BMS-986163, a Negative Allosteric Modulator of GluN2B with Potential Utility in Major Depressive Disorder.

Lawrence R. Marcin*[,1], Jayakumar Warrier†[,2], Srinivasan Thangathirupathy†[,2], Jianliang Shi[3], George N. Karageorge[£,1], Bradley C. Pearce[1], Alicia Ng[1], Hyunsoo Park[3], James Kempson[3], Jianqing Li[3], Huiping Zhang[3], Arvind Mathur[3], Aliphedi B. Reddy[2], G. Nagaraju[2], Gopikishan Tonukunuru[2], Grandhi V. R. K. M. Gupta[2], Manjunatha Kamble[2], Raju Mannoori[2], Srinivas Cheruku[2], Srinivas Jogi[2], Jyoti Gulia[2], Tanmaya Bastia[2], Charulatha Sanmathi[2], Jayant Aher[2], Rajareddy Kallem[2], Bettadapura N. Srikumar[2], Kumar Kuchibhotla Vijaya[2], Pattipati S. Naidu[2], Mahesh Paschapur[2], Narasimharaju Kalidindi[2], Reeba Vikramadithyan[2], Manjunath Ramarao[2], Rex Denton[3], Thaddeus Molski[1], Eric Shields[1], Murali Subramanian[2], Xiaoliang Zhuo[1], Michelle Nophsker[1], Jean Simmermacher[^,1], Michael Sinz[2], Charlie Albright[¥,1], Linda J. Bristow[¶,1], Imadul Islam[Ω,2], Joanne J. Bronson[1], Richard E. Olson[1], Dalton King[1], Lorin A. Thompson[€,1], John E. Macor[£,1].

[1]Bristol-Myers Squibb Research and Development, 5 Research Parkway, Wallingford, CT 06492, USA.

[2]Biocon Bristol-Myers Squibb Research Center, Bangalore, India.

[3]Bristol-Myers Squibb Research and Development, 3551 Lawrenceville Road, Princeton, NJ 08648, USA.

[¥] Editas Medicine, Inc. Cambridge, MA, USA.
[£] Sanofi, Waltham, MA 02451, USA.
[^] ViiV Healthcare, Branford, CT, USA.
[¶] Sunovion Pharmaceuticals, Marlborough, MA, USA.
[€] Fulcrum Therapeutics, Cambridge, MA, USA.
[Ω] King Abdullah International Medical Research Center, KSAU-HS, Ministry of National Guard-Health Affairs, Riyadh, Saudi Arabia.

Supporting Information

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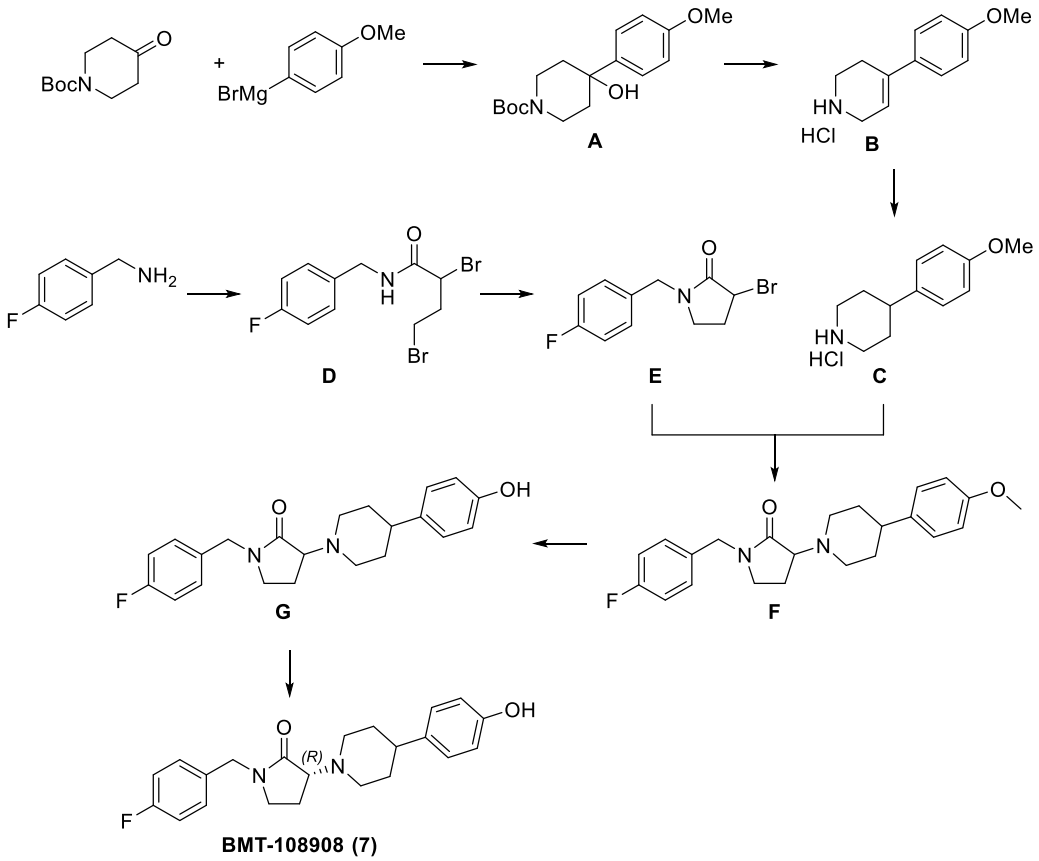
Preparation of (*R*)-1-(4-fluorobenzyl)-3-(4-(4-hydroxyphenyl)piperidin-1-yl)pyrrolidin-2-one (BMT-108908, compound 7).



tert-butyl 4-hydroxy-4-(4-methoxyphenyl)piperidine-1-carboxylate (intermediate **A**). A solution of commercial *tert*-butyl 4-oxopiperidine-1-carboxylate (2.0 g, 10 mmol) in diethyl ether (30 mL) was cooled to 0 °C. To this mixture was added dropwise a solution of (4-methoxyphenyl)magnesium bromide (0.5 M in diethyl ether, 30 mL, 15 mmol). After complete addition, the reaction mixture was allowed to warm to rt. After 2 h, the reaction mixture was slowly quenched with 150 mL of ice cold water. The resulting mixture was extracted with dichloromethane. The organic layers were combined, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified using silica gel column chromatography (30% ethyl acetate/hexanes) to provide *tert*-butyl 4-hydroxy-4-(4-methoxyphenyl)piperidine-1-carboxylate (3.0 g, 100 % yield): ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.37 (q, *J*=1.0 Hz, 2H), 6.86 (q, *J*=1.0 Hz, 2H), 4.94 (s, 1H), 3.82 (d, *J*=11.5 Hz, 2H), 3.73 (s, 3H), 3.13 (br. s, 2H), 1.75 (td, *J*=12.9, 4.8 Hz, 2H), 1.56 (d, *J*=12.3 Hz, 2H), 1.41 (s, 9H).

4-(4-Methoxyphenyl)-1,2,3,6-tetrahydropyridine, hydrochloride (intermediate **B**). A mixture of intermediate **A** (700 mg, 2.27 mmol) and 4.0 M HCl in dioxane (4.0 mL, 16 mmol) was stirred at rt for 3 h. The reaction mixture was concentrated under vacuum and the solid residue was washed with dichloromethane to remove non-polar impurities. 4-(4-Methoxyphenyl)-1,2,3,6-tetrahydropyridine, hydrochloride was collected as a fine solid (480 mg, 93% yield): LCMS (ES-API) m/z 190.2 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.37 (d, *J*=9.0 Hz, 2H), 6.98 (d, *J*=9.0 Hz, 2H), 6.08 - 5.98 (m, 1H), 5.11 (s, 1H), 3.97 (br. s., 1H), 3.52 (s, 1H), 3.32 (s, 3H), 2.47 - 2.37 (m, 1H).

4-(4-Methoxyphenyl)piperidine, hydrochloride (intermediate **C**). To a stirred solution of intermediate **B** (3.00 g, 13.3 mmol) in methanol (20 mL) was added 10% palladium on carbon (1.4 g) and the reaction mixture was stirred under 20 psi of hydrogen for 12 h. The reaction mixture was filtered through a pad of celite, which was washed with ethyl acetate. The combined organic filtrate was concentrated to afford 4-(4-methoxyphenyl)piperidine, hydrochloride as a white solid (2.0 g, 70% yield): LCMS (ES-API) m/z 192.1 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.13 - 8.36 (m, 2H), 7.14 (d, *J*=8.7 Hz, 2H), 6.90 (d, *J*=8.7 Hz, 2H), 3.73 (s, 3H), 3.07 - 2.87 (m, 4H), 2.87 - 2.65 (m, 4H).

2,4-Dibromo-N-(4-fluorobenzyl)butanamide (intermediate **D**). TEA (8.9 mL, 64 mmol) and 2,4-dibromobutanoyl chloride (5.1 mL, 38 mmol) were sequentially added to solution of commercial (4-fluorophenyl)methanamine (4.0 g, 32 mmol) in diethyl ether (15 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stir for an additional 24 h. The reaction mixture was filtered. The solids were washed with diethyl ether . The combined filtrates were concentrated in vacuo to afford a crude mixture containing 2,4-dibromo-N-(4-fluorobenzyl)butanamide (8.0 g, 71 % yield): LCMS (ES-API), m/z 354, 356 $(M+H)^+$.

3-Bromo-1-(4-fluorobenzyl)pyrrolidin-2-one (intermediate **E**). A 60% dispersion of NaH in mineral oil (1.70 g, 42.5 mmol) was added to a stirred solution of intermediate **D** (10.0 g, 28.3 mmol**)** in THF (25 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stir for an additional 2 h. The reaction mixture was carefully quenched with ice and diluted with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with water and then brine solution. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified using silica gel column chromatography (10% EtOAc/hexanes) to afford 3-bromo-1-(4-fluorobenzyl)pyrrolidin-2-one (5.9 g, 64 % yield): LCMS (ES-API), m/z 272.4, 274.3

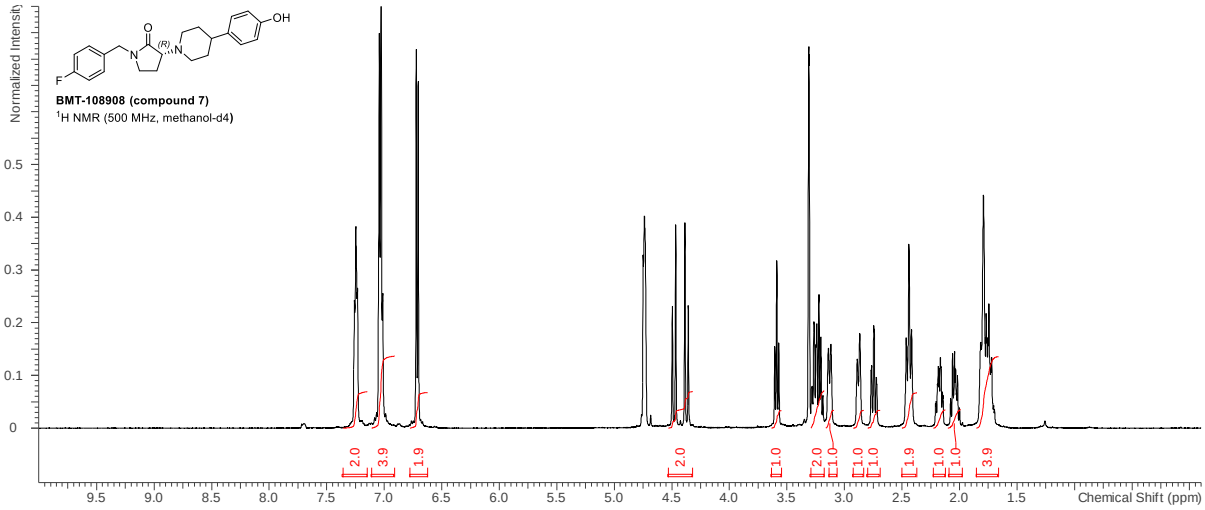
$(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.12 - 2.27 (m, 1 H) 2.56 - 2.68 (m, 1 H) 3.27 (dd, *J*=7.78, 3.26 Hz, 2 H) 4.29 - 4.38 (m, 1 H) 4.40 - 4.57 (m, 1 H) 4.73 (dd, *J*=7.03, 3.01 Hz, 1 H) 7.04 - 7.35 (m, 4 H).

1-(4-Fluorobenzyl)-3-(4-(4-methoxyphenyl)piperidin-1-yl)pyrrolidin-2-one (intermediate **F**). TEA (0.768 mL, 5.51 mmol) was added to a stirred solution of intermediate **D** (0.30 g, 1.1 mmol) and intermediate **C** (0.28 g, 1.2 mmol) in acetonitrile (10 mL). The reaction mixture was sealed in a microwave vial and heated in a chemistry microwave reactor at 100 °C for 1 h. The reaction mixture was cooled to rt and concentrated in vacuo. The residue was diluted with EtOAc. The organic mixture was washed with water and brine solution . The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo to afford a crude mixture containing 1-(4-fluorobenzyl)-3-(4-(4-methoxyphenyl)piperidin-1-yl)pyrrolidin-2-one (0.35 g, 83 % yield): LCMS (ES-API), m/z 383.2 $(M+H)^+$.

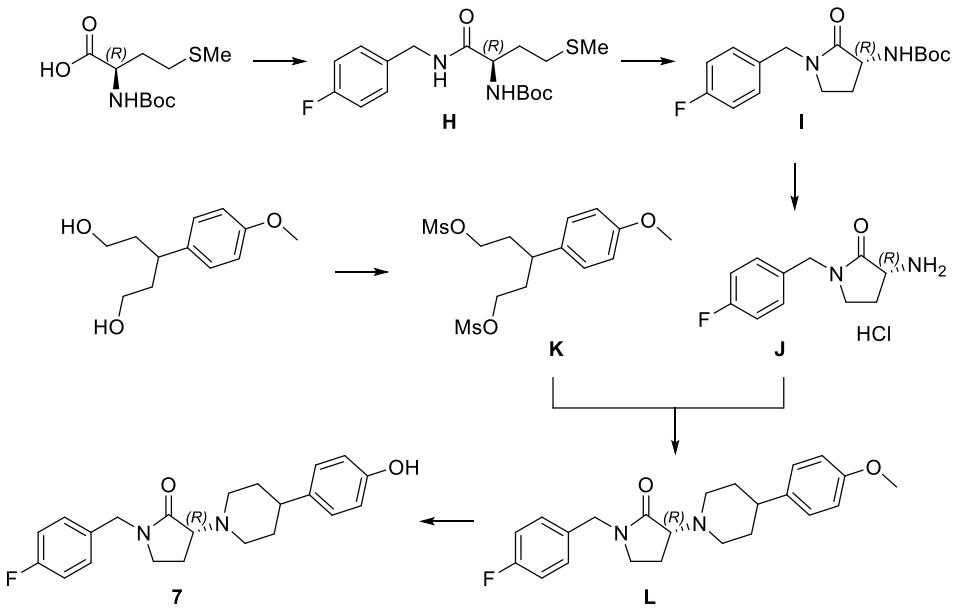
1-(4-Fluorobenzyl)-3-(4-(4-hydroxyphenyl)piperidin-1-yl)pyrrolidin-2-one (intermediate **G**). To a solution of intermediate **F** (3.0 g, 7.9 mmol) in dry dichloromethane (100 mL) under a N_2 atmosphere at -78 °C was added 1 M boron tribromide in dichloromethane (39 mL, 39 mmol) and the resulting mixture was allowed to warm to rt over 3 h, with stirring. The reaction mixture was quenched with water (30 mL) and the organic layer was separated, washed with water, washed with brine, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (15% EtOAc/ petroleum ether) to yield 1-(4-fluorobenzyl)-3-(4-(4-hydroxyphenyl)piperidin-1-yl)pyrrolidin-2-one (2.1 g, 73% yield): LCMS (ES-API), 369.2 m/z $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.49 - 1.74 (m, 4 H) 1.90 - 2.11 (m, 2 H) 2.24 - 2.42 (m, 2 H) 2.65 - 2.80 (m, 2 H) 2.99 - 3.23 (m, 3 H) 3.40 - 3.54 (m, 1 H) 4.27 - 4.46 (m, 2 H) 6.61 - 6.70 (m, 2 H) 6.95 - 7.04 (m, 2 H) 7.17 - 7.31 (m, 4 H) 9.10 - 9.16 (m, 1 H).

(R)-1-(4-Fluorobenzyl)-3-(4-(4-hydroxyphenyl)piperidin-1-yl)pyrrolidin-2-one (BMT-108908, compound **7**). A portion of intermediate **G** (40 mg) was separated using preparative chiral SFC (Chiralpak-IA (250 x 4.6 mm) 5 μm column, eluting with 35% solvent B, where solvent A = CO_2 and solvent B = 0.3% DEA in methanol at a total flow of 3 mL/min) to afford 11 mg (28 % recovery) of peak 1 or (*S*)-1-(4-fluorobenzyl)-3-(4-(4-hydroxyphenyl)-piperidin-1-yl)pyrrolidin-2-one) with a retention time of 4.35 min and 13 mg (33 % recovery) of peak 2 or (*R*)-1-(4-fluorobenzyl)-3-(4-(4-hydroxyphenyl)piperidin-1-yl)pyrrolidin-2-one (BMT-108908, compound **7**) with a retention time of 6.29 min. The

absolute stereochemistry of BMT-108908 was unambiguously confirmed through independent chiral synthesis (see following procedure). Data for BMT-108908 (compound **7**): LCMS ($C_{22}H_{25}FN_2O_2$, MW 368.2, ES-API), 369.2 m/z $(M+H)^+$; $[\alpha]_D^{20}$ = +27.0 (c = 9.75, MeOH); ^{1}H NMR (500 MHz, methanol-d_4) δ 7.30 - 7.19 (m, 2H), 7.07 - 7.00 (m, 4H), 6.71 (d, *J*=8.2 Hz, 2H), 4.53 - 4.31 (m, 2H), 3.59 (t, *J*=8.9 Hz, 1H), 3.29 - 3.18 (m, 2H), 3.16 - 3.07 (m, 1H), 2.88 (br d, *J*=10.8 Hz, 1H), 2.82 - 2.66 (m, 1H), 2.44 (br t, *J*=11.6 Hz, 2H), 2.23 - 2.12 (m, 1H), 2.11 - 1.96 (m, 1H), 1.85 - 1.69 (m, 4H). Corresponding ^{1}H NMR spectrum of compound **7** is shown below.



Alternative asymmetric synthesis of (*R*)-1-(4-fluorobenzyl)-3-(4-(4-hydroxyphenyl)piperidin-1-yl)pyrrolidin-2-one (BMT-108908, compound 7).



tert-Butyl (R)-(1-((4-fluorobenzyl)amino)-4-(methylthio)-1-oxobutan-2-yl)carbamate (intermediate **H**). To a solution of (*R*)-2-((*tert*-butoxycarbonyl)amino)-4-(methylthio)butanoic acid (aka. Boc-D-methionine) (15.6 g, 62.6 mmol) in dichloromethane (200 mL) was added HATU (28.5 g, 75.0 mmol) followed by DIPEA (21.9 mL, 125 mmol). After stirring at rt for 10 min, (4-fluorophenyl)methanamine (10.2 g, 81.0 mmol) was added. The reaction mixture was stirred at rt for 18 h. The reaction mixture was diluted with brine (400 mL) and extracted with dichloromethane. The combined organic layers were back washed with water, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was recrystalized from EtOAc/Hexanes (1:4 approximate ratio). The impure solid was passed through a short column of silica gel (50 % ethyl acetate/hexanes) to afford tert-butyl (R)-(1-((4-fluorobenzyl)amino)-4-(methylthio)-1-oxobutan-2-yl)carbamate (21 g, 94 % yield) as a solid: LCMS (ES-API), 357.1 m/z $(M+H)^+$; ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.28 - 7.23 (m, 2H), 7.06 - 6.99 (m, 2H), 6.67 - 6.53 (m, 1H), 5.26 - 5.05 (m, 1H), 4.43 (br s, 2H), 4.28 (br d, *J*=6.9 Hz, 1H), 2.67 - 2.43 (m, 2H), 2.19 - 2.08 (m, 4H), 2.02 - 1.89 (m, 1H), 1.44 (s, 9H).

(R)-(3-((tert-Butoxycarbonyl)amino)-4-((4-fluorobenzyl)amino)-4-oxobutyl)dimethylsulfonium iodide. To intemediate **H** (21.0 g, 58.9 mmol) was added iodomethane (111 mL, 1.77 mol). The mixture was gently warmed until all of the solids dissolved. The solution was stirred at rt for 24 h. The resulting slurry was concentrated in vacuo. The residue was triturated with diethyl ether. The solid was collected using vacuum

filtration to afford (*R*)-(3-((*tert*-butoxycarbonyl)amino)-4-((4-fluorobenzyl)amino)-4-oxobutyl)dimethylsulfonium iodide (29.4 g, 100 % yield): LCMS (ES-API), 371.1 m/z $(M+H)^+$.

tert-Butyl (R)-(1-(4-fluorobenzyl)-2-oxopyrrolidin-3-yl)carbamate (intermediate **I**). To a solution of crude (*R*)-(3-((*tert*-butoxycarbonyl)amino)-4-((4-fluorobenzyl)amino)-4-oxobutyl)dimethylsulfonium iodide (29.0 g, 58.2 mmol) in THF (200 mL) at -10 °C was added lithium bis(trimethylsilyl)amide (1.0 M in THF, 55.3 mL, 55.3 mmol). The mixture was allowed to gradually warm to 5 °C over 5 h. The reaction was quenched with a saturated solution of aqueous ammonium chloride. The aqueous mixture was extracted with ethyl acetate (600 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was passed through a short column of silica gel (50% ethyl acetate/hexanes, then 100% ethyl acetate, step gradient). The more polar eluent was concentrated in vacuo, and the residue was recrystalized from EtOAc/hexanes to afford *tert*-butyl (*R*)-(1-(4-fluorobenzyl)-2-oxopyrrolidin-3-yl)carbamate (12.8 g, 71 % yield): LCMS (ES-API), 309.1 m/z $(M+H)^+$; ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.26 - 7.20 (m, 2H), 7.07 - 7.01 (m, 2H), 5.16 (br s, 1H), 4.46 (br d, *J*=15.1 Hz, 2H), 4.28 - 4.16 (m, 1H), 3.25 - 3.19 (m, 2H), 2.63 (br dd, *J*=8.0, 4.3 Hz, 1H), 1.86 (dq, *J*=12.6, 9.9 Hz, 1H), 1.51 - 1.44 (m, 9H).

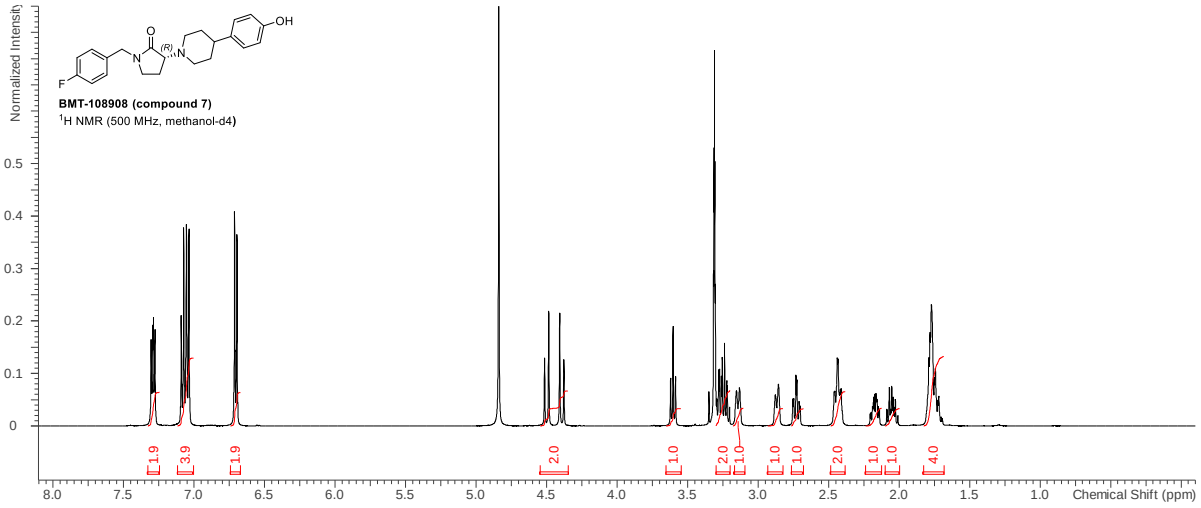
(R)-3-Amino-1-(4-fluorobenzyl)pyrrolidin-2-one, hydrochloride (intermediate **J**). To a stirred solution of intermediate **I** (1.0 g, 3.2 mmol) in dichloromethane (25 mL) was added a solution of 4.0 M HCl in dioxane (4.1 mL, 16 mmol). The resulting mixture was allowed to stir at rt for 16 h. The reaction mixture was concentrated to dryness in vacuo to afford (*R*)-3-amino-1-(4-fluorobenzyl)pyrrolidin-2-one, hydrochloride (0.66 g, 97 % yield): LCMS (ES-API) 209.1 m/z $(M+H)^+$.

3-(4-Methoxyphenyl)pentane-1,5-diyl dimethanesulfonate (intermediate **K**). To a stirred solution of 3-(4-methoxyphenyl)pentane-1, 5-diol (4.0 g, 19 mmol)[1] in dichloromethane (10 mL) at 0 °C was added pyridine (15 mL, 190 mmol) and then methanesulfonyl chloride (8.9 mL, 110 mmol). After warming to rt and allowing to stir for 16 h, the reaction mixture was quenched with water (200 mL). The resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with 10% solution of aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude residue was purified using silica gel column chromatography (25-35% ethyl acetate/pet ether, step gradient) to afford 3-(4-methoxyphenyl)pentane-1,5-diyl dimethanesulfonate (4.2 g, 57 % yield) as colorless liquid: ^{1}H NMR (400 MHz, DMSO-d_6) δ

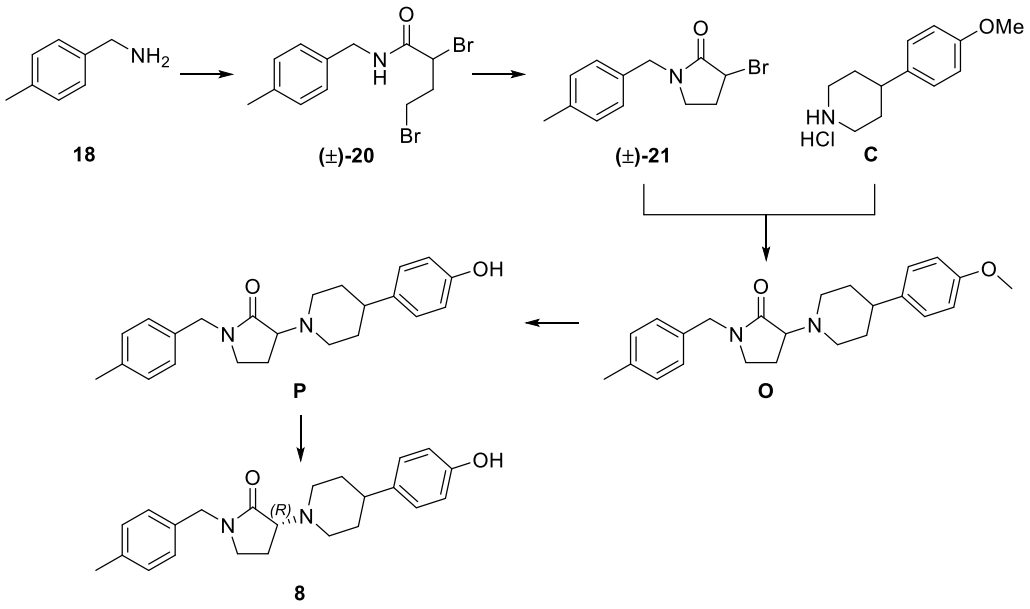
1.92-1.96 (m, 2H), 2.02-2.08 (m, 2H), 2.79-2.82 (m, 1H), 3.09 (s, 6H), 3.72 (s, 3H), 3.88-3.94 (m, 2H), 4.01-4.06 (m, 2H), 6.90 (d, J = 8.40 Hz, 2H), 7.18 (d, J = 8.80 Hz, 2H).

(R)-1-(4-Fluorobenzyl)-3-(4-(4-methoxyphenyl)piperidin-1-yl)pyrrolidin-2-one (**L**). To a stirred solution of intermediate **J** (397 mg, 1.62 mmol) in acetonitrile (10 mL) was added intermediate **K** (595 mg, 1.62 mmol) followed by DIEA (0.850 mL, 4.87 mmol). The reaction mixture was heated in a sealed vial at 120 °C for 24 h. The solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate (100 mL) and sequentially washed with water (30 mL) and then brine (30 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. The crude residue was purified using silica gel column chromatography (20% EtOAc/hexanes) to afford (*R*)-1-(4-fluorobenzyl)-3-(4-(4-methoxyphenyl)piperidin-1-yl)pyrrolidin-2-one (190 mg, 25 % yield) as brown viscous oil: LCMS (ES-API), 383.1 m/z $(M+H)^+$.

(R)-1-(4-Fluorobenzyl)-3-(4-(4-hydroxyphenyl)piperidin-1-yl)pyrrolidin-2-one (BMT-108908, compound **7**)**.** To a solution of intermediate **L** (190 mg, 0.497 mmol) in dry dichloromethane (10 mL) under a N_2 atmosphere at -78 °C was added boron tribromide (1 M in dichloromethane, 5.0 mL, 5.0 mmol) and the resulting mixture was allowed to warm to rt over 3 h, with stirring. The reaction was quenched with water (30 mL) and the organic layer was separated, washed with water and brine, and then concentrated. The crude product was purified using reverse phase preparative HPLC to afford (*R*)-1-(4-fluorobenzyl)-3-(4-(4-hydroxyphenyl)piperidin-1-yl)pyrrolidin-2-one (83 mg, 44% yield). ^{1}H NMR, LCMS, chiral SFC data were clean and consistent with peak 2 (BMT-108908, compound **7**) resulting from the chiral separation of intermediate **G**. The enantiomeric ratio of the final product was 64:1 (*R*:*S*) as determined by chiral SFC (Chiralpak-IA (4.6 x 250 mm) 5 μm; BPR pressure: 100 bar, temperature 24 °C, flow rate: 3 mL/min, mobile phase: 30% MeOH w/0.3% DEA in CO_2, detector wavelength: 210 nm); LCMS ($C_{22}H_{25}FN_2O_2$, MW 368.2, ES-API), observed 369.2 m/z $(M+H)^+$; ^{1}H NMR (500 MHz, methanol-d_4) δ 7.34 - 7.24 (m, 2H), 7.10 - 7.02 (m, 4H), 6.74 - 6.67 (m, 2H), 4.55 - 4.33 (m, 2H), 3.60 (t, *J*=8.8 Hz, 1H), 3.30 - 3.20 (m, 2H), 3.14 (br d, *J*=10.8 Hz, 1H), 2.87 (br d, *J*=11.0 Hz, 1H), 2.73 (td, *J*=11.2, 3.2 Hz, 1H), 2.48 - 2.39 (m, 2H), 2.22 - 2.12 (m, 1H), 2.05 (dq, *J*=13.0, 8.6 Hz, 1H), 1.82 - 1.69 (m, 4H). Corresponding ^{1}H NMR spectrum for compound **7** is shown below.


BMT-108908 (compound 7)
1H NMR (500 MHz, methanol-d4)
Normalized Intensity
Chemical Shift (ppm)
1.9
3.9
1.9
2.0
1.0
2.0
1.0
1.0
1.0
2.0
1.0
1.0
4.0

Preparation of (*R*)-3-(4-(4-Hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (compound 8).



2,4-Dibromo-N-(4-methylbenzyl)butanamide (intermediate (±)-**20**). TEA (3.45 mL, 24.8 mmol) and 2,4-dibromobutanoyl chloride (2.62 mL, 19.8 mmol) were sequentially added to solution of commercial *p*-tolylmethanamine (2.00 g, 16.5 mmol) in diethyl ether (20 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stir for an additional 24 h. The reaction mixture was diluted with water (150 mL). The aqueous mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, and filtered. The filtrate was concentrated in vacuo to afford a crude mixture containing 2,4-dibromo-*N*-(4-methylbenzyl)butanamide (5.5 g, 95 % yield): LCMS (ES-API), m/z 349.4 $(M+H)^+$.

3-Bromo-1-(4-methylbenzyl)pyrrolidin-2-one (intermediate (±)-**21**). A 60% dispersion of NaH in mineral oil (1.70 g, 42.5 mmol) was added to a stirred solution of intermediate (±)-**20** (5.50 g, 15.8 mmol**)** in THF (40 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stir for an additional 2 h. The reaction mixture was carefully quenched with ice and diluted with water. The resulting mixture was extracted with EtOAc. The combined organic layers were washed with water and then brine solution. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified using silica gel column chromatography (10% EtOAc/hexanes) to afford 3-

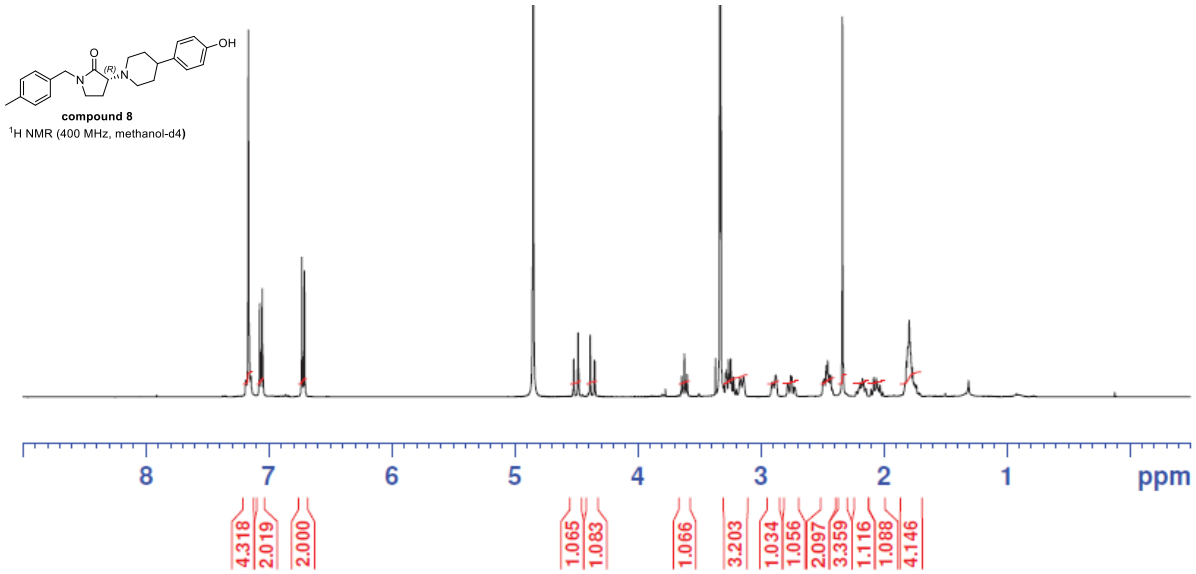
bromo-1-(4-methylbenzyl)pyrrolidin-2-one (3.1 g, 73 % yield): LCMS (ES-API), m/z 268, 270 $(M+H)^+$; ^{1}H NMR (400 MHz, chloroform-*d*) δ ppm 2.20 - 2.30 (m, 1 H) 2.34 (s, 3 H) 2.54 (s, 1 H) 3.19 (s, 1 H) 3.36 - 3.45 (m, 1 H) 4.36 - 4.54 (m, 3 H) 7.15 (s, 4 H).

3-(4-(4-Methoxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (intermediate **O**). DIEA (1.6 mL, 9.0 mmol) was added to a stirred solution of intermediate (±)-**21** (0.80 g, 3.0 mmol) and intermediate **C** (0.68 g, 3.0 mmol) in acetonitrile (10 mL). The reaction mixture was heated at reflux for 16 h. The reaction mixture was cooled to rt and concentrated in vacuo. The residue was diluted with EtOAc. The organic mixture was washed with water and brine solution. The organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was purified using silica gel column chromatography (50% EtOAc/hexanes) to afford 3-(4-(4-methoxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one as an off-white solid (0.80 g, 69 % yield): LCMS (ES-API), m/z 379.4 $(M+H)^+$.

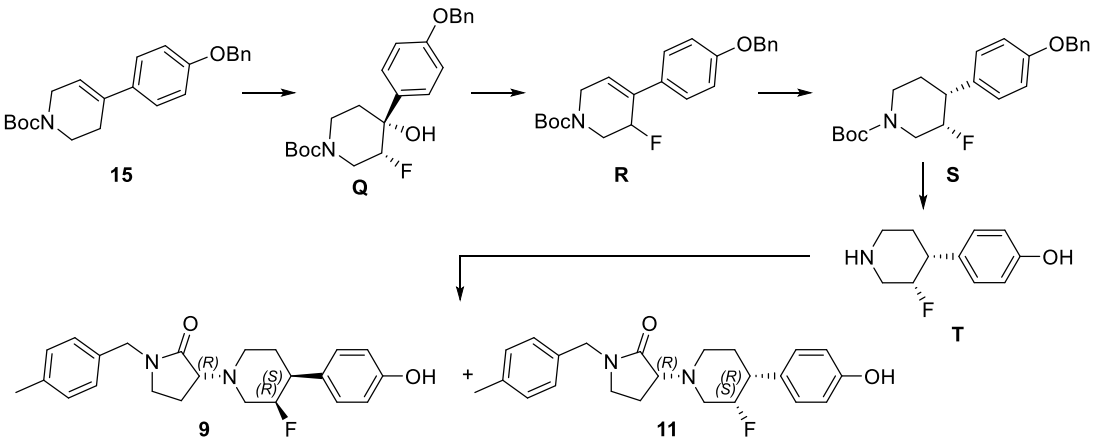
3-(4-(4-Hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (intermediate **P**). To a solution of intermediate **O** (1.00 g, 2.64 mmol) in dry dichloromethane (20 mL) under a N_2 atmosphere at -78 °C was added boron tribromide (1 M in dichloromethane, 7.93 mL, 7.93 mmol) and the resulting mixture was allowed to warm to room temperature and stir for 16 h. The reaction mixture was quenched with a solution of 10% aqueous sodium bcarbonate and extracted with dichloromethane. The combined organic layers were dried with sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified using preparative LC/MS (Column: Waters Xbridge C18, 19 x 150 mm, 5 μm; Guard Column: Waters XBridge C18,19 x 10 mm, 5μm; Mobile Phase A: 5:95 acetonitrile:water with 10 mM NH_4OAc; Mobile Phase B: 95:5 acetonitrile:water with 10 mM NH_4OAc; Gradient:10-40% B over 25 min, followed by a 10 min hold at 40% B and 5 minute hold at 100% B; Flow:15 mL/min). Fractions containing the desired product were combined and dried using a centrifugal evaporator to afford 3-(4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (348 mg, 36 % yield) as a yellow solid: LCMS (ES-API), m/z 365.2 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.44 - 1.61 (m, 2 H) 1.66 - 1.77 (m, 2 H) 1.91 (s, 2 H) 1.99 - 2.09 (m, 1 H) 2.23 - 2.41 (m, 2 H) 2.60 - 2.80 (m, 2 H) 3.08 (s, 3 H) 3.42 - 3.52 (m, 1 H) 3.91 (s, 1 H) 4.20 - 4.34 (m, 2 H) 6.60 - 6.77 (m, 4 H) 7.02 (d, J=8.03 Hz, 4 H) 9.10 (s, 1 H) 9.34 (s, 1 H).

(R)-3-(4-(4-Hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one. (compound **8**). A portion of intermediate **P** (250 mg) was separated using chiral SFC

(Chiralpak-IA (250 x 4.6 mm) 5 μm column eluting with 30% solvent B, where solvent A = CO_2 and solvent B = 0.3% DEA in methanol at a total flow of 3 mL/min) to afford 84 mg (33 % recovery) of peak 1 or (*S*)-3-(4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one with a retention time of 6.67 min and 96 mg (37 % recovery) of peak 2 or (*R*)-3-(4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (compound **8**) with a retention time of 9.74 min. The absolute stereochemistry of compound **8** was assigned in analogy to compound **7**. Data for compound **8**: LCMS ($C_{23}H_{28}N_2O_2$, MW 364.2, ES-API), observed 365.2 m/z $(M+H)^+$; $[\alpha]_D^{20}$ = +28.3 (c = 1.0, MeOH). ^{1}H NMR (400 MHz, methanol-d_4) δ 1.66 - 1.84 (m, 4 H) 2.01 - 2.21 (m, 2 H) 2.33 (s, 3 H) 2.36 - 2.49 (m, 2 H) 2.73 (m, 1 H) 2.86 (m, 1 H) 3.06 - 3.28 (m, 3 H) 3.30 - 3.33 (m, 1 H) 3.60 (s, 1 H) 4.30 - 4.53 (m, 2 H) 6.72 (d, *J*=8.53 Hz, 2 H) 7.05 (d, *J*=8.03 Hz, 2 H) 7.10 - 7.22 (m, 4 H). Corresponding ^{1}H NMR spectrum for compound **8** is shown below.



Preparation of (*R*)-3-((3*R*,4*S*)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (compound 9) and (*R*)-3-((3*S*,4*R*)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrolrolidin-2-one (compound 11).



tert-Butyl 4-(4-(benzyloxy)phenyl)-5,6-dihydropyridine-1(2H)-carboxylate (intermediate **15**). To a stirring mixture of *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (16.5 g, 53.0 mmol), dimethoxyethane (200 mL), and water (50 mL) was added 1-(benzyloxy)-4-bromobenzene (14 g, 53 mmol), sodium carbonate (16.9 g, 160 mmol) and *bis*-(triphenylphosphine)palladium(II) chloride (1.87 g, 2.66 mmol) at rt. The reaction mixture was purged with nitrogen for 15 min, then heated at 80° C for 4 h. The mixture was allowed to cool to rt and was filtered through Celite and diluted with water (200 mL). The aqueous mixture was extracted ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified using silica gel chromatography (20% ethyl acetate/petroleum ether) to afford tert-butyl 4-(4-(benzyloxy)phenyl)-5,6-dihydropyridine-1(2H)-carboxylate (16 g, 82 % yield) as an off-white solid: LCMS (ES-API), m/z 366 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.47 (s, 9H), 2.42 (d, J = 1.50 Hz, 2H), 3.52 (t, J = 11.40 Hz, 2H), 3.97 (s, 2H), 5.11 (s, 2H), 6.04 (s, 1H), 6.98 (d, J = 9.00 Hz, 2H), 7.30-7.46 (m, 7H).

cis-tert-Butyl 4-(4-(benzyloxy)phenyl)-3-fluoro-4-hydroxypiperidine-1-carboxylate (intermediate **Q**). To a cloudy solution of intermediate **15** (2.8 g, 7.7 mmol) in acetonitrile (30 mL) and water (8 mL) was added Selectfluor (3.27 g, 9.24 mmol) at rt. After stirring at rt for 1 h, an additional portion of Selectfluor (1.36 g, 3.85 mmol) was added, and the mixture

was stirred at 50 °C for 30 min. A saturated $NaHCO_3$ solution (100 mL) was added and the resulting mixture was extracted with EtOAc. The combined organic layers were concentrated in vacuo. The residue was dissolved in dichloromethane (20 mL). Triethylamine (3.20 mL, 23 mmol) was added followed by di-*tert*butyldicarbonate (4.45 mL, 19.2 mmol). The mixture was stirred at rt for 2 h, and the reaction mixture was concentrated. The crude residue was purified using silica gel chromatography (80 g of silica) eluting with a gradient of 0 to 100% ethyl acetate in hexanes. The first eluting spot was isolated to give *cis-tert*-butyl 4-(4-(benzyloxy)phenyl)-3-fluoro-4-hydroxypiperidine-1-carboxylate (2.0 g, 65 % yield): ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.55 - 7.31 (m, 7H), 7.09 - 6.90 (m, 2H), 5.09 (s, 2H), 5.05 - 4.93 (m, 1H), 4.89 (br. s., 1H), 4.31 (br. s., 1H), 3.92 (br. s., 1H), 3.29 (br. s., 1H), 3.25 - 3.04 (m, 1H), 2.00 - 1.86 (m, 1H), 1.83 (br. s., 1H), 1.55 - 1.45 (m, 9H).

tert-Butyl 4-(4-(benzyloxy)phenyl)-5-fluoro-5,6-dihydropyridine-1(2H)-carboxylate (intermediate **R**). To a solution of intermediate **Q** (2.0 g, 5.0 mmol) in CH_2Cl_2 (25 mL) was added TFA (6 mL) dropwise at rt. The mixture was stirred at rt for 2 h. An additional portion of TFA (8 mL) was added. After stirring for 1 h, more TFA (3 mL) was added. The mixture was concentrated to dryness in vacuo at rt, then 10 mL of CH_2Cl_2 and Et_3N (4.2 mL, 30 mmol) were added followed by bis-(*tert*)butyldicarbonate (3.5 mL, 15 mmol) and the resulting mixture was stirred for 16 h. The mixture was concentrated in vacuo. The crude residue was purified using silica gel chromatography (40 g of silica) eluting with a gradient of 0-20% ethyl acetate in hexanes to provide *tert*-butyl 4-(4-(benzyloxy)phenyl)-5-fluoro-5,6-dihydropyridine-1(2H)-carboxylate (1.4 g, 71 % yield): ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.48 - 7.38 (m, 6H), 7.38 - 7.32 (m, 1H), 6.99 (d, *J*=8.8 Hz, 2H), 6.34 - 6.16 (m, 1H), 5.45 - 5.20 (m, 1H), 5.10 (s, 2H), 4.61 - 4.37 (m, 2H), 3.81 (br. s., 1H), 3.39 - 3.24 (m, 1H), 1.59 (s, 3H), 1.52 (s, 9H).

cis-tert-Butyl 4-(4-(benzyloxy)phenyl)-3-fluoropiperidine-1-carboxylate (intermediate **S**). To 10% Pd/C (220 mg) under nitrogen was added a solution of intermediate **R** (1.35 g, 3.5 mmol) in ethyl acetate (20 mL). The mixture was stirred at rt under a hydrogen atmosphere at balloon pressure for 45 min. The Pd/C was removed by filtration, and the filtrate was concentrated in vacuo. The residue was purified using silica gel chromatography (40 g of silica gel) eluting with a gradient of 0-100% ethyl acetate in hexanes to give *cis-tert*-butyl 4-(4-(benzyloxy)phenyl)-3-fluoropiperidine-1-carboxylate (1.1 g, 77 % yield): ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.45 (d, *J*=7.6 Hz, 2H), 7.40 (t, *J*=7.5 Hz, 2H), 7.34 (t, *J*=7.0 Hz, 1H), 7.22 (d, *J*=8.4 Hz, 2H), 6.96 (ddd, *J*=8.9, 2.7, 2.0 Hz, 2H), 5.07 (s, 2H), 4.79 -

4.60 (m, 1H), 4.55 - 4.23 (m, 2H), 3.08 - 2.81 (m, 2H), 2.75 (ddd, *J*=36.0, 13.4, 3.1 Hz, 1H), 2.21 (qd, *J*=12.9, 4.3 Hz, 1H), 1.69 (d, *J*=11.7 Hz, 1H), 1.59 (s, 3H), 1.51 (s, 9H). The structure of intermediate **S** was verified by single-crystal X-ray analysis (see Supplemental Figure S1).

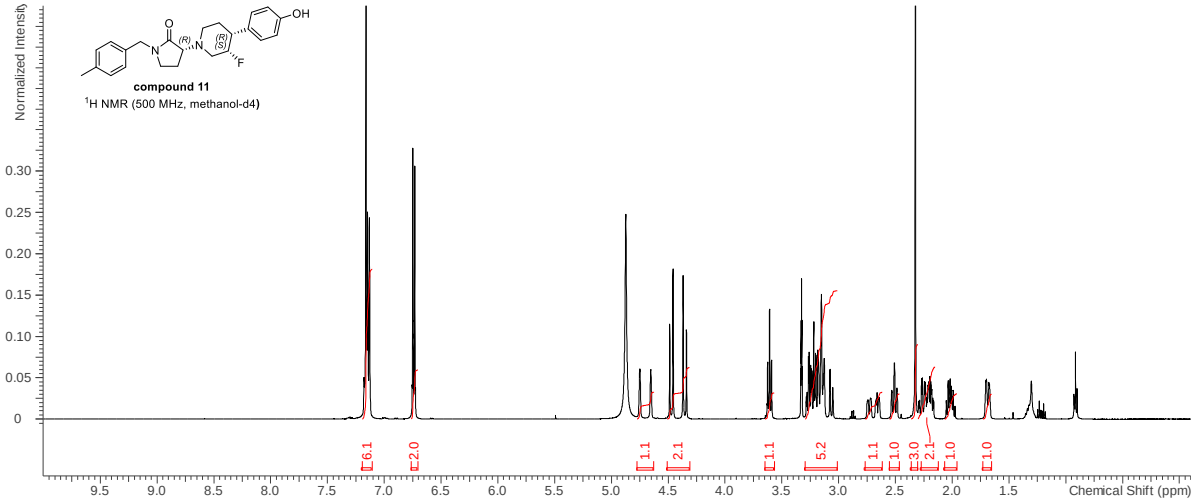
cis-4-(4-(Benzyloxy)phenyl)-3-fluoropiperidine. To a solution of intermediate **S** (400 mg, 1.04 mmol) in CH_2Cl_2 (4 mL) was dropwise added TFA (1.0 mL, 13 mmol) at rt. The mixture was stirred at rt for 2 h and then concentrated in vacuo. To the residue was added saturated aqueous sodium bicarbonate (50 mL) and the mixture was extracted with dichloromethane. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo afford *cis*-4-(4-(benzyloxy)phenyl)-3-fluoropiperidine (270 mg, 91 % yield): LCMS (ES-API), m/z 286.3 $(M+H)^+$; ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.49 - 7.38 (m, 4H), 7.34 (t, *J*=7.5 Hz, 1H), 7.26 - 7.20 (m, *J*=8.5 Hz, 2H), 7.01 - 6.93 (m, 2H), 5.08 (s, 2H), 4.70 (d, *J*=49.0 Hz, 1H), 3.38 (t, *J*=12.5 Hz, 1H), 3.25 (dt, *J*=13.4, 2.0 Hz, 1H), 2.93 (d, *J*=14.3 Hz, 1H), 2.90 - 2.68 (m, 3H), 2.09 (qd, *J*=12.9, 4.1 Hz, 1H), 1.69 (d, *J*=14.3 Hz, 1H).

cis-4-(3-Fluoropiperidin-4-yl)phenol (intermediate **T**). To a flask charged with 10% Pd/C (40 mg) under nitrogen was added a solution of *cis*-4-(4-(benzyloxy)phenyl)-3-fluoropiperidine (140 mg, 0.49 mmol) in IPA (4 mL). The mixture was stirred under a hydrogen atmosphere using balloon pressure at rt for 2 h. The vessel was vented and flushed with nitrogen. The Pd/C was removed by filtration through a glass fiber filter. The filtrate was concentrated in vacuo to afford *cis*-4-(3-Fluoropiperidin-4-yl)phenol (90 mg, 94 % yield). LCMS (ES-API), m/z 196.3 $(M+H)^+$; ^{1}H NMR (500 MHz, methanol-d_4) δ 7.14 (d, *J*=8.4 Hz, 2H), 6.74 (d, *J*=8.7 Hz, 2H), 4.63 (d, *J*=48.4 Hz, 1H), 3.30 - 3.22 (m, 1H), 3.15 (dt, *J*=13.1, 2.0 Hz, 1H), 2.95 - 2.66 (m, 3H), 2.12 (qd, *J*=13.0, 4.2 Hz, 1H), 1.64 (dd, *J*=13.4, 3.0 Hz, 1H).

(R)-3-((3R,4S)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (compound **9**) and *(R)-3-((3S,4R)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one* (compound **11**). To a solution of intermediate **T** (60 mg, 0.31 mmol) in acetonitrile (1 mL) and DIPEA (0.2 mL, 1.2 mmol) at 80 °C was added a solution of (*S*)-1-(4-methylbenzyl)-2-oxopyrrolidin-3-yl methanesulfonate (87 mg, 0.3 mmol)[2] in 0.5 mL of CH_3CN over 1.5 h. The mixture was then stirred at 80 °C for 16 h. The mixture was allowed to cool to rt and was then concentrated. The residue was purified via silica gel chromatography (4 g of silica) eluting with a gradient of 0-100% EtOAc in hexanes to give the product as a mixture of two diastereomers. The two

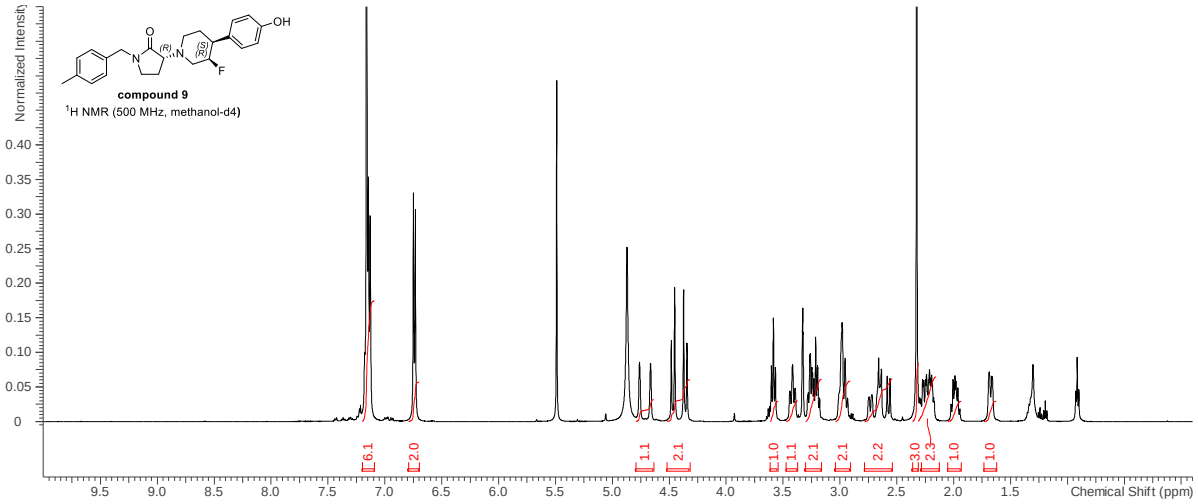
diastereomers were separated using chiral HPLC (Chiralcel OD (21 x 250 mm) 10 μm column, eluting with an isocratic mixture of 30% B where solvent A = 0.1% diethylamine in *n*-heptane and solvent B = 100% ethanol) to afford 33.8 mg (28 % yield) of peak 1 or (*R*)-3-((3*S*,4*R*)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (compound **11**) with a retention time of 8.87 min and 35.2 mg (27.3 % yield) of (*R*)-3-((3R,4S)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (compound **9**) with a retention time of 11.97 min. The relative stereochemistry of compound **11** was unambiguously confirmed through single crystal X-ray analysis (see Supplemental Figure S2), and the absolute stereochemistry was assigned from the known chirality of the starting mesylate. The relative and absolute stereochemistry of compound **9** was assigned by default.

Data for compound **11**: LCMS ($C_{23}H_{27}FN_2O_2$, MW 382.2, ES-API), observed 383.3 m/z $(M+H)^+$; ^{1}H NMR (500 MHz, methanol-d_4) δ 7.21 - 7.07 (m, 6H), 6.78 - 6.68 (m, 2H), 4.70 (d, *J*=48.8 Hz, 1H), 4.41 (dd, *J*=58.0, 14.5 Hz, 2H), 3.61 (t, *J*=8.8 Hz, 1H), 3.30 - 3.03 (m, 5H), 2.77 - 2.60 (m, 1H), 2.51 (t, *J*=11.1 Hz, 1H), 2.32 (s, 3H), 2.31 - 2.15 (m, 2H), 2.01 (dq, *J*=13.2, 8.4 Hz, 1H), 1.69 (dd, *J*=13.1, 2.6 Hz, 1H). Corresponding ^{1}H NMR spectrum for compound **11** is shown below.

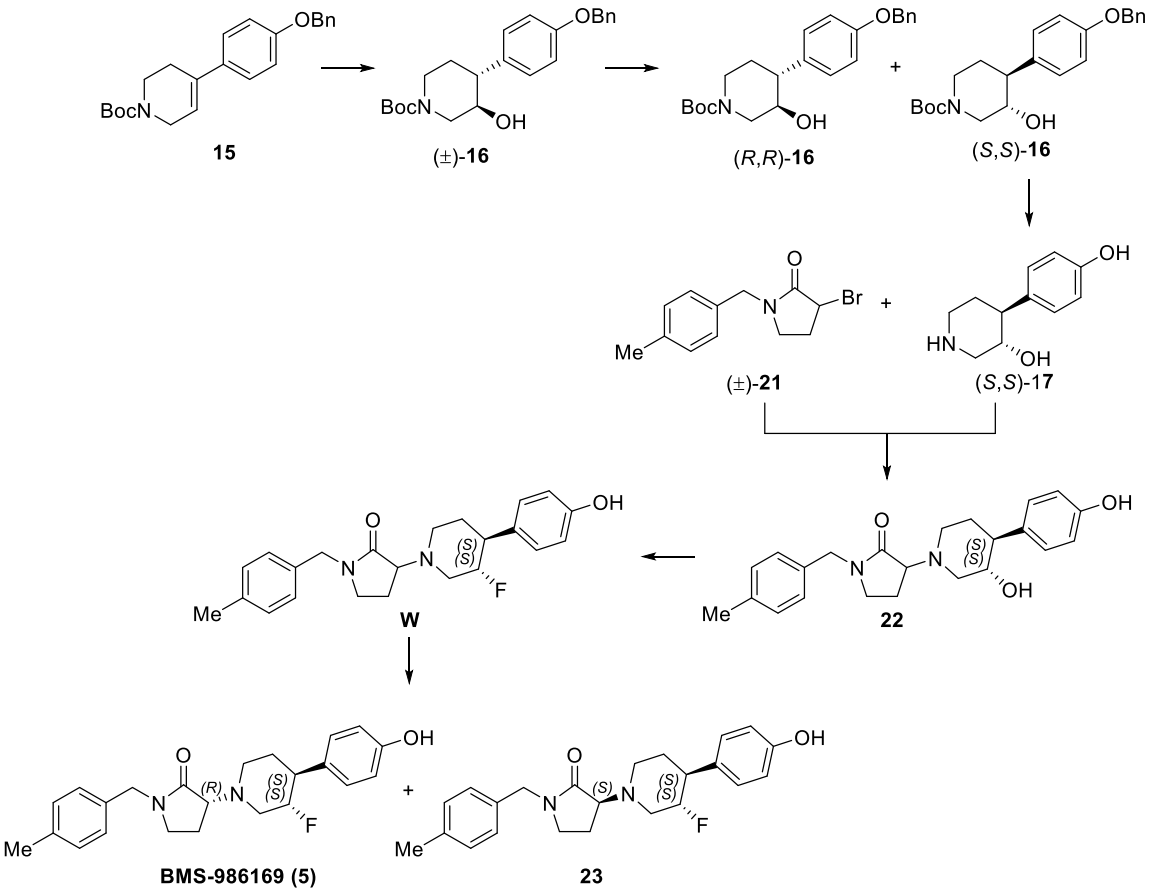


Data for compound **9**: LCMS ($C_{23}H_{27}FN_2O_2$, MW 382.2, ES-API), observed 383.3 m/z $(M+H)^+$; ^{1}H NMR (500 MHz, methanol-d_4) δ 7.19 - 7.08 (m, 6H), 6.74 (d, *J*=8.4 Hz, 2H), 4.66 (d, *J*=47.9 Hz, 1H), 4.41 (dd, *J*=53.7, 14.8 Hz, 2H), 3.58 (t, *J*=8.8 Hz, 1H), 3.42 (t, *J*=10.8 Hz, 1H), 3.30 - 3.14 (m, 2H), 3.05 - 2.88 (m, 2H), 2.79 - 2.51 (m, 2H), 2.33 (s, 3H),

2.31 - 2.13 (m, 2H), 2.06 - 1.90 (m, 1H), 1.67 (d, *J*=10.8 Hz, 1H). Corresponding ^{1}H NMR spectrum for compound **9** is shown below.



Preparation of (*S*)-3-((3*S*,4*S*)-3-Fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (compound 23) and (*R*)-3-((3*S*,4*S*)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (BMS-986169, compound 5).



tert-butyl (±)-rel-(3R,4R)-4-(4-(benzyloxy)phenyl)-3-hydroxypiperidine-1-carboxylate (intermediate (±)-**16**). To a suspension of sodium tetrahydroborate (5.18 g, 137 mmol) in THF (100 mL) at rt under a nitrogen atmosphere was added dropwise boron trifluoride etherate (17.5 mL, 137 mmol). The resulting mixture was stirred for 2 h, then intermediate **15** (20.0 g, 54.7 mmol) dissolved in THF (50 mL) was added. The mixture was stirred at rt for 3 h. The reaction was then quenched by the slow dropwise addition of a 1:1 water/ethanol mixture (200 mL). Next were added a 10% aqueous sodium hydroxide solution and 30% hydrogen peroxide (9.31 mL, 274 mmol). The resulting mixture was stirred at reflux for 5 h. After cooling to rt, the reaction mixture was concentrated in vacuo to remove ethanol and was neutralized using 1.5 N aqueous hydrochloric acid. The resulting aqueous mixture was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered,

and concentrated in vacuo to provide *tert*-butyl (±)-*rel*-(3*R*,4*R*)-4-(4-(benzyloxy)phenyl)-3-hydroxypiperidine-1-carboxylate (20 g, 87% yield) which was used without further purification: ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.50 - 7.33 (m, 5H), 7.19 (d, *J*=8.5 Hz, 2H), 7.02 - 6.96 (m, 2H), 5.08 (s, 2H), 4.58 - 4.17 (m, 2H), 3.65 (br s, 1H), 2.86 - 2.57 (m, 2H), 2.53 - 2.46 (m, 1H), 1.86 - 1.67 (m, 2H), 1.64 (d, *J*=2.6 Hz, 1H), 1.51 (s, 9H).

tert-butyl (3R,4R)-4-(4-(benzyloxy)phenyl)-3-hydroxypiperidine-1-carboxylate (intermediate (*R*,*R*)-**16**) and *tert-butyl (3S,4S)-4-(4-(benzyloxy)phenyl)-3-hydroxypiperidine-1-carboxylate* (intermediate (*S*,*S*)-**16**). A portion of intermediate (±)-**16** (20 g) was separated using chiral SFC (Lux-Cellulose-2 (250 x 21 mm) 5 μm column eluting with 60% CO_2 and 40% of a solution of 0.3% diethylamine in methanol at a flow rate of 100.0 g/min) to afford 23.5 g (45 % recovery) of peak 1 or intermediate (*S*,*S*)-**16** and 22.5 g (43 % recovery) of peak 2 or intermediate (*R*,*R*)-**16**). Analytical data of the separated enantiomers matched those of the corresponding racemate. Absolute stereochemical assignment of (*S*,*S*)-**16** was confirmed via crystallographic analysis of the final product **5**.

tert-butyl (3S,4S)-3-hydroxy-4-(4-hydroxyphenyl)piperidine-1-carboxylate. To a stirred solution of intermediate (*S*,*S*)-**16** (10 g, 26 mmol) in methanol (100 mL) under nitrogren was carefully added 10% palladium/carbon (5.55 g, 5.22 mmol). The vessel was evacuated and charged with hydrogen (113 psi). After 6 h, the reaction vessel was vented, purged with nitrogen, and the contents filtered through Celite. The filtrate was concentrated under reduced pressure to afford *tert*-butyl (3*S*,4*S*)-3-hydroxy-4-(4-hydroxyphenyl)piperidine-1-carboxylate (7.0 g, 85 % yield): LCMS (ES-API), m/z 294 $(M+H)^+$.

(3S,4S)-4-(4-Hydroxyphenyl)piperidin-3-ol, hydrochloride (intermediate (*S*,*S*)-**17)**. To a solution of *tert*-butyl (3*S*,4*S*)-3-hydroxy-4-(4-hydroxyphenyl)piperidine-1-carboxylate (7.0 g, 24 mmol) in MeOH (100 mL) was added 4 M HCl in dioxane (29.8 mL, 119 mmol). The resulting mixture was stirred at rt for 2 h, then evaporated in vacuo. The residue was titurated with diethyl ether (100 mL) to give (3*S*,4*S*)-4-(4-hydroxyphenyl)piperidin-3-ol, hydrochloride (5.0 g, 87 % yield). LCMS (ES-API), m/z 194 $(M+H)^+$.

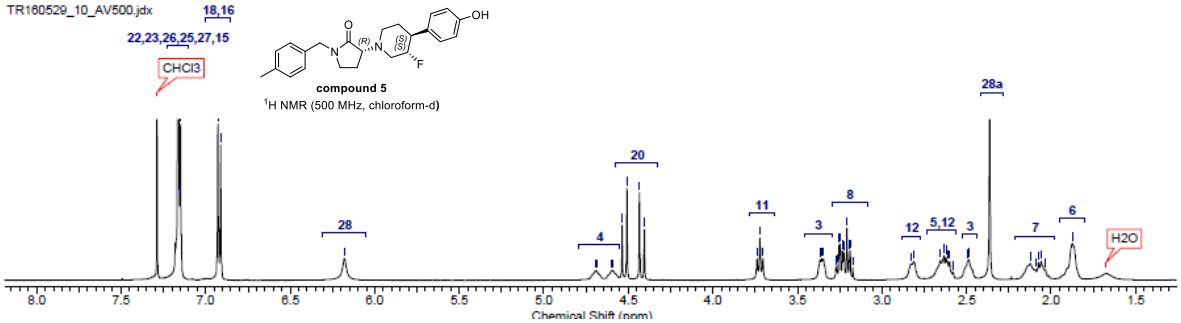
3-((3S,4S)-3-Hydroxy-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (intermediate **22**). To a mixture of intermdiate (*S*,*S*)-**19** (1.50 g, 6.53 mmol) and intermediate (±)-**21** (1.95 g, 7.26 mmol) in DMF (40 mL) under nitrogen was added and DIPEA (6.51 mL, 36.3 mmol). The reaction mixture was heated at 100 °C for 2 h. After cooling to rt, the resulting mixture was diluted with 1.5 N aqueous HCl (200 mL).

The aqueous mixture was extracted with ethyl acetate. The organic extract was discarded. The aqueous layer was made basic with saturated aqueous sodium bicarbonate solution. The basic solution was extracted with ethyl acetate. The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo to afford 3-((3*S*,4*S*)-3-hydroxy-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (2.1 g, 74 % yield): LCMS (ES-API), m/z 381 $(M+H)^+$.

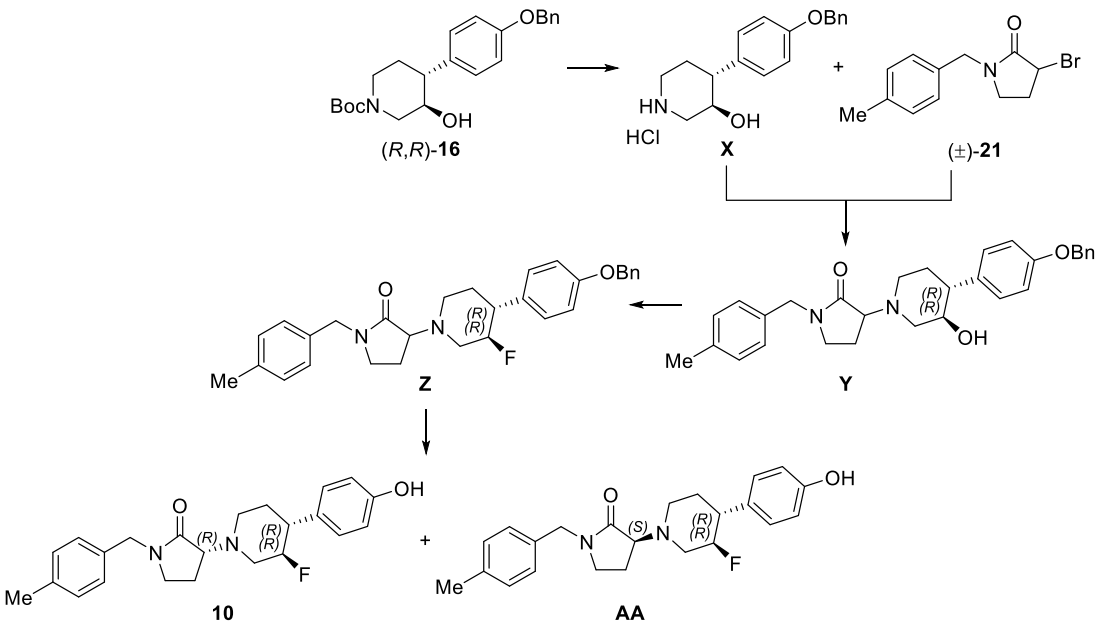
3-((3S,4S)-3-Fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (intermediate **W**). To a solution of intermediate **22** (1.85 g, 4.86 mmol) in dichloromethane (150 mL) was added Deoxofluor (2.7 mL, 15 mmol) under nitrogen at –10 °C. The reaction mixture was stirred at the same temperature for 15 min, then quenched with water and diluted with 5% aqueous NaOH solution. The resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The crude product was purified using reverse phase preparatory HPLC. Fractions containing the pure product were combined and concentrated to afford 3-((3*S*,4*S*)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (580 mg, 27 % yield): LCMS (ES-API), m/z 383 $(M+H)^+$.

(S)-3-((3S,4S)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (compound **23**) and *(R)-3-((3S,4S)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one* (BMS-986169, compound **5**). A portion of intermediate **W** (580 mg) was separated using chiral SFC (ChiralPak AD H (250 x 21 mm) 5 μm column eluting with 55% CO_2 and 45% of a solution of 0.3% diethylamine in methanol at a flow rate of 60 g/min, pressure: 102 bar) to afford peak 1 or compound **25** and 280 mg (48 % recovery) of peak 2 or BMS-986169 (compound **5**). The relative and absolute stereochemistry of BMS-986169 was unambiguously established through single crystal X-ray diffraction using anomalous scattering refinement (see Figure S3). Analytical data for BMS-986169 (compound **5**): LCMS ($C_{23}H_{27}FN_2O_2$, MW 382.2, ES-API), observed 383.2 m/z $(M+H)^+$; $[\alpha]_D^{20}$ = +6.09 (c = 1.15, MeOH); Anal. Calcd for $C_{23}H_{27}FN_2O_2$ (382.21): C, 72.22; H, 7.12; N, 7.32. Found: C, 72.26; H, 7.05; N, 7.31; HRMS (ESI) Calcd for $C_{23}H_{27}N_2O_2$, 383.2118. Found, 383.2129; ^{13}C NMR (126 MHz, chloroform-*d*) δ 172.4, 155.0, 137.5, 133.0, 132.8, 129.4, 128.6, 128.2, 115.6, 91.6 (d, *J*=173.5 Hz), 65.0, 54.5 (d, *J*=25.4 Hz), 48.3, 47.7 (d, *J*=17.3 Hz), 46.7, 43.6, 31.5, 21.1, 19.2; ^1H NMR

(500 MHz, chloroform-*d*) δ 7.23 - 7.11 (m, 5H), 6.92 (d, *J*=8.5 Hz, 2H), 6.18 (br. s., 1H), 4.79 - 4.55 (m, 1H), 4.57 - 4.33 (m, 2H), 3.72 (t, *J*=8.7 Hz, 1H), 3.46 - 3.30 (m, 1H), 3.30 - 3.09 (m, 2H), 2.82 (d, *J*=8.5 Hz, 1H), 2.73 - 2.56 (m, 2H), 2.49 (d, *J*=2.5 Hz, 1H), 2.36 (s, 3H), 2.21 - 1.98 (m, 2H), 1.87 (br. s., 2H). The corresponding ^{1}H NMR spectrum for compound **5** is shown below.



Preparation of (*R*)-3-((3*R*,4*R*)-3-Fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (compound 10).



(3R,4R)-4-(4-(Benzyloxy)phenyl)piperidin-3-ol, hydrochloride (intermediate **X**). A mixture of intermediate (*R*,*R*)-**16** (750 mg, 2.0 mmol), dioxane (4.0 mL), and 4 M HCl in dioxane (4.9 mL) was stirred at rt for 2 h. The reaction was then evaporated to dryness to yield (3*R*,4*R*)-4-(4-(benzyloxy)phenyl)piperidin-3-ol, hydrochloride (550 mg, 88 % yield)

which was used in the next step without further purification. LCMS (ES-API), m/z 284 $(M+H)^+$.

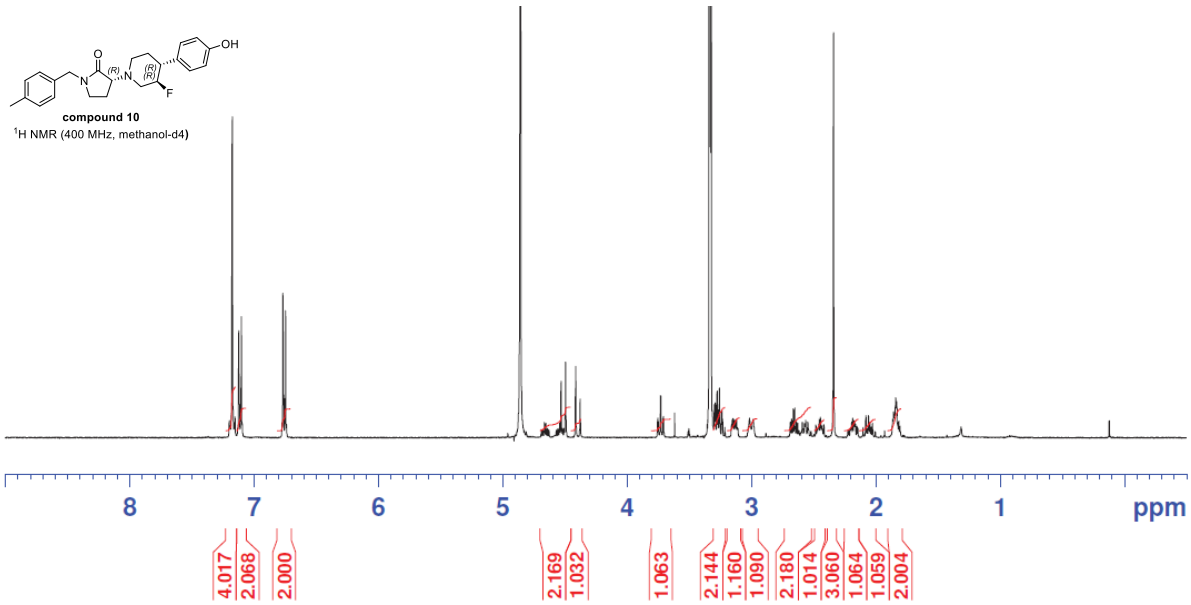
3-((3R,4R)-4-(4-(Benzyloxy)phenyl)-3-hydroxypiperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (intermediate **Y**). **A** mixture of intermediate (±)-**21** (220 mg, 0.82 mmol), intermediate **X** (262 mg, 0.82 mmol), and triethylamine (11 mL, 8.2 mmol) was stirred at 60 °C for 1 h, 80 °C for 1 h, 100 °C for 1 h, and finally, 120 °C for 1 h. The reaction mixture was allowed to cool to rt, diluted with water (40 mL), and extracted with chloroform. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford a crude mixture containing the two diastereomers of 3-((3*R*,4*R*)-4-(4-(benzyloxy)phenyl)-3-hydroxypiperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (382 mg, 99 % crude yield). The crude mixture was used in the next step without purification. LCMS (ES-API), m/z 471 $(M+H)^+$.

3-((*3R,4R*)-4-(4-(Benzyloxy)phenyl)-3-fluoropiperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (intermediate **Z**). A solution containing intermediate **Y** (382 mg, 0.81 mmol) in dichloromethane (5 mL) at 0 °C was treated dropwise with DAST (0.32 mL, 2.4 mmol) over 3 min. The reaction mixture was then allowed to warm to rt and was stirred for 2 h. The reaction was then quenched with 50 mL of 10% aqueous sodium bicarbonate solution and extracted dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to yield a crude mixture containing the two diastereomers of 3-((*3R,4R*)-4-(4-(benzyloxy)phenyl)-3-fluoropiperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (intermediate **Z**) as well as some impurities. The crude mixture was used in the next step without purification. LCMS (ES-API), m/z 473 $(M+H)^+$.

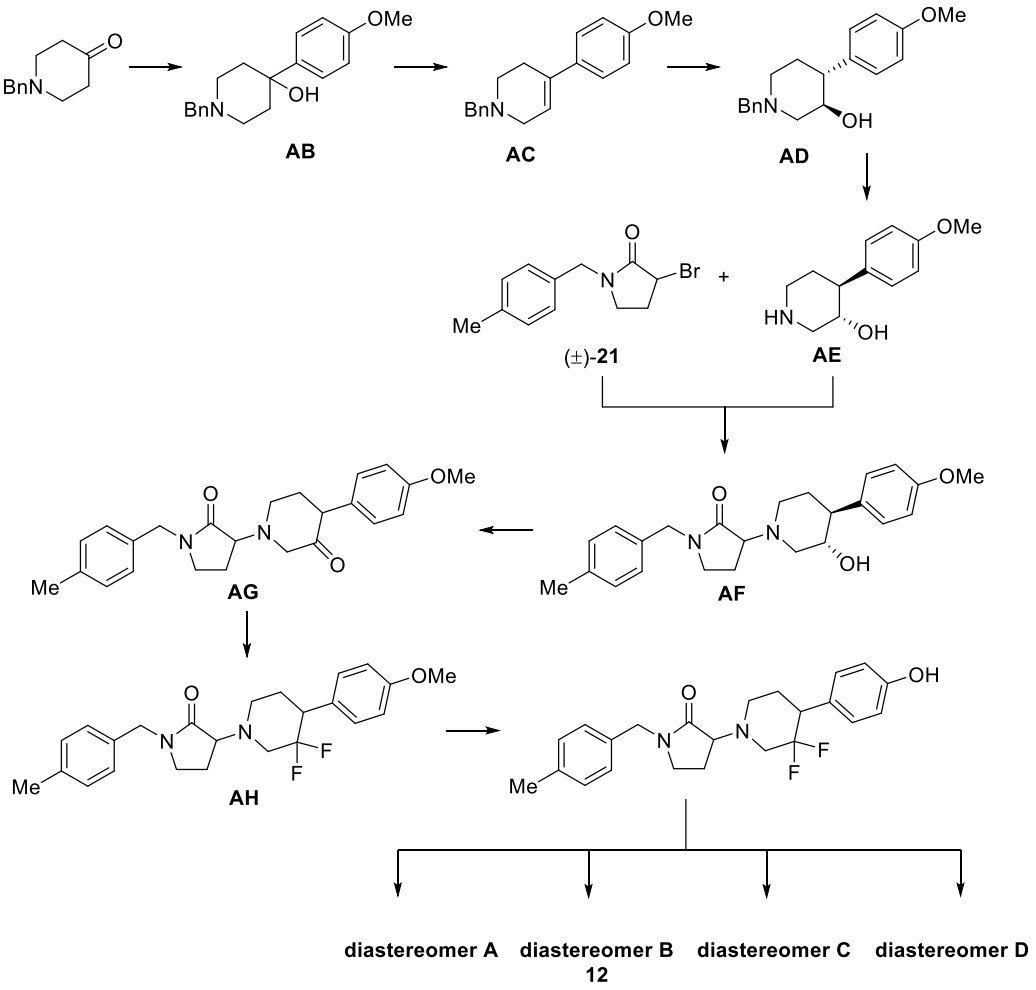
3-((3R,4R)-3-fluoro-4-(4-hydroxyphenyl)-piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one. A reaction vessel charged with mixture of intermediate **Z** (382 mg, 0.81 mmol) and methanol (4 mL) was flushed with nitrogen, followed by the addition of 10% Pd/C (172 mg). The vessel was pressurized with hydrogen (25-99 psi) and stirred at rt for 16 h. The reaction contents were carefully transferred to a 100 mL autoclave vessel and stirred under hydrogen (7 kg/cm^2) for 4 additional days. The vessel was purged with nitrogen, the catalyst was removed by filtration through Celite, and the filtrate was concentrated in vacuo. The crude product was subjected to HPLC purification (ZORBAX SB C18 (4.6 × 50 mm) 5 μm column eluting with Solvent A = 10 % MeOH: 90% H_2O: 0.1 % TFA; Solvent B = 90 % AcCN: 10 % H_2O: 0.1 % TFA; gradient 0-100 % B over 2 min; 3

min run time) to yield a diastereomeric mixture of 3-((*3R,4R*)-3-fluoro-4-(4-hydroxyphenyl)-piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (77 mg): LCMS (ES-API), m/z 383.0 $(M+H)^+$.

(S)-3-((3R,4R)-3-Fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (compound **AA**) and *(R)-3-((3R,4R)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one* (compound **10**). A diastereomeric mixture 3-((*3R,4R*)-3-fluoro-4-(4-hydroxyphenyl)-piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (77 mg) was separated using chiral SFC (ChiralPak AD H (250 x 21 mm) 5 µm column eluting with 55% CO_2 and 45% of a solution of 0.3% diethylamine in methanol at a flow rate of 60 g/min, 102 bar back pressure) to afford compound **AA** (peak 1, 29 mg, 38 % recovery) and (*R*)-3-((3*R*,4*R*)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (peak 2, 33 mg, 43 % recovery). Data for compound **10**: LCMS ($C_{23}H_{27}FN_2O_2$, MW 382.2, ES-API), observed m/z 383.2 $(M+H)^+$, 405.2 $(M+Na^+)^+$; ^{19}F NMR δ ppm -184.311; ^1H NMR (400 MHz, methanol-d_4) δ ppm 1.81 - 1.87 (m, 2 H) 2.07 (m, 1 H) 2.19 (m, 1 H) 2.34 (s, 3 H) 2.41 - 2.48 (m, 1 H) 2.55 (m, 1 H) 2.66 (m, 1 H) 3.00 (m, 1 H) 3.10 - 3.18 (m, 1 H) 3.20 - 3.30 (m, 2 H) 3.73 (t, *J* = 8.8 Hz, 1 H) 4.40 (d, J = 14.4 Hz, 1 H) 4.49-4.68 (m, 2 H) 6.70 - 6.80 (m, 2 H) 7.05 - 7.13 (m, 2 H) 7.13 - 7.22 (m, 4 H). Corresponding ^1H NMR spectrum for compound **10** is shown below.



Preparation of 3-(3,3-difluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (compound 12).



1-Benzyl-4-(4-methoxyphenyl)piperidin-4-ol (intermediate **AB**). To a solution of 1-bromo-4-methoxybenzene (5.0 g, 27 mmol) in THF (100 mL) at -78°C was added a solution of 1.6 M N-butyl lithium/hexanes (18.4 mL, 29.4 mmol), and the reaction mixture was stirred for 1 hr. Then a solution of 1-benzylpiperidin-4-one (4.81 g, 25.4 mmol) in THF (50 mL) was added. After the addition, the mixture was allowed to warm up to rt and was stirred for 1 h. The reaction was then quenched by the addition of 1.5 M aqueous HCl (100 mL) and the resulting mixture was extracted with ethyl acetate (200 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo to yield 1-benzyl-4-(4-methoxyphenyl)piperidin-4-ol (7.1 g, 72% yield): LCMS (ES-API), m/z 298.4 $(M+H)^+$; ^1H NMR (300 MHz, DMSO-d_6) δ 6.94-7.39 (m, 9H), 6.84-6.94 (m, 2H), 4.66 (s, 1H), 3.74 (s,

1H), 3.72 (s, 3H), 3.32 (s, 2H), 2.50-2.67 (m, 2H), 2.34-2.45 (m, 3H), 1.83-1.90 (m, 2H), 1.55 (d, J= 11 Hz, 2H)

1-Benzyl-4-(4-methoxyphenyl)-1,2,3,6-tetrahydropyridine (intermediate **AC**).To a solution of 1-benzyl-4-(4-methoxyphenyl)piperidin-4-ol (7.0 g, 24 mmol) in dichloromethane (150 mL) was added trifluoroacetic acid (2.68 g, 23.5 mmol) and the reaction mixture was stirred at rt overnight. The mixture was then evaporated under reduced pressure and partitioned between saturated aqueous sodium bicarbonate (500 mL) and ethyl acetate (500 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and evaporated under reduced pressure to yield 1-benzyl-4-(4-methoxyphenyl)-1,2,3,6-tetrahydropyridine (5.9 g, 88 % yield). LCMS (ES-API), m/z 280.4 $(M+H)^+$.

(±)-rel-(3S,4S)-1-Benzyl-4-(4-methoxyphenyl)piperidin-3-ol (intermediate **AD**). To a suspension of $NaBH_4$ (2.7 g, 72 mmol) in THF (150 mL) at -10°C was added boron trifluoride etherate (9.1 mL, 72 mmol) and the solution was stirred for 15 minutes. Then a solution of 1-benzyl-4-(4-methoxyphenyl)-1,2,3,6-tetrahydropyridine (10 g, 36 mmol) in THF (100 mL) was added and the mixture was stirred for an additional hour. Next were sequentially added 25 mL of water, 25 mL of 10% aqueous sodium hydroxide, 50 mL of ethanol, and 12.8 mL of 30 % aqueous hydrogen peroxide. The resulting mixture was heated at reflux for 20 h. The mixture was allowed to cool to rt and was then diluted with water (200 mL) and extracted with ethyl acetate (300 mL). The organic layer was separated, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was triturated with diethyl ether to yield (±)-*rel*-(3*S*,4*S*)-1-benzyl-4-(4-methoxyphenyl)piperidin-3-ol (7.5 g, 57%, yield). LCMS (ES-API), m/z 298.4 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.28 - 7.35 (m, 5 H) 7.14 (d, *J*=8.69 Hz, 2 H) 6.83 (d, *J*=8.69 Hz, 2 H) 4.43 (d, *J*=6.04 Hz, 1 H) 3.51 (d, *J*=19.26 Hz, 4 H) 3.33 (s, 3 H) 2.97 (dd, *J*=10.01, 3.59 Hz, 1 H) 2.81 (d, *J*=10.95 Hz, 1 H) 2.19 - 2.29 (m, 1 H) 1.96-1.98 (m, 1 H) 1.78 (t, *J*=10.20 Hz, 1 H) 1.58 - 1.68 (m, 2 H).

(±)-rel-(3S,4S)-4-(4-Methoxyphenyl)piperidin-3-ol (intermediate **AE**). To a solution of (±)-*rel*-(3S,4S)-1-benzyl-4-(4-methoxyphenyl)piperidin-3-ol (7.0 g, 23.5 mmol) in methanol (100 mL) was added 10% Pd/C (3.76 g) and the reaction mixture was stirred for 16 h under a hydrogen atmosphere (balloon pressure). The catalyst was removed by filtration through Celite and the solvent was evaporated under reduced pressure to give (±)-*rel*-(3*S*,4*S*)-4-(4-methoxyphenyl)piperidin-3-ol (4.8 g, 89 % yield). LCMS (ES-API), m/z 207.8 $(M+H)^+$; ^{1}H NMR (DMSO-d_6) δ 7.133 (d, *J*=7, 2H), 6.83 (d, *J*=7, 2H), 4.31 (br s, 1H), 3.7 (s, 3H),

3.02 (m, 1H), 2.86 (d, *J*=12, 1H), 2.45 (m,. 1H), 2.22-2.39 (m, 2H), 1.62-1.61 (m, 1H), 1.610-1.46 (m, 1H).

(±)-rel-3-((3R,4R)-3-Hydroxy-4-(4-methoxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (intermediate **AF**). A mixture of intermediate (±)-**21** (450 mg, 1.68 mmol), (±)-*rel*-(3S,4S)-4-(4-methoxyphenyl)piperidin-3-ol (intermediate **AE**, 313 mg, 1.5 mmol) and triethylamine (23 mL, 16.8 mmol) was stirred at 60 °C for 1 h, followed by heating at 85 °C for 1 h, 120 °C for 1 h and at 140 °C for 1 h.The mixture was cooled and then quenched with 40 mL of water and extracted with chloroform. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified using silica gel chromatography (24 g column, gradient of 0-80% ethyl acetate/petroleum ether) to yield (±)-*rel*-3-((3R,4R)-3-hydroxy-4-(4-methoxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (375 mg) of as a mixture of four diastereomers. The product mixture was used directly in the next step. LCMS (ES-API), m/z 395.2 $(M+H)^+$; ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 7.31 - 7.41 (m, 8 H) 6.86 (d, *J*=9.07 Hz, 2 H) 4.66 (s, 1 H) 3.73 (s, 3 H) 3.49 (s, 2 H) 2.59 (d, *J*=10.58 Hz, 2 H) 2.32 - 2.47 (m, 3 H) 1.89 (td, *J*=12.65, 4.53 Hz, 2 H) 1.56 (d, *J*=11.71 Hz, 2 H).

4-(4-Methoxyphenyl)-1-(1-(4-methylbenzyl)-2-oxopyrrolidin-3-yl)piperidin-3-one (intermediate **AG**). A mixture of DMSO (0.17 mL, 2.46 mmol) and dichloromethane (4 mL) was cooled to -78 °C, and oxalyl chloride (0.2 mL, 2.3 mmol) was added dropwise over 2 min. Following the addition, the mixture was stirred at the same temperature for 10 min. To the reaction was added dropwise (±)-*rel*-3-((3*R*,4*R*)-3-hydroxy-4-(4-methoxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (375 mg, 0.95 mmol, mixture of four diastereomers) in dichloromethane over 5 min. The reaction was stirred for 1 h and then triethylamine (1 mL, 7.6 mmol) was added. The resulting mixture was stirred for 15 min, slowly warmed to rt, and then extracted with dichloromethane. The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to yield 4-(4-methoxyphenyl)-1-(1-(4-methylbenzyl)-2-oxopyrrolidin-3-yl)piperidin-3-one (345 mg) as a mixture of 4 diastereomers. The crude product mixture was used directly in the next step. LCMS (ES-API), m/z 393 $(M+H)^+$.

3-(3,3-Difluoro-4-(4-methoxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (intermediate **AH**). A mixture of 4-(4-methoxyphenyl)-1-(1-(4-methylbenzyl)-2-oxopyrrolidin-3-yl)piperidin-3-one (370 mg, 0.94 mmol) and dichloromethane (5 mL) was cooled to 0 °C, followed by the dropwise addition of DAST (0.62 mL, 4.7 mmol) over 2

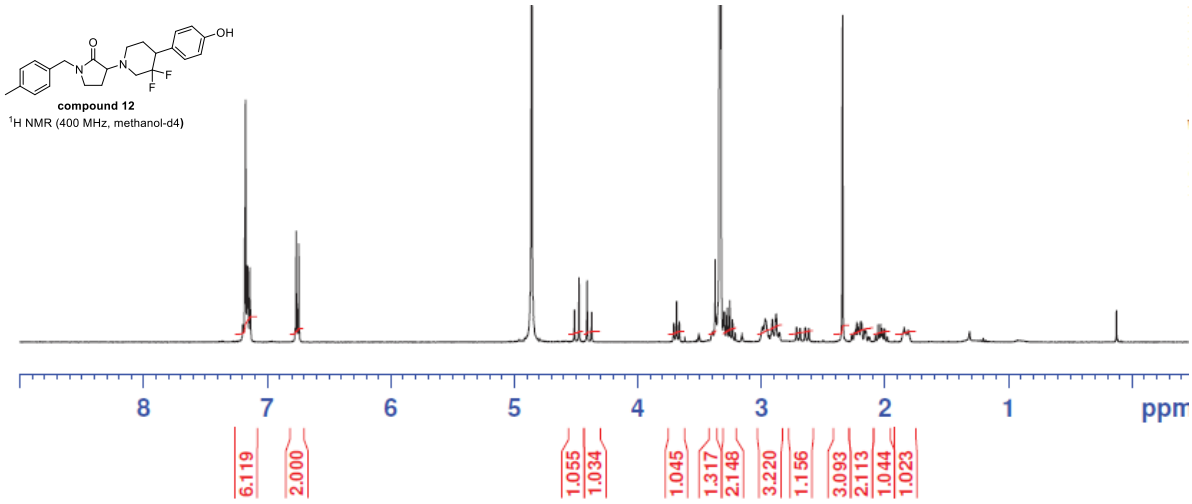
minutes. The mixture was warmed to rt and stirred overnight. The reaction was then quenched with aqueous sodium bicarbonate (50 mL) and extracted with dichloromethane. The combined organic layers were washed with brine, separated, dried over Na_2SO_4, filtered, and concentrated in vacuo to yield 3-(3,3-difluoro-4-(4-methoxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (380 mg) as a mixture of 4 diastereomers. The crude product mixture was used directly in the next step. LCMS (ES-API), m/z 415.2 $(M+H)^+$.

3-(3,3-Difluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (diastereomeric mixture). A mixture of 3-(3,3-difluoro-4-(4-methoxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (230 mg, 0.55 mmol) and 4 mL DCM was cooled to -78 °C, followed by the dropwise addition of boron tribromide (0.05 mL, 0.55 mmol). The mixture was then allowed to warm up to rt over 4 h. The reaction was then quenched with a 10% solution of aqueous sodium bicarbonate (50 mL) and extracted with dichloromethane. The combined organic fractions were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue was subjected to preparative HPLC (ZORBAX SB C18 (4.6 × 50 mm) 5 μm; Solvent A = 10 % MeOH: 90% H_2O: 0.1 % TFA; Solvent B = 90 % AcCN: 10 % H_2O: 0.1 % TFA; gradient 0-100 % B over 2 min; 3 min run time) to afford 3-(3,3-difluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one as a mixture of 4 diastereomers (28.1 mg). LCMS (ES-API), m/z 401 $(M+H)^+$.

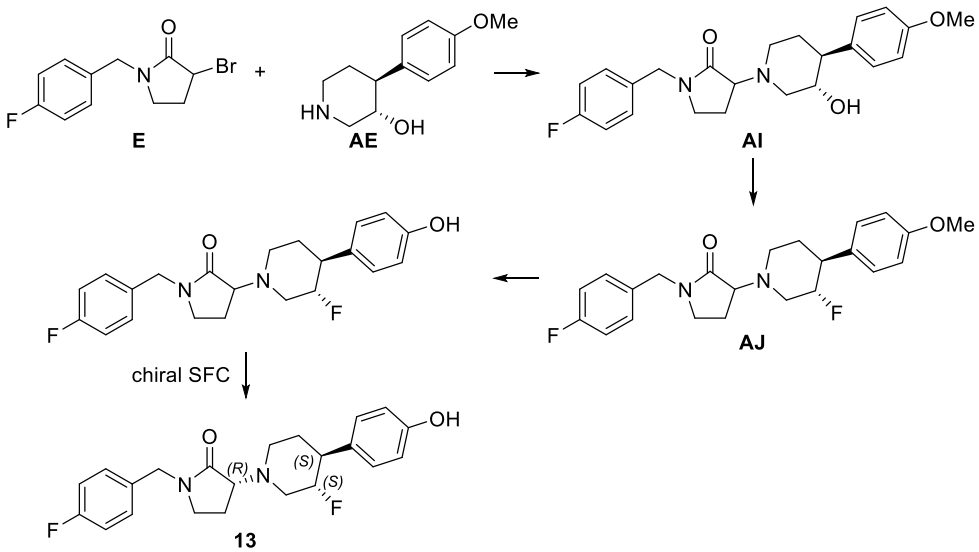
3-(3,3-Difluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (compound **12**). A mixture of 4 diastereomers of 3-(3,3-difluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (34 mg) was separated using chiral SFC (Chiralpak-AS H (4.6 x 250 mm) 5 μm; BPR pressure: 102 bar, temperature 24 °C, flow rate: 80 g/min, mobile phase: 40% MeOH w/0.3% DEA in CO_2) to yield homochiral diastereomer A (peak 1, 6.8 mg), compound **12** (peak 2, 3.7 mg), diastereomer C (peak 3, 3.7 mg), and diastereomer D (peak 4, 4.5 mg). The absolute and relative stereochemistry of each diastereomer was undetermined. Rat GluN2B binding data for all diastereomers is provided in Table S3. Compound **12** displayed the most potent binding affinity.

Data for compound **12**: LCMS ($C_{23}H_{26}F_2N_2O_2$, MW 400.2, ES-API), observed 401.0 m/z $(M+H)^+$; ^{1}H NMR (400 MHz, methanol-d_4) δ = 7.18 - 7.12 (m, 6 H), 6.77 - 6.73 (m, 2 H), 4.44 (q, *J* = 1.0 Hz, 2 H), 3.68 (t, *J* = 8.8 Hz, 1 H), 3.41 - 3.35 (m, 1 H), 3.31 - 3.20 (m, 2 H), 3.01 - 2.83 (m, 3 H), 2.72 - 2.60 (m, 1 H), 2.34 (s, 3 H), 2.27 - 2.11 (m, 2 H), 2.08 - 1.96 (m,

1 H), 1.82 (tdd, *J* = 2.5, 5.0, 13.1 Hz, 1 H). Corresponding ^{1}H NMR spectrum for compound **12** is shown below.



Preparation of (*R*)-3-((3*S*,4*S*)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (compound 13).



(±)-rel-1-(4-Fluorobenzyl)-3-((3S,4S)-3-hydroxy-4-(4-methoxyphenyl)piperidin-1-yl)pyrrolidin-2-one (intermediate **AI**). To a solution of 3-bromo-1-(4-fluorobenzyl)pyrrolidin-2-one (intermediate **E**, 300 mg, 1.1 mmol) and (±)-*rel*-(3S,4S)-4-(4-methoxyphenyl)piperidin-3-ol (intermediate **AE**, 240 mg, 1.16 mmol) in acetonitrile (10 mL) was added triethylamine (560 mg, 5.5 mmol) and the mixture was heated at 120 ^{o}C in a chemistry microwave reactor for 1 h. The reaction mixture was then diluted with water and

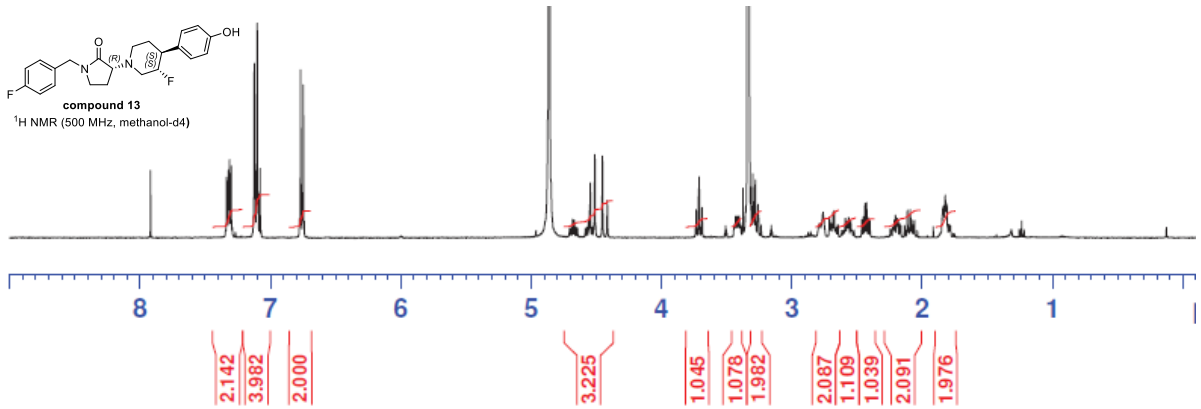
extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford (±)-*rel*-1-(4-fluorobenzyl)-3-((3*S*,4*S*)-3-hydroxy-4-(4-methoxyphenyl)piperidin-1-yl)pyrrolidin-2-one (450 mg, 0.7 mmol) as a mixture of four diastereomers. The crude product mixture was used directly in the next step. LCMS (ES-API), m/z 399.1 $(M+H)^+$.

(±)-rel-3-((3S,4S)-3-Fluoro-4-(4-methoxyphenyl)piperidin-1-yl)-1-(4-fluorobenzyl)pyrrolidin-2-one (intermediate **AJ**). To a solution of (±)-*rel*-1-(4-fluorobenzyl)-3-((3*S*,4*S*)-3-hydroxy-4-(4-methoxyphenyl)piperidin-1-yl)pyrrolidin-2-one (2.5 g, 6.3 mmol) in dichloromethane (50 mL) was added DAST (4.1 mL, 31 mmol). The reaction mixture was stirred at rt for 1 h. The reaction was then quenched with a saturated sodium bicarbonate solution (200 mL). The resulting aqueous mixture was extracted with dichloromethane. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified via silica gel chromatography eluting (28% ethyl acetate in hexane) to give (±)-*rel*-3-((3*S*,4*S*)-3-fluoro-4-(4-methoxyphenyl)piperidin-1-yl)-1-(4-fluorobenzyl)pyrrolidin-2-one (900 mg, 1.6 mmol) as a mixture of four diastereomers. LCMS (ES-API), m/z 401.2 $(M+H)^+$.

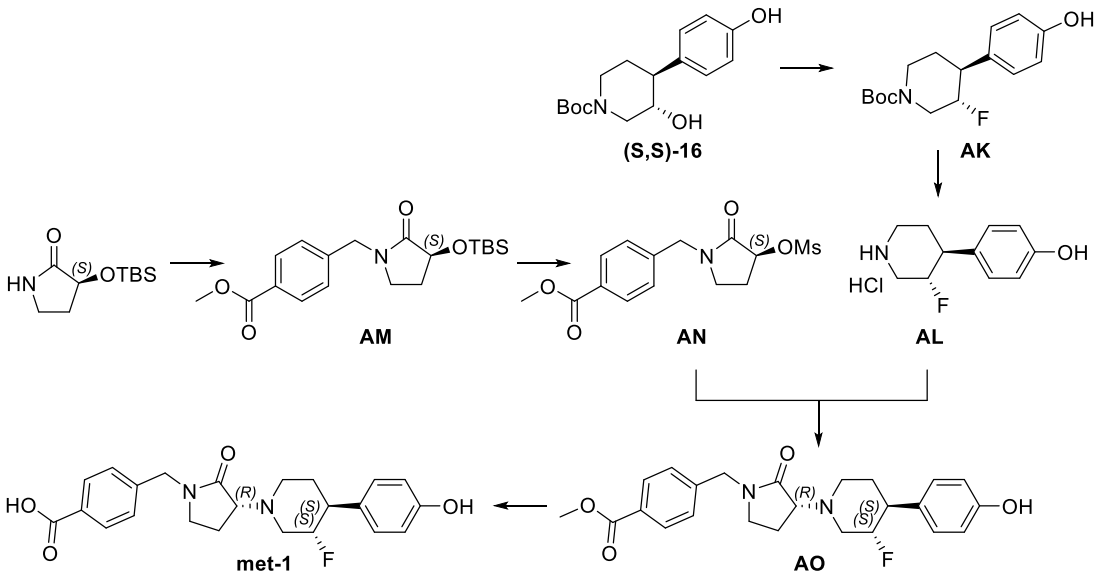
(±)-rel-3-((3*S*,4*S*)-3-Fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-fluorobenzyl)pyrrolidin-2-one (diasteromeric mixture). To a solution of (*trans*-3-fluoro-4-(4-methoxyphenyl)piperidin-1-yl)-1-(4-fluorobenzyl)pyrrolidin-2-one (700 mg, 1.75 mmol) in dichloromethane (50 mL) at 0 °C was added BBr_3 (0.3 mL, 3.5 mmol). The reaction mixture was allowed to warm up to room temperature over 1 h. The mixture was then diluted with saturated aqueous sodium bicarbonate and extracted with dichloromethane. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by preparative HPLC (Symmetry C_8 (300 x 19 mm) 7 μm column; Mobile phase A: 10 mM aqueous ammonium acetate, mobile phase B: methanol; Isocratic run with 25% B in A; run time = 20 minutes) to yield 120 mg of *(±)-rel*-3-((3*S*,4*S*)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-fluorobenzyl)pyrrolidin-2-one as a mixture of four diastereomers. LCMS (ES-API), m/z 387.0 $(M+H)^+$.

(R)-3-((3S,4S)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (compound **13**). A sample of *(±)-rel*-3-((3*S*,4*S*)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-fluorobenzyl)pyrrolidin-2-one (120 mg) was separated using chiral HPLC (CHIRALPAK AD-H (250 x 4.6 mm) 5μm, eluting with 20% IPA w/0.2% DEA in heptane) to yield homochiral diastereomer A (peak 1, 30 mg), diastereomer

B (peak 2, 15 mg), compound **13** (peak 3, 14 mg), and diastereomer D (peak 4, 28 mg). The stereochemical assignment for compound **13** was made through analogy to compound **5**. Data for compound **13**: LCMS ($C_{22}H_{24}F_2N_2O_2$, MW 386.2, ES-API), observed 387.0 m/z $(M+H)^+$; ^{1}H NMR (400 MHz, methanol-d_4) δ ppm 7.29 - 7.34 (m, 2 H) 7.07 - 7.13 (m, 4 H) 6.74 - 6.78 (m, 2 H) 4.40 - 4.55 (m, 2 H) 3.71 (t, *J*=9.04 Hz, 1 H) 3.38 - 3.45 (m, 1 H) 3.23 - 3.31 (m, 2 H) 2.76 (br. s., 1 H) 2.64 - 2.72 (m, 1 H) 2.57 (dd, *J*=10.54, 6.02 Hz, 1 H) 2.43 (td, *J*=10.04, 5.02 Hz, 1 H) 2.16 - 2.25 (m, 1 H) 2.05 - 2.14 (m, 1 H) 1.77 - 1.87 (m, 2 H). Corresponding ^{1}H NMR spectrum for compound **13** is shown below.



Preparation of 4-(((*R*)-3-((3*S*,4*S*)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-2-oxopyrrolidin-1-yl)methyl)benzoic acid (met-1).



(3S,4S)-tert-Butyl 3-fluoro-4-(4-hydroxyphenyl)piperidine-1-carboxylate (intermediate **AK**). To a solution of (3*S*,4*S*)-*tert*-butyl 3-hydroxy-4-(4-hydroxyphenyl)piperidine-1-carboxylate (intermediate (*S*,*S*)-**16A**, 400 mg, 1.36 mmol) in dichloromethane (5 mL) cooled to 0 °C was added dropwise DAST (0.54 mL, 4.1 mmol) over 10 min. The mixture was allowed to warm up to rt and was stirred for 2 h. The reaction was slowly quenched with 10% aqueous sodium bicarbonate solution (50 mL) and extracted with dichloromethane (4x50 mL). The combined organic layers were washed with brine (75 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to afford of (3*S*,4*S*)-*tert*-butyl 3-fluoro-4-(4-hydroxyphenyl)piperidine-1-carboxylate (390 mg) which was used without further purification. LCMS (ES-API), m/z 240.1 $(M+H)^+$.

4-((3S,4S)-3-Fluoropiperidin-4-yl)phenol, hydrochloride (intermediate **AL**). A mixture of (*3S,4S*)-*tert*-butyl 3-fluoro-4-(4-hydroxyphenyl)piperidine-1-carboxylate (intermediate **AK**, 390 mg, 1.3 mmol) and 4 M HCl in dioxane (3.3 mL, 13 mmol) in dioxane (4 mL) was stirred at rt for 2 hr. The reaction contents were concentrated to dryness, washed with 10 mL of 5% DCM/diethyl ether mixture and the solid was isolated by filtration to afford 4-((*3S,4S*)-3-fluoropiperidin-4-yl)phenol, hydrochloride (260 mg). LCMS (ES-API), m/z 196.1 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 9.57 (br. s., 4 H), 8.92 - 8.68 (m, 1 H), 7.14 (d, *J* = 8.5 Hz, 1 H), 7.06 (d, *J* = 8.5 Hz, 2 H), 6.82 - 6.73 (m, 2 H), 5.07 - 4.85 (m, 1 H), 3.77 - 3.36 (m, 9 H), 3.32 - 3.22 (m, 2 H), 3.13 - 2.85 (m, 5 H), 2.06 - 1.88 (m, H).

Methyl (S)-4-((3-((tert-butyldimethylsilyl)oxy)-2-oxopyrrolidin-1-yl)methyl)benzoate (intermediate **AM**). (*S*)-3-((*tert*-Butyldimethylsilyl)oxy)pyrrolidin-2-one (6.5 g, 30 mmol)[3] was dissolved in anhydrous THF (50 mL) and the reaction mixture was cooled to 0 °C under a nitrogen atmosphere. A 60% dispersion of sodium hydride in mineral oil (1.21 g, 30.2 mmol) was added in a single portion and the reaction mixture was allowed to stir for 5 min before the dropwise addition of a solution containing methyl 4-(bromomethyl)benzoate (6.91 g, 30.2 mmol) in anhydrous THF (50 mL). The reaction was allowed to warm to rt and was stirred for 12 h. The reaction was cautiously quenched with ice and water (100 mL) and then extracted with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, and filtered. Evaporation of the filtrate in vacuo provided the crude product (10 g, oil) which was then purified by silica gel chromatography eluting with 20 % ethyl acetate in hexanes to provide methyl (*S*)-4-((3-((tert-butyldimethylsilyl)oxy)-2-oxopyrrolidin-1-yl)methyl)benzoate (6.9 g, 59 % yield). LCMS (ES-API), m/z 364.1 $(M+H)^+$.

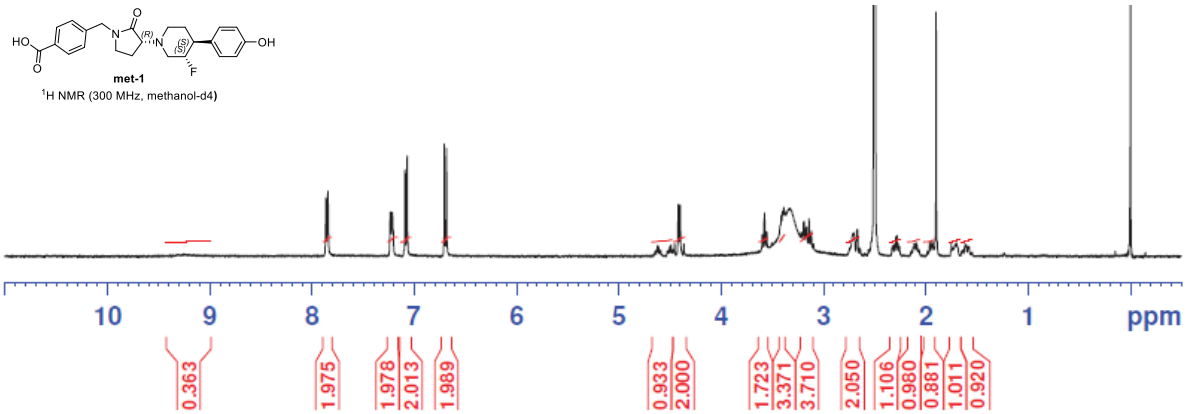
Methyl (S)-4-((3-hydroxy-2-oxopyrrolidin-1-yl)methyl)benzoate. A 4.0 M solution of HCl in dioxane (47.5 mL, 190 mmol) was added in one portion to a solution of methyl (*S*)-4-((3-((*tert*-butyldimethylsilyl)oxy)-2-oxopyrrolidin-1-yl)methyl)benzoate (intermediate **AM**, 6.90 g, 19.0 mmol) in anyhdrous dioxane at 0 °C. The reaction mixture was allowed to warm to rt and stir for 12 h. The reaction mixture was concentrated in vacuo. The residue was triturated with diethyl ether (2x5 mL) to afford methyl (*S*)-4-((3-hydroxy-2-oxopyrrolidin-1-yl)methyl)benzoate (4.5 g, 95 % yield): LCMS (ES-API), m/z 250.1 $(M+H)^+$; ^{1}H NMR (400MHz, DMSO-d_6) d = 7.94 (dd, J = 8.0 Hz, 2 H), 7.36 (dd, J = 8.0 Hz, 2 H), 4.45 (s, 2 H), 4.2 - 4.16 (m, 1 H), 3.84 (s, 3 H), 3.71- 3.70 (m, 1 H), 3.69- 3.41 (m, 2 H), 3.39- 3.10 (m, 2 H), 2.50- 2.27 (m, 1 H), 1.74- 1.69 (m, 1 H).

Methyl (S)-4-((3-((methylsulfonyl)oxy)-2-oxopyrrolidin-1-yl)methyl)benzoate (intermediate **AN**). Triethylamine (7.6 mL, 54 mmol) was added to a cooled solution of (*S*)-4-((3-hydroxy-2-oxopyrrolidin-1-yl)methyl)benzoate (4.5 g, 18 mmol) in anhydrous dichloromethane at 0 °C under a nitrogen atmosphere. Methanesulfonyl chloride (1.7 mL, 22 mmol) was then added dropwise and the reaction was allowed to stir at 0 °C for 1 h before quenching with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo to afford methyl (*S*)-4-((3-((methylsulfonyl)oxy)-2-oxopyrrolidin-1-yl)methyl)benzoate (5.5 g, 93 % yield). LCMS (ES-API), m/z 328.1 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (dd, J = 8.00, Hz, 2H), 7.39 (dd, J = 8.00, Hz, 2H), 5.36-5.32 (m, 1H), 4.51 (s, 2H), 3.80 (s, 1H), 3.73-3.70 (m, 2H), 3.32 (t, J = 8.00 Hz, 3H), 3.30-3.17 (m, 2H), 2.55-2.49 (m, 1H), 2.12-2.01 (m, 1H)

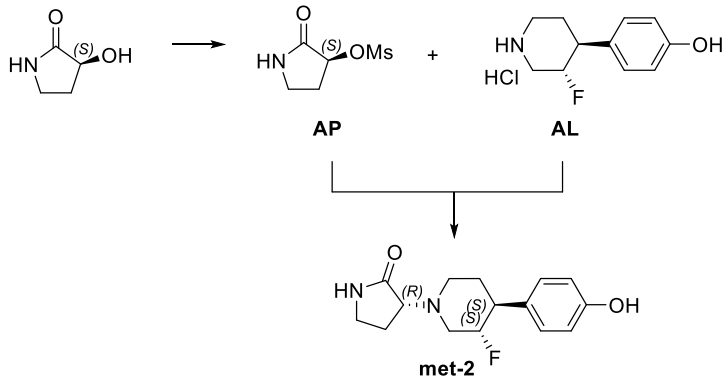
Methyl 4-(((R)-3-((3S,4S)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-2-oxopyrrolidin-1-yl)methyl)benzoate (intermediate **AO**). To a solution of 4-((*3S,4S*)-3-fluoropiperidin-4-yl)phenol, hydrochloride (intermediate **AL**, 0.984 g, 4.24 mmol) in acetonitrile (30 mL) at 0 °C was added DIEA (2.0 mL, 11 mmol). The resulting mixture was heated to 80 °C and a solution of (*S*)-4-((3-((methylsulfonyl)oxy)-2-oxopyrrolidin-1-yl)methyl)benzoate (intermediate **AN**, 1.5 g, 4.6 mmol) in acetonitrile (10 mL) was added.[2] The reaction mixture was maintained at 80 °C for 14 h. The reaction mixture was concentrated in vacuo and diluted with ice water. The aqueous mixture was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified using silica gel column chromatography to afford methyl 4-(((*R*)-3-((3*S*,4*S*)-3-fluoro-4-(4-hydroxyphenyl)piperidin-

1-yl)-2-oxopyrrolidin-1-yl)methyl)benzoate (1.0 g, 55 % yield). LCMS (ES-API), m/z 427.3 $(M+H)^+$.

4-(((R)-3-((3S,4S)-3-Fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-2-oxopyrrolidin-1-yl)methyl)benzoic acid (**met-1**). Sodium hydroxide (0.11 g, 2.8 mmol) was added to a stirred solution of methyl 4-(((*R*)-3-((3*S*,4*S*)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-2-oxopyrrolidin-1-yl)methyl)benzoate (0.80 g, 1.9 mmol) in MeOH (10 mL) and water (5 mL). at 0 °C. The reaction mixture was allowed to warm to rt and was stirred for 14 h. The reaction mixture was diluted with ice and acidified with 1.5 N HCl. The aqueous mixture was extracted with ethyl acetate. The combined organic layer was separated, dried over anhydrous sodium sulfate, filtered and concentrated in vacuo. The crude residue was purified using preparatory HPLC (Xselect Cyano (250 mm x 19 mm), 5 μm column eluting with Solvent A = 50 mM NH_4OAc in water; Solvent B = acetonitrile; flow 16 mL/min, gradient 0-100% B). Fractions containing the product were combined and lyophilized to afford 0.42 g of 4-(((*R*)-3-((3*S*,4*S*)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-2-oxopyrrolidin-1-yl)methyl)benzoic acid as a white solid. The product was determined to be contaminated with 2.8% of a minor diasteromer by analytical chiral SFC (Chiralpak AS H (250 mm x 4.6 mm) 5 μm column eluting with 30% methanol w/0.3% DEA and 70% CO_2). The product (420 mg) was then purified using preparatory chiral SFC (ChiralPak AS-H (250 x 21 mm) 5 μm column, eluting with 35% solvent B, where solvent A = CO_2 and solvent B = 0.25% DEA in methanol at a total flow of 60 g/min, 100 bar, 25 °C, λ = 225 nm) to afford 370 mg of product. The product was again repurified using preparatory HPLC (Xselect Cyano (250 x 19 mm) 5 μm column eluting with Solvent A = 50 mM NH_4OAc in water; Solvent B = acetonitrile; flow 16 mL/min, gradient 0-100% B) to afford 3-((3*S*,4*S*)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-2-oxopyrrolidin-1-yl)methyl)benzoic acid (233 mg, 30 % yield): LCMS ($C_{23}H_{25}FN_2O_2$, MW 412.2, ES-API), observed 413.2 m/z $(M+H)^+$; ^{1}H NMR (300 MHz, methanol-d_4) δ 7.93 (d, J = 6.00 Hz, 2H), 7.26 (d, *J* = 9.00 Hz, 2H), 7.09 (d, *J* = 6.00 Hz, 2H), 6.73 (d, *J* = 6.00 Hz, 2H), 4.94-4.48 (m, 3H), 3.71 (t, J = 18.00 Hz, 1H), 3.26-2.98 (m, 3H), 2.77-2.43 (m, 4H), 2.41-2.08 (m, 2H), 1.90-1.79 (m, 2H). Corresponding ^{1}H NMR spectrum for **met-1** is shown below.



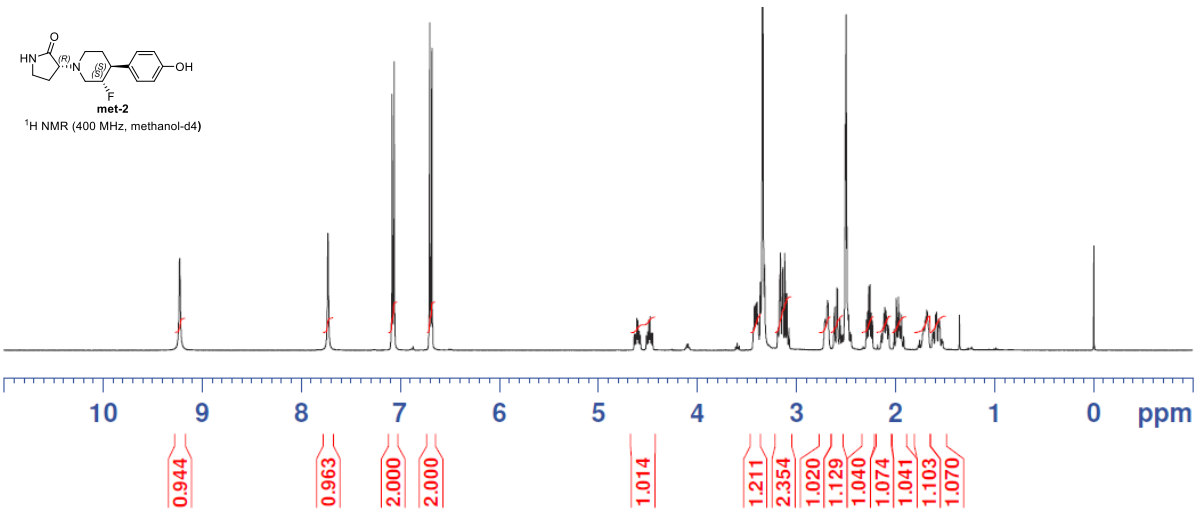
Preparation of (*R*)-3-((3*S*,4*S*)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)pyrrolidin-2-one (Met-2).



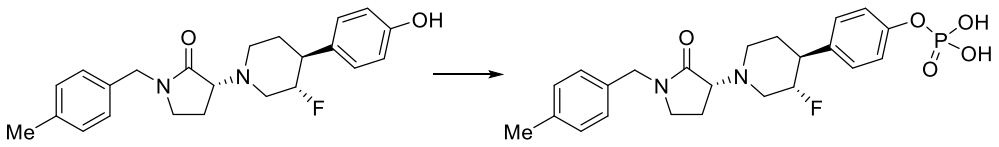
(S)-2-Oxopyrrolidin-3-yl methanesulfonate (intermediate **AP**). Triethylamine (8.3 mL, 59 mmol) was added to a solution of commercial (*S*)-3-hydroxypyrrolidin-2-one (2.0 g, 20 mmol) in anhydrous dichloromethane at 0 °C under a nitrogen atmosphere. Methanesulfonyl chloride (1.9 mL, 24 mmol) was then added dropwise and the reaction was allowed to stir at 0 °C for 1 h. The reaction was quenced with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, filtered and concentrated in vacuo to afford (*S*)-2-oxopyrrolidin-3-yl methanesulfonate (1.5 g, 42 % yield). LCMS (ES-API), m/z 180.2 $(M+H)^+$.

(R)-3-((3S,4S)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)pyrrolidin-2-one (compound 15). To a solution of 4-((*3S,4S*)-3-fluoropiperidin-4-yl)phenol, hydrochloride (intermediate **AL**, 1.2 g, 5.2 mmol) in acetonitrile (20 mL) at 0 °C was added DIEA (2.4 mL, 14 mmol). The resulting mixture was heated to 80 °C and a solution of (*S*)-4-((3-((methylsulfonyl)oxy)-2-oxopyrrolidin-1-yl)methyl)benzoate (intermediate **AP**, 1.0 g, 5.6 mmol) in acetonitrile (10 mL) was added.[2] The reaction mixture was maintained at 80 °C for

14 h. The reaction mixture was concentrated in vacuo and diluted with ice water. The aqueous mixture was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford (*R*)-3-((3*S*,4*S*)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)pyrrolidin-2-one (285 mg, 19 % yield). The diastereomeric purity of the product was determined to be 98.7:1.7 using analytical chiral SFC (Welk-0-1-(*R*,*R*) 5 um column). The mixture was further purified using preparatory chiral SFC (Welk-0-1-(*R*,*R*) 5 μm; BPR pressure: 100 bar, temperature 25 °C, flow rate: 3 mL/min, mobile phase: 30% MeOH w/0.25% DEA in CO_2, detector wavelength: 220 nm) to afford (*R*)-3-((3*S*,4*S*)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)pyrrolidin-2-one (249 mg, 16 % yield). LCMS ($C_{15}H_{19}FN_2O_2$, MW 278.1, ES-API), observed 279.2 m/z $(M+H)^+$; ^{1}H NMR (400 MHz, methanol-d_4) δ 7.08 (d, J = 8.00 Hz, 2H), 6.73 (d, J = 8.00 Hz, 2H), 4.83-4.52 (m, 2H), 3.60 (t, J = 20.00 Hz, 1H), 3.36 (d, J = 36.00 Hz, 1H), 3.31-3.30 (m, 2H), 2.77 (d, J = 8.00 Hz, 2H), 2.63-2.42 (m, 2H), 2.25-2.15 (m, 2H), 1.81-1.29 (m, 2H). Corresponding ^{1}H NMR spectrum for **met-2** is shown below.

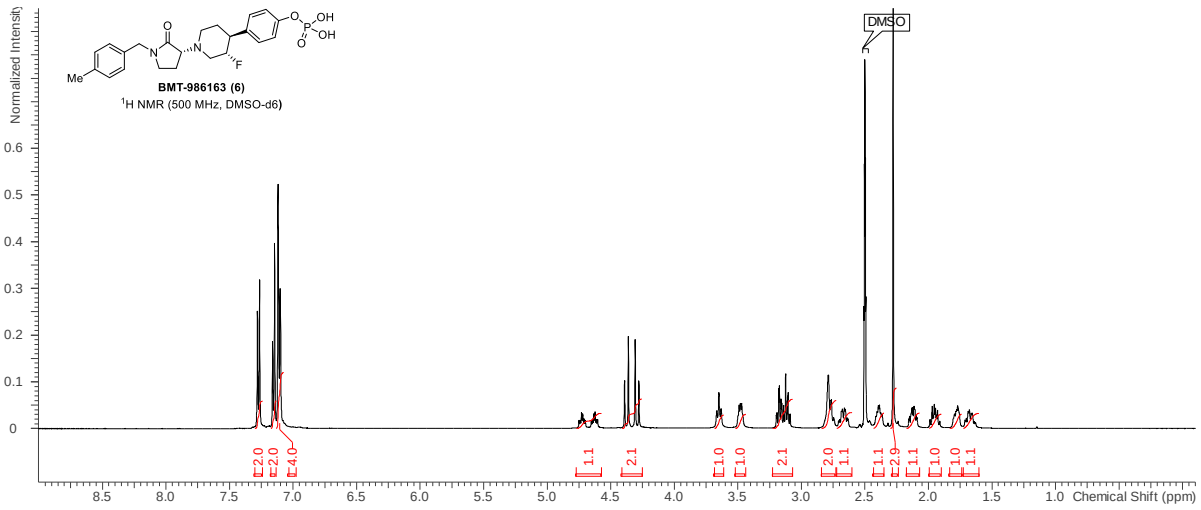


Preparation of 4-((3*S*,4*S*)-3-Fluoro-1-((*R*)-1-(4-methylbenzyl)-2-oxopyrrolidin-3-yl)piperidin-4-yl)phenyl dihydrogen phosphate (BMS-986163, compound 6).



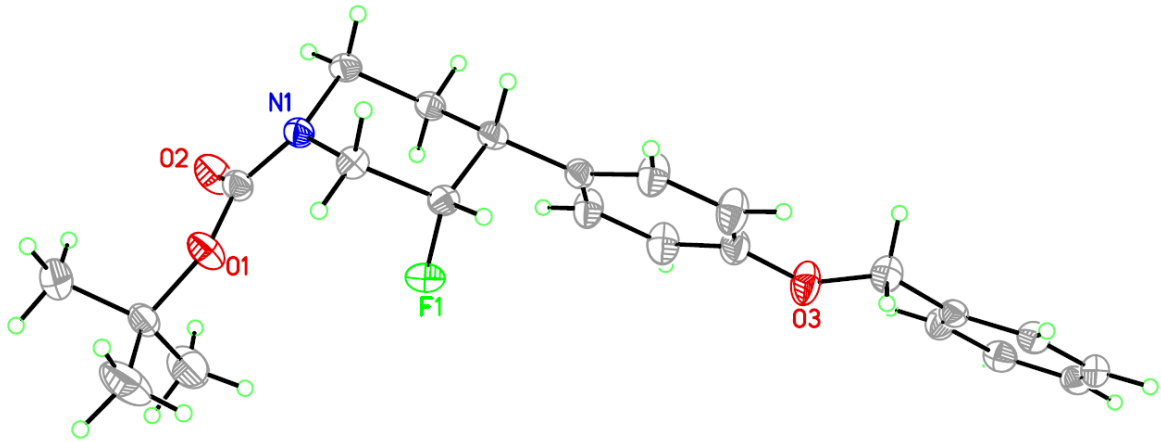
BMT-986169 (**5**) BMT-986163 (**6**)

To a suspension of (*R*)-3-((3*S*,4*S*)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (compound **5**, 100 mg, 0.261 mmol) in 10 mL of dichloromethane was added pyridine (0.106 mL, 1.31 mmol) and DMAP (160 mg, 1.31 mmol). The reaction mixtue was chilled to -20 °C. To the chilled solution was added $POCl_3$ (0.122 mL, 1.31 mmol) dropwise, and then the reaction mixture was allowed to warm to rt and was stirred for 1 h. Water (10 mL) was added and the mixture was stirred for an additional 1.5 h. The organic layer was separated, dried over Na_2SO_4, and evaporated to dryness. The crude product was purified by HPLC (Symmetry C8 (300 x17 mm) 7 um column eluting with a gradient of 20% B to 50% B over 7 minutes at 15 mL/min where solvent A = 10 mM ammonium acetate in water pH 4.5 and solvent B = acetonitrile). The desired product (5.8 mg, 4.7 % yield) was isolated from the appropriate fractions by lyophilization as a white solid. LCMS ($C_{23}H_{28}FN_2O_5P$, MW 462.2, ES-API), observed 463.2 m/z $(M+H)^+$; $[\alpha]_D^{20}$ = +4.4 (c = 4.27, DMSO); ^{19}F NMR (376 MHz, methanol-d4) δ -185.143; ^{31}P NMR (162 MHz, methanol-d_4) δ -4.260; ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.9, 150.4 (d, *J*=5.9 Hz, 1C), 136.7, 136.4, 133.5, 129.1 (s, 2C), 128.3 (s, 2C), 127.6 (s, 2C), 120.0 (d, *J*=4.2 Hz, 2C), 90.9 (d, *J*=173.3 Hz, 1C), 63.5, 52.3 (d, *J*=27.8 Hz, 1C), 49.0, 47.1 (d, *J*=17.7 Hz, 1C), 45.4, 43.0, 31.1 (d, *J*=8.4 Hz, 1C), 20.6, 20.4. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.27 (d, *J*=8.5 Hz, 2H), 7.19 - 7.13 (m, 2H), 7.13 - 7.08 (m, 4H), 4.77 - 4.58 (m, 1H), 4.43 - 4.25 (m, 2H), 3.65 (br t, *J*=8.7 Hz, 1H), 3.56 - 3.39 (m, 1H), 3.22 - 3.06 (m, 2H), 2.84 - 2.73 (m, 2H), 2.73 - 2.61 (m, 1H), 2.39 (td, *J*=9.7, 5.2 Hz, 1H), 2.28 (s, 3H), 2.17 - 2.07 (m, 1H), 2.02 - 1.89 (m, 1H), 1.83 - 1.74 (m, 1H), 1.74 - 1.60 (m, 1H). Corresponding ^{1}H NMR spectrum for compound **6** is shown below.


BMT-986163 (6)
1H NMR (500 MHz, DMSO-d6)
Normalized Intensity
DMSO
Chemical Shift (ppm)

Supplemental Figures:

Structure of intermediate S by X-ray crystallography:



Crystal Data:

Chemical formula: $C_{23}H_{28}FNO_3$
Fw = 385.46
Crystal system: Monoclinic
Space Group : $P2_1/c$
a = 22.097(4)Å $\alpha = 90°$
b = 8.371(2)Å $\beta = 104.274(8)°$
c = 11.718(2)Å $\gamma = 90°$
V = 2100.7(7)Å^3
Z = 4
d_x = 1.219 g cm^{-3} μ = 0.086 mm^{-1}
θ range for lattice parameters (°): 3.02 to 20.66

Experimental:

Crystallization
Crystal source: EtOAc-hexanes
Crystal description: plate
Crystal size (mm): 0.424 x 0.342 x 0.037

Data Collection
Temperature (K): 296
θ_{max} (°): 24.95 (Mo Kα)
No. of reflections measured: 13778
No. of independent reflections: 3627 (R_{int} = 0.0394)
No. of observed reflections ($I \geq 2\sigma$): 2226

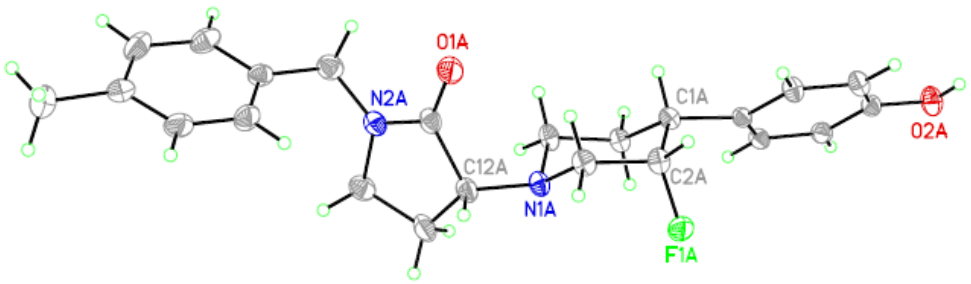
Refinement:

No. of parameters refined: 256; No. of reflections used: 3627; $-0.433 \leq \Delta\rho \leq 0.433$ e/Å^3
R1 = 0.0572; *wR2* = 0.1758; *S* = 1.079; $w = 1/[\sigma^2(Fo^2) + (0.1411P)^2 + 0.2446P]$; $P = (Fo^2 + 2Fc^2)/3$

Treatment of Hydrogen Atoms:
All hydrogen atoms were calculated using idealized geometry with standard bond lengths and angles during structure refinement. They were assigned isotropic temperature factors and were included in structure factor calculations with fixed parameters.

Figure S1. ORTEP illustration and supporting information of crystal structure for *cis-tert*-butyl 4-(4-(benzyloxy)phenyl)-3-fluoropiperidine-1-carboxylate (intermediate **S)** obtained by X-ray crystallography.[4]

Structure of compound 11 by X-ray crystallography:



Crystal Data:

Chemical formula: $C_{23}H_{27}FN_2O_2 \bullet CH_4O$
Fw = 414.51
Crystal system: Monoclinic
Space Group : $P2_1$
a = 12.636(2)Å $\alpha = 90°$
b = 9.489(2)Å $\beta = 95.128(7)°$
c = 19.122(4)Å $\gamma = 90°$
V = 2283.7(7)Å^3
Z = 4
d_x = 1.206 g cm^{-3} μ = 0.085 mm^{-1}
θ range for lattice parameters (°): 3.03 to 23.63

Experimental:

Crystallization
Crystal source: MeOH
Crystal description: prism
Crystal size (mm): 0.38 x 0.25 x 0.12

Data Collection
Temperature (K): 273
θ_{max} (°): 26.05 (Mo Kα)
No. of reflections measured: 17275
No. of independent reflections: 7948 (R_{int} = 0.0238)
No. of observed reflections ($I \geq 2\sigma$): 5521

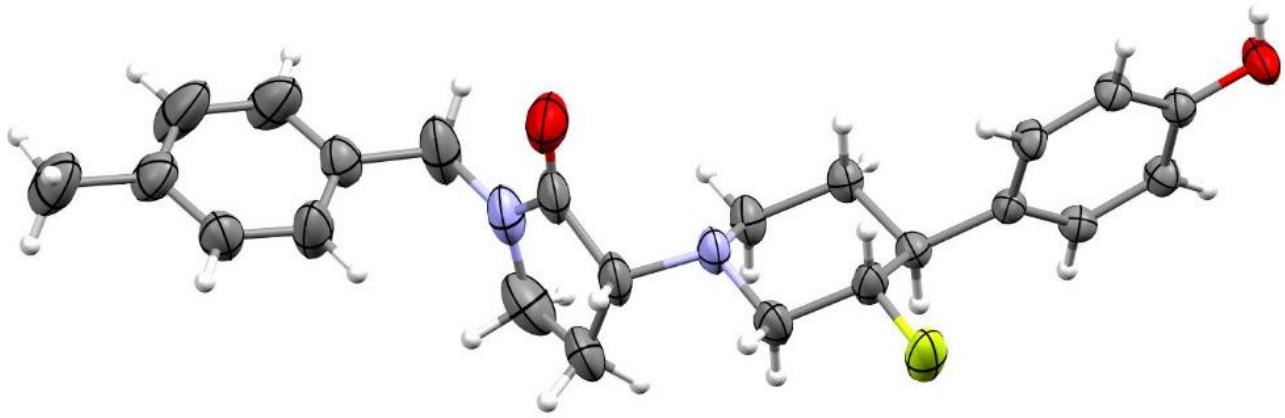
Refinement:

No. of parameters refined: 547 No. of reflections used: 7948 $-0.375 \leq \Delta\rho \leq 0.381$ e/Å^3
R1 = 0.0516 *wR2* = 0.1368 *S* = 1.057 $w = 1/[\sigma^2 (Fo^2) + (0.1134P)^2 + 0.0000P]$ $P = (Fo^2 + 2Fc^2)/3$
Flack = -0.2(4)

Treatment of Hydrogen Atoms:
All hydrogen atoms were calculated using idealized geometry with standard bond lengths and angles during structure refinement. They were assigned isotropic temperature factors and were included in structure factor calculations with fixed parameters.

Figure S2. ORTEP illustration and supporting information of crystal structure for (*R*)-3-((3*S*,4*R*)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one (compound **11)** obtained by X-ray crystallography.[5]

Structure of BMS-986169 (compound 5) by X-ray crystallography:



Crystal Data:	**Experimental:**
Chemical formula: $C_{23}H_{27}FN_2O_2$	*Crystallization*
MW = 382.48	Crystal source: MeOH
Crystal system: Monoclinic Space Group: $P2_1$	Crystal description: colorless plate
a = 10.2313(3) Å α = 90°	Crystal size (mm^3): 0.28 x 0.26 x 0.10
b = 9.7990(3) Å β = 95.716(1)°	
c = 20.3249(5) Å γ = 90°	*Data Collection*
V = 2027.6(1) $Å^3$	Temperature (K): 203
No. of molecules/cell: Z = 4	Instrument: Bruker APEX with MicroStarH
No. of unique molecules per asymmetric unit: Z' = 2	
Calculated crystal density: d_x = 1.253 g cm^{-3}	

Refinement:

Final R [I>2sigma(I)]: R1 = 0.0327, wR2 = 0.0821 Final R (all): R1 = 0.0343, wR2 = 0.0867

Goodness-of-fit on F^2: 1.049 Flack(x) = -0.05(4) P3true = 1.000 Hooft(y) = -0.05(4)

Inverted structure: R1 = 0.0346, wR2 = 0.0872, Flack x = 1.05(4), Hooft y = 1.05(4)

Treatment of Hydrogen Atoms:

All hydrogen atom positions were calculated using idealized geometry with standard bond lengths and angles during structure refinement. They were assigned isotropic temperature factors and were included in structure factor calculations with fixed parameters.

Figure S3. ORTEP illustration and supporting information of crystal structure for *(R)-3-((3S,4S)-3-fluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one* (BMS-986169, compound **5**) determined by X-ray crystallography.[6]

Biological Methods:

Radioligand binding assay. Binding experiments to determine binding to NR2B-subtype NMDA receptors were performed on forebrains of 8-10 weeks old male Sprague Dawley rats (Harlan, Netherlands) using ^{3}H Ro 25-6981 (Mutel V; Buchy D; Klingelschmidt A; Messer J; Bleuel Z; Kemp JA; Richards JG . *Journal of Neurochemistry* , 1998, 70(5):2147-2155. Rats were decapitated without anesthesia using a Guillotine (approved by animal ethics committee) and the harvested brains were snap-frozen and stored at -80 ^{o}C for 3-6 months for membrane preparation.

For membrane preparation, rat forebrains were thawed on ice for 20 minutes in homogenization buffer composed of 50mM KH_2PO_4 (pH adjusted to 7.4 with KOH), 1mM EDTA, 0.005% Triton X 100 and protease inhibitor cocktail (Sigma Aldrich). Thawed brains were homogenized using a Dounce homogenizer and centrifuged at 48000 X g for 20 min. The pellet was resuspended in cold buffer and homogenized again using a Dounce homogenizer. Subsequently, the homogenate was aliquoted, snap-frozen and stored at -80 ^{o}C for not more than 3-4 months.

To perform the competition binding assay, thawed membrane homogenate was added to each well of a 96-well plate (20 µg/well). The experimental compounds were serially diluted in 100% DMSO and added to each row of the assay plate to achieve desired compound concentrations, keeping the DMSO concentration in the assay plate at 1.33 % of the final reaction volume. Next, ^{3}H Ro 25-6981 (4 nM) was added to the assay plate. After incubation for 1 hr at room temperature, the membrane bound radioligand was harvested on to GF/B filter plates (treated with 0.5% PEI for 1 hr at room temperature). The filter plates were dried at 50 ^{o}C for 20 mins, incubated with microscint 20 for 10 minutes and finally, the counts were read on TopCount (Perkin Elmer). Non-specific binding was determined using MK-0657 (the preparation of this compound is described as example 1 in WO 2004 108705 (40 µM). CPM values were converted to % inhibition and the concentration response curves were plotted using custom made software. Each experiment was repeated at least twice to obtain the final binding K_i values for experimental compounds.

Functional Inhibition of NMDA receptor subtypes in vitro. Studies to demonstrate functional inhibition of GluN2B receptor mediated currents in Xenopus oocytes were conducted at BBRC. Prior to surgery, frogs were anesthetized using 3-amino-benzoic acid

ethyl ester (1g/l, pH 7.0 adjusted using sodium bicarbonate), the ovarian lobes removed using aseptic surgical techniques, and the animals then singly housed for a 24 h recovery period with post-operative monitoring for up to a week post-surgery. Following removal the ovarian lobes were incubated in cold Xenopus oocyte buffer A (Biopredic International; Saint Gregoire, France) for 1 h. The oocytes were then mechanically isolated in small clusters followed by collagenase treatment (1.5 to 2 mg/ml) for at least 1 h on a shaking platform at 18°C to remove the follicular layer. The defolliculated oocytes were treated with Xenopus oocyte buffer A, B and C (Biopredic International) for 15 min each in series at 18°C and then maintained in Barth's solution (pH 7.4) composed of 88 mM NaCl, 1 mM KCl, 2.4 mM $NaHCO_3$, 10 mM HEPES, 0.82 mM $MgSO_4$, 0.33 mM $Ca(NO_3)_2$, 0.91 mM $CaCl_2$ and supplemented with gentamycin (100 µg/ml), penicillin (10 µg/ml) and streptomycin (10 µg/ml). To determine functional inhibition of GluN2B receptors, oocytes were injected with 8-15 ng each of human GluN1a and GluN2B cRNA within 24 h of isolation. Two electrode voltage clamp recordings were made 2-7 days post injection. Oocytes were placed in a plexiglass chamber and impaled with glass microelectrodes filled with 3M KCl. The oocytes were clamped at -40 mV and perfused with buffer containing 90 mM NaCl, 1 mM KCl, 10 mM HEPES, 0.01 mM EDTA and 0.5 mM $BaCl_2$, pH 7.4. NMDA receptor currents were activated by the application of 50 µM glutamate and 30 µM glycine and recorded using an Axoclamp 900A amplifier and pClamp 10 data acquisition software. The concentration response was determined using 4-7 concentrations of the test compound and each concentration was applied for 15-20 min on a different oocyte. The baseline leak current at -40 mV was recorded at the beginning and the end of the recording and the full current trace was linearly corrected for any change in leak current. The level of inhibition was expressed as percent of the initial glutamate/glycine response in the absence of compound and the IC_{50} values were obtained by concentration response curve fitting using the following equation in GraphPad Prism (v5.01): Y=Bottom + (Top-Bottom)/(1+10^((LogIC_{50}-X)*HillSlope)) where X= log of concentration, Y= % inhibition and the top and bottom were constrained to 100 and 0, respectively. To determine functional inhibition at other NMDA receptor subtypes, isolated oocytes were injected with 0.2-0.5 ng of human GluN1a and 0.5-1 ng of human GluN2A or 45-60 ng of human GluN1a and 35-55 ng of human GluN2C or GluN2D. The voltage clamp recording procedure was as described above except that oocytes were clamped at -80 mV to record GluN2C or GluN2D receptor currents and compound was applied at 3 µM only for 10-

15 min. The level of inhibition at 3 μM was calculated as a percent of the initial glutamate/glycine mediated current.

hERG electrophysiology assay. The experimental compounds were assessed for hERG activity on HEK 293 cells stably expressing hERG channels using patch clamp technique. Coverslips plated with hERG expressing cells were placed in the experimental chamber and were perfused with a solution composed of (in mM): 140 NaCl, 4 KCl, 1.8 $CaCl_2$, 1 $MgCl_2$, 10 Glucose, 10 HEPES (pH 7.4, NaOH) at room temperature. Borosilicate patch pipettes had tip resistances of 2-4 Mohms when filled with an internal solution containing: 130 KCl, 1 $MgCl_2$, 1 $CaCl_2$, 10 EGTA, 10 HEPES, 5 ATP-K_2 (pH 7.2, KOH). The cells were clamped at -80 mV in whole cell configuration using an Axopatch 200B (Axon instruments, Union City, CA) patch clamp amplifier controlled by pClamp (Axon instruments) software. Upon formation of a gigaseal, the following voltage protocol was repeatedly (0.05 Hz) applied to record tail currents: depolarization step from -80 mV to +20 mV for 2 seconds followed by a hyperpolarization step to -65 mV (3 seconds) to elicit tail currents and then, back to the holding potential. Compounds were applied after stabilization of tail current. First, tail currents were recorded in presence of extracellular solution alone (control) and subsequently, in extracellular solution containing increasing compound concentrations. Each compound concentration was applied for 2-5 minutes. The percentage inhibition at each concentration was calculated as reduction in peak tail current with respect to the peak tail current recorded in the presence of control solution. Data analysis was performed in custom made software. The percent inhibitions at different concentrations were plotted to obtain a concentration response curve, which was subsequently fitted with a four parameter equation to calculate the hERG IC_{50} value.

Animal Studies and PK Experiments: All animal studies were performed under the approval of the Bristol-Myers Squibb Animal Care and Use Committee and in accordance with the American Association for Accreditation of Laboratory Animal Care (AAALAC). The pharmacokinetics parameters were obtained by noncompartmental analysis of plasma concentration versus time data (KINETICA software, version 2.4, InnaPhase Corporation, Philadelphia, PA). The peak concentration (Cmax) and time for Cmax (Tmax) were recorded directly from experimental observations. The area under the curve from time zero to the last sampling time (AUC0−T) and the area under the curve from time zero to infinity (AUCINF) were calculated using a combination of linear and log trapezoidal summations. The whole

body plasma clearance (CL), steady-state volume of distribution (Vss), apparent terminal t1/2, and mean residence time (MRT) were estimated following intravenous administration. The absolute oral bioavailability (F) was estimated as the ratio of dose-normalized AUC values following PO and IV doses.

Ex vivo occupancy assay. 7-9 Weeks old male CD-1 mice were dosed intravenously in a vehicle consisting of 10% dimethylacetamide, 40% PEG-400, 30% hydroxypropyl betacyclodextrin, and 30% water with experimental compounds and the forebrains were harvested 15 minutes post-dosing by decapitation. The brain samples were immediately snap-frozen and stored at -80 ^{o}C. On the following day, the dosed brain samples were thawed on ice for 15-20 minutes followed by homogenization using Polytron for 10 seconds in cold homogenization buffer composed of 50 mM KH_2PO_4 (pH adjusted to 7.4 with KOH), 1mM EDTA, 0.005% Triton X 100 and protease inhibitor cocktail (Sigma Aldrich). The crude homogenates were further homogenized using a Dounce homogenizer and the homogenized membrane aliquots from all animals were flash-frozen and stored at -80 ^{o}C until further use. The whole homogenization process was performed on ice.

For determining occupancy, the membrane homogenates were first thawed on ice and then needle-homogenized using a 25 gauge needle. The homogenized membrane (6.4 mg/mL) was added to a 96-well plate followed by addition of ^{3}H Ro 25-6981 (6 nM). The reaction mixture was incubated for 5 minutes on a shaker at 4 ^{o}C and then harvested onto GF/B filter plates (treated with 0.5% PEI for 1 hr at room temperature). The filter plates were dried at 50 ^{o}C for 20 mins, incubated with microscint 20 for 10 minutes and read on TopCount (Perkin Elmer). Each dose or compound group consisted of 4-5 animals. The control group of animals was dosed with vehicle alone. Membrane from each animal was added in triplicates to the assay plate. Non-specific binding was determined using 10 µM Ro 25-6981 added to the wells containing membrane homogenates from vehicle-dosed animals. Specific counts/minute was converted to % occupancy at each dose of a compound for each animal using the following equation:

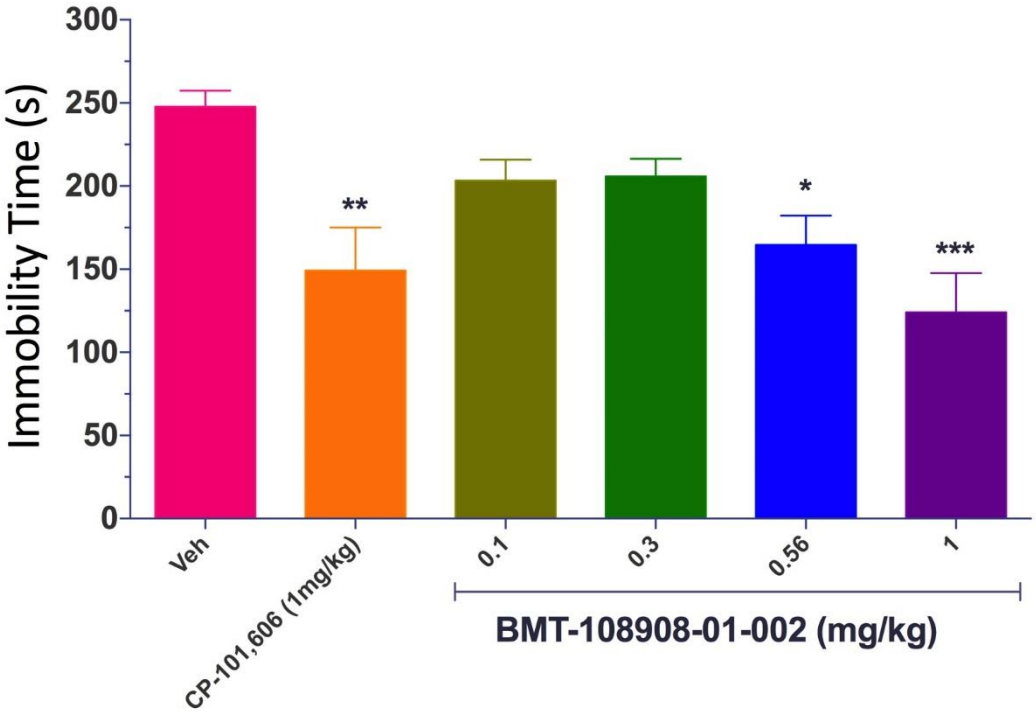
$$\%\ Occupancy\ (animal\ A) = 100 - \left(\frac{specific\ CPM\ of\ animal\ A}{Average\ CPM\ from\ control\ group} \times 100\right)$$

Mouse Forced swim test (mFST). Forced Swim Test (FST) is an animal model used to assess antidepressant compounds in preclinical studies. The FST was performed similar to the method of Porsolt et al. with modifications (Porsolt RD, Bertin A, Jalfre M. Behavioral

despair in mice: a primary screening test for antidepressants. Arch Int Pharmacodyn Thér 1977; 229:327–36). All studies were conducted between 09.00-13.30 h and were performed under dim light and low noise conditions. Behavior was recorded and quantified using the automated CleverSys forced swim test apparatus (CleverSys, Reston, VA) and investigators were unblinded to dosing solutions. Animals (n = 8-12/group) were randomly assigned to treatment with either vehicle (30% hydroxypropyl-β-cyclodextrin/70% citrate buffer, pH 4; 5 ml/kg, i.v.), CP-101,606 (1 mg/kg, i.v.) or the test compound (0.1, 0.3, 0.56 or 1 mg/kg, i.v.) and 15 min later placed in plexiglass swim tanks (20 cm diameter, 40 cm height) filled with water up to a height of 20 cm at a temperature of 25 ± 1°C. Swim tanks were positioned inside a box made of plastic and separated from each other by opaque plastic sheets to the height of cylinders. Individual animals were placed in one of the 3 swim tanks and behavior recorded in a 6 min testing session. The total immobility duration, defined as the time spent passively floating with only small movements necessary to keep the nose/head above water and remain afloat during the 6 min test, was measured using the automated CleverSys software. Results were analyzed by 1 way ANOVA followed by Dunnett's post-hoc test (GraphPad Prism v7.02). Upon completion of testing (~25 min after drug treatment) a subset of animals (n = 4-6/group) were euthanized by rapid decapitation and blood and brain samples collected for GluN2B occupancy and drug exposure measurements as previously described.

Supplemental Tables:

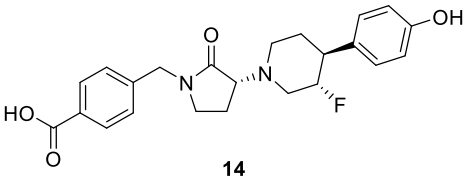
Supplemental Table S1. Plasma and brain BMT-108908 concentrations and GluN2B occupancy in mice tested in the forced swim test (FST).



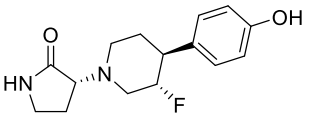
agent	time (min)	dose (mg/kg, i.v.)	total plasma conc. BMT-108908 mean ± S.D. (nM) *no. of animals = 6*	total brain conc. BMT-108908 mean ± S.D. (nM) *no. of animals = 6*	% GluN2B brain occupancy mean *no. of animals = 4-6*
BMS-108908	~ 25	0.1	23 ± 10	150 ± 60	29
		0.3	92 ± 30	250 ± 50	66
		0.56	150 ± 70	340 ± 90	75*
		1.0	350 ± 50	540 ± 90	95**

Male in-house bred CD1 mice; Age: 5-6 weeks old; n=8-12/group; Route: slow IV bolus; Vehicle: 30%HPBCD+70% Citrate Buffer pH4; Dose volume: 5 mL/kg; Pretreatment time: 15 min; *p<0.05, **p<0.01, ***p<0.001 vs. vehicle group, one-way ANOVA followed by Dunnett's post-hoc test. Traxoprodil (CP-101,606) was used as a positive control.

Supplemental Table S2. Evaluation of metabolites **14** and **15** in a broad panel of pharmacologically relevant targets.



14

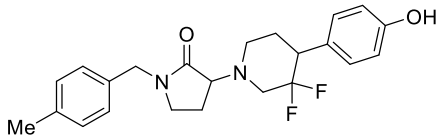


15

target	species	assay type	compound **14**	compound **15**
GluN2B Ki	rat	binding	IC_{50} >10 μM	IC_{50} >10 μM
GluN2B Ki	cyno	binding	IC_{50} >10 μM	IC_{50} >10 μM
GluN2B Ki	human	binding	IC_{50} >10 μM	IC_{50} >10 μM
GluN2B oocyte EP % inhibition at 3 uM	human	functional antagonist	3.2	-2.6
GluN2A/2C/2D oocyte EP % inhibition at 3 uM	human	functional antagonist	-5.9/-6.6/-5.5	-8.3/-2.9/-1.8
Adenosine A2a receptor	human	binding	IC_{50} >30 μM	IC_{50} >30 μM
Adrenergic α1B receptor	human	binding	IC_{50} >30 μM	IC_{50} >30 μM
Adrenergic α1D receptor	human	binding	IC_{50} >30 μM	IC_{50} >30 μM
Adrenergic α2A receptor	human	binding	IC_{50} >30 μM	IC_{50} >30 μM
Adrenergic α2C receptor	human	binding	IC_{50} >30 μM	IC_{50} >30 μM
Adrenergic β1 receptor	human	binding	IC_{50} >30 μM	IC_{50} >30 μM
Adrenergic β2 receptor	human	binding	IC_{50} >30 μM	IC_{50} >30 μM
Cannabinoid CB1 receptor	human	binding	IC_{50} >30 μM	IC_{50} >30 μM
Dopamine D1 receptor	human	binding	IC_{50} >30 μM	IC_{50} >30 μM
Dopamine D2 receptor	human	binding	IC_{50} >30 μM	IC_{50} >30 μM
Histamine H1 receptor	human	binding	IC_{50} >30 μM	IC_{50} >30 μM
Histamine H2 receptor	human	binding	IC_{50} >30 μM	IC_{50} >30 μM
Muscarinic M2 receptor	human	binding	IC_{50} >30 μM	IC_{50} >30 μM
Opioid kappa receptor	human	binding	IC_{50} >30 μM	IC_{50} >30 μM
Opioid mu receptor	human	binding	IC_{50} >30 μM	IC_{50} >30 μM
Serotonin 5HT1B receptor	human	binding	IC_{50} >30 μM	IC_{50} >30 μM
Serotonin 5HT4 receptor	human	binding	IC_{50} >30 μM	IC_{50} >30 μM
Dopamine transporter	human	binding	IC_{50} >30 μM	IC_{50} >30 μM
Norepinephrine transporter	human	binding	IC_{50} >30 μM	IC_{50} >30 μM
Serotonin transporter	human	binding	IC_{50} >30 μM	IC_{50} >30 μM
Androgen receptor	Rat	binding	IC_{50} >1.1μM	IC_{50} >150 μM
Glucocorticoid receptor	human	binding	IC_{50} >150 μM	IC_{50} >150 μM
Progesterone receptor	human	binding	IC_{50} >150 μM	IC_{50} >150 μM
Calcium Channel L type (Cav1.2)	human	functional; antagonist	EC_{50} >25 μM	EC_{50} >25 μM
Calcium Channel T type	human	functional;	EC_{50} >25 μM	EC_{50} >25 μM

(Cav3.2)		activator		
Cardiac Sodium Channel (NAV1.5)	human	functional; antagonist	IC_{50} >30 μM	IC_{50} >30 μM
GABA-A (α1β2γ2) receptor	Rat	functional; antagonist	IC_{50} >30 μM	IC_{50} >30 μM
GABA-A (α1β2γ2) receptor	Rat	functional; potentiator	EC_{50} >30 μM	EC_{50} >30 μM
GABA-A (α5β2γ2) receptor	Rat	functional; antagonist	IC_{50} >30 μM	IC_{50} >30 μM
Nicotinic Acetylcholine α1 receptor	Rat	functional; antagonist	IC_{50} >30 μM	IC_{50} >30 μM
Nicotinic Acetylcholine α4β2 receptor	Rat	functional; agonist	EC_{50} >30 μM	EC_{50} >30 μM
Nicotinic Acetylcholine α7 receptor	Rat	functional; antagonist	IC_{50} >30 μM	IC_{50} >30 μM
NMDA GluN1a/GluN2A receptor	human	functional; agonist	EC_{50} >30 μM	EC_{50} >30 μM
NMDA GluN1a/GluN2A receptor	human	functional; antagonist	IC_{50} >30 μM	IC_{50} >30 μM
NMDA GluN1a/GluN2B receptor	human	functional; agonist	EC_{50} >30 μM	EC_{50} >30 μM
Acetylcholinesterase	human	Enzyme inhibition	IC_{50} >30 μM	IC_{50} >30 μM
Monoamine oxidase A	human	Enzyme inhibition	IC_{50} >30 μM	IC_{50} >30 μM
Monoamine oxidase B	human	Enzyme inhibition	IC_{50} >30 μM	IC_{50} >30 μM
Phosphodiesterase 3	human	Enzyme inhibition	IC_{50} >50 μM	IC_{50} >50 μM
Phosphodiesterase 4	human	Enzyme inhibition	IC_{50} >50 μM	IC_{50} >50 μM

Supplemental Table S3. Rat GluN2B binding data for separated diasteromers of 3-(3,3-difluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one.

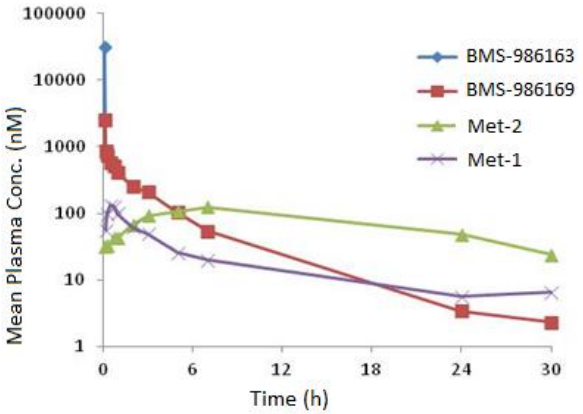


diastereomer A **diastereomer B** **diastereomer C** **diastereomer D**
12

3-(3,3-Difluoro-4-(4-hydroxyphenyl)piperidin-1-yl)-1-(4-methylbenzyl)pyrrolidin-2-one	rat GluN2B Ki (nM)[a]
diastereomer A	660
diastereomer B, compound **12**	7.6
diastereomer C	30
diastereomer D	11

[a] Displacement of [^{3}H]Ro 25-6981 binding to GluN2B receptors in rat forebrain.

Supplemental Table S4. Cynomolgus monkey PK profile of parent BMS-986169 (5) after administration of BMS-986163 (6, 1.2 mg/kg, i.v.)



	AUC total (nM*h)	CL (mL/ min/kg)	$T_{1/2}$ (min)	Vss (L/kg)
parent **5** [a]	3100 ± 1000	15	2.6	2.1
parent **5** from prodrug **6** [b]	1900 ± 520	-	-	-
metabolite **met-1** from prodrug **6** [b]	690 ± 200	-	-	-
metabolite **met-2** from prodrug **6** [b]	2500 ± 1100	-	-	-

[a] 1 mg/kg, 5 min i.v. infusion of **5**, vehicle = 10% DMAC, 10% EtOH, 30% HPBCD, 50% water (results not shown on graph); [b] 1.2 mg/kg, i.v. infusion of **6**, vehicle = saline adjusted to pH 7.4 with phosphate buffer, n = 3 crossover design.

References:

(1) Rios-Lombardia, N.; Gotor-Fernandez, V.; Gotor, V. Complementary Lipase-Mediated Desymmetrization Processes of 3-Aryl-1,5-Disubstituted Fragments. Enantiopure Synthetic Valuable Carboxylic Acid Derivatives. *J. Org. Chem.* **2011**, *76*, 811-819.

(2) For the synthesis of (S)-1-(4-methylbenzyl)-2-oxopyrrolidin-3-yl methanesulfonate and the first precedent for the chiral lactam mesylate displacement by a piperidine nucleophile see: Kempson, J.; Zhang, H.; Wong, M. K. Y.; Li, J.; Li, P.; Wu, D.-R.; Rampulla, R.; Galella, M. A.; Dabros, M.; Traeger, S.; Vetrichelvan, M.; Gupta, A.; Nayagam, A. P.; Islam, I.; Thangathirupathy, S.; Warrier, J.; Macor, J. E.; Thompson, L. A.; Marcin, L. R.; Mathur, A. The Evolution of a Practical Synthesis to a Potent NR2B Inhibitor and its Prodrug. *submission pending*.

(3) Zheng, X.; Feng, C.-G.; Ye, J.-L.; Huang, P.-Q. Samarium Diiodide Promoted Generation and Asymmetric Hydroxyalkylation of N,O-Diprotected (3S)-3-Pyrrolidinol 2-Carbanions. *Org. Lett.* **2005**, *7*, 553-556.

(4) Full crystallographic data have been deposited to the Cambridge Crystallographic Data Center (CCDC reference number 1827708). Copies of the data can be obtained free of charge via the internet at www.ccdc.cam.ac.uk/.

(5) Full crystallographic data have been deposited to the Cambridge Crystallographic Data Center (CCDC reference number 1827709). Copies of the data can be obtained free of charge via the internet at www.ccdc.cam.ac.uk/.

(6) Full crystallographic data have been deposited to the Cambridge Crystallographic Data Center (CCDC reference number 1831022). Copies of the data can be obtained free of charge via the internet at www.ccdc.cam.ac.uk/.