SUPPORTING INFORMATION

The discovery of kinase inhibitors by combination of diversity-oriented synthesis and selective screening

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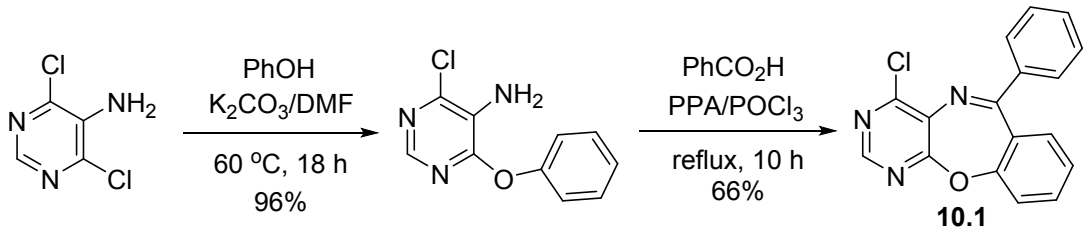
Chemistry. Phosphoryl trichloride ($POCl_3$) was freshly distilled. Dichloromethane (CH_2Cl_2) was dried over P_2O_5 and distilled. Acetonitrile (CH_3CN) was dried over CaH_2 and distilled. All other commercial reagents were used as received without additional purification. Melting points were determined by XT5 melting point apparatus and are uncorrected. Mass spectra and HPLC data was recorded on an 1100 LC/MS system (Agilent Technology Corporation) with Alltech ELSD 2000. The ^1H and ^{13}C NMR data were obtained on a Varian Mercury (300 MHz) NMR spectrometer with TMS as the internal standard and $CDCl_3$ as solvent unless otherwise stated. Multiplicities are indicated as the following: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doubled doublet; br, broad. Coupling constants (*J* values) where noted are quoted in Hertz. Compounds **1.1**[1], **2.1**[2], **3.1**[3], **4.1**[3], **5.1**[4], **6.1**[5], **7.1**[6], **8.1**[7], and **9.1**[8] have been synthesized in our previous reports. Purity of all compounds tested in biological assays were determined to be >95% by HPLC.

Preparation of 4-chloro-6-phenylbenzo[*f*]pyrimido[4,5-*b*][1,4]oxazepine 10.1.



10.1

To a stirred solution of 4,6-dichloropyrimidin-5-amine (328 mg, 2.0 mmol) and phenol (226 mg, 2.4 mmol) in DMF (6 mL) was added K_2CO_3 (828 g, 6.0 mmol). The resulting solution was stirred for 18 h at 60 °C, water (50 mL) was added, and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (Petroleum ether/EtOAc = 50:1 to 20:1, v/v) afforded the desired 4-chloro-6-phenoxypyrimidin-5-amine (426 mg, 96%). mp: 92–94 °C; ^1H NMR: δ 7.99 (s, 1H), 7.48–7.42 (m, 2H), 7.32–7.26 (m, 1H), 7.20–7.15 (m, 2H), 4.29 (br, 2H); MS (ESI): *m/z* 222.0 [M + H^+].

4-Chloro-6-phenoxypyrimidin-5-amine (221 mg, 1.0 mmol), benzoic acid (183 mg, 1.5 mmol), and PPA (507 mg, 1.5 mmol) were dissolved in $POCl_3$ (5.0 mL) and

the mixture stirred for 10 h at reflux. The reaction mixture was concentrated *in vacuo* and diluted with ethyl acetate (30 mL), and water (30 mL) was added slowly. The water layer was treated with 5 N aqueous NaOH to pH 9 and extracted with EtOAc (2 x 30 mL). The combined EtOAc layer was washed with saturated Na_2CO_3 (45 mL) and brine (45 mL), dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (Petroleum ether/EtOAc = 30:1 to 10:1, v/v) afforded the desired product **10.1** (203 mg, 66%). mp: 167–169 ^oC; ^1H NMR: δ 8.55 (s, 1H), 7.91–7.87 (m, 2H), 7.65–7.41 (m, 5H), 7.32–7.26 (m, 2H); ^{13}C NMR: δ 170.6, 162.9, 158.9, 158.7 154.4, 138.4, 134.3, 131.70, 131.67, 131.1, 130.1, 128.4, 126.2, 125.7, 122.2; MS (ESI): *m/z* 308.0 [M + H^+].

Some benzo[*f*]pyrimido[4,5-*b*][1,4]thiazepines (**5.1-5.4**, **5.6-5.8**, **5.11**, **5.16-5.19**, **5.21-5.23**, **5.25**, **5.26**, **5.28-5.31**, and **5.34-5.36**) have been synthesized in our previous reports,[4,5] and the other required benzo[*f*]pyrimido[4,5-*b*][1,4]thiazepines were prepared according to our previously reported method.[4]

General Procedure for Oxidation with *m*-CPBA. Corresponding benzo[*f*]pyrimido[4,5-*b*][1,4]thiazepine (1.0 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0–5 °C in an ice bath. A solution of *m*-CPBA (206 mg, 1.2 mmol) in CH_2Cl_2 (15 mL) was added dropwise over 30 min. After complete consumption of the starting material benzo[*f*]pyrimido[4,5-*b*][1,4]thiazepine by TLC, the reaction mixture was treated with saturated $NaHSO_3$, saturated Na_2CO_3, and brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography with petroleum ether/EtOAc (5:1, v/v) as eluent to afford the desired product.

8-Chloro-4-((4-chlorophenyl)sulfinyl)-6-(*p*-tolyl)benzo[*f*]pyrimido[4,5-*b*][1,4]thiazepine (5.5). Compound **5.5** was synthesized from 8-chloro-4-((4-chlorophenyl)thio) -6-(*p*-tolyl)benzo[*f*]pyrimido[4,5-*b*][1,4]thiazepine[4] (480 mg, 1.0 mmol) following the general procedure for oxidation with *m*-CPBA. Yield: 303 mg (61%); mp: 212–213 ^oC; ^1H NMR: δ 8.95 (s, 1H), 7.79 (br s, 3H), 7.56–7.25 (m, 7H), 6.95 (br s, 1H), 2.50 (s, 3H); MS (ESI): *m/z* 496.1 [M + H^+].

8-Methyl-6-(*p*-tolyl)-4-(*p*-tolylsulfinyl)benzo[*f*]pyrimido[4,5-*b*][1,4]thiazepine (5.9). Compound **5.9** was synthesized from 8-methyl-6-(*p*-tolyl)-4-(*p*-tolylthio)benzo [*f*]pyrimido[4,5-*b*][1,4]thiazepine[4] (440 mg, 1.0 mmol) following the general procedure for oxidation with *m*-CPBA. Yield: 228 mg (50%); mp: 231–232 ^{o}C; ^{1}H NMR: δ 8.93 (s, 1H), 7.82 (br s, 3H), 7.51–7.27 (m, 6H), 7.04 (br s, 1H), 6.70 (br s, 1H), 2.49 (s, 3H), 2.26 (s, 6H); MS (ESI): *m/z* 456.1 [M + H^{+}].

4-(Phenylsulfinyl)-6-propylbenzo[*f*]pyrimido[4,5-*b*][1,4]thiazepine (5.10). Compound **5.10** was synthesized from 4-(phenylthio)-6-propylbenzo[*f*]pyrimido[4,5-*b*] [1,4]thiazepine[4] (364 mg, 1.0 mmol) following the general procedure for oxidation with *m*-CPBA. Yield: 254 mg (67%); mp: 140–141 ^{o}C; ^{1}H NMR: δ 8.95 (s, 1H), 7.74 (br s, 2H), 7.47–7.34 (m, 6H), 7.18 (br s, 1H), 2.96 (t, J = 7.5, 2H), 1.81–1.73 (m, 2H), 1.07 (t, J = 7.5, 3H); MS (ESI): *m/z* 380.1 [M + H^{+}].

6-(4-Fluorophenyl)-8-methyl-4-(*p*-tolylsulfinyl)benzo[*f*]pyrimido[4,5-*b*][1,4]thiazepine. Title compound was synthesized from 6-(4-fluorophenyl)-8-methyl-4-(*p*-tolyl thio)benzo[*f*]pyrimido[4,5-*b*][1,4]thiazepine[4] (444 mg, 1.0 mmol) following the general procedure for oxidation with *m*-CPBA. Yield: 248 mg (54%); mp: 235–236 ^{o}C; ^{1}H NMR: δ 8.94 (s, 1H), 7.93 (br s, 3H), 7.43 (br s, 3H), 7.27–7.20 (m, 3H), 7.07 (br s, 1H), 6.69 (br s, 1H), 2.28 (s, 6H); MS (ESI): *m/z* 460.2 [M + H^{+}].

8-Methoxy-4-((4-methoxyphenyl)thio)-6-(*p*-tolyl)benzo[*f*]pyrimido[4,5-*b*][1,4]thiazepine (5.12). 4,6-Bis((4-methoxyphenyl)thio)pyrimidin-5-amine[4] (186 mg, 0.50 mmol), 4-methylbenzoic acid (102 mg, 0.75 mmol), and PPA (253 mg, 0.75 mmol) were dissolved in $POCl_3$ (5.0 mL) and the mixture stirred under reflux for 23 h. The reaction mixture was concentrated *in vacuo* and diluted with ethyl acetate (15 mL), and water (15 mL) was added slowly. The water layer was treated with 5 N aqueous NaOH to pH 10 and extracted with EtOAc (2 x 15 mL). The combined EtOAc layer was washed with saturated Na_2CO_3 and brine, dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by flash chromatography with petroleum ether/EtOAc (15:1, v/v) as eluent to afford 134 mg (57%) of **5.12** as a yellow solid. mp: 175–176 ^{o}C; ^{1}H NMR (DMSO-*d6*): δ 8.43 (s, 1H), 7.80 (d, J = 8.4, 2H), 7.58 (d,

J = 8.7, 1H), 7.49 (d, *J* = 8.7, 2H), 7.39 (d, *J* = 7.8, 2H), 7.24 (dd, *J* = 8.7, 3.0, 1H), 7.03 (d, *J* = 9.0, 2H), 6.83 (d, *J* = 2.7, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 2.42 (s, 3H); MS (ESI): *m/z* 472.1 [M + H^+].

General Procedure for Nucleophilic Displacement. Corresponding 4-(phenylsulfinyl)pyrimido[4,5-*b*][1,4]benzothiazepine (0.25 mmol) was dissolved in dry CH_3CN (2.5 mL). The appropriate amine (0.75 mmol) was added at room temperature. After complete consumption of the starting material 4-(phenylsulfinyl)pyrimido[4,5-*b*][1,4]benzothiazepine by TLC, the reaction mixture was concentrated *in vacuo* and purified by flash chromatography with petroleum ether/EtOAc (8:1, v/v) as eluent to afford the desired product.

6-Benzyl-*N*-cyclohexyl-8-methylbenzo[*f*]pyrimido[4,5-*b*][1,4]thiazepin-4-amine (5.13). Compound **5.13** was synthesized from 6-benzyl-8-methyl-4-(*p*-tolylthio)benzo [*f*]pyrimido[4,5-*b*][1,4]thiazepine[4] (220 mg, 0.5 mmol) and cyclohexanamine (68 μL, 0.59 mmol) following the general procedure for oxidation with *m*-CPBA and nucleophilic displacement. Yield: 73 mg (35%); mp: 175–176 ^oC; ^1H NMR: δ 8.21 (s, 1H), 7.39–7.32 (m, 5H), 7.31–7.20 (m, 3H), 5.36 (d, *J* = 8.4, 1H), 4.32 (s, 2H), 3.92–3.84 (m, 1H), 2.36 (s, 3H), 1.94–1.90 (m, 2H), 1.71–1.60 (m, 3H), 1.45–1.12 (m, 5H); MS (ESI): *m/z* 415.3 [M + H^+].

***N*,6-Dibenzyl-8-methylbenzo[*f*]pyrimido[4,5-*b*][1,4]thiazepin-4-amine (5.14).** Compound **5.14** was synthesized from 6-benzyl-8-methyl-4-(*p*-tolylthio)benzo[*f*] pyrimido[4,5-*b*][1,4]thiazepine[4] (220 mg, 0.5 mmol) and benzylamine (65 μL, 0.59 mmol) following the general procedure for oxidation with *m*-CPBA and nucleophilic displacement. Yield: 78 mg (37%); mp: 141–143 ^oC; ^1H NMR: δ 8.27 (s, 1H), 7.37–7.16 (m, 13H), 5.75 (br, 1H), 4.60 (d, *J* = 5.7, 2H), 4.27 (s, 2H), 2.34 (s, 3H); MS (ESI): *m/z* 423.1 [M + H^+].

***N*-Benzyl-8-methyl-6-(pyridin-3-yl)benzo[*f*]pyrimido[4,5-*b*][1,4]thiazepin-4-amine (5.15).** Compound **5.15** was synthesized from 8-methyl-6-(pyridin-3-yl)-4- (*p*-tolylthio)benzo[*f*]pyrimido[4,5-*b*][1,4]thiazepine[4] (213 mg, 0.5 mmol) and benzylamine (82 μL, 0.75 mmol) following the general procedure for oxidation with

m-CPBA and nucleophilic displacement. Yield: 61 mg (30%); mp: 76–78 ^{o}C; ^{1}H NMR: δ 8.99 (d, J = 2.1, 1H), 8.72 (d, J = 3.6, 1H), 8.35 (s, 1H), 8.06 (d, J = 8.1, 1H), 7.52 (d, J = 7.8, 1H), 7.41–7.31 (m, 7H), 7.00 (s, 1H), 6.03 (t, J = 5.7, 1H), 4.78 (d, J = 6.0, 2H), 2.30 (s, 3H); MS (ESI): *m/z* 410.2 [M + H^{+}].

8-Chloro-*N*-cyclohexyl-6-(*p*-tolyl)benzo[*f*]pyrimido[4,5-*b*][1,4]thiazepin-4-amine (5.20). Compound **5.20** was synthesized from 8-chloro-4-((4-chlorophenyl)sulfinyl) -6-(*p*-tolyl)benzo[*f*]pyrimido[4,5-*b*][1,4]thiazepine **5.5** (124 mg, 0.25 mmol) and cyclohexanamine (86 μL, 0.75 mmol) following the general procedure for nucleophilic displacement. Yield: 86 mg (78%); mp: 204–205 ^{o}C; ^{1}H NMR: δ 8.27 (s, 1H), 7.65 (d, J = 7.5, 2H), 7.56–7.44 (m, 2H), 7.30–7.23 (m, 3H), 5.65 (d, J = 7.5, 1H), 4.06–3.98 (m, 1H), 2.45 (s, 3H), 2.14–2.05 (m, 2H), 1.77–1.66 (m, 3H), 1.53–1.26 (m, 5H); MS (ESI): *m/z* 435.1 [M + H^{+}].

***N*-Benzyl-6-propylbenzo[*f*]pyrimido[4,5-*b*][1,4]thiazepin-4-amine (5.24).** Compound **5.24** was synthesized from 4-(phenylsulfinyl)-6-propylbenzo[*f*]pyrimido [4,5-*b*][1,4]thiazepine **5.10** (95 mg, 0.25 mmol) and benzylamine (82 μL, 0.75 mmol) following the general procedure for nucleophilic displacement. Yield: 79 mg (88%); mp: 121–122 ^{o}C; ^{1}H NMR: δ 8.29 (s, 1H), 7.54–7.51 (m, 1H), 7.44–7.29 (m, 8H), 5.97 (br, 1H), 4.70 (d, J = 6.0, 2H), 2.94 (t, J = 6.9, 2H), 1.80–1.66 (m, 2H), 1.01 (t, J = 7.2, 3H); MS (ESI): *m/z* 361.1 [M + H^{+}].

6-(4-Fluorophenyl)-8-methylbenzo[*f*]pyrimido[4,5-*b*][1,4]thiazepin-4-amine (5.27). Compound **5.27** was synthesized from 6-(4-fluorophenyl)-8-methyl-4- (*p*-tolylsulfinyl)benzo[*f*]pyrimido[4,5-*b*][1,4]thiazepine (115 mg, 0.25 mmol) and ammonia (12% in ethanol, 0.25 mL) following the general procedure for nucleophilic displacement. Yield: 56 mg (66%); mp: 285–286 ^{o}C; ^{1}H NMR: δ 8.26 (s, 1H), 7.85–7.81 (m, 2H), 7.50 (d, J = 8.1, 1H), 7.34–7.31 (m, 1H), 7.18–7.12 (m, 2H), 7.03 (d, J = 1.5, 1H), 5.50 (br, 2H), 2.31 (s, 3H); MS (ESI): *m/z* 337.0 [M + H^{+}].

***N*-Benzyl-8-chloro-6-(*p*-tolyl)benzo[*f*]pyrimido[4,5-*b*][1,4]thiazepin-4-amine (5.32).** Compound **5.32** was synthesized from 8-chloro-4-((4-chlorophenyl)sulfinyl) -6-(*p*-tolyl)benzo[*f*]pyrimido[4,5-*b*][1,4]thiazepine **5.5** (124 mg, 0.25 mmol) and

benzylamine (82 μL, 0.75 mmol) following the general procedure for nucleophilic displacement. Yield: 105 mg (95%); mp: 118–120 ^{o}C; ^{1}H NMR: δ 8.32 (s, 1H), 7.63 (d, J = 8.1, 2H), 7.56–7.44 (m, 2H), 7.39–7.31 (m, 5H), 7.26–7.21 (m, 3H), 6.05 (br, 1H), 4.78 (d, J = 5.4, 2H), 2.43 (s, 3H); MS (ESI): *m/z* 443.1 [M + H^+].

2-((6-(4-Fluorophenyl)-8-methylbenzo[*f*]pyrimido[4,5-*b*][1,4]thiazepin-4-yl)amino)ethanol (5.33). Compound **5.33** was synthesized from 6-(4-fluorophenyl)-8-methyl -4-(*p*-tolylsulfinyl)benzo[*f*]pyrimido[4,5-*b*][1,4]thiazepine (115 mg, 0.25 mmol) and 2-aminoethanol (45 μL, 0.75 mmol) following the general procedure for nucleophilic displacement. Yield: 81 mg (85%); mp: 201–202 ^{o}C; ^{1}H NMR: δ 8.25 (s, 1H), 7.85–7.80 (m, 2H), 7.49 (d, J = 8.1, 1H), 7.31 (d, J = 8.1, 1H), 7.14 (t, J = 8.7, 2H), 7.02 (s, 1H), 6.16 (t, J = 5.1, 1H), 3.88 (t, J = 4.8, 2H), 3.72 (br s, 3H), 2.31 (s, 3H); MS (ESI): *m/z* 381.1 [M + H^+].

Biological assays

FRET Based Enzymatic Assay: Compounds were tested in the Z′-LYTE™ assay using the SelectScreen™ Kinase Profiling Service (Invitrogen Corporation) in a Corning 384-well microtiter plate. All test compounds were initially solubilized in 100% DMSO, then diluted further to working concentrations for the assay in kinase buffer (50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM $MgCl_2$, 1 mM EGTA). The final concentration of DMSO in the assay well is 1%. The 2X MAPK14 (p38 alpha) / inactive MAPKAPK2 / Ser/Thr 04 Peptide Mixture is prepared in 50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM $MgCl_2$, 1 mM EGTA. The final kinase reaction consists of 0.005-0.020 ng MAPK14 (p38 alpha), 5 ng inactive MAPKAPK2, and 2 μM Ser/Thr 04 Peptide in 50 mM HEPES pH 7.5, 0.01% BRIJ-35, 10 mM $MgCl_2$, 1 mM EGTA. After a 1 hour incubation, 5 μL of a 1:1024 dilution of Development Reagent A is added. After an additional hour of incubation, the signal was measured at 445/520 nm emission ratio on a fluorescence plate reader.

Western Blot Analysis: The compounds were diluted to a final DMSO concentration of 0.2% and incubated with the multiple myeloma cell lines, MM1S and U266. Then,

the cells were lysed and Western blots were carried out to probe for phospho-p38 (Cell Signaling Antibody, cat. # 9211) or tubulin as a loading control.

Table S1 Data against 40 representative kinases (Compounds **1.1**-**10.1**) at 10 μM

Kinase	% Inh.									
	1.1	**2.1**	**3.1**	**4.1**	**5.1**	**6.1**	**7.1**	**8.1**	**9.1**	**10.1**
ABL1	11	6	5	8	12	14	14	13	1	9
PKBα	2	4	3	3	5	3	5	5	1	4
BTK	11	5	6	9	3	6	5	17	4	8
CDK1/cyclin B	14	9	18	11	8	4	0	16	3	10
CHK1	3	-4	-1	0	3	1	1	4	5	9
CK1γ2	-1	7	5	3	6	9	13	7	3	3
CK2α1	0	5	4	3	3	1	5	4	4	1
DYRK3	14	44	14	13	8	6	4	10	1	0
EGFR	5	5	6	3	1	12	2	0	2	-1
EPHA2	4	6	2	5	9	4	6	4	1	4
HER2	-3	-10	-8	-5	-4	-7	-4	-8	-6	-6
FGFR1	-1	0	-1	-2	-4	-3	9	-3	-1	-3
FLT3	4	20	7	10	6	10	7	11	5	6
GSK3β	5	15	7	6	7	9	7	38	5	5
IGF1R	-2	3	2	3	2	1	2	1	2	1
INSR	0	3	1	3	2	2	2	2	1	-1
IRAK4	4	1	-1	5	3	-3	-1	8	-3	1
JAK3	2	3	1	1	-1	0	2	2	-1	-4
KDR	2	9	7	8	12	17	0	9	4	9
KIT	10	6	5	5	3	-1	0	5	0	1
LCK	2	9	8	12	10	9	9	8	7	13
MEK1	4	-4	1	3	2	1	1	4	0	-10
HGK	10	32	13	16	15	19	6	44	13	20
p38α	2	5	2	6	74	19	-2	10	0	4
ERK1	2	4	1	6	5	2	5	16	3	-2
MAPKAPK2	0	4	2	-2	8	5	0	1	8	3
MET	25	26	22	21	14	11	8	13	4	5
TRKA	9	19	21	20	2	15	12	10	13	13

PDGFRβ	-4	2	1	1	-1	6	3	0	0	-1
PHKG2	0	-2	1	-1	2	-3	-3	0	-2	1
PIM1	2	51	4	2	3	-1	-2	6	-2	1
PKACα	-2	-7	-7	-12	-14	-16	-8	-14	-15	-6
PKCβI	4	-3	-1	0	1	-4	-7	-3	-13	-6
RET	5	8	6	9	7	12	8	21	6	6
ROCK1	13	0	0	-1	2	-4	-3	14	-4	1
p70S6K	8	11	0	0	1	-4	-4	4	-3	0
SRC	5	6	6	6	3	4	5	3	3	6
Aurora A	5	7	-1	16	6	5	5	12	-1	3
SYK	-2	7	3	9	-3	19	11	9	3	-5
TIE2	-2	-2	-3	4	11	-2	-3	0	4	10

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