7.43 (d, *J* = 3.0 Hz, 1H), 7.32 (d, *J* = 3.0 Hz, 1H), 7.04 (d, *J* = 9.0 Hz, 2H), 4.27 (t, *J* = 5.5 Hz, 2H), 3.00 (m, 2H), 2.74 (m, 4H), 1.73 (m, 4H), 1.52 (m, 2H).

Synthesis of substituted pyrazolo[1,5-a]pyridine derivatives (Method E).

3-(4-Methoxyphenyl)pyridine (30)[19]**:** A mixture of 3-bromopyridine, (**29**, 190 mg, 1.20 mmol), 4-methoxyphenylboronic acid (152 mg, 1.00 mmol), $Pd(PPh_3)_4$ (35.0 mg, 0.0300 mmol) and K_3PO_4 (430 mg, 2.00 mmol) in 1,4-dioxane (10 mL) was heated at 100 °C for 18 h. The solvent was removed under reduced pressure and ethyl acetate was added to the solid residue. The organic layer was washed sequentially with water, brine, and then dried over anhydrous Na_2SO_4. Concentration of the filtrate followed by chromatography [silica, hexanes/ethyl acetate (3:1)] gave **30** as a white solid (108 mg, 58% yield), mp 61–63 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.86 (s, 3H), 7.01 (d, *J* = 8.5 Hz, 2H), 7.33 (dd, *J* = 5.0, 8.0 Hz, 1H), 7.52 (d, *J* = 8.5 Hz, 2H), 7.81–7.83 (m, 1H), 8.54 (dd, *J* = 2.0, 5.0 Hz, 1H), 8.81 (br s, 1H).

Methyl 6-(4-methoxyphenyl)pyrazolo[1,5-a]pyridine-3-carboxylate (32a) and methyl 4-(4-methoxyphenyl)pyrazolo[1,5-a]pyridine-3-carboxylate (32b): A mixture of **30** (545 mg, 3.00 mmol) and 2,4-di-NO_2PhONH_2 (645 mg, 3.25 mmol) in CH_3CN (2 mL) was stirred at 40 °C for 20 h. The reaction mixture was concentrated and the resulting residue was triturated with Et_2O (3 x 10 mL) to give **31a** as a yellow solid, which was dried under vacuum and used in the next step without further purification. To a mixture of **31a** in DMF (6 mL) at 0 °C were added K_2CO_3 (620 mg, 4.50 mmol) and methyl propiolate (378 mg, 4.50 mmol). The mixture was stirred vigorously at room temperature for 18 h and then the solvent was removed under reduced pressure to obtain a dark brown residue. The residue was dissolved in $CHCl_3$ and the insoluble material was removed by

filtration. Concentration of the filtrate followed by chromatography [silica, hexanes/ethyl acetate (3:1)] gave **32a** as a white solid (90 mg, 10% yield) and **32b** as a pale yellow solid (200 mg, 23% yield).

32a: mp 162–164 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.87 (s, 3H), 3.93 (s, 3H), 7.02 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.65 (dd, *J* = 2.0, 9.5 Hz, 1H), 8.18 (d, *J* = 9.5 Hz, 1H), 8.40 (s, 1H), 8.67 (br s, 1H).

32b: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.39 (s, 3H), 3.87 (s, 3H), 6.96 (d, *J* = 8.5 Hz, 2H), 7.00 (t, *J* = 7.0 Hz, 1H), 7.24 (d, *J* = 7.0 Hz, 1H), 7.32 (d, *J* = 8.5 Hz, 2H), 8.43 (s, 1H), 8.52 (d, *J* = 7.0 Hz, 1H).

4-[6-(4-Methoxyphenyl)pyrazolo[1,5-a]pyridin-3-yl]quinoline (35): To a stirred suspension of **32a** (195 mg, 0.690 mmol) in EtOH (6 mL) was added a solution of NaOH (97.0 mg, 2.40 mmol) in H_2O (1 mL) and the resulting suspension was heated at reflux for 3 h. The reaction mixture became a clear solution at elevated temperature. The solvent was completed evaporated under reduced pressure and the solid residue was acidified with 1N HCl at 0 °C. The corresponding acid precipitated as a white solid. This solid was collected by filtration, dried under vacuum overnight and used without further purification. A heterogeneous mixture of the crude acid, K_2CO_3 (55 mg, 0.40 mmol) and 4 Å molecular sieves (100 mg) in NMP (2 mL) under an argon atmosphere was heated at 50 – 60 °C for 30 min. Then 4-bromoquinoline (62 mg, 0.30 mmol), palladium acetylacetonate (2.0 mg, 0.0065 mmol), copper(I) iodide (4.0 mg, 0.021 mmol) and 1,10-phenantholine (6.0 mg, 0.033 mmol) were added to the reaction mixture sequentially at room temperature. The reaction mixture was then heated at 165 °C for 24 h. The solvent was concentrated and CH_2Cl_2 was added to the residue. The heterogeneous mixture was filtered and the filtrate was washed sequentially with water, brine, and then dried over anhydrous Na_2SO_4. Filtration and concentration followed by chromatography of the crude mixture on silica gel using hexane / ethyl acetate (1:1) gave **35** as a pale yellow solid (24 mg, 22% yield): mp 150–152 °C; ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.82 (s, 3H), 7.08 (d, *J* = 9.0 Hz, 2H), 7.61–7.66 (m, 2H), 7.71–7.74 (m, 2H), 7.78 (d, *J* = 9.0 Hz, 2H), 7.79–7.85 (m, 1H), 8.15 (d, *J* = 9.5 Hz, 1H), 8.18 (d, *J* = 9.5 Hz, 1H), 8.46 (s, 1H), 8.90 (d, *J* = 9.5 Hz, 1H), 9.18 (s, 1H); HRMS *m/z* 352.1444 (calc for $C_{23}H_{18}N_3O$, MH^+, 352.1445).

Methyl 6-bromopyrazolo[1,5-a]pyridine-3-carboxylate (33a) and methyl 4-bromopyrazolo[1,5-a]pyridine-3-carboxylate (33b): Following the procedures described above for **32a, 33a** and **33b** were prepared from **29** in 11% and 26% yields, respectively.

33a: mp 116–118 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.92 (s, 3H), 7.48 (dd, *J* = 1.5, 9.5 Hz, 1H), 8.07 (d, *J* = 9.5 Hz, 1H), 8.36 (s, 1H), 8.68 (br s, 1H).

33b: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.91 (s, 3H), 6.82 (t, *J* = 7.0 Hz, 1H), 7.65 (d, *J* = 7.0 Hz, 1H), 8.43 (s, 1H), 8.53 (d, *J* = 7.0 Hz, 1H).

Methyl 6-(4-piperazin-1-ylphenyl)pyrazolo[1,5-a]pyridine-3-carboxylate (34): To a stirring solution of **33a** (128 mg, 0.500 mmol) and t*ert*-butyl 4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenylpiperazinecarboxylate (233 mg, 0.600 mmol) in dioxane (5 mL) was added an aqueous solution of K_2CO_3 (104 mg, 0.750 mmol) (dissolved in minimum amount of water) followed by $Pd(PPh_3)_4$ (29.0 mg, 0.0250 mmol) and the homogeneous mixture was heated at 110 °C for 5 h. The solvent was removed under reduced pressure and excess CH_2Cl_2 was added to the solid residue. The organic layer was washed with water (3 x 10 mL), brine, and dried over Na_2SO_4. Concentration of

the filtrate followed by chromatography [silica, hexanes/ethyl acetate (3:2)] gave **34** as a pale yellow solid (160 mg, 73% yield), mp 211–213 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.50 (s, 9H), 3.21–3.23 (m, 4H), 3.60–3.62 (m, 4H), 3.93 (s, 3H), 7.03 (d, *J* = 9.0 Hz, 2H), 7.52 (d, *J* = 9.0 Hz, 2H), 7.66 (dd, *J* = 2.0, 9.0 Hz, 1H), 8.18 (d, *J* = 9.0 Hz, 1H), 8.40 (s, 1H), 8.67 (s, 1H).

N-Boc-4-[6-(4-Piperazin-1-ylphenyl)pyrazolo[1,5-a]pyridin-3-yl]-quinoline (36): Following a procedure described above for **35,** compound **36** was prepared from **34** in10% yield: mp 198–200 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (s, 9H), 3.22–3.24 (m, 4H), 3.61–3.63 (m, 4H), 7.03 (d, *J* = 9.0 Hz, 2H), 7.44–7.50 (m, 2H), 7.53–7.56 (m, 3H), 7.65–7.69 (m, 1H), 7.75–7.79 (m, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 8.21 (d, *J* = 8.0 Hz, 1H), 8.25 (s, 1H), 8.75 (br s, 1H), 8.96 (d, *J* = 9.5 Hz, 1H).

4-[6-(4-Piperazin-1-ylphenyl)pyrazolo[1,5-a]pyridin-3-yl]-quinoline (37): A stirred suspension of **36** (37 mg, 0.073 mmol) in MeOH (2.5 mL) was treated with 4N HCl in dioxane (0.25 mL, 0.60 mmol) dropwise at room temperature. A clear solution was developed after 10-15 min, which was then stirred at room temperature for 24 h. The solvent was concentrated under reduced pressure to obtain a yellow solid. The solid was dissolved in MeOH (3 mL) and the heterogeneous mixture was filtered off. Concentration of the filtrate followed by reverse-phase HPLC purification gave **37** as a yellow solid (4 mg, 12% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.22-3.40 (m, 8H), 7.12 (d, *J* = 9.0 Hz, 2H), 7.63–7.67 (m, 2H), 7.70–7.73 (m, 2H), 7.76 (d, *J* = 9.0 Hz, 2H), 7.83 (d, *J* = 8.0 Hz, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 8.46 (s, 1H), 8.96 (d, *J* = 5.0 Hz, 1H), 9.16 (s, 1H); HRMS *m/z* 406.2026 (calc for $C_{26}H_{24}N_5$, MH^+, 406.2030).

Evaluation of BMP4-induced phosphorylation of SMAD1/5/8.

Murine pulmonary artery smooth muscle cells were isolated, explanted and cultured as previously described[23a] and then grown to confluence in 96 well tissue culture plates. Cell were incubated in serum-free medium for 18 h, and then incubated with recombinant BMP4 ligand (R&D Systems, Minneapolis, MN) at varying concentrations in duplicate for 20 minutes. Cells were fixed, and then blocked with 2% bovine serum albumin in phosphate buffered saline overnight. Cells were incubated with rabbit polyclonal anti-phospho-SMAD1/5/8 (1:1000, Cell Signaling Technologies), followed by HRP-conjugated anti-rabbit IgG, and then developed with ultra high sensitivity chemiluminescent substrate (BioFx, Maryland) and read on a Victor multilabel counter (Perkin Elmer).

Determination of microsomal stability in pooled mouse liver microsomes. Test compound (3 μM final concentration) along with 0.5 mg/mL microsome protein and 1 mM NADPH was incubated for 0, 5, 15, 30 and 60 min. Incubation of test compound and microsomes in the absence of NADPH served as a negative control. The samples were quenched with methanol and centrifuged for 20 min at 2500 rpm to precipitate proteins. Sample supernatants were analyzed (N=3) by LC/MS. The ln peak area ratio (compound peak area/internal standard peak area) was plotted against time and the slope of the line determined to give the elimination rate constant [k = (-1)(slope)]. The half life ($t_{1/2}$ in minutes) and the *in vitro* intrinsic clearance (CL_{int} in μL/min/mg protein) values were calculated according to the following equations, where V = incubation volume in μL/mg protein:

$$t_{1/2} = \frac{0.693}{k}; CL_{\text{int}} = \frac{V(0.693)}{t_{1/2}}.$$

Pharmacokinetic analysis of 13·HCl. The pharmacokinetics of **13·HCl** was evaluated after a single bolus intraperitoneal administration (3 mg/kg) in male and female C57B16 mice on a commercial rodent diet and water *ad libitum* prior to the study. Compound plasma levels were determined by LC-MS/MS and the pharmacokinetic parameters were determined using WinNonlin software, Pharsight Co., Mountain View, CA). Dosing solutions (0.6 mg/mL) were prepared in a vehicle comprising 2% hydropropyl-β-cyclodextrin in PBS. Each time point (pre-dose, 5, 10, 15, 30, 60, 120, 240, 480, 1440 min post-dose) was dosed as N=3/sex. Each blood sample was collected via cardiac puncture after euthanasia with CO_2 and placed in chilled tubes containing sodium heparin. Samples were centrifuged at 4º C at 13,000 rpm for 5 min followed by extracted with acetonitrile and then analyzed.