Supporting information

Discovery, synthesis, and structure-activity relationship of *N*-benzyl-2-phenylpyrimidin-4-amine derivatives as potent USP1/UAF1 deubiquitinase inhibitors with anticancer activity against non-small cell lung cancer

Thomas S. Dexheimer, Andrew S. Rosenthal, Diane K. Luci, Qin Liang, Mark A. Villamil, Junjun Chen, Hongmao Sun, Edward H. Kerns, Anton Simeonov, Ajit Jadhav, Zhihao Zhuang, David J. Maloney

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Supplementary info

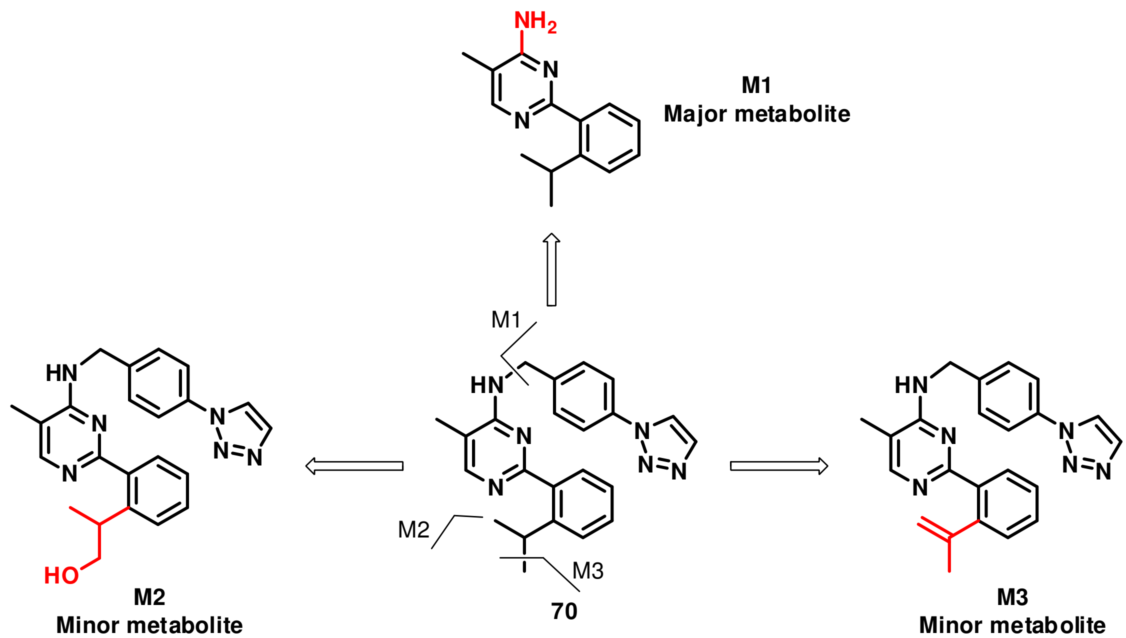


Figure S1. Metabolites of **70** as determined by LC-MS/MS upon incubation with mouse liver microsomes.

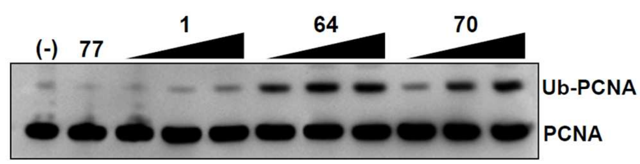


Figure S2. Dose-dependent increase of PCNA monoubiquitination in H1299 cells. A) H1299 cells were treated with increasing concentrations of the indicated compounds (1, 5, and 25 μM) or a single concentration (25 μM) of **77** for 4 hr. Whole cell extracts were separated on 4-12% gradient SDS-PAGE and subjected to Western blotting with an antibody against PCNA.

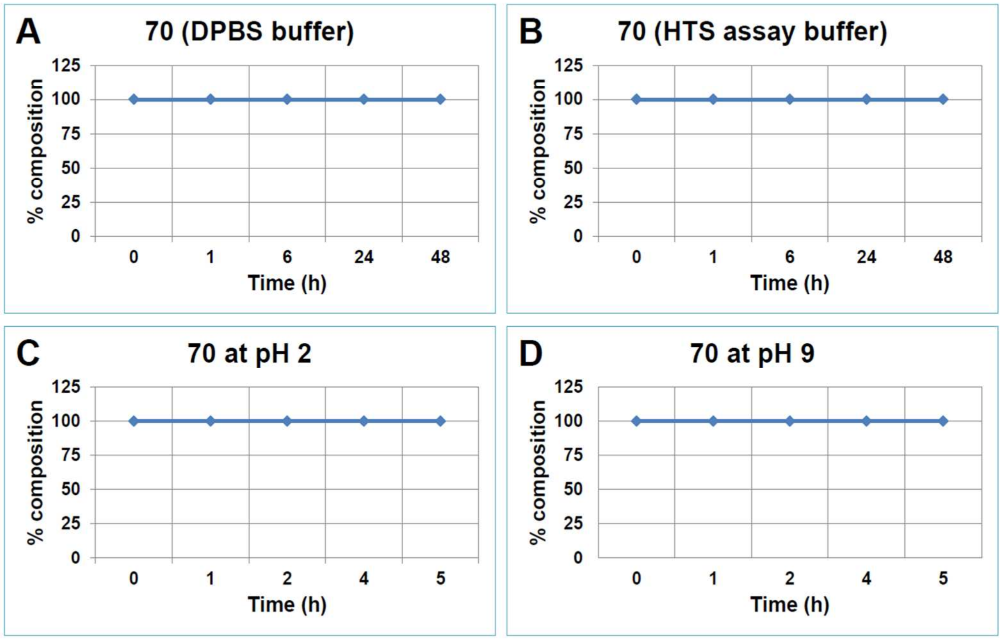


Figure S3. Chemical stability of **70** measured as percent composition of molecule in aqueous solution at room temperature in A) DPBS pH 7.4 buffer; B) USP1/UAF1 HTS assay buffer at pH 7.8 (50 mM HEPES, 0.5 mM EDTA, 100 mM NaCl, 1 mM TCEP, 0.1 mg/mL BSA, and 0.01% Tween-20); C) USP1/UAF1 HTS assay buffer at pH 2 and D) at pH 9 buffer.

General Methods for Chemistry. All air or moisture sensitive reactions were performed under positive pressure of nitrogen with oven-dried glassware. Chemical reagents and anhydrous solvents were obtained from commercial sources and used as-is. Preparative purification was performed on a Waters semi-preparative HPLC. The column used was a Phenomenex Luna C18 (5 micron, 30 x 75 mm) at a flow rate of 45 mL/min. The mobile phase consisted of acetonitrile and water (each containing 0.1% trifluoroacetic acid). A gradient of 10% to 50% acetonitrile over 8 minutes was used during the purification. Fraction collection was triggered by UV detection (220 nm). Analytical analysis was performed on an Agilent 1200 LC-MS (Agilent Technologies). Method 1: A 3 minute gradient of 4% to 100% Acetonitrile (containing 0.025% trifluoroacetic acid) in water (containing 0.05% trifluoroacetic acid) was used with an 8 minute run time at a flow rate of 1 mL/min. Method 2: A 7 minute gradient of 4% to 100% Acetonitrile (containing 0.025% trifluoroacetic acid) in water (containing 0.05% trifluoroacetic acid) was used with a 4.5 minute run time at a flow rate of 1 mL/min. A Phenomenex Luna C18 column (3 micron, 3 x 75 mm) was used at a temperature of 50 °C. All of the analogs for assay have purity greater than 95% based on both analytical methods. ^{1}H and ^{13}C NMR spectra were recorded on a Varian 400 (100) MHz spectrometer. High resolution mass spectrometry was recorded on Agilent 6210 Time-of-Flight LC-MS system.

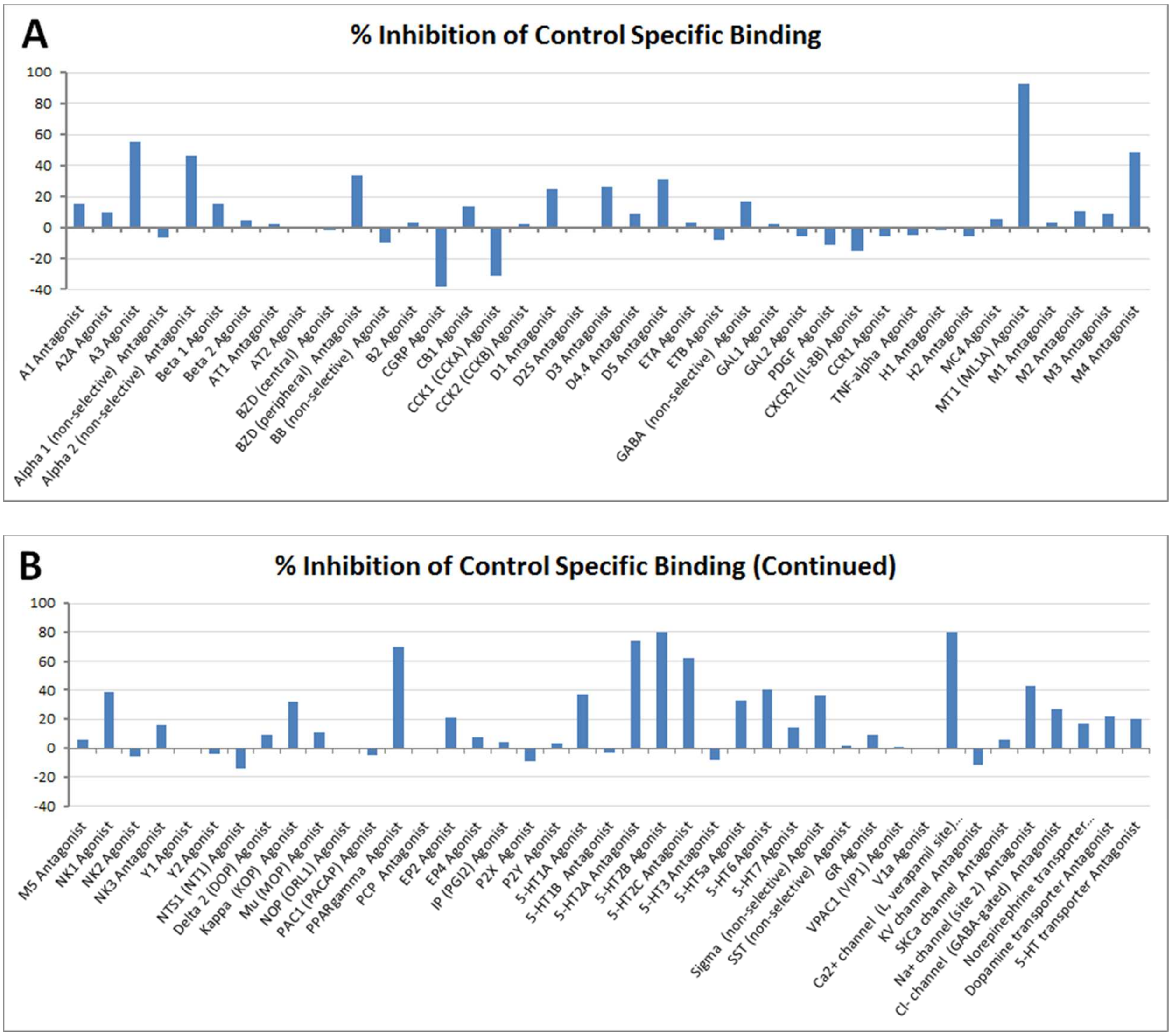
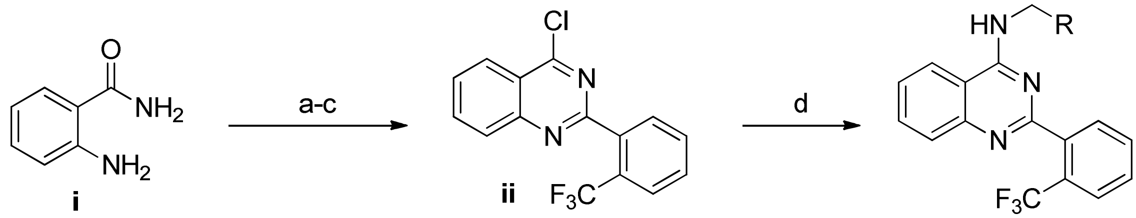


Figure S4. Activity of compound **70** tested in duplicate against 80 different targets (GPCRs, ion channels and transporters). X-axis represents the mechanism of interest and Y-axis represents the % inhibition at 10 μM. Compound binding was calculated as a % inhibition of the binding of a radioactively labeled ligand specific for each target.

Method A:

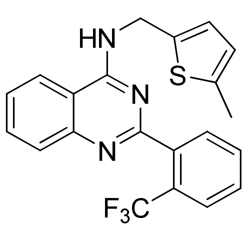


(a) 2-(trifluoromethyl) benzoic acid (1.2 equiv), Et_3N (3.0 equiv), $CHCl_3$ (b) 5% NaOH (1.0 equiv), reflux 3 h (c) *N,N*-dimethylaniline (10.0 equiv), $POCl_3$ (10.0 equiv), toluene, reflux 1 h (d) **R**NH_2, iPr_2NEt, DMF, 18 h, 60 °C

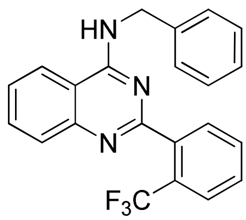
***N*-(2-Carbamoylphenyl)-2-(trifluoromethyl)benzamide (a):** 2-(Trifluoromethyl)benzoic acid (1.40g 7.34 mmol), triethylamine (TEA) (3.07 mL, 22.03 mmol), 1-hydroxybenzotriazole hydrate (HOBT) (1.35 g, 8.81 mmol), 2-aminobenzamide (1.00 g, 7.34 mmol), and *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (EDC) (1.69g, 8.81 mmol) in dichloromethane (DCM) (20 mL) was stirred at room temperature for 72 h. The reaction was quenched with water, separated, dried over Na_2SO_4, filtered, concentrated, and purified using 0-10% gradient of methanol/DCM to give 700 mg of the desired product in a 31% yield: LC-MS retention time (Method 1): 3.240 min.

2-(2-(Trifluoromethyl)phenyl)quinazolin-4(3H)-one (b): *N*-(2-carbamoylphenyl)-2-(trifluoromethyl)benzamide (700 mg, 2.27 mmol) in 5% NaOH (10 mL, 2.27 mmol) was heated to 100 ºC for 3 h. The reaction was cooled to rt and acidified with acetic acid, a solid precipitated which was filtered, washed with water, dried on a high vacuum pump overnight, and used as is in the next reaction: LC-MS retention time (Method 1): 3.223 min.

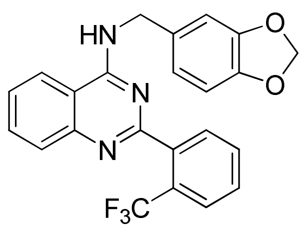
4-Chloro-2-(2-(trifluoromethyl)phenyl)quinazoline (ii): 2-(2-(trifluoromethyl)phenyl)quinazolin-4(3*H*)-one (0.20 g, 0.69 mmol) was suspended in toluene (3 ml), and *N,N*-dimethylaniline (0.87 mL, 6.89 mmol), followed by $POCl_3$ (0.64 mL, 6.89 mmol) which was added at room temperature (rt). This mixture was refluxed for 1 h, cooled to rt, and slowly added to a cold solution of saturated sodium bicarbonate. The solution was extracted with EtOAc (2 X), dried over Na_2SO_4, filtered, concentrated, and used as-is in the next reaction: LC-MS retention time (Method 1): 3.996 min.



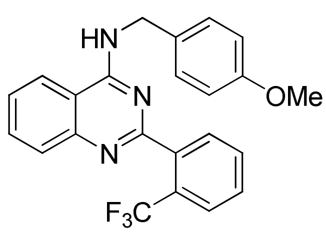
***N*-((5-methylthiophen-2-yl)methyl)-2-(2-(trifluoromethyl)phenyl)quinazolin-4-amine TFA (2):** 4-Chloro-2-(2-(trifluoromethyl)phenyl)quinazoline (0.16 mmol), (5-methylthiophen-2-yl)methanamine (0.19 mmol), and diisopropylethyl amine (DIPEA), (0.32 mmol) was heated in DMF (1 mL) to 60 °C for 18 h. The reaction was allowed to come to rt and purified using a reverse phase HPLC (gradient 10-100% acetonitrile w/ 0.1% TFA in water w/ 0.1% TFA) to give the desired product: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.37 – 8.47 (m, 1 H), 7.84 – 8.01 (m, 4 H), 7.76 – 7.84 (m, 2 H), 7.66 – 7.76 (m, 1 H), 6.79 – 6.89 (m, 1 H), 6.59 – 6.66 (m, 1 H), 4.94 (d, *J* = 5.48 Hz, 2 H), and 2.35 (s, 3 H); LC-MS retention time (Method 1): 3.187 min; (Method 2): 4.923 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{21}H_{17}F_3N_3S$ 400.1090) found, 400.1085.



***N*-Benzyl-2-(2-(trifluoromethyl)phenyl)quinazolin-4-amine TFA (3):** Follow the synthesis for compound **2**, (**Method A**) but substitute phenylmethanamine for (5-methylthiophen-2-yl)methanamine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 – 8.53 (m, 1 H), 7.96 – 8.05 (m, 1 H), 7.90 – 7.96 (m, 1 H), 7.84 – 7.89 (m, 2 H), 7.70 – 7.83 (m, 3 H), 7.34 (s, 5 H), and 4.90 (d, *J* = 5.67 Hz, 2 H); LC-MS retention time (Method 1): 3.128 min; (Method 2): 4.808 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{22}H_{17}F_3N_3$ 380.1369) found, 380.1361.

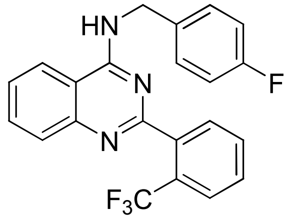


***N*-(benzo[d][1,3]dioxol-5-ylmethyl)-2-(2-(trifluoromethyl)phenyl)quinazolin-4-amine TFA (4):** Follow the synthesis for compound **2**, (**Method A**) but substitute benzo[d][1,3]dioxol-5-ylmethanamine for (5-methylthiophen-2-yl)methanamine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.46 (s, 1 H), 7.68 – 8.05 (m, 8 H), 6.91 (s, 1 H), 6.79 – 6.88 (m, 2 H), 5.97 (s, 2 H), and 4.80 (d, *J* = 5.67 Hz, 2 H); LC-MS retention time (Method 1): 3.119 min; (Method 2): 4.761 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{23}H_{17}F_3N_3O_2$ 424.1267) found, 424.1276.

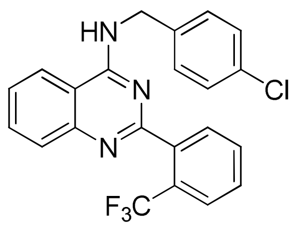


***N*-(4-methoxybenzyl)-2-(2-(trifluoromethyl)phenyl)quinazolin-4-amine (5):** Follow the synthesis for compound **2**, (**Method A**) but substitute (4-methoxyphenyl)methanamine for (5-methylthiophen-2-yl)methanamine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 – 8.53 (m, 1 H), 7.96 (d, *J* = 8.02 Hz, 2 H), 7.89 (br. s., 2 H), 7.81 (d, *J* = 8.22 Hz, 2 H), 7.68 – 7.78 (m, 1 H), 7.28 (d, *J* = 8.61 Hz, 2 H), 6.88 (d, *J* = 8.61 Hz, 2 H), 4.83 (d, *J* = 5.67 Hz, 2 H), and 3.71 (s, 3 H); LC-

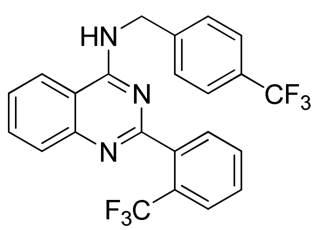
MS retention time (Method 1): 3.116 min; (Method 2): 4.811 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{23}H_{19}F_3N_3O$ 410.1475) found, 410.1485.



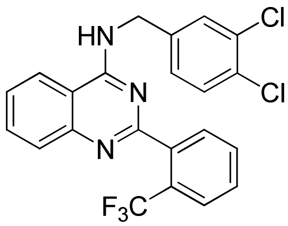
***N*-(4-fluorobenzyl)-2-(2-(trifluoromethyl)phenyl)quinazolin-4-amine TFA (6):** Follow the synthesis for compound **2**, (**Method A**) but substitute (4-fluorophenyl)methanamine for (5-methylthiophen-2-yl)methanamine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 – 8.53 (m, 1 H), 7.96 – 8.03 (m, 1 H), 7.91 – 7.96 (m, 1 H), 7.87 (d, *J* = 3.91 Hz, 2 H), 7.82 (d, *J* = 8.02 Hz, 2 H), 7.75 (br. s., 1 H), 7.39 (dd, *J* = 5.67, and 8.41Hz, 2 H), 7.15 (t, *J* = 8.80 Hz, 2 H), and 4.88 (d, *J* = 5.67 Hz, 2 H); LC-MS retention time (Method 1): 3.165 min; (Method 2): 4.840 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{22}H_{16}F_4N_3$ 398.1275) found, 398.1278.



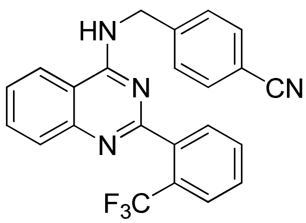
***N*-(4-chlorobenzyl)-2-(2-(trifluoromethyl)phenyl)quinazolin-4-amine TFA (7):** Follow the synthesis for compound **2**, (**Method A**) but substitute (4-chlorophenyl)methanamine for (5-methylthiophen-2-yl)methanamine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 – 8.53 (m, 1 H), 7.70 – 8.05 (m, 8 H), 7.37 (br. s., 4 H), and 4.88 (d, *J* = 2.93 Hz, 2 H); LC-MS retention time (Method 1): 3.239 min; (Method 2): 5.073 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{22}H_{16}ClF_3N_3$ 414.0979) found, 414.0978.



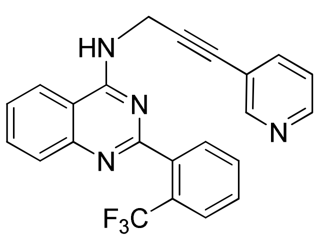
***N*-(4-trifluoromethylbenzyl)-2-(2-(trifluoromethyl)phenyl)quinazolin-4-amine TFA (8):** Follow the synthesis for compound **2**, (**Method A**) but substitute (4-trifluoromethylphenyl)methanamine for (5-methylthiophen-2-yl)methanamine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.43 – 8.50 (m, 1 H), 7.92 – 8.03 (m, 1 H), 7.86 – 7.92 (m, 1 H), 7.65 – 7.85 (m, 7 H), 7.55 (d, *J* = 8.22 Hz, 2 H), and 4.96 (d, *J* = 5.28 Hz, 2 H); LC-MS retention time (Method 1): 3.256 min; (Method 2): 5.201 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{23}H_{16}F_6N_3$ 448.1243) found, 448.1243.



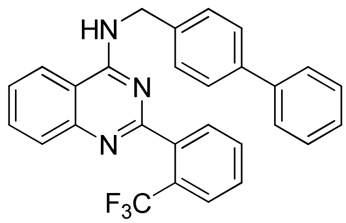
***N*-(3,4-dichlorobenzyl)-2-(2-(trifluoromethyl)phenyl)quinazolin-4-amine TFA (9):** Follow the synthesis for compound **2**, (**Method A**) but substitute (3, 4-dichlorophenyl)methanamine for (5-methylthiophen-2-yl)methanamine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 – 8.48 (m, 1 H), 7.94 – 8.01 (m, 1 H), 7.88 – 7.94 (m, 1 H), 7.68 – 7.88 (m, 5 H), 7.55 – 7.63 (m, 2 H), 7.33 (d, *J* = 1.57 Hz, 1 H), and 4.86 (d, *J* = 5.67 Hz, 2 H); LC-MS retention time (Method 1): 3.296 min; (Method 2): 5.270 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{22}H_{15}Cl_2F_3N_3$ 448.0590) found, 448.0581.



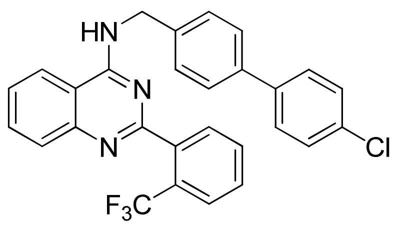
4-((2-(2-(trifluoromethyl)phenyl)quinazolin-4-ylamino)methyl)benzonitrile TFA (10): Follow the synthesis for compound **2**, (**Method A**) but substitute 4-(aminomethyl)benzonitrile for (5-methylthiophen-2-yl)methanamine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 – 8.50 (m, 1 H), 7.94 – 8.02 (m, 1 H), 7.86 – 7.93 (m, 1 H), 7.79 (d, *J* = 8.41 Hz, 7 H), 7.52 (d, *J* = 8.02 Hz, 2 H), and 4.95 (d, *J* = 5.48 Hz, 2 H); LC-MS retention time (Method 1): 3.050 min; (Method 2): 4.621 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{23}H_{16}F_3N_4$ 405.1322) found, 405.1307.



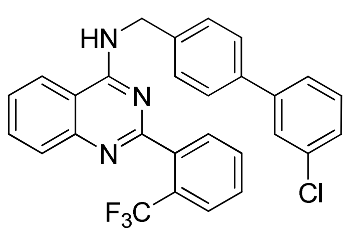
***N*-(3-(pyridin-3-yl)prop-2-ynyl)-2-(2-(trifluoromethyl)phenyl)quinazolin-4-amine TFA (11):** Follow the synthesis for compound **2**, (**Method A**) but substitute 3-(pyridin-3-yl)prop-2-yn-1-amine for (5-methylthiophen-2-yl)methanamine which was synthesized in the following manner. *Tert*-butyl prop-2-ynylcarbamate 0.20 g, 1.29 mmol), 3-bromopyridine (0.19 g, 1.17 mmol), triethylamine (0.24 mL, 2.34 mmol), bis(triphenylphosphine)palladium(II)chloride (0.02 g, 0.02 mmol), copper(II)iodide (2.23 mg, 0.1 mmol) in THF (4 mL) was heated to 60 ºC for 18 h. The reaction was cooled, poured into brine, extracted with EtOAc, concentrated, and the residue taken up in a 20% TFA/DCM and stirred for 30 min. The solution was concentrated to give the desired compound without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.62 – 9.95 (m, 1 H), 8.60 (s, 1 H), 8.52 – 8.58 (m, 1 H), 8.38 – 8.48 (m, 1 H), 7.68 – 8.02 (m, 8 H), 7.42 (dd, *J* = 4.89, and 7.63 Hz, 1 H), and 4.74 (d, *J* = 5.09 Hz, 2 H); LC-MS retention time (Method 1): 2.900 min; (Method 2): 4.034 min. HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{23}H_{16}F_3N_4$ 405.1322) found, 405.1316.



***N*-(biphenyl-4-ylmethyl)-2-(2-(trifluoromethyl)phenyl)quinazolin-4-amine TFA (12):** Follow the synthesis for compound **2**, (**Method A**) but substitute [1,1'-biphenyl]-4-ylmethanamine for (5-methylthiophen-2-yl)methanamine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.47 – 8.55 (m, 1 H), 7.95 (d, *J* = 7.63 Hz, 2 H), 7.72 – 7.92 (m, 5 H), 7.58 – 7.66 (m, 4 H), 7.44 (d, *J* = 6.85 Hz, 4 H), 7.30 – 7.39 (m, 1 H), and 4.95 (d, *J* = 5.48 Hz, 2 H); LC-MS retention time (Method 1): 3.359 min; (Method 2): 5.428 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{28}H_{21}F_3N_3$ 456.1682) found, 456.1699.

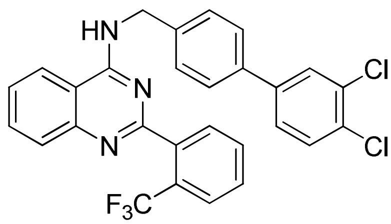


***N*-((4'-chlorobiphenyl-4-yl)methyl)-2-(2-(trifluoromethyl)phenyl)quinazolin-4-amine TFA (13)**: Follow the synthesis for compound **2**, (**Method A**) but substitute (4'-chloro-[1,1'-biphenyl]-4-yl)methanamine for (5-methylthiophen-2-yl)methanamine ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 – 8.54 (m, 1 H), 7.89 – 8.04 (m, 2 H), 7.70 – 7.90 (m, 6 H), 7.65 (dd, *J* = 8.22, and 14.48 Hz, 4 H), 7.50 (d, *J* = 8.41 Hz, 2 H), 7.44 (d, *J* = 8.22 Hz, 2 H), and 4.93 (d, *J* = 5.28 Hz, 2 H); LC-MS retention time (Method 1): 3.435 min; (Method 2): 5.608 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{28}H_{20}ClF_3N_3$ 490.1292) found, 490.1293.

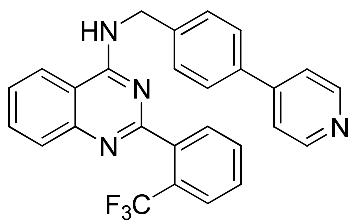


***N*-((3'-chlorobiphenyl-4-yl)methyl)-2-(2-(trifluoromethyl)phenyl)quinazolin-4-amine TFA (14):** Follow the synthesis for compound **2**, (**Method A**) but substitute (3'-chloro-[1,1'-biphenyl]-4-yl)methanamine for (5-methylthiophen-2-yl)methanamine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 – 8.54 (m, 1 H), 7.71 – 8.04 (m, 8 H), 7.64 – 7.70 (m, 3 H), 7.61 (d, *J* = 7.63 Hz, 1 H), 7.36

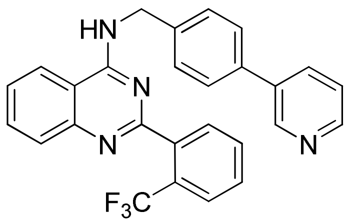
– 7.51 (m, 4 H), and 4.95 (d, *J* = 5.48 Hz, 2 H); LC-MS retention time (Method 1): 3.437 min; (Method 2): 5.585 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{28}H_{20}ClF_3N_3$490.1292) found, 490.1292.



***N*-((3',4'-dichlorobiphenyl-4-yl)methyl)-2-(2-(trifluoromethyl)phenyl)quinazolin-4-amine TFA (15):** Follow the synthesis for compound **2**, (**Method A**) but substitute (3',4'-dichloro-[1,1'-biphenyl]-4-yl)methanamine for (5-methylthiophen-2-yl)methanamine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.44 – 8.55 (m, 1H), 7.72 – 8.05 (m, 9 H), 7.61 – 7.72 (m, 4 H), 7.45 (d, *J* = 8.02 Hz, 2 H), and 4.95 (d, *J* = 5.48 Hz, 2 H); LC-MS retention time (Method 1): 3.510 min; (Method 2): 5.813 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{28}H_{19}Cl_2F_3N_3$ 524.0903) found, 524.0921.

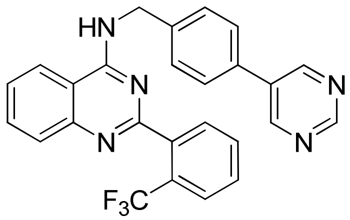


***N*-(4-(pyridin-4-yl)benzyl)-2-(2-(trifluoromethyl)phenyl)quinazolin-4-amine TFA (16):** Follow the synthesis for compound **2**, (**Method A**) but substitute (4-(pyridin-4-yl)phenyl)methanamine for (5-methylthiophen-2-yl)methanamine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.79 – 10.12 (m, 1 H), 8.78 (d, *J* = 6.46 Hz, 2 H), 8.02–8.08 (m, 2 H), 7.96 – 8.02 (m, 1 H), 7.71 – 7.95 (m, 8 H), 7.54 (d, *J* = 8.22 Hz, 2 H), and 4.98 (d, *J* = 5.67 Hz, 2 H); LC-MS retention time (Method 1): 2.712 min; (Method 2): 3.622 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{27}H_{20}F_3N_4$ 457.1635) found, 457.162.

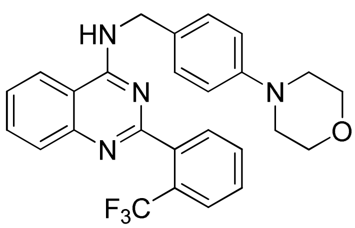


***N*-(4-(pyridin-3-yl)benzyl)-2-(2-(trifluoromethyl)phenyl)quinazolin-4-amine TFA (17):** Follow the synthesis for compound **2**, (**Method A**) but substitute (4-(pyridin-3-yl)phenyl)methanamine for (5-methylthiophen-2-yl)methanamine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.04 – 10.32 (m, 1 H), 8.88 – 9.02 (m, 1 H), 8.57 – 8.68 (m, 1 H), 8.44 – 8.57 (m, 1 H), 8.17 – 8.31 (m, 1 H), 7.68 – 8.08 (m, 9 H), 7.62 (brs, 1 H), 7.39 – 7.55 (m, 2 H), and 4.97 (d, *J* =

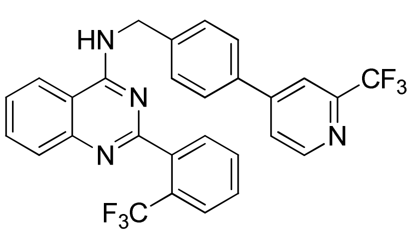
6.65 Hz, 2 H); LC-MS retention time (Method 1): 2.772 min; (Method 2): 3.760 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{27}H_{21}F_3N_4$ 457.1635) found, 457.1635.



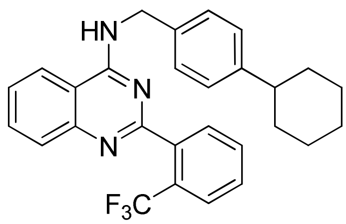
***N*-(4-(pyrimidin-5-yl)benzyl)-2-(2-(trifluoromethyl)phenyl)quinazolin-4-amine TFA (18):** Follow the synthesis for compound **2**, (**Method A**) but substitute (4-(pyrimidin-5-yl)phenyl)methanamine for (5-methylthiophen-2-yl)methanamine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.14 – 9.20 (m, 1 H), 9.07 – 9.14 (m, 2 H), 8.43 – 8.52 (m, 1 H), 7.88 – 8.03 (m, 2 H), 7.69 – 7.88 (m, 7 H), 7.43 – 7.56 (m, 2 H), and 4.96 (d, *J* = 4.30 Hz, 2 H); LC-MS retention time (Method 1): 3.027 min; (Method 2): 4.326 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{26}H_{19}F_3N_5$ 458.1587) found, 458.1595.



***N*-(4-morpholinobenzyl)-2-(2-(trifluoromethyl)phenyl)quinazolin-4-amine TFA (19):** Follow the synthesis for compound **2**, (**Method A**) but substitute (4-morpholinophenyl)methanamine for (5-methylthiophen-2-yl)methanamine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.40 – 8.53 (m, 1 H), 7.62 – 8.03 (m, 8 H), 7.22 (d, *J* = 8.61 Hz, 2 H), 6.89 (d, *J* = 8.61 Hz, 2 H), 4.79 (d, *J* = 5.09 Hz, 2 H), 3.67 – 3.74 (m, 4 H), and 3.01 – 3.09 (m, 4 H); LC-MS retention time (Method 1): 3.007 min; (Method 2): 4.354 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{26}H_{24}F_3N_4O$ 465.1897) found, 465.1889.

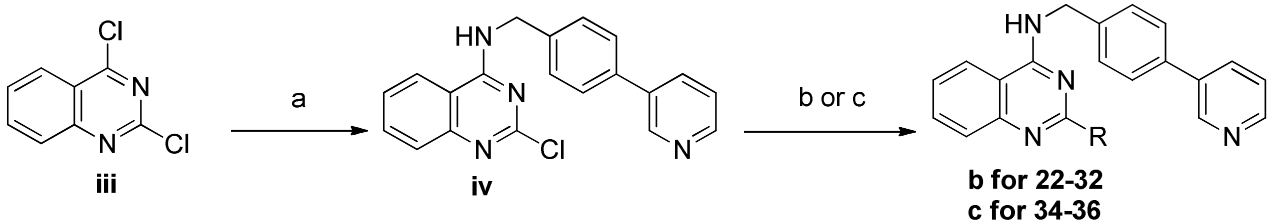


2-(2-(trifluoromethyl)phenyl)-*N*-(4-(6-(trifluoromethyl)pyridin-3-yl)benzyl)quinazolin-4-amine TFA (20): Follow the synthesis for compound **2**, (**Method A**) but substitute 4-bromo benzyl amine for (5-methylthiophen-2-yl)methanamine: Once the 4-bromo precursor was in hand the cross coupling product was synthesized in the following manner. *N*-(4-bromobenzyl)-2-(2-(trifluoromethyl)phenyl)quinazolin-4-amine (0.05 g, 0.11 mmol), 2-(trifluoromethyl)pyridine-5-boronic acid (0.02 g, 0.16 mmol), $Pd(PPh_3)_4$ (13.0 mg, 0.01 mmol), Na_2CO_3 (2M, 0.27 mL, 0.55 mmol) in DME (1 mL) was sealed in a microwave vial and heated in a Biotage Initiator microwave reactor to 150 ºC for 10 min. The reaction was cooled, filtered over celite, concentrated, and purified via reversed phase HPLC to give the desired product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 – 9.12 (m, 1 H), 8.45 – 8.56 (m, 1 H), 8.28 – 8.40 (m, 1 H), 7.90 – 8.05 (m, 3 H), 7.69 – 7.91 (m, 7 H), 7.52 (d, J = 8.22 Hz, 3 H), and 4.97 (d, J = 5.48 Hz, 2 H); LC-MS retention time (Method 1): 2.502 min; (Method 2): 5.389 min; HRMS: m/z $(M+H)^+$ = (Calculated for $C_{28}H_{19}F_6N_4$ 525.1508) found, 525.1522.



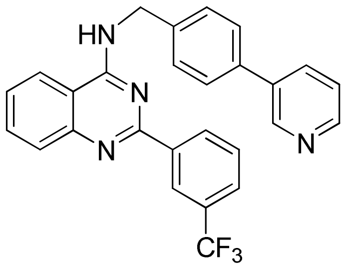
***N*-(4-cyclohexylbenzyl)-2-(2-(trifluoromethyl)phenyl)quinazolin-4-amine TFA (21):** Follow the synthesis for compound **2**, (**Method A**) but substitute (4-cyclohexylphenyl)methanamine for (5-methylthiophen-2-yl)methanamine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.41 – 8.52 (m, 1 H), 7.67 – 8.03 (m, 7 H), 7.12 – 7.28 (m, 5 H), 4.85 (d, J = 5.09 Hz, 2 H), 1.69 – 1.80 (m, 5 H), 1.27 – 1.46 (m, 5 H), and 1.23 (brs, 1 H); LC-MS retention time (Method 1): 3.628 min; (Method 2): 5.955 min; HRMS: m/z $(M+H)^+$ = (Calculated for $C_{28}H_{27}F_3N_3$ 462.2152) found, 462.2153.

Method B:

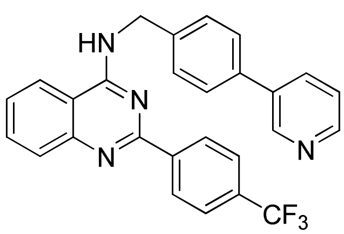


(a) (4-(pyridin-3-yl)phenyl)methanamine, Et_3N (3.0 equiv), $CHCl_3$, 18 h, 60 °C (b) **R**$B(OH)_2$ (3.0 equiv), 2M Na_2CO_4 (4.0 equiv), DPP-Pd silica bound (0.3 equiv), or $Pd(PPh_3)_4$ (0.2 equiv), DME, MW, 150 °C, 45 min (c) amine (1.2 equiv) , THF, reflux. 18 h.

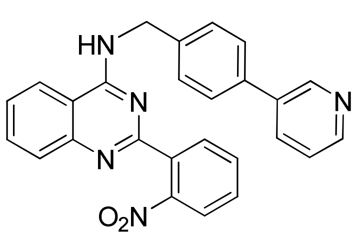
2-Chloro-*N*-(4-(6-methylpyridin-3-yl)benzyl)quinazolin-4-amine (iv): 2,4-Dichloroquinazoline (70 mg, 0.35 mmol) **(iii)**, (4-(6-methylpyridin-3-yl)phenyl)methanamine (77 mg, 0.39 mmol), Et_3N (0.15 mL, 1.06 mmol), in $CHCl_3$ (2 mL), was heated in a sealed tube for 3 h at 50 °C. The resulting mixture was cooled and placed on a silica column for purification with EtOAc/Hex 0 to 100% gradient over 20 min, to give the desired product in a 70% yield. LC-MS retention time (Method 1): 2.760 min;



N-(4-(pyridin-3-yl)benzyl)-2-(3-(trifluoromethyl)phenyl)quinazolin-4-amine TFA (22): 2-Chloro-*N*-(4-(6-methylpyridin-3-yl)benzyl)quinazolin-4-amine **(iv)** (107 mg, 0.31 mmol), 3-trifluoromethylphenyl boronic acid (56 mg, 0.37 mmol), $Pd(PPh_3)_4$ (36.0 mg, 0.03 mmol), 2 M solution of Na_2CO_3 (0.30 mL, 0.62 mmol) in DME (1 mL) was sealed in a microwave vial and heated in a Biotage Initiator microwave reactor to 150 ºC for 30 min. The reaction was cooled, filtered over celite, concentrated, and purified to give the desired product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.59 – 9.76 (m, 1 H), 8.92 – 9.00 (m, 1 H), 8.60 (d, J = 8.02 Hz, 3 H), 8.40 – 8.47 (m, 1 H), 8.23 – 8.31 (m, 1 H), 7.88 – 7.97 (m, 4 H), 7.76 (d, J = 7.43 Hz, 2 H), 7.64 (d, J = 7.83 Hz, 4 H), and 5.04 (d, J = 5.28 Hz, 2 H); LC-MS retention time (Method 1): 2.938 min; (Method 2): 4.181 min; HRMS: m/z (M+H)$^+$ (Calculated for $C_{27}H_{20}F_3N_4$ 457.1635) found, 457.1627.

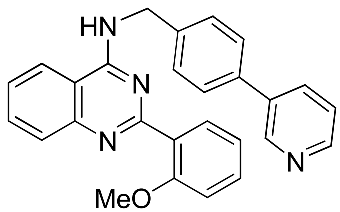


N-(4-(pyridin-3-yl)benzyl)-2-(4-(trifluoromethyl)phenyl)quinazolin-4-amine TFA (23): Follow the procedure for compound **22**, (**Method B**) but substitute 4-trifluoromethylphenylboronic acid for 3-trifluoromethylphenylboronic acid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.40 – 9.67 (m, 1 H), 8.94 (brs, 1 H), 8.53 – 8.67 (m, 3 H), 8.41 (brs, 1 H), 8.21 (br. s., 1 H), 7.90 (brs, 4 H), 7.69 – 7.79 (m, 2 H), 7.64 (d, J = 7.83 Hz, 4 H), and 5.03 (brs, 2 H); LC-MS retention time (Method 1): 2.937 min; (Method 2): 4.176 min; HRMS: m/z (M+H)$^+$ = (Calculated for $C_{27}H_{20}F_3N_4$ 457.1635) found, 457.1627.

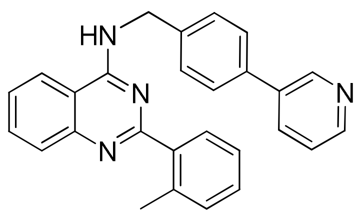


2-(2-nitrophenyl)-N-(4-(pyridin-3-yl)benzyl)quinazolin-4-amine TFA (24): Follow the procedure for compound **22**, (**Method B**) but substitute 2-nitrophenylboronic acid for 3-trifluoromethylphenylboronic acid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.55 – 9.71 (m, 1 H), 9.02 (s, 1 H), 8.69 (d, J = 4.70 Hz, 1 H), 8.42 (s, 2 H), 8.11 (d, J = 7.83 Hz, 1 H), 7.88 – 8.02 (m, 2

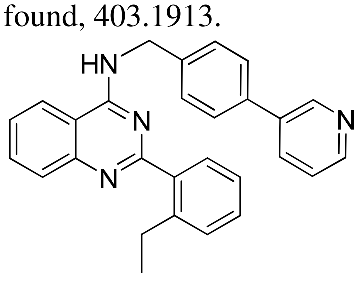
H), 7.63 – 7.88 (m, 7 H), 7.53 (d, *J* = 8.22 Hz, 2 H), and 4.85 (d, *J* = 5.48 Hz, 2 H); LC-MS retention time (Method 1): 2.635 min; (Method 2): 3.627 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{26}H_{20}N_5O_2$ 434.1612) found, 434.1618.



2-(2-methoxyphenyl)-*N*-(4-(pyridin-3-yl)benzyl)quinazolin-4-amine TFA (25): Follow the procedure for compound **22**, (**Method B**) but substitute 2-methyloxyphenylboronic acid for 3-trifluoromethylphenylboronic acid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.67 – 10.79 (m, 1 H), 8.89 – 8.97 (m, 1 H), 8.61 (d, *J* = 3.52 Hz, 1 H), 8.55 (d, *J* = 8.22 Hz, 1 H), 8.18 (d, *J* = 8.22 Hz, 1 H), 8.08 (t, *J* = 7.83 Hz, 1 H), 7.98 (d, *J* = 8.22 Hz, 1 H), 7.91 (dd, *J* = 1.57, and 7.83 Hz, 1 H), 7.83 (t, *J* = 7.43 Hz, 1 H), 7.77 (d, *J* = 8.22 Hz, 2 H), 7.64 – 7.74 (m, 1 H), 7.54 – 7.62 (m, 3 H), 7.34 (d, *J* = 8.61 Hz, 1 H), 7.15 – 7.25 (m, 1 H), 5.07 (d, *J* = 5.48 Hz, 2 H), and 3.94 (s, 3 H); LC-MS retention time (Method 1): 2.692 min; (Method 2): 1.473 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{27}H_{23}N_4O$ 419.1866) found, 419.1863.

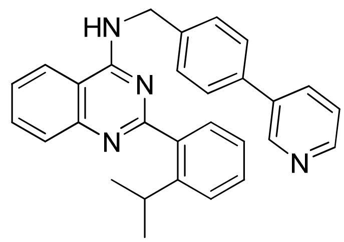


***N*-(4-(pyridin-3-yl)benzyl)-2-o-tolylquinazolin-4-amine TFA (26):** Follow the procedure for compound **22**, (**Method B**) but substitute 2-methylphenylboronic acid for 3-trifluoromethylphenylboronic acid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 – 8.97 (m, 1 H), 8.54 – 8.65 (m, 2 H), 8.16 – 8.22 (m, 1 H), 8.05 – 8.13 (m, 1 H), 7.88 – 7.93 (m, 1 H), 7.81 – 7.87 (m, 1 H), 7.75 (d, *J* = 8.22 Hz, 2 H), 7.71 (d, *J* = 7.83 Hz, 1 H), 7.52 – 7.61 (m, 4 H), 7.39 – 7.47 (m, 2 H), 5.05 (d, *J* = 5.87 Hz, 2 H), and 2.37 (s, 3 H); LC-MS retention time (Method 1): 2.644 min; (Method 2): 3.748 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{27}H_{23}N_4$ 403.1917) found, 403.1913.

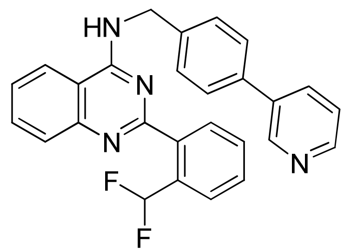


2-(2-ethylphenyl)-*N*-(4-(pyridin-3-yl)benzyl)quinazolin-4-amine TFA (27): Follow the procedure for compound **22**, (**Method B**) but substitute 2-ethylphenylboronic acid for 3-trifluoromethylphenylboronic acid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (s, 1 H), 8.62 – 8.69

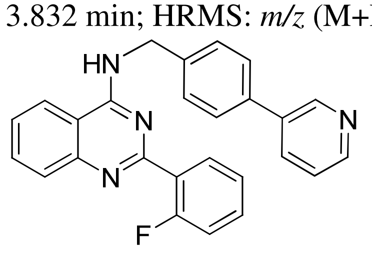
(m, 1 H), 8.54 – 8.63 (m, 1 H), 8.22 – 8.30 (m, 1 H), 8.10 (s, 1 H), 7.81 – 7.94 (m, 2 H), 7.76 (d, *J* = 8.22 Hz, 2 H), 7.56 – 7.72 (m, 2 H), 7.53 (d, *J* = 7.83 Hz, 2 H), 7.39 – 7.49 (m, 2 H), 7.22 (t, *J* = 7.63 Hz, 1 H), 6.83 (d, *J* = 8.22 Hz, 1 H), 5.05 (d, *J* = 5.87 Hz, 2 H), 2.68 (q, *J* = 7.04 Hz, 2 H), and 0.98 (t, *J* = 7.43 Hz, 3 H); LC-MS retention time (Method 1): 2.709 min; (Method 2): 3.853 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{28}H_{26}N_4$ 417.2074) found, 417.2073.



2-(2-isopropylphenyl)-*N*-(4-(pyridin-3-yl)benzyl)quinazolin-4-amine TFA (28): Follow the procedure for compound **22**, (**Method B**) but substitute 2-isopropylphenylboronic acid for 3-trifluoromethylphenylboronic acid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.71 (d, *J* = 2.35 Hz, 1 H), 8.87 – 8.94 (m, 1 H), 8.60 (brs, 2 H), 8.06 – 8.18 (m, 2 H), 7.87 (s, 2 H), 7.73 (d, *J* = 8.22 Hz, 2 H), 7.59 – 7.66 (m, 2 H), 7.53 – 7.59 (m, 2 H), 7.50 (d, *J* = 8.22 Hz, 2 H), 7.43 (s, 1 H), 5.04 (d, *J* = 5.87 Hz, 2 H), 3.24 (dt, *J* = 6.80, and 13.40 Hz, 1 H), 1.07 (s, 3 H), and 1.05 (s, 3 H); LC-MS retention time (Method 1): 2.776 min; (Method 2): 3.985 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{29}H_{27}N_4$ 431.2230) found, 431.2238.

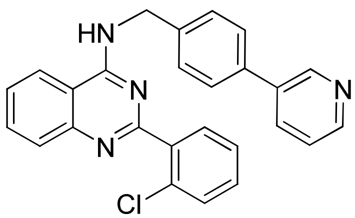


2-(2-(difluoromethyl)phenyl)-5-methyl-*N*-(4-(pyridin-3-yl)benzyl)pyrimidin-4-amine TFA (29): Follow the procedure for compound **22**, (**Method B**) but substitute 2-(2-(difluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane for 3-trifluoromethylphenylboronic acid: LC-MS retention time (Method 1): 2.705 min; (Method 2): 3.832 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{27}H_{21}F_2N_4$ 439.1729) found, 439.1728.

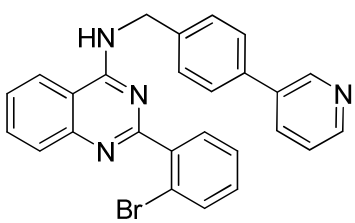


2-(2-fluorophenyl)-*N*-(4-(pyridin-3-yl)benzyl)quinazolin-4-amine TFA (30): Follow the procedure for compound **22**, (**Method B**) but substitute 2-fluorophenylboronic acid for 3-trifluoromethylphenylboronic acid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 – 8.97 (m, 1 H), 8.59 – 8.64 (m, 1 H), 8.46 – 8.54 (m, 1 H), 8.18 – 8.24 (m, 1 H), 7.95 – 8.08 (m, 2 H), 7.88 –

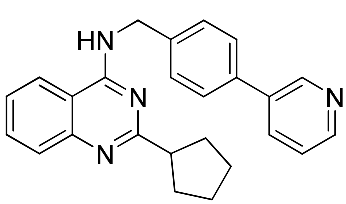
7.94 (m, 1 H), 7.76 (d, *J* = 8.22 Hz, 4 H), 7.59 (d, *J* = 8.22 Hz, 3 H), 7.40 – 7.53 (m, 2 H), and 5.04 (d, *J* = 5.87 Hz, 2 H); LC-MS retention time (Method 1): 2.633 min; (Method 2): 3.606 min; HRMS: *m/z* $(M+H)^+$ = Calculated for $C_{26}H_{20}FN_4$ 407.1667) found, 407.1662.



2-(2-chlorophenyl)-*N*-(4-(pyridin-3-yl)benzyl)quinazolin-4-amine TFA (31): Follow the procedure for compound **22**, (**Method B**) but substitute 2-chlorophenylboronic acid for 3-trifluoromethylphenylboronic acid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 – 8.97 (m, 1 H), 8.61 – 8.66 (m, 1 H), 8.52 – 8.59 (m, 1 H), 8.19 – 8.26 (m, 1 H), 8.01 – 8.10 (m, 1 H), 7.82 (s, 3 H), 7.75 (d, *J* = 7.83 Hz, 2 H), 7.56 (d, *J* = 7.83 Hz, 6 H), and 5.02 (d, *J* = 5.48 Hz, 2 H); LC-MS retention time (Method 1): 2.648 min; (Method 2): 3.718 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{26}H_{20}ClN_4$ 423.1371) found, 423.1378.

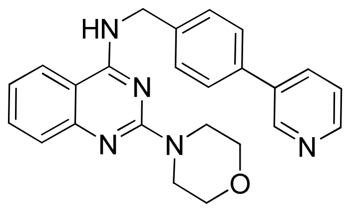


2-(2-bromophenyl)-*N*-(4-(pyridin-3-yl)benzyl)quinazolin-4-amine TFA (32): Follow the procedure for compound **22**, (**Method B**) but substitute 2-bromophenylboronic acid for 3-trifluoromethylphenylboronic acid: ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.42 – 10.59 (m, 1 H), 8.87 – 9.02 (m, 1 H), 8.59 – 8.66 (m, 1 H), 8.51 – 8.59 (m, 1 H), 8.17 – 8.26 (m, 1 H), 8.01 – 8.10 (m, 1 H), 7.70 – 7.90 (m, 6 H), 7.49 – 7.65 (m, 5 H), and 5.03 (d, *J* = 5.87 Hz, 2 H); LC-MS retention time (Method 1): 2.648 min; (Method 2): 3.762 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{26}H_{20}BrN_4$ 469.0849) found, 469.0834.

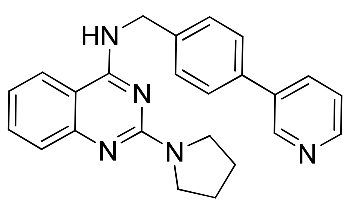


2-cyclopentyl-*N*-(4-(pyridin-3-yl)benzyl)quinazolin-4-amine (33): Follow the procedure for compound **2**, (**Method A**) but substitute cyclopentanecarbonyl chloride for 2-(trifluoromethyl)benzoic acid, and substitute (4-(pyrimidin-5-yl)phenyl)methanamine for thiophen-2-ylmethanamine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62 – 10.74 (m, 1 H), 8.88 – 8.97 (m, 1 H), 8.57 – 8.67 (m, 1 H), 8.42 – 8.54 (m, 1 H), 8.11 – 8.21 (m, 1 H), 8.05 (d, *J* = 7.63

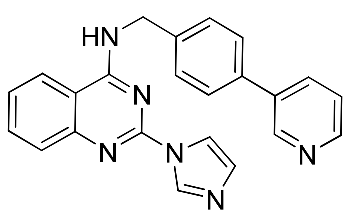
Hz, 1 H), 7.69 – 7.86 (m, 4 H), 7.49 – 7.63 (m, 3 H), 4.98 (d, *J* = 4.89 Hz, 2 H), 3.23 – 3.38 (m, 1 H), 2.05 (br. s., 2 H), 1.93 (d, *J* = 5.87 Hz, 2 H), 1.74 – 1.86 (m, 2 H), and 1.68 (d, *J* = 3.33 Hz, 2 H); LC-MS retention time (Method 1): 2.728 min; (Method 2): 3.667 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{25}H_{25}N_4$ 381.2074) found, 381.2075.



2-morpholino-*N*-(4-(pyridin-3-yl)benzyl)quinazolin-4-amine TFA (34): Follow the procedure for the synthesis of 2-chloro-*N*-(4-(6-methylpyridin-3-yl)benzyl)quinazolin-4-amine (**iv**) **Method B**. Step **c** 2-Chloro-*N*-(4-(6-methylpyridin-3-yl)benzyl)quinazolin-4-amine (50 mg, 0.14 mmol), mopholine (15 µL, 0.17 mmol), in THF (1 mL), was heated in a sealed tube to reflux for 24 h. The mixture was cooled, concentrated, and purified to give the desired product. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.03 – 10.19 (m, 1 H), 9.49 – 9.65 (m, 1 H), 8.68 – 8.99 (m, 2 H), 8.53 – 8.65 (m, 1 H), 8.32 (d, *J* = 8.02 Hz, 1 H), 8.21 (d, *J* = 7.63 Hz, 1 H), 8.12 (d, *J* = 8.22 Hz, 1 H), 7.79 – 7.99 (m, 2 H), 7.61 – 7.77 (m, 3 H), 4.87 (d, *J* = 5.09 Hz, 2 H), and 3.71 (brs, 8 H); LC-MS retention time (Method 1): 2.521 min; (Method 2): 3.315 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{24}H_{24}N_5O$ 398.1975) found, 398.1968.



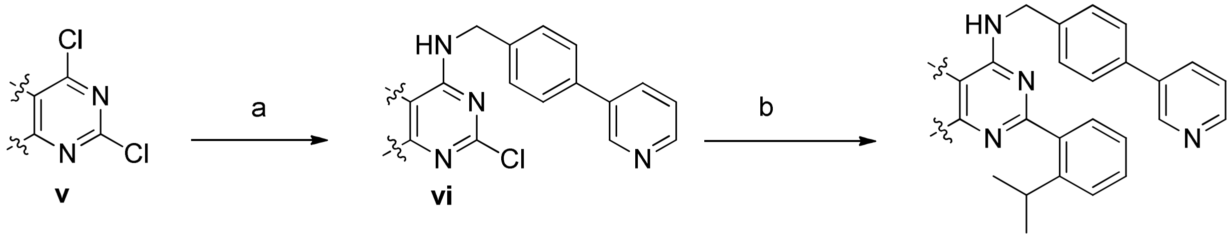
***N*-(4-(pyridin-3-yl)benzyl)-2-(pyrrolidin-1-yl)quinazolin-4-amine TFA (35):** Follow the procedure for compound **34**, (**Method B**) but substitute pyrrolidine for mopholine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 – 10.06 (m, 1 H), 8.83 – 8.92 (m, 1 H), 8.53 – 8.62 (m, 1 H), 8.25 – 8.33 (m, 1 H), 8.01 – 8.13 (m, 1 H), 7.77 – 7.89 (m, 1 H), 7.65 – 7.76 (m, 3 H), 7.40 – 7.62 (m, 4 H), 4.86 (d, *J* = 5.48 Hz, 2 H), 3.59 (br. s., 4 H), and 1.87 – 2.13 (m, 4 H); LC-MS retention time (Method 1): 2.662 min; (Method 2): 3.578 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{24}H_{24}N_5$ 382.2026) found, 382.2021.



2-(1H-imidazol-1-yl)-*N*-(4-(pyridin-3-yl)benzyl)quinazolin-4-amine (36): Follow the procedure for compound **34 (Method B)** but substitute 1*H*-imidazole for mopholine: ^{1}H NMR

(400 MHz, DMSO-d_6) δ 9.49 – 9.72 (m, 1 H), 8.83 – 8.99 (m, 1 H), 8.49 – 8.69 (m, 1 H), 8.24 – 8.48 (m, 2 H), 8.08 – 8.24 (m, 1 H), 7.41 – 7.96 (m, 10 H), and 4.95 (brs, 2 H); LC-MS retention time (Method 1): 2.586 min; (Method 2): 3.413 min; HRMS: m/z $(M+H)^+$ = (Calculated for $C_{23}H_{19}N_6$ 379.1666) found, 379.1663.

Method C:

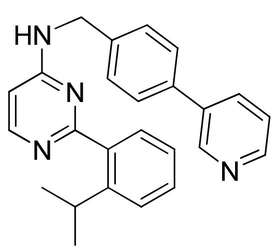


37-53 & 71-75

(a) (4-(pyridin-3-yl)phenyl)methanamine, NEt_3, $CHCl_3$, 18 h, 60 °C (f) 2-isopropylphenyl boronic acid (3.0 equiv), 2M Na_2CO_4 (4 equiv), DPP-Pd silica bound (0.3 equiv), DME, MW, 150 °C, 45 min.

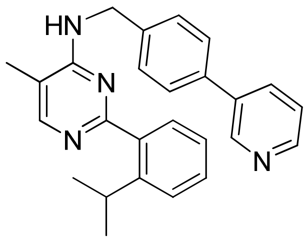
2-Chloro-5-methyl-*N*-(4-(pyridin-3-yl)benzyl)pyrimidin-4-amine TFA (vi): (4-(pyridin-3-yl)phenyl)methanamine (0.37 mmol), 2,4-dichloropyrimidine (**v**) (0.41 mmol), and triethylamine (1.10 mmol), were heated overnight to 60 ºC in $CHCl_3$ (1 mL). Once completed the reaction was poured into water and extracted with dichloromethane. The organic layer was washed with water (1X), saturated sodium bicarbonate (1X), dried over Na_2SO_4, filtered, concentrated, and purified on a prep-HPLC system (gradient 10-100% acetonitrile w/ 0.1% TFA in water w/ 0.1% TFA) to give the desired product: LC-MS retention time (Method 1): 2.617 min. This intermediate was used without further characterization.

General Method C for Suzuki coupling: In a sealed tube containing 2-chloro-*N*-(4-(pyridin-3-yl)benzyl)pyrimidin-4-amine **(vi)** (0.32 mmol) was added 2-isopropylphenylboronic acid (0.39 mmol), sodium carbonate (2.0 M in water, 0.64 mmol), and $Pd(PPh_3)_4$ (0.03 mmol) in DME (2 mL), and heated at 150 ºC for 30-45 min in a Biotage Initiator microwave reactor. The resulting mixture was filtered over celite and purified via reversed phase HPLC (unless otherwise stated) to give the desired products:

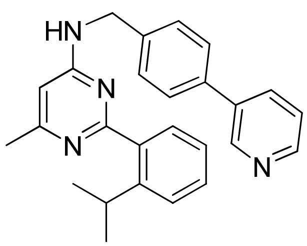


2-(2-Isopropylphenyl)-*N*-(4-(pyridin-3-yl)benzyl)pyrimidin-4-amine TFA (37): Follow synthesis **General Method C** using 2,4-dichloropyrimidine as the core: ^1H NMR (400 MHz, DMSO-d_6) δ 9.71 – 9.94 (m, 1 H), 8.92 (s, 1 H), 8.60 (d, J = 3.52 Hz, 1 H), 8.28 (d, J = 7.04 Hz, 1 H), 8.14 (d, J = 7.83 Hz, 1 H), 7.75 (d, J = 7.83 Hz, 2 H), 7.31 – 7.63 (m, 7 H), 6.88 (d, J = 7.04 Hz, 1 H), 4.64 – 4.85 (m, 2 H), 3.10 – 3.21 (m, 1 H), and 1.08 (d, J = 6.65 Hz, 6 H);

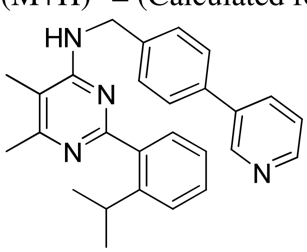
LC/MS: LC-MS retention time (Method 1): 2.739 min; (Method 2): 3.801 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{25}H_{26}N_4$ 381.2074) found, 381.2059.



2-(2-Isopropylphenyl)-5-methyl-*N*-(4-(pyridin-3-yl)benzyl)pyrimidin-4-amine (38): Follow synthesis **General Method C** using 2,4-dichloro-5-methylpyrimidine, for the core: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.25 – 9.40 (m, 1 H), 8.90 (d, *J* = 1.96 Hz, 1 H), 8.59 (d, *J* = 4.70 Hz, 1 H), 8.31 (s, 1 H), 8.12 (d, *J* = 8.22 Hz, 1 H), 7.71 (d, *J* = 8.22 Hz, 2 H), 7.31–7.61 (m, 7 H), 4.83 (d, *J* = 5.87 Hz, 2 H), 3.06 (dt, *J* = 6.70, and 13.60 Hz, 1 H), 2.26 (s, 3 H), and 0.99 (d, *J* = 6.65 Hz, 6 H); LC-MS retention time (Method 1): 2.759 min; (Method 2): 3.831 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{26}H_{27}N_4$ 395.2230found, 395.2242.

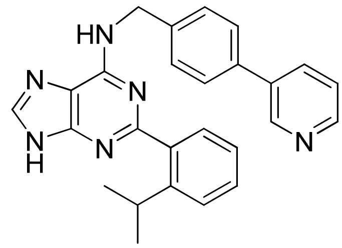


2-(2-Isopropylphenyl)-6-methyl-*N*-(4-(pyridin-3-yl)benzyl)pyrimidin-4-amine (39): Follow **General Method C** using 2,4-dichloro-6-methylpyrimidine for the core: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.02 – 10.28 (m, 1 H), 9.29 (s, 1 H), 8.97 (d, *J* = 3.52 Hz, 1 H), 8.45 – 8.58 (m, 1 H), 8.10 (d, *J* = 7.83 Hz, 2 H), 7.84 – 8.00 (m, 5 H), 7.71 – 7.82 (m, 2 H), 7.09 (s, 1 H), 5.13 (d, *J* = 5.48 Hz, 2 H), 3.45 (dt, *J* = 6.65, and 13.30 Hz, 1 H), 2.76 – 2.84 (m, 3 H), 1.44 (s, 3 H), and 1.43 (s, 3 H); LC-MS retention time (Method 1): 2.688 min; (Method 2): 3.828 min. HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{26}H_{27}N_4$ 395.2230) found, 395.2224.

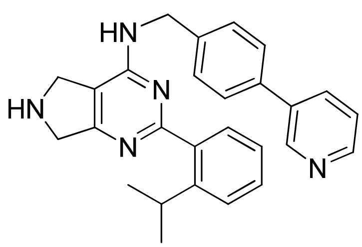


2-(2-Isopropylphenyl)-5,6-dimethyl-N-(4-(pyridin-3-yl)benzyl)pyrimidin-4-amine TFA (40): Follow **General Method C** using 2,4-dichloro-5,6-dimethylpyrimidine for the core: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 – 9.25 (m, 1 H), 8.89 (d, *J* = 1.96 Hz, 1 H), 8.54 – 8.61 (m, 1 H), 8.04 – 8.13 (m, 1 H), 7.69 (d, *J* = 8.22 Hz, 2 H), 7.45 – 7.62 (m, 4 H), 7.39 (d, *J* = 8.22 Hz, 3 H), 4.81 (d, *J* = 5.87 Hz, 2 H), 3.45 (s, 3 H), 2.99 (dt, *J* = 6.65, and 13.30 Hz, 1 H), 2.21 (s, 3

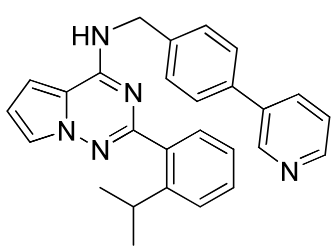
H), 0.99 (s, 3 H), 0.98 (s, 3 H); LC/MS retention time: (Method 1), 1.497 min; (Method 2): 2.695 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{27}H_{29}N_4$ 409.2387) found, 409.2387.



2-(2-Isopropylphenyl)-*N*-(4-(pyridin-3-yl)benzyl)-9H-purin-6-amine TFA (41): Follow **General Method C** using 2,6-dichloropurine for the core: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (d, *J* = 1.56 Hz, 1 H), 8.64 (d, *J* = 3.91 Hz, 1 H), 8.31 (br. s., 2 H), 7.73 (d, *J* = 8.22 Hz, 2 H), 7.61 – 7.70 (m, 1 H), 7.47 (d, *J* = 7.43 Hz, 3 H), 7.39 (d, *J* = 3.52 Hz, 2 H), 7.24 (dd, *J* = 3.33, and 7.63 Hz, 1 H), 4.74 – 4.92 (m, 2 H), 3.45 (d, *J* = 7.04 Hz, 1 H), and 0.93 – 1.14 (m, 6 H); LC-MS retention time (Method 1): 2.756 min; (Method 2): 3.939 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{26}H_{25}N_6$ 421.2135) found, 421.2129.

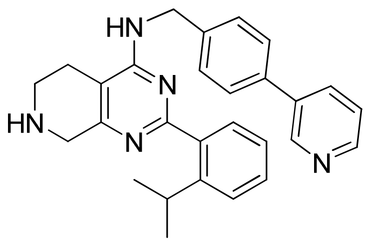


2-(2-Isopropylphenyl)-*N*-(4-(pyridin-3-yl)benzyl)-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidin-4-amine TFA (42): Follow **General Method C** using 2,4-dichloro-6,7-dihydro-5H-pyrrolo[3,4-d]pyrimidine hydrochloride for the core: ^{1}H NMR (400 MHz, MeOD-d_4) δ 9.36 – 9.56 (m, 1 H), 8.89 – 8.99 (m, 1 H), 8.57 – 8.66 (m, 1 H), 8.17 – 8.26 (m, 1 H), 7.73 (d, *J* = 8.22 Hz, 2 H), 7.56 – 7.66 (m, 1 H), 7.40 – 7.48 (m, 2 H), 7.38 (d, *J* = 3.91 Hz, 2 H), 7.16 – 7.27 (m, 1 H), 4.74 (d, *J* = 5.87 Hz, 2 H), 4.45 (d, *J* = 18.39 Hz, 4 H), 3.28 – 3.62 (m, 1 H), and 1.02 (d, *J* = 6.65 Hz, 6 H); LC-MS retention time (Method 1): 1.435 min; (Method 2): 2.710 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{27}H_{28}N_5$ 422.2339) found, 422.2328.

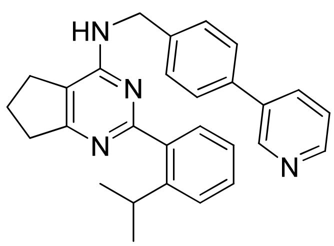


2-(2-Isopropylphenyl)-*N*-(4-(pyridin-3-yl)benzyl)pyrrolo[1,2-f][1,2,4]triazin-4-amine TFA (43): Follow General Method C using 2,4-dichloropyrrolo[1,2-f][1,2,4]triazine for the core: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1 H), 8.85 – 8.95 (m, 1 H), 8.62 – 8.70 (m, 1 H), 8.27 –

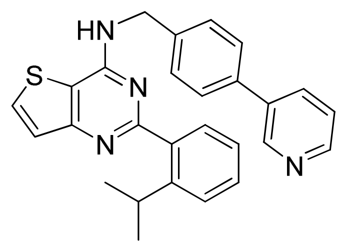
8.37 (m, 1 H), 7.74 (d, *J* = 8.22 Hz, 2 H), 7.65 – 7.72 (m, 2 H), 7.47 (d, *J* = 8.22 Hz, 2 H), 7.42 (d, *J* = 7.43 Hz, 1 H), 7.37 (d, *J* = 3.91 Hz, 2 H), 7.21 (ddd, *J* = 4.01, 4.30, and 7.73 Hz, 1 H), 6.99 (d, *J* = 2.74 Hz, 1 H), 6.65 – 6.72 (m, 1 H), 4.82 (d, *J* = 5.87 Hz, 2 H), 3.30 – 3.43 (m, 1 H), and 1.06 (d, *J* = 6.65 Hz, 6 H); LC-MS retention time (Method 1): 2.209 min; (Method 2): 3.246 min. HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{27}H_{26}N_5$ 420.2183) found, 420.2182.



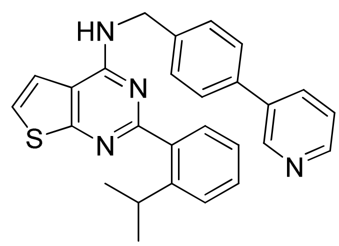
2-(2-Isopropylphenyl)-*N*-(4-(pyridin-3-yl)benzyl)-5,6,7,8-tetrahydropyrido[3,4-d]pyrimidin-4-amine TFA (44): Follow **General Method C** using tert-butyl 2,4-dichloro-5,6-dihydropyrido[3,4-d]pyrimidine-7(8H)-carboxylate for the core. The *tert*-butylcarbamate group was removed with a 20% solution of TFA/DCM stirred for 30 min and concentrated: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 – 9.28 (m, 2 H), 8.95 (s, 1 H), 8.59 – 8.68 (m, 1 H), 8.19 – 8.28 (m, 1 H), 7.97 – 8.07 (m, 1 H), 7.71 (d, *J* = 8.22 Hz, 2 H), 7.59 – 7.67 (m, 1 H), 7.41 (d, *J* = 7.83 Hz, 3 H), 7.37 (d, *J* = 3.91 Hz, 2 H), 7.15 – 7.26 (m, 1 H), 4.75 (d, *J* = 5.48 Hz, 2 H), 4.19 (brs, 2 H), 3.53 (br. s., 2 H), 3.35 – 3.45 (m, 1 H), 2.72 – 2.81 (m, 2 H), 1.01 (s, 3 H), and 0.99 (s, 3 H); LC-MS retention time (Method 1): 2.616 min; (Method 2): 1.323 min. HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{28}H_{30}N_5$ 436.2496) found, 436.2493.



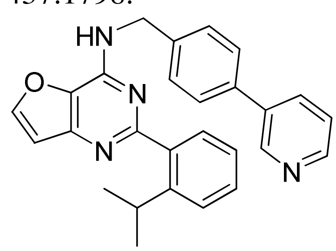
2-(2-Isopropylphenyl)-*N*-(4-(pyridin-3-yl)benzyl)-6,7-dihydro-5H-cyclopenta[d]pyrimidin-4-amine TFA (45): Follow **General Method C** using 2,4-dichloro-6,7-dihydro-5h-cyclopenta[d]pyrimidine for the core: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.32 – 9.51 (m, 1 H), 8.90 (d, *J* = 1.96 Hz, 1 H), 8.59 (dd, *J* = 1.57, and 4.70 Hz, 1 H), 8.12 (d, *J* = 7.83 Hz, 1 H), 7.71 (d, *J* = 8.22 Hz, 2 H), 7.45–7.62 (m, 4 H), 7.32 – 7.45 (m, 3 H), 4.73 – 4.87 (m, 2 H), 2.98 – 3.15 (m, 3 H), 2.87 (t, *J* = 7.24 Hz, 2 H), 2.13 – 2.28 (m, 2 H), and 0.94 – 1.09 (m, 6 H); LC-MS retention time (Method 1): 2.799 min; (Method 2): 3.941 min. HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{28}H_{29}N_4$ 421.2387) found, 421.2386.



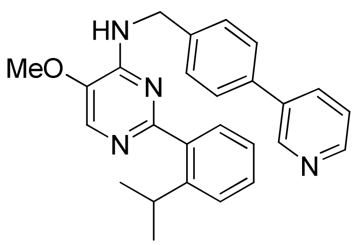
2-(2-Isopropylphenyl)-*N*-(4-(pyridin-3-yl)benzyl)thieno[3,2-d]pyrimidin-4-amine TFA (46): Follow **General Method C** using 2,4-dichlorothieno[3,2-d]pyrimidine for the core: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.59 – 9.93 (m, 1 H), 8.93 (d, *J* = 1.96 Hz, 1 H), 8.62 (d, *J* = 4.70 Hz, 1 H), 8.40 (d, *J* = 5.09 Hz, 1 H), 8.19 (d, *J* = 8.22 Hz, 1 H), 7.73 (d, *J* = 8.22 Hz, 2 H), 7.40 – 7.64 (m, 7 H), 7.30 – 7.40 (m, 1 H), 4.91 (d, *J* = 5.87 Hz, 2 H), 3.24 – 3.34 (m, 1 H), and 0.94 – 1.05 (m, 6 H); LC-MS retention time (Method 1): 2.808 min; (Method 2): 3.989 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{27}H_{25}N_4S$ 437.1794) found 437.1796.



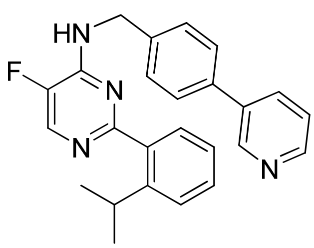
2-(2-Isopropylphenyl)-5-methyl-*N*-((1-(pyridin-3-yl)piperidin-4-yl)methyl)pyrimidin-4-amine TFA (47): Follow **General Method C** using 2,4-dichlorothieno[2,3-d]pyrimidine for the core: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 – 8.93 (m, 1 H), 8.62 – 8.70 (m, 1 H), 8.58 (br. s., 1 H), 8.08 – 8 .18 (m, 1 H), 7.71 (d, *J* = 5.09 Hz, 3 H), 7.60 – 7.65 (m, 1 H), 7.52 (s, 2 H), 7.46 (d, *J* = 7.83 Hz, 2 H), 7.32 – 7.39 (m, 2 H), 7.16 – 7.25 (m, 1 H), 4.84 (d, *J* = 5.87 Hz, 2 H), 3.34 – 3.44 (m, 1 H), 1.04 (s, 3 H), and 1.03 (s, 3 H); LC-MS retention time (Method 1): 3.120 min; (Method 2): 4.676 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{27}H_{25}N_4O$ 437.1794) found, 437.1798.



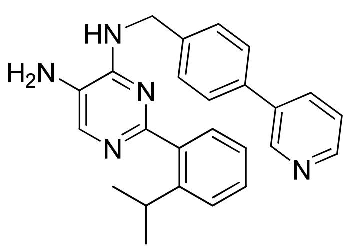
2-(2-Isopropylphenyl)-*N*-(4-(pyridin-3-yl)benzyl)furo[3,2-d]pyrimidin-4-amine TFA (48): Follow **General Method C** uisng 2,4-dichlorofuro[3,2-d]pyrimidine for 2,4-dichloro-5-methylpyrimidine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.46 (brs, 1 H), 8.95 (d, *J* = 1.96 Hz, 1 H), 8.63 (d, *J* = 5.09 Hz, 1 H), 8.47 (s, 1 H), 8.23 (d, *J* = 7.83 Hz, 1 H), 7.73 (d, *J* = 8.22 Hz, 2 H), 7.62 (dd, *J* = 5.09, and 7.83 Hz, 1 H), 7.40–7.53 (m, 5 H), 7.24–7.33 (m, 1 H), 7.12 (d, *J* = 1.96 Hz, 1 H), 4.86 (d, *J* = 5.87 Hz, 2 H), 3.31 (ddd, *J* = 6.85, 7.04, and 13.50 Hz, 1 H), 1.05 (s, 3 H), and 1.03 (s, 3 H); LC-MS retention time (Method 1): 2.706 min; (Method 2): 4.214 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{27}H_{26}N_4O$ 421.2023) found, 421.2011.



2-(2-Isopropylphenyl)-5-methoxy-*N*-(4-(pyridin-3-yl)benzyl)pyrimidin-4-amine TFA (49): Follow **General Method C** using 2,4-dichloro-5-methoxypyrimidine for 2,4-dichloro-5-methylpyrimidine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.51–9.67 (m, 1 H), 8.88–8.97 (m, 1 H), 8.63 (d, *J* = 4.70 Hz, 1 H), 8.16–8.25 (m, 1 H), 8.11 (s, 1 H), 7.71 (d, *J* = 8.22 Hz, 2 H), 7.32–7.64 (m, 7 H), 4.78 (d, *J* = 5.87 Hz, 2 H), 3.97–4.08 (m, 3 H), 2.98–3.10 (ddd, *J* = 6.46, 6.60, 6.73, and 13.52 Hz, 1 H), 1.02 (s, 3 H), and 1.01 (s, 3 H); LC-MS retention time (Method 1): 2.738 min; (Method 2): 1.489 min; HRMS: *m/z* (M+H)$^+$ = (Calculated for $C_{26}H_{27}N_4O$ 411.2179) found, 411.2181.

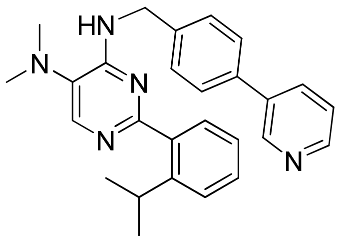


5-Fluoro-2-(2-isopropylphenyl)-*N*-(4-(pyridin-3-yl)benzyl)pyrimidin-4-amine (50): Follow **General Method C** using 2,4-dichloro-5-fluoropyrimidine for the core: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 – 9.03 (m, 1 H), 8.62 – 8.73 (m, 2 H), 8.36 – 8.43 (m, 1 H), 8.26 – 8.36 (m, 1 H), 7.74 (d, *J* = 7.83 Hz, 2 H), 7.63 – 7.72 (m, 1 H), 7.44 (t, *J* = 7.43 Hz, 3 H), 7.38 (d, *J* = 3.52 Hz, 2 H), 7.22 (ddd, *J* = 4.01, 4.30, and 7.73 Hz, 1 H), 4.66 – 4.77 (m, 2 H), 3.31 – 3.42 (m, 1 H), 1.03 (s, 3 H), and 1.01 (s, 3 H); LC-MS retention time (Method 1): 1.557 min; (Method 2): 2.798 min. HRMS: *m/z* (M+H)$^+$ = (Calculated for $C_{25}H_{24}FN_4$ 399.1980) found, 399.1978.

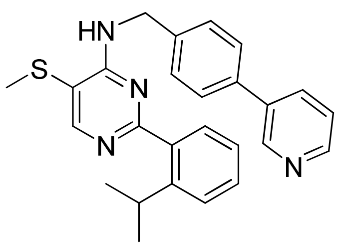


2-(2-Isopropylphenyl)-*N*-4-(4-(pyridin-3-yl)benzyl)pyrimidine-4,5-diamine TFA (51): Follow **General Method C** using 5-amino-2,4-dichloropyrimidine for the core: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 – 8.98 (m, 1 H), 8.88 – 8.92 (m, 1 H), 8.56 – 8.62 (m, 1 H), 8.10 – 8.17 (m, 1 H), 7.72 (d, *J* = 8.22 Hz, 2 H), 7.62 (s, 1 H), 7.45 – 7.58 (m, 3 H), 7.42 (d, *J* = 8.22 Hz, 3 H), 7.33 (t, *J* = 7.43 Hz, 1 H), 5.60 – 6.04 (m, 1 H), 4.83 (d, *J* = 5.48 Hz, 2 H), 2.99 – 3.11

(m, 1 H), 1.01 (s, 3 H), and 1.00 (s, 3 H); LC-MS retention time (Method 1): 2.727 min; (Method 2): 3.840 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{25}H_{26}N_5$ 396.2183) found, 396.2180.

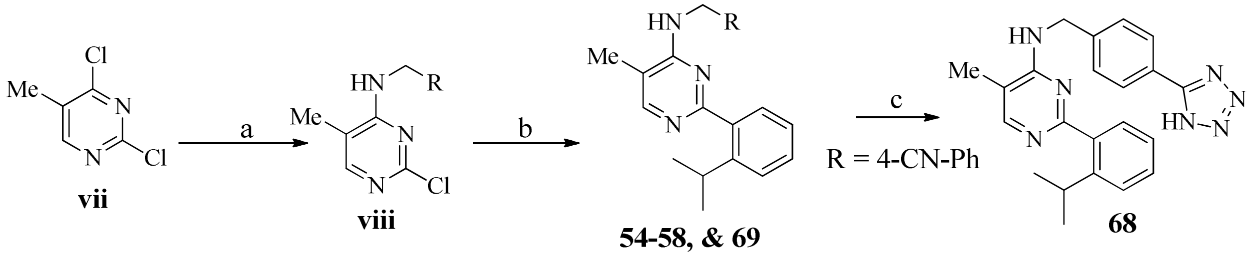


2-(2-Isopropylphenyl)-*N*5,*N*5-dimethyl-*N*-4-(4-(pyridin-3-yl)benzyl)pyrimidine-4,5-diamine TFA (52): Follow **General Method C** using (2,4-dichloro-pyrimidin-5-yl)-dimethyl amine for the core: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.33 – 9.44 (m, 1 H), 8.92 (d, J = 1.96 Hz, 1 H), 8.59 – 8.65 (m, 1 H), 8.14 – 8.21 (m, 1 H), 8.03 (s, 1 H), 7.71 (d, J = 8.22 Hz, 2 H), 7.30 – 7.62 (m, 7 H), 4.82 (d, J = 6.26 Hz, 2 H), 3.06 (dt, J = 6.70, and 13.60 Hz, 1 H), 2.76 (s, 6 H), 1.02 (s, 3 H), and 1.00 (s, 3 H); LC-MS retention time (Method 1): 2.782 min; (Method 2): 3.902 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{27}H_{30}N_5$ 424.2496) found, 424.2495.



2-(2-Isopropylphenyl)-5-(methylthio)-N-(4-(pyridin-3-yl)benzyl)pyrimidin-4-amine TFA (53): Follow **General Method C** using 2,4-dichloro-5-(methylthio)pyrimidine for the core. Synthesis of 2,4-dichloro-5-(methylthio)pyrimidine was achieved by combining 5-bromopyrimidine-2,4(1H,3H)-dione (0.50 g, 2.62 mmol), sodium thiomethoxide (0.33 g, 4.71 mmol) and DMSO (5 mL) in a 10-20 mL microwave vial. The vial was sealed and heated to 100 ºC for 30 min in a Biotage Initiator microwave reactor, cooled to rt, poured into water and extracted with EtOAc (2X). The organic layers were combined and washed with water (3X), dried over Na_2SO_4, filtered, concentrate and purified on prep HPLC (gradient 10-100% acetonitrile w/ 0.1% TFA in water w/ 0.1% TFA). 5-(methylthio)pyrimidine-2,4(1H,3H)-dione TFA (0.50 g, 0.32 mmol), *N,N*-dimethylaniline (0.40 mL, 3.16 mmol), and $POCl_3$ (1.00 mL, 10.73 mmol) were refluxed for 5 h, cooled to rt, poured into a cold solution of sodium bicarbonate, extracted with EtOAc (1X), dried with Na_2SO_4, filtered, concentrated, and used without further purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1 H), 8.62 – 8.70 (m, 1 H), 8.37 (s, 1 H), 8.26 – 8.33 (m, 1 H), 7.73 (d, J = 8.22 Hz, 2 H), 7.63 – 7.71 (m, 1 H), 7.35 – 7.54 (m, 6 H), 7.28 – 7.35 (m, 1 H), 4.77 – 4.86 (m, 2 H), 3.14 – 3.28 (m, 1 H), 2.58 (s, 3 H), 1.01 (s, 3 H), and 0.99 (s, 3 H); LC-MS retention time (Method 1): 2.738 min; (Method 2): 3.946 min. HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{26}H_{27}N_4S$ 427.1951) found, 427.1953.

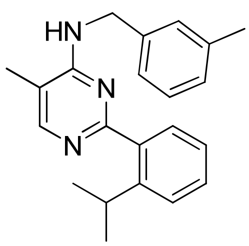
Method D



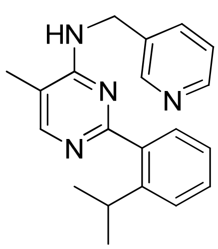
(a) 4-**R**-amine (1.1 equiv), Et_3N (3.0 equiv), DMF, 100 ºC 18 h (b) 2-isoproylphenyl boronic acid (3.0 equiv), 2 M Na_2HCO_3 (4.0 equiv), DPP-Pd silica bound Silicycle, DME, MW, 150 ºC, 30 min (c) For R = CN; NaN_3 (8.0 equiv), NH_4Cl (8.0 equiv), DMF 130 ^oC, 30 min

General Method D: Step a 2,4-dichloro-5-methylpyrimidine (0.35 mmol) **(vii)**, (**R**)methanamine (0.39 mmol), Et_3N (1.06 mmol), in $CHCl_3$ (2 mL), was heated in a sealed tube for 18 h to 100 ^oC. The resulting mixture was cooled and placed on a silica column for purification with EtOAc/Hex 0 to 100% gradient over 20 min.

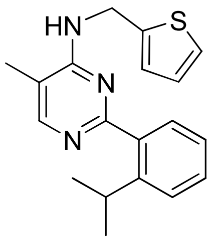
Step b: In a sealed tube 2-chloro-*N*-(**R**)-5-methylpyrimidin-4-amine **viii** (0.32 mmol) was combined with (2-isopropylphenyl)boronic acid (0.39 mmol), sodium carbonate (2.0 M in water, 0.64 mmol), and DPP-Pd silica bound Silicycle (0.26 mmol/g, 19 mol %) in DME (2.00 mL), and heated at 150 ºC for 30 min in a Biotage Initiator microwave reactor. The resulting mixture was filtered over celite and purified to give the desired products:



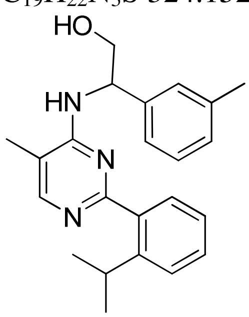
2-(2-Isopropylphenyl)-5-methyl-*N*-(3-methylbenzyl)pyrimidin-4-amine TFA (54): Follow **General Method D**: ^1H NMR (400 MHz, DMSO-d_6) δ 8.97 – 9.24 (m, 1 H), 8.22 – 8.30 (m, 1 H), 7.41 – 7.58 (m, 3 H), 7.36 (s, 1 H), 7.16 – 7.24 (m, 1 H), 7.01 – 7.12 (m, 3 H), 4.62–4.79 (m, 2 H), 3.03–3.16 (m, 1 H), 2.26 (s, 3 H), 2.22 (s, 3 H), 1.01 (s, 3 H), and 1.00 (s, 3 H); LC-MS retention time (Method 1): 3.231 min; (Method 2): 5.037 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{22}H_{26}N_3$ 332.2121) found, 332.2124.



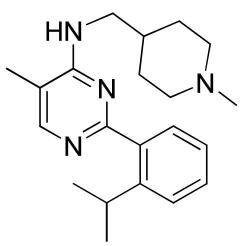
2-(2-Isopropylphenyl)-5-methyl-N-(pyridin-3-ylmethyl)pyrimidin-4-amine TFA (55): Follow **General Method D:** ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.18 – 9.35 (m, 1 H), 8.59 (s, 1 H), 8.52 – 8.57 (m, 1 H), 8.29 – 8.34 (m, 1 H), 7.82 – 7.88 (m, 1 H), 7.41 – 7.60 (m, 4 H), 7.32 – 7.40 (m, 1 H), 4.82 (d, *J* = 5.87 Hz, 2 H), 3.01 (d, *J* = 6.72 Hz, 1 H), 2.24 (s, 3 H), 1.00 (s, 3 H), and 0.98 (s, 3 H); LC/MS retention time (Method 1): 2.512 min; (Method 2): 3.250 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{20}H_{24}N_4$ 319.1917 found, 19.1921.



2-(2-Isopropylphenyl)-5-methyl-*N*-(thiophen-2-ylmethyl)pyrimidin-4-amine TFA (56): Follow **General Method D**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 – 9.26 (m, 1 H), 8.26 (s, 1 H), 7.28 – 7.61 (m, 5 H), 7.01 (d, *J* = 2.74 Hz, 1 H), 6.90 – 6.99 (m, 1 H), 4.89 (d, *J* = 5.87 Hz, 2 H), 3.15 – 3.27 (m, 1 H), 2.17 (s, 3 H), 1.13 (s, 3 H), and 1.11 (s, 3 H); LC-MS retention time (Method 1): 3.053 min; (Method 2): 4.755 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{19}H_{22}N_3S$ 324.1529) found, 324.1531.



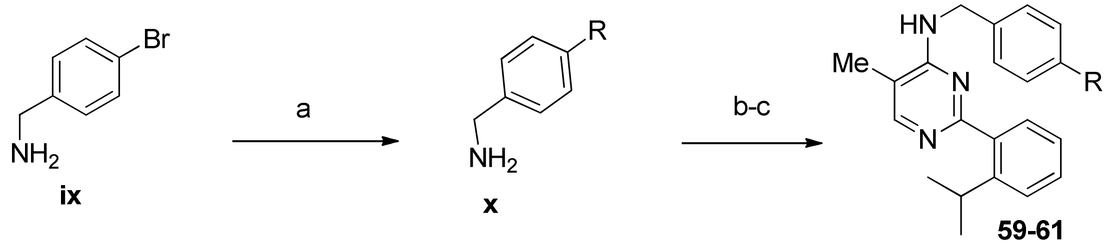
2-(2-(2-Isopropylphenyl)-5-methylpyrimidin-4-ylamino)-2-m-tolylethanol TFA (57): Follow **General Method D**: LC/MS: (Method 1): 3.106 min; (Method 2): 1.950 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{23}H_{28}N_3O$ 362.2227) found, 362.2225.



2-(2-Isopropylphenyl)-5-methyl-*N*-((1-methylpiperidin-4-yl)methyl)pyrimidin-4-amine (58): Follow synthesis **General Method D**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00 (s, 1 H), 7.35 (d, *J* = 3.91 Hz, 2 H), 7.25 (d, *J* = 7.43 Hz, 1 H), 7.07 – 7.21 (m, 1 H), 3.31 – 3.37 (m, 1 H), 3.10 – 3.25 (m, 4 H), 2.95 – 3.07 (m, 1 H), 2.93 (s, 1 H), 2.61 (q, *J* = 11.09 Hz, 2 H), 2.27 (s, 2 H), 1.93 (s, 3 H), 1.62 (d, *J* = 11.74 Hz, 3 H), 1.15 (br. s., 2 H), 0.99 (s, 3 H), and 0.97 (s, 3 H); LC-

MS retention time (Method 1): 2.494 min; (Method 2): 3.341 min; HRMS: m/z $(M+H)^+$ = (Calculated for $C_{21}H_{31}N_4$ 339.2543) found, 339.2534.

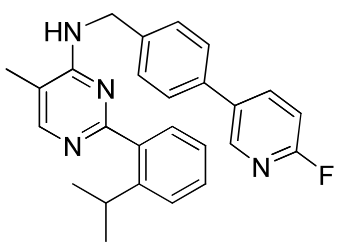
Method E



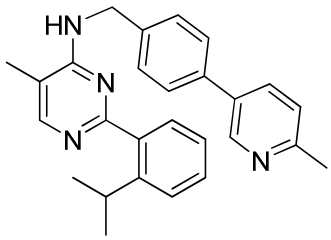
(a) $RB(OH)_2$ (1.3 equiv), $Pd(PPh_3)_4$ (10 mol%) or DPP-Pd silica bound Silicycle, , 2 M Na_2CO_3 (2.0 equiv), DME, MW, 150 ºC, 10 min, (b) 2,4-dichloro-5-methylpyrimidine, Et_3N(3.0 equiv), DMF, 100 ºC 18h (c) 2-isopropylphenyl boronic acid(3.0 equiv), 2 M Na_2HCO_3(4.0 equiv), DPP-Pd silica bound Silicycle, DME, MW, 150 ºC, 30 min, 35-70% yield.

(4-(2-(R)-pyridin-4-yl)phenyl)methanamine (x) : (4-bromophenyl)methanamine **(ix)** (1.08 mmol), (**R**)-(pyridin-4-yl)boronic acid (1.40 mmol), Na_2CO_3 solution in water (2 M, 2.15 mmol), DPP-Pd silica bound Silicycle (0.26 mol/g, 19 mol %) in DME (4 mL) was sealed in a microwave vial and heated in a Biotage Initiator microwave reactor to 150 ºC for 10 min. The reaction was filtered over celite, concentrated, and purified on silica gel 0-5% gradient MeOH/DCM with 1% ammonia to give the desired product.

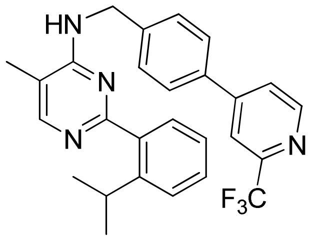
2-Chloro-5-methyl-*N*-((2-(R)-methyl)pyridin-4-yl)benzyl)pyrimidin-4-amine TFA (Step b)**:** 2,4-dichloro-5-methylpyrimidine (0.40 mmol), (4-((**R**)-methyl)pyridin-4-yl)phenyl)methanamine (0.48 mmol), Et_3N (1.2 mmol), in DMF was heated to 100 ºC for 18 h. The reaction was poured into water and extracted with EtOAc (1X). The organic layer were washed with water (3 X), dried over Na_2SO_4, filtered, concentrated, and purified on a prep-HPLC (gradient 10-100% acetonitrile w/ 0.1% TFA in water w/ 0.1% TFA) to give the desired product.



***N*-(4-(6-fluoropyridin-3-yl)benzyl)-2-(2-isopropylphenyl)-5-methylpyrimidin-4-amine TFA (59):** Follow **Method E** for step **a** with 6-(fluoro)pyridine-3-boronic acid and **General Method C** for Suzuki coupling**:** ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.02 – 9.28 (m, 1 H), 8.52 (d, J = 1.96 Hz, 1 H), 8.19 – 8.31 (m, 2 H), 7.68 (d, J = 8.22 Hz, 2 H), 7.53 (d, J = 7.04 Hz, 1 H), 7.44 – 7.51 (m, 2 H), 7.40 (d, J = 8.22 Hz, 2 H), 7.35 (t, J = 7.24 Hz, 1 H), 7.28 (dd, J = 2.54, and 8.41 Hz, 1 H), 4.81 (d, J = 5.87 Hz, 2 H), 3.05 – 3.16 (m, 1 H), 2.24 (s, 3 H), 1.01 (s, 3 H), and 0.99 (s, 3 H); LC-MS retention time (Method 1): 2.102 min; HRMS: m/z $(M+H)^+$ = (Calculated for $C_{26}H_{26}FN_4$ 413.2136) found, 413.2121.

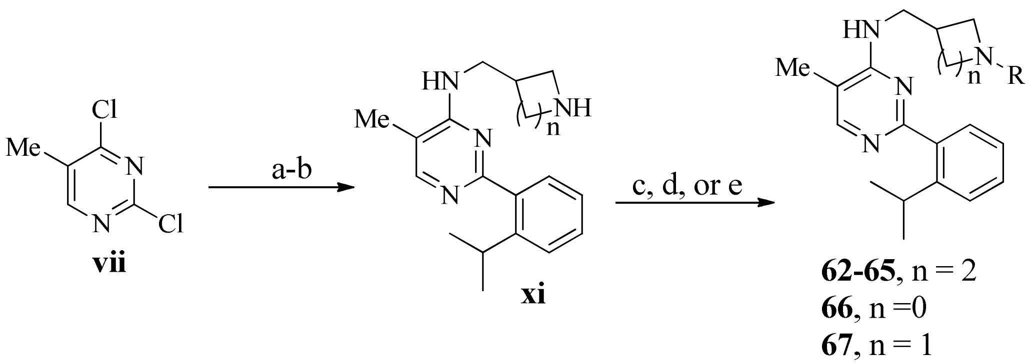


2-(2-Isopropylphenyl)-5-methyl-*N*-(4-(6-methylpyridin-3-yl)benzyl)pyrimidin-4-amine (60): Follow **Method E** for step **a** with 2-methylpyridine-5-boronic acid and **General Method C** for Suzuki coupling: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 – 9.40 (m, 1 H), 8.79 – 8.87 (m, 1 H), 8.30 (s, 1 H), 8.07 – 8.21 (m, 1 H), 7.70 (d, *J* = 8.22 Hz, 2 H), 7.29 – 7.60 (m, 7 H), 4.82 (d, *J* = 5.87 Hz, 2 H), 3.07 (dt, *J* = 6.70, and 13.60 Hz, 1 H), 2.57 (s, 3 H), 2.25 (s, 3 H), 1.00 (s, 3 H), and 0.98 (s, 3 H); LC-MS retention time (Method 1): 2.727 min; (Method 2): 3.803 min. HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{27}H_{29}N_4$ 409.2387) found, 409.2375.



2-(2-Isopropylphenyl)-5-methyl-*N*-(4-(2-(trifluoromethyl)pyridin-4-yl)benzyl)pyrimidin-4-amine (61): Follow **Method E** for step **a** with 2-triflouormethylpyridine-4-boronic acid and **General Method C** for Suzuki coupling: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.16 – 9.31 (m, 1 H), 8.77 – 8.85 (m, 1 H), 8.27 – 8.35 (m, 1 H), 8.14 (s, 1 H), 7.99 – 8.06 (m, 1 H), 7.89 (d, *J* = 8.22 Hz, 2 H), 7.46 (d, *J* = 7.83 Hz, 5 H), 7.30 – 7.40 (m, 1 H), 4.84 (d, *J* = 5.87 Hz, 2 H), 3.08 (dt, *J* = 6.70, and 13.60 Hz, 1 H), 2.25 (s, 3 H), 0.99 (s, 3 H), and 0.98 (s, 3 H); LC-MS retention time (Method 1): 3.297 min; (Method 2): 2.262 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{27}H_{26}F_3N_4$ 463.2104) found, 463.2095.

Method F



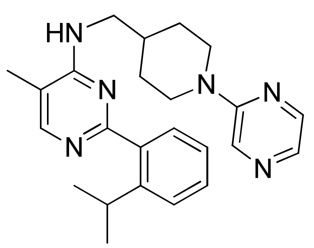
(a) *tert*-butyl 4-(aminomethyl)piperidine-1-carboxylate (1.1 equiv), NEt_3 (3.0 equiv), DMF, 100 ºC 18 h (b) 2-isoproylphenyl boronic acid (3.0 equiv), 2 M Na_2HCO_3 (4.0 equiv), $Pd(PPh_3)_4$ (0.1 equive), DME, 150 ºC, 30 min, (c) $NaBH(AcO)_3$ (10.0 equiv), oxetan-3-one, DCM, 2 h (d) **R**Br (1.2 equiv), Cs_2CO_3, dicyclohexyl(2',4',6'-triisopropyl-3,6-dimethoxybiphenyl-2-

yl)phosphine, RuPhos palladacycle, toluene, sealed tube, 100°C, 18 h or (e) **R**Br (1.2 equiv), NaOtBu, $Pd_2(dba)_3$ (0.02 equiv), DavePhos (0.02 equiv), xylenes, sealed tube, 100 °C, 1 h.

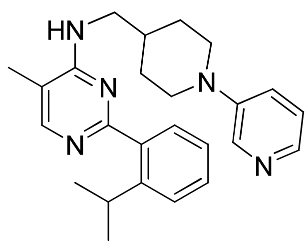
General Method F

2-(2-Isopropylphenyl)-5-methyl-*N*-(piperidin-4-ylmethyl)pyrimidin-4-amine TFA (xi): 2,4-Dichloro-5-methylpyrimidine (**vii**) (0.20 g, 1.23 mmol), *tert*-butyl 4-(aminomethyl)piperidine-1-carboxylate (**62-65**), *tert*-butyl 3-(aminomethyl)azetidine-1-carboxylate (**66**), or *tert*-butyl 3-(aminomethyl)pyrrolidine-1-carboxylate (**67**), (1.47 mmol), Et_3N (0.51 mL, 3.86), $CHCl_3$ (3 mL), was heated to 60 °C for 18 h. The reaction mixture was cooled to rt, poured into $NaHCO_3$ and washed (2 X), dried over Na_2SO_4, concentrated and purified on silica gel DCM/MeOH. *Tert*-butyl 4-((2-chloro-5-methylpyrimidin-4-ylamino)methyl)piperidine-1-carboxylate (0.25 g, 0.72 mmol), 2-isopropylphenylboronic acid (0.14 g, 0.86 mmol), $Pd(PPh_3)_4$, (0.08 g, 0.07 mmol), Na_2CO_3 (2 M, 0.72 mL, 1.44 mmol) in DME (2 mL), was sealed in a microwave vial and heated to 150 °C for 30 min. The mixture was cooled to rt and filtered through celite, concentrated and purified on reverse phase with $MeCN/H_2O$ with 0.1% TFA gradient 10 to 100 % over 20 min. This compound was used as is with no further characterization. Follow **General Method D** for the Suzuki coupling.

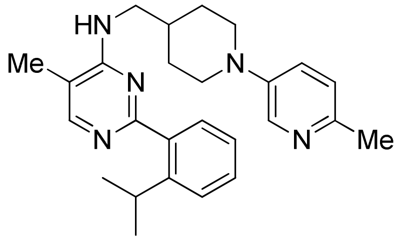
***N*-(4-(1*H*-1,2,3-triazol-1-yl)benzyl)-2-(2-*tert*-butylphenyl)-5-methylpyrimidin-4-amine TFA (62): Method F** step **c**: 2-(2-isopropylphenyl)-5-methyl-*N*-(piperidin-4-ylmethyl)pyrimidin-4-amine (0.13 g, 0.39 mmol), $NaBH(AcO)_3$ (0.82 g, 3.85 mmol), and oxetan-3-one (0.02 mL, 0.39 mmol), were stirred in DCE (2 ml) for 2 h. When complete the reaction mixture was poured into saturated solution of sodium bicarbonate and extracted with DCM, dried over Na_2SO_4, filtered, concentrated, and purified to give the desired product: ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.12 (br. s., 1 H), 8.21 (br. s., 1 H), 7.56 (d, J = 2.35 Hz, 2 H), 7.48 (d, J = 7.83 Hz, 1 H), 7.36 (d, J = 3.91 Hz, 1 H), 4.70 (d, J = 5.87 Hz, 4 H), 2.64–2.83 (m, 2 H), 2.54 (br. s., 1 H), 2.45 (br. s., 1 H), 2.15 (s, 3 H), 1.88 (d, J = 11.74 Hz, 3 H), 1.38 (d, J = 13.69 Hz, 2 H), 1.22 (s, 3 H), and 1.20 (s, 3 H); LC-MS retention time (Method 1): 2.365 min; (Method 2): 3.163 min; HRMS: m/z $(M+H)^+$ = (Calculated for $C_{23}H_{33}N_4O$ 381.2649) found, 381.2640.



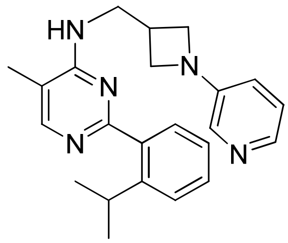
2-(2-isopropylphenyl)-5-methyl-*N*-((1-(pyrazin-2-yl)piperidin-4-yl)methyl)pyrimidin-4-amine TFA (63) Method F step **d:** To degassed toluene (1 mL) 2-(2-isopropylphenyl)-5-methyl-*N*-(piperidin-4-ylmethyl)pyrimidin-4-amine (0.05 g, 0.15 mmol), Cs_2CO_3 (0.06 g, 0.18 mmol), dicyclohexyl(2',4',6'-triisopropyl-3,6-dimethoxybiphenyl-2-yl)phosphine (0.83 mg, 1.54 μmol), RuPhos palladacycle (1.20 mg, 1.54 μmol), and 2-bromopyrazine (0.03 g, 0.19 mmol) were added and heated to 100 ºC for 18h. The reaction was allowed to cool to rt, filtered, and placed on reverse phase HPLC (gradient 20-100% acetonitrile w/ 0.1% TFA in water w/ 0.1% TFA) for purification to give the desired product: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 – 8.85 (m, 1 H), 8.27 – 8.32 (m, 1 H), 8.22 (s, 1 H), 8.00 – 8.07 (m, 1 H), 7.78 (d, J = 2.74 Hz, 1 H), 7.57 (s, 2 H), 7.47 (s, 1 H), 7.34 – 7.42 (m, 1 H), 4.33 (d, J = 13.30 Hz, 2 H), 3.42 – 3.49 (m, 2 H), 3.24 (dt, J = 6.80, and 13.40 Hz, 1 H), 2.82 (t, J = 11.93 Hz, 2 H), 2.18 (s, 3 H), 1.88 – 2.02 (m, 1 H), 1.74 (d, J = 11.74 Hz, 2 H), 1.18 (s, 3 H), and 1.17 (s, 3 H); LC-MS retention time (Method 1): 1.809 min; HRMS: m/z $(M+H)^+$ = (Calculated for $C_{24}H_{31}N_6$ 403.2605) found, 403.2591.



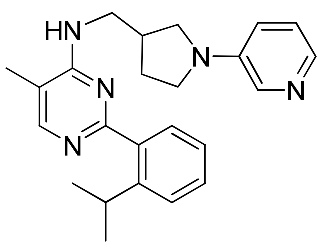
2-(2-isopropylphenyl)-5-methyl-*N*-((1-(pyridin-3-yl)piperidin-4-yl)methyl)pyrimidin-4-amine TFA (64): Method F step **d** as in compound **63** but substitute 3-bromopyridine in step **a** for 5-bromo-2-methylpyridine: ^1H NMR (400 MHz, DMSO-d_6) δ 8.67 – 8.79 (m, 1 H), 8.37 (d, J = 2.74 Hz, 1 H), 8.23 (s, 1 H), 8.08 (d, J = 5.09 Hz, 1 H), 7.72 – 7.83 (m, 1 H), 7.53 – 7.62 (m, 3 H), 7.45 – 7.52 (m, 1 H), 7.34 – 7.43 (m, 1 H), 3.81 – 3.94 (m, 2 H), 3.19 – 3.28 (m, 1 H), 2.80 (t, J = 11.74 Hz, 2 H), 2.18 (s, 3 H), 1.89 (td, J = 3.72, and 7.14 Hz, 1 H), 1.78 (d, J = 12.13 Hz, 2 H), 1.21 – 1.32 (m, 3 H), 1.20 (s, 3 H), and 1.18 (s, 3 H); LC-MS retention time (Method 1): 2.683 min; (Method 2): 3.717 min; HRMS: m/z $(M+H)^+$ = (Calculated for $C_{25}H_{32}N_5$ 402.2653) found, 402.2655.



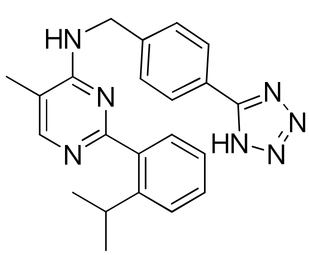
2-(2-isopropylphenyl)-5-methyl-N-((1-(6-methylpyridin-3-yl)piperidin-4-yl)methyl)pyrimidin-4-amine TFA (65): Method F and step **f**. To degassed xylene (1 ml), was added 2-(2-isopropylphenyl)-5-methyl-N-(piperidin-4-ylmethyl)pyrimidin-4-amine (0.13 g, 0.39 mmol), 2'-(dicyclohexylphosphino)-N,N-dimethylbiphenyl-2-amine (DavePhos) (7.6 mg, 0.02 mmol), sodium tert-butoxide (0.05 g, 0.54 mmol), $Pd_2(dba)_3$, and 5-bromo-2-methylpyridine (0.08 g, 0.46 mmol), and the contents were heated in a sealed tube at 100 °C for 1 h. The reaction material was loaded directly onto silica gel and purified using (0-10% MeOH/DCM): LC-MS retention time (Method 1): 1.485 min; HRMS: m/z $(M+H)^+$ = (Calculated for $C_{26}H_{34}N_5$ 416.2809) found, 416.2819.



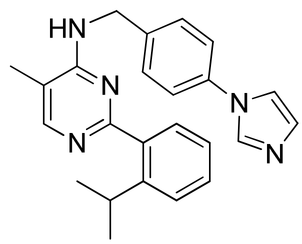
2-(2-isopropylphenyl)-5-methyl-N-((1-(pyridin-3-yl)azetidin-3-yl)methyl)pyrimidin-4-amine (66): Use **Method F** and substitute *tert*-butyl 3-(aminomethyl)azetidine-1-carboxylate for *tert*-butyl 4-(aminomethyl)piperidine-1-carboxylate. Follow (step **f**) for compound **65** but substitute 3-bromopyridine for 5-bromo-2-methylpyridine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 (s, 1 H), 8.80 (d, *J* = 1.1 Hz, 1 H), 8.24 (s, 1 H), 7.97 (d, *J* = 1.1 Hz, 1 H), 7.94 – 7.85 (m, 2 H), 7.78 (dd, *J* = 1.8, and 7.7 Hz, 1 H), 7.60 (dd, *J* = 5.0, and 7.5 Hz, 3 H), 7.29 (d, *J* = 8.5 Hz, 1 H), 7.17 – 7.08 (m, 1 H), 4.90 (d, *J* = 5.5 Hz, 2 H), 4.76 (p, *J* = 6.1 Hz, 1 H), 4.58-4.62 (m, 2 H), 3.00-3.06 (m, 1 H), 2.24 (s, 3 H), 1.30 (d, *J* = 6.0 Hz, 6 H); LC-MS retention time (Method 1): 2.973 min; (Method 2): 4.306 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{23}H_{28}N_5$ 374.2339) found, 374.2339.



2-(2-Isopropylphenyl)-5-methyl-*N*-((1-(pyridin-3-yl)pyrrolidin-3-yl)methyl)pyrimidin-4-amine TFA (67): Method F step **a** but substitute *tert*-butyl 3-(aminomethyl)pyrrolidine-1-carboxylate for *tert*-butyl 4-(aminomethyl)piperidine-1-carboxylate. Follow synthesis for compound **65** and substitute 3-bromopyridine for 5-bromo-2-methylpyridine: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 – 8.92 (m, 1 H), 8.27 (s, 1 H), 7.96 – 8.05 (m, 2 H), 7.67 (d, *J* = 8.80, 5.28 Hz, 1 H), 7.51 – 7.61 (m, 2 H), 7.43 – 7.51 (m, 2 H), 7.31 – 7.40 (m, 1 H), 3.51 – 3.68 (m, 2 H), 3.38 – 3.48 (m, 2 H), 3.28 – 3.38 (m, 1 H), 3.12 – 3.24 (m, 2 H), 2.69 – 2.79 (m, 1 H), 2.19 (s, 3 H), 2.08 – 2.17 (m, 1 H), 1.86 (dd, *J* = 6.46, and 12.72 Hz, 1 H), 1.17 (d, *J* = 3.13 Hz, 3 H), and 1.16 (d, *J* = 3.13 Hz, 3 H); LC-MS retention time (Method 1): 2.582 min; (Method 2): 3.450 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{24}H_{30}N_5$ 388.2496) found, 388.2493.

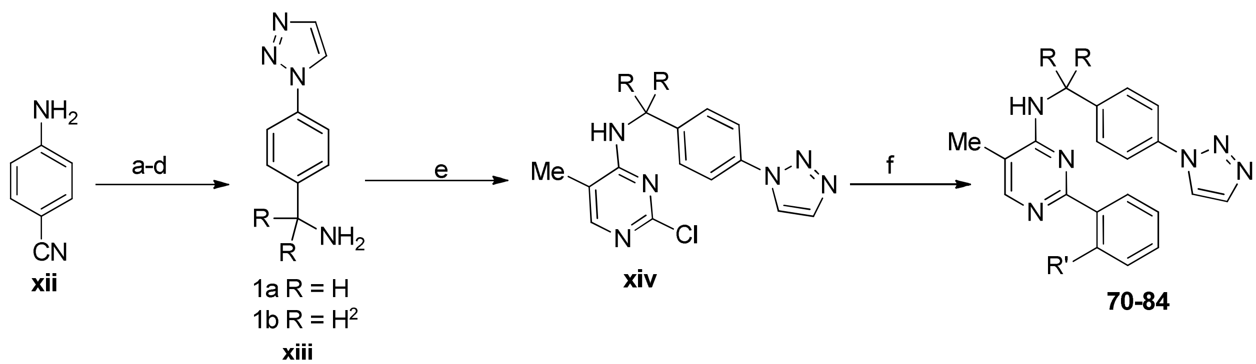


***N*-(4-(1H-tetrazol-5-yl)benzyl)-2-(2-isopropylphenyl)-5-methylpyrimidin-4-amine TFA (68):** Follow **General Method D** starting with 4-(aminomethyl)benzonitrile. Step **c** 4-((2-(2-isopropylphenyl)-5-methylpyrimidin-4-ylamino)methyl)benzonitrile (45 mg, 0.13 mmol), sodium azide (68 mg, 1.05 mmol), ammonium chloride (56 mg, 1.05 mmol) was heated in microwave for 15 min at 130 °C in DMF (1 mL) to give the desired product in a 56% yield after purification. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.31 (s, 1 H), 7.99 (d, *J* = 7.83 Hz, 2 H), 7.41 – 7.58 (m, 6 H), 7.34 (s, 1 H), 4.84 (d, *J* = 5.87 Hz, 2 H), 3.06 (dt, *J* = 6.65, and 13.30Hz, 1 H), 2.26 (s, 3 H), 0.95 (s, 3 H), and 0.93 (s, 3 H); LC-MS retention time (Method 1): 1.683 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{22}H_{24}N_7$ 386.2088) found, 386.2093.



***N*-(4-(1H-imidazol-1-yl)benzyl)-2-(2-isopropylphenyl)-5-methylpyrimidin-4-amine (69):** Follow **General Method D** and use (4-(1H-imidazol-1-yl)phenyl)methanamine. which was synthesized by heating 1-(4-(chloromethyl)phenyl)-1H-imidazole (0.50g, 2.6 mmol), and potassium phthalimide (0.58 g, 3.1 mmol) in DMF (2.5 mL) at 120 °C for 18 h. The reaction mixture was cooled to 0 °C**,** poured into water, the solids were filtered, and washed with water to give 2-(4-(1H-imidazol-1-yl)benzyl)isoindoline-1,3-dione. The dried 2-(4-(1H-imidazol-1-yl)benzyl)isoindoline-1,3-dione (0.40g, 1.32 mmol) was heated to 95 °C in a mixture of EtOH and hydrazine (4:1) for 1 h, cooled and the solids filtered and washed with EtOH to give (4-(1*H*-imidazol-1-yl)phenyl)methanamine in an 88% yield. This material was used in the synthesis of *N*-(4-(1H-imidazol-1-yl)benzyl)-2-chloro-5-methylpyrimidin-4-amine. ^1H NMR (400 MHz, DMSO-d_6) δ 9.21 (d, *J* = 2.52 Hz, 1 H), 9.14 (s, 1 H), 8.29 (d, *J* = 1.26 Hz, 1 H), 8.07 (t, *J* = 1.64 Hz, 1 H), 7.73 – 7.64 (m, 3 H), 7.57 – 7.39 (m, 5 H), 7.33 (ddd, *J* = 1.44, 6.97, and 7.67 Hz, 1 H), 4.81 (d, *J* = 5.97 Hz, 2 H), 3.10 (td, *J* = 7.44, 13.64, and 14.23 Hz, 1 H), 2.22 (d, *J* = 1.02 Hz, 3 H), and 1.00 (d, *J* = 6.80 Hz, 6 H); LC-MS retention time (Method 2): 3.428 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{24}H_{26}N_5$ 384.2183) found, 384.2169.

Method G



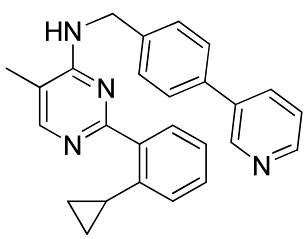
(a) TFA(1.0 equiv), rt, 5 min *t*butyl nitrite (1.5 equiv), azidotrimethylsilane (1.4 equiv), 0 ºC, 30 min. (98%) (b) 4-azidobenzonitrile, ethynyltrimethylsilane (6.0 equiv), sodium ascorbate (0.8 equiv), Cu(II)SO_4 (0.07 equiv), DMSO/H_2O, 80 ºC 24 h (c) TFA (2.8 equiv), acetonitrile, reflux, 3 h, (57%). (d) 1a. H-Cube Pro, 70 x4 mm 10% Pd/C Catcart, 50 ºC, 40 bar, TFA, MeOH/DMF (10/1), (98%) (d') LAD (3.0 equiv), THF, 0 ºC, 1.5 h, (40%) (e) 2,4-dichloro-5-methylpyrimidine, Et_3N (3.0 equiv), DMF, 100 ºC, 18 h. (f) boronic acid (3.0 equiv), 2 M

Na_2HCO_3 (4.0 equiv), DPP-Pd silica bound Silicycle, DME, MW, 150 ºC, 30 min, 35-70% yield.

General Method G: (steps a-c) are reported in the main text.

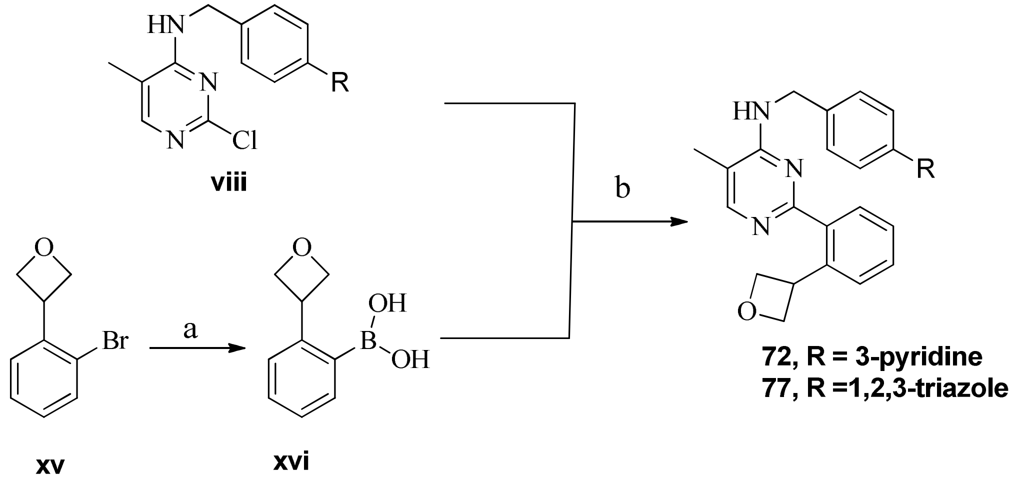
4-(1*H*-1,2,3-triazol-1-yl)-*N*-benzyl-*α,α-d*$_2$-amine TFA (xiii, 1b): 4-(1*H*-1,2,3-triazol-1-yl)benzonitrile (0.45 g, 2.64 mmol), in THF (2.40 mL), was cooled to 0 ºC, treated by dropwise addition of lithium aluminum deuteride (7.93 ml, 7.93 mmol) once the addition was completed the reaction was allowed to warm to rt, and stirred for 1.5 h. The reaction was quenched by treating with 3 mL of 1 N NaOH and 2 mL of water at 0 ºC. A white solid was filtered after 20 min and washed with THF, followed by ethyl acetate. The filtrate was concentrated to an orange/brown residue and purify by prep-HPLC system (gradient 10-100% acetonitrile w/ 0.1% TFA in water w/ 0.1% TFA) to give the desired product in a 40% yield: ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.58 (d, *J* = 1.20 Hz, 1H), 8.17–7.78 (m, 3 H), and 7.79–7.57 (m, 2 H); LC-MS retention time (Method 1): 0.700 min.

***N*-(4-(1H-1,2,3-triazol-1-yl)benzyl)-2-chloro-5-methylpyrimidin-4-amine TFA (xiv):** (4-(1*H*-1,2,3-triazol-1-yl)phenyl)methanamine, TFA (**1a** or **1b**) (0.52 g, 1.88 mmol), 2,4-dichloro-5-methylpyrimidine (0.29 g, 1.88 mmol), and triethylamine (1.00 mL, 7.20 mmol), in DMF (7 mL) was heated overnight to 100 ºC. Once completed the reaction was poured into water (30 mL) and extracted with ethyl acetate and seperated. The ethyl acetate layer was wash with water (2 X), saturated sodium bicarbonate, dried over Na_2SO_4, filtered, concentrated, and purified by prep HPLC (gradient 10-100% acetonitrile w/ 0.1% TFA in water w/ 0.1% TFA) to give 0.19 g of desired product: LC-MS retention time (Method 1): 2.770 min.

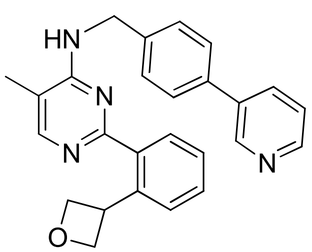


2-(2-Cyclopropylphenyl)-5-methyl-*N*-(4-(pyridin-3-yl)benzyl)pyrimidin-4-amine) TFA (71): Follow General **Method C** using (2-cyclopropylphenyl)boronic acid for (2-isopropylphenyl)boronic acid which was synthesized using 2-(2-chlorophenyl)-5-methyl-*N*-(4-(pyridin-3-yl)benzyl)pyrimidin-4-amine (0.05 g, 0.13 mmol), (2-cyclopropyl)boronic acid (0.01 g, 0.16 mmol), K_3PO_4 (0.08 g, 0.39 mmol) and tricyclohexylphosphine (0.02 mL, 0.01 mmol) in toluene (2 mL) and water (0.10 mL). The mixture was placed under nitrogen and $PdOAc_2$ (1.45 mg, 6.46 µmol), was added and heated to 150 °C for 30 min. The reaction was allowed to cool to rt, then filtered and purified to give the desired product: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.29 – 9.42 (m, 1 H), 8.90 (d, *J* = 1.96 Hz, 1 H), 8.55 – 8.63 (m, 1 H), 8.32 (s, 1 H), 8.11 (s, 1 H), 7.70 (d, *J* = 8.22 Hz, 3 H), 7.55 (dd, *J* = 5.09, and 7.83 Hz, 1 H), 7.41 – 7.52 (m, 3 H), 7.36 (d, *J* = 7.43 Hz, 1 H), 7.10 (d, *J* = 7.83 Hz, 1 H), 4.84 (d, *J* = 5.87 Hz, 2 H), 2.23 – 2.29 (m, 3 H), 1.90 – 2.03 (m, 1 H), and 0.44 – 0.60 (m, 4 H); LC-MS retention time (Method 1): 2.638 min; (Method 2): 3.714 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{26}H_{25}N_4$ 393.2074) found, 393.2065.

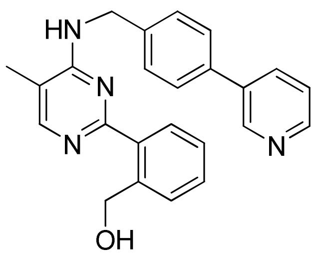
Method H



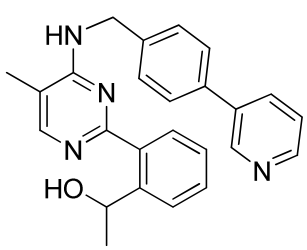
(a) *N*-butyllithium (2.0 equiv), triisopropyl borate (2.0 equiv) THF, -78 °C, 18 h; (b), 2 M Na_2CO_3 (4.0 equiv), DPP-Pd silica bound Silicycle 0.26 mmol/g (19 mol%), DME, MW, 150 ºC, 30 min.



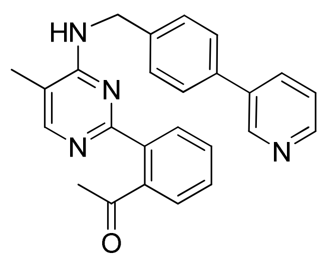
5-methyl-2-(2-(oxetan-3-yl)phenyl)-N-(4-(pyridin-3-yl)benzyl)pyrimidin-4-amine TFA (72): Follow **Method C** for **viii**: The synthesis for compound **xv** 3-(2-bromophenyl)oxetane was achieved using the method described by Jacobsen et. al, except diethyl 2-(2-bromophenyl)malonate was used as the starting material instead of diethyl 2-(2-(benzyloxy)phenyl)malonate. This synthetic sequence was carried on without further purification/characterization of the intermediates. In an oven-dried 50 mL round bottom flask, 3-(2-bromophenyl)oxetane **xv** (0.14 g, 0.66 mmol) and THF (4 mL) was cooled to -78 ºC. The dropwise addition of *N*-butyllithium (0.85 mL, 1.36 mmol), by syringe occurred over a 15 min period. After this time, the reaction mixture was allowed to stir at -78 ºC for an additional 2 h and contents transferred via cannula to a second 50 mL oven-dried round bottom flask containing a stirred solution of triisopropyl borate (0.29 mL, 1.32 mmol), and THF (2.0 mL) cooled to -78 ºC. Once transferred, the mixture was allowed to stir at -78 ºC for 10 min after which time the ice bath was removed and the reaction mixture stirred overnight. 1 N HCl was used to adjust the pH to ~1, and the acidic mixture was stirred for 45 min, poured into water, and extracted with diethyl ether (3 X). The organic layers were combined, dried over $MgSO_4$, concentrated, and once the solvent was evaporated, an ~1 M solution of the crude (2-(oxetan-3-yl)phenyl)boronic acid (**xvi**) in 1,2-DME was made and used in next step with no further purification. In a sealed tube 2-chloro-5-methyl-N-(4-(pyridin-3-yl)benzyl)pyrimidin-4-amine (0.33 mmol) was combined with (2-oxetainphenyl)boronic acid (**xvi**) as a 1 M solution of 0.66 mmol in DME, sodium carbonate (2.0 M in water, 0.33 mL, 0.67 mmol), DPP-Pd Silicycle 0.26 mmol/g (0.20 g) in DME (2.0 mL), and heated at 150 ºC for 30 min in a Biotage Initiator microwave reactor. The resulting mixture was filtered over celite and purified by reversed-phase HPLC (gradient 20-100% acetonitrile w/ 0.1% TFA in water w/ 0.1% TFA) to give the desired product: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.41 (t, J = 6.1 Hz, 1 H), 8.89 (d, J = 2.4 Hz, 1 H), 8.57 (dd, J = 1.6, and 4.9, Hz, 1 H), 8.34 – 8.25 (m, 3 H), 8.11 (dt, J = 1.9, and 8.0, Hz, 1 H), 7.78 – 7.71 (m, 1 H), 7.66 (td, J = 1.4, and 7.5, Hz, 1 H), 7.62 – 7.55 (m, 2 H), 7.52 (ddd, J = 5.8, 7.9, and 10.1, Hz, 2 H), 4.92 (d, J = 5.8 Hz, 2 H), 4.44 (d, J = 3.9 Hz, 2 H), 3.60 (dd, J = 4.6, and 10.6 Hz, 1H), 3.36 – 3.27 (m, 2H), and 2.20 (s, 3 H); LC-MS retention time (Method 1): 3.102 min; HRMS: m/z $(M+H)^+$ = (Calculated for $C_{26}H_{25}N_4O$ 409.2023) found, 409.2015.



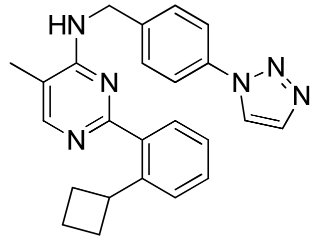
(2-(5-methyl-4-(4-(pyridin-3-yl)benzylamino)pyrimidin-2-yl)phenyl)methanol TFA (73): Follow **General Method C** and use 2-(hydroxymethyl)phenylboronic acid for (2-isopropyl)phenylboronic acid in step **b**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.15 – 9.28 (m, 1 H), 8.92 (s, 1 H), 8.57 – 8.63 (m, 1 H), 8.24 – 8.31 (m, 1 H), 8.10 – 8.20 (m, 1 H), 7.72 (d, J = 8.22 Hz, 2 H), 7.62 (d, J = 4.70 Hz, 4 H), 7.48 (d, J = 8.22 Hz, 3 H), 4.84 (d, J = 5.87 Hz, 2 H), 4.62 (s, 2 H), and 2.20 – 2.26 (m, 3 H); LC-MS retention time (Method 1): 1.146 min. HRMS: m/z $(M+H)^+$ = (Calculated for $C_{24}H_{23}N_4O$ 383.1866) found, 383.1870.



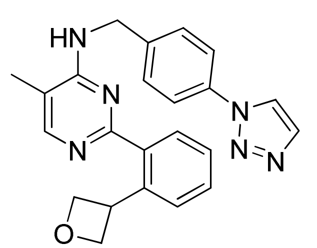
1-(2-(5-methyl-4-(4-(pyridin-3-yl)benzylamino)pyrimidin-2-yl)phenyl)ethanol TFA (74): Follow **General Method C** using (2-acetylphenyl)boronic acid for (2-isopropylphenyl)boronic acid in step **b**. 1-(2-(5-methyl-4-(4-(pyridin-3-yl)benzylamino)pyrimidin-2-yl)phenyl)ethanone (0.04 g, 0.10 mmol) was dissolved in methanol (1 mL), treated with sodium borohydride (0.04 g, 1.02 mmol) and stirred for 2 h. The solution was poured into water and extracted with EtOAc (2 X), the organic layers were combine, concentrated, and purified on a prep HPLC to give the desired product: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.20 − 9.35 (m, 1 H), 8.90 − 8.97 (m, 1 H), 8.59 − 8.67 (m, 1 H), 8.30 (s, 1 H), 8.16 − 8.24 (m, 1 H), 7.72 (d, *J* = 8.22 Hz, 2 H), 7.67 (s, 1 H), 7.61 (d, *J* = 7.83 Hz, 2 H), 7.51 (s, 1 H), 7.40 − 7.48 (m, 3 H), 4.95 − 5.04 (m, 1 H), 4.85 (d, *J* = 5.87 Hz, 2 H), 2.25 (s, 3 H), and 1.19 (d, *J* = 6.26 Hz, 3 H); LC-MS retention time (Method 1): 1.410 min; HRMS: *m/z* (M+H)$^+$ = (Calculated for $C_{25}H_{25}N_4O$ 397.2023) found, 297.2021.



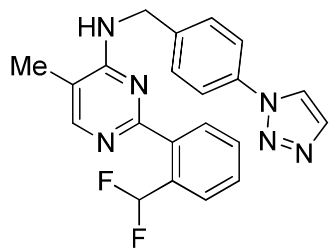
1-(2-(5-methyl-4-(4-(pyridin-3-yl)benzylamino)pyrimidin-2-yl)phenyl)ethanone TFA (75): Follow **Method C** using (2-acetylphenyl)boronic acid for (2-isopropylphenyl)boronic acid in step **b**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 − 9.71 (m, 1 H), 8.92 (s, 1 H), 8.69 − 8.74 (m, 1 H), 8.56 − 8.64 (m, 1 H), 8.13 − 8.19 (m, 1 H), 8.07 − 8.13 (m, 1 H), 7.84 (d, *J* = 3.91 Hz, 2 H), 7.69 − 7.79 (m, 3 H), 7.64 (d, *J* = 8.22 Hz, 2 H), 4.90 − 5.02 (m, 2 H), 2.27 (s, 3 H), and 1.85 −1.94 (m, 3 H); LC-MS retention time (Method 1): 1.479 min; HRMS: *m/z* (M+H)+ = (Calculated for $C_{25}H_{23}N_4O$ 395.1866) found, 395.1864.



***N*-(4-(1H-1,2,3-triazol-1-yl)benzyl)-2-(2-cyclobutylphenyl)-5-methylpyrimidin-4-amine TFA (76):** Follow **Method G** and **General Method D** Step **b** using (2-cyclobutanephenyl)boronic acid for (2-isopropylphenyl)boronic acid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.23 (s, 1 H), 8.79 (d, *J* = 1.17 Hz, 1 H), 8.29 – 8.24 (m, 1 H), 7.98 – 7.85 (m, 3 H), 7.59 – 7.47 (m, 3 H), 7.46–7.29 (m, 3 H), 4.81 (d, *J* = 5.95 Hz, 2 H), 3.68 – 3.40 (m, 1 H), 2.24 (d, *J* = 1.00 Hz, 3 H), 1.87 – 1.68 (m, 4 H), and 1.58 – 1.45 (m, 2 H); LC-MS retention time: (Method 2): 4.274 min; HRMS (ESI) m/z (M+H)$^+$ (Calculated for $C_{24}H_{25}N_6$, 397.2135) found 397.2125.

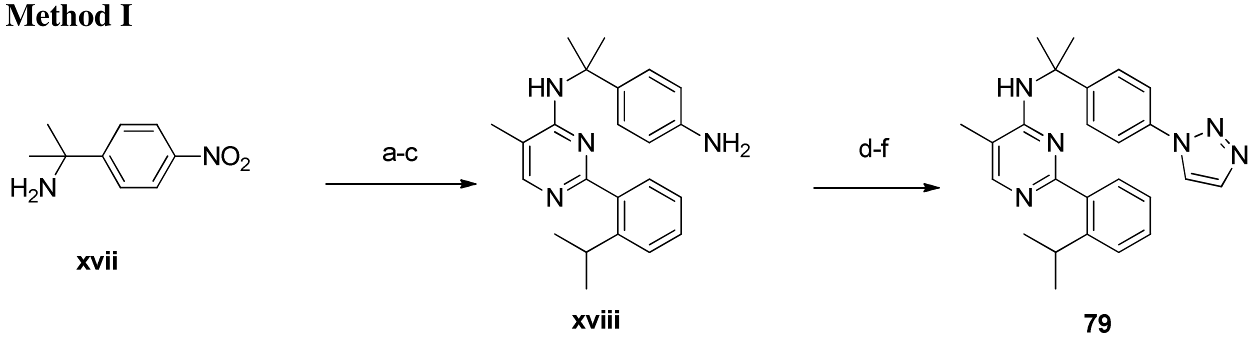


N-(4-(1H-1,2,3-triazol-1-yl)benzyl)-5-methyl-2-(2-(oxetan-3-yl)phenyl)pyrimidin-4-amine TFA (77): Follow **Method G** and **Method H** for the synthesis of the (2-oxetain)boronic acid**:** ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.36 – 9.47 (m, 1 H), 8.80 (s, 1 H), 8.35 (s, 1 H), 8.29 (d, J = 7.83 Hz, 1 H), 7.97 (s, 1 H), 7.90 (d, J = 8.22 Hz, 2 H), 7.68 (d, J = 8.61 Hz, 3 H), 7.52 (s, 2 H), 5.12 (br. s., 1 H), 4.93 – 5.00 (m, 2 H), 4.41 – 4.50 (m, 2 H), 3.61 (dd, J = 4.30, 10.56 Hz, 2 H), and 2.22 (s, 3 H); LC/MS retention time: (Method 1): 2.526 min; HRMS: m/z $(M+H)^+$ = (Calculated for $C_{23}H_{23}N_6O$ 399.1928) found, 399.1924.



N-(4-(1H-1,2,3-triazol-1-yl)benzyl)-2-(2-(difluoromethyl)phenyl)-5-methylpyrimidin-4-amine TFA (78): Follow **Method G** and **General Method D** for **Step b** using 2-(2-(difluoromethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane for (2-isopropylphenyl)boronic acid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (s, 1 H), 8.26 (s, 1 H), 7.95 (s, 1 H), 7.86 (d, J = 8.61 Hz, 4 H), 7.74 – 7.80 (m, 1 H), 7.66 – 7.73 (m, 2 H), 7.54 (d, J = 8.22 Hz, 2 H), 4.82 (d, J = 5.87 Hz, 2 H), and 2.22 (s, 3 H); LC/MS retention time: (Method 1): 1.870 min; HRMS: m/z $(M+H)^+$ = (Calculated for $C_{21}H_{19}FN_6$ 393.1634) found, 393.1647.

Method I

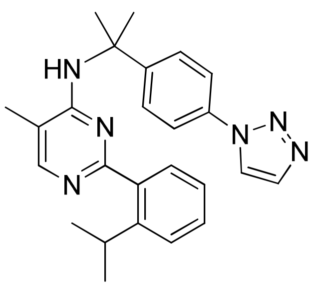


(a) 2,4-dichloro-5-methylpyrimidine, Et_3N, DMF, MW, 150 °C, 1 h (b) boronic acid (3.0 equiv), 2 M Na_2HCO_3(4.0 equiv), DPP-Pd silica bound Silicycle (19 mol%), DME, MW, 150 ºC, 30 min, 35-70% yield (c) zinc (5.0 equiv), AcOH (10.0 equiv), MeOH, 1 h (d) TFA (1.0 equiv), rt, 5 min ^{t}butyl nitrite (1.5 equiv), azidotrimethylsilane (1.4 equiv), 0 ºC, 30 min. (98%) (e) 4-azidobenzonitrile, ethynyltrimethylsilane (6.0 equiv), sodium ascorbate (0.8 equiv), Cu(II)SO_4(0.07 equiv), DMSO/H_2O, 80 ºC 24 h (f) TFA (2.8 equiv), acetonitrile, reflux, 3 h, (57%).

2-chloro-5-methyl-N-(2-(4-nitrophenyl)propan-2-yl)pyrimidin-4-amine TFA (a): 2-(4-nitrophenyl)propan-2-amine, HCl (**xvii**) (0.60 g, 2.77 mmol), 2,4-dichloro-5-methylpyrimidine (0.45 g, 2.77 mmol), Et_3N (1.15 mL, 8.31 mmol), in DMF (8.2 mL) was sealed in a microwave vial and heated to 150 °C for 1 h. The reaction was cooled, and poured into EtOAc, washed with water (2 X), dried over Na_2SO_4, filtered, and concentrated. The residue was purified using reverse phase over 30 min and gradient of 10-100 water/CH_3CN 0.01% TFA to give the desired compound: LC/MS retention time: (Method 1): 3.478 min.

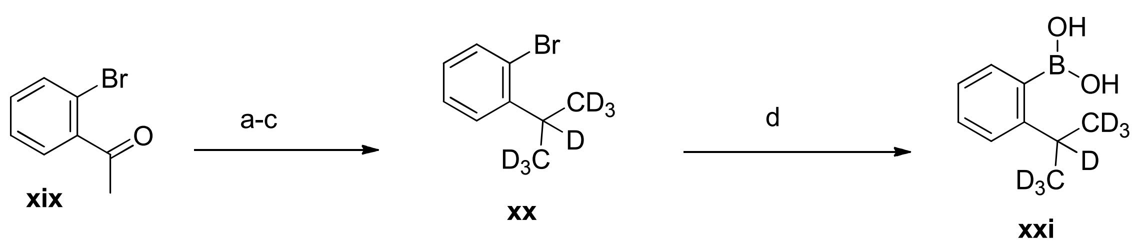
2-(2-isopropylphenyl)-5-methyl-N-(2-(4-nitrophenyl)propan-2-yl)pyrimidin-4-amine TFA (b): Follow **General Method D** Step **b**: LC/MS retention time: (Method 1): 3.144 min.

***N*-(2-(4-aminophenyl)propan-2-yl)-2-(2-isopropylphenyl)-5-methylpyrimidin-4-amine xviii:** 2-(2-isopropylphenyl)-5-methyl-*N*-(2-(4-nitrophenyl)propan-2-yl)pyrimidin-4-amine, TFA (0.28 g, 0.55 mmol), acetic acid (0,37 mL, 6.54 mmol), and zinc (0.18 g, 2.73 mmol), was stirred in CH_3OH (5.50 mL) for 1 hour. The reaction mixture was filtered through a pad of celite, rinsed with CH_3OH, concentrated and used as in with no further purification or characterization: LC/MS retention time: (Method 1): 2.670 min.



***N*-(2-(4-(1*H*-1,2,3-triazol-1-yl)phenyl)propan-2-yl)-2-(2-isopropylphenyl)-5-methylpyrimidin-4-amine TFA (79):** Follow **General Method I**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (d, J = 1.17 Hz, 1 H), 8.23 (s, 1 H), 7.94 (d, J = 1.13 Hz, 1 H), 7.81 – 7.73 (m, 2 H), 7.55 – 7.47 (m, 2 H), 7.40 (t, J = 7.60 Hz, 1H), 7.33 – 7.26 (m, 1H), 7.16 (t, J = 7.54 Hz, 1 H), 7.02 (d, J = 7.64 Hz, 1 H), 3.05 – 3.17 (m, 1 H), 2.33 (d, J = 1.06 Hz, 3 H), 1.78 (s, 6 H), and 0.72 (d, J = 6.80 Hz, 6 H); LC/MS retention time: (Method 2): 4.378 min; HRMS: m/z $(M+H)^+$ = (Calculated for $C_{25}H_{29}N_6$ 413.2448) found, 413.2447.

Method J



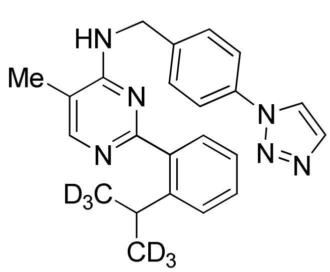
(a) Deuterated water, 4 Å molecular sieves, MW, 180 ºC, 30 min, (87%) (b) methyl(d_3)magnesium iodide (1.3 equiv), diethyl ether, -8 ºC, 2 h, (76%) (c) triethylsilane(d), TFA (d), DCM, 45 min (73%) (d) *N*-butyllithium(2.0 equiv), THF -78 ºC, (2.0 equiv) triisopropyl borate, THF, rt, 18 h.

1-(2-bromophenyl)ethanone (d_3) (a): 1-(2-bromophenyl)ethanone **(xix)** (1.00 ml, 7.44 mmol), D_2O (13.46 ml, 744 mmol), and 4Å molecular sieves (~10 beads) were combined in a 10-20 mL microwave vial, which was sealed and heated to 180 ºC for 30 min. The biphasic mixture was allow to cool to rt, poured into water, extracted with ether (3 X), dried over $MgSO_4$ and concentrated to give 1.3 g as clear glasslike oil. The compound was used as-is in the next reaction: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.59 (ddt, *J* = 1.3, 2.6, and 8.0 Hz, 1 H), 7.46 (dd, *J* = 1.6, and 7.9 Hz, 1 H), 7.35 (m, 1 H), and 7.28 (tq, *J* = 1.7, and 7.7 Hz, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.24, 149.22, 141.30, 134.27, 133.27, 131.84, 128.32, and 29.13; LC-MS retention time (Method 1): 3.337 min.

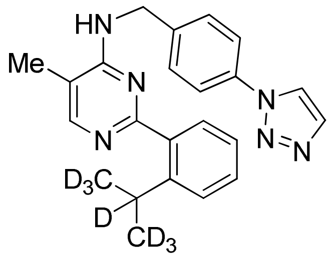
2-(2-Bromophenyl)propan-2-ol (*d_6*) (b): 2-bromo-acetophenone (*d_3*) (1.0 g, 14.9 mmol) and diethyl ether (148 mL) were chilled to -8 ºC. 1 M methyl (*d_3*) magnesium iodide in diethyl ether (20.0 mL, 20.0 mmol) was added by syringe over a 45 min keeping the temperature at -8 ºC. The milky white solution which was allowed to stir for 2 h at -8 ºC, was poured into ice with saturated NH_4Cl and extract with ether (3X). The organic layers were combined, dried over $MgSO_4$, filtered, concentrated, and purified withEtOAc/Hex 0- 20% gradient to give 2.5 g of a clear glasslike oil in a 76% yield: ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65 (dd, *J* = 1.71, and 7.95 Hz, 1 H), 7.56 (dd, *J* = 1.34, and 7.90 Hz, 1 H), 7.33 – 7.20 (m, 1 H), 7.12 – 7.02 (m, 1 H), and 2.92 (s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.04, 135.07, 128.50, 127.52, 127.26, 127.19, 120.45, 73.26, and 28.56: LC-MS retention time (Method 1): 3.749 min.

1-Bromo-2-isopropyl(*d_7*)benzene (xx): 2-(2-bromophenyl)propan-2-ol (*d_6*) (0.63 g, 2.87 mmol), trimethylsilane(*d*) (0.70 mL, 4.30 mmol), TFA(*d*) (2.20 mL, 28.70 mmol) was stirred in anhydrous DCM (4.5 ml) and followed by TLC (80/20 hexanes/EtOAc, with *p*-anisaldehyde (PAA) stain) for 45 min. The reaction mixture was concentrated, and purified with 0-20% EtOAc/Hex to give the desired product as a clear glasslike oil in a 73% yield: LC-MS retention time (Method 1): 3.941 min. (For the *d_6* compound used trimethylsilane and TFA).

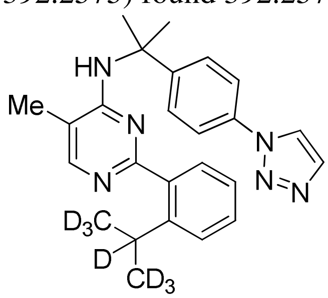
(2-isopropyl(*d_7*)phenyl)boronic acid (xxi): In an oven dried 100 mL round bottom flask 1-bromo-2-isopropyl(*d_7*)benzene (0.70 g, 3.40 mmol) and THF (14 mL) were cooled to -78 ºC. The dropwise addition of *N*-butyllithium (4.25 mL, 6.80 mmol), by syringe, occurred over a 15 min period and the reaction continued to stir at -78 ºC for 2 h. The contents were transferred by cannula to a second 100 mL oven dried round bottom flask containing a stirred solution of triisopropyl borate (1.50 mL, 6.79 mmol), and THF (7.0 mL) at -78 ºC. Once transferred, the mixture was allowed to stir at -78 ºC for 10 min at which time the ice bath was removed and the reaction stirred overnight. 1N HCl was used to adjust the pH to 1, and the acidic mixture was stirred for 45 min, poured into water, and extracted with diethyl ether (3 X). The organic layers were combined, dried over MgSO4, concentrated, and once the solvent was removed by evaporation, a 1 M solution of 3.40 mmol in 1,2-DME was made and used in next step with no further purification or characterization.



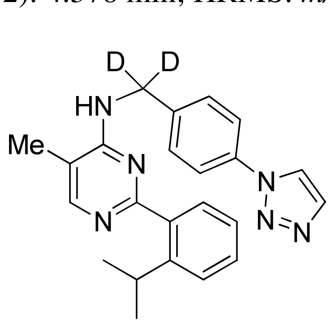
***N*-(4-(1*H*-1,2,3-triazol-1-yl)benzyl)-5-methyl-2-(2-isopropyl(d_6)phenyl)pyrimidin-4-amine TFA (80):** Follow the synthesis for **Method G xiii 1a** and **Method J** but in step **c** substitute trimethylsilane for triethylsilane(*d*) : ^{1}H NMR (400 MHz, Methanol-d_4) δ 8.49 (s, 1 H), 8.03 (q, *J* = 1.02 Hz, 1 H), 7.88 (s, 1 H), 7.77 – 7.65 (m, 2 H), 7.51 – 7.36 (m, 4 H), 7.36 – 7.18 (m, 2 H), 4.86 (s, 2 H), 2.96 (s, 1 H), and 2.26 – 2.15 (m, 3H); ; LC-MS retention time: (Method 2): 4.239 min; HRMS (ESI) m/z $(M+H)^+$ (Calculated for $C_{23}H_{19}D_6N_6$, 391.2512) found 391.2507.



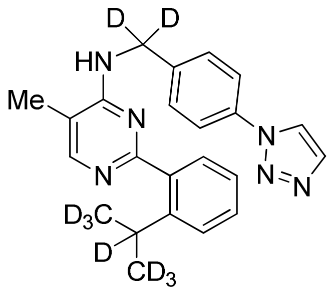
***N*-(4-(1*H*-1,2,3-triazol-1-yl)benzyl)-5-methyl-2-(2-isopropyl(d_7)phenyl)pyrimidin-4-amine TFA (81):** Follow the synthesis for **Method G xiii 1a** and **Method J**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (d, *J* = 1.19 Hz, 1 H), 8.28 (d, *J* = 1.21 Hz, 1 H), 7.94 (d, *J* = 1.14 Hz, 1 H), 7.88 – 7.80 (m, 2 H), 7.56 – 7.26 (m, 6 H), 4.82 (d, *J* = 5.92 Hz, 2 H), and 2.23 (s, 3 H); LC-MS retention time: (Method 2): 4.190 min; HRMS (ESI) m/z $(M+H)^+$ (Calculated for $C_{23}H_{18}D_7N_6$, 392.2575) found 392.2571.



***N*-(2-(4-(1*H*-1,2,3-triazol-1-yl)phenyl)propan-2-yl)-2-(2-isopropyl(d_7)phenyl)-5-methylpyrimidin-4-amine TFA (82):** Follow **Method I** and **Method J**: ^{1}H NMR (400 MHz, DMSO-d6) δ 8.75 (d, *J* = 1.13 Hz, 1H), 8.23 (s, 1H), 7.94 (d, *J* = 1.13 Hz, 1H), 7.81–7.73 (m, 2H), 7.55–7.47 (m, 2H), 7.40 (t, *J* = 7.60 Hz, 1H), 7.33–7.26 (m, 1H), 7.16 (t, *J* = 7.54 Hz, 1H), 7.02 (d, *J* = 7.64 Hz, 1H), 2.36-2.31 (m, 3H), and 1.78 (s, 6H); LC/MS retention time: (Method 2): 4.378 min; HRMS: *m/z* $(M+H)^+$ = (Calculated for $C_{25}H_{29}N_6$ 413.2448) found, 413.2447.



***N*-(4-(1*H*-1,2,3-triazol-1-yl)benzyl-α,α-*d*$_2$)-5-methyl-2-(2-isopropylphenyl)pyrimidin-4-amine TFA (83):** Follow the synthesis for **Method G xiii 1b**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (d, J = 1.17 Hz, 1 H), 8.30 (d, J = 1.16 Hz, 1 H), 7.95 (d, J = 1.16 Hz, 1 H), 7.91 – 7.80 (m, 2 H), 7.59 – 7.41 (m, 5 H), 7.35 (ddd, J = 1.35, 7.14, 7.67 Hz, 1 H), 3.03 (m, 1H), 2.24 (d, J = 1.03 Hz, 3H), and 0.97 (d, J = 6.82 Hz, 6 H); LC-MS retention time: (Method 2): 4.156 min; HRMS (ESI) m/z (M+H)$^+$ (Calculated for $C_{23}H_{23}D_2N_6$, 387.2261) found 387.2259.



***N*-(4-(1*H*-1,2,3-triazol-1-yl)benzyl-α,α-*d*$_2$)-5-methyl-2-(2-isopropyl(*d*$_7$)phenyl)pyrimidin-4-amine TFA (84):** Follow the synthesis for **Method G xii 1b** and **Method J**: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (d, J = 1.19 Hz, 1 H), 8.28 (d, J = 1.24 Hz, 1 H), 7.95 (d, J = 1.15 Hz, 1 H), 7.90 – 7.79 (m, 2 H), 7.62 – 7.37 (m, 5 H), 7.38 – 7.29 (m, 1 H), and 2.23 (s, 3 H); LC-MS retention time: (Method 2): 4.182 min; HRMS (ESI) m/z (M+H)$^+$ (Calculated for $C_{23}H_{16}D_9N_6$, 395.2729) found 395.2734.