SUPPORTING INFORMATION

Discovery of A-1331852, a First-in-Class, Potent and Orally-Bioavailable BCL-X\textsubscript{L} Inhibitor

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IN-VITRO BIOLOGY

Time Resolved-Fluorescence Resonance Energy Transfer (TR-FRET) Assays.

Test compounds were serially diluted in dimethyl sulfoxide starting at 500 \textmu M (20x starting concentration; 100% dimethylsulfoxide) followed by a 1:10 dilution of the compound dimethyl sulfoxide plate into assay buffer. 10 \textmu L of the compound in 10% dimethyl sulfoxide was then transferred into a 384-well plate (low volume Corning #3673 assay plate). Then 10 \textmu L of a 2x protein/probe/antibody mix is added to each well at final concentrations listed in the table below.

| Protein    | Probe                        | [Protein], nM | [Probe], nM | Antibody       | [Antibody], nM |
|------------|------------------------------|---------------|-------------|----------------|----------------|
| GST-BCL-X\textsubscript{L} | F-Bak (GQVGRQLAIIGDK(6-FAM)INR-amide) | 1             | 100         | Tb-anti-GST    | 1              |
| GST-BCL-2  | F-Bak (GQVGRQLAIIGDK(6-FAM)INR-amide) | 1             | 100         | Tb-anti-GST    | 1              |

The samples are then mixed on a shaker for 1 minute then incubated for an additional 1 hour at room temperature. For each assay plate, a probe/antibody and protein/antibody/probe mixture were included as a negative and a positive control, respectively. Fluorescence was measured on the Envision (Perkin Elmer) using a 340/35 nm excitation filter and 520/525 (F-Bak) and 495/510 nm (Tb-labeled anti-GST antibody) emission filters. Dissociation constants (K) were determined using Wang’s equation (Wang, Z.X. An exact mathematical expression for describing competitive binding of two different
ligands to a protein molecule. *FEBS Lett.* **1995, 360,** 111-114). The TR-FRET assay can be performed in the presence of varying concentrations of human serum (HS) to determine apparent IC50 after serum protein binding.

**Cellular Viability Assay: MOLT-4 and RS4;11 cells.**

Molt-4 (ATCC, Manassas, VA) human acute lymphoblastic leukemia cells or RS4;11 (ATCC, Manassas, VA) human acute lymphoblastic leukemia were plated 50,000 cells per well in 96-well tissue culture plates in a total volume of 100 μL tissue culture medium supplemented with 10% human serum (Invitrogen, Carlsbad, CA) and treated with a 3-fold serial dilution of the compounds of interest from 5 μM to 0.020 μL. Each concentration was tested in duplicate at least 3 separate times. The number of viable cells following 48 hours of compound treatment was determined using the CellTiter-Glo® luminescent cell viability assay according to manufacturer's recommendations (Promega Corp., Madison, WI). EC50 values were calculated using a sigmoidal fit of the concentration/inhibition response curves using GraphPad Prism 5.

**CHEMISTRY**

**General:** 1H NMR spectra were obtained on a Varian UNITY or Inova (500 MHz), Varian UNITY (400 MHz), or Varian UNITY plus or Mercury (300 MHz) instrument. Chemical shifts are reported as values (ppm) downfield relative to TMS as an internal standard, with multiplicities reported in the usual manner. Mass spectral analyses were performed on a Finnigan SSQ7000 GC/MS mass spectrometer using different techniques, including electrospray ionization (ESI), desorption chemical ionization (DCI) and atmospheric pressure chemical ionization (APCI), as specified for individual compounds. Exact mass measurements were performed on a Finnigan FTMS Newstar T70 mass spectrometer. The compound is determined to be "consistent" with the chemical formula if the exact mass measurement is within 5.0 ppm relative mass error (RME) of the exact monoisotopic mass.

Analytical LC-MS were performed on a Finnigan Navigator mass spectrometer and Agilent 1100 HPLC system running Xcalibur 1.2 and Open-Access 1.3 software. The mass spectrometer was operated under positive APCI ionization conditions. The HPLC system comprised an Agilent Quaternary pump, degasser, column compartment, autosampler and diode-array detector, with a Sedere Sedex 75 evaporative light-
scattering detector. The column used was a Phenomenex Luna Combi-HTS C8(2) 5μm 100Å (2.1mm × 30mm), utilizing Method A or Method B, as detailed below. TFA Method (Method A): A gradient of 10-100% acetonitrile (solvent 1) and 0.1% trifluoroacetic acid in water (solvent 2) was used, at a flow rate of 2 mL/min (0-0.1 min 10% solvent 1, 0.1-2.6 min 10-100% solvent 1, 2.6-2.9 min 100% solvent 1, 2.9-3.0 min 100-10% solvent 1). Ammonium acetate Method (Method B): A gradient of 10-100% acetonitrile (solvent 1) and 10 mM NH₄OAc in water (solvent 2) was used, at a flow rate of 1.5 mL/min (0-0.1 min 10% solvent 1, 0.1-3.1 min 10-100% solvent 1, 3.1-3.9 min 100% solvent 1, 3.9-4.0 min 100-10% solvent 1). All final analogs were >95% pure as determined by these methods.

Preparative reverse phase HPLC was performed on an automated Gilson HPLC system, using a SymmetryPrep Shield RP18 prep cartridge, 250 mm × 21.20 mm i.d., 10 μm, and a flow rate of 25 mL/min; λ = 214, 245 nm; mobile phase A, 0.1% trifluoroacetic acid in water; mobile phase B, acetonitrile, using a linear gradient 0-70% of B over 40 minutes, unless otherwise stated.

**Synthesis of Intermediate S-10**

![Synthesis Diagram]

**Supplemental Scheme 1.** Reagents: a) BnBr, EtOH, 80 °C, 87% yield; b) NaCNBH₃, MeOH, 55%; c) 1-chloroethyl carbonochloridate then MeOH, 80 °C, 77% yield; d) di-tert-butyl dicarbonate, Na₂CO₃, 81% yield; e) Pd(dppf)₂, CO (50 psi), MeOH, 66% yield; f) NaOH, water, 45 °C, 89% yield; g) CDI, DBU, CH₃CN, 60 °C, 87% yield; h) HCl, EtOAc, 99% yield; i) S-11, Cs₂CO₃, DMA, 120 °C, 32% yield.
2-benzyl-8-bromoisoquinolin-2-ium bromide (S-2). To a solution of 8-bromoisoquinoline (25 g, 120 mmol) in ethanol (500 mL) was added (bromomethyl)benzene (25 mL, 211 mmol). The reaction was heated at 80 °C for 12 hrs. The reaction mixture was concentrated under reduced pressure to give a residue, which was triturated with ethyl acetate to give the title compound (31 g, 87% yield) as a white solid. \(^1\)H NMR (400 MHz, dimethylsulfoxide-\(d_6\)) \(\delta \) 6.15 (s, 2 H) 7.35 - 7.51 (m, 3 H) 7.60 (dd, \(J = 7.7, 1.7\) Hz, 2 H) 8.06 - 8.18 (m, 1 H) 8.30 - 8.48 (m, 2 H) 8.59 - 8.71 (m, 1 H) 8.88 (dd, \(J = 6.7, 1.10\) Hz, 1 H) 10.24 (s, 1 H).

2-benzyl-8-bromo-1,2,3,4-tetrahydroisoquinoline (S-3). To a solution of S-2 (50 g, 132 mmol) in methanol (500 mL) was added sodium cyanoborohydride (16.58 g, 264 mmol), and the mixture was stirred at 25 °C for 12 hrs. The mixture was poured into water (1 L) and extracted with ethyl acetate (3 × 500 mL). The organic layer was washed with brine (500 mL) and dried over anhydrous sodium sulfate, filtered and concentrated under reduce pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=10/1) to obtain the title compound (21.9 g, 55% yield) as a yellow oil. \(^1\)H NMR (400 MHz, chloroform-\(d\)) \(\delta \) 2.63 - 2.74 (m, 2 H) 2.83 - 2.95 (m, 2 H) 3.67 (s, 2 H) 3.75 (s, 2 H) 6.96 - 7.13 (m, 2 H) 7.28 - 7.32 (m, 1 H) 7.33 - 7.44 (m, 5 H).

8-bromo-1,2,3,4-tetrahydroisoquinoline (S-4). To a solution of S-3 (30 g, 99 mmol) in 1,2-dichloroethane (300 mL) was added 1-chloroethyl carbonochloridate (28.4 g, 199 mmol) at 0 °C. The reaction was heated to 25°C for 2 hrs. To the reaction mixture was added methanol (500 mL), and the mixture was heated to 80 °C for 1 hr. The reaction mixture was concentrated under reduced pressure. The residue was washed with ethyl acetate (500 mL) to obtain the title compound (16 g, 77% yield) as white solid. \(^1\)H NMR (400 MHz, methanol-\(d_4\)) \(\delta \) 3.15 (t, \(J = 6.2\) Hz, 2 H) 3.50 (t, \(J = 6.3\) Hz, 2 H) 4.34 (s, 2 H) 7.16 - 7.34 (m, 2 H) 7.55 (d, \(J = 7.6\) Hz, 1 H).

tert-butyl 8-bromo-3,4-dihydroisoquinoline-2(1H)-carboxylate (S-5). To a solution of S-4 (30 g, 141 mmol) in methanol (200 mL) was added sodium carbonate (75.0 g, 707 mmol) in water (200 mL), followed by di-tert-butyl dicarbonate (36.1 mL, 156 mmol). The reaction was stirred at 25 °C for 1 hr. The mixture was poured into water (500 mL) and extracted with ethyl acetate (3 × 300 mL). The organic
layer was washed with brine (500 mL) and dried over anhydrous sodium sulfate, filtered and concentrated under reduce pressure to give a yellow oil. The oil was trituated with petroleum ether at -78 °C to give the title compound (35.6 g, 81% yield) as white solid. 1H NMR (400 MHz, dimethylsulfoxide-\textit{d}_6) \( \delta \) 1.43 (s, 9 H) 2.79 (br t, \( J = 5.50 \) Hz, 2 H) 3.50 - 3.60 (m, 2 H) 4.44 (br s, 2 H) 7.11 - 7.24 (m, 2 H) 7.48 (br d, \( J = 7.8 \) Hz, 1 H). MS (ESI) m/z calculated for C\textsubscript{14}H\textsubscript{18}BrNO\textsubscript{2}, 311.05, 313.05; found 256.0, 258.0 (M-tertBu+H)+.

2-tert-butyl 8-methyl 3,4-dihydroisoquinoline-2,8(1H)-dicarboxylate (S-6). To a solution of S-5 (25 g, 80 mmol) in methanol (200 mL) and N,N-dimethylformamide (100 mL) was added 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium(II) dichloromethane complex (3.27 g, 4.00 mmol) and triethylamine (44.6 mL, 320 mmol). The reaction was heated at 80 °C under an atmosphere of CO (50 psi) for 12 hrs. The reaction was cooled to 25 °C and filtered through celite, eluting with ethyl acetate (200 mL). The organic phase was concentrated under reduced pressure. The residue was diluted with ethyl acetate (800 mL) and washed with 1N aqueous hydrochloride solution (500 mL), brine (500 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=10/1) to obtain the title compound (15.4 g, 66% yield) as white solid. 1H NMR (400 MHz, dimethylsulfoxide-\textit{d}_6) \( \delta \) 1.41 (s, 9 H) 2.85 (br t, \( J = 5.6 \) Hz, 2 H) 3.55 (br s, 2 H) 3.84 (s, 3 H) 4.81 (br s, 2 H) 7.27 - 7.35 (m, 1 H) 7.41 (br d, \( J = 7.3 \) Hz, 1 H) 7.76 (br d, \( J = 7.5 \) Hz, 1 H). MS (ESI) m/z calculated for C\textsubscript{16}H\textsubscript{21}NO\textsubscript{4}, 291.1, found 236.0 (M-tertBu+H)+.

2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-8-carboxylic acid (S-7). To a solution of S-6 (30 g, 103 mmol) in methanol (150 mL) was added a solution of sodium hydroxide (16.47 g, 412 mmol) in water (150 mL). The reaction was stirred at 45 °C for 2 hrs. The reaction was cooled to ambient temperature, and the mixture was extracted with ethyl acetate (200 mL). The organic phase was discarded, and the water layer was adjusted to pH = 5 by 1N aqueous hydrochloride solution. The solid was filtered, washed with water (200 mL) and dried under vacuum to give the title compound (25.4 g, 89% yield). 1H NMR (400 MHz, dimethylsulfoxide-\textit{d}_6) \( \delta \) 1.21 - 1.58 (m, 9 H) 2.74 - 2.96 (m, 2 H) 3.54 (br s, 2 H) 4.83 (br s, 2 H) 7.19 - 7.43 (m, 2 H) 7.74 (br d, \( J = 7.3 \) Hz, 1 H). MS (ESI) m/z calculated for C\textsubscript{16}H\textsubscript{19}NO\textsubscript{4}, 277.13; found 222.1 (M-tertBu+H)+.
**tert-butyl 8-(benzo[d]thiazol-2-ylcarbamoyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (S-8).** To a solution of S-7 (24 g, 87 mmol) in acetonitrile (300 mL) was added carbonyl diimidazole (CDI) (17.54 g, 108 mmol). The reaction was stirred at 25 °C for 30 minutes. To the reaction mixture was added 1,8-diazabicyclo[5.4.0]undec-7-ene (21.08 g, 138 mmol), and the reaction was stirred at 25 °C for another 30 minutes. Benzo[d]thiazol-2-amine (16.25 g, 108 mmol) was added, and the reaction was stirred at 60 °C for 12 hours. The reaction was cooled to ambient temperature, and the mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate (1 L) and washed with 1N aqueous hydrochloride solution (500 mL), saturated aqueous sodium bicarbonate solution (500 mL) and brine (500 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The solid was washed with methyl tert-butyl ether (500 mL) to give the title compound (31.0 g, 87% yield) as white solid. H NMR (400 MHz, DMSO-d6) δ ppm 1.39 (br s, 9 H) 2.88 (br s, 2 H) 3.57 (br s, 2 H) 4.70 (br s, 2 H) 7.37 (dt, J = 15.2, 7.43 Hz, 3 H) 7.47 (br t, J = 7.3 Hz, 1 H) 7.59 (br d, J = 6.9 Hz, 1 H) 7.79 (br d, J = 7.8 Hz, 1 H) 8.03 (br d, J = 7.8 Hz, 1 H) 12.85 (br s, 1 H). MS (ESI) m/z calculated C22H23N3O3S, 409.15; found 410.1 (M+H)+.

**N-(benzo[d]thiazol-2-yl)-1,2,3,4-tetrahydroisoquinoline-8-carboxamide (S-9), HCl salt.** To a solution of S-8 (30 g, 73.3 mmol) in ethyl acetate (200 mL) was added aqueous hydrochloride solution (200 mL, 800 mmol, 4M in ethyl acetate). The reaction was stirred at 25 °C for 12 hrs. The reaction mixture was filtered, and the filter cake was washed with ethyl acetate (200 mL) and air-dried to give the title compound (25.0g, 99% yield) as white solid. H NMR (400 MHz, methanol-d4) δ ppm 3.16 - 3.28 (m, 2 H) 3.55 (br t, J = 6.3 Hz, 2 H) 4.69 (s, 2 H) 7.33 - 7.44 (m, 1 H) 7.46 - 7.62 (m, 3 H) 7.82 (br d, J = 8.4 Hz, 2 H) 7.95 (d, J = 7.9 Hz, 1 H). MS (ESI) m/z calculated for C17H15N3OS, 309.09; found 310.1 (M+H)+.

**tert-butyl 6-(8-(benzo[d]thiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl)-3-bromopicolinate (S-10).** To a solution of S-9 (24 g, 69.4 mmol) in dimethylacetamide (200 mL) were added S-11 (20.30 g, 69.4 mmol), 4 Angstrom molecular sieves (12 g, 69.4 mmol) and cesium carbonate (22.61 g, 69.4 mmol). The reaction was stirred at 120 °C for 12 hours under nitrogen atmosphere. The reaction was cooled to ambient temperature, and the mixture was filtered through the celite. The filter cake was washed with ethyl acetate (1 L). The filtrate was washed with 10% aqueous citric acid solution (800 mL), brine (500 mL)
mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The solid was triturated with ethyl acetate (200 mL) and air-dried to give the title compound (12.4 g, 31.6% yield) as a white solid. ¹H NMR (400 MHz, dimethylsulfoxide- d₆) δ ppm 1.33 (s, 9 H) 3.00 (br t, J = 5.9 Hz, 2 H) 3.77 (t, J = 6.0 Hz, 2 H) 4.93 (s, 2 H) 6.86 (d, J = 9.2 Hz, 1 H) 7.30 - 7.39 (m, 2 H) 7.40 - 7.50 (m, 2 H) 7.58 (d, J = 7.3 Hz, 1 H) 7.71 - 7.83 (m, 2 H) 8.02 (d, J = 7.8 Hz, 1 H) 12.87 (br s, 1 H). MS (ESI) m/z calculated for C₂₇H₂₅BrN₄O₃S, 564.08, 566.08; found 565.1, 567.2 (M+H)⁺.

tert-butyl 3-bromo-6-chloropicolinate (S-11). To a solution of 3-bromo-6-chloropicolinic acid (20 g, 85 mmol) and pyridine (45.8 mL, 567 mmol) in tert-butanol (200 mL) was added p-toluenesulfonyl chloride (38.7 g, 203 mmol). The mixture was stirred at 25 °C for 12 hrs. The mixture was quenched with aqueous sodium bicarbonate solution (800 mL) and extracted with ethyl acetate (3 x 800 mL). The organic layer was washed with brine (800 mL) and dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate=10/1) to obtain S-11 (20 g, 80% yield) as a white solid. ¹H NMR (400 MHz, dimethylsulfoxide- d₆) δ ppm 1.56 (s, 9 H) 7.62 (d, J = 2.6 Hz, 1 H) 8.25(d, J = 8.4 Hz, 1 H). MS(ESI) m/z calculated for C₁₀H₁₁BrClNO₂, 290.97, 292.96; found 237.9 (M-tertBu+H)⁺.

Synthesis of Compound A-1331852 (13)
Supplemental Scheme 2. Reagents: a) NaH, N,N-DMF, 80 °C, 77% yield; b) nBuLi, -78 °C then MeI, ~99% yield; c) NBS, N,N-dimethylacetamide, rt, 83% yield; d) nBuLi, B(O'Pr)3, -78 °C then pinacol, 50% yield; e) 2.5 mol% Pd2(dba)3, 10 mol% S-17, K3PO4, 1:1 1,4-dioxane:H2O, 90 °C, 53% yield; f) TFA, DCM, rt, 70% yield.

(1s,3s)-1-(bromomethyl)adamantane (S-12). To a solution of zinc(II) bromide (298 g, 1323 mmol) in 40% HBr (700 mL) was added (1s,3s)-adamantan-1-ylmethanol (110 g, 662 mmol). The suspension was stirred at 125 °C for 16 hours. The mixture was cooled to ambient temperature and extracted with dichloromethane (2 x 750 mL). The organic layer was washed with saturated aqueous sodium bicarbonate solution, water and brine. The organic layer was dried over anhydrous sodium sulfate,
filtered and concentrated to give the title compound (145 g, 96 % yield) as a white solid. \(^1\)H NMR (400 MHz, chloroform-\(d\)) \(\delta\) ppm 1.57 (d, \(J = 2.2\) Hz, 6 H) 1.60 - 1.66 (m, 3 H) 1.67 - 1.74 (m, 3 H) 2.01 (br s, 3 H) 3.16 (s, 2 H).

\textbf{1-((1s,3s)-adamantan-1-ylmethyl)-1H-pyrazole (S-13).} To a solution of \textbf{S-12} (135 g, 589 mmol) in N,N-dimethylformamide (900 mL) was added sodium hydride (58.9 g, 1473 mmol, 60% wt in mineral oil) portion-wise at 0 °C over 1 hour under nitrogen. Then to above mixture was added 1H-pyrazole (80 g, 1178 mmol) in N,N-dimethylformamide (200 mL) dropwise at 0 °C. Then the reaction was stirred at 80 °C for 12 hrs. The reaction was cooled to 20 °C, and the mixture was poured into ice-water (5 L). The mixture was extracted with ethyl acetate (3 × 1 L). The organic layer was washed with brine (1 L) and dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with petroleum ether /ethyl acetate = 100/1 to 3/1, to give the title compound (100.8 g, 77 %) as a white solid. \(^1\)H NMR (400 MHz, chloroform-\(d\)) \(\delta\) ppm 1.52 (d, \(J = 2.4\) Hz, 6 H) 1.56 - 1.65 (m, 4 H) 1.66 - 1.77 (m, 3 H) 1.99 (br s, 3 H) 3.81 (s, 2 H) 6.24 (t, \(J = 2.0\) Hz, 1 H) 7.31 (d, \(J = 2.2\) Hz, 1 H) 7.49 (d, \(J = 1.5\) Hz, 1 H). MS (ESI) m/z calculated for C\(_{14}\)H\(_{20}\)N\(_2\), 216.16; found 217.3 (M+H\(^+\)).

\textbf{1-((1s,3s)-adamantan-1-ylmethyl)-5-methyl-1H-pyrazole (S-14).} To a cold (-50 °C bath) solution of compound \textbf{S-13} (60 g, 277 mmol) in tetrahydrofuran (600 mL) was added n-butyl lithium (144 mL, 361 mmol) dropwise. The reaction was stirred for 1.5 h during which time the temperature raised to -20 °C. Methyl iodide (23.41 mL, 374 mmol) was added dropwise. The reaction was stirred for 0.5 h between -20 °C and -15 °C and then quenched by the addition of 500 mL of water and extracted with ethyl acetate (3 × 600 mL). The combined organics were washed with brine, dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the title compound (63.3 g, 99 % yield) as a light yellow solid, which was used in the subsequent step without further purification. \(^1\)H NMR (400 MHz, chloroform-\(d\)) \(\delta\) ppm 1.55 - 1.75 (m, 12 H), 1.99 (br s, 3 H) 2.28 (s, 3 H), 3.70 (s, 2 H), 5.99 (d, \(J = 0.9\) Hz, 1 H), 7.39 (d, \(J = 1.6\) Hz, 1 H). MS (ESI) m/z calculated C\(_{15}\)H\(_{22}\)N\(_2\), 230.18; found 231.3 (M+H\(^+\)).
1-((1s,3s)-adamant-1-ylmethyl)-4-bromo-5-methyl-1H-pyrazole (S-15). To a solution of compound S-14 (63.3 g, 275 mmol) in N,N-dimethylacetamide (650 mL) was added N-bromosuccinimide (53.8 g, 302 mmol). The mixture became thick, and stirring was continued overnight. The reaction mixture was diluted with water (3 L), and the precipitate was collected by filtration. The solid was washed with water, 20% aqueous sodium thiosulfate, 20% aqueous sodium carbonate and water. The solid was dissolved in ethyl acetate, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain the title compound (74.3 g, 83 % yield) as a white solid, which was used in the subsequent step without further purification. 1H NMR (400 MHz, chloroform-d) δ ppm 7.39 (s, 1H), 3.71 (s, 2H), 2.24 (s, 3H), 1.97 (bs, 3H), 1.73 - 1.53 (m, 12H). MS (ESI) m/z calculated for C16H22BrN2, 308.09, 310.09; found 309.2 and 311.2 (M+H)+.

1-((1s,3s)-adamant-1-ylmethyl)-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (S-16). To a cold (-78 °C) solution of compound S-15 (70 g, 226 mmol) and triisopropyl borate (79 mL, 340 mmol) in a mixture of tetrahydrofuran (450 mL) and toluene (450 mL) was added n-butyl lithium (145 mL, 362 mmol) dropwise, keeping the internal temperature less than -55 °C. The mixture was stirred for 20 min, and a solution of pinacol (134 g, 1132 mmol) in tetrahydrofuran (200 mL) was added. The cooling bath was removed, and the reaction was stirred at room temperature overnight. The reaction was diluted with water (1000 mL) and ethyl acetate (2000 mL). The precipitate was filtered, and the filtrate was extracted with ethyl acetate (1 x 800 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was recrystallized from dichloromethane and petroleum ether (1:100, 450 mL). The solid was filtered and air-dried to give the title compound (40 g, 49.6 % yield) as a white solid. 1H NMR (400MHz, chloroform-d) δ ppm 1.32 (s, 12 H), 1.55 - 1.73 (m, 12 H), 1.98 (br s, 3 H), 2.43 (s, 3 H), 3.72 (s, 2 H), 7.69 (s, 1 H). MS (ESI) m/z calculated for C23H33BN2O2, 356.26; found 357.4 (M+H)+.

tert-butyl 3-((1s,3s)-adamant-1-ylmethyl)-5-methyl-1H-pyrazol-4-yl)-6-(8-(benzo[d]thiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl)picolinate (S-18). A 250-mL 2-neck round-bottom flask equipped with a stir bar, septum and reflux condenser was charged with S-10 (10.35 g, 18.30 mmol), S-16 (7.5 g, 21.05 mmol), potassium phosphate (13.57 g, 64.1 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.419 g, 0.458 mmol) and (1R,3S,5S,7R)-1,3,5,7-tetramethyl-
8-phenyl-2,4,6-trioxo-8-phosphaadamantane (0.535 g, 1.830 mmol) was degassed for 20 minutes with a sweep of nitrogen. In a separate flask, 1,4-dioxane (51 mL) and water (51 mL) was sparged with nitrogen for 20 minutes. The solution of 1,4-dioxane and water was added via cannula to the flask containing the solid reagents. The reaction was heated to 90 °C and stirred for 2 hours under a positive pressure of nitrogen. The reaction was cooled to ambient temperature and quenched by the addition of saturated aqueous sodium bicarbonate solution and ethyl acetate (100 mL each). The layers were separated, and the aqueous was extracted with additional ethyl acetate (2 x 100 mL). The combined organics were dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (300 g), eluting with a gradient of 0 to 50% ethyl acetate in heptane, to give the title compound as a yellow foam (7.0 g, 53.5%).

1H NMR (400 MHz, dimethylsulfoxide- $d_6$) δ ppm 12.85 (s, 1H), 8.01 (d, $J = 8.0$ Hz, 1H), 7.77 (d, $J = 8.0$ Hz, 1H), 7.58 (d, $J = 7.5$, 1H), 7.49 – 7.40 (m, 3H), 7.39 – 7.30 (m, 2H), 7.20 (s, 1H), 6.91 (d, $J = 8.8$ Hz, 1H), 4.96 (s, 2H), 3.83 (t, $J = 6.1$ Hz, 2H), 3.70 (s, 2H), 3.02 (t, $J = 6.0$ Hz, 2H), 2.08 (s, 3H), 1.93 - 1.88 (m, 3H), 1.66 - 1.60 (m, 3H), 1.58 – 1.48 (m, 9H), 1.16 (s, 9H).

MS (ESI) m/z calculated for $C_{42}H_{46}N_6O_3S$, 714.34; found 715.1 (M+H)$^+$.  

3-(1-((1S,3s)-adamantan-1-ylmethyl)-5-methyl-1H-pyrazol-4-yl)-6-(8-(benzo[d]thiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl)picolinic acid (A-1331852, 13). To an ambient solution of S-17 (20.27 g, 28.4 mmol) in dichloromethane (200 mL) was added trifluoroacetic acid (200 mL, 2596 mmol). The reaction flask was covered with foil and stirred overnight. The reaction mixture was concentrated under reduced pressure to a thick syrup. The residue was dissolved in dichloromethane (250 mL), and the solution was washed with water (7 x 350 mL). The last wash water layer had pH of ~5. The dichloromethane solution (which has some solid trying to crash out) was dried over anhydrous Na$_2$SO$_4$ and filtered, then partially concentrated to a volume of ~ 100 mL, at which point there was a fine solid in the mixture. This semi-suspension was stirred while acetonitrile (~ 350 mL) was gradually added. Following addition of the acetonitrile, the resulting suspension was stirred at room temperature for 1 hour. The solid was collected by filtration, rinsing with acetonitrile. The solid was air-dried for 30 minutes and transferred to an amber vial and dried overnight under vacuum to give the title compound (13.2 g, 70%). 1H NMR (400 MHz, dimethylsulfoxide- $d_6$) δ ppm 12.82 (br s, 2H), 8.18 – 7.92 (m, 1H), 7.79 (d, $J = 7.9$ Hz, 1H), 7.62 (dd, $J = 7.6$, 1.5 Hz, 1H), 7.50 (d, $J = 8.7$ Hz, 1H), 7.48 - 7.41 (m, 2H), 7.40 – 7.31 (m, 2H), 7.27 (s, 1H), 6.94 (d, $J = 8.9$ Hz, 1H), 4.95 (s, 2H), 3.88 (t, $J = 5.9$ Hz, 2H), 3.70 (s, 2H), 3.01 (t, $J = 6.0$ Hz, 2H), 2.10 (s, 3H), 1.94 - 1.89 (m, 3H), 1.70 – 1.44 (m, 12H). 13C NMR (101 MHz,
dimethylsulfoxide-d$_6$) δ ppm 168.42, 167.64, 158.41, 155.92, 148.53, 148.39, 140.81, 136.99, 136.54, 136.46, 133.76, 131.87, 131.51, 131.49, 126.57, 126.24, 126.21, 123.76, 121.76, 120.53, 115.58, 115.43, 107.98, 59.85, 44.92, 41.82, 40.12, 36.34, 35.06, 28.11, 27.73, 24.97, 10.53, 1.17. MS (ESI) m/z calculated for C$_{38}$H$_{38}$N$_6$O$_3$S, 658.27; found 659.2 (M+H)$^+$.

**Synthesis of Compound 5**

![Chemical structure](image)

**Supplemental Scheme 3.** Reagents: a) NaH, BnBr, N,N-DMF, 52% yield; b) Pd(PPh$_3$)$_4$, CsF, DME, MeOH, microwave heating, 135 °C, 39% yield; c) TFA, DCM, 55% yield.

**1-benzyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole (S-20).** To a cold (0 °C) suspension of sodium hydride (0.178 g, 4.44 mmol, 60 weight % in mineral oil) in N,N-dimethyl formamide (10 mL) was added 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrole (0.84 g, 3.70 mmol) as a solution in N,N-dimethylformamide. The reaction was stirred for 1 hour, and (bromomethyl)benzene (0.439 mL, 3.70 mmol) was added. The cold bath was removed, and the reaction stirred for 6 hours. The reaction was quenched by the addition of ethyl acetate (50 mL) and saturated aqueous sodium bicarbonate solution (100 mL). The layers were separated, and the aqueous was
extracted with ethyl acetate (2 x 50 mL). The combined organics were washed with brine, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with 10% ethyl acetate in heptanes to give the title compound as an oil (0.54 g, 52%). $^1$H NMR (400 MHz, dimethylsulfoxide-$d_6$) δ 7.36 – 7.30 (m, 2H), 7.30 – 7.25 (m, 1H), 7.24 – 7.20 (m, 2H), 7.14 (t, $J = 1.8$ Hz, 1H), 6.84 (t, $J = 2.3$ Hz, 1H), 6.22 (dd, $J = 2.7, 1.6$ Hz, 1H), 5.10 (s, 2H), 1.22 (s, 12H).

MS (APCI+) m/z calculated for C_{17}H_{22}BNO_{2}, 283.17; found 284.5.

**tert-butyl 6-(8-(benzodithiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl)-3-(1-benzyl-1H-pyrrol-3-yl)picolinate (S-21).** A mixture of S-10 (0.15 g, 0.265 mmol), S-20 (0.090 g, 0.318 mmol), tetrakis(triphenylphosphine)palladium(0) (0.031 g, 0.027 mmol), and cesium fluoride (0.121 g, 0.796 mmol) in 1,2-dimethoxyethane (2 mL) and methanol (1 mL) was heated under microwave conditions (135 °C, 45 min). After cooling, the reaction mixture was loaded onto a 24 g silica column and dried. The column was eluted with 40% ethyl acetate in heptanes to give the title compound (0.067 g, 39% yield).

$^1$H NMR (500 MHz, dimethylsulfoxide-$d_6$) δ ppm 12.84 (s, 1H), 8.03 (dd, $J = 8.0, 1.1$ Hz, 1H), 7.78 (d, $J = 8.0$ Hz, 1H), 7.62 (d, $J = 8.8$ Hz, 1H), 7.56 (d, $J = 7.4$ Hz, 1H), 7.47 (td, $J = 7.8, 1.3$ Hz, 1H), 7.42 (d, $J = 7.6$ Hz, 1H), 7.36 (dt, $J = 7.6, 3.9$ Hz, 2H), 7.35 – 7.20 (m, 4H), 7.19 (dd, $J = 6.9, 1.8$ Hz, 2H), 6.90 (d, $J = 9.0$ Hz, 1H), 6.84 (p, $J = 2.2$ Hz, 2H), 6.16 – 6.12 (m, 1H), 5.07 (s, 2H), 4.93 (s, 2H), 3.79 (t, $J = 6.1$ Hz, 2H), 3.01 (t, $J = 6.0$ Hz, 2H), 1.18 (s, 9H). MS (ESI) m/z calculated for C_{38}H_{35}N_{5}O_{3}S, 641.25; found 642.8 (M+H)^+.

**6-(8-(benzodithiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl)-3-(1-benzyl-1H-pyrrol-3-yl)picolinic acid (S).** To a solution of S-21 (0.05 g, 0.078 mmol) in dichloromethane (2 mL) was added trifluoroacetic acid (1 mL). The reaction was stirred for 16 hours and concentrated under reduced pressure. The residue was purified by Prep HPLC using Gilson system eluting with 20-80% acetonitrile in water containing 0.1% v/v trifluoroacetic acid to give the title compound (0.025 g, 55%). $^1$H NMR (400 MHz, dimethylsulfoxide-$d_6$) δ ppm 12.86 (s, 1H), 8.04 (d, 1H), 7.79 (d, 1H), 7.67 (d, 1H), 7.60 (d, 1H), 7.45 (m, 2H), 7.34 (m, 4H), 7.23 (m, 3H), 6.96 (t, 1H), 6.89 (d, 1H), 6.81 (m, 1H), 6.19 (m, 1H), 5.08 (s, 2H), 4.91 (s, 2H), 3.84 (t, 2H), 2.99 (t, 2H). MS (ESI) m/z calculated for C_{34}H_{27}N_{5}O_{3}S, 585.18; found 586.1 (M+H)^+.

**Synthesis of Compound 6**
Supplemental Scheme 4. Reagents: a) 2.5 mol% Pd$_2$(dba)$_3$, 10 mol% S-19, K$_3$PO$_4$, 1:1 1,4-dioxane:HzO, 90 °C, 63% yield; b) TFA, DCM, rt, 85% yield.

**tert-butyl 6-(8-(benzo[d]thiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl)-3-(1-benzyl-1H-pyrazol-4-yl)picolinate (S-22).** In an amber via was placed S-10 (0.162 g, 0.286 mmol), 1-benzyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.114 g, 0.401 mmol), potassium phosphate (0.213 g, 1.003 mmol), tris(dibenzylideneacetone)dipalladium(0) (6.56 mg, 7.16 µmol) and (1S,3R,5R,7S)-1,3,5,7-tetramethyl-8-tetradecyl-2,4,6-trioxa-8-phosphaadamantane (0.012 g, 0.029 mmol). To the reaction were added 1,4-dioxane (0.5 mL) and water (0.5 mL). The head spaced was flushed with nitrogen, and the vial was sealed and heated to 90 °C overnight. The reaction was cooled to ambient. The organic layer was decanted with a pipette and loaded onto a silica gel column (Reveleris 40 g). The column was eluted with a gradient of 5% to 50% ethyl acetate in heptane over 30 minutes to give the title compound (0.115 g, 62.5 % yield) as a white solid. $^1$H NMR (500 MHz, dimethyl sulfoxide- d$_6$) δ ppm 12.85 (s, 1H), 8.05 - 8.00 (m, 1H), 7.80 (s, 1H), 7.78 (d, $J = 8.0$ Hz, 1H), 7.66 (d, $J = 8.8$ Hz, 1H), 7.56 (d, $J =
7.5 Hz, 1H), 7.52 (s, 1H), 7.47 (ddd, \( J = 8.2, 7.2, 1.3 \) Hz, 1H), 7.42 (d, \( J = 7.7 \) Hz, 1H), 7.38 - 7.25 (m, 5H), 7.25 - 7.22 (m, 2H), 6.94 (d, \( J = 8.9 \) Hz, 1H), 5.31 (s, 2H), 4.96 (s, 2H), 3.81 (t, \( J = 6.1 \) Hz, 2H), 3.01 (t, \( J = 6.0 \) Hz, 2H), 1.17 (s, 9H). MS (ESI) m/z calculated for \( \text{C}_{37}\text{H}_{38}\text{N}_{6}\text{O}_{3}\text{S}, 642.24 \); found 643.2 (M+H)⁺.

6-(8-(benzo[d]thiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl)-3-(1-benzyl-1H-pyrazol-4-yl)picolinic acid (6). To a solution of S-22 (0.116 g, 0.180 mmol) in dichloromethane (1 mL) was added trifluoroacetic acid (0.5 ml, 6.49 mmol), and the reaction was stirred overnight. The reaction was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (Reveleris 40 g), eluting with a gradient of 0.5% to 5% methanol in dichloromethane to give the title compound (0.090 g, 85 % yield). \(^1\)H NMR (501 MHz, dimethylsulfoxide-\( d_6 \)) \( \delta \) ppm 13.07 - 12.63 (m, 2H), 8.03 (d, \( J = 8.0 \) Hz, 1H), 7.90 (s, 1H), 7.78 (d, \( J = 8.0 \) Hz, 1H), 7.70 (d, \( J = 8.9 \) Hz, 1H), 7.60 (d, \( J = 7.5 \) Hz, 1H), 7.56 (s, 1H), 7.50 - 7.43 (m, 1H), 7.41 (d, \( J = 7.6 \) Hz, 1H), 7.37 - 7.25 (m, 5H), 7.25 - 7.21 (m, 2H), 6.93 (d, \( J = 8.9 \) Hz, 1H), 5.31 (s, 2H), 4.93 (s, 2H), 3.85 (t, \( J = 6.0 \) Hz, 2H), 2.99 (t, \( J = 6.0 \) Hz, 2H). MS (ESI) m/z calculated for \( \text{C}_{33}\text{H}_{26}\text{N}_{6}\text{O}_{3}\text{S}, 586.18 \); found 587.1 (M+H)⁺.

**Synthesis of Compound 7**
Supplemental Scheme 5. Reagents: a) TMS-acetylene, Et$_3$N, CuI, N,N-DMF, 85% yield; b) BnBr, NaN$_3$, CuSO$_4$, sodium ascorbate, N,N-DMF 70 °C, 79% yield; c) TFA, DCM, rt, 66% yield.

tert-butyl 6-(8-(benzo[d]thiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl)-3-ethynylpicolinate (S-23). To a 50 mL pressure flask was added S-10 (0.843 g, 1.49 mmol), ethynyltrimethylsilane (2.1 mL, 14.9 mmol), and triethylamine (1.03 mL, 7.45 mmol) in N,N-dimethylformamide (14.9 mL). Tetrakis(triphenylphosphine)palladium (0.345 g, 0.298 mmol) and copper (I) iodide (0.028 g, 0.149 mmol) were added, and the flask was flushed with nitrogen and sealed. The reaction was heated to 85 °C for 36 hours, cooled and passed through a plug of silica gel. After rinsing the silica gel with dichloromethane, the combined filtrates were concentrated by rotary evaporation and taken up in tetrahydrofuran (9 mL). tetra-n-Butylammonium fluoride (1M in tetrahydrofuran, 1.72 mL, 1.72 mmol) was added dropwise at room temperature. The reaction was allowed to stir for 2 hours. Saturated aqueous ammonium chloride solution was added and the aqueous portion was extracted three times with dichloromethane. The combined organics were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by regular phase flash column chromatography (Analogix, 0-100% ethyl acetate in hexanes) to provide the title compound (410 mg, 54%). $^1$H NMR (300 MHz, dimethylsulfoxide-d$_6$) δ 12.83 (s, 1H), 8.01 (d, $J = 8.0, 1.1$ Hz, 1H), 7.76 (d, $J = 8.5$ Hz, 1H), 7.65 (d, $J = 8.9$ Hz, 1H).
Hz, 1H), 7.57 (d, J = 7.4 Hz, 1H), 7.49 – 7.39 (m, 2H), 7.39 – 7.29 (m, 2H), 6.89 (d, J = 9.0 Hz, 1H), 4.98 (s, 2H), 4.17 (s, 1H), 3.82 (t, J = 6.0 Hz, 2H), 3.00 (q, J = 6.0, 5.0 Hz, 2H), 1.33 (s, 9H). MS (ESI) m/z calculated for C_{23}H_{28}N_{4}O_{3}S, 510.17; found 511.4 (M+H)^{+}.

tert-butyl 6-(8-(benzo[d]thiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl)-3-(1-benzyl-1H-1,2,3-triazol-4-yl)picolinate (S-24). To a 4 mL vial was added S-23 (150 mg, 0.294 mmol), benzyl bromide (45 μL, 0.382 mmol), and sodium azide (28 mg, 0.44 mmol) in N,N-dimethylformamide (0.78 mL) and water (0.19 mL). Sodium ascorbate (5.8 mg, 0.029 mmol) and copper (II) sulfate pentahydrate (3.67 mg, 0.015 mmol) was added and the mixture was heated at 70 °C overnight, cooled, and chromatographed by regular phase flash column chromatography (Analogix, 0-100% ethyl acetate in hexanes) to provide the title compound (150 mg, 79%). MS (ESI) m/z calculated for C_{36}H_{33}N_{7}O_{3}S, 643.24; found 644.5 (M+H)^{+}.

6-(8-(benzo[d]thiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl)-3-(1-benzyl-1H-1,2,3-triazol-4-yl)picolinic acid (7). To a 10 mL round-bottomed flask was added S-24 (150 mg, 15.58 mmol) in dichloromethane (2.3 mL). Trifluoroacetic acid (1.2 mL, 15.6 mmol) was added and the mixture was stirred for 2 hours. The volatiles were removed under a stream of N₂. The residue was placed on high-vacuum for 1 hour and then purified by regular phase flash column chromatography (Analogix, 0-100% ethyl acetate in hexanes) to provide the title compound (90 mg, 66%). ¹H NMR (300 MHz, dimethylsulfoxide- d₆) δ ppm 13.07 (s, 2H), 8.21 (s, 1H), 8.04 (ddd, J = 7.9, 1.4, 0.7 Hz, 1H), 7.98 (d, J = 8.9 Hz, 1H), 7.79 (d, J = 8.3 Hz, 1H), 7.62 (d, J = 7.5 Hz, 1H), 7.51 – 7.28 (m, 9H), 5.62 (s, 2H), 4.98 (s, 2H), 3.90 (t, J = 5.8 Hz, 2H), 3.01 (t, J = 5.8 Hz, 2H). MS (ESI) m/z calculated for C_{32}H_{25}N_{7}O_{3}S, 587.17; found 587.9 (M+H)^{+}.

**Synthesis of Compound 8**
**Supplemental Scheme 6.** Reagents: a) P(PPh₃)₄, CsF, DME, MeOH, microwave heating, 120 °C, 48% yield; b) TFA, DCM, 69% yield.

**tert-butyl 6-[(8-[benzo[d]thiazol-2-ylcarbamoyl]-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-[(pyridin-4-ylmethyl)-1H-pyrazol-4-yl]picolinate (S-26).** A mixture of S-10 (0.113 g, 0.20 mmol), 4-[(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazol-1-yl)methyl]pyridine (0.063 g, 0.24 mmol), tetrakis(triphenylphosphine)palladium(0) (0.023 g, 0.020 mmol) and cesium fluoride (0.091 g, 0.60 mmol) in 1,2-dimethoxyethane (3 mL) and methanol (1.5 mL) was heated at 120 °C for 30 minutes under microwave heating conditions. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate twice. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 50% ethyl acetate in hexanes to afford the title compound (62 mg, 48% yield). MS (ESI) m/z calculated for C₃₆H₃₃N₇O₃S, 643.24; found 644.25 (M+H)+.

**6-[(8-[benzo[d]thiazol-2-ylcarbamoyl]-3,4-dihydroisoquinolin-2(1H)-yl]-3-(1-[(pyridin-4-ylmethyl)-1H-pyrazol-4-yl]picolinic acid (8).** A solution of S-26 (55 mg) in dichloromethane (3 mL) was treated with trifluoroacetic acid (3 mL). The reaction mixture was stirred at room temperature for 4 hours. The
volatiles were removed under reduced pressure. The residue was purified by Prep HPLC using Gilson system eluting with 20-80% acetonitrile in water containing 0.1% v/v trifluoroacetic acid. The desired fractions were combined and freeze-dried to provide the title compound as a TFA salt (55 mg, 69% yield)

$^1$H NMR (400 MHz, dimethylsulfoxide-$d_6$) δ 12.87 (s, 2H), 8.78 – 8.66 (m, 2H), 8.06 – 8.00 (m, 2H), 7.80 (d, $J = 8.0$ Hz, 1H), 7.73 (d, $J = 8.9$ Hz, 1H), 7.67 (d, $J = 0.8$ Hz, 1H), 7.64 – 7.59 (m, 1H), 7.48 (ddd, $J = 8.2, 7.2, 1.3$ Hz, 1H), 7.46 – 7.40 (m, 3H), 7.40 – 7.33 (m, 2H), 6.97 (d, $J = 8.9$ Hz, 1H), 5.59 (s, 2H), 4.96 (s, 2H), 3.88 (t, $J = 5.9$ Hz, 2H), 3.01 (t, $J = 6.0$ Hz, 2H). MS (ESI) m/z calculated for C$_{32}$H$_{25}$N$_7$O$_3$S, 587.17; found 588.0 (M+H)$^+$. 

**Synthesis of Intermediates S-27 and S-28**

Supplemental Scheme 7. Reagents: a) NaH, BnBr, N,N-DMF, 55% yield S-27, 41% yield S-28.

1-benzyl-3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (S-27) and 1-benzyl-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (S-28). To a cold (0 °C bath) suspension of sodium hydride (0.264 g, 6.60 mmol, 60 weight % in mineral oil) in N,N-dimethylformamide (10 mL) was added 3-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.624 g, 3.0 mmol) as a solution in N,N-dimethylformamide. The reaction was stirred for 1 hour, and (bromomethyl)benzene (0.564 g, 3.3 mmol) was added. The cold bath was removed, and the reaction stirred overnight. The reaction was quenched by the addition of saturated sodium bicarbonate solution (50 mL), and the mixture was extracted with ethyl acetate (3 x 50mL). The combined organic layers were washed with brine (1 x 100 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was dissolved in DMSO and purified by high pressure reverse-phase liquid chromatography (system, column), eluting with 20-100% acetonitrile in water containing 0.1% v/v trifluoroacetic acid. Pure fractions were lyophilized to give the title compounds S-27 (0.49 g, 55%) and S-28 (0.37 g, 41%)
**S-27** \(^1\)H NMR (300 MHz, dimethylsulfoxide- \(d_6\)) \(\delta\) ppm 7.89 (s, 1 H), 7.37 – 7.27 (m, 3 H), 7.27 – 7.20 (m, 2 H), 5.22 (s, 2 H), 2.21 (s, 3 H) and 1.24 (s, 12 H). MS (ESI) m/z calculated for C\(_{17}\)H\(_{23}\)BN\(_2\)O\(_2\), 298.19; found 299.1 (M+H\(^+\)).

**S-28** \(^1\)H NMR (300 MHz, dimethylsulfoxide- \(d_6\)) \(\delta\) 7.50 (s, 1 H), 7.35 – 7.23 (m, 3 H), 7.11 – 7.07 (m, 2 H), 5.29 (s, 2 H), 2.32 (s, 3 H), 1.23 (s, 12 H). MS (ESI) m/z calculated for C\(_{17}\)H\(_{23}\)BN\(_2\)O\(_2\), 298.19; found 299.1 (M+H\(^+\)).

**Synthesis of Compound 9**

Supplemental Scheme 8. Reagents: a) Pd(PPh\(_3\))\(_4\), CsF, DME, MeOH, microwave heating, 140°C, 59% yield; b) TFA, DCM, 68% yield.

tert-butyl 6-(8-(benzo[d]thiazol-2-yl)carbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl)-3-(1-benzyl-3-methyl-1H-pyrazol-4-yl)picolinate (S-29). A mixture of S-10 (0.113 g, 0.20 mmol), S-27 (0.072 g, 0.24 mmol), tetrakis(triphenylphosphine)palladium(0) (0.023 g, 0.020 mmol) and cesium fluoride (0.091 g, 0.60
mmol) in 1,2-dimethoxyethane (3 mL) and methanol (1.5 mL) was heated at 140 °C for 40 minutes under microwave heating conditions. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate twice. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 35% ethyl acetate in hexanes to afford the title compound. MS (ESI) m/z calculated for C_{38}H_{36}N_{6}O_{3}S, 656.26; found 657.3 (M+H)^+.

6-(8-(benzo[d]thiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl)-3-(1-benzyl-3-methyl-1H-pyrazol-4-yl)picolinic acid (9). A solution of S-29 (72mg) in dichloromethane (3 mL) was treated with trifluoroacetic acid (3 mL). The reaction mixture was stirred at room temperature for 4 hours. The volatiles were removed under reduced pressure. The residue was purified by Prep HPLC using Gilson system eluting with 20-80% acetonitrile in water containing 0.1% v/v trifluoroacetic acid. The desired fractions were combined and freeze-dried to provide the title compound (45 mg, 68% yield) \(^{1}H\) NMR (500 MHz, dimethylsulfoxide- \(d_{6}\)) δ ppm 12.85 (s, 1H), 8.01 (dd, \(J = 7.9, 1.2\) Hz, 1H), 7.77 (d, \(J = 8.0\) Hz, 1H), 7.66 (s, 1H), 7.59 (d, \(J = 7.6\) Hz, 1H), 7.50 (d, \(J = 8.7\) Hz, 1H), 7.45 (td, \(J = 7.8, 1.3\) Hz, 1H), 7.41 (d, \(J = 7.5\) Hz, 1H), 7.37 – 7.29 (m, 4H), 7.28 – 7.24 (m, 1H), 7.22 – 7.18 (m, 2H), 6.87 (d, \(J = 8.8\) Hz, 1H), 5.19 (s, 2H), 4.92 (s, 2H), 3.86 (t, \(J = 6.0\) Hz, 2H), 2.98 (t, \(J = 6.0\) Hz, 2H), 2.02 (s, 3H). \(^{13}C\) NMR (101 MHz, dimethylsulfoxide-\(d_{6}\)) δ ppm 168.69, 167.67, 158.45, 155.91, 149.14, 148.38, 145.79, 140.41, 137.75, 136.44, 133.75, 131.89, 131.51, 129.79, 128.48, 127.54, 127.48, 126.58, 126.22, 123.75, 121.78, 120.47, 116.14, 114.52, 107.60, 54.44, 44.93, 41.75, 28.13, 12.20. MS (ESI) m/z calculated for C_{34}H_{38}N_{6}O_{3}S, 600.19; found 601.0 (M+H)^+.

**Synthesis of Compound 10**
Supplemental Scheme 9. Reagents: a) Pd(PPh₃)₄, CsF, DME, MeOH, microwave heating, 140 °C, 57% yield; b) TFA, DCM, 80% yield.

*tert-butyl 6-(8-{benzo[d]thiazol-2-ylcarbamoyl}-3,4-dihydroisoquinolin-2(1H)-yl)-3-(1-benzyl-5-methyl-1H-pyrazol-4-yl)picolinate (S-30).* A mixture of S-10 (0.113 g, 0.20 mmol), S-28 (0.072 g, 0.24 mmol), tetrakis(triphenylphosphine)palladium(0) (0.023 g, 0.020 mmol) and cesium fluoride (0.091 g, 0.60 mmol) in 1,2-dimethoxyethane (3 mL) and methanol (1.5 mL) was heated at 140 °C for 40 minutes under microwave heating conditions. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate twice. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel eluting with 35% ethyl acetate in hexanes to afford the title compound (75 mg, 57%). MS (ESI) m/z calculated for C₃₈H₃₆N₆O₃S, 656.26; found 657.3 (M+H)⁺.
6-(8-(benzo[d]thiazol-2-ylcarbamoyl)-3,4-dihydroisoquinol-2(1H)-yl)-3-(1-benzyl-5-methyl-1H-pyrazol-4-yl)picolinic acid (10). A solution of S-30 (71 mg) in dichloromethane (3 mL) was treated with trifluoroacetic acid (3 mL). The reaction mixture was stirred at room temperature for 4 hours. The volatiles were removed under reduced pressure. The residue was purified by Prep HPLC using Gilson system eluting with 20-80% acetonitrile in water containing 0.1% v/v trifluoroacetic acid. The desired fractions were combined and freeze-dried to provide the title compound (52 mg, 80%). ^1H NMR (500 MHz, dimethylsulfoxide- d$_6$) δ ppm 12.86 (s, 1H), 8.01 (d, J = 7.9 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 7.4 Hz, 1H), 7.49 – 7.43 (m, 2H), 7.41 (d, J = 7.6 Hz, 1H), 7.36 – 7.28 (m, 5H), 7.27 – 7.22 (m, 1H), 7.09 (d, J = 7.4 Hz, 2H), 6.90 (d, J = 8.8 Hz, 1H), 5.29 (s, 2H), 4.93 (s, 2H), 3.86 (t, J = 6.0 Hz, 2H), 2.98 (t, J = 6.0 Hz, 2H), 2.07 (s, 3H). ^13C NMR (101 MHz, dimethylsulfoxide-d$_6$) δ 168.69, 167.68, 158.47, 155.96, 149.32, 148.36, 140.54, 137.79, 137.50, 136.43, 135.86, 133.74, 131.84, 131.54, 131.49, 128.57, 127.53, 127.32, 126.84, 126.55, 126.19, 123.72, 121.75, 120.48, 116.50, 114.77, 107.61, 52.26, 44.94, 41.77, 28.08, 9.70. MS (ESI) m/z calculated for C$_{34}$H$_{28}$N$_6$O$_3$S, 600.19; found 601.1 (M+H)$^+$.  

**Synthesis of Compound 11**

![Synthesis Diagram](attachment:synthesis_diagram.png)
Supplemental Scheme 10. Reagents: a) NaH, N,N-DMF, 80 °C, 93% yield; b) 2.5 mol% Pd2(dba)3, 10 mol% S-17, K3PO4, 1:1 1,4-dioxane:H2O, 90 °C, 9% yield; f) TFA, DCM, rt, 42% yield.

1-benzyl-3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (S-31). To a cold (0 °C) suspension of sodium hydride (0.297 g, 7.43 mmol, 60 weight % in mineral oil) in N,N-dimethyl formamide (22.51 mL) was added 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.5 g, 6.75 mmol) as a solution in N,N-dimethyl formamide. The reaction was stirred for 1 hour, and (bromomethyl)benzene (0.802 mL, 6.75 mmol) was added. The cold bath was removed, and the reaction stirred until complete. The reaction was quenched by the addition of ethyl acetate (50 mL) and saturated aqueous sodium bicarbonate solution (100 mL). The layers were separated, and the aqueous was extracted with ethyl acetate (2 x 50 mL). The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give an oil (1.96 g, 93%), which was used in the subsequent reaction without further purification. 1H NMR (400 MHz, dimethylsulfoxide- d6) δ ppm 7.35 – 7.29 (m, 2 H), 7.28 – 7.22 (m, 1 H), 7.11 – 7.06 (m, 2 H), 5.20 (s, 2 H), 2.29 (s, 3 H), 2.19 (s, 3 H), 1.24 (s, 14 H). MS (ESI) m/z calculated for C18H25BN2O2, 312.20; found 313.18.

tert-butyl 6-(8-(benzo[d]thiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl)-3-(1-benzyl-3,5-dimethyl-1H-pyrazol-4-yl)picolinate (S-32). A 25-mL 2-neck round-bottom flask equipped with a stir bar, septum and reflux condenser was charged with S-10 (0.906 g, 1.60 mmol), S-31 (1.0 g, 3.20 mmol), potassium phosphate (1.187 g, 5.61 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.037 g, 0.040 mmol) and (1R,3S,5S,7R)-1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxa-8-phosphaadamantane (0.047 g, 0.160 mmol) was degassed for 20 minutes with a sweep of nitrogen. In a separate flask, 1,4-dioxane (5 mL) and water (5 mL) was sparged with nitrogen for 20 minutes. The solution of 1,4-dioxane and water was added via syringe to the flask containing the solid reagents. The reaction was heated to 90 °C and stirred for 2 hours under a positive pressure of nitrogen. The reaction was cooled to ambient temperature and quenched by the addition of saturated aqueous bicarbonate solution and ethyl acetate (50 mL each). The layers were separated, and the aqueous was extracted with additional ethyl acetate (2 x 50 mL). The combined organics were dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (50 g),
eluting with a gradient of 0 to 70% ethyl acetate in heptane, to give the title compound as a yellow oil (100 mg, 9%). \(^1\)H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ ppm 12.84 (s, 1H), 8.01 (d, \(J = 7.8\) Hz, 1H), 7.77 (d, \(J = 8.0\) Hz, 1H), 7.59 (d, \(J = 7.7\) Hz, 1H), 7.48 – 7.22 (m, 10H), 7.21 – 7.15 (m, 2H), 6.91 (d, \(J = 8.8\) Hz, 1H), 5.20 (s, 2H), 4.96 (s, 2H), 3.83 (t, \(J = 6.0\) Hz, 2H), 3.03 (t, \(J = 6.0\) Hz, 2H), 1.93 (d, \(J = 0.9\) Hz, 3H), 1.90 (s, 2H), 1.03 (s, 9H). MS (ESI) m/z calculated for C<sub>39</sub>H<sub>38</sub>N<sub>6</sub>O<sub>3</sub>S, 670.27; found 671.3.

6-(8-(benzo[d]thiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl)-3-(1-benzyl-3,5-dimethyl-1H-pyrazol-4-yl)picolinic acid (11). To a solution of the S-32 (0.065 g, 0.097 mmol) in dichloromethane (1 mL) was added trifluoroacetic acid (0.5 mL). The reaction was stirred at room temperature for h hours. The reaction was concentrated under reduced pressure to an oil. The residue was dissolved in dimethylsulfoxide (1 mL) and methanol (1 mL) and purified by high-pressure reverse-phase chromatography (Gilson PLC 2020 instrument, Phenomenex Luna 250 mm x 50 mm column, 70 mL/min flow rate), eluting with a gradient of 30 to 95% acetonitrile in 10 mM aqueous ammonium acetate solution. The fractions containing the products were lyophilized to give the title compound as a solid (25 mg, 42%). \(^1\)H NMR (400 MHz, dimethylsulfoxide-d<sub>6</sub>) δ ppm 12.90 (s, 1H), 8.14 – 7.97 (m, 2H), 7.79 (d, \(J = 8.1\) Hz, 1H), 7.68 (d, \(J = 7.5\) Hz, 1H), 7.51 – 7.45 (m, 2H), 7.43 – 7.29 (m, 4H), 7.29 – 7.23 (m, 1H), 7.09 (dd, \(J = 6.9\), 1.8 Hz, 2H), 5.24 (s, 2H), 4.89 (s, 2H), 3.75 (t, \(J = 5.9\) Hz, 2H), 3.07 (t, \(J = 6.0\) Hz, 2H), 2.06 (s, 3H), 2.02 (s, 3H). \(^{13}\)C NMR (101 MHz, dimethylsulfoxide-d<sub>6</sub>) δ ppm 168.77, 168.15, 158.93, 156.63, 150.07, 148.83, 145.48, 142.14, 138.31, 137.25, 136.94, 134.18, 132.27, 131.99, 131.96, 129.00, 127.63, 127.18, 127.15, 127.03, 126.68, 126.64, 124.17, 122.21, 120.95, 115.86, 108.31, 52.24, 45.30, 42.14, 28.68, 12.60, 10.31. MS (ESI) m/z calculated for C<sub>35</sub>H<sub>30</sub>N<sub>6</sub>O<sub>3</sub>S, 614.21; found 615.0 (M+H)<sup>+</sup>.

Synthesis of Intermediate S-35

![Synthesis of Intermediate S-35](image)
Supplemental Scheme 11. Reagents: a) nBuLi, -78 °C then Mel, 88% yield; b) NBS, N,N-dimethylacetamide, rt, 76% yield; c) nBuLi, B(OiPr)_3, -78 °C then pinacol, 68% yield

1-(cyclohexylmethyl)-5-methyl-1H-pyrazole (S-33). To a cold (-50 °C) solution of 1-(cyclohexylmethyl)-1H-pyrazole (4.2 g, 25.6 mmol) in tetrahydrofuran (40 mL) was added n-butyllithium (13.30 mL, 33.2 mmol) dropwise. The reaction was stirred for 1.5 hours during which time the temperature rose to -20 °C. Iodomethane (2.149 mL, 34.5 mmol) was added dropwise. The reaction was stirred for 0.5 h between -20 °C and -15 °C and then quenched by addition of 20 mL of water and extracted with ethyl acetate three times. The combined organics were washed with brine, dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the title compound, which was used without further purification (4.0 g, 88 % yield). ^1H NMR (400 MHz, dimethylsulfoxide-d_6) δ 7.23 (d, J = 1.7 Hz, 1H), 5.93 (dd, J = 1.7, 0.9 Hz, 1H), 3.78 (d, J = 7.3 Hz, 2H), 2.19 (s, 3H), 0.88-1.74 (m, 11H). LC/MS (APCI+) m/z calculated for C_{11}H_{18}N_2, 178.15; found 179.5 (M+H)^+.

4-bromo-1-(cyclohexylmethyl)-5-methyl-1H-pyrazole (S-34). To a solution of (S-33) (4.0 g, 22.44 mmol) in N,N-dimethylacetamide (40 mL) was added N-bromosuccinimide (4.39 g, 24.68 mmol). The mixture became thick, and stirring was continued overnight. The reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate twice. The combined organics were washed with 20% aqueous sodium thiosulfate, 20% aqueous sodium bicarbonate and brine. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with 10% ethyl acetate in heptanes to give the title compound (4.4 g, 76 % yield). ^1H NMR (400 MHz, dimethylsulfoxide- d_6) δ 7.41 (s, 1H), 3.85 (d, J = 7.3 Hz, 2H), 2.18 (s, 3H), 0.87-1.79 (m, 11H). LC/MS (APCI+) m/z calculated for C_{11}H_{17}BrN_2, 258.06; found 259.6 (M+H)^+.

1-(cyclohexylmethyl)-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (S-35). To a cold (-78 °C) solution of S-34 (4.4 g, 17.11 mmol) and trisopropyl borate (5.96 mL, 25.7 mmol) in a mixture of tetrahydrofuran (40 mL) and toluene (40 mL) was added n-butyllithium (145 mL, 362 mmol, 2.5 M in hexane) dropwise, keeping the internal temperature less than -55 °C. The mixture was stirred
for 20 min, and a solution of pinacol (10.11 g, 86 mmol) in tetrahydrofuran (20 mL) was added. The cooling bath was removed, and the reaction was stirred at room temperature overnight. The reaction was diluted with water (50 mL) and ethyl acetate (200 mL). The precipitate was filtered, and the filtrate was extracted with ethyl acetate (1 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with 15% ethyl acetate in heptanes to give the title compound (3.56 g, 68.4 % yield) as a yellow solid. $^1$H NMR (400 MHz, dimethylsulfoxide- $d_6$) $d$ 7.41 (s, 1H), 3.79 (t, $J$ = 7.3 Hz, 2H), 2.32 (s, 3H), 0.87-1.74 (m, 23H). LC/MS (APCI+) m/z calculated for C$_{17}$H$_{29}$BN$_2$O$_2$, 304.23; found 305.3 (M+H)$^+$. 

**Synthesis of Compound 12**

![Chemical structure](image)

**Supplemental Scheme 12.** Reagents: a) 2.5 mol% Pd$_2$(dba)$_3$, 10 mol% S-17, K$_3$PO$_4$, 1:1 1,4-dioxane:H$_2$O, 90 °C,97% yield; f) TFA, DCM, rt, 43% yield.

tert-butyl 6-(8-(benzo[d]thiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl)-3-(1-(cyclohexylmethyl)-5-methyl-1H-pyrazol-4-yl)picolinate (S-36). A mixture of S-10 (0.15 g, 0.265 mmol), S-35 (0.121 g, 0.398 mmol), S-17 (7.75 mg, 0.027 mmol), tris(dibenzylideneacetone)dipalladium(0) (6.07 mg, 6.63 µmol), and potassium phosphate (0.197 g, 0.928 mmol) in 1,4-dioxane (3 mL) and water (0.75 mL) was degassed and back-filled with nitrogen several times. The reaction mixture was heated at 80 °C
overnight. After cooling, the reaction mixture was partitioned between water and ethyl acetate. The aqueous layer was extracted with additional ethyl acetate twice. The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with 40% ethyl acetate in heptanes to give the title compound (0.17 g, 97 % yield).

1H NMR (400 MHz, dimethylsulfoxide-d6) δ ppm 12.81 (s, 1H), 8.03 – 7.95 (m, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.61 – 7.51 (m, 1H), 7.47 – 7.36 (m, 3H), 7.36 – 7.27 (m, 2H), 7.16 (s, 1H), 6.88 (d, J = 8.8 Hz, 1H), 4.93 (s, 2H), 3.89 – 3.74 (m, 4H), 2.99 (t, J = 6.0 Hz, 2H), 2.04 (s, 3H), 0.75-1.64 (m, 20H).

LC/MS (APCI+) m/z calculated for C38H42N6O3S, 662.30; found 663.2 (M+H)+.

6-(8-(benzo[d]thiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl)-3-(1-(cyclohexylmethyl)-5-methyl-1H-pyrazol-4-yl)picolinic acid (12). A mixture of S-36 (0.17 g, 0.256 mmol) and trifluoroacetic acid (0.988 mL, 12.82 mmol) in dichloromethane (3 ml) was stirred at rt overnight. The solvent was removed, and the residue was purified by reverse phase Prep HPLC on a C18 column eluting with 20-100% acetonitrile in 0.1% TFA water solution to give 6-(8-(benzo[d]thiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl)-3-(1-(cyclohexylmethyl)-5-methyl-1H-pyrazol-4-yl)picolinic acid (0.067 g, 43 % yield). 1H NMR (400 MHz, dimethylsulfoxide-d6) δ ppm 12.81 (s, 1H), 8.00 (dd, J = 8.0, 1.3 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.58 (dd, J = 7.5, 1.4 Hz, 1H), 7.51 – 7.28 (m, 6H), 7.24 (s, 1H), 6.91 (d, J = 8.8 Hz, 1H), 4.92 (s, 2H), 3.89 – 3.78 (m, 4H), 2.98 (t, J = 5.9 Hz, 2H), 2.07 (s, 3H), 1.67 – 1.45 (m, 6H), 1.22 – 1.05 (m, 3H), 0.93 (qd, J = 11.8, 3.3 Hz, 2H). LC/MS (APCI+) m/z calculated for C34H34N6O3S, 606.24; found 606.9 (M+H)+.

**Synthesis of Intermediate S-42**
**Supplemental Scheme 13.** Reagents: a) borane-THF complex, THF, 81% yield; b) cyanomethylenetri-butylphosphorane, 70 °C; c) silver sulfate, methanol, microwave irradiation, 100 °C, 60% yield; d) nBuLi, -40 °C then MeI, 99% yield; 3) NBS, THF, 94% yield; f) nBuLi, B(OPr)$_3$, -78 °C then pinacol, 88% yield.

**((1r,3r)-3-bromoadamantan-1-yl)methanol (S-37).** In a 500 mL round-bottomed flask, 3-bromoadamantane-1-carboxylic acid (10.0 g, 38.6 mmol) was dissolved in tetrahydrofuran (80 mL). Borane tetrahydrofuran complex (1M in hexane, 78 mL) was added slowly. The mixture was stirred at room temperature overnight. Aqueous 1 N aqueous sodium hydroxide solution (70 mL) was added to the solution slowly. The mixture was extracted with diethyl ether (300 mL). The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (250 g), eluting with 20% ethyl acetate in hexanes to give the title compound (7.7 g, 81%) as a white solid. $^1$H NMR (400 MHz, dimethylsulfoxide-d$_6$) δ 4.49 (t, $J = 5.6$ Hz, 1H), 3.02 (d, $J = 5.6$ Hz, 2H), 2.28 (d, $J = 11.8$ Hz, 2H), 2.21 (d, $J = 12.0$ Hz, 2H), 2.11 (p, $J = 3.2$ Hz, 2H), 2.08 – 2.05 (m, 2H), 1.70 – 1.63 (m, 1H), 1.59 – 1.53 (m, 1H), 1.52 – 1.44 (m, 2H), 1.40 (d, $J = 12.0$ Hz, 2H).

**1-(((1r,3r)-3-bromoadamantan-1-yl)methyl)-1H-pyrazole (S-38).** To as solution of 1H-pyrazole (3 g, 44.1 mmol) and S-37 (1.93 g, 7.87 mmol) in 1:1 toluene: tetrahydrofuran (20 mL) was added cyanomethylenetri-butylphosphorane (5 g, 20.72 mmol). The reaction mixture was heated at 70 °C for 16 hours. The reaction was concentrated under reduced pressure. The residue was purified by
chromatography on silica gel (Analogix, SF65-200g, UV 218), eluting with 0-50% ethyl acetate in hexanes to give the title compound. $^1$H NMR (300 MHz, dimethylsulfoxide-$d_6$) $\delta$ 7.63 (dd, $J = 2.3, 0.8$ Hz, 1H), 7.43 (dd, $J = 1.9, 0.8$ Hz, 1H), 6.23 (t, $J = 2.1$ Hz, 1H), 3.87 (s, 2H), 2.25 (d, $J = 11.1$ Hz, 2H), 2.18 – 2.03 (m, 6H), 1.64 (d, $J = 12.9$ Hz, 1H), 1.56 – 1.42 (m, 5H). MS (ESI) m/z calculated for C$_{14}$H$_{19}$BrN$_2$, 294.07, 296.07; found 295.1 (M+H)$^+$.  

1-(((1r,3r)-3-methoxyadamantan-1-yl)methyl)-1H-pyrazole (S-39). To a 20 mL microwave tube equipped with a stir bar was added S-38 (5 g, 16.94 mmol), silver sulfate (6 g, 19.24 mmol) and methanol (15 mL, 370 mmol) to give a suspension. The vessel was sealed, and the reaction mixture was heated under microwave irradiation to 110 °C 1 hour. The reaction was cooled to room temperature and diluted with ethyl acetate (15 mL) and filtered. The eluent was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (200 g) column, eluting with 0-70% ethyl acetate in hexane to provide the title compound (2.5 g, 60%). $^1$H NMR (300 MHz, dimethylsulfoxide-$d_6$) $\delta$ 7.61 (dd, $J = 2.2, 0.7$ Hz, 1H), 7.40 (dd, $J = 1.8, 0.7$ Hz, 1H), 6.21 (dd, $J = 2.2, 1.8$ Hz, 1H), 3.86 (s, 2H), 3.07 (s, 3H), 2.21 – 2.09 (m, 2H), 1.60 (d, $J = 12.4$ Hz, 2H), 1.53 – 1.41 (m, 4H), 1.36 (d, $J = 9.1$ Hz, 6H). MS (ESI) m/z calculated for C$_{15}$H$_{22}$N$_2$O, 246.17; found 247.2 (M+H)$^+$. 

1-(((1r,3r)-3-methoxyadamantan-1-yl)methyl)-5-methyl-1H-pyrazole (S-40). To a cold (-40 °C bath) solution of compound S-39 (2.5 g, 10.2 mmol) in tetrahydrofuran (20 mL) was added n-butyllithium (5 mL, 12.5 mmol, 2.5 M in hexane) dropwise. The reaction was stirred for 1.5 h during which time the temperature raised to ~20 °C. Methyl iodide (1.0 mL, 16.03 mmol) was added dropwise. The reaction was allowed to warm to -5 °C over 90 minutes and was then quenched by the addition of 50 mL of water and extracted with ethyl acetate (3 × 50 mL). The combined organics were washed with brine, dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give compound the title compound (2.63 g, 99 % yield), which was used in the subsequent step without further purification. $^1$H NMR (300 MHz, dimethylsulfoxide-$d_6$) $\delta$ 7.31 – 7.27 (m, 1H), 6.01 – 5.96 (m, 1H), 3.76 (s, 2H), 3.08 (s, 3H), 2.24 (s, 3H), 2.20 – 2.11 (m, 2H), 1.67 – 1.55 (m, 2H), 1.55 – 1.33 (m, 10H). MS (ESI) m/z calculated for C$_{16}$H$_{24}$N$_2$O, 260.19; found 261.2 (M+H)$^+$. 

4-bromo-1-(((1r,3r)-3-methoxyadamantan-1-yl)methyl)-5-methyl-1H-pyrazole (S-41). To a solution of compound S-40 (2.63 g, 10 mmol) in tetrahydrofuran (20 mL) was added N-bromosuccinimide (3.0 g, 16.9 mmol), and the reaction was stirred for 90 minutes. The reaction mixture was diluted with ethyl
acetate (100 mL) and washed with 10% aqueous sodium carbonate (2 x 300 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography on silica gel (120 g), eluting with 0-50% ethyl acetate in hexane to provide the title compound (3.21 g, 94%).  

1H NMR (300 MHz, dimethylsulfoxide-d6) $\delta$ 7.48 (s, 1H), 3.83 (s, 2H), 3.08 (s, 3H), 2.23 (s, 3H), 2.19 – 2.10 (m, 2H), 1.64 – 1.56 (m, 2H), 1.55 – 1.32 (m, 10H). MS (ESI) m/z calculated for C16H23BrN2O, 338.10, 340.10; found 339.0, 341.2 (M+H)$^+$.

1-(((1r,3r)-3-methoxyadamantan-1-yl)methyl)-5-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (S-42). To a cold (-78 °C) solution of compound S-41 (3.0 g, 8.84 mmol) and triisopropyl borate (2.6 mL, 11.3 mmol) in a mixture of tetrahydrofuran (25 mL) and toluene (25mL) was added n-butyllithium (5 mL, 12.5 mmol, 2.5 M in hexane) dropwise, keeping the internal temperature less than -55 °C. The mixture was stirred for 20 min, and a solution of pinacol (5.2g, 44 mmol) in tetrahydrofuran (10 mL) was added. The cooling bath was removed, and the reaction was stirred at room temperature for 2.5 hours. The reaction was diluted with water (200 mL) and ethyl acetate (200 mL), and the layers were separated. The aqueous was extracted with ethyl acetate (2 x 50 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (100 g), eluting with 0-40% ethyl acetate in hexane to give the title compound (3.0 g, 88%). 1H NMR (300 MHz, dimethylsulfoxide-d6) $\delta$ 7.46 (s, 1H), 3.78 (s, 2H), 3.08 (s, 3H), 2.36 (s, 3H), 2.18 – 2.10 (m, 2H), 1.60 (d, J = 11.5 Hz, 2H), 1.55 – 1.34 (m, 10H), 1.25 (s, 12H). MS (ESI) m/z calculated for C22H35BN2O3, 386.27; found 387.3 (M+H)$^+$.

**Synthesis of Compound 14**
Supplemental Scheme 14. Reagents: a) 2.5 mol% Pd$_2$(dba)$_3$, 10 mol% S-17, K$_3$PO$_4$, 3:1 THF:H$_2$O, microwave irradiation, 140 °C, 48% yield; f) TFA, DCM, rt, 88% yield.

tert-butyl 6-(8-(benzo[d]thiazol-2-y)carbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl)-3-(1-(((1r,3r)-3-methoxyadamantan-1-yl)methyl)-5-methyl-1H-pyrazol-4-yl)picolinate (S-43). A microwave tube equipped with a stir bar was charged with S-10 (0.5 g, 0.884 mmol), S-42 (0.47 g, 0.876 mmol), potassium phosphate (0.6 g, 2.83 mmol), tris(dibenzylideneacetone)dipalladium(0) (0.052 g, 0.057 mmol) and (1R,3S,5S,7R)-1,3,5,7-tetramethyl-8-phenyl-2,4,6-trioxo-8-phosphaadamantane S-17 (0.084 g, 0.287 mmol). A mixture of tetrahydrofuran:water (3:1, 10 mL) was added to the vessel containing the solid reagents. The head space was swept with nitrogen gas, and the tube was sealed with a septum. The reaction was heated to 140 °C for 5 minutes under microwave conditions. The reaction was cooled to ambient temperature and quenched by the addition of saturated aqueous bicarbonate solution and ethyl acetate (25 mL each). The layers were separated, and the aqueous was extracted with additional ethyl acetate (2 x 25 mL). The combined organics were dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (40 g), eluting with a gradient of 0 to 10% methanol in dichloromethane, to give the title compound as a yellow oil (0.31 g, 48%). MS (ESI) m/z calculated for C$_{43}$H$_{48}$N$_6$O$_4$S, 744.35; found 745.7 (M+H)$^+$. 
6-(8-(benzo[d]thiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)-yl)-3-((1r,3r)-3-methoxyadamantan-1-yl)methyl)-5-methyl-1H-pyrazol-4-yl)picolinic acid (14). To a solution of S-43 (0.5 g, 0.672 mmol) in dichloromethane (10 mL) was added trifluoroacetic acid (5 mL). The reaction was stirred overnight, and the reaction was concentrated under reduced pressure. The residue was purified by silica gel chromatography (40 g SiO2), eluting with a gradient of 0-10% methanol in dichloromethane to give the title compound (0.41 g, 88%) as a solid. 1H NMR (300 MHz, dimethylsulfoxide-d6) δ 12.85 (s, 1H), 8.03 (d, J = 7.6 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.54 – 7.41 (m, 3H), 7.40 – 7.32 (m, 2H), 7.28 (s, 1H), 6.95 (d, J = 8.8 Hz, 1H), 4.95 (s, 2H), 3.89 (t, J = 5.9 Hz, 2H), 3.79 (s, 2H), 3.08 (s, 3H), 3.01 (t, J = 5.8 Hz, 2H), 2.12 (d, J = 12.2 Hz, 5H), 1.68 – 1.33 (m, 12H). MS (ESI) m/z calculated for C39H40N6O4S, 688.28; found 689.1 (M+H)+.

Single Dose Pharmacokinetics in Rats

The single dose pharmacokinetics of select compounds were evaluated in Sprague–Dawley rats (Charles River) after a 5 mg/kg oral dose (n = 3) (10% dimethylsulfoxide in PEG-400) administered by gavage or by 5 mg/kg IV bolus dose (n = 3) (10% dimethylsulfoxide in PEG-400). Compound and the internal standard were separated from each other and co-extracted contaminants on a 50 mm × 3 mm Keystone Betasil CN 5 μm column with an acetonitrile/0.1% trifluoroacetic acid mobile phase (50:50, by volume) at a flow rate of 0.7 mL/min. Analysis was performed on a Sciex API3000 biomolecular mass analyzer with a heated nebulizer interface. Compound and internal standard peak areas were determined using Sciex MacQuan software. The plasma drug concentration of each sample was calculated by least-squares linear regression analysis (nonweighted) of the peak area ratio (parent/internal standard) of the spiked plasma standards versus concentration. The plasma concentration data were submitted to multiexponential curve fitting using WinNonlin.3. The area under the plasma concentration–time curve was calculated using the linear trapezoidal rule for the plasma concentration–time profiles

In Vivo Pharmacology

Mice and husbandry

All experiments were conducted in compliance with Abbvie Institutional Animal Care and Use Committee and the National Institutes of Health Guide for Care and Use of Laboratory Animals guidelines in a facility accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care. SCID/bg
female mice (6 to 8 weeks) were obtained from Charles River (Wilmington, MA). Maximally 10 mice were housed per cage; food and water were provided ad libitum. Animals were tested during the light phase of a 12-hour light: 12-hour dark schedule (lights on at 06:00 hours).

**Generation of tumor bearing mice**

Colo205 cells (human colon cancer) were obtained from ATCC (Manassas, VA) and maintained in RPMI 1640 medium (Invitrogen, Carlsbad, CA) supplemented with 10% heat-inactivated fetal bovine serum (FBS) (GE Healthcare HyClone™, Logan, UT). Cells were detached from monolayer cultures at 80 to 90% confluence with a mixture of 0.5 mM EDTA and 0.05% trypsin in DMEM. Viable cells were counted using a hemocytometer and re-suspended in ice-cold S-MEM (Invitrogen). Two million viable cells were inoculated subcutaneously into the right flank of mice in 0.2 mL/mouse of 1:1 mixture of S-MEM and Matrigel (Corning, Bedford, MA).

**Trial design**

Tumor bearing animals were size-matched for tumors with an approximate volume of 200 mm$^3$. Thirty-two mice were divided in 4 groups. Mice were treated with drug vehicle, irinotecan, A-1331852 (13) or a combination of irinotecan and A-1331852 (13). Treatment was initiated at 9 days after the inoculation of tumor cells. Therapy began 24 hours after size matching of the tumors. A-1331852 was formulated in 2.5 % dimethylsulfoxide, 10% EtOH, 27.5 % PEG 400 and 60% Phosal 50 PG and administered once a day orally (PO) at a dose of 25 mg/kg/day for 14 days (QDx14). Irinotecan was obtained as a mono-hydrochloric acid salt from Clinigen (Batch lot A013771AA) and diluted in physiological saline and injected intraperitoneally (IP). A total of 4 doses (30 mg/kg/day) was given with an interval of 3 days between administrations (Q3Dx4). When combined at the same day irinotecan was given two hours after A-1331852.

Mice were euthanized when tumor volume reached 3,000 mm$^3$ or skin ulcerations occurred or at the first indication of distress, whichever occurred earlier.

**Data collection and analysis**

Tumor volume was estimated one to two times weekly. Measurements of the length (L) and width (W) of the tumor were taken via electronic caliper and tumor volume was calculated according to the following equation: $V = L \times W^2/2$. Parameters of amplitude (maximum tumor growth inhibition, TGI$_{max}$) and durability (tumor growth delay, TGD) of therapeutic response are used to qualify the efficacy of the drug. TGI indicates the divergence between the mean tumor volume of a drug-treated group and the mean
tumor volume of the control group treated with drug vehicle and is expressed as a percentage of the mean volume of the control group. TGI_{max} value is determined at the time when the difference between treated and control group is maximal. The TGD indicates the difference of the median time of a drug treated group to reach a tumor defined volume (1 cm^3) as compared to the median time of a control group treated with vehicle to reach that volume. This difference is expressed as a percentage of the median time of the control group to reach the specified tumor volume. Two-tailed Student’s t-test was used to determine significance of differences in tumor growth size. To determine significance of tumor growth delay, the non-parametric Mann-Whitney U-test was employed. In Figure 5 of the manuscript, each point of a curve represents the mean of 8 tumors. Error bars depict the standard error of the mean.

**Crystallization Methods**

**Protein**

The following clone was used for structure studies [Bcl-xL (1-25)-GGGGGG-83-209] W24A, E158K, D189A]-LE-6His. In this form of the protein, an extended loop, residues 26-82 has been deleted and replaced with seven glycine residues. The protein was expressed in *E.coli*. After cell lysis, the protein was purified by Ni-NTA chromatography, the eluant was pH adjusted to 8.1 and then precipitated with 70% saturated ammonium sulfate. The precipitate was separated from the supernatant by centrifugation. The precipitant pellet was dissolved in 20 mM Tris pH 7.6, 10 mM NaCl, 10% (v/v) glycerol, 2 mM DTT, and the protein further purified using anion exchange chromatography. All purifications were conducted at 4°C. The protein was then dialyzed into 25 mM Tris pH 7.6, 100 mM NaCl, 10% (v/v) glycerol, 1 mM DTT.

**Compounds**

The compounds were dissolved in DMSO. Compound and protein were then diluted and combined in buffer (25 mM Tris, 0.1 M NaCl, 10% (v/v) glycerol, 1 mM DTT pH 8.0) to give 10.73 µM compound and 2.14 µM protein (a 5:1 compound to protein ratio) with final DMSO concentration of 2% (v/v). Each sample was left to complex overnight at 4 °C, then concentrated and used in crystallization.

**Compound 8**

Protein compound complex was concentrated to 12 mg/mL. Crystals were grown by vapor diffusion at 290K. The reservoir solution was 30% (w/v) PEG 10,000, 0.1 M Tris HCl pH 8.5. The crystals grew as plates. A cryo-protective solution was made using the reservoir solution with 10% (v/v) propylene glycol. Crystals were swished through the cryo-protective solution and cryo-cooled in liquid nitrogen.

**Compound 14**
Protein compound complex was concentrated to 19 mg/mL. Crystals were grown by vapor diffusion at 290K. The reservoir solution was 1.0 M sodium acetate, 0.1 M HEPES pH 7.5, 0.05M Cadmium sulfate. The crystals grew as plates. A cryo-protective solution was made using the reservoir solution with 20% (v/v) propylene glycol. Crystals were swished through the cryo-protective solution and cryo-cooled in liquid nitrogen.

Diffraction data were collected at the Advanced Photon Source (Argonne, IL) at the 17ID beamline under gaseous nitrogen at 100K.

PDB accession code for BCL-X<sub>L</sub> complex with compound 8 is 6VWC. PDB coordinates and refinement statistics for BCL-X<sub>L</sub> protein in complex with compound 8 and compound 14 each are included as supplemental information.