Supporting Information

Design of Potent and Orally Active GPR119 Agonists for the Treatment of Type II Diabetes

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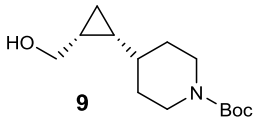
General Information. All reagents were purchased from Aldrich and used without further purification unless otherwise stated. Column chromatography was carried out on flash silica gel (Merck 230-400 mesh). TLC analysis was conducted on ANALTECH silica gel plates. The LC/MS analyses were performed using a MICROMASS ZMD mass spectrometer coupled to an AGILENT 1100 Series HPLC utilizing a YMC ODS-A 4.6 x 50 mm column eluting at 4.5 mL/min with a solvent gradient of 10 to 95% B over 2.5 min, followed by 0.5 min at 95% B: solvent A = 0.06% TFA in water; solvent B = 0.05% TFA in acetonitrile. ^{1}H-NMR spectra were obtained on a 500 MHz VARIAN Spectrometer in $CDCl_3$ or CD_3OD as indicated and chemical shifts are reported as δ using the solvent peak as reference and coupling constants are reported in hertz (Hz). All the assayed compounds described in this manuscript were at least 95% pure as judged by LC/MS and NMR.

For selectivity counter-screen, 168 radioligand binding or enzymatic assays were carried at MDS Pharma Services (Current name: Eurofins Panlab Taiwan, Ltd.) as a contract service to Merck. A summary of each assay protocol and the reference for each assay are listed in the Eurofins Panlab Taiwan catalog.

Synthesis of *tert*-Butyl 4-[(1*R*,2*R*)-2-(hydroxymethyl)cyclopropyl]piperdine-1-carboxylate (9)



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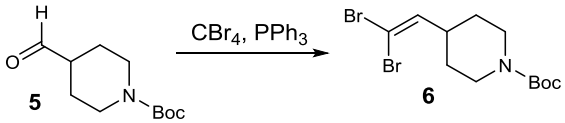
Step 1: *tert*-butyl 4-(2,2-dibromovinyl)piperidine-1-carboxylate (**6**)

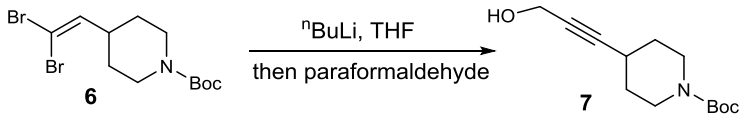


5 **6**

Carbon tetrabromide (2.332 g, 7.03 mmol) was dissolved in CH_2Cl_2 (30.2 ml, 469 mmol) and the solution was cooled in a 0°C bath. Triphenylphosphine (3.69 g, 14.07 mmol) was added, giving an orange colored solution as it dissolved. After 25 min *tert*-butyl 4-formylpiperidine-1-carboxylate (compound **5**, 1 g, 4.69 mmol) was added in one portion to the 0°C solution. After 50 min, the solution was concentrated to about 1/3 the original volume, causing a precipitate. Cyclopentylmethyl ether was then added slowly, causing more precipitation. The suspension was filtered, rinsing with CPME. More precipitate appeared in the filtrate, so it was filtered again. The filtrate was partitioned with water. The aqueous layer was removed. The organic layer was washed with dilute aqueous sodium bisulfite followed by water. The final organic layer was concentrated to a mixture of solid and oil. The residue was triturated with 40% ethyl acetate/hexanes and filtered through a pad of silica. The filtrate was concentrated to yield the dibromoalkene (**6**) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.23 (d, *J*

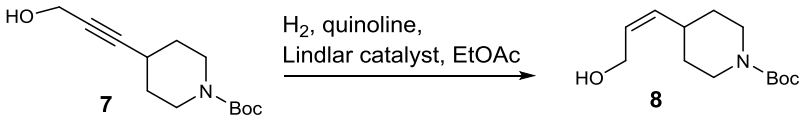
8.9 Hz, 1H), 4.15-3.98 (m, 2H), 2.83-2.72 (m, 2H), 2.48-2.40 (m, 1H), 1.75-1.67 (m, 2H), 1.45 (s, 9H), 1.37-1.26 (m, 2H).

Step 2: *tert*-butyl 4-(3-hydroxyprop-1-yn-1-yl)piperidine-1-carboxylate (**7**)



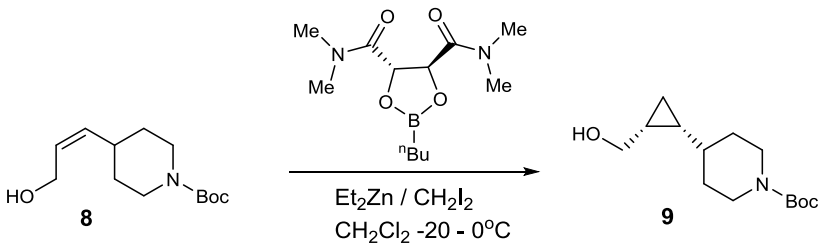
Product from step 1 (compound **6**, 0.5 g, 1.355 mmol) was dissolved in dry THF (4.99 ml, 61.0 mmol) under nitrogen. The solution was cooled in a bath at -45°C and to it was added *n*-BuLi (1.6 M in hexanes, 1.736 ml, 2.78 mmol) over ca. 2 min. The solution was stirred at -45°C to -38°C for 45 min, then paraformaldehyde (0.122 g, 4.06 mmol) was added. The suspension was allowed to warm slowly to room temp. After stirring at room temp overnight, the reaction was quenched with aqueous 10% NH_4Cl and extracted with ethyl acetate. The organic layer was washed with water and evaporated to yield a crude material which was subjected to silica gel chromatography (gradient elution 9% to 70% EtOAc in hexanes) to provide the desired product (**7**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (d, 2H), 3.80-3.68 (m, 2H), 3.22-3.11 (m, 2H), 2.68-2.58 (m, 1H), 1.86-1.75 (m, 2H), 1.64-1.53 (m, 2H), 1.49 (s, 9H).

Step 3: *tert*-butyl 4-[(1Z)-3-hydroxyprop-1-en-1-yl]piperidine-1-carboxylate (**8**)



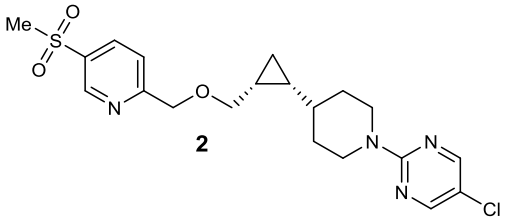
The alkyne **7** from step 2 (6.5 g, 27.2 mmol) and quinoline (0.55 mL, 4.62 mmol) were dissolved in EtOAc (120 mL). Lindlar's catalyst (740 mg) was added and the reaction was stirred under hydrogen atmosphere (1 atm) for 40 minutes. The reaction was filtered and concentrated to yield a crude residue which was purified by silica gel chromatography (gradient elution, 0% to 100% EtOAc in hexanes) to yield the desired allylic alcohol (**8**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.58 (m, 1H), 5.37 (dd, *J* 10.8 & 9.6 Hz, 1H), 4.22 (d, 2H), 4.16-3.99 (m, 2H), 2.80-2.78 (m, 2H), 2.52-2.40 (m, 1H), 1.61-1.56 (m, 2H), 1.45 (s, 9H), 1.36-1.22 (m, 2H).

Step 4: *tert*-Butyl 4-[(1R,2R)-2-(hydroxymethyl)cyclopropyl]piperdine-1-carboxylate (**9**)

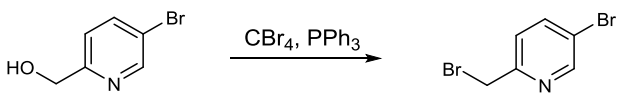


To a 3 L round bottomed flask equipped with overhead stirrer was added CH_2Cl_2 (850 mL) under a nitrogen atmosphere. The flask was cooled to -30°C and diethyl zinc (528 mL, 528 mmol) was added, followed by DME (55 mL, 528 mmol). The mixture was stirred for 20 min at -20°C followed by slow addition of diiodomethane (85 mL, 1057 mmol) over ~20 min. The mixture was stirred at -20°C for 45 min resulting in a white slurry. To a separate 1 L flask was charged the cis-allylic alcohol **8** (51 g, 211 mmol) and (4*S*,5*S*)-2-butyl-*N4*,*N4*,*N5*,*N5*-tetramethyl-1,3,2-dioxaborolane-4,5-dicarboxamide (68.5g, 254 mmol) in DCM (400 mL). This mixture was then added to the diethylzinc solution slowly over 1h at -15°C. The reaction was stirred overnight, allowing it to warm to RT. The reaction was then cooled to < 5°C, quenched with 5 % aqueous NH_4Cl (500 mL). A solid precipitate formed during the quench. The liquid was decanted liquid into a 4 L Sep funnel, and the layers were separated. Dichloromethane (350 mL) and aqueous NH_4Cl (400 mL) were added into the reaction flask and the mixture was stirred for ~1h to dissolve some of the solids. The layers were separated and both organic layers were combined, washed with 5 % aqueous NH_4Cl (500 mL), then brine (500 mL), dried over anhydrous $MgSO_4$, filtered and concentrated. The resulting residue was subjected to silica gel chromatography (EtOAc/hexanes) and the product recrystallized from heptane to give (*R*,*R*)-**9** with > 98% de and > 98% ee as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.18-4.00 (m, 2H), 3.68 (d, *J* 7.3 Hz, 2H), 2.76-2.63 (m, 2H), 1.83-1.72 (m, 2H), 1.49 (s, 9H), 1.39-1.25 (m, 2H), 1.24-1.14 (m, 1H), 1.05-0.95 (m, 1H), 0.78-0.71 (m, 2H), 0.07-0.01 (m, 1H).

5-Chloro-2-{4-[(1*R*, 2*R*)-2-({[5-(methylsulfonyl)pyridin-2-yl]methoxy}methyl) cyclopropyl]piperidin-1-yl}pyrimidine (2)

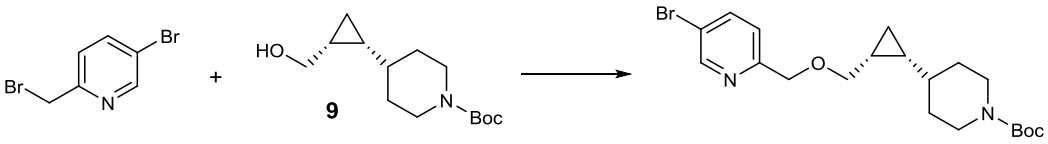


Step 1: 5-bromo-2-(bromomethyl)pyridine



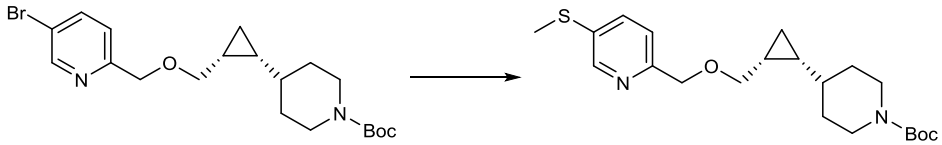
5-Bromo-2-hydroxymethylpyridine (1 g, 5.32 mmol) was dissolved in dichloromethane (26.6 ml) and cooled to 0 °C. Triphenylphosphine (1.604 g, 6.12 mmol) was added followed by carbon tetrabromide (2.028 g, 6.12 mmol) which caused the reaction to become yellow and heterogeneous. After 48 h, the mixture was concentrated by half and directly purified by silica gel column chromatography (0–37%, EtOAc–hexanes) to yield 5-bromo-2-(bromomethyl)pyridine. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (t, *J* 2.7 Hz, 1H), 7.82 (m, 1H), 7.35 (dd, *J* 7.8 & 3.1 Hz, 1H), 4.51 (s, 2H).

Step 2: *tert*-butyl 4-((1*R*, 2*R*)-2-{[(5-bromopyridin-2-yl)methoxy]methyl}cyclopropyl)piperidi ne-1-carboxylate



To a solution of **9** (3.5 g, 13.71 mmol) in THF (40 mL) was added NaHMDS (16.45 mL of a 1.0M soln in THF, 16.45 mmol) followed by the product of step 1 (4.13 g, 16.45 mmol) and the resulting mixture heated at reflux overnight. The mixture was cooled and poured into water (100 mL) and extracted with EtOAc (2 x 75 mL); combined EtOAc layers washed with sat. NaCl, dried over $MgSO_4$, filtered and evaporated in vacuo. Residue purified by silica gel column chromatography (eluent: gradient 0-25% EtOAc in Hexanes) to give the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (d, *J* 2.0 Hz, 1H), 7.84 (dd, *J* 8.0 & 2.0 Hz, 1H), 7.38 (d, *J* 8.0 Hz, 1H), 4.65 (d, *J* 13.5 Hz, 1H), 4.57 (d, *J* 13.5 Hz, 1H), 4.18-3.97 (br m, 2H), 3.64-3.58 (m, 1H), 3.58-3.52 (m, 1H), 2.74-2.58 (m, 2H), 1.86-1.79 (m, 1H), 1.77-1.69 (m, 1H), 1.47 (s, 9H), 1.36-1.20 (m, 3H), 0.98-0.89 (m, 1H), 0.79-0.68 (m, 2H), 0.07-0.03 (m, 1H).

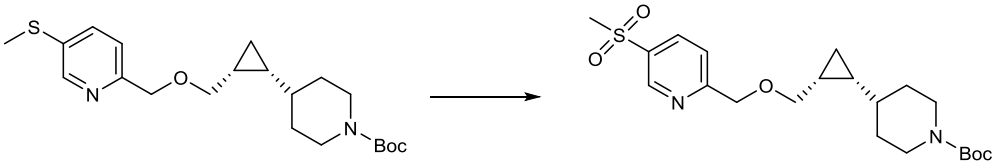
Step 3: *tert*-butyl 4-[(1*R*, 2*R*)-2-({[5-(methylthio)pyridin-2-yl]methoxy}methyl)cyclopropyl] piperidine-1-carboxylate



To a solution of the aryl bromide from step 2 (680 mg, 1.60 mmol) dissolved in THF (10.7 mL) cooled at –78 °C was added *n*-butyllithium in hexanes (1.5 M, 1.12 mL, 1.68 mmol). After 10 min, dimethyldisulfide (0.16 mL, 1.76 mmol) was added. At 45 min, the reaction was quenched at –78 °C with saturated aqueous NH_4Cl (2 mL). The mixture was warmed to room temperature, diluted with EtOAc and washed with H_2O (1x) and saturated aqueous NaCl (1x). The aqueous was back-extracted with EtOAc (3x), and the combined organic layer was dried over Na_2SO_4, filtered and evaporated in

vacuo to yield a crude oil that was purified by silica gel column chromatography (10–70%, EtOAc–hexanes) to yield the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (d, *J* 2.0 Hz, 1H), 7.62 (dd, *J* 8.0 & 2.0 Hz, 1H), 7.39 (d, *J* 8.0 Hz, 1H), 4.68 (d, *J* 13.5 Hz, 1H), 4.59 (d, *J* 13.5 Hz, 1H), 4.18-3.98 (br m, 2H), 3.66-3.60 (m, 1H), 3.57-3.51 (m, 1H), 2.75-2.58 (m, 2H), 2.53 (s, 3H), 1.88-1.82 (m, 1H), 1.77-1.69 (m, 1H), 1.47 (s, 9H), 1.37-1.21 (m, 3H), 0.98-0.90 (m, 1H), 0.79-0.68 (m, 2H), 0.07-0.03 (m, 1H).

Step 4: *tert*-butyl 4-[(1*R*, 2*R*)-2-({[5-(methylsulfonyl)pyridin-2-yl]methoxy}methyl)cycloprop yl]piperidine-1-carboxylate



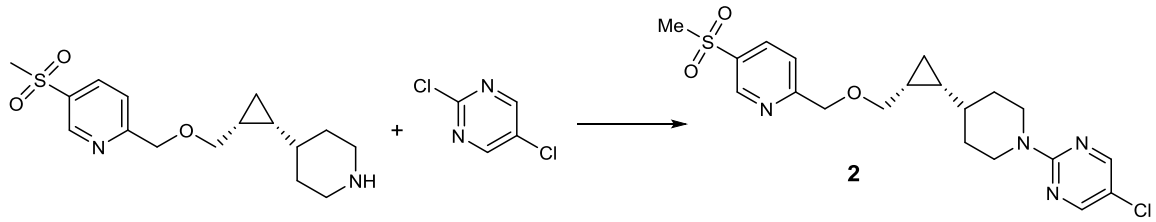
The sulfide from step 3 (200 mg, 0.509 mmol) was dissolved in MeOH (3.09 mL), and a solution of oxone (940 mg, 1.528 mmol) in water (7.1 mL) was added. The reaction became warm and heterogeneous with a white precipitate. At 45 min, the reaction was diluted with dichloromethane and washed with H_2O (1x) and saturated aqueous NaCl (1x). The aqueous was back-extracted with DCM (2x), and the combined organic layer was dried over Na_2SO_4, filtered and evaporated in vacuo to give the crude product that was purified by silica gel column chromatography (20–100%, EtOAc–hexanes) to yield the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.10 (d, 1H), 8.26 (dd, 1H), 7.73 (d, 1H), 4.81 (d, 1H), 4.73 (d, 1H), 4.20-4.00 (m, 2H), 3.69-3.61 (m, 2H), 3.14 (s, 3H), 2.75-2.60 (m, 2H), 1.87-1.82 (m, 1H), 1.78-1.72 (m, 1H), 1.47 (s, 9H), 1.38-1.24 (m, 3H), 1.02-0.93 (m, 1H), 0.83-0.72 (m, 2H), 0.11-0.06 (m, 1H). MS: *m*/*z* = 425 $[M+H]^+$.

Step 5: 5-(methylsulfonyl)-2-({[(1*R* ,2*R*)-2-piperidin-4-ylcyclopropyl]methoxy}methyl) pyridine

The product of step 4 (207 mg, 0.488 mmol) was dissolved in dichloromethane (1.63 mL) and trifluoroacetic acid (1.62 mL, 21.0 mmol) was added. At 1.75 h the volatiles were removed to yield an oil, which was dissolved in 1 mL of MeOH and 1.5 mL of 7 M NH_3 in MeOH. After 30 min all volatiles were removed. The free base was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.10 (d, 1H), 8.26 (dd, 1H), 7.68 (d, 1H), 4.78 (d, 1H), 4.71 (d, 1H), 3.89-3.84 (m, 1H), 3.53-3.49 (m, 1H), 3.46-3.41 (m, 1H), 3.15 (s, 3H), 2.93-2.81 (m, 2H), 2.19-2.12 (m, 1H), 2.02-1.94 (m, 1H),

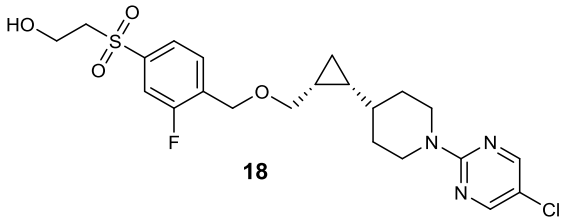
1.80-1.68 (m, 2H), 1.80-1.68 (m, 2H), 1.38-1.30 (m, 1H), 1.19-1.09 (m, 1H), 0.89-0.22 (m, 2H), 0.11-0.06 (m, 1H). MS: *m*/*z* = 325 $[M+H]^+$.

Step 6: 5-Chloro-2-{4-[(1*R*, 2*R*)-2-({[5-(methylsulfonyl)pyridin-2-yl]methoxy}methyl) cyclopropyl]piperidin-1-yl}pyrimidine (**2**)

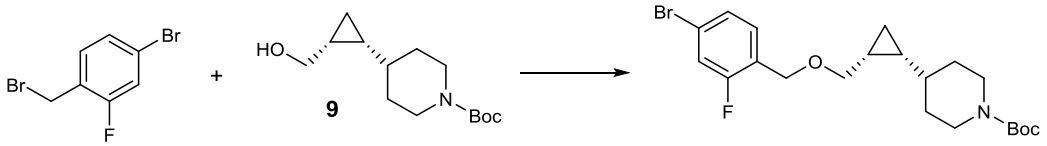


Step 5 product (158 mg, 0.488 mmol) was dissolved in DMSO (2 mL) and treated with cesium carbonate (270 mg, 0.830 mmol). After 5 min, 2,5-dichloropyrimidine (80 mg, 0.537 mmol) in 0.4 mL of DMSO was added to the above reaction solution. After stirring at rt for 20 h, the reaction was diluted with EtOAc and washed with H_2O and brine. The combined aqueous layers was back-extracted with EtOAc (3x), and the combined organic layers were dried over Na_2SO_4, filtered and evaporated in vacuo to give a crude oil that was purified by silica gel column chromatography (10–80%, EtOAc–hexanes) to yield compound **2**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.07 (d, *J* 2.1 Hz, 1H), 8.23 (dd, *J* 8.2 & 2.1 Hz, 1H), 8.19 (s, 2H), 7.71 (d, *J* 8.2 Hz, 1H), 4.78 (d, *J* 14.6 Hz, 1H), 4.71 (d, *J* 14.6 Hz, 1H), 4.69-4.64 (m, 1H), 4.63-4.58 (m, 1H), 3.70-3.65 (m, 1H), 3.65-3.60 (m, 1H), 3.11 (s, 3H), 2.89-2.78 (m, 2H), 1.95-1.90 (m, 1H), 1.85-1.80 (m, 1H), 1.41-1.31 (m, 2H), 1.30-1.22 (m, 2H), 1.12-1.04 (m, 1H), 0.82-0.76 (m, 1H), 0.76-0.70 (m, 2H), 0.11-0.06 (m, 1H). MS: *m*/*z* = 437 $[M+H]^+$.

2-({4-[({(1*R*, 2*R*))-2-[1-(5-chloropyrimidin-2-yl)piperidin-4-yl]cyclopropy l}methoxy)methyl]-3-fluorophenyl}sulfonyl)ethanol (18)

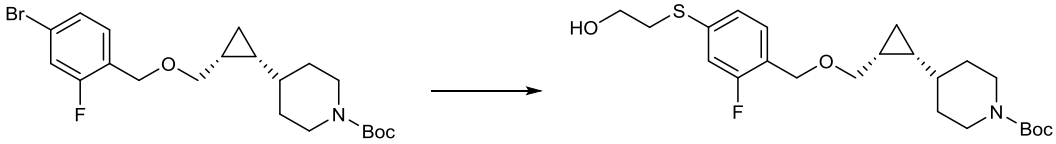


Step 1: *tert*-butyl 4-[(1*R*,2*R*)-2-{[(4-bromo-2-fluorobenzyl)oxy]methylcyclopropyl)piper idine-1-carboxylate



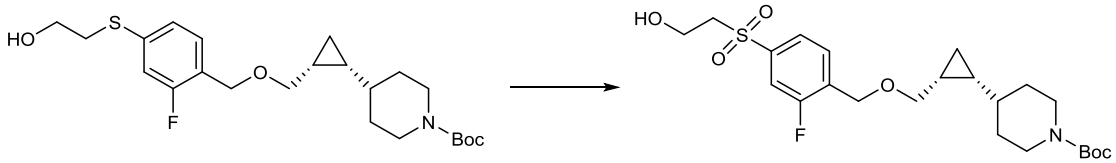
The title compound was prepared **9** and 4-bromo-2-fluorobenzyl bromide following procedures described in Step 2 for compound **2**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35-7.24 (m, 3H), 4.58 (d, 1H), 4.50 (d, 1H), 4.20-3.96 (br m, 2H), 3.63-3.58 (m, 1H), 3.45-3.40 (m, 1H), 2.72-2.58 (m, 2H), 1.84 (d, 1H), 1.71 (d, 1H), 1.49 (s, 9H), 1.37-1.18 (m, 3H), 0.95-0.85 (m, 1H), 0.78-0.66 (m, 2H), 0.05-0.00 (m, 1H).

Step 2: *tert*-butyl 4-{(1*R*, 2*R*)-2-[({2-fluoro-4-[(2-hydroxyethyl)thio]benzyl}oxy)methyl]cyclopropyl}piperidine-1-carboxylate



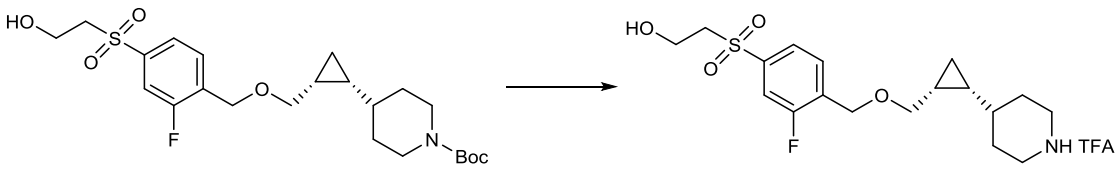
To a solution of Step 1 product (415 mg, 0.938 mmol) in 1,4-dioxane (10 mL) was added Hunig's base (0.328 mL, 1.876 mmol). The mixture was evacuated and backfilled with N_2 (3x). Pd_2dba_3 (25.8 mg, 0.028 mmol), 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (54.3 mg, 0.094 mmol) and 2-mercaptoethanol (73.3 mg, 0.94 mmol) were added sequentially and the mixture was degassed (2x). The mixture was heated to reflux for 2 h, then cooled and evaporated. The residue was purified by silica gel column chromatography (gradient 15~40% EtOAC in hexane) to yield the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (m, 1H), 7.15 (dd, 1H), 7.08 (dd, 1H), 4.59 (d, 1H), 4.48 (d, 1H), 4.18-3.96 (m, 2H), 3.82-3.77 (m, 2H), 3.41-3.36 (m, 1H), 3.15 (t, 2H), 2.70-2.63 (m, 1H), 1.82 (d, 1H), 1.79 (d, 1H), 1.48 (s, 9H), 1.36-1.17 (m, 3H), 0.92-0.83 (m, 1H), 0.77-0.64 (m, 2H), 0.04-0.00 (m, 1H).

Step 3: *tert*-butyl 4-{(1*R*, 2*R*)-2-[({2-fluoro-4-[(2-hydroxyethyl)sulfonyl]benzyl} oxy)methyl] cyclopropyl}piperidine-1-carboxylate



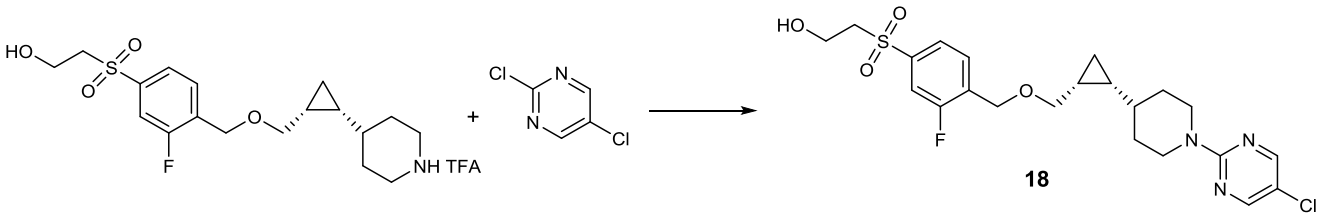
This compound was prepared from the product of step 2, according to the procedures described in Step 4 for compound **2**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78-7.70 (m, 2H), 7.66 (dd, 1H), 4.71 (d, 1H), 4.63 (d, 1H), 4.17-3.98 (m, 4H), 3.68 (dd, 1H), 3.56-3.51 (m, 1H),3.40 (t, 2H), 2.73-2.65 (m, 2H), 1.82 (d, 1H), 1.73 (d, 1H), 1.48 (s, 9H), 1.36-1.22 (m, 3H), 0.98-0.89 (m, 1H), 0.82-0.71 (m, 2H), 0.09-0.06 (m, 1H). MS: *m*/*z* = 494 $[M+Na]^+$.

Step 4: 2-{[3-fluoro-4-({[(1*R*, 2*R*)-2-piperidin-4-ylcyclopropyl]methoxy}methyl)phenyl] sulfonyl}ethanol TFA salt



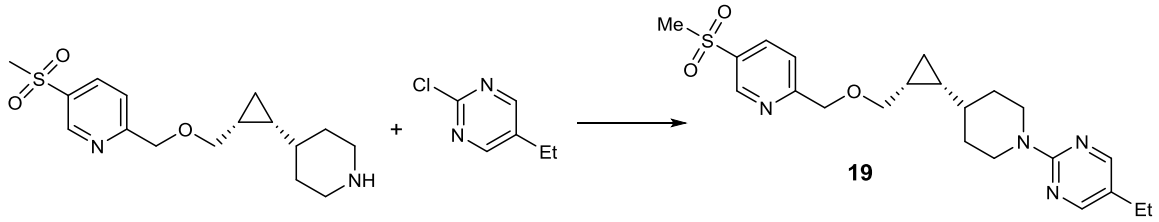
This compound was prepared by teating Step 3 product in DCM with excess TFA, followed by evaporating the volatiles. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (br s, 1H), 8.78 (br s, 1H), 7.77 (dd, 1H), 7.68-7.63 (m, 2H), 4.72 (d, 1H), 4.57 (d, 1H), 4.08-3.99 (m, 2H), 3.81 (dd, 1H), 3.43-3.37 (m, 2H), 3.37-3.27 (m, 2H), 2.90-2.79 (m, 1H), 2.79-2.69 (m, 1H), 2.15 (d, 1H), 1.94 (d, 1H), 1.75-1.60 (m, 2H), 1.37-1.27 (m 1H), 1.06-0.95 (m, 1H), 0.84-0.77 (m, 2H), 0.07-0.03 (m, 1H). MS: *m*/*z* = 372 $[M+H]^+$.

Step 5: 2-({4-[({(1*R*, 2*R*))-2-[1-(5-chloropyrimidin-2-yl)piperidin-4-yl]cyclopropy l}methoxy)methyl]-3-fluorophenyl}sulfonyl)ethanol (**18**)



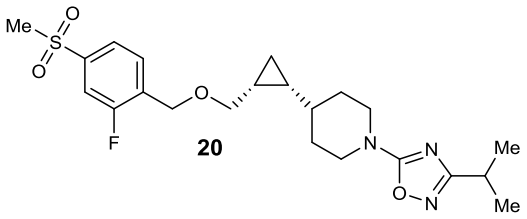
Compound **18** was prepared from the product of step 4 and 2,5-dichloropyrimidine according to the procedure described in Step 6 for compound **2**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 2H), 7.79-7.72 (m, 2H), 7.66 (dd, 1H), 4.75-4.58 (m, 4H), 4.08-4.03 (m, 2H), 3.73 (dd, 1H), 3.57 (t, 1H), 3.40 (t, 2H), 2.92-2.84 (m, 1H), 2.84-2.71 (m 1H), 1.95 (d, 1H), 1.85 (d, 1H), 1.43-1.23 (m, 3H), 1.14-1.04 (m, 1H), 0.84-0.72 (m, 2H), 0.13-0.09 (m, 1H). MS: *m*/*z* = 484 $[M+H]^+$.

5-Ethyl-2-{4-[(1*R*, 2*R*)-2-({[5-(methylsulfonyl)pyridin-2-yl]methoxy}methyl) cyclopropyl]piperidin-1-yl}pyrimidine (19)



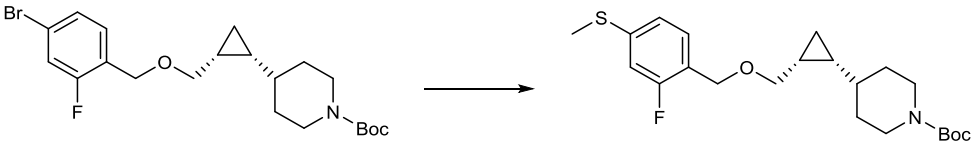
Compound **19** was prepared using 2-choro-5-ethylpyrimidine and following procedures similar to those described in Step 6 for compound **2**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.11 (d, 1H), 8.24 (dd, Hz, 1H), 8.18 (s, 2H), 7.78 (d, 1H), 4.79 (AB q, 2H), 4.69 (m, 2H), 3.71 (m, 2H), 3.17 (s, 3H), 2.84 (m, 2H), 2.46 (q, 2H), 1.90 (dd, 2H), 1.32 (m, 2H), 1.24 (m, 2H), 1.21 (t, 3H), 1.06 (m, 1H), 0.80 (m, 2H), 0.77 (m, 1H), 0.14 (m, 1H). MS: *m*/*z* = 431 $[M+H]^+$.

4-[(1*R*, 2*R*)-2-({[2-Fluoro-4-(methylsulfonyl)benzyl]oxy}methyl)cyclopropyl l]-1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidine (20)



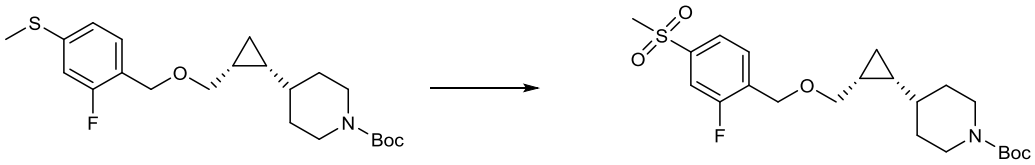
20

Step 1: *tert*-butyl 4-[(1*R*, 2*R*)-2-({[2-fluoro-4-(methylthio)benzyl]oxy}methyl) cyclopropyl] piperidine-1-carboxylate



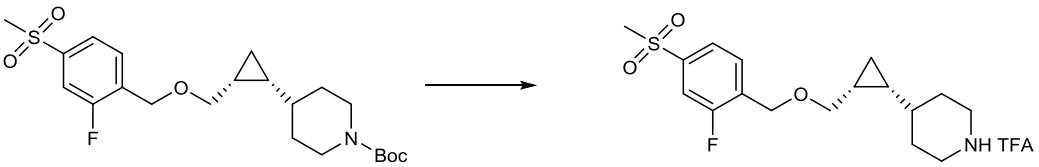
The title compound was prepared using Step 1 product from preparation of compound **18** following similar procedures described in Step 3 for compound **2**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (m, 1H), 7.03 (dd, 1H), 6.95 (dd, 1H), 4.58 (d, 1H), 4.49 (d, 1H), 4.19-3.96 (br m, 2H), 3.62 (dd, 1H), 3.42-3.37 (m, 1H), 2.71-2.57 (m, 2H), 2.50 (s, 3H), 1.84 (d, 1H), 1.71 (d, 1H), 1.48 (s, 9H), 1.36-1.18 (m, 3H), 0.94-0.84 (m, 1H), 0.76-0.64 (m, 2H), 0.03-0.00 (m, 1H).

Step 2: *tert*-butyl 4-[(1*R*, 2*R*)-2-({[2-fluoro-4-(methylsulfonyl)benzyl]oxy}methyl) cyclopropyl]piperidine-1-carboxylate



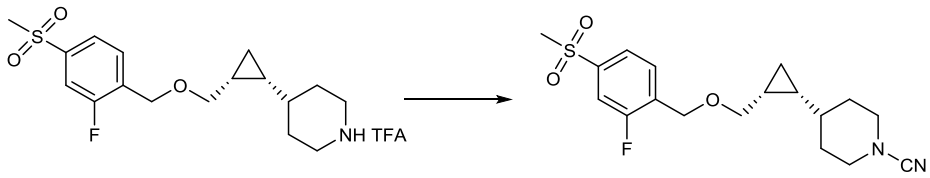
The title compound was prepared according to the procedures described in Step 4 for compound **2**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, 1H), 7.71 (m, 1H), 7.66 (dd, 1H), 4.71 (d, 1H), 4.64 (d, 1H), 4.18-4.00 (br m, 2H), 3.67-3.63 (m, 1H), 3.57-3.52 (m, 1H), 3.09 (s, 3H), 2.75-2.60 (m, 2H), 1.83 (d, 1H), 1.75 (d, 1H), 1.49 (s, 9H), 1.31-1.22 (m, 3H), 0.99-0.90 (m, 1H), 0.82-0.70 (m, 2H), 0.10-0.05 (m, 1H).

Step 3: 4-[(1*R*, 2*R*)-2-({[2-fluoro-4-(methylsulfonyl)benzyl]oxy}methyl)cyclopropyl]piperidine trifluoroacetate



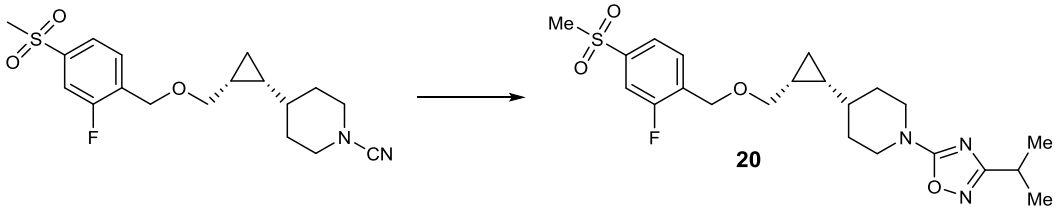
This compound was prepared by teating Step 2 product in DCM with excess TFA, followed by evaporating the volatiles. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, 1H), 7.70-7.65 (m, 2H), 4.64 (q, 2H), 4.64 (d, 1H), 3.79-3.73 (m, 1H), 3.46-3.33 (m, 3H), 3.10 (s, 3H), 2.92-2.78 (m, 2H), 2.15 (d, 1H), 1.97 (d, 1H), 1.79-1.69 (m, 2H), 1.36-1.27 (m 2H), 1.14-1.05 (m, 1H), 0.85-0.00 (m, 2H), 0.10-0.06 (m, 1H).

Step 4: 4-((1R,2R)-2-(((2-fluoro-4-(methylsulfonyl)benzyl)oxy)methyl)cyclopropyl)piperidine-1-carbonitrile



The product from step 3 (170 mg, 0.450 mmol) was suspended in CH_2Cl_2 (6 ml) and $NaHCO_3$ (151 mg, 1.799 mmol) in 3 mL of water was added. The mixture was stirred at 0 °C for 5 min, then BrCN (0.165 ml, 0.495 mmol) in CH_2Cl_2 (3 M solution) was added. The mixture was stirred at 0 °C for 30 min and at rt for 1 h. The two phases were separated and the water phase was extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated to yield a crude material, which was purified by silica gel column chromatography (gradient elution 0% to 100% EtOAc in hexanes) to give the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, 1H), 7.71-7.64 (m, 2H), 4.66 (q, 2H), 3.68 (dd, 1H), 3.49-3.39 (m, 3H), 3.09 (s, 3H), 3.03-2.91 (m, 2H), 1.94 (d, 1H), 1.81 (d, 1H), 1.59-1.49 (m, 2H), 1.32-1.24 (m, 1H), 0.97-0.88 (m, 1H), 0.83-0.74 (m, 2H), 0.07-0.04 (m, 1H).

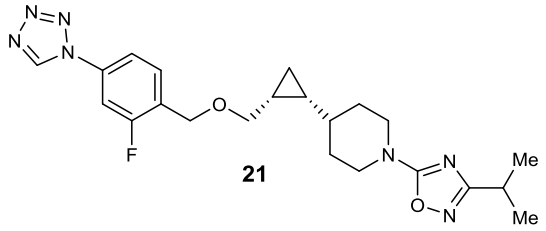
Step 5: 4-[(1*R*, 2*R*)-2-({[2-fluoro-4-(methylsulfonyl)benzyl]oxy}methyl)cyclopropy l]-1-(3-isopropyl-1,2,4-oxadiazol-5-yl)piperidine (**20**)



Step 4 product (110 mg, 0.3 mmol) was dissolved in 3 mL of THF. *N'*-hydroxy-2-methylpropanimidamide (46 mg, 0.45 mmol) in 3 mL of THF was added to the above solution. The mixture was allowed to stir for 5 min. Zinc dichloride (0.9 mL, 0.45 mmol) was added dropwise at room temperature. The reaction was heated to 85 °C for 3 hours. The mixture was cooled to rt and p-toluenesulfonic acid monohydrate (171 mg, 0.9 mmol) was added. The reaciton was heated to 85 °C for 2 h. The mixture was diluted with EtOAc, washed with sat. $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated in cacuo. The crude material was purified by flash column (10 g SNAP, 20~50 EtOAc in

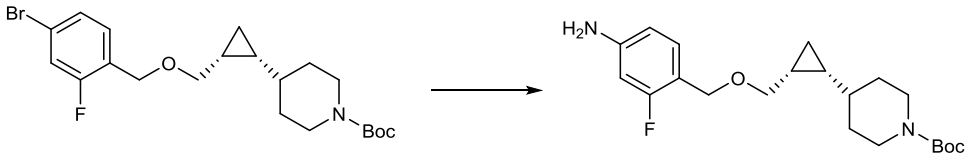
hexane) to afford compound **20**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, 1H), 7.71 (m, 1H), 7.61 (dd, 1H), 4.67 (q, 2H), 4.18-4.09 (m, 2H), 3.71 (dd, 1H), 3.51 (dd, 1H), 3.09 (s, 3H), 3.07-2.95 (m, 2H), 2.90 (sept, 1H), 1.99 (d, 1H), 1.86 (d, 1H), 1.53-1.43 (m, 2H), 1.31 (d, 6H), 1.32-1.24 (m, 1H), 1.09-1.00 (m, 1H), 0.83-0.74 (m, 2H), 0.07-0.04 (m, 1H). MS: *m/z* = 452 $[M+H]^+$.

5-(4-((1R,2R)-2-((2-fluoro-4-(1H-tetrazol-1-yl)benzyloxy)methyl)cyclopropyl)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole (21)



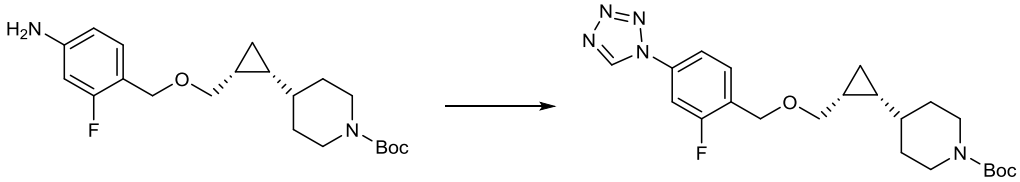
21

Step 1: tert-butyl 4-((1R,2R)-2-((4-amino-2-fluorobenzyloxy)methyl)cyclopropyl)piperidine-1-carboxylate



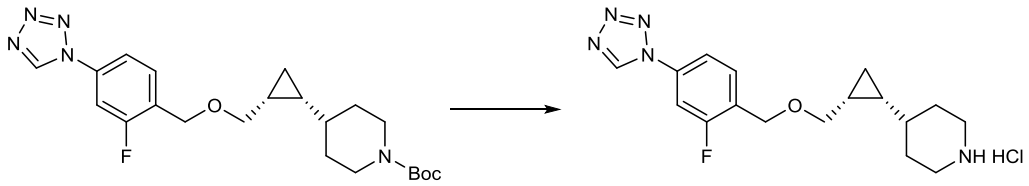
LiHMDS (2.94 ml, 2.94 mmol) was charged to a microwave vial containing 1.0 g (2.261 mmol) of Step 1 product from compound **18** synthesis, [1,1'-biphenyl]-2-yldicyclohexylphosphane (0.095 g, 0.271 mmol), and Pd_2dba_3 (0.104 g, 0.113 mmol) under N_2. The resulting solution was degassed for 5 min, then heated to 65 °C overnight. The following morning LC/MS analysis demonstrated all the SM to have been consumed. The reaction mixture was cooled to rt and TBAF (6.78 ml, 6.78 mmol) was added. The resulting solution was left to stir for a subsequent 10 min. The volatiles were then removed under reduced pressure and the crude oil taken up in Et_2O. This organic layer was washed with water (x 2), dried over $MgSO_4$, and concentrated under reduced pressure to afford an amber crude oil. The desired product was isolated by MPLC (25g SNAP column, Biotage system) eluting with a range of 2-6% MeOH/DCM. MS: *m/z* = 379 $(M+H)^+$.

Step 2: 3 tert-butyl 4-((1R,2R)-2-((2-fluoro-4-(1H-tetrazol-1-yl)benzyloxy)methyl)cyclopropyl)piperidine-1-carboxylate



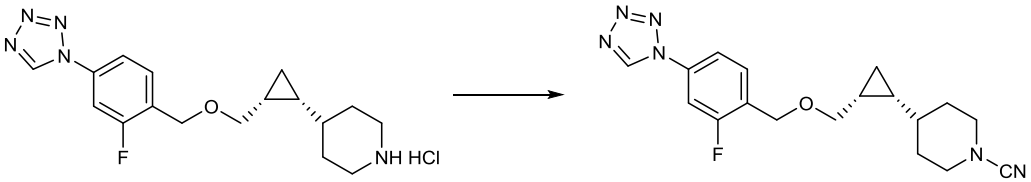
Triethyl orthoformate (1868 µl, 11.23 mmol) was added to a stirring solution of Step 1 product (850 mg, 2.246 mmol) and sodium azide (730 mg, 11.23 mmol) in acetic acid (8983 µl) that had been placed under N2 in a microwave vial. The vial was capped and the mixture heated to 100 °C for 3 h. LCMS analysis at this point demonstrated the SM to have been completely consumed. The reaction was cooled to rt and concentrated under reduced pressure. The resulting crude was partitioned between EtOAc and water and the layers separated. The aqueous phase was extracted with EtOAc (x 2). The combined organic layers were dried over MgSO4, filtered and concentrated under reduced pressure to afford an amber oil. The crude was purified by MPLC (25g SNAP column, Biotage system) eluting with a range of 30-60% EtOAc/Hex to afford the desired product as an amber oil. MS: *m/z* = 432 $(M+H)^+$.

Step 3: 4-((1R,2R)-2-((2-fluoro-4-(1H-tetrazol-1-yl)benzyloxy)methyl)cyclopropyl)piperidinium chloride



A solution of HCl (2607 µl, 10.43 mmol) in dioxane was added to Step 2 product (450 mg, 1.043 mmol) in DCM (3476 µl). The reaction was stirred for 1 h at rt, after which LCMS analysis demonstrated complete conversion of the SM to the desired product. The excess solvent was removed under reduced pressure to afford the title compound as a crude product to be used for the next step. MS: *m/z* = 332 $(M+H)^+$.

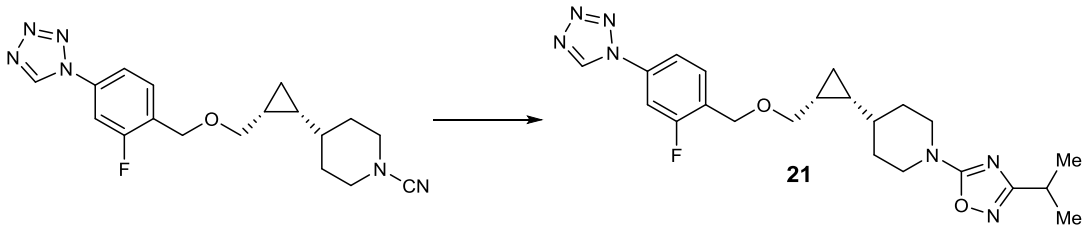
Step 4: 4-((1R,2R)-2-((2-fluoro-4-(1H-tetrazol-1-yl)benzyloxy)methyl)cyclopropyl)piperidine-1-carbonitrile



A solution of 3 M cyanogen bromide in DCM (120 µl, 0.359 mmol) was added to a preformed mixture of 4-((1R,2R)-2-((2-fluoro-4-(1H-tetrazol-1-yl)benzyloxy)methyl)cyclopropyl)piperidinium chloride (Step 3 product, 120 mg, 0.326 mmol) and sodium bicarbonate (69 mg, 0.816 mmol) in DCM (1.5 mL) and water (1.5 mL) that had been cooled to 0 ^oC in an ice bath. The reaction was stirred at 0 ^oC for 30 min then warmed to rt and stirred for 1 hr. The layers were cut and the aqueous phase extracted with DCM (2 mL x 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated

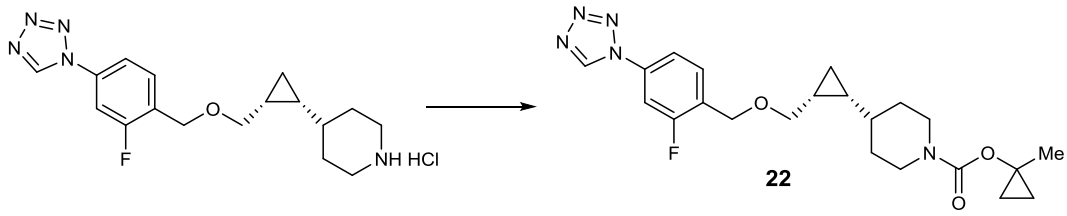
under reduced pressure to afford the title compound as a crude product to be used for the next step. MS: *m*/*z* = 357 $(M+H)^+$.

Step 5: 5-(4-((1R,2R)-2-((2-fluoro-4-(1H-tetrazol-1-yl)benzyloxy)methyl)cyclopropyl)piperidin-1-yl)-3-isopropyl-1,2,4-oxadiazole



A solution of 0.5 M zinc chloride in THF (505 µl, 0.253 mmol) was introduced to a mixture of Step 4 product (60 mg, 0.168 mmol), N-hydroxyisobutyrimidamide (26 mg, 0.253 mmol) and *p*-toluenesulfonic acid monohydrate (96 mg, 0.505 mmol) in THF (1 mL). The reaction vessel was fitted with a reflux condenser and refluxed for 3 hours. The reaction mixture was cooled to rt, diluted with EtOAc (5 mL) and neutralized by the addition of saturated aqueous sodium bicarbonate solution (5 mL). The layers were cut and the aqueous phase extracted with EtOAc (5 mL x 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was loaded onto 2 x 2000 micron silica preparative TLC plates (uv 254 active) which were developed using 50% EtOAc/Hex as the solvent system. The desired silica (Rf = 0.4 @ 50% EtOAc/Hex) was collected and extracted to give compound **21**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.04 (s, 1H), 7.72 (t, 1H), 7.55 (d, 2H), 4.66 (q, 2H), 4.14 (q, 2H), 3.72 (t, 1H), 3.49 (t, 1H), 2.99 (p, 2H), 2.91 (p, 1H), 2.01 (d, 1H), 1.85 (d, 1H), 1.47 (m, 2H), 1.29 (m, 7H), 1.04 (m, 1H), 0.84-0.73 (m, 2H), 0.09 (q, 1H). MS: *m*/*z* = 442 $(M+H)^+$.

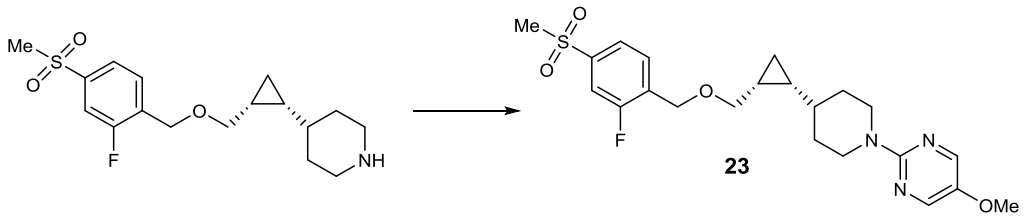
1-Methylcyclopropyl 4-((1R,2R)-2-((2-fluoro-4-(1H-tetrazol-1-yl)benzyloxy)methyl)cyclopropyl)piperidine-1-carboxylate (22)



A solution of the Step 3 product of compound **21** above (50 mg, 0.136 mmol), 2,5-dioxopyrrolidin-1-yl 1-methylcyclopropyl carbonate (compound **12**, commercially available, 48 mg, 0.177 mmol), and triethylamine (48 µl, 0.34 mmol) in anhydrous MeCN (1.4 mL) was stirred for 1 hr at rt. The reaction mixture was concentrated under reduced pressure then diluted with EtOAc (5 mL) and water (5 mL). The layers were cut and the aqueous phase extracted with EtOAc (5 mL x 2). The combined organic

layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was loaded onto 2 x 2000 micron silica preparative TLC plates (uv 254 active) which were developed using 50% EtOAc/Hex as the solvent system. The desired silica (Rf = 0.5 @ 50% EtOAc/Hex) was collected and extracted to give compound **22**. ^{1}H NMR (500 MHz, CD_3CN) δ 9.38 (s, 1H), 7.64 (m, 3H), 4.61 (q, 2H), 4.08-3.80 (m, 2H), 3.66 (dd, 1H), 3.42 (dd, 1H), 2.63 (m, 2H), 1.83 (d, 1H), 1.67 (d, 1H), 1.49 (s, 3H), 1.23-1.11 (m, 3H), 0.97 (m, 1H), 0.79 (t, 2H), 0.69-0.63 (m, 2H), 0.58 (t, 2H), 0.01 (d, 1H). MS: *m*/*z* = 430 $(M+H)^+$.

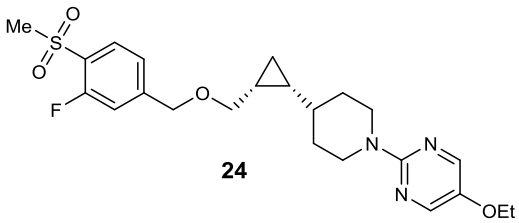
2-(4-((1R,2R)-2-(((2-fluoro-4-(methylsulfonyl)benzyl)oxy)methyl)cyclopropyl)piperidin-1-yl)-5-methoxypyrimidine (23)



23

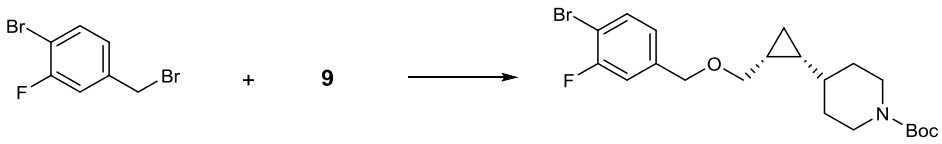
The Step 3 product from compouond **20** (50 mg, 0.146 mmol) was dissolved in DMSO (3 mL) at rt under N_2 and Cs_2CO_3 (119 mg, 0.366 mmol) was added. The mixture was stirred at rt for 5 min and 2-chloro-5-methoxypyrimidine (25.4 mg, 0.176 mmol) in DMSO (0.5 mL) was added. The mixture was stirred at 100 °C overnight. Then the reaction mixture was diluted with EtOAc, washed with sat. NH_4Cl, dried over MgSO4, and concentrated. The crude material was purified by prep TLC (50% EtOAc in hexane) to afford compound **23**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (s, 2H), 7.80-7.72 (m, 2H), 7.65 (d, 1H), 4.76 (AB q, 2H), 4.61 (dd, 1H), 3.83 (s, 3H), 3.71 (m, 1H), 3.59 (m, 1H), 3.09 (s, 3H), 2.81 (m, 2H), 1.92 (d, 1H), 1.84 (d, 1H), 1.41 (m, 2H), 1.25 (m, 2H), 1.07 (m, 1H), 0.80 (m, 2H), 0.74 (m, 1H), 0.13 (m, 1H). MS: *m*/*z* = 450 $[M+H]^+$.

5-ethoxy-2-(4-((1R,2R)-2-(((3-fluoro-4-(methylsulfonyl)benzyl)oxy) methyl)cyclopropyl)piperidin-1-yl)pyrimidine (24)



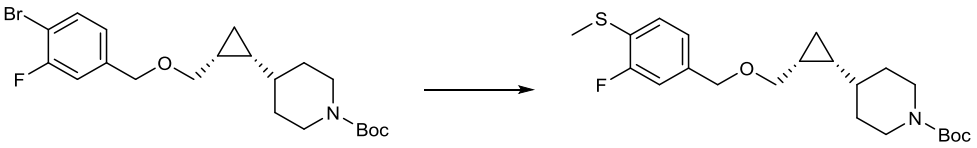
24

Step 1: tert-butyl 4-((1R,2R)-2-(((4-bromo-3-fluorobenzyl)oxy)methyl) cyclopropyl)piperidine-1-carboxylate



Compound **9** (4.5g, 17.6 mmol) was dissolved in 50 mL of DMF. The mixture was cooled to 0°C and NaH (60% dispersion, 1 g, 26.4 mmol) was added portionwise. The mixture was stirred for 5 min and 1-bromo-4-(bromomethyl)-2-fluorobenzene (5.67 g, 21.1 mmol) in DMF (15 mL) was added dropwise. The mixture was stirred at 0 °C for 30 min and at rt overnight. The reaction was quenched with sat. $NaHCO_3$ and extracted with EtOAc. The EtOAc phase was washed with water and brine, dried over $MgSO_4$, and evaporated to dryness. The crude material was purified by flash column (100 g SNAP, 10~50% EtOAc in hexane) to afford the desired product product. Rf was 0.5 @ 20% EtOAc in hexanes (blue spot on CAM stain).

Step 2: tert-butyl 4-((1R,2R)-2-(((3-fluoro-4-(methylthio)benzyl)oxy)methyl) cyclopropyl)piperidine-1-carboxylate



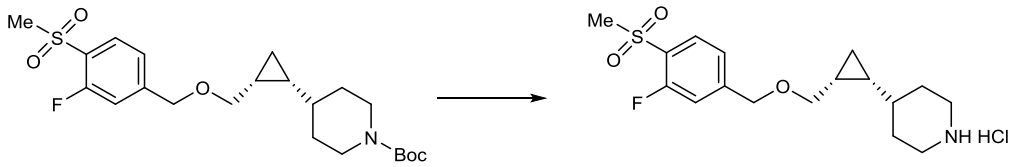
Step 1 product (7.7 g, 17.4 mmol) was dissolved in diethyl ether (70 ml) and cooled to -78 °C. The mixture was stirred for 5 min, then n-Butyllithium in hexane (2.5 M, 7.66 ml, 19.15 mmol) was added dropwise. The mixture was stirred at -78 °C for 10 min and dimethyl disulfide (1.85 ml, 20.9 mmol) was added dropwise. After the mixture was stirred at -78 °C for 30 min, it was quenched with sat. NH_4Cl at -78 °C. The reaction mixture was warmed up to rt and extracted with EtOAc (2x). The EtOAc phase was washed with brine, dried over MgSO4, and concentrated to afford the crude product that was used for the next step without further purification.

Step 3: tert-butyl 4-((1R,2R)-2-(((3-fluoro-4-(methylsulfonyl)benzyl)oxy)methyl) cyclopropyl)piperidine-1-carboxylate

Step 2 product (7.2 g, 17.58 mmol) was dissolved in CH_2Cl_2 (100 ml) at rt. To this mixture was added mCPBA (10.62 g, 61.5 mmol). The mixture was stirred at rtfor 2 h. LCMS showed no SM left. The reaction mixture was diluted with DCM, washed with sat. $Na_2S_2O_3$ (2x), sat. $NaHCO_3$ (2x), brine, dried over $MgSO_4$, and evaporated to dryness. The crude material was purified by flash column (100 g,

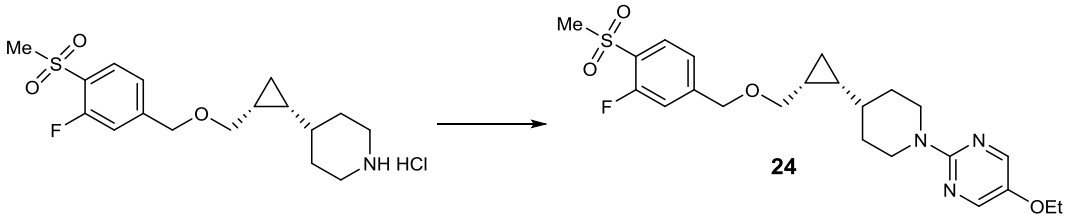
SNAP, 20~50% EtOAc in hexane) to afford the desired product. MS: *m/z* = 442 $(M+H)^+$. Rf was 0.3 @ 50% EtOAc in hexanes (blue spot on CAM stain).

Step 4: 4-((1R,2R)-2-(((3-fluoro-4-(methylsulfonyl)benzyl)oxy)methyl)cyclopropyl) piperidine hydrochloride



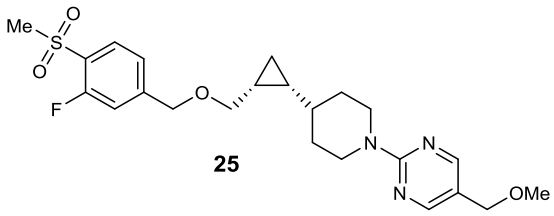
Step 3 product (2.7 g, 6.11 mmol) was dissolved in DCM (45 ml) and HCl in dioxane(4 M solution, 15.3 ml, 61.1 mmol) was added. The mixture was stirred at rt for 1 h. The solvents were evaporated to afford the desired product which was used without further purification. MS: *m/z* = 342 $(M+H)^+$.

Step 5: 5-ethoxy-2-(4-((1R,2R)-2-(((3-fluoro-4-(methylsulfonyl)benzyl)oxy)methyl) cyclopropyl)piperidin-1-yl)pyrimidine (**24**)



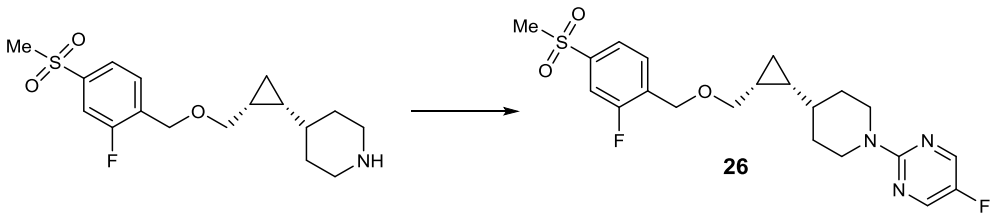
Step 4 product (200 mg, 0.53 mmol) was dissolved in DMSO (5 ml) at rt under N_2 and Cs_2CO_3 (517 mg, 1.588 mmol) was added. The mixture was stirred at rt for 5 min and 2-chloro-5-ethoxypyrimidine (101 mg, 0.635 mmol) in DMSO (0.5 mL) was added. The mixture was stirred at 100 °C overnight. Then the mixture was diluted with EtOAc, washed with sat. NH_4Cl, dried over $MgSO_4$, and evaporated. The crude material was purified by flash column (25 g SNAP, 15~50% EtOAc in hexane) to afford compound **24**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 2H), 7.90 (m, 1H), 7.30 (m, 2H), 4.60 (m, 4H), 4.00 (t, 2H), 3.60 (m, 2H), 3.20 (s, 3H), 2.93-2.80 (m, 2H), 1.96 (d, 1H), 1.85 (d, 1H), 1.43 (m, 5H), 1.25(m, 1H), 1.15 (m, 1H), 0.80-0.71 (m, 2H), 0.12-0.08 (m, 1H). MS: *m/z* = 464 $[M+H]^+$.

2-(4-((1R,2R)-2-(((3-fluoro-4-(methylsulfonyl)benzyl)oxy)methyl) cyclopropyl)piperidin-1-yl)-5-(methoxymethyl)pyrimidine (25)



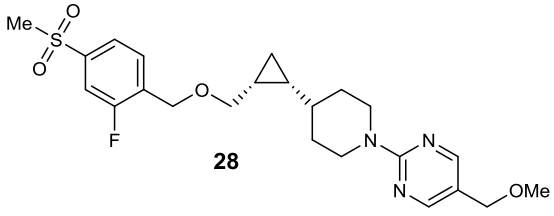
Step 4 product (1 g, 2.65 mmol) from compound **24** was dissolved in DMSO (15 mL), to which was added cesium carbonate (3.02 g, 9.26 mmol) under nitrogen. Then 2-chloro-5-(methoxymethyl)pyrimidine (504 mg, 3.18 mmol) in 2 mL of DMSO was dissolved. The reaction was stirred at 60 ^{o}C overnight. The reaction mixture was cooled to rt and diluted with EtOAc and water. The layers were cut and the aqueous phase extracted with EtOAc. The combined organic layers were washed with aqueous NH_4Cl and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column (20~50% EtOAc in hexane) to afford 670 mg (54.6%) of compound **25** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 2H), 7.94 (dd, 1H), 7.33-7.28 (m, 2H), 4.73 (m, 2H), 4.63 (ABq, 2H), 4.25 (s, 2H), 3.63-3.56 (m, 2H), 3.38 (s, 3H), 3.04 (s, 3H), 2.92-2.81 (m, 2H), 1.95 (d, 1H), 1.84 (d, 1H), 1.44-1.22 (m, 3H), 1.15-1.04 (m, 1H), 0.84-0.71 (m, 2H), 0.12-0.07 (m, 1H). MS: *m*/*z* = 464 $[M+H]^+$.

2-(4-((1R,2R)-2-(((2-fluoro-4-(methylsulfonyl)benzyl)oxy)methyl)cyclopropyl)piperidin-1-yl)-5-fluoropyrimidine (26)

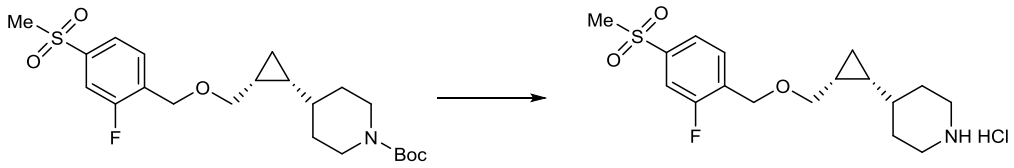


The Step 3 product from compouond **20** (50 mg, 0.146 mmol) was dissolved in DMSO (2 mL) at rt under N_2 and Cs_2CO_3 (143 mg, 0.439 mmol) was added. The mixture was stirred at rt for 5 min and 2-chloro-5-fluoropyrimidine (29 mg, 0.22 mmol) in DMSO (0.5 mL) was added. The mixture was stirred at rt overnight. Then the reaction mixture was diluted with EtOAc, washed with sat. NH_4Cl, dried over MgSO4, and concentrated. The crude material was purified by prep TLC (50% EtOAc in hexane) to afford compound **26**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (s, 2H), 7.80-7.74 (m, 2H), 7.68 (d, 1H), 4.71 (AB q, 2H), 4.68-4.60 (m, 2H), 3.76-3.71 (m, 1H), 3.60-3.57 (m, 1H), 3.07 (s, 3H), 2.92-2.78 (m, 2H), 1.97 (d, 1H), 1.83 (dd, 1H), 1.40 (m, 2H), 1.26 (m, 2H), 1.06 (m, 1H), 0.81 (m, 2H), 0.75 (m, 1H), 0.14 (m, 1H). MS: *m*/*z* = $[M+H]^+$.

2-(4-((1R,2R)-2-(((2-fluoro-4-(methylsulfonyl)benzyl)oxy)methyl) cyclopropyl)piperidin-1-yl)-5-(methoxymethyl)pyrimidine (28)

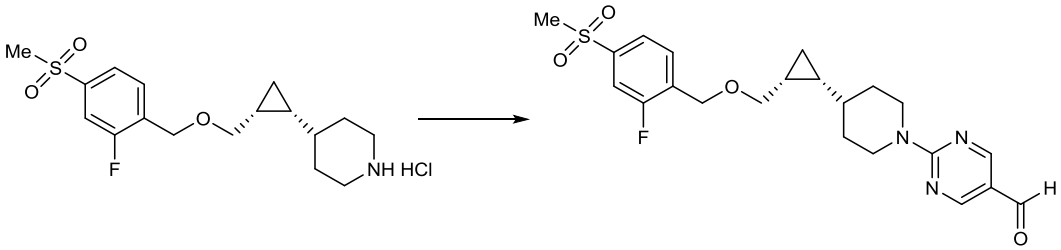


Step 1: 4-((1R,2R)-2-(((2-fluoro-4-(methylsulfonyl)benzyl)oxy)methyl) cyclopropyl) piperidine hydrochloride



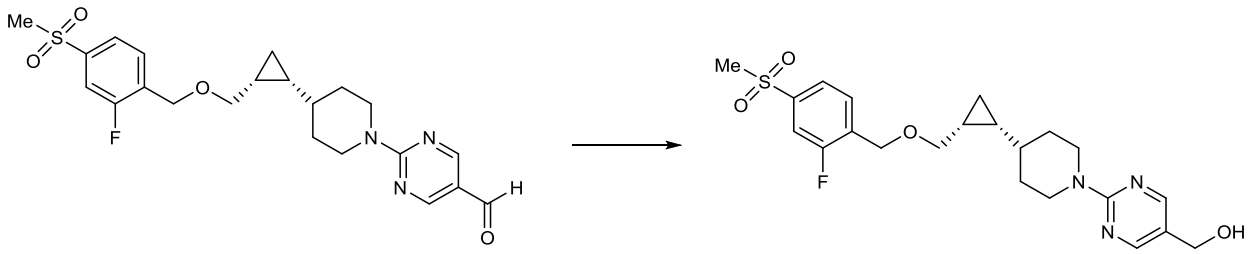
Step 2 product from compound **20** (1.13 g, 2.56 mmol) was dissolved in DCM (20 ml) and HCl in dioxane(4 M solution, 9.60 ml, 38.4 mmol) was added. The mixture was stirred at rt for 1 h. The solvents were evaporated to afford 0.97 g of the desired product (100%) which was used in the next step without further purification. MS: *m*/*z* = 378 $(M+H)^+$.

Step 2: 2-(4-((1R,2R)-2-(((2-fluoro-4-(methylsulfonyl)benzyl)oxy)methyl) cyclopropyl) piperidin-1-yl)pyrimidine-5-carbaldehyde



Step 1 product was dissolved in DMSO (7 ml) at rt under N_2 and Cs_2CO_3 (539 mg, 1.654 mmol) was added. The mixture was stirred at rt for 5 min and 2-chloropyrimidine-5-carbaldehyde (113 mg, 0.794 mmol) in DMSO (1 mL) was added. The mixture was stirred at rt overnight. Then the reaction mixture was diluted with EtOAc, washed with sat. NH_4Cl, dried over $MgSO_4$, and concentrated to dryness. The crude material was purified by flash column (25 g SNAP, 25~60% EtOAc in hexane) to afford 200 mg of the desired product (67.6%) as a white solid. MS: *m*/*z* = 448 $(M+H)^+$.

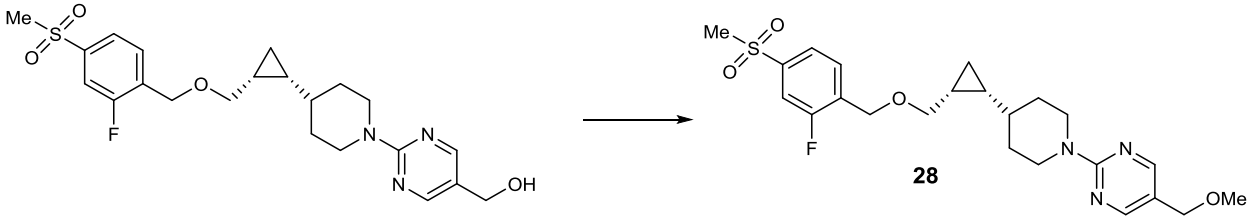
Step 3: (2-(4-((1R,2R)-2-(((2-fluoro-4-(methylsulfonyl)benzyl)oxy)methyl)cyclopropyl) piperidin-1-yl)pyrimidin-5-yl)methanol



Step 2 product (200 mg, 0.447 mmol) was dissolved in MeOH (20 ml) at rt and $NaBH_4$ (66.2 mg, 0.670 mmol) was added. The mixture was stirred at rt for 30 min and TLC showed the SM was completely consumed. The mixture was diluted with EtOAc, washed with water, dried over $MgSO_4$,

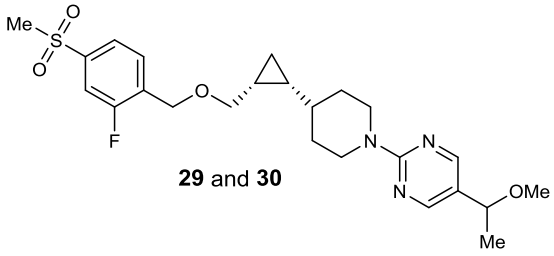
and concentrated to afford 198 mg of the desired product (99%) which was used in the next step without further purificatoin. MS: *m/z* = 450 $(M+H)^+$.

Step 4: 2-(4-((1R,2R)-2-(((2-fluoro-4-(methylsulfonyl)benzyl)oxy)methyl)cyclopropyl) piperidin-1-yl)-5-(methoxymethyl)pyrimidine (**28**)

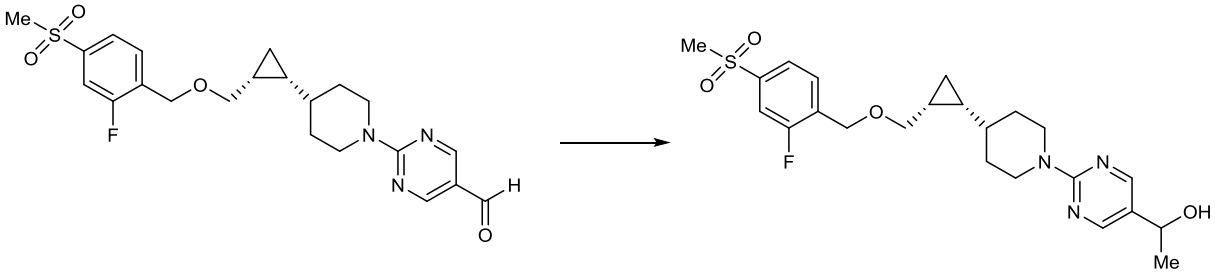


Step 3 product (198 mg, 0.44 mmol) was dissolved in acetonitrile (6 mL) at room temperature under N_2 and sodium hydride (26 mg of a 60% dispersion in oil, 0.66 mmol) was added followed by CH_3I (0.137 mL, 2.2 mmol). The mixture was stirred at rt overnight. Then the reaction mixture was diluted with EtOAc, washed with sat. NH_4Cl, dried over $MgSO_4$, filtered and evaporated in vacuo. The crude material was purified by column chromatography (SNAP, 10 g, 70% EtOAc in hexane) to afford 150 mg (73.5%) of compound **28**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 2H), 7.78 (dd, 1H), 7.73 (m, 1H), 7.67 (dd, 1H), 4.80-4.64 (m, 4H), 4.28 (s, 2H), 3.71 (dd, 1H), 3.61-3.54 (m, 1H), 3.37 (s, 3H), 3.08 (s, 3H), 2.93-2.80 (m, 2H), 1.96 (d, 1H), 1.85 (d, 1H), 1.43-1.22 (m, 3H), 1.15-1.04 (m, 1H), 0.94-0.71 (m, 2H), 0.12-0.08 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4, 160.8, 158.3, 141.3, 132.4, 130.6, 123.3, 118.2, 114.6, 71.8, 70.0, 65.6, 57.6, 44.5, 44.0, 36.4, 32.4, 22.2, 15.4, 8.4. MS: *m/z* = 464 $[M+H]^+$. $[\alpha]^{25}_D$ -2.4º (*c* = 1.0, $CHCl_3$).

2-(4-((1R,2R)-2-(((2-fluoro-4-(methylsulfonyl)benzyl)oxy)methyl) cyclopropyl)piperidin-1-yl)-5-(1-methoxyethyl)pyrimidine (29 and 30)

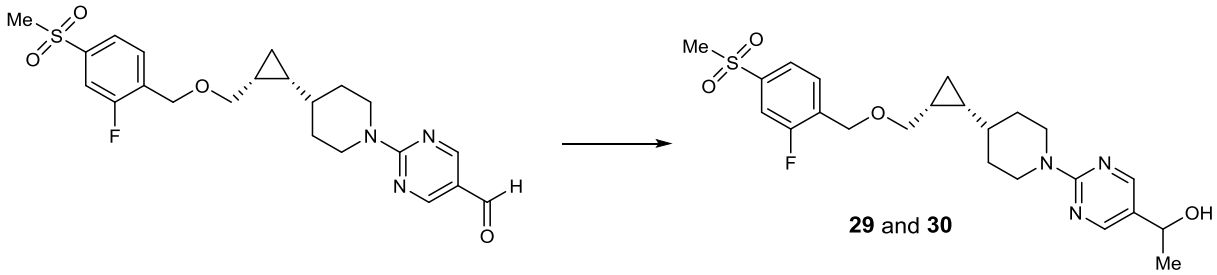


Step 1: 1-(2-(4-((1R,2R)-2-(((2-fluoro-4-(methylsulfonyl)benzyl)oxy)methyl) cyclopropyl)piperidin-1-yl)pyrimidin-5-yl)ethanol



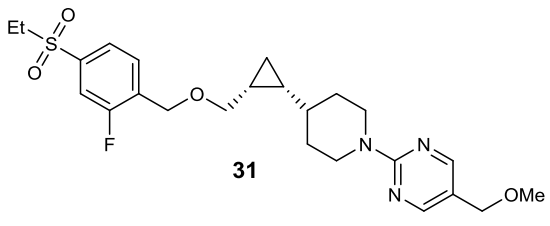
Step 2 product of compound **28** (130 mg, 0.29 mmol) was dissolved in THF (5 ml) at 0 °C under N_2 and CH_3MgCl (3 M solution, 0.145 ml, 0.436 mmol) was added. The mixture was stirred at rt for 30 min and TLC showed the SM was completely consumed. The reaction mixture was diluted with EtOAc, washed with water, dried over MgSO4, and concentrated to afford the desired product that was used in the next step without further purification. Rf was 0.4 @ 50% EtOAc in hexanes (blue spot on CAM stain). MS: *m*/*z* = 464 $(M+H)^+$.

Step 2: 2-(4-((1R,2R)-2-(((2-fluoro-4-(methylsulfonyl)benzyl)oxy)methyl)cyclopropyl) piperidin-1-yl)-5-(1-methoxyethyl)pyrimidine (**29** and **30**)



Step 1 product (110 mg, 0.24 mmol) was dissolved in CH_3CN (5 mL) at rt and NaH (60% dispersion, 28.5 mg, 0.712 mmol) was added followed by CH_3I (0.148 ml, 2.373 mmol). The mixture was stirred at rt for 2 h. Then the reaction mixture was diluted with EtOAc, washed with sat. NH_4Cl, dried over MgSO4, and concentrated. The crude material was purified by prep TLC (50% EtOAc in hexane) to afford 92 mg (81%) of the desired diastereoisomer mixture. Rf was 0.5 @ 50% EtOAc in hexanes (blue spot on CAM stain). The diastereoisomer mixture was resolved by chiral HPLC using OJ column to obtain two pure diastereomers. The faster diastereomer was compound **29** and the slower diastereomer was compound **30**. ^1H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 2H), 7.78 (m, 2H), 7.70 (d, 1H), 4.80-4.64 (m, 4H), 4.18 (m, 1H), 3.71 (dd, 1H), 3.61(m, 2H), 3.25 (s, 3H), 3.08 (s, 3H), 2.93-2.80 (m, 2H), 1.96-1.80 (m, 2H), 1.43 (d, 3H), 1.4~1.0 (m, 5H), 0.8 (m, 2H), 0.12-0.08 (m, 1H). MS: *m*/*z* = 478 $[M+H]^+$.

2-(4-((1R,2R)-2-(((4-(ethylsulfonyl)-2-fluorobenzyl)oxy)methyl) cyclopropyl)piperidin-1-yl)-5-(methoxymethyl)pyrimidine (31)

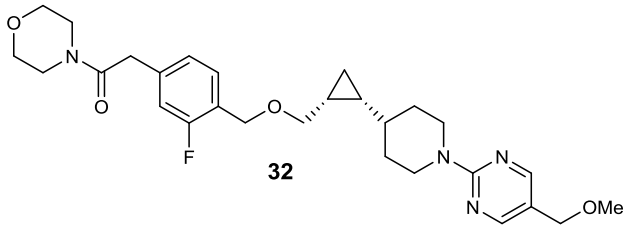


31

Compound **31** was prepared following the procedure described for compound **28** with minor modification during the preparation of the intermediate where dimethyl disulfide was replaced by diethyl disulfide. ^1H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 2H), 7.78 (m, 2H), 7.73 (d, 1H), 4.70-4.60 (m, 4H),

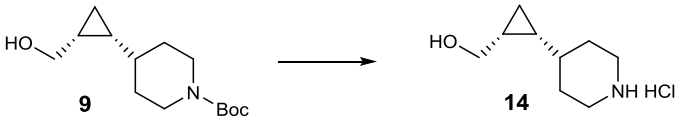
4.28 (s, 2H), 3.71-3.60 (m, 2H), 3.37 (s, 3H), 3.08 (m, 2H), 2.93-2.80 (m, 2H), 1.96 (d, 1H), 1.85 (d, 1H), 1.40-1.22 (m, 6H), 1.15-1.04 (m, 1H), 0.94-0.71 (m, 2H), 0.12-0.08 (m, 1H). MS: *m*/*z* = 478 $[M+H]^+$.

2-(3-Fluoro-4-((((1R,2R)-2-(1-(5-(methoxymethyl)pyrimidin-2-yl)piperidin-4-yl)cyclopropyl)methoxy)methyl)phenyl)-1-morpholinoethan-1-one (32)



32

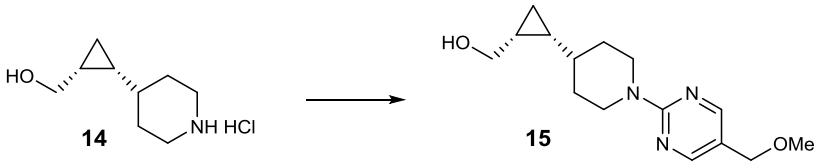
Step 1: ((1R,2R)-2-(piperidin-4-yl)cyclopropyl)methanol hydrochloride



9 **14**

Intermediate **9** (15.37 g, 60.2 mmol) was dissolved in DCM (100 ml), to whcih was added HCl (4 M in dioxane) (75 ml, 301 mmol). The reaction mixture was stirred at rt for 2 hrs. TLC showed the reaction was completed (CAM stain). The mixture was concentrated to dryness to afford **14** that was used in the next step without purification.

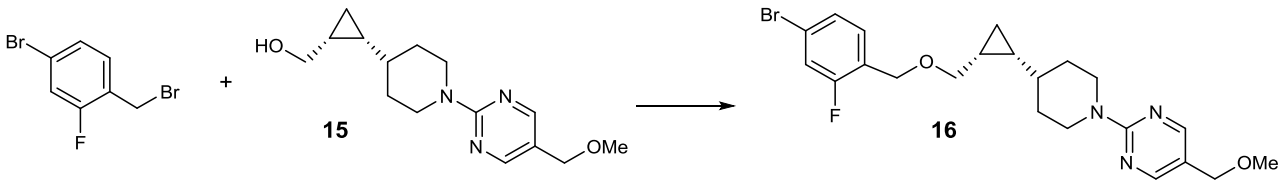
Step 2: ((1R,2R)-2-(1-(5-(methoxymethyl)pyrimidin-2-yl)piperidin-4-yl)cyclopropyl)methanol



14 **15**

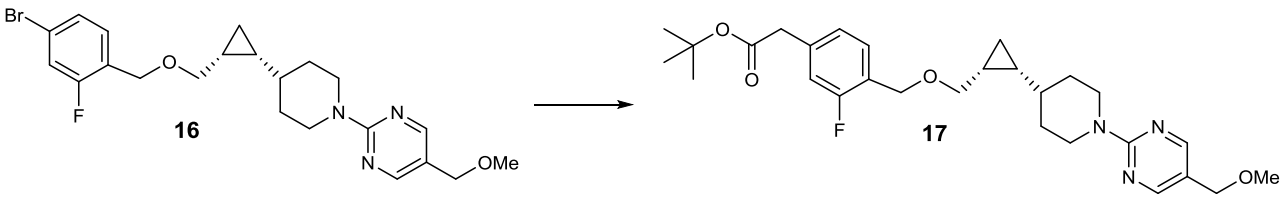
Compound **14** (1.3 g, 6.78 mmol) was dissolved in 20 mL of DMSO at rt under N_2 and Cs_2CO_3 (6.63 g, 20.34 mmol) was added. After stirring at rt for 5 min, 2-chloro-5-(methoxymethyl)pyrimidine (commercially available, 1.075 g, 6.78 mmol) in DMSO (2 mL) was added. The reaction mixture was stirred at 60 °C overnight. Then it was diluted with EtOAc, washed with sat. NH_4Cl, dried over $MgSO_4$ and concentrated to dryness. The crude material was purified by flash silica column (25 g SNAP, 20~60 EtOAc in hexane) to afford 1.43 g (76%) of compound **15**. MS: *m*/*z* = 278 $(M+H)^+$.

Step 3: 2-(4-((1R,2R)-2-(((4-bromo-2-fluorobenzyl)oxy)methyl)cyclopropyl)piperidin-1-yl)-5-(methoxymethyl)pyrimidine



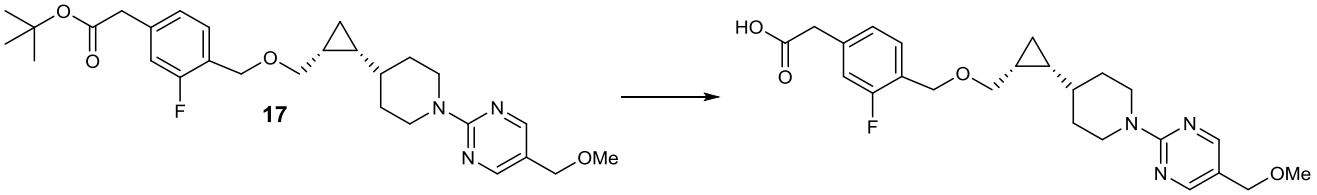
Compound **15** (1 g, 3.61 mmol) was dissolved in 10 mL of DMF. The mixture was cooled to 0°C and NaH (60% dispersion, 0.22 g, 5.41 mmol) was added portionwise. The mixture was stirred for 5 min and 4-bromo-1-(bromomethyl)-2-fluorobenzene in DMF (2 mL) was added dropwise. The mixture was stirred at 0 °C for 30 min and at rt overnight. The mixture was quenched with sat. $NaHCO_3$ and extracted with EtOAc. The EtOAc phase was washed with water and brine, dried over $MgSO_4$, and concentrated to dryness. The crude material was purified by flash column (25 g SNAP, 10~50% EtOAc in hexane) to afford compound **16** (1.6 g, 96%). Rf was 0.5 @ 50% EtOAc in hexanes (blue spot on CAM stain).

Step 4: tert-butyl 2-(3-fluoro-4-((((1R,2R)-2-(1-(5-(methoxymethyl)pyrimidin-2-yl) piperidin-4-yl)cyclopropyl)methoxy)methyl)phenyl)acetate



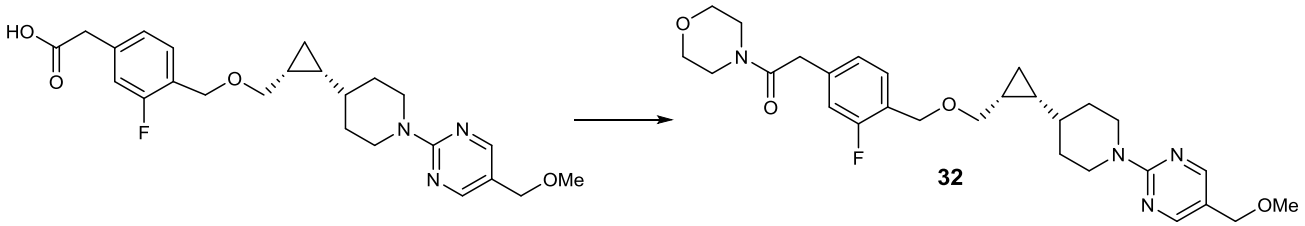
Compound **16** (1.0 g, 2.15 mmol) was dissolved in anhydrous THF (3 ml). The mixture was stirred for 5 min and $Pd_2(dba)_3$ (0.099 g, 0.108 mmol) and X-PHOS (0.103 g, 0.215 mmol) were added, followed by (2-(tert-butoxy)-2-oxoethyl)zinc(II) bromide (0.5 M solution in ether, 12.92 ml, 6.46 mmol). The mixture was heated at 60 °C overnight. The reaction mixture was quenched with aqueous NH_4Cl, and the aqueous layer was extracted with EtOAc. The organic extracts were washed with brine, dried, and evaporated to give the crude product. The crude was purified by flash column (25 g SNAP, 5~30% EtOAc in hexane) to afford 1.05 g (98%) of compound **17**. Rf was 0.3 @ 20% EtOAc in hexanes (blue spot on CAM stain).

Step 5: 2-(3-fluoro-4-((((1R,2R)-2-(1-(5-(methoxymethyl)pyrimidin-2-yl)piperidin-4-yl)cyclopropyl)methoxy)methyl)phenyl)acetic acid



Compound **17** (1 g, 2.0 mmol) was dissolved in DCM (10 ml) and TFA (5.80 ml, 78 mmol) was added. The mixture was stirred at rt for 2 h. The solvents were evaporated to afford 1.5 g of the crude material. This crude material was dissolved in EtOAc (50 mL), washed with 20 mL of sat. $NaHCO_3$ and sat. NH_4Cl. The combined water phase was extracted with EtOAc (30 mL). The combined EtOAc phases were dried over MgSO4 and concentrated to dryness to afford 0.9 g (100%) of the desired acid. MS: m/z = 444 $(M+H)^+$.

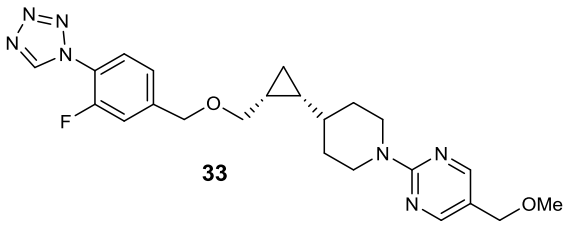
Step 6: 2-(3-Fluoro-4-((((1R,2R)-2-(1-(5-(methoxymethyl)pyrimidin-2-yl)piperidin-4-yl)cyclopropyl)methoxy)methyl)phenyl)-1-morpholinoethan-1-one (**32**)



32

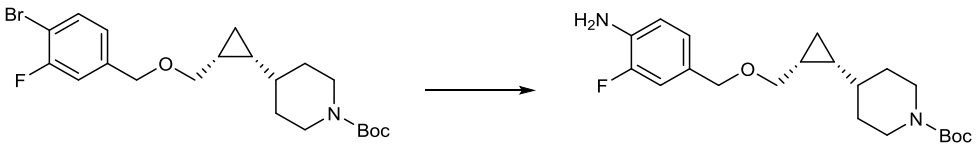
Step 5 product (50 mg, 0.113 mmol), 1-hydroxybenzotriazole hydrate (25.9 mg, 0.169 mmol) and (E)-3-(ethyldiazenyl)-N,N-dimethylpropan-1-amine hydrochloride (30.4 mg, 0.169 mmol) were dissolved in DCM (3 mL), and the mixture was stirred at rt for 10 min. Then morpholine (14.73 mg, 0.169 mmol) was added and the reaction was stirred at rt overnight. LCMS showed the acid starting material was completely consumed. The mixture was diluted with DCM, washed with water, dried over $MgSO_4$, and concentrated to dryness. The crude mixture was purified by prep TLC developped by EtOAc to afford 40 mg (69%) of compound **32**. ^1H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 2H), 7.39 (m, 1H), 7.02 (m, 1H), 6.98 (m, 1H), 4.72 (dd, 2H), 4.58 (AB q, 2H), 4.25 (s, 2H), 3.74 (s, 2H), 3.64 (m, 4H), 3.58 (m, 2H), 3.42 (m, 2H), 3.38 (s, 3H), 2.83 (m, 2H), 1.98 (m, 1H), 1.81 (m, 2H), 1.38 (m, 2H), 1.22 (m, 1H), 1.03 (m, 1H), 0.72 (m, 2H), 0.40 (m, 1H). MS: m/z = 513 $(M+H)^+$.

2-(4-((1R,2R)-2-((3-fluoro-4-(1H-tetrazol-1-yl)benzyloxy)methyl)cyclopropyl)piperidin-1-yl)-5-(methoxymethyl)pyrimidine (33)



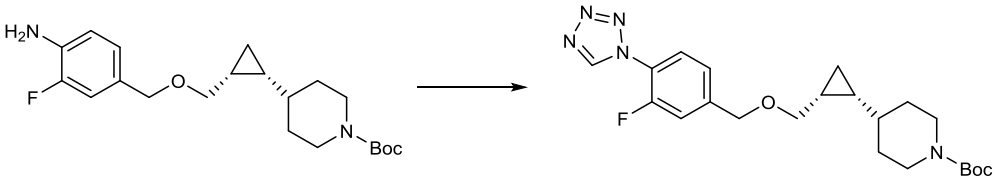
33

Step 1: tert-butyl 4-((1R,2R)-2-((4-amino-3-fluorobenzyloxy)methyl)cyclopropyl)piperidine-1-carboxylate



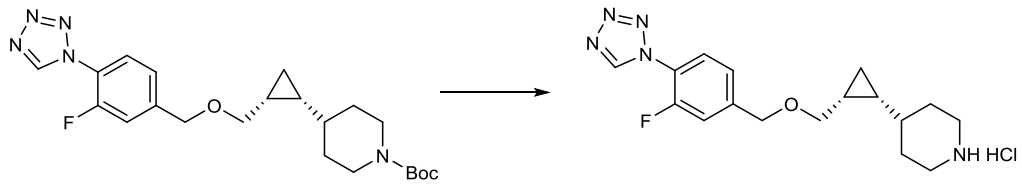
Ammonium hydroxide (14.9 mL, 107 mmol) was quickly added to a solution of tert-butyl 4-((1R,2R)-2-((4-bromo-3-fluorobenzyloxy)methyl)cyclopropyl)piperidine-1-carboxylate (Step 1 product of compound **24**, 1.58 g, 3.57 mmol), (2S,4R)-4-hydroxypyrrolidine-2-carboxylic acid (1.3 g, 7.86 mmol), Copper(I) iodide (1.36 g, 7.14 mmol), and potassium carbonate (1.53 g, 11.1 mmol) in DMSO (12 mL) that had been placed under an inert atmosphere in a sealed tube. The reaction mixture was subsequently heated at 85 ^{o}C for 48 hrs in the sealed tube. The solution was cooled to rt and diluted with EtOAc (25 mL) and water (25 mL). The layers were separated and the aqueous phase extracted with EtOAc (25 mL x 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was loaded onto a silica column (KP-Sil 50 g SNAP column, Biotage system) initially eluting with a range of 10-20% EtOAc/Hex over 6 CV, followed by a range of 25-60% EtOAc/Hex over 7 CV to give the desired compound (802 mg, 59%). MS: *m*/*z* = 379 $(M+H)^+$.

Step 2: tert-butyl 4-((1R,2R)-2-((3-fluoro-4-(1H-tetrazol-1-yl)benzyloxy)methyl)cyclopropyl)piperidine-1-carboxylate



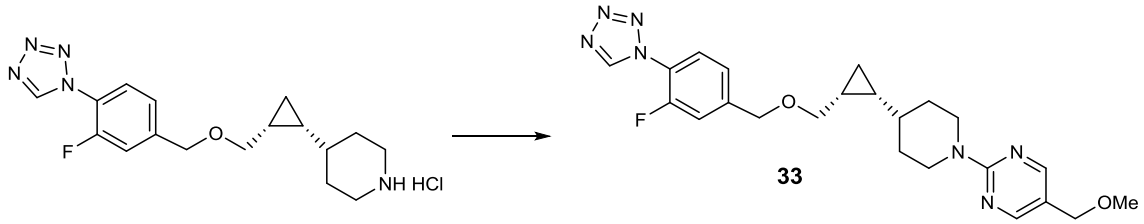
A solution of Step 1 product (400 mg, 1.06 mmol), triethyl orthoformate (0.88 mL, 5.28 mmol), and sodium azide (344 mg, 5.28 mmol) in acetic acid (4.3 mL) that had been placed under an inert atmosphere was heat in a sealed vial at 100 ^{o}C for 3 hours. The reaction mixture was cooled to rt and concentrated under reduced pressure. The residue was partitioned between EtOAc (20 mL) and water (20 mL) and the layers were cut. The aqueous phase was extracted with EtOAc (20 mL x 2) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude was loaded onto a silica column (KP-Sil 25 g SNAP column, Biotage system) eluting with a range of 20-60% EtOAc/Hex over 12 CV to give the desired compound (415 mg, 91%). MS: *m*/*z* = 432 $(M+H)^+$.

Step 3: 4-((1R,2R)-2-((3-fluoro-4-(1H-tetrazol-1-yl)benzyloxy)methyl)cyclopropyl)piperidinium chloride



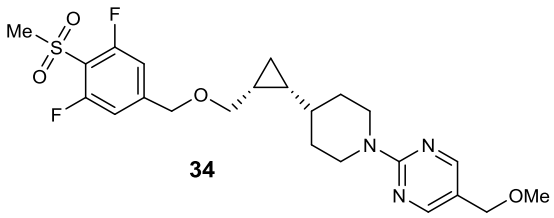
A solution of 4 M HCl in dioxane (2.4 mL, 9.62 mmol) was added to a solution of Step 2 product (415 mg, 0.962 mmol) in DCM (3 mL). This mixture was stirred at rt for 1 hr. The reaction mixture was subsequently concentrated under reduced pressure to afford the title compound (351 mg, 99%) as a crude product to be used for the next step. MS: *m*/*z* = 332 $(M+H)^+$.

Step 4: 2-(4-((1R,2R)-2-((3-fluoro-4-(1H-tetrazol-1-yl)benzyloxy)methyl)cyclopropyl)piperidin-1-yl)-5-(methoxymethyl)pyrimidine (**33**)

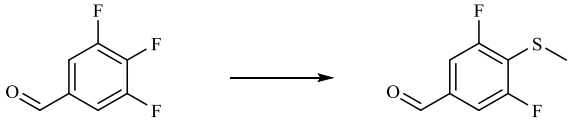


Step 3 product (45 mg, 0.122 mmol) and 2-chloro-5-(methoxymethyl)pyrimidine (22 mg, 0.136 mmol) were dissolved in DMF (0.6 mL), to which was added cesium carbonate (100 mg, 0.306 mmol). The reaction was heated at 55 ^oC overnight. The reaction mixture was cooled to rt and diluted with EtOAc (5 mL) and water (5 mL). The layers were cut and the aqueous phase extracted with EtOAc (5 mL x 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was loaded onto 2 x 2000 micron silica preparative TLC plates (uv 254 active) which were developed using 50% EtOAc/Hex as the solvent system. The desired silica (Rf = 0.4 @ 50% EtOAc/Hex) was collected and extracted to give compound **33** (32 mg, 57%). ^1H NMR (500 MHz, $CDCl_3$) δ 9.14 (s, 1H), 8.39 (s, 2H), 7.94 (t, 1H), 7.40 (dd, 2H), 4.73 (t, 2H), 4.65 (q, 2H), 4.29 (s, 2H), 3.61 (td, 2H), 3.38 (s, 3H), 2.95 (m, 2H), 1.95 (dd, 2H), 1.43 (m, 2H), 1.28 (m, 1H), 1.22 (m, 1H), 0.85-0.73 (m, 2H), 0.11 (q, 1H). MS: *m*/*z* = 454 $(M+H)^+$.

2-(4-((1R,2R)-2-(((3,5-difluoro-4-(methylsulfonyl)benzyl)oxy)methyl) cyclopropyl)piperidin-1-yl)-5-(methoxymethyl)pyrimidine (34)

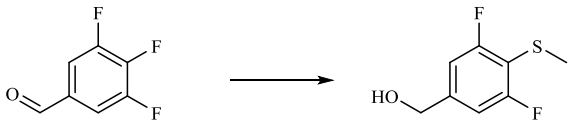


Step 1: 3,5-Difluoro-4-(methylthio)benzaldehyde



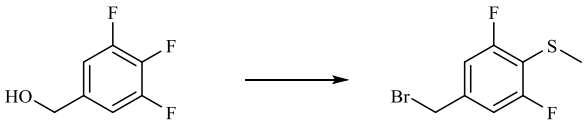
A solution of 3,4,5-trifluorobenzaldehyde (1.0 g, 6.3 mmol) in DMSO (7.8 mL) was treated with a slurry of sodium methanethiolate (0.438 g, 6.25 mmol) in DMSO (0.3 mL). The solution was heated at 125 ^{o}C for 17 min in a microwave. After it was cooled to rt, the reaction mixture was diluted with EtOAc and washed with H_2O and brine. The combined aqueous layers were back-extracted with EtOAc (3x), and the combined organic layers were dried over Na_2SO_4, filtered and evaporated in vacuo to yield a crude oil that was purified by silica gel column chromatography (0–30%, EtOAc–hexanes) to yield the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.88 (s, 1H), 7.39 (d, *J* 7.0 Hz, 2H), 2.58 (s, 3H).

Step 2: [3,5-Difluoro-4-(methylthio)phenyl]methanol



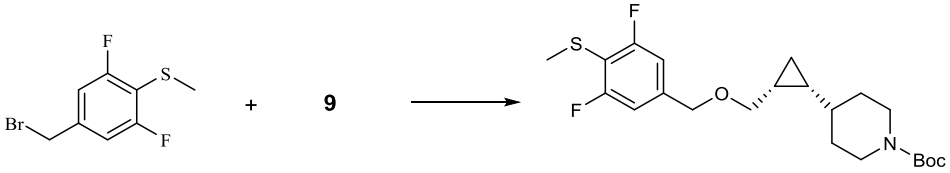
Sodium borohydride (25 mg, 0.66 mmol) was added to a 0 °C slurry of the product of step 1 (124 mg, 0.659 mmol) in methanol (4.39 mL). After 30 min the reaction mixture was warmed to room temperature. After stirring at rt for 60 min the reaction was diluted with DCM and quenched with 0.1 N HCl. After the layers were separated, the aqueous layer was back extracted with DCM (2 x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated in vacuo to yield the title compound. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.81 (d, *J* 7.5 Hz, 2H), 4.55 (s, 2H), 3.23 (s, 1H), 2.37 (s, 3H).

Step 3: 5-(Bromomethyl)-1,3-difluoro-2-(methylthio)benzene



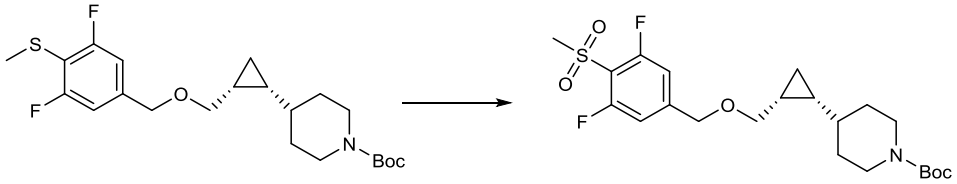
The product from step 2 was converted to the bromide according to the procedure described in step 1 for compound **2**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* 7.5 Hz, 2H), 4.82 (s, 2H), 2.88 (s, 3H).

Step 4: tert-butyl 4-((1R,2R)-2-(((3,5-difluoro-4-(methylthio)benzyl)oxy)methyl) cyclopropyl)piperidine-1-carboxylate



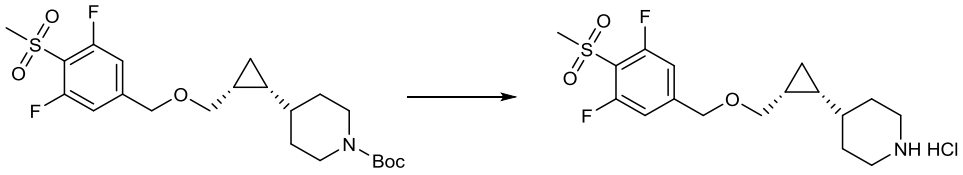
Intermediate **9** (1.7 g, 6.66 mmol) was dissolved in 20 mL of DM. The mixture was cooled to 0 °C and NaH (60% dispersion, 0.4 g, 10 mmol) was added portionwise. The mixture was stirred for 5 min and Step 3 product (1.05 equiv) in DMF (3 mL) was added dropwise. The mixture was stirred at 0 °C for 30 min and at rt overnight. The reaction was quenched with sat. $NaHCO_3$ and extracted with EtOAc. The EtOAc phase was washed with water and brine, dried over MgSO4, and concentrated. The crude material was purified by flash column (50 g SNAP, 10~50% EtOAc in hexane) to afford 2.77 g (97%) of the desired product. Rf was 0.3 at 20% EtOAc in hexanes (blue spot on CAM stain).

Step 5: tert-butyl 4-((1R,2R)-2-(((3,5-difluoro-4-(methylsulfonyl)benzyl)oxy)methyl) cyclopropyl)piperidine-1-carboxylate



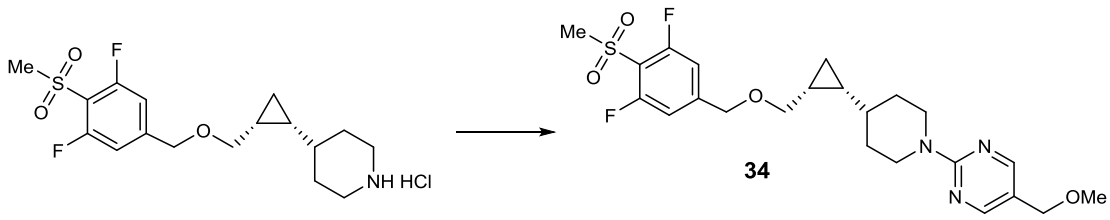
Step 4 product (2.77 g, 6.48 mmol) was dissolved in CH_2Cl_2 (40 ml) at rt, to which was added 3-chloroperoxybenzoic acid (3.91 g, 22.68 mmol). The mixture was stirred at rt overnight. LCMS showed that the starting material was consumed. The mixture was diluted with EtOAc, washed with sat. $Na_2S_2O_3$ (2 x), sat. $NaHCO_3$ (2x) and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated to dryness. The crude material was purified by flash column (50 g, SNAP, 20~50% EtOAc in hexane) to afford 1.85 g (62%) of the desired product. Rf was 0.4 at 50% EtOAc in hexanes (blue spot on CAM stain).

Step 6: 4-((1R,2R)-2-(((3,5-difluoro-4-(methylsulfonyl)benzyl)oxy)methyl) cyclopropyl)piperidine hydrochloride



Step 5 product (1.85 g, 4.03 mmol) was dissolved in DCM (20 mL) and HCl in dioxane (4 M solution, 10.60 mL, 40 mmol) was added. The mixture was stirred at rt for 1 h. The solvents were evaporated to afford 1.6 g (100%) of the desired product which was used without further purification. MS: *m/z* = 360 $(M+H)^+$.

Step 7: 2-(4-((1R,2R)-2-(((3,5-difluoro-4-(methylsulfonyl)benzyl)oxy)methyl) cyclopropyl)piperidin-1-yl)-5-(methoxymethyl)pyrimidine (**34**)



Step 6 product (100 mg, 0.25 mmol) was dissolved in DMSO (3 ml) at rt under N_2 and Cs_2CO_3 (288 mg, 0.884 mmol) was added. The mixture was stirred at rt for 5 min and 2-chloro-5-(methoxymethyl)pyrimidine in DMSO (0.5 mL) was added. The mixture was stirred at 60 ^oC overnight. The reaction mixture was diluted with EtOAc, washed with sat. NH_4Cl, dried over $MgSO_4$, and concentrated to dryness. The crude material was purified by preparative TLC developed by 60% EtOAc in hexane to afford 50.5 mg (41.5%) of compound **34**. ^1H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 2H), 7.15 (dd, 2H), 4.80-4.64 (m, 4H), 4.25 (s, 2H), 3.60 (m, 2H), 3.37 (s, 3H), 3.35 (s, 3H), 2.93-2.80 (m, 2H), 1.96-1.80 (m, 2H), 1.40-1.10 (m, 4H), 0.94-0.71 (m, 2H), 0.12-0.08 (m, 1H). MS: *m*/*z* = 482 $(M+H)^+$.

GPR119 cGMP assays. Measurement of GPR119 Signaling Using LANCE 384-well cAMP kit

Human embryonic kidney (HEK) 293 cell lines stably transfected with human GPR119 were maintained in DMEM media containing FBS, penicillin-streptomycin, HEPES, and hygromycin. For the cAMP assay, the transfected cells were harvested using a non-enzymatic cell dissociation solution (GIBCO 2672), pelleted and resuspended in stimulation buffer (DMEM, 25 mM Hepes, 0.1% BSA, pH 7.4 in the presence of 100μM phosphodiesterase inhibitors). The adenylate cyclase assay was constructed following the LANCE™ cAMP Kit (Perkin Elmer, AD0264) instructions. Briefly, cells with Alexa Fluor® 647-anti cAMP antibody were incubated with 10 point series diluted test article in stimulation buffer with a final concentration of 2.5% DMSO for 45 minutes. The reaction was stopped by incubating with the supplied detection buffer containing the europium chelate of the Eu-SA/Biotin-cAMP tracer for 3 hours. The assay was performed in duplicate in a 384 well plate for duplicate plates. Fluorescence at 665 nm was measured using a PHERAstar instrument. Basal activity was determined using a DMSO control and maximum response was defined as cAMP stimulation produced by an internal agonist control. Standard cAMP concentrations were assayed concurrently for conversion of fluorescence signal to cAMP level. The data was analyzed using 4-parameter curve fit in Microsoft Excel.

Measurement of GPR119 Signaling Using a Cyclic AMP (cAMP) Homogenous Time Resolved Fluorescence (HTRF) Assay

Chinese hamster ovary (CHO) cell lines stably transfected with the permissive guanine nucleotide binding protein alpha 15 (Gα15) and murine GPR119 were maintained in DMEM media containing

FBS, penicillin-streptomycin, puromycin, and G418 (geneticin). Alternatively, human embryonic kidney (HEK)293 Flp-In cells (Invitrogen, Carlsbad, CA) were stably transfected with a human SNP variant (S309L) of GPR119 and maintained in DMEM media containing FBS, penicillin-streptomycin, and hygromycin. Agonist activation of the GPR119 receptor was measured in receptor transfected cells described above, treated with compounds of this invention, using a commercial homogenous time resolved fluorescence (HTRF) kit for measurement of cAMP (CisBio, Bedford, MA). The assay was performed in 96-well half-volume plates (murine) or 384-well plates (human) following the manufacturers instructions. Briefly, suspended cells were incubated with a dose titration of test compound at RT for 60 min, lysed, and incubated with HTRF reagents for an additional 60 min. The plate was read using an Envision multilabel reader (Perkin Elmer) adjusted to read time resolved fluorescence and the cAMP concentrations were extrapolated from a cAMP calibration curve. GPR119 agonists will exhibit a concentration-dependent increase in intracellular cAMP. The concentration of test compound required to stimulate a half-maximal response (EC50), and efficacy as compared to an internal agonist control, was determined from a sigmoidal 4-parameter curve fit of the resulting plot of normalized activity versus compound concentration.

Protocol for pharmacokinetic studies. The pharmacokinetics of the compounds were studied in male Wistar Han rats after intravenous (IV) administration. For IV dosing at 0.5 mg/kg in rat, compounds were formulated as a solution in DMSO/PEG400/water (20/60/20, by volume). Plasma samples obtained from dosed animals were prepared for analysis by means of a single step protein precipitation technique by adding 200 µL of acetonitrile to 50 µL aliquots of individual subject samples. Samples were mixed by vortex for homogeneity and then subjected to centrifugation at 3500 rpm for 10 min. The supernatant (200 µL) was collected and injected into the LC-MS/MS for analysis. Pharmacokinetic parameters were calculated using established non-compartmental methods.

Protocol for pharmacodynamic studies. Eleven-week old, lean C57BL/6 Tac mice (n = 8 / group) were used in the oGTT studies. Overnight fasted mice were administered compound by oral gavage; vehicle: PEG400 / 23.5% HPBCD (15/85 v/v). One hour later they received an oral glucose challenge (5 g/kg). Blood glucose was measured via tail knick using a glucometer at 0, 20, 40, 60 and 120 minutes post-glucose challenge. The area under the curve (AUC) for the glucose response was calculated for each mouse. The glucose AUC of compound treated mice was compared to that of vehicle-treated mice using an unpaired Student's t-test or One-Way ANOVA where appropriate. The data is expressed as the % change of the Glucose AUC relative to vehicle.