Statistical Analysis of Tethering hits. A chemical entity is considered to be preferred when there is a significant enrichment of hits containing that particular entity for a given mutant. Enrichment is defined as the abundance of a given chemical entity in the population of hits relative to its abundance in the entire disulfide library. A hit is defined as a library member that labels the protein by more than 25% (by MS at 2 mM 2-mercaptoethanol).[1] The analysis was done at the $p \leq 0.01$ significance level.

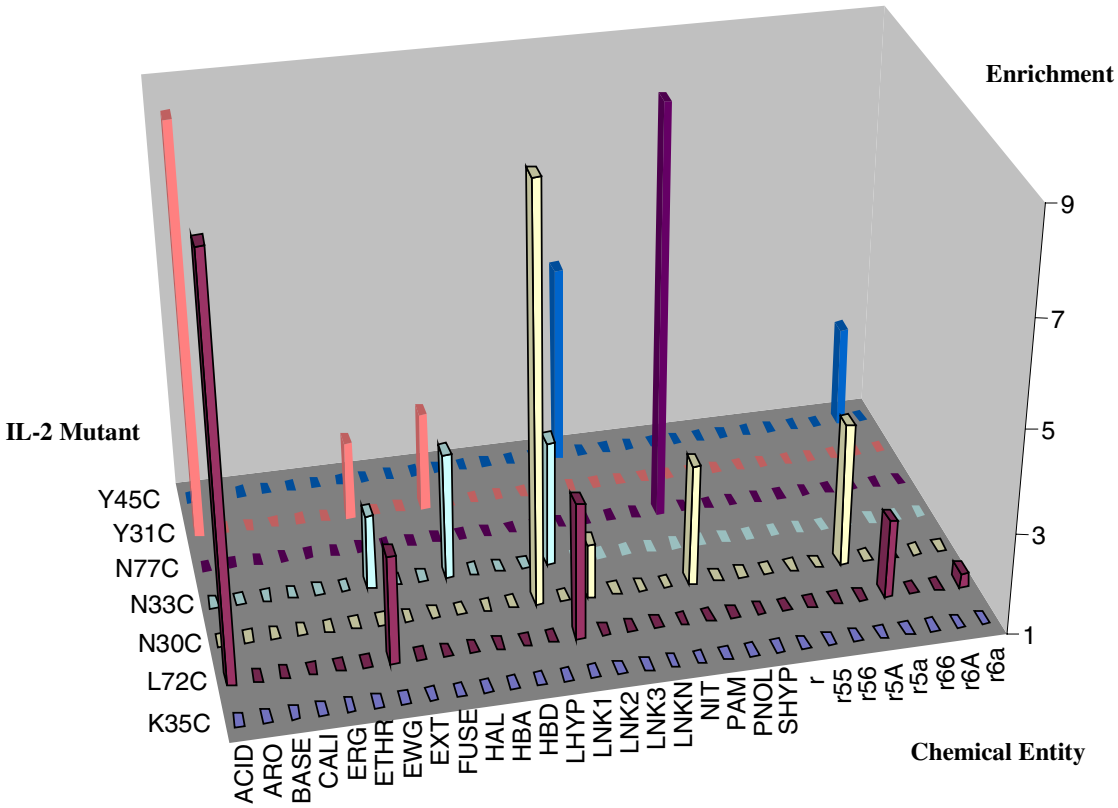


***Chart S1*. Significant enrichments of chemical entities for selected mutants.** ACID: Acidic functionalities (e.g., carboxylic acids, acylsulfonamides, and tetrazoles). ARO: aromatics. BASE: Basic functionalities (e.g., amines). CALI: aliphatic rings. ERG: Electron releasing groups. ETHR: Ethers. EWG: Electron withdrawing groups. EXT: Extended structure (e.g., *n*-butyl or similar). FUSE: Fused ring systems. HAL: halogen containing aromatics. HBA: Hydrogen bond acceptor. HBD: Hydrogen bond donor. LHYP: Large hydrophobics. LNK#: Ring linked by indicated number of bonds. LNKN: rings linked by four or more exocyclic bonds. NIT: Nitro. PAM: Primary amines. PNOL: Aromatic hydroxyl SHYP: Small hydrophobics. r: Any ring. A: Aliphatic ring. a: aromatic ring.

Computational Analysis of Potential Binding Modes of Identified Fragments. Possible binding modes of fragments were initially defined by considering the conformations that could be accessed by the L72C disulfide bond. Analysis of helical cysteine side chains in the Protein Data Bank indicated 3 dominant rotamers at 1 and 2 respectively: (-60, -60), (-180, 60), and (180, -60). The first two rotamers would project the fragment away from the protein surface and were discounted. The third rotamer would place the disulfide bond in the same hydrophobic site as the dichlorophenyl ring of compound **3**, and direct the fragment either towards the the IL-2R binding site or

towards the adaptive region within the 4-helical bundle. Inhibition experiments indicated that the tethered protein adducts retained binding to IL-2R , suggesting that the selected fragments occupied a previously unidentified binding site within the helical bundle. *Monte Carlo* calculations conducted using the ICM program (Molsoft Inc., La Jolla) indicated that minor sidechain rearrangement within the adaptive region could create a hydrophobic cleft for burying the tethered fragments (cf. fig.2), and that the *para* position of the dichlorophenyl ring would present a convenient vector for targeting that cleft.

Binding Analysis

Cloning and expression of IL-2, IL-2 mutants, and IL-2 receptor were performed as described.[1] Screening of the tethering library and characterization by surface plasmon resonance were carried out as reported previously.[1] *Scintillation Proximity Assay (SPA).* The inhibitory constant (IC_{50}) is defined as the ligand concentration at 50% inhibition of the IL-2 – IL-2R complex. The IC_{50} values for all compounds were determined by SPA using twelve 3-fold serial dilutions of compound. Each well of a 12-point titration included compound, 10 nM IL-2 labeled with tritiated propionic acid, and scintillant-containing beads labeled with streptavidin and saturated with biotinylated IL-2R (0.7mg/ml beads; streptavidin beads from Amersham), in a final volume of 100 l Superblock™ with 1% DMSO. Scintillation due to IL-2 bound to IL-2R was read on a Trilux scintillation counter (Applied Biosystems). IC_{50} values were determined from curves of scintillation counts versus compound concentration using a nonlinear regression analysis.

STAT5 Phosphorylation Assay.

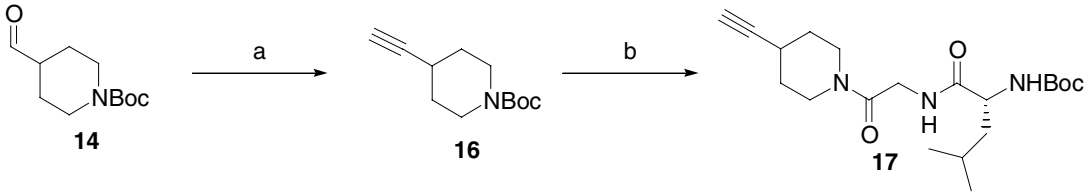
Cell Culture CTLL-2 cells were stimulated with IL-2, which activates a signal-transduction cascade and causes phosphorylation of STAT5. Compound activity was determined by inhibition of this phosphorylation visualized via Western blot analysis. CTLL-2 cells were grown to approximately 1x10^6 cells/ml then grown without IL-2 overnight. Compound dilutions from 100uM final concentration with 2 fold dilutions were then added to the cells in media supplemented with 0.1ng/ml IL-2. The cell/compound mixture was incubated for 30 min at 37 degrees C. The amount of STAT5 phosphorylation was then quantified by western blot, using Anti-phospho STAT 5 (Upstate Biotechnology : 05-495) as a primary antibody and HRP-conjugated Rabbit anti-Mouse antibody (Zymed) as a secondary antibody. Selectivity studies monitored STAT5 phosphorylation in response to IL-15, using the analogous assay.

Syntheses of Compounds

General. Optical rotations were determined with a Jasco model P-1020 polarimeter in 50 mm cells at 25°C. ESI mass spectra were obtained on a HP 1100MSD mass spectrometer. Infrared spectra were recorded on a Jasco FT/IR 460 plus. ^{1}H NMR spectra were recorded on a Bruker 400 MHz spectrometer with chemical shifts reported in units of parts per million (ppm). High resolution mass spectra (HRMS) were determined on an Applied Biosystems Qstar Pulsar-i. Flash column chromatography was

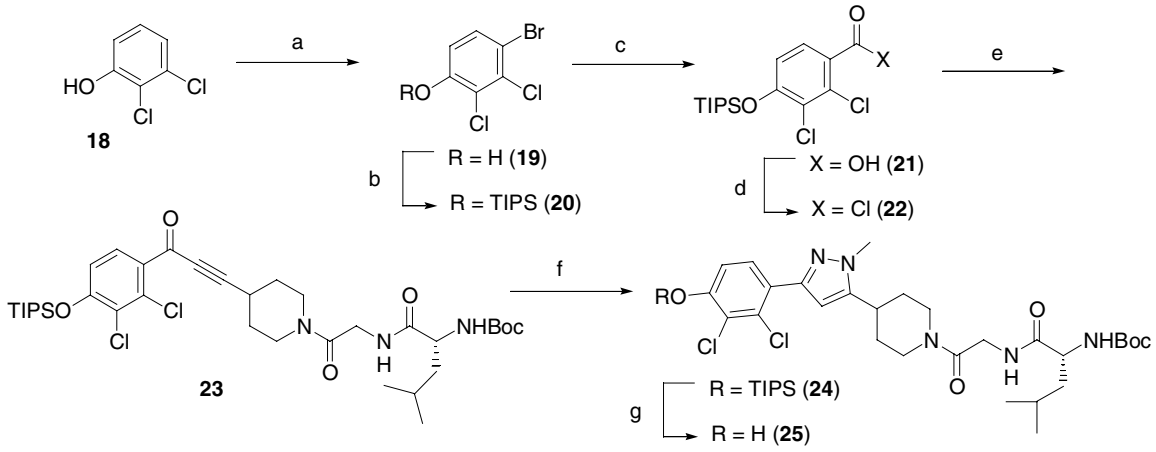
performed using EM Science silica gel 60 (230-400 mesh). Solvents for chromatography are listed as volume/volume ratios. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ. Analytical thin layer chromatograms (TLCs) were run using glass thin layer plates coated with silica gel as supplied by E. Merck and were visualized by viewing under 254 nm UV or by exposure to a potassium permanganate solution in ethanol. Analytical HPLC was conducted on an Agilent 1100 LC/MS system using a C-18 Synergi Hydro-RP 4.6 mm x 150 mm (Phenomenex) at a flow rate of 1.5 mL per minute. The mobile phase consisted of water and acetonitrile each containing 0.1% trifluoroacetic acid by volume. Two methods were employed to assess the purity of compounds. In Method I, the gradient began at 5% acetonitrile and ramped linearly to 100% over 25 minutes. In Method II, the mobile phase was kept isocratic at 35% acetonitrile for 24 minutes, then ramped up to 100% over one minute. UV absorbance was monitered at 220 nm and 254 nm. Preparative reverse phase high pressure liquid chromatography (RP-HPLC) was carried out on a Gilson HPLC fitted with a Waters Nova-Pak C-18 (25 x 100 mm) column eluting at 25 mL/min employing a gradient of acetonitrile:water (each containing 0.1% TFA) from 10% to 100% acetonitrile over 20 min and holding at 100% acetonitrile for 3 min. Solvents and reagents were obtained from Aldrich Chemical Co., Lancaster, Nova Biochem, Fluka, Bionet, or Advanced ChemTech and used as received unless otherwise stated.

Scheme 1



a. **15**, K_2CO_3, MeOH, r.t. (96%).
b. i) HCl/Dioxane.
ii) *N*-Boc-glycine, EDC, HOBt.
iii) HCl/Dioxane.
iv) *N*-Boc-*D*-Leucine, EDC, HOBt (61%).

Scheme 2



a. Br_2, CH_2Cl_2, r.t. (53%).

b. TIPSCl, NEt_3, THF, r.t. (99%).

c. i) *n*-BuLi, THF, -78 °C ii) CO_2 (g), -78 °C iii) H^+ (47%).

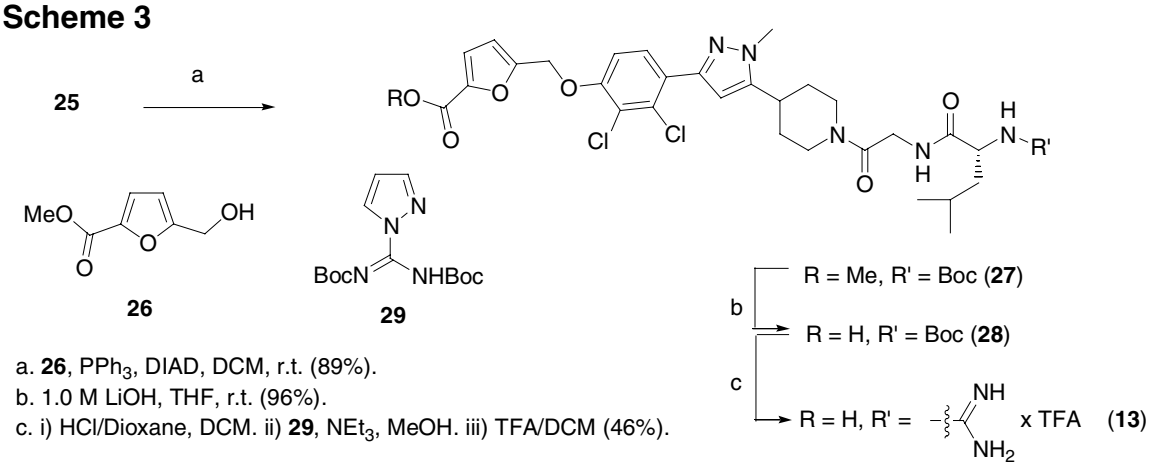
d. $(COCl)_2$, DMF, DCM.

e. cat. $PdCl_2(PPh_3)_2$, cat. CuI, **17**, NEt_3, PhMe, r.t.

f. $MeNHNH_2$, EtOH, r.t. (52% from **21**).

g. TBAF, THF, r.t. (90%).

Scheme 3

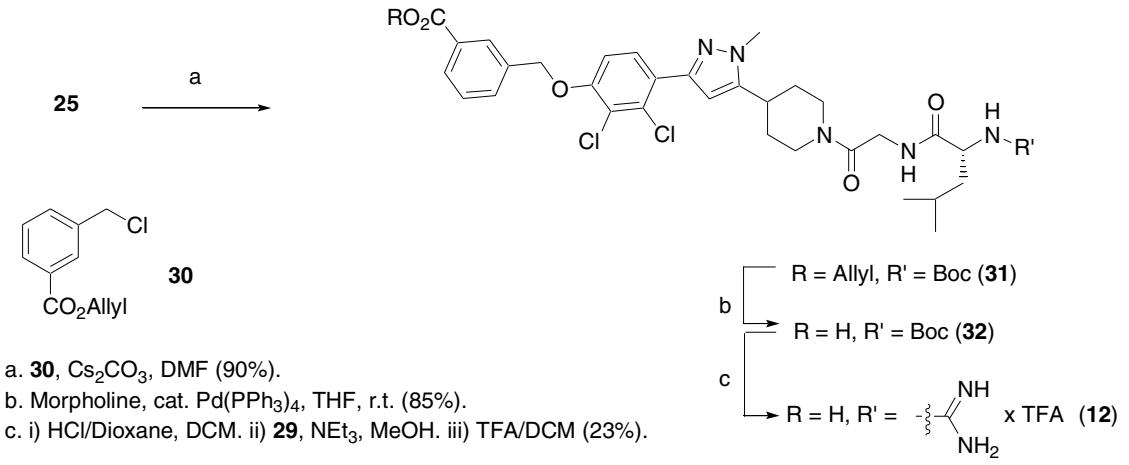


a. **26**, PPh_3, DIAD, DCM, r.t. (89%).

b. 1.0 M LiOH, THF, r.t. (96%).

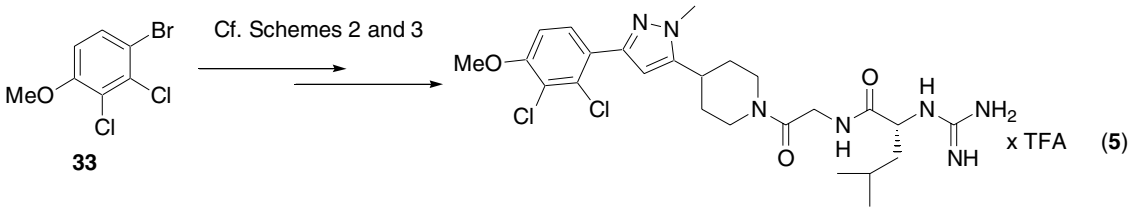
c. i) HCl/Dioxane, DCM. ii) **29**, NEt_3, MeOH. iii) TFA/DCM (46%).

Scheme 4

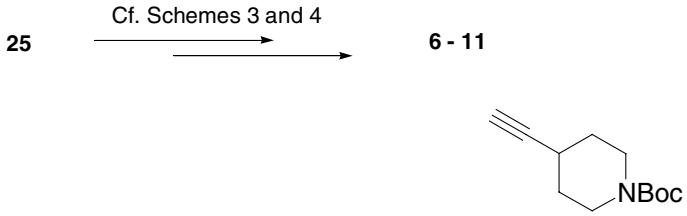


a. **30**, Cs_2CO_3, DMF (90%).
b. Morpholine, cat. $Pd(PPh_3)_4$, THF, r.t. (85%).
c. i) HCl/Dioxane, DCM. ii) **29**, NEt_3, MeOH. iii) TFA/DCM (23%).

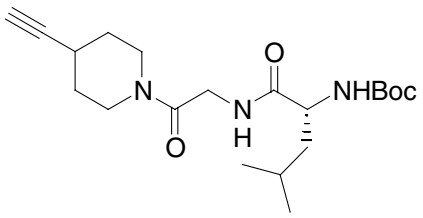
Scheme 5



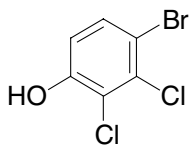
Scheme 6



4-Ethynyl-piperidine-1-carboxylic acid *tert*-butyl ester (16). To a mixture of 4-formyl-piperidine-1-carboxylic acid *tert*-butyl ester[2] (**14**, 23.7 g, 110 mmol) and potassium carbonate (30.7 g, 220 mmol) in MeOH (1.0 L) was added dropwise dimethyl-1-diazo-2-oxopropylphosphonate[3] (**15**, 21.3 g, 110 mmol) in MeOH (100 mL). The resulting mixture was stirred for 3 hours and was then concentrated under reduced pressure. The residue was diluted with diethyl ether (500 mL) and 5% aqueous $NaHCO_3$ (700 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 500 mL). The combined organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to yield 22.4 g (96%) of a solid. IR (thin film): 3253, 2926, 1679, 1424, 1232, 1164 cm^{-1}. ^1H NMR ($CDCl_3$) 3.67 (m, 2 H), 3.20-3.15 (m, 2 H), 2.58 (m, 1 H), 2.09 (s, 1 H), 1.77-1.75 (m, 2 H), 1.60-1.57 (m, 2 H), 1.45 (s, 9 H). ES (+) MS m/e = 154 $(M - t\text{-Bu} + 2H)^+$.

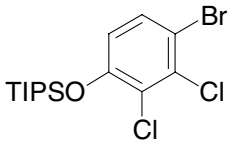


(*R*)-{1-[2-(4-Ethynyl-piperidin-1-yl)-2-oxo-ethylcarbamoyl]-3-methyl-butyl}-carbamic acid *tert*-butyl ester (17). A solution of **16** (6.00 g, 28.7 mmol) in HCl/dioxane (4.0 N, 50 mL) was stirred at room temperature for 30 minutes. Removal of the solvent under reduced pressure afforded 4.20 g (100%) of material. The crude product obtained was added to a solution of *N*-Boc-glycine (5.0 g, 28.7 mmol), EDC (6.60 g, 34.4 mmol), HOBt monohydrate (4.61 g, 34.4 mmol), and triethylamine (9.60 mL, 68.8 mmol) in dichloromethane (120 mL). The resulting mixture was stirred at room temperature overnight followed by the addition of water (100 mL). After separating the phases, the aqueous layer was extracted with dichloromethane (2 100 mL). The combined organic layer was washed with 1 N HCl (100 mL) and saturated $NaHCO_3$ (100 mL) followed by drying over Na_2SO_4. Evaporation of the solvent in vacuo yielded 7.7 g (100%) of a crude product that was taken up in HCl/dioxane (4.0 N, 50 mL). After stirring at room temperature for 30 minutes, the mixture was concentrated and dried under high vacuum to yield 5.80 g (100%) of a solid. The crude hydrochloride salt thus obtained was added to a solution of *N*-Boc-D-leucine (6.60 g, 28.7 mmol), EDC (6.62 g, 34.4 mmol), HOBt monohydrate (4.60 g, 34.4 mmol) and triethylamine (9.60 mL, 68.9 mmol), in dichloromethane (120 mL). After stirring at room temperature for 4 h, the reaction mixture was partitioned with water (100 mL) and separated. The aqueous layer was extracted with dichloromethane (2 100 mL), and the combined organic layer was washed with 1 N HCl (100 mL), saturated $NaHCO_3$ (100 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to provide a crude product that was purified by flash chromatography (25% ethyl acetate in hexanes) to yield 6.60 g (61% for 4 steps) of a white solid. [ ]$_D$ = 12.3° (*c* 0.67, $CHCl_3$). IR (thin film): 3300, 1709, 1638, 1511, 1469, 1251, 1167 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) 7.04 (br s, 1 H), 4.91 (br s, 1 H), 4.20 (br s, 1 H), 4.04 (m, 2 H), 3.80 (m, 1 H), 3.56 (m, 2 H), 3.28 (m, 1 H), 2.73 (br s, 1 H), 2.14 (s, 1 H), 1.80 (m, 2 H), 1.68 (m, 4 H), 1.48 (m, 1 H), 1.44 (s, 9 H), 0.94 (m, 6 H). ES (+) MS m/e = 324 $(M - t\text{-Bu} + 2H)^+$. Anal. Calcd for $C_{20}H_{33}N_3O_4$: C, 63.30; H, 8.76; N, 11.07. Found: C, 62.99; H, 8.98; N, 10.99.

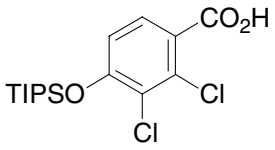


4-Bromo-2,3-dichloro-phenol (19). To a solution of 2,3-dichlorophenol (**18**, 10.0 g, 61.3 mmol) in dichloromethane (50 mL) was added bromine (**CAUTION**.[4] 4.11 mL, 79.8 mmol) dropwise. After 2 h, HPLC indicated complete consumption of the starting material. The reaction mixture was slowly poured into a 10% aqueous sodium thiosulfate

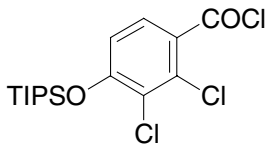
solution. The phases were separated and the aqueous layer was extracted with dichloromethane (3). The combined organic layers were dried (Na_2SO_4) and concentrated. Purification of the crude residue by flash column chromatography (0-20% ethyl acetate in hexane) yielded 7.86 g (53%) of a white solid, R_f 0.29 (20% ethyl acetate in hexane) with spectroscopic data identical to that of commercially available 4-bromo-2,3-dichloro-phenol from ChemService Inc. The regiochemistry of the bromination was also verified by NOE difference spectroscopic analysis of compound **13** (*vide infra*). ^{1}H NMR (400 MHz, $CDCl_3$) 7.44 (d, 1 H, J = 8.9 Hz), 6.86 (d, 1 H, J = 8.9 Hz), 5.72 (s, 1 H).



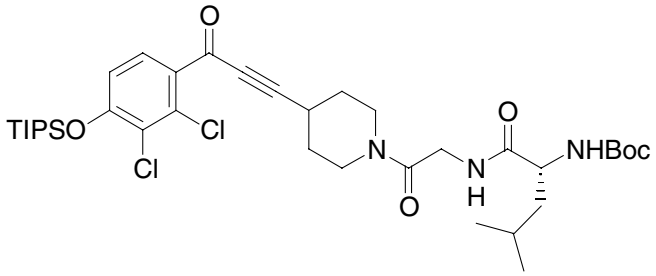
(4-Bromo-2,3-dichloro-phenoxy)-triisopropyl-silane (20). To a solution of **19** (11.7 g, 48.4 mmol) in dry THF (100 mL) was added triethylamine (7.40 mL, 53.2 mmol) followed by triisopropylsilyl chloride (11.4 mL, 53.2 mmol). The reaction was stirred for 1 h at room temperature. Water (250 mL) and ethyl acetate (250 mL) were added followed by separation of the phases. The aqueous layer was washed with ethyl acetate (200 mL). The organic layers were combined, dried ($MgSO_4$), filtered through a short plug of silica gel, concentrated under reduced pressure, and dried under high vacuum at 50°C for 48 h to yield 19.0 g (99%) of a viscous oil. IR (thin film): 2946, 2868, 1569, 1444, 1301, 963, 772 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) 7.36 (d, 1 H, J = 8.9 Hz), 6.72 (d, 1 H, J = 8.9 Hz), 1.32–1.27 (m, 3 H), 1.10 (d, 18 H, J = 7.7 Hz). Anal. calcd for $C_{15}H_{23}BrCl_2OSi$: C, 45.24; H, 5.82. Found: C, 45.30; H, 5.80.



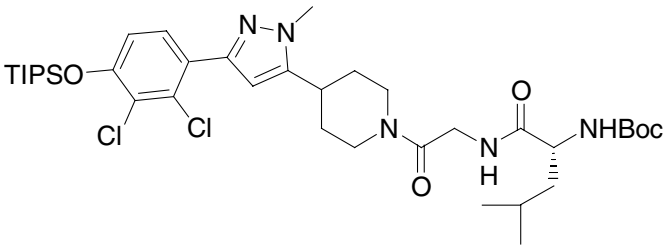
2,3-Dichloro-4-triisopropylsilanyloxy-benzoic acid (21). To a –78°C solution of **20** (15.4 g, 38.7 mmol) in anhydrous THF (385 mL) under nitrogen was added *n*-butyl lithium (1.57M in hexane, 24.6 mL, 38.7 mmol) dropwise. After 10 min at –78 C, carbon dioxide was bubbled through the solution for approximately 10 minutes. The mixture was allowed to reach room temperature and was quenched by careful addition of water (310 mL) followed by aqueous HCl (1.0 N, 38.7 mL, 38.7 mmol). The mixture was extracted with diethyl ether (3) and the combined organic layer was dried ($MgSO_4$) and concentrated. The crude residue was purified by flash column chromatography (0-70% ethyl acetate in hexane) to yield 6.65 g (47%) of a white solid, R_f 0.39 (30% ethyl acetate in hexane). IR (thin film): 3076, 2947, 2869, 2636, 2536, 1693, 1579, 1283, 973 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) 7.88 (d, 1 H, J = 8.8 Hz), 6.89 (d, 1 H, J = 8.8 Hz), 1.32–1.27 (m, 3 H), 1.15 (d, 18 H, J = 7.4 Hz). ES (+) MS m/e = 363 $(M + H)^+$. Anal. calcd for $C_{16}H_{24}Cl_2O_3Si$: C, 52.89; H, 6.66. Found: C, 52.79; H, 6.60.



2,3-Dichloro-4-triisopropylsilanyloxy-benzoyl chloride (22). To a solution of **21** (6.45 g, 17.8 mmol) in anhydrous dichloromethane (120 mL) under nitrogen was added DMF (1.38 mL, 17.8 mmol) followed by dropwise addition of oxalyl chloride (2.01 mL, 23.1 mmol). After 10 min HPLC indicated complete consumption of the starting material and 1,2-dichloroethane was added. The solvent was removed *in vacuo* and the excess oxalyl chloride was removed by co-evaporation with 1,2-dichloroethane (3x). The residue was dried under high vacuum and was then used without further purification.

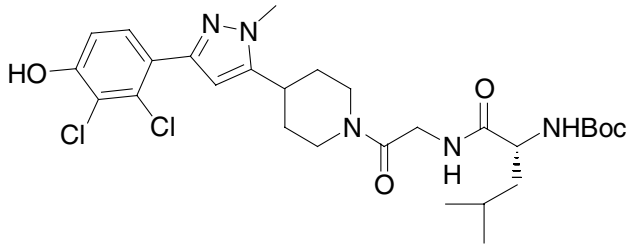


(*R*)-[1-(2-{4-[3-(2,3-Dichloro-4-triisopropylsilanyloxy-phenyl)-3-oxo-prop-1-ynyl]-piperidin-1-yl}-2-oxo-ethylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert*-butyl ester (23). A round bottom flask containing **22** (~17.8 mmol), CuI (0.170 g, 0.890 mmol), $PdCl_2(PPh_3)_2$ (0.630 mg, 0.890 mmol), and **17** (6.75 g, 17.8 mmol) was flushed with nitrogen for several minutes and was then charged with a degassed solution of triethylamine (4.97 mL, 35.6 mmol) in toluene (120 mL). The reaction was monitored by HPLC and the solvent was removed when **22** had been completely consumed. The crude residue was immediately used in the following step. ES (+) MS m/e = 724 $(M + H)^+$.

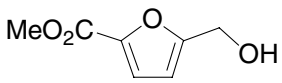


(*R*)-[1-(2-{4-[5-(2,3-Dichloro-4-triisopropylsilanyloxy-phenyl)-2-methyl-2*H*-pyrazol-3-yl]-piperidin-1-yl}-2-oxo-ethylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert*-butyl ester (24). A solution of **23** and methylhydrazine (9.47 mL, 178 mmol) in ethanol (120 mL) was stirred at ambient temperature for 1.5 h. The reaction mixture was concentrated and then re-dissolved in dichloromethane. The organic phase was washed with water and the resulting aqueous layer was extracted with dichloromethane (2). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude residue was

purified by flash column chromatography (50-100% ethyl acetate in hexane) to yield 7.01 g (52% for three steps from **21**) of a single regioisomer (**24**) as a white foam, R_f 0.19 (ethyl acetate). The regiochemistry of the addition was verified by NOE difference spectroscopy analysis performed on compound **13** (*vide infra*). [ ]$_D$ = 4.5° (*c* 0.45, $CHCl_3$).[5] IR (thin film): 3314, 2948, 2868, 1710, 1642, 1426, 737. cm^{-1} ^{1}H NMR (400 MHz, $CDCl_3$) 7.47 (d, 1 H, *J* = 8.6 Hz), 7.09 (br s, 1 H), 6.84 (d, 1 H, *J* = 8.6 Hz), 6.43 (s, 1 H), 4.93 (br s, 1 H), 4.73 (d, 1 H, *J* = 12.1 Hz), 4.28-4.13 (m, 3 H), 3.88 (s, 3 H), 3.85 (m, 1 H), 3.17 (app t, 1 H, *J* = 11.9 Hz), 2.84 (m, 1 H), 2.77 (app t, 1 H, *J* = 12.9 Hz), 2.03 (m, 2 H), 1.66-1.59 (m, 4 H), 1.45 (m, 1 H), 1.43 (s, 9 H), 1.33 (m, 3 H), 1.12 (m, 18 H), 0.93 (m, 6 H). ES (+) MS m/e = 752 (M + H)$^+$. Anal. calcd for $C_{37}H_{59}Cl_2N_5O_5Si$: C, 59.03; H, 7.90; N, 9.30. Found: C, 59.11; H, 7.70; N, 9.12.

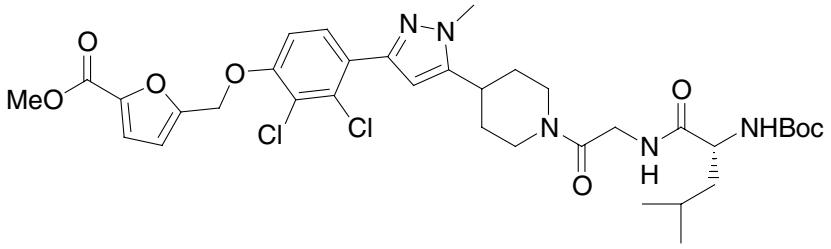


(*R*)-[1-(2-{4-[5-(2,3-Dichloro-4-hydroxy-phenyl)-2-methyl-2*H*-pyrazol-3-yl]-piperidin-1-yl}-2-oxo-ethylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert*-butyl ester (25). To a 0 C solution of **24** (7.00 g, 9.30 mmol) in anhydrous THF (50 mL) was added tetrabutylammonium fluoride (1.0 M in THF, 14 mL, 14 mmol) dropwise. The reaction mixture was stirred for 30 min and then partitioned between water (200 mL) and ethyl acetate (200 mL). The aqueous layer was extracted with ethyl acetate (3 200 mL). The combined organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (0-10% methanol in dichloromethane) to yield 5.00 g (90%) of an off-white solid, R_f 0.10 (5% methanol in dichloromethane). [ ]$_D$ = 9.1° (*c* 0.51, $CHCl_3$). IR (thin film): 3230, 2956, 2863, 1700, 1637, 1168, 736 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD) 7.35 (d, 1 H, *J* = 8.5 Hz), 7.14 (d, 1 H, *J* = 8.8 Hz), 6.40 (s, 1 H), 4.61 (d, 1 H, *J* = 12.8 Hz), 4.16-4.05 (m, 4 H), 3.88 (s, 3 H), 3.25 (m, 1 H), 3.06 (m, 1 H), 2.83 (m, 1 H), 2.01 (m, 2 H), 1.71-1.53 (m, 5 H), 1.44 (s, 9 H), 0.90 (m, 6 H). ES (+) MS m/e = 596 (M + H)$^+$. HRMS (TOF): calcd for $C_{28}H_{40}Cl_2N_5O_5$ (M + H)$^+$, 596.2406; found, 596.2432. Anal. calcd for $C_{28}H_{39}Cl_2N_5O_5$: C, 56.37; H, 6.59; N, 11.74. Found: C, 56.15; H, 6.51; N, 11.56.

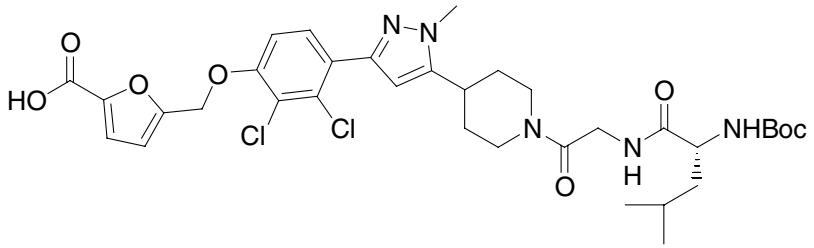


5-Hydroxymethyl-furan-2-carboxylic acid methyl ester (26). To a solution of 5-formyl-2-furancarboxylic acid[6] (0.280 g, 2.00 mmol) in benzene/methanol (5:1, 5.0 mL) at room temperature was added (trimethylsilyl)diazomethane (2.0 M in hexanes, 1.00 mL, 2.00 mmol). The resulting solution was stirred at room temperature for 1 hour and was then concentrated under reduced pressure. The residue was dissolved in methanol (2.0 mL) and treated with sodium borohydride (83.0 mg, 2.20 mmol). After 2 h

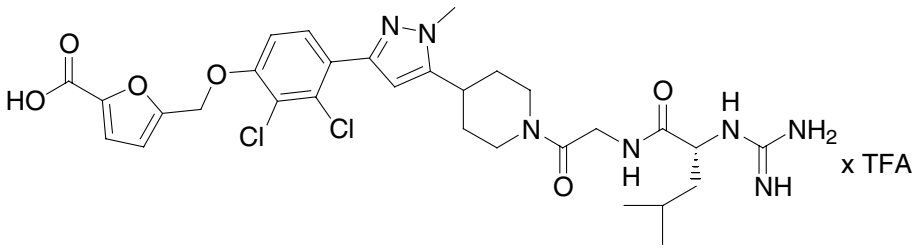
the reaction mixture was partitioned between water (20 mL) and ethyl acetate (20 mL). The aqueous layer was washed with ethyl acetate (2 x 20 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to afford 240 mg (77%) of a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) d, 1 H, J = 3.4 Hz), 6.41 (d, 1 H, J = 3.4 Hz), 4.67 (s, 2 H), 3.89 (s, 3H). ES (+) MS m/e = 157 $(M + H)^+$.



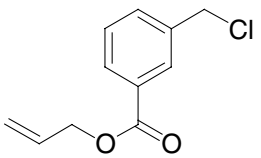
(*R*)-5-[4-(5-{1-[2-(2-*tert*-Butoxycarbonylamino-4-methyl-pentanoylamino)-acetyl]-piperidin-4-yl}-1-methyl-1*H*-pyrazol-3-yl)-2,3-dichloro-phenoxymethyl]-furan-2-carboxylic acid methyl ester (27). To a solution of **25** (740 mg, 1.20 mmol), **26** (240 mg, 1.5 mmol), and triphenylphosphine (440 mg, 1.70 mmol) in CH_2Cl_2 (8.0 mL) at room temperature was added diethyl azodicarboxylate (0.270 mL, 1.70 mmol). The resulting solution was stirred for 16 hours at room temperature and was then partitioned between water and ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated. The crude residue was purified by flash chromatography (ethyl acetate, then 0-5% MeOH in dichloromethane) to yield 814 mg (89%) of a solid. ^{1}H NMR (400 MHz, CD_3OD) 7.51 (d, 1 H, J = 8.7 Hz), 7.23 – 7.21 (m, 2 H), 6.70 (d, 1 H, J = 3.5 Hz), 6.44 (s, 1 H), 5.24 (s, 2 H), 4.55–4.50 (m, 1 H), 4.16–4.05 (m, 4 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 3.29 (m, 1 H), 3.12 (m, 1 H), 2.88 (m, 1 H), 2.02 – 2.01 (m, 2 H), 1.72–1.69 (m, 2 H), 1.60–1.53 (m, 3 H), 1.44 (s, 9 H), 0.96–0.89 (m, 6 H). ES (+) MS m/e = 734 $(M + H)^+$.



(*R*)-5-[4-(5-{1-[2-(2-*tert*-Butoxycarbonylamino-4-methyl-pentanoylamino)-acetyl]-piperidin-4-yl}-1-methyl-1*H*-pyrazol-3-yl)-2,3-dichloro-phenoxymethyl]-furan-2-carboxylic acid (28). To a solution of **27** (814 mg, 1.10 mmol) in THF (30 mL) was added 1.0 M LiOH (1.10 mL, 1.10 mmol). The resulting mixture was stirred at room temperature overnight and was then acidified with 1 N HCl to pH 3-4. The aqueous layer was extracted with ethyl acetate (2 x 50 mL). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to yield 0.764 g (96%) of a colorless oil. ES (+) MS m/e = 720 $(M + H)^+$.

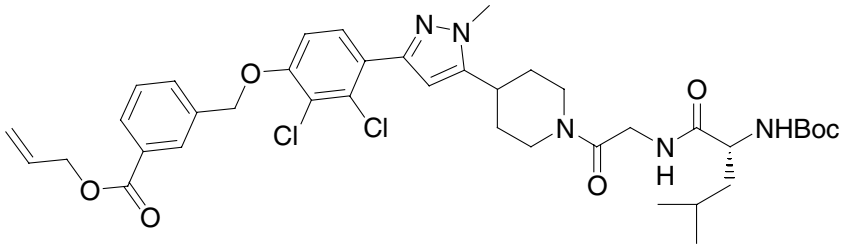


(*R*)-5-[2,3-Dichloro-4-(5-{1-[2-(2-guanidino-4-methyl-pentanoylamino)-acetyl]-piperidin-4-yl}-1-methyl-1*H*-pyrazol-3-yl)-phenoxymethyl]-furan-2-carboxylic acid trifluoroacetate (13). Deprotection-Guanidinylation-Deprotection Sequence. General Procedure A: The crude residue obtained in the previous step (~ 1.10 mmol of **28**) was dissolved in dichloromethane (2.0 mL) and treated with HCl (4.0 N in dioxane, 10.0 mL) at room temperature for 1 h. The mixure was concentrated *in vacuo* and the crude residue was taken up in methanol (6.0 mL). To the resulting solution was added triethylamine (0.460 mL, 3.30 mmol) followed by *N*,*N*′-bis-boc-1-guanylpyrazole (**29**, 510 mg, 1.65 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residue was treated with TFA/dichloromethane (1:4, 14.0 mL) at room temperature. When LC/MS indicated complete deprotection, the mixture was concentrated to yield a crude product that was purified by RP HPLC. The fractions containing pure compound were combined and concentrated. The residue was lyophilized under high-vacuum to yield 400 mg (46%) of the corresponding TFA salt as a white powder. The regiochemical assignment was verified by NOE spectroscopy.[7] [ ]$_D$ = 13.1° (*c* 1.2, MeOH). IR (thin film): 3343, 3175, 2956, 1664, 1426, 1278, 1201,1138, 1015, 800, 721 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d$_6$) 8.10 (s, 1 H), 7.85 (d, 1 H, *J* = 10.6 Hz), 7.66 (d, 1 H, *J* = 8.8 Hz), 7.38 (d, 1 H, *J* = 9.0 Hz), 7.22 (d, 1 H, *J* = 3.6 Hz), 6.81 (d, 1 H, *J* = 3.5 Hz), 6.49 (s, 1 H), 5.32 (s, 2 H), 4.48 (d, 1 H, *J* = 10.8 Hz), 4.25 (br s, 1 H), 4.06 (m, 2 H), 3.86 (m, 1 H), 3.81 (s, 3 H), 3.17 (app t, 1 H, *J* = 14.7 Hz), 3.09 (app t, 1 H, *J* = 11.4 Hz), 2.75 (app t, 1 H, *J* = 12.4 Hz), 1.94 (d, 2 H, *J* = 10.8 Hz), 1.58-1.41 (m, 4 H), 1.37 (m, 1 H), 0.90 (m, 6 H). ^{1}H NMR (400 MHz, CD$_3$OD)[8] 7.55 (d, 1 H, *J* = 8.7 Hz, H-5), 7.26 (d, 1 H, *J* = 8.8 Hz, H-4), 7.21 (d, 1 H, *J* = 3.4 Hz, H-1), 6.71 (d, 1 H, *J* = 3.5 Hz, H-2), 6.46 (s, 1 H, H-6), 5.26 (s, 2 H, H-3), 4.79 (d, 1 H, *J* = 13.2 Hz, H-9ax`), 4.34-4.02 (m, 4 H, H-9ax``, COC*H*$_2$NHCO, and H-10), 3.92 (s, 3 H, NC*H*$_3$), 3.29 (m, 1 H, H-9eq`), 3.12 (m, 1 H, H-7), 2.88 (m, 1 H, H-9eq``), 2.06 (app t, 2 H, *J* = 11.2 Hz, H-8eq), 1.75-1.60 (m, 5 H, 2 H-8ax, (Me)$_2$C*H*C*H*$_2$), 1.01 (m, 6 H, CH(C*H*$_3$)$_2$). ES (+) MS m/e = 662 (M + H)$^+$. Anal. calcd for $C_{30}H_{37}Cl_2N_7O_6 \cdot CF_3CO_2H$: C, 49.49; H, 4.93; N, 12.63. Found: C, 49.64; H, 4.99; N, 12.78.

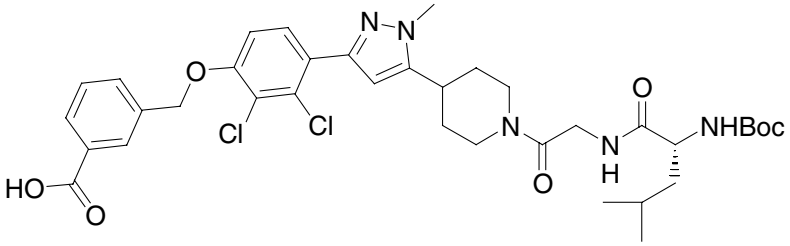


3-Chloromethyl-benzoic acid allyl ester (30). To a mixture of 3-(chloromethyl)benzoic acid (1.00 g, 5.85 mmol), EDC (1.80 g, 9.40 mmol), and DMAP (75.0 mg, 0.61 mmol) in dichloromethane (20 mL) was added allyl alcohol (600 L, 8.82

mmol). After 2 h at ambient temperature LC/MS indicated complete conversion. The solution was concentrated and taken up in ethyl acetate. The mixture was washed with aqueous 1N HCl (3x), aqueous sat. $NaHCO_3$ (1x), and brine (1x). The organic phase was dried ($MgSO_4$) and concentrated to yield 796 mg (64%) of a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) 8.06 (s, 1 H), 8.00 (d, 1 H, J = 7.8 Hz), 7.57 (d, 1 H, J = 7.6 Hz), 7.43 (app t, 1 H, J = 7.7 Hz), 6.03 (m, 1 H), 5.40 (d, 1 H, J = 17.2 Hz), 5.28 (d, 1 H, J = 10.4 Hz), 4.81 (dd, 2 H, J_1 = 5.6 Hz, J_2 = 0.8 Hz), 4.60 (s, 2 H). ES (+) MS m/e = 211 $(M + H)^+$.

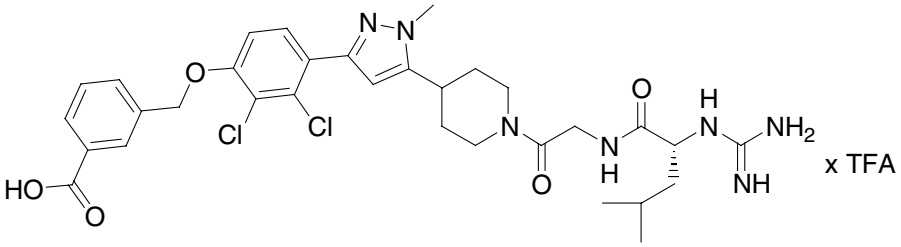


(*R*)-3-[4-(5-{1-[2-(2-*tert*-Butoxycarbonylamino-4-methyl-pentanoylamino)-acetyl]-piperidin-4-yl}-1-methyl-1*H*-pyrazol-3-yl)-2,3-dichloro-phenoxymethyl]-benzoic acid allyl ester (31). General Procedure B: A mixture of **25** (700 mg, 1.17 mmol), **30** (247 mg, 1.17 mmol), and Cs_2CO_3 (762 mg, 2.34 mmol) in DMF (7.0 mL) was stirred at 70 C for 3 h. After cooling to ambient temperature the mixture was diluted with water and extracted with dichloromethane (3x). The combined organic phases were washed with brine, dried ($MgSO_4$), and concentrated. The crude residue was purified by flash column chromatography (0-5% methanol in dichloromethane) to yield 807 mg (90%) of a white foam, R_f 0.25 (5% methanol in dichloromethane). ^{1}H NMR (400 MHz, $CDCl_3$) 8.10 (s, 1 H), 7.99 (d, 1 H, J = 7.7 Hz), 7.65 (d, 1 H, J = 7.5 Hz), 7.53 (d, 1 H, J = 8.7 Hz), 7.43 (app t, 1 H, J = 7.7 Hz), 7.14 (br s, 1 H), 6.88 (d, 1 H, J = 8.8 Hz), 6.39 (s, 1 H), 6.00 (m, 1 H), 5.37 (dd, 1 H, J_1 = 17.2 Hz, J_2 = 1.3 Hz), 5.25 (d, 1 H, J = 10.4 Hz), 5.17 (s, 2 H), 5.10 (br s, 1 H), 4.78 (m, 2 H), 4.66 (d, 1 H, J = 12.0 Hz), 4.18 (m, 1 H), 4.06 (m, 2 H), 3.90 (m, 1 H), 3.83 (s, 3 H), 3.13 (app t, 1 H, J = 12.0 Hz), 2.86 (m, 1 H), 2.73 (app t, 1 H, J = 12.9 Hz), 1.99 (app t, 2 H, J = 9.9 Hz), 1.63-1.50 (m, 4 H), 1.46 (m, 1 H), 1.40 (s, 9 H), 0.90 (m, 6 H). ES (+) MS m/e = 770 $(M + H)^+$.

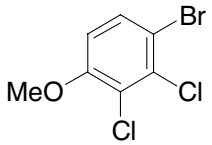


(*R*)-3-[4-(5-{1-[2-(2-*tert*-Butoxycarbonylamino-4-methyl-pentanoylamino)-acetyl]-piperidin-4-yl}-1-methyl-1*H*-pyrazol-3-yl)-2,3-dichloro-phenoxymethyl]-benzoic acid (32). To a solution of **31** (719 mg, 0.933 mmol) and $Pd(PPh_3)_4$ (54.0 mg, 0.0466 mmol) in THF (4.0 mL) under nitrogen was added morpholine (407 L, 4.66

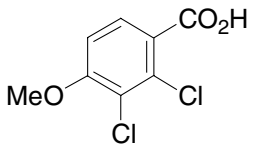
mmol). The resulting mixture was stirred at ambient temperature for 1 h. The solvent was then removed *in vacuo* and the crude residue was purified by flash column chromatography (0.5% AcOH and 0-5% methanol in dichloromethane) to yield 577 mg (85%) of a tan solid, R_f 0.18 (0.5% AcOH and 5% methanol in dichloromethane). [ ]$_D$ = 10.2° (*c* 0.65, $CHCl_3$).[9] IR (thin film): 3300, 2955, 1710, 1641, 1494, 1426, 1367, 1275, 1167, 1010, 749 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) 9.31 (br s, 1 H), 8.13 (s, 1 H), 8.02 (d, 1 H, *J* = 7.7 Hz), 7.66 (d, 1 H, *J* = 7.6 Hz), 7.54 (d, 1 H, *J* = 8.7 Hz), 7.44 (app t, 1 H, *J* = 7.6 Hz), 7.13 (d, 1 H, *J* = 7.1 Hz), 6.89 (d, 1 H, *J* = 8.9 Hz), 6.39 (s, 1 H), 5.32 (br s, 1 H), 5.16 (s, 2 H), 4.70 (d, 1 H, *J* = 12.1 Hz), 4.28-4.13 (m, 3 H), 3.88 (m, 1 H), 3.85 (s, 3 H), 3.15 (app t, 1 H, *J* = 12.1 Hz), 2.84 (m, 1 H), 2.78 (app t, 1 H, *J* = 12.9 Hz), 1.99 (m, 2 H), 1.66-1.41 (m, 5 H), 1.40 (s, 9 H), 0.91 (m, 6 H). ES (+) MS m/e = 730 (M + H)$^+$. Anal. calcd for $C_{36}H_{45}Cl_2N_5O_7$: C, 59.18; H, 6.21; N, 9.58. Found: C, 58.97; H, 6.27; N, 9.44.



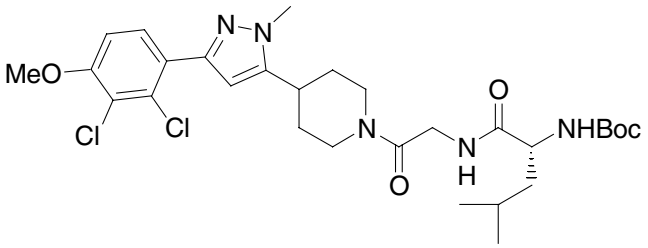
(*R*)-3-[2,3-Dichloro-4-(5-{1-[2-(2-guanidino-4-methyl-pentanoylamino)-acetyl]-piperidin-4-yl}-1-methyl-1*H*-pyrazol-3-yl)-phenoxymethyl]-benzoic acid trifluoracetate (12). The title compound was prepared according to General Procedure A using **32** (120 mg, 0.164). White powder, 30.2 mg (23% from **32**). [ ]$_D$ = 10.2° (*c* 0.27, MeOH). IR (thin film): 3330, 3200, 2955, 1668, 1426, 1274, 1201, 1137, 1024, 800, 751 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD) 8.15 (s, 1 H), 7.99 (d, 1 H, *J* = 7.7 Hz), 7.72 (d, 1 H, *J* = 7.6 Hz), 7.52-7.47 (m, 2 H), 7.15 (d, 1 H, *J* = 8.8 Hz), 6.41 (s, 1 H), 5.28 (s, 2 H), 4.62 (d, 1 H, *J* = 13.0 Hz), 4.30-4.01 (m, 4 H), 3.88 (s, 3 H), 3.27 (m, 1 H), 3.07 (m, 1 H), 2.84 (m, 1 H), 1.99 (app t, 2 H, *J* = 14.2 Hz), 1.76-1.68 (m, 4 H), 1.51 (m, 1 H), 0.98 (m, 6 H). ES (+) MS m/e = 672 (M + H)$^+$. Anal. calcd for $C_{32}H_{39}Cl_2N_7O_5 \cdot CF_3CO_2H$: C, 51.91; H, 5.31; N, 12.46. Found: C, 51.82; H, 5.32; N, 12.34.



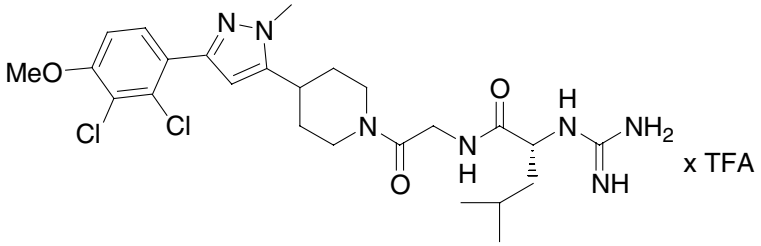
2,3-Dichloro-4-bromoanisole (33). The title compound was prepared according to General Procedure B using **19** (637 mg, 2.63 mmol), methyliodide (0.660 mL, 10.5 mmol), and Cs_2CO_3 (1.72 g, 5.26 mmol) in DMF (8.0 mL). White fluffy solid (520 mg, 77%), R_f 0.35 (5% ethyl acetate in hexane). IR (thin film): 2925, 2863, 1570, 1460, 1430, 1281, 1258, 1038, 796, 640 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) *J* = 9.0 Hz), 6.75 *J* = 9.0 Hz), 3.90 (s, 3 H).



2,3-Dichloro-4-methoxy-benzoic acid (34). Following the procedure described for the synthesis of **21** but using **33** (400 mg, 1.56 mmoL) in place of **20**, the title compound was prepared as a white powder (280 mg, 81%), R_f 0.21 (2% AcOH and 50% ethyl acetate in hexane). ^{1}H NMR (400 MHz, $CDCl_3$) 8.00 (d, 1 H, J = 8.9 Hz), 6.92 d, 1 H, J = 8.9 Hz), 3.99 (s, 3 H).

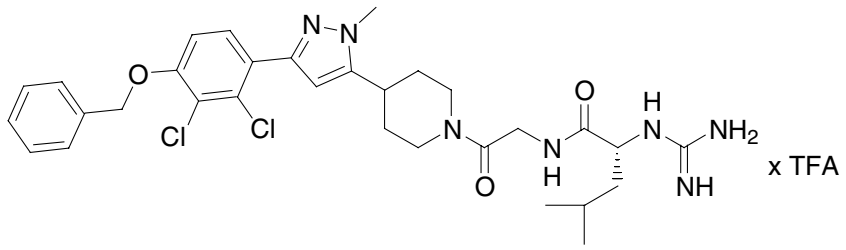


(*R*)-[1-(2-{4-[5-(2,3-Dichloro-4-methoxy-phenyl)-2-methyl-2*H*-pyrazol-3-yl]-piperidin-1-yl}-2-oxo-ethylcarbamoyl)-3-methyl-butyl]-carbamic acid *tert*-butyl ester (35).[10] Following the procedures described for the synthesis of **24** but using **34** (140 mg, 1.56 mmol) in place of **21**, the title compound was prepared as a tan solid, R_f 0.13 (5% MeOH in dichloromethane). [ ]$_D$ = 18.1° (c 1.02, MeOH). IR (thin film): 3312, 2954, 1709,1641, 1468, 1420, 1281, 1166, 736 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD) 7.52 (d, 1 H, J = 8.7 Hz), 7.11 (d, 1 H, J = 8.8 Hz), 6.45 (s, 1 H), 4.64 (d, 1 H, J = 12.9 Hz), 4.18-3.99 (m, 4 H), 3.95 (s, 3 H), 3.91 (s, 3 H), 3.28 (app t, 1 H, J = 12.8 Hz), 3.10 (m, 1 H), 2.85 (app t, 1 H, J = 11.8 Hz), 2.04 (m, 2 H), 1.73 (m, 2 H), 1.59 (m, 3 H), 1.46 (s, 9 H), 0.98 (d, 3 H, J = 7.0 Hz), 0.96 (d, 3 H, J = 7.1 Hz). ES (+) MS m/e = 610 (M + H)$^+$. HRMS (TOF): calcd for $C_{24}H_{34}Cl_2N_5O_3$ (M – Boc + 2H)$^+$, 510.2039; found, 510.2103.

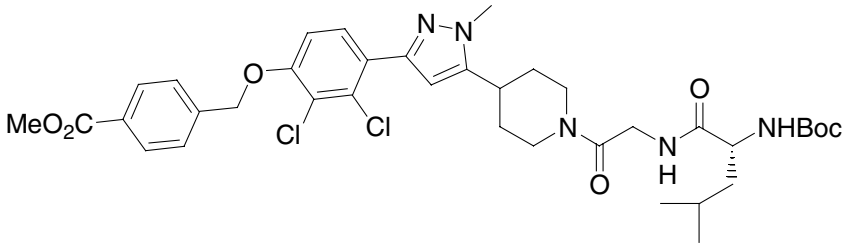


(*R*)-2-Guanidino-4-methyl-pentanoic acid (2-{4-[5-(2,3-dichloro-4-methoxy-phenyl)-2-methyl-2*H*-pyrazol-3-yl]-piperidin-1-yl}-2-oxo-ethyl)-amide trifluoroacetate (5). The title compound was prepared according to General Procedure A using **35**. White powder, 13.6 mg (3.2% overall for 6 steps from **34**). [ ]$_D$ = 19.8° (c = 0.13, MeOH). IR (thin film): 3346, 3163, 1665, 1420, 1201, 1135, 801, 721 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD) 7.51 (d, 1 H, J = 8.7 Hz), 7.09 (d, J = 8.8 Hz), 6.42 (s, 1 H), 4.61 (d, 1 H, J = 12.9 Hz), 4.30-3.97 (m, 4 H), 3.93 (s, 3 H), 3.89 (s, 3 H), 3.30 (m, 1 H),

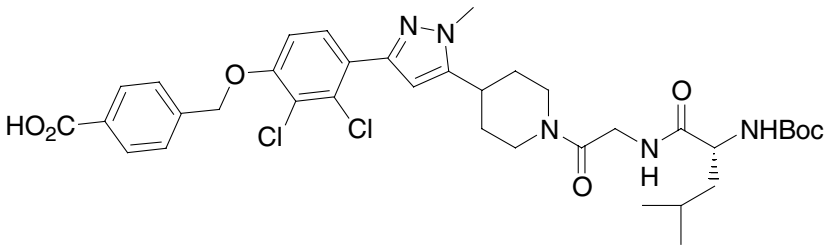
3.07 (m, 1 H), 2.84 (m, 1 H), 2.03 (app t, 2 H, J = 13.9 Hz), 1.76-1.68 (m 4 H), 1.51 (m,1 H), 0.99 (m, 6 H). ES (+) MS m/e = 552 $(M + H)^+$. Anal. calcd for $C_{25}H_{35}Cl_2N_7O_3 \cdot 1.5CF_3CO_2H$: C, 46.48; H, 5.08; N, 13.55. Found: C, 46.43; H, 4.95; N, 13.70.



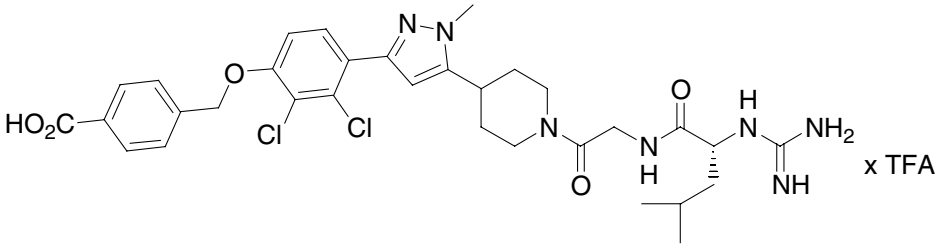
(*R*)-2-Guanidino-4-methyl-pentanoic acid (2-{4-[5-(4-benzyloxy-2,3-dichloro-phenyl)-2-methyl-2*H*-pyrazol-3-yl]-piperidin-1-yl}-2-oxo-ethyl)-amide trifluoroacetate (6). The title compound was prepared according to General Procedures B and A using benzylbromide in place of **30**. White powder, 4.0 mg (4.5% for 4 steps from **25**). [ ]$_D$ = 59.0° (c 0.02, MeOH). IR (thin film): 3328, 3138, 1670, 1426, 1202, 680, 640.cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD) 7.69-7.33 (m, 6 H), 7.17 (d, 1 H, J = 8.8 Hz), 6.45 (s, 1 H), 5.36 (s, 2 H), 4.66 (d, 1 H, J = 13.2 Hz), 4.33-4.00 (m, 4H), 3.91 (s, 3 H), 3.28 (m, 1 H), 3.12 (m, 1 H), 2.87 (m, 1 H), 2.06 (m, 2 H), 1.75-1.55 (m, 5 H), 1.03-0.99 (m, 6 H). ES (+) MS m/e = 628 $(M + H)^+$. Anal. calcd for $C_{31}H_{39}Cl_2N_7O_3 \cdot 2CF_3CO_2H$: C, 49.07; H, 4.82; N, 11.45. Found: C, 48.71; H, 4.88; N, 11.51.



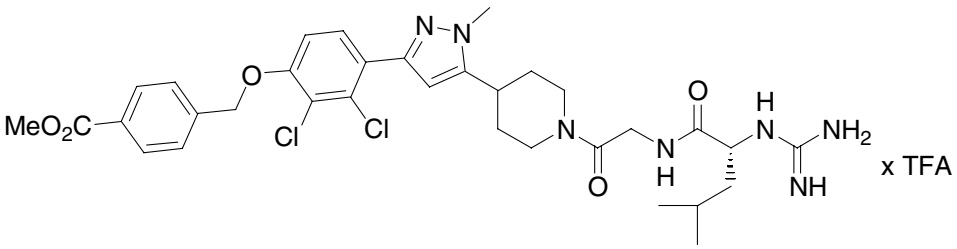
(*R*)-4-[4-(5-{1-[2-(2-tert-Butoxycarbonylamino-4-methyl-pentanoylamino)-acetyl]-piperidin-4-yl}-1-methyl-1H-pyrazol-3-yl)-2,3-dichloro-phenoxymethyl]-benzoic acid methyl ester (36). The title compound was prepared according to General Procedure B using **25** (75 mg, 0.120 mmol) and 4-bromomethyl-benzoic acid methyl ester (43 mg, 0.190 mmol), and K_2CO_3 (35 mg, 0.250 mmol) in DMF (0.5 mL). The crude product was used without further purification. Yield 76 mg, 85%. ES (+) MS m/e = 744 $(M + H)^+$.



(*R*)-4-[4-(5-{1-[2-(2-*tert*-Butoxycarbonylamino-4-methyl-pentanoylamino)-acetyl]-piperidin-4-yl}-1-methyl-1*H*-pyrazol-3-yl)-2,3-dichloro-phenoxymethyl]-benzoic acid (37). The title compound (**37**) was obtained by hydrolysis of **36** (75 mg, 0.12 mmol) using a procedure similar to that used for the preparation of compound **28**. The crude product was purified by RP HPLC to afford 36 mg (39%) of a film. ES (+) MS m/e = 730 $(M + H)^+$.



(*R*)-4-[2,3-Dichloro-4-(5-{1-[2-(2-guanidino-4-methyl-pentanoylamino)-acetyl]-piperidin-4-yl}-1-methyl-1*H*-pyrazol-3-yl)-phenoxymethyl]-benzoic acid trifluoroacetate (7). The title compound was prepared according to General Procedure A using **37** (36 mg, 0.05 mmol). White powder, 4.0 mg (12% overall for 3 steps from **37**). $[\ ]_D$ = 13.3° (*c* 0.47, MeOH). IR (thin film): 3343, 3175, 1674, 1430, 1203, 1137, 802, 668 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) 8.07 (d, 2 H, *J* = 8.2 Hz), 7.62 (d, 2 H, *J* = 8.1 Hz), 7.51 (d, 1 H, *J* = 8.7 Hz), 7.18 (d, 1 H, *J* = 8.9 Hz), 6.46 (s, 1 H), 5.35 (s, 2 H), 4.65 (m, 1 H), 4.21–4.00 (m, 4 H), 3.92 (s, 3 H), 3.30 (m, 1 H), 3.15 (m, 1 H), 2.88 (m, 1 H), 2.07 (m, 2 H), 1.75–1.55 (m, 5 H), 1.03–0.99 (m, 6 H). HRMS (TOF): calcd for $C_{32}H_{40}Cl_2N_7O_5$ $(M + H)^+$, 672.2468; found, 672.2441. HPLC: Purity ≥ 98%.



(*R*)-4-[2,3-Dichloro-4-(5-{1-[2-(2-guanidino-4-methyl-pentanoylamino)-acetyl]-piperidin-4-yl}-1-methyl-1*H*-pyrazol-3-yl)-phenoxymethyl]-benzoic acid methyl ester trifluoroacetate (8). The title compound was prepared according to General Procedure A using **36** (76 mg, 0.10 mmol). White powder, 4.0 mg (4.9% overall from **36**). $[\ ]_D$ = 34.4° (*c* 0.15, MeOH). IR (thin film): 3345, 3163, 1674, 1437, 1283, 1205, 1137, 802, 724 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) 8.07 (d, 2 H, *J* = 8.3 Hz),

7.63 (d, 2 H, *J* = 8.3 Hz), 7.51 (d, 1 H, *J* = 8.7 Hz), 7.17 (d, 1 H, *J* = 8.8 Hz), 6.46 (s, 1 H), 5.34 (s, 2 H), 4.65 (d, 1 H, *J* = 13.2 Hz), 4.29–4.02 (m, 4 H), 3.93 (s, 3 H), 3.91 (s, 3H), 3.30 (m, 1 H), 3.30 - 3.10 (m, 2 H), 2.88 (m, 1 H), 2.06 (m, 1 H) 1.78-1.71 (m 4 H), 1.50 (m, 1 H), 1.01 (m, 6 H). HRMS (TOF): calcd for $C_{33}H_{42}Cl_2N_7O_5$ $(M+H)^+$, 686.2624; found, 686.2614. HPLC: Purity ≥ 98%.

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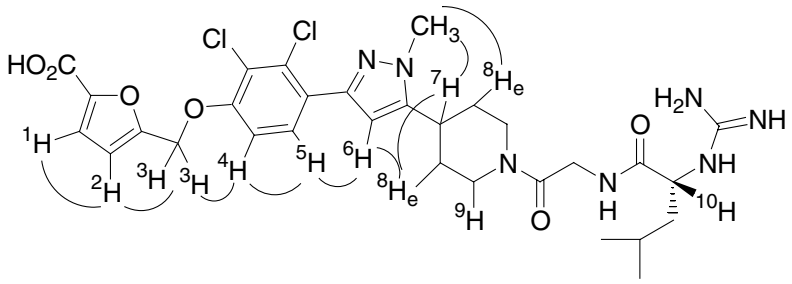
1) Arkin, M. R.; Randal, M; Delano, W. L.; Hyde, J.; Luong, T. N.; Oslob, J. D.; Raphael, D. R.; Taylor, L., Wang, J.; McDowell, R. S.; Wells, J. A.; Braisted, A. C. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *in press*.
2) Klein, S. I.; Moino, B. F.; Czekaj, M.; Gardner, C. J.; Chu, V.; Brown, K.; Sabatino, R. D.; Bostwick, J. S.; Kasiewski, C.; Bentley, R.; Windisch, V.; Perrone, M.; Dunwiddie, C. T.; Leadley, R. J. *J. Med. Chem.* **1998**, *41*, 2492-2502.
3) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521-522.

4) **CAUTION**: Like all other experimental operations described in this manuscript, this reaction should be performed in a well ventilated fume hood in order to avoid exposure to bromine (highly toxic) and the HBr formed.
5) Re-subjecting the purified compound to the reaction conditions for 2 h followed by isolation of the product had no effect on the optical rotation, indicating that little or no racemization takes place under these conditions.
6) Commercially available from TCI America.
7) The positions of the *N*-methyl substituent and of the *O*-benzyl moiety were confirmed by NOE difference spectroscopy and NOESY (400 MHz, CD_3OD). Selected enhancements:



No NOEs between the dichlorophenol moiety and the pyrazol *N*-Me substituent were observed. Enhancements between the pyrazol/piperidine fragment and the furan portion were also absent.
8) See reference 7 for the numbering of protons.
9) Re-subjecting the purified compound to the reaction conditions for 1 h followed by isolation of the product had no effect on the optical rotation. Furthermore, subjecting **32** to the conditions used to hydrolyze ester **27** to acid **28** for 12 h did not diminish the value of [ ], suggesting that little or no racemization of these compounds takes place under these conditions.
10) The title compound could also be prepared according to General Procedure B using **25** (150 mg, 0.251 mmol), methyliodide (31 L, 0.503 mmol), and Cs_2CO_3 (123 mg, 0.377 mmol) in DMF (1.0 mL) at 50 C for 15 min. Work-up and purification yielded

a white solid (149 mg, 97%) with spectroscopic and optical properties identical to those of **35**. This verifies the position of the *N*-methyl substituent on the pyrazole moiety of this derivative.