MurE Experimental

**General Procedure A** (*for the synthesis of 2,4-dimethyl-6-(amino)pyrimidines*). 4-Chloro-2,6-dimethylpyrimidine was dissolved in acetonitrile (0.35 M) and the desired amine (1.2 equiv) was added, followed by the addition of DIPEA (1.2 equiv). The reaction was stirred overnight at 50 ºC, then concentrated and purified the stated method.

**General Procedure B** (*for the synthesis of boc-deprotected amines*). The *boc*-protected starting material was dissolved or suspended in 4 M HCl in dioxane (5-10 equiv) and the reaction progress was monitored by TLC. Upon completion, the reaction mixture was concentrated and the crude material was purified by the stated method.

**General Procedure C** (*for the synthesis of 2- or 4-aryl substituted aminopyrimidines*). The desired chloropyrimidine, desired boronic acid or ester (1.2 equiv), K2CO3 (3.0 equiv), and PdCl2(dppf)•CH2Cl2 (5 mol%) were combined in a reaction vial that was filled with argon and evacuated three times. 3:1 Dioxane:water (0.10 M) was added and the reaction mixture was degassed before heating at 100 ºC overnight. The reaction mixture was diluted with EtOAc and filtered through celite and the crude material was concentrated and purified by the stated method.



**Scheme X.** Synthesis of 2,4-dimethyl-6-chloropyrimidine derivatives. *Reagents and conditions*: *a*) Desired amine, DIPEA, acetonitrile, 50-80 °C, 12-48 h (XX-XX%). *b*) Desired alcohol, NaH, dry THF, rt, 12 h (XX-XX%). *c*) 4 M HCl/dioxane, rt, 1-3 h (XX-XX%). d) Methyl iodide, NaH, dry DMF, rt, 12 h (XX-XX%).

***tert*-Butyl 4-(2,6-dimethylpyrimidin-4-yl)piperazine-1-carboxylate (2).** 4-Chloro-2,6-dimethylpyrimidine (0.042 ml, 0.348 mmol) was dissolved in acetonitrile (1.0 ml, 0.35 M) and *tert*-butyl piperazine-1-carboxylate (78 mg, 0.419 mmol) was added, followed by the addition of DIPEA (0.073 ml, 0.419 mmol). The reaction was stirred overnight at 50 ºC. The reaction temperature was then increased to 80 ºC and the reaction was run another ~24 h. The reaction mixture was concentrated and the crude material purified by flash chromatography (1-5% MeOH:DCM) to afford the title compound as a viscous orange oil (66 mg, 65%). LCMS [M+H]+ 293.2 m/z. 1H NMR (400 MHz, METHANOL-d4) δ ppm 6.47 (s, 1 H) 3.68 (dd, J=6.3, 4.0 Hz, 4 H) 3.45 - 3.56 (m, 4 H) 2.40 (s, 3 H) 2.30 (s, 3 H) 1.48 (s, 9 H).

**2,4-Dimethyl-6-(piperazin-1-yl)pyrimidine (OSA\_000051\_XX\_01).** The title compound was prepared according to General Procedure B using *tert*-butyl 4-(2,6-dimethylpyrimidin-4-yl)piperazine-1-carboxylate (66 mg, 0.256 mmol). Starting material was consumed after 1 h and the crude material purified by flash chromatography (10-20% 5% NH4OH/MeOH:DCM) to afford the title compound as a light yellow oil (41 mg, 95%). LCMS [M+H]+ 193.1 m/z. 1H NMR (400 MHz, METHANOL-d4) δ ppm 6.45 (s, 1 H) 3.63 - 3.71 (m, 4 H) 2.85 - 2.93 (m, 4 H) 2.40 (s, 3 H) 2.29 (s, 3 H). 13C NMR (500 MHz, METHANOL-d4) δ ppm 23.4, 25.3, 45.2, 46.0, 99.9, 163.8, 165.9, 167.6.

**2,4-Dimethyl-6-(4-methylpiperazin-1-yl)pyrimidine (OSA\_000049\_XX\_01).** The title compound was synthesized according to General Procedure A on a 50-mg scale using 1-methylpiperazine. The crude material was purified by flash chromatography (2-20% 5% NH4OH/MeOH:DCM) to afford the title compound as a viscous orange oil (49 mg, 68%). LCMS [M+H]+ 207.1 m/z. 1H NMR (400 MHz, METHANOL-d4) δ ppm 6.46 (s, 1 H) 3.66 - 3.74 (m, 4 H) 2.47 - 2.52 (m, 4 H) 2.40 (s, 3 H) 2.33 (s, 3 H) 2.29 (s, 3 H). 13C NMR (400 MHz, METHANOL-d4) δ ppm 23.3, 25.3, 44.4, 46.1, 55.5, 99.9, 163.7, 165.7, 167.5.

**2,4-Dimethyl-6-(piperidin-1-yl)pyrimidine (OSA\_000050\_XX\_01).** The title compound was synthesized according to General Procedure A on a 50-mg scale using piperidine. The crude material was purified by flash chromatography (20% EtOAc:Hex - 5-20% MeOH:DCM), then repurified by flash chromatography (5% MeOH:EtOAc) to afford the title compound as a colorless oil (17 mg, 25%). LCMS [M+H]+ 192.2 m/z. 1H NMR (400 MHz, METHANOL-d4) δ ppm 6.40 (s, 1 H) 3.60 - 3.69 (m, 4 H) 2.37 (s, 3 H) 2.26 (s, 3 H) 1.67 - 1.75 (m, 2 H) 1.54 - 1.63 (m, 4 H). 13C NMR (400 MHz, METHANOL-d4) δ ppm 23.4, 25.4, 25.8, 26.7, 46.0, 99.5, 163.5, 165.5, 167.6.

**4-(2,6-Dimethylpyrimidin-4-yl)morpholine (OSA\_000059\_XX\_01).** The title compound was synthesized according to General Procedure A on a 50-mg scale using morpholine. The crude material was purified by flash chromatography (2-20% 5% NH4OH/MeOH:DCM) to afford the title compound as an off-white solid (50 mg, 74%). LCMS [M+H]+ 194.0 m/z. 1H NMR (400 MHz, METHANOL-d4) δ ppm 6.45 (s, 1 H) 3.70 - 3.75 (m, 4 H) 3.60 - 3.67 (m, 4 H) 2.40 (s, 3 H) 2.30 (s, 3 H). 13C NMR (400 MHz, METHANOL-d4) δ ppm 23.4, 25.3, 45.3, 67.6, 99.8, 164.1, 166.0, 167.6.

**1-(2,6-Dimethylpyrimidin-4-yl)piperidin-4-ol (OSA\_000068\_XX\_01).** The title compound was synthesized according to General Procedure A on a 120-mg scale using piperidin-4-ol. The crude materail purified by flash chromatography (2-10% MeOH:DCM, stepwise gradient), then dried for ~5 days under high vacuum to remove excess DIPEA to afford the title compound as a white solid (130 mg, 76%). LCMS [M+H]+ 208.1 m/z. 1H NMR (500 MHz, METHANOL-d4) δ ppm 6.78 (s, 1 H) 4.11 - 4.31 (m, 2 H) 3.97 (tt, J=8.0, 3.9 Hz, 1 H) 3.58 (br. t, J=9.8, 9.8 Hz, 2 H) 2.47 - 2.55 (m, 3 H) 2.39 (s, 3 H) 1.95 (ddt, J=12.9, 6.3, 3.3, 3.3 Hz, 2 H) 1.56 (dtd, J=12.9, 8.7, 8.7, 3.9 Hz, 2 H). 13C NMR (500 MHz, METHANOL-d4) δ ppm 19.7, 22.5, 34.7, 43.4, 67.1, 100.4, 157.8, 162.4, 163.4.

***tert*-Butyl ((1*s*,3*s*)-3-((2,6-dimethylpyrimidin-4-yl)oxy)cyclobutyl)-carbamate (3a).** *tert*-Butyl ((cis)3-hydroxycyclobutyl)carbamate (100 mg, 0.534 mmol) was dissolved in dry THF (1.80 ml, 0.30 M) and the reaction mixture was cooled to 0 °C. NaH (60% wt dispersion in mineral oil, 46 mg, 1.15 mmol) was added, upon which the reaction went from a clear to a cloudy solution. The reaction was stirred for ~1h at 0 °C under argon, after which 4-chloro-2,6-dimethylpyrimidine (80 µL, 0.662 mmol) was added. The reaction was allowed to warm to room temperature overnight while stirring under argon. The reaction mixture was diluted with EtOAc and poured over water; the aqueous layer was extracted twice more with EtOAc. The combined organic layers were washed once with brine, dried with magnesium sulfate, and concentrated. The crude material was purified by flash chromatography (20-50% EtOAc:hex) to afford the title compound as a white solid (103 mg, 66%). LCMS [M+H]+ 294.2 m/z. 1H NMR (400 MHz, METHANOL-d4) δ ppm 6.50 (s, 1 H) 4.93 (quin, J=7.3 Hz, 1 H) 3.78 (tt, J=8.0, 7.1 Hz, 1 H) 2.81 - 2.91 (m, 2 H) 2.50 (s, 3 H) 2.38 (s, 3 H) 1.97 - 2.08 (m, 2 H) 1.43 (s, 9 H).

***tert*-Butyl ((1*s*,4*s*)-4-((2,6-dimethylpyrimidin-4-yl)oxy)cyclohexyl)-carbamate (3b).** *tert*-Butyl ((1s,4s)-4-hydroxycyclohexyl)carbamate(100 mg, 0.464 mmol) was dissolved in dry THF (1.6 ml, 0.30 M). The reaction was put under argon and cooled to 0 ºC, after which NaH (56 mg, 1.40 mmol) was added. The reaction was stirred at 0 ºC for ~1 h. 4-Chloro-2,6-dimethylpyrimidine (0.067 ml, 0.554 mmol) was added and the reaction was warmed to room temperature, then heated to 50 ºC overnight, stirring under argon. The reaction mixture was diluted with EtOAc and poured over water; the aqueous layer was extracted twice more with EtOAc. The combined organic layers were washed once with brine, dried with magnesium sulfate, and concentrated. The crude material was purified by flash chromatography (0-50% EtOAc:Pentane) to afford the title compound as a colorless oil (18 mg, 12%). LCMS [M+H]+ 322.2 m/z. 1H NMR (400 MHz, METHANOL-d4) δ ppm 6.50 - 6.54 (m, 1 H) 5.24 - 5.30 (m, 1 H) 3.40 - 3.50 (m, 1 H) 2.50 (s, 3 H) 2.37 (s, 3 H) 1.93 - 2.05 (m, 2 H) 1.67 - 1.78 (m, 4 H) 1.55 - 1.66 (m, 2 H) 1.44 (s, 9 H).

**(1*s*,3*s*)-3-((2,6-Dimethylpyrimidin-4-yl)oxy)cyclobutan-1-amine (OSA\_ 00052\_XX\_01).** The title compound was prepared according to General Procedure B using *tert-*butyl((1s,3s)-3-((2,6-dimethylpyrimidin-4-yl)oxy)cyclobutyl)carbamate (103 mg, 0.351 mmol). Starting material was consumed after 1 h and the crude material was purified by flash chromatography (10-30% 5% NH4OH/MeOH:DCM) to afford the title compound as a colorless oil (63 mg, 92%). LCMS [M+H]+ 194.1 m/z. 1H NMR (400 MHz, METHANOL-d4) δ ppm 6.51 (s, 1 H) 4.93 (quin, J=7.3 Hz, 1 H) 3.15 - 3.25 (m, 1 H) 2.81 - 2.92 (m, 2 H) 2.50 (s, 3 H) 2.38 (s, 3 H) 1.91 - 2.01 (m, 2 H). 13C NMR (500 MHz, METHANOL-d4) δ ppm 23.2, 25.3, 39.3, 40.8, 65.4, 104.7, 168.73, 168.84, 170.5.

**(1*s*,4*s*)-4-((2,6-Dimethylpyrimidin-4-yl)oxy)cyclohexan-1-amine (OSA\_ 000054\_XX\_01).** The title compound was prepared according to General Procedure B using tert-butyl ((1s,4s)-4-((2,6-dimethylpyrimidin-4-yl)oxy)cyclohexyl)carbamate (18 mg, 0.056 mmol). Starting material was consumed after 1 h and the crude material was purified by flash chromatography (20% 10% NH4OH/MeOH:EtOAc), then repurified by flash chromatography (5-20% 10% NH4OH/MeOH:EtOAc) to afford the title compound as a white solid (6 mg, 49%). LCMS [M+H]+ 222.0 m/z. 1H NMR (400 MHz, METHANOL-d4) δ ppm 6.53 (s, 1 H) 5.32 (d, J=2.5 Hz, 1 H) 2.93 (s, 1 H) 2.51 (s, 3 H) 2.38 (s, 3 H) 2.07 (dd, J=11.9, 2.5 Hz, 2 H) 1.56 - 1.83 (m, 6 H). 13C NMR (400 MHz, METHANOL-d4) δ ppm 23.2, 25.3, 29.3, 30.5, 50.2, 71.6, 105.3, 168.57, 168.67, 170.82.

***tert*-Butyl 4-((2,6-dimethylpyrimidin-4-yl)amino)piperidine-1-carb-oxylate (4a).** 4-Chloro-2,6-dimethylpyrimidine (0.084 ml, 0.695 mmol) was dissolved in acetonitrile (2.0 ml, 0.35 M) and *tert*-butyl 4-aminopiperidine-1-carboxylate (170 mg, 0.849 mmol) was added, followed by the addition of DIPEA (0.0145 ml, 0.832 mmol). The reaction was stirred overnight at 50 ºC. The reaction temperature was then increased to 80 ºC and the reaction was run another ~48 h. The reaction was then cooled to room temperature, upon which a precipitate was observed. The reaction was filtered and the filtrate was concentrated and purified by flash chromatography (20-100% EtOAc:Hex - 0-5% MeOH:EtOAc) to afford the title compound as a yellow oil (31 mg, 15%). LCMS [M+H]+ 307.2 m/z. 1H NMR (400 MHz, METHANOL-d4) δ ppm 6.15 (s, 1 H) 4.03 (d, J=13.4 Hz, 2 H) 2.86 - 3.09 (m, 2 H) 2.37 (s, 3 H) 2.23 (s, 3 H) 1.94 (m, J=12.8, 3.2 Hz, 2 H) 1.44 - 1.50 (m, 6 H) 1.38 (qd, J=11.8, 4.3 Hz, 2 H).

***N*-((1*r*,4*r*)-4-(Benzyloxy)cyclohexyl)-2,6-dimethylpyrimidin-4-amine (4b).**(1*r*,4*r*)-4-(Benzyloxy)cyclohexan-1-amine was dissolved in acetonitrile (1.0 ml, 0.35 M) and 4-chloro-2,6-dimethylpyrimidine (0.040 ml, 0.331 mmol) was added, followed by the addition of DIPEA (0.060 ml, 0.341 mmol). The reaction was stirred at 80 °C for two days. The reaction mixture was concentrated and purified by flash chromatography (0-100% EtOAc:Hex - 0-10% MeOH:EtOAc) to afford the title compound as a yellow oil (21 mg, 20%). LCMS [M+H]+213.1 m/z. 1H NMR (400 MHz, METHANOL-d4) δ ppm 7.21 - 7.38 (m, 5 H) 6.11 (br. s, 1 H) 4.57 (s, 2 H) 3.69 - 3.90 (m, 1 H) 3.43 (tt, J=10.3, 4.1 Hz, 1 H) 2.37 (s, 3 H) 2.22 (s, 3 H) 2.08 - 2.18 (m, 2 H) 2.02 - 2.07 (m, 2 H) 1.45 (m, J=3.3 Hz, 2 H) 1.24 - 1.36 (m, 2 H).

***tert*-Butyl 4-((2,6-dimethylpyrimidin-4-yl)(methyl)amino)piperidine-1-carboxylate (5).** tert-Butyl 4-((2,6-dimethylpyrimidin-4-yl)amino)piperidine-1-carboxylate (31 mg, 0.101 mmol) was dissolved in dry DMF (1.0 ml, 0.1 M) and NaH (60% wt in mineral oil, 14 mg, 0.350 mmol) was added under argon. The reaction was stirred at room temperature for ~15 minutes before iodomethane (15 μL, 0.21 mmol) was added. The reaction was stirred at room temperature overnight under argon. The reaction was quenched with water and extracted three times with EtOAc. The combined organic layers were washed once with brine, dried with sodium sulfate, and concentrated before being purified by flash chromatography (5% MeOH:EtOAc) to afford the title compound as a colorless oil (17 mg, 53%). LCMS [M+H]+ 321.2 m/z. 1H NMR (400 MHz, METHANOL-d4) δ ppm 6.34 (s, 1 H) 4.69 - 4.82 (m, 1 H) 4.15 - 4.25 (m, 2 H) 2.79 - 2.96 (m, 5 H) 2.40 (s, 3 H) 2.29 (s, 3 H) 1.66 (br. s., 4 H) 1.47 (s, 9 H).

***N*,2,6-Trimethyl-*N*-(piperidin-4-yl)pyrimidin-4-amine (OSA\_000053\_XX\_ 01).** The title compound was prepared according to General Procedure B using *tert*-butyl 4-((2,6-dimethylpyrimidin-4-yl)(methyl)amino)piperidine-1-carboxylate (17 mg, 0.053 mmol). Starting material was consumed after 1 h and the crude material was purified by flash chromatography (30% 10% NH4OH/MeOH:EtOAc) to afford the title compound as a colorless oil (10 mg, 83%). LCMS [M+H]+ 221.1 m/z. 1H NMR (400 MHz, METHANOL-d4) δ ppm 6.69 (br. s., 1 H) 4.95 - 5.14 (m, 1 H) 3.54 (d, J=12.9 Hz, 2 H) 3.22 (td, J=12.9, 2.4 Hz, 2 H) 3.08 (s, 3 H) 2.53 (s, 3 H) 2.42 (s, 3 H) 2.14 (qd, J=13.1, 4.0 Hz, 2 H) 1.91 - 2.00 (m, 2 H). 13C NMR (400 MHz, METHANOL-d4) δ ppm 20.7, 23.2, 26.7, 30.8, 44.8, 101.0, 142.4, 144.4, 163.7, 182.6.

***N*-((1*r*,4*r*)-4-(Benzyloxy)cyclohexyl)-*N*,2,6-trimethylpyrimidin-4-amine** (**OSA\_ 000056\_XX\_01).** *N*-((1r,4r)-4-(Benzyloxy)cyclohexyl)-2,6-dimethylpyrimidin-4-amine (21 mg, 0.067 mmol) was dissolved in dry DMF (0.70 ml, 0.07 M) and NaH (60% wt in mineral oil, 9 mg, 0.236 mmol) was added The reaction was stirred at room temperature for ~15 minutes before iodomethane (9 µL, 0.145 mmol) was added and the reaction was stirred at room temperature overnight. The reaction was quenched with water and extracted three times with EtOAc. The combined organic layers were washed once with brine, dried with sodium sulfate, and concentrated before drying under high vacuum overnight. The crude material was purified by flash chromatography (5% MeOH:DCM) to afford the title compound as a colorless oil (13 mg, 61%). LCMS [M+H]+ 326.2 m/z. 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.36 (d, J=4.3 Hz, 4 H) 7.27 - 7.32 (m, 1 H) 6.08 (s, 1 H) 4.58 (s, 2 H) 4.41 (br. s, 1 H) 3.29 - 3.40 (m, 1 H) 2.87 (s, 3 H) 2.51 (s, 3 H) 2.35 (s, 3 H) 2.14 - 2.26 (m, 2 H) 1.69 - 1.82 (m, 2 H) 1.45 - 1.63 (m, 4 H). 13C NMR (400 MHz, CHLOROFORM-d) δ ppm 23.8, 25.8, 27.5, 29.0, 31.3, 53.1, 70.1, 76.6, 98.3, 127.5, 128.4, 138.9, 162.2, 163.9, 166.2.



**Scheme X.** Synthesis of 2,4-dicholorpyrimidine derivatives. *Reagents and conditions*: *a*) *tert*-butyl 4-(methylamino)piperidine-1-carboxylate, dry THF, RT, overnight (XX-XX%). *b*) Boronic acid or ester, K2CO3, PdCl2(dppf)·CH2Cl2, 3:1 dioxane:water, 100 C, overnight (XX-XX%). *c*) Desired amine, DIPEA, acetonitrile, 80 °C, 48 h (XX-XX%).

***tert*-Butyl 4-((2-chloropyrimidin-4-yl)(methyl)amino)piperidine-1-carboxylate (2)**. 2,4-Dichloropyrimidine (1.50 g, 10.07 mmol) was suspended in dry THF (14.0 ml, 0.70 M) and *tert*-butyl 4-(methylamino)piperidine-1-carboxylate (3.0 ml, 14.07 mmol) was added. The reaction was stirred at room temperature overnight. The volatiles were removed and the crude material was purified by flash chromatography (0-60% EtOAc:Hex) to afford the title compound as an off-white solid (1.30 g, 39%). LCMS [M+H]+ 327.2 m/z (35Cl), 329.1 m/z (37Cl). 1H NMR (400 MHz, CHLOROFORM-d) d ppm 8.05 (d, J=6.3 Hz, 1 H) 6.33 (d, J=6.3 Hz, 1 H) 4.44 - 5.05 (m, 1 H) 4.17 - 4.35 (m, 2 H) 2.76 - 2.96 (m, 5 H) 1.61 - 1.71 (m, 4 H) 1.49 (s, 9 H).

***tert*-Butyl 4-((4-chloropyrimidin-2-yl)(methyl)amino)piperidine-1-carboxylate (3)**. 2,4-Dichloropyrimidine (1.50 g, 10.07 mmol) was suspended in dry THF (14.0 ml, 0.70 M) and *tert*-butyl 4-(methylamino)piperidine-1-carboxylate (3.0 ml, 14.07 mmol) was added. The reaction was stirred at room temperature overnight. The volatiles were removed and the crude material was purified by flash chromatography (0-60% EtOAc:Hex) to afford the title compound as a white solid (341 mg, 10%). 1H NMR (400 MHz, CHLOROFORM-d) d ppm 8.16 (d, J=5.1 Hz, 1 H) 6.50 (d, J=5.1 Hz, 1 H) 4.69 - 4.82 (m, 1 H) 4.16 - 4.35 (m, 2 H) 3.01 (s, 3 H) 2.75 - 2.94 (m, 2 H) 1.63 - 1.73 (m, 4 H) 1.48 (s, 9 H).

***tert*-Butyl 4-(methyl(2-phenylpyrimidin-4-yl)amino)piperidine-1-carboxylate (OSA\_000061\_XX\_01).** The title compound was synthesized according to General Procedure C using *tert*-butyl 4-( (2-chloropyrimidin-4-yl)(methyl)amino)piperidine-1-carboxylate (60 mg, 0.183 mmol) and phenylboronic acid. The crude material was purified by flash chromatography (0-50% EtOAc:Hex) to afford the title compound as a white solid (10 mg, 15%). LCMS [M+H]+ 369.1 m/z. 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.39 (dd, J=6.7, 3.2 Hz, 2 H) 8.33 (d, J=6.3 Hz, 1 H) 7.41 - 7.53 (m, 3 H) 6.37 (d, J=6.1 Hz, 1 H) 4.63 - 5.09 (m, 1 H) 4.16 - 4.41 (m, 2 H) 2.98 (s, 3 H) 2.83 - 2.95 (m, 2 H) 1.64 - 1.81 (m, 4 H) 1.50 (s, 9 H). 13C NMR (500 MHz, CHLOROFORM-d) δ ppm 28.5, 29.0, 29.4, 43.4, 52.4, 79.8, 101.1, 128.0, 128.3, 130.3, 138.2, 154.7, 155.5, 161.6, 163.1.

***tert*-Butyl 4-(methyl(2-(naphthalen-2-yl)pyrimidin-4-yl)amino) piperidine-1-carboxylate(4).** The title compound was synthesized according to General Procedure C using *tert*-butyl 4-( (2-chloropyrimidin-4-yl)(methyl)amino)piperidine-1-carboxylate (150 mg, 0.459 mmol) and naphthalen-2-ylboronic acid. The crude material was purified by flash chromatography (20-50% EtOAc:Hex) to afford the title compound as a yellow oil (186 mg, 97%). LCMS [M+H]+ 419.1. 1H NMR (500 MHz, CHLOROFORM-d) δ ppm 8.93 (s, 1 H) 8.48 (dd, J=8.5, 1.6 Hz, 1 H) 8.38 (d, J=6.0 Hz, 1 H) 7.96 - 8.02 (m, 1 H) 7.93 (d, J=8.5 Hz, 1 H) 7.85 - 7.90 (m, 1 H) 7.48 - 7.57 (m, 2 H) 6.40 (d, J=6.3 Hz, 1 H) 4.66 - 5.32 (m, 1 H) 4.17 - 4.55 (m, 2 H) 3.01 (br. s., 3 H) 2.82 - 2.97 (m, 2 H) 1.68 - 1.86 (m, 4 H) 1.47 - 1.53 (m, 9 H).

***N*-methyl-2-phenyl-N-(piperidin-4-yl)pyrimidin-4-amine**(**OSA\_000064\_XX\_ 01).** The title compound was synthesized according to General Procedure B using *tert*-butyl 4-(methyl(2-phenylpyrimidin-4-yl)amino)piperidine-1-carboxylate (118 mg, 0.320 mmol). Starting material was consumed after ~1 h and the crude material was purified by flash chromatography (30% 10% NH4OH/MeOH:EtOAc), then repurified (20-30% 10% NH4OH/MeOH:DCM) to afford the title compound as an off-white solid (8 mg, 9%). LCMS [M+H]+ 269.1 m/z. 1H NMR (500 MHz, METHANOL-d4) δ ppm 8.24 - 8.32 (m, 3 H) 7.43 - 7.52 (m, 3 H) 6.68 (d, J=6.3 Hz, 1 H) 4.57 - 4.70 (m, 1 H) 3.56 (dt, J=12.8, 2.0 Hz, 2 H) 3.23 - 3.30 (m, 2 H) 3.06 (s, 3 H) 2.13 (q, J=12.8 Hz, 2 H) 1.96 - 2.05 (m, 2 H). 13C NMR (500 MHz, METHANOL-d4) δ ppm 27.0, 29.9, 45.1, 51.0, 102.8, 129.2, 129.5, 131.6, 139.2, 156.3, 163.3.

***N*-Methyl-2-(naphthalen-2-yl)-N-(piperidin-4-yl)pyrimidin-4-amine(OSA\_000067\_XX\_01).** The title compound was synthesized according to General Procedure B using tert-butyl 4-(methyl(2-(naphthalen-2-yl)pyrimidin-4-yl)amino)piperidine-1-carboxylate (186 mg, 0.444 mmol). Starting material was consumed after ~1 h and the crude material was purified by flash chromatography (10-25% 10% NH4OH/MeOH:DCM) to afford the title compound as a yellow solid (89 mg, 63%). LCMS [M+H]+ 319.1 m/z. 1H NMR (400 MHz, METHANOL-d4) δ ppm 8.78 (s, 1 H) 8.38 (dd, J=8.6, 1.8 Hz, 1 H) 8.26 (d, J=6.3 Hz, 1 H) 7.87 - 8.00 (m, 3 H) 7.49 - 7.57 (m, 2 H) 6.62 (d, J=6.3 Hz, 1 H) 3.21 (d, J=12.6 Hz, 2 H) 3.07 (br. s., 3 H) 2.84 (td, J=12.2, 3.2 Hz, 2 H) 1.73 - 1.92 (m, 4 H). 13C NMR (400 MHz, METHANOL-d4) δ ppm 29.7, 30.4, 46.6, 49.9, 102.5, 126.2, 127.4, 128.1, 128.7, 128.9, 129.1, 130.0, 134.6, 136.0, 137.0, 156.2, 163.1, 164.7

***tert*-Butyl 4-(methyl(4-phenylpyrimidin-2-yl)amino)piperidine-1-carboxylate(OSA\_000060\_XX\_01).** The title compound was synthesized according to General Procedure C using *tert*-butyl 4-((4-chloropyrimidin-2-yl)(methyl)amino)piperidine-1-carboxylate (59 mg, 1.80 mmol) and phenylboronic acid. The crude material was purified by flash chromatography (0-50% EtOAc:Hex) to afford the title compound as a tan solid (29 mg, 44%). LCMS [M+H]+ 369.2 m/z. 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 8.39 (d, J=5.1 Hz, 1 H) 8.01 - 8.10 (m, 2 H) 7.44 - 7.54 (m, 3 H) 6.96 (d, J=4.8 Hz, 1 H) 4.93 (dt, J=15.6, 8.0 Hz, 1 H) 4.16 - 4.37 (m, 2 H) 3.13 (s, 3 H) 2.76 - 2.99 (m, 2 H) 1.71 - 1.80 (m, 4 H) 1.50 (s, 9 H). 13C NMR (500 MHz, CHLOROFORM-d) δ ppm 28.5, 29.0, 29.1, 43.6, 52.6, 79.6, 105.2, 127.0, 128.7, 130.5, 137.7, 154.8, 157.9, 161.6, 164.3.

***N*-Methyl-4-phenyl-N-(piperidin-4-yl)pyrimidin-2-amine(OSA\_000063\_XX\_ 01).** The title compound was synthesized according to General Procedure B using *tert*-butyl 4-(methyl(4-phenylpyrimidin-2-yl)amino)piperidine-1-carboxylate (103 mg, 0.279 mmol). Starting material was consumed after ~1 h and the crude material was purified by flash chromatography (30% 10% NH4OH/MeOH:EtOAc), then repurified (20-30% 10% NH4OH/MeOH:DCM) to afford the title compound as a light yellow oil (10 mg, 13%). LCMS [M+H]+ 269.1 m/z. 1H NMR (400 MHz, METHANOL-d4) δ ppm 8.33 (d, J=5.3 Hz, 1 H) 8.06 - 8.13 (m, 2 H) 7.43 - 7.51 (m, 3 H) 7.06 (d, J=5.3 Hz, 1 H) 3.17 (d, J=12.4 Hz, 2 H) 3.11 (s, 3 H) 2.76 (td, J=12.3, 2.9 Hz, 2 H) 1.69 - 1.88 (m, 4 H). \*Piperidine H obscured by water peak. 13C NMR (400 MHz, METHANOL-d4) δ ppm 29.4, 30.7, 46.8, 53.8, 106.1, 128.1, 129.7, 131.7, 138.9, 159.3, 163.0, 165.8.

***tert*-Butyl 4-(methyl(2-(piperidin-1-yl)pyrimidin-4-yl)amino) piperidine-1-carboxylate(5a).** *tert*-Butyl 4-((2-chloropyrimidin-4-yl)(methyl)amino)piperidine-1-carboxylate (150 mg, 0.459 mmol) was dissolved in acetonitrile (1.5 ml, 0.3 M) and piperidine (0.050 ml, 0.506 mmol) was added, followed by the addition of DIPEA (0.100 ml, 0.574 mmol). The reaction was stirred for two days at 80 °C. The reaction mixture was concentrated and the crude material was purified by flash chromatography (2-10% MeOH:DCM) to afford the title compound as a yellow oil (105 mg, 61%). LCMS [M+H]+ 376.3 m/z. 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.93 (d, J=6.1 Hz, 1 H) 5.78 (d, J=6.3 Hz, 1 H) 4.40 - 4.65 (m, 1 H) 4.12 - 4.38 (m, 2 H) 3.69 - 3.77 (m, 4 H) 2.86 (s, 3 H) 2.80 (br. t, J=11.0, 11.0 Hz, 2 H) 1.56 - 1.72 (m, 10 H) 1.48 (s, 9 H).

***tert*-Butyl 4-(methyl(2-(4-methylpiperazin-1-yl)pyrimidin-4-yl)amino) piperidine-1-carboxylate (5b).** *tert*-Butyl 4-((2-chloropyrimidin-4-yl)(methyl)amino)piperidine-1-carboxylate (150 mg, 0.459 mmol) was dissolved in acetonitrile (1.5 ml, 0.3 M) and *N*-methylpiperidine (0.060 ml, 0.541 mmol) was added, followed by the addition of DIPEA (0.100 ml, 0.574 mmol). The reaction was stirred for two days at 80 °C. The crude material was purified by flash chromatography (5-20% MeOH:DCM) to afford the title compound as an orange oil (179 mg, quant.). LCMS [M+H]+ 391.2 m/z. 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.93 (d, J=6.1 Hz, 1 H) 5.82 (d, J=6.1 Hz, 1 H) 4.38 - 4.59 (m, 1 H) 4.14 - 4.34 (m, 2 H) 3.78 - 3.88 (m, 4 H) 2.85 (s, 3 H) 2.71 - 2.83 (m, 2 H) 2.52 (t, J=4.8 Hz, 4 H) 2.38 (s, 3 H) 1.58 - 1.73 (m, 4 H) 1.48 (s, 9 H).

***tert*-Butyl 4-(methyl(2-morpholinopyrimidin-4-yl)amino)piperidine-1-carboxylate(5c).** *tert*-Butyl 4-((2-chloropyrimidin-4-yl)(methyl)amino) piperidine-1-carboxylate (150 mg, 0.459 mmol) was dissolved in acetonitrile (1.5 ml, 0.3 M) and morpholine (0.050 ml, 0.580 mmol) was added, followed by the addition of DIPEA (0.100 ml, 0.574 mmol). The reaction was stirred for two days at 80 °C. The crude material was purified by flash chromatography (2-20% MeOH:DCM) to afford the title compound as a yellow oil (139 mg, 80%). LCMS [M+H]+ 378.1 m/z. 1H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.94 (d, J=6.3 Hz, 1 H) 5.85 (d, J=6.1 Hz, 1 H) 4.39 - 4.59 (m, 1 H) 4.14 - 4.36 (m, 2 H) 3.70 - 3.80 (m, 8 H) 2.87 (s, 3 H) 2.71 - 2.84 (m, 2 H) 1.59 - 1.72 (m, 4 H) 1.48 (s, 9 H).

***N*-Methyl-2-(piperidin-1-yl)-N-(piperidin-4-yl)pyrimidin-4-amine (OSA\_ 000062\_XX\_01).** The title compound was synthesized according to General Procedure B using *tert*-butyl 4-(methyl(2-(piperidin-1-yl)pyrimidin-4-yl)amino)piperidine-1-carboxylate (105 mg, 0.280 mmol).Starting material was consmed after ~1 h and the crude material was purified by flash chromatography (5-15% 10% NH4OH/MeOH:DCM) to afford the title compound as a yellow oil (64 mg, 84%). LCMS [M+H]+ 276.1 m/z. 1H NMR (400 MHz, METHANOL-d4) δ ppm 7.78 (d, J=6.1 Hz, 1 H) 5.93 (d, J=6.3 Hz, 1 H) 4.40 - 4.61 (m, 1 H) 3.63 - 3.72 (m, 4 H) 3.16 (m, J=2.3 Hz, 2 H) 2.90 (s, 3 H) 2.72 (td, J=12.2, 2.9 Hz, 2 H) 1.62 - 1.81 (m, 6 H) 1.51 - 1.60 (m, 4 H). 13C NMR (400 MHz, METHANOL-d4) δ ppm 26.0, 26.8, 29.5, 30.4, 46.2, 46.6, 93.9, 119.3, 156.4, 162.3, 163.6.

***N*-Methyl-2-(4-methylpiperazin-1-yl)-N-(piperidin-4-yl)pyrimidin-4-amine(OSA\_ 000065\_XX\_01).** The title compound was synthesized according to General Procedure B using *tert*-butyl 4-(methyl(2-(4-methylpiperazin-1-yl)pyrimidin-4-yl)amino)piperidine-1-carboxylate (179 mg, 0.458 mmol). Starting material was consumed after ~2 h and the crude material was purified by flash chromatography (10-25% 10% NH4OH/MeOH:DCM) to afford the title compound as an orange oil (75 mg, 56%). LCMS [M+H]+ 291.1 m/z. 1H NMR (400 MHz, METHANOL-d4) δ ppm 7.81 (d, J=6.3 Hz, 1 H) 6.00 (d, J=6.1 Hz, 1 H) 4.39 - 4.65 (m, 1 H) 3.67 - 3.79 (m, 4 H) 3.17 (d, J=12.6 Hz, 2 H) 2.91 (s, 3 H) 2.74 (td, J=12.4, 3.0 Hz, 2 H) 2.48 (t, J=5.1 Hz, 4 H) 2.32 (s, 3 H) 1.63 - 1.83 (m, 4 H). 13C NMR (400 MHz, METHANOL-d4) δ ppm 29.5, 30.2, 44.7, 46.2 46.5, 53.5, 55.8, 94.8, 156.5, 162.4, 163.6.

***N*-Methyl-2-morpholino-N-(piperidin-4-yl)pyrimidin-4-amine(OSA\_ 000066 \_XX\_01).** The title compound was synthesized according to General Procedure B using *tert*-butyl 4-(methyl(2-morpholinopyrimidin-4-yl)amino)piperidine-1-carboxylate (139 mg, 0.368 mmol). Starting material was consumed after ~3 h and the crude material was purified by flash chromatography (10-25% 10% NH4OH/MeOH:DCM) to afford the title compound as a yellow oil (65 mg, 64%). LCMS [M+H]+ 278.1 m/z. 1H NMR (500 MHz, METHANOL-d4) δ ppm 7.82 (d, J=6.0 Hz, 1 H) 6.01 (d, J=6.3 Hz, 1 H) 4.27 - 4.72 (m, 1 H) 3.69 - 3.74 (m, 4 H) 3.63 - 3.68 (m, 4 H) 3.14 (d, J=12.6 Hz, 2 H) 2.91 (s, 3 H) 2.71 (td, J=12.4, 2.4 Hz, 2 H) 1.74 (qd, J=8.2, 4.4 Hz, 2 H) 1.62 - 1.69 (m, 2 H). 13C NMR (500 MHz, METHANOL-d4) δ ppm 29.6, 30.5, 45.8, 46.6, 53.6, 67.9, 95.0, 156.5, 162.6, 163.5.

***tert*-Butyl ((1s,4s)-4-((2-methylpyrimidin-4-yl)oxy)cyclohexyl)carb-amate.** *tert*-Butyl ((1s,4s)-4-hydroxycyclohexyl)carbamate (100 mg, 0.464 mmol) was dissolved in dry THF (1.6 ml, 0.30 M). The reaction was put under argon and cooled to 0 ºC, after which NaH (56 mg, 1.40 mmol) was added. The reaction was stirred at 0 ºC for ~1 h. 4-Chloro-2-methylpyrimidine (0.072 ml, 0.559 mmol) was added and the reaction was warmed to room temperature, then heated to 50 ºC overnight, stirring under argon. The reaction mixture was diluted with EtOAc and poured over water; the aqueous layer was extracted twice more with EtOAc. The combined organic layers were washed once with brine, dried with magnesium sulfate, and concentrated. The crude material was purified by flash chromatography (0-50% EtOAc:Pentane) to afford the title compound as a light yellow solid (58 mg, 41%). LCMS [M+H]+ 308.2 m/z. 1H NMR (400 MHz, METHANOL-d4) d ppm 8.27 - 8.32 (m, 1 H) 6.63 - 6.68 (m, 1 H) 5.28 - 5.36 (m, 1 H) 3.41 - 3.51 (m, 1 H) 2.54 (s, 3 H) 2.01 (s, 2 H) 1.69 - 1.80 (m, 4 H) 1.55 - 1.68 (m, 2 H) 1.44 (s, 9 H).

**(1*s*,4*s*)-4-((2-Methylpyrimidin-4-yl)oxy)cyclohexan-1-amine** (**OSA\_ 000055\_XX\_01).** The title compound was prepared according to General Procedure B using ((1s,4s)-4-((2-methylpyrimidin-4-yl)oxy)cyclohexyl)carb-amate (58 mg, 0.89 mmol). Starting material was consumed after 1 h and the crude material was purified by flash chromatography (30% 10% NH4OH/MeOH:EtOAc) to afford the title compound as a white solid (39 mg, quantitative yield). LCMS [M+H]+ 208.1 m/z. 1H NMR (400 MHz, METHANOL-d4) δ ppm 8.33 (d, J=6.1 Hz, 1 H) 6.72 (d, J=5.8 Hz, 1 H) 5.42 (br. s., 1 H) 3.20 - 3.29 (m, 1 H) 2.55 (s, 3 H) 2.16 (d, J=8.6 Hz, 2 H) 1.88 - 2.01 (m, 2 H) 1.72 - 1.87 (m, 4 H). 13C NMR (400 MHz, METHANOL-d4) δ ppm 25.5, 26.3, 28.7, 50.5, 70.6, 107.2, 158.0, 169.2, 170.1.

***tert*-Butyl ((1r,4r)-4-(benzyloxy)cyclohexyl)carbamate.** *tert*-Butyl ((1r,4r)-4-hydroxycyclohexyl)carbamate (300 mg, 1.39 mmol) was dissovled in dry THF (4.6 ml, 0.30 M) and the reaction mixture was cooled to 0 ºC. NaH (167 mg, 4.18 mmol) was added and the reaction was stirred at 0 ºC for ~1 h. Benzyl bromide (0.30 ml, 2.53 mmol) was added and the reaction was heated to 50 ºC overnight, stirring under argon. The reaction was poured over water and extracted three times with EtOAc. The combined organic layers were washed once with brine, dried with magnesium sulfate, and concentrated. The crude material was used in the next reaction without further purification. ​

**(1*r*,4*r*)-4-(Benzyloxy)cyclohexan-1-amine.** The title compound was prepared according to General Procedure B using *tert*-butyl ((1r,4r)-4-(benzyloxy)cyclohexyl)carbamate (212 mg, 0.694 mmol). Starting material was consumed after 1 h and the crude material was purified by flash chromatography (20% 10% NH4OH/MeOH:DCM) to afford the title compound as a white solid (70 mg, 50%). LCMS [M+H]+ 206.1 m/z. 1H NMR (400 MHz, METHANOL-d4) d ppm 7.32 (m, J=4.5 Hz, 4 H) 7.23 - 7.29 (m, 1 H) 4.56 (s, 2 H) 3.39 (m, J=6.3 Hz, 1 H) 2.80 - 2.91 (m, 1 H) 2.06 - 2.17 (m, 2 H) 1.91 - 2.02 (m, 2 H) 1.21 - 1.43 (m, 4 H).