Supporting Information

Discovery of Quinazolines That Activate SOS1-Mediated Nucleotide Exchange on RAS

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■ ABBREVIATIONS USED

NH_4Cl, ammonium chloride; NH_4OH, ammonium hydroxide; (±)-BINAP, (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene; $Pd(dppf)Cl_2$, [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II); Cs_2CO_3, cesium carbonate; CH_2Cl_2, dichloromethane; RuPhos, 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl; Et_2O, diethyl ether; *i*-Pr_2NEt, *N,N*-diisopropylethylamine; EGF, epidermal growth factor; EtOH, ethanol; EtOAc, ethyl acetate; ERK1/2, extracellular regulated kinases 1 and 2; HCl, hydrogen chloride/hydrochloride; $LiAlH_4$, lithium aluminum hydride; $LiBH_4$, lithium borohydride; $MgSO_4$, magnesium sulfate; MeOH, methanol; $Pd(OAc)_2$, palladium(II) acetate; $POCl_3$, phosphorus(V) oxychloride; pERK1/2, phosphorylated ERK1/2; K_2CO_3, potassium carbonate; K_3PO_4, potassium phosphate tribasic; $NaHCO_3$, sodium bicarbonate; NaO*t*-Bu, sodium *tert*-butoxide; NaH, sodium hydride; Na_2SO_4, sodium sulfate; SOS1, son of sevenless homologue 1; TLC, thin layer chromatography; $Ti(OEt)_4$, titanium(IV) ethoxide; Et_3N, triethylamine; TFA, trifluoroacetic acid/trifluoroacetate; H_2O, water.

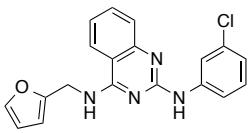
■ CHEMISTRY EXPERIMENTAL SECTION

General Procedures. All chemical reagents and reaction solvents were purchased from commercial suppliers and used as received. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded at either 400 MHz or 600 MHz on a Bruker spectrometer. For ^1H NMR spectra, chemical shifts are reported in parts per million (ppm) and are reported relative to residual non-deuterated solvent signals. Coupling constants are reported in hertz (Hz). The following abbreviations (or a combination, thereof) are used

to describe splitting patterns: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; comp, overlapping multiplets of non-magnetically equivalent protons; br, broad. All compounds were of 95% purity or higher, unless otherwise noted, as measured by analytical reversed-phase HPLC. Analytical HPLC was performed on an Agilent 1200 series system with UV detection at 214 and 254 nm, along with evaporative light scattering detection (ELSD). Low-resolution mass spectra were obtained on an Agilent 6140 mass spectrometer with electrospray ionization (ESI). LC-MS experiments were performed with the following parameters: Phenomenex Kinetex 2.6 μm XB-C18 100 Å, LC column 50 x 2.1 mm; 2 min gradient, 5%–95% MeCN in H_2O, and 0.1% TFA or 0.1% formic acid. Analytical TLC was performed on Kieselgel 60 F_{254} glass plates precoated with a 0.25 mm thickness of silica gel. TLC plates were visualized with UV light and iodine. Silica gel chromatography was performed using a Teledyne Isco Combiflash® Rf system. Preparative reversed-phase HPLC was performed on a Gilson instrument equipped with a Phenomenex Kinetex C18 column, using varying concentrations of MeCN in H_2O, and 0.1% TFA.

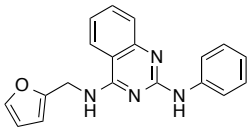
Chemical Synthesis. Compounds **1**–**3**, **6**–**8**, and **12** were purchased from commercial suppliers and used as received. Compounds **17** and **18** were synthesized by and purchased from Viva Biotech (Shanghai, China).

N^2-(3-Chlorophenyl)-N^4-(furan-2-ylmethyl)quinazoline-2,4-diamine (1)



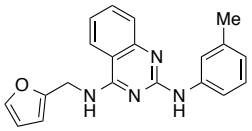
The title compound was purchased as its corresponding HCl salt from Vitas-M (Vendor ID: STK841755). Stated purity >95%.

N^4-(Furan-2-ylmethyl)-N^2-phenylquinazoline-2,4-diamine (2)



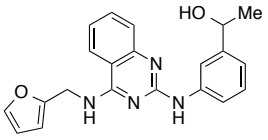
The title compound was purchased as its corresponding HCl salt from Life Chemicals (Vendor ID: F3007-0027). Stated purity >95%.

N^4-(Furan-2-ylmethyl)-N^2-(*m*-tolyl)quinazoline-2,4-diamine (3)



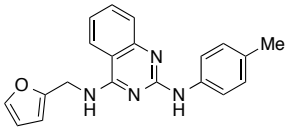
The title compound was purchased as its corresponding HCl salt from ChemBridge (Vendor ID: 6694921). Stated purity >95%.

1-(3-((4-((Furan-2-ylmethyl)amino)quinazolin-2-yl)amino)phenyl)ethan-1-ol (6)



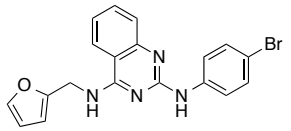
The title compound was purchased from ChemBridge (Vendor ID: 9261554). Stated purity >95%.

N^4-(Furan-2-ylmethyl)-N^2-(*p*-tolyl)quinazoline-2,4-diamine (7)



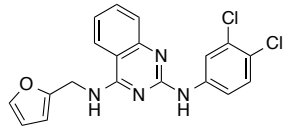
The title compound was purchased as its corresponding HCl salt from ChemBridge (Vendor ID: 6654874). Stated purity >95%.

N^2-(4-Bromophenyl)-N^4-(furan-2-ylmethyl)quinazoline-2,4-diamine (8)



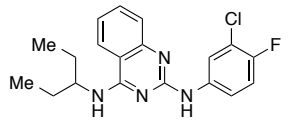
The title compound was purchased as its corresponding HCl salt from Pharmeks Ltd (Vendor ID: PHAR036031). Stated purity >95%.

N^2-(3,4-Dichlorophenyl)-N^4-(furan-2-ylmethyl)quinazoline-2,4-diamine (12)



The title compound was purchased as its corresponding HCl salt from Vitas-M (Vendor ID: STK542551). Stated purity >95%.

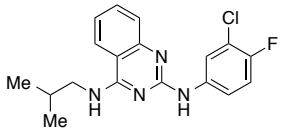
N^2-(3-Chloro-4-fluorophenyl)-N^4-(pentan-3-yl)quinazoline-2,4-diamine (17)



White solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.11 (dd, J = 6.8, 2.7 Hz, 1H), 8.08 (dd, J = 8.3, 0.8 Hz, 1H), 7.64–7.60 (m, 1H), 7.47 (ddd, J = 9.2, 4.1, 2.7 Hz, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.25–7.21 (m, 1H), 7.15 (t, J = 9.0 Hz, 1H), 4.38–4.31 (m, 1H), 1.81–1.72

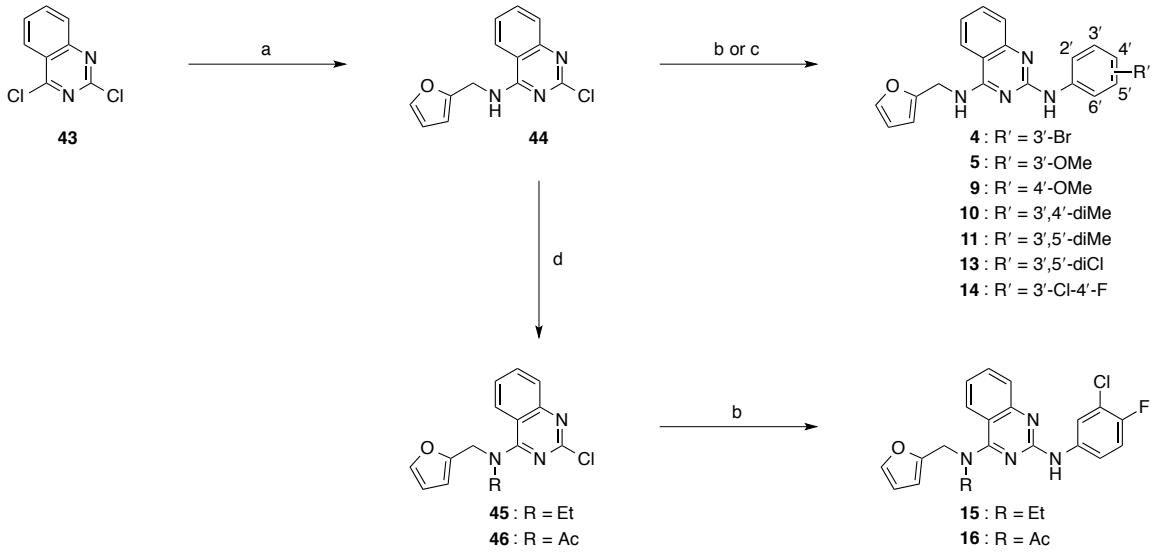
(m, 2H), 1.71–1.62 (m, 2H), 0.98 (t, J = 7.5 Hz, 6H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{21}ClFN_4$ 359.1; found 359.1. LC-MS ^{t}R (UV 214): 1.586 min.

N^2-(3-Chloro-4-fluorophenyl)-N^4-isobutylquinazoline-2,4-diamine (18)



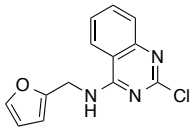
White solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.04 (dd, J = 6.7, 2.8 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.68 (t, J = 7.8 Hz, 1H), 7.49–7.45 (comp, 2H), 7.30 (t, J = 7.7 Hz, 1H), 7.20 (t, J = 9.0 Hz, 1H), 3.45 (d, J = 7.2 Hz, 2H), 2.16–2.06 (m, 1H), 1.00 (d, J = 6.7 Hz, 6H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{19}ClFN_4$ 345.1; found 345.0. LC-MS ^{t}R (UV 214): 1.466 min.

Scheme S1. Preparation of Compounds 4, 5, 9–11, and 13–16[a]



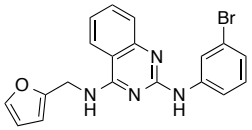
[a]Reagents and conditions: (a) Furan-2-ylmethanamine, Et_3N, THF, 60 °C. (b) Aromatic amine, DMF, 160 °C μW. (c) Aromatic amine, 4 M HCl in dioxane, *i*-PrOH, 180 °C μW. (d) EtI or AcCl, NaH, DMF, 0 to 23 °C.

2-Chloro-*N*-(furan-2-ylmethyl)quinazolin-4-amine (44)



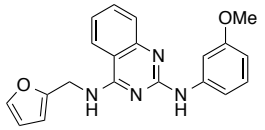
To a solution of 2,4-dichloroquinazoline **43** (2.00 g, 10.0 mmol, 1.00 equiv) in THF (33 mL) were added Et_3N (1.75 mL, 1.27 g, 12.6 mmol, 1.25 equiv) and furan-2-ylmethanamine (0.932 mL, 1.03 g, 10.6 mmol, 1.05 equiv). The resulting mixture was heated to 60 °C and the progress of the reaction was monitored by LC-MS analysis. When the starting material had been completely consumed, the mixture was allowed to cool to room temperature and concentrated in vacuo. The residue was partitioned between EtOAc (100 mL) and saturated aqueous NH_4Cl (100 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2 x 50 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residual solid was purified by silica gel chromatography to provide 2-chloro-*N*-(furan-2-ylmethyl)quinazolin-4-amine **44** (2.38 g, 9.17 mmol, 91% yield). White solid. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.82 (d, J = 8.5 Hz, 1H), 7.76–7.73 (comp, 2H), 7.49–7.44 (m, 1H), 7.41 (s, 1H), 6.40 (d, J = 3.0 Hz, 1H), 6.37 (dd, J = 2.8, 1.8 Hz, 1H), 4.88 (d, J = 5.2 Hz, 2H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{11}ClN_3O$ 260.1; found 260.1. LC-MS ^{t}R (UV 214): 1.423 min. Characterization data for this compound were in good agreement with the data previously reported.[1]

N^2-(3-Bromophenyl)-N^4-(furan-2-ylmethyl)quinazoline-2,4-diamine (4)



To a microwave vial were added **44** (25.0 mg, 0.0963 mmol, 1.00 equiv), 3-bromoaniline (33.1 mg, 0.193 mmol, 2.00 equiv), and DMF (1.0 mL). The resulting mixture was heated to 160 °C in a microwave reactor for 30 min, after which time the mixture was concentrated in vacuo. The residue was purified by reversed-phase preparative HPLC. The title compound was obtained as its corresponding TFA salt (19.3 mg, 0.0379 mmol, 39% yield). Tan solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.17 (d, J = 8.2 Hz, 1H), 7.93 (t, J = 1.7 Hz, 1H), 7.85 (t, J = 7.8 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.51–7.43 (comp, 4H), 7.36 (t, J = 8.0 Hz, 1H), 6.36 (dd, J = 3.0, 2.0 Hz, 1H), 6.28 (d, J = 3.0 Hz, 1H), 4.86 (s, 2H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{16}BrN_4O$ 395.1 (^{79}Br) and 397.1 (^{81}Br); found 394.9 (^{79}Br) and 396.9 (^{81}Br). LC-MS ^{t}R (UV 214): 1.417 min.

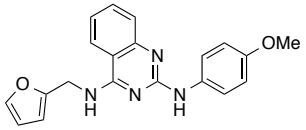
N^4-(Furan-2-ylmethyl)-N^2-(3-methoxyphenyl)quinazoline-2,4-diamine (5)



The title compound was obtained as its corresponding TFA salt from **44** and 3-methoxyaniline using a procedure similar to that described for the synthesis of **4** (67% yield). Tan solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.16 (d, J = 8.2 Hz, 1H), 7.83 (t, J = 7.9 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.50–7.46 (comp, 2H), 7.37 (t, J = 8.2 Hz, 1H), 7.19 (t, J = 1.8 Hz, 1H), 7.08 (dd, J = 8.0, 1.9 Hz, 1H), 6.90 (dd, J = 8.4, 2.3 Hz, 1H),

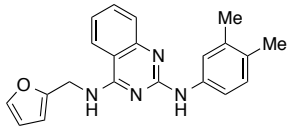
6.36 (dd, J = 3.1, 2.0 Hz, 1H), 6.31 (d, J = 3.1 Hz, 1H), 4.87 (s, 2H), 3.81 (s, 3H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{19}N_4O_2$ 347.2; found 347.1. LC-MS ^{t}R (UV 214): 1.279 min.

N^4-(Furan-2-ylmethyl)-N^2-(4-methoxyphenyl)quinazoline-2,4-diamine (9)



The title compound was obtained as its corresponding TFA salt from **44** and 4-methoxyaniline using a procedure similar to that described for the synthesis of **4** (37% yield). Tan solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.14 (d, J = 8.2 Hz, 1H), 7.80 (t, J = 7.8 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 7.47–7.39 (comp, 4H), 7.03 (d, J = 8.8 Hz, 2H), 6.36 (dd, J = 3.0, 1.9 Hz, 1H), 6.26 (br s, 1H), 4.83 (s, 2H), 3.85 (s, 3H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{19}N_4O_2$ 347.2; found 347.1. LC-MS ^{t}R (UV 214): 1.240 min.

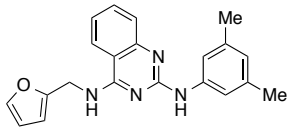
N^2-(3,4-Dimethylphenyl)-N^4-(furan-2-ylmethyl)quinazoline-2,4-diamine (10)



The title compound was obtained as its corresponding TFA salt from **44** and 3,4-dimethylaniline using a procedure similar to that described for the synthesis of **4** (43% yield). Tan solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.14 (d, J = 8.2 Hz, 1H), 7.81 (t, J = 7.8 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.48–7.44 (comp, 2H), 7.32 (s, 1H), 7.22 (s, 2H), 6.36 (dd, J = 3.0, 2.0 Hz, 1H), 6.27 (br s, 1H), 2.31 (s, 3H), 2.30 (s, 3H). LRMS (ESI)

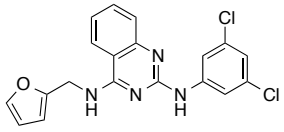
m/z: $[M+H]^+$ calcd for $C_{21}H_{21}N_4O$ 345.2; found 345.1. LC-MS ^{t}R (UV 214 nm): 1.411 min.

N^2-(3,5-Dimethylphenyl)-N^4-(furan-2-ylmethyl)quinazoline-2,4-diamine (11)



The title compound was obtained as its corresponding TFA salt from **44** and 3,5-dimethylaniline using a procedure similar to that described for the synthesis of **4** (54% yield). White solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.14 (d, J = 8.1 Hz, 1H), 7.82 (t, J = 7.8 Hz, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.49–7.45 (comp, 2H), 7.17 (s, 2H), 6.98 (s, 1H), 6.36 (dd, J = 3.1, 2.1 Hz, 1H), 6.28 (br d, J = 2.9 Hz, 1H), 4.87 (s, 2H), 2.33 (s, 6H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{21}N_4O$ 345.2; found 345.1. LC-MS ^{t}R (UV 214): 1.442 min.

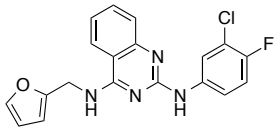
N^2-(3,5-Dichlorophenyl)-N^4-(furan-2-ylmethyl)quinazoline-2,4-diamine (13)



To a microwave vial were added **44** (50.0 mg, 0.193 mmol, 1.00 equiv), 3,5-dichloroaniline (46.8 mg, 0.289 mmol, 1.50 equiv), 2-propanol (0.48 mL), and 4 M HCl in dioxane (3 drops). The resulting mixture was heated to 180 °C for 30 min in a microwave reactor, after which time the mixture was concentrated in vacuo. The residue was purified by reversed-phase preparative HPLC. The title compound was obtained as its corresponding TFA salt (26.0 mg, 0.0521 mmol, 27% yield). Tan solid. ^{1}H NMR (400

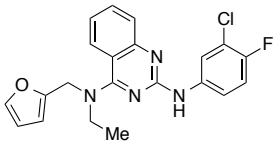
MHz, CD_3OD, δ): 8.18 (d, *J* = 8.3 Hz, 1H), 7.89–7.85 (m, 1H), 7.70 (d, *J* = 1.8 Hz, 2H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.53–7.49 (m, 1H), 7.47 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.33 (t, *J* = 1.7 Hz, 1H), 6.37 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.32 (br d, *J* = 3.2 Hz, 1H), 4.88 (s, 2H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{15}Cl_2N_4O$ 385.1; found 384.9. LC-MS ^{t}R (UV 214): 1.536 min.

N^2-(3-Chloro-4-fluorophenyl)-N^4-(furan-2-ylmethyl)quinazoline-2,4-diamine (14)



The title compound was obtained as its corresponding TFA salt from **44** and 3-chloro-4-fluoroaniline using a procedure similar to that described for the synthesis of **13** (43% yield). Tan solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.17 (d, *J* = 8.4 Hz, 1H), 7.87–7.82 (comp, 2H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.52–7.45 (comp, 3H), 7.33 (t, *J* = 8.8 Hz, 1H), 6.37 (dd, *J* = 3.2, 2.0 Hz, 1H), 6.27 (d, *J* = 2.6 Hz, 1H), 4.84 (s, 2H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{15}ClFN_4O$ 369.1; found 369.0. LC-MS ^{t}R (UV 214): 1.378 min.

N^2-(3-Chloro-4-fluorophenyl)-N^4-ethyl-N^4-(furan-2-ylmethyl)quinazoline-2,4-diamine (15)

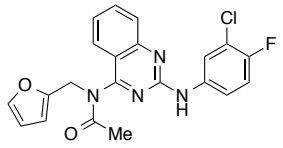


STEP 1: A solution of **44** (50.0 mg, 0.193 mmol, 1.00 equiv) in DMF (2.0 mL) was stirred at room temperature. Next, NaH (60% dispersion in mineral oil) (8.5 mg, 0.21 mmol, 1.10 equiv) was added. The mixture was allowed to stir for 10 min and then

iodoethane (0.019 mL, 36 mg, 0.23 mmol, 1.20 equiv) was added. The progress of the reaction was monitored by LC-MS analysis. When the starting material had been completely consumed, the reaction mixture was diluted with H_2O (25 mL) and extracted with CH_2Cl_2 (25 mL). The resulting mixture was passed through a phase separator and concentrated in vacuo. The product 2-chloro-*N*-ethyl-*N*-(furan-2-ylmethyl)quinazolin-4-amine **45** was used without further purification.

STEP 2: To a microwave vial were added **45** (theoretically 0.193 mmol, 1.00 equiv), 3-chloro-4-fluoroaniline (56.1 mg, 0.385 mmol, 2.00 equiv), and DMF (2.0 mL). The resulting mixture was heated to 160 °C in a microwave reactor for 30 min, after which time the mixture was concentrated in vacuo. The residue was purified by reversed-phase preparative HPLC. The title compound was obtained as its corresponding TFA salt (15.1 mg, 0.0296 mmol, 15% yield over two steps). Tan solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.22 (d, J = 8.5 Hz, 1H), 7.86–7.81 (comp, 2H), 7.59 (d, J = 8.2 Hz, 1H), 7.55 (s, 1H), 7.48–7.40 (comp, 2H), 7.29 (t, J = 8.8 Hz, 1H), 6.45–6.43 (m, 1H), 6.41 (br s, 1H), 5.07 (s, 2H), 3.92 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{19}ClFN_4O$ 397.1; found 397.0. LC-MS ^{t}R (UV 214): 1.575 min.

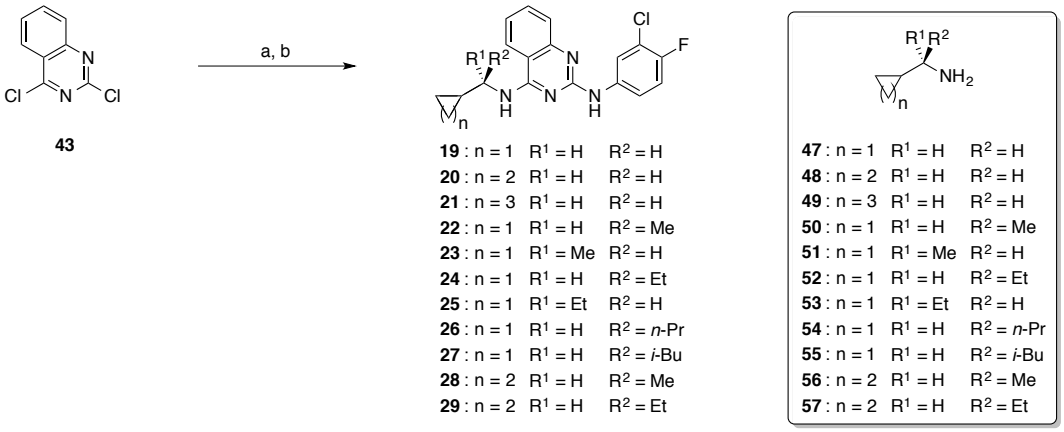
_N_-(2-((3-Chloro-4-fluorophenyl)amino)quinazolin-4-yl)-_N_-(furan-2-ylmethyl)acetamide (16)



The title compound was obtained as its corresponding TFA salt from **44**, acetyl chloride, and 3-chloro-4-fluoroaniline using a procedure similar to that described for the synthesis

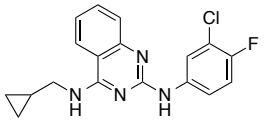
of **15** (8% yield over two steps). Tan solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.20 (dd, *J* = 6.7, 2.7 Hz, 1H), 7.81–7.72 (comp, 3H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.34–7.29 (comp, 2H), 7.20 (t, *J* = 9.0 Hz, 1H), 6.21 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.19 (d, *J* = 3.2 Hz, 1H), 5.14 (s, 2H), 2.00 (s, 3H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{17}ClFN_4O_2$ 411.1; found 411.0. LC-MS ^{t}R (UV 214): 1.857 min.

Scheme S2. Preparation of Compounds 19–29[a]



[a]Reagents and conditions: (a) **47**–**57**, Et_3N, THF, 60 °C. (b) 3-Chloro-4-fluoroaniline, 4 M HCl in dioxane, EtOH, 120 °C μW.

N^2-(3-Chloro-4-fluorophenyl)-*N*^{4}-(cyclopropylmethyl)quinazoline-2,4-diamine (19)

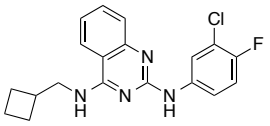


STEP 1: To a solution of 2,4-dichloroquinazoline **43** (250 mg, 1.26 mmol, 1.00 equiv) in THF (4.2 mL) were added Et_3N (0.219 mL, 159 mg, 1.57 mmol, 1.25 equiv) and cyclopropylmethanamine **47** (0.113 mL, 93.8 mg, 1.32 mmol, 1.05 equiv). The resulting mixture was heated to 60 °C and the progress of the reaction was monitored by LC-MS

analysis. When the starting material had been completely consumed, the mixture was allowed to cool to room temperature and concentrated in vacuo. The residue was partitioned between EtOAc (25 mL) and saturated aqueous NH_4Cl (25 mL). The layers were separated and the aqueous phase was extracted with EtOAc (2 x 10 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography to provide 2-chloro-*N*-(cyclopropylmethyl)quinazolin-4-amine (259 mg, 1.11 mmol, 88% yield). White solid. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.78–7.71 (comp, 3H), 7.48–7.44 (m, 1H), 6.10 (br s, 1H), 3.52 (dd, *J* = 7.2, 5.1 Hz, 2H), 1.21–1.14 (m, 1H), 0.65–0.60 (m, 2H), 0.38–0.34 (m, 2H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{12}H_{13}ClN_3$ 234.1; found 234.1. LC-MS ^{t}R (UV 214): 1.401 min.

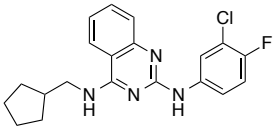
STEP 2: To a microwave vial were added 2-chloro-*N*-(cyclopropylmethyl)quinazolin-4-amine (30.0 mg, 0.128 mmol, 1.00 equiv), 3-chloro-4-fluoroaniline (37.4 mg, 0.257 mmol, 2.00 equiv), 4 M HCl in dioxane (0.032 mL, 0.13 mmol, 1.00 equiv), and EtOH (0.64 mL). The resulting mixture was heated to 120 °C in a microwave reactor for 30 min, after which time the mixture was concentrated in vacuo. The residue was purified by reversed-phase preparative HPLC. The title compound was obtained as its corresponding TFA salt (43.0 mg, 0.0941 mmol, 73% yield). White solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.19 (d, *J* = 8.4 Hz, 1H), 7.91 (dd, *J* = 6.5, 2.5 Hz, 1H), 7.86–7.82 (m, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.52–7.48 (m, 1H), 7.44 (ddd, *J* = 8.8, 4.2, 2.7 Hz, 1H), 7.32 (t, *J* = 8.9 Hz, 1H), 3.53 (d, *J* = 7.1 Hz, 2H), 1.31–1.21 (m, 1H), 0.61–0.56 (m, 2H), 0.35–0.31 (m, 2H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{18}H_{17}ClFN_4$ 343.1; found 343.0. LC-MS ^{t}R (UV 214): 1.420 min.

N^2-(3-Chloro-4-fluorophenyl)-N^4-(cyclobutylmethyl)quinazoline-2,4-diamine (20)



The title compound was obtained as its corresponding TFA salt from 2,4-dichloroquinazoline **43**, cyclobutylmethanamine **48**, and 3-chloro-4-fluoroaniline using a procedure similar to that described for the synthesis of **19** (36% yield over two steps). White solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.14 (dd, J = 8.3, 0.8 Hz, 1H), 7.93 (dd, J = 6.7, 2.6 Hz, 1H), 7.83 (ddd, J = 8.3, 7.3, 1.3 Hz, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.48 (ddd, J = 8.2, 7.3, 1.1 Hz, 1H), 7.46–7.42 (m, 1H), 7.33 (t, J = 8.8 Hz, 1H), 3.70 (d, J = 7.4 Hz, 2H), 2.84–2.73 (m, 1H), 2.16–2.08 (m, 2H), 1.98–1.88 (m, 2H), 1.87–1.77 (m, 2H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{19}ClFN_4$ 357.1; found 357.0. LC-MS ^{t}R (UV 214): 1.641 min.

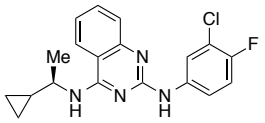
N^2-(3-Chloro-4-fluorophenyl)-N^4-(cyclopentylmethyl)quinazoline-2,4-diamine (21)



The title compound was obtained as its corresponding TFA salt from 2,4-dichloroquinazoline **43**, cyclopentylmethanamine **49** HCl salt, and 3-chloro-4-fluoroaniline using a procedure similar to that described for the synthesis of **19** (39% yield over two steps). White solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.16 (d, J = 8.4 Hz, 1H), 7.88 (dd, J = 6.6, 2.5 Hz, 1H), 7.84 (td, J = 7.7, 1.2 Hz, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.49 (td, J = 7.7, 0.9 Hz, 1H), 7.44 (ddd, J = 9.0, 4.0, 2.6 Hz, 1H), 7.33 (t, J = 8.9

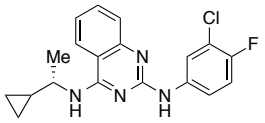
Hz, 1H), 3.59 (d, *J* = 7.6 Hz, 2H), 2.43–2.32 (m, 1H), 1.83–1.75 (m, 2H), 1.70–1.54 (m, 4H), 1.36–1.30 (m, 2H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{21}ClFN_4$ 371.1; found 371.1. LC-MS ^{t}R (UV 214): 1.864 min.

(*R*)-*N*^{2}-(3-Chloro-4-fluorophenyl)-*N*^{4}-(1-cyclopropylethyl)quinazoline-2,4-diamine (22)



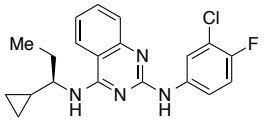
The title compound was obtained as its corresponding TFA salt from 2,4-dichloroquinazoline **43**, (*R*)-1-cyclopropylethan-1-amine **50**, and 3-chloro-4-fluoroaniline using a procedure similar to that described for the synthesis of **19** (67% yield over two steps). White solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.27 (d, *J* = 8.2 Hz, 1H), 7.85–7.82 (comp, 2H), 7.53 (d, *J* = 8.6 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.40–7.36 (m, 1H), 7.33 (t, *J* = 8.7 Hz, 1H), 3.83 (dq, *J* = 8.0, 6.7 Hz, 1H), 1.42 (d, *J* = 6.7 Hz, 3H), 1.21–1.13 (m, 1H), 0.68–0.62 (m, 1H), 0.57–0.49 (m, 1H), 0.38–0.32 (m, 1H), 0.32–0.26 (m, 1H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{19}ClFN_4$ 357.1; found 357.0. LC-MS ^{t}R (UV 214): 1.543 min.

(*S*)-*N*^{2}-(3-Chloro-4-fluorophenyl)-*N*^{4}-(1-cyclopropylethyl)quinazoline-2,4-diamine (23)



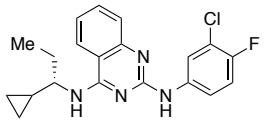
The title compound was obtained as its corresponding TFA salt from 2,4-dichloroquinazoline **43**, (*S*)-1-cyclopropylethan-1-amine **51**, and 3-chloro-4-fluoroaniline using a procedure similar to that described for the synthesis of **19** (69% yield over two steps). White solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.27 (d, *J* = 8.2 Hz, 1H), 7.86–7.82 (comp, 2H), 7.53 (d, *J* = 8.4 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.40–7.36 (m, 1H), 7.32 (t, *J* = 8.7 Hz, 1H), 3.83 (dq, *J* = 8.0, 6.7 Hz, 1H), 1.42 (d, *J* = 6.7 Hz, 3H), 1.22–1.13 (m, 1H), 0.68–0.62 (m, 1H), 0.58–0.49 (m, 1H), 0.38–0.32 (m, 1H), 0.32–0.26 (m, 1H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{19}ClFN_4$ 357.1; found 357.0. LC-MS ^{t}R (UV 214): 1.539 min.

(*R*)-N^2-(3-Chloro-4-fluorophenyl)-N^4-(1-cyclopropylpropyl)quinazoline-2,4-diamine (24)



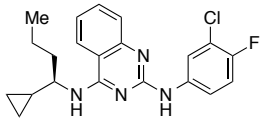
The title compound was obtained as its corresponding TFA salt from 2,4-dichloroquinazoline **43**, (*R*)-1-cyclopropylpropan-1-amine **52** HCl salt, and 3-chloro-4-fluoroaniline using a procedure similar to that described for the synthesis of **19** (49% yield over two steps). White solid. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.97 (dd, *J* = 6.6, 2.6 Hz, 1H), 7.74–7.68 (comp, 3H), 7.40–7.34 (comp, 2H), 7.10 (t, *J* = 8.7 Hz, 1H), 6.55 (d, *J* = 8.0 Hz, 1H), 3.70–3.62 (m, 1H), 1.92–1.81 (comp, 2H), 1.05 (t, *J* = 7.5 Hz, 3H), 1.06–0.99 (m, 1H), 0.78–0.71 (m, 1H), 0.56–0.51 (m, 1H), 0.51–0.43 (m, 1H), 0.35–0.29 (m, 1H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{21}ClFN_4$ 371.1; found 371.1. LC-MS ^{t}R (UV 214 nm): 1.542 min.

(*S*)-N^2-(3-Chloro-4-fluorophenyl)-N^4-(1-cyclopropylpropyl)quinazoline-2,4-diamine (25)



The title compound was obtained as its corresponding TFA salt from 2,4-dichloroquinazoline **43**, (*S*)-1-cyclopropylpropan-1-amine **53** HCl salt, and 3-chloro-4-fluoroaniline using a procedure similar to that described for the synthesis of **19** (45% yield over two steps). White solid. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.97 (dd, J = 6.6, 2.6 Hz, 1H), 7.75–7.68 (comp, 3H), 7.40–7.34 (comp, 2H), 7.11 (t, J = 8.7 Hz, 1H), 6.53 (d, J = 8.0 Hz, 1H), 3.70–3.62 (m, 1H), 1.92–1.81 (comp, 2H), 1.05 (t, J = 7.5 Hz, 3H), 1.06–0.99 (m, 1H), 0.78–0.71 (m, 1H), 0.56–0.51 (m, 1H), 0.50–0.43 (m, 1H), 0.35–0.29 (m, 1H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{21}ClFN_4$ 371.1; found 371.1. LC-MS ^{t}R (UV 214): 1.535 min.

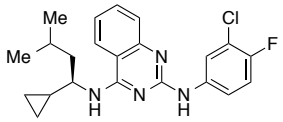
(*R*)-N^2-(3-Chloro-4-fluorophenyl)-N^4-(1-cyclopropylbutyl)quinazoline-2,4-diamine (26)



The title compound was obtained as its corresponding TFA salt from 2,4-dichloroquinazoline **43**, (*R*)-1-cyclopropylbutan-1-amine **54** HCl salt, and 3-chloro-4-fluoroaniline using a procedure similar to that described for the synthesis of **19** (29% yield over two steps). White solid. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.95 (dd, J = 6.6, 2.6

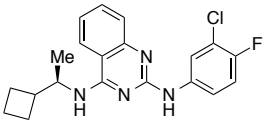
Hz, 1H), 7.73–7.66 (comp, 3H), 7.39–7.34 (comp, 2H), 7.10 (t, *J* = 8.7 Hz, 1H), 6.58 (d, *J* = 8.4 Hz, 1H), 3.81–3.73 (m, 1H), 1.85–1.74 (comp, 2H), 1.51–1.42 (comp, 2H), 1.07–0.98 (m, 1H), 0.91 (t, *J* = 7.3 Hz, 3H), 0.75–0.68 (m, 1H), 0.54–0.49 (m, 1H), 0.48–0.41 (m, 1H), 0.36–0.30 (m, 1H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{23}ClFN_4$ 385.2; found 385.0. LC-MS ^{t}R (UV 214): 1.606 min.

(*R*)-N^2-(3-Chloro-4-fluorophenyl)-N^4-(1-cyclopropyl-3-methylbutyl)quinazoline-2,4-diamine (27)



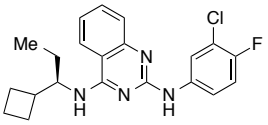
The title compound was obtained as its corresponding TFA salt from 2,4-dichloroquinazoline **43**, (*R*)-1-cyclopropyl-3-methylbutan-1-amine **55** HCl salt, and 3-chloro-4-fluoroaniline using a procedure similar to that described for the synthesis of **19** (35% yield over two steps). White solid. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.91 (dd, *J* = 6.6, 2.6 Hz, 1H), 7.72–7.66 (comp, 3H), 7.39–7.32 (comp, 2H), 7.09 (t, *J* = 8.7 Hz, 1H), 6.54 (d, *J* = 8.9 Hz, 1H), 4.01–3.93 (m, 1H), 1.73–1.66 (comp, 4H), 1.02–0.96 (m, 1H), 0.90 (d, *J* = 6.0 Hz, 3H), 0.84 (d, *J* = 6.0 Hz, 3H), 0.70–0.64 (m, 1H), 0.50–0.35 (comp, 3H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{25}ClFN_4$ 399.2; found 399.1. LC-MS ^{t}R (UV 214): 1.649 min.

(*R*)-N^2-(3-Chloro-4-fluorophenyl)-N^4-(1-cyclobutylethyl)quinazoline-2,4-diamine (28)



The title compound was obtained as its corresponding TFA salt from 2,4-dichloroquinazoline **43**, (*R*)-1-cyclobutylethan-1-amine **56** HCl salt, and 3-chloro-4-fluoroaniline using a procedure similar to that described for the synthesis of **19** (45% yield over two steps). White solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.24 (dd, *J* = 8.3, 0.8 Hz, 1H), 7.96 (dd, *J* = 6.6, 2.6 Hz, 1H), 7.84 (ddd, *J* = 8.4, 7.3, 1.3 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.48 (ddd, *J* = 8.3, 7.3, 1.1 Hz, 1H), 7.44–7.40 (m, 1H), 7.35 (t, *J* = 8.8 Hz, 1H), 4.56–4.49 (m, 1H), 2.67–2.56 (m, 1H), 2.18–2.10 (m, 1H), 2.07–2.00 (m, 1H), 1.95–1.88 (m, 1H), 1.86–1.76 (comp, 3H), 1.23 (d, *J* = 6.6 Hz, 3H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{21}ClFN_4$ 371.1; found 371.0. LC-MS ^{t}R (UV 214): 1.663 min.

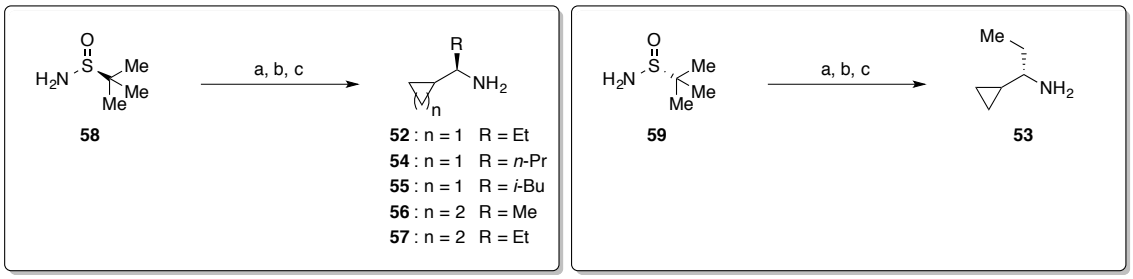
(*R*)-N^2-(3-Chloro-4-fluorophenyl)-N^4-(1-cyclobutylpropyl)quinazoline-2,4-diamine (29)



The title compound was obtained as its corresponding TFA salt from 2,4-dichloroquinazoline **43**, (*R*)-1-cyclobutylpropan-1-amine **57** HCl salt, and 3-chloro-4-fluoroaniline using a procedure similar to that described for the synthesis of **19** (31% yield over two steps). White solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.26 (dd, *J* = 8.3, 0.7 Hz, 1H), 7.96 (dd, *J* = 6.6, 2.5 Hz, 1H), 7.84 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.49 (ddd, *J* = 8.3, 7.2, 1.1 Hz, 1H), 7.44–7.40 (m, 1H), 7.35 (t, *J* = 8.7 Hz, 1H), 4.44 (td, *J* = 9.5, 4.1 Hz, 1H), 2.66–2.58 (m, 1H), 2.17–2.09 (m, 1H), 2.03–1.96 (m,

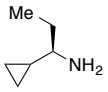
1H), 1.95–1.88 (m, 1H), 1.85–1.68 (comp, 4H), 1.59–1.48 (m, 1H), 0.91 (t, J = 7.5 Hz, 3H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{23}ClFN_4$ 385.2; found 385.0. LC-MS ^tR (UV 214): 1.699 min.

Scheme S3. Preparation of Amines 52–57 Used for the Synthesis of Compounds 24–29[a]



(a) Cycloalkylcarboxaldehyde, $Ti(OEt)_4$, THF. (b) RMgX, CH_2Cl_2, −61 to 23 °C. (c) 4 M HCl in dioxane, MeOH.

(*R*)-1-Cyclopropylpropan-1-amine (52)



STEP 1: According to the procedure reported by Ellman and coworkers,[2] $Ti(OEt)_4$ (6.92 mL, 7.53 g, 33.0 mmol, 2.00 equiv) and cyclopropanecarboxaldehyde (1.36 mL, 1.27 g, 18.2 mmol, 1.10 equiv) were dissolved in THF (33 mL). The resulting mixture was stirred at room temperature and (*S*)-(−)-2-methyl-2-propanesulfinamide **58** (2.00 g, 16.5 mmol, 1.00 equiv) was added. After 4 h, the reaction mixture was poured into brine and the resulting mixture was filtered over diatomaceous earth with the aid of CH_2Cl_2. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (100 mL). The

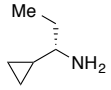
organic layers were combined, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography to provide (*S*)-*N*-(cyclopropylmethylene)-2-methylpropane-2-sulfinamide (2.65 g, 15.3 mmol, 93% yield). Clear oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.46 (d, *J* = 8.0 Hz, 1H), 2.03–1.94 (m, 1H), 1.19 (s, 9H), 1.11–1.07 (comp, 2H), 0.96–0.94 (comp, 2H). Characterization data for this compound were in good agreement with the data previously reported.[3]

STEP 2: According to the procedure reported by Ellman and coworkers,[4] (*S*)-*N*-(cyclopropylmethylene)-2-methylpropane-2-sulfinamide (1.04 g, 6.00 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (35 mL). The solution was cooled to –61 °C and ethylmagnesium bromide (3 M in Et_2O) (4.00 mL, 12.0 mmol, 2.00 equiv) was added. The resulting mixture was stirred at –61 °C for 2 h and then allowed to warm to room temperature. After an additional 18 h, the reaction was quenched with saturated aqueous NH_4Cl (200 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated in vacuo. The resulting diastereomeric mixture was separated by silica gel chromatography to give (*S*)-*N*-((*R*)-1-cyclopropylpropyl)-2-methylpropane-2-sulfinamide (1.08 g, 5.33 mmol, 89% yield). White solid. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 3.11 (br s, 1H), 2.51–2.45 (m, 1H), 1.74–1.66 (comp, 2H), 1.22 (s, 9H), 1.01 (t, *J* = 7.5 Hz, 3H), 0.83–0.74 (m, 1H), 0.59–0.48 (comp, 2H), 0.38–0.33 (m, 1H), 0.23–0.18 (m, 1H).

STEP 3: To a flask containing (*S*)-*N*-((*R*)-1-cyclopropylpropyl)-2-methylpropane-2-sulfinamide (1.08 g, 5.33 mmol, 1.00 equiv) were added MeOH (2.7 mL) and 4 M HCl in dioxane (2.66 mL, 10.7 mmol, 2.00 equiv). The resulting mixture was stirred at room temperature for 30 min and then concentrated to near dryness. The residue was diluted

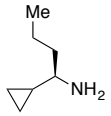
with Et_2O to precipitate the amine HCl salt, which was collected by filtration. The solid was washed with Et_2O/hexanes (1:1 v/v) and then dried in vacuo to give (*R*)-1-cyclopropylpropan-1-amine **52** as its corresponding HCl salt (667 mg, 4.92 mmol, 92% yield). White solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 2.34 (dt, *J* = 10.0, 6.8 Hz, 1H), 1.79 (quint, *J* = 7.3 Hz, 2H), 1.08 (t, *J* = 7.5 Hz, 3H), 0.95–0.87 (m, 1H), 0.77–0.72 (m, 1H), 0.67–0.62 (m, 1H), 0.45–0.38 (comp, 2H).

(*S*)-1-Cyclopropylpropan-1-amine (53)



The title compound was obtained as its corresponding HCl salt from (*R*)-(+)-2-methylpropane-2-sulfinamide **59**, cyclopropanecarboxaldehyde, and ethylmagnesium bromide using a procedure similar to that described for the synthesis of **52** (55% yield over three steps). White solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 2.34 (dt, *J* = 10.0, 6.8 Hz, 1H), 1.79 (quint, *J* = 7.3 Hz, 2H), 1.08 (t, *J* = 7.5 Hz, 3H), 0.96–0.87 (m, 1H), 0.77–0.72 (m, 1H), 0.68–0.63 (m, 1H), 0.45–0.38 (comp, 2H).

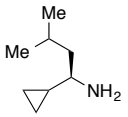
(*R*)-1-Cyclopropylbutan-1-amine (54)



The title compound was obtained as its corresponding HCl salt from (*S*)-(–)-2-methyl-2-propanesulfinamide **58**, cyclopropanecarboxaldehyde, and propylmagnesium chloride using a procedure similar to that described for the synthesis of **52** (61% yield over three steps). White solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 2.41 (dt, *J* = 10.0, 6.8 Hz, 1H),

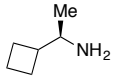
1.76–1.70 (comp, 2H), 1.59–1.44 (comp, 2H), 0.99 (t, J = 7.3 Hz, 3H), 0.95–0.87 (m, 1H), 0.76–0.70 (m, 1H), 0.68–0.63 (m, 1H), 0.45–0.37 (comp, 2H).

(*R*)-1-Cyclopropyl-3-methylbutan-1-amine (55)



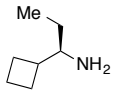
The title compound was obtained as its corresponding HCl salt from (*S*)-(–)-2-methyl-2-propanesulfinamide **58**, cyclopropanecarboxaldehyde, and isobutylmagnesium bromide using a procedure similar to that described for the synthesis of **52** (42% yield over three steps). White solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 2.49 (dt, J = 9.9, 7.1 Hz, 1H), 1.92–1.82 (m, 1H), 1.68–1.56 (comp, 2H), 0.98 (d, J = 2.3 Hz, 3H), 0.96 (d, J = 2.3 Hz, 3H), 0.94–0.86 (m, 1H), 0.78–0.71 (m, 1H), 0.69–0.63 (m, 1H), 0.49–0.38 (comp, 2H).

(*R*)-1-Cyclobutylethan-1-amine (56)



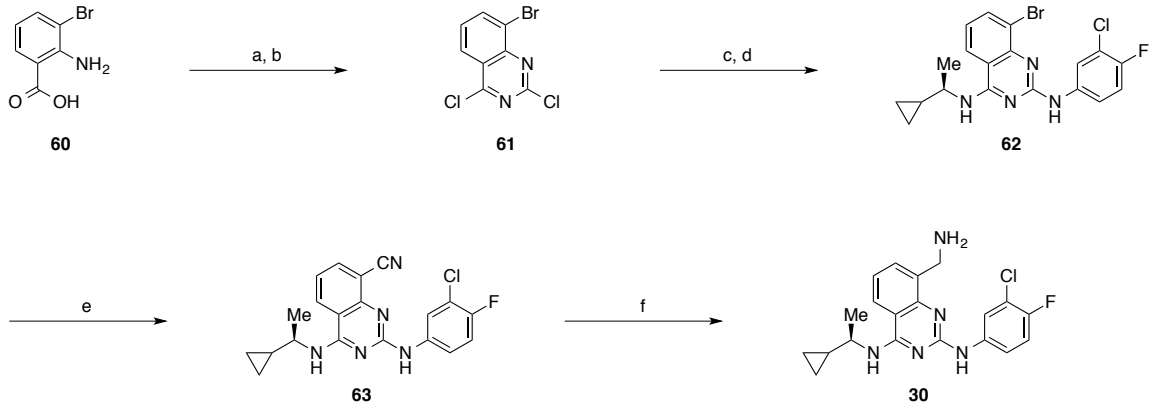
The title compound was obtained as its corresponding HCl salt from (*S*)-(–)-2-methyl-2-propanesulfinamide **58**, cyclobutanecarboxaldehyde, and methylmagnesium bromide using a procedure similar to that described for the synthesis of **52** (53% yield over three steps). White solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 3.20 (dq, J = 9.5, 6.6 Hz, 1H), 2.47–2.37 (m, 1H), 2.15–2.04 (comp, 2H), 2.01–1.78 (comp, 4H), 1.19 (d, J = 6.6 Hz, 3H).

(*R*)-1-Cyclobutylpropan-1-amine (57)



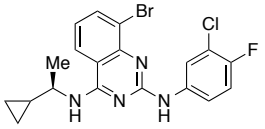
The title compound was obtained as its corresponding HCl salt from (*S*)-(–)-2-methyl-2-propanesulfinamide **58**, cyclobutanecarboxaldehyde, and ethylmagnesium bromide using a procedure similar to that described for the synthesis of **52** (46% yield over three steps). White solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 3.04 (ddd, J = 9.6, 7.2, 5.0 Hz, 1H), 2.55–2.44 (m, 1H), 2.15–2.05 (comp, 2H), 2.01–1.80 (comp, 4H), 1.72–1.61 (m, 1H), 1.56–1.45 (m, 1H), 1.00 (t, J = 7.6 Hz, 3H).

Scheme S4. Preparation of Compound 30[a]



[a]Reagents and conditions: (a) Urea, 160 °C. (b) $POCl_3$, 100 °C. (c) (*R*)-1-Cyclopropylethan-1-amine, *i*-Pr_2NEt, *i*-PrOH, 60 °C. (d) 3-Chloro-4-fluoroaniline, 4 M HCl in dioxane, *i*-PrOH, 180 °C μW. (e) CuCN, NMP, 150 °C. (f) $ZnCl_2$, $LiBH_4$, THF, 60 °C.

(*R*)-8-Bromo-N^2-(3-chloro-4-fluorophenyl)-N^4-(1-cyclopropylethyl)quinazoline-2,4-diamine (62)



STEP 1: A vial containing 2-amino-3-bromobenzoic acid **60** (1.00 g, 4.63 mmol, 1.00 equiv) was heated to 160 °C as urea (2.78 g, 46.3 mmol, 10.00 equiv) was added in portions. After 12 h, more urea (2.78 g, 46.3 mmol, 10.00 equiv) was added in portions. The reaction mixture was stirred for an additional 8 h. The vial was then cooled to 100 °C and H_2O (20 mL) was added. The resulting suspension was stirred for 1 h at 100 °C before being allowed to cool to room temperature. The solid was collected by filtration. The product 8-bromoquinazoline-2,4(1*H*,3*H*)-dione was used without further purification (883 mg, 3.66 mmol, 79% yield). Tan solid. ^{1}H NMR (400 MHz, DMSO-d_6, δ): 10.76 (br s, 2H), 7.93 (d, J = 7.8 Hz, 2H), 7.13 (t, J = 7.8 Hz, 1H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_8H_6BrN_2O_2$ 241.0 (^{79}Br) and 243.0 (^{81}Br); found 241.0 (^{79}Br) and 243.0 (^{81}Br). LC-MS ^{t}R (UV 214): 0.866 min. Characterization data for this compound were in good agreement with the data previously reported.[5-7]

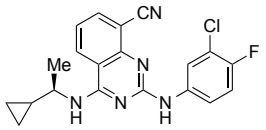
STEP 2: To a flask containing 8-bromoquinazoline-2,4(1*H*,3*H*)-dione (500 mg, 2.07 mmol, 1.00 equiv) was slowly added $POCl_3$ (4.83 mL, 51.9 mmol, 25.00 equiv). The resulting mixture was heated to 100 °C and the progress of the reaction was monitored by TLC analysis (hexanes/EtOAc 2:1 v/v). Upon complete consumption of the starting material, the reaction mixture was cooled to room temperature and transferred in portions to an Erlenmeyer flask containing crushed ice with the aid of CH_2Cl_2. The resulting mixture was stirred for 20 min and then extracted with CH_2Cl_2. The organic phases were combined, washed with saturated aqueous $NaHCO_3$ (3 x 40 mL), brine, dried over Na_2SO_4, and concentrated in vacuo. The crude solid was purified by silica gel

chromatography to provide 8-bromo-2,4-dichloroquinazoline **61** (377 mg, 1.36 mmol, 65% yield). White solid. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.29 (d, J = 7.6 Hz, 1H), 8.26 (d, J = 8.4 Hz, 1H), 7.60 (t, J = 8.1 Hz, 1H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_8H_4BrCl_2N_2$ 276.9 (^{79}Br) and 278.9 (^{81}Br); found 276.9 (^{79}Br) and 278.9 (^{81}Br). LC-MS ^{t}R (UV 214): 1.511 min. Characterization data for this compound were in good agreement with the data previously reported.[5-7]

STEP 3: To a flask containing **61** (4.53 g, 16.3 mmol, 1.00 equiv) was added 2-propanol (55 mL). Next, *i*-Pr_2NEt (3.55 mL, 2.63 g, 20.4 mmol, 1.25 equiv) was added, followed by (*R*)-1-cyclopropylethan-1-amine (1.58 mL, 1.46 g, 17.1 mmol, 1.05 equiv). The resulting mixture was heated to 60 °C and the progress of the reaction was monitored by TLC analysis (hexanes/EtOAc 2:1 v/v). Upon complete consumption of the starting material, the reaction mixture was allowed to cool to room temperature and concentrated in vacuo. The residual oil was dissolved in EtOAc (300 mL) and treated with 50% aqueous NH_4Cl (200 mL). The layers were separated and the aqueous phase was extracted with EtOAc (100 mL). The organic phases were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography to provide (*R*)-8-bromo-2-chloro-*N*-(1-cyclopropylethyl)quinazolin-4-amine (5.12 g, 15.7 mmol, 96% yield). Tan solid. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.02 (d, J = 7.6 Hz, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.29 (t, J = 7.8 Hz, 1H), 5.98 (br d, J = 6.4 Hz, 1H), 3.91–3.82 (m, 1H), 1.37 (d, J = 6.5 Hz, 3H), 1.04–0.95 (m, 1H), 0.64–0.60 (m, 1H), 0.55–0.50 (m, 1H), 0.50–0.44 (m, 1H), 0.40–0.34 (m, 1H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{13}H_{14}BrClN_3$ 326.0 (^{79}Br) and 328.0 (^{81}Br); found 325.9 (^{79}Br) and 327.9 (^{81}Br). LC-MS ^{t}R (UV 214): 1.704 min.

STEP 4: To a flask containing (*R*)-8-bromo-2-chloro-*N*-(1-cyclopropylethyl)quinazolin-4-amine (200 mg, 0.612 mmol, 1.00 equiv) was added 2-propanol (1.5 mL). Next, 3-chloro-4-fluoroaniline (93.6 mg, 0.643 mmol, 1.05 equiv) was added, followed by 4 M HCl in dioxane (3 drops). The resulting mixture was heated to 180 °C for 30 min in a microwave reactor, after which time the mixture was concentrated in vacuo. The residue was purified by reversed-phase preparative HPLC. The title compound was obtained as its free base by washing with a solution of K_2CO_3 (221 mg, 0.507 mmol, 83% yield). White solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.66 (dd, *J* = 6.8, 2.2 Hz, 1H), 8.02 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.91 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.59 (ddd, *J* = 9.4, 3.6, 2.7 Hz, 1H), 7.11 (t, *J* = 9.0 Hz, 1H), 7.07 (dd, *J* = 8.1, 7.7 Hz, 1H), 3.94 (dq, *J* = 9.1, 6.7 Hz, 1H), 1.39 (d, *J* = 6.7 Hz, 3H), 1.18–1.10 (m, 1H), 0.62–0.56 (m, 1H), 0.53–0.47 (m, 1H), 0.45–0.41 (m, 1H), 0.33–0.27 (m, 1H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{19}H_{18}BrClFN_4$ 435.0 (^{79}Br) and 437.0 (^{81}Br); found 434.8 (^{79}Br) and 436.9 (^{81}Br). LC-MS ^{t}R (UV 214): 1.509 min.

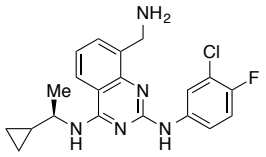
(*R*)-2-((3-Chloro-4-fluorophenyl)amino)-4-((1-cyclopropylethyl)amino)quinazoline-8-carbonitrile (63)



To a vial were added **62** (500 mg, 1.15 mmol, 1.00 equiv), copper(I) cyanide (617 mg, 6.89 mmol, 6.00 equiv), and NMP (3.8 mL). The resulting mixture was heated to 150 °C and the progress of the reaction was monitored by LC-MS analysis. Upon complete consumption of the starting material, the mixture was allowed to cool to room

temperature, whereupon EtOAc (50 mL) and saturated aqueous NH_4Cl/NH_4OH (9:1 v/v) (50 mL) were added. The resulting biphasic mixture was stirred vigorously for 30 min before being filtered over a plug of cotton. The layers of the filtrate were separated and the aqueous phase was extracted with EtOAc (2 x 25 mL). The organic phases were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel chromatography to provide **63** (396 mg, 1.04 mmol, 90% yield). Tan solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.35 (dd, *J* = 6.9, 2.7 Hz, 1H), 8.29 (d, *J* = 8.2 Hz, 1H), 7.97 (d, *J* = 7.5 Hz, 1H), 7.69 (br s, 1H), 7.23 (dd, *J* = 8.0, 7.5 Hz, 1H), 7.12 (t, *J* = 9.0 Hz, 1H), 3.93 (dq, *J* = 9.0, 6.9 Hz, 1H), 1.40 (d, *J* = 6.7 Hz, 3H), 1.18–1.10 (m, 1H), 0.64–0.57 (m, 1H), 0.53–0.48 (m, 1H), 0.46–0.40 (m, 1H), 0.34–0.28 (m, 1H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{18}ClFN_5$ 382.1; found 382.0. LC-MS Ret time (UV 214): 1.488 min.

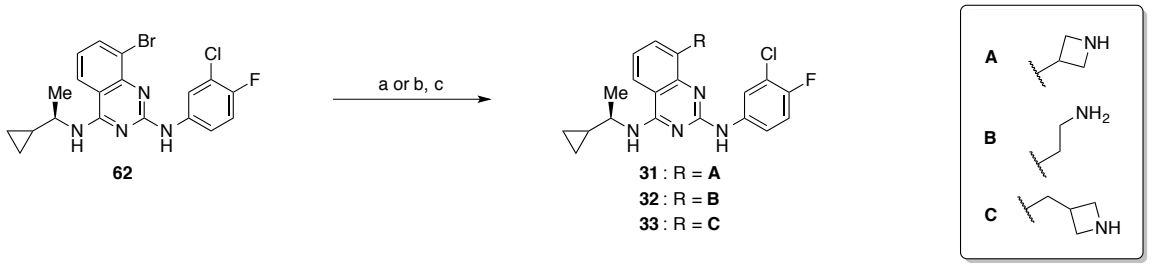
(*R*)-8-(Aminomethyl)-N^2-(3-chloro-4-fluorophenyl)-N^4-(1-cyclopropylethyl)quinazoline-2,4-diamine (30)



To a vial were added zinc(II) chloride (22.4 mg, 0.164 mmol, 1.10 equiv) and THF (0.20 mL). To this suspension was added $LiBH_4$ (2 M in THF) (0.164 mL, 0.328 mmol, 2.20 equiv), and the resulting mixture was heated to 50 °C. After 50 min, a solution of **63** TFA salt—prepared as described for **63**, except that the product was purified by reversed-phase preparative HPLC—(74.0 mg, 0.149 mmol, 1.00 equiv) in THF (0.40 + 0.40 mL) was added. The temperature was increased to 60 °C and the progress of the reaction was

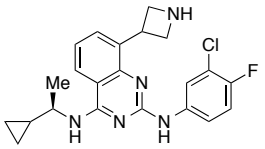
monitored by LC-MS analysis. After 18 h, a second portion of $Zn(BH_4)_2$ (0.0820 mmol)—prepared as above—was added. After an additional 3 h, the reaction mixture was allowed to cool to room temperature and quenched by the slow addition of H_2O (15 mL). When the effervescence had ceased, the mixture was extracted with EtOAc (2 x 20 mL). The organic phases were combined, washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by reversed-phase preparative HPLC. The title compound was obtained as its corresponding TFA salt (37.0 mg, 0.0740 mmol, 50% yield). White Solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.35–8.30 (m, 1H), 8.05–8.02 (m, 1H), 7.91–7.85 (m, 1H), 7.51–7.43 (comp, 2H), 7.26 (t, J = 8.9 Hz, 1H), 4.53 (s, 2H), 3.87–3.84 (m, 1H), 1.44 (d, J = 6.6 Hz, 3H), 1.23–1.19 (m, 1H), 0.68–0.63 (m, 1H), 0.56–0.51 (m, 1H), 0.34–0.29 (comp, 2H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{22}ClFN_5$ 386.2; found 386.1. LC-MS ^{t}R (UV 214): 1.266 min.

Scheme S5. Preparation of Compounds 31–33[a]



[a]Reagents and conditions: (a) Potassium (*N*-Boc-aminoalkyl)trifluoroborate, $Pd(OAc)_2$, RuPhos, Cs_2CO_3, PhMe/H_2O (3:1 v/v), 85 °C. (b) Potassium (*N*-Boc-aminoalkyl)trifluoroborate, $Pd(OAc)_2$, RuPhos, K_3PO_4, DME/H_2O (5:2 v/v), 120 °C. (c) TFA, CH_2Cl_2.

(*R*)-8-(Azetidin-3-yl)-N^2-(3-chloro-4-fluorophenyl)-N^4-(1-cyclopropylethyl)quinazoline-2,4-diamine (31)

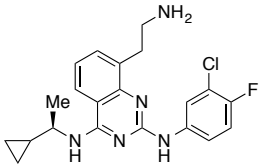


STEP 1: To a vial were added **62** (75.0 mg, 0.172 mmol, 1.00 equiv), potassium (1-(*tert*-butoxycarbonyl)azetidin-3-yl)trifluoroborate (67.9 mg, 0.258 mmol, 1.50 equiv), $Pd(OAc)_2$ (3.9 mg, 0.017 mmol, 0.10 equiv), RuPhos (16.1 mg, 0.0344 mmol, 0.20 equiv) and Cs_2CO_3 (168 mg, 0.516 mmol, 3.00 equiv). The vial was sealed and subsequently evacuated/refilled with N_2. The evacuation/refill cycle was repeated two additional times and then degassed toluene/H_2O (3:1 v/v) (0.86 mL) was added. The reaction mixture was heated to 95 °C. After 72 h, the reaction mixture was allowed to cool to room temperature and diluted with CH_2Cl_2 (5 mL) and saturated aqueous NH_4Cl (5 mL). The resulting biphasic mixture was passed through a phase separator and concentrated in vacuo to give *tert*-butyl (*R*)-3-(2-((3-chloro-4-fluorophenyl)amino)-4-((1-cyclopropylethyl)amino)quinazolin-8-yl)azetidine-1-carboxylate, which was used without further purification.

STEP 2: To a vial containing *tert*-butyl (*R*)-3-(2-((3-chloro-4-fluorophenyl)amino)-4-((1-cyclopropylethyl)amino)quinazolin-8-yl)azetidine-1-carboxylate (theoretically 0.172 mmol) was added CH_2Cl_2 (4.0 mL). Next, TFA (1.0 mL) was added and the resulting mixture was stirred at room temperature. The progress of the reaction was monitored by LC-MS analysis. Upon complete consumption of the starting material, the reaction mixture was concentrated in vacuo and purified by reversed-phase preparative HPLC. The title compound was obtained as its corresponding TFA salt (4.0 mg, 0.0067 mmol,

4% yield over two steps). White solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.25–8.19 (m, 1H), 8.05–7.86 (comp, 2H), 7.53–7.45 (m, 1H), 7.39 (ddd, 8.9, 4.1, 2.7 Hz, 1H), 7.30–7.24 (m, 1H), 4.78–4.68 (m, 1H), 4.63–4.59 (comp, 2H), 4.41–4.37 (comp, 2H), 3.90–3.84 (m, 1H), 1.43 (d, J = 6.6 Hz, 3H), 1.22–1.13 (m, 1H), 0.67–0.61 (m, 1H), 0.55–0.49 (m, 1H), 0.39–0.26 (comp, 2H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{22}H_{24}ClFN_5$ 412.2; found 412.1. LC-MS ^{t}R (UV 214): 1.281 min.

(*R*)-8-(2-Aminoethyl)-*N*^{2}-(3-chloro-4-fluorophenyl)-*N*^{4}-(1-cyclopropylethyl)quinazoline-2,4-diamine (32)

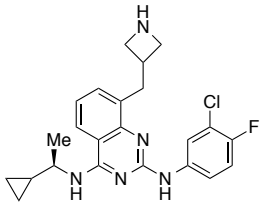


STEP 1: To a vial were added **62** (100 mg, 0.230 mmol, 1.00 equiv), potassium *tert*-butyl *N*-[2-(trifluoroboranuidyl)ethyl]carbamate (86.4 mg, 0.344 mmol, 1.50 equiv), $Pd(OAc)_2$ (7.7 mg, 0.034 mmol, 0.15 equiv), RuPhos (32.1 mg, 0.0689 mmol, 0.30 equiv) and K_3PO_4 (146 mg, 0.689 mmol, 3.00 equiv). The vial was sealed and subsequently evacuated/refilled with N_2. The evacuation/refill cycle was repeated two additional times and then degassed DME/H_2O (5:2 v/v) (0.60 mL) was added. The reaction mixture was heated to 120 °C. After 3 h, more potassium *tert*-butyl *N*-[2-(trifluoroboranuidyl)ethyl]carbamate (86.4 mg, 0.344 mmol), $Pd(OAc)_2$ (7.7 mg, 0.034 mmol), and RuPhos (32.1 mg, 0.0689 mmol) were added. After an additional 17 h, the reaction mixture was allowed to cool to room temperature and diluted with 50% aqueous NH_4Cl (50 mL). The resulting mixture was extracted with EtOAc (3 x 25 mL). The organic phases were combined, washed with brine, dried over Na_2SO_4, and concentrated

in vacuo. The residue was partially purified by silica gel chromatography to give *tert*-butyl (*R*)-(2-(2-((3-chloro-4-fluorophenyl)amino)-4-((1-cyclopropylethyl)amino)quinazolin-8-yl)ethyl)carbamate.

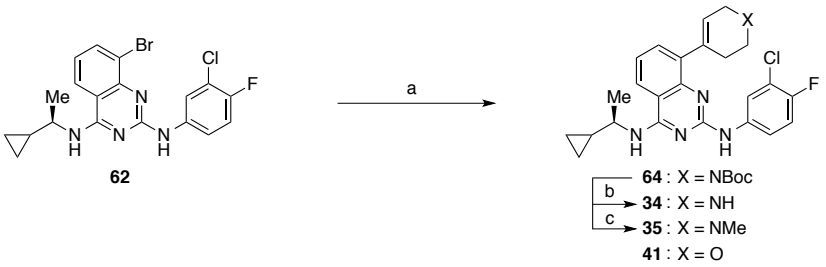
STEP 2: To a vial containing *tert*-butyl (*R*)-(2-(2-((3-chloro-4-fluorophenyl)amino)-4-((1-cyclopropylethyl)amino)quinazolin-8-yl)ethyl)carbamate (theoretically 0.230 mmol) was added CH_2Cl_2 (4.0 mL). Next, TFA (1.0 mL) was added and the resulting mixture was stirred at room temperature. The progress of the reaction was monitored by LC-MS analysis. Upon complete consumption of the starting material, the reaction mixture was concentrated in vacuo and purified by reversed-phase preparative HPLC. The title compound was obtained as its corresponding TFA salt (33.0 mg, 0.0642 mmol, 28% yield over two steps). White solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.24 (d, *J* = 8.4 Hz, 1H), 8.02 (dd, *J* = 6.6, 2.6 Hz, 1H), 7.77 (d, *J* = 6.9 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.42 (ddd, *J* = 9.0, 4.0, 2.7 Hz, 1H), 7.30 (t, *J* = 8.9 Hz, 1H), 3.85 (dq, *J* = 9.1, 6.6 Hz, 1H), 3.35–3.33 (comp, 2H), 3.27–3.22 (comp, 2H), 1.45 (d, *J* = 6.7 Hz, 3H), 1.24–1.15 (m, 1H), 0.69–0.64 (m, 1H), 0.56–0.51 (m, 1H), 0.37–0.29 (comp, 2H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{24}ClFN_5$ 400.2; found 400.2. LC-MS ^{t}R (UV 214): 1.330 min.

(*R*)-8-(Azetidin-3-ylmethyl)-*N*^{2}-(3-chloro-4-fluorophenyl)-*N*^{4}-(1-cyclopropylethyl)quinazoline-2,4-diamine (33)



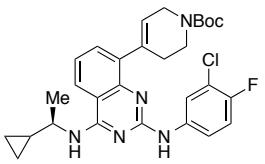
The title compound was obtained as its corresponding TFA salt from **62** and potassium (1-Boc-azetidin-3-yl)methyltrifluoroborate using a procedure similar to that described for the synthesis of **32** (6% yield over two steps). White solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.21 (dd, *J* = 8.2, 1.0 Hz, 1H), 8.00 (dd, *J* = 6.6, 2.6 Hz, 1H), 7.71 (d, *J* = 7.3 Hz, 1H), 7.45 (t, *J* = 7.9 Hz, 1H), 7.42 (ddd, *J* = 8.9, 4.1, 2.7 Hz, 1H), 7.29 (t, *J* = 8.9 Hz, 1H), 4.16 (dd, *J* = 10.4, 8.1 Hz, 2H), 3.95 (dd, *J* = 10.8, 6.0 Hz, 2H), 3.84 (dq, *J* = 9.1, 6.7 Hz, 1H), 3.35 (br s, 3H), 1.44 (d, *J* = 6.8 Hz, 3H), 1.23–1.15 (m, 1H), 0.68–0.63 (m, 1H), 0.56–0.50 (m, 1H), 0.36–0.28 (comp, 2H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{26}ClFN_5$ 426.2; found 426.1. LC-MS ^{t}R (UV 214): 1.291 min.

Scheme S6. Preparation of Compounds 34, 35, and 41[a]



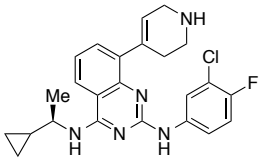
(a) Boronate ester, $Pd(dppf)Cl_2$, K_2CO_3, DMF/EtOH (4:1 v/v) 90 °C. (b) TFA, CH_2Cl_2. (c) $LiAlH_4$, THF, 60 °C.

***tert*-Butyl (*R*)-4-(2-((3-chloro-4-fluorophenyl)amino)-4-((1-cyclopropylethyl)amino)quinazolin-8-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (64)**



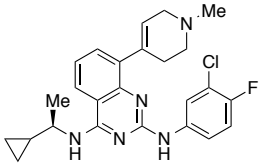
To a vial were added **62** (65.0 mg, 0.149 mmol, 1.00 equiv), *N*-Boc-3,6-dihydro-2*H*-pyridine-4-boronic acid pinacol ester (69.2 mg, 0.224 mmol, 1.50 equiv), Pd(dppf)Cl_2 (10.9 mg, 0.0149 mmol, 0.10 equiv), and K_2CO_3 (61.9 mg, 0.448 mmol, 3.00 equiv). The vial was sealed and subsequently evacuated/refilled with N_2. The evacuation/refill cycle was repeated two additional times and then degassed DMF/EtOH (4:1 v/v) (1.5 mL) was added. The mixture was heated to 90 °C and the progress of the reaction was monitored by LC-MS analysis. Upon complete consumption of the starting material, the reaction mixture was allowed to cool to room temperature and then diluted with CH_2Cl_2 (20 mL) and saturated aqueous NH_4Cl (10 mL). The resulting biphasic mixture was passed through a phase separator and concentrated in vacuo. The residue was purified by silica gel chromatography to provide **64** (74.0 mg, 0.138 mmol, 92% yield). Light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.14 (dd, *J* = 6.7, 2.6 Hz, 1H), 7.51 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.44 (dd, *J* = 7.2, 1.1 Hz, 1H), 7.35 (ddd, *J* = 9.0, 3.7, 2.8 Hz, 1H), 7.16 (t, *J* = 7.7 Hz, 1H), 7.05 (t, *J* = 8.8 Hz, 1H), 5.87–5.84 (br m, 1H), 5.62 (d, *J* = 7.3 Hz, 1H), 4.14 (br d, *J* = 2.3 Hz, 2H), 3.87–3.78 (m, 1H), 3.72 (t, *J* = 5.5 Hz, 2H), 2.69 (br s, 2H), 1.52 (s, 9H), 1.38 (d, *J* = 6.5 Hz, 3H), 1.07–1.00 (m, 1H), 0.65–0.58 (m, 1H), 0.56–0.49 (m, 1H), 0.45–0.39 (m, 1H), 0.39–0.33 (m, 1H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{29}H_{34}ClFN_5O_2$ 538.2; found 538.0. LC-MS Ret time (UV 214): 2.006 min.

(*R*)-N^2-(3-Chloro-4-fluorophenyl)-N^4-(1-cyclopropylethyl)-8-(1,2,3,6-tetrahydropyridin-4-yl)quinazoline-2,4-diamine (34)



To a vial containing **64** (98.0 mg, 0.182 mmol) was added CH_2Cl_2 (4.0 mL). Next, TFA (1.0 mL) was added and the resulting mixture was stirred at room temperature. The progress of the reaction was monitored by LC-MS analysis. Upon complete consumption of the starting material, the reaction mixture was concentrated in vacuo and purified by reversed-phase preparative HPLC. The title compound was obtained as its corresponding TFA salt (78.0 mg, 0.141 mmol, 78% yield). White solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.28 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.97 (dd, *J* = 6.6, 2.6 Hz, 1H), 7.72 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 1H), 7.41 (ddd, *J* = 8.9, 4.2, 2.7 Hz, 1H), 7.31 (t, *J* = 8.9 Hz, 1H), 6.03–6.01 (m, 1H), 3.93 (dd, *J* = 5.5, 2.4 Hz, 2H), 3.85 (dq, *J* = 9.1, 6.6 Hz, 1H), 3.62 (t, *J* = 6.1 Hz, 2H), 2.79–2.76 (comp, 2H), 1.45 (d, *J* = 6.7 Hz, 3H), 1.25–1.16 (m, 1H), 0.71–0.65 (m, 1H), 0.58–0.52 (m, 1H), 0.38–0.29 (comp, 2H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{26}ClFN_5$ 438.2; found 438.1. LC-MS ^{t}R (UV 214): 1.349 min.

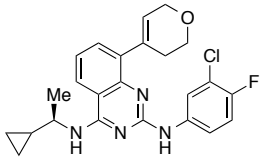
(*R*)-*N*^{2}-(3-Chloro-4-fluorophenyl)-*N*^{4}-(1-cyclopropylethyl)-8-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)quinazoline-2,4-diamine (35)



A flask containing a solution of **64** (74.0 mg, 0.138 mmol, 1.00 equiv) in THF (1.4 mL) was cooled to 0 °C. Solid $LiAlH_4$ (15.7 mg, 0.413 mmol, 3.00 equiv) was then added. The cooling bath was removed and the mixture was heated to 60 °C. After stirring at this

temperature for 1 h, the mixture was recooled to 0 °C and slowly quenched by the sequential addition of H_2O (0.016 mL), 3 M NaOH (0.016 mL), and H_2O (0.048 mL).[8] The suspension was warmed to room temperature and stirred for 15 min. The resulting mixture was filtered over diatomaceous earth and the filter cake was washed with EtOAc. The layers of the filtrate were separated. The organic phase was dried over Na_2SO_4, concentrated in vacuo, and purified by reversed-phase preparative HPLC. The title compound was obtained as its corresponding TFA salt (21.0 mg, 0.0371 mmol, 27% yield). White solid. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 11.24 (br s, 1H), 8.63 (br s, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 7.87 (dd, *J* = 6.6, 2.6 Hz, 1H), 7.50 (d, *J* = 7.3 Hz, 1H), 7.30–7.24 (comp, 2H), 7.12 (t, *J* = 8.7 Hz, 1H), 5.80 (s, 1H), 3.99–3.89 (comp, 2H), 3.82–3.70 (comp, 2H), 3.59 (dd, *J* = 11.0, 5.7 Hz, 1H), 3.17–2.99 (m, 1H), 2.99 (s, 3H), 2.51 (br d, *J* = 16.7 Hz, 1H), 1.41 (d, *J* = 6.4 Hz, 3H), 1.22–1.14 (m, 1H), 0.65–0.60 (m, 1H), 0.52–0.48 (m, 1H), 0.33–0.25 (comp, 2H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{25}H_{28}ClFN_5$ 452.2; found 452.1. LC-MS ^{t}R (UV 214): 1.383 min.

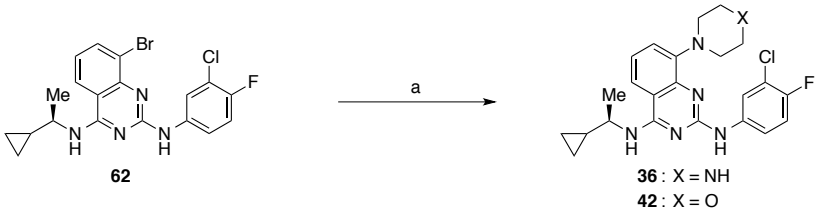
(*R*)-*N*^{2}-(3-Chloro-4-fluorophenyl)-*N*^{4}-(1-cyclopropylethyl)-8-(3,6-dihydro-2*H*-pyran-4-yl)quinazoline-2,4-diamine (41)



The title compound was obtained as its corresponding TFA salt from **62** and 3,6-dihydro-2*H*-pyran-4-boronic acid pinacol ester using a procedure similar to that described for the synthesis of **64** (32.4 mg, 0.0587 mmol, 39% yield). Tan solid. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.91 (dd, *J* = 6.6, 2.6 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 1H), 7.57 (d, *J* = 7.3 Hz,

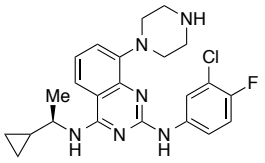
1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.34–7.30 (m, 1H), 7.09 (t, *J* = 8.7 Hz, 1H), 7.00 (d, *J* = 7.3 Hz, 1H), 5.97 (s, 1H), 4.35 (dd, *J* = 5.3, 2.6 Hz, 2H), 4.10 (t, *J* = 5.3 Hz, 2H), 3.83–3.73 (m, 1H), 2.41 (s, 2H), 1.41 (d, *J* = 6.5 Hz, 3H), 1.13–1.04 (m, 1H), 0.70–0.65 (m, 1H), 0.57–0.52 (m, 1H), 0.40–0.32 (comp, 2H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{24}H_{25}ClFN_4O$ 439.2; found 439.0. LC-MS ^tR (UV 214): 1.529 min.

Scheme S7. Preparation of Compounds 36 and 42[a]



[a]Reagents and conditions: (a) Secondary amine, $Pd(OAc)_2$, (±)-BINAP, NaO*t*-Bu, dioxane, 80 °C.

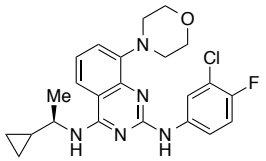
(*R*)-N^2-(3-Chloro-4-fluorophenyl)-N^4-(1-cyclopropylethyl)-8-(piperazin-1-yl)quinazoline-2,4-diamine (36)



To a vial were added **62** (50.0 mg, 0.115 mmol, 1.00 equiv), piperazine (14.8 mg, 0.172 mmol, 1.50 equiv), $Pd(OAc)_2$ (2.6 mg, 0.011 mmol, 0.10 equiv), (±)-BINAP (7.9 mg, 0.013 mmol, 0.11 equiv) and NaO*t*-Bu (22.1 mg, 0.229 mmol, 2.00 equiv). The vial was sealed and subsequently evacuated/refilled with N_2. The evacuation/refill cycle was repeated two additional times and then degassed dioxane (0.38 mL) was added. The

resulting mixture was heated to 80 °C and the progress of the reaction was monitored by LC-MS analysis. Upon complete consumption of the starting material, the reaction mixture was allowed to cool to room temperature and diluted with CH_2Cl_2 (10 mL) and saturated aqueous NH_4Cl (5 mL). The resulting biphasic mixture was passed through a phase separator and concentrated in vacuo. The residue was purified by reversed-phase preparative HPLC. The title compound was obtained as its corresponding TFA salt (26.0 mg, 0.0468 mmol, 41% yield). White solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.15 (dd, *J* = 8.3, 1.1 Hz, 1H), 8.00 (dd, *J* = 6.6, 2.6 Hz, 1H), 7.81 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.40 (ddd, *J* = 8.9, 4.1, 2.6 Hz, 1H), 7.31 (t, *J* = 8.8 Hz, 1H), 3.84 (dq, *J* = 9.2, 6.7 Hz, 1H), 3.58 (br s, 4H), 3.26–3.23 (br m, 4H), 1.45 (d, *J* = 6.7 Hz, 3H), 1.24–1.15 (m, 1H), 0.69–0.64 (m, 1H), 0.56–0.51 (m, 1H), 0.37–0.29 (comp, 2H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{27}ClFN_6$ 441.2; found 441.1. LC-MS ^{t}R (UV 214): 1.227 min.

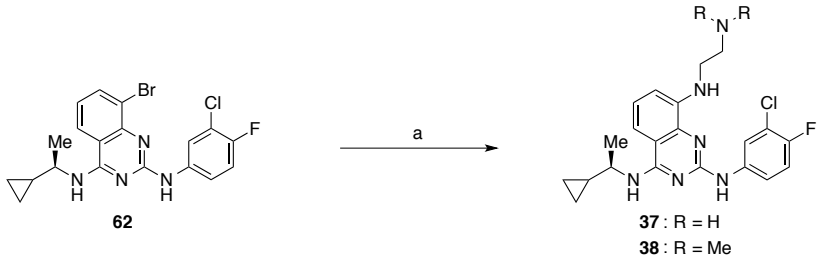
(*R*)-*N*^{2}-(3-Chloro-4-fluorophenyl)-*N*^{4}-(1-cyclopropylethyl)-8-morpholinoquinazoline-2,4-diamine (42)



The title compound was obtained as its corresponding TFA salt from **62** and morpholine using a procedure similar to that described for the synthesis of **36** (34% yield). White solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.09 (dd, *J* = 8.3, 0.9 Hz, 1H), 8.00 (d, *J* = 6.5 Hz, 1H), 7.80 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.50 (t, *J* = 8.1 Hz, 1H), 7.37–7.33 (comp, 2H), 3.95 (t, *J* = 4.0 Hz, 4H), 3.90–3.82 (m, 1H), 3.00 (t, *J* = 4.0 Hz, 4H), 1.46 (d, *J* = 6.7 Hz, 3H), 1.25–1.16 (m, 1H), 0.70–0.65 (m, 1H), 0.57–0.52 (m, 1H), 0.39–0.30 (comp, 2H). LRMS

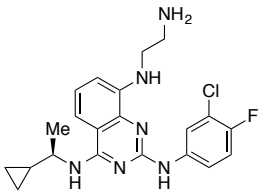
(ESI) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{26}ClFN_5O$ 442.2; found 442.0. LC-MS ^tR (UV 214): 1.630 min.

Scheme S8. Preparation of Compounds 37 and 38[a]



[a]Reagents and conditions: (a) Primary amine, $Pd(OAc)_2$, (±)-BINAP, NaO*t*-Bu, dioxane, 150 °C μW.

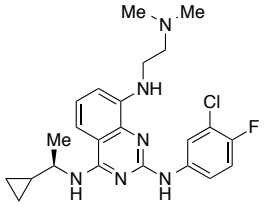
(*R*)-N^8-(2-Aminoethyl)-N^2-(3-chloro-4-fluorophenyl)-N^4-(1-cyclopropylethyl)quinazoline-2,4,8-triamine (37)



To a microwave vial were added **62** (75.0 mg, 0.172 mmol, 1.00 equiv), 1,2-diaminoethane (0.115 mL, 103 mg, 1.72 mmol, 10.00 equiv), $Pd(OAc)_2$ (5.8 mg, 0.026 mmol, 0.15 equiv), (±)-BINAP (16.1 mg, 0.0258 mmol, 0.15 equiv), and NaO*t*-Bu (49.6 mg, 0.516 mmol, 3.00 equiv). The vial was sealed and subsequently evacuated/refilled with N_2. The evacuation/refill cycle was repeated two additional times and then degassed dioxane (0.57 mL) was added. The resulting mixture was heated to 150 °C in a microwave reactor for 1.5 h, after which time the mixture was diluted with EtOAc (10

mL) and filtered over diatomaceous earth. The filtrate was concentrated in vacuo and the residue was purified by reversed-phase preparative HPLC. The title compound was obtained as its corresponding TFA salt (27.0 mg, 0.0510 mmol, 30% yield). Tan solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.04 (dd, *J* = 6.7, 2.6 Hz, 1H), 7.68 (d, *J* = 8.1 Hz, 1H), 7.45 (ddd, *J* = 9.0, 4.0, 2.7 Hz, 1H), 7.36 (t, *J* = 8.1 Hz, 1H), 7.26 (t, *J* = 8.9 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 1H), 3.86 (dq, *J* = 9.1, 6.7 Hz, 1H), 3.54 (dd, *J* = 7.0, 5.1 Hz, 2H), 3.35 (dd, *J* = 6.0, 4.0 Hz, 2H), 1.44 (d, *J* = 6.7 Hz, 3H), 1.24–1.15 (m, 1H), 0.68–0.63 (m, 1H), 0.56–0.50 (m, 1H), 0.37–0.29 (comp, 2H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{25}ClFN_6$ 415.2; found 415.1. LC-MS ^{t}R (UV 214): 1.354 min.

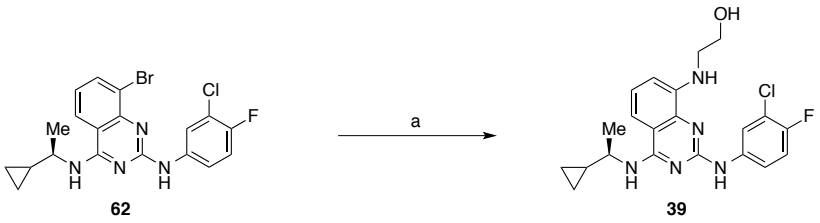
(*R*)-*N*^{2}-(3-Chloro-4-fluorophenyl)-*N*^{4}-(1-cyclopropylethyl)-*N*^{8}-(2-(dimethylamino)ethyl)quinazoline-2,4,8-triamine (38)



The title compound was obtained as its corresponding TFA salt from **62** and 2-(dimethylamino)ethylamine using a procedure similar to that described for the synthesis of **37** (16% yield). Tan solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.03 (dd, *J* = 6.7, 2.6 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.43 (ddd, *J* = 8.9, 4.1, 2.7 Hz, 1H), 7.37 (t, *J* = 8.1 Hz, 1H), 7.26 (t, *J* = 8.9 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 3.85 (dq, *J* = 9.1, 6.6 Hz, 1H), 3.68 (t, *J* = 5.9 Hz, 2H), 3.55 (t, *J* = 5.9 Hz, 2H), 2.99 (s, 6H), 1.44 (d, *J* = 6.7 Hz, 3H), 1.24–1.15 (m, 1H), 0.68–0.63 (m, 1H), 0.56–0.50 (m, 1H), 0.37–0.29 (comp, 2H). LRMS

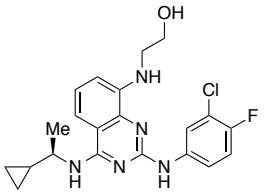
(ESI) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{29}ClFN_6$ 443.2; found 443.1. LC-MS ^tR (UV 214): 1.423 min.

Scheme S9. Preparation of Compound 39[a]



(a) $CuSO_4$, NMP, 110 °C.

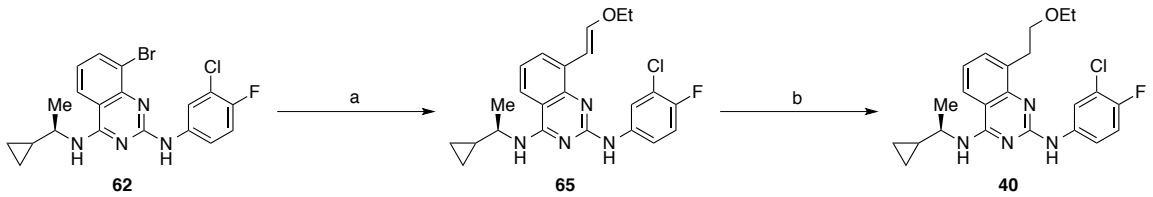
(*R*)-2-((2-((3-Chloro-4-fluorophenyl)amino)-4-((1-cyclopropylethyl)amino)quinazolin-8-yl)amino)ethan-1-ol (39)



To a vial were added **62** (100 mg, 0.229 mmol, 1.00 equiv), 2-amino-1-ethanol (0.277 mL, 280 mg, 4.59 mmol, 20.00 equiv), and copper(II) sulfate (36.6 mg, 0.229 mmol, 1.00 equiv). The vial was sealed and subsequently evacuated/refilled with N_2. The evacuation/refill cycle was repeated two additional times and then degassed NMP (0.23 mL) was added. The resulting mixture was heated to 110 °C and the progress of the reaction was monitored by LC-MS analysis. Upon complete consumption of the starting material, the mixture was allowed to cool to room temperature. Next, H_2O (30 mL) was added and the resulting mixture was extracted with EtOAc (3 x 15 mL). The organic phases were combined, washed with H_2O, brine, dried over Na_2SO_4, and concentrated in

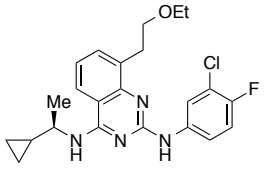
vacuo. The residue was purified first by silica gel chromatography and then by reversed-phase preparative HPLC. The title compound was obtained as its corresponding TFA salt (37.0 mg, 0.0698 mmol, 30% yield). Tan solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 7.97 (dd, *J* = 6.6, 2.6 Hz, 1H), 7.59 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.38 (ddd, *J* = 9.0, 4.1, 2.6 Hz, 1H), 7.35 (t, *J* = 8.1 Hz, 1H), 7.28 (t, *J* = 8.8 Hz, 1H), 7.15 (d, *J* = 8.0 Hz, 1H), 3.88 (t, *J* = 5.4 Hz, 2H), 3.83 (dq, *J* = 9.1, 6.7 Hz, 1H), 3.36 (t, *J* = 5.6 Hz, 2H), 1.43 (d, *J* = 6.7 Hz, 3H), 1.23–1.14 (m, 1H), 0.68–0.62 (m, 1H), 0.55–0.49 (m, 1H), 0.37–0.27 (comp, 2H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{21}H_{24}ClFN_5O$ 416.2; found 416.1. LC-MS ^{t}R (UV 214): 1.477 min.

Scheme S10. Preparation of Compound 40[a]



(a) (*E*)-2-ethoxyvinylboronic acid pinacol ester, $Pd(dppf)Cl_2$, K_2CO_3, DMF/EtOH (4:1 v/v) 90 °C. (b) Pt/C, H_2, EtOAc/MeOH (1:1 v/v).

(*R*)-N^2-(3-Chloro-4-fluorophenyl)-N^4-(1-cyclopropylethyl)-8-(2-ethoxyethyl)quinazoline-2,4-diamine (40)



STEP 1: To a vial were added **62** (284 mg, 0.652 mmol, 1.00 equiv), (*E*)-2-ethoxyvinylboronic acid pinacol ester (194 mg, 0.978 mmol, 1.50 equiv), $Pd(dppf)Cl_2$

(47.7 mg, 0.0652 mmol, 0.10 equiv), and K_2CO_3 (270 mg, 1.96 mmol, 3.00 equiv). The vial was sealed and subsequently evacuated/refilled with N_2. The evacuation/refill cycle was repeated two additional times and then degassed DMF/EtOH (4:1 v/v) (3.3 mL) was added. The mixture was heated to 90 °C and the progress of the reaction was monitored by LC-MS analysis. Upon complete consumption of the starting material, the reaction mixture was allowed to cool to room temperature and then diluted with CH_2Cl_2 (20 mL) and saturated aqueous NH_4Cl (10 mL). The resulting biphasic mixture was passed through a phase separator and concentrated in vacuo. The residue was purified by silica gel chromatography to provide (*R*,*E*)-N^2-(3-chloro-4-fluorophenyl)-N^4-(1-cyclopropylethyl)-8-(2-ethoxyvinyl)quinazoline-2,4-diamine **65** (158 mg, 0.370 mmol, 57% yield). Orange, glassy solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.46 (dd, *J* = 6.9, 2.7 Hz, 1H), 7.79 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.63 (dd, *J* = 7.4, 1.0 Hz, 1H), 7.43 (ddd, *J* = 8.9, 4.1, 2.7 Hz, 1H), 7.27 (d, *J* = 13.2 Hz, 1H), 7.12–7.08 (comp, 2H), 6.69 (d, *J* = 13.2 Hz, 1H), 3.49 (q, *J* = 7.0 Hz, 2H), 3.97–3.90 (m, 1H), 1.38 (d, *J* = 6.6 Hz, 3H), 1.37 (t, *J* = 7.0 Hz, 3H), 1.17–1.10 (m, 1H), 0.61–0.55 (m, 1H), 0.52–0.47 (m, 1H), 0.47–0.40 (m, 1H), 0.32–0.26 (m, 1H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{25}ClFN_4O$ 427.2; found 427.0. LC-MS ^{t}R (UV 214): 1.844 min.

STEP 2: A vial containing **65** (77.0 mg, 0.180 mmol, 1.00 equiv) and EtOAc/MeOH (1:1 v/v) (1.8 mL) was purged with N_2. To this solution was added Pt/C (5% w/w) (10.0 mg). The flask was then placed under an atmosphere of H_2 (balloon) and the reaction mixture was stirred for 18 h. After this time, the flask was purged with N_2 and the reaction mixture was filtered over diatomaceous earth. The filtrate was concentrated in vacuo and purified by reversed-phase preparative HPLC. The title compound was obtained as its

corresponding TFA salt (30.2 mg, 0.0556 mmol, 31% yield). White solid. ^{1}H NMR (400 MHz, CD_3OD, δ): 8.19 (d, *J* = 8.1 Hz, 1H), 7.95 (dd, *J* = 6.5, 2.2 Hz, 1H), 7.77 (d, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.39–7.31 (comp, 2H), 3.89–3.81 (m, 1H), 3.77 (t, *J* = 5.8 Hz, 2H), 3.49 (q, *J* = 7.0 Hz, 2H), 3.14 (t, *J* = 5.8 Hz, 2H), 1.44 (d, *J* = 6.7 Hz, 3H), 1.24–1.16 (m, 1H), 1.12 (t, *J* = 7.0 Hz, 3H), 0.70–0.63 (m, 1H), 0.57–0.51 (m, 1H), 0.39–0.29 (comp, 2H). LRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{27}ClFN_4O$ 429.2; found 429.1. LC-MS ^{t}R (UV 214): 1.582 min.

■ BIOLOGY EXPERIMENTAL SECTION

Nucleotide Exchange Assay. Nucleotide exchange assays were conducted as reported previously.[9-11]

Cell Culture and Compounds. HeLa (ATCC CCL-2) and NCI-H727 (ATCC CRL-5815) cells were obtained from the ATCC and cultured in DMEM or RPMI supplemented with 10% (v/v) FBS, where appropriate. Cell lines were authenticated by STR profiling using PowerPlex 16HS technology and were tested negative for mycoplasma using the eMYCO Plus kit PCR test in October 2017 (Genetica DNA Laboratories). After thawing from liquid N_2, cells were passaged at least twice before use in experiments, and passaged for a maximum of 25 times.

Active RAS-GTP Pull-Down and Western Blotting. Cells were seeded to reach 70% confluency after 24 h incubation, and subsequently treated as indicated. Lysates were resolved by SDS-PAGE and transferred onto Immobilon-FL PVDF membranes (Millipore). Membranes were probed with primary antibodies as indicated, incubated with labeled secondary antibody, and scanned using an Odyssey imager (LI-COR). Levels of RAS-GTP were determined using an active RAS pull-down and detection kit according to the manufacturer's instructions (Thermo Scientific #16117). Total RAS and α-tubulin were included as input loading controls for the RAF1-RBD pull-down. ERK1/2 lysates were prepared separately using 1X LI-COR Protein Loading Buffer with 10 mM DTT. Primary antibodies used for western blotting—pan-RAS (KRAS, NRAS and HRAS isoforms; #3339), ERK1/2 (#9102), pERK1/2$^{T202/Y204}$ (#9106), and α-tubulin (#3873)—were all purchased from Cell Signaling. EGF was purchased from R&D Systems. Quantification of western blots was performed using ImageJ64 software.

Table S1. Quantification of Western Blots From Figure 4[a]

	(μM)	pERK$^{T202/Y204}$			RAS-GTP		
		Rep 1	Rep 2	Rep 3	Rep 1	Rep 2	Rep 3
Compound 22	DMSO	1.00	1.00	1.00	1.00	1.00	1.00
	3.13	1.16	1.11	1.28	0.95	0.82	1.03
	6.25	1.03	1.03	1.83	0.85	1.05	0.84
	12.5	1.67	1.67	2.73	0.53	1.07	0.89
	25.0	1.61	2.36	3.83	0.69	0.95	1.24
	50.0	3.68	5.55	9.34	1.26	0.93	1.00
	100	4.01	8.34	9.95	1.39	1.23	1.32
	EGF	5.34	7.38	12.4	2.83	1.85	1.81
Compound 30	DMSO	1.00	1.00	1.00	1.00	1.00	1.00
	3.13	1.05	1.23	0.88	1.15	0.85	1.00
	6.25	0.94	1.25	1.16	1.39	1.02	0.80
	12.5	1.83	1.76	0.94	0.98	1.24	1.06
	25.0	2.52	2.04	2.23	1.18	0.89	1.28
	50.0	2.43	2.52	1.66	1.14	0.92	1.36
	100	0.59	0.96	1.13	1.54	1.20	1.60
	EGF	4.83	4.18	5.50	1.87	1.77	6.10
Compound 32	DMSO	1.00	1.00	1.00	1.00	1.00	1.00
	3.13	1.11	1.03	1.17	1.22	1.31	1.04
	6.25	1.82	1.16	2.45	1.64	1.05	1.24
	12.5	1.59	1.77	2.36	0.97	1.36	1.02
	25.0	1.87	2.19	2.03	1.58	1.41	1.41
	50.0	1.18	0.89	1.89	1.61	1.39	1.54
	100	0.44	0.51	0.83	1.66	2.22	3.48
	EGF	4.61	6.16	6.29	2.54	3.89	6.09
Compound 34	DMSO	1.00	1.00	1.00	1.00	1.00	1.00
	3.13	1.43	0.91	1.46	1.41	1.18	1.52
	6.25	1.29	1.60	2.01	1.08	1.00	1.53
	12.5	1.98	4.22	2.47	1.72	1.19	1.51
	25.0	1.98	4.13	3.20	1.60	1.33	1.19
	50.0	1.16	1.46	2.75	1.56	0.98	1.82
	100	0.58	1.13	0.89	1.51	3.28	3.99
	EGF	4.62	8.93	7.04	2.64	8.22	3.41

[a]Quantification of western blots from Figure 4 assessing compound effects on RAS-GTP and pERK1/2$^{T202/Y204}$ protein levels. The levels of RAS-GTP were normalized to the total RAS protein levels and to the DMSO control. The levels of pERK1/2$^{T202/Y204}$ were normalized to the total ERK1/2 protein levels and to the DMSO control. Trends are highlighted by conditional formatting of the data.

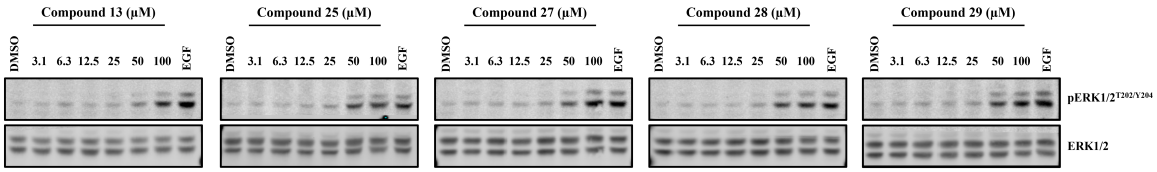


Figure S1. pERK1/2$^{T202/Y204}$ and total ERK1/2 protein levels from HeLa cells that were treated for 30 min with up to 100 μM of compound **13**, **25**, **27**, **28** or **29**. EGF treatment (50 ng/mL for 5 min) was used as a positive control for pathway activation. Data are representative of two independent experiments.

■ STRUCTURAL BIOLOGY EXPERIMENTAL SECTION

Protein Expression and Purification. Details regarding protein expression and purification have been reported previously.[9-10,12]

Crystallization, X-ray Data Collection, Structure Solution, and Refinement. Details regarding X-ray crystallography have been reported previously.[9-10,12] Individual refinement statistics for all new structures are given in Table S2.

Table S2. X-ray Data Collection and Refinement Statistics

$HRAS^{WT}$:$SOS1^{cat}$:$HRAS^{Y64A}$:GppNHp Complex	Compound 1	Compound 22	Compound 34
PDB Entry	6CUO	6CUP	6CUR
Data collection			
Space group	I 4 2 2	I 4 2 2	I 4 2 2
Cell dimensions			
a, b, c (Å)	183.81, 183.81, 178.87	184.65, 184.65, 179.35	184.05, 184.05, 179.13
α, β, γ (°)	90.00, 90.00, 90.00	90.00, 90.00, 90.00	90.00, 90.00, 90.00
Resolution (Å)[a]	36.05–1.73 (1.76–1.73)	37.51–1.83 (1.86–1.83)	35.17–1.73 (1.76–1.73)
R_{merge}[b]	11.4 (136.6)	13.2 (134.3)	9.6 (96.6)
$I / \sigma I$	18.87 (2.00)	15.67 (1.75)	22.12 (2.82)
Completeness (%)	100.00 (100.00)	100.00 (100.00)	100.00 (100.00)
Redundancy	12.2 (11.8)	12.0 (11.5)	11.4 (10.2)
Structure Refinement			
No. reflections	157959	134176	158314
R_{work} / R_{free}	16.34 / 17.76	15.99 / 17.37	15.87 / 17.78
B-factors[c]			
Protein	24.95	34.57	20.61
Water	39.98	47.15	37.66
Ligand	32.89	43.43	23.64
R.m.s. deviations			
Bond lengths (Å)	0.007	0.008	0.008
Bond angles (°)	1.14	1.18	1.19

[a]Values in parentheses describe the highest resolution shell.

[b]$R_{merge} = \Sigma_{hkl}\Sigma_i|I_i(hkl) - (I(hkl))|/\Sigma_{hkl}\Sigma_i I_i(hkl)$, where $I_i(hkl)$ is the observed intensity and is the average intensity obtained from multiple observations of symmetry-related reflections.

[c]Mean *B* factors were calculated with Analyze Model Geometry program from CCP4 suite, version 7.0.045.

Table S3. Reaction Biology Corp. Kinase Profiling Report for Compound 22[a,b,c]

Kinase	% Enzyme Activity[d]			IC_{50} (M) Staurosporine[e,f]	IC_{50} (M) Alternate Control Compd[g]	Alternate Compd ID
	Data 1	Data 2	Average			
ABL1	69.09	70.03	69.56	4.94×10^{-8}		
ABL2/ARG	66.42	65.06	65.74	2.01×10^{-8}		
ACK1	60.67	58.51	59.59	4.91×10^{-8}		
AKT1	85.90	81.96	83.93	9.10×10^{-9}		
AKT2	64.19	73.08	68.63	2.43×10^{-8}		
AKT3	63.13	61.41	62.27	4.29×10^{-9}		
ALK	70.34	69.97	70.15	2.86×10^{-9}		
ALK1/ACVRL1	87.39	97.22	92.31	ND	6.41×10^{-9}	LDN193189
ALK2/ACVR1	57.23	53.13	55.18	ND	1.86×10^{-8}	LDN193189
ALK3/BMPR1A	129.55	148.17	138.86	ND	4.97×10^{-9}	LDN193189
ALK4/ACVR1B	70.90	69.18	70.04	ND	4.88×10^{-7}	LDN193189
ALK5/TGFBR1	53.03	58.85	55.94	ND	3.20×10^{-7}	LDN193189
ALK6/BMPR1B	139.26	131.10	135.18	ND	3.67×10^{-9}	LDN193189
ARAF	83.91	76.11	80.01	ND	5.68×10^{-9}	GW5074
ARK5/NUAK1	52.70	52.15	52.42	7.94×10^{-10}		
ASK1/MAP3K5	63.31	62.69	63.00	2.44×10^{-8}		
Aurora A	66.62	72.50	69.56	1.71×10^{-9}		
Aurora B	20.74	23.00	21.87	1.28×10^{-8}		
Aurora C	36.72	36.36	36.54	3.15×10^{-9}		
AXL	24.54	24.21	24.38	1.13×10^{-8}		
BLK	29.46	33.27	31.37	2.80×10^{-9}		
BMPR2	62.07	64.23	63.15	5.23×10^{-7}		
BMX/ETK	80.56	79.71	80.14	8.67×10^{-9}		
BRAF	85.37	83.84	84.60	ND	9.88×10^{-9}	GW5074
BRK	43.23	42.50	42.87	1.09×10^{-7}		

BRSK1	74.06	71.99	73.02	2.96×10^{-10}		
BRSK2	101.38	96.54	98.96	5.78×10^{-9}		
BTK	70.90	68.32	69.61	1.73×10^{-8}		
c-Kit	115.23	111.47	113.35	2.27×10^{-8}		
c-MER	61.85	62.27	62.06	1.82×10^{-8}		
c-MET	18.15	16.52	17.33	5.91×10^{-8}		
c-Src	90.33	88.29	89.31	3.08×10^{-9}		
CAMK1a	0.28	0.25	0.26	3.15×10^{-9}		
CAMK1b	0.33	0.42	0.37	2.25×10^{-8}		
CAMK1d	1.78	0.72	1.25	3.97×10^{-10}		
CAMK1g	3.25	7.10	5.18	7.73×10^{-9}		
CAMK2a	1.30	0.76	1.03	1.08×10^{-10}		
CAMK2b	7.79	7.19	7.49	9.85×10^{-11}		
CAMK2d	1.53	1.84	1.68	$<7.63 \times 10^{-11}$		
CAMK2g	1.40	0.60	1.00	1.24×10^{-9}		
CAMK4	1.78	1.01	1.40	5.20×10^{-7}		
CAMKK1	7.24	4.31	5.77	2.95×10^{-8}		
CAMKK2	70.67	69.98	70.32	4.47×10^{-8}		
CDC7/DBF4	96.29	90.51	93.40	3.46×10^{-8}		
CDK1/cyclin A	55.12	53.02	54.07	5.46×10^{-9}		
CDK1/cyclin B	51.13	55.10	53.12	3.06×10^{-9}		
CDK1/cyclin E	25.22	30.84	28.03	3.49×10^{-9}		
CDK16/cyclin Y (PCTAIRE)	26.87	29.69	28.28	1.75×10^{-8}		
CDK2/cyclin A	66.55	66.03	66.29	1.27×10^{-9}		
CDK2/cyclin A1	44.70	47.50	46.10	2.47×10^{-9}		
CDK2/cyclin E	64.52	67.87	66.19	1.10×10^{-9}		
CDK3/cyclin E	62.41	62.34	62.38	7.80×10^{-9}		
CDK4/cyclin D1	63.90	55.57	59.74	2.12×10^{-8}		
CDK4/cyclin D3	76.36	74.68	75.52	7.11×10^{-8}		
CDK5/p25	86.20	85.13	85.67	3.19×10^{-9}		

CDK5/p35	72.70	72.65	72.67	2.46×10^{-9}		
CDK6/cyclin D1	73.31	71.07	72.19	6.93×10^{-9}		
CDK6/cyclin D3	84.25	80.75	82.50	1.15×10^{-7}		
CDK7/cyclin H	93.95	90.69	92.32	4.65×10^{-7}		
CDK9/cyclin K	68.28	75.33	71.81	3.81×10^{-8}		
CDK9/cyclin T1	105.37	98.73	102.05	2.49×10^{-8}		
CHK1	81.02	75.14	78.08	9.80×10^{-11}		
CHK2	55.51	55.35	55.43	6.03×10^{-9}		
CK1a1	45.17	41.74	43.46	7.27×10^{-6}		
CK1d	24.23	23.49	23.86	ND	1.51×10^{-7}	**D4476**
CK1epsilon	39.08	38.36	38.72	ND	2.87×10^{-7}	**D4476**
CK1g1	9.37	9.21	9.29	1.05×10^{-5}		
CK1g2	2.09	2.45	2.27	2.88×10^{-6}		
CK1g3	9.77	9.42	9.60	2.71×10^{-6}		
CK2a	74.31	71.65	72.98	ND	1.69×10^{-7}	**GW5074**
CK2a2	151.54	142.54	147.04	6.04×10^{-7}		
CLK1	21.51	26.49	24.00	1.43×10^{-8}		
CLK2	8.49	7.92	8.21	6.40×10^{-9}		
CLK3	59.82	61.14	60.48	2.47×10^{-6}		
CLK4	21.61	22.82	22.22	3.56×10^{-8}		
COT1/MAP3K8	70.01	73.36	71.69	ND	1.56×10^{-5}	**Ro-31-8220**
CSK	94.82	96.07	95.45	1.28×10^{-8}		
CTK/MATK	39.46	42.68	41.07	2.38×10^{-6}		
DAPK1	51.07	49.55	50.31	3.06×10^{-8}		
DAPK2	2.31	5.54	3.93	1.19×10^{-8}		
DCAMKL1	75.86	68.98	72.42	7.93×10^{-7}		
DCAMKL2	75.47	72.19	73.83	4.78×10^{-8}		
DDR1	47.52	51.73	49.62	3.71×10^{-9}		
DDR2	33.85	34.22	34.03	2.14×10^{-8}		
DLK/MAP3K12	44.70	45.74	45.22	6.74×10^{-9}		

DMPK	103.60	98.93	101.26	8.33×10^{-8}		
DMPK2	2.92	2.95	2.93	8.66×10^{-10}		
DRAK1/STK17A	3.91	1.88	2.89	2.51×10^{-8}		
DYRK1/DYRK1A	3.86	3.07	3.47	3.78×10^{-9}		
DYRK1B	6.59	5.00	5.80	1.47×10^{-9}		
DYRK2	76.65	71.51	74.08	3.50×10^{-7}		
DYRK3	53.65	57.18	55.42	4.97×10^{-8}		
DYRK4	87.55	88.82	88.19	ND	3.97×10^{-6}	**GW5074**
EGFR	87.53	88.36	87.95	1.79×10^{-7}		
EPHA1	84.01	81.49	82.75	1.90×10^{-7}		
EPHA2	97.93	99.55	98.74	6.03×10^{-8}		
EPHA3	61.57	55.44	58.51	3.68×10^{-8}		
EPHA4	96.63	102.78	99.70	1.55×10^{-8}		
EPHA5	95.00	96.42	95.71	3.37×10^{-8}		
EPHA6	12.15	15.74	13.95	1.31×10^{-8}		
EPHA7	86.90	87.09	86.99	4.47×10^{-8}		
EPHA8	92.78	92.84	92.81	2.24×10^{-7}		
EPHB1	90.77	86.08	88.43	3.70×10^{-8}		
EPHB2	108.70	101.66	105.18	1.06×10^{-7}		
EPHB3	93.01	87.54	90.27	1.63×10^{-6}		
EPHB4	87.03	83.61	85.32	2.73×10^{-7}		
ERBB2/HER2	94.16	92.81	93.49	2.67×10^{-7}		
ERBB4/HER4	86.20	86.26	86.23	4.46×10^{-7}		
ERK1	89.34	94.07	91.71	$>2.00 \times 10^{-5}$		
ERK2/MAPK1	79.55	78.28	78.92	1.38×10^{-5}		
ERK5/MAPK7	51.28	61.23	56.25	$>2.00 \times 10^{-5}$		
ERK7/MAPK15	31.88	27.26	29.57	1.22×10^{-8}		
FAK/PTK2	86.64	86.81	86.72	1.06×10^{-8}		
FER	51.30	50.87	51.08	6.78×10^{-10}		
FES/FPS	77.81	74.71	76.26	1.25×10^{-9}		

FGFR1	84.35	82.20	83.27	7.44×10^{-9}		
FGFR2	105.78	96.67	101.23	3.87×10^{-9}		
FGFR3	86.01	92.42	89.22	2.03×10^{-8}		
FGFR4	24.89	30.03	27.46	1.61×10^{-7}		
FGR	70.18	70.70	70.44	1.22×10^{-9}		
FLT1/VEGFR1	74.08	74.65	74.37	9.75×10^{-9}		
FLT3	1.64	1.59	1.61	9.57×10^{-10}		
FLT4/VEGFR3	102.31	98.63	100.47	5.85×10^{-9}		
FMS	57.71	60.20	58.96	1.29×10^{-9}		
FRK/PTK5	86.77	93.71	90.24	1.56×10^{-8}		
FYN	86.49	88.31	87.40	2.17×10^{-9}		
GCK/MAP4K2	62.54	55.58	59.06	3.44×10^{-10}		
GLK/MAP4K3	68.20	65.01	66.61	8.74×10^{-11}		
GRK1	112.79	135.35	124.07	9.49×10^{-8}		
GRK2	96.59	102.82	99.70	1.28×10^{-6}		
GRK3	122.16	128.42	125.29	7.31×10^{-7}		
GRK4	105.57	104.46	105.02	1.52×10^{-7}		
GRK5	102.39	101.35	101.87	8.99×10^{-8}		
GRK6	107.63	112.43	110.03	5.56×10^{-8}		
GRK7	210.19	215.81	213.00	7.08×10^{-9}		
GSK3a	77.10	75.90	76.50	1.00×10^{-8}		
GSK3b	76.92	72.59	74.75	1.38×10^{-8}		
Haspin	81.64	75.27	78.45	2.66×10^{-8}		
HCK	33.96	30.33	32.15	1.38×10^{-9}		
HGK/MAP4K4	35.08	37.61	36.35	5.51×10^{-10}		
HIPK1	38.07	39.95	39.01	ND	3.21×10^{-7}	**Ro-31-8220**
HIPK2	71.21	72.13	71.67	2.37×10^{-6}		
HIPK3	78.01	76.30	77.15	1.89×10^{-6}		
HIPK4	48.58	41.68	45.13	8.27×10^{-7}		
HPK1/MAP4K1	78.75	80.69	79.72	ND	6.15×10^{-8}	**Ro-31-8220**

IGF1R	90.40	90.36	90.38	3.88×10^{-8}		
IKKa/CHUK	51.12	47.93	49.53	2.42×10^{-7}		
IKKb/IKBKB	72.52	72.60	72.56	3.31×10^{-7}		
IKKe/IKBKE	122.53	134.45	128.49	2.55×10^{-10}		
IR	79.98	67.80	73.89	1.99×10^{-8}		
IRAK1	50.24	46.35	48.30	1.10×10^{-7}		
IRAK4	28.45	28.17	28.31	2.22×10^{-8}		
IRR/INSRR	3.23	3.32	3.28	2.01×10^{-8}		
ITK	47.52	44.67	46.09	3.14×10^{-8}		
JAK1	78.52	91.15	84.83	9.36×10^{-10}		
JAK2	52.42	51.79	52.11	7.25×10^{-10}		
JAK3	74.41	74.32	74.37	7.68×10^{-11}		
JNK1	64.31	66.70	65.50	1.76×10^{-6}		
JNK2	59.19	57.56	58.37	4.97×10^{-6}		
JNK3	78.41	80.18	79.29	ND	3.27×10^{-7}	**JNKi VIII**
KDR/VEGFR2	93.97	93.48	93.72	1.82×10^{-8}		
KHS/MAP4K5	59.82	58.60	59.21	3.29×10^{-10}		
LATS1	59.20	58.09	58.65	1.43×10^{-8}		
LATS2	26.79	26.17	26.48	5.68×10^{-9}		
LCK	37.43	35.95	36.69	2.63×10^{-9}		
LCK2/ICK	−0.73	3.73	3.73	1.54×10^{-7}		
LIMK1	99.90	99.79	99.84	7.85×10^{-9}		
LIMK2	76.19	80.22	78.20	1.54×10^{-7}		
LKB1	26.47	28.49	27.48	9.33×10^{-8}		
LOK/STK10	24.46	24.15	24.30	4.90×10^{-9}		
LRRK2	7.95	8.07	8.01	1.28×10^{-8}		
LYN	85.60	83.87	84.74	1.29×10^{-9}		
LYN B	104.09	103.84	103.96	4.58×10^{-9}		
MAPKAPK2	106.87	106.55	106.71	2.70×10^{-7}		
MAPKAPK3	55.65	59.77	57.71	4.48×10^{-6}		

MAPKAPK5/PRAK	81.84	77.19	79.52	4.14×10^{-7}		
MARK1	87.21	94.06	90.63	1.02×10^{-10}		
MARK2/PAR-1Ba	92.37	90.93	91.65	1.09×10^{-10}		
MARK3	95.25	93.52	94.39	2.59×10^{-10}		
MARK4	82.92	81.61	82.26	1.18×10^{-10}		
MEK1	98.91	93.57	96.24	3.33×10^{-8}		
MEK2	81.17	84.60	82.88	3.78×10^{-8}		
MEK3	98.27	88.10	93.19	6.86×10^{-8}		
MEKK1	104.19	104.32	104.26	8.09×10^{-7}		
MEKK2	99.83	95.79	97.81	2.70×10^{-8}		
MEKK3	74.56	79.72	77.14	9.01×10^{-9}		
MELK	1.39	0.63	1.01	5.05×10^{-10}		
MINK/MINK1	57.05	57.60	57.32	1.41×10^{-9}		
MKK4	87.26	90.03	88.64	1.84×10^{-6}		
MKK6	122.66	125.26	123.96	1.33×10^{-8}		
MLCK/MYLK	8.19	6.38	7.28	3.43×10^{-8}		
MLCK2/MYLK2	9.22	16.55	12.89	3.84×10^{-8}		
MLK1/MAP3K9	48.70	49.49	49.09	3.90×10^{-10}		
MLK2/MAP3K10	14.66	14.13	14.40	3.85×10^{-9}		
MLK3/MAP3K11	37.25	37.13	37.19	6.76×10^{-9}		
MNK1	17.93	18.36	18.14	6.80×10^{-8}		
MNK2	62.34	62.38	62.36	2.83×10^{-8}		
MRCKa/CDC42BPA	27.76	25.00	26.38	1.12×10^{-8}		
MRCKb/CDC42BPB	9.95	10.35	10.15	6.88×10^{-9}		
MSK1/RPS6KA5	12.49	12.89	12.69	7.22×10^{-10}		
MSK2/RPS6KA4	7.04	6.71	6.87	2.10×10^{-9}		
MSSK1/STK23	27.00	26.66	26.83	1.37×10^{-6}		
MST1/STK4	51.61	50.94	51.27	4.96×10^{-10}		
MST2/STK3	83.10	86.41	84.75	5.36×10^{-9}		
MST3/STK24	59.93	54.92	57.42	2.61×10^{-9}		

MST4	8.21	8.49	8.35	3.96×10^{-9}		
MUSK	33.81	33.26	33.53	1.59×10^{-7}		
MYLK3	99.01	93.24	96.12	2.02×10^{-7}		
MYO3b	57.33	58.41	57.87	1.08×10^{-8}		
NEK1	108.62	96.47	102.54	1.96×10^{-8}		
NEK11	26.46	25.45	25.95	1.22×10^{-6}		
NEK2	−0.19	2.02	2.02	5.60×10^{-7}		
NEK3	103.22	109.89	106.55	1.24×10^{-5}		
NEK4	39.38	37.58	38.48	1.57×10^{-7}		
NEK5	50.61	52.14	51.37	9.17×10^{-8}		
NEK6	50.12	47.52	48.82	ND	$>2.00 \times 10^{-5}$	**PKR Inhibitor**
NEK7	95.49	92.95	94.22	ND	2.71×10^{-6}	**PKR Inhibitor**
NEK9	59.47	52.20	55.84	1.85×10^{-7}		
NLK	62.22	67.16	64.69	8.34×10^{-8}		
OSR1/OXSR1	4.64	3.93	4.29	1.08×10^{-7}		
P38a/MAPK14	57.70	57.12	57.41	ND	7.10×10^{-9}	**SB202190**
P38b/MAPK11	69.61	65.03	67.32	ND	1.64×10^{-8}	**SB202190**
P38d/MAPK13	109.83	111.23	110.53	3.12×10^{-7}		
P38g	117.26	102.31	109.79	2.08×10^{-7}		
p70S6K/RPS6KB1	48.18	50.55	49.36	5.61×10^{-10}		
p70S6Kb/RPS6KB2	15.81	13.62	14.71	3.34×10^{-9}		
PAK1	87.61	99.85	93.73	5.00×10^{-10}		
PAK2	81.35	84.64	82.99	2.21×10^{-9}		
PAK3	97.68	90.46	94.07	4.07×10^{-10}		
PAK4	89.08	84.99	87.03	3.96×10^{-8}		
PAK5	98.57	100.48	99.52	3.56×10^{-9}		
PAK6	101.10	99.25	100.18	8.15×10^{-8}		
PASK	2.01	3.73	2.87	1.50×10^{-8}		
PBK/TOPK	65.18	76.40	70.79	8.26×10^{-8}		
PDGFRa	80.02	83.59	81.80	9.19×10^{-10}		

PDGFRb	66.70	65.33	66.02	1.60×10^{-9}		
PDK1/PDPK1	113.47	119.11	116.29	1.35×10^{-9}		
PHKg1	44.53	36.83	40.68	8.66×10^{-10}		
PHKg2	28.36	21.47	24.91	6.06×10^{-10}		
PIM1	6.12	4.94	5.53	5.86×10^{-9}		
PIM2	75.88	80.36	78.12	6.75×10^{-8}		
PIM3	12.09	14.51	13.30	1.58×10^{-10}		
PKA	82.65	83.49	83.07	1.64×10^{-9}		
PKAcb	15.36	15.51	15.43	2.21×10^{-9}		
PKAcg	24.77	23.26	24.02	1.25×10^{-8}		
PKCa	78.65	77.59	78.12	5.51×10^{-10}		
PKCb1	25.77	25.63	25.70	3.39×10^{-9}		
PKCb2	16.31	16.39	16.35	7.33×10^{-10}		
PKCd	71.69	72.89	72.29	1.16×10^{-10}		
PKCepsilon	38.83	35.73	37.28	1.62×10^{-10}		
PKCeta	50.03	48.09	49.06	3.72×10^{-9}		
PKCg	81.61	65.31	73.46	2.49×10^{-9}		
PKCiota	72.17	72.85	72.51	2.54×10^{-8}		
PKCmu/PRKD1	32.56	33.29	32.93	1.92×10^{-9}		
PKCnu/PRKD3	15.87	15.80	15.84	1.46×10^{-9}		
PKCtheta	55.13	56.74	55.93	1.58×10^{-9}		
PKCzeta	80.67	83.02	81.84	9.76×10^{-8}		
PKD2/PRKD2	31.93	34.93	33.43	1.96×10^{-9}		
PKG1a	88.24	88.97	88.60	1.06×10^{-9}		
PKG1b	90.62	90.96	90.79	2.49×10^{-9}		
PKG2/PRKG2	95.18	91.73	93.45	3.73×10^{-9}		
PKN1/PRK1	18.53	18.53	18.53	7.76×10^{-11}		
PKN2/PRK2	36.54	38.34	37.44	5.42×10^{-10}		
PKN3/PRK3	112.24	112.48	112.36	2.51×10^{-8}		
PLK1	91.25	89.60	90.42	2.16×10^{-7}		

PLK2	93.59	102.07	97.83	1.05×10^{-6}		
PLK3	93.18	102.11	97.65	4.04×10^{-7}		
PLK4/SAK	103.45	98.90	101.17	2.08×10^{-8}		
PRKX	97.71	96.44	97.08	2.71×10^{-9}		
PYK2	82.30	83.32	82.81	5.75×10^{-9}		
RAF1	90.17	96.15	93.16	ND	3.26×10^{-9}	**GW5074**
RET	28.27	28.92	28.60	3.72×10^{-9}		
RIPK2	63.11	62.79	62.95	2.21×10^{-7}		
RIPK3	117.84	115.61	116.73	ND	1.08×10^{-5}	**GW5074**
RIPK5	9.98	10.06	10.02	6.68×10^{-8}		
ROCK1	87.90	86.19	87.04	1.05×10^{-9}		
ROCK2	92.93	89.02	90.98	4.27×10^{-10}		
RON/MST1R	39.52	42.40	40.96	3.17×10^{-7}		
ROS/ROS1	15.77	14.43	15.10	1.77×10^{-10}		
RSK1	26.44	24.94	25.69	2.39×10^{-10}		
RSK2	55.08	57.13	56.11	1.97×10^{-10}		
RSK3	36.92	40.46	38.69	2.95×10^{-10}		
RSK4	33.21	32.06	32.64	1.44×10^{-10}		
SGK1	49.35	57.06	53.21	1.37×10^{-8}		
SGK2	6.57	9.77	8.17	3.52×10^{-8}		
SGK3/SGKL	75.96	78.47	77.22	1.19×10^{-7}		
SIK1	69.45	62.36	65.91	5.17×10^{-10}		
SIK2	34.67	34.91	34.79	2.38×10^{-10}		
SIK3	32.29	34.48	33.39	1.74×10^{-9}		
SLK/STK2	72.28	71.23	71.75	5.10×10^{-9}		
SNARK/NUAK2	91.08	91.09	91.09	4.11×10^{-8}		
SRMS	28.23	29.92	29.07	1.91×10^{-5}		
SRPK1	25.65	21.66	23.66	3.94×10^{-8}		
SRPK2	62.17	65.49	63.83	2.95×10^{-7}		
SSTK/TSSK6	64.89	70.73	67.81	2.51×10^{-7}		

STK16	66.52	75.58	71.05	3.70×10^{-7}		
STK22D/TSSK1	89.63	89.91	89.77	8.50×10^{-11}		
STK25/YSK1	57.09	55.70	56.39	1.64×10^{-9}		
STK32B/YANK2	98.86	98.92	98.89	1.75×10^{-7}		
STK32C/YANK3	61.81	54.65	58.23	2.86×10^{-7}		
STK33	16.11	17.89	17.00	2.71×10^{-8}		
STK38/NDR1	88.99	93.70	91.34	1.99×10^{-8}		
STK38L/NDR2	81.08	79.95	80.51	1.60×10^{-9}		
STK39/STLK3	2.23	0.97	1.60	5.78×10^{-8}		
SYK	80.34	75.39	77.86	1.89×10^{-10}		
TAK1	74.49	78.97	76.73	3.77×10^{-8}		
TAOK1	29.31	32.47	30.89	1.45×10^{-9}		
TAOK2/TAO1	23.55	25.84	24.70	3.23×10^{-9}		
TAOK3/JIK	48.29	50.74	49.51	1.67×10^{-9}		
TBK1	126.55	126.61	126.58	1.76×10^{-9}		
TEC	67.14	62.93	65.04	6.35×10^{-8}		
TESK1	26.36	36.74	31.55	9.39×10^{-7}		
TGFBR2	109.10	93.42	101.26	ND	7.20×10^{-6}	**GW5074**
TIE2/TEK	52.02	50.08	51.05	9.51×10^{-8}		
TLK1	90.50	87.49	88.99	4.19×10^{-8}		
TLK2	93.03	99.68	96.35	4.02×10^{-9}		
TNIK	19.11	17.56	18.33	5.86×10^{-10}		
TNK1	27.56	26.53	27.04	1.41×10^{-9}		
TRKA	6.34	4.99	5.67	2.23×10^{-9}		
TRKB	88.82	87.84	88.33	1.23×10^{-10}		
TRKC	64.27	62.19	63.23	4.73×10^{-10}		
TSSK2	85.27	83.49	84.38	9.51×10^{-9}		
TSSK3/STK22C	1.27	0.73	1.00	1.01×10^{-8}		
TTBK1	76.81	75.16	75.99	$>2.00 \times 10^{-5}$		
TTBK2	71.16	66.74	68.95	$>2.00 \times 10^{-5}$		

TXK	34.55	33.24	33.89	2.28×10^{-8}		
TYK1/LTK	50.89	51.78	51.34	2.22×10^{-8}		
TYK2	41.19	41.81	41.50	2.47×10^{-10}		
TYRO3/SKY	63.50	62.54	63.02	6.22×10^{-9}		
ULK1	83.31	88.63	85.97	7.34×10^{-9}		
ULK2	91.22	87.02	89.12	4.16×10^{-9}		
ULK3	156.53	193.52	175.03	2.14×10^{-9}		
VRK1	93.33	95.78	94.55	ND	6.42×10^{-7}	**Ro-31-8220**
VRK2	158.16	164.66	161.41	ND	1.39×10^{-5}	**Ro-31-8220**
WEE1	101.13	100.20	100.67	ND	9.95×10^{-8}	**Wee1 inhibitor**
WNK1	79.41	51.46	65.44	$>2.00 \times 10^{-5}$		
WNK2	49.41	50.07	49.74	1.51×10^{-6}		
WNK3	78.43	72.95	75.69	ND	2.32×10^{-6}	**Wee1 inhibitor**
YES/YES1	90.21	87.78	89.00	2.25×10^{-9}		
ZAK/MLTK	43.83	44.23	44.03	ND	1.18×10^{-6}	**GW5074**
ZAP70	45.23	43.81	44.52	1.01×10^{-8}		
ZIPK/DAPK3	10.97	9.46	10.21	4.81×10^{-9}		

[a]Compound **22** was tested in single dose duplicate mode at a concentration of 20 μM.

[b]Reactions were carried out at 10 μM ATP.

[c]Curve fit was performed where the enzyme activity at the highest concentration of compound was less than 65%.

[d]Relative to DMSO controls.

[e]Staurosporine was tested in 10-dose IC_{50} mode with 4-fold serial dilution starting at 20 μM.

[f]ND = not tested.

[g]Alternate control compounds were tested in 10-dose IC_{50} mode with 3-fold serial dilution starting at 20 μM.

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