SUPPORTING INFORMATION

Rapid Discovery and Structure–Activity Relationships of Pyrazolopyrimidines that Potently Suppress Breast Cancer Cell Growth via SRC Kinase Inhibition with Exceptional Selectivity over ABL Kinase

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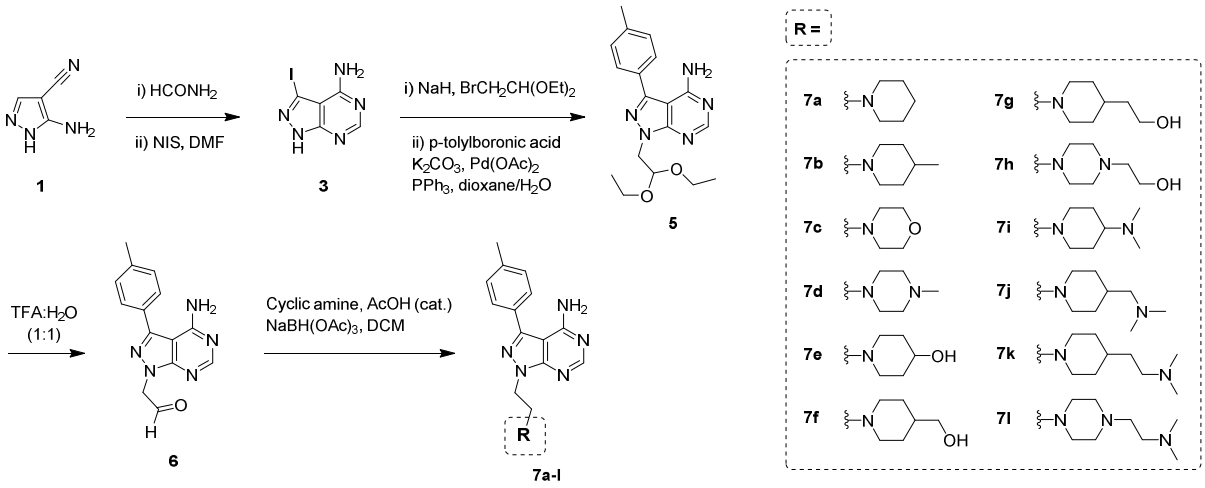
1. General experimental protocols

Microwave-irradiated reactions were carried out in a Biotage Initiator microwave synthesizer. Non-microwave reactions were performed under an inert atmosphere of nitrogen using anhydrous solvents. All commercially available chemicals were obtained from either Fisher Scientic, Matrix Scientic, Sigma-Aldrich or VWR International Ltd. NMR spectra were recorded at ambient temperature on a 500 MHz Bruker Avance III spectrometer. Samples were dissolved in deuterated solvents commercially available from Sigma-Aldrich. ^{1}H NMR spectra: chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane. The data is presented as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (in Hertz, Hz) and interpretation. ^{13}C NMR spectra were referenced to the solvent carbon peak. The data is presented as follows: chemical shift and assignment; and were confirmed by DEPTQ90, 2D-HSQC and 2D-COSY spectra. TLCs were ran on Merck TLC Silica gel 60 F254 plates, typically 5 cm x 10 cm, and monitored using a 254 nm UV source or permanganate staining. Purifications were carried out using flash column chromatography with commercially available silica gel and solvents. All compounds used in the biological screenings were determined to be >95% pure by analytical HPLC with evaporative light scattering detection (Agilent).

2. Synthesis and characterization of compounds 7a-l



1*H*-pyrazolo[3,4-d]pyrimidin-4-amine (2). 5-amino-1*H*-pyrazole-4-carbonitrile (3 g, 27.77 mmol) and formamide (15 ml) were added to a 20 ml microwave vial and the mixture heated at 180 °C for 2 h using microwave radiation. The precipitate formed on cooling was filtered off and washed with water (50 ml) and allowed to dry giving the product as a pale brown solid (3.5 g, 25.9 mmol, 93 %). The experiment was repeated to give a second batch of product (3.44 g, 25.5 mmol, 92 %). ^{1}H NMR (500

MHz, DMSO) δ 13.34 (s, 1H), 8.13 (s, 1H), 8.07 (s, 1H), 7.69 (br. m, 2H); ^{13}C NMR (126 MHz, DMSO) δ 158.19 (CH), 156.03 (C), 154.98 (C), 132.79 (CH), 99.83 (C); MS (ES +ve) $(M+H)^+$: 136.0, 157.9 (+Na), (ES -ve) $(M-H)^-$: 133.9.

3-iodo-1*H*-pyrazolo[3,4-d]pyrimidin-4-amine (3). 1*H*-pyrazolo[3,4-d]pyrimidin-4-amine (1.5 g, 11.11 mmol) was suspended in 15 ml of DMF and *N*-iodosuccinimide (1.2 eq., 3.0 g, 13.3 mmol) added. The mixture was heated at 180 °C in the microwave for 40 min. EtOH (80 ml) was added to the reaction and a precipitate began to form, which was aided by sonication. The precipitate was filtered and washed with EtOH (x3, 20 ml) and allowed to dry in an oven at 40 °C overnight to give a sand colored solid (2.115 g, 8.1 mmol, 73 %). ^{1}H NMR (500 MHz, DMSO) δ 13.80 (s, 1H), 8.16 (s, 1H), 7.79 - 6.44 (m, 2H); ^{13}C NMR (126 MHz, DMSO) δ 157.60 (C), 156.08 (CH), 155.04 (C), 102.50 (C), 89.82 (C); MS (ES +ve) $(M+H)^+$: 283.9 (+Na), (ES -ve) $(M-H)^-$: 259.9, 287.8 (+Na).

1-(2,2-diethoxyethyl)-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine (4). To a solution of 3-iodo-1*H*-pyrazolo[3,4-d]pyrimidin-4-amine (500 mg, 1.9 mmol) in DMF (15 ml) was added sodium hydride (1.5 eq., 2.9 mmol, 60 % dispersion in mineral oil, 115.2 mg) and the solution allowed to stir for 30 min until the gas evolution stopped. Bromoacetaldehyde diethyl acetal (1.5 eq. 2.9 mmol, 0.435 ml) was then added dropwise and the mixture heated at 150 °C in the microwave for 40 min. EtOAc and water (50 ml) were added to the mixture and the organics separated. The aqueous layer was washed with EtOAc (50 ml, x3) and the organics combined and washed with water (x3, 30 ml), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography MeOH/DCM (0-5 %) to give a light orange solid (461 mg, 1.2 mmol, 64 %). ^{1}H NMR (500 MHz, DMSO) δ 8.21 (s, 1H), 7.90 - 6.30 (m, 2H), 4.93 (t, J = 5.7, 1H), 4.33 (d, J = 5.8, 2H), 3.62 (dq, J = 9.4, 6.9, 2H), 3.40 (dq, J = 9.6, 7.0, 2H), 0.98 (t, J = 7.0, 6H); ^{13}C NMR (126 MHz, DMSO) δ 157.86 (C), 156.30 (CH), 154.03 (C), 103.18 (CH), 99.50 (C), 89.51 (C), 61.39 (CH_2), 48.76 (CH_2), 15.39 (CH_3); MS (ES +ve) $(M+H)^+$: 377.8, 400.0 (+Na), (ES -ve) $(M-H)^-$: 376.0.

1-(2,2-diethoxyethyl)-3-(p-tolyl)pyrazolo[3,4-d]pyrimidin-4-amine (5). To a solution of 1-(2,2-diethoxyethyl)-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine (1.135 g, 3.0 mmol) in dioxane/water (10 ml/1 ml) was added p-tolylboronic acid (1.5 eq., 614 mg, 4.5 mmol), potassium carbonate (1.5 eq., 624.7 mg, 4.5 mmol) and followed by palladium acetate (5 mol %, 33.8 mg) and the mixture heated in the microwave at 120 °C for 1 h. EtOAc and water (50 ml) were added to the mixture and the organic layer separated, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography, MeOH/DCM (0-5 %) to give a light brown solid (902 mg, 2.6 mmol, 88 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.58 (d, J = 8.0, 2H), 7.34 (d, J = 7.8, 2H), 5.12 (t, J = 5.8, 1H), 4.58 (d, J = 5.8, 2H), 3.78 (dq, J = 9.4, 7.0, 2H), 3.52 (dq, J = 9.4, 7.0, 2H), 2.44 (s, 3H), 1.12 (t, J = 7.0, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.28 (C), 156.43 (C), 155.55 (CH), 145.25 (C), 139.76 (C), 131.90 (CH), 128.93 (CH), 100.49 (CH), 62.46 (CH_2), 49.53 (CH_2), 21.09 (CH_3), 15.78 (CH_3); MS (ES +ve) $(M+1)^+$: 341.19, (ES -ve) $(M-1)^-$: 340.0.

2-[4-amino-3-(p-tolyl)pyrazolo[3,4-d]pyrimidin-1-yl]ethane-1,1-diol (6). To a suspension of 1-(2,2-diethoxyethyl)-3-(p-tolyl)pyrazolo[3,4-d]pyrimidin-4-amine (400 mg, 1.17 mmol) in 5 ml of water was added 5 ml of TFA and the mixture heated to 100 °C for 30 min in the microwave. The mixture was transferred to a RBF, washed with DCM and concentrated in vacuo. The product was washed with DCM and Et_2O and dried *in vacuo* to give a light brown solid (quantitative yield) and used without further purification for the reductive amination step.

General protocol for the synthesis of compounds 7a-l. To a suspension of 2-[4-amino-3-(p-tolyl)pyrazolo[3,4-d]pyrimidin-1-yl]ethane-1,1-diol (40 mg, 0.1 mmol) in DCM (1 ml) was added either piperidine, 4-methylpiperidine, morpholine, 1-methylpiperazine, piperidin-4-ol, 4-piperidylmethanol, 2-(4-piperidyl)ethanol, 2-piperazin-1-ylethanol, 4-(*N*,*N*-dimethylamino)piperidine or *N*,*N*-dimethyl-2-piperazin-1-yl-ethanamine (**7a-l**, respectively, 1 eq., 0.1 mmol), and a drop of AcOH and the mixture allowed to stir for 10 mins. Sodium triacetoxyborohydride (22.2 mg, 0.1 mmol) was then added and the mixture stirred until complete (~ 1h). The reaction mixture was concentrated *in vacuo* and purified without any further workup due to the high solubility of the products in the aqueous layer.

1-[2-(1-piperidyl)ethyl]-3-(p-tolyl)pyrazolo[3,4-d]pyrimidin-4-amine (7a). Purified by column chromatography (MeOH/DCM 0-10%) to give a light brown solid (20 mg, 0.059 mmol, 57 %). **^{1}H NMR** (500 MHz, MeOH) δ 8.31 (s, 1H), 7.61 (d, J = 8.0, 2H), 7.42 (d, J = 7.8, 2H), 4.75 (t, J = 6.3, 2H), 3.45 (m, 2H), 3.18 – 3.14 (m, 2H), 2.47 (s, 3H), 1.83 – 1.70 (m, 6H), 1.63 (s, 2H). **^{13}C NMR** (151 MHz, MeOH) δ 177.66 (C), 155.72 (CH), 145.87 (C), 139.30 (C), 129.64 (2x CH), 128.04 (2x CH), 109.85 (C), 97.95 (C), 56.01 (CH_2), 53.55 (CH_2), 44.34 (CH_2), 23.69 (CH_2), 22.38 (CH_2), 21.64 (2x CH_2), 19.95 (CH_3).; **MS** (ES +ve) $[M+1]^+$: 337.0; **HRMS** (ES +ve), $C_{19}H_{24}N_6$ $[M+H]^+$: calculated 337.21352, found 337.213381.

1-[2-(4-methyl-1-piperidyl)ethyl]-3-(p-tolyl)pyrazolo[3,4-d]pyrimidin-4-amine (7b). Purified by column chromatography (MeOH/DCM 0-8%) to give a light brown solid (16 mg, 0.046 mmol, 44 %). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.57 (d, J = 8.0, 2H), 7.37 (d, J = 7.8, 2H), 4.85 (t, J = 6.3,

2H), 3.64 (m, 2H), 3.40 (d, J = 12.7, 2H), 2.87 (dd, J = 12.8, 10.2, 2H), 2.46 (s, 3H), 1.83 (d, J = 13.2, 2H), 1.64 (m, 1H), 1.52 (td, J = 14.6, 3.9, 2H), 1.02 (d, J = 6.5, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.55 (C), 155.04 (CH), 154.44 (C), 145.98 (C), 139.71 (C), 130.20 (2x CH), 129.48 (C), 128.27 (2x CH), 98.51 (C), 53.44 (CH_2), 43.99 (2x CH_2), 41.68 (CH_2), 30.36 (2x CH_2), 29.13 (CH), 21.37 (CH_3), 21.28 (CH_3); **MS** (ES +ve) $[M+1]^+$: 351.1; **HRMS** (ES +ve), $C_{20}H_{27}N_6$ $[M+H]^+$: calculated 351.22917, found 351.229656.

1-(2-morpholinoethyl)-3-(p-tolyl)pyrazolo[3,4-d]pyrimidin-4-amine (7c). Purified by column chromatography (MeOH/DCM 0-5 %) to give a pale yellow solid (17 mg, 0.05 mmol, 48 %). **^{1}H NMR** (500 MHz, MeOD) δ 8.27 (s, 1H), 7.60 (d, *J* = 8.1, 2H), 7.42 (d, *J* = 7.8, 2H), 4.58 (t, *J* = 6.5, 2H), 3.67 – 3.61 (m, 4H), 2.97 (t, *J* = 6.5, 2H), 2.61 (s, 4H), 2.47 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.60 (C), 156.29 (CH), 155.24 (C), 145.23 (C), 138.81 (C), 130.95 (C), 130.35 (CH), 129.05 (CH), 99.05 (C), 67.59 (2x CH_2), 58.02 (CH_2), 54.16 (CH_3), 44.93 (CH_2), 22.12 (2x CH_2); **MS** (ES +ve) (M+1)+: 339.1, 361.0 (+Na), (ES -ve) $(M-1)^-$: 377.0; **HRMS** (ES +ve), $C_{18}H_{22}N_6O$ $(M+H)^+$: calculated 339.19279, found 339.193067.

1-[2-(4-methylpiperazin-1-yl)ethyl]-3-(p-tolyl)pyrazolo[3,4-d]pyrimidin-4-amine (7d). Purified by column chromatography (MeOH/DCM 0-10% - 10% MeOH with 3 drops of NH_3 aq. per 20 ml) to give a pale orange solid (20 mg, 0.057 mmol, 54 %). **^{1}H NMR** (500 MHz, MeOD) δ 8.27 (s, 1H), 7.60 (d, *J* = 8.1, 2H), 7.41 (d, *J* = 7.8, 2H), 4.57 (t, *J* = 6.5, 2H), 2.97 (t, *J* = 6.5, 2H), 2.53 (m, 8H), 2.47 (s, 3H), 2.37 (s, 3H).; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.02 (C), 155.87 (CH), 154.77 (C), 144.58 (C), 139.25 (C), 130.45 (C), 130.14 (CH), 128.50 (CH), 98.59 (C), 56.89 (CH_2), 54.91 (CH_2), 52.50 (CH_2), 45.59 (CH_3), 44.60 (CH_2), 21.47 (CH_3); **MS** (ES +ve) $(M+1)^+$: 352.0, 374.2 (+Na), (ES -ve) $(M-1)^-$: 350.2; **HRMS** (ES +ve), $C_{19}H_{26}N_7$ $(M+H)^+$: calculated 352.22442, found 352.224816.

1-[2-[4-amino-3-(p-tolyl)pyrazolo[3,4-d]pyrimidin-1-yl]ethyl]piperidin-4-ol (7e). Purified by column chromatography (MeOH/DCM 5-10% - 10% MeOH with 10 drops of NH_3 aq. per 50 ml) to give a light brown solid (8 mg, 0.023 mmol, 22 %). **^{1}H NMR** (500 MHz, MeOD) δ 8.33 (s, 1H), 7.63 (d, *J* = 8.1, 2H), 7.43 (d, *J* = 7.8, 2H), 4.82 (t, *J* = 5.9, 2H), 3.96 (s, 1H), 3.66 (s, 2H), 3.53 (s, 2H), 3.32 – 3.16 (m, 2H), 2.47 (s, 3H), 2.03 (s, 2H), 1.82 (s, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.59 (C), 154.87 (CH), 154.55 (C), 145.87 (C), 139.77 (C), 130.28 (CH), 129.74 (C), 128.37 (CH), 98.57 (C), 55.54 (CH_2), 53.57 (CH_2), 48.95 (CH_2), 42.60 (CH_2), 31.59 (CH_2), 21.45 (CH_3); **MS** (ES +ve) $(M+1)^+$: 353.2, 375.1 (+Na); **HRMS** (ES +ve), $C_{19}H_{25}N_6O$ $(M+H)^+$: calculated 353.20844, found 353.208248.

[1-[2-[4-amino-3-(p-tolyl)pyrazolo[3,4-d]pyrimidin-1-yl]ethyl]-4-piperidyl]methanol (7f). Purified by column chromatography (MeOH/DCM 5-10% - 10% MeOH with 10 drops of NH_3 aq. per 100 ml) to give a light brown solid (7 mg, 0.019 mmol, 18 %). **^{1}H NMR** (400 MHz, MeOD) δ 8.28 (s, 1H), 7.61 (d, *J* = 8.1, 2H), 7.42 (d, *J* = 7.8, 2H), 4.61 (t, *J* = 6.7, 2H), 3.42 – 3.36 (m, 4H), 3.16 (s, 2H), 3.03 (s, 2H), 2.47 (s, 3H), 2.23 (s, 2H), 1.77 (d, *J* = 11.9, 2H), 1.56 – 1.49 (m, 1H), 1.26 (m, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.69 (C), 155.74 (CH), 154.38 (C), 144.35 (C), 139.05 (C), 130.27 (C), 129.99 (CH), 128.30 (CH), 98.40 (C), 67.76 (CH_2), 57.10 (CH_2), 53.31 (CH_2), 44.67 (CH_2), 38.26 (CH), 28.56 (CH_2), 21.29 (CH_3); **MS** (ES +ve) $(M+1)^+$: 367.3, 338.9 (+Na); **HRMS** (ES +ve), $C_{20}H_{27}N_6O$ $(M+H)^+$: calculated 367.22409, found 367.223856.

2-[1-[2-[4-amino-3-(p-tolyl)pyrazolo[3,4-d]pyrimidin-1-yl]ethyl]-4-piperidyl]ethanol (7g). Purified by column chromatography (MeOH/DCM 5-10% - 10% MeOH with 2 drops of NH_3 aq. per 10 ml) to give a light orange solid (13 mg, 0.034 mmol, 33 %). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.58 (d, J = 8.1, 2H), 7.37 (d, J = 7.8, 2H), 5.94 (br. s, 2H), 4.79 (t, J = 6.4, 2H), 3.74 3.67 (m, 2H), 3.49 (m, 4H), 2.56 (br. s, 2H), 2.46 (s, 3H), 1.85 (d, J = 11.0, 2H), 1.58 (m, 5H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.02 (C), 155.80 (CH), 154.96 (C), 145.91 (C), 139.94 (C), 130.55 (CH), 130.13 (C), 128.65 (CH), 118.15 (C), 115.83 (C), 98.92 (CH), 60.29 (CH_2), 51.28 (CH_2), 42.73 (CH_2), 38.56 (CH_2), 31.34 (CH_2), 30.08 (CH_2), 21.76 (CH_3); **MS** (ES +ve) $(M+1)^+$: 381.1, (ES -ve) $(M-1)^-$: 378.7; **HRMS** (ES +ve), $C_{21}H_{29}N_6O$ $(M+H)^+$: calculated 381.23974, found 381.239592.

2-[4-[2-[4-amino-3-(p-tolyl)pyrazolo[3,4-d]pyrimidin-1-yl]ethyl]piperazin-1-yl]ethanol (7h). Purified by column chromatography (MeOH/DCM 5-10% - 10% MeOH with 10-30 drops of NH_3 aq. per 100 ml) to give a pale orange solid (15 mg, 0.039 mmol, 38 %). **^{1}H NMR** (500 MHz, MeOD) δ 8.27 (s, 1H), 7.60 (d, *J* = 8.0, 2H), 7.41 (d, *J* = 7.9, 2H), 4.57 (t, *J* = 6.4, 2H), 3.73 (t, *J* = 5.7, 2H), 2.99 (t, *J* = 6.4, 2H), 2.74 (m, 10H), 2.46 (s, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.70 (C), 155.50 (CH), 154.57 (C), 144.39 (C), 139.07 (C), 130.26 (C), 129.93 (CH), 128.24 (CH), 98.28 (C), 59.13 (CH_2), 57.16 (CH_2), 56.58 (CH_2), 52.80 (CH_2), 52.04 (CH_2), 44.34 (CH_2), 21.23 (CH_3); **MS** (ES +ve) $(M+1)^+$: 382.0, 404.2 (+Na), (ES -ve) $(M-1)^-$: 379.9; **HRMS** (ES +ve), $C_{20}H_{28}N_7O$ $(M+H)^+$: calculated 382.23499, found 382.234597.

1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]-3-(p-tolyl)pyrazolo[3,4-d]pyramidin-4-amine (7i). Purified by column chromatography (MeOH/DCM 10% - 10% MeOH with 20 drops of NH_3 aq. per 50 ml) to give a light brown solid (13 mg, 0.034 mmol, 33 %). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.56 (d, J = 8.0, 2H), 7.33 (d, J = 7.8, 2H), 5.68 (s, 2H), 4.54 (t, J = 7.0, 2H), 3.08 (d, J = 11.8, 2H),

2.93 (t, J = 7.0, 2H), 2.43 (s, 3H), 2.41 (m, 1H), 2.40 (s, 6H), 2.10 (dd, J = 11.8, 9.9, 2H), 1.84 (d, J = 12.3, 2H), 1.52 (qd, J = 12.1, 3.7, 2H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.16 (C), 156.04 (CH), 154.87 (C), 144.69 (C), 139.38 (C), 130.60 (C), 130.32 (CH), 128.57 (CH), 98.70 (C), 62.72 (CH), 56.96 (CH_2), 52.86 (2x CH_2), 45.13 (CH_2), 41.01 (2x CH_3), 27.71 (CH_2), 21.61 (CH_3); **MS** (ES +ve) $(M+1)^+$: 380.2, 402.1 (+Na); **HRMS** (ES +ve), $C_{21}H_{30}N_7$ $(M+H)^+$: calculated 380.25572, found 380.255345.

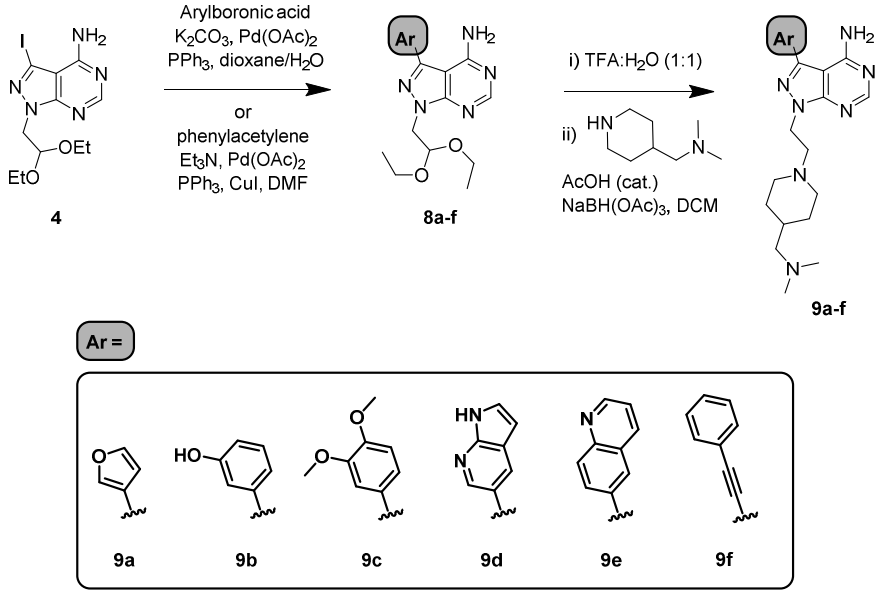
1-[2-[4-(dimethylaminomethyl)-1-piperidyl]ethyl]-3-(p-tolyl)pyrazolo[3,4-d]pyrimidin-4-amine (7j). To a suspension of 2-[4-amino-3-(p-tolyl)pyrazolo[3,4-d]pyrimidin-1-yl]acealdehyde (100 mg, 0.374 mmol) in DCM (2 ml) was added N,N-Dimethyl-1-piperidin-4-ylmethanamine (1 eq. 53.2 mg, 0.374 mmol) and a drop of AcOH and the mixture allowed to stir for 10 min. Sodium triacetoxyborohydride (79.3 mg, 0.374 mmol) was then added and the mixture allowed to stir for 18 h. The mixture was reduced in vacuo and purified, without a work up, by column chromatography MeOH/DCM (0-10 % - 10 % with 10 drops NH_3 aq. per 100 ml) to give a light orange solid (48 mg, 0.122 mmol, 32.6 %). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.55 (d, J = 8.1, 2H), 7.32 (d, J = 7.8, 2H), 4.54 (t, J = 6.8, 2H), 3.04 (d, J = 11.6, 2H), 2.95 (t, J = 6.8, 2H), 2.57 (s, 6H), 2.41 (s, 3H), 2.11 (t, J = 10.9, 2H), 1.74 (d, J = 12.6, 2H), 1.63 (s, 2H), 1.26 (m, 3H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.06 (C), 155.40 (CH), 154.56 (C), 144.79 (C), 139.23 (C), 130.36 (C), 130.16 (CH), 128.40 (CH), 98.53 (C), 64.32 (CH_2), 56.97 (CH_2), 53.15 (CH_2), 44.52 (CH_2), 44.42 (CH_3), 32.62 (CH), 30.14 (CH_2), 21.44 (CH_3); **MS** (ES +ve) $[M+1]^+$: 394.3, 416.2 (+Na); **HRMS** (ES +ve), $C_{22}H_{32}N_7$ $[M+H]^+$: calculated 394.27137, found 394.271595.

1-[2-[4-(2-dimethylaminoethyl)-1-piperidyl]ethyl]-3-(p-tolyl)pyrazolo[3,4-d]pyrimidin-4-amine (7k). To a suspension of 2-[4-amino-3-(p-tolyl)pyrazolo[3,4-d]pyrimidin-1-yl]acealdehyde (100 mg, 0.374 mmol) in DCM (2 ml) was added dimethyl-(2-piperidin-4-yl-ethyl)-amine (1 eq. 58.4 mg, 0.374 mmol) and a drop of AcOH and the mixture allowed to stir for 10 min. Sodium triacetoxyborohydride (79.3 mg, 0.374 mmol) was then added and the mixture allowed to stir for 18 h. The mixture was reduced in vacuo and purified, without a work up, by column chromatography MeOH/DCM (0-10 % - 10 % with 0-10 drops NH_3 aq per 100 ml) to give a light yellow solid (69.8 mg, 0.171 mmol, 45.8 %)**.** **^{1}H NMR** (500 MHz, MeOD) δ 8.25 (s, 1H), 7.59 – 7.55 (m, 2H), 7.38 (d, *J* = 7.8, 2H), 4.58 (t, *J* = 6.6, 2H), 3.14 (d, *J* = 11.8, 2H), 3.09 – 2.99 (m, 4H), 2.79 (s, 6H), 2.43 (s, 3H), 2.23 (t, *J* = 11.0, 2H), 1.74 (d, *J* = 12.9, 2H), 1.65 – 1.57 (m, 2H), 1.44 – 1.36 (m, 1H), 1.27 (dd, *J* = 21.1, 11.8, 2H); **^{13}C NMR** (126 MHz, MeOD) δ 158.50 (C). 155.45 (CH), 154.14 (C), 145.30 (C), 139.23 (C), 129.79 (C), 129.60 (CH), 128.09 (CH), 97.83 (C), 56.50 (CH_2), 55.70 (CH_2), 52.99 (2x CH_2), 43.45 (CH_2), 42.14 (2x CH_3),

32.84 (CH), 30.88 (2x CH_2), 30.64 (CH_2), 19.97 (CH_3); **MS** (ES +ve) $[M+1]^+$: 408.1; **HRMS** (ES +ve), $C_{23}H_{34}N_7$ $[M+H]^+$: calculated 408.28702, found 408.286812.

1-[2-[4-(2-dimethylaminoethyl)piperazin-1-yl]ethyl]-3-(p-tolyl)pyrazolo[3,4-d]pyrimidin-4-amine (7l). Purified by column chromatography (MeOH/DCM 5-10% - 10% MeOH with 25 drops of NH_3 aq. per 100 ml) to give a pale orange solid (5 mg, 0.031 mmol, 11.7). **^{1}H NMR** (500 MHz, MeOD) δ 8.27 (s, 1H), 7.59 (d, *J* = 8.0, 2H), 7.41 (d, *J* = 8.0, 2H), 4.56 (t, *J* = 6.6, 2H), 2.96 (t, *J* = 6.6, 2H), 2.89 (t, *J* = 6.6, 2H), 2.76 – 2.60 (m, 6H), 2.60 (s, 6H), 2.51 (m, 4H), 2.46 (s, 3H); **^{13}C NMR** (126 MHz, MeOD) δ 158.50 (C), 155.39 (CH), 154.14 (C), 145.16 (C), 139.21 (C), 129.83 (C), 129.60 (CH), 128.10 (CH), 97.76 (C), 56.40 (CH_2), 54.64 (CH_2), 53.51 (CH_2), 52.56 (CH_2), 52.24 (CH_2), 43.79 (CH_2), 43.36 (CH_3), 19.97 (CH_3); **MS** (ES +ve) $(M+1)^+$: 409.3, 431.2 (+Na); **HRMS** (ES +ve), $C_{22}H_{33}N_8$ $(M+H)^+$: calculated 409.28227, found 409.282102.

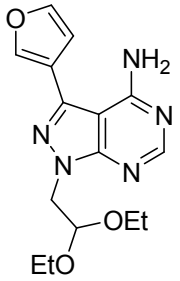
3. Synthesis and characterization of compounds 8a-f and 9a-f



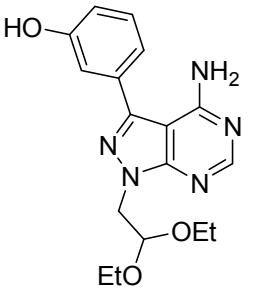
3.1. Synthesis and characterization of compounds 8a-e. To a solution of 1-(2,2-diethoxyethyl)-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine **4** (1.135 g, 3.0 mmol) in dioxane/water (10 ml/1 ml) was added the corresponding boronic acid / boronate ester (1.5 eq., 614 mg, 4.5 mmol), potassium carbonate (1.5 eq., 624.7 mg, 4.5 mmol) and followed by palladium acetate (5 mol %, 33.8 mg) and the mixture heated in the microwave at 120 °C for 1 h. EtOAc and water (50 ml) were added to the mixture and the organic layer separated, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude products were purified by column chromatography.

SUPPORTING INFORMATION

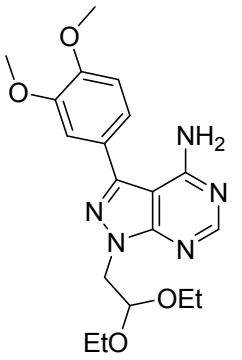
1-(2,2-diethoxyethyl)-3-(3-furyl)pyrazolo[3,4-d]pyrimidin-4-amine (8a). Purified by column chromatography, MeOH/DCM (0-2 %) to give a light brown colored solid, (66.8 mg, 0.211 mmol, 80 %). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.83 (dd, J = 1.4, 0.9, 1H), 7.61 (t, J = 1.7, 1H), 6.77 (dd, J = 1.8, 0.8, 1H), 5.82 (s, 2H), 5.09 (t, J = 5.8, 1H), 4.55 (d, J = 5.8, 2H), 3.76 (dq, J = 9.4, 7.0, 2H), 3.52 (dq, J = 9.4, 7.0, 2H), 1.11 (t, J = 7.0, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.93 (C), 154.38 (C), 154.12 (CH), 144.66 (CH), 141.11 (CH), 136.98 (C), 118.52 (C), 110.29 (CH), 99.73 (CH), 98.61 (C), 61.92 (2x CH2), 49.04 (CH2), 15.17 (2x CH3); **MS** (ES +ve) $[M+H]^+$: 318.2, 340.2(+Na), 657.2 (2M+Na), (ES –ve) $[M-H]^-$: 317.2; **HRMS** (ES +ve), $C_{15}H_{20}N_5O_3$ $(M+H)^+$: calculated 318.15607, found 318.15400.



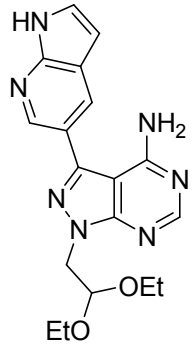
3-[4-amino-1-(2,2-diethoxyethyl)pyrazolo[3,4-d]pyrimidin-3-yl]phenol (8b). Purified by column chromatography, MeOH/DCM (0-3%) to give a light brown colored solid (80 mg, 0.233 mmol, 88 %). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.38 (t, J = 7.9, 1H), 7.20 (d, J = 7.5, 1H), 7.12 (s, 1H), 6.95 (d, J = 8.1, 1H), 5.89 (s, 2H), 5.10 (t, J = 5.7, 1H), 4.57 (d, J = 5.7, 2H), 3.76 (tt, J = 14.1, 7.0, 2H), 3.52 (tt, J = 14.1, 7.0, 2H), 1.11 (t, J = 7.0, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.10 (C), 155.85 (CH), 153.86 (C), 152.23 (C), 145.53 (C), 133.41 (C), 131.04 (CH), 120.31 (CH), 117.10 (CH), 115.15 (CH), 99.75 (CH), 97.78 (C), 62.16 (2x CH_2), 49.22 (CH_2), 15.17 (2x CH_3); **MS** (ES +ve) $[M+H]^+$: 344.2, 366.2 (+Na), (ES –ve) $[M-H]^-$: 342.2; **HRMS** (ES +ve), $C_{17}H_{22}N_5O_3$ $(M+H)^+$: calculated 344.17172, found 344.17000.



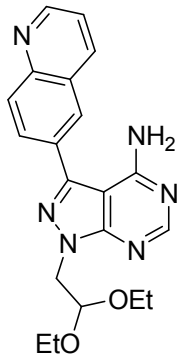
1-(2,2-diethoxyethyl)-3-(3,4-dimethoxyphenyl)pyrazolo[3,4-d]pyrimidin-4-amine (8c). Purified by column chromatography, MeOH/DCM (0-2%) to give a pale yellow solid (97 mg, 0.251 mmol, 94 %). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.23 – 7.19 (m, 2H), 7.02 (d, J = 8.7, 1H), 5.94 (s, 2H), 5.12 (t, J = 5.7, 1H), 4.57 (d, J = 5.8, 2H), 3.97 (d, J = 9.8, 6H), 3.78 (dq, J = 9.4, 7.0, 2H), 3.53 (dq, J = 9.4, 7.0, 2H), 1.13 (t, J = 7.0, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.59 (C), 155.28 (CH), 154.78 (C), 149.94 (C), 149.69 (C), 144.70 (C), 125.68 (C), 120.81 (CH), 111.61 (CH), 111.56 (CH), 99.82 (CH), 98.32 (C), 61.81 (2x CH_2), 56.06 (2x CH_3), 48.88 (CH_2), 15.19 (2x CH_3); **MS** (ES +ve) $[M+H]^+$: 388.2, (ES –ve) $[M-H]^-$: 368.2; **HRMS** (ES +ve), $C_{19}H_{26}N_5O_4$ $(M+H)^+$: calculated 388.19793, found 388.19620.



1-(2,2-diethoxyethyl)-3-(1H-pyrrolo[2,3-b]pyridin-5-yl)pyrazolo[3,4-d]pyrimidin-4-amine (8d). Purified by column chromatography, MeOH/DCM (0-6 %) to give a white solid (93 mg, 0.253 mmol, 96 %). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.53 (s, 1H), 8.62 (d, J = 1.9, 1H), 8.41 (s, 1H), 8.24 (d, J = 2.0, 1H), 7.45 (d, J = 3.4, 1H), 6.62 (d, J = 3.5, 1H), 6.29 – 5.86 (br. s, 2H), 5.14 (t, J = 5.7, 1H), 4.62 (d, J = 5.7, 2H), 3.79 (dq, J = 9.4, 7.0, 2H), 3.55 (dq, J = 9.4, 7.0, 2H), 1.14 (t, J = 7.0, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.75 (C), 154.58 (C), 153.42 (CH), 148.87 (C), 143.78 (C), 142.83 (CH), 128.83 (CH), 126.85 (CH), 121.30 (C), 120.46 (C), 101.80 (CH), 99.93 (CH), 98.47 (C), 62.17 (2x CH_2), 49.33 (CH_2), 15.34 (2x CH_3); **MS** (ES +ve) $[M+H]^+$: 368.2, 390.2 (+Na), (ES –ve) $[M-H]^-$: 366.2; **HRMS** (ES +ve), $C_{18}H_{22}N_7O_2$ $(M+H)^+$: calculated 368.18295, found 368.18090.



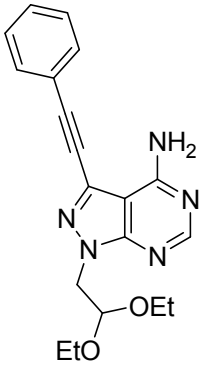
1-(2,2-diethoxyethyl)-3-(6-quinolyl)pyrazolo[3,4-d]pyrimidin-4-amine (8e). Purified by column chromatography, MeOH/DCM (0-5 %) to give a pale orange solid (86 mg, 0.227 mmol, 86 %). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 8.59 (d, J = 6.0, 1H), 8.47 (s, 1H), 8.16 (d, J = 8.2, 1H), 7.93 (dd, J = 7.1, 1.2, 1H), 7.84 (d, J = 6.0, 1H), 7.79 (dd, J = 8.2, 7.2, 1H), 5.18 (t, J = 5.7, 1H), 4.68 (d, J = 5.8, 2H), 3.83 (dq, J = 9.4, 7.0, 2H), 3.58 (dq, J = 9.4, 7.0, 2H), 1.21 – 1.13 (m, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.36 (C), 155.87 (CH), 154.77 (C), 152.99 (CH), 144.34 (CH), 141.21 (C), 134.32 (C), 132.29 (CH), 129.43 (CH), 129.32 (C), 128.98 (C), 127.01 (CH), 118.25 (CH), 99.92 (C), 99.80 (CH), 61.94 (2x CH_2), 49.18 (CH_2), 15.23 (2x CH_3); **MS** (ES +ve) $[M+H]^+$: 379.2, 401.2 (+Na), (ES –ve) $[M-H]^-$: 377.2; **HRMS** (ES +ve), $C_{20}H_{23}N_6O_2$ $(M+H)^+$: calculated 379.18770, found 379.18660.



3.2. Synthesis and characterization of compound 8f.

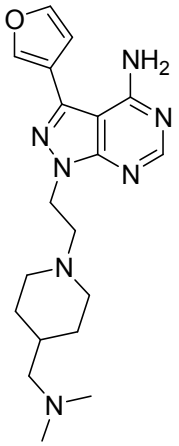
1-(2,2-diethoxyethyl)-3-(2-phenylethynyl)pyrazolo[3,4-d]pyrimidin-4-amine.

To a solution of 1-(2,2-diethoxyethyl)-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine **4** (100 mg, 0.265 mmol) in THF (5 ml) was added phenylacetylene (1.5 eq., 0.397 mmol, 40.5 mg, 37.7 µl), triethylamine (1.5 eq., 0.397 mmol, 29.1 µl), palladium acetate (5 mol %, 4.5 mg), triphenylphosphine (20 mol %, 20.8 mg) and copper iodide (5 mol %, 2.5 mg). The mixture was heated at 70 °C for 2 h. EtOAc and water were added to the mixture and the organic layer separated, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography, MeOH/DCM (0-2%) to give a light yellow solid (52 mg, 0.148 mmol, 56 %). **^{1}H NMR** (500 MHz, $CDCl_3$)

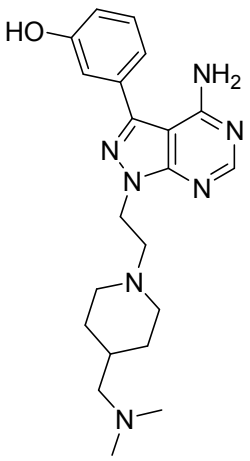


δ 8.90 – 8.35 (m, 1H), 7.59 (dd, J = 7.7, 1.7, 2H), 7.45 – 7.36 (m, 3H), 6.20 (s, 2H), 5.09 (t, J = 5.6, 1H), 4.53 (d, J = 5.7, 2H), 3.74 (dq, J = 9.3, 7.0, 2H), 3.50 (dq, J = 14.4, 7.2, 2H), 1.10 (t, J = 7.0, 6H); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 153.88 (CH), 131.82 (2x CH), 129.58 (CH), 128.67 (2x CH), 121.45 (C), 99.81 (CH), 94.33 (C), 80.63 (C), 62.07 (2x CH_2), 49.41 (CH_2), 15.16 (2x CH_3); **MS** (ES +ve) $[M+H]^+$: 352.2, 725.2 (2M +Na), (ES –ve) $[M-H]^-$: 350.2; **HRMS** (ES +ve), $C_{19}H_{22}N_5O_2$ $(M+H)^+$: calculated 352.17680, found 352.17680.

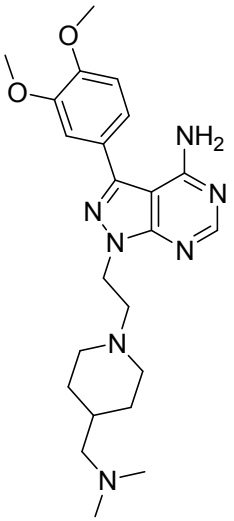
3.3. Synthesis and characterization of compounds 9a-f



1-[2-[4-(dimethylaminomethyl)-1-piperidyl]ethyl]-3-(3-furyl)pyrazolo[3,4-d]pyrimidin-4-amine (9a). 52 mg (0.164 mmol) of 1-(2,2-diethoxyethyl)-3-(3-furyl)pyrazolo[3,4-d]pyrimidin-4-amine (**8a**) was added to a 20 ml microwave vial. 5 ml of water was added followed by 5 ml of TFA and the mixture heated at 100 °C for 1 h. The mixture was concentrated *in vacuo* to leave a light brown oil which was used without further purification**.** Compound was dissolved in 4 ml of DCM. *N*,*N*-dimethyl-1-(4-piperidyl)methanamine (1.5 eq., 0.25 mmol, 35.0 mg) was added followed by a drop of acetic acid and the mixture allowed to stir for 10 min. Sodium triacetoxyborohydride (1.5 eq., 0.25 mmol, 52.1 mg) was added and the mixture allowed to stir over the weekend. The mixture was concentrated *in vacuo* and the product purified by column chromatography, MeOH/DCM (5-10 % then 10-20 drops of NH_3 aq per 100 ml) to give a dark golden brown solid (45.7 mg, 0.124 mmol, 76 %). **^{1}H NMR** (500 MHz, MeOD) δ 8.23 (s, 1H), 7.96 (dd, J = 1.4, 0.9, 1H), 7.71 (t, J = 1.7, 1H), 6.82 (dd, J = 1.8, 0.8, 1H), 4.53 (t, J = 6.7, 2H), 3.08 (d, J = 11.7, 2H), 2.94 (t, J = 6.7, 2H), 2.62 (d, J = 6.6, 2H), 2.57 (s, 6H), 2.16 (dd, J = 11.8, 10.0, 2H), 1.72 (d, J = 12.9, 2H), 1.68 (m, 1H), 1.26 – 1.18 (m, 2H); **^{13}C NMR** (126 MHz, MeOD) δ 158.57 (C), 155.45 (CH), 153.98 (C), 144.34 (CH), 141.47 (CH), 137.22 (C), 118.30 (C), 109.73 (CH), 98.17 (C), 63.97 (CH_2), 56.59 (CH_2), 52.62 (2x CH_2), 43.73 (CH_2), 43.43 (2x CH_3), 32.02 (CH), 29.27 (2x CH_2); **MS** (ES +ve) $[M+H]^+$: 370.2; **HRMS** (ES +ve), $C_{19}H_{27}N_7O$ $[M+H]^+$: calculated 370.22716, found 370.227049.



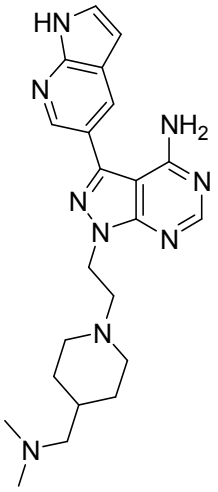
3-[4-amino-1-[2-[4-(dimethylaminomethyl)-1-piperidyl]ethyl]pyrazolo[3,4-d]pyrimidin-3-yl]phenol (9b). 60 mg (0.175 mmol) of 3-[4-amino-1-(2,2-diethoxyethyl)pyrazolo[3,4-d]pyrimidin-3-yl]phenol (**8b**) was added to a 20 ml microwave vial. 5 ml of water was added followed by 5 ml of TFA and the mixture heated at 100°C for 1 h. The mixture was concentrated *in vacuo* to leave a light brown oil which was used without further purification. The crude compound was dissolved in 4 ml of DCM. *N*,*N*-dimethyl-1-(4-piperidyl)methanamine (1.5 eq., 0.262 mmol, 37.2 mg) was added followed by a drop of acetic acid and the mixture allowed to stir for 10 min. Sodium triacetoxyborohydride (1.5 eq., 0.262 mmol, 55.5 mg) was added and the mixture allowed to stir for 20 h. The mixture was concentrated *in vacuo* and the product purified by column chromatography, MeOH/DCM (10 % then 0-20 drops of NH_3 aq per 100 ml) to give a dark orange solid (5.5 mg, 0.0139 mmol, 8 %). **^{1}H NMR** (500 MHz, MeOD) δ 8.26 (s, 1H), 7.39 (t, J = 7.9, 1H), 7.17 – 7.09 (m, 2H), 6.95 (dd, J = 7.8, 2.1, 1H), 4.57 (t, J = 6.7, 2H), 3.08 (d, J = 11.7, 2H), 2.96 (t, J = 6.7, 2H), 2.47 (m, 8H), 2.16 (t, J = 11.0, 2H), 1.74 (d, J = 12.9, 2H), 1.64 (m, 1H), 1.21 (dd, J = 21.1, 12.0, 2H); **^{13}C NMR** (126 MHz, MeOD) δ 158.44 (C), 158.06 (C), 155.42 (CH), 154.06 (C), 145.17 (C), 133.97 (C), 130.16 (CH), 119.09 (CH), 115.96 (CH), 114.92 (CH), 97.73 (C), 64.57 (CH_2), 56.66 (CH_2), 52.78 (2x CH_2), 43.83 (2x CH_3), 43.77 (CH_2), 32.46 (CH), 29.58 (2x CH_2). **MS** (ES +ve) $[M+H]^+$: 396.4; **HRMS** (ES +ve), $C_{21}H_{29}N_7O$ $[M+H]^+$: calculated 396.24281, found 396.242971.

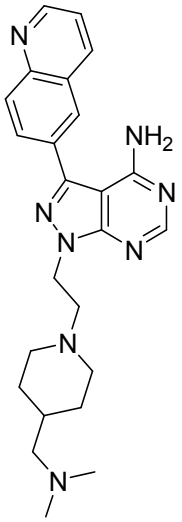


3-(3,4-dimethoxyphenyl)-1-[2-[4-(dimethylaminomethyl)-1-piperidyl]ethyl]pyrazolo[3,4-d]pyrimidin-4-amine (9c). 70 mg (0.181 mmol) of 1-(2,2-diethoxyethyl)-3-(3,4-dimethoxyphenyl)pyrazolo[3,4-d]pyrimidin-4-amine (**8c**) was added to a 20 ml microwave vial. 5 ml of water was added followed by 5 ml of TFA and the mixture heated at 100°C for 1 h. The mixture was concentrated *in vacuo* to leave a light brown oil which was used without further purification. The crude compound was dissolved in 4 ml of DCM. *N*,*N*-dimethyl-1-(4-piperidyl)methanamine (1.5 eq., 0.271 mmol, 38.5 mg) was added followed by a drop of acetic acid and the mixture allowed to stir for 10 min. Sodium triacetoxyborohydride (1.5 eq., 0.271 mmol, 57.4 mg) was added and the mixture allowed to stir for 17 h. The mixture was concentrated *in vacuo* and the product purified by column chromatography, MeOH/DCM (5-10 % then 10 drops of NH_3 aq per 100 ml) to give a light yellow solid (14.5 mg, 0.033 mmol, 21 %). **^{1}H NMR** (500 MHz, MeOD) δ 8.26 (s, 1H), 7.27 (s, 1H), 7.25 (d, J = 8.2,

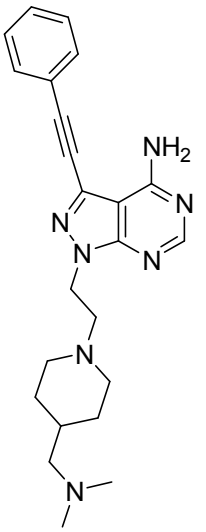
1H), 7.14 (d, J = 8.2, 1H), 4.63 (t, J = 6.3, 2H), 3.91 (s, 6H), 3.18 (s, 2H), 2.98 (d, J = 7.2, 2H), 2.85 (s, 6H), 2.45 (m, 2H), 1.92 (m, 1H), 1.83 (d, J = 13.2, 2H), 1.35 (dd, J = 22.2, 11.5, 2H); **^{13}C NMR** (126 MHz, MeOD) δ 158.58 (C), 155.51 (CH), 154.22 (C), 150.22 (C), 149.67 (C), 145.44 (C), 125.19 (C), 120.91 (CH), 111.94 (CH), 111.73 (CH), 97.82 (C), 62.49 (CH_2), 56.18 (CH_2), 55.13 (2x CH_3), 52.16 (2x CH_2), 43.08 (CH_2), 42.69 (2x CH_3), 30.70 (CH), 28.13 (2x CH_2); **MS** (ES +ve) $[M+H]^+$: 440.2; **HRMS** (ES +ve), $C_{23}H_{33}N_7O_2$ $[M+H]^+$: calculated 440.26902, found 440.268379.

1-[2-[4-(dimethylaminomethyl)-1-piperidyl]ethyl]-3-(1H-pyrrolo[2,3-b]pyridin-5-yl)pyrazolo[3,4-d]pyrimidin-4-amine (9d). 60 mg (0.163 mmol) of 1-(2,2-diethoxyethyl)-3-(1H-pyrrolo[2,3-b]pyridin-5-yl)pyrazolo[3,4-d]pyrimidin-4-amine (**8d**) was added to a 20 ml microwave vial. 5 ml of water was added followed by 5 ml of TFA and the mixture heated at 100°C for 1 h. The mixture was concentrated *in vacuo* to leave a light brown oil which was used without further purification. The crude compound was dissolved in 2 ml of DCM. *N*,*N*-dimethyl-1-(4-piperidyl)methanamine (1.5 eq., 0.245 mmol, 34.8 mg) was added followed by a drop of acetic acid. The mixture was allowed to stir for 10 mins then sodium triacetoxyborohydride (1.5 eq., 0.245 mmol, 51.9 mg) added and the mixture allowed to stir for 2 h. The mixture was concentrated *in vacuo* and the product purified by column chromatography, MeOH/DCM (5-10% then 10% with 5-20 drops of NH_3 aq. Per 100 ml) to give a light orange solid (15.3 mg, 0.0365 mmol, 15 %). **^{1}H NMR** (500 MHz, MeOD) δ 8.52 (s, 1H), 8.29 (d, J = 2.0, 1H), 8.28 (s, 1H), 7.52 (d, J = 3.5, 1H), 6.62 (d, J = 3.5, 1H), 4.64 (t, J = 6.4, 2H), 3.25 (d, J = 11.7, 2H), 3.13 (t, J = 6.3, 2H), 2.96 (d, J = 7.2, 2H), 2.84 (s, 6H), 2.37 (t, J = 11.4, 2H), 1.88 (m, 1H), 1.80 (d, J = 13.1, 2H), 1.36 – 1.31 (m, 2H); **^{13}C NMR** (126 MHz, MeOD) δ 161.79 (C), 158.65 (C), 155.54 (CH), 154.33 (C), 148.16 (C), 143.72 (C), 141.84 (CH), 128.67 (CH), 127.12 (CH), 120.73 (C), 100.63 (CH), 98.19 (C), 62.67 (CH_2), 56.31 (CH_2), 52.22 (2x CH_2), 43.41 (CH_2), 42.72 (2x CH_3), 30.93 (CH), 28.39 (2x CH_2); **MS** (ES +ve) $[M+H]^+$: 420.2; **HRMS** (ES +ve), $C_{22}H_{29}N_9$ $[M+H]^+$: calculated 420.25404, found 420.254249.





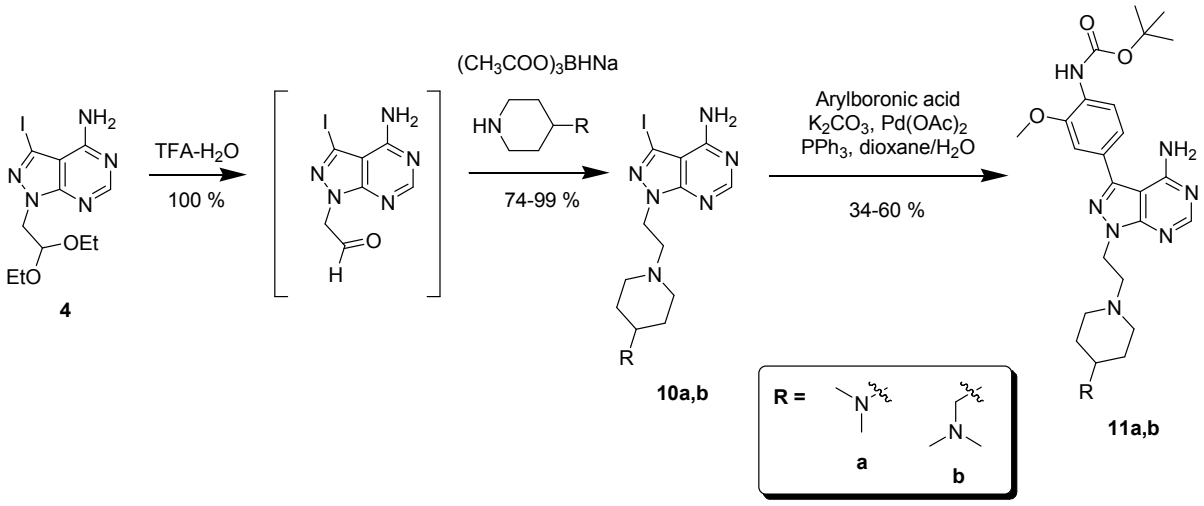
1-[2-[4-(dimethylaminomethyl)-1-piperidyl]ethyl]-3-(6-quinolyl)pyrazolo[3,4-d]pyrimidin-4-amine (9e). 60 mg (0.159 mmol) of 1-(2,2-diethoxyethyl)-3-(6-quinolyl)pyrazolo[3,4-d]pyrimidin-4-amine (**8e**) was added to a 20 ml microwave vial. 5 ml of water was added followed by 5 ml of TFA and the mixture heated at 100°C for 1 h. The mixture was concentrated *in vacuo* to give a brown oil which was used without further purification. The crude compound was dissolved in 2 ml of DCM. *N*,*N*-dimethyl-1-(4-piperidyl)methanamine (1.5 eq., 0.238 mmol, 33.9 mg) was added followed by a drop of acetic acid and the mixture allowed to stir for 10 mins. Sodium triacetoxyborohydride (1.5 eq., 0.238 mmol, 50.4 mg) was added and the mixture allowed to stir for 17 h. The mixture was concentrated *in vacuo* and purified by column chromatography, MeOH/DCM (5-10% then 20 drops NH_3 aq per 100 ml) to give a bright yellow colored solid (48.9 mg, 0.122 mmol, 71 %). **^{1}H NMR** (500 MHz, MeOD) δ 9.37 (s, 1H), 8.47 (d, J = 6.0, 1H), 8.31 (m, 2H), 7.99 (dd, J = 7.1, 1.2, 1H), 7.90 – 7.84 (m, 2H), 4.65 (t, J = 6.7, 2H), 3.09 (d, J = 11.7, 2H), 2.99 (t, J = 6.7, 2H), 2.28 (s, 6H), 2.27 (m, 2H), 2.18 – 2.11 (m, 2H), 1.75 (d, J = 12.4, 2H), 1.57 (ddd, J = 11.3, 7.4, 3.9, 1H), 1.24 – 1.12 (m, 2H); **^{13}C NMR** (126 MHz, MeOD) δ 158.26 (C), 155.67 (CH), 154.06 (C), 152.47 (CH), 142.47 (CH), 141.58 (C), 134.67 (C), 132.89 (CH), 129.35 (CH), 129.21 (c), 129.11 (C), 127.33 (CH), 118.82 (CH), 99.55 (C), 65.35 (CH_2), 56.79 (CH_2), 53.22 (2x CH_2), 44.34 (2x CH_3), 44.05 (CH_2), 33.06 (CH), 30.04 (2x CH_2); **MS** (ES +ve) $[M+H]^+$: 431.2; **HRMS** (ES +ve), $C_{24}H_{30}N_9$ $[M+H]^+$: calculated 431.25879, found 431.258695.



1-[2-[4-(dimethylaminomethyl)-1-piperidyl]ethyl]-3-(2-phenylethynyl)pyrazolo[3,4-d]pyrimidin-4-amine (9f). 50 mg (0.142 mmol) of 1-(2,2-diethoxyethyl)-3-(2-phenylethynyl)pyrazolo[3,4-d]pyrimidin-4-amine (**8f**) was added to a 20 ml microwave vial. 5 ml of water was added followed by 5 ml of TFA and the mixture heated at 100 °C for 1 h. The mixture was concentrated *in vacuo* to leave a dark brown oil which was used without further purification. The crude compound was suspended in 4 ml of DCM. *N*,*N*-dimethyl-1-(4-piperidyl)methanamine (1.5 eq., 0.213 mmol, 30.3 mg) was added followed by a drop of acetic acid and the mixture allowed to stir for 10 min. Sodium triacetoxyborohydride (1.5 eq., 0.213 mmol, 45.1 mg) was added and the mixture allowed to stir for 1 h. The mixture was concentrated *in vacuo* and the product purified by column chromatography, MeOH/DCM (5-10 % then 5-10 drops of NH_3 aq per 100 ml) to give a dark orange solid (23.4 mg, 0.058 mmol, 41 %). **^{1}H NMR** (500 MHz, MeOD) δ 8.23 (s, 1H), 7.69 – 7.61 (m, 2H), 7.46 – 7.40 (m,

3H), 4.51 (t, J = 6.7, 2H), 3.02 (d, J = 11.7, 2H), 2.90 (t, J = 6.7, 2H), 2.29 (s, 6H), 2.28 – 2.25 (m, 2H), 2.10 (td, J = 11.8, 2.3, 2H), 1.71 (d, J = 12.8, 2H), 1.54 (dtd, J = 14.6, 7.5, 3.7, 1H), 1.15 (qd, J = 12.5, 3.7, 2H); **^{13}C NMR** (126 MHz, MeOD) δ 158.22 (C), 156.07 (CH), 153.13 (C), 131.48 (CH x2), 129.25 (CH), 128.38 (CH x2), 126.72 (C), 121.47 (C), 100.98 (C), 93.76 (C), 79.88 (C), 65.21 (CH_2), 56.68 (CH_2), 52.96 (CH_2 x2), 44.27 (CH_3 x2), 44.22 (CH_2), 32.94 (CH), 29.92 (CH_2 x2); **MS** (ES +ve) $[M+H]^+$: 404.3; **HRMS** (ES +ve), $C_{23}H_{29}N_7$ $[M+H]^+$: calculated 404.24790, found 404.247888.

4. Synthesis and characterization of compounds 11a,b



1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine (10a). 150 mg (0.398 mmol) of 1-(2,2-diethoxyethyl)-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine (**4**) was added to a 10 ml microwave tube. 2.5 ml of water and 2.5 ml of TFA were added and the mixture heated to 100°C for 1 h. The mixture was concentrated *in vacuo* to give a white solid which was used without further purification. The aldehyde intermediate was suspended in 3 ml of DCM. 4-(*N*,*N*-dimethylamino)piperidine (1.5 eq., 0.598 mmol, 76.6 mg) was added followed by a drop of acetic acid and the mixture allowed to stir for 10 min. Sodium triacetoxyborohydride (1.5 eq., 0.598 mmol, 126.8 mg) was added and the mixture allowed to stir for 17 h overnight. The mixture was concentrated *in vacuo* and the product purified by column chromatography, MeOH/DCM (0-10 % then 5-20 drops of NH_3 aq. per 100 ml) to give a light orange/brown solid (163.8 mg, 0.405 mmol, 99 %). **^{1}H NMR** (500 MHz, MeOD) δ 8.22 (s, 1H), 4.49 (t, *J* = 6.4, 2H), 3.32 (s, 3H), 3.15 (d, *J* = 12.1, 2H), 2.96 (ddd, *J* = 16.0, 8.0, 4.0, 1H), 2.91 (t, *J* = 6.4, 2H), 2.72 (s, 6H), 2.15 (td, *J* = 12.0, 2.0, 2H), 2.04 – 1.96 (m, 2H), 1.54 (qd, *J* = 12.2, 3.9, 2H); **^{13}C NMR** (126 MHz, MeOD) δ 158.07 (C), 155.67 (CH),

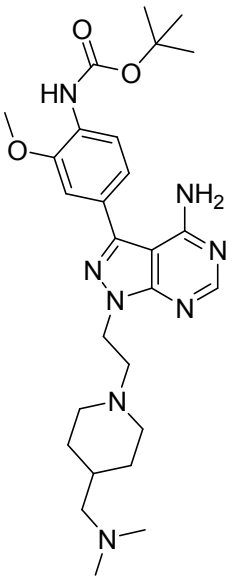
153.70 (C), 103.59 (C), 86.97 (C), 63.18 (CH), 55.86 (CH_2), 51.38 (2x CH_2), 44.37 (CH_2), 39.31 (2x CH_3), 26.42 (2x CH_2); **MS** (ES +ve) $[M+H]^+$: 416.2.

1-[2-[4-(dimethylaminomethyl)-1-piperidyl]ethyl]-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine (10b). 75 mg (0.199 mmol) of 1-(2,2-diethoxyethyl)-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine (**4**) was added to a 10 ml microwave tube. 2.5 ml of water and 2.5 ml of TFA were added and the mixture heated to 100 °C for 1 h. The mixture was concentrated *in vacuo* to give a white solid which was used without further purification. The intermediate was suspended in 3 ml of DCM. *N*,*N*-dimethyl-1-(4-piperidyl)methanamine (1.5 eq., 0.3 mmol, 42.2 mg) was added followed by a drop of acetic acid and the mixture allowed to stir for 10 min. Sodium triacetoxyborohydride (1.5 eq., 0.3 mmol, 63.4 mg) was added and the mixture allowed to stir for 17 h. The mixture was concentrated *in vacuo* and purified by column chromatography, MeOH/DCM (0-10 % then 5-15 drops of NH_3 aq. per 100 ml) to give a light yellow coloured solid (63.6 mg, 0.148 mmol, 74.5 %). **^{1}H NMR** (500 MHz, MeOD) δ 8.20 (s, 1H), 4.49 (t, *J* = 6.7, 2H), 3.01 (d, *J* = 11.7, 2H), 2.87 (t, *J* = 6.7, 2H), 2.28 (s, 6H), 2.27 (d, 2H), 2.10 (td, *J* = 11.8, 2.3, 2H), 1.72 (d, *J* = 13.0, 2H), 1.55 (ddt, *J* = 15.0, 7.6, 3.8, 1H), 1.15 (qd, *J* = 12.3, 3.7, 2H); **^{13}C NMR** (126 MHz, MeOD) δ 158.05 (C), 155.63 (CH), 153.58 (C), 103.66 (C), 86.95 (C), 65.27 (CH_2), 56.73 (CH_2), 52.96 (2x CH_2), 44.30 (2x CH_3), 44.15 (CH_2), 32.97 (CH), 30.09 (2x CH_2); **MS** (ES +ve) $[M+H]^+$: 430.2.

Tert-butyl N-[4-[4-amino-1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxy-phenyl]carbamate (11a). To a solution of **10a** (50 mg, 0.1205 mmol) in dioxane/water (4.5 ml/0.5 ml) was added [4-(tert-butoxycarbonylamino)-3-methoxy-phenyl]boronic acid (1.5 eq., 48.3 mg, 0.181 mmol), potassium carbonate (1.5 eq., 25.0 mg, 0.181 mmol) and triphenylphosphine (20 mol %, 9.5 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 1 h. EtOAc (50 ml) and water (50 ml) were added to the mixture and the organic layer separated. The aqueous layer was washed with EtOAc (20 ml, x2) and the organics combined dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography, MeOH/DCM (0-10 % then 5-20 drops of NH_3 aq. per 100 ml) to give a light brown solid (23.1 mg, 0.0453 mmol, 37.5 %). **^{1}H NMR** (500 MHz, MeOD) δ 8.27 (s, 1H),

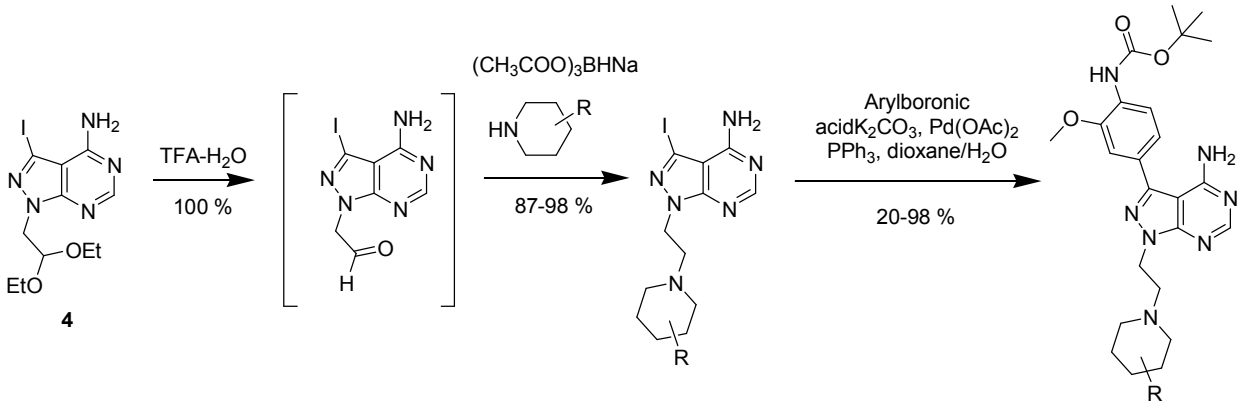
8.08 (d, *J* = 8.2, 1H), 7.30 (d, *J* = 1.8, 1H), 7.26 (dd, *J* = 8.2, 1.9, 1H), 4.56 (t, *J* = 6.7, 2H), 3.98 (s, 3H), 3.14 (d, *J* = 11.9, 2H), 2.94 (t, *J* = 6.7, 2H), 2.39 (m, 7H), 2.14 (dd, *J* = 12.0, 10.0, 2H), 1.90 (d, *J* = 12.5, 2H), 1.57 (s, 9H), 1.49 (qd, *J* = 12.1, 3.6, 2H); **^{13}C NMR** (126 MHz, MeOD) δ 158.53 (C), 155.40 (CH), 154.12 (C), 153.46 (C), 149.24 (C), 145.02 (C), 128.78 (C), 127.38 (C), 120.43 (CH), 119.56 (CH), 110.28 (CH), 97.73 (C), 80.18 (C), 62.29 (CH), 56.22 (CH_2), 55.07 (CH_3), 52.20 (2x CH_2), 44.00 (CH_2), 40.06 (2x CH_3), 27.24 (2x CH_2), 27.21 (3x CH_3); **MS** (ES +ve) $[M+H]^+$: 511.3; **HRMS** (ES +ve), $C_{26}H_{38}N_8O_3$ $[M+H]^+$: calculated 511.31396, found 511.3151.

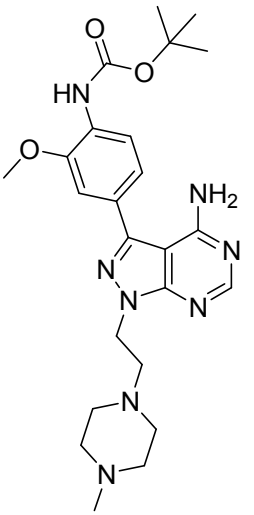
Tert-butyl N-[4-[4-amino-1-[2-[4-(dimethylaminomethyl)-1-piperidyl]ethyl]pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxy-phenyl]carbamate (11b). To a solution of **10b** (50 mg, 0.1165 mmol) in dioxane/water (4.5 ml/0.5 ml) was added [4-(tert-butoxycarbonylamino)-3-methoxy-phenyl]boronic acid (1.5 eq., 46.7 mg, 0.175 mmol), potassium carbonate (1.5 eq., 24.2 mg, 0.175 mmol) and triphenylphosphine (20 mol %, 9.2 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 45 min. EtOAc (50 ml) and water (50 ml) were added to the mixture and the organic layer separated. The aqueous layer was washed with EtOAc (20 ml, x3) and the organics combined dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography, MeOH/DCM (0-10 % then 5-20 drops of NH_3 aq. per 100 ml) to give a dark brown solid (36.5 mg, 0.07 mmol, 60 %). **^{1}H NMR** (500 MHz, MeOD) δ 8.27 (s, 1H), 8.08 (d, *J* = 8.2, 1H), 7.30 (d, *J* = 1.8, 1H), 7.26 (dd, *J* = 8.2, 1.8, 1H), 4.58 (t, *J* = 6.8, 2H), 3.98 (s, 3H), 3.08 (d, *J* = 11.7, 2H), 2.96 (t, *J* = 6.8, 2H), 2.34 (s, 6H), 2.32 (d, *J* = 7.2, 2H), 2.16 (dd, *J* = 11.8, 9.6, 2H), 1.76 (d, *J* = 12.3, 2H), 1.63 – 1.58 (m, 1H), 1.57 (s, 9H), 1.24 – 1.16 (m, 2H); **^{13}C NMR** (126 MHz, MeOD) δ 158.52 (C), 155.40 (CH), 154.07 (C), 153.46 (C), 149.24 (C), 145.04 (C), 128.77 (C), 127.39 (C), 120.43 (CH), 119.56 (CH), 110.29 (CH), 97.78 (C), 80.18 (C), 65.19 (CH_2), 56.76 (CH_2), 55.08 (CH_3), 52.96 (2x CH_2), 44.24 (2x CH_3), 43.79 (CH_2), 32.92 (CH), 29.89 (2x CH_2), 27.22 (3x CH_3); **MS** (ES +ve) $[M+H]^+$: 525.4, (ES –ve) $[M-H]^-$: 523.3; **HRMS** (ES +ve), $C_{27}H_{41}N_8O_3$ $(M+H)^+$: calculated 525.32961, found 525.32890.



5. Synthesis and characterization of compounds 12a-y

5.1. Synthesis and characterization of compounds 12a-e



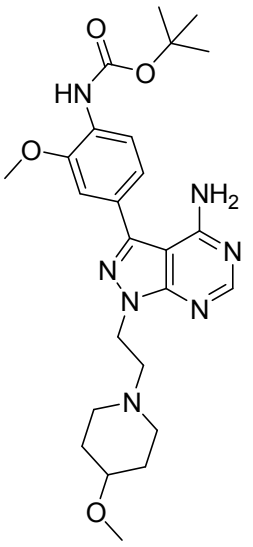


Tert-butyl N-[4-[4-amino-1-[2-(4-methylpiperazin-1-yl)ethyl]pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxy-phenyl]carbamate (12a). 100 mg, 0.265 mmol of 1-(2,2-diethoxyethyl)-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine was added to a 5 ml microwave tube. 2.5 ml of water and 2.5 ml of TFA were then added and the mixture heated to 100 °C for 30 min in the microwave. The solvents were removed in vacuo to give a dark brown oil. 0.265 mmol of the corresponding acetaldehyde was suspended in 3 ml of DCM. 1-methylpiperizine (1.5 eq., 0.399 mmol, 39.8 mg, 44.1 ul) was added followed by a drop of acetic acid and the mixture allowed to stir for 10 min. Sodium triacetoxyborohydride (1.5 eq., 0.399 mmol, 84.6 mg) was added and the mixture allowed to stir for 17 h. The mixture was concentrated in vacuo and purified by column chromatography, MeOH/DCM (5-10 % then 0-15 drops of NEt_3 per 100 ml) to give the reductive amination product as a light orange thick oil (89.1 mg, 0.2302 mmol, 87 %). ^{1}H NMR (500 MHz, MeOD) δ 8.22 (s, 1H), 4.51 (t, J = 6.0, 2H), 3.33 (d, J = 1.7, 4H), 3.20 – 3.04 (m, 4H), 2.98 (t, J = 6.0, 2H), 2.83 (s, 3H); ^{13}C NMR (126 MHz, MeOD) δ 158.05 (C), 155.67 (CH), 153.80 (C), 103.55 (C), 87.02 (C), 55.51 (CH_2), 53.44 (CH_2), 49.45 (CH_2), 44.18 (CH_2), 43.07 (CH_2), 42.03 (CH_3); MS (ES +ve) $(M+H)^+$: 388.4. To a solution 3-iodo-1-[2-(4-methylpiperazin-1-yl)ethyl]pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.129 mmol) in dioxane/water (4.5 ml/0.5 ml) was added [4-(tert-butoxycarbonylamino)-3-methoxy-phenyl]boronic acid (1.5 eq., 51.8 mg, 0.194 mmol), potassium carbonate (1.5 eq., 26.8 mg, 0.194 mmol) and triphenylphosphine (20 mol %, 10.2 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 30 min. The mixture was concentrated in vacuo and purified by column chromatography,

MeOH/DCM (10 % then 0-20 drops of NEt_3 per 100 ml), to give compound **12a** as a brown solid (55.4 mg, 0.115 mmol, 89 %). ^{1}H NMR (500 MHz, MeOD) δ 8.25 (s, 1H), 8.06 (d, J = 8.2, 1H), 7.29 (d, J = 1.8, 1H), 7.24 (dd, J = 8.2, 1.8, 1H), 4.55 (t, J = 6.5, 2H), 3.97 (s, 3H), 2.95 (t, J = 6.5, 2H), 2.57 (s, 8H), 2.35 (s, 3H), 1.55 (s, 9H); ^{13}C NMR (126 MHz, MeOD) δ 158.54 (C), 155.42 (CH), 154.21 (C), 153.48 (C), 149.29 (C), 145.02 (C), 128.80 (C), 127.42 (C), 120.44 (CH), 119.61 (CH), 110.16 (CH), 97.74 (C), 80.21 (C), 56.21 (CH_2), 55.10 (CH_3), 54.16 (2x CH_2), 51.64 (2x CH2), 44.06 (CH_3), 43.84 (CH_2), 27.21 (3x CH_3); MS (ES +ve) (M+H)+: 483.6; HRMS (ES +ve), $C_{24}H_{35}N_8O_3$ $(M+H)^+$: calculated 483.28266, found 483.28200.

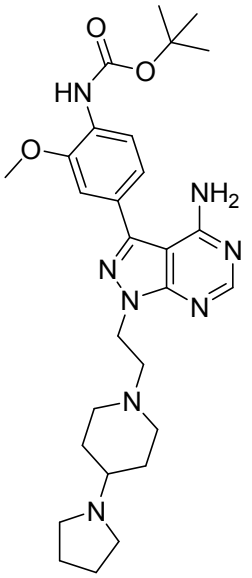
Tert-butyl N-[4-[4-amino-1-[2-[3-(dimethylamino)-1-piperidyl]ethyl]pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxy-phenyl]carbamate (12b). 100 mg, 0.287 mmol of 1-(2,2-dimethoxyethyl)-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine was added to a 5 ml microwave tube. 2.5 ml of water and 2.5 ml of TFA were then added and the mixture heated to 100 °C for 30 min in the microwave. The product was then concentrated in vacuo. 0.287 mmol of the corresponding acetaldehyde was suspended in 3 ml of DCM. 3-dimethylaminopiperidine (1.5 eq., 0.430 mmol, 55.1 mg) was added followed by a drop of acetic acid and the mixture allowed to stir for 10 min. Sodium triacetoxyborohydride (1.5 eq., 0.430 mmol, 91.1 mg) was added and the mixture allowed to stir for 18 h. The mixture was concentrated in vacuo and purified by column chromatography, MeOH/DCM (5-10 %), to give the reductive amination product as a pale yellow solid (117.5 mg, 0.283 mmol, 98.5 %). ^{1}H NMR (500 MHz, MeOD) δ 8.22 (s, 1H), 4.54 – 4.43 (m, 2H), 3.08 (m, 1H), 2.99 – 2.90 (m, 3H), 2.84 (s, 6H), 2.65 (m, 2H), 2.38 (m, 1H), 1.88 (m, 1H), 1.75 – 1.65 (m, 2H), 1.55 – 1.47 (m, 1H); ^{13}C NMR (126 MHz, MeOD) δ 158.13 (C), 155.80 (CH), 153.62 (C), 103.65 (C), 87.01 (C), 62.48 (CH), 56.37 (CH_2), 52.78 (CH_2), 52.75 (CH_2), 44.50 (CH_2), 40.40 (2x CH_3), 24.67 (CH_2), 21.95 (CH_2); MS (ES +ve) $(M+H)^+$: 415.8. To a solution of 1-[2-[3-(dimethylamino)-1-piperidyl]ethyl]-3-iodo-pyrazolo[3,4- d]pyrimidin-4-amine (50 mg, 0.1205 mmol) in dioxane/water (4.5 ml/0.5 ml) was added [4-(tert-butoxycarbonylamino)-3-methoxy-phenyl]boronic acid (1.5 eq., 48.3 mg, 0.181 mmol), potassium carbonate (1.5 eq., 25.0 mg, 0.181 mmol) and triphenylphosphine (20 mol %, 9.5 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 30 min. The mixture was concentrated in vacuo and purified by column chromatography, MeOH/DCM (5-10 %), to give compound **12b** as a dark red solid (60.5 mg, 0.119 mmol, 98 %). ^{1}H NMR (500 MHz, MeOD) δ 8.25 (s, 1H), 8.05 (d, J = 8.2, 1H), 7.26 (d, J = 1.8, 1H), 7.22 (dd, J = 8.2,

1.8, 1H), 4.58 – 4.48 (m, 2H), 3.94 (s, 3H), 3.13 (m, 1H), 2.97 (m, 3H), 2.82 (s, 6H), 2.66 (m, 2H), 2.42 (m, 1H), 1.86 (m, 1H), 1.71 (m, 2H), 1.52 (m, 10H); 13C NMR (126 MHz, MeOD) δ 158.61 (C), 155.59 (CH), 154.11 (C), 153.49 (C), 149.33 (C), 145.10 (C), 128.93 (C), 127.24 (C), 120.44 (CH), 119.66 (CH), 110.28 (CH), 97.76 (C), 80.24 (C), 62.58 (CH), 56.39 (CH_2), 55.12 (CH_3), 52.86 (CH_2), 52.73 (CH_2), 44.28 (CH_2), 40.32 (2x CH_3), 27.20 (3x CH_3), 24.59 (CH_2), 21.84 (CH_2); MS (ES +ve) $[M+H]^+$: 511.0; HRMS (ES +ve), $C_{26}H_{39}N_8O_3$ $(M+H)^+$: calculated 511.31396, found 511.31140.



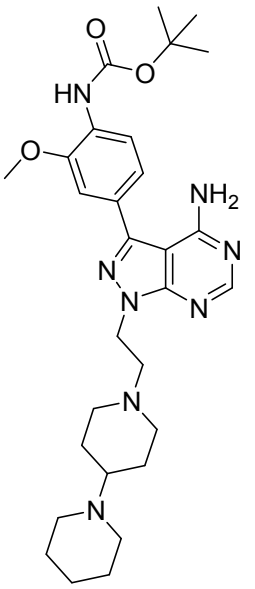
Tert-butyl N-[4-[4-amino-1-[2-(4-methoxy-1-piperidyl)ethyl]pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxy-phenyl]carbamate (12c). 100 mg, 0.287 mmol of 1-(2,2-dimethoxyethyl)-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine was added to a 5 ml micro wave tube. The mixture was then concentrated in vacuo. 0.287 mmol of the corresponding acetaldehyde was suspended in 3 ml of DCM. 4-methoxypiperidine (1.5 eq., 0.430 mmol, 49.5 mg) was added followed by a drop of acetic acid and the mixture allowed to stir for 10 min. Sodium triacetoxyborohydride (1.5 eq., 0.430 mmol, 91.1 mg) was then added and the mixture allowed to stir for 72 h. The product was concentrated in vacuo and the product purified by column chromatography, MeOH/DCM (0-8 %), to give a pale yellow solid (112 mg, 0.279 mmol, 97 %). ^{1}H NMR (500 MHz, MeOD) δ 8.23 (s, 1H), 4.53 (t, J = 6.6, 2H), 3.29 (s, 1H), 2.98 (t, J = 6.5, 2H), 2.91 (s, 2H), 2.45 (s, 2H), 1.89 (s, 2H), 1.57 (s, 2H); ^{13}C NMR (126 MHz, MeOD) δ 158.09 (C), 155.71 (CH), 153.68 (C), 103.71 (C), 87.16 (C), 75.13 (CH), 56.19 (CH_2), 54.43 (CH_3), 50.24 (2x CH_2), 43.96 (CH_2), 29.68 (2x CH_2); MS (ES +ve) $(M+H)^+$: 403.0. To a solution of 3-iodo-1-[2-(4-methoxy-1-piperidyl)ethyl]pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.124 mmol) in dioxane/water (4.5 ml/0.5 ml) was added [4-(tert-butoxycarbonylamino)-3-methoxy-phenyl]boronic acid (1.5 eq., 49.8 mg, 0.187 mmol), potassium carbonate (1.5 eq., 25.8 mg, 0.181 mmol) and triphenylphosphine (20 mol %, 6.5 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 30 min. The mixture was concentrated in vacuo and purified by column chromatography, MeOH/DCM (0-10 %), to give compound **12c** as a pale yellow solid (60.0 mg, 0.121 mmol, 97 %). ^{1}H NMR (500 MHz, MeOD) δ 8.29 (s, 1H), 8.08 (d, J = 8.2, 1H), 7.31 (d, J = 1.8, 1H), 7.27 (dd, J = 8.2, 1.8, 1H), 4.63 (t, J = 6.6, 2H), 3.98 (s, 3H), 3.34 (s, 3H), 3.12 (m, 2H), 3.02 (m, 2H), 2.60 (m, 2H), 1.93 (m, 2H), 1.65 (m, 2H), 1.57 (s, 9H); ^{13}C NMR (126 MHz, MeOD) δ 158.53 (C), 155.46 (CH), 154.22 (C), 153.42 (C), 149.28 (C), 145.17 (C), 128.73 (C), 127.38 (C), 120.44 (CH), 119.50 (CH), 110.33 (CH), 97.94 (C), 80.15 (C), 75.12 (CH), 56.21 (CH_2), 55.10 (CH_3), 54.79 (CH_3), 50.02 (2x CH_2), 43.60 (CH_2), 29.69 (2x CH_2),

27.21 (3x CH_3); MS (ES +ve) $[M+H]^+$: 498.2; HRMS (ES +ve), $C_{25}H_{35}N_7O_4$ $[M+H]^+$: calculated 498.28233, found 498.2850.



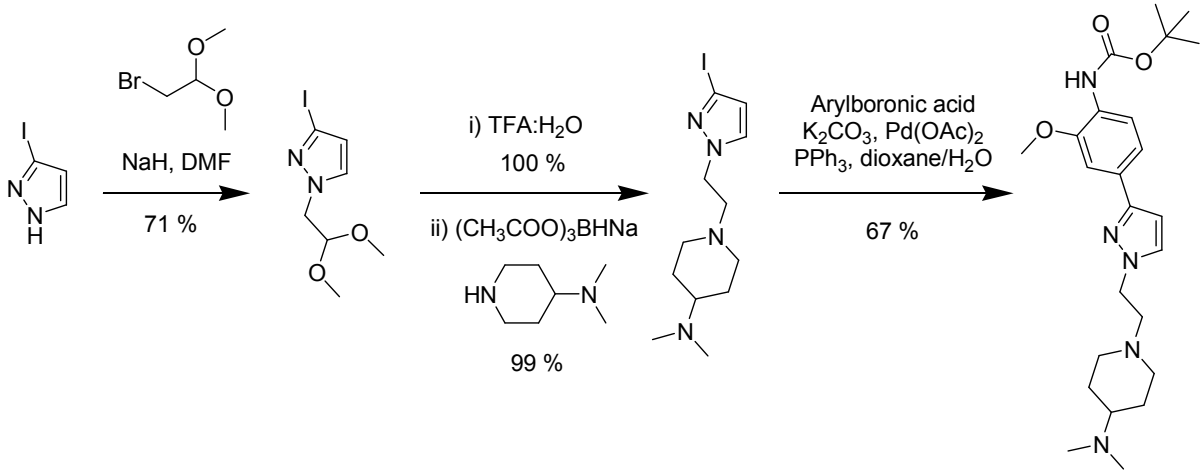
Tert-butyl N-[4-[4-amino-1-[2-(4-(1-pyrrolidin)piperidin-1-yl)ethyl]pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxy-phenyl]carbamate (12d). 300 mg, 0.8646 mmol of 1-(1,3-dioxolan-2-yl methyl)-3-iodo-pyrazolo[3,4-d]pyrimidin-4- amine was added to a 10 ml microwave tube. 2.5 ml of water and 2.5 ml of TFA were added and the mixture heated to 100 °C for 3 h. The product was concentrated in vacuo and used without further purification. 0.432 mmol of the resulting acetaldehyde derivative was suspended in 3 ml of DCM. 4-(1-pyrrolidinyl)piperidine (1.5 eq., 0.648 mmol, 99.9 mg) was added followed by a drop of acetic acid and the mixture allowed to stir for 10 min. Sodium triacetoxyborohydride (1.5 eq., 0.648 mmol, 137.3 mg) was added and the mixture allowed to stir for 17 h. The mixture was concentrated in vacuo and purified by column chromatography, MeOH/DCM (0-10 %), to give the reductive amination product as a brownish solid (183.1 mg, 0.415 mmol, 96 %). ^{1}H NMR (500 MHz, MeOD) δ 8.22 (s, 1H), 4.50 (t, J = 6.3, 2H), 3.34 (m, 4H), 3.12 (d, J = 12.0, 2H), 3.06 (dd, J = 13.9, 9.7, 1H), 2.90 (t, J = 6.3, 2H), 2.21 – 2.00 (m, 8H), 1.52 (td, J = 12.1, 8.1, 2H); MS (ES +ve) $(M+H)^+$: 442.2. To a solution of 3-iodo-1-[2-(4-pyrrolidin-1-yl-1-piperidyl)ethyl]pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.113 mmol) in dioxane/water (4.5 ml/0.5 ml) was added [4-(tert-butoxycarbonylamino)-3-methoxy-phenyl]boronic acid (1.5 eq., 45.4 mg, 0.170 mmol), potassium carbonate (1.5 eq., 23.5 mg, 0.170 mmol) and triphenylphosphine (20 mol %, 8.9 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 1 h. EtOAc (50 ml) and water (50 ml) were added to the mixture and the organic layer separated. The aqueous layer was washed with EtOAc (20 ml x2) and the organics combined and washed with brine then dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography, MeOH/DCM (0-10 % then 5-25 drops of NH_3 aq. per 100 ml), to give compound **12d** a light orange solid (16.69 mg, 31.12 µmol, 27.5 %). ^{1}H NMR (500 MHz, MeOD) δ 8.27 (s, 1H), 8.08 (d, J = 8.2, 1H), 7.30 (d, J = 1.8, 1H), 7.25 (dd, J = 8.2, 1.8, 1H), 4.56 (t, J = 6.6, 2H), 3.98 (s, 3H), 3.12 (d, J = 12.0, 2H), 2.94 (m, 6H), 2.53 (m, 1H), 2.15 (t, J = 11.1, 2H), 2.01 (d, J = 12.2, 2H), 1.93 (dd, J = 8.3, 5.0, 4H), 1.57 (s, 9H), 1.55 – 1.48 (m, 2H); ^{13}C NMR (126 MHz, MeOD) δ 158.52 (C), 155.40 (CH), 154.15 (C), 153.45 (C), 149.24 (C), 145.00 (C), 128.80 (C), 127.36 (C), 120.43 (CH), 119.55 (CH), 110.27 (CH), 97.69 (C), 80.19 (C), 62.00 (CH), 56.16 (CH_2), 55.08 (CH_3), 51.62 (2x CH_2), 51.22 (2x CH_2), 44.01 (CH_2), 29.65 (2x CH_2), 27.22 (3x

CH_3), 22.49 (2x CH_2); MS (ES +ve) [M+H]+: 537.4, (ES -ve) [M-H]-: 535.3; HRMS (ES +ve) $C_{28}H_{40}N_8O_3$ $[M+H]^+$: calculated 537.32961, found 537.3281.

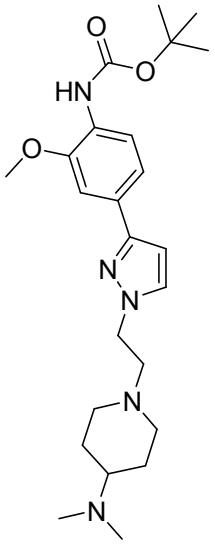


Tert-butyl N-[4-[4-amino-1-[2-(4-(1-piperidinyl)piperidin-1-yl)ethyl]pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxy-phenyl]carbamate (12e). 300 mg, 0.8646 mmol of 1-(1,3-dioxolan-2-ylmethyl)-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine was added to a 10 ml microwave tube. 2.5 ml of water and 2.5 ml of TFA were added and the mixture heated to 100 °C for 3 hours. The product was concentrated in vacuo and used without further purification. 0.432 mmol of the resulting acetaldehyde derivative was suspended in 3 ml of DCM. 1,4-bipiperidine (1.5 eq., 0.648 mmol, 108.9 mg) was added followed by a drop of acetic acid and the mixture allowed to stir for 10 min. Sodium triacetoxyborohydride (1.5 eq., 0.648 mmol, 137.3 mg) was added and the mixture allowed to stir for 17 h. The mixture was concentrated in vacuo and purified by column chromatography, MeOH/DCM (0-10 %), to give the reductive amination product as a dark brown thick oil (191.6 mg, 0.421 mmol, 97.5%). ^{1}H NMR (601 MHz, DMSO) δ 8.21 (s, 1H), 4.38 (t, J = 6.6, 2H), 2.85 (broad m, 9H), 1.98 (m, 2H), 1.54 (broad m, 10H); MS (ES +ve) $(M+H)^+$: 456.2. To a solution of 3-iodo-1-[2-[4-(1-piperidyl)-1-piperidyl]ethyl]pyrazolo[3,4-d]pyrimidin-4- amine (50 mg, 0.110 mmol) in dioxane/water (4.5 ml/0.5 ml) was added [4-(tert-butoxycarbonylamino)-3-methoxy-phenyl]boronic acid (1.5 eq., 44.0 mg, 0.165 mmol), potassium carbonate (1.5 eq., 22.8 mg, 0.165 mmol) and triphenylphosphine (20 mol %, 5.8 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 1 h. EtOAc (50 ml) and water (50 ml) were added to the mixture and the organic layer separated. The aqueous layer was washed with EtOAc (20 ml x2) and the organics combined, dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by column chromatography, MeOH/DCM (0-10 %, then 5-15 drops of NH_3 aq. per 100 ml) to give a light brown solid (12.3 mg, 22.35 µmol, 20 %). ^{1}H NMR (500 MHz, MeOD) δ 8.27 (s, 1H), 8.08 (d, J = 8.2, 1H), 7.30 (d, J = 1.7, 1H), 7.26 (dd, J = 8.2, 1.8, 1H), 4.55 (t, J = 6.6, 2H), 3.96 (s, 3H), 3.15 (d, J = 11.8, 2H), 2.93 (t, J = 6.6, 2H), 2.74 (br. s, 4H), 2.51 (br. s, 1H), 2.13 (t, J = 11.1, 2H), 1.91 (d, J = 12.0, 2H), 1.72 – 1.62 (m, 4H), 1.55 (m, 13H); ^{13}C NMR (126 MHz, MeOD) δ 158.52 (C), 155.40 (CH), 154.13 (C), 153.45 (C), 149.24 (C), 145.02 (C), 128.79 (C), 127.37 (C), 120.43 (CH), 119.56 (CH), 110.28 (CH), 97.73 (C), 80.19 (C), 62.69 (CH), 56.21 (CH_2), 55.08 (CH3), 52.43 (2x CH_2), 49.83 (2x CH_2), 44.00 (CH_2), 27.22 (3x CH_3), 26.78 (2x CH_2), 24.68 (2x CH_2), 23.34 (CH_2); MS (ES +ve) $[M+H]^+$: 551.2; HRMS (ES +ve), $C_{29}H_{42}N_8O_3$ $[M+H]^+$: calculated 551.34526, found 551.3469.

5.2. Synthesis and characterization of compound 12f



12f

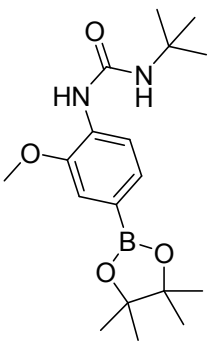


Tert-butyl N-[4-[1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]pyrazol-3-yl]-2-methoxy-phenyl]carbamate (12f). To a solution of 3-iodo-1H-pyrazole (500 mg, 2.578 mmol) in DMF (10 ml) was added sodium hydride (1.5 eq., 3.867 mmol, 60% dispersion in mineral oil, 154.7 mg) and the suspension allowed to stir for 30 min until the gas evolution had subsided. Bromoacetaldehyde dimethyl acetal (1.5 eq. 3.867 mmol, 649.6 mg, 0.454 ml) was then added dropwise and the mixture heated at 150 °C in the microwave for 1 h. The mixture was concentrated in vacuo in order to remove as much DMF as possible. EtOAc and water were then added to the mixture and the organic layer separated. The aqueous layer was washed twice with EtOAc and organics combined, dried over $MgSO_4$ and concentrated in vacuo. The product was purified by column chromatography, MeOH/DCM (0-1 %), to give the alkylated derivative as a light orange solid, (519.2 mg, 1.841 mmol, 71 %). ^{1}H NMR (500 MHz, CDCl3) δ 7.28 (d, J = 2.3, 1H), 6.40 (d, J = 2.3, 1H), 4.62 (t, J = 5.4, 1H), 4.20 (d, J = 5.4, 2H), 3.37 (d, J = 2.4, 6H); ^{13}C NMR (126 MHz, CDCl3) δ 132.61 (CH), 114.84 (CH), 103.29 (CH_2), 94.49 (C), 55.20 (2x CH_3), 54.55 (CH); MS (ES +ve) $(M+H)^+$: 304.6 (Na^+). 1-(2,2-dimethoxyethyl)-3-iodo-pyrazole (250 mg, 0.887 mmol) was added to a microwave vial followed by water (0.25 ml) and TFA (0.25 ml) and the mixture heated to 100 °C in the microwave for 1 h. The product was concentrated in vacuo and used without further purification. 0.887 mmol of the corresponding acetaldehyde was suspended in 5 ml of DCM. 4-(*N*,*N*-dimethylamino)piperidine (1.5 eq., 1.33 mmol, 170.5 mg) was added followed by a drop of acetic acid and the mixture allowed to stir for 10 min. Sodium triacetoxyborohydride (1.5 eq., 1.33 mmol, 281.9 mg) was added and the mixture

allowed to stir for 72 h. The mixture was concentrated in vacuo and purified by column chromatography, MeOH/DCM (5-10 % then 10-20 drops of NEt_3 per 100 ml), to give the reductive amination product as a thick light orange oil (306.3 mg, 0.880 mmol, 99 %). 1H NMR (500 MHz, MeOD) δ 7.54 (d, J = 2.3, 1H), 6.43 (d, J = 2.3, 1H), 4.27 (t, J = 6.4, 2H), 3.10 – 3.05 (m, 1H), 3.05 – 2.99 (m, 2H), 2.85 – 2.76 (m, 8H), 2.17 (td, J = 12.0, 2.3, 2H), 2.01 (d, J = 13.2, 2H), 1.67 (tt, J = 12.1, 6.1, 2H); 13C NMR (126 MHz, MeOD) δ 132.70 (CH), 114.34 (CH), 93.40 (C), 63.39 (CH), 56.57 (CH_2), 51.40 (2x CH_2), 49.59 (CH_2), 39.17 (2x CH_2), 26.24 (CH_2); MS (ES +ve) $(M+H)^+$: 348.8. To a solution of 1-[2-(3-iodopyrazol-1-yl)ethyl]-N,N-dimethyl-piperidin-4-amine (50 mg, 0.1436 mmol) in dioxane/water (4.5 ml/0.5 ml) was added [4-(tert-butoxycarbonylamino)-3- methoxy-phenyl]boronic acid (1.5 eq., 57.6 mg, 0.215 mmol), potassium carbonate (1.5 eq., 29.7 mg, 0.215 mmol) and triphenylphosphine (20 mol %, 7.5 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 1 h. The reaction was concentrated in vacuo and purified by column chromatography, MeOH/DCM (5-10 %), to give compound **12f** as a dark orange solid (42.7 mg, 0.0963 mmol, 67 %). ^{1}H NMR (500 MHz, MeOD) δ 7.88 (s, 1H), 7.69 (d, J = 2.3, 1H), 7.42 (d, J = 1.7, 1H), 7.33 (dd, J = 8.3, 1.8, 1H), 6.62 (d, J = 2.3, 1H), 4.33 (t, J = 6.4, 2H), 3.96 (s, 3H), 3.22 – 3.15 (m, 1H), 3.11 (s, 2H), 2.94 (s, 2H), 2.85 (d, J = 14.6, 6H), 2.26 (s, 2H), 2.05 (s, 2H), 1.73 (d, J = 8.3, 2H), 1.55 (d, J = 4.2, 9H); ^{13}C NMR (126 MHz, MeOD) δ 153.56 (C), 151.55 (C), 149.10 (C), 131.77 (CH), 128.50 (C), 127.36 (C), 123.00 (C), 119.24 (CH), 117.75 (CH), 107.31 (CH), 102.25 (CH), 63.48 (CH), 56.69 (CH_2), 54.95 (CH_3), 51.21 (2x CH_2), 49.11 (CH_2), 39.19 (2x CH_3), 27.23 (3x CH_3), 26.22 (2x CH_2); MS (ES +ve) $(M+H)^+$: 444.2; HRMS (ES +ve), $C_{24}H_{38}N_5O_3$ $(M+H)^+$: calculated 444.29692, found 444.29650.

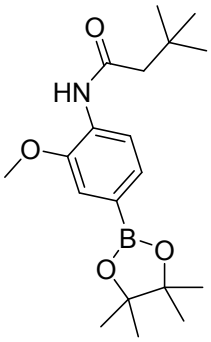
5.3. Synthesis and characterization of compounds 12g-y

Synthesis and characterization of non-commercial boronic acids and esters

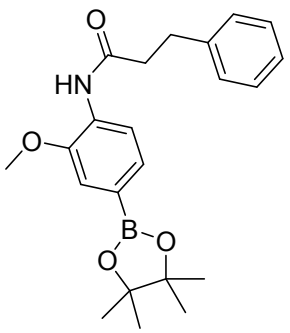


1-tert-butyl-3-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]urea. To a solution of 4-amino-3-methoxybenzeneboronic acid, pinacol ester (150 mg, 0.602 mmol), in DCM (3 ml) was added t-butylisocyanate (20 eq., 12.04 mmol, 1.19 g) and the mixture left to stir at for 72 h. DCM and water were added to the mixture and the organic layer separated, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The product was purified by column chromatography, MeOH/DCM (0-2%), to give a dark brown solid, (40.9 mg, 0.117 mmol, 20 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.0, 1H), 7.44 (dd, *J* = 8.0, 1.2, 1H), 7.27 (d, *J* = 1.0,

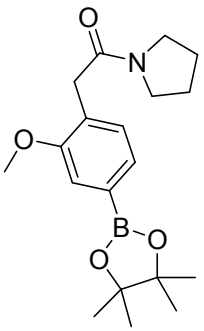
1H), 6.88 (s, 1H), 3.92 (s, 3H), 1.42 (s, 9H), 1.37 (d, *J* = 3.9, 12H); ^{13}C NMR (126 MHz, CDCl3) δ 153.97 (C), 146.81 (C), 131.78 (C), 128.70 (CH), 117.77 (CH), 115.36 (CH), 83.65 (CH), 55.74 (C), 50.97 (CH_3), 29.36 (C), 29.09 (3x CH_3), 24.87 (4x CH_3); MS (ES +ve) $[M+H]^+$: 349.7, 371.6 (Na^+)



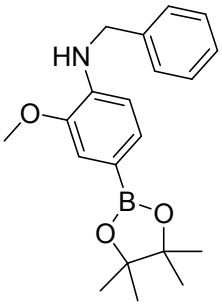
N-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-3,3-dimethyl-butanamide. To a solution of 4-amino-3-methoxy-benzeneboronic acid, pinacol ester (150 mg, 0.602 mmol), in DCM (2 ml) was added triethylamine (1.2 eq., 0.722 mmol, 73.1 mg, 100.76 µl) followed by t-butyl-acetal chloride (1.2 eq., 0.722 mmol, 96.8 mg, 99.9 µl) and the mixture stirred for 20 h. Water was added to the mixture and the organic layer separated, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The product was purified by column chromatography, MeOH/DCM (0-3%), to give a brown solid (195.7 mg, 0.564 mmol, 94 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, *J* = 8.0, 1H), 7.83 (s, 1H), 7.47 (dd, *J* = 8.0, 1.0, 1H), 7.32 – 7.29 (m, 1H), 3.95 (s, 3H), 2.31 – 2.27 (m, 2H), 1.36 (s, 12H), 1.13 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.06 (C), 169.99 (C), 146.89 (C), 130.52 (C), 128.54 (CH), 118.61 (CH), 115.22 (CH), 83.75 (2x C), 55.86 (CH_3), 52.08 (CH_2), 31.22 (C), 29.81 (3x CH_3), 24.86 (4x CH_3); MS (ES +ve) [M+H]+: 348.6, 370.6 (Na^+).



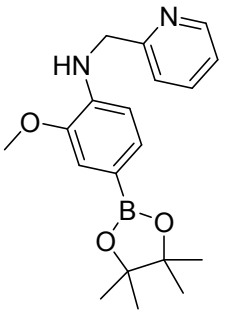
N-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-3-phenyl-propanamide. To a solution of 4-amino-3-methoxybenzeneboronic acid, pinacol ester (150 mg, 0.602 mmol), in DCM (2 ml) was added triethylamine (1.2 eq., 0.722 mmol, 73.1 mg, 100.76 µl) followed by hydrocinnamoyl chloride (1.2 eq., 0.722 mmol, 121.3 mg, 106.9 µl) and the mixture allowed to stir for 23 h. The mixture was concentrated *in vacuo* and purified by column chromatography, MeOH/DCM (0-2 %), to give a brown solid, (240.0 mg, 0.629 mmol, 100 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (d, J = 8.0, 1H), 7.83 (s, 1H), 7.47 (d, J = 8.0, 1H), 7.35 – 7.30 (m, 2H), 7.28 – 7.21 (m, 4H), 3.90 (s, 3H), 3.14 – 3.04 (m, 2H), 2.79 – 2.72 (m, 2H), 1.37 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.25 (C), 170.17 (C), 146.82 (C), 140.70 (C), 130.40 (C), 128.56 (CH), 128.52 (CH), 128.40 (CH), 126.34 (CH), 118.68 (CH), 115.21 (CH), 83.78 (2x C), 55.84 (CH_3), 39.72 (CH_2), 31.42 (CH_2), 24.87 (4x CH_3); MS (ES +ve) $[M+H]^+$: 382.7, 390.6 (Na^+)



2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-pyrrolidin-1-yl-ethanone. To a solution of 2-(4-bromo-2-methoxy-phenyl)-1-pyrrolidin-1-yl-ethanone (150 mg, 0.505 mmol) in dioxane/water (4.5/0.5 ml) was added bis(pinacolato)diboron (1.5 eq., 192.5 mg, 0.758 mmol), potassium carbonate (1.5 eq., 104.8 mg, 0.758 mmol) and triphenylphosphine (20 mol %, 26.5 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 1 h. Water and DCM were added to the mixture and the organic layer, separated, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The product was purified by column chromatography, EtOAc/hexane (20-80 %), to give a pale yellow oil (85.6 mg, 0.248 mmol, 49 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (dd, J = 7.4, 0.9, 1H), 7.31 – 7.27 (m, 2H), 3.88 (s, 3H), 3.69 (d, J = 5.0, 2H), 3.53 – 3.39 (m, 4H), 1.92 – 1.84 (m, 4H), 1.36 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.83 (C), 156.58 (C), 132.95 (C), 129.61 (CH), 127.54 (CH), 127.19 (C), 115.86 (CH), 83.77 (C), 55.52 (CH_3), 46.71 (CH_2), 45.87 (CH_2), 35.99 (CH_2), 26.13 (CH_2), 24.72 (4x CH_3), 24.43 (CH_2); MS (ES +ve) $(M+H)^+$: 346.4.



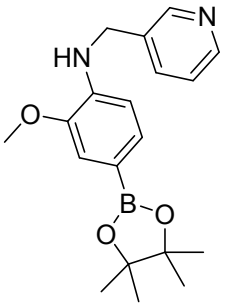
N-benzyl-2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline. To a solution of 4-amino-3-methoxybenzeneboronic acid, pinacol ester (150 mg, 0.602 mmol), in DCM (2 ml) was added triethylamine (1.2 eq., 0.722 mmol, 73.1 mg, 100.76 µl) followed by benzyl chloroformate (1.2 eq., 0.722 mmol, 123.2 mg, 103.07 µl) and the mixture stirred for 18 h. The product was concentrated *in vacuo* and purified by chromatography, (100% DCM), to give a light brown oil (65.9 mg, 0.172 mmol, 29 %). Only after characterisation was it discovered that the alkylated product had been produced instead of the benzylcarbamate derivative. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43 – 7.26 (m, 8H), 6.68 (d, *J* = 7.6, 1H), 4.41 (s, 2H), 3.91 (s, 3H), 1.35 (s, 12H); ^{13}C NMR (126 MHz, MeOD) δ 158.39 (C), 146.09 (C), 141.18 (C), 139.78 (C), 128.82 (CH), 128.08 (CH), 126.76 (CH), 126.52 (CH), 114.34 (CH), 108.93 (CH), 83.13 (CH_2), 54.55 (CH_3), 46.58 (C), 23.73 (4x CH_3); MS (ES +ve) $[M+H]^+$: 340.6.



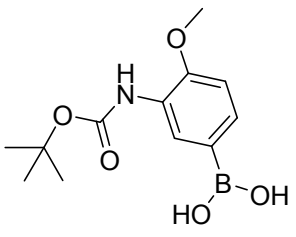
2-methoxy-N-(2-pyridylmethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline. To a solution of 4-amino-3-methoxybenzeneboronic acid, pinacol ester (150 mg, 0.602 mmol), in DCM (5 ml) was added triethylamine (3 eq., 1.806 mmol, 182.7 mg, 251.9 µl) followed by 2-(bromomethyl)pyridine HBr (2.4 eq., 1.44 mmol, 362.2 mg) and the mixture allowed to stir for 72 h. Water and

DCM were added and the organic layer separated, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The product was purified by column chromatography, EtOAc/Hexane (20 %), to give a dark brown solid, (86.2 mg, 0.253 mmol, 42 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (d, *J* = 4.2, 1H), 7.68 (d, *J* = 7.6, 1H), 7.37 (d, *J* = 7.9, 1H), 7.31 (dd, *J* = 7.8, 1.2, 1H), 7.23 (d, *J* = 6.8, 1H), 7.18 (d, *J* = 1.1, 1H), 6.79 (d, *J* = 8.0, 1H), 6.50 (d, *J* = 7.8, 1H), 4.60 (s, 2H), 3.92 (s, 3H), 1.31 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.33 (C), 148.11 (CH), 147.04 (C), 146.18 (C), 140.29 (C), 137.81 (CH), 129.23 (CH), 122.39 (CH), 121.24 (CH), 114.68 (CH), 109.22 (CH), 83.30 (C), 55.56 (CH_3), 48.14 (CH_2), 24.73 (4x CH_3); MS (ES +ve) $(M+H)^+$: 341.2.

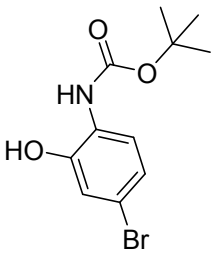
2-methoxy-N-(3-pyridylmethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline. To a solution of 4-amino-3-methoxybenzeneboronic acid, pinacol ester (150 mg, 0.602 mmol), in THF (5 ml) was added triethylamine (6 eq., 3.612 mmol, 365.4.7 mg, 503.8 µl) followed by 3-(bromomethyl)pyridine hydrobromide (2.4 eq., 1.444 mmol, 362.2 mg) and the mixture heated to 180 °C in the microwave for 4 h. Water and DCM were added and the organic layer separated, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The product was purified by column chromatography, EtOAc/Hexane (20-50 %), to give a dark brown solid, (80.9 mg, 0.238 mmol, 40 %). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, *J* = 1.6, 1H), 8.53 (dd, *J* = 4.9, 1.5, 1H), 7.75 (d, *J* = 8.2, 1H), 7.36 – 7.29 (m, 2H), 7.19 (d, *J* = 1.1, 1H), 6.51 (d, *J* = 7.8, 1H), 4.93 (s, 1H), 4.43 (d, *J* = 11.7, 2H), 3.90 (s, 3H), 1.33 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.03 (CH), 147.60 (CH), 146.06 (C), 140.12 (C), 136.07 (CH), 135.46 (C), 129.22 (CH), 123.90 (CH), 114.76 (CH), 109.13 (CH), 83.36 (C), 55.59 (CH_3), 44.96 (CH_2), 29.71 (CH_2), 24.84 (4x CH_3); MS (ES +ve) $(M+H)^+$: 341.6, 363.6 (Na^+).



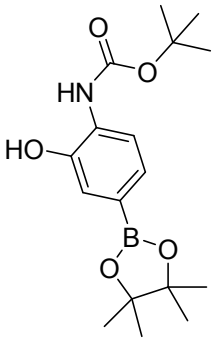
[3-(tert-butoxycarbonylamino)-4-methoxy-phenyl]boronic acid. (3-Amino-4-methoxyphenyl)boronic acid (150 mg, 0.898 mmol) was suspended in DCM (5 ml). Di-tertbutyldicarbonate (1.5 eq., 1.347 mmol, 294.0 mg) was added followed by a small spatula of DMAP and the reaction allowed to stir for 18 h. Water was added to the mixture and the organic layer separated, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The product was purified by column chromatography, MeOH/DCM (0-4 %), to give a dark brown solid (189.9 mg, 0.711 mmol, 79 %). ^{1}H NMR (500 MHz, MeOD) δ 8.12 (s, 1H), 7.34 (dd, J = 8.2, 1.5, 1H), 6.98 (d, J = 8.2, 1H), 3.88 (s, J = 4.9, 3H), 1.53 (s, 9H); ^{13}C NMR (126 MHz, MeOD) δ 153.77 (C), 150.52 (C), 129.82



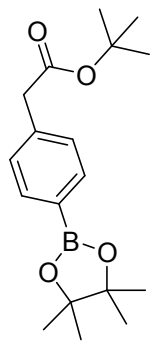
(CH), 129.49 (CH), 126.76 (C), 125.18 (C), 109.48 (CH), 79.78 (C), 54.74 (CH_3), 27.26 (3x CH_3); MS (ES +ve) $[M+H]^+$: 268.5.



Tert-butyl N-(4-bromo-2-hydroxy-phenyl)carbamate. 2-Amino-5-bromophenol (250 mg, 1.34 mmol) was suspended in DCM (5 ml). Ditertbutyl-dicarbonate (1 eq., 1.34 mmol, 292.2 mg) was added followed by a small spatula of DMAP and the reaction stirred for 18 h. Water was added and the organic layer separated, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The product was purified, EtOAc/Hexane (0-20 %), to give a brown solid (177.3 mg, 0.618 mmol, 46.1 %). ^{1}H NMR (500 MHz, MeOD) δ 7.63 (d, J = 8.4, 1H), 6.97 (d, J = 2.2, 1H), 6.93 (dd, J = 8.6, 2.2, 1H), 1.54 (s, 9H); ^{13}C NMR (126 MHz, MeOD) δ 153.72 (C), 147.85 (C), 126.01 (C), 121.88 (CH), 120.93 (CH), 117.43 (CH), 84.51 (C), 80.08 (C), 27.19 (3x CH_3); MS (ES +ve) $(M+H)^+$: 286.0/288.0.

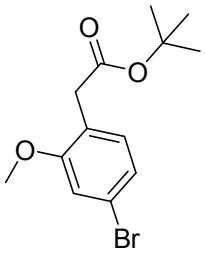


Tert-butyl N-[2-hydroxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate. To a solution of tert-butyl *N*-(4-bromo-2-hydroxy-phenyl)carbamate (50 mg, 0.174 mmol) in dioxane/water (4.5/0.5 ml) was added bis(pinacolato)diboron (1.5 eq., 66.4 mg, 0.261 mmol), potassium carbonate (1.5 eq., 36.1 mg, 0.261 mmol) and triphenylphosphine (20 mol %, 13.7 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 30 min. EtOAc and water were added to the mixture and the organic layer separated, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The product was purified by column chromatography, EtOAc/Hexane (0-20%), to give a white solid (26.4 mg, 0.0788 mmol, 23 %). The reaction was repeated to give a second batch of product. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (s, 1H), 7.33 – 7.28 (m, 2H), 6.78 (s, 1H), 1.52 (s, 9H), 1.34 (d, J = 10.2, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.27 (C), 145.75 (C), 128.66 (C), 127.70 (CH), 124.11 (CH), 119.94 (CH), 119.84 (C), 83.76 (C), 81.86 (C), 28.27 (3x CH_3), 24.86 (4x CH_3).

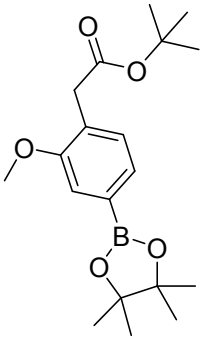


Tert-butyl 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]acetate. 4-(Carboxymethyl)phenylboronic acid pinacol ester (150 mg, 0.572 mmol) was dissolved in 5 ml of dry toluene. Thionyl chloride (1.2 eq., 0.686 mmol, 81.6 mg, 49.8 ul) was added followed by a drop of DMF and the reaction heated to reflux (120 °C) for 2 h. The reaction was cooled to r.t. then t-butylalcohol (5 eq., 2.86 mmol, 211.8 mg, 0.273 ml) and triethylamine (2.5 eq., 1.43 mmol, 199.3 ul) added and the mixture allowed to stir for 18 h. Water and DCM were added to the mixture and the organic

layer separated, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography, (100 % DCM), to give a light brown oil (60 mg, 0.189 mmol, 33 %). MS (ES +ve) $(M+H)^+$: 340.8 (Na^+)



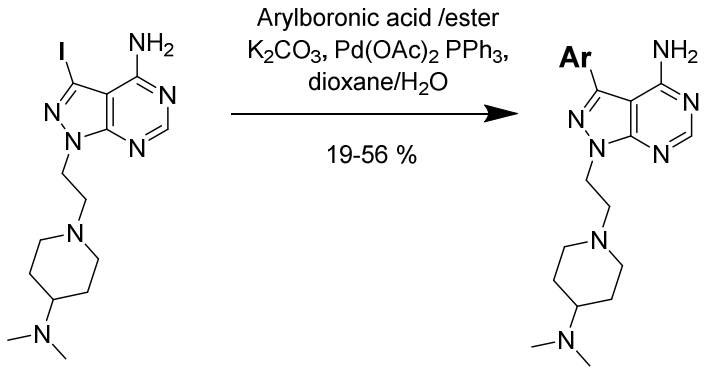
Tert-butyl 2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]acetate. 2-(4-Bromo-2-methoxyphenyl)acetic acid (2 g, 8.198 mmol) was dissolved in 20 ml of dry THF. Thionyl chloride (1.2 eq., 9.837 mmol, 1.17 g, 0.714 ml) was added followed by a drop of DMF and the reaction heated to reflux (80 °C) for 2 h. The reaction was cooled to r.t. then t-butylalcohol (5 eq., 40.99 mmol, 3.04 g, 3.92 ml) and triethylamine (2.5 eq., 20.49 mmol, 2.86 ml) added and the mixture left to stir for 20 h. Water and EtOAc were added to the mixture and the organic layer separated, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The product was purified by column chromatography, EtOAC/Hexane (0-4%), to give a light orange liquid (694.8 mg, 2.316 mmol, 28 %). ^1H NMR (500 MHz, MeOD) δ 7.10 (s, 1H), 7.07 – 7.02 (m, 2H), 3.81 s, 3H), 3.47 (s, 2H), 1.42 (s, 9H); ^{13}C NMR (126 MHz, MeOD) δ 171.39 (C), 158.43 (C), 131.77 (CH), 122.99 (C), 122.98 (CH), 121.02 (C), 113.67 (CH), 80.51 (C), 54.84 (CH_3), 36.42 (CH_2), 26.85 (3x CH_3); MS (ES +ve) $(M+H)^+$: 323.2/324.8 (Na^+).



Tert-butyl 2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]acetate. To a solution of tert-butyl 2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2- yl)phenyl]acetate (600 mg, 2.0 mmol) in dioxane/water (18/2 ml) was added bis(pinacolato)diboron (1.5 eq., 762.6 mg, 3.0 mmol), potassium carbonate (1.5 eq., 414.6 mg, 3.0 mmol) and triphenylphosphine (20 mol %, 104.9 mg) followed by palladium acetate (5 mol %, 22.5 mg) and the mixture heated in the microwave at 120 °C for 1 h. Traces of starting materials was shown by SM so the mixture was heated for an extra hour. MS and TLC showed the reaction was complete. EtOAc and water were added to the mixture and the organic layer separated, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The product was purified by column chromatography, EtOAc/Hexane (0-10%), to give a colourless oil (322.4 mg, 0.926 mmol, 46 %). ^1H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.0, 1H), 7.26 (d, *J* = 3.0, 1H), 7.18 (d, *J* = 7.3, 1H), 3.86 (s, 3H), 3.54 (s, 2H), 1.42 (s, 9H), 1.34 (s, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.96 (C), 157.02 (C), 130.25 (CH), 127.29 (C), 127.28 (CH), 115.89 (CH), 109.97 (C), 83.75 (C), 80.34 (C), 55.46 (CH_3), 37.58 (CH_2), 28.03 (3x CH_3), 24.85 (4x CH_3); MS (ES +ve) $[M+H]^+$: 349.7.

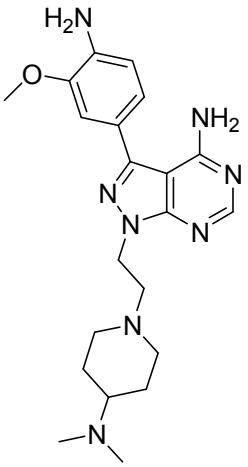
SUPPORTING INFORMATION

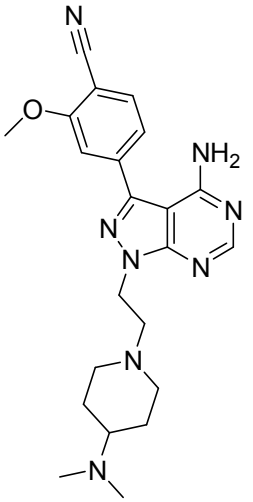
Synthesis and characterization of compounds 12g-y



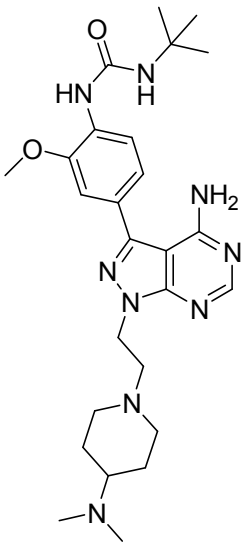
10a **12g-x**

3-(4-amino-3-methoxy-phenyl)-1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]pyrazolo[3,4-d]pyrimidin-4-amine (12g). To a solution of 1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.1205 mmol) in dioxane/water (4.5 ml/0.5 ml) was added phenyl *N*-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (1.5 eq., 66.8 mg, 0.181 mmol), potassium carbonate (1.5 eq., 25.0 mg, 0.181 mmol) and triphenylphosphine (20 mol %, 9.5 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 30 min. The mixture was concentrated *in vacuo* and the product purified by column chromatography, MeOH/DCM (10% then 0-30 drops of NEt_3 per 100 ml), to give a brown solid (19.4 mg, 0.0473 mmol, 39 %). ^{1}H NMR (600 MHz, MeOD) δ 8.25 (s, 1H), 7.16 (d, J = 1.8, 1H), 7.09 (dd, J = 7.9, 1.8, 1H), 6.91 (d, J = 7.9, 1H), 4.54 (t, J = 6.7, 2H), 3.95 (s, 3H), 3.14 (d, J = 12.0, 2H), 2.93 (t, J = 6.7, 2H), 2.40 (m, 7H), 2.14 (t, J = 11.0, 2H), 1.90 (d, J = 12.3, 2H), 1.49 (d, J = 12.1, 2H); ^{13}C NMR (126 MHz, MeOD) δ 158.62 (C), 155.35 (CH), 153.98 (C), 147.74 (C), 146.01 (C), 138.32 (C), 121.70 (CH), 121.07 (C), 114.69 (CH), 110.25 (CH), 109.97 (C), 62.19 (CH_2), 56.24 (CH_3), 54.74 (2x CH_2), 52.29 (CH), 43.91 (CH_2), 40.14 (2x CH_3), 27.35 (2x CH_2); MS (ES +ve) $(M+H)^+$: 411.6; HRMS (ES +ve), $C_{21}H_{31}N_8O_1$ $(M+H)^+$: calculated 411.26208, found 411.26270.



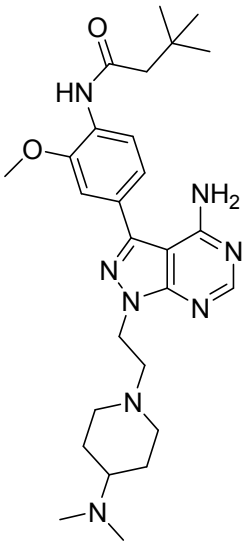


2-[4-[4-amino-1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]pyrazolo[3,4-d]pyrimidin-3-yl]phenyl]acetonitrile (12h). To a solution of 1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]-3-iodo-pyrazolo[3,4- d]pyrimidin-4-amine (50 mg, 0.1205 mmol) in dioxane/water (4.5/0.5 ml) was added 4-(cyanomethyl)benzeneboronic acid, (1 eq., 29.1 mg, 0.181 mmol), potassium carbonate (1.5 eq., 25.0 mg, 0.181 mmol) and triphenylphosphine (20 mol %, 9.5 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 30 min. The mixture was concentrated *in vacuo* and purified by column chromatography, MeOH/DCM (5-10 % then 20 drops of NEt_3 per 100 ml), to give a light brown solid (41.8 mg, 0.1034 mmol, 86 %). ^{1}H NMR (500 MHz, MeOD) δ 8.27 (s, 1H), 7.79 – 7.70 (m, 2H), 7.59 (d, J = 8.3, 2H), 4.56 (t, J = 6.4, 2H), 4.03 (s, 2H), 3.18 (d, J = 5.8, 2H), 3.04 – 2.93 (m, 3H), 2.74 (s, 6H), 2.17 (dd, J = 15.1, 6.9, 2H), 1.99 (d, J = 12.8, 2H), 1.61 – 1.51 (m, 2H); ^{13}C NMR (126 MHz, MeOD) δ 158.49 (C), 155.47 (CH), 154.36 (C), 144.35 (C), 132.22 (C), 128.84 (2x CH), 128.70 (2x CH), 117.95 (C), 110.00 (C), 97.74 (C), 63.27 (CH), 55.84 (CH_2), 51.39 (2x CH_2), 44.11 (CH_2), 39.27 (2x CH_3), 26.32 (2x CH_2), 21.98 (CH_2); MS (ES +ve) $[M+H]^+$: 405.0; HRMS (ES +ve), $C_{22}H_{29}N_8$ $(M+H)^+$: calculated 405.25097, found 405.24950.

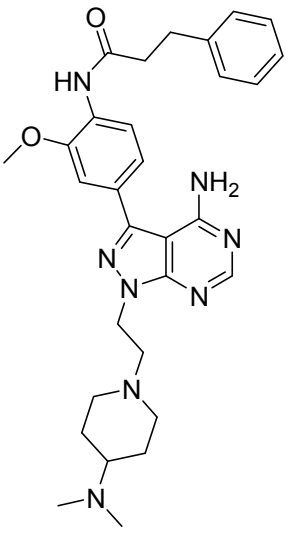


1-[4-[4-amino-1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxy-phenyl]-3-tert-butyl-urea (12i). To a solution of 1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.1205 mmol) in dioxane/water (4.5/0.5 ml) was added 1-*tert*-butyl-3-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]urea (1.5 eq., 62.9 mg, 0.181 mmol), potassium carbonate (1.5 eq., 25.0 mg, 0.181 mmol) and triphenylphosphine (20 mol %, 9.5 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 30 min. The mixture was concentrated *in vacuo* and purified by column chromatography, MeOH/DCM (10% then 0-30 drops of NEt_3 per 100 ml to give a light brown solid (30.4 mg, 0.0597 mmol, 49.5 %). 1H NMR (500 MHz, MeOD) δ 8.24 (s, 1H), 8.16 (d, *J* = 8.3, 1H), 7.25 (d, *J* = 1.8, 1H), 7.19 (dd, *J* = 8.3, 1.9, 1H), 4.53 (t, *J* = 6.7, 2H), 3.96 (s, 3H), 3.12 (d, *J* = 11.9, 2H), 2.92 (t, *J* = 6.7, 2H), 2.36 (m, 7H), 2.12 (t, *J* = 11.1, 2H), 1.87 (d, *J* = 12.5, 2H), 1.51 – 1.42 (m, 2H), 1.38 (s, 9H); 13C NMR (126 MHz, MeOD) δ 155.74 (C), 155.40 (CH), 154.09 (C), 148.52 (C), 145.33 (C), 130.34 (C), 125.66 (C), 120.49 (CH), 118.66 (CH), 110.02 (CH), 97.73 (C), 62.27 (CH), 56.23 (CH_2), 55.02 (CH_3), 52.22 (2x CH_2), 49.71 (C), 43.97 (CH_2), 40.07 (2x CH_3), 28.15

(3x CH_3), 27.20 (2x CH_2); MS (ES +ve) $[M+H]^+$: 510.8; HRMS (ES +ve), $C_{26}H_{40}N_9O_2$ $(M+H)^+$: calculated 510.32995, found 510.32830.

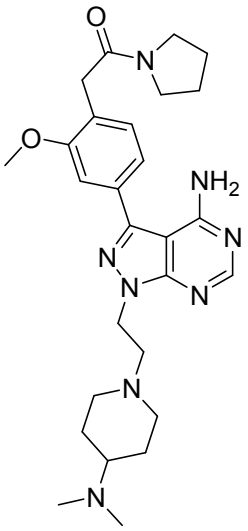


N-[4-[4-amino-1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxy-phenyl]-3,3-dimethyl-butanamide (12j). To a solution of 1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.1205 mmol) in dioxane/water (4.5 ml/0.5 ml) was added *N*-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-3,3-dimethyl-butanamide (1.5 eq., 63.1 mg, 0.181 mmol), potassium carbonate (1.5 eq., 25.0 mg, 0.181 mmol) and triphenylphosphine (20 mol %, 9.5 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 30 min. The product was concentrated *in vacuo* and purified by column chromatography, MeOH/DCM (5-10% then 0- 30 drops of triethylamine per 100 ml), to give a sand coloured solid (34.3 mg, 0.0675 mmol, 56 %). ^{1}H NMR (500 MHz, MeOD) δ 8.28 (s, 1H), 8.10 (d, *J* = 8.1, 1H), 7.35 (d, *J* = 1.8, 1H), 7.28 (dd, *J* = 8.1, 1.8, 1H), 4.57 (t, *J* = 6.7, 2H), 3.99 (s, 3H), 3.15 (m, 2H), 2.95 (t, *J* = 6.7, 2H), 2.39 (m, 9H), 2.15 (t, *J* = 11.0, 2H), 1.91 (d, *J* = 16.8, 2H), 1.49 (m, 2H), 1.14 (s, 9H); ^{13}C NMR (126 MHz, MeOD) δ 172.20 (C), 158.53 (C), 155.44 (CH), 154.22 (C), 151.00 (C), 144.89 (C), 129.52 (C), 127.69 (C), 123.12 (CH), 120.22 (CH), 110.74 (CH), 97.79 (C), 62.24 (CH), 56.24 (CH_2), 55.08 (CH_3), 52.23 (2x CH_2), 49.79 (CH_2), 44.04 (CH_2), 40.11 (2x CH_3), 30.67 (C), 28.81 (3x CH_3), 27.31 (2x CH_2); MS (ES +ve) $[M+H]^+$: 509.6; HRMS (ES +ve), $C_{27}H_{41}N_8O_2$ $[M+H]^+$: calculated 509.33470, found 509.3363.

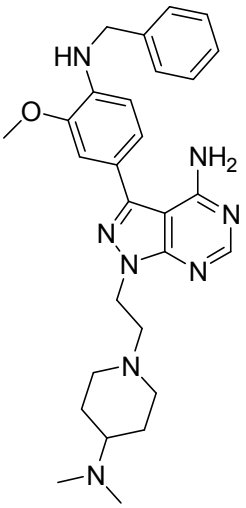


N-[4-[4-amino-1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxy-phenyl]-3-phenyl-propanamide (12k). To a solution of 1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.1205 mmol) in dioxane/water (4.5 ml/0.5 ml) was added *N*-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-3-phenyl-propanamide (1.5 eq., 69.0 mg, 0.181 mmol), potassium carbonate (1.5 eq., 25.0 mg, 0.181 mmol) and triphenylphosphine (20 mol %, 9.5 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 30 min. The product was concentrated *in vacuo* and purified by column chromatography, MeOH/DCM (10% then 0-30 drops of triethylamine per 100 ml), to give a light brown solid (36.0 mg, 0.0664 mmol, 55 %). ^{1}H

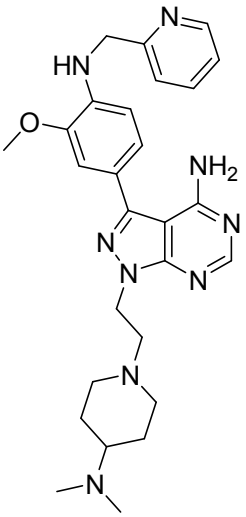
NMR (600 MHz, MeOD) δ 8.27 (s, 1H), 8.13 (d, *J* = 8.1, 1H), 7.27 (d, *J* = 1.7, 5H), 7.26 (dd, *J* = 8.2, 1.8, 1H), 7.21 (dd, *J* = 8.6, 4.4, 1H), 4.57 (t, *J* = 6.7, 2H), 3.95 (s, 3H), 3.15 (d, *J* = 11.8, 2H), 3.05 (m, 3H), 2.95 (t, *J* = 6.7, 2H), 2.81 (t, *J* = 7.7, 2H), 2.41 (s, 6H), 2.14 (t, *J* = 11.0, 2H), 1.91 (d, *J* = 17.2, 3H), 1.49 (d, *J* = 8.7, 2H); ^{13}C NMR (126 MHz, MeOD) δ 172.65 (C), 158.53 (CH), 155.44 (C), 154.18 (C), 150.64 (C), 144.88 (C), 140.73 (C), 129.32 (C), 128.15 (CH), 127.76 (C), 125.85 (CH), 122.70 (CH), 120.20 (CH), 110.65 (CH), 97.77 (CH), 62.38 (C), 56.18 (CH_2), 55.06 (CH_3), 52.14 (2x CH_2), 46.33 (CH_2), 44.04 (CH_2), 39.99 (2x CH_3), 38.18 (CH_2), 31.38 (CH_2), 27.17 (2x CH_2); MS (ES +ve) $[M+H]^+$: 543.6; HRMS (ES +ve), $C_{30}H_{39}N_8O_2$ $[M+H]^+$: calculated 543.31905, found 543.32040.



2-[4-[4-amino-1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxy-phenyl]-1-pyrrolidin-1-yl-ethanone (12l). To a solution of 1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.1205 mmol) in dioxane/water (4.5/0.5 ml) was added 2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-1-pyrrolidin-1-yl-ethanone (1.5 eq., 62.5 mg, 0.181 mmol), potassium carbonate (1.5 eq., 25.0 mg, 0.181 mmol) and triphenylphosphine (20 mol %, 9.5 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 30 min. The mixture was concentrated *in vacuo* and purified by column chromatography, MeOH/DCM (10 % then 0-30 drops of NEt_3 per 100 ml), to give a white solid (34.6 mg, 0.0683 mmol, 57 %). ^{1}H NMR (500 MHz, MeOD) δ 8.25 (s, 1H), 7.33 (d, J = 7.6, 1H), 7.23 (s, 1H), 7.21 (dd, J = 7.5, 1.6, 1H), 4.54 (t, J = 6.7, 2H), 3.89 (s, 3H), 3.74 (s, 2H), 3.64 (t, J = 6.8, 2H), 3.46 (t, J = 6.9, 2H), 3.11 (d, J = 11.9, 2H), 2.92 (t, J = 6.7, 2H), 2.34 (m, 7H), 2.12 (t, J = 10.9, 2H), 2.02 (dd, J = 13.3, 6.7, 2H), 1.96 – 1.90 (m, 2H), 1.86 (d, J = 12.7, 2H), 1.46 (m, 2H); ^{13}C NMR (126 MHz, MeOD) δ 170.77 (C), 158.57 (C), 158.03 (C), 155.45 (CH), 154.13 (C), 145.18 (C), 132.80 (C), 131.39 (CH), 125.01 (C), 120.32 (CH), 110.50 (CH), 97.84 (C), 62.22 (CH), 56.23 (CH_2), 54.76 (CH_3), 52.27 (2x CH_2), 46.79 (CH_2), 45.71 (CH_2), 44.05 (CH_2), 40.11 (2x CH_3), 35.42 (CH_2), 27.32 (2x CH_2), 25.63 (CH_2), 24.02 (CH_2); MS (ES +ve) [M+H]+: 507.6; HRMS (ES +ve), $C_{27}H_{39}N_8O_2$ $[M+H]^+$: calculated 507.31905, found 507.31830.

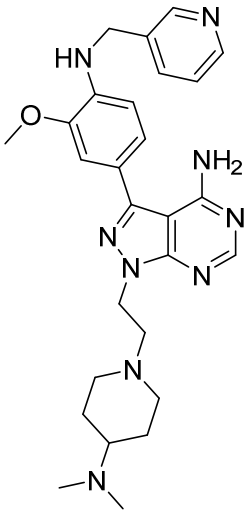


3-[4-(benzylamino)-3-methoxy-phenyl]-1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]pyrazolo[3,4-d]pyrimidin-4-amine (12m). To a solution of 1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.1205 mmol) in dioxane/water (4.5 ml/0.5 ml) was added *N*-benzyl-2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.5 eq., 61.4 mg, 0.181 mmol), potassium carbonate (1.5 eq., 25.0 mg, 0.181 mmol) and triphenylphosphine (20 mol %, 9.5 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 30 min. The mixture was concentrated in vacuo without and purified by column chromatography, MeOH/DCM (10% then 5-20 drops of NEt_3 per 100 ml), to give a light brown coloured solid (31.8 mg, 0.0584, 48.5 %). ^{1}H NMR (500 MHz, MeOD) δ 8.24 (s, 1H), 7.40 (d, *J* = 7.5, 2H), 7.33 (t, *J* = 7.5, 2H), 7.24 (t, *J* = 7.3, 1H), 7.15 (d, *J* = 1.8, 1H), 7.08 (dd, *J* = 8.1, 1.8, 1H), 6.67 (d, *J* = 8.1, 1H), 4.52 (t, *J* = 6.7, 2H), 4.47 (s, 2H), 3.98 (s, 3H), 3.13 (d, *J* = 11.9, 2H), 2.92 (t, *J* = 6.7, 2H), 2.37 (s, 7H), 2.13 (t, *J* = 11.0, 2H), 1.88 (d, *J* = 12.3, 2H), 1.47 (d, *J* = 8.5, 2H); ^{13}C NMR (126 MHz, MeOD) δ 166.23 (C), 158.62 (C), 155.34 (CH), 153.97 (C), 147.34 (C), 139.75 (C), 139.27 (C), 128.13 (2x CH), 126.78 (2x CH), 126.58 (CH), 121.15 (CH), 119.94 (C), 109.78 (CH), 109.27 (CH), 97.66 (C), 62.17 (CH), 56.20 (CH_2), 54.81 (CH_3), 52.22 (2x CH_2), 46.71 (CH_2), 43.89 (CH_2), 40.08 (2x CH_3), 27.28 (2x CH_2); MS (ES +ve) $[M+H]^+$: 501.4; HRMS (ES +ve), $C_{28}H_{37}N8O_1$ $[M+H]^+$: calculated 501.30848, found 501.3087.

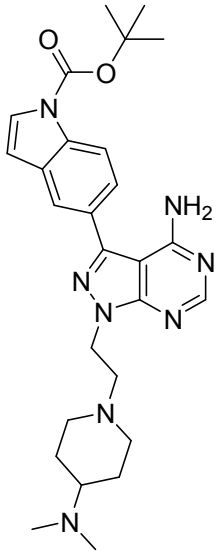


1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]-3-[3-methoxy-4-(2-pyridylmethylamino)phenyl]pyrazolo[3,4-d]pyrimidin-4-amine (12n). To a solution of 1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.1205 mmol) in dioxane/water (4.5/0.5 ml) was 2-methoxy-N-(2-pyridylmethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1 eq., 41 mg, 0.1205 mmol), potassium carbonate (1.5 eq., 25.0 mg, 0.181 mmol) and triphenylphosphine (20 mol %, 9.5 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 30 min. The mixture was concentrated *in vacuo* and purified by column chromatography, MeOH/DCM (10 % then 10-30 drops of NEt_3 per 100 ml), to give a sand coloured solid (37 mg, 0.0738 mmol, 61 %). ^{1}H NMR (500 MHz, MeOD) δ 8.50 (d, *J* = 4.2, 1H), 8.21 (s, 1H), 7.77 (dd, *J* = 7.7, 6.0, 1H), 7.46 (d, *J* = 7.9, 1H), 7.29 (d, *J* = 5.3, 1H), 7.14 (d, *J* = 1.8, 1H), 7.05 (dd, *J* = 8.1, 1.9, 1H), 6.58 (d, *J* = 8.1, 1H), 4.55 (s, 2H), 4.49 (t, *J* = 6.6, 2H), 3.96 (s, 3H), 3.12 (d, *J* = 12.5,

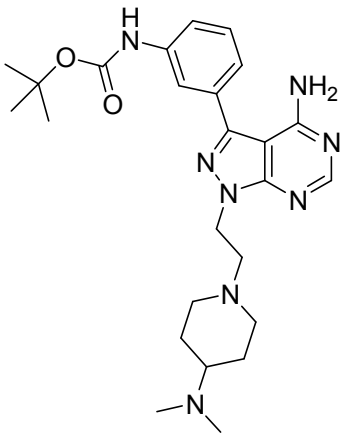
2H), 2.90 (t, *J* = 6.6, 2H), 2.64 – 2.58 (m, 1H), 2.50 (s, 6H), 2.12 (t, *J* = 11.0, 2H), 1.90 (s, 2H), 1.49 (d, *J* = 8.4, 2H); ^{13}C NMR (126 MHz, MeOD) δ 159.35 (C), 158.62 (C), 155.36 (CH), 154.03 (C), 148.39 (CH), 147.49 (C), 146.03 (C), 138.91 (C), 137.40 (CH), 122.27 (CH), 121.57 (CH), 121.15 (CH), 120.38 (C), 109.62 (CH), 109.42 (CH), 97.64 (C), 62.72 (CH), 56.04 (CH_2), 54.85 (CH_3), 51.85 (2x CH_2), 47.48 (CH_2), 43.92 (CH_2), 39.73 (2x CH_3), 26.86 (2x CH_2); MS (ES +ve) [M+H]+: 502.2; HRMS (ES +ve), $C_{27}H_{36}N_9O_1$ [M+H]$^+$: calculated 502.30373, found 502.30320.



1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]-3-[3-methoxy-4-(3-pyridylmethylamino)phenyl]pyrazolo[3,4-d]pyrimidin-4-amine (12o). To a solution of 1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.1205 mmol) in dioxane/water (4.5/0.5 ml) was 2-methoxy-N-(3-pyridylmethyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1.5 eq., 61.6 mg, 0.181 mmol), potassium carbonate (1.5 eq., 25.0 mg, 0.181 mmol) and triphenylphosphine (20 mol %, 9.5 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 30 min. The mixture was concentrated *in vacuo* and purified by column chromatography, MeOH/DCM (10 % then 0-25 drops of NEt_3 per 100 ml), to give a light brown solid (41.6 mg, 0.083 mmol, 69 %). ^{1}H NMR (500 MHz, MeOD) δ 8.57 (s, 1H), 8.42 (d, *J* = 3.4, 1H), 8.23 (s, 1H), 7.87 (d, *J* = 7.9, 1H), 7.41 (dd, *J* = 7.9, 4.9, 1H), 7.16 (d, *J* = 1.8, 1H), 7.08 (dd, *J* = 8.1, 1.9, 1H), 6.65 (d, *J* = 8.1, 1H), 4.55 (s, 2H), 4.51 (t, *J* = 6.6, 2H), 3.97 (s, 3H), 3.13 (d, *J* = 7.3, 2H), 2.92 (t, *J* = 6.6, 2H), 2.59 (s, 1H), 2.50 (s, 6H), 2.14 (t, *J* = 11.0, 2H), 1.91 (d, *J* = 9.2, 2H), 1.50 (d, *J* = 8.5, 2H); ^{13}C NMR (126 MHz, MeOD) δ 158.61 (C), 155.36 (CH), 154.02 (C), 147.77 (CH), 147.48 (C), 147.18 (CH), 146.00 (C), 138.73 (C), 136.44 (C), 135.79 (CH), 123.80 (CH), 121.13 (CH), 120.43 (C), 109.71 (CH), 109.45 (CH), 97.64 (C), 62.71 (CH), 55.96 (CH_2), 54.84 (CH_3), 51.85 (2x CH_2), 43.95 (CH_2), 43.92 (CH_2), 39.71 (2x CH_3), 26.84 (2x CH_2); MS (ES +ve) [M+H]$^+$: 502.4; HRMS (ES +ve), $C_{27}H_{36}N_9O_1$ [M+H]$^+$: calculated 502.30373, found 502.30140.

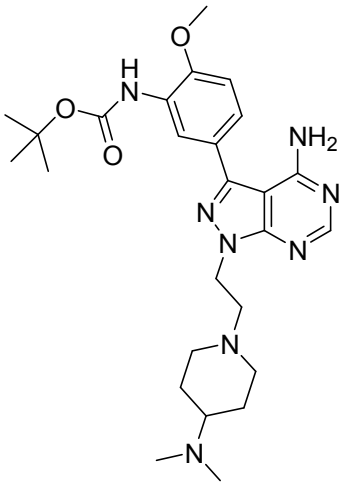


Tert-butyl 5-[4-amino-1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]pyrazolo[3,4-d]pyrimidin-3-yl]indole-1-carboxylate (12p). To a solution of 1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.1205 mmol) in dioxane/water (4.5/0.5 ml) was added 1-Boc-indole-5-boronic acid pinacol ester (1.5 eq., 62.1 mg, 0.181 mmol), potassium carbonate (1.5 eq., 25.0 mg, 0.181 mmol) and triphenylphosphine (20 mol %, 9.5 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 30 min. The mixture was concentrated *in vacuo* and purified by column chromatography, MeOH/DCM (10 % then 10-30 drops of NEt_3 per 100 ml) to give a light cream solid (31.2 mg, 0.0619 mmol, 51 %). ^{1}H NMR (500 MHz, MeOD) δ 8.35 (d, *J* = 8.5, 1H), 8.29 (s, 1H), 7.92 (d, *J* = 1.3, 1H), 7.76 (d, *J* = 3.7, 1H), 7.65 (dd, *J* = 8.5, 1.7, 1H), 6.77 (d, *J* = 3.5, 1H), 4.58 (t, *J* = 6.6, 2H), 3.16 (d, *J* = 11.9, 2H), 2.97 (t, *J* = 6.6, 2H), 2.43 (s, 7H), 2.16 (t, *J* = 11.0, 2H), 1.91 (d, *J* = 12.7, 2H), 1.73 (s, 9H), 1.50 (td, *J* = 12.1, 8.5, 2H); ^{13}C NMR (126 MHz, MeOD) δ 158.56 (C), 155.44 (CH), 154.16 (C), 149.49 (C), 145.58 (C), 135.55 (C), 131.29 (C), 127.17 (C), 126.91 (CH), 124.19 (CH), 120.88 (CH), 115.42 (CH), 107.14 (CH), 97.90 (C), 84.04 (C), 62.38 (CH), 56.19 (CH_2), 52.15 (2x CH_2), 44.02 (CH_2), 40.00 (2x CH_3), 27.19 (2x CH_2), 26.95 (3x CH_3); MS (ES +ve) $[M+H]^+$: 505.0.0; HRMS (ES +ve), $C_{27}H_{37}N_8O_2$ $[M+H]^+$: calculated 505.30340, found 505.30430.

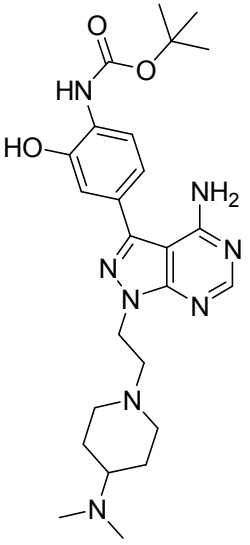


Tert-butyl N-[3-[4-amino-1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]pyrazolo[3,4-d]pyrimidin-3-yl]phenyl]carbamate (12q). To a solution of 1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.1205 mmol) in dioxane/water (4.5/0.5 ml) was added 3-(Boc-amino)benzeneboronic acid (1.5 eq., 42.9 mg, 0.181 mmol), potassium carbonate (1.5 eq., 25.0 mg, 0.181 mmol) and triphenylphosphine (20 mol %, 9.5 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 30 min. The mixture was concentrated *in vacuo* and purified by column chromatography, MeOH/DCM (10% then 0-30 drops NEt_3 per 100 ml), to give a light brown solid (28.0 mg, 0.0583 mmol, 48 %). ^{1}H NMR (500 MHz, MeOD) δ 8.27 (s, 1H), 7.88 (s, 1H), 7.50 – 7.44 (m, 2H), 7.37 (d, *J* = 7.0, 1H), 4.57 (t, *J* = 6.7, 2H), 3.16 – 3.10 (m, 2H), 2.95 (t, *J* = 6.7, 2H), 2.35 (m, 7H), 2.14 (t, *J* = 11.0, 2H), 1.88 (d, *J* = 12.7, 2H), 1.56 (s, 9H), 1.47 (m, 2H); ^{13}C NMR (126 MHz, MeOD) δ 158.42 (C), 155.37 (CH), 154.22 (C), 154.00 (C), 144.97 (C), 140.14 (C), 133.30 (C), 129.46 (CH),

122.27 (CH), 119.16 (CH), 118.54 (CH), 97.74 (C), 79.72 (C), 62.16 (CH), 56.21 (CH_2), 52.29 (2x CH_2), 44.06 (CH_2), 40.16 (2x CH_3), 27.38 (2x CH_2), 27.28 (3x CH_3); MS (ES +ve) $[M+H]^+$: 481.4; HRMS (ES +ve), $C_{25}H_{37}N_8O_2$ $[M+H]^+$: calculated 480.30340, found 481.30540.



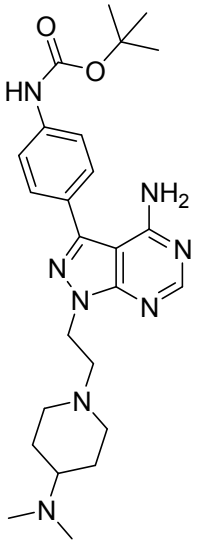
Tert-butyl N-[5-[4-amino-1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]pyrazolo[3, 4-d]pyrimidin-3-yl]-2-methoxy-phenyl]carbamate (12r). To a solution of 1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.1205 mmol) in dioxane/water (4.5/0.5 ml) was added [3-(*tert*-butoxycarbonylamino)-4-methoxy-phenyl]boronic acid (1.5 eq., 48.4 mg, 0.181 mmol), potassium carbonate (1.5 eq., 25.0 mg, 0.181 mmol) and triphenylphosphine (20 mol %, 9.5 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 30 min. The mixture was concentrated *in vacuo* and purified by column chromatography, MeOH/DCM (0-10 % then 0-20 drops of NEt_3 per 100 ml), to give a light brown solid (32.9 mg, 0.0645 mmol, 53.5 %). ^{1}H NMR (500 MHz, MeOD) δ 8.26 (d, J = 5.2, 1H), 8.19 (d, J = 2.1, 1H), 7.41 (dd, J = 8.4, 2.2, 1H), 7.19 (d, J = 8.5, 1H), 4.56 (t, J = 6.6, 2H), 3.99 (d, J = 5.1, 3H), 3.15 (d, J = 12.1, 2H), 2.96 (t, J = 6.6, 2H), 2.54 (m, 1H), 2.48 (s, 6H), 2.16 (t, J = 10.9, 2H), 1.92 (d, J = 10.5, 2H), 1.56 (d, J = 5.1, 9H), 1.55 – 1.46 (m, 2H); ^{13}C NMR (126 MHz, MeOD) δ 158.48 (C), 155.35 (CH), 154.20 (C), 153.82 (C), 149.93 (C), 145.03 (C), 128.25 (C), 124.95 (C), 123.27 (CH), 119.69 (CH), 111.00 (CH), 97.67 (C), 80.15 (C), 62.52 (CH), 56.07 (CH_2), 55.11 (CH_3), 51.99 (2x CH_2), 44.01 (CH_2), 39.86 (2x CH_3), 27.22 (3x CH_3), 27.03 (2x CH_2); MS (ES +ve) $[M+H]^+$: 511.4; HRMS (ES +ve), $C_{26}H_{39}N_8O_3$ $[M+H]^+$: calculated 511.31396, found 511.31660.

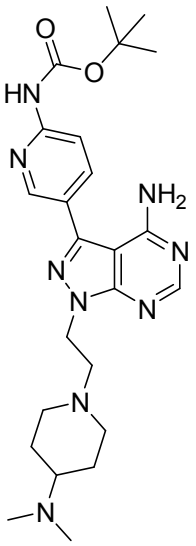


Tert-butyl N-[4-[4-amino-1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]pyrazolo[3,4-d]pyrimidin-3-yl]-2-hydroxy-phenyl]carbamate (12s). To a solution of 1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine (42.7 mg, 0.103 mmol) in dioxane/water (4.5/0.5 ml) was added *tert*-butyl N-[2-hydroxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]carbamate (1 eq., 34.4 mg, 0.103 mmol, limiting reagent), potassium carbonate (1.5 eq., 21.3 mg, 0.154 mmol) and triphenylphosphine (20 mol %, 8.1 mg) followed by palladium acetate (5

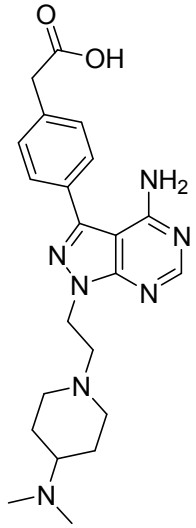
mol %) and the mixture heated in the microwave at 120 °C for 30 min. MS showed the reaction was complete. The product was purified by column chromatography, MeOH/DCM (10 % then 10-40 drops of NEt_3 per 100 ml) to give a light brown/grey solid (27.1 mg, 0.0546 mmol, 53 %). ^{1}H NMR (500 MHz, MeOD) δ 8.26 (s, 1H), 7.95 (d, J = 8.1, 1H), 7.17 (d, J = 1.9, 1H), 7.14 (dd, J = 8.2, 1.9, 1H), 4.60 – 4.52 (m, 2H), 3.14 (m, 2H), 3.01 – 2.90 (m, 2H), 2.36 (m, 7H), 2.14 (t, J = 12.0, 2H), 1.88 (m, 2H), 1.57 (s, 9H), 1.47 (m, 2H); ^{13}C NMR (126 MHz, MeOD) δ 158.53 (C), 155.40 (CH), 147.42 (C), 145.04 (C), 144.84 (C), 144.67 (C), 141.18 (C), 127.83 (C), 126.66 (C), 120.09 (CH), 119.29 (CH), 114.47 (CH), 110.24 (C), 97.09 (C), 62.20 (CH), 56.22 (CH_2), 52.27 (2x CH_2), 44.00 (CH_2), 40.14 (2x CH_3), 27.37 (2x CH_2), 27.22 (3x CH_3); MS (ES +ve) $(M+H)^+$: 497.4; HRMS (ES +ve), $C_{25}H_{37}N_8O_3$ $(M+H)^+$: calculated 497.29831, found 497.29770.

Tert-butyl N-[4-[4-amino-1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]pyrazolo[3,4-d]pyrimidin-3-yl]phenyl]carbamate (12t). To a solution of 1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.1205 mmol) in dioxane/water (4.5/0.5 ml) was added 4- (boc-amino)benzeneboronic acid (1.5 eq., 42.9 mg, 0.181 mmol), potassium carbonate (1.5 eq., 25.0 mg, 0.181 mmol) and triphenylphosphine (20 mol %, 9.5 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 30 min. The mixture was concentrated *in vacuo* and purified by column chromatography, MeOH/DCM (10% then 0-30 drops NEt_3 per 100 ml), to give a light brown coloured solid (26.0 mg, 0.0541 mmol, 45 %). ^{1}H NMR (500 MHz, MeOD) δ 8.24 (s, 1H), 7.65 – 7.57 (m, 4H), 4.53 (t, *J* = 6.6, 2H), 3.12 (d, *J* = 12.0, 2H), 2.92 (t, *J* = 6.6, 2H), 2.41 (m, 7H), 2.12 (t, *J* = 11.0, 2H), 1.88 (d, *J* = 14.4, 2H), 1.54 (s, 9H), 1.47 (m, 2H); ^{13}C NMR (126 MHz, MeOD) δ 158.54 (C), 155.40 (CH), 154.15 (C), 153.74 (C), 144.96 (C), 140.47 (C), 128.68 (2x CH), 126.62 (C), 118.79 (2x CH), 97.74 (C), 79.76 (C), 62.43 (CH), 56.15 (CH_2), 52.09 (2x CH_2), 43.99 (CH_2), 39.95 (2x CH_3), 27.27 (3x CH_3), 27.13 (2x CH_2); MS (ES +ve) $[M+H]^+$: 481.6; HRMS (ES +ve), $C_{25}H_{37}N_8O_2$ $[M+H]^+$: calculated 481.30340, found 481.3046.

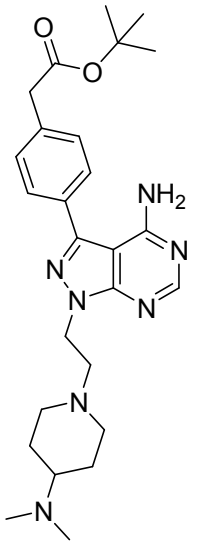




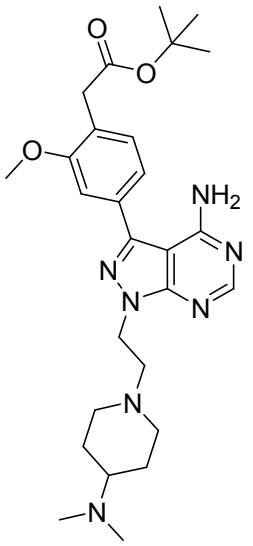
Tert-butyl N-[5-[4-amino-1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]pyrazolo[3, 4-d]pyrimidin-3-yl]-2-pyridyl]carbamate (12u). To a solution of 1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]-3-iodo-pyrazolo[3,4- d]pyrimidin-4-amine (50 mg, 0.1205 mmol) in dioxane/water (4.5/0.5 ml) was added (6- ((tert-Butoxycarbonyl)amino)pyridin-3-yl)boronic acid (1.5 eq., 43.1 mg, 0.181 mmol), potassium carbonate (1.5 eq., 25.0 mg, 0.181 mmol) and triphenylphosphine (20 mol %, 9.5 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 30 min. The mixture was concentrated *in vacuo* and purified by column chromatography, MeOH/DCM (10 % then 10-30 drops of NEt_3 per 100 ml), to give a white solid (23.8 mg, 0.0495 mmol, 41 %). ^{1}H NMR (500 MHz, MeOD) δ 8.55 – 8.51 (m, 1H), 8.26 (s, 1H), 8.06 – 8.01 (m, 2H), 4.55 (t, *J* = 6.5, 2H), 3.14 (d, *J* = 12.0, 2H), 2.94 (t, *J* = 6.5, 2H), 2.68 (m, 1H), 2.55 (s, 6H), 2.14 (t, *J* = 11.0, 2H), 1.92 (d, *J* = 12.7, 2H), 1.55 (s, 9H), 1.53 – 1.46 (m, 2H); ^{13}C NMR (126 MHz, MeOD) δ 158.58 (C), 155.47 (CH), 154.40 (C), 153.05 (C), 152.96 (C), 147.13 (CH), 141.83 (C), 137.78 (CH), 123.46 (C), 112.28 (CH), 97.92 (C), 80.49 (C), 62.79 (CH), 56.00 (CH_2), 51.78 (2x CH_2), 44.12 (CH_2), 39.64 (2x CH_3), 27.16 (3x CH_3), 26.76 (2x CH_2); MS (ES +ve) $[M+H]^+$: 481.8; HRMS (ES +ve), $C_{24}H_{36}N_9O_2$ $[M+H]^+$: calculated 482.29865, found 482.30040.



2-[4-[4-amino-1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]pyrazolo[3,4-d]pyrimidin-3-yl]phenyl]acetic acid (12v). To a solution of 1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]-3-iodo-pyrazolo[3,4- d]pyrimidin-4-amine (50 mg, 0.1205 mmol) in dioxane/water (4.5/0.5 ml) was added 4-(Carboxymethyl)phenylboronic acid pinacol ester (1.5 eq., 47.4 mg, 0.181 mmol), potassium carbonate (1.5 eq., 25.0 mg, 0.181 mmol) and triphenylphosphine (20 mol %, 9.5 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 30 min. The mixture was concentrated *in vacuo* and purified by column chromatography, MeOH/DCM (10 % then 0-50 drops of NEt_3 per 100 ml), to give a cream solid (25.0 mg, 0.0591 mmol, 49 %). ^{1}H NMR (500 MHz, MeOD) δ 8.26 (s, 1H), 7.59 (d, *J* = 8.2, 2H), 7.49 (d, *J* = 8.2, 2H), 4.55 (t, *J* = 6.3, 2H), 3.62 (s, 2H), 3.20 – 3.15 (m, 2H), 2.98 (t, *J* = 6.3, 3H), 2.74 (s, 6H), 2.18 (t, *J* = 11.0, 2H), 2.03 – 1.96 (m, 2H), 1.56 (dd, *J* = 12.1, 3.9, 2H); ^{13}C NMR (126 MHz, MeOD) δ 177.81 (C), 158.57 (C), 155.42 (CH), 154.16 (C), 145.31 (C), 139.11 (C), 130.29 (C), 129.88 (2x CH), 128.10 (2x CH), 97.82 (C), 63.29 (CH_2), 55.78 (CH_2), 51.37 (2x CH_2), 44.08 (CH_2), 39.26 (2x CH_3), 29.53 (CH), 26.34 (2x CH_2); MS (ES +ve) $[M+H]^+$: 424.4; HRMS (ES +ve), $C_{22}H_{30}N_7O_2$ $[M+H]^+$: calculated 424.24555, found 424.24750.



Tert-butyl 2-[4-[4-amino-1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]pyrazolo[3,4-d]pyrimidin-3-yl]phenyl]acetate (12w). To a solution of 1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine (50 mg, 0.1205 mmol) in dioxane/water (4.5/0.5 ml) was added *tert*-butyl 2-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]acetate (1.5 eq., 57.6 mg, 0.181 mmol), potassium carbonate (1.5 eq., 25.0 mg, 0.181 mmol) and triphenylphosphine (20 mol %, 9.5 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 30 min. The mixture was concentrated *in vacuo* and purified by column chromatography, MeOH/DCM (10 % then 0-30 drops of NEt_3 per 100 ml), to give a light brown thick oil (40.5 mg, 0.0845 mmol, 70 %). ^{1}H NMR (500 MHz, MeOD) δ 8.26 (s, 1H), 7.68 – 7.63 (m, 2H), 7.47 (d, *J* = 8.2, 2H), 4.55 (t, *J* = 6.6, 2H), 3.68 (s, 2H), 3.12 (d, *J* = 11.9, 2H), 2.93 (t, *J* = 6.6, 2H), 2.43 (m, 7H), 2.13 (t, *J* = 11.0, 2H), 1.87 (m, 2H), 1.47 (m, 11H); ^{13}C NMR (126 MHz, MeOD) δ 171.52 (C), 158.52 (C), 155.44 (CH), 154.21 (C), 144.85 (C), 136.00 (C), 131.41 (C), 129.95 (2x CH), 128.45 (2x CH), 97.81 (C), 81.01 (C), 62.40 (CH), 56.15 (CH_2), 52.10 (2x CH_2), 44.04 (CH_2), 41.58 (CH_2), 39.95 (2x CH_3), 27.13 (2x CH_2), 26.88 (3x CH_3); MS (ES +ve) $[M+H]^+$: 480.0; HRMS (ES +ve), $C_{26}H_{38}N_7O_2$ $[M+H]^+$: calculated 480.30815, found 480.31210.



Tert-butyl 2-[4-[4-amino-1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]pyrazolo[3,4-d]pyrimidin-3-yl]-2-methoxy-phenyl]acetate (12x). To a solution of 1-[2-[4-(dimethylamino)-1-piperidyl]ethyl]-3-iodo-pyrazolo[3,4-d]pyrimidin-4-amine (34.7 mg, 0.0836 mmol) in dioxane/water (4.5/0.5 ml) was added *tert*-butyl 2-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]acetate (1 eq., 29.1 mg, 0.0836 mmol), potassium carbonate (1.5 eq., 17.3 mg, 0.125 mmol) and triphenylphosphine (20 mol %, 4.4 mg) followed by palladium acetate (5 mol %) and the mixture heated in the microwave at 120 °C for 30 min. The mixture was concentrated *in vacuo* and purified by column chromatography, MeOH/DCM (0-10 % then 0-30 drops of NEt_3 per 100 ml), to give a light brown solid (19 mg, 0.0373 mmol, 44.5 %). ^{1}H NMR (500 MHz, MeOD) δ 8.26 (s, 1H), 7.35 (d, J = 7.6, 1H), 7.26 (d, J = 1.4, 1H), 7.22 (dd, J = 7.5, 1.6, 1H), 4.56 (t, J = 6.7, 2H), 3.91 (s, 3H), 3.64 (s, 2H), 3.13 (d, J = 11.9, 2H), 2.94 (t, J = 6.7, 2H), 2.37 (m, 7H), 2.13 (t, J = 11.0, 2H), 1.91 – 1.85 (m, 2H), 1.48 (m, 11H); ^{13}C NMR (126 MHz, MeOD) δ 172.07 (C), 158.55 (C), 158.18 (C), 155.46 (CH), 154.14 (C), 145.09 (C), 133.02 (C), 131.48 (CH), 124.76 (C), 120.21 (CH), 110.45 (CH), 97.82

(C), 80.76 (C), 62.26 (CH), 56.22 (CH_2), 54.70 (CH_3), 52.24 (2x CH_2), 44.04 (CH_2), 40.09 (2x CH_3), 36.61 (CH_2), 27.28 (2x CH_2), 26.90 (3x CH_3); MS (ES +ve) $[M+H]^+$: 510.2; HRMS (ES +ve), $C_{27}H_{40}N_7O_3$ $[M+H]^+$: calculated 510.31872, found 510.31850.

6. *In vitro* ADME-Tox Methods

hERG channel inhibition. The experiments were performed on an IonWorks™ HT Instrument (Molecular Devices Corporation), which automatically performs electrophysiology measurements in 48 single cells simultaneously. In a specialised 384-well plate (PatchPlate™), all cell suspensions, buffers and test compound solutions were at room temperature during the experiment. The cells used were Chinese hamster ovary (CHO) cells stably transfected with hERG (cell-line obtained from Cytomyx, UK). A single-cell suspension was prepared in extracellular solution (Dulbecco's phosphate buffered saline with calcium and magnesium pH 7-7.2) and aliquots added automatically to each well of a PatchPlate™. The cells were then positioned over a small hole at the bottom of each well by applying a vacuum beneath the plate to form an electrical seal. The vacuum was applied through a single compartment common to all wells which was filled with intracellular solution (buffered to pH 7.2 with HEPES). The resistance of each seal was measured via a common ground-electrode in the intracellular compartment and individual electrodes placed into each of the upper wells. Electrical access to the cells was then achieved by circulating a perforating agent, amphotericin, underneath the PatchPlate™ and then measuring the pre-compound hERG current. An electrode was positioned in the extracellular compartment and a holding potential of -80 mV applied for 15 s. The hERG channels were then activated by applying a depolarising step to +40 mV for 5 s and then clamped at -50 mV for 4 s to elicit the hERG tail current, before returning to -80 mV for 0.3 s. The compound was then added automatically to the upper wells of the PatchPlate™ from a 96-well *microtitre* plate containing a range of concentrations of each compound. Solutions were prepared by diluting 10 mM DMSO solutions of the test compound into extracellular buffer such that the final concentrations tested are 0.008, 0.04, 0.2, 1, 5 and 25 μM *(*final DMSO concentration 0.25%). **11a** was left in contact with the cells for 300 s before recording currents using the some voltage-step protocol as in the pre-compound scan. Quinidine, an established hERG inhibitor, was included as a positive control and buffer containing 0.25% DMSO was included as a negative control. The results were rejected and the experiment repeated if the IC_{50} value for quinidine or the negative control was outside quality-control limits. Each concentration was tested in 4 replicate wells on the PatchPlate™. However, only cells with a seal resistance greater than 50 MOhm and a pre-compound current of at least 0.1 nA were used to

evaluate hERG blockade. Post-compound currents were then expressed as a percentage of pre-compound currents and plotted against concentration for each compound. Where concentration-dependent inhibition was observed, the data were fitted to the following equation and an IC_{50} value calculated: $Y = (V_{max}-V_{min})/(1+X/X_{50})^3 + Y_{min}$

Cytochrome P450 enzyme inhibition. The P450-Glo screening system (Promega) was used to determine any effects of compounds on the activity of the CYP450 enzymes responsible for drug metabolism. The substrates used in this system are converted to a luciferin product by the CYP enzymes; luminescence is measured and represents the activity of the relevant enzyme. **11a** was assayed at a concentration of 10 μM. Positive inhibitor control varied for each CYP enzyme assayed (see Fig S5). **11a** was added at 40 μM to a separate well of a white walled 96 well plate in a volume of 12.5 μL. **11a** solution was prepared in luciferin-free water (with a final DMSO concentration of 1%) and assayed in duplicate. High controls contained luciferin-free water with DMSO (final concentration 1%) and low controls contained luciferin-free water only. Positive control inhibitors were assayed at a final concentration of 10 μM. Reaction mixture containing 12.5 μL of the relevant assay buffer, substrate and CYP membranes were added to **11a**, positive inhibitor and high control wells. To the low control wells, 12.5 μL of reaction mixture was added which contained CYP-free control membranes. The plates were sealed and placed on a plate shaker briefly to mix the contents of each well. Plates were then pre-incubated at the assay reaction temperature of 37 °C for ten min. The reaction was initiated by the addition of 25 μL of NADPH regeneration system. Plates were incubated at 37 °C for the duration of the activity assay. Following incubation, luciferin detection reagent was added at a volume of 50 μL per well and the luminescence signal was left to stabilize for twenty minutes at room temperature. The luminescence signal in each well was read using a TECAN M1000 Infinite plate reader with an integration time of 1 second. The signal detected in the low control wells was averaged and subtracted from the average signal from all other wells. The signal was represented in relative light units (RLU). Measurements obtained in the high control (vehicle only) wells were used to calculate the % inhibition of CYP activity.

Plasma protein binding. The degree of plasma protein binding was determined for **11a** using rapid equilibrium dialysis (RED) device inserts in their corresponding base plates. **11a** was diluted separately to a concentration of 10 μM in 200 μL of human plasma and transferred to the sample chamber of the RED device (indicated by red ring). 350 μL of PBS was added to the buffer chamber before the plate was sealed and incubated for 24 hours at 37˚C with rotation at 100 rpm. Following equilibrium dialysis, a 50 μL sample was obtained from both chambers of the RED device. 50 μL of

PBS was added to the plasma samples (from the sample chamber) and 50 µL of plasma was added to the PBS samples (from the buffer chamber). To precipitate protein in the samples, 300 µL of ice-cold 90:10 acetonitrile:water with 0.1% formic acid (F.A.) was added to each sample. Samples were vortexed briefly then incubated on ice for 30 min. Samples were subject to centrifugation at 13,000 rpm for 10 minutes before the supernatant fraction was transferred to a 96 well deep well block. The supernatant was dried down under nitrogen and re-constituted in 70 µL of solvent (90:10 acetonitrile:water with 0.1% F.A.) before being transferred to a U-bottom 96 well plate for MS analysis. Zero time point samples for each compound (no 24 hour dialysis) were prepared and used as controls. Plates were frozen at -20˚C prior to MS analysis. LC-MS/MS was used to quantify the peak area of **11a** in each compartment of the RED devices using MS tune settings established and validated for each compound. The peak areas detected in the 0 and 24 h time point samples were utilised to calculate the % of compound which is bound to plasma protein.

Human liver microsome stability. The microsomal stability of each compound was determined using human (or rat) liver microsomes. Microsomes were thawed and diluted to a concentration of 2 mg/mL in 50 mM $NaPO_4$ buffer pH 7.4. **11a** was diluted in 4 mM NADPH (made in the phosphate buffer above) to a concentration of 10 µM. Two identical incubation plates were prepared to act as a 0 minute and a 30 min time point assay. 30 µL of **11a** dilution was added in duplicate to the wells of a U-bottom 96 well plate and warmed at 37˚C for approximately 5 min. Verapamil, lidocaine and propranolol were utilised as reference compounds in this experiment. Microsomes were also pre-warmed at 37˚C before the addition of 30 µL to each well of the plate resulting in a final concentration of 1 mg/mL. The reaction was terminated at the appropriate time point (0 or 30 min) by addition of 60 µL of ice-cold 0.3 M trichloroacetic acid (TCA) per well. The plates were centrifuged for 10 min at 1000 rpm and the supernatant fraction transferred to a fresh U-bottom 96 well plate. Plates were sealed and frozen at -20 °C prior to MS analysis. LC-MS/MS was used to quantify the peak area response of **11a** before and after incubation with human liver microsomes using MS tune settings established and validated for each compound. These peak intensity measurements were used to calculate the % remaining after incubation with human microsomes for **11a**.

Human, mouse and rat plasma stability. Plasma was adjusted to pH 7.4 using either hydrochloric acid or sodium hydroxide depending on the initial pH of the plasma. Incubations were performed at a test or control compound concentration of 1 µM in plasma, pH 7.4, at 37 °C. The final DMSO concentration in the incubation was 2.5%. Reactions were terminated following 0, 15, 30, 60 and 120 min by methanol containing internal standard. The sampling plate was centrifuged (2500rpm, 45 min,

4 °C) and the supernatants from each time point pooled in cassettes. Samples were analysed for parent compound by LC-MS/MS using Cyprotex generic analytical conditions. The percentage of parent compound remaining at each time point relative to the 0 min sample was then calculated from LC-MS/MS peak area ratios (compound peak area/internal standard peak area).

Stability in primary hepatocytes. Cryopreserved pooled hepatocytes were stored in liquid nitrogen prior to use. Williams E media supplemented with 2 mM L-glutamine and 25 mM HEPES and **11a** (final substrate concentration 3 µM; final DMSO concentration 0.25 %) were pre-incubated at 37 °C prior to the addition of a suspension of cryopreserved hepatocytes (final cell density 0.5 x $l0^6$ viable cells/ml in Williams E media supplemented with 2 mM L-glutamine and 25 mM HEPES) to initiate the reaction. The final incubation volume was 500 µl. A control incubation was included for **11a** where lysed cells were added instead of viable cells. Two control compounds were included with each species. The reactions were stopped by transferring 50 µl of incubate to 100 µl methanol containing internal standard at the appropriate time points. The control (lysed cells) was incubated for 60 min only. The termination plates were centrifuged at 2500 rpm at 4 °C for 30 min to precipitate the protein. Following protein precipitation, the sample supernatants were combined in cassettes and analysed using Cyprotex generic LC-MS/MS conditions. The gradient of the line was determined from a plot of in peak area ratio (compound peak area/internal standard peak area) against time. Subsequently, half-life ($t_{1/2}$) and intrinsic clearance (CL_{int}) were calculated using the following equations: elimination rate constant (k) = (-gradient); half-life ($t_{1/2}$) (min) = 0693/k; intrinsic clearance (CL_{int}) (µl/min/million cells) = (V x 0.393)/$t_{1/2}$, where V = incubation volume (µl)/number of cells.

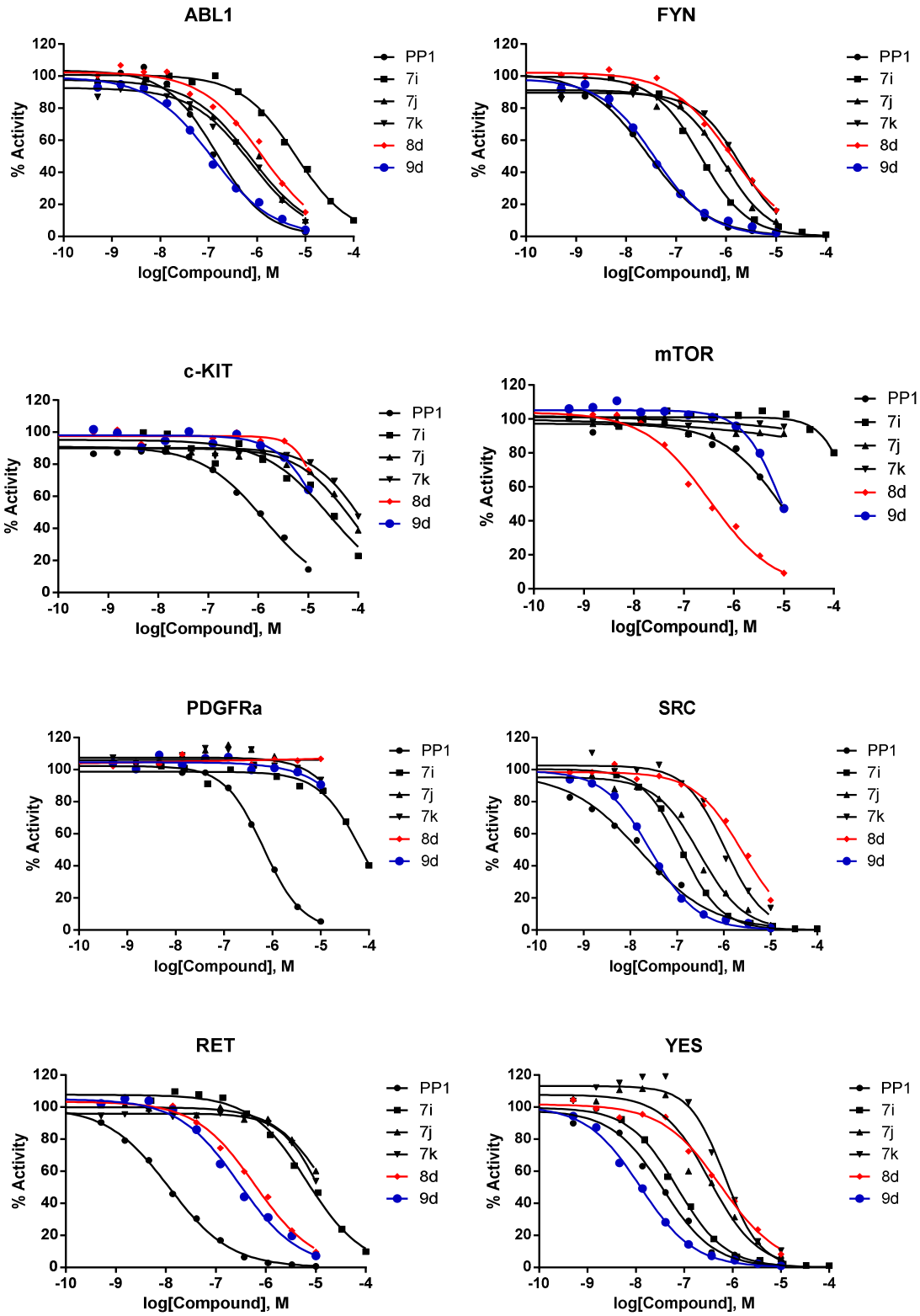


Fig S1 | Kinase profiling of compounds PP1, **7i-k**, **8d**, and **9d** in a selection of 8 kinases. Compounds were tested in 10-dose IC_{50} mode with 3-fold serial dilution starting at 10 μM. Reactions were carried out at 10 μM ATP. Curve fits were performed where the enzyme activities at the highest concentration of compounds were < 65%.

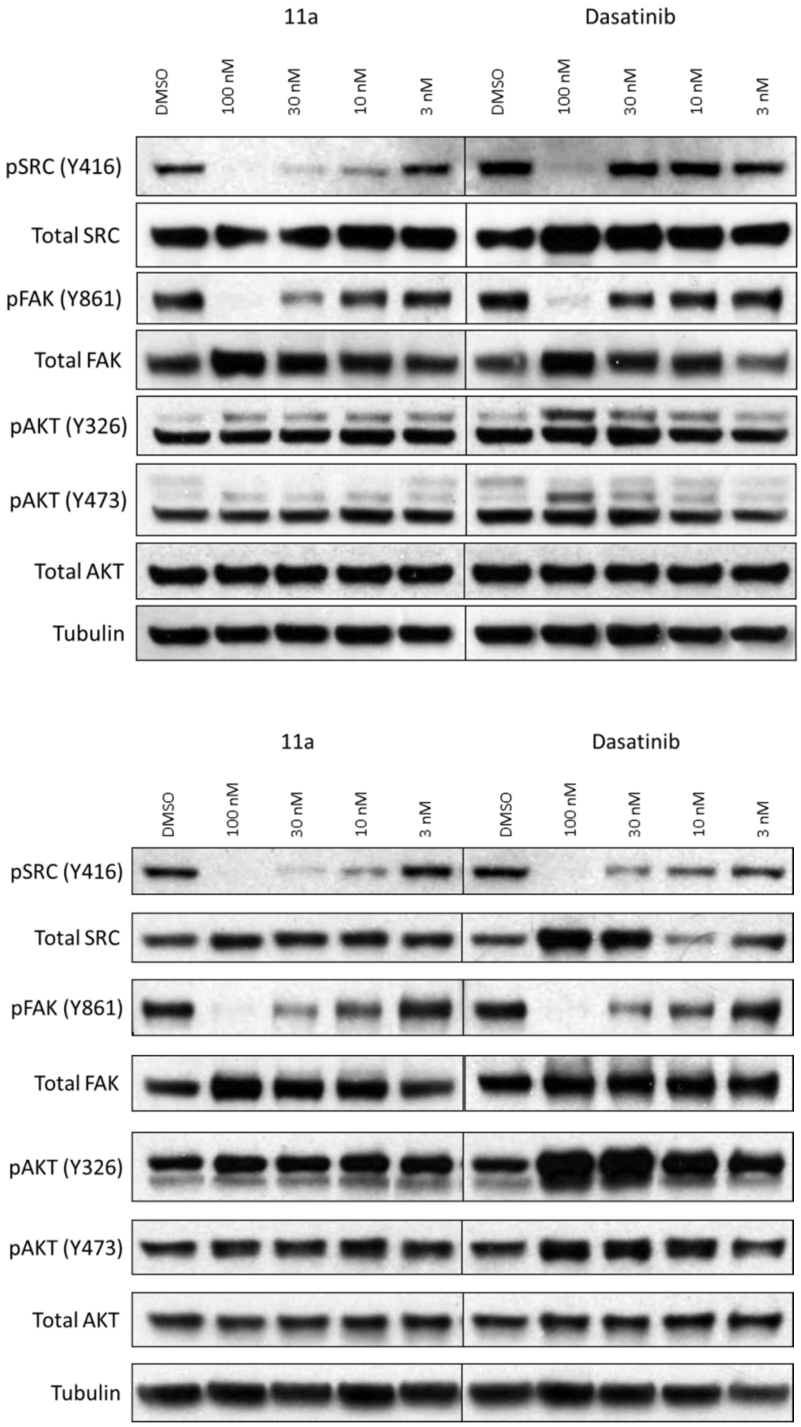


Fig S2 | Western Blot analysis of MCF7 (**top**) and MDA-MB-231 (**bottom**) lysates after treatment with compound **11a** and dasatinib. Tubulin was used as a loading control. Compound **11a** was able to inhibit the autophosphorylation of SRC down to 10 nM in MCF7 and MDA-MB-231 cells. Inhibition of SRC-mediated phosphorylation of FAK was observed at similar concentration. Dasatinib showed slightly lower activity and off target effects (increased AKT phosphorylation). **11a** treatment did not increase the total levels of SRC as dasatinib did at higher concentrations.

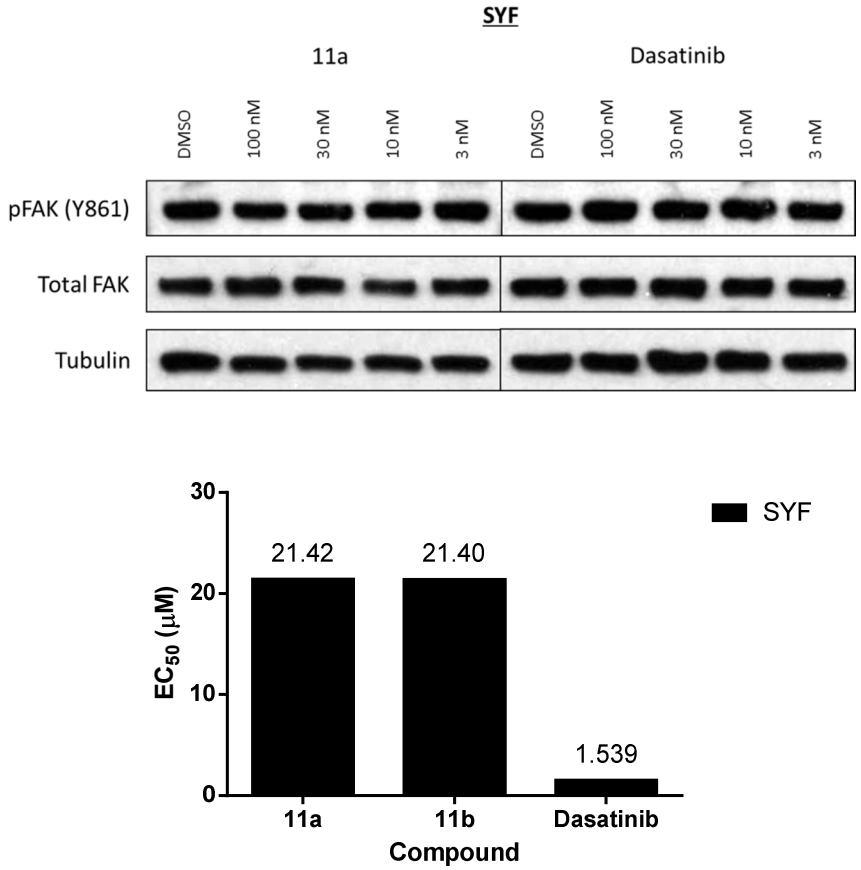


Fig S3 | Western blot and proliferation analysis of SYF cells under treatment with compound **11a** and dasatinib. **Top,** Western blot of SYF cells lysates after treatment with compound **11a** and dasatinib at concentrations 3-100 nM. Tubulin was used as a loading control. As expected, levels of FAK phosphorylation were unaffected by drug treatments, indicating that inhibition of pFAK (Y861) in the breast cancer cell lines was mediated via inhibition of SRC phosphorylation and not through either direct FAK inhibition or off-target effects. **Bottom,** EC_{50} values calculated by dose response studies of SYF cells treated with **11a**, **11b** and dasatinib. Mouse SYF cells lack expression of the SFK members SRC, YES and FYN, and therefore are expected to be unaffected by treatment with Src inhibitors.

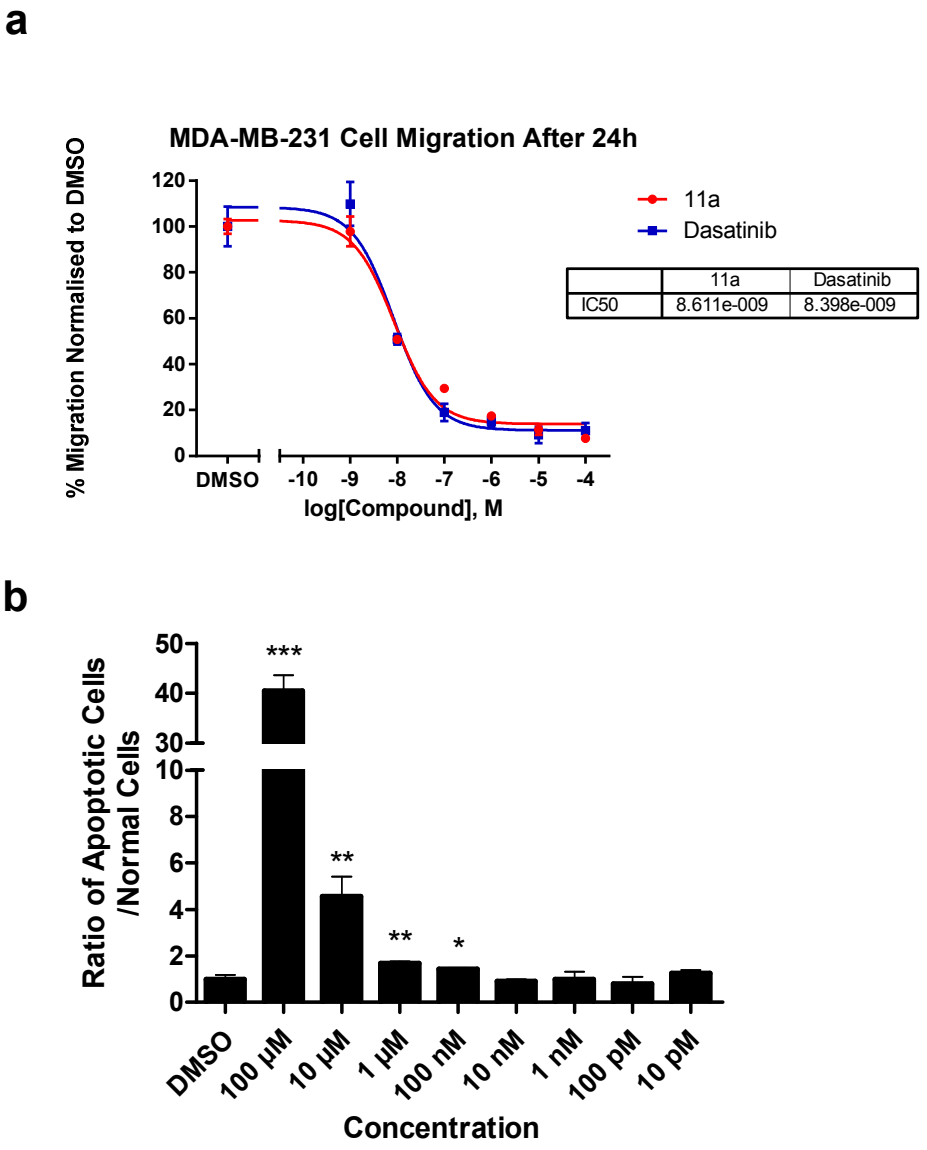


Fig S4 | **(a)** Comparative dose response analysis of MDA-MB-231 cell migration treated with **11a** or Dasatinib (1nM to 100 µM) relative to DMSO. Curves were plotted and EC_{50} values calculated using GraphPad Prism 6. **(b)** Study of caspase activity in MCF7 cells after treatment with **11a**. Cells were incubated for 48h prior to addition of the compounds. The media was replaced with fresh media containing **11a** (10 pM to 100 µM) or DMSO (0.1% v/v) and NucView™ 488 (caspase 3/7 reagent, Biotium) and the plates placed in the IncuCyte™ ZOOM device. Cell growth was monitored over 5 d using phase contrast and fluorescent microscopy (ex 460 nm / em 524 nm). Cell confluence vs apoptotic (green) cell count was performed by the IncuCyte software. Resulting numbers were divided so as to create a ratio of apoptotic cells to normal cells. Results were then normalised to DMSO to account for the decreased number of cells found in higher concentrations of drug treatment. ($p<0.001$, ***; $p<0.01$, **; $p<0.05$, *; n = 3; error bars denote standard deviation).

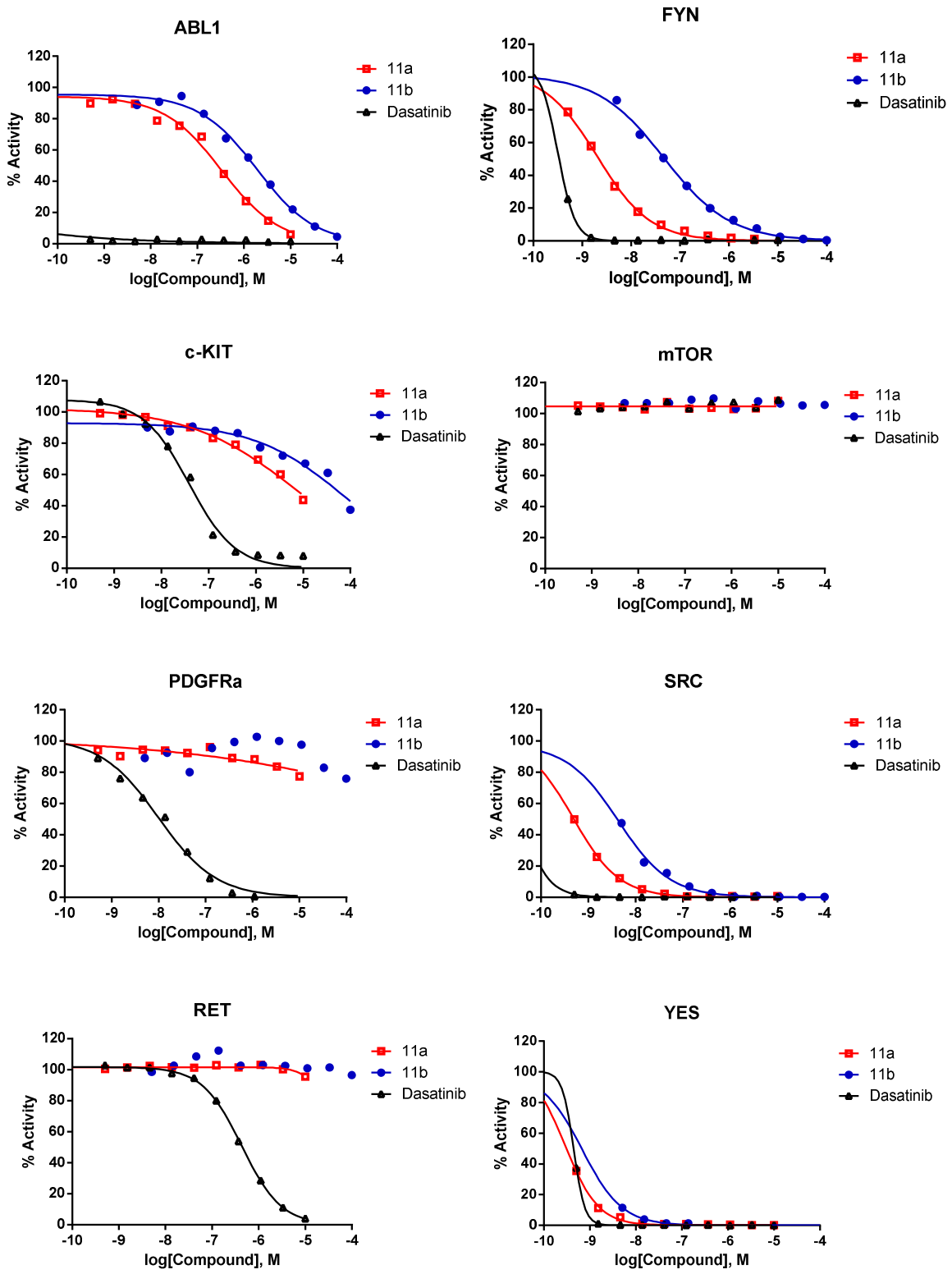


Fig S5 | Kinase profiling of compounds **11a**, **11b** and dasatinib in a selection of eight kinases: ABL, FYN, KIT, mTOR, PDGFRα, SRC, RET and YES. Compounds were tested in 10-dose IC_{50} mode with 3-fold serial dilution starting at 10 μM. Reactions were carried out at 10 μM ATP.

SUPPORTING INFORMATION

Table S1 | *IC_{50} (nM) values calculated for **PP1**, **7i-k**, **8d**, **9d**, **11a** and dasatinib in a selection of 15 recombinant kinases.*

Kinase \ Hit	PP1	7i	7j	7k	8d	9d	11a	Dasatinib
ABL	147	6,323	7,525	7,249	1,207	116	479	< 0.5
BLK	268	1,545	2,846	7,072	>10^4	110	5.4	< 0.5
FGR	7.6	115	400	601	2,130	45	< 0.5	< 0.5
FRK/PTK5	63.0	916	1,635	3,700	2,690	106	2.8	< 0.5
FYN	27	311	913	1,964	1,226	38	2.1	< 0.5
HCK	167	1,523	6,009	11,630	6,771	361	2.8	2.0
KIT	1,318	>10^4	>10^4	>10^4	>10^4	>10^4	>10^4	39
LCK	174	727	1,542	4,344	8,609	233	< 0.5	< 0.5
LYN	88.0	285	1,068	2,508	2,305	25	0.8	< 0.5
mTOR	9,318	>10^4	>10^4	>10^4	328	8,565	>10^4	>10^4
PDGFRα	657	>10^4	>10^4	>10^4	>10^4	>10^4	>10^4	9.9
SRC	17	126	303	1,040	2,453	27	< 0.5	< 0.5
RET	11	6,584	>10^4	>10^4	598	289	>10^4	433
YES	36	71	344	696	566	12	< 0.5	< 0.5
IC_{50} (ABL) / IC_{50} (SRC)	**8**	**50**	**25**	**7**	**0.5**	**4**	**>950**	**1**

Member of SRC family of kinases are highlighted in RED.

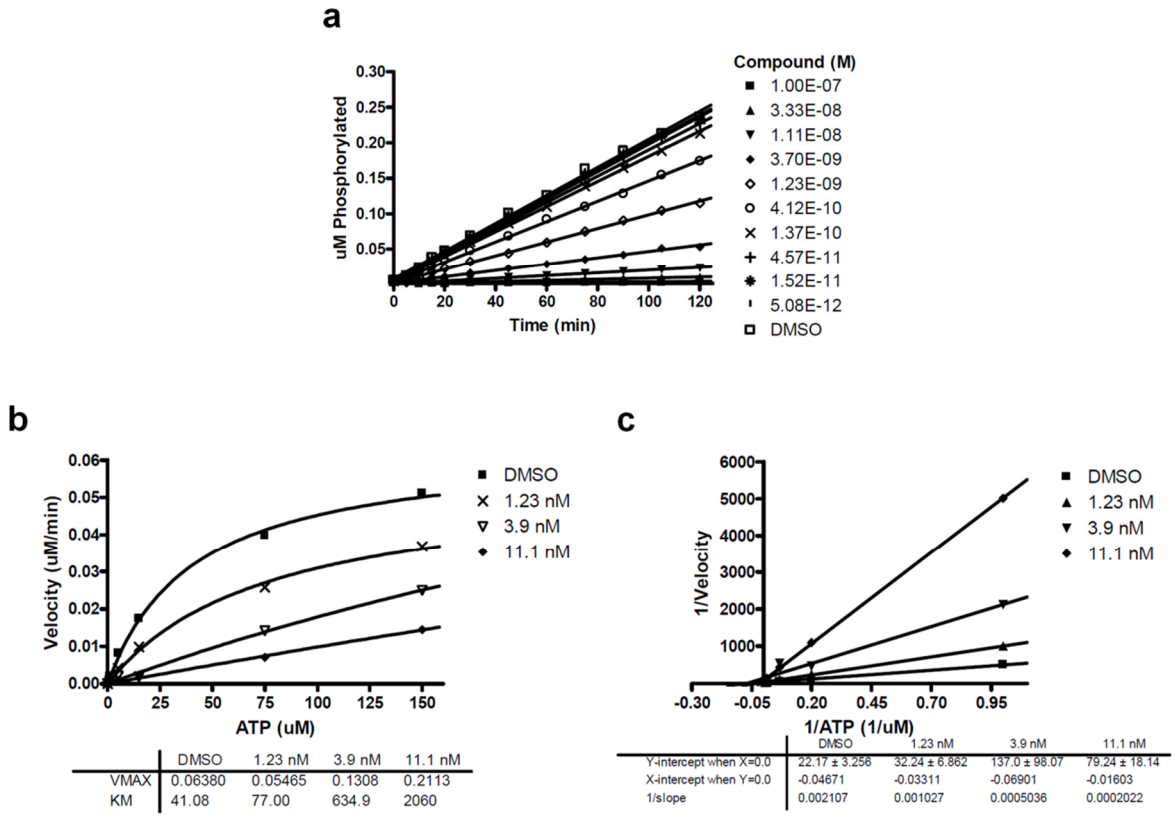
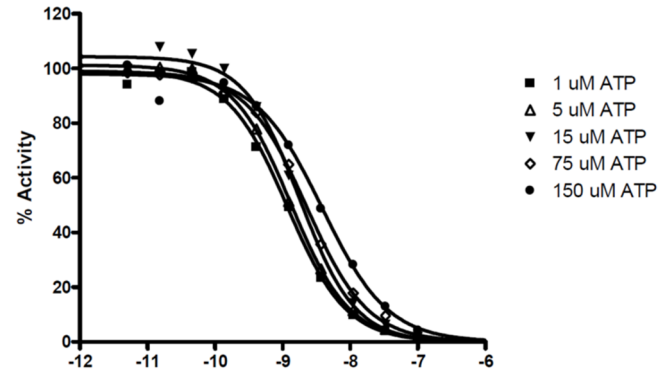


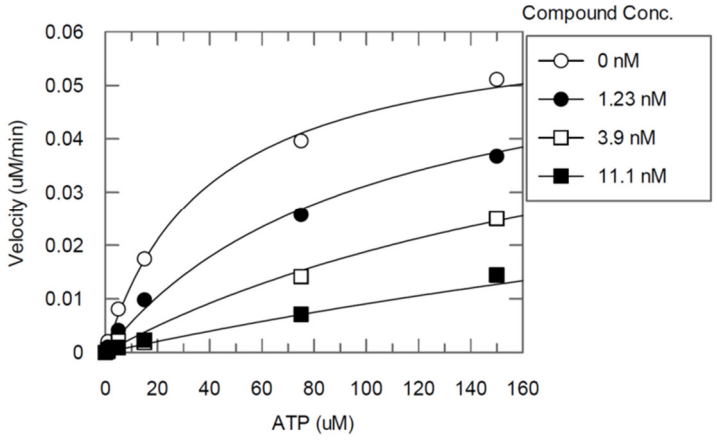
Fig S6 | ATP competition studies I. **(a)** Progress curves for SRC / **11a** binding. The progress curves for SRC reactions were linear with time in the absence and presence of the compound for 120 min, suggesting the inhibition by **11a** is not time-dependent. **(b,c)** Slopes plotted against ATP concentrations for **(b)** Michaelis-Menten Plot and **(c)** Lineweaver-Burk Plot for SRC with **11a** using GraphPad Prism. The apparent Km is increased when inhibitor concentration is increased in Michaelis-Menten plot and all lines are converged on the Y-axis in the double-reciprocal plot, suggesting that the compound is competitive with respect to ATP against SRC.

a



	1 uM ATP	5 uM ATP	15 uM ATP	75 uM ATP	150 uM ATP
HILLSLOPE	-0.9922	-1.002	-1.057	-0.9606	-0.8910
EC50	1.171e-009	1.322e-009	1.794e-009	2.261e-009	3.834e-009

b



Parameter	Value	Std. Error
Vmax	0.0627	0.0020
Km	39.6508	3.9466
Ki	0.7973	0.0685
Ki' value	7.54966e+027	0.0000

Fig S7 | ATP competition studies II. **(a)** Dose response curves of SRC inhibition by **11a** at different concentrations of ATP and calculated IC_{50} values. Although differences were small, IC_{50} values were increased when ATP concentration was increased, as expected for competitive inhibitors. **(b)** Global fit of Michaelis-Menten Plots by GraFit software for SRC. The very large value of Ki' (almost infinity) means the compound has negligible affinity to enzyme/ATP complex, which turns purely competitive inhibition with respect to ATP and Km value of 39.7 μM.

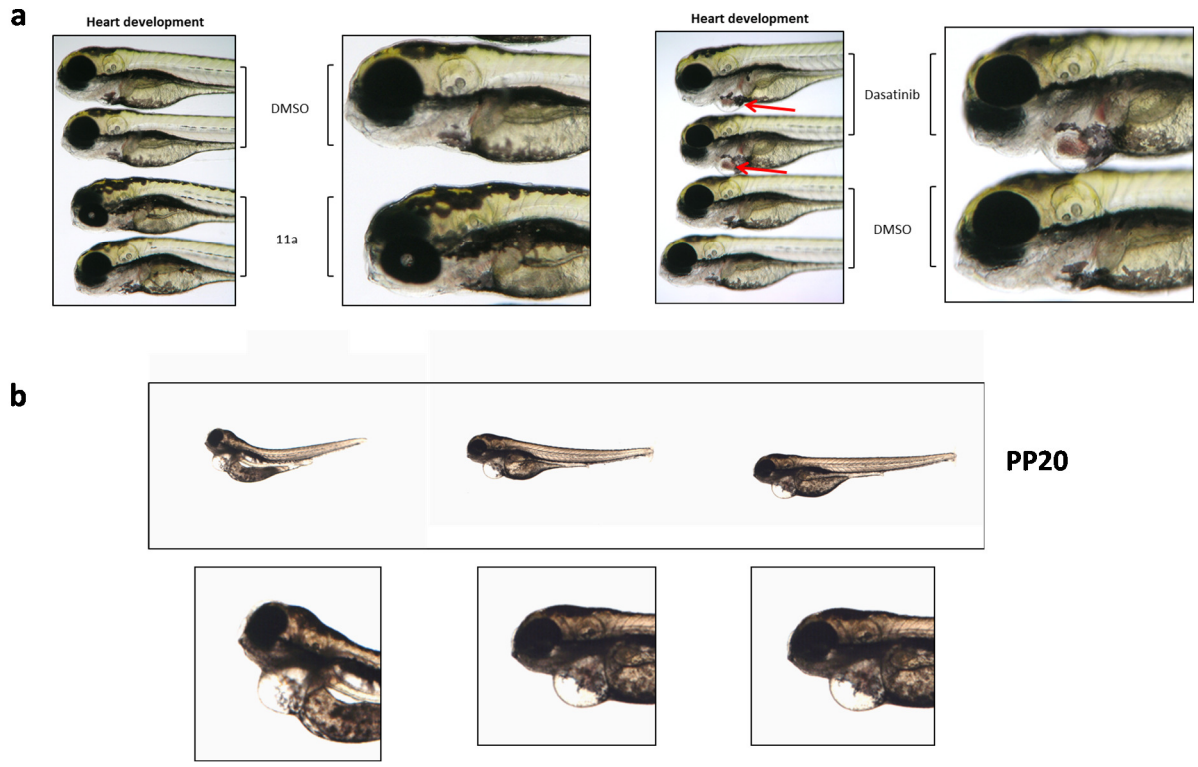
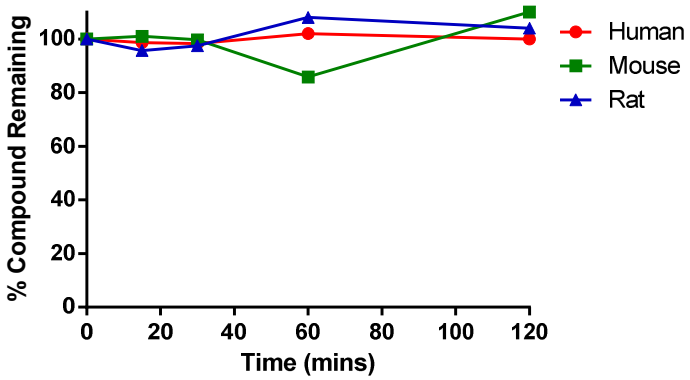
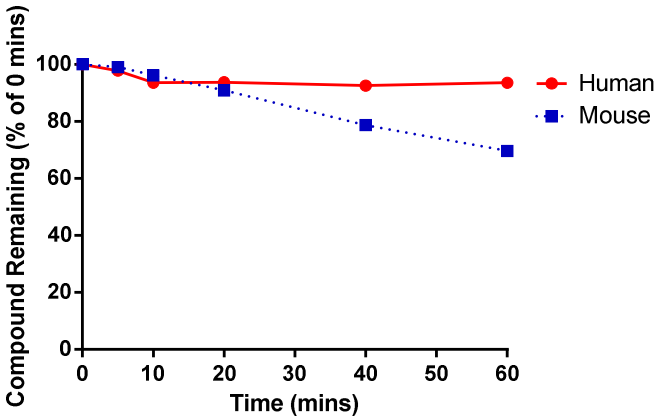


Fig S8 | Study of zebrafish development under treatment. **(a)** Either dasatinib (10 μM) or compound **11a** (500 μM) were added 2 dpf and incubated for 4 h. Subsequently, fresh media was added and fish incubated for additional 48 h. Negative control= DMSO. **(b)** PP20 (1 μM) was added 2 dpf and incubated for 2 h. Subsequently, fresh media was added and fish incubated for additional 48 h. Results: Zebrafish treated with dasatinib or PP20 treated showed severe heart enlargement (cardiotoxicity) at low concentrations (1 μM). Compound **11a** and DMSO showed normal heart development and no toxicity.

Compound	CYP1A2	CYP3A4	CYP2C9	CYP2D6	CYP2C19
11a	24.54	≤0	≤0	≤0	≤0
Naphthoflavone (1A2, 2C19)	99.82				99.29
Ketaconazole (3A4)		92.62			
Sulphenazole (2C9)			95.57		
Quinidine (2D6)				88.09	

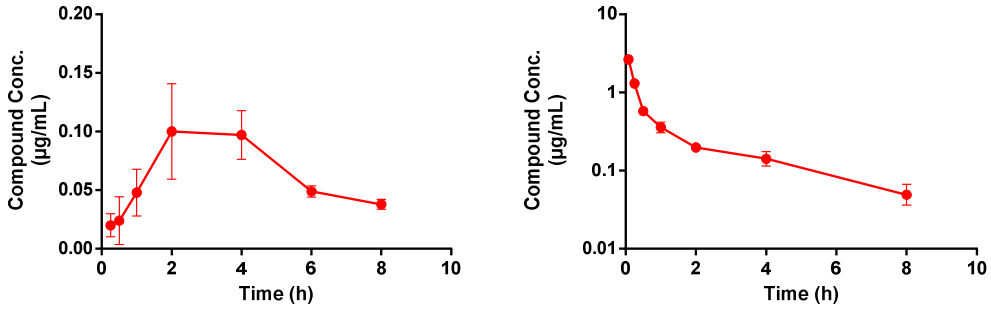
Fig S9 | Study of the inhibition of cytochrome P450 enzymes by compound **11a** at 10 μM. Experiments were performed in duplicate and average values calculated. Naphthoflavone, ketoconazole, sulphenazole and quinidine (10 μM) were used as positive control drugs. 0 indicates zero or negative values. Blank spaces indicate non-tested.





Compound	CL_{int} (µL/min/10^6 cells)	SE CL_{int}	$t_{1/2}$ (min)
11a - Human	1.84	0.989	751
11a - Mouse	12.5	0.447	110
verapamil - Human	60.8	1.3	22.8
verapamil - Mouse	317	21.6	4.4
umbelliferone - Human	150	0.8	9.7
umbelliferone - Mouse	983	135	1.4

Fig S10 | Plasma stability study of compound **11a. (a)** Compound stability in a) human, b) mouse or c) rat plasma over 2 h. All compounds showed >90% recovery after 2 h incubation. **(b)** Compound stability in human and mouse hepatocytes over 60 min incubation. Calculated factors from hepatocyte study - intrinsic clearance (CL_{int}) with standard error (SE) and half-life ($t_{1/2}$).



Compound	Dose (mg/kg)	AUC (µg-hr/ml)	$T_{1/2}$ (hrs)	C_{max} (µg/ml)	T_{max} (hrs)	CL (ml/min/kg)	% F
IV 11a	10	2.07[a]	2.9			72.3	
IV Dasatinib[1]	10	5.60[b]	0.9			61.7	
PO 11a	10	0.53[a]		0.100	2		25
PO Dasatinib[1]	5	0.46[b]		0.104	2		17
PO Dasatinib[2]	5	0.42[c]		0.058	1		45

[a] 0-8h; [b] total; [c] 0-24h

Fig S11 | In vivo pharmacokinetic data of compound **11a**. Average compound concentration over 8 hours following, a) oral administration and, b) IV administration. In vivo half-life and bioavailability based on the PK data for compounds **11a**.

Referrences:

1. Kamath, A. V., Wang, J., Lee, F. Y. & Marathe, P. H. Preclinical pharmacokinetics and in vitro metabolism of dasatinib (BMS-354825): a potent oral multi-targeted kinase inhibitor against SRC and BCR-ABL. *Cancer Chemother. Pharmacol.* **61**, 365-376 (2008).
2. Luo, F. R., et al. Dasatinib (BMS-354825) pharmacokinetics and pharmacodynamic biomarkers in animal models predict optimal clinical exposure. *Clin. Cancer Res.* **12**, 7180-7186 (2006).

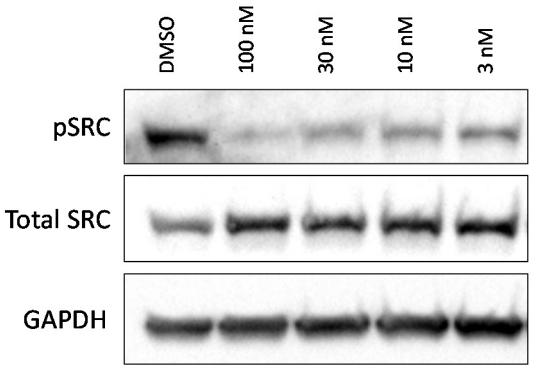


Fig S12 | Western Blot analysis of HCT116 cell lysates after treatment with compound **11a**. GADPH was used as a loading control. Similarly to the activity found in breast cancer cells, compound **11a** was able to inhibit the autophosphorylation of SRC at low nanomolar levels.