Synergistic effects of stereochemistry and appendages on the performance diversity of a collection of synthetic compounds

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Supplementary Figures and Tables

Table SI-1. Structural and calculated physical descriptors of compound series.

series	MW (g/mol)	SlogP	TPSA (Å^2)	rot.	HBA	HBD
1	101.1	-0.6	49.3	2	3	2
2	323.3	2.3	62.3	4	5	1
3	382.3	3.8	54.0	3	4	2
4	317.4	3.2	54.0	3	4	2
5	356.2	3.3	66.8	6	5	1
6	342.2	3.6	49.8	6	4	1
7	242.1	2	32.3	3	2	2
8	341.3	2.7	35.5	6	3	2
9	325.2	2.5	52.6	6	4	2
10	341.4	3.2	75.6	7	6	1
11	241.3	1.6	58.0	4	4	2
12	425.3	3.1	59.1	6	6	0
13	408.3	2	61.9	6	6	1
14	407.5	1.6	87.7	7	8	1
15	424.5	2.7	84.9	7	8	0
16	339.2	2.2	69.6	6	5	2
17	484.4	3.8	61.9	7	6	1

SlogP, topological polar surface area (TPSA) and number of rotatable bonds (rot.) calculated using Cresset software. HBA: number of hydrogen-bond acceptors, defined as the sum of N and O. HBD: number of hydrogen-bond donors, defined as the sum of NH and OH.

Table SI-2. Stains used in cell-painting assay for imaging with Opera Phenix.

dye	excitation wavelength (nm)	emission wavelength (nm)	organelle or cellular component
Hoechst 33342	405	435 – 480	nucleus
concanavalin A Alexa Fluor 488 conjugate	488	500 – 550	endoplasmic reticulum
SYTO 14 green fluorescent nucleic acid stain	488	570 – 630	nucleoli, cytoplasmic RNA
Alexa Fluor 568 phalloidin conjugate, wheat germ agglutinin (WGA) Alexa Fluor 555 conjugate	561	570 – 630	F-actin cytoskeleton, Golgi, plasma membrane
MitoTracker Deep Red	640	650 – 760	mitochondria

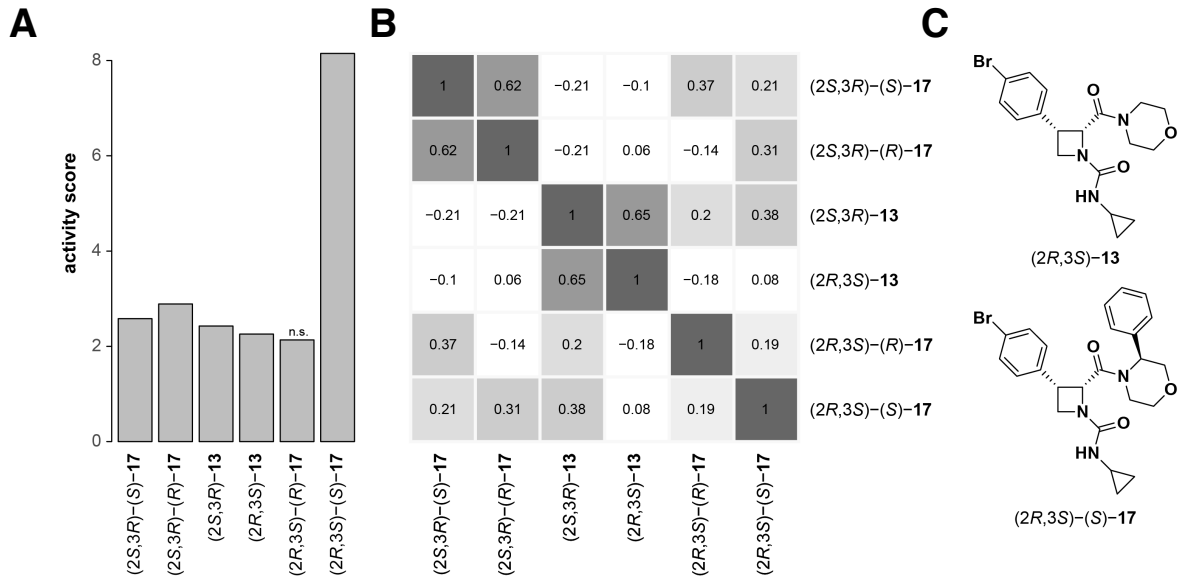


Figure SI-1. Biological effects of analogs containing an additional stereogenic element external to the azetidine core are also significantly dependent on stereoconfiguration. (A) Mahalanobis distances to vehicle control were calculated for series **17** compounds, and the *cis*-diastereomers of series **13**. The corresponding mp-values were calculated following the method developed by Hutz et al.;[1] mp < 0.05 except where marked "n.s." (not significant). (B) Similarities between the compounds cited previously (see A) were quantified using Pearson correlations. (C) Chemical structures of relevant analogs.

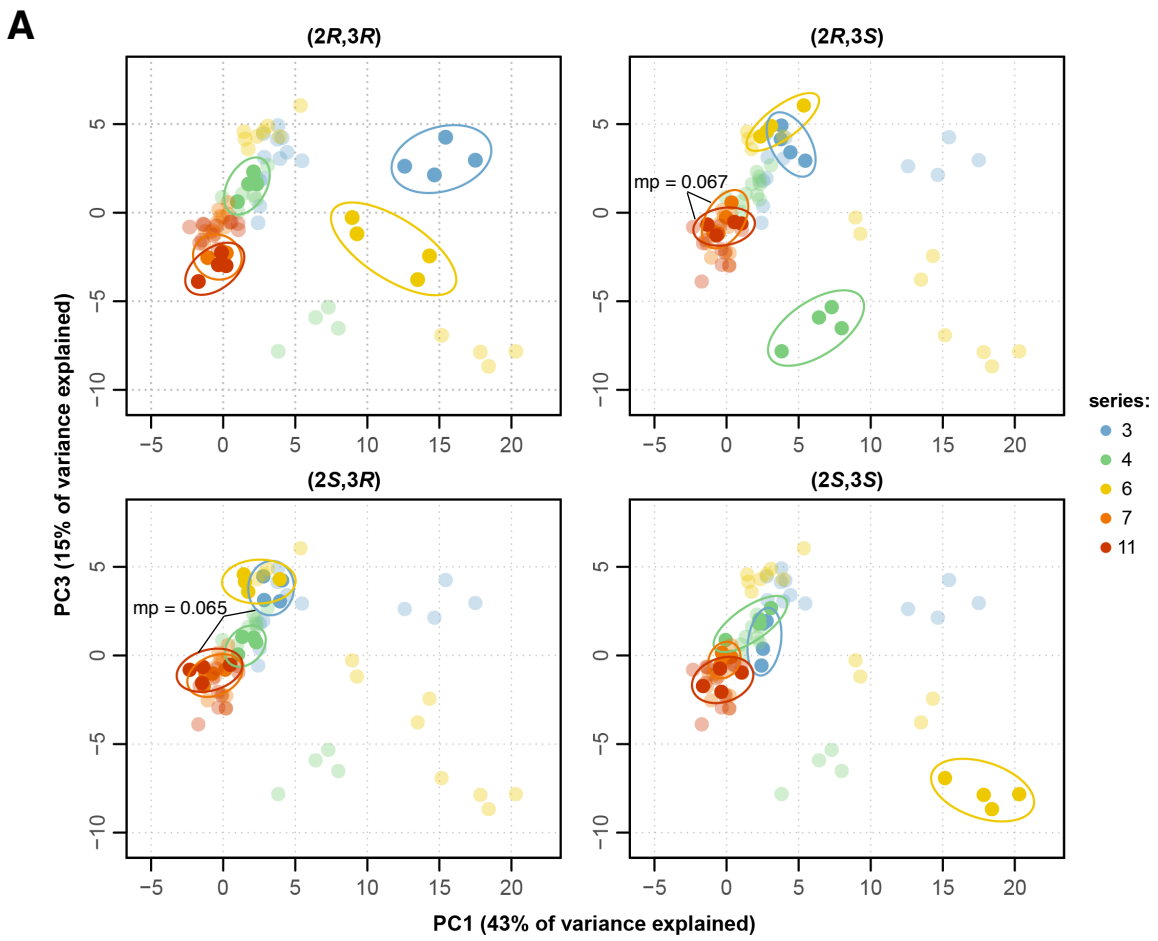


Figure SI-2. Stereochemical diversity can be a driver of performance diversity. (A) The morphological profiles of all stereoisomers of series **3**, **4**, **6**, **7,** and **11** were studied concurrently by principal component analysis. Identical data is represented in the four quadrants of this figure, with a different core stereochemical configuration emphasized (bolded) on each plot and only 100 µM data (four replicates each) are shown for clarity; clockwise from top left: (2*R*,3*R*), (2*R*,3*S*), (2*S*,3S), (2*S*,3*R*). Circled point clusters are those deemed distinct from all their congeners of same core stereoconfiguration (mp < 0.05 with the method of Hutz et al.)[1] except where noted.

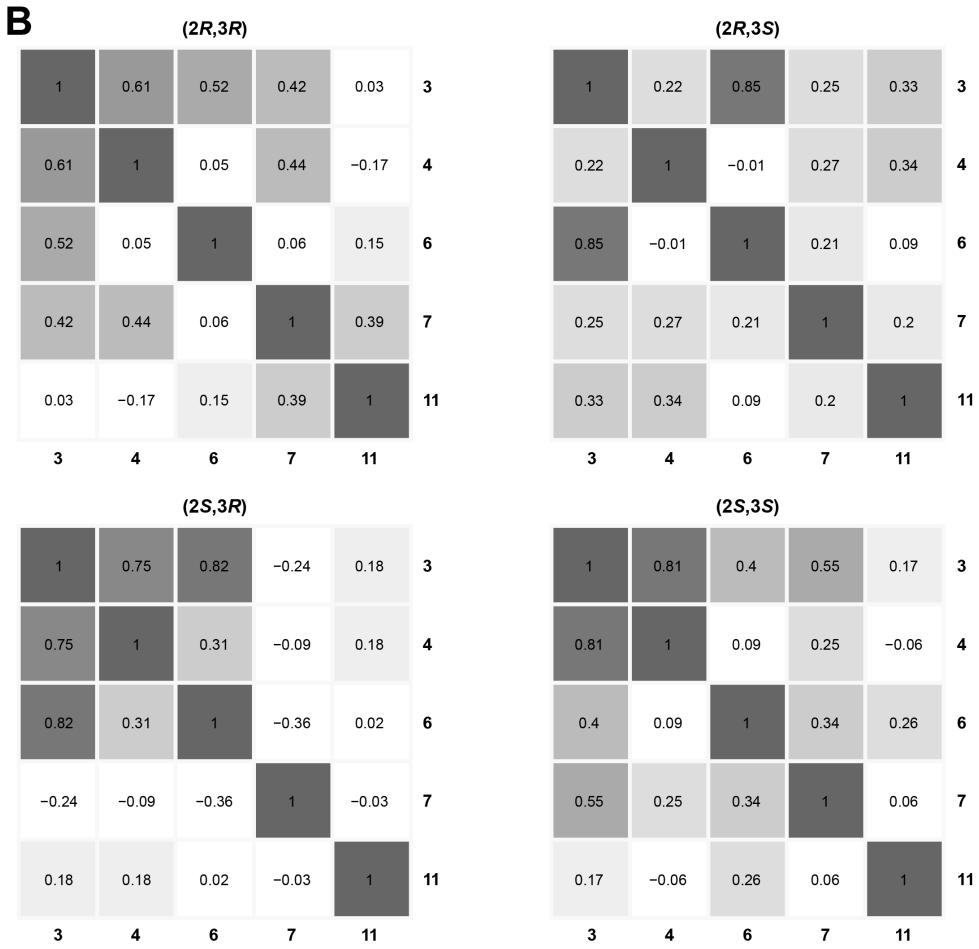


Figure SI-2. Stereochemical diversity can be a driver of performance diversity. (B) Heat maps showing the relationships between chemical analogs of same stereochemical configuration: the similarities of their morphological profiles are assessed by Pearson correlation coefficients, calculated pairwise at 100 µM.

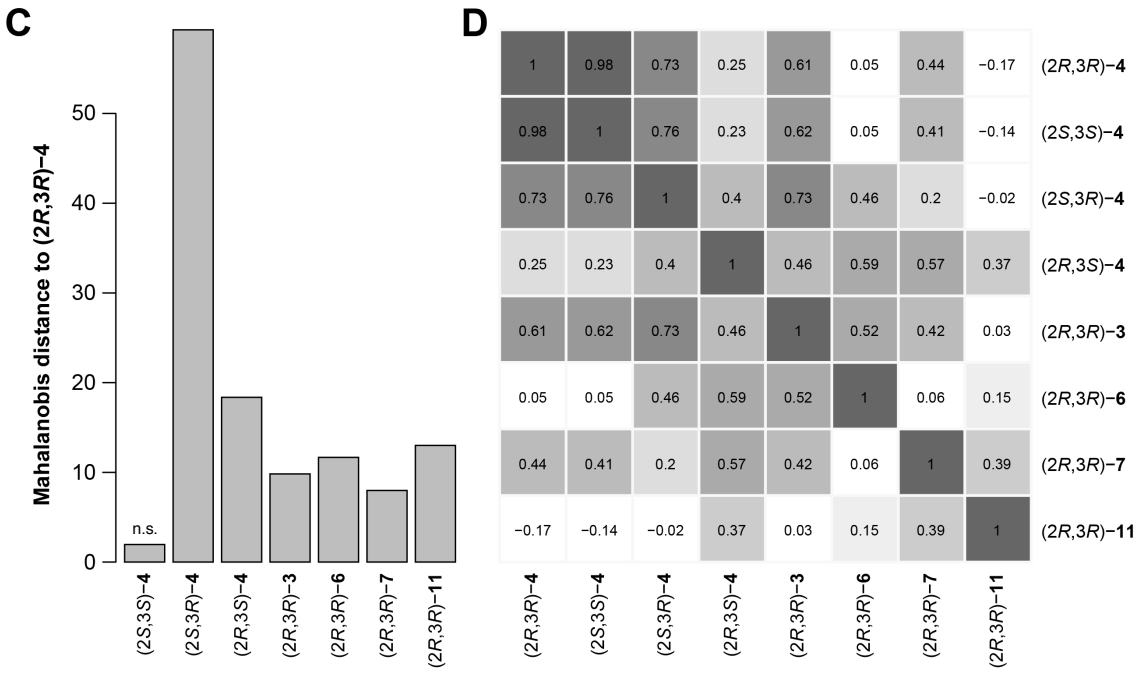


Figure SI-2. Stereochemical diversity can be a driver of performance diversity. (C) Mahalanobis distances to the effect of compound (2*R*,3*R*)-**4** were successively calculated for its stereoisomers, and its analogs from series **3**, **6**, **7,** and **11** all at a concentration of 100 µM; the corresponding mp-values were calculated following the method developed by Hutz et al.;[1] mp < 0.05, except where marked "n.s." (not significant). (D) Similarities between (2*R*,3*R*)-**4** and the compounds cited previously (see SI-2A) were quantified using Pearson correlations.

Computational Methods

We used CellProfiler[2] to process the raw images and obtain the morphological profiles for each cell imaged, following the pipeline described by Bray et al.[3] For our analyses, we used 1,140 morphological features relating to size, texture, intensity, local density, and radial distribution of nuclei, cytoplasm, and entire cells. To obtain profiles for each well, these features were averaged across all cells and then normalized by calculating robust *z*-scores based on the population of individual vehicle-treated cells found on the same assay plate.

All post-processing numerical analyses were performed in R (version 3.4.4).[4] Calculations of Mahalanobis distances and multidimensional perturbation values were performed as outlined by Hutz et al.[1] Principal component analysis was performed using the *stats* package (version 3.3.3).[1] Pearson correlations were calculated on *z*-scored profiles corresponding to compound treatments at the specified concentrations using the *stats* package (version 3.3.3).[1] Variances were also calculated using the *stats* package (version 3.3.3).[1]

All plots were generated in R using core functions[1] and the ggplot2 package.[5]

Biological Annotation Method (Cell Painting Assay)

The protocols outlined in Gustafsdottir et al.,[6] Wawer et al.,[7] Gerry et al.,[8] and Bray et al.,[3] have been adapted, per Nelson et al.[9] U-2 OS cells (ATCC, #HTB-96) were confirmed to be free from *Mycoplasma* contamination with the MycoAlert PLUS assay (Lonza, #LT07-705), then approximately 1,500 cells were seeded in 50 µL complete media (*vide infra*) per well in 384-well clear bottom, black, tissue culture treated imaging plates (Perkin-Elmer, #6057308). After incubating for 24 h at 37 °C, compounds (6-point concentration, 2.0-fold dilution, range: 100 to 3.125 µM assay concentration) were pin-transferred to the assay plates using a CyBi-Well robotic pin tool. Treatments were performed in quadruplicate. Following transfer, cells were allowed to incubate for a further 24 h at 37 °C.

A 1 mM DMSO solution of MitoTracker Deep Red (Thermo Fisher, #M22426) was prepared and added to pre-warmed complete media (*vide infra*) to afford a staining solution (SS1) of 500 nM MitoTracker. After 40 µL of media were carefully removed from each well of the assay plates (~10 µL remaining volume), 30 µL of SS1 were added to each well (~12 mL/plate). After incubating for 30 min at 37 °C, cells were fixed for 20 min at rt with 10 µL/well of 16% (wt/vol) aq paraformaldehyde (methanol-free) solution (#15710-S, Electron Microscopy Services). Wells were then washed with 70 µL 1× HBSS (Thermo Fisher, #14065-057 [as 10×]), twice.

A 0.1% HBSS solution of Triton X-100 (Sigma-Aldrich, #T8787) was added to each well (30 µL/well) to permeabilize the cells. After incubating for 15 min at rt, wells were washed with 70 µL 1× HBSS, twice.

A 1 mg/mL dH_2O solution of Wheat Germ Agglutinin (WGA), Alexa Fluor® 555 conjugate (Thermo Fisher, #W32464); 1 mg/mL solution in 0.1 M aq $NaHCO_3$ of Concanavalin A, Alexa Fluor® 488 conjugate (Thermo Fisher, #C11252); and a 1.5 mL/vial MeOH solution of Phalloidin, Alexa Fluor 568 conjugate (Thermo Fisher, #A12380) were combined with a 10 mg/mL aq solution of Hoechst 33342 (Thermo Fisher, #H3570) and a 5 mM DMSO solution of SYTO 14 Green Fluorescent Nucleic Acid Stain (Thermo Fisher, #S7576) in 1× HBSS supplemented with 1% bovine serum albumin to afford a staining solution (SS2) of 1.5 µg/mL WGA, 100 µg/mL Concanavalin A, 2.5 µL Phalloidin/mL, 5 µg/mL Hoechst 33342, and 3 µM SYTO 14. 30 µL of SS2 were then added to each of the wells and the fixed, permeabilized cells were allowed to incubate at rt for 30 min. Wells were then washed with 70 µL of 1× HBSS, thrice (no final aspiration) and the plates were sealed with foil (Corning, #PCR-AS-200). Stained plates were stored at +4 °C in the dark until imaging.

We captured images on an Opera Phenix™ High-Content Screening System in wide-field mode with a water-immersion 20× objective and four excitation laser wavelengths (Table S2): 405 (Hoechst), 488 (Concanavalin A and SYTO 14), 561 (Phalloidin and WGA), and 640 nm (Mito-Tracker). Photobleaching of low-intensity dyes is avoided by imaging in the order of: MitoTracker,

WGA, Phalloidin, SYTO 14, Concanavalin A, and Hoechst 33342. Nine sites were imaged per well in a 3 × 3 array, with laser-based autofocus on the first site per well. Brightfield images were also collected, but were not used in the automated image processing pipeline.

Image analysis and data processing were performed as outlined in Gerry et al.[8]

Assay Materials

- U-2 OS cells (ATCC, #HTB-96)
- MycoAlert™ Mycoplasma Detection Kit (Lonza, #LT07-705)
- CellCarrier-384 Ultra Microplates, tissue culture treated, black, 384-well with lid (Perkin-Elmer, #6057308)
- DMEM (Thermo Fisher, #10564011)
- FBS (Thermo Fisher, #10437028)
- Penicillin/streptomycin, PS (Thermo Fisher, #1540122)
- Complete media: DMEM, 10% FBS, 1% PS
- Hank's Balanced Salt Solution, HBSS (Thermo Fisher, #14065-056)
- MitoTracker Deep Red (Thermo Fisher, #M22426)
- Wheat Germ Agglutinin, Alexa Fluor® 555 conjugate (Thermo Fisher, #W32464)
- Concanavalin A, Alexa Fluor® 488 conjugate (Thermo Fisher, #C11252)
- Phalloidin, Alexa Fluor® 568 conjugate (Thermo Fisher, #A12380)
- Hoechst 33342 (Thermo Fisher, #H3570)
- SYTO 14 green fluorescent nucleic acid stain (Thermo Fisher, #S7576)
- Paraformaldehyde 16%, methanol free (Electron Microscopy Services, #15710-S)
- Triton-X-100 (Sigma-Aldrich, #T8787)
- Bovine serum albumin
- DMSO (molecular biology grade)
- Methanol
- Sodium bicarbonate
- Axygen PCR 35 µm aluminum sealing film (Corning, #PCR-AS-200)
- Opera Phenix™ High-Content Screening System

General Chemistry Information

Oxygen- and/or moisture-sensitive reactions were carried out in oven- or flame-dried glassware under nitrogen atmosphere. All reagents and solvents were purchased and used as received from commercial vendors or synthesized according to cited procedures. In particular, L-, D-, and racemic azetidine-2-carboxylic acid (**(2*S*)-1**, **(2*R*)-1** and **(±)-1**) were purchased from Combi-Blocks.

All yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. Reaction progress was monitored by analytical thin-layer chromatography (TLC) and TLC analyses were performed using E. Merck silica gel 60 F254 pre-coated plates (250 μm). Compound spots were visualized by UV light (254 nm) and potassium permanganate staining. Optical rotations were measured on an Autopol IV automatic polarimeter from Rudolph Research Analytical. Flash column chromatography was performed using a Teledyne ISCO CombiFlash Rf purification system. NMR spectra were recorded on Bruker UltraShield 300 (^{1}H, 300 MHz; ^{13}C, 75 MHz) or 400 (^{1}H, 400 MHz; ^{13}C, 100 MHz) spectrometers at 298 K unless otherwise noted. Chemical shifts are reported in parts per million (ppm) relative to the appropriate solvent. Multiplicity abbreviations are as follows: br = broad, s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet. All deuterated solvents were purchased from Cambridge Isotope Laboratories. Tandem liquid chromatography/mass spectrometry (LCMS) was performed on a Waters 2795 separations module and 3100 mass detector. High-resolution mass-spectra were acquired on an Agilent 1290 Infinity separations module coupled to a 6230 time-of-flight (TOF) mass detector operating in ESI+ or ESI- mode. Masses were confirmed using the "Find by Formula" feature in MassHunter Qualitative Analysis vB.06.00. All values are averages of three independent measurements. Enantiopurity of selected compounds were determined by analytical supercritical fluid chromatography coupled to mass spectrometry (SFC-MS) on a Waters UPC^{2} convergence chromatography system including a polydiode array UV detector connected to a QDa single quadrupole mass spectrometer using chiral stationary phase with solvent mixtures and temperatures as indicated in each entry. Elemental analysis was outsourced to Robertson Microlit (Ledgewood, NJ).

Methods for Analytical Supercritical Fluid Chromatography (SFC)

Functionalization of C–H arylation products for determination of enantiopurity

C–H arylation products were inseparable by SFC, which called for derivatization prior to analysis in order to enable sufficient separation and quantitation of enantiopurity. Racemates (used as SFC standards) and compounds of interest were functionalized as specified below.

Derivatization Procedure 1: Racemic C–H arylation products

Racemic starting material (1.0 equiv) was added to a reaction vessel and dissolved in CH_2Cl_2 (0.05 M), then ethyl isocyanate (1.2 equiv) was added and the reaction mixture was stirred for 1 h at rt. The reaction was quenched with MeOH and concentrated *in vacuo* before purification by flash column chromatography.

Derivatization Procedure 2: Enantiopure C–H arylation products

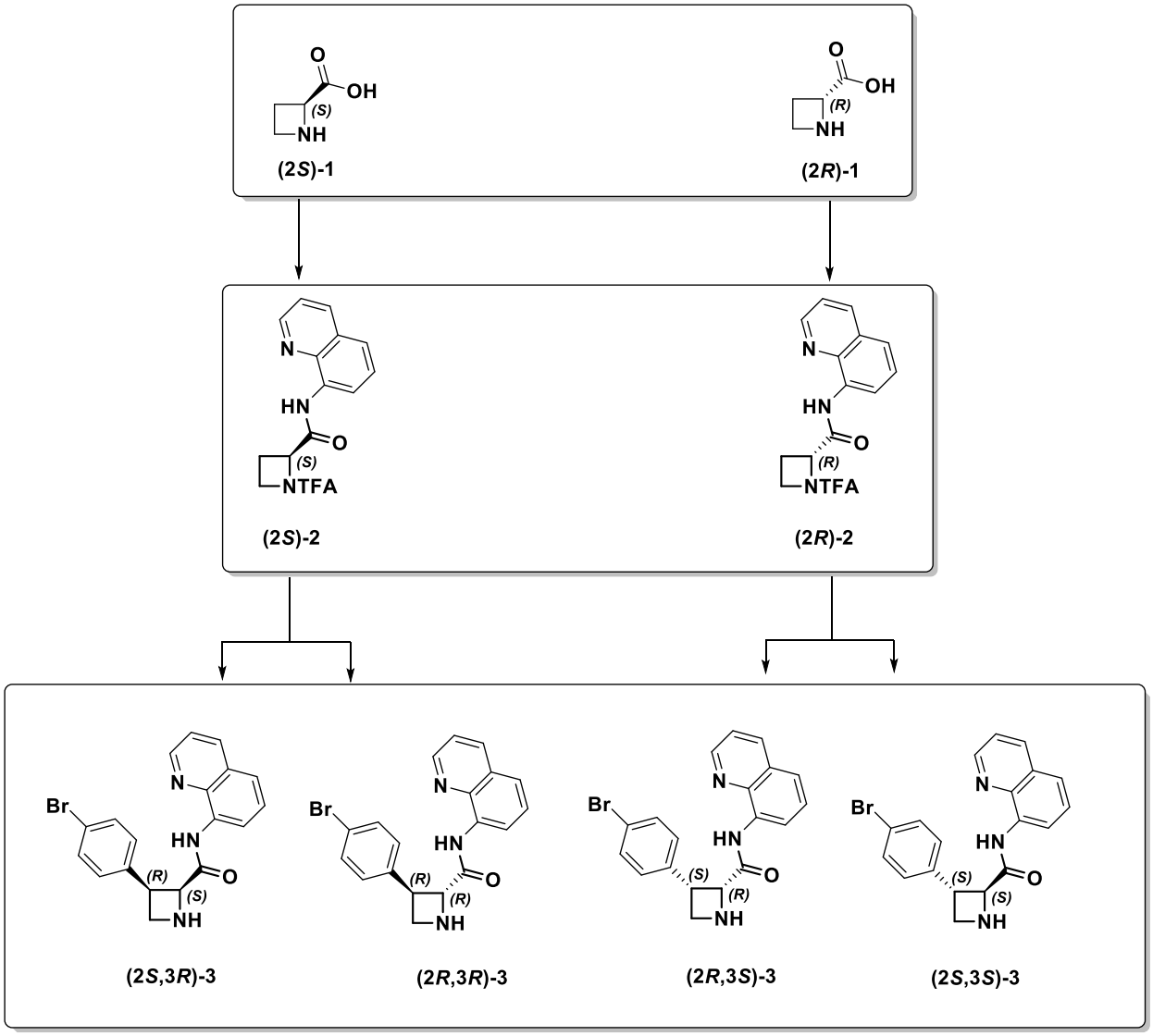
Enantiopure starting material (1-2 mg, 1.0 equiv) was added to a reaction vessel and dissolved in CH_2Cl_2 (~100 μL), then ethyl isocyanate (~1.2 equiv) was added and the reaction mixture was stirred for 20 minutes at rt. The reaction was quenched with MeOH and concentrated *in vacuo*.

SFC Method

Mobile phase A consisted of supercritical carbon dioxide, while mobile phase B consisted of 0.05% triethylamine in MeOH. The gradient ran from 3% to 50% mobile phase B over 5.0 min at 1.5 mL/min, followed by a 1.5 min hold at 50% B before returning to starting conditions. A ChiralPak AS-H, 4.6×250 mm column was used with column temperature maintained at 45 °C. 1-2 mg of the appropriate compound was dissolved in 1 mL MeOH, and 5 μL of this solution was injected.

Synthesis and Characterization of Compounds

***Series 1-3*:**



Compounds in chemical ***Series 1*** were purchased from Combi-Blocks and used as received.

Compounds in chemical ***Series 2*** were prepared according to literature procedures.[10]

Series 3: 3-(4-bromophenyl)-N-(quinolin-8-yl)azetidine-2-carboxamide

Cis isomers **(2*S*,3*R*)-3** and **(2*R*,3*S*)-3** were prepared according to literature procedures. Analytical data are in agreement with previously reported data.[10]

Trans isomers **(2*R*,3*R*)-3** and **(2*S*,3*S*)-3** were prepared as specified below:

General Procedure 3: A reaction vessel was charged with substrate **2** (1.0 equiv), dibenzyl phosphate (20 mol%), AgOAc (2.0 equiv), aryl iodide (3.0 equiv), and $Pd(OAc)_2$ (10 mol%). The reaction vessel was evacuated and refilled with N_2 (3×) prior to addition of DCE (1.0 M), then stirred for 24 h in a heat block previously pre-heated to 110 ºC. The reaction mixture was allowed to cool to ambient temperature, diluted with CH_2Cl_2, filtered through a pad of Celite, and further eluted with additional CH_2Cl_2. The solvent was then removed *in vacuo* and LiO*t*-Bu (2.5 equiv) was added to the reaction vessel containing crude material. The reaction vessel was evacuated and refilled with N_2 (3×) prior to addition of toluene (0.2 M), then warmed up to 50 ºC and stirred for 24 h. The reaction mixture was then allowed to cool to ambient temperature, filtered through a pad of Celite, and further eluted with CH_2Cl_2, before the addition of 7 *N* NH_3 in MeOH solution (3 mL). The mixture was allowed to stir at ambient temperature for 3 h before being concentrated *in vacuo.* Purification by flash column chromatography ($MeOH/CH_2Cl_2$) followed by reverse flash column chromatography (deionized H_2O/MeCN + 0.1% trifluoroacetic acid) afforded the desired product.

(2*R*,3*R*)-3: Prepared according to General Procedure 3 from **(2*S*)-2** (64.6 mg) to afford the desired product (23.9 mg, 31%) as an amorphous solid.
(2*S*,3*S*)-3: Prepared according to General Procedure 3 from **(2*R*)-2** (64.6 mg) to afford the desired product (20.3 mg, 27%) as an amorphous solid.
$[\alpha]^{24}_{D}$ = –116.4 (c = 0.1, $CHCl_3$) **(2*R*,3*R*)-3**
$[\alpha]^{24}_{D}$ = +106.4 (c = 0.1, $CHCl_3$) **(2*S*,3*S*)-3**
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.53 (s, 1H), 8.92 (dd, *J* = 4.2 Hz, *J* = 1.7 Hz, 1H), 8.87 (dd, *J* = 6.0 Hz, *J* = 3.1 Hz, 1H), 8.18 (dd, *J* = 8.3 Hz, *J* = 1.7 Hz, 1H), 7.58 – 7.53 (m, 2H), 7.51 – 7.44 (m, 3H), 7.34 – 7.29 (m, 2H), 4.59 (d, *J* = 7.0 Hz, 1H), 4.07 – 3.87 (m, 3H), 2.44 (bs, 1H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 148.9, 140.2, 139.3, 136.4, 134.4, 131.8, 128.8, 128.3, 127.5, 122.2, 121.7, 120.8, 116.8, 67.1, 50.0, 44.4.
HRMS (ESI^+) m/z calculated for $C_{19}H_{17}BrN_3O$ $[M+H]^+$ 382.0555; Found 382.0542.

Functionalization for SFC

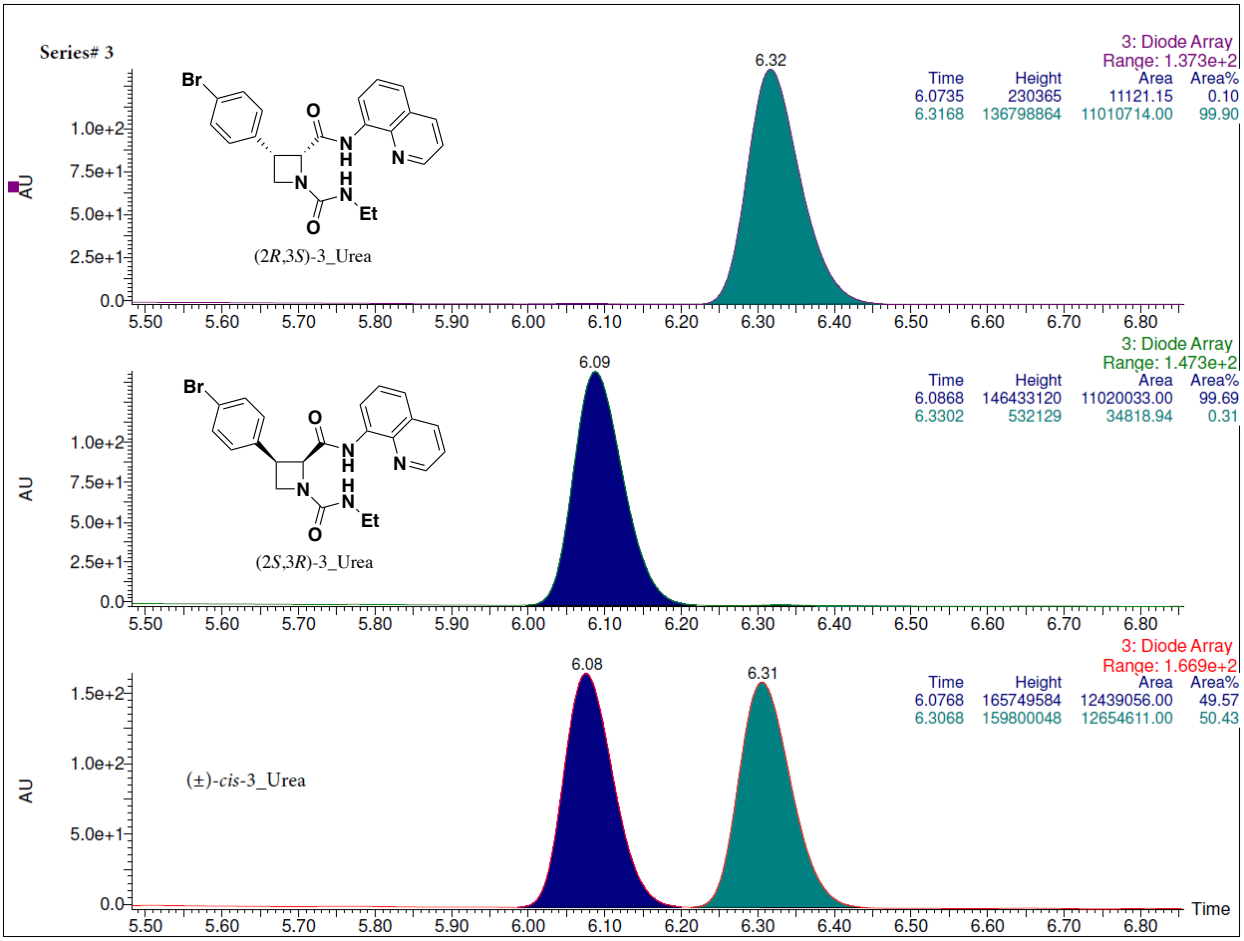
3_Urea: 3-(4-bromophenyl)-N^1-ethyl-N^2-(quinolin-8-yl)-azetidine-1,2-dicarboxamide

***Cis* stereoisomers:**

Racemate **(±)-*cis*-3_Urea** was prepared according to literature procedures.[10] Analytical data were in agreement with previously reported data.

Single stereoisomers **(2*R*,3*S*)-3_Urea** and **(2*S*,3*R*)-3_Urea** were in turn prepared according to **Derivatization Procedure 2**.

Retention of enantiopurity was determined by SFC (see below). T_{rac} = 6.08 and 6.31 min.



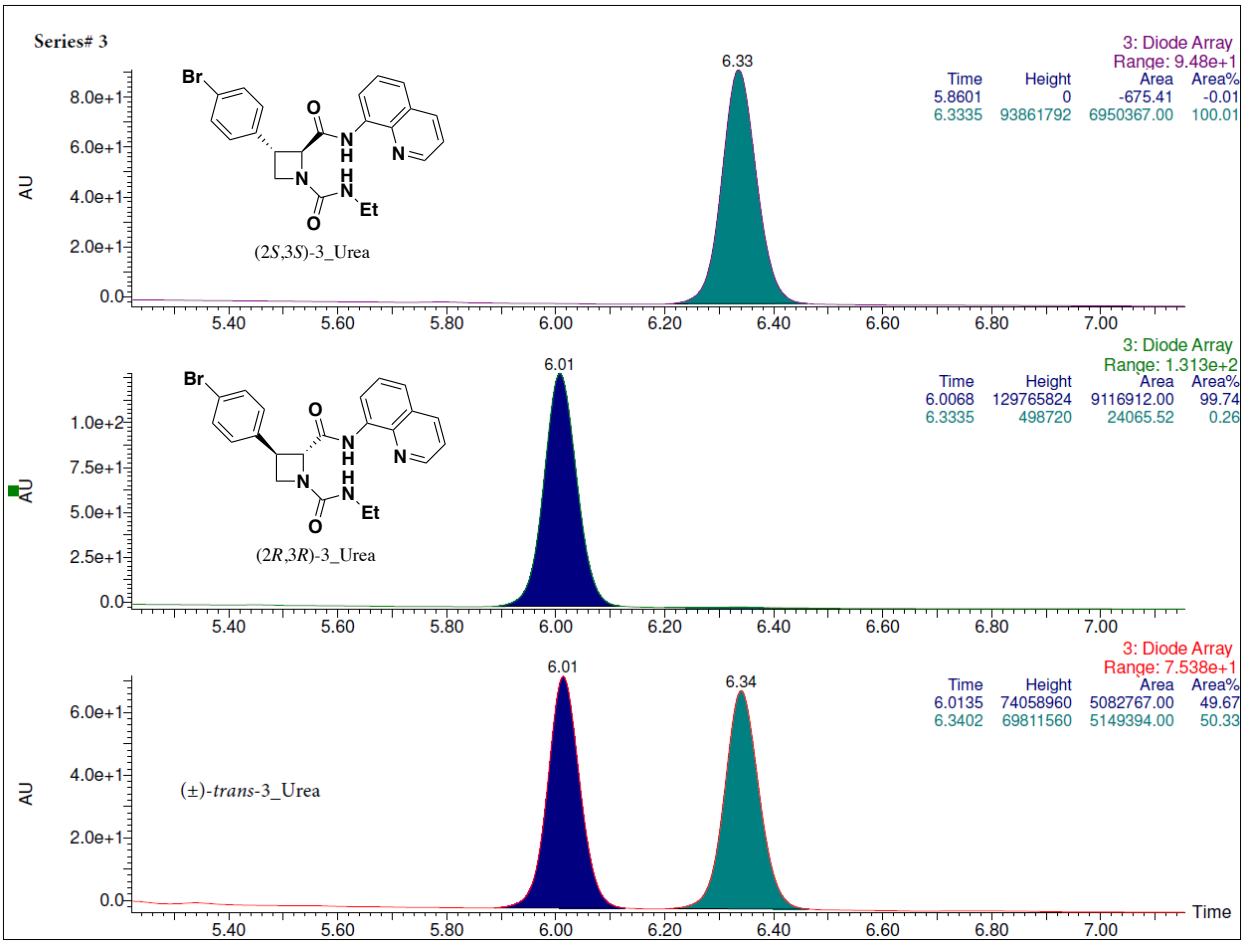
***Trans* stereoisomers:**

Racemate **(±)-*trans*-3_Urea** was prepared according to **Derivatization Procedure 1** from **(±)-*trans*-3** (3.6 mg). Purification by flash column chromatography ($MeOH/CH_2Cl_2$) provided 3.4 mg (80%) of the desired product.

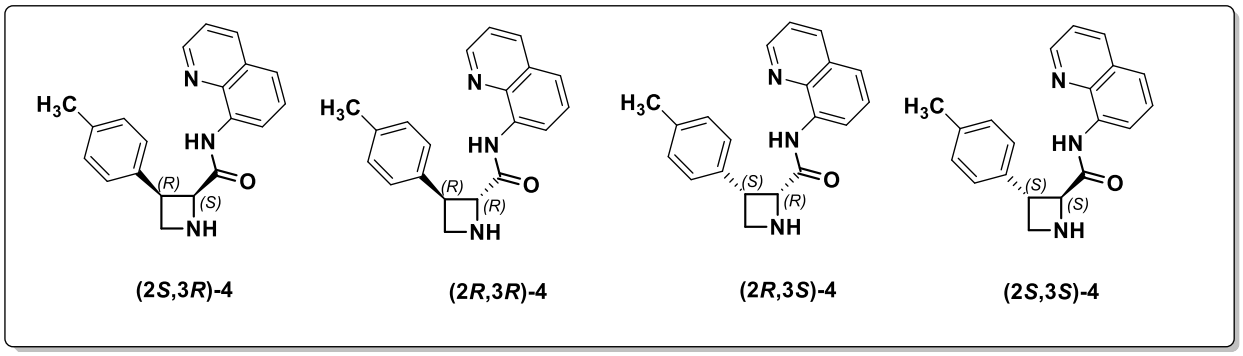
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.86 (s, 1H), 8.83 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.79 (dd, *J* = 4.9, 4.0 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.59 – 7.54 (m, 4H), 7.46 (dd, *J* = 8.3 4.2 Hz, 1H), 7.36 – 7.30 (m, 2H), 4.94 (t, *J* = 5.7 Hz, 1H), 4.84 (d, *J* = 7.3 Hz, 1H), 4.32 – 4.25 (m, 1H), 4.15 – 4.03 (m, 2H), 3.39 – 3.30 (m, 2H), 1.19 (t, *J* = 7.2 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 160.7, 148.7, 138.9, 138.5, 136.2, 133.9, 132.0, 128.9, 128.0, 127.2, 122.4, 121.7, 121.4, 117.0, 70.2, 52.9, 38.4, 35.4, 15.5.
HRMS (ESI^+) m/z calculated for $C_{44}H_{44}Br_2N_8O_4Na$ $[2M+Na]^+$ 927.1594; Found 927.1580.

Single stereoisomers **(2*S*,3*S*)-3_Urea** and **(2*R*,3*R*)-3_Urea** were prepared according to **Derivatization Procedure 2**.

Retention of enantiopurity was determined by SFC (see below). T_{rac} = 6.01 and 6.34 min.



Series 4: N-(quinolin-8-yl)-3-(p-tolyl)azetidine-2-carboxamide



(2*S*,3*R*)-4: Prepared according to literature procedures.[10] Analytical data were in agreement with previously reported data.
(2*R*,3*S*)-4: Prepared according to literature procedures[10] from **(2*R*)-2** (64.6 mg) to afford the desired product (40.7 mg, 64%) as an amorphous solid.
$[\alpha]^{24}_{D}$ = –179.1 (c = 1.0, $CHCl_3$) **(2*R*,3*S*)-4**

General Procedure 4 (for *trans* stereoisomers):
A reaction vessel was charged with substrate **2** (1.0 equiv), dibenzyl phosphate (20 mol%), AgOAc (2.0 equiv), aryl iodide (3.0 equiv), and $Pd(OAc)_2$ (10 mol%). The reaction vessel was evacuated and refilled with N_2 (3×) prior to addition of DCE (1.0 M), then stirred for 24 h in a heat block previously pre-heated to 110 ºC. The reaction mixture was allowed to cool to ambient temperature, diluted with CH_2Cl_2, filtered through a pad of Celite, and further eluted with additional CH_2Cl_2. The solvent was then removed *in vacuo* and LiO*t*-Bu (2.0 equiv) was added to the reaction vessel containing crude material. The reaction vessel was evacuated and refilled with N_2 (3×) prior to addition of toluene (0.2 M), then warmed up to 50 ºC and stirred for 24 h. The reaction mixture was then allowed to cool to ambient temperature, filtered through a pad of Celite, and further eluted with CH_2Cl_2. The solvent was removed *in vacuo* and purification by flash column chromatography ($MeOH/CH_2Cl_2$ and EtOAc/hexanes) afforded the desired product.

(2*R*,3*R*)-4: Prepared according to General Procedure 4 from **(2*S*)-2** (64.6 mg) to afford desired product (19.5 mg, 31%) as an amorphous solid.
(2*S*,3*S*)-4: Prepared according to General Procedure 4 from **(2*R*)-2** (64.6 mg) to afford desired product (20.1 mg, 32%) as an amorphous solid.
$[\alpha]^{24}_{D}$ = –141.3 (c = 1.0, $CHCl_3$) **(2*R*,3*R*)-4**
$[\alpha]^{24}_{D}$ = +130.8 (c = 1.0, $CHCl_3$) **(2*S*,3*S*)-4**
^{1}H NMR (400 MHz, $CDCl_3$) δ 11.51 (s, 1H), 8.93 – 8.87 (m, 2H), 8.16 (d, *J* = 8.3 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.49 – 7.43 (m, 1H), 7.33 (d, *J* = 7.7 Hz, 2H), 7.18 (d, *J* = 7.6 Hz, 2H), 4.63 (d, *J* = 7.2 Hz, 1H), 4.09 – 3.97 (m, 2H), 3.91 (t, *J* = 7.0 Hz, 1H), 2.81 (bs, 1H), 2.35 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 148.7, 139.2, 138.0, 136.6, 136.3, 134.4, 129.4, 128.2, 127.4, 126.9, 122.0, 121.6, 116.7, 67.4, 50.3, 44.6, 21.2.
HRMS (ESI^+) m/z calculated for $C_{20}H_{20}N_3O$ $[M+H]^+$ 318.1606; Found 318.1607

Functionalization for Analysis by SFC

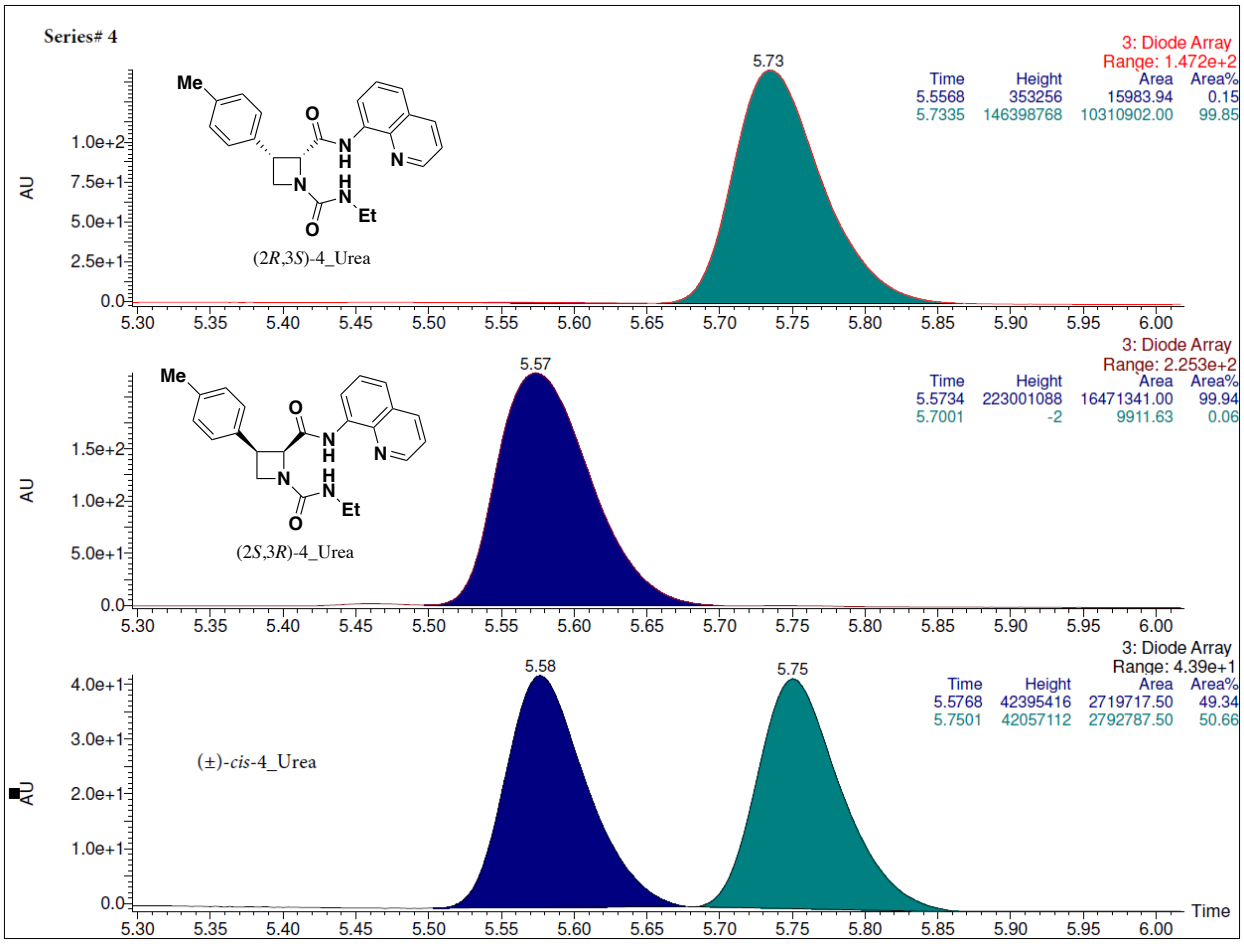
4_Urea: N^1-ethyl-N^2-(quinolin-8-yl)-3-(p-tolyl)azetidine-1,2-dicarboxamide

***Cis* stereoisomers:**

Compound **(±)-*cis*-4_Urea** was prepared according to literature procedures.[10] Analytical data were in agreement with previously reported data.

Single stereoisomers **(2*R*,3*S*)-4_Urea** and **(2*S*,3*R*)-4_Urea** were in turn prepared according to **Derivatization Procedure 2**.

Retention of enantiopurity was determined by SFC (see below). T_{rac} = 5.58 and 5.75 min.



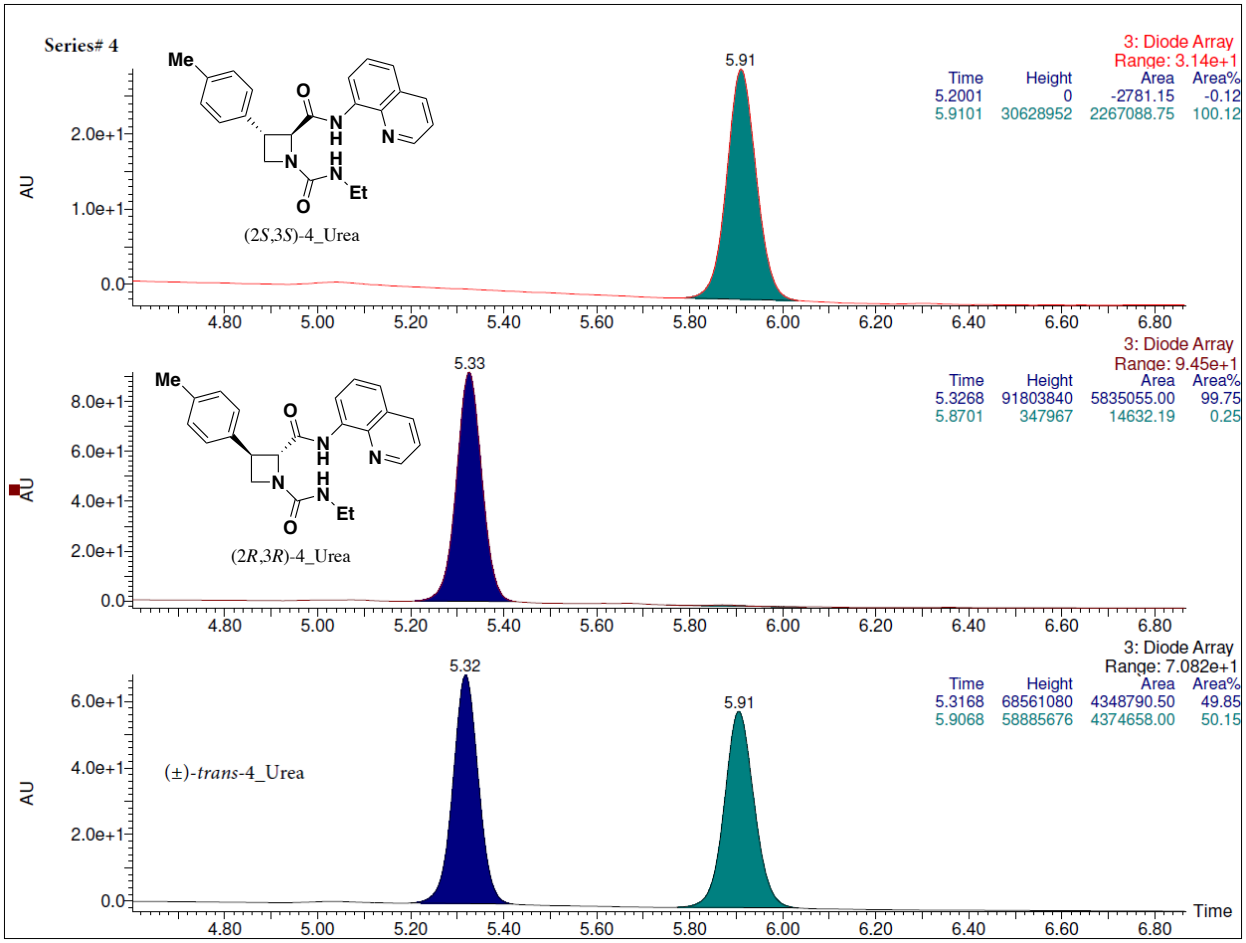
***Trans* stereoisomers:**

Racemate **(±)-*trans*-4_Urea** was prepared according to **Derivatization Procedure 1** from of **(±)-(*trans*)-4** (7.7 mg). Purification by flash column chromatography ($MeOH/CH_2Cl_2$) provided 5.3 mg (56%) of the desired product.

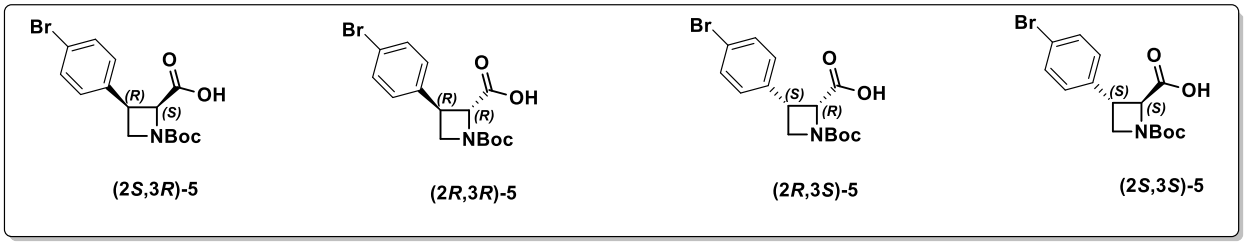
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.82 (s, 1H), 8.88 – 7.73 (m, 2H), 8.16 (d, *J* = 8.2, Hz, 1H), 7.59 – 7.51 (m, 2H), 7.50 – 7.41 (m, 1H), 7.35 (d, *J* = 7.7 Hz, 2H), 7.21 (d, *J* = 7.7, Hz, 2H), 5.07 (t, *J* = 6.0 Hz, 1H), 4.84 (d, *J* = 6.9 Hz, 1H), 4.27 (t, *J* = 7.9 Hz, 1H), 4.15 (t, *J* = 7.5 Hz, 1H), 4.07 (q, *J* = 7.7 Hz, 1H), 3.39 – 3.30 (m, 2H), 2.37 (s, 3H), 1.19 (t, *J* = 7.4 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 161.0, 148.8, 139.1, 137.4, 136.6, 136.3, 134.2, 129.7, 128.1, 127.32, 127.25, 122.4, 121.8, 117.1, 70.8, 53.4, 38.9, 35.5, 21.3, 15.7.
HRMS (ESI^+) m/z calculated for $C_{46}H_{48}N_8O_4Na$ $[2M+Na]^+$ 799.3696; Found 799.3678.

Single stereoisomers **(2*S*,3*S*)-4_Urea** and **(2*R*,3*R*)-4_Urea** were prepared according to **Derivatization Procedure 2**.

Retention of enantiopurity was determined by SFC (see below). T_{rac} = 5.32 and 5.91 min.



Series 5: 3-(4-bromophenyl)-1-(tert-butoxycarbonyl)azetidine-2-carboxylic acid

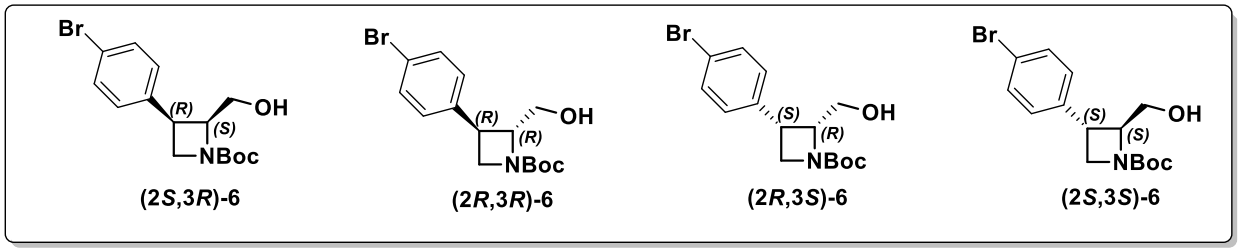


All stereoisomers of chemical series **5** were prepared according to literature procedures.[10] Analytical data were in agreement with previously reported data.

(2*S*,3*R*)-5: Prepared from **(2*S*,3*R*)-3** (1.5 g) to afford the desired product (0.93 g, 67%) as a colorless solid.
(2*R*,3*S*)-5: Prepared from **(2*R*,3*S*)-3** (2.5 g) to afford the desired product (1.6 g, 68%) as a colorless solid.

(2*R*,3*R*)-5: Prepared from **(2*R*,3*R*)-3** (1.0 g) to afford the desired product (0.70 g, 75%) as a brown foamy solid.
(2*S*,3*S*)-5: Prepared from **(2*S*,3*S*)-3** (2.6 g) to afford the desired product (1.2 g, 50%) as a brown foamy solid.

Series 6: tert-butyl 3-(4-bromophenyl)-2-(hydroxymethyl)azetidine-1-carboxylate

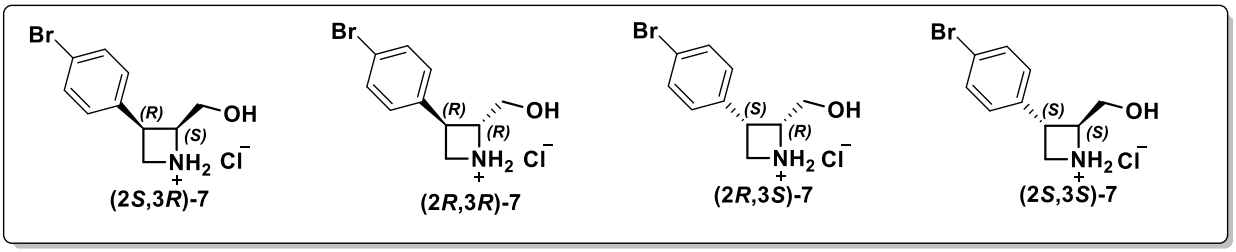


General Procedure 6: To a solution of substrate **5** (1.0 equiv) in THF (0.2 M) at 0 °C was added borane-tetrahydrofuran complex (1.0 M solution in THF, 3.0 equiv) dropwise over 1 min. The reaction was then heated to 50 ºC and stirred for 2 h. Upon completion, the mixture was cooled to 0 °C and MeOH was added dropwise (until bubbling ceased) to quench excess reducing agent. The solvent was removed *in vacuo* and the crude mixture was purified by flash column chromatography (EtOAc/hexanes) to afford product **6**.

(2*S*,3*R*)-6: Prepared according to General Procedure 6 from **(2*S*,3*R*)-5** (200 mg) to afford the desired product (156 mg, 82%) as an amorphous solid.
(2*R*,3*S*)-6: Prepared according to General Procedure 6 from **(2*R*,3*S*)-5** (400 mg) to afford the desired product (302 mg, 79%) as an amorphous solid.
$[\alpha]^{23}_{D}$ = +71.7 (c = 0.5, $CHCl_3$), **(2*S*,3*R*)-6**
$[\alpha]^{23}_{D}$ = −70.1 (c = 0.5, $CHCl_3$), **(2*R*,3*S*)-6**
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.44 (m, 2H), 7.20 – 7.15 (m, 2H), 4.63 (t, *J* = 7.8 Hz, 1H), 4.27 (t, *J* = 8.9 Hz, 1H), 4.05 (dd, *J* = 9.1, 5.1 Hz, 1H), 3.82 – 3.70 (m, 1H), 3.50 (t, *J* = 10.5 Hz, 1H), 3.17 (bs, 1H), 1.49 (s, 9H). One exchangeable proton (hydroxyl O-H) not observed.
^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 131.7, 129.7, 121.3, 81.0, 66.3, 64.5, 52.6, 35.8, 28.4. ^{13}C resonance not observed (Boc carbonyl).
HRMS (ESI^+) m/z calculated for $C_{15}H_{20}BrNO_3Na$ $[M+Na]^+$ 364.0524; Found 364.0517.

(2*R*,3*R*)-6: Prepared according to General Procedure 6 from **(2*R*,3*R*)-5** (200 mg) to afford the desired product (133 mg, 70%) as a colorless oil.
(2*S*,3*S*)-6: Prepared according to General Procedure 6 from **(2*S*,3*S*)-5** (400 mg) to afford the desired product (352 mg, 92%) as a colorless oil.
$[\alpha]^{23}_{D}$ = −0.9 (c = 0.5, $CHCl_3$), **(2*R*,3*R*)-6**
$[\alpha]^{23}_{D}$ = +0.7 (c = 0.5, $CHCl_3$), **(2*S*,3*S*)-6**
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.44 (m, 2H), 7.16 – 7.09 (m, 2H), 4.37 (bs, 1H), 4.15 (t, *J* = 8.6 Hz, 1H), 3.90 (t, *J* = 7.5 Hz, 1H), 3.86 – 3.78 (m, 2H), 3.45 (bs, 1H), 1.47 (s, 9H). One exchangeable proton (hydroxyl O-H) not observed.
^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 132.0, 128.8, 121.2, 80.9, 71.1, 66.0, 53.9, 36.0, 28.5. One ^{13}C resonance not observed (Boc carbonyl).
HRMS (ESI^+) m/z calculated for $C_{15}H_{20}BrNO_3Na$ $[M+Na]^+$ 364.0524; Found 364.0514.

S*eries 7: 3-(4-bromophenyl)-2-(hydroxymethyl)azetidin-1-ium chloride*

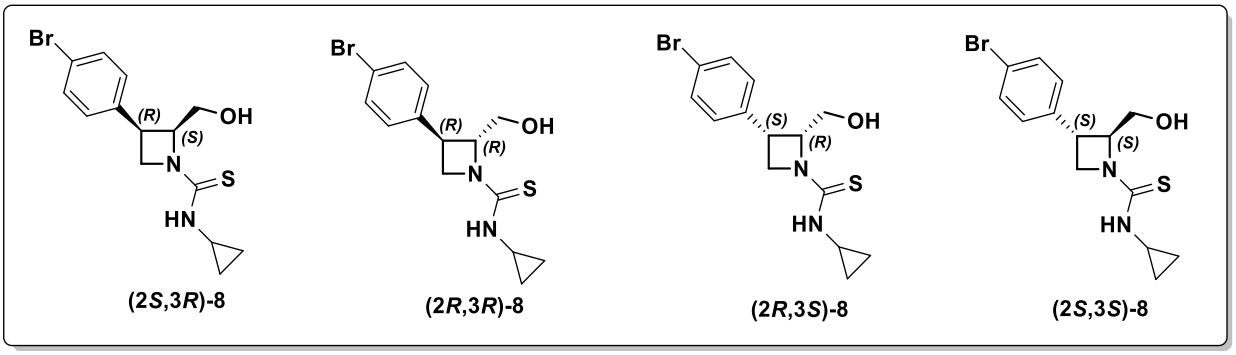


General Procedure 7: To a solution of substrate **6** (1.0 equiv) in CH_2Cl_2 (0.1 M) at ambient temperature was added HCl (4.0 M solution in dioxane, 10 equiv). The mixture was stirred for 2 h at 50 ºC. Upon completion, the reaction mixture was concentrated *in vacuo* to afford product **7**.

(2*S*,3*R*)-7: Prepared according to General Procedure 7 from **(2*S*,3*R*)-6** (18.1 mg) to afford the desired product (15.0 mg, quant.) as a colorless solid.
(2*R*,3*S*)-7: Prepared according to General Procedure 7 from **(2*R*,3*S*)-6** (16.7 mg) to afford the desired product (13.6 mg, quant.) as a colorless solid.
$[\alpha]^{23}_{D}$ = +67.0 (c = 0.5, MeOH), **(2*S*,3*R*)-7**
$[\alpha]^{23}_{D}$ = −66.5 (c = 0.5, MeOH), **(2*R*,3*S*)-7**
^{1}H NMR (400 MHz, CD_3OD) δ 7.58 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 4.80 – 4.71 (m, 1H), 4.54 (t, *J* = 9.0 Hz, 1H), 4.48 – 4.31 (m, 2H), 3.69 – 3.53 (m, 2 H). Three exchangeable protons (2 × ammonium N-H and hydroxyl O-H) not observed.
^{13}C NMR (100 MHz CD_3OD) δ 134.9, 131.1, 130.2, 120.4, 63.5, 58.0, 46.5, 36.7.
HRMS (ESI^+) m/z calculated for $C_{10}H_{13}BrNO$ $[M+H]^+$ 242.0175; Found 242.0172.

(2*R*,3*R*)-7: Prepared according to General Procedure 7 from **(2*R*,3*R*)-6** (15.8 mg) to afford the desired product (13.0 mg, quant.) as a colorless solid.
(2*S*,3*S*)-7: Prepared according to General Procedure 7 from **(2*S*,3*S*)-6** (16.9 mg) to afford the desired product (13.2 mg, 97%) as a colorless solid.
$[\alpha]^{23}_{D}$ = −46.0 (c = 0.5, MeOH), **(2*R*,3*R*)-7**
$[\alpha]^{23}_{D}$ = +46.9 (c = 0.5, MeOH), **(2*S*,3*S*)-7**
^{1}H NMR (400 MHz, CD_3OD) δ 7.62 – 7.57 (m, 2H), 7.39 – 7.34 (m, 2H), 4.65 – 4.56 (m, 1H), 4.27 – 4.13 (m, 3H), 3.94 – 3.85 (m, 2H). Three exchangeable protons (2 × ammonium N-H and hydroxyl O-H) not observed.
^{13}C NMR (100 MHz, CD_3OD) δ 138.6, 133.2, 130.1, 122.8, 69.6, 60.5, 49.8, 38.9.
HRMS (ESI^+) m/z calculated for $C_{10}H_{13}BrNO$ $[M+H]^+$ 242.0175; Found 242.0171.

Series 8: 3-(4-bromophenyl)-N-cyclopropyl-2-(hydroxymethyl)azetidine-1-carbothioamide

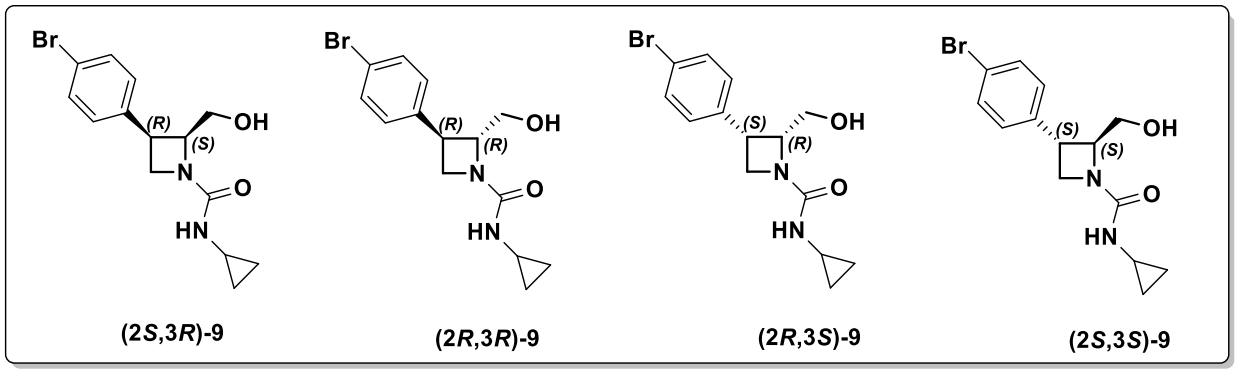


General Procedure 8: To a solution of substrate **7** (1.0 equiv) in DCE (0.2 M) at ambient temperature was added *N*,*N*-diisopropylethylamine (2.0 equiv) and cyclopropyl isothiocyanate (1.0 equiv). The reaction mixture was then heated to 50 °C and stirred for 2 h. Upon completion, the mixture was allowed to reach ambient temperature and MeOH (2 mL) was added to the reaction mixture to quench excess electrophile. The mixture was then concentrated *in vacuo* and purified by flash column chromatography ($MeOH/CH_2Cl_2$) to afford product **8**.

(2*S*,3*R*)-8: Prepared according to General Procedure 8 from **(2*S*,3*R*)-7** (37 mg) to afford the desired product (30 mg, 67%) as an amorphous solid.
(2*R*,3*S*)-8: Prepared according to General Procedure 8 from **(2*R*,3*S*)-7** (20 mg) to afford the desired product (17 mg, 85%) as an amorphous solid.
$[\alpha]^{23}_D$ = +63.5 (c = 0.5, MeOH), **(2*S*,3*R*)-8**
$[\alpha]^{23}_D$ = −58.4 (c = 0.5, $CHCl_3$), **(2*R*,3*S*)-8**
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.2 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 4.61 (bs, 1H), 4.54 (t, *J* = 9.5 Hz, 1H), 4.23 (dd, *J* = 9.9, 4.9 Hz, 1H), 3.79 (td, *J* = 8.8, 4.8 Hz, 1H), 3.52 (t, *J* = 10.6 Hz, 1H), 3.27 (d, *J* = 11.3 Hz, 1H), 3.05 – 2.95 (m, 1H), 0.90 – 0.75 (m, 2H), 0.64 – 0.48 (m, 2H). Two exchangeable protons (thiourea N-H and hydroxyl O-H) not observed.
^{13}C NMR (100 MHz, $CDCl_3$) δ 184.8, 135.9, 131.9, 130.0, 121.8, 68.5, 65.0, 55.3, 34.9, 27.5, 7.7, 7.3.
HRMS (ESI^+) m/z calculated for $C_{14}H_{18}BrN_2OS$ $[M+H]^+$ 341.0323; Found 341.0313.

(2*R*,3*R*)-8: Prepared according to General Procedure 8 from **(2*R*,3*R*)-7** (108 mg) to afford the desired product (73 mg, 55%) as an amorphous solid.
(2*S*,3*S*)-8: Prepared according to General Procedure 8 from **(2*S*,3*S*)-7** (20 mg) to afford the desired product (15 mg, 75%) as an amorphous solid.
$[\alpha]^{23}_D$ = +44.2 (c = 0.5, $CHCl_3$), **(2*R*,3*R*)-8**
$[\alpha]^{23}_D$ = −45.5 (c = 0.5, $CHCl_3$), **(2*S*,3*S*)-8**
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.42 (m, 2H), 7.15 – 7.08 (m, 2H), 4.40 (bs, 1H), 4.33 (t, *J* = 8.9 Hz, 1H), 4.13 (t, *J* = 8.1 Hz, 1H), 4.00 – 3.87 (m, 2H), 3.57 (bs, 1H), 3.31 (q, *J* = 7.5 Hz, 1H), 3.04 – 2.93 (m, 1H), 0.87 – 0.77 (m, 2H), 0.65 – 0.47 (m, 2H). One exchangeable proton (thiourea N-H) not observed.
^{13}C NMR (100 MHz, $CDCl_3$) δ 184.7, 138.6, 132.1, 128.9, 121.5, 73.4, 65.9, 56.2, 35.5, 27.4, 7.7, 7.4.
HRMS (ESI^+) m/z calculated for $C_{14}H_{18}BrN_2OS$ $[M+H]^+$ 341.0323; Found 341.0313.

Series 9: 3-(4-bromophenyl)-N-cyclopropyl-2-(hydroxymethyl)azetidine-1-carboxamide

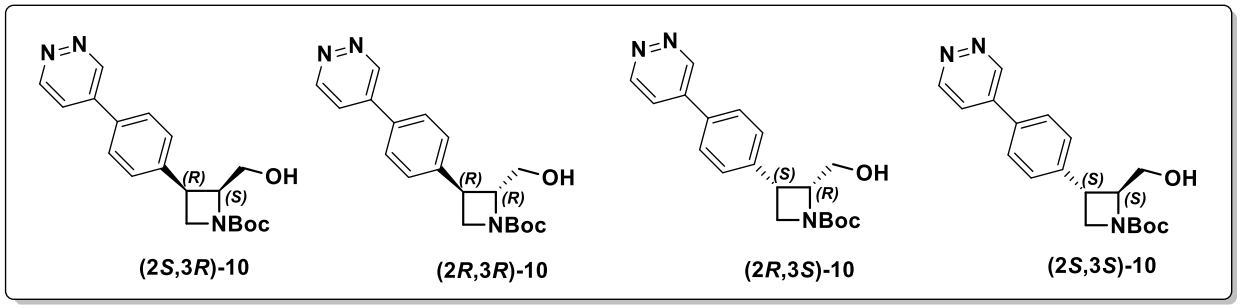


General Procedure 9: To a solution of substrate **7** (1.0 equiv) in CH_2Cl_2 (0.1 M) at ambient temperature were added *N*,*N*-diisopropylethylamine (1.1 equiv) and cyclopropyl isocyanate (1.0 equiv). The reaction mixture was then stirred at ambient temperature for 10 min. Methanol was added to the reaction mixture to quench excess electrophile. The mixture was then concentrated *in vacuo* and purified by flash column chromatography ($MeOH/CH_2Cl_2$) to afford desired product **9**.

(2*S*,3*R*)-9: Prepared according to General Procedure 9 from **(2*S*,3*R*)-7** (14.0 mg) to afford the desired product (14.0 mg, 85%) as a colorless solid.
(2*R*,3*S*)-9: Prepared according to General Procedure 9 from **(2*R*,3*S*)-7** (12.0 mg) to afford the desired product (11.7 mg, 84%) as a colorless solid.
$[\alpha]^{23}_D$ = +59.6 (c = 0.5, MeOH), **(2*S*,3*R*)-9**
$[\alpha]^{23}_D$ = −63.4 (c = 0.5, MeOH), **(2*R*,3*S*)-9**
^{1}H NMR (400 MHz, CD_3OD) δ 7.53 – 7.46 (m, 2H), 7.31 – 7.25 (m, 2H), 4.49 (td, *J* = 9.2, 3.0 Hz, 1H), 4.26 (t, *J* = 8.7 Hz, 1H), 3.96 (dd, *J* = 8.6, 4.5 Hz, 1H), 3.81 (td, *J* = 8.9, 4.4 Hz, 1H), 3.36 – 3.32 (m, 1H), 3.16 (dd, *J* = 11.1, 3.0 Hz, 1H), 2.57 – 2.48 (m, 1H), 0.71 – 0.64 (m, 2H), 0.46 – 0.39 (m, 2H). Two exchangeable protons (urea N-H and hydroxyl O-H) not observed.
^{13}C NMR (100 MHz CD_3OD) δ 164.2, 138.5, 132.6, 131.3, 122.0, 67.5, 64.8, 52.9, 36.7, 23.3, 7.1, 6.7.
HRMS (ESI^+) m/z calculated for $C_{14}H_{18}BrN_2O_2$ $[M+H]^+$ 325.0552; Found 325.0543.

(2*R*,3*R*)-9: Prepared according to General Procedure 9 from **(2*R*,3*R*)-7** (12.0 mg) to afford the desired product (11.0 mg, 79%) as a colorless solid.
(2*S*,3*S*)-9: Prepared according to General Procedure 9 from **(2*S*,3*S*)-7** (11.5 mg) to afford the desired product (10.8 mg, 81%) as a colorless solid.
$[\alpha]^{23}_D$ = +10.1 (c = 0.5, $CHCl_3$), **(2*R*,3*R*)-9**
$[\alpha]^{23}_D$ = −8.6 (c = 0.5, $CHCl_3$), **(2*S*,3*S*)-9**
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 5.30 (d, *J* = 4.2 Hz, 1H), 4.44 – 4.30 (m, 2H), 4.12 (t, *J* = 8.0 Hz, 1H), 3.88 (t, *J* = 7.4 Hz, 1H), 3.85 – 3.76 (m, 2H), 3.35 (q, *J* = 7.7 Hz, 1H), 2.64 – 2.57 (m, 1H), 0.76 – 0.68 (m, 2H), 0.53 – 0.45 (m, 2H). One exchangeable proton (hydroxyl O-H) not observed.
^{13}C NMR (100 MHz $CDCl_3$) δ 161.4, 138.9, 132.0, 128.8, 121.3, 71.1, 66.6, 53.3, 36.3, 23.0, 7.0, 6.9.
HRMS (ESI^+) m/z calculated for $C_{14}H_{18}BrN_2O_2$ $[M+H]^+$ 325.0552 Found 325.0545.

Series 10: tert-butyl (2-(hydroxymethyl)-3-(4-(pyridazin-4-yl)phenyl)azetidine-1-carboxylate

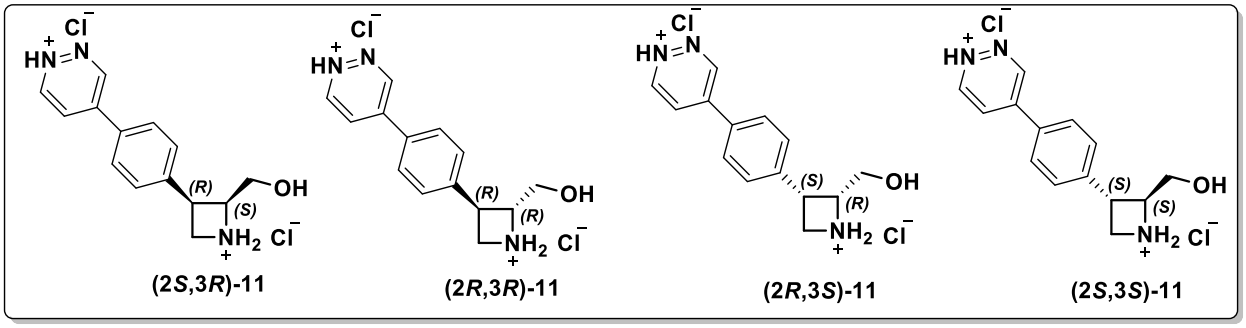


General Procedure 10: To a vial containing substrate **6** (1.0 equiv) were added pyridazine-4-boronic acid pinacol ester (1.2 equiv), XPhos-Pd-G3 (10 mol%), and K_2CO_3 (2.0 equiv). The vial was sealed and then evacuated and backfilled with N_2 (3×). THF and deionized H_2O (2:1, 0.2 M) were added, and the reaction mixture was heated to 80 °C for 15 h. Upon completion, the reaction was allowed to reach ambient temperature, and the crude material was concentrated *in vacuo* and purified by flash column chromatography ($MeOH/CH_2Cl_2$) to afford product **10**.

(2*S*,3*R*)-10: Prepared according to General Procedure 10 from **(2*S*,3*R*)-6** (37.0 mg) to afford the desired product (30.0 mg, 67%) as an amorphous solid.
(2*R*,3*S*)-10: Prepared according to General Procedure 10 from **(2*R*,3*S*)-6** (44.0 mg) to afford desired the product (24.0 mg, 55%) as an amorphous solid.
$[\alpha]^{23}_D$ = +69.2 (c = 0.5, $CHCl_3$), **(2*S*,3*R*)-10**
$[\alpha]^{23}_D$ = −66.0 (c = 0.5, $CHCl_3$), **(2*R*,3*S*)-10**
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1H), 9.23 (d, *J* = 5.3 Hz, 1H), 7.70 – 7.62 (m, 3H), 7.49 (d, *J* = 7.9 Hz, 2H), 4.70 (t, *J* = 8.1 Hz, 1H), 4.32 (t, *J* = 8.8 Hz, 1H), 4.14 (dd, *J* = 9.2, 5.1 Hz, 1H), 4.08 (bs, 1H), 3.89 (s, 1H), 3.55 (t, *J* = 9.7 Hz, 1H), 3.23 (bs, 1H), 1.50 (s, 9H).
^{13}C NMR (100 MHz $CDCl_3$) δ 151.6, 149.9, 139.7, 138.0, 133.8, 129.5, 127.4, 123.2, 81.2, 66.6, 64.5, 52.5, 36.2, 28.5. One ^{13}C resonance not observed (Boc carbonyl).
HRMS (ESI^+) m/z calculated for $C_{19}H_{24}N_3O_3$ $[M+H]^+$ 342.1818; Found 342.1807.

(2*R*,3*R*)-10: Prepared according to General Procedure 10 from **(2*R*,3*R*)-6** (32.0 mg) to afford the desired product (17.5 mg, 54%) as an amorphous solid.
(2*S*,3*S*)-10: Prepared according to General Procedure 10 from **(2*S*,3*S*)-6** (150 mg) to afford the desired product (119 mg, 80%) as an amorphous solid.
$[\alpha]^{23}_D$ = −3.2 (c = 0.5, $CHCl_3$), **(2*R*,3*R*)-10**
$[\alpha]^{23}_D$ = +3.8 (c = 0.5, $CHCl_3$), **(2*S*,3*S*)-10**
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1H), 9.22 (d, *J* = 5.3 Hz, 1H), 7.70 – 7.60 (m, 3H), 7.44 (d, *J* = 7.8 Hz, 2H), 4.45 (bs, 1H), 4.21 (t, *J* = 8.6 Hz, 1H), 3.99 (t, *J* = 7.8 Hz, 1H), 3.89 (s, 2H), 3.59 (bs, 1H), 1.48 (s, 9H). One exchangeable protons (hydroxyl O-H) not observed.
^{13}C NMR (100 MHz $CDCl_3$) δ 151.5, 149.9, 142.8, 138.1, 133.6, 128.4, 127.6, 123.2, 81.0, 71.1, 65.8, 53.7, 36.2, 28.5. One ^{13}C resonance not observed (Boc carbonyl).
HRMS (ESI^+) m/z calculated for $C_{19}H_{24}N_3O_3$ $[M+H]^+$ 342.1818; Found 342.1806.

Series 11: 4-(4-2-(hydroxymethyl)azetidin-1-ium-3-yl)phenyl)pyridazin-1-ium dichloride

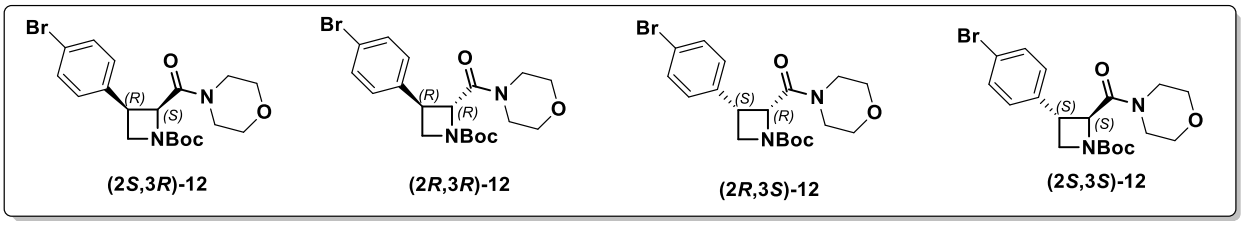


General Procedure 11: To a solution of substrate **10** (1.0 equiv) in dioxane (0.1 M) at ambient temperature was added HCl (4.0 M solution in dioxane, 15 equiv). The mixture was stirred for 2 h at 50 ºC. Upon completion, the reaction mixture was concentrated *in vacuo* to afford product **11**.

(2*S*,3*R*)-11: Prepared according to General Procedure 11 from **(2*S*,3*R*)-10** (25.0 mg) to afford the desired product (23.0 mg, quant.) as an amorphous solid.
(2*R*,3*S*)-11: Prepared according to General Procedure 11 from **(2*R*,3*S*)-10** (15.0 mg) to afford the desired product (14.3 mg, quant.) as an amorphous solid.
$[\alpha]^{24}_{D}$ = +71.8 (c = 0.1, MeOH), **(2*S*,3*R*)-11**
$[\alpha]^{23}_{D}$ = −68.4 (c = 0.1, MeOH), **(2*R*,3*S*)-11**
^{1}H NMR (400 MHz, D_2O) δ 9.73 (dd, *J* = 2.5, 1.1 Hz, 1H), 9.41 (dd, *J* = 5.9, 1.1 Hz, 1H), 8.53 (dd, *J* = 5.9, 2.5 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.3 Hz, 2H), 4.89 (ddd, *J* = 12.3, 7.4, 3.2 Hz, 1H), 4.70 – 4.55 (m, 2H), 4.52 – 4.39 (m, 1H), 3.75 (dd, *J* = 12.8, 7.7 Hz, 1H), 3.66 (dd, *J* = 12.8, 4.4 Hz, 1H). All four exchangeable protons not observed.
^{13}C NMR (100 MHz D_2O) δ 150.2, 149.4, 145.1, 139.0, 131.4, 129.1, 128.7, 128.4, 64.4, 58.3, 47.5, 37.4.
HRMS (ESI^+) m/z calculated for $C_{14}H_{16}N_3O$ $[M+H]^+$ 242.1288; Found 242.1285.
Elemental Analysis calculated for $C_{14}H_{17}Cl_2N_3O$: C 53.52%, H 5.45%, N 13.37%, Cl 22.56%; found: C 50.83%, H 5.38%, N 12.67%, Cl 23.03%.

(2*R*,3*R*)-11: Prepared according to General Procedure 11 from **(2*R*,3*R*)-10** (17.5 mg) to afford desired product (16.0 mg, quant.) as an amorphous solid.
(2*S*,3*S*)-11: Prepared according to General Procedure 11 from **(2*S*,3*S*)-10** (24.8 mg) to afford desired product (22.7 mg, quant.) as an amorphous solid.
$[\alpha]^{24}_{D}$ = −64.8 (c = 0.2, MeOH), **(2*R*,3*R*)-11**
$[\alpha]^{24}_{D}$ = +65.0 (c = 0.1, MeOH), **(2*S*,3*S*)-11**
^{1}H NMR (400 MHz, D_2O) δ 9.73 – 9.71 (m, 1H), 9.41 (d, *J* = 5.9 Hz, 1H), 8.58 (dd, *J* = 5.9, 2.4 Hz, 1H), 7.97 (d, *J* = 8.3 Hz, 2H), 7.64 – 7.57 (m, 2H), 4.75 – 4.72 (m, 1H), 4.34 – 4.20 (m, 3H), 3.96 (d, *J* = 4.4 Hz, 2H). All four exchangeable protons not observed.
^{13}C NMR (100 MHz D_2O) δ 150.7, 149.5, 146.5, 142.7, 131.6, 129.8, 129.3, 129.0, 68.0, 60.1, 49.2, 38.4.
HRMS (ESI^+) m/z calculated for $C_{14}H_{16}N_3O$ $[M+H]^+$ 242.1288; Found 242.1285.
Elemental Analysis calculated for $C_{14}H_{17}Cl_2N_3O$: C 53.52%, H 5.45%, N 13.37%, Cl 22.56%; found: C 53.31%, H 5.62%, N 12.67%, Cl 21.00%.

Series 12: tert-butyl 3-(4-bromophenyl)-2-(morpholine-4-carbonyl)azetidine-1-carboxylate

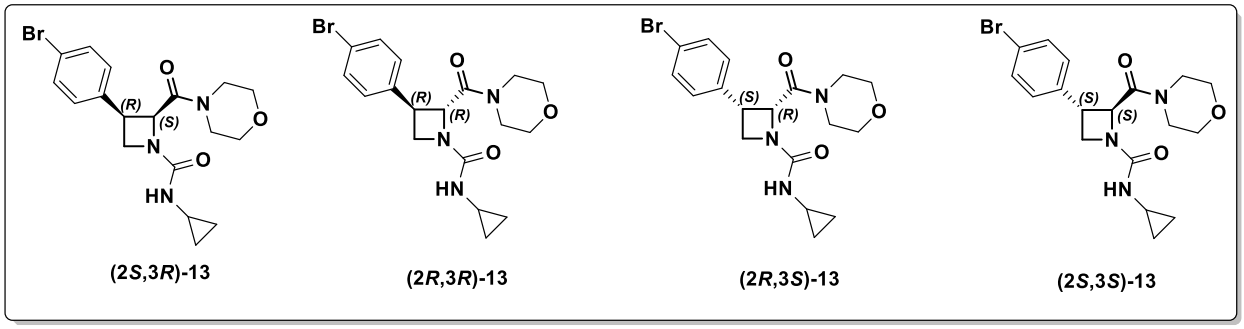


General Procedure 12: To a solution of substrate **5** (1.0 equiv) in DMF (0.25 M) at 0 °C were added *N*,*N*-diisopropylethylamine (2.0 equiv), HATU (1.0 equiv), and morpholine (1.1 equiv). The reaction mixture was allowed to reach ambient temperature and was stirred for 30 min. Upon completion, the reaction mixture was diluted with saturated $NaHCO_3$ and extracted with EtOAc (3×). The combined organic layers were washed with saturated $NaHCO_3$ (2×), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (EtOAc/hexanes) provided product **12**.

(2*S*,3*R*)-12: Prepared according to General Procedure 12 from **(2*S*,3*R*)-5** (280 mg) to afford the desired product (245 mg, 73%) as a colorless amorphous solid.
(2*R*,3*S*)-12: Prepared according to General Procedure 12 from **(2*R*,3*S*)-5** (380 mg) to afford desired product (327 mg, 72%) as a colorless amorphous solid.
$[\alpha]^{23}_{D}$ = +10.4 (c = 0.5, $CHCl_3$), **(2*S*,3*R*)-12**
$[\alpha]^{23}_{D}$ = −11.6 (c = 0.5, $CHCl_3$), **(2*R*,3*S*)-12**
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 5.17 (d, *J* = 9.0 Hz, 1H), 4.22 – 4.12 (m, 2H), 3.99 (q, *J* = 8.4 Hz, 1H), 3.57 – 3.50 (m, 1H), 3.46 – 3.39 (m, 2H), 3.30 – 3.21 (m, 1H), 3.17 – 3.03 (m, 2H), 2.74 – 2.65 (m, 2H), 1.47 (s, 9H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 155.8, 135.9, 131.7, 130.4, 122.2, 80.2, 66.5, 65.9, 64.8, 55.1, 44.5, 41.7, 37.7, 28.4.
HRMS (ESI^+) m/z calculated for $C_{19}H_{25}BrN_2O_4Na$ $[M+Na]^+$ 447.0895; Found 447.0879.

(2*R*,3*R*)-12: Prepared according to General Procedure 12 from **(2*R*,3*R*)-5** (100 mg) to afford the desired product (107 mg, 90%) as an amorphous solid.
(2*S*,3*S*)-12: Prepared according to General Procedure 12 from **(2*S*,3*S*)-5** (350 mg) to afford desired product (326 mg, 78%) as an amorphous solid.
$[\alpha]^{22}_{D}$ = −38.0 (c = 0.5, $CHCl_3$), **(2*R*,3*R*)-12**
$[\alpha]^{24}_{D}$ = +36.4 (c = 0.5, $CHCl_3$), **(2*S*,3*S*)-12**
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.9 Hz, 2H), 7.24 (d, *J* = 8.1 Hz, 2H), 4.82 (d, *J* = 4.8 Hz, 1H), 4.43 (t, *J* = 8.3 Hz, 1H), 3.84 (t, *J* = 6.8 Hz, 1H), 3.77 – 3.52 (m, 6H), 3.50 – 3.43 (m, 1H), 3.31 (s, 1H), 3.20 – 3.09 (m, 1H), 1.46 (s, 9H).
^{13}C NMR (100 MHz $CDCl_3$) δ 167.95, 155.85, 139.75, 132.39, 128.74, 121.83, 80.49, 66.98, 66.75, 66.31, 55.30, 45.75, 42.71, 38.59, 28.51.
HRMS (ESI^+) m/z calculated for $C_{19}H_{25}BrN_2O_4Na$ $[M+Na]^+$ 447.0895; Found 447.0885.

Series 13: 3-(4-bromophenyl)-N-cyclopropyl-2-(morpholine-4-carbonyl)azetidine-1-carboxamide



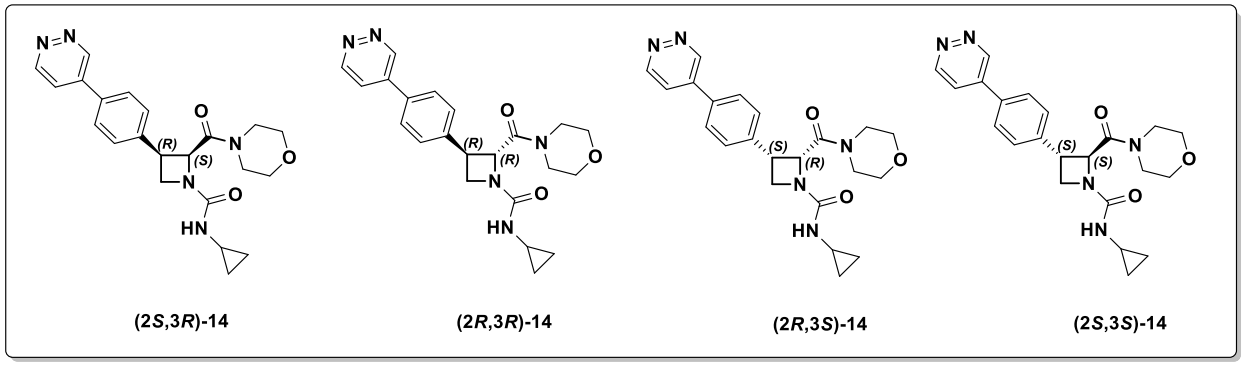
General Procedure 13: To a solution of substrate **12** (1.0 equiv) in dioxane (0.4 M) at ambient temperature was added HCl (4.0 M solution in dioxane, 10 equiv), and the reaction was allowed to stir for 2 h. The reaction was then diluted tenfold with additional dioxane, and triethylamine (15 equiv) and cyclopropyl isocyanate (1.5 equiv) were added sequentially, and the mixture was allowed to stir for an additional hour. Upon completion, the reaction mixture was diluted with water and extracted with CH_2Cl_2 (3×). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography ($MeOH/CH_2Cl_2$) provided product **13**.

(2*S*,3*R*)-13: Prepared according to General Procedure 13 from **(2*S*,3*R*)-12** (25.0 mg) to afford the desired product (21.0 mg, 88%) as a colorless amorphous solid.
(2*R*,3*S*)-13: Prepared according to General Procedure 13 from **(2*R*,3*S*)-12** (110 mg) to afford the desired product (90.0 mg, 86%) as a colorless amorphous solid.
$[\alpha]^{22}_D$ = −129.9 (c = 0.5, $CHCl_3$), **(2*S*,3*R*)-13**
$[\alpha]^{22}_D$ = +130.9 (c = 0.5, $CHCl_3$), **(2*R*,3*S*)-13**
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 7.3 Hz, 2H), 5.82 (bs, 1H), 5.07 (d, *J* = 8.5 Hz, 1H), 4.41 (t, *J* = 8.2 Hz, 1H), 3.76 (td, *J* = 8.5, 3.5 Hz, 1H), 3.62 – 3.46 (m, 3H), 3.31 (m, 2H), 3.17 – 3.06 (m, 2H), 2.89 – 2.76 (m, 2H), 2.63 (s, 1H), 0.75 – 0.62 (m, 2H), 0.53 – 0.42 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 161.8, 137.8, 131.9, 129.6, 122.0, 67.0, 66.4, 65.8, 53.8, 44.5, 41.7, 39.2, 22.8, 7.1, 6.2.
HRMS (ESI^+) m/z calculated for $C_{18}H_{23}BrN_3O_3$ $[M+H]^+$ 408.0923; Found 408.0911.

(2*R*,3*R*)-13: Prepared according to General Procedure 13 from **(2*R*,3*R*)-12** (42 mg) to afford the desired product (35.0 mg, 87%) as a colorless amorphous solid.
(2*S*,3*S*)-13: Prepared according to General Procedure 13 from **(2*S*,3*S*)-12** (26.0 mg) to afford the desired product (22.0 mg, 88%) as a colorless amorphous solid.
$[\alpha]^{22}_D$ = +3.3 (c = 0.5, $CHCl_3$), **(2*R*,3*R*)-13**
$[\alpha]^{22}_D$ = −3.2 (c = 0.5, $CHCl_3$), **(2*S*,3*S*)-13**
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.9 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 5.19 (bs, 1H), 4.86 (d, *J* = 6.2 Hz, 1H), 4.24 (t, *J* = 8.0 Hz, 1H), 3.89 (t, *J* = 7.0 Hz, 1H), 3.77 – 3.59 (m, 5H), 3.54 – 3.38 (m, 2H), 3.28 – 3.18 (m, 1H), 3.12 – 2.98 (m, 1H), 2.66 – 2.58 (m, 1H), 0.77 – 0.65 (m, 2H), 0.55 – 0.45 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 160.9, 138.9, 132.3, 128.9, 122.0, 67.6, 66.7, 66.5, 54.7, 45.7, 42.7, 39.1, 22.9, 7.0, 6.6.

HRMS (ESI^+) m/z calculated for $C_{18}H_{23}BrN_3O_3$ $[M+H]^+$ 408.0923; Found 408.0913.

Series 14: N-cyclopropyl-2-(morpholine-4-carbonyl)-3-(4-(pyridazin-4-yl)phenyl)azetidine-1-carboxamide



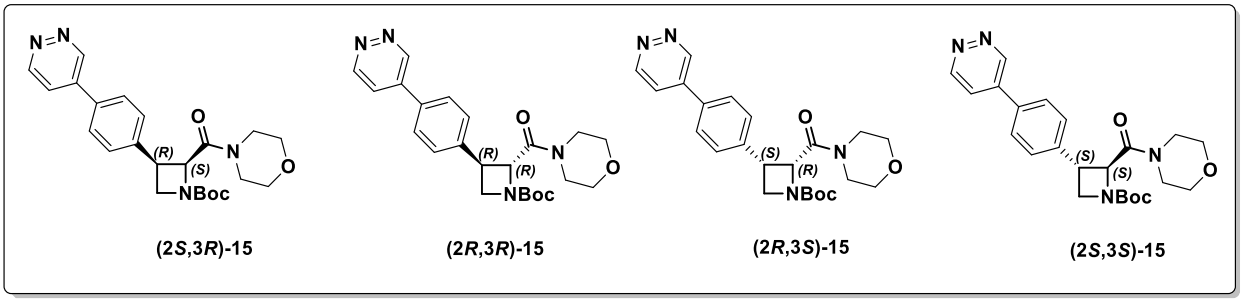
General Procedure 14: To a vial containing substrate **13** (1.0 equiv) were added pyridazine-4-boronic acid pinacol ester (1.25 equiv), XPhos-Pd-G3 (10 mol%), and K_2CO_3 (2.0 equiv). The vial was sealed and then evacuated and backfilled with N_2 (3×). THF and deionized H_2O (2:1, 0.3 M) were added, and the reaction mixture was heated to 80 °C for 15 h. Upon completion, the reaction was allowed to reach ambient temperature, and the crude material was concentrated *in vacuo* and purified by flash column chromatography ($MeOH/CH_2Cl_2$) to afford product **14**.

(2*S*,3*R*)-14: Prepared according to General Procedure 14 from **(2*S*,3*R*)-13** (50.0 mg) to afford the desired product (20.0 mg, 40%) as a yellow amorphous solid.
(2*R*,3*S*)-14: Prepared according to General Procedure 14 from **(2*R*,3*S*)-13** (50.0 mg) to afford the desired product (20.5 mg, 41%) as a yellow amorphous solid.
$[\alpha]^{22}_D$ = +109.0 (c = 0.5, $CHCl_3$), **(2*S*,3*R*)-14**
$[\alpha]^{22}_D$ = −116.7 (c = 0.5, $CHCl_3$), **(2*R*,3*S*)-14**
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1H), 9.24 (d, *J* = 5.4 Hz, 1H), 7.69 (d, *J* = 7.9 Hz, 2H), 7.67 – 7.63 (m, 1H), 7.59 (d, *J* = 7.9 Hz, 2H), 5.87 (s, 1H), 5.13 (d, *J* = 8.5 Hz, 1H), 4.47 (t, *J* = 8.3 Hz, 1H), 3.92 – 3.84 (m, 1H), 3.70 – 3.64 (m, 1H), 3.57 – 3.45 (m, 2H), 3.38 – 3.24 (m, 2H), 3.21 – 3.12 (m, 1H), 3.11 – 3.02 (m, 1H), 2.94 – 2.85 (m, 2H), 2.68 – 2.60 (m, 1H), 0.78 – 0.64 (m, 2H), 0.56 – 0.43 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0, 161.9, 151.4, 149.6, 141.2, 137.5, 134.3, 129.2, 127.4, 123.0, 67.0, 66.4, 65.9, 53.8, 44.5, 41.8, 39.4, 22.8, 7.1, 6.3.
HRMS (ESI^+) m/z calculated for $C_{22}H_{26}N_5O_3$ $[M+H]^+$ 408.2036; Found 408.2020.

(2*R*,3*R*)-14: Prepared according to General Procedure 14 from **(2*R*,3*R*)-13** (33.0 mg) to afford the desired product (19.5 mg, 59%) as a colorless amorphous solid.
(2*S*,3*S*)-14: Prepared according to General Procedure 14 from **(2*S*,3*S*)-13** (21.0 mg) to afford the desired product (11.0 mg, 53%) as a colorless amorphous solid.
$[\alpha]^{22}_D$ = −23.8 (c = 0.5, $CHCl_3$), **(2R,3*R*)-14**
$[\alpha]^{22}_D$ = +26.0 (c = 0.5, $CHCl_3$), **(2*S*,3*S*)-14**
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1H), 9.24 (d, *J* = 5.4 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 2H), 7.66 – 7.62 (m, 1H), 7.54 (d, *J* = 7.9 Hz, 2H), 5.17 (s, 1H), 4.96 (d, *J* = 5.9 Hz, 1H), 4.31 (t, *J* = 7.8 Hz, 1H), 3.96 (t, *J* = 6.9 Hz, 1H), 3.89 (q, *J* = 6.9 Hz, 1H), 3.77 – 3.60 (m, 4H), 3.57 – 3.40 (m, 2H), 3.37 – 3.25 (m, 1H), 3.18 – 3.06 (m, 1H), 2.69 – 2.60 (m, 1H), 0.80 – 0.65 (m, 2H), 0.57 – 0.45 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 160.8, 151.5, 149.7, 142.2, 137.5, 134.3, 128.4, 127.9, 123.1, 67.3, 66.7, 66.6, 54.8, 45.8, 42.7, 39.1, 22.9, 7.0, 6.7.
HRMS (ESI^+) m/z calculated for $C_{22}H_{26}N_5O_3$ $[M+H]^+$ 408.2036; Found 408.2020.

Series 15: tert-butyl 2-(morpholine-4-carbonyl)-3-(4-(pyridazin-4-yl)phenyl)azetidine-1-carboxylate

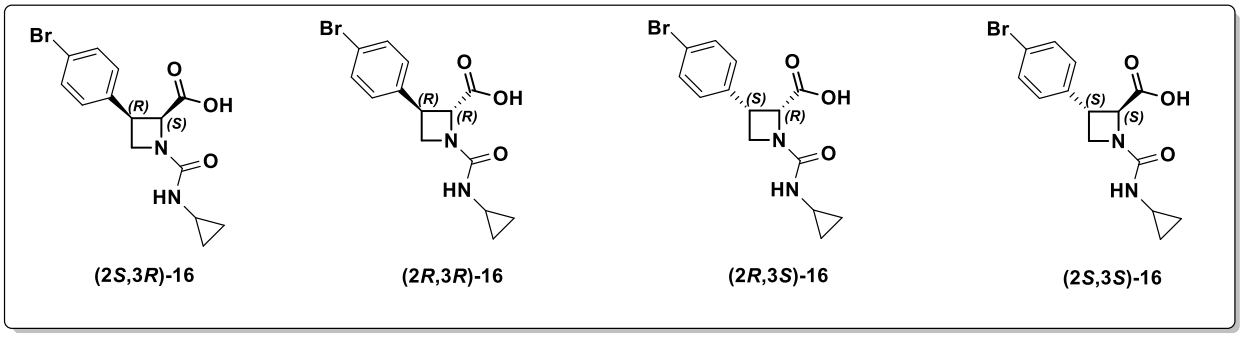


General Procedure 15: To a vial containing substrate **12** (1.0 equiv) were added pyridazine-4-boronic acid pinacol ester (1.25 equiv), XPhos-Pd-G3 (10 mol%), and K_2CO_3 (2.0 equiv). The vial was sealed and then evacuated and backfilled with N_2 (3×). THF and deionized H_2O (2:1, 0.3 M) were added, and the reaction mixture was heated to 80 °C for 15 h. Upon completion, the reaction was allowed to reach ambient temperature, and the crude material was concentrated *in vacuo* and purified by flash column chromatography ($MeOH/CH_2Cl_2$) to afford product **15**.

(2*S*,3*R*)-15 Prepared according to General Procedure 15 from **(2*S*,3*R*)-12** (51.0 mg) to afford the desired product (23.0 mg, 46%) as a yellow amorphous solid.
(2*R*,3*S*)-15: Prepared according to General Procedure 15 from **(2*R*,3*S*)-12** (20.0 mg) to afford the desired product (10.0 mg, 50%) as a yellow amorphous solid.
$[\alpha]^{24}_D$ = +15.0 (c = 0.5, $CHCl_3$), **(2*S*,3*R*)-15**
$[\alpha]^{22}_D$ = −14.2 (c = 0.5, $CHCl_3$), **(2*R*,3*S*)-15**
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.45 (s, 1H), 9.23 (d, *J* = 5.4 Hz, 1H), 7.69 – 7.61 (m, 3H), 7.55 (d, *J* = 7.8 Hz, 2H), 5.23 (d, *J* = 9.0 Hz, 1H), 4.23 (d, *J* = 7.9 Hz, 2H), 4.11 (q, *J* = 8.3 Hz, 1H), 3.53 – 3.32 (m, 3H), 3.31 – 3.16 (m, 2H), 3.06 – 2.94 (m, 1H), 2.84 – 2.66 (m, 2H), 1.48 (s, 9H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 155.9, 151.4, 149.6, 139.3, 137.5, 134.3, 130.0, 127.1, 123.1, 80.3, 66.5, 65.9, 64.7, 55.1, 44.6, 41.7, 37.9, 28.4.
HRMS (ESI^+) m/z calculated for $C_{23}H_{29}N_4O_4$ $[M+H]^+$ 425.2019; Found 425.2175.

(2*R*,3*R*)-15: Prepared according to General Procedure 15 from **(2*R*,3*R*)-12** (40.0 mg) to afford the desired product (33.0 mg, 83%) as a colorless amorphous solid.
(2*S*,3*S*)-15: Prepared according to General Procedure 15 from **(2*S*,3*S*)-12** (55.0 mg) to afford the desired product (50.0 mg, 92%) as a colorless amorphous solid.
$[\alpha]^{22}_D$ = −51.6 (c = 0.5, $CHCl_3$), **(2R,3*R*)-15**
$[\alpha]^{22}_D$ = 50.6 (c = 0.5, $CHCl_3$), **(2*S*,3*S*)-15**
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 9.25 (d, *J* = 5.4 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 2H), 7.67 – 7.62 (m, 1H), 7.55 (d, *J* = 7.8 Hz, 2H), 4.91 (d, , *J* = 2.3 Hz, 1H), 4.50 (t, *J* = 8.4 Hz, 1H), 3.92 (t, *J* = 6.7 Hz, 1H), 3.80 – 3.52 (m, 6H), 3.55 – 3.46 (m, 1H), 3.45 –3.32 (m, 1H), 3.25 – 3.18 (m, 1H), 1.48 (s, 9H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 155.8, 151.4, 149.7, 143.0, 137.7, 134.1, 128.2, 127.8, 123.1, 80.5, 66.9, 66.6, 66.1, 55.4, 45.7, 42.6, 38.6, 28.4.
HRMS (ESI^+) m/z calculated for $C_{23}H_{29}N_4O_4$ $[M+H]^+$ 425.2019; Found 425.2172.

Series 16: 3-(4-bromophenyl)-1-(cyclopropylcarbamoyl)azetidine-2-carboxylic acid

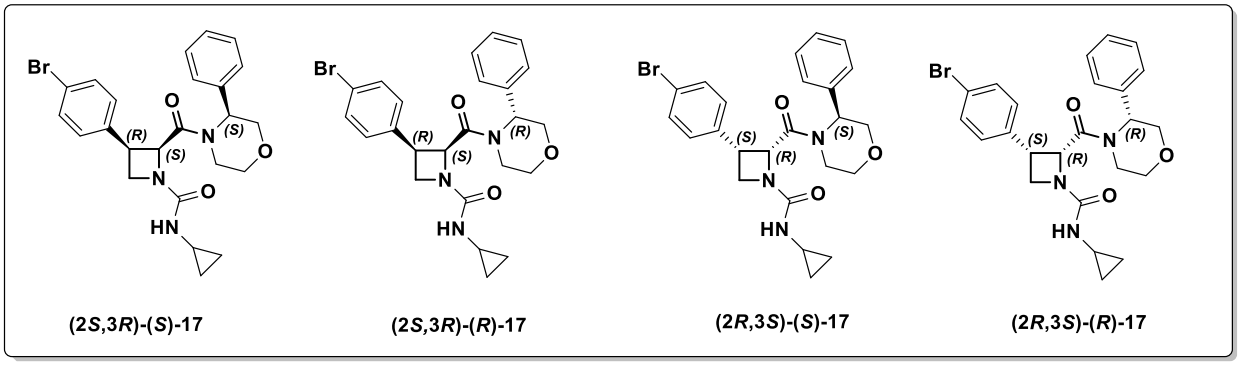


General Procedure 16: To a solution of substrate **5** (1.0 equiv) in dioxane (0.4 M) at ambient temperature was added HCl (4.0 M solution in dioxane, 10 equiv), and the reaction was allowed to stir for 5 h. The reaction was then diluted tenfold with additional dioxane, followed by addition of triethylamine (15 equiv) and cyclopropyl isocyanate (1.1 equiv). The resulting slurry was allowed to stir for an additional hour. The reaction mixture was then diluted with 1 M aqueous HCl and extracted with EtOAc (3×). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography ($MeOH/CH_2Cl_2$) provided product **16**.

(2*S*,3*R*)-16: Prepared according to General Procedure 16 from **(2*S*,3*R*)-5** (50.0 mg) to afford the desired product (26.0 mg, 55%) as a colorless amorphous solid.
(2*R*,3*S*)-16: Prepared according to General Procedure 16 from **(2*R*,3*S*)-5** (30.0 mg) to afford the desired product (17.0 mg, 60%) as a colorless amorphous solid.
$[\alpha]^{23}_D$ = +37.5 (c = 0.5, $CHCl_3$), **(2*S*,3*R*)-16**
$[\alpha]^{23}_D$ = −36.4 (c = 0.5, $CHCl_3$), **(2*R*,3*S*)-16**
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (bs, 1H), 7.40 (d, *J* = 7.9 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 5.53 (s, 1H), 4.98 (d, *J* = 9.0 Hz, 1H), 4.15 (t, *J* = 8.1 Hz, 1H), 3.87 – 3.78 (m, 1H), 3.77 – 3.70 (m, 1H), 2.47 – 2.41 (m, 1H), 0.68 – 0.56 (m, 2H), 0.52 – 0.38 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 161.8, 137.4, 131.7, 129.5, 121.6, 66.2, 53.2, 37.5, 22.8, 7.1, 6.8.
HRMS (ESI^+) m/z calculated for $C_{14}H_{16}BrN_2O_3$ $[M+H]^+$ 339.0344; Found 339.0338.

(2*R*,3*R*)-16: Prepared according to General Procedure 16 from **(2*R*,3*R*)-5** (30.0 mg) to afford the desired product (20.0 mg, 70%) as a colorless amorphous solid.
(2*S*,3*S*)-16: Prepared according to General Procedure 16 from **(2*S*,3*S*)-5** (40.0 mg) to afford the desired product (26.0 mg, 69%) as a colorless amorphous solid.
$[\alpha]^{23}_D$ = +95.1 (c = 0.5, $CHCl_3$), **(2R,3*R*)-16**
$[\alpha]^{23}_D$ = −103.0 (c = 0.5, $CHCl_3$), **(2*S*,3*S*)-16**
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 5.02 (s, 1H), 4.76 (d, *J* = 6.9 Hz, 1H), 4.22 – 4.09 (m, 2H), 3.98 (t, *J* = 6.6 Hz, 1H), 2.69 – 2.62 (m, 1H), 0.83 – 0.76 (m, 2H), 0.62 – 0.55 (m, 2H). One exchangeable proton (carboxylic acid O-H) not observed.
^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 161.8, 137.5, 132.0, 128.6, 121.6, 68.2, 52.5, 37.4, 23.0, 7.1, 6.9.
HRMS (ESI^+) m/z calculated for $C_{14}H_{16}BrN_2O_3$ $[M+H]^+$ 339.0344; Found 339.0337.

Series 17: 3-(4-bromophenyl)-N-cyclopropyl-2-(3-phenylmorpholine-4-carbonyl)azetidine-1-carboxamide



General Procedure 17: To a solution of substrate **16** (1.0 equiv) in DMF (0.25 M) at 0 °C was added *N*,*N*-diisopropylethylamine (2.0 equiv), HATU (1.0 equiv), and 3-phenylmorpholine (1.1 equiv). The reaction mixture was allowed to reach ambient temperature and was stirred for 2 h. Upon completion, the reaction mixture was diluted with 1 M aqueous HCl and extracted with EtOAc (3×). The combined organic layers were washed with brine (5×), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by flash column chromatography (EtOAc/hexanes for **(2*S*,3*R*)-(*S*)-17** and **(2*R*,3*S*)-(*R*)-17**; MeOH/CH_2Cl_2 for **(2*S*,3*R*)-(*R*)-17** and **(2*R*,3*S*)-(*S*)-17**) provided product **17**.

(2*S*,3*R*)-(*S*)-17: Prepared according to General Procedure 17 from **(2*S*,3*R*)-16** (20.0 mg) to afford the desired product (17.5 mg, 61%) as a colorless amorphous solid.
(2*R*,3*S*)-(*R*)-17: Prepared according to General Procedure 17 from **(2*R*,3*S*)-16** (15.0 mg) to afford the desired product (13.5 mg, 60%) as a colorless amorphous solid.
$[\alpha]^{23}_{365nm}$ = +44.6 (c = 0.5, $CHCl_3$), **(2*S*,3*R*)-(*S*)-17**
$[\alpha]^{24}_{365nm}$ = −48.4 (c = 0.5, $CHCl_3$), **(2*R*,3*S*)-(*R*)-17**
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 2H), 7.43 (d, *J* = 7.4 Hz, 2H), 7.37 – 7.27 (m, 5H), 5.75 (s, 1H), 5.36 (s, 1H), 4.99 (d, *J* = 8.6 Hz, 1H), 4.43 (*t*, *J* = 8.2 Hz, 1H), 4.23 (d, *J* = 12.1 Hz, 1H), 3.78 (td, *J* = 8.4, 3.9 Hz, 1H), 3.66 (dd, *J* = 7.9, 4.0 Hz, 1H), 3.61 (dd, *J* = 11.6, 3.4 Hz, 1H), 3.25 – 3.15 (m, 2H), 3.09 (d, *J* = 12.2 Hz, 1H), 2.80 (d, *J* = 13.2 Hz, 1H), 2.68 – 2.60 (m, 1H), 2.37 (t, *J* = 11.6 Hz, 1H), 0.76 – 0.62 (m, 2H), 0.46 – 0.36 (m, 2H).
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 161.8, 138.1, 137.9, 132.1, 129.7, 128.6, 128.0, 127.7, 122.2, 68.6, 67.4, 66.2, 54.0, 50.9, 40.5, 39.3, 22.7, 7.2, 6.2.
HRMS (ESI^+) m/z calculated for $C_{24}H_{27}BrN_3O_3$ $[M+H]^+$ 484.1236; Found 484.1220.

(2*S*,3*R*)-(*R*)-17: Prepared according to General Procedure 17 from **(2*S*,3*R*)-16** (26.0 mg) to afford the desired product (24.0 mg, 65%) as a colorless amorphous solid.
(2*R*,3*S*)-(*S*)-17: Prepared according to General Procedure 17 from **(2*R*,3*S*)-16** (105.0 mg) to afford desired the product (113.0 mg, 76%) as a colorless amorphous solid.
$[\alpha]^{23}_{D}$ = −248.7 (c = 0.2, $CHCl_3$), **(2*S*,3*R*)-(*R*)-17**
$[\alpha]^{23}_{D}$ = +228.5 (c = 0.2, $CHCl_3$), **(2*R*,3*S*)-(*S*)-17**
^{1}H NMR (400 MHz, DMSO-d_6, mixture of conformers A & B, ratio 0.69:0.31) δ 7.62 – 7.29 (m, $5H_A$ + $5H_B$), 7.20 – 7.10 (m, $2H_A$ + $2H_B$), 6.56 – 6.48 (m, $2H_A$ + $2H_B$), 5.40 (d, *J* = 8.8 Hz, $1H_A$), 5.20 (s, $1H_A$), 5.05 (d, *J* = 9.0 Hz, $1H_B$), 4.54 (s, $1H_B$), 4.29 –3.85 (m, $4H_A$ + $4H_B$), 3.69 – 3.42 (m,

$4H_A + 4H_B$), 2.70 – 2.55 (m, $1H_A + 1H_B$), 2.53 – 2.38 (m, $1H_A + 1H_B$), 0.65 – 0.50 (m, $2H_A + 2H_B$), 0.45 – 0.35 (m, $2HA + 2H_B$).
^{13}C NMR (100 MHz, DMSO-d_6, mixture of conformers) δ 167.7, 167.6, 161.1, 160.0, 139.0, 138.3, 138.2, 138.0, 131.9, 131.6, 131.4, 130.9, 129.0, 128.4, 127.6, 127.3, 127.2, 126.8, 121.3, 121.1, 69.0, 68.8, 66.5, 64.9, 64.6, 55.4, 54.7, 53.8, 51.2, 41.1, 37.8, 37.4, 36.9, 23.1, 6.7, 6.62, 6.56, 6.5.
HRMS (ESI^+) m/z calculated for $C_{24}H_{27}BrN_3O_3$ $[M+H]^+$ 484.1236; Found 484.1222.

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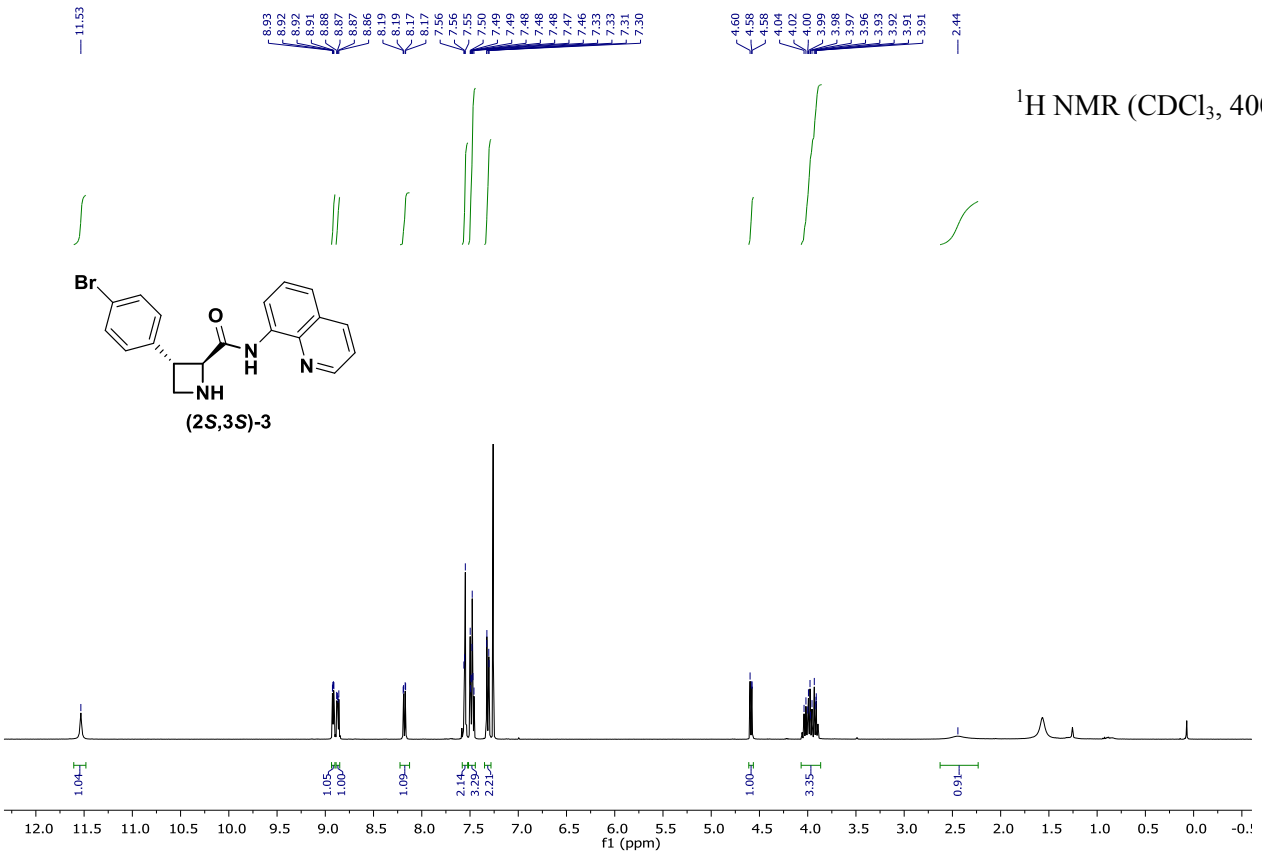

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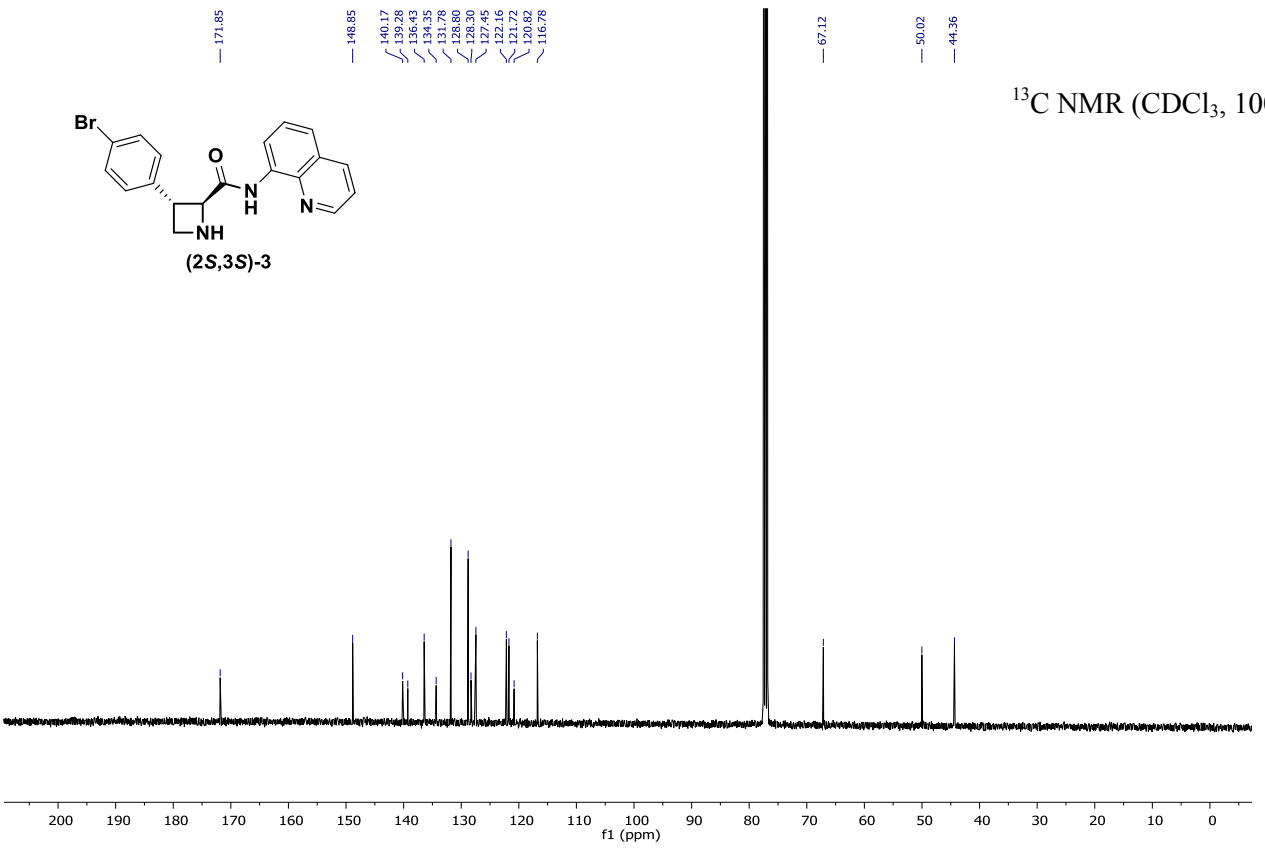
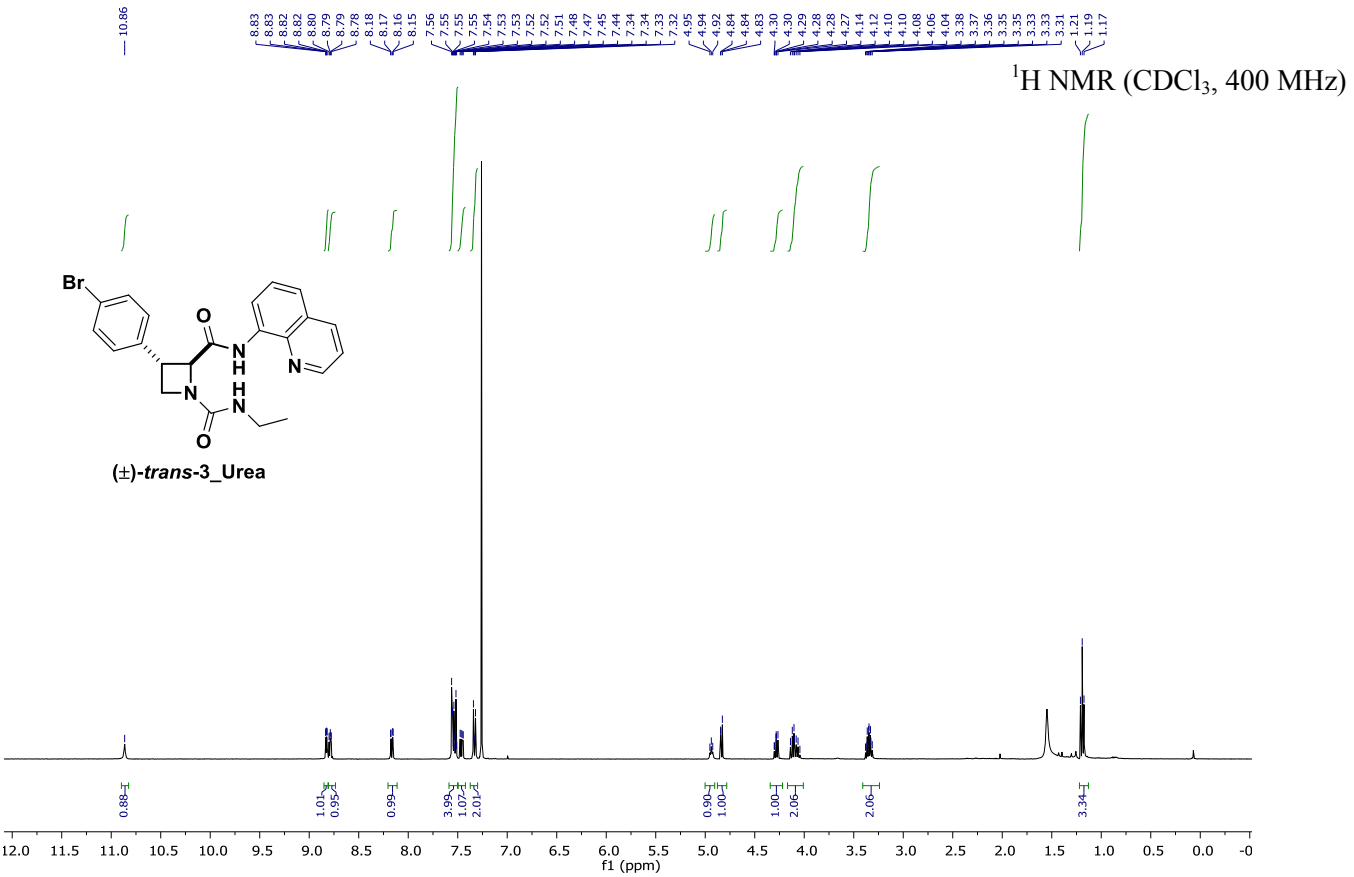


^{13}C NMR ($CDCl_3$, 100 MHz)

^{1}H NMR ($CDCl_3$, 400 MHz)



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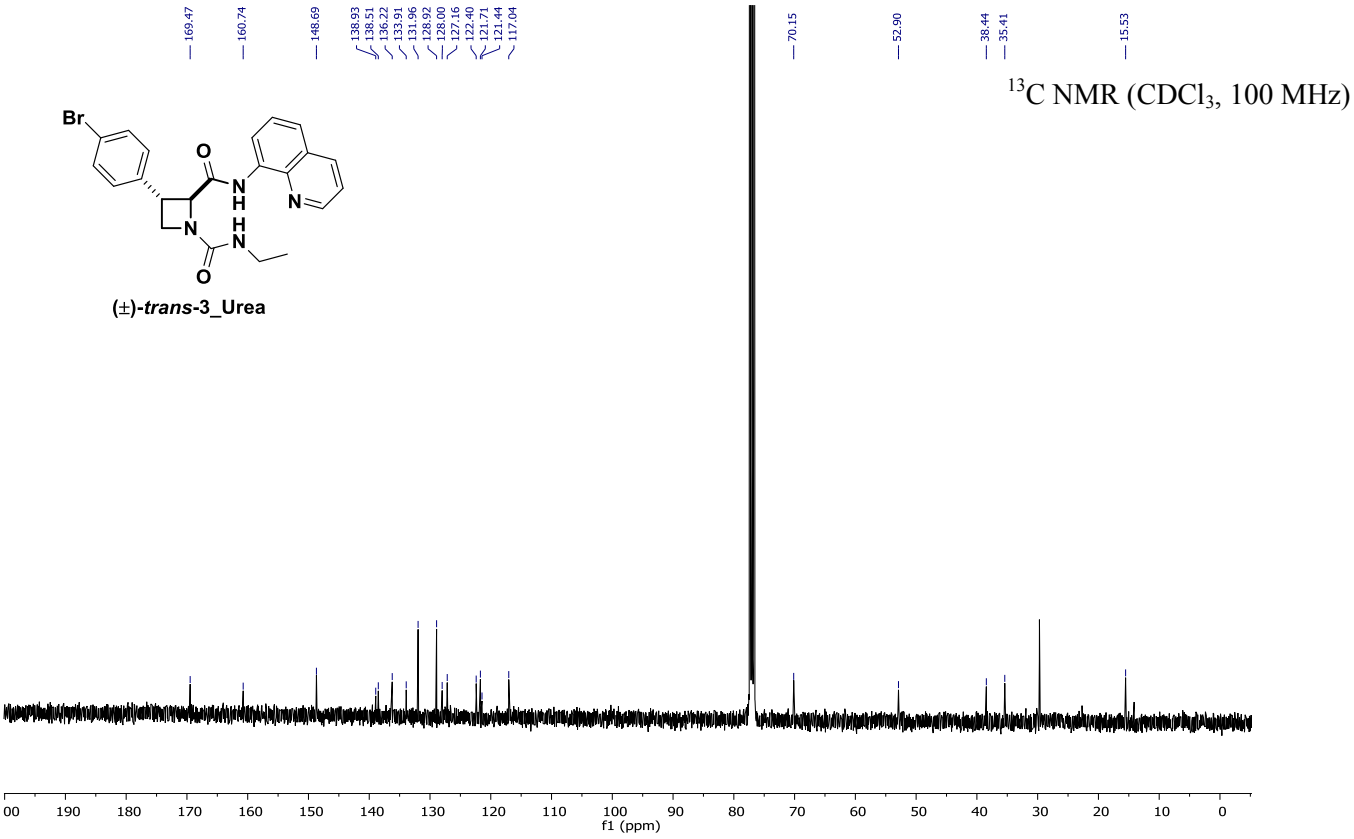

(±)-*trans*-3_Urea

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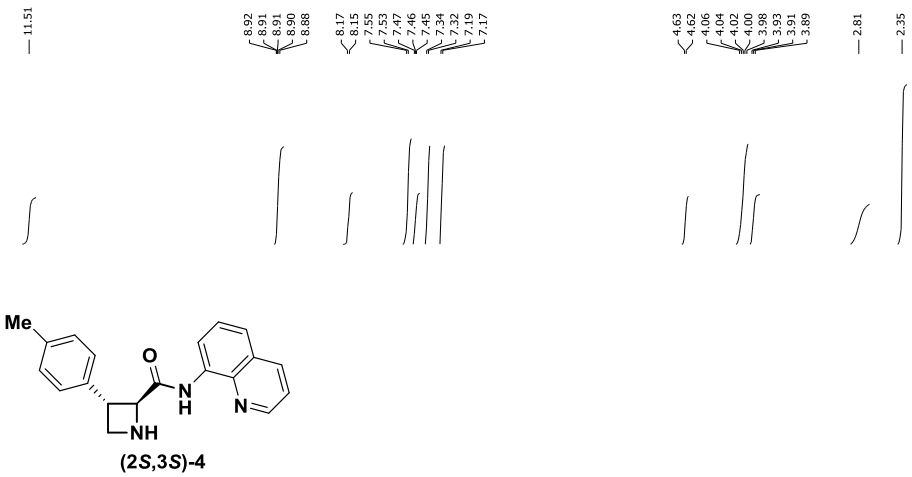
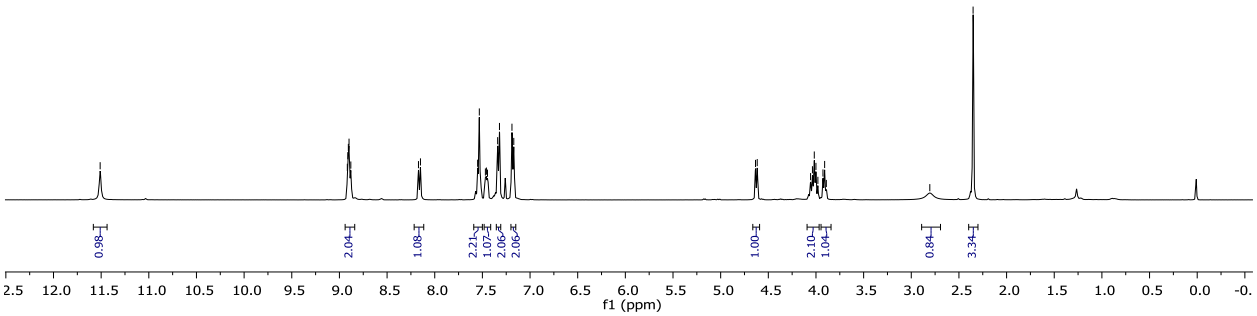


(2*S*,3*S*)-4



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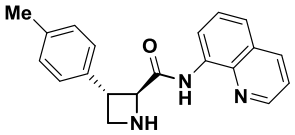

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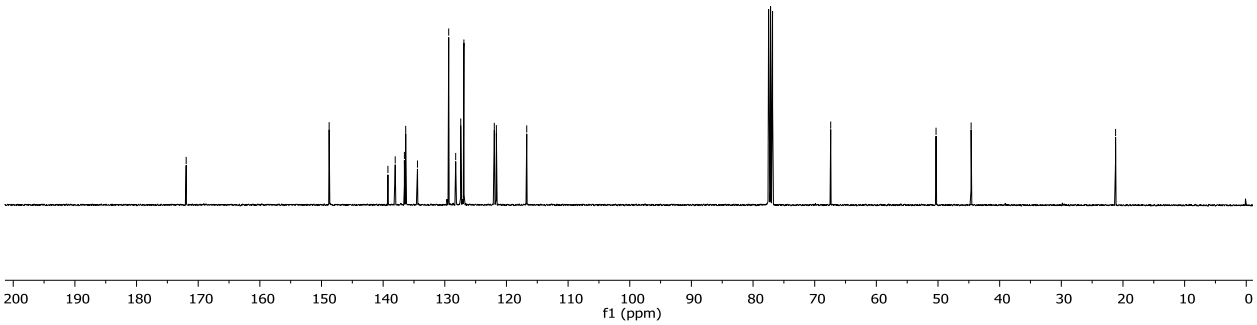

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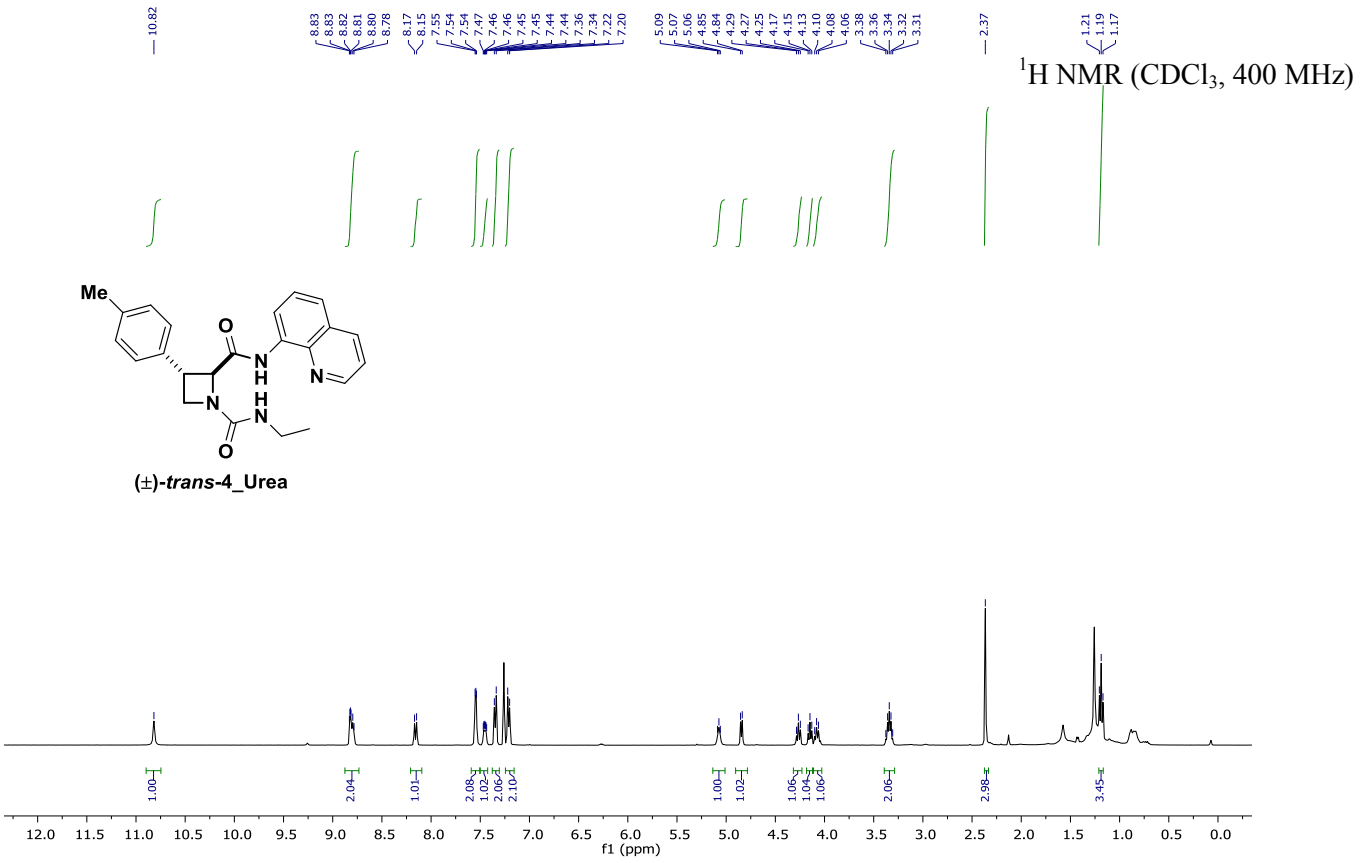

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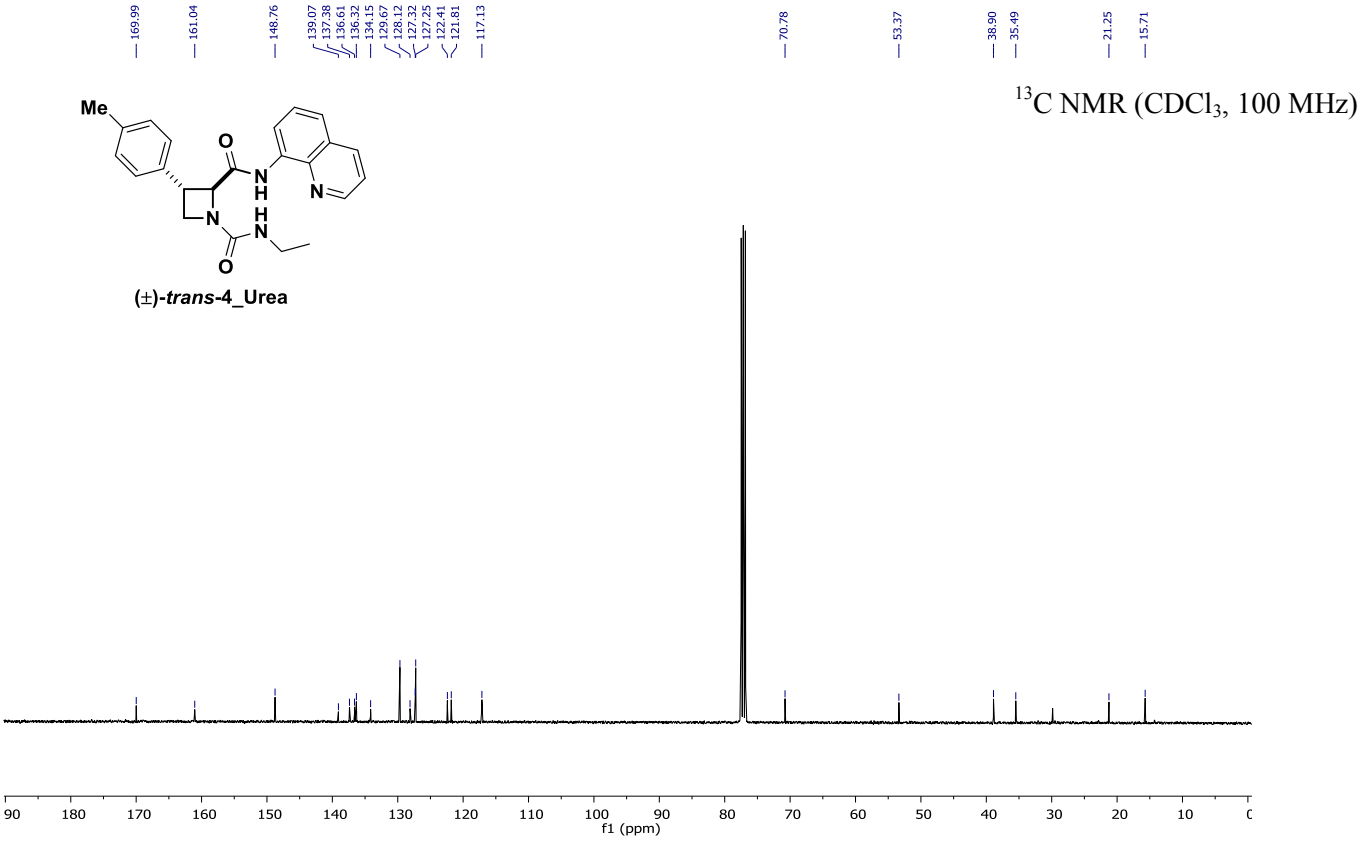

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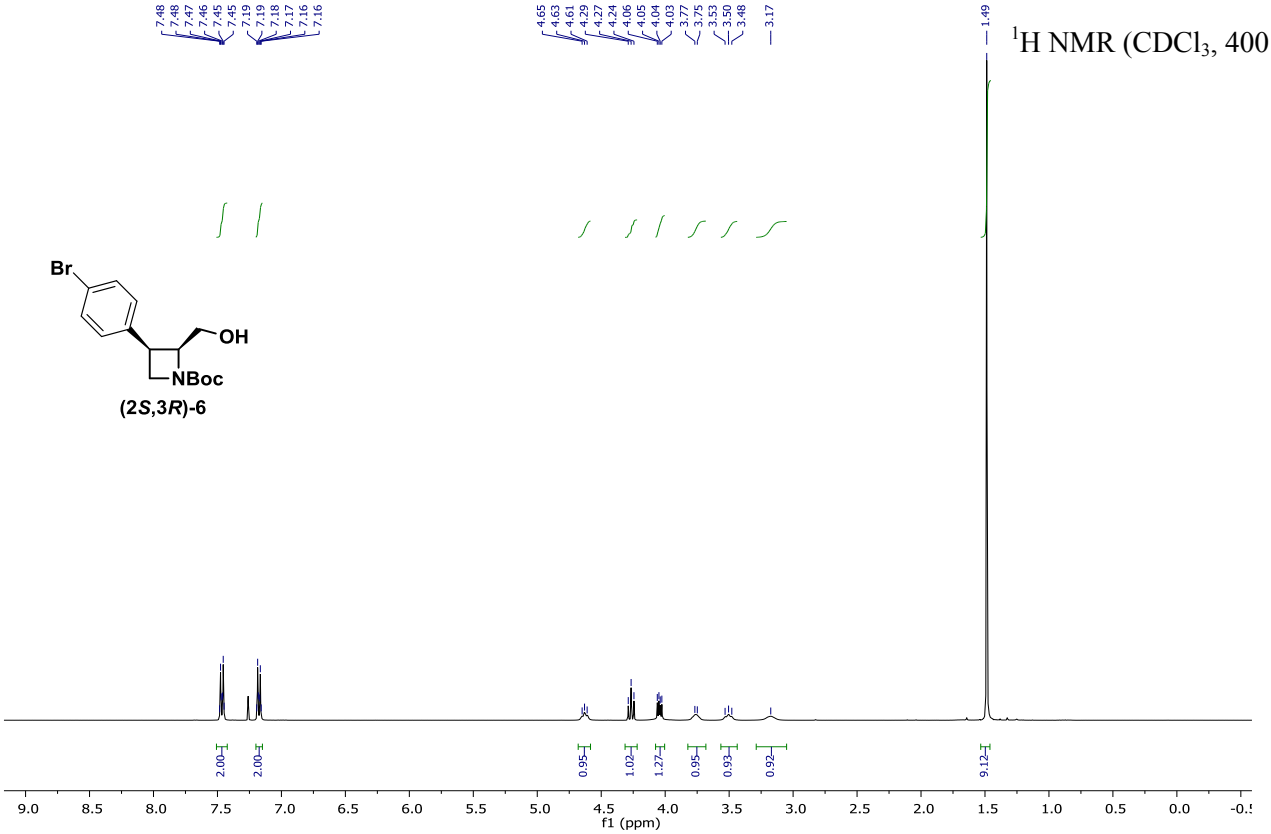

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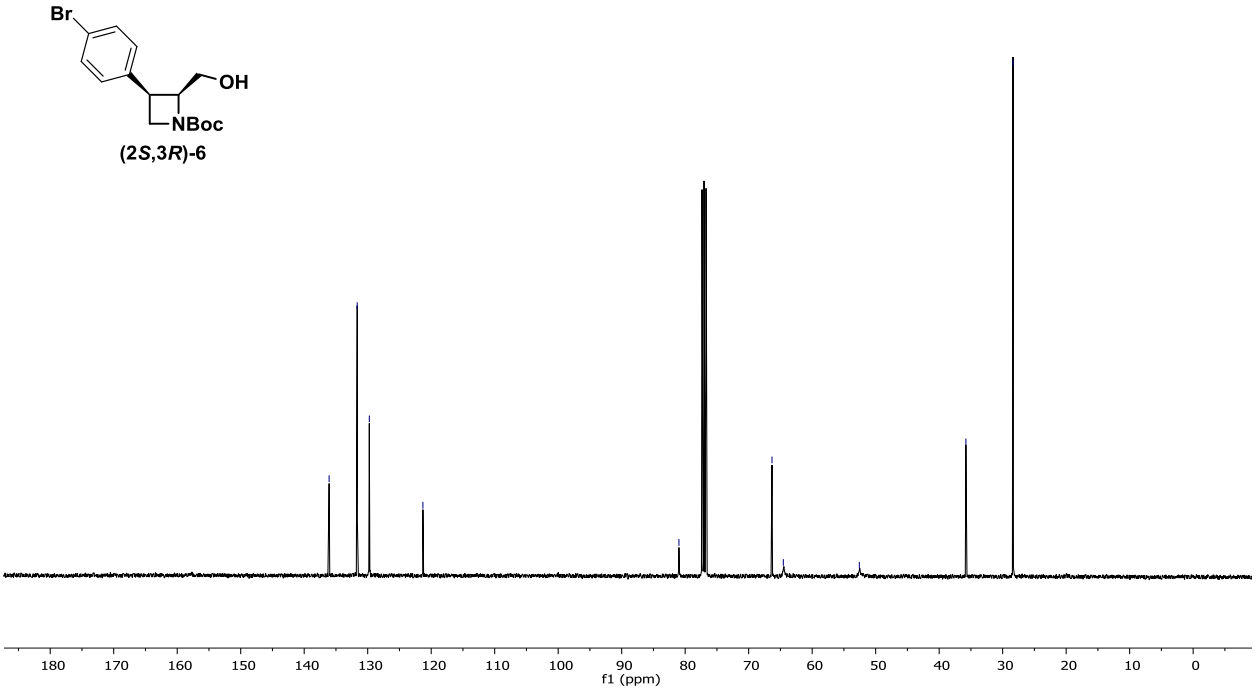

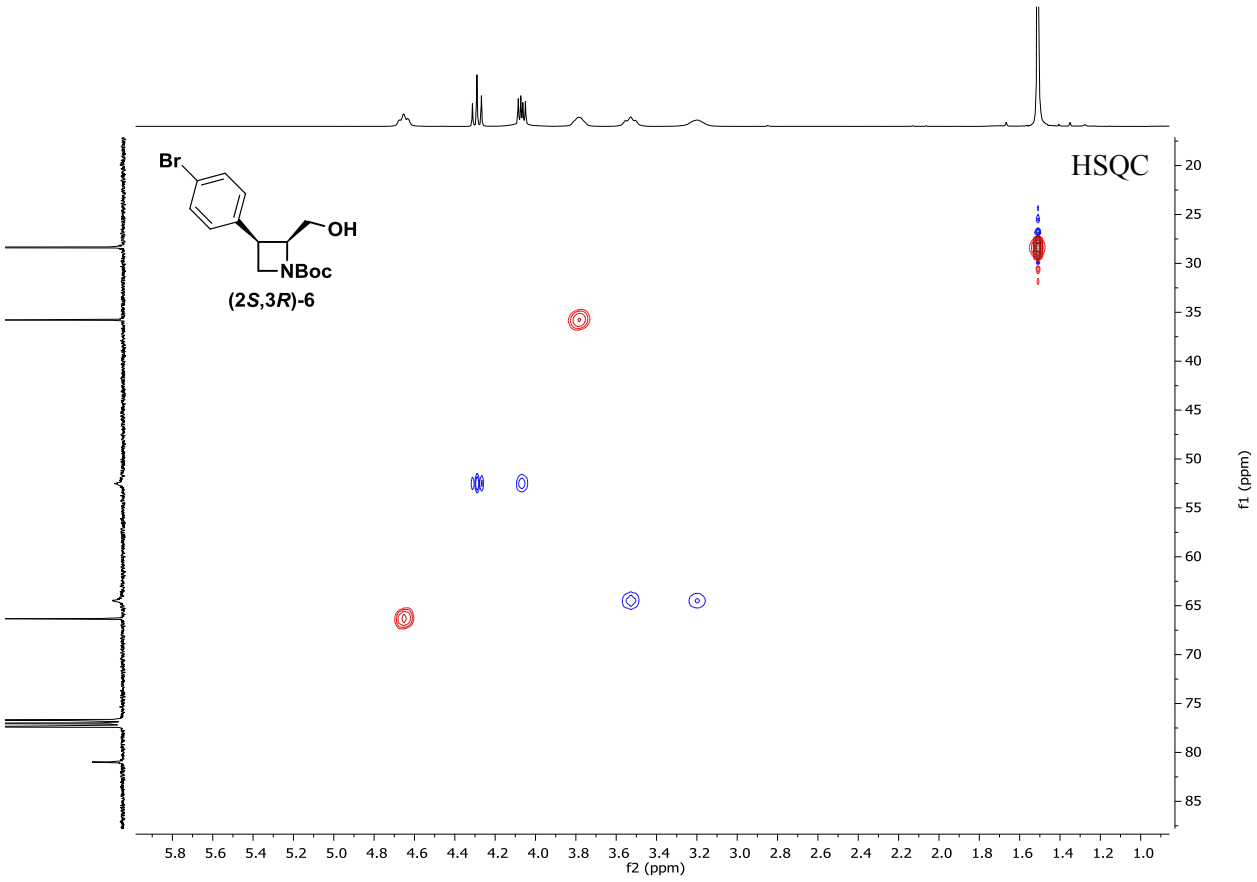
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OH
NBoc
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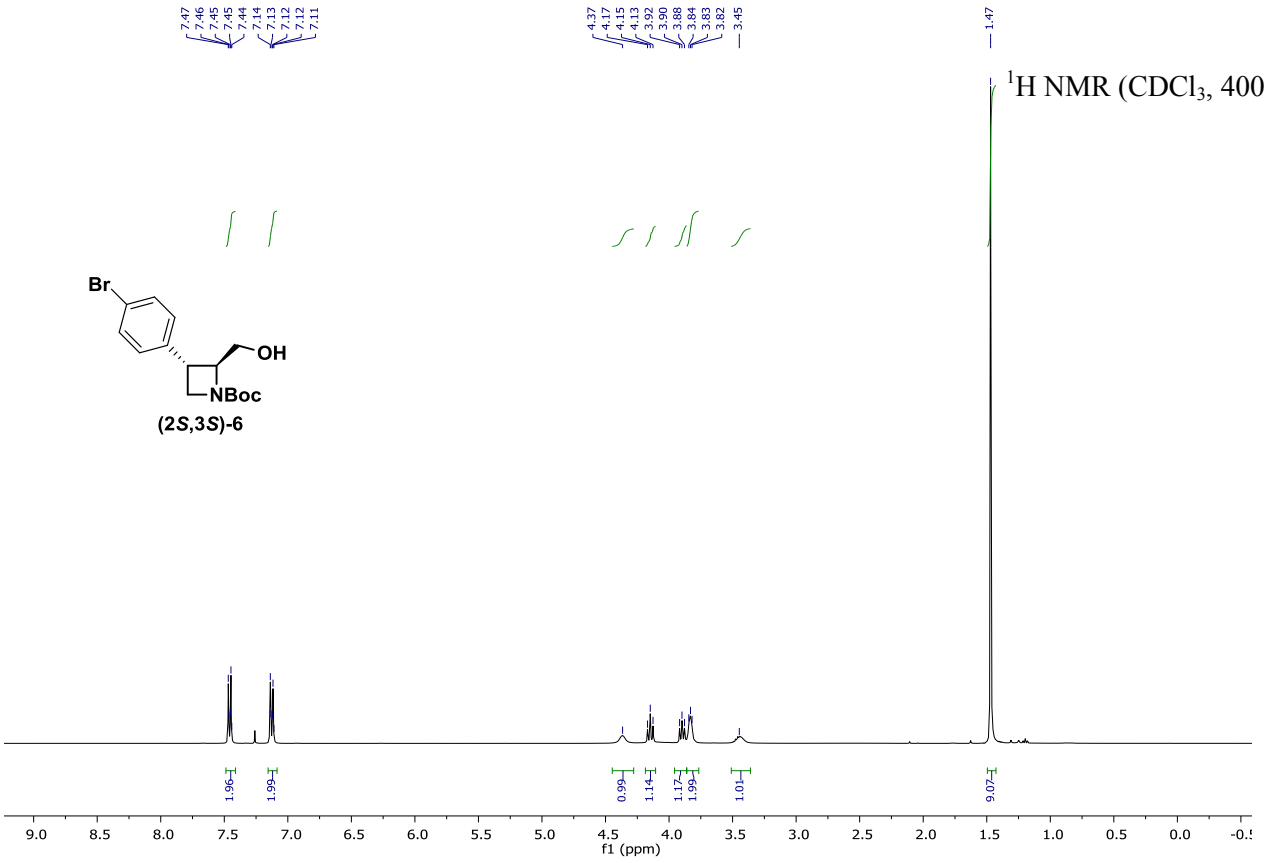
f2 (ppm)
f1 (ppm)

^{1}H NMR ($CDCl_3$, 400 MHz)



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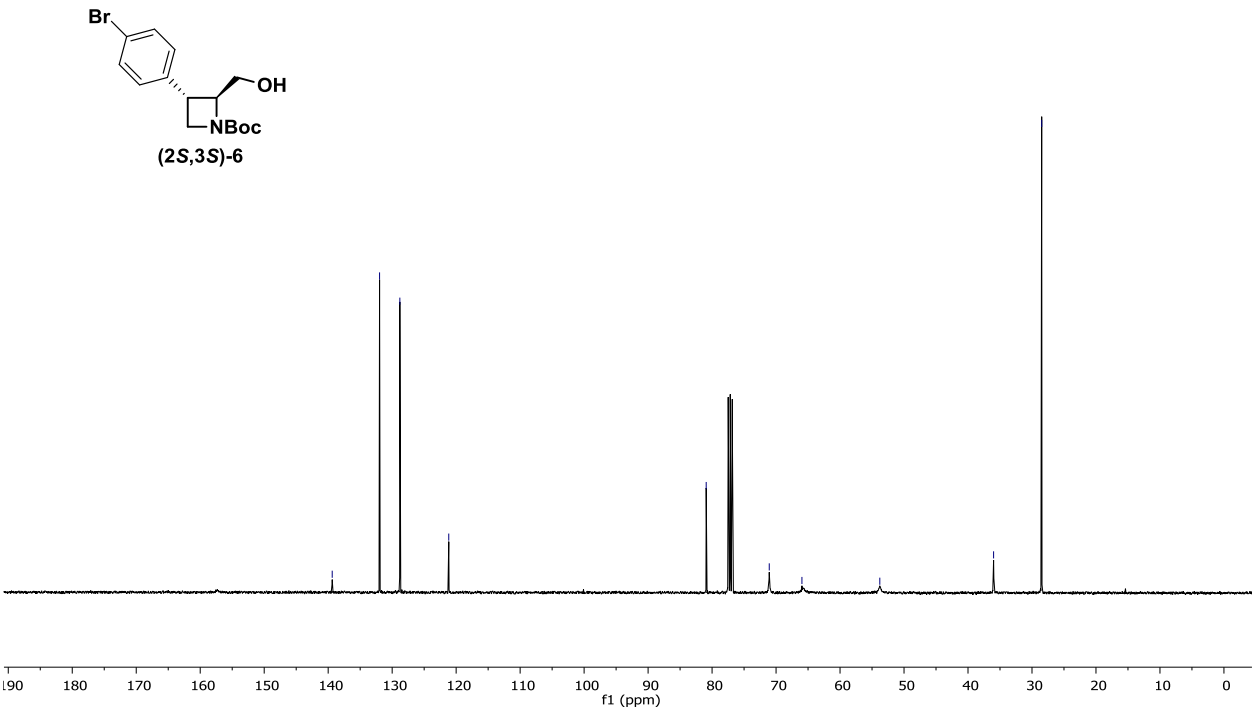

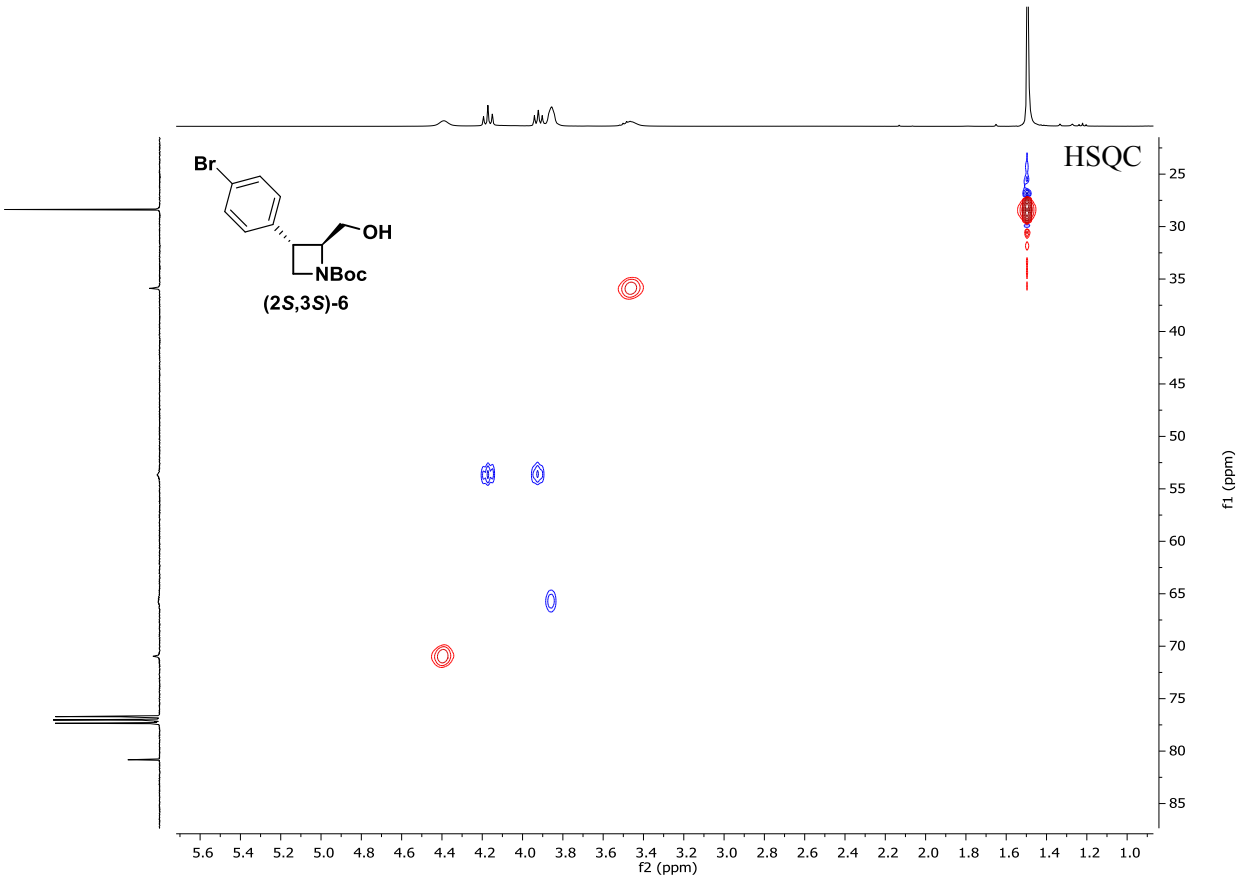
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NBoc
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f1 (ppm)
f2 (ppm)

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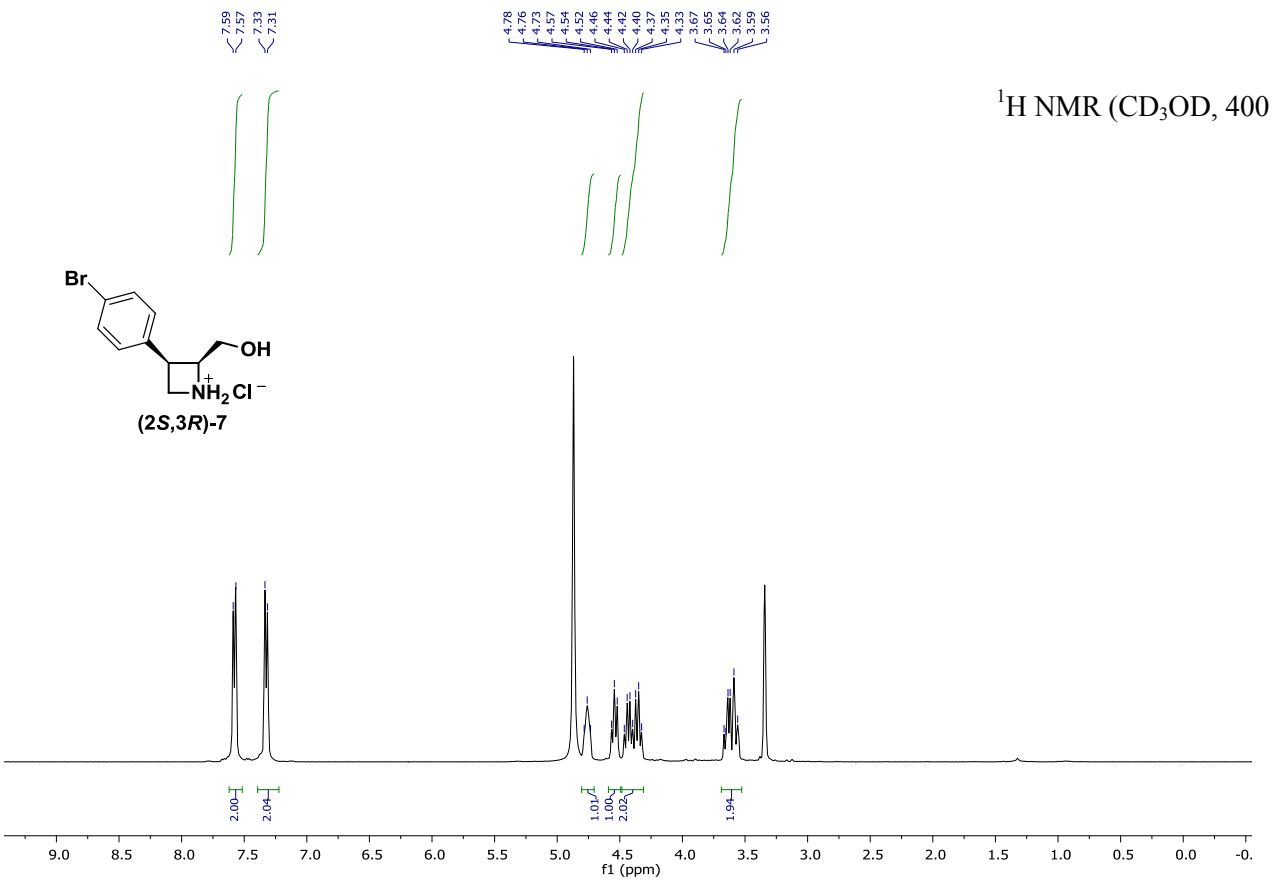

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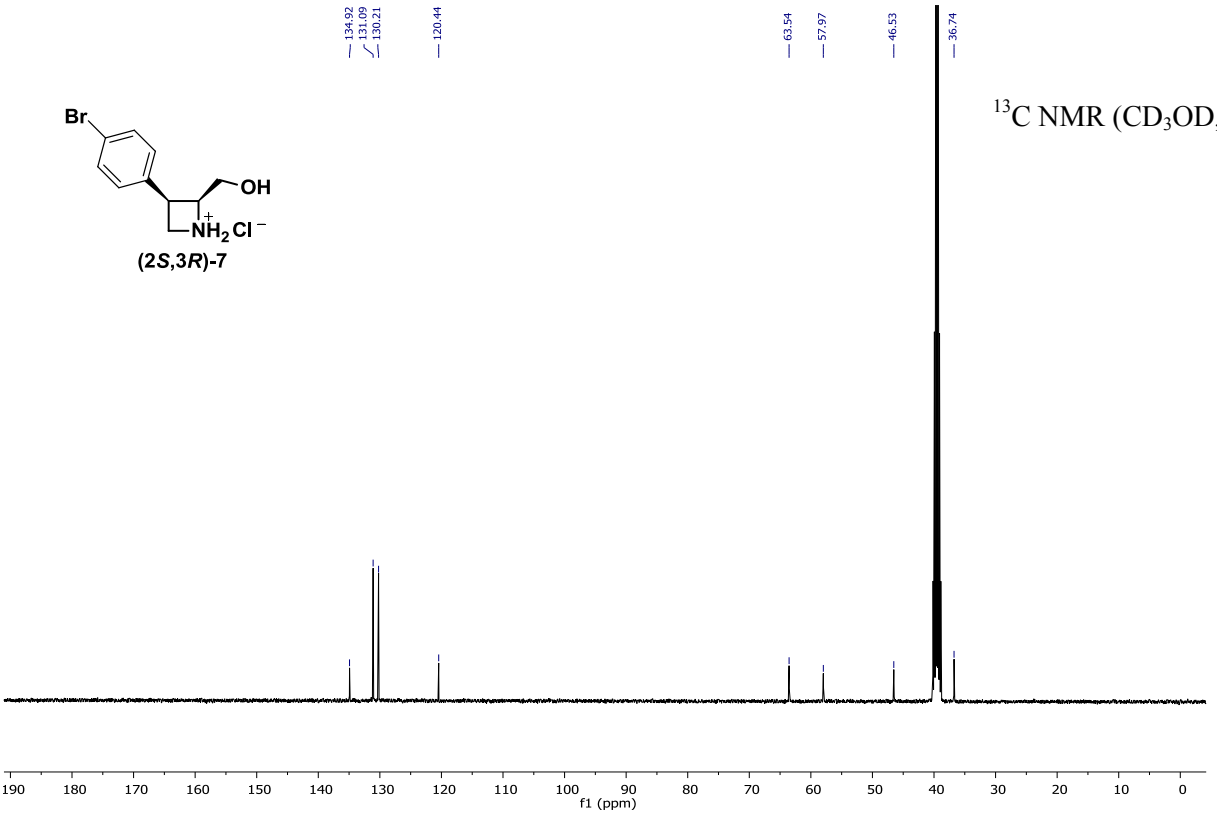

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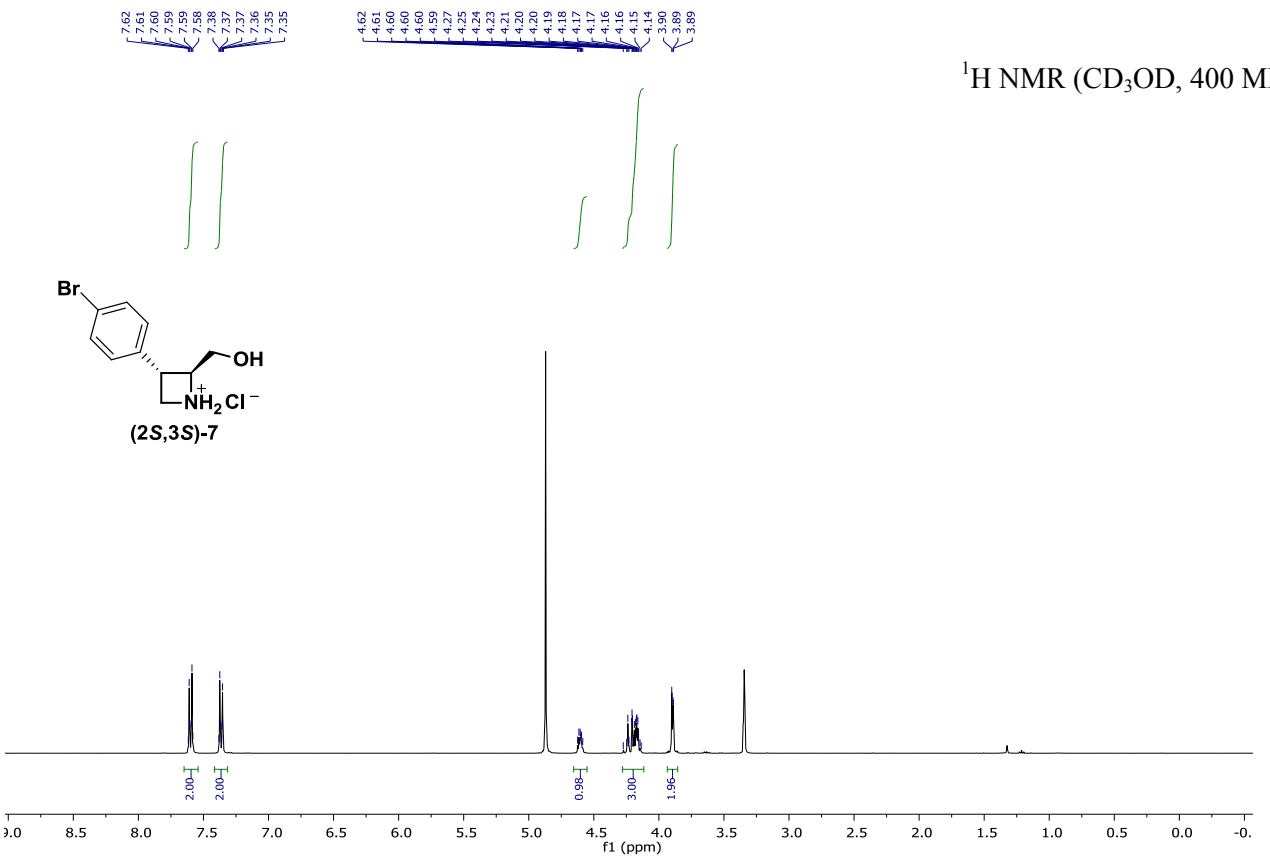

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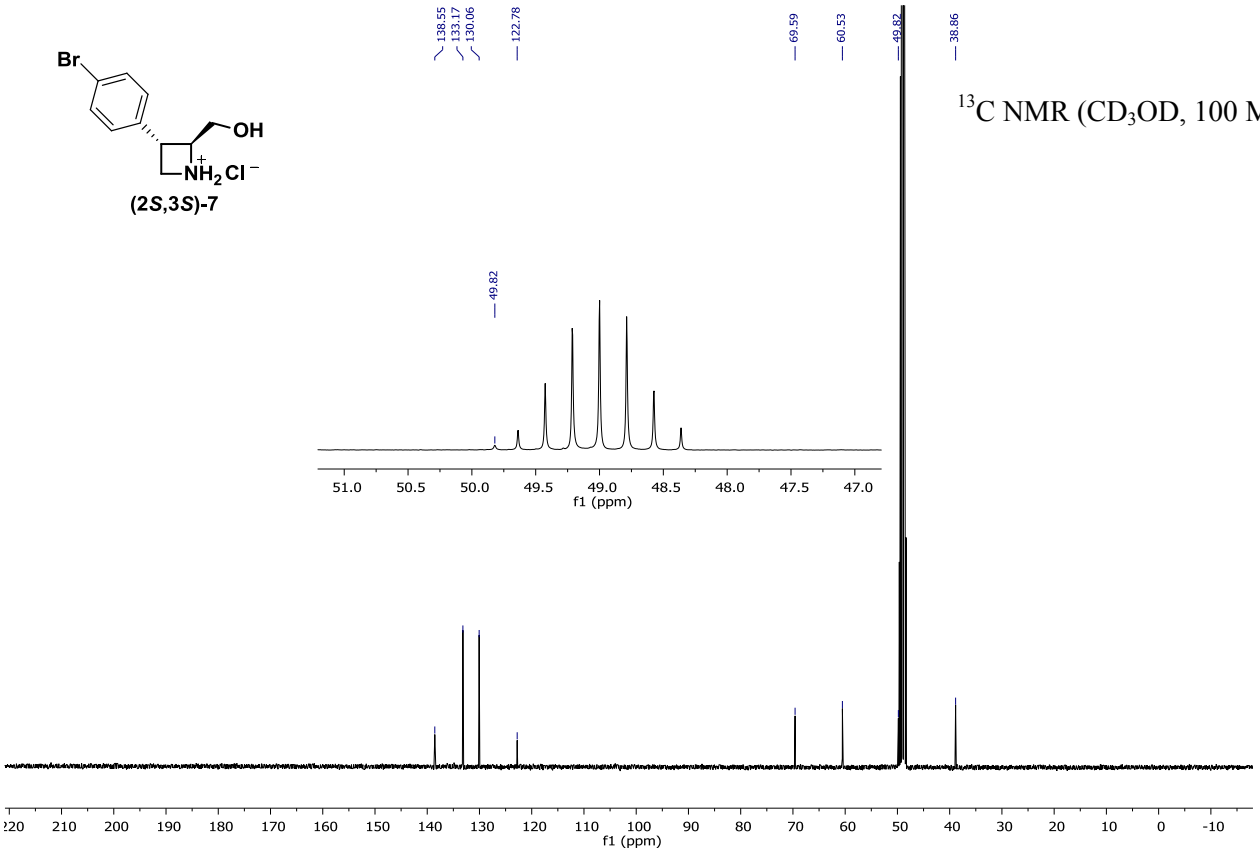

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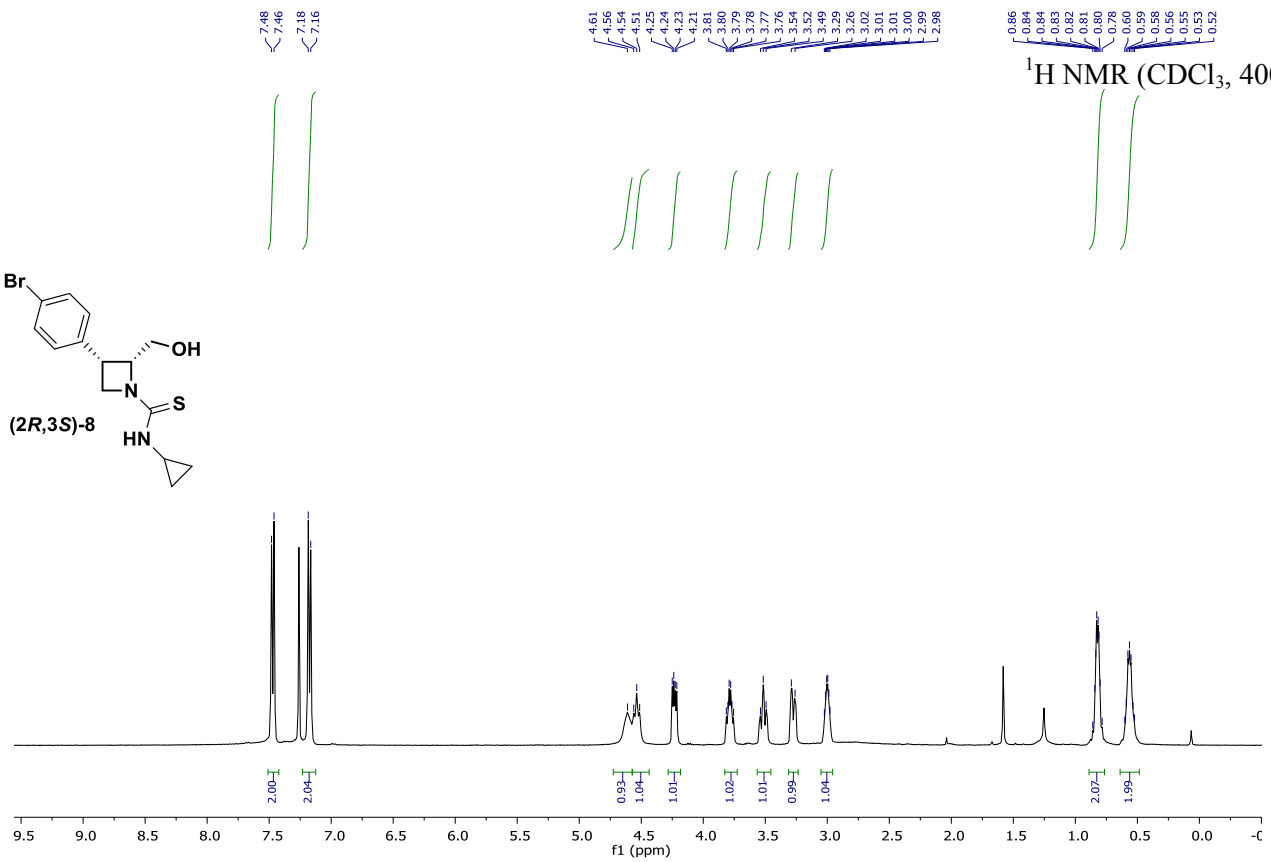

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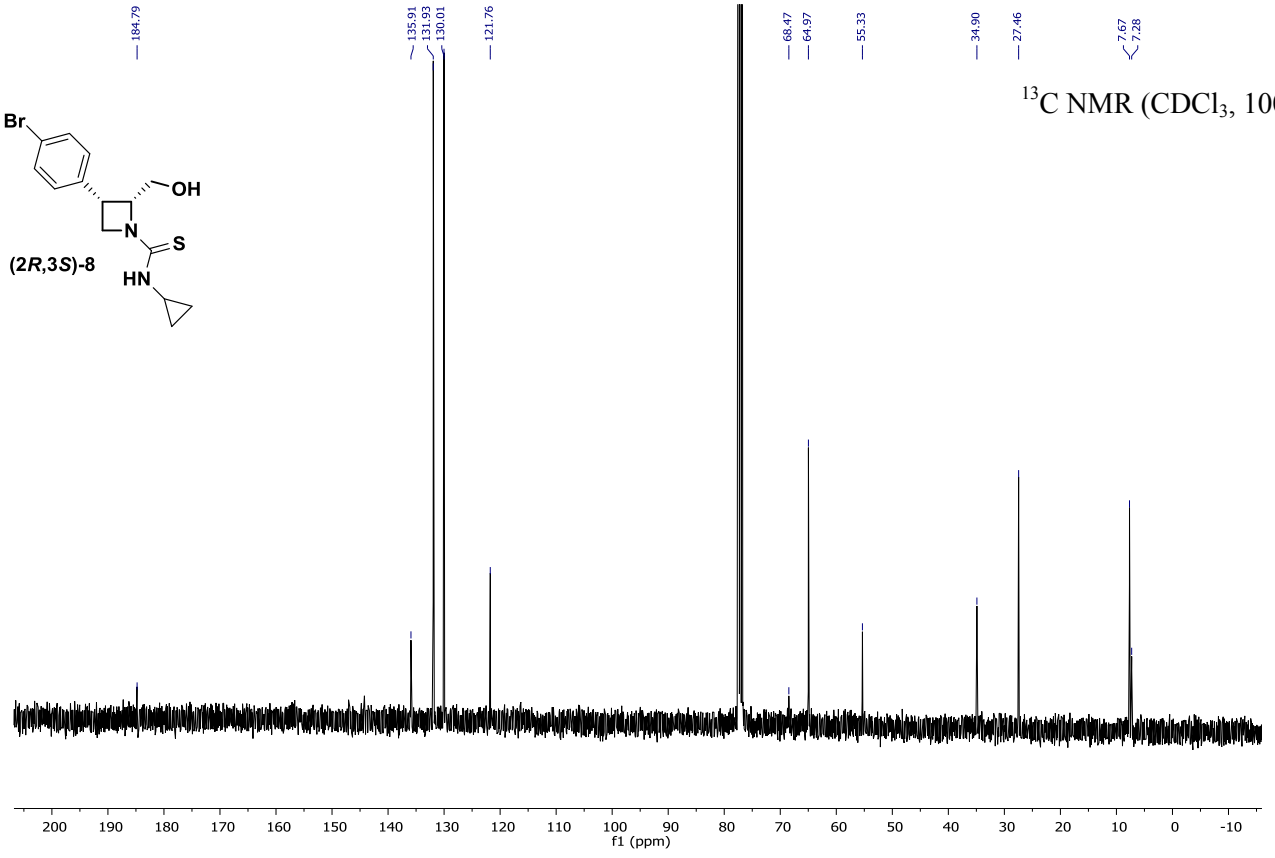

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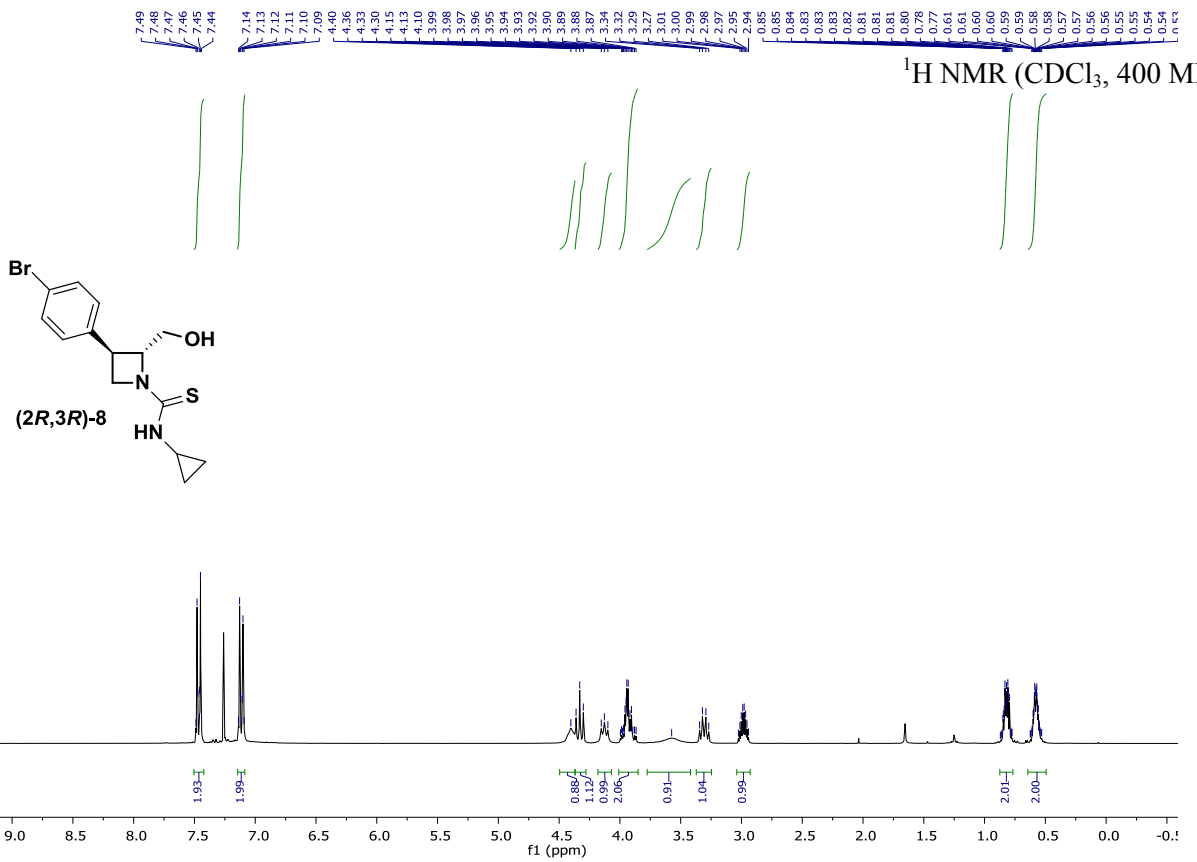

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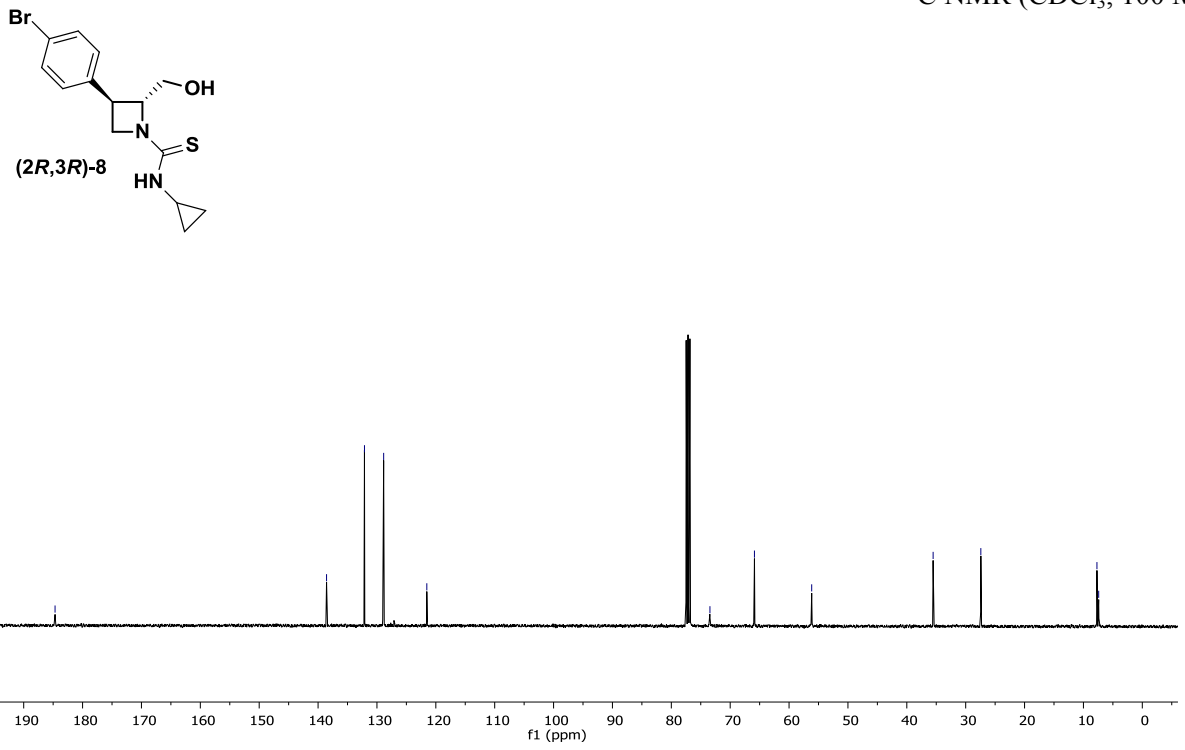

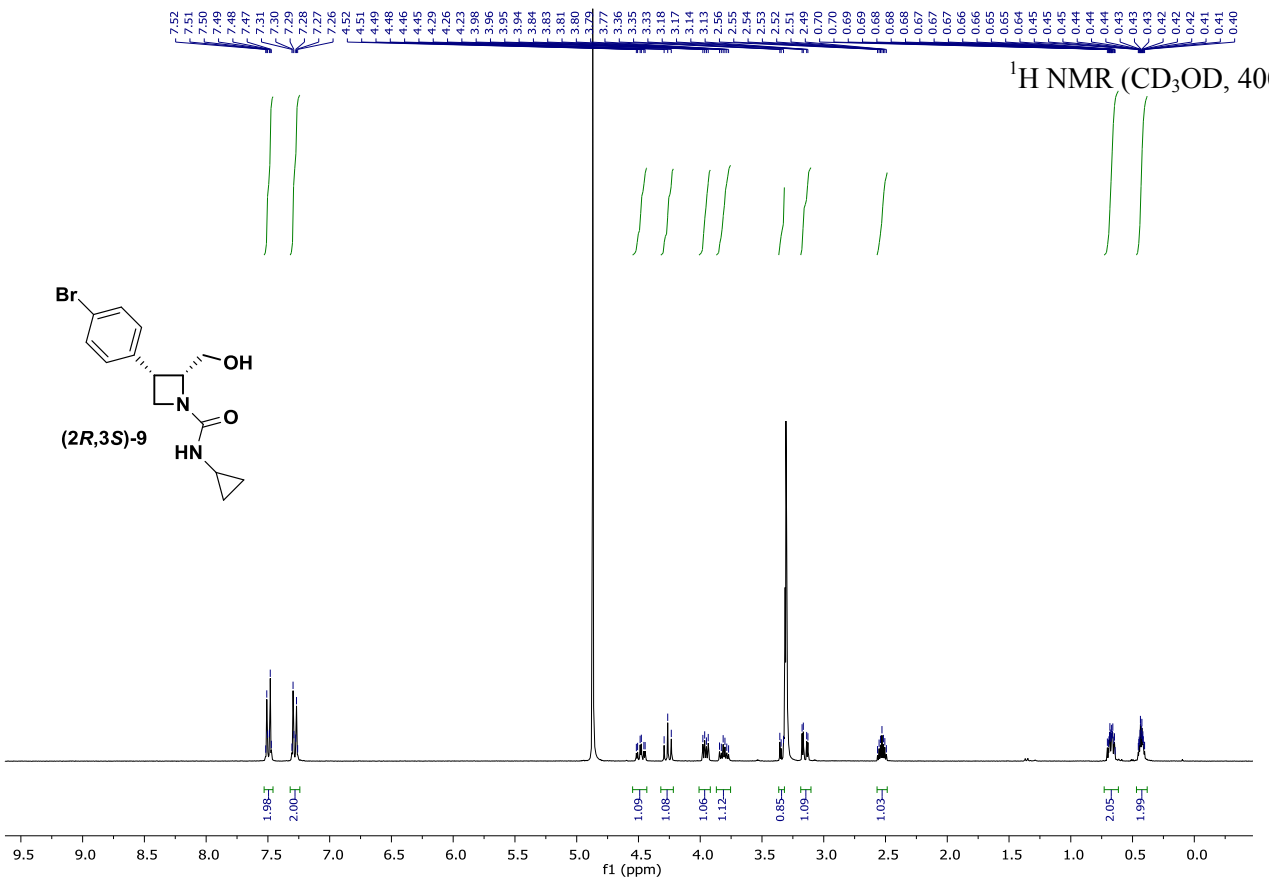

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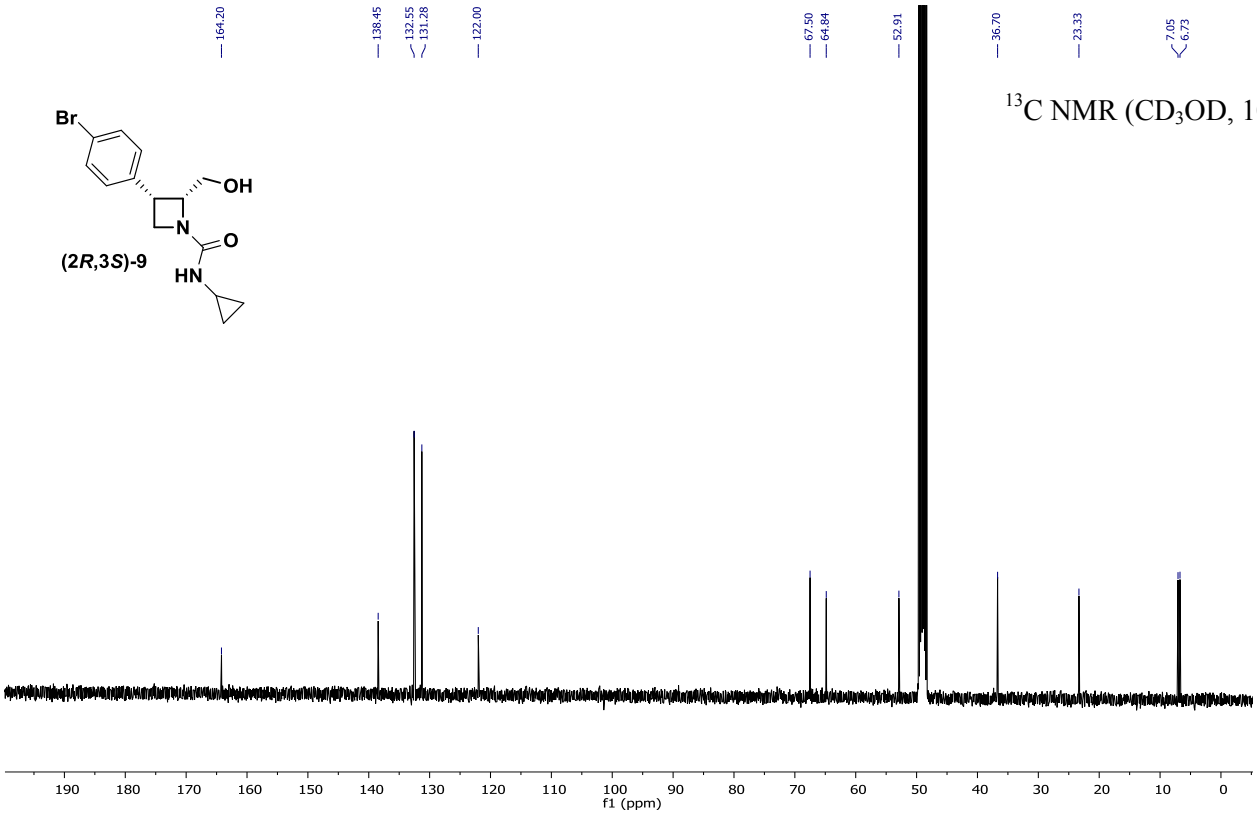

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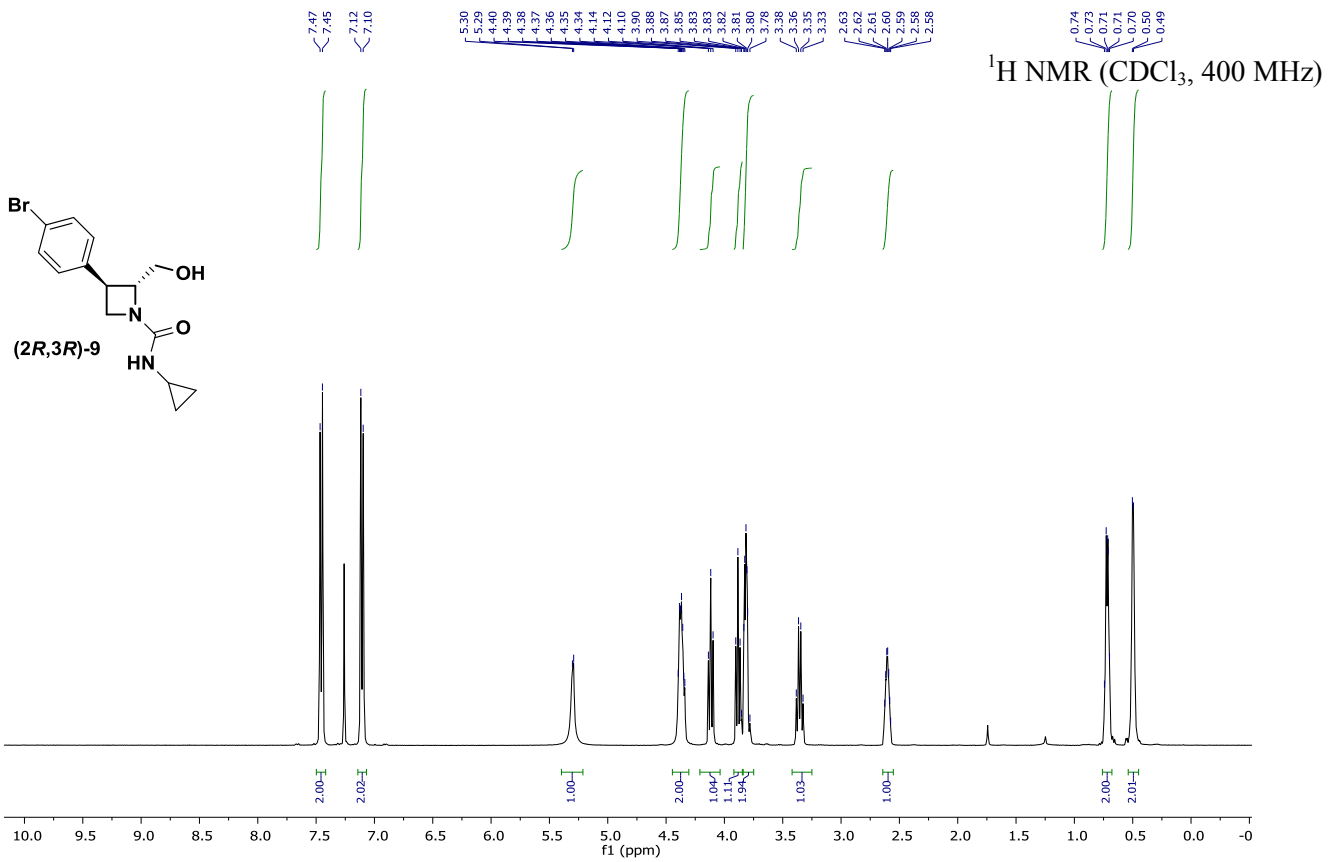

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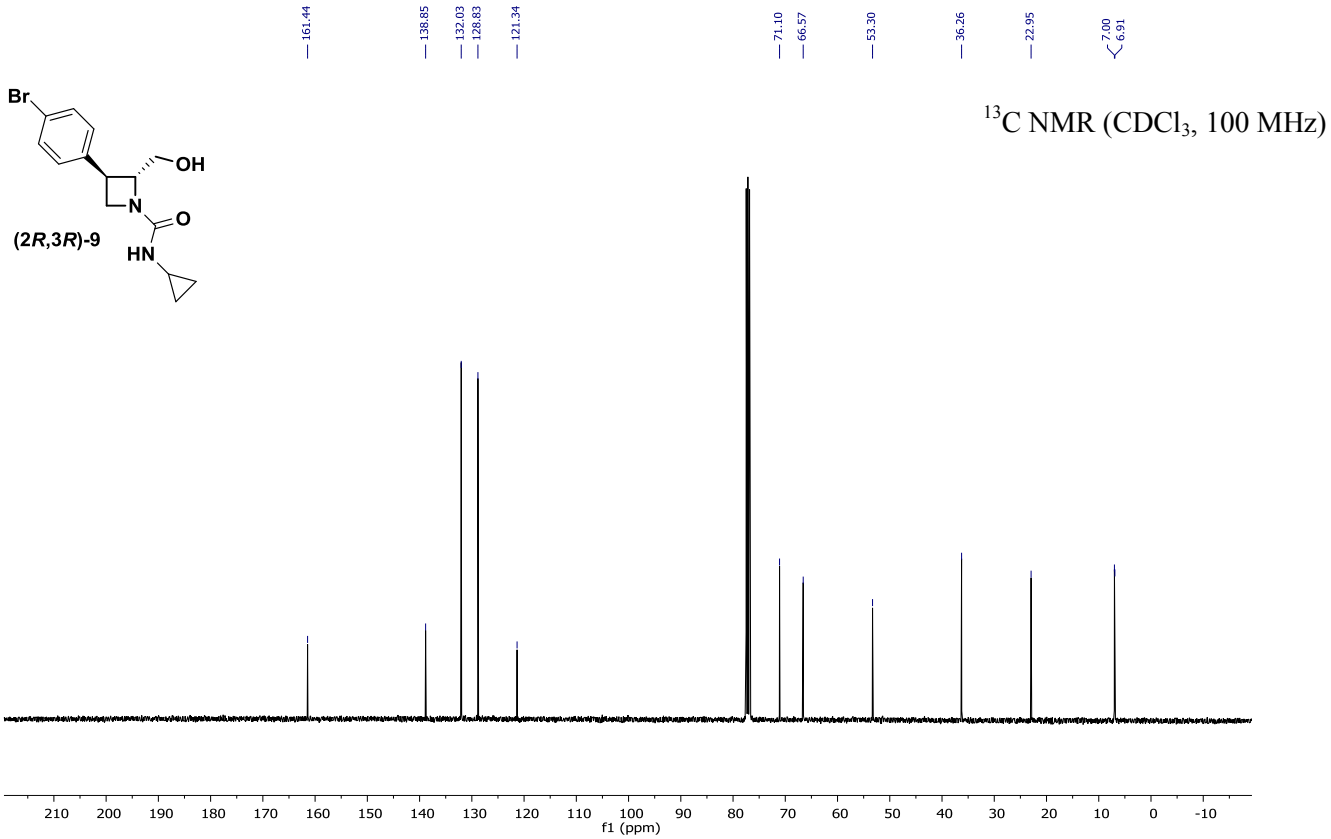

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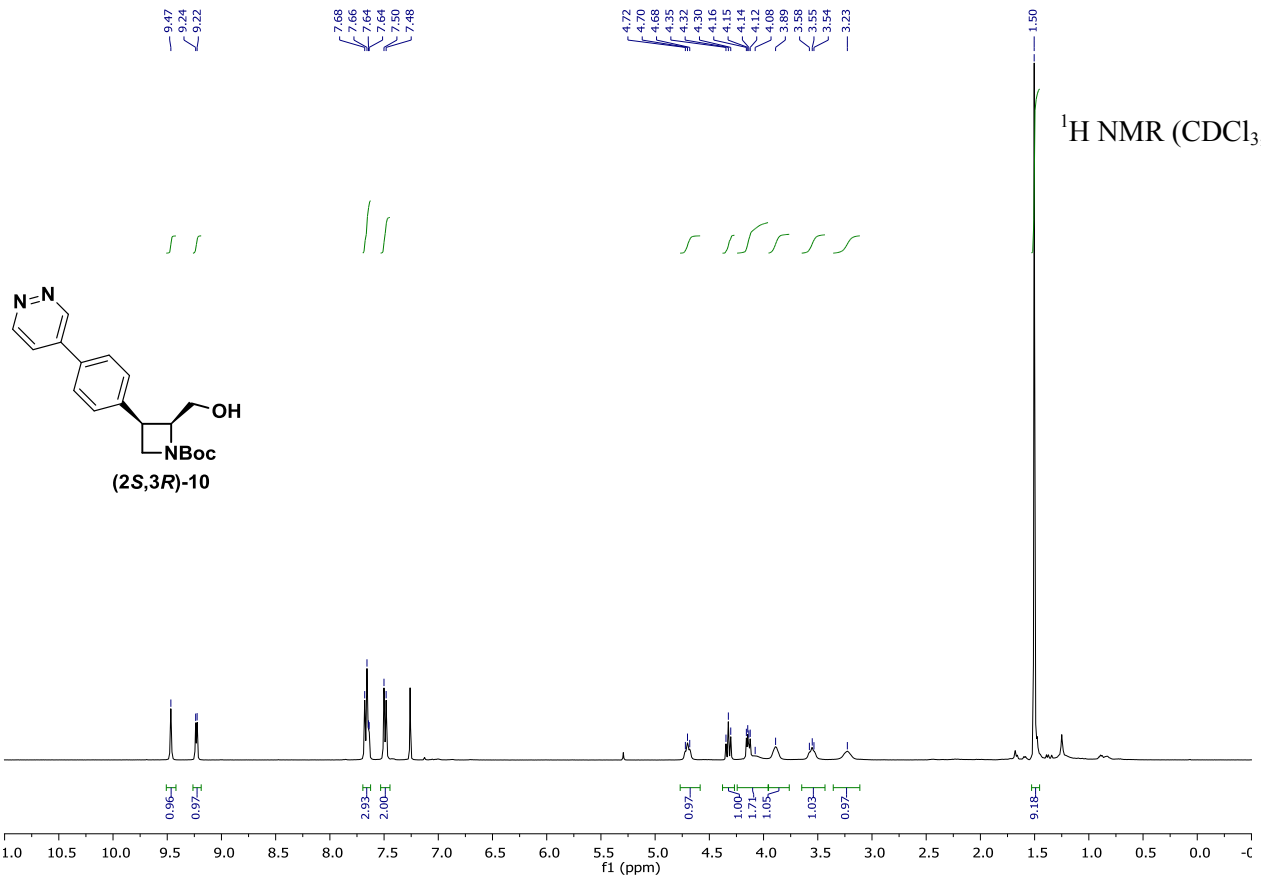

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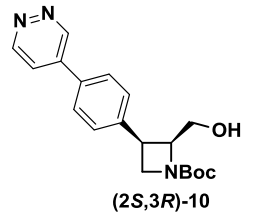
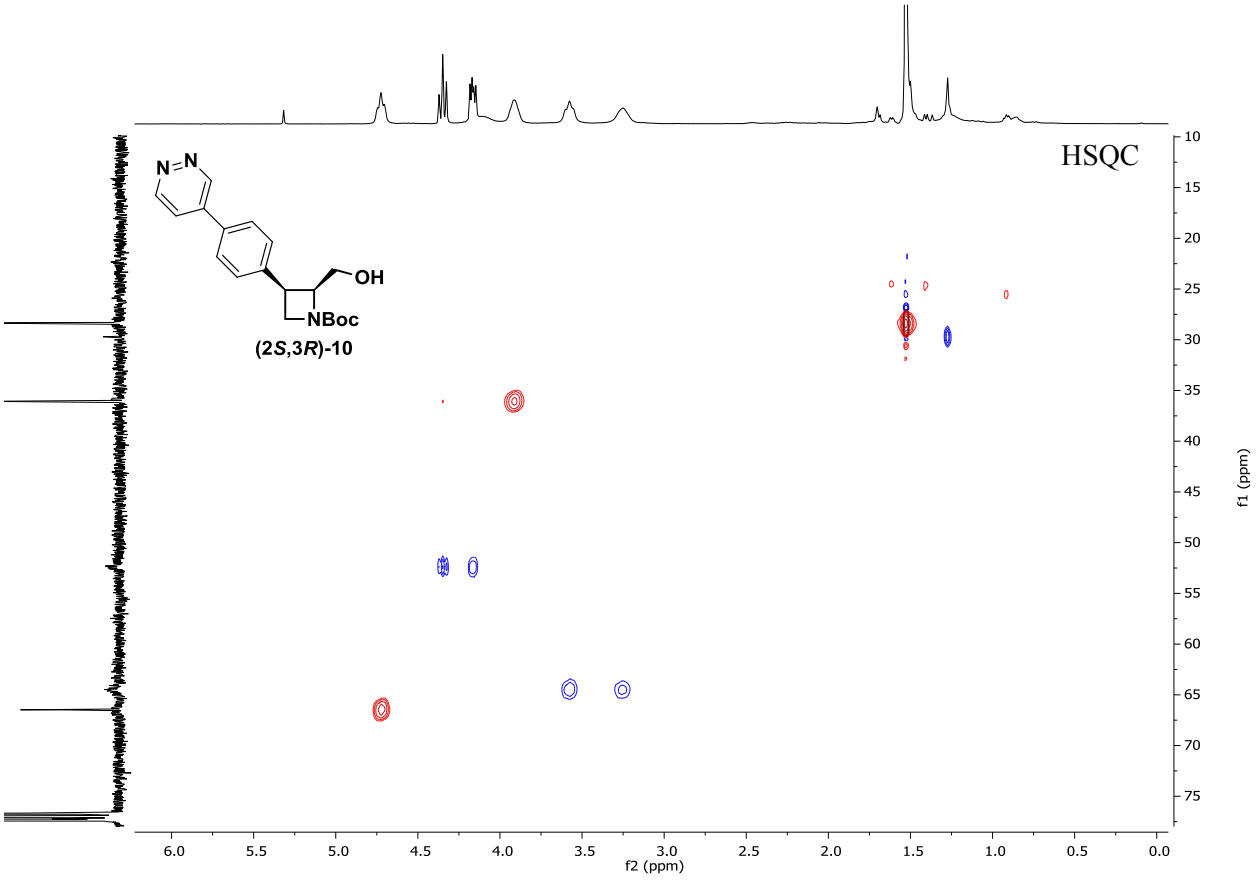


(2*S*,3*R*)-10

^{13}C NMR ($CDCl_3$, 100 MHz)

(2*S*,3*R*)-10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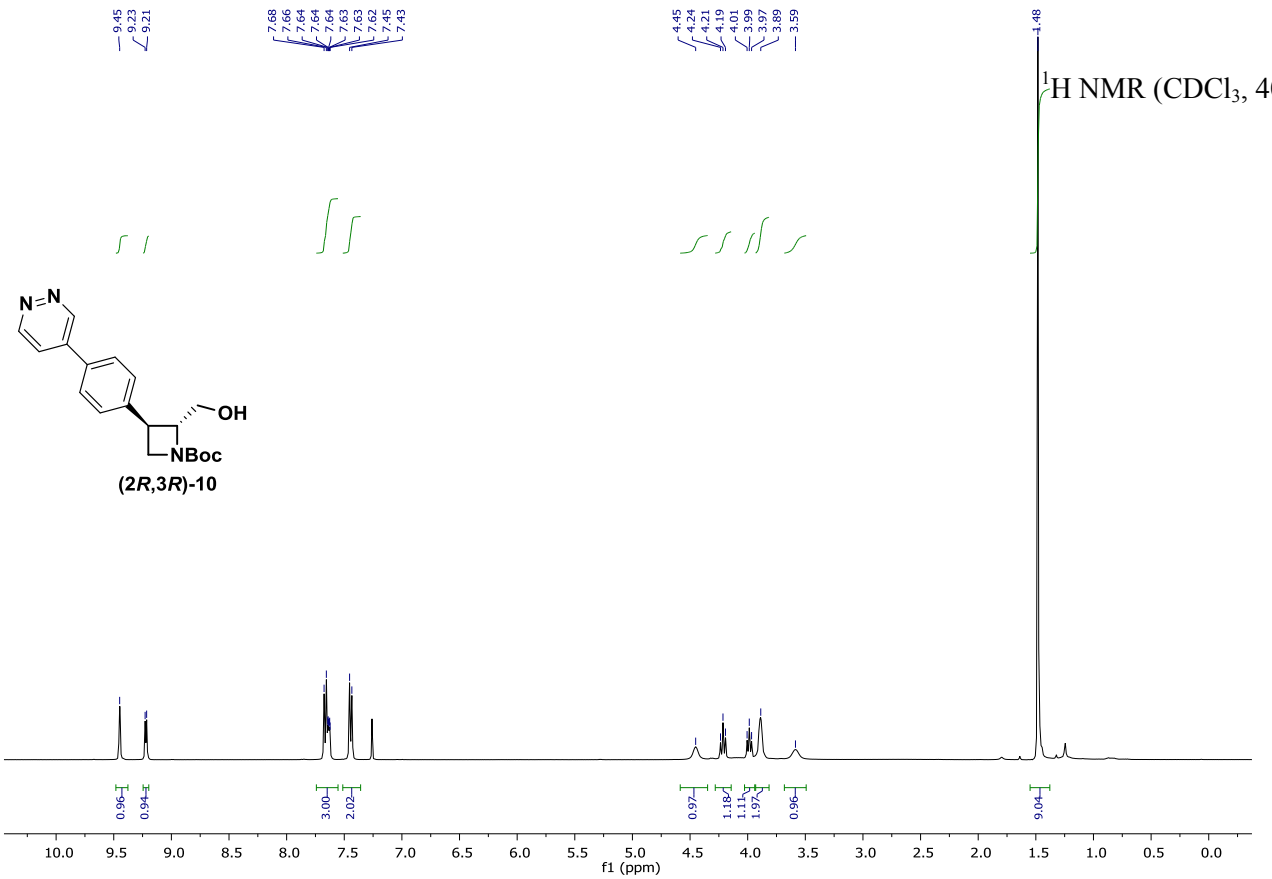
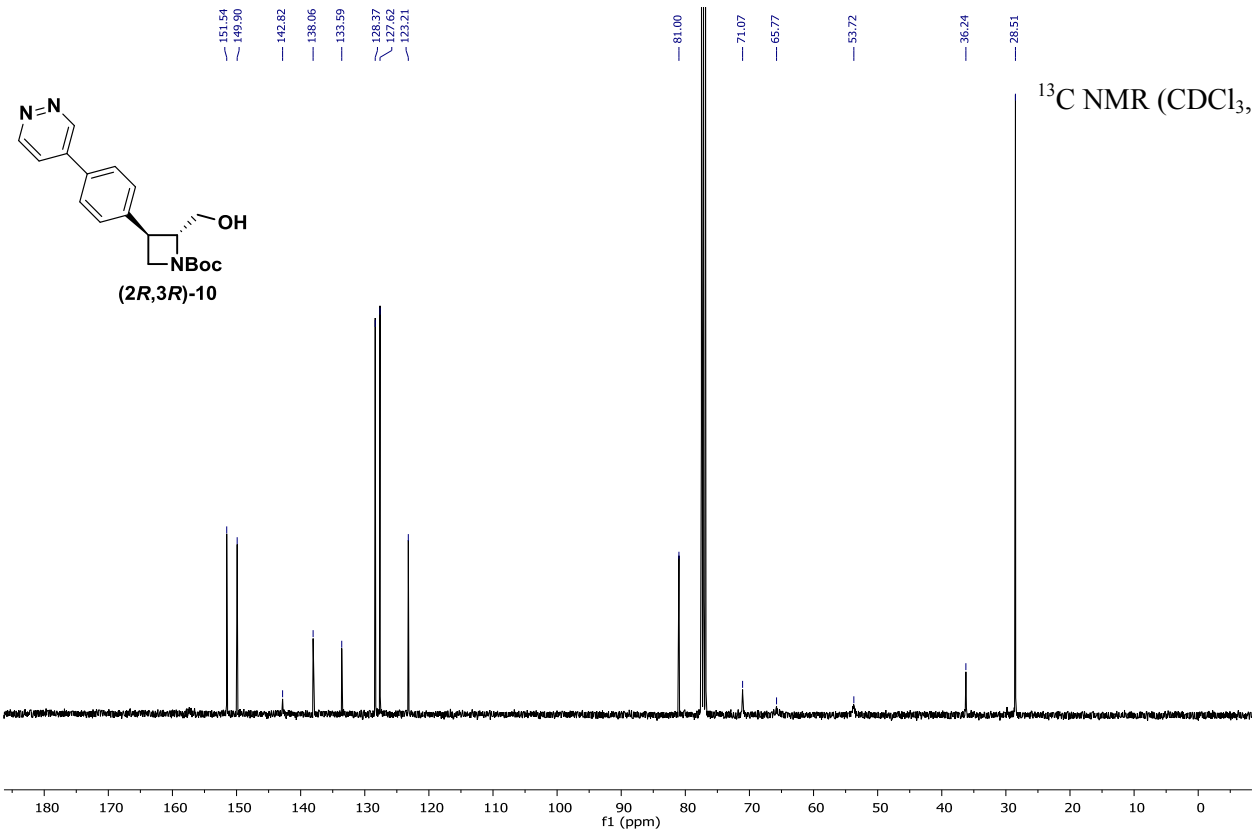


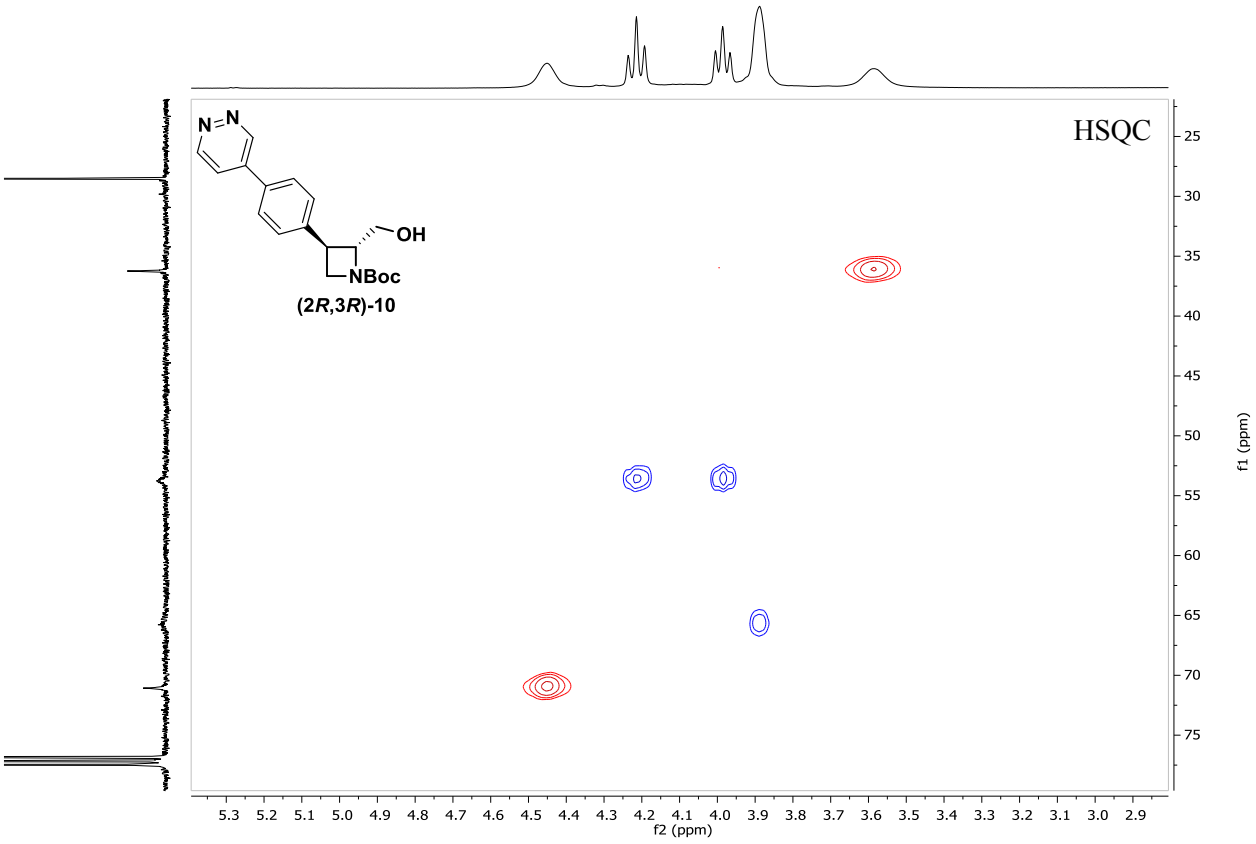
^{1}H NMR ($CDCl_3$, 400 MHz)

(2*R*,3*R*)-10

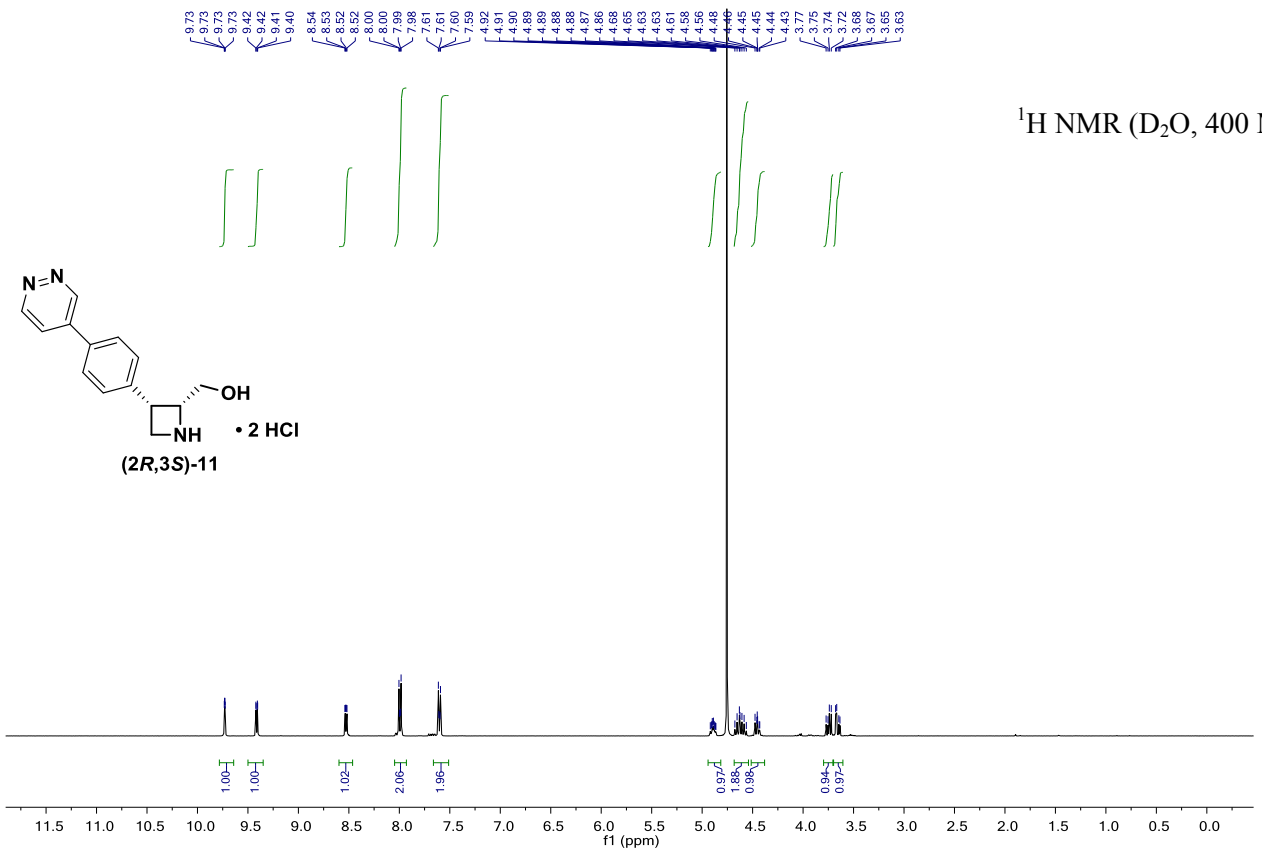


^{13}C NMR ($CDCl_3$, 100 MHz)

(2*R*,3*R*)-10

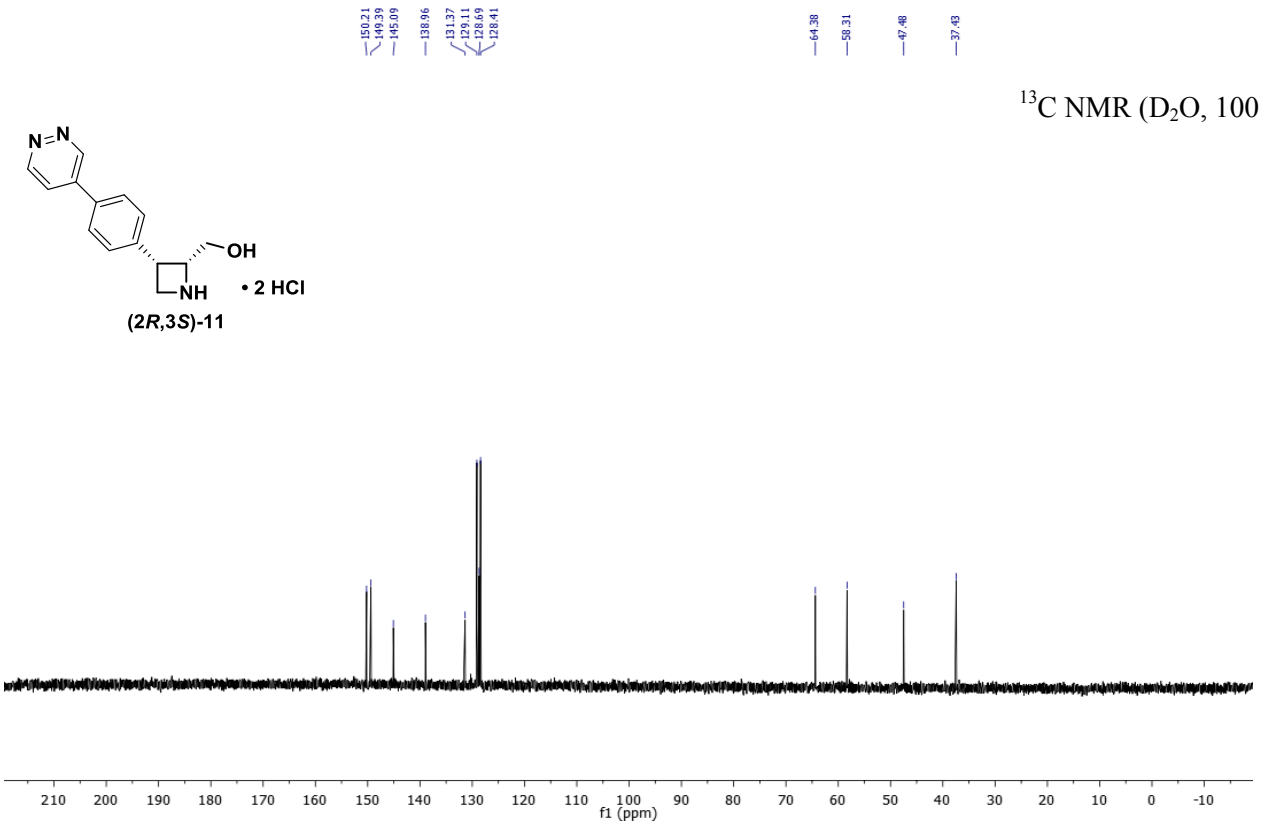

HSQC
OH
NBoc
(2R,3R)-10
f2 (ppm)
f1 (ppm)

^{1}H NMR (D_2O, 400 MHz)

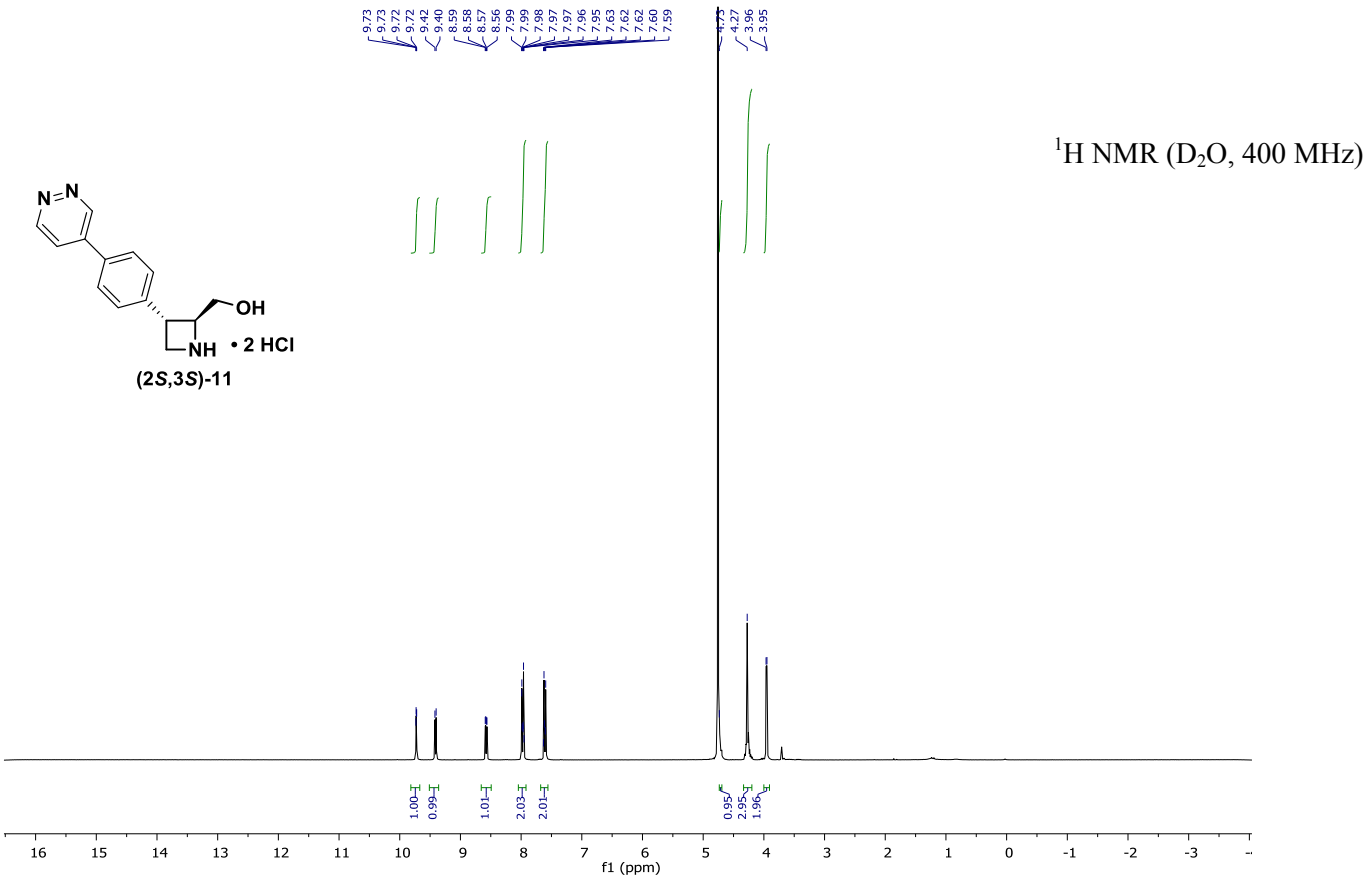


(2*R*,3*S*)-11

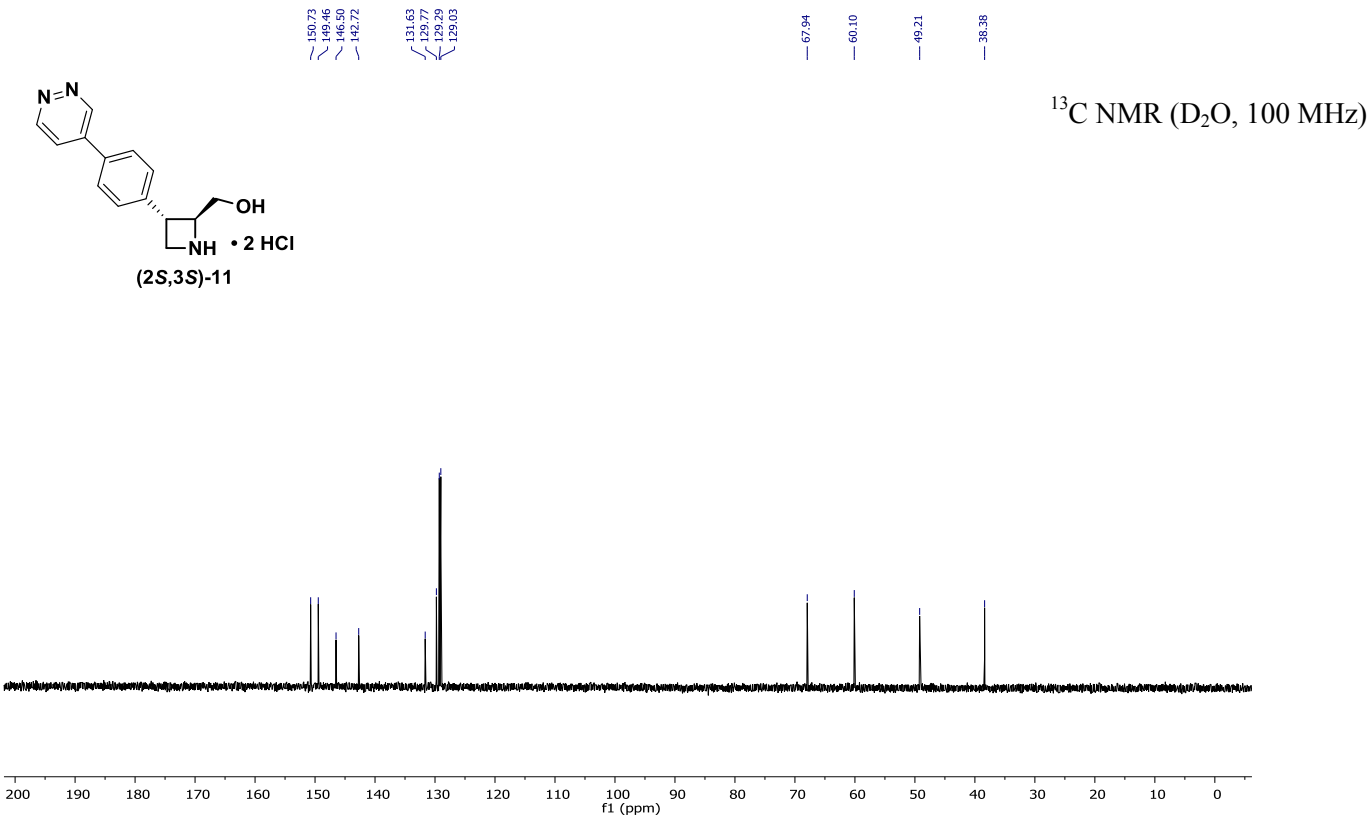
^{13}C NMR (D_2O, 100 MHz)



(2*R*,3*S*)-11

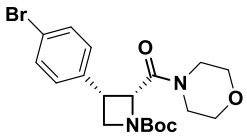


^{1}H NMR (D_2O, 400 MHz)

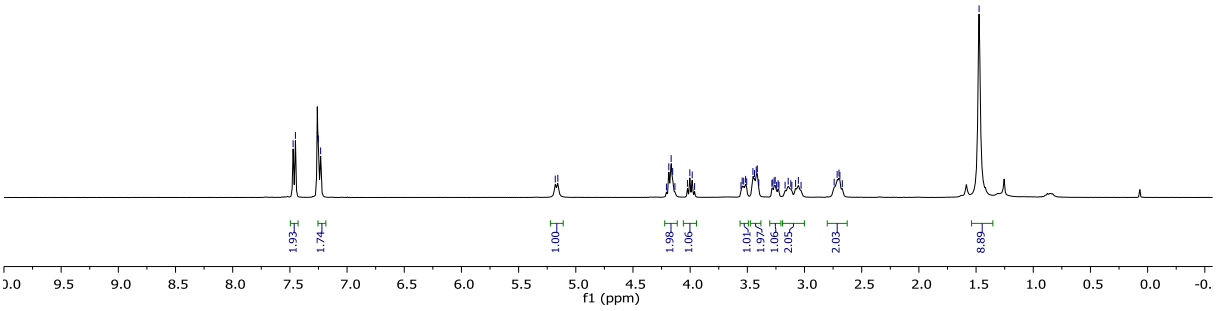


^{13}C NMR (D_2O, 100 MHz)

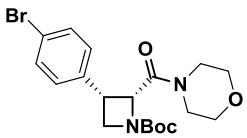
^{1}H NMR ($CDCl_3$, 400 MHz)



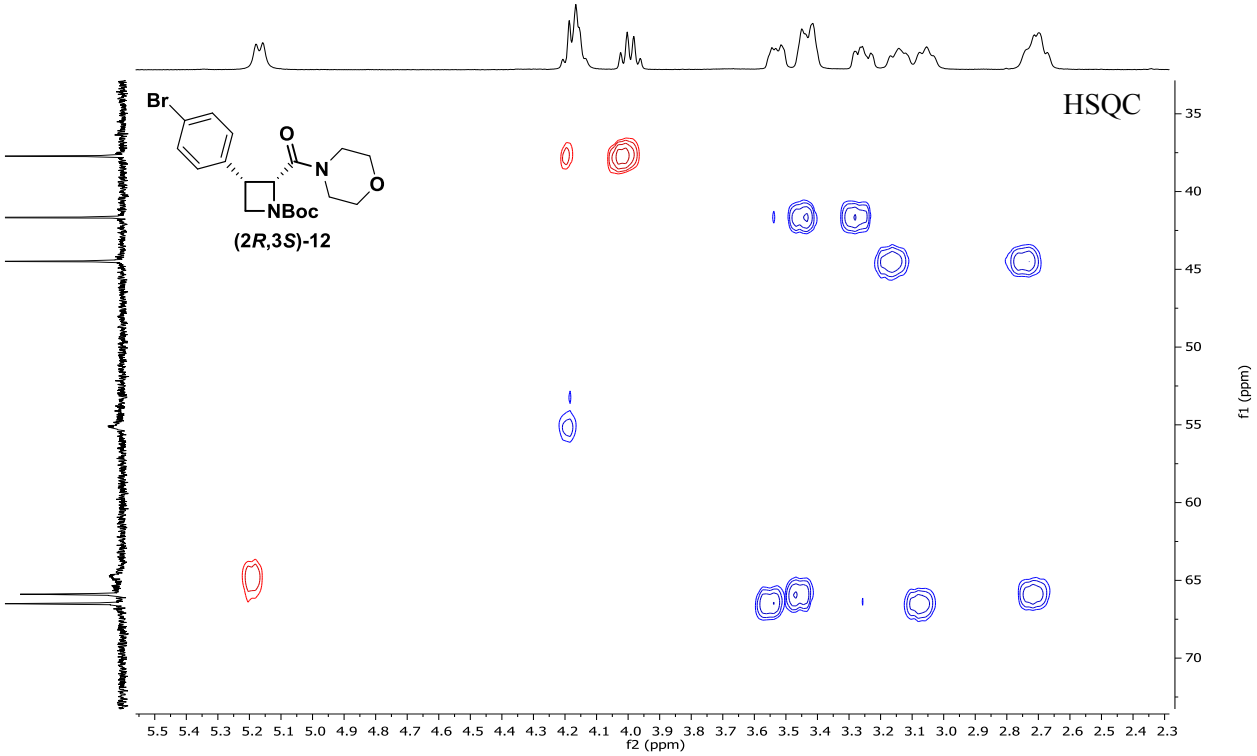
(2*R*,3*S*)-12

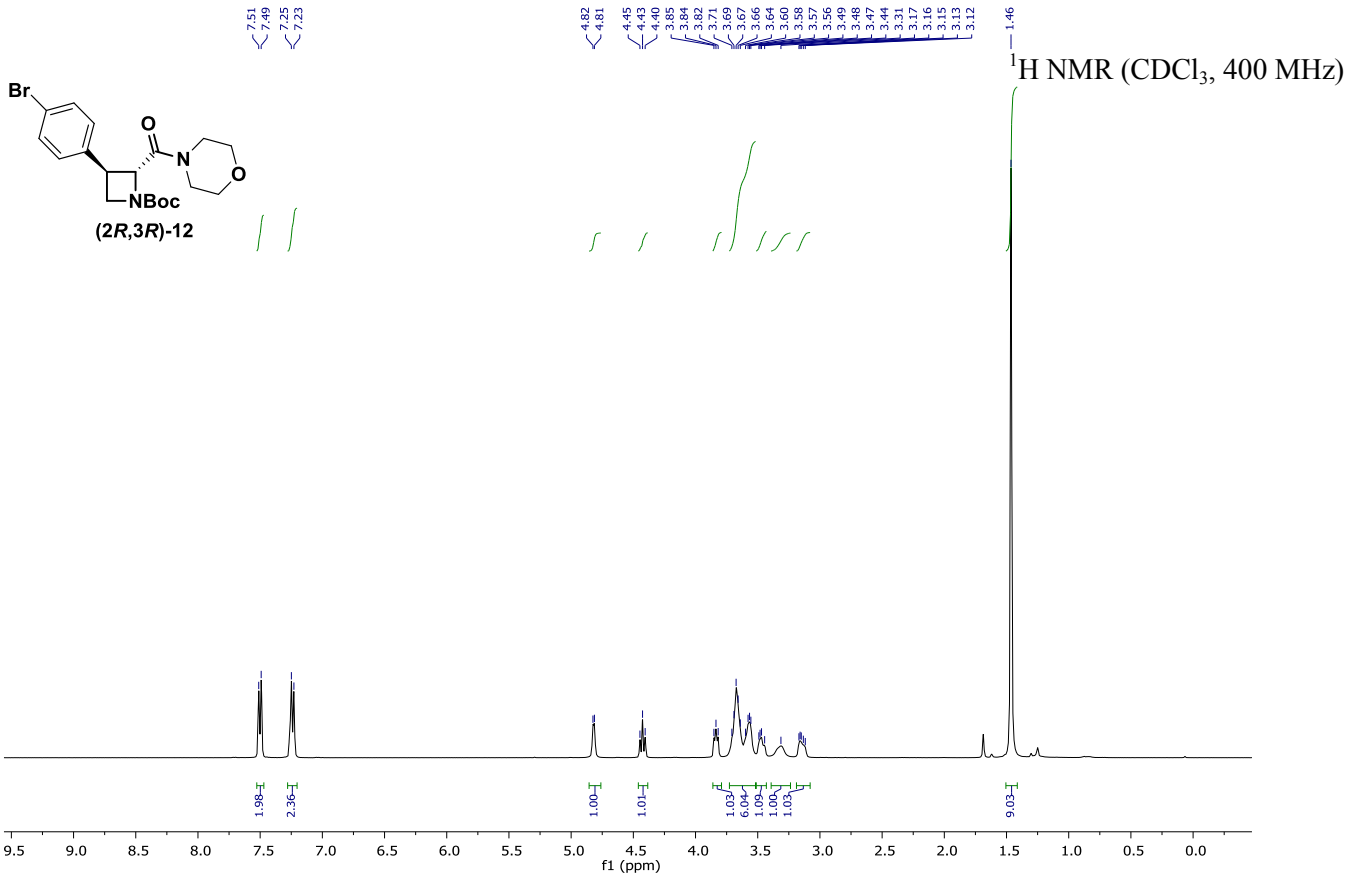


^{13}C NMR ($CDCl_3$, 100 MHz)

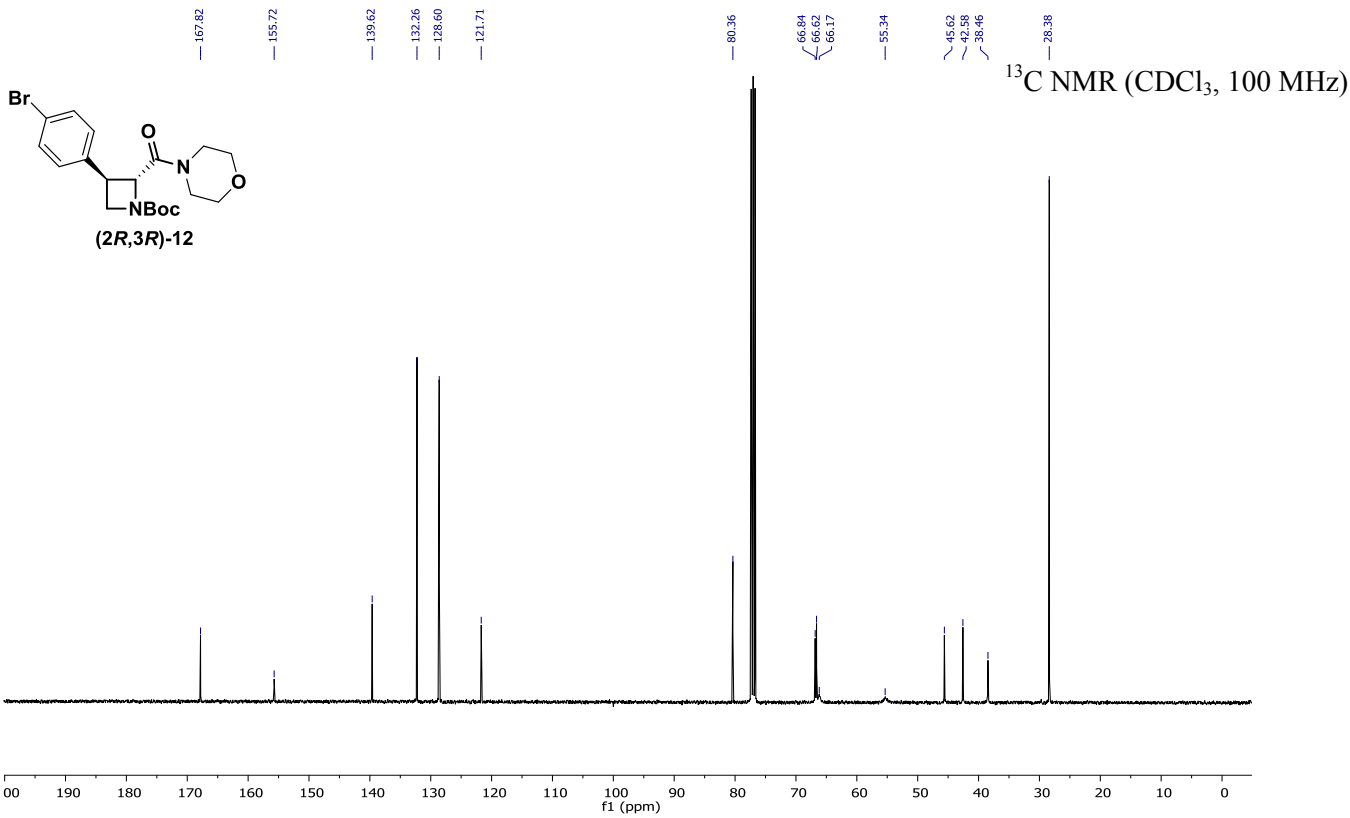


(2*R*,3*S*)-12

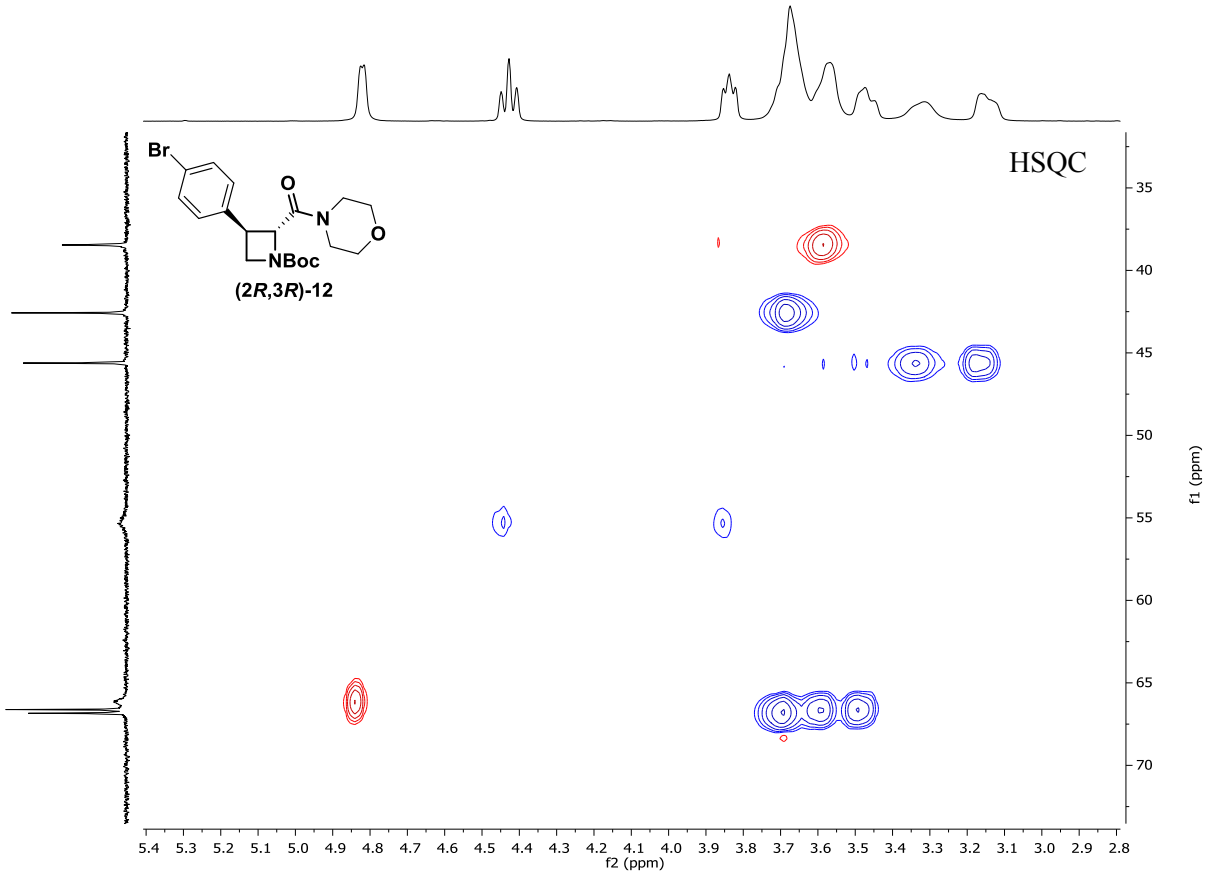

HSQC
Br
O
N
O
NBoc
(2R,3S)-12
f1 (ppm)
f2 (ppm)

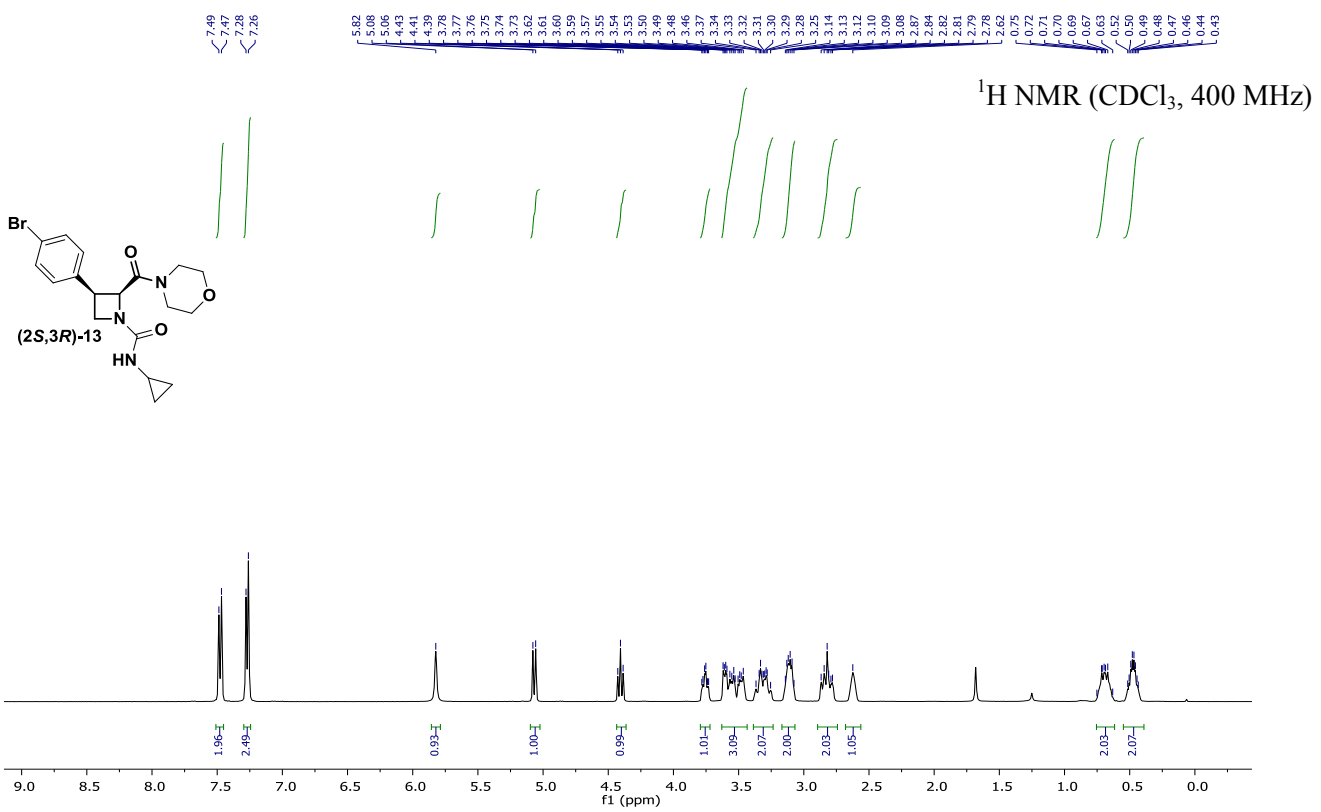


^{1}H NMR ($CDCl_3$, 400 MHz)

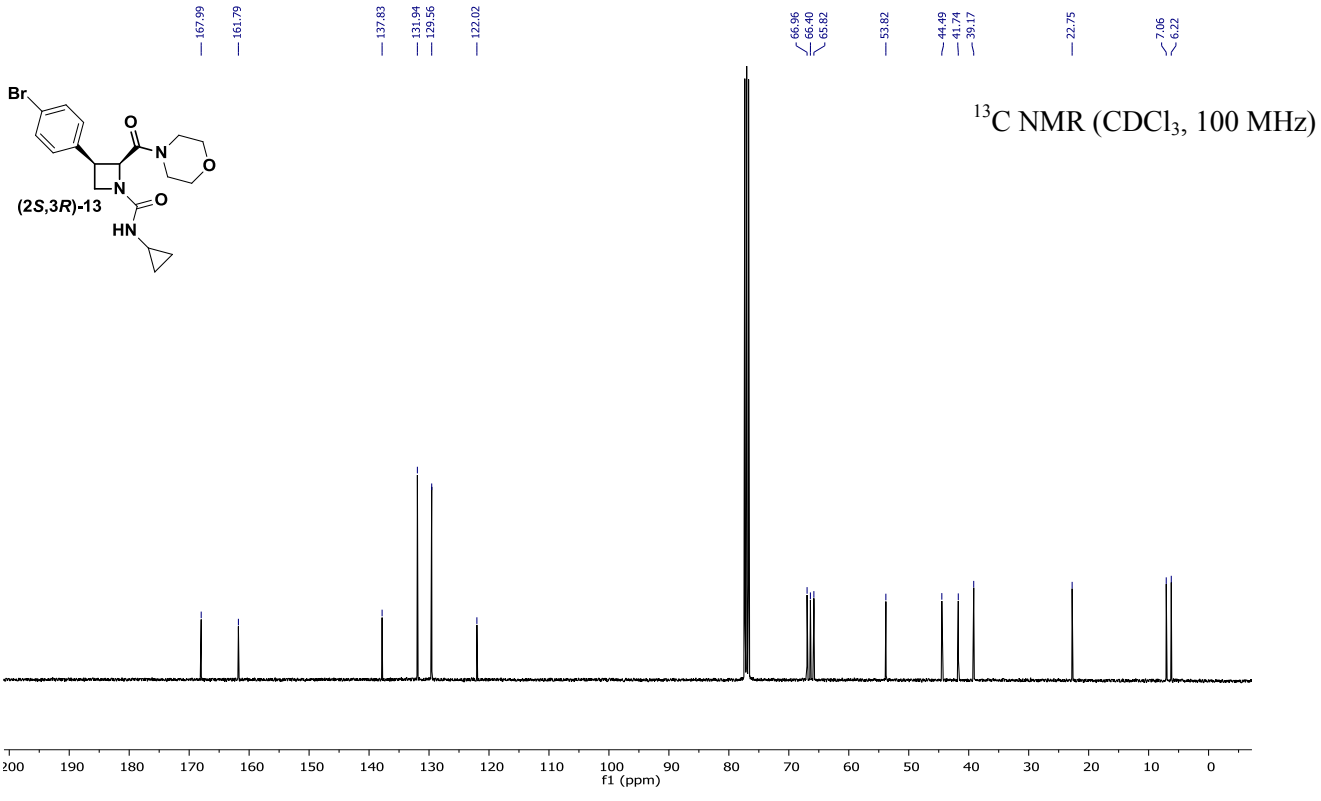


^{13}C NMR ($CDCl_3$, 100 MHz)

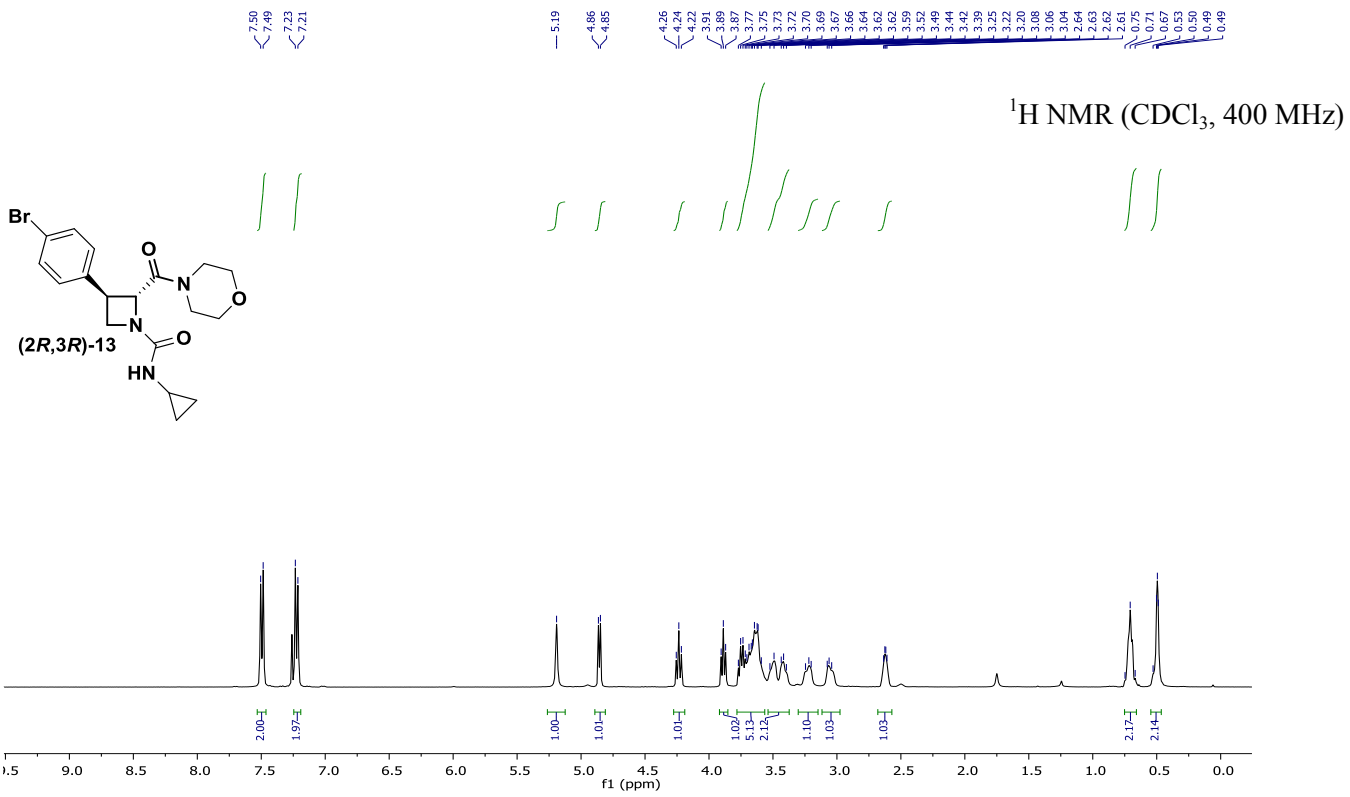

HSQC
Br
O
N
O
NBoc
(2R,3R)-12
35
40
45
50
55
60
65
70
f1 (ppm)
5.4 5.3 5.2 5.1 5.0 4.9 4.8 4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8
f2 (ppm)



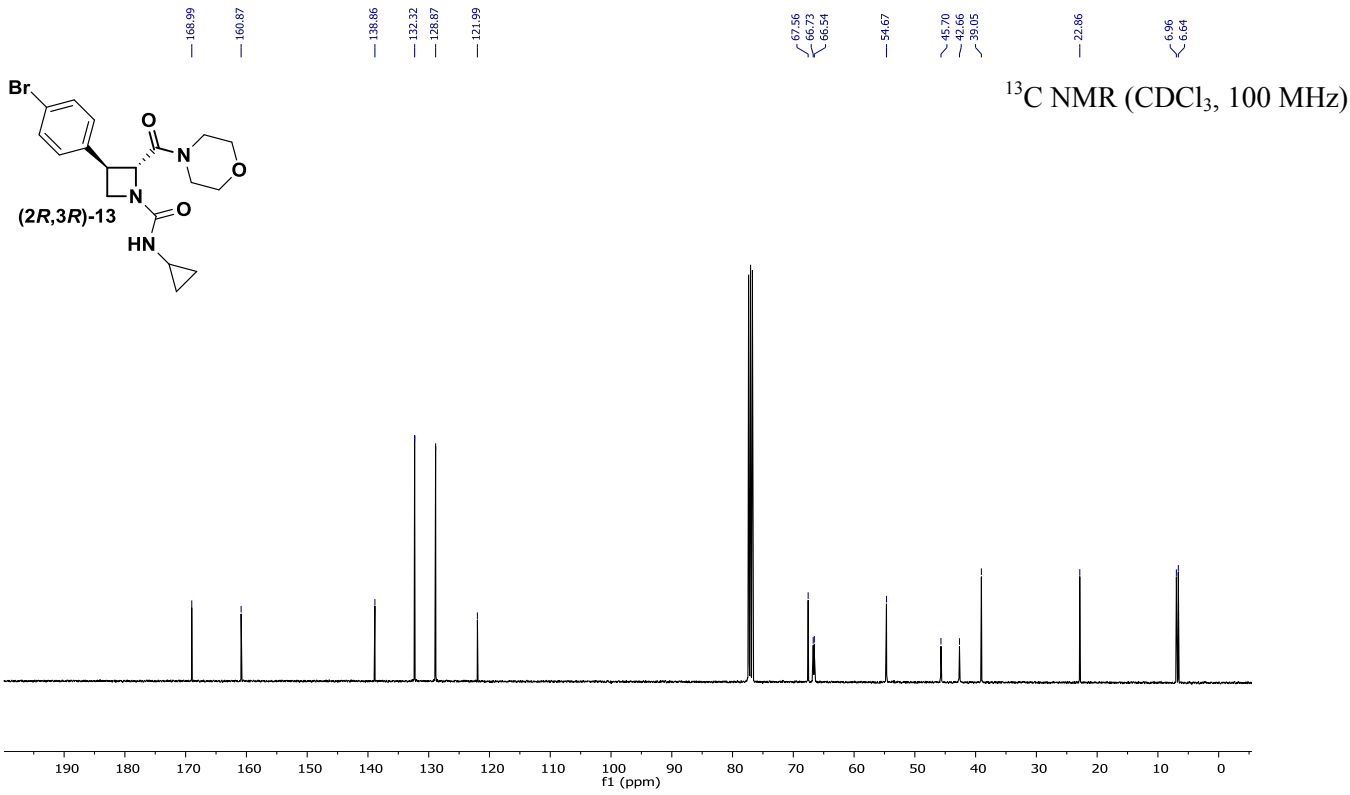
^{1}H NMR ($CDCl_3$, 400 MHz)



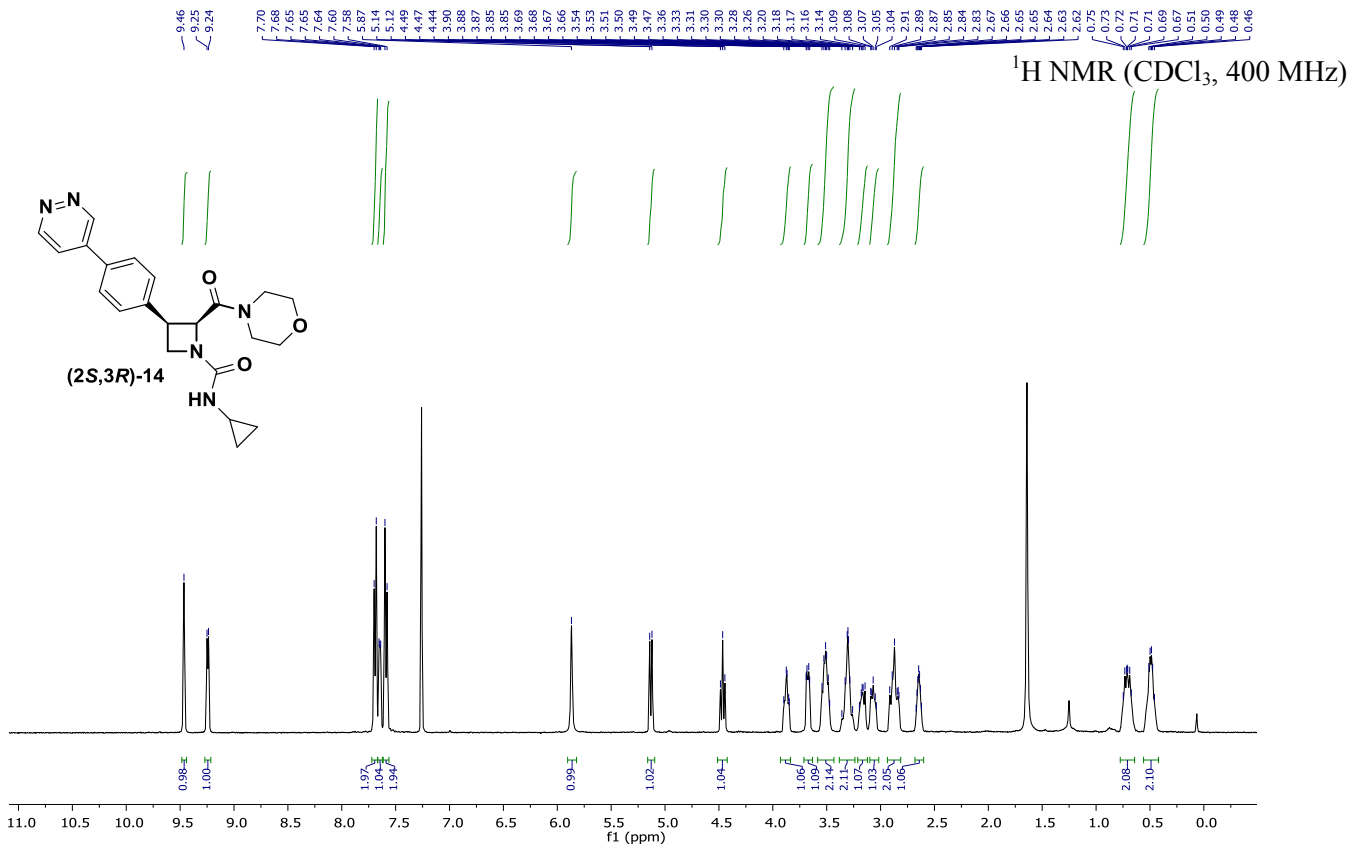
^{13}C NMR ($CDCl_3$, 100 MHz)



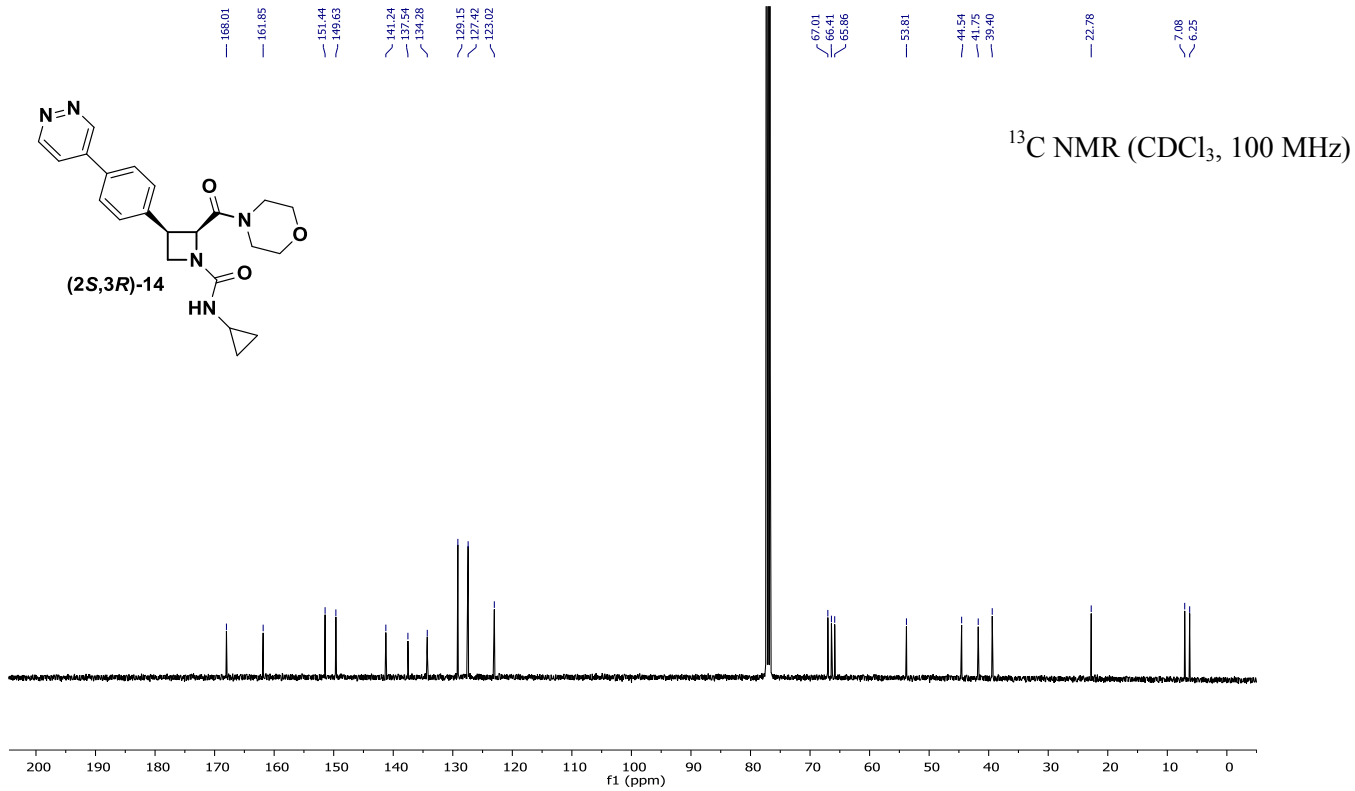
^{1}H NMR ($CDCl_3$, 400 MHz)



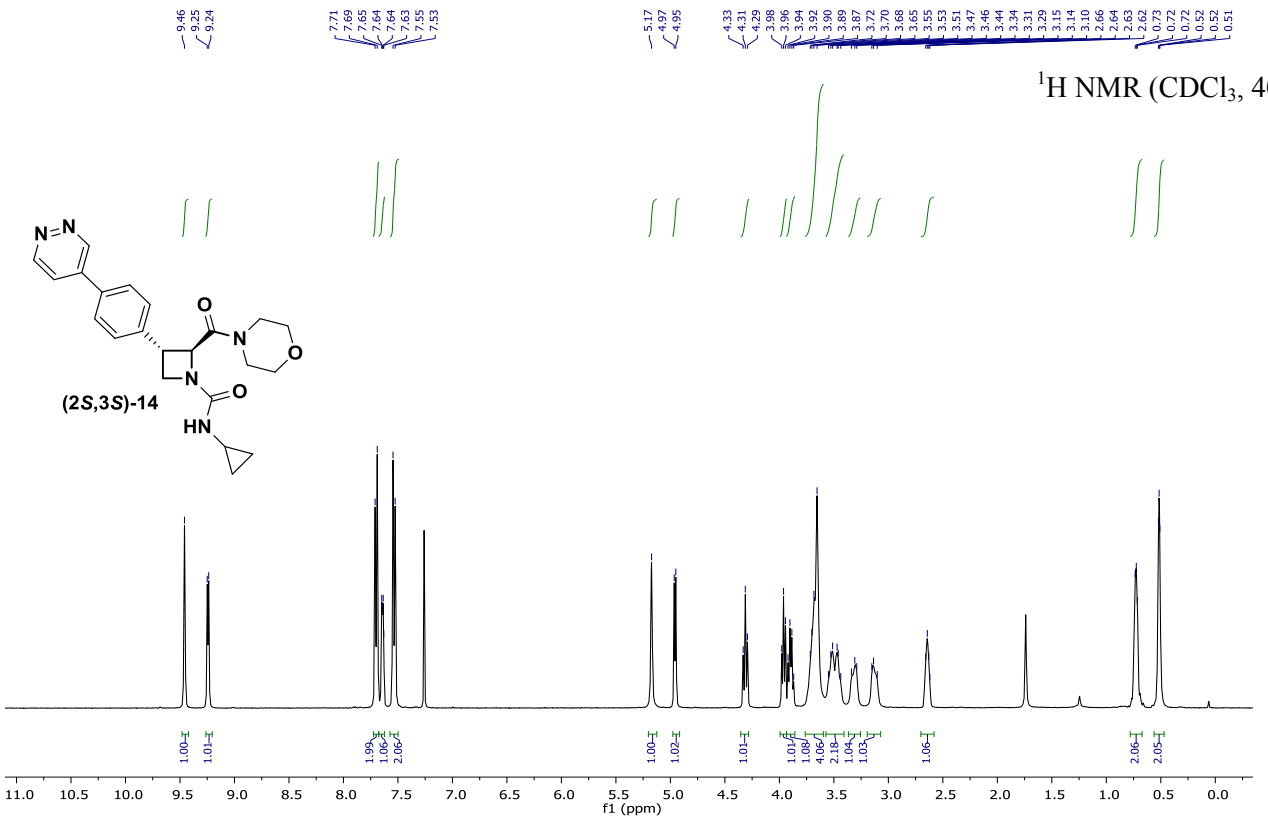
^{13}C NMR ($CDCl_3$, 100 MHz)



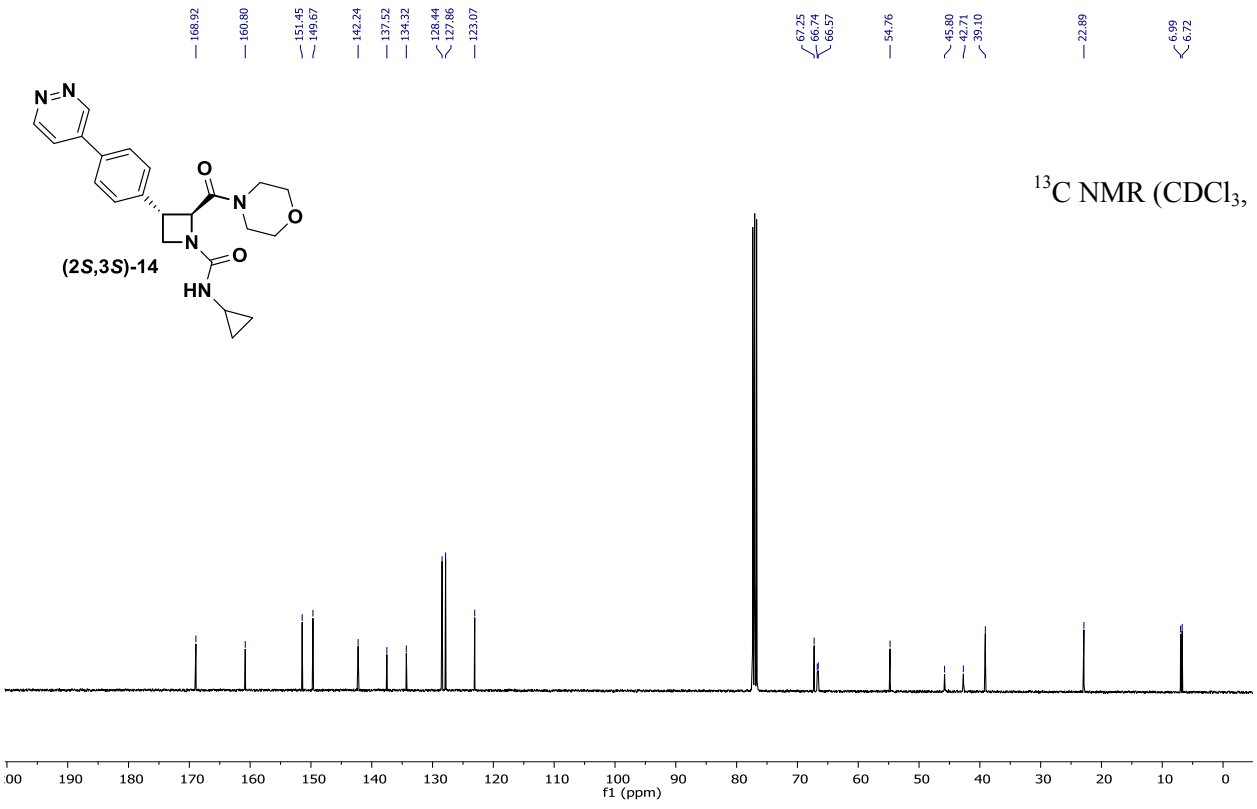
^{1}H NMR ($CDCl_3$, 400 MHz)



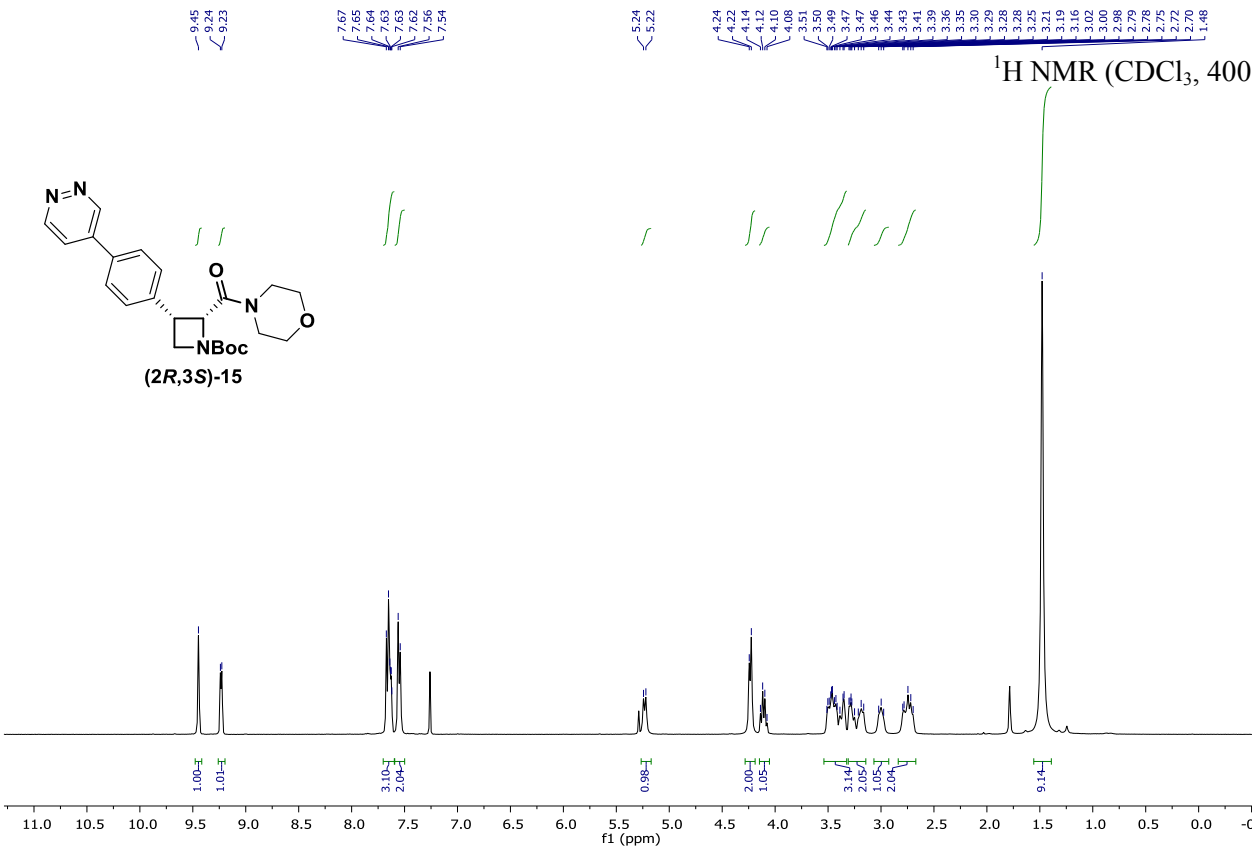
^{13}C NMR ($CDCl_3$, 100 MHz)



^{1}H NMR ($CDCl_3$, 400 MHz)

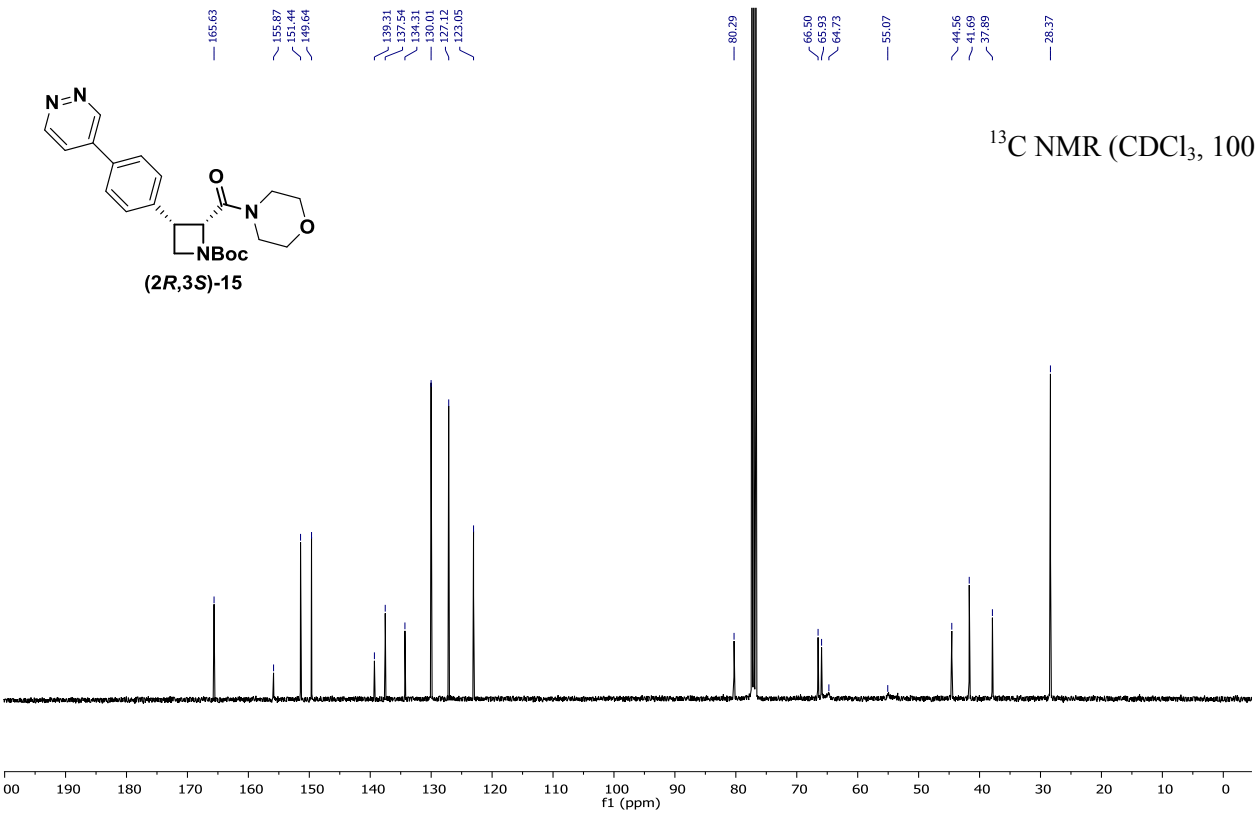


^{13}C NMR ($CDCl_3$, 100 MHz)



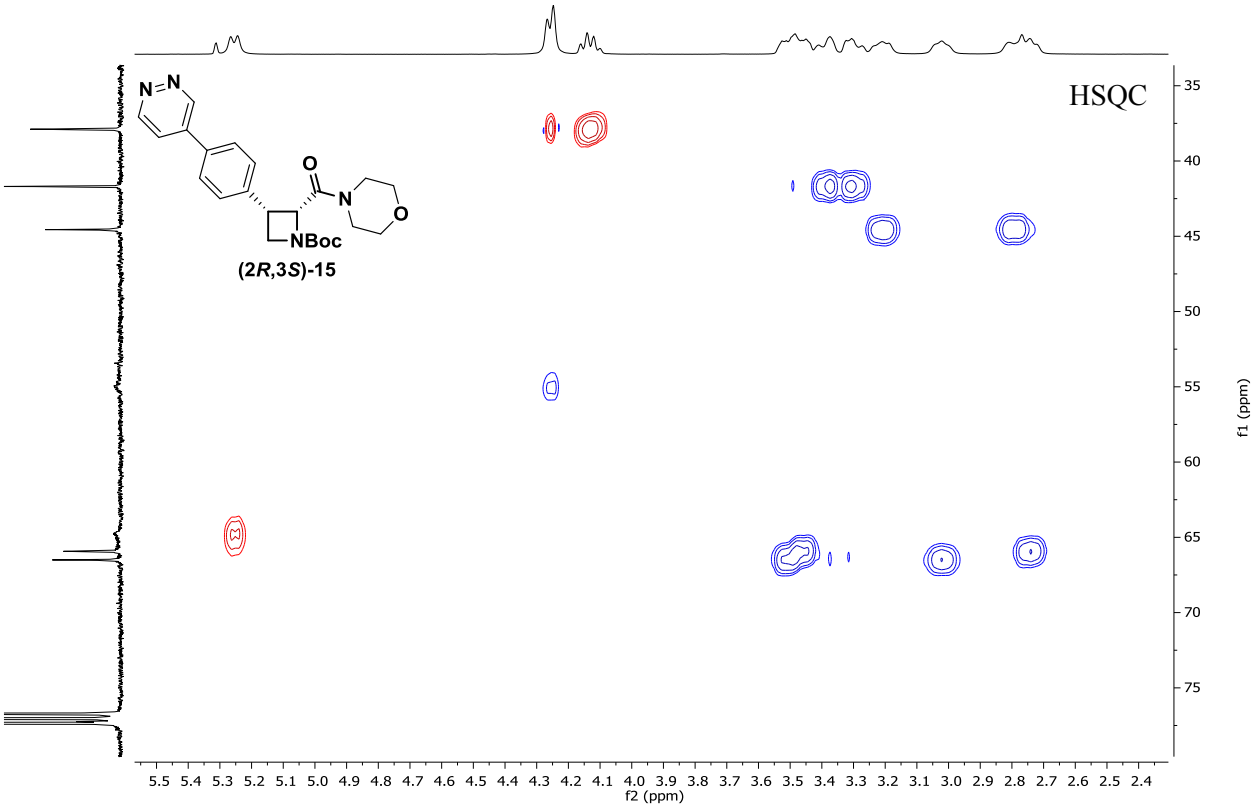
(2*R*,3*S*)-15

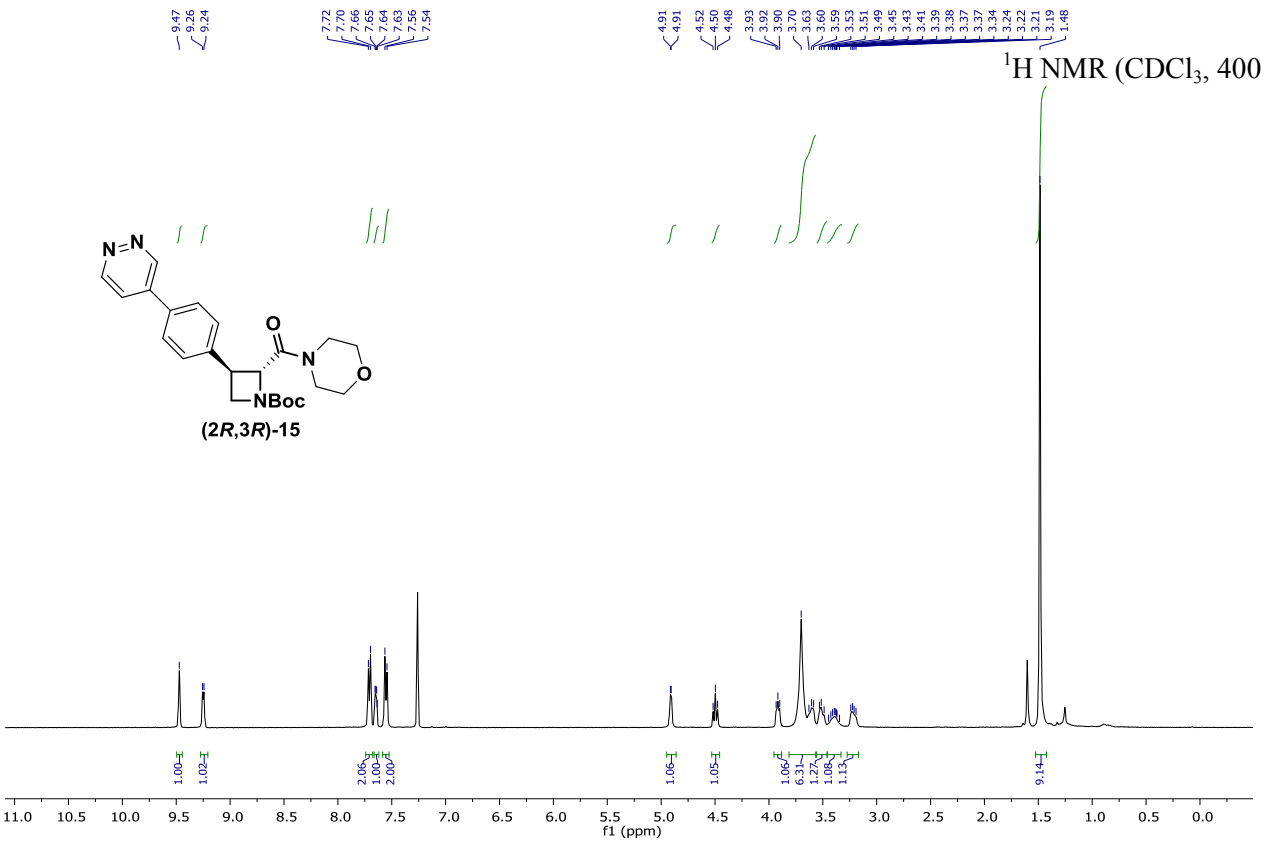
^{1}H NMR ($CDCl_3$, 400 MHz)



(2*R*,3*S*)-15

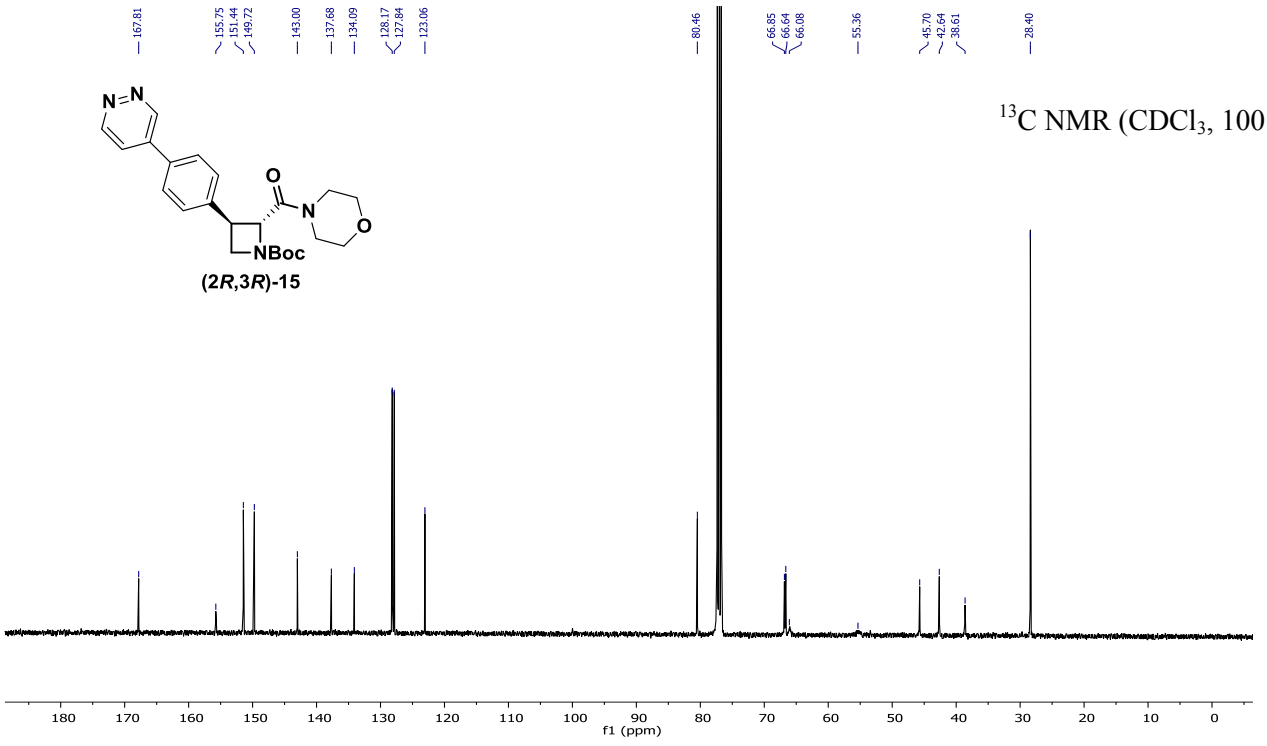
^{13}C NMR ($CDCl_3$, 100 MHz)


HSQC
(2R,3S)-15
f2 (ppm)
f1 (ppm)



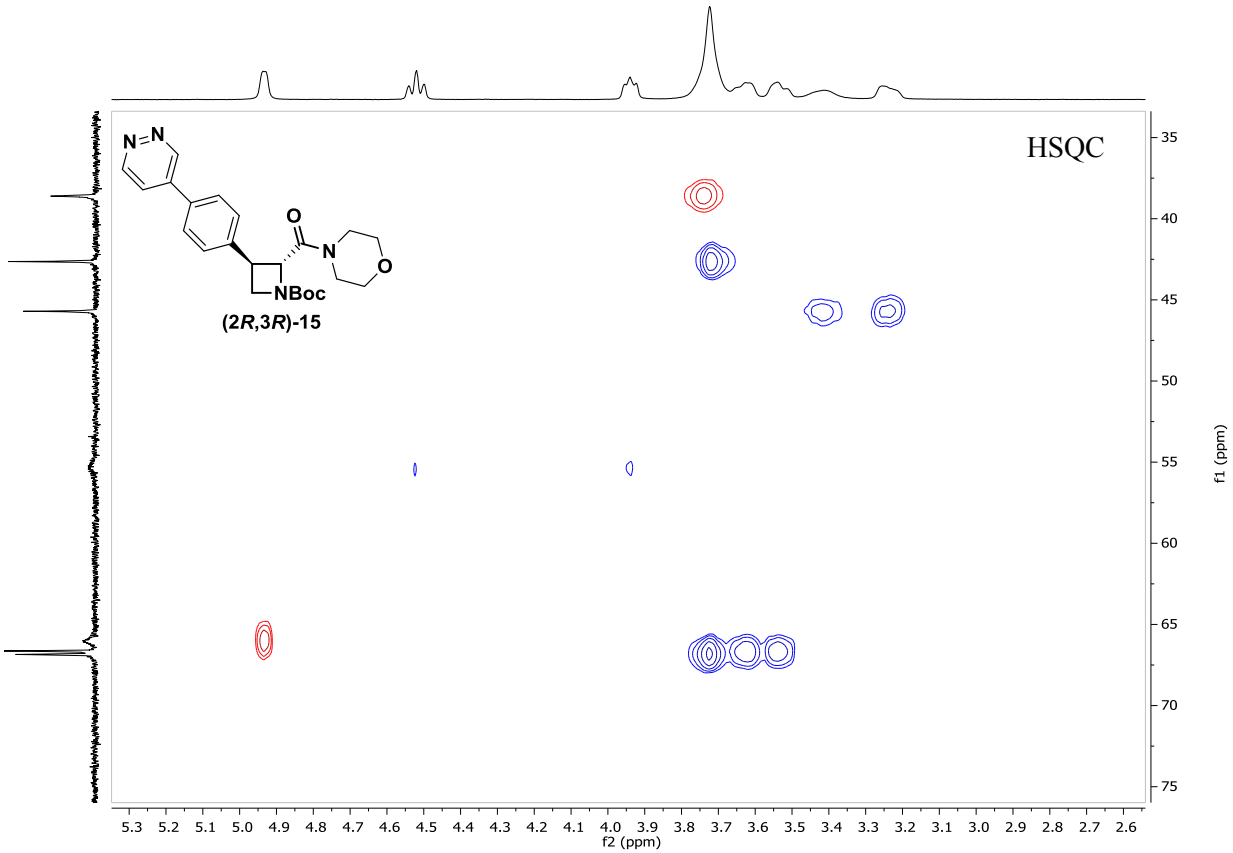
(2*R*,3*R*)-15

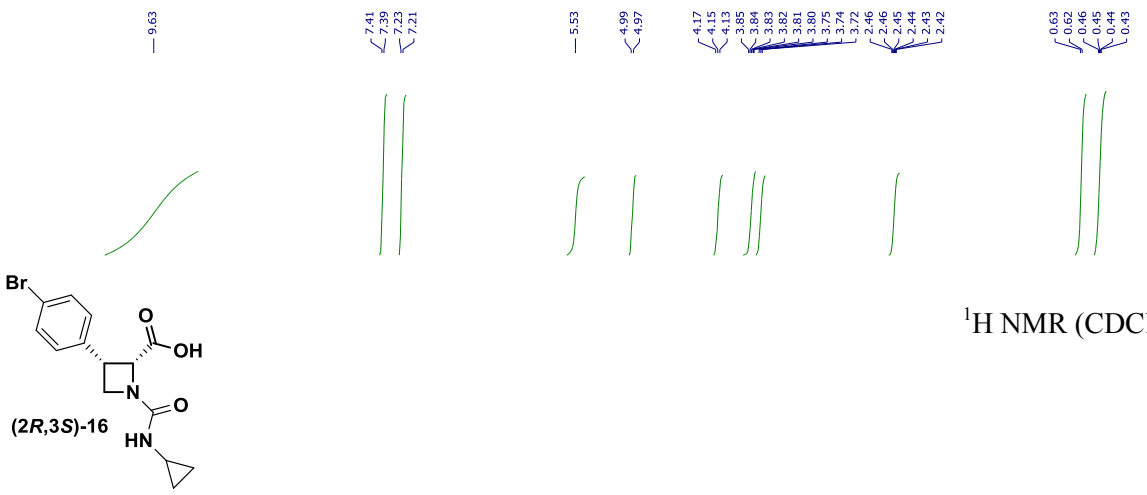
^{1}H NMR ($CDCl_3$, 400 MHz)



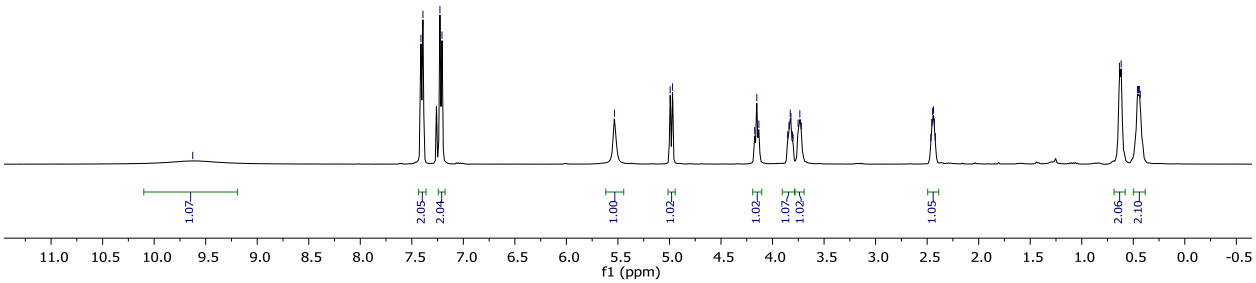
(2*R*,3*R*)-15

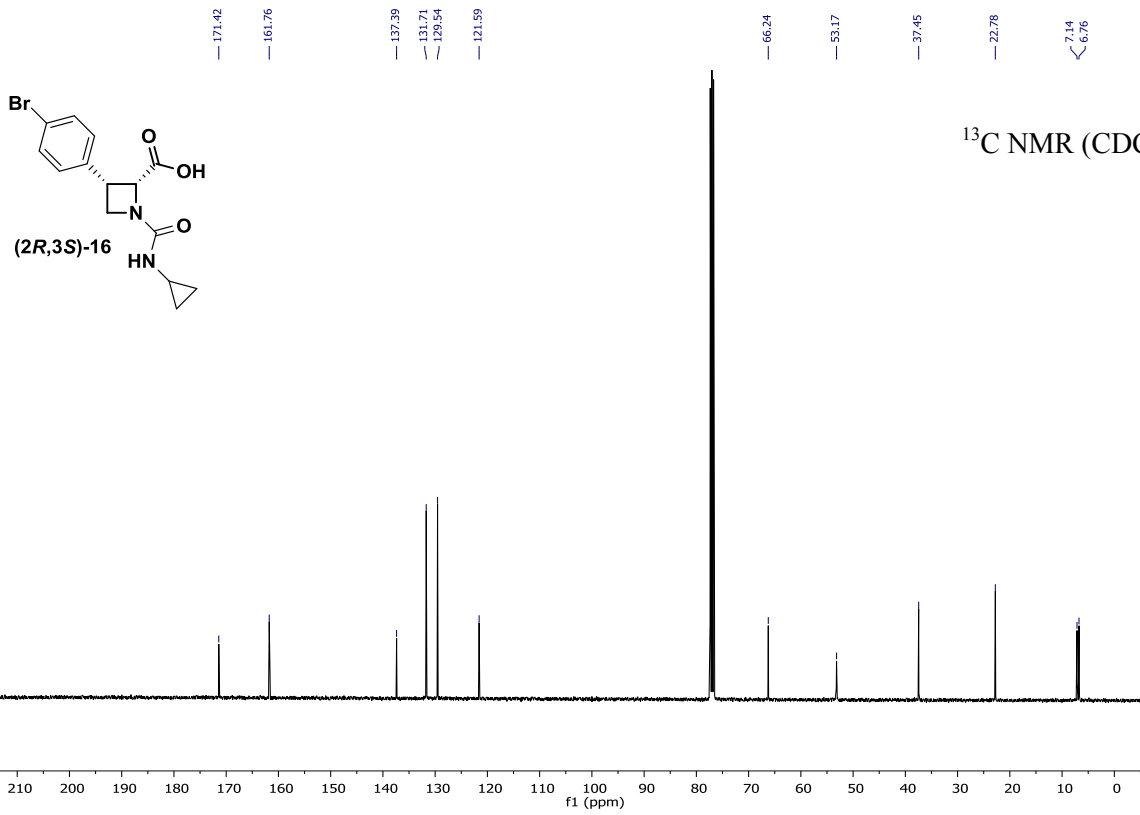
^{13}C NMR ($CDCl_3$, 100 MHz)


HSQC
(2R,3R)-15
f2 (ppm)
f1 (ppm)

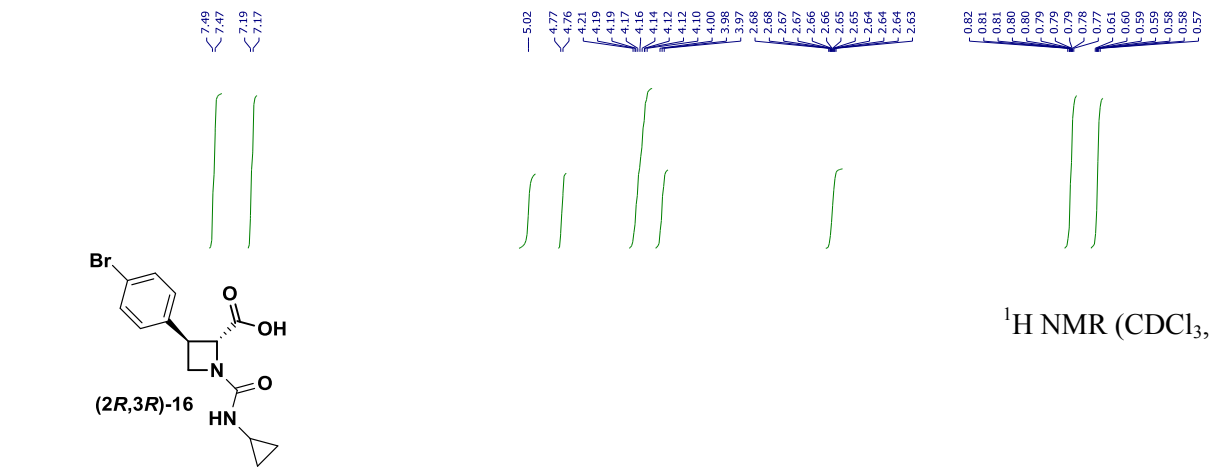


^{1}H NMR ($CDCl_3$, 400 MHz)



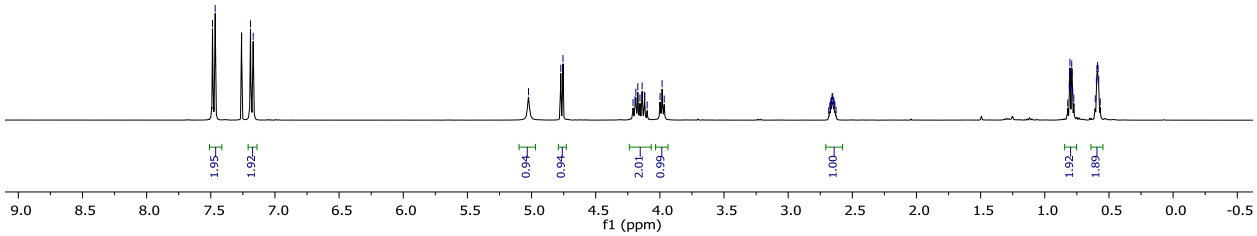


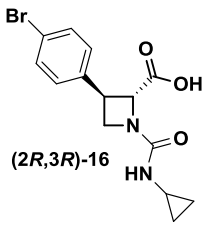
^{13}C NMR ($CDCl_3$, 100 MHz)



(2*R*,3*R*)-16

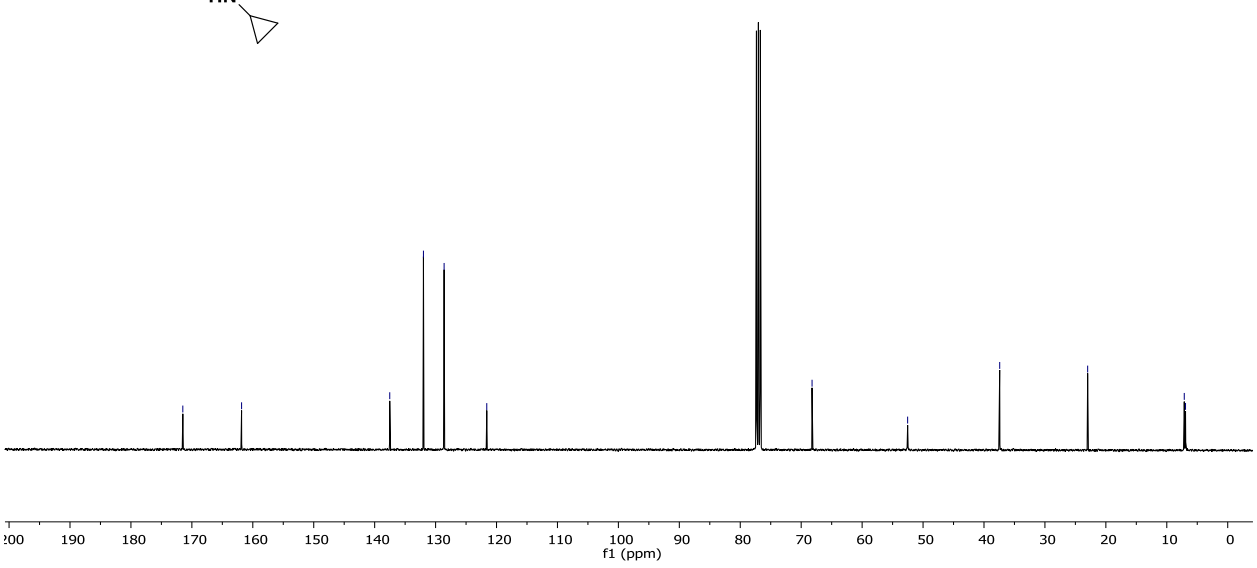
^{1}H NMR ($CDCl_3$, 400 MHz)



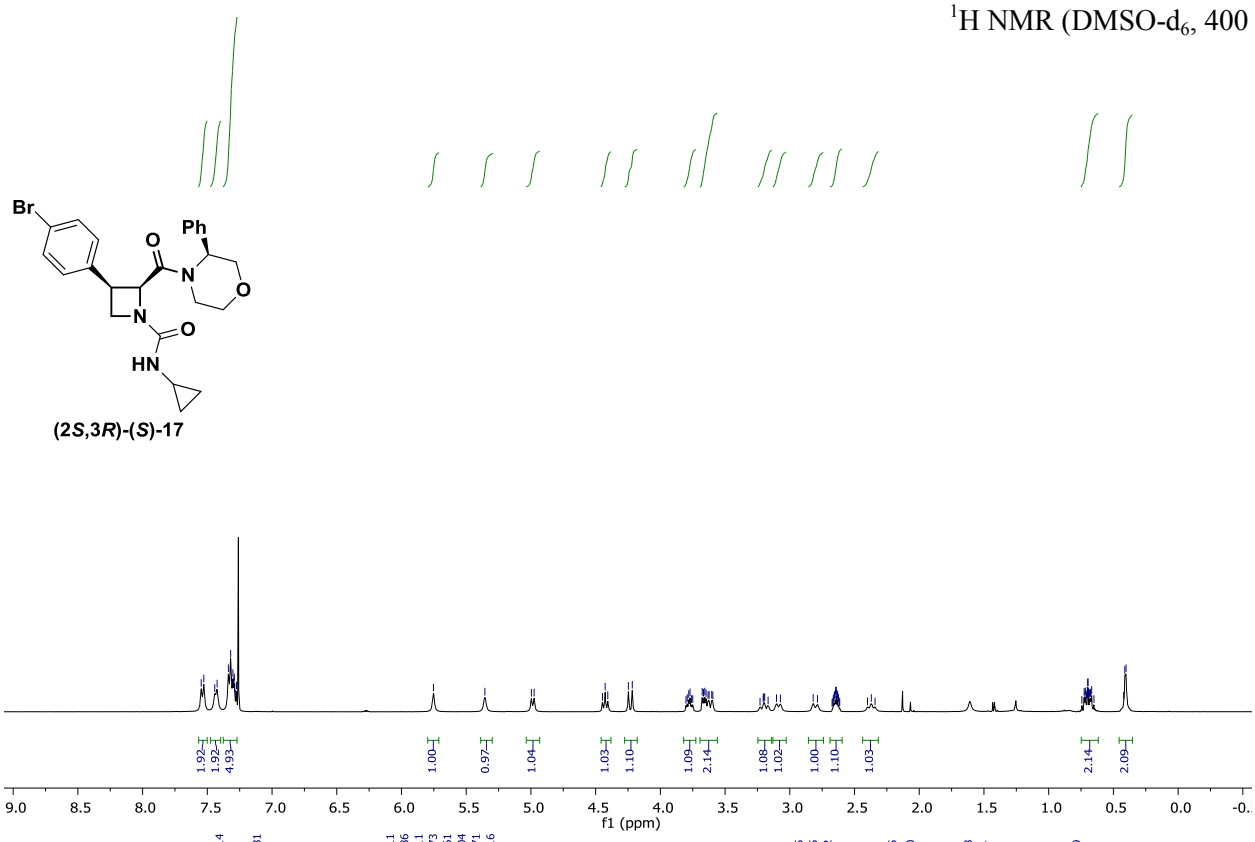


(2*R*,3*R*)-16

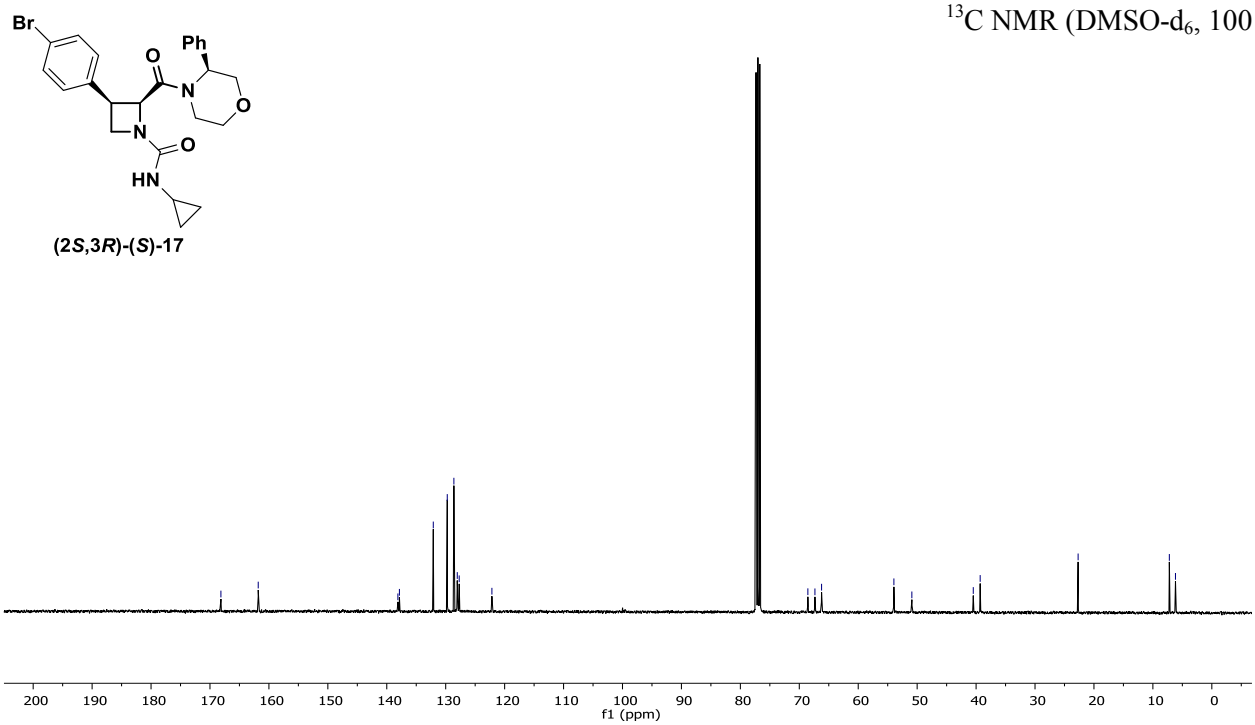
^{13}C NMR ($CDCl_3$, 100 MHz)



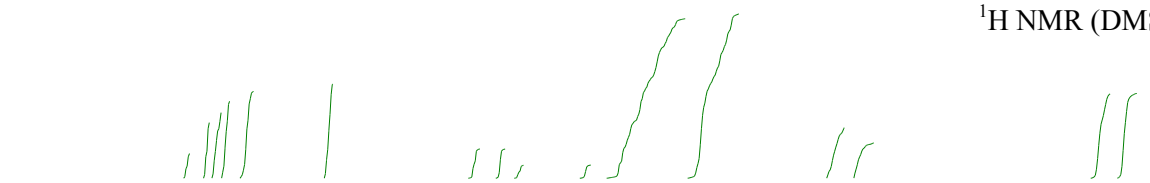
^{1}H NMR (DMSO-d$_6$, 400 MHz)

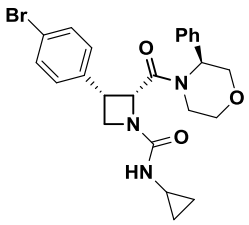


^{13}C NMR (DMSO-d$_6$, 100 MHz)

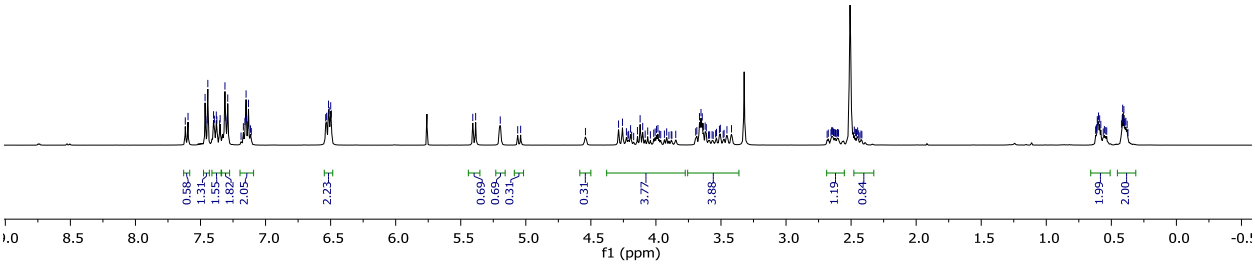


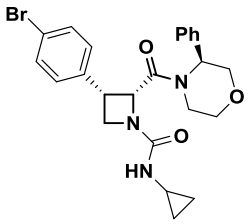
^{1}H NMR (DMSO-d$_6$, 400 MHz)





(2*R*,3*S*)-(*S*)-17





(2*R*,3*S*)-(*S*)-17

^{13}C NMR (DMSO-d$_6$, 100 MHz)