CNS penetrant TEAD1,2,4 inhibitor MSC-4070 derived from phenotypic screening hit optimization

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Activities in TEAD reporter and viability assays with standard deviation and number of repetitions

Table1

(Table 2 from main manuscript file)

No	Reporter pIC_{50}	STD	rep	NCI-H226 pIC_{50}	STD	rep
1	7.27	0.08	3	6.11	0.28	3
MSC-2723	7.71	0.14	7	7.68	0.11	5
MSC-9643	7.46	0.15	12	7.28	0.21	10
MSC-4071	7.82	0.12	6	7.57	0.17	5
2	6.92			6.66		
3	6.92			6.61	0.26	2
4	5.46			5.01		

Table 2

(Table 5 from main manuscript file)

No	R	Reporter pIC_{50}	STD	rep	NCI-H226 pIC_{50}	STD	rep	MSTO-211H pIC_{50}	STD	rep
5	H	6.20			5.96					
6	Me	6.28			5.92			6.15		
7	H	7.57			7.21			6.58	0.50	
8	Me	7.19			7.34			7.02		
9	H	7.61	0.16	3	7.06	0.43	3	7.58	0.27	3
10	Me	7.70			7.70					
11	H	7.62						6.80		
12	Me	7.37						6.44		
13	H	7.15			6.52					
14	Me	7.28			6.85			6.42		
15	H	6.54						5.55		
16	Me	6.43						5.37		
17	H	7.41						6.58		
18	Me	7.20						6.01		
19	H	7.41			7.44			6.67	0.04	
20	Me	7.20						6.27		
21	H	7.11	0.13	2	6.70			6.63	0.28	2
22	Me	6.72						5.77		
23	H	7.96	0.24	2	7.77			6.77		
24	Me	7.52						7.00	0.17	2
25	H	7.05	0.05	2				6.22	0.31	2
26	Me	6.74						5.72		
27	H	7.42						6.49		
28	Me	7.26						6.51		
29	H	7.84	0.05	3	7.51	0.09	3	7.27	0.13	3
MSC-4070	Me	7.85	0.28	3	7.51	0.17	3	6.90	0.19	8
30	H	7.48	0.04	2	7.40	0.14	3	6.64		
31	Me	7.39						6.82		
32	H	7.55	0.15	4	7.16	0.10	3	7.05	0.14	3
33	Me	7.17						6.74		

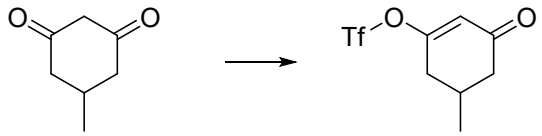
Experimental procedures

All reactions were carried out under a nitrogen atmosphere or in sealed vials unless otherwise noted. Dry solvents and reagents were of commercial quality and were used as purchased. Reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using Merck silica gel 60 F254 by fluorescence quenching under UV light or by high-pressure liquid chromatography with subsequent mass detection, except if otherwise indicated. The purity of the compounds reported in the manuscript was analyzed through HPLC-MS methodology (> 95%). Chromatographic purification of products (flash chromatography) was performed on Isco Combiflash systems using Redisep columns and ethyl acetate (EtOAc)/heptane gradients. Concentration under reduced pressure was performed by rotary evaporation at 40 °C at the appropriate pressure unless otherwise stated. ^{1}H NMR (in DMSO-d_6) and mass spectra are in agreement with the structures and were recorded on spectrometers, with the given field strengths given in MHz (TMS as an internal standard) and Vacuum Generators VG 70-70 or 70-250 at 70 eV, respectively. All compounds reported in the manuscript have a purity ≥ 95% unless noted otherwise.

LCMS conditions:

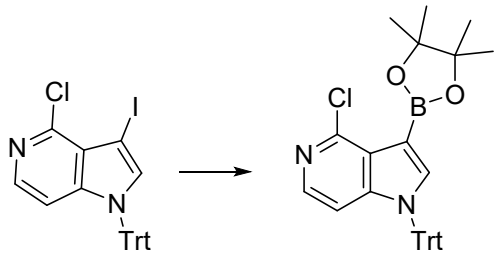
Method 1: XBridge C18 5um, 50-4.6 mm; buffer A: water + 0.1% TFA; buffer B: acetonitrile; gradient: 30% - 70% B in 6.5 min. Method 2: Chromolith HR RP-18e, 50-4.6 mm; flow: 3.3 mL/min; T: 40 °C; buffer A: water + 0.05% FA; buffer B: acetonitrile + 0.04% FA+ 1% water; gradient: 1-99% B (0 – 2.0 min), 99% B (2 – 2.5 min). Method 3: HALO C18 2 µm 3.0-30 mm; flow: 1.5 mL/min; T: 40 °C; buffer A: water + 0.05% TFA; buffer B: acetonitrile + 0.05% TFA; gradient: 5% – 95% B (0 - 1.2 min), 95% B (1.2 - 1.8 min), 95% – 5% B (1.8 - 1.82 min). Method 4: Chromolith HR RP-18e, 50-4.6 mm; flow: 3.3 mL/min; T: 45 °C; buffer A: water + 0.05 % FA; buffer B: acetonitrile + 0.04% FA; gradient: 1-99% B (0 – 2.0 min), 99% B (2 – 2.5 min). Method 5: Chromolith SpeedRod RP-18e 5 µm, 50-4.6 mm; flow: 3.3 mL/min; T: 40 °C; buffer A: water + 0.1% TFA; buffer B: acetonitrile + 0.1% TFA; gradient: 1 - 99% B in 2 min – 99% B from 2 - 2.5 min. Method 6: HALO 90A C18 2 µm, 3.0-30 mm; flow: 1.5 mL/min; T: 40 °C; buffer A: water + 0.1% FA; buffer B: acetonitrile + 0.1% FA; gradient: 5% – 95% B (0 - 1.2 min) 95% B (1.2 - 1.8 min) 95% – 5% B (1.8 - 1.82 min). Method 7: HALO C18 2 µm, 3.0-30 mm; flow: 1.2 mL/min; T: 40 °C; buffer A: water + 0.05% TFA; buffer B: acetonitrile + 0.05% TFA; gradient: 5% – 95% B (0 - 1.2 min), 95% B (1.2 - 1.8 min), 95% – 5% B (1.8 - 1.82 min). Method 8: Shim-Pack Scepter C18-120 3.0 µm 3.0-33 mm; flow: 1.5 mL/min; T: 40 °C; buffer A: water + 6.5 mM NH_4HCO_3+NH_4OH (pH=10); buffer B: acetonitrile; gradient: 30% – 95% B (0 - 2.1 min), 95% B (2.1 - 2.7 min), 95% - 30% B (2.7 - 2.75 min). Method 9: EC-C18 4 µm, 50-3.0 mm; flow: 1.0 mL/min; T: 40 °C; buffer A: water + 0.05% TFA; buffer B: acetonitrile; gradient: 30% - 95% B in 6.5 min. Method 10: HALO 90A C18 2 µm, 3.0-30 mm; flow: 1.5 mL/min; T: 40 °C; buffer A: water + 0.1% FA; buffer B: acetonitrile + 0.1% FA; gradient: 5% – 95% B (0 - 1.2 min) 95% B (1.2 - 1.8 min) 95% – 5% B (1.8 - 1.82 min). Method 11: HALO 90A C18 2 µm, 3.0-30 mm; flow: 1.5 mL/min; T: 40 °C; buffer A: water + 0.05% TFA; buffer B: acetonitrile + 0.05% TFA; gradient: 5% – 100% B (0 – 0.7 min), 100% B (0.7 – 1.1 min), 100% – 5% B (1.1 - 1.12 min). Method 12: HALO 90A C18 2 µm, 3.0-30 mm; flow: 1.5 mL/min; T: 40 °C; buffer A: water + 0.1% FA; buffer B: acetonitrile + 0.1% FA; gradient: 5% – 100% B (0 – 0.7 min), 100% B (0.7 – 1.1 min), 100% – 5% B (1.1 - 1.12 min). Method 13: XSelect CSH Fluoro 2.5 µm, 3.0-50 mm; flow: 1.5 mL/min; T: 40 °C; buffer A: water + 0.1% FA; buffer B: acetonitrile + 0.1% FA; gradient: 5% – 95% B (0 – 1.20 min), 95% B (1.20 - 1.80 min), 95% – 5% B (1.80 - 1.82 min). Method 14: Shim-Pack Scepter C18-120 3.0 µm, 3.0-33 mm; flow: 1.5 mL/min; T: 40 °C; buffer A: water + 6.5 mM NH_4HCO_3+NH_4OH (pH=10); buffer B: acetonitrile; gradient: 10% – 95% B (0 - 1.2 min), 95% B (1.2 - 1.8 min), 95% - 10% B (1.8 - 1.82 min). Method 15: HALO C18 2 µm, 3.0-30 mm; flow: 1.2 mL/min; T: 40 °C; buffer A: water + 0.05% TFA; buffer B: acetonitrile + 0.05 % TFA; gradient: 5% – 100% B (0 – 0.7 min), 100% B (0.7 – 1.1 min), 100% – 5% B (1.1 - 1.12 min). Method 16: Shim-Pack C18 3.0 µm 3.0-33 mm; flow: 1.2 mL/min; T: 40 °C; buffer A: water + 5mM NH_4HCO_3; buffer B: acetonitrile; gradient: 30 % – 95 % B (0 - 2.1 min), 95% B (2.1 - 2.7 min), 95% - 30% B (2.7 - 2.75 min). Method 17: Shim-Pack Scepter C18-120 3.0 µm 3.0-33 mm; flow: 1.2 mL/min; T: 40 °C; buffer A: water + 6.5mM NH_4HCO_3+NH_4OH (pH=10); buffer B: acetonitrile; gradient: 30% – 95% B (0 - 2.1 min), 95% B (2.1 - 2.7 min), 95% - 30% B (2.7 - 2.75 min).

5-methyl-3-oxocyclohex-1-en-1-yl trifluoromethanesulfonate



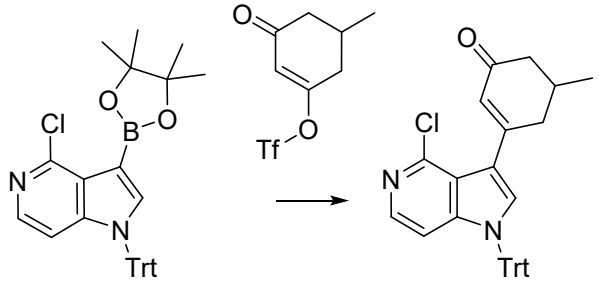
To a stirred mixture of 5-methylcyclohexane-1,3-dione (5.00 g; 37.65 mmol) and TEA (16.53 ml; 112.96 mmol) in DCM (100 mL) was added Tf_2O (8 mL; 45.18 mmol) at 0 °C. The resulting mixture was stirred for 5 h at 25 °C. For work-up mixture was extracted with DCM and the organic layer was washed with brine and dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated under reduced pressure to give the crude product (9.80 g; 36.90 mmol; 98%; yellow oil) that was used in the next step without further purification. LCMS: 0.87 min, 259.0 [M+H], Method 15.

4-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(triphenylmethyl)-1H-pyrrolo[3,2-c]pyridine



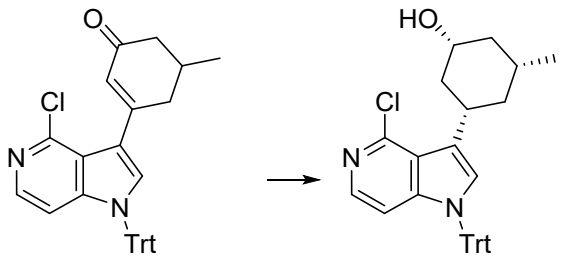
To a stirred solution of 4-chloro-3-iodo-1-(triphenylmethyl)-1H-pyrrolo[3,2-c]pyridine (5.00 g; 9.02 mmol) in dioxane (150 mL) was added 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.53 g; 27.06 mmol), TEA (50 mL) and $Pd(PPh_3)_4$ (1.10 g; 0.90 mmol). The mixture was stirred for 2 h at 100 °C. For work up the mixture was diluted with EtOAC and then washed with brine. The organic layer was dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was purified by chromatography to afford the product (4.10 g; 84%) as yellow solid. LCMS: 1.14 min, 521.3 [M+H], Method 13.

3-[4-chloro-1-(triphenylmethyl)-1H-pyrrolo[3,2-c]pyridin-3-yl]-5-methylcyclohex-2-en-1-one



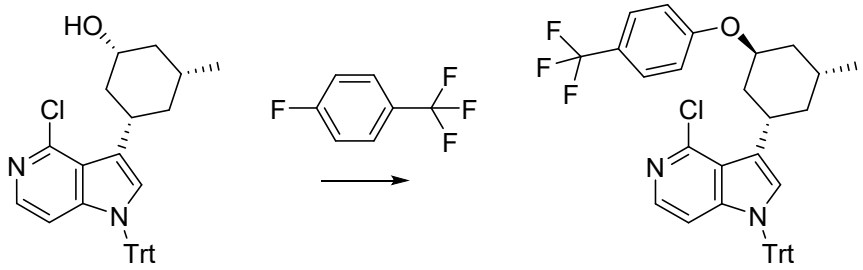
To a stirred mixture of 5-methyl-3-oxocyclohex-1-en-1-yl trifluoromethanesulfonate (2.00 g; 7.62 mmol) and 4-chloro-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(triphenylmethyl)-1H-pyrrolo[3,2-c]pyridine (4.00 g; 7.00 mmol) in dioxane (60 mL) and H_2O (10 mL) was added $Pd(dppf)Cl_2$ (0.59 g; 0.76 mmol) and Na_2CO_3 (2.55 g; 22.85 mmol) at 25 °C. The resulting mixture was stirred for 2 h at 100 °C under nitrogen atmosphere and then concentrated under vacuum. The residue was purified by chromatography to afford the product (2.80 g; 70%) as yellow solid. LCMS: 0.89 min, 503.2 [M+H], Method 11.

(5R)-3-[4-chloro-1-(triphenylmethyl)-1H-pyrrolo[3,2-c]pyridin-3-yl]-5-methylcyclohexan-1-ol



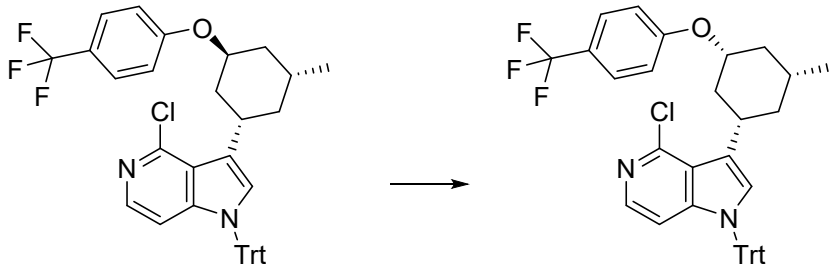
To a solution of 3-[4-chloro-1-(triphenylmethyl)-1H-pyrrolo[3,2-c]pyridin-3-yl]-5-methylcyclohex-2-en-1-one (1.80 g; 3.27 mmol) in AcOEt (100 mL) was added dioxoplatinum (1.00 g; 4.18 mmol). The mixture was hydrogenated at RT for 6 h using a hydrogen balloon. For work up the mixture was filtered through a Celite pad and concentrated under reduced pressure. The residue was purified by chromatography to afford the product (1.20 g; 69%) as white solid. LCMS: 0.86 min, 507.1 [M+H], Method 12.

4-chloro-3-((1S,3R,5S)-3-methyl-5-(4-(trifluoromethyl)phenoxy)cyclohexyl)-1-trityl-1H-pyrrolo[3,2-c]pyridine



To a stirred solution of (5R)-3-[4-chloro-1-(triphenylmethyl)-1H-pyrrolo[3,2-c]pyridin-3-yl]-5-methylcyclohexan-1-ol (1.20 g; 2.25 mmol) in DMF (20 mL) was added NaH (180 mg; 4.50 mmol) at 0 °C. 1-fluoro-4-(trifluoromethyl)benzene (1.56 g; 9.02 mmol) was added after 30 mins at 0 °C. The resulting mixture was stirred for 6 h at 80 °C. For work up the reaction was quenched by the addition of ice water. The resulting mixture was diluted with EtOAc and then washed with brine. The organic layer was dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was purified by chromatography to afford the product (1.10 g; 75%) as white solid. LCMS: 1.13 min, 651.3 [M+H], Method 15.

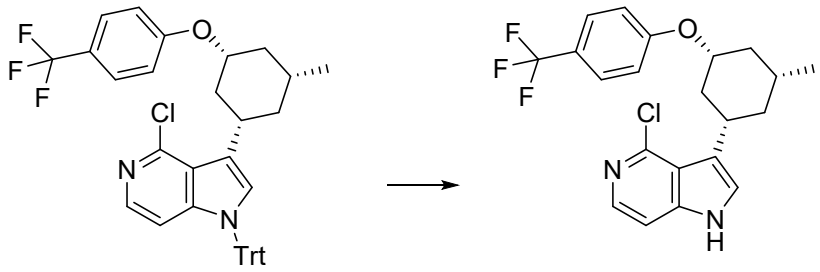
4-chloro-3-[(1S,3R,5R)-3-methyl-5-[4-(trifluoromethyl)phenoxy]cyclohexyl]-1-(triphenylmethyl)-1H-pyrrolo[3,2-c]pyridine



4-chloro-3-((1S,3R,5S)-3-methyl-5-(4-(trifluoromethyl)phenoxy)cyclohexyl)-1-trityl-1H-pyrrolo[3,2-c]pyridine (1.10 g; 1.67 mmol; 1.00 eq.) was purified by Prep-Chiral-HPLC with the following conditions Column: CHIRALPAK IE, 2*25 cm, 5 μm; Mobile Phase A: HEX(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH:DCM = 1:1; Flow rate: 20 mL/min; Gradient (B%): isocratic 5; Wave Length:

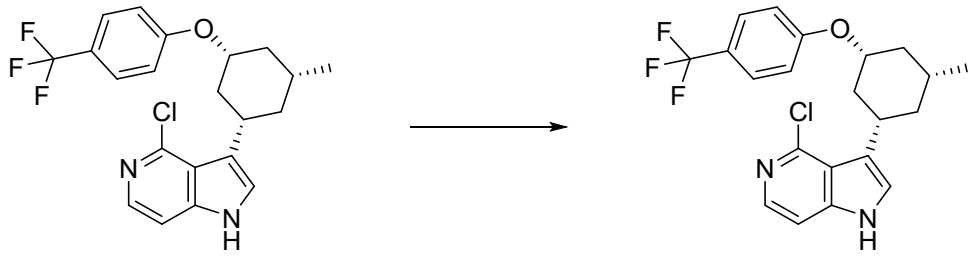
220/254 nm; RT1(min): 11.363; RT2(min): 15.43; Sample Solvent: EtOH; Injection Volume: 0.7 mL; Number Of Runs: 24 to afford 4-chloro-3-[(1S,3R,5R)-3-methyl-5-[4-(trifluoromethyl)phenoxy]cyclohexyl]-1-(triphenylmethyl)-1H-pyrrolo[3,2-c]pyridine (600 mg; 53%) as white solid. LCMS: 1.65 min, 651.3 [M+H], Method 7.

4-chloro-3-[(1S,3R,5R)-3-methyl-5-[4-(trifluoromethyl)phenoxy]cyclohexyl]-1H-pyrrolo[3,2-c]pyridine



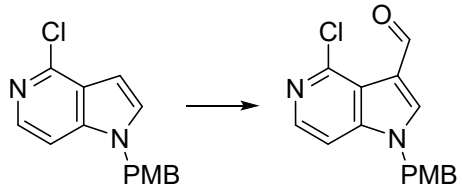
To a stirred solution of 4-chloro-3-[(1S,3R,5R)-3-methyl-5-[4-(trifluoromethyl) phenoxy]cyclohexyl]-1-(triphenylmethyl)-1H-pyrrolo[3,2-c]pyridine (600 mg; 0.91 mmol) in dioxane (30 mL) was added HCl (3 mL; 36 mmol). The resulting mixture was stirred for 6 h at 100 °C. For work up the pH value of the solution was adjusted to 6~7 with $NaHCO_3$. The resulting mixture was diluted with EtOAc and then washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was purified by chromatography to afford the product (160 mg; 42%) as white solid. LCMS: 1.17 min, 409.1 [M+H], Method 6.

4-chloro-3-[(1S,3R,5R)-3-methyl-5-[4-(trifluoromethyl)phenoxy]cyclohexyl]-1H-pyrrolo[3,2-c]pyridine (**2**)



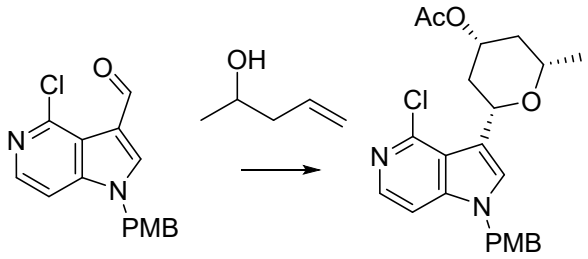
The 4-chloro-3-[(1S,3R,5R)-3-methyl-5-[4-(trifluoromethyl)phenoxy]cyclohexyl]-1H-pyrrolo[3,2-c]pyridine (100 mg; 0.21 mmol) was re-purified by chromatography (67.70 mg; 70%) white solid. LCMS: 1.10 min, 409.0 [M+H], Method 7. ^{1}H NMR (300 MHz, DMSO) 11.70 (s, 1H), 7.90 (d, J = 5.6 Hz, 1H), 7.62 (d, J = 8.5 Hz, 2H), 7.43 - 7.29 (m, 2H), 7.17 (d, J = 8.5 Hz, 2H), 4.80 - 4.56 (m, 1H), 3.70 (dqd, J = 8.7, 4.4, 1.5 Hz, 1H), 3.54 -3.35 (m, 2H), 2.45 (d, J = 11.5 Hz, 1H), 2.16 (d, J = 12.0 Hz, 1H), 2.04 (s, 1H), 1.83 (s, 1H), 1.49 (q, J = 11.8 Hz, 1H), 1.22 - 1.09 (m, 2H), 1.04 - 0.93 (m, 3H).

4-chloro-1-[(4-methoxyphenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-3-carbaldehyde



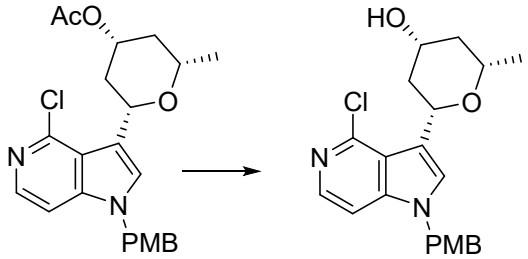
A solution of 4-chloro-1-[(4-methoxyphenyl)methyl]-1H-pyrrolo[3,2-c]pyridine (15 g; 53.35 mmol) in DMF (200 mL) was treated for 0.5 h at 0 °C under nitrogen atmosphere with $POCl_3$ (24.67 g; 161 mmol). The mixture was stirred overnight at 60 °C. The reaction was quenched by the addition of H_2O at 0 °C and the mixture was basified to pH 7 with NaOH in H_2O. The precipitated solids were collected by filtration and washed with H_2O affording the crude product (15 g; 92%) as yellow solid. LCMS: 0.67 min, 301.1 [M+H], Method 11.

(2S,4R,6S)-2-{4-chloro-1-[(4-methoxyphenyl)methyl]-1H-pyrrolo[3,2-c]pyridin-3-yl}-6-methyloxan-4-yl acetate and enantiomer



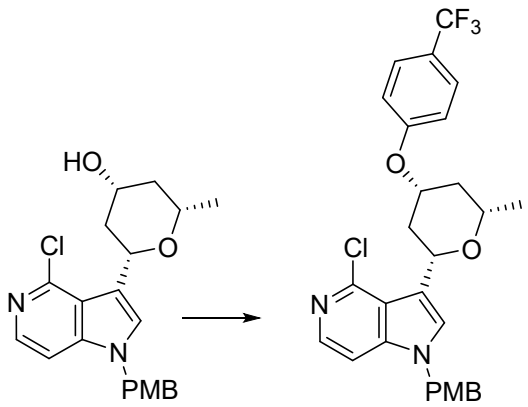
To a stirred solution of 4-chloro-1-[(4-methoxyphenyl)methyl]-1H-pyrrolo[3,2-c]pyridine-3-carbaldehyde (5 g; 16.13 mmol) in DCM (10 mL) was added pent-4-en-2-ol (3 g; 33.09 mmol), AcOH (10 mL), trimethylsilyl acetate (17 g; 126 mmol) and $BF_3.Et_2O$ (9 mL; 67.470 mmol) at RT under N_2 atmosphere. After 12 h the reaction was quenched by the addition of H_2O at 0 °C and the resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by chromatography to afford the product as racemic mixture (420 mg; 6%) as off-white solid. LCMS: 0.71 min, 429.2 [M+H], Method 12.

(2S,4R,6S)-2-{4-chloro-1-[(4-methoxyphenyl)methyl]-1H-pyrrolo[3,2-c]pyridin-3-yl}-6-methyloxan-4-ol and enantiomer



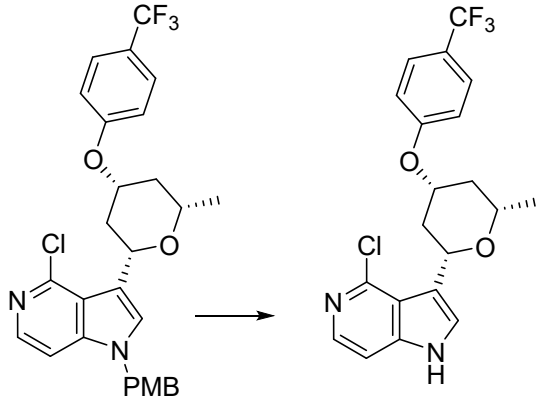
To a stirred solution of racemic "all-cis" 2-{4-chloro-1-[(4-methoxyphenyl)methyl]-1H-pyrrolo[3,2-c]pyridin-3-yl}-6-methyloxan-4-yl acetate (420 mg; 0.87 mmol) in MeOH (5 mL) was added K_2CO_3 (220 mg; 1.51 mmol) at RT. The resulting mixture was stirred for 2 h and then neutralized with conc. HCl. The solution was extracted with EtOAc and the combined organic layers were washed with brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by chromatography to afford racemic "all-cis" 2-{4-chloro-1-[(4-methoxyphenyl)methyl]-1H-pyrrolo[3,2-c]pyridin-3-yl}-6-methyloxan-4-ol (260 mg; 72%) as white solid. LCMS: 0.55 min, 387.15 [M+H], Method 11.

4-chloro-1-[(4-methoxyphenyl)methyl]-3-[(2S,4R,6S)-6-methyl-4-[4-(trifluoromethyl)phenoxy]oxan-2-yl]-1H-pyrrolo[3,2-c]pyridine and enantiomer



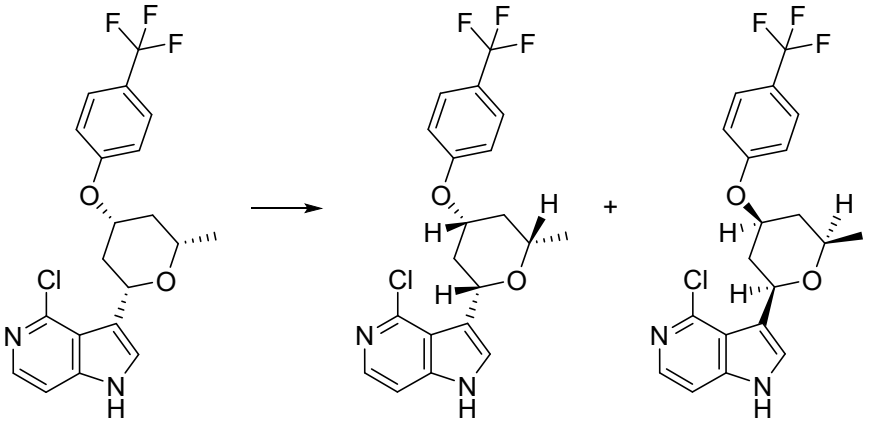
To a stirred solution of racemic "all-cis" 2-{4-chloro-1-[(4-methoxyphenyl)methyl]-1H-pyrrolo[3,2-c]pyridin-3-yl}-6-methyloxan-4-ol (100 mg; 0.24 mmol) in DMF (5 mL) was added NaH (20 mg; 0.5 mmol) at 0 °C. After 0.5 h 1-fluoro-4-(trifluoromethyl)benzene (64 mg; 0.37 mmol) was added to the mixture at the same temperature and the resulting mixture was stirred overnight at RT. The reaction was quenched by the addition of H_2O at 0 °C and the resulting mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by chromatography to afford the racemic product (100 mg; 75%) as yellow solid. LCMS: 0.86 min, 531.2 [M+H], Method 12.

Racemic 4-chloro-3-[(2S,4R,6S)-6-methyl-4-[4-(trifluoromethyl)phenoxy]oxan-2-yl]-1H-pyrrolo[3,2-c]pyridine



To a stirred solution of 4-chloro-1-[(4-methoxyphenyl)methyl]-3-[(2S,4R,6S)-6-methyl-4-[4-(trifluoromethyl)phenoxy]oxan-2-yl]-1H-pyrrolo[3,2-c]pyridine (100 mg; 0.175 mmol) in DMSO (3 mL) was added t-BuOK in THF (3 mL; 3 mmol) dropwise at 0 °C. The resulting mixture was stirred overnight at RT under oxygen atmosphere. After neutralization with aq. HCl the solution was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by chromatography to afford the racemic product (30 mg; 41%) as white solid. LCMS: 0.68 min, 411.2 [M+H], Method 11.

rel-4-chloro-3-[(2R,4S,6R)-6-methyl-4-[4-(trifluoromethyl)phenoxy]oxan-2-yl]-1H-pyrrolo[3,2-c]pyridine (**3**) and rel-4-chloro-3-[(2S,4R,6S)-6-methyl-4-[4-(trifluoromethyl)phenoxy]oxan-2-yl]-1H-pyrrolo[3,2-c]pyridine

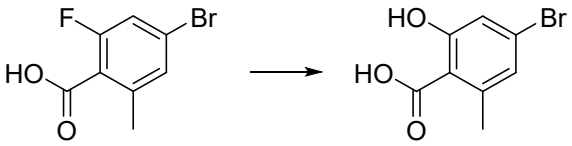


Racemic 4-chloro-3-[6-methyl-4-[4-(trifluoromethyl)phenoxy]oxan-2-yl]-1H-pyrrolo[3,2-c]pyridine (30 mg; 0.070 mmol) was purified by Prep-CHIRAL-HPLC with the following conditions: Column: CHIRAL ART Cellulose-SB, 2*25 cm, 5 μm; Mobile Phase A: HEX(0.5% 2M NH_3-MeOH), Mobile Phase B: EtOH:DCM = 1:1; Flow rate: 20 mL/min.

rel-4-chloro-3-[(2R,4S,6R)-6-methyl-4-[4-(trifluoromethyl)phenoxy]oxan-2-yl]-1H-pyrrolo[3,2-c]pyridine (9.4 mg; 33 %) was obtained as white solid. LCMS: 1.79 min, 411.1 [M+H], Method 16. ^{1}H NMR (300 MHz, DMSO) 11.84 (s, 1H), 7.94 (d, J = 5.6 Hz, 1H), 7.64 (d, J = 8.7 Hz, 2H), 7.58 (d, J = 2.4 Hz, 1H), 7.38 (d, J = 5.6 Hz, 1H), 7.23 (d, J = 8.6 Hz, 2H), 5.11 (d, J = 11.2 Hz, 1H), 4.94 (tt, J = 10.3, 4.6 Hz, 1H), 3.92 - 3.80 (m, 1H), 2.29 - 2.14 (m, 1H), 1.80 (q, J = 11.5 Hz, 1H), 1.37 - 1.26 (m, 1H), 1.24 (s, 1H), 1.20 (d, J = 6.1 Hz, 3H).

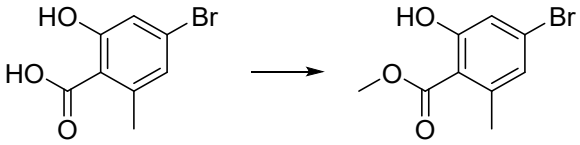
rel-4-chloro-3-[(2S,4R,6S)-6-methyl-4-[4-(trifluoromethyl)phenoxy]oxan-2-yl]-1H-pyrrolo[3,2-c]pyridine (9.2 mg; 32 %) as obtained as white solid. LCMS: 1.78 min, 411.1 [M+H], Method 16. ^{1}H NMR (300 MHz, DMSO) 11.84 (s, 1H), 7.94 (d, J = 5.6 Hz, 1H), 7.64 (d, J = 8.6 Hz, 2H), 7.58 (d, J = 2.3 Hz, 1H), 7.38 (d, J = 5.6 Hz, 1H), 7.23 (d, J = 8.6 Hz, 2H), 5.11 (d, J = 11.1 Hz, 1H), 4.94 (dt, J = 10.8, 6.0 Hz, 1H), 3.85 (dd, J = 9.7, 5.9 Hz, 1H), 2.21 (d, J = 11.2 Hz, 1H), 1.80 (q, J = 11.5 Hz, 1H), 1.37 - 1.27 (m, 1H), 1.24 (s, 1H), 1.20 (d, J = 6.2 Hz, 3H).

4-bromo-2-hydroxy-6-methylbenzoic acid



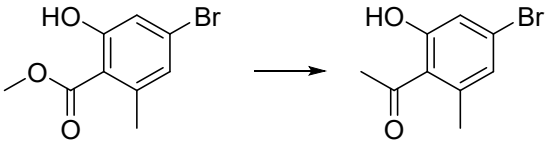
To a solution of 4-bromo-2-fluoro-6-methylbenzoic acid (4.90 g; 19.98 mmol) in 1,3-Dimethyl-2-imidazolidinone (55 mL) was added NaOH (3.50 g; 83.15 mmol) at 0 °C. The resulting mixture was stirred for 3 h at 120 °C. The mixture was diluted with 600 mL H_2O and then acidified to pH 3 with 2M HCl (aq.). The precipitated solids were collected by filtration, washed with water and dried under vacuum to afford the product (4.43 g; 85%) as white solid. LCMS: 1.23 min, 231.1 [M+H], Method 13.

methyl 4-bromo-2-hydroxy-6-methylbenzoate



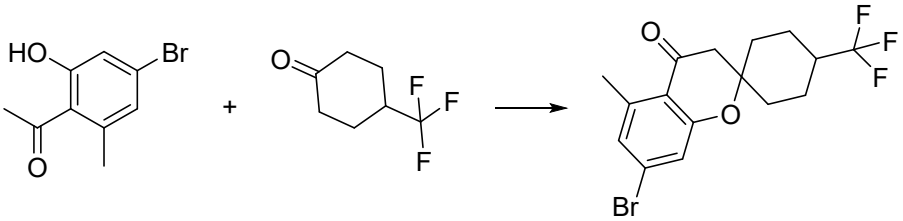
To a stirred solution of 4-bromo-2-hydroxy-6-methylbenzoic acid (4.40 g; 16.86 mmol) in MeOH (120 mL) was added H_2SO_4 (3.04 mL; 55.96 mmol) dropwise. The resulting mixture was stirred for 40 h at 80 °C. Then the mixture was concentrated under reduced pressure and the residue was diluted with EtOAc and ice. The mixture was neutralized with saturated $NaHCO_3$ (aq.) and the resulting mixture was extracted with EtOAc. The combined organic layers were washed with $NaHCO_3$ and brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by chromatography to afford the product (2.20 g; 53%) as off-white oil. LCMS: 0.94 min, [no mass detected], Method 13.

1-(4-bromo-2-hydroxy-6-methylphenyl)ethan-1-one



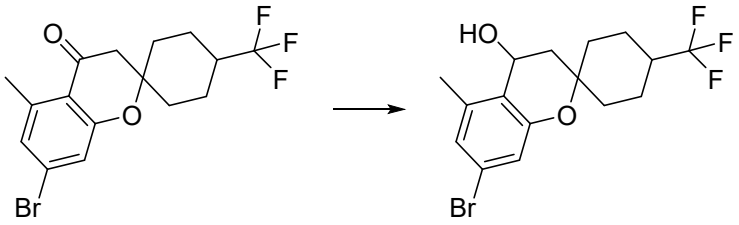
To a stirred solution of in Toluene (2 mL) was added sodium methanesulfinate (2.39 g; 22.21 mmol) and LiHMDS (1 M in toluene) (22 mL; 22.00 mmol) at 0 °C. The resulting mixture was stirred for 3 h at 80 °C. The resulting mixture was diluted with sat. NH_4Cl and extracted with EtOAc. The combined organic layers were dried over anhydrous Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by chromatography to afford the product (810 mg; 38%) as colorless oil. LCMS: 0.86 min, 231.1 [M+H], Method 13.

7-bromo-5-methyl-4'-(trifluoromethyl)-3,4-dihydrospiro[1-benzopyran-2,1'-cyclohexan]-4-one



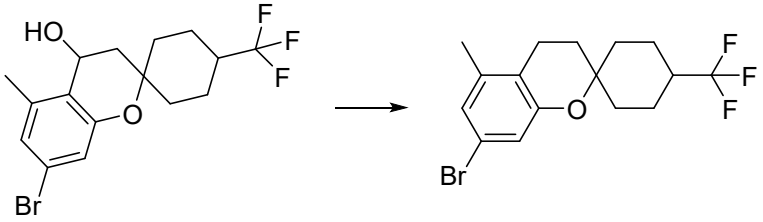
To a stirred solution of 1-(4-bromo-2-hydroxy-6-methylphenyl)ethan-1-one (760 mg; 3.20 mmol) and 4-(trifluoromethyl)cyclohexan-1-one (588 mg; 3.36 mmol) in MeOH (5 mL) was added pyrrolidine (312 mg; 4.17 mmol) dropwise at 0 °C. The resulting mixture was stirred for 2 h at 67 °C. For work up the mixture was concentrated under reduced pressure and the residue was diluted with 35 mL DCM. The mixture was extracted with 1N HCl (20 mL) and sat. NaCl (20 mL). The combined organic layers were dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by chromatography to afford the product (710 mg; 57%) as light-yellow oil. LCMS: 1.11 min, 379.1 [M+H], Method 13.

7-bromo-5-methyl-4'-(trifluoromethyl)-3,4-dihydrospiro[1-benzopyran-2,1'-cyclohexan]-4-ol



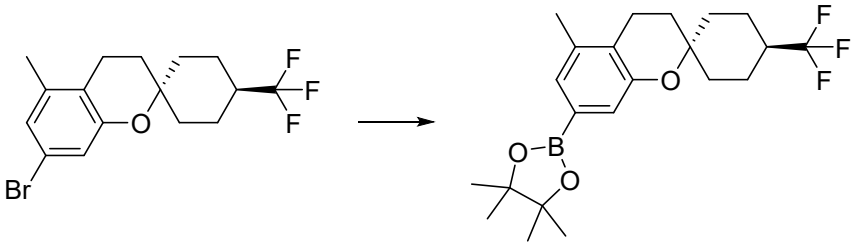
To a stirred solution of 7-bromo-5-methyl-4'-(trifluoromethyl)-3,4-dihydrospiro[1-benzopyran-2,1'-cyclohexan]-4-one (540 mg; 1.38 mmol) in THF (14 mL) was added $LiBH_4$ (2M in THF) (1.10 ml; 2.20 mmol) dropwise at 0 °C. After completion of the reaction the mixture was diluted with H_2O and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford the crude product (500 mg; 59%) as colorless oil that was used in the next step without further purification. LCMS: 1.30 min, 376.9 [M-H], Method 14

7-bromo-5-methyl-4'-(trifluoromethyl)-3,4-dihydrospiro[1-benzopyran-2,1'-cyclohexane]



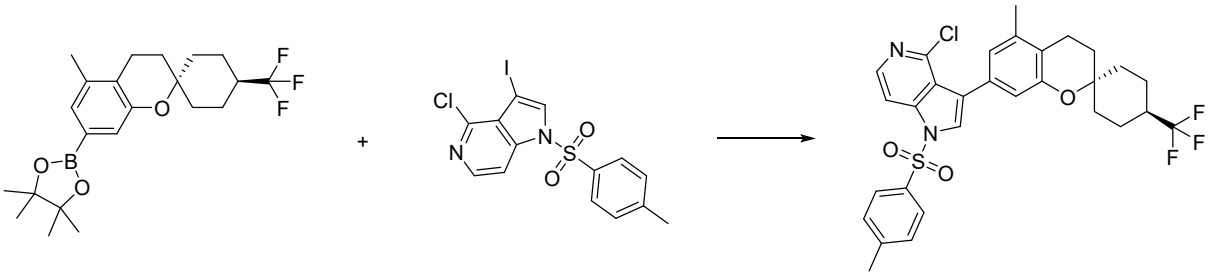
To a stirred solution of 7-bromo-5-methyl-4'-(trifluoromethyl)-3,4-dihydrospiro[1-benzopyran-2,1'-cyclohexan]-4-ol (470 mg; 0.77 mmol) in DCM (1.80 mL) was added TFA (0.87 mL) and triethylsilane (0.28 ml; 1.67 mmol) dropwise at 0 °C. The resulting mixture was stirred at room temperature until completion. Then the mixture was concentrated under reduced pressure. The residue was diluted with H_2O and extracted with DCM. The combined organic layers were dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to afford the crude product (285 mg; 99%) as off-white solid. GC-MS Column: SH-Rxi-5Sil MS; 30.0 m * 250 um * 0.25 um): 8.61 min; 362.0 [M+H].

rel-4,4,5,5-tetramethyl-2-[(2r)-5-methyl-4'-(trifluoromethyl)-3,4-dihydrospiro[1-benzopyran-2,1'-cyclohexan]-7-yl]-1,3,2-dioxaborolane



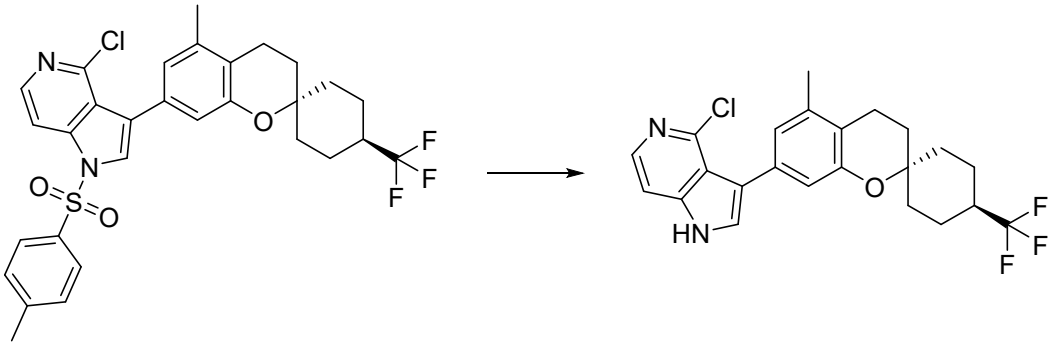
To a solution of rel-(2r)-7-bromo-5-methyl-4'-(trifluoromethyl)-3,4-dihydrospiro[1-benzopyran-2,1'-cyclohexane] (375 mg; 1.01 mmol) and BPD (427 mg; 1.51 mmol) in dioxane (10 mL) were added KOAc (220 mg; 2.02 mmol) and $Pd(dppf)Cl_2$.DCM (87 mg; 0.10 mmol). After stirring for 3 h at 90 °C, the resulting mixture was concentrated under reduced pressure. The residue was diluted with water and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure and the residue was purified by chromatography to afford the product (400 mg; 55%) as light-yellow oil. LCMS: 1.15 min, 411.4 [M+H], Method 14.

rel-4-chloro-1-(4-methylbenzenesulfonyl)-3-[(2r)-5-methyl-4'-(trifluoromethyl)-3,4-dihydrospiro[1-benzopyran-2,1'-cyclohexan]-7-yl]-1H-pyrrolo[3,2-c]pyridine



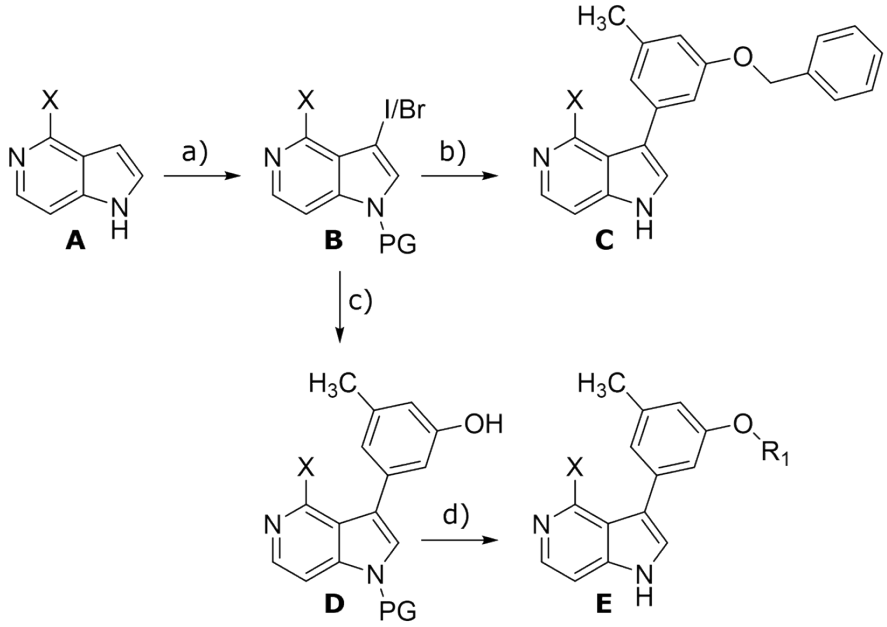
To a solution of rel-4,4,5,5-tetramethyl-2-[(2r)-5-methyl-4'-(trifluoromethyl)-3,4-dihydrospiro[1-benzopyran-2,1'-cyclohexan]-7-yl]-1,3,2-dioxaborolane (370 mg; 0.52 mmol) and 4-chloro-3-iodo-1-(4-methylbenzenesulfonyl)-1H-pyrrolo[3,2-c]pyridine (467 mg; 1.04 mmol) in dioxane (8 mL) and H_2O (2 mL) were added K_2CO_3 (300 mg; 2.06 mmol) and $Pd(PPh_3)_4$ (90 mg; 0.07 mmol). After stirring overnight at 80 °C, the mixture was concentrated under reduced pressure. The residue was diluted with H_2O and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by chromatography to afford the product (160 mg; 52%) as white solid. LCMS: 1.21 min, 589.2 [M+H], Method 14.

rel-4-chloro-3-[(2r)-5-methyl-4'-(trifluoromethyl)-3,4-dihydrospiro[1-benzopyran-2,1'-cyclohexan]-7-yl]-1H-pyrrolo[3,2-c]pyridine (**4**)



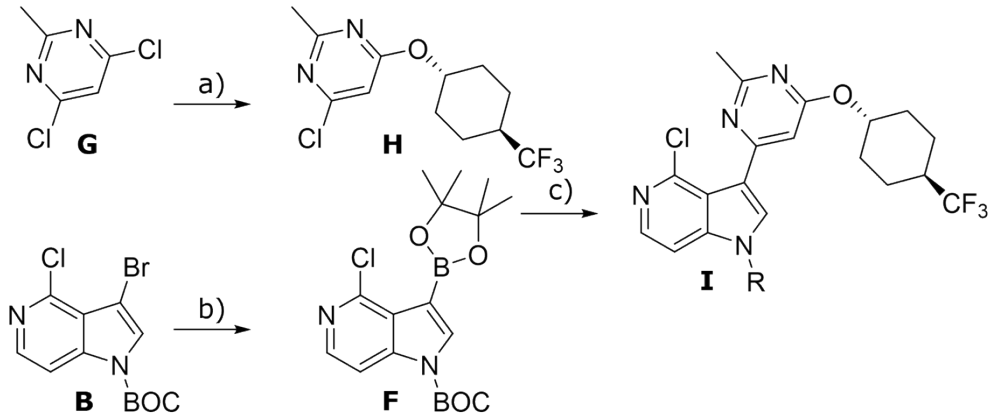
To a stirred solution of rel-4-chloro-1-(4-methylbenzenesulfonyl)-3-[(2r)-5-methyl-4'-(trifluoromethyl)-3,4-dihydrospiro[1-benzopyran-2,1'-cyclohexan]-7-yl]-1H-pyrrolo[3,2-c]pyridine (40 mg; 0.06 mmol) in EtOH (1 mL) was added EtONa/EtOH (w/w 21%) (0.02 mL; 0.10 mmol) dropwise. The resulting mixture was stirred for 1 h at RT. After evaporation of the solvent the crude product was purified by chromatography to afford the product (15.60 mg; 64%) as white solid. LCMS: 1.74 min, 435.1 [M+H], Method 17. ^{1}H NMR (300 MHz, DMSO) 12.03 (s, 1H), 7.98 (d, J = 5.6 Hz, 1H), 7.55 (d, J = 2.4 Hz, 1H), 7.45 (d, J = 5.6 Hz, 1H), 6.84 (s, 1H), 6.75 - 6.69 (m, 1H), 2.64 (t, J = 6.8 Hz, 2H), 2.38 (s, 1H), 2.22 (s, 3H), 1.89 (d, J = 13.3 Hz, 2H), 1.81 (t, J = 6.8 Hz, 2H), 1.64 (d, J = 22.4 Hz, 4H), 1.51 - 1.40 (m, 2H).

Schemes for scaffold syntheses



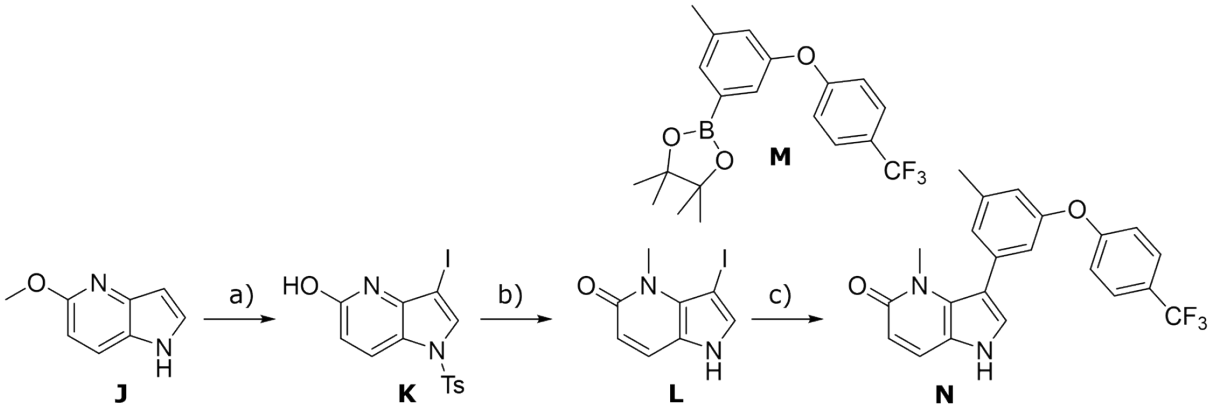
Reagents and Conditions for X = CF_3, Cl and PG = BOC, SEM a) *i*. DMF, NIS, 3 h, 25 °C, not isolated; *ii*. DCM, DMAP, BOC_2O, 16 h, 25 °C, 87%; b) *i*. dioxane, H_2O, diverse boronic acids, K_2CO_3, $Pd(dppf)_2$, 2 h, 70 °C, 42% - 64% *ii*. DCM, TFA, 25 °C, 3 h, 11% - 100%; c) dioxane, H_2O, 3-hydroxyphenyl boronic acid, K_2CO_3, $Pd(dppf)_2$, 3 h, 80 °C, 54%; or DMF, 3-methyl-5 hydroxyphenyl boronic acid pinacol ester, Cs_2CO_3, $Pd(PPh_3)_2Cl_2$, 2 h, 80 °C, 85%; d) *i*. R_1: aryl: DMSO, aryl iodide, N,N-dimethylglycine, CuI, K_2CO_3, 16 h, 120 °C, 98%; R_1: alkyl: DMF, alkyl mesylate, K_2CO_3, 12 h, RT, 18% - 97%; *ii*. DCM, TFA, 0 °C to RT, 3 h, 59% - 91%.

Commercially available 5-azaindole (**A**, X: H) and 4-yl analogues (X: Cl, CF_3) were either iodinated or brominated in position 3 followed by indole NH protection (PG: BOC, SEM). Building blocks **B** were coupled with commercially available boronic acids under Suzuki conditions to compounds **C**. In an alternative approach, a BOC or SEM protected 4-chloro-3-iodo 5-azaindole building block **B** was coupled under Suzuki conditions with 3-hydroxy phenyl or 3-hydroxy-5-methylphenyl boronic acid or pinacol ester to intermediates **D**. The hydroxy function was either converted into aryl or alkyl ethers followed by nitrogen deprotection (**E**).



Reagents and Conditions: a) THF, trans-4-(trifluoromethyl)cyclohexanol, NaH, 0 °C, 30 min., RT, 12 h, 68%; b) THF, nBuLi, 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, -78 °C, 3 h, 73%; c) *i*. dioxane, H_2O, $Pd(PPh_3)_4$, K_2CO_3, 12 h, 60 °C, 25% (R: BOC); *ii*. DCM, TFA, 48 h, RT, 72%.

4,6-dichloro-2-methyl pyrimdine **G** was converted into the corresponding ether **H** and BOC protected 3-Bromo-4-chloro 5-azaindole **B** was borylated to building block **F**. Under Suzuki conditions these building blocks were coupled to **I** (R = BOC) which was deprotected under acidic conditions.



Reagents and Conditions: a) *i*. DMF, NIS, 12 h, R, 42%; *ii*. DCM, TEA, DMAP, 4-methylbenzene-1-sulfonyl chloride, 0 °C to RT, 12 h, 98%; *iii*. AcOH, HBr in H_2O, 4 h, 80 °C; b) *i*. DMF, LiHMDS, MeI, 0 °C to RT, 12 h; 46%; *ii.* EtOH, EtONa, 25 °C, 5 h, 84%; c) dioxane, H_2O, **M**, $Pd(Amphos)_2Cl_2$, K_2CO_3, 50 °C, 4 h, 62%.

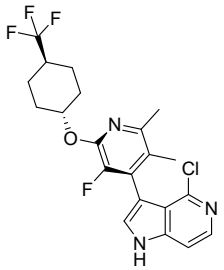
Commercially available 5-methoxy-1H-pyrrolo[3,2-b]pyridine **J** was iodinated with NIS in position 3 and after nitrogen tosylation the methyl ether was cleaved with HBr to intermediate **K**. Methylation of the hydroxy-pyridine substructure provided a mixture of the methyl ether precursor and the N-methyl lactam **L** in different ratios. We found exclusive N-methylation when using LiHMDS as base though the yield was limited to 46 % on 100 g scale. After tosyl cleavage under basic conditions the mixture was coupled under Suzuki conditions with boronate **M** to **N**.

General protocol for scaffold methylation

To a stirred solution of the NH-scaffold (1 eq.) in THF (3 ml/mmol) was added NaH (2 eq.) at 0 °C under nitrogen atmosphere. The mixture was stirred for 10 min at 0 °C, CH_3I (1.5 eq.) was added dropwise, and the resulting mixture was stirred for additional 2 h at RT. Then the mixture was concentrated under reduced pressure and the residue was purified by chromatography to afford the respective products.

Analytical data for all compounds from table 3

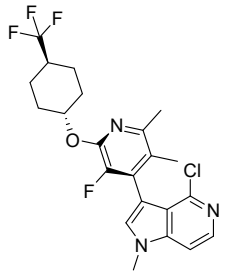
rel-(4P)-4-{4-chloro-1H-pyrrolo[3,2-c]pyridin-3-yl}-3-fluoro-5,6-dimethyl-2-{[(1r,4r)-4-(trifluoromethyl)cyclohexyl]oxy}pyridine (**5**) was prepared as described in ref. 9 .



LCMS: 1.13 min, 442.2 [M+H], Method 3.

[1]H NMR (300 MHz, DMSO) 12.26 (s, 1H), 8.02 (d, J = 5.6 Hz, 1H), 7.62 (s, 1H), 7.51 (d, J = 5.7 Hz, 1H), 5.06 (d, J = 10.4 Hz, 1H), 2.39 (s, 4H), 2.20 (s, 2H), 1.94 (s, 5H), 1.50 (d, J = 10.6 Hz, 4H).

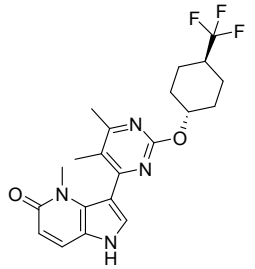
rel-(4P)-4-{4-chloro-1-methyl-1H-pyrrolo[3,2-c]pyridin-3-yl}-3-fluoro-5,6-dimethyl-2-{[(1r,4r)-4-(trifluoromethyl)cyclohexyl]oxy}pyridine (**6**).



LCMS: 1.21 min, 456.2 [M+H], Method 3.

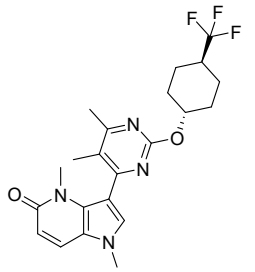
[1]H NMR (300 MHz, DMSO) 8.08 (d, J = 5.7 Hz, 1H), 7.69-7.60 (m, 2H), 5.04 (q, J=6.1 Hz, 1H), 3.91 (s, 3H), 2.40 (s, 4H), 2.20 (s, 2H), 1.95 (s, 5H), 1.52 (p, J = 12.4 Hz, 4H).

3-(5,6-dimethyl-2-{[(1r,4r)-4-(trifluoromethyl)cyclohexyl]oxy}pyrimidin-4-yl)-4-methyl-1H,4H,5H-pyrrolo[3,2-b]pyridin-5-one (**7**).



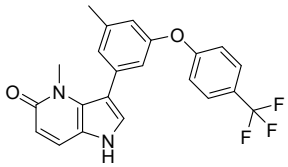
LCMS: 1.54 min, 421.1 [M+H], Method 4. [1]H NMR (500 MHz, DMSO) 11.73 (d, J = 3.0 Hz, 1H), 7.64 (d, J = 9.3 Hz, 1H), 7.35 (d, J = 2.9 Hz, 1H), 6.20 (d, J = 9.3 Hz, 1H), 4.92 – 4.82 (m, 1H), 3.19 (s, 3H), 2.43 (s, 3H), 2.36 (s, 1H), 2.18 – 2.11 (m, 2H), 2.10 (s, 3H), 1.95 – 1.88 (m, 2H), 1.53 – 1.34 (m, 4H).

3-(5,6-dimethyl-2-{[(1r,4r)-4-(trifluoromethyl)cyclohexyl]oxy}pyrimidin-4-yl)-1,4-dimethyl-1H,4H,5H-pyrrolo[3,2-b]pyridin-5-one (**8**).



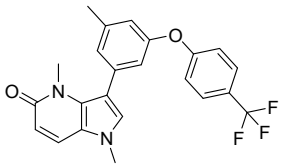
LCMS: 1.63 min, 435.2 [M+H], Method 4. [1]H NMR (400 MHz, DMSO) 7.79 (d, J = 9.4 Hz, 1H), 7.36 (s, 1H), 6.23 (d, J = 9.4 Hz, 1H), 4.91 – 4.80 (m, 1H), 3.78 (s, 3H), 3.18 (s, 3H), 2.43 (s, 3H), 2.36 – 2.32 (m, 1H), 2.18 – 2.10 (m, 2H), 2.10 (s, 3H), 1.95 – 1.88 (m, 2H), 1.56 – 1.28 (m, 4H).

4-methyl-3-{3-methyl-5-[4-(trifluoromethyl)phenoxy]phenyl}-1H,4H,5H-pyrrolo[3,2-b]pyridin-5-one (**9**) was published in ref. 9.



LCMS: 2.94 min, 339.0 [M+H], Method 9.

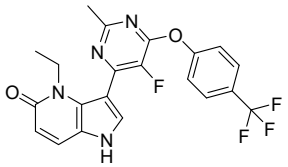
1,4-dimethyl-3-{3-methyl-5-[4-(trifluoromethyl)phenoxy]phenyl}-1H,4H,5H-pyrrolo[3,2-b]pyridin-5-one (**10**).



LCMS: 1.90 min, 413.1 [M+H], Method 4.

^{1}H NMR (500 MHz, DMSO) 7.75 (t, J = 8.5 Hz, 3H), 7.26 (s, 1H), 7.17 (d, J = 8.4 Hz, 2H), 7.10 (s, 1H), 6.95 (d, J = 1.9 Hz, 1H), 6.93 (d, J = 1.9 Hz, 1H), 6.19 (d, J = 9.4 Hz, 1H), 3.74 (s, 3H), 3.24 (s, 3H), 2.36 (s, 3H).

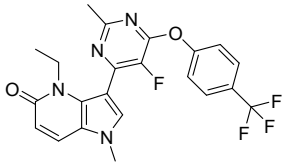
4-ethyl-3-{5-fluoro-2-methyl-6-[4-(trifluoromethyl)phenoxy]pyrimidin-4-yl}-1H,4H,5H-pyrrolo[3,2-b]pyridin-5-one (**11**).



LCMS: 1.69 min, 433.1 [M+H], Method 2.

^{1}H NMR (500 MHz, DMSO) 12.02 (s, 1H), 7.89 (d, J = 8.5 Hz, 2H), 7.70 – 7.64 (m, 2H), 7.59 (d, J = 8.4 Hz, 2H), 6.24 (d, J = 9.3 Hz, 1H), 4.17 (q, J = 6.9 Hz, 2H), 2.43 (s, 3H), 1.04 (t, J = 6.9 Hz, 3H).

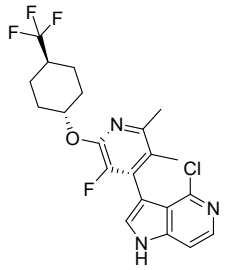
4-ethyl-3-{5-fluoro-2-methyl-6-[4-(trifluoromethyl)phenoxy]pyrimidin-4-yl}-1-methyl-1H,4H,5H-pyrrolo[3,2-b]pyridin-5-one (**12**).



LCMS: 1.78 min, 447.1 [M+H], Method 2.

^{1}H NMR (500 MHz, DMSO) 7.88 (d, J = 8.5 Hz, 2H), 7.83 (d, J = 9.5 Hz, 1H), 7.69 (d, J = 2.1 Hz, 1H), 7.59 (d, J = 8.4 Hz, 2H), 6.28 (d, J = 9.4 Hz, 1H), 4.17 (q, J = 6.9 Hz, 2H), 3.83 (s, 3H), 2.43 (s, 3H), 1.23 (s, 0H), 1.04 (t, J = 6.9 Hz, 3H).

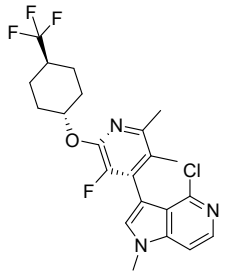
rel-(4M)-4-{4-chloro-1H-pyrrolo[3,2-c]pyridin-3-yl}-3-fluoro-5,6-dimethyl-2-{[(1r,4r)-4-(trifluoromethyl)cyclohexyl]oxy}pyridine (**13**).



LCMS: 1.12 min, 442.2 [M+H], Method 3.

^{1}H NMR (300 MHz, DMSO) 12.26 (s, 1H), 8.02 (d, J = 5.6 Hz, 1H), 7.62 (s, 1H), 7.51 (d, J = 5.7 Hz, 1H), 5.06 (d, J = 10.4 Hz, 1H), 2.39 (s, 4H), 2.20 (s, 2H), 1.94 (s, 5H), 1.50 (d, J = 10.6 Hz, 4H).

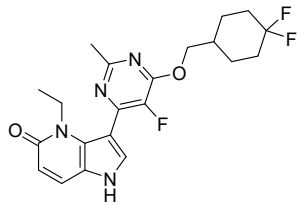
rel-(4M)-4-{4-chloro-1-methyl-1H-pyrrolo[3,2-c]pyridin-3-yl}-3-fluoro-5,6-dimethyl-2-{[(1r,4r)-4-(trifluoromethyl)cyclohexyl]oxy}pyridine (**14**).



LCMS: 1.20 min, 456.2 [M+H], Method 3.

^{1}H NMR (300 MHz, DMSO) 8.08 (d, J = 5.7 Hz, 1H), 7.69-7.60 (m, 2H), 5.04 (q, J=6.1 Hz, 1H), 3.91 (s, 3H), 2.40 (s, 4H), 2.20 (s, 2H), 1.95 (s, 5H), 1.52 (p, J = 12.4 Hz, 4H).

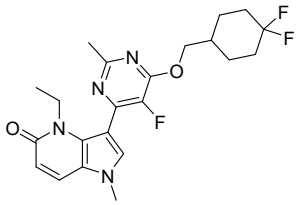
3-{6-[(4,4-difluorocyclohexyl)methoxy]-5-fluoro-2-methylpyrimidin-4-yl}-4-ethyl-1H,4H,5H-pyrrolo[3,2-b]pyridin-5-one (**15**).



LCMS: 1.62 min, 421.2 [M+H], Method 2.

^{1}H NMR (500 MHz, DMSO) 11.92 (s, 1H), 7.64 (d, J = 9.3 Hz, 1H), 7.56 (d, J = 1.8 Hz, 1H), 6.22 (d, J = 9.3 Hz, 1H), 4.34 (d, J = 6.5 Hz, 2H), 4.12 (q, J = 7.0 Hz, 2H), 2.52 (s, 3H), 2.11 – 2.01 (m, 2H), 2.01 – 1.97 (m, 1H), 1.95 – 1.78 (m, 4H), 1.42 – 1.31 (m, 2H), 0.97 (t, J = 7.0 Hz, 3H).

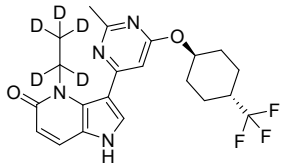
3-{6-[(4,4-difluorocyclohexyl)methoxy]-5-fluoro-2-methylpyrimidin-4-yl}-4-ethyl-1-methyl-1H,4H,5H-pyrrolo[3,2-b]pyridin-5-one (**16**).



LCMS: 1.72 min, 435.2 [M+H], Method 2.

^{1}H NMR (500 MHz, DMSO) 7.80 (d, J = 9.4 Hz, 1H), 7.59 (s, 1H), 6.26 (d, J = 9.4 Hz, 1H), 4.34 (d, J = 6.5 Hz, 2H), 4.13 (q, J = 7.0 Hz, 2H), 3.80 (s, 3H), 2.52 (s, 3H), 2.10 – 2.03 (m, 2H), 2.02 – 1.95 (m, 1H), 1.95 – 1.89 (m, 2H), 1.88 – 1.78 (m, 2H), 1.42 – 1.31 (m, 2H), 0.96 (t, J = 7.0 Hz, 3H).

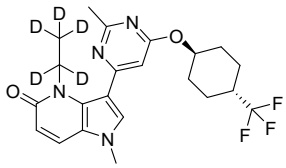
rel-4-[(1,1,2,2,2-2H5)ethyl]-3-(2-methyl-6-{[(1r,4r)-4-(trifluoromethyl)cyclohexyl]oxy}pyrimidin-4-yl)-1H,4H,5H-pyrrolo[3,2-b]pyridin-5-one (**17**).



LCMS: 1.67 min, 426.2 [M+H], Method 2.

^{1}H NMR (500 MHz, DMSO) 11.84 (s, 1H), 7.61 (d, J = 9.3 Hz, 1H), 7.59 (s, 1H), 6.84 (s, 1H), 6.20 (d, J = 9.3 Hz, 1H), 5.08 (tt, J = 10.4, 4.4 Hz, 1H), 2.54 (s, 3H), 2.42 – 2.34 (m, 1H), 2.24 – 2.18 (m, 2H), 2.02 – 1.92 (m, 2H), 1.57 – 1.42 (m, 4H).

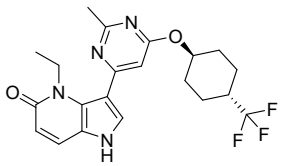
rel-4-[(1,1,2,2,2-2H5)ethyl]-1-methyl-3-(2-methyl-6-{[(1r,4r)-4-(trifluoromethyl)cyclohexyl]oxy}pyrimidin-4-yl)-1H,4H,5H-pyrrolo[3,2-b]pyridin-5-one (**18**).



LCMS: 1.77 min, 440.2 [M+H], Method 2.

^{1}H NMR (500 MHz, MeOD) 7.83 (d, J = 9.4 Hz, 1H), 7.44 (s, 1H), 6.77 (s, 1H), 6.44 (d, J = 9.4 Hz, 1H), 5.20 – 5.11 (m, 1H), 3.84 (s, 3H), 2.59 (s, 3H), 2.32 – 2.27 (m, 2H), 2.27 – 2.18 (m, 1H), 2.09 – 2.00 (m, 2H), 1.61 – 1.47 (m, 4H).

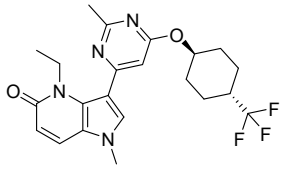
4-ethyl-3-(2-methyl-6-{[(1r,4r)-4-(trifluoromethyl)cyclohexyl]oxy}pyrimidin-4-yl)-1H,4H,5H-pyrrolo[3,2-b]pyridin-5-one (**19**).



LCMS: 0.80 min, 421.1 [M+H], Method 3.

^{1}H NMR (300 MHz, DMSO-d6) 11.85 (s, 1H), 7.62 (d, J = 10.1 Hz, 2H), 6.84 (s, 1H), 6.21 (d, J = 9.3 Hz, 1H), 5.09 (s, 1H), 4.38 (d, J = 7.3 Hz, 2H), 2.54 (s, 3H), 2.40 (s, 1H), 2.21 (s, 2H), 1.97 (s, 2H), 1.50 (s, 4H), 0.99 (t, J = 6.9 Hz, 3H).

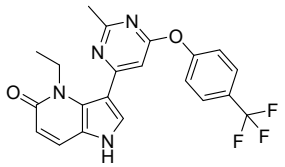
rel-4-ethyl-1-methyl-3-(2-methyl-6-{[(1r,4r)-4-(trifluoromethyl)cyclohexyl]oxy}pyrimidin-4-yl)-1H,4H,5H-pyrrolo[3,2-b]pyridin-5-one (**20**).



LCMS: 1.78 min, 435.1 [M+H], Method 2.

^{1}H NMR (500 MHz, DMSO) 7.77 (d, J = 9.4 Hz, 1H), 7.61 (s, 1H), 6.79 (s, 1H), 6.24 (d, J = 9.4 Hz, 1H), 5.07 (dq, J = 10.3, 5.0 Hz, 1H), 4.37 (q, J = 7.0 Hz, 2H), 3.76 (s, 3H), 2.53 (s, 3H), 2.20 (d, J = 9.1 Hz, 2H), 1.95 (d, J = 9.9 Hz, 2H), 1.47 (dd, J = 14.9, 5.8 Hz, 3H), 0.96 (t, J = 6.9 Hz, 3H).

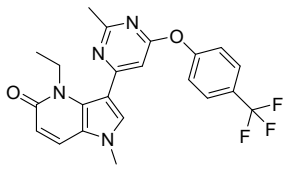
4-ethyl-3-{2-methyl-6-[4-(trifluoromethyl)phenoxy]pyrimidin-4-yl}-1H,4H,5H-pyrrolo[3,2-b]pyridin-5-one (**21**).



LCMS: 1.63 min, 415.1 [M+H], Method 2.

^{1}H NMR (500 MHz, DMSO) 11.96 (s, 1H), 7.85 (d, J = 8.5 Hz, 2H), 7.71 (s, 1H), 7.64 (d, J = 9.3 Hz, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.20 (s, 1H), 6.23 (d, J = 9.3 Hz, 1H), 4.41 (q, J = 6.9 Hz, 2H), 2.48 (s, 3H), 1.04 (t, J = 6.9 Hz, 3H).

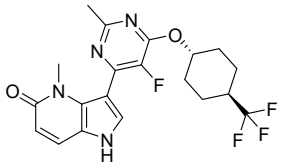
4-ethyl-1-methyl-3-{2-methyl-6-[4-(trifluoromethyl)phenoxy]pyrimidin-4-yl}-1H,4H,5H-pyrrolo[3,2-b]pyridin-5-one (**22**).



LCMS: 1.58 min, 415.1 [M+H], Method 5.

^{1}H NMR (500 MHz, DMSO) 12.97 (s, 1H), 7.81 (d, J = 9.5 Hz, 1H), 7.48 (s, 1H), 6.21 (d, J = 9.5 Hz, 1H), 4.96 (t, J = 5.1 Hz, 1H), 4.18 (t, J = 5.2 Hz, 2H), 4.08 (q, J = 6.9 Hz, 2H), 3.68 (q, J = 5.1 Hz, 2H), 2.30 (s, 3H), 1.04 (t, J = 7.0 Hz, 3H).

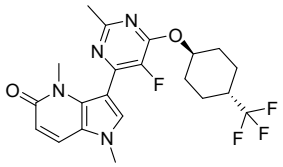
rel-3-(5-fluoro-2-methyl-6-{[(1r,4r)-4-(trifluoromethyl)cyclohexyl]oxy}pyrimidin-4-yl)-4-methyl-1H,4H,5H-pyrrolo[3,2-b]pyridin-5-one (**23**).



LCMS: 1.66 min, 425.2 [M+H], Method 2.

^{1}H NMR (300 MHz, DMSO-d6) 11.94 (d, J = 3.4 Hz, 1H), 7.74 - 7.51 (m, 2H), 6.23 (d, J = 9.3 Hz, 1H), 5.14 (dt, J = 10.7, 5.6 Hz, 1H), 2.23 (d, J = 10.1 Hz, 2H), 2.03 - 1.92 (m, 2H), 1.63 - 1.40 (m, 4H).

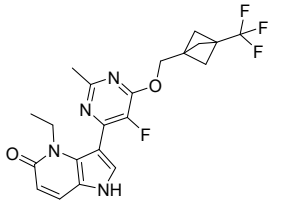
rel-3-(5-fluoro-2-methyl-6-{[(1r,4r)-4-(trifluoromethyl)cyclohexyl]oxy}pyrimidin-4-yl)-1,4-dimethyl-1H,4H,5H-pyrrolo[3,2-b]pyridin-5-one (**24**).



LCMS: 1.76 min, 439.1 [M+H], Method 2.

^{1}H NMR (500 MHz, DMSO) 7.81 (d, J = 9.5 Hz, 1H), 7.61 (d, J = 1.7 Hz, 1H), 6.27 (d, J = 9.4 Hz, 1H), 5.14 (td, J = 10.7, 5.3 Hz, 1H), 3.80 (s, 3H), 3.39 (s, 3H), 2.63 (p, J = 1.8 Hz, 1H), 2.52 (s, 3H), 2.40 (d, J = 12.7 Hz, 1H), 2.23 (d, J = 11.0 Hz, 2H), 1.97 (d, J = 12.5 Hz, 2H), 1.63 – 1.43 (m, 4H).

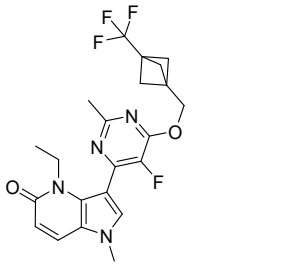
4-ethyl-3-(5-fluoro-2-methyl-6-{[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]methoxy}pyrimidin-4-yl)-1H,4H,5H-pyrrolo[3,2-b]pyridin-5-one (**25**).



LCMS: 1.44 min, 439.0 [M+H], Method 2.

^{1}H NMR (500 MHz, DMSO) 11.93 (d, J = 3.3 Hz, 1H), 7.64 (d, J = 9.3 Hz, 1H), 7.58 (dd, J = 3.3, 1.8 Hz, 1H), 6.22 (d, J = 9.3 Hz, 1H), 4.58 (s, 2H), 4.13 (q, J = 7.0 Hz, 2H), 2.03 (s, 6H), 0.96 (t, J = 7.0 Hz, 3H).

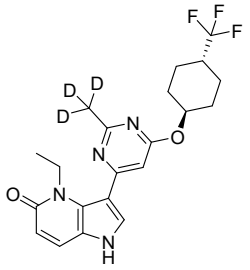
4-ethyl-3-(5-fluoro-2-methyl-6-{[3-(trifluoromethyl)bicyclo[1.1.1]pentan-1-yl]methoxy}pyrimidin-4-yl)-1-methyl-1H,4H,5H-pyrrolo[3,2-b]pyridin-5-one (**26**).



LCMS: 1.82 min, 451.1 [M+H], Method 2.

^{1}H NMR (500 MHz, DMSO) 7.80 (d, J = 9.5 Hz, 1H), 7.60 (d, J = 1.8 Hz, 1H), 6.25 (d, J = 9.5 Hz, 1H), 4.57 (s, 2H), 4.13 (q, J = 7.0 Hz, 2H), 3.79 (s, 3H), 2.02 (s, 6H), 0.94 (t, J = 7.0 Hz, 3H).

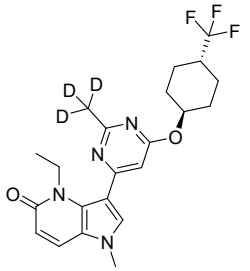
rel-4-ethyl-3-[2-(2H3)methyl-6-{[(1r,4r)-4-(trifluoromethyl)cyclohexyl]oxy}pyrimidin-4-yl]-1H,4H,5H-pyrrolo[3,2-b]pyridin-5-one (**27**).



LCMS: 1.68 min, 424.2 [M+H], Method 4.

^{1}H NMR (500 MHz, DMSO) 11.84 (d, J = 3.4 Hz, 1H), 7.63 – 7.56 (m, 2H), 6.83 (s, 1H), 6.20 (d, J = 9.3 Hz, 1H), 5.12 – 5.03 (m, 1H), 4.37 (q, J = 6.9 Hz, 2H), 2.37 (s, 1H), 2.23 – 2.17 (m, 2H), 1.98 – 1.92 (m, 2H), 1.56 – 1.41 (m, 4H), 1.00 – 0.94 (m, 3H).

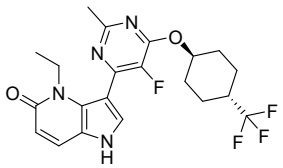
rel-4-ethyl-1-methyl-3-[2-(2H3)methyl-6-{[(1r,4r)-4-(trifluoromethyl)cyclohexyl]oxy}pyrimidin-4-yl]-1H,4H,5H-pyrrolo[3,2-b]pyridin-5-one (**28**).



LCMS: 1.77 min, 438.2 [M+H], Method 4.

^{1}H NMR (500 MHz, DMSO) 7.77 (d, J = 9.4 Hz, 1H), 7.61 (s, 1H), 6.79 (s, 1H), 6.24 (d, J = 9.4 Hz, 1H), 5.12 – 5.03 (m, 1H), 4.37 (q, J = 6.9 Hz, 2H), 3.76 (s, 3H), 2.40 – 2.37 (m, 1H), 2.23 – 2.17 (m, 2H), 1.98 – 1.92 (m, 2H), 1.56 – 1.41 (m, 4H), 0.96 (t, J = 6.9 Hz, 3H).

rel-4-ethyl-3-(5-fluoro-2-methyl-6-{[(1r,4r)-4-(trifluoromethyl)cyclohexyl]oxy}pyrimidin-4-yl)-^{1}H,4H,5H-pyrrolo[3,2-b]pyridin-5-one (**29**) was published before (ref 9).

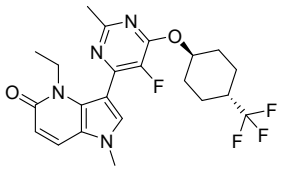


LCMS: 0.97 min, 439.1 [M+H], Method 10.

^{1}H NMR (500 MHz, DMSO) 11.93 (d, J = 2.8 Hz, 1H), 7.64 (d, J = 9.3 Hz, 1H), 7.56 (t, J = 2.2 Hz, 1H), 6.21 (d, J = 9.4 Hz, 1H), 5.15 (tt, J = 10.9, 4.4 Hz, 1H), 4.11 (q, J = 7.0 Hz, 2H), 2.53 - 2.50 (m,

3H), 2.45 - 2.35 (m, 1H), 2.22 (dd, J = 11.2, 4.7 Hz, 2H), 2.00 - 1.93 (m, 2H), 1.63 - 1.42 (m, 4H), 0.96 (t, J = 7.0 Hz, 3H).

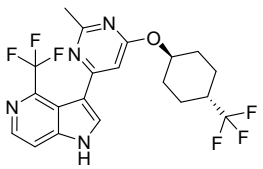
rel-4-ethyl-3-(5-fluoro-2-methyl-6-{[(1r,4r)-4-(trifluoromethyl)cyclohexyl]oxy}pyrimidin-4-yl)-1-methyl-1H,4H,5H-pyrrolo[3,2-b]pyridin-5-one (**MSC-4070**).



LCMS: 1.80 min, 453.1 [M+H], Method 5.

^{1}H NMR (300 MHz, DMSO) 7.80 (d, J = 9.5 Hz, 1H), 7.59 (d, J = 1.9 Hz, 1H), 6.26 (d, J = 9.4 Hz, 1H), 5.23 - 5.04 (m, 1H), 4.13 (q, J = 6.9 Hz, 2H), 3.79 (s, 3H), 2.52 (d, J = 1.0 Hz, 3H), 2.38 (s, 1H), 2.29 - 2.17 (m, 2H), 1.97 (d, J = 12.5 Hz, 2H), 1.67 - 1.39 (m, 4H), 0.97 (t, J = 6.9 Hz, 3H).

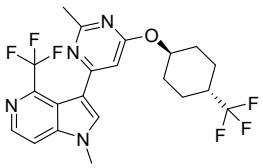
2-methyl-4-{[(1r,4r)-4-(trifluoromethyl)cyclohexyl]oxy}-6-[4-(trifluoromethyl)-1H-pyrrolo[3,2-c]pyridin-3-yl]pyrimidine (**30**).



LCMS: 1.57 min, 445.1 [M+H], Method 5.

^{1}H NMR (500 MHz, DMSO) 12.44 (s, 1H), 8.38 (d, J = 5.5 Hz, 1H), 8.02 (s, 1H), 7.76 (d, J = 5.5 Hz, 1H), 5.08 (tt, J = 10.3, 4.4 Hz, 1H), 2.50 (s, 3H), 2.42 – 2.33 (m, 1H), 2.21 (d, J = 8.9 Hz, 2H), 2.04 – 1.93 (m, 2H), 1.51 (d, J = 11.1 Hz, 2H), 1.47 (d, J = 12.1 Hz, 2H).

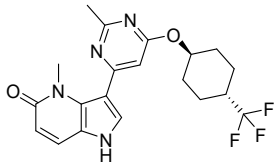
2-methyl-4-[1-methyl-4-(trifluoromethyl)-1H-pyrrolo[3,2-c]pyridin-3-yl]-6-{[(1r,4r)-4-(trifluoromethyl)cyclohexyl]oxy}pyrimidine (**31**).



LCMS: 1.62 min, 459.1 [M+H], Method 5.

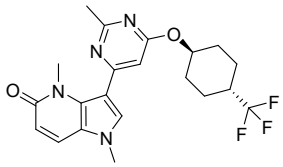
^{1}H NMR (500 MHz, DMSO) 8.45 (d, J = 5.6 Hz, 1H), 8.05 (s, 1H), 7.91 (d, J = 5.6 Hz, 1H), 6.77 (s, 1H), 5.14 – 5.04 (m, 1H), 3.94 (s, 3H), 2.51 (s, 3H), 2.42 – 2.31 (m, 1H), 2.21 (t, J = 6.3 Hz, 2H), 2.05 – 1.93 (m, 2H), 1.58 – 1.50 (m, 2H), 1.50 – 1.42 (m, 2H).

4-methyl-3-(2-methyl-6-{[(1r,4r)-4-(trifluoromethyl)cyclohexyl]oxy}pyrimidin-4-yl)-1H,4H,5H-pyrrolo[3,2-b]pyridin-5-one (**32**) was published before (ref 9).



LCMS: 0.74 min, 407.1 [M+H], Method 3.

rel-1,4-dimethyl-3-(2-methyl-6-{[(1r,4r)-4-(trifluoromethyl)cyclohexyl]oxy}pyrimidin-4-yl)-1H,4H,5H-pyrrolo[3,2-b]pyridin-5-one (**33**).



LCMS: 1.66 min, 421.2 [M+H], Method 2.

^{1}H NMR (500 MHz, DMSO) d 7.85 (d, J= 9.4 Hz, 1H), 7.69 (s, 1H), 6.87 (s, 1H), 6.32 (d, J = 9.4 Hz, 1H), 5.12 (dq, J = 10.5, 5.0 Hz, 1H), 3.83 (s, 3H), 3.57 (s, 3H), 2.59 (s, 3H), 2.43 (s, 1H), 2.26 (d, J = 9.1 Hz, 2H), 2.07 – 1.99 (m, 2H), 1.62 – 1.47 (m).