Supporting Information

Discovery of INCB3284, a Potent, Selective and Orally Bioavailable hCCR2 Antagonist

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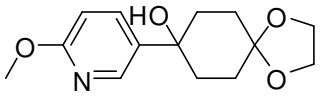
Contents:

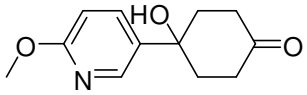
1. Experimental procedures for the synthesis of compound 13 and characterization data for compounds 1-14

8-(6-Methoxypyridin-3-yl)-1,4-dioxaspiro[4.5]decan-8-ol



In a dried 3-neck flask, 5-bromo-2-methoxypyridine (12.6 g, 67.2 mmol) was dissolved in dry THF (130 mL) and the solution was cooled to –78 °C under N_2. To the solution was added dropwise a solution of 2.5 M n-BuLi in hexanes (28.2 mL, 70.4 mmol). After being stirred at ~78 °C for 50 min, a solution of 1,4-cyclohexanedione mono-ethylene ketal (10.0 g, 64.0 mmol) in dry THF (25 mL) was slowly added. The resulting mixture was stirred at –78 °C for 80 min and quenched with saturated NH_4Cl aqueous solution. The solution was extracted with CH_2Cl_2 three times. The combined extracts were dried ($MgSO_4$), filtered, and concentrated to give a yellow oil. Flash chromatography on silica gel eluting with 10% MeOH/CH_2Cl_2 afforded the title compound as a yellow solid (16.5 g, 97%). MS *m/z* = 266.1 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.31 (dd, *J* = 2.4 & 0.8 Hz, 1H), 7.72 (dd, *J* = 8.8 & 2.4 Hz, 1H), 6.72 (dd, *J* = 8.8 & 2.4 Hz, 1H), 4.00 (m, 4H), 3.93 (s, 3H), 2.11 (s, 1H), 2.08 (m, 4H), 1.85 (m, 2H), 1.69 (m, 2H).

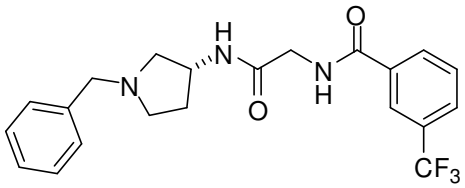
4-Hydroxy-4-(6-methoxypyridin-3-yl)cyclohexanone



To a solution of 8-(6-Methoxypyridin-3-yl)-1,4-dioxaspiro[4.5]decan-8-ol (11.5 g, 43.3 mmol) in THF (100 mL) was added 3 N HCl (75 mL) and the solution stirred at room temperature overnight. The pH of the solution was adjusted to ~11 by addition of 3 N NaOH solution. After removal of most of the THF by rotary evaporation, the solution was extracted with CH_2Cl_2 three times. The combined extracts were dried ($MgSO_4$), filtered, and concentrated to give the title compound as a yellow solid (8.2 g, 86%). MS *m/z* = 222.1 $(M+H)^+$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.29 (dd, *J* = 2.4 & 0.8 Hz, 1H),

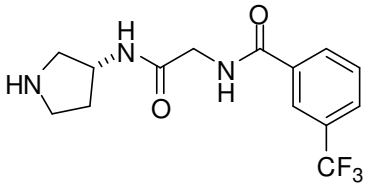
7.75 (dd, *J* = 8.8 & 2.4 Hz, 1H), 6.76 (dd, *J* = 8.8 & 2.4 Hz, 1H), 3.93 (s, 3H), 2.93 (m, 2H), 2.35 (m, 2H), 2.23 (m, 4H), 2.15 (s, 1H).

(*R*)-*N*-(2-(1-Benzylpyrrolidin-3-ylamino)-2-oxoethyl)-3-(trifluoromethyl)benzamide



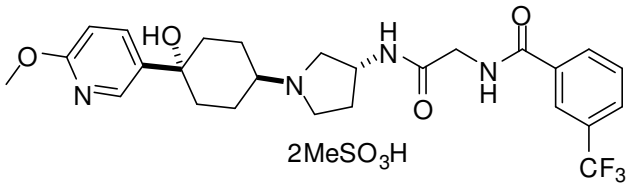
To a solution of 2-(3-(trifluoromethyl)benzamido)acetic acid (4.2 g, 17 mmol) and NMM (2.8 mL, 25.5 mmol) in dry THF (30 mL) at –10 to –15 ^{o}C under N_2, was slowly added isobutylchloroformate (2.4 mL, 17.85 mmol) via syringe. The reaction mixture gradually became pink. After15 min, a solution of (3*R*)-1-benzylpyrrolidin-3-amine (3.0 g, 17 mmol) in THF (15 mL) was dropwise added to the above mixed anhydride over 20 min, maintaining reaction temperature < -10 ^{o}C. The reaction mixture became a dark red color. After being stirred for 1 h, the reaction mixture was allowed to warm to room temperature, quenched with water (25 mL), and extracted with EtOAc three times. The combined extracts were dried ($MgSO_4$), filtered and concentrated to give an orange solid. MeCN (15-20 mL) was added and the mixture was chilled in ice bath and stirred for 30 min. After filtration, the solid product was rinsed with cold MeCN (10-15 mL) until the filtrate was colorless. After being dried under high vacuum overnight, a pale yellow solid product (5.0 g, 73%) was obtained. MS *m/z* = 406.2 ($M+H^+$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (s, 1H), 8.00 (d, *J* = 7.6 Hz, 1H), 7.76 (dd, *J* = 7.2 & 0.8 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.29 (m, 6H), 6.55 (m, 1H), 4.47 (m, 1H), 4.10 (d, *J* = 4.8 Hz, 2H), 3.60 (d, *J* = 2.0 Hz, 2H), 2.88 (m, 1H), 2.60 (m, 2H), 2.32 (m, 2H), 1.62 (m, 1H).

(*R*)-*N*-(2-Oxo-2-(pyrrolidin-3-ylamino)ethyl)-3-(trifluoromethyl)benzamide



To a Parr flask was added a solution of (*R*)-*N*-(2-(1-benzylpyrrolidin-3-ylamino)-2-oxoethyl)-3-(trifluoromethyl)benzamide (14.0 g, 34.5 mmol) in methanol (50 mL). To this mixture was added palladium hydroxide (2.8 g, 20 wt%) and the suspension was shaken under hydrogen overnight at room temperature at 55 psi. The reaction solution was filtered through Celite and the Celite rinsed with methylene chloride several times. The filtrate was concentrated in vacuo to yield 10.5 g (96%) of a white powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 1H), 8.02 (d, *J* = 7.2 Hz, 1H), 7.77 (t, *J* = 7.2 Hz, 1H), 7.76 (s, 1H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.21 (d, *J* = 7.2 Hz, 1H), 4.40 (m, 1H), 4.14 (d, *J* = 5.2 Hz, 2H), 3.10 (m, 2H), 2.92 (m, 1H), 2.85 (m, 1H), 2.27 (m, 1H), 2.16 (m, 1H), 1.69 (m, 1H).

_N_-(2-((_R_)-1-(_trans_-4-Hydroxy-4-(6-methoxypyridin-3-yl)cyclohexyl)pyrrolidin-3-ylamino)-2-oxoethyl)-3-(trifluoromethyl)benzamide Bismethanesulfonate (13)



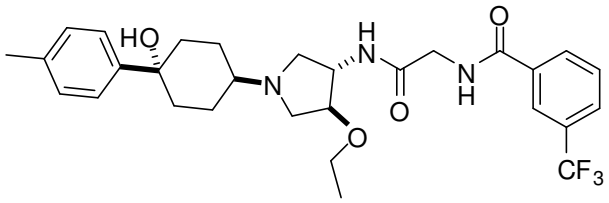
To a solution of (*R*)-*N*-(2-oxo-2-(pyrrolidin-3-ylamino)ethyl)-3-(trifluoromethyl)benzamide (3.5 g, 11.1 mmol) and 4-hydroxy-4-(6-methoxypyridin-3-yl)cyclohexanone (2.58 g, 11.6 mmol) in dichloromethane (35 mL) in a Parr bottle was added 5% platinum on aluminum oxide (350 mg). The bottle was purged with nitrogen three separate times followed by three separate hydrogen purges. The bottle was then shaken under hydrogen (60 psi) for ~18 hours. The reaction mixture was diluted with methanol (8 mL), the resultant slurry stirred for 30 mins and then filtered through Celite. The filtrate was treated with Activated Carbon for 30 mins. The slurry was filtered through Celite and the filter cake rinsed with methanol. The filtrate was concentrated under vacuum to give an oily crude product.

The above residue was dissolved in ethanol (15 mL), ethyl acetate (38 mL) and water (2 mL). To the resultant solution was added a preformed solution of methanesulfonic acid (2 g) in ethanol (6 mL) and ethyl acetate (15 mL). After seeding with a crystal of INCB3284•2MsOH, the mixture was stirred for 2 hrs. The resultant

precipitate was filtered. The filter cake was rinsed with a premixed solution of ethanol and ethyl acetate and dried overnight. This afforded a total of 4.35 g (54%) of INCB3284•2MsOH.

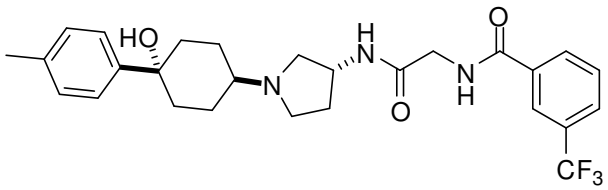
To a solution of the above salt (5 g, 7 mmol) in THF (10 mL) was added a 1.0 N solution of NaOH (18 mL). The resulting solution was stirred at room temperature for 1 h and extracted with CH_2Cl_2 three times. The combined organic layers were washed with water, dried over $MgSO_4$, filtered, concentrated and dried under high vacuum to afford 3.6 g (99%) of INCB3284 free base as white powders. MS *m/z*= 521.2 $(M+H)^+$.
The above obtained INCB3284 free base was recrystallized with methanesulfonic acid from a mixed solvent of ethanol/ethyl acetate/water following the procedures described above to provide pure (99.7%) crystals of NCB3284•2MsOH in 70% yield. ^{1}H NMR (400 MHz, CD_3OD): δ 8.75 (m, 2H), 8.45 (m, 1H), 8.14 (m, 2H), 7.86 (m, 1H), 7.67 (m, 1H), 7.60 (m, 1H), 7.45 (m, 1H), 4.58 (m, 1H), 4.17 (s, 2H), 4.08 (s, 3H), 4.02 (m, 1H), 3.79 (m, 1H), 3.61 (m, 1H), 3.48 (m, 2H), 3.20 (m, 1H), 2.69 (s, 6H), 2.33 (m, 3H), 2.22 (m, 2H), 2.02 (m, 2H), 1.77 (m, 2H). Anal. ($C_{28}H_{39}F_3N_4O_{10}S_2·0.5H_2O$): calcd C 46.59, H 5.59, N 7.76; found C 46.38, H 5.70, N 7.79.

_N_-(2-(_trans_-4-Ethoxy-1-(_trans_-4-Hydroxy-4-_p_-tolyl)cyclohexyl)pyrrolidin-3-ylamino)-2-oxoethyl)-3-(trifluoromethyl)benzamide (1)



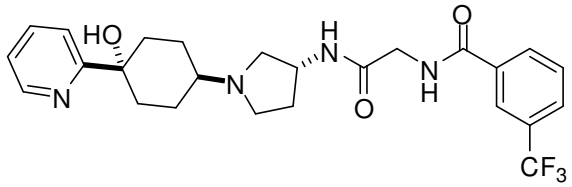
^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.10 (s, 1H), 8.18 (m, 3H), 7.90 (d, 1H), 7.71 (t, 1H), 7.32 (d, 2H), 7.08 (d, 2H), 4.62 (s, 1H), 4.05 (m, 1H), 3.88 (d, 2H), 3.80 (m, 1H), 3.50 (m, 1H), 3.40 (m, 1H), 2.80 (m, 1H), 2.40 (m, 2H), 2.24 (s, 3H), 2.10 (m, 2H), 1.80 (m, 2 H), 1.48 (m, 3H), 1.35 (m, 3H), 1.07 (t, 3H). MS *m/z*= 548.2 $(M+H)^+$. Anal. ($C_{29}H_{36}F_3N_4O_4·0.5H_2O$): calcd C 62.58, H 6.70, N 7.55; found C 62.28, H 6.35, N 7.39.

***N*-(2-((*R*)-1-(*trans*-4-Hydroxy-4-*p*-tolylcyclohexyl)pyrrolidin-3-ylamino)-2-oxoethyl)-3-(trifluoromethyl)benzamide (2)**



^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.09 (s, 1H), 7.97 (d, *J*=7.78 Hz, 1H), 7.77 (d, *J*=7.78Hz, 1H), 7.56 (t, *J*=7.7 Hz, 1H), 7.42 (d, *J*=8.0 Hz, 2H), 7.17 (m, 3H), 6.41 (bs, 1H), 4.48 (bs, 1H), 4.10 (d, *J*=4.9 Hz, 2H), 2.92 (m, 1H), 2.64 (m, 2H), 2.34 (s, 3H), 2.30 (m, 5H), 1.95 (m, 2H), 1.74-1.52 (m, 6H). MS *m/z*= 504.2 $(M+H)^+$. Anal. ($C_{27}H_{32}F_3N_3O_3 \cdot 0.3H_2O$): calcd C 63.64, H 6.46, N 8.25; found C 63.80, H 6.16, N 8.15.

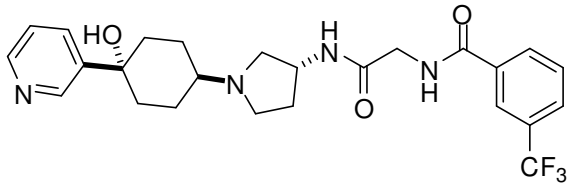
***N*-(2-((*R*)-1-(*trans*-4-Hydroxy-4-(pyridin-2-yl)cyclohexyl)pyrrolidin-3-ylamino)-2-oxoethyl)-3-(trifluoromethyl)benzamide (3)**



^{1}H NMR (DMSO-d_6, 400 MHz, TFA salt) δ: 9.74 (bs, 1H), 9.65 (bs, 1H), 9.10(d, *J* = 6 Hz, 1H), 8.56 (d, *J* = 4.8 Hz, 1H), 8.38 (m, 1H), 8.22 (m, 2H), 7.93 (m, 2H), 7.74 (d, *J* = 7.4 Hz, 2H), 7.39 (d, *J* = 6.8, 1H), 4.37 (s, 1H), 3.90 (d, *J* = 6 Hz, 2H), 3.84-3.46 (m, 2H), 3.34 (m, 2H), 3.13-2.98 (m, 1H), 2.36 (m, 2H), 2.16 – 1.86 (m, 4H), 1.76 – 1.59 (m, 5H).

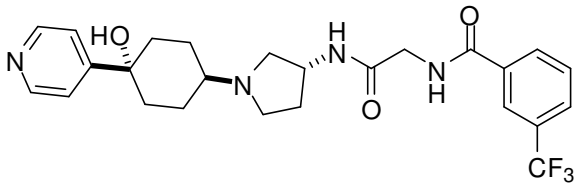
MS *m/z*= 491.2 $(M+H)^+$. Anal. ($C_{25}H_{29}F_3N_4O_3 \cdot 0.5H_2O$): calcd C 60.11, H 6.05, N 11.22; found C 60.07, H 6.00, N 11.18.

***N*-(2-((*R*)-1-(*trans*-4-Hydroxy-4-(pyridin-3-yl)cyclohexyl)pyrrolidin-3-ylamino)-2-oxoethyl)-3-(trifluoromethyl)benzamide (4)**



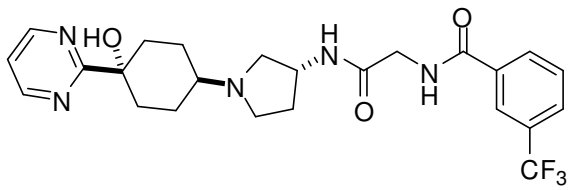
^{1}H NMR (400 MHz, DMSO-d_6): δ 8.99 (t, *J* = 6.0 Hz, 1H), 8.69 (d, *J* = 2.6 Hz, 1H), 8.42 (dd, *J* = 1.6 Hz & 4.8 Hz, 1H), 8.22 (s, 1H), 8.16 (m, 2H), 7.92 (d, *J* = 7.8 Hz, 1H), 7.82 (m, 1H), 7.73 (t, *J* = 7.9 Hz, 1H), 7.33 (dd, *J* = 4.9 Hz & 8.0 Hz, 1H), 4.96 (s, 1H), 4.21 (m, 1H), 3.88 (m, 2H), 2.67 (m, 2H), 2.40 (m, 2H), 2.19 (m, 1H), 2.11 (m, 3H), 1.88 (m, 2H), 1.58 (m, 3H), 1.43 (m, 2H). MS *m/z*= 491.2 $(M+H)^+$. Anal. ($C_{25}H_{29}F_3N_4O_3 \cdot H_2O$): calcd C 59.05, H 6.14, N 11.02; found C 59.15, H 5.92, N 11.01

_N_-(2-((_R_)-1-(_trans_-4-Hydroxy-4-(pyridin-4-yl)cyclohexyl)pyrrolidin-3-ylamino)-2-oxoethyl)-3-(trifluoromethyl)benzamide (5)



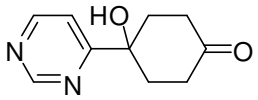
^{1}H NMR (400 MHz, DMSO-d_6): δ 9.02 (d, *J* = 5.6Hz, 1H)), 8.46 (m, 1H), 8.21 (s, 1H), 8.16 (d, *J* = 7.2Hz, 2H), 7.91(d, *J* = 7.6Hz, 1H), 7.72 (m, 1H), 7.42 (m, 1H), 5.01 (s, 1H), 4.15 (s, 1H), 3.86 (m, 2H), 2.70 (m, 2H), 2.48 (m, 4H), 2.43 (m, 2H), 2.30 (m, 1H), 2.05 (m, 2H), 1.80 (m, 1H), 1.68 (m, 2H), 1.60 (m, 2H). HPLC purity: 98.5% (condition A: 0.025% TFA in water/acetonitrile, pH=2); 98.4 (condition B: 0.05% ammonium hydroxide in water/acetonitrile, pH=10). LC-MS $(M+H)^+$=491.2. HRMS $(M+H)^+$: calcd 491.2270; found 491.2274.

_N_-(2-((_R_)-1-(_trans_-4-Hydroxy-4-(pyrimidin-2-yl)cyclohexyl)pyrrolidin-3-ylamino)-2-oxoethyl)-3-(trifluoromethyl)benzamide (6)



^{1}H NMR (500 MHz, CD_3OD) δ 8.77 (d, *J* = 4.9 Hz, 2H), 8.20 (s, 1H), 8.12 (d, *J* = 7.9 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 4.9 Hz, 1H), 4.38 (tt, *J* = 8.9, 4.5 Hz, 1H), 4.01 (s, 2H), 2.85 (dd, *J* = 13.7, 8.7 Hz, 1H), 2.76 (dd, *J* = 9.6, 7.4 Hz, 1H), 2.70 – 2.53 (m, 3H), 2.46 (dd, *J* = 16.2, 8.1 Hz, 1H), 2.29 – 2.16 (m, 2H), 2.03 – 1.91 (m, 2H), 1.74 – 1.55 (m, 3H), 1.48 (d, *J* = 7.9 Hz, 2H). LC-MS $(M+H)^+$ = 492.2. Anal. ($C_{24}H_{28}F_3N_5O_3$): calcd C 58.65, H 5.74, N 14.25; found C 58.64, H 5.68, N 14.26.

4-Hydroxy-4-(pyrimidin-4-yl)cyclohexanone (19a)

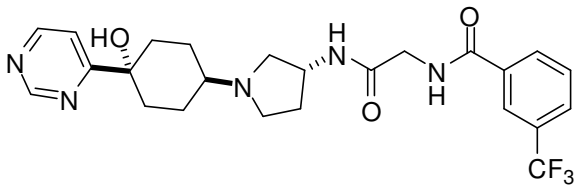


To a solution of diisopropylamine (1.11 g, 11 mmol) in THF (30 mL) was added a 1.6 M solution of n-butyllithium (6.9 mL, 11 mmol). The solution was stirred for 30 min and cannulated to a solution of 5-bromopyrimidine (1.59 g, 10 mmol) in THF (20 mL) at -78 °C. After being stirred at –78 ˚C for 1 h, a solution of 1,4-dioxa-spiro[4.5]decan-8-one (1.72 g, 11 mmol) in THF (20 mL) was added. The reaction was stirred for 2 h at –78 ˚C at which point it was quenched with a solution of NH_4Cl. After being allowed to warm to ambient temperature, the reaction mixture was extracted with EtOAc three times. The organic layers were combined, dried over $MgSO_4$ and concentrated. The residue was purified using flash chromatography (5% MeOH/CH_2Cl_2) to afford the desired product (630 mg, 20% yield). MS $[M+H]^+$: 315.0, 317.0.

To a solution of the above product (630 mg, 2 mmol) in MeOH (30 mL) was added triethylamine (1 mL) and 10% Pd/C (100 mg). The mixture was stirred under hydrogen for 5 h and filtered. The filtrate was concentrated to give the de-bromo product.

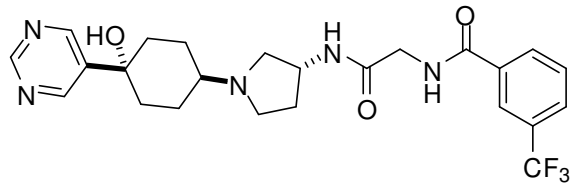
To the de-bromo product in THF (10 mL) was added 3 N HCl (10 mL, 30 mmol). The reaction was stirred at room temperature overnight and quenched using Na_2CO_3. The mixture was extracted with EtOAc three times. The organic layers were combined, dried (Na_2SO_4) and concentrated in vacuo to afford the desired ketone **19a** (232 mg, 60% yield). MS $[M+H]^+$: 193.1.

***N*-(2-((*R*)-1-(*trans*-4-Hydroxy-4-(pyrimidin-4-yl)cyclohexyl)pyrrolidin-3-ylamino)-2-oxoethyl)-3-(trifluoromethyl)benzamide (7)**



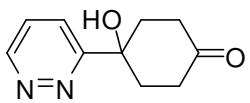
^{1}H NMR (500 MHz, CD_3OD) δ 9.02 (d, *J* = 1.2 Hz, 1H), 8.72 (d, *J* = 5.4 Hz, 1H), 8.18 (s, 1H), 8.11 (d, *J* = 7.9 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.76 (dd, *J* = 5.4, 1.3 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 4.45 – 4.37 (m, 1H), 4.05 (s, 2H), 2.88 (td, *J* = 8.7, 4.7 Hz, 1H), 2.69 (dd, *J* = 9.7, 6.9 Hz, 1H), 2.61 (dd, *J* = 9.7, 3.8 Hz, 1H), 2.46 – 2.35 (m, 3H), 2.29 – 2.18 (m, 2H), 2.00 – 1.90 (m, 2H), 1.75 – 1.61 (m, 3H), 1.53 – 1.42 (m, 2H). LC-MS $(M+H)^+$=492.2. Anal. ($C_{24}H_{28}F_3N_5O_3$): calcd C 58.65, H 5.74, N 14.25; found C 58.53, H 5.75, N 14.33.

***N*-(2-((*R*)-1-(*trans*-4-Hydroxy-4-(pyrimidin-5-yl)cyclohexyl)pyrrolidin-3-ylamino)-2-oxoethyl)-3-(trifluoromethyl)benzamide (8)**



^{1}H NMR (500 MHz, CD_3OD) δ 9.01 (s, 1H), 8.94 (s, 2H), 8.17 (s, 1H), 8.11 (d, *J* = 7.9 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 4.39 (tt, *J* = 9.0, 4.6 Hz, 1H), 4.02 (s, 2H), 3.02 – 2.78 (m, 2H), 2.76 – 2.61 (m, 1H), 2.61 – 2.48 (m, 1H), 2.46 – 2.34 (m, 1H), 2.34 – 2.21 (m, 3H), 2.12 – 1.96 (m, 2H), 1.85 – 1.55 (m, 5H). LC-MS $(M+H)^+$=492.2. HRMS $(M+H)^+$: calcd 492.2222; found 492.2209. Anal. ($C_{24}H_{28}F_3N_5O_3H_2O$): calcd C 56.57, H 5.93, N 13.74; found C 56.32, H 5.59, N 13.38.

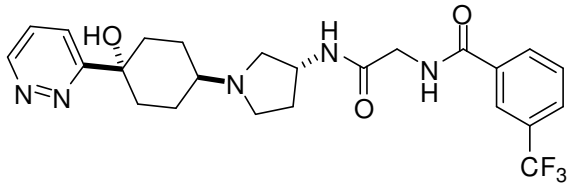
4-Hydroxy-4-(pyridazin-3-yl)cyclohexanone (19c)



To a solution of 2,2,6,6-tetramethylpiperidine (1.72 mL, 11 mmol) at –78 ˚C was added a 1.6 M solution of n-butyllithium in hexanes (6.9 mL, 11 mmol). After being stirred for 30 min, the solution was cannulated to a solution of pyridazine (1.59 g, 10 mmol) in THF (60 mL) at -78 °C. The solution was stirred for 1 h and a solution of 1,4-dioxa-spiro[4.5]decan-8-one (1.72 g, 11 mmol) in THF (20 mL) was added. The reaction was stirred for 5 h at –78 ˚C at which point it was quenched using a solution of NH_4Cl. After being allowed to warm to ambient temperature, the reaction mixture was extracted with EtOAc three times. The organic layers were combined, dried over $MgSO_4$ and concentrated. The residue was purified using flash chromatography to afford two products (0.5 g (12% yield) of fast moving product and 0.42 g (10% yield) of slow moving product). MS $[M+H]^+$: 237.1.

To the fast moving product (0.45 g, 1.9 mmol) in THF (10 mL) was added 3 N HCl (10 mL, 30 mmol). The reaction was stirred at room temperature overnight and quenched using Na_2CO_3. The mixture was extracted with EtOAc three times. The organic layers were combined, dried (Na_2SO_4) and concentrated in vacuo to afford the desired ketone **19c** (183 mg, 50% yield). MS $[M+H]^+$: 193.1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.00 (d, *J*=4.8 Hz, 1H), 7.50 (dd, *J*=8.4 & 4.8 Hz, 1H), 7.10 (d, *J*=8.4 Hz, 1H), 5.40 (s, 1H), 2.2-2.0 (m, 8H).

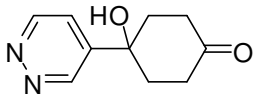
***N*-(2-((*R*)-1-(*trans*-4-Hydroxy-4-(pyridazin-3-yl)cyclohexyl)pyrrolidin-3-ylamino)-2-oxoethyl)-3-(trifluoromethyl)benzamide (9)**



^{1}H NMR (500 MHz, CD_3OD) δ 9.03 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.22 (s, 1H), 8.14 (d, *J* = 7.9 Hz, 1H), 7.99 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.72 – 7.65 (m, 2H), 4.46 – 4.37 (m, 1H), 4.03 (s, 2H), 2.96 (dd, *J* = 10.1, 7.4 Hz, 1H), 2.90 (td, *J* = 8.7, 5.5 Hz, 1H), 2.67 – 2.59 (m, 2H), 2.26 (m, 2H), 2.21 – 2.11 (m, 2H), 1.98 – 1.88 (m, 2H), 1.87 – 1.76 (m, 4H), 1.75 – 1.66 (m, 1H). LC-MS $(M+H)^+$ = 492.2. HRMS $(M+H)^+$:

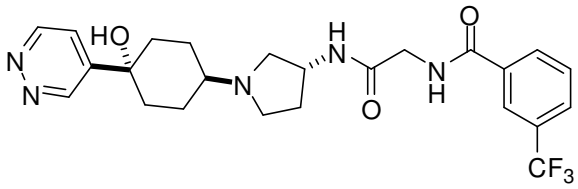
calcd 492.2222; found 492.2225. Anal. ($C_{24}H_{28}F_3N_5O_3H_2O$): calcd C 56.57, H 5.93, N 13.74; found C 56.77, H 5.69, N 13.50.

4-Hydroxy-4-(pyridazin-4-yl)cyclohexanone (19d)



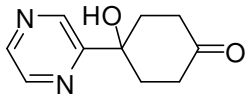
To the slow moving product obtained from the first step for **19c** (0.40 g, 1.7 mmol) in THF (10 mL) was added 3 N HCl (10 mL, 30 mmol). The reaction was stirred at room temperature overnight and quenched using Na_2CO_3. The mixture was extracted with EtOAc three times. The organic layers were combined, dried (Na_2SO_4) and concentrated in vacuo to afford the desired ketone **19d** (164 mg, 50% yield). MS $[M+H]^+$: 193.1. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.30 (s, 1H), 9.20 (d, *J*=7.8 Hz, 1H); 7.8 (d, *J*=7.8 Hz, 1 H), 4.50 (s, 1H), 2.2-2.0 (m, 8H).

***N*-(2-((*R*)-1-(*trans*-4-Hydroxy-4-(pyridazin-4-yl)cyclohexyl)pyrrolidin-3-ylamino)-2-oxoethyl)-3-(trifluoromethyl)benzamide (10)**



^{1}H NMR (500 MHz, CD_3OD) δ 9.37 (dd, *J* = 2.3, 1.1 Hz, 1H), 9.09 (dd, *J* = 5.5, 1.0 Hz, 1H), 8.18 (s, 1H), 8.11 (d, *J* = 7.9 Hz, 1H), 7.86 – 7.80 (m, 2H), 7.66 (t, *J* = 7.8 Hz, 1H), 4.40 (tt, *J* = 9.1, 4.7 Hz, 1H), 4.03 (s, 2H), 2.88 – 2.78 (m, 2H), 2.57 (dd, *J* = 9.7, 4.4 Hz, 1H), 2.51 (dd, *J* = 15.7, 8.4 Hz, 1H), 2.34 – 2.19 (m, 4H), 2.05 – 1.95 (m, 2H), 1.78 – 1.65 (m, 3H), 1.58 – 1.49 (m, 2H). HPLC purity: 99.0% (condition A); 98.9% (condition B). LC-MS $(M+H)^+$=492.2. HRMS $(M+H)^+$: calcd 492.2222; found 492.2218.

4-Hydroxy-4-(pyrazin-2-yl)cyclohexanone (19b)

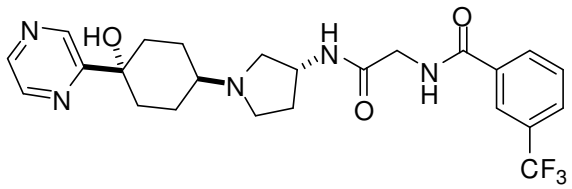


To a solution of diisopropylamine (1.11 g, 11 mmol) in THF (30 mL) was added a 1.6 M solution of n-butyllithium (6.9 mL, 11 mmol). The solution was stirred for 30 min and cannulated to a solution of 2,6-dichloropyridazine (1.49 g, 10 mmol) in THF (20 mL) at -78 °C. After being stirred at –78 ˚C for 1 h, a solution of 1,4-dioxa-spiro[4.5]decan-8-one (1.72 g, 11 mmol) in THF (20 mL) was added. The reaction was stirred for 2 h at –78 ˚C at which point it was quenched with a solution of NH_4Cl. After being allowed to warm to ambient temperature, the reaction mixture was extracted with EtOAc three times. The organic layers were combined, dried over $MgSO_4$ and concentrated. The residue was purified using flash chromatography (5% MeOH/CH_2Cl_2) to afford the desired product (763 mg, 25% yield). MS $[M+H]^+$: 305.0.

To a solution of the above product (610 mg, 2 mmol) in MeOH (30 mL) was added triethylamine (1 mL) and 10% Pd/C (180 mg). The mixture was stirred under hydrogen for 5 h and filtered. The filtrate was concentrated to give the de-chloro product.

To the de-chloro product in THF (10 mL) was added 2 N HCl (20 mL, 40 mmol). The reaction was stirred at room temperature overnight and quenched using Na_2CO_3. The mixture was extracted with EtOAc three times. The organic layers were combined, dried (Na_2SO_4) and concentrated in vacuo to afford the desired ketone **19b** (212 mg, 55% yield). MS $[M+H]^+$ 193.1.

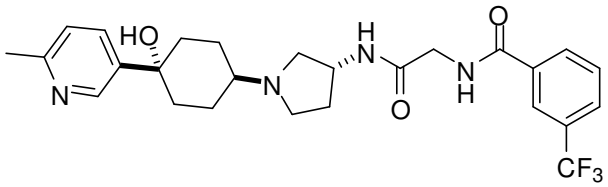
***N*-(2-((*R*)-1-(*trans*-4-Hydroxy-4-(pyrazin-2-yl)cyclohexyl)pyrrolidin-3-ylamino)-2-oxoethyl)-3-(trifluoromethyl)benzamide (11)**



^{1}H NMR (500 MHz, CD_3OD) δ 8.90 (d, *J* = 1.4 Hz, 1H), 8.51 (dd, *J* = 2.5, 1.6 Hz, 1H), 8.44 (d, *J* = 2.6 Hz, 1H), 8.18 (s, 1H), 8.11 (d, *J* = 7.9 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 4.43 – 4.36 (m, 1H), 4.04 (s, 2H), 2.88 (td, *J* = 8.6, 5.0 Hz, 1H), 2.76 (dd, *J* = 9.8, 7.1 Hz, 1H), 2.63 (dd, *J* = 9.9, 3.9 Hz, 1H), 2.51 – 2.41 (m, 3H), 2.33 – 2.27 (m, 1H), 2.27 – 2.18 (m, 1H), 2.03 – 1.94 (m, 2H), 1.75 – 1.54 (m, 5H).

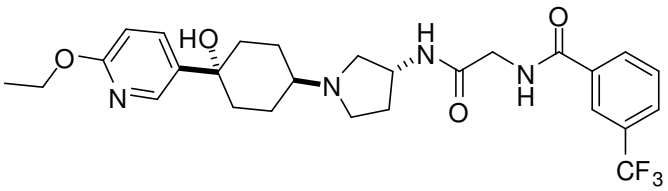
LC-MS $(M+H)^+$=492.2. Anal. ($C_{24}H_{28}F_3N_5O_3 \cdot 0.5H_2O$): calcd C 57.59, H 5.84, N 13.99; found C 57.59, H 5.69, N 13.95.

***N*-(2-((*R*)-1-(*trans*-4-Hydroxy-4-(6-methylpyridin-3-yl)cyclohexyl)pyrrolidin-3-ylamino)-2-oxoethyl)-3-(trifluoromethyl)benzamide (12)**



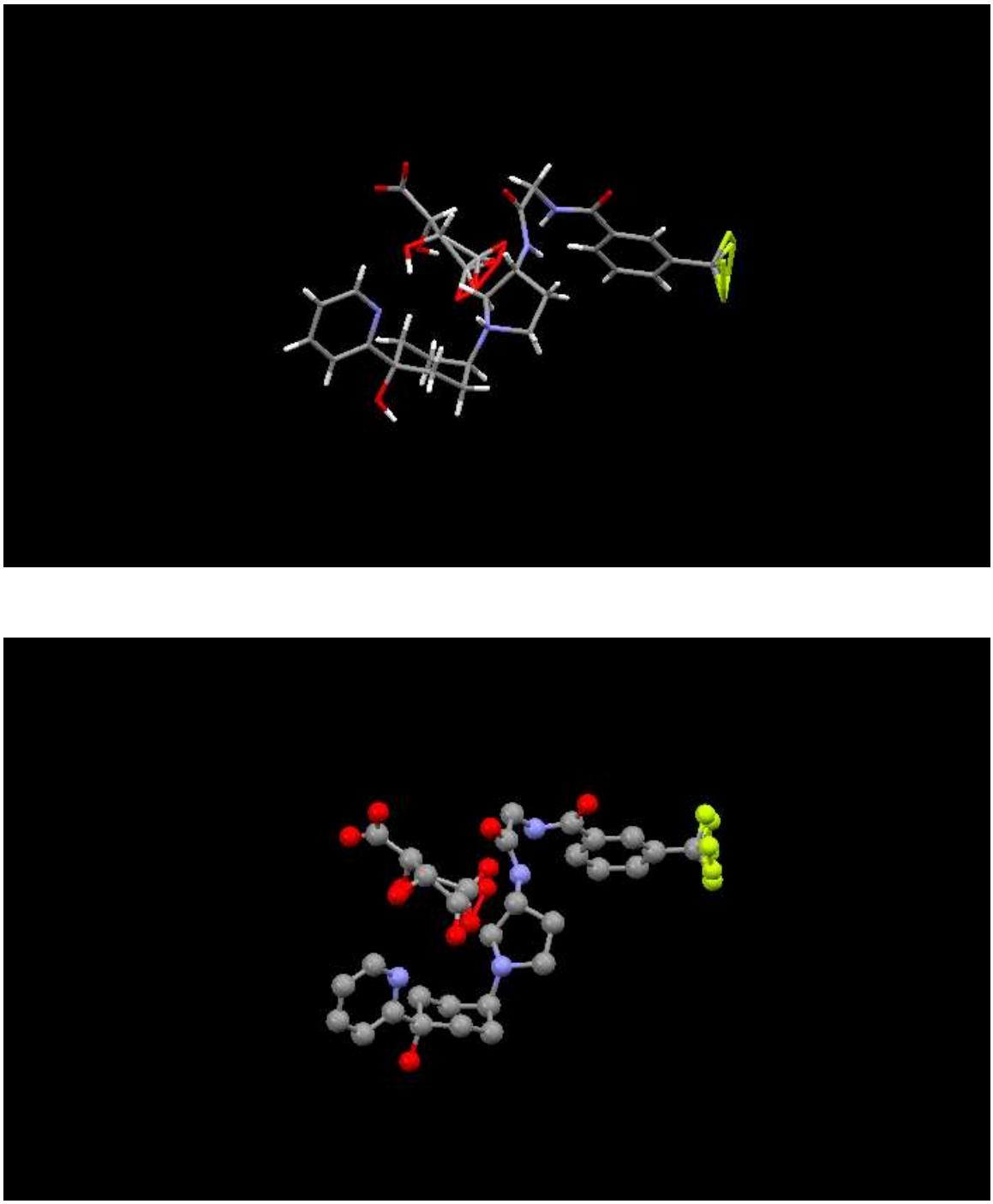
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.61 (d, 1H), 8.11 (s, 1H), 8.00 (d, 1H), 7.76 (d, 1H), 7.74 (d, 1H), 7.56 (d, 1H), 7.52 (m, 1H), 7.13 (d, 1H), 6.60 (bs, 1H), 4.50 (s, 1H), 4.12 (m, 2H), 2.95 (m, 1H), 2.75 (m, 1H), 2.60 (m, 1H), 2.52 (s, 3H), 2.30 (m, 5H), 1.90 (m, 2H), 1.85 (m, 1H), 1.65 (m, 5H). LC-MS $(M+H)^+$=505.2. Anal. ($C_{26}H_{31}F_3N_4O_3 \cdot 0.5H_2O$): calcd C 60.81, H 6.28, N 10.91; found C 60.54, H 6.15, N 10.82.

***N*-(2-((*R*)-1-(*trans*-4-Hydroxy-4-(6-ethoxypyridin-3-yl)cyclohexyl)pyrrolidin-3-ylamino)-2-oxoethyl)-3-(trifluoromethyl)benzamide (14)**



^{1}H NMR (400 MHz, DMSO-d_6): δ 8.97 (t, 1H), 8.19 (s, 2H), 8.13 (m, 2H), 7.90 (d, 1H), 7.71 (m, 2H), 6.70 (d, 1H), 4.79 (s, 1H), 4.25 (q, 2H), 4.18 (m, 1H), 3.85 (m, 2H), 2.66 (m, 2H), 2.40 (m, 2H), 2.16 (m, 1H), 2.07 (m, 3H), 1.83 (m, 2H), 1.60 (m, 1H), 1.54 – 1.37 (m, 4H), 1.27 (t, 3H). HPLC purity: 98.8% (condition A); 99.0% (condition B). LC-MS $(M+H)^+$=535.2. HRMS: calcd 535.2225; found 535.2230.

2. X-ray crystal structure of the tartaric acid salt of 3



The X-ray crystal structure of the tartaric acid salt of **3** is shown with hydrogen atoms using capped sticks (top panel) and without hydrogen atoms using balls and sticks (lower panel). Grey color: carbon atoms; White color: hydrogen atoms; Blue color: nitrogen atoms; Red color: oxygen atoms; Green color: fluorine atoms.