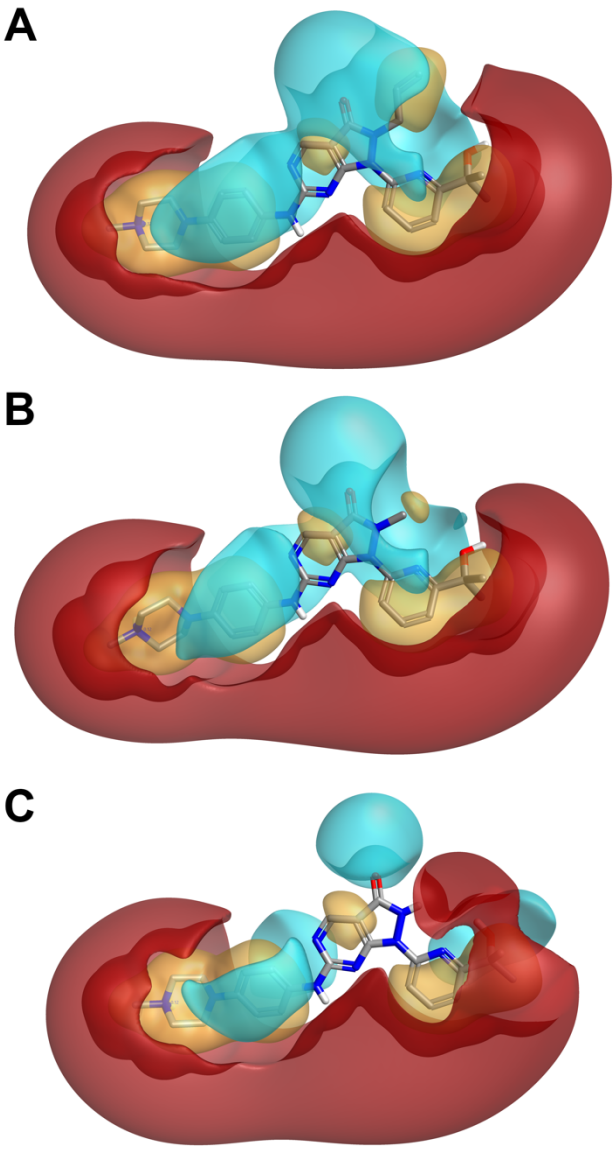


Figure S1. Molecular characteristics of AZD1775 and select analogs. Positive electrostatic (red), negative electrostatic (cyan), and hydrophobic (tan) fields of **(A)** AZD1775, **(B) 32**, and **(C) 35**.

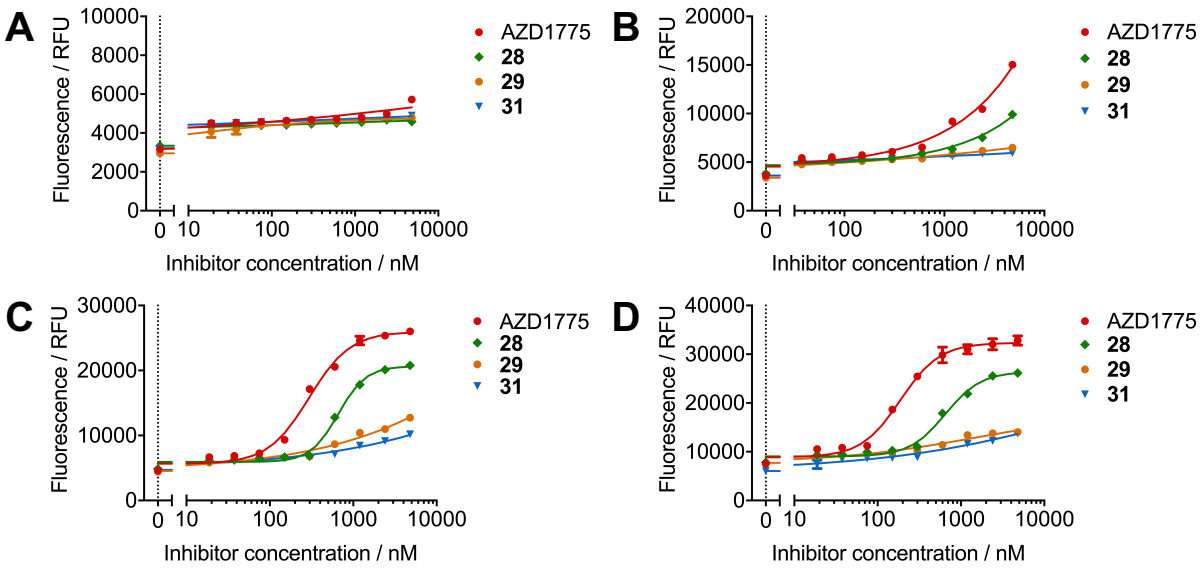


Figure S2. Cytotoxicity dose-response curves of WEE1 inhibitors. Daoy cells with media containing CellTox green dye were treated with WEE1 inhibitors over a concentration range and fluorescence (Ex 485 nm; Em 520 nm) was measured at **A)** 1, **B)** 24, **C)** 48, and **D)** 72 hours.

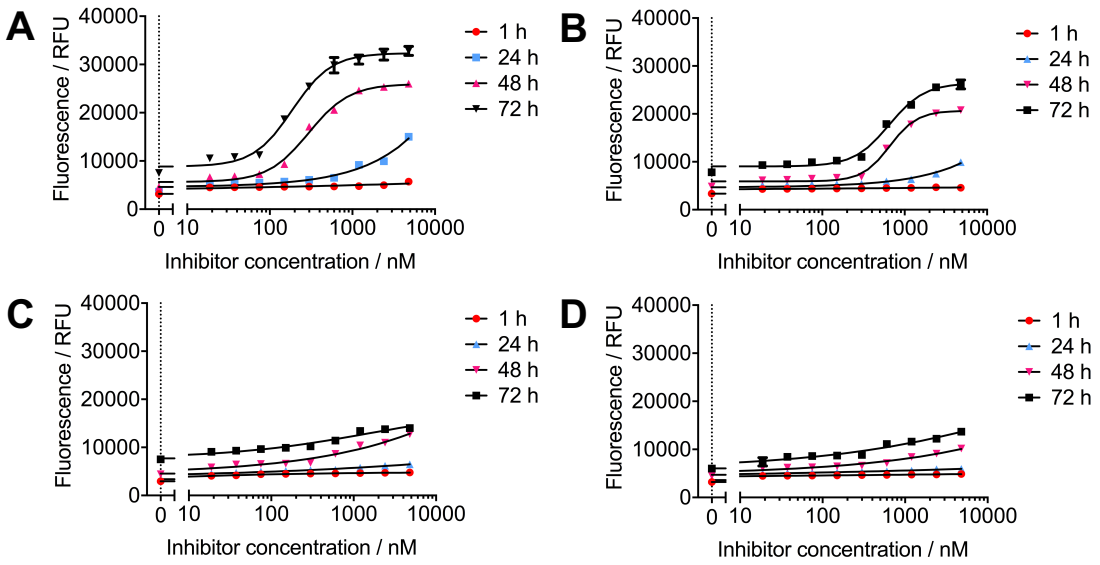


Figure S3. Cytotoxicity of WEE1 inhibitors is concentration- exposure time-dependent. Daoy cells with media containing CellTox green dye were treated with WEE1 inhibitors: **A)** AZD1775, **B) 28**, **C) 29**, and **D) 31**. Fluorescence (Ex 485 nm; Em 520 nm) was measured at 1, 24, 48, and 72 hours.

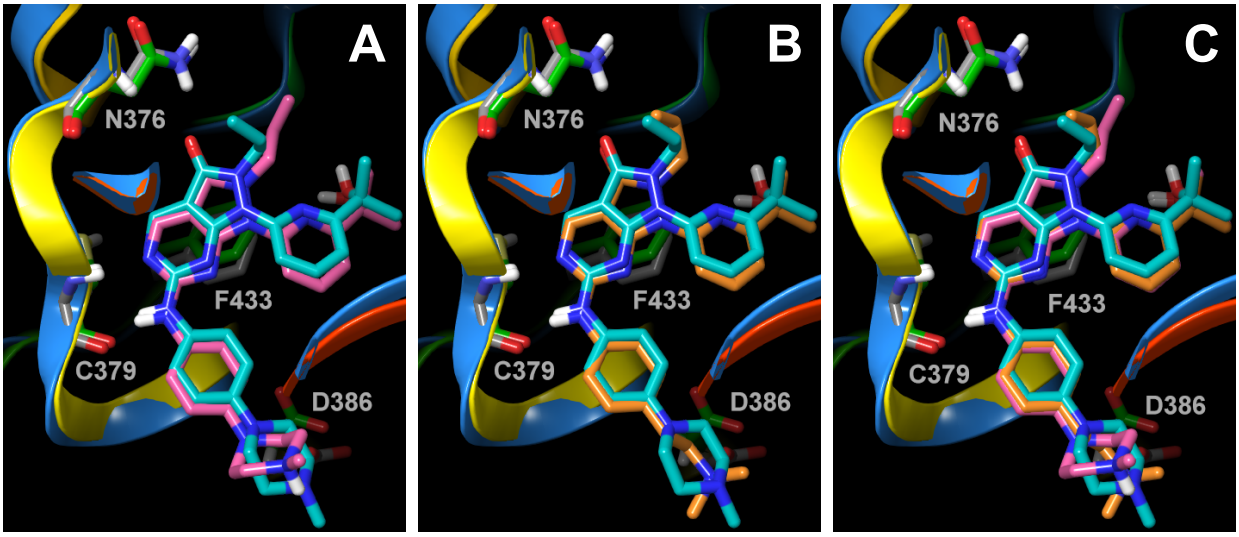
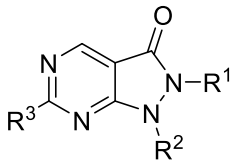
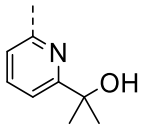
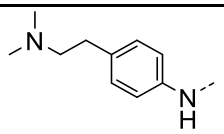
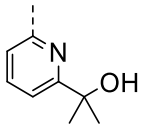
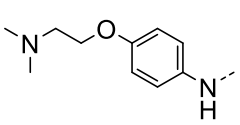
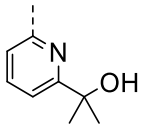
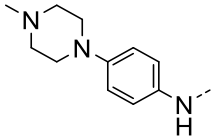
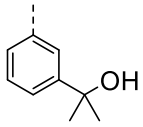
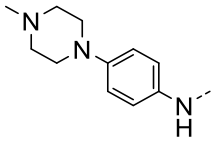


Figure S4. Overlays of computational molecular docking of WEE1 inhibitors on the WEE1-AZD1775 co-crystal structure. A) Overlay of AZD1775 (pink) docked into the WEE1 crystal structure (PDB: 1X8B; ribbon colored blue) on the WEE1-AZD1775 co-crystal structure (PDB: 5V5Y; AZD1775 colored cyan, ribbon colored by residue position). **B)** Overlay of compound **28** (orange) docked into WEE1 crystal structure (PDB: 1X8B; ribbon colored blue) on the WEE1-AZD1775 co-crystal structure (PDB: 5V5Y; AZD1775 colored cyan, ribbon colored by residue position). **C)** Overlay of AZD1775 (pink) and compound **28** (orange) docked into WEE1 crystal structure (PDB: 1X8B; ribbon colored blue) on the WEE1-AZD1775 co-crystal structure (PDB: 5V5Y; AZD1775 carbons colored cyan, ribbon colored by residue position).

Table S1. Structures and PLK1 inhibitory activities of active WEE1 inhibitors.



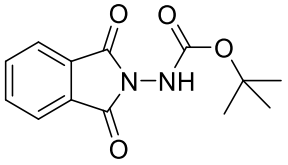
Compound	R^1	R^2	R^3	IC_{50} (nM)
28				270 ± 29
29				161 ± 10
AZD1775				77.6 ± 9.3
31				394 ± 37

Inhibitory activity for the synthesized compounds from a recombinant PLK1 TR-FRET activity assay are given as the half maximal inhibitory concentration (IC_{50}) in nM.

METHODS

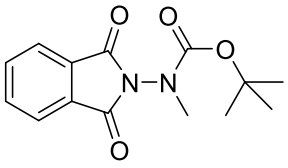
General. Where appropriate, reactions were carried out under an inert atmosphere of nitrogen with dry solvents, unless otherwise stated. Dry solvents were obtained directly from manufacturer and used without further purification. Yields refer to chromatographically and spectroscopically pure isolated yields. Reagents were purchased at the highest commercial-quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60 F254) using ultraviolet light as visualizing agent. All melting points were determined using a Stuart Scientific SMP40 melting point apparatus and are uncorrected. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were obtained as solutions in deuterated solvents DMSO-d_6 or $CDCl_3$ using a Bruker Avance III 400 spectrometer recording at 400 MHz. Chemical shifts (δ) are reported in parts per million (ppm) and the spin-multiplicity abbreviated as: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sept (septet), m (multiplet), or br (broad), with coupling constants (*J*) given in Hertz (Hz). Mass Spectrometry (MS) was carried out on an API 4000. Fourier Transform Infrared (FTIR) spectra were obtained using a Bruker Alpha Platinum-ATR as a neat sample.

Chemical Synthesis.

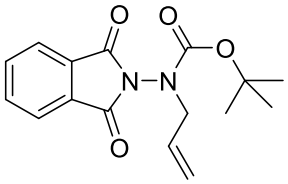


Synthesis of *tert*-butyl (1,3-dioxoisoindolin-2-yl)carbamate (3). *tert*-Butyl carbazate (9.40 g, 70.9 mmol) was added portion-wise to a solution of phthalic anhydride (**2**; 10.0 g, 67.5 mmol) in refluxing toluene (110 ml). The resultant suspension was heated under reflux conditions for 18 h, before being cooled and the precipitate removed by filtration. The filtrand was washed with hexanes and dried under vacuum to give the desired product as a white crystalline solid (16.1 g, 61.4 mmol, 91%). Rf 0.68 (1:1 Hexane:EtOAc); M.p. 191-194°C (Lit. = 186°C);[35] IR (cm^{-1}) 3316, 2979, 1796, 1730, 1614, 1490; ^{1}H NMR (400 MHz, DMSO-d_6) 1.45 (9H, s, -OC(CH_3)$_3$), 7.87-8.04 (4H, m, H-4/5/6/7), 9.86 (1H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6) 28.3 (C(*C*H_3)$_3$), 81.6 (*C*(CH$_3$)$_3$), 124.2 (Ar-C), 129.8 (Ar-C), 135.8 (Ar-C), 154.4 (C=O), 165.9 (C=O).

General Procedure for the alkylation of tert-butyl (1,3-dioxoisoindolin-2-yl)carbamate (4-6). To a suspension of the carbamate (**3**) (1.0 equiv.) in MeCN (2 mL/mmol) was added benzyltriethylammonium chloride (0.1-0.2 equiv.), K_2CO_3 (4.0 equiv.) and the relevant alkylhalide (1.5-5.0 equiv.) sequentially. The reaction mixture was stirred at RT or 50°C for 18 -48 h, before water (2 mL/mmol) was added and the organic phase was extracted with Et_2O (2 x 5 mL/mmol). The combined organic extracts were dried ($MgSO_4$) and evaporated to dryness and were purified by chromatography on silica.

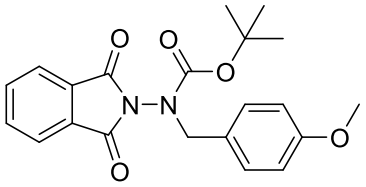


Synthesis of tert-butyl (1,3-dioxoisoindolin-2-yl)(methyl)carbamate (4). tert-Butyl (1,3-dioxoisoindolin-2-yl)carbamate (**3**, 100 mg, 0.38 mmol), benzyltriethylammonium chloride (17 mg, 0.08 mmol), K_2CO_3 (210 mg, 1.52 mmol) and methyl iodide (118 µL, 1.90 mmol) were reacted in MeCN (1 mL) according to the described general procedure with heating at 50°C for 48 h required for completion. Purification on silica gel (1:1 Hexanes:EtOAc) afforded the target compound as a white crystalline solid (93 mg, 0.34 mmol, 89%). Rf 0.38 (1:1 Hexanes:EtOAc); M.p. 118-120°C (Lit. = 123°C);[35] IR (cm^{-1}) 2972, 2934, 1791, 1723, 1609; ^{1}H NMR (400 MHz, $CDCl_3$) 1.34 (5.1H, s, $C(CH_3)_{3\text{-major}}$), 1.53 (3.9H, s, $C(CH_3)_{3\text{-minor}}$), 3.29 (1.7H, s, $N\text{-}CH_{3\text{-major}}$), 3.32 (1.3H, s, $N\text{-}CH_{3\text{-minor}}$), 7.74-7.93 (4H, m, H-4/5/6/7); ^{13}C NMR (100 MHz, $CDCl_3$) 27.9 ($C(CH_3)_{3\text{-major}}$), 28.1($C(CH_3)_{3\text{-minor}}$), 36.5 ($N\text{-}CH_{3\text{-major}}$), 38.1 ($N\text{-}CH_{3\text{-minor}}$), 82.2 ($C(CH_3)_{3\text{-major}}$), 82.9 ($C(CH_3)_{3\text{-minor}}$), 123.8 (Ar-C), 129.9 (Ar-C), 130.1 (Ar-C), 134.6 (Ar-C), 134.7 (Ar-C), 153.6 ($C{=}O_{\text{-major}}$), 153.8 ($C{=}O_{\text{-minor}}$), 165.0 ($C{=}O_{\text{-major}}$), 165.3 ($C{=}O_{\text{-minor}}$); MS $[M+H]^+$ *m*/*z* 276.8.



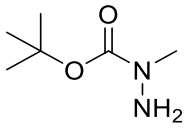
Synthesis of *tert*-butyl allyl(1,3-dioxoisoindolin-2-yl)carbamate (5). tert-Butyl (1,3-dioxoisoindolin-2-yl)carbamate (**3**, 16.1 g, 61.2 mmol), benzyltriethylammonium chloride (1.39 g, 6.12 mmol), K_2CO_3 (16.1 g, 116 mmol) and allyl bromide (8.00 mL, 91.8 mmol) were reacted in

MeCN (110 mL) according to the described general procedure with stirring at RT for 18 h required for completion. Trituration with hexanes at 0°C afforded the desired product as a white crystalline solid (15.7 g, 52.1 mmol, 85%) with no further purification needed. Rf 0.52 (4:1 Hexane:EtOAc); M.p. 72-75°C (Lit. = 76-78°C);[35] IR (cm^{-1}) 2978, 2936, 1792, 1719, 1641; ^{1}H NMR (400 MHz, DMSO-d_6) 1.25 & 1.46 (9H, s, $C(CH_3)_3$), 4.19 (2H, d_{app}, J = 6.1 Hz, N-CH_2), 5.10-5.17 (1H, m, allyl C-H^{trans}), 5.27 (1H, dd, J = 17.3, 1.3 Hz, allyl C-H^{cis}), 5.78-5.93 (1H, m, allyl C-H), 7.93-8.02 (4H, m, H-4/5/6/7); ^{13}C NMR (100 MHz, DMSO-d_6) 27.9 ($C(CH_3)_{3\text{-major}}$), 28.1 ($C(CH_3)_{3\text{-minor}}$), 51.7 (N-$CH_{2\text{-major}}$), 53.7 (N-$CH_{2\text{-minor}}$), 82.1 ($C(CH_3)_{3\text{-major}}$), 82.8 ($C(CH_3)_{3\text{-minor}}$), 119.1 (allyl-$CH_{2\text{-major}}$), 119.7 (allyl-$CH_{2\text{-minor}}$), 124.3, 124.4, 129.5, 129.6, 132.8 (Ar-C), 133.3 (Ar-C), 135.9 (Ar-C), 136.0 (Ar-C), 153.0 ($C{=}O_{\text{-major}}$), 153.1 ($C{=}O_{\text{-minor}}$), 165.3 ($C{=}O_{\text{-major}}$), 165.5 ($C{=}O_{\text{-minor}}$).

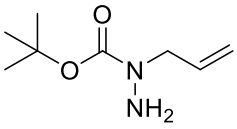


Synthesis of tert-butyl (1,3-dioxoisoindolin-2-yl)(4-methoxybenzyl)carbamate (6). Diethyl azodicarboxylate (45 µL, 0.29 mmol) in dry THF (0.5 mL) was added dropwise over 10 minutes to a solution of tert-butyl (1,3-dioxoisoindolin-2-yl)carbamate (**3**, 50 mg, 0.19 mmol), 4-methoxybenzyl alcohol (72 uL, 0.57 mmol) and triphenylphosphine (75 mg, 0.29 mmol) in dry THF (1 mL) at RT. The mixture was stirred for 16 h at RT before being concentrated *in vacuo* and the residue triturated in EtOAc (2 mL) and stored at 4°C overnight. The precipitated PPh_3O was removed by filtration and the filtrate was concentrated and purified on silica gel (3:1 Hexanes:EtOAc) to give the target compound as a pale orange solid observed to be a pair of rotamers by NMR (65 mg, 0.17 mmol, 89%). Rf 0.42 (3:1 Hexanes:EtOAc); M.p. 106-108°C; IR (cm^{-1}) 3003, 2979, 2962, 2934, 2836, 1793, 1737, 1715, 1610, 1511; ^{1}H NMR (400 MHz, $CDCl_3$) 1.37 (5.4H, s, $C(CH_3)_{3\text{-major}}$), 1.55 (3.6H, s, $C(CH_3)_{3\text{-minor}}$), 3.77 (1.8H, s, $OCH_{3\text{-major}}$), 3.78 (1.2H, s, $OCH_{3\text{-minor}}$), 4.80 (0.8H, s, benzyl $CH_{2\text{-minor}}$), 4.83 (1.2H, s, benzyl $CH_{2\text{-major}}$), 6.82 (2H, dd, J = 10.0, 8.5 Hz, H-4/7), 7.31 (2H, dd, J = 10.0, 8.5 Hz, H-5/6), 7.72-7.77 (2H, m, benzyl H-3/5), 7.80-7.86 (2H, m, benzyl H-2/6); ^{13}C NMR (100 MHz, $CDCl_3$) 27.9 ($C(CH_3)_{3\text{-major}}$), 28.2 ($C(CH_3)_{3\text{-minor}}$), 52.0 (benzyl-$CH_{2\text{-major}}$), 53.9 (benzyl-$CH_{2\text{-minor}}$), 55.2 (OCH_3), 82.4 ($C(CH_3)_{3\text{-major}}$), 83.2 ($C(CH_3)_{3\text{-minor}}$), 113.7 (Ar-C), 123.7 (Ar-C), 127.1 (Ar-C), 129.8 (Ar-C), 130.0 (Ar-C), 130.5 (Ar-C), 134.5 (Ar-C), 153.5 ($C{=}O_{\text{minor}}$), 159.3 ($C{=}O_{\text{major}}$), 165.0 ($C{=}O_{\text{major}}$), 165.4 ($C{=}O_{\text{minor}}$); MS $[M+NH_4]^+$ m/z 400.2.

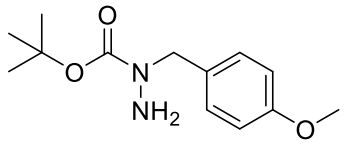
General procedure for the removal of phthlalimide protecting groups (7-9). Methylhydrazine (1.25 equiv.) was added to an ice cooled solution of phthalimide **4-6** (1.0 equiv.) in THF (2 mL/mmol). The reaction mixture was allowed to warm to RT and was stirred for 18 h. The resultant suspension was passed through a filter, and the filtrate was concentrated *in vacuo*. A mixture of Hexanes:EtOAc (3:1, 1 mL/mmol) was added, and the precipitate formed was removed *via* filtration. This process was repeated a further 2 times, and the final filtrate was concentrated to give the target compound.



Synthesis of tert-butyl 1-methylhydrazine-1-carboxylate (7). Methylhydrazine (198 µL, 3.77 mmol) and tert-butyl (1,3-dioxoisoindolin-2-yl)(methyl)carbamate (**4**, 0.833 g, 3.01 mmol) were reacted in THF (6 mL) according to the described general procedure. The target compound was obtained as a pale-yellow oil (0.338 g, 2.31 mmol, 77%). Rf 0.20 (1:1 Hexanes:EtOAc); IR (cm^{-1}) 3247, 2924, 2854, 1697, 1640, 1568; ^{1}H NMR (400 MHz, $CDCl_3$) 1.47 (9H, s, $C(CH_3)_3$), 3.05 (3H, s, $N\text{-}CH_3$), 4.10 (2H, br s, NH_2).

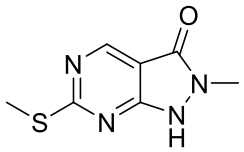


Synthesis of *tert*-butyl 1-allylhydrazine-1-carboxylate (8). Methylhydrazine (3.40 mL, 64.3 mmol) and *tert*-butyl allyl(1,3-dioxoisoindolin-2-yl)carbamate (**5**, 15.6 g, 51.5 mmol) were reacted in THF (100 mL) according to the described general procedure. The target compound was obtained as a pale-yellow oil (8.47 g, 49.2 mmol, 96%). Rf 0.22 (4:1 Hexane:EtOAc); IR (cm^{-1}) 3336, 2977, 2932, 1690; ^{1}H NMR (400 MHz, DMSO-d_6) 1.40 (9H, s, $-C(CH_3)_3$), 3.85 (2H, ddd, J = 5.5, 1.4, 1.4 Hz, $N\text{-}CH_2$), 4.46 (2H, s, NH_2), 5.06-5.09 (1H, m, allyl $C\text{-}H^{trans}$), 5.11 (1H, br, allyl $C\text{-}H^{cis}$), 5.74-5.86 (1H, m, allyl C-H); ^{13}C NMR (125 MHz, DMSO-d_6) 28.5 ($C(CH_3)_3$), 53.6 ($N\text{-}CH_2$), 79.4 ($C(CH_3)_3$), 116.2 (allyl-CH_2), 134.6 (allyl-CH), 156.5 (C=O).

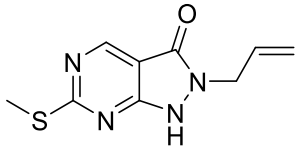


Synthesis of tert-butyl 1-(4-methoxybenzyl)hydrazine-1-carboxylate (9). Methylhydrazine (80 µL, 1.80 mmol) and tert-butyl (1,3-dioxoisoindolin-2-yl)(4-methoxybenzyl)carbamate (**6**, 0.470 g, 1.44 mmol) were reacted in THF (3 mL) according to the described general procedure. Following purification on silica gel (4:1 Hexanes:EtoAc) the target compound was obtained as a pale yellow oil (0.275 g, 1.09 mmol, 76%). Rf 0.24 (4:1 Hexane:EtOAc); IR (cm^{-1}) 3336, 2975, 2933, 2836, 1688, 1612, 1511; ^{1}H NMR (400 MHz, $CDCl_3$) 1.51 (9H, s, $C(CH_3)_3$), 3.81 (3H, s, OCH_3), 4.04 (2H, br s, NH_2), 4.50 (2H, s, $N\text{-}CH_2$), 6.88 (2H, d, *J* = 8.4 Hz, H-3/5), 7.24 (2H, d, *J* = 8.4 Hz, H-2/6); ^{13}C NMR (100 MHz, $CDCl_3$) 28.5 ($C(CH_3)_3$), 53.7 (OCH_3), 55.3 (NCH_2), 80.7 ($C(CH_3)_3$), 113.9 (Ar-C), 129.3 (Ar-C), 130.0 (Ar-C), 156.8 (Ar-C), 159.0 (C=O); MS $[M+H]^+$ *m*/*z* 253.2.

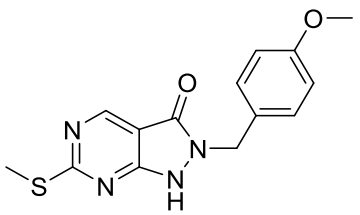
General procedure for the synthesis of pyrazolopyrimidinones (11-13). DIPEA (2.5 equiv.) and the relevant hydrazine **7**-**9** (1.05 equiv.) were added to a solution of ethyl 4-chloro-2-methylthio-5-pyrimidinecarboxylate (**10**; 1.0 equiv.) in THF (3 mL/mmol). The reaction mixture was heated at reflux for 72 h, before being concentrated *in vacuo*. Et_2O (1 mL/mmol) was added to the residue, and the resultant precipitate was collected by filtration. The filtrate was evaporated to dryness, and the residue was cooled in an ice bath, after which TFA (1 mL/mmol) was added. The resultant solution was stirred at RT for 1 h, followed by 70°C for 1 h. The solvent was removed *in vacuo* and the residue was dissolved in EtOH (1 mL/mmol) and cooled in an ice bath, after which 6M NaOH (2 mL/mmol) was added. The resultant solution was stirred at RT for 15 min, before being acidified (pH 3) *via* the addition of conc. HCl. The solution was evaporated to dryness and the resultant residue was partitioned between chloroform (2 mL/mmol) and water (2 mL/mmol), and the organic phase was washed with brine (1 mL/mmol), dried ($MgSO_4$), and concentrated *in vacuo* to afford the target compound.



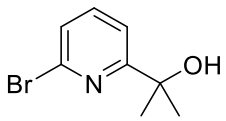
Synthesis of 1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-2-methyl-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (11). Ethyl 4-chloro-2-methylthio-5-pyrimidinecarboxylate (**10**, 0.480 g, 2.06 mmol), *tert*-butyl 1-methylhydrazine-1-carboxylate (**7**, 0.316 g, 2.16 mmol) and DIPEA (1.87 mL, 10.7 mmol) were reacted in THF (6 mL) according to the described general procedure. Purification on KP-NH silica (4:1 DCM:MeOH) yielded the desired compound as a yellow solid (0.302 g, 1.54 mmol, 75%). Rf 0.23 (4:1 DCM:MeOH); M.p. 256-265°C (decomposed); IR (cm^{-1}) 3336, 3024, 2940, 1683, 1638, 1587; ^{1}H NMR (400 MHz, DMSO-d_6) 2.53 (3H, s, SCH_3), 3.36 (3H, s, N^2-CH_3), 8.68 (1H, s, H-4), 12.60 (1H, br s, N^1-H); ^{13}C NMR (100 MHz, DMSO-d_6) 13.9 (SCH_3), 31.0 (N^2-CH_3), 103.8, 158.1; MS $[M+H]^+$ *m*/*z* 196.8.



Synthesis of 2-allyl-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (12). Ethyl 4-chloro-2-methylthio-5-pyrimidinecarboxylate (**10**, 11.1 g, 47.8 mmol), *tert*-butyl 1-allylhydrazine-1-carboxylate (**8**, 8.64 g, 50.2 mmol) and DIPEA (20.8 mL, 120 mmol) were reacted in THF (150 mL) according to the described general procedure. Trituration with hexanes afforded the target compound as a yellow solid (5.44 g, 24.5 mmol, 51%). Rf 0.45 (9:1 DCM:MeOH); M.p. 125-128°C; IR (cm^{-1}) 3032, 2979, 2926, 2659, 1656, 1615, 1566, 1514; ^{1}H NMR (400 MHz, DMSO-d_6) 2.53 (3H, s, SCH_3), 4.38 (2H, d_{app}, J = 5.2 Hz, N^2-CH_2), 5.06-5.20 (2H, m, allyl C-$H^{cis/trans}$), 5.87 (1H, ddt, J = 17.2, 10.5, 5.3 Hz, alkene C-H), 8.67 (1H, s, H-4), 12.65 (1H, br, N^1-H); MS $[M+H]^+$ *m*/*z* 223.1.



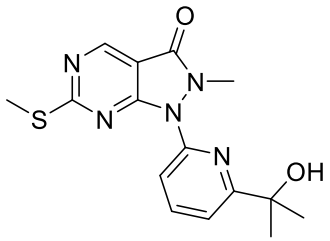
Synthesis of 2-(4-methoxybenzyl)-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (13). DIPEA (806 µL, 4.63 mmol) was added to a solution of ethyl 4-chloro-2-methylthio-5-pyrimidinecarboxylate (0.207 g, 0.89 mmol) and tert-butyl 1-(4-methoxybenzyl)hydrazine-1-carboxylate (**10**, 0.235 g, 0.94 mmol) in THF (3 mL) and the reaction mixture was heated at reflux for 72 h. The solvent was removed *in vacuo* and the residue was partitioned between DCM (20 mL) and 0.1M HCl (15 mL) and the organic phase was washed with brine (10 mL) and dried ($MgSO_4$) before being concentrated *in vacuo*. The residue was dissolved in DCM (4 mL) and TFA (1.37 mL, 17.8 mmol) was added, with stirring at RT for 18 h. The solvent was removed *in vacuo* and the residue was taken up in DCM (20 mL) and washed with sat. $NaHCO_3$ (3 x 15 mL). The organic extract was washed with brine (10 mL) and dried ($MgSO_4$) before being evaporated to dryness. The residue was suspended in 0.5M NaOH (10 mL), and the mixture was refluxed with rapid stirring until the yellow oil residue entered solution after approximately 4 h. The solution was acidified to pH 2 (2M HCl), extracted with EtOAc (2 x 20 mL) before being dried ($MgSO_4$) and evaporated to dryness. The resultant residue was purified by chromatography on silica gel (9:1 DCM:MeOH) to afford the desired compound as a yellow solid (0.142 g, 0.47 mmol, 50%). Rf 0.41 (9:1 DCM:MeOH); M.p. 209-212°C; IR (cm^{-1}) 3034, 2930, 1609, 1577, 1510; ^{1}H NMR (400 MHz, $CDCl_3$) 2.53 (3H, s, SCH_3), 3.78 (3H, s, OCH_3), 5.03 (2H, s, N^2-CH_2), 6.84 (2H, d, *J* = 8.5 Hz, benzyl H-3/5), 7.28 (2H, d, *J* = 8.5 Hz, benzyl H-2/6), 8.66 (1H, s, H-4); ^{13}C NMR (100 MHz, DMSO-d_6) 13.8 (SCH_3), 46.8 (N^2-CH_2), 55.5 (OCH_3), 103.7, 114.0, 114.1, 114.3, 129.5, 130.5, 158.3, 159.1; MS $[M+H]^+$ *m*/*z* 303.2.



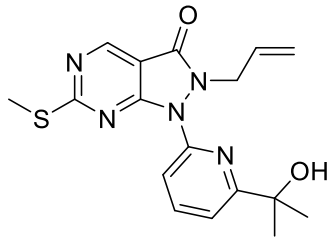
Synthesis of 2-(6-bromopyridin-2-yl)propan-2-ol (14). Methylmagnesium iodide (3M in Et_2O, 1.50 ml, 4.48 mmol) was added to a solution of methyl 6-bromopyridine-2-carboxylate (0.430 g, 1.99 mmol) in dry Et_2O (15 ml) under N_2. After 5 min at RT the reaction was quenched with 1M HCl (10 ml) and extracted with EtOAc (15 ml). The organic extract was washed with sat. $NaHCO_3$ solution (15 ml) and brine (10 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The desired product was obtained as a yellow oil (0.365 g, 1.69 mmol, 85%). Rf 0.60 (1:1 Hexane:EtOAc); IR (cm^{-1}) 3420, 2975, 2930, 1731, 1701, 1580, 1553; ^{1}H NMR (400 MHz, DMSO-d_6) 1.42 (6H, s, $C(CH_2)_2$), 5.33 (1H, s, OH), 7.47 (1H, dd, *J* = 7.7, 0.9 Hz, H-5), 7.67 (1H, dd, *J* = 7.7, 0.9 Hz, H-3), 7.73 (1H,

dd, *J* = 7.7, 7.7 Hz, H-4); ^{13}C NMR (100 MHz, DMSO-d_6) 30.9 (C(CH$_2$)$_2$), 72.6 (C(CH$_2$)$_2$), 118.5 (Ar-C), 126.0 (Ar-C), 140.4 (Ar-C), 140.5 (Ar-C), 170.8 (Ar-C).

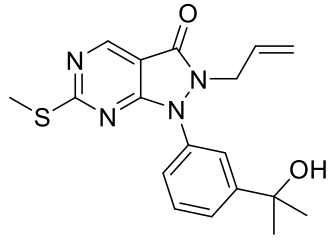
General procedure for the preparation of pyridyl pyrazolopyrimidinones (17-21). *N*,*N*'-Dimethylethylenediamine (2.0 equiv.) was added to a solution of the relevant pyrazolopyrimidinone **11-13** (1.0 equiv.), the relevant bromopyridine (**14-16,** 1.3 equiv.), copper iodide (1.0 equiv.) and K_2CO_3 (1.4 equiv.) in 1,4-dioxane (2 mL/mmol) at 80°C. The resultant suspension was heated at 95°C for 18 h, over which time a color change of orange to dark green occurred. The reaction mixture was cooled to RT and diluted with NH_4OH (10 mL/mmol) before being extracted with EtOAc (2 x 10 mL/mmol). The combined organic extracts were washed with brine (10 mL/mmol), dried ($MgSO_4$) and evaporated to dryness before the crude material was purified *via* chromatography on silica.



Synthesis of 1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-2-methyl-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (17). 1-(6-(2-Hydroxypropan-2-yl)pyridin-2-yl)-2-methyl-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (**11**, 0.177 g, 0.90 mmol), 2-(6-bromopyridin-2-yl)propan-2-ol (**14**, 0.253 g, 1.17 mmol), copper iodide (0.172 g, 0.90 mmol), K_2CO_3 (0.174 g, 1.26 mmol) and *N*,*N*'-dimethylethylenediamine (194 µL, 1.80 mmol) were reacted in 1,4-dioxane (2 mL) according to the described general procedure. Purification on silica gel (19:1 DCM:MeOH) gave the desired compound as a white solid (0.215 g, 0.65 mmol, 72%). Rf 0.34 (19:1 DCM:MeOH); M.p. 155-158°C; IR (cm^{-1}) 3432, 2973, 2928, 1683, 1604, 1562; ^{1}H NMR (400 MHz, DMSO-d_6) 1.46 (6H, s, C(CH$_3$)$_2$), 2.56 (3H, s, SCH$_3$), 3.49 (3H, s, N^2-CH$_3$), 5.35 (1H, s, OH), 7.67 (1H, d$_{app}$, *J* = 7.7 Hz, H-5'), 7.79 (1H, d$_{app}$, *J* = 8.2 Hz, H-3'), 8.06 (1H, dd$_{app}$, *J* = 8.2, 7.7 Hz, H-4'), 9.00 (1H, s, H-4); ^{13}C NMR (100 MHz, DMSO-d_6) 14.4 (SCH$_3$), 30.9 (C(CH$_3$)$_2$), 32.8 (N^2-CH$_3$), 72.8 (C(CH$_3$)$_2$), 104.8, 116.6, 117.5, 139.7, 146.8, 154.7, 158.3, 160.4, 168.4, 175.9; MS [M+H]$^+$ *m*/*z* 332.6.

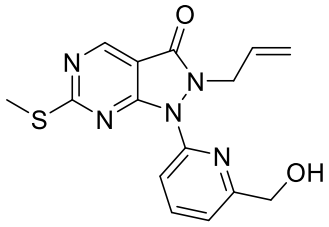


Synthesis of 2-allyl-1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (18). 2-Allyl-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (**12**, 0.500 g, 2.25 mmol), 2-(6-bromopyridin-2-yl)propan-2-ol (**14**, 0.643 g, 2.93 mmol), copper iodide (0.428 g, 2.25 mmol), K_2CO_3 (0.435 g, 3.15 mmol) and *N*,*N*'-dimethylethylenediamine (266 µL, 4.47 mmol) were reacted in 1,4-dioxane (5 mL) according to the described general procedure. Purification on silica gel (1:1 Hexanes:EtOAc) gave the desired compound as a white solid (0.653 g, 1.82 mmol, 81%). Rf 0.63 (9:1 DCM:MeOH); M.p. 108-111°C; IR (cm^{-1}) 3337, 3081, 2966, 2924, 1663, 1601, 1559; ^{1}H NMR (400 MHz, $CDCl_3$) 1.61 (6H, s, $C(CH_3)_2$), 2.61 (3H, s, S-CH_3), 3.77 (1H, s, OH), 4.82 (2H, d_{app}, *J* = 5.9 Hz, N^2-CH_2), 4.95 (1H, d_{app}, *J* = 16.9 Hz, alkene C-H^{trans}), 5.08 (1H, d_{app}, *J* = 10.3 Hz, alkene C-H^{cis}), 5.72 (1H, ddt, *J* = 16.9, 10.3, 5.9 Hz, alkene C-H), 7.42 (1H, d_{app}, *J* = 7.7 Hz, H-5'), 7.78 (1H, d_{app}, *J* = 8.0 Hz, H-3'), 7.93 (1H, dd, *J* = 8.0, 7.7 Hz, H-4'), 8.96 (1H, s, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) 14.5 (SCH_3), 30.5 ($C(CH_3)_2$), 47.5 (N^2-CH_2), 72.5 ($C(CH_3)_2$), 116.4 (Ar-C), 116.6 (Ar-C), 119.3 (allyl-CH_2), 131.2, 139.2, 147.0 (Ar-C), 154.3 (Ar-C), 159.2 (C=O), 161.0 (Ar-C), 166.1 (Ar-C), 177.0 (Ar-C); MS $[M+H]^+$ *m*/*z* 359.3.

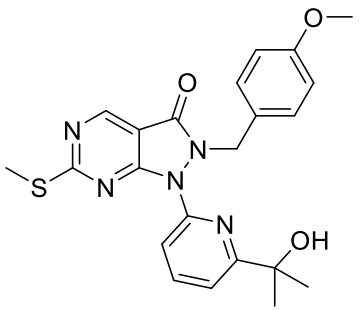


Synthesis of 2-allyl-1-(3-(2-hydroxypropan-2-yl)phenyl)-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (19). 2-Allyl-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (**12**, 0.200 g, 0.90 mmol), 2-(3-bromophenyl)propan-2-ol (0.252 g, 1.17 mmol), copper iodide (0.171 g, 0.90 mmol), K_2CO_3 (0.175 g, 1.26 mmol) and *N*,*N*'-dimethylethylenediamine (194 µL, 1.80 mmol) were reacted in 1,4-dioxane (2 mL) according to the described general procedure. Purification on silica gel (19:1 DCM:MeOH) gave the desired

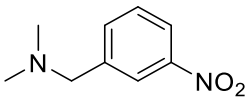
compound as a colorless oil (0.245 g, 0.68 mmol, 76%). Rf 0.26 (19:1 DCM:MeOH); IR (cm^{-1}) 3400, 3077, 2973, 2928, 2871, 1676, 1594, 1561; ^{1}H NMR (400 MHz, $CDCl_3$) 1.64 (6H, s, $C(CH_3)_2$), 2.51 (3H, s, SCH_3), 4.45 (2H, d_{app}, J = 6.0 Hz, N2-CH_2), 4.99 (1H, d_{app}, J = 17.0, allyl C-H^{trans}), 5.14 (1H, d_{app}, J = 10.2 Hz, allyl C-H^{cis}), 5.71 (1H, ddt, J = 17.0, 10.2, 6.0 Hz, allyl C-H), 7.29 (1H, d_{app}, J = 7.2 Hz, H-6'), 7.47-7.56 (2H, m, H-4'/5'), 7.58 (1H, s_{app}, H-2'), 8.92 (1H, s, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) 14.3 (SCH_3), 31.9 ($C(CH_3)_2$), 46.2 (N^2-CH_2), 72.3 ($C(CH_3)_2$), 104.1, 119.4, 121.5, 123.2, 124.3, 129.3, 130.8, 135.4, 151.1, 154.3, 160.4, 161.6, 177.0; MS $[M+H]^+$ *m*/*z* 357.2.



Synthesis of 2-allyl-1-(6-(hydroxymethyl)pyridin-2-yl)-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (20). 2-Allyl-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (**12**, 0.200 g, 0.90 mmol), (6-bromopyridin-2-yl)methanol (0.220 g, 1.17 mmol), copper iodide (0.171 g, 0.90 mmol), K_2CO_3 (0.174 g, 1.26 mmol) and *N*,*N*'-dimethylethylenediamine (194 µL, 1.80 mmol) were reacted in 1,4-dioxane (2 mL) according to the described general procedure. Purification on silica gel (19:1 DCM:MeOH) gave the desired compound as a white solid (0.201 g, 0.61 mmol, 68%). Rf 0.23 (19:1 DCM:MeOH); M.p. 105-107°C; IR (cm^{-1}) 3361, 3239, 2924, 2838, 1695, 1666, 1590, 1559; ^{1}H NMR (400 MHz, $CDCl_3$) 2.60 (3H, s, SCH_3), 3.04 (1H, br, OH), 4.76-4.86 (4H, m, N^2-CH_2/CH_2OH), 4.97 (1H, d_{app}, J = 17.1, allyl C-H^{trans}), 5.09 (1H, d_{app}, J = 10.3 Hz, allyl C-H^{cis}), 5.73 (1H, ddt, J = 17.1, 10.3, 6.2 Hz, allyl C-H), 7.30 (1H, d_{app}, J = 8.0 Hz, H-5'), 7.80 (1H, d_{app}, J = 8.1 Hz, H-3'), 7.92 (1H, dd_{app}, J = 8.1, 8.0 Hz, H-4'), 8.96 (1H, s, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) 14.5 (SCH_3), 47.5 (N^2-CH_2), 64.4 (CH_2OH), 104.5, 117.0, 118.4, 119.3, 131.2, 138.9, 147.8, 154.3, 159.2, 161.0, 177.0; MS $[M+H]^+$ *m*/*z* 330.0.

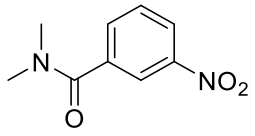


Synthesis of 1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-2-(4-methoxybenzyl)-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (21). 2-(4-Methoxybenzyl)-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (**13**, 80 mg, 0.26 mmol), 2-(6-bromopyridin-2-yl)propan-2-ol (**14**, 74 mg, 0.34 mmol), copper iodide (50 mg, 0.26 mmol), K_2CO_3 (50 mg, 0.37 mmol) and *N*,*N*'-dimethylethylenediamine (57 µL, 0.53 mmol) were reacted in 1,4-dioxane (1 mL) according to the described general procedure. Purification on silica gel (1:1 Hexanes:EtOAc) gave the desired compound as an off-white solid (84 mg, 0.19 mmol, 74%). Rf 0.26 (1:1 Hexanes:EtOAc); M.p. 143-145°C; IR (cm^{-1}) 3349, 2972, 2929, 2829, 1691, 1601, 1560; ^{1}H NMR (400 MHz, $CDCl_3$) 1.65 (6H, s, $C(CH_3)_2$), 2.55 (3H, s, SCH_3), 3.73 (3H, s, OCH_3), 5.34 (2H, s, N^2-CH_2), 6.68 (2H, d, *J* = 8.4 Hz, benzyl H-3/5), 6.83 (2H, d, *J* = 8.4 Hz, benzyl H2/6), 7.44 (1H, d_{app}, *J* = 7.5 Hz, H-5'), 7.56 (1H, d_{app}, *J* = 8.0 Hz, H-3'), 7.87 (1H, dd_{app}, *J* = 8.0, 7.5 Hz, H-4'), 8.95 (1H, s, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) 14.4 (SCH_3), 30.6 ($C(CH_3)_2$), 47.9 (N^2-CH_2), 55.2 (OCH_3), 72.6 ($C(CH_3)_2$), 104.5, 114.0, 116.6, 127.3, 129.4, 139.2, 146.9, 154.3, 158.9, 159.4, 161.3, 166.1, 176.9; MS $[M+H]^+$ *m*/*z* 438.2.

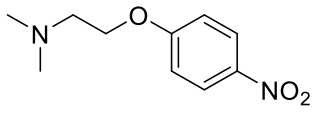


Synthesis of *N,N*-dimethyl-1-(3-nitrophenyl)methanamine (36). Triethylamine (1.94 mL, 13.8 mmol) was added dropwise to a solution of 3-nitrobenzylbromide (1.00 g, 4.63 mmol) and dimethylamine hydrochloride (0.755 g, 9.26 mmol) in DCM (10 mL). The resultant mixture was stirred at RT for 2 h, before being evaporated to dryness and the residue partitioned between EtOAc (50 mL) and water (30 mL). The organic phase was washed with brine (20 mL) and dried ($MgSO_4$), before being evaporated to dryness to give the target compound as a yellow oil (0.601 g, 3.34 mmol, 72%). Rf 0.28 (1:1 Hexanes:EtOAc); IR (cm^{-1}) 2976, 2944, 2859, 2820, 2774, 1523;

^{1}H NMR (400 MHz, $CDCl_3$) 2.28 (6H, s, $N(CH_3)_2$), 3.53 (2H, s, $ArCH_2$), 7.51 (1H, dd, *J* = 8.0, 7.9 Hz, H-5), 7.68 (1H, d_{app}, *J* = 7.9 Hz, H-6), 8.13 (1H, dd, *J* = 8.0, 2.0 Hz, H-4), 8.21 (1H, s_{app}, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) 45.4 ($N(CH_3)_2$), 63.4 (NCH_2), 122.2 (Ar-C), 123.7 (Ar-C), 129.2 (Ar-C), 135.0 (Ar-C), 141.4 (Ar-C), 148.4 (Ar-C).



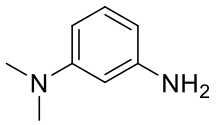
Synthesis of *N,N*-dimethyl-3-nitrobenzamide (37). 1,1'-Carbonyldiimidazole (0.970 g, 5.98 mmol) and DIPEA (1.56 mL, 8.97 mmol) were added to a solution of 3-nitrobenzoic acid (0.500 g, 2.99 mmol) in dry DMF (20 mL). After stirring at RT for 2 h, dimethylamine hydrochloride (0.487 g, 5.98 mmol) was added and the resultant mixture was stirred at RT for a further 16 h. The solvent was removed *in vacuo* and the residue was dissolved in EtOAc (40 mL) and washed with saturated $NaHCO_3$ solution (30 mL) and 0.1M HCl (20 mL), followed by brine (20 mL) and drying ($MgSO_4$). The solvent was evaporated under vacuum to afford the desired compound as a pale-yellow oil/low-melting solid (0.468 g, 2.41 mmol, 81%). Rf 0.23 (1:1 Hexanes:EtOAc); IR (cm^{-1}) 3081, 3027, 2929, 2869, 1625, 1527; ^{1}H NMR (400 MHz, $CDCl_3$) 3.01 (3H, s, NCH_3), 3.14 (3H, s, NCH_3), 7.62 (1H, dd_{app}, *J* = 8.0, 7.8 Hz, H-5), 7.77 (1H, ddd, *J* = 7.8, 1.3, 1.2 Hz, H-6), 8.24-8.29 (2H, m, H-2/4); ^{13}C NMR (100 MHz, $CDCl_3$) 35.5 (NCH_3), 39.5 (NCH_3), 112.3 (Ar-C), 124.4 (Ar-C), 129.7 (Ar-C), 133.1 (Ar-C), 137.9 (Ar-C), 148.0 (Ar-C), 168.9 (C=O).



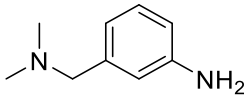
Synthesis of *N,N*-dimethyl-2-(4-nitrophenoxy)ethan-1-amine (38). K_2CO_3 (2.81 g, 2.03 mmol) and dimethylamine hydrochloride (1.65 g, 2.03 mmol) were added to a solution of 1-(2-bromoethoxy)-4-nitrobenzene (1.00 g, 4.10 mmol) in dry MeCN (3 mL) and the mixture was heated in a sealed tube at 80°C for 2 h. The solvent was removed *in vacuo* and the crude residue was partitioned between DCM (50 mL) and water (50 mL). The organic phase was washed with water (50 mL) and brine (20 mL) before being dried ($MgSO_4$) and evaporated to dryness. The

target compound was obtained as a yellow oil (0.860 g, 4.09, 100%). Rf 0.27 (19:1 DCM:MeOH); IR (cm^{-1}) 3114, 3084, 2945, 2824, 2774, 1737, 1591, 1508; ^{1}H NMR (400 MHz, $CDCl_3$) 2.36 (6H, s, $N(CH_3)_2$), 2.78 (2H, t, J = 5.6 Hz, OCH_2CH_2), 4.17 (2H, t, J = 5.6 Hz, OCH_2CH_2), 6.99 (2H, d, J = 9.2 Hz, H-2/6), 8.20 (2H, d, J = 9.2 Hz, H-3/5); ^{13}C NMR (100 MHz, $CDCl_3$) 45.9 ($N(CH_3)_2$), 57.9 (OCH_2CH_2), 66.8 (OCH_2CH_2), 114.5 (Ar-C), 125.9 (Ar-C), 141.6 (Ar-C), 163.8 (Ar-C).

General procedure for the reduction of aromatic nitro groups with iron powder. Iron powder (10.0 equiv.) was added to a solution of the relevant nitro aromatic (1.0 equiv.) in acetic acid (5 mL/mmol). The reaction mixture was stirred at 50°C for 1 h, before being filtered through celite. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc (10 mL/mmol) and washed with saturated $NaHCO_3$ solution (2 x 10 mL/mmol). The organic phase was washed with water (10 mL/mmol) and brine (5 mL/mmol) before being dried ($MgSO_4$) and concentrated *in vacuo*. The material was purified *via* chromatography if necessary.

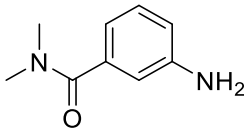


Synthesis of N^1,N^1-dimethylbenzene-1,3-diamine (39). *N,N*-Dimethyl-3-nitroaniline (0.500 g, 3.01 mmol) and iron powder (1.68 g, 30.1 mmol) were reacted in acetic acid (15 mL) according to the described general procedure. Purification on silica gel (1:1 Hexanes:EtOAc) afforded the target compound as a red oil (0.328 g, 2.40 mmol, 80%). Rf 0.44 (1:1 Hexanes:EtOAc); IR (cm^{-1}) 3343, 3220, 2878, 2800, 1606, 1579, 1501; ^{1}H NMR (400 MHz, $CDCl_3$) 2.94 (6H, s, $N(CH_3)_2$), 3.62 (2H, br s, NH_2), 6.10-6.16 (2H, m, H-2/6), 6.24 (1H, dd, J = 8.1, 2.3 Hz, H-4), 7.07 (1H, dd, J = 8.1, 7.9 Hz, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) 40.6 ($N(CH_3)_2$), 99.6 (Ar-C), 103.8 (Ar-C), 104.3 (Ar-C), 129.9 (Ar-C), 147.3 (Ar-C), 151.9 (Ar-C).

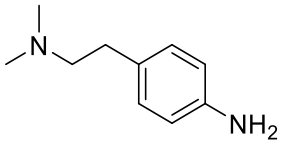


Synthesis of 3-((dimethylamino)methyl)aniline (40). *N,N*-dimethyl-1-(3-nitrophenyl)-methanamine (**36**, 0.579 g, 3.21 mmol) and iron powder (1.79 g, 32.1 mmol) were reacted in acetic acid (16 mL) according to the described general procedure. Purification on silica gel (19:1 DCM:MeOH) afforded the target compound as a pale red oil (0.347 g, 2.31 mmol, 72%). Rf 0.16 (19:1 DCM:MeOH); IR (cm^{-1}) 3270, 3147, 3079, 2974, 2942, 2858, 2816, 2774, 1666, 1610, 1552;

^{1}H NMR (400 MHz, $CDCl_3$) 2.26 (6H, s, $N(CH_3)_2$), 3.35 (2H, s, $ArCH_2$), 3.65 (2H, br s, NH_2), 6.59-6.62 (1H, m, H-4), 6.69-6.72 (2H, m, H-2/6), 7.12 (1H, dd, *J* = 8.0, 7.9 Hz, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) 45.3 ($N(CH_3)_2$), 64.1 ($ArCH_2$), 118.9 (Ar-C), 120.5 (Ar-C), 125.0 (Ar-C), 128.9 (Ar-C), 138.1 (Ar-C), 139.6 (Ar-C).

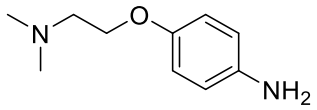


Synthesis of 3-amino-*N,N*-dimethylbenzamide (41). *N,N*-dimethyl-3-nitrobenzamide (**37**, 0.455 g, 2.34 mmol) and iron powder (1.31 g, 23.4 mmol) were reacted in acetic acid (12 mL) according to the described general procedure. Purification on silica gel (1:1 Hexanes:EtOAc) afforded the target compound as an off-white solid (0.327 g, 1.99 mmol, 85%). Rf 0.26 (19:1 DCM:MeOH); M.p. 87-89°C; IR (cm^{-1}) 3419, 3345, 3240, 2928, 2850, 1649, 1579; ^{1}H NMR (400 MHz, $CDCl_3$) 2.99 (3H, s, NCH_3), 3.11 (3H, s, NCH_3), 3.76 (2H, br s, NH_2), 6.68-6.80 (3H, m, H-2/4/6), 7.18 (1H, dd, J = 7.7, 7.6 Hz, H-5); ^{13}C NMR (100 MHz, $CDCl_3$) 35.2 (NCH_3), 39.5 (NCH_3), 113.5 (Ar-C), 116.0 (Ar-C), 116.9 (Ar-C), 129.2 (Ar-C), 137.5 (Ar-C), 146.6 (Ar-C), 171.8 (C=O).



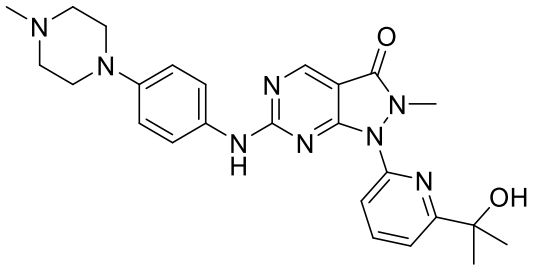
Synthesis of 4-(2-(dimethylamino)ethyl)aniline (42). To a solution of 4-nitrophenethyl bromide (1.02 g, 4.35 mmol) and dimethylamine hydrochloride (1.46 g, 17.4 mmol) in dry DCM (10 mL) was added triethylamine dropwise (3.00 mL, 21.5 mmol) and the reaction was stirred at RT for 16 h. The reaction mixture was concentrated *in vacuo* before the sample was partitioned between EtOAc (40 mL) and H_2O (30 mL). The aqueous phase was extracted with EtOAc (2 x 40 mL), and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude nitro aromatic was dissolved in MeOH (30 mL) to which palladium on carbon was added (10% Pd, 0.150 g) and the mixture was stirred under H_2 at RT for 16 h. The catalyst was removed over celite and the solvent removed under reduced pressure. Purification of the crude material on silica gel (9:1 DCM:MeOH) yielded the target compound as a yellow oil (0.422 g, 2.57 mmol, 59% - 2 steps). Rf 0.16 (9:1 DCM:MeOH); IR (cm^{-1}) 3317, 3018, 2771, 2705, 2448, 1612, 1518; ^{1}H NMR (400 MHz, $CDCl_3$) 2.33 (6H, s, $N(CH_3)_2$), 2.50-2.55 (2H, m, $ArCH_2CH_2$), 2.68-2.73 (2H, m,

$ArCH_2CH_2$), 3.55 (2H, br s, NH_2), 6.65 (2H, d, *J* = 8.5 Hz, H-2/6), 7.01 (2H, d, *J* = 8.5 Hz, H-3/5); ^{13}C NMR (100 MHz, $CDCl_3$) 33.2 ($ArCH_2CH_2$), 45.3 ($N(CH_3)_2$), 61.8 ($ArCH_2CH_2$), 115.3 (Ar-C), 129.4 (Ar-C), 130.0 (Ar-C), 144.2 (Ar-C).

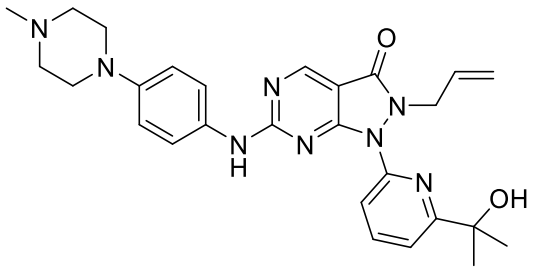


Synthesis of 4-(2-(dimethylamino)ethoxy)aniline (43). Palladium on carbon (10% Pd, 85 mg) was added to a solution of *N,N*-dimethyl-2-(4-nitrophenoxy)ethan-1-amine (**38**, 854 mg, 4.06 mmol) in MeOH (40 mL). The reaction flask was evacuated under vacuum and backflushed with H_2, before being stirred for 16 h at RT under a H_2 atmosphere. The catalyst was removed over celite and the solvent was removed *in vacuo* to afford the target compound as a brown oil (0.673 g, 3.74 mmol, 92%). Rf 0.38 (9:1 DCM:MeOH); IR (cm^{-1}) 3335, 3216, 2943, 2867, 2822, 2774, 1627, 1508; ^1H NMR (400 MHz, $CDCl_3$) 2.35 (6H, s, $N(CH_3)_2$), 2.70 (2H, t, *J* = 5.8 Hz, OCH_2CH_2), 3.47 (2H, br s, NH_2), 4.00 (2H, t, *J* = 5.8 Hz, OCH_2CH_2), 6.64 (2H, d, *J* = 8.8 Hz, H-3/5), 6.78 (2H, d, *J* = 8.8 Hz, H-2/6); ^{13}C NMR (100 MHz, $CDCl_3$) 45.8 ($N(CH_3)_2$), 58.4 (OCH_2CH_2), 66.6 (OCH_2CH_2), 115.8 (Ar-C), 116.4 (Ar-C), 140.1 (Ar-C), 152.0 (Ar-C).

General procedure for the preparation of aniline pyridyl pyrazolopyrimidinones (22-33). mCPBA (1.1 equiv.) was added to a solution of pyrazolopyrimidinones **17-21** (1.0 equiv.) in toluene (10 mL/mmol) and the resulting mixture was stirred at RT for 1 h. DIPEA (5.2 equiv.) and the relevant substituted aniline **39-43** or amine (1.3 equiv.) were added, and the reaction mixture was stirred at RT for 18 h. Saturated $NaHCO_3$ solution (15 mL/mmol) was added, and the mixture was extracted with EtOAc (2 x 20 mL/mmol). The combined organic extracts were washed with brine (5 mL/mmol), dried ($MgSO_4$) and concentrated *in vacuo*. The resultant residues were purified *via* chromatography on silica to give the target compounds (12-89%).

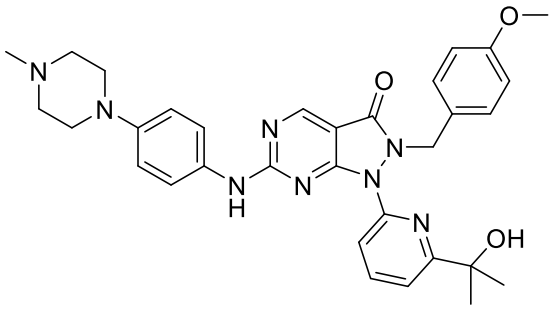


Synthesis of 1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-2-methyl-6-((4-(4-methylpiperazin-1-yl)phenyl)amino)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (32). 1-(6-(2-Hydroxypropan-2-yl)pyridin-2-yl)-2-methyl-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (**17**, 0.101 g, 0.29 mmol), mCPBA (70% w/w, 83 mg, 0.34 mmol), 4-methyl-1-(4-aminophenyl)piperazine (75 mg, 0.40 mmol) and DIPEA (275 µL, 1.58 mmol) were reacted in toluene (3 mL) according to the described general procedure. Purification via silica gel chromatography (9:1 DCM:MeOH) afforded the target compound as a yellow solid (0.16 mmol, 56%). Rf 0.39 (9:1 DCM:MeOH); M.p. 192-195°C; IR (cm^{-1}) 3265, 3184, 3090, 2972, 2928, 2810, 1668, 1619, 1536, 1512; ^{1}H NMR (400 MHz, DMSO-d_6) 1.46 (6H, s, $C(CH_3)_2$), 2.23 (3H, s, $N(CH_2CH_2)_2NCH_3$), 2.44-2.49 (4H, m, $N(CH_2CH_2)_2NMe$), 3.08-3.13 (4H, m, $N(CH_2CH_2)_2NMe$), 3.42 (3H, s, N^2-CH_3), 5.32 (1H, s, OH), 6.93 (2H, d, *J* = 9.0 Hz, H-3''/5''), 7.59 (1H, d_{app}, *J* = 7.9 Hz, H-5'), 7.62 (2H, d, *J* = 9.0 Hz, H-2''/6''), 7.80 (1H, d_{app}, *J* = 7.5 Hz, H-3'), 8.08 (1H, dd, *J* = 7.9, 7.5 Hz, H-4'), 8.81 (1H, s, H-4). 10.11 (1H, br s, C^6-NH); ^{13}C NMR (100 MHz, DMSO-d_6) 30.9 ($C(CH_3)_2$), 33.0 (N^2-CH_3), 46.3 (piperazine N-CH_3), 49.0 (piperazine-CH_2), 55.1 (piperazine-CH_2), 72.8 ($C(CH_3)_2$), 116.0, 116.7, 121.5, 131.4, 139.3, 147.6, 156.2, 160.9, 161.8, 168.1; MS $[M+H]^+$ *m*/*z* 475.2.



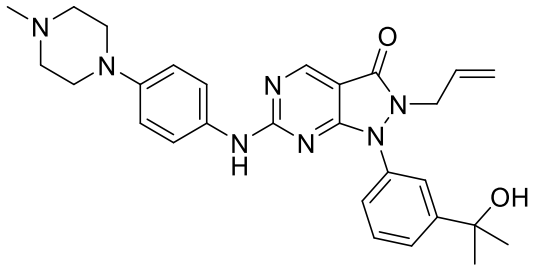
Synthesis of 2-allyl-1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-6-((4-(4-methylpiperazin-1-yl)phenyl)amino)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (AZD-1775). 2-Allyl-1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (**18**, 0.110 g, 0.31 mmol), mCPBA (70% w/w, 76 mg, 0.34 mmol), 4-methyl-1-(4-

aminophenyl)piperazine (77 mg, 0.40 mmol) and DIPEA (270 µL, 1.63 mmol) were reacted in toluene (3 mL) according to the described general procedure. Purification via silica gel chromatography (9:1 DCM:MeOH) afforded the target compound as a yellow solid (87 mg, 0.17 mmol, 55%).Rf 0.25 (9:1 DCM:MeOH); M.p. 170-174°C; IR (cm^{-1}) 3420, 2969, 2810, 2364, 1639, 1602, 1541, 1512; ^{1}H NMR (400 MHz, DMSO-d_6) 1.47 (6H, s, $C(CH_3)_2$), 2.23 (3H, s, N-CH_3), 2.42-2.50 (4H, m, N-(CH_2CH_2)$_2$-NMe), 3.05-3.14 (4H, m, N-CH_2CH_2-NMe), 4.69 (2H, d_{app}, J = 5.9 Hz, N^2-CH_2), 4.83 (1H, dd, J = 17.1, 1.3 Hz, alkene C-H^{trans}), 5.00 (1H, dd, J = 10.3, 1.3 Hz, alkene C-H^{cis}), 5.32 (1H, s, OH), 5.67 (1H, ddt, J = 17.1, 10.3, 5.9 Hz, alkene C-H), 6.93 (2H, d, J = 9.1 Hz, H-3''/5''), 7.54-7.60 (1H, m, H-5'), 7.61 (2H, d, J = 9.1 Hz, H-2''/6''), 7.76 (1H, d_{app}, J = 8.1 Hz, H-3'), 8.06 (1H, dd, J = 8.1, 7.3 Hz, H-4'), 8.83 (1H, s, H-4), 10.1 (1H, br, C^6-NH); ^{13}C NMR (100 MHz, DMSO-d_6) 30.9 ($C(CH_3)_2$), 46.2 (N-CH_3), 47.1 (N^2-CH_2), 48.9 (piperazine-CH_2), 55.1 (piperazine-CH_2), 72.8 ($C(CH_3)_2$), 116.0, 116.7, 118.7, 121.6, 131.3, 132.7, 139.3, 147.6, 156.5, 161.0, 161.6, 168.0; MS $[M+H]^+$ m/z 501.4.

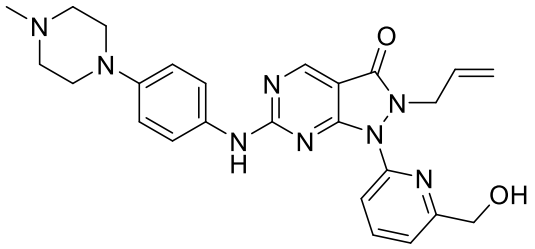


Synthesis of 1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-2-(4-methoxybenzyl)-6-((4-(4-methylpiperazin-1-yl)phenyl)amino)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (33). 1-(6-(2-Hydroxypropan-2-yl)pyridin-2-yl)-2-(4-methoxybenzyl)-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (**21**, 0.156 g, 0.36 mmol), mCPBA (70% w/w, 98 mg, 0.39 mmol), 4-methyl-1-(4-aminophenyl)piperazine (87 mg, 0.46 mmol) and DIPEA (310 µL, 1.78 mmol) were reacted in toluene (4 mL) according to the described general procedure. Purification via silica gel chromatography (9:1 DCM:MeOH) afforded the target compound as a yellow solid (0.188 g, 0.32 mmol, 89%). Rf 0.46 (9:1 DCM:MeOH); M.p. 196-199°C; IR (cm^{-1}) 3275, 3186, 2963, 2936, 2838, 1684, 1603, 1536, 1512; ^{1}H NMR (400 MHz, $CDCl_3$) 1.64 (6H, s, $C(CH_3)_2$), 2.40 (3H, s, N-CH_3), 2.62-2.67 (4H, m, N-(CH_2CH_2)$_2$-NMe), 3.20-3.25 (4H, m, N-CH_2CH_2-NMe), 3.72 (3H, s, OCH_3), 5.29 (2H, s, N^2-CH_2), 6.67 (2H, d, J = 8.6 Hz, benzyl H-2/6), 6.85 (2H, d, J = 8.6 Hz, benzyl H-3/5), 6.91 (2H, d, J = 8.7 Hz, H-3''/5''), 7.37 (1H, d_{app}, J = 7.8 Hz, H-5'), 7.43 (2H, d, J = 8.7 Hz,

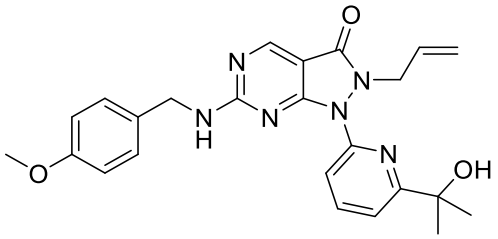
H-2''/6''), 7.57 (1H, d_{app}, *J* = 8.1 Hz, H-3'), 7.82 (1H, dd, *J* = 8.1, 7.8 Hz, H-4'), 8.83 (1H, s, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) 30.6 (C(CH_3)$_2$), 46.0 (N-CH_3), 48.1 (N^2-CH_2), 49.4 (piperazine-CH_2), 55.0 (OCH_3), 55.2 (piperazine-CH_2), 72.5 (*C*(CH_3)$_2$), 113.9, 116.0, 116.3, 116.5, 122.1, 127.7, 129.5, 130.4, 138.8, 147.4, 148.1, 156.3, 159.2, 161.0, 162.5, 165.8; MS $[M+H]^+$ *m*/*z* 581.4.



Synthesis of 2-allyl-1-(3-(2-hydroxypropan-2-yl)phenyl)-6-((4-(4-methylpiperazin-1-yl)phenyl)amino)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (31). 2-Allyl-1-(3-(2-hydroxypropan-2-yl)phenyl)-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (**19**, 60 mg, 0.17 mmol), mCPBA (70% w/w, 46 mg, 0.19 mmol), 4-methyl-1-(4-aminophenyl)piperazine (42 mg, 0.22 mmol) and DIPEA (155 µL, 0.88 mmol) were reacted in toluene (2 mL) according to the described general procedure. Purification via silica gel chromatography (9:1 DCM:MeOH) afforded the target compound as a pale yellow solid (53 mg, 0.11 mmol, 64%). Rf 0.39 (9:1 DCM:MeOH); M.p. 164-167°C; IR (cm^{-1}) 3287, 2972, 2935, 2838, 2798, 1701, 1668, 1606, 1542, 1512; ^{1}H NMR (400 MHz, $CDCl_3$) 1.64 (6H, s, C(CH_3)$_2$), 2.39 (3H, s, N-CH_3), 2.60-2.64 (4H, m, N-($CH_2C\mathit{H}_2$)$_2$-NMe), 3.18-3.23 (4H, m, N-CH_2CH_2-NMe), 4.40 (2H, d_{app}, *J* = 6.1 Hz, N^2-CH_2), 5.00 (1H, d_{app}, *J* = 17.2, alkene C-H^{trans}), 5.12 (1H, d_{app}, *J* = 10.1 Hz, alkene C-H^{cis}), 5.73 (1H, ddt, *J* = 17.2, 10.1, 6.1 Hz, alkene C-H), 6.90 (2H, d, *J* = 8.8 Hz, H-3''/5''), 7.29-7.34 (1H, m, H-5'), 7.45 (2H, d, *J* = 8.8 Hz, H-2''/6''), 7.49 (2H, d_{app}, *J* = 4.8 Hz, H-4'/6'), 7.60 (1H, s_{app}, H-2'), 8.83 (1H, s, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) 31.9 (C(CH_3)$_2$), 46.1 (N-CH_3), 46.5 (N^2-CH_2), 49.4 (piperazine-CH_2), 55.0 (piperazine-CH_2), 72.4 (*C*(CH_3)$_2$), 116.6, 119.2, 123.7, 129.1, 130.7, 131.1, 136.2, 150.9, 156.3, 162.7; MS $[M+H]^+$ *m*/*z* 500.2.

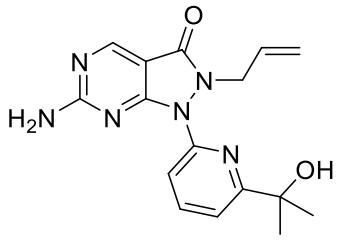


Synthesis of 2-allyl-1-(6-(hydroxymethyl)pyridin-2-yl)-6-((4-(4-methylpiperazin-1-yl)phenyl)amino)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (30). 2-Allyl-1-(6-(hydroxymethyl)pyridin-2-yl)-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (**20**, 0.156 g, 0.47 mmol), mCPBA (70% w/w, 0.127 g, 0.52 mmol), 4-methyl-1-(4-aminophenyl)piperazine (0.117 g, 0.61 mmol) and DIPEA (425 µL, 2.44 mmol) were reacted in toluene (5 mL) according to the described general procedure. Purification via silica gel chromatography (9:1 DCM:MeOH) afforded the target compound as a yellow solid (0.134 g, 0.29 mmol, 61%). Rf 0.34 (9:1 DCM:MeOH); M.p. 197-200°C; IR (cm^{-1}) 3253, 3176, 3065, 2939, 2818, 1687, 1674, 1610; ^{1}H NMR (400 MHz, $CDCl_3$) 2.39 (3H, s, N-CH_3), 2.59-2.64 (4H, m, N-(CH_2CH_2)$_2$-NMe), 3.19-3.25 (4H, m, N-CH_2CH_2-NMe), 4.73 (2H, d_{app}, *J* = 6.0 Hz, N^2-CH_2), 4.82 (2H, s, CH_2OH), 4.98 (1H, d_{app}, *J* = 17.2, alkene C-H^{trans}), 5.07 (1H, d_{app}, *J* = 10.2 Hz, alkene C-H^{cis}), 5.73 (1H, ddt, *J* = 17.2, 10.2, 6.0 Hz, alkene C-H), 6.94 (2H, d, *J* = 8.6 Hz, H-3''/5''), 7.24 (1H, dapp, *J* = 7.5 Hz, H-5'), 7.47 (2H, d, *J* = 8.6 Hz, H-2''/6''), 7.77 (1H, d_{app}, *J* = 8.1 Hz, H-3'), 7.87 (1H, dd, *J* = 8.1, 7.5 Hz, H-4'), 8.84 (1H, s, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) 46.1 (N-CH_3), 47.8 (N2-CH_2), 49.5 (piperazine-CH_2), 55.1 (piperazine-CH_2), 64.3 (CH_2OH), 116.4, 116.7, 117.8, 119.1, 122.0, 130.4, 131.6, 138.6, 148.2, 148.4, 156.3, 158.9, 161.4, 162.4; MS $[M+H]^+$ *m*/*z* 473.2.

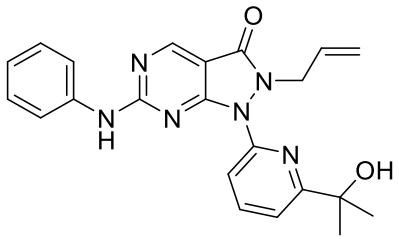


Synthesis of 2-allyl-1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-6-((4-methoxybenzyl)amino)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (23). 2-Allyl-1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (**18**, 0.203 g, 0.56 mmol), mCPBA (70% w/w, 0.157 g, 0.62 mmol), 4-methoxybenzylamine (95 µL, 0.73 mmol) and DIPEA (0.50 mL, 2.91 mmol) were reacted in toluene (5 mL) according to the described general

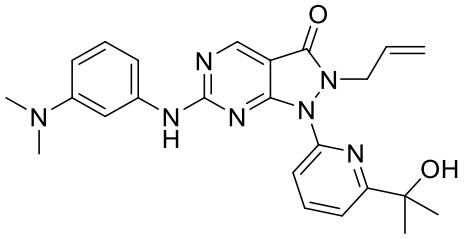
procedure. Purification *via* silica gel chromatography (19:1 DCM:MeOH) afforded the target compound as an off-white solid (55 mg, 0.12 mmol, 22%). Rf 0.38 (19:1 DCM:MeOH); M.p. 136-138°C; IR (cm^{-1}) 3442, 3219, 2972, 2922, 1667, 1614, 1593, 1546; ^{1}H NMR (400 MHz, $CDCl_3$) 1.60 (6H, s, $C(CH_3)_2$), 3.82 (3H, s, OCH_3), 3.98 (1H, s, OH), 4.55-4.61 (2H, m, $NHCH_2$), 4.71-4.78 (2H, m, N^2-CH_2), 4.96 (1H, d_{app}, J = 16.4 Hz, alkene C-H^{trans}), 5.06 (1H, d_{app}, J = 9.9 Hz, alkene C-H^{cis}), 5.72 (1H, ddt, J = 16.4, 9.9, 6.2 Hz, alkene C-H), 6.89 (2H, d, J = 8.5 Hz, benzyl H-3/5), 7.26 (2H, d, J = 8.5 Hz, benzyl H-2/6), 7.33 (1H, d_{app}, J = 7.7 Hz, H-5'), 7.73 (1H, d_{app}, J = 8.1 Hz, H-3'), 7.85 (1H, dd_{app}, J = 8.1, 7.7 Hz, H-4'), 8.73 (1H, s, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) 30.5 ($C(CH_3)_2$), 42.3 (benzyl CH_2), 47.8 (N^2-CH_2), 55.3 (OCH_3), 72.4 ($C(CH_3)_2$), 114.1, 115.7, 115.9, 119.0, 129.0, 130.0, 131.7, 138.8, 147.6, 156.3, 159.2, 161.6, 162.7, 163.4, 166.6; MS $[M+H]^+$ *m*/*z* 447.4.



Synthesis of 2-allyl-6-amino-1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (22). 2-Allyl-1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (**18**, 50 mg, 0.14 mmol), mCPBA (70% w/w, 32 mg, 0.15 mmol) and ammonia (2M in EtOH, 0.35 mL, 0.70 mmol) were reacted in toluene (2 mL) according to the described general procedure. Purification via KP-NH silica chromatography (19:1 DCM:MeOH) afforded the target compound as a white solid (13 mg, 0.04 mmol, 29%). Rf 0.53 (KP-NH – 19:1 DCM:MeOH); M.p. 195-197°C; IR (cm^{-1}) 3325, 3187, 2979, 2924, 2856, 1667, 1649, 1616, 1563; ^{1}H NMR (400 MHz, DMSO-d_6) 1.46 (6H, s, $C(CH_3)_2$), 4.62 (2H, d_{app}, J = 5.6 Hz, N^2-CH_2), 4.81 (1H, d_{app}, J = 17.1 Hz, alkene C-H^{trans}), 4.98 (1H, d_{app}, J = 10.0 Hz, alkene C-H^{cis}), 5.32 (1H, s, OH), 5.64 (1H, ddt, J = 17.1, 10.0, 5.6 Hz, alkene C-H), 7.53 (2H, br s, NH_2), 7.59 (1H, d_{app}, J = 7.7 Hz, H-5'), 7.71 (1H, d_{app}, J = 8.1 Hz, H-3'), 7.95 (1H, d_{app}, J = 8.1, 7.7 Hz, H-4'), 8.70 (1H, s, H-4); ^{13}C NMR (100 MHz, DMSO-d_6) 30.9 ($C(CH_3)_2$), 47.1 (N^2-CH_2), 72.8 ($C(CH_3)_2$), 98.9, 116.4, 116.6, 118.6, 132.7, 139.2, 147.8, 156.8, 161.9, 162.0, 165.4, 168.0; MS $[M+H]^+$ *m*/*z* 327.2.

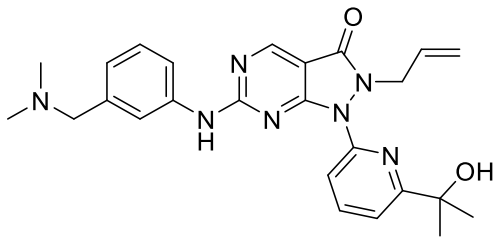


Synthesis of 2-allyl-1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-6-(phenylamino)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (24). 2-Allyl-1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (**18**, 0.101 g, 0.28 mmol), mCPBA (70% w/w, 77 mg, 0.31 mmol), aniline (33 µL, 0.36 mmol) and DIPEA (0.25 mL, 1.45 mmol) were reacted in toluene (3 mL) according to the described general procedure. Purification via silica gel chromatography (19:1 DCM:MeOH) afforded the target compound as a white solid (35 mg, 0.09 mmol, 31%). Rf 0.50 (19:1 DCM:MeOH); M.p. 153-155°C; IR (cm^{-1}) 3245, 3191, 3080, 3056, 2975, 2929, 1671, 1615, 1540; ^{1}H NMR (400 MHz, $CDCl_3$) 1.61 (6H, s, $C(CH_3)_2$), 3.97 (1H, s, OH), 4.78 (2H, d_{app}, J = 6.2 Hz, N^2-CH_2), 4.96 (1H, dd, J = 17.0, 1.1 Hz, alkene C-H^{trans}), 5.07 (1H, dd, J = 10.2, 1.1 Hz, alkene C-H^{cis}), 5.73 (1H, ddt, J = 17.0, 10.2, 6.2 Hz, alkene C-H), 7.15 (1H, dd, J = 7.4, 7.3 Hz, H-4''), 7.36-7.41 (3H, m, H-5'/3''/5''), 7.63 (2H, d_{app}, J = 7.8 Hz, H-2''/6''), 7.79 (1H, d_{app}, J = 7.9 Hz, H-3'), 7.91 (1H, dd_{app}, J = 7.9, 7.8 Hz, H-4'), 8.90 (1H, s, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) 30.6 ($C(CH_3)_2$), 47.6 (N^2-CH_2), 72.5 ($C(CH_3)_2$), 101.1, 116.2, 116.3, 119.1, 120.6, 124.0, 128.9, 131.5, 138.2, 138.9, 147.4, 156.3, 161.0, 161.3, 162.0, 165.9; MS $[M+H]^+$ m/z 403.4.

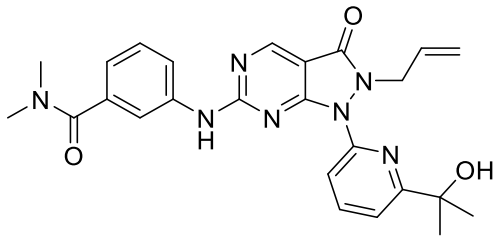


Synthesis of 2-allyl-6-((3-(dimethylamino)phenyl)amino)-1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (25). 2-Allyl-1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (**18**, 0.102 g, 0.28 mmol), mCPBA (70% w/w, 80 mg, 0.31 mmol), N^1,N^1-dimethylbenzene-1,3-diamine (**39**, 68 mg, 0.36 mmol) and DIPEA (0.25 mL, 1.45 mmol) were reacted in toluene (3 mL) according to the described general procedure. Purification via silica gel chromatography (19:1 DCM:MeOH) afforded the target compound as a pale yellow/green solid (29 mg, 0.06 mmol,

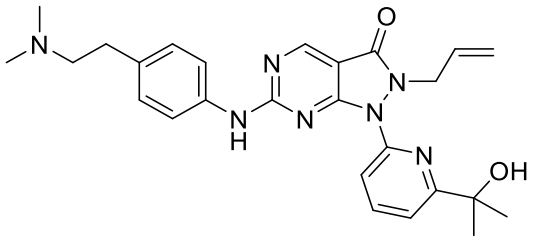
23%). Rf 0.30 (19:1 DCM:MeOH); M.p. 81-84°C; IR (cm^{-1}) 3407, 3219, 3080, 2963, 2926, 1694, 1605, 1572, 1548; ^{1}H NMR (400 MHz, $CDCl_3$) 1.61 (6H, s, $C(CH_3)_2$), 2.95 (6H, s, $N(CH_3)_2$, 3.92 (1H, s, OH), 4.76 (2H, d_{app}, *J* = 6.0 Hz, N^2-CH_2), 4.95 (1H, d_{app}, *J* = 17.2 Hz, alkene C-H^{trans}), 5.06 (1H, d_{app}, *J* = 10.1 Hz, alkene C-H^{cis}), 5.73 (1H, ddt, *J* = 17.2, 10.1, 6.0 Hz, alkene C-H), 6.54 (1H, dd, *J* = 8.4, 2.0 Hz, H-4''), 6.87 (1H, br s, H-2''), 7.05 (1H, d_{app}, *J* = 7.9 Hz, H-6''), 7.23 (1H, dd, *J* = 8.4, 7.9 Hz, H-5''), 7.37 (1H, d_{app}, *J* = 7.6 Hz, H-5'), 7.50 (1H, br s, N-H), 7.81 (1H, d_{app}, *J* = 7.9 Hz, H-3'), 7.87 (1H, dd_{app}, *J* = 7.9, 7.6 Hz, H-4'), 8.88 (1H, s, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) 30.5 ($C(CH_3)_2$), 40.6 ($N(CH_3)_2$), 47.6 (N^2-CH_2), 72.5 ($C(CH_3)_2$), 101.0, 104.8, 108.7, 109.2, 116.1, 116.5, 119.0, 129.4, 131.6, 138.9, 139.0, 147.5, 151.3, 156.3, 161.2, 161.4, 162.1, 165.9; MS $[M+H]^+$ *m*/*z* 446.2.



Synthesis of 2-allyl-6-((3-((dimethylamino)methyl)phenyl)amino)-1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (26). 2-Allyl-1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (**18**, 0.103 g, 0.28 mmol), mCPBA (70% w/w, 80 mg, 0.31 mmol), 3-((dimethylamino) methyl)aniline (**40**, 60 mg, 0.36 mmol) and DIPEA (0.25 mL, 1.45 mmol) were reacted in toluene (3 mL) according to the described general procedure. Purification via silica gel chromatography (EtOAc) afforded the target compound as an off-white solid (35 mg, 0.08 mmol, 27%). Rf 0.18 (EtOAc); M.p. 121-123°C; IR (cm^{-1}) 3407, 3230, 2975, 2927, 2772, 1665, 1610, 1542; ^{1}H NMR (400 MHz, $CDCl_3$) 1.61 (6H, s, $C(CH_3)_2$), 2.29 (6H, s, $N(CH_3)_2$), 3.47 (2H, s, $ArCH_2$), 4.78 (2H, d_{app}, *J* = 6.1 Hz, N^2-CH_2), 4.96 (1H, d_{app}, *J* = 17.1 Hz, alkene C-H^{trans}), 5.07 (1H, d_{app}, *J* = 10.1 Hz, alkene C-H^{cis}), 5.73 (1H, ddt, *J* = 17.1, 10.1, 6.1 Hz, alkene C-H), 7.10 (1H, d_{app}, *J* = 7.5 Hz, H-4''), 7.33 (1H, dd_{app}, *J* = 7.9, 7.5 Hz, H-5''), 7.39 (1H, d_{app}, *J* = 7.6 Hz, H-5'), 7.54-7.62 (2H, m, H-2''/6''), 7.82 (1H, d_{app}, *J* = 7.9 Hz, H-3'), 7.92 (1H, dd_{app}, *J* = 7.9, 7.6 Hz, H-4'), 8.89 (1H, s, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) 30.5 ($C(CH_3)_2$), 45.4 ($N(CH_3)_2$), 47.6 (N^2-CH_2), 64.3 (Ar-CH_2), 72.5 ($C(CH_3)_2$), 101.2, 116.1, 116.4, 119.1, 119.2, 120.8, 124.6, 128.8, 131.6, 138.3, 138.9, 139.7, 147.4, 156.3, 161.1, 161.2, 162.0, 165.9; MS $[M+H]^+$ *m*/*z* 460.0.

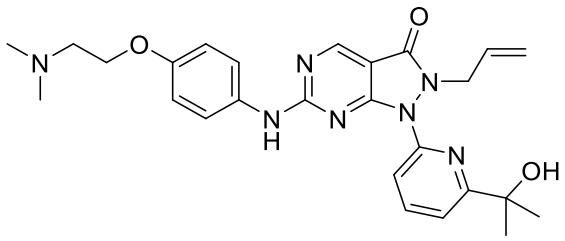


Synthesis of 3-((2-allyl-1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-3-oxo-2,3-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl)amino)-*N,N*-dimethylbenzamide (27). 2-Allyl-1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (**18**, 0.104 g, 0.28 mmol), mCPBA (70% w/w, 80 mg, 0.31 mmol), 3-amino-*N,N*-dimethylbenzamide (**41**, 60 mg, 0.36 mmol) and DIPEA (0.25 mL, 1.45 mmol) were reacted in toluene (3 mL) according to the described general procedure. Purification via silica gel chromatography (19:1 DCM:MeOH) afforded the target compound as a white solid (16 mg, 0.03 mmol, 12%). Rf 0.34 (19:1 DCM:MeOH); M.p. 93-96°C; IR (cm^{-1}) 3405, 3270, 2972, 2929, 1673, 1615, 1541; ^{1}H NMR (400 MHz, $CDCl_3$) 1.60 (6H, s, $C(CH_3)_2$), 2.97 (3H, s, NCH_3), 3.16 (3H, s, NCH_3), 3.97 (1H, s, OH), 4.79 (2H, d_{app}, *J* = 6.0 Hz, N^2-CH_2), 4.95 (1H, d_{app}, *J* = 17.0 Hz, alkene C-H^{trans}), 5.06 (1H, d_{app}, *J* = 10.3 Hz, alkene C-H^{cis}), 5.72 (1H, ddt, *J* = 17.0, 10.3, 6.0 Hz, alkene C-H), 7.14 (1H, d_{app}, *J* = 7.5 Hz, H-4''), 7.35-7.41 (2H, m, H-5'/5''), 7.48 (1H, d_{app}, *J* = 8.1 Hz, H-6''), 7.82 (1H, d_{app}, *J* = 8.1 Hz, H-3'), 7.94 (1H, br s, N-H), 7.98-8.05 (2H, m, H-4'/2''), 8.89 (1H, s, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) 30.5 (($C(CH_3)_2$), 35.4 (NCH_3), 39.6 (NCH_3), 47.6 N^2-CH_2), 72.5 ($C(CH_3)_2$), 101.5, 116.3, 116.6, 118.8, 119.1, 120.9, 121.9, 128.9, 131.5, 137.2, 138.6, 139.6, 147.2, 156.4, 160.8, 161.0, 161.8, 165.8, 171.2; MS $[M+H]^+$ *m/z* 474.2.



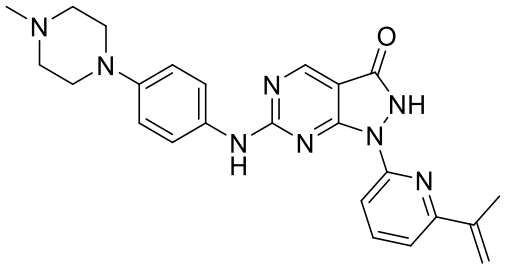
Synthesis of 2-allyl-6-((4-(2-(dimethylamino)ethyl)phenyl)amino)-1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (28). 2-Allyl-1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (**18**, 0.150 g, 0.42 mmol), mCPBA (70% w/w, 0.114 g, 0.46 mmol), 4-(2-(dimethylamino) ethyl)aniline (**42**, 90 mg, 0.55 mmol) and DIPEA (0.38 mL, 2.18 mmol) were reacted in toluene (4

mL) according to the described general procedure. Purification via KP-NH silica chromatography (19:1 DCM:MeOH) afforded the target compound as an off-white solid (36 mg, 0.08 mmol, 18%). Rf 0.14 (9:1 DCM:MeOH); M.p. 116-119°C; IR (cm^{-1}) 3252, 3191, 3099, 2968, 2929, 2855, 2827, 2782, 1745, 1672, 1603, 1568; ^{1}H NMR (400 MHz, $CDCl_3$) 1.61 (6H, s, $C(CH_3)_2$), 2.33 (6H, s, $N(CH_3)_2$), 2.53-2.59 (2H, m, $ArCH_2CH_2$), 2.76-2.82 (2H, m, $ArCH_2CH_2$), 4.77 (2H, d_{app}, J = 5.8 Hz, N^2-CH_2), 4.96 (1H, d_{app}, J = 17.2 Hz, alkene C-H^{trans}), 5.06 (1H, d_{app}, J = 10.3 Hz, alkene C-H^{cis}), 5.73 (1H, ddt, J = 17.2, 10.3, 5.8 Hz, alkene C-H), 7.21 (2H, d, J = 8.2 Hz, H-3''/5''), 7.39 (1H, d_{app}, J = 7.7 Hz, H-5'), 7.53 (2H, d, J = 8.2 Hz, H-2''/6''), 7.78 (1H, d_{app}, J = 7.9 Hz, H-3'), 7.90 (1H, dd, J = 7.9, 7.7 Hz, H-4'), 8.87 (1H, s, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) 30.6 ($C(CH_3)_2$), 33.8 ($ArCH_2CH_2$), 45.5 ($N(CH_3)_2$), 47.6 (N^2-CH_2), 61.5 ($ArCH_2CH_2$), 72.5 ($C(CH_3)_2$), 101.1, 116.2, 116.3, 119.1, 120.6, 129.0, 131.6, 136.1, 136.2, 138.9, 147.5, 156.4, 161.1, 161.3, 162.1, 165.9; MS $[M+H]^+$ m/z 474.4.

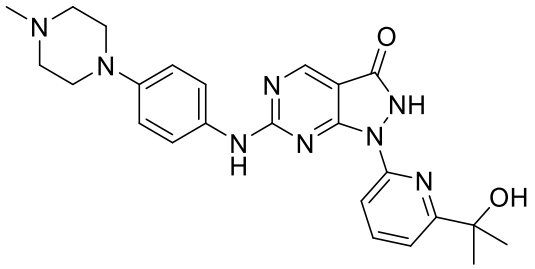


Synthesis of 2-allyl-6-((4-(2-(dimethylamino)ethoxy)phenyl)amino)-1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (29). 2-Allyl-1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-6-(methylthio)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (**18**, 0.102 g, 0.28 mmol), mCPBA (70% w/w, 78 mg, 0.31 mmol), 4-(2-(dimethylamino) ethoxy)aniline (**43**, 67 mg, 0.37 mmol) and DIPEA (258 µL, 1.48 mmol) were reacted in toluene (3 mL) according to the described general procedure. Purification via silica gel chromatography (9:1 DCM:MeOH) afforded the target compound as an off-white solid (47 mg, 0.11 mmol, 38%). Rf 0.28 (9:1 DCM:MeOH); M.p. 123-126°C; IR (cm^{-1}) 3248, 3081, 2976, 2937, 2870, 2821, 2773, 1680, 1614, 1512; ^{1}H NMR (400 MHz, DMSO-d_6) 1.47 (6H, s, $C(CH_3)_2$), 2.28 (6H, s, $N(CH_3)_2$), 2.69 (2H, t, J = 5.2 Hz, OCH_2CH_2), 4.06 (2H, t, J = 5.2 Hz, OCH_2CH_2), 4.69 (2H, d_{app}, J = 5.4 Hz, N^2-CH_2), 4.83 (1H, d_{app}, J = 17.1 Hz, alkene C-H^{trans}), 5.00 (1H, d_{app}, J = 10.3 Hz, alkene C-H^{cis}), 5.33 (1H, s, OH), 5.67 (1H, ddt, J = 17.1, 10.3, 5.4 Hz, alkene C-H), 6.94 (2H, d, J = 8.4 Hz, H-3''/5''), 7.59-7.66 (3H, m, H-5'/2''/6''), 7.75 (1H, d_{app}, J = 7.4 Hz, H-3'), 8.05 (1H, dd, J = 7.8, 7.4 Hz, H-4'), 8.85 (1H, s, H-4), 10.19 (1H, br s, C^6-NH); ^{13}C NMR (100 MHz, DMSO-d_6) 30.9

($C(CH_3)_2$, 45.8 ($N(CH_3)_2$), 47.0 (N^2-CH_2), 58.1 (OCH_2CH_2), 66.2 (OCH_2CH_2), 72.8 ($C(CH_3)_2$), 114.8, 116.8, 118.7, 132.7, 139.3, 147.5, 154.9, 156.6, 161.6, 168.1; MS $[M+H]^+$ *m*/*z* 490.4.



Synthesis of 6-((4-(4-methylpiperazin-1-yl)phenyl)amino)-1-(6-(prop-1-en-2-yl)pyridin-2-yl)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (34). 1-(6-(2-Hydroxypropan-2-yl)pyridin-2-yl)-2-(4-methoxybenzyl)-6-((4-(4-methylpiperazin-1-yl)phenyl)amino)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (**33**, 56 mg, 0.10 mmol) was dissolved in TFA (2 mL) and the mixture was heated at reflux for 16 h. The solvent was removed *in vacuo* and the resultant residue was partitioned between EtOAc (10 mL) and saturated $NaHCO_3$ solution (10 mL). The organic phase was washed with brine (10 mL) and dried ($MgSO_4$) before being evaporated to dryness. Purification via silica gel chromatography (9:1 DCM:MeOH) afforded the target compound as a pale yellow solid (39 mg, 0.09 mmol, 91%). Rf 0.36 (9:1 DCM:MeOH); M.p. 260-270°C (decomposed); IR (cm^{-1}) 3245, 3175, 2933, 2836, 2791, 1691, 1611; ^{1}H NMR (400 MHz, DMSO-d_6) 2.20 (3H, s, CCH_3), 2.25 (3H, s, N-CH_3), 2.47-2.51 (4H, m, N-(CH_2CH_2)$_2$-NMe), 3.09-3.13 (4H, m, N-CH_2CH_2-NMe), 5.37 (1H, s, alkene C-H), 6.12 (1H, s, alkene C-H), 6.93 (2H, d, *J* = 8.9 Hz, H-3''/5''), 7.45 (1H, d_{app}, *J* = 7.5 Hz, H-3'), 7.67 (2H, d, *J* = 8.9 Hz, H-2''/6''), 7.98 (1H, dd, *J* = 7.8, 7.5 Hz, H-4'), 8.09-8.16 (1H, m, H-5'), 8.83 (1H, s, H-4), 9.88 (1H, s, C^6-NH), 11.95 (1H, br s, N^2-H); ^{13}C NMR (100 MHz, DMSO-d_6) 20.7 ($C(CH_2)CH_3$), 46.1 (N-CH_3), 49.1 (piperazine-CH_2), 55.1 (piperazine-CH_2), 113.4, 116.2, 116.6, 117.3, 121.5, 132.1, 139.4, 142.5, 147.2, 154.7, 156.7, 157.4, 160.3; MS $[M+H]^+$ *m*/*z* 443.4.



Synthesis of 1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-6-((4-(4-methylpiperazin-1-yl)phenyl)amino)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (35). Sodium *para*-toluenesulfinate tetrahydrate (25 mg, 0.10 mmol) in MeOH (0.5 mL) was added to a solution of 2-allyl-1-(6-(2-hydroxypropan-2-yl)pyridin-2-yl)-6-((4-(4-methylpiperazin-1-yl)phenyl)amino)-1,2-dihydro-3H-pyrazolo[3,4-d]pyrimidin-3-one (**AZD-1775**, 50 mg, 0.10 mmol) and tetrakis(triphenylphosphine)palladium(0) (17 mg, 0.015 mmol) in THF (1 mL). The reaction mixture was stirred at RT for 2 h before EtOAc (5 mL) was added and the resultant off-white precipitate was collected by filtration (36 mg, 0.08 mmol, 80%). Rf 0.21 (1:1 DCM:MeOH); M.p. >350°C; IR (cm^{-1}) 3248, 3168, 2974, 2936, 2791, 1612, 1535; ^{1}H NMR (400 MHz, DMSO-d_6) 1.52 (6H, s, $C(CH_3)_2$), 2.23 (3H, s, N-CH_3), 2.45-2.49 (4H, m, N-(CH_2CH_2)$_2$-NMe), 3.05-3.09 (4H, m, N-CH_2CH_2-NMe), 5.83 (1H, s, OH), 6.91 (2H, d, J = 9.1 Hz, H-3''/5''), 7.19 (1H, d_{app}, J = 7.5 Hz, H-5'), 7.69 (2H, d, J = 9.1 Hz, H-2''/6''), 7.80 (1H, dd, J = 7.9, 7.5 Hz, H-4'), 8.13 (1H, d_{app}, J = 7.9 Hz, H-3'), 8.45 (1H, s, H-4), 9.23 (1H, s, C^6-NH); ^{13}C NMR (100 MHz, DMSO-d_6) 31.2 ($C(CH_3)_2$), 46.3 (N-CH_3), 49.5 (piperazine-CH_2), 55.2 (piperazine-CH_2), 72.3 ($C(CH_3)_2$), 116.4, 120.5, 133.5, 138.6, 146.4, 150.5, 152.5, 159.1, 166.4; MS $[M+H]^+$ m/z 461.2.