Supporting Information

Discovery and preclinical profiling of 3-[4-(morpholin-4-yl)-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl]benzonitrile (PF-06447475), a highly potent, selective, brain penetrant, and *in vivo* active LRRK2 kinase inhibitor

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Experimental. Compounds **7-13**, **15-24**, **26-27**, and **29-43**

(S)-3-(4-(3-methylpiperidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (7) Prepared from **47** (300 mg, 1.18 mmol) and (S)-3-methylpiperidine (117 mg, 1.18 mmol) using method B. Yield 160 mg, 43% as a white solid. LCMS *m/z* 318.3 [M+H$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.55 (br s, 1H), 8.49 (s, 1H), 7.83 (br s, 1H), 7.75 (br d, *J*=7.5 Hz, 1H), 7.61 (br d, *J*=7.5 Hz, 1H), 7.54 (dd, *J*=8.0, 7.5 Hz, 1H), 7.23 (s, 1H), 3.84 (br d, *J*=13 Hz, 1H), 3.77 (br d, *J*=13 Hz, 1H), 2.61-2.70 (m, 1H), 2.34 (dd, *J*=12.0, 11.5 Hz, 1H), 1.65-1.77 (m, 1H), 1.29-1.55 (m, 3H), 0.91-1.03 (m, 1H), 0.68 (d, *J*=6.5 Hz, 3H).

(R)-3-(4-(3-methylpiperidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (8) Prepared from **47** and (R)-3-methylpiperidine using method B in library format. LCMS *m/z* 303.9 [M+H$^+$]. ^{1}H NMR (400 MHz, MeOH-d_4) δ 8.30 (s, 1 H), 7.80-7.84 (m, 2 H), 7.59-7.568 (m, 2 H), 7.39 (s, 1 H) , 3.81(d, *J*=12.8 Hz, 1 H), 3.712-3.681 (d, *J*=12.4 Hz, 1 H), 2.61-2.68 (m, 1 H) , 2.29 (t, *J*=11.8 Hz, 1 H) , 1.70 (d, *J*=11.2 Hz, 1 H) , 1.49-1.54 (m, 1 H) , 1.36-1.44 (m, 2 H) , 0.95-1.02 (m, 1 H) , 0.61-0.62 (d, *J*=0.8 Hz, 3 H).

3-(4-(piperidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (9). Prepared from **47** and piperidine using method B in library format. LCMS *m/z* 303.9 [M+H$^+$]. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.21 (br s, 1H), 8.35 (s, 1H), 7.95 (br s, 1H), 7.85 (br d, *J*=7.5 Hz, 1H), 7.74 (br d, *J*=7.5 Hz, 1H), 7.61-7.67 (m, 2H), 3.13-3.19 (m, 4H), 1.40-1.48 (m, 2H), 1.29-1.38 (m, 4H).

3-(4-(pyrrolidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (10). Prepared from **47** and pyrrolidine using method B in library format. LCMS *m/z* 290.1 [M+H$^+$]. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (s, 1H), 7.92 (s, 1H), 7.85 (d, *J*=7.5 Hz, 1H), 7.76 (d, *J*=7.5 Hz, 1H), 7.63 (dd, *J*=8.0, 7.5 Hz, 1H), 7.57 (br s, 1H), 3.19-3.3 (br m, 4H), 1.70-1.79 (br m, 4H).

3-(4-(azetidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (11). Prepared from **47** (127 mg, 0.5 mmol) and azetidine (41 mg, 0.5 mmol) using method B. Yield 57 mg, 41% as a white solid. LCMS *m/z* 276.1 [M+H$^+$]. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.06 (s, 1H), 8.24 (s, 1H), 7.87 (s, 1H), 7.79 (d, *J*=8.4 Hz, 1H), 7.73 (d, *J*=7.6 Hz, 1H), 7.64 (t, *J*=7.6 Hz, 1H), 7.38 (s, 1H), 3.66 (t, *J*=7.6 Hz, 4H), 2.07 (t, *J*=7.6 Hz, 2H).

3-(4-(dimethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (12). A mixture of 3-(4-chloro-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)benzonitrile (**47**) (157 mg, 0.616 mmol), dimethylamine (189 mg, 4.19 mmol) and triethylamine (182 mg, 1.80 mmol) in *n*-butanol (12 mL) was heated under microwave irradiation at 150 °C for 25 minutes. After concentration *in vacuo*, the residue was purified by preparative HPLC (Column: Phenomenex Gemini C18, 8 μm; Mobile phase A: ammonia in water, pH 10; Mobile phase B: acetonitrile; Gradient: 25% to 65% B) to give the product as a white solid. Yield: 72.1 mg, 0.27 mmol, 44%. LCMS *m/z* 263.8 [M+H$^+$]. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.15 (br s, 1H), 8.28 (s, 1H), 7.93 (br s, 1H), 7.78 (br d, *J*=7.8 Hz, 1H), 7.73 (br d, *J*=7.8 Hz, 1H), 7.62 (br dd, *J*=8.0, 7.8 Hz, 1H), 7.57 (br s, 1H), 2.73 (s, 6H).

3-(4-(diethylamino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (13). Prepared from **47** and diethylamine using method B. LCMS *m/z* 292.0 [M+H$^+$]. ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O) δ 8.29 (s, 1H) 7.88-7.90 (m, 1H), 7.84 (br d, *J*=8.5 Hz, 1H), 7.71 (br d, *J*=8.0 Hz, 1H), 7.61 (dd, *J*=8.0, 7.5 Hz, 1H), 7.56 (s, 1H), 3.20 (q, *J*=7.0 Hz, 4H), 0.88 (t, *J*=7.0 Hz, 6H).

3-(4-(4-methylpiperazin-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (15). Prepared from **47** (100 mg, 0.39 mmol) and piperazine (39 mg, 0.39 mmol) using method B. Yield 67 mg, 53% as a white solid. LCMS *m/z* 319.2 [M+H$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.79 (s, 1H), 8.44 (s, 1H), 7.78 (s, 1H), 7.70 (d, *J*=7.6 Hz, 1H), 7.54 (d, *J*=8.0 Hz, 1H), 7.47 (t, *J*=8.0 Hz, 1H), 7.19 (s, 1H), 3.29 (bs, 4H), 2.21 (bs, 4H), 2.18 (bs, 3H).

3-(4-(3-methoxypiperidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (16). Prepared in library format using method B from **47** and 3-methoxypiperidine. LCMS *m/z* 334 [M+H$^+$]. Retention time 2.46 minutes.

3-(4-(4-methoxypiperidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (17). Prepared in library format using method B from **47** and 4-methoxypiperidine. LCMS *m/z* 334 [M+H$^+$]. Retention time 2.43 minutes.

3-(4-(3-(methoxymethyl)piperidin-1-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (18). Prepared in library format using method B from **47** and 3-(methoxymethyl)piperidine. LCMS *m/z* 348 [M+H$^+$]. Retention time 2.58 minutes.

4-(5-phenyl-7H-pyrrolo[2,3-d]pyrimidin-4-yl)morpholine (19). Prepared in library format using method A from **46** and bromobenzene. LCMS *m/z* 281 [M+H$^+$]. Retention time: 2.40 minutes[9]

4-(5-(3-methoxyphenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)morpholine (20). Prepared in library format using method A from **46** and 1-bromo-3-methoxybenzene. LCMS *m/z* 311 [M+H$^+$]. Retention time: 2.42 minutes[9]

4-(5-(3-chlorophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)morpholine (21). Prepared in library format using method A from **46** and 1-bromo-3-chlorobenzene. LCMS *m/z* 315 [M+H$^+$]. Retention time: 2.39 minutes[10]

2-fluoro-3-(4-morpholino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (22). Prepared from **46** (464 mg, 1.01 mmol) and (3-cyano-2-fluorophenyl)boronic acid (200 mg, 1.21 mmol) using method A. Yield 43.5 mg, 13% as a yellow solid. LCMS *m/z* 323.9 [M+H$^+$]. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (s, 1H), 7.80-7.90 (m, 2H), 7.64 (d, *J*=1.0 Hz, 1H), 7.52 (dd, *J*=8.0, 7.5 Hz, 1H), 3.35-3.41 (m, 4H), 3.09-3.15 (m, 4H).

2-fluoro-5-(4-morpholino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (23). Prepared from **46** (116 mg, 0.25 mmol) and (3-cyano-4-fluorophenyl)boronic acid (50 mg, 0.3 mmol) using method A. Yield 35.4 mg, 44% as a yellow solid. LCMS *m/z* 324.2 [M+H$^+$]. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.31 (s, 1H), 8.40 (s, 1H), 8.08 (dd, *J*=6.4, 2.4 Hz, 1H), 7.91-7.95 (m, 1H), 7.64-7.69 (m, 2H), 3.48-3.49 (m, 4H), 3.15-3.16 (m, 4H).

3-fluoro-5-(4-morpholino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (24). Prepared from **46** (150 mg, 0.33 mmol) and (3-cyano-5-fluorophenyl)boronic acid (65 mg, 0.39 mmol) using method A. Yield 20 mg, 19% as a white solid. LCMS *m/z* 324.2 [M+H$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.82 (s, 1H), 8.55 (s, 1H), 7.68 (s, 1H), 7.54 (d, *J*=1.2 Hz, 1H), 7.31- 7.34 (m, 2H), 3.59- 3.61 (m, 4H), 3.32- 3.35 (m, 4H).

4-(4-morpholino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)picolinonitrile (26). Prepared from **48** (140 mg, 0.3 mmol) and 4-bromopicolinonitrile (47 mg, 0.25 mmol) using method C. Yield 36.6 mg, 48% as a pale yellow solid. LCMS *m/z* 307.2 [M+H$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H), 8.75 (d, *J*=5.2 Hz, 1H), 8.56 (s, 1H), 7.93 (s, 1H), 7.70 (d, *J*=5.2 Hz, 1H), 7.44 (s, 1H), 3.62- 3.64 (m, 4H), 3.34- 3.36 (m, 4H).

5-(4-morpholino-7H-pyrrolo[2,3-d]pyrimidin-5-yl)nicotinonitrile (27). Prepared from **48** (223 mg, 0.48 mmol) and 5-bromonicotinonitrile (80 mg, 0.44 mmol) using method C. Yield 29.2 mg, 22% as a white solid. LCMS *m/z* 307.2 [M+H$^+$]. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.07 (d, *J*=2.0 Hz, 1H), 8.90 (d, *J*=2.0 Hz, 1H), 8.45 (s, 1H), 8.41 (s, 1H), 7.83 (s, 1H), 3.48-3.49 (m, 4H), 3.14-3.15 (m, 4H).

4-(5-(1-methyl-1H-pyrazol-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)morpholine (29). Prepared from **48** (133 mg, 0.29 mmol) and 3-bromo-1-methyl-1H-pyrazole (50 mg, 0.24 mmol) using method C. Yield 18.8 mg, 28% as a white solid. LCMS *m/z* 285.2 [M+H$^+$]. ^{1}H

NMR (400 MHz, $CDCl_3$) δ 9.70 (br s, 1H), 8.45 (s, 1H), 7.43 (d, *J*=2.0 Hz, 1H), 7.33 (d, *J*=2.0 Hz, 1H), 6.43 (d, *J*=2.0 Hz, 1H), 3.99 (s, 3H), 3.66 (dd, *J*=4.8, 4.8 Hz, 4H), 3.42 (dd, *J*=4.9, 4.4 Hz, 4H).

4-(5-(5-methylpyridin-3-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)morpholine (30). Prepared from **48** (296 mg, 0.64 mmol) and 3-bromo-5-methylpyridine (100 mg, 0.58 mmol) using method C. Yield 9.5 mg, 5% as a white solid. LCMS *m/z* 296.0 [$M+H^+$]. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (br d, *J*=1.5 Hz, 1H), 8.39 (s, 1H), 8.33-8.36 (m, 1H), 7.73-7.76 (m, 1H), 7.63 (s, 1H), 3.40-3.47 (m, 4H, assumed; partially obscured by water peak), 3.12-3.17 (m, 4H), 2.38 (s 3H);

4-(5-(pyrazin-2-yl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)morpholine (31). Prepared from **48** (246 mg, 0.53 mmol) and 2-iodopyrazine (100 mg, 0.49 mmol) using method C. Yield 11 mg, 8% as a white solid. LCMS *m/z* 283.1 [$M+H^+$]. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.92 (s, 1H), 8.68 (s, 1H), 8.51 (s, 1H), 8.40 (s, 1H), 7.86 (s, 1H), 3.50 (bs, 4H), 3.22 (bs, 4H).

(R)-3-(4-(2-methylmorpholino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (32). Prepared from **47** (100 mg, 0.39 mmol) and (2*R*)-2-methylmorpholine (54 mg, 0.53 mmol) using method B. Yield: 47.1 mg, 37.5% as a white solid. LCMS *m/z* 319.9 [$M+H^+$]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.02 (br s, 1H), 8.53 (s, 1H), 7.85 (s, 1H), 7.78 (d, *J*=7.0 Hz, 1H), 7.53-7.68 (m, 2H), 7.30 (s, 1H), 3.57-3.77 (m, 3H), 3.39-3.54 (m, 2H), 2.92 (br dd, *J*=12, 12 Hz, 1H), 2.59 (dd, *J*=11.5, 11.0 Hz, 1H), 0.98 (d, *J*=6.0 Hz, 3H).

(S)-3-(4-(2-methylmorpholino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (33). Prepared from **47** (100 mg, 0.39 mmol) and (2*S*)-2-methylmorpholine (54 mg, 0.53 mmol) using method B. Yield: 17.5 mg, 14% as a white solid. LCMS *m/z* 320.2 [$M+H^+$]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.71 (br s, 1H), 8.53 (br s, 1H), 7.73-7.89 (m, 2H), 7.51-7.69 (m, 2H), 7.28 (s, 1H, assumed;

partially obscured by solvent peak), 3.56-3.77 (m, 3H), 3.39-3.54 (m, 2H), 2.86-2.98 (m, 1H), 2.53-2.65 (m, 1H), 0.93-1.03 (m, 3H).

4-(5-(3-cyanophenyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)morpholine-2-carbonitrile (34). Prepared from **47** (100 mg, 0.39 mmol) and morpholine-2-carbonitrile (58 mg, 0.59 mmol) using method B. Yield 9.4 mg, 7% as a white solid. LCMS *m/z* 353.1 [M+Na$^+$]. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.04 (br s, 1H), 7.91 (br d, *J*=8 Hz, 1H), 7.80 (br d, *J*=8 Hz, 1H), 7.76 (s, 1H), 7.66 (dd, *J*=8, 8 Hz, 1H), 5.06-5.09 (m, 1H), 3.79-3.86 (m, 1H), 3.43-3.52 (m, 2H), 3.3-3.41 (m, 1H, assumed; partially obscured by water peak), 3.10-3.18 (m, 1H), 2.82-2.91 (m, 1H).

3-(4-(2-(cyanomethyl)morpholino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (35). Prepared from **47** (254 mg, 1 mmol) and 2-(morpholin-2-yl)acetonitrile (126 mg, 1 mmol) using method B. Yield 13.5 mg, 4% as a brown solid. LCMS *m/z* 344.9 [M+H$^+$]. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.38 (br s, 1H), 8.42 (s, 1H), 8.00 (dd, *J*=1.6, 1.4 Hz, 1H), 7.86 (ddd, *J*=7.7, 1.7, 1.4 Hz, 1H), 7.77 (ddd, *J*=7.6, 1.5, 1.4 Hz, 1H), 7.71-7.73 (m, 1H), 7.69 (dd, *J*=8.0, 7.5 Hz, 1H), 3.72-3.79 (m, 1H), 3.60-3.68 (m, 2H), 2.63-2.77 (m, 4H).

3-(4-(2-(isoxazol-5-yl)morpholino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (36). Prepared from **47** (40 mg, 0.155 mmol) and 2-(isoxazol-5-yl)morpholine (20 mg, 0.13 mmol) using method B. Yield 1.2 mg, 3% as a white solid. LCMS *m/z* 394.9 [M+Na$^+$]. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.40 (br s, 1H), 8.53 (d, *J*=1.5 Hz, 1H), 8.44 (s, 1H), 8.00-8.02 (m, 1H), 7.86 (br d, *J*=8 Hz, 1H), 7.75 (br d, *J*=8 Hz, 1H), 7.71 (d, *J*=2.5 Hz, 1H), 7.66 (dd, *J*=8, 8 Hz, 1H), 6.39 (d, *J*=1.5 Hz, 1H), 4.66-4.71 (m, 1H), 3.80-3.86 (m, 1H), 3.72-3.78 (m, 1H), 3.04-3.11 (m, 1H), 2.88-2.97 (m, 1H).

3-(4-(2-(3-methyl-1,2,4-oxadiazol-5-yl)morpholino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (37). Prepared from **47** (100 mg, 0.39 mmol) and 2-(3-methyl-1,2,4-oxadiazol-5-yl)morpholine (87 mg, 0.39 mmol) using method B. Yield 12.8 mg, 8% as a white solid. LCMS *m/z* 388.2 [M+H$^+$]. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.35 (br s, 1H), 8.43 (s, 1H), 8.01 (br s, 1H), 7.69-7.81 (m, 3H), 7.59 (dd, *J*=7.5, 7.5 Hz, 1H), 4.94 (br d, *J*=8 Hz, 1H), 3.91 (br d, *J*=13.5 Hz, 1H), 3.62-3.70 (m, 1H), 3.43-3.51 (m, 1H), 2.88-2.97 (m, 1H), 2.35 (s, 3H).

(S)-3-(4-(2-(5-methyl-1,2,4-oxadiazol-3-yl)morpholino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (38). Prepared from **47** (400 mg, 1.6 mmol) and 2-(5-methyl-1,2,4-oxadiazol-3-yl)morpholine (620 mg, 4.8 mmol) using method B. Racemate was separated using SFC (Column: Chiral Technologies Chiralpak® AS, 5 μm; Eluent: 63:37 CO_2/MeOH (containing 0.05% ammonium hydroxide)) to yield the title compound and its enantiomer (**39**) as white solids. LCMS *m/z* 388.1 [M+H$^+$]. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.37 (br s, 1H), 8.43 (s, 1H), 7.99-8.02 (m, 1H), 7.85 (ddd, *J*=7.8, 1, 1 Hz, 1H), 1H), 7.75 (ddd, *J*=7.8, 1, 1 Hz, 1H), 7.71 (s, 1H), 7.65 (dd, *J*=7.8, 7.8 Hz, 1H), 4.67 (dd, *J*=9.5, 2.5 Hz, 1H), 3.85 (br d, *J*=13 Hz, 1H), 3.68-3.74 (m, 1H), 3.18 (dd, *J*=13, 9 Hz, 1H), 2.86-2.94 (m, 1H), 2.57 (s, 3H).

(R)-3-(4-(2-(5-methyl-1,2,4-oxadiazol-3-yl)morpholino)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (39). LCMS *m/z* 388.1 [M+H$^+$]. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.37 (br s, 1H), 8.43 (s, 1H), 8.00 (dd, *J*=1.5, 1.5 Hz, 1H), 7.85 (ddd, *J*=7.8, 1.5, 1.5 Hz, 1H), 7.75 (ddd, *J*=7.8, 1.5, 1.2 Hz, 1H), 7.71 (s, 1H), 7.65 (dd, *J*=7.8, 7.8 Hz, 1H), 4.67 (dd, *J*=9.7, 2.6 Hz, 1H), 3.85 (br d, *J*=13 Hz, 1H), 3.68-3.74 (m, 1H), 3.18 (dd, *J*=13.0, 9.5 Hz, 1H), 2.86-2.94 (m, 1H), 2.57 (s, 3H).

3-(4-(1,4-oxazepan-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (40). Prepared from **47** (110 mg, 0.43 mmol) and 1,4-oxazepane (87 mg, 0.86 mmol) using method B. Yield 28.7

mg, 21% as a white solid. LCMS *m/z* 320.1 [M+H$^+$]. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.15 (s, 1H), 8.26 (s, 1H), 7.90 (s, 1H), 7.74 (d, *J*=8 Hz, 2H), 7.61 (t, *J*=8 Hz, 1H), 7.52 (s, 1H), 3.47-3.52 (m, 6H), 3.38-3.42 (m, 2H) 1.67-1.69 (m, 2H).

3-(4-(2-oxa-6-azaspiro[3.3]heptan-6-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (41). Prepared from **47** (254 mg, 1 mmol) and 2-oxa-6-azaspiro[3.3]heptane (99 mg, 1 mmol) using method B. Yield 4 mg, 1.3% as a white solid. LCMS *m/z* 318.1 [M+H$^+$]. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12 (s, 1H), 8.27 (s, 1H), 7.89 (s, 1H), 7.82 (d, *J*=7.6 Hz, 1H), 7.73 (t, *J*=7.6 Hz, 1H), 7.65 (t, *J*=7.6 Hz, 1H), 7.45 (s, 1H), 4.50 (s, 4H), 3.81 (s, 2H).

3-(4-(hexahydro-5H-furo[2,3-c]pyrrol-5-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (42). Prepared from **47** (100 mg, 0.39 mmol) and hexahydro-2H-furo[2,3-c]pyrrole (90 mg, 0.8 mmol) using method B. Yield 52 mg, 40% as a white solid. LCMS *m/z* 331.9 [M+H$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.32 (br s, 1H), 8.42 (s, 1H), 7.78 (br s, 1H), 7.72 (br d, *J*=7.8 Hz, 1H), 7.62 (br d, *J*=7.8 Hz, 1H), 7.52 (dd, *J*=7.8, 7.8 Hz, 1H), 7.18 (s, 1H), 4.34 (br dd, *J*=5, 5 Hz, 1H), 3.83-3.91 (m, 1H), 3.74 (ddd, *J*=8.3, 7.8, 5.3 Hz, 1H), 3.46-3.56 (m, 3H), 3.19 (dd, *J*=12.4, 4.9 Hz, 1H), 2.74-2.84 (m, 1H), 1.99-2.10 (m, 1H).

3-(4-(tetrahydro-1H-furo[3,4-c]pyrrol-5(3H)-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl)benzonitrile (43). Prepared from **47** (100 mg, 0.39 mmol) and hexahydro-1H-furo[3,4-c]pyrrole (90 mg, 0.8 mmol) using method B. Yield 19.7 mg, 15% as a white solid. LCMS *m/z* 331.9 [M+H$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (br s, 1H), 8.43 (s, 1H), 7.81 (br s, 1H), 7.73 (br d, *J*=7.8 Hz, 1H), 7.63 (br d, *J*=7.8 Hz, 1H), 7.54 (dd, *J*=7.8, 7.7 Hz, 1H), 7.18 (s, 1H), 3.71 (br dd, *J*=9.0, 6.2 Hz, 2H), 3.56 (br dd, *J*=11.3, 7.2 Hz, 2H), 3.47 (dd, *J*=9.0, 2.6 Hz, 2H), 3.21 (dd, *J*=11.4, 4.1 Hz, 2H), 2.75-2.81 (m, 2H).

Table S1: Data collection and refinement statistics

	14 (PF-06447475) 4U8Z	**28** (PF-06454589) 4W8D	**38** 4W8E
Data collection			
Space group	C2	C2	$P2_1$
Cell dimensions			
a, *b*, *c* (Å)	99.1, 59.0, 61.8	100, 58.6, 61.9	47.5, 56.5, 61.1
β (°)	93.8	93.9	111.4
Resolution (Å)	37.4-1.63 (1.72-1.63)*	49.9-1.77 (1.86-1.77)*	43.4- 1.79 (1.89-1.79)*
R_{sym} or R_{merge}	0.03 (0.18)	0.03 (0.27)	0.02 (0.36)
$I/\sigma I$	16.4 (2.4)	16.2 (2.2)	22.1 (2.9)
Completeness (%)	96.3 (85)	97.1 (86)	96.4 (95.7)
Redundancy	3.1 (2.3)	3.0 (1.8)	3.4 (3.4)
Refinement			
Resolution (Å)	37.40-1.63	40.16-1.77	21.61- 1.79
No. reflections	42607	33898	27227
$R_{work/}$ R_{free}	0.19 / 0.22	0.17 / 0.18	0.17 (0.21)
No. atoms			
Protein	2308	2308	2314
Ligand/ion	296	324	261
Water	261	292	221
B-factors			
Protein	37.8	36.8	45.6
Ligand/ion	33.5	31.4	60.1
Water	44.3	46.6	50.1
R.m.s deviations			
Bond lengths (Å)	0.01	0.01	0.01
Bond angles (°)	1.07	1.06	1.03

*Highest resolution shell is shown in parenthesis.

Figure S1. Profiling of **12:** panel A, potency and ADMET; panel B, *ex vivo* kinase selectivity panel (ActivX KiNativ)

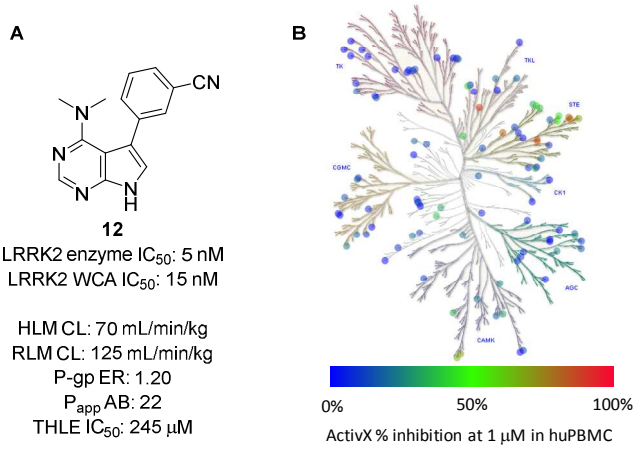

Figure S2. Detailed profiling of **28**: panel A, potency and ADMET; panel B, *in vitro* kinase selectivity (DiscoveRx KINOMEscan); and panel C, *ex vivo* kinase selectivity (ActivX KiNativ)

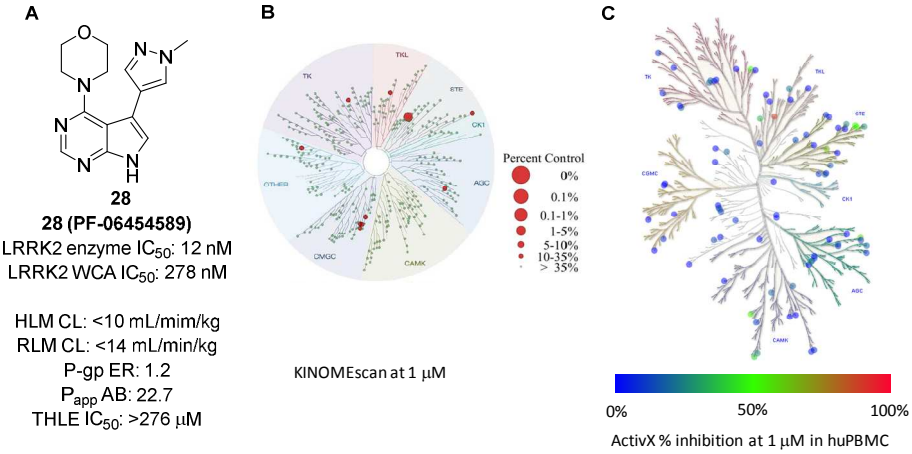

Figure S3. Plot of drug tissue exposure vs time. Data for unbound concentrations of **14** in plasma, brain, and kidney indicating instantaneous equilibration at all time points.

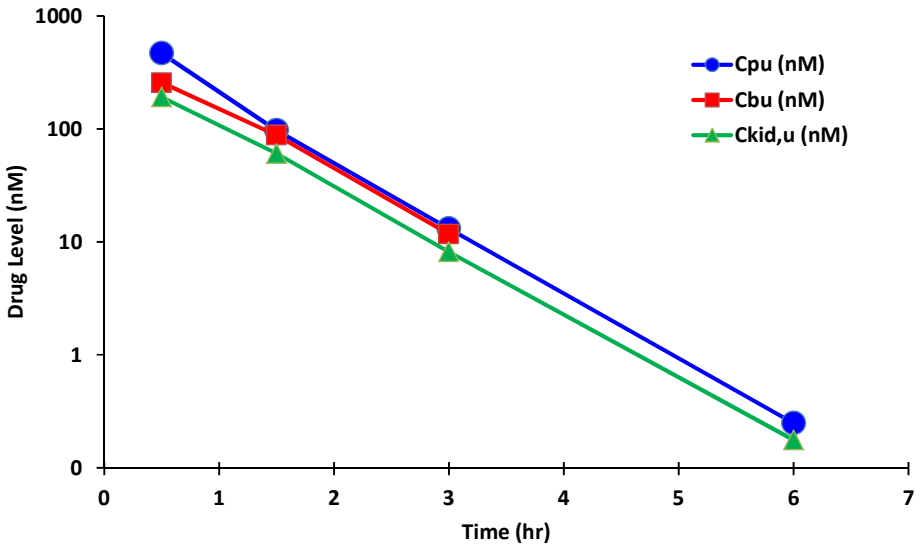

Table S2. Ambit data for compounds **14** and **28** profiled at 1 μM.

KINOMEscan Gene Symbol	Compound	Percent Control	Compound	Percent Control
AAK1	14	14	28	56
ABL1(E255K)-phosphorylated	14	90	28	100
ABL1(F317I)-nonphosphorylated	14	84	28	100
ABL1(F317I)-phosphorylated	14	100	28	100
ABL1(F317L)-nonphosphorylated	14	82	28	100
ABL1(F317L)-phosphorylated	14	88	28	100
ABL1(H396P)-nonphosphorylated	14	34	28	100
ABL1(H396P)-phosphorylated	14	88	28	100
ABL1(M351T)-phosphorylated	14	79	28	100
ABL1(Q252H)-nonphosphorylated	14	64	28	97
ABL1(Q252H)-phosphorylated	14	89	28	100
ABL1(T315I)-nonphosphorylated	14	73	28	100
ABL1(T315I)-phosphorylated	14	86	28	100
ABL1(Y253F)-phosphorylated	14	92	28	100
ABL1-nonphosphorylated	14	81	28	74
ABL1-phosphorylated	14	100	28	100
ABL2	14	100	28	100
ACVR1	14	100	28	98
ACVR1B	14	97	28	100
ACVR2A	14	77	28	100
ACVR2B	14	83	28	95
ACVRL1	14	100	28	100
ADCK3	14	100	28	100
ADCK4	14	100	28	77
AKT1	14	100	28	100

AKT2	14	100	28	95
AKT3	14	100	28	100
ALK	14	100	28	100
AMPK-alpha1	14	71	28	84
AMPK-alpha2	14	22	28	67
ANKK1	14	98	28	94
ARK5	14	71	28	63
ASK1	14	26	28	47
ASK2	14	57	28	87
AURKA	14	57	28	28
AURKB	14	26	28	56
AURKC	14	43	28	48
AXL	14	99	28	100
BIKE	14	54	28	92
BLK	14	72	28	100
BMPR1A	14	98	28	100
BMPR1B	14	31	28	32
BMPR2	14	80	28	100
BMX	14	97	28	100
BRAF	14	80	28	100
BRAF(V600E)	14	69	28	100
BRK	14	72	28	100
BRSK1	14	100	28	63
BRSK2	14	85	28	80
BTK	14	100	28	100
BUB1	14	86	28	100
CAMK1	14	89	28	100
CAMK1D	14	88	28	100
CAMK1G	14	100	28	79
CAMK2A	14	79	28	87
CAMK2B	14	83	28	76
CAMK2D	14	80	28	94
CAMK2G	14	100	28	100
CAMK4	14	100	28	100
CAMKK1	14	100	28	100
CAMKK2	14	78	28	100
CASK	14	66	28	94
CDC2L1	14	100	28	75
CDC2L2	14	100	28	100
CDC2L5	14	100	28	100
CDK11	14	48	28	88
CDK2	14	89	28	100
CDK3	14	93	28	90
CDK4-cyclinD1	14	65	28	100
CDK4-cyclinD3	14	100	28	100

CDK5	14	92	28	100
CDK7	14	81	28	100
CDK8	14	80	28	100
CDK9	14	97	28	64
CDKL1	14	100	28	92
CDKL2	14	98	28	100
CDKL3	14	100	28	92
CDKL5	14	100	28	100
CHEK1	14	94	28	100
CHEK2	14	100	28	100
CIT	14	100	28	100
CLK1	14	63	28	21
CLK2	14	64	28	17
CLK3	14	78	28	78
CLK4	14	38	28	16
CSF1R	14	100	28	100
CSF1R-autoinhibited	14	87	28	100
CSK	14	96	28	96
CSNK1A1	14	100	28	100
CSNK1A1L	14	96	28	100
CSNK1D	14	100	28	93
CSNK1E	14	75	28	95
CSNK1G1	14	100	28	96
CSNK1G2	14	89	28	100
CSNK1G3	14	100	28	91
CSNK2A1	14	75	28	100
CSNK2A2	14	45	28	100
CTK	14	82	28	100
DAPK1	14	89	28	84
DAPK2	14	100	28	97
DAPK3	14	100	28	91
DCAMKL1	14	100	28	100
DCAMKL2	14	100	28	100
DCAMKL3	14	100	28	77
DDR1	14	100	28	100
DDR2	14	71	28	100
DLK	14	96	28	100
DMPK	14	87	28	100
DMPK2	14	100	28	100
DRAK1	14	88	28	100
DRAK2	14	100	28	100
DYRK1A	14	78	28	100
DYRK1B	14	70	28	83
DYRK2	14	92	28	100
EGFR	14	100	28	88

EGFR(E746-A750del)	14	77	28	82
EGFR(G719C)	14	84	28	100
EGFR(G719S)	14	100	28	100
EGFR(L747-E749del, A750P)	14	83	28	100
EGFR(L747-S752del, P753S)	14	79	28	84
EGFR(L747-T751del,Sins)	14	82	28	100
EGFR(L858R)	14	78	28	92
EGFR(L858R,T790M)	14	100	28	100
EGFR(L861Q)	14	86	28	100
EGFR(S752-I759del)	14	100	28	100
EGFR(T790M)	14	81	28	100
EIF2AK1	14	100	28	100
EPHA1	14	100	28	100
EPHA2	14	100	28	98
EPHA3	14	66	28	90
EPHA4	14	100	28	100
EPHA5	14	99	28	100
EPHA6	14	100	28	100
EPHA7	14	100	28	100
EPHA8	14	100	28	100
EPHB1	14	100	28	100
EPHB2	14	92	28	100
EPHB3	14	100	28	100
EPHB4	14	100	28	100
EPHB6	14	86	28	100
ERBB2	14	73	28	100
ERBB3	14	51	28	87
ERBB4	14	100	28	92
ERK1	14	87	28	100
ERK2	14	98	28	100
ERK3	14	100	28	100
ERK4	14	95	28	78
ERK5	14	100	28	74
ERK8	14	56	28	74
ERN1	14	74	28	100
FAK	14	100	28	100
FER	14	84	28	100
FES	14	100	28	100
FGFR1	14	100	28	85
FGFR2	14	100	28	82
FGFR3	14	100	28	98
FGFR3(G697C)	14	100	28	91
FGFR4	14	74	28	100
FGR	14	100	28	100
FLT1	14	73	28	94

FLT3	14	89	28	100
FLT3(D835H)	14	72	28	56
FLT3(D835Y)	14	65	28	41
FLT3(ITD)	14	100	28	86
FLT3(K663Q)	14	71	28	100
FLT3(N841I)	14	100	28	100
FLT3(R834Q)	14	93	28	82
FLT3-autoinhibited	14	92	28	93
FLT4	14	100	28	100
FRK	14	88	28	100
FYN	14	86	28	100
GAK	14	100	28	78
GCN2(Kin.Dom.2,S808G)	14	100	28	100
GRK1	14	74	28	100
GRK4	14	52	28	100
GRK7	14	37	28	88
GSK3A	14	100	28	100
GSK3B	14	94	28	100
HASPIN	14	46	28	65
HCK	14	100	28	100
HIPK1	14	77	28	78
HIPK2	14	65	28	100
HIPK3	14	47	28	100
HIPK4	14	100	28	100
HPK1	14	79	28	82
HUNK	14	100	28	100
ICK	14	96	28	100
IGF1R	14	87	28	100
IKK-alpha	14	71	28	100
IKK-beta	14	90	28	100
IKK-epsilon	14	100	28	100
INSR	14	100	28	100
INSRR	14	100	28	100
IRAK1	14	23	28	100
IRAK3	14	74	28	47
IRAK4	14	69	28	100
ITK	14	100	28	100
JAK1(JH1domain-catalytic)	14	100	28	100
JAK1(JH2domain-pseudokinase)	14	94	28	44
JAK2(JH1domain-catalytic)	14	71	28	100
JAK3(JH1domain-catalytic)	14	2.7	28	22
JNK1	14	62	28	100
JNK2	14	87	28	100
JNK3	14	100	28	100
KIT	14	100	28	82

KIT(A829P)	14	50	28	100
KIT(D816H)	14	92	28	100
KIT(D816V)	14	99	28	79
KIT(L576P)	14	89	28	87
KIT(V559D)	14	100	28	89
KIT(V559D,T670I)	14	100	28	100
KIT(V559D,V654A)	14	72	28	100
KIT-autoinhibited	14	100	28	100
LATS1	14	100	28	100
LATS2	14	87	28	100
LCK	14	95	28	100
LIMK1	14	93	28	100
LIMK2	14	96	28	100
LKB1	14	100	28	90
LOK	14	33	28	88
LRRK2	14	43	28	54
LRRK2(G2019S)	14	75	28	61
LTK	14	100	28	100
LYN	14	91	28	100
LZK	14	62	28	100
MAK	14	94	28	100
MAP3K1	14	82	28	100
MAP3K15	14	74	28	32
MAP3K2	14	21	28	91
MAP3K3	14	8.2	28	100
MAP3K4	14	100	28	100
MAP4K2	14	3.4	28	64
MAP4K3	14	4.8	28	50
MAP4K4	14	71	28	94
MAP4K5	14	53	28	96
MAPKAPK2	14	100	28	100
MAPKAPK5	14	100	28	100
MARK1	14	91	28	44
MARK2	14	43	28	60
MARK3	14	100	28	73
MARK4	14	82	28	56
MAST1	14	73	28	100
MEK1	14	13	28	72
MEK2	14	19	28	79
MEK3	14	71	28	55
MEK4	14	100	28	57
MEK5	14	14	28	86
MEK6	14	80	28	80
MELK	14	69	28	40
MERTK	14	100	28	100

MET	14	93	28	99
MET(M1250T)	14	96	28	90
MET(Y1235D)	14	93	28	100
MINK	14	46	28	100
MKK7	14	80	28	100
MKNK1	14	100	28	100
MKNK2	14	90	28	70
MLCK	14	93	28	100
MLK1	14	72	28	89
MLK2	14	100	28	100
MLK3	14	100	28	100
MRCKA	14	100	28	97
MRCKB	14	83	28	92
MST1	14	18	28	84
MST1R	14	95	28	100
MST2	14	1.8	28	2.7
MST3	14	60	28	87
MST4	14	7	28	89
MTOR	14	58	28	100
MUSK	14	95	28	100
MYLK	14	100	28	100
MYLK2	14	92	28	100
MYLK4	14	100	28	63
MYO3A	14	94	28	95
MYO3B	14	100	28	100
NDR1	14	89	28	100
NDR2	14	100	28	88
NEK1	14	100	28	78
NEK11	14	100	28	100
NEK2	14	100	28	84
NEK3	14	100	28	100
NEK4	14	100	28	100
NEK5	14	100	28	100
NEK6	14	100	28	96
NEK7	14	100	28	100
NEK9	14	97	28	100
NIM1	14	80	28	100
NLK	14	85	28	91
OSR1	14	90	28	97
p38-alpha	14	100	28	100
p38-beta	14	100	28	100
p38-delta	14	70	28	100
p38-gamma	14	100	28	100
PAK1	14	100	28	84
PAK2	14	100	28	79

PAK3	14	74	28	89
PAK4	14	100	28	99
PAK6	14	78	28	73
PAK7	14	66	28	76
PCTK1	14	90	28	100
PCTK2	14	100	28	65
PCTK3	14	100	28	100
PDGFRA	14	100	28	69
PDGFRB	14	90	28	78
PDPK1	14	100	28	100
PFCDPK1(P.falciparum)	14	78	28	96
PFPK5(P.falciparum)	14	100	28	100
PFTAIRE2	14	100	28	100
PFTK1	14	100	28	99
PHKG1	14	81	28	100
PHKG2	14	40	28	90
PIK3C2B	14	100	28	100
PIK3C2G	14	100	28	100
PIK3CA	14	100	28	100
PIK3CA(C420R)	14	95	28	100
PIK3CA(E542K)	14	90	28	79
PIK3CA(E545A)	14	100	28	100
PIK3CA(E545K)	14	96	28	100
PIK3CA(H1047L)	14	90	28	86
PIK3CA(H1047Y)	14	76	28	90
PIK3CA(I800L)	14	88	28	92
PIK3CA(M1043I)	14	100	28	100
PIK3CA(Q546K)	14	97	28	86
PIK3CB	14	100	28	96
PIK3CD	14	100	28	80
PIK3CG	14	79	28	100
PIK4CB	14	71	28	100
PIM1	14	100	28	100
PIM2	14	100	28	100
PIM3	14	100	28	88
PIP5K1A	14	20	28	19
PIP5K1C	14	70	28	68
PIP5K2B	14	23	28	99
PIP5K2C	14	21	28	86
PKAC-alpha	14	94	28	100
PKAC-beta	14	84	28	97
PKMYT1	14	73	28	98
PKN1	14	62	28	90
PKN2	14	35	28	85
PKNB(M.tuberculosis)	14	47	28	88

PLK1	14	100	28	100
PLK2	14	100	28	100
PLK3	14	100	28	100
PLK4	14	33	28	77
PRKCD	14	67	28	96
PRKCE	14	12	28	87
PRKCH	14	41	28	99
PRKCI	14	100	28	92
PRKCQ	14	77	28	100
PRKD1	14	100	28	40
PRKD2	14	100	28	77
PRKD3	14	64	28	43
PRKG1	14	99	28	72
PRKG2	14	100	28	100
PRKR	14	100	28	75
PRKX	14	100	28	100
PRP4	14	92	28	82
PYK2	14	100	28	100
QSK	14	100	28	100
RAF1	14	71	28	100
RET	14	78	28	100
RET(M918T)	14	70	28	100
RET(V804L)	14	95	28	98
RET(V804M)	14	58	28	91
RIOK1	14	38	28	65
RIOK2	14	75	28	100
RIOK3	14	4.8	28	10
RIPK1	14	100	28	100
RIPK2	14	84	28	100
RIPK4	14	57	28	100
RIPK5	14	91	28	94
ROCK1	14	85	28	100
ROCK2	14	75	28	100
ROS1	14	90	28	100
RPS6KA4(Kin.Dom.1-N-terminal)	14	71	28	81
RPS6KA4(Kin.Dom.2-C-terminal)	14	100	28	100
RPS6KA5(Kin.Dom.1-N-terminal)	14	74	28	100
RPS6KA5(Kin.Dom.2-C-terminal)	14	100	28	90
RSK1(Kin.Dom.1-N-terminal)	14	100	28	89
RSK1(Kin.Dom.2-C-terminal)	14	27	28	54
RSK2(Kin.Dom.1-N-terminal)	14	46	28	91
RSK2(Kin.Dom.2-C-terminal)	14	38	28	100
RSK3(Kin.Dom.1-N-terminal)	14	100	28	89
RSK3(Kin.Dom.2-C-terminal)	14	82	28	78
RSK4(Kin.Dom.1-N-terminal)	14	9.8	28	15

RSK4(Kin.Dom.2-C-terminal)	14	29	28	80
S6K1	14	100	28	100
SBK1	14	100	28	100
SGK	14	65	28	90
SgK110	14	100	28	100
SGK3	14	100	28	100
SIK	14	84	28	97
SIK2	14	32	28	78
SLK	14	25	28	89
SNARK	14	18	28	48
SNRK	14	100	28	100
SRC	14	100	28	100
SRMS	14	94	28	100
SRPK1	14	25	28	25
SRPK2	14	70	28	100
SRPK3	14	27	28	100
STK16	14	33	28	60
STK33	14	60	28	64
STK35	14	62	28	93
STK36	14	100	28	100
STK39	14	92	28	100
SYK	14	100	28	100
TAK1	14	55	28	100
TAOK1	14	6.4	28	86
TAOK2	14	100	28	100
TAOK3	14	36	28	100
TBK1	14	100	28	100
TEC	14	100	28	100
TESK1	14	100	28	100
TGFBR1	14	79	28	95
TGFBR2	14	100	28	81
TIE1	14	80	28	81
TIE2	14	100	28	100
TLK1	14	99	28	66
TLK2	14	93	28	92
TNIK	14	45	28	84
TNK1	14	32	28	78
TNK2	14	98	28	100
TNNI3K	14	74	28	100
TRKA	14	88	28	97
TRKB	14	63	28	74
TRKC	14	84	28	100
TRPM6	14	100	28	100
TSSK1B	14	75	28	84
TTK	14	92	28	37

TXK	14	100	28	100
TYK2(JH1domain-catalytic)	14	69	28	90
TYK2(JH2domain-pseudokinase)	14	75	28	100
TYRO3	14	100	28	100
ULK1	14	65	28	77
ULK2	14	69	28	100
ULK3	14	25	28	46
VEGFR2	14	62	28	98
VRK2	14	100	28	100
WEE1	14	100	28	93
WEE2	14	96	28	100
WNK1	14	100	28	100
WNK3	14	100	28	100
YANK1	14	100	28	100
YANK2	14	53	28	100
YANK3	14	100	28	100
YES	14	95	28	100
YSK1	14	28	28	85
YSK4	14	3.8	28	43
ZAK	14	86	28	98
ZAP70	14	96	28	100

Table S3. ActivX data for compounds **12**, **14**, and **28** as determined in human PBMCs at 1 μM.

Kinase	**Sequence**	**Labeling Site**	**12**	**14**	**28**
ABL,ARG	YSLTVAVKTLkEDTMEVEEFLK	Lys1	8	-53	14
ABL,ARG	LMTGDTYTAHAGAkFPIK	Activation Loop	-18	-1	23
ACK	TVSVAVkCLKPDVLSQPEAMDDFIR	Lys1	-12	8	-8
AKT1	GTFGkVILVK	ATP Loop	8	-6	19
AKT2,AKT3	GTFGkVILVR	ATP Loop	20	7	11
AMPKa1	IGHYILGDTLGVGTFGkVK	ATP Loop	35	16	27

AMPKa1,AMPKa2	DLkPENVLLDAHMNAK	Lys2	17	33	50
AMPKa1,AMPKa2	VAVkILNR	Lys1	32	27	54
ATR	FYIMMCkPK	ATP	6	25	-23
BARK1	DLkPANILLDEHGHVR	Lys2	6	-5	14
BRAF	DLkSNNIFLHEDLTVK	Lys2	18	-1	-52
BTK	YVLDDEYTSSVGSkFPVR	Activation Loop	6	13	9
BTK	GQYDVAIkMIK	Lys1	-17	10	4
CaMK1a	LVAIkCIAK	Lys1	11	2	6
CaMK1d	LFAVkCIPK	Lys1	-6	1	3
CaMK2d	IPTGQEYAAkIINTKK	Lys1		11	-38
CaMK2d	IPTGQEYAAkIINTK	Lys1	19	4	-10
CaMK2g	KTSTQEYAAkIINTK	Lys1	31	-12	-23
CaMK2g	TSTQEYAAkIINTK	Lys1	13	3	-16

CaMK2g	KTSTQEYAAkIINTKK	Lys1	31	10	8
CaMKK2	LAYNENDNTYYAMkVLSK	Lys1	35	49	34
CDC2	DLkPQNLLIDDKGTIK	Lys2	10	13	15
CDK11,CDK8	DLkPANILVMGEGPER	Lys2	35	36	2
CDK2	NKLTGEVVALkK	Lys1	25	9	10
CDK2	DLkPQNLLINTEGAIK	Lys2	21	8	-22
CDK5	DLkPQNLLINR	Lys2	-1	0	-35
CDK5	NRETHEIVALkR	Lys1	19	-9	6
CDK9	DMkAANVLITR	Lys2	-1	22	17
CHED	DIkCSNILLNNRGQIK	Lys2	9	3	-34
CHK2	VAIkIISK	Lys1	24	2	18
CK1a	DIkPDNFLMGIGR	Lys2	-5	-7	-14
COT	GAFGkVYLAQDIK	ATP Loop	12		

CSK	VSDFGLTkEASSTQDTGKLPVK	Activation Loop	-3	-2	9
CSK	EASSTQDTGkLPVK	Activation Loop	5	-2	-15
CSK	VSDFGLTkEASSTQDTGKLPVKWTA PEALR	Activation Loop	19	-45	-5
DGKA	IDPVPNTHPLLVFVNPkSGGK	ATP	15	-9	-17
DNAPK	kGGSWIQEINVAEK	ATP	15	15	-30
DNAPK	GHDEREHPFLVkGGEDLRQDQR	ATP	16	-4	2
DNAPK	GHDEREHPFLVkGGEDLR	ATP	12	-6	-16
DNAPK	EHPFLVkGGEDLR	ATP	9	-2	-35
eEF2K	YIkYNSNSGFVR	ATP	12	3	-7
EphA1	LLDDFDGTYETQGGkIPIR	Activation Loop	3	-3	20
Erk1,Erk2	DLkPSNLLINTTCDLK	Lys2	0	3	-26
Erk5	DLkPSNLLVNENCELK	Lys2	14	-6	-42
FAK	YMEDSTYYkASK	Activation Loop	-40	11	20

FAK	CIGEGQFGDVHQGIYMSPENPALAV AIkTCK	Lys1	-31		
FER	QEDGGVYSSSGLkQIPIK	Activation Loop	10	2	-18
FER	TSVAVkTCKEDLPQELK	Lys1	18	12	21
FES	ADNTLVAVkSCR	Lys1	7	7	-1
FES	LRADNTLVAVkSCR	Lys1	-2	2	12
FGR	LIKDDEYNPCQGSkFPIKWTAPEAAL FGR	Activation Loop	-4	-34	-43
FGR	LIKDDEYNPCQGSkFPIK	Activation Loop	0	2	5
FRAP	IQSIAPSLQVITSkQRPR	ATP	7	10	-1
FYN	VAIkTLKPGTMSPESFLEEAQIMK	Lys1	-38	-9	-10
FYN,SRC,YES	QGAkFPIKWTAPEAALYGR	Activation Loop	5	-9	-56
FYN,SRC,YES	LIEDNEYTARQGAkFPIK	Activation Loop	-20		
GCK	DTVTSELAAVkIVK	Lys1	48	31	-7
GCK	DIkGANLLLTLQGDVK	Lys2	35	24	-6

GCN2 domain2	DLkPVNIFLDSDDHVK	Lys2	11	1	-25
GCN2 domain2	VQNKLDGCCYAVkR	Lys1	10	22	20
GPRK6	DLkPENILLDDHGHIR	Lys2	-6	11	24
GSK3A	DIkPQNLLVDPDTAVLK	Lys2	21	7	-11
GSK3B	DIkPQNLLLDPDTAVLK	Lys2	9	7	-5
HCK	VAVkTMKPGSMSVEAFLAEANVMK	Lys1	-24	21	-5
HPK1	DIkGANILINDAGEVR	Lys2	15	6	-15
HPK1	VSGDLVALkMVK	Lys1	-6	26	12
HPK1	DKVSGDLVALkMVK	Lys1	-16	7	-21
IKKa	DLkPENIVLQDVGGK	Lys2	11	-7	-41
IKKb	DLkPENIVLQQGEQR	Lys2	-1	-16	11
IKKe	SGELVAVkVFNTTSYLRPR	Lys1	22	7	18
IKKe,TBK1	DIkPGNIMR	Lys2	-3	19	24

ILK	WQGNDIVVkVLK	Lys1	-20	-32	-57
ILK	ISMADVkFSFQCPGR	Protein Kinase Domain	-30	14	-3
ILK	LNENHSGELWkGR	ATP Loop	0	-12	-14
IRAK1	AIQFLHQDSPSLIHGDIkSSNVLLDER	Lys2	3	2	-9
IRAK3	VEIQNLTYAVkLFK	Lys1	41	34	69
IRAK3	SHLEHQSCTINMTSSSSkHLWYMPEEYIR	Protein Kinase Domain	-25		
IRAK4	GYVNNTTVAVkK	Lys1	25	11	35
IRAK4	DIkSANILLDEAFTAK	Lys2	20	16	23
IRE1	DLkPHNILISMPNAHGK	Lys2	-23	2	-8
ITPK1	ESIFFNSHNVSkPESSSVLTELDKIEGVFERPSDEVIR	Other	31	-28	-20
JAK1	QLASALSYLEDKDLVHGNVCTkNLLLAR	Other	-3	5	54
JAK1 domain2	IGDFGLTkAIETDKEYYTVK	Activation Loop	7	19	-14
JAK1 domain2	IGDFGLTkAIETDKEYYTVKDDR	Activation Loop	5	-4	-29

JAK1 domain2	YDPEGDNTGEQVAVkSLKPESGGNHIADLKK	Lys1	-5	-1	1
JAK2 domain2	IGDFGLTkVLPQDKEYYK	Activation Loop	-3		
JAK2 domain2	YDPLQDNTGEVVAVkK	Lys1		16	17
JAK3 domain2	IADFGLAkLLPLDKDYYVVR	Activation Loop	17	7	-5
JAK3 domain2	YDPLGDNTGALVAVkQLQHSGPDQQR	Lys1	7	6	-23
JNK1,JNK2,JNK3	DLkPSNIVVK	Lys2	2	5	8
KHS1	DIkGANILLTDHGDVKLADFGVAAK	Lys2	27	-13	-24
KHS1	DIkGANILLTDHGDVK	Lys2	30	16	20
KHS1	NVHTGELAAVkIIK	Lys1	44	13	25
KSR1,KSR2	SkNVFYDNGK	Activation Loop	18	12	-14
LATS1	ALYATkTLR	Lys1	7	5	-16
LATS2	VDTHALYAMkTLR	Lys1	-33	16	11
LCK	EGAkFPIKWTAPEAINYGTFTIK	Activation Loop	-10		

LKB1	DIkPGNLLLTTGGTLK	Lys2	23	17	-14
LOK	DLkAGNVLMTLEGDIR	Lys2	60	54	23
LOK	ETGALAAAkVIETK	Lys1	89	79	67
LOK	NKETGALAAAkVIETK	Lys1	87	77	67
LOK	IIHRDLkAGNVLMTLEGDIR	Lys2	60	60	25
LRRK2	DLkPHNVLLFTLYPNAAIIAK	Lys2	92	94	88
LRRK2	AAYEGEEVAVkIFNK	Lys1	>90		
LYN	VAVkTLKPGTMSVQAFLEEANLMK	Lys1	-17	1	8
MAP2K1	IMHRDVkPSNILVNSR	Lys2	21	14	17
MAP2K1,MAP2K2	kLIHLEIKPAIR	Lys1	43	0	-20
MAP2K1,MAP2K2	DVkPSNILVNSR	Lys2	32	6	-2
MAP2K3	DVkPSNVLINK	Lys2	-2	6	-9
MAP2K3	HAQSGTIMAVkR	Lys1	-22	-5	-18

MAP2K4	MVHKPSGQIMAVkR	Lys1	-19	19	10
MAP2K4	DIkPSNILLDR	Lys2	4	2	-12
MAP2K4	IIHRDIkPSNILLDR	Lys2	9	-17	-8
MAP2K6	HVPSGQIMAVkR	Lys1	18	14	19
MAP2K6	DVkPSNVLINALGQVK	Lys2	32	9	-13
MAP3K1	DVkGANLLIDSTGQR	Lys2	86	45	12
MAP3K2	ELAVkQVQFDPDSPETSKEVNALECEIQLLK	Lys1	30	22	-25
MAP3K2	VYLCYDVDTGRELAVkQVQFDPDSPETSKEVNALECEIQLLK	Lys1	30	15	-19
MAP3K2,MAP3K3	DIkGANILR	Lys2	8	13	3
MAP3K3	ELASkQVQFDPDSPETSKEVSALECEIQLLK	Lys1	44	7	7
MAP3K4	DIkGANIFLTSSGLIK	Lys2	9	30	7
MAP3K5	DIkGDNVLINTYSGVLK	Lys2	38	21	2
MAP3K5,MAP3K6,MAP3K7	IAIkEIPERDSR	Lys1	37	21	27

MAP3K7,TAK1	DLkPPNLLLVAGGTVLK	Lys2	10	8	2
MAPKAPK2	FALkMLQDCPK	Lys1	8		
MARK2	EVAVkIIDKTQLNSSSLQK	Lys1	63	27	42
MARK2	HILTGKEVAVkIIDKTQLNSSSLQK	Lys1	66	41	42
MARK3	EVAIKIIDkTQLNPTSLQK	Lys1	67	24	29
MAST3	DLkPDNLLITSLGHIK	Lys2	11	1	-7
MLK3	DLkSNNILLLQPIESDDMEHK	Lys2	0	20	5
MLKL	APVAIkVFK	Lys1	37	15	8
MPSK1	DLkPTNILLGDEGQPVLMDLGSMNQ ACIHVEGSR	Lys2	30	63	49
MSK1 domain1	DIkLENILLDSNGHVVLTDFGLSK	Lys2	8	-4	-30
MSK1,MSK2 domain1	VLGTGAYGkVFLVR	ATP Loop	14	20	-18
MST1	ETGQIVAIkQVPVESDLQEIIK	Lys1	82	82	51
MST1	AIHKETGQIVAIkQVPVESDLQEIIK	Lys1	82	80	51

MST1	ETGQIVAIkQVPVESDLQEIIKEISIMQQCDSPHVVK	Lys1	78	84	62
MST1,MST2	DIkAGNILLNTEGHAK	Lys2	73	71	25
MST1,MST2	IHRDIkAGNILLNTEGHAK	Lys2	81	69	40
MST1,MST2	LADFGVAGQLTDTMAkR	Activation Loop	76	74	61
MST2	ESGQVVAIkQVPVESDLQEIIK	Lys1	84	83	49
MST3	DIkAANVLLSEHGEVK	Lys2	69	46	28
MST3,MST4,YSK1	LADFGVAGQLTDTQIkR	Activation Loop	54	39	20
MST4,YSK1	DIkAANVLLSEQGDVK	Lys2	80	61	15
MST4,YSK1	IHRDIkAANVLLSEQGDVK	Lys2	81	65	25
NDR1	DTGHVYAMkILR	Lys1	-27	2	-8
NDR1	DIkPDNLLLDSK	Lys2	11	4	5
NDR1,NDR2	LSDFGLCTGLkK	Activation Loop	-3	3	-4
NDR2	DTGHIYAMkILR	Lys1	-28	22	31

NDR2	KDTGHIYAMkILR	Lys1	-7	20	24
NEK1	DIkSQNIFLTK	Lys2	-5	-2	-10
NEK4	DLkTQNVFLTR	Lys2	10		
NEK6,NEK7	DIkPANVFITATGVVK	Lys2	2	-5	-17
NEK7	AACLLDGVPVALkK	Lys1	9	7	-19
NEK7	FFSSkTTAAHSLVGTPYYMSPER	Activation Loop	-14		
NEK9	LGDYGLAkK	Activation Loop	18	3	15
NEK9	DIkTLNIFLTK	Lys2	18	1	13
NEK9	RTEDDSLVVWkEVDLTR	Lys1	21	-16	-43
NEK9	TEDDSLVVWkEVDLTR	Lys1	5	-31	14
NuaK2	LVAIkSIR	Lys1	59	18	9
OSR1	DVkAGNILLGEDGSVQIADFGVSAFL ATGGDITR	Lys2	7	-55	-4
p38a	QELNkTIWEVPER	Other	-1	-15	-65

p38a	DLkPSNLAVNEDCELK	Lys2	4	-2	-20
p38b	QELNkTVWEVPQR	Other	-14		
p38d,p38g	DLkPGNLAVNEDCELK	Lys2	13	-6	-24
p70S6K	DLkPENIMLNHQGHVK	Lys2	-33	11	19
p70S6K,p70S6Kb	GGYGkVFQVR	ATP Loop	3	-10	-4
p70S6Kb	DLkPENIMLSSQGHIK	Lys2	-16	19	10
PAN3	VMDPTkILITGK	Protein Kinase Domain	-19	15	1
PCTAIRE2,PCTAIRE3	SKLTENLVALkEIR	Lys1	18	25	-3
PI4KA,PI4KAP2	SGTPMQSAAkAPYLAK	ATP	-6	6	-10
PI4KB	VPHTQAVVLNSkDK	ATP	2	5	16
PI4KB	VPHTQAVVLNSkDKAPYLIYVEVLECENFDTTSVPAR	ATP	33		
PI4KB	VPHTQAVVLNSkDKAPYLIYVEVLECENFDTTSVPARIPENR	ATP	14	-27	-4
PIK3C3	TEDGGKYPVIFkHGDDLRQDQLILQIISLMDK	ATP	-2	14	5

PIK3C3	TEDGGKYPVIFkHGDDLR	ATP	8	-17	-19
PIK3CB	VFGEDSVGVIFkNGDDLR	ATP	21	-1	-25
PIK3CB	VFGEDSVGVIFkNGDDLRQDMLTLQMLR	ATP	-18	-3	-30
PIK3CD	TKVNWLAHNVSkDNRQ	ATP	27		
PIK3CD	VNWLAHNVSkDNRQ	ATP	28	-12	-65
PIK3CG	KkPLWLEFK	ATP	4	-6	-63
PIP4K2A	AkELPTLKDNDFINEGQK	ATP	-9	2	7
PIP4K2A,PIP4K2B	TVkHGAGAEISTVNPEQYSK	ATP	14	15	10
PIP4K2A,PIP4K2B	TVkHGAGAEISTVNPEQYSKR	ATP	18	16	1
PIP4K2C	VKELPTLkDMDFLNK	ATP	69	54	1
PIP4K2C	TLVIkEVSSEDIADMHSNLSNYHQYIVK	ATP	66	58	-1
PIP5K3	GGkSGAAFYATEDDRFILK	ATP	14	22	15
PITSLRE	DLkTSNLLLSHAGILK	Lys2	7	11	-3

PKACa,PKACg	DLkPENLLIDQQGYIQVTDFGFAK	Lys2	11		
PKCa,PKCb	DLkLDNVMLDSEGHIK	Lys2	20	57	27
PKD2	DVAVkVIDK	Lys1	21	9	20
PKD2	DVAVkVIDKLR	Lys1	15	-2	34
PKD3	DVAIkVIDK	Lys1	21		
PKN1	GHFGkVLLSEFRPSGELFAIK	Lys1	25	31	25
PKR	DLkPSNIFLVDTK	Lys2	19	7	-17
PKR	IGDFGLVTSLKNDGkR	Activation Loop	5	12	-3
PRPK	FLSGLELVkQGAEAR	ATP Loop	14	-4	-14
PYK2	YIEDEDYYkASVTR	Activation Loop	7	3	20
RIPK3	DLkPSNVLLDPELHVK	Lys2	-2	8	-4
ROCK1	kLQLELNQER	Other	-8	-3	-26
ROCK1,ROCK2	DVkPDNMLLDK	Lys2	1	2	18

RSK1 domain1	KVTRPDSGHLYAMkVLK	Lys1	-6	33	60
RSK1 domain1	LTDFGLSkEAIDHEK	Activation Loop	19	-1	-4
RSK1 domain2	DLkPSNILYVDESGNPECLR	Lys2	17	56	18
RSK1,RSK2,RSK3 domain1	DLkPENILLDEEGHIK	Lys2	17	13	19
RSK1,RSK2,RSK3 domain1	DLkPENILLDEEGHIKLTDFGLSK	Lys2	24	-3	9
RSK2 domain1	DLKPENILLDEEGHIKLTDFGLSkESIDHEK	Lys2	24	-11	6
RSK2 domain1	LTDFGLSkESIDHEK	Activation Loop	28	6	10
RSK2 domain2	SkRDPTEEIEILLR	Protein Kinase Domain	-19	10	-13
RSK2 domain2	TVEYLHAQGVVHRDLkPSNILYVDESGNPESIR	Lys2	29		
RSK2 domain2	DLkPSNILYVDESGNPESIR	Lys2	4	21	9
RSKL1 domain1	VLGVIDkVLLVMDTR	Protein Kinase Domain	-36	-2	0
SGK3	FYAVkVLQK	Lys1	15	-1	10
SLK	IIHRDLkAGNILFTLDGDIK	Lys2	84		

SLK	DLkAGNILFTLDGDIK	Lys2	79	66	32
SLK	AQNKETSVLAAAkVIDTK	Lys1	82	61	51
SMG1	DTVTIHSVGGTITILPTkTKPK	Other	7	13	-19
smMLCK	LGSGkFGQVFR	ATP Loop	11	13	6
smMLCK	QGIVHLDLkPENIMCVNK	Lys2	-29	16	-2
SRC	VAIkTLKPGTMSPEAFLQEAQVMKK	Lys1	-48	-2	10
SRC	VAIkTLKPGTMSPEAFLQEAQVMK	Lys1	-33	30	0
STLK5	YSVkVLPWLSPEVLQQNLQGYDAK	Activation Loop	0	1	-47
SYK	TVAVkILK	Lys1	0	0	5
SYK	AQTHGkWPVK	Activation Loop	-5	-12	-51
SYK	ISDFGLSkALRADENYYK	Activation Loop	6	6	-10
SYK	ISDFGLSKALR	Activation Loop	5	7	-6
SYK	TVAVKILKNEANDPALKDELLAEAN VMQQLDNPYIVR	Lys1	-3	1	20

TAO1,TAO3	DIkAGNILLTEPGQVK	Lys2	36	6	-15
TAO2	DVkAGNILLSEPGLVK	Lys2	9	-3	-24
TBK1	TGDLFAIkVFNNISFLRPVDVQMR	Lys1	1	16	13
TLK1	YAAVkIHQLNK	Lys1	6	-4	3
TLK1,TLK2	YLNEIkPPIIHYDLKPGNILLVDGTAC GEIK	Lys2	-2	6	-1
TLK2	YVAVkIHQLNK	Lys1		-9	-21
ULK3	NISHLDLkPQNILLSSLEKPHLK	Lys2	38	5	8
VRK2	MLDVLEYIHENEYVHGDIkAANLLL GYK	Lys2	-20		
Wnk1,Wnk2,Wnk3	DLkCDNIFITGPTGSVK	Lys2	11	-6	-24
Wnk1,Wnk2,Wnk4	IGDLGLATLkR	Activation Loop	9	-1	-14
ZAK	WISQDKEVAVKk	Lys1	23	-42	23
ZAP70	ISDFGLSkALGADDSYYTAR	Activation Loop	16	7	3
ZAP70	SAGkWPLKWYAPECINFRK	Activation Loop	-4	-33	-2

ZAP70	SAGkWPLK	Activation Loop	-28	-3	-30
ZC1/HGK	TGQLAAIkVMDVTEDEEEEIKLEINMLK	Lys1	54		
ZC1/HGK	TGQLAAIkVMDVTEDEEEEIKLEINMLKK	Lys1	46		
ZC1/HGK,ZC2/TNIK,ZC3/MINK	DIkGQNVLLTENAEVK	Lys2	54	15	5
ZC2/TNIK	TGQLAAIkVMDVTGDEEEEIKQEINMLKK	Lys1	46	29	31