Structure-guided rescaffolding of selective antagonists of BCL-X_L

Michael F.T. Koehler*†, Philippe Bergeron†, Edna F. Choo‖, Kevin Lau†, Chudi Ndubaku†, Danette Dudley†, Paul Gibbons†, Brad E. Sleebs‡,#, Carl S. Rye‡,#, George Nikolakopoulos‡,#, Chinh Bui‡,#, Sanji Kulasegaram‡,#, Wilhelmus J.A. Kersten‡,#, Brian J. Smith‡,#, Peter E. Czabotar‡,#, Peter M. Colman‡,#, David C.S. Huang‡,#, Jonathan B. Baell‡,#, Keith G. Watson‡,#, Lisa Hasvold‖, Zhi-Fu Tao‖, Le Wang‖, Andrew J. Souers‖, Steven W. Elmore‖, John A. Flygare†, Wayne J. Fairbrother§, and Guillaume Lessene‡,#

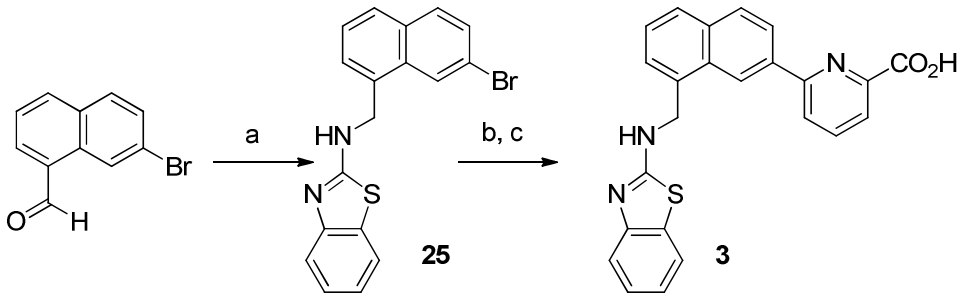
Departments of †Discovery Chemistry, ‖Drug Metabolism and Pharmacokinetics, §Early Discovery Biochemistry, Genentech Inc, 1 DNA Way, South San Francisco, CA 94080 USA, ‡Walter and Eliza Hall Institute of Medical Research, 1G Royal Parade, Parkville VIC 3052, Australia, #Department of Medical Biology, The University of Melbourne, Parkville, Victoria, Australia. ‖AbbVie Inc., 1 North Waukegan Rd, North Chicago, IL 60064 USA

1- Chemistry

Experimental details:

General. Unless otherwise indicated, all reagents and solvents were purchased from commercial sources and were used without further purification Moisture or oxygen sensitive reactions were conducted under an atmosphere of argon or nitrogen gas. Unless otherwise stated, ^{1}H NMR spectra were recorded at 300 or 400 MHz using Varian or Bruker instruments operating at the indicated frequencies. Chemical shifts are expressed in ppm relative to a tetramethylsilane (ppm = 0.00) internal standard. The following abbreviations are used: br = broad signal, s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, p = pentet, m = multiplet. Purification by silica gel chromatography was carried out using Isco systems with prepacked cartridges. Chemical purities were >95% for all final compounds, as assessed by LC/MS analysis at UV 220 nm.

Scheme S1. Synthesis of naphthalene amine 3.[a]



[a]Reagents and conditions: (a) 2-aminobenzothiazole, $NaBH(OAc)_3$, DCE; (b) bis(pinacolato)diboron, $Pd(PPh_3)_2Cl_2$, KOAc, toluene; (c) 6-bromopicolinic acid, $Pd(PPh_3)_2Cl_2$, Bu_4NBr, K_2CO_3, 1,4-dioxane/H_2O

Synthesis of compound **25**:

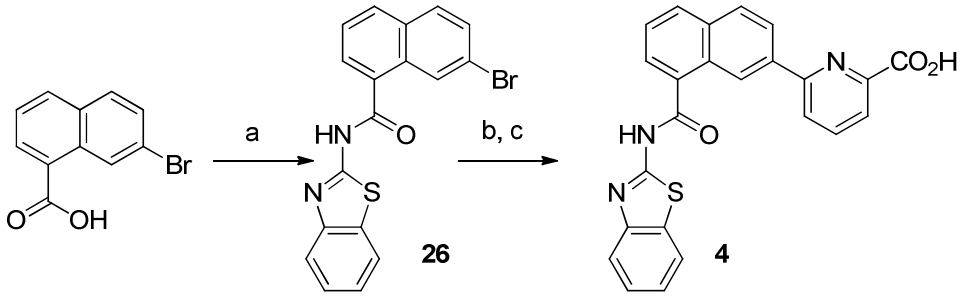
7-bromo-1-naphthaldehyde (0.167 g, 0.710 mmol) was dissolved in dry 1,2-dichloroethane (5.00 mL). 2-aminobenzothiazole (0.130 g, 0.866 mmol) was then added, followed by sodium triacetoxyborohydride (0.252 g, 1.19 mmol). The reaction was stirred overnight at room temperature, then diluted with saturated aqueous $NaHCO_3$, extracted three times with 10% MeOH in dichloromethane, dried over anhydrous magnesium sulfate, filtered and concentrated. The reaction was chromatographed using silica gel (4g column, 0-30% EtOAc in hexanes). The product containing fractions were recrystallized from EtOAc/hexanes and dried under vacuum to give N-((7-bromonaphthalen-1-yl)methyl)benzo[d]thiazol-2-amine (108 mg, 0.292 mmol, 41%).

Synthesis of compound **3**:

Step 1: Bis(pinacolato)diboron (0.109 g, 0.43 mmol), bis(triphenylphosphine)palladium(II) chloride (0.0130 g, 0.0185 mmol), and potassium acetate (0.064 g, 0.65 mmol) were combined in a reaction vial, which was evacuated, then purged with N_2 a total of three times. N-((7-bromonaphthalen-1-yl)methyl)benzo[d]thiazol-2-amine (0.108 g, 0.292 mmol) was dissolved in dry toluene (8.00 mL), then cannulated into the reaction vial. The reaction mixture was concentrated to about 5mL in volume by blowing N_2 over the sample. The reaction was microwaved using a maximum power of 300 W at 150°C for 5 minutes. The crude reaction mixture was filtered through Celite using 10% MeOH in dichloromethane as the eluent. This was concentrated to give N-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)methyl)benzo[d]thiazol-2-amine, which was used without further purification.

Step 2: 6-bromopicolinic acid (0.070 g, 0.35 mmol), bis(triphenylphosphine)palladium(II) chloride (0.020 g, 0.028 mmol), tetra-N-butylammonium bromide (0.013 g, 0.040 mmol), and K_2CO_3 (0.080 g, 0.58 mmol) were combined in a reaction vial, which was evacuated, then purged with N_2 a total of three times. N-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)methyl)benzo[d]thiazol-2-amine (0.293 mmol) was dissolved in 1,4-dioxane (8.00 mL, 102 mmol) and deoxygenated water (1.50 mL, 83.3 mmol), then cannulated into the reaction vial. The sample was concentrated to about 5mL in volume by blowing N2 through the vial. The reaction was microwaved using up to 300 W of power at a temperature of 150°C for 10 minutes. The reaction mixture was cooled, then diluted with H_2O, extracted three times with 10% MeOH in dichloromethane, dried over anhydrous magnesium sulfate, filtered, and concentrated to an oil. This was then purified by reverse phase HPLC to give 6-(8-((benzo[d]thiazol-2-ylamino)methyl)naphthalen-2-yl)picolinic acid (3) (37.3 mg, 0.091mmol, 31%). %). ^{1}H NMR (400 MHz, DMSO-D_6) δ 8.93 (s, 1H), 8.85 (s, 1H), 8.47 (dd, J = 8.6, 1.7 Hz, 1H), 8.28 (dd, J = 8.0, 1.0 Hz, 1H), 8.13 (d, J = 8.6 Hz, 1H), 8.00 (dd, J = 7.7, 1.0 Hz, 1H), 7.97 – 7.94 (m, 1H), 7.90 (t, J = 7.8 Hz, 1H), 7.73 – 7.69 (m, 1H), 7.66 – 7.53 (m, 2H), 7.51 – 7.47 (m, 1H), 7.32 – 7.27 (m, 1H), 7.11 – 7.05 (m, 1H), 5.25 (d, J = 5.5 Hz, 2H). MS (ESI(+)): m/z 412.1(M+H).

Scheme S2. Synthesis of naphthalene amide 4.[a]



[a]Reagents and conditions: (a) 2-aminobenzothiazole, EDC, DMAP, DMF; (b) bis(pinacolato)diboron, bis(diphenylphosphino)ferrocene]dichloropalladium(II), KOAc, DMF; (c) 6-bromopicolinic acid, $Pd(PPh_3)_2Cl_2$, Bu_4NBr, K_2CO_3, 1,4-dioxane/H_2O

Synthesis of compound **26**:

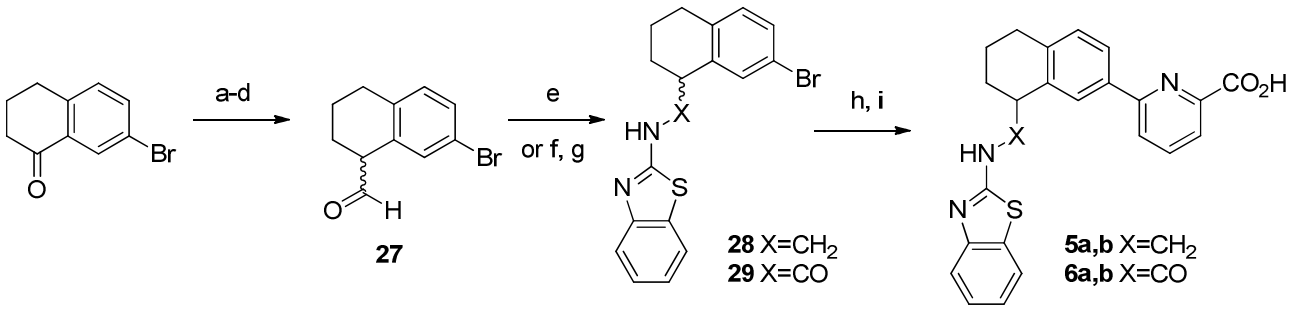
7-bromo-1-naphthalenecarboxylic acid (0.203 g, 0.808 mmol), 2-aminobenzothiazole (0.163 g, 1.08 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.235 g, 1.22 mmol), 4-dimethylaminopyridine (0.300 g, 2.46 mmol), and dry N,N-dimethylformamide (6.00 mL) were combined and stirred overnight. The sample was then concentrated under reduced pressure and chromatographed through silica gel (4g column, 0-5% MeOH in dichloromethane) to give N-(benzo[d]thiazol-2-yl)-7-bromo-1-naphthamide (**26)** (0.204g, 0.532 mmol, 66%).

Synthesis of compound **4**:

Step 1: Bis(pinacolato)diboron (3.013 g, 11.86 mmol), KOAc (1.180 g, 12.02 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (0.175 g, 0.214 mmol) were combined in a reaction vial, which was evacuated, then purged with N_2 a total of three times. N-(benzo[d]thiazol-2-yl)-7-bromo-1-naphthamide (1.493 g, 3.895 mmol) was dissolved in dry N,N-dimethylformamide (27.0 mL), added to the reaction vial and the resulting solution was freeze-pump-thawed three times, then heated at 80°C overnight. Both the desired pinacolboronate as well as the dehalogenated starting amide were observed by LC/MS at the end of the reaction. The sample was chromatographed through silica gel (80g 0-100% EtOAc in hexanes). LC-MS shows the deborolated material is still present. The sample was chromatographed through silica gel (80g column, CH_2Cl_2) to give N-(benzo[d]thiazol-2-yl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthamide (0.844g, 1.96 mmol, 50%).

Step 2: 6-bromopicolinic acid (0.052 g, 0.26 mmol), bis(triphenylphosphine)palladium(II) chloride (0.018 g, 0.026 mmol), tetra-N-butylammonium bromide (0.0046 g, 0.014 mmol), and potassium carbonate (0.072 g, 0.52 mmol) were combined in a reaction vial, which was evacuated, then purged with N_2 a total of three times. N-(benzo[d]thiazol-2-yl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-naphthamide (98 mg, 0.23 mmol) was dissolved in 1,4-dioxane (7.5 mL) and deoxygenated water (2.5 mL), then cannulated into the reaction mixture. The reaction was microwaved using up to 300 W of power at a temperature of 150°C for 5 minutes. The reaction was allowed to cool to room temperature and stirred overnight during which time a solid formed. The solid was collected through vacuum filtration and washed with additional 1,4-dioxane and water to give 6-(8-(benzo[d]thiazol-2-ylcarbamoyl)naphthalen-2-yl)picolinic acid (**4**) (53.2 mg, 0.125 mmol, 55%). ^{1}H NMR (400 MHz, DMSO-D_6) δ 9.06 (s, 1H), 8.44 – 8.37 (m, 1H), 8.25 – 8.17 (m, 2H), 8.16 – 8.10 (m, 1H), 8.08 – 8.00 (m, 3H), 7.98 – 7.92 (m, 1H), 7.83 – 7.78 (m, 1H), 7.73 – 7.66 (m, 1H), 7.51 – 7.45 (m, 1H), 7.39 – 7.33 (m, 1H). MS (ESI(+)): m/z 426.1 (M+H).

Scheme S3. Synthesis of tetrahydronaphthalenes 5 and 6.[a]



[a]Reagents and conditions: (a) Ph_3PMeBr, n-BuLi, THF; (b) BH_3, THF; (c) H_2O_2; (d) $NaIO_4$, CCl_4, CH_3CN, H_2O, $RuCl_3$; (e) 2-aminobenzothiazole, $NaBH(OAc)_3$, DCE; (f) $NaClO_2$, acetone/H_2O; (g) 2-aminobenzothiazole, EDC, DMAP, DMF; (h) bis(pinacolato)diboron, $Pd(PPh_3)_2Cl_2$, KOAc, toluene; (i) 6-bromopicolinic acid, $Pd(PPh_3)_2Cl_2$, Bu_4NBr, K_2CO_3, 1,4-dioxane/H_2O

Synthesis of compound **27**:

Step 1: Methyltriphenylphosphonium bromide (5.318 g, 14.89 mmol) was suspended in dry tetrahydrofuran (60.0 mL) and was cooled to -45°C. A 2.5 M solution of n-butyllithium in tetrahydrofuran (5.25 mL, 0.0131 mol) was added dropwise to the solution at -45°C. The reaction was stirred for one hour at -45°C. 7-bromo-1-tetralone (2.019 g, 8.97 mmol) in dry tetrahydrofuran (12.0 mL, 0.148 mol) was added dropwise to the sample at -45°C . The reaction was allowed to warm slowly to RT and was stirred overnight. The reaction mixture was then poured slowly into water, extracted three times with ethyl acetate, dried over anhydrous magnesium sulfate, filtered, concentrated, and chromatographed through silica gel (40g, 100% hexanes) to give 7-bromo-1-methylene-1,2,3,4-tetrahydronaphthalene (1.035 g, 4.369 mmol, 52%).

Step 2: 7-bromo-1-methylene-1,2,3,4-tetrahydronaphthalene (1.035 g, 4.639 mmol) was dissolved in tetrahydrofuran (28.0 mL, 0.345 mol) and was cooled at 0°C. Into the mixture was added 1 M borane in tetrahydrofuran (20.0 mL, 20.0 mmol) dropwise at 0°C. The reaction was warmed to room temperature and was stirred for three hours. The reaction was cooled to 0°C and sodium hydroxide (2.067 g, 0.05168 mol) in water (9.00 mL, 0.500 mol) was added dropwise followed by adding 30% hydrogen peroxide in water (3:7, hydrogen peroxide:water, 7.00 mL, 0.0265 mol) dropwise. The mixture was warmed to room temperature and was stirred for three hours. The sample was diluted with water, extracted three times with ether, dried over anhydrous magnesium sulfate, filtered, and concentrated. The mixture was chromatographed through silica gel (40g, 0-35% ethyl aceteate in hexanes) to give (7-bromo-1,2,3,4-tetrahydronaphthalen-1-yl)methanol (1.054g, 4.371 mmol, 94%).

Step 3: (7-Bromo-1,2,3,4-tetrahydronaphthalen-1-yl)methanol (0.476 g, 1.97 mmol) was dissolved in dry methylene chloride (100 mL, 2 mol) and then Dess-Martin periodinane (1.319 g, 3.110 mmol) was added. The mixture was stirred for one hour. Into the mixture was added 10% aqueous sodium thiosulfate (61 mL, 3.9 mmol) and saturated aqueous sodium bicarbonate (61mL). The mixture was stirred for thirty minutes, then extracted three times with dichloromethane, dried over anhydrous magnesium sulfate, filtered, and concentrated. The mixture was chromatographed through silica gel (12g, 0-5% ethyl acetate in hexanes) to give 7-bromo-1,2,3,4-tetrahydronaphthalene-1-carbaldehyde (**27**) (0.352g, 1.47 mmol, 75%).

Synthesis of compound **28**:

7-bromo-1,2,3,4-tetrahydronaphthalene-1-carbaldehyde (**27**) (0.267 g, 1.12 mmol) was dissolved in dry 1,2-dichloroethane (20 mL, 0.2 mol) then 2-aminobenzothiazole (0.217 g, 1.44 mmol) was added followed by sodium triacetoxyborohydride (0.413 g, 1.95 mmol). The mixture was stirred overnight. The mixture was then diluted with saturated aqueous sodium bicarbonate, extracted three times with 10% methanol in dichloromethane, dried over anhydrous magnesium sulfate, filtered, and concentrated. The mixture was chromatographed through silica gel (4g, 0-30% ethyl acetate in hexanes) to give N-((7-bromo-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)benzo[d]thiazol-2-amine (**28**) (0.194g, 0.520mmol, 46%)

Synthesis of compounds **5a** and **5b**:

Step 1: Bis(pinacolato)diboron (0.1792 g, 0.7057 mmol), bis(triphenylphosphine)palladium(II) chloride (0.019 g, 0.027 mmol) and potassium acetate (0.117 g, 1.19 mmol) were combined in a reaction vial which was evacuated then purged with nitrogen a total of three times. N-((7-bromo-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)benzo[d]thiazol-2-amine (**28**) (0.194 g, 0.520 mmol) in dry toluene (2.00 mL, 0.0188 mol) was added by canula. The mixture was microwaved using a maximum power of 300 W, with PowerMAX enabled, at 150°C for forty minutes. The sample was filtered through Celite using 10% methanol in dichloromethane as the eluent and concentrated to give N-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)benzo[d]thiazol-2-amine.

Step 2: 6-Bromopicolinic acid (0.109 g, 0.540 mmol), bis(triphenylphosphine)palladium(II) chloride (0.034 g, 0.048 mmol), tetra-N-butylammonium bromide (0.025 g, 0.078 mmol), and potassium carbonate (0.186 g, 1.35 mmol) were combined, evacuated, and then purged with nitrogen a total of three times. N-((7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydronaphthalen-1-yl)methyl)benzo[d]thiazol-2-amine (0.218 g, 0.518 mmol) in dry 1,4-dioxane (2.00 mL, 25.6 mmol) and deoxyenated water (1.00 mL, 55.5 mmol) was added by cannula. The mixture was microwaved using a maximum power of 300 W, with PowerMAX enabled, at 150°C for 10 minutes. The sample was diluted with water, extracted three times with 10% methanol in dichloromethane, dried over anhydrous magnesium sulfate, filtered, and concentrated. SFC was used to isolate the enantiomers **5a** (11.9mg, 0.0286 mmol, 6%) and **5b** (11.4mg, 0.0274 mmol, 5%)

4a ^{1}H NMR (400 MHz, DMSO-D_6) δ 8.32 – 8.25 (m, 1H), 8.11 – 8.08 (m, 1H), 8.06 – 8.02 (m, 1H), 7.97 – 7.87 (m, 3H), 7.69 – 7.66 (m, 1H), 7.44 – 7.41 (m, 1H), 7.25 – 7.20 (m, 2H), 7.04 – 6.99 (m, 1H), 3.80 – 3.71 (m, 1H), 3.65 – 3.50 (m, 1H), 3.28 – 3.22 (m, 1H), 2.89 – 2.70 (m, 2H), 1.96 – 1.69 (m, 4H). MS (ESI(+)): m/z 416.2 (M+H)

4b ^{1}H NMR (400 MHz, DMSO-D_6) δ 8.33 – 8.26 (m, 1H), 8.11 – 8.06 (m, 1H), 8.03 – 7.97 (m, 1H), 7.95 – 7.84 (m, 3H), 7.68 – 7.66 (m, 1H), 7.45 – 7.41 (m, 1H), 7.25 – 7.20 (m, 2H), 7.04 – 6.98 (m, 1H), 3.79 – 3.71 (m, 1H), 3.59 – 3.50 (m, 1H), 3.30 – 3.22 (m, 1H), 2.91 – 2.71 (m, 2H), 1.96 – 1.68 (m, 4H). MS (ESI(+)): m/z 416.2 (M+H)

Synthesis of compound **29**:

Step 1: 7-Bromo-1,2,3,4-tetrahydronaphthalene-1-carbaldehyde (**27**) (0.311 g, 1.30 mmol) was dissolved in acetone (5.00 mL) and was cooled at 0°C , and Jones' reagent was added dropwise until the sample remained a red color. The mixture was stirred at 0°C for one hour. The sample was diluted with water, extracted three times with dichloromethane, dried over anhydrous magnesium sulfate, filtered, and concentrated to give 7-bromo-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (0.316g, 1.24 mmol, 95%).

Step 2: 7-Bromo-1,2,3,4-tetrahydronaphthalene-1-carboxylic acid (0.386 g, 1.51 mmol), 2-aminobenzothiazole (0.257 g, 1.71 mmol), N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.386 g, 2.01 mmol), 4-dimethylaminopyridine (0.589 g, 4.82 mmol) and dry acetonitrile (20 mL) were combined and stirred overnight. The mixture was diluted with water, extracted three times with 10% methanol in dichloromethane, dried over anhydrous magnesium sulfate, filtered, and concentrated. The mixture was chromatographed through silica gel (4g, 0-30% ethyl acetate in hexanes) to give N-(benzo[d]thiazol-2-yl)-7-bromo-1,2,3,4-tetrahydronaphthalene-1-carboxamide (**29**) (0.137g, 0.354 mmol, 23%)

Synthesis of compounds **6a and 6b**:

Step 1: Bis(pinacolato)diboron (0.120 g, 0.472 mmol), bis(triphenylphosphine)palladium(II) chloride (0.015 g, 0.021 mmol), potassium acetate (0.083 g, 0.84 mmol) were combined, evacuated, then purged with nitrogen a total of three times. N-(Benzo[d]thiazol-2-yl)-7-bromo-1,2,3,4-tetrahydronaphthalene-1-carboxamide (**29**) (0.137 g, 0.354 mmol) in dry toluene (4.00 mL) was added via cannula. The mixture was microwaved at 150°C using a maximum power of 300 W , PowerMAX enabled for forty minutes. The sample was filtered through Celite using 10% methanol in dichloromethane as the eluent and concentrated to give N-(benzo[d]thiazol-2-yl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide

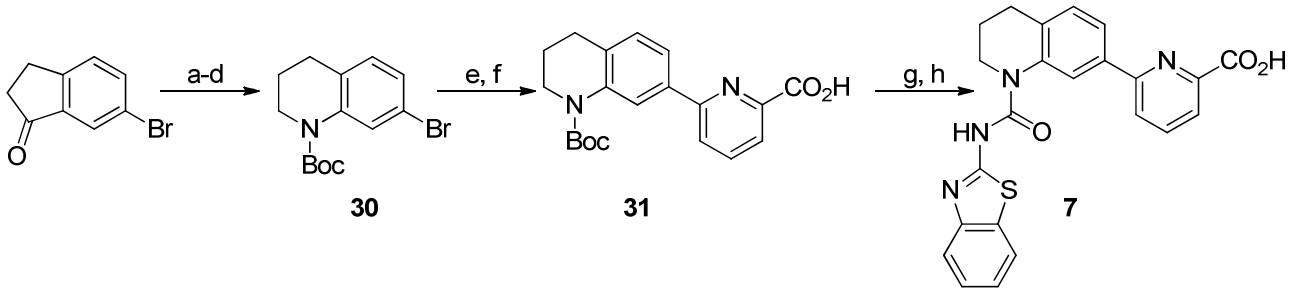
Step 2: 6-Bromopicolinic acid (0.081 g, 0.40 mmol), bis(triphenylphosphine)palladium(II) chloride (0.027 g, 0.038 mmol), tetra-N-butylammonium bromide (0.015 g, 0.046 mmol), and potassium carbonate (0.099 g, 0.72 mmol) were combined in a reaction vial which was evacuated then purged with nitrogen a total of three times. N-(Benzo[d]thiazol-2-yl)-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,3,4-tetrahydronaphthalene-1-carboxamide (0.154 g, 0.354 mmol) in dry 1,4-dioxane (3.00 mL, 38.4

mmol) and deoxyenated water (1.50 mL, 83.3 mmol) was added by canula. The mixture was microwaved using a maximum power of 300 W, with PowerMAX enabled, at 150°C for 10 minutes. The sample was diluted with water, extracted three times with 10% methanol in dichloromethane, dried over anhydrous magnesium sulfate, filtered, and concentrated. SFC was used to the enantiomers **6a** (7.8mg, 0.0182 mmol, 5%) and **6b** (21.8mg, 0.0508 mmol, 14%).

6a ^{1}H NMR (400 MHz, DMSO-D_6) δ 8.02 – 7.84 (m, 6H), 7.79 – 7.74 (m, 1H), 7.47 – 7.40 (m, 1H), 7.33 – 7.26 (m, 2H), 4.28 – 4.22 (m, 1H), 3.14 – 3.06 (m, 1H), 2.90 – 2.75 (m, 1H), 2.61 – 2.53 (m, 1H), 2.15 – 1.96 (m, 3H), 1.79 – 1.69 (m, 1H). MS (ESI(+)): 430.1 m/z (M+H) SFC RT = 1.77 minutes

6b ^{1}H NMR (400 MHz, DMSO-D_6) δ 8.00 – 7.84 (m, 6H), 7.79 – 7.74 (m, 1H), 7.47 – 7.41 (m, 1H), 7.33 – 7.26 (m, 2H), 4.27 (s, 1H), 3.14 – 3.06 (m, 1H), 2.94 – 2.75 (m, 1H), 2.60 – 2.54 (m, 1H), 2.15 – 1.94 (m, 3H), 1.80 – 1.68 (m, 1H). MS (ESI(+)): 430.1 m/z (M+H) SFC RT = 2.03 minutes

Scheme S4. Synthesis of urea 7.[a]



[a]Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, KOH, H_2O, MeOH, 95%; (b) MsCl, Et_3N, DCM, then H+, 88%; (c) LAH, THF, 40%; (d) Boc_2O, Et_3N, THF, DMAP 70°C, 60%; (e) bis(pinacolato)diboron, $Pd(PPh_3)_2Cl_2$, KOAc, toluene; (f) methyl 6-bromopicolinate, $Pd(PPh_3)_2Cl_2$, Bu_4NBr, K_2CO_3, 1,4-dioxane/H_2O; (g) 4N HCl/1,4-dioxane; (h) 4-nitrophenyl benzothiazol-2-yl-carbamate;

Synthesis of compound **30:**

Step 1: 6-Bromo-1-indanone (1.58 g, 7.49 mmol) was dissolved in methanol (30.0 mL). Hydroxylamine hydrochloride (780 mg, 11 mmol) was added, followed by a solution of 8.9 M potassium hydroxide in water (2.5 mL, 22 mmol). The reaction was heated to reflux for 3h. The mixture was cooled down to room temperature and acidified with 1N HCl. The resulting precipitate was collected by filtration and washed with water to give 6-bromo-2,3-dihydro-1H-inden-1-one oxime (1.60 g, 7.08 mmol, 94%) ^{1}H NMR (500 MHz, DMSO-D_6) δ 11.14 (s, 1H), 7.70 (d, *J* = 1.9 Hz, 1H), 7.56 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.40 (d, *J* = 8.2 Hz, 1H), 3.02 (t, *J* = 6.7 Hz, 2H), 2.88 – 2.84 (m, 2H).

Step 2: Methanesulfonyl chloride (657 uL, 8.49 mmol) was slowly added to a solution of 6-bromo-2,3-dihydro-1H-inden-1-one oxime (1.60 g, 7.08 mmol) and triethylamine (1.97 mL, 14.2 mmol) in methylene chloride (35 mL) at -15°C. The reaction was stirred for two hours, then diluted with 30 mL of DCM and washed with ice-cold 1N HCl, followed by saturated aqueous $NaHCO_3$. The organic layer was dried over anhydrous magnesium sulfate, filtered and concentrated. Chromatography through silica gel (80g, 0 to 30% EtOAc in hexanes) gave 7-bromo-3,4-dihydroquinolin-2(1H)-one (1.41 g, 6.2 mmol, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 1.8 Hz, 1H), 7.58 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.36 – 7.05 (m, 1H), 3.17 – 2.95 (m, 4H).

Step 3: Lithium aluminum hydride (350 mg, 9.3 mmol) was added to a solution of 7-bromo-3,4-dihydroquinolin-2(1H)-one (1.4 g, 6.2 mmol) in tetrahydrofuran (25 mL) at room temperature. The reacton was stirred for 30 minutes then cooled to 0°C and quenched by addition of saturated aqueous $NaHCO_3$. The aqueous phase was extracted with EtOAc (3x30 mL). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated. Chromatography through silica gel (40g, 0 to 25% EtOAc in hexanes) gave 7-bromo-1,2,3,4-tetrahydroquinoline (480 mg, 2.2 mmol, 37%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.77 (dt, *J* = 7.9, 1.0 Hz, 1H), 6.68 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.59 (d, *J* = 2.0 Hz, 1H), 3.32 – 3.22 (m, 2H), 2.68 (t, *J* = 6.4 Hz, 2H), 1.91 (ddd, *J* = 11.2, 6.7, 5.9 Hz, 2H).

Step 4: A mixture of 7-bromo-1,2,3,4-tetrahydroquinoline (470 mg, 2.2 mmol) di-tert-butyldicarbonate (720 mg, 3.3 mmol), 4-dimethylaminopyridine (270 mg, 2.2 mmol) and triethylamine (460 uL, 3.3 mmol) in tetrahydrofuran (10 mL) was stirred overnight at 60°C. The mixture was then concentrated and chromatographed through silica gel (40g, 0 to 25% EtOAc in hexanes) to give tert-butyl 7-bromo-3,4-dihydroquinoline-1(2H)-carboxylate **27** (240 mg, 0.77 mmol, 35%).

Synthesis of compound **31:**

Step 1: Tert-butyl 7-bromo-3,4-dihydroquinoline-1(2H)-carboxylate (230 mg, 0.74 mmol), bis(pinacolato)diboron (240 mg, 0.965 mmol), bis(triphenylphosphine)palladium(II) chloride (26 mg, 0.037 mmol) and potassium acetate (140 mg, 1.5 mmol) were

dissolved in toluene (2.5 mL) and were combined in a reaction vial, which was evacuated, then purged with N_2 a total of three times. The reaction was microwaved using up to 90 W of power at a temperature of 150°C for 5 minutes. The mixture was then concentrated and chromatographed through silica gel (12g, 0 to 25% EtOAc in hexanes) to give tert-butyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroquinoline-1(2H)-carboxylate (151 mg, 0.42mmol, 57%).

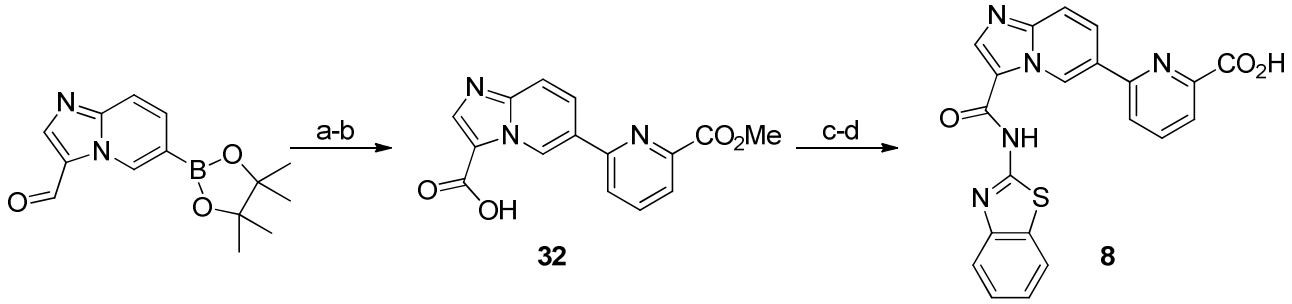
Step 2: tert-butyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroquinoline-1(2H)-carboxylate (250 mg, 0.69 mmol), 6-bromopicolinic acid (140 mg, 0.69 mmol), bis(triphenylphosphine)palladium(II) chloride (48 mg, 0.069 mmol), tetra-N-butylammonium bromide (22 mg, 0.069 mmol) and potassium carbonate (250 mg, 1.8 mmol) were mixed in 1,4-dioxane (3.0 mL, 38 mmol) and water (1.5 mL, 83 mmol) and were combined in a reaction vial, which was evacuated, then purged with N_2 a total of three times. The reaction was microwaved using up to 100 W of power at a temperature of 150°C for 5 minutes. The reaction was diluted with 1N NaOH. The aqueous phase was extracted with ether (2x20 mL) and acidified to pH 4 with 1N HCl. The aqueous phase was then extracted with methylene chloride (3x20mL). The combined organic phases were dried over anhydrous magnesium sulfate, filtered and concentrated to give 6-(1-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroquinolin-7-yl)picolinic acid **28** (240 mg, 0.68 mmol, 98%) which was used in the next step without further purification.

Synthesis of compound **7**:

Step1: 6-(1-(Tert-butoxycarbonyl)-1,2,3,4-tetrahydroquinolin-7-yl)picolinic acid (240 mg, 0.68 mmol) was stirred in a 4N HCl in 1,4-dioxane (2.5 mL, 10 mmol) at room temperature for 30 minutes. The mixture was then concentrated and the residue was taken up in 20 mL of methylene chloride. The organic phase was washed with saturated aqueous $NaHCO_3$, dried over anhydrous magnesium sulfate, filtered and concentrated to give 6-(1,2,3,4-tetrahydroquinolin-7-yl)picolinic acid (127 mg, 0.50 mmol, 74%). The compound was carried on to the next step without further purification.

Step 2: A mixture of 4-nitrophenyl benzo[d]thiazol-2-ylcarbamate (127 mg, 0.403 mmol) and 6-(1,2,3,4-tetrahydroquinolin-7-yl)picolinic acid (85 mg, 0.34 mmol) in acetonitrile (2.0 mL) was stirred at reflux for 5h. The reaction was then cooled to room temperature, resulting in the formation of a precipitate. The precipitate was collected by filtration, washed with cold acetonitrile and dried *in vacuo* to give 6-(1-(benzo[d]thiazol-2-ylcarbamoyl)-1,2,3,4-tetrahydroquinolin-7-yl)picolinic acid (75 mg, 0.17 mmol, 52%). ^{1}H NMR (500 MHz, DMSO-D_6) δ 8.41 (s, 1H), 8.14 – 8.09 (m, 1H), 8.05 (t, *J* = 7.7 Hz, 1H), 7.98 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.87 – 7.78 (m, 2H), 7.47 (s, 1H), 7.37 (ddd, *J* = 8.3, 7.3, 1.3 Hz, 1H), 7.30 (d, *J* = 7.9 Hz, 1H), 7.25 – 7.19 (m, 1H), 3.95 (s, 1H), 2.83 (t, *J* = 6.6 Hz, 2H), 1.95 (p, *J* = 6.4 Hz, 2H). LCMS m/z 431.2 (M+H)

Scheme S5 Synthesis of imidazopyridine amide 8.[a]



[a]Reagents and conditions: (a) methyl 6-bromopicolinate, $Pd(PPh_3)_4$, K_3PO_4, DMF; (b) sodium chlorite, sulfamic acid, acetone, H_2O; (c) 2-aminobenzothiazole, EDC, DMAP, DMF; (d) LiOH, MeOH, H_2O

Synthesis of compound **32**:

Step 1 : Methyl 6-bromopicolinate (0.436 g, 2.02 mmol), 3-formylimidazo[1,2-a]pyridin-6-ylboronic acid (0.287 g, 1.51 mmol), tetrakis(triphenylphosphine)palladium(0) (0.103 g, 0.0891 mmol), potassium phosphate (0.976 g, 4.60 mmol) were combined in a reaction vial, which was evacuated then purged with nitrogen a total of three times. Dry N,N-dimethylformamide (10.5 mL, 136 mmol) was then added and the mixture was heated at 120°C for one hour then cooled to room temperature. The reaction mixture was diluted with water, extracted three times with 10% methanol in dichloromethane, dried over anhydrous magnesium sulfate, filtered, and concentrated. The sample was chromatographed through silica gel (40g, 0-10% methanol in dichloromethane) to give methyl 6-(3-formylimidazo[1,2-a]pyridin-6-yl)picolinate.

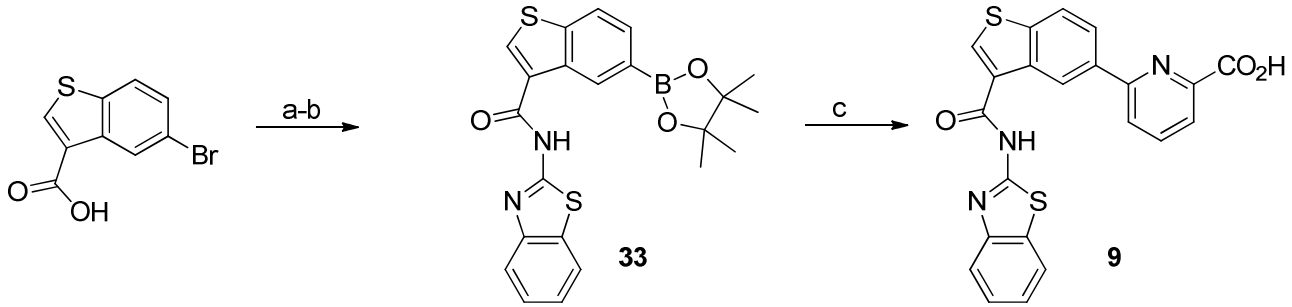
Step 2: To a solution of methyl 6-(3-formylimidazo[1,2-a]pyridin-6-yl)picolinate (0.428 g, 1.52 mmol) in acetone (8.50 mL) and water (4.20 mL) at 0°C was added sulfamic acid (0.536 g, 5.52 mmol) followed by sodium chlorite (0.282 g, 3.12 mmol). The reaction was stirred at at 0°C for two hours and was then vacuum filtered and washed with water and acetone to give 6-(6-(methoxycarbonyl)pyridin-2-yl)imidazo[1,2-a]pyridine-3-carboxylic acid (**29**) (0.244g, 0.821 mmol, 54%).

Synthesis of compound **8**:

Step 1: 6-(6-(Methoxycarbonyl)pyridin-2-yl)imidazo[1,2-a]pyridine-3-carboxylic acid (**29**) (0.244 g, 0.821 mmol), 2-aminobenzothiazole (0.161 g, 1.07 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.238 g, 1.24 mmol), 4-dimethylaminopyridine (0.304 g, 2.49 mol), and dry N,N-dimethylformamide (5.50 mL) were combined and stirred overnight. The mixture was vacuum filtered and washed with N,N-dimethylformamide, dichloromethane, and water to give methyl 6-(3-(benzo[d]thiazol-2-ylcarbamoyl)imidazo[1,2-a]pyridin-6-yl)picolinate (0.200g, 0.466 mmol, 57%).

Step 2: To a solution of methyl 6-(3-(benzo[d]thiazol-2-ylcarbamoyl)imidazo[1,2-a]pyridin-6-yl)picolinate (0.138 g, 0.321 mmol) in methanol (12.0 mL) and water (5.20 mL) was added lithium hydroxide, monohydrate (0.140 g, 3.34 mmol). The reaction was stirred at room temperature for one hour, concentrated, and purified by reverse phase HPLC to give 6-(3-(benzo[d]thiazol-2-ylcarbamoyl)imidazo[1,2-a]pyridin-6-yl)picolinic acid (**8**) (0.217g, 0.522 mmol, 163%) ^{1}H NMR (500 MHz, DMSO-D_6) δ 10.54 – 10.53 (m, 1H), 8.15 (s, 1H), 8.09 – 7.99 (m, 3H), 7.90 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.75 (dd, *J* = 9.3, 0.9 Hz, 1H), 7.65 – 7.62 (m, 1H), 7.47 – 7.44 (m, 1H), 7.20 – 7.16 (m, 1H), 7.01 – 6.97 (m, 1H). MS (ESI(+)):416.1 m/z (M+H)

Scheme S6 Synthesis of benzothiophene amide 9.[a]



[a]Reagents and conditions: (a) 2-aminobenzothiazole, EDC, DMAP, DMF; (b) bis(pinacolato)diboron, $Pd(PPh_3)_2Cl_2$, KOAc, DMF; (c) 6-bromopicolinic acid, $Pd(PPh_3)_2Cl_2$, $(Bu)_4NBr$, K_2CO_3, 1,4-dioxane, H_2O.

Synthesis of compound **33**:

Step 1: 5-Bromobenzo[b]thiophene-3-carboxylic acid (0.500 g, 1.94 mmol), 2-aminobenzothiazole (0.386 g, 2.57 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.560 g, 2.92 mmol), 4-dimethylaminopyridine (0.718 g, 5.88 mmol), and dry N,N-dimethylformamide (14.0 mL) were combined and stirred for three days. The reaction mixture was concentrated, diluted with water, extracted three times with 10% methanol in dichloromethane, dried over anhydrous magnesium sulfate, filtered, and concentrated. The crude product was chromatographed through silica gel (80g, 0-30% ethyl acetate in hexanes) to give 6-(3-(benzo[d]thiazol-2-ylcarbamoyl)imidazo[1,2-a]pyridin-6-yl)picolinic acid (0.540g, 1.39 mmol, 71%).

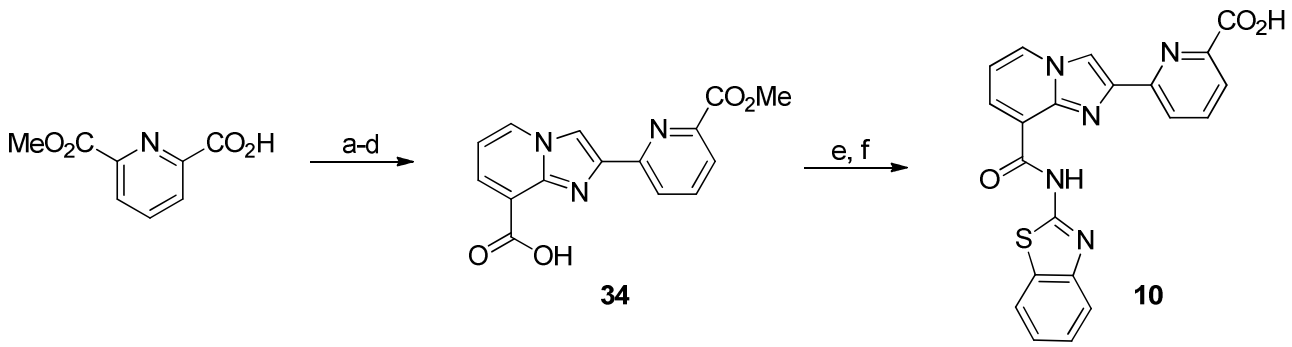
Step 2: Bis(pinacolato)diboron (0.395 g, 1.56 mmol), 6-(3-(benzo[d]thiazol-2-ylcarbamoyl)imidazo[1,2-a]pyridin-6-yl)picolinic acid (0.197 g, 0.506 mmol), potassium acetate (0.163 g, 1.66 mmol), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (0.030 g, 0.037 mmol) were combined in a reaction vial which was evacuated then purged with nitrogen a total of three times. N,N-dimethylformamide (3.60 mL) was added to the mixture which was heated at 80°C overnight. LC-MS shows about a 1:1 mixture of starting material to product. Bis(pinacolato)diboron (0.395g), potassium acetate (0.161g), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) (0.027g) were added to the mixture, which was heated at 80°C for an additional eight hours, then filtered through Celite, concentrated, and chromatographed through silica gel (40g, 0-30% ethyl acetate in hexanes) to give N-(benzo[d]thiazol-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophene-3-carboxamide (**33**) (0.218g, 0.500 mmol, 99%).

Synthesis of compound **9**:

6-Bromopicolinic acid (0.106 g, 0.525 mmol), bis(triphenylphosphine)palladium(II) chloride (0.036 g, 0.051 mmol), tetra-N-butylammonium bromide (0.018 g, 0.056 mmol), and potassium carbonate (0.139 g, 1.00 mmol) were combined, evacuated, then purged with nitrogen a total of three times. N-(benzo[d]thiazol-2-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[b]thiophene-3-carboxamide (**30**) (0.218 g, 0.500 mmol) in dry 1,4-dioxane (12.0 mL, 154 mmol) and deoxyenated water (4.40 mL, 244 mmol) was added by cannula. The reaction was microwaved using up to 300 W of power at a temperature of 150°C for five minutes. The sample was allowed to cool to room temperature and was stirred overnight, resulting in the formation of a precipitate. The solid was vacuum filtered and washed with 1,4-dioxane and water to give 6-(3-(benzo[d]thiazol-2-

ylcarbamoyl)benzo[b]thiophen-5-yl)picolinic acid (**9**) (0.071 g, 0.16 mmol, 33%). ^{1}H NMR (500 MHz, DMSO-D_6) δ 9.46 – 9.39 (m, 1H), 8.88 – 8.79 (m, 1H), 8.22 – 8.15 (m, 2H), 8.00 – 7.83 (m, 4H), 7.73 – 7.65 (m, 1H), 7.42 – 7.35 (m, 1H), 7.28 – 7.19 (m, 1H). MS (ESI(+)): 432.1 m/z (M+H)

Scheme S7 Synthesis of imidazopyridine amide 10.[a]



[a]Reagents and conditions: (a) Oxalyl chloride, DMF, CH_2Cl_2; (b) diazomethane, DIPEA, CH_2Cl_2; (c) HBr, AcOH; (d) 2-aminonicotinic acid, EtOH; (e) 2-aminobenzothiazole, EDC, DMAP, DMF; (f) LiOH, MeOH, H_2O.

Synthesis of compound **34**:

Step 1: To a solution of 6-(methoxycarbonyl)picolinic acid (1.504 g, 8.303 mmol) in dry methylene chloride (48.0 mL) cooled to 0°C, was added dry N,N-dimethylformamide (0.100 mL, 1.29 mmol) followed by dropwise addition of oxalyl chloride (0.77 mL, 9.1 mmol). The reaction was warmed to room temperature and stirred for 3.5 hours. The mixture was concentrated, diluted with dry methylene chloride (48.0 mL), cooled to 0°C, and then N,N-diisopropylethylamine (2.90 mL, 0.0166 mol) was slowly added, followed by addition of diazomethane to the mixture. The mixture was allowed to warm slowly to room temperature and was stirred overnight. The sample was concentrated and then chromatographed through silica gel (80g, 0-40% ethyl acetate in hexanes) to give methyl 6-(2-diazoacetyl)picolinate (0.802 g, 3.91 mmol, 47%).

Step 2: Methyl 6-(2-diazoacetyl)picolinate (0.400 g, 1.95 mmol) was dissolved in acetic acid (10.0 mL) and was cooled to 0°C. 48% hydrogen bromide (48:52, hydrogen bromide:water, 0.330 mL, 2.92 mmol) was added, and then the reaction was warmed to room temperature and stirred for thirty minutes. The sample was poured onto ice, sodium bicarbonate was added, and the resulting solution was extracted three times with ethyl acetate, washed four times with saturated aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered, and concentrated to give methyl 6-(2-bromoacetyl)picolinate (0.475 g, 1.84 mmol, 94%).

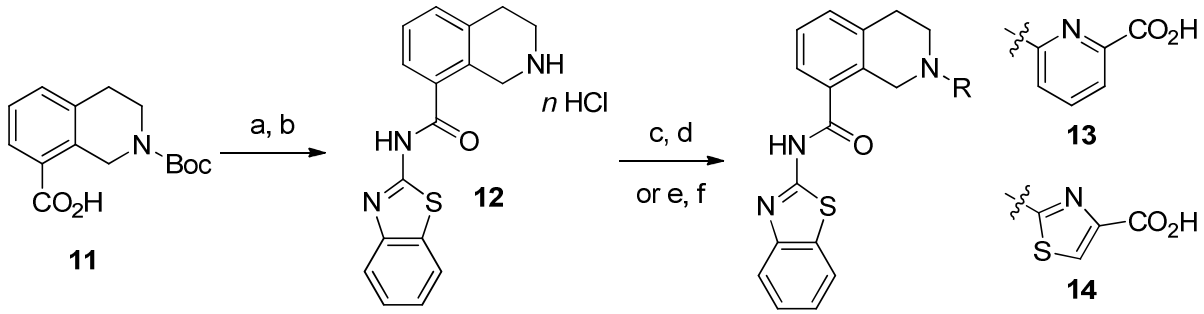
Step 3: Methyl 6-(2-bromoacetyl)picolinate (0.475 g, 1.84 mmol), 2-aminonicotinic acid (0.254 g, 1.84 mmol), and ethanol (10.0 mL) were combined, heated at 78°C and stirred overnight. The mixture was concentrated, slurried in ethyl acetate, and vacuum filtered. The filtrate was slurried in dichloromethane and vacuum filtered, then slurried in ethanol and vacuum filtered to give 2-(6-(methoxycarbonyl)pyridin-2-yl)imidazo[1,2-a]pyridine-8-carboxylic acid (**34**) (0.136 g, 0.458 mmol, 25%).

Synthesis of compound **10**:

Step 1: 2-(6-(Methoxycarbonyl)pyridin-2-yl)imidazo[1,2-a]pyridine-8-carboxylic acid (**34**) (0.136 g, 0.458 mmol), 2-aminobenzothiazole (0.092 g, 0.61 mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.140 g, 0.730 mmol), 4-dimethylaminopyridine (0.174 g, 1.42 mmol), and dry N,N-dimethylformamide (3.20 mL) were combined and stirred for three days. The mixture was concentrated and chromatographed through silica gel (12g, 0-100% ethyl acetate in hexanes) to give methyl 6-(8-(benzo[d]thiazol-2-ylcarbamoyl)imidazo[1,2-a]pyridin-2-yl)picolinate (0.073 g, 0.17 mmol, 37%).

Step 2: To a solution of methyl 6-(8-(benzo[d]thiazol-2-ylcarbamoyl)imidazo[1,2-a]pyridin-2-yl)picolinate (0.073 g, 0.00017 mol) was dissolved in methanol (6.50 mL) and water (2.80 mL) was added lithium hydroxide, monohydrate (0.0760 g, 1.81 mmol). The reaction was stirred at room temperature for two hours, concentrated, redissolved in tetrahydrofuran (10.0 mL) and water (10.0 mL), and 4.0 M of hydrogen chloride in 1,4-dioxane(0.450 mL, 0.00180 mol) was added dropwise. The reaction mixture was stirred for five minutes, during which time a precipitate formed, vacuum filtered, and washed with water and dichloromethane to give 6-(8-(benzo[d]thiazol-2-ylcarbamoyl)imidazo[1,2-a]pyridin-2-yl)picolinic acid (**10**) (0.053 g, 0.13 mmol, 75%). ^{1}H NMR (500 MHz, DMSO-D_6) δ 13.82 (s, 1H), 13.28 (s, 1H), 8.99 (dd, *J* = 6.7, 1.2 Hz, 1H), 8.93 (s, 1H), 8.40 (dd, *J* = 7.8, 1.0 Hz, 1H), 8.31 (dd, *J* = 7.2, 1.2 Hz, 1H), 8.28 (t, *J* = 7.8 Hz, 1H), 8.10 – 8.06 (m, 2H), 7.93 – 7.89 (m, 1H), 7.54 – 7.49 (m, 1H), 7.41 – 7.37 (m, 1H), 7.33 – 7.28 (m, 1H). MS (ESI(+)): 416.2 m/z (M+H)

Scheme S8 Synthesis of compounds 13 and 14.[a]



[a]Reagents and conditions: (a) benzo [*d*]thiazol-2-amine, EDCI, DMAP, CH_2Cl_2; (b) 2N HCl/Et_2O, DCM; (c) t-butyl 6-fluoropyridine-2-carboxylate, $CsCO_3$, DMA, sieves, 100°C, 29%; (d) HCl, EtOH, H_2O, 67%; (e) methyl 2-chlorothiazole-4-carboxylate, Cs_2CO_3, DMA, 50°C, 67%; (f) 2N NaOH, THF/MeOH, 50°C.

Synthesis of compound **12**:

Step 1: To a solution of 2(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-8-carboxylic acid (**11**) (6.8g, 24.5mmol) and benzo [*d*]thiazol-2-amine (5.52g, 36.8 mmol) in dichloromethane (80 mL) was added EDCI (9.4g, 49.04 mmol) and DMAP (6g, 49 mmol). The mixture was stirred at room temperature overnight. The reaction mixture was diluted with DCM (400 mL), washed with 5% aqueous HCl, water and brine, dried over Na_2SO_4, and concentrated under reduced pressure to provide 8.5 g of *tert*-butyl 8-(benzo[*d*]thiazol-2-ylcarbamoyl)-3,4- dihydroisoquinoline-2(*1H*)-carboxylate: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (1H, m), 7.48 (1H, d), 7.34 (4H, m), 7.19 (1H, t), 4.91 (2H, m), 3.67 (2H, t), 2.92 (2H, t), 1.47 (9H, m). MS (ESI(+)): m/z 410 (M+H).

Step 2: To a solution of *tert*-butyl 8-(benzo[*d*]thiazol-2-ylcarbamoyl)-3,4-dihydroisoquinoline-2(*1H*)-carboxylate (8.5 g, 20.75 mmol) in DCM (80 mL) was added 2N HCl in ether (80 mL, 160 mmole). The reaction mixture was stirred at room temperature overnight and concentrated under reduced pressure to provide *N*-(benzo[*d*]thiazol-2-yl)- 1,2,3,4-tetrahydroisoquinoline-8-carboxamide dihydrochloride (**12**): LC/MS(APCI): m/z 309.9 (M+H).

Synthesis of compound **13**:

Step 1: Cs_2CO_3 (831 mg, 2.55 mmol) and 500 mg of 4Å sieves were dried under high vacuum at 150°C for 6 hours before the start of the reaction. After cooling, *tert*-butyl 6-fluoropyridine-2-carboxylate (100 mg, 0.51 mmol) and *N*-(benzo[*d*]thiazol-2-yl)- l,2,3,4-tetrahydroisoquinoline-8-carboxamide dihydrochloride (**12**) (327 mg, 0.61 mmol) were transferred to the reaction vessel and the atmosphere was purged with nitrogen. 1.5 mL of anhydrous DMA was then added and the reaction was stirred at 90°C for 3 hours and then 100°C for 2 hours. The cooled reaction mixture was then diluted with ethyl acetate and 10% aqueous citric acid. The organic phase was washed three times with 10% aqueous citric acid, once with water and brine, and dried over Na_2SO_4. Concentration of the organic phase afforded an orange film/foam. This residue was purified by flash chromatography using SiO_2 (EtOAc/petroleum ether. 0:100 to 40:60).to provide *tert*-butyl 6-(8-(benzo[*d*]thiazol-2-ylcarbamoyl)-3,4- dihydroisoquinolin-2(lH)-yl)picolinate as a white solid (72 mg, 29 % yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54 (s, 9H), 3.01 (t, *J* = 5.85 Hz, 2H), 4.05 (t, *J* = 6 Hz, 2H), 5.04 (s, 2H), 6.92 (dd, *J* = 8.55 and 0.63 Hz, 1H),7.09-7.29 (m, 5H), 7.34 (dd, *J* = 7.32 and 0.63 Hz, 1H), 7.60-7.51 (m, 2H), 7.81 (d, *J* = 9 Hz, 1H).

Step 2: *tert*-butyl 6-(8-(benzo[*d*]thiazol-2-ylcarbamoyl)-3,4- dihydroisoquinolin-2(lH)-yl)picolinate (71 mg, 0.15 mmol) was dissolved in 2 mL of EtOH. Two mL of water were then added followed by 2 mL of concentrated HCl. The reaction was stirred at room temperature for 72 hours. Nitrogen gas was bubbled through the mixture to remove HCl and EtOH; a white solid precipitated. It was collected by filtration, rinsed with water and a small amount of Et_2O and dried under vacuum to provide the product as a white solid (42 mg, 67%): ^{1}H NMR (300 MHz, DMSO-D_6) δ 2.98 (t, *J* = 6.15 Hz, 2H), 3.92 (t, *J* = 6.06 Hz, 2H), 4.95 (s, 2H), 7.02 (d, *J* = 8.5 Hz, 1H), 7.27 (d, *J* = 7.3 Hz, 7.31-7.49 (m, 4H), 758 (d, *J* = 7.5 Hz, 1H), 7.66-7.71 (m, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 7.9 Hz);LCMS m/z 431.0 (M+H).

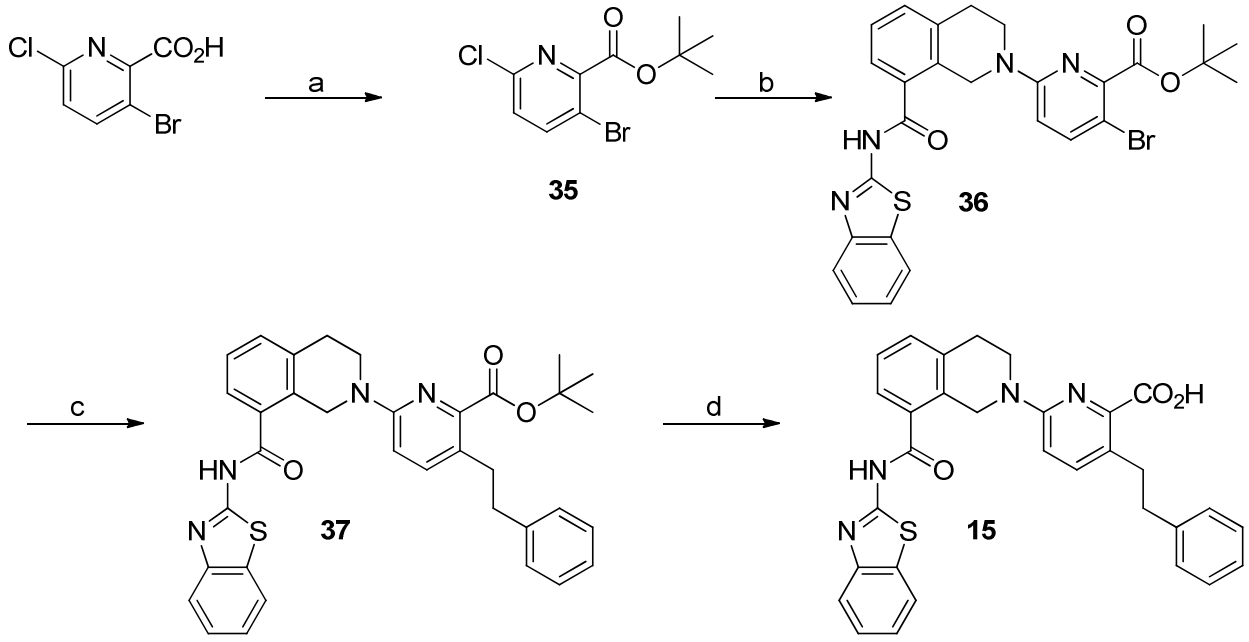
Synthesis of compound **14**:

Step 1: To a solution of *N*-(benzo[*d*]thiazol-2-yl)- l,2,3,4-tetrahydroisoquinoline-8-carboxamide dihydrochloride (**12**) (5.3 g, 13.86 mmol) and methyl 2-chlorothiazole-4- carboxylate (2.5 g, 14 mmol) in DMA (60 mL) was added Cs_2CO_3 (25 g, 70 mmol). The reaction mixture was stirred at 50°C overnight. The reaction mixture was cooled to room temperature, acidified with 5% HCl, extracted with DCM, washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude mate-

rial was purified by column chromatography on silica gel eluting with 5% MeOH in DCM to provide 4.2 g (67%) of methyl 2-(8-(benzo[*d*]thiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)- yl)thiazole-4-carboxylate: LC/MS (APCI): m/z 451.0 (M+H).

Step 2: To a solution of methyl 2-(8-(benzo[*d*]thiazol-2-ylcarbamoyl)-3,4-dihydroisoquinolin-2(1H)- yl)thiazole-4-carboxylate (180 mg, 4 mmol) in THF (4 mL) and MeOH (2mL) was added 2N NaOH (2mL). The reaction mixture was stirred at 50°C for 4 hours and neutralized by slowly adding 5% aq. HCl. The precipitate was then filtered, dried, dissolved in DMSO/MeOH (1:1) and purified by column chromatography on silica gel to provide the desired 2-(8-(benzo[*d*]thiazol-2-ylcarbamoyl)-3,4- dihydroisoquinolin-2(1H)-yl)thiazole-4-carboxylic acid (**14**): ^{1}H NMR (300 MHz, DMSO-D_6) δ 8.03 (d, *J* = 7.7 Hz, 1 H), 7.79 (d, *J* = 7.5 Hz, 1 H), 7.68 (d, *J* = 7.0 Hz, 1 H), 7.61 (s, 1 H), 7.28 - 7.53 (m, 4 H), 4.89 (s, 2 H), 3.76 (t, *J* = 5.9 Hz, 2 H), 3.06 (t, *J* = 5.7 Hz, 2 H).

Scheme S9 Synthesis of compound 15.[a]



[a]Reagents and conditions: (a) TsCl, pyridine, tBuOH, 0°C to room temperature; (b) **12**, Cs_2CO_3, DMA, 4 Å sieves, 120°C; (c) $Ph(CH_2)_2ZnBr$, $Pd(OAc)_2$, S-PHOS, THF; (d)LiOH, EtOH/H_2O, 60°C.

Step 1: Tosyl chloride (7.7 g, 40.4 mmol) was added to a solution of 2-chloro-5-bromo picolinic acid (4.0 g, 17 mmol) and pyridine (9.2 mL, 114 mmol) in 33 mL of t-BuOH at 0°C. The reaction was then stirred at room temperature for 12 hours. $NaHCO_3$ (sat.) was then added and the mixture was extracted 3 times with ethyl acetate. The combined organic phases were washed with brine and dried over Na_2SO_4. Concentration afforded compound **35** (quantitative yield). It was used in the next step without further purification: ^{1}H NMR (300 MHz, CDCl3) δ 8.24 (d, *J* = 8.58 Hz, 1H), 7.61 (d, *J* = 8.36 Hz, 1H), 1.55 (s, 9H).

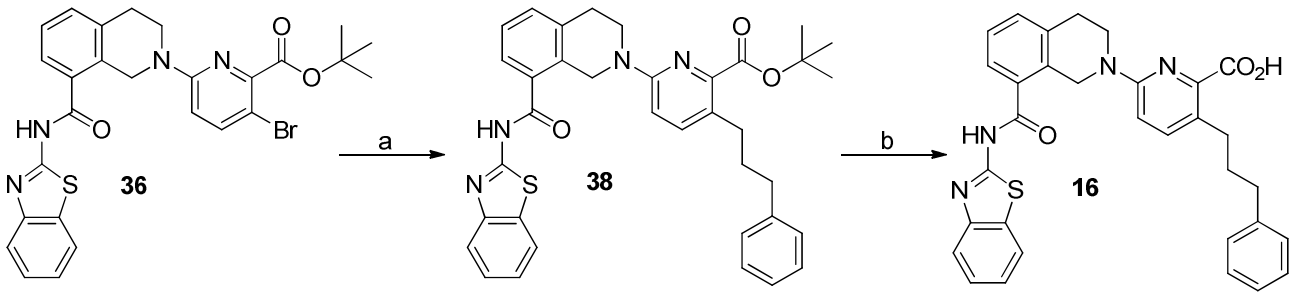
Step 2: Cs_2CO_3 (4.10 g, 12.6 mmol) and 4Å sieves were dried under high vacuum at 150°C for 6 to 10 hours before the start of the reaction. Once cooled down, compound **35** (0.736 g, 2.53 mmol) and compound **12** (1.6 g, 3.0 mmol) were transferred to the reaction vessel and the atmosphere was purged with nitrogen. 12 mL of anhydrous DMA were then added and the reaction was stirred at 120°C for 12 hours. The cooled reaction mixture was then diluted with ethyl acetate and citric acid 10%. The organic phase was washed three times with citric acid, once with water and brine, and dried over Na_2SO_4. Concentration of the organic phase afforded an orange foam. The residue was purified using flash chromatography (ethyl acetate/petroleum ether 0:100 to 40:60) to afford the product **36** as a white solid (1.15 g, 80 % yield): ^{1}H NMR (300 MHz, CDCl3) δ 8.01 (dt, *J* = 7.92, 0.66 Hz, 1H), 7.72 - 7.80 (m, 2H), 7.53 - 7.60 (m, 1H), 7.29 - 7.49 (m, 4H), 6.84 (d, *J* = 9.24 Hz, 1H), 4.91 (s, 2H), 3.76 (t, *J* = 6.05 Hz, 2H), 2.99 (t, *J* = 6.05 Hz, 2H), 1.32 (m, 9H).

Step 3: To a solution of compound **36** (120 g, 0.212 mmol) in anhydrous THF (2 mL) were added $Pd(OAc)_2$ (5 mg, 1 mol%) and S-Phos (17 mg, 2 mol%) and the mixture was stirred for 5 minutes. Phenethylzinc bromide (1.06 mL, 0.5 M in THF, 0.53 mmol) was added and the mixture was stirred for 20 hours. At this time another portion of $Pd(OAc)_2$ (5 mg, 1 mol%), S-PHOS (17 mg, 2 mol%) and phenethylzinc bromide (1.06 mL, 0.5 M in THF, 0.53 mmol) were added and the mixture was stirred for 8 h. The

mixture was diluted in ethyl acetate (5 mL) and washed with saturated ammonium chloride (5 mL) and brine (2 x 5 mL). The organic layer was concentrated *in vacuo* affording a crude orange foam which was purified by flash chromatography (ethyl acetate/petroleum ether 0:100 to 30:70) to give **37** as an orange oil (65 mg, 52%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 - 7.82 (m ,2H), 7.52 - 7.58 (m, 2H), 7.04 - 7.35 (m, 9H), 6.74 - 6.77 (m, 1H), 5.00 (s, 2H), 3.96 - 4.14 (m, 2H), 2.93 - 3.06 (m, 4H), 2.79 - 2.90 (m, 2H), 1.57 (s, 9H).

Step 4: To a solution of compound **37** (62 mg, 0.105 mmol) in ethanol (2 mL) and water (0.5 mL) was added LiOH (75 mg, 3.15 mmol) and the mixture was stirred for 16 hours while heating at 60°C. After cooling, the solvent was removed *in vacuo* affording a crude residue, which was dissolved in water (5 mL) and washed with ethyl acetate (2 x 5 mL). The organic layers were combined and washed with 1M HCl (5 mL) and water (5 mL). The organic phase was reduced *in vacuo* to afford compound **15** as a brown paste (26 mg, 46%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.4 Hz, 1H), 7.77 (d, *J* = 7.4 Hz, 1H), 7.55 - 7.61 (m, 1H), 7.13 - 7.49 (m, 10H), 6.87 - 6.90 (m, 1H), 5.12 (s, 2H), 3.79 - 3.83 (m, 2H), 3.28 - 3.33 (m, 2H), 3.07 (m, 2H), 2.85 - 2.89 (m, 2H). MS (ESI(+)): m/z 535.1 (M+H).

Scheme S10 Synthesis of compound 16.[a]

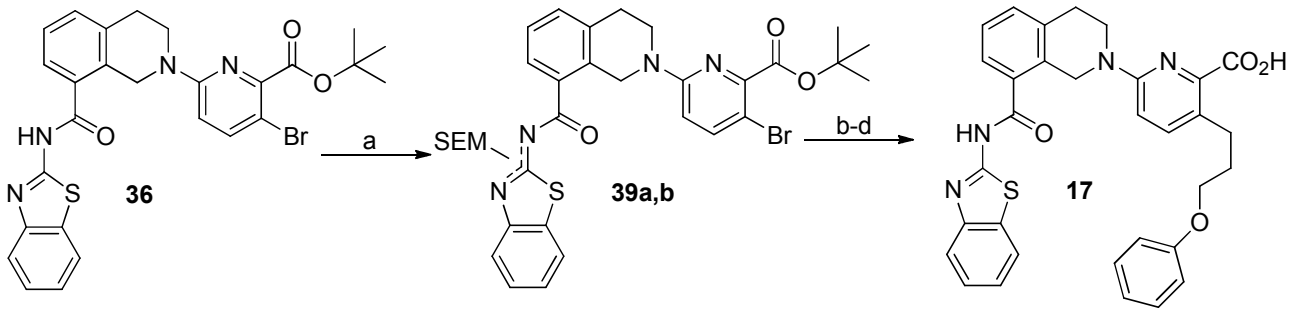


[a]Reagents and conditions: (a) $Ph(CH_2)_3ZnBr$, $Pd(OAc)_2$, S-PHOS, THF; (b) LiOH, $EtOH/H_2O$, 60°C.

Step 1: To a solution of Compound **33** (120 mg, 0.212 mmol) in anhydrous THF (2 mL) were added $Pd(OAc)_2$ (5 mg, 1 mol%) and S-Phos (17 mg, 2 mol%) and the mixture was stirred for 5 minutes. 3-Phenyl-1-propylzinc bromide (1.06 mL, 0.5 M in THF, 0.53 mmol) was added and the mixture was stirred for 16 h. At this time another portion of $Pd(OAc)_2$ (5 mg, 1 mol%), S-PHOS (17 mg, 2 mol%) and 3-phenyl-1-propylzinc bromide (1.06 mL, 0.5 M in THF, 0.53 mmol) were added and the mixture was stirred for 7 h. The mixture was diluted in ethyl acetate (5 mL) and washed with saturated ammonium chloride (5 mL) and brine (2 x 5 mL). The organic layer was concentrated *in vacuo* affording a crude oil, which was purified by flash chromatography (ethyl acetate/petroleum ether 0:100 to 40:70) to give compound **35** as an orange solid (55 mg, 43%). ^{1}H NMR (300 MHz, $CDCl_3$) 7.78 - 7.81 (m, 1H), 7.51 - 7.53 (m, 1H), 7.32-7.35 (m, 1H), 7.22 – 7.27 (m, 4H), 7.07 - 7.17 (m, 4H), 6.77 – 6.80 (m, 1H), 4.97 (s, 2H), 3.94 (t, *J* = 5.6 Hz, 2H), 2.98 (t, *J* = 5.6 Hz, 2H), 2.61 – 2.72 (m, 4H), 1.53 (s, 9H).

Step 2: To a solution of compound **35** (55 mg, 9.1 x 10^{-2} mmol) in ethanol (2 mL) and water (0.5 mL) was added LiOH (65 mg, 2.73 mmol) and the mixture was stirred for 16 hours while heating at 60°C. After cooling, the solvent was removed *in vacuo* affording a crude residue, which was dissolved in water (5 mL) and washed with ethyl acetate (2 x 5 mL). The organic layers were combined and washed with 1M HCl (5 mL) and water (5 mL). The organic phase was reduced *in vacuo* to afford compound **16** as a brown paste (32 mg, 64%). ^{1}H NMR (300 MHz, DMSO-D_6) δ 8.35 (d, *J* = 7.7 Hz, 1H), 7.79 (1H, d, *J* = 7.7 Hz), 7.09 - 7.65 (12H, m), 6.94 (m, 1H), 4.92 (s, 2H), 3.86 (t, *J* = 5.9 Hz, 2H), 2.98 (t, *J* = 5.9 Hz, 2H), 2.65 - 2.75 (m, 2H), 2.58 (m, 2H), 1.73 - 1.86 (m, 2H). MS(ESI(+)): m/z 549.2 (M+H).

Scheme S11 Synthesis of compound 17.[a]



[a]Reagents and conditions: (a) SEMCl, NEt_3, THF; (b) Phenyl propargyl ether, X-Phos, $Pd(CH_3CN)_2Cl_2$, Cs_2CO_3, propionitrile, 105°C. $Ph(CH_2)_3ZnBr$, $Pd(OAc)_2$, S-PHOS, THF; (c) H_2, PtO_2, EtOAc; (d) HCl(conc), EtOH, 50°C.

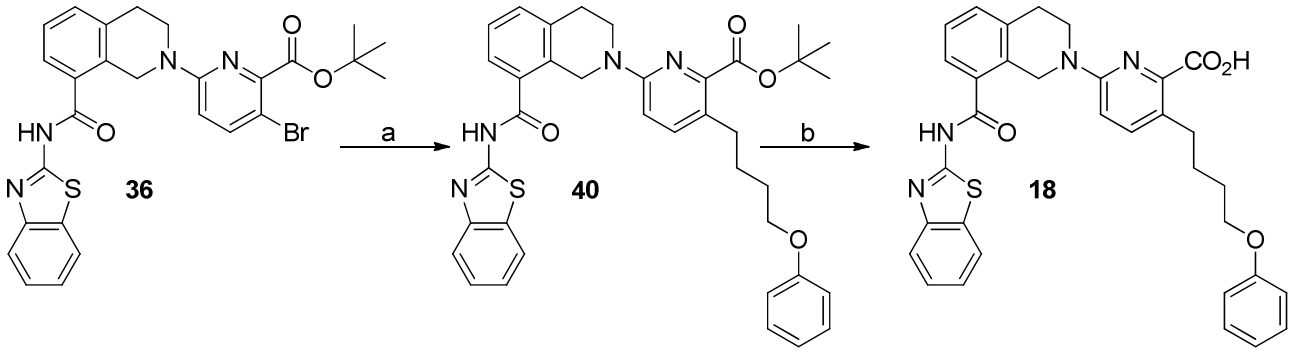
Step 1: Compound **33** (0.35 g, 0.62 mmol) was dissolved in THF. NEt_3 (127 µL, 0.91 mmol) and SEMCl (135 µL, 0.74 mmol) were added successively. The reaction was stirred at room temperature for 1 hour. It was then concentrated. The residue was taken into ethyl acetate and water. The aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. After concentration, the residue was purified by flash chromatography (ethyl acetate/petroleum ether 0:100 to 30:70). A pale yellow foamy solid containing isomers **39a** and **39b** in a ratio of 0.6 to 1 was obtained (276 mg, 64%).

Step 2: To pre-dried Cs_2CO_3 (378 mg, 1.16 mmol) was added isomers **39a** and **39b** (180 mg, 0.26 mmol), 2-dicyclohexylphosphino-2',4',6'-tri-iso-propyl-1,1'-biphenyl (18 mg, 0.04 mmol) and bis(acetonitrile)dichloropalladium(II) (3.2 mg, 0.012 mmol). The atmosphere was purged with nitrogen and following the addition of propionitrile (3.0 mL) the mixture was stirred at room temperature for 10 minutes. before phenyl propargyl ether (205 mg, 1.54 mmol) was added. The mixture was heated at 105°C for 1 hour, cooled to room temperature, concentrated, diluted with saturated NH_4Cl and extracted three times with ethyl acetate. The organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude material was purified by flash chromatography (ethyl acetate/petroleum ether 0:100 to 15:85) to give the corresponding alkyne isomers (90 mg, 47%):

Step 3: PtO_2 (4.8 mg, 0.020 mmol) was added to a solution of the previously prepared alkyne isomers (60 mg, 0.080 mmol) in ethyl acetate (2.0 mL) and the mixture was stirred under H_2 atmosphere for 2 hours. The mixture was filtered, washed with ethyl acetate and concentrated to give the reduced products, again as a mixture of SEM isomers (55 mg, 92%):

Step 4: The product from the previous reaction (55 mg, 0.073 mmol) was dissolved in 1 mL of EtOH. Water (1 mL) was added followed by 1 mL of concentrated HCl. The reaction was stirred at 50°C for 12 hours. The solids that precipitated were collected by filtration and rinsed with water. The solid was purified by preparative HPLC to give **17** as a white solid: ^{1}H NMR (300 MHz, DMSO-D_6) δ 7.85 (m, 1H), 7.62 (m, 1H), 7.57-7.19 (m, 9H), 6.99-6.80 (m, 4H), 5.11 (s, 2H), 3.97 (t, *J* = 6.2 Hz, 2H), 3.82 (t, *J* = 5.9 Hz, 2H), 3.21 (t, *J* = 7.4 Hz, 2H), 3.06 (t, *J* = 5.3 Hz, 2H), 2.09 (t, *J* = 8.8 Hz, 2H); MS (ESI(+)): m/z 565.7 (M+H).

Scheme S12 Synthesis of compound 18.[a]

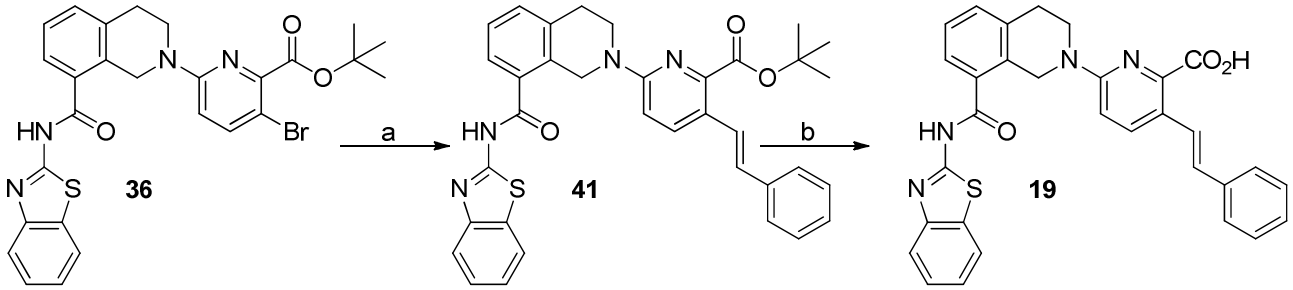


[a]Reagents and conditions: (a) $PhO(CH_2)_4ZnBr$, $Pd(OAc)_2$, S-PHOS, THF; (b) LiOH, $EtOH/H_2O$, 60°C.

Step 1: To a solution of compound **36** (154 mg, 0.272 mmol) in anhydrous THF (2 mL) were added $Pd(OAc)_2$ (6 mg, 1 mol%) and S-Phos (22 mg, 2 mol%) and the mixture was stirred for 5 minutes. 4-Phenoxybutylzinc bromide (1.36 mL, 0.5 M in THF, 0.68 mmol) was added and the mixture was stirred for 20 h. At this time another portion of $Pd(OAc)_2$ (6 mg, 1 mol%), S-PHOS (22 mg, 2 mol%) and 4-phenoxybutylzinc bromide (1.36 mL, 0.5 M in THF, 0.68 mmol) were added and the mixture was stirred for 8 h. The mixture was diluted in ethyl acetate (5 mL) and washed with saturated ammonium chloride (5 mL) and brine (2 x 5 mL). The organic layer was concentrated *in vacuo* affording a crude, which was purified by flash chromatography (ethyl acetate/petroleum ether 0:100 to 50:50) to give compound **40** as a yellow oil (158 mg, 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 – 7.81 (m, 1H), 7.36 - 7.39 (m, 1H), 7.20 - 7.30 (m, 6H), 7.09 - 7.21 (m, 1H), 6.77 - 6.97 (m, 5H), 4.99 (2H, s), 3.88 - 4.02 (4H, m), 2.94 - 3.04 (2H, m), 2.73 (2H, m), 1.55 (9H, s). MS (ESI(+)): m/z 635.1 (M+H).

Step 2: To a solution of compound **40** (80 mg, 1.26 x 10^{-2} mmol) in ethanol (2 mL) and water (0.5 mL) was added LiOH (91 mg, 3.78 mmol) and the mixture was stirred for 16 h while heating at 60°C. After cooling, the solvent was removed *in vacuo* affording a crude residue, which was dissolved in water (5 mL) and washed with ethyl acetate (2 x 5 mL). The organic layers were combined and washed with 1M HCl (5 mL) and water (5 mL). The organic phase was concentrated *in vacuo* to afford compound **18** as a light brown oil (50 mg, 68%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (m, 1H), 7.70 (m, 1H), 7.51 (m, 2H), 7.21 - 7.35 (m, 5H), 6.79 - 7.00 (m, 5H), 5.11 (s, 2H), 3.99 (m, 2H), 3.82 (m, 2H), 3.01 - 3.15 (m, 4H), 1.66 - 1.95 (m, 4H). MS (ESI(+)): m/z 579.1 (M+H).

Scheme S13 Synthesis of compound 19.[a]

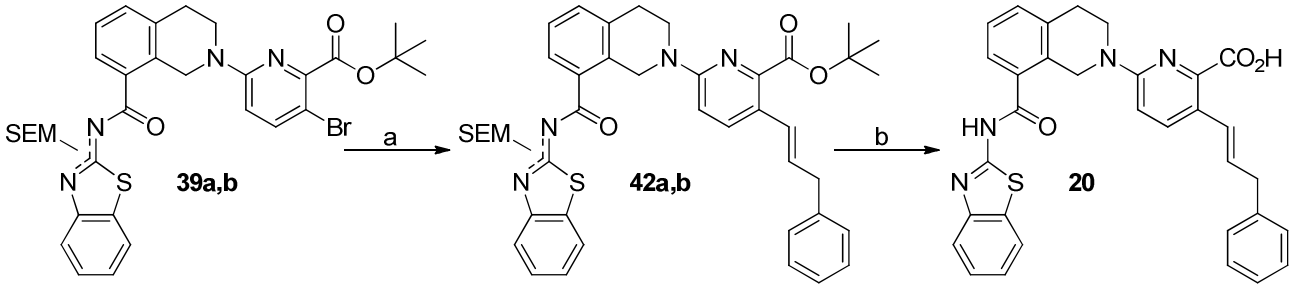


[a]Reagents and conditions: (a) Trans-2-phenylvinylboronic acid, $Pd(PPh3)_2Cl_2$, Bu_4NBr, K_2CO_3, 1,4-dioxane, water, 90°C; (b) LiOH, $EtOH/H_2O$, 60°C.

Step 1: A solution of compound **36** (92 mg, 0.162 mmol), trans-2-phenylvinylboronic acid (48 mg, 0.324 mmol), $Pd(PPh_3)_2Cl_2$ (11 mg, 1.62 x 10^{-2} mmol), tetrabutylammonium bromide (5 mg, 1.62 x 10^{-2} mmol) and potassium carbonate (22 mg, 0.162 mmol) were heated to 90°C in 1,4-dioxane (3 mL) and water (1 mL) for 20 h. After cooling, the mixture was diluted in ethyl acetate (5 mL) and washed with brine (3 x 5 mL). The organic layer was concentrated *in vacuo* to afford a crude mixture, which was purified by flash chromatography (ethyl acetate/petroleum ether 0:100 to 50:50) to give compound **41** as a pale yellow oil (64 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 – 7.84 (m, 2H), 7.41 - 7.55 (m, 4H), 6.97 - 7.40 (m, 8H), 6.76 - 6.90 (m, 2H), 5.05 (s, 2H), 3.92 - 4.00 (m, 2H), 2.99 (s, 2H), 1.56 - 1.63 (m, 9H).

Step 2: To a solution of compound **41** (64 mg, 0.109 mmol) in ethanol (2 mL) and water (0.5 mL) was added LiOH (78 mg, 3.26 mmol) and the mixture was stirred for 16 h while heating at 60°C. After cooling, the solvent was removed *in vacuo* affording a crude residue, which was dissolved in water (5 mL) and extracted with ethyl acetate (2 x 5 mL). The organic layers were combined and washed with 1M HCl (5 mL) and water (5 mL). The organic phase was reduced *in vacuo* to afford **19** as a light yellow gum (8 mg, 14%). ^{1}H NMR (300 MHz, DMSO-D_6) δ 8.09 (m, 1H), 8.04 (m, 1H), 7.78 (m, 1H), 7.62 (s, 2H), 7.23 - 7.49 (m, 9H), 7.02 - 7.08 (m, 2H), 5.02 (s, 2H), 3.94 (m, 2H), 3.02 (m, 2H). MS (ESI(+)): m/z 533.1 (M+H).

Scheme S14 Synthesis of compound 20.[a]

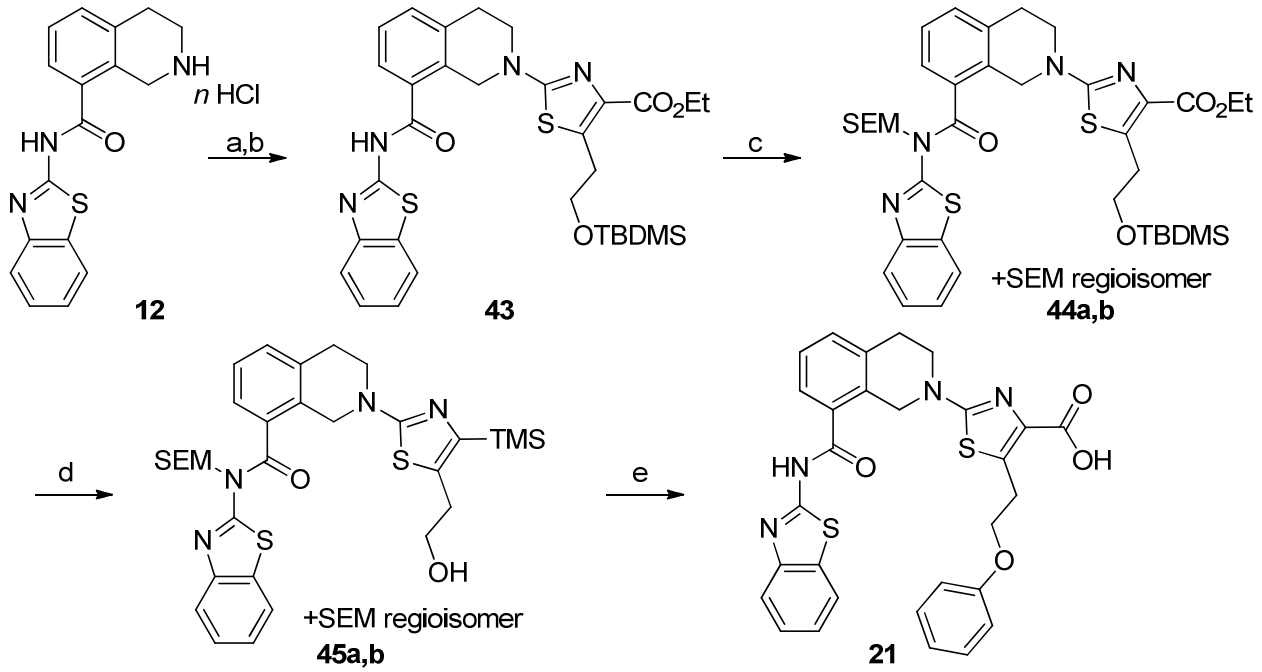


[a]Reagents and conditions: (a) Trans-3-Phenyl-1-propen-1-ylboronic acid, $Pd(OAc)_2$, *J*ohnPHOS, KF, THF, 60°C; (b) 5M HCl, $EtOH/H_2O$, 50°C.

Step 1: An oven dried Schlenk tube was evacuated and backfilled with nitrogen gas and charged with $Pd(OAc)_2$ (1 mg, 3.6 x 10^{-3} mmol), *J*ohnPhos (2 mg, 7.2 x 10^{-3} mmol), trans-3-phenyl-1-propen-1-ylboronic acid (87 mg, 0.54 mmol) and potassium fluoride (63 mg, 1.08 mmol). A mixture of compounds **39a** and **39b** (250 mg, 0.36 mmol) was added and the flask was evacuated and back-filled with nitrogen gas again. Anhydrous THF (5 mL) was added and the mixture was stirred while heating to 60°C for 24 hours. After cooling, the mixture was diluted in ethyl acetate (5 mL) and washed with water (2 x 10 mL) and brine (10 mL). The organic layer was concentrated *in vacuo* to afford a crude mixture, which was purified by flash chromatography (ethyl acetate/petroleum ether 5:95 to 30:70) to give compounds **42a** and **42b** as a clear oil (112 mg, 42%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 - 8.30 (m, 1H), 7.78 - 7.90 (m, 2H), 7.69 - 7.73 (m, 1H), 7.51 – 7.60 (m, 1H), 7.42 - 7.52 (m, 4H), 7.20 - 7.40 (m, 5H), 6.94 - 6.99 (m, 1H) 6.71 - 6.88 (m, 1H), 5.99 (s, 2H) 5.28 (s, 2H) 4.06 – 4.08 (m, 2H), 3.70 - 3.81 (m, 2H), 3.04 – 3.06 (m, 2H), 1.65 (s, 9H), 0.080 – 0.089 (m, 2H), 0.01 (s, 9H).

Step 2: To a solution of compounds **42a** and **42b** (75 mg, 0.102 mmol) in ethanol (1 mL) and water (1 mL) was added 5M HCl (1 mL) and the mixture was stirred for 16 hours while heating at 50°C. After cooling, the solvent was removed *in vacuo* affording a crude solid, which was filtered off and washed with water (5 mL) and a small amount of ethanol. The crude solid was purified by semi-preparative HPLC affording compound **20** (5 mg, 8%). ^{1}H NMR (300 MHz, DMSO-D_6) δ 7.89 (s, 1H), 7.80 (d, 1H), 7.77 (d, 1H), 7.62 (d, 1H), 7.50-7.19 (m, 7H), 6.95 (d, 1H), 6.80 (d, 1H), 6.23 (m, 1H), 4.96 (br s, 2H), 3.88 (t, *J* = 5.8 Hz, 2H), 3.48 (d, *J* = 5.8 Hz, 2H), 2.99 (m, 1H). MS (ESI(+)): m/z 547.2 (M+H).

Scheme S15 Synthesis of compound 21.[a]



[a]Reagents and conditions: (a) Et_3N, DMF then di(1H-imidazol-1-yl)methanethione then NH_3; (b) 3-(tert-butyldimethylsilyloxy)propanal, 5 ethyl 2,2-dichloroacetate, NaOEt, EtOH, 0°C. then 50°C; (c) SEM-Cl, Et_3N, DMF; (d) 1% HCl in MeOH; (e) phenol, DEAD, PPh_3, THF, then 4N HCl in 1,4-dioxane, then 4N NaOH, 1,4-dioxane.

Step 1: To a mixture of compound **12** (3.25 g, 8.50 mmol) in DMF (50 mL) was added Et_3N (4.71 mL, 34.0 mmol). The resulting mixture was stirred for 10 minutes and di(1H-imidazol-1-yl)methanethione (1.818 g, 10.20 mmol) was added. The reaction mixture was stirred at room temperature for 30 minutes. Ammonia (7 N in MeOH) (48.6 mL, 340 mmol) was added and the resulting mixture was stirred overnight. The reaction mixture was concentrated to remove the ammonia and MeOH. The DMF solution was directly used for the next step without further purification. LCMS (APCI): m/z 369 (M+H).

Step 2: To a solution of 3-(tert-butyldimethylsilyloxy)propanal (1 g, 5.31 mmol) and ethyl 2,2-dichloroacetate (0.651 mL, 5.31 mmol) in Et_2O (4 mL) at 0°C was added sodium ethanolate (0.397 g, 5.84 mmol) in EtOH (4 mL) dropwise. The reaction mixture was stirred at 0°C for 1.5 hours and diluted with Et_2O. The resulting mixture was washed with brine and the organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dried in vacuo and dissolved in EtOH (8 mL). To the resulting solution was added the crude thiourea prepared in step 1 (1 eq) in DMF. The reaction mixture was heated at 50°C for 8 hours and concentrated under reduced pressure. The residue was dissolved in DCM and purified by column chromatography on silica gel eluting with 0% to 17% EtOAc in hexanes, then with 0% to 15% EtOAc in DCM to provide compound **43**. LCMS (APCI): m/z 623 (M+H).

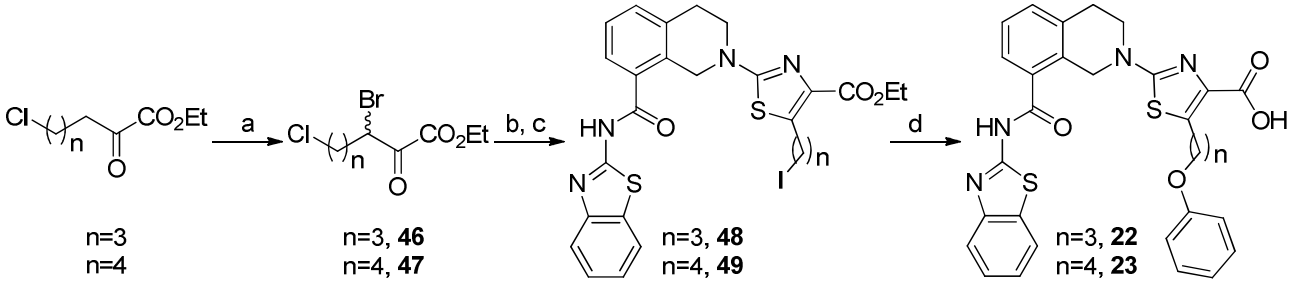
Step 3: To a mixture of **43** (365 mg, 0.586 mmol) and (2-(chloromethoxy)ethyl)trimethylsilane (0.109 mL, 0.615 mmol) in DMF (5 mL) was added Et_3N (0.163 mL, 1.172 mmol) dropwise. The reaction mixture was stirred at room temperature for 10 minutes. Two regioisomeric SEM protected 2-aminobenzothiazole amides, **44a** and **44b** were observed. The reaction was diluted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude products were used in the next step without further purification.

Step 4: To a solution of **44a** and **44b** (400 mg, 0.531 mmol) in DCM (2 mL) was added MeOH (50 mL). 1% HCl in MeOH (3.87 mL, 1.062 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 5 hours and was diluted with EtOAc (250 mL) and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in DCM and purified by column chromatography on silica gel eluting with a gradient of 0% to 25% EtOAc in DCM to provide alcohols **45a** and **45b**: LCMS (APCI): m/z 639 (M+H).

Step 5: Compounds **45a** and **45b** (51 mg, 0.08 mmol), phenol (11 mg, 0.12 mmol) and triphenylphosphine (31 mg, 0.12 mmol) were combined with THF (2 ml) and stirred at ambient temperature for 20 minutes. Di-tert-butyl azodicarboxylate (21 mg, 0.092 mmol) was added and stirring was continued overnight. The reaction mixture was diluted with EtOAc, washed with water and brine, dried (anhydrous magnesium sulfate), filtered and concentrated. The concentrate was purified by column chromatography on silica gel eluting with a gradient of 10-50% EtOAc in hexanes. The resulting material was taken up in 1,4-dioxane (2 ml), treated with HCl (4N in 1,4-dioxane) (0.4 ml, 1.6 mmol) and heated at 70°C for several hours. The reaction mixture was cooled

to room temperature and concentrated. The concentrate was taken up in 1,4-dioxane (2 ml), treated with 4N aqueous NaOH (0.2 ml, 0.8 mmol) and heated at 50°C for four hours. The reaction mixture was cooled to room temperature and treated with 1N HCl (aq.) to induce precipitation of the product. The solid was filtered, rinsed with water, slurried in Et_2O, filtered, rinsed with Et_2O, slurried in 1:1 DMSO/MeOH, filtered and rinsed with MeOH to provide **21** as a white solid. ^{1}H NMR (300 MHz, DMSO-D_6) δ 12.88 (s, 1H), 12.66 (s, 1H), 8.04 (d, *J* = 7.93 Hz, 1H), 7.80 (d, *J* = 7.93 Hz, 1H), 7.66 (d, *J* = 7.14 Hz, 1H), 7.43 (m, 4H), 7.22 (m, 2H), 6.90 (m, 3H), 4.83 (s, 2H), 4.13 (t, *J* = 6.15 Hz, 2H), 3.73 (t, *J* = 5.95 Hz, 2H), 3.47 (t, *J* = 6.35 Hz, 2H), 3.03 (t, *J* = 5.75 Hz, 2H). MS (ESI(+)) m/e 557 (M+H).

Scheme S16 Synthesis of compounds 22 and 23.[a]



[a]Reagents and conditions: (a) Br_2, CCl_4; (b) Et_3N, DMF then di(1H-imidazol-1-yl)methanethione then NH3, then **46** or **47**, EtOH, 50°C; (c) NaI, CH_3CN, 90°C; (d) 1% HCl in MeOH; (e) phenol, DEAD, PPh3, THF, then 4N HCl in 1,4-dioxane, then 4N NaOH, 1,4-dioxane.

Step 1: To ethyl 6-chloro-2-oxohexanoate (2.9 g, 15 mmol) in carbon tetrachloride (30 mL) was added bromine (0.85 mL, 16.5 mmol) and the solution was stirred at room temperature for 1 hour. The reaction mixture was diluted with EtOAc, washed with $Na_2S_2O_3$ solution, water and brine, then dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel eluting with a gradient of 0 to 10% EtOAc in hexanes to provide **46** in 95% yield. ^{1}H NMR (300 MHz, DMSO-D_6) δ 5.25 (dd, *J* = 8.82, 4.75 Hz, 1H), 4.29 (q, *J* = 7.12 Hz, 2H), 3.71 (t, *J* = 6.27 Hz, 2H), 2.16 (m, 1H), 1.91 (m, 3H), 1.29 (t, *J* = 7.12 Hz, 3H).

Step 2: To **12** (11.5 g, 30 mmol) in DMF (125 mL) was added Et_3N (16.7 mL, 120 mmol) and the solution was stirred at room temperature for 15 minutes. Di(1H-imidazol-1-yl)methanethione (6.53 g, 33 mmol) was added and the reaction mixture was stirred at room temperature for 1 hour. 7N Ammonia in MeOH (171 mL, 1.2 mol) was added and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated to remove ammonia, Et_3N, and MeOH. To the concentrate was added a solution of **46** (11.4 g, 42 mmol) in EtOH (40 mL). The reaction mixture was heated at 50°C under nitrogen for 4.5 hours. Additional **46** (0.815 g, 3 mmol) in EtOH (3 mL) was added and heating was continued for 1.5 hours. The reaction mixture was concentrated under reduced pressure to remove EtOH and then extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The concentrate was purified by column chromatography on silica gel eluting with a gradient of 30 to 50% EtOAc in hexanes to provide the desired thiazole in 69% yield. ^{1}H NMR (300 MHz, DMSO-D_6) δ 12.89 (s, 1H), 8.04 (d, *J* = 7.46 Hz, 1H), 7.79 (d, *J* = 8.14 Hz, 1H), 7.67 (d, *J* = 7.12 Hz, 1H), 7.42 (m, 4H), 4.83 (s, 2H), 4.19 (q, *J* = 7.12 Hz, 2H), 3.72 (t, *J* = 5.93 Hz, 2H), 3.64 (t, *J* = 6.27 Hz, 2H), 3.13 (dd, *J* = 8.14, 6.78 Hz, 2H), 3.04 (t, *J* = 5.93 Hz, 2H), 2.00 (m, 2H), 1.21 (t, *J* = 6.95 Hz, 3H).

Step 3: To the previously prepared thiazole (9.3 g, 17.2 mmol) in acetonitrile (125 mL) was added sodium iodide (25.8 g, 172 mmol). The reaction mixture was purged with nitrogen twice. The reaction mixture was then heated at 90°C for 5 hours, cooled to room temperature, and concentrated under reduced pressure. The concentrate was diluted with EtOAc, washed with water, brine, dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude material was slurried in Et_2O, filtered, washed with additional Et_2O and dried under reduced pressure to **48** in 93% yield. ^{1}H NMR (300 MHz, DMSO-D_6) δ 12.89 (s, 1H), 8.04 (d, *J* = 7.46 Hz, 1H), 7.79 (d, *J* = 8.14 Hz, 1H), 7.66 (d, *J* = 6.78 Hz, 1H), 7.43 (m, 4H), 4.83 (s, 2H), 4.19 (q, *J* = 7.12 Hz, 2H), 3.72 (t, *J* = 5.93 Hz, 2H), 3.26 (t, *J* = 6.78 Hz, 2H), 3.06 (m, 2H), 2.03 (m, 2H), 1.21 (t, *J* = 7.12 Hz, 3H).

Step 4: To phenol (22.6 mg, 0.24 mmol) in DMF (2 mL) was added NaH (60% oil dispersion) (24 mg, 0.6 mmol). After stirring at room temperature for 5 minutes, **48** (127 mg, 0.2 mmol) was added and stirring was continued for 1 hour. The reaction mixture was acidified with 1N HCl and the precipitate was filtered and washed with water. The precipitate was slurried in Et_2O, filtered and washed with additional Et_2O. The resulting solid was purified by column chromatography on silica gel eluting with a gradient of 0 to 2% MeOH in DCM. To the purified material in DMF (1mL) was added NaOH (4N aq) (0.5 mL, 2 mmol). The mixture was heated at 50°C for 5 hours, cooled to room temperature, and acidified with 1N HCl. The precipitate was filtered, washed with water, slurried in Et_2O, filtered, washed with Et_2O and dried in a vacuum oven to provide **22** in 37% yield. ^{1}H NMR (300 MHz, DMSO-D_6) δ 12.86 (s, 1H), 12.52 (s, 1H), 8.04 (d, *J* = 7.46 Hz, 1H), 7.79 (d, *J* = 7.80 Hz, 1H), 7.67 (d, *J* = 7.80 Hz, 1H), 7.41 (m, 4H), 7.24 (m, 2H), 6.87 (m, 3H), 4.82 (s, 2H), 3.96 (t, *J* = 6.27 Hz, 2H), 3.72 (t, *J* = 5.93 Hz, 2H), 3.17 (m, 2H), 3.03 (t, *J* = 5.76 Hz, 2H), 2.00 (m, 2H). MS (ESI(+)): m/z 571 (M+H).

Compound **23** was prepared in an identical fashion, substituting ethyl-7-chloro-2-oxoheptanoate for ethyl-6-chloro-2-oxohexanoate. ^{1}H NMR (400 MHz, DMSO-D_6) δ 12.86 (s, 1H), 8.02 (d, *J* = 7.98 Hz, 1H), 7.78 (d, *J* = 7.98 Hz, 1H), 7.66 (d, *J* = 7.36 Hz, 1H), 7.46 (m, 2H), 7.36 (m, 2H), 7.23 (t, *J* = 7.98 Hz, 2H), 6.88 (m, 3H), 4.81 (s, 2H), 3.94 (t, *J* = 5.68 Hz, 2H), 3.72 (t, *J* = 5.98 Hz, 2H), 3.09 (t, *J* = 6.75 Hz, 2H), 3.02 (t, *J* = 5.68 Hz, 2H), 1.70 (m, 4H). MS(ESI(+)): m/z 585 (M+H).

2- crystallographic data

Crystallography was performed as previously described for the WEHI-539•BCL-X_L complex.[1] Crystals of compound with BCL-X_L (possessing C-terminal and α1-α2 loop truncations; Δ27-82, ΔC24)[2] were obtained in 9% PEG3350, 0.1 M Sodium Acetate pH 5.0, 4% DMSO and 0.2 M Magnesium Acetate. Crystals were frozen in well solution with increased PEG3350 (11%) and data collected at 100K using an in-house RAXIS-IV++ detector with a micro-max007 X-ray source. Data were processed with HKL2000[3] and the structure solved by molecular replacement with PHASER[4] using BCL-X_L from the WEHI-539•BCL-X_L structure as a search model. Model building was performed in COOT[5] and refinement in REFMAC[6] and PHENIX[7] incorporating simulated annealing. The final model contained four copies of BCL-X_L in the asymmetric unit however only one copy (chain A) had ligand bound. Residues 105 to 111 of Chain B and 24 to 25 of Chain C were not built as the density for these regions was poorly defined and ambiguous.

Table S1. Crystallographic data collection and refinement statistics. Values for the highest resolution shell are shown in parenthesis.

Data Collection	
Space group	P 2_1
Unit cell dimensions	59.86, 81.09, 68.78, β=111.15°
Wavelength (Å)	1.5418
Resolution range (Å)	50.0-2.35 (2.43-2.35)
No. reflections	24901 (2387)
R-merge	0.121 (0.543)
Mean I/sigma(I)	14.16 (2.24)
Completeness (%)	97.2 (93.4)
Redundancy	4.4 (3.1)
Wilson B-factor	42.68
Refinement	
Resolution range (Å)	33.02-2.35 (2.44-2.35)
No. reflections	24874 (2442)
R-work	0.2067 (0.2793)
R-free	0.2587 (0.3516)
No. atoms	4753
macromolecules	4529
ligands	48
water	176
Average B-factor	47.3
macromolecules	47.3
ligands	49.4
solvent	46.7
RMS(bonds)	0.008
RMS(angles)	1.19
Ramachandran favored (%)	99
Ramachandran outliers (%)	0

3- Binding affinity measurements

a- AlphaScreen™ assay

Binding affinity measurements of the compounds included in this paper have been obtained using a bead-based luminescence proximity competition assay (AlphaScreen™). The methods for this assay have been previously described in details. [1,8]

b- Biacore 3000 for selectivity panel (Table 1 and S2)

The selectivity profile of compounds **13**, **14** (Table S2) and **22** (Table 1) were obtained using a Surface Plasmon Resonance competition assay on a Biacore 3000 instrument. The methods for this assay have been previously described in detail. [8]

4- Cell based assay

In vitro cellular activity reported in table 1 were obtained using *mcl-1*$^{-/-}$MEF cells in presence of 1%FBS. The methods for this assay have been previously described in detail. [8]

5- Pharmacokinetic Study in Rat

Studies were performed at Genentech Inc. (South San Francisco CA). Jugular vein cannulated male Spargue-Dawley rats (12 weeks old, ~200g) were purchased from Taconic (Germantown, NY). Animals were acclimatized for 48 h prior to study initiation. Food and water were available ad libitum except for animals that were administered oral (PO) doses, which were fasted overnight prior to dosing of compound. Three rats each were given a single IV (1 mg/kg; in 80% propylethylene glycol 400) or PO (5 mg/kg in 0.5% (w/v) methylcellulose/0.2% (v/v) Tween) dose of compound. Blood samples (approximately 0.2 mL per sample) were drawn from each animal via the jugular vein cannulae at predose and 0.02, 0.08, 0.25, 0.5, 1, 2, 4, 8, 12, and 24 hr post-dose. The samples were collected into tubes containing K_2EDTA as an anticoagulant. In all studies, blood samples were collected into tubes containing K_2EDTA as the anticoagulant. Plasma was isolated and stored at -80° C until analysis. The concentration of compound in each plasma and/or tissue sample was determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis.

References:

(1) Lessene, G.; Czabotar, P. E.; Sleebs, B. E.; Zobel, K.; Lowes, K. N.; Adams, J. M.; Baell, J. B.; Colman, P. M.; Deshayes, K.; Fairbrother, W. J.; et al. Structure-Guided Design of a Selective BCL-XL Inhibitor. Nat Chem Biol 2013.

(2) Kvansakul, M.; Yang, H.; Fairlie, W. D.; Czabotar, P. E.; Fischer, S. F.; Perugini, M. A.; Huang, D. C. S.; Colman, P. M. Vaccinia Virus Anti-Apoptotic F1L Is a Novel Bcl-2-Like Domain-Swapped Dimer That Binds a Highly Selective Subset of BH3-Containing Death Ligands. Cell Death Differ 2008, 15, 1564–1571.

(3) Otwinowski, Z.; Minor, W. Processing of X-Ray Diffraction Data. Methods Enzymol 1997.

(4) McCoy, A. J.; Grosse-Kunstleve, R. W.; Adams, P. D.; Winn, M. D.; Storoni, L. C.; Read, R. J. Phasercrystallographic Software. J Appl Crystallogr 2007, 40, 658–674.

(5) Emsley, P.; Cowtan, K. Coot: Model-Building Tools for Molecular Graphics. Acta Crystallogr. D Biol. Crystallogr. 2004, 60, 2126–2132.

(6) Murshudov, G. N.; Vagin, A. A.; Dodson, E. J. Refinement of Macromolecular Structures by the Maximum-Likelihood Method. Acta Crystallogr. D Biol. Crystallogr. 1997, 53, 240–255.

(7) Adams, P. D.; Afonine, P. V.; Bunkóczi, G.; Chen, V. B.; Davis, I. W.; Echols, N.; Headd, J. J.; Hung, L.-W.; Kapral, G. J.; Grosse-Kunstleve, R. W.; et al. PHENIX: a Comprehensive Python-Based System for Macromolecular Structure Solution. Acta Crystallogr. D Biol. Crystallogr. 2010, 66, 213–221.

(8) Sleebs, B. E.; Kersten, W. J. A.; Kulasegaram, S.; Nikolakopoulos, G.; Hatzis, E.; Moss, R. M.; Parisot, J. P.; Yang, H.; Czabotar, P. E.; Fairlie, W. D.; et al. Discovery of Potent and Selective Benzothiazole Hydrazone Inhibitors of Bcl-X L. J. Med. Chem. 2013, 56, 5514–5540.