

Piperazine Sulfonamides as Potent, Selective and Orally Available 11 β -HSD1 Inhibitors with Efficacy in the Rat Cortisone-Induced Hyperinsulinemia Model

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I. Supporting Info: Biological Assays

a. Determination of IC₅₀ against human 11β-HSD1

Compounds described herein can be tested in a cell-based assay using a stable Chinese Hamster Ovary (CHO) cell line expressing human 11β-HSD1. Cells are plated at 20,000 cells/well in 384 well plates and incubated overnight (12-16 hrs) at 37°C/5% CO₂. Cells are treated with different concentration of compound in 90 microliter serum-free media and incubated for 30 minutes at 37°C/5%CO₂. 10 μL of 5μM cortisone (final concentration 500nM) is then added to the cells and the plate is incubated at 37°C/5%CO₂ for 120 minutes. 15 microliter of media is withdrawn and amount of cortisol in the media is measured using the DiscoverX HitHunter Cortisol Assay (DiscoverX corp, CA), following manufacturer's instructions. Briefly, 15ul media is transferred to white 384 well assay plate. 5ul of anti-cortisol antibody and 10ul of ED complex is added to each well of the assay plate. The assay plate is incubated at room temperature for 60 minutes with gentle shaking. Galacton Star, Emerald Green, and chemiluminescence substrate buffer are mixed 1:5:19. The mixture is then combined in equal parts with EA complex. 20μl of the mix is added to each well of the assay plate and the assay plate is incubated at room temperature for another 60 minutes. The plate is read in Envision multilabel plate reader (Perkin Elmer, MA) in the enhanced luminescence mode. Background subtracted data is fitted to $y = a + (b/(1+x / IC_{50}))$ and IC₅₀ values are calculated using XLFit (IDBS, MA).

b. Determination of IC₅₀ against mouse 11β-HSD1

To determine the IC₅₀ against mouse 11β-HSD1, a stable CHO cell line expressing mouse 11β-HSD1 is used and the above procedure is followed.

c. Determination of IC₅₀ against mouse 11β-HSD1 in the presence of serum

To determine the IC₅₀ against mouse 11β-HSD1 in the presence of serum, 10% defibrinated, delipidized, charcoal stripped human serum (Seracare Life Sciences, CA) was added during the incubation with compound and cortisone. The above procedure is followed.

d. Evaluation of inhibition of human 11β-HSD2

To determine the potency of compounds against mouse 11β-HSD2, a stable CHO cell line expressing human 11β-HSD2 is generated. Cells are plated at 20,000 cells/well in 96 well plates and incubated overnight (12-16 hrs) at 37°C/5% CO₂. Cells are treated with different concentration of compound in 90 microliter serum-free media and incubated for 30 minutes at 37°C/5%CO₂. 10 μl of 500nM [³H]-Cortisone (ARC Inc, MO) is then added to each well of the plate (final concentration = 50 nM). The plate is incubated for 120 minutes. Cortisone and Cortisol are separated on a PRP-1 (Hamilton Inc, NV) on an Agilent 1100 high pressure liquid chromatography system with a 500TR

flow scintillation analyzer (Perkin Elmer, MA). Carbenoxolone (Sigma, MO) is used as a control 11 β -HSD2 inhibitor.

e. Evaluation of 11 β -HSD1 inhibitors in mouse ex vivo assay

To characterize the inhibitors of 11 β -HSD1, inhibitors were tested in mouse ex vivo assay. Male, C57Bl6 mice 8-10 weeks of age were grouped based on body weight (Taconic Farms on standard chow diet). All mice were orally dosed and sacrificed 2 to 5 hours after dosing (n=4). Liver and epididymal fat tissues were collected and frozen in liquid nitrogen. Tissue 11 β -HSD1 ex vivo assay measures the conversion of [³H]-cortisone to [³H]-cortisol and percent inhibition of 11 β -HSD1 activity in the liver was determined in reference to vehicle treated mice. 50-60 mg of frozen liver tissues were placed in 48-well plates (kept on dry ice). The tissues/48-well plates were thawed at room temperature for 15 minutes. 250 μ l of PBS were added to each well and incubated for additional 15 minutes at room temperature. 48-well plate was placed on a 37 °C Eppendorf Thermomixer R plate shaker and 250 μ l of PBS containing 2.5 μ Ci of [³H]-cortisone was added to each well and allowed to incubate for 30 minutes. The reaction was stopped by adding 50 μ l of 10% TFA. 20 μ l of reaction aliquot was analyzed by HPLC and percent conversion of [³H]-cortisone to [³H]-cortisol determined (t-test, *P < 0.05).

f. Evaluation of 11 β -HSD1 inhibitors in rat ex vivo assay

Male, SD rat 10 weeks of age (Taconic Farm) were used to evaluate 11 β -HSD1 inhibitors. All inhibitors were orally dosed and rats (n=3 to 4) were sacrificed 3 to 5 hours after dosing. The rat ex vivo assay was carried out as described above for mice except for following modifications. The activity of 11 β -HSD1 in rat liver tissue was considerably higher than in mice liver tissue therefore the reaction time was decreased to 15 minutes.

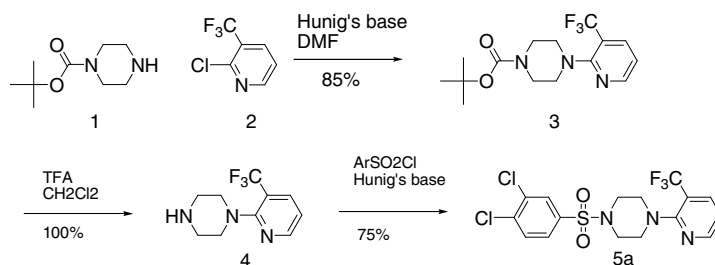
g. Evaluation of 11 β -HSD1 inhibitors in rat cortisone induced hyperinsulinemia model

Male, SD rat 12-14 weeks of age (Taconic Farm) were used to evaluate the inhibitors in 11 β -HSD1 mechanism based disease model. The rats were grouped based on body weight. In order to induce hyperinsulinemia in all rats, cortisone was provided in the drinking water at a dose of 1.5 mg/ml for 7 days. One hour prior to the initiation of cortisone treatment (10 am), rats were orally dosed with 11 β -HSD1 inhibitors or vehicle (0.5 % methyl cellulose and 2 % tween) and for the following 7 days all rats were dosed twice a day (BID) and were allowed to have free access to cortisone/water. Body weight, food and liquid intake were recorded on day 6 and on day 7 rats were bleed (tail) and serum was collected.

II. Supporting Info: Chemistry

All reagents and solvents were of commercial quality and used without further purification. Column chromatography was performed using Merck silica gel 60 (230-400 mesh). Proton nuclear magnetic spectroscopy ^1H NMR spectra (400 MHz) were obtained on a Bruker 400 spectrometer. Chemical shifts are reported in parts per million relative to Me_4Si as internal standard. Low-resolution mass spectra (MS) were obtained using a Micromass Platform Electrospray Ionization Quadrupole mass spectrometer. High-resolution exact mass measurements (HRMS) were performed on a Bruker ApexIII 7T FT/ICR/MS. All intermediates were characterized by ^1H NMRs. All new final SAR compounds were determined to be consistent with proposed structure by ^1H NMR, MS, HRMS and were greater than 95% pure in two solvent systems (HPLC Method 1: H_2O - CH_3CN and HPLC Method 2: H_2O - MeOH) as determined using an Agilent 1100 HPLC instrument on a C18 column.

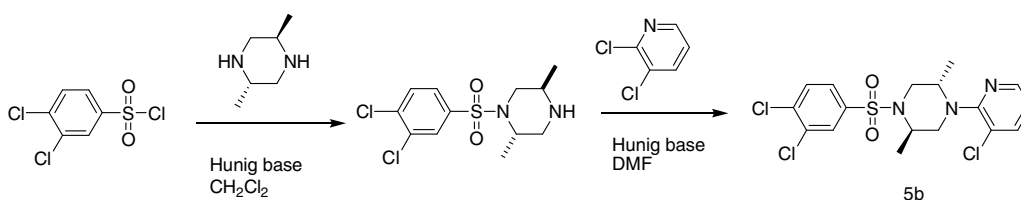
a. Synthesis of piperazine sulfonamides with pyridine at right hand side



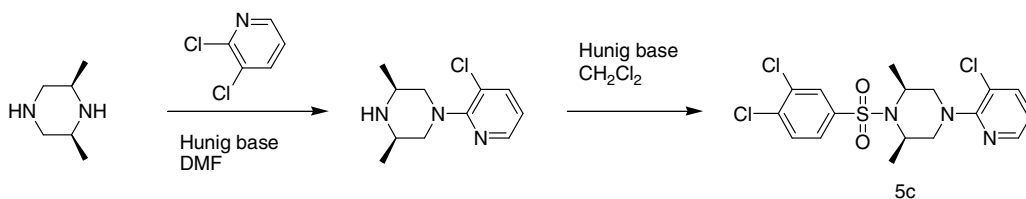
1-[(3,4-dichlorophenyl)sulfonyl]-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine (5a). *tert*-butyl piperazine-1-carboxylate **1** (1.0g, 5.37 mmol) and 2,3-dichloropyridine **2** (795 mg, 5.37 mmol) charged to a microwave vial was added with diisopropylethylamine (2.34 mL, 13.42 mmol) and DMF (1.0 mL). The reaction mixture was subjected to microwave irradiation at 165°C for 30 minutes. Reaction mixture was partitioned between EtOAc and water, organic layer was washed with brine and dried over MgSO_4 . The crude product obtained by solvent evaporation was purified via flash column chromatography. *tert*-butyl 4-(3-chloropyridin-2-yl)piperazine-1-carboxylate **3** was obtained in 85% yield (1.34 g) as yellow oil. ^1H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.49 (s, 9 H) 3.26 - 3.34 (m, 4 H) 3.53 - 3.64 (m, 4 H) 6.86 (dd, $J=7.71, 4.67$ Hz, 1 H) 7.60 (dd, $J=7.83, 1.77$ Hz, 1 H) 8.18 (dd, $J=4.80, 1.77$ Hz, 1 H); HRMS: calcd for $\text{C}_{14}\text{H}_{20}\text{ClN}_3\text{O}_2 + \text{H}^+$, 298.13168; found (ESI-FTMS, $[\text{M}+\text{H}]^{1+}$), 298.1319; HPLC Method 1: room temperature, 6.05 min, 97.69%, HPLC Method 2: room temperature, 7.08 min, 98.91%.

To a clear solution of *tert*-butyl 4-(3-chloropyridin-2-yl)piperazine-1-carboxylate **3** in anhydrous dichloromethane (25 mL) was added TFA (25 mL) dropwise. The yellow solution was stirred at room temperature for 2.5 hour. Reaction was complete as determined by TLC. TFA was azeotroped with dichloroethane to give 1-(3-chloropyridin-2-yl)piperazine **4** in quantitative yield (1.265 g). ^1H NMR (400 MHz, DMSO-D_6) δ ppm 3.19 - 3.32 (m, 4 H) 3.39 - 3.51 (m, 4 H) 7.10 (dd, $J=7.83, 4.55$ Hz, 2 H) 7.87 (dd, $J=7.83, 1.52$ Hz, 2 H) 8.27 (dd, $J=4.80, 1.52$ Hz, 2 H) 8.87 (s, 1 H).

To a stirred solution of 1-(3-chloropyridin-2-yl)piperazine **4** (316 mg, 1.6 mmol) in anhydrous dichloromethane (5 mL) was added diisopropylethylamine (0.975 mL, 5.6 mmol) then 3,4-dichlorobenzene-1-sulfonyl chloride (393 mg, 1.6 mmol). The mixture was stirred at room temperature for 1.5 hour. Reaction was complete as determined by TLC. The reaction mixture was purified with flash column chromatography to yield 1-[(3,4-dichlorophenyl)sulfonyl]-4-[3-(trifluoromethyl)pyridin-2-yl]piperazine **5a** in 75% yield (527 mg) as white solid. ¹H NMR (400 MHz, DMF) δ ppm 3.41 - 3.50 (m, 4 H) 3.49 - 3.57 (m, 4 H) 8.06 (dd, *J*=8.46, 2.15 Hz, 1 H) 8.21 (s, 1 H) 8.26 (d, *J*=2.02 Hz, 1 H) 8.30 (dd, *J*=7.83, 1.52 Hz, 1 H) 8.75 (d, *J*=4.80, 1.26 Hz, 1 H); HRMS: calcd for C₁₆H₁₄Cl₂F₃N₃O₂S + H⁺, 440.02086; found (ESI-FTMS, [M+H]¹⁺), 440.0214. HPLC Method 1: room temperature, 6.78 min, 99.05%. HPLC Method 2: room temperature, 7.48 min, 99.44%.

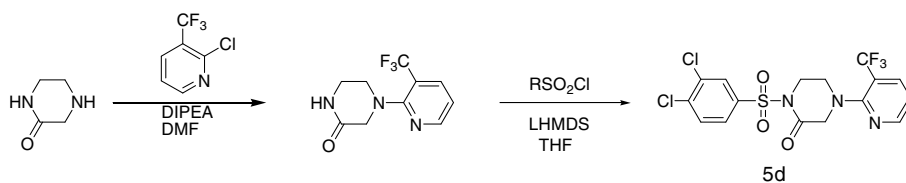


1-(3-chloropyridin-2-yl)-4-[(3,4-dichlorophenyl)sulfonyl]-2,5-dimethylpiperazine (5b). To a stirred solution of 3,4-dichlorobenzene-1-sulfonyl chloride (840 mg, 3.42 mmol) and 2,5-dimethylpiperazine (1.171 g, 10.26 mmol) in anhydrous dichloromethane (5 mL) was added diisopropylethylamine (1.2 mL, 6.84 mmol). The mixture was stirred overnight at room temperature. Reaction was complete as determined by TLC. The reaction mixture was diluted with dichloromethane, washed with water and dried over MgSO₄. After solvent evaporation crude product was treated with ethyl acetate /hexanes. Solid impurity was filtered of and the filtrate was concentrated to afford 1-(3-chloropyridin-2-yl)-4-[(3,4dichlorophenyl)sulfonyl]-2,5-dimethylpiperazine in quantitative yield. It was carried to the next step without further purification. 1-(3-chloropyridin-2-yl)-4-[(3,4dichlorophenyl)sulfonyl]-2,5-dimethylpiperazine (1.04g, 3.22 mmol), 2,3-dichloropyridine (476.5 mg, 3.22 mmol), diisopropylethylamine (1.4 mL, 8.05 mmol) and DMF (1.2 mL) were charged to a microwave vial and the mixture was irradiated at 200°C for 1 hour. Reaction was complete as determined by TLC. The reaction mixture was diluted with ethyl acetate and washed with water. After solvent evaporation crude product was purified with flash column chromatography to yield 1-(3-chloropyridin-2-yl)-4-[(3,4-dichlorophenyl)sulfonyl]-2,5- dimethylpiperazine in 2 % yield (27 mg) as yellow solid. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.08 (d, *J*=6.57 Hz, 3 H) 1.12 (d, *J*=6.57 Hz, 3 H) 3.26 (d, *J*=13.39 Hz, 1 H) 3.44 - 3.52 (m, 1 H) 3.54 - 3.66 (m, 2 H) 4.14 - 4.37 (m, 2 H) 6.84 (dd, *J*=7.58, 4.80 Hz, 1 H) 7.50 - 7.70 (m, 3 H) 7.93 (d, *J*=2.02 Hz, 1 H) 8.15 (dd, *J*=4.80, 1.77 Hz, 1 H); HRMS: calcd for C₁₇H₁₈Cl₃N₃O₂S + H⁺, 434.02580; found (ESI-FTMS, [M+H]¹⁺), 434.028; HPLC Method 1: room temperature, 7.14 min, 99.62%, HPLC Method 2: room temperature, 7.68 min, 99.56%.



4-(3-chloropyridin-2-yl)-1-[(3,4-dichlorophenyl)sulfonyl]-2,6-dimethylpiperazine (5c). 2,6-dimethylpiperazine (291 mg, 2.55 mmol) and 2,3-dichloropyridine (377 mg, 2.55 mmol) were charged to a microwave vial, dissolved in DMF (0.25 mL) and added with diisopropylethylamine (1.1 mL, 6.38 mmol). The reaction mixture was irradiated at 165°C for 30 minutes. The reaction was complete as determined by TLC. After solvent removal the crude product was purified via flush column chromatography to afford 1-(3-chloropyridin-2-yl)-3,5-dimethylpiperazine in 64.4% yield (370 mg). ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.18 (d, *J*=6.32 Hz, 6 H) 2.40 - 2.63 (m, 2 H) 3.02 - 3.24 (m, 2 H) 3.66 - 3.82 (m, 2 H) 6.83 (dd, *J*=7.58, 4.80 Hz, 1 H) 7.58 (dd, *J*=7.71, 1.64 Hz, 1 H) 8.18 (dd, *J*=4.80, 1.77 Hz, 1 H).

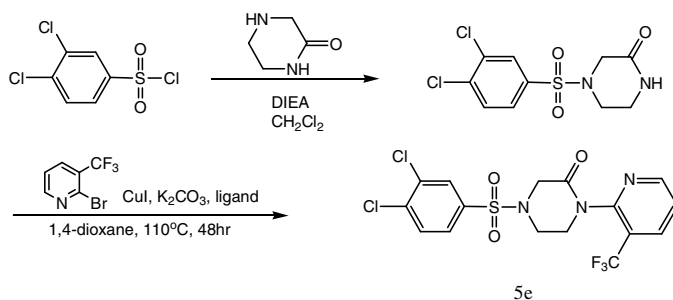
1-(3-chloropyridin-2-yl)-3,5-dimethylpiperazine (370 mg, 1.644 mmol) was dissolved in anhydrous dichloromethane (6 mL) added with 3,4-dichlorobenzene sulfonyl chloride (509 mg, 1.97 mmol) and diisopropylethylamine (0.72 mL, 4.11 mmol). The reaction mixture thus prepared was stirred overnight at room temperature. The reaction was complete as determined by TLC. It was purified via flush column chromatography to afford 4-(3-chloropyridin-2-yl)-1-[(3,4-dichlorophenyl)sulfonyl]-2,6-dimethylpiperazine in 13% yield (110 mg) as a sticky solid. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.60 (d, *J*=6.82 Hz, 6 H) 2.69 (dd, *J*=12.38, 4.29 Hz, 2 H) 3.56 (d, *J*=12.38 Hz, 2 H) 4.01 - 4.36 (m, 2 H) 6.90 (dd, *J*=7.83, 4.80 Hz, 1 H) 7.56 (d, *J*=8.34 Hz, 1 H) 7.61 (d, *J*=6.06 Hz, 1 H) 7.66 (d, *J*=8.34 Hz, 1 H) 7.94 (s, 1 H) 8.15 (d, *J*=6.57 Hz, 1 H); HRMS: calcd for C₁₇H₁₈Cl₃N₃O₂S + H⁺, 434.02580; found (ESI-FTMS, [M+H]¹⁺), 434.0272; HPLC Method 1: room temperature, 7.21 min, 100%, HPLC Method 2: room temperature, 7.78 min, 100%.



1-[(3,4-dichlorophenyl)sulfonyl]-4-[3-(trifluoromethyl)pyridin-2-yl]piperazin-2-one (5d). To a solution of piperazin-2-one (1.0 g, 10.0 mmol) in DMF (1.0 mL) was added 2-chloro-3-trifluoromethyl pyridine (2.0 g, 11.0 mmol) and DIPEA (2.0 mL, 12.0 mmol). The reaction mixture was heated to 150°C under microwave conditions for one hour, after which maximum attainable conversion to desired product was judged complete by

LCMS. The crude reaction mixture was quenched with H₂O (5 mL), resulting in precipitation of the desired product, in >75% purity. The crude solid was then dissolved in ethyl acetate (25 mL) and washed with brine (2 x 10 mL). The organic layer was dried over Na₂SO₄, decanted, and concentrated in vacuo, and the resultant crude oil was purified via normal phase SiO₂ column chromatography using a 50%-100% ethyl acetate / hexanes solvent gradient. The desired product was isolated in 30% yield (720 mg). ¹H NMR (400 MHz, DMSO-D₆) δ ppm 3.21 - 3.28 (m, 2 H) 3.39 - 3.46 (m, 2 H) 3.76 (s, 2 H) 7.23 (dd, *J*=7.58, 5.05 Hz, 1 H) 7.96 (s, 1 H) 8.11 (dd, *J*=7.83, 1.77 Hz, 1 H) 8.54 (dd, *J*=4.80, 1.52 Hz, 1 H); LCMS: calcd for C₁₀H₁₀F₃N₃O + H⁺, 246.08; found ([M+H]¹⁺), 246.19; HPLC Method 1: room temperature, 4.16 min, 99.30%. HPLC Method 2: room temperature, 4.12 min, 95.92%.

A solution of 4-(3-(trifluoromethyl)pyridin-2-yl)piperazin-2-one (150 mg, 0.61 mmol) in anhydrous THF (2.0 mL) was cooled to -78°C, followed by dropwise addition of LHMDS (0.92 mL, 0.92 mmol (1.0 M in THF)). The reaction was allowed to stir five minutes after which a solution of 3,4-dichloro-benzenesulfonyl chloride in anhydrous THF (123 μL, 0.79 mmol in 1mL) was added dropwise. The reaction mixture was allowed to stir at -78°C for approximately two hours, after which it was judged complete by TLC. The reaction was quenched with excess H₂O (10 mL), extracted into ethyl acetate (3 x 10 mL), and finally washed with aqueous NaHCO₃ (2 x 10 mL). The organic layers were combined and dried over Na₂SO₄, decanted, and concentrated in vacuo. The resultant crude oil was purified via normal phase SiO₂ column chromatography using a 5%-20% EA/Hex solvent gradient, affording 271 mg of the desired sulfonamide **5e** in 98% yield. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 3.51 - 3.73 (m, 2 H) 3.86 - 4.05 (m, 4 H) 7.16 (dd, *J*=7.83, 4.80 Hz, 1 H) 7.64 (d, *J*=8.59 Hz, 1 H) 7.82 - 8.01 (m, 2 H) 8.09 (d, *J*=2.27 Hz, 1 H) 8.35 (dd, *J*=4.80, 1.77 Hz, 1 H); LCMS: calcd for C₁₆H₁₂Cl₂F₃N₃O₃S + H⁺, 452.99; found ([M+H]¹⁺), 453.89; HPLC Method 1: room temperature, 7.93 min, 100%, HPLC Method 2: room temperature, 7.50 min, 100%.

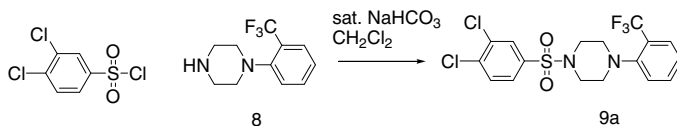


4-(3,4-dichloro-benzenesulfonyl)-1-(3-trifluoromethyl-pyridin-2-yl)-piperazin-2-one (5e). To a stirred solution of piperazine-2-one (326.2 mg, 3.3 mmol) and 3,4-dichlorobenzene-sulfonyl chloride (800 mg, 3.3 mmol) in anhydrous dichloromethane (15 mL) was added diisopropylethylamine (1.42 mL, 8.2 mmol) slowly. The mixture was

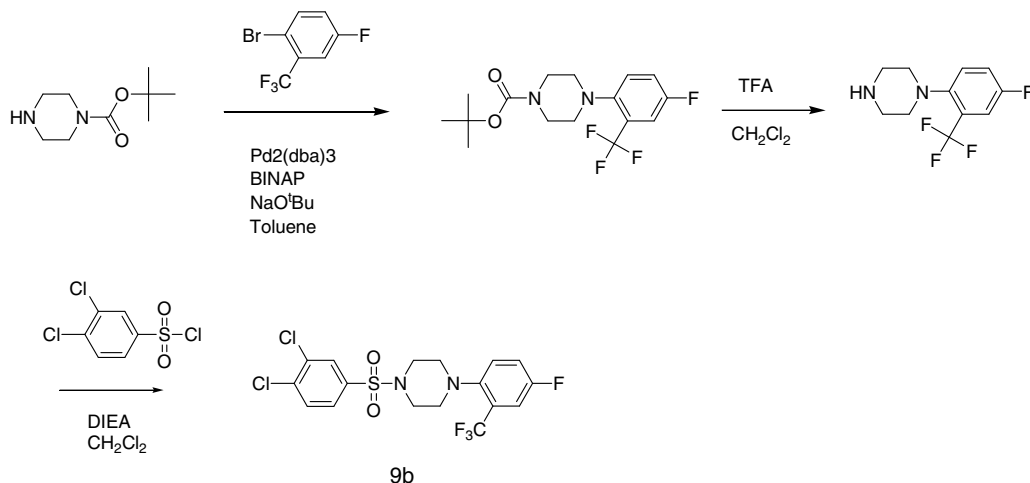
stirred for 15 min at room temperature. Reaction was complete as determined by TLC. The reaction mixture was filtered, washed with dichloromethane to give 4-(3,4-dichlorobenzenesulfonyl)-piperazin-2-one as white solid (912 mg, 90.3% yield). ¹H NMR (400 MHz, DMSO-D6) δ ppm 3.17 - 3.24 (m, 2 H) 3.25 - 3.30 (m, 2 H) 3.59 (s, 2 H) 7.79 (dd, *J*=8.46, 2.15 Hz, 1 H) 7.94 (d, *J*=8.34 Hz, 1 H) 8.06 (d, *J*=2.02 Hz, 1 H) 8.08 (s, 1 H).

An oven-dried microwave vial was charged with of of 4-(3,4-dichlorobenzenesulfonyl)-piperazin-2-one (150 mg, 0.49 mmol), 2-bromo-3-trifluoromethyl pyridine (164.5 mg, 0.73 mmol), powdered anhydrous potassium carbonate (134.1 mg, 0.97 mmol), and CuI (9.2 mg, 0.049mmol). The vial was purged with N₂. Anhydrous 1,4-dioxane (1.8 mL) was added, followed by 5.2 μL (0.049 mmol) of N, N'-dimethyl-1,2-ethylenediamine. The blue suspension was heated in a 110°C oil bath for 48 hr. After cooling to room temperature, the brown suspension was diluted with H₂O and EtOAc. The layers were separated, and the aqueous layer was washed with EtOAc (2x). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by prep HPLC to provide 21 mg (10%) of 4-(3,4-dichlorobenzenesulfonyl)-1-(3-trifluoromethyl-pyridin-2-yl)-piperazin-2-one **5f** as an off-white solid. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 3.38 - 3.47 (m, 1 H) 3.57 - 3.65 (m, 1 H) 3.68 - 3.76 (m, 1 H) 3.82 - 3.89 (m, 1 H) 3.98 - 4.08 (m, 2 H) 7.46 - 7.53 (m, 1 H) 7.64 - 7.72 (m, 2 H) 7.93 (d, *J*=1.77 Hz, 1 H) 8.09 (dd, *J*=7.96, 1.39 Hz, 1 H) 8.75 (dd, *J*=4.80, 1.26 Hz, 1 H); HRMS: calcd for C₁₆H₁₂Cl₂F₃N₃O₃S + H⁺, 454.00013; found (ESI-FTMS, [M+H]¹⁺), 454; HPLC Method 1: room temperature, 5.48 min, 100%, HPLC Method 2: room temperature, 6.42 min, 97.52%.

b. Synthesis of piperazine sulfonamides with benzene ring at right hand side



1-[(3,4-dichlorophenyl)sulfonyl]-4-[2-(trifluoromethyl)phenyl]piperazine (9a). To a stirred solution of 1-(2-(trifluoromethyl)phenyl)piperazine (100 mg, 0.43 mmol) and 3,4-dichlorobenzene-1-sulfonyl chloride (130 mg, 0.52 mmol) in anhydrous dichloromethane (3 mL) was added sat. NaHCO₃ (3 mL). The mixture was stirred at room temperature overnight. Reaction was complete as determined by TLC. The reaction mixture was diluted with dichloromethane, washed with water and then brine. Organic layer was dried over MgSO₄. The reaction mixture was purified via flash column chromatography to yield 186 mg of 1-[(3,4-dichlorophenyl)sulfonyl]-4-[2-(trifluoromethyl)phenyl]piperazine in 82% yield. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 3.02 (t, *J*=4.80 Hz, 4 H) 3.20 (s, 4 H) 7.35 (d, *J*=8.08 Hz, 1 H) 7.59 - 7.64 (m, 3 H) 7.65 - 7.69 (m, 1 H) 7.72 (d, *J*=8.59 Hz, 1 H) 8.14 (d, *J*=2.27 Hz, 1 H); HRMS: calcd for C₁₇H₁₅Cl₂F₃N₂O₂S + H⁺, 439.02561; found (ESI-FTMS, [M+H]¹⁺), 439.0251; HPLC Method 1: room temperature, 7.93 min, 99.1%, HPLC Method 2: room temperature, 8.36 min, 98%.

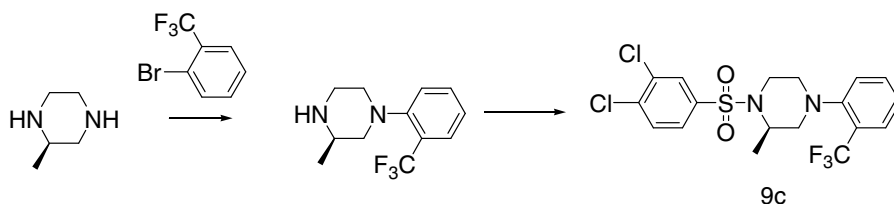


1-[(3,4-dichlorophenyl)sulfonyl]-4-[4-fluoro-2-(trifluoromethyl)phenyl]piperazine (9b). A mixture of tert-butyl piperazine-1-carboxylate 1.04 g, (5.6 mmol), 2-bromo, 5-fluoro benzotrifluoride (1.21 g, 5.0 mmol), tris(dibenzylideneacetone)dipalladium (0) (45.8 mg, 0.05 mmol), rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (93.4 mg, 0.15 mmol) and sodium tert-butoxide (600 mg, 6.25 mmol) were charged to a microwave vial. Toluene (10.0 mL) was introduced under nitrogen atmosphere and the reaction mixture was irradiated at 110°C for 30 minutes. Reaction was complete as determined by TLC. The reaction was repeated four times. Reaction mixtures were combined, diluted with ethyl acetate, washed with water, saturated brine then dried over MgSO₄ and concentrated. The crude product was purified via flash column chromatography to yield tert-butyl 4-(4-fluoro-2-(trifluoromethyl)phenyl)piperazine-1-carboxylate in quantitative yield (6.8 g) as yellow oil. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.49 (s, 9 H) 2.82 (t, *J*=4.80 Hz, 4 H) 3.55 (s, 4 H) 7.15 - 7.26 (m, 1 H) 7.27 - 7.39 (m, 2 H); HPLC Method 1: room temperature, 7.00 min, 96.34%. HPLC Method 2: room temperature, 7.61 min, 97.90%.

To a stirred solution of tert-butyl 4-(4-fluoro-2-(trifluoromethyl)phenyl)piperazine-1-carboxylate (6.8 g, 19.5 mmol) in anhydrous dichloromethane (90 mL) was added TFA (45 mL) dropwise at 0°C. The reaction mixture was stirred at 0°C for 15 minutes then the cooling bath was removed and it was allowed to stir at room temperature for 2 hours. Reaction was complete as determined by TLC. Most of TFA was azeotroped with dichloroethane. The residue was then diluted with dichloromethane and washed with saturated Na₂CO₃ (aq.). Organic layer was dried over MgSO₄. Solvent evaporation afforded 1-(4-fluoro-2-(trifluoromethyl)phenyl)piperazine in 80% yield (3.86 g) as light brown oil. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 2.78 - 2.90 (m, 4 H) 2.96 - 3.04 (m, 4 H) 7.18 - 7.25 (m, 1 H) 7.29 - 7.42 (m, 2 H).

To a stirred solution of 1-(4-fluoro-2-(trifluoromethyl)phenyl)piperazine (386 mg, 1.555 mmol) and 3,4-dichlorobenzene-1-sulfonyl chloride (381.8 mg, 1.555 mmol) in

anhydrous dichloromethane (3 mL) was added diisopropylethylamine (1.35 mL, 7.775 mmol). The mixture was stirred at room temperature for 30 minutes. Reaction was complete as determined by TLC. The reaction mixture was diluted with dichloromethane, washed with saturated Na₂CO₃ (aq.), water then brine. Organic layer was dried over MgSO₄. The reaction mixture was purified via flash column chromatography to yield 1-[(3,4-dichlorophenyl)sulfonyl]-4-[4-fluoro-2-trifluoromethylphenyl]piperazine **9b** in 76% yield (538 mg) as white solid. ¹H NMR (400 MHz, DMSO-D₆) δ ppm 2.93 (t, *J*=4.67 Hz, 4 H) 3.08 (s, 4 H) 7.47 - 7.61 (m, 2 H) 7.68 - 7.82 (m, 2 H) 7.94 - 8.04 (m, 2 H); HRMS: calcd for C₁₇H₁₄Cl₂F₄N₂O₂S + H⁺, 457.01619; found (ESI-FTMS, [M+H]¹⁺), 457.0168; HPLC Method 1: room temperature, 7.21 min, 99.42%. HPLC Method 2: room temperature, 7.77 min, 99.76%.

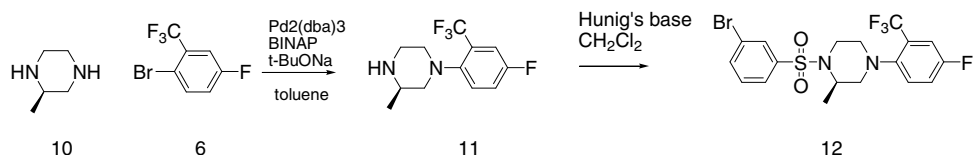


(2R)-1-[(3,4-dichlorophenyl)sulfonyl]-2-methyl-4-[2-(trifluoromethyl)phenyl]piperazine (9c). A mixture of (R)-2-methyl-piperazine (300 mg, 2.99 mmol), 2-bromo benzotrifluoride (612 mg, 2.72 mmol), tris(dibenzylideneacetone)dipalladium (0) (24.72 mg, 0.027 mmol), rac-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (51.06 mg, 0.082 mmol) and sodium tert-butoxide (326.77 mg, 3.4 mmol) were charged to a microwave vial. Toluene (3.0 mL) was introduced under nitrogen atmosphere and the reaction mixture was irradiated at 110°C for 30 minutes. Reaction was complete as determined by TLC. The reaction was repeated at (R)-2-methyl-piperazine (1.0 g, 9.98 mmol). Reaction mixtures were combined, diluted with dichloromethane, washed with water, saturated brine then dried over Na₂SO₄ and concentrated. The crude product was purified via flash column chromatography to yield (R)-3-methyl-1-(2-trifluoromethyl-phenyl)-piperazine as yellow oil (1.23 g, 39.6% yield). ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.07 (d, *J*=6.32 Hz, 3 H) 2.41 - 2.51 (m, 1 H) 2.74 - 2.84 (m, 1 H) 2.90 - 2.98 (m, 2 H) 3.00 - 3.13 (m, 3 H) 7.18 - 7.25 (m, 1 H) 7.35 (d, *J*=8.08 Hz, 1 H) 7.47 - 7.55 (m, 1 H) 7.62 (d, *J*=7.83 Hz, 1 H).

To a stirred solution of (R)-3-methyl-1-(2-trifluoromethyl-phenyl)-piperazine (90 mg, 0.37 mmol) and 3,4-dichloro-benzenesulfonyl chloride (90.8 mg, 0.37 mmol) in anhydrous dichloromethane (1.5 mL) was added diisopropylethylamine (0.13 mL, 0.74 mmol). The mixture was stirred at room temperature for over night. Reaction was complete as determined by TLC. The reaction mixture was purified via flash column chromatography to yield (2R)-1-[(3,4-dichlorophenyl)sulfonyl]-2-methyl-4-[2-(trifluoromethyl)phenyl]piperazine in 92.3% yield (154.9 mg) as off-white oil. ¹H NMR (400 MHz, CHLOROFORM-D) δ ppm 1.20 - 1.29 (m, 3 H) 2.74 - 2.86 (m, 2 H) 2.93 - 3.12 (m, 2 H) 3.32 - 3.43 (m, 1 H) 3.71 (d, *J*=12.63 Hz, 1 H) 4.18 - 4.27 (m, 1 H) 7.23 - 7.32 (m, 3 H) 7.53 (t, *J*=7.83 Hz, 1 H) 7.59 - 7.70 (m, 3 H) 7.94 (d, *J*=2.02 Hz, 1 H);

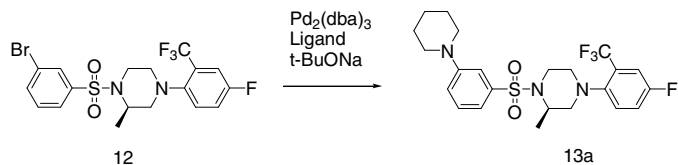
HRMS: calcd for $C_{18}H_{17}Cl_2F_3N_2O_2S + H^+$, 453.04126; found (ESI-FTMS, $[M+H]^{1+}$), 453.0417; HPLC Method 1: room temperature, 7.36 min, 96.36%, HPLC Method 2: room temperature, 7.85min, 96.64%.

c. Synthesis of 2-methylpiperazine sulfonamides

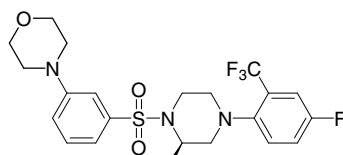


(2R)-1-[(3-bromophenyl)sulfonyl]-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methylpiperazine (12). A mixture of **10** (7.92 g, 79.07 mmol), **6** (18.3 g, 75.3 mmol), BINAP (2.81 g, 4.52 mmol), tBuONa (10.86 g, 112.95 mmol) and $Pd_2(dba)_3$ (2.07 g, 2.259 mmol) was mixed and purged with N_2 . Anhydrous toluene (200 mL) was added and purged with N_2 again. The resultant mixture was heated in an oil bath at $100\text{ }^\circ\text{C}$ under N_2 for 5 hours. After cooling, diluted with EtOAc (200 mL), filtered through a pad of Celite and washed with EtOAc (200 mL). The combined organic layer was washed with aq. $NaHCO_3$. The aqueous layer was back extracted with EtOAc (2 x 100 mL). The combined organic layer was dried over Na_2SO_4 . The crude product was purified on SiO_2 gel column eluted with 0-25% MeOH in EtOAc to give **11** as a light yellow oil (14.5 g, 73%).

To a solution of (R)-1-(4-fluoro-2-(trifluoromethyl)phenyl)-3-methylpiperazine **11** (5 g, 19 mmol) in DCM (50 mL) at $0\text{ }^\circ\text{C}$ was added DIPEA (6.62 mL, 38 mmol) and 3-bromophenylsulfonyl chloride (3.29 mL, 22.8 mmol). The resultant mixture was stirred at room temp. overnight, then washed with aq. $NaHCO_3$. The aqueous layer was extracted with DCM (2 x 50 mL). The combined organic layer was dried over Na_2SO_4 . The crude product was purified on SiO_2 gel column eluted with 5-15% EtOAc in hexanes to give **12** as a white solid (7.9g, 86%). 1H NMR (400 MHz, $CHLOROFORM-d$) δ ppm 1.24 (d, $J=6.82$ Hz, 3 H) 2.60 - 2.87 (m, 2 H) 2.87 - 2.98 (m, 1 H) 3.05 (dd, $J=11.12, 3.54$ Hz, 1 H) 3.39 (dd, $J=12.13, 9.09$ Hz, 1 H) 3.75 (d, $J=12.88$ Hz, 1 H) 4.26 (d, $J=6.82$ Hz, 1 H) 7.21 - 7.34 (m, 2 H) 7.36 (dd, $J=8.72, 2.91$ Hz, 1 H) 7.44 (t, $J=7.96$ Hz, 1 H) 7.70 - 7.77 (m, 1 H) 7.78 - 7.83 (m, 1 H) 8.02 (t, $J=1.77$ Hz, 1 H); HRMS: calcd for $C_{18}H_{17}BrF_4N_2O_2S + H^+$, 481.02030; found (ESI-FTMS, $[M+H]^{1+}$), 481.0208; HPLC Method 1: room temperature, 7.29 min, 100%, HPLC Method 2: room temperature, 7.75 min, 99.22%.

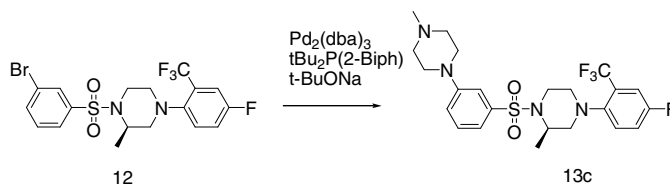


(2R)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methyl-1-[(3-piperidin-1-yl)phenyl]sulfonylpiperazine (13a) A mixture of (2R)-1-[(3-bromophenyl)sulfonyl]-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methylpiperazine (193 mg, 0.4 mmol), piperidine (0.047 mL, 0.48 mmol, 1.2 eq.), Di-t-Bu-biphenylphosphine (12 mg, 0.04 mmol, 0.1 eq.), t-BuONa (112 mg, 1.12 mmol, 2.8 eq.) and Pd₂(dba)₃ (18.2 mg, 0.02 mmol, 0.05 eq.) was mixed and purged with N₂. Anhydrous toluene (4 mL) was added and purged with N₂ again. The resultant mixture was heated in an oil bath at 100 °C under N₂ for 3 hours. After cooling, diluted with EtOAc (20 mL), filtered through a pad of Celite and washed with EtOAc (20 mL). The combined organic layer was washed with aq. NaHCO₃. The aqueous layer was back extracted with EtOAc (2 x 10 mL). The combined organic layer was dried over Na₂SO₄. The crude product was purified on SiO₂ gel column eluted with EtOAc/Hexane to give the desired product as a light yellow solid (129 mg, 67%). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.20 (d, *J*=6.82 Hz, 3 H) 1.57 - 1.67 (m, 2 H) 1.66 - 1.77 (m, 4 H) 2.64 - 2.74 (m, 1 H) 2.78 (dd, *J*=11.37, 3.28 Hz, 1 H) 2.83 - 2.95 (m, 1 H) 3.02 (dd, *J*=10.86, 3.54 Hz, 1 H) 3.20 - 3.27 (m, 4 H) 3.27 - 3.41 (m, 1 H) 3.63 - 3.82 (m, 1 H) 4.15 - 4.28 (m, 1 H); HRMS: calcd for C₂₃H₂₇F₄N₃O₂S + H⁺, 486.18328; found (ESI-FTMS, [M+H]¹⁺), 486.1836; HPLC Method 1: room temperature, 8.26 min, 100%, HPLC Method 2: room temperature, 8.51 min, 100%.

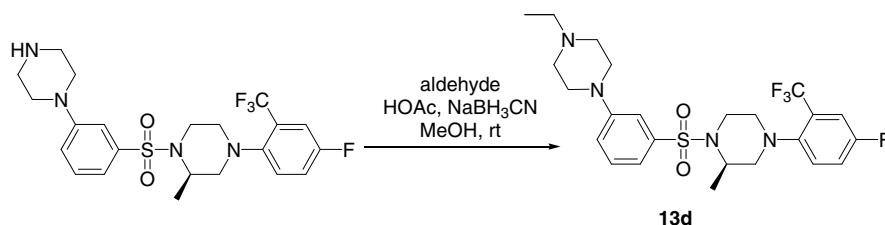


13b

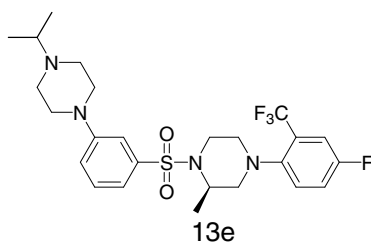
4-[3-((2R)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methylpiperazin-1-yl)sulfonylphenyl]morpholine (13b). The title compound was prepared according to a similar procedure used to synthesize **13a**. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.20 (d, *J*=6.82 Hz, 3 H) 2.66 - 2.76 (m, 1 H) 2.79 (dd, *J*=11.49, 3.16 Hz, 1 H) 2.86 - 2.93 (m, 1 H) 3.03 (dd, *J*=11.12, 3.54 Hz, 1 H) 3.16 - 3.26 (m, 4 H) 3.26 - 3.40 (m, 1 H) 3.72 (d, *J*=12.63 Hz, 1 H) 3.82 - 3.93 (m, 4 H) 4.15 - 4.28 (m, 1 H) 7.02 - 7.12 (m, 1 H) 7.17 - 7.36 (m, 5 H) 7.35 - 7.46 (m, 1 H); HRMS: calcd for C₂₂H₂₅F₄N₃O₃S + H⁺, 488.16255; found (ESI-FTMS, [M+H]¹⁺), 488.163; HPLC Method 1: room temperature, 7.71 min, 100%, HPLC Method 2: room temperature, 8.16 min, 100%.



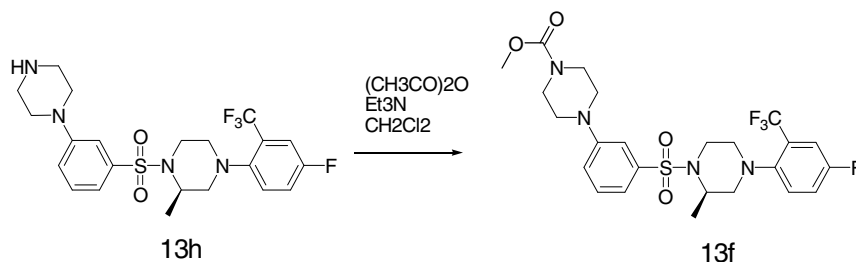
(2R)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methyl-1-[[3-(4-methylpiperazin-1-yl)phenyl]sulfonyl]piperazine (13c). A mixture of (2R)-1-[(3-bromophenyl)sulfonyl]-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methylpiperazine (8g, 16.667 mmol), N-Me-piperazine (2.22 mL, 20 mmol), bis-*t*-Bu-biphenylphosphine (298.2 mg, 1.0 mmol), *t*BuONa (2.4 g, 25 mmol) and Pd₂(dba)₃ (305.2 mg, 0.333 mmol) was mixed and purged with N₂. Anhydrous toluene (80 mL) was added and purged with N₂ again. The resultant mixture was heated in an oil bath at 110 °C under N₂ for 5 hours. After cooling, diluted with EtOAc (100 mL), filtered through a pad of Celite and washed with EtOAc (100 mL). The combined organic layer was washed with aq. NaHCO₃. The aqueous layer was back extracted with EtOAc (2 x 50 mL). The combined organic layer was dried over Na₂SO₄. The crude product was purified on SiO₂ gel column eluted with 0-25% MeOH in EtOAc to give the desired product as a light yellow solid (6.5 g, 78%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.07 (d, *J*=6.82 Hz, 3 H) 2.39 - 2.48 (m, 4 H) 2.61 - 2.72 (m, 2 H) 2.75 - 2.84 (m, 1 H) 2.88 - 2.96 (m, 1 H) 3.12 - 3.27 (m, 5 H) 3.62 - 3.74 (m, 1 H) 4.06 - 4.17 (m, 1 H) 7.13 - 7.22 (m, 1 H) 7.21 - 7.33 (m, 2 H) 7.34 - 7.48 (m, 1 H) 7.47 - 7.61 (m, 3 H); HRMS: calcd for C₂₃H₂₈F₄N₄O₂S + H⁺, 501.1942; found ([M+H]¹⁺), 501.1944; HPLC Method 1: room temperature, 6.21 min, 100%, HPLC Method 2: room temperature, 7.03 min, 100%.



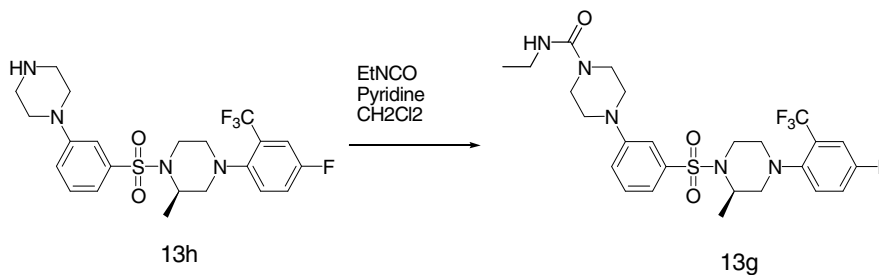
(2R)-1-[[3-(4-ethylpiperazin-1-yl)phenyl]sulfonyl]-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methylpiperazine (13d). To a solution of (2R)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methyl-1-[[3-(4-methylpiperazin-1-yl)phenyl]sulfonyl]piperazine (120 mg, 0.247 mmol) in MeOH (2 mL) was added CH₃CHO (12 mg, 0.27 mmol), HOAc (17.7 μL, 0.3 mmol) and NaBH₃CN (8 mg, 0.125 mmol) at room temperature. The resultant mixture was stirred till disappearance of starting material as monitored by LCMS. The solvent was removed. The crude product was purified by SiO₂ column eluted with DCM/MeOH to give the desired product as a light yellow solid (116 mg, 100%). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.14 (t, *J*=7.20 Hz, 3 H) 1.20 (d, *J*=6.82 Hz, 3 H) 2.49 (q, *J*=7.24 Hz, 2 H) 2.59 - 2.67 (m, 4 H) 2.68 - 2.73 (m, 1 H) 2.77 (dd, *J*=11.37, 3.28 Hz, 1 H) 2.82 - 2.93 (m, 1 H) 3.01 (dd, *J*=10.99, 3.41 Hz, 1 H) 3.26 - 3.33 (m, 4 H) 3.33 - 3.41 (m, 1 H) 3.72 (d, *J*=12.88 Hz, 1 H) 4.14 - 4.30 (m, 1 H) 7.09 (dd, *J*=7.83, 2.27 Hz, 1 H) 7.18 - 7.45 (m, 6 H) HRMS: calcd for C₂₄H₃₀F₄N₄O₂S + H⁺, 515.20983; found (ESI-FTMS, [M+H]¹⁺), 515.20891. HPLC Method 1: room temperature, 4.73 min, 99.60%, HPLC Method 2: room temperature, 5.81 min, 99.80%.



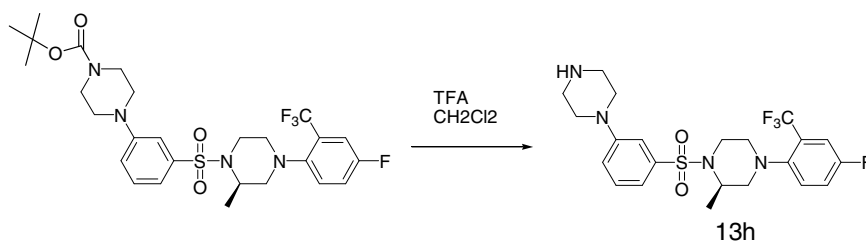
(2R)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-1-[[3-(4-isopropylpiperazin-1-yl)phenyl]sulfonyl]-2-methylpiperazine (13e). The title compound was prepared according to a similar procedure used to synthesize **13c**. Yield 100%. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.10 (d, $J=6.57$ Hz, 6 H) 1.20 (d, $J=6.82$ Hz, 3 H) 2.68 - 2.72 (m, 4 H) 2.72 - 2.79 (m, 1 H) 2.83 - 2.93 (m, 1 H) 3.01 (dd, $J=10.99, 3.41$ Hz, 1 H) 3.24 - 3.30 (m, 4 H) 3.30 - 3.40 (m, 1 H) 3.65 - 3.77 (m, 1 H) 4.13 - 4.29 (m, 1 H) 7.05 - 7.12 (m, 1 H) 7.16 - 7.41 (m, 6 H); HRMS: calcd for C₂₅H₃₂F₄N₄O₂S + H⁺, 529.22548; found (ESI-FTMS, [M+H]¹⁺), 529.22456; HPLC Method 1: room temperature, 4.83 min, 98.71%, HPLC Method 2: room temperature, 5.89 min, 99.89%.



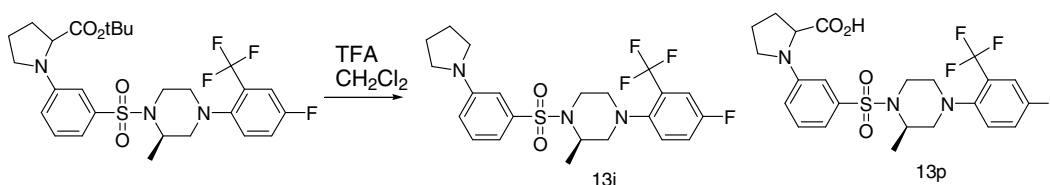
Methyl 4-[3-((2R)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methylpiperazin-1-yl)sulfonyl]phenyl]piperazine-1-carboxylate (13f). Yield 97%. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.19 (d, $J=6.82$ Hz, 3 H) 2.69 - 2.74 (m, 1 H) 2.74 - 2.83 (m, 1 H) 2.86 - 2.95 (m, 1 H) 3.04 (dd, $J=10.86, 3.54$ Hz, 1 H) 3.17 - 3.27 (m, 4 H) 3.27 - 3.40 (m, 1 H) 3.62 - 3.69 (m, 4 H) 3.68 - 3.74 (m, 1 H) 3.74 (s, 3 H) 4.12 - 4.27 (m, 1 H) 6.95 - 7.04 (m, 1 H) 7.05 - 7.15 (m, 1 H) 7.17 - 7.25 (m, 1 H) 7.26 - 7.36 (m, 3 H) 7.41 (t, $J=7.96$ Hz, 1 H); HRMS: calcd for C₂₄H₂₈F₄N₄O₄S + H⁺, 545.18401; found (ESI-FTMS, [M+H]¹⁺), 545.1827; HPLC Method 1: room temperature, 7.71 min, 97.99%, HPLC Method 2: room temperature, 8.20 min, 98.44%.



***N*-ethyl-4-[3-((2*R*)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methylpiperazin-1-yl)sulfonylphenyl]piperazine-1-carboxamide (13g).** Yield 71%. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.18 (t, 3 H, *J*=6.3 Hz) 1.19 (d, *J*=6.82 Hz, 3 H) 2.67 - 2.85 (m, 2 H) 2.86 - 2.95 (m, 1 H) 3.04 (dd, *J*=11.12, 3.54 Hz, 1 H) 3.18 - 3.39 (m, 6 H) 3.55 (dd, *J*=6.06, 4.29 Hz, 4 H) 3.72 (d, *J*=12.63 Hz, 1 H) 4.14 - 4.29 (m, 1 H) 4.45 (t, *J*=4.42 Hz, 1 H) 7.04 - 7.10 (m, 1 H) 7.17 - 7.36 (m, 5 H) 7.37 - 7.44 (m, 1 H)
 HRMS: calcd for C₂₄H₂₈F₄N₄O₄S + H⁺, 545.18401; found (ESI-FTMS, [M+H]¹⁺), 545.1827; HPLC Method 1: room temperature, 7.46 min, 99.38%, HPLC Method 2: room temperature, 8.16 min, 98.76%.

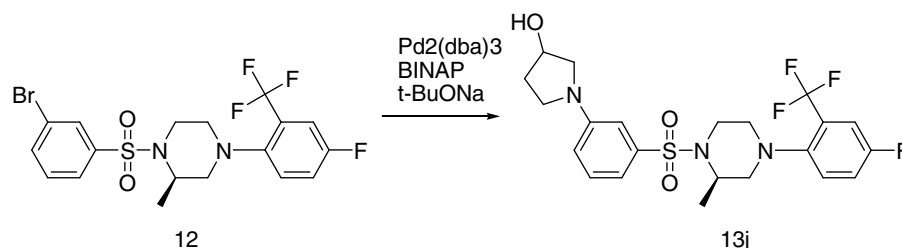


(2*R*)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methyl-1-[(3-piperazin-1-yl)phenyl)sulfonyl]piperazine (13h). To a solution of (R)-tert-butyl 4-(3-(4-(4-fluoro-2-(trifluoromethyl)phenyl)-2-methylpiperazin-1-ylsulfonyl)phenyl)piperazine-1-carboxylate (970 mg, 1.655 mmol) in DCM (15 mL) was added TFA (5 mL) at room temperature. The resultant mixture was stirred for 4 h then basified with 5% aq. NH₃. The precipitate was collected and washed with water to give the desired product as a light yellow solid (795 mg, 99%). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.20 (d, *J*=6.57 Hz, 3 H) 2.66 - 2.82 (m, 2 H) 2.91 (dd, *J*=10.74, 1.89 Hz, 1 H) 3.04 (dd, *J*=11.12, 3.28 Hz, 1 H) 3.33 - 3.41 (m, 5 H) 3.45 - 3.54 (m, 4 H) 3.71 (d, *J*=12.63 Hz, 1 H) 4.08 - 4.28 (m, 1 H) 7.06 - 7.14 (m, 1 H) 7.19 - 7.36 (m, 4 H) 7.36 - 7.42 (m, 2 H) 7.46 (t, *J*=7.96 Hz, 1 H); HRMS: calcd for C₂₂H₂₆F₄N₄O₂S + H⁺, 487.17853; found (ESI-FTMS, [M+H]¹⁺), 487.17747; HPLC Method 1: room temperature, 6.53 min, 96.50%, HPLC Method 2: room temperature, 7.40 min, 95.59%.

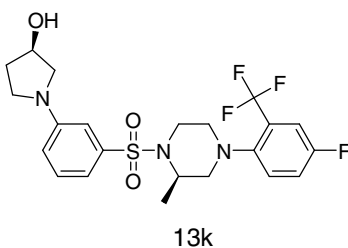


(2*R*)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methyl-1-[(3-pyrrolidin-1-yl)phenyl)sulfonyl]piperazine (13i). tert-butyl 1-(3-((R)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-2-methylpiperazin-1-ylsulfonyl)phenyl)pyrrolidine-2-carboxylate (40 mg, 0.07 mmol) dissolved in CH₂Cl₂ (5 mL) was added with TFA (5 mL) and stirred at room temperature for 3 hours. Reaction was monitored by TLC. More TFA (2 mL) was added to the reaction mixture and it was allowed to stir an additional 2 hours.

Solvent was removed and crude product was purified by column chromatography using 25% to 100% EtOAc/Hexane then 5% MeOH/Ethyl acetate to afford both **13i** and **13p**. **13i** was obtained in 22% yield (8 mg). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.21 (d, *J*=6.82 Hz, 3 H) 1.99 – 2.09 (m, 4 H) 2.63 – 2.83 (m, 2 H) 2.84 – 2.94 (m, 1 H) 3.04 (dd, *J*=10.99, 3.41 Hz, 1 H) 3.28 – 3.41 (m, 5 H) 3.73 (d, *J*=12.63 Hz, 1 H) 4.23 (d, *J*=9.35 Hz, 1 H) 6.70 (dd, *J*=7.96, 2.15 Hz, 1 H) 6.94 – 6.98 (m, 1 H) 7.07 (dd, *J*=7.71, 0.88 Hz, 1 H) 7.22 (dd, *J*=7.71, 2.65 Hz, 1 H) 7.27 – 7.36 (m, 3 H); HRMS: calcd for C₂₂H₂₅F₄N₃O₂S + H⁺, 472.16763; found (ESI-FTMS, [M+H]¹⁺), 472.16822; HPLC Method 1: room temperature, 8.35 min, 98.15%, HPLC Method 2: room temperature, 8.69 min, 95.44%.

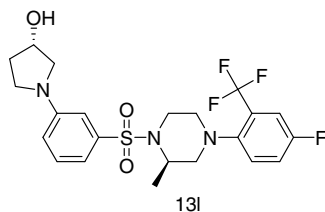


1-[3-((2*R*)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methylpiperazin-1-yl)sulfonyl]phenyl]pyrrolidin-3-ol (13j). The title compound was prepared according to a similar procedure used to synthesize **13a** except that BINAP was used as ligand. Yield 5.3 g (58%). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.21 (d, *J*=6.57 Hz, 3 H) 1.74 (d, *J*=4.04 Hz, 1 H) 2.06 - 2.30 (m, 2 H) 2.64 - 2.83 (m, 2 H) 2.82 - 2.93 (m, 1 H) 3.03 (dd, *J*=10.99, 3.41 Hz, 1 H) 3.22 - 3.46 (m, 3 H) 3.51 - 3.62 (m, 2 H) 3.72 (d, *J*=12.63 Hz, 1 H) 4.16 - 4.28 (m, 1 H) 4.66 (s, 1 H) 6.71 (dd, *J*=8.34, 2.27 Hz, 1 H) 6.97 (t, *J*=2.02 Hz, 1 H) 7.11 (d, *J*=7.83 Hz, 1 H) 7.24 - 7.38 (m, 4 H); HRMS: calcd for C₂₂H₂₅F₄N₃O₃S + H⁺, 488.16255; found (ESI-FTMS, [M+H]¹⁺), 488.16308; HPLC Method 1: room temperature, 6.65 min, 99.58%, HPLC Method 2: room temperature, 7.56 min, 100%.

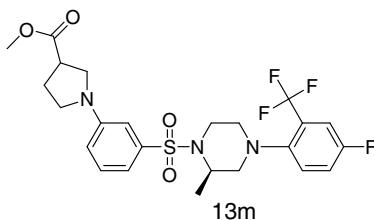


(3*R*)-1-[3-((2*R*)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methylpiperazin-1-yl)sulfonyl]phenyl]pyrrolidin-3-ol (13k). The title compound was prepared according to a similar procedure used to synthesize **13j**. 325 mg of the desired product was isolated in 77%. ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.21 (d, *J*=6.82 Hz, 3 H) 1.67 (dd, 1 H) 2.04 - 2.30 (m, 2 H) 2.62 - 2.82 (m, 2 H) 2.84 - 2.93 (m, 1 H) 3.03 (dd, *J*=10.74, 3.41 Hz, 1 H) 3.29 - 3.60 (m, 5 H) 3.73 (d, *J*=12.63 Hz, 1 H) 4.22 (t, *J*=7.45 Hz, 1 H)

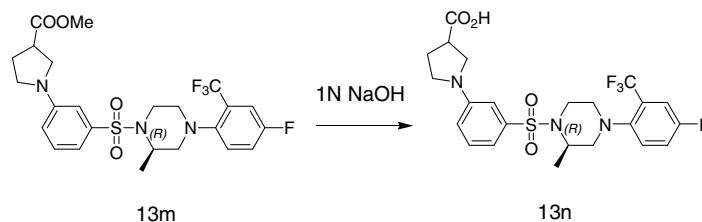
4.61 - 4.70 (m, 1 H) 6.69 - 6.74 (m, 1 H) 6.94 - 6.99 (m, 1 H) 7.11 (d, $J=7.83$ Hz, 1 H) 7.16 - 7.37 (m, 4 H); HRMS: calcd for $C_{22}H_{25}F_4N_3O_3S + H^+$, 488.16255; found (ESI-FTMS, $[M+H]^{1+}$), 488.16359; HPLC Method 1: room temperature, 6.50 min, 95.32%, HPLC Method 2: room temperature, 7.46 min, 95.41%.



(3S)-1-[3-({(2R)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methylpiperazin-1-yl)sulfonyl}phenyl)pyrrolidin-3-ol (13l). The title compound was prepared according to a similar procedure used to synthesize **13j**. 160 mg in 65% yield. 1H NMR (400 MHz, MeOD) δ ppm 1.43 (d, $J=6.82$ Hz, 3 H) 2.24 - 2.48 (m, 2 H) 2.85 - 3.00 (m, 2 H) 3.06 (dd, $J=9.85, 1.52$ Hz, 1 H) 3.19 (dd, $J=11.12, 3.54$ Hz, 1 H) 3.40 - 3.81 (m, 6 H) 3.94 (d, $J=12.88$ Hz, 1 H) 4.36 - 4.49 (m, 1 H) 4.66 - 4.85 (m, 1 H) 7.04 (dd, $J=8.34, 1.77$ Hz, 1 H) 7.15 - 7.19 (m, 1 H) 7.27 - 7.33 (m, 1 H) 7.51 - 7.66 (m, 4 H); HRMS: calcd for $C_{22}H_{25}F_4N_3O_3S + H^+$, 488.16255; found (ESI-FTMS, $[M+H]^{1+}$), 488.16074; HPLC Method 1: room temperature, 6.53 min, 96.86%, HPLC Method 2: room temperature, 7.46 min, 96.25%.

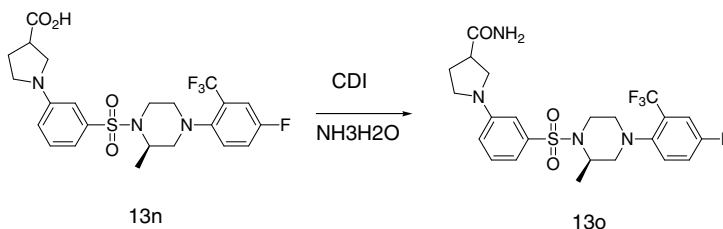


(Methyl 1-[3-({(2R)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methylpiperazin-1-yl)sulfonyl}phenyl)pyrrolidine-3-carboxylate (13m). The title compound was prepared according to a similar procedure used to synthesize **13j**. Yield 1.0g (20.5%). 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.21 (dd, $J=6.57, 1.26$ Hz, 3 H) 2.27 - 2.38 (m, 2 H) 2.70 (d, $J=11.12$ Hz, 1 H) 2.74 - 2.82 (m, 1 H) 2.85 - 2.91 (m, 1 H) 3.03 (dd, $J=11.12, 3.54$ Hz, 1 H) 3.19 - 3.53 (m, 4 H) 3.58 - 3.62 (m, 2 H) 3.71 (d, $J=1.77$ Hz, 1 H) 3.75 (s, 3 H) 4.22 (d, $J=5.81$ Hz, 1 H) 6.71 (dd, $J=9.09, 2.53$ Hz, 1 H) 6.95 - 6.99 (m, 1 H) 7.12 (dd, $J=6.95, 0.88$ Hz, 1 H) 7.18 - 7.25 (m, 1 H) 7.27 - 7.37 (m, 3 H); HRMS: calcd for $C_{24}H_{27}F_4N_3O_4S + H^+$, 530.17312; found (ESI-FTMS, $[M+H]^{1+}$), 530.17141; HPLC Method 1: room temperature, 7.44 min, 99.71%, HPLC Method 2: room temperature, 7.90 min, 99.60%.



1-[3-((2R)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methylpiperazin-1-yl)sulfonylphenyl]pyrrolidine-3-carboxylic acid (13n).

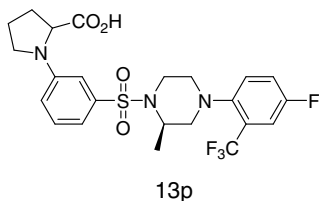
The title compound was obtained by hydrolyzing (1-(3-((R)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-2-methylpiperazin-1-yl)sulfonylphenyl)pyrrolidin-2-yl)methyl acetate **13m** using 1N NaOH. Yield 864 mg (89%). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.09 (d, *J*=6.57 Hz, 3 H) 2.12 - 2.31 (m, 2 H) 2.65 (d, *J*=11.37 Hz, 2 H) 2.77 - 2.86 (m, 1 H) 2.95 (d, *J*=11.12 Hz, 1 H) 3.09 - 3.28 (m, 2 H) 3.27 - 3.40 (m, 2 H) 3.46 (d, *J*=3.79 Hz, 2 H) 3.67 (d, *J*=12.88 Hz, 1 H) 4.10 (d, *J*=6.57 Hz, 1 H) 6.81 - 6.87 (m, 2 H) 7.04 (d, *J*=7.58 Hz, 1 H) 7.40 (t, *J*=7.83 Hz, 1 H) 7.49 - 7.59 (m, 3 H) 12.54 (s, 1 H); HRMS: calcd for C₂₃H₂₅F₄N₃O₄S + H⁺, 516.15747; found (ESI-FTMS, [M+H]¹⁺), 516.15631; HPLC Method 1: room temperature, 6.638 min, 98.24%, HPLC Method 2: room temperature, 7.60 min, 98.13%.



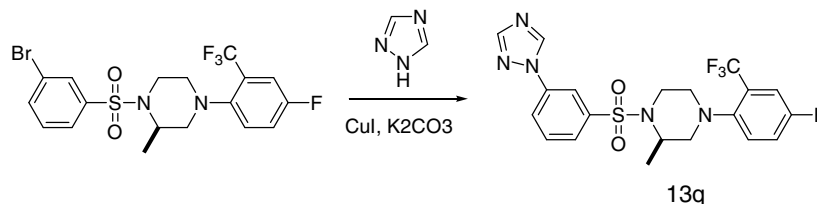
1-[3-((2R)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methylpiperazin-1-yl)sulfonylphenyl]pyrrolidine-3-carboxamide (13o).

1-[3-((2R)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methylpiperazin-1-yl)sulfonylphenyl]pyrrolidine-3-carboxylic acid (359 mg, 0.696 mmol) charged to a reaction flask was dissolved in THF (6 mL). To it was added CDI (226 mg, 1.39 mmol) and the reaction mixture was heated to 65°C for 1 hour. After cooling down to room temperature, excess NH₄OH (28% NH₃, 5 ml) was added dropwise via addition funnel. It was left to stir at room temperature for 5 minutes. Then it was diluted with ethyl acetate, acidified to pH 3 using 10 % HCl (aq.), organic layer was separated, washed with brine, dried over MgSO₄ and concentrated. Crude product was purified via flash column chromatography (2-20% MeOH / DCM) to yield 1-[3-((2R)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methylpiperazin-1-yl)sulfonylphenyl]pyrrolidine-3-carboxamide as pale yellow solid (185 mg, 52% yield). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.09 (dd, *J*=6.69, 2.65 Hz, 3 H) 2.03 - 2.28 (m, 2 H) 2.60 - 2.75 (m, 2 H) 2.76 - 2.86 (m, 1 H) 2.95 (d, *J*=10.61 Hz, 1 H) 3.03 - 3.23 (m, 2 H) 3.26 - 3.32 (m, 1 H) 3.33 - 3.42 (m, 2 H) 3.42 - 3.54 (m, 1 H) 3.66 (d, *J*=12.63 Hz, 1 H) 4.10 (d, *J*=8.34 Hz, 1 H) 6.74 - 6.87 (m, 2 H) 6.92 - 7.06 (m, 2 H) 7.39 (t, *J*=7.83 Hz, 1 H) 7.50 (s, 1 H) 7.53 (s, 1 H) 7.54 - 7.58 (m, 2 H); HRMS: calcd for C₂₃H₂₆F₄N₄O₃S + H⁺, 515.17345; found (ESI-FTMS, [M+H]¹⁺), 515.17243; HPLC Method 1: room

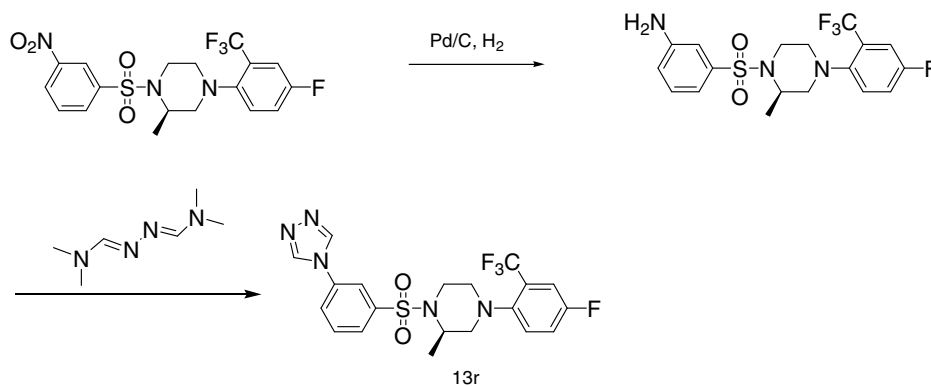
temperature, 6.31 min, 96.84%, HPLC Method 2: room temperature, 7.84 min, 95.12%.



1-(3-((R)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-2-methylpiperazin-1-ylsulfonyl)phenyl)pyrrolidine-2-carboxylic acid (13p). The title compound was isolated as another product (26 mg, 72% yield) from the procedure used to synthesize **13i**. ¹H NMR (400 MHz, MeOD) δ ppm 1.47 (dd, *J*=6.69, 2.91 Hz, 3 H) 2.25 - 2.68 (m, 4 H) 2.83 - 3.20 (m, 4 H) 3.56 - 3.69 (m, 2 H) 3.82 (s, 1 H) 3.92 (d, *J*=11.87 Hz, 1 H) 4.37 (s, 1 H) 4.48 (s, 1 H) 7.05 (d, *J*=5.05 Hz, 1 H) 7.18 (d, *J*=1.77 Hz, 1 H) 7.34 (d, *J*=8.34 Hz, 1 H) 7.49 - 7.66 (m, 4 H); HRMS: calcd for C₂₃H₂₅F₄N₃O₄S + H⁺, 516.15747; found (ESI-FTMS, [M+H]¹⁺), 516.15865; HPLC Method 1: room temperature, 7.65 min, 96.83%, HPLC Method 2: room temperature, 8.35 min, 98.18%.



(2R)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methyl-1-[[3-(1H-1,2,4-triazol-1-yl)phenyl]sulfonyl]piperazine (13q). Prepared from (R)-1-(3-bromophenylsulfonyl)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-2-methylpiperazine, as a white solid in 70% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.12 (d, *J*=6.82 Hz, 3 H) 2.62 - 2.76 (m, 2 H) 2.75 - 2.90 (m, 1 H) 2.88 - 3.02 (m, 1 H) 3.13 - 3.30 (m, 1 H) 3.62 - 3.87 (m, 1 H) 4.11 - 4.29 (m, 1 H) 7.43 - 7.62 (m, 3 H) 7.77 - 7.96 (m, 2 H) 8.17 - 8.26 (m, 1 H) 8.25 - 8.38 (m, 2 H) 9.49 (s, 1 H); HPLC Method 1: room temperature, 6.44 min, 96.52%. HPLC Method 2: room temperature, 7.33 min, 95.90%; HRMS: calcd for C₂₀H₁₉F₄N₅O₂S + H⁺, 470.12683; found (ESI-FTMS, [M+H]¹⁺), 470.1276; HPLC Method 1: room temperature, 7.656 min, 100%, HPLC Method 2: room temperature, 8.28 min, 100%.

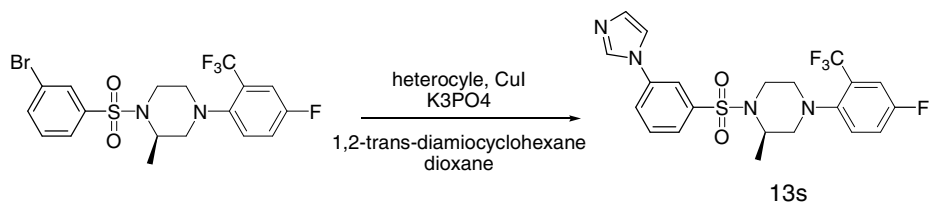


(2R)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methyl-1-[[3-(4H-1,2,4-triazol-4-yl)phenyl]sulfonyl]piperazine (13r).

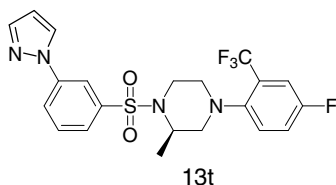
Starting material 4-(4-Fluoro-2-trifluoromethyl-phenyl)-2-methyl-1-(3-nitrobenzenesulfonyl)-piperazine was prepared according to the procedures used to synthesize **12**. 330mg was isolated in 47% yield.

A solution of 4-(4-Fluoro-2-trifluoromethyl-phenyl)-2-methyl-1-(3-nitrobenzenesulfonyl)-piperazine (330 mg, 0.8 mmol) and a catalytic amount of 10% Pd/C in EtOAc (25 mL) was stirred under H₂ (1 atm) at ambient temperature for two hours, after which the reduction was judged complete by TLC. The H₂ removed under vacuum, and the reaction mixture was filtered through celite, and rinsed with EtOAc (3X 25 mL), and the filtrate was concentrated in vacuo, affording 180 mg of the desired 3-((2R)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methylpiperazin-1-yl)sulfonylaniline in >95% purity (62% yield). HRMS: calcd for C₁₈H₁₉F₄N₃O₂S + H⁺, 418.12068; found ([M+H]⁺), 418.12119.

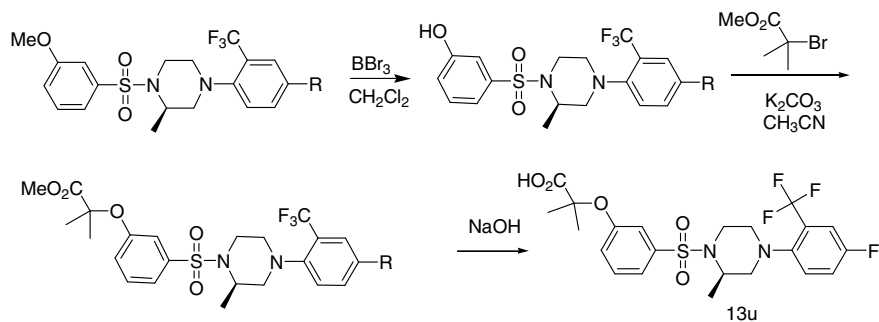
A solution of the aniline (400 mg, 0.96 mmol), N, N-dimethyl-formyl-hydrazine (140 mg, 1.15 mmol), and a catalytic amount of pTSA in toluene (20 mL) was heated at reflux (130°C) under N₂ over a 12-16 hour period, after which the reaction was judged complete by LCMS. The reaction was then cooled to ambient temperature and the solvent was concentrated in vacuo, affording a crude oil which was purified by reversed phase HPLC under neutral conditions (30%-90% ACN/H₂O), affording the desired 1,3,4-triazole compound in 53% yield. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.13 (d, *J*=6.57 Hz, 3 H) 2.61 - 2.79 (m, 2 H) 2.74 - 2.88 (m, 1 H) 2.84 - 3.01 (m, 1 H) 3.14 - 3.30 (m, 1 H) 3.63 - 3.88 (m, 1 H) 4.08 - 4.28 (m, 1 H) 7.41 - 7.63 (m, 3 H) 7.85 (d, *J*=7.83 Hz, 1 H) 7.84 - 7.96 (m, 1 H) 7.97 - 8.09 (m, 1 H) 8.16 (t, *J*=1.89 Hz, 1 H) 9.28 (s, 2 H); HRMS: calcd for C₂₀H₁₉F₄N₅O₂S + H⁺, 470.12683; found ([M+H]⁺), 470.12538; HPLC Method 1: room temperature, 7.04 min, 100%, HPLC Method 2: room temperature, 7.83 min, 100%.



(2R)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methyl-1-[[3-(1H-pyrazol-1-yl)phenyl]sulfonyl]piperazine (13s). A suspension of (R)-1-(3-bromophenylsulfonyl)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-2-methylpiperazine (168 mg, 0.35 mmol), 1,2-trans-diaminomethylcyclohexane (2.9 mg, 0.015 mmol), K_3PO_4 (8.5 mmg, 0.06 mmol) and Imidazole (41 mg, 0.6 mmol) in dioxane (0.6 mL) was degassed and heated to 120 °C in a sealed tube till disappearance of starting material as monitored by LCMS. The crude reaction mixture was filtered through a pad of Celite and washed with EtOAc. The crude product was purified on SiO_2 column eluted with hexanes/EtOAc to give the desired product as a white solid (123 mg, 75%). 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.23 (d, $J=6.82$ Hz, 3 H) 2.72 - 2.85 (m, 2 H) 2.86 - 2.98 (m, 1 H) 3.07 (dd, $J=11.12, 3.54$ Hz, 1 H) 3.32 - 3.46 (m, 1 H) 3.67 - 3.82 (m, 1 H) 4.22 - 4.32 (m, 1 H) 7.14 - 7.40 (m, 5 H) 7.58 - 7.75 (m, 2 H) 7.79 - 7.96 (m, 3 H); HRMS: calcd for $C_{21}H_{20}F_4N_4O_2S + H^+$, 469.13158; found (ESI-FTMS, $[M+H]^+$), 469.13336; HPLC Method 1: room temperature, 6.53 min, 100%, HPLC Method 2: room temperature, 7.60 min, 100%.



(2R)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methyl-1-[[3-(1H-pyrazol-1-yl)phenyl]sulfonyl]piperazine (13t). The title compound was prepared according to a similar procedure used to synthesize **13s**. A white solid was isolated in 93% yield ((152 mg). 1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.24 (d, $J=6.82$ Hz, 3 H) 2.64 - 2.85 (m, 2 H) 2.87 - 2.97 (m, 1 H) 3.04 (dd, $J=11.12, 3.54$ Hz, 1 H) 3.31 - 3.47 (m, 1 H) 3.79 (d, $J=12.63$ Hz, 1 H) 4.21 - 4.32 (m, 1 H) 6.47 - 6.58 (m, 1 H) 7.15 - 7.25 (m, 1 H) 7.25 - 7.35 (m, 2 H) 7.63 (t, $J=7.96$ Hz, 1 H) 7.71 - 7.81 (m, 2 H) 7.92 - 7.99 (m, 1 H) 8.02 (d, $J=2.53$ Hz, 1 H) 8.20 (t, $J=1.77$ Hz, 1 H); HRMS: calcd for $C_{21}H_{20}F_4N_4O_2S + H^+$, 469.13158; found (ESI-FTMS, $[M+H]^+$), 469.13318; HPLC Method 1: room temperature, 7.78 min, 100%, HPLC Method 2: room temperature, 8.22 min, 100%.



2-[3-((2R)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methylpiperazin-1-yl)sulfonyl]phenoxy]-2-methylpropanoic acid (13u).

Starting material 3-methoxybenzenesulfonyl-2-methylpiperazine-1-yl-4-(4-fluoro-2-(trifluoromethyl)phenyl) was prepared according to a similar procedure used to synthesize **12**. A white solid was obtained in quantitative yield (5.10 g).

A stirred solution of (R)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-1-(3-methoxyphenylsulfonyl)-2-methylpiperazine (2.22 g, 5.13 mmol) in anhydrous dichloromethane (60 mL) was cooled down to -50°C (acetone + dry ice bath). BBr_3 (1M in CH_2Cl_2) was added dropwise via addition funnel while keeping the temperature between -50°C and -55°C . Then the reaction mixture was stirred at -50°C to -20°C for 3 hours. Reaction was complete as determined by TLC. The reaction mixture was quenched with water and diluted with dichloromethane. pH was adjusted to 7 using saturated NaHCO_3 (aqueous) and it was allowed to stir for 20 minutes.

The layers were separated; the organic layer was dried over MgSO_4 and concentrated. The reaction was repeated in 2.85 g scale. The combined crude products were purified via flash column chromatography to yield 3-((2R)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methylpiperazin-1-yl)sulfonylphenol in 96% yield (4.07g) as a white solid. ^1H NMR (400 MHz, $\text{CHLOROFORM-}d$) δ ppm 1.21 (d, $J=6.82$ Hz, 3 H) 2.61 - 2.80 (m, 2 H) 2.88 (dd, $J=9.98$, 1.39 Hz, 1 H) 3.01 (dd, $J=11.24$, 3.41 Hz, 1 H) 3.31 - 3.43 (m, 1 H) 3.71 (d, $J=12.63$ Hz, 1 H) 4.21 (d, $J=6.82$ Hz, 1 H) 5.95 (s, 1 H) 7.05 - 7.11 (m, 1 H) 7.18 - 7.29 (m, 2 H) 7.32 (dd, $J=8.72$, 2.91 Hz, 1 H) 7.36 - 7.44 (m, 3 H); HRMS: calcd for $\text{C}_{18}\text{H}_{18}\text{F}_4\text{N}_2\text{O}_3\text{S} + \text{H}^+$, 419.10470; found (ESI-FTMS, $[\text{M}+\text{H}]^{1+}$), 419.104; HPLC Method 1: room temperature, 6.32 min, 100%, HPLC Method 2: room temperature, 7.22 min, 99.48%.

3-((2R)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methylpiperazin-1-yl)sulfonylphenol (418 mg, 1.0 mmol), Methyl α -bromoisobutyrate (905mg, 5.0 mmol) and K_2CO_3 (691 mg, 5.0 mmol) were charged to a microwave vial and added with CH_3CN (12 mL). The reaction mixture was stirred at room temperature for 20 minutes then subjected to microwave irradiation for 0.5 hour at 110°C . TLC confirmed reaction completion. The reaction mixture was diluted with CH_2Cl_2 , solid was filtered off then filtrate was evaporated under reduced pressure. Residue thus obtained was partitioned in CH_2Cl_2 / H_2O , washed with water, saturated brine, dried over MgSO_4 , solvent removed. Crude product was then purified via flash chromatography using 7% to 50% Ethylacetate / Hexane as eluent to afford methyl 2-[3-((2R)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-

methylpiperazin-1-yl)sulfonyl)phenoxy]-2-methylpropanoate as a white solid in 88% yield (456 mg). ¹H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.19 (d, *J*=6.57 Hz, 3 H) 1.63 (s, 6 H) 2.59 - 2.81 (m, 2 H) 2.89 (d, *J*=9.85 Hz, 1 H) 3.01 (dd, *J*=10.99, 3.66 Hz, 1 H) 3.26 - 3.43 (m, 1 H) 3.71 (d, *J*=12.63 Hz, 1 H) 3.79 (s, 3 H) 4.20 (d, *J*=5.05 Hz, 1 H) 7.17 - 7.35 (m, 5 H) 7.40 (t, *J*=7.96 Hz, 1 H) 7.45 - 7.50 (m, 1 H); HRMS: calcd for C₂₃H₂₆F₄N₂O₅S + H⁺, 519.15713; found (ESI-FTMS, [M+H]¹⁺), 519.1564; HPLC Method 1: room temperature, 7.24 min, 100%, HPLC Method 2: room temperature, 7.68 min, 99.2%.

Methyl 2-[3-({(2*R*)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methylpiperazin-1-yl)sulfonyl)phenoxy]-2-methylpropanoate (392.0 mg, 0.756 mmol) was dissolved in THF (6 mL). To it was added 1N NaOH (aqueous) (3 mL) then methanol (6 mL). The clear solution was stirred at room temperature. Reaction was complete as determined by TLC. The reaction mixture was poured into water and the pH was adjusted to 3 using 2N HCl (aqueous). This mixture was extracted with ethylacetate, organic layer was washed with saturated brine, dried over MgSO₄, concentrated and lyophilized overnight to afford 2-[3-({(2*R*)-4-[4-fluoro-2-(trifluoromethyl)phenyl]-2-methylpiperazin-1-yl)sulfonyl)phenoxy]-2-methylpropanoic acid as a white solid in 65.6% yield (250.0 mg). ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 1.07 (d, *J*=6.57 Hz, 3 H) 2.44 - 2.56 (m, 6 H) 2.61 - 2.73 (m, 2 H) 2.82 (d, *J*=11.62 Hz, 1 H) 2.91 (dd, *J*=11.37, 3.54 Hz, 1 H) 3.20 (dd, *J*=24.38, 3.16 Hz, 1 H) 3.64 (d, *J*=12.88 Hz, 1 H) 4.08 (d, *J*=6.57 Hz, 1 H) 7.14 - 7.19 (m, 1 H) 7.21 - 7.24 (m, 1 H) 7.42 - 7.48 (m, 1 H) 7.54 (dd, *J*=7.33, 3.79 Hz, 4 H) 13.31 (s, 1 H); HRMS: calcd for C₂₂H₂₄F₄N₂O₅S + H⁺, 505.14148; found (ESI-FTMS, [M+H]¹⁺), 505.14263; HPLC Method 1: room temperature, 6.58 min, 100%, HPLC Method 2: room temperature, 7.46 min, 100%.