Supporting Information

Structure-guided development of covalent TAK1 inhibitors

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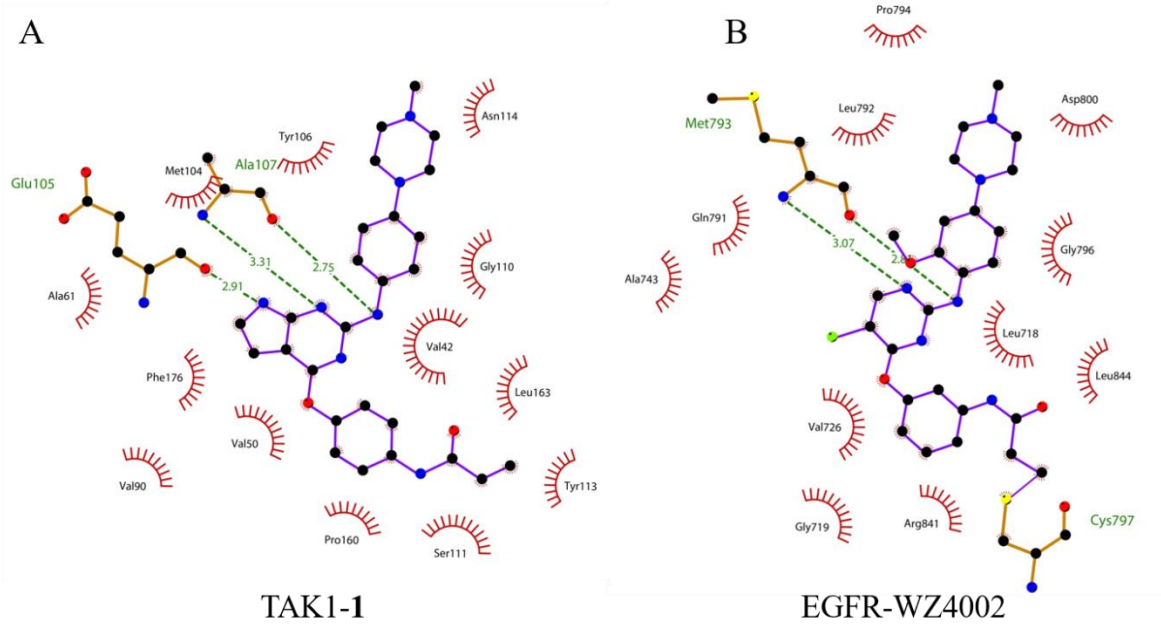
Supplementary Figures

Figure S1. **(**A) Ligplot describing interactions of **1** bound to TAK1-TAB1 (PDB ID: 5J9L). Hydrogen bonding interactions (green lines) with Glu105 and Ala107 are shown; (B) Structural interactions for WZ4002 bound to the EGFR mutant (PDB ID: 3IKA). Hydrogen bonding interactions (green lines) with Met793 are shown. Equivalent hydrophobic residues between both TAK1 and EGFR are also shown (curved red lines with spikes).



TAK1-**1** EGFR-WZ4002

Figure S2. (A) Fo-Fc map (green mesh), contoured at 2.5σ for **1** in the ATP binding site of TAK1-TAB1. The 2-position of the 4-acrylamidophenyl group of **1** is located 4.5 Å away from the thiol of Cys174; (B) Fo-Fc map (green mesh), contoured at 2.5σ for **2**, which demonstrates continuous density with Cys-174 indicating covalent linkage.

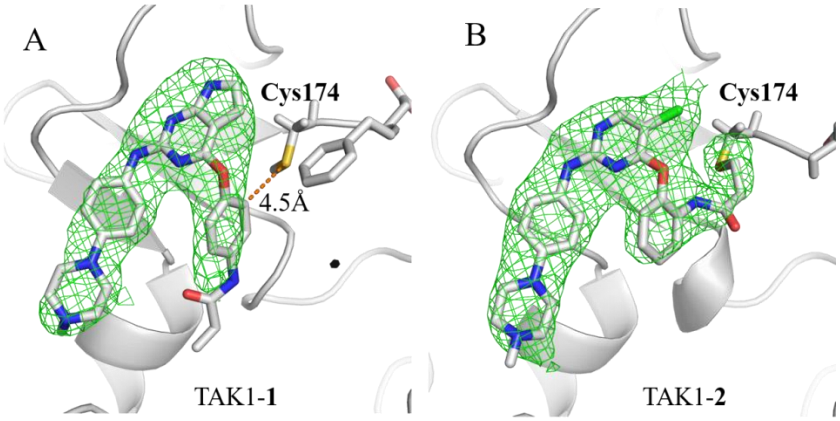


Figure S3. Compound **2** covalently labels TAK1 at Cys174. Raw (A, C) and deconvoluted (B, D) mass spectra obtained for TAK1 after treatment with (A, B) DMSO and (C, D) 2. FT-HCD MS/MS spectrum of inhibitor modified TAK1 peptide I(C*)DEGTACDIQTHMTNNK (residues 173-190). Ions of type b and y are shown in blue and red, respectively. Note b2 and b3 ions localize the site of modification to C174. No other labeled cysteine residues were detected. (C* denotes compound **2** modified cysteine residue).

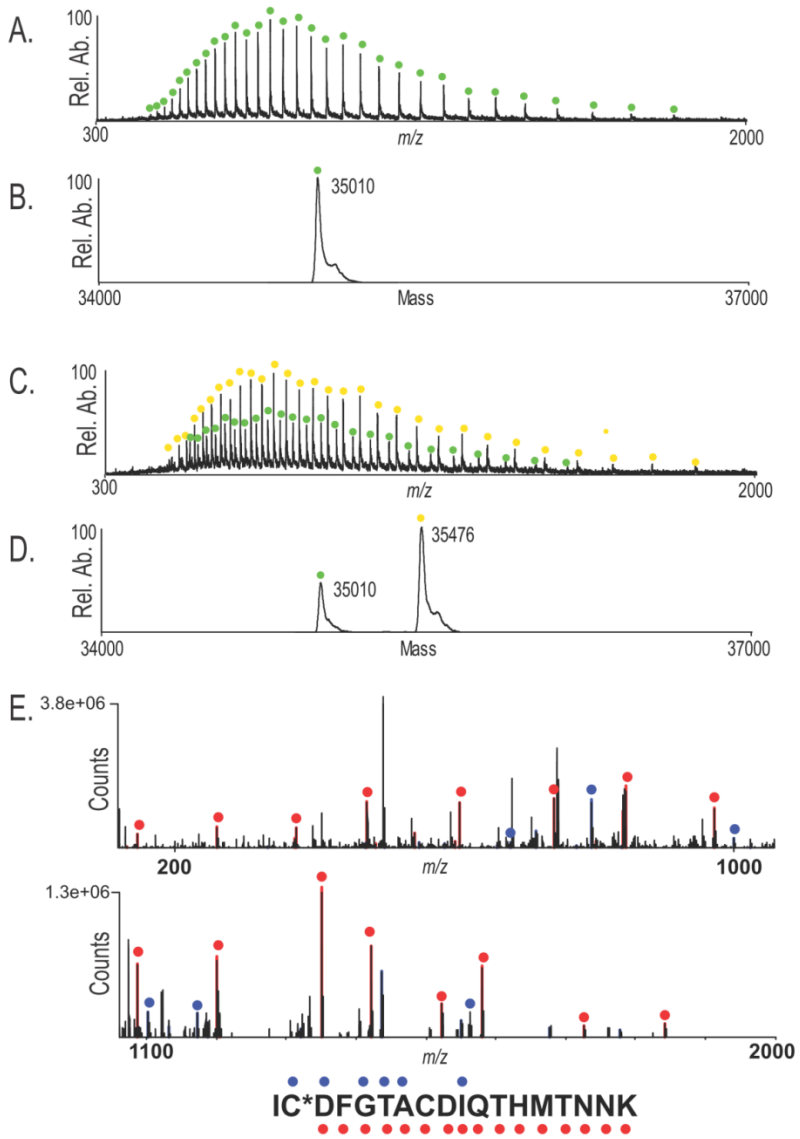
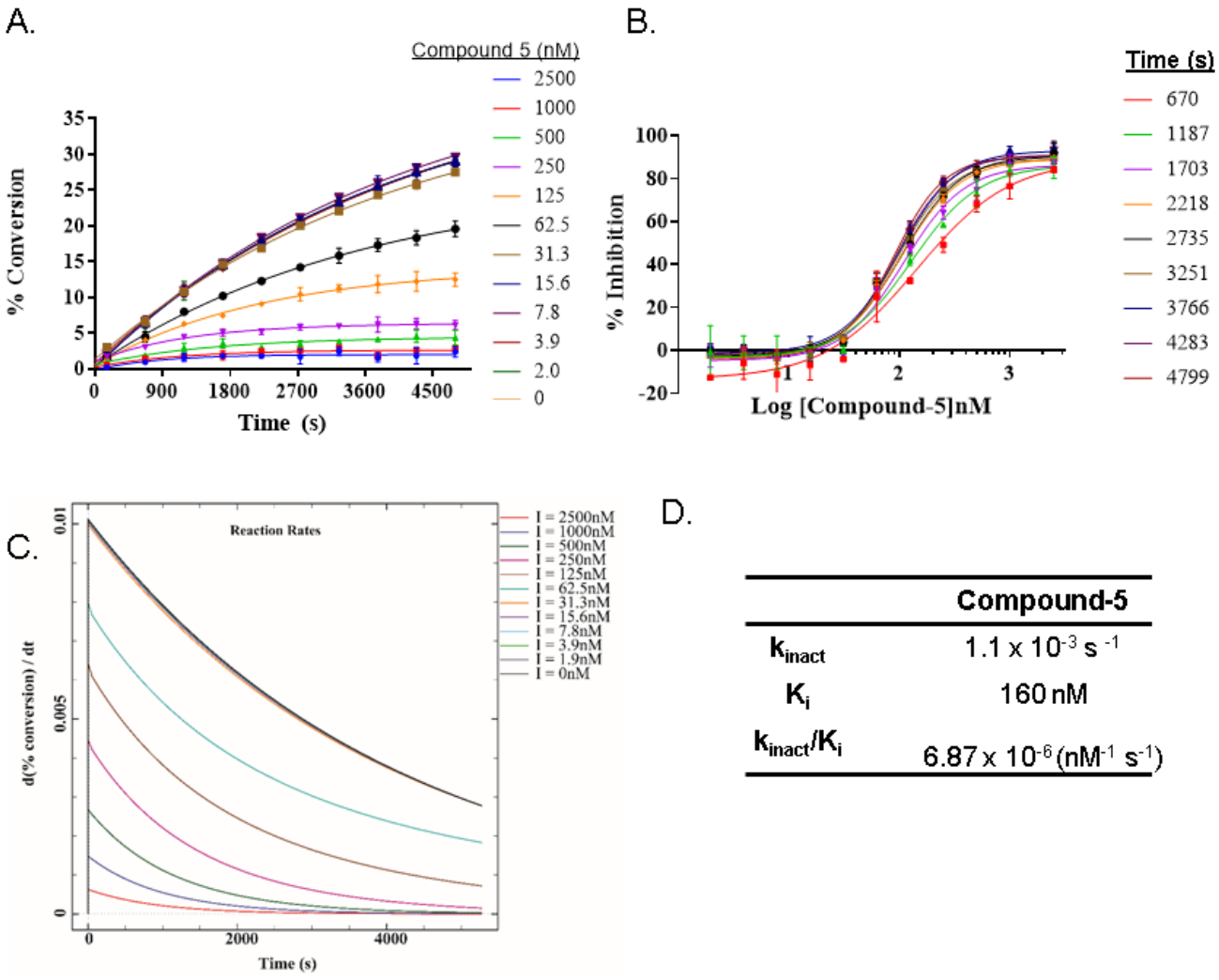
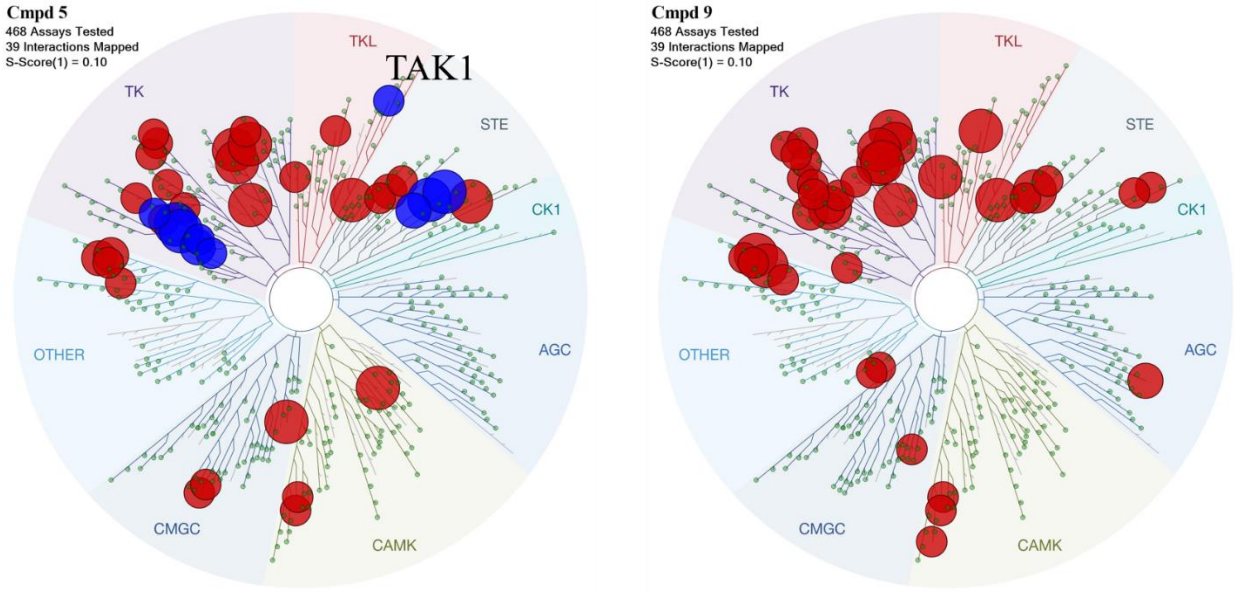


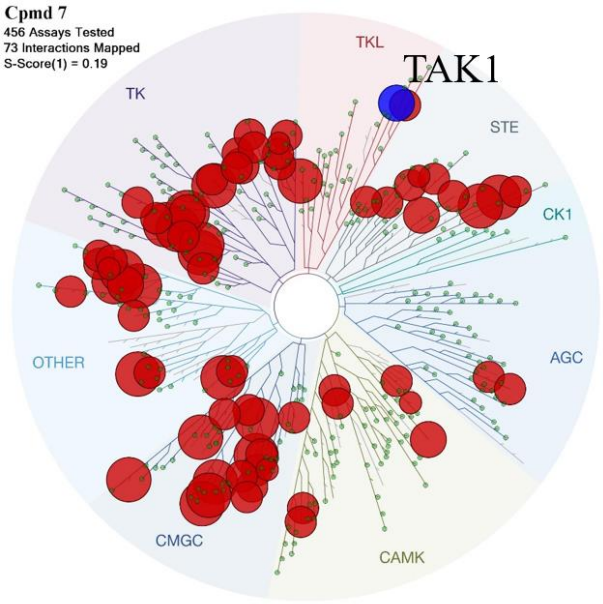
Figure S4: Determination of K_{inact}/K_i for **5**. (A) Time-dependent inhibition of TAK1 by **5**. TAK1 activity was measured using a peptide substrate mobility shift assay. (B) Transform of data to show time-dependent leftward shift in IC50 values indicative of TAK1 inactivation. (C) Inactivation rates were determined using nonlinear least-squares regression. (D) K_{inact}/K_i values for compound **5** on TAK1.



	Compound-5
k_{inact}	$1.1 \times 10^{-3}\ s^{-1}$
K_i	160 nM
k_{inact}/K_i	$6.87 \times 10^{-6}\ (nM^{-1}\ s^{-1})$

Figure S5. TREE*spot* kinase interaction maps based on the KINOMEscan profiling results of compounds **5**, **7**, **9**, **23** and **25**. The kinases with a DFG-1 cysteine residue were highlighted with blue color in the All three inhibitors were profiled at a concentration of 1 μM against a diverse panel of more than 456 kinases and mutants. Scores for primary screen hits are reported as a percent of the DMSO control (% control), the lower the Kd is likely to be, such that scores of zero represent strong hits. Scores are related to the probability of a hit but are not strictly an affinity measurement, and bigger spots in the maps reflect lower scores.




Cpmd 7
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73 Interactions Mapped
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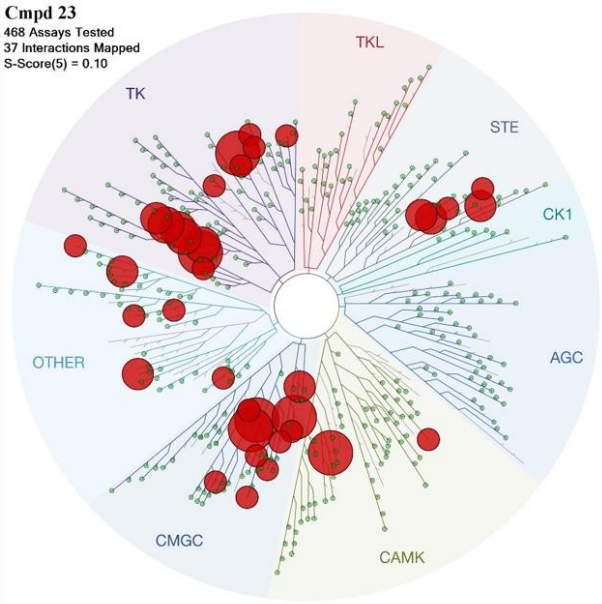
TAK1
TKL
TK
STE
CK1
OTHER
AGC
CMGC
CAMK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37 Interactions Mapped
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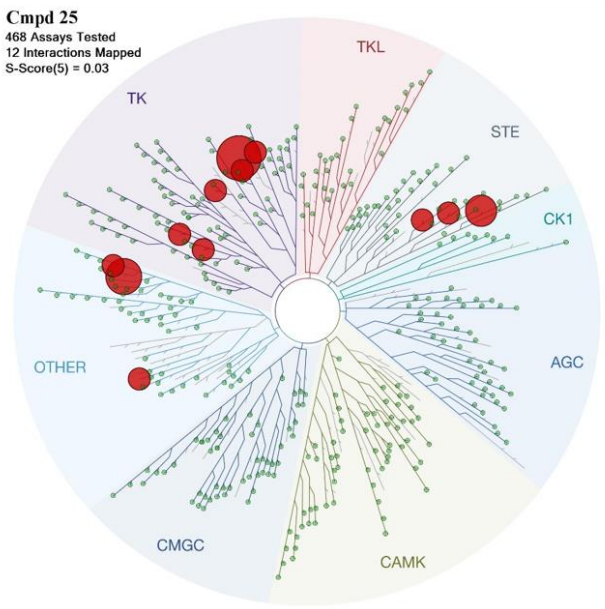
TK
STE
CK1
OTHER
AGC
CMGC
CAMK


Cmpd 25
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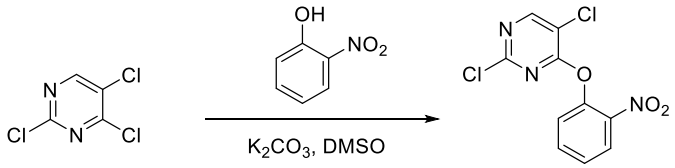
12 Interactions Mapped
S-Score(5) = 0.03
TKL
TK
STE
CK1
OTHER
AGC
CMGC
CAMK

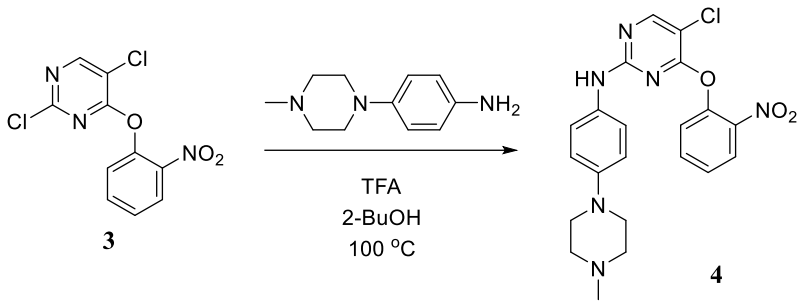
Experimental Procedures

Chemistry. Unless otherwise noted, reagents and solvents were obtained from commercial suppliers and were used without further purification. ^{1}H NMR spectra were recorded on 600 or 500 MHz (Varian AS600 or Bruker A500), and chemical shifts are reported in parts per million (ppm, δ) downfield from tetramethylsilane (TMS). Coupling constants (*J*) are reported in Hz. Spin multiplicities are described as s (singlet), br (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Mass spectra were obtained on a Waters Micromass ZQ instrument. Preparative HPLC was performed on a Waters Sunfire C18 column (19 x 50 mm, 5 µM) using a gradient of 15-95% methanol in water containing 0.05% trifluoroacetic acid (TFA) over 22 min (28 min run time) at a flow rate of 20 mL/min. Purities of assayed compounds were in all cases greater than 95%, as determined by reverse-phase HPLC analysis.

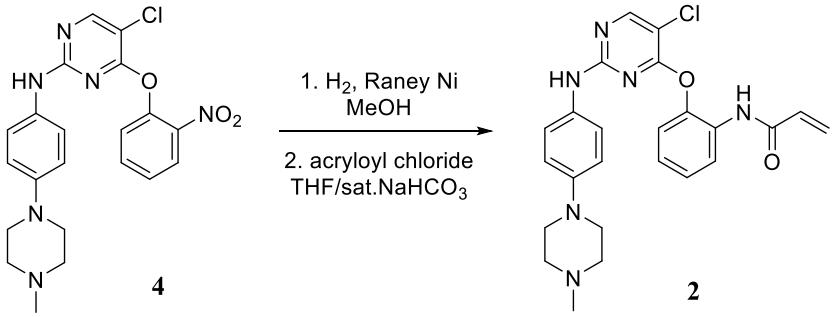


3

2,5-dichloro-4-(2-nitrophenoxy)pyrimidine (3). 2-Nitrophenol (840 mg, 6.0 mmol) and potassium carbonate (800 mg, 6.0 mmol) were combined in dimethyl sulfoxide (DMSO) (10 mL) and stirred for 15 min, then 2,4,5-trichloropyrimidine (560 µL, 5.0 mmol) was added and the mixture was stirred overnight. The mixture was then diluted with ethyl acetate and washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (hexane:ethyl acetate = 3:1) to yield 1.2 g (70%) of **3** as a white solid. MS (ESI) m/z 286 $(M+H)^+$.

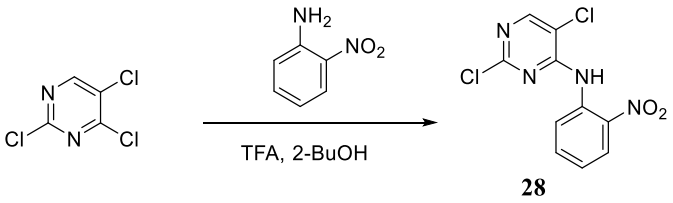


5-chloro-*N*-(4-(4-methylpiperazin-1-yl)phenyl)-4-(2-nitrophenoxy)pyrimidin-2-amine (4). To **3** (570 mg, 2.0 mmol) and 2-methoxy-4-(4-methylpiperazin-1-yl)aniline (390 mg, 2.0 mmol) in *sec*-butanol (4 mL) was added trifluoroacetic acid (154 μL, 2.0 mmol) and the mixture was stirred overnight at 75 °C. The mixture was then concentrated, neutralized with ammonia in methanol and purified by column chromatography (dichloromethane:methanol = 10:1) to yield 265 mg (60%) of **4** as a pale-yellow solid. MS (ESI) m/z 441 $(M+H)^+$.



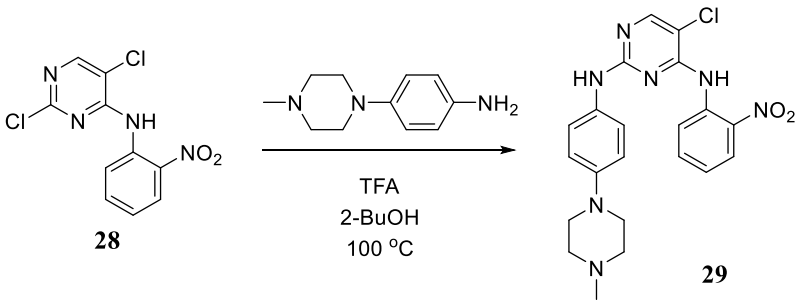
***N*-(2-((5-chloro-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)oxy)phenyl)acrylamide (2)**. To **4** (88 mg, 0.2 mmol) in methanol (10 mL) was added 1 mL Raney nickel suspension in methanol. The reaction mixture was stirred for 3 h under 1 atm of hydrogen. The mixture was then filtered with celite, and the filtrate was concentrated and dried under vacuum to give a crude product as a white solid. To the obtained white solid in tetrahydrofuran (3 mL) was added saturated $NaHCO_3$ solution (3 mL), the stirred mixture was then cooled to 0 °C, and acryloyl chloride was added (25 μL, 0.3 mmol) dropwise. The reaction mixture was stirred at 0 °C for 10 min, another batch of acryloyl chloride was added (8 μL, 0.1

mmol) dropwise. After another 5 min the mixture was allowed to recover to room temperature (RT), and diluted with ethyl acetate and washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The crude product was then purified by reverse phase HPLC to give 58 mg (63% for 2 steps) of **2** as a white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.68 (br, 1H), 9.58 (s, 1H), 9.52 (br, 1H), 8.40 (s, 1H), 8.05 (m, 1H), 7.32 (dd, *J* = 8.4, 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 6.72 (m, 2H), 6.55 (dd, *J* = 16.8, 10.8 Hz, 1H), 6.20 (d, *J* = 16.8 Hz, 1H), 5.71 (d, *J* = 10.8 Hz, 1H), 3.66 (m, 2H), 3.50 (m, 2H), 3.14 (m, 2H), 2.85 (s, 3H), 2.83 (m, 2H). MS (ESI) *m/z* 465 $(M+H)^+$.



28

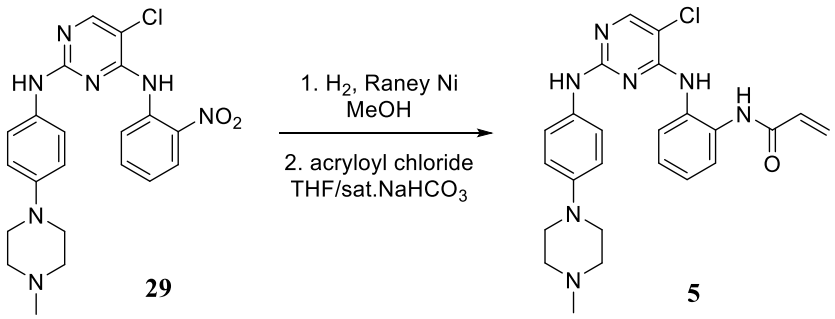
2,5-dichloro-*N*-(2-nitrophenyl)pyrimidin-4-amine (28). To 2,4,5-trichloropyrimidine (560 µL mg, 5.0 mmol) and 2-nitroaniline (700 mg, 5.0 mmol) in *sec*-butanol (25 mL) was added trifluoroacetic acid (383 µL, 5.0 mmol) and the mixture was stirred overnight at 60 °C. The mixture was then concentrated, neutralized with ammonia in methanol and purified by column chromatography (hexane:ethyl acetate = 2:1) to yield 640 mg (45%) of **28** as a yellow solid. MS (ESI) m/z 285 $(M+H)^+$.



28 **29**

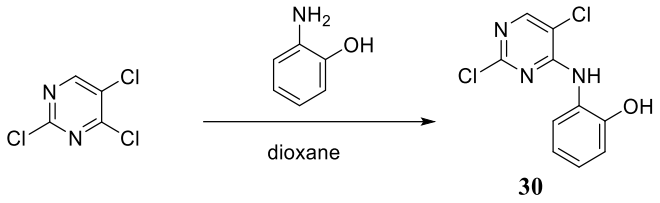
5-chloro-N^2-(4-(4-methylpiperazin-1-yl)phenyl)-N^4-(2-nitrophenyl)pyrimidine-2,4-diamine (29). To **28** (570 mg, 2.0 mmol) and 2-methoxy-4-(4-methylpiperazin-1-yl)aniline (390 mg, 2.0

mmol) in *sec*-butanol (4 mL) was added trifluoroacetic acid (154 μL, 2.0 mmol) and the mixture was stirred overnight at 85 °C. The mixture was then concentrated, neutralized with ammonia in methanol and purified by column chromatography (dichloromethane:methanol = 10:1) to yield 680 mg (76%) of **29** as a pale-yellow solid. MS (ESI) m/z 440 $(M+H)^+$.



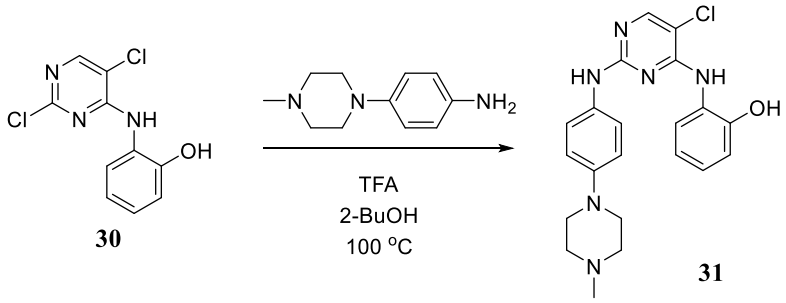
***N*-(2-((5-chloro-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)acrylamide (5)**. To **29** (88 mg, 0.2 mmol) in methanol (10 mL) was added 1 mL Raney nickel suspension in methanol. The reaction mixture was stirred for 3 h under 1 atm of hydrogen. The mixture was then filtered with celite, and the filtrate was concentrated and dried under vacuum to give a crude product as a white solid. To the obtained white solid in tetrahydrofuran (3 mL) was added saturated $NaHCO_3$ solution (3 mL), the stirred mixture was then cooled to 0 °C, and acryloyl chloride was added (25 μL, 0.3 mmol) dropwise. The reaction mixture was stirred at 0 °C for 10 min, another batch of acryloyl chloride was added (8 μL, 0.1 mmol) dropwise. After another 5 min the mixture was allowed to recover to room temperature (RT), and diluted with ethyl acetate and washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The crude product was then purified by reverse phase HPLC to give 55 mg (60% for 2 steps) of **5** as a white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.16 (s, 1H), 9.67 (br, 1H), 9.20 (br, 1H), 8.56 (s, 1H), 8.09 (s, 1H), 7.74 (d, J = 7.2 Hz, 1H), 7.46 (d, J = 6.6 Hz, 1H), 7.40 (d, J = 9.0 Hz, 2H), 7.32 (dd, J = 7.2, 7.2 Hz, 1H), 7.24 (dd, J = 7.8, 7.2 Hz, 1H), 6.78 (d, J = 9.6

Hz, 1H), 6.50 (dd, *J* = 16.8, 10.8 Hz, 1H), 6.30 (d, *J* = 17.4 Hz, 1H), 5.79 (d, *J* = 10.8 Hz, 1H), 3.66 (m, 2H), 3.49 (m, 2H), 3.14 (m, 2H), 2.84 (s, 3H), 2.83 (m, 2H). MS (ESI) *m/z* 464 $(M+H)^+$.



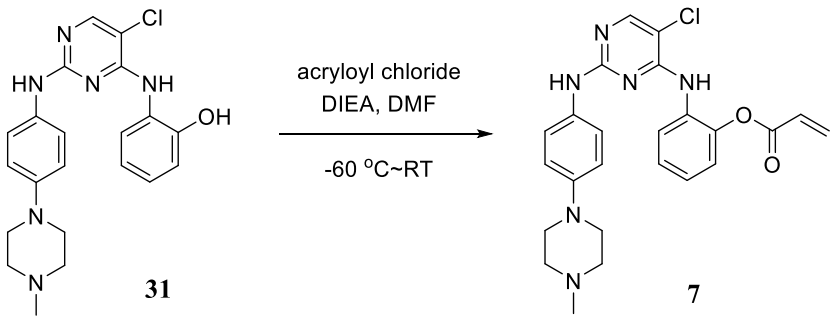
30

2-((2,5-dichloropyrimidin-4-yl)amino)phenol (30). To 2-aminophenol (550 mg, 5.0 mmol) in dioxane (10 mL) was added 2,4,5-trichloropyrimidine (560 µL mg, 5.0 mmol), the mixture was stirred overnight at RT. The mixture was then diluted with ethyl acetate and washed with water and brine, dried over Na_2SO_4, filtered and concentrated to give 1.02 g (80%) of the crude product **30** as a white solid, which was directly used in the next step. MS (ESI) m/z 256 $(M+H)^+$.



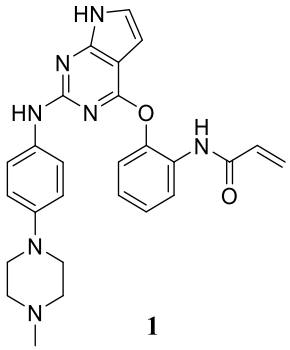
30 **31**

2-((5-chloro-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)phenol (31). To **30** (510 mg, 2.0 mmol) and 2-methoxy-4-(4-methylpiperazin-1-yl)aniline (575 mg, 3.0 mmol) in *sec*-butanol (5 mL) was added trifluoroacetic acid (230 µL, 3.0 mmol) and the mixture was stirred overnight at 100 °C. The mixture was then concentrated, neutralized with ammonia in methanol and purified by column chromatography (dichloromethane:methanol = 10:1) to yield 680 mg (76%) of **31** as a white solid. MS (ESI) m/z 411 $(M+H)^+$.



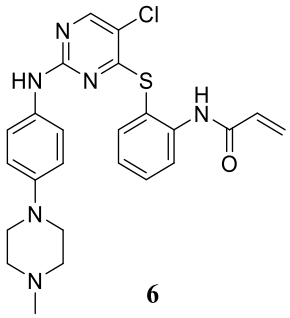
31 7

2-((5-chloro-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl acrylate (7). To **31** (82 mg, 0.2 mmol) in dimethylformamide (2 mL) was added diisopropylethylamine (53 μL, 0.3 mmol), the stirred mixture was then cooled to -60 °C, and acryloyl chloride (17.8 μL, 0.22 mmol) was added dropwise. The reaction mixture was stirred at -60 °C for 10 min, allowed to recover to RT (room temperature) gradually in 30 min, and purified by reverse phase HPLC to give 64 mg (TFA salt, 56% for 2 steps) of **7** as a white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.96 (br, 1H), 8.36 (s, 1H), 8.04 (s, 1H), 7.72 (br, 1H), 7.34 (d, J = 9.0 Hz, 2H), 7.30 (m, 3H), 6.70 (d, J = 9.0 Hz, 2H), 6.37 (d, J = 16.8, 1H), 6.26 (dd, J = 17.4, 10.2 Hz, 1H), 5.79 (d, J = 10.8 Hz, 1H), 3.02 (m, 4H), 2.54 (m, 4H), 2.28 (br, 3H), 2.84 (s, 3H). MS (ESI) *m/z* 465 $(M+H)^+$.



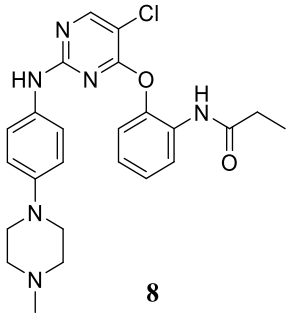
1

***N*-(2-((2-((4-(4-methylpiperazin-1-yl)phenyl)amino)-7*H*-pyrrolo[2,3-d]pyrimidin-4-yl)oxy)phenyl)acrylamide (1).** MS (ESI) *m/z* 470 $(M+H)^+$.



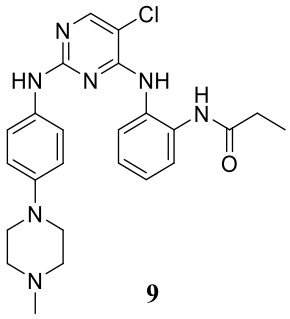
6

2-((5-chloro-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl acrylate (6). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.82 (br, 1H), 9.60 (s, 1H), 9.50 (br, 1H), 8.43 (br, 1H), 8.10 (s, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.68 (dd, *J* = 7.8, 7.2 Hz, 2H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 6.85 (br, 1H), 6.59 (dd, *J* = 16.8, 10.8 Hz, 1H), 6.20 (d, *J* = 16.8 Hz, 1H), 5.72 (d, *J* = 10.8 Hz, 1H), 3.65 (m, 2H), 3.51 (m, 2H), 3.15 (m, 2H), 2.86 (s, 3H), 2.84 (m, 2H). MS (ESI) *m/z* 465 $(M+H)^+$.



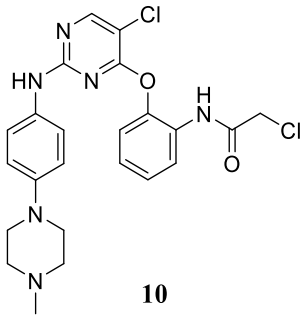
8

***N*-(2-((5-chloro-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)oxy)phenyl)propionamide (8)**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.69 (br, 1H), 9.48 (br, 1H), 9.28 (s, 1H), 8.38 (s, 1H), 7.89 (d, *J* = 7.2 Hz, 1H), 7.28 (d, *J* = 7.2 Hz, 2H), 7.24 (m, 1H), 7.22 (d, *J* = 7.2 Hz, 1H), 6.70 (m, 2H), 3.63 (m, 2H), 3.48 (m, 2H), 3.13 (m, 2H), 2.84 (s, 3H), 2.82 (m, 2H), 2.26 (m, 2H), 0.98 (t, *J* = 7.2 Hz, 3H). MS (ESI) *m/z* 467 $(M+H)^+$.



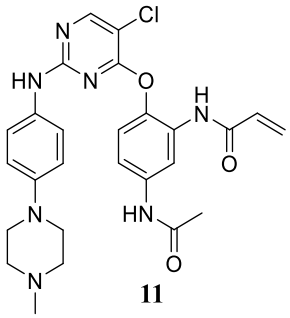
9

***N*-(2-((5-chloro-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl)propionamide (9)**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.95 (s, 1H), 9.71 (br, 1H), 9.26 (br, 1H), 8.52 (s, 1H), 8.12 (s, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.42 (d, *J* = 9.0 Hz, 2H), 7.34 (d, *J* = 7.2 Hz, 2H), 7.31 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.24 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.81 (d, *J* = 9.0 Hz, 2H), 3.68 (m, 2H), 3.51 (m, 2H), 3.16 (m, 2H), 2.87 (m, 2H), 2.86 (s, 3H), 2.37 (q, *J* = 7.8 Hz, 2H), 1.10 (t, *J* = 7.8 Hz, 3H). MS (ESI) *m/z* 466 $(M+H)^+$.



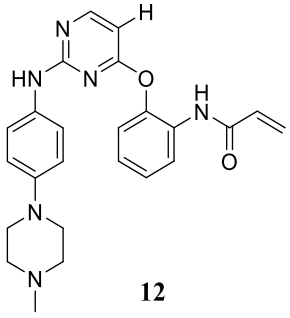
10

2-chloro-*N*-(2-((5-chloro-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)oxy)phenyl)acetamide (10). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.69 (br, 1H), 9.68 (s, 1H), 9.54 (br, 1H), 8.42 (s, 1H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.34 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.28 (dd, *J* = 7.2 Hz, 1H), 7.24 (m, 1H), 6.71 (m, 2H), 4.26 (s, 2H), 3.65 (m, 2H), 3.50 (m, 2H), 3.14 (m, 2H), 2.85 (s, 3H), 2.84 (m, 2H). MS (ESI) *m/z* 487 $(M+H)^+$.



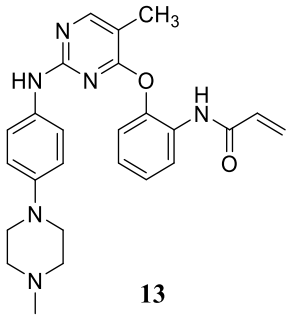
11

***N*-(5-acetamido-2-((5-chloro-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)oxy)phenyl)acrylamide (11)**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.11 (s, 1H), 9.73 (br, 1H), 9.51 (br, 1H), 9.50 (s, 1H), 8.38 (s, 1H), 8.20 (s, 1H), 7.52 (d, *J* = 9.0 Hz, 1H), 7.22 (br, 1H), 7.19 (d, *J* = 9.0 Hz, 1H), 6.71 (m, 2H), 6.53 (dd, *J* = 16.8, 10.8 Hz, 1H), 6.19 (d, *J* = 16.8 Hz, 1H), 5.70 (d, *J* = 10.8 Hz, 1H), 3.65 (m, 2H), 3.49 (m, 2H), 3.14 (m, 2H), 2.85 (s, 3H), 2.84 (m, 2H), 2.08 (s, 3H). MS (ESI) *m/z* 522 $(M+H)^+$.



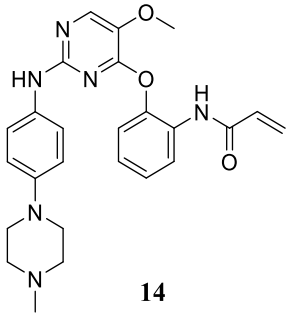
12

***N*-(2-((2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)oxy)phenyl)acrylamide (12)**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.68 (br, 1H), 9.62 (s, 1H), 9.38 (br, 1H), 8.30 (s, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.36 (m, 1H), 7.29 (dd, *J* = 7.2, 7.2 Hz, 2H), 7.23 (m, 2H), 6.76 (d, *J* = 7.2 Hz, 1H), 6.55 (dd, *J* = 16.8, 10.8 Hz, 1H), 6.39 (d, *J* = 5.4 Hz, 1H), 6.19 (d, *J* = 16.8 Hz, 1H), 5.69 (d, *J* = 10.8 Hz, 1H), 3.66 (m, 2H), 3.50 (m, 2H), 3.15 (m, 2H), 2.86 (s, 3H), 2.84 (m, 2H). MS (ESI) *m/z* 431 $(M+H)^+$.



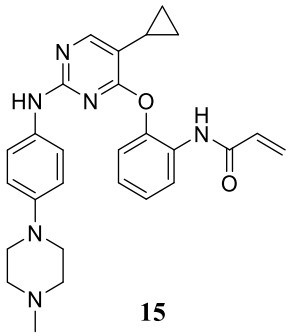
13

***N*-(2-((5-methyl-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)oxy)phenyl)acrylamide (12)**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.68 (br, 1H), 9.52 (s, 1H), 9.20 (br, 1H), 8.17 (s, 1H), 8.04 (br, 1H), 7.29 (m, 3H), 7.25 (m, 2H), 6.71 (d, *J* = 9.0 Hz, 1H), 6.54 (dd, *J* = 16.8, 10.8 Hz, 1H), 6.19 (d, *J* = 16.8 Hz, 1H), 5.70 (d, *J* = 10.8 Hz, 1H), 3.63 (m, 2H), 3.50 (m, 2H), 3.15 (m, 2H), 2.85 (s, 3H), 2.83 (m, 2H), 2.17 (s, 3H). MS (ESI) *m/z* 445 $(M+H)^+$.



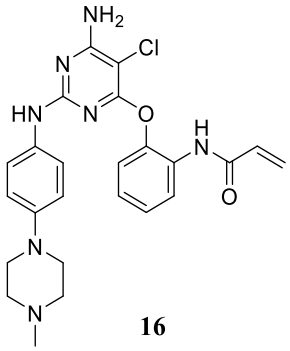
14

***N*-(2-((5-methoxy-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)oxy)phenyl)acrylamide (14)**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.50 (br, 1H), 9.59 (s, 1H), 9.06 (br, 1H), 8.16 (s, 1H), 8.09 (br, 1H), 7.29 (m, 3H), 7.23 (m, 1H), 6.71 (d, *J* = 9.0 Hz, 1H), 6.58 (dd, *J* = 16.8, 10.8 Hz, 1H), 6.20 (d, *J* = 16.8 Hz, 1H), 5.69 (d, *J* = 10.8 Hz, 1H), 3.86 (s, 3H), 3.62 (m, 2H), 3.50 (m, 2H), 3.15 (m, 2H), 2.86 (s, 3H), 2.82 (m, 2H). MS (ESI) *m/z* 461 $(M+H)^+$.



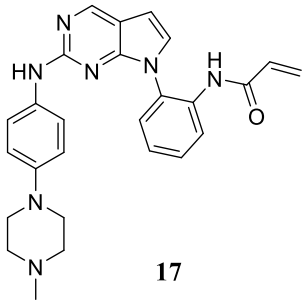
15

***N*-(2-((5-cyclopropyl-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)oxy)phenyl)acrylamide (15)**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.67 (br, 1H), 9.50 (s, 1H), 9.21 (br, 1H), 8.02 (s, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.28 (m, 3H), 7.24 (m, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 6.52 (dd, *J* = 16.8, 10.8 Hz, 1H), 6.18 (d, *J* = 16.8 Hz, 1H), 5.68 (d, *J* = 10.8 Hz, 1H), 3.61 (m, 2H), 3.48 (m, 2H), 3.12 (m, 2H), 2.83 (s, 3H), 2.82 (m, 2H), 1.94 (m, 1H), 0.83 (m, 2H), 0.74 (m, 2H). MS (ESI) *m/z* 471 $(M+H)^+$.



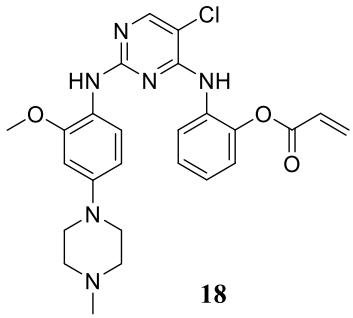
16

***N*-(2-((6-amino-5-chloro-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)oxy)phenyl)acrylamide (16)**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.67 (br, 1H), 9.49 (s, 1H), 8.81 (s, 1H), 8.07 (br, 1H), 7.31 (m, 2H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.15 (m, 2H), 6.82 (m, 1H), 6.67 (d, *J* = 7.8 Hz, 2H), 6.61 (dd, *J* = 16.8, 10.8 Hz, 1H), 6.19 (d, *J* = 16.8 Hz, 1H), 5.68 (d, *J* = 10.8 Hz, 1H), 3.60 (m, 2H), 3.48 (m, 2H), 3.12 (m, 2H), 2.83 (s, 3H), 2.81 (m, 2H). MS (ESI) *m/z* 480 $(M+H)^+$.



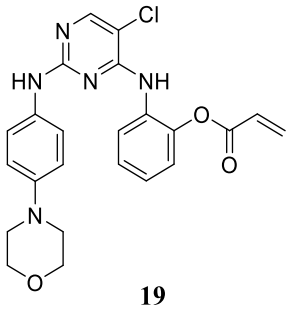
17

***N*-(2-(2-((4-(4-methylpiperazin-1-yl)phenyl)amino)-7*H*-pyrrolo[2,3-*d*]pyrimidin-7-yl)phenyl)acrylamide (17)**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.56 (s, 1H), 9.21 (s, 1H), 8.73 (s, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.48 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.48 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.19 (d, *J* = 3.6 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 1H), 6.62 (d, *J* = 3.6 Hz, 1H), 6.27 (dd, *J* = 16.8, 10.8 Hz, 1H), 6.11 (d, *J* = 16.8 Hz, 1H), 5.62 (d, *J* = 10.8 Hz, 1H), 3.13 (m, 4H), 3.89 (m, 4H), 2.54 (m, 3H). MS (ESI) *m/z* 454 $(M+H)^+$.



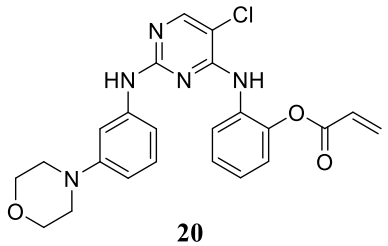
18

2-((5-chloro-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)phenyl acrylate (12). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.22 (br, 1H), 8.66 (br, 1H), 8.10 (s, 1H), 7.70 (br, 1H), 7.37 (d, *J* = 7.2 Hz, 2H), 7.33 (m, 3H), 6.80 (m, 2H), 6.61 (s, 1H), 6.39 (d, *J* = 16.8 Hz, 1H), 6.34 (d, *J* = 7.2 Hz, 1H), 6.27 (dd, *J* = 16.8, 10.8 Hz, 1H), 6.05 (d, *J* = 10.8 Hz, 1H), 3.79 (s, 3H), 3.48 (m, 4H), 2.74 (m, 4H), 2.43 (m, 3H). MS (ESI) *m/z* 495 $(M+H)^+$.



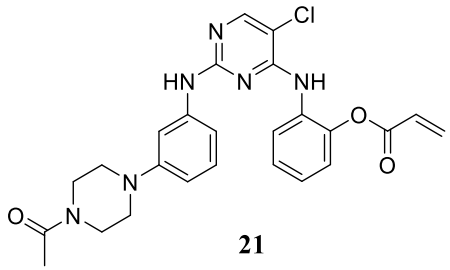
19

2-((5-chloro-2-((4-morpholinophenyl)amino)pyrimidin-4-yl)amino)phenyl acrylate (19). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.68 (br, 1H), 9.52 (s, 1H), 9.20 (br, 1H), 8.17 (s, 1H), 8.04 (br, 1H), 7.29 (m, 3H), 7.25 (m, 2H), 6.71 (d, *J* = 9.0 Hz, 1H), 6.39 (d, *J* = 16.8 Hz, 1H), 6.28 (dd, *J* = 16.8, 10.8 Hz, 1H), 6.08 (d, *J* = 10.8 Hz, 1H), 3.75 (m, 4H), 3. 50 (m, 4H). MS (ESI) *m/z* 452 $(M+H)^+$.



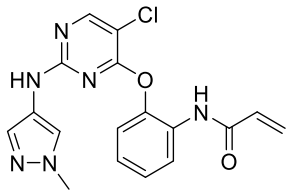
20

2-((5-chloro-2-((3-morpholinophenyl)amino)pyrimidin-4-yl)amino)phenyl acrylate (20). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.21 (br, 1H), 8.67 (s, 1H), 8.14 (s, 1H), 7.68 (m, 1H), 7.32 (s, 1H), 7.31 (m, 2H), 7.08 (br, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 6.97 (dd, *J* = 8.4, 8.4 Hz, 1H), 6.52 (d, *J* = 8.4, 1H), 6.39 (d, *J* = 16.8 Hz, 1H), 6.27 (dd, *J* = 16.8, 10.8 Hz, 1H), 6.07 (d, *J* = 10.8 Hz, 1H), 3.67 (m, 4H), 2.90 (m, 4H). MS (ESI) *m/z* 452 $(M+H)^+$.



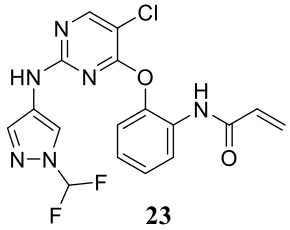
21

2-((2-((3-(4-acetylpiperazin-1-yl)phenyl)amino)-5-chloropyrimidin-4-yl)amino)phenyl acrylate (21). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.15 (br, 1H), 8.57 (s, 1H), 8.13 (s, 1H), 7.70 (br, 1H), 7.30 (m, 3H), 7.09 (br, 1H), 7.05 (d, *J* = 8.4 Hz, 1H), 6.96 (dd, *J* = 8.4, 7.8 Hz, 1H), 6.52 (d, *J* = 8.4, 1H), 6.39 (d, *J* = 16.8 Hz, 1H), 6.27 (dd, *J* = 16.8, 10.8 Hz, 1H), 6.07 (d, *J* = 10.8 Hz, 1H), 3.51 (m, 4H), 2.96 (m, 2H), 2.89 (m, 2H), 2.03 (s, 3H). MS (ESI) *m/z* 493 $(M+H)^+$.



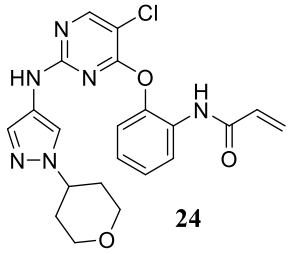
22

***N*-(2-((5-chloro-2-((1-methyl-1*H*-pyrazol-4-yl)amino)pyrimidin-4-yl)oxy)phenyl)acrylamide (22)**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.72 (br, 1H), 9.60 (s, 1H), 8.37 (s, 1H), 8.10 (br, 1H), 7.41 (br, 1H), 7.30 (m, 2H), 7.05 (s, 1H), 6.75 (s, 1H), 6.53 (m, 1H), 6.20 (d, *J* = 16.8 Hz, 1H), 5.70 (d, *J* = 10.8 Hz, 1H), 3.53 (m, 3H). MS (ESI) *m/z* 371 $(M+H)^+$.



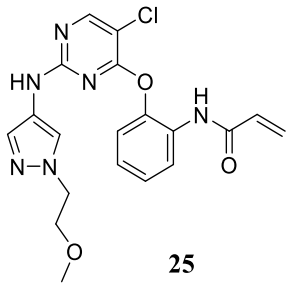
23

***N*-(2-((5-chloro-2-((1-(difluoromethyl)-1*H*-pyrazol-4-yl)amino)pyrimidin-4-yl)oxy)phenyl)acrylamide (23)**. MS (ESI) *m/z* 407 $(M+H)^+$.



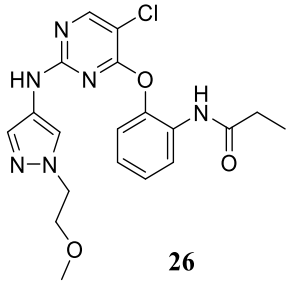
24

***N*-(2-((5-chloro-2-((1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrazol-4-yl)amino)pyrimidin-4-yl)oxy)phenyl)acrylamide (22)**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.76 (br, 1H), 9.61 (s, 1H), 8.38 (s, 1H), 8.10 (br, 1H), 7.41 (br, 1H), 7.31 (m, 2H), 7.13 (s, 1H), 6.91 (s, 1H), 6.53 (m, 1H), 6.19 (d, *J* = 16.8 Hz, 1H), 5.70 (d, *J* = 10.8 Hz, 1H), 3.95 (m, 5H), 3.44 (m, 4H). MS (ESI) *m/z* 441 $(M+H)^+$.



25

***N*-(2-((5-chloro-2-((1-(2-methoxyethyl)-1*H*-pyrazol-4-yl)amino)pyrimidin-4-yl)oxy)phenyl)acrylamide (25)**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.74 (br, 1H), 9.59 (s, 1H), 8.38 (s, 1H), 8.10 (br, 1H), 7.38 (br, 1H), 7.30 (m, 2H), 7.17 (br, 1H), 6.84 (br, 1H), 6.54 (m, 1H), 6.20 (d, *J* = 16.8 Hz, 1H), 5.70 (d, *J* = 10.8 Hz, 1H), 3.90 (m, 2H), 3.50 (m, 2H), 3.18 (s, 3H). MS (ESI) *m/z* 415 $(M+H)^+$.



26

***N*-(2-((5-chloro-2-((1-(2-methoxyethyl)-1*H*-pyrazol-4-yl)amino)pyrimidin-4-yl)oxy)phenyl)propionamide (26)**. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.71 (br, 1H), 9.31 (s, 1H), 8.37 (s, 1H), 7.95 (br, 1H), 7.35 (br, 1H), 7.27 (m, 2H), 7.08 (br, 1H), 6.83 (br, 1H), 3.89 (m, 2H), 3.49 (m, 2H), 3.18 (s, 3H), 2.26 (m, 2H), 0.96 (m, 3H). MS (ESI) *m/z* 417 $(M+H)^+$.

Mass spectrometry procedures. TAK1 protein (20 µg) was labeled with an equimolar amount of inhibitor or DMSO for 1 hour at room temperature. Analysis of intact protein was performed as described [1]. Briefy, ~5 µg protein was injected onto a self-packed reversed-phase column (500 µm inner diameter, 5 cm of POROS 50R2 resin). After washing to remove salts, TAK1 was eluted with an HPLC gradient (0%–100% B in 1 min, A = 0.2 M acetic acid in water, B = 0.2 M acetic acid in acetonitrile, flow rate = 10 µl/min) into a linear ion trap mass spectrometer (LTQ, Thermo Fisher Scientific, San Jose, CA). Data were acquired in profile mode scanning m/z 300-2000, and mass spectra were deconvoluted using MagTran software (version 1.03b2) [2]. The site of covalent modification was determined using nanoLC-MS. Desalted proteins were reduced with tris(2-carboxyethyl)phosphine (10 mM, 30 minutes room temperature), alkylated with methylmethanethiosulfonate (20 mM, 30 minutes room temperature), and digested with trypsin at 37 ℃ overnight. Digests were analyzed by nanoLC-ESI-MS as described with modifications [3]. Peptides were loaded onto a self-packed pre-column (4 cm POROS10R2), resolved on an analytical column (30 µm I.D., packed with 50 cm C18) and eluted into the mass spectrometer (hybrid quadrupole-orbitrap mass spectrometer, QExactiv HF, Thermo Fisher Scientific) using an HPLC gradient (Waters NanoAcquity, Milford, MA; 0%–35% B in 60 min, A = 0.2 M acetic acid in water, B = 0.2 M acetic acid in acetonitrile, flow rate = ~30 nl/min). The instrument was operated in data dependent mode such that the top 10 most abundant precursors were subjected to MS/MS (image current detection, normalized collision energy 27%, resolution=15,000). Raw data files were converted to .mgf using in-house software [4] and searched using Mascot 2.2.1 against a forward-reverse human refseq database. Search parameters specified variable oxidation of methionine, variable compound 2 modification of cysteine, and fixed methylthio modification of cysteine (i.e. cysteines are considered methylthio or inhibitor labeled).

Covalent inhibition kinetics using Mobility Shift Assay:

K_{inact}/K_i measurements were determined from kinetic TAK1 enzyme activity data obtained using a peptide substrate mobility shift assay similar to previous descriptions [5]. Reactions containing 50 nM TAK1-TAB1 protein, 1 μM fluorescently labeled LRRKtide (FAM-RLGRDKYKTLRQIRQ), 100 μM ATP, and inhibitor were performed in 100 mM Hepes pH 7.3, 0.015% Brij-35, 0.004% Tween-20, 10 mM $MgCl_2$. Peptides were separated and detected using a LabChip EZ Reader® (PerkinElmer). Separation buffer consisted of 100 mM Hepes pH 7.3, 0.015% Brij-35, 1 mM disodium EDTA, 0.1% coating reagent 3, 5% DMSO and 1X coating reagent 8. Phosphorylated and non-phosphorylated peaks were analyzed using LabChip EZ Reader Software V3.0. Assay data were exported to the DynaFit software package [6] to obtain K_{inact}/K_i values as described [7].

Supplementary Tables

Table S1. X-ray reflection data and model refinement statistics

	C-1 (5J9L)	**C-2 (5J8I)**	**C-5 (5J7S)**	**C-7 (5JH6)**	**C-10 (5E7R)**	**C-22 (5JK3)**
Data Collection						
Space Group	I2 2 2					
Unit Cell Dimensions						
a, *b*, *c* (Å)	58.208, 133.407, 144.898	58.248, 133.343, 145.039	58.234, 134.06, 146.81	58.303, 133.58, 145.70	58.41, 133.422, 145.769	58.272, 133.59, 144.20
α,β, γ (°)	90.0, 90.0, 90.0					
Wavelength (Å)	0.97926	0.97932	0.97932	0.97918	0.97918	0.97932
Resolution (Å)	49.01 - 2.75 (2.85 - 2.75)	49.08 - 2.40 (2.49 - 2.40)	49.50 - 2.37 (2.42 - 2.37)	50.0 - 2.34 (2.38 - 2.34)	50.0 - 2.10 (2.14 - 2.10)	50.0 - 2.40 (2.44 - 2.40)
Unique Reflections	13,998	21,238	23,015	22,477	32,105	21,503
Redundancy	5.0 (4.4)	8.3 (5.6)	9.9 (6.4)	8.9 (5.9)	8.0 (6.4)	5.9 (4.8)
Completeness	92.9 (76.0)	96.3 (80.1)	96.3 (90.9)	96.8 (89.9)	96.7 (98.4)	93.7 (69.7)
R_{merge}	0.081 (0.579)	0.124 (1.571)	0.129 (1.486)	0.106 (0.901)	0.243 (NA)	0.090 (0.923)
<I/σ>	15.2 (1.6)	18.9 (1.1)	17.8 (0.87)	19.27 (1.25)	6.3 (1.68)	17.2 (2.0)
Wilson B-factor ($Å^2$)	58.7	53.9	48.9	55.5	38.7	47.8
Refinement and Model Statistics						
Refinement Resolution (Å)	49.01 - 2.75	49.08 - 2.40	49.50 - 2.37	45.64 - 2.36	42.15 - 2.11	35.38 - 2.40
No. of reflections used	13,979	21,171	22,973	22,432	32,065	21,465
Reflections for R-Free	703 (5%)	1057 (5%)	1150 (5%)	1088 (5%)	1281 (4%)	1071 (5%)
R-work	0.212	0.223	0.239	0.225	0.220	0.234

R-free	0.243	0.249	0.246	0.252	0.245	0.265
RMS deviations						
Bond lengths (Å)	0.003	0.003	0.003	0.004	0.007	0.003
Bond Angles ( )	0.55	0.63	0.58	0.557	0.956	0.569
Average B-factor (Å^2)	79	94	95	97	69	88
Ramachandran plot (%)						
Favored/allowed/disallowed	94.0 / 5.9 / 0.0	92.1 / 7.9 / 0.0	95.8 / 4.2 / 0.0	97.5 / 2.5 / 0.0	95.4 / 4.6 / 0.0	94.5 / 5.5 / 0.0

Table S2-7. KINOMEscan kinase selectivity profiles for **7**, **23**, **25** and 5Z7**.** All three inhibitors were profiled at a concentration of 1 μM against a diverse panel of more than 456 kinases (354 non-mutants kinases), whereas 5Z7 was profiled at both 1 and 10 μM. Scores for primary screen hits are reported as a percent of the DMSO control (% control). For kinases where no score is shown, no measurable binding was detected. The lower the score, the lower the Kd is likely to be, such that scores of zero represent strong hits. Scores are related to the probability of a hit but are not strictly an affinity measurement. Those hits with a DFG-1 cysteine were highlighted.

Table S2. KINOMEscan kinase selectivity profiles for **5**.

Kinases	**Scores**	**Kinases**	**Scores**
AAK1	11	LZK	12
ABL1(E255K)-phosphorylated	0.75	MAK	100
ABL1(F317I)-nonphosphorylated	40	MAP3K1	94
ABL1(F317I)-phosphorylated	36	MAP3K15	72
ABL1(F317L)-nonphosphorylated	16	MAP3K2	11
ABL1(F317L)-phosphorylated	20	MAP3K3	18
ABL1(H396P)-nonphosphorylated	0	MAP3K4	5.4
ABL1(H396P)-phosphorylated	1.1	MAP4K2	27
ABL1(M351T)-phosphorylated	3.9	MAP4K3	4.9
ABL1(Q252H)-nonphosphorylated	0	MAP4K4	59
ABL1(Q252H)-phosphorylated	1.1	MAP4K5	68
ABL1(T315I)-nonphosphorylated	0	MAPKAPK2	100

ABL1(T315I)-phosphorylated	0.7	MAPKAPK5	0
ABL1(Y253F)-phosphorylated	1.1	MARK1	15
ABL1-nonphosphorylated	0.8	MARK2	17
ABL1-phosphorylated	1.1	MARK3	18
ABL2	18	MARK4	19
ACVR1	2.3	MAST1	75
ACVR1B	11	MEK1	0
ACVR2A	55	MEK2	0
ACVR2B	87	MEK3	3.5
ACVRL1	18	MEK4	3.5
ADCK3	97	MEK5	0.1
ADCK4	89	MEK6	23
AKT1	100	MELK	30
AKT2	100	MERTK	4.8
AKT3	100	MET	23
ALK	53	MET(M1250T)	1.6
ALK(C1156Y)	12	MET(Y1235D)	23
ALK(L1196M)	9.6	MINK	29
AMPK-alpha1	2.4	MKK7	22
AMPK-alpha2	5.5	MKNK1	74
ANKK1	96	MKNK2	4.4
ARK5	0.9	MLCK	100
ASK1	100	MLK1	15
ASK2	91	MLK2	45
AURKA	1.2	MLK3	61
AURKB	0.1	MRCKA	100
AURKC	0.2	MRCKB	100
AXL	3	MST1	49
BIKE	2.6	MST1R	63
BLK	1.2	MST2	84
BMPR1A	70	MST3	85
BMPR1B	0.15	MST4	98
BMPR2	87	MTOR	100
BMX	29	MUSK	15
BRAF	90	MYLK	79
BRAF(V600E)	89	MYLK2	55
BRK	1.6	MYLK4	96
BRSK1	30	MYO3A	89
BRSK2	30	MYO3B	42
BTK	3.1	NDR1	39
BUB1	100	NDR2	42
CAMK1	73	NEK1	100
CAMK1B	78	NEK10	88
CAMK1D	65	NEK11	57
CAMK1G	93	NEK2	75
CAMK2A	96	NEK3	52

CAMK2B	97	NEK4	94
CAMK2D	94	NEK5	100
CAMK2G	96	NEK6	100
CAMK4	100	NEK7	98
CAMKK1	29	NEK9	95
CAMKK2	15	NIK	100
CASK	92	NIM1	67
CDC2L1	5.4	NLK	93
CDC2L2	90	OSR1	100
CDC2L5	100	p38-alpha	96
CDK11	100	p38-beta	100
CDK2	98	p38-delta	91
CDK3	89	p38-gamma	61
CDK4	95	PAK1	21
CDK4-cyclinD1	91	PAK2	59
CDK4-cyclinD3	58	PAK3	0
CDK5	61	PAK4	65
CDK7	10	PAK6	77
CDK8	91	PAK7	58
CDK9	9.4	PCTK1	100
CDKL1	33	PCTK2	87
CDKL2	1.4	PCTK3	91
CDKL3	0	PDGFRA	0.5
CDKL5	100	PDGFRB	0.1
CHEK1	76	PDPK1	72
CHEK2	2	PFCDPK1(P.falciparum)	47
CIT	92	PFPK5(P.falciparum)	100
CLK1	2.3	PFTAIRE2	89
CLK2	8.2	PFTK1	90
CLK3	57	PHKG1	22
CLK4	7.8	PHKG2	21
CSF1R	11	PIK3C2B	90
CSF1R-autoinhibited	17	PIK3C2G	92
CSK	46	PIK3CA	97
CSNK1A1	79	PIK3CA(C420R)	99
CSNK1A1L	95	PIK3CA(E542K)	76
CSNK1D	71	PIK3CA(E545A)	94
CSNK1E	100	PIK3CA(E545K)	64
CSNK1G1	98	PIK3CA(H1047L)	74
CSNK1G2	81	PIK3CA(H1047Y)	100
CSNK1G3	98	PIK3CA(I800L)	100
CSNK2A1	39	PIK3CA(M1043I)	87
CSNK2A2	30	PIK3CA(Q546K)	77
CTK	89	PIK3CB	57
DAPK1	59	PIK3CD	99
DAPK2	95	PIK3CG	77

DAPK3	69	PIK4CB	97
DCAMKL1	47	PIKFYVE	76
DCAMKL2	65	PIM1	86
DCAMKL3	100	PIM2	100
DDR1	8.4	PIM3	96
DDR2	27	PIP5K1A	7.8
DLK	8.4	PIP5K1C	91
DMPK	100	PIP5K2B	7.1
DMPK2	94	PIP5K2C	69
DRAK1	44	PKAC-alpha	77
DRAK2	100	PKAC-beta	100
DYRK1A	79	PKMYT1	97
DYRK1B	49	PKN1	61
DYRK2	56	PKN2	51
EGFR	39	PKNB(M.tuberculosis)	6
EGFR(E746-A750del)	36	PLK1	77
EGFR(G719C)	90	PLK2	59
EGFR(G719S)	81	PLK3	65
EGFR(L747-E749del, A750P)	34	PLK4	0.1
EGFR(L747-S752del, P753S)	54	PRKCD	94
EGFR(L747-T751del,Sins)	83	PRKCE	86
EGFR(L858R)	37	PRKCH	100
EGFR(L858R,T790M)	8.1	PRKCI	69
EGFR(L861Q)	52	PRKCQ	67
EGFR(S752-I759del)	85	PRKD1	54
EGFR(T790M)	7	PRKD2	15
EIF2AK1	80	PRKD3	24
EPHA1	21	PRKG1	55
EPHA2	89	PRKG2	75
EPHA3	57	PRKR	47
EPHA4	99	PRKX	100
EPHA5	100	PRP4	67
EPHA6	72	PYK2	9.9
EPHA7	97	QSK	100
EPHA8	97	RAF1	100
EPHB1	68	RET	1.1
EPHB2	97	RET(M918T)	2.4
EPHB3	92	RET(V804L)	1
EPHB4	94	RET(V804M)	1.4
EPHB6	2.5	RIOK1	5.7
ERBB2	72	RIOK2	89
ERBB3	80	RIOK3	11
ERBB4	43	RIPK1	83
ERK1	23	RIPK2	98
ERK2	15	RIPK4	71
ERK3	3.6	RIPK5	48

ERK4	22	ROCK1	66
ERK5	29	ROCK2	44
ERK8	4.8	ROS1	12
ERN1	38	RPS6KA4(Kin.Dom.1-N-terminal)	17
FAK	3.4	RPS6KA4(Kin.Dom.2-C-terminal)	60
FER	16	RPS6KA5(Kin.Dom.1-N-terminal)	88
FES	67	RPS6KA5(Kin.Dom.2-C-terminal)	98
FGFR1	0.8	RSK1(Kin.Dom.1-N-terminal)	7
FGFR2	7.6	RSK1(Kin.Dom.2-C-terminal)	90
FGFR3	5.7	RSK2(Kin.Dom.1-N-terminal)	1.2
FGFR3(G697C)	8.6	RSK2(Kin.Dom.2-C-terminal)	100
FGFR4	43	RSK3(Kin.Dom.1-N-terminal)	4.3
FGR	2.6	RSK3(Kin.Dom.2-C-terminal)	67
FLT1	0.95	RSK4(Kin.Dom.1-N-terminal)	20
FLT3	1.1	RSK4(Kin.Dom.2-C-terminal)	85
FLT3(D835H)	0.8	S6K1	19
FLT3(D835V)	0	SBK1	6.3
FLT3(D835Y)	0.2	SGK	29
FLT3(ITD)	1	SgK110	8.9
FLT3(ITD,D835V)	0	SGK2	90
FLT3(ITD,F691L)	0	SGK3	67
FLT3(K663Q)	0.15	SIK	1.1
FLT3(N841I)	0	SIK2	8.2
FLT3(R834Q)	0	SLK	0.2
FLT3-autoinhibited	0.5	SNARK	0.7
FLT4	0	SNRK	73
FRK	24	SRC	0.2
FYN	16	SRMS	73
GAK	8.3	SRPK1	4.5
GCN2(Kin.Dom.2,S808G)	1.9	SRPK2	94
GRK1	66	SRPK3	24
GRK2	89	STK16	1.3
GRK3	57	STK33	18
GRK4	32	STK35	55
GRK7	92	STK36	0.2
GSK3A	100	STK39	83
GSK3B	95	SYK	26
HASPIN	100	**TAK1**	0.95
HCK	3.7	TAOK1	44
HIPK1	24	TAOK2	100
HIPK2	25	TAOK3	62
HIPK3	33	TBK1	16
HIPK4	2.6	TEC	2.6

HPK1	0.7	TESK1	69
HUNK	100	TGFBR1	24
ICK	93	TGFBR2	100
IGF1R	1.9	TIE1	4
IKK-alpha	81	TIE2	11
IKK-beta	83	TLK1	82
IKK-epsilon	16	TLK2	91
INSR	2.3	TNIK	30
INSRR	2.1	TNK1	0
IRAK1	0.4	TNK2	7.1
IRAK3	8.5	TNNI3K	100
IRAK4	7.8	TRKA	0
ITK	0.95	TRKB	0.4
JAK1(JH1domain-catalytic)	47	TRKC	11
JAK1(JH2domain-pseudokinase)	3.8	TRPM6	100
JAK2(JH1domain-catalytic)	0	TSSK1B	39
JAK3(JH1domain-catalytic)	0	TSSK3	83
JNK1	0.95	TTK	6.1
JNK2	10	TXK	26
JNK3	0.8	TYK2(JH1domain-catalytic)	12
KIT	0.05	TYK2(JH2domain-pseudokinase)	18
KIT(A829P)	0	TYRO3	44
KIT(D816H)	12	ULK1	11
KIT(D816V)	2.5	ULK2	22
KIT(L576P)	0.95	ULK3	1.2
KIT(V559D)	0	VEGFR2	0.3
KIT(V559D,T670I)	1	VPS34	83
KIT(V559D,V654A)	28	VRK2	92
KIT-autoinhibited	0.5	WEE1	2.4
LATS1	30	WEE2	7.6
LATS2	41	WNK1	100
LCK	0.75	WNK2	100
LIMK1	16	WNK3	100
LIMK2	96	WNK4	100
LKB1	75	YANK1	70
LOK	0.1	YANK2	100
LRRK2	48	YANK3	100
LRRK2(G2019S)	100	YES	0.6
LTK	41	YSK1	89
LYN	32	YSK4	0
LZK	12	ZAK	62
MAK	100	ZAP70	66

Table S3. KINOMEscan kinase selectivity profiles for **9**.

Kinase	Scores	Kinase	Scores
AAK1	12	MAK	94
ABL1(E255K)-phosphorylated	0.4	MAP3K1	72
ABL1(F317I)-nonphosphorylated	11	MAP3K15	93
ABL1(F317I)-phosphorylated	11	MAP3K2	0.65
ABL1(F317L)-nonphosphorylated	2.4	MAP3K3	0.5
ABL1(F317L)-phosphorylated	2.6	MAP3K4	9
ABL1(H396P)-nonphosphorylated	0	MAP4K2	14
ABL1(H396P)-phosphorylated	0.1	MAP4K3	3.9
ABL1(M351T)-phosphorylated	1.3	MAP4K4	81
ABL1(Q252H)-nonphosphorylated	0	MAP4K5	39
ABL1(Q252H)-phosphorylated	0.15	MAPKAPK2	100
ABL1(T315I)-nonphosphorylated	0	MAPKAPK5	74
ABL1(T315I)-phosphorylated	0.6	MARK1	3.7
ABL1(Y253F)-phosphorylated	0.1	MARK2	14
ABL1-nonphosphorylated	0	MARK3	19
ABL1-phosphorylated	0.2	MARK4	12
ABL2	7.8	MAST1	72
ACVR1	1.2	MEK1	13
ACVR1B	4.7	MEK2	7.8
ACVR2A	47	MEK3	68
ACVR2B	58	MEK4	92
ACVRL1	18	MEK5	5.2
ADCK3	100	MEK6	100
ADCK4	99	MELK	26
AKT1	100	MERTK	11
AKT2	100	MET	14
AKT3	100	MET(M1250T)	3.8
ALK	11	MET(Y1235D)	12
ALK(C1156Y)	4.5	MINK	32
ALK(L1196M)	7.5	MKK7	100
AMPK-alpha1	1.2	MKNK1	86
AMPK-alpha2	4.7	MKNK2	24
ANKK1	15	MLCK	100
ARK5	0.6	MLK1	21
ASK1	100	MLK2	80
ASK2	80	MLK3	88
AURKA	0.05	MRCKA	100
AURKB	0.15	MRCKB	100
AURKC	0.2	MST1	51
AXL	1.1	MST1R	36

BIKE	2.4	MST2	73
BLK	0.65	MST3	91
BMPR1A	44	MST4	91
BMPR1B	0	MTOR	100
BMPR2	92	MUSK	6.7
BMX	17	MYLK	61
BRAF	83	MYLK2	47
BRAF(V600E)	76	MYLK4	100
BRK	0.15	MYO3A	99
BRSK1	27	MYO3B	37
BRSK2	26	NDR1	32
BTK	0.25	NDR2	39
BUB1	100	NEK1	100
CAMK1	70	NEK10	34
CAMK1B	28	NEK11	6.7
CAMK1D	59	NEK2	82
CAMK1G	93	NEK3	56
CAMK2A	97	NEK4	66
CAMK2B	94	NEK5	91
CAMK2D	96	NEK6	100
CAMK2G	92	NEK7	76
CAMK4	100	NEK9	79
CAMKK1	29	NIK	95
CAMKK2	13	NIM1	66
CASK	71	NLK	92
CDC2L1	95	OSR1	100
CDC2L2	100	p38-alpha	100
CDC2L5	100	p38-beta	100
CDK11	100	p38-delta	100
CDK2	98	p38-gamma	74
CDK3	74	PAK1	27
CDK4	88	PAK2	68
CDK4-cyclinD1	30	PAK3	0
CDK4-cyclinD3	39	PAK4	59
CDK5	89	PAK6	63
CDK7	3.4	PAK7	48
CDK8	97	PCTK1	100
CDK9	98	PCTK2	86
CDKL1	100	PCTK3	98
CDKL2	8.3	PDGFRA	40
CDKL3	86	PDGFRB	5.3
CDKL5	100	PDPK1	74
CHEK1	61	PFCDPK1(P.falciparum)	32
CHEK2	6.3	PFPK5(P.falciparum)	99
CIT	87	PFTAIRE2	75
CLK1	0.9	PFTK1	96

CLK2	5.3	PHKG1	25
CLK3	29	PHKG2	19
CLK4	5.2	PIK3C2B	90
CSF1R	3.7	PIK3C2G	88
CSF1R-autoinhibited	6.3	PIK3CA	95
CSK	28	PIK3CA(C420R)	99
CSNK1A1	67	PIK3CA(E542K)	81
CSNK1A1L	98	PIK3CA(E545A)	95
CSNK1D	95	PIK3CA(E545K)	67
CSNK1E	96	PIK3CA(H1047L)	83
CSNK1G1	97	PIK3CA(H1047Y)	100
CSNK1G2	88	PIK3CA(I800L)	90
CSNK1G3	95	PIK3CA(M1043I)	76
CSNK2A1	44	PIK3CA(Q546K)	88
CSNK2A2	15	PIK3CB	62
CTK	80	PIK3CD	100
DAPK1	93	PIK3CG	87
DAPK2	93	PIK4CB	90
DAPK3	73	PIKFYVE	89
DCAMKL1	6.2	PIM1	94
DCAMKL2	16	PIM2	100
DCAMKL3	72	PIM3	100
DDR1	5.3	PIP5K1A	13
DDR2	21	PIP5K1C	87
DLK	5	PIP5K2B	6.9
DMPK	100	PIP5K2C	85
DMPK2	84	PKAC-alpha	88
DRAK1	97	PKAC-beta	94
DRAK2	100	PKMYT1	76
DYRK1A	84	PKN1	35
DYRK1B	63	PKN2	49
DYRK2	40	PKNB(M.tuberculosis)	5
EGFR	24	PLK1	87
EGFR(E746-A750del)	12	PLK2	70
EGFR(G719C)	94	PLK3	78
EGFR(G719S)	75	PLK4	0
EGFR(L747-E749del, A750P)	10	PRKCD	94
EGFR(L747-S752del, P753S)	31	PRKCE	69
EGFR(L747-T751del,Sins)	40	PRKCH	100
EGFR(L858R)	30	PRKCI	76
EGFR(L858R,T790M)	3.8	PRKCQ	59
EGFR(L861Q)	44	PRKD1	62
EGFR(S752-I759del)	74	PRKD2	43
EGFR(T790M)	4.7	PRKD3	26
EIF2AK1	83	PRKG1	60
EPHA1	8	PRKG2	95

EPHA2	78	PRKR	70
EPHA3	56	PRKX	95
EPHA4	96	PRP4	83
EPHA5	100	PYK2	0.85
EPHA6	55	QSK	100
EPHA7	64	RAF1	98
EPHA8	71	RET	0.1
EPHB1	30	RET(M918T)	0.6
EPHB2	96	RET(V804L)	0.3
EPHB3	93	RET(V804M)	0.5
EPHB4	81	RIOK1	3.6
EPHB6	1.2	RIOK2	65
ERBB2	78	RIOK3	11
ERBB3	56	RIPK1	92
ERBB4	35	RIPK2	79
ERK1	95	RIPK4	44
ERK2	96	RIPK5	35
ERK3	19	ROCK1	47
ERK4	57	ROCK2	64
ERK5	20	ROS1	3.2
ERK8	26	RPS6KA4(Kin.Dom.1-N-terminal)	22
ERN1	29	RPS6KA4(Kin.Dom.2-C-terminal)	80
FAK	1.6	RPS6KA5(Kin.Dom.1-N-terminal)	98
FER	5.7	RPS6KA5(Kin.Dom.2-C-terminal)	90
FES	58	RSK1(Kin.Dom.1-N-terminal)	3.5
FGFR1	1.6	RSK1(Kin.Dom.2-C-terminal)	97
FGFR2	13	RSK2(Kin.Dom.1-N-terminal)	0.1
FGFR3	11	RSK2(Kin.Dom.2-C-terminal)	100
FGFR3(G697C)	11	RSK3(Kin.Dom.1-N-terminal)	2.7
FGFR4	51	RSK3(Kin.Dom.2-C-terminal)	85
FGR	7.3	RSK4(Kin.Dom.1-N-terminal)	7.3
FLT1	43	RSK4(Kin.Dom.2-C-terminal)	100
FLT3	4.7	S6K1	36
FLT3(D835H)	6.7	SBK1	6
FLT3(D835V)	1.6	SGK	31
FLT3(D835Y)	0.65	SgK110	6.7
FLT3(ITD)	4.2	SGK2	80
FLT3(ITD,D835V)	2.1	SGK3	45
FLT3(ITD,F691L)	0	SIK	0.8
FLT3(K663Q)	1.5	SIK2	6.3
FLT3(N841I)	0	SLK	0.25
FLT3(R834Q)	12	SNARK	0.6
FLT3-autoinhibited	50	SNRK	80

FLT4	54	SRC	0.7
FRK	13	SRMS	17
FYN	12	SRPK1	11
GAK	9.8	SRPK2	100
GCN2(Kin.Dom.2,S808G)	2.3	SRPK3	14
GRK1	61	STK16	2.6
GRK2	91	STK33	10
GRK3	67	STK35	33
GRK4	16	STK36	46
GRK7	78	STK39	83
GSK3A	100	SYK	27
GSK3B	92	TAK1	45
HASPIN	100	TAOK1	6.6
HCK	0.8	TAOK2	55
HIPK1	2.6	TAOK3	10
HIPK2	2.2	TBK1	28
HIPK3	11	TEC	0.95
HIPK4	1.6	TESK1	32
HPK1	0.25	TGFBR1	9.8
HUNK	100	TGFBR2	100
ICK	60	TIE1	1.1
IGF1R	3.8	TIE2	5.2
IKK-alpha	83	TLK1	88
IKK-beta	93	TLK2	100
IKK-epsilon	33	TNIK	38
INSR	7.4	TNK1	0
INSRR	8	TNK2	2.8
IRAK1	0	TNNI3K	81
IRAK3	6.2	TRKA	0
IRAK4	6.1	TRKB	0
ITK	0.35	TRKC	3.6
JAK1(JH1domain-catalytic)	41	TRPM6	100
JAK1(JH2domain-pseudokinase)	0.3	TSSK1B	22
JAK2(JH1domain-catalytic)	0	TSSK3	66
JAK3(JH1domain-catalytic)	0	TTK	10
JNK1	2	TXK	8.7
JNK2	15	TYK2(JH1domain-catalytic)	0
JNK3	1.7	TYK2(JH2domain-pseudokinase)	5
KIT	58	TYRO3	42
KIT(A829P)	38	ULK1	6.1
KIT(D816H)	26	ULK2	6.6
KIT(D816V)	13	ULK3	0.95
KIT(L576P)	41	VEGFR2	38
KIT(V559D)	53	VPS34	71
KIT(V559D,T670I)	92	VRK2	74

KIT(V559D,V654A)	100	WEE1	0.55
KIT-autoinhibited	60	WEE2	0.2
LATS1	52	WNK1	99
LATS2	39	WNK2	100
LCK	0.35	WNK3	96
LIMK1	36	WNK4	100
LIMK2	53	YANK1	65
LKB1	75	YANK2	100
LOK	0	YANK3	100
LRRK2	21	YES	3.3
LRRK2(G2019S)	45	YSK1	100
LTK	15	YSK4	1.9
LYN	28	ZAK	73
LZK	3.4	ZAP70	69

Table S4. KINOMEscan kinase selectivity profiles for **7**.

Kinases	**Scores**	**Kinases**	**Scores**
AAK1	3.8	MAP3K1	60
ABL1(E255K)-phosphorylated	0	MAP3K15	28
ABL1(F317I)-nonphosphorylated	31	MAP3K2	0
ABL1(F317I)-phosphorylated	5.8	MAP3K3	0.6
ABL1(F317L)-nonphosphorylated	12	MAP3K4	1.4
ABL1(F317L)-phosphorylated	0.3	MAP4K2	1
ABL1(H396P)-nonphosphorylated	0	MAP4K3	4
ABL1(H396P)-phosphorylated	0	MAP4K4	7.3
ABL1(M351T)-phosphorylated	0.1	MAP4K5	26
ABL1(Q252H)-nonphosphorylated	0	MAPKAPK2	100
ABL1(Q252H)-phosphorylated	0	MAPKAPK5	75
ABL1(T315I)-nonphosphorylated	0	MARK1	11
ABL1(T315I)-phosphorylated	0.15	MARK2	4.4
ABL1(Y253F)-phosphorylated	0	MARK3	5
ABL1-nonphosphorylated	0.1	MARK4	8.9
ABL1-phosphorylated	0	MAST1	38
ABL2	5.6	MEK1	2
ACVR1	77	MEK2	0.7
ACVR1B	94	MEK3	5.5
ACVR2A	100	MEK4	6.6
ACVR2B	92	MEK5	0.1
ACVRL1	100	MEK6	3.2
ADCK3	100	MELK	18

ADCK4	6.2	MERTK	0.35
AKT1	100	MET	12
AKT2	99	MET(M1250T)	3.4
AKT3	100	MET(Y1235D)	12
ALK	4.2	MINK	2.6
ALK(C1156Y)	3.3	MKK7	92
ALK(L1196M)	4.1	MKNK1	50
AMPK-alpha1	6	MKNK2	1.3
AMPK-alpha2	5.4	MLCK	18
ANKK1	77	MLK1	1.1
ARK5	0.7	MLK2	0.85
ASK1	100	MLK3	6.8
ASK2	87	MRCKA	82
AURKA	0	MRCKB	100
AURKB	0.6	MST1	20
AURKC	1	MST1R	85
AXL	1.4	MST2	5
BIKE	0.6	MST3	1.6
BLK	1.1	MST4	10
BMPR1A	100	MTOR	100
BMPR1B	4.6	MUSK	2.4
BMPR2	83	MYLK	35
BMX	47	MYLK2	33
BRAF	56	MYLK4	0.1
BRAF(V600E)	49	MYO3A	40
BRK	31	MYO3B	100
BRSK1	79	NDR1	31
BRSK2	77	NDR2	40
BTK	5.3	NEK1	7
BUB1	16	NEK10	5.8
CAMK1	45	NEK11	11
CAMK1D	5.9	NEK2	2.8
CAMK1G	28	NEK3	0.75
CAMK2A	32	NEK4	6.6
CAMK2B	55	NEK5	11
CAMK2D	49	NEK6	2.9
CAMK2G	51	NEK7	1.5
CAMK4	100	NEK9	8.6
CAMKK1	5.4	NIK	22
CAMKK2	6.8	NIM1	3.2
CASK	62	NLK	70
CDC2L1	79	OSR1	22
CDC2L2	72	p38-alpha	93
CDC2L5	26	p38-beta	100
CDK11	100	p38-delta	100

CDK2	70	p38-gamma	90
CDK3	83	PAK1	4.8
CDK4-cyclinD1	0	PAK2	2.1
CDK4-cyclinD3	0.1	PAK3	16
CDK5	78	PAK4	3.5
CDK7	0.85	PAK6	1.9
CDK8	94	PAK7	0.4
CDK9	66	PCTK1	0
CDKL1	28	PCTK2	1.3
CDKL2	0.2	PCTK3	17
CDKL3	1.6	PDGFRA	1.6
CDKL5	21	PDGFRB	0
CHEK1	8.4	PDPK1	100
CHEK2	0.85	PFCDPK1(P.falciparum)	0.35
CIT	7	PFPK5(P.falciparum)	95
CLK1	1.4	PFTAIRE2	45
CLK2	2.4	PFTK1	40
CLK3	68	PHKG1	3.6
CLK4	1	PHKG2	13
CSF1R	16	PIK3C2B	94
CSF1R-autoinhibited	29	PIK3C2G	99
CSK	64	PIK3CA	93
CSNK1A1	37	PIK3CA(C420R)	100
CSNK1A1L	98	PIK3CA(E542K)	100
CSNK1D	100	PIK3CA(E545A)	94
CSNK1E	98	PIK3CA(E545K)	99
CSNK1G1	40	PIK3CA(H1047L)	98
CSNK1G2	72	PIK3CA(H1047Y)	97
CSNK1G3	72	PIK3CA(I800L)	74
CSNK2A1	0.35	PIK3CA(M1043I)	100
CSNK2A2	0	PIK3CA(Q546K)	87
CTK	53	PIK3CB	97
DAPK1	1	PIK3CD	100
DAPK2	15	PIK3CG	86
DAPK3	5	PIK4CB	57
DCAMKL1	4.8	PIM1	51
DCAMKL2	2.4	PIM2	100
DCAMKL3	6.4	PIM3	7.8
DDR1	15	PIP5K1A	7
DDR2	8.7	PIP5K1C	14
DLK	9.4	PIP5K2B	15
DMPK	37	PIP5K2C	25
DMPK2	80	PKAC-alpha	56
DRAK1	0.2	PKAC-beta	55
DRAK2	7	PKMYT1	100

DYRK1A	1.4	PKN1	24
DYRK1B	0	PKN2	43
DYRK2	0.2	PKNB(M.tuberculosis)	0.15
EGFR	73	PLK1	0.45
EGFR(E746-A750del)	40	PLK2	3
EGFR(G719C)	67	PLK3	4.8
EGFR(G719S)	79	PLK4	0.2
EGFR(L747-E749del, A750P)	22	PRKCD	23
EGFR(L747-S752del, P753S)	33	PRKCE	19
EGFR(L747-T751del,Sins)	20	PRKCH	100
EGFR(L858R)	36	PRKCI	81
EGFR(L858R,T790M)	2.8	PRKCQ	37
EGFR(L861Q)	37	PRKD1	10
EGFR(S752-I759del)	56	PRKD2	0.25
EGFR(T790M)	4.4	PRKD3	1.9
EIF2AK1	0.15	PRKG1	100
EPHA1	15	PRKG2	76
EPHA2	83	PRKR	4.8
EPHA3	22	PRKX	100
EPHA4	85	PRP4	18
EPHA5	96	PYK2	9.4
EPHA6	70	QSK	66
EPHA7	48	RAF1	93
EPHA8	96	RET	1.4
EPHB1	65	RET(M918T)	1.1
EPHB2	89	RET(V804L)	1
EPHB3	91	RET(V804M)	0.65
EPHB4	71	RIOK1	12
EPHB6	0.65	RIOK2	6.8
ERBB2	74	RIOK3	9
ERBB3	26	RIPK1	17
ERBB4	47	RIPK2	72
ERK1	100	RIPK4	47
ERK2	100	RIPK5	7.2
ERK3	0	ROCK1	4.6
ERK4	4.3	ROCK2	2.1
ERK5	52	ROS1	15
ERK8	0.5	RPS6KA4(Kin.Dom.1-N-terminal)	56
ERN1	8.4	RPS6KA4(Kin.Dom.2-C-terminal)	3.5
FAK	3	RPS6KA5(Kin.Dom.1-N-terminal)	79
FER	10	RPS6KA5(Kin.Dom.2-C-terminal)	30

FES	4.4	RSK1(Kin.Dom.1-N-terminal)	0.6
FGFR1	0.7	RSK1(Kin.Dom.2-C-terminal)	14
FGFR2	7.4	RSK2(Kin.Dom.1-N-terminal)	0.2
FGFR3	11	RSK2(Kin.Dom.2-C-terminal)	84
FGFR3(G697C)	8.9	RSK3(Kin.Dom.1-N-terminal)	8
FGFR4	44	RSK3(Kin.Dom.2-C-terminal)	17
FGR	23	RSK4(Kin.Dom.1-N-terminal)	4.2
FLT1	0.6	RSK4(Kin.Dom.2-C-terminal)	20
FLT3	0.1	S6K1	3.2
FLT3(D835H)	0.45	SBK1	6.4
FLT3(D835Y)	0.25	SGK	9.2
FLT3(ITD)	0.2	SgK110	53
FLT3(K663Q)	0	SGK2	62
FLT3(N841I)	0	SGK3	36
FLT3(R834Q)	0.05	SIK	40
FLT3-autoinhibited	0	SIK2	16
FLT4	0	SLK	0.65
FRK	14	SNARK	0.35
FYN	14	SNRK	50
GAK	1.8	SRC	1.6
GCN2(Kin.Dom.2,S808G)	0.05	SRMS	4.5
GRK1	51	SRPK1	3.2
GRK4	35	SRPK2	14
GRK7	52	SRPK3	25
GSK3A	100	STK16	1.4
GSK3B	78	STK33	2.3
HASPIN	35	STK35	79
HCK	34	STK36	2.2
HIPK1	0.2	STK39	19
HIPK2	0.15	SYK	12
HIPK3	0.65	**TAK1**	0.1
HIPK4	0.75	TAOK1	7.7
HPK1	0.75	TAOK2	7.2
HUNK	86	TAOK3	7.4
ICK	11	TBK1	1.8
IGF1R	1	TEC	69
IKK-alpha	1.4	TESK1	95
IKK-beta	2.6	TGFBR1	85
IKK-epsilon	5.8	TGFBR2	100
INSR	0.25	TIE1	7.5
INSRR	0.35	TIE2	35
IRAK1	0	TLK1	3.5
IRAK3	3.4	TLK2	5
IRAK4	3.2	TNIK	0.65
ITK	2	TNK1	1.1

JAK1(JH1domain-catalytic)	3.4	TNK2	20
JAK1(JH2domain-pseudokinase)	0	TNNI3K	59
JAK2(JH1domain-catalytic)	0.1	TRKA	0.25
JAK3(JH1domain-catalytic)	0.6	TRKB	0.15
JNK1	0	TRKC	3
JNK2	0	TRPM6	67
JNK3	0	TSSK1B	39
KIT	0.3	TTK	4.9
KIT(A829P)	0	TXK	21
KIT(D816H)	1.8	TYK2(JH1domain-catalytic)	0.3
KIT(D816V)	0.5	TYK2(JH2domain-pseudokinase)	0.2
KIT(L576P)	1.6	TYRO3	94
KIT(V559D)	0.25	ULK1	0.1
KIT(V559D,T670I)	1.7	ULK2	0.05
KIT(V559D,V654A)	35	ULK3	0
KIT-autoinhibited	28	VEGFR2	0.05
LATS1	49	VRK2	85
LATS2	7.4	WEE1	6
LCK	2	WEE2	4.1
LIMK1	97	WNK1	78
LIMK2	54	WNK3	89
LKB1	48	YANK1	34
LOK	3.7	YANK2	100
LRRK2	1.4	YANK3	100
LRRK2(G2019S)	1.1	YES	12
LTK	15	YSK1	4.2
LYN	27	YSK4	0
LZK	4.2	ZAK	31
MAK	95	ZAP70	8.8

Table S5. KINOMEscan kinase selectivity profiles for **23**.

Kinases	**Scores**	**Kinases**	**Scores**
AAK1	46	MAK	48
ABL1(E255K)-phosphorylated	11	MAP3K1	98
ABL1(F317I)-nonphosphorylated	94	MAP3K15	99
ABL1(F317I)-phosphorylated	100	MAP3K2	9.9
ABL1(F317L)-nonphosphorylated	83	MAP3K3	13
ABL1(F317L)-phosphorylated	46	MAP3K4	56
ABL1(H396P)-nonphosphorylated	37	MAP4K2	48
ABL1(H396P)-phosphorylated	28	MAP4K3	73

ABL1(M351T)-phosphorylated	21	MAP4K4	62
ABL1(Q252H)-nonphosphorylated	22	MAP4K5	72
ABL1(Q252H)-phosphorylated	18	MAPKAPK2	100
ABL1(T315I)-nonphosphorylated	26	MAPKAPK5	94
ABL1(T315I)-phosphorylated	1.9	MARK1	36
ABL1(Y253F)-phosphorylated	23	MARK2	46
ABL1-nonphosphorylated	41	MARK3	33
ABL1-phosphorylated	24	MARK4	48
ABL2	55	MAST1	51
ACVR1	100	MEK1	19
ACVR1B	83	MEK2	28
ACVR2A	100	MEK3	4.1
ACVR2B	100	MEK4	2.4
ACVRL1	100	MEK5	0.3
ADCK3	100	MEK6	11
ADCK4	9.4	MELK	38
AKT1	100	MERTK	2.8
AKT2	100	MET	28
AKT3	100	MET(M1250T)	25
ALK	91	MET(Y1235D)	49
ALK(C1156Y)	65	MINK	27
ALK(L1196M)	72	MKK7	0.95
AMPK-alpha1	48	MKNK1	100
AMPK-alpha2	18	MKNK2	73
ANKK1	100	MLCK	48
ARK5	16	MLK1	5.9
ASK1	100	MLK2	17
ASK2	100	MLK3	23
AURKA	0.35	MRCKA	100
AURKB	14	MRCKB	100
AURKC	22	MST1	86
AXL	6.2	MST1R	87
BIKE	2.6	MST2	8.2
BLK	50	MST3	50
BMPR1A	75	MST4	69
BMPR1B	73	MTOR	100
BMPR2	46	MUSK	85
BMX	80	MYLK	74
BRAF	100	MYLK2	65
BRAF(V600E)	100	MYLK4	1
BRK	100	MYO3A	87
BRSK1	89	MYO3B	100
BRSK2	80	NDR1	68
BTK	60	NDR2	74
BUB1	100	NEK1	47

CAMK1	50	NEK10	100
CAMK1B	100	NEK11	72
CAMK1D	58	NEK2	53
CAMK1G	100	NEK3	32
CAMK2A	73	NEK4	81
CAMK2B	83	NEK5	24
CAMK2D	100	NEK6	50
CAMK2G	92	NEK7	33
CAMK4	100	NEK9	45
CAMKK1	55	NIK	91
CAMKK2	79	NIM1	67
CASK	59	NLK	100
CDC2L1	89	OSR1	65
CDC2L2	72	p38-alpha	93
CDC2L5	96	p38-beta	94
CDK11	63	p38-delta	72
CDK2	22	p38-gamma	42
CDK3	61	PAK1	80
CDK4	83	PAK2	63
CDK4-cyclinD1	29	PAK3	90
CDK4-cyclinD3	61	PAK4	37
CDK5	21	PAK6	28
CDK7	27	PAK7	73
CDK8	100	PCTK1	16
CDK9	62	PCTK2	16
CDKL1	27	PCTK3	39
CDKL2	0.05	PDGFRA	9.6
CDKL3	2.1	PDGFRB	0
CDKL5	83	PDPK1	89
CHEK1	0	PFCDPK1(P.falciparum)	29
CHEK2	29	PFPK5(P.falciparum)	100
CIT	78	PFTAIRE2	46
CLK1	30	PFTK1	37
CLK2	12	PHKG1	92
CLK3	83	PHKG2	79
CLK4	3.9	PIK3C2B	56
CSF1R	36	PIK3C2G	54
CSF1R-autoinhibited	91	PIK3CA	60
CSK	82	PIK3CA(C420R)	91
CSNK1A1	63	PIK3CA(E542K)	77
CSNK1A1L	74	PIK3CA(E545A)	84
CSNK1D	92	PIK3CA(E545K)	50
CSNK1E	100	PIK3CA(H1047L)	84
CSNK1G1	90	PIK3CA(H1047Y)	63
CSNK1G2	98	PIK3CA(I800L)	59
CSNK1G3	100	PIK3CA(M1043I)	93

CSNK2A1	9.4	PIK3CA(Q546K)	93
CSNK2A2	0.55	PIK3CB	100
CTK	98	PIK3CD	82
DAPK1	60	PIK3CG	42
DAPK2	72	PIK4CB	85
DAPK3	55	PIKFYVE	98
DCAMKL1	85	PIM1	100
DCAMKL2	68	PIM2	100
DCAMKL3	22	PIM3	79
DDR1	60	PIP5K1A	41
DDR2	100	PIP5K1C	44
DLK	64	PIP5K2B	57
DMPK	100	PIP5K2C	11
DMPK2	100	PKAC-alpha	100
DRAK1	24	PKAC-beta	100
DRAK2	73	PKMYT1	100
DYRK1A	15	PKN1	73
DYRK1B	3.5	PKN2	100
DYRK2	18	PKNB(M.tuberculosis)	0.75
EGFR	100	PLK1	66
EGFR(E746-A750del)	50	PLK2	3.4
EGFR(G719C)	66	PLK3	47
EGFR(G719S)	80	PLK4	5.9
EGFR(L747-E749del, A750P)	100	PRKCD	83
EGFR(L747-S752del, P753S)	70	PRKCE	85
EGFR(L747-T751del,Sins)	89	PRKCH	58
EGFR(L858R)	100	PRKCI	55
EGFR(L858R,T790M)	67	PRKCQ	55
EGFR(L861Q)	82	PRKD1	100
EGFR(S752-I759del)	83	PRKD2	100
EGFR(T790M)	48	PRKD3	72
EIF2AK1	22	PRKG1	100
EPHA1	53	PRKG2	92
EPHA2	100	PRKR	47
EPHA3	99	PRKX	100
EPHA4	86	PRP4	56
EPHA5	79	PYK2	47
EPHA6	75	QSK	99
EPHA7	72	RAF1	90
EPHA8	97	RET	36
EPHB1	90	RET(M918T)	16
EPHB2	100	RET(V804L)	15
EPHB3	99	RET(V804M)	20
EPHB4	76	RIOK1	54
EPHB6	4	RIOK2	24
ERBB2	89	RIOK3	48

ERBB3	100	RIPK1	67
ERBB4	77	RIPK2	91
ERK1	85	RIPK4	24
ERK2	62	RIPK5	55
ERK3	0	ROCK1	76
ERK4	0	ROCK2	69
ERK5	94	ROS1	49
ERK8	4.8	RPS6KA4(Kin.Dom.1-N-terminal)	100
ERN1	63	RPS6KA4(Kin.Dom.2-C-terminal)	26
FAK	51	RPS6KA5(Kin.Dom.1-N-terminal)	54
FER	94	RPS6KA5(Kin.Dom.2-C-terminal)	43
FES	64	RSK1(Kin.Dom.1-N-terminal)	11
FGFR1	29	RSK1(Kin.Dom.2-C-terminal)	80
FGFR2	52	RSK2(Kin.Dom.1-N-terminal)	7.8
FGFR3	51	RSK2(Kin.Dom.2-C-terminal)	100
FGFR3(G697C)	23	RSK3(Kin.Dom.1-N-terminal)	27
FGFR4	95	RSK3(Kin.Dom.2-C-terminal)	85
FGR	55	RSK4(Kin.Dom.1-N-terminal)	23
FLT1	0.45	RSK4(Kin.Dom.2-C-terminal)	82
FLT3	0.1	S6K1	36
FLT3(D835H)	0	SBK1	61
FLT3(D835V)	0.25	SGK	33
FLT3(D835Y)	2.4	SgK110	86
FLT3(ITD)	0.05	SGK2	69
FLT3(ITD,D835V)	0	SGK3	65
FLT3(ITD,F691L)	1.3	SIK	37
FLT3(K663Q)	0.75	SIK2	58
FLT3(N841I)	0.35	SLK	31
FLT3(R834Q)	3	SNARK	6.8
FLT3-autoinhibited	18	SNRK	93
FLT4	0.1	SRC	87
FRK	95	SRMS	56
FYN	93	SRPK1	4.8
GAK	7	SRPK2	83
GCN2(Kin.Dom.2,S808G)	1.7	SRPK3	56
GRK1	100	STK16	1
GRK2	100	STK33	58
GRK3	100	STK35	100
GRK4	47	STK36	57
GRK7	32	STK39	98
GSK3A	0.95	SYK	57
GSK3B	61	**TAK1**	5.5
HASPIN	8.5	TAOK1	22

HCK	100	TAOK2	65
HIPK1	7.9	TAOK3	66
HIPK2	3.1	TBK1	29
HIPK3	7.4	TEC	91
HIPK4	13	TESK1	87
HPK1	42	TGFBR1	68
HUNK	100	TGFBR2	100
ICK	18	TIE1	92
IGF1R	28	TIE2	55
IKK-alpha	72	TLK1	64
IKK-beta	43	TLK2	42
IKK-epsilon	46	TNIK	39
INSR	8	TNK1	100
INSRR	49	TNK2	88
IRAK1	6.6	TNNI3K	100
IRAK3	8.6	TRKA	3.5
IRAK4	81	TRKB	2
ITK	19	TRKC	26
JAK1(JH1domain-catalytic)	39	TRPM6	100
JAK1(JH2domain-pseudokinase)	1.2	TSSK1B	100
JAK2(JH1domain-catalytic)	1.3	TSSK3	92
JAK3(JH1domain-catalytic)	0	TTK	9.9
JNK1	5.8	TXK	51
JNK2	3.1	TYK2(JH1domain-catalytic)	14
JNK3	6	TYK2(JH2domain-pseudokinase)	20
KIT	0.1	TYRO3	71
KIT(A829P)	0.85	ULK1	34
KIT(D816H)	8.5	ULK2	53
KIT(D816V)	7.5	ULK3	6.1
KIT(L576P)	4.3	VEGFR2	0.1
KIT(V559D)	0.05	VPS34	37
KIT(V559D,T670I)	0.9	VRK2	94
KIT(V559D,V654A)	56	WEE1	95
KIT-autoinhibited	99	WEE2	53
LATS1	100	WNK1	89
LATS2	58	WNK2	100
LCK	97	WNK3	81
LIMK1	99	WNK4	90
LIMK2	96	YANK1	86
LKB1	87	YANK2	71
LOK	84	YANK3	83
LRRK2	31	YES	82
LRRK2(G2019S)	42	YSK1	43
LTK	97	YSK4	0.7
LYN	100	ZAK	51

LZK	83	ZAP70	82

Table S6. KINOMEscan kinase selectivity profiles for **25**.

Kinases	**Scores**	**Kinases**	**Scores**
AAK1	41	MAK	84
ABL1(E255K)-phosphorylated	49	MAP3K1	100
ABL1(F317I)-nonphosphorylated	90	MAP3K15	100
ABL1(F317I)-phosphorylated	100	MAP3K2	36
ABL1(F317L)-nonphosphorylated	87	MAP3K3	25
ABL1(F317L)-phosphorylated	65	MAP3K4	78
ABL1(H396P)-nonphosphorylated	23	MAP4K2	99
ABL1(H396P)-phosphorylated	66	MAP4K3	82
ABL1(M351T)-phosphorylated	57	MAP4K4	100
ABL1(Q252H)-nonphosphorylated	60	MAP4K5	100
ABL1(Q252H)-phosphorylated	51	MAPKAPK2	100
ABL1(T315I)-nonphosphorylated	25	MAPKAPK5	97
ABL1(T315I)-phosphorylated	6.9	MARK1	83
ABL1(Y253F)-phosphorylated	67	MARK2	98
ABL1-nonphosphorylated	52	MARK3	86
ABL1-phosphorylated	54	MARK4	81
ABL2	99	MAST1	85
ACVR1	100	MEK1	71
ACVR1B	89	MEK2	79
ACVR2A	96	MEK3	21
ACVR2B	100	MEK4	1.6
ACVRL1	75	MEK5	1.5
ADCK3	100	MEK6	41
ADCK4	93	MELK	100
AKT1	100	MERTK	63
AKT2	89	MET	66
AKT3	100	MET(M1250T)	66
ALK	100	MET(Y1235D)	67
ALK(C1156Y)	64	MINK	86
ALK(L1196M)	90	MKK7	100
AMPK-alpha1	97	MKNK1	100
AMPK-alpha2	86	MKNK2	91
ANKK1	100	MLCK	93
ARK5	88	MLK1	47
ASK1	99	MLK2	60
ASK2	100	MLK3	39
AURKA	0.1	MRCKA	96
AURKB	9.8	MRCKB	93
AURKC	33	MST1	87
AXL	70	MST1R	92
BIKE	32	MST2	21

BLK	79	MST3	96
BMPR1A	100	MST4	100
BMPR1B	100	MTOR	100
BMPR2	95	MUSK	84
BMX	74	MYLK	75
BRAF	100	MYLK2	94
BRAF(V600E)	100	MYLK4	77
BRK	96	MYO3A	89
BRSK1	83	MYO3B	94
BRSK2	85	NDR1	92
BTK	60	NDR2	97
BUB1	100	NEK1	100
CAMK1	83	NEK10	100
CAMK1B	100	NEK11	100
CAMK1D	85	NEK2	81
CAMK1G	94	NEK3	56
CAMK2A	96	NEK4	83
CAMK2B	100	NEK5	95
CAMK2D	94	NEK6	99
CAMK2G	95	NEK7	85
CAMK4	90	NEK9	98
CAMKK1	82	NIK	71
CAMKK2	82	NIM1	100
CASK	100	NLK	66
CDC2L1	100	OSR1	100
CDC2L2	99	p38-alpha	100
CDC2L5	100	p38-beta	88
CDK11	87	p38-delta	84
CDK2	95	p38-gamma	100
CDK3	95	PAK1	100
CDK4	100	PAK2	93
CDK4-cyclinD1	100	PAK3	92
CDK4-cyclinD3	100	PAK4	64
CDK5	91	PAK6	84
CDK7	83	PAK7	100
CDK8	100	PCTK1	100
CDK9	97	PCTK2	92
CDKL1	67	PCTK3	81
CDKL2	35	PDGFRA	24
CDKL3	44	PDGFRB	11
CDKL5	100	PDPK1	93
CHEK1	94	PFCDPK1(P.falciparum)	84
CHEK2	78	PFPK5(P.falciparum)	100
CIT	84	PFTAIRE2	94
CLK1	80	PFTK1	76
CLK2	85	PHKG1	81

CLK3	81	PHKG2	93
CLK4	92	PIK3C2B	96
CSF1R	82	PIK3C2G	99
CSF1R-autoinhibited	96	PIK3CA	100
CSK	91	PIK3CA(C420R)	85
CSNK1A1	59	PIK3CA(E542K)	87
CSNK1A1L	99	PIK3CA(E545A)	93
CSNK1D	96	PIK3CA(E545K)	88
CSNK1E	91	PIK3CA(H1047L)	100
CSNK1G1	84	PIK3CA(H1047Y)	100
CSNK1G2	100	PIK3CA(I800L)	59
CSNK1G3	86	PIK3CA(M1043I)	100
CSNK2A1	18	PIK3CA(Q546K)	100
CSNK2A2	4.3	PIK3CB	81
CTK	100	PIK3CD	100
DAPK1	94	PIK3CG	84
DAPK2	91	PIK4CB	100
DAPK3	100	PIKFYVE	94
DCAMKL1	82	PIM1	97
DCAMKL2	98	PIM2	100
DCAMKL3	67	PIM3	94
DDR1	77	PIP5K1A	65
DDR2	100	PIP5K1C	100
DLK	73	PIP5K2B	100
DMPK	100	PIP5K2C	40
DMPK2	94	PKAC-alpha	100
DRAK1	88	PKAC-beta	100
DRAK2	85	PKMYT1	82
DYRK1A	100	PKN1	78
DYRK1B	73	PKN2	100
DYRK2	100	PKNB(M.tuberculosis)	6.1
EGFR	76	PLK1	100
EGFR(E746-A750del)	94	PLK2	91
EGFR(G719C)	95	PLK3	82
EGFR(G719S)	94	PLK4	4.5
EGFR(L747-E749del, A750P)	67	PRKCD	70
EGFR(L747-S752del, P753S)	88	PRKCE	100
EGFR(L747-T751del,Sins)	82	PRKCH	95
EGFR(L858R)	88	PRKCI	87
EGFR(L858R,T790M)	95	PRKCQ	96
EGFR(L861Q)	88	PRKD1	79
EGFR(S752-I759del)	91	PRKD2	92
EGFR(T790M)	59	PRKD3	100
EIF2AK1	100	PRKG1	100
EPHA1	72	PRKG2	88
EPHA2	90	PRKR	68

EPHA3	100	PRKX	93
EPHA4	91	PRP4	100
EPHA5	93	PYK2	75
EPHA6	90	QSK	100
EPHA7	100	RAF1	86
EPHA8	100	RET	81
EPHB1	99	RET(M918T)	69
EPHB2	76	RET(V804L)	69
EPHB3	93	RET(V804M)	54
EPHB4	94	RIOK1	71
EPHB6	6.3	RIOK2	92
ERBB2	95	RIOK3	77
ERBB3	100	RIPK1	100
ERBB4	92	RIPK2	99
ERK1	84	RIPK4	100
ERK2	77	RIPK5	100
ERK3	43	ROCK1	100
ERK4	72	ROCK2	95
ERK5	100	ROS1	41
ERK8	68	RPS6KA4(Kin.Dom.1-N-terminal)	100
ERN1	100	RPS6KA4(Kin.Dom.2-C-terminal)	100
FAK	82	RPS6KA5(Kin.Dom.1-N-terminal)	93
FER	75	RPS6KA5(Kin.Dom.2-C-terminal)	100
FES	86	RSK1(Kin.Dom.1-N-terminal)	100
FGFR1	22	RSK1(Kin.Dom.2-C-terminal)	94
FGFR2	23	RSK2(Kin.Dom.1-N-terminal)	53
FGFR3	31	RSK2(Kin.Dom.2-C-terminal)	100
FGFR3(G697C)	27	RSK3(Kin.Dom.1-N-terminal)	69
FGFR4	73	RSK3(Kin.Dom.2-C-terminal)	91
FGR	81	RSK4(Kin.Dom.1-N-terminal)	79
FLT1	10	RSK4(Kin.Dom.2-C-terminal)	100
FLT3	3.3	S6K1	67
FLT3(D835H)	28	SBK1	95
FLT3(D835V)	0.6	SGK	100
FLT3(D835Y)	7.4	SgK110	83
FLT3(ITD)	3.5	SGK2	100
FLT3(ITD,D835V)	0.55	SGK3	100
FLT3(ITD,F691L)	1.4	SIK	93
FLT3(K663Q)	12	SIK2	80
FLT3(N841I)	0	SLK	14
FLT3(R834Q)	13	SNARK	28
FLT3-autoinhibited	19	SNRK	100
FLT4	2.1	SRC	76

FRK	100	SRMS	76
FYN	83	SRPK1	66
GAK	20	SRPK2	76
GCN2(Kin.Dom.2,S808G)	24	SRPK3	93
GRK1	94	STK16	6
GRK2	100	STK33	95
GRK3	100	STK35	91
GRK4	100	STK36	87
GRK7	96	STK39	61
GSK3A	47	SYK	45
GSK3B	92	**TAK1**	12
HASPIN	84	TAOK1	100
HCK	79	TAOK2	100
HIPK1	23	TAOK3	100
HIPK2	41	TBK1	27
HIPK3	56	TEC	85
HIPK4	78	TESK1	90
HPK1	82	TGFBR1	98
HUNK	100	TGFBR2	86
ICK	100	TIE1	66
IGF1R	70	TIE2	57
IKK-alpha	100	TLK1	98
IKK-beta	100	TLK2	100
IKK-epsilon	69	TNIK	81
INSR	12	TNK1	71
INSRR	75	TNK2	100
IRAK1	46	TNNI3K	97
IRAK3	37	TRKA	1.4
IRAK4	100	TRKB	8
ITK	60	TRKC	41
JAK1(JH1domain-catalytic)	69	TRPM6	99
JAK1(JH2domain-pseudokinase)	3.1	TSSK1B	100
JAK2(JH1domain-catalytic)	4.5	TSSK3	100
JAK3(JH1domain-catalytic)	0	TTK	72
JNK1	39	TXK	73
JNK2	59	TYK2(JH1domain-catalytic)	24
JNK3	63	TYK2(JH2domain-pseudokinase)	87
KIT	18	TYRO3	70
KIT(A829P)	100	ULK1	93
KIT(D816H)	100	ULK2	96
KIT(D816V)	22	ULK3	28
KIT(L576P)	36	VEGFR2	6.9
KIT(V559D)	22	VPS34	96
KIT(V559D,T670I)	63	VRK2	100
KIT(V559D,V654A)	78	WEE1	100
KIT-autoinhibited	69	WEE2	77

LATS1	100	WNK1	100
LATS2	74	WNK2	100
LCK	83	WNK3	100
LIMK1	99	WNK4	100
LIMK2	100	YANK1	100
LKB1	100	YANK2	100
LOK	57	YANK3	94
LRRK2	21	YES	99
LRRK2(G2019S)	79	YSK1	100
LTK	72	YSK4	0.6
LYN	87	ZAK	81
LZK	93	ZAP70	100

Table S7. KINOMEscan kinase selectivity profiles for 5Z7.

Kinases	**Scores**	
	1 µM	**10 µM**
AAK1	61	13
ABL1(E255K)-phosphorylated	81	85
ABL1(F317I)-nonphosphorylated	97	93
ABL1(F317I)-phosphorylated	100	96
ABL1(F317L)-nonphosphorylated	100	95
ABL1(F317L)-phosphorylated	100	100
ABL1(H396P)-nonphosphorylated	96	97
ABL1(H396P)-phosphorylated	95	93
ABL1(M351T)-phosphorylated	84	100
ABL1(Q252H)-nonphosphorylated	98	88
ABL1(Q252H)-phosphorylated	100	95
ABL1(T315I)-nonphosphorylated	100	91
ABL1(T315I)-phosphorylated	80	92
ABL1(Y253F)-phosphorylated	100	90
ABL1-nonphosphorylated	78	72
ABL1-phosphorylated	81	82
ABL2	87	100
ACVR1	21	1.9
ACVR1B	100	69
ACVR2A	89	18
ACVR2B	81	46
ACVRL1	46	24
ADCK3	97	97
ADCK4	87	54
AKT1	96	95
AKT2	98	93
AKT3	100	95
ALK	100	73
ALK(C1156Y)	100	97

ALK(L1196M)	100	100
AMPK-alpha1	96	100
AMPK-alpha2	92	90
ANKK1	61	66
ARK5	100	100
ASK1	93	96
ASK2	100	100
AURKA	100	100
AURKB	100	100
AURKC	97	99
AXL	100	85
BIKE	68	3.8
BLK	76	57
BMPR1A	84	19
BMPR1B	88	76
BMPR2	100	90
BMX	94	90
BRAF	100	100
BRAF(V600E)	100	100
BRK	100	78
BRSK1	100	80
BRSK2	74	83
BTK	86	99
BUB1	100	98
CAMK1	98	100
CAMK1D	100	100
CAMK1G	100	100
CAMK2A	97	72
CAMK2B	95	66
CAMK2D	100	97
CAMK2G	94	100
CAMK4	100	100
CAMKK1	100	92
CAMKK2	92	88
CASK	79	76
CDC2L1	94	100
CDC2L2	90	77
CDC2L5	92	98
CDK11	92	94
CDK2	86	83
CDK3	94	94
CDK4-cyclinD1	91	95
CDK4-cyclinD3	100	100
CDK5	100	96
CDK7	100	100
CDK8	84	77

CDK9	93	79
CDKL1	88	82
CDKL2	76	8.6
CDKL3	85	24
CDKL5	100	100
CHEK1	100	100
CHEK2	86	81
CIT	88	87
CLK1	96	93
CLK2	98	67
CLK3	87	93
CLK4	100	100
CSF1R	82	62
CSF1R-autoinhibited	64	81
CSK	100	87
CSNK1A1	100	98
CSNK1A1L	100	88
CSNK1D	93	70
CSNK1E	92	99
CSNK1G1	100	100
CSNK1G2	89	62
CSNK1G3	97	94
CSNK2A1	67	55
CSNK2A2	82	60
CTK	100	100
DAPK1	94	74
DAPK2	94	86
DAPK3	93	79
DCAMKL1	80	74
DCAMKL2	100	100
DCAMKL3	100	100
DDR1	100	100
DDR2	93	100
DLK	94	96
DMPK	100	100
DMPK2	91	91
DRAK1	100	100
DRAK2	100	100
DYRK1A	100	100
DYRK1B	69	86
DYRK2	100	95
EGFR	100	99
EGFR(E746-A750del)	100	91
EGFR(G719C)	75	76
EGFR(G719S)	90	93
EGFR(L747-E749del, A750P)	79	79

EGFR(L747-S752del, P753S)	84	71
EGFR(L747-T751del,Sins)	92	89
EGFR(L858R)	93	80
EGFR(L858R,T790M)	100	100
EGFR(L861Q)	100	100
EGFR(S752-I759del)	96	100
EGFR(T790M)	100	100
EIF2AK1	100	100
EPHA1	80	62
EPHA2	88	74
EPHA3	79	68
EPHA4	94	85
EPHA5	92	91
EPHA6	99	76
EPHA7	83	92
EPHA8	84	96
EPHB1	98	98
EPHB2	100	87
EPHB3	93	100
EPHB4	94	85
EPHB6	71	12
ERBB2	100	100
ERBB3	100	100
ERBB4	87	81
ERK1	97	58
ERK2	92	64
ERK3	96	98
ERK4	100	100
ERK5	100	100
ERK8	75	13
ERN1	93	77
FAK	100	100
FER	88	93
FES	90	88
FGFR1	96	100
FGFR2	94	82
FGFR3	100	95
FGFR3(G697C)	96	83
FGFR4	80	93
FGR	89	84
FLT1	16	0.5
FLT3	4.2	0.55
FLT3(D835H)	13	11
FLT3(D835Y)	8	16
FLT3(ITD)	4.2	0.25
FLT3(K663Q)	8.6	6.4

FLT3(N841I)	2.6	0.85
FLT3(R834Q)	77	23
FLT3-autoinhibited	100	100
FLT4	8.2	0.3
FRK	100	97
FYN	100	99
GAK	10	10
GCN2(Kin.Dom.2,S808G)	100	100
GRK1	96	87
GRK4	95	42
GRK7	100	100
GSK3A	100	100
GSK3B	99	100
HASPIN	100	94
HCK	58	45
HIPK1	70	71
HIPK2	100	100
HIPK3	100	100
HIPK4	93	82
HPK1	94	76
HUNK	82	69
ICK	100	100
IGF1R	87	80
IKK-alpha	100	100
IKK-beta	75	79
IKK-epsilon	100	95
INSR	77	71
INSRR	82	71
IRAK1	100	84
IRAK3	90	63
IRAK4	74	70
ITK	82	100
JAK1(JH1domain-catalytic)	89	100
JAK1(JH2domain-pseudokinase)	96	99
JAK2(JH1domain-catalytic)	100	95
JAK3(JH1domain-catalytic)	100	77
JNK1	87	92
JNK2	95	100
JNK3	93	95
KIT	20	0.6
KIT(A829P)	43	10
KIT(D816H)	43	7.6
KIT(D816V)	1	0.4
KIT(L576P)	17	0.7
KIT(V559D)	14	0.3
KIT(V559D,T670I)	56	2.6

KIT(V559D,V654A)	51	3.5
KIT-autoinhibited	100	100
LATS1	100	100
LATS2	100	100
LCK	90	60
LIMK1	100	84
LIMK2	88	86
LKB1	100	88
LOK	100	62
LRRK2	100	96
LRRK2(G2019S)	96	98
LTK	88	70
LYN	100	88
LZK	90	100
MAK	90	96
MAP3K1	100	100
MAP3K15	100	99
MAP3K2	100	79
MAP3K3	100	100
MAP3K4	97	86
MAP4K2	100	100
MAP4K3	87	91
MAP4K4	91	84
MAP4K5	92	76
MAPKAPK2	100	100
MAPKAPK5	95	47
MARK1	84	83
MARK2	100	96
MARK3	100	100
MARK4	92	93
MAST1	97	89
MEK1	0.65	0.05
MEK2	0.75	0.05
MEK3	22	1.4
MEK4	19	0.35
MEK5	0.2	0.1
MEK6	23	21
MELK	88	92
MERTK	56	82
MET	100	100
MET(M1250T)	84	92
MET(Y1235D)	97	100
MINK	86	89
MKK7	97	61
MKNK1	100	100
MKNK2	80	11

MLCK	100	100
MLK1	95	100
MLK2	100	77
MLK3	91	84
MRCKA	96	89
MRCKB	100	100
MST1	94	100
MST1R	92	88
MST2	47	52
MST3	88	99
MST4	64	62
MTOR	84	94
MUSK	100	91
MYLK	85	84
MYLK2	92	80
MYLK4	78	84
MYO3A	96	93
MYO3B	100	100
NDR1	69	75
NDR2	100	99
NEK1	100	100
NEK10	100	96
NEK11	90	91
NEK2	100	94
NEK3	83	85
NEK4	100	100
NEK5	89	92
NEK6	85	81
NEK7	91	81
NEK9	94	90
NIK	98	71
NIM1	100	100
NLK	100	70
OSR1	64	87
p38-alpha	100	93
p38-beta	81	78
p38-delta	96	95
p38-gamma	90	81
PAK1	95	93
PAK2	100	100
PAK3	76	48
PAK4	96	86
PAK6	100	98
PAK7	86	79
PCTK1	100	100
PCTK2	100	95

PCTK3	100	100
PDGFRA	44	1.4
PDGFRB	1.5	0.05
PDPK1	69	72
PFCDPK1(P.falciparum)	97	89
PFPK5(P.falciparum)	100	100
PFTAIRE2	100	90
PFTK1	99	100
PHKG1	99	97
PHKG2	100	82
PIK3C2B	100	100
PIK3C2G	99	93
PIK3CA	100	100
PIK3CA(C420R)	80	79
PIK3CA(E542K)	100	99
PIK3CA(E545A)	61	67
PIK3CA(E545K)	68	69
PIK3CA(H1047L)	100	98
PIK3CA(H1047Y)	67	63
PIK3CA(I800L)	75	63
PIK3CA(M1043I)	100	100
PIK3CA(Q546K)	93	96
PIK3CB	71	77
PIK3CD	99	100
PIK3CG	100	100
PIK4CB	100	100
PIM1	98	89
PIM2	90	97
PIM3	100	79
PIP5K1A	83	58
PIP5K1C	100	100
PIP5K2B	87	26
PIP5K2C	100	92
PKAC-alpha	79	70
PKAC-beta	96	100
PKMYT1	100	97
PKN1	84	75
PKN2	98	93
PKNB(M.tuberculosis)	100	99
PLK1	100	100
PLK2	74	69
PLK3	94	83
PLK4	59	55
PRKCD	78	100
PRKCE	100	74
PRKCH	99	82

PRKCI	97	100
PRKCQ	100	100
PRKD1	75	10
PRKD2	72	2.5
PRKD3	100	12
PRKG1	98	99
PRKG2	84	82
PRKR	100	94
PRKX	100	100
PRP4	77	95
PYK2	99	88
QSK	100	99
RAF1	100	100
RET	100	97
RET(M918T)	100	99
RET(V804L)	98	93
RET(V804M)	100	100
RIOK1	77	15
RIOK2	100	100
RIOK3	74	0
RIPK1	89	96
RIPK2	91	76
RIPK4	100	89
RIPK5	100	95
ROCK1	100	99
ROCK2	100	96
ROS1	98	83
RPS6KA4(Kin.Dom.1-N-terminal)	100	100
RPS6KA4(Kin.Dom.2-C-terminal)	96	85
RPS6KA5(Kin.Dom.1-N-terminal)	100	100
RPS6KA5(Kin.Dom.2-C-terminal)	100	87
RSK1(Kin.Dom.1-N-terminal)	67	74
RSK1(Kin.Dom.2-C-terminal)	89	27
RSK2(Kin.Dom.1-N-terminal)	82	69
RSK2(Kin.Dom.2-C-terminal)	100	100
RSK3(Kin.Dom.1-N-terminal)	100	100
RSK3(Kin.Dom.2-C-terminal)	70	18
RSK4(Kin.Dom.1-N-terminal)	78	62
RSK4(Kin.Dom.2-C-terminal)	34	3
S6K1	100	100
SBK1	62	70
SGK	100	100
SgK110	100	100
SGK2	100	100
SGK3	100	98
SIK	90	96

SIK2	84	66
SLK	83	34
SNARK	100	100
SNRK	100	92
SRC	96	74
SRMS	94	84
SRPK1	68	83
SRPK2	100	100
SRPK3	73	47
STK16	100	100
STK33	92	100
STK35	94	82
STK36	7.1	0.95
STK39	99	100
SYK	87	82
TAK1	58	3.6
TAOK1	100	100
TAOK2	100	97
TAOK3	86	76
TBK1	83	80
TEC	91	98
TESK1	84	86
TGFBR1	82	57
TGFBR2	3.8	0.9
TIE1	100	100
TIE2	96	82
TLK1	94	93
TLK2	95	100
TNIK	76	74
TNK1	40	25
TNK2	97	67
TNNI3K	95	77
TRKA	75	82
TRKB	94	77
TRKC	96	91
TRPM6	98	88
TSSK1B	58	79
TTK	100	100
TXK	100	85
TYK2(JH1domain-catalytic)	100	100
TYK2(JH2domain-pseudokinase)	100	100
TYRO3	96	69
ULK1	83	79
ULK2	99	96
ULK3	74	83
VEGFR2	78	5.2

VRK2	100	100
WEE1	83	78
WEE2	100	81
WNK1	97	97
WNK3	92	75
YANK1	100	100
YANK2	95	100
YANK3	100	82
YES	97	100
YSK1	100	100
YSK4	100	100
ZAK	5.6	2.2
ZAP70	83	86

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