Supporting Information

Structure-based design of orally bioavailable 1*H*-pyrrolo[3,2-*c*] pyridine inhibitors of the mitotic kinase monopolar spindle 1 (MPS1).

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Contents

Preparations for compounds in Table 1 (Scheme 2):

***N*-(4-Methoxyphenyl)-2-(1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-amine (21)**

To *tert*-butyl 6-bromo-2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (**17** (50 mg, 0.108 mmol) was added 4-methoxyaniline (16 mg, 0.129 mmol) followed by cesium carbonate (70 mg, 0.216 mmol) and Xantphos (6.2 mg, 0.0108 mmol). Dioxane (1.2 mL) was added and the flask flushed twice with nitrogen. Tris(dibenzylideneacetone)dipalladium(0) (5 mg, 0.0054 mmol) was added and the flask was flushed again with nitrogen and heated at 80 °C for 2 h. The reaction was cooled and diluted with EtOAc. The solution was washed with water and with brine, dried and evaporated to leave a gum. This was applied in chloroform to a 1 mm, 20 x 20 cm silica prep TLC plate which was eluted with CH_2Cl_2/EtOAc (9/1). The product band was recovered with acetone to give *tert*-butyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-4-yl)-6-(4-methoxyphenylamino)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (37 mg, 68%). ^{1}H NMR (500 MHz, DMSO *d*-6): δ 1.45 (s, 9H), 1.60 (s, 9H), 3.72 (s, 3H), 6.78 (d, *J* = 0.6 Hz, 1H), 6.87 (d, *J* = 9.1 Hz, 2H), 7.39 (t, *J* = 1.0 Hz, 1H), 7.48 (d, *J* = 9.1 Hz, 2H), 8.02 (d, *J* = 0.6 Hz, 1H), 8.41 (d, *J* = 1.0 Hz, 1H), 8.43 (d, *J* = 0.6 Hz, 1H), 8.73 (br s, 1H); LC (Method A)-MS (ESI, *m/z*) t_R 2.47 min, 506 [(M+H$^+$), 100%]. *tert*-Butyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-4-yl)-6-(4-methoxyphenylamino)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (37 mg, 0.073 mmol) was dissolved in CH_2Cl_2 (0.6 mL) and TFA (0.6 mL) was added to the solution. The reaction was stirred at rt for 2.5 h. The solvents were evaporated and the residue partitioned between $NaHCO_3$ solution and EtOAc. The aqueous layer was again extracted with EtOAc. The combined organics were washed with brine, dried and evaporated. This left a glass-like residue, which was triturated with ether to give a solid. The ether was removed by pipette and the solid dried, leaving product **21** (19 mg, 79%). ^{1}H NMR

(500 MHz, CD_3OD): δ 3.80 (s, 3H), 6.57 (d, *J* = 1.0 Hz, 1H), 6.75 (m, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 7.22 (d, *J* = 8.8 Hz, 2H), 7.97 (br s, 2H), 8.28 (d, *J* = 1.0 Hz, 1H); ESI-HRMS Found: 306.1375, calcd for $C_{17}H_{16}N_5O$ $[M+H]^+$: 306.1349.

4-(2-(1*H*-Pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-ylamino)-*N*,*N*-dimethylbenzenesulfonamide (22)

To *tert*-butyl 6-bromo-2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate **17** (50 mg, 0.108 mmol) was added cesium carbonate (70 mg, 0.216 mmol) and Xantphos (6.2 mg, 0.0108 mmol), and 4-(*N*,*N*-dimethylsulfonamido)aniline (26 mg, 0.13 mmol). Dioxane (1.2 mL) was added and the flask flushed with argon. Tris(dibenzylideneacetone)dipalladium(0) (5 mg, 0.0054 mmol) was added and the flask was flushed again with argon and heated at 80 °C for 3 h. The reaction was cooled and diluted with EtOAc. The solution was washed with water and with brine, dried and evaporated. The residue was applied in chloroform to two 1 mm 20 x 20 cm silica prep TLC plates which were eluted with CH_2Cl_2/EtOAc (100/15). The product band was recovered with acetone yielding *tert*-butyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-4-yl)-6-(4-(*N*,*N*-dimethylsulfamoyl)phenylamino)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate as a gummy solid (58 mg, 92%). ^1H NMR (500 MHz, DMSO *d*-6): δ 1.48 (s, 9H), 1.60 (s, 9H), 2.58 (s, 9H), 6.87 (d, *J* = 0.6 Hz, 1H), 7.61 (d, *J* = 9.1 Hz, 2H), 7.65 (s, 1H), 7.90 (d, *J* = 8.8 Hz, 2H), 8.05 (d, *J* = 0.6 Hz, 1H), 8.49 (d, *J* = 0.6 Hz, 1H), 8.57 (d, *J* = 1.0 Hz, 1H), 9.67 (s, 1H); ESI-HRMS Found: 583.2372, calcd for $C_{28}H_{35}N_6O_6S$ $[M+H]^+$: 583.2333. *tert*-Butyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-4-yl)-6-(4-(*N*,*N*-dimethylsulfamoyl)phenylamino)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (54 mg, 0.092 mmol) was dissolved in CH_2Cl_2 (0.6 mL). To the solution was added TFA (0.6 mL). Reaction stirred at rt for 4 h. The solution was evaporated. The residue was partitioned between EtOAc and

$NaHCO_3$ solution. The layers were shaken and separated. The aqueous was again extracted with EtOAc. The organic layers were washed with brine, dried and evaporated. The residue was triturated with ether to give product **22** (34 mg, 97%). ^{1}H NMR (500 MHz, DMSO *d*-6): δ 2.57 (s, 6H), 6.59 (d, *J* = 1.0 Hz, 1H), 6.90 (s, 1H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.79 (d, *J* = 8.8 Hz, 2H), 7.95 (br s, 1H), 8.16 (br s, 1H), 8.45 (s, 1H), 9.27 (s, 1H), 11.37 (s, 1H), 13.01 (br s, 1H); ESI-HRMS Found: 383.1293, calcd for $C_{18}H_{19}N_6O_2S$ $[M+H]^+$: 383.1285.

_N_-(4-((1_H_-Pyrazol-1-yl)methyl)phenyl)-2-(1_H_-pyrazol-4-yl)-1_H_-pyrrolo[3,2-_c_]pyridin-6-amine (23)

To a solution of *tert*-butyl 6-bromo-2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate **17** (70 mg, 0.151 mmol) in dry 1,4-dioxane (2 mL) was added 4-((1*H*-pyrazol-1-yl)methyl)aniline (31.3 mg, 0.181 mmol), cesium carbonate (98 mg, 0.3 mmol) and Xantphos (8.6 mg, 0.015 mmol). The flask was flushed with dry nitrogen and tris(dibenzylideneacetone)dipalladium(0) (7 mg, 0.0075 mmol) was added. The flask was flushed again with nitrogen and the reaction heated at 80 °C for 3 h. The reaction was cooled and diluted with EtOAc. The solution was washed with water, brine, dried and evaporated to leave an oily residue. This crude was purified on a silica flash column eluting with a gradient of 20% hexane in EtOAc to neat EtOAc. The pure fractions provided *tert*-butyl 6-(4-((1*H*-pyrazol-1-yl)methyl)phenylamino)-2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate as a yellow gum (12 mg, 14 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.49 (s, 9H), 1.69 (s, 9H), 5.20 (s, 2H), 6.32 (s, 1H), 6.58 (s, 1H), 6.66 (d, *J* = 8.3 Hz, 2H), 7.00 (d, *J* = 8.5 Hz, 1H), 7.06 (d, *J* = 8.3 Hz, 2H), 7.23 (d, *J* = 8.5 Hz, 1H), 7.33 (m, 1H), 7.62 (s, 1H), 7.82 (s, 1H), 8.21 (s, 1H), 8.45 (s, 1H); LC (Method B)-MS (ESI, *m/z*) t_R 2.90 min, 556 [$(M+H^+)$, 100%]. *tert*-Butyl 6-(4-((1*H*-pyrazol-1-yl)methyl)phenylamino)-2-(1-(*tert*-butoxycarbonyl)-1*H*-

pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (12 mg, 0.0216 mmol) was dissolved in CH_2Cl_2 (1 mL) and TFA (1 mL) was added to the solution. The reaction was stirred at rt for 3 h. The solvents were removed and the residue partitioned between saturated $NaHCO_3$ solution and EtOAc. The organic solution was collected, dried over sodium sulphate and concentrated in vacuo. The residue was purified by flash silica chromatography, eluting with EtOAc/hexane/Et_3N (10/5/2). The fractions containing the product were combined and the residue obtained was further purified on an ion-exchange SCX-2 cartridge. It was first eluted with 20% MeOH in EtOAc followed by 1 M ammonia in MeOH. The alkaline collection provided the title compound **23** as a pale brown solid (7 mg, 91%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.22 (s, 2H), 6.25 (d, *J* = 2.0 Hz, 1H), 6.57 (s, 1H), 6.82 (s, 1H), 7.14 (d, *J* = 8.5 Hz, 2H), 7.44 (s, 1H), 7.46 (d, *J* = 8.5 Hz, 2H), 7.75 (d, *J* = 2.0 Hz, 1H), 8.38 (s, 1H), 8.69 (s, 1H), 11.30 (s, 1H), 13.00 (s, 1H); ESI-HRMS Found: 355.1548, calcd for $C_{20}H_{18}N_7$ $[M+H]^+$: 355.1545.

_N_-(4-(2-Morpholinoethoxy)phenyl)-2-(1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-amine (24)

To a solution of *tert*-butyl 6-bromo-2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate **17** (100 mg, 0.216 mmol) in dry 1,4-dioxane (1.5 mL) was added 4-(2-morpholinoethoxy)aniline (58 mg, 0.26 mmol), cesium carbonate (140 mg, 0.432 mmol) and Xantphos (12.4 mg, 0.0216 mmol). The flask was flushed with dry nitrogen and tris(dibenzylideneacetone)dipalladium(0) (10.1 mg, 0.0108 mmol) was added. The flask was flushed again with nitrogen and the reaction heated at 80 °C for 3 h. The reaction was cooled and diluted with EtOAc. The solution was washed with water, brine, dried and evaporated to leave an oily residue. This crude was purified on a silica flash column eluting with 20% hexane in EtOAc. The pure fractions provided *tert*-butyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-4-yl)-6-(4-(2-

morpholinoethoxy)phenylamino)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate as a colourless gum (20 mg, 15 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 (s, 9H), 1.67 (s, 9H), 2.58 (m, 4H), 2.80 (t, *J* = 5.8 Hz, 2H), 3.73 (m, 4H), 4.11 (t, *J* = 5.8 Hz, 2H), 6.54 (s, 1H), 6.60 (s, 1H), 6.91 (d, *J* = 8.9 Hz, 2H), 7.27 (d, *J* = 8.9 Hz, 2H), 7.37 (s, 1H), 7.80 (s, 1H), 8.19 (s, 1H), 8.39 (s, 1H); LC (Method B)-MS (ESI, *m/z*) t_R 2.30 min, 605 [($M+H^+$), 100%]. *tert*-Butyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-4-yl)-6-(4-(2-morpholinoethoxy)phenylamino)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (20 mg, 0.033 mmol) was dissolved in CH_2Cl_2 (1 mL) and TFA (1 mL) was added to the solution. The reaction was stirred at rt for 3 h. The solvents were removed and the residue partitioned between saturated $NaHCO_3$ solution and EtOAc. The organic solution was collected, dried over sodium sulphate and concentrated in vacuo. The residue was purified on an ion-exchange SCX-2 cartridge. It was first eluted with 20% MeOH in EtOAc followed by 1 M ammonia in MeOH. The alkaline collection was concentrated and the residue triturated with ether which provided the title compound **24** as a pale brown solid (5 mg, 37%). ^{1}H NMR (500 MHz, DMSO *d*-6): δ 2.49 (br s, 4H), 2.68 (t, *J* = 5.7 Hz, 2H), 3.58 (m, 4H), 4.02 (t, *J* = 5.7 Hz, 2H), 6.50 (s, 1H), 6.69 (s, 1H), 6.84 (d, *J* = 9.0 Hz, 2H), 7.42 (d, *J* = 9.0 Hz, 2H), 8.10 (br s, 1H), 8.15 (br s, 1H), 8.25 (s, 1H), 8.32 (s, 1H), 11.10 (s, 1H), 12.96 (s, 1H); ESI-HRMS Found: 404.1976, calcd for $C_{22}H_{25}N_6O_2$ $[M+H]^+$: 404.1961.

_N_-(2-Methoxyphenyl)-2-(1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-amine (25)

To *tert*-butyl 6-bromo-2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate **17** (50 mg, 0.108 mmol) was added cesium carbonate (70 mg, 0.216 mmol) and Xantphos (6.2 mg, 0.0108 mmol), then a solution of 2-methoxyaniline (16 mg, 0.129 mmol) in dioxane (0.1 mL). Dioxane (1.1 mL) was added and the flask flushed with nitrogen. Tris(dibenzylideneacetone)dipalladium(0) (5 mg, 0.0054 mmol) was added and the flask was

flushed again with nitrogen and heated at 80 °C for 2.5 h. The reaction was cooled and diluted with EtOAc. The solution was washed with water and with brine, then dried and evaporated. The residue was applied in chloroform to one 1 mm 20 x 20 cm silica prep TLC plate which was eluted with CH_2Cl_2/EtOAc (9/1). The product band was recovered with acetone to give *tert*-butyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-4-yl)-6-(2-methoxyphenylamino)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (26 mg, 48%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.53 (s, 9H), 1.69 (s, 9H), 3.92 (s, 3H), 6.58 (d, *J* = 1.0 Hz, 1H), 6.91-6.99 (m, 3H), 7.08 (br s, 1H), 7.66 (m, 1H), 7.83 (d, *J* = 1.0 Hz, 1H), 7.92-7.95 (m, 1H), 8.33 (d, *J* = 0.6 Hz, 1H), 8.49 (d, *J* = 1.0 Hz, 1H); LC (Method A)-MS (ESI, *m/z*) t_R 2.52 min, 506 [($M+H^+$), 100%]. To *tert*-butyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-4-yl)-6-(2-methoxyphenylamino)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (26 mg, 0.051 mmol) was added CH_2Cl_2 (0.6 mL) and to the resulting solution was added TFA (0.6 mL). The reaction was stirred at rt for 3 h and then evaporated. The residue was partitioned between EtOAc and $NaHCO_3$ solution. The layers were separated and the aqueous again extracted with EtOAc. The organic layers were washed with brine, dried and evaporated (15 mg). This residue was triturated with a little ether to give the solid product **25** (12 mg, 76%). ^{1}H NMR (500 MHz, CD_3OD): δ 3.92 (s, 3H), 6.61 (d, *J* = 1.0 Hz, 1H), 6.91-6.97 (m, 2H), 7.00-7.03 (m, 2H), 7.51 (dd, *J* = 7.6, 1.9 Hz, 1H), 8.00 (br s, 2H), 8.35 (d, *J* = 1.0 Hz, 1H); ESI-HRMS Found: 306.1340, calcd for $C_{17}H_{16}N_5O$ $[M+H]^+$: 306.1349.

_N_-(2-Ethoxyphenyl)-2-(1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-amine (26)

To *tert*-butyl 6-bromo-2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate **17** (50 mg, 0.108 mmol) was added cesium carbonate (70 mg, 0.216 mmol) and Xantphos (6.2 mg, 0.0108 mmol), then a solution of 2-ethoxyaniline (18 mg, 0.13 mmol) in dioxane (0.3 mL). Dioxane (0.9 mL) was added and the flask flushed with nitrogen.

Tris(dibenzylideneacetone)dipalladium(0) (5 mg, 0.0054 mmol) was added and the flask was flushed again with nitrogen and heated at 80 °C for 5.5 h The reaction was cooled and diluted with EtOAc. The solution was washed with water and with brine, dried and evaporated. The residue was applied in chloroform to two 1 mm 20 x 20 cm silica prep TLC plates which were eluted with CH_2Cl_2/EtOAc (9/1). The product band was recovered with acetone to give *tert*-butyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-4-yl)-6-(2-ethoxyphenylamino)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (19 mg, 33%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 (t, *J* = 6.9 Hz, 3H), 1.54 (s, 9H), 1.69 (s, 9H), 4.14 (q, *J* = 6.9 Hz, 2H), 6.59 (d, *J* = 0.6 Hz, 1H), 6.91-6.98 (m, 3H), 7.11 (br s, 1H), 7.70 (m, 1H), 7.83 (d, *J* = 0.6 Hz, 1H), 7.91 (br d, *J* = 8.2 Hz, 1H), 8.33 (d, *J* = 0.6 Hz, 1H), 8.49 (s, 1H); LC (Method B)-MS (ESI, *m/z*) t_R 2.96 min, 520 [(M+H$^+$), 100%]. *tert*-Butyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-4-yl)-6-(2-ethoxyphenylamino)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (35 mg, 0.067 mmol) was dissolved in CH_2Cl_2 (0.6 mL). To the solution was added TFA (0.6 mL). The reaction was stirred at rt for about 4 h. The solution was evaporated and the residue partitioned between EtOAc and $NaHCO_3$ solution. The layers were shaken and separated. The aqueous was again extracted with EtOAc. The organic layers were washed with brine, dried and evaporated. The residue (about 26 mg) was triturated with ether to give the product **26** (19 mg, 88%). ^{1}H NMR (500 MHz, DMSO *d*-6): δ 1.40 (t, *J* = 6.9 Hz, 3H), 4.11 (q, *J* = 6.9 Hz, 2H), 6.54 (m, 1H), 6.79-6.89 (m, 2H), 6.94 (m, 1H), 6.97 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.35 (s, 1H), 7.93 (br s, 1H), 7.95 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.14 (br s, 1H), 8.36 (s, 1H), 11.23 (br s, 1H), 12.98 (br s, 1H); ESI-HRMS Found: 320.1517, calcd for $C_{18}H_{18}N_5O$ [M+H]$^+$: 320.1506.

***N*-(2-Chlorophenyl)-2-(1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-amine (27)**

To *tert*-butyl 6-bromo-2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate **17** (50 mg, 0.108 mmol) was added cesium carbonate (70 mg, 0.216 mmol) and Xantphos (6.2 mg, 0.0108 mmol) and then a solution of 2-chloro-aniline (17.6 mg, 0.138 mmol) in dioxane (1.2 mL). The flask was flushed with nitrogen. Tris(dibenzylideneacetone)dipalladium(0) (5 mg, 0.0054 mmol) was added and the flask was flushed again with nitrogen and heated at 80 °C for about 2.25 h. The reaction was cooled and diluted with EtOAc. The solution was washed with water and with brine, dried and evaporated. The residue was applied in chloroform to one 1 mm 20 x 20 cm silica prep TLC plate which was eluted with CH_2Cl_2/EtOAc (9/1). The product band was recovered with acetone and the solution evaporated to leave impure *tert*-butyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-4-yl)-6-(2-chlorophenylamino)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (37 mg). Impure samples of *tert*-butyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-4-yl)-6-(2-chlorophenylamino)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (total 72 mg) were combined and dissolved in CH_2Cl_2 (1.2 mL). To the solution was added TFA (1.2 mL) and the reaction was stirred at rt for 4 h. The solution was evaporated and the residue partitioned between EtOAc and $NaHCO_3$ solution. The aqueous layer was again extracted with EtOAc. The organic layers were washed with brine, dried and evaporated. The mixture was applied in MeOH to a 2 g SCX-2 column and more MeOH used to wash through. Bases were then recovered with 2 M ammonia in MeOH. The recovered mixture was applied to two 1 mm 20 x 20 cm silica prep TLC plates which were eluted twice with CH_2Cl_2/2 M ammonia in MeOH (9/1). The product band was recovered with EtOH/2 M ammonia in MeOH (4/1), yielding the title compound **27** (20 mg). ^{1}H NMR (500 MHz, CD_3OD): δ 6.64 (d, J = 1.0 Hz, 1H), 6.91 (m, 1H), 7.02 (m, 1H), 7.22 (m, 1H), 7.41 (dd, J = 8.2, 1.6 Hz,

1H), 7.55 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.01 (br s, 2H), 8.41 (s, 1H); ESI-HRMS Found: 310.0869, calcd for $C_{16}H_{13}ClN_5$ $[M+H]^+$: 310.0854.

_N_-(2-Chloro-4-methoxyphenyl)-2-(1_H_-pyrazol-4-yl)-1_H_-pyrrolo[3,2-_c_]pyridin-6-amine (28)

To *tert*-butyl 6-bromo-2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate **17** (50 mg, 0.108 mmol) was added cesium carbonate (70 mg, 0.216 mmol) and Xantphos (6.2 mg, 0.0108 mmol) and then a solution of 2-chloro-4-methoxyaniline (21 mg, 0.130 mmol) in dioxane (1.2 mL). The flask was flushed with nitrogen. Tris(dibenzylideneacetone)dipalladium(0) (5 mg, 0.0054 mmol) was added and the flask was flushed again with nitrogen and heated at 80 °C for about 2.5 h. The reaction was cooled and diluted with EtOAc. The solution was washed with water and with brine, dried and evaporated. The residue was applied in chloroform to one 1 mm 20 x 20 cm silica prep TLC plate which was eluted with CH_2Cl_2/EtOAc (9/1). The product band was recovered with acetone; evaporation of the solution left *tert*-Butyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-4-yl)-6-(2-chloro-4-methoxyphenylamino)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (42 mg, 72%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.49 (s, 9H), 1.69 (s, 9H), 3.82 (s, 3H), 6.58 (d, *J* = 1.0 Hz, 1H over br s, 1H), 6.86 (dd, *J* = 9.0, 2.8 Hz, 1H), 7.03 (d, *J* = 2.8 Hz, 1H), 7.38 (m, 1H), 7.73 (d, *J* = 9.0 Hz, 1H), 7.82 (d, *J* = 0.6 Hz, 1H), 8.21 (d, *J* = 0.6 Hz, 1H), 8.46 (d, *J* = 0.6 Hz, 1H); LC (Method B)-MS (ESI, *m/z*) t_R 3.00 min, 540 [$(M+H^+)$]. To *tert*-Butyl 2-(1-(*tert*-butoxycarbonyl)-1*H*-pyrazol-4-yl)-6-(2-chloro-4-methoxyphenylamino)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (42 mg, 0.078 mmol) was added CH_2Cl_2 (0.6 mL) and to the resulting solution was added TFA (0.6 mL). The reaction was stirred at rt for 4 h and then evaporated. The residue was partitioned between EtOAc and $NaHCO_3$ solution. The layers were shaken and separated. The aqueous was again extracted with EtOAc. The organic layers were washed with brine, dried and evaporated. This

residue was triturated with a little ether to give solid product **28** (25 mg, 96%). ^{1}H NMR (500 MHz, DMSO *d*-6): δ 3.76 (s, 3H), 6.51 (m, 1H), 6.65 (m, 1H), 6.89 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.05 (d, *J* = 2.8 Hz, 1H), 7.60 (s, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.91 (br s, 1H), 8.12 (br s, 1H), 8.29 (s, 1H), 11.15 (br s, 1H), 12.96 (br s, 1H); ESI-HRMS Found: 340.0971, calcd for $C_{17}H_{15}ClN_5O$ $[M+H]^+$: 340.0960.

Preparation for compounds from Table 2

***N*-(2-Methoxyphenyl)-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-amine (29)**

tert-Butyl 6-bromo-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate **47** (50 mg, 0.133 mmol) was added cesium carbonate (86 mg, 0.265 mmol), Xantphos (7.6 mg, 0.0132 mmol), and 2-methoxyaniline (18 μL, 0.16 mmol). Dioxane (1.5 mL) was added and the flask flushed with nitrogen. Tris(dibenzylideneacetone)dipalladium(0) (6.1 mg, 0.0066 mmol) was added and the flask was flushed again with nitrogen and heated at 80 °C for 2.5 h. The reaction was cooled and diluted with EtOAc. The solution was washed with water and with brine, dried and evaporated. The residue was applied in chloroform to two 1 mm 20 x 20 cm silica prep TLC plates which were eluted with CH_2Cl_2/EtOAc (4/1). The product band was recovered with acetone (38 mg, 68%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.52 (s, 9H), 3.92 (s, 3H), 3.96 (s, 3H), 6.49 (d, *J* = 0.6 Hz, 1H), 6.91-6.99 (m, 3H), 7.04 (br s, 1H), 7.54 (s, 1H), 7.60 (s, 1H), 7.66 (s, 1H), 7.93 (m, 1H), 8.46 (d, *J* = 1.0 Hz, 1H); ESI-HRMS Found: 420.2050, calcd for $C_{23}H_{26}N_5O_4$ $[M+H]^+$: 420.2030. *tert*-Butyl 6-(2-methoxyphenylamino)-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (38 mg, 0.091 mmol) was dissolved in CH_2Cl_2 (0.6 mL). To the solution was added TFA (0.6 mL) and the reaction was stirred at rt for about 3.5 h. The solution was evaporated. The residue was partitioned between EtOAc and $NaHCO_3$

solution. The aqueous was again extracted with EtOAc. The organic layers were washed with brine, dried and evaporated. The residue was triturated with ether to give **29** (27 mg, 93%). ^{1}H NMR (500 MHz, DMSO *d*-6): δ 3.86 (s, 3H), 3.89 (s, 3H), 6.49 (d, *J* = 1.0 Hz, 1H), 6.81-6.89 (m, 2H), 6.93 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.50 (s, 1H), 7.86 (s, 1H), 8.04-8.08 (s over dd, 2H), 8.36 (s, 1H), 11.23 (br s, 1H); ESI-HRMS Found: 320.1522, calcd for $C_{18}H_{18}N_5O$ $[M+H]^+$: 320.1506.

Preparation of *N*-(2-Methoxyphenyl)-2-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-amine (30)

4-Iodo-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole: A mixture of 4-iodo-pyrazole (582 mg, 3.0 mmol) and cesium carbonate (1.96 g, 6.0 mmol) was stirred with DMF (6 mL) for 5 min. Trifluoroethyl triflate (0.52 mL, 3.75 mmol) was added and the reaction was stirred at rt for 4.5 h. The reaction was added to water (60 mL) and extracted with ether. The combined extracts were washed with water and with brine and then dried and evaporated to leave the product (737 mg, 89%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.72 (q, *J* = 8.2, 2H), 7.58 (s, 1H), 7.61 (s, 1H); ^{19}F NMR (470.385 MHz, $CDCl_3$): δ -71.69; LC (Method A)-MS (ESI, *m/z*) t_R 2.01 min, 277 [$(M+H^+)$, 100%].

1-(2,2,2-Trifluoroethyl)-4-((trimethylsilyl)ethynyl)-1*H*-pyrazole: 4-Iodo-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole (737 mg, 2.67 mmol) was dissolved in DMF (4.9 mL) and TMS-acetylene (0.7 mL, 4.95 mmol) was added; followed by diisopropylamine (0.65 mL, 4.64 mmol), copper(I) iodide (44 mg, 0.23 mmol) and triphenylphosphine (184 mg, 0.70 mmol). The reaction was flushed with nitrogen. Palladium acetate (52.5 mg, 0.23 mmol) was added and the reaction flushed again with nitrogen. It was heated at 60 °C for 60 min. The reaction was cooled and added to water. The product was extracted with ether. The combined organics were washed with

water and with brine, then dried and evaporated to leave a black oil. This was adsorbed on to silica from CH_2Cl_2 solution. This silica was applied to the top of a silica flash column prepared in EtOAc/cyclohexane (1/2) and the column was eluted with the same solvent. Product containing fractions yielded an oil (844 mg, 97%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.24 (s, 9H), 4.68 (q, J = 8.2, 2H), 7.66 (s, 1H), 7.67 (s, 1H); ^{19}F NMR (470.385 MHz, $CDCl_3$): δ -71.69; LC (Method A)-MS (ESI, m/z) t_R 2.57 min, 247 [($M+H^+$), 100%].

4-Ethynyl-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole: 1-(2,2,2-Trifluoroethyl)-4-((trimethylsilyl)ethynyl)-1*H*-pyrazole (1.19 g) was dissolved in MeOH (7 mL) and potassium carbonate (30 mg, 0.22 mmol) was added. The reaction was stirred at rt for 3.5 h. The MeOH was evaporated and the residue taken up in CH_2Cl_2 and applied to a pad of silica (2 cm thick, 5 cm diameter) in a sinter. The product was flushed through with more CH_2Cl_2. Evaporation of the filtrate gave the product (494 mg). By NMR this is 66% solids; the yield (326 mg, 53%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.06 (s, 1H), 4.70 (q, J = 8.2 Hz, 2H), 7.69 (s, 1H), 7.70 (s, 1H); ^{19}F NMR (470.385 MHz, $CDCl_3$): δ -71.69.

6-Bromo-1-(methylsulfonyl)-2-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine: 4-Ethynyl-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole (326 mg, 1.87 mmol) was dissolved in DMF (4.9 mL) and *N*-(2-bromo-5-iodopyridin-4-yl)methanesulfonamide **16** (565 mg, 1.50 mmol) was added. To the solution was added Et_3N (0.91 mL, 6.5 mmol) and copper(I) iodide (10 mg, 0.052 mmol). The reaction was flushed with nitrogen. Bis(triphenylphosphine)palladium dichloride (37 mg, 0.052 mmol) was added and the reaction was again flushed with nitrogen. The reaction was heated at 60 °C for 110 min then cooled and added to water. The products were extracted into EtOAc. The combined extracts were washed with water and with brine, dried and evaporated. The residue was flash columned; silica, eluting with CH_2Cl_2, 5% EtOAc in CH_2Cl_2,

10% EtOAc in CH_2Cl_2, 20% EtOAc in CH_2Cl_2 and 30% EtOAc in CH_2Cl_2 to give product (300 mg, 47%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.98 (s, 3H), 4.80 (q, *J* = 8.2 Hz, 2H), 6.76 (d, *J* = 1.0 Hz, 1H), 7.84 (d, *J* = 0.6 Hz, 1H), 7.94 (s, 1H), 8.25 (t, *J* = 1.0 Hz, 1H), 8.67 (d, *J* = 1.0 Hz, 1H); ^{19}F NMR (470.385 MHz, $CDCl_3$): δ -71.56; LC (Method A)-MS (ESI, *m/z*) t_R 2.28 min, 423 [$(M+H^+)$, 100%].

***tert*-Butyl-6-bromo-2-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate**: 6-Bromo-1-(methylsulfonyl)-2-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine (300 mg, 0.71 mmol) was stirred in MeOH (3 mL) and 1 M sodium hydroxide in water (0.8 mL, 0.8 mmol) was added and the reaction stirred at rt for 140 min. The MeOH was evaporated, the residue taken up in EtOAc, the solution washed with water and with brine and then dried and evaporated. The residue was dissolved in EtOAc (3 mL) and Et_3N (0.15 mL, 1.06 mmol) was added, followed by a crystal of DMAP and di-*tert*-butyl dicarbonate (240 mg, 1.1 mmol). The reaction was stirred at rt for 2 h and then evaporated. The residue was applied in chloroform to three 2 mm 20 x 20 cm silica prep TLC plates, which were eluted with CH_2Cl_2/EtOAc (4/1) and the product band was recovered with acetone to give the title compound (251 mg, 79%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.54 (s, 9H), 4.78 (q, *J* = 8.5 Hz, 2H), 6.61 (d, *J* = 0.6 Hz, 1H), 7.72 (s, 1H), 7.74 (s, 1H), 8.24 (s, 1H), 8.59 (d, *J* = 0.6 Hz, 1H); ^{19}F NMR (470.385 MHz, $CDCl_3$): δ -71.59; LC (Method A)-MS (ESI, *m/z*) t_R 2.69 min, 388 [$(M+H^+-C_4H_8)$, 100%].

***tert*-Butyl-6-(2-methoxyphenylamino)-2-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate**: To *tert*-Butyl 6-bromo-2-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (48.1 mg, 0.108 mmol) was added cesium carbonate (70 mg, 0.216 mmol) and Xantphos (6.2 mg, 0.0108 mmol) and then 2-

methoxyaniline (16 mg, 0.13 mmol) in dioxane (0.4 mL). Dioxane (0.8 mL) was added and the flask flushed with nitrogen. Tris(dibenzylideneacetone)dipalladium(0) (5 mg, 0.0054 mmol) was added and the flask was flushed again with nitrogen and heated at 80 °C for 4 h. The reaction was cooled and diluted with EtOAc. The solution was washed with water and with brine, dried and evaporated. The residue was applied to two 1 mm 20 x 20 cm silica prep TLC plates, which were eluted with CH_2Cl_2/EtOAc (4/1). The product band was recovered with acetone to give the product (46 mg, 88%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.50 (s, 9H), 3.92 (s, 3H), 4.76 (q, *J* = 8.5 Hz, 2H), 6.53 (d, *J* = 0.6 Hz, 1H), 6.91-7.01 (m, 3H), 7.07 (br s, 1H), 7.68 (s, 1H), 7.69 (s, 1H), 7.70 (d, *J* = 0.6 Hz, 1H), 7.96 (dd, *J* = 7.2, 1.9 Hz, 1H), 8.48 (s, 1H); ^{19}F NMR (470.385 MHz, $CDCl_3$): δ -71.61; LC (Method A)-MS (ESI, *m/z*) t_R 2.12 min, 488 [($M+H^+$), 100%].

***N*-(2-Methoxyphenyl)-2-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-amine (30)**: *tert*-Butyl-6-(2-methoxyphenylamino)-2-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (46 mg, 0.094 mmol) was dissolved in CH_2Cl_2 (1.4 mL) and TFA (1.4 mL) was added. The reaction was stirred at rt for 3.5 h. The solvents were evaporated. The residue was kept in a vacuum desiccator over NaOH for 1 h. It was then partitioned between EtOAc and $NaHCO_3$ solution. The aqueous was washed with EtOAc and the organics were combined and washed with brine, dried and evaporated to leave crude product (38 mg). This was triturated with ether giving an off-white/cream solid. The ether was removed by pipette and the solid dried under vacuum. Yield (30 mg, 82%). ^{1}H NMR (500 MHz, acetone *d*-6): δ 3.90 (s, 3H), 5.11 (q, *J* = 8.8 Hz, 2H), 6.67 (m, 1H), 6.81-6.93 (m, 2H), 6.96-7.00 (m, 2H), 7.21 (br s, 0.4H), 8.02 (d, *J* = 0.6 Hz, 1H), 8.14 (td, *J* = 7.9, 1.9 Hz,1H), 8.25 (s, 1H), 8.47 (s, 1H), 10.53 (br s, 0.4H). The partial NH signals are due to exchange with the acetone *d*-6. ^{19}F

NMR (470.385 MHz, acetone *d*-6): δ -72.25; ESI-HRMS Found: 388.1369, calcd for $C_{19}H_{16}F_3N_5O$ $[M+H]^+$: 388.1380.

Preparation of 2-(1-(Difluoromethyl)-1*H*-pyrazol-4-yl)-*N*-(2-methoxyphenyl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-amine (31)

1-(Difluoromethyl)-4-((trimethylsilyl)ethynyl)-1*H*-pyrazole: 4-Iodo-1-difluoromethylpyrazole (521 mg, 1.81 mmol) was dissolved in DMF (3 mL). TMS-acetylene (0.43 mL, 3.04 mmol) was added followed by diisopropylamine (395 μL, 2.81 mmol), copper(I) iodide (27 mg, 0.14 mmol) and triphenylphosphine (112 mg, 0.43 mmol). The reaction was flushed with nitrogen. Palladium acetate (32 mg, 0.14 mmol) was added and the reaction flushed again with nitrogen and was heated at 60 °C for 65 min. The reaction was cooled and diluted with EtOAc. The solution was washed with water and with brine then dried and concentrated in vacuo. The residue was purified using preparative TLC eluting with CH_2Cl_2/cyclohexane (1/1) to afford the title compound (413 mg over theory, contains solvent). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.25 (s, 9H), 7.15 (t, J = 60.2 Hz, 1H), 7.71 (s, 1H), 7.94 (s, 1H); LC (Method A)-MS (ESI, *m/z*) t_R 2.55 min, no ions.

1-(Difluoromethyl)-4-ethynyl-1*H*-pyrazole: 1-(Difluoromethyl)-4-((trimethylsilyl)ethynyl)-1*H*-pyrazole (413 mg, 1.9 mmol) was stirred with MeOH (4 mL). Potassium carbonate (17 mg, 0.12 mmol) was added and stirred at rt for 50 min. The solvent was evaporated and the residue was filtered in CH_2Cl_2 through a short pad of silica to afford the title compound (187 mg, 72%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.08 (s, 1H), 7.17 (t, J = 60.5 Hz, 1H), 7.75 (s, 1H), 7.97 (s, 1H).

6-Bromo-2-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-1-(methylsulfonyl)-1*H*-pyrrolo[3,2-*c*]pyridine: 1-(Difluoromethyl)-4-ethynyl-1*H*-pyrazole (187 mg, 1.31 mmol) was dissolved in DMF (4.2 mL) and *N*-(2-bromo-5-iodopyridin-4-yl)methanesulfonamide **16** (444 mg, 1.17

mmol) was added. To the solution was added Et_3N (0.80 mL, 5.7 mmol) and copper(I) iodide (9 mg, 0.047 mmol). The reaction was sealed and flushed with nitrogen. Bis(triphenylphosphine)palladium dichloride (37.6 mg, 0.046 mmol) was added and the reaction was again flushed with nitrogen and then heated at 60 °C for 140 min. The reaction was added to EtOAc and the solution washed with water and with brine, then dried and concentrated in vacuo. The residue was purified using preparative TLC eluting with 5% EtOAc in chloroform to afford the title compound (157 mg, 34%). ^{1}H NMR (500 MHz, acetone *d*-6): δ 3.37 (s, 3H), 7.06 (d, J = 0.6 Hz, 1H), 7.70 (t, J = 59.6 Hz, 1H), 8.04 (s, 1H), 8.16 (m, 1H), 8.51 (s, 1H), 8.73 (d, J = 1.0 Hz, 1H); LC (Method A)-MS (ESI, *m/z*) t_R 2.22 min, 391 [(M+H$^+$), 100%].

***tert*-Butyl-6-bromo-2-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate:** 6-Bromo-2-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-1-(methylsulfonyl)-1*H*-pyrrolo[3,2-*c*]pyridine (189 mg, 0.48 mmol) was stirred in MeOH (2.1 mL) and 1 M sodium hydroxide in water (0.53 mL, 0.53 mmol) was added. The reaction was stirred at 25 °C for 85 min. The MeOH was evaporated and the residue taken up in EtOAc. The solution was washed with water and with brine and then dried and concentrated in vacuo. The residue was stirred with EtOAc (2 mL) and Et_3N (101 μL, 0.72 mmol) was added, along with a small crystal of DMAP. Di-*tert*-butyl dicarbonate (157 mg, 0.72 mmol) was added and the reaction stirred at rt for 1.5 h. The solvent was concentrated in vacuo and purified using preparative TLC (silica plates) eluting with EtOAc/cyclohexane (1/2) to afford the title compound (131 mg, 66%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.53 (s, 9H), 6.65 (d, J = 0.6 Hz, 1H), 7.25 (t, J = 60.5 Hz, 1H), 7.79 (s, 1H), 8.01 (s, 1H), 8.27 (m, 1H), 8.62 (d, J = 0.6 Hz, 1H); ^{19}F NMR (470.385 MHz, $CDCl_3$): δ -93.43; LC (Method A)-MS (ESI, *m/z*) t_R 2.66 min, 357 [(M+H$^+$-C_4H_8), 100%].

***tert*-Butyl-2-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-6-(2-methoxyphenylamino)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate:** To *tert*-Butyl 6-bromo-2-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (44.6 mg, 0.108 mmol) was added cesium carbonate (70 mg, 0.216 mmol) and Xantphos (6.2 mg, 0.0108 mmol) and then 2-methoxyaniline (16 mg, 0.13 mmol) in dioxane (0.4 mL). Dioxane (0.8 mL) was added and the flask flushed with nitrogen. Tris(dibenzylideneacetone)dipalladium(0) (5 mg, 0.0054 mmol) was added and the flask was flushed again with nitrogen and heated at 80 °C for 4.75 h. The reaction was cooled and diluted with EtOAc. The solution was washed with water and with brine, dried and evaporated. The residue was applied to two 1 mm 20 x 20 cm silica prep TLC plates, which were eluted with CH_2Cl_2/EtOAc (5/1). The product band was recovered with acetone giving product (21 mg, 42%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.50 (s, 9H), 3.92 (s, 3H), 6.57 (d, J = 0.6 Hz, 1H), 6.91-7.01 (m, 3H), 7.09 (s, 1H), 7.24 (t, J = 6.5 Hz, 1H), 7.69 (s, 1H), 7.77 (s, 1H), 7.95-8.01 (m, 2H), 8.49 (s, 1H); ^{19}F NMR (470.385 MHz, $CDCl_3$): δ -93.22; LC (Method A)-MS (ESI, m/z) t_R 2.12 min, 456 [($M+H^+$), 100%].

2-(1-(Difluoromethyl)-1*H*-pyrazol-4-yl)-*N*-(2-methoxyphenyl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-amine (31)

tert-Butyl 2-(1-(difluoromethyl)-1*H*-pyrazol-4-yl)-6-(2-methoxyphenylamino)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (21 mg, 0.046 mmol) was dissolved in CH_2Cl_2 (1.5 mL) and TFA (1.5 mL) was added. The reaction was stirred at rt for 3.5 h. The solvents were evaporated and the residue stored under vacuum over NaOH for 1 h. The residue was partitioned between EtOAc and $NaHCO_3$ solution. The organic layer was washed with brine, dried and evaporated to leave product 16 mg. Crystallization was observed after storage overnight. The sample was triturated with ether, the mother liquor removed and the solid dried at the pump to give **31** (10 mg, 61%).

^{1}H NMR (500 MHz, acetone *d*-6): δ 3.90 (s, 3H), 6.79 (s, 1H), 6.83-6.93 (m, 2H), 6.98 (d, *J* = 7.9 Hz, 1H), 7.01 (s, 1H), 7.25 (br s, 0.5H), 7.68 (t, *J* = 59.9 Hz, 1H), 8.15 (td, *J* = 7.9, 1.6 Hz, 1H), 8.20 (s, 1H), 8.50 (s, 1H), 8.54 (s, 1H), 10.58 (br s, 0.5H). The partial NH signals arise from exchange with the acetone *d*-6. ^{19}F NMR (470.385 MHz, acetone *d*-6): δ -95.39; ESI-HRMS Found: 356.1322, calcd for $C_{18}H_{16}F_2N_5O$ $[M+H]^+$: 356.1318.

Preparation of *N*-(2,4-Dimethoxyphenyl)-2-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-amine (32)

4-Iodo-1-methyl-3-(trifluoromethyl)-1*H*-pyrazole: 4-Iodo-3-trifluoromethylpyrazole (524 mg, 2.0 mmol) was dissolved in DMF (4 mL) and stirred with potassium carbonate (346 mg, 2.5 mmol) whilst iodomethane (250 μL, 4.0 mmol) was added. The reaction was stirred at rt for 1.5 h, was added to water and extracted with EtOAc. The combined extracts were washed with water and with brine, dried and evaporated. The residue (about 0.61 g) was purified by prep TLC on silica plates (elution with EtOAc/cyclohexane (1/3), product recovery with acetone) to give the title compound (383 mg, 69%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.98 (s, 3H), 7.50 (s, 1H); ^{19}F NMR (470.385 MHz, $CDCl_3$): δ -61.73; LC (Method A)-MS (ESI, *m/z*) t_R 2.17 min, no ions.

1-Methyl-3-(trifluoromethyl)-4-((trimethylsilyl)ethynyl)-1*H*-pyrazole: 4-Iodo-1-methyl-3-(trifluoromethyl)-1*H*-pyrazole (570 mg, 2.06 mmol) was dissolved in DMF (2.8 mL) and ethynyltrimethylsilane (0.40 mL, 2.83 mmol) was added followed by diisopropylamine (0.37 mL, 2.64 mmol), copper(I) iodide (25 mg, 0.13 mmol) and triphenylphosphine (105 mg, 0.40 mmol). The reaction was flushed with nitrogen. Palladium acetate (30 mg, 0.13 mmol) was added, the reaction was again flushed with nitrogen and heated at 60 °C for 130 min. The reaction was cooled and added to water. The products were extracted with EtOAc. The combined

organics were washed with water and with brine, then dried and evaporated, leaving a crude product (667 mg). This was applied in chloroform to three 2 mm 20 x 20 cm silica prep TLC plates. These were eluted with EtOAc/cyclohexane (40/60) and the product band recovered with acetone to give product (340 mg, 67%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.24 (s, 9H), 3.92 (s, 3H), 7.54 (s, 1H); ^{19}F NMR (470.385 MHz, $CDCl_3$): δ -62.11; LC (Method A)-MS (ESI, *m/z*) t_R 2.63 min, no ions.

4-Ethynyl-1-methyl-3-(trifluoromethyl)-1*H*-pyrazole: 1-Methyl-3-(trifluoromethyl)-4-((trimethylsilyl)ethynyl)-1*H*-pyrazole (340 mg, 1.38 mmol) was dissolved in MeOH (2.8 mL) and potassium carbonate (13.8 mg) was added and the mix stirred at rt for 1 h. The solvent was evaporated to low volume and the residue was applied to one 2 mm 20 x 20 cm silica prep TLC plate, which was eluted with EtOAc/cyclohexane (1/1) and the product band was recovered with acetone (158 mg, 65%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.15 (s, 1H), 3.94 (s, 3H), 7.59 (s, 1H); ^{19}F NMR (470.385 MHz, $CDCl_3$): δ -62.04; LC (Method A)-MS (ESI, *m/z*) t_R 1.97 min, no ions.

6-Bromo-2-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)-1-(methylsulfonyl)-1*H*-pyrrolo[3,2-*c*]pyridine: 4-Ethynyl-1-methyl-3-(trifluoromethyl)-1*H*-pyrazole (154 mg, 0.885 mmol) was dissolved in DMF (2.9 mL) and *N*-(2-bromo-5-iodopyridin-4-yl)methanesulfonamide **16** (332 mg, 0.885 mmol) was added. To the solution was added Et_3N (0.54 mL, 3.84 mmol) and copper(I) iodide (6 mg, 0.031 mmol). The reaction was sealed and flushed with nitrogen. Bis(triphenylphosphine)palladium dichloride (22 mg, 0.031 mmol) was added and the reaction was again flushed with nitrogen. It was heated at 60 °C for 70 min and then allowed to stand at rt for 30 min. The reaction was added to water and extracted with EtOAc. The extracts were washed with water and with brine, then dried and evaporated. The residue was applied to two 2 mm 20 x 20 cm silica prep TLC plates, which were eluted with EtOAc/cyclohexane (3/1). The

product band was recovered with acetone to give the product (160 mg, 42%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.98 (s, 3H), 4.06 (s, 3H), 6.80 (s, 1H), 7.70 (s, 1H), 8.22 (t, *J* = 1.0 Hz, 1H), 8.71 (d, *J* = 1.0 Hz, 1H); ^{19}F NMR (470.385 MHz, $CDCl_3$): δ -59.41; LC (Method A)-MS (ESI, *m/z*) t_R 2.27 min, 423 [($M+H^+$), 100%].

***tert*-Butyl-6-bromo-2-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate:** 6-Bromo-2-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)-1-(methylsulfonyl)-1*H*-pyrrolo[3,2-*c*]pyridine (156 mg, 0.37 mmol) was stirred in MeOH (1.6 mL) and 1 M sodium hydroxide in water (0.41 mL, 0.41 mmol) was added. The reaction was stirred at rt for 170 min. The MeOH was evaporated and EtOAc was added. The solution was washed with water and with brine, dried and evaporated. The residue was taken up in EtOAc (1.5 mL) and Et_3N (78 μL, 0.55 mmol) was added along with a crystal of DMAP. Di-*tert*-butyl dicarbonate (121 mg, 0.55 mmol) was added and the reaction stirred at rt for 4.75 h. It was evaporated and left at rt overnight. The residue was applied to one 2 mm 20 x 20 cm silica prep TLC plate, which was eluted with EtOAc/cyclohexane (1/1). The product band was recovered with acetone to give product (146 mg, 88% over 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.46 (s, 9H), 4.03 (s, 3H), 6.62 (d, *J* = 1.0 Hz, 1H), 7.51 (s, 1H), 8.30 (t, *J* = 1.0 Hz, 1H), 8.62 (d, *J* = 1.0 Hz, 1H); ^{19}F NMR (470.385 MHz, $CDCl_3$): δ -60.74; LC (Method A)-MS (ESI, *m/z*) t_R 2.22 min, 345 [($M+H^+$-Boc), 100%].

***tert*-Butyl 6-(2,4-dimethoxyphenylamino)-2-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate:** To *tert*-butyl 6-bromo-2-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (48 mg, 0.108 mmol) was added cesium carbonate (70 mg, 0.216 mmol) and Xantphos (6.2 mg, 0.0108 mmol) and then 2,4-dimethoxyaniline (20 mg, 0.129 mmol). Dioxane (1.2 mL) was added and the flask

flushed with nitrogen. Tris(dibenzylideneacetone)dipalladium(0) (5 mg, 0.0054 mmol) was added and the flask was flushed again with nitrogen and heated at 80 °C for 3 h. The reaction was cooled and diluted with EtOAc. The solution was washed with water and with brine, dried and evaporated. The residue was applied to one 2 mm 20 x 20 cm silica prep TLC plate, which was eluted with EtOAc. The product band was recovered with acetone giving product (45 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.40 (s, 9H, 3.83 (s, 3H), 3.87 (s, 3H, 4.01 (s, 3H), 6.49 (d, J = 0.6 Hz, 1H), 6.53 (dd, J = 8.5, 2.5 Hz, 1H), 6.57 (d, J = 2.5 Hz, 1H), 6.67 (s, 1H), 7.46 (s, 1H), 7.49 (s, 1H), 7.71 (d, J = 8.8 Hz, 1H), 8.44 (d, J = 1.0 Hz, 1H); ^{19}F NMR (470.385 MHz, $CDCl_3$): δ -60.72; LC (Method A)-MS (ESI, m/z) t_R 2.09 min, 518 [($M+H^+$), 100%].

_N_-(2,4-Dimethoxyphenyl)-2-(1-methyl-3-(trifluoromethyl)-1_H_-pyrazol-4-yl)-1_H_-pyrrolo[3,2-_c_]pyridin-6-amine (32)

tert-Butyl-6-(2,4-dimethoxyphenylamino)-2-(1-methyl-3-(trifluoromethyl)-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (45 mg, 0.087 mmol) was dissolved in CH_2Cl_2 (1 mL) and TFA (1 mL) was added. The reaction was stirred at rt for 3 h. The solvents were evaporated. The residue was partitioned between EtOAc and saturated $NaHCO_3$. The organic solution was washed with brine, then dried and evaporated. The residue was triturated with a small volume of ether to leave a grey solid, the product (27 mg, 75%). ^{1}H NMR (500 MHz, DMSO *d*-6): δ 3.75 (s, 3H), 3.81 (s, 3H), 3.98 (s, 3H), 6.46 (s, 1H), 6.50 (dd, J = 8.8, 2.8 Hz, 1H), 6.63 (m, 2H), 7.27 (s, 1H), 7.67 (d, J = 8.8 Hz, 1H), 8.20 (s, 1H), 8.37 (s, 1H), 11.09 (s, 1H); ^{19}F NMR (470.385 MHz, DMSO *d*-6): δ -59.86; ESI-HRMS Found: 418.1506, calcd for $C_{20}H_{19}F_3N_5O_2$ $[M+H]^+$: 418.1485.

Preparation of 2-(1,5-Dimethyl-1*H*-pyrazol-4-yl)-*N*-(2-methoxyphenyl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-amine (33)

1,5-Dimethyl-4-((trimethylsilyl)ethynyl)-1*H*-pyrazole: 4-Iodo-1,5-dimethyl-1*H*-pyrazole (401 mg, 1.8 mmol) was dissolved in DMF (2.5 mL) and TMS-acetylene (0.36 mL, 2.54 mmol) was added; followed by diisopropylamine (0.33 mL, 2.35 mmol), copper(I) iodide (22.5 mg, 0.12 mmol) and triphenylphosphine (94 mg, 0.36 mmol). The reaction was flushed with nitrogen. Palladium acetate (26.8 mg, 0.12 mmol) was added and the reaction flushed again with nitrogen. It was heated at 40 °C during which time (about 10 min, amine hydriodide was seen to deposit) and then at 60 °C for 65 min. The reaction was then cooled and added to water. The product was extracted with EtOAc. The combined organics were washed with water and with brine, then dried and evaporated to leave a dark oil. This was applied to three 2 mm 20 x 20 cm silica prep TLC plates which were eluted with EtOAc/cyclohexane (1/3). The product band was recovered with acetone to give product (293 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.23 (s, 9H), 2.32 (s, 3H), 3.76 (s, 3H), 7.49 (s, 1H); LC (Method A)-MS (ESI, *m/z*) t_R 2.56 min, 193 [($M+H^+$), 100%].

4-Ethynyl-1,5-dimethyl-1*H*-pyrazole: 1,5-Dimethyl-4-((trimethylsilyl)ethynyl)-1*H*-pyrazole (600 mg, 3.1 mmol) was dissolved in MeOH (6 mL). Potassium carbonate (30 mg, 0.22 mmol) was added and the mixture was stirred at rt for 2.5 h. The MeOH was evaporated and CH_2Cl_2 was added to the residue. The solution was washed with water, dried and evaporated. The residue was flash columned eluting with cyclohexane/EtOAc (3/1) and then cyclohexane/EtOAc (2/1) giving product (238 mg, 63%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.34 (s, 3H), 3.10 (s, 1H), 3.79 (s, 3H), 7.52 (s, 1H).

6-Bromo-2-(1,5-dimethyl-1*H*-pyrazol-4-yl)-1-(methylsulfonyl)-1*H*-pyrrolo[3,2-*c*]pyridine: To a solution of 4-ethynyl-1,5-dimethyl-1*H*-pyrazole (153 mg, 1.27 mmol) and *N*-(2-bromo-5-iodopyridin-4-yl)methanesulfonamide **16** (400 mg, 1.06 mmol) in DMF (3.4 mL) was added copper(I) iodide (7.1 mg, 0.037 mmol) and Et_3N (0.64 mL, 4.5 mmol). The reaction was placed under nitrogen. Bis(triphenylphosphine)palladium dichloride (26.1 mg, 0.037 mmol) was added and the reaction was flushed again with nitrogen, then heated at 60 °C for 4 h. The reaction was cooled and added to water. The products were extracted with EtOAc. The combined organics were washed with water, with brine and then dried and evaporated. The residue was applied to three 2 mm 20 x 20 cm silica prep TLC plates which were eluted twice with EtOAc/CH_2Cl_2 (1/1). The product band was recovered with acetone to give product (157 mg, 40%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.27 (s, 3H), 2.97 (s, 3H), 3.88 (s, 3H), 6.62 (d, J = 0.6 Hz, 1H), 7.54 (s, 1H), 8.24 (t, J = 1.0 Hz, 1H), 8.66 (d, J = 1.0 Hz, 1H); LC (Method A)-MS (ESI, m/z) t_R 2.10 min, 369 [($M+H^+$), 100%].

***tert*-Butyl 6-bromo-2-(1,5-dimethyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate:** 6-Bromo-2-(1,5-dimethyl-1*H*-pyrazol-4-yl)-1-(methylsulfonyl)-1*H*-pyrrolo[3,2-*c*]pyridine (157 mg, 0.43 mmol) was stirred with MeOH (2 mL) and 1 M sodium hydroxide solution (0.51 mL, 0.51 mmol) at 25 °C for 3 h. The MeOH was evaporated and the residue was taken up in EtOAc. The solution was washed with water and with brine, dried and evaporated. The residue was dissolved in EtOAc (2.5 mL) and di-*tert*-butyl dicarbonate (140 mg, 0.64 mmol) was added, followed by Et_3N (75 μL, 0.53 mmol) and a crystal of DMAP. The reaction was stirred at rt for 1 h. Solvent was evaporated and the residue was applied to three 1 mm 20 x 20 cm silica prep TLC plates, which were eluted with EtOAc (twice) and the product band was recovered with acetone. This gave the desired Boc-protected compound (123 mg, 73%). ^{1}H

NMR (500 MHz, $CDCl_3$): δ 1.47 (s, 9H), 2.26 (s, 3H), 3.86 (s, 3H), 6.49 (d, *J* = 0.6 Hz, 1H), 7.45 (s, 1H), 8.26 (t, *J* = 1.0 Hz, 1H), 8.59 (d, *J* = 1.0 Hz, 1H); LC (Method A)-MS (ESI, *m/z*) t_R 2.59 min, 335 [$(M+H^+-C_4H_8)$, 100%].

***tert*-Butyl-2-(1,5-dimethyl-1*H*-pyrazol-4-yl)-6-(2-methoxyphenylamino)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate:** To *tert*-butyl 6-bromo-2-(1,5-dimethyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (42 mg, 0.108 mmol) was added cesium carbonate (70 mg, 0.216 mmol) and Xantphos (6.2 mg, 0.0108 mmol) and then 2-methoxyaniline (16 mg, 0.13 mmol) in dioxane (0.4 mL). Dioxane (0.8 mL) was added and the flask flushed with nitrogen. Tris(dibenzylideneacetone)dipalladium(0) (5 mg, 0.0054 mmol) was added and the flask was flushed again with nitrogen and heated at 80 °C for 4.5 h. The reaction was cooled and diluted with EtOAc. The organic solution was washed with water and with brine; dried and evaporated. The residue was applied to one 1 mm 20 x 20 cm silica prep TLC plate which was eluted with CH_2Cl_2/EtOAc (1/1). The product band was recovered with acetone to give a mixture (35 mg) containing (by NMR) both the product (78%w/w) and starting material. Prep HPLC provided a sample of the product (21 mg, 45%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44 (s, 9H), 2.19 (s, 3H), 3.85 (s, 3H), 3.92 (s, 3H), 6.40 (d, *J* = 1.0 Hz, 1H), 6.91-7.00 (m, 3H), 7.08 (br s, 1H), 7.44 (s, 1H), 7.70 (t, *J* = 1.0 Hz, 1H), 7.99 (dd, *J* = 7.6, 1.6 Hz, 1H), 8.48 (d, *J* = 1.0 Hz, 1H); LC (Method A)-MS (ESI, *m/z*) t_R 1.99 min, 434 [$(M+H^+)$, 100%].

2-(1,5-Dimethyl-1*H*-pyrazol-4-yl)-*N*-(2-methoxyphenyl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-amine (33)

tert-Butyl-2-(1,5-dimethyl-1*H*-pyrazol-4-yl)-6-(2-methoxyphenylamino)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (21 mg) was dissolved in CH_2Cl_2 (0.8 mL) and TFA (0.8 mL) and

stirred at rt for about 6 h. The solution was evaporated and the residue kept in a vacuum desiccator over NaOH overnight. The residue was partitioned between EtOAc and $NaHCO_3$ solution. The aqueous was washed again with EtOAc and the combined organics dried and evaporated to leave the crude product (14 mg). This was triturated with ether to give the title compound (12 mg, 74%). ^{1}H NMR (500 MHz, CD_3OD): δ 2.53 (s, 3H), 3.87 (s, 3H), 3.91 (s, 3H), 6.47 (d, *J* = 1.0 Hz, 1H), 6.89-6.97 (m, 2H), 7.00-7.03 (m, 2H), 7.52 (m, 1H), 7.71 (s, 1H), 8.37 (s, 1H); ESI-HRMS Found: 334.1659, calcd for $C_{19}H_{20}N_5O$ $[M+H]^+$: 334.1662.

Preparation of 2-(3,5-Dimethylisoxazol-4-yl)-*N*-(2-methoxyphenyl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-amine (35)

3,5-Dimethyl-4-((trimethylsilyl)ethynyl)isoxazole: 3,5-Dimethylisoxazole (1.96 mL, 20 mmol) was dissolved in acetonitrile and iodine (3.05 g, 12 mmol) and ceric ammonium nitrate (6.58 g, 12.0 mmol) were added. The reaction was stirred at rt for 20 h. The solvent was evaporated and EtOAc was added. The organic solution/suspension was washed with 5% sodium hydrogen sulfite solution and with brine, and the resulting solution was dried and evaporated to give 4-iodo-3,5-dimethylisoxazole as a white solid (2.66 g, 59%) which was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.26 (s, 3H), 2.45 (s, 3H). 4-Iodo-3,5-dimethylisoxazole (446 mg, 2.0 mmol) was dissolved in DMF (2.8 mL) and ethynyltrimethylsilane (0.395 mL, 2.8 mmol) was added followed by diisopropylamine (0.372 mL, 2.64 mmol), copper(I) iodide (24.7 mg, 0.13 mmol) and triphenylphosphine (105 mg, 0.40 mmol). The reaction was flushed with nitrogen. Palladium acetate (29.6 mg, 0.13 mmol) was added and the reaction was again flushed with nitrogen and then heated at 60 °C for 55 min. The reaction was cooled, diluted with water and extracted with EtOAc. The combined organics were washed with water and with brine, dried and evaporated. The resulting dark oil was applied to

three 2 mm 20 x 20 cm silica prep TLC plates, which were eluted with EtOAc/cyclohexane (1/10) and the product band was recovered with acetone, evaporating to yield 281 mg, 72%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.26 (s, 9H), 2.28 (s, 3H), 2.45 (s, 3H).

4-Ethynyl-3,5-dimethylisoxazole: 3,5-Dimethyl-4-((trimethylsilyl)ethynyl)isoxazole (281 mg, 1.45 mmol) was dissolved in THF (3.5 mL) and the solution cooled to 0-5 °C in an ice bath. Tetrabutylammonium fluoride (1 M in THF, 1.6 mL, 1.6 mmol) was added and the reaction was stirred for 15 min in the ice bath. The solvent was evaporated to low volume and EtOAc was added. The solution was washed with water and with brine, dried and evaporated. The crude product was passed through a very short silica pad in a sinter using EtOAc. The filtrate was carefully evaporated to small volume leaving (122 mg, 69%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.30 (s, 3H), 2.46 (s, 3H), 3.20 (s, 1H).

4-(6-Bromo-1-(methylsulfonyl)-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-3,5-dimethylisoxazole: To 4-ethynyl-3,5-dimethylisoxazole (122 mg, 1.0 mmol) was added *N*-(2-bromo-5-iodopyridin-4-yl)methanesulfonamide **16** (314 mg, 0.83 mmol), copper(I) iodide (5.6 mg, 0.0294 mmol), DMF (2.75 mL), Et_3N (0.52 mL, 3.66 mmol) and bis(triphenylphosphine)palladium dichloride (20.7 mg, 0.0295 mmol). The reaction was placed under nitrogen and heated at 60 °C for 65 min. The reaction was cooled and partitioned between water and EtOAc. Filtration through a paper was necessary to aid separation of the phases. The aqueous was extracted twice more with EtOAc. The combined organics were washed with water and with brine, dried and evaporated. The residue was applied in acetone to two 2 mm 20 x 20 cm silica prep TLC plates. These were eluted with EtOAc/cyclohexane (3/1), and bands recovered with acetone. The mobile product band yielded 64 mg (20%). More crude product (135 mg) relatively insoluble in the eluant was recovered from the baseline area. This crude substance was applied in chloroform to two 1 mm

20 x 20 cm silica prep TLC plates, which were eluted with 4% MeOH in CH_2Cl_2. The product band was recovered with acetone to give more of the desired product (53 mg, 17%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.24 (s, 3H), 2.41 (s, 3H), 2.99 (s, 3H), 6.71 (d, *J* = 1.0 Hz, 1H), 8.23 (m, 1H), 8.72 (d, *J* = 1.0, 1H); LC (Method B)-MS (ESI, *m/z*) t_R 2.61 min, 370 [$(M+H^+)$].

***tert*-Butyl 6-bromo-2-(3,5-dimethylisoxazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate:** 4-(6-Bromo-1-(methylsulfonyl)-1*H*-pyrrolo[3,2-*c*]pyridin-2-yl)-3,5-dimethylisoxazole (117 mg, 0.316 mmol) was stirred in THF (2 mL)/MeOH (1 mL) and DBU (71 μL, 0.474 mmol) was added. The mix was heated at 45-50 °C for 2.5 h. The solution was evaporated and the residue taken up in EtOAc and the solution washed with water and with brine. The solution was dried and evaporated. To the residue was added EtOAc (2 mL), Et_3N (56 μL, 0.4 mmol), a crystal of DMAP and di-*tert*-butyl dicarbonate (98 mg, 0.45 mmol). The reaction was stirred at rt for 2 h, then evaporated. The residue was applied to two 1 mm 20 x 20 cm prep TLC plates. These were eluted with EtOAc/cyclohexane (1/1) and the product bands recovered with acetone to give product (81 mg, 65%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.48 (s, 9H), 2.16 (s, 3H), 2.36 (s, 3H), 6.59 (d, *J* = 0.6 Hz, 1H), 8.35 (t, *J* = 0.6 Hz, 1H), 8.65 (d, *J* = 0.6 Hz, 1H); LC (Method B)-MS (ESI, *m/z*) t_R 3.11 min, 336 [$(M+H^+-C_4H_8)$, 100%].

***tert*-Butyl-2-(3,5-dimethylisoxazol-4-yl)-6-(2-methoxyphenylamino)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate:** To *tert*-butyl 6-bromo-2-(3,5-dimethylisoxazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (44 mg, 0.112 mmol) was added cesium carbonate (73 mg, 0.225 mmol), Xantphos (6.4 mg, 0.0111 mmol) and 2-methoxyaniline (16 μL, 0.14 mmol). Dioxane (1.2 mL) was added and the flask flushed with nitrogen. Tris(dibenzylideneacetone)dipalladium(0) (6.1 mg, 0.0056 mmol) was added and the flask was flushed again with nitrogen and heated at 80 °C for 2.75 h. The reaction was cooled and diluted

with EtOAc. The solution was washed with water and with brine, dried and evaporated. The residue was applied in chloroform to two 1 mm 20 x 20 cm silica prep TLC plates which were eluted with CH_2Cl_2/EtOAc (7/1). The product band was recovered with acetone, giving the title compound (39 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 (s, 9H), 2.18 (s, 9H), 2.36 (s, 3H), 3.92 (s, 3H), 6.48 (d, *J* = 1.0 Hz, 1H), 6.92-7.02 (m, 3H), 7.11 (br s, 1H), 7.74 (s, 1H), 8.02 (dd, *J* = 7.6, 1.9 Hz, 1H), 8.52 (s, 1H); LC (Method B)-MS (ESI, *m/z*) t_R 2.65 min, 435 [$(M+H^+)$].

2-(3,5-Dimethylisoxazol-4-yl)-*N*-(2-methoxyphenyl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-amine (35)

tert-Butyl-2-(3,5-dimethylisoxazol-4-yl)-6-(2-methoxyphenylamino)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (39 mg) was taken up in CH_2Cl_2 (0.6 mL) and TFA (0.6 mL) was added. The reaction was stirred at rt for 4.5 h. The solvent and reagent were evaporated and the residue was partitioned between $NaHCO_3$ solution and EtOAc. The aqueous was extracted again with EtOAc and the combined organics were washed with brine, dried and evaporated to leave a gum (32 mg). This was triturated with ether/cyclohexane to give **30** as a solid (26 mg, 86%). ^{1}H NMR (500 MHz, DMSO *d*-6): δ 2.33 (s, 3H), 2.52 (s, 3H), 3.85 (s, 3H), 6.52 (m, 1H), 6.84-6.91 (m, 2H), 6.97 (s, 1H), 7.00 (m, 1H), 7.56 (s, 1H), 7.98 (m, 1H), 8.47 (s, 1H), 11.07 (s, 1H); ESI-HRMS Found: 335.1495, calcd for $C_{19}H_{19}N_4O_2$ $[M+H]^+$: 335.1503.

Preparation of *N*-(2-Methoxyphenyl)-2-(1-methyl-1*H*-imidazol-5-yl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-amine (36)

6-Bromo-2-(1-methyl-1*H*-imidazol-5-yl)-1-(methylsulfonyl)-1*H*-pyrrolo[3,2-*c*]pyridine

5-Ethynyl-1-methylimidazole (159 mg, 1.5 mmol) and *N*-(2-bromo-5-iodopyridin-4-yl)methanesulfonamide **16** (453 mg, 1.20 mmol) were dissolved in DMF (3.9 mL) and to the

solution was added Et_3N (0.73 mL, 5.2 mmol) and copper(I) iodide (8 mg, 0.042 mmol). The reaction was flushed with nitrogen and then was added bis(triphenylphosphine)palladium dichloride (29.6 mg, 0.042 mmol). The reaction was flushed with nitrogen and heated at 60 °C for 90 min. Water was added and the products were extracted into EtOAc. Some flocculent solids were filtered from the organic solution and washed with EtOAc. The filtrate was washed with water and with brine, then dried and evaporated. The residue (337 mg) was applied to four 2 mm 20 x 20 cm silica prep TLC plates and these were eluted with CH_2Cl_2/MeOH/Et_3N (10/1/0.1). The product band was recovered with EtOH containing about 2% of 7 M ammonia in MeOH giving product (155 mg, 36%). ^{1}H NMR (500 MHz, CD_3OD): δ 3.23 (s, 3H), 3.62 (s, 3H), 7.12 (d, *J* = 1.0 Hz, 1H), 7.32 (br s, 1H), 7.86 (br s, 1H), 8.25 (t, *J* = 1.0 Hz, 1H), 8.77 (d, *J* = 1.0 Hz, 1H); LC (Method A)-MS (ESI, *m/z*) t_R 1.20 min, 355 [($M+H^+$), 100%].

***tert*-Butyl 6-bromo-2-(1-methyl-1*H*-imidazol-5-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate:** 6-Bromo-2-(1-methyl-1*H*-imidazol-5-yl)-1-(methylsulfonyl)-1*H*-pyrrolo[3,2-*c*]pyridine (151 mg, 0.43 mmol) was stirred in MeOH (2 mL) and 1 M sodium hydroxide (0.51 mL) was added. The reaction was stirred at rt for 140 min; it became homogeneous. The MeOH was evaporated and the residue was taken up in EtOAc and the solution washed with water and with brine. The organic solution was dried and evaporated. The residue was taken up in EtOAc and Et_3N (96 μL, 0.69 mmol) was added along with a crystal of DMAP. Di-*tert*-butyl dicarbonate (151 mg, 0.69 mmol) was added and the reaction was stirred at rt for about 2 h (complete by LCMS after 55 min). The solvent was evaporated and the residue was applied in EtOAc to two 1.5 mm 20 x 20 cm alumina prep TLC plates. These were eluted with EtOAc and the product band recovered with acetone. This gave product (57 mg, 35%, over 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44 (s, 9H), 3.51 (s, 3H), 6.73 (d, *J* = 0.6 Hz, 1H), 7.14 (d, *J* = 1.0 Hz, 1H), 7.59 (d, *J* = 1.0 Hz, 1H),

8.36 (t, J = 1.0 Hz, 1H), 8.67 (d, J = 1.0 Hz, 1H); LC (Method A)-MS (ESI, m/z) t_R 1.70 min, 321 [($M+H^+-C_4H_8$), 100%].

***tert*-Butyl-6-(2-methoxyphenylamino)-2-(1-methyl-1*H*-imidazol-5-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate:** To *tert*-Butyl 6-bromo-2-(1-methyl-1*H*-imidazol-5-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (41 mg, 0.108 mmol) was added cesium carbonate (70 mg, 0.216 mmol) and Xantphos (6.2 mg, 0.0108 mmol) and then 2-methoxyaniline (16 mg, 0.13 mmol) in dioxane (0.4 mL). Dioxane (0.8 mL) was added and the flask flushed with nitrogen. Tris(dibenzylideneacetone)dipalladium(0) (5 mg, 0.0054 mmol) was added and the flask was flushed again with nitrogen and heated at 80 °C for 23 h. The reaction was cooled and diluted with EtOAc. The solution was washed with water and with brine, dried and evaporated. The residue (56 mg) was applied to two 1 mm 20 x 20 cm silica prep TLC plates which were eluted with CH_2Cl_2/MeOH/Et_3N (10/1/1). Bands were recovered with EtOH containing 1% Et_3N. One band gave a mixture (20 mg) containing unchanged starting material and product in a 3:2 ratio. This was further purified by prep HPLC to give a sample of the product (6 mg, 13%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.40 (s, 9H), 3.51 (s, 3H), 3.92 (s, 3H), 6.63 (d, J = 0.6 Hz, 1H), 6.91-7.02 (m, 3H), 7.10 (s, 1H), 7.18 (s, 1H), 7.58 (s, 1H), 7.74 (m, 1H), 8.02 (m, 1H), 8.53 (d, J = 1.0 Hz, 1H); LC (Method B)-MS (ESI, m/z) t_R 1.96 min, 420 [($M+H^+$)].

***N*-(2-Methoxyphenyl)-2-(1-methyl-1*H*-imidazol-5-yl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-amine (36)**

tert-Butyl-6-(2-methoxyphenylamino)-2-(1-methyl-1*H*-imidazol-5-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate was stirred at rt in a mix of CH_2Cl_2 (0.5 mL) and TFA (0.5 mL) for 6 h. The solvents were evaporated and the residue kept overnight in a vacuum desiccator over NaOH. The residue was partitioned between EtOAc and 10% sodium carbonate. The layers were shaken

and separated and the aqueous was again extracted with EtOAc. The combined organics were dried and evaporated to leave the title compound (3.5 mg, 76%). ^{1}H NMR (500 MHz, CD_3OD): δ 3.90 (s, 3H), 3.91 (s, 3H), 6.72 (d, *J* = 0.6 Hz, 1H), 6.91-7.05 (m, 3H), 7.01 (t, *J* = 1.0 Hz, 1H), 7.32 (d, *J* = 1.0 Hz, 1H), 7.55 (dd, *J* = 7.6, 1.9 Hz, 1H), 7.75 (s, 1H), 8.45 (d, *J* = 1.0 Hz, 1H); LC (Method A)-MS (ESI, *m/z*) t_R 0.96 min, 320 [($M+H^+$), 100%].

_N_-(2-Methoxy-5-(trifluoromethyl)phenyl)-2-(1-methyl-1_H_-pyrazol-4-yl)-1_H_-pyrrolo[3,2-_c_]pyridin-6-amine (37)

Tris(dibenzylideneacetone)dipalladium(0) (4.9 mg, 5.30 μmol) was added to a mixture of *tert*-butyl 6-bromo-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate **47** (40 mg, 0.106 mmol), cesium carbonate (69 mg, 0.212 mmol), 2-methoxy-5-(trifluoromethyl)aniline (24.3 mg, 0.127 mmol) and Xantphos (6.1 mg, 10.60 μmol) in DMA (1.2 mL). The vial was flushed with dry argon and the reaction mixture was heated at 80 °C for 3 h. It was then filtered on SCX-2 column and concentrated under vacuum. The residue was purified *via* Biotage silica gel column chromatography eluting with CH_2Cl_2/EtOH (99/1 to 95/5) to afford *tert*-Butyl 6-(2-methoxy-5-(trifluoromethyl)phenylamino)-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate as a white solid (43 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.50 (s, 9H), 3.97 (s, 3H), 3.98 (s, 3H), 6.51 (d, *J* = 0.9 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 7.13 (s, 1H), 7.18 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.55 (s, 1H), 7.61 (s, 1H), 7.65 (m, 1H), 8.44 (d, *J* = 2.1 Hz, 1H), 8.51 (d, *J* = 1.0 Hz, 1H); LC (Method B)-MS (ESI, *m/z*) t_R 2.88 min, 488 [($M+H^+$), 100%]. *tert*-Butyl 6-(2-methoxy-5-(trifluoromethyl)phenylamino)-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (43 mg, 0.088 mmol) in TFA (900 μL) was stirred for 3 h at rt. The reaction mixture was then concentrated, the residue was then dissolved in MeOH and filtered through an Isolute Flash NH_2 column to afford **37** as a white solid (32 mg, 94%).^{1}H

NMR (500 MHz, CD_3OD): δ 3.95 (s, 3H), 4.00 (s, 3H), 6.59 (d, *J* = 0.9 Hz, 1H), 7.04 (t, *J* = 0.9 Hz, 1H), 7.09 (d, *J* = 8.5 Hz, 1H), 7.16 (m, 1H), 7.86 (d, *J* = 0.8 Hz, 1H), 7.94–7.96 (m, 2H), 8.43 (d, *J* = 1.0 Hz, 1H); ESI-HRMS Found: 388.1379, calcd for $C_{19}H_{17}FN_5O$ $[M+H]^+$: 388.1380.

_N_-(2-Chlorophenyl)-2-(1-methyl-1_H_-pyrazol-4-yl)-1_H_-pyrrolo[3,2-_c_]pyridin-6-amine (38)

tert-Butyl 6-(2-chlorophenylamino)-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate **49** (23 mg, 0.054 mmol) in TFA (540 μL) was stirred for 2 h at rt. It was then concentrated and filtered on an Isolute Flash NH_2 column to afford the title product as a yellow solid (16 mg, 91%). ^1H NMR (500 MHz, CD_3OD): δ 3.95 (s, 3H), 6.60 (d, *J* = 0.9 Hz, 1H), 6.90 (ddd, *J* = 8.0, 7.4, 1.5 Hz, 1H), 7.00 (t, *J* = 0.9 Hz, 1H), 7.18–7.23 (m, 1H), 7.40 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.54 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.85 (s, 1H), 7.96 (s, 1H), 8.39 (d, *J* = 0.9 Hz, 1H); ESI-HRMS Found 324.1007, calcd for $C_{17}H_{15}ClN_5$ $[M+H]^+$: 324.1010.

3-Chloro-_N_,_N_-dimethyl-4-(2-(1-methyl-1_H_-pyrazol-4-yl)-1_H_-pyrrolo[3,2-_c_]pyridin-6-ylamino)benzenesulfonamide (41)

tert-Butyl 6-(2-chloro-4-(*N*,*N*-dimethylsulfamoyl)phenylamino)-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate **50** (21 mg, 0.040 mmol) in TFA (395 μL) was stirred for 1 h at rt. The reaction mixture was then concentrated and the residue dissolved in MeOH and filtered through an Isolute Flash NH_2 column and concentrated under vacuum to afford the title product as a yellow solid (17 mg, 100%). ^1H NMR (500 MHz, CD_3OD): δ 2.68 (s, 6H), 3.96 (s, 3H), 6.67 (d, *J* = 0.9 Hz, 1H), 7.19 (t, *J* = 0.9 Hz, 1H), 7.53 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.68 (d, *J* = 8.8 Hz, 1H), 7.75 (d, *J* = 2.2 Hz, 1H), 7.88 (s, 1H), 8.01 (s, 1H), 8.50 (d, *J* = 0.9 Hz, 1H). ESI-HRMS Found 431.1042, calcd for $C_{19}H_{20}ClN_6O_2S$ $[M+H]^+$: 431.1051.

(3-Chloro-4-(2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-ylamino)phenyl)(4-methoxypiperidin-1-yl)methanone (42)

tert-Butyl-6-(2-chloro-4-(4-methoxypiperidine-1-carbonyl)phenylamino)-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate **52** (18 mg, 0.032 mmol) was stirred in 2 mL of 50% TFA in CH_2Cl_2 for 2 h. Volatiles were removed in vacuum and the residue applied to an Isolute Flash NH_2 column. The column was eluted with 50% MeOH in CH_2Cl_2 and the solvents removed in vacuum. The residue was triturated with ether/ hexane to afford the title compound as a pale brown powder (14 mg, 94%). ^{1}H NMR (500 MHz, DMSO *d*-6): δ 1.46 (br s, 2H), 1.85 (br s, 2H), 3.26 (br s, 4H), 3.29 (s, 3H), 3.46 (br s, 1H), 3.90 (s, 3H), 6.57 (s, 1H), 7.11 (s, 1H), 7.43 (d, *J* = 1.9 Hz, 1H), 7.89 (s, 1H), 8.10 (m, 3H), 8.42 (s, 1H), 11.50 (s, 1H); ESI-HRMS Found: 465.1789, calcd for $C_{24}H_{25}ClN_6O_2$ $[M+H]^+$: 465.18.

(3-Chloro-4-(2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-ylamino)phenyl)(4-(dimethylamino)piperidin-1-yl)methanone (43)

tert-Butyl-6-(2-chloro-4-(4-(dimethylamino)piperidine-1-carbonyl)phenylamino)-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate **53** (20 mg, 0.035 mmol) was stirred in 2 mL of 50% TFA in CH_2Cl_2 for 2 h. Volatiles were removed in vacuum and the residue applied to an Isolute Flash NH_2 column. The column was eluted with 50% MeOH in CH_2Cl_2 and the solvents removed in vacuum. The residue was triturated with ether/hexane to afford the title compound as a pale brown powder (16 mg, 97%). ^{1}H NMR (500 MHz, DMSO *d*-6): δ 1.35 (m, 2H), 1.75 (br s, 2H), 2.16 (s, 6H), 2.32 (t, *J* = 7.0 Hz, 1H), 2.90 (br s, 2H), 3.90 (s, 3H), 4.05 (br s, 2H), 6.57 (s, 1H), 7.11 (s, 1H), 7.28 (d, *J* = 8.2 Hz, 1H), 7.43 (d, *J* = 2.0 Hz, 1H), 7.89 (s, 1H),

8.09 (m, 3H), 8.42 (s, 1H), 11.45 (s, 1H); ESI-HRMS Found: 478.2099, calcd for $C_{25}H_{28}ClN_7O$ $[M+H]^+$: 478.2117.

(3-Chloro-4-(2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridin-6-ylamino)phenyl)(*S*,*S*-dioxo-thiomorpholino)methanone (44)

tert-Butyl 6-(2-chloro-4-(*S*,*S*-dioxo-thiomorpholine-4-carbonyl)phenylamino)-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate **54** (15 mg, 0.0256 mmol) was stirred in 2 mL of 50% TFA in CH_2Cl_2 for 2 h. Volatiles were removed in vacuum and the residue applied to an Isolute Flash NH_2 column. The column was eluted with 50% MeOH in CH_2Cl_2 and the solvents removed in vacuo. The residue was triturated with ether/hexane to afford the pure title compound as a white powder (11 mg, 89%). ^{1}H NMR (500 MHz, DMSO *d*-6): δ 3.22 (s, 3H), 3.89 (s, 3H), 4.23 (m, 4H), 4.50 (br s, 1H), 6.57 (s, 1H), 7.16 (s, 1H), 7.49 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.65 (d, *J* = 2.1 Hz, 1H), 7.90 (s, 1H), 8.11 (s, 1H), 8.13 (d, *J* = 2.1 Hz, 1H), 8.21 (s, 1H), 8.44 (s, 1H), 11.55 (s, 1H); ESI-HRMS Found: 437.1757, calcd for $C_{22}H_{21}ClN_6O_2$ $[M+H]^+$: 437.1772.

Preparation of compounds in Table 5

***tert*-Butyl-6-(2-chlorophenylamino)-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (49)**

Tris(dibenzylideneacetone)dipalladium(0) (4.9 mg, 5.30 μmol) was added to a mixture of *tert*-butyl 6-bromo-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate **47** (40 mg, 0.106 mmol), cesium carbonate (69 mg, 0.212 mmol), 2-chloroaniline (13 μL, 0.127 mmol) and Xantphos (6.1 mg, 10.60 μmol) in DMA (1.2 mL). The vial was flushed with dry argon and

the reaction mixture was heated at 80 °C for 3 h. It was then filtered on SCX-2 column and concentrated under vacuum. The residue was purified *via* Biotage silica gel column chromatography eluting with CH_2Cl_2/EtOH (99/1) to afford the title product as a white solid (33 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.51 (s, 9H), 3.97 (s, 3H), 6.51 (d, *J* = 1.0 Hz, 1H), 6.89–6.95 (m, 2H), 7.34 (ddd, *J* = 8.2, 7.4, 1.5 Hz, 1H), 7.41 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.55 (s, 1H), 7.61 (s, 1H), 7.65 (t, *J* = 1.0 Hz, 1H), 7.97 (dd, *J* = 8.2, 1.5 Hz, 1H), 8.49 (d, *J* = 1.0 Hz, 1H); ESI-HRMS Found: 424.1529, calcd for $C_{22}H_{23}ClN_5O_2$ $[M+H]^+$: 421.1535.

***tert*-Butyl 6-(2-chloro-4-(*N*,*N*-dimethylsulfamoyl)phenylamino)-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (50)**

Tris(dibenzylideneacetone)dipalladium(0) (4.9 mg, 5.30 μmol) was added to a mixture of *tert*-butyl 6-bromo-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate **47** (40 mg, 0.106 mmol), cesium carbonate (69 mg, 0.212 mmol), 4-amino-3-chloro-*N*,*N*-dimethylbenzenesulfonamide (29.9 mg, 0.127 mmol) and Xantphos (6.1 mg, 10.60 μmol) in DMA (1.2 mL). The vial was flushed with dry argon and the reaction mixture was heated at 80 °C for 3 h. It was then filtered on SCX-2 column and concentrated under vacuum. The residue was purified *via* Biotage silica gel column chromatography eluting with CH_2Cl_2/EtOH (99/1 to 97/3) to afford the title product as a white solid (43 mg, 76%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.52 (s, 9H), 2.74 (s, 6H), 3.99 (s, 3H), 6.56 (d, *J* = 0.6 Hz, 1H), 7.28 (s, 1H), 7.57 (s, 1H), 7.62 (s, 1H), 7.63 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.78 (s, 1H), 7.82 (d, *J* = 2.1 Hz, 1H), 8.40 (d, *J* = 8.8 Hz, 1H), 8.57 (s, 1H); ESI-HRMS Found 531.1570, calcd for $C_{24}H_{28}ClN_6O_4S$ $[M+H]^+$: 531.1576.

4-Amino-3-chloro-*N*,*N*-dimethylbenzenesulfonamide: A suspension of 4-acetamido-3-chlorobenzene-1-sulfonyl chloride (0.96g, 3.58 mmol) in a dimethylamine solution (2 M in

MeOH, 5.4 mL, 10.7 mmol) was stirred under argon at room temperature for 2.5 h. The reaction mixture was concentrated under reduced pressure and the residue was then redissolved in MeOH (17.9 mL). A 1 M HCl solution in MeOH (5.4 mL, 5.37 mmol) was added and the reaction mixture was refluxed for 6 h before being concentrated under reduced pressure. The residue was purified *via* Biotage silica gel column chromatography eluting with cyclohexane/EtOAc (80/20 to 60/40) to afford the title product as a white solid (133 mg, 16%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.70 (s, 6H), 4.54 (br s, 2H), 6.83 (d, J = 8.5 Hz, 1H), 7.48 (dd, J = 8.5, 2.1 Hz, 1H), 7.70 (d, J = 2.1 Hz, 1H); LC (Method B)-MS (ESI, m/z) t_R 2.24 min, 235 [$(M+H^+)$, 100%].

tert-Butyl-6-((4-(azetidine-1-carbonyl)-2-chlorophenyl)amino)-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (51)

Tris(dibenzylideneacetone)dipalladium(0) (6.9 mg, 7.55 μmol) was added to a mixture of *tert*-butyl 6-bromo-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate **47** (0.057 g, 0.15 mmol), (4-amino-3-chlorophenyl)(azetidin-1-yl)methanone (38.2 mg, 0.18 mmol), Xantphos (8.7 mg, 0.015 mmol), cesium carbonate (0.098 g, 0.30 mmol), and anhydrous DMA (1.8 mL). The 2-5 mL Biotage microwave vial was flushed with nitrogen, capped, and heated at 80 °C for 2.5 h. More Pd catalyst (3.0 mg) and ligand (3.0 mg) were then added and heating was continued at 80 °C for an additional 1 h. The DMA was removed by evaporation (Biotage V10) and the residue was partitioned between EtOAc and water. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was loaded on a prep TLC plate (20 x 20 cm, 1 mm) which eluted with 2% MeOH in EtOAc/CH_2Cl_2 (1/1). Product band was recovered and stirred with 2% MeOH in EtOAc/CH_2Cl_2 (1/1). The silica was removed by filtration, washed with EtOAc/CH_2Cl_2 (1/1) and acetone. The desired product was thus obtained as an off-white solid (0.012 g, 16%). ^{1}H NMR (500 MHz, DMSO *d*-6): δ 1.45 (s, 9H), 2.26 (m,

2H), 3.88 (s, 3H), 4.04 (br s, 2H), 4.38 (br s, 2H), 6.66 (s, 1H), 7.52 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.61 (d, *J* = 0.9 Hz, 1H), 7.66 (d, *J* = 2.0 Hz, 1H), 7.76 (s, 1H), 7.94 (s, 1H), 8.12 (d, *J* = 8.6 Hz, 1H), 8.48 (d, *J* = 0.9 Hz, 1H), 8.63 (s, 1H); ESI-HRMS Found: 507.1911, calcd for $C_{26}H_{28}ClN_6O_3$ $[M+H]^+$: 507.1906.

(4-Amino-3-chlorophenyl)(azetidin-1-yl)methanone

To a solution of 4-amino-3-chlorobenzoic acid (0.342 g, 2.00 mmol) in anhydrous DMF (2.0 mL) was added azetidine hydrochloride (0.223 g, 2.39 mmol) followed by HATU (0.832 g, 2.19 mmol) and DIPEA (0.97 mL, 0.721 g, 5.58 mmol). The reaction mixture was stirred at rt for 2.5 h under argon; the DMF was then removed by evaporation (Biotage V10). The residue was partitioned between EtOAc and a saturated $NaHCO_3$ solution. The organic layer was washed with a saturated $NaHCO_3$ solution and brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was absorbed on silica gel and the free-running powder was placed on an Isolute silica column which was eluted with EtOAc/CH_2Cl_2 (1/1), 1% and 2.5% MeOH EtOAc/CH_2Cl_2 (1/1). The title compound was obtained as a white solid (0.080 g, 19%) after trituration with diethyl ether. ^{1}H NMR (500 MHz, DMSO *d*-6): δ 2.23 (m, 2H), 3.98 (br s, 2H), 4.30 (br s, 2H), 5.90 (s, 2H), 6.75 (d, *J* = 8.5, 1H), 7.32 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.46 (d, *J* = 1.9 Hz, 1H); LC (Method A)-MS (ESI, *m/z*) t_R 1.68 min, 211 [$(M+H^+)$, 100%].

***tert*-Butyl 6-(2-chloro-4-(4-methoxypiperidine-1-carbonyl)phenylamino)-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (52)**

Tris(dibenzylideneacetone)dipalladium(0) (10 mg, 0.011 mmol) was added to a mixture of *tert*-butyl 6-bromo-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate **47** (52 mg, 0.14 mmol), cesium carbonate (91 mg, 0.28 mmol), (4-amino-3-chlorophenyl)(4-methoxypiperidin-1-yl)methanone (45 mg, 0.168 mmol) and Xantphos (12.3 mg, 0.0212 mmol) in DMA (1.2 mL). The vial was flushed with dry argon and the reaction mixture was heated at 80 °C for 3 h. It was then filtered on SCX-2 column and concentrated under vacuum. The residue was purified by silica column chromatography eluting with 5% MeOH in EtOAc. The pure fractions afforded the title product as a white powder (45 mg, 57%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29 (br s, 2H), 1.39 (s, 9H), 1.70 (m, 2H), 1.95 (m, 2H), 3.30 (br s, 1H), 3.39 (s, 3H), 3.50 (m, 1H), 3.60 (br s, 1H), 3.96 (s, 3H), 6.55 (s, 1H), 7.30 (s, 1H), 7.30 (s, 1H), 7.35 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.56 (m, 4H), 8.18 (s, 1H); ESI-HRMS Found: 565.2233, calcd for $C_{29}H_{33}ClN_6O_4$ $[M+H]^+$: 565.2235.

(4-Amino-3-chlorophenyl)(4-methoxypiperidin-1-yl)methanone: HATU (0.66 g, 1.75 mmol) was added to a solution of 4-amino-3-chlorobenzoic acid (0.3 g, 1.75 mmol), DIPEA (0.45 mL, 1.75 mmol) in dry THF (10 mL). After stirring for 1 h, 4-methoxypiperidine (201 mg, 1.75 mmol) was added. The reaction was allowed to stir for 1 h at rt. Volatiles were removed in vacuum and the crude was purified by silica column chromatography eluting with 3% MeOH in EtOAc. The pure fractions afforded the title compound as a thick oil which solidified on standing (260 mg, 55%). ^{1}H NMR (500 MHz, DMSO *d*-6): δ 1.41 (m, 2H), 1.81 (m, 2H), 3.20 (m, 5H), 3.41 (m, 1H), 3.60 (br s, 2H), 6.76 (d, *J* = 8.3 Hz, 1H), 7.08 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.23 (d, *J* = 1.9 Hz,1H); LC (Method B)-MS (ESI, *m/z*) t_R 2.21 min, 269 [$(M+H^+)$, 100%].

***tert*-Butyl 6-(2-chloro-4-(4-(dimethylamino)piperidine-1-carbonyl)phenylamino)-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (53)**

Tris(dibenzylideneacetone)dipalladium(0) (10 mg, 0.011 mmol) was added to a mixture of *tert*-butyl 6-bromo-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate **47** (52 mg, 0.14 mmol), cesium carbonate (91 mg, 0.28 mmol), (4-amino-3-chlorophenyl)(4-(dimethylamino)piperidin-1-yl)methanone (47 mg, 0.168 mmol) and Xantphos (12.3 mg, 0.022 mmol) in DMA (1.2 mL). The vial was flushed with dry argon and the reaction mixture was heated at 80 °C for 3 h. It was then filtered on SCX-2 column and concentrated under vacuum. The residue was purified by silica column chromatography eluting with a gradient of 10 to 15% MeOH in EtOAc. The pure fractions afforded the title product as a white powder (73 mg, 91%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42 (br s, 2H), 1.50 (s, 9H), 1.90 (br s, 2H), 2.29 (s, 6H), 2.40 (m, 1H), 2.90 (br s, 2H), 3.96 (s, 3H), 4.30 (br s, 2H), 6.51 (s, 1H), 7.08 (s, 1H), 7.29 (d, *J* = 8.5 Hz, 1H), 7.50 (d, *J* = 1.9 Hz, 1H), 7.54 (s, 1H), 7.59 (s, 1H), 7.70 (s, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 8.51 (s, 1H); ESI-HRMS Found: 578.2623, calcd for $C_{30}H_{36}ClN_7O_3$ $[M+H]^+$: 578.2641.

(4-Amino-3-chlorophenyl)(4-(dimethylamino)piperidin-1-yl)methanone: HATU (0.66 g, 1.75 mmol) was added to a solution of 4-amino-3-chlorobenzoic acid (0.3 g, 1.75 mmol), DIPEA (0.45 mL, 1.75 mmol) in dry THF (10 mL). After stirring for 1 h, N,N-dimethylpiperidin-4-amine (224 mg, 1.75 mmol) was added. The reaction was allowed to stir for 1 h at rt. Volatiles were removed in vacuum and the crude was purified by silica column chromatography eluting with 20% MeOH in EtOAc. The pure fractions afforded the title compound as a thick oil which solidified on standing (280 mg, 56%). 1H NMR (500 MHz, DMSO *d*-6): δ 1.31 (dd, *J* = 11.7, 3.8 Hz, 2H), 1.73 (d, *J* = 10.7 Hz, 2H), 2.19 (s, 6H), 2.40 (t, *J* = 5.6 Hz, 1H), 2.88 (br s, 2H), 3.45 (br s, 2H), 4.05 (br s, 2H), 6.76 (d, *J* = 8.3 Hz, 1H), 7.08 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.23 (d, *J* = 1.9 Hz,1H); LC (Method B)-MS (ESI, *m/z*) t_R 0.56 min, 282 [$(M+H^+)$, 100%].

***tert*-Butyl-6-(2-chloro-4-(*S*,*S*-dioxo-thiomorpholine-4-carbonyl)phenylamino)-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (54)**

Tris(dibenzylideneacetone)dipalladium(0) (10 mg, 0.011 mmol) was added to a mixture of *tert*-butyl 6-bromo-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate **47** (52 mg, 0.14 mmol), cesium carbonate (91 mg, 0.28 mmol), (4-amino-3-chlorophenyl)(*S*,*S*-dioxo-thiomorpholino)methanone (48 mg, 0.168 mmol) and Xantphos (12.3 mg, 0.0212 mmol) in DMA (1.2 mL). The vial was flushed with dry argon and the reaction mixture was heated at 80 °C for 3 h. It was then filtered on SCX-2 column and concentrated under vacuum. The residue was purified by silica column chromatography eluting with 3% MeOH in EtOAc. The pure fractions afforded the title product as a white powder (50 mg, 62%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.50 (s, 9H), 3.09 (br s, 4H), 3.97 (s, 3H), 4.14 (br s, 4H), 6.53 (s, 1H), 7.17 (s, 1H), 7.32 (d, *J* = 8.6 Hz, 1H), 7.55 (m, 2H), 7.60 (s, 1H), 7.74 (s, 1H), 8.27 (d, *J* = 8.6 Hz, 1H), 8.53 (s, 1H); ESI-HRMS Found: 585.2117, calcd for $C_{27}H_{29}ClN_6O_5S$ $[M+H]^+$: 585.2112.

(4-Amino-3-chlorophenyl)(*S*,*S*-dioxo-thiomorpholino)methanone: HATU (0.487 g, 1.175 mmol) was added to a solution of 4-amino-3-chlorobenzoic acid (300 mg, 1.75 mmol), DIPEA (0.4 mL, 1.75 mmol) in dry THF (10 mL). After stirring for 1 h, *S*,*S*-dioxo-thiomorpholine (236 mg, 1.75 mmol) was added. The reaction was allowed to stir for 1 h at rt. Volatiles were removed in vacuum and the crude was purified by silica column chromatography eluting with neat EtOAc. The pure fractions afforded the title compound as thick oil (320 mg, 63%). ^{1}H NMR (500 MHz, DMSO *d*-6): δ 3.21 (br s, 4H), 3.85 (br s, 4H), 6.77 (d, *J* = 8.3 Hz, 1H), 7.18 (dd, *J* = 8.3, 1.9 Hz, 1H), 7.37 (d, *J* = 1.9 Hz, 1H); LC (Method B)-MS (ESI, *m/z*) t_R 1.62 min, 289 [$(M+H^+)$, 100%].

Preparation of compounds in Table 6

***tert*-Butyl 6-(2-chloro-4-(1-methyl-1*H*-pyrazol-4-yl) phenylamino)-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (61)**

Tris(dibenzylideneacetone)dipalladium(0) (4.9 mg, 5.30 μmol) was added to a mixture of *tert*-butyl 6-bromo-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate **47** (40 mg, 0.106 mmol), cesium carbonate (69 mg, 0.212 mmol), 2-chloro-4-(1-methyl-1*H*-pyrazol-4-yl)aniline (26 mg, 0.127 mmol) and Xantphos (6.1 mg, 10.60 μmol) in DMA (1.2 mL). The vial was flushed with dry argon and the reaction mixture was heated at 80 °C for 3 h. It was then filtered on SCX-2 column and concentrated under vacuum. The residue was purified *via* Biotage silica gel column chromatography eluting with CH_2Cl_2/EtOH (99/1 to 97/3) to afford the title product as a white solid (45 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.51 (s, 9H), 3.97 (s, 3H), 3.98 (s, 3H), 6.52 (s, 1H), 6.90 (s, 1H), 7.36 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.54 (d, *J* = 2.0 Hz, 1H), 7.56 (s, 1H), 7.59 (s, 1H), 7.62 (s, 1H), 7.65 (s, 1H), 7.74 (s, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 8.50 (s, 1H); ESI-HRMS Found 504.1897, calcd for $C_{26}H_{27}ClN_7O_2$ $[M+H]^+$: 504.1909.

2-Chloro-4-(1-methyl-1*H*-pyrazol-4-yl)aniline: $PdCl_2(dppf).CH_2Cl_2$ (0.040 g, 0.049 mmol) was added to a solution of 4-bromo-2-chloroaniline (0.102 g, 0.494 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (0.134 g, 0.642 mmol) and sodium carbonate (0.115 g, 1.087 mmol) in THF/H_2O (3/1, 2.4 mL). The vial was flushed with dry argon and the reaction mixture was refluxed overnight. It was then diluted with EtOAc and quenched with water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude mixture was purified *via* Biotage silica gel column chromatography eluting with Cyclohexane/EtOAc (80/20 to 60/40) to give the title product as a white solid (62 mg, 60%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.92 (s, 3H), 4.05 (br s, 2H), 6.76 (d, *J* = 8.2 Hz, 1H), 7.17 (dd, *J* =

8.2, 2.0 Hz, 1H), 7.36 (d, *J* = 2.0 Hz, 1H), 7.49 (s, 1H), 7.65 (s, 1H); LC (Method B)-MS (ESI, *m/z*) t_R 2.23 min, 208 [($M+H^+$), 100%].

_N_-(2-Chlorophenyl)-2-(1-methyl-1_H_-pyrazol-4-yl)-1_H_-pyrrolo[3,2-_c_]pyridin-6-amine (62)

tert-Butyl 6-(2-chlorophenylamino)-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (33 mg, 0.065 mmol) in TFA (650 μL) was stirred for 2 h at rt. It was then concentrated and filtered on an Isolute Flash NH_2 column to afford the title product as a white solid (26 mg, 98%). ^{1}H NMR (500 MHz, CD_3OD): δ 3.90 (s, 3H), 3.93 (s, 3H), 6.57 (s, 1H), 6.97 (s, 1H), 7.35 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.58 (d, *J* = 1.9 Hz, 1H), 7.75 (s, 1H), 7.84 (s, 1H), 7.86 (s, 1H), 7.93 (s, 1H), 8.37 (s, 1H); ESI-HRMS Found 404.1377, calcd for $C_{21}H_{19}ClN_7$ $[M+H]^+$: 404.1385.

***tert*-Butyl 6-(2-chloro-4-(1-methyl-1_H_-pyrazol-3-yl) phenylamino)-2-(1-methyl-1_H_-pyrazol-4-yl)-1_H_-pyrrolo[3,2-_c_]pyridine-1-carboxylate (63)**

Tris(dibenzylideneacetone)dipalladium(0) (6.1 mg, 6.63 μmol) was added to a mixture of *tert*-butyl 6-bromo-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate **47** (50 mg, 0.133 mmol), cesium carbonate (86 mg, 0.265 mmol), 2-chloro-4-(1-methyl-1*H*-pyrazol-3-yl)aniline (33.0 mg, 0.159 mmol) and Xantphos (7.7 mg, 0.013 mmol) in DMA (1.4 mL). The vial was flushed with dry argon and the reaction mixture was heated at 80 °C for 3 h. It was then filtered on SCX-2 column and concentrated under vacuum. The residue was purified *via* Biotage silica gel column chromatography eluting with CH_2Cl_2/EtOH (99/1 to 97/3) to afford the title product as a white solid (53 mg, 79%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.51 (s, 9H), 3.96 (s, 3H), 3.97 (s, 3H), 6.49 (d, *J* = 2.2 Hz, 1H), 6.51 (d, *J* = 1.0 Hz, 1H), 6.96 (s, 1H), 7.38 (d, *J* = 2.2 Hz, 1H), 7.55 (s, 1H), 7.61 (s, 1H), 7.66 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.69 (t, *J* = 1.0 Hz, 1H), 7.88 (d, *J*

= 2.0 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 1H), 8.50 (d, *J* = 1.0 Hz, 1H); ESI-HRMS Found 504.1898, calcd for $C_{26}H_{27}ClN_7O_2$ $[M+H]^+$: 504.1909.

2-Chloro-4-(1-methyl-1*H*-pyrazol-3-yl)aniline: Tetrakis(triphenylphosphine)palladium (0.046 g, 0.039 mmol) was added to a solution of 2-chloro-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.1 g, 0.394 mmol), 3-iodo-1-methyl-1*H*-pyrazole (0.123 g, 0.592 mmol) and sodium carbonate (0.125 g, 1.183 mmol) in DME/H_2O 3/1 (2.0 mL). The vial was flushed with dry argon and the reaction mixture was heated for 1 h at 135 °C under microwave irradiation before being diluted with EtOAc and quenched with water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude mixture was purified *via* Biotage silica gel column chromatography eluting with Cyclohexane/EtOAc (80/20 to 60/40) to afford the title product as a yellow solid (60 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.93 (s, 3H), 4.09 (br s, 2H), 6.42 (d, *J* = 2.3 Hz, 1H), 6.79 (d, *J* = 8.3 Hz, 1H), 7.34 (d, *J* = 2.3 Hz, 1H), 7.50 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.71 (d, *J* = 2.0 Hz, 1H); LC (Method B)-MS (ESI, *m/z*) t_R 2.35 min, 208 [$(M+H^+)$, 100%].

***tert*-Butyl-6-(2-chloro-4-(oxazol-5-yl)phenylamino)-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (64)**

Tris(dibenzylideneacetone)dipalladium(0) (6.5 mg, 7.07 μmol) was added to a mixture of *tert*-butyl 6-bromo-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate **47** (0.053 g, 0.141 mmol), cesium carbonate (0.092 g, 0.283 mmol), 2-chloro-4-(oxazol-5-yl)aniline (0.033

g, 0.170 mmol) and Xantphos (8.2 mg, 0.014 mmol) in DMA (1.6 mL). The vial was flushed with dry argon and the reaction mixture was heated at 80 °C for 1.5 h. It was then filtered on SCX-2 column and concentrated under vacuum. The residue was purified *via* Biotage silica gel column chromatography eluting with cyclohexane/EtOAc (70/30 to 40/60, KP-NH column) to afford the title product as a white solid (2 mg, 3%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.53 (s, 9H), 3.99 (s, 3H), 6.54 (d, *J* = 0.8 Hz, 1H), 7.08 (s, 1H), 7.29 (s, 1H), 7.54 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.57 (s, 1H), 7.62 (s, 1H), 7.72–7.74 (m, 2H), 7.91 (s, 1H), 8.19 (d, *J* = 8.6 Hz, 1H), 8.54 (d, *J* = 0.9 Hz, 1H); ESI-HRMS Found 491.1583, calcd for $C_{25}H_{24}ClN_6O_3$ $[M+H]^+$: 491.1593.

2-Chloro-4-(oxazol-5-yl)aniline: Palladium acetate (5.4 mg, 0.024 mmol) was added to a solution of 4-bromo-2-chloroaniline (0.1 g, 0.484 mmol), oxazole (0.064 mL, 0.969 mmol), di(1-adamantyl)-*n*-butylphosphine (0.017 g, 0.048 mmol), pivalic acid (0.020 g, 0.194 mmol) and potassium carbonate (0.201 g, 1.453 mmol) in DMA (2.4 mL). The vial was flushed with dry argon and the reaction mixture was heated at 110 °C overnight before being diluted with EtOAc and quenched with water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude mixture was purified *via* Biotage silica gel column chromatography eluting with Cyclohexane/EtOAc (80/20 to 60/40) to give the title product as a white solid (35 mg, 37%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.25 (br s, 2H), 6.82 (d, *J* = 8.3 Hz, 1H), 7.20 (s, 1H), 7.38 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.58 (d, *J* = 2.0 Hz, 1H), 7.87 (s, 1H); LC (Method B)-MS (ESI, *m/z*) t_R 2.47 min, 195 [$(M+H^+)$, 100%].

***tert*-Butyl-6-(2-chloro-4-(pyridin-3-yl)phenylamino)-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (66)**

Tris(dibenzylideneacetone)dipalladium(0) (6.1 mg, 6.63 μmol) was added to a mixture of *tert*-butyl 6-bromo-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate **47** (0.05 g, 0.133 mmol), cesium carbonate (0.086 g, 0.265 mmol), 2-chloro-4-(pyridin-3-yl)aniline (0.033 g, 0.159 mmol) and Xantphos (7.7 mg, 0.013 mmol) in DMA (1.5 mL). The vial was flushed with dry argon and the reaction mixture was heated at 80 °C for 3 h. It was then filtered on SCX-2 column and concentrated under vacuum. The residue was purified *via* Biotage silica gel column chromatography eluting with CH_2Cl_2/EtOH (99/1 to 97/3) and *via* prep TLC eluting with CH_2Cl_2/EtOH (95/5) to afford the title product as a white solid (30 mg, 45%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.52 (s, 9H), 3.97 (s, 3H), 6.52 (d, *J* = 0.9 Hz, 1H), 7.06 (s, 1H), 7.37 (ddd, *J* = 7.9, 4.8, 0.9 Hz, 1H), 7.48 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.55 (d, *J* = 0.8 Hz, 1H), 7.61 (d, *J* = 0.8 Hz, 1H), 7.65 (d, *J* = 2.2 Hz, 1H), 7.72 (t, *J* = 0.9 Hz, 1H), 7.85 (ddd, *J* = 7.9, 2.4, 1.6 Hz, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 8.52 (d, *J* = 0.9 Hz, 1H), 8.58 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.83 (dd, *J* = 2.4, 0.9 Hz, 1H); ESI-HRMS Found 501.1790, calcd for $C_{27}H_{26}ClN_6O_2$ $[M+H]^+$: 501.1800.

2-Chloro-4-(pyridin-3-yl)aniline: Tetrakis(triphenylphosphine)palladium (0.056 g, 0.048 mmol) was added to a solution of 4-bromo-2-chloroaniline (0.1 g, 0.484 mmol), pyridin-3-ylboronic acid (0.089 g, 0.727 mmol) and cesium fluoride (0.221 g, 1.453 mmol) in DME/MeOH 2/1 (3.0 mL). The vial was flushed with dry argon and the reaction mixture was heated under microwave irradiation at 150 °C for 10 min. It was then diluted with EtOAc and quenched with water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude mixture was purified *via* Biotage silica gel column chromatography eluting with CH_2Cl_2/EtOH (99/1 to 97/3) and filtered on SCX-2 column to afford the title product as a yellow oil (93 mg, 94%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.96 (br s, 2H), 6.87 (d, *J* = 8.2 Hz, 1H), 7.32

(dd, *J* = 8.2, 2.2 Hz, 1H), 7.35 (ddd, *J* = 7.9, 4.8, 1.0 Hz, 1H), 7.51 (d, *J* = 2.2 Hz, 1H), 7.80 (ddd, *J* = 7.9, 2.3, 1.6 Hz, 1H), 8.54 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.79 (dd, *J* = 2.3, 1.0 Hz, 1H); LC (Method B)-MS (ESI, *m/z*) t_R 1.41 min, 205 [($M+H^+$), 100%].

***tert*-Butyl-6-((2-chloro-4-(pyrazin-2-yl)phenyl)amino)-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (67)**

Tris(dibenzylideneacetone)dipalladium(0) (6.6 mg, 7.16 μmol) was added to a mixture of *tert*-butyl 6-bromo-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate **47** (0.054 g, 0.14 mmol), 2-chloro-4-(pyrazin-2-yl)aniline (32.0 mg, 0.16 mmol), Xantphos (8.28 mg, 0.014 mmol), cesium carbonate (0.093 g, 0.29 mmol), and anhydrous DMA (1.5 mL). The 2-5 mL Biotage microwave vial was flushed with nitrogen, capped, and heated at 80 °C for 2 h. The reaction mixture was partitioned between EtOAc and water. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was loaded on a prep TLC plate (20 x 20 cm, 1 mm) which eluted with 35% EtOAc in CH_2Cl_2. Product band was recovered and stirred with 2% MeOH in EtOAc/CH_2Cl_2 (1/1). The silica was removed by filtration, washed with EtOAc/CH_2Cl_2 (1/1) and acetone. The material obtained was successively purified by semiprep HPLC and on a prep TLC plate as described above. The title compound was thus obtained as a yellow solid (0.009 g, 13%). ^{1}H NMR (500 MHz, DMSO *d*-6): δ 1.45 (s, 9H), 3.88 (s, 3H), 6.65 (s, 1H), 7.62 (s, 1H), 7.75 (s, 1H), 7.94 (s, 1H), 8.07 (dd, *J* = 8.8, 2.1 Hz, 1H), 8.19 (d, *J* = 8.8 Hz, 1H), 8.24 (d, *J* = 2.1 Hz, 1H), 8.49 (s, 1H), 8.56 (d, *J* = 2.4 Hz, 1H), 8.64 (s, 1H), 8.68 (dd, *J* = 2.5, 1.6 Hz, 1H), 9.27 (d, *J* = 1.3 Hz, 1H); ESI-HRMS Found: 502.1766, calcd for $C_{26}H_{25}ClN_7O_2$ $[M+H]^+$: 502.1753.

2-Chloro-4-(pyrazin-2-yl)aniline: To a mixture of 4-amino-3-chlorophenylboronic acid pinacol ester (0.110 g, 0.434 mmol), 2-bromopyrazine (0.090 g, 0.56 mmol), 1,1'-bis(diphenylphosphino)ferrocene)-dichloropalladium(II) CH_2Cl_2 complex (24 mg, 0.029 mmol) was added anhydrous DME (3.0 mL) followed by 2 M aqueous sodium carbonate (0.53 mL, 1.06 mmol). The 2-5 mL Biotage microwave vial was flushed with nitrogen and then heated at 75 °C for 40 min under microwave irradiation. At this point more catalyst (0.012 g) was added and the vial was heated at 90 °C for 25 min under microwave irradiation. More 2-bromopyrazine (0.060 g), catalyst (12 mg) and 2 M aqueous sodium carbonate (0.25 mL) were added and the reaction mixture was heated at 90 °C for an additional 30 min under microwave irradiation, it was then partitioned between EtOAc and a saturated aqueous $NaHCO_3$ solution. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated in vacuo. This material was loaded on a prep TLC plate (20 x 20 cm, 1 mm) which eluted with 7% EtOAc in CH_2Cl_2. Product band was recovered and stirred with 2% MeOH in EtOAc/CH_2Cl_2 (1/10). The silica was removed by filtration, washed with EtOAc/CH_2Cl_2 (1/5) and acetone to give the title compound as an off-white solid (0.039 g, 44%). ^{1}H NMR (500 MHz, DMSO *d*-6): δ 5.86 (s, 2H), 6.89 (d, *J* = 8.5 Hz, 1H), 7.85 (dd, *J* = 8.5, 2.1 Hz, 1H), 8.02 (d, *J* = 2.1 Hz, 1H), 8.44 (d, *J* = 2.5 Hz, 1H), 8.57 (dd, *J* = 2.5, 1.6 Hz, 1H), 9.12 (d, *J* = 1.5 Hz, 1H); LC (Method A)-MS (ESI, *m/z*) t_R 2.05 min, 206 [($M+H^+$), 100%].

***tert*-Butyl 6-((2-chloro-4-(pyrimidin-5-yl)phenyl)amino)-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate (68)**

Tris(dibenzylideneacetone)dipalladium(0) (6.9 mg, 7.55 μmol) was added to a mixture of *tert*-butyl 6-bromo-2-(1-methyl-1*H*-pyrazol-4-yl)-1*H*-pyrrolo[3,2-*c*]pyridine-1-carboxylate **47** (0.057

g, 0.15 mmol), 2-chloro-4-(pyrimidin-5-yl)aniline (34.2 mg, 0.17 mmol), Xantphos (8.7 mg, 0.015 mmol), cesium carbonate (98 mg, 0.30 mmol), and anhydrous DMA (1.5 mL). The 2-5 mL Biotage microwave vial was flushed with nitrogen, capped, and heated at 80 °C for 2 h. More catalyst (3.0 mg) and ligand (3.0 mg) were then added and the reaction mixture was heated 80 °C for 2 h. The reaction mixture was partitioned between EtOAc and water. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. The residue was loaded on a prep TLC plate (20 x 20 cm, 1 mm) which eluted with 35% EtOAc in CH_2Cl_2. Product band was recovered and stirred with 2% MeOH in EtOAc/CH_2Cl_2 (1/1). The silica was removed by filtration, washed with EtOAc/CH_2Cl_2 (1/1) and acetone. The material obtained was triturated with diethyl ether to afford the title compound as an off-white solid (22 mg, 29%). ^{1}H NMR (500 MHz, DMSO *d*-6): δ 1.45 (s, 9H), 3.88 (s, 3H), 6.64 (s, 1H), 7.61 (d, *J* = 0.6 Hz, 1H), 7.70 (s, 1H), 7.75 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.93 (s, 1H), 7.98 (d, *J* = 2.3 Hz, 1H), 8.16 (d, *J* = 8.8 Hz, 1H), 8.46 (d, *J* = 0.6 Hz, 1H), 8.61 (s, 1H), 9.15 and 9.17 (2 s, 3H); ESI-HRMS Found: 502.1768, calcd for $C_{26}H_{25}ClN_7O_2$ $[M+H]^+$: 502.1753.

2-Chloro-4-(pyrimidin-5-yl)aniline: To a mixture of 4-amino-3-chlorophenylboronic acid pinacol ester (0.110 g, 0.434 mmol), 5-bromopyrimidine (0.090 g, 0.56 mmol), 1,1'-bis(diphenylphosphino)ferrocene)-dichloropalladium(II) CH_2Cl_2 complex (23 mg, 0.028 mmol) was added anhydrous DME (3.0 mL) followed by 2 M aqueous sodium carbonate (0.53 mL, 1.06 mmol). The 2-5 mL Biotage microwave vial was flushed with nitrogen and was then heated at 150 °C for 15 min under microwave irradiation. The reaction mixture was then partitioned between EtOAc and a saturated aqueous $NaHCO_3$ solution. The organic layer was washed with a saturated aqueous $NaHCO_3$ solution, dried (Na_2SO_4) and concentrated in vacuo. This material was loaded on a prep TLC plate (20 x 20 cm, 1 mm) which eluted with 20% EtOAc in CH_2Cl_2.

Product band was recovered and stirred with 2% MeOH in EtOAc/CH_2Cl_2 (1/5). The silica was removed by filtration, washed with EtOAc/CH_2Cl_2 (1/1) and acetone to give the title compound as a white solid (0.075 g, 84%). ^{1}H NMR (500 MHz, DMSO *d*-6): δ 5.72 (s, 2H), 6.91(d, *J* = 8.4 Hz, 1H), 7.51 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.72 (d, *J* = 2.2 Hz, 1H), 9.04, 9.05 (2 s, 3H); LC (Method A)-MS (ESI, *m/z*) t_R 1.86 min, 206 [(M+H$^+$), 100%].

Characterisation of compounds in Table 7

AZD3146 (4)

Prepared according to methods reported in: Andrews, D. M.; Jones, C. D.; Simpson, I.; Ward, R. A., 2-Anilinopurin-8-one derivatives as TKK/MPS1 inhibitors and their preparation, pharmaceutical compositions and use in the treatment of proliferative disorders. WO 2009024824, 2009. ^{1}H NMR (500 MHz, DMSO *d*-6): δ 1.53-1.70 (m, 4H), 1.79-1.97 (m, 6H), 2.07-2.16 (m, 2H), 2.19-2.30 (m, 5H), 2.63-2.70 (m, 2H), 3.28 (s, 3H), 3.80 (s, 3H), 4.30-4.37 (m, 1H), 4.68 (quin, *J* = 8.2 Hz, 1H), 6.52 (dd, *J* = 2.6, 8.5 Hz, 1H), 6.62 (d, *J* = 2.6 Hz, 1H), 7.61 (s, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 8.04 (s, 1H); LC (Method B)-MS (ESI, *m/z*) t_R 2.04 min, 453 [(M+H$^+$), 100%].

NMS-P715 (5)

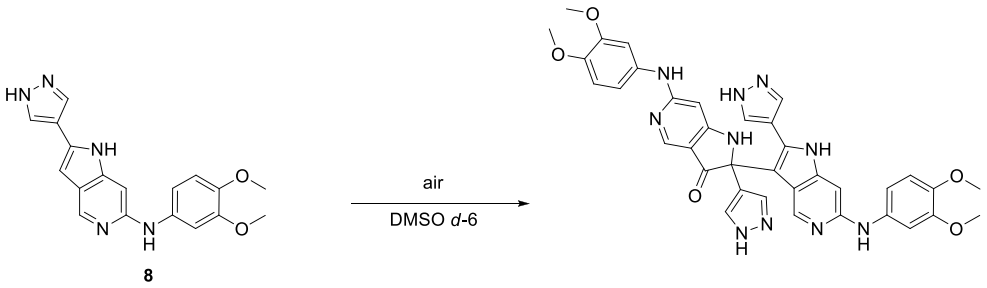
Prepared according to methods reported in: Brasca, M.G.; Amboldi, N.; Ballinari, D.; Cameron, A.; Casale, E.; Cervi, G.; Colombo, M.; Colotta, F.; Croci, V.; D'Alessio, R.; Fiorentini, F.; Isacchi, A.; Mercurio, C.; Moretti, W.; Panzeri, A.; Pastori, W.; Pevarello, P.; Quartieri, F.; Roletto, F.; Traquandi, G.; Vianello, P; Vulpetti, A.; Ciomei, M. Identification of *N*,1,4,4-Tetramethyl-8-{[4-(4-methylpiperazin-1-yl)phenyl]amino}-4,5-dihydro-1*H*-pyrazolo[4,3-*h*]quinazoline-3-carboxamide (PHA-848125), a Potent, Orally Available Cyclin Dependent

Kinase Inhibitor *J. Med. Chem.*, **2009**, 52, 5152 - 5163; Caldarelli, M.; Angiolini, M.; Disingrini, T.; Donati, D.; Guanci, M.; Nuvoloni, S.; Posteri, H.; Quartieri, F.; Silvagni, M.; Colombo, R. Synthesis and SAR of new pyrazolo[4,3-h]quinazoline-3-carboxamide derivatives as potent and selective MPS1 kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2011,** 21, 4507-451; and Caldarelli, M.; Angiolini, M.; Colombo, R.; Disingrini, T.; Nuvoloni, S.; Posteri, H.; Salsa, M.; Silvagni, M.; Pyrazolo-quinazolines. WO2009156315, 2009. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (t, *J* = 7.5 Hz, 6H), 2.09–2.26 (m, 4H), 2.70 (q, *J* = 7.5 Hz, 4H), 2.74 (s, 3H), 2.75–2.84 (m, 2H), 2.94 (t, *J* = 7.6 Hz, 2H), 3.22 (t, *J* = 7.6 Hz, 2H), 3.44–3.54 (m, 2H), 4.20–4.30 (m, 1H), 4.44 (s, 3H), 7.10 (d, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 2H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.54 (s, 1H), 7.80 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.88 (s, 1H), 8.27 (s, 1H), 8.38 (s, 1H), 8.68 (d, *J* = 8.7 Hz, 1H); LC (Method A)-MS (ESI, *m/z*) t_R 2.30 min, 677 [($M+H^+$), 95%].

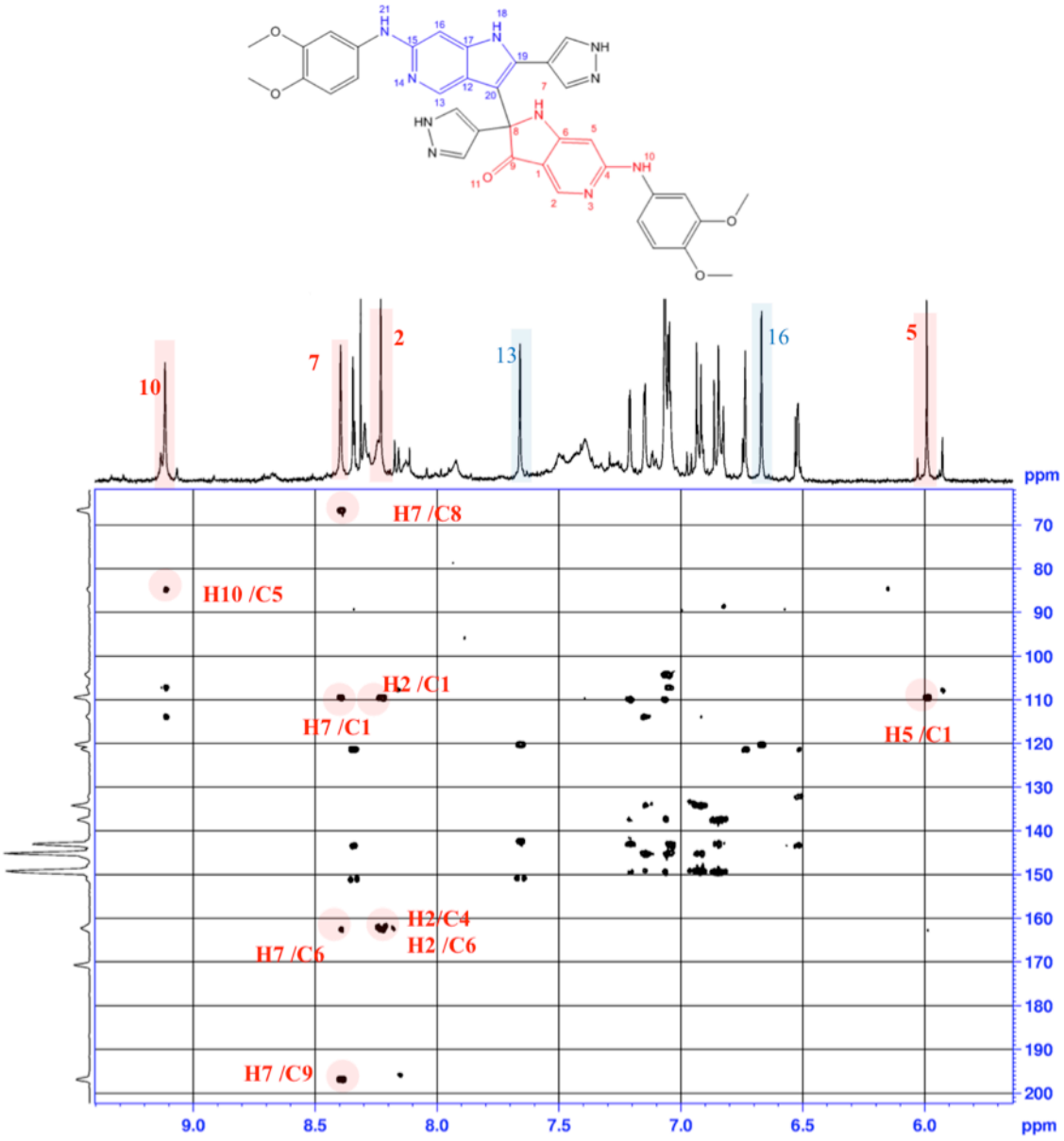
4-(4-Amino-6-(tert-butylamino)-5-cyanopyridin-2-ylamino)benzamide (6)

Prepared according to methods reported in: Kusakabe, K. *et. al.*, Diaminopyridine-Based Potent and Selective Mps1 Kinase Inhibitors Binding to an Unusual Flipped-Peptide Conformation. *ACS Med. Chem. Lett.* **2012,** 3, 560-564.^{1}H NMR (500 MHz, DMSO *d*-6): δ 1.43 (s, 9H), 5.09 (s, 1H), 5.53 (s, 1H), 6.21(s, 2H), 7.1 (s, 1H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.75 (d, *J* = 8.8 Hz, 3H), 9.02 (s, 1H); LC (Method B)-MS (ESI, *m/z*) t_R 2.55 min, 325 [($M+H^+$), 100%].

a)


air
DMSO d-6
8

b)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7
2
13
16
5
ppm
H7 /C8
H10 /C5
H2 /C1
H7 /C1
H5 /C1
H2/C4
H2 /C6
H7 /C6
H7 /C9
9.0
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7.5
7.0
6.5
6.0
ppm

c)

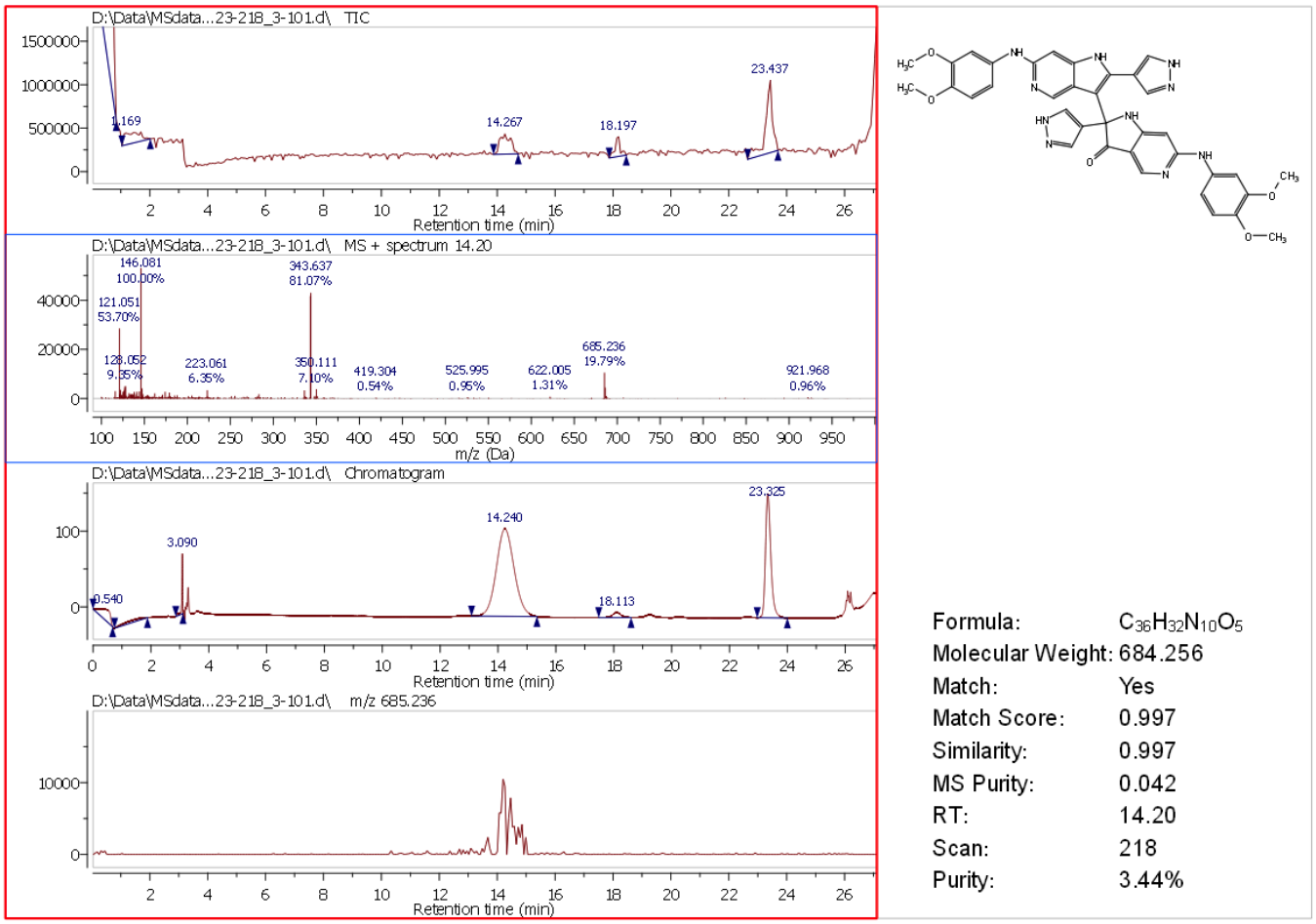

Figure S1: a) Putative dimer formed upon standing of compound **8** in DMSO-d^6 solution (8 mg/mL) for 2 months at room temperature which we postulate to arise by nucleophilic attack of one parent monomer upon a second molecule which has suffered air oxidation of the *C*2-*C*3 double bond. b) Structure elucidation by HMBC spectral analysis of a 3-fold dilution of the DMSO-d^6 solution of the dimer. The HMBC correlation of H-7 to a carbon at 66.63 ppm (*C*8) and another carbon at 196.83 ppm (*C*9) is consistent with the presence of an indolin-3-one. The chemical shift of *C*8 (66.63 ppm) is consistent with C8 being a quaternary carbon atom linked to two other carbon atoms. No definitive evidence for linkage of the two monomer moieties was observed by NMR. c) LC-MS data for the putative dimer indicating a molecular weight consistent with the proposed dimeric structure.

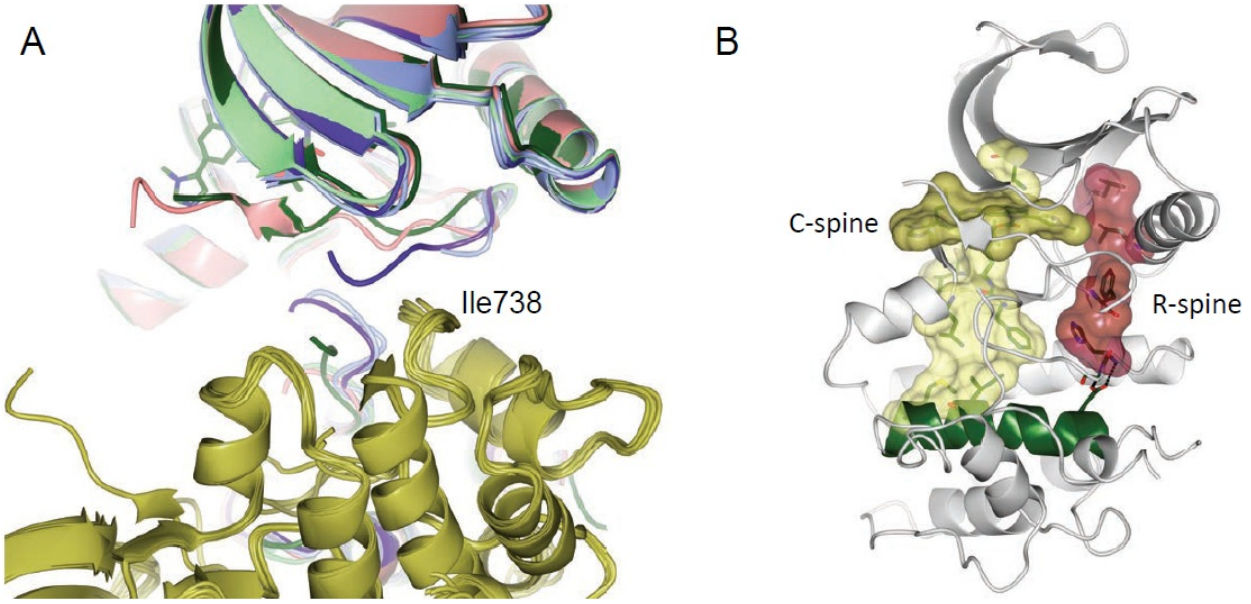

Figure S2: Crystallographic analysis of MPS1 with compound **65** (CCT251455). A) Superposition of the structures of MPS1 with compounds **8** (purple), **34**, **48** and **55** (light blue) and **65** (dark green) along with the published MPS1 structures 3H9F (pink) and 3GFW (light green). Crystallographically related molecules in the vicinity of the activation loop are shown as yellow ribbons. B) Conformational analysis of MPS1 with compound **65**. The catalytic C-spine and regulatory R-spine are shown. The C-spine consists of residues Val539, Leu609, Phe653, Leu654, Ile655, Ile723, Met727 and the hinge-binding aromatic region of the ligand, and is highlighted in yellow. The R-spine consists of residues Leu575, Leu588, His645 and Phe665, and is highlighted in red. The main chain nitrogen atom of His645 at the base of the R-spine interacts with Asp716 of the αF helix, highlighted in dark green, which serves to link the R- and C-spines together.

Table S1: Kinase selectivity profiling for compound **65** at 1 μM concentration.

Kinase	*Percentage Inhibition*[a]	*Kinase*	*Percentage Inhibition*[a]
MPS1 (TTK)	107 ± 4	CDK9/cyclin T1	33 ± 10
NLK	105 ± 1	MAPK12 (p38 gamma)	33 ± 4
MAPK9 (JNK2)	91 ± 4	CDK8/cyclin C	30 ± 3
MAPK10 (JNK3)	81 ± 0	DYRK3	29 ± 5
MAPK8 (JNK1)	71 ± 0	KIT	28 ± 0
CLK2	67 ± 7	ROCK2	24 ± 5
MAPK13 (p38 delta)	67 ± 7	PAK2 (PAK65)	21 ± 5
LRRK2	64 ± 5	CDC42 BPA (MRCKA)	21 ± 3
STK16 (PKL12)	63 ± 6	CDK2/cyclin A	21 ± 5
MAPK11 (p38 beta)	59 ± 3	CDK1/cyclin B	20 ± 1
CAMKK2 (CaMKK beta)	50 ± 2	TAOK2 (TAO1)	20 ± 1
RIPK2	49 ± 4	RAF1 (cRAF) Y340D Y341D	20 ± 10
FLT3	46 ± 6	CHEK2 (CHK2)	19 ± 4
STK17A (DRAK1)	45 ± 9	SRPK2	18 ± 1
NTRK3 (TRKC)	39 ± 7	WNK2	16 ± 7
STK33	36 ± 0	MAP2K2 (MEK2)	16 ± 9
DYRK1A	36 ± 9	PRKD2 (PKD2)	16 ± 11
PLK2	35 ± 4	CDK5/p25	15 ± 1

<15% inhibition: ABL1, ACVR1 (ALK2), ADRBK2 (GRK3), AKT1 (PKB alpha), AMPK A2/B1/G1, BMPR1A (ALK3), BRAF, CDK7/cyclin H/MNAT1, CHEK1 (CHK1), CLK3, CSNK1G3 (CK1 gamma 3), DMPK, EGFR (ErbB1), EPHB2, EPHB4, FGFR1, FLT1 (VEGFR1), FLT4 (VEGFR3), HIPK2, HIPK3 (YAK1), HIPK4, IKBKE (IKK epsilon), IRAK4, JAK1, JAK2, JAK3, KDR (VEGFR2), LCK, LIMK2, LYN A, MAP2K1 (MEK1), MAP3K11 (MLK3), MAP3K2 (MEKK2), MAP3K3 (MEKK3), MAP3K5 (ASK1), MAP3K8 (COT), MAP3K9 (MLK1), MAPK1 (ERK2), MAPKAPK2, MAPKAPK3, MARK4, NEK7, NEK9, NTRK1 (TRKA), PAK7 (KIAA1264), PIM1, PIM2, PKN1 (PRK1), PLK1, PLK3, PRKACA (PKA), PRKCG (PKC gamma), PRKCN (PKD3), PRKCQ (PKC theta), PRKD1 (PKC mu), PRKG1, PRKX, ROS1, RPS6KA1 (RSK1), RPS6KA2 (RSK3), RPS6KA3 (RSK2), RPS6KA4 (MSK2), RPS6KA6 (RSK4), SGKL (SGK3), SLK, SNF1LK2, SRC, SRPK1, STK22B (TSSK2), STK22D (TSSK1), STK23 (MSSK1), STK25 (YSK1), STK3 (MST2), STK4 (MST1), TAOK3 (JIK), TEC, TEK (Tie2), TGFBR1 (ALK5), TNK2 (ACK), TXK, TYRO3 (RSE), WEE1, YES1, ZAK, ZAP70

[a]Percentage inhibition values are expressed as the mean ± standard error from duplicate measurements. The assays were performed by Life Technologies.

Table S2: Data collection and refinement statistics for crystal structures of the MPS1 kinase domain with compounds **8**, **34**, **39**, **48**, **55** and **65**

Ligand	**8**	**34**	**39**
Crystals			
Space group	I222	I222	I222
Lattice constants			
a (Å)	70.94	70.58	70.932
b (Å)	111.79	111.33	111.8984
c (Å)	113.40	112.12	112.6763
α, β, γ (°)	90	90	90
Data collection			
Beamline	Diamond I04	Diamond I04-1	Diamond I03
Wavelength (Å)	0.9793	0.9173	0.9762
Resolution range (Å)	60.14-2.60	59.73-2.36	41.04-2.65
(highest-resolution shell values)	(2.72-2.60)	(2.45-2.36)	(2.78-2.65)
Observations	56682 (7400)	77035 (7867)	60478 (7216)
Unique reflections	14184 (1729)	18181 (1819)	13230 (1687)
Completeness (%)	99.7 (99.8)	98.3 (95.4)	99.1 (96.8)
Multiplicity	4.1 (4.3)	4.2 (4.3)	4.6 (4.3)
R_{merge} (%)	5.6 (53.2)	4.3 (86.9)	4.3 (115)
I/σ(I)	10.3 (1.2)	8.7 (0.8)	8.8 (0.6)
Mean I/σ(I)	14.3 (2.3)	16.3 (1.8)	15.1 (1.6)
$CC_{1/2}$[a]	0.999 (0.800)	0.996 (0.708)	0.998 (0.774)
Average Mosaicity (º)	0.98	0.25	0.15
Refinement			
No. of amino acids	257	255	252
No. of water molecules	38	28	8
No. of PEG molecules	6	3	2
No. of EDO molecules	0	3	2
Identity of ligand bound	**8**	**34**	**48**[b]
R-factor (%)	18.7	19.4	19.4
R_{free} (%)	21.2	22.2	22.2
Ramachandran plot			
Favored (%)	98.0	97.6	98.0
Outliers (%)	0.0	0.0	0.0
RMSD bonds (Å)	0.010	0.010	0.010
RMSD angles (°)	1.120	1.090	1.150

[a] Half-dataset correlation coefficient, see: Karplus, P. A.; Diederichs, K. Linking Crystallographic Model and Data Quality. *Science* **2012,** *336,* 1030-1033.

[b] Compound **48**, a synthetic precursor of compound **39**, was present as a <2% impurity in the sample of **39** used in the crystallization experiment.

Table S2 continued

Ligand	**48**	**55**	**65**
Crystals			
Space group	I222	I222	I222
Lattice constants			
a (Å)	69.67	69.77	69.83
b (Å)	104.69	105.22	108.37
c (Å)	111.78	112.25	112.70
α, β, γ (°)	90	90	90
Data collection			
Beamline	Diamond I04-1	Diamond I04-1	Diamond I04-1
Wavelength (Å)	0.9173	0.9173	0.9173
Resolution range (Å)	58.00-2.80	39.34-2.65	40.65-2.50
(highest-resolution shell values)	(2.95-2.80)	(2.78-2.65)	(2.60-2.50)
Observations	33602 (3813)	63043 (8133)	69817 (7885)
Unique reflections	9139 (1205)	12262 (1585)	14969 (1684)
Completeness (%)	88.8 (83.1)	99.4 (99.6)	98.9 (99.5)
Multiplicity	3.7 (3.2)	5.1 (5.1)	4.7 (4.7)
R_{merge} (%)	5.3 (47.7)	5.9 (81.8)	5.4 (97.5)
I/σ(I)	6.3 (1.3)	9.2 (0.8)	10.4 (0.7)
Mean I/σ(I)	13.5 (2.0)	12.3 (1.6)	11.8 (1.2)
$CC_{1/2}$[a]	0.914 (0.740)	0.999 (0.756)	0.999 (0.749)
Average Mosaicity (º)	1.86	0.46	0.25
Refinement			
No. of amino acids	248	253	262
No. of water molecules	6	1	11
No. of PEG molecules	1	1	0
No. of EDO molecules	0	0	0
Identity of ligand bound	**48**	**55**	**65**
R-factor (%)	19.7	19.1	19.3
R_{free} (%)	24.1	21.4	21.0
Ramachandran plot			
Favoured (%)	97.5	98.4	98.0
Outliers (%)	0.0	0.0	0.0
RMSD bonds (Å)	0.010	0.010	0.010
RMSD angles (°)	1.140	1.130	1.150

[a] Half-dataset correlation coefficient, see: Karplus, P. A.; Diederichs, K. Linking Crystallographic Model and Data Quality. *Science* **2012,** *336,* 1030-1033.