Development of *Toxoplasma gondii* Calcium-Dependent Protein Kinase 1 (*Tg*CDPK1) Inhibitors with Potent Anti-*Toxoplasma* Activity

Supporting Information

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Table S1: IC_{50}-fold differences between human kinases and *Tg*CDPK1.

	Enzymatic IC_{50}-Fold Differences (Kinase IC_{50} / *Tg*CDPK1 IC_{50})							
Compound	***Tg*CDPK1**	**SRC**	**ABL**	**LCK**	**p38α**	**EPHA3**	**CSK**	**EGFR**
14a	**1**	110	140	13	1700	260	440	85
14n	**1**	2000	2000	120	2000	2000	2000	2000
15a	**1**	75	340	10	2000	750	630	140
15h	**1**	2300	4200	50	4200	4200	4200	4200
15n	**1**	4000	4000	380	4000	4000	4000	4000
15o	**1**	3400	1600	1100	3400	3400	3400	3400
16n	**1**	2900	2900	2900	2900	2900	2900	2900

Figure S1: Correlation between SRC and *Tg*CDPK1 enzymatic IC_{50} results. The solid lines at IC_{50} >10 and >5 μM represent the upper detection limits for compounds tested in the respective assays.

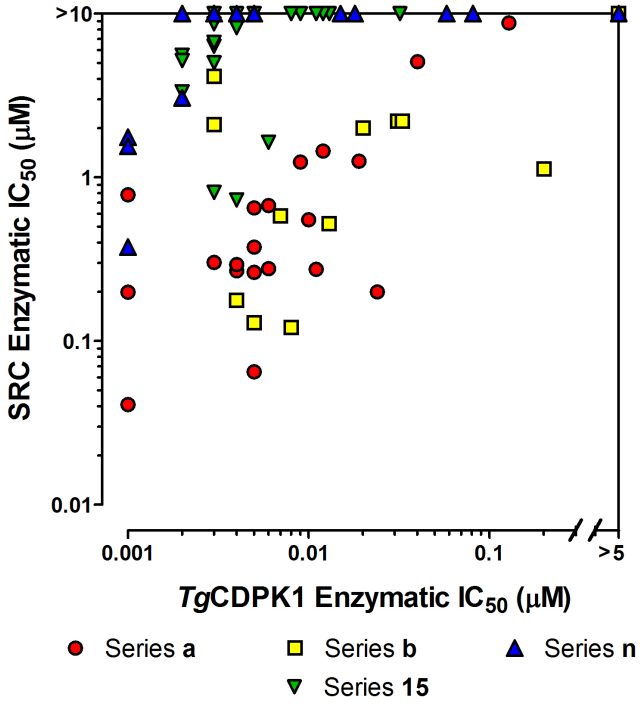
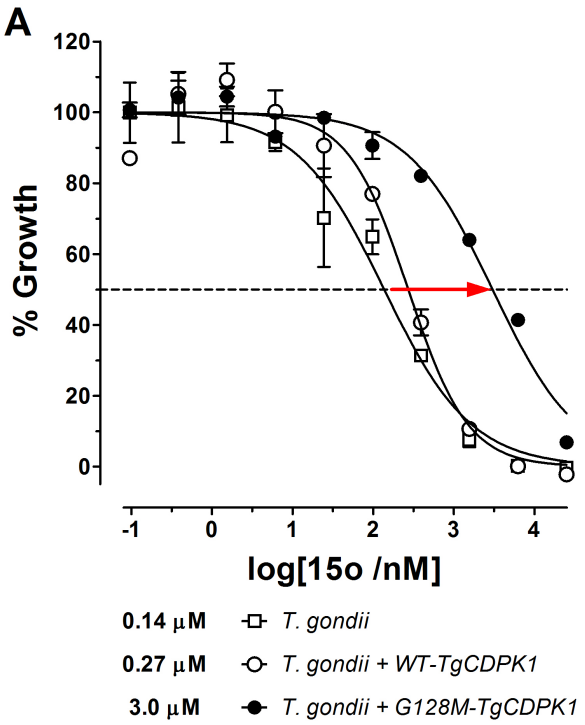
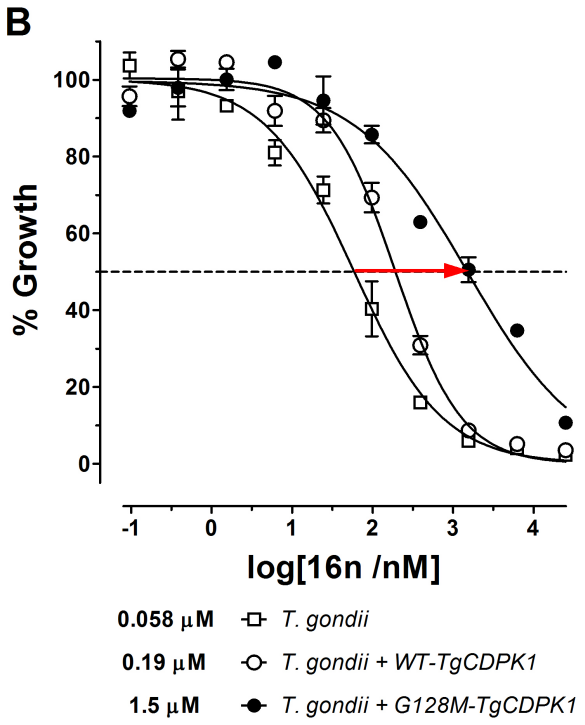


Figure S2: Correlation of proliferation EC_{50} curves between native *T. gondii* (open squares) and parasites expressing either wild type *Tg*CDPK1 (open circles) or the drug resistant G128M-*Tg*CDPK1 mutant (closed circles). Expression of the drug resistant G128M-*Tg*CDPK1 mutant rescues cells from the potent anti-proliferative effects of inhibitors **15o** (panel A) and **16n** (panel **B**).

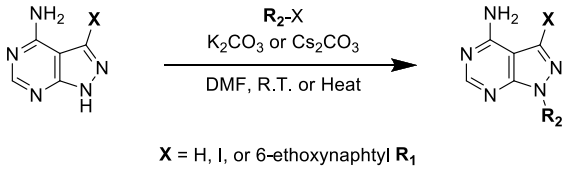




General Synthetic Procedures.

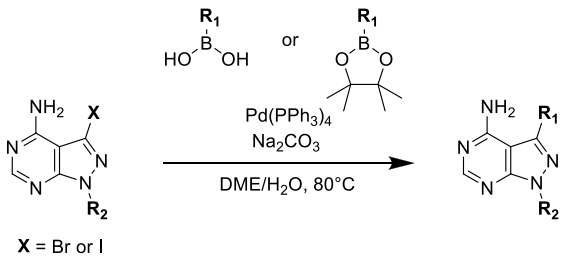
Unless otherwise stated, all chemicals were purchased from commercial suppliers and used without further purification. Reaction progress was monitored by thin-layer chromatography on silica gel 60 F254 coated glass plates (EM Sciences). Chromatography was performed using an IntelliFlash 280 automated flash chromatography system, eluting on pre-packed Varian SuperFlash silica gel columns with hexanes/EtOAc or CH_2Cl_2/MeOH gradient solvent systems. For preparatory HPLC purification, samples were chromatographically separated using a Varian Dynamax Microsorb 100-5 C_{18} column (250 mm x 21.4 mm), eluting with H_2O/CH_3CN or H_2O/ MeOH gradient solvent systems (+0.05% TFA). The purity of all final compounds was determined by two analytical RP-HPLC methods, using an Agilent ZORBAX SB-C_{18} (2.1 mm x 150 mm) or Varian Microsorb-MV 100-5 C_{18} column (4.6 mm x 150 mm), and eluting with either H_2O/CH_3CN or H_2O/ MeOH gradient solvent systems (+0.05% TFA) run over 30 min. Products were detected by UV at λ=254 nm, with all final compounds displaying >95% purity. NMR spectra were recorded on Bruker 300 or 500 MHz spectrometers at ambient temperature. Chemical shifts are reported in parts per million (δ) and coupling constants in Hz. ^{1}H-NMR spectra were referenced to the residual solvent peaks as internal standards (7.26 ppm for $CDCl_3$, 2.50 ppm for *d*$_6$-DMSO, and 3.34 ppm for CD_3OD). Mass spectra were recorded with a Bruker Esquire Liquid Chromatograph - Ion Trap Mass Spectrometer. Inhibitors were synthesized through several different routes, as represented in **Schemes 1-3**. Syntheses of compounds **1b**, **3a**, **4a**, **5a**, **10a**, **10b**, **10n**, **11a**, **11b**, **12a**, **14a**, **15a**, **26**, **27**, **31**, and **32** have been previously reported.[1, 2] All other syntheses and compound characterization data are presented below.

General pyrazolopyrimidine R_2 alkylation procedure:



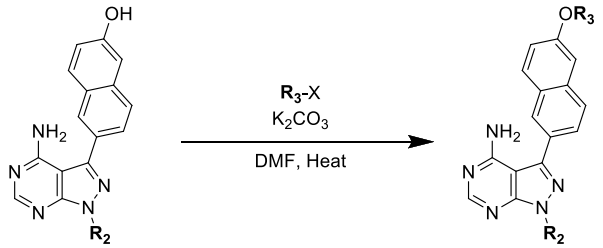
The pyrazolopyrimidine (1 eq.), K_2CO_3 or Cs_2CO_3 (1.5-2 equiv), and appropriate **R_2**-halide (1.1 equiv) or **R_2**-mesylate (1.1 equiv) were stirred in dry DMF at room temperature or 80 °C. Upon completion (as monitored by thin layer chromatography), the reaction was extracted into EtOAc and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified via flash chromatography over silica, eluting with either a hexanes/EtOAc or CH_2Cl_2/MeOH gradient. Product fractions were collected and concentrated to a solid.

General Suzuki coupling procedure:



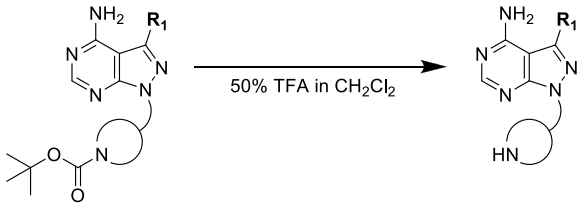
The respective halide (1 eq.), Na_2CO_3 (2-4 eq.), $Pd(PPh_3)_4$ (.05 eq.), and appropriate boronic acid or pinacol ester (1-2 eq.) were stirred in dimethoxyethane (DME, 1.5 ml) and water (0.5 ml) and heated in a microwave at 80 °C for one hour. The reaction was then cooled to room temperature, extracted into ethyl acetate, washed with brine, and the organic layer dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified via flash chromatography over silica, eluting with either a hexanes/EtOAc or CH_2Cl_2/MeOH gradient. Product fractions were collected and concentrated to a solid. Further purification, if necessary, was performed via preparatory RP-HPLC, eluting with either a H_2O/CH_3CN or H_2O/MeOH gradient (+0.05% TFA). Product fractions were collected, concentrated, frozen, and lyophilized to a powder. Final compounds were then extracted into EtOAc, washed with sat. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated to afford the purified product as a solid.

General naphthol alkylation procedure:



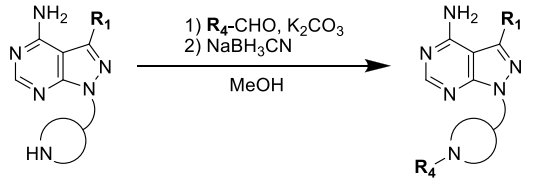
The naphthol (1 eq.), K_2CO_3 (1.5-2 equiv), and appropriate alkyl halide (1.1 equiv) were stirred in dry DMF at room temperature or 80°C. Upon completion (as monitored by thin layer chromatography), the reaction was extracted into EtOAc and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was then purified via flash chromatography over silica, eluting with either a hexanes/EtOAc or CH_2Cl_2/MeOH gradient. Product fractions were collected and concentrated to a solid. Further purification, if necessary, was performed via preparatory RP-HPLC, eluting with either a H_2O/CH_3CN or H_2O/ MeOH gradient (+0.05% TFA). Product fractions were collected, concentrated, frozen, and lyophilized to a powder. For final compounds, this was then extracted into EtOAc, washed with sat. $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated to afford the purified product as a solid.

General boc-deprotection procedure:



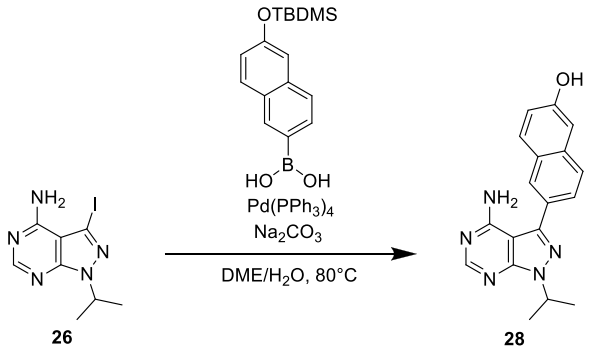
The boc-amine is stirred in 50% TFA in CH_2Cl_2 for ~3 h. The reaction was then concentrated and purified via preparatory RP-HPLC, eluting with either a H_2O/CH_3CN or H_2O/ MeOH gradient (+0.05% TFA). Product fractions were collected, concentrated, frozen, and lyophilized to a powder. The product was then re-concentrated from 1.25 M HCl in EtOH to afford the final, purified product as a bis-HCl salt.

General reductive alkylation procedure:



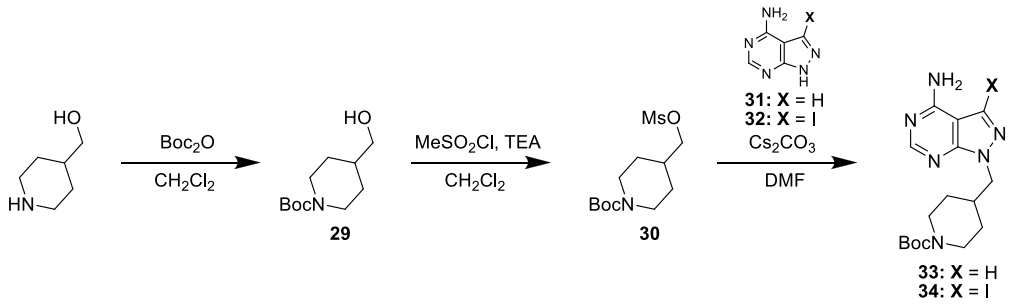
The TFA-amine salt (1 eq.) was dissolved in methanol and neutralized with sodium methoxide. A solution containing 2% acetic acid was added with the appropriate aldehyde (5-10 eq.) and stirred at room temperature for 10 min. Sodium cyanoborohydride (5 eq.) was then added and the reaction was left to stir until completion (typically ~2 h). The reaction was then filtered and purified via preparatory RP-HPLC, eluting with either a H_2O/CH_3CN or H_2O/ MeOH gradient (+0.05% TFA). Product fractions were collected and concentrated. The residue was dissolved in a small amount of 2 M HCl in methanol and, after concentration *in vacuo*, the final product was obtained as an HCl salt.

Synthesis and characterization of intermediate compounds:



28: 6-(4-amino-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-3-yl)naphthalen-2-ol.
This compound was synthesized following the ***general Suzuki coupling procedure*** and using 6-(*tert*-butyldimethylsilyloxy)naphthalen-2-boronic acid as the aryl coupling reagent and **26** as the

aryl-halide. After purification, characterization revealed the loss of the TBMDS protecting group, affording **28** as the free naphthol. ^{1}H-NMR (300 MHz, CD_3OD) δ 8.25 (s, 1H), 8.05 (s, 1H), 7.81-7.87 (m, 2H), 7.68-7.73 (m, 1H), 7.14-7.21 (m, 2H), 5.15 (septet, 1H, *J*=6.8 Hz), 1.59 (d, 6H, *J*=6.8 Hz); MS (ESI) 320.4 *m/z* [MH^+], $C_{18}H_{18}N_5O$ requires 320.2.



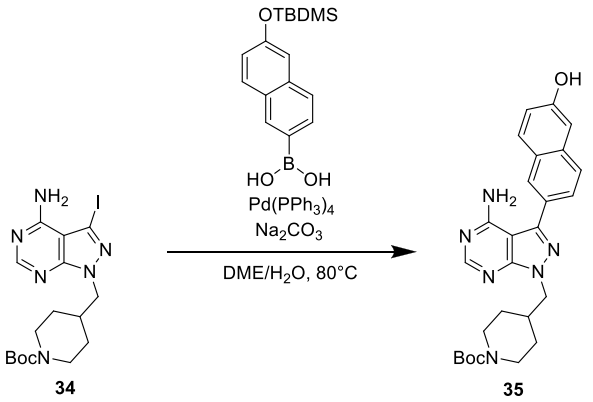
29: *Tert*-butyl-4-(hydroxymethyl)piperidine-1-carboxylate. Dichloromethane (25 mL) was added to a flask containing 4-piperidinemethanol (2.74 g, 23.8 mmol) and di-*tert*-butyl dicarbonate (5.26 g, 24.1 mmol). The reaction was then stirred for 18 h at ROOM TEMPERATURE under a nitrogen atmosphere. Flash chromatographic purification over silica (CH_2Cl_2/MeOH gradient elution) afforded **29** as a white solid (4.88 g). ^{1}H-NMR (300 MHz, *d*$_6$-DMSO) δ 4.44 (t, 1H, *J*=5.3 Hz), 3.86-3.98 (m, 2H), 3.23 (t, 2H, *J*=5.9 Hz), 2.56-2.74 (m, 2H), 1.42-1.66 (m, 3H), 1.38 (s, 9H), 0.88-1.04 (m, 2H); MS (ESI) 238.1 *m/z* [MNa^+], $C_{11}H_{21}NaNO_2$ requires 238.1.

30: *Tert*-butyl-4-((methylsulfonyloxy)methyl)piperidine-1-carboxylate. Methanesulfonyl chloride (1.18 mL, 15.2 mmol) was added drop-wise at 0 °C to a stirring mixture of **29** (2.98 g, 13.8 mmol) and triethylamine (3.9 mL, 28 mmol) in dichloromethane (30 mL). After 1 h, the reaction was diluted with dichloromethane and washed with sat. $NaHCO_3$. The organic layer was dried over Na_2SO_4, filtered, and concentrated. Flash chromatographic purification over silica (Hexanes/EtOAc gradient elution) afforded **30** as a white solid (3.89 g). ^{1}H-NMR (300 MHz, *d*$_6$-DMSO) δ 4.06 (d, 2H, *J*=6.4 Hz), 3.90-4.00 (m, 2H), 3.17 (s, 3H), 2.60-2.80 (m, 2H), 1.78-1.92 (m, 1H), 1.58-1.70 (m, 2H), 1.39 (s, 9H), 1.00-1.20 (m, 2H); MS (ESI) 316.3 *m/z* [MNa^+], $C_{12}H_{23}NaNO_5S$ requires 316.1.

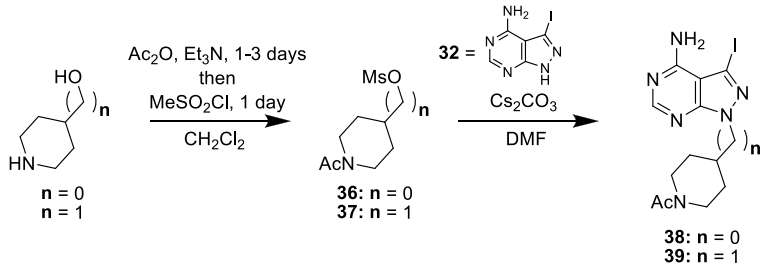
33: *Tert*-butyl 4-((4-amino-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)piperidine-1-carboxylate. This compound was synthesized following the ***general pyrazolopyrimidine R$_2$ alkylation procedure*** and using **31** as the pyrazolopyrimidine scaffold (49.7 mg, 0.368 mmol – synthesis of **31** has been previously reported),[1, 2] **30** as the **R$_2$**-mesylate (101 mg, 0.344 mmol), and Cs_2CO_3 as base (232 mg, 0.711 mmol) in anhydrous DMF (3.5 mL) at room temperature for 3 days, affording **33** as a white solid (59.5 mg).^{1}H-NMR (300 MHz, *d*$_6$-DMSO) δ 8.16 (s, 1H), 8.08 (s, 1H), 4.16 (d, 2H, *J*=7.0 Hz), 3.82-3.94 (m, 2H), 2.54-2.74 (m, 2H), 1.98-2.12 (m, 1H), 1.34-1.48 (m, 11H), 0.98-1.14 (m, 2H); MS (ESI) 333.4 *m/z* [MH^+], $C_{16}H_{25}N_6O_2$ requires 333.2; HPLC = 97% pure.

34: *Tert*-butyl-4-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)piperidine-1-carboxylate. This compound was synthesized following the ***general pyrazolopyrimidine R$_2$ alkylation procedure*** and using **32** as the pyrazolopyrimidine scaffold (541 mg, 2.07 mmol –

synthesis of **32** has been previously reported),[1, 2] **30** as the $\mathbf{R_2}$-mesylate (616 mg, 2.10 mmol), and Cs_2CO_3 as base (1.02 g, 3.13 mmol) in anhydrous DMF (11 mL) at 80 °C for 18 h, affording **34** as an orange solid (512 mg). ^{1}H-NMR (300 MHz, d_6-DMSO) δ 8.19 (s, 1H), 4.17 (d, 2H, J=7.0 Hz), 3.82-3.94 (m, 2H), 2.56-2.76 (m, 2H), 1.96-2.12 (m, 1H), 1.34-1.48 (m, 11H), 0.96-1.14 (m, 2H); MS (ESI) 459.1 *m/z* [MH^+], $C_{16}H_{24}IN_6O_2$ requires 459.1; HPLC = 97% pure.



35: *Tert*-butyl 4-((4-amino-3-(6-hydroxynaphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)piperidine-1-carboxylate. This compound was synthesized following the ***general Suzuki coupling procedure***, using 6-(*tert*-butyldimethylsilyloxy)naphthalen-2-boronic acid as the aryl coupling reagent (148 mg, 0.490 mmol) and **34** as the aryl-halide (161 mg, 0.352 mmol). After purification, characterization revealed the loss of the TBMDS protecting group, affording **35** as the free naphthol (174 mg). ^{1}H-NMR (300 MHz, d_6-DMSO) δ 9.90 (s, 1H), 8.26 (s, 1H), 8.06 (s, 1H), 8.01 (s, 1H), 7.82-7.92 (m, 2H), 7.04-7.20 (m, 2H), 4.26 (d, 2H, J=6.9 Hz), 3.84-3.96 (m, 2H), 2.58-2.76 (m, 2H), 2.06-2.20 (m, 1H), 1.46-1.58 (m, 2H), 1.37 (s, 9H), 1.06-1.22 (m, 2H); MS (ESI) 475.3 *m/z* [MH^+], $C_{26}H_{31}N_6O_3$ requires 475.3; HPLC = 92% pure.

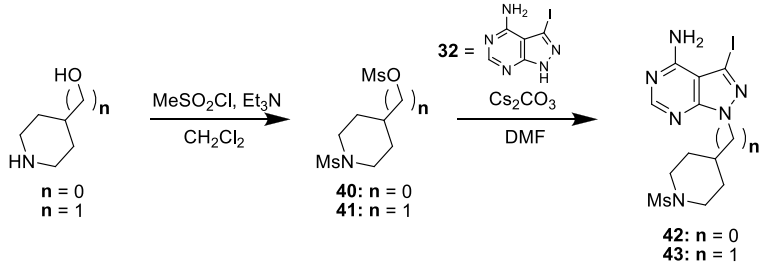


36: 1-Acetylpiperidin-4-yl methanesulfonate. Acetic anhydride (2.0 mL, 21 mmol) was added slowly to a stirring mixture of 4-hydroxypiperidine (2.01 g, 19.9 mmol) and triethylamine (6.9 mL, 50 mmol) in dichloromethane (30 mL), then left to stir at room temperature. The following day, methanesulfonyl chloride (2.3 mL, 30 mmol) was slowly added and the reaction was left to stir for an additional day. The reaction was then diluted into EtOAc and washed with sat. $NaHCO_3$, 1 N HCl, and brine. The organics were dried over Na_2SO_4, filtered, and concentrated. Flash chromatographic purification over silica (CH_2Cl_2/MeOH gradient elution) afforded **36** as an off-white solid (1.40 g). ^{1}H-NMR (300 MHz, d_6-DMSO) δ 4.82-4.92 (m, 1H), 3.74-3.84 (m, 1H), 3.56-3.66 (m, 1H), 3.14-3.34 (m, 5H), 1.84-2.02 (m, 5H), 1.50-1.76 (m, 2H); MS (ESI) 222.2 *m/z* [MH^+], $C_8H_{16}NO_4S$ requires 222.1.

37: (1-Acetylpiperidin-4-yl)methyl methanesulfonate. Acetic anhydride (1.20 mL, 12.7 mmol) was added slowly to a stirring mixture of 4-piperidinemethanol (1.39 g, 12.0 mmol) and triethylamine (4.2 mL, 30 mmol) in dichloromethane (20 mL), then left to stir at room temperature. The following day, methanesulfonyl chloride (1.40 mL, 18.1 mmol) was slowly added and the reaction was left to stir for 3 additional days. The reaction was then diluted into EtOAc and washed with sat. $NaHCO_3$, 1 N HCl, and brine. The organics were dried over Na_2SO_4, filtered, and concentrated. Flash chromatographic purification over silica (CH_2Cl_2/MeOH gradient elution) afforded **37** as a pale-amber syrup (1.70 g). ^{1}H-NMR (300 MHz, d_6-DMSO) δ 4.32-4.42 (m, 1H), 4.07 (d, 2H, *J*=6.3 Hz), 3.76-3.88 (m, 1H), 3.17 (s, 3H), 2.94-3.06 (m, 1H), 2.44-2.56 (m, 1H), 1.86-2.02 (m, 4H), 1.60-1.74 (m, 2H), 0.94-1.24 (m, 2H); MS (ESI) 236.3 *m/z* [MH^+], $C_9H_{18}NO_4S$ requires 236.1.

38: 1-(4-(4-Amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)ethanone. This compound was synthesized following the ***general pyrazolopyrimidine R_2 alkylation procedure*** and using **32** as the pyrazolopyrimidine scaffold (543 mg, 2.08 mmol), **36** as the $\mathbf{R_2}$-mesylate (508 mg, 2.29 mmol), and Cs_2CO_3 as base (1.01 g, 3.10 mmol) in anhydrous DMF (10 mL) at 80 °C for 18 h, affording **38** as a pale-yellow solid (164 mg). ^{1}H-NMR (300 MHz, d_6-DMSO) δ 8.2 (s, 1H), 4.82-4.94 (m, 1H), 4.42-4.52 (m, 1H), 3.88-3.98 (m, 1H), 3.16-3.32 (m, 1H), 2.68-2.80 (m, 1H), 2.05 (s, 3H), 1.80-2.00 (m, 2H), 1.14-1.26 (m, 2H); MS (ESI) 387.3 *m/z* [MH^+], $C_{12}H_{16}IN_6O$ requires 387.0; HPLC = 100% pure.

39: 1-(4-((4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)piperidin-1-yl)ethanone. This compound was synthesized following the ***general pyrazolopyrimidine R_2 alkylation procedure*** and using **32** as the pyrazolopyrimidine scaffold (604 mg, 2.31 mmol), **37** as the $\mathbf{R_2}$-mesylate (610 mg, 2.59 mmol), and Cs_2CO_3 as base (1.14 g, 3.49 mmol) in anhydrous DMF (12 mL) at 80°C for 18 h, affording **39** as a yellow-orange solid (607 mg). ^{1}H-NMR (300 MHz, d_6-DMSO) δ 8.20 (s, 1H), 4.26-4.36 (m, 1H), 4.17 (d, 2H, *J*=7.0 Hz), 3.70-3.80 (m, 1H), 2.88-3.00 (m, 1H), 2.04-2.18 (m, 1H), 1.95 (s, 3H), 1.42-1.52 (m, 2H), 0.94-1.24 (m, 3H); MS (ESI) 401.4 *m/z* [MH^+], $C_{13}H_{18}IN_6O$ requires 401.1; HPLC = 100% pure.



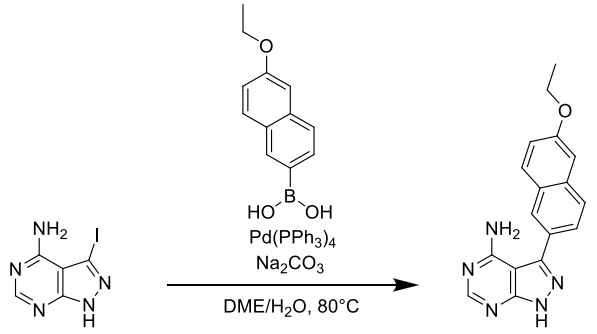
40: 1-(Methylsulfonyl)piperidin-4-yl methanesulfonate. Methanesulfonyl chloride (4.6 mL, 59 mmol) was added slowly to a stirring mixture of 4-hydroxypiperidine (1.98 g, 19.6 mmol) and triethylamine (6.9 mL, 50 mmol) in dichloromethane (40 mL), then left to stir at room temperature. After 18 h, the reaction was diluted into EtOAc and washed with sat. $NaHCO_3$, 1 N HCl, and brine. The organics were dried over Na_2SO_4, filtered, and concentrated to afford **40** as a white powder (4.67 g). ^{1}H-NMR (300 MHz, d_6-DMSO) δ 4.78-4.88 (m, 1H), 3.23-3.33 (m, 2H),

3.22 (s, 3H), 3.08-3.18 (m, 2H), 2.90 (s, 3H), 1.94-2.06 (m, 2H), 1.76-1.88 (m, 2H); MS (ESI) 258.1 *m/z* [MH^+], $C_7H_{16}NO_5S_2$ requires 258.1.

41: (1-(Methylsulfonyl)piperidin-4-yl)methyl methanesulfonate. Methanesulfonyl chloride (1.21 mL, 15.6 mmol) was added slowly to a stirring mixture of 4-piperidinemethanol (722 mg, 6.27 mmol) and triethylamine (1.85 mL, 13.3 mmol) in dichloromethane (20 mL), then left to stir at room temperature. After 18 h, the reaction was diluted into EtOAc and washed with sat. $NaHCO_3$, 1 N HCl, and brine. The organics were dried over Na_2SO_4, filtered, and concentrated. Flash chromatographic purification over silica (CH_2Cl_2/MeOH gradient elution) afforded **41** as a white powder (1.20 g). ^{1}H-NMR (300 MHz, *d*$_6$-DMSO) δ 4.10 (d, 2H, *J*=6.1 Hz), 3.52-3.62 (m, 2H), 3.18 (s, 3H), 2.85 (s, 3H), 2.70 (m, 2H), 1.72-1.84 (m, 3H), 1.20-1.36 (m, 2H); MS (ESI) 272.1 *m/z* [MH^+], $C_8H_{18}NO_5S_2$ requires 272.1.

42: 3-Iodo-1-(1-(methylsulfonyl)piperidin-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general pyrazolopyrimidine R$_2$ alkylation procedure*** and using **32** as the pyrazolopyrimidine scaffold (537 mg, 2.06 mmol), **40** as the **R$_2$**-mesylate (557 mg, 2.16 mmol), and Cs_2CO_3 as base (1.04 g, 3.18 mmol) in anhydrous DMF (10 mL) at 80°C for 18 h, affording **42** as a pale-yellow solid (310 mg). ^{1}H-NMR (300 MHz, *d*$_6$-DMSO) δ 8.20 (s, 1H), 4.68-4.84 (m, 1H), 3.64-3.74 (m, 2H), 2.90-3.06 (m, 5H), 1.94-2.20 (m, 4H); MS (ESI) 423.2 *m/z* [MH^+], $C_{11}H_{16}IN_6OS$ requires 423.0; HPLC = 100% pure.

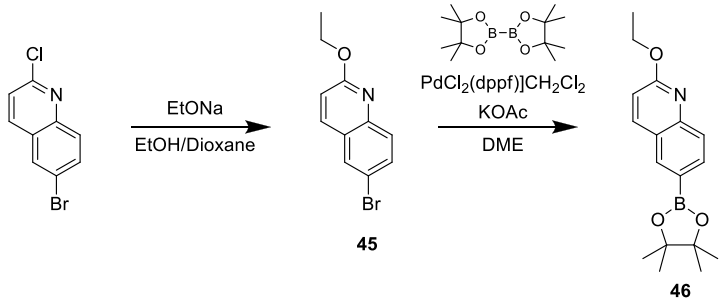
43: 3-Iodo-1-((1-(methylsulfonyl)piperidin-4-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general pyrazolopyrimidine R$_2$ alkylation procedure*** and using **32** as the pyrazolopyrimidine scaffold (538 mg, 2.06 mmol), **41** as the **R$_2$**-mesylate (590 mg, 2.17 mmol), and Cs_2CO_3 as base (1.06 g, 3.26 mmol) in anhydrous DMF (10 mL) at 80 °C for 18 h, affording **43** as a pale-yellow solid (446 mg). ^{1}H-NMR (300 MHz, *d*$_6$-DMSO) δ 8.20 (s, 1H), 4.21 (d, 2H, *J*=7.0 Hz), 3.46-3.56 (m, 2H), 2.82 (s, 3H), 2.58-2.72 (m, 2H), 1.94-2.10 (m, 1H), 1.50-1.64 (m, 2H), 1.14-1.34 (m, 2H); MS (ESI) 437.1 *m/z* [MH^+], $C_{12}H_{18}IN_6O_2S$ requires 437.0; HPLC = 100% pure.



32 44

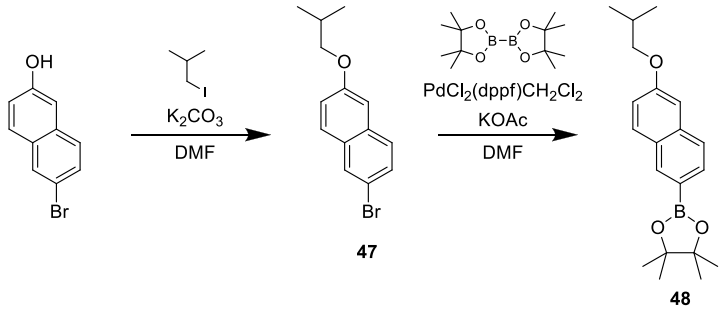
44: 3-(6-Ethoxynaphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. Compound **32** (1 eq.), Na_2CO_3 (4 eq.), $Pd(PPh_3)_4$ (.01 eq.), and 6-ethoxynaphthalene-2-boronic acid (2 eq.) were stirred in dimethoxyethane (DME, 0.5 ml) and water (0.8 ml) and reacted in a microwave at 110°C for one hour. The reaction was then cooled to room temperature, extracted into ethyl acetate, and washed with 0.02 N HCl and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product is then purified via flash chromatography

over silica, eluting with CH_2Cl_2/MeOH gradient. Product fractions were collected and further recrystallized in EtOAc to afford **44** as a white solid. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.39 (s, 1H), 8.10 (d, 1H, *J*=1.4 Hz), 7.98 (d, 1H, *J*=8.2 Hz), 7.86 (d, 1H, *J*=8.4 Hz), 7.72 (dd,1H, *J*=1.9, 8.6 Hz), 7.35 (d, 1H, *J*=2.4 Hz), 7.26 (dd, 1H, *J*=2.5, 8.6 Hz), 4.42 (d, 2H, *J*=6.6 Hz), 1.49 (t, 3H, *J*=7.0 Hz). MS (ESI) 306.5 *m/z* [MH^+] $C_{17}H_{16}N_5O$ requires 306.1.



45: 6-Bromo-2-ethoxyquinoline. 6-Bromo-2-chloroquinoline (133 mg, 0.550 mmol) and sodium ethoxide (341 mg, 5.01 mmol) were stirred in a 50% mixture of EtOH in 1,4-dioxane (6 mL) and reacted in a microwave at 100 °C for 2 h. The reaction was extracted into EtOAc and the organics were washed with H_2O, dried over Na_2SO_4, filtered, and concentrated. Flash chromatographic purification over silica (hexanes/EtOAc gradient elution) afforded **45** as a white solid (112 mg). ^{1}H-NMR (300 MHz, *d*$_6$-DMSO) δ 8.22 (d, 1H, *J*=8.8 Hz), 8.15 (d, 1H, *J*=2.2 Hz), 7.76 (dd, 1H, *J*=2.3, 8.9 Hz), 7.68 (d, 1H, *J*=8.9 Hz), 7.05 (d, 1H, *J*=8.9 Hz), 4.45 (q, 2H, *J*=7.1 Hz), 1.37 (t, 3H, *J*=7.1 Hz); MS (ESI) 252.2/254.1 *m/z* [MH^+], $C_{11}H_{11}BrNO$ requires 252.0/254.0; HPLC = 98% pure.

46: 2-Ethoxy-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinoline.
Bis(pinacolato)diboron (134 mg, 0.529 mmol), **45** (103 mg, 0.407 mmol), $PdCl_2(dppf)CH_2Cl_2$ (18.8 mg, 0.0230 mmol), and KOAc (132 mg, 1.34 mmol) were stirred in anhydrous DMF (3 mL) at 80 °C for 5 h. The reaction was extracted into EtOAc and the organics were washed with H_2O, dried over Na_2SO_4, filtered, and concentrated. Flash chromatographic purification over silica (CH_2Cl_2/MeOH gradient elution) afforded **46** as a white solid (51.1 mg). ^{1}H-NMR (300 MHz, *d*$_6$-DMSO) δ 8.31 (d, 1H, *J*=8.8 Hz), 8.26 (s, 1H), 7.86 (dd, 1H, *J*=1.4, 8.3 Hz), 7.71 (d, 1H, *J*=8.4 Hz), 7.01 (d, 1H, *J*=8.8 Hz), 4.47 (q, 2H, *J*=7.1 Hz), 1.38 (t, 3H, *J*=7.1 Hz), 1.33 (s, 12H); MS (ESI) 300.3 *m/z* [MH^+], $C_{17}H_{23}BNO_3$ requires 300.2.



47: 2-Bromo-6-isobutoxynaphthalene. 6-Bromo-2-naphthol (986 mg, 4.42 mmol), 1-iodo-2-methylpropane (0.76 mL, 6.6 mmol), and K_2CO_3 (1.27 g, 9.19 mmol) were stirred in DMF at

room temperature overnight, then at 80 °C for 6 h. The reaction was extracted into CH_2Cl_2 and the organics were washed with 1 N NaOH, dried over Na_2SO_4, filtered, and concentrated. The syrup was triturated with H_2O and the solid was filtered off, rinsed with H_2O, and dissolved into CH_2Cl_2. The organics were dried over Na_2SO_4, filtered, and concentrated to afford **47** as a brown solid (345 mg). ^{1}H-NMR (300 MHz, d_6-DMSO) δ 8.10 (d, 1H, *J*=1.8 Hz), 7.81 (d, 1H, *J*=9.0 Hz), 7.77 (d, 1H, *J*=8.8 Hz), 7.55 (dd, 1H, *J*=2.0, 8.7 Hz), 7.34 (d, 1H, *J*=2.4 Hz), 7.22 (dd, 1H, *J*=2.5, 9.0 Hz), 3.86 (d, 2H, *J*=6.5 Hz), 2.02-2.16 (m, 1H), 1.02 (d, 6H, *J*=6.7 Hz).

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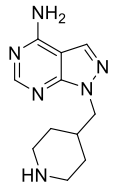
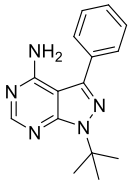
48: 2-(6-Isobutoxynaphthalen-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. Bis(pinacolato)diboron (255 mg, 1.00 mmol), **47** (209 mg, 0.796 mmol), $PdCl_2(dppf)CH_2Cl_2$ (32.5 mg, 0.0398 mmol), and KOAc (158 mg, 1.60 mmol) were stirred in anhydrous DMF (5 mL) at 100 °C for 2 h under a nitrogen atmosphere. The reaction was extracted into EtOAc and the organics were washed with H_2O, dried over Na_2SO_4, filtered, and concentrated. Flash chromatographic purification over silica (hexanes/EtOAc gradient elution) afforded **48** as a white solid (186 mg). ^{1}H-NMR (300 MHz, d_6-DMSO) δ 8.22 (s, 1H), 7.91 (d, 1H, *J*=9.0 Hz), 7.77 (d, 1H, *J*=8.3 Hz), 7.64 (d, 1H, *J*=8.2 Hz), 7.30 (d, 1H, *J*=2.2 Hz), 7.17 (dd, 1H, *J*=2.4, 8.9 Hz), 3.87 (d, 2H, *J*=6.5 Hz), 2.02-2.16 (m, 1H), 1.32 (s, 12H), 1.02 (d, 6H, *J*=6.7 Hz); MS (ESI) 327.4 *m/z* [MH^+], $C_{20}H_{28}BO_3$ requires 327.2.

Synthesis and characterization of final compounds:



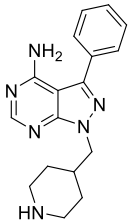
1n

1n: 1-(Piperidin-4-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general boc-deprotection procedure*** and using **33** as the boc-protected piperidine precursor. ^{1}H-NMR (300 MHz, d_6-DMSO) δ 8.45 (s, 1H), 8.43 (s, 1H), 4.28 (d, 2H, *J*=7.0 Hz), 3.16-3.26 (m, 2H), 2.72-2.88 (m, 2H), 2.12-2.26 (m, 1H), 1.56-1.68 (m, 2H), 1.32-1.50 (m, 2H); MS (ESI) 233.1 *m/z* [MH^+], $C_{11}H_{17}N_6$ requires 233.2; HPLC = 100% pure.



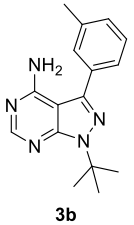
2b

2b: 1-*Tert*-butyl-3-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general Suzuki coupling procedure***, using phenylboronic acid as the aryl coupling reagent and **27** as the aryl-halide. ^{1}H-NMR (300 MHz, d_6-DMSO) δ 8.24 (s, 1H), 7.62-7.68 (m, 2H), 7.46-7.58 (m, 3H), 1.75 (s, 9H); MS (ESI) 268.2 *m/z* [MH^+], $C_{15}H_{18}N_5$ requires 268.2; HPLC-1 = 98% pure, HPLC-2 = 100% pure.



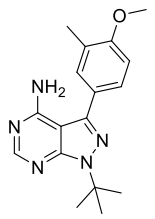
2n

2n: 3-Phenyl-1-(piperidin-4-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general Suzuki coupling procedure***, using phenylboronic acid as the aryl coupling reagent and **34** as the aryl-halide, followed by the ***general boc-deprotection procedure***. ^{1}H-NMR (300 MHz, d_6-DMSO) δ 8.46 (s, 1H), 7.64-7.72 (m, 2H), 7.50-7.62 (m, 3H), 4.33 (d, 2H, *J*=6.9 Hz), 3.18-3.28 (m, 2H), 2.74-2.90 (m, 2H), 2.18-2.32 (m, 1H), 1.64-1.76 (m, 1H), 1.38-1.54 (m, 2H); MS (ESI) 309.3 *m/z* [MH^+], $C_{17}H_{21}N_6$ requires 309.2; HPLC-1 = 100% pure, HPLC-2 = 100% pure.



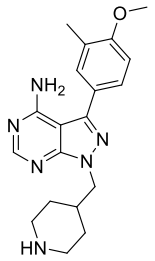
3b

3b: 1-*Tert*-butyl-3-m-tolyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general Suzuki coupling procedure***, using 3-methylphenylboronic acid as the aryl coupling reagent and **27** as the aryl-halide. ^{1}H-NMR (300 MHz, d_6-DMSO) δ 8.23 (s, 1H), 7.40-7.48 (m, 3H), 7.26-7.34 (m, 1H), 2.40 (s, 3H), 1.75 (s, 9H); MS (ESI) 282.2 *m/z* [MH^+], $C_{16}H_{20}N_5$ requires 282.2; HPLC-1 = 100% pure, HPLC-2 = 100% pure.



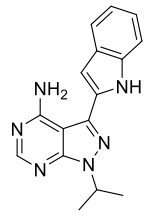
5b

5b: 1-*Tert*-butyl-3-(4-methoxy-3-methylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general Suzuki coupling procedure***, using 4-methoxy-3-methylphenylboronic acid as the aryl coupling reagent and **27** as the aryl-halide. ^{1}H-NMR (300 MHz, d_6-DMSO) δ 8.22 (s, 1H), 7.38-7.46 (m, 2H), 7.06-7.12 (m, 1H), 3.85 (s, 3H), 2.23 (s, 3H), 1.74 (s, 9H); MS (ESI) 312.2 *m/z* [MH^+], $C_{17}H_{22}N_5O$ requires 312.2; HPLC-1 = 100% pure, HPLC-2 = 97% pure.



5n

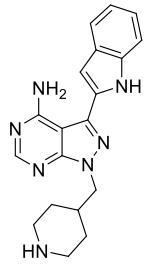
5n: 3-(4-Methoxy-3-methylphenyl)-1-(piperidin-4-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general Suzuki coupling procedure***, using 4-methoxy-3-methylphenylboronic acid as the aryl coupling reagent and **34** as the aryl-halide, followed by the ***general boc-deprotection procedure***. ^{1}H-NMR (300 MHz, d_6-DMSO) δ 8.45 (s, 1H), 7.42-7.50 (m, 2H), 7.13 (d, 1H, *J*=8.3 Hz), 4.31 (d, 2H, *J*=6.9 Hz), 3.87 (s, 3H), 3.18-3.28 (m, 2H), 2.74-2.90 (m, 2H), 2.18-2.30 (m, 4H), 1.64-1.74 (m, 2H), 1.36-1.54 (m, 2H); MS (ESI) 353.4 *m/z* [MH^+], $C_{19}H_{25}N_6O$ requires 353.2; HPLC-1 = 100% pure, HPLC-2 = 97% pure.



6a

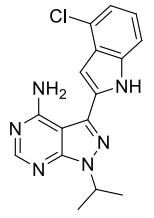
6a: 3-(1H-Indol-2-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general Suzuki coupling procedure***, using N-boc-indole-2-boronic acid as the aryl coupling reagent and **26** as the aryl-halide, followed by the ***general boc-deprotection procedure***. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.95 (br s, 1H), 8.40 (s, 1H), 7.65-7.71 (m, 1H), 7.45-7.50 (m, 1H), 7.27-7.32 (m, 1H), 7.13-7.20 (m, 1H), 6.88-6.92 (s, 1H), 5.20

(septet, 1H, *J*=6.8 Hz), 1.62 (d, *J*=6.8 Hz, 6H); MS (ESI) 293.4 *m/z* [MH^+], $C_{16}H_{17}N_6$ requires 293.2; HPLC-1 = 97% pure, HPLC-2 = 98% pure.



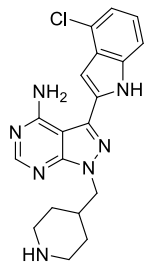
6n

6n: 3-(1H-Indol-2-yl)-1-(piperidin-4-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general Suzuki coupling procedure***, using N-boc-indole-2-boronic acid as the aryl coupling reagent and **34** as the aryl-halide, followed by the ***general boc-deprotection procedure***. ^{1}H-NMR (300 MHz, CD_3OD) δ 8.34 (s, 1H), 7.64-7.68 (m, 1H), 7.46-7.51 (m, 1H), 7.21-7.27 (m, 1H), 7.08-7.15 (m, 1H), 6.92 (m, 1H), 4.44 (d, 2H, *J*=6.9 Hz), 3.37-3.45 (m, 2H), 2.92-3.04 (m, 2H), 2.36-2.47 (m, 1H), 1.87-1.97 (m, 2H), 1.54-1.66 (m, 2H); MS (ESI) 348.4 *m/z* [MH^+], $C_{19}H_{22}N_7$ requires 348.2; HPLC-1 = 96% pure, HPLC-2 = 98% pure.



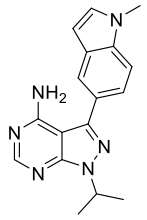
7a

7a: 3-(4-Chloro-1H-indol-2-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general Suzuki coupling procedure***, using 4-chloro-N-boc-indole-2-boronic acid as the aryl coupling reagent and **26** as the aryl-halide, followed by the ***general boc-deprotection procedure***. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.10 (br s, 1H), 8.41 (s, 1H), 7.35-7.39 (m, 1H), 7.16-7.21 (m, 2H), 6.96-6.99 (s, 1H), 5.21 (septet, 1H, *J*=6.8 Hz), 1.62 (d, *J*=6.8 Hz, 6H); MS (ESI) 327.8 *m/z* [MH^+], $C_{16}H_{16}ClN_6$ requires 327.1; HPLC-1 = 100% pure, HPLC-2 = 99% pure.



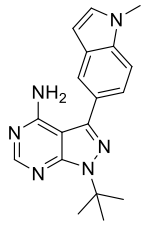
7n

7n: 3-(4-Chloro-1H-indol-2-yl)-1-(piperidin-4-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general Suzuki coupling procedure***, using 4-chloro-N-boc-indole-2-boronic acid as the aryl coupling reagent and **34** as the aryl-halide, followed by the ***general boc-deprotection procedure***. ^{1}H-NMR (300 MHz, CD_3OD) δ 8.34 (s, 1H), 7.45-7.48 (m, 1H), 7.17-7.22 (m, 1H), 7.08-7.15 (m, 1H), 6.96 (m, 1H), 4.44 (d, 2H, *J*=6.9 Hz), 3.37-3.45 (m, 2H), 2.92-3.04 (m, 2H), 2.36-2.47 (m, 1H), 1.87-1.97 (m, 2H), 1.54-1.66 (m, 2H); MS (ESI) 382.9 *m/z* [MH^+], $C_{19}H_{21}ClN_7$ requires 382.2; HPLC-1 = 98% pure, HPLC-2 = 99% pure.



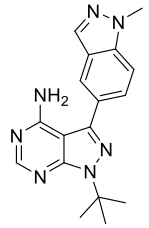
8a

8a: 1-Isopropyl-3-(1-methyl-1H-indol-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general Suzuki coupling procedure***, using 1-methylindole-5-boronic acid pinacol ester as the aryl coupling reagent and **26** as the aryl-halide. ^{1}H-NMR (300 MHz, CD_3OD) δ 8.23 (s, 1H), 7.73 (dd, 1H, *J*=0.6, 8.1 Hz), 7.67-7.69 (m, 1H), 7.34 (dd, 1H, *J*=1.5, 8.1 Hz), 7.28 (d, 1H, *J*=3.1 Hz), 6.52 (dd, 1H, *J*=0.9, 3.1 Hz), 5.14 (septet, 1H, *J*=6.7 Hz), 3.87 (s, 3H), 1.58 (d, 6H, *J*=6.7 Hz); MS (ESI) 307.2 *m/z* [MH^+], $C_{17}H_{19}N_6$ requires 307.2; HPLC-1 = 99% pure, HPLC-2 = 99% pure.



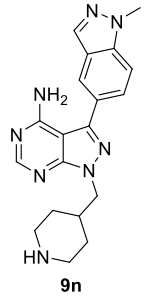
8b

8b: 1-*Tert*-butyl-3-(1-methyl-1H-indol-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general Suzuki coupling procedure***, using 1-methylindole-5-boronic acid pinacol ester as the aryl coupling reagent and **27** as the aryl-halide. ^{1}H-NMR (300 MHz, d_6-DMSO) δ 8.23 (s, 1H), 7.81 (s, 1H), 7.61 (d, 1H, *J*=8.5 Hz), 7.38-7.46 (m, 2H), 6.55 (d, 1H, *J*=3.0 Hz), 3.85 (s, 3H), 1.76 (s, 9H); MS (ESI) 321.4 *m/z* [MH^+], $C_{18}H_{21}N_6$ requires 321.2; HPLC-1 = 97% pure, HPLC-2 = 100% pure.



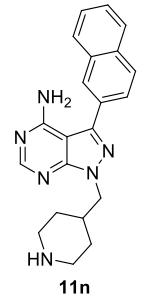
9b

9b: 1-*Tert*-butyl-3-(1-methyl-1H-indazol-5-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general Suzuki coupling procedure***, using 1-methylindazole-5-boronic acid as the aryl coupling reagent and **27** as the aryl-halide. ^{1}H-NMR (300 MHz, d_6-DMSO) δ 8.48 (s, 1H), 8.18 (s, 1H), 8.03 (s, 1H), 7.83 (d, 1H, *J*=8.7 Hz), 7.68 (dd, 1H, *J*=1.4, 8.7 Hz), 4.11 (s, 3H), 1.78 (s, 9H); MS (ESI) 322.3 *m/z* [MH^+], $C_{17}H_{20}N_7$ requires 322.2; HPLC-1 = 100% pure, HPLC-2 = 100% pure.



9n

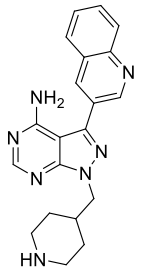
9n: 3-(1-Methyl-1H-indazol-5-yl)-1-(piperidin-4-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general Suzuki coupling procedure***, using 1-methylindazole-5-boronic acid as the aryl coupling reagent and **34** as the aryl-halide, followed by the ***general boc-deprotection procedure***. ^{1}H-NMR (300 MHz, d_6-DMSO) δ 8.48 (s, 1H), 8.19 (s, 1H), 8.04 (s, 1H), 7.84 (d, 1H, *J*=8.7 Hz), 7.69 (dd, 1H, *J*=1.4, 8.7 Hz), 4.34 (d, 2H, *J*=6.8 Hz), 4.12 (s, 3H), 3.18-3.28 (m, 2H), 2.74-2.92 (m, 2H), 2.20-2.32 (m, 1H), 1.66-1.76 (m, 2H), 1.40-1.56 (m, 2H); MS (ESI) 363.3 *m/z* [MH^+], $C_{19}H_{23}N_8$ requires 363.2; HPLC-1 = 100% pure, HPLC-2 = 99% pure.



11n

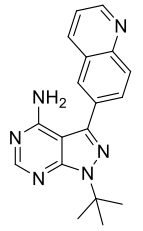
11n: 3-(Naphthalen-2-yl)-1-(piperidin-4-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general Suzuki coupling procedure***, using 2-naphthaleneboronic acid as the aryl coupling reagent and **34** as the aryl-halide, followed by the ***general boc-deprotection procedure***. ^{1}H-NMR (300 MHz, d_6-DMSO) δ 8.47 (s, 1H), 8.21 (s,

1H), 8.10 (d, 1H, *J*=8.5 Hz), 8.00-8.07 (m, 2H), 7.82 (dd, 1H, *J*=1.6, 8.5 Hz), 7.58-7.65 (m, 2H), 4.37 (d, 2H, *J*=6.9 Hz), 3.20-3.30 (m, 2H), 2.76-2.92 (m, 2H), 2.22-2.35 (m, 1H), 1.67-1.78 (m, 2H), 1.40-1.57 (m, 2H); MS (ESI) 359.3 *m/z* [MH^+], $C_{21}H_{23}N_6$ requires 359.2; HPLC-1 = 99% pure, HPLC-2 = 99% pure.



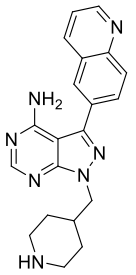
12n

12n: 1-(Piperidin-4-ylmethyl)-3-(quinolin-3-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general Suzuki coupling procedure***, using 3-quinolineboronic acid as the aryl coupling reagent and **34** as the aryl-halide, followed by the ***general boc-deprotection procedure***. ^{1}H-NMR (300 MHz, d_6-DMSO) δ 9.30 (d, 1H, *J*=2.0 Hz), 8.9 (s, 1H), 8.60 (s, 1H), 8.25 (dd, 2H, *J*=3.9, 8.3 Hz), 8.00 (dt, 1H, *J*=1.2, 7.0 Hz), 7.82 (t, 1H, *J*=7.9 Hz), 4.41 (d, 2H, *J*=6.9 Hz), 3.18-3.28 (m, 2H), 2.74-2.92 (m, 2H), 2.22-2.36 (m, 1H), 1.66-1.78 (m, 2H), 1.46-1.62 (m, 2H), 1.10-1.30 (m, 1H); MS (ESI) 360.3 *m/z* [MH^+], $C_{20}H_{22}N_7$ requires 360.2; HPLC-1 = 98% pure, HPLC-2 = 100% pure.



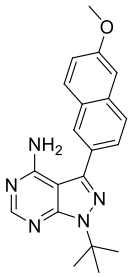
13b

13b: 1-*Tert*-butyl-3-(quinolin-6-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general Suzuki coupling procedure***, using quinoline-6-boronic acid pinacol ester as the aryl coupling reagent and **27** as the aryl-halide. ^{1}H-NMR (300 MHz, d_6-DMSO) δ 9.17 (dd, 1H, *J*=1.3, 4.5 Hz), 8.86 (d, 1H, *J*=8.1 Hz), 8.54 (s, 1H), 8.42 (d, 1H, *J*=1.6 Hz), 8.36 (d, 1H, *J*=8.7 Hz), 8.20 (dd, 1H, *J*=1.8, 8.8 Hz), 7.88 (dd, 1H, *J*=4.7, 8.3 Hz), 1.81 (s, 9H); MS (ESI) 319.3 *m/z* [MH^+], $C_{18}H_{19}N_6$ requires 319.2; HPLC-1 = 99% pure, HPLC-2 = 100% pure.



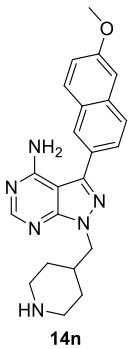
13n

13n: 1-(Piperidin-4-ylmethyl)-3-(quinolin-6-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general Suzuki coupling procedure***, using quinoline-6-boronic acid pinacol ester as the aryl coupling reagent and **34** as the aryl-halide, followed by the ***general boc-deprotection procedure***. ^{1}H-NMR (300 MHz, d_6-DMSO) δ 9.09 (d, 1H, *J*=4.0 Hz), 8.73 (d, 1H, *J*=7.9 Hz), 8.48 (s, 1H), 8.37 (s, 1H), 8.29 (d, 1H, *J*=8.8 Hz), 8.16 (d, 1H, *J*=8.9 Hz), 7.74-7.82 (m, 1H), 4.38 (d, 2H, *J*=6.8 Hz), 3.20-3.30 (m, 2H), 2.76-2.92 (m, 2H), 2.22-2.34 (m, 1H), 1.66-1.78 (m, 2H), 1.40-1.58 (m, 2H); MS (ESI) 360.4 *m/z* [MH^+], $C_{20}H_{21}N_7$ requires 360.2; HPLC-1 = 100% pure, HPLC-2 = 100% pure.



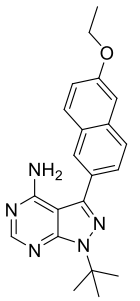
14b

14b: 1-*Tert*-butyl-3-(6-methoxynaphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general Suzuki coupling procedure***, using 6-methoxynaphthalene-2-boronic acid as the aryl coupling reagent and **27** as the aryl-halide. ^{1}H-NMR (300 MHz, d_6-DMSO) δ 8.25 (s, 1H), 8.10 (s, 1H), 7.92-8.00 (m, 2H), 7.75 (dd, 1H, *J*=1.6, 8.5 Hz), 7.41 (d, 1H, *J*=2.4 Hz), 7.23 (dd, 1H, *J*=2.5, 9.0 Hz), 3.91 (s, 3H), 1.78 (s, 9H); MS (ESI) 348.3 *m/z* [MH^+], $C_{20}H_{22}N_5O$ requires 348.2; HPLC-1 = 97% pure, HPLC-2 = 99% pure.



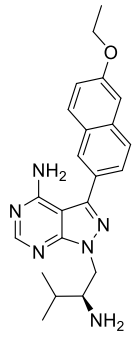
14n

14n: 3-(6-Methoxynaphthalen-2-yl)-1-(piperidin-4-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general Suzuki coupling procedure***, using 6-methoxynaphthalene-2-boronic acid as the aryl coupling reagent and **34** as the aryl-halide, followed by the ***general boc-deprotection procedure***. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.02 (s, 1H), 7.91-7.97 (d, 1H, *J*=8.4 Hz), 7.80-7.85 (d, 1H, *J*=9.0 Hz), 7.63-7.68 (m, 1H), 7.20-7.30 (m, 2H), 4.43-4.49 (d, 2H, *J*=6.3 Hz), 3.98 (s, 3H), 3.44-3.54 (m, 2H), 2.82-3.00 (m, 2H), 2.30-2.45 (m, 1H), 1.86-1.96 (m, 2H), 1.67-1.82 (m, 2H); MS (ESI) 389.5 *m/z* [MH^+], $C_{22}H_{25}N_6O$ requires 389.2; HPLC-1 = 100% pure, HPLC-2 = 100% pure.



15b

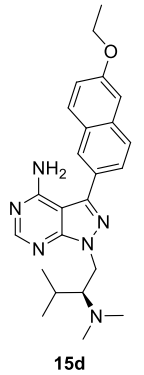
15b: 1-*Tert*-butyl-3-(6-ethoxynaphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general Suzuki coupling procedure***, using 6-ethoxynaphthalene-2-boronic acid as the aryl coupling reagent and **27** as the aryl-halide. ^{1}H-NMR (300 MHz, d_6-DMSO) δ 8.25 (s, 1H), 8.09 (s, 1H), 7.95 (d, 2H, *J*=8.4 Hz), 7.73 (dd, 1H, *J*=1.7, 8.4 Hz), 7.39 (d, 1H, *J*=2.3 Hz), 7.22 (dd, 1H, *J*=2.5, 8.9 Hz), 4.18 (q, 2H, *J*=7.0 Hz), 1.78 (s, 9H), 1.42 (t, 3H, *J*=6.9 Hz); MS (ESI) 362.3 *m/z* [MH^+], $C_{21}H_{24}N_5O$ requires 362.2; HPLC-1 = 100% pure, HPLC-2 = 100% pure.



15c

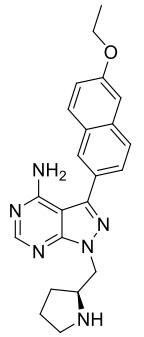
15c: (S)-1-(2-Amino-3-methylbutyl)-3-(6-ethoxynaphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. A mixture of **44** (1 eq.) and Boc-L-valinol (2 eq.) in dry THF was added to polymer-supported triphenylphosphine (2 eq.), stirred at room temperature for 20 min, then DIAD (2 eq.) was added. The mixture was then reacted in a microwave at 70 °C for 20 min. The resin was filtered off and washed with dichloromethane, concentrated *in vacuo*, and purified by silica gel flash chromatography with CH_2Cl_2/MeOH elution. The desired product was collected and subsequently deprotected by stirring in a mixture of TFA and DCM for 30 min. After concentrating, the residue was further purified by preparatory RP-HPLC and converted to the HCl salt. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.50 (s, 1H), 8.16 (s, 1H), 7.97 (d, 1H, *J*=8.4 Hz), 7.88

(d, 1H, *J*=9.1 Hz), 7.79 (dd, 1H, *J*=1.7, 8.5), 7.33 (d, 1H, *J*=2.3 Hz), 7.22 (dd, 1H, *J*=1.9, 8.4 Hz), 4.79 (d, 2H, *J*=8.9 Hz), 4.19 (q, 2H, *J*=7.0 Hz), 3.72 (m, 1H), 1.92-2.12 (m, 1H), 1.46 (t, 3H, *J*=7.0 Hz), 1.16 (m, 6H); MS (ESI) 391.6 *m/z* [MH^+], $C_{22}H_{27}N_6O$ requires 391.2; HPLC-1 = 100% pure, HPLC-2 = 100% pure.



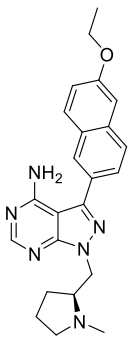
15d

15d: (S)-1-(2-(Dimethylamino)-3-methylbutyl)-3-(6-ethoxynaphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general reductive alkylation procedure***, using **15c** as the amine. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.55 (s, 1H), 8.17 (s, 1H), 7.99 (d, 1H, *J*=8.8 Hz), 7.90 (d, 1H, *J*=8.6 Hz), 7.79 (dd, 1H, *J*=1.6, 8.4 Hz), 7.35 (d, 1H, *J*=2.4 Hz), 7.25 (m, 1H), 5.05 (m, 1H), 4.91 (d, 1H, *J*=6.8 Hz), 4.21 (q, 2H, *J*=6.8 Hz), 4.00 (dd, 1H, *J*=4.3, 8.4 Hz), 3.02 (s, 6H), 2.40-2.57 (m, 1H), 1.48 (t, 3H, *J*=7.0 Hz), 1.22 (m, 6H); MS (ESI) 419.6 *m/z* [MH^+], $C_{24}H_{31}N_6O$ requires 419.3; HPLC-1 = 98% pure, HPLC-2 = 97% pure.



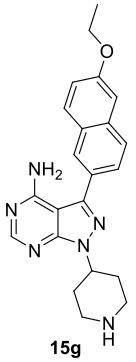
15e

15e: (R)-3-(6-Ethoxynaphthalen-2-yl)-1-(pyrrolidin-2-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the same method as for **15c** by using Boc-L-prolinol. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.52 (s, 1H), 8.19 (s, 1H), 7.99 (d, 1H, *J*=8.3 Hz), 7.90 (d, 1H, *J*=8.9 Hz), 7.81 (dd, 1H, *J*=1.6, 8.6 Hz), 7.34 (d, 1H, *J*=2.4 Hz), 7.24 (dd, 1H, *J*=2.5, 8.9 Hz), 5.02 (m, 1H), 4.77 (m, 1H), 4.11-4.29 (m, 3H), 3.44 (m, 1H), 3.33-3.40 (m, 1H), 2.31-2.46 (m, 1H), 2.02-2.24 (m, 2H), 1.85-2.02 (m, 1H), 1.41-1.56 (m, 3H); MS (ESI) 389.6 *m/z* [MH^+], $C_{22}H_{25}N_6O$ requires 389.2; HPLC-1 = 97% pure, HPLC-2 = 97% pure.



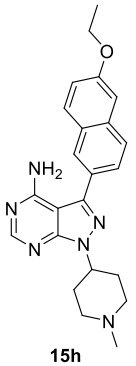
15f

15f: (R)-3-(6-Ethoxynaphthalen-2-yl)-1-((1-methylpyrrolidin-2-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general reductive alkylation procedure***, using **15e** as the amine. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.52 (s, 1H), 8.16 (s, 1H), 7.98 (d, 1H, *J*=9.1 Hz), 7.89 (d, 1H, *J*=8.9 Hz), 7.78 (dd, 1H, *J*=1.5, 8.3 Hz), 7.34 (d, 1H, *J*=2.4 Hz), 7.24 (dd, 1H, *J*=2.0, 9.4 Hz), 4.93-5.05 (m, 2H), 4.15-4.27 (m, 2H), 4.02-4.15 (m, 1H), 3.72-3.85 (m, 1H), 3.26 (dd, 1H, *J*=5.1, 9.0 Hz), 3.07 (s, 3H), 2.42 (m, 1H), 2.11 (m, 3H), 1.47 (t, 3H, *J*=7.0 Hz); MS (ESI) 403.6 *m/z* [MH^+], $C_{23}H_{27}N_6O$ requires 403.2; HPLC-1 = 98% pure, HPLC-2 = 98% pure.



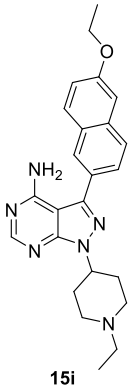
15g

15g: 3-(6-Ethoxynaphthalen-2-yl)-1-(piperidin-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the same method as for **15c** by using tert-butyl-4-hydroxypiperidine-1-carboxylate. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.46 (s, 1H), 8.12 (d,1H, *J*=0.8 Hz), 7.98 (d, 1H, *J*=8.6 Hz), 7.89 (d, 1H, *J*=9.0 Hz), 7.75 (dd, 1H, *J*=1.7, 8.4 Hz), 7.34 (d, 1H, *J*=2.6 Hz), 7.25 (dd, 1H, *J*=1.9, 9.6 Hz), 5.18-5.37 (m, 1H), 4.21 (q, 2H, *J*=6.9 Hz), 3.65 (d, 2H, *J*=12.9 Hz), 3.36 (2H, overlapped with solvent peak), 2.46-2.66 (m, 2H), 2.36 (m, 2H), 1.43-1.58 (m, 3H); MS (ESI) 389.6 *m/z* [MH^+], $C_{22}H_{25}N_6O$ requires 389.2; HPLC-1 = 100% pure, HPLC-2 = 100% pure.



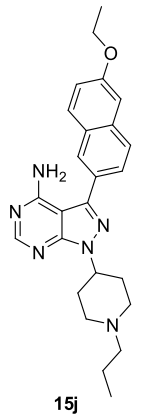
15h

15h: 3-(6-Ethoxynaphthalen-2-yl)-1-(1-methylpiperidin-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general reductive alkylation procedure***, using **15g** as the amine. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.49 (s, 1H), 8.12 (s, 1H), 7.98 (d, 1H, *J*=8.4 Hz), 7.89 (d, 1H, *J*=9.0 Hz), 7.75 (d, 1H, *J*=8.3 Hz), 7.34 (d, 1H, *J*=2.3 Hz), 7.24 (dd, 1H, *J*=2.2, 8.8 Hz), 5.21-5.34 (m, 1H), 4.21 (q, 2H, *J*=7.0 Hz), 3.75 (d, 2H, *J*=13.7 Hz), 3.38 (t, 2H, *J*=11.9 Hz), 2.98 (s, 3H), 2.66 (m, 2H), 2.40 (d, 2H, *J*=12.1 Hz), 1.48 (t, 3H, *J*=6.9 Hz); MS (ESI) 403.6 *m/z* [MH^+], $C_{23}H_{27}N_6O$ requires 403.2; HPLC-1 = 97% pure, HPLC-2 = 98% pure.



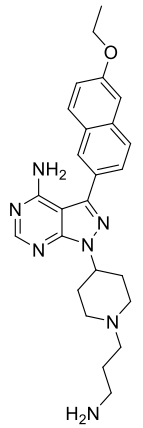
15i

15i: 3-(6-Ethoxynaphthalen-2-yl)-1-(1-ethylpiperidin-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general reductive alkylation procedure***, using **15g** as the amine. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.49 (s, 1H), 8.12 (s, 1H), 7.98 (d, 1H, *J*=8.5 Hz), 7.89 (d, 1H, *J*=9.0 Hz), 7.75 (d, 1H, *J*=8.7 Hz), 7.35 (d, 1H, *J*=2.2 Hz), 7.24 (dd, 1H, *J*=2.4, 8.9 Hz), 5.30 (m, 1H), 4.13-4.28 (m, 2H), 3.81 (d, 2H, *J*=12.1 Hz), 3.35 (4H, overlapped with solvent peak), 2.67 (m, 2H), 2.42 (d, 2H, *J*=15.6 Hz), 1.48 (t, 3H, *J*=7.0 Hz), 1.42 (t, 3H, *J*=8.0 Hz); MS (ESI) 417.7 *m/z* [MH^+], $C_{24}H_{29}N_6O$ requires 417.2; HPLC-1 = 97% pure, HPLC-2 = 97% pure.



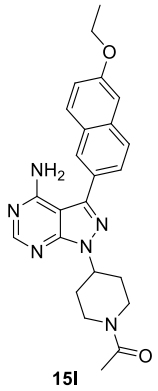
15j

15j: 3-(6-Ethoxynaphthalen-2-yl)-1-(1-propylpiperidin-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general reductive alkylation procedure***, using **15g** as the amine. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.55 (s, 1H), 8.14 (s, 1H), 7.98 (d, 1H, *J*=8.4 Hz), 7.89 (d, 1H, *J*=9.0 Hz), 7.75 (d, 1H, *J*=8.3 Hz), 7.34 (d, 1H, *J*=2.4 Hz), 7.24 (dd, 1H, *J*=1.9, 9.2 Hz), 5.19-5.32 (m, 1H), 4.21 (q, 2H, *J*=7.0 Hz), 3.70 (d, 2H, *J*=13.2 Hz), 3.28-3.40 (m, 4H), 2.45-2.66 (m, 2H), 2.40 (d, 2H, *J*=12.4 Hz), 2.28 (d, 2H, *J*=15.4 Hz), 1.48 (t, 3H, *J*=6.9 Hz), 0.95 (t, 3H, *J*=8.1 Hz); MS (ESI) 431.6 *m/z* [MH^+], $C_{25}H_{31}N_6O$ requires 431.3; HPLC-1 = 98% pure, HPLC-2 = 98% pure.



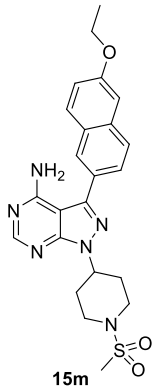
15k

15k: 1-(1-(3-Aminopropyl)piperidin-4-yl)-3-(6-ethoxynaphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general reductive alkylation procedure***, using **15g** as the amine and tert-butyl 2-formylethylcarbamate, followed by the ***general boc-deprotection procedure***. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.54 (s, 1H), 8.15 (s, 1H), 8.01 (d, 1H, *J*=8.6 Hz), 7.92 (d, 1H, *J*=8.5 Hz), 7.85 (d, 1H, *J*=8.0 Hz), 7.38 (d, 1H, *J*=2.2 Hz), 7.26 (dd, 1H, *J*=1.9, 9.2 Hz), 5.21-5.34 (m, 1H), 4.20 (q, 2H, *J*=6.9 Hz), 3.75 (d, 2H, *J*=13.6 Hz), 3.32-3.44 (m, 6H), 2.52-2.68 (m, 2H), 2.44 (d, 2H, *J*=12.6 Hz), 2.14-2.28 (m, 2H), 1.48 (t, 3H, *J*=7.0 Hz); MS (ESI) 446.9 *m/z* [MH^+], $C_{25}H_{32}N_7O$ requires 446.3; HPLC-1 = 100% pure, HPLC-2 = 100% pure.



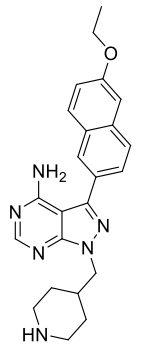
15l

15l: 1-(4-(4-Amino-3-(6-ethoxynaphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)piperidin-1-yl)ethanone. This compound was synthesized following the ***general Suzuki coupling procedure***, using 6-ethoxynaphthalene-2-boronic acid as the aryl coupling reagent and **38** as the aryl-halide. ^{1}H-NMR (300 MHz, d_6-DMSO) δ 8.27 (s, 1H), 8.10 (d, 1H, *J*=1.2 Hz), 7.95 (d, 2H, *J*=8.6 Hz), 7.75 (dd, 1H, *J*=1.6, 8.4 Hz), 7.40 (d, 1H, *J*=2.4 Hz), 7.22 (dd, 1H, *J*=2.5, 8.9 Hz), 4.94-5.08 (m, 1H), 4.48-4.58 (m, 1H), 4.18 (q, 2H, *J*=7.0 Hz), 3.92-4.04 (m, 1H), 2.70-2.86 (m, 1H), 2.08-2.28 (m, 2H), 2.06 (s, 3H), 1.92-2.04 (m, 3H), 1.42 (t, 3H, *J*=6.9 Hz); MS (ESI) 431.5 *m/z* [MH^+], $C_{24}H_{27}N_6O_2$ requires 431.2; HPLC-1 = 100% pure, HPLC-2 = 100% pure.



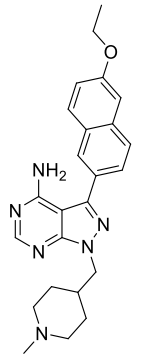
15m

15m: 3-(6-Ethoxynaphthalen-2-yl)-1-(1-(methylsulfonyl)piperidin-4-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general Suzuki coupling procedure***, using 6-ethoxynaphthalene-2-boronic acid as the aryl coupling reagent and **42** as the aryl-halide. ^{1}H-NMR (300 MHz, d_6-DMSO) δ 8.27 (s, 1H), 8.12 (d, 1H, *J*=1.2 Hz), 7.95 (dd, 2H, *J*=2.1, 8.7 Hz), 7.76 (dd, 1H, *J*=1.7, 8.5 Hz), 7.40 (d, 1H, *J*=2.4 Hz), 7.22 (dd, 1H, *J*=2.5, 8.9 Hz), 4.82-4.96 (m, 1H), 4.19 (q, 2H, *J*=7.0 Hz), 3.68-3.78 (m, 2H), 2.98-3.10 (m, 2H), 2.95 (s, 3H), 2.18-2.34 (m, 2H), 2.04-2.14 (m, 2H), 1.42 (t, 3H, *J*=6.9 Hz); MS (ESI) 467.4 *m/z* [MH^+], $C_{23}H_{27}N_6O_3S$ requires 467.2; HPLC-1 = 100% pure, HPLC-2 = 100% pure.



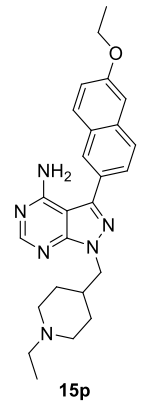
15n

15n: 3-(6-Ethoxynaphthalen-2-yl)-1-(piperidin-4-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general Suzuki coupling procedure***, using 6-ethoxynaphthalene-2-boronic acid as the aryl coupling reagent and **34** as the aryl-halide, followed by the ***general boc-deprotection procedure***. ^{1}H-NMR (300 MHz, d_6-DMSO) δ 8.50 (s, 1H), 8.12 (s, 1H), 7.97 (t, 2H, *J*=8.3 Hz), 7.75 (dd, 1H, *J*=1.7, 8.4 Hz), 7.43 (d, 1H, *J*=2.4 Hz), 7.24 (dd, 1H, *J*=2.5, 9.0 Hz), 4.36 (d, 2H, *J*=7.0 Hz), 4.19 (q, 2H, *J*=7.0 Hz), 3.20-3.30 (m, 2H), 2.75-2.92 (m, 2H), 2.20-2.32 (m, 1H), 1.66-1.76 (m, 2H), 1.38-1.56 (m, 5H); MS (ESI) 403.5 *m/z* [MH^+], $C_{23}H_{27}N_6O$ requires 403.2; HPLC-1 = 100% pure, HPLC-2 = 97% pure.



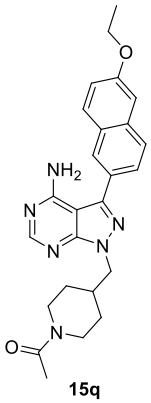
15o

15o: 3-(6-Ethoxynaphthalen-2-yl)-1-((1-methylpiperidin-4-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general reductive alkylation procedure***, using **15n** as the amine. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.47 (s, 1H), 8.13 (s, 1H), 7.98 (d, 1H, *J*=8.4 Hz), 7.89 (d, 1H, *J*=9.0 Hz), 7.76 (d, 1H, *J*=7.8 Hz), 7.34 (d, 1H, *J*=2.4 Hz), 7.24 (m, 1H), 4.51 (d, 2H, *J*=6.7 Hz), 4.21 (q, 2H, *J*=7.0 Hz), 3.53 (d, 2H, *J*=11.2 Hz), 3.01 (t, 2H, *J*=11.7 Hz), 2.84 (s, 3H), 2.31-2.52 (m, 1H), 1.98 (d, 2H, *J*=14.3 Hz), 1.71 (m, 2H), 1.48 (t, 3H, *J*=7.0 Hz); MS (ESI) 417.6 *m/z* [MH^+], $C_{24}H_{29}N_6O$ requires 417.2; HPLC-1 = 100% pure, HPLC-2 = 100% pure.



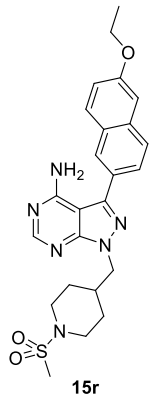
15p

15p: 3-(6-Ethoxynaphthalen-2-yl)-1-((1-ethylpiperidin-4-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general reductive alkylation procedure***, using **15n** as the amine. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.47 (s, 1H), 8.13 (d, 1H, *J*=3.9 Hz), 7.98 (d, 1H, *J*=8.6 Hz), 7.89 (d, 1H, *J*=9.1 Hz), 7.76 (m, 1H), 7.35 (d, 1H, *J*=2.4 Hz), 7.25 (m, 1H), 4.52 (d, 2H, *J*=6.6 Hz), 4.14-4.32 (m, 2H), 3.59 (d, 2H, *J*=8.0 Hz), 3.16 (m, 2H), 2.95 (t, 2H, *J*=11.1 Hz), 2.45 (s, 1H), 2.01 (d, 2H, *J*=13.6 Hz), 1.71 (m, 2H), 1.48 (t, 3H, *J*=7.0 Hz), 1.34 (t, 3H, *J*=7.3 Hz); MS (ESI) 431.6 *m/z* [MH^+], $C_{25}H_{31}N_6O$ requires 431.3; HPLC-1 = 97% pure, HPLC-2 = 97% pure.



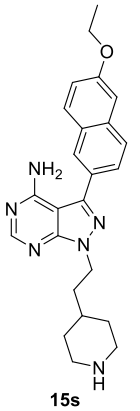
15q

15q: 1-(4-((4-Amino-3-(6-ethoxynaphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-1-yl)methyl)piperidin-1-yl)ethanone. This compound was synthesized following the ***general Suzuki coupling procedure***, using 6-ethoxynaphthalene-2-boronic acid as the aryl coupling reagent and **39** as the aryl-halide. ^{1}H-NMR (300 MHz, d_6-DMSO) δ 8.27 (s, 1H), 8.12 (s, 1H), 7.95 (d, 2H, *J*=8.7 Hz), 7.76 (dd, 1H, *J*=1.5, 8.4 Hz), 7.39 (d, 1H, *J*=2.2 Hz), 7.22 (dd, 1H, *J*=2.4, 9.0 Hz), 4.24-4.38 (m, 3H), 4.19 (q, 2H, *J*=7.0 Hz), 3.74-3.82 (m, 1H), 2.90-3.02 (m, 1H), 2.14-2.28 (m, 1H), 1.96 (s, 3H), 1.50-1.60 (m, 2H), 1.42 (t, 3H, *J*=6.9 Hz), 1.02-1.28 (m, 3H); MS (ESI) 445.4 *m/z* [MH^+], $C_{25}H_{29}N_6O_2$ requires 445.2; HPLC-1 = 100% pure, HPLC-2 = 100% pure.



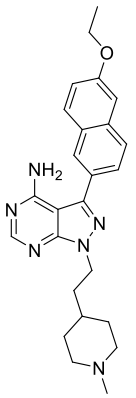
15r

15r: 3-(6-Ethoxynaphthalen-2-yl)-1-((1-(methylsulfonyl)piperidin-4-yl)methyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general Suzuki coupling procedure***, using 6-ethoxynaphthalene-2-boronic acid as the aryl coupling reagent and **43** as the aryl-halide. ^{1}H-NMR (300 MHz, d_6-DMSO) δ 8.27 (s, 1H), 8.12 (s, 1H), 7.95 (dd, 2H, *J*=1.6, 7.5 Hz), 7.76 (dd, 1H, *J*=1.6, 8.4 Hz), 7.39 (d, 1H, , *J*=2.3 Hz), 7.22 (dd, 1H, *J*=2.5, 8.9 Hz), 4.31 (d, 2H, *J*=6.9 Hz), 4.19 (q, 2H, *J*=7.0 Hz), 3.48-3.58 (m, 2H), 2.82 (s, 3H), 2.60-2.74 (m, 2H), 2.04-2.20 (m, 1H), 1.60-1.70 (m, 2H), 1.42 (t, 3H, *J*=6.9 Hz), 1.22-1.38 (m, 2H); MS (ESI) 481.4 *m/z* [MH^+], $C_{24}H_{29}N_6O_3S$ requires 481.2; HPLC-1 = 99% pure, HPLC-2 = 98% pure.



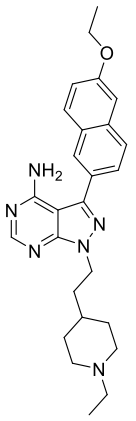
15s

15s: 3-(6-Ethoxynaphthalen-2-yl)-1-(2-(piperidin-4-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following procedure for **15c**, using **44** as the pyrazolopyrimidine scaffold, and tert-butyl-4-(2-hydroxyethyl)piperidine-1-carboxylate. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.39 (s, 1H), 8.04-8.15 (m, 1H), 7.95 (d, 1H, *J*=8.6 Hz), 7.87 (d, 1H, *J*=9.0 Hz), 7.73 (dd, 1H, *J*=1.8, 8.5 Hz), 7.31 (d, 1H, *J*=2.8 Hz), 7.22 (dd, 1H, *J*=2.5, 8.9 Hz), 4.49-4.66 (m, 2H), 4.11-4.29 (m, 2H), 3.36 (d, 2H, *J*=13.2 Hz), 2.92 (t, 2H, *J*=11.8 Hz), 2.06 (d, 2H, *J*=13.4 Hz), 1.94-2.02 (m, 2H), 1.56-1.66 (m, 1H), 1.31-1.49 (m, 5H); MS (ESI) 417.6 *m/z* [MH^+], $C_{24}H_{29}N_6O$ requires 417.2; HPLC-1 = 100% pure, HPLC-2 = 100% pure.



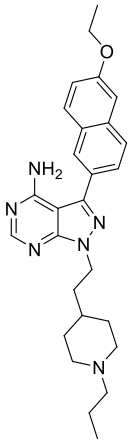
15t

15t: 3-(6-Ethoxynaphthalen-2-yl)-1-(2-(1-methylpiperidin-4-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general reductive alkylation procedure***, using **15s** as the amine. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.39 (s, 1H), 8.09 (s, 1H), 7.95 (d, 1H, *J*=8.6 Hz), 7.87 (d, 1H, *J*=9.0 Hz), 7.73 (dd, 1H, *J*=1.8, 8.5 Hz), 7.32 (d, 1H, *J*=2.5 Hz), 7.22 (dd, 1H, *J*=2.5, 8.9 Hz), 4.56 (t, 2H, *J*=6.6 Hz), 4.19 (q, 2H, *J*=7.0 Hz), 3.56 (d, 2H, *J*=12.2 Hz), 2.96-3.12 (m, 2H), 2.81 (s, 3H), 2.10 (d, 2H, *J*=15.2 Hz), 1.70 (m, 2H), 1.58-1.65 (m, 1H), 1.42-1.50 (m, 5H); MS (ESI) 431.6 *m/z* [MH^+], $C_{25}H_{31}N_6O$ requires 431.3; HPLC-1 = 100% pure, HPLC-2 = 100% pure.



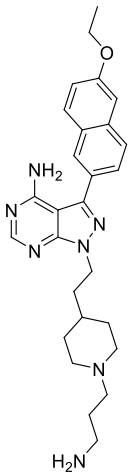
15u

15u: 3-(6-Ethoxynaphthalen-2-yl)-1-(2-(1-ethylpiperidin-4-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general reductive alkylation procedure***, using **15s** as the amine. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.41 (s, 1H), 8.11 (s, 1H), 7.96 (d, 1H, *J*=8.6 Hz), 7.97 (d, 1H, *J*=9.0 Hz), 7.83 (dd, 1H, *J*=1.7, 8.4 Hz), 7.38 (d, 1H, *J*=2.6 Hz), 7.24 (dd, 1H, *J*=1.9, 9.6 Hz), 4.56 (t, 2H, *J*=7.2 Hz), 4.16-4.29 (m, 2H), 3.49 (d, 2H, *J*=14.2 Hz), 3.05-3.20 (m, 2H), 2.86 (t, 2H, *J*=11.2 Hz), 2.08 (d, 2H, *J*=15.6 Hz), 1.69 (m, 2H), 1.50-1.62 (m, 1H), 1.34-1.47 (m, 5H), 1.28 (t, 3H, *J*=8.6 Hz); MS (ESI) 445.7 *m/z* [MH^+], $C_{26}H_{32}N_6O$ requires 445.3; HPLC-1 = 100% pure, HPLC-2 = 100% pure.



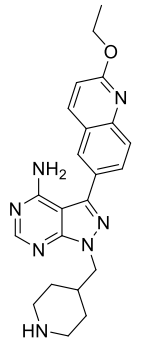
15v

15v: 3-(6-Ethoxynaphthalen-2-yl)-1-(2-(1-propylpiperidin-4-yl)ethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general reductive alkylation procedure***, using **15s** as the amine. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.39 (s, 1H), 8.09 (s, 1H), 7.95 (d, 1H, *J*=8.5 Hz), 7.87 (d, 1H, *J*=9.0 Hz), 7.73 (dd, 1H, *J*=1.7, 8.4 Hz), 7.32 (d, 1H, *J*=2.5 Hz), 7.22 (dd, 1H, *J*=2.5, 8.9 Hz), 4.57 (t, 2H, *J*=6.9 Hz), 4.19 (q, 2H, *J*=7.0 Hz), 3.55 (d, 2H, *J*=14.8 Hz), 2.94-3.06 (m, 2H), 2.87 (t, 2H, *J*=11.1 Hz), 2.12 (d, 2H, *J*=15.4 Hz), 1.92-2.03 (m, 2H), 1.72 (m, 2H), 1.54-1.66 (m, 1H), 1.42-1.50 (m, 5H), 0.98 (t, 3H, *J*=8.1 Hz); MS (ESI) 459.7 *m/z* [MH^+], $C_{27}H_{35}N_6O$ requires 459.3; HPLC-1 = 100% pure, HPLC-2 = 100% pure.



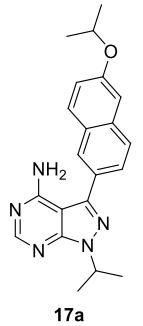
15w

15w: 1-(2-(1-(3-Aminopropyl)piperidin-4-yl)ethyl)-3-(6-ethoxynaphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the procedure for **15k**, using **15s** as the amine. ^{1}H-NMR (500 MHz, CD_3OD) δ 8.38 (s, 1H), 8.09 (d, 1H, *J*=1.4 Hz), 7.95 (d, 1H, *J*=8.7 Hz), 7.87 (d, 1H, *J*=8.9 Hz), 7.73 (dd, 1H, *J*=1.9, 8.6 Hz), 7.32 (d, 1H, *J*=2.4 Hz), 7.22 (dd, 1H, *J*=2.5, 8.8 Hz), 4.56 (t, 2H, *J*=6.2 Hz), 4.19 (q, 2H, *J*=6.9 Hz), 3.57 (d, 2H, *J*=12.2 Hz), 3.08-3.22 (m, 2H), 3.00 (m, 2H), 2.91 (t, 2H, *J*=10.9 Hz), 2.10 (m, 4H), 1.92-2.05 (m, 2H), 1.81 (m, 1H), 1.57 (m, 2H), 1.47 (t, 3H, *J*=7.0 Hz); MS (ESI) 474.7 *m/z* [MH^+], $C_{27}H_{36}N_7O$ requires 474.3; HPLC-1 = 100% pure, HPLC-2 = 100% pure.



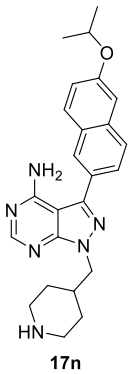
16n

16n: 3-(2-Ethoxyquinolin-6-yl)-1-(piperidin-4-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general Suzuki coupling procedure***, using **46** as the aryl coupling reagent and **34** as the aryl-halide, followed by the ***general boc-deprotection procedure***. ^{1}H-NMR (300 MHz, d_6-DMSO) δ 8.57 (s, 1H), 8.37 (d, 1H, *J*=9.0 Hz), 8.18 (s, 1H), 7.94 (s, 2H), 7.10 (d, 1H, *J*=8.8 Hz), 4.51 (d, 2H, *J*=7.0 Hz), 4.35-4.41 (m, 2H), 3.20-3.30 (m, 2H), 2.76-2.92 (m, 2H), 2.24-2.34 (m, 1H), 1.68-1.78 (m, 2H), 1.45-1.60 (m, 2H), 1.41(t, 3H, *J*=7.1 Hz); MS (ESI) 404.4 *m/z* [MH^+], $C_{22}H_{26}N_7O$ requires 404.2; HPLC-1 = 99% pure, HPLC-2 = 99% pure.



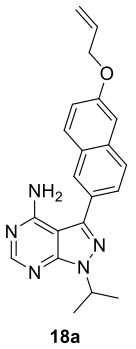
17a

17a: 3-(6-Isopropoxynaphthalen-2-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general naphthol alkylation procedure***, using **28** as the naphthol scaffold and isopropyl iodide as the $\mathbf{R_3}$-halide. ^{1}H-NMR (300 MHz, CD_3OD) δ 8.27 (s, 1H), 8.10 (s, 1H), 7.88-7.97 (m, 2H), 7.76 (d, 1H, *J*=9.0 Hz), 7.35 (s, 1H), 7.19-7.24 (m, 1H), 5.13-5.22 (m, 1H), 1.60-1.63 (m, 6H), 1.41-1.45 (m, 6H); MS (ESI) 362.4 *m/z* [MH^+], $C_{21}H_{24}N_5O$ requires 362.2; HPLC-1 = 95% pure, HPLC-2 = 95% pure.



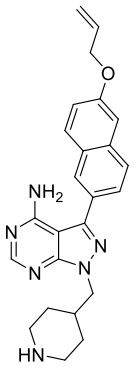
17n

17n: 3-(6-Isopropoxynaphthalen-2-yl)-1-(piperidin-4-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general naphthol alkylation procedure***, using **35** as the naphthol scaffold and isopropyl iodide as the $\mathbf{R_3}$-halide, followed by the ***general boc-deprotection procedure***. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.02 (s, 1H), 7.87-7.94 (d, 1H, *J*=8.4 Hz), 7.77-7.84 (d, 1H, *J*=9.0 Hz), 7.60-7.67 (m, 1H), 7.20-7.28 (m, 2H), 4.71-4.82 (septet, 1H, *J*=6.0 Hz), 4.40-4.48 (m, 2H), 3.40-3.52 (m, 2H), 2.80-2.93 (m, 2H), 2.30-2.44 (m, 1H), 1.83-1.96 (m, 2H), 1.67-1.81 (m, 2H), 1.41-1.46 (d, 6H, *J*=6.0 Hz); MS (ESI) 417.5 *m/z* [MH^+], $C_{24}H_{29}N_6O$ requires 417.2; HPLC-1 = 100% pure, HPLC-2 = 100% pure.



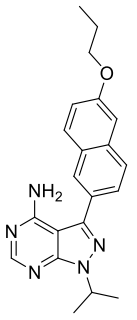
18a

18a: 3-(6-(Allyloxy)naphthalen-2-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general naphthol alkylation procedure***, using **28** as the naphthol scaffold and allyl bromide as the $\mathbf{R_3}$-halide. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.04 (s, 1H), 7.90-7.95 (d, 1H, *J*=8.4 Hz), 7.81-7.87 (d, 1H, *J*=9.0 Hz), 7.66-7.72 (m, 1H), 7.19-7.33 (m, 2H), 6.07-6.22 (m, 1H), 5.45-5.55 (m, 1H), 5.32-5.40 (m, 1H), 5.23 (septet, 1H, *J*=6.9 Hz), 4.67-4.74 (m, 2H), 1.65 (d, 6H, *J*=6.9 Hz); MS (ESI) 360.5 *m/z* [MH^+], $C_{21}H_{22}N_5O$ requires 360.2; HPLC-1 = 98% pure, HPLC-2 = 100% pure.



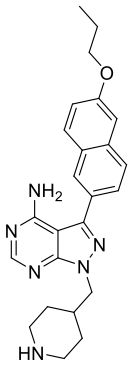
18n

18n: 3-(6-(Allyloxy)naphthalen-2-yl)-1-(piperidin-4-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general naphthol alkylation procedure***, using **35** as the naphthol scaffold and allyl bromide as the $\mathbf{R_3}$-halide, followed by the ***general boc-deprotection procedure***. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.02 (s, 1H), 7.90-7.95 (d, 1H, *J*=8.4 Hz), 7.80-7.85 (d, 1H, *J*=9.0 Hz), 7.62-7.68 (m, 1H), 7.22-7.34 (m, 2H), 6.06-6.21 (m, 1H), 5.45-5.54 (m, 1H), 5.33-5.41 (m, 1H), 4.68-4.73 (m, 2H), 4.43-4.49 (d, 2H, *J*=6.6 Hz), 3.40-3.54 (m, 2H), 2.82-3.00 (m, 2H), 2.30-2.45 (m, 1H), 1.60-1.98 (m, 4H); MS (ESI) 415.5 *m/z* [MH^+], $C_{24}H_{27}N_6O$ requires 415.2; HPLC-1 = 100% pure, HPLC-2 = 100% pure.



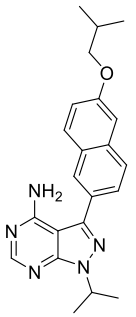
19a

19a: 1-Isopropyl-3-(6-propoxynaphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general naphthol alkylation procedure***, using **28** as the naphthol scaffold and 1-iodopropane as the $\mathbf{R_3}$-halide. ^{1}H-NMR (300 MHz, CD_3OD) δ 8.27 (s, 1H), 8.10 (s, 1H), 7.96 (d, 1H, *J*=9.0 Hz), 7.90 (d, 1H, *J*=9.0 Hz), 7.76 (dd, 1H, *J*=3.0, 9.0 Hz), 7.33-7.34 (m, 1H), 7.24 (dd, 1H, *J*=3.0, 9.0 Hz), 5.13-5.22 (m, 1H), 4.12 (t, 2H, *J*=6.0 Hz), 1.85-1.96 (m, 2H), 1.61 (d, 6H, *J*=3.0 Hz), 1.13 (t, 3H, *J*=9.0 Hz); MS (ESI) 362.3 *m/z* [MH^+], $C_{21}H_{24}N_5O$ requires 362.2; HPLC-1 = 95% pure, HPLC-2 = 95% pure.



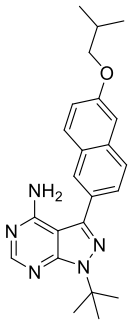
19n

19n: 1-(Piperidin-4-ylmethyl)-3-(6-propoxynaphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general naphthol alkylation procedure***, using **35** as the naphthol scaffold and 1-iodopropane as the $\mathbf{R_3}$-halide, followed by the ***general boc-deprotection procedure***. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.02 (s, 1H), 7.87-7.94 (d, 1H, *J*=8.4 Hz), 7.77-7.83 (d, 1H, *J*=9.0 Hz), 7.62-7.67 (m, 1H), 7.18-7.30 (m, 2H), 4.42-4.48 (d, 2H, *J*=6.6 Hz), 4.04-4.11 (t, 2H, *J*=6.6 Hz), 3.40-3.52 (m, 2H), 2.81-2.94 (m, 2H), 2.30-2.44 (m, 1H), 1.83-1.96 (m, 4H), 1.67-1.80 (m, 2H), 1.07-1.14 (t, 3H, *J*=7.5 Hz); MS (ESI) 417.5 *m/z* [MH^+], $C_{24}H_{29}N_6O$ requires 417.2; HPLC-1 = 100% pure, HPLC-2 = 100% pure.



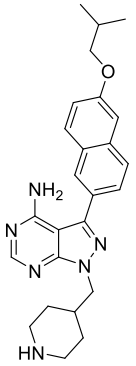
20a

20a: 3-(6-Tsobutoxynaphthalen-2-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general naphthol alkylation procedure***, using **28** as the naphthol scaffold and isobutyl iodide as the $\mathbf{R_3}$-halide. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.03 (s, 1H), 7.89-7.94 (d, 1H, *J*=8.4 Hz), 7.78-7.84 (d, 1H, *J*=9.0 Hz), 7.65-7.70 (m, 1H), 7.18-7.29 (m, 2H), 5.23 (septet, 1H, *J*=6.9 Hz), 3.89 (d, 2H, *J*=6.6 Hz), 2.12-2.26 (m, 1H), 1.65 (d, 6H, *J*=6.9 Hz), 1.09 (d, 6H, *J*=6.6 Hz); MS (ESI) 376.5 *m/z* [MH^+], $C_{22}H_{26}N_5O$ requires 376.2; HPLC-1 = 99% pure, HPLC-2 = 96% pure.



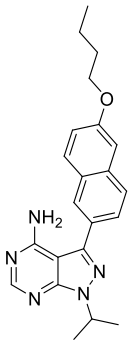
20b

20b: 1-*Tert*-butyl-3-(6-isobutoxynaphthalen-2-yl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general Suzuki coupling procedure***, using **48** as the aryl coupling reagent and **27** as the aryl-halide. ^{1}H-NMR (300 MHz, d_6-DMSO) δ 8.25 (s, 1H), 8.09 (s, 1H), 7.95 (d, 2H, *J*=6.6 Hz), 7.73 (d, 1H, *J*=8.1 Hz), 7.41 (s, 1H), 7.24 (d, 1H, *J*=8.0 Hz), 3.91 (d, 2H, *J*=6.2 Hz), 2.11 (m, 1H), 1.78 (s, 9H), 1.04 (d, 6H, *J*=6.4 Hz); MS (ESI) 390.4 *m/z* [MH^+], $C_{23}H_{28}N_5O$ requires 390.2; HPLC-1 = 100% pure, HPLC-2 = 100% pure.



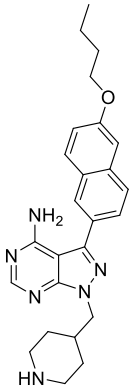
20n

20n: 3-(6-Isobutoxynaphthalen-2-yl)-1-(piperidin-4-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general naphthol alkylation procedure***, using **35** as the naphthol scaffold and isobutyl iodide as the $\mathbf{R_3}$-halide, followed by the ***general boc-deprotection procedure***. ^{1}H-NMR (300 MHz, d_6-DMSO) δ 8.48 (s, 1H), 8.12 (s, 1H), 7.97 (t, 2H, *J*=8.5 Hz), 7.74 (dd, 1H, *J*=1.5, 8.5 Hz), 7.43 (d, 1H, *J*=2.3 Hz), 7.26 (dd, 1H, *J*=2.4, 8.9 Hz), 4.35 (d, 2H, *J*=6.8 Hz), 3.91 (d, 2H, *J*=6.6 Hz), 3.24 (m, 2H), 2.84 (m, 2H), 2.20-2.35 (m, 1H), 2.11 (m, 1H), 1.72 (m, 2H), 1.48 (m, 2H), 1.10-1.30 (m, 2H), 1.04 (d, 6H, *J*=6.7 Hz); MS (ESI) 431.4 *m/z* [MH^+], $C_{25}H_{31}N_6O$ requires 430.55; HPLC-1 = 100% pure, HPLC-2 = 99% pure.



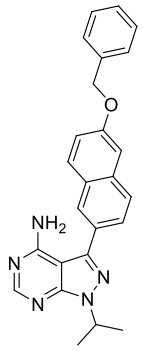
21a

21a: 3-(6-Butoxynaphthalen-2-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general naphthol alkylation procedure***, using **28** as the naphthol scaffold and 1-iodobutane as the $\mathbf{R_3}$-halide. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.23 (s, 1H), 8.02 (s, 1H), 7.88-7.94 (d, 1H, *J*=8.4 Hz), 7.78-7.84 (d, 1H, *J*=9.0 Hz), 7.65-7.70 (m, 1H), 7.18-7.29 (m, 2H), 5.23 (septet, 1H, *J*=6.9 Hz), 4.13 (t, 2H, *J*=6.6 Hz), 1.81-1.92 (m, 2H), 1.67 (d, 6H, *J*=6.9 Hz), 1.50-1.62 (m, 2H), 1.02 (t, 3H, *J*=7.2 Hz); MS (ESI) 376.5 *m/z* [MH^+], $C_{22}H_{26}N_5O$ requires 376.2; HPLC-1 = 99% pure, HPLC-2 = 100% pure.



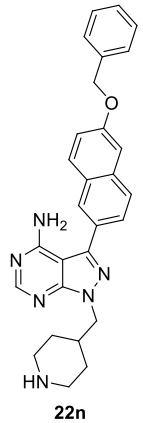
21n

21n: 3-(6-Butoxynaphthalen-2-yl)-1-(piperidin-4-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general naphthol alkylation procedure***, using **35** as the naphthol scaffold and 1-iodobutane as the $\mathbf{R_3}$-halide, followed by the ***general boc-deprotection procedure***. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.01 (s, 1H), 7.88-7.94 (d, 1H, *J*=8.4 Hz), 7.77-7.83 (d, 1H, *J*=9.0 Hz), 7.60-7.67 (m, 1H), 7.17-7.30 (m, 2H), 4.40-4.48 (m, 2H), 4.08-4.15 (m, 2H), 3.40-3.52 (m, 2H), 2.80-2.95 (m, 2H), 2.30-2.44 (m, 1H), 1.83-1.96 (m, 4H), 1.67-1.80 (m, 2H), 1.45-1.52 (m, 2H), 1.07-1.14 (m, 3H); MS (ESI) 431.5 *m/z* [MH^+], $C_{25}H_{31}N_6O$ requires 431.3; HPLC-1 = 97% pure, HPLC-2 = 96% pure.



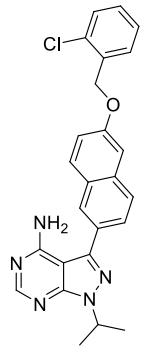
22a

22a: 3-(6-(Benzyloxy)naphthalen-2-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general naphthol alkylation procedure***, using **28** as the naphthol scaffold and benzyl bromide as the **R_3**-halide. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.09 (s, 1H), 7.75-7.91 (m, 3H), 7.48-7.54 (m, 2H), 7.27-7.46 (m, 5H), 5.16-5.26 (m, 3H), 1.63 (d, 6H, *J*=6.9 Hz); MS (ESI) 410.5 *m/z* [MH^+], $C_{25}H_{24}N_5O$ requires 410.2; HPLC-1 = 96% pure, HPLC-2 = 98% pure.



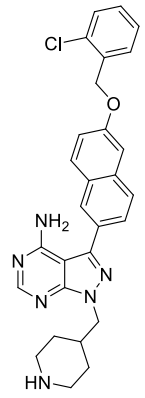
22n

22n: 3-(6-(Benzyloxy)naphthalen-2-yl)-1-(piperidin-4-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general naphthol alkylation procedure***, using **35** as the naphthol scaffold and benzyl bromide as the **R_3**-halide, followed by the ***general boc-deprotection procedure***. ^{1}H-NMR (300 MHz, CD_3OD) δ 8.42 (s, 1H), 8.10 (s, 1H), 7.82-7.96 (m, 2H), 7.67-7.76 (m, 1H), 7.24-7.49 (m, 7H), 5.20 (s, 2H), 4.43-4.49 (m, 2H), 3.24-3.38 (m, 2H), 2.86-3.05 (m, 2H), 2.32-2.48 (m, 1H), 1.82-1.98 (m, 2H), 1.51-1.68 (m, 2H); MS (ESI) 465.5 *m/z* [MH^+], $C_{28}H_{29}N_6O$ requires 465.2; HPLC-1 = 97% pure, HPLC-2 = 95% pure.



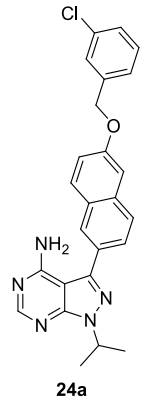
23a

23a: 3-(6-(2-Chlorobenzyloxy)naphthalen-2-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general naphthol alkylation procedure***, using **28** as the naphthol scaffold and 2-chlorobenzyl bromide as the $\mathbf{R_3}$-halide. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.05 (s, 1H), 7.92-7.97 (d, 1H, *J*=8.4 Hz), 7.83-7.89 (d, 1H, *J*=9.0 Hz), 7.68-7.73 (m, 1H), 7.60-7.65 (m, 1H), 7.42-7.48 (m, 1H), 7.35-7.40 (m, 1H), 7.28-7.34 (m, 3H), 5.34 (s, 2H), 5.23 (septet, 1H, *J*=6.9 Hz), 1.65 (d, 6H, *J*=6.9 Hz); MS (ESI) 445.0 *m/z* [MH^+], $C_{25}H_{24}ClN_5O$ requires 444.2; HPLC-1 = 99% pure, HPLC-2 = 96% pure.



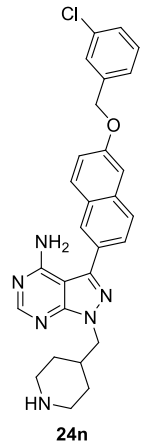
23n

23n: 3-(6-(2-Chlorobenzyloxy)naphthalen-2-yl)-1-(piperidin-4-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general naphthol alkylation procedure***, using **35** as the naphthol scaffold and 2-chlorobenzyl bromide as the $\mathbf{R_3}$-halide, followed by the ***general boc-deprotection procedure***. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.02 (s, 1H), 7.91-7.97 (d, 1H, *J*=8.4 Hz), 7.82-7.88 (d, 1H, *J*=9.0 Hz), 7.59-7.69 (m, 2H), 7.29-7.47 (m, 5H), 5.33 (s, 2H), 4.43-4.49 (d, 2H, *J*=6.6 Hz), 3.38-3.50 (m, 2H), 2.79-2.94 (m, 2H), 2.28-2.42 (m, 1H), 1.68-1.96 (m, 4H); MS (ESI) 500.0 *m/z* [MH^+], $C_{28}H_{28}ClN_6O$ requires 499.2; HPLC-1 = 100% pure, HPLC-2 = 99% pure.



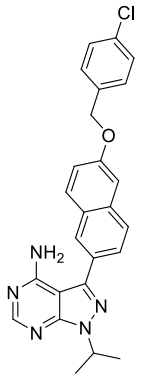
24a

24a: 3-(6-(3-Chlorobenzyloxy)naphthalen-2-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general naphthol alkylation procedure***, using **28** as the naphthol scaffold and 3-chlorobenzyl bromide as the **R_3**-halide. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.05 (s, 1H), 7.91-7.96 (d, 1H, *J*=8.4 Hz), 7.84-7.89 (d, 1H, *J*=9.0 Hz), 7.68-7.73 (m, 1H), 7.52 (s, 1H), 7.32-7.39 (m, 3H), 7.23-7.29 (m, 2H), 5.15-5.28 (m, 3H), 1.65 (d, 6H, *J*=6.9 Hz); (ESI) 445.0 *m/z* [MH^+], $C_{25}H_{23}ClN_5O$ requires 444.2; HPLC-1 = 100% pure, HPLC-2 = 100% pure.



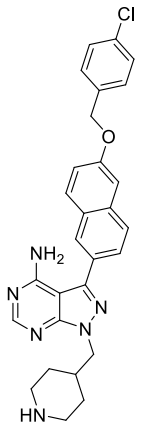
24n

24n: 3-(6-(3-Chlorobenzyloxy)naphthalen-2-yl)-1-(piperidin-4-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general naphthol alkylation procedure***, using **35** as the naphthol scaffold and 3-chlorobenzyl bromide as the **R_3**-halide, followed by the ***general boc-deprotection procedure***. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.03 (s, 1H), 7.90-7.96 (d, 1H, *J*=8.4), 7.82-7.88 (d, 1H, *J*=9.0 Hz), 7.63-7.69 (m, 1H), 7.50 (s, 1H), 7.32-7.40 (m, 5H), 5.21 (s, 2H), 4.43-4.49 (d, 2H, *J*=6.6 Hz), 3.44-3.54 (m, 2H), 2.82-2.96 (m, 2H), 2.30-2.45 (m, 1H), 1.70-1.96 (m, 4H); MS (ESI) 500.0 *m/z* [MH^+], $C_{28}H_{28}ClN_6O$ requires 499.2; HPLC-1 = 98% pure, HPLC-2 = 98% pure.



25a

25a: 3-(6-(4-Chlorobenzyloxy)naphthalen-2-yl)-1-isopropyl-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general naphthol alkylation procedure***, using **28** as the naphthol scaffold and 4-chlorobenzyl bromide as the $\mathbf{R_3}$-halide. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.05 (s, 1H), 7.91-7.96 (d, 1H, *J*=8.4 Hz), 7.84-7.89 (d, 1H, *J*=9.0 Hz), 7.68-7.73 (m, 1H),7.38-7.47 (m, 4H), 7.30-7.36 (m, 1H), 7.27-7.29 (m, 1H), 5.17-5.28 (m, 3H), 1.66 (d, 6H, *J*=6.9 Hz); MS (ESI) 445.0 *m/z* [MH^+], $C_{25}H_{23}ClN_5O$ requires 444.2; HPLC-1 = 100% pure, HPLC-2 = 99% pure.



25n

25n: 3-(6-(4-Chlorobenzyloxy)naphthalen-2-yl)-1-(piperidin-4-ylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-4-amine. This compound was synthesized following the ***general naphthol alkylation procedure***, using **35** as the naphthol scaffold and 4-chlorobenzyl bromide as the $\mathbf{R_3}$-halide, followed by the ***general boc-deprotection procedure***. ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.26 (s, 1H), 8.02 (s, 1H), 7.89-7.94 (d, 1H, *J*=8.4 Hz), 7.82-7.87 (d, 1H, *J*=9.0 Hz), 7.64-7.69 (m, 1H), 7.32-7.47 (m, 6H), 5.20 (s, 2H), 4.43-4.49 (d, 2H, *J*=6.3 Hz), 3.98 (s, 3H), 3.44-3.54 (m, 2H), 2.82-3.00 (m, 2H), 2.30-2.45 (m, 1H), 1.86-1.96 (m, 2H), 1.67-1.82 (m, 2H); MS (ESI) 500.0 *m/z* [MH^+], $C_{28}H_{28}ClN_6O$ requires 499.2; HPLC-1 = 97% pure, HPLC-2 = 97% pure.

Supporting Information References:

1. Murphy, R. C.; Ojo, K. K.; Larson, E. T.; Castellanos-Gonzalez, A.; Perera, B. G.; Keyloun, K. R.; Kim, J. E.; Bhandari, J. G.; Muller, N. R.; Verlinde, C. L.; White, A. C., Jr.; Merritt, E. A.; Van Voorhis, W. C.; Maly, D. J. Discovery of Potent and Selective Inhibitors of Calcium-Dependent Protein Kinase 1 (CDPK1) from C. parvum and T. gondii. *ACS Med Chem Lett* **2010**, *1*, 331-335.

2. Bulawa, C. E.; Devit, M.; Elbaum, D. Preparation of pyrazolopyrimidinamines as modulators of protein trafficking. WO2009062118A2, 2009.