Supporting Information

8-Substituted pyrido[3,4-*d*]pyrimidin-4(3*H*)-one derivatives as potent, cell permeable, KDM4 (JMJD2) and KDM5 (JARID1) histone lysine demethylase inhibitors.

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S3–S50: Experimental procedures for compounds **7a,b,d, 9a,b, 16, 21, 22, 24, 25, 17-19, 27, 28, 29a,b, 30a,b, 36-40, 41a,b, 42, 43, 44a-g, 48, 55-57, 49a-c, 49e-g, 52a-c, 52e-g, 59** and preparation of intermediates for the synthesis of **59, 50a-i, 53a-i, 51b-i, 51l-n, 54b-i, 54l-n.**

S51–S55: Table S1: Crystallographic data collection and refinement statistics for compounds **15, 16, 30a, 30b, 37, 40, 52d, 53a, 54a, 54j, and 58**.

S56–S57: Table S2: Kinase selectivity profiling of compound **54k**.

S58: Figure S1: Cellular activity of **54k** in HeLa cells assessed by immunofluorescence assay

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3-(Methylsulfonyl)-*N*-(4-(pyridin-2-yl)thiazol-2-yl)benzamide (7a): To a mixture of 3-(methylsulfonyl)benzoic acid (0.090 g, 0.45 mmol, 1 equiv.), 1-hydroxybenzotriazole hydrate (0.067 g, 0.49 mmol, 1.1 equiv.), EDCI (0.103 g, 0.54 mmol, 1.2 equiv.) and anhydrous CH_2Cl_2 (4 mL, 0.11 M) was added 2-amino-4-(2-pyridy)thiazole (0.092 g, 0.52 mmol, 1.2 equiv.). The reaction mixture was stirred at room temp for 3.5 h under argon, a white precipitate gradually formed, at this point CH_2Cl_2 (3 mL) was added and stirring was continued at room temperature overnight under argon. The reaction mixture was then diluted with CH_2Cl_2 (50 mL) and washed with saturated $NaHCO_3$ solution (20 mL) and brine (2 × 20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. This residue was absorbed on silica gel and the free running powder was placed on a 20 g Isolute silica II column which was eluted with 50% EtOAc in CH_2Cl_2, and then 75% EtOAc in CH_2Cl_2 to give the desired product as a white solid (0.054 g, 33%); ^{1}H NMR (500 MHz, DMSO-d_6) 3.32 (s, 3H), 7.36 (dd, J = 4.9, 7.2 Hz, 1H), 7.86 (t, J = 8.0 Hz, 1H), 7.91 (td, J = 1.7, 7.7 Hz, 1H), 7.95 (s, 1H), 8.03 (d, J = 7.9 Hz, 1H), 8.20 (d, J = 8.2 Hz, 1H), 8.42 (d, J = 7.9 Hz, 1H), 8.63 (d, J = 4.5 Hz, 1H), 8.67 (s, 1H), 13.13 (s, 1H); LC-MS (Method A, ESI, *m/z*) t_R = 1.93 min - 360 $(M+H)^+$; HRMS (Method B): found 360.0463; calculated for $C_{16}H_{14}N_3O_3S_2$ $(M+H)^+$ 360.0471.

4-(Ethylsulfonyl)-*N*-(4-(pyridin-2-yl)thiazol-2-yl)benzamide (7b): To a mixture of 4-(ethylsulfonyl)benzoic acid (0.090 g, 0.42 mmol, 1 equiv.), 1-hydroxybenzotriazole hydrate (0.062 g, 0.46 mmol, 1.1 equiv.), EDCI (0.097 g, 0.50 mmol, 1.2 equiv.) and anhydrous CH_2Cl_2 (4 mL, 0.11 M) was added 2-amino-4-(2-pyridy)thiazole (0.089 g, 0.50 mmol, 1.2 equiv.).The reaction mixture was stirred at room temp for 3.5 h under argon and a white precipitate gradually formed. The reaction mixture was diluted with CH_2Cl_2 (40 mL) and washed with a saturated $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organics were washed with saturated brine solution (2 × 20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. This residue was absorbed on silica and

the free running powder was placed on a 20 g Isolute silica II column which was eluted with 50% EtOAc in CH_2Cl_2 and then 75% EtOAc in CH_2Cl_2. The product was obtained as a white solid (0.040 g, 25%). ^{1}H NMR (500 MHz, DMSO-d_6) 1.13 (t, J = 7.3 Hz, 3H), 3.42 (q, J = 7.3 Hz, 2H), 7.36 (ddd, J = 1.0, 4.7, 7.5 Hz, 1H), 7.90 (td, J = 1.8, 7.6 Hz, 1H), 7.95 (s, 1H), 8.03 (d, J = 7.9 Hz, 1H), 8.07 (d, J = 8.6 Hz, 2H), 8.35 (d, J = 8.4 Hz, 2H), 8.62-865 (m, 1H), 13.13 (s, 1H); LC-MS (Method B, ESI, *m/z*) t_R = 2.37 min - 374 $(M+H)^+$; HRMS (Method B): found 374.0616; calculated for $C_{17}H_{16}N_3O_3S_2$ $(M+H)^+$ 374.0628.

***N*-(4-(pyridin-2-yl)thiazol-2-yl)benzamide (7d):**[35] To a mixture of benzoic acid (0.098 g, 0.80 mmol, 1 equiv.), 1-hydroxybenzotriazole hydrate (0.119 g, 0.88 mmol, 1.1 equiv.), EDCI (0.185 g, 0.96 mmol, 1.2 equiv.) and anhydrous CH_2Cl_2 (7.5 mL, 0.11 M) was added 2-amino-4-(2-pyridy)thiazole (0.149 g, 0.84 mmol, 1.05 equiv.). The reaction mixture was stirred at room temp for 36 h under argon, then diluted with CH_2Cl_2 (50 mL) and washed with a saturated $NaHCO_3$ solution (2 × 20 mL) and saturated brine solution (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. This residue was absorbed on silica gel and the free running powder was placed on a 20 g Isolute silica II column which was eluted with a gradient of EtOAc (10% to 40%) in CH_2Cl_2. The title compound was obtained as a white solid (0.114 g, 50%). ^{1}H NMR (500 MHz, DMSO-d_6) 7.36 (ddd, J = 1.1, 4.8, 7.4 Hz, 1H), 7.58 (t, J = 7.8 Hz, 2H), 7.67 (tt, J = 1.2, 7.4 Hz, 1H), 7.92 (td, J = 1.8, 7.8 Hz, 1H), 7.92 (s, 1H), 8.04 (dt, J = 1.0, 7.9 Hz, 1H), 8.13 – 8.17 (m, 2H), 8.61-8.63 (m, 1H), 12.83 (s, 1H); LC-MS (Method B, ESI, *m/z*) t_R = 2.44 min - 282 $(M+H)^+$; HRMS (Method B): found 282.0688; calculated for $C_{15}H_{12}N_3OS$ $(M+H)^+$ 282.0696.

3-(Methylsulfonyl)-*N*-(4-(pyridin-3-yl)thiazol-2-yl)benzamide (9a): To a mixture of 3-(methylsulfonyl)benzoic acid (0.090 g, 0.45 mmol, 1 equiv.), 1-hydroxybenzotriazole hydrate (0.067 g, 0.50 mmol, 1.1 equiv.), EDCI (0.103 g, 0.54 mmol, 1.2 equiv.) and anhydrous

CH_2Cl_2 (6.5 mL, 0.07 M) was added 2-amino-4-(3-pyridy)thiazole (0.084 g, 0.47 mmol, 1.05 equiv.). The reaction mixture was stirred at room temperature for 1.5 h under argon, anhydrous DMF (2.2 mL) was added and the nearly clear solution was stirred at room temperature for an additional 36 h under argon. At this point additional 3-(methylsulfonyl)benzoic acid (0.040 g) and EDCI (0.040 g) were added and stirring was continued at room temperature for 6 h under argon. The reaction mixture was then diluted with CH_2Cl_2 (50 mL) and washed with a saturated $NaHCO_3$ solution (3 × 20 mL) and saturated brine solution (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a residue containing DMF. On standing at room temperature overnight a white precipitate formed, this mixture was diluted with CH_2Cl_2 (3 mL) and the white solid was collected by filtration and washed with CH_2Cl_2 (3 × 1 mL) to obtain the title compound as a white solid (0.045 g, 28%); ^{1}H NMR (500 MHz, DMSO-d_6) 3.32 (s, 3H), 7.49 (dd, J = 4.8, 8.0 Hz, 1H), 7.84 (t, J = 8.0 Hz, 1H), 7.93 (s, 1H), 8.18 (dt, J = 1.2, 8.0 Hz, 1H), 8.29 (dt, J = 2.0, 8.0 Hz, 1H), 8.41 (dt, J = 1.1, 8.0 Hz, 1H), 8.55 (dd, J = 1.6, 4.8 Hz, 1H), 8.67 (t, J = 1.7 Hz, 1H), 9.18 (d, J = 1.9 Hz, 1H), 13.16 (s, 1H); LC-MS (Method B, ESI, *m/z*) t_R = 1.99 min - 360 $(M+H)^+$; HRMS (Method B): found 360.0470; calculated for $C_{16}H_{14}N_3O_3S_2$ $(M+H)^+$ 360.0471.

4-(Ethylsulfonyl)-*N*-(4-(pyridin-3-yl)thiazol-2-yl)benzamide (9b): To a mixture of 4-(ethylsulfonyl)benzoic acid (0.090 g, 0.42 mmol, 1 equiv.), 1-hydroxybenzotriazole hydrate (0.062 g, 0.46 mmol, 1.1 equiv.), EDCI (0.097 g, 0.50 mmol, 1.2 equiv.) and anhydrous CH_2Cl_2 (6 mL, 0.07 M) was added 2-amino-4-(3-pyridy)thiazole (0.078 g, 0.44 mmol, 1.05 equiv.). The reaction mixture was stirred at room temperature for 3 h under argon, anhydrous DMF (3 mL) was then added and the nearly clear solution was stirred at room temperature for an additional 18 h under argon. The reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with a saturated $NaHCO_3$ solution (3 × 20 mL) and saturated brine solution (20 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a residue containing DMF. To this solution

a small amount of CH_2Cl_2 (~0.5 mL) was added, and the product was precipitated by the addition of Et_2O. The precipitate was collected by filtration washed with 10% CH_2Cl_2 in Et_2O, and Et_2O to afford the title compound as a white solid (0.025 g, 16%). ^{1}H NMR (500 MHz, DMSO-d_6) 1.13 (t, J = 7.7 Hz, 3H), 3.41 (q, J = 7.7 Hz, 2H), 7.48 (ddd, J = 0.8, 4.9, 8.0 Hz, 1H), 7.93 (s, 1H), 8.07 (d, J = 8.8 Hz, 2H), 8.29 (dt, J = 1.9, 8.0 Hz, 1H), 8.36 (d, J = 8.6 Hz, 2H), 8.55 (dd, J = 1.7, 4.7 Hz, 1H), 9.18 (dd, J = 0.7, 2.3 Hz, 1H), 13.12 (s, 1H); LC-MS (Method B, ESI, *m/z*) t_R = 2.15 min - 374 $(M+H)^+$; HRMS (Method B): found 374.0608; calculated for $C_{17}H_{16}N_3O_3S_2$ $(M+H)^+$ 374.0628.

2-(2-Aminothiazol-4-yl)isonicotinamide (16): Methyl 2-(2-((*tert*-butoxycarbonyl)amino)-thiazol-4-yl)isonicotinate (0.02 g, 0.06 mmol) was dissolved in a 7N ammonia in methanol solution (1 mL) in a microwave tube. The tube was sealed and the reaction stirred at 80 ^{o}C for 18 h. The reaction was concentrated *in vacuo* and the residue treated with a 4M HCl in dioxane solution (1 mL) at room temperature for 1 h. Volatiles were removed *in vacuo* and the residue was desalted by passing through an isolute-NH_2 cartridge eluting with methanol to give the target compound as a brown powder (0.012 g, 91%); ^{1}H NMR (500 MHz, DMSO-d_6) 7.14 (s, 2H), 7.29 (s, 1H), 7.61 (dd, J = 0.8, 4.1 Hz, 1H), 7.65 (br s, 1H), 8.22 (s, 1H), 8.26 (br s, 1H), 8.64 (dd, J = 0.4, 4.2 Hz, 1H); LC - MS (Method C; ESI, *m/z*) t_R = 0.71 min - 221 $(M+H)^+$; HRMS (Method B): found 221.0498; calculated for $C_9H_9N_4OS$ $(M+H)^+$ 221.0492.

Methyl 2-(thiazol-4-yl)isonicotinate (21): Methyl 2-bromoisonicotinate (0.104 g, 0.48 mmol, 1 equiv.), silver oxide (0.111 g, 0.48 mmol, 1 equiv.) and tetrakis(triphenylphosphine)palladium (0.060 g, 0.052 mmol, 11 mol%) were suspended in anhydrous DMF (10 mL, 0.05 M) and heated at 100 ^{o}C under nitrogen for 5 min. 4-(Tributylstannyl)thiazole (0.200 g, 0.534 mmol, 1.1 equiv.) dissolved in anhydrous DMF (1

mL) was added and the reaction stirred for a further 1 h. The reaction was cooled to room temperature and the reaction mixture applied to an SCX cartridge eluting first with 50% methanol in chloroform followed by 7N ammonia in methanol. The ammoniacal solution was concentrated *in vacuo* and the residue purified by flash silica gel column chromatography, eluted with 50% hexane in EtOAc. The product was isolated as viscous oil (0.075 g, 64%). ^{1}H NMR (500 MHz, DMSO-d_6) 3.94 (s, 3H), 7.80 (dd, J = 1.6, 5.0 Hz, 1H), 8.43 (d, J = 2.1 Hz, 1H), 8.54 (s, 1H), 8.84 (dd, J = 0.75, 4.9 Hz, 1H), 9.27 (d, J = 2.1 Hz, 1H); LC - MS (Method C; ESI, *m/z*) t_R = 1.21 min – 221 $(M+H)^+$; HRMS (Method B): found 221.0391; calculated for $C_{10}H_9N_2O_2S$ $(M+H)^+$ 221.0379.

2-(Thiazol-4-yl)isonicotinic acid (22): To a stirred solution of methyl 2-(thiazol-4-yl)isonicotinate (0.030 g, 0.136 mmol) in methanol (3 mL, 0.05 M) was added NaOH solution (0.1 M, 5 mL). After 1 h at room temperature, the volatiles were removed *in vacuo* and the residue taken up in water (5 mL). The aqueous solution was acidified with aqueous 1 M HCl to pH 5. The solution was saturated with sodium chloride and then extracted with EtOAc (20 mL) and chloroform (20 mL). The combined organic solutions were dried ($MgSO_4$) and concentrated to afford the pure product as a pale yellow powder (0.013 g, 46%). ^{1}H NMR (500 MHz, DMSO-d_6) 7.76 (dd, J = 1.5, 4.9 Hz, 1H), 8.39 (d, J = 2.0 Hz, 1H), 8.52 (s, 1H), 8.77 (d, J = 4.9 Hz, 1H), 9.26 (d, J = 2.0 Hz, 1H), 14.00 (br s, 1H); LC - MS (Method C; ESI, *m/z*) t_R = 0.87 min - 207 $(M+H)^+$; HRMS (Method B): found 207.0234; calculated for $C_9H_7N_2O_2S$ $(M+H)^+$ 207.0223.

Methyl 2-(2-methylthiazol-4-yl)isonicotinate (24): A mixture of methyl 2-(2-bromoacetyl)isonicotinate (0.230g, 0.89 mmol), thioacetamide (0.067 g, 0.89 mmol), ethanol (5 mL) and triethylamine (0.25 mL, 1.78 mmol) was stirred at reflux for 1 h under argon. Volatiles were removed in vacuo, the residue was dried packed, placed on a 20 g Isolute silica II column which was eluted with 90% EtOAc in hexane and 95% EtOAc in hexane.

The obtained material was dissolved in EtOAc (50 mL) and the solution was washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The residue was rechromatographed as described above to give a brown solid (0.078 g). ^{1}H NMR was consistent with the hydrated cyclised intermediate. This material was dissolved in ethanol (4 mL), concentrated HCl (2 drops) was added and the solution was heated at reflux for 20 min. The reaction mixture was allowed to cool to room temperature, diluted with saturated aqueous $NaHCO_3$ (15 mL) and water (5 mL) and extracted with EtOAc (3 x 30 mL). The extracts were combined, dried (Na_2SO_4), and concentrated in vacuo. This material was dry packed, placed on a 20 g Isolute silica II column which was eluted with EtOAc/hexanes (v/v; 1:1). The title compound was obtained as a light brown solid (0.048 g, 23%). ^{1}H NMR (500 MHz, DMSO-d_6) 2.76 (s, 3H), 3.94 (s, 3H), 7.78 (dd, J = 1.6, 4.9 Hz, 1H), 8.21 (s, 1H), 8.46 (dd, J = 0.7, 1.5 Hz, 1H), 8.81 (dd, J = 0.8, 5.0 Hz, 1H); LC-MS (Method F, ESI, *m/z*) t_R = 1.21 min - 235 $(M+H)^+$.

2-(2-Methylthiazol-4-yl)isonicotinic acid (25): To a solution of methyl 2-(2-methylthiazol-4-yl)isonicotinate (0.043g, 0.18 mmol, 1 equiv.) in MeOH (0.7 mL, 0.25 M) was added 1M aqueous NaOH (0.46 mL, 0.46 mmol, 2.6 equiv.) followed by water (0.3 mL). The reaction mixture was stirred at room temperature for 50 min, the organics were removed *in vacuo*, the remainder was diluted with water (0.4 mL) and the pH was adjusted to approximately 5.5 with 1M aqueous HCl. The precipitate was collected by filtration, washed with water (3 × 1 mL) and dried to give the title compound as a white solid (0.018 g, 45%). ^{1}H NMR (500 MHz, DMSO-d_6) 2.76 (s, 3H), 7.76 (dd, J = 1.6, 5.0 Hz, 1H), 8.19 (s, 1H), 8.46 (dd, J = 0.8, 1.5 Hz, 1H), 8.79 (dd, J = 0.8, 5.0 Hz, 1H), 13.75 (br s, 1H); LC-MS (Method F, ESI, *m/z*) t_R = 1.03 min (100% purity) - 221 $(M+H)^+$; HRMS (Method B): found 221.0385; calculated for $C_{10}H_9N_2O_2S$ $(M+H)^+$ 221.0379.

Methyl 2-(2-aminothiazol-4-yl)isonicotinate (17): A solution of 4M HCl in dioxane (1 mL) was added to methyl 2-(2-((*tert*-butoxycarbonyl)amino)thiazol-4-yl)isonicotinate (0.012 g, 0.036 mmol) and the reaction mixture was stirred at room temperature for 1 h. Volatiles were removed *in vacuo* and the residue was desalted by passing through an isolute-NH_2 cartridge eluting with methanol to afford a brown solid (0.007 g, 83%); ^{1}H NMR (500 MHz, DMSO-d_6) 3.92 (s, 3H), 7.22 (s, 2H), 7.34 (s, 1H), 7.69 (dd, J = 1.7, 5.0 Hz, 1H), 8.31 (dd, J = 0.7, 1.5 Hz, 1H), 8.73 (dd, J = 0.7, 5.0 Hz, 1H); LC - MS (Method B; ESI, *m/z*) t_R = 0.96 min - 236 $(M+H)^+$; HRMS (Method C): found 236.0483; calculated for $C_{10}H_{10}N_3O_2S$ $(M+H)^+$ 236.0488.

Methyl 2-(2-benzamidothiazol-4-yl)isonicotinate (18): Methyl 2-(2-aminothiazol-4-yl)isonicotinate (0.020 g, 0.085 mmol, 1 equiv.) was dissolved in anhydrous CH_2Cl_2 (2 mL, 0.04 M). Triethylamine (0.01 g, 0.1 mmol, 1.2 equiv.) was added followed by benzoyl chloride (0.012 g, 0.085 mmol, 1 equiv.) and the mixture stirred for 2 h at room temperature. The volatiles were removed *in vacuo* and the residue purified by flash silica gel column chromatography eluting with 10% EtOAc in CH_2Cl_2. The target compound was obtained as a white powder (0.01g, 35%). ^{1}H NMR (500 MHz, $CDCl_3$) 4.01 (s, 3H), 7.51 (t, J = 7.4 Hz, 2H), 7.60 (t, J = 1.1 Hz, 1H), 7.78 (s, 1H), 7.84 (s, 1H), 7.96 (d, J = 7.5 Hz, 2H), 8.47 (s, 1H), 8.8 (s, 1H), 10.05 (br s, 1H); LC - MS (Method C; ESI, *m/z*) t_R = 1.62 min - 340 $(M+H)^+$.

2-(2-Benzamidothiazol-4-yl)isonicotinic acid (19): Methyl 2-(2-benzamidothiazol-4-yl)isonicotinate (0.010 g, 0.029 mmol) was dissolved in 50% THF in methanol (2 mL). To the stirred solution was added sodium hydroxide solution (3.75 M, 0.3 mL). After 1 h at room temperature, acetic acid (0.067 g, 1.125 mmol) was added and volatiles were removed *in vacuo*. The crude product was purified by flash silica gel column chromatography eluting with 15% methanol in EtOAc to afford the target compound as a white powder (0.0038 g, 40%). ^{1}H NMR (500 MHz, DMSO-d_6) 7.54 – 7.60 (m, 2H), 7.63 – 7.69 (m, 1H), 7.75 (dd, J

= 1.6, 4.9 Hz, 1H), 7.98 (s, 1H), 8.15 (dd, *J* = 1.3, 8.4 Hz, 2H), 8.58 (dd, *J* = 0.8, 1.6 Hz, 1H), 8.79 (dd, *J* = 0.9, 5.0 Hz, 1H), 12.85 (s, 1H); LC - MS (Method C; ESI, *m/z*) t_R = 1.37 min – 326 $(M+H)^+$; HRMS (Method B): found 326.0597; calculated for $C_{16}H_{12}N_3O_3S$ $(M+H)^+$ 326.0594.

Diethyl pyridine-2,4-dicarboxylate (27): Synthesis of this compound has been reported by Kojima et. al. *Chemistry A European Journal*, 2007, 13, 8212. *para*-Toluenesulfonic acid (11.37 g, 190.2 mmol, 1.03 equiv.) was added to a suspension of pyridine-2,4-dicarboxylic acid (5.27 g, 185.1 mmol, 1 equiv.) in ethanol (100 mL, 1.9 M) and the resulting suspension stirred at room temperature for 10 min. A colourless solution formed that was heated at 80 °C for 16 h. The ethanol was removed in vacuo, 60 mL water was added followed by 60 mL saturated sodium carbonate solution and the resulting suspension extracted with diethyl ether (3 × 80 mL). The organic layers were combined, dried over Na2SO4 and concentrated in vacuo to give the title compound as a colourless oil (5.00 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) 1.43 (t, J = 7.0 z, 3H), 1.46 (t, J = 7.0 Hz, 3H), 4.45 (q, J = 7.0 Hz, 2H), 4.51 (q, J = 7.0 Hz, 2H), 8.03 (dd, J = 5.0, 1.5 Hz, 1H), 8.64 (dd, J = 1.5, 1.0 Hz, 1H), 8.91 (dd, J = 5.0, 1.0 Hz, 1H).

Ethyl 2-formylisonicotinate (28): Synthesis reported by Queguiner *et al*. *Bulletin de la Société Chimique de France*, 1969, *10*, 3678. Diisobutylaluminum hydride (1 M in THF, 22.4 mL, 22.4 mmol, 1 equiv.) was added dropwise over 30 min to a solution of diethyl pyridine-2,4-dicarboxylate (5.00 g, 22.4 mmol, 1 equiv.) in toluene (150 mL, 0.15 M) at –78 °C under an atmosphere of nitrogen and the resulting solution stirred at –78 °C for 30 min. An additional equivalent of diisobutylaluminum hydride (22.4 mL, 22.4 mmol, 1 equiv.) was added dropwise over 10 min and the resulting solution stirred at –78 °C for a further 2 h. Acetic acid (10 mL) was added dropwise over 5 min followed by Et_2O (75 mL) and the reaction mixture allowed to warm to room temperature then filtered and washed with Et_2O (2

× 10 mL). The filtrate was concentrated *in vacuo* to give a yellow solid that was purified by flash column chromatography with a gradient of 25 to 50% Et_2O in cyclohexane to give the title compound as an off-white solid (1.56 g, 39%). ^{1}H NMR (400 MHz, $CDCl_3$) 1.44 (t, *J* = 7.0 Hz, 3H), 4.46 (q, *J* = 7.0 Hz, 2H), 8.10 (dd, *J* = 5.0, 1.5 Hz, 1H), 8.49 (app. s, 1H), 8.95 (d, *J* = 5.0 Hz, 1H), 10.15 (s, 1H). LC-MS: (Method L, ESI, *m/z*) t_R = 15.9 min; *m/z* 333 $(M+H)^+$.

Ethyl 2-((benzylamino)methyl)isonicotinate (29b): A solution of ethyl 2-formylisonicotinate (45 mg, 0.25 mmol) in CH_2Cl_2 (2 mL, 0.13 M) was added to benzylamine (42 µL, 0.38 mmol, 1.5 equiv.). Glacial acetic acid (1 drop) was added and the resulting suspension stirred at room temperature for 15 min. Sodium triacetoxyborohydride (80 mg, 0.38 mmol) was added and the resulting suspension stirred at room temperature for 16 h. The reaction mixture was diluted with water (5 mL), extracted with CH_2Cl_2 (2 × 5 mL), the organic layers combined, concentrated *in vacuo* and purified by flash column chromatography with a gradient of 0 to 8% MeOH in DCM, to give the title compound as a yellow oil (63 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) 1.43 (t, *J* = 7.0 Hz, 3H), 2.47 (s, 1H), 3.88 (s, 2H), 4.02 (s, 2H), 4.42 (q, *J* = 7.0 Hz, 2H), 7.24–7.41 (m, 5H), 7.74 (d, *J* = 5.0 Hz, 1H), 7.90 (s, 1H), 8.72 (d, *J* = 5.0 Hz, 1H). LC-MS: (Method C, ESI, *m/z*) t_R = 9.2 min – 271 $(M+H)^+$. HRMS (Method J): found: 271.1443, calculated for $C_{16}H_{19}N_2O_2$ $(M+H)^+$ 271.1441.

Lithium 2-((benzylamino)methyl)isonicotinate (30b): Lithium hydroxide (1 M, aq, 0.11 mL, 0.11 mmol, 1 equiv.) was added to a solution of ethyl 2-[(benzylamino)methyl]-isonicotinate (30 mg, 0.11 mmol, 1equiv.) in THF (0.6 mL, 0.18 M) and water (0.5 mL) and the resulting suspension stirred at room temperature for 16 h. The volatile components were evaporated, the residue washed with CH_2Cl_2 (3 × 1 mL) then dried *in vacuo* to give the title compound as a yellow gum (30 mg, quant.); ^{1}H NMR (400 MHz, MeOH-d_4) 3.80 (s, 2H), 3.93 (s, 2H), 7.21–7.39 (m, 5H), 7.69–7.73 (m, 1H), 7.87 (s, 1H), 8.52–8.55 (m, 1H),NH

signal not observed. LC-MS: (Method L, ESI, *m/z*) t_R = 7.9 min – 241 $(M–Li)^-$. HRMS (Method J): found: 265.0947, calculated for $C_{14}H_{14}N_2NaO_2$ $(M+H)^+$ 265.0947.

2-(((Furan-2-ylmethyl)amino)methyl)isonicotinic acid (30a): A solution of ethyl 2-formylisonicotinate (103 mg, 0.57 mmol) in dichloromethane (4 mL) was added to 2-aminomethylfuran (76 µL, 0.86 mmol), glacial acetic acid added (1 drop) and the resulting suspension was stirred at room temperature for 30 minutes. Sodium triacetoxyborohydride (180 mg, 0.86 mmol) was added and the resulting suspension stirred at room temperature overnight. The reaction mixture was diluted with water (15 mL), extracted with dichloromethane (2 x 10 mL), the organic layers combined, concentrated in vacuo and purified by flash column chromatography 1% MeOH in CH_2Cl_2 to give 2-(((furan-2-ylmethyl)amino)methyl)isonicotinic acid ethyl ester **29a** (147 mg, 99% yield). Lithium hydroxide (13 mg, 0.56 mmol) was added to a solution of the ester (147 mg, 0.56 mmol) in acetonitrile (1 mL) and water (1 mL) and the resulting suspension was stirred at room temperature overnight. Water (10mL) was added, washed with dichloromethane (3 x 5 mL) then dried in vacuo to give the title compound (140 mg, quant.). ^{1}H NMR (300 MHz, Methanol-d_4) 3.78 (s, 2H), 3.90 (s, 2H), 6.27 (d, J = 3.5 Hz, 1H), 6.34 (m, 1H), 7.43 (m, 1H), 7.70 (dd, J = 1.5, 5.0 Hz, 1H), 7.84 (app. S, 1H), 8.52 (d, J = 5.0 Hz, 1H); LC-HRMS (Method J): found 233.0923; calculated for $C_{12}H_{13}N_2O_3$ $(M+H)^+$ 233.0921.

8-(1-Ethoxyvinyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (38): To a mixture of 8-chloropyrido[3,4-*d*]pyrimidin-4(3*H*)-one (0.10 g, 0.55 mmol, 1 equiv.) and tributyl(1-ethoxyvinyl)stannane (0.234 g, 0.65 mmol, 1.2 equiv.) and 1,4-dioxane (2 mL, 0.28 M) was added tetrakis(triphenylphosphine)palladium (0.020 g, 0.017 mmol, 3 mol%). The reaction mixture was heated at reflux for 2 h under nitrogen. Anhydrous DMF (1 mL) was added to solubilise the reaction contents. LCMS revealed very slow reaction. After 4 h additional .

tetrakis(triphenylphosphine)palladium (0.05 g) and tributyl(1-ethoxyvinyl)stannane (0.05 g) were added to the reaction mixture. After 2 h, the reaction was cooled to room temperature and filtered through a pad of celite washing with EtOAc and the combined organics were dried and concentrated *in vacuo*. The residue was triturated with 50% Et_2O in hexane to afford a brown solid which was filtered and dried (0.076 g, 64%). ^{1}H NMR (500 MHz, DMSO-d_6) 1.28 (t, J = 7.0 Hz, 3H), 3.90 (q, J = 7.0 Hz, 2H), 4.54 (d, J = 2.2 Hz, 1H), 4.62 (d, J = 2.2 Hz, 1H), 7.96 (d, J = 5.1 Hz, 1H), 8.20 (s, 1H), 8.60 (d, J = 5.1 Hz, 1H), 12.7 (s br, 1H); LC - MS (Method C; ESI, *m/z*) t_R = 0.85 min - 190 [(M – C_2H_5) + H].

8-(2-Bromoacetyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (39): A mixture of 8-(1-ethoxyvinyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (0.070 g, 0.32 mmol, 1 equiv.) and 1-bromopyrrolidine-2,5-dione (0.057 g, 0.32 mmol, 1 equiv.) was suspended in 10% water in THF (5 mL). The reaction was stirred at room temperature for 1 h. Volatiles were removed *in vacuo* and the residue was taken up in EtOAc (20 mL) and water (20 mL). The organic solution was dried ($MgSO_4$) and concentrated *in vacuo*. The residue obtained was suspended in Et_2O (2 mL) to afford a brown powder, which was filtered and dried (0.062 g, 72%); ^{1}H NMR (500 MHz, DMSO-d_6) 4.98 (s, 2H), 8.16 (d, J = 5.1 Hz, 1H), 8.29 (s, 1H), 8.72 (d, J = 5.1 Hz, 1H), 12.80 (br s, 1H); LC - MS (Method C; ESI, *m/z*) t_R = 0.87 min – 268, 270 [$(M+H)^+$, Br isotopic pattern].

8-(2-Aminothiazol-4-yl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (40): A mixture of 8-(2-bromoacetyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (0.060 g, 0.224 mmol, 1 equiv.), thiourea (0.017 g, 0.224 mmol, 1 equiv.) and triethylamine (0.0224 g, 0.224 mmol, 1 equiv.) in ethanol (2 mL, 0.11 M) was heated at reflux for 1 h. Volatiles were removed in vacuo and the residue purified by flash silica gel column chromatography eluting with 10% methanol in EtOAc to give the product as a brown powder (7 mg, 13%). ^{1}H NMR (500 MHz, DMSO-d_6)

7.07 (br s, 2H), 7.74 (s, 1H), 7.84 (d, *J* = 5.0 Hz, 1H), 8.28 (s, 1 H), 8.61 (d, *J* = 5.0 Hz, 1H), 12.80 (br s, 1H); LC - MS (Method C; ESI, *m/z*) t_R = 0.55 min – 246 $(M + H)^+$; HRMS (Method B): found 246.0454; calculated for $C_{10}H_8N_5OS$ $(M+H)^+$ 246.0444.

8-(Thiazol-4-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (36): 8-Chloro-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (0.081 g, 0.26 mmol, 1 equiv.), silver oxide (0.063 g, 0.26 mmol, 1 equiv.) and tetrakis(triphenylphosphine)palladium (0.03 g, 0.026 mmol, 10 mol%) were suspended in anhydrous DMF (6 mL, 0.04 M) and heated at 100 ˚C under nitrogen for 5 min. 4-(Tributylstannyl)thiazole (0.110 g, 0.294 mmol, 1.1 equiv.) dissolved in anhydrous DMF (1 mL) was added and the reaction stirred for a further 2 h. The reaction was cooled to room temperature and diluted with EtOAc (20 mL) and washed with water (20 mL). The organic solution was dried and concentrated *in vacuo*. The crude product was purified by flash column chromatography eluting with 5% methanol in EtOAc. The residue obtained was further purified on an SCX cartridge eluting first with 50% methanol in chloroform followed by 7N ammonia in methanol. The solution was evaporated to afford the desired product as a yellow gum (0.03 g, 32%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.01 (s, 9H), 0.97 – 1.00 (m, 2H), 3.69 – 3.72 (m, 2H), 5.48 (s, 2H), 8.1 (d, *J* = 5.0 Hz, 1H), 8.31 (s, 1H), 8.81 (d, *J* = 2.0 Hz, 1H), 8.88 (d, *J* = 5.0 Hz, 1 H), 8.99 (d, *J* = 2.0 Hz, 1H); LC - MS (Method C; ESI, *m/z*) t_R = 1.48 min - 361 $(M+H)^+$.

8-(Thiazol-4-yl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (37): Following General Procedure 4, 8-(thiazol-4-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (0.030 g, 0.083 mmol) and hydrochloric acid (6 M, 1 mL) were reacted together in THF (1 mL) for 4 h. Purification was achieved by desalting on an isolute-NH_2 cartridge, eluting first with 50% methanol in chloroform followed by 10% [7N ammonia in methanol] in chloroform. The ammoniacal solution was concentrated *in vacuo*. Water (1 mL) was added to the residue and

a pink solid separated out which was filtered and dried (0.018 g, 94%); ^{1}H NMR (500 MHz, DMSO-d_6) 7.98 (d, J = 5.1 Hz, 1H), 8.29 (s, 1H), 8.63 (s, 1H), 8.73 (d, J = 5.1 Hz, 1H), 9.22 (s, 1H), 12.80 (br s, 1H); LC - MS (Method C; ESI, *m/z*) t_R = 0.72 min – 231 $(M+H)^+$; HRMS (Method B): found 231.034; calculated for $C_{10}H_7N_4OS$ $(M+H)^+$ 231.0335.

8-(1*H*-Pyrazol-3-yl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (41a): A microwave vial was charged with 8-chloropyrido[3,4-*d*]pyrimidin-4(3*H*)-one (35 mg, 0.193 mmol, 1 equiv.), palladium tetrakistriphenylphosphine (33 mg, 0.029 mmol, 15 mol%), saturated Na_2CO_3 (0.75 mL) and (1*H*-pyrazol-3-yl)boronic acid hydrochloride (57 mg, 0.386 mmol, 2 equiv.). The vial was sealed and backfilled with nitrogen. Previously degassed anhydrous DMA (2 mL) was added to the vial and the reaction was heated in a microwave reactor for 2 h at 100 ˚C. The yellow suspension was diluted with water and filtered. The filtrate was concentrated to dryness and purified by flash chromatography eluting with a gradient of 0 to 20% MeOH in CH_2Cl_2. The title compound was obtained as off-white powder (5 mg, 12%); ^{1}H NMR (400 MHz, DMSO-d_6) 7.36 (s, 1H), 7.65 (s, 1H), 7.92 (d, J=5.0 Hz, 1H), 8.31 (s, 1H), 8.69 (d, J = 5.0 Hz, 1H), 12.75 (br s, 1H), 13.54 (br s, 1H). LC-MS: (Method J, ESI, *m/z*) t_R = 1.12 min – 214 $(M+H)^+$. HRMS (Method J): found 214.0722; calculated for $C_{10}H_8N_5O$ $(M+H)^+$ 214.0723.

8-(1-Methyl-1*H*-pyrazol-3-yl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (41b): The title compound was synthesised as for compound **41a**, starting from 8-chloropyrido[3,4-*d*]pyrimidin-4(3*H*)-one (35 mg, 0.193 mmol, 1 equiv.), palladium tetrakistriphenylphosphine (33 mg, 0.029 mmol, 15 mol%), saturated Na_2CO_3 (0.75 mL) and 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (80 mg, 0.386 mmol, 2 equiv.). The compound was obtained as an off-white solid, (9 mg, 21%); ^{1}H NMR (400 MHz, DMSO-d_6) 3.96 (s, 3H), 7.13 (d, J = 2.1 Hz, 1H), 7.79 (d, J = 2.0 Hz, 1H), 7.90 (d, J= 5.0 Hz, 1H), 8.28 (s, 1H) , 8.66 (d, J= 5.1 Hz, 1H), 12.59 - 12.59 (m, 1H). LC-MS: (Method K, ESI, *m/z*) t_R =

1.53 min – 228 $(M+H)^+$. HRMS (Method J): found 228.0874; calculated for $C_{11}H_{10}N_5O$ $(M+H)^+$ 228.0880.

8-(1*H*-Pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (55): 8-Chloro-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-d]pyrimidin-4(3*H*)-one (0.070 g, 0.224 mmol, 1 equiv.), 1*H*-pyrazole (18.3 mg, 0.27 mmol) and cesium carbonate (146 mg, 0.45 mmol, 2 equiv.) were added to anhydrous acetonitrile (3 mL) in a microwave tube. The tube was sealed under nitrogen and the reaction was heated at 110 °C for 3h. The reaction was cooled to room temperature and diluted with EtOAc (20 mL) and water (20 mL). The organic solution was dried (Na_2SO_4) and concentrated *in vacuo*. The crude was purified by silica gel column chromatography eluting with neat EtOAc. The pure fractions afforded the product as a colorless oil (62 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.01 (s, 9H), 0.97 – 1.00 (m, 2H), 3.69 – 3.72 (m, 2H), 5.47 (s, 2H), 6.56 (t, J = 2.1 Hz, 1H), 7.92 (d, J = 1.4 Hz, 1H), 8.10 (d, J = 5.1 Hz, 1H), 8.32 (s, 1H), 8.66 (d, J = 5.1 Hz, 1H), 8.74 (d, J = 2.5 Hz, 1H); LC - MS (Method H; ESI, *m/z*) t_R = 1.4 min - 286 $(M+H)^+$.

8-(1*H*-Pyrazol-1-yl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (56): According to General Procedure 4, 8-(1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4*d*]pyrimidin-4(3*H*)-one (62.0 mg, 0.181 mmol) and hydrochloric acid (6 M, 1 mL) were reacted together in THF (1 mL). The crude product was purified by passing through an SCX cartridge eluting first with methanol followed by a solution of 7N ammonia in methanol. The ammoniacal solution was concentrated *in vacuo* and the residue triturated with Et_2O. The pale yellow powder was further purified on a short silica gel column eluting with 3% of 7 N ammonia/methanol solution in EtOAc to produce the title compound as a pale white powder (27 mg, 70%). ^{1}H NMR (500 MHz, DMSO-d_6) 6.56 (t, J = 2.1 Hz, 1H), 7.82 (s, 1H), 8.02 (d, J = 5.1 Hz, 1H), 8.28 (s, 1H), 8.53 (d, J = 2.2 Hz, 1H), 8.58 (d, J = 5.1 Hz, 1H), 12.81 (br s, 1H); HRMS (Method I): found 214.0737; calculated for $C_{10}H_8N_5O$ $(M+H)^+$ 214.0729.

8-Methylpyrido[3,4-*d*]pyrimidin-4(3*H*)-one (42): A 5 mL microwave vial was charged with potassium carbonate (226 mg, 1.636 mmol), palladium tetrakis(triphenylphosphine) (21 mg, 0.018 mmol) and 8-chloropyrido[3,4-*d*]pyrimidin-4(3*H*)-one (66 mg, 0.363 mmol). The vial was sealed and the air was replaced with nitrogen 3 times, then previously degassed DME (3 mL) was added with a syringe. To the yellowish suspension was added 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (0.203 mL, 1.454 mmol) with a syringe and the mixture turned dark yellow. The vial was heated in a microwave reactor at 90 °C for 6 h. The dark purple suspension was diluted with EtOAc (10 mL) and filtered through a celite pad. The filtrate was concentrated under reduced pressure and purified by flash chromatography on a Biotage Isolera one system eluting with a gradient of 2% to 20% MeOH in DCM. The product was isolated as an off-white powder (35 mg, 59%). ^{1}H NMR (400 MHz, DMSO-d_6) 2.76 (s, 3H), 7.79 (d, J = 5.3 Hz, 1H), 8.23 (s, 1H), 8.50 (d, J = 5.3 Hz, 1H), 12.60 (br s, 1H). LC-MS: (Method J; ESI, *m/z*) t_R = 0.35 min – 162 $(M+H)^+$.

4-Oxo-3,4-dihydropyrido[3,4-*d*]pyrimidine-8-carbaldehyde (43): Selenium dioxide (27.3 mg, 0.246 mmol, 1.2 equiv.) was added to a solution of 8-methylpyrido[3,4-*d*]pyrimidin-4(3*H*)-one (33 mg, 0.205 mmol, 1 equiv.) in 1,4-dioxane (5 mL, 0.04 M). The suspension was heated to 90 °C for 8 h. The reaction was cooled to room temperature and filtered through a celite pad. The filtrate was concentrated under reduced pressure and purified by flash chromatography on a Biotage Isolera one system, eluting with a gradient of 2 to 20% MeOH in CH_2Cl_2 to give the title compound as an off-white solid (5 mg, 14%); LC-MS: (Method J, ESI, *m/z*) t_R = 0.43 min – 176 $(M+H)^+$.

8-((Benzylamino)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (44a): Phenylmethanamine (0.021 mL, 0.188 mmol, 1.1 equiv.) was added to a suspension of 4-oxo-3,4-dihydropyrido[3,4-*d*]pyrimidine-8-carbaldehyde (0.030 g, 0.171 mmol, 1 equiv.) in a mixture of CH_2Cl_2:MeOH 2:1 (3 mL).The reaction was stirred at room temperature for 1.5 h then

sodium triacetoxyborohydride (0.051 g, 0.240 mmol, 1.4 equiv.) was added followed by one drop of acetic acid. The reaction was stirred for 2 h at room temperature. The solvents were evaporated under reduced pressure and the crude residue was purified by flash chromatography on Biotage Isolera One eluting with a gradient of 0 to 5% MeOH in CH_2Cl_2. The title compound was obtained as a white powder (25 mg, 55%); ^{1}H NMR (400 MHz, DMSO-d_6) 3.80 (s, 2H), 4.22 (s, 2H), 7.24 - 7.20 (m, 1H), 7.36 - 7.28 (m, 4H), 7.86 (d, J = 5.3 Hz, 1H), 8.22 (s, 1H), 8.59 (d, J = 5.1 Hz, 1H), NH signal not observed. LC-MS: (Method J, ESI, *m/z*) t_R = 1.01 min – 266 $[M+H]^+$; HRMS (Method J): found 267.1246; calculated for $C_{15}H_{15}N_4O$ 267.1240 $(M+H)^+$.

8-(((Furan-2-ylmethyl)amino)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (44b): The title compound was prepared with the same procedure for compound **44a**, starting with furan-2-ylmethanamine (0.021 g, 0.220 mmol), 4-oxo-3,4-dihydropyrido[3,4-d]pyrimidine-8-carbaldehyde (0.035 g, 0.200 mmol), sodium triacetoxyborohydride (0.059 g, 0.280 mmol) and CH_2Cl_2: MeOH 2:1 (3 mL). The product was obtained as a white powder (21 mg, 41%). ^{1}H NMR (400 MHz, DMSO-d_6) 3.17 (s,1H), 3.79 (s, 2H), 4.23 (s, 2H), 6.25 (d, J = 3.1 Hz, 1H), 6.38 - 6.35 (m, 1H), 7.54 (s, 1H), 7.85 (d, J = 5.3 Hz, 1H), 8.24 (s, 1H), 8.58 (d, J = 5.1 Hz, 1H), NH signal not observed. LC-MS: (Method J, ESI, *m/z*) t_R = 0.66 min – 257 $(M+H)^+$. HRMS (Method J): found 257.1027; calculated for $C_{13}H_{13}N_4O_2^+$ $(M+H)^+$ 257.1033.

8-((4-Methylpiperazin-1-yl)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (44c): The title compound was prepared with the same procedure for compound **44a**, starting with 1-methylpiperazine (0.019 ml, 0.171 mmol), 4-oxo-3,4-dihydropyrido[3,4-*d*]pyrimidine-8-carbaldehyde (0.030 g, 0.171 mmol), sodium triacetoxyborohydride (0.036 g, 0.171 mmol) and CH_2Cl_2: MeOH 2:1 (3 mL). The product was obtained as a pale yellow powder (10 mg, 22%). ^{1}H NMR (400 MHz, DMSO-d_6) 2.11 (s, 3H), 2.32 - 2.20 (m, 4H), 3.67 (s, 4H), 4.01 (s,

2H), 7.88 (d, *J* = 5.3 Hz, 1H), 8.24 (s, 1H), 8.59 (d, *J* = 5.1 Hz, 1H), NH signal not observed. LC-MS: (Method J, ESI, *m/z*) t_R = 0.35 min – 260 $(M+H)^+$; HRMS (Method J): found 260.1501; calculated for $C_{13}H_{18}N_5O$ $(M+H)^+$ 260.1506.

8-((Dimethylamino)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (44d): The title compound was prepared with the same procedure for compound **44a**, starting with dimethylamine hydrochloride (6.98 mg, 0.086 mmol), 4-oxo-3,4-dihydropyrido[3,4-*d*]pyrimidine-8-carbaldehyde (0.015 g, 0.086 mmol), triethylamine (0.012 mL, 0.086 mmol), sodium triacetoxyborohydride (0.018 g, 0.086 mmol) and MeOH (0.5 mL) the product was isolated as pale brown solid (2 mg, 12%). ^{1}H NMR (400 MHz, MeOH-d_4) 2.78 (s, 6H), 4.62 (s, 2H), 8.07 (d, J = 5.3 Hz, 1H), 8.22 (s, 1H), 8.69 (d, J = 5.1 Hz, 1H), NH signal not observed. LC-MS: (Method J, ESI, *m/z*) t_R = 0.32 min – 205.26 $(M+H)^+$; HRMS (Method J): found 205.1081; calculated for $C_{10}H_{13}N_4O$ $(M+H)^+$ 205.1084.

8-(Piperidin-1-ylmethyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (44e): The title compound was prepared with the same procedure for compound **44a**, starting with piperidine (0.012 mL, 0.118 mmol), 4-oxo-3,4-dihydropyrido[3,4-*d*]pyrimidine-8-carbaldehyde (0.023 g, 0.131 mmol), sodium triacetoxyborohydride (0.028 g, 0.131 mmol) and a mixture of CH_2Cl_2:MeOH 2:1 (1.5 mL). The crude residue was purified by preparative HPLC and the desired product was isolated as a brown solid (4 mg, 13%). ^{1}H NMR (400 MHz, DMSO-d_6) 1.36 - 1.32 (m, 2H), 1.48 - 1.41 (m, 4H), 2.49 - 2.45 (m, 4H), 3.98 (s, 2H), 7.86 (d, J = 5.3 Hz, 1H), 8.23 (s, 1H), 8.57 (d, J = 5.3 Hz, 1H), NH signal not observed. LC-MS: (Method K, ESI, *m/z*) t_R = 0.83 min – 245.16 $(M+H)^+$. HRMS (Method J): found 245.1394; calculated for $C_{13}H_{17}N_4O$ $(M+H)^+$ 245.1397.

8-((4-Phenylpiperazin-1-yl)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (44f): The title compound was prepared with the same procedure for compound **44a**, starting with 1-phenylpiperazine (0.030 mL, 0.194 mmol), 4-oxo-3,4-dihydropyrido[3,4-*d*]pyrimidine-8-carbaldehyde (0.034 g, 0.194 mmol), sodium triacetoxyborohydride (0.041 g, 0.194 mmol) and CH_2Cl_2:MeOH 2:1 (1.5 mL). The crude material was purified by preparative HPLC and the product was isolated as a brown solid (12 mg, 19%); ^{1}H NMR (400 MHz, DMSO) 2.68 (t, *J* = 4.9 Hz, 4H), 3.11 - 3.05 (m, 4H), 4.10 (s, 2H), 6.75 (t, *J* = 7.2 Hz, 1H), 6.89 (d, *J* = 7.9 Hz, 2H), 7.21 - 7.15 (m, 2H), 7.88 (d, *J* = 5.1 Hz, 1H), 8.26 (s, 1H), 8.59 (d, *J* = 5.3 Hz, 1H), NH signal not observed. LC-MS: (Method K, ESI, *m/z*) t_R =1.19 min - 322.41 $(M+H)^+$; HRMS (Method J): found 322.1659; calculated for $C_{18}H_{20}N_5O$ $(M+H)^+$ 322.1662.

8-((4-(Pyridin-2-yl)piperazin-1-yl)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (44g): The title compound was prepared using the same procedure as for compound **44a**, starting with 4-oxo-3,4-dihydropyrido[3,4-*d*]pyrimidine-8-carbaldehyde (0.029 g, 0.166 mmol), 1-(pyridin-2-yl)piperazine (0.025 ml, 0.166 mmol), sodium triacetoxyborohydride (0.035 g, 0.166 mmol) and a mixture of DCM:MeOH 2:1 (1.5 mL). ^{1}H NMR (400 MHz, DMSO-d_6) 2.63 (t, *J* = 5.0 Hz, 4H), 3.47 - 3.39 (m, 4H), 4.10 (s, 2H), 6.61 (dd, *J* = 5.1, 6.8 Hz, 1H), 6.78 (d, *J* = 8.7 Hz, 1H), 7.53 - 7.47 (m, 1H), 7.91 (d, *J* = 5.3 Hz, 1H), 8.09 (dd, *J* = 1.3, 4.9 Hz, 1H), 8.26 (s, 1H), 8.63 (d, *J* = 5.1 Hz, 1H), 12.58 - 12.58 (m, 1H). LC-MS: (Method K, ESI, *m/z*) t_R = 1.82 min - 323.26 $(M+H)^+$; HRMS (Method J): found 323.1611; calculated for $C_{17}H_{19}N_6O$ $(M+H)^+$ 323.1615.

4-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)-1*H*-pyrazole (intermediate for the synthesis of **59**): Prepared *via* the procedure described for **45** using *tert*-butylchlorodimethylsilane (1.24 g, 8.26 mmol, 1.05 equiv.), 1*H*-imidazole (0.562 g, 8.26 mmol, 1.1 equiv.) and 3-(1*H*-pyrazol-4-yl)propan-1-ol (0.992 g, 7.86 mmol, 1 equiv.) in DMF (9 mL, 0.9 M) to give the product as

a pale yellow oil (1.93 g, quant.); ^{1}H NMR (500 MHz, $CDCl_3$) 0.07 (s, 6H), 0.92 (s, 9H), 1.77-1.84 (m, 2H), 2.58 (t, *J* = 7.6 Hz, 2H), 3.66 (t, *J* = 6.4 Hz, 2H), 7.43 (s, 2H), 10.50 (br s, 1H); LC - MS (Method H; ESI, *m/z*) t_R = 1.52 min – 241 [$(M+H)^+$]; HRMS (Method I): found 241.1740; calculated for $C_{12}H_{25}N_2OSi$ $(M+H)^+$ 241.1736.

8-(4-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)-ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (intermediate for the synthesis of **59**): Prepared *via* the procedure described for **46** using cesium carbonate (606 mg, 1.860 mmol, 2 equiv.), 4-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-1*H*-pyrazole (447 mg, 1.860 mmol, 2 equiv.) and 8-chloro-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (290 mg, 0.930 mmol, 1 equiv.) in MeCN (6 mL, 0.15 M). Purification by KP-Sil snap cartridge (30% EtOAc in cyclohexane) gave the product as a pale yellow solid (193 mg, 40%); ^{1}H NMR (500 MHz, $CDCl_3$) 0.02 (s, 9H), 0.04 (s, 6H), 0.89 (s, 9H), 0.92-0.97 (m, 2H), 1.81 (m, 2H), 2.63 (t, *J* = 7.7 Hz, 2H), 3.64-3.69 (m, 4H), 5.43 (s, 2H), 7.72 (s, 1H), 8.01 (d, *J* = 5.1 Hz, 1H), 8.27 (s, 1H), 8.51 (br d, *J* = 0.7 Hz, 1H), 8.58 (d, *J* = 5.1 Hz, 1H); LC - MS (Method C; ESI, *m/z*) t_R = 1.88 min – 516 [$(M+H)^+$]; HRMS (Method B): found 516.2825; calculated for $C_{25}H_{42}N_5O_3Si_2$ $(M+H)^+$ 516.2821.

8-(4-(3-Hydroxypropyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)-pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (intermediate for the synthesis of **59**): Prepared *via* the procedure described for **47** using hydrochloric acid (1 M, 3 mL, 10 equiv.) 8-(4-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)-ethoxy)methyl)-pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (151.5 mg, 0.294 mmol) in MeOH (3 ml, 0.1 M) to give the product as a white solid (117 mg, 99%); ^{1}H NMR (500 MHz, $CDCl_3$) 0.01 (s, 9H), 0.94-0.99 (m, 2H), 1.88-1.95 (m, 2H), 2.68 (t, *J* = 7.7 Hz, 2H), 3.65-3.70 (m, 2H), 3.72 (t, *J* = 6.4 Hz, 2H), 5.45 (s, 2H), 7.74 (s, 1H), 8.04 (d, *J* = 5.1 Hz, 1H), 8.29 (s, 1H), 8.52 (s, 1H), 8.60

(d, J = 5.1 Hz, 1H), OH signal not observed; LC - MS (Method H; ESI, *m/z*) t_R = 1.34 min – 402 [$(M+H)^+$]; HRMS (Method I): found 402.1960; calculated for $C_{19}H_{28}N_5O_3Si$ $(M+H)^+$ 402.1961.

3-(1-(4-Oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)propyl methanesulfonate (intermediate for the synthesis of **59**): Prepared *via* the procedure used for **49d** using 8-(4-(3-hydroxypropyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (121.9 mg, 0.304 mmol, 1 equiv.), triethylamine (0.1 ml, 0.717 mmol, 2 equiv.) and methanesulfonic anhydride (79 mg, 0.455 mmol, 1.5 equiv.) in anhydrous CH_2Cl_2 (3 mL, 0.1 M) to give the product as a pale yellow oil, which was used without further purification; ^{1}H NMR (500 MHz, $CDCl_3$) 0.04 (s, 9H), 0.90-0.97 (m, 2H), 2.06 (quintet, J = 6.8 Hz, 2H), 2.70 (t, J = 7.4 Hz, 2H), 2.98 (s, 3H), 3.63-3.67 (m, 2H), 4.26 (t, J = 6.3 Hz, 2H), 5.42 (s, 2H), 7.71 (s, 1H), 8.02 (d, J = 5.0 Hz, 1H), 8.27 (s, 1H), 8.55 (s, 1H), 8.57 (d, J = 5.0 Hz, 1H); LC - MS (Method H; ESI, *m/z*) t_R = 1.37 min – 480 [$(M+H)^+$].

2-(1-(4-Oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)acetaldehyde (48): To a round bottomed flask was added 8-(4-(2-hydroxyethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (94.0 mg, 0.243 mmol, 1 equiv.) and the flask purged with argon followed by the addition of anhydrous CH_2Cl_2 (5 mL) and the mixture stirred for 5 min after which Dess-Martin Periodinane (154 mg, 0.364 mmol, 1.5 equiv.) was added in one portion. The mixture was stirred at room temperature until TLC analysis (10% MeOH/CH_2Cl_2) indicated complete consumption of starting material and saturated $Na_2S_2O_3$ solution (5 mL) and saturated $NaHCO_3$ solution (5 mL) was added and the mixture stirred vigorously for 30 min. The mixture was then extracted with CH_2Cl_2 (3 × 15 mL), the combined organic layers washed with saturated brine solution (10 mL), dried with Na_2SO_4, filtered and concentrated to afford

a viscous yellow oil which was used without further purification. Aldehyde signal in ^{1}H NMR was used as a diagnostic marker for product formation.

8-(4-(2-Hydroxyethyl)-1*H*-pyrazol-1-yl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (57): According to General Procedure 4, 8-(4-(2-((*tert*-butyldimethylsilyl)oxy)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (47.3 mg, 0.094 mmol) and hydrochloric acid (6 M, 1 mL) were reacted together in THF (1 mL). Purified on KP-Sil snap cartridge (20% EtOH in EtOAc) to give the product as a white solid (18.3 mg, 75%). ^{1}H NMR (500 MHz, MeOH-d_4) 2.84 (t, J = 6.4 Hz, 2H), 3.81 (t, J = 6.4 Hz, 2H), 7.94 (s, 1H), 8.05 (br d, J = 4.5 Hz, 1H), 8.64 (br s, 1H), 8.78 (s, 1H), 8.84 (br s, 1H), NH and OH signals not observed; LC - MS (Method H; ESI, *m/z*) t_R = 0.69 min – 258 [$(M+H)^+$; HRMS (Method I): found 258.0995; calculated for $C_{12}H_{12}N_5O_2$ $(M+H)^+$ 258.0991.

8-(4-(2-(Dimethylamino)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)-pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (49a): According to General Procedure 1, cesium carbonate (113 mg, 0.346 mmol), 2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4yl)-ethyl methanesulfonate (53.7 mg, 0.115 mmol) and dimethylamine (0.231 mL, 0.461 mmol, 2M in THF) were reacted together in anhydrous DMF (1 mL). Purified on KP-Sil snap cartridge (50% EtOH in CH_2Cl_2) to give the product as a pale yellow oil (40.3 mg, 84%); ^{1}H NMR (500 MHz, $CDCl_3$) 0.02 (s, 9H), 0.96-1.02 (m, 2H), 2.33 (s, 6H), 2.57-2.63 (m, 2H), 2.75-2.81 (m, 2H), 3.67-3.73 (m, 2H), 5.47 (s, 2H), 7.79 (s, 1H), 8.07 (d, J = 5.1 Hz, 1H), 8.32 (s, 1H), 8.56 (s, 1H), 8.63 (d, J = 5.1 Hz, 1H).

8-(4-(2-(Dimethylamino)ethyl)-1*H*-pyrazol-1-yl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (52a): According to General Procedure 4, 8-(4-(2-(dimethylamino)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (54 mg, 0.130 mmol) and

hydrochloric acid (6 M, 1.5 mL) were reacted together in THF (1.5 mL). Purification by HPLC then SCX column gave the product as a white solid (1.5 mg, 4%). ^{1}H NMR (500 MHz, MeOH-d_4) 2.44 (s, 6H), 2.75-2.81 (m, 2H), 2.82-2.88 (m, 2H), 7.80 (s, 1H), 8.06 (d, J = 5.1 Hz, 1H), 8.27 (s, 1H), 8.54 (d, J = 5.1 Hz, 1H), 8.74 (br d, J = 0.6 Hz, 1H), NH signal not observed; LC - MS (Method H; ESI, *m/z*) t_R = 0.39 min – 285 [$(M+H)^+$]; HRMS (Method B): found 285.1454; calculated for $C_{14}H_{17}N_6O$ $(M+H)^+$ 285.1458.

8-(4-(2-(Pyrrolidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)-pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (49b): According to General Procedure 1, cesium carbonate (189 mg, 0.580 mmol), 2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)ethyl methanesulfonate (90 mg, 0.193 mmol) and pyrrolidine (0.05 mL, 0.605 mmol) were reacted together in anhydrous DMF (2 mL). Purification on a KP-NH snap cartridge (4% EtOH in CH_2Cl_2) gave the product as a pale yellow oil (69.1 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.01 (s, 9H), 0.96-1.01 (m, 2H), 1.81-1.85 (m, 4H), 2.58-2.64 (m, 4H), 2.74-2.79 (m, 2H), 2.80-2.85 (m, 2H), 3.67-3.72 (m, 2H), 5.47 (s, 2H), 7.79 (s, 1H), 8.06 (d, J = 5.1 Hz, 1H), 8.32 (s, 1H), 8.55 (s, 1H), 8.63 (d, J = 5.1 Hz, 1H); LC - MS (Method H; ESI, *m/z*) t_R = 1.09 min – 441 [$(M+H)^+$]; HRMS (Method B): found 441.2415; calculated for $C_{22}H_{33}N_6O_2Si$ $(M+H)^+$ 441.2429.

8-(4-(2-(Pyrrolidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (52b): According to General Procedure 4, 8-(4-(2-(pyrrolidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (14 mg, 0.032 mmol) and hydrochloric acid (6 M, 0.35 mL) were reacted together in THF (0.35 mL). Purification by SCX column gave the product as a pale yellow solid (9.0 mg, 91%). ^{1}H NMR (500 MHz, MeOH-d_4) 1.92-1.96 (m, 4H), 2.88-2.94 (m, 6H), 3.00-3.05 (m, 2H), 7.78 (s, 1H), 8.00 (d, J = 5.1 Hz, 1H), 8.25 (s, 1H), 8.45 (d, J = 5.1 Hz, 1H), 8.73 (s, 1H), NH signal not observed;

LC - MS (Method H; ESI, *m/z*) t_R = 0.45 min – 311 [$(M+H)^+$]; HRMS (Method I): found 311.1623; calculated for $C_{16}H_{19}N_6O$ $(M+H)^+$ 311.1620.

8-(4-(2-(Piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)-pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (49c): According to General Procedure **3**, 2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)acetaldehyde (56 mg, 0.145 mmol), piperidine (19 mg, 0.218 mmol) and sodium triacetoxyborohydride (49 mg, 0.232 mmol) were reacted together in 1,2-dichloroethane (4 mL). Following workup procedure A, the title compound was obtained (16 mg, 24%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) 0.02 (s, 9H), 0.96-1.02 (m, 2H), 1.41-1.52 (m, 2H), 1.58-1.67 (m, 4H), 1.69-1.77 (m, 2H), 2.44-2.54 (m, 2H), 2.60-2.65 (m, 2H), 2.78-2.83 (m, 2H), 3.67-3.72 (m, 2H), 5.48 (s, 2H), 7.79 (s, 1H), 8.07 (d, *J* = 5.1 Hz, 1H), 8.32 (s, 1H), 8.55 (s, 1H), 8.62 (d, *J* = 5.1 Hz, 1H); LC- HRMS (Method I) t_R = 2.29 min, HRMS: Found 455.2589 Calculated for $C_{23}H_{35}N_6O_2Si$ [$(M+H)^+$]. 455.2591.

8-(4-(2-(Piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (52c): According to General Procedure **5** 8-(4-(2-(piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (16 mg, 0.035 mmol) was reacted with HCl in 1,4-dioxane (4 M, 0.22 mL, 0.880 mmol) in 1,4 dioxane/water at 50 ^{o}C for 12 hours. After workup and flash column chromatography the product was obtained (7 mg, 61%) as a beige solid. ^{1}H NMR (500 MHz, DMSO- d_6) 1.33-1.46 (m, 2H), 1.65-1.75 (m, 2H), 1.78-1.90 (m, 4H), 2.84-2.95 (m, 2H), 3.03-3.08 (m, 2H), 3.25-3.29 (m, 2H), 7.77 (s, 1H), 8.02 (d, *J* = 4.8 Hz, 1H), 8.29 (s, 1H), 8.47 (s, 1H), 8.56 (d, *J* = 5.1 Hz, 1H), 12.80 (br s, 1H); LC- HRMS (Method I) t_R = 0.89 min - HRMS: Found 325.1777 Calculated for $C_{17}H_{21}N_6O$ [$(M+H)^+$] 325.1777.

8-(4-(2-((3,4-Dichlorobenzyl)(methyl)amino)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (49e): During the course of the mesylate displacement reaction using General Method 1, SEM-deprotection began to occur. The reaction mixture was subjected to aqueous work-up as detailed in General Method 1 and used without further purification as the combined material.

8-(4-(2-((3,4-Dichlorobenzyl)(methyl)amino)ethyl)-1*H*-pyrazol-1-yl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (52e): According to General Procedure 4, 8-(4-(2-((3,4-dichlorobenzyl)(methyl)amino)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl-)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (137 mg, 0.245 mmol) and hydrochloric acid (6 M, 3 mL) were reacted together in THF (3 mL). Purified on KP-NH snap cartridge (25% EtOH in CH_2Cl_2) to give the product as a white solid (9.4 mg, 9% from mesylate). ^{1}H NMR (500 MHz, MeOH-d_4) 2.38 (s, 3H), 2.78 (t, J = 7.2 Hz, 2H), 2.86 (t, J = 7.2 Hz, 2H), 3.66 (s, 2H), 7.27 (dd, J = 8.3, 1.9 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.51 (d, J = 1.9 Hz, 1H), 7.77 (s, 1H), 8.05 (d, J = 5.1 Hz, 1H), 8.23 (s, 1H), 8.56 (d, J = 5.1 Hz, 1H), 8.72 (s, 1H), NH signal not observed; LC - MS (Method H; ESI, *m/z*) t_R = 0.96 min – 429, 431 [$(M+H)^+$, Cl isotopic pattern]; HRMS (Method I): found 429.0992; calculated for $C_{20}H_{19}Cl_2N_6O$ $(M+H)^+$ 429.0997.

8-(4-(2-(Methyl(4-(methylsulfonyl)benzyl)amino)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (49f): According to General Procedure 2, triethylamine (0.04 mL, 0.287 mmol), 2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)-ethyl methanesulfonate (64.2 mg, 0.138 mmol) and *N*-methyl-1-(4-(methylsulfonyl)phenyl)methanamine (33.0 mg, 0.165 mmol) were reacted together in anhydrous DMF (1 mL). Purification on a KP-Sil snap cartridge (4% EtOH in CH_2Cl_2) gave the product as a pale yellow oil (18.2 mg, 23%); ^{1}H NMR (500 MHz, $CDCl_3$) 0.01 (s, 9H),

0.95-1.01 (m, 2H), 2.33 (s, 3H), 2.69 (t, *J* = 7.3 Hz, 2H), 2.80 (t, *J* = 7.3 Hz, 2H), 3.04 (s, 3H), 3.65 (s, 2H), 3.68-3.72 (m, 2H), 5.48 (s, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.77 (s, 1H), 7.85 (d, *J* = 8.3 Hz, 2H), 8.07 (d, *J* = 5.1 Hz, 1H), 8.30 (s, 1H), 8.53 (s, 1H), 8.63 (d, *J* = 5.1 Hz, 1H); LC - MS (Method H; ESI, *m/z*) t_R = 1.06 min – 569 [$(M+H)^+$]; HRMS (Method I): found 569.2372; calculated for $C_{27}H_{37}N_6O_4SSi$ $(M+H)^+$ 569.2366.

8-(4-(2-(Methyl(4-(methylsulfonyl)benzyl)amino)ethyl)-1*H*-pyrazol-1-yl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (52f): According to General Procedure 4, 8-(4-(2-(methyl(4-(methylsulfonyl)benzyl)amino)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)-pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (17.5 mg, 0.031 mmol) and hydrochloric acid (6 M, 0.4 mL) were reacted together in THF (0.4 mL). Purified on KP-NH snap cartridge (40% EtOH in CH_2Cl_2) to give the product as a white solid (13.1 mg, 97%); ^{1}H NMR (500 MHz, DMSO-d_6) 2.22 (s, 3H), 2.64 (t, *J* = 7.4 Hz, 2H), 2.74 (t, *J* = 7.4 Hz, 2H), 3.19 (s, 3H), 3.66 (s, 2H), 7.56 (d, *J* = 8.1 Hz, 2H), 7.69 (s, 1H), 7.85 (d, *J* = 8.1 Hz, 2H), 7.98 (d, *J* = 5.1 Hz, 1H), 8.28 (s, 1H), 8.40 (s, 1H), 8.55 (d, *J* = 5.1 Hz, 1H), 12.81 (br s, 1H); LC - MS (Method H; ESI, *m/z*) t_R = 0.54 min – 439 [$(M+H)^+$]; HRMS (Method I): found 439.1558; calculated for $C_{21}H_{23}N_6O_3S$ $(M+H)^+$ 439.1552.

4-((Methyl(2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)ethyl)amino)methyl)benzonitrile (49g): According to General Procedure 2, triethylamine (0.057 mL, 0.406 mmol), 2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)-ethyl methanesulfonate (94.6 mg, 0.203 mmol) and 4-((methylamino)methyl)benzonitrile (59.4 mg, 0.406 mmol) were reacted together in anhydrous DMF (1 mL). Purified on KP-Sil snap cartridge (5% EtOH in CH_2Cl_2) to give the product as a pale yellow oil (42.6 mg, 41%); ^{1}H NMR (500 MHz, $CDCl_3$) 0.01 (s, 9H), 0.96-1.00 (m, 2H), 2.29 (s, 3H), 2.69 (t, *J* = 7.4 Hz, 2H), 2.79 (t, *J* = 7.4 Hz, 2H), 3.61 (s, 2H), 3.67-3.72 (m, 2H), 5.47 (s, 2H), 7.43 (d, *J* = 8.1

Hz, 2H), 7.58 (d, *J* = 8.1 Hz, 2H), 7.78 (s, 1H), 8.07 (d, *J* = 5.1 Hz, 1H), 8.30 (s, 1H), 8.52 (s, 1H), 8.63 (d, *J* = 5.1 Hz, 1H); LC - MS (Method H; ESI, *m/z*) t_R = 1.11 min – 516 [$(M+H)^+$]; HRMS (Method I): found 516.2543; calculated for $C_{27}H_{34}N_7O_2Si$ $(M+H)^+$ 516.2543.

4-((Methyl(2-(1-(4-oxo-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)ethyl)amino)methyl)benzonitrile (52g): According to General Procedure 4, 4-((methyl(2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)ethyl)amino)methyl)benzonitrile (12.9 mg, 0.025 mmol) and hydrochloric acid (6M, 0.25 mL) were reacted together in THF (0.25 mL). Purification on a KP-NH snap cartridge (40% EtOH in CH_2Cl_2) gave the product as a white solid (3.5 mg, 36%); ^{1}H NMR (500 MHz, MeOH-d_4) 2.33 (s, 3H), 2.71 (t, *J* = 7.4 Hz, 2H), 2.84 (t, *J* = 7.4 Hz, 2H), 3.68 (s, 2H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.64-7.67 (m, 2H), 7.75 (s, 1H), 8.06 (d, *J* = 5.1 Hz, 1H), 8.25 (s, 1H), 8.56 (d, *J* = 5.1 Hz, 1H), 8.70 (s, 1H), NH signal not observed; LC - MS (Method H; ESI, *m/z*) t_R = 0.61 min – 386 [$(M+H)^+$]; HRMS (Method I): found 386.1743; calculated for $C_{21}H_{20}N_7O$ $(M+H)^+$ 386.1729.

4-((Methyl(3-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)propyl)amino)methyl)benzonitrile (intermediate for the synthesis of **59):** According to General Procedure 2, triethylamine (0.05 mL, 0.359 mmol), 3-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)propyl methanesulfonate (50.8 mg, 0.106 mmol) and 4-((methylamino)methyl)benzonitrile (31.0 mg, 0.212 mmol) were reacted together in anhydrous DMF (1 mL). Purified on KP-Sil snap cartridge (3% EtOH in CH_2Cl_2) to give the product as a pale yellow oil (9.5 mg, 17%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.02 (s, 9H), 0.97-1.02 (m, 2H), 1.88 (quintet, *J* = 7.3 Hz, 2H), 2.23 (s, 3H), 2.47 (t, *J* = 7.3 Hz, 2H), 2.64 (t, *J* = 7.3 Hz, 2H), 3.56 (s, 2H), 3.68-3.73 (m, 2H), 5.48 (s, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.59-7.62 (m, 2H), 7.76 (s, 1H), 8.08 (d, *J* = 5.1 Hz, 1H), 8.30 (s, 1H), 8.48 (s, 1H), 8.64 (d, *J* = 5.1 Hz,

1H); LC - MS (Method H; ESI, *m/z*) t_R = 1.13 min – 530 [$(M+H)^+$]; HRMS (Method I): found 530.2703; calculated for $C_{28}H_{36}N_7O_2Si$ $(M+H)^+$ 530.2700.

4-((Methyl(3-(1-(4-oxo-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)propyl)amino)methyl)benzonitrile (59): According to General Procedure 4, 4-((methyl(3-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]-pyrimidin-8-yl)-1*H*-pyrazol-4-yl)propyl)amino)methyl)benzonitrile (7.2 mg, 0.014 mmol) and hydrochloric acid (6 M, 0.2 mL) were reacted together in THF (0.2 mL). Purified on KP-NH snap cartridge (40% EtOH in CH_2Cl_2) to give the product as a white solid (3.7 mg, 68%). ^{1}H NMR (500 MHz, MeOH-d_4) 1.90 (quintet, *J* = 7.3 Hz, 2H), 2.27 (s, 3H), 2.48 (t, *J* = 7.3 Hz, 2H), 2.64 (t, *J* = 7.3 Hz, 2H), 3.62 (s, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.63-7.66 (m, 2H), 7.72 (s, 1H), 8.05 (d, *J* = 5.1 Hz, 1H), 8.23 (s, 1H), 8.56 (d, *J* = 5.1 Hz, 1H), 8.62 (br d, *J* = 0.6 Hz, 1H), NH signal not observed; LC - MS (Method H; ESI, *m/z*) t_R = 0.64 min – 400 [$(M+H)^+$]; HRMS (Method I): found 400.1887; calculated for $C_{22}H_{22}N_7O$ $(M+H)^+$ 400.1886.

8-(4-(2-(4-(4-Chlorobenzyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)-ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (50a): According to General Procedure 2, 2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)ethyl methanesulfonate (100 mg, 0.215 mmol), 4-(4-chlorobenzyl)piperidine (67.6 mg, 0.322 mmol) and triethylamine (43 mg, 0.43 mmol) were reacted together in anhydrous DMF (1 mL) for 18 h. Purification by flash column chromatography eluting with 5% 7N ammonia in methanol in CH_2Cl_2 gave the title compound as a colorless oil (52 mg, 42%); ^{1}H NMR (500 MHz, $CDCl_3$) 0.03 (s, 9H), 0.96 – 0.99 (m, 2H), 1.33 – 1.41 (m, 2H), 1.42 – 1.56 (m, 1H), 1.63 – 1.68 (m, 2H), 1.97 – 2.03 (m, 2H), 2.51 (d, *J* = 7.1 Hz, 2H), 2.65 (t, *J* = 7.3 Hz, 2H), 2.80 (t, *J* = 8.5 Hz, 2H), 3.02 (d, *J* = 11.0 Hz, 2H), 3.67 – 3.71 (m, 2H), 5.46 (s, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.77 (s, 1H), 8.05 (d, *J* = 5.1

Hz, 1H), 8.30 (s, 1H), 8.54 (s, 1H), 8.61 (d, *J* = 5.1 Hz, 1H); LC - MS (Method H); ESI, *m/z*) t_R = 1.3 min - 579 $(M+H)^+$.

8-(4-(2-(4-(4-Chlorobenzyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)pyrido[3,4-*d*]-pyrimidin-4(3*H*)-one (53a): According to General Procedure 4, 8-(4-(2-(4-(4-Chlorobenzyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)-pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (52.0 mg, 0.09 mmol) and hydrochloric acid (6 M, 1 mL) were reacted together in THF (1 mL) for 4h. Purification by passing through an SCX cartridge eluting first with methanol and then with 7N ammonia in methanol followed by concentration of the ammoniacal solution *in vacuo* gave a solid residue that was triturated with Et_2O. The pale yellow powder obtained was filtered and dried (36 mg, 89 %). ^{1}H NMR (500 MHz, DMSO-d_6) 1.18 – 1.26 (m, 2H), 1.49 – 1.57 (m, 4H), 2.01 – 2.05 (m, 2H), 2.57 – 2.65 (m, 3H), 2.69 (t, *J* = 7.7 Hz, 2H), 2.96 -3.02 (m, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.70 (s, 1H), 7.98 (d, *J* = 5.1 Hz, 1H), 8.28 (s, 1H), 8.40 (s, 1H), 8.55 (d, *J* = 5.1 Hz, 1H), 12.4 (br s, 1H); LC - MS (Method A; ESI, *m/z*) t_R = 1.96 min -449 $(M+H)^+$; HRMS (Method I): found 449.1849; calculated for $C_{24}H_{25}ClN_6O$ $(M+H)^+$ 449.1856.

8-(4-(2-(4-Benzylpiperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)-methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (50b): According to General Procedure 1, 2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)ethyl methanesulfonate (121 mg, 0.26 mmol), 4-benzylpiperidine (52.6 mg, 0.3 mmol) and cesium carbonate (98 mg, 0.3 mmol) were reacted together in anhydrous DMF (2 mL). Purification by flash column chromatography eluting with 7% 7 N ammonia in methanol in CH_2Cl_2 gave the title compound as a yellow solid (51 mg, 36 %). ^{1}H NMR (500 MHz, $CDCl_3$) 0.01 (s, 9H), 0.96 – 0.99 (m, 2H), 1.35 – 1.42 (m, 2H), 1.50 – 1.58 (m, 1H), 1.66 – 1.69 (m, 2H), 2.01 – 2.05 (m, 2H), 2.55 (d, *J* = 7.0 Hz, 2H), 2.67 (t, *J* = 7.2 Hz, 2H), 2.83 (t, *J* = 8.5 Hz, 2H), 3.04 (d, *J* = 11.0 Hz, 2H), 3.70 – 3.72 (m, 2H), 5.46 (s, 2H), 7.14 –

7.20 (m, 3H), 7.25 – 7.29 (m, 2H), 7.76 (s, 1H), 8.04 (d, *J* = 5.1 Hz, 1H), 8.30 (s, 1H), 8.57 (s, 1H), 8.60 (d, *J* = 5.1 Hz, 1H); LC - MS (Method C); ESI, *m/z*) t_R = 1.40 min - 545 $(M+H)^+$.

8-(4-(2-(4-Benzylpiperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)pyrido[3,4-d]pyrimidin-4(3*H*)-one (53b): According to General Procedure 4, 8-(4-(2-(4-benzylpiperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (51 mg, 0.094 mmol) and hydrochloric acid (6 M, 1 mL) were reacted together in THF (1 mL). This was purified by passing through an SCX cartridge eluting first with methanol followed by 7N ammonia in methanol. The ammoniacal solution was concentrated *in vacuo* and the residue triturated with Et_2O. The cream powder obtained was filtered and dried (28 mg, 72%). ^{1}H NMR (500 MHz, DMSO-d_6) 1.16 – 1.25 (m, 2H), 1.46 – 1.58 (m, 4H), 1.88 – 1.95 (m, 2H), 2.57 – 2.65 (m, 3H), 2.65 (t, *J* = 7.7 Hz, 2H), 2.92 – 2.96 (m, 2H), 7.15 – 7.19 (m, 3H), 7.26 – 7.29 (m, 2H), 7.69 (s, 1H), 7.97 (d, *J* = 5.1 Hz, 1H), 8.28 (s, 1H), 8.39 (s, 1H), 8.54 (d, *J* = 5.1 Hz, 1H), 12.33 (br s, 1H); HRMS (Method I): found 415.2244 ; calculated for $C_{24}H_{27}N_6O$ $(M+H)^+$ 415.2246.

8-(4-(2-(4-(4-Fluorobenzyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)-ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (50c): According to General Procedure 2, 2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)ethyl methanesulfonate (51.0 mg, 0.11 mmol), 4-(4-fluorobenzyl)piperidine (31.8 mg, 0.164 mmol) and triethylamine (22 mg, 0.22 mmol) were reacted together in anhydrous DMF (1 mL) for 18 h. Purification by flash column chromatography eluting with 5% 7N ammonia in methanol in CH_2Cl_2 gave the title product as a colorless oil (26 mg, 42%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.01 (s, 9H), 0.96 – 0.99 (m, 2H), 1.38 – 1.44 (m, 2H), 1.50 – 1.57 (m, 1H), 1.62 – 1.66 (m, 2H), 2.02 – 2.06 (m, 2H), 2.53 (d, *J* = 7.0 Hz, 2H), 2.71 (t, *J* = 7.3 Hz, 2H), 2.83 (t , *J* = 8.5 Hz, 2H), 3.07 (d, *J* = 10.6 Hz, 2H), 3.67 – 3.73 (m, 2H),

5.46 (s, 2H), 6.94 – 6.98 (m, 2H), 7.08 – 7.11 (m, 2H), 7.77 (s, 1H), 8.05 (d, *J* = 5.1 Hz, 1H), 8.30 (s, 1H), 8.56 (s, 1H), 8.61 (d, *J* = 5.1 Hz, 1H); LC - MS (Method H); ESI, *m/z*) t_R = 1.28 min - 563 $(M+H)^+$.

8-(4-(2-(4-(4-Fluorobenzyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)pyrido[3,4-*d*]-pyrimidin-4(3*H*)-one (53c): According to General Procedure 4, 8-(4-(2-(4-(4-fluorobenzyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)-pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (26.0 mg, 0.046 mmol) and hydrochloric acid (6 M, 1 mL) were reacted together in THF (1 mL) for 4h. This was purified by passing through an SCX cartridge eluting first with methanol followed by 7N ammonia in methanol. The ammoniacal solution was concentrated *in vacuo* and the residue triturated with Et_2O. The beige powder obtained was filtered and dried (15 mg, 75 %). ^{1}H NMR (500 MHz, DMSO-d_6) 1.19 – 1.25 (m, 2H), 1.48 – 1.57 (m, 3H), 1.98 – 2.03 (m, 2H), 2.56 – 2.63 (m, 2H), 2.68 (t, *J* = 7.7 Hz, 2H), 2.96 (d , *J* = 10.5 Hz, 2H), 3.37 – 3.40 (m, 2H), 7.07 – 7.11 (m, 2H), 7.18 – 7.21 (m, 2H), 7.70 (s, 1H), 7.98 (d, *J* = 5.1 Hz, 1H), 8.28 (s, 1H), 8.39 (s, 1H), 8.54 (d, *J* = 5.1 Hz, 1H), 12.50 (br s, 1H); LC - MS (Method H); ESI, *m/z*) t_R = 0.90 min - 433 $(M+H)^+$; HRMS (Method I): found 433.2146; calculated for $C_{24}H_{26}FN_6O$ $(M+H)^+$ 433.2152.

8-(4-(2-(4-(4-(Trifluoromethyl)benzyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (50d): According to General Procedure 2, 2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido-[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)ethyl methanesulfonate (51.0 mg, 0.11 mmol), 4-(4-(trifluoromethyl)benzyl)piperidine (40.0 mg, 0.164 mmol) and triethylamine (22 mg, 0.22 mmol) were reacted together in anhydrous DMF (1 mL) for 18 h. Purification by flash column chromatography eluting with 5% [7N ammonia in methanol] in CH_2Cl_2 gave the title product as a colorless oil (31 mg, 46%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.01 (s, 9H), 0.97 – 1.00 (m, 2H), 1.42 – 1.52 (m, 2H), 1.59 – 1.64 (m, 1H), 1.66 – 1.69 (m, 2H), 2.07 – 2.10 (m,

2H), 2.63 (d, *J* = 7.0 Hz, 2H), 2.68 – 2.72 (m, 2H), 2.83 – 2.86 (m, 2H), 3.08 – 3.11 (m, 2H), 3.68 – 3.72 (m, 2H), 5.47 (s, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.78 (s, 1H), 8.06 (d, *J* = 5.1 Hz, 1H), 8.31 (s, 1H), 8.57 (s, 1H), 8.62 (d, *J* = 5.1 Hz, 1H); LC - MS (Method C; ESI, *m/z*) t_R = 1.40 min - 613 $(M+H)^+$.

8-(4-(2-(4-(4-(Trifluoromethyl)benzyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (53d): According to General Procedure 4, 8-(4-(2-(4-(4-(trifluoromethyl)benzyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)-methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (31.0 mg, 0.051 mmol) and hydrochloric acid (6 M, 1 mL) were reacted together in THF (1 mL) for 4 h. Purification by passing through an SCX cartridge eluting first with methanol followed by 7N ammonia in methanol. The ammoniacal solution was concentrated *in vacuo* and the residue triturated with Et_2O. The white powder obtained was filtered and dried (15 mg, 62%); ^{1}H NMR (500 MHz, MeOH-d_4) 1.37 – 1.44 (m, 2H), 1.68 – 1.74 (m, 3H), 2.18 – 2.23 (m, 2H), 2.69 (d, *J* = 6.5 Hz, 2H), 2.74 – 2.77 (m, 2H), 2.85 – 2.87 (m, 2H), 3.13 – 3.16 (m, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.70 (s, 1H), 7.98 (d, *J* = 5.1 Hz, 1H), 8.28 (s, 1H), 8.40 (s, 1H), 8.55 (d, *J* = 5.1 Hz, 1H), 12.4 (br s, 1H); HRMS (Method I): found 483.2116; calculated for $C_{25}H_{26}F_3N_6O$ $(M+H)^+$ 483.2120.

8-(4-(2-(4-(3,4-Dichlorobenzyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (50e): According to general procedure 3, 2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)acetaldehyde (92 mg, 0.239 mmol), 4-(3,4-dichlorobenzyl)piperidine (87 mg, 0.358 mmol) and sodium triacetoxyborohydride (81 mg, 0.382 mmol) were reacted together in 1,2-dichloroethane (4 mL). Following workup procedure B, the title compound was obtained (63 mg, 43%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) 0.02 (s, 9H), 0.79 (m, 1H), 0.95-1.00 (m, 2H), 1.19-1.32 (m, 3H), 1.58-1.83

(m, 5H), 2.02 (s, 2H), 2.38-2.48 (m, 1H), 2.54 (d, *J* = 6.7 Hz, 2H), 3.44 (br s, 1H), 3.46 (br s, 1H), 3.66-3.72 (m, 2H), 5.45 (s, 2H), 6.96 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.23 (d, *J* = 2.0 Hz, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.75 (s, 1H), 8.06 (d, *J* = 5.1 Hz, 1H), 8.30 (s, 1H), 8.60 (d, *J* = 5.1 Hz, 1H), 8.63 (s, 1H); LC- HRMS (Method I) t_R = 2.86 min - HRMS: Found 613.2294 (Cl isotopic pattern); Calculated for $C_{30}H_{39}Cl_2N_6O_2Si$ $[(M+H)^+]$ 613.2281.

8-(4-(2-(4-(3,4-Dichlorobenzyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)pyrido[3,4-*d*]-pyrimidin-4(3*H*)-one (53e): According to general procedure 5 8-(4-(2-(4-(3,4-dichlorobenzyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)-pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (39 mg, 0.064 mmol) was reacted with HCl in 1,4-dioxane (4 M, 0.4 mL, 1.489 mmol) in 1,4 dioxane/water at 50 ^oC for 7 h. After workup and flash column chromatography the product was obtained (14 mg, 45%) as a beige solid. ^1H NMR (500 MHz, DMSO- d_6) 1.12-1.29 (m, 4H), 1.38-1.55 (m, 4H), 1.89 (t, *J* = 11.0 Hz, 2H), 2.52 (s, 2H), 2.65 (t, *J* = 7.3 Hz, 2H), 2.88 – 2.93 (m, 1H), 7.18 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.52 (d, *J* = 8.3 Hz, 1H), 7.69 (s, 1H), 7.97 (d, *J* = 5.0 Hz, 1H), 8.28 (s, 1H), 8.39 (s, 1H), 8.54 (d, *J* = 5.0 Hz, 1H), 12.69 (br s, 1H); LC- HRMS (Method I) t_R = 2.16 min - HRMS: Found 483.1465 Calculated for $C_{24}H_{25}Cl_2N_6O$ $[(M+H)^+]$. 483.1467.

8-(4-(2-(4-(3-Methoxybenzyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (50f): According to general procedure 3, 2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)acetaldehyde (69 mg, 0.179 mmol), 4-(3-methoxybenzyl)piperidine (55 mg, 0.268 mmol) and sodium triacetoxyborohydride (61 mg, 0.286 mmol) were reacted together in 1,2-dichloroethane (4 mL). Following workup procedure B, the title compound was obtained (27 mg, 26%) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$) 0.00 (s, 9H), 0.81-0.90 (m, 1H), 0.94-1.01 (m, 3H), 1.21-1.34 (m, 3H), 1.37 (d, *J* = 6.8 Hz, 1H), 1.72-1.98 (m, 4H), 2.60 (d, *J* = 6.8 Hz, 2H), 3.21 (s, 1H), 3.58-3.73 (m, 4H),

5.30 (s, 2H), 5.46 (s, 3H), 6.65-6.68 (m, 1H), 6.72 (d, *J* = 7.3 Hz, 1H), 6.76 (dd, *J* = 7.3, 2.2 Hz, 1H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.79 (br s, 1H), 8.07 (br s, 1H), 8.31 (br s, 1H), 8.62 (br s, 1H), 8.74 (br s, 1H); LC- HRMS (Method E) t_R = 2.78 min - HRMS: Found 575.3133; Calculated for $C_{31}H_{43}N_6O_3Si$ $[(M+H)^+]$ 575.3160.

8-(4-(2-(4-(3-Methoxybenzyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)pyrido[3,4-*d*]-pyrimidin-4(3*H*)-one (53f): According to general procedure 5 8-(4-(2-(4-(3-methoxybenzyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)-pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (21 mg, 0.037 mmol) was reacted with HCl in 1,4-dioxane (4M, 0.23 mL, 0.913 mmol) in 1,4 dioxane/water at 50 ^oC for 6 h. After workup and flash column chromatography the product was obtained (4 mg, 25%) as a beige solid. ^1H NMR (500 MHz, MeOH-d_4) 1.40-1.49 (m, 2H), 1.79-1.85 (m, 2H), 2.50-2.60 (m, 4H), 2.92-2.96 (m, 2H), 3.00-3.04 (m, 2H), 3.31-3.34 (m, 2H), 3.35-3.37 (m, 1H), 4.88 (s, 3H) 6.73-6.78 (m, 3H), 7.19 (t, *J* = 8.2 Hz, 1H), 7.80 (s, 1H), 8.06 (d, *J* = 5.0 Hz, 1H), 8.23 (s, 1H), 8.54 (d, *J* = 5.0 Hz, 1H), 8.78 (s, 1H), NH signal not observed; LC- HRMS (Method I) t_R = 1.78 min - HRMS: Found 445.2356; Calculated for $C_{25}H_{29}N_6O_2$ $[(M+H)^+]$ 445.2352.

8-(4-(2-(4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (50g): According to General Procedure 2, triethylamine (0.070 mL, 0.505 mmol), 2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)-ethyl methanesulfonate (78.3 mg, 0.168 mmol) and 4-(benzo[*d*][1,3]dioxol-5-ylmethyl)piperidin-1-ium chloride (51.6 mg, 0.202 mmol) were reacted together in anhydrous DMF (1 mL). Purified on KP-Sil snap cartridge (7% [0.2M NH_3 in MeOH] in CH_2Cl_2) as a pale yellow oil (23.7 mg, 24%); ^1H NMR (500 MHz, $CDCl_3$) 0.01 (s, 9H), 0.96-1.01 (m, 2H), 1.34 (qd, *J* = 12.5, 3.3 Hz, 2H), 1.45-1.55 (m, 1H), 1.68 (br d, *J* = 12.8 Hz, 2H), 1.99 (t, *J* = 11.4 Hz, 2H), 2.48 (br d, *J* = 7.1 Hz, 2H), 2.61-2.66 (m, 2H), 2.77-2.82 (m, 2H), 3.01 (br d, *J*

= 11.4 Hz, 2H), 3.67-3.72 (m, 2H), 5.47 (s, 2H), 5.93 (s, 2H), 6.60 (dd, *J* = 7.9, 1.6 Hz, 1H), 6.65 (d, *J* = 1.6 Hz, 1H), 6.73 (d, *J* = 7.9 Hz, 1H), 7.78 (s, 1H), 8.06 (d, *J* = 5.1 Hz, 1H), 8.31 (s, 1H), 8.54 (s, 1H), 8.62 (d, *J* = 5.1 Hz, 1H); LC - MS (Method H; ESI, *m/z*) t_R = 1.23 min – 589 [$(M+H)^+$]; HRMS (Method I): found 589.2964; calculated for $C_{31}H_{41}N_6O_4Si$ $(M+H)^+$ 589.2958.

8-(4-(2-(4-(Benzo[*d*][1,3]dioxol-5-ylmethyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (53g). According to General Procedure 4, 8-(4-(2-(4-(benzo[*d*][1,3]dioxol-5-ylmethyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (21.5 mg, 0.037 mmol) and hydrochloric acid (6 M, 0.4 mL) were reacted together in THF (0.4 mL). Purification on a KP-NH snap cartridge (40% EtOH in CH_2Cl_2) gave the product as a white solid (10.5 mg, 63%); ^{1}H NMR (500 MHz, MeOH-d_4) 1.36 (qd, *J* = 12.4, 3.3 Hz, 2H), 1.56-1.66 (m, 1H), 1.73 (br d, *J* = 12.4 Hz, 2H), 2.22 (td, *J* = 11.9, 1.9 Hz, 2H), 2.50 (d, *J* = 7.0 Hz, 2H), 2.75-2.80 (m, 2H), 2.83-2.89 (m, 2H), 3.15 (br d, *J* = 11.8 Hz, 2H), 5.89 (s, 2H), 6.62 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.68 (d, *J* = 1.7 Hz, 1H), 6.72 (d, *J* = 7.9 Hz, 1H), 7.78 (s, 1H), 8.04 (d, *J* = 5.1 Hz, 1H), 8.26 (s, 1H), 8.52 (d, *J* = 5.1 Hz, 1H), 8.72 (s, 1H), NH signal not observed; LC - MS (Method H; ESI, *m/z*) t_R = 0.88 min – 459 [$(M+H)^+$]; HRMS (Method I): found 459.2147; calculated for $C_{25}H_{27}N_6O_3$ $(M+H)^+$ 459.2144.

8-(4-(2-(4-(Pyridin-3-ylmethyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (50h): According to General Procedure 2, triethylamine (0.038 mL, 0.272 mmol), 2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)ethyl methanesulfonate (63.3 mg, 0.136 mmol) and 3-(piperidin-4-ylmethyl)pyridine (28.8 mg, 0.163 mmol) were reacted together in anhydrous DMF (1 mL). Purification on a KP-Sil snap cartridge (7% [0.2M NH_3 in MeOH] in CH_2Cl_2) gave the product as a pale yellow oil

(33.1 mg, 45%); ^{1}H NMR (500 MHz, $CDCl_3$) 0.01 (s, 9H), 0.93-0.99 (m, 2H), 1.35 (qd, *J* = 11.9, 3.3 Hz, 2H), 1.49-1.59 (m, 1H), 1.65 (br d, *J* = 12.7 Hz, 2H), 1.97 (t, *J* = 11.4 Hz, 2H), 2.54 (d, *J* = 7.2 Hz, 2H), 2.58-2.64 (m, 2H), 2.74-2.80 (m, 2H), 2.99 (br d, *J* = 11.4 Hz, 2H), 3.65-3.70 (m, 2H), 5.45 (s, 2H), 7.20 (dd, *J* = 7.7, 4.7 Hz, 1H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.75 (s, 1H), 8.04 (d, *J* = 5.1 Hz, 1H), 8.29 (s, 1H), 8.41 (br d, *J* = 1.4 Hz, 1H), 8.43 (dd, *J* = 4.7, 1.4 Hz, 1H), 8.52 (s, 1H), 8.60 (d, *J* = 5.1 Hz, 1H); LC - MS (Method H; ESI, *m/z*) t_R = 0.94 min – 546 [$(M+H)^+$]; HRMS (Method I): found 546.3019; calculated for $C_{29}H_{40}N_7O_2Si$ $(M+H)^+$ 546.3013.

8-(4-(2-(4-(Pyridin-3-ylmethyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (53h): According to General Procedure 4, 8-(4-(2-(4-(pyridin-3-ylmethyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)-pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (29 mg, 0.053 mmol) and hydrochloric acid (6 M, 0.55 mL) were reacted together in THF (0.55 mL). Purification on a KP-NH snap cartridge (40% EtOH in CH_2Cl_2) to give the product as a white solid (14.2 mg, 64%); ^{1}H NMR (500 MHz, MeOH-d_4) 1.40 (qd, *J* = 12.2, 2.9 Hz, 2H), 1.63-1.75 (m, 3H), 2.20 (t, *J* = 12.1, 2H), 2.64 (d, *J* = 6.7 Hz, 2H), 2.72-2.77 (m, 2H), 2.81-2.86 (m, 2H), 3.14 (br d, *J* = 11.9 Hz, 2H), 7.38 (ddd, *J* = 7.8, 5.1, 0.4 Hz, 1H), 7.70 (dt, *J* = 7.8, 1.8 Hz, 1H), 7.76 (s, 1H), 8.01 (d, *J* = 5.1 Hz, 1H), 8.24 (s, 1H), 8.37-8.40 (m, 2H), 8.50 (d, *J* = 5.1 Hz, 1H), 8.72 (s, 1H), NH signal not observed; LC - MS (Method H; ESI, *m/z*) t_R = 0.37 min – 416 [$(M+H)^+$]; HRMS (Method I): found 416.2206; calculated for $C_{23}H_{26}N_7O$ $(M+H)^+$ 416.2199.

8-(4-(2-(4-((5-Cyclopropyl-1,2,4-oxadiazol-3-yl)methyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (50i): According to General Procedure 2, triethylamine (0.037 mL, 0.266 mmol), 2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)ethyl methanesulfonate (62 mg, 0.133 mmol) and 5-cyclopropyl-3-(piperidin-4-ylmethyl)-

1,2,4-oxadiazole (33.1 mg, 0.160 mmol) were reacted together in anhydrous DMF (1 mL). Purified on KP-Sil snap cartridge (8% [0.2 M NH_3 in MeOH] in CH_2Cl_2) to give the product as a pale yellow oil (17.2 mg, 23%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.00 (s, 9H), 0.95-1.00 (m, 2H), 1.18-1.25 (m, 4H), 1.41 (qd, *J* = 12.0, 3.3 Hz, 2H), 1.73 (br d, *J* = 13.0 Hz, 2H), 1.77-1.86 (m, 1H), 2.05 (t, *J* = 12.0 Hz, 2H), 2.14-2.20 (m, 1H), 2.59-2.66 (m, 4H), 2.75-2.82 (m, 2H), 3.01 (br d, *J* = 11.2 Hz, 2H), 3.66-3.72 (m, 2H), 5.46 (s, 2H), 7.76 (s, 1H), 8.05 (d, *J* = 5.0 Hz, 1H), 8.31 (s, 1H), 8.55 (s, 1H), 8.62 (d, *J* = 5.0 Hz, 1H); LC - MS (Method H; ESI, *m/z*) t_R = 1.17 min – 577 [$(M+H)^+$]; HRMS (Method I): found 577.3083; calculated for $C_{29}H_{41}N_8O_3Si$ $(M+H)^+$ 577.3071.

8-(4-(2-(4-((5-Cyclopropyl-1,2,4-oxadiazol-3-yl)methyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (53i): According to General Procedure 4, 8-(4-(2-(4-((5-cyclopropyl-1,2,4-oxadiazol-3-yl)methyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (20 mg, 0.035 mmol) and hydrochloric acid (6 M, 0.4 mL) were reacted together in THF (0.4 mL). Purification on a KP-NH snap cartridge (40% EtOH in CH_2Cl_2) gave the product as a white solid (10.2 mg, 66%). ^{1}H NMR (500 MHz, MeOH-d_4) 1.14-1.19 (m, 2H), 1.24-1.29 (m, 2H), 1.42 (qd, *J* = 12.3, 3.5 Hz, 2H), 1.78 (br d, *J* = 13.4 Hz, 2H), 1.81-1.91 (m, 1H), 2.18-2.28 (m, 3H), 2.64 (d, *J* = 6.9 Hz, 2H), 2.72-2.78 (m, 2H), 2.82-2.88 (m, 2H), 3.13 (br d, *J* = 11.6 Hz, 2H), 7.78 (s, 1H), 8.04 (d, *J* = 5.0 Hz, 1H), 8.26 (s, 1H), 8.53 (d, *J* = 5.0 Hz, 1H), 8.74 (s, 1H) NH signal not observed; LC - MS (Method H; ESI, *m/z*) t_R = 0.73 min – 447 [$(M+H)^+$]; HRMS (Method I): found 447.2254; calculated for $C_{23}H_{27}N_8O_2$ $(M+H)^+$ 447.2257.

8-(4-(2-(4-(4-Fluorophenyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)-ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (51b): According to general procedure 3, 2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)acetaldehyde (46 mg, 0.119 mmol), 4-(4-fluorophenyl)piperidine (26 mg,

0.143 mmol) and sodium triacetoxyborohydride (38 mg, 0.179 mmol) were reacted together in 1,2-dichloroethane (4 mL). Following workup procedure A, the title compound was obtained (45 mg, 69%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) 0.02 (s, 9H), 0.97-1.02 (m, 2H), 1.75-1.89 (m, 5H), 2.16 (dt, *J* = 11.5, 2.9 Hz, 2H), 2.68-2.72 (m, 2H), 2.82-2.86 (m, 2H), 3.15 (d, *J* = 11.5 Hz, 2H), 3.67-3.73 (m, 2H), 5.48 (s, 2H), 6.96-7.03 (m, 2H), 7.16-7.22 (m, 2H), 7.81 (s, 1H), 8.08 (d, *J* = 5.1 Hz, 1H), 8.32 (s, 1H), 8.58 (s, 1H), 8.64 (d, *J* = 5.1 Hz, 1H); LC- HRMS (Method I) t_R = 2.59 min - HRMS: Found 549.2805; Calculated for $C_{29}H_{38}FN_6O_2Si$ [$(M+H)^+$] 549.2809.

8-(4-(2-(4-(4-Fluorophenyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (54b): According to general procedure 5, 8-(4-(2-(4-(4-fluorophenyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)-pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (45 mg, 0.082 mmol) was reacted with HCl in 1,4-dioxane (4 M, 0.513 mL, 2.05 mmol) in 1,4 dioxane/water at 50 ^{o}C overnight. After workup and trituration, the product was obtained (28 mg, 82%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO- d_6) 1.67-2.04 (m, 5H), 2.53-2.78 (m, 4H), 2.82-3.04 (m, 3H), 3.16 (s, 1H), 7.07-7.18 (m, 2H), 7.23-7.33 (m, 2H), 7.76 (s, 1H), 8.01 (d, *J* = 5.1 Hz, 1H), 8.29 (s, 1H), 8.46 (s, 1H), 8.57 (d, *J* = 5.1 Hz, 1H), 12.79 (br s, 1H).; LC- HRMS (Method I) t_R = 1.59 min – Found 419.1985; Calculated for $C_{23}H_{24}FN_6O$ [$(M+H)^+$] 419.1996.

8-(4-(2-(4-(4-Methoxyphenyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (51c): According to General Procedure 2, 2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)ethyl methanesulfonate (70 mg, 0.15 mmol), 4-(4-methoxyphenyl)piperidine (43.1 mg, 0.226 mmol) and triethylamine (30 mg, 0.3 mmol) were reacted together in anhydrous DMF (1 mL) for 18 h. Purification by flash column chromatography eluting with 5% [7N ammonia in methanol] in EtOAc gave the title

compound as a colorless oil (38 mg, 45%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.03 (s, 9H), 0.96 – 0.99 (m, 2H), 1.80 – 1.84 (m, 4H), 2.08 – 2.12 (m, 2H), 2.45 – 2.52 (m, 1H), 2.71 (t, *J* = 8.4 Hz, 2H), 2.82 (t, *J* = 8.3 Hz, 2H), 3.13 – 3.16 (m, 2H), 3.63 – 3.67 (m, 2H), 3.78 (s, 3H), 5.45 (s, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.80 (s, 1H), 8.05 (d, *J* = 5.1 Hz, 1H), 8.30 (s, 1H), 8.58 (s, 1H), 8.61 (d, *J* = 5.1 Hz, 1H); LC - MS (Method H); ESI, *m/z*) t_R = 1.19 min - 561 $(M+H)^+$.

8-(4-(2-(4-(4-Methoxyphenyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (54c): According to General Procedure 4, 8-(4-(2-(4-(4-methoxyphenyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)-pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (38.0 mg, 0.068 mmol) and hydrochloric acid (6 M, 1 mL) were reacted together in THF (1 mL) for 4 h. Purified by passing through an SCX cartridge eluting first with methanol followed by 7N ammonia in methanol. The ammoniacal solution was concentrated *in vacuo* and the residue triturated with Et_2O. The beige powder obtained was filtered and dried (20 mg, 69%). ^{1}H NMR (500 MHz, DMSO-d_6) 1.62 – 1.67 (m, 2H), 1.72 – 1.75 (m, 2H), 2.08 – 2.11 (m, 2H), 2.42 – 2.48 (m, 1H), 2.60 (t, *J* = 8.0 Hz, 2H), 2.72 (t, *J* = 8.0 Hz, 2H), 3.05 – 3.08 (m, 2H), 3.71 (s, 3H), 6.84 (d, *J* = 8.7 Hz, 2H), 7.15 (d, *J* = 8.7 Hz, 2H), 7.73 (s, 1H), 7.98 (d, *J* = 5.1 Hz, 1H), 8.29 (s, 1H), 8.43 (s, 1H), 8.55 (d, *J* = 5.1 Hz, 1H), 12.5 (br s, 1H); LC - MS (Method H; ESI, *m/z*) t_R = 0.78 min - 431 $(M+H)^+$; HRMS (Method B): found 431.2184; calculated for $C_{24}H_{27}N_6O_2$ $(M+H)^+$ 431.2190.

8-(4-(2-(4-(4-(Methylsulfonyl)phenyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (51d): According to General Procedure 2, 2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido-[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)ethyl methanesulfonate (70.0 mg, 0.15 mmol), 4-(4-(methylsulfonyl)phenyl)piperidine (54.0 mg, 0.226 mmol) and triethylamine (30 mg, 0.3 mmol) were reacted together in anhydrous DMF (1 mL) for 18 h. Purification by flash

column chromatography eluting with 7% [7N ammonia in methanol] in EtOAc gave the title compound as a colorless oil (42 mg, 46%); ^{1}H NMR (500 MHz, $CDCl_3$) 0.03 (s, 9H), 0.96 – 1.00 (m, 2H), 1.86 – 1.92 (m, 4H), 2.17 – 2.24 (m, 2H), 2.62 – 2.70 (m, 1H), 2.72 (t, *J* = 8.4 Hz, 2H), 2.84 (t, *J* = 8.4 Hz, 2H), 3.05 (s, 3H), 3.17 – 3.21 (m, 2H), 3.68 – 3.71 (m, 2H), 5.47 (s, 2H), 7.43 (d, *J* = 8.4 Hz, 2H), 7.81 (s, 1H), 7.87 (d, *J* = 8.4 Hz, 2H), 8.06 (d, *J* = 5.1 Hz, 1H), 8.31 (s, 1H), 8.56 (s, 1H), 8.62 (d, *J* = 5.1 Hz, 1H); LC - MS (Method H; ESI, *m/z*) t_R = 1.10 min - 609 $(M+H)^+$.

8-(4-(2-(4-(4-(Methylsulfonyl)phenyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (54d): According to General Procedure 4, 8-(4-(2-(4-(4-(methylsulfonyl)phenyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)-methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (42.0 mg, 0.069 mmol) and hydrochloric acid (6 m, 1 mL) were reacted together in THF (1 mL) for 4 h. Purification by passing through an SCX cartridge eluting first with methanol followed by 7N ammonia in methanol gave an ammoniacal solution that was concentrated *in vacuo* and the residue triturated with Et_2O. The pale yellow powder obtained was filtered and dried (19 mg, 58%). ^{1}H NMR (500 MHz, DMSO-d_6) 2.04 – 2.10 (m, 4H), 2.96 – 3.04 (m, 1H), 3.05 – 3.15 (m, 4H), 3.21 (s, 3H), 3.35 – 3.45 (m, 2H), 3.68 – 3.72 (m, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.80 (s, 1H), 7.91 (d, *J* = 8.4 Hz, 2H), 8.03 (d, *J* = 5.1 Hz, 1H), 8.29 (s, 1H), 8.50 (s, 1H), 8.58 (d, *J* = 5.1 Hz, 1H), 12.80 (br s, 1H); LC - MS (Method H; ESI, *m/z*) t_R = 0.63 min - 479 $(M+H)^+$; HRMS (Method I): found 479.1868; calculated for $C_{24}H_{27}N_6O_3S$ $(M+H)^+$ 479.1865.

4-(1-(2-(1-(4-Oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)ethyl)piperidin-4-yl)benzonitrile (51e): According to General Procedure 2, 2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido-[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)ethyl methanesulfonate (70.0 mg, 0.15 mmol), 4-(piperidin-4-yl)benzonitrile (42.0 mg, 0.226 mmol) and triethylamine (30 mg, 0.3 mmol)

were reacted together in anhydrous DMF (1 mL) for 18 h. Purification by flash column chromatography eluting with 5% [7N ammonia in methanol] in EtOAc gave the title compound as a colorless oil (35 mg, 42%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.03 (s, 9H), 0.97 – 1.00 (m, 2H), 1.85 – 1.90 (m, 4H), 2.20 – 2.26 (m, 2H), 2.60 – 2.63 (m, 1H), 2.75 (t, *J* = 8.4 Hz, 2H), 2.84 (t, *J* = 8.3 Hz, 2H), 3.20 – 3.23 (m, 2H), 3.68 – 3.72 (m, 2H), 5.47 (s, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.81 (s, 1H), 8.08 (d, *J* = 5.1 Hz, 1H), 8.32 (s, 1H), 8.58 (s, 1H), 8.63 (d, *J* = 5.1 Hz, 1H); LC - MS (Method H, ESI, *m/z*) t_R = 1.14 min - 556 $(M+H)^+$.

4-(1-(2-(1-(4-Oxo-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)ethyl)piperidin-4-yl)benzonitrile (54e): According to General Procedure 4, 4-(1-(2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)ethyl)piperidin-4-yl)benzonitrile (35.0 mg, 0.063 mmol) and hydrochloric acid (6 M, 1 mL) were reacted together in THF (1 mL) for 4 h. Purification by passing through an SCX cartridge eluting first with methanol followed by 7N ammonia in methanol gave an ammoniacal solution that was concentrated *in vacuo* and the residue triturated with Et_2O. The pale yellow powder obtained was filtered and dried (17 mg, 63%). ^{1}H NMR (500 MHz, DMSO-d_6) 1.65 – 1.72 (m, 2H), 1.75 – 1.80 (m, 2H), 2.07 – 2.10 (m, 2H), 2.57 – 2.68 (m, 3H), 2.71 (t, *J* = 8.0 Hz, 2H), 3.05 – 3.08 (m 2H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.72 (s, 1H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.97 (d, *J* = 5.1 Hz, 1H), 8.28 (s, 1H), 8.43 (s, 1H), 8.54 (d, *J* = 5.1 Hz, 1H), 12.5 (br s, 1H); LC - MS (Method H; ESI, *m/z*) t_R = 0.73 min - 426 $(M+H)^+$; HRMS (Method I): found 426.2047; calculated for $C_{24}H_{24}N_7O$ $(M+H)^+$ 426.2042.

8-(4-(2-(4-(2-Chlorophenyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)-ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (51f): According to General Procedure 2, triethylamine (0.036 mL, 0.258 mmol), 2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)ethyl methanesulfonate (60 mg,

0.129 mmol) and 4-(2-chlorophenyl)piperidine (30.3 mg, 0.155 mmol) were reacted together in anhydrous DMF (1 mL). Purification on a KP-Sil snap cartridge (7% [0.2M NH_3 in MeOH] in CH_2Cl_2) gave the product as a pale yellow oil (30.2 mg, 42%); ^{1}H NMR (500 MHz, $CDCl_3$) 0.01 (s, 9H), 0.96-1.01 (m, 2H), 1.82 (qd, *J* = 12.1, 2.6 Hz, 2H), 1.88-1.96 (m, 2H), 2.25 (t, *J* = 11.4 Hz, 2H), 2.70-2.76 (m, 2H), 2.83-2.89 (m, 2H), 3.07 (tt, *J* = 12.1, 3.6 Hz, 1H), 3.19 (br d, *J* = 11.4 Hz, 2H), 3.67-3.73 (m, 2H), 5.47 (s, 2H), 7.14 (td, *J* = 7.7, 1.7 Hz, 1H), 7.25 (td, *J* = 7.7, 1.3 Hz, 1H), 7.32 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.36 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.81 (s, 1H), 8.07 (d, *J* = 5.0 Hz, 1H), 8.32 (s, 1H), 8.58 (s, 1H), 8.64 (d, *J* = 5.0 Hz, 1H); LC - MS (Method H; ESI, *m/z*) t_R = 1.22 min – 565, 567 [$(M+H)^+$, Cl isotopic pattern]; HRMS (Method I): found 565.2505; calculated for $C_{29}H_{38}ClN_6O_2Si$ $(M+H)^+$ 565.2514.

8-(4-(2-(4-(2-Chlorophenyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)pyrido[3,4-*d*]-pyrimidin-4(3*H*)-one (54f): According to General Procedure 4, 8-(4-(2-(4-(2-chlorophenyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)-pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (20 mg, 0.035 mmol) and hydrochloric acid (6 M, 0.5 mL) were reacted together in THF (0.5 mL). Purification on a KP-NH snap cartridge (40% EtOH in CH_2Cl_2) gave the product as a white solid (8.6 mg, 56%). ^{1}H NMR (500 MHz, MeOH-d_4) 1.83 (qd, *J* = 12.0, 3.1 Hz, 2H), 1.88-1.94 (m, 2H), 2.32 (t, *J* = 11.6 Hz, 2H), 2.75-2.81 (m, 3H), 2.86-2.92 (m, 2H), 3.13 (tt, *J* = 12.0, 3.8 Hz, 1H), 3.25 (br d, *J* = 11.3 Hz, 2H), 7.19 (td, *J* = 7.6, 1.5 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.38 (br d, *J* = 8.0 Hz, 2H), 7.81 (s, 1H), 8.05 (d, *J* = 5.0 Hz, 1H), 8.29 (s, 1H), 8.49-8.53 (m, 1H), 8.76 (s, 1H); LC - MS (Method H; ESI, *m/z*) t_R = 0.90 min – 435, 437 [$(M+H)^+$, Cl isotopic pattern]; HRMS (Method I): found 435.1696; calculated for $C_{23}H_{24}ClN_6O$ $(M+H)^+$ 435.1700.

8-(4-(2-(4-Phenylpiperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2

(trimethylsilyl)ethoxy)methyl)-pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (51g): According to General Procedure 2, 2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)ethyl methanesulfonate (123 mg, 0.264 mmol), 4-phenylpiperidine (64 mg, 0.396 mmol) and triethylamine (0.057 mL, 0.409 mmol) in DMF was reacted at 50 ^{o}C for 3 days. After workup the oil obtained was purified by flash column chromatography to afford the product (34 mg, 24%) as a yellow oil which solidified upon standing. ^{1}H NMR (500 MHz, $CDCl_3$) 0.02 (s, 9H), 0.96-1.02 (m, 2H), 1.90 (br s, 4H), 2.18-2.28 (m, 2H), 2.52 -2.61 (m, 1H), 2.74 (t, *J* = 7.3 Hz, 2H), 2.88 (t, *J* = 7.3 Hz, 2H), 3.18-3.23 (m, 2H), 3.68-3.73 (m, 2H), 5.47 (s, 2H), 7.20-7.25 (m, 3H), 7.30-7.35 (m, 2H), 7.81 (s, 1H), 8.08 (d, *J* = 5.0 Hz, 1H), 8.32 (s, 1H), 8.59 (s, 1H), 8.64 (d, *J* = 5.0 Hz, 1H); LC- HRMS (Method I) t_R = 2.57 min - HRMS: Found 531.2911; Calculated for $C_{29}H_{39}N_6O_2Si$ [$(M+H)^+$] 531.2903.

8-(4-(2-(4-Phenylpiperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (54g): According to General Procedure 5, 8-(4-(2-(4-phenylpiperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (34 mg, 0.064 mmol) was reacted with HCl in 1,4-dioxane (4 M, 0.16 mL, 0.641 mmol) in 1,4 dioxane/water at 50 $^{\circ}$C overnight. After workup and trituration with Et_2O the product was purified by flash column chromatography and the product was obtained (4 mg, 16 %) as a yellow solid.^{1}H NMR (500 MHz, DMSO- d_6):1.68-1.87 (m, 4H), 2.56-2.66 (m, 2H), 2.70-2.89 (m, 4H), 3.14-3.27 (m, 3H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.25 (d, *J* = 6.9 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 2H), 7.75 (s, 1H), 8.00 (d, *J* = 5.1 Hz, 1H), 8.29 (s, 1H), 8.44 (s, 1H), 8.57 (d, *J* = 5.1 Hz, 1H), 12.61 (br s, 1H); LCMS (Method I) t_R = 1.93 min; LC- HRMS Found 401.2065; Calculated for $C_{23}H_{25}N_6O$ [$(M+H)^+$] 401.2084.

8-(4-(2-(4-(Pyridin-4-yl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (51h): According to

General Procedure 2, triethylamine (0.05 mL, 0.359 mmol), 2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)ethyl methanesulfonate (78 mg, 0.168 mmol) and 4-(piperidin-4-yl)pyridine (54.4 mg, 0.335 mmol) were reacted together in anhydrous DMF (1 mL). Purification on a KP-Sil snap cartridge (7% [0.2M NH_3 in MeOH] in CH_2Cl_2) gave the product as a pale yellow oil (54.2 mg, 61%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.00 (s, 9H), 0.94-0.99 (m, 2H), 1.78-1.91 (m, 4H), 2.18 (td, *J* = 11.4, 2.8 Hz, 2H), 2.53 (tt, *J* = 11.4, 4.3, 1H), 2.68-2.73 (m, 2H), 2.81-2.86 (m, 2H), 3.17 (br d, *J* = 11.4 Hz, 2H), 3.66-3.71 (m, 2H), 5.45 (s, 2H), 7.14-7.17 (m, 2H), 7.79 (s, 1H), 8.06 (d, *J* = 5.1 Hz, 1H), 8.30 (s, 1H), 8.49-8.52 (m, 2H), 8.56 (s, 1H), 8.62 (d, *J* = 5.1 Hz, 1H); LC - MS (Method H; ESI, *m/z*) t_R = 0.92 minn– 532 [$(M+H)^+$]; HRMS (Method I): found 532.2852; calculated for $C_{28}H_{38}N_7O_2Si$ $(M+H)^+$ 532.2856.

8-(4-(2-(4-(Pyridin-4-yl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (54h): According to General Procedure 4, 8-(4-(2-(4-(pyridin-4-yl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (42.4 mg, 0.080 mmol) and hydrochloric acid (6 M, 1 mL) were reacted together in THF (1 mL). Purification on a KP-NH snap cartridge (40% EtOH in CH_2Cl_2) gave the product as a white solid (25 mg, 78%). ^{1}H NMR (500 MHz, MeOH-d_4) 1.86 (qd, *J* = 12.4, 3.4 Hz, 2H), 1.93-1.99 (m, 2H), 2.35 (td, *J* = 12.1, 2.4 Hz, 2H), 2.71 (tt, *J* = 12.1, 3.6 Hz, 1H), 2.78-2.83 (m, 2H), 2.87-2.92 (m, 2H), 3.27 (br d, *J* = 11.9 Hz, 2H), 7.35-7.38 (m, 2H), 7.82 (s, 1H), 8.05 (d, *J* = 5.1 Hz, 1H), 8.26 (s, 1H), 8.44-8.47 (m, 2H), 8.55 (d, *J* = 5.1 Hz, 1H), 8.78 (s, 1H) NH signal not observed; LC - MS (Method C; ESI, *m/z*) t_R = 0.19 min – 402 [$(M+H)^+$]; HRMS (Method B): found 402.2024; calculated for $C_{22}H_{24}N_7O$ $(M+H)^+$ 402.2037.

8-(4-(2-(4-(Thiophen-2-yl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)-ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (51i): According to General Procedure 2, 2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido-[3,4-*d*]pyrimidin-8-

yl)-1*H*-pyrazol-4-yl)ethyl methanesulfonate (60 mg, 0.129 mmol), 4-(thiophen-2-yl)piperidine (32.0 mg, 0.193 mmol) and triethylamine (26 mg, 0.26 mmol) were reacted together in anhydrous DMF (1 mL). Purification by flash column chromatography eluting with 8% [7 N ammonia in methanol] in CH_2Cl_2 gave the title compound as a colorless oil (26 mg, 38%); ^{1}H NMR (500 MHz, $CDCl_3$) 0.01 (s, 9H), 0.97 – 1.00 (m, 2H), 1.86 – 1.93 (m, 4H), 2.22 – 2.26 (m, 3H), 2.71 (t, *J* = 8.4 Hz, 2H), 2.86 (t, *J* = 8.3 Hz, 2H), 3.25 (br d, 2H), 3.68 – 3.71 (m, 2H), 5.46 (s, 2H), 6.84 (d, *J* = 4.9 Hz, 1H), 6.94 – 6.96 (m, 1H), 7.13 (dd, *J* = 1.1, 4.9 Hz, 1H), 7.80 (s, 1H), 8.06 (d, *J* = 5.1 Hz, 1H), 8.30 (s, 1H), 8.61 (s, 1H), 8.62 (d, *J* = 5.1 Hz, 1H); LC - MS (Method H), ESI, *m/z*) t_R = 1.19 min - 537.247 $(M+H)^+$.

8-(4-(2-(4-(Thiophen-2-yl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (54i): According to General Procedure 4, 8-(4-(2-(4-(thiophen-2-yl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (26 mg, 0.048 mmol) and hydrochloric acid (6 M, 1 mL) were reacted together in THF (1 mL). This was purified by passing through an SCX cartridge eluting first with methanol followed by 7N ammonia in methanol. The ammoniacal solution was concentrated *in vacuo* and the residue triturated with Et_2O. The beige powder obtained was filtered and dried (16 mg, 81%). ^{1}H NMR (500 MHz, DMSO-d_6) 1.66 – 1.71 (m, 2H), 1.77 – 1.81 (m, 2H), 2.04 – 2.08 (m 2H), 2.57 – 2.66 (m, 3H), 2.71 (t, *J* = 8.1 Hz, 2H), 2.88 – 2.91 (m, 2H), 6.91 (d, *J* = 4.9 Hz, 1H), 6.95 – 6.97 (m, 1H), 7.33 (d, *J* = 4.9 Hz, 1H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.98 (d, *J* = 5.1 Hz, 1H), 8.28 (s, 1H), 8.43 (s, 1H), 8.55 (d, *J* = 5.1 Hz, 1H), 12.81 (br s, 1H); HRMS (Method E): found 407.1635; calculated for $C_{21}H_{23}N_6OS$ $(M+H)^+$ 407.1649.

8-(4-(2-(4-(3,5-Difluorophenyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (51l): According to General Procedure 2, 2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)ethyl methanesulfonate (60.0 mg,

0.129 mmol), 4-(3,5-difluorophenyl)piperidine (38.1 mg, 0.193 mmol) and triethylamine (26.0 mg, 0.258 mmol) were reacted together in anhydrous DMF (1 mL) for 18 h. Purification by flash column chromatography eluting with 5% [7N ammonia in methanol] in CH_2Cl_2 gave the title product as a colorless oil (29 mg, 40%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.01 (s, 9H), 0.96 – 0.99 (m, 2H), 1.87 – 1.92 (m, 4H), 2.24 – 2.31 (m, 2H), 2.55 – 2.58 (m, 1H), 2.79 (t, *J* = 8.2 Hz, 2H), 2.91 (t, *J* = 8.2 Hz, 2H), 3.24 (d, *J* = 9.2 Hz, 2H), 3.68 – 3.71 (m, 2H), 5.47 (s, 2H), 6.62 – 6.67 (m, 1H), 6.75 – 6.78 (m, 2H), 7.80 (s, 1H), 8.07 (d, *J* = 5.1 Hz, 1H), 8.31 (s, 1H), 8.60 (s, 1H), 8.62 (d, *J* = 5.1 Hz, 1H); LC - MS (Method H; ESI, *m/z*) t_R = 1.20 min - 563 $(M+H)^+$.

8-(4-(2-(4-(3,5-Difluorophenyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (54l): According to General Procedure 4, 8-(4-(2-(4-(3,5-difluorophenyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)-pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (29.0 mg, 0.051 mmol) and hydrochloric acid (6 M, 1 mL) were reacted together in THF (1 mL) for 4 h. Purification by passing through an SCX cartridge eluting first with methanol followed by 7N ammonia in methanol gave an ammoniacal solution that was concentrated *in vacuo* and the residue triturated with Et_2O. The beige powder obtained was filtered and dried (21 mg, 94 %). ^{1}H NMR (500 MHz, MeOH-d_4) 1.78 – 1.87 (m, 2H), 1.91 – 1.97 (m, 2H), 2.32 – 2.38 (m, 2H), 2.66 – 2.72 (m, 1H), 2.80 – 2.85 (m, 2H), 2.87 – 2.92 (m, 2H), 3.23 – 3.26 (m, 2H), 6.75 – 6.80 (m, 1H), 6.87 – 6.92 (m, 2H), 7.82 (s, 1H), 8.06 (d, *J* = 5.1 Hz, 1H), 8.26 (s, 1H), 8.55 (d, *J* = 5.1 Hz, 1H), 8.77 (s, 1H), NH signal not observed; LC - MS (Method H; ESI, *m/z*) t_R = 0.81 min - 437 $(M+H)^+$; HRMS (Method I): found 437.1903; calculated for $C_{23}H_{23}F_2N_6O$ $(M+H)^+$ 437.1901.

8-(4-(2-(4-(2,4-Difluorophenyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (51m): According to General Procedure 2, triethylamine (0.06 mL, 0.430 mmol), 2-(1-(4-oxo-3-((2-

(trimethylsilyl)ethoxy)methyl)-3,4-dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)ethyl methanesulfonate (65 mg, 0.140 mmol) and 4-(2,4-difluorophenyl)piperidin-1-ium chloride (39.1 mg, 0.168 mmol) were reacted together in anhydrous DMF (1 mL). Purification on a KP-Sil snap cartridge (7% [0.2M NH_3 in MeOH] in CH_2Cl_2) gave the product as a pale yellow oil (26.3 mg, 33%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.01 (s, 9H), 0.96-1.01 (m, 2H), 1.75 (br d, *J* = 12.3 Hz, 2H), 2.12-2.30 (m, 4H), 2.67-2.73 (m, 2H), 2.81-2.87 (m, 2H), 3.03 (tt, *J* = 12.3, 3.5 Hz, 1H), 3.16 (br d, *J* = 11.0 Hz, 2H), 3.68-3.73 (m, 2H), 5.48 (s, 2H), 6.84 (t, *J* = 8.4 Hz, 2H), 7.09-7.17 (m, 1H), 7.81 (s, 1H), 8.07 (d, *J* = 5.1 Hz, 1H), 8.33 (s, 1H), 8.62 (s, 1H), 8.64 (d, *J* = 5.1 Hz, 1H); LC - MS (Method H; ESI, *m/z*) t_R = 1.22 min – 567 [$(M+H)^+$]; HRMS (Method I): found 567.2723; calculated for $C_{29}H_{37}F_2N_6O_2Si$ $(M+H)^+$ 567.2715.

8-(4-(2-(4-(2,4-Difluorophenyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (54m): According to General Procedure 4, 8-(4-(2-(4-(2,4-difluorophenyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)-pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (23.2 mg, 0.041 mmol) and hydrochloric acid (6 M, 0.5 mL) were reacted together in THF (0.5 mL). Purified on KP-NH snap cartridge (40% EtOH in CH_2Cl_2) to give the product as a white solid (7.5 mg, 42%). ^{1}H NMR (500 MHz, MeOH-d_4) 1.75-1.81 (m, 2H), 2.22-2.34 (m, 4H), 2.74-2.79 (m, 2H), 2.86-2.92 (m, 2H), 3.07-3.15 (m, 1H), 3.24 (br d, *J* = 7.5 Hz, 2H), 6.94 (t, *J* = 8.7 Hz, 2H), 7.21-7.28 (m, 1H), 7.81 (s, 1H), 8.06 (d, *J* = 5.1 Hz, 1H), 8.28 (s, 1H), 8.54 (d, *J* = 5.1 Hz, 1H), 8.78 (s, 1H), NH signal not observed; LC - MS (Method H; ESI, *m/z*) t_R = 0.84 min – 437 [$(M+H)^+$]; HRMS (Method I): found 437.1895; calculated for $C_{23}H_{23}F_2N_6O$ $(M+H)^+$ 437.1901.

8-(4-(2-(4-(3-(Trifluoromethyl)phenyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (51n): According to General Procedure 2, 2-(1-(4-oxo-3-((2-(trimethylsilyl)ethoxy)methyl)-3,4-

dihydropyrido[3,4-*d*]pyrimidin-8-yl)-1*H*-pyrazol-4-yl)ethyl methanesulfonate (60.0 mg, 0.129 mmol), 4-(3-(trifluoromethyl)phenyl)piperidine (44.3 mg, 0.193 mmol) and triethylamine (26 mg, 0.258 mmol) were reacted together in anhydrous DMF (1 mL) for 18 h. Purification by flash silica gel chromatography eluting with 5% [7N ammonia in methanol] in CH_2Cl_2 gave the title product as a colorless oil (33 mg, 43%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.01(s, 9H), 0.96 – 0.99 (m, 2H), 1.86 – 1.93 (m, 4H), 2.22 – 2.27 (m, 2H), 2.61 – 2.64 (m, 1H), 2.76 (t, *J* = 8.5 Hz, 2H), 2.88 (t, *J* = 8.0 Hz, 2H), 3.21 (d, *J* = 11.1 Hz, 2H), 3.68 – 3.71 (m, 2H), 5.46 (s, 2H), 7.42 – 7.47 (m, 3H), 7.50 (s, 1H), 7.80 (br s, 1H), 8.06 (d, *J* = 5.1 Hz, 1H), 8.31 (s, 1H), 8.59 (s, 1H), 8.62 (d, *J* = 5.1 Hz, 1H); LC - MS (Method H); ESI, *m/z*) t_R = 1.23 min - 599 $(M+H)^+$.

8-(4-(2-(4-(3-(Trifluoromethyl)phenyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (54n): According to General Procedure 4, 8-(4-(2-(4-(3-(trifluoromethyl)phenyl)piperidin-1-yl)ethyl)-1*H*-pyrazol-1-yl)-3-((2-(trimethylsilyl)-ethoxy)methyl)pyrido[3,4-*d*]pyrimidin-4(3*H*)-one (33.0 mg, 0.055 mmol) and hydrochloric acid (6 M, 1 mL) were reacted together in THF (1 mL). Aqueous 6M HCl (1 mL). This was purified by passing through an SCX cartridge eluting first with methanol followed by 7N ammonia in methanol. The ammoniacal solution was concentrated *in vacuo* and the residue triturated with Et_2O. The beige powder obtained was filtered and dried (25 mg, 97 %); ^{1}H NMR (500 MHz, MeOH-d_4) 1.85 – 1.1.92 (m, 2H), 1.93 – 1.97 (m, 2H), 2.33 – 2.38 (m, 2H), 2.71 – 2.78 (m, 1H), 2.79 – 2.82 (m, 2H), 2.89 – 2.92 (m, 2H), 3.23 – 3.26 (m, 2H), 7.49 – 7.53 (m, 2H), 7.54 – 7.56 (m, 2H), 7.82 (s, 1H), 8.05 (d, *J* = 5.1 Hz, 1H), 8.26 (s, 1H), 8.55 (d, *J* = 5.1 Hz, 1H), 8.77 (s, 1H), NH signal not observed; HRMS (Method I): found 469.1970; calculated for $C_{24}H_{23}F_3N_6O$ $(M+H)^+$ 469.1970.

Table S1: Crystallographic data collection and refinement statistics.

Protein construct	KDM4A 1-359	KDM4A 1-359	KDM4A 1-359
Ligand	**15**	**16**	**30b**
PDB code	5F2S	5F2W	5F5I
Crystal			
Space group	P 1 2_1 1	P 1 2_1 1	P 2_1 2_1 2
Unit cell dimensions (a/b/c in Å)	57.45/102.32/142.25	57.39/102.04/142.15	101.03/149.58/57.92
Unit cell angles (α/β/γ in °)	90/99.82/90	90/99.7/90	90/90/90
Data collection and processing			
Beamline	DLS I04	ESRF ID23	DLS I04-1
Wavelength (Å)	0.9200	0.8729	0.9200
Integration program	XDS	XDS	XDS
Reduction program	AIMLESS	AIMLESS	AIMLESS
Resolution range	57.82 – 2.08	49.48 – 2.60	54.01 – 2.63
Number of unique reflections [a]	95776 (7169)	47658 (4680)	26629 (1913)
Completeness [a]	98.5 (98.9)	95.8 (96.7)	99.2 (99.8)
Redundancy [a]	3.3 (3.3)	3.1 (3)	6.6 (6.9)
R_{merge} (%) [a]	5.8 (48.7)	10.9 (68)	10.5 (90.7)
I/σ(I) [a]	11.8 (2.3)	7.5 (1.4)	15.5 (2.3)
$CC_{1/2}$ [a, b]	0.997 (0.699)	0.990 (0.340)	0.998 (0.728)
Refinement			
Program	BUSTER	BUSTER	REFMAC
R_{work} (%)	16.31	17.91	21.09
R_{free} (%)	19.10	22.56	24.33
Number of residues	1390	1391	689
Number of water molecules	939	215	152
Average B-factor (Å^2)	39.24	54.06	54.3
Ramachandran favoured (%)	98.92	97.90	97.52
Ramachandran outliers (%)	0	0	0.29
RMSD bonds (Å)	0.010	0.010	0.008
RMSD angles (°)	0.98	1.07	1.212

[a] Values in parentheses are for the highest resolution shell.

[b] Half-dataset correlation coefficient, see: Karplus, P. A.; Diederichs, K. Linking crystallographic model and data quality. *Science* **2012**, *336*, 1030−1033.

Protein construct	KDM4D 1-342	KDM4A 1-359	KDM4A 1-359
Ligand	**30a**	**58**	**40**
PDB code	5F5A	5F37	5F32
Crystal			
Space group	P 4_3 2_1 2	P 1 2_1 1	P 1 2_1 1
Unit cell dimensions (a/b/c in Å)	71.28/71.28/150.40	57.33/102.43/142.46	57.22/102.59/141.74
Unit cell angles (α/β/γ in °)	90/90/90	90/99.83/90	90/99.29/90
Data collection and processing			
Beamline	DLS I04-1	DLS I04	DLS I03
Wavelength (Å)	0.9200	0.9200	1.0721
Integration program	XDS	XDS	XDS
Reduction program	AIMLESS	AIMLESS	AIMLESS
Resolution range	50.40 – 1.41	48.21 – 2.22	48.86 – 2.05
Number of unique reflections [a]	75484 (5477)	78706 (4476)	89282 (2244)
Completeness [a]	100 (99.9)	98.3 (98.7)	88.3 (43.9)
Redundancy [a]	13.1 (12.8)	3.3 (3.3)	5.9 (1.5)
R_{merge} (%) [a]	8.3 (72.2)	13.5 (109.9)	7.9 (69.2)
I/σ(I) [a]	18.6 (3.7)	6.9 (1)	10.3 (0.5)
$CC_{1/2}$ [a, b]	0.998 (0.901)	0.990 (0.323)	0.998 (0.256)
Refinement			
Program	REFMAC	BUSTER	BUSTER
R_{work} (%)	13.11	16.94	16.81
R_{free} (%)	16.47	20.88	20.31
Number of residues	330	1403	1384
Number of water molecules	344	771	765
Average B-factor (Å^2)	20.2	41.29	57.78
Ramachandran favoured (%)	98.86	98.57	98.34
Ramachandran outliers (%)	0	0	0
RMSD bonds (Å)	0.012	0.010	0.010
RMSD angles (°)	1.532	1.05	1.04

[a] Values in parentheses are for the highest resolution shell.

[b] Half-dataset correlation coefficient, see: Karplus, P. A.; Diederichs, K. Linking crystallographic model and data quality. *Science* **2012**, *336*, 1030−1033.

Protein construct	KDM4A 1-359	KDM4D 1-342	KDM4A 1-359
Ligand	**37**	**44a**	**52d**
PDB code	5F39	5F5C	5F3C
Crystal			
Space group	P 1 2_1 1	P 4_3 2_1 2	P 1 2_1 1
Unit cell dimensions (a/b/c in Å)	58.41/102.06/143.47	71.59/71.59/150.79	58.10/101.73/142.76
Unit cell angles (α/β/γ in °)	90/99.82/90	90/90/90	90/99.53/90
Data collection and processing			
Beamline	DLS I03	In-house Bruker	DLS I02
Wavelength (Å)	1.0721	1.5419	0.9795
Integration program	XDS	SAINT	XDS
Reduction program	AIMLESS	SADABS	AIMLESS
Resolution range	49.63 – 2.65	64.67 – 1.88	49.35 – 2.06
Number of unique reflections [a]	46569 (4500)	32700 (4492)	101106 (4953)
Completeness [a]	96.6 (95.7)	99.7 (98.1)	99.9 (100)
Redundancy [a]	1.9 (1.7)	10.4 (4.3)	6.8 (7)
R_{merge} (%) [a]	8.9 (109.7)	11.4 (47.5)	6.3 (179.7)
I/σ(I) [a]	5.1 (0.6)	13.5 (2.3)	15.4 (1)
$CC_{1/2}$ [a, b]	0.996 (0.364)	0.994 (0.686)	0.999 (0.339)
Refinement			
Program	BUSTER	REFMAC	BUSTER
R_{work} (%)	16.90	17.15	16.06
R_{free} (%)	20.97	21.08	19.55
Number of residues	1379	330	1361
Number of water molecules	325	411	1041
Average B-factor (Å^2)	73.75	14.8	56.67
Ramachandran favoured (%)	98.03	99.14	98.74
Ramachandran outliers (%)	0	0	0
RMSD bonds (Å)	0.010	0.016	0.010
RMSD angles (°)	1.11	1.693	1.02

[a] Values in parentheses are for the highest resolution shell.

[b] Half-dataset correlation coefficient, see: Karplus, P. A.; Diederichs, K. Linking crystallographic model and data quality. *Science* **2012**, *336*, 1030−1033.

Protein construct	KDM4A 1-359	KDM4A 1-359	KDM4A 1-359
Ligand	**53a**	**54a**	**54j**
PDB code	5F3G	5F3E	5F3I
Crystal			
Space group	P 1 2_1 1	P 1 2_1 1	P 1 2_1 1
Unit cell dimensions (a/b/c in Å)	57.27/100.57/142.59	57.91/101.63/142.41	57.79/101.57/142.33
Unit cell angles (α/β/γ in °)	90/99.43/90	90/99.41/90	90/99.42/90
Data collection and processing			
Beamline	In-house Rigaku	In-house Rigaku	DLS I03
Wavelength (Å)	1.5419	1.5419	0.9763
Integration program	XDS	XDS	XDS
Reduction program	AIMLESS	AIMLESS	AIMLESS
Resolution range	48.06 – 2.50	48.36 – 2.16	49.72 – 2.24
Number of unique reflections [a]	54102 (3594)	87262 (4396)	77606 (4545)
Completeness [a]	97.5 (79.6)	100 (100)	99.8 (37.9)
Redundancy [a]	13.9 (9.2)	18 (11.3)	6.9 (7.1)
R_{merge} (%) [a]	19.5 (306.1)	22.3 (214.9)	9.1 (164.6)
I/σ(I) [a]	11.1 (1.2)	10.9 (1.3)	11.6 (1.1)
$CC_{1/2}$ [a, b]	0.993 (0.314)	0.997 (0.388)	0.998 (0.379)
Refinement			
Program	BUSTER	BUSTER	BUSTER
R_{work} (%)	20.27	16.23	16.86
R_{free} (%)	24.64	21.03	21.29
Number of residues	1350	1347	1357
Number of water molecules	363	1009	613
Average B-factor (Å^2)	53.42	44.55	60.20
Ramachandran favoured (%)	97.37	98.58	97.61
Ramachandran outliers (%)	0	0	0
RMSD bonds (Å)	0.010	0.010	0.010
RMSD angles (°)	1.08	1.04	1.05

[a] Values in parentheses are for the highest resolution shell.

[b] Half-dataset correlation coefficient, see: Karplus, P. A.; Diederichs, K. Linking crystallographic model and data quality. *Science* **2012**, *336*, 1030−1033.

Protein construct	KDM5B 26-770
Ligand	**52d**
PDB code	5FPI
Crystal	
Space group	P 6_5 2 2
Unit cell dimensions (a/b/c in Å)	142.91/142.91/152.10
Unit cell angles (α/β/γ in °)	90/90/120
Data collection and processing	
Beamline	DLS I04-1
Wavelength (Å)	0.9795
Integration program	XDS
Reduction program	AIMLESS
Resolution range	47.17 – 2.35
Number of unique reflections [a]	38565 (3796)
Completeness [a]	99.7 (100)
Redundancy [a]	19.7 (20.1)
R_{merge} (%) [a]	14.7 (136.3)
I/σ(I) [a]	14.3 (2.6)
$CC_{1/2}$ [a, b]	0.997 (0.821)
Refinement	
Program	BUSTER
R_{work} (%)	18.56
R_{free} (%)	21.01
Number of residues	456
Number of water molecules	279
Average B-factor (Å^2)	53.13
Ramachandran favoured (%)	98
Ramachandran outliers (%)	0
RMSD bonds (Å)	0.013
RMSD angles (°)	1.78

[a] Values in parentheses are for the highest resolution shell.

[b] Half-dataset correlation coefficient, see: Karplus, P. A.; Diederichs, K. Linking crystallographic model and data quality. *Science* **2012**, *336*, 1030−1033.

Table S2: Kinase selectivity profiling of compound **54k** in a 50-kinase panel screened at a concentration of 1 μM. The results are displayed as average % activity remaining of assay duplicates with a standard deviation.

	% activity remaining	SD
MKK1	**104**	13
JNK1	**104**	19
p38a MAPK	**107**	2
RSK1	**90**	19
PDK1	**105**	17
PKBa	**99**	5
SGK1	**103**	27
S6K1	**96**	12
PKA	**107**	12
ROCK 2	**100**	10
PRK2	**91**	3
PKCa	**86**	19
PKD1	**78**	4
MSK1	**117**	2
CAMKKb	**108**	3
CAMK1	**106**	18
SmMLCK	**141**	10
CHK2	**100**	10
GSK3b	**91**	2
PLK1	**107**	22
Aurora B	**114**	2
LKB1	**102**	2
AMPK (hum)	**110**	3
MARK3	**94**	1
CK1δ	**114**	3
CK2	**93**	8
DYRK1A	**88**	5
NEK6	**120**	6
TBK1	**115**	0
PIM1	**99**	2
SRPK1	**102**	5
EF2K	**115**	3
HIPK2	**93**	11

PAK4	**89**	9
MST2	**101**	12
MLK3	**97**	11
TAK1	**91**	1
IRAK4	**99**	6
RIPK2	**97**	16
TTK	**105**	3
Src	**124**	3
Lck	**101**	18
BTK	**68**	10
JAK2	**111**	10
SYK	**101**	1
EPH-A2	**113**	28
HER4	**106**	8
IGF-1R	**102**	20
TrkA	**77**	8
VEG-FR	**131**	9

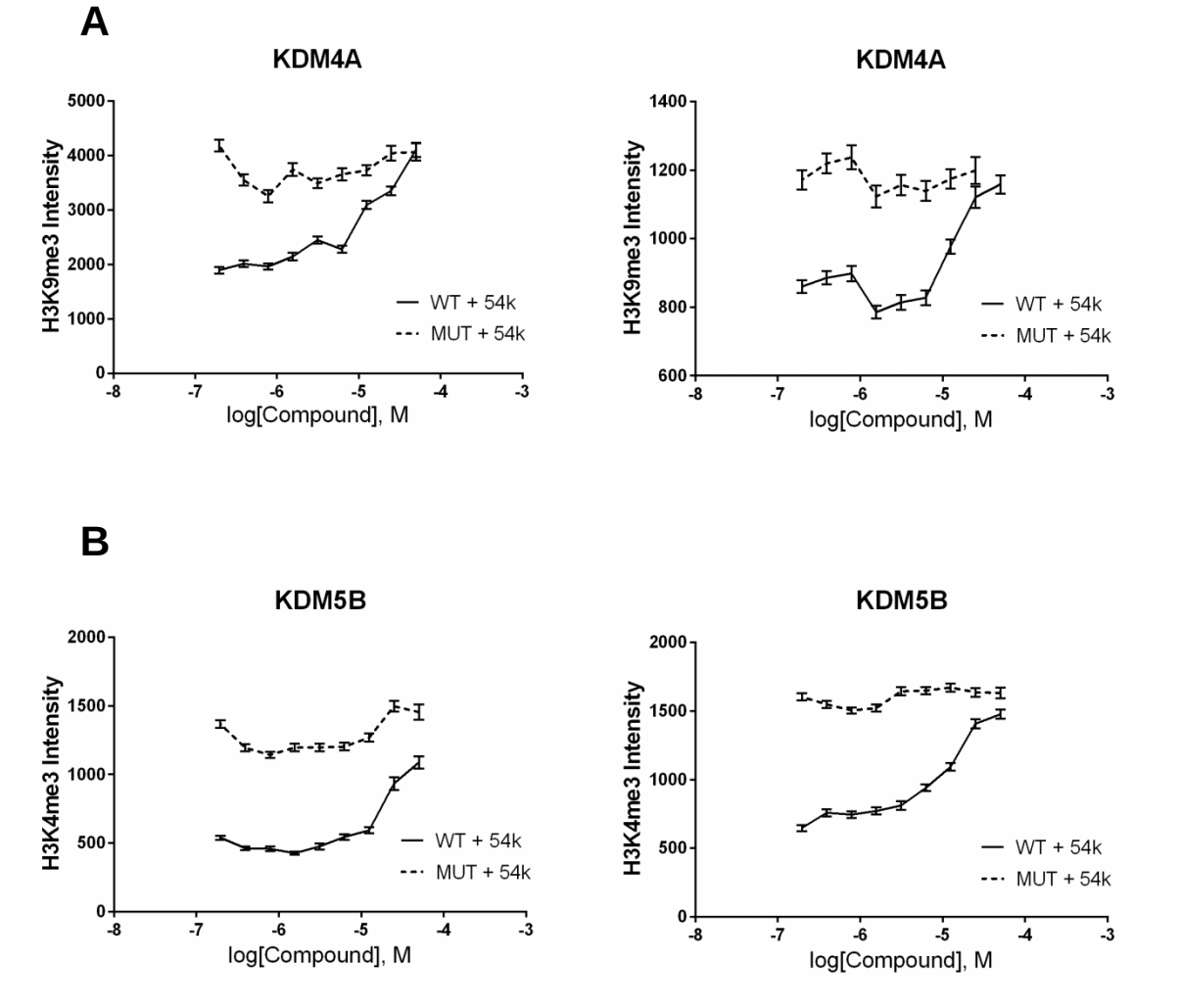

Figure S1: Cellular activity of **54k** in HeLa cells assessed by immunofluorescence assay. HeLa cells transiently overexpressing KDM4A wildtype (WT) or a catalytic dead mutant (MUT) were assayed for H3K9me3 levels (A) or H3K4me3 levels for cells overexpressing KDM5B wildtype (WT) or the respective catalytic dead mutant (MUT) (B). Shown are 2 independent biological replicates. Data represents the average and standard error of at least 100 cells.