Experimental Section

Supporting Information for:

Synthesis of a Drug-Like Focused Library of Trisubstituted Pyrrolidines Using Integrated Flow Chemistry and Batch Methods

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General information:

^{1}H NMR spectra were recorded on a Bruker DRX-600, Avance 600 cryo-TCI, Avance 400 BBFO, Avance 400 QNP Cryo, or Avance 500 Cryo spectrometer with the residual solvent peak as the internal reference (i.e. $CDCl_3$ = 7.26 ppm, d_3-MeCN = 1.94 ppm). ^{1}H resonances are reported to the nearest 0.01 ppm. ^{13}C NMR spectra were recorded using the same machines with the central resonance of the solvent peak used as the internal reference ($CDCl_3$ = 77.16 ppm, d_3-MeCN = 118.26 ppm). All ^{13}C resonances are recorded to the nearest 0.1 ppm. Other techniques such as DEPT 135, HMQC, HMBC and nOe experiments were employed in the assignment of the signals. The multiplicities of signals are given as s = singlet, d = doublet, t = triplet, q = quartet, br. = broad and combinations thereof. Coupling constants (*J*) are reported to the nearest 0.1 Hz. Where appropriate average values of the signals from peaks displaying multiplicity were used to calculate the value of the coupling constant. ^{19}F NMR spectra were recorded on an Avance QNP Cryo or Avance BBFO spectrometer using $CFCl_3$ (δ = 0.00 Hz) as external standard.

IR spectra were recorded neat using a Thermo Scientific Continuum Infrared Microscope, equipped with an ATR crystal (diamond) and MCT detector in the spectral range between 4000 cm^{-1} and 600 cm^{-1}, at resolution 2 cm^{-1} and 100 coadded scans, or a PerkinElmer Spectrum One FT-IR spectrometer using Universal ATR sampling accessories. Letters in parentheses refer to the relative strength of the absorbency of the peak: w = weak (<40% of most intense peak), m = medium (41-69%) and s = strong (>69%).

HPLC-MS analysis: Method A: performed on an Agilent HP 1100 series system (Mercury Luna 3u C18 column) attached to a Waters ZQ2000 mass spectrometer with ESCi ionisation source in ESI mode. Elution was carried out at a flow rate of 0.6 mL/min using a reverse phase gradient of MeCN and water containing 0.1% formic acid. The gradient run starts with 1 min at 5% MeCN, increasing to 95% MeCN within the next 3 min and keeping this percentage for 1 min before going back to 5 % MeCN in 2 min (total time 8 min).

Method B: performed on an Agilent HP 1100 series analytical HPLC using a Gemini-NX C18, 110A, 50x4.6 mm column equipped with a Gilson Liquid Handler 215 autosampler, a Sedex ELSD 75 lightscatter and a Dionex UVD 340S UV detector. Elution was carried out at a flow rate of 1.5 mL/min using a reverse phase gradient of MeCN and water containing 0.1% formic acid. The gradient run starts at 10% MeCN, increasing to 95% MeCN within the next 1.75 min and keeping this percentage for 1.75 min before going back to 10 % MeCN (total time 3.52 min).

Method C: performed on an Agilent HP 1100 series analytical HPLC using a Gemini-NX C18, 110A, 50x4.6 mm column equipped with a Gilson Liquid Handler 215 autosampler, a Sedex ELSD 75 lightscatter and a Dionex UVD 340S UV detector. Elution was carried out at a flow rate of 1.5 mL/min using a reverse phase gradient of MeOH and water containing 0.1% formic acid. The gradient run starts at 10% MeOH, increasing to 95% MeOH within the next 1.75 min and keeping this percentage for 1.75 min before going back to 10 % MeOH (total time 3.52 min).

High resolution mass spectrometry (HRMS) was performed on a Waters Micromass LCT Premier and Agilent 6520 spectrometers using time of flight (TOF) with positive ESI or EI at 70 eV within a tolerance of ± 5 ppm of the theoretical value.

Experimental Section

Structure elucidation by ^{1}H NMR spectroscopy

The (*E*)-configuration in the nitro-styrenes **6f-i** was confirmed by the vicinal proton couplings in the ^{1}H-NMR spectra. The doublebond protons in β-nitrostyrene typically show 13.6 Hz for the (*E*)- and 9.6 Hz for the (*Z*)-configuration.[S1] The ^{1}H-NMR spectra of the nitro-styrenes **6f-i** reveal coupling constants between 13.6 and 13.9 Hz. The relative stereochemistry of the pyrrolidine heterocycles was determined by NOE measurements and vicinal proton couplings from ^{1}H-NMR. A strong NOE crosspeak in the 2D NOESY NMR, e.g. in **11h**{5} between protons 2 and 4 of the 4-(pyridine-3-yl) group and proton 3 (R_2 residue) of the pyrrolidine ring clearly indicates the (*E*)-configuration. Based on NOE measurements of several compounds a "quint" signal with about 7 Hz coupling for proton 3 could be identified as indicative signal for the *cis*-configuration for all pyrrolidines of the series **11f-i**. For the octahydro-isoindol compounds of the series **j** a strong NOE between the NH at position 3a and proton 7a, e.g. for compound **13j**{5,12}, was found clearly confirming the *cis*-configuration. In addition, proton 7a did not show a large bis-axial coupling. The symmetrical "quint"-like signal with about 6 Hz is typically caused by an equatorial orientation and confirms the *cis*-configuration in addition to the NOE data.

In vitro Assays.

Lysa. Samples were prepared in duplicate from 10 mM DMSO stock solutions. After evaporation (1 h) of DMSO with a centrifugal vacuum evaporator (Genevac Technologies), the compounds were dissolved in 50 mM phosphate buffer (pH 6.5), stirred for 1 h, and shaken 2 h. After one night, the solutions were filtered by using a microtiter filter plate (Millipore MSDV N65), and the filtrate and its 1/10 dilution were analyzed by direct UV measurement or by HPLC-UV. In addition, a four-point calibration curve was prepared from the 10 mM stock solutions and used for the solubility determination of the compounds. The results are expressed in

µg/mL. Starting from a 10 mM stock solution, the measurement range for MW 500 was 0-666 µg/mL. In the case where the percentage of sample measured in solution after evaporation divided by the calculated maximum of sample amount was larger than 80%, the solubility was reported as larger than this value.

logD. Distribution coefficients are determined using the CAMDIS© (CArrier Mediated DIstribution System)[SI-1] method, which is derived from the conventional 'shake flask' method. CAMDIS© is carried out in 96-well microtiterplates in combination with DIFI©-tubes (Weidmann Plastics Technology AG, Rapperswil, Switzerland), which provide a hydrophobic layer for the 1-octanol phase. The hydrophobic layer (0.45 µm PVDF membranes) fixed on the bottom of each DIFI©-tube is coated (Microfluidic Dispenser BioRAPTR, Bechman Coulter) with 1.0 µl of 1-octanol. Next, the filter membranes are dipped into a 96-well plate which has been prefilled with 150 µl of aqueous buffer solution (25 mM Phosphate, pH 7.4) containing the compound of interest at a starting concentration of 100 µM. The plate is sealed and shaken for 24 h at room temperature (23 °C) to ensure that the partition equilibrium is reached. At the next day, the DIFI©-tubes are removed from the 96-well plate and an aliquot of the aqueous solution is analyzed by LC/MS. The distribution coefficient is calculated from the concentration of the compound in the aqueous phase and the control experiment without 1-octanol. Sample preparation is carried out using a TECAN robotic system (RSP 100, 8 channels).

PAMPA. For PAMPA (Parallel Artificial Membrane Permeation Assay) measurements, a "sandwich is formed from a 96-well filter plate and a 96-well in-house made Teflon plate, such that each well is divided into two chambers: donor phase at the bottom and acceptor compartment at the top, separated by a microfilter with a pore size of 0.45 µm (Millipore, PVDF), coated with a 10% (w/v) egg-phosphatidylcholine and 0.5% (w/v) cholesterol solution in dodecane. Compounds were introduced as 10 mM DMSO stock solutions in a 96-well microtitre plate. An automated liquid handling system draws an aliquot of the DMSO stock solution and mixes it into a buffer solution (0.05 M MOPSO with 0.5% (w/v) glycocholic acid at pH 6.5), so that the final sample concentration is 150 µM and the DMSO concentration is 1.5% (v/v). A part of the sample solutions was filtered, using a 96-well PVDF filter plate (Corning, PVDF), and added to the donor compartments. In the acceptor compartment the same buffer system at the same pH is used than in the donor phase, but devoid of glycocholic acid. After 18 h, the sandwich plates were separated and both the donor and acceptor compartments were measured for the amount of material present, by comparison with the UV spectra (250 to 500 nm) obtained from reference standards. Mass balance was used to determine the amount of material remaining in the membrane barrier. All measurements were done in triplicate and the reproducibility was ±4%. Effective permeability values (Pe) were calculated as described by Avdeef *et al.* using the PAMPA Evolution Software V. 2.2 from pION INC.[S2-3]

Mouse and Human Microsomal Clearances. Mouse or human microsome incubations were conducted by an automated procedure implemented on a Genesis workstation (Tecan, Switzerland). Compounds (2 µM) were incubated in microsomes at 0.5 mg protein per mL in a 50 mM potassium phosphate buffer, pH 7.4, at 37 °C. Cofactor (reduced nicotinamide adenine dinucleotide phosphate, NADPH) was produced by a generating system (glucose-6-phosphate 3.2 mM, nicotinamide adenine dinucleotide phosphate 2.6 mM, $MgCl_2$ 6.5 mM). Addition of the NADPH generating system to the pre-warmed microsomes containing the test compound started the reaction. Aliquots (50 µL) were taken at six defined time points within 30 min and transferred into 100 µL of methanol containing an internal standard. Concentration of each compound was analyzed by LC-MS/MS by using a Synergy-4-Polar RP 18 column (Phenomenex, Torrance, CA). Quantitative detection was achieved on a

SCIEX 2000 instrument (MDS Sciex, Concord, ON, Canada) by using electron spray ionization. Concentrations were determined by the ratio of test compound and internal-standard peaks and given as a percentage of the concentration measured at the first time point (substrate depletion). Stability is expressed as intrinsic clearance (CLint, in μL/min/mg microsomal protein), which is the rate constant first the first-order decay of the test compound, normalized for the protein concentration in the incubation.

References

SI-1 Miller, D. B.; Flanagan, P. W.; Shechter, H. *J. Org. Chem.* **1976**, *41*, 2112-2120.

SI-2 Patent application EP2005102211A.

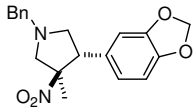
SI-3 Avdeef, A.; Strafford, M.; Block, E.; Balogh, M. P.; Chambliss, W.; Khan, I. *Eur. J. Pharm. Sci.* **2001**, *14*, 271-280.

Experimental procedures and spectroscopic data:

General flow procedure for the preparation of 3-nitropyrrolidines:

A mixture of the desired nitro alkene and TFA was prepared in dry DCM at concentrations between 0.2-0.5 M and combined within the T-piece of the R2+/R4 unit with a second stream containing the *N*-(methoxymethyl)-*N*-(trimethylsilyl)benzylamine reagent (DCM) at the same concentration. The united stream is then directed into a CFC reactor at elevated temperature before flowing through a glass column filled with QP-BZA resin (4 equivalents) to remove excess nitro alkene and TFA. In order to remove coloured impurities the out-coming stream is subsequently directed through a second column containing silica gel (2 g).

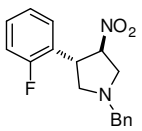
***trans*-4-Benzo[1,3]dioxol-5-yl-1-benzyl-3-methyl-3-nitropyrrolidine, 8a:**



Prepared from *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (**5**, 1.0 mmol, DCM) and *trans*-5-(2-nitroprop-1-en-1-yl)benzo[*d*][1,3]dioxole (290 mg, 1.4 mmol) with a residence time of 50 min at 70 °C according to the above general procedure. The desired product was obtained as amorphous solid after removal of the solvent by evaporation (purity 98%).

Yield: 87%, Rt = 3.83 min (method A), m/z = 341.1 [M+H$^+$]. ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm 7.32-7.38 (4H, m), 7.27-7.29 (1H, m), 6.88 (1H, s), 6.74-6.80 (2H, m), 5.96 (2H, s), 4.16 (1H, t, *J* = 7.2 Hz), 3.74 (1H, d, *J* = 13.2 Hz), 3.67-3.73 (2H, m), 3.21 (1H, dd, *J* = 8.4 Hz), 2.83 (1H, dd, *J* = 7.2, 9.0 Hz), 2.67 (1H, d, *J* = 10.8 Hz), 1.27 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm 147.8 (C), 146.9 (C), 138.1 (C), 131.6 (C), 128.5 (2CH), 128.4 (2CH), 127.3 (CH), 122.4 (CH), 109.2 (CH), 108.1 (CH), 101.1 (CH_2), 96.3 (C), 64.5 (CH_2), 59.5 (CH_2), 59.1 (CH_2), 51.6 (CH), 23.4 (CH_3). IR (neat) ν = 2907.7 (w), 2804.0 (w), 1538.3 (s), 1504.3 (s), 1490.3 (s), 1444.6 (m), 1378.7 (w), 1344.3 (w), 1250.6 (m), 1237.0 (m), 1105.3 (w), 1038.5 (s), 933.9 (m), 858.9 (m), 811.1 (w), 739.3 (m), 700.1 (m) cm^{-1}. HRMS calculated for $C_{19}H_{21}N_2O_4$ 341.1501, found: 341.1510.

***trans*-1-Benzyl-3-(2-fluorophenyl)-4-nitropyrrolidine, 8b:**

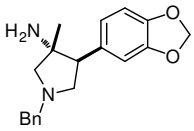


Prepared from *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (**5**, 1.0 mmol, DCM), TFA (114 mg, 1.0 mmol) and *trans*-1-fluoro-2-(2-nitrovinyl)benzene (201 mg, 1.2 mmol) with a residence time of 60 min at 70 °C according to according to the above general procedure. The desired product was obtained as yellow oil after removal of the solvent by evaporation (purity 93%).

Yield: 90%, Rt = 4.23 min (method A), m/z = 300.9 [M+H$^+$]. ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm 7.25-7.45 (7H, m), 7.17 (1H, t, *J* = 7.8 Hz), 7.10 (1H, dd, *J* = 8.4, 10.8 Hz), 5.07 (1H, ddd, *J* = 3.0, 4.8, 7.8 Hz), 4.30 (1H, ddd, *J* = 5.4, 7.8, 10.2 Hz), 3.78 (1H, d, *J* = 13.2 Hz), 3.74 (1H, d, *J* = 13.2 Hz), 3.52 (1H, dd, *J* = 3.0, 5.4 Hz), 3.32 (1H, t, *J* = 9.0 Hz), 3.13 (1H, dd, *J* = 7.8, 11.4 Hz), 2.70 (1H, t, *J* = 9.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm 160.8 (C, d, *J* = 245 Hz), 138.0 (C), 129.6 (CH, d, *J* = 5 Hz), 129.3 (CH, d, *J* = 9 Hz), 128.6 (2CH), 128.5 (2CH), 127.4 (CH), 127.0 (C, d, *J* = 7 Hz), 124.6 (CH, d, *J* = 5 Hz), 116.0 (CH, d, *J* = 23 Hz), 89.9 (CH), 59.4 (CH_2), 59.2 (CH_2), 58.2 (CH_2), 44.1 (CH). IR (neat) ν = 2807 (w), 1547.5 (s), 1493.2 (s), 1454.3 (m),

1372.4 (m), 1232.1 (m), 855.33 (m), 755.3 (s), 698.4 (s) cm^{-1}. HRMS calculated for $C_{17}H_{18}N_2O_2F$ 301.1352, found: 301.1362.

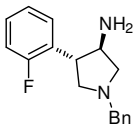
***trans*-4-Benzo[1,3]dioxol-5-yl-1-benzyl-3-methylpyrrolidin-3-ylamine, 9a:**



Prepared from 4-(benzo[*d*][1,3]dioxol-5-yl)-1-benzyl-3-methyl-3-nitro-pyrrolidine (**8a**, 2.0 mmol, in EtOAc/ EtOH, 0.1 M) by passage through the H-Cube™ flow hydrogenator using a small sized Raney-Nickel cartridge heated at 60 °C (full hydrogen mode, 0.2 mL/min). The desired product was obtained as colorless oil upon evaporation of the solvents.

Yield: 96%, Rt = 0.34 min (method A), m/z 310.8 [M+H^+]. ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm 7.36 (2H, d, *J* = 7.2 Hz), 7.31 (2H, t, *J* = 7.2 Hz), 7.24 (1H, t, *J* = 7.2 Hz), 6.78 (1H, s), 6.72 (1H, d, *J* = 7.8 Hz), 6.67 (1H, d, *J* = 7.8 Hz), 5.88 (2H, d, *J* = 3.9 Hz), 3.71 (1H, d, *J* = 13.2 Hz), 3.64 (1H, d, *J* = 13.2 Hz), 3.16 (1H, t, *J* = 8.0 Hz), 3.06 (1H, t, *J* = 8.0 Hz), 2.74 (1H, t, *J* = 9.0 Hz), 2.70 (1H, d, *J* = 9.0 Hz), 2.55 (1H, d, *J* = 9.0 Hz), 2.02 (2H, br s), 0.83 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm 147.4 (C), 146.1 (C), 139.1 (C), 134.4 (C), 128.4 (2CH), 128.3 (2CH), 127.0 (CH), 121.6 (CH), 108.7 (CH), 107.8 (CH), 100.8 (CH_2), 69.3 (CH_2), 60.4 (CH_2), 60.1 (C), 59.3 (CH_2), 57.2 (CH), 25.3 (CH_3). IR (neat) ν = 2895.9 (m), 2791.6 (m), 1607.5 (m), 1503.5 (s), 1489.2 (s), 1441.2 (s), 1375.0 (m), 1250.6 (s), 1235.1 (s), 1191.3 (m), 1126.9 (m), 1040.6 (s), 934.6 (s), 864.1 (m), 808.0 (m), 736.8 (s), 700.4 (s) cm^{-1}. HRMS calculated for $C_{19}H_{23}N_2O_2$ 311.1760, found: 311.1767.

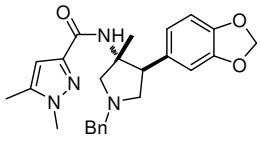
***trans*-1-Benzyl-4-(2-fluorophenyl)-pyrrolidin-3-ylamine, 9b:**



Prepared from 1-benzyl-3-(2-fluorophenyl)-4-nitropyrrolidine (**8b**, 2.0 mmol, in EtOAc/ EtOH, 0.1 M) by passage through the H-Cube™ flow hydrogenator using a small sized Raney-Nickel cartridge heated at 60 °C (full hydrogen mode, 0.2 mL/min). The desired product was obtained as pale colourless oil upon evaporation of the solvents.

Yield: 91%, Rt = 0.24 min (method A), m/z 270.9 [M+H^+]. ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm 7.36 (2H, d, *J* = 7.2 Hz), 7.30-7.34 (3H, m), 7.25 (1H, t, *J* = 7.2 Hz), 7.18 (1H, m), 7.10 (1H, t, *J* = 7.2 Hz), 7.01 (1H, 9.0 Hz), 3.71 (1H, d, *J* = 13.2 Hz), 3.63 (1H, d, *J* = 13.2 Hz), 3.53 (1H, dd, *J* = 6.0, 12.0 Hz), 3.27 (1H, dd, *J* = 7.8, 13.8 Hz), 3.08 (1H, t, *J* = 9.0 Hz), 3.00 (1H, dd, *J* = 7.2, 9.0 Hz), 2.67 (1H, t, *J* = 8.4 Hz), 2.55 (1H, dd, *J* = 5.4, 10.2 Hz), 1.79 (2H, br. s); ^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm 160.9 (C, d, *J* = 240 Hz), 138.9 (C), 130.1 (C, d, *J* = 15 Hz), 128.7 (2CH + CH)), 128.2 (2CH), 127.8 (CH, d, *J* = 8 Hz), 127.0 (CH), 124.3 (CH, d, *J* = 3 Hz), 115.2 (CH, d, *J* = 23 Hz), 63.3 (CH_2), 60.4 (CH_2), 59.8 (CH_2), 59.2 (CH), 48.1 (CH). IR (neat) ν = 2794.6 (m), 1583.9 (w), 1543.0 (w), 1491.4 (s), 1453.1 (m), 1227.6 (m), 1097.2 (m), 855.4 (m), 754.4 (s), 699.0 (s) cm^{-1}. HRMS calculated for $C_{17}H_{20}N_2F$ 271.1611, found: 271.1614.

***N*-(4-(benzo[*d*][1,3]dioxol-5-yl)-1-benzyl-3-methylpyrrolidin-3-yl)-1,5-dimethyl-1*H*-pyrazole-3-carboxamide, 11a:**

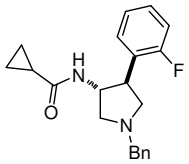


A solution containing 4-(benzo[*d*][1,3]dioxol-5-yl)-1-benzyl-3-methylpyrrolidin-3-amine (**9a**, 50 mg, 0.16 mmol) and triethylamine (28 μL, 0.2 mmol) was prepared in MeCN (2 mL) and combined with a second stream of 1,5-dimethyl-1*H*-pyrrazole-3-

carbonyl chloride (32 mg, 0.2 mmol) dissolved in MeCN (2 mL) using a T-piece. The resulting mixture was directed through a CFC reactor (10 mL, rt, 30 min residence time) and subsequently passed a glass column filled with QP-BZA (1 mmol) to remove residual acid chloride. After evaporation of the solvent the desired amide was obtained as amorphous solid.

Yield: 91%, Rt = 3.81 min (method A), m/z 433.2 [M+H$^+$]. ^{1}H NMR (600 MHz, d$_3$-MeCN): δ/ppm 7.50 (2H, d, *J* = 7.2 Hz), 7.36 (2H, t, *J* = 7.2 H), 7.30 (1H, t, *J* = 7.2 Hz), 7.05 (1H, s, NH), 6.88 (1H, s), 6.77 (2H, m), 6.42 (1H, s), 5.92 (2H, s), 3.98 (1H, d, *J* = 13.8 Hz), 3.95 (1H, d, *J* = 13.8 Hz), 3.90 (1H, t, *J* = 7.8 Hz), 3.73 (3H, s), 3.39 (1H, d, *J* = 10.2 Hz), 3.30 (1H, t, *J* = 10.2 Hz), 3.18 (1H, t, *J* = 10.2 Hz), 2.97 (1H, d, *J* = 10.2 Hz), 2.24 (3H, s), 1.11 (3H, s); ^{13}C NMR (150 MHz, d$_3$-MeCN): δ/ppm 161.7 (C), 147.6 (C), 146.6 (C), 145.1 (C), 141.0 (C), 136.6 (C), 132.4 (C), 129.4 (2CH), 128.5 (2CH), 127.8 (CH), 122.2 (CH), 109.0 (CH), 107.8 (CH), 105.1 (CH), 101.3 (CH_2), 63.8 (CH_2), 61.5 (C), 59.3 (CH_2), 57.1 (CH_2), 51.1 (CH), 36.2 (CH_3), 21.8 (CH_3), 10.3 (CH_3). IR (neat) ν = 3397.2 (w), 2909.4 (w), 1662.9 (s), 1529.3 (s), 1504.5 (s), 1488.9 (s), 1441.0 (s), 1372.6 (m), 1235.5 (s), 1104.7 (m), 1036.0 (s), 931.4 (m), 858.6 (m), 813.2 (m), 775.8 (m), 752.6 (m), 701.2 (s) cm^{-1}. HRMS calculated for $C_{25}H_{29}N_4O_3$ 433.2240, found: 433.2222.

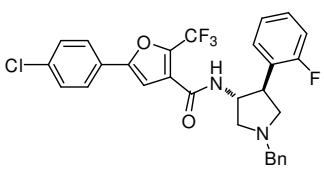
***N*-(1-benzyl-4-(2-fluorophenyl)pyrrolidin-3-yl)cyclopropanecarboxamide, 11b:**



A solution containing 1-benzyl-4-(2-fluorophenyl)pyrrolidin-3-amine (**9b**, 100 mg, 0.37 mmol) and triethylamine (56 μL, 0.4 mmol) was prepared in MeCN (2 mL) and combined with a second stream of cyclopropane carbonyl chloride (42 mg, 0.4 mmol) dissolved in MeCN (2 mL) using a T-piece. The resulting mixture was directed through a CFC reactor (10 mL, rt, 30 min residence time) and subsequently passed a glass column filled with QP-BZA (1 mmol) to remove residual acid chloride. After evaporation of the solvent the desired amide was obtained as brownish amorphous solid.

Yield: 96%, Rt = 3.90 min (method A), m/z 339.0 [M+H$^+$]. ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm 7.30-7.36 (5H, m), 7.26-7.29 (1H, m), 7.18 (1H, dd, *J* = 7.2, 13.8 Hz), 7.09 (1H, t, *J* = 7.2 Hz), 7.00 (1H, t, *J* = 9.0 Hz), 6.27 (1H, d, *J* = 7.2 Hz), 4.59-4.64 (1H, m), 3.67 (2H, s), 3.44 (1H, dq, *J* = 6.6, 7.8 Hz), 3.25 (1H, t, *J* = 9.0 Hz), 2.97 (1H, dd, *J* = 7.8, 10.2 Hz), 2.79 (1H, dd, *J* = 3.6, 10.2 Hz), 2.45 (1H, t, *J* = 9.0 Hz), 1.30 (1H, m), 0.90 (2H, m), 0.68 (2H, ddd, *J* = 7.2, 7.2, 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm 173.1 (C), 160.8 (C, d, *J* = 240 Hz), 138.3 (C), 128.9 (2CH), 128.8 (CH, d, *J* = 4 Hz), 128.5 (C, d, *J* = 14 Hz), 128.4 (2CH), 128.2 (CH, d, *J* = 8 Hz), 127.3 (CH), 124.4 (CH, d, *J* = 3 Hz), 115.4 (CH, d, *J* = 23 Hz), 61.2 (CH_2), 60.1 (CH_2), 59.9 (CH_2), 55.2 (CH), 45.2 (CH), 14.7 (CH), 7.2 (CH_2), 7.1 (CH_2). IR (neat) ν = 3257.1 (w), 2798.2 (w), 1634.8 (m), 1543.2 (m), 1492.8 (m), 1453.3 (m), 1405.0 (m), 1252.1 (m), 1229.5 (m), 1107.4 (m), 1057.1 (m), 856.3 (m), 753.4 (s), 696.9 (s) cm^{-1}. HRMS calculated for $C_{21}H_{24}N_2OF$ 339.1873, found: 339.1874.

***N*-(1-benzyl-4-(2-fluorophenyl)pyrrolidin-3-yl)-5-(4-chlorophenyl)-2-(trifluoromethyl)furan-3-carboxamide, 11c:**

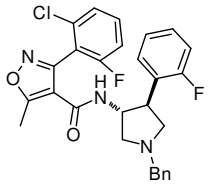


Using the R2+/R4 system a solution containing 1-benzyl-4-(2-fluorophenyl)pyrrolidin-3-amine (**9b**, 100 mg, 0.37 mmol) and triethylamine

(52 µL, 0.37 mmol) was prepared in MeCN (2 mL, stream 1) and combined with a second stream containing 5-(4-chlorophenyl)-2-trifluoromethyl)furan-3-carbonyl chloride (114 mg, 0.37 mmol) dissolved in MeCN (2 mL) using a T-piece. The resulting mixture was directed through a CFC reactor (10 mL, 50 °C, 30 min residence time) and subsequently passed a glass column filled with QP-DMA (0.5 mmol) to remove residual acid chloride. The solvent was removed *in vacuo* giving the desired amide as yellow solid.

Yield: 91 %, Rt = 4.56 min (method A), m/z 542.9 [M+H$^+$]. ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm 7.58 (2H, d, *J* = 8.4 Hz), 7.38 (2H, d, *J* = 8.4 Hz), 7.30-7.35 (5H, m), 7.25-7.28 (1H, m), 7.20 (1H, dt, *J* = 6.0, 6.6 Hz), 7.10 (1H, t, *J* = 7.8 Hz), 7.01 (1H, t, *J* = 7.8 Hz), 6.88 (1H, s), 6.63 (1H, d, *J* = 7.8 Hz), 4.71-4.75 (1H, m), 3.70 (1H, d, *J* = 12.6 Hz), 3.66 (1H, d, *J* = 12.6 Hz), 3.49 (1H, dt, *J* = 6.0, 6.6 Hz), 3.27 (1H, t, *J* = 9.0 Hz), 3.01 (1H, dd, *J* = 7.2, 9.6 Hz), 2.85 (1H, dd, *J* = 2.4, 9.6 Hz), 2.50 (1H, t, *J* = 9.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm 160.7 (C, d, *J* = 243 Hz), 159.9 (C), 154.1 (C), 138.3 (C, q, *J* = 42 Hz), 138.1 (C), 135.3 (C), 129.2 (2CH), 128.7 (2CH), 128.7 (CH), 128.5 (CH, d, *J* = 8 Hz), 128.4 (2CH), 128.2 (C, d, *J* = 14 Hz), 127.3 (CH), 126.8 (CH), 125.8 (CH), 125.2 (C, q, *J* = 3 Hz), 124.46 (CH, d, *J* = 3 Hz), 118.9 (C, q, *J* = 267 Hz), 115.5 (CH, d, *J* = 22 Hz), 106.7 (CH), 60.7 (CH_2), 59.9 (CH_2), 59.8 (CH_2), 55.8 (CH), 45.4 (CH). ^{19}F-NMR (376 MHz, $CDCl_3$): δ/ppm -60.7 (s), -117.4 (s). IR (neat) ν = 1647.5 (m), 1537.3 (m), 1481.9 (s), 1413.6 (m), 1307.1 (m), 1172.5 (s), 1128.5 (s), 1092.9 (s), 930.3 (s), 821.9 (s), 821.9 (s), 753.9 (s), 733.3 (s), 698.9 (s) cm^{-1}. HRMS calculated for $C_{29}H_{24}N_2O_2ClF_4$ 543.1462, found: 543.1476.

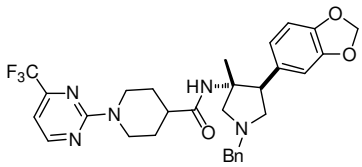
_N_-(1-benzyl-4-(2-fluorophenyl)pyrrolidin-3-yl)-3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carboxamide, 11d



Using the R2+/R4 system a solution containing 1-benzyl-4-(2-fluorophenyl)pyrrolidin-3-amine (**9b**, 22 mg, 0.08 mmol) and triethylamine (14 µL, 0.1 mmol) was prepared in MeCN (2 mL, stream 1) and combined with a second stream containing 3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carboxylic acid chloride (28 mg, 0.1 mmol) dissolved in MeCN (2 mL) using a T-piece. The resulting mixture was directed through a CFC reactor (10 mL, 50 °C, 30 min residence time) and subsequently passed a glass column filled with QP-DMA (0.5 mmol) to remove residual acid chloride. The solvent was removed *in vacuo* giving the desired amide as yellow oil.

Yield: 93 %, Rt = 4.17 min (method A), m/z 507.9 [M+H$^+$]. ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm 7.44 (1H, dt, *J* = 6.0, 8.4 Hz), 7.15-7.35 (8H, m), 7.13 (1H, t, *J* = 8.4 Hz), 7.08 (1H, t, *J* = 8.4 Hz), 6.98 (1H, t, *J* = 9.0 Hz), 5.70 (1H, s, NH), 4.57 (1H, br. s), 3.60 (1H, d, *J* = 13.2 Hz), 3.57 (1H, d, *J* = 13.2 Hz), 3.07 (1H, t, *J* = 8.4 Hz), 3.01 (1H, dt, *J* = 6.0, 7.2 Hz), 2.91 (1H, dd, 3.0, 7.2 Hz), 2.73 (3H, s), 2.59 (1H, d, *J* = 4.2 Hz), 2.34 (1H, t, *J* = 8.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm 174. (C), 161.5 (C, d, *J* = 23 Hz), 160.1 (C), 159.8 (C, d, *J* = 13 Hz), 152.9 (C), 138.2 (C), 135.4 (C, d, *J* = 3 Hz), 132.5 (CH, d, *J* = 9 Hz), 128.6 (2CH), 128.5 (C, d, *J* = 5 Hz; + 2xCH), 128.4 (CH), 128.3 (2CH), 125.9 (CH, d, *J* = 4 Hz), 124.4 (CH, d, *J* = 3 Hz), 116.7 (C, d, *J* = 18 Hz), 115.4 (CH, d, *J* = 23 Hz), 114.8 (CH, d, *J* = 23 Hz), 112.1 (C), 60.5 (CH2), 59.7 (CH2), 59.6 (CH2), 54.8 (CH), 45.9 (CH), 12.3 (CH_3). IR (neat) ν = 2799.5 (w), 1663.8 (m), 1610.5 (m), 1493.2 (m), 1454.0 (m), 1249.8 (m), 1231.2 (m), 1186.7 (m), 1165.2 (m), 897.6 (m), 854.8 (m), 785.2 (s), 733.5 (s), 699.1 (s) cm^{-1}. HRMS calculated for $C_{28}H_{25}ClF_3N_3O_2$ 508.1603, found: 508.1625.

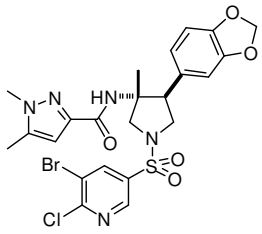
***N*-(4-(benzo[*d*][1,3]dioxol-5-yl)-1-benzyl-3-methylpyrrolidin-3-yl)-1-(4-(trifluoromethyl)-pyrimidin-2-yl)piperidine-4-carboxamide, 11e:**



A solution containing 4-(benzo[*d*][1,3]dioxol-5-yl)-1-benzyl-3-methylpyrrolidin-3-amine (**9a**, 50 mg, 0.16 mmol) and triethylamine (28 µL, 0.2 mmol) was prepared in MeCN (2 mL) and combined with a second stream of 1-(4-(trifluoromethyl)pyrimidin-2-yl)-piperidine-4-carbonyl chloride hydrochloride (66 mg, 0.2 mmol) and triethylamine (28 µL, 0.2 mmol) dissolved in MeCN (2 mL) using a T-piece. The resulting mixture was directed through a CFC reactor (10 mL, 50 °C, 30 min residence time) and subsequently passed a glass column filled with QP-BZA (1 mmol) to remove residual acid chloride. After evaporation of the solvent the desired amide was obtained as amorphous solid.

Yield: 87%, Rt = 4.42 min (method A), m/z 568.2 [M+H$^+$]. ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm 8.45 (1H, d, *J* = 4.5 Hz), 8.00 (1H, br s, NH), 7.37 (2H, d, *J* = 7.2 Hz), 7.28 (2H, t, J 7.2 Hz), 7.22 (1H, t, *J* = 7.2 Hz), 6.85 (1H, s), 6.79 (1H, d, *J* = 7.8 Hz), 6.68-6.72 (2H, m), 5.91 (2H, s), 4.64 (2H, d, *J* = 12.0 Hz), 3.80 (1H, d, *J* = 13.2 Hz), 3.74 (1H, d, *J* = 13.2 Hz), 3.52 (1H, t, *J* = 7.8 Hz), 3.41 (1H, t, *J* = 9.0 Hz), 3.11 (1H, d, *J* = 7.8 Hz), 3.03 (2H, t, *J* = 12.0 Hz), 2.78 (1H, t, *J* = 9.0 Hz), 2.67 (1H, d, *J* = 7.8 Hz), 2.48 (1H, m), 1.93 (2H, d, *J* = 12.0 Hz), 1.62 (2H, m), 1.10 (3H, s); ^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm 180.0 (C), 161.3 (C), 160.0 (CH), 156.2 (C, q, *J* = 35 Hz), 147.6 (C), 146.7 (C), 137.2 (C), 132.1 (C), 128.8 (2CH), 128.4 (2CH), 127.5 (CH), 122.4 (CH), 120.6 (CF_3, q, *J* = 274 Hz), 109.1 (CH), 108.1 (CH), 104.1 (CH), 101.0 (CH_2), 64.5 (CH_2), 62.3 (C), 59.2 (CH_2), 58.8 (CH_2), 52.7 (CH), 43.4 ($2CH_2$), 42.6 (CH), 28.3 ($2CH_2$), 21.5 (CH_3). IR (neat) ν = 2924.9 (m), 1591.1 (s), 1562.4 (m), 1505.7 (s), 1490.1 (s), 1446.0 (s), 1393.5 (m), 1354.2 (m), 1326.4 (s), 1233.7 (m), 1216.1 (m), 1194.4 (m), 1144.5 (s), 1129.6 (s), 1112.3 (s), 1084.2 (m), 1036.9 (s), 983.5 (s), 958.3 (m), 933.3 (m), 813.1 (s), 734.7 (s), 699.6 s), 670.3 (s) cm^{-1}. HRMS calculated for $C_{30}H_{33}F_3N_5O_3$ 568.2536, found: 568.2552.

***N*-(4-(benzo[*d*][1,3]dioxol-5-yl)-1-((5-bromo-6-chloropyridin-3-yl)sulfonyl)-3-methylpyrrolidin-3-yl)-1,5-dimethyl-1*H*-pyrazole-3-carboxamide, 13a:**

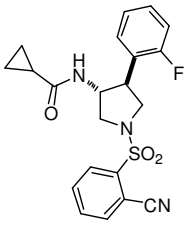


A solution containing *N*-((-4-(benzo[*d*][1,3]dioxol-5-yl)-3-methylpyrrolidin-3-yl)-1,5-dimethyl-1*H*-pyrazole-3-carboxamide (**12a**, 30 mg, 0.09 mmol) and triethylamine (18 µL, 0.13 mmol) was prepared in MeCN (2 mL) and combined with a second stream of 5-bromo-6-chloropyridin-3-sulfonyl chloride (38 mg, 0.13 mmol) dissolved in MeCN (2 mL) using a T-piece. The resulting mixture was directed through a CFC reactor (10 mL, 60 °C, 30 min residence time) and subsequently passed a glass column filled with QP-BZA (1 mmol) to remove residual sulfonyl chloride. After evaporation of the solvent the desired amide was obtained as amorphous solid.

Yield: 94 %, Rt = 4.90 min (method A), m/z 596.1 [M+H$^+$]. ^{1}H NMR (500 MHz, $CDCl_3$): δ/ppm 8.71 (1H, d, *J* = 3.0 Hz), 8.30 (1H, d, *J* = 3.0 Hz), 6.77 (1H, d, *J* = 8.0 Hz), 6.72 (1H, d, *J* = 1.7 Hz), 6.69 (1H, dd, *J* = 1.7, 8.0 Hz), 6.41 (1H, d, *J* = 0.6 Hz), 6.35 (1H, NH), 5.96 (2H, s), 4.32 (1H, d, *J* = 7.5 Hz), 3.77 – 3.81 (2H, m), 3.73 (3H, s), 3.47 (1H, d, *J* = 11.5 Hz), 3.43 (1H, dd, *J* = 4.5, 6.5 Hz), 2.28 (3H, s), 1.10 (3H, s); ^{13}C NMR (125

MHz, $CDCl_3$): δ/ppm 161.7 (C), 154.2 (C), 148.1 (C), 147.2 (C), 146.0 (CH), 144.2 (C), 140.7 (CH), 140.6 (C), 133.4 (C), 130.8 (C), 121.6 (CH), 120.7 (C), 108.5 (CH), 108.4 (CH), 106.0 (CH), 101.3 (CH_2), 62.1 (C), 54.6 (CH_2), 52.2 (CH_2), 52.1 (CH), 36.6 (CH_3), 19.5 (CH_3), 11.4 (CH_3). IR (neat) ν = 1665.9 (m), 1530.4 (m), 1503.9 (m), 1489.1 (m), 1436.2 (m), 1404.8 (m), 1358.0 (s), 1235.6 (s), 1162.1 (m), 1104.1 (s), 1032.3 (s), 932.9 (m), 830.6 (s), 775.4 (m), 724.0 (s) cm^{-1}. HRMS calculated for $C_{23}H_{24}BrClSN_5O_5$ 596.0356, found: 596.0370.

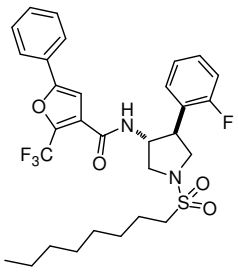
***N*-(1-((2-cyanophenyl)sulfonyl)-4-(2-fluorophenyl)pyrrolidin-3-yl)cyclopropanecarboxamide, 13b:**



A solution containing *N*-(1-benzyl-4-(2-fluorophenyl)pyrrolidin-3-yl)cyclopropane-carboxamide (68 mg, 0.2 mmol) in methanol (0.1 M) was prepared and pumped through a small Pd-cartridge (10% Pd/C, 60°C, 0.2 mL/min) using the H-Cube™ system in full hydrogen mode. As LC-MS analysis indicated full conversion to the debenzylated pyrrolidine, the methanol was evaporated and exchanged for MeCN (0.1 M). After triethylamine (28 µL, 0.2 mmol) was added to this solution, the material was loaded in a sample loop of the Vapourtec system and combined using a T-piece with a second stream of 2-cyanobenzene sulfonylchloride (40 mg, 0.2 mmol) dissolved in MeCN (2 mL) and dispensed from a second sample loop. The resulting mixture was directed through a CFC reactor (10 mL, 50 °C, 30 min residence time) and subsequently passed a glass column filled with QP-BZA (1 mmol) to remove residual sulfonyl chloride. After evaporation of the solvent the desired amide was obtained as a colourless film.

Yield: 93 %, Rt = 4.62 min (method A), m/z 413.9 [$M+H^+$]. ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm 8.11 (1H, d, *J* = 7.8 Hz), 7.90 (1H, d, *J* = 7.8 Hz), 7.76 (1H, t, *J* = 7.8 Hz), 7.71 (1H, t, *J* = 7.8 Hz), 7.21-7.29 (2H, m), 7.11 (1H, t, *J* = 7.2 Hz), 7.03 (1H, t, *J* = 9.0 Hz), 5.97 (1H, d, *J* = 7.2 Hz), 4.62 (1H, ddt, *J* = 7.2, 7.2, 15.6 Hz), 4.05 (1H, t, *J* = 9.0 Hz), 3.89 (1H, dd, *J* = 7.2, 9.0 Hz), 3.65 (1H, app. q, *J* = 9.0 Hz), 3.51 (1H, t, *J* = 9.0 Hz), 3.34 (1H, dd, *J* = 7.2, 9.0 Hz), 1.21-1.29 (1H, m), 0.85-0.90 (2H, m), 0.63-0.72 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm 173.7 (C), 161.1 (C, d, *J* = 245 Hz), 141.3 (C), 135.6 (CH), 133.1 (CH), 132.9 (CH), 130.4 (CH), 129.3 (CH, d, *J* = 8 Hz), 128.0 (CH, d, *J* = 5 Hz), 124.8 (CH, d, *J* = 5 Hz), 124.2 (C, d, *J* = 15 Hz), 116.5 (C), 115.7 (CH, d, *J* = 23 Hz), 110.6 (C), 53.8 (CH), 52.1 (CH_2), 51.3 (CH_2), 43.2 (CH), 14.5 (CH), 7.6 (CH_2), 7.5 (CH_2). IR (neat) ν = 3281.9 (w), 2921.3 (w), 2231.9 (w), 1646.0 (m), 1537.9 (m), 1494.2 (m), 1348.8 (m), 1230.5 (m), 1165.2 (s), 1030.0 (m), 943.5 (m), 758.4 (s), 682.5 (s) cm^{-1}. HRMS calculated for $C_{21}H_{21}FSN_3O_3$ 414.1288, found: 414.1302.

***N*-(4-(2-fluorophenyl)-1-(octylsulfonyl)pyrrolidin-3-yl)-5-phenyl-2-(trifluoromethyl)furan-3-carboxamide, 13c:**

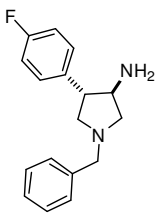


A solution containing *N*-(4-(2-fluorophenyl)pyrrolidin-3-yl)-5-phenyl-2-(trifluoromethyl)furan-3-carboxamide (50 mg, 0.12 mmol) and triethylamine (18 µL, 0.13 mmol) was prepared in MeCN (2 mL) and combined with a second stream of octylsulfonyl chloride (25 mg, 0.12 mmol) dissolved in MeCN (2 mL) using a T-piece. The resulting mixture was directed through a CFC reactor (10 mL, 50 °C, 30 min residence time) and subsequently passed a glass column filled with QP-BZA (1 mmol)

to remove residual sulfonyl chloride. After evaporation of the solvent the desired amide was obtained as a white waxy solid.

Yield: 90 %, Rt = 5.65 min (method A), m/z 594.9 [M+H$^+$]. ^{1}H NMR (600 MHz, $CDCl_3$): δ/ppm 7.66 (2H, d, *J* = 7.8 Hz), 7.42 (2H, t, *J* = 7.8 Hz), 7.37 (1H, d, *J* = 7.8 Hz), 7.34 (1H, t, *J* = 7.8 Hz), 7.28 (1H, dt, *J* = 6.0, 7.2 Hz), 7.15 (1H, t, *J* = 7.8 Hz), 7.08 (1H, t, *J* = 9.6 Hz), 6.86 (1H, s), 6.36 (1H, d, *J* = 7.2 Hz), 4.85 (1H, ddt, *J* = 7.2, 7.2, 15.6 Hz), 4.03 (1H, t, *J* = 9.0 Hz), 3.98 (1H, dd, *J* = 7.2, 10.2 Hz), 3.70 (1H, dt, *J* = 8.2, 9.0 Hz), 3.44 (2H, m), 3.04 (2H, m), 1.84 (2H, m), 1.40-1.45 (2H, m), 1.23-1.30 (8H, m), 0.88 (3H, t, *J* = 6.4 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ/ppm 161.1 (C, d, *J* = 243 Hz), 160.7 (C), 155.5 (C), 138.5 (C, q, *J* = 41 Hz), 129.5 (CH, d, *J* = 11 Hz), 129.5 (CH), 128.9 (2CH), 128.3 (CH, d, *J* = 5 Hz), 128.2 (C), 124.8 (CH, d, *J* = 5 Hz), 124.6 (2CH), 124.3 (C), 124.1 (C, d, *J* = 14 Hz), 118.9 (C, q, *J* = 267 Hz), 115.8 (CH, d, *J* = 23 Hz), 105.9 (CH), 54.4 (CH), 51.9 (CH_2), 51.2 (CH_2), 50.8 (CH_2), 44.1 (CH), 31.7 (CH_2), 29.0 (CH_2), 28.9 (CH_2), 28.3 (CH_2), 23.2 (CH_2), 22.5 (CH_2), 14.0 (CH_3); ^{19}F-NMR (376 MHz, $CDCl_3$): δ/ppm -60.7 (s), -117.3 (s). IR (neat) ν = 3279.6 (w), 2923.5 (w), 28.54.5 (w), 1658.8 (m), 1542.3 (m), 1451.7 (m), 1393.8 (m), 1327.9 (m), 1234.7 (m), 1197.8 (m), 1179.0 (m), 1144.5 (s), 1118.5 (s), 1035.9 (s), 1017.6 (s), 931.8 (m), 822.5 (m), 760.9 (s), 720.2 (m), 687.7 (m) cm^{-1}. HRMS calculated for $C_{30}H_{35}F_4SN_2O_4$ 595.2254, found: 595.2278.

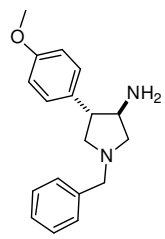
***trans*-1-Benzyl-4-(4-fluorophenyl)-pyrrolidin-3-ylamine, 9f:**



A 0.86 M solution of *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (**5**, 3.04 g, 12.8 mmol) in DCM (15 mL) and a 0.55 M solution of *trans*-4-fluoro-ß-nitrostyrene (**6f**, 1.44 g, 8.60 mmol) and TFA (66 µl, 0.86 mmol) in DCM (15 mL) were prepared. The two reactant streams were mixed using a simple T-piece and directed through a CFC reactor (volume = 10 mL) heated at 50 °C at a total flow rate of 1.0 mL min^{-1}, equating to a residence time of 10 min. The product stream was collected in saturated solution of $NaHCO_3$. Extraction with DCM and evaporation of the solvent provided the nitro compound as light yellow oil. Without further purification the crude reaction product was dissolved in a mixture of EtOH:ethyl acetate (1:10; 44 mL) and treated with tin(II) chloride dihydrate (5.82 g, 25.80 mmol). After stirring for 150 min at 90 °C, the reaction mixture was poured onto ice-water and the pH adjusted to 14 by addition of a 1 M NaOH solution. After stirring for 15 min, the mixture was filtered over Decalite, acidified by addition of a 1 M HCl solution and extracted with ethyl acetate. The aqueous phase was again adjusted to pH 14, the solution extracted with ethyl acetate and the combined organic phases dried over $MgSO_4$. The solvent was evaporated under reduced pressure providing the title compound as light brown oil.

Yield: 83 %, Rt = 1.13 (method B), m/z 271.2 [M+H+].

***trans*-1-Benzyl-4-(4-methoxyphenyl)-pyrrolidin-3-ylamine, 9g:**

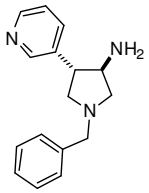


A 0.86 M solution of *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (**5**, 3.04 g, 12.8 mmol) in DCM (15 mL) and a 0.55 M solution of *trans*-4-methoxy-ß-nitrostyrene (**6g**, 1.54 g, 8.60 mmol) and TFA (66 µl, 0.86 mmol) in DCM (15 mL) were prepared. The two reactant streams were mixed using a simple T-piece and directed through a CFC reactor

(volume = 10 mL) heated at 50 °C at a total flow rate of 1.0 mL min^{-1}, equating to a residence time of 10 min. The product stream was collected in saturated solution of $NaHCO_3$. Extraction with DCM and evaporation of the solvent provided the nitro compound as light yellow oil. Without further purification the crude reaction product was dissolved in a mixture of EtOH:ethyl acetate (1:1; 54 mL, 0.16 M) and pumped through a small Raney-Nickel cartridge (RaNi, 60°C, 60 bar, 1.0 mL/min) using the H-Cube™ system. After evaporation of the solvent mixture, water was added and acidified by addition of a 1 M HCl solution and extracted with ethyl acetate. The aqueous phase was again adjusted to pH 14, the solution extracted with ethyl acetate and the combined organic phases dried over $MgSO_4$. The solvent was evaporated under reduced pressure providing the title compound as light brown oil.

Yield: 87 %, Rt = 1.18 (method B), m/z 283.5 [M+H+]. ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm 7.24 - 7.39 (5H, m), 7.20 (2H, d, *J* = 8.9 Hz), 6.85 (2H, d, *J* = 8.9 Hz), 3.79 (3H, s), 3.67 - 3.73 (1H, m), 3.59 - 3.66 (1H, m), 3.39 - 3.46 (1H, m), 3.06 - 3.13 (1H, m), 2.98 (1H, dd, *J* = 9.4, 7.3 Hz), 2.84 - 2.92 (1H, m), 2.61 (1H, dd, *J* = 9.4, 7.8 Hz), 2.56 (1H, dd, *J* = 9.4, 5.6 Hz).

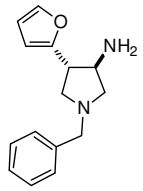
***trans*-1-Benzyl-4-pyridin-3-yl-pyrrolidin-3-ylamine, 9h:**



A 0.86 M solution of *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (**5**, 3.04 g, 12.8 mmol) in DCM (15 mL) and a 0.55 M solution of *trans*-3-(2-nitroethenyl)pyridine (**6h**, 1.29 g, 8.60 mmol) and TFA (66 µl, 0.86 mmol) in DCM (15 mL) were prepared. The two reactant streams were mixed using a simple T-piece and directed through a CFC reactor (volume = 10 mL) heated at 80 °C at a total flow rate of 0.5 mL min^{-1}, equating to a residence time of 20 min. The product stream was collected in saturated solution of $NaHCO_3$. Extraction with DCM and evaporation of the solvent provided the nitro compound as light yellow oil. Without further purification the crude reaction product was dissolved in a mixture of EtOH:ethyl acetate (1:10; 44 mL) and treated with tin(II) chloride dihydrate (5.82 g, 25.80 mmol). After stirring for 240 min at 90 °C, the reaction mixture was poured onto ice-water and the pH adjusted to 14 by addition of a 1 M NaOH solution. After stirring for 15 min, the mixture was filtered over Decalite, acidified by addition of a 1 M HCl solution and extracted with ethyl acetate. The aqueous phase was again adjusted to pH 14, the solution extracted with ethyl acetate and the combined organic phases dried over $MgSO_4$. The solvent was evaporated under reduced pressure providing the title compound as a light brown oil.

Yield: 76 %, Rt = 1.27 (method B), m/z 254.4 [M+H+].

***trans*-1-Benzyl-4-furan-2-yl-pyrrolidin-3-ylamine, 9i:**

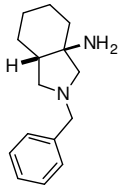


A 0.86 M solution of *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (**5**, 3.04 g, 12.8 mmol) in DCM (15 mL) and a 0.55 M solution of *trans*-2-(2-nitrovinyl)furan (**6i**, 1.20 g, 8.60 mmol) and TFA (66 µl, 0.86 mmol) in DCM (15 mL) were prepared. The two reactant streams were mixed using a simple T-piece and directed through a CFC reactor (volume = 10 mL) heated at 50 °C at a total flow rate of 1.0 mL min^{-1}, equating to a residence time of 10 min. The product stream was collected in saturated solution of $NaHCO_3$. Extraction with DCM and evaporation of the solvent provided the nitro compound as light yellow oil. Without further purification the crude reaction product

was dissolved in a mixture of EtOH:ethyl acetate (1:1; 54 mL, 0.16 M) and pumped through a small Raney-Nickel cartridge (RaNi, 60°C, 60 bar, 0.2 mL/min) using the H-Cube™ system. After evaporation of the solvent mixture, water was added and acidified by addition of a 1 M HCl solution and extracted with ethyl acetate. The aqueous phase was again adjusted to pH 14, the solution extracted with ethyl acetate and the combined organic phases dried over $MgSO_4$. The solvent was evaporated under reduced pressure providing the title compound as light yellow oil.

Yield: 67 %, Rt = 0.50 (method B), m/z 243.4 [M+H+].

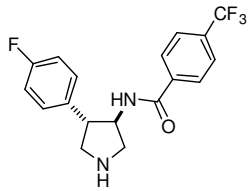
***cis*-2-Benzyloctahydroisoindol-3a-ylamine, 9j:**



A 0.86 M solution of *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (**5**, 3.04 g, 12.8 mmol) in DCM (15 mL) and a 0.55 M solution of 1-nitro-1-cyclohexene (**6j**, 1.09 g, 8.60 mmol) and TFA (66 µl, 0.86 mmol) in DCM (15 mL) were prepared. The two reactant streams were mixed using a simple T-piece and directed through a CFC reactor (volume = 10 mL) heated at 170 °C at a total flow rate of 1.0 mL min^{-1}, equating to a residence time of 10 min. The product stream was collected in saturated solution of $NaHCO_3$. Extraction with DCM and evaporation of the solvent provided the nitro compound as light yellow oil. Without further purification the crude reaction product was dissolved in a mixture of EtOH:ethyl acetate (1:10; 44 mL) and treated with tin(II) chloride dihydrate (5.82 g, 25.80 mmol). After stirring for 120 min at 90 °C, the reaction mixture was poured onto ice-water and the pH adjusted to 14 by addition of a 1 M NaOH solution. After stirring for 15 min, the mixture was filtered over Decalite, acidified by addition of a 1 M HCl solution and extracted with ethyl acetate. The aqueous phase was again adjusted to pH 14, the solution extracted with ethyl acetate and the combined organic phases dried over $MgSO_4$. The solvent was evaporated under reduced pressure providing the title compound as light brown oil.

Yield: 92 %, Rt = 1.26 (method B), m/z 231.3 [M+H+].

***N*-[*trans*-4-(4-fluorophenyl)-pyrrolidin-3-yl]-4-trifluoromethylbenzamide, 12f**{2}**:**

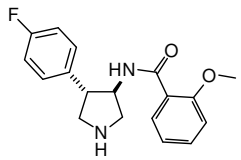


To a solution of *trans*-1-benzyl-4-(4-fluoro-phenyl)-pyrrolidin-3-ylamine (**9f**, 1.0 g, 3.7 mmol) in DCM (10 mL) was added triethylamine (0.75 g, 7.4 mmol) and 4-(trifluoromethyl)benzoyl chloride (0.85 g, 4.07 mmol). The reaction mixture was stirred for 1.5 h at rt a saturated solution of $NaHCO_3$ was added and the solution extracted with DCM. Evaporation of the solvent provided the pyrrolidine intermediate as light brown oil, which was dissolved in a mixture of MeOH:ethyl acetate (9:2; 22 mL, 0.17 M) and pumped through a small Pd-cartridge (10% Pd/C, 100°C, 80 bar, 0.5 mL/min) using the H-Cube™ system. After evaporation of the solvent mixture, water was added and acidified by addition of a 1 M HCl solution and extracted with ethyl acetate. The aqueous phase was again adjusted to pH 14, the solution extracted with ethyl acetate and the combined organic phases dried over $MgSO_4$. The solvent was evaporated under reduced pressure providing the title compound as light brown oil.

Yield: 14 %, Rt = 1.74 (method B), m/z 353.0 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm 8.75 (1H, d, J = 7.8 Hz), 8.00 (2H, d, J = 8.2 Hz), 7.84 (2H, d, J = 8.3 Hz), 7.36 (2H, dd, J = 8.7, 5.5 Hz), 7.11 (2H, t, J = 8.9

Hz), 4.40 (1H, quin, *J* = 7.2 Hz), 3.33 - 3.39 (1H, m), 3.21 - 3.28 (1H, m), 2.80 (1H, dd, *J* = 10.4, 7.6 Hz), 2.75 - 2.79 (1H, m), 2.51 - 2.53 (1H, m).

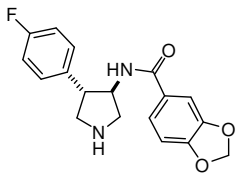
***N*-[*trans*-4-(4-fluorophenyl)-pyrrolidin-3-yl]-2-methoxybenzamide, 12f**{3}**:**



To a solution of *trans*-1-benzyl-4-(4-fluoro-phenyl)-pyrrolidin-3-ylamine (**9f**, 1.0 g, 3.7 mmol) in DCM (15 mL) was added diisopropylethylamine (1.43 g, 11.1 mmol) and 2-methoxybenzoyl chloride (0.69 g, 4.07 mmol). The reaction mixture was stirred for 3 h at rt a saturated solution of $NaHCO_3$ was added and the solution extracted with DCM. Evaporation of the solvent provided the pyrrolidine intermediate as light brown oil, which was dissolved in MeOH (20 mL) and 10% Pd/C (118 mg, 1.11 mmol) was added. The mixture was stirred under an atmosphere of hydrogen (2.5 bar) at 50 °C over night. After filtration over Decalite the solvent was evaporated, water added and acidified by addition of a 1 M HCl solution and extracted with ethyl acetate. The aqueous phase was again adjusted to pH 14, the solution extracted with ethyl acetate and the combined organic phases dried over $MgSO_4$. The solvent was evaporated under reduced pressure providing the title compound as light yellow oil.

Yield: 10 %, Rt = 1.53 (method B), m/z 315.1 [M+H+].

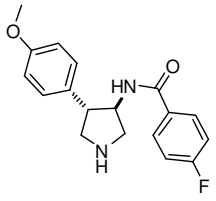
***N*-(4-(4-fluorophenyl)pyrrolidin-3-yl)benzo[*d*][1,3]dioxole-5-carboxamide, 12f**{5}**:**



To a solution of *trans*-1-benzyl-4-(4-fluoro-phenyl)-pyrrolidin-3-ylamine (**9f**, 1.0 g, 3.7 mmol) in DCM (10 mL) was added triethylamine (0.75 g, 7.4 mmol) and benzo[1,3]dioxole-5-carbonyl chloride (0.75 g, 4.07 mmol). The reaction mixture was stirred for 1.5 h at rt a saturated solution of $NaHCO_3$ was added and the solution extracted with DCM. Evaporation of the solvent provided the pyrrolidine intermediate as light brown oil, which was dissolved in a mixture of MeOH:ethyl acetate (1:1; 30 mL, 0.12 M) and pumped through a small Pd-cartridge (10% Pd/C, 100°C, full hydrogen mode, 1.0 mL/min) using the H-Cube™ system. After evaporation of the solvent mixture, water was added and acidified by addition of a 1 M HCl solution and extracted with ethyl acetate. The aqueous phase was again adjusted to pH 14, the solution extracted with ethyl acetate and the combined organic phases dried over $MgSO_4$. The solvent was evaporated under reduced pressure providing the title compound as a light brown oil.

Yield: 22 %, Rt = 1.54 (method B), m/z 329.3 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm 8.32 (1H, d, *J* = 8.0 Hz), 7.41 (1H, dd, *J* = 8.2, 1.8 Hz), 7.32 - 7.37 (2H, m), 7.07 - 7.13 (3H, m), 6.96 (1H, d, *J* = 8.2 Hz), 6.07 - 6.09 (2H, m), 4.32 - 4.38 (1H, m), 3.23 - 3.27 (1H, m), 3.18 - 3.23 (1H, m), 2.77 (1H, dd, *J* = 10.7, 7.9 Hz), 2.68 - 2.74 (1H, m), 2.51 - 2.53 (1H, m).

4-Fluoro-*N*-[*trans*-4-(4-methoxyphenyl)-pyrrolidin-3-yl]-benzamide, 12g{1}**:**

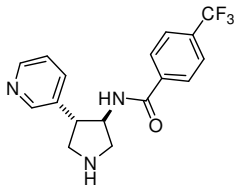


To a solution of 4-fluorobenzoic acid (0.63 g, 4.5 mmol) in DMF (20 mL) was added diisopropylethylamine (1.44 g, 11.2 mmol) and *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HATU, 1.7 g, 4.46 mmol). After stirring for 0.5 h at rt, *trans*-1-benzyl-4-(4-methoxy-phenyl)-pyrrolidin-3-ylamine (**9g**, 1.05 g, 3.72

mmol) was added and stirring of the reaction mixture continued at 50 °C for 3 h. Evaporation of the solvent provided the pyrrolidine intermediate as light brown oil, which was dissolved in MeOH (20 mL) and 10% Pd/C (118 mg, 1.11 mmol) was added. The mixture was stirred under an atmosphere of hydrogen (2.5 bar) at 50 °C over night. After filtration over Decalite the solvent was evaporated, water added and acidified by addition of a 1 M HCl solution and extracted with ethyl acetate. The aqueous phase was again adjusted to pH 14, the solution extracted with ethyl acetate and the combined organic phases dried over $MgSO_4$. The solvent was evaporated under reduced pressure providing the title compound as light yellow oil.

Yield: 16 %, Rt = 1.51 (method B), m/z 315.2 [M+H+].

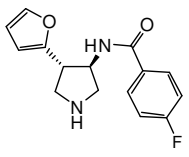
***N*-(*trans*-4-pyridin-3-yl-pyrrolidin-3-yl)-4-trifluoromethylbenzamide, 12h**{2}**:**



To a solution of *trans*-1-benzyl-4-pyridin-3-yl-pyrrolidin-3-ylamine (**9h**, 1.0 g, 3.95 mmol) in DCM (10 mL) was added triethylamine (0.75 g, 7.4 mmol) and 4-(trifluoromethyl)benzoyl chloride (0.85 g, 4.07 mmol). The reaction mixture was stirred for 1.5 h at rt saturated solution of $NaHCO_3$ was added and the solution extracted with DCM. Evaporation of the solvent provided the pyrrolidine intermediate as light brown oil, which was dissolved in MeOH (20 mL) and 20% $Pd(OH)_2/C$ (55 mg, 0.40 mmol) was added. The mixture was stirred under an atmosphere of hydrogen (2.5 bar) at rt over night. After filtration over Decalite the solvent was evaporated, water added and acidified by addition of a 1 M HCl solution and extracted with ethyl acetate. The aqueous phase was again adjusted to pH 14, the solution extracted with ethyl acetate and the combined organic phases dried over $MgSO_4$. The solvent was evaporated under reduced pressure providing the title compound as light brown oil.

Yield: 43 %, Rt = 1.37 (method B), m/z 336.5 [M+H+].

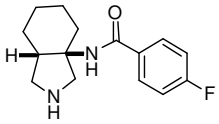
4-Fluoro-*N*-(*trans*-4-furan-2-yl-pyrrolidin-3-yl)-benzamide, 12i{1}**:**



To a solution of *trans*-1-benzyl-4-furan-2-yl-pyrrolidin-3-ylamine (**9i**, 0.49 g, 2.0 mmol) in DCM (10 mL) was added triethylamine (0.41 g, 4.0 mmol) and 4-fluorobenzoyl chloride (0.35 g, 2.22 mmol). The reaction mixture was stirred for 1 h at rt a saturated solution of $NaHCO_3$ was added and the solution extracted with DCM. Evaporation of the solvent provided the pyrrolidine intermediate as light brown oil, which was dissolved in MeOH (10 mL) and 10% Pd/C (43 mg, 0.40 mmol) was added. The mixture was stirred under an atmosphere of hydrogen (2.5 bar) at 50 °C over night. After filtration over Decalite the solvent was evaporated, water added and acidified by addition of a 1 M HCl solution and extracted with ethyl acetate. The aqueous phase was again adjusted to pH 14, the solution extracted with ethyl acetate and the combined organic phases dried over $MgSO_4$. The solvent was evaporated under reduced pressure providing the title compound as a light yellow oil.

Yield: 38 %, Rt = 1.53 (method B), m/z 275.2 [M+H+].

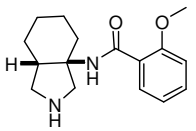
4-Fluoro-*N-cis*-octahydro-isoindol-3a-yl-benzamide, 12j{1}**:**



To a solution of *cis*-2-benzyl-octahydro-isoindol-3a-ylamine (**9j**, 1.0 g, 3.7 mmol) in DCM (10 mL) was added triethylamine (0.88 g, 7.4 mmol) and 4-fluorobenzoyl chloride (0.76 g, 4.8 mmol). The reaction mixture was stirred for 1.5 h at rt a saturated solution of $NaHCO_3$ was added and the solution extracted with DCM. Evaporation of the solvent provided the pyrrolidine intermediate as light brown oil, which was dissolved in MeOH (10 mL) and 10% Pd/C (115 mg, 1.1 mmol) was added. The mixture was stirred under an atmosphere of hydrogen (2.5 bar) at 50 °C over night. After filtration over Decalite the solvent was evaporated, water added and acidified by addition of a 1 M HCl solution and extracted with ethyl acetate. The aqueous phase was again adjusted to pH 14, the solution extracted with ethyl acetate and the combined organic phases dried over $MgSO_4$. The solvent was evaporated under reduced pressure providing the title compound as light yellow oil.

Yield: 27 %, Rt = 1.41 (method B), m/z 263.4 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm 8.14 (1H, s), 7.90 (2H, dd, *J* = 8.8, 5.5 Hz), 7.30 (2H, t, *J* = 8.8 Hz), 3.56 (1H, d, *J* = 11.7 Hz), 3.39 (1H, d, *J* = 12.1 Hz), 3.26 - 3.32 (1H, m), 3.00 (1H, dd, *J* = 11.4, 5.9 Hz), 2.55 - 2.60 (1H, m), 1.92 - 2.03 (2H, m), 1.77 - 1.84 (1H, m), 1.45 - 1.58 (2H, m), 1.31 - 1.43 (3H, m).

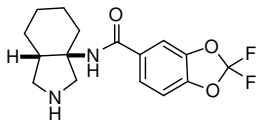
2-Methoxy-*N*-*cis*-octahydroisoindol-3a-yl-benzamide, 12j{3}**:**



To a solution of *cis*-2-benzyloctahydroisoindol-3a-ylamine (**9j**, 1.0 g, 3.7 mmol) in DCM (10 mL) was added triethylamine (0.88 g, 7.4 mmol) and 2-methoxybenzoyl chloride (0.82 g, 4.8 mmol). The reaction mixture was stirred for 3 h at 0 °C. A saturated solution of $NaHCO_3$ was added and the solution extracted with DCM. Evaporation of the solvent provided the pyrrolidine intermediate as light brown oil, which was dissolved in a mixture of MeOH:ethyl acetate (5:1; 30 mL, 0.12 M) and cycled four times through a small Pd-cartridge (10% Pd/C, 100°C, full hydrogen mode, 2.0 mL/min) using the H-Cube™ system. After evaporation of the solvent mixture, water was added and acidified by addition of a 1 M HCl solution and extracted with ethyl acetate. The aqueous phase was again adjusted to pH 14, the solution extracted with ethyl acetate and the combined organic phases dried over $MgSO_4$. The solvent was evaporated under reduced pressure providing the title compound as light yellow oil.

Yield: 22 %, Rt = 1.45 (method B), m/z 275.1 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm 8.07 (1H, d, *J* = 2.5 Hz), 7.67 (1H, dd, *J* = 7.6, 1.8 Hz), 7.46 (1H, d, *J* = 1.2 Hz), 7.14 (1H, dd, *J* = 8.2, 5.2 Hz), 6.98 - 7.07 (1H, m), 3.90 (3H, s), 3.66 (1H, d, *J* = 11.0 Hz), 3.49 (1H, d, *J* = 11.0 Hz), 3.09 (1H, dd, *J* = 10.7, 7.9 Hz), 2.84 - 2.93 (1H, m), 2.34 (1H, t, *J* = 6.5 Hz), 2.02 - 2.10 (1H, m), 1.61 - 1.80 (3H, m), 1.32 - 1.53 (4H, m).

2,2-Difluoro-*N*-*cis*-(octahydroisoindol-3a-yl)benzo[*d*][1,3]dioxole-5-carboxamide, 12j{6}**:**

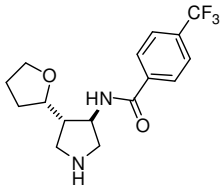


To a solution of *cis*-2-benzyl-octahydro-isoindol-3a-ylamine (**9j**, 1.0 g, 3.7 mmol) in DCM (10 mL) was added triethylamine (0.88 g, 7.4 mmol) and 2,2-difluorobenzo[*d*][1,3]dioxole-5-carbonyl chloride (1.06 g, 4.8 mmol). The reaction mixture was stirred for 3 h at 0 °C. A saturated solution of $NaHCO_3$ was added and the solution extracted with DCM. Evaporation of the solvent provided the crude pyrrolidine intermediate, which was purified by silica medium pressure liquid chromatography (MPLC) using a gradient of heptane / ethyl acetate. The isolated product was dissolved in a mixture of MeOH:ethyl acetate (5:1; 30 mL, 0.12 M) and pumped through a small

Pd-cartridge (10% Pd/C, 100°C, full hydrogen mode, 0.25 mL/min) using the H-Cube™ system. After evaporation of the solvent mixture, water was added and acidified by addition of a 1 M HCl solution and extracted with ethyl acetate. The aqueous phase was again adjusted to pH 14, the solution extracted with ethyl acetate and the combined organic phases dried over $MgSO_4$. The solvent was evaporated under reduced pressure providing the title compound as light yellow oil.

Yield: 10 %, Rt = 1.35 (method B), m/z 325.3 [M+H+].

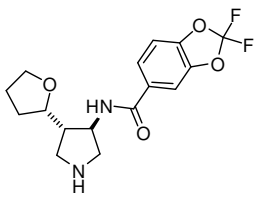
***N*-[*trans*-4-(tetrahydrofuran-2-yl)-pyrrolidin-3-yl]-4-trifluoromethylbenzamide, 12i'**{2}**:**



To a solution of *trans*-1-benzyl-4-furan-2-yl-pyrrolidin-3-ylamine (**9i**, 0.90 g, 3.7 mmol) in DCM (10 mL) was added triethylamine (0.88 g, 7.4 mmol) and 4-(trifluoromethyl)benzoyl chloride (1.00 g, 4.8 mmol). The reaction mixture was stirred for 2 h at rt a saturated solution of $NaHCO_3$ was added and the solution extracted with DCM. Evaporation of the solvent provided the pyrrolidine intermediate as light brown oil, which was dissolved in MeOH (20 mL) and 20% $Pd(OH)_2/C$ (0.10 g, 0.71 mmol) was added. The mixture was stirred under an atmosphere of hydrogen (2.5 bar) at rt over night. After filtration over Decalite the solvent was evaporated, water added and acidified by addition of a 1 M HCl solution and extracted with ethyl acetate. The aqueous phase was again adjusted to pH 14, the solution extracted with ethyl acetate and the combined organic phases dried over $MgSO_4$. The solvent was evaporated under reduced pressure providing the title compound as light yellow oil.

Yield: 14 %, Rt = 1.31 (method B), m/z 329.3 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6, diastereomeric mixture ~ 1:0.85) δ/ppm 8.67 (1H, d, *J* = 7.7 Hz), 8.62 (1H, d, *J* = 7.5 Hz), 8.03 (1H, d, *J* = 8.0 Hz), 7.85 (1H, dd, *J* = 8.2, 3.9 Hz), 4.22 - 4.32 (1H, m), 4.15 (1H, dt, *J* = 13.6, 6.6 Hz), 3.69 - 3.81 (4H, m), 3.55 - 3.64 (2H, m), 3.01 - 3.13 (4H, m), 2.65 - 2.71 (1H, m), 2.59 (1H, dd, *J* = 11.3, 6.4 Hz), 2.26 - 2.32 (1H, m), 2.12 - 2.20 (1H, m), 1.87 - 1.96 (4H, m), 1.73 - 1.86 (8H, m), 1.52 (4H, dt, *J* = 12.0, 8.3 Hz).

2,2-Difluoro-N-(4-(tetrahydrofuran-2-yl)pyrrolidin-3-yl)benzo[*d*][*1,3*]dioxole-5-carboxamide, 12i'{6}**:**



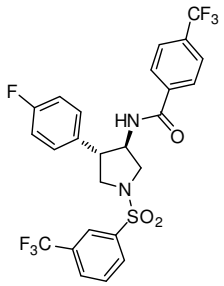
To a solution of *trans*-1-benzyl-4-furan-2-yl-pyrrolidin-3-ylamine (**9i**, 0.90 g, 3.7 mmol) in DCM (10 mL) was added triethylamine (0.88 g, 7.4 mmol) and 2,2-difluorobenzo[*d*][1,3]dioxole-5-carbonyl chloride (1.06 g, 4.8 mmol). The reaction mixture was stirred for 2 h at rt a saturated solution of $NaHCO_3$ was added and the solution extracted with DCM. Evaporation of the solvent provided the crude pyrrolidine intermediate, which was purified by silica medium pressure liquid chromatography (MPLC) using a gradient of heptane / ethyl acetate. The isolated product was dissolved in MeOH (20 mL) and 20% $Pd(OH)_2/C$ (0.10 g, 0.71 mmol) was added. The mixture was stirred under an atmosphere of hydrogen (2.5 bar) at rt over night. After filtration over Decalite the solvent was evaporated, water added and acidified by addition of a 1 M HCl solution and extracted with ethyl acetate. The aqueous phase was again adjusted to pH 14, the solution extracted with ethyl acetate and the combined organic phases dried over $MgSO_4$. The solvent was evaporated under reduced pressure providing the title compound as light yellow oil.

Yield: 6 %, Rt = 1.32 (method B), m/z 341.1 [M+H+]. ^{1}H NMR (600 MHz, DMSO-$d_{6,}$ diastereomeric mixture ~ 1:0.85) δ/ppm 8.49 (1H, d, *J* = 7.8 Hz), 8.44 (1H, d, *J* = 7.4 Hz), 7.81 - 7.89 (2H, m), 7.76 (2H, dd, *J* = 8.4, 1.8 Hz), 7.46 - 7.57 (2H, m), 4.19 - 4.27 (1H, m), 4.13 (1H, quin, *J* = 6.7 Hz), 3.67 - 3.84 (4H, m), 3.54 - 3.63 (2H, m), 2.98 - 3.14 (5H, m), 2.74 - 2.80 (1H, m), 2.67 (1H, dd, *J* = 11.4, 4.8 Hz), 2.58 (1H, dd, *J* = 11.5, 6.5 Hz), 2.24 - 2.32 (1H, m), 2.08 - 2.17 (1H, m), 1.85 - 1.97 (2H, m), 1.69 - 1.85 (4H, m), 1.52 (2H, dt, *J* = 12.0, 8.3 Hz).

General Procedure for the Preparation of the Sulfonamide Library:

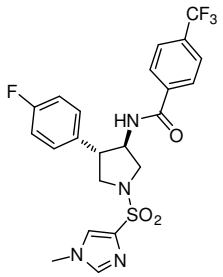
To a stirred solution of building blocks **12f-i'** (1 mL, 0.2 M stock solution in DMF) was added diisopropylethylamine (52 mg, 0.4 mmol, 2.0 equiv) and the corresponding sulfonyl chloride (0.22 mmol, 1.1 equiv.). After shaking at rt for 2 h the solvent was removed under reduced pressure, the residues dissolved in DMSO, filtered and purified by reverse phase preparative HPLC.

***N*-[*trans*-4-(4-Fluorophenyl)-1-(3-trifluoromethylbenzenesulfonyl)-pyrrolidin-3-yl]-4-trifluoromethyl-benzamide, 13f**{2,8}:



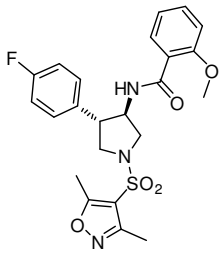
Yield: 10 %, Rt = 2.22 (method B), m/z 561.1 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm 8.79 (1H, d, *J* = 7.9 Hz), 8.22 (1H, d, *J* = 8.0 Hz), 8.14 (1H, d, *J* = 7.9 Hz), 8.09 (1H, s), 7.93 (1H, t, *J* = 7.9 Hz), 7.90 (2H, d, *J* = 8.2 Hz), 7.81 (2H, d, *J* = 8.4 Hz), 7.30 (2H, dd, *J* = 8.8, 5.5 Hz), 7.10 (2H, t, *J* = 8.9 Hz), 4.50 - 4.61 (1H, m), 3.92 (1H, dd, *J* = 10.0, 7.9 Hz), 3.74 (1H, dd, *J* = 9.9, 7.7 Hz), 3.42 - 3.50 (1H, m), 3.32 - 3.35 (1H, m), 3.18 (1H, dd, *J* = 10.0, 7.9 Hz); (*E*)-stereoisomer ~ 85%. ^{19}F NMR (377 MHz, DMSO-d_6) δ/ppm -61.2 (3F, s), -61.4 (3F, s), -115.6 (1F, s). IR (neat) ν = 3289 (w), 3077 (w), 2898 (w), 1645 (m), 1609 (w), 1544 (m), 1513 (m), 1323 (s), 1282 (m), 1232 (m), 1158 (s), 1121 (s), 1102 (s), 1066 (s), 1033 (m), 1017 (m), 856 (m), 843 (m), 804 (w), 769 (w), 722 (w), 691 (m), 654 (m) cm^{-1}. HRMS calculated for $C_{25}H_{19}F_7SN_2O_3$ 560.1005, found: 560.1001.

***N*-[*trans*-4-(4-Fluorophenyl)-1-(1-methyl-1*H*-imidazole-4-sulfonyl)pyrrolidin-3-yl]-4-trifluoromethyl-benzamide, 13f**{2,12}:



Yield: 17 %, Rt = 1.95 (method B), m/z 497.1 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm 8.79 (1H, d, *J* = 8.0 Hz), 7.92 (2H, d, *J* = 8.3 Hz), 7.91 (2H, s), 7.83 (2H, d, *J* = 8.4 Hz), 7.28 - 7.32 (2H, m), 7.12 (2H, t, *J* = 8.9 Hz), 4.41 - 4.50 (1H, m), 3.87 (1H, dd, *J* = 9.9, 8.0 Hz), 3.74 (3H, s), 3.73 - 3.77 (1H, m), 3.46 - 3.53 (1H, m), 3.38 (1H, t, *J* = 9.9 Hz), 3.20 (1H, dd, *J* = 10.1, 8.5 Hz); (*E*)-stereoisomer ~ 85%. ^{19}F NMR (377 MHz, DMSO-d_6) δ/ppm -61.34 (3F, s), -115.63 (1F, s). IR (neat) ν = 3281 (w), 3121 (w), 3067 (w), 2889 (w), 1649 (m), 1580 (w), 1530 (m), 1512 (m), 1325 (s), 1225 (m), 1159 (s), 1121 (s), 1065 (s), 1016 (m), 963 (w), 857 (m), 837 (m), 772 (w), 693 (m) cm^{-1}. HRMS calculated for $C_{22}H_{20}F_4SN_4O_3$ 496.1192, found: 496.1193.

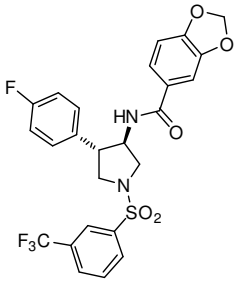
***N*-[*trans*-1-(3,5-Dimethylisoxazole-4-sulfonyl)-4-(4-fluorophenyl)pyrrolidin-3-yl]-2-methoxybenzamide, 13f**{3,13}:



Yield: 17 %, Rt = 2.07 (method B), m/z 474.1 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm 8.33 (1H, d, *J* = 7.7 Hz), 7.54 (1H, dd, *J* = 7.7, 1.8 Hz), 7.40 - 7.46 (3H, m), 7.13 - 7.19 (2H, m), 7.09 (1H, d, *J* = 8.1 Hz), 6.98 (1H, td, *J* = 7.5, 0.9 Hz), 4.58 - 4.65 (1H, m), 3.78 - 3.81 (3H, m), 3.74 - 3.80 (2H, m), 3.52 - 3.58 (1H, m), 3.34 (1H, t, *J* = 9.6 Hz), 3.18 (1H, dd, *J* = 9.4, 7.8 Hz), 2.64 - 2.67 (3H, m), 2.38 (3H, s); (*E*)-stereoisomer ~ 85%. ^{19}F NMR (377 MHz, DMSO-d_6) δ ppm -115.58 (1F, s). IR (neat) ν = 3302 (w), 3072 (w),

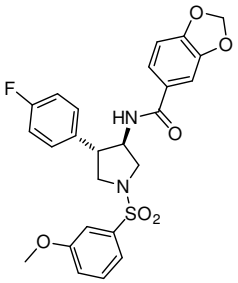
2941 (w), 2890 (w), 2840 (w), 1637 (s), 1601 (m), 1536 (m), 1513 (s), 1486 (m), 1466 (m), 1437 (w), 1408 (m), 1371 (m), 1335 (s), 1298 (m), 1246 (s), 1227 (s), 1175 (s), 1163 (m), 1136 (s), 1108 (s), 1023 (s), 878 (w), 845 (m), 812 (m), 753 (s), 684 (m), 659 (w) cm^{-1}. HRMS calculated for $C_{23}H_{24}FSN_3O_5$ 473.1421, found: 473.1417.

***N*-(4-(4-fluorophenyl)-1-((3-(trifluoromethyl)phenyl)sulfonyl)pyrrolidin-3-yl)benzo[*d*][*1,3*]dioxole-5-carboxamide, 13f**{5,8}:



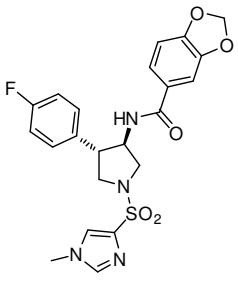
Yield: 6 %, Rt = 2.29 (method B), m/z 537.0 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm 8.36 (1H, d, *J* = 7.6 Hz), 8.21 (1H, d, *J* = 8.0 Hz), 8.14 (1H, d, *J* = 7.7 Hz), 8.09 (1H, s), 7.93 (1H, t, *J* = 7.8 Hz), 7.27 - 7.31 (3H, m), 7.24 (1H, d, *J* = 1.7 Hz), 7.09 (2H, t, *J* = 8.9 Hz), 6.94 (1H, d, *J* = 8.2 Hz), 6.08 (1H, d, *J* = 0.9 Hz), 6.07 (1H, d, *J* = 0.9 Hz), 4.46 - 4.53 (1H, m), 3.89 (1H, dd, *J* = 10.0, 7.8 Hz), 3.70 (1H, dd, *J* = 9.9, 7.7 Hz), 3.41 - 3.47 (1H, m), 3.28 - 3.32 (1H, m), 3.13 (1H, dd, *J* = 9.8, 8.0 Hz); (*E*)-stereoisomer ~ 85%. ^{19}F NMR (377 MHz, DMSO-d_6) δ/ppm -61.22 (3F, s), -115.60 (1F, s). IR (neat) ν = 3269 (w), 3077 (w), 2985 (w), 2783 (w), 1639 (m), 1606 (m), 1539 (m), 1513 (m), 1484 (s), 1437 (m), 1346 (m), 1324 (s), 1254 (m), 1227 (m), 1158 (s), 1121 (s), 1101 (s), 1069 (s), 1032 (s), 925 (m), 833 (m), 804 (m), 758 (w), 721 (w), 692 (m), 653 (m) cm^{-1}. HRMS calculated for $C_{25}H_{20}F_4SN_2O_5$ 536.1029, found: 536.1024.

***N*-(4-(4-fluorophenyl)-1-((3-methoxyphenyl)sulfonyl)pyrrolidin-3-yl)benzo[*d*][*1,3*]dioxole-5-carboxamide, 13f**{5,9}:



Yield: 7 %, Rt = 2.06 (method B), m/z 499.1 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm 8.36 (1H, d, *J* = 7.9 Hz), 7.56 - 7.64 (1H, m), 7.44 (1H, dt, *J* = 7.8, 1.2 Hz), 7.29 - 7.33 (4H, m), 7.23 - 7.27 (2H, m), 7.09 (2H, t, *J* = 8.9 Hz), 6.94 (1H, d, *J* = 8.2 Hz), 6.08 (1H, d, *J* = 0.9 Hz), 6.07 (1H, d, *J* = 0.9 Hz), 4.39 - 4.47 (1H, m), 3.86 (3H, s), 3.80 - 3.85 (1H, m), 3.65 - 3.71 (1H, m), 3.41 (1H, q, *J* = 9.2 Hz), 3.25 (1H, t, *J* = 9.9 Hz), 3.09 (1 H, dd, *J* = 9.9, 8.2 Hz); (*E*)-stereoisomer ~ 85%. ^{19}F NMR (377 MHz, DMSO-d_6) δ/ppm -115.7 (1F, s). IR (neat) ν = 3291 (w), 3075 (w), 2940 (w), 2899 (w), 2838 (w), 1641 (m), 1598 (m), 1536 (m), 1511 (s), 1478 (s), 1434 (m), 1391 (m), 1316 (m), 1286 (m), 1240 (s), 1153 (s), 1096 (m), 1032 (s), 990 (m), 925 (m), 834 (m), 786 (m), 757 (m), 684 (m) cm^{-1}. HRMS calculated for $C_{25}H_{23}FSN_2O_6$ 498.1261, found: 498.1258.

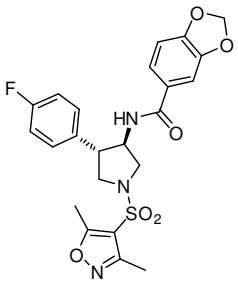
***N*-(4-(4-fluorophenyl)-1-((1-methyl-1*H*-imidazol-4-yl)sulfonyl)pyrrolidin-3-yl)benzo[*d*][*1,3*]dioxole-5-carboxamide, 13f**{5,12}**:**



Yield: 3 %, Rt = 1.78 (method B), m/z 473.1 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm 8.36 (1H, d, *J* = 7.9 Hz), 7.90 (1H, d, *J* = 2.3 Hz), 7.33 (1H, dd, *J* = 8.2, 1.7 Hz), 7.26 - 7.31 (4H, m), 7.12 (2H, t, *J* = 8.9 Hz), 6.95 (1H, d, *J* = 8.2 Hz), 6.08 (1H, d, *J* = 0.9 Hz), 6.07 (1H, d, *J* = 0.9 Hz), 4.36 - 4.43 (1H, m), 3.85 (1H, dd, *J* = 9.8, 8.0 Hz), 3.74 - 3.75 (3H, m), 3.71 (1H, dt, *J* = 9.8, 3.9 Hz), 3.44 - 3.50 (1H, m), 3.35 - 3.39 (1H, m), 3.14 (1H, dd, *J* = 10.0, 8.6 Hz); (*E*)-stereoisomer ~ 85%. ^{19}F NMR (377 MHz, DMSO-d_6) δ/ppm -115.7 (1F, s). IR (neat) ν = 3128 (w), 2941 (w), 2879 (w), 1641 (m), 1603 (m), 1528 (m),

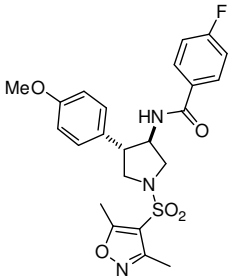
1509 (m), 1481 (s), 1436 (m), 1334 (m), 1250 (m), 1222 (m), 1155 (s), 1114 (s), 1032 (s), 963 (w), 923 (m), 835 (m), 806 (m), 757 (m), 718 (w), 692 (m) cm^{-1}. HRMS calculated for $C_{22}H_{21}FSN_4O_5$ 472.1217, found: 472.1206.

***N*-(1-((3,5-dimethylisoxazol-4-yl)sulfonyl)-4-(4-fluorophenyl)pyrrolidin-3-yl)benzo[*d*][*1,3*]dioxole-5-carboxamide, 13f**{5,13}**:**



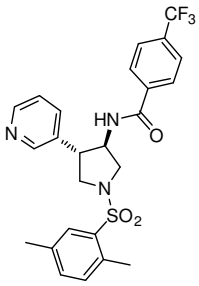
Yield: 3 %, Rt = 2.01 (method B), m/z 488.1 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm 8.45 (1H, d, *J* = 8.1 Hz), 7.37 - 7.42 (2H, m), 7.35 (1H, dd, *J* = 8.2, 1.7 Hz), 7.29 (1H, d, *J* = 1.7 Hz), 7.10 - 7.15 (2H, m), 6.96 (1H, d, *J* = 8.2 Hz), 6.08 (1H, d, *J* = 0.9 Hz), 6.07 (1H, d, *J* = 0.9 Hz), 4.64 - 4.73 (1H, m), 3.80 (1H, dd, *J* = 9.5, 7.9 Hz), 3.71 (1H, dd, *J* = 9.5, 8.1 Hz), 3.49 - 3.57 (1H, m), 3.33 - 3.39 (1H, m), 3.17 (1H, dd, *J* = 9.5, 7.8 Hz), 2.64 (3H, s), 2.38 (3H, s); (*E*)-stereoisomer ~ 85%. ^{19}F NMR (377 MHz, DMSO-d_6) δ/ppm -115.7 (1F, s). IR (neat) ν = 3292 (w), 3076 (w), 2896 (w), 1640 (m), 1621 (m), 1590 (m), 1538 (m), 1512 (s), 1483 (s), 1439 (m), 1407 (m), 1335 (s), 1255 (s), 1225 (s), 1174 (s), 1162 (m), 1109 (s), 1032 (s), 926 (m), 880 (w), 833 (m), 810 (m), 757 (m), 684 (m) cm^{-1}. HRMS calculated for $C_{23}H_{22}FSN_3O_6$ 487.1213, found: 487.1210.

***N*-[*trans*-1-(3,5-Dimethylisoxazole-4-sulfonyl)-4-(4-methoxyphenyl)-pyrrolidin-3-yl]-4-fluorobenzamide, 13g**{1,13}:



Yield: 18 %, Rt = 2.06 (method B), m/z 474.1 [M+H+]. ^{1}H NMR (600 MHz, $CDCl_3$) δ/ppm 7.68 - 7.74 (2H, m), 7.14 - 7.20 (2H, m), 7.07 - 7.13 (2H, m), 6.86 - 6.90 (2H, m), 6.25 (1H, d, *J* = 6.7 Hz), 4.59 (1H, quin, *J* = 6.9 Hz), 3.92 (1H, dd, *J* = 10.2, 7.8 Hz), 3.88 (1H, dd, *J* = 10.6, 6.9 Hz), 3.79 (3H, s), 3.46 (1H, q, *J* = 8.0 Hz), 3.37 (1H, dd, *J* = 10.6, 6.1 Hz), 3.29 (1H, dd, *J* = 10.2, 8.3 Hz), 2.69 (3H, s), 2.47 (3H, s); (*E*)-stereoisomer ~ 90%**.** ^{19}F NMR (377 MHz, $CDCl_3$) δ/ppm -107.1 (1F, s). IR (neat) ν = 3286 (w), 3070 (w), 3000 (w), 2935 (w), 2838 (w), 1640 (s), 1604 (m), 1591 (m), 1541 (m), 1515 (s), 1502 (s), 1408 (m), 1372 (m), 1335 (s), 1246 (s), 1227 (s), 1174 (s), 1159 (m), 1104 (s), 1031 (s), 846 (m), 809 (m), 766 (m), 722 (w), 684 (m) cm^{-1}. HRMS calculated for $C_{23}H_{24}FSN_3O_5$ 473.1421, found: 473.1411.

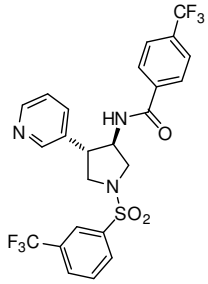
***N*-[*trans*-1-(2,5-Dimethylbenzenesulfonyl)-4-pyridin-3-yl-pyrrolidin-3-yl]-4-trifluoromethylbenzamide, 13h**{2,7}**:**



Yield: 3 %, Rt = 1.93 (method B), m/z 504.1 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm 8.91 (1H, d, *J* = 8.0 Hz), 8.56 (1H, d, *J* = 2.0 Hz), 8.46 (1H, dd, *J* = 4.8, 1.4 Hz), 7.94 (2H, d, *J* = 8.2 Hz), 7.85 (1H, d, *J* = 7.9 Hz), 7.83 (2H, d, *J* = 8.3 Hz), 7.70 (1H, s), 7.39 - 7.42 (1H, m), 7.38 - 7.39 (1H, m), 7.35 - 7.38 (1H, m), 4.74 - 4.83 (1H, m), 3.87 (1H, dd, *J* = 9.7, 8.0 Hz), 3.75 (1H, dd, *J* = 9.5, 7.9 Hz), 3.56 - 3.64 (1H, m), 3.37 - 3.43 (1H, m), 3.24 (1H, dd, *J* = 9.5, 8.2 Hz), 2.57 (3H, s), 2.36 (3H, s); (*E*)-stereoisomer > 99%. ^{19}F NMR (377 MHz, DMSO-d_6) δ/ppm -61.4 (3F, s). IR (neat) ν = 3274 (w), 3057 (w), 2928 (w),

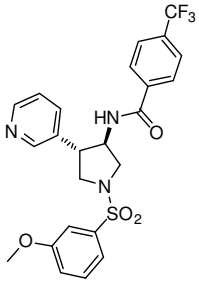
2884 (w), 1653 (m), 1578 (w), 1540 (m), 1491 (m), 1431 (w), 1322 (s), 1222 (w), 1156 (s), 1122 (s), 1065 (s), 1015 (s), 857 (m), 816 (m), 769 (m), 698 (m) cm^{-1}. HRMS calculated for $C_{25}H_{24}F_3SN_3O_3$ 503.1491, found: 503.1489.

***N*-[*trans*-4-pyridin-3-yl-1-(3-trifluoromethylbenzenesulfonyl)-pyrrolidin-3-yl]-4-trifluoromethyl-benzamide, 13h**{2,8}**:**



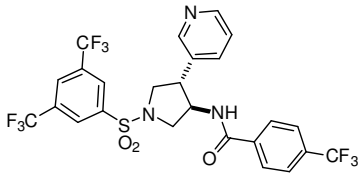
Yield: 4 %, Rt = 1.95 (method B), m/z 544.0 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm 8.83 (1H, d, *J* = 8.1 Hz), 8.51 (1H, d, *J* = 1.2 Hz), 8.45 (1H, dd, *J* = 4.9, 1.0 Hz), 8.23 (1H, d, *J* = 8.1 Hz), 8.15 (1H, d, *J* = 7.9 Hz), 8.10 (1H, s), 7.94 (1H, t, *J* = 7.9 Hz), 7.90 (2H, d, *J* = 8.3 Hz), 7.82 (2H, d, *J* = 8.3 Hz), 7.77 - 7.80 (1H, m), 7.34 - 7.39 (1H, m), 4.63 - 4.70 (1H, m), 3.96 (1H, dd, *J* = 9.8, 7.7 Hz), 3.77 (1H, dd, *J* = 9.9, 7.9 Hz), 3.46 - 3.51 (1H, m), 3.41 (1H, m, *J* = 9.8 Hz), 3.22 (1H, dd, *J* = 9.9, 8.0 Hz); (*E*)-stereoisomer > 99%. ^{19}F NMR (377 MHz, DMSO-d_6) δ/ppm -61.4 (3F, s), -61.2 (3F, s). IR (neat) ν = 3284 (w), 3073 (w), 1644 (w), 1542 (w), 1508 (w), 1430 (w), 1349 (w), 1324 (s), 1227 (w), 1161 (s), 1121 (s), 1066 (s), 1033 (m), 1017 (m), 858 (w), 804 (w), 769 (w), 693 (m), 654 (m) cm^{-1}. HRMS calculated for $C_{24}H_{19}F_6SN_3O_3$ 543.1051, found: 543.1047.

***N*-[*trans*-1-(3-methoxybenzenesulfonyl)-4-pyridin-3-yl-pyrrolidin-3-yl]-4-trifluoromethylbenzamide, 13h**{2,9}**:**



Yield: 5 %, Rt = 1.80 (method B), m/z 506.1 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm 8.83 (1H, d, *J* = 7.9 Hz), 8.45 (1H, d, *J* = 2.0 Hz), 8.42 (1H, dd, *J* = 4.7, 1.6 Hz), 7.91 (2H, d, *J* = 8.2 Hz), 7.82 (2H, d, *J* = 8.3 Hz), 7.69 (1H, dt, *J* = 8.0, 1.8 Hz), 7.57 - 7.63 (1H, m), 7.43 - 7.48 (1H, m), 7.29 - 7.34 (3H, m), 4.55 - 4.62 (1H, m), 3.89 (1H, dd, *J* = 10.0, 8.0 Hz), 3.85 - 3.87 (3H, m), 3.72 - 3.77 (1H, m), 3.41 - 3.47 (1H, m), 3.36 (1H, t, *J* = 9.9 Hz), 3.18 (1H, dd, *J* = 9.9, 8.2 Hz); (*E*)-stereoisomer > 99%. ^{19}F NMR (377 MHz, DMSO-d_6) δ/ppm -61.3 (3F, s). IR (neat) ν = 3291 (w), 3060 (w), 2959 (w), 2840 (w), 1647 (w), 1596 (w), 1578 (w), 1543 (w), 1480 (w), 1430 (w), 1324 (s), 1243 (m), 1159 (m), 1124 (m), 1065 (m), 1017 (m), 857 (m), 769 (w), 695 (m) cm^{-1}. HRMS calculated for $C_{24}H_{22}F_3SN_3O_4$ 505.1283, found: 505.1285.

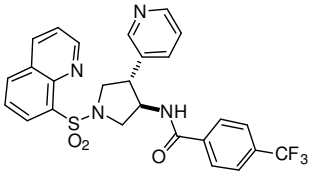
***N*-[*trans*-1-(3,5-bis-trifluoromethylbenzenesulfonyl)-4-pyridin-3-yl-pyrrolidin-3-yl]-4-trifluoromethyl-benzamide, 13h**{2,10}**:**



Yield: 3 %, Rt = 2.09 (method B), m/z 612.0 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm 8.84 (1H, d, *J* = 8.1 Hz), 8.58 (1H, s), 8.54 (1H, d, *J* = 1.4 Hz), 8.47 (1H, d, *J* = 3.7 Hz), 8.44 (2H, s), 7.90 (2H, d, *J* = 8.2 Hz), 7.83 - 7.87 (1H, m), 7.82 (2H, d, *J* = 8.3 Hz), 7.38 - 7.43 (1H, m), 4.68 - 4.81 (1H, m), 4.05 (1H, dd, *J* = 9.6, 7.5 Hz), 3.82 (1H, dd, *J* = 10.0, 8.1 Hz), 3.49 - 3.56 (1H, m), 3.45 (1H, t, *J* = 9.8 Hz), 3.30 (1H, dd, *J* = 10.0, 7.7 Hz); (*E*)-stereoisomer > 95%. ^{19}F NMR (377 MHz, DMSO-d_6) δ/ppm -61.5 (3F, s), -61.4 (3F, s), -61.2 (3F, s). IR (neat) ν = 3284 (w), 3084 (w), 1647 (m), 1625 (w), 1578 (w), 1543 (m), 1479 (w), 1358 (m), 1326 (m), 1277 (s), 1230 (m), 1162 (s), 1123 (s), 1104 (s), 1066 (s), 1040 (s), 1017 (m), 928 (w), 904

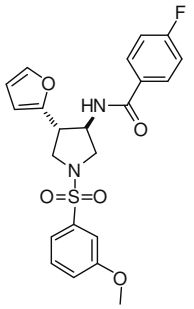
(m), 878 (w), 857 (m), 843 (m), 698 (m), 681 (m) cm^{-1}. HRMS calculated for $C_{25}H_{18}F_9SN_3O_3$ 611.0925, found: 611.0918.

***N*-[*trans*-4-pyridin-3-yl-1-(quinoline-8-sulfonyl)-pyrrolidin-3-yl]-4-trifluoromethylbenzamide, 13h**{2,11}:



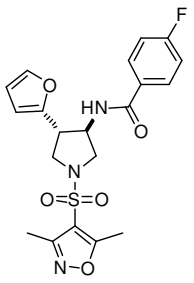
Yield: 5 %, Rt = 1.72 (method B), m/z 527.1 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm 9.17 (1H, dd, *J* = 4.2, 1.8 Hz), 8.73 (1H, d, *J* = 8.2 Hz), 8.60 (1H, dd, *J* = 8.4, 1.8 Hz), 8.44 (1H, dd, *J* = 7.4, 1.4 Hz), 8.39 - 8.41 (2H, m), 8.36 (1H, dd, *J* = 8.3, 1.4 Hz), 7.85 (2H, d, *J* = 8.2 Hz), 7.75 - 7.82 (4H, m), 7.62 (1H, dt, *J* = 7.9, 1.9 Hz), 7.27 (1H, ddd, *J* = 7.9, 4.8, 0.8 Hz), 4.67 - 4.75 (1H, m), 4.43 (1H, dd, *J* = 9.4, 7.9 Hz), 4.14 (1H, dd, *J* = 9.5, 7.8 Hz), 3.51 - 3.60 (1H, m), 3.48 (1H, td, *J* = 10.1, 7.9 Hz), 3.26 (1H, t, *J* = 9.1 Hz); (*E*)-stereoisomer > 99%. ^{19}F NMR (377 MHz, DMSO-d_6) δ/ppm -61.4 (3F, s). IR (neat) ν = 3317 (w), 3056 (w), 2944 (w), 2871 (w), 1659 (m), 1596 (w), 1578 (w), 1540 (m), 1494 (m), 1323 (s), 1212 (w), 1161 (s), 1123 (s), 1065 (s), 1016 (m), 859 (m), 834 (m), 790 (m), 769 (w), 714 (w), 673 (m) cm^{-1}. HRMS calculated for $C_{26}H_{21}F_3SN_4O_3$ 526.1286, found: 526.1277.

4-Fluoro-*N*-[*trans*-4-furan-2-yl-1-(3-methoxybenzenesulfonyl)-pyrrolidin-3-yl]-benzamide, 13i{1,9}:



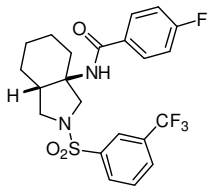
Yield: 15 %, Rt = 2.26 (method C), m/z 445.1 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm 8.63 (1H, d, *J* = 7.5 Hz), 7.82 (2H, dd, *J* = 8.9, 5.5 Hz), 7.57 (1H, dd, *J* = 9.0, 7.8 Hz), 7.51 (1H, dd, *J* = 1.8, 0.7 Hz), 7.41 (1H, dt, *J* = 7.8, 1.2 Hz), 7.26 - 7.32 (4H, m), 6.31 (1H, dd, *J* = 3.2, 1.8 Hz), 6.15 (1H, d, *J* = 3.2 Hz), 4.44 (1H, quin, *J* = 7.5 Hz), 3.84 (3H, s), 3.78 (1H, dd, *J* = 10.1, 8.0 Hz), 3.62 (1H, dd, *J* = 10.2, 7.3 Hz), 3.54 (1H, q, *J* = 7.9 Hz), 3.31 (1H, dd, *J* = 10.2, 8.0 Hz), 3.18 (1H, dd, *J* = 10.2, 7.2 Hz). IR (neat) ν = 3305 (m), 2953 (s), 2923 (s), 2853 (s), 2724 (w), 1641 (s), 1603 (m), 1583 (w), 1544 (m), 1505 (s), 1479 (m), 1464 (s), 1376 (m), 1343 (m), 1322 (m), 1287 (m), 1251 (m), 1240 (m), 1155 (s), 1096 (m), 1076 (w), 1033 (m), 1012 (w), 849 (m), 807 (w), 767 (w), 738 (w), 695 (m), 681 (m), 628 (m), 585 (m) cm^{-1}. HRMS calculated for $C_{22}H_{21}FSN_2O_5$ 444.1155, found: 444.1163.

***N*-[*trans*-1-(3,5-Dimethylisoxazole-4-sulfonyl)-4-furan-2-yl-pyrrolidin-3-yl]-4-fluorobenzamide, 3i**{1,13}**:**



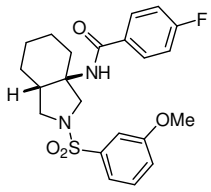
Yield: 8 %, Rt = 2.23 (method C), m/z 434.1 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm 8.75 (1H, d, *J* = 7.7 Hz), 7.88 (2H, dd, *J* = 8.9, 5.5 Hz), 7.56 (1H, dd, *J* = 1.8, 0.8 Hz), 7.27 - 7.37 (2H, m), 6.36 (1H, dd, *J* = 3.2, 1.8 Hz), 6.27 (1H, d, *J* = 3.2 Hz), 4.66 (1H, quin, *J* = 7.4 Hz), 3.80 (1H, dd, *J* = 9.8, 7.9 Hz), 3.69 (1H, dd, *J* = 9.9, 7.6 Hz), 3.63 (1H, q, *J* = 7.8 Hz), 3.37 - 3.41 (1H, m), 3.24 (1H, dd, *J* = 9.9, 6.7 Hz), 2.64 (3H, s), 2.35 (3H, s). HRMS calculated for $C_{20}H_{20}FSN_3O_5$ 433.1108, found: 433.1111.

4-Fluoro-*N*-(*cis*-2-(3-trifluoromethylbenzenesulfonyl)-octahydroisoindol-3*a*-yl]-benzamide, 13j{1,8}:



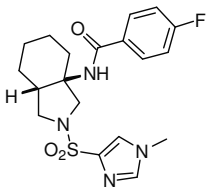
Yield: 8 %, Rt = 2.15 (method B), m/z 471.1 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm 8.06 (1H, d, *J* = 7.9 Hz), 7.94 (1H, s), 7.80 (1H, d, *J* = 8.0 Hz), 7.74 (1H, s), 7.68 - 7.73 (1H, m), 7.56 (2H, dd, *J* = 8.9, 5.5 Hz), 7.18 (2H, t, *J* = 8.9 Hz), 3.83 (1H, d, *J* = 11.2 Hz), 3.59 (1H, d, *J* = 11.3 Hz), 3.45 (1H, dd, *J* = 9.6, 6.4 Hz), 3.18 (1H, dd, *J* = 9.6, 4.1 Hz), 2.41 - 2.45 (1H, m), 1.80 - 1.88 (1H, m), 1.67 - 1.77 (1H, m), 1.58 (1H, ddd, *J* = 13.7, 10.2, 3.2 Hz), 1.38 - 1.48 (2H, m), 1.09 - 1.34 (3H, m). ^{19}F NMR (377 MHz, DMSO-d_6) δ/ppm -109.5 (1F, s), -61.5 (3F, s). IR (neat) ν = 3349 (w), 3079 (w), 2935 (w), 2862 (w), 1641 (m), 1604 (m), 1532 (m), 1497 (s), 1323 (s), 1232 (m), 1157 (s), 1127 (s), 1103 (s), 1068 (s), 885 (w), 850 (m), 806 (m), 766 (m), 720 (m), 695 (m), 654 (m) cm^{-1}. HRMS calculated for $C_{22}H_{22}F_4SN_2O_3$ 470.1287, found: 470.1279.

4-Fluoro-*N*-[*cis*-2-(3-methoxybenzenesulfonyl)octahydroisoindol-3*a*-yl]-benzamide, 13j{1,9}:



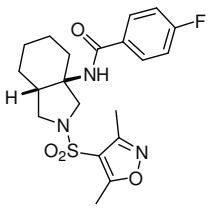
Yield: 11 %, Rt = 2.04 (method B), m/z 433.2 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm 7.76 (1H, s), 7.61 (2H, dd, *J* = 8.9, 5.5 Hz), 7.36 - 7.42 (1H, m), 7.29 - 7.34 (1H, m), 7.21 (2H, t, *J* = 8.9 Hz), 7.15 - 7.18 (1H, m), 6.96 - 6.99 (1H, m), 3.79 (1H, d, *J* = 11.1 Hz), 3.71 - 3.75 (3H, m), 3.57 (1H, d, *J* = 11.1 Hz), 3.40 (1H, dd, *J* = 9.5, 6.7 Hz), 3.13 (1H, dd, *J* = 9.5, 4.5 Hz), 2.39 - 2.43 (1H, m), 1.78 - 1.86 (1H, m), 1.68 - 1.76 (1H, m), 1.57 - 1.65 (1H, m), 1.37 - 1.48 (2H, m), 1.16 - 1.34 (3H, m). ^{19}F NMR (377 MHz, DMSO-d_6) δ/ppm -109.6 (1F, s). IR (neat) ν = 3373 (w), 3074 (w), 2925 (m), 2867 (m), 1659 (m), 1646 (m), 1601 (m), 1532 (m), 1498 (s), 1479 (s), 1433 (m), 1338 (s), 1318 (s), 1286 (s), 1240 (s), 1154 (s), 1096 (m), 1077 (m), 1039 (s), 992 (w), 886 (w), 851 (m), 791 (w), 766 (m), 694 (m) cm^{-1}. HRMS calculated for $C_{22}H_{25}FSN_2O_4$ 432.1519, found: 432.1508.

4-Fluoro-*N*-[*cis*-2-(1-methyl-1*H*-imidazole-4-sulfonyl)-octahydroisoindol-3*a*-yl]-benzamide, 13j{1,12}:



Yield: 14 %, Rt = 1.73 (method B), m/z 407.2 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm 7.89 (1H, s), 7.76 (2H, dd, *J* = 9.0, 5.5 Hz), 7.74 (1H, d, *J* = 1.3 Hz), 7.59 (1H, d, *J* = 1.1 Hz), 7.25 - 7.31 (2H, m), 3.61 (2H, s), 3.56 (1H, dd, *J* = 9.6, 7.1 Hz), 3.52 (3H, s), 3.18 (1H, dd, *J* = 9.6, 6.0 Hz), 2.40 - 2.45 (1H, m), 1.77 - 1.84 (1H, m), 1.67 - 1.77 (2H, m), 1.36 - 1.48 (2H, m), 1.21 - 1.35 (3H, m). ^{19}F NMR (377 MHz, DMSO-d_6) δ/ppm -109.4 (1F, s). IR (neat) ν = 3366 (w), 3139 (w), 3116 (w), 3063 (w), 2932 (m), 2863 (w), 1646 (m), 1603 (m), 1528 (m), 1497 (s), 1451 (m), 1330 (s), 1225 (s), 1154 (s), 1118 (s), 1069 (m), 1044 (m), 1016 (m), 962 (m), 850 (m), 801 (m), 766 (m), 691 (m) cm^{-1}. HRMS calculated for $C_{19}H_{23}FSN_4O_3$ 406.1475, found: 406.1468.

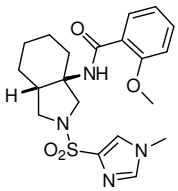
***N*-[*cis*-2-(3,5-Dimethylisoxazole-4-sulfonyl)-octahydroisoindol-3a-yl]-4-fluorobenzamide, 13j**{1,13}:



Yield: 9 %, Rt = 2.04 (method B), m/z 422.1 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm 7.94 (1H, s), 7.75 (2H, dd, *J* = 9.0, 5.5 Hz), 7.26 (2H, t, *J* = 8.9 Hz), 3.84 (1H, d, *J* = 10.9 Hz), 3.61 (1H, d, *J* = 10.9 Hz), 3.49 (1H, dd, *J* = 9.4, 6.6 Hz), 3.16 (1H, dd, *J* = 9.4, 4.4 Hz), 2.59 (3H, s), 2.47 (1H, dd, *J* = 3.6, 1.9 Hz), 2.31 (3H, s), 1.98 - 2.08 (1H, m), 1.76 - 1.84 (1H, m), 1.72 (1H, ddd, *J* = 13.9, 10.0, 3.7 Hz), 1.44 - 1.54 (2H, m), 1.35 - 1.41 (1H,

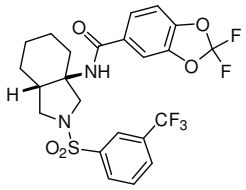
m), 1.21 - 1.33 (2H, m). ^{19}F NMR (377 MHz, DMSO-d_6) δ/ppm -109.5 (1F, s). IR (neat) ν = 3371 (w), 3306 (w), 3070 (w), 2934 (m), 2863 (w), 1661 (m), 1642 (s), 1603 (s), 1589 (s), 1532 (m), 1497 (s), 1449 (m), 1405 (m), 1370 (m), 1336 (s), 1262 (m), 1227 (s), 1174 (s), 1120 (s), 1043 (m), 984 (w), 886 (w), 850 (s), 815 (m), 766 (m), 686 (m) cm^{-1}. HRMS calculated for $C_{20}H_{24}FSN_3O_4$ 421.1472, found: 421.1470.

2-Methoxy-*N*-[*cis*-2-(1-methyl-1*H*-imidazole-4-sulfonyl)-octahydroisoindol-3a-yl]-benzamide, 13j{3,12}:



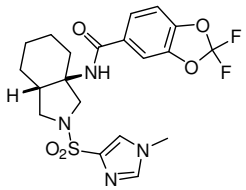
Yield: 9 %, Rt = 1.74 (method B), m/z 419.2 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm 8.01 (1H, s), 7.78 (1H, d, *J* = 1.2 Hz), 7.60 - 7.64 (2H, m), 7.45 - 7.49 (1H, m), 7.13 (1H, d, *J* = 8.2 Hz), 7.03 (1H, td, *J* = 7.5, 0.8 Hz), 3.87 (3H, s), 3.64 (1H, d, *J* = 10.4 Hz), 3.59 (3H, s), 3.46 - 3.52 (2H, m), 3.23 (1H, dd, *J* = 9.7, 7.8 Hz), 2.27 - 2.33 (1H, m), 1.85 - 1.93 (1H, m), 1.57 - 1.68 (1H, m), 1.46 - 1.54 (1H, m), 1.28 - 1.44 (5H, m). IR (neat) ν = 3371 (w), 3112 (w), 2933 (w), 2860 (w), 1649 (m), 1599 (m), 1526 (s), 1481 (m), 1336 (s), 1306 (m), 1234 (m), 1155 (s), 1117 (s), 1045 (m), 1016 (m), 961 (m), 886 (w), 845 (m), 804 (m), 757 (m), 692 (m) cm^{-1}. HRMS calculated for $C_{20}H_{26}SN_4O_4$ 418.1675, found: 418.1670.

2,2-Difluoro-*N*-(2-((3-(trifluoromethyl)phenyl)sulfonyl)octahydro-1*H*-isoindol-3a-yl)benzo[*d*][*1,3*]dioxole-5-carboxamide, 13j{6,8}:



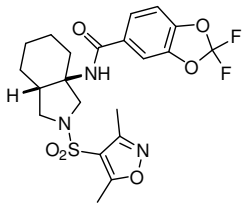
Yield: 28 %, Rt = 2.23 (method B), m/z 533.0 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm 8.05 (1H, d, *J* = 7.7 Hz), 7.91 (1H, s), 7.70 - 7.74 (2H, m), 7.66 - 7.70 (1H, m), 7.48 (1H, s), 7.40 - 7.42 (2H, m), 3.85 (1H, d, *J* = 11.3 Hz), 3.60 (1H, d, *J* = 11.4 Hz), 3.47 (1H, dd, *J* = 9.6, 6.3 Hz), 3.19 (1H, dd, *J* = 9.6, 3.6 Hz), 2.41 (1H, dd, *J* = 6.0, 2.9 Hz), 1.91 - 1.98 (1H, m), 1.69 - 1.78 (1H, m), 1.53 (1H, ddd, *J* = 13.8, 10.5, 3.6 Hz), 1.39 - 1.50 (2H, m), 1.25 - 1.35 (1H, m), 1.15 - 1.25 (2H, m). ^{19}F NMR (377 MHz, DMSO-d_6) δ/ppm -49.1 (2F, s), -61.6 (3F, s). IR (neat) ν = 3356 (w), 3078 (w), 2938 (w), 2865 (w), 1649 (m), 1629 (m), 1619 (m), 1532 (m), 1489 (s), 1440 (w), 1325 (s), 1236 (s), 1158 (s), 1124 (s), 1102 (s), 1068 (s), 1031 (m), 946 (w), 902 (m), 806 (w), 758 (m), 721 (w), 696 (m), 654 (m) cm^{-1}. HRMS calculated for $C_{23}H_{21}F_5SN_2O_5$ 532.1091, found: 532.1089.

2,2-Difluoro-*N*-(2-((1-methyl-1*H*-imidazol-4-yl)sulfonyl)octahydro-1*H*-isoindol-3*a*-yl)benzo[*d*][*1,3*]-dioxole-5-carboxamide, 13j{6,12}:



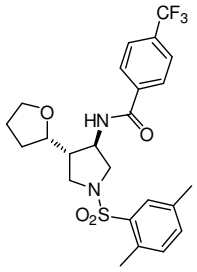
Yield: 13 %, Rt = 1.89 (method B), m/z 469.1 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm 7.92 (1H, s), 7.76 (1H, d, *J* = 1.2 Hz), 7.73 (1H, d, *J* = 1.6 Hz), 7.61 (1H, dd, *J* = 8.4, 1.7 Hz), 7.59 (1H, d, *J* = 1.0 Hz), 7.50 (1H, d, *J* = 8.4 Hz), 3.62 (1H, d, *J* = 10.8 Hz), 3.59 (1H, d, *J* = 10.8 Hz), 3.56 (3H, s), 3.54 - 3.58 (1H, m), 3.19 (1H, dd, *J* = 9.7, 6.1 Hz), 2.42 (1H, quin, *J* = 6.3 Hz), 1.78 - 1.84 (1H, m), 1.71 - 1.77 (1H, m), 1.65 - 1.71 (1H, m), 1.36 - 1.46 (2H, m), 1.21 - 1.35 (3H, m). ^{19}F NMR (377 MHz, DMSO-d_6) δ/ppm -49.5 (2F, s). IR (neat) ν = 3341 (w), 3120 (w), 3056 (w), 2928 (w), 2862 (w), 1654 (m), 1632 (m), 1528 (m), 1489 (s), 1441 (w), 1338 (m), 1233 (s), 1153 (s), 1116 (s), 1033 (m), 902 (w), 836 (w), 804 (m), 759 (m), 693 (m) cm^{-1}. HRMS calculated for $C_{20}H_{22}F_2SN_4O_5$ 468.1279, found: 468.1275.

***N*-(2-((3,5-Dimethylisoxazol-4-yl)sulfonyl)octahydro-1*H*-isoindol-3*a*-yl)-2,2-difluorobenzo[*d*][*1,3*]dioxole-5-carboxamide, 13j**{6,13}**:**



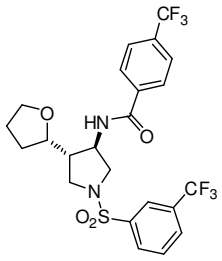
Yield: 21 %, Rt = 2.15 (method B), m/z 484.1 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6) δ/ppm 7.95 (1H, s), 7.69 (1H, d, *J* = 1.7 Hz), 7.61 (1H, dd, *J* = 8.4, 1.7 Hz), 7.49 (1H, d, *J* = 8.5 Hz), 3.83 (1H, d, *J* = 10.9 Hz), 3.61 (1H, d, *J* = 11.0 Hz), 3.50 (1H, dd, *J* = 9.4, 6.7 Hz), 3.16 (1H, dd, *J* = 9.5, 4.2 Hz), 2.59 (3H, s), 2.44 - 2.47 (1H, m), 2.31 (3H, s), 2.00 - 2.09 (1H, m), 1.75 - 1.85 (1H, m), 1.70 (1H, ddd, *J* = 14.0, 10.1, 3.9 Hz), 1.44 - 1.55 (2H, m), 1.22 - 1.42 (3H, m). ^{19}F NMR (377 MHz, DMSO-d_6) δ/ppm -49.0 (2F, s). IR (neat) ν = 3307 (w), 3073 (w), 2934 (w), 2864 (w), 1649 (m), 1619 (m), 1588 (m), 1531 (m), 1487 (s), 1441 (m), 1406 (m), 1339 (m), 1227 (s), 1173 (s), 1149 (s), 1117 (s), 1032 (s), 947 (m), 901 (m), 874 (m), 803 (m), 757 (m), 704 (w), 687 (m) cm^{-1}. HRMS calculated for $C_{21}H_{23}F_2SN_3O_6$ 483.1276, found: 483.1268.

***N*-[*trans*-1-(2,5-Dimethylbenzenesulfonyl)-4-(tetrahydrofuran-2-yl)-pyrrolidin-3-yl]-4-trifluoromethyl-benzamide, 13i'**{2,7}**:**



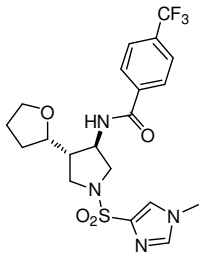
Yield: 16 %, Rt = 2.17 (method B), m/z 497.2 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6, diastereomeric mixture ~ 1:0.85) δ/ppm 8.80 (1H, d, *J* = 7.6 Hz), 8.76 (1H, d, *J* = 7.1 Hz), 7.96 - 8.03 (4H, m), 7.86 (4H, dd, *J* = 8.4, 3.4 Hz), 7.64 (2H, d, *J* = 1.4 Hz), 7.30 - 7.41 (4H, m), 4.35 - 4.40 (1H, m), 4.31 - 4.36 (1H, m), 3.62 - 3.76 (4H, m), 3.45 - 3.59 (6H, m), 3.01 - 3.18 (4H, m), 2.54 (3H, s), 2.53 (3H, s), 2.40 - 2.44 (1H, m), 2.35 (3H, s), 2.33 (3H, s), 2.28 - 2.36 (1H, m), 1.84 - 1.92 (2H, m), 1.72 - 1.81 (4H, m), 1.42 - 1.53 (2H, m). ^{19}F NMR (377 MHz, DMSO-d_6) δ/ppm -61.3 (3F, s). IR (neat) ν = 3303 (w), 2973 (w), 2871 (w), 1644 (s), 1621 (w), 1547 (s), 1493 (m), 1334 (s), 1219 (m), 1157 (s), 1119 (s), 1106 (s), 1065 (s), 1017 (s), 882 (m), 856 (m), 808 (m), 771 (m), 707 (m), 694 (m) cm^{-1}. HRMS calculated for $C_{24}H_{27}F_3SN_2O_4$ 496.1644, found: 496.1638.

***N*-[*trans*-4-(Tetrahydrofuran-2-yl)-1-(3-trifluoromethylbenzenesulfonyl)-pyrrolidin-3-yl]-4-trifluoro-methylbenzamide, 13i'**{2,8}**:**



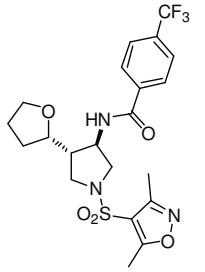
Yield: 28 %, Rt = 2.16 (method B), m/z 537.1 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6, diastereomeric mixture ~ 1:0.65) δ/ppm 8.73 (1H, d, *J* = 7.4 Hz), 8.65 (1H, d, *J* = 6.8 Hz), 7.79 - 8.18 (16H, m), 4.25 - 4.31 (1H, m), 4.20 (1H, quin, *J* = 6.9 Hz), 3.64 - 3.69 (1H, m), 3.46 - 3.59 (9H, m), 3.04 - 3.19 (4H, m), 2.41 - 2.45 (1H, m), 2.29 - 2.36 (1H, m), 1.78 - 1.88 (2H, m), 1.66 - 1.78 (4H, m), 1.38 - 1.47 (2H, m). ^{19}F NMR (377 MHz, DMSO-d_6) δ/ppm -61.4 (6F, s), -61.3 (6F, s). IR (neat) ν = 3292 (w), 3084 (w), 2959 (w), 2873 (w), 1643 (s), 1547 (s), 1508 (w),1347 (m), 1323 (s), 1283 (m), 1225 (w), 1160 (s), 1119 (s), 1064 (s), 1016 (s), 911 (w), 857 (m), 800 (m), 771 (m), 722 (m), 691 (m), 653 (m) cm^{-1}. HRMS calculated for $C_{23}H_{22}F_6SN_2O_4$ 536.1204, found: 536.1193.

***N*-[*trans*-1-(1-Methyl-1*H*-imidazole-4-sulfonyl)-4-(tetrahydrofuran-2-yl)-pyrrolidin-3-yl]-4-trifluoromethylbenzamide, 13i'**{2,12}**:**



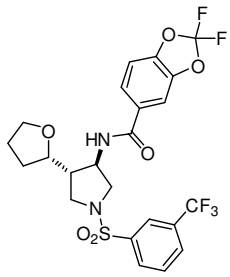
Yield: 17 %, Rt = 1.79 (method B), m/z 473.1 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6, diastereomeric mixture ~ 1:0.85) δ/ppm 8.73 (1H, d, *J* = 7.7 Hz), 8.68 (1H, d, *J* = 7.1 Hz), 7.96 - 8.03 (4H, m), 7.83 - 7.88 (7H, m), 7.81 (1H, d, *J* = 1.0 Hz), 4.28 (1H, quin, *J* = 6.5 Hz), 4.22 (1H, quin, *J* = 7.7 Hz), 3.71 (3H, s), 3.69 - 3.74 (1H, m), 3.68 (3H, s), 3.63 - 3.67 (1H, m), 3.50 - 3.63 (8H, m), 3.12 - 3.19 (2H, m), 3.08 (2H, ddd, *J* = 10.0, 8.9, 7.2 Hz), 2.41 - 2.46 (1H, m), 2.32 (1H, quin, *J* = 7.9 Hz), 1.81 - 1.89 (2H, m), 1.71 - 1.81 (4H, m), 1.40 - 1.49 (2H, m). ^{19}F NMR (377 MHz, DMSO-d_6) δ/ppm -61.3 (3F, s), -61.2 (3F, s). IR (neat) ν = 3313 (w), 3124 (w), 3030 (w), 2951 (w), 2873 (w), 1646 (m), 1529 (m), 1508 (w), 1323 (s), 1225 (w), 1158 (s), 1116 (s), 1065 (s), 1015 (m), 961 (w), 858 (m), 772 (m), 692 (m) cm^{-1}. HRMS calculated for $C_{20}H_{23}F_3SN_4O_4$ 472.1392, found: 472.1386.

_N_-[*trans*-1-(3,5-Dimethylisoxazole-4-sulfonyl)-4-(tetrahydrofuran-2-yl)-pyrrolidin-3-yl]-4-trifluoromethylbenzamide, 13i'{2,13}**:**



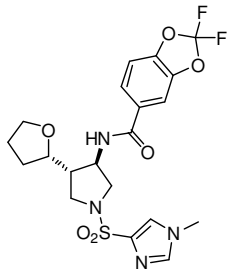
Yield: 18 %, Rt = 2.05 (method B), m/z 488.1 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6, diastereomeric mixture ~ 1:0.85) δ/ppm 8.82 (1H, d, *J* = 7.6 Hz), 8.78 (1H, d, *J* = 7.2 Hz), 7.97 - 8.04 (4H, m), 7.83 - 7.89 (4H, m), 4.40 (1H, quin, *J* = 6.3 Hz), 4.33 (1H, quin, *J* = 7.1 Hz), 3.70 - 3.79 (2H, m), 3.63 - 3.70 (2H, m), 3.48 - 3.62 (6H, m), 3.10 - 3.21 (3H, m), 3.03 (1H, dd, *J* = 10.0, 6.5 Hz), 2.64 (3H, s), 2.63 (3H, s), 2.37 (3H, s), 2.35 (3H, s), 2.33 - 2.42 (2H, m), 1.86 - 1.94 (2H, m), 1.74 - 1.83 (4H, m), 1.46 - 1.59 (2H, m). ^{19}F NMR (377 MHz, DMSO-d_6) δ/ppm -61.3 (3F, s). IR (neat) ν = 3284 (w), 3082 (w), 2944 (w), 2873 (w), 1645 (m), 1591 (m), 1546 (m), 1509 (w), 1408 (m), 1373 (m), 1324 (s), 1266 (w), 1221 (m), 1175 (m), 1164 (m), 1121 (s), 1108 (s), 1065 (s), 1015 (s), 858 (m), 814 (m), 771 (m), 684 (m) cm^{-1}. HRMS calculated for $C_{21}H_{24}F_3SN_3O_5$ 487.1389, found: 487.1387.

2,2-Difluoro-_N_-(4-(tetrahydrofuran-2-yl)-1-((3-(trifluoromethyl)phenyl)sulfonyl)pyrrolidin-3-yl)benzo[*d*][*1,3*]dioxole-5-carboxamide, 13i'{6,8}**:**



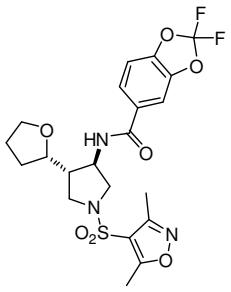
Yield: 24 %, Rt = 2.16 (method B), m/z 549.1 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6, diastereomeric mixture ~ 1:0.5) δ/ppm 8.53 (1H, d, *J* = 7.2 Hz), 8.42 (1H, d, *J* = 6.5 Hz), 8.12 - 8.17 (2H, m), 8.10 (1H, d, *J* = 7.8 Hz), 8.00 - 8.06 (3H, m), 7.90 (1H, t, *J* = 7.9 Hz), 7.86 (1H, t, *J* = 7.9 Hz), 7.76 (1H, d, *J* = 1.7 Hz), 7.70 (1H, d, *J* = 1.6 Hz), 7.68 (1H, dd, *J* = 8.4, 1.8 Hz), 7.64 (1H, dd, *J* = 8.5, 1.7 Hz), 7.46 - 7.53 (2H, m), 4.21 - 4.27 (1H, m), 4.16 (1H, quin, *J* = 6.9 Hz), 3.64 - 3.70 (2H, m), 3.44 - 3.60 (8H, m), 3.13 - 3.19 (2H, m), 3.05 - 3.12 (2H, m), 2.40 - 2.44 (1H, m), 2.31 (1H, quin, *J* = 7.1 Hz), 1.78 - 1.87 (2H, m), 1.66 - 1.77 (4H, m), 1.38 - 1.49 (2H, m). ^{19}F NMR (377 MHz, DMSO-d_6) δ/ppm -48.9 (4F, s), -61.4 (3F, s), -61.3 (3F, s). IR (neat) ν = 3308 (w), 3087 (w), 2981 (w), 2949 (w), 2876 (w), 1645 (m), 1629 (m), 1620 (m), 1549 (m), 1493 (s), 1445 (m), 1349 (m), 1325 (s), 1235 (s), 1157 (s), 1122 (s), 1098 (s), 1068 (s), 1030 (s), 943 (m), 903 (m), 885 (m), 825 (m), 801 (m), 760 (w), 721 (m), 692 (m), 653 (m) cm^{-1}. HRMS calculated for $C_{23}H_{21}F_5SN_2O_6$ 548.1040, found: 548.1033.

2,2-Difluoro-*N*-(1-((1-methyl-1*H*-imidazol-4-yl)sulfonyl)-4-(tetrahydrofuran-2-yl)pyrrolidin-3-yl)benzo-[*d*][*1,3*]dioxole-5-carboxamide, 13i'{6,12}**:**



Yield: 19 %, Rt = 1.79 (method B), m/z 485.1 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6, diastereomeric mixture ~ 1:0.9) δ/ppm 8.55 (1H, d, *J* = 7.8 Hz), 8.49 (1H, d, *J* = 7.1 Hz), 7.85 (2H, dd, *J* = 2.4, 1.3 Hz), 7.83 (1H, d, *J* = 1.0 Hz), 7.81 (1H, d, *J* = 1.6 Hz), 7.80 (2H, d, *J* = 1.4 Hz), 7.72 (2H, ddd, *J* = 8.6, 7.2, 1.7 Hz), 7.52 (2H, dd, *J* = 8.5, 1.1 Hz), 4.25 (1H, quin, *J* = 6.5 Hz), 4.19 (1H, quin, *J* = 7.7 Hz), 3.71 (3H, s), 3.69 (3H, s), 3.68 - 3.74 (1H, m), 3.63 - 3.68 (1H, m), 3.50 - 3.62 (8H, m), 3.10 - 3.18 (2H, m), 3.07 (2H, dd, *J* = 10.1, 7.2 Hz), 2.43 (1H, quin, *J* = 7.1 Hz), 2.26 - 2.33 (1H, m), 1.80 - 1.88 (2H, m), 1.70 - 1.79 (4H, m), 1.40 - 1.48 (2H, m). ^{19}F NMR (377 MHz, DMSO-d_6) δ/ppm -48.9 (2F, s). IR (neat) ν = 3348 (w), 3121 (w), 2956 (w), 2873 (w), 1653 (m), 1618 (m), 1529 (m), 1491 (s), 1443 (m), 1339 (m), 1231 (s), 1152 (s), 1115 (s), 1029 (s), 962 (m), 902 (m), 834 (w), 757 (m), 691 (m) cm^{-1}. HRMS calculated for $C_{20}H_{22}F_2SN_4O_6$ 484.1228, found: 484.1231.

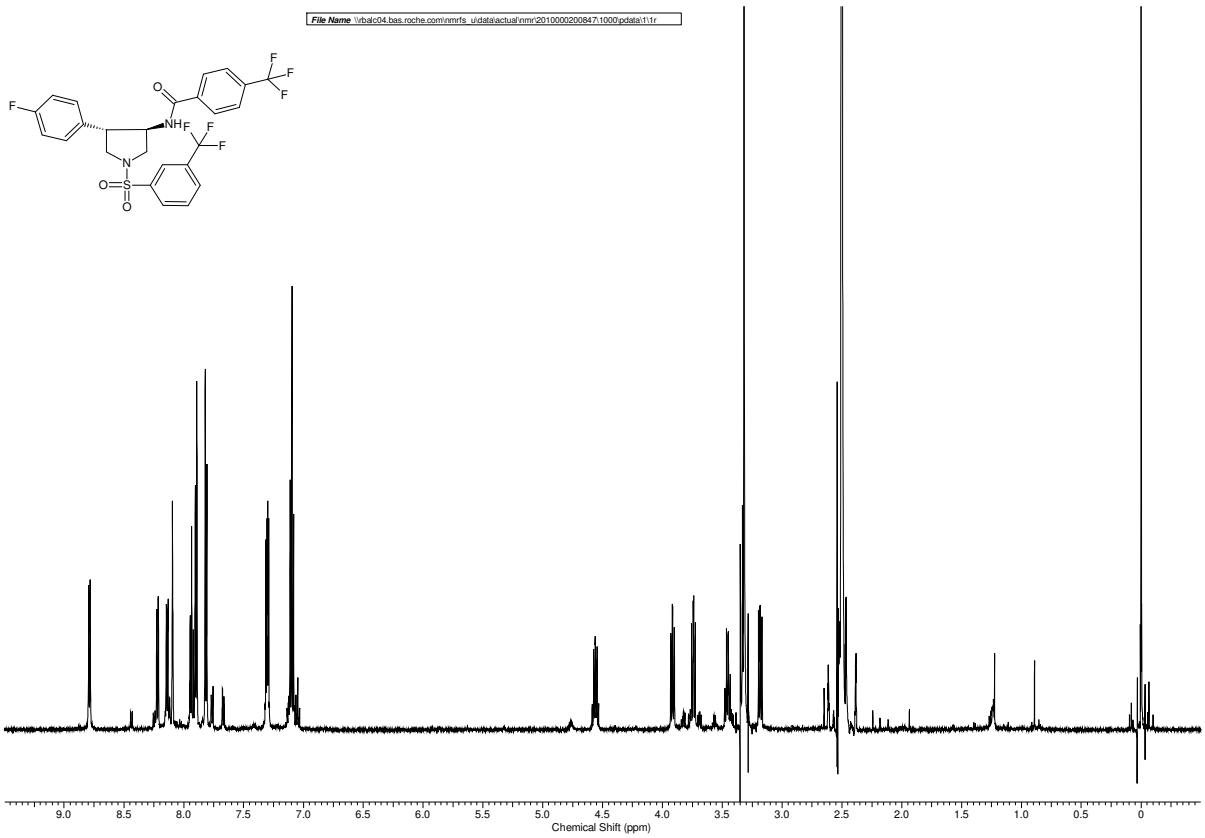
***N*-(1-((3,5-dimethylisoxazol-4-yl)sulfonyl)-4-(tetrahydrofuran-2-yl)pyrrolidin-3-yl)-2,2-difluorobenzo-[*d*][*1,3*]dioxole-5-carboxamide, 13i'**{6,13}**:**



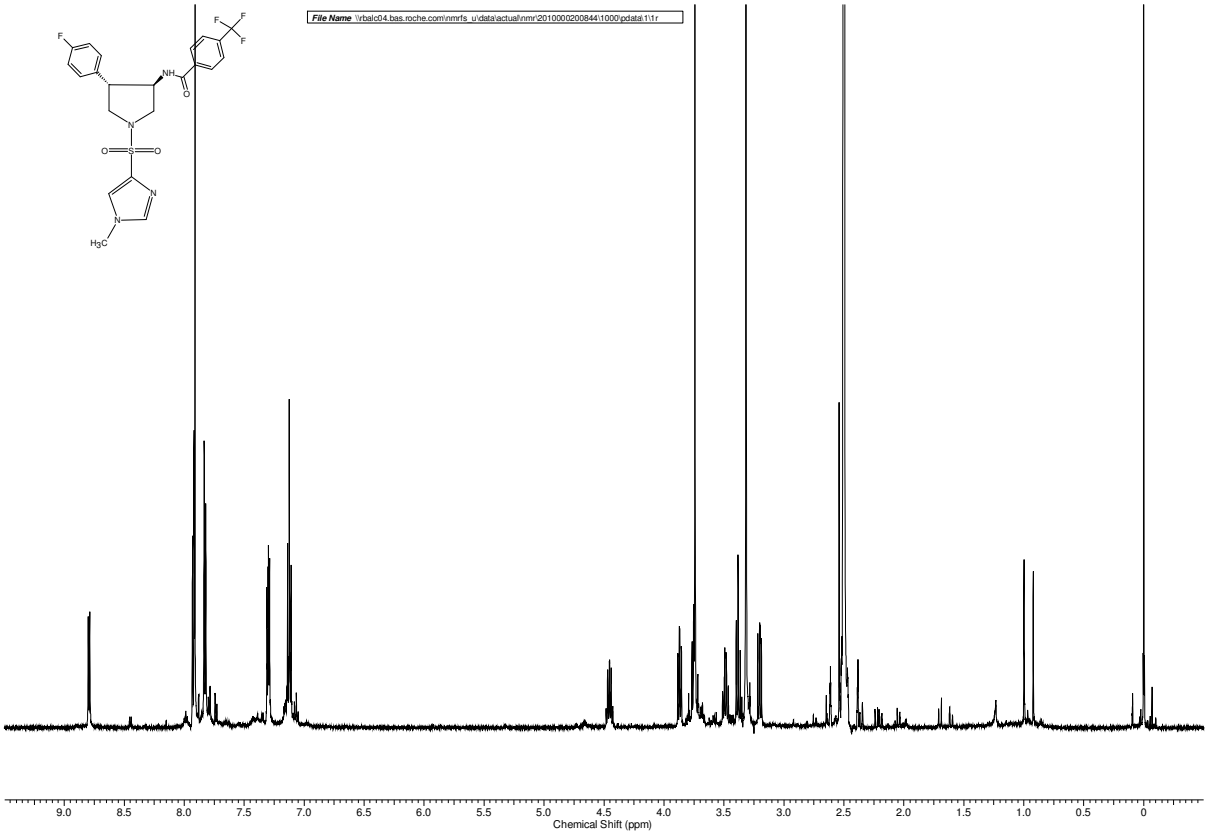
Yield: 18 %, Rt = 2.05 (method B), m/z 500.1 [M+H+]. ^{1}H NMR (600 MHz, DMSO-d_6, diastereomeric mixture ~ 1:0.75) δ/ppm 8.63 (1H, d, *J* = 7.5 Hz), 8.58 (1H, d, *J* = 7.0 Hz), 7.83 (1H, d, *J* = 1.7 Hz), 7.80 (1H, d, *J* = 1.7 Hz), 7.70 - 7.75 (2H, m), 7.51 - 7.54 (2H, m), 4.33 - 4.38 (1H, m), 4.29 (1H, quin, *J* = 7.1 Hz), 3.70 - 3.78 (2H, m), 3.63 - 3.69 (2H, m), 3.47 - 3.61 (6H, m), 3.08 - 3.21 (3H, m), 3.03 (1H, dd, *J* = 10.0, 6.3 Hz), 2.64 (3H, s), 2.63 (3H, s), 2.37 - 2.41 (2H, m), 2.36 (3H, s), 2.34 (3H, s), 1.85 - 1.93 (2H, m), 1.72 - 1.84 (4H, m), 1.46 - 1.58 (2H, m). ^{19}F NMR (377 MHz, DMSO-d_6) δ/ppm -48.9 (2F, s). IR (neat) ν = 3281 (w), 3085 (w), 2975 (w), 2871 (w), 1647 (m), 1630 (m), 1591 (m), 1547 (m), 1493 (s), 1440 (m), 1408 (m), 1373 (m), 1336 (s), 1235 (s), 1174 (s), 1145 (s), 1030 (s), 945 (m), 903 (m), 811 (m), 758 (m), 684 (m) cm^{-1}. HRMS calculated for $C_{21}H_{23F2}SN_3O_7$ 499.1225, found: 499.1234.

NMR Spectra:

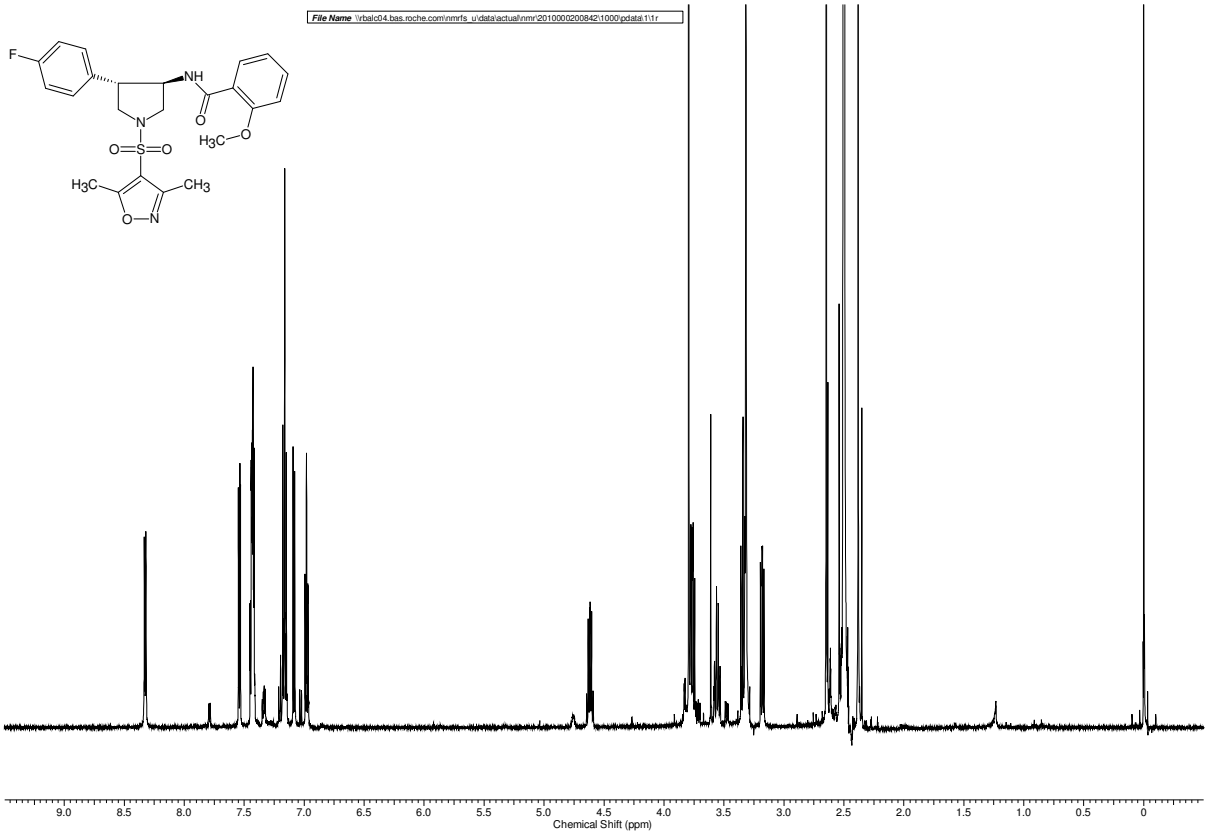
***N*-[*trans*-4-(4-Fluorophenyl)-1-(3-trifluoromethylbenzenesulfonyl)-pyrrolidin-3-yl]-4-trifluoromethyl-benzamide, 13f**{2,8}:



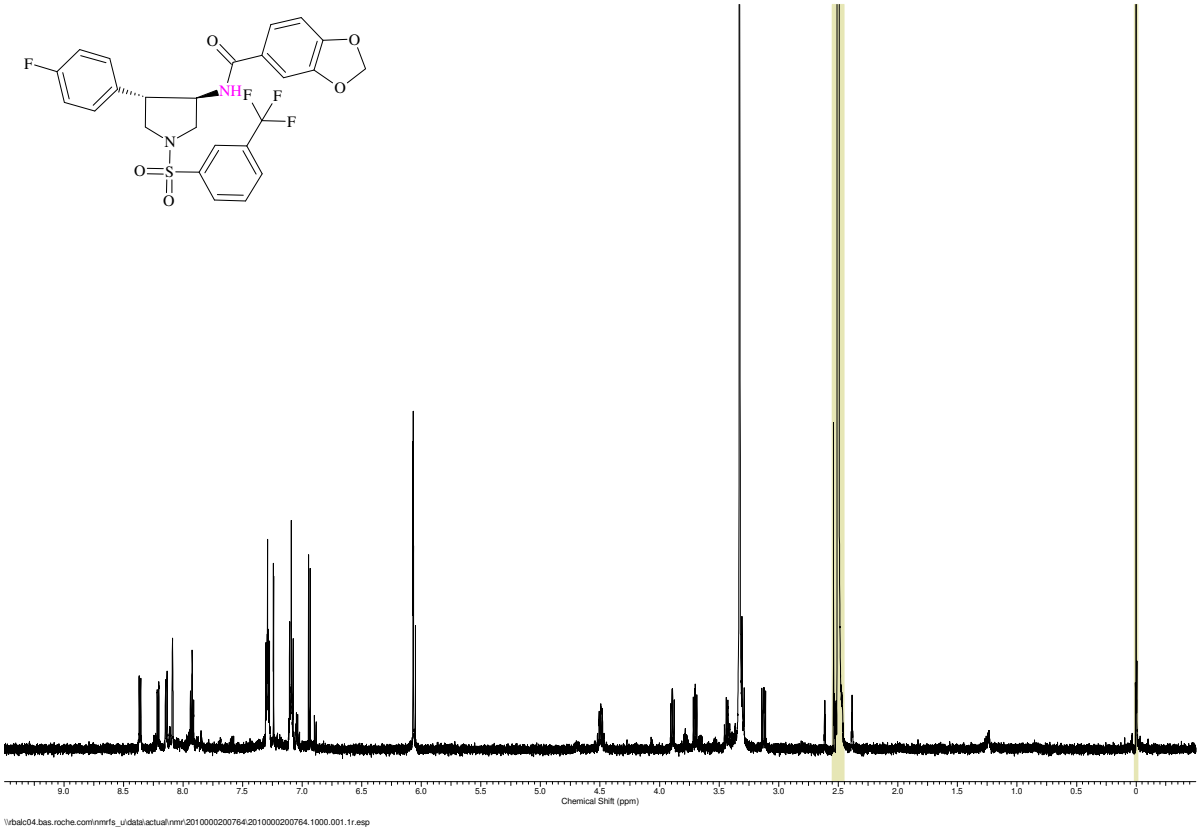
***N*-[*trans*-4-(4-Fluorophenyl)-1-(1-methyl-1*H*-imidazole-4-sulfonyl)pyrrolidin-3-yl]-4-trifluoromethyl-benzamide, 13f**{2,12}:



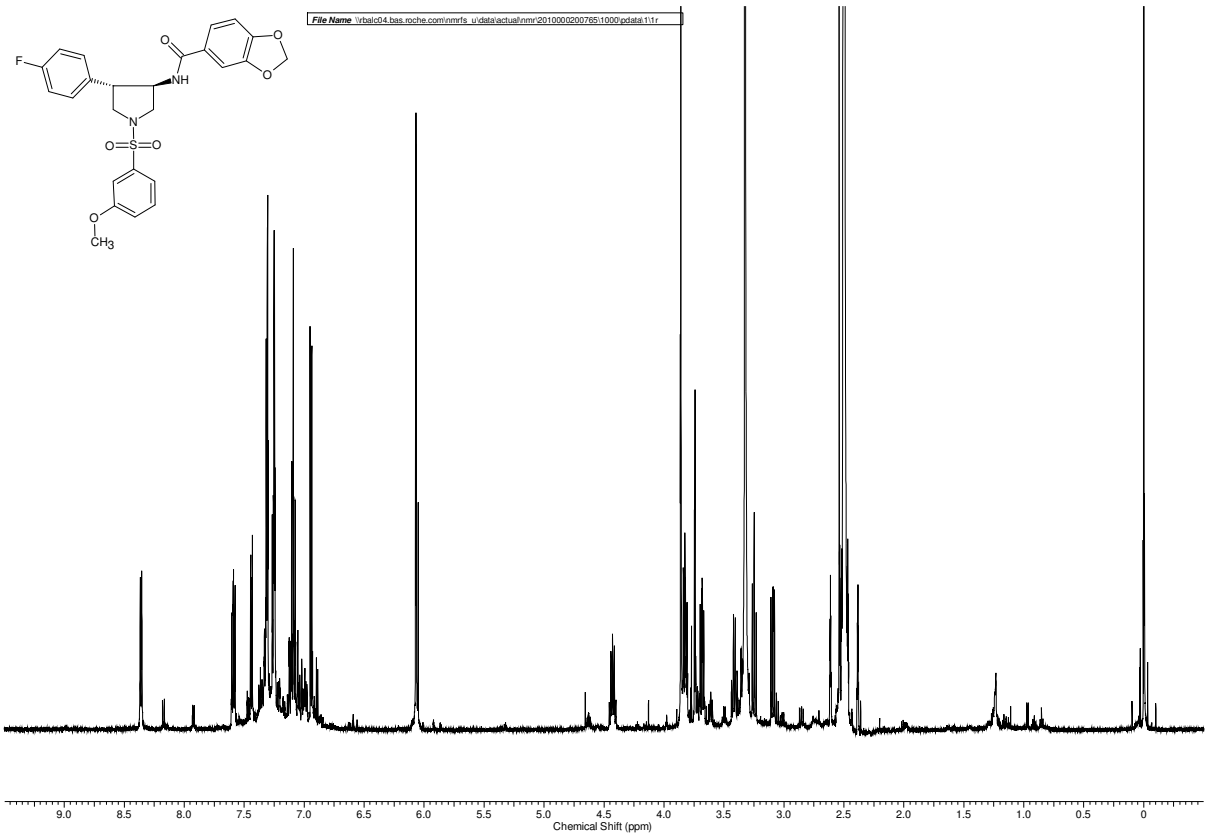
***N*-[*trans*-1-(3,5-Dimethylisoxazole-4-sulfonyl)-4-(4-fluorophenyl)pyrrolidin-3-yl]-2-methoxybenzamide, 13f**{3,13}:



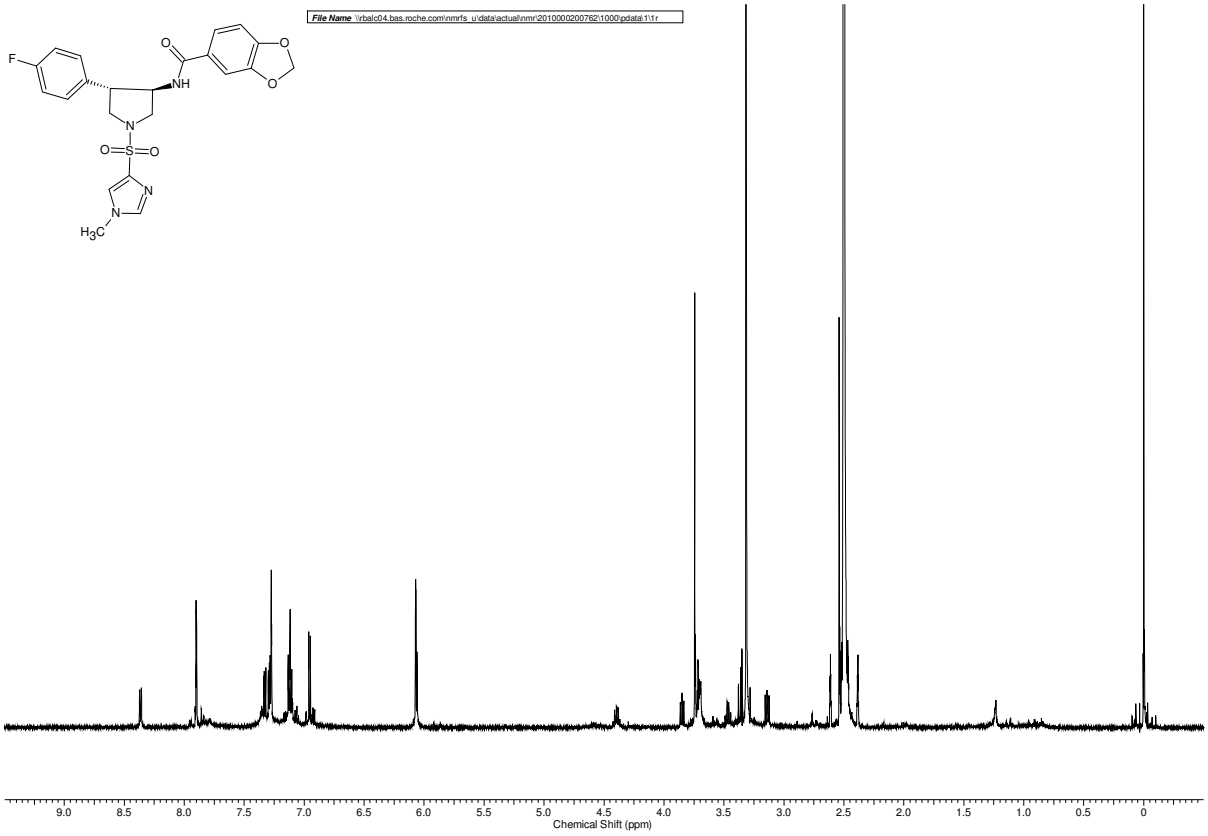
***N*-(4-(4-fluorophenyl)-1-((3-(trifluoromethyl)phenyl)sulfonyl)pyrrolidin-3-yl)benzo[*d*][*1,3*]dioxole-5-carboxamide, 13f**{5,8}:



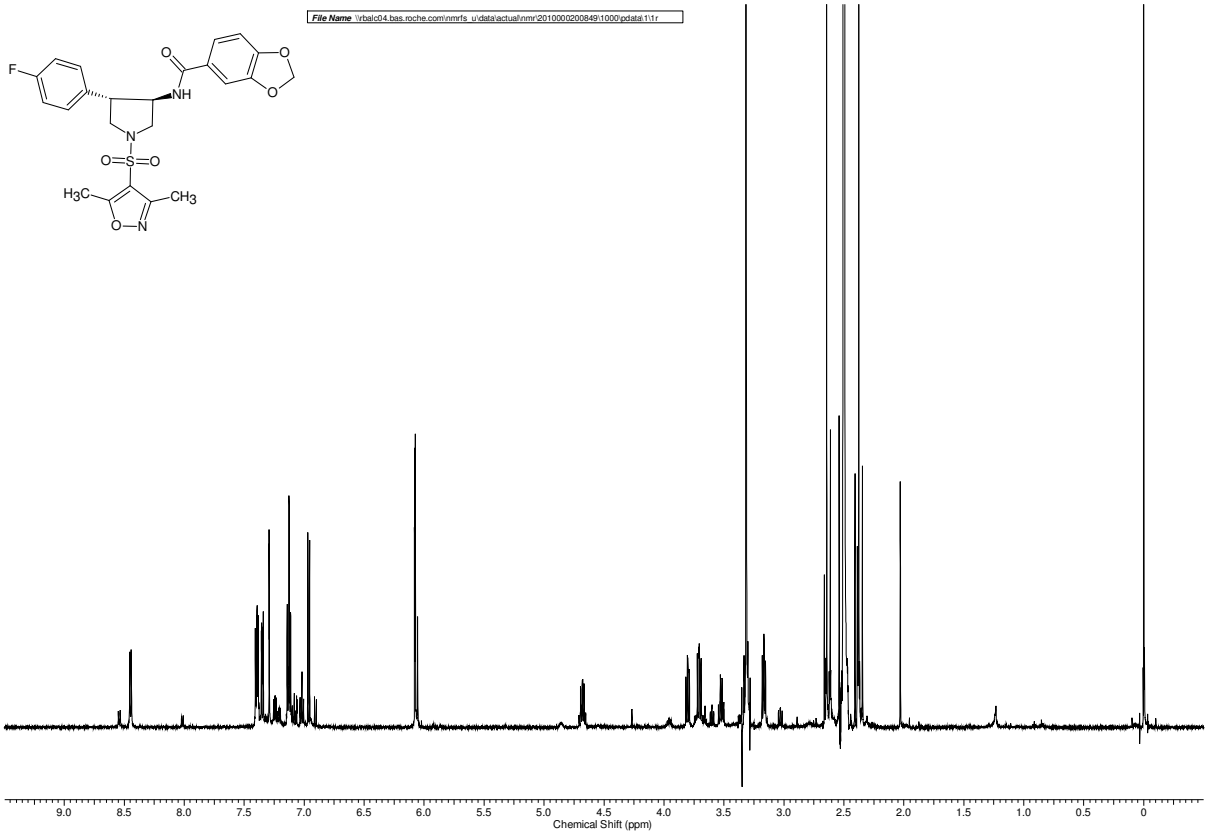
***N*-(4-(4-fluorophenyl)-1-((3-methoxyphenyl)sulfonyl)pyrrolidin-3-yl)benzo[*d*][*1,3*]dioxole-5-carboxamide, 13f**{5,9}:



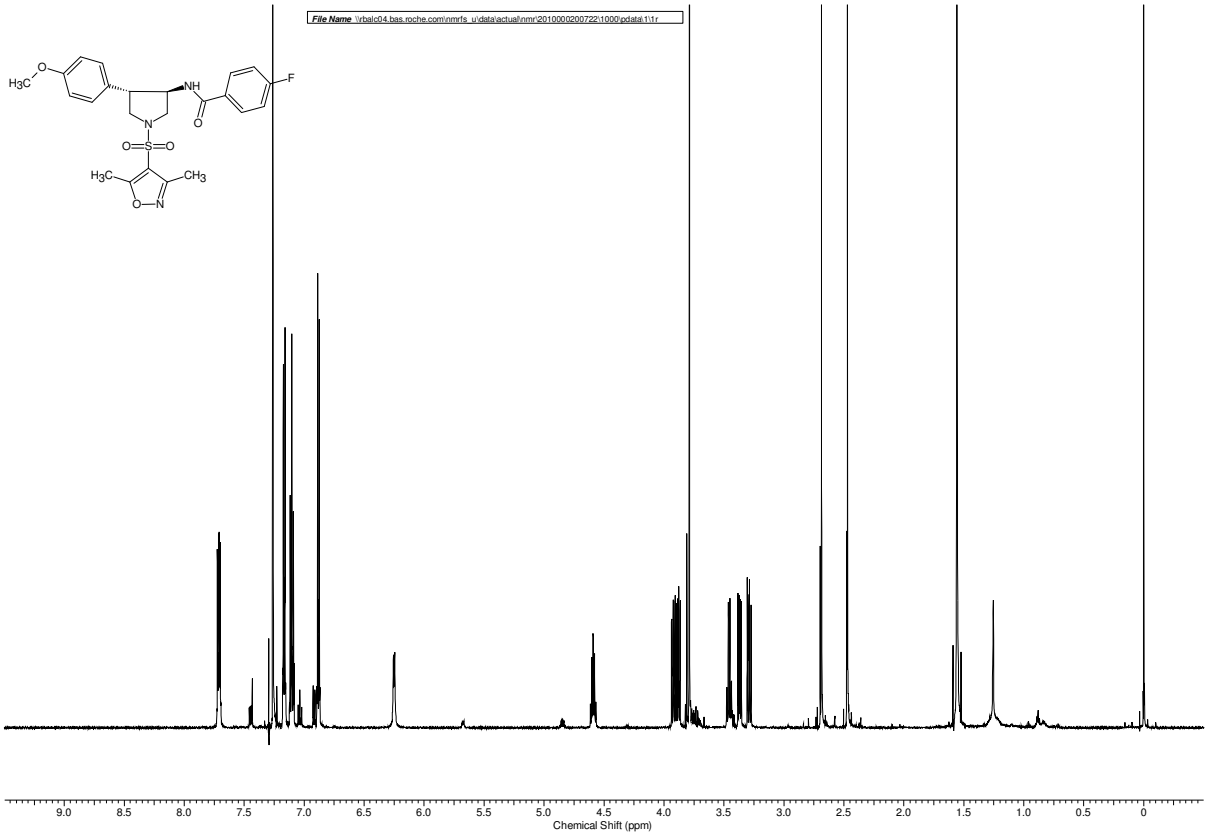
***N*-(4-(4-fluorophenyl)-1-((1-methyl-1*H*-imidazol-4-yl)sulfonyl)pyrrolidin-3-yl)benzo[*d*][*1,3*]dioxole-5-carboxamide, 13f**{5,12}**:**



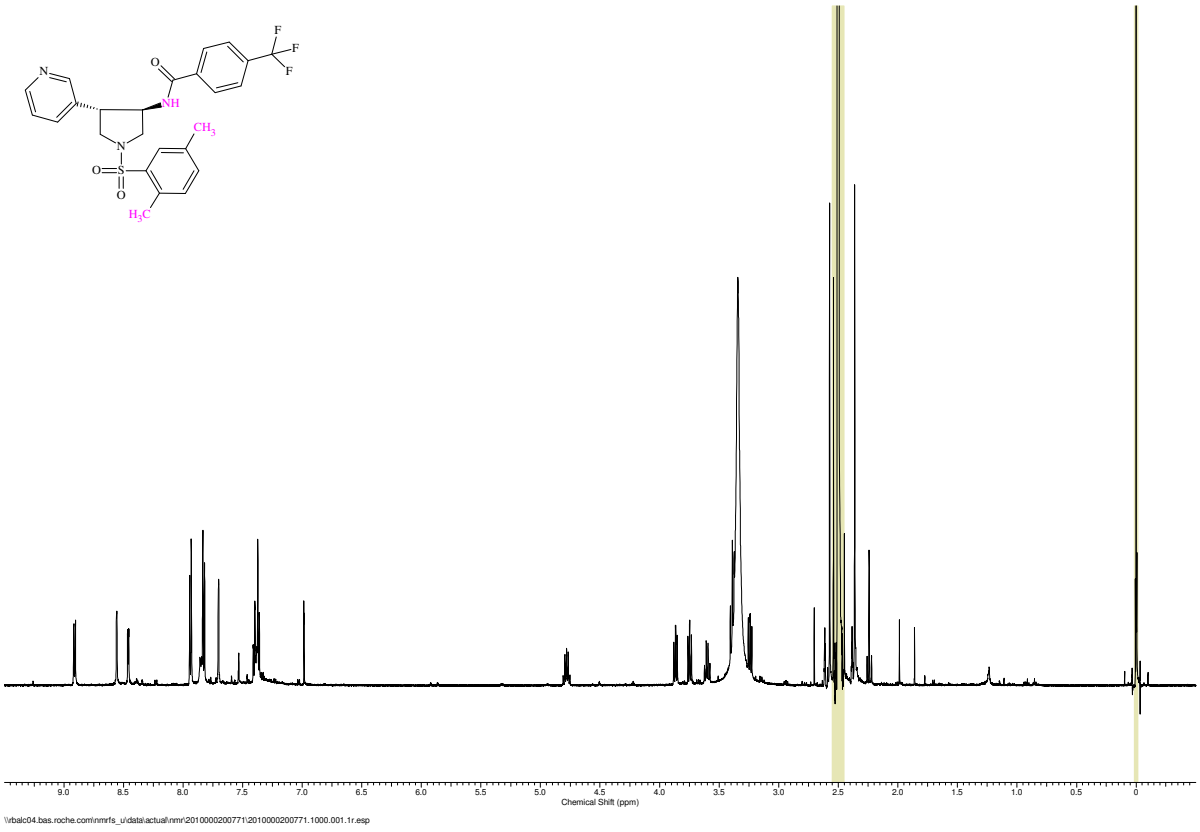
***N*-(1-((3,5-dimethylisoxazol-4-yl)sulfonyl)-4-(4-fluorophenyl)pyrrolidin-3-yl)benzo[*d*][*1,3*]dioxole-5-carboxamide, 13f**{5,13}**:**



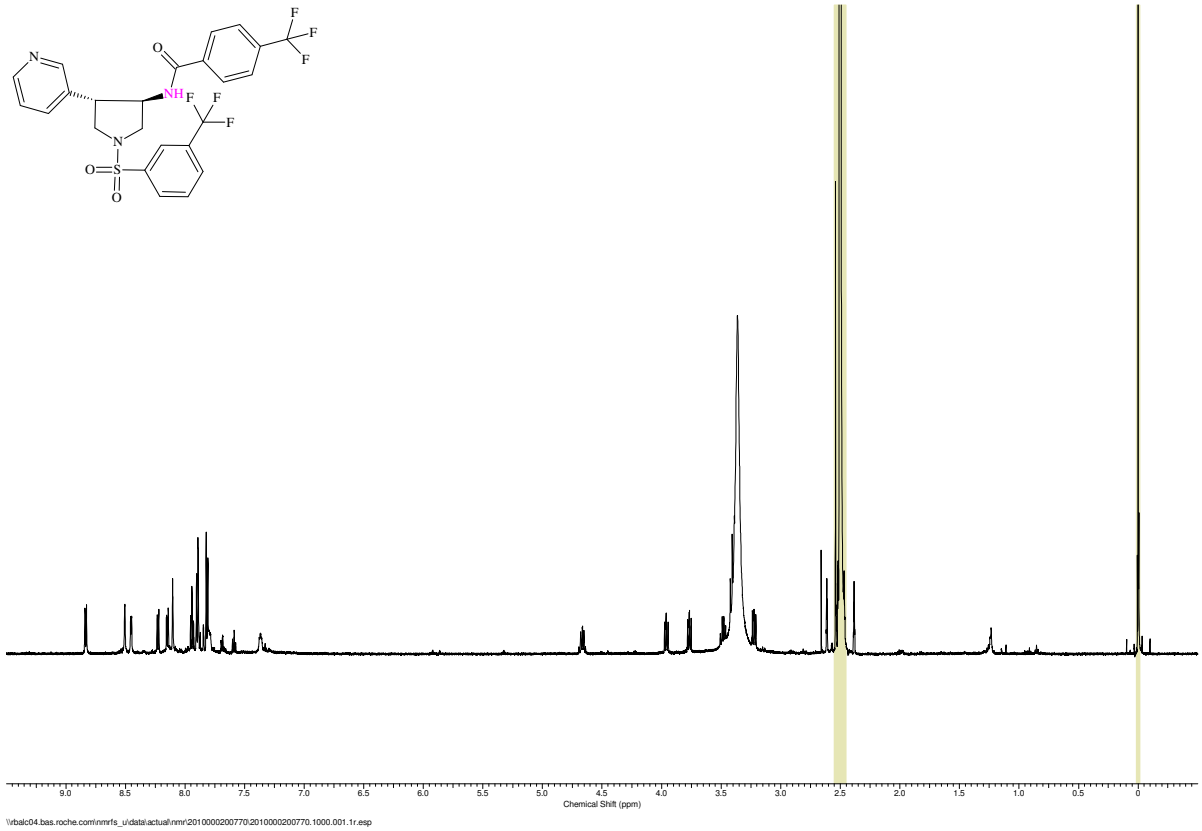
***N*-[*trans*-1-(3,5-Dimethylisoxazole-4-sulfonyl)-4-(4-methoxyphenyl)-pyrrolidin-3-yl]-4-fluorobenzamide, 13g**{1,13}:



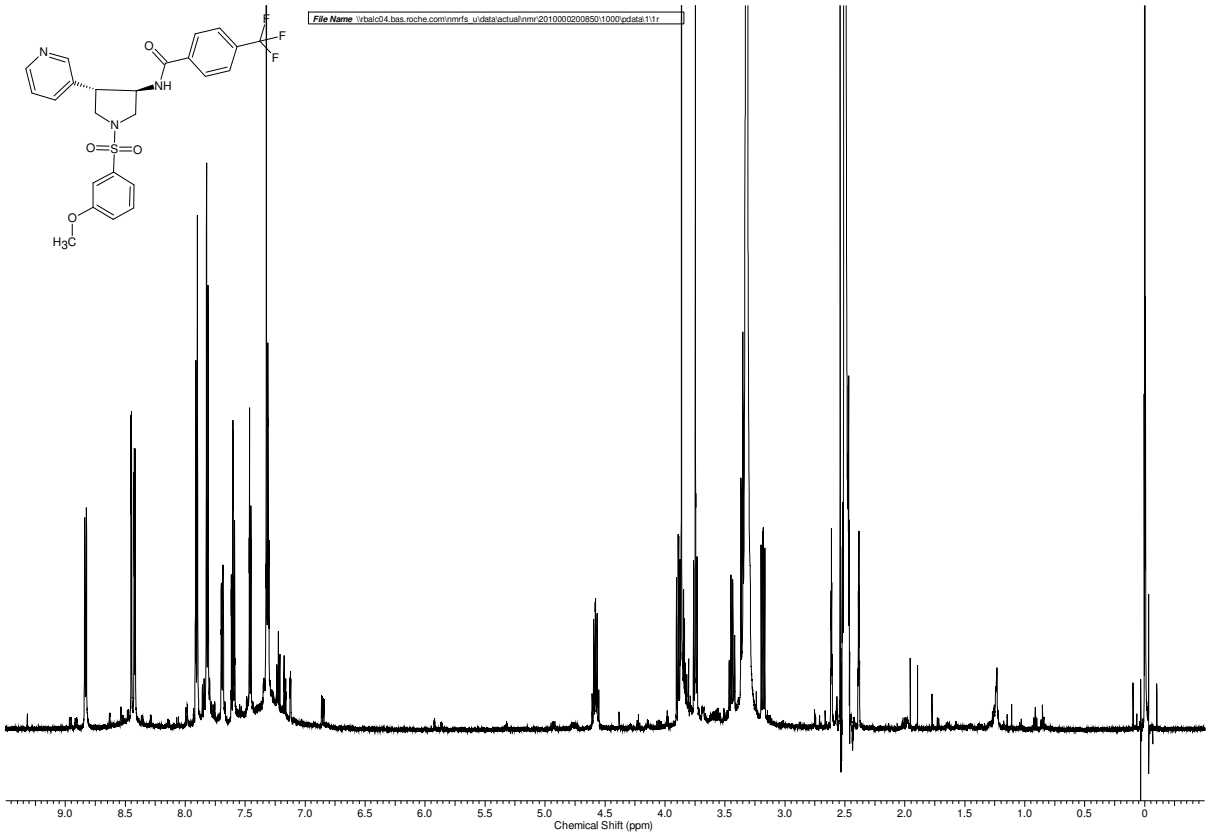
***N*-[*trans*-1-(2,5-Dimethylbenzenesulfonyl)-4-pyridin-3-yl-pyrrolidin-3-yl]-4-trifluoromethylbenzamide, 13h**{2,7}**:**



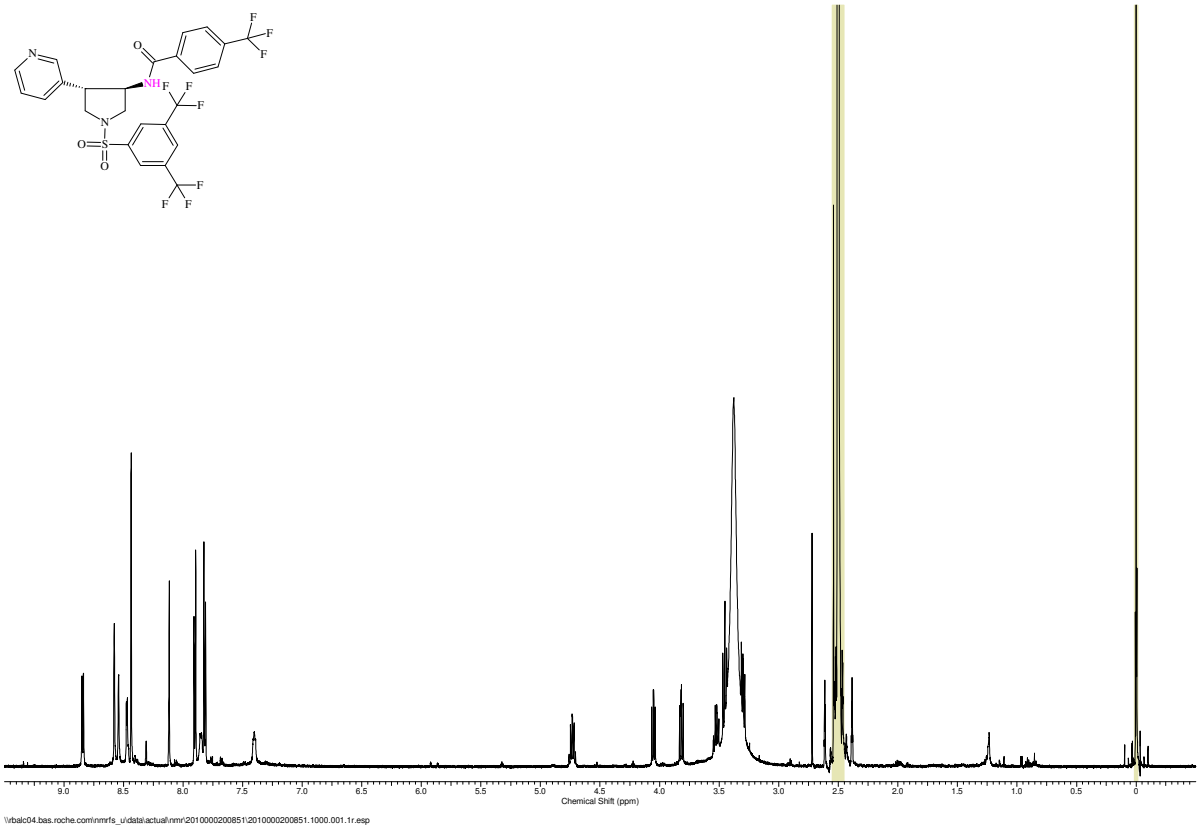
***N*-[*trans*-4-pyridin-3-yl-1-(3-trifluoromethylbenzenesulfonyl)-pyrrolidin-3-yl]-4-trifluoromethyl-benzamide, 13h**{2,8}**:**



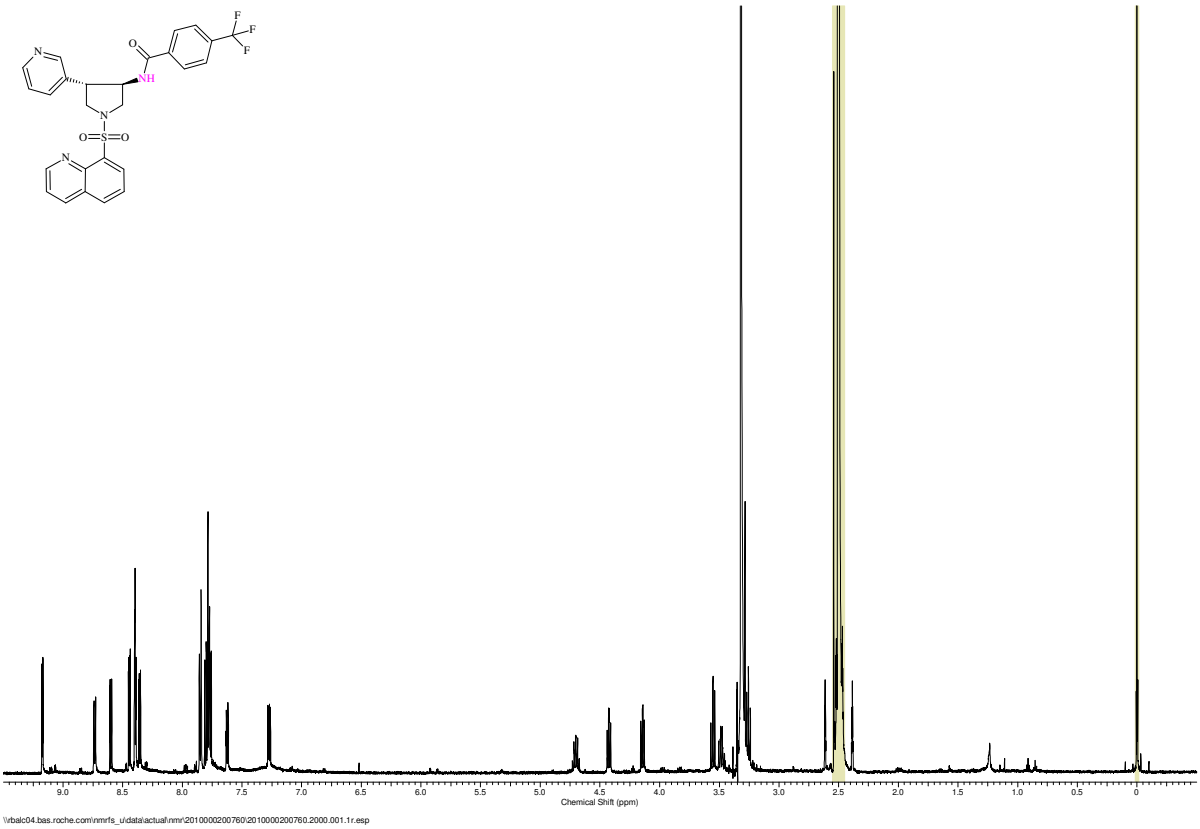
***N*-[*trans*-1-(3-methoxybenzenesulfonyl)-4-pyridin-3-yl-pyrrolidin-3-yl]-4-trifluoromethylbenzamide, 13h**{2,9}**:**



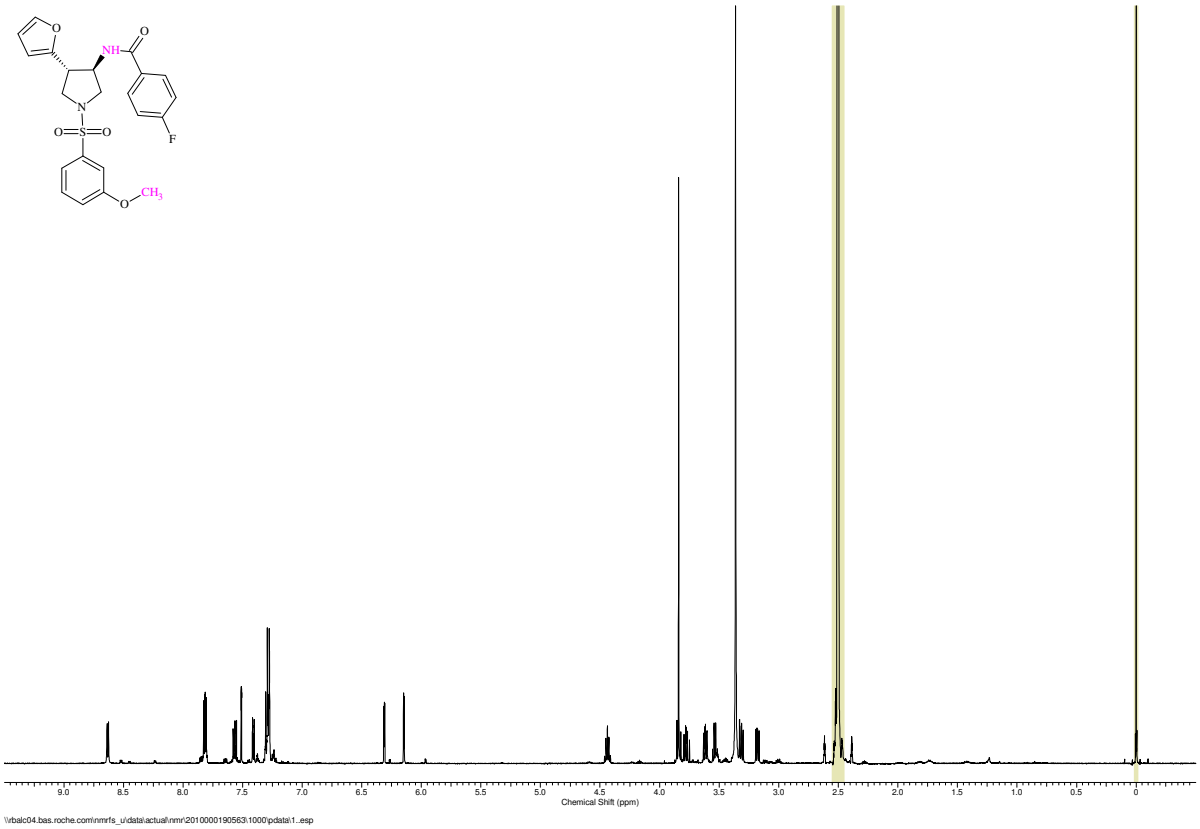
***N*-[*trans*-1-(3,5-bis-trifluoromethylbenzenesulfonyl)-4-pyridin-3-yl-pyrrolidin-3-yl]-4-trifluoromethyl-benzamide, 13h**{2,10}**:**



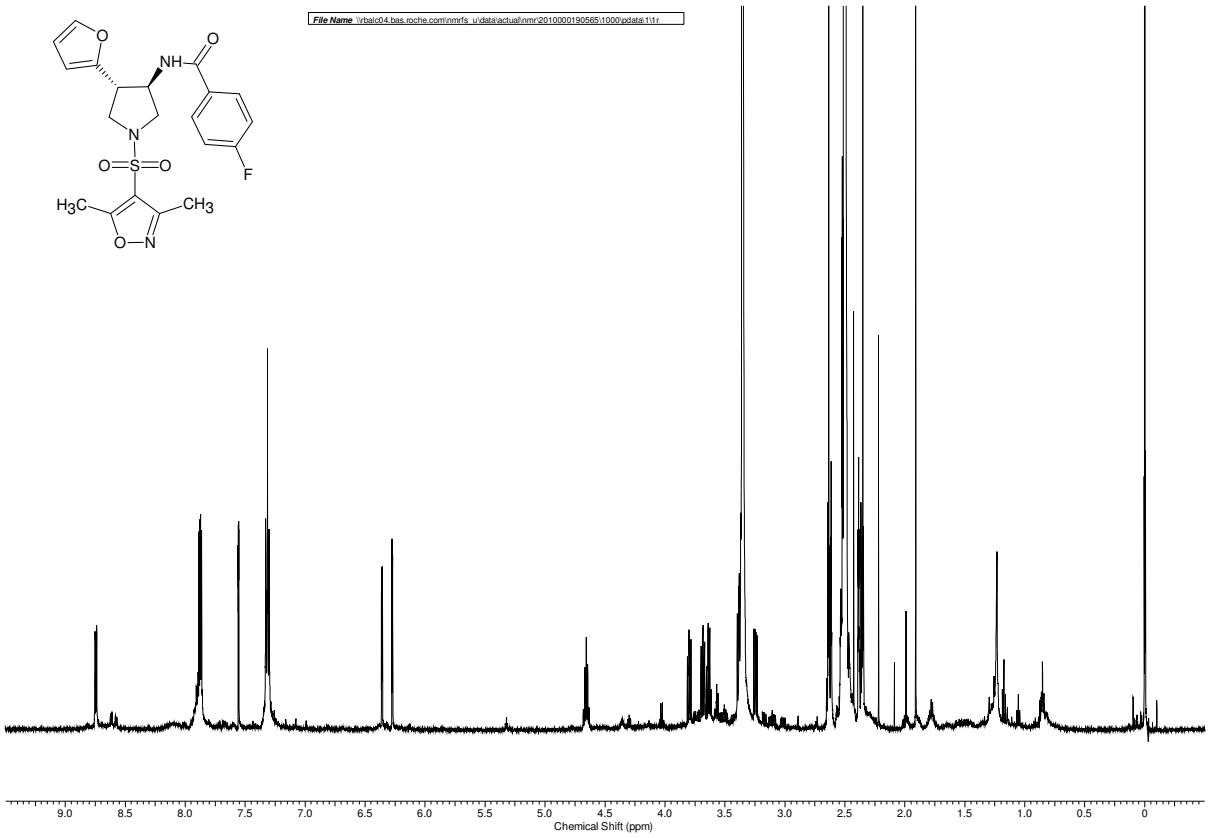
***N*-[*trans*-4-pyridin-3-yl-1-(quinoline-8-sulfonyl)-pyrrolidin-3-yl]-4-trifluoromethylbenzamide, 13h**{2,11}:



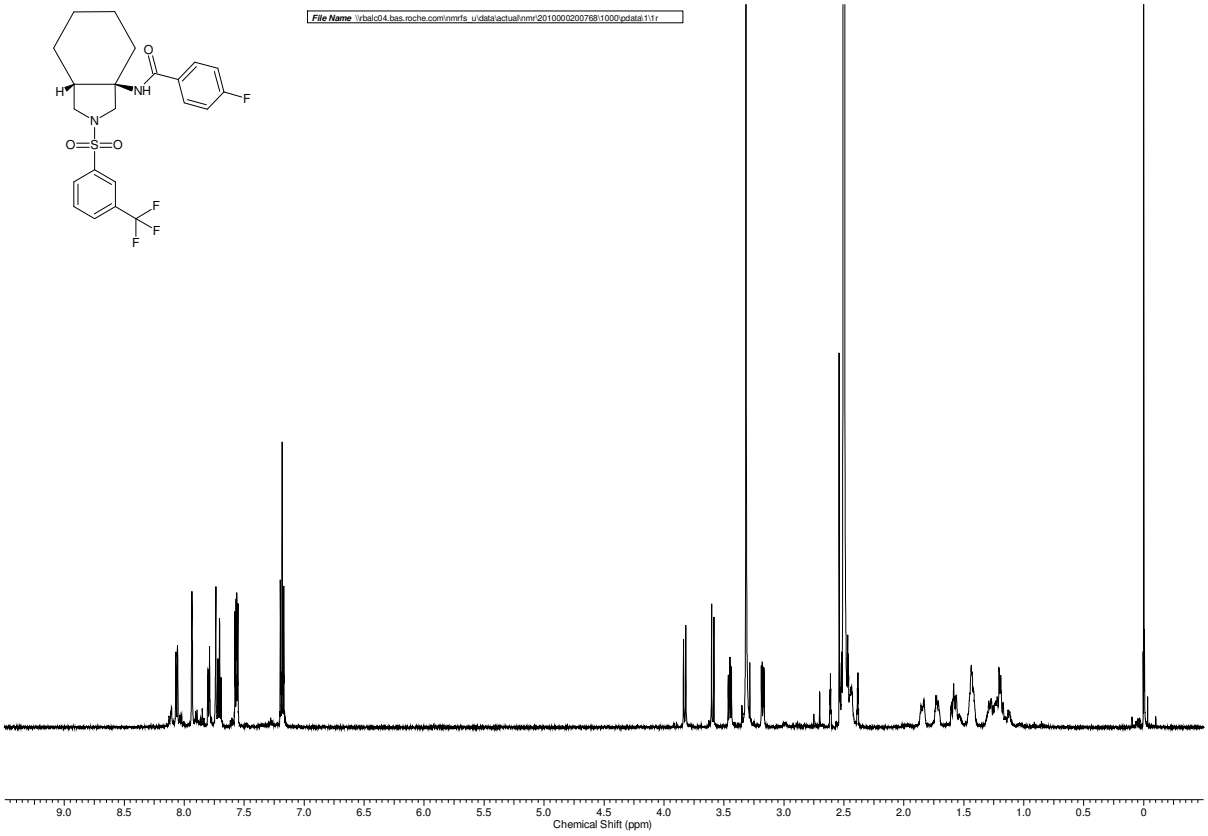
4-Fluoro-*N*-[*trans*-4-furan-2-yl-1-(3-methoxybenzenesulfonyl)-pyrrolidin-3-yl]-benzamide, 13i{1,9}:



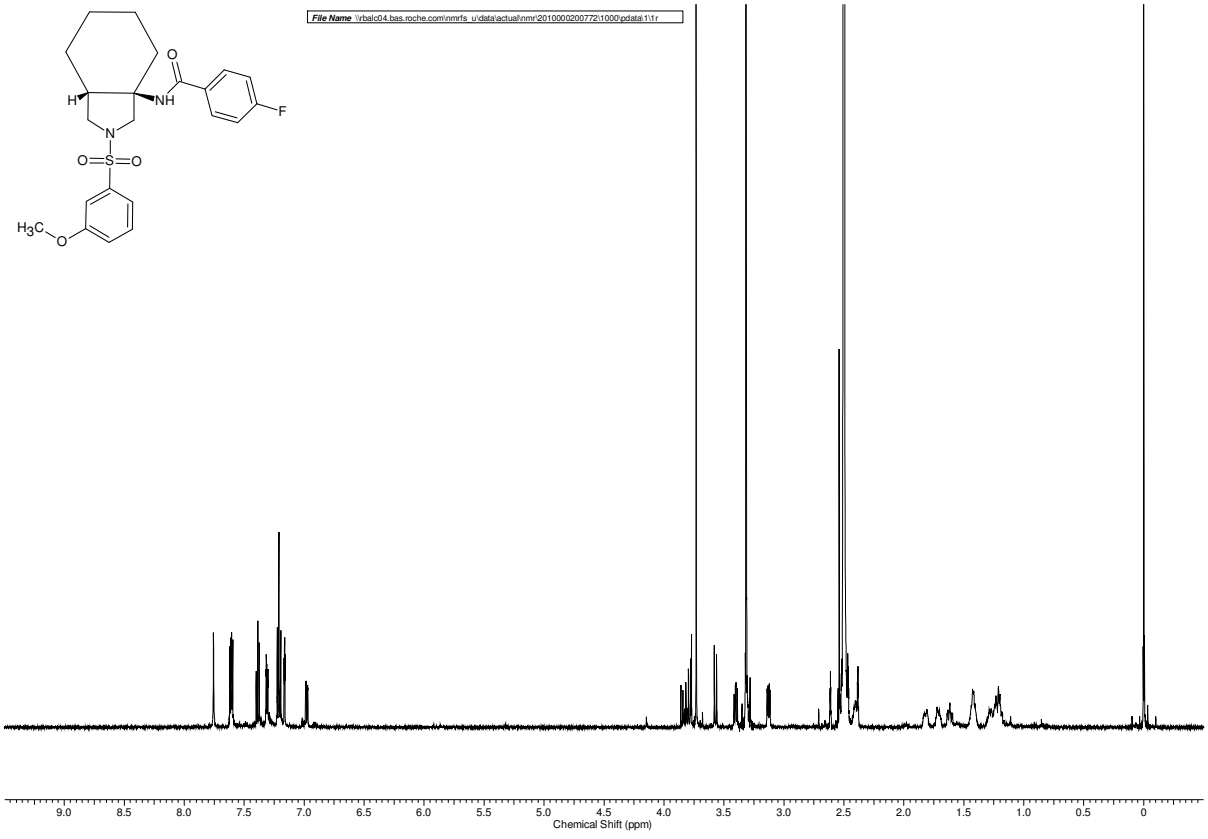
***N*-[*trans*-1-(3,5-Dimethylisoxazole-4-sulfonyl)-4-furan-2-yl-pyrrolidin-3-yl]-4-fluorobenzamide, 3i**{1,13}**:**



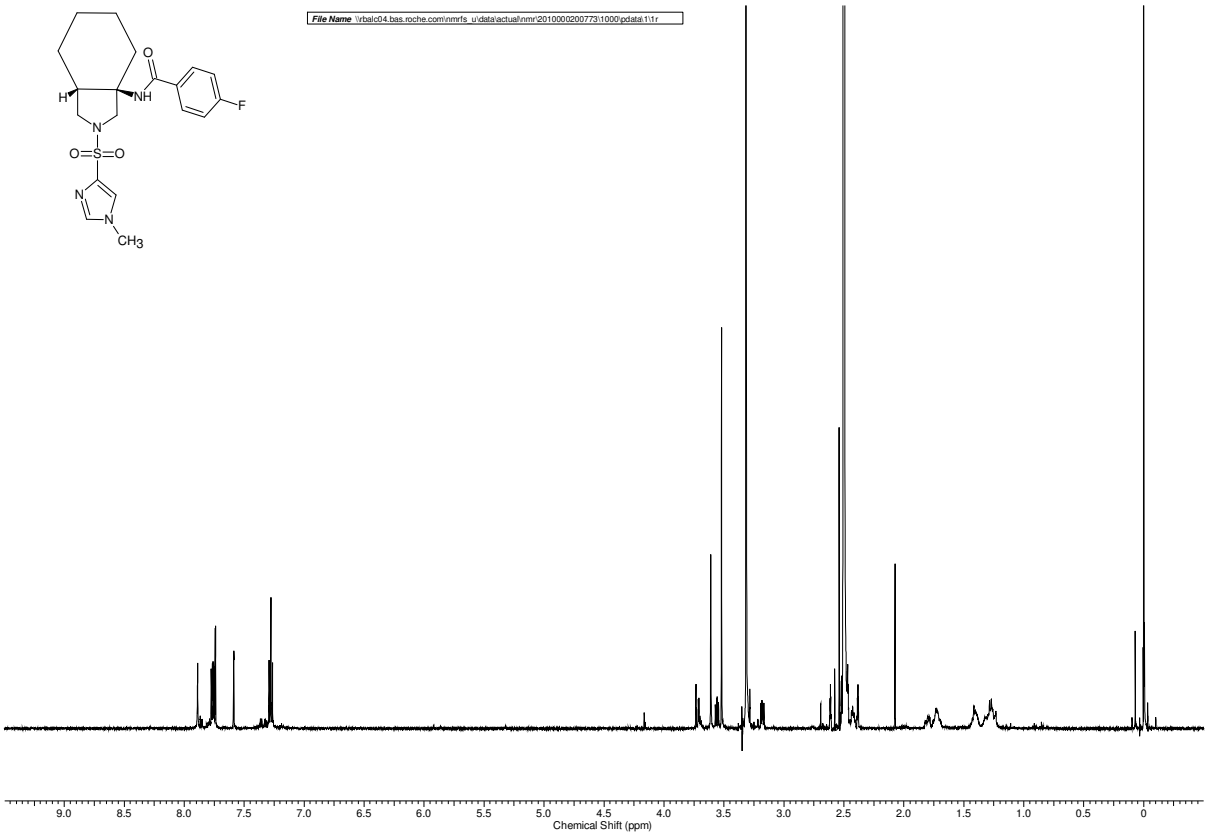
4-Fluoro-*N*-(*cis*-2-(3-trifluoromethylbenzenesulfonyl)-octahydroisoindol-3*a*-yl]-benzamide, 13j{1,8}:



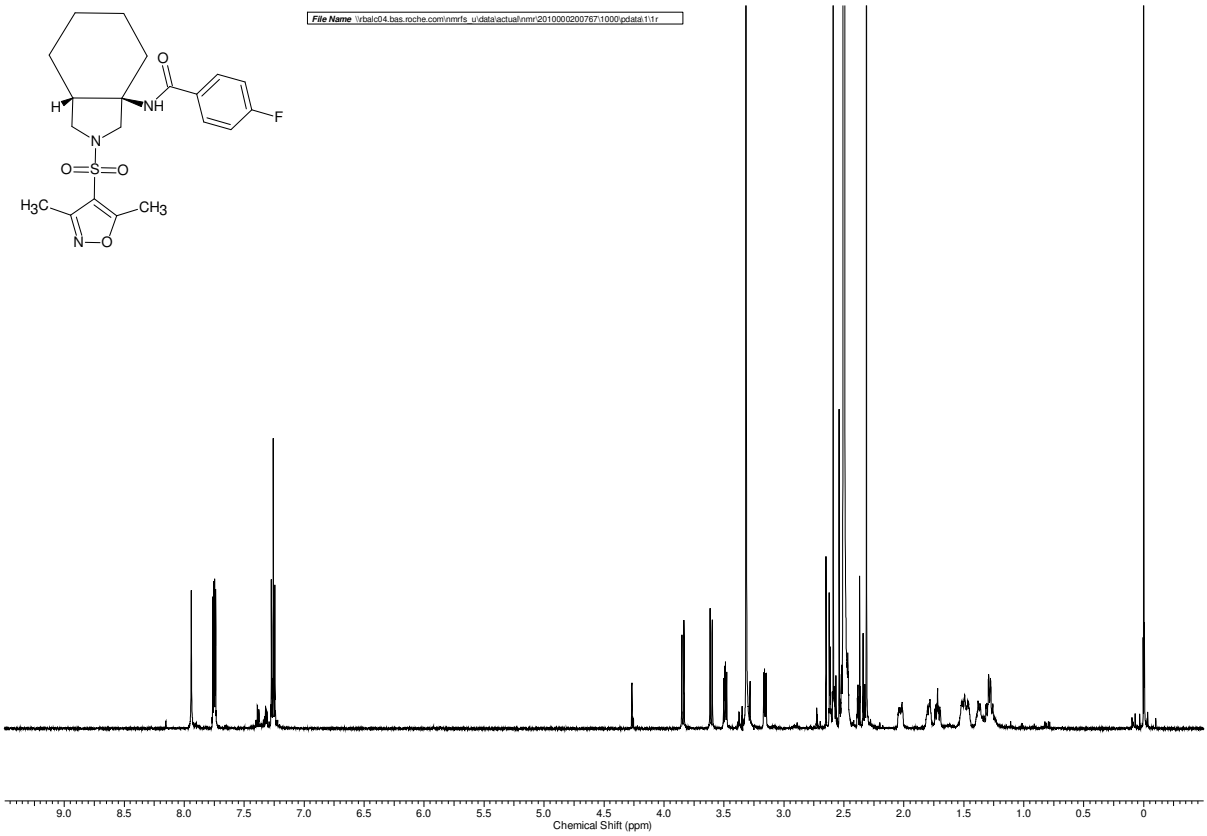
4-Fluoro-*N*-[*cis*-2-(3-methoxybenzenesulfonyl)octahydroisoindol-3*a*-yl]-benzamide, 13j{1,9}:



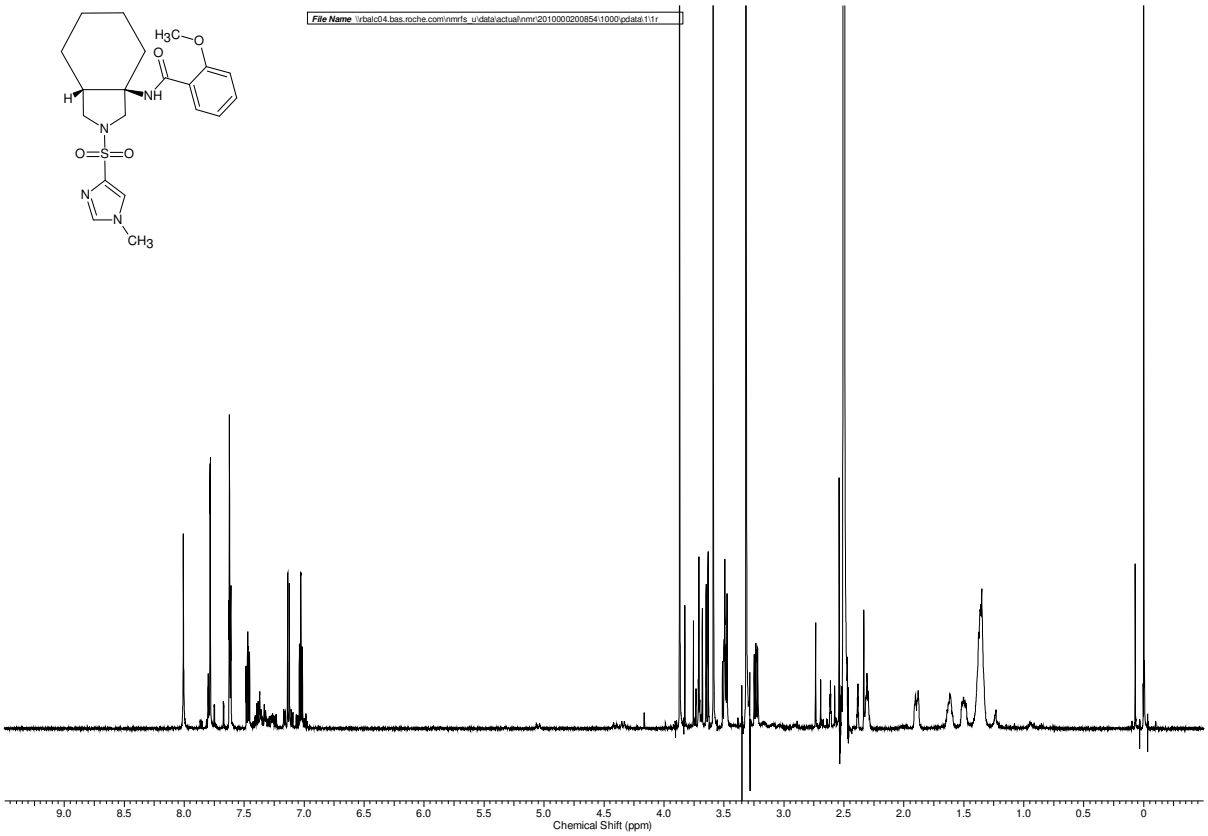
4-Fluoro-*N*-[*cis*-2-(1-methyl-1*H*-imidazole-4-sulfonyl)-octahydroisoindol-3*a*-yl]-benzamide, 13j{1,12}:



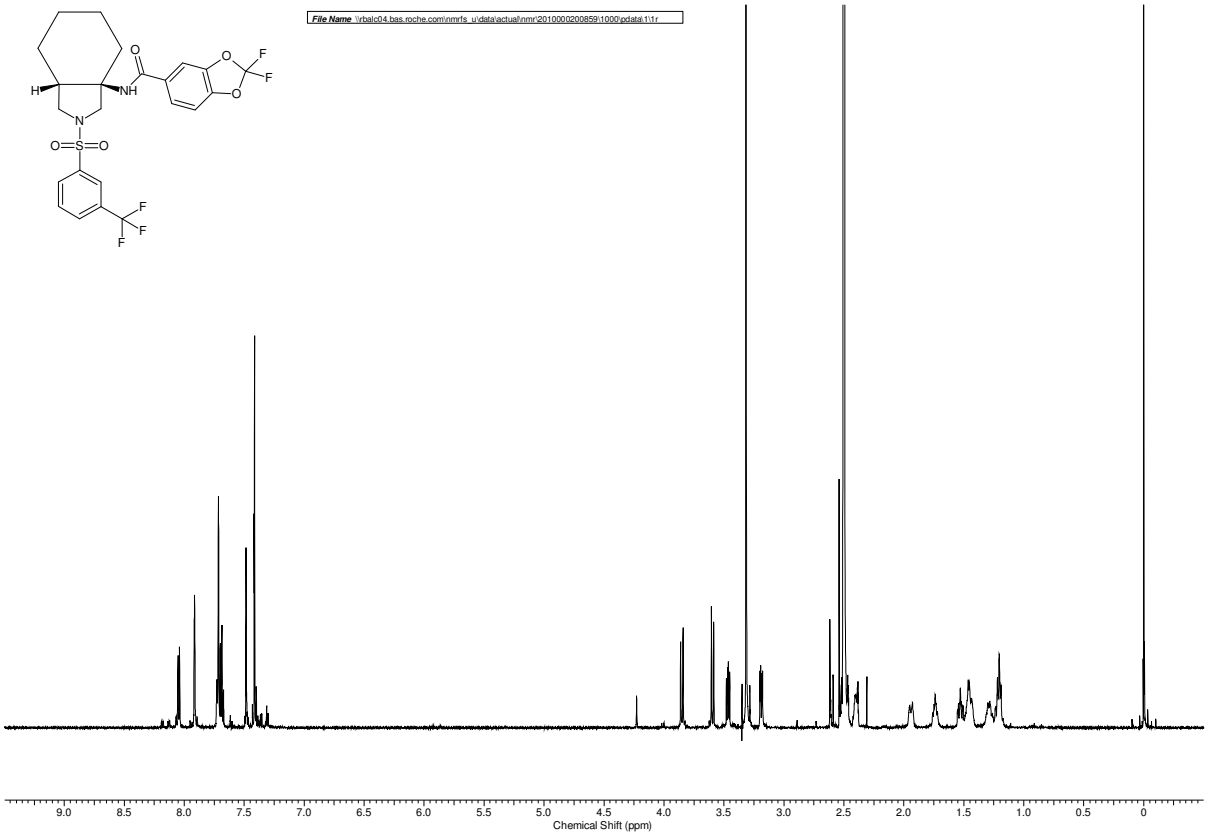
***N*-[*cis*-2-(3,5-Dimethylisoxazole-4-sulfonyl)-octahydroisoindol-3a-yl]-4-fluorobenzamide, 13j**{1,13}:



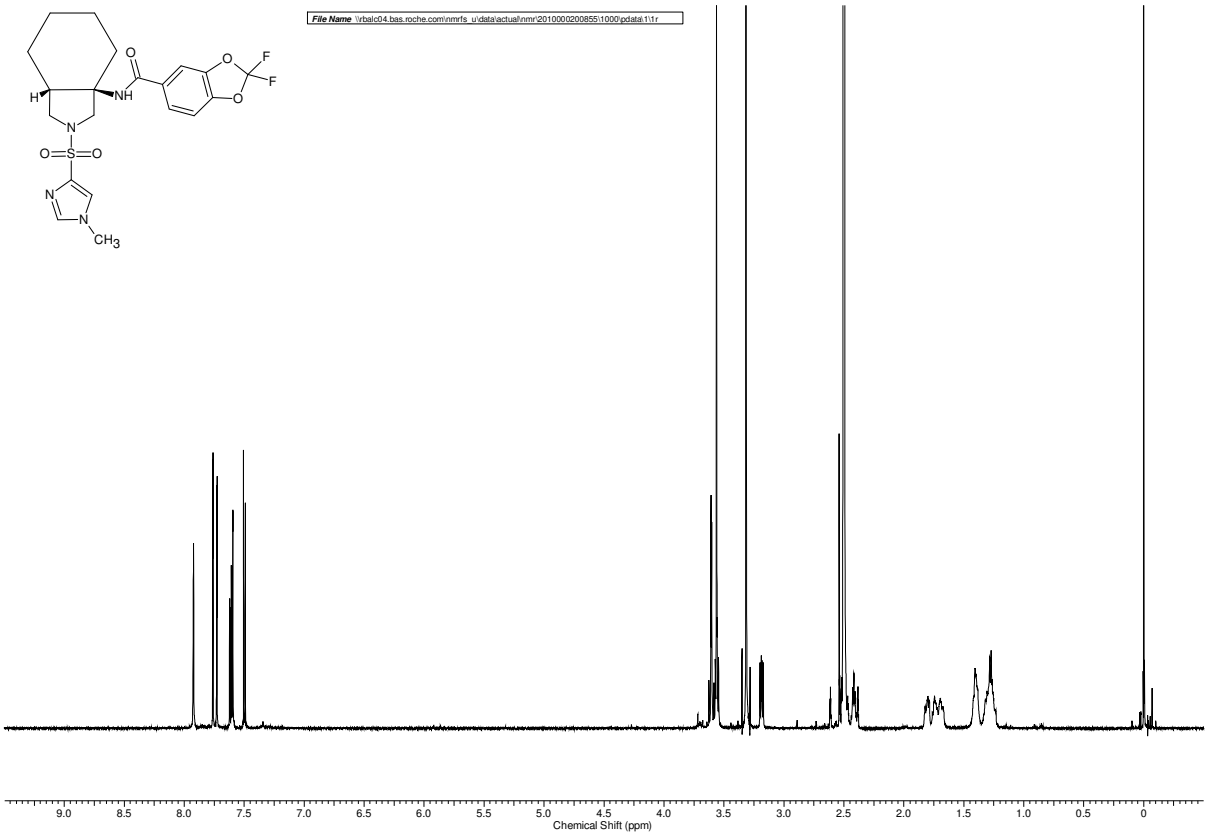
2-Methoxy-*N*-[*cis*-2-(1-methyl-1*H*-imidazole-4-sulfonyl)-octahydroisoindol-3a-yl]-benzamide, 13j{3,12}:



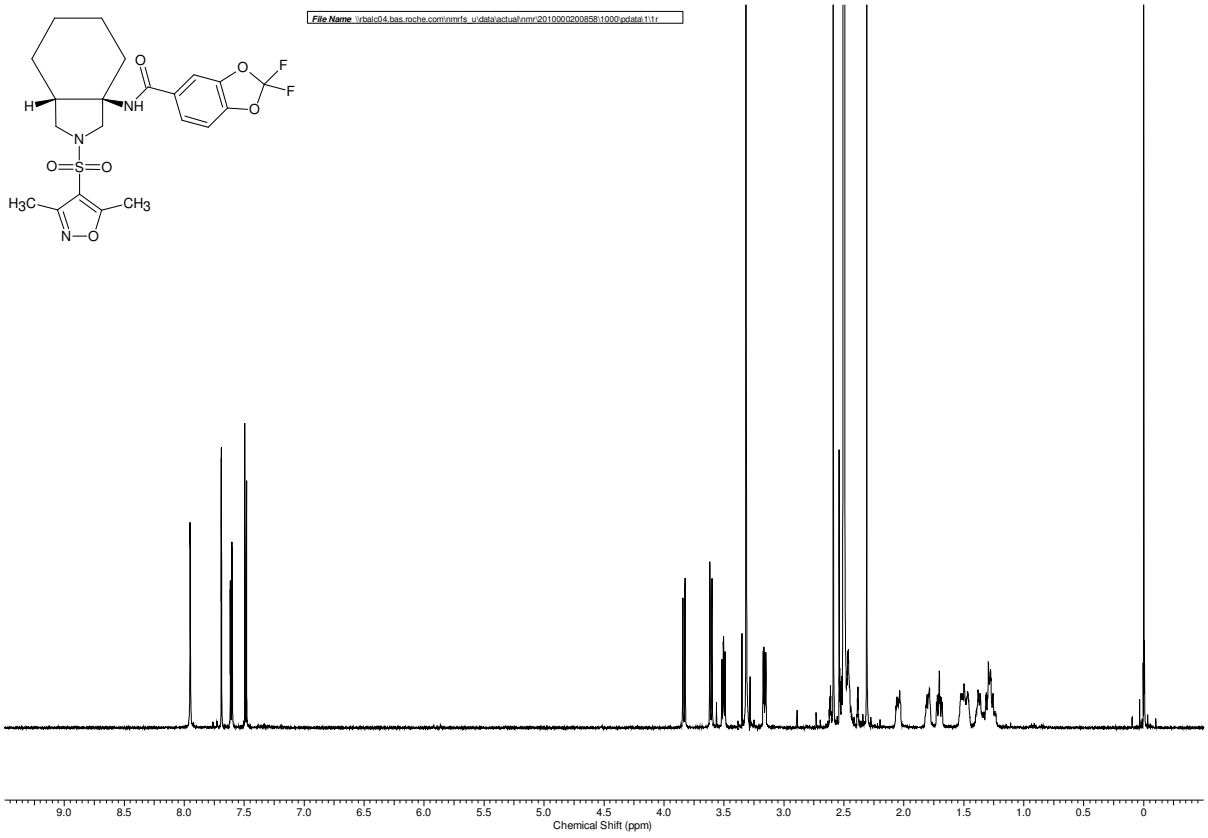
2,2-Difluoro-*N*-(2-((3-(trifluoromethyl)phenyl)sulfonyl)octahydro-1*H*-isoindol-3a-yl)benzo[*d*][*1,3*]dioxole-5-carboxamide, 13j{6,8}:



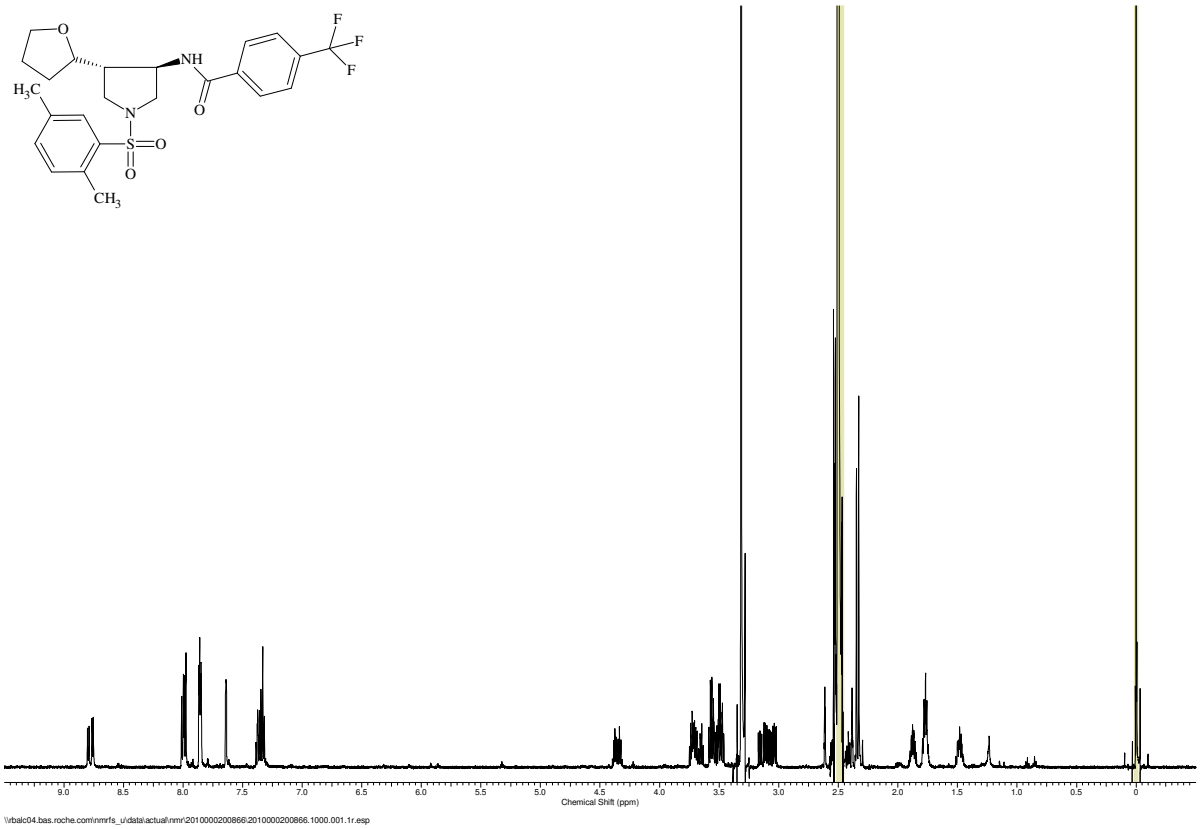
2,2-Difluoro-*N*-(2-((1-methyl-1*H*-imidazol-4-yl)sulfonyl)octahydro-1*H*-isoindol-3*a*-yl)benzo[*d*][*1,3*]-dioxole-5-carboxamide, 13j{6,12}:



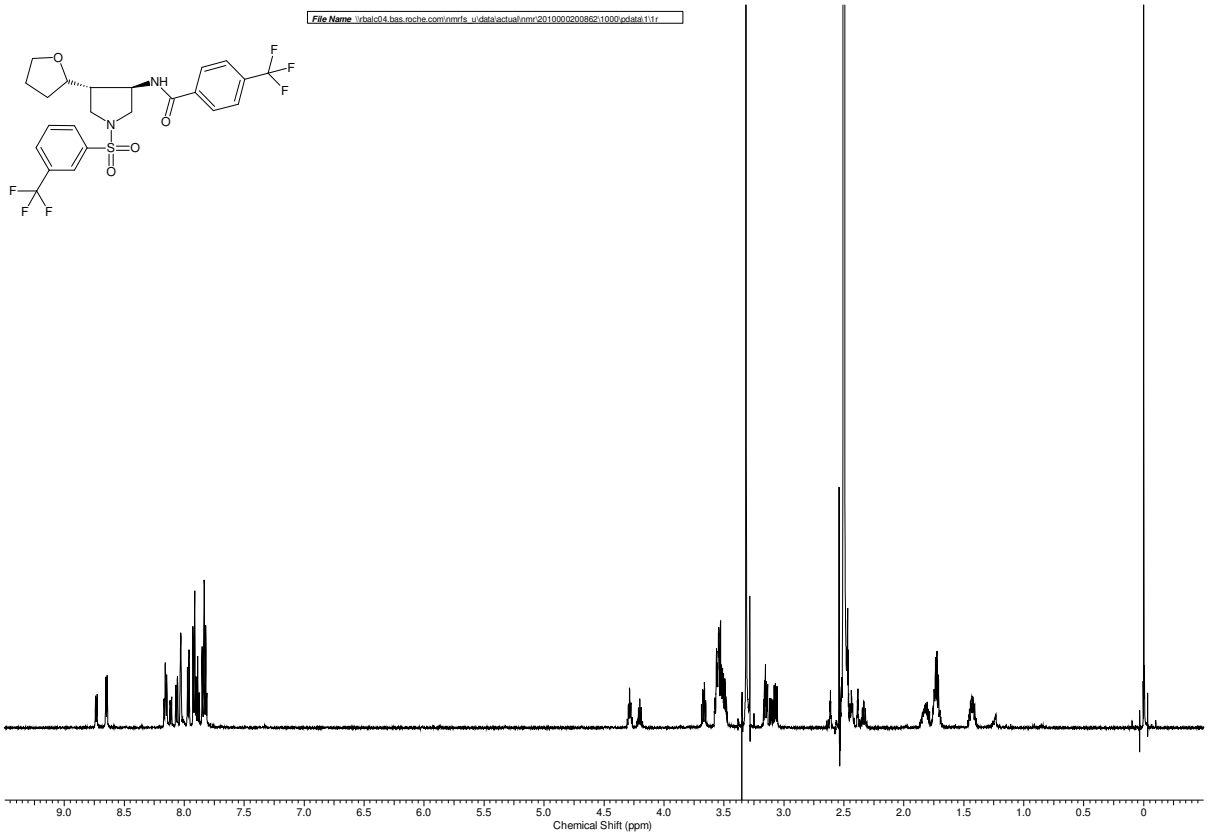
***N*-(2-((3,5-Dimethylisoxazol-4-yl)sulfonyl)octahydro-1*H*-isoindol-3*a*-yl)-2,2-difluorobenzo[*d*][*1*,*3*]dioxole-5-carboxamide, 13j**{6,13}**:**



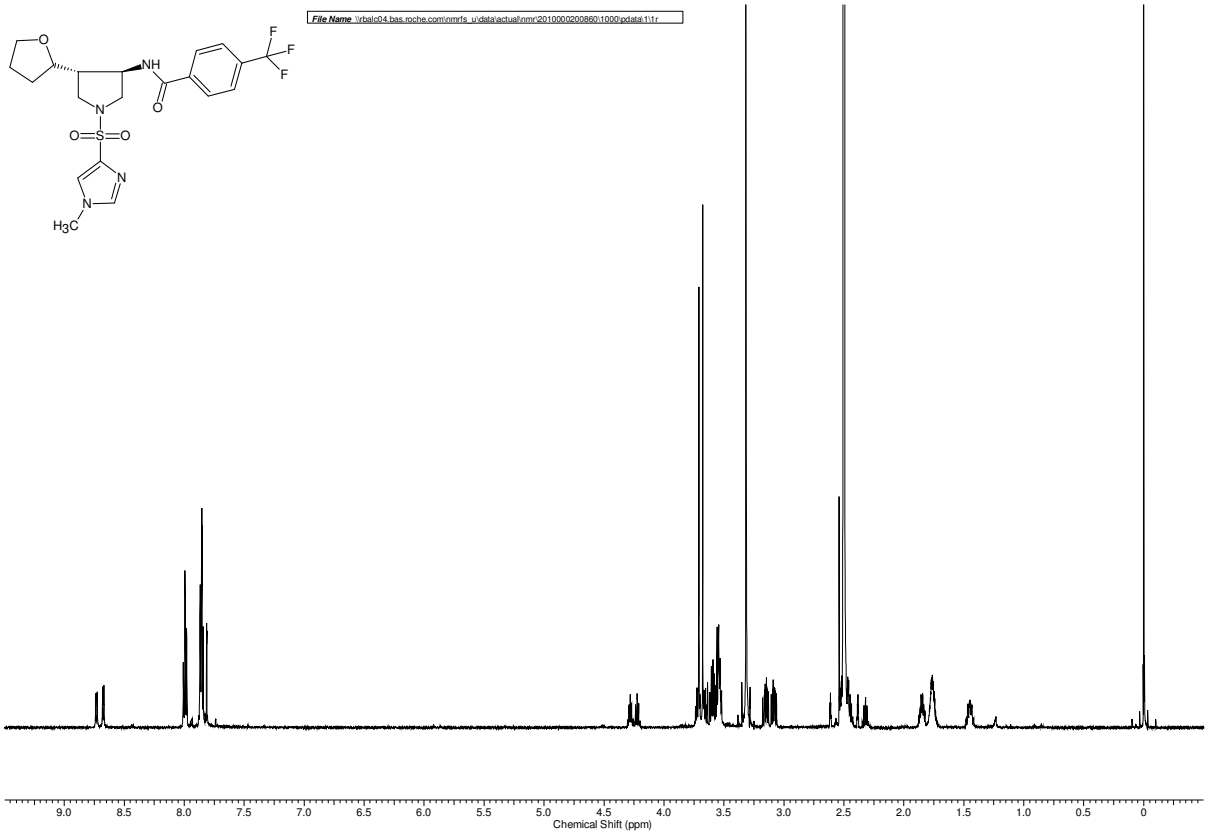
***N*-[*trans*-1-(2,5-Dimethylbenzenesulfonyl)-4-(tetrahydrofuran-2-yl)-pyrrolidin-3-yl]-4-trifluoromethyl-benzamide, 13i'**{2,7}**:**



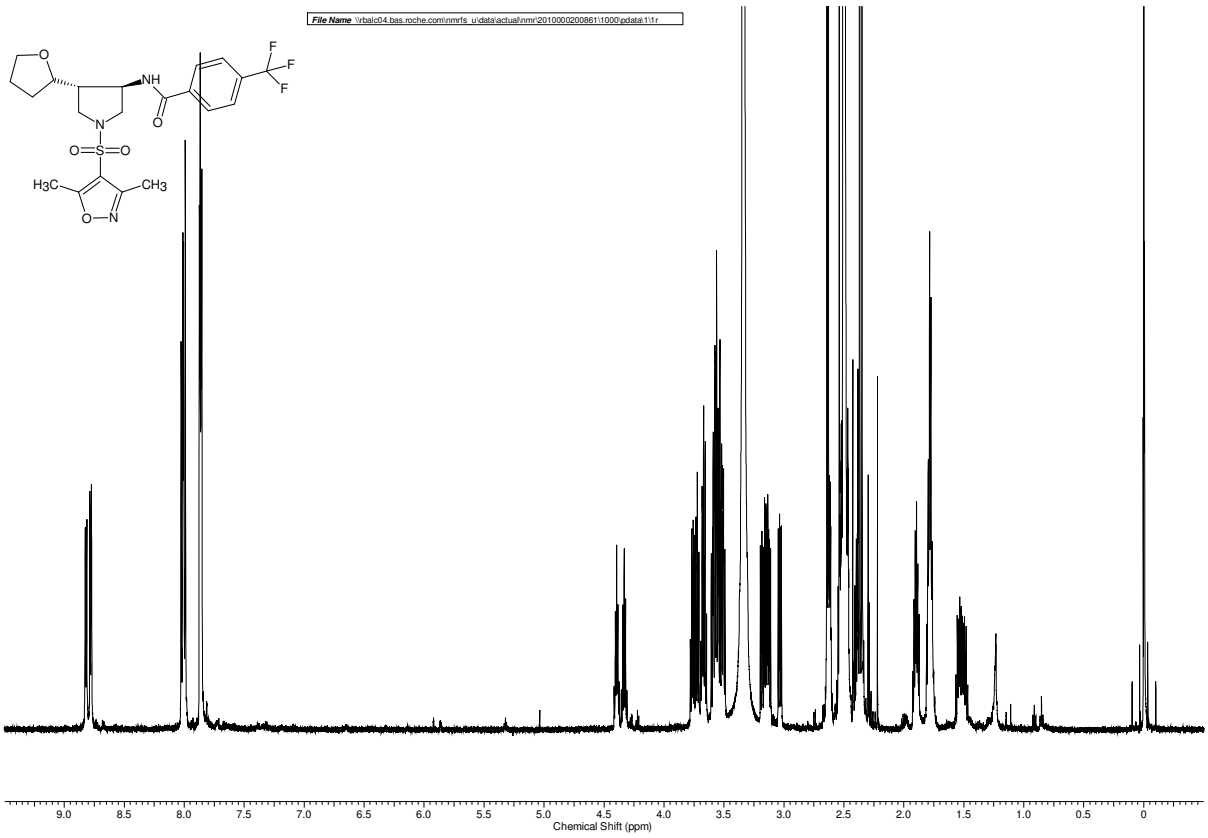
***N*-[*trans*-4-(Tetrahydrofuran-2-yl)-1-(3-trifluoromethylbenzenesulfonyl)-pyrrolidin-3-yl]-4-trifluoro-methylbenzamide, 13i'**{2,8}**:**



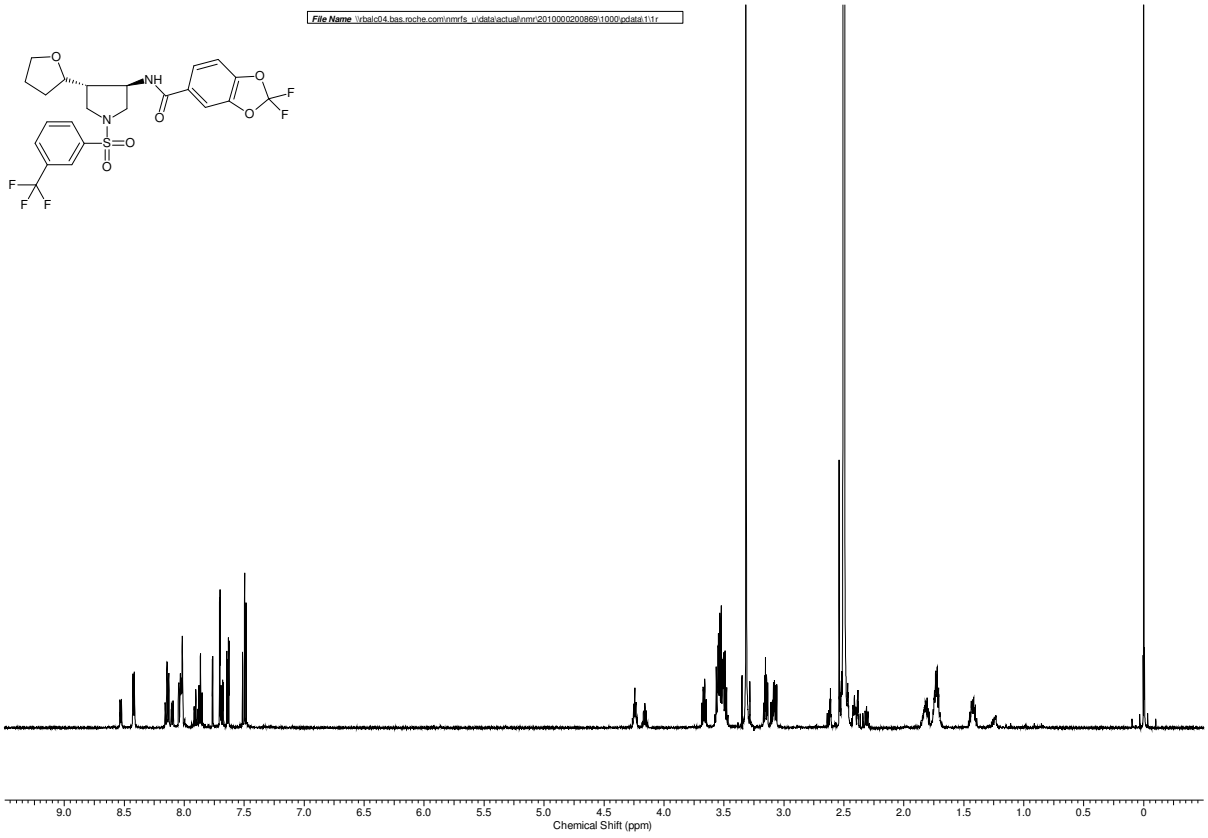
***N*-[*trans*-1-(1-Methyl-1*H*-imidazole-4-sulfonyl)-4-(tetrahydrofuran-2-yl)-pyrrolidin-3-yl]-4-trifluoromethylbenzamide, 13i'**{2,12}**:**



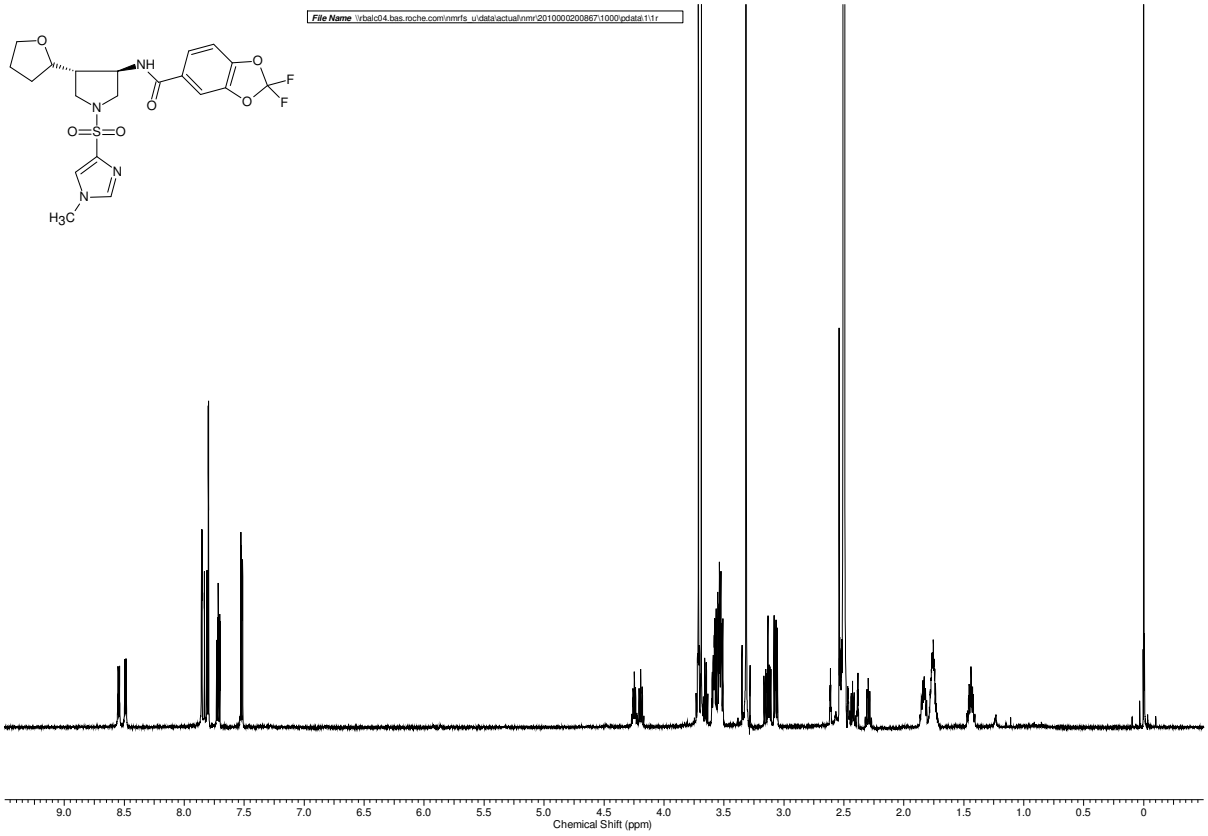
***N*-[*trans*-1-(3,5-Dimethylisoxazole-4-sulfonyl)-4-(tetrahydrofuran-2-yl)-pyrrolidin-3-yl]-4-trifluoro-methylbenzamide, 13i'**{2,13}**:**



2,2-Difluoro-*N*-(4-(tetrahydrofuran-2-yl)-1-((3-(trifluoromethyl)phenyl)sulfonyl)pyrrolidin-3-yl)benzo-[*d*][*1,3*]dioxole-5-carboxamide, 13i'{6,8}**:**



2,2-Difluoro-*N*-(1-((1-methyl-1*H*-imidazol-4-yl)sulfonyl)-4-(tetrahydrofuran-2-yl)pyrrolidin-3-yl)benzo-[*d*][*1,3*]dioxole-5-carboxamide, 13i'{6,12}**:**



***N*-(1-((3,5-dimethylisoxazol-4-yl)sulfonyl)-4-(tetrahydrofuran-2-yl)pyrrolidin-3-yl)-2,2-difluorobenzo-[*d*][*1,3*]dioxole-5-carboxamide, 13i'**{6,13}**:**