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*Supporting Information*

# A Vending Machine for Drug-like Molecules – Automated Synthesis of Virtual Screening Hits

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# Virtual Library

## Building Blocks

| Functional Group | Source | Source 2 | Filters Applied | Final number of members |
|---|---|---|---|---|
| Aromatic aldehydes | Enamine Heteroarmoatic aldehydes 20220317 (https://enamine.net/building-blocks/functional-classes/aldehydes, accessed 25/04/22) | Manually curated aromatic aldehydes from Scifinder | Acid Chloride = 0<br>Carboxylic Acid = 0<br>Sulfonyl Chloride = 0<br>Amine = 0<br>Boronic Acid = 0<br>Isocyanate = 0<br>Alcohol = 0<br>Aromatic Aldehyde = 1<br>Aliphatic Aldehyde = 0<br>Duplicates removed<br>Molecular weight < 200<br>LogP < 2 | 1497 |
| Aldehydes | Enamine stock aldehydes (https://enamine.net/building-blocks/functional-classes/aldehydes, accessed 25/04/22) | None | Acid Chloride = 0<br>Carboxylic Acid = 0<br>Sulfonyl Chloride = 0<br>Amine = 0<br>Boronic Acid = 0<br>Isocyanate = 0<br>Alcohol = 0<br>Aldehyde = 1 | 6852 |
| Carboxylic acids | Enamine stock carboxylic acids (https://enamine.net/building-blocks/functional-classes/acids, accessed 25/04/22) | None | Acid Chloride = 0<br>Aromatic Carboxylic Acid <= 1<br>Aliphatic Carboxylic Acid <= 1<br>Sulfonyl Chloride = 0<br>Amine = 0<br>Boronic Acid = 0<br>Isocyanate = 0<br>Alcohol = 0<br>Aldehyde = 0 | 35178 |
| Phenols | Emolecules (https://www.emolecules.com, accessed 25/04/22) | None | Acid Chloride = 0<br>Carboxylic Acid = 0<br>Amine = 0<br>Boronic Acid = 0<br>Isocyanate = 0<br>Aromatic Alcohol = 1<br>Aliphatic Alcohol = 0<br>Aldehyde = 0 | 4760 |
| Amines | Enamine stock primary amines (https://enamine.net/building-blocks/functional-classes/primary-amines, accessed 25/04/22) | Enamine stock secondary amines (https://enamine.net/building-blocks/functional-classes/secondary-amines, accessed 25/04/22) | Acid Chloride = 0<br>Carboxylic Acid = 0<br>Sulfonyl Chloride = 0<br>Amine = 1<br>Boronic Acid = 0<br>Isocyanate = 0<br>Alcohol = 0<br>Aldehyde = 0 | 56410 |
| Primary Amines | Enamine stock primary amines (https://enamine.net/building-blocks/functional-classes/primary-amines, accessed 25/04/22) | Manually curated primary amines from Scifinder | Primary Amine = 1<br>Secondary Amine =0<br>Aromatic amine = 0<br>Duplicates removed<br>Molecular weight < 200<br>LogP < 2 | 8872 |
| Boc-diamines | Manually sourced* boc-diamines from Scifinder(listed below) | Emolecules (https://www.emolecules.com, accessed 25/04/22) | Amine = 1<br>Boc-amine = 1 | 2441 |
| Boc-amino acids | Manually sourced* Boc-amino acids from Scifinder | Emolecules (https://www.emolecules.com, accessed 25/04/22) | Carboxylic Acid = 1<br>Boc-amine = 1 | 1706 |
| Carbonyl-OSi | Manually sourced* Carbonyl-OSi from Scifinder | Emolecules (https://www.emolecules.com, accessed 25/04/22) | Duplicates removed<br>Manual inspection | 16 |
| Amine-OSi | Manually sourced* Amine-OSi from Scifinder | Emolecules (https://www.emolecules.com, accessed 25/04/22) | Duplicates removed<br>Manual inspection | 57 |

*Manually sourced from the Scifinder database using sub-structure search function.[1]

[1] CAS Scifinder$^n$, https://scifinder-n.cas.org, (accessed August 2020).

**Enumeration**

Enumerations were carried out using RDKit 1 and 2 component reaction nodes in KNIME.[2,3] Input materials were used in SMILES format and transformations were defined using SMARTS.[4]

**iSnAP nomenclature**

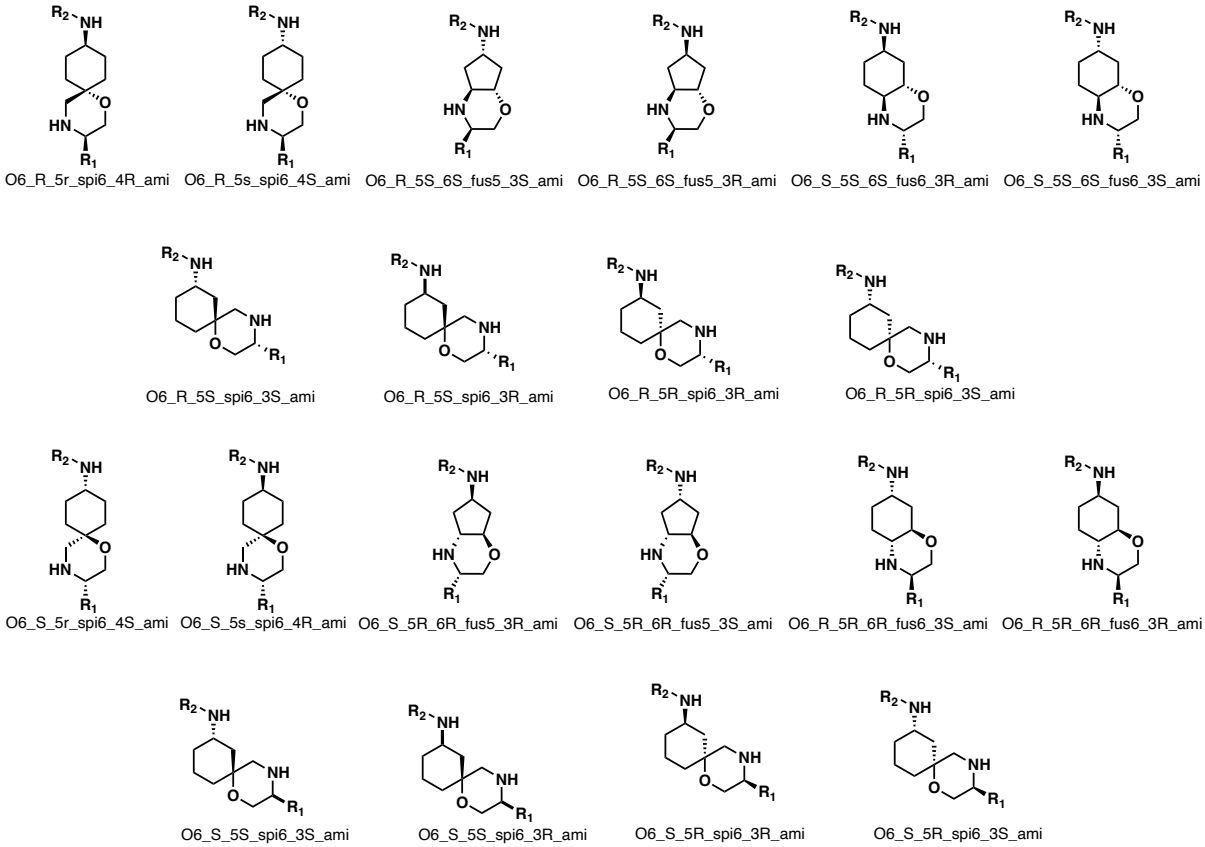
An in-house nomenclature was used for the naming of computational jobs. The one-line representation can hold chemical information about the X heteroatom used, scaffold motif, ring size(s), bridge head position(s) (if any), position of reductive amination, and stereochemistry. Consisting only of letters, numbers and underscores, the nomenclature is suitable for filename and command line usage. The heteroatom and ring size formed in the SnAP reaction are written first (e.g. O6 meaning morpholine), followed by the stereochemical assignment of the substituted carbon derived from the imine (e.g. O6_R). Next, numbers are used to denote the position of substitution on the newly formed ring, with the nature of the substitution being denoted as “spi” or “fus”, meaning spirocyclic or fused (e.g. O6_R_5_spi). The ring size is then combined with any “spi” or “fus” descriptors, and finally, the shortest number of carbons to the site of functionalization is included with stereochemistry (e.g. O6_R_5_spi6_3R_ami).

[2] M. R. Berthold, N. Cebron, F. Dill, T. R. Gabriel, T. Kötter, Thorsten Meinl, Peter Ohl, Christoph Sieb, Kilian Thiel, Bernd Wiswedel, *Data analysis, machine learning and applications: proceedings of the 31st Annual Conference of the Gesellschaft für Klassifikation e.V., Albert-Ludwigs-Universität Freiburg, March 7-9, 2007*, Springer, Berlin, 2008, ch. 4, pp 319.

[3] Open-source cheminformatics; http://www.rdkit.org

[4] Daylight Chemical Information Systems; https://www.daylight.com

## iSnAP Cores




## Filtering and analysis

Properties were generated using RDKit property generator in KNIME. Lipinski's rule of 5 was defined as MW ≤ 500, -5 ≤ LogP ≥ 5, HBD ≤ 5, HBA ≤ 10. These property ranges were applied to the iSnAP library using a rule-based filter, 98.6% passed the filter. Row filter node was used to randomly select sub-populations from libraries.

MW vs LogP scatter plot was generated using seaborn and matplotlib python libraries.[5]

Morgan fingerprint descriptors (radius = 6, nBits = 2048) were generated from SMILES using RDkit and reduced in dimension using UMAP (metric = jaccard, n_neighbours = 10, min_distance = 0.25) from sklearn.[6] The resulting plot was generated using seaborn.

[5] M. Waskom, *JOSS*, 2021, **6**, 3021.

[6] F. Pedregosa, G. Varoquaux, A. Gramfort, V. Michel, B. Thirion, O. Grisel, M. Blondel, P. Prettenhofer, R. Weiss, V. Dubourg, J. Vanderplas, A. Passos and D. Cournapeau, *Journal of Machine Learning Research*, 2011, **12**, 2825.

## Synthesis

### General Remarks

Unless otherwise noted, all reactions were performed under $N_2$ with anhydrous conditions. All reagents were used as received from commercial suppliers.

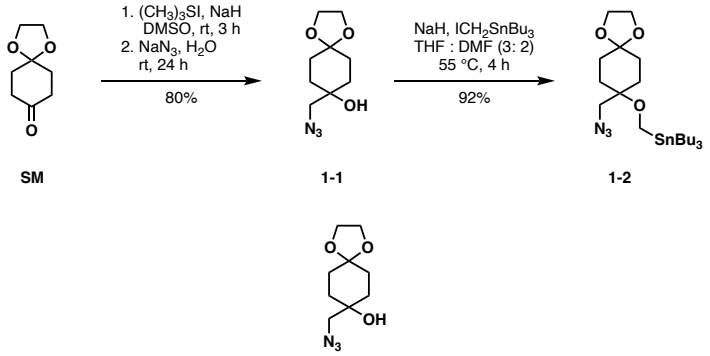
Reactions were monitored by thin layer chromatography (TLC) on Merck precoated aluminum-backed silica gel 60 F254 plates with UV at 254 nm, or by subjecting to NMR analysis. Flash chromatography purification was performed on Silicycle Silica Flash F60 (230–400 Mesh) silica gel using a forced flow of eluent at 0.2-0.3 bar.

NMR spectra were recorded on Bruker Avance III at 400 or 500 MHz (H) and at 100, 125 MHz (C), respectively, using $CDCl_3$ as the solvent unless indicated otherwise. Chemical shifts (δ) are reported in ppm, using the residual solvent peak in $CDCl_3$ (H: δ = 7.26 ppm and C: δ = 77.16 ppm) as reference. All $^{13}C$ spectra were measured with proton decoupling. NMR coupling constants (*J*) are reported in Hertz (Hz), and splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; dd, doublet of doublet; ddd, doublet of doublet of doublet; dt, doublet of triplet; t, triplet; q, quartet; quint; quintet; sext, sextet; m, multiplet.

High resolution mass spectra were measured by the Mass Spectrometry Service Facility of Molecular and Biomolecular Analysis Service (MoBiAS), Department of Chemistry and Applied Biosciences at ETH Zurich on a Bruker Daltonics maXis for ESI-Q-TOF spectrometer (ESI-MS).

## Synthesis of iSnAP Resins

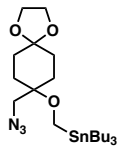
### Resin 1






**8-(azidomethyl)-1,4-dioxaspiro[4.5]decan-8-ol (1-1)**

Trimethylsulfonium iodide (50.7 g, 230 mmol, 1.20 equiv) was dissolved in anhydrous DMSO (600 mL) and cooled with an ice bath. NaH (60 wt%, 14.7 g, 231 mmol, 1.20 equiv) was added portionwise then 1,4-dioxaspiro[4.5]decan-8-one (30.0 g, 192 mmol, 1.00 equiv) in DMSO (300 mL) was added dropwise. The reaction was allowed to return to rt over 3 h. The reaction was diluted with $H_2O$ (600 mL) and the product was extracted in MTBE (5 x 500 mL). The organic phase was washed with $H_2O$ (300 mL) and concentrated to afford a clear oil. $H_2O$ (600 mL) and $NaN_3$ (62.4 g, 960 mmol, 5.00 equiv) were added. After stirring at rt for 24 h the product was extracted in EtOAc (5 x 200 mL). The organic phase was dried over anhydrous $Na_2SO_4$ then concentrated to dryness to afford a crystalline solid. The product was recrystallized in 400 mL of a 1:1 $Et_2O$ : *n*-hexane solution to afford the title compound as a colorless crystalline solid (32.9 g, 154 mmol, 80% yield); $^1$H NMR ($CDCl_3$, 300 MHz): $\delta$ 4.03–3.91 (m, 4H), 3.32 (s, 2H), 2.00–1.84 (m, 2H), 1.81–1.57 (m, 7H); $^{13}$C NMR ($CDCl_3$, 100 MHz): $\delta$ 108.4, 70.6, 64.4, 64.2, 61.7, 32.5 (2C), 30.0 (2C); HRMS (ESI) *m/z* for $C_9H_{15}N_3O_3$ $[M+Na]^+$ calcd. 236.1006, found 236.1011; IR ($\nu$/cm$^{-1}$, thin film) 3458, 2932, 2102, 1373, 1282, 1105, 1036, 923; m.p. 45 °C.

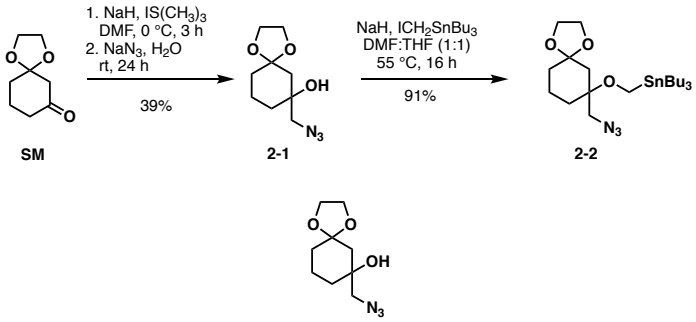


**(((8-(azidomethyl)-1,4-dioxaspiro[4.5]decan-8-yl)oxy)methyl)tributylstannane (1-2)**

NaH (60 wt%, 3.38 g, 84.4 mmol, 1.20 equiv) and anhydrous THF (110 mL) were added to a dry 500 mL r.b. flask. 8-(Azidomethyl)-1,4-dioxaspiro[4.5]decan-8-ol (15.0 g, 70.3 mmol, 1.00 equiv) was dissolved in DMF (75 mL) and added dropwise to the reaction. After stirring at 55 °C for 30 mins, the slurry became a light orange solution. Tributyl(iodomethyl)stannane (36.4 g, 84.4 mmol, 1.20 equiv) was added dropwise and a white precipitate began to form. After 3 h at 55 °C the reaction was cooled to rt and diluted with $H_2O$ (200 mL). The product was extracted in MTBE (4 x 100 mL), dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. The product was purified by flash silica chromatography (5% EtOAc in *n*-hexane) to afford the title compound as a clear oil (33.4 g, 64.7 mmol, 92% yield); $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 4.02–3.89 (m, 4H), 3.44 (t, $J$ = 12.0 Hz, 2H), 3.23 (s, 2H), 1.97–1.87 (m, 2H), 1.81–1.70 (m, 2H), 1.58–1.48 (m, 10H), 1.39–1.25 (m, 6H), 0.97–0.88 (m, 15H); $^{13}$C NMR

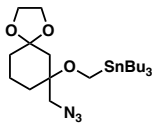
($CDCl_3$, 100 MHz): $\delta$ 108.7, 75.6, 64.3, 64.2, 54.8, 49.9, 29.9 (2C), 29.2 (3C), 28.9 (2C), 27.4 (3C), 13.8 (3C), 9.0 (3C); HRMS (ESI) *m/z* for $C_{22}H_{43}N_3O_3Sn$ $[M+Na]^+$ calcd. 540.2223, found 540.2224; IR ($\nu$/$cm^{-1}$, thin film) 3446, 2956, 2360, 2097, 1635, 730, 688 cm.

**Resin 2**




**7-(azidomethyl)-1,4-dioxaspiro[4.5]decan-7-ol (2-1)**

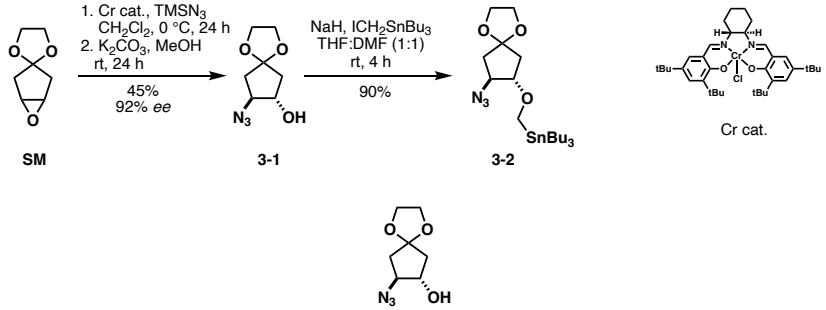
NaH (60 wt%, 0.66 g, 16.5 mmol, 1.60 equiv) was added to a solution of trimethylsulfonium iodide (2.95 g, 14.4 mmol, 1.40 equiv) in anhydrous DMF (52 mL) at 0 °C. After 15 mins, 1,4-dioxaspiro[4.5]decan-7-one (1.61 g, 10.3 mmol, 1.00 equiv) was added and the reaction was allowed to return to rt over 3 h. The reaction was quenched with $H_2O$ (100 mL) and the product was extracted in EtOAc (5 x 50 mL). The extractions were combined and concentrated to dryness. $NaN_3$ (3.35 g, 51.5 mmol, 5.00 equiv) in $H_2O$ (100 mL) was added to the resulting oil and the mixture was stirred at rt for 24 h. The product was extracted in EtOAc (5 x 50 mL), dried over anhydrous $Na_2SO_4$, concentrated to dryness and purified by flash silica chromatography (0-30% EtOAc in *n*-hexane) to afford the title compound as a clear oil (0.86 g, 4.06 mmol, 39% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 4.07 – 3.89 (m, 4H), 3.27 (d, *J* = 12.4 Hz, 1H), 3.11 (d, *J* = 12.4 Hz, 1H), 1.92 – 1.58 (m, 6H), 1.54 – 1.43 (m, 1H), 1.36 – 1.25 (m, 1H), exchangeable 1 x OH not observed; $^{13}$C NMR (100 MHz, $CDCl_3$) δ 109.2, 72.4, 64.6, 64.2, 60.7, 41.4, 34.5, 34.1, 18.6; HRMS (ESI) *m/z* calcd. for $C_9H_{15}N_3O_3$ $[M+Na]^+$ 236.1006 found 236.1012; IR (ν/cm$^{-1}$, thin film) 3506, 2948, 2886, 2102, 1449, 1277, 1168, 1077, 947, 834.




**(((7-(azidomethyl)-1,4-dioxaspiro[4.5]decan-7-yl)oxy)methyl)tributylstannane (2-2)**

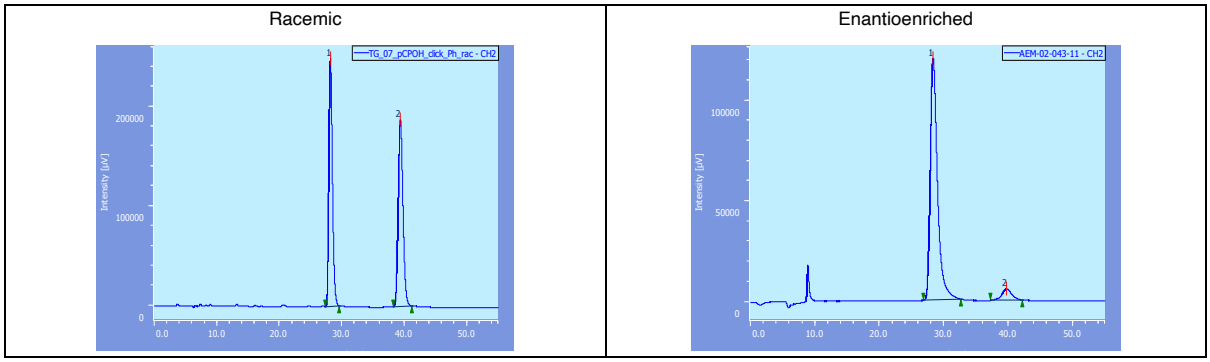
NaH (60 wt%, 226 mg, 5.65 mmol, 1.40 equiv) was added to a solution of 7-(azidomethyl)-1,4-dioxaspiro[4.5]decan-7-ol (0.86 g, 4.03 mmol, 1.00 equiv) in THF:DMF (1:1 40 mL) at 0 °C. After 0.4 h, tributyl(iodomethyl)stannane (2.09 g, 4.84 mmol, 1.20 equiv) was added and the reaction was stirred for 3 h. The reaction was then heated to 55 °C for 15 h. After returning to rt, the reaction was quenched with $H_2O$ (150 mL) and the product was extracted in EtOAc (4 x 80 mL). The organic phase was dried over anhydrous $Na_2SO_4$, concentrated and the product was purified by flash silica chromatography (0-10% EtOAc in *n*-hexane) to afford the title compound as a clear oil (1.89 g, 3.66 mmol, 91% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 4.03 – 3.88 (m, 4H), 3.56 – 3.33 (m, 4H), 1.87 – 1.79 (m, 2H), 1.79 – 1.62 (m, 3H), 1.60 – 1.42 (m, 9H), 1.38 – 1.25 (m, 6H), 1.03 – 0.85 (m, 15H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 109.1, 78.6, 64.4, 64.1, 53.9, 49.4, 38.9, 34.7, 30.7, 29.1 (3C), 27.3 (3C), 19.6, 13.8 (3C), 9.0 (3C); HRMS (ESI) *m/z* calcd. for $C_{22}H_{43}N_3O_3Sn$ $[M+Na]^+$ 540.2223, found 540.2229; IR (ν/cm$^{-1}$, thin film) 2954, 2925, 2098, 1455, 1340, 1311, 1067, 952, 864.

## Resin 3

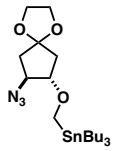



### (7*S*,8*S*)-8-azido-1,4-dioxaspiro[4.4]nonan-7-ol (3-1)

6-oxaspiro[bicyclo[3.1.0]hexane-3,2'-[1,3]dioxolane (3.07 g, 21.6 mmol, 1.00 equiv), (*R*,*R*)-*N*,*N*′-*bis*(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminochromium(III) chloride (0.63 g, 0.43 mmol, 0.02 equiv) and trimethylsilyl azide (2.97 g, 43.1 mmol, 2.00 equiv) were combined and stirred at rt for 24 h. The reaction was cooled to 0 °C and added dropwise to a cold solution of aq NaOH (2 M, 200 mL). The product was extracted in EtOAc (4 x 50 mL). The organic phase was washed with $H_2O$, dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure to dryness. Potassium carbonate (5.96 g, 43.2 mmol, 2.00 equiv) and MeOH (100 mL) were added to the resulting oil and the slurry was stirred at rt for 24 h. The slurry was passed through a filter and the filtrate was concentrated and purified by flash silica chromatography (25% EtOAc in *n*-hexane) to afford the title compound as a clear oil (1.78 g, 9.60 mmol, 45% yield, 92% *ee*); $^1$H NMR (400 MHz, $CDCl_3$) δ 4.19 – 4.08 (m 1H), 3.99 – 3.90 (m, 4H), 3.85 (ddd, *J* = 7.4, 7.4, 4.9 Hz, 1H), 2.40 (ddd, *J* = 14.3, 7.8, 1.3 Hz, 1H), 2.34 – 2.26 (m, 2H), 1.97 – 1.86 (m, 2H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 113.9, 75.4, 66.4, 65.0, 64.4, 42.9, 40.4; HRMS (ESI) *m/z* for $C_7H_{11}N_3O_3$ $[M+Na]^+$ calcd. 208.0693, found 208.0693, IR (ν/cm$^{-1}$, thin film) 3431, 2889, 2102, 1320, 1262, 1086, 1058, 1011 cm$^{-1}$; determination of enantiomeric excess was achieved using a copper catalyzed azide alkyne click reaction with phenyl acetylene and analyzed using normal phase chiral HPLC according to a previous report.[7] NP-HPLC, column: Daicel Chiralpak ADH (4.6 x 250 mm); eluent: EtOH : *n*-hexane 1:1; flow rate: 0.5 mL/min; detection: 254 nm; retention time: 28.6 min (major), 40.2 min (minor).



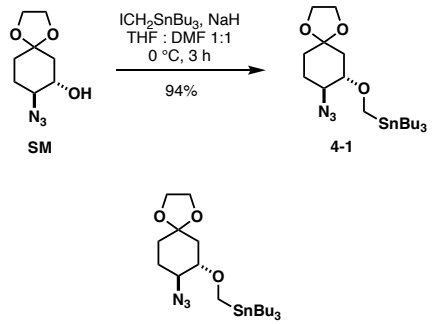

[7] F. Saito, N. Trapp and J. Bode, *J. Am. Chem. Soc.*, 2019, **141**, 5544.




**((((7*S*,8*S*)-8-azido-1,4-dioxaspiro[4.4]nonan-7-yl)oxy)methyl)tributylstannane (3-2)**

NaH (60 wt%, 0.42 g, 10.4 mmol, 1.20 equiv) was added to a solution of (7*S*,8*S*)-8-azido-1,4-dioxaspiro[4.4]nonan-7-ol (1.60 g, 8.65 mmol, 1.00 equiv) in THF (43 mL) at 0 °C. After 30 mins, tributyl(iodomethyl)stannane (4.47 g, 10.4 mmol, 1.20 equiv) was added. The reaction was allowed to warm to rt over 4 h. The reaction was quenched with $H_2O$ (200 mL) and the product was extracted in MTBE (4 x 100 mL). The organic phases were combined and dried over anhydrous $Na_2SO_4$, concentrated to dryness and purified by flash silica chromatography (0-15% EtOAc in *n*-hexane) to afford the title compound as a clear oil (3.79 g, 7.77 mmol, 90 % yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 3.96 – 3.89 (m, 4H), 3.83 (td, *J* = 7.7, 5.5 Hz, 1H), 3.78 – 3.67 (m, 2H), 3.66 (td, *J* = 7.1, 5.5 Hz, 1H), 2.34 (ddd, *J* = 13.9, 7.5, 1.4 Hz, 1H), 2.27 (ddd, *J* = 14.0, 8.2, 1.1 Hz, 1H), 1.90 – 1.80 (m, 2H), 1.65 – 1.41 (m, 6H), 1.39 – 1.25 (m, 6H), 1.03 – 0.82 (m, 15H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 113.8, 86.5, 64.4, 64.4, 64.2, 60.5, 40.9, 40.1, 29.1(3C), 27.3(3C), 13.7(3C), 8.9(3C); HRMS (ESI) *m/z* for $C_{20}H_{39}N_3O_3Sn$ $[M+Na]^+$ calcd. 512.1909, found 512.1918; IR (ν/cm$^{-1}$, thin film) 2954, 2922, 2360, 2102, 1463, 1259, 874, 684; $[\alpha]^{25}$ +28° (c 0.4, $CH_2Cl_2$).

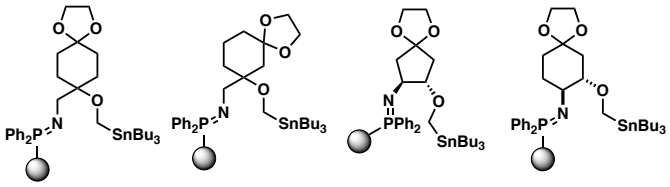
**Resin 4**




**((((7*S*,8*S*)-8-azido-1,4-dioxaspiro[4.5]decan-7-yl)oxy)methyl)tributylstannane (4-1)**
(7*S*,8*S*)-8-azido-1,4-dioxaspiro[4.5]decan-7-ol (1.24 g, 6.23 mmol, 1.00 equiv) was dissolved in a mixture of DMF and THF (60 mL, 1:1) and cooled to 0 °C. NaH (0.30 g, 7.48 mmol, 1.20 equiv) was added and the reaction was stirred for 20 mins. Tributyl(iodomethyl)stannane (3.22 g, 7.47 mmol, 1.20 equiv) was added and the reaction was stirred at 0 °C for 3 h. The reaction was quenched with $H_2O$ (100 mL) and the product was extracted in EtOAc (4 x 100 mL). The organic phase was dried over anhydrous $MgSO_4$, concentrated and the product was purified by flash silica chromatography (0-10% EtOAc in *n*-hexane) to afford the title compound as a clear oil (2.94 g, 5.86 mmol, 94% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 4.07 – 3.81 (m, 5H), 3.73 – 3.58 (m, 1H), 3.36 – 3.13 (m, 2H), 2.29 (ddd, *J* = 12.7, 4.2, 3.0 Hz, 1H), 1.90 – 1.83 (m, 1H), 1.73 (dq, *J* = 12.3, 3.0 Hz, 1H), 1.66 – 1.41 (m, 9H), 1.40 – 1.26 (m, 6H), 1.07 – 0.83 (m, 15H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 108.3, 83.8, 64.5, 64.4, 64.1, 59.6, 38.4, 32.8, 29.1 (3C), 27.3 (3C), 26.6, 13.7 (3C), 8.9 (3C); HRMS (ESI) *m/z* for $C_{21}H_{41}N_3O_3Sn$ $[M+H]^+$ calcd. 526.2066, found 526.2060; IR (ν/cm$^{-1}$, thin film) 2953, 2923, 2098, 1456, 1262, 1068, 921.

**Loading of iSnAP resins**

A solution of the iSnAP reagent in $CH_2Cl_2$ (0.2 mol/L, 1.0 equiv) was added to polystyrene-supported triphenylphosphine (1.5 eq) and stirred at rt for 24 h. The solvent was removed under reduced pressure to afford the iSnAP resin. Loading was determined by allowing the resin to react with an excess of 4-bromobenzaldehyde in $CH_2Cl_2$ and determining the conversion after 24 h by $^1$H NMR.




**1** 0.46 mmol/g **2** 0.60 mmol/g **3** 0.64 mmol/g **4** 0.35 mmol/g

**Synthesis of Library Members**

**Capsule Contents**

iSnAP Capsule
Cartridge 1: iSnAP resin (0.5 mmol, 1.0 equiv), 4 Å molecular sieves (100 mg)
Cartridge 2: $Cu(OTf)_2$ (0.5 mmol, 1.0 equiv), lutidinium triflate (0.5 mmol, 1.0 equiv)
Cartridge 3: SCX-2 (2.0 mmol, 4.0 equiv)
Cartridge 4: Silica (5 g)

Reductive Amination Capsule
Cartridge 1: silica supported cyanoborohydride (1.0 mmol, 2.0 equiv)
Cartridge 2: SCX-2 (2.0 mmol, 4.0 equiv)
Cartridge 3: polystyrene supported benzaldehyde (1.0 mmol, 2.0 equiv)

**General Procedure**

The aldehyde (0.5 mmol) and a stirring bar were added to a vial. The vial was inserted into the vial holder of console and the line cap was attached. The iSnAP capsule was scanned to load the correct program and placed into the capsule holder, which was closed and locked. The ketal deprotection time was set using the "edit recipe" menu [resin **1**, 5 h; resin **2**, 5 h; resin **3**, 24 h; resin **4** 12 h]. After checking the solvents were full and the waste container was not, the program was initiated by pressing "run" on the touch screen interphase. Upon program competition, the solution in the vial was concentrated using a vial adaptor and standard rotary evaporator.

The amine (0.5 mmol) was added to the product containing vial from step 1 and the vial was returned to the console. The reductive amination capsule was scanned to load the program, and placed to the capsule holder, which was closed and locked. The reaction time was set using the "edit recipe" menu [resin **1**, 3 h; resin **2**, 3 h; resin **3**, 12 h; resin **4** 12 h]. The program was initiated by pressing "run" on the touch screen interphase. Upon program completion, the stirring bar was removed, the solution was concentrated as before and trimethoxybenzene (0.1 mmol) was added (as an internal standard). The crude yield was determined by $^1$H NMR and the product was purified by high pressure liquid chromatography.

**Preparative HPLC**

Preparative reverse phase high performance liquid chromatography was carried out on a Jasco preparative instrument with dual pumps, mixer, in-line degasser, Rheodyne 7725i injector with 10 mL injection loop and a variable wavelength UV with detection at 220, 254 and 301 nm. The generic method used a CAPCELL PAK C18 (20 mml.D x 250 mm, 5 $\mu$m, Cat. No. 92539) column and ran the following gradient at a flow rate of 10 mL/min. Time (min), mobile phase (% of $CH_3CN$ in $H_2O$ with 0.1% TFA).

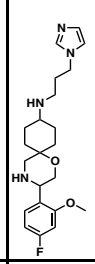
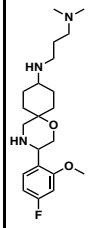
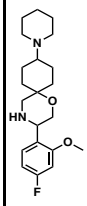
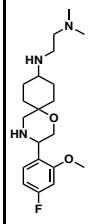
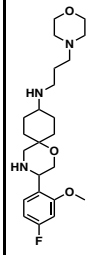
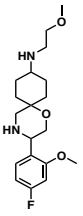
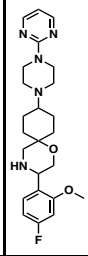
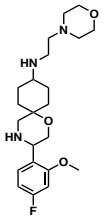
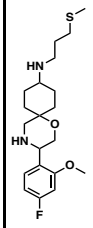
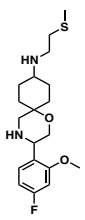
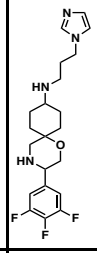
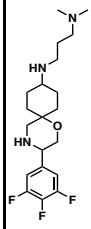
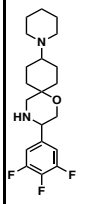
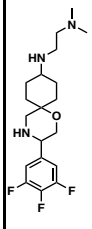
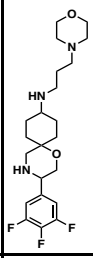
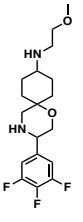
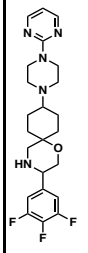
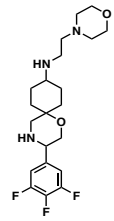
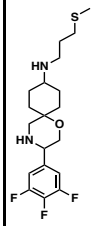
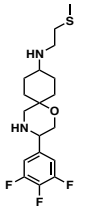
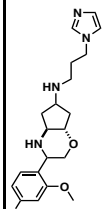
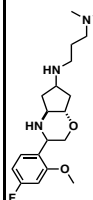
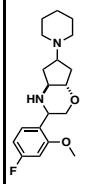
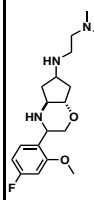
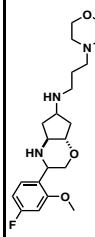
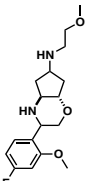
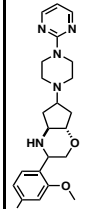
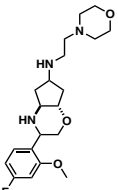
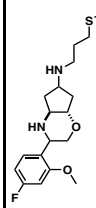
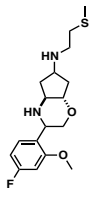
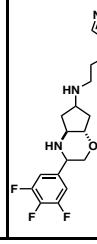
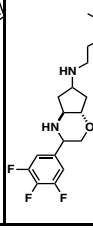
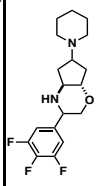
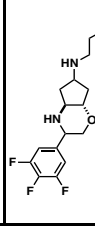
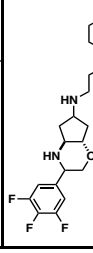
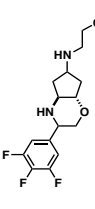
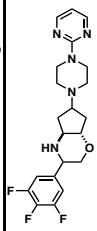
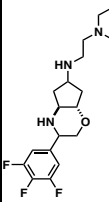
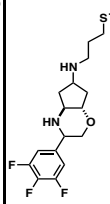
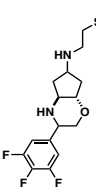
Time 00 Mobile Phase 5,
Time 10 Mobile Phase 70,
Time 30 Mobile Phase 95,
Time 35 Mobile Phase 95,
Time 36 Mobile Phase 10.

Compound elution occurred between 10 and 20 min and the internal standard (1,3,5-trimethoxybenzene) eluted at 31 min.

**Plate Diversification**

Silica supported cyanoborohydride (10 mg, 1.0 mmol/g, 10 $\mu$mol, 2.5 equiv) was added to each well of a 96-well filtration plate. The filter base of the plate was sealed from below using pre-cut sealing tape for 96-well plates. A solution of each ketone (30 $\mu$L, 130 mM in $CH_2Cl_2$, 4.0 μmol, 1.0 equiv) was distributed in each row of the plate. A solution of each amine (10 μL, 600 mM in HFIP, 6.0 $\mu$mol, 1.5 equiv) was distributed to each column of the plate. The plate was agitated for 12 h at rt. $CH_3CN$ (200 μL) was added to each well of the plate. The sealing tape was removed from the based, the filtration plate was stacked onto a collection plate and centrifuged to transfer the solution. The crude material was obtained by concentrating the solutions with $N_2$ using a blow down apparatus. Each product was dissolved in $CH_3CN$ (1 mL) and diluted 100-fold prior to analysis.

Plate layout with the structures of expected products.

| (<5 umol/ well) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| A |  |  |  |  |  |  |  |  |  |  |
| B |  |  |  |  |  |  |  |  |  |  |
| C |  |  |  |  |  |  |  |  |  |  |
| D |  |  |  |  |  |  |  |  |  |  |

## Processed results with sum formula, extracted ion chromatogram area and area %

| Plate Well | Ketone Formula | Alcohol Formula | Product Formula | Ketone Area | Alcohol Area | Product Area | Ketone Area % | Alcohol Area % | Product Area % |
|---|---|---|---|---|---|---|---|---|---|
| A1 | C16H20FNO3 | C16H22FNO3 | C22H31FN4O2 | 0 | 159205 | 278799 | 0.0 | 36.3 | 63.7 |
| A2 | C16H20FNO3 | C16H22FNO3 | C21H34FN3O2 | 25220 | 14523738 | 7023891 | 0.1 | 67.3 | 32.6 |
| A3 | C16H20FNO3 | C16H22FNO3 | C21H31FN2O2 | 101639 | 43634719 | 8663670 | 0.2 | 83.3 | 16.5 |
| A4 | C16H20FNO3 | C16H22FNO3 | C20H32FN3O2 | 0 | 3460857 | 10150292 | 0.0 | 25.4 | 74.6 |
| A5 | C16H20FNO3 | C16H22FNO3 | C23H36FN3O3 | 0 | 3313868 | 3524346 | 0.0 | 48.5 | 51.5 |
| A6 | C16H20FNO3 | C16H22FNO3 | C19H29FN2O3 | 42729 | 9594204 | 15337054 | 0.2 | 38.4 | 61.4 |
| A7 | C16H20FNO3 | C16H22FNO3 | C24H32FN5O2 | 169425 | 47608084 | 73102188 | 0.1 | 39.4 | 60.5 |
| A8 | C16H20FNO3 | C16H22FNO3 | C22H34FN3O3 | 0 | 2720522 | 130425360 | 0.0 | 2.0 | 98.0 |
| A9 | C16H20FNO3 | C16H22FNO3 | C20H31FN2O2S | 42755 | 18105242 | 37994303 | 0.1 | 32.2 | 67.7 |
| A10 | C16H20FNO3 | C16H22FNO3 | C19H29FN2O2S | 13538 | 9159878 | 5477447 | 0.1 | 62.5 | 37.4 |
| B1 | C15H16F3NO2 | C15H18F3NO2 | C21H27F3N4O | 0 | 3692833 | 48745380 | 0.0 | 7.0 | 93.0 |
| B2 | C15H16F3NO2 | C15H18F3NO2 | C20H30F3N3O | 0 | 915915 | 17226837 | 0.0 | 5.0 | 95.0 |
| B3 | C15H16F3NO2 | C15H18F3NO2 | C20H27F3N2O | 6768 | 8941057 | 6599151 | 0.0 | 57.5 | 42.4 |
| B4 | C15H16F3NO2 | C15H18F3NO2 | C19H28F3N3O | 0 | 3913288 | 27176190 | 0.0 | 12.6 | 87.4 |
| B5 | C15H16F3NO2 | C15H18F3NO2 | C22H32F3N3O2 | 0 | 1918345 | 20972093 | 0.0 | 8.4 | 91.6 |
| B6 | C15H16F3NO2 | C15H18F3NO2 | C18H25F3N2O2 | 35563 | 8450674 | 30859625 | 0.1 | 21.5 | 78.4 |
| B7 | C15H16F3NO2 | C15H18F3NO2 | C23H28F3N5O | 13012 | 7694328 | 47643524 | 0.0 | 13.9 | 86.1 |
| B8 | C15H16F3NO2 | C15H18F3NO2 | C21H30F3N3O2 | 0 | 2776532 | 69016722 | 0.0 | 3.9 | 96.1 |
| B9 | C15H16F3NO2 | C15H18F3NO2 | C19H27F3N2OS | 32528 | 8468340 | 39467353 | 0.1 | 17.7 | 82.3 |
| B10 | C15H16F3NO2 | C15H18F3NO2 | C18H25F3N2OS | 65757 | 16887279 | 39645378 | 0.1 | 29.8 | 70.0 |
| C1 | C14H16FNO3 | C14H18FNO3 | C20H27FN4O2 | 14518 | 2814773 | 20915534 | 0.1 | 11.9 | 88.1 |
| C2 | C14H16FNO3 | C14H18FNO3 | C19H30FN3O2 | 11911 | 1509804 | 24488142 | 0.0 | 5.8 | 94.1 |
| C3 | C14H16FNO3 | C14H18FNO3 | C19H27FN2O2 | 1553192 | 4272740 | 16744440 | 6.9 | 18.9 | 74.2 |
| C4 | C14H16FNO3 | C14H18FNO3 | C18H28FN3O2 | 30865 | 153442 | 30327122 | 0.1 | 0.5 | 99.4 |
| C5 | C14H16FNO3 | C14H18FNO3 | C21H32FN3O3 | 10047 | 1201219 | 23979274 | 0.0 | 4.8 | 95.2 |
| C6 | C14H16FNO3 | C14H18FNO3 | C17H25FN2O3 | 111384 | 357812 | 8275297 | 1.3 | 4.1 | 94.6 |
| C7 | C14H16FNO3 | C14H18FNO3 | C22H28FN5O2 | 102575 | 771051 | 28686968 | 0.3 | 2.6 | 97.0 |
| C8 | C14H16FNO3 | C14H18FNO3 | C20H30FN3O3 | 37002 | 85470 | 20139430 | 0.2 | 0.4 | 99.4 |
| C9 | C14H16FNO3 | C14H18FNO3 | C18H27FN2O2S | 4341282 | 3712608 | 67592223 | 5.7 | 4.9 | 89.4 |
| C10 | C14H16FNO3 | C14H18FNO3 | C17H25FN2O2S | 61914 | 672925 | 15692000 | 0.4 | 4.1 | 95.5 |
| D1 | C13H12F3NO2 | C13H14F3NO2 | C19H23F3N4O | 0 | 1089035 | 14824338 | 0.0 | 6.8 | 93.2 |
| D2 | C13H12F3NO2 | C13H14F3NO2 | C18H26F3N3O | 0 | 1134972 | 29681904 | 0.0 | 3.7 | 96.3 |
| D3 | C13H12F3NO2 | C13H14F3NO2 | C18H23F3N2O | 336393 | 3443601 | 38644024 | 0.8 | 8.1 | 91.1 |
| D4 | C13H12F3NO2 | C13H14F3NO2 | C17H24F3N3O | 165107 | 458887 | 25265318 | 0.6 | 1.8 | 97.6 |
| D5 | C13H12F3NO2 | C13H14F3NO2 | C20H28F3N3O2 | 0 | 840060 | 32619832 | 0.0 | 2.5 | 97.5 |
| D6 | C13H12F3NO2 | C13H14F3NO2 | C16H21F3N2O2 | 57824 | 247782 | 14849718 | 0.4 | 1.6 | 98.0 |
| D7 | C13H12F3NO2 | C13H14F3NO2 | C21H24F3N5O | 0 | 348007 | 5131707 | 0.0 | 6.4 | 93.6 |
| D8 | C13H12F3NO2 | C13H14F3NO2 | C19H26F3N3O2 | 0 | 43900 | 19149445 | 0.0 | 0.2 | 99.8 |
| D9 | C13H12F3NO2 | C13H14F3NO2 | C17H23F3N2OS | 149232 | 512095 | 24427744 | 0.6 | 2.0 | 97.4 |
| D10 | C13H12F3NO2 | C13H14F3NO2 | C16H21F3N2OS | 327935 | 567438 | 6926796 | 4.2 | 7.3 | 88.6 |

## Processed results of desired product, alcohol and ketone area % plotted as a heat map

Desired Product area %

| | A | B | C | D | E | F | G | H | I | J |
|---|---|---|---|---|---|---|---|---|---|---|
| 28 | 63.7 | 32.6 | 16.5 | 74.6 | 51.5 | 61.4 | 60.5 | 98.0 | 67.7 | 37.4 |
| 29 | 93.0 | 95.0 | 42.4 | 87.4 | 91.6 | 78.4 | 86.1 | 96.1 | 82.3 | 70.0 |
| 30 | 88.1 | 94.1 | 74.2 | 99.4 | 95.2 | 94.6 | 97.0 | 99.4 | 89.4 | 95.5 |
| 31 | 93.2 | 96.3 | 91.1 | 97.6 | 97.5 | 98.0 | 93.6 | 99.8 | 97.4 | 88.6 |

Alcohol area %

| | A | B | C | D | E | F | G | H | I | J |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 36.3 | 67.3 | 83.3 | 25.4 | 48.5 | 38.4 | 39.4 | 2.0 | 32.2 | 62.5 |
| 2 | 7.0 | 5.0 | 57.5 | 12.6 | 8.4 | 21.5 | 13.9 | 3.9 | 17.7 | 29.8 |
| 3 | 11.9 | 5.8 | 18.9 | 0.5 | 4.8 | 4.1 | 2.6 | 0.4 | 4.9 | 4.1 |
| 4 | 6.8 | 3.7 | 8.1 | 1.8 | 2.5 | 1.6 | 6.4 | 0.2 | 2.0 | 7.3 |

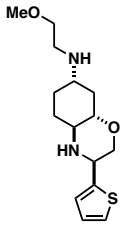
Ketone area %

| | A | B | C | D | E | F | G | H | I | J |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 0.0 | 0.1 | 0.2 | 0.0 | 0.0 | 0.2 | 0.1 | 0.0 | 0.1 | 0.1 |
| 2 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.1 | 0.0 | 0.0 | 0.1 | 0.1 |
| 3 | 0.1 | 0.0 | 6.9 | 0.1 | 0.0 | 1.3 | 0.3 | 0.2 | 5.7 | 0.4 |
| 4 | 0.0 | 0.0 | 0.8 | 0.6 | 0.0 | 0.4 | 0.0 | 0.0 | 0.6 | 4.2 |

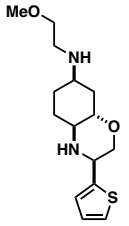
**Synthesis of Compounds 5-34**

**(3*S*,4a*S*,8a*S*)-*N*-(2-methoxyethyl)-3-(thiophen-2-yl)octahydro-2*H*-benzo[*b*][1,4]oxazin-7-amine 5**

Thiophene-2-carbaldehyde (56 mg, 0.50 mmol, 1.0 equiv), 2-methoxyethan-1-amine (38 mg, 0.50 mmol, 1.0 equiv) and iSnAP resin **4** were reacted according to the General Procedure to afford the title compound (0.18 mmol, 35% NMR yield, *dr* 56:44).

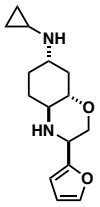



(3*S*,4a*S*,7*S*,8a*S*)-*N*-(2-methoxyethyl)-3-(thiophen-2-yl)octahydro-2*H*-benzo[*b*][1,4]oxazin-7-amine (major, 28 mg, 95 $\mu$mol, 19% isolated yield); $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 4.9, 1.3 Hz, 1H), 7.03 – 6.94 (m, 2H), 4.35 (ddd, *J* = 10.3, 3.4, 0.7 Hz, 1H), 3.94 (dd, *J* = 11.0, 3.3 Hz, 1H), 3.54 – 3.47 (m, 3H), 3.37 (s, 3H), 3.18 (ddd, *J* = 11.6, 8.8, 4.1 Hz, 1H), 2.86 – 2.81 (m, 2H), 2.64 (m, 2H), 2.20 – 2.14 (m, 1H), 2.05 – 1.86 (m, 3H), 1.77 – 1.68 (m, 1H), 1.47 – 1.35 (m, 1H), 1.35 – 1.18 (m, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 144.4, 126.6, 124.3, 124.1, 78.6, 74.0, 72.1, 60.3, 58.8, 56.3, 55.4, 46.7, 37.2, 31.3, 28.9; HRMS (ESI) *m/z* for $C_{15}H_{24}N_2O_2S$ $[M+H]^+$ calcd. 297.1631, found 297.1632; IR ($\nu$/cm$^{-1}$, thin film) 2924, 2849, 1681, 1098, 1051, 704.

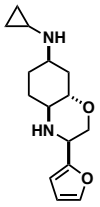



(3*S*,4a*S*,7*R*,8a*S*)-*N*-(2-methoxyethyl)-3-(thiophen-2-yl)octahydro-2*H*-benzo[*b*][1,4]oxazin-7-amine (minor, 16 mg, 54 $\mu$mol, 11% isolated yield); $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.23 (dd, *J* = 4.9, 1.4 Hz, 1H), 7.01 – 6.95 (m, 2H), 4.35 (dd, *J* = 10.4, 3.4 Hz, 1H), 3.96 (dd, *J* = 11.0, 3.4 Hz, 1H), 3.58 – 3.49 (m, 4H), 3.38 (s, 3H), 3.09 (m, 1H), 2.83 – 2.73 (m, 2H), 2.65 – 2.59 (m, 1H), 2.08 – 1.67 (m, 5H), 1.62 – 1.46 (m, 3H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 143.8, 126.6, 124.3, 124.0, 76.1, 74.2, 72.1, 61.5, 58.8, 56.4, 53.2, 47.5, 34.6, 28.6, 25.9; HRMS (ESI) *m/z* for $C_{15}H_{24}N_2O_2S$ $[M+H]^+$ calcd. 297.1631, found 297.1633; IR ($\nu$/cm$^{-1}$, thin film) 2924, 2850, 1443, 1113, 700.

**(3*S*,4a*S*,8a*S*)-*N*-cyclopropyl-3-(furan-2-yl)octahydro-2*H*-benzo[*b*][1,4]oxazin-7-amine 6**
Furan-2-carbaldehyde (48 mg, 0.50 mmol, 1.0 equiv), cyclopropanamine (29 mg, 0.50 mmol, 1.0 equiv) and iSnAP resin **4** were reacted according to the General Procedure to afford the title compound (0.23 mmol, 46% NMR yield, *dr* 68:32).



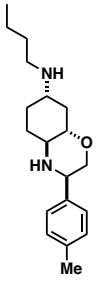

(3*S*,4a*S*,7*S*,8a*S*)-*N*-cyclopropyl-3-(furan-2-yl)octahydro-2*H*-benzo[*b*][1,4]oxazin-7-amine (major, 12 mg, 46 $\mu$mol, 9% isolated yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.33 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.22 (m, 1H), 4.16 (d, *J* = 3.3 Hz, 1H), 4.04 (dd, *J* = 11.0, 3.3 Hz, 1H), 3.66 (t, *J* = 10.8 Hz, 1H), 3.18 (ddd, *J* = 11.5, 8.8, 4.1 Hz, 1H), 2.80 (tt, *J* = 11.4, 3.9 Hz, 1H), 2.59 (ddd, *J* = 11.5, 8.8, 4.0 Hz, 1H), 2.29 (dtd, *J* = 12.0, 4.0, 2.2 Hz, 1H), 2.16 (tt, *J* = 6.7, 3.7 Hz, 1H), 2.07 – 1.98 (m, 1H), 1.89 (br. s, 2H), 1.76 (m, 1H), 1.47 – 1.34 (m, 1H), 1.34 – 1.16 (m, 2H), 0.55 – 0.42 (m, 2H), 0.43 – 0.32 (m, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 153.3, 142.0, 110.1, 105.9, 78.9, 70.8, 59.9, 55.9, 54.1, 37.6, 31.8, 28.9, 28.4, 6.6, 6.3; HRMS (ESI) *m/z* for $C_{15}H_{22}N_2O_2$ [M+H]$^+$ calcd. 263.1754, found 263.1752; IR ($\nu$/cm$^{-1}$, thin film) 2924, 2856, 1448, 1358, 1097, 737.



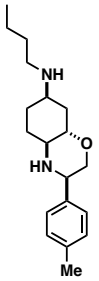

(3*S*,4a*S*,7*R*,8a*S*)-*N*-cyclopropyl-3-(furan-2-yl)octahydro-2*H*-benzo[*b*][1,4]oxazin-7-amine (minor, isolated 16 mg, 61 $\mu$mol, 12% isolated yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 1.8, 0.8 Hz, 1H), 6.32 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.24 – 6.18 (m, 1H), 4.15 (dd, *J* = 10.6, 3.5 Hz, 1H), 4.03 (dd, *J* = 11.0, 3.3 Hz, 1H), 3.64 (t, *J* = 10.8 Hz, 1H), 3.45 (ddd, *J* = 11.8, 8.9, 4.2 Hz, 1H), 3.23 (m, 1H), 2.63 – 2.54 (m, 1H), 2.13 – 2.03 (m, 2H), 1.93 – 1.83 (m, 1H), 1.73 (s, 1H), 1.69 – 1.43 (m, 5H), 0.51 – 0.41 (m, 2H), 0.39 – 0.29 (m, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 153.4, 141.9, 110.1, 105.8, 76.6, 71.2, 60.5, 54.2, 53.7, 35.0, 29.1, 28.9, 26.0, 6.3, 6.1; HRMS (ESI) *m/z* for $C_{15}H_{22}N_2O_2$ [M+H]$^+$ calcd. 263.1754, found 263.1755; IR ($\nu$/cm$^{-1}$, thin film) 2924, 2856, 1673, 1340, 1097, 1010, 736.

**(3*R*,4a*S*,8a*S*)-*N*-butyl-3-(*p*-tolyl)octahydro-2*H*-benzo[*b*][1,4]oxazin-7-amine 7**

4-Methylbenzaldehyde (60 mg, 0.50 mmol, 1.0 equiv), butan-1-amine (37 mg, 0.50 mmol, 1.0 equiv) and iSnAP resin **4** were reacted according to the General Procedure to afford the title compound (0.10 mmol, 20% NMR yield, *dr* 72:28).



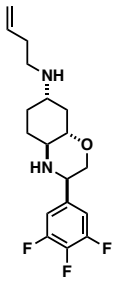

(3*R*,4a*S*,7*S*,8a*S*)-*N*-butyl-3-(*p*-tolyl)octahydro-2*H*-benzo[*b*][1,4]oxazin-7-amine (major, 18 mg, 60 $\mu$mol, 12% isolated yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 5.8 Hz, 2H), 7.15 (d, *J* = 7.8 Hz, 2H), 4.01 (dd, *J* = 10.3, 3.2 Hz, 1H), 3.86 (dd, *J* = 11.0, 3.3 Hz, 1H), 3.45 (t, *J* = 10.7 Hz, 1H), 3.18 (ddd, *J* = 11.6, 8.7, 4.1 Hz, 1H), 2.74 – 2.65 (m, 3H), 2.62 (ddd, *J* = 11.4, 8.8, 4.1 Hz, 1H), 2.35 (s, 3H), 2.24 – 2.16 (m, 1H), 2.04 – 1.95 (m, 1H), 1.79 – 1.68 (m, 1H), 1.57 – 1.45 (m, 2H), 1.45 – 1.25 (m, 5H), 0.94 (t, *J* = 7.3 Hz, 3H), exchangeable 2 x NH not observed; $^{13}$C NMR (101 MHz, $CDCl_3$) δ 137.4, 137.3, 129.1 (2C), 127.1 (2C), 78.5, 73.7, 60.7, 60.4, 55.5, 46.8, 37.1, 32.1, 31.1, 29.0, 21.1, 20.5, 14.0; HRMS (ESI) *m/z* for $C_{19}H_{30}N_2O$ $[M+H]^+$ calcd. 303.2431, found 303.2429, IR ($\nu$/cm$^{-1}$, thin film) 2923, 2854, 2361, 1663, 1451, 1131, 764, 750.



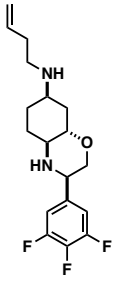

(3*R*,4a*S*,7*R*,8a*S*)-*N*-butyl-3-(*p*-tolyl)octahydro-2*H*-benzo[*b*][1,4]oxazin-7-amine (minor, 12 mg, 40 $\mu$mol, 8% isolated yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 4.01 (dd, *J* = 10.4, 3.3 Hz, 1H), 3.87 (dd, *J* = 11.1, 3.3 Hz, 1H), 3.55 – 3.44 (m, 2H), 3.17 – 3.09 (m, 1H), 2.72 – 2.57 (m, 3H), 2.35 (s, 3H), 2.08 – 1.99 (m, 1H), 1.88 – 1.78 (m, 1H), 1.77 – 1.67 (m, 1H), 1.64 – 1.45 (m, 6H), 1.44 – 1.31 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H), exchangeable 1 x NH not observed; $^{13}$C NMR (101 MHz, $CDCl_3$) δ 137.4, 137.3, 129.1 (2C), 127.1 (2C), 76.0, 74.0, 61.1, 60.7, 53.4, 47.3, 34.4, 32.0, 28.5, 26.0, 21.1, 20.5, 14.0; HRMS (ESI) *m/z* for $C_{19}H_{30}N_2O$ $[M+H]^+$ calcd. 303.2431, found 303.2431; IR ($\nu$/cm$^{-1}$, thin film) 2923, 2854, 1681, 1455, 1201, 1094.

**(3*R*,4a*S*,8a*S*)-*N*-(but-3-en-1-yl)-3-(3,4,5-trifluorophenyl)octahydro-2*H*-benzo[*b*][1,4]oxazin-7-amine 8**

3,4,5-Trifluorobenzaldehyde (80 mg, 0.50 mmol, 1.0 equiv), but-3-en-1-amine (36 mg, 0.50 mmol, 1.0 equiv) and iSnAP resin **4** were reacted according to the General Procedure to afford the title compound (0.18 mmol, 35% NMR yield, *dr* 60:40).



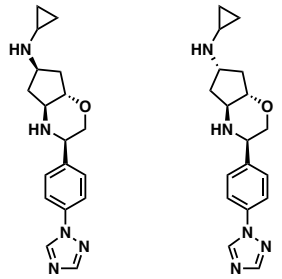

(3*R*,4a*S*,7*S*,8a*S*)-*N*-(but-3-en-1-yl)-3-(3,4,5-trifluorophenyl)octahydro-2*H*-benzo[*b*][1,4]oxazin-7-amine (major, 30 mg, 88 μmol, 18% isolated yield); $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.12 – 7.00 (m, 2H), 5.79 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.16 – 5.03 (m, 2H), 3.98 (dd, *J* = 10.2, 3.3 Hz, 1H), 3.81 (dd, *J* = 11.1, 3.3 Hz, 1H), 3.31 (dd, *J* = 11.1, 10.2 Hz, 1H), 3.14 (ddd, *J* = 11.5, 8.8, 4.1 Hz, 1H), 2.74 (m, 2H), 2.67 (tt, *J* = 11.3, 3.9 Hz, 1H), 2.60 (ddd, *J* = 11.4, 8.8, 4.1 Hz, 1H), 2.31 – 2.24 (m, 2H), 2.16 (dtd, *J* = 11.9, 4.0, 2.2 Hz, 1H), 2.00 – 1.92 (m, 1H), 1.87 – 1.52 (m, 3H), 1.45 – 1.35 (m, 1H), 1.32 – 1.18 (m, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 151.2 (ddd, *J* = 249.9, 9.9, 3.9 Hz, 2C), 139.0 (dt, *J* = 251.2, 15.4 Hz), 136.8 (td, *J* = 7.0, 6.9, 4.4 Hz), 136.2, 116.6, 111.1 (dd, *J* = 16.5, 5.1 Hz, 2C), 78.6, 73.4, 60.0, 59.7, 55.3, 46.1, 37.2, 34.3, 31.3, 29.0; HRMS (ESI) *m/z* for $C_{18}H_{23}F_3N_2O$ $[M+H]^+$ calcd. 341.1834, found 342.1835; IR (ν/cm$^{-1}$, thin film) 2928, 2853, 1527, 1445, 1349, 1095, 1041, 711.




(3*R*,4a*S*,7*R*,8a*S*)-*N*-(but-3-en-1-yl)-3-(3,4,5-trifluorophenyl)octahydro-2*H*-benzo[*b*][1,4]oxazin-7-amine (minor, 17 mg, 50 μmol, 10% isolated yield); $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.12 – 7.03 (m, 2H), 5.82 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.16 – 5.03 (m, 2H), 3.98 (dd, *J* = 10.3, 3.3 Hz, 1H), 3.82 (dd, *J* = 11.0, 3.3 Hz, 1H), 3.50 (ddd, *J* = 11.8, 8.8, 4.2 Hz, 1H), 3.35 (dd, *J* = 11.0, 10.3 Hz, 1H), 3.11 (m, 1H), 2.69 (td, *J* = 6.9, 2.2 Hz, 2H), 2.61 (ddd, *J* = 11.4, 8.9, 4.1 Hz, 1H), 2.28 (qt, *J* = 6.9, 1.4 Hz, 2H), 1.99 (ddt, *J* = 13.2, 4.5, 2.5 Hz, 1H), 1.83 – 1.69 (m, 3H), 1.62 – 1.46 (m, 4H), $^{13}$C NMR (126 MHz, $CDCl_3$) δ 151.2 (ddd, *J* = 249.9, 9.9, 3.8 Hz, 2C), 139.1 (dt, *J* = 251.1, 15.6 Hz), 136.9 (td, *J* = 6.7, 4.4 Hz), 136.4, 116.4, 111.1 (dd, *J* = 16.6, 5.0 Hz, 2C), 76.1, 73.6, 60.7, 59.8, 53.0, 46.5, 34.6, 34.2, 28.5, 26.0; HRMS (ESI) *m/z* for $C_{18}H_{23}F_3N_2O$ $[M+H]^+$ calcd. 341.1834, found 342.1837; IR (ν/cm$^{-1}$, thin film) 2928, 2854, 2360, 1620, 1527, 1443, 1350, 1094, 1034, 706.

**(3*R*,4a*S*,7a*S*)-3-(4-(1*H*-1,2,4-triazol-1-yl)phenyl)-*N*-cyclopropyloctahydrocyclopenta[*b*][1,4]oxazin-6-amine 9**

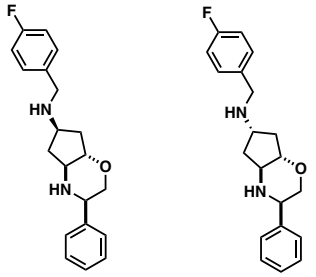
4-(1*H*-1,2,4-triazol-1-yl)benzaldehyde (87 mg, 0.50 mmol, 1.0 equiv), cyclopropanamine (29 mg, 0.50 mmol, 1.0 equiv) and iSnAP resin **3** were reacted according to the General Procedure to afford the title compound (0.14 mmol, 28% NMR yield, *dr* 50:50).




(3*R*,4a*S*,7a*S*)-3-(4-(1*H*-1,2,4-triazol-1-yl)phenyl)-*N*-cyclopropyloctahydrocyclopenta[*b*][1,4]oxazin-6-amine (mixture, 20 mg, 62 *μ*mol, 12% isolated yield); diastereomer A $^{1}$H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.08 (s, 1H), 7.68 – 7.60 (m, 2H), 7.60 – 7.52 (m, 2H), 4.12 – 4.01 (m, 1H), 3.92 – 3.83 (m, 1H), 3.57 – 3.48 (m, 1H), 3.49 – 3.41 (m, 2H), 2.80 (ddd, *J* = 12.0, 9.1, 6.4 Hz, 1H), 2.29 (ddd, *J* = 12.1, 7.6, 6.4 Hz, 1H), 2.25 (br. s, 2H), 2.13 (tt, *J* = 6.7, 3.2 Hz, 1H), 1.99 – 1.83 (m, 2H), 1.37 (td, *J* = 12.1, 7.8 Hz, 1H), 0.53 – 0.43 (m, 2H), 0.46 – 0.36 (m, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 152.7, 140,9m 140.4, 136.6, 128.9 (2C), 120.2 (2C), 81.3, 70.25, 60.8, 60.7, 53.7, 36.2, 34.2, 29.1, 6.3 (2C); diastereomer B $^{1}$H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.08 (s, 1H), 7.68 – 7.60 (m, 2H), 7.60 – 7.52 (m, 2H), 4.12 – 4.01 (m, 1H), 3.92 – 3.83 (m, 1H), 3.49 – 3.41 (m, 2H), 3.32 (ddd, *J* = 11.4, 9.2, 6.7 Hz, 1H), 3.07 – 2.97 (m, 1H), 2.40 (ddd, *J* = 12.1, 7.6, 6.7 Hz, 1H), 2.25 (br. s, 2H), 2.13 (tt, *J* = 6.7, 3.2 Hz, 1H), 1.86 – 1.70 (m, 2H), 1.51 (td, *J* = 11.7, 7.2 Hz, 1H), 0.53 – 0.43 (m, 2H), 0.46 – 0.36 (m, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 152.7, 140,9, 140.4, 136.6, 128.9 (2C), 120.2 (2C), 81.1, 70.25, 60.7, 60.1, 53.7, 36.0, 34.2, 29.1, 6.3 (2C); HRMS (ESI) *m/z* for $C_{18}H_{23}N_5O$ $[M+H]^+$ calcd. 326.1975, found 326.1977; IR (ν/cm$^{-1}$, thin film) 2957, 2850, 1338, 1124, 982, 836, 729, 546 cm; $[\alpha]^{24}$ -27.8° (c 1.00, $CH_2Cl_2$).

**(3*R*,4a*S*,7a*S*)-*N*-(4-fluorobenzyl)-3-phenyloctahydrocyclopenta[*b*][1,4]oxazin-6-amine 10**

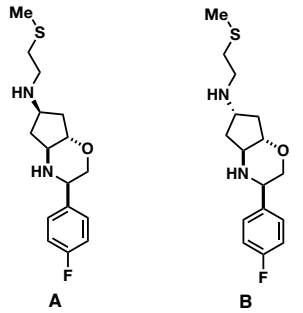
Benzaldehyde (53 mg, 0.50 mmol, 1.0 equiv), (4-fluorophenyl)methanamine (63 mg, 0.50 mmol, 1.0 equiv) and iSnAP resin **3** were reacted according to the General Procedure to afford the title compound (0.14 mmol, 28% NMR yield, *dr* 50:50).




(3*R*,4a*S*,7a*S*)-*N*-(4-fluorobenzyl)-3-phenyloctahydrocyclopenta[*b*][1,4]oxazin-6-amine (mixture, 14 mg, 43 $\mu$mol, 9% isolated yield); diastereomer A $^1$H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 2H), 7.29 – 7.17 (m, 5H), 6.97 – 6.89 (m, 2H), 3.93 (ddd, *J* = 11.8, 10.5, 3.4 Hz, 1H), 3.82 (ddd, *J* = 11.8, 10.5, 3.4 Hz, 1H), 3.66 (d, *J* = 1.6 Hz, 2H), 3.53 – 3.46 (m, 1H), 3.46 – 3.37 (m, 1H), 3.34 – 3.20 (m, 1H), 2.72 (ddd, *J* = 11.9, 9.1, 6.5 Hz, 1H), 2.17 (ddd, *J* = 12.0, 7.6, 6.5 Hz, 1H), 1.90 (br s, 2H), 1.83 – 1.73 (m, 2H), 1.32 (td, *J* = 12.0, 7.5 Hz, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 162.0 (d, *J* = 244.9 Hz), 139.0, 129.8 (d, *J* = 8.0 Hz, 2C), 128.5 (2C), 127.4 (2C), 127.4 (2C), 115.3 (d, *J* = 21.3 Hz, 2C), 81.1, 74.3, 61.2, 61.1, 52.7, 51.3, 36.0, 34.3; diastereomer B $^1$H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.30 (m, 2H), 7.29 – 7.17 (m, 5H), 6.97 – 6.89 (m, 2H), 3.82 (ddd, *J* = 11.8, 10.5, 3.4 Hz, 1H), 3.9 (ddd, *J* = 11.8, 10.5, 3.4 Hz, 1H), 3.66 (d, *J* = 1.6 Hz, 2H), 3.53 – 3.46 (m, 1H), 3.34 – 3.20 (m, 2H), 2.99 (ddd, *J* = 11.3, 9.3, 8.2 Hz, 1H), 2.29 (ddd, *J* = 12.0, 7.6, 6.8 Hz, 1H), 1.9 (br s, 2H), 1.71 – 1.64 (m, 2H), 1.43 (td, *J* = 11.6, 7.0 Hz, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 162.0 (d, *J* = 244.9 Hz), 139.0, 129.8 (dd, *J* = 8.0 Hz, 2C), 128.5 (2C), 127.4 (2C), 127.4 (2C), 115.3 (d, *J* = 21.3 Hz, 2C), 81.1, 74.3, 61.2, 60.4, 52.7, 51.3, 36.0, 34.3; HRMS (ESI) *m/z* for $C_{20}H_{23}FN_2O$ $[M+Na]^+$ calcd. 349.1687, found 349.1684; IR ($\nu$/cm$^{-1}$, thin film) 2923, 2854, 1664, 1450, 1131, 1098, 813; $[\alpha]^{25}$ -33.2° (c 0.85 $CH_2Cl_2$).

**(3*R*,4a*S*,7a*S*)-3-(4-fluorophenyl)-*N*-(2-(methylthio)ethyl)octahydrocyclopenta[*b*][1,4]oxazin-6-amine 11**

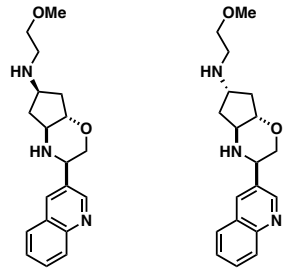
4-Fluorobenzaldehyde (62 mg, 0.50 mmol, 1.0 equiv), 2-(methylthio)ethan-1-amine (46 mg, 0.50 mmol, 1.0 equiv) and iSnAP resin 3 were reacted according to the General Procedure to afford the title compound (0.11 mmol, 23% NMR yield, *dr* 60:40).




(3*R*,4a*S*,7a*S*)-3-(4-fluorophenyl)-*N*-(2-(methylthio)ethyl)octahydrocyclopenta[*b*][1,4]oxazin-6-amine (mixture, 22 mg, 71 $\mu$mol, 14% isolated yield); diastereomer A $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 2H), 7.04 – 6.95 (m, 2H), 3.97 (td, *J* = 10.7, 3.4 Hz, 1H), 3.84 (ddd, *J* = 11.4, 3.5, 0.7 Hz, 1H), 3.56 – 3.53 (m, 1H), 3.52 – 3.49 (m, 2H), 3.41 (dt, *J* = 11.4, 10.3 Hz, 1H), 3.36 (s, 3H), 3.34 – 3.26 (m, 1H), 2.82 – 2.70 (m, 3H), 2.34 (ddd, *J* = 11.9, 7.6, 6.7 Hz, 1H), 1.98 (br s, 2H), 1.88 – 1.79 (m, 2H), 1.34 (td, *J* = 12.0, 7.6 Hz, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 162.3 (d, *J* = 245.8 Hz), 135.8 (d, *J* = 3.2 Hz), 129.0 (d, *J* = 8.0 Hz, 2C), 115.3 (d, *J* = 21.2 Hz, 2C), 81.1, 74.4, 74.2, 71.9, 60.9, 60.3, 58.8, 53.5, 47.6, 35.9; diastereomer B $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.33 (m, 2H), 7.04 – 6.95 (m, 2H), 3.97 (td, *J* = 10.7, 3.4 Hz, 1H), 3.84 (ddd, *J* = 11.4, 3.5, 0.7 Hz, 1H), 3.52 – 3.49 (m, 2H), 3.41 (dt, *J* = 11.4, 10.3 Hz, 1H), 3.36 (s, 3H), 3.34 – 3.26 (m, 2H), 3.03 (ddd, *J* = 11.3, 9.3, 8.2 Hz, 1H), 2.82 – 2.70 (m, 2H), 2.22 (ddd, *J* = 12.0, 7.5, 6.4 Hz, 1H), 1.98 (br s, 2H), 1.76 – 1.67 (m, 2H), 1.47 (td, *J* = 11.6, 7.1 Hz, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 162.3 (d, *J* = 245.8 Hz), 135.8 (d, *J* = 3.2 Hz), 129.0 (d, *J* = 8.0 Hz, 2C), 115.3 (d, *J* = 21.2 Hz, 2C), 81.0, 74.4, 74.2 71.9, 60.5, 60.3, 58.8, 53.5, 47.6, 34.3; HRMS (ESI) *m/z* for $C_{16}H_{23}FN_2OS$ $[M+H]^+$ 311.1558, calcd. found 311.1586; IR ($\nu$/cm$^{-1}$, thin film) 2924, 2850, 1677, 1509, 1220, 1124, 835; $[\alpha]^{25}$ -25.9° (c 0.85 $CH_2Cl_2$).

**(3*R*,4a*S*,7a*S*)-*N*-(2-methoxyethyl)-3-(quinolin-3-yl)octahydrocyclopenta[*b*][1,4]oxazin-6-amine 12**

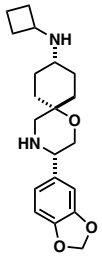
Quinoline-3-carbaldehyde (79 mg, 0.50 mmol, 1.0 equiv), 2-methoxyethan-1-amine (75 mg, 0.50 mmol, 1.0 equiv) and iSnAP resin **3** were reacted according to the General Procedure to afford the title compound (0.20 mmol, 39% NMR yield, *dr* 59:41).



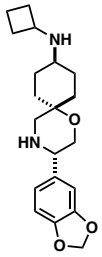

(3*R*,4a*S*,7a*S*)-*N*-(2-methoxyethyl)-3-(quinolin-3-yl)octahydrocyclopenta[*b*][1,4]oxazin-6-amine (mixture, 18 mg, 55 $\mu$mol, 11% isolated yield); diastereomer A $^{1}$H NMR (500 MHz, $CDCl_3$) δ 8.93 (t, *J* = 2.5 Hz, 1H), 8.93 (t, *J* = 2.5 Hz, 1H), 8.11 (dt, *J* = 8.5, 1.0 Hz, 1H), 7.85 – 7.81 (m, 1H), 7.71 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.56 (m, 1H), 4.24 (td, *J* = 10.3, 3.4 Hz, 1H), 3.99 (ddd, *J* = 11.5, 3.5, 0.7 Hz, 1H), 3.65 – 3.59 (m, 1H), 3.59 – 3.51 (m, 3H), 3.44 – 3.33 (m, 4H), 2.88 (ddd, *J* = 11.9, 9.1, 6.5 Hz, 1H), 2.83 – 2.74 (m, 2H), 2.30 (ddd, *J* = 12.0, 7.5, 6.5 Hz, 1H), 2.02 (br s, 2H), 1.94 – 1.87 (m, 2H), 1.43 (td, *J* = 12.0, 7.6 Hz, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 150.5, 148.0, 134.2, 132.8, 129.4, 129.3, 128.0, 127.7, 126.8, 81.1, 74.1, 71.9, 60.9, 58.9, 58.8, 53.5, 47.3, 35.9, 34.3; diastereomer B $^{1}$H NMR (500 MHz, $CDCl_3$) δ 8.93 (t, *J* = 2.5 Hz, 1H), 8.93 (t, *J* = 2.5 Hz, 1H), 8.11 (dt, *J* = 8.5, 1.0 Hz, 1H), 7.85 – 7.81 (m, 1H), 7.71 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.56 (m, 1H), 4.24 (td, *J* = 10.3, 3.4 Hz, 1H), 3.99 (ddd, *J* = 11.5, 3.5, 0.7 Hz, 1H), 3.59 – 3.51 (m, 3H), 3.44 – 3.33 (m, 5H), 3.13 (q, *J* = 9.5 Hz, 1H), 2.83 – 2.74 (m, 2H), 2.39 (ddd, *J* = 12.0, 7.5, 6.7 Hz, 1H), 2.02 (br s, 2H), 1.82 – 1.78 (m, 2H), 1.53 (td, *J* = 11.7, 7.1 Hz, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 150.5, 148.0, 134.2, 132.8, 129.4, 129.3, 128.0, 127.7, 126.8, 81.1, 74.1, 71.9, 60.3, 58.9, 58.8, 53.5, 47.3, 35.9, 34.3; HRMS (ESI) *m/z* for $C_{19}H_{25}N_3O_2$ $[M+H]^+$ calcd. 328.2020, found 328.2020; IR ($\nu$/cm$^{-1}$, thin film) 2932, 2843, 1446, 1326, 1123, 788, 754; $[\alpha]^{25}$ -53.8° (c 0.05 $CH_2Cl_2$).

**(3*R*)-3-(benzo[*d*][1,3]dioxol-5-yl)-*N*-cyclobutyl-1-oxa-4-azaspiro[5.5]undecan-9-amine 13**

Benzo[*d*][1,3]dioxole-5-carbaldehyde (75 mg, 0.50 mmol, 1.0 equiv), cyclobutanamine (36 mg, 0.50 mmol, 1.0 equiv) and iSnAP resin **1** were reacted according to the General Procedure to afford the title compound (0.09 mmol, 18% NMR yield, *dr* 70:30).

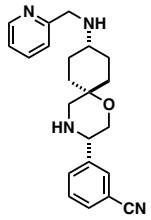



(3*S*,6*s*,9*R*)-3-(benzo[*d*][1,3]dioxol-5-yl)-*N*-cyclobutyl-1-oxa-4-azaspiro[5.5]undecan-9-amine (major, 14 mg, 41 $\mu$mol, 8% isolated yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.94 (d, *J* = 1.6 Hz, 1H), 6.85 (dd, *J* = 8.1, 1.7 Hz, 1H), 6.77 (d, *J* = 7.9 Hz, 1H), 5.99 – 5.90 (m, 2H), 3.78 (dd, *J* = 10.3, 3.8 Hz, 1H), 3.59 – 3.41 (m, 3H), 2.92 – 2.72 (m, 4H), 2.61 (tt, *J* = 10.9, 4.0 Hz, 1H), 2.30 – 2.16 (m, 2H), 1.93 – 1.78 (m, 2H), 1.78 – 1.55 (m, 7H), 1.46 – 1.20 (m, 2H), 1.18 – 1.05 (m, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 147.6, 146.9, 134.8, 120.3, 108.2, 107.6, 100.9, 69.9, 67.0, 60.5, 56.0, 55.3, 51.5, 35.1, 31.4, 27.4, 27.1, 26.9 (2C), 15.1; HRMS (ESI) *m/z* for $C_{20}H_{28}N_2O_3$ $[M+H]^+$ calcd. 345.2173, measured 345.2174, IR ($\nu$/cm$^{-1}$ thin film) 2935, 2361, 1672, 1485, 1247, 1038, 931, 729.

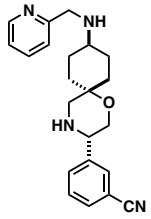



(3*S*,6*r*,9*S*)-3-(benzo[*d*][1,3]dioxol-5-yl)-*N*-cyclobutyl-1-oxa-4-azaspiro[5.5]undecan-9-amine (minor, 6 mg, 17 $\mu$mol, 3% isolated yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 6.95 (d, *J* = 1.7 Hz, 1H), 6.86 (dd, *J* = 8.3, 1.6 Hz, 1H), 6.80 – 6.74 (m, 1H), 5.95 (s, 2H), 3.79 (dd, *J* = 10.2, 3.8 Hz, 1H), 3.66 – 3.59 (m, 2H), 3.41 (p, *J* = 7.6 Hz, 1H), 3.25 (d, *J* = 11.7 Hz, 1H), 2.75 – 2.66 (m, 2H), 2.63 – 2.54 (m, 1H), 2.31 – 2.19 (m, 3H), 1.96 – 1.59 (m, 8H), 1.60 – 1.44 (m, 2H), 1.41 – 1.25 (m, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 147.6, 146.9, 134.8, 120.3, 108.1, 107.6, 101.0, 71.7, 67.6, 60.7, 53.8, 52.3, 51.8, 50.8, 34.8, 31.5, 28.7, 28.3, 26.6, 15.0; HRMS (ESI) *m/z* for $C_{20}H_{28}N_2O_3$ $[M+H]^+$ calcd. 345.2173, measured 345.2175; IR ($\nu$/cm$^{-1}$ thin film) 2935, 1504, 1485, 1439, 1246, 1089, 1038, 808.

**3-((3*R*)-9-((pyridin-2-ylmethyl)amino)-1-oxa-4-azaspiro[5.5]undecan-3-yl)benzonitrile 14**
3-Formylbenzonitrile (66 mg, 0.50 mmol, 1.0 equiv), pyridin-2-ylmethanamine (54 mg, 0.50 mmol, 1.0 equiv) and iSnAP resin **1** were reacted according to the General Procedure to afford the title compound (0.22 mmol, 44% NMR yield, *dr* 64:36).

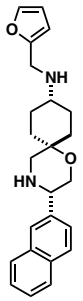



3-((3*S*,6*s*,9*R*)-9-((pyridin-2-ylmethyl)amino)-1-oxa-4-azaspiro[5.5]undecan-3-yl)benzonitrile (major, 46 mg, 127 $\mu$mol, 25% isolated yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.55 (ddd, *J* = 4.9, 1.9, 1.0 Hz, 1H), 7.79 – 7.73 (m, 1H), 7.69 – 7.60 (m, 2H), 7.57 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.43 (t, *J* = 7.7 Hz, 1H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.18 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H), 4.04 (s, 2H), 3.90 (dd, *J* = 10.2, 3.7 Hz, 1H), 3.59 (dd, *J* = 11.6, 3.7 Hz, 1H), 3.48 (dd, *J* = 11.5, 10.3 Hz, 1H), 2.89 – 2.76 (m, 3H), 2.73 – 2.63 (m, 1H), 1.89 – 1.78 (m, 2H), 1.75 – 1.64 (m, 2H), 1.50 – 1.30 (m, 2H), 1.16 (td, *J* = 14.0, 3.5 Hz, 1H), exchangeable NH x 2 not observed; $^{13}$C NMR (101 MHz, $CDCl_3$) δ 158.6, 149.2, 142.4, 136.6, 131.8, 131.3, 130.8, 129.2, 122.4, 122.2, 118.7, 112.6, 70.3, 66.6, 60.0, 56.7, 55.5, 51.7, 34.9, 27.1, 26.9, 26.8; HRMS (ESI) *m/z* for $C_{22}H_{26}N_4O$ $[M+Na]^+$ calcd. 385.1999, found 385.1995; IR (ν/cm$^{-1}$, thin film) 2934, 2228, 1672, 1591, 1433, 1091, 730.

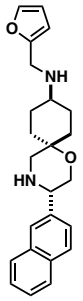



3-((3*S*,6*r*,9*S*)-9-((pyridin-2-ylmethyl)amino)-1-oxa-4-azaspiro[5.5]undecan-3-yl)benzonitrile (minor, 19 mg, 52 $\mu$mol, 10% isolated yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.58 (ddd, *J* = 4.9, 1.8, 0.9 Hz, 1H), 7.81 – 7.74 (m, 1H), 7.70 – 7.62 (m, 2H), 7.58 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.19 (ddd, *J* = 7.6, 4.9, 1.2 Hz, 1H), 3.97 (s, 2H), 3.92 (dd, *J* = 9.2, 4.8 Hz, 1H), 3.66 – 3.53 (m, 2H), 3.25 (d, *J* = 11.7 Hz, 1H), 2.78 – 2.70 (m, 2H), 2.57 – 2.49 (m, 1H), 1.99 – 1.90 (m, 2H), 1.79 – 1.71 (m, 1H), 1.62 (ddd, *J* = 13.6, 10.7, 3.9 Hz, 1H), 1.53 (ddd, *J* = 13.2, 11.0, 3.9 Hz, 1H), 1.46 – 1.31 (m, 2H), exchangeable NH x 2 not observed; $^{13}$C NMR (101 MHz, $CDCl_3$) δ 159.3, 149.3, 142.4, 136.5, 131.8, 131.4, 130.8, 129.2, 122.4, 122.0, 118.8, 112.6, 72.0, 67.2, 60.2, 55.4, 52.6, 52.3, 33.9, 28.4, 28.1, 26.3; HRMS (ESI) *m/z* for $C_{22}H_{26}N_4O$ $[M+H]^+$ calcd. 363.2179, found 363.2178; IR (ν/cm$^{-1}$, thin film) 2933, 2228, 1671, 1590, 1433, 1087, 730.

**(3*R*)-*N*-(furan-2-ylmethyl)-3-(naphthalen-2-yl)-1-oxa-4-azaspiro[5.5]undecan-9-amine 15**
2-Naphthaldehyde (78 mg, 0.50 mmol, 1.0 equiv), furan-2-ylmethanamine (48 mg, 0.50 mmol, 1.0 equiv) and iSnAP resin 1 were reacted according to the General Procedure to afford the title compound (0.22 mmol, 44% NMR yield, *dr* 60:40).



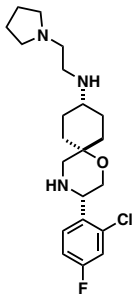

(3*S*,6*s*,9*R*)-*N*-(furan-2-ylmethyl)-3-(naphthalen-2-yl)-1-oxa-4-azaspiro[5.5]undecan-9-amine (major, 25 mg, 66 $\mu$mol, 13% isolated yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.91 – 7.87 (m, 1H), 7.86 – 7.81 (m, 3H), 7.52 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.50 – 7.46 (m, 2H), 7.38 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.33 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.23 – 6.18 (m, 1H), 4.05 (dd, *J* = 10.2, 3.9 Hz, 1H), 3.88 (s, 2H), 3.74 – 3.62 (m, 2H), 2.97 – 2.83 (m, 3H), 2.58 (tt, *J* = 10.9, 3.9 Hz, 1H), 1.86 (s, 2H), 1.83 – 1.75 (m, 2H), 1.75 – 1.68 (m, 1H), 1.68 – 1.58 (m, 1H), 1.46 – 1.36 (m, 2H), 1.20 (td, *J* = 13.9, 3.5 Hz, 1H), $^{13}$C NMR (101 MHz, $CDCl_3$) δ 154.4, 141.7, 138.3, 133.4, 133.1, 128.0, 127.8, 127.7, 126.1, 125.8, 125.7, 125.5, 110.1, 106.5, 70.3, 66.9, 60.9, 56.1, 55.9, 43.4, 35.2, 27.7, 27.5, 27.0; HRMS (ESI) *m/z* for $C_{24}H_{28}N_2O_2$ $[M+H]^+$ calcd. 377.2224, found 377.2225; IR ($\nu$/cm$^{-1}$, thin film) 2932, 2855, 1440, 1086, 1065, 731, 479.



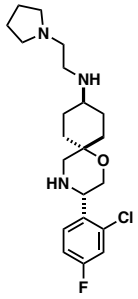

(3*S*,6*r*,9*S*)-*N*-(furan-2-ylmethyl)-3-(naphthalen-2-yl)-1-oxa-4-azaspiro[5.5]undecan-9-amine (minor, 15 mg, 40 $\mu$mol, 8% isolated yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.92 – 7.88 (m, 1H), 7.88 – 7.79 (m, 3H), 7.53 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.51 – 7.44 (m, 2H), 7.39 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.35 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.23 – 6.20 (m, 1H), 4.05 (dd, *J* = 10.3, 3.8 Hz, 1H), 3.86 (s, 2H), 3.78 (dd, *J* = 11.5, 10.3 Hz, 1H), 3.70 (dd, *J* = 11.5, 3.8 Hz, 1H), 3.30 (d, *J* = 11.7 Hz, 1H), 2.81 (dd, *J* = 11.8, 1.0 Hz, 1H), 2.71 (tt, *J* = 8.5, 3.9 Hz, 1H), 2.64 – 2.57 (m, 1H), 1.96 – 1.89 (m, 4H), 1.80 – 1.74 (m, 1H), 1.70 – 1.63 (m, 1H), 1.55 (ddd, *J* = 13.2, 11.0, 4.1 Hz, 1H), 1.44 – 1.28 (m, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 154.6, 141.8, 138.3, 133.4, 133.1, 128.0, 127.8, 127.7, 126.1, 125.8, 125.7, 125.5, 110.1, 106.7, 71.9, 67.5, 61.1, 54.6, 52.7, 43.8, 34.7, 28.6, 28.2, 26.0; HRMS (ESI) *m/z* for $C_{24}H_{28}N_2O_2$ $[M+H]^+$ calcd. 377.2224, found 377.2220; IR ($\nu$/cm$^{-1}$, thin film) 2930, 2859, 1450, 1084, 819, 731, 479.

**(3*R*)-3-(2-chloro-4-fluorophenyl)-*N*-(2-(pyrrolidin-1-yl)ethyl)-1-oxa-4-azaspiro[5.5]undecan-9-amine 16**

4-Fluorobenzaldehyde (79 mg, 0.50 mmol, 1.0 equiv), 2-(pyrrolidin-1-yl)ethan-1-amine (57 mg, 0.50 mmol, 1.0 equiv) and iSnAP resin **1** were reacted according to the General Procedure to afford the title compound (0.16 mmol, 32% NMR yield, *dr* 64:36).

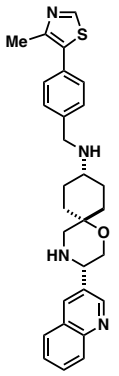



(3*S*,6*s*,9*R*)-3-(2-chloro-4-fluorophenyl)-*N*-(2-(pyrrolidin-1-yl)ethyl)-1-oxa-4-azaspiro[5.5]undecan-9-amine (major, 45 mg, 114 $\mu$mol, 23% isolated yield); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 8.7, 6.3 Hz, 1H), 7.09 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.98 (td, *J* = 8.4, 2.6 Hz, 1H), 4.28 (dd, *J* = 10.0, 3.5 Hz, 1H), 3.70 (dd, *J* = 11.5, 3.6 Hz, 1H), 3.40 (dd, *J* = 11.4, 10.0 Hz, 1H), 2.29 (br. s, 2H), 2.90 (d, *J* = 11.4 Hz, 1H), 2.85 – 2.75 (m, 4H), 2.65 – 2.59 (m, 2H), 2.56 – 2.47 (m, 5H), 1.83 – 1.67 (m, 7H), 1.61 – 1.49 (m, 1H), 1.41 – 1.25 (m, 2H), 1.14 (td, *J* = 13.8, 3.4 Hz, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 161.5 (d, *J* = 249.3 Hz), 134.2 (d, *J* = 3.5 Hz), 133.8 (d, *J* = 10.0 Hz), 129.5 (d, *J* = 8.6 Hz), 116.7 (d, *J* = 24.6 Hz), 114.2 (d, *J* = 20.6 Hz), 70.4, 64.9, 57.0, 56.4, 56.2, 55.9, 54.1 (2C), 45.5, 35.0, 27.7, 27.5, 27.2, 23.5 (2C); HRMS (ESI) *m/z* for $C_{21}H_{31}ClFN_3O$ $[M+H]^+$ calcd. 396.2212, found 396.2208; IR (ν/cm$^{-1}$, thin film) 2930, 2856, 2794, 1487, 1231, 1087, 732, 589.

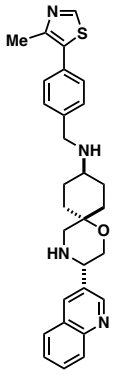



(3*S*,6*r*,9*S*)-3-(2-chloro-4-fluorophenyl)-*N*-(2-(pyrrolidin-1-yl)ethyl)-1-oxa-4-azaspiro[5.5]undecan-9-amine (minor, 12 mg, 30 $\mu$mol, 6% isolated yield); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.66 (m, 1H), 7.10 (dd, *J* = 8.5, 2.6 Hz, 1H), 7.00 (td, *J* = 8.3, 2.6 Hz, 1H), 4.45 – 4.25 (m, 2H), 3.90 (s, 1H), 3.73 (dd, *J* = 11.3, 3.6 Hz, 1H), 3.53 (dd, *J* = 11.3, 10.0 Hz, 1H), 3.25 (d, *J* = 11.6 Hz, 1H), 2.85 – 2.72 (m, 3H), 2.70 – 2.50 (m, 7H), 1.98 – 1.68 (m, 7H), 1.62 – 1.44 (m, 2H), 1.40 – 1.19 (m, 2H), exchangeable NH x 1 not observed; $^{13}$C NMR (101 MHz, $CDCl_3$) δ 161.6 (d, *J* = 249.3 Hz), 134.1 (d, *J* = 3.4 Hz), 133.7 (d, *J* = 10.1 Hz), 129.5 (d, *J* = 8.6 Hz), 116.7 (d, *J* = 24.7 Hz), 114.2 (d, *J* = 20.7 Hz), 72.0, 65.5, 56.45, 56.1, 55.6, 54.1 (2C), 52.0, 45.6, 35.3, 28.6, 28.3, 27.0, 23.4 (2C); HRMS (ESI) *m/z* for $C_{21}H_{31}ClFN_3O$ $[M+H]^+$ calcd. 396.2212, found 396.2212; IR (ν/cm$^{-1}$, thin film) 2932, 2859, 2796, 2360, 1683, 1488, 1230, 1089, 856.

**(3*R*)-*N*-(furan-2-ylmethyl)-3-(naphthalen-2-yl)-1-oxa-4-azaspiro[5.5]undecan-9-amine 17**
Quinoline-3-carbaldehyde (79 mg, 0.50 mmol, 1.0 equiv), (4-(4-methylthiazol-5-yl)phenyl)methanamine (102 mg, 0.50 mmol, 1.0 equiv) and iSnAP resin **1** were reacted according to the General Procedure to afford the title compound (0.27 mmol, 54% NMR yield, *dr* 57:43).



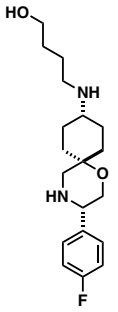

(3*S*,6*s*,9*R*)-*N*-(4-(4-methylthiazol-5-yl)benzyl)-3-(quinolin-3-yl)-1-oxa-4-azaspiro[5.5]undecan-9-amine (major, 17 mg, 61 $\mu$mol, 12% isolated yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.95 (d, *J* = 2.2 Hz, 1H), 8.69 (s, 1H), 8.22 (d, *J* = 2.2 Hz, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 7.84 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.72 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.57 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.42 (s, 3H), 4.12 (dd, *J* = 10.1, 3.8 Hz, 1H), 3.91 (s, 2H), 3.77 – 3.63 (m, 2H), 2.98 – 2.86 (m, 3H), 2.63 (tt, *J* = 10.8, 3.9 Hz, 1H), 2.56 (s, 3H), 1.85 (dt, *J* = 12.3, 3.6 Hz, 2H), 1.79 – 1.58 (m, 4H), 1.49 – 1.37 (m, 2H), 1.24 (td, *J* = 13.8, 3.4 Hz, 1H), exchangeable NH x 1 not observed; $^{13}$C NMR (101 MHz, $CDCl_3$) δ 150.4, 150.1, 148.4, 148.0, 140.8, 133.8, 133.6, 131.8, 130.5, 129.3 (3C), 129.3, 128.4 (2C), 128.0, 127.7, 126.8, 70.5, 66.8, 58.6, 56.3, 55.8, 51.1, 35.1, 27.9, 27.7, 27.0, 16.8; HRMS (ESI) *m/z* for $C_{29}H_{32}N_4OS$ $[M+H]^+$ calcd. 485.2370, found 285.2368, IR ($\nu$/cm$^{-1}$, thin film) 2931, 2856, 1495, 1319, 1124, 909, 728.



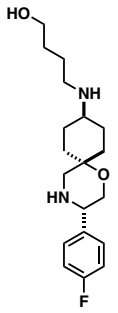

(3*S*,6*r*,9*S*)-*N*-(4-(4-methylthiazol-5-yl)benzyl)-3-(quinolin-3-yl)-1-oxa-4-azaspiro[5.5]undecan-9-amine (minor, 9 mg, 19 $\mu$mol, 4% isolated yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 8.95 (d, *J* = 2.2 Hz, 1H), 8.70 (s, 1H), 8.24 (d, *J* = 2.2 Hz, 1H), 8.12 (d, *J* = 9.2 Hz, 1H), 7.87 – 7.80 (m, 1H), 7.72 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 7.57 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.44 (t, *J* = 1.2 Hz, 4H), 4.13 (dd, *J* = 9.8, 4.1 Hz, 1H), 3.88 (s, 2H), 3.82 – 3.68 (m, 2H), 3.31 (d, *J* = 11.7 Hz, 1H), 2.87 – 2.75 (m, 2H), 2.57 (s, 3H), 2.03 – 1.91 (m, 2H), 1.86 – 1.68 (m, 2H), 1.66 – 1.51 (m, 4H), 1.49 – 1.33 (m, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 150.5, 150.2, 148.5, 148.0, 140.7, 133.9, 133.6, 131.8, 130.6, 129.4 (2C), 129.3, 129.3, 128.4 (2C), 128.0, 127.7, 126.8, 72.0,

67.3, 58.8, 55.0, 52.7, 51.2, 34.5, 28.6, 28.3, 26.3, 16.1; HRMS (ESI) *m/z* for $C_{29}H_{32}N_4OS$ $[M+H]^+$ calcd. 485.2370, found 485.2366; IR ($\nu$/cm$^{-1}$, thin film) 2932, 2858, 2359, 1445, 1089, 910, 729.

**4-(((3*R*)-3-(4-fluorophenyl)-1-oxa-4-azaspiro[5.5]undecan-9-yl)amino)butan-1-ol 18**
4-Fluorobenzaldehyde (62 mg, 0.50 mmol, 1.0 equiv), 4-aminobutan-1-ol (45 mg, 0.50 mmol, 1.0 equiv) and iSnAP resin **1** were reacted according to the General Procedure to afford the title compound (0.12 mmol, 24% NMR yield, *dr* 62:38).

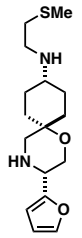



4-(((3*S*,6*s*,9*R*)-3-(4-fluorophenyl)-1-oxa-4-azaspiro[5.5]undecan-9-yl)amino)butan-1-ol (major, 13 mg, 39 $\mu$mol, 8% isolated yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.24 (m, 2H), 7.02 – 6.87 (m, 2H), 3.76 (dd, *J* = 10.3, 3.8 Hz, 1H), 3.53 – 3.37 (m, 4H), 2.82 – 2.68 (m, 3H), 2.67 – 2.59 (m, 2H), 2.42 (tt, *J* = 11.1, 4.0 Hz, 1H), 1.78 – 1.67 (m, 2H), 1.65 – 1.39 (m, 6H), 1.33 – 1.20 (m, 2H), 1.19 (d, *J* = 2.5 Hz, 3H), 1.05 (td, *J* = 13.9, 3.5 Hz, 1H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 162.4 (d, *J* = 245.7 Hz), 136.6 (d, *J* = 3.1 Hz), 128.8 (d, *J* = 7.9 Hz, 2C), 115.4 (d, *J* = 21.2 Hz, 2C), 70.0, 67.1, 62.4, 60.2, 56.8, 56.1, 46.2, 35.2, 32.2, 28.2, 27.1, 26.7, 26.4; HRMS (ESI) *m/z* for $C_{19}H_{29}FN_2O_2$ $[M+H]^+$ calcd. 337.2286, found 337.2287; IR ($\nu$/cm$^{-1}$, thin film) 2925, 2852, 1508, 1221, 1064, 835.

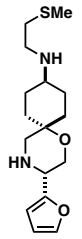



4-(((3*S*,6*r*,9*S*)-3-(4-fluorophenyl)-1-oxa-4-azaspiro[5.5]undecan-9-yl)amino)butan-1-ol (minor, 18 mg, 54 $\mu$mol, 11% isolated yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 2H), 7.06 – 7.00 (m, 2H), 3.86 (dd, *J* = 10.1, 4.0 Hz, 1H), 3.65 – 3.54 (m, 4H), 3.22 (d, *J* = 11.7 Hz, 1H), 2.76 – 2.65 (m, 4H), 2.50 – 2.43 (m, 1H), 1.99 – 1.87 (m, 2H), 1.76 – 1.61 (m, 6H), 1.58 – 1.47 (m, 1H), 1.39 – 1.25 (m, 3H), exchangeable NH/OH x 2 not observed; $^{13}$C NMR (126 MHz, $CDCl_3$) δ 162.3 (d, *J* = 245.5 Hz), 136.6 (d, *J* = 3.1 Hz), 128.7 (d, *J* = 7.9 Hz, 2C), 115.2 (d, *J* = 21.2 Hz, 2C), 71.6, 67.6, 62.6, 60.2, 55.5, 52.7, 47.3, 34.5, 32.7, 29.5, 28.3, 27.9, 26.3; HRMS (ESI) *m/z* for $C_{19}H_{29}FN_2O_2$ $[M+H]^+$ calcd. 337.2286, found 337.2283; IR ($\nu$/cm$^{-1}$, thin film) 2925, 2856, 2360, 1509, 1221, 1090, 835.

**(3*S*)-3-(furan-2-yl)-*N*-(2-(methylthio)ethyl)-1-oxa-4-azaspiro[5.5]undecan-9-amine 19**
Furan-2-carbaldehyde (48 mg, 0.5 mmol, 1.0 equiv), 2-(methylthio)ethan-1-amine (46 mg, 0.5 mmol, 1.0 equiv) and iSnAP resin 1 were reacted according to the General Procedure to afford the title compound (0.17 mmol, 33% NMR yield, *dr* 64:36).

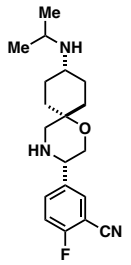



(3*R*,6*s*,9*S*)-3-(furan-2-yl)-*N*-(2-(methylthio)ethyl)-1-oxa-4-azaspiro[5.5]undecan-9-amine (major, 11 mg, 35 $\mu$mol, 7% isolated yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.33 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.22 (d, *J* = 3.3 Hz, 1H), 3.97 (dd, *J* = 9.4, 4.2 Hz, 1H), 3.82 – 3.67 (m, 2H), 2.88 (t, *J* = 6.5 Hz, 2H), 2.79 (q, *J* = 12.1 Hz, 2H), 2.71 – 2.60 (m, 3H), 2.52 (tt, *J* = 11.0, 3.9 Hz, 1H), 2.11 (s, 3H), 1.83 – 1.65 (m, 5H), 1.62 – 1.49 (m, 1H), 1.45 – 1.25 (m, 2H), 1.12 (td, *J* = 13.8, 3.5 Hz, 1H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 153.8, 141.4, 110.1, 105.9, 70.0, 63.6, 56.5, 55.1, 53.4, 44.9, 34.8, 34.5, 27.9, 27.6, 26.6, 15.2; HRMS (ESI) *m/z* for $C_{16}H_{26}N_2O_2S$ $[M+H]^+$ calcd. 311.1788, found 311.1784; IR (thin film, $\nu$/cm$^{-1}$) 2920, 2856, 1680, 1442, 1092, 737.

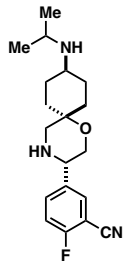



(3*R*,6*r*,9*R*)-3-(furan-2-yl)-*N*-(2-(methylthio)ethyl)-1-oxa-4-azaspiro[5.5]undecan-9-amine (minor, 13 mg, 42 $\mu$mol, 8% isolated yield);$^1$H NMR (400 MHz, $CDCl_3$) δ 7.37 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.34 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.24 (dt, *J* = 3.2, 0.8 Hz, 1H), 3.98 (dd, *J* = 9.5, 3.9 Hz, 1H), 3.90 – 3.76 (m, 2H), 3.15 (d, *J* = 12.2 Hz, 1H), 2.90 (t, *J* = 6.5 Hz, 3H), 2.79 – 2.67 (m, 4H), 2.42 – 2.31 (m, 1H), 2.13 (s, 3H), 1.98 – 1.86 (m, 2H), 1.82 – 1.73 (m, 1H), 1.65 – 1.48 (m, 2H), 1.42 – 1.25 (m, 2H), exchangeable NH x 1 not observed; $^{13}$C NMR (101 MHz, $CDCl_3$) δ 153.8, 141.9, 110.1, 106.0, 71.5, 64.2, 55.3, 53.5, 51.6, 45.0, 33.9, 33.6, 28.0, 27.9, 26.8, 15.2; HRMS (ESI) *m/z* for $C_{16}H_{26}N_2O_2S$ $[M+H]^+$ calcd. 311.1788, found 311.1785; IR ($\nu$/cm$^{-1}$, thin film) 2922, 2855, 2362, 1677, 1455, 1093, 738.

**2-fluoro-5-((3*R*)-9-(isopropylamino)-1-oxa-4-azaspiro[5.5]undecan-3-yl)benzonitrile 20**
2-Fluoro-5-formylbenzonitrile (75 mg, 0.50 mmol, 1.0 equiv), propan-2-amine (30 mg, 0.50 mmol, 1.0 equiv) and iSnAP resin **1** were reacted according to the General Procedure to afford the title compound (0.19 mmol, 38% NMR yield, *dr* 54:46).



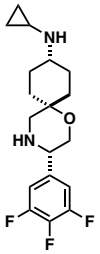

2-Fluoro-5-((3*S*,6*s*,9*R*)-9-(isopropylamino)-1-oxa-4-azaspiro[5.5]undecan-3-yl)benzonitrile (major, 26 mg, 79 μmol, 16% isolated yield); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 6.1, 2.2 Hz, 1H), 7.64 (ddd, *J* = 8.8, 5.1, 2.3 Hz, 1H), 7.18 (t, *J* = 8.7 Hz, 1H), 3.88 (dd, *J* = 10.2, 3.7 Hz, 1H), 3.56 (dd, *J* = 11.6, 3.7 Hz, 1H), 3.45 (dd, *J* = 11.5, 10.3 Hz, 1H), 3.05 (p, *J* = 6.3 Hz, 1H), 2.90 – 2.75 (m, 3H), 2.69 – 2.59 (m, 1H), 1.81 – 1.71 (m, 2H), 1.67 (m, 1H), 1.58 – 1.46 (m, 1H), 1.39 (dd, *J* = 13.2, 3.9 Hz, 1H), 1.35 – 1.23 (m, 1H), 1.16 (td, *J* = 13.9, 3.3 Hz, 1H), 1.08 (d, *J* = 6.3 Hz, 6H), exchangeable NH x 2 not observed; $^{13}$C NMR (101 MHz, $CDCl_3$) δ 162.5 (d, *J* = 259.1 Hz), 138.1 (d, *J* = 3.6 Hz), 133.9 (d, *J* = 8.2 Hz), 132.1 (2C), 116.4 (d, *J* = 19.5 Hz), 113.9, 101.5 (d, *J* = 15.5 Hz), 70.4, 66.6, 59.4, 55.6, 53.4, 44.5, 35.2, 27.8, 27.6, 27.1, 22.6; HRMS (ESI) *m/z* for $C_{19}H_{26}FN_3O$ $[M+H]^+$ calcd. 332.2133, found 332.2132; IR (ν/cm$^{-1}$, thin film) 2929, 2858, 1680, 1442, 1114, 880, 732.



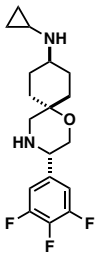

2-fluoro-5-((3*S*,6*r*,9*S*)-9-(isopropylamino)-1-oxa-4-azaspiro[5.5]undecan-3-yl)benzonitrile (minor, 22 mg, 66 μmol, 13% isolated yield); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 6.1, 2.3 Hz, 1H), 7.68 – 7.60 (m, 1H), 7.18 (t, *J* = 8.7 Hz, 1H), 3.89 (dd, *J* = 9.0, 5.0 Hz, 1H), 3.63 – 3.52 (m, 2H), 3.26 (d, *J* = 11.7 Hz, 1H), 2.98 (p, *J* = 6.3 Hz, 1H), 2.79 – 2.67 (m, 2H), 2.63 – 2.53 (m, 1H), 1.96 – 1.82 (m, 2H), 1.75 – 1.60 (m, 2H), 1.60 – 1.44 (m, 2H), 1.34 – 1.16 (m, 2H), 1.10 (d, *J* = 6.2 Hz, 6H), exchangeable NH x 1 not observed; $^{13}$C NMR (101 MHz, $CDCl_3$) δ 162.5 (d, *J* = 259.1 Hz), 138.1 (d, *J* = 3.6 Hz), 133.9 (d, *J* = 8.2 Hz), 132.1, 116.4 (d, *J* = 19.5 Hz), 113.9, 101.5 (d, *J* = 15.5 Hz), 72.1, 67.2, 59.5, 52.6, 51.8, 45.4, 35.0, 29.1, 28.8, 26.9, 23.2, 23.1; HRMS (ESI) *m/z* for $C_{19}H_{26}FN_3O$ $[M+H]^+$ calcd. 332.2133, found 332.2133; IR (ν/cm$^{-1}$, thin film) 2929, 2859, 1679, 1497, 1088, 831, 731.

**_N_-cyclopropyl-3-(3,4,5-trifluorophenyl)-1-oxa-4-azaspiro[5.5]undecan-9-amine 21**

3,4,5-Trifluorobenzaldehyde (80 mg, 0.50 mmol, 1.0 equiv), cyclopropanamine (29 mg, 0.50 mmol, 1.0 equiv) and iSnAP resin **1** were reacted according to the General Procedure to afford the title compound (0.20 mmol, 40% NMR yield, *dr* 50:50).



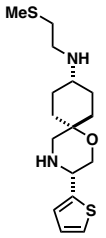

(3*S*,6*s*,9*R*)-*N*-cyclopropyl-3-(3,4,5-trifluorophenyl)-1-oxa-4-azaspiro[5.5]undecan-9-amine (major, 19 mg, 56 μmol, 11% isolated yield); $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.13 – 7.03 (m, 2H), 3.81 (dd, *J* = 10.3, 3.7 Hz, 1H), 3.56 (dd, *J* = 11.6, 3.7 Hz, 1H), 3.44 (dd, *J* = 11.5, 10.3 Hz, 1H), 2.88 – 2.79 (m, 2H), 2.79 – 2.73 (m, 1H), 2.65 (tt, *J* = 11.0, 4.0 Hz, 1H), 2.17 (tt, *J* = 6.7, 3.7 Hz, 1H), 1.86 – 1.79 (m, 2H), 1.71 – 1.63 (m, 2H), 1.60 – 1.48 (m, 1H), 1.44 – 1.26 (m, 2H), 1.17 (td, *J* = 13.9, 3.4 Hz, 1H), 0.49 – 0.43 (m, 2H), 0.39 – 0.34 (m, 2H), exchangeable NH x 1 not observed; $^{13}$C NMR (126 MHz, $CDCl_3$) δ 151.2 (ddd, *J* = 249.9, 9.9, 3.9 Hz, 2C), 138.9 (dt, *J* = 251.0, 15.3 Hz), 137.3 (td, *J* = 6.8, 4.4 Hz); 111.0 (dd, *J* = 16.5, 5.0 Hz, 2C), 70.5, 66.6, 59.6, 57.2, 55.6, 35.1, 28.2, 28.0, 27.8, 27.0, 6.4 (2C); HRMS (ESI) *m/z* for $C_{18}H_{23}F_3N_2O$ $[M+H]^+$ calcd. 341.1835, found 341.1837; IR (ν/cm$^{-1}$, thin film) 2937, 2857, 1618, 1528, 1442, 1350, 1089, 1048, 825, 710.



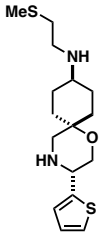

(3*S*,6*r*,9*S*)-*N*-cyclopropyl-3-(3,4,5-trifluorophenyl)-1-oxa-4-azaspiro[5.5]undecan-9-amine (minor, 8 mg, 34 μmol, 5% isolated yield); $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.10 – 7.01 (m, 2H), 3.83 – 3.76 (m, 1H), 3.59 – 3.50 (m, 2H), 3.19 (d, *J* = 11.7 Hz, 1H), 2.78 (tt, *J* = 8.7, 3.9 Hz, 1H), 2.68 (dd, *J* = 11.7, 1.1 Hz, 1H), 2.51 – 2.42 (m, 1H), 2.11 (tt, *J* = 6.6, 3.7 Hz, 1H), 1.97 – 1.89 (m, 2H), 1.75 (s, 1H), 1.71 – 1.64 (m, 1H), 1.59 – 1.47 (m, 2H), 1.34 – 1.21 (m, 2H), 0.50 – 0.45 (m, 2H), 0.38 – 0.33 (m, 2H); exchangeable NH x 1 not observed; $^{13}$C NMR (126 MHz, $CDCl_3$) δ151.2 (ddd, *J* = 250.0, 9.9, 3.9 Hz, 2C), 138.9 (dt, *J* = 251.0, 15.3 Hz), 137.3 (td, *J* = 6.8, 4.3 Hz), 111.1 (dd, *J* = 16.5, 4.9 Hz, 2C), 72.1, 67.1, 59.7, 56.2, 52.1, 34.7, 28.8, 28.7, 28.5, 26.5, 6.4, 6.3; HRMS (ESI) *m/z* for $C_{18}H_{23}F_3N_2O$ $[M+H]^+$ calcd. 341.1835, found 341.1835; IR (ν/cm$^{-1}$, thin film) 2937, 2860, 1618, 1530, 1443, 1351, 1090, 1048, 855, 711.

***N*-(2-(methylthio)ethyl)-3-(thiophen-2-yl)-1-oxa-4-azaspiro[5.5]undecan-9-amine 22**

Thiophene-2-carbaldehyde (56 mg, 0.50 mmol, 1.0 equiv), 2-(methylthio)ethan-1-amine (46 mg, 0.50 mmol, 1.0 equiv) and iSnAP resin **1** were reacted according to the General Procedure to afford the title compound (0.13 mmol, 26% NMR yield, *dr* 50:50).



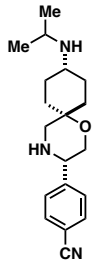

(3*R*,6*s*,9*S*)-*N*-(2-(methylthio)ethyl)-3-(thiophen-2-yl)-1-oxa-4-azaspiro[5.5]undecan-9-amine (major, 17 mg, 52 $\mu$mol, 10% isolated yield) $^1$H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.21 (m, 1H), 7.00 – 6.96 (m, 2H), 4.18 (dd, *J* = 10.1, 3.9 Hz, 1H), 3.70 (dd, *J* = 11.6, 3.9 Hz, 1H), 3.61 (dd, *J* = 11.5, 10.1 Hz, 1H), 2.90 – 2.84 (m, 3H), 2.82 – 2.73 (m, 2H), 2.67 (td, *J* = 6.5, 0.5 Hz, 2H), 2.52 (tt, *J* = 11.0, 4.0 Hz, 1H), 2.11 (s, 3H), 1.82 – 1.64 (m, 4H), 1.56 (tdd, *J* = 12.5, 10.8, 3.6 Hz, 1H), 1.41 – 1.28 (m, 2H), 1.19 – 1.09 (m, 1H), exchangeable NH x 1 not observed; $^{13}$C NMR (101 MHz, $CDCl_3$) δ 144.2, 126.6, 124.3, 123.9, 70.2, 67.0, 56.5, 55.9, 55.7, 44.9, 35.0, 34.8, 27.9, 27.6, 26.9, 15.2; HRMS (ESI) *m/z* for $C_{16}H_{26}N_2OS_2$ $[M+H]^+$ calcd. 327.1559, found 327.1559; IR ($\nu$/cm$^{-1}$, thin film) 2918, 2856, 1669, 1439, 1312, 1089, 1065, 701.



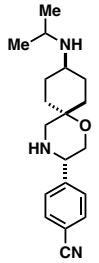

(3*R*,6*r*,9*R*)-*N*-(2-(methylthio)ethyl)-3-(thiophen-2-yl)-1-oxa-4-azaspiro[5.5]undecan-9-amine (minor, 8 mg, 25 $\mu$mol, 5% isolated yield) $^1$H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.22 (m, 1H), 7.02 – 6.96 (m, 2H), 4.18 (dd, *J* = 9.4, 4.4 Hz, 1H), 3.79 – 3.68 (m, 2H), 3.21 (d, *J* = 12.0 Hz, 1H), 2.91 – 2.84 (m, 2H), 2.77 – 2.65 (m, 5H), 2.53 – 2.44 (m, 1H), 2.12 (d, *J* = 0.3 Hz, 4H), 1.96 – 1.85 (m, 2H), 1.79 – 1.69 (m, 1H), 1.64 – 1.48 (m, 2H), 1.33 (td, *J* = 14.3, 7.0 Hz, 2H); $^{13}$C NMR (101 MHz, $CDCl_3$) δ 144.1, 126.6, 124.3, 124.0, 71.7, 67.6, 56.0, 55.3, 52.2, 45.0, 34.4, 34.3, 28.5, 28.2, 26.4, 15.2; HRMS (ESI) *m/z* for $C_{16}H_{26}N_2OS_2$ $[M+H]^+$ calcd. 327.1559, found 327.1557; IR ($\nu$/cm$^{-1}$, thin film) 2916, 2857, 2806, 1671, 1438, 1199, 1088, 701.

**4-(9-(isopropylamino)-1-oxa-4-azaspiro[5.5]undecan-3-yl)benzonitrile 23**

4-Formylbenzonitrile (65 mg, 0.50 mmol, 1.0 equiv), propan-2-amine (30 mg, 0.50 mmol, 1.0 equiv) and iSnAP resin **1** were reacted according to the General Procedure to afford the title compound (0.21 mmol, 43% NMR yield, *dr* 45:55).



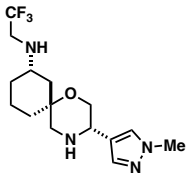

4-((3*S*,6*s*,9*R*)-9-(isopropylamino)-1-oxa-4-azaspiro[5.5]undecan-3-yl)benzonitrile (major, 46 mg, 147 $\mu$mol, 29% isolated yield) $^1$H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.58 (m, 2H), 7.57 – 7.50 (m, 2H), 3.93 (dd, *J* = 10.3, 3.7 Hz, 1H), 3.59 (dd, *J* = 11.6, 3.7 Hz, 1H), 3.48 (dd, *J* = 11.6, 10.2 Hz, 1H), 3.10 – 3.00 (m, 1H), 2.91 – 2.75 (m, 3H), 2.69 – 2.58 (m, 1H), 1.75 (ddt, *J* = 12.1, 3.8, 2.0 Hz, 2H), 1.67 (dq, *J* = 13.3, 3.3 Hz, 1H), 1.58 – 1.46 (m, 1H), 1.42 – 1.24 (m, 3H), 1.15 (td, *J* = 13.9, 3.3 Hz, 1H), 1.08 (d, *J* = 6.2 Hz, 6H), exchangeable NH x 1 not observed; $^{13}$C NMR (101 MHz, $CDCl_3$) δ 146.2, 132.3 (2C), 127.9 (2C), 118.8, 111.5, 70.4, 66.5, 60.5, 55.6, 53.4, 44.9, 35.2, 27.8, 27.6, 27.1, 23.0, 23.0; HRMS (ESI) *m/z* for $C_{19}H_{27}N_3O$ $[M+Na]^+$ calcd. 336.2046, found 336.2049; IR ($\nu$/cm$^{-1}$, thin film) 2931. 2857, 2226, 1441, 1376, 1168, 1087, 1065, 834, 729.




4-((3*S*,6*r*,9*S*)-9-(isopropylamino)-1-oxa-4-azaspiro[5.5]undecan-3-yl)benzonitrile (minor, 23 mg, 73 $\mu$mol, 15% isolated yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.58 (m, 2H), 7.57 – 7.50 (m, 2H), 3.93 (dd, *J* = 9.3, 4.6 Hz, 1H), 3.67 – 3.54 (m, 2H), 3.27 (d, *J* = 11.7 Hz, 1H), 3.03 – 2.89 (m, 1H), 2.78 – 2.67 (m, 2H), 2.64 – 2.54 (m, 1H), 1.94 – 1.84 (m, 2H), 1.74 – 1.66 (m, 2H), 1.59 – 1.45 (m, 2H), 1.31 – 1.15 (m, 2H), 1.08 (d, *J* = 6.3 Hz, 6H), exchangeable NH x 1 not observed; $^{13}$C NMR (101 MHz, $CDCl_3$) δ 146.3, 132.3 (2C), 128.0 (2C), 118.8, 111.5, 72.1, 67.1, 60.6, 52.6, 51.8, 45.4, 35.1, 29.4, 29.0, 27.0, 23.4, 23.3; HRMS (ESI) *m/z* for $C_{19}H_{27}N_3O$ $[M+H]^+$ calcd. 314.227, found 314.225; IR ($\nu$/cm$^{-1}$, thin film) 2916, 2857, 2806, 1671, 1438, 1199, 1131, 1088, 701.

**3-(1-methyl-1*H*-pyrazol-4-yl)-*N*-(2,2,2-trifluoroethyl)-1-oxa-4-azaspiro[5.5]undecan-8-amine 24**

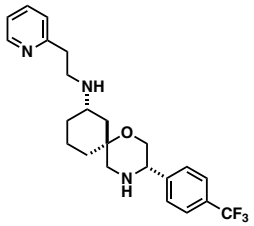
1-Methyl-1*H*-pyrazole-4-carbaldehyde (55 mg, 0.50 mmol, 1.0 equiv), 2,2,2-trifluoroethan-1-amine (50 mg, 0.50 mmol, 1.0 equiv) and iSnAP resin **2** were reacted according to the General Procedure to afford the title compound (0.09 mmol, 19% NMR yield, *dr* 20:30:20:30).




(3*S*,6*R*,8*S*)-3-(1-methyl-1*H*-pyrazol-4-yl)-*N*-(2,2,2-trifluoroethyl)-1-oxa-4-azaspiro[5.5]undecan-8-amine (10 mg, 30 $\mu$mol, 6% isolated yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.36 (s, 1H), 3.94 – 3.89 (m, 1H), 3.88 (s, 3H), 3.74 – 3.61 (m, 2H), 3.20 (q, *J* = 9.4 Hz, 2H), 2.99 (d, *J* = 12.1 Hz, 1H), 2.76 (d, *J* = 12.2 Hz, 1H), 2.75 (s, 1H), 2.16 – 2.08 (m, 1H), 1.82 – 1.68 (m, 4H), 1.49 (dd, *J* = 13.1, 8.5 Hz, 1H), 1.43 – 1.31 (m, 2H), exchangeable NH x 2 not observed; $^{13}$C NMR (126 MHz, $CDCl_3$) δ 137.6, 128.2, 125.6 (d, *J* = 277.8 Hz), 120.5, 72.3, 66.2, 52.9, 52.6, 51.5, 48.0 (q, *J* = 31.2 Hz), 42.2, 38.9, 32.0, 29.1, 18.9; HRMS (ESI) *m/z* for $C_{15}H_{23}F_3N_4O$ $[M+H]^+$ calcd. 333.1897, found 333.1897; IR ($\nu$/cm$^{-1}$, thin film) 2933, 2860, 2361, 1671, 1270, 1143, 1090, 856.

***N*-(2-(pyridin-2-yl)ethyl)-3-(4-(trifluoromethyl)phenyl)-1-oxa-4-azaspiro[5.5]undecan-8-amine 25**

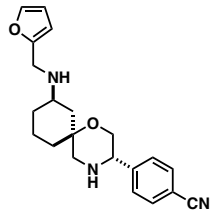
4-(trifluoromethyl)benzaldehyde (87 mg, 0.50 mmol, 1.0 equiv), 2-(pyridin-2-yl)ethan-1-amine (61 mg, 0.50 mmol, 1.0 equiv) and iSnAP resin **2** were reacted according to the General Procedure to afford the title compound (0.17 mmol, 35% NMR yield, *dr* 12:19:31:38).




(3*S*,6*R*,8*S*)-*N*-(2-(pyridin-2-yl)ethyl)-3-(4-(trifluoromethyl)phenyl)-1-oxa-4-azaspiro[5.5]undecan-8-amine (5 mg, 12 $\mu$mol, 2% isolated yield); 1H NMR (400 MHz, $CDCl_3$) δ 8.54 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.71 – 7.43 (m, 5H), 7.25 – 7.04 (m, 2H), 3.94 (dd, *J* = 10.2, 3.8 Hz, 1H), 3.65 (t, *J* = 10.8 Hz, 1H), 3.56 (dd, *J* = 11.4, 3.8 Hz, 1H), 3.21 – 2.93 (m, 5H), 2.82 – 2.60 (m, 2H), 2.54 – 2.40 (m, 1H), 1.81 (dtt, *J* = 24.2, 13.3, 4.1 Hz, 3H), 1.64 (s, 1H), 1.57 – 1.23 (m, 5H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 160.2, 149.3, 144.9, 136.4, 129.9 (d, *J* = 32.3 Hz), 127.5 (3C), 125.4 (q, *J* = 3.8 Hz, 2C), 123.3, 121.3, 72.9, 67.0, 60.4, 53.4, 52.6, 46.5, 43.5, 38.6, 32.3, 29.2, 20.1; HRMS (ESI) *m/z* for $C_{23}H_{28}F_3N_3O$ $[M+H]^+$ calcd. 420.2257, measured 420.2253; IR ($\nu$/cm$^{-1}$, thin film) 2932, 2858, 1590, 1474, 1324, 1162, 1122, 1066, 838, 605.

**4-(8-((furan-2-ylmethyl)amino)-1-oxa-4-azaspiro[5.5]undecan-3-yl)benzonitrile 26**

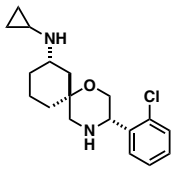
4-Formylbenzonitrile (66 mg, 0.50 mmol, 1.0 equiv), furan-2-ylmethanamine (48 mg, 0.50 mmol, 1.0 equiv) and iSnAP resin **2** were reacted according to the General Procedure to afford the title compound (0.17 mmol, 33% NMR yield, *dr* 12:25:16:47).



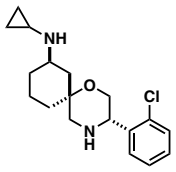
4-((3*S*,6*S*,8*R*)-8-((furan-2-ylmethyl)amino)-1-oxa-4-azaspiro[5.5]undecan-3-yl)benzonitrile (3 mg, 9 $\mu$mol, 2% isolated yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.68 – 7.64 (m, 2H), 7.58 – 7.54 (m, 2H), 7.35 (dd, *J* = 1.8, 0.9 Hz, 1H), 6.34 – 6.29 (m, 2H), 4.07 – 3.96 (m, 2H), 3.92 (dd, *J* = 10.1, 3.8 Hz, 1H), 3.60 – 3.47 (m, 2H), 3.21 (d, *J* = 13.8 Hz, 1H), 2.94 – 2.83 (m, 3H), 2.13 – 2.03 (m, 2H), 1.73 (dt, *J* = 13.2, 3.7 Hz, 1H), 1.70 – 1.59 (m, 2H), 1.34 – 1.26 (m, 2H), 1.11 (t, *J* = 12.8 Hz, 1H), exchangeable x 1NH not observed; $^{13}$C NMR (126 MHz, $CDCl_3$) δ 145.9, 142.7 (2C), 132.3 (2C), 128.0 (2C), 118.7, 111.7, 110.6 (2C), 71.9, 66.5, 60.5, 55.8, 51.5, 41.9, 35.6, 33.3, 31.4, 19.3; HRMS (ESI) *m/z* for $C_{21}H_{25}N_3O_2$ $[M+H]^+$ calcd. 352.2020, measured 352.2017; IR (ν/cm$^{-1}$, thin film) 2939, 2359, 2341, 1674, 1200, 1131, 1068, 835, 742.

**3-(2-chlorophenyl)-*N*-cyclopropyl-1-oxa-4-azaspiro[5.5]undecan-8-amine 27**

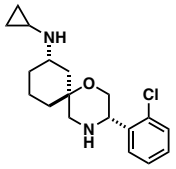
2-Chlorobenzaldehyde (70 mg, 0.50 mmol, 1.0 equiv), cyclopropanamine (29 mg, 0.50 mmol, 1.0 equiv) and iSnAP resin **2** were reacted according to the General Procedure to afford the title compound (0.10 mmol, 22% NMR yield, *dr* 36:18:27:18).



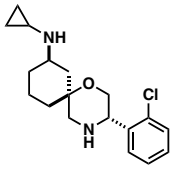
(3*S*,6*R*,8*S*)-3-(2-chlorophenyl)-*N*-cyclopropyl-1-oxa-4-azaspiro[5.5]undecan-8-amine (8 mg, 25 $\mu$mol, 5% isolated yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.71 (dd, J = 7.7, 1.8 Hz, 1H), 7.36 (dd, J = 7.9, 1.4 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.25 – 7.18 (m, 1H), 4.37 (dd, J = 10.1, 3.5 Hz, 1H), 3.77 (dd, J = 11.3, 3.5 Hz, 1H), 3.60 (dd, J = 11.3, 10.1 Hz, 1H), 3.16 (d, J = 11.6 Hz, 1H), 2.91 – 2.80 (m, 2H), 2.44 – 2.32 (m, 1H), 2.24 (tt, J = 6.5, 3.9 Hz, 1H), 1.94 – 1.86 (m, 2H), 1.78 (m, 1H), 1.69 – 1.60 (m, 1H), 1.52 (d, J = 11.1 Hz, 1H), 1.43 (q, J = 10.6 Hz, 2H), 0.56 – 0.44 (m, 4H), exchangeable NH x 2 not observed; $^{13}$C NMR (126 MHz, CDCl3) δ 138.0, 133.3, 129.5, 128.6, 128.3, 127.1, 73.0, 65.3, 56.9, 54.0, 53.0, 42.8, 32.3, 29.2, 28.1, 19.8, 6.1 (2C); HRMS (ESI) *m/z* for $C_{18}H_{25}ClN_2O$ $[M+H]^+$ calcd. 321.1728, measured 321.1726; IR (ν/cm$^{-1}$, thin film) 2932, 2860, 1441, 1335, 1085, 1072, 755, 730.



(3*S*,6*R*,8*R*)-3-(2-chlorophenyl)-*N*-cyclopropyl-1-oxa-4-azaspiro[5.5]undecan-8-amine (4 mg, 13 μmol, 3% isolated yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.74 (ddt, *J* = 7.8, 1.8, 0.5 Hz, 1H), 7.37 – 7.33 (m, 1H), 7.31 – 7.26 (m, 1H), 7.22 (ddd, *J* = 7.9, 7.4, 1.8 Hz, 1H), 4.36 (dd, *J* = 9.9, 3.6 Hz, 1H), 3.82 – 3.74 (m, 1H), 3.68 (dd, *J* = 11.4, 9.9 Hz, 1H), 3.19 (d, *J* = 11.8 Hz, 1H), 2.81 (dt, *J* = 11.8, 4.3 Hz, 3H), 2.31 – 2.22 (m, 1H), 2.08 – 1.96 (m, 2H), 1.78 (tt, *J* = 9.8, 5.2 Hz, 1H), 1.67 (d, *J* = 13.6 Hz, 1H), 1.54 (td, *J* = 12.3, 4.2 Hz, 1H), 1.43 – 1.26 (m, 3H), 0.57 – 0.43 (m, 5H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 138.0, 133.2, 129.4, 128.6, 128.5, 127.1, 72.6, 65.3, 57.0, 54.5, 53.1, 36.9, 36.1, 32.3, 28.1, 19.9, 6.7, 5.6; HRMS (ESI) *m/z* for $C_{18}H_{25}ClN_2O$ $[M+H]^+$ calcd. 321.1728, measured 321.1726; IR (ν/cm$^{-1}$, thin film) 2932, 2860, 1471, 1441, 1085, 1072, 755, 730.

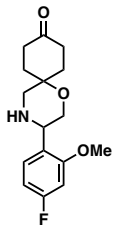


(3*S*,6*S*,8*S*)-3-(2-chlorophenyl)-*N*-cyclopropyl-1-oxa-4-azaspiro[5.5]undecan-8-amine (8 mg, 25 μmol, 5% isolated yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.36 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.31 – 7.25 (m, 1H), 7.24 – 7.16 (m, 1H), 4.37 (dd, *J* = 10.1, 3.6 Hz, 1H), 3.77 (dd, *J* = 11.4, 3.5 Hz, 1H), 3.45 (dd, *J* = 11.4, 10.1 Hz, 1H), 3.08 (tt, *J* = 11.5, 4.1 Hz, 1H), 2.94 (d, *J* = 11.4 Hz, 1H), 2.87 (d, *J* = 11.5 Hz, 1H), 2.83 (d, *J* = 15.5 Hz, 1H), 2.21 (tt, *J* = 6.7, 3.7 Hz, 1H), 2.13 – 2.08 (m, 1H), 2.04 – 1.97 (m, 1H), 1.62 (dt, *J* = 13.5, 3.6 Hz, 1H), 1.52 (qt, *J* = 13.4, 3.5 Hz, 1H), 1.13 (dd, *J* = 12.8, 11.6 Hz, 1H), 1.10 – 0.98 (m, 2H), 0.54 – 0.46 (m, 2H), 0.45 – 0.37 (m, 2H), exchangeable NH x 2 not observed;$^{13}$C NMR (126 MHz, $CDCl_3$) δ 138.1, 133.3, 129.5, 128.5, 128.3, 127.1, 72.3, 64.9, 56.9, 56.2, 52.9, 43.2, 33.5, 28.3 (2C), 19.4, 6.3 (2C); HRMS (ESI) *m/z* for $C_{18}H_{25}ClN_2O$ $[M+H]^+$ calcd. 321.1728, measured 321.1729; IR (ν/cm$^{-1}$, thin film) 2931, 2861, 1674, 1447, 1200, 1085, 755, 721.



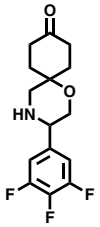
(3*S*,6*S*,8*R*)-3-(2-chlorophenyl)-*N*-cyclopropyl-1-oxa-4-azaspiro[5.5]undecan-8-amine (6 mg, 19 μmol, 4% isolated yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.73 (ddt, *J* = 7.8, 1.8, 0.5 Hz, 1H), 7.38 – 7.34 (m, 1H), 7.31 – 7.26 (m, 1H), 7.22 (ddd, *J* = 7.9, 7.4, 1.8 Hz, 1H), 4.36 (dd, *J* = 10.0, 3.5 Hz, 1H), 3.80 (dd, *J* = 11.5, 3.5 Hz, 1H), 3.54 (dd, *J* = 11.3, 10.0 Hz, 1H), 3.17 (dd, *J* = 13.8, 3.1 Hz, 1H), 2.94 (d, *J* = 11.5 Hz, 1H), 2.91 – 2.82 (m, 2H), 2.24 (tt, *J* = 6.7, 3.8 Hz, 1H), 2.15 – 2.10 (m, 1H), 2.06 – 1.91 (m, 2H), 1.83 – 1.72 (m, 1H), 1.72 – 1.59 (m, 2H), 1.32 – 1.22 (m, 1H), 1.16 – 1.04 (m, 1H), 0.93 (dd, *J* = 13.7, 11.8 Hz, 1H), 0.51 (dddd, *J* = 6.5, 4.1, 2.8, 1.2 Hz, 2H), 0.48 – 0.41 (m, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 138.1, 133.3, 129.5, 128.5,

128.4, 127.1, 72.1, 65.0, 56.9, 56.3, 52.7, 36.0, 35.5, 33.0, 28.2, 19.7, 6.9, 5.2; HRMS (ESI) *m/z* for $C_{18}H_{25}ClN_2O$ $[M+H]^+$ calcd. 321.1728, measured 321.1732; IR ($\nu$/cm$^{-1}$, thin film) 2934, 2857, 1472, 1442, 1091, 1066, 754.



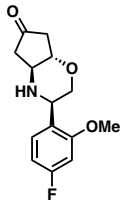

**3-(4-fluoro-2-methoxyphenyl)-1-oxa-4-azaspiro[5.5]undecan-9-one 28**

4-Fluoro-2-methoxybenzaldehyde (77 mg, 0.50 mmol, 1.0 equiv) and iSnAP resin **1** were reacted according to the General Procedure. The ketone was purified using the generic HPLC method to afford the title compound (39 mg, 0.13 mmol, 27% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 8.5, 6.8 Hz, 1H), 6.72 – 6.58 (m, 2H), 4.28 (dd, *J* = 10.0, 3.5 Hz, 1H), 3.88 – 3.76 (m, 4H), 3.58 (dd, *J* = 11.4, 10.0 Hz, 1H), 3.04 – 2.86 (m, 3H), 2.80 – 2.66 (m, 1H), 2.57 – 2.43 (m, 1H), 2.35 – 2.20 (m, 2H), 2.07 – 1.94 (m, 1H), 1.76 (td, *J* = 13.3, 5.2 Hz, 1H), 1.65 (ddd, *J* = 14.4, 13.4, 4.5 Hz, 1H), exchangeable NH x 1 not observed; $^{13}$C NMR (126 MHz, $CDCl_3$) δ 211.9, 163.1 (d, *J* = 245.6 Hz), 158.12 (d, *J* = 9.7 Hz), 128.52 (d, *J* = 9.9 Hz), 123.5, 106.94 (d, *J* = 20.9 Hz), 98.85 (d, *J* = 25.8 Hz), 69.6, 65.4, 55.6, 54.6, 54.0, 36.4, 36.1, 35.8, 28.8; HRMS (ESI) *m/z* for $C_{16}H_{20}FNO_3$ $[M+H]^+$ calcd. 294.1500, measured 294.1497; IR ($\nu$/cm$^{-1}$, thin film) 2851, 1750, 1607, 1500, 1412, 1117, 952.



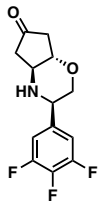

**3-(3,4,5-trifluorophenyl)-1-oxa-4-azaspiro[5.5]undecan-9-one 29**

3,4,5-trifluorobenzaldehyde (80 mg, 0.50 mmol, 1.0 equiv) and iSnAP resin **1** were reacted according to the General Procedure. The ketone was purified using the generic HPLC method to afford the title compound (36 mg, 0.12 mmol, 24% yield); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.10 (dd, *J* = 8.4, 6.6 Hz, 2H), 3.89 (dd, *J* = 10.3, 3.6 Hz, 1H), 3.68 (dd, *J* = 11.5, 3.7 Hz, 1H), 3.50 (dd, *J* = 11.5, 10.3 Hz, 1H), 3.06 – 2.84 (m, 3H), 2.78 – 2.65 (m, 1H), 2.54 – 2.40 (m, 1H), 2.32 – 2.23 (m, 2H), 2.02 – 1.93 (m, 1H), 1.89 – 1.60 (m, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 211.7, 151.3 (ddd, *J* = 250.2, 9.9, 4.0 Hz, 2C), 139.1 (dt, *J* = 251.6, 15.4 Hz), 137.06 – 136.41 (m), 111.66 – 110.40 (m, 2C), 70.0, 67.3, 59.5, 54.3, 36.3, 36.1, 35.8, 27.9; HRMS (ESI) *m/z* for $C_{15}H_{16}F_3NO_2$ $[M+H]^+$ calcd. 300.1206, measured 300.1202; IR ($\nu$/cm$^{-1}$, thin film) 2854, 1751, 1529, 1446, 1116.



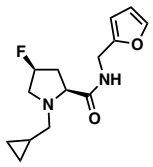

**(3*R*,4a*S*,7a*S*)-3-(4-fluoro-2-methoxyphenyl)hexahydrocyclopenta[*b*][1,4]oxazin-6(2*H*)-one 30**

4-fluoro-2-methoxybenzaldehyde (77 mg, 0.50 mmol, 1.0 equiv) and iSnAP resin **3** were reacted according to the General Procedure. The ketone was purified using the generic HPLC method to afford the title compound (26 mg, 0.10 mmol, 20% yield); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.52 (ddd, *J* = 8.5, 6.7, 0.6 Hz, 1H), 6.72 – 6.56 (m, 2H), 4.56 (dd, *J* = 10.3, 3.3 Hz, 1H), 4.07 (dd, *J* = 11.3, 3.4 Hz, 1H), 3.85 (s, 3H), 3.80 – 3.70 (m, 1H), 3.56 (t, *J* = 10.9 Hz, 1H), 3.28 (ddd, *J* = 13.0, 8.9, 7.2 Hz, 1H), 2.67 (ddt, *J* = 17.6, 7.4, 0.9 Hz, 1H), 2.61 – 2.52 (m, 1H), 2.43 – 2.21 (m, 2H), exchangeable NH x 1 not observed; $^{13}$C NMR (126 MHz, $CDCl_3$) δ 209.7, 164.4, 161.9. 157.9 (d, *J* = 9.7 Hz), 128.5 (d, *J* = 9.9 Hz), 107.0 (d, *J* = 20.9 Hz), 98.8 (d, *J* = 25.9 Hz), 79.4, 72.5, 60.2, 55.6, 54.1, 43.8, 43.1; HRMS (ESI) *m/z* for $C_{14}H_{16}FNO_3$ $[M+H]^+$ calcd. 266.1187, measured 266.1183; IR (ν/cm$^{-1}$, thin film) 2940, 2861, 1708, 1606, 1500, 1275, 1146, 1032, 834; $[\alpha]^{25}$ +15.94° (c 2.60 $CDCl_3$).




**(3*R*,4a*S*,7a*S*)-3-(3,4,5-trifluorophenyl)hexahydrocyclopenta[*b*][1,4]oxazin-6(2*H*)-one 31**

3,4,5-trifluorobenzaldehyde (80 mg, 0.50 mmol, 1.0 equiv) and iSnAP resin **3** were reacted according to the General Procedure. The ketone was purified using the generic HPLC method to afford the title compound (36 mg, 0.13 mmol, 27% yield); $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.12 (dd, *J* = 8.3, 6.6 Hz, 2H), 4.13 (dd, *J* = 10.5, 3.5 Hz, 1H), 3.93 (dd, *J* = 11.5, 3.5 Hz, 1H), 3.72 (ddd, *J* = 12.1, 8.9, 7.4 Hz, 1H), 3.50 (dd, *J* = 11.5, 10.5 Hz, 1H), 3.22 (ddd, *J* = 12.9, 8.9, 7.1 Hz, 1H), 2.61 (dddt, *J* = 31.3, 17.4, 7.2, 0.9 Hz, 2H), 2.46 – 2.16 (m, 3H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 209.1, 151.3 (ddd, *J* = 250.5, 10.0, 4.0 Hz, 2C), 139.3 (dt, *J* = 251.9, 15.4 Hz), 135.7 (td, *J* = 6.9, 4.5 Hz), 111.4 (d, *J* = 21.9 Hz, 2C), 79.4, 74.0, 59.9, 59.6, 43.8, 42.9; HRMS (ESI) *m/z* for $C_{13}H_{12}F_3NO_2$ $[M+H]^+$ calcd. 272.0893, measured 272.0891; IR (ν/cm$^{-1}$, thin film) 2854, 1751, 1620, 1529, 1352, 1116, 1044; $[\alpha]^{25}$ +4.70° (c 4.00 $CH_2Cl_2$).




**(2*S*,4*S*)-1-(cyclopropylmethyl)-4-fluoro-*N*-(furan-2-ylmethyl)pyrrolidine-2-carboxamide 32**

Furan-2-ylmethanamine (48 mg, 0.50 mmol, 1.0 equiv), (2*S*,4*S*)-1-(*tert*-butoxycarbonyl)-4-fluoropyrrolidine-2-carboxylic acid (128 mg, 0.55 mmol, 1.1 equiv), anhydrous EtOH (2.0 mL), anhydrous $CH_2Cl_2$ (2.0 mL) and a stirring bar were added to a reaction vial. The vial was inserted into the vial holder of the console and the line cap was attached. The "amide formation" capsule was scanned to load the appropriate program and inserted into the capsule holder.[8] After checking the solvents were full and the waste container was not, the program was initiated by pressing "run" on the touch screen interphase. Upon program completion, the solution in the vial was concentrated using a vial adaptor and standard rotary evaporator.

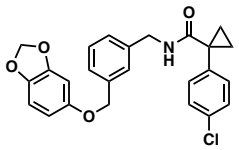
The reaction vial was returned to the vial holder of the console and the line cap was attached. A "Boc deprotection" capsule was scanned and inserted into the capsule holder.[9] The program was initiated by pressing "run" on the touch screen interphase. Upon program completion, the solution in the vial was concentrated using a vial adaptor and standard rotary evaporator.

Cyclopropanecarbaldehyde (35 mg, 0.50 mmol, 1.0 equiv), *i*-$Pr_2NEt$ (174 $\mu$L, 1.0 mmol, 2.0 equiv.), anhydrous $CH_2Cl_2$ (4.0 mL) and anhydrous HFIP (1.0 mL) were added to the reaction vial. The reaction vial was returned to the vial holder of the console and the line cap was attached. A "reductive amination" capsule was scanned and inserted into the capsule holder.[10] Reaction program "aldehyde + secondary amine" was selected and initiated by pressing "run" on the touch screen interphase. Upon program completion, the solution in the vial was concentrated and the product purified using the generic HPLC method to afford the title compound (56 mg, 0.21 mmol, 42% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.34 (dd, *J* = 1.9, 0.9 Hz, 1H), 6.31 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.21 (dq, *J* = 3.2, 0.8 Hz, 1H), 5.19 – 5.05 (m, 1H), 4.55 (dd, *J* = 15.7, 6.6 Hz, 1H), 4.40 – 4.32 (m, 1H), 3.53 (ddd, *J* = 16.9, 11.6, 2.5 Hz, 1H), 3.18 (dd, *J* = 11.2, 4.1 Hz, 1H), 2.62 – 2.39 (m, 3H), 2.38 – 2.33 (m, 1H), 2.26 – 2.14 (m, 1H), 0.84 – 0.75 (m, 1H), 0.48 – 0.40 (m, 2H), 0.10 – 0.02 (m, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 174.0, 151.8, 142.1, 110.5, 107.1, 92.8 (d, *J* = 176.8 Hz), 65.9, 60.3, 60.2 (d, *J* = 20.5 Hz), 38.0 (d, *J* = 22.3 Hz), 36.2, 10.1, 4.2, 3.8; HRMS (ESI) *m/z* for $C_{14}H_{19}FN_2O_2$ $[M+H]^+$ calcd. 267.1503, measured 267.1505; IR (ν/cm$^{-1}$, thin film) 2988,1668, 1198, 1131, 800, 720, 598; $[\alpha]^{24}$ -111.60° (c 0.90 $CDCl_3$).

[8] Synple Chem, https://www.synplechem.com/solutions/cartridges#AmideSec, (accessed October 2022).

[9] Synple Chem, https://www.synplechem.com/solutions/cartridges#Bocdeprotsec (accessed October 2022).

[10] Synple Chem, https://www.synplechem.com/solutions/cartridges#redamin (accessed October 2022).



**_N_-(3-((benzo[_d_][1,3]dioxol-5-yloxy)methyl)benzyl)-1-(4-chlorophenyl)cyclopropane-1-carboxamide 33**

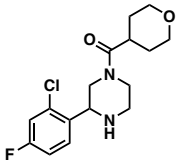
(3-(((*tert*-butyldimethylsilyl)oxy)methyl)phenyl)methanamine (126 mg, 0.50 mmol, 1.0 equiv), 1-(4-chlorophenyl)cyclopropane-1-carboxylic acid (98 mg, 0.55 mmol, 1.1 equiv), anhydrous EtOH (2.0 mL), anhydrous $CH_2Cl_2$ (2.0 mL) and a stirring bar were added to a reaction vial. The vial was inserted into the vial holder of the console and the line cap was attached. The "amide formation" capsule was scanned to load the appropriate program and inserted into the capsule holder.[8] After checking the solvents were full and the waste container was not, the program was initiated by pressing "run" on the touch screen interphase. Upon program completion, the solution in the vial was concentrated using a vial adaptor and standard rotary evaporator.

The reaction vial was returned to the vial holder of the console, MeOH (2.0 mL) was added and the line cap was attached. A "silyl deprotection" capsule was scanned and inserted into the capsule holder.[11] The program was initiated by pressing "run" on the touch screen interphase. Upon program completion, the solution in the vial was concentrated using a vial adaptor and standard rotary evaporator.

Benzo[*d*][1,3]dioxol-5-ol (104 mg, 0.75 mmol, 1.5 equiv) was added to the reaction vial. The reaction vial was returned to the vial holder of the console and the line cap was attached. A "Mitsunobu" capsule was scanned and placed into the capsule holder.[12] Reaction program "Mitsunobu standard" was selected and initiated by pressing "run" on the touch screen interphase. Upon program completion, the solution in the vial was concentrated and the product purified using the generic HPLC method to afford the title compound (113 mg, 0.26 mmol, 52% yield); $^1$H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 6H), 7.22 – 7.18 (m, 1H), 7.12 – 7.09 (m, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 6.54 (d, *J* = 2.5 Hz, 1H), 6.37 (dd, *J* = 8.5, 2.5 Hz, 1H), 5.92 (s, 2H), 5.61 – 5.56 (m, 1H), 4.94 (s, 2H), 4.39 (d, *J* = 5.9 Hz, 2H), 1.67 – 1.63 (m, 2H), 1.06 – 1.03 (m, 2H); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 173.5, 154.3, 148.4, 142.0, 139.0, 138.3, 137.6, 134.1, 132.5 (2C), 129.4 (2C), 129.0, 127.0, 126.5, 126.4, 108.1, 106.2, 101.3, 98.5, 70.9, 43.9, 30.0, 15.9 (2C); HRMS (ESI) *m/z* for $C_{25}H_{22}ClNO_4$ $[M+H]^+$ calcd. 436.1310, measured 436.1313; IR (ν/cm$^{-1}$, thin film) 3490, 1651, 1485, 1241, 1180, 1099, 1034, 927.

[11] Synple Chem, https://www.synplechem.com/solutions/cartridges#SilylSec, (accessed October 2022).

[12] Synple Chem, https://www.synplechem.com/solutions/cartridges#mitsunobusec, (accessed October 2022).



**(3-(2-chloro-4-fluorophenyl)piperazin-1-yl)(tetrahydro-2*H*-pyran-4-yl)methanone 34**
2-Chloro-4-fluorobenzaldehyde (79 mg, 0.50 mmol, 1.0 equiv) and a stirring bar were added to a reaction vial. The vial was inserted into the vial holder of the console and the line cap was attached to the vial. The "SnAP Piperazine N-Heterocycle formation" capsule was scanned to load the appropriate program and inserted into the capsule holder.[13] After checking the solvents were full and the waste container was not, the program was initiated by pressing "run" on the touch screen interphase. Upon program completion, the solution in the vial was concentrated using a vial adaptor and standard rotary evaporator.

The reaction vial was returned to the vial holder of the console and the line cap was attached. A "Boc deprotection" capsule was scanned and inserted into the capsule holder.[9] The program was initiated by pressing "run" on the touch screen interphase. Upon program completion, the solution in the vial was concentrated using a vial adaptor and standard rotary evaporator.

Tetrahydro-2*H*-pyran-4-carboxylic acid (65 mg, 0.50 mmol, 1.0 equiv), *i*-$Pr_2NEt$ (174 $\mu$L, 1.0 mmol, 2.0 equiv.), anhydrous EtOH (2.0 mL), anhydrous $CH_2Cl_2$ (2.0 mL) and a stirring bar were added to a reaction vial. The vial was inserted into the vial holder of the console and the line cap was attached. An "amide formation" capsule was scanned to load the appropriate program and inserted into the capsule holder.[8] The program was initiated by pressing "run" on the touch screen interphase. Upon program completion, the solution in the vial was concentrated and the product purified using the generic HPLC method to afford the title compound (31 mg, 0.10 mmol, 19% yield). NMR spectroscopy revealed the presence of two partially resolved conformer populations consistent with previous reports on acylated piperazines.[14] This was confirmed using temperature-dependant $^1$H NMR spectroscopy. NMR characterisation was performed at 328.15 K. $^1$H NMR (600 MHz, $CDCl_3$, 328.15 K) δ 7.80 – 7.55 (m, 1H), 7.22 – 7.10 (m, 1H), 7.09 – 6.97 (m, 1H), 4.82 – 4.54 (m, 1H), 4.18 – 4.10 (m, 1H), 4.09 – 3.76 (m, 3H), 3.52 – 3.40 (m, 2H), 3.19 (m, 1H), 2.97 – 2.90 (m, 1H), 2.88 – 2.74 (m, 2H), 2.08 – 1.89 (m, 2H), 1.89 – 1.64 (m, 2H), 1.63 – 1.47 (m, 2H); $^{13}$C NMR (151 MHz, $CDCl_3$, 328.15 K) δ 172.9, 161.9 (d, $J$ = 250.3 Hz), 134.3, 133.3, 129.2, 117.0 (d, $J$ = 24.8 Hz), 114.5, 67.2 (2C), 56.8, 51.4, 46.1, 42.0, 37.7, 29.6, 29.0; HRMS (ESI) *m/z* for $C_{16}H_{20}ClFN_2O_2$ $[M+H]^+$ calcd. 327.1270, measured 327.1264; IR (ν/cm$^{-1}$, thin film) 3298, 2954, 2844, 1634, 1444, 1132, 822.

[13] Synple Chem, https://www.synplechem.com/solutions/cartridges#rclasses, (accessed October 2022).

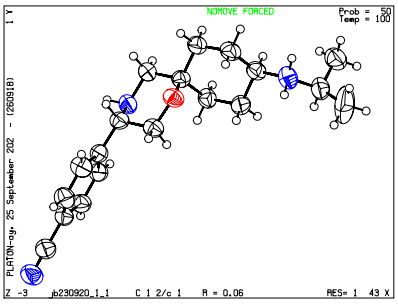
[14] R. Wodtke, J. Steinberg, M. Köckerling, R. Löser and C. Mamat, *RSC Adv.*, 2018, **8**, 40921.

## Relative Stereochemical Assignments

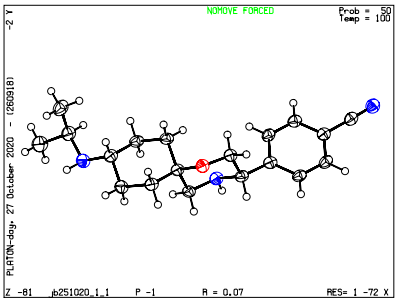
### X-Ray Crystallography

### Crystallization of 23

Compound **23 DiaA** was crystalized using slow evaporation in EtOAc with 2 equiv of TFA. (CCDC 2064033)

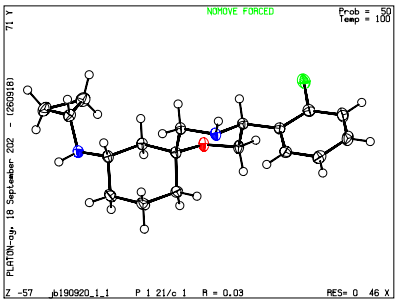



Compound **23 DiaB** was crystalized, as the freebase, using slow evaporation in EtOAc with 2 equiv of TFA. (CCDC 2064034)

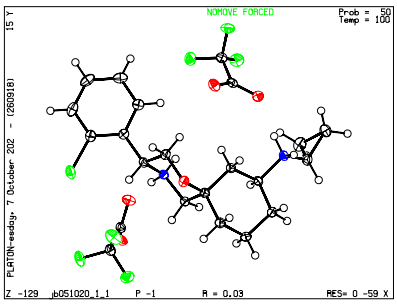



### Crystallization of 27

Compound **27 DiaA** was crystalized, as the freebase, using slow evaporation in EtOAc. (CCDC 2169258)

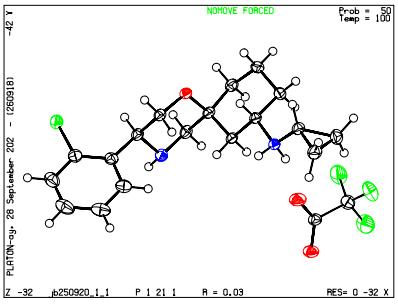


Compound **27 DiaB** was crystalized using slow evaporation in EtOAc with 2 equiv of TFA. (CCDC 2169260)



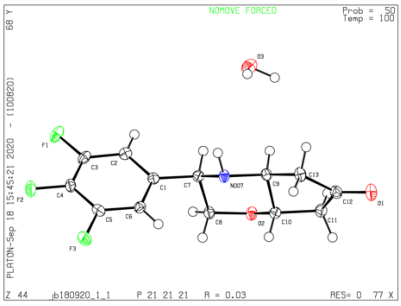

Compound **27 DiaC** formed an oil under slow evaporation in EtOAc, both as the free base and with 2 eq. of TFA.

Compound **27 DiaD** was crystalized using slow evaporation in EtOAc with 2 equiv of TFA. (CCDC 2169267)



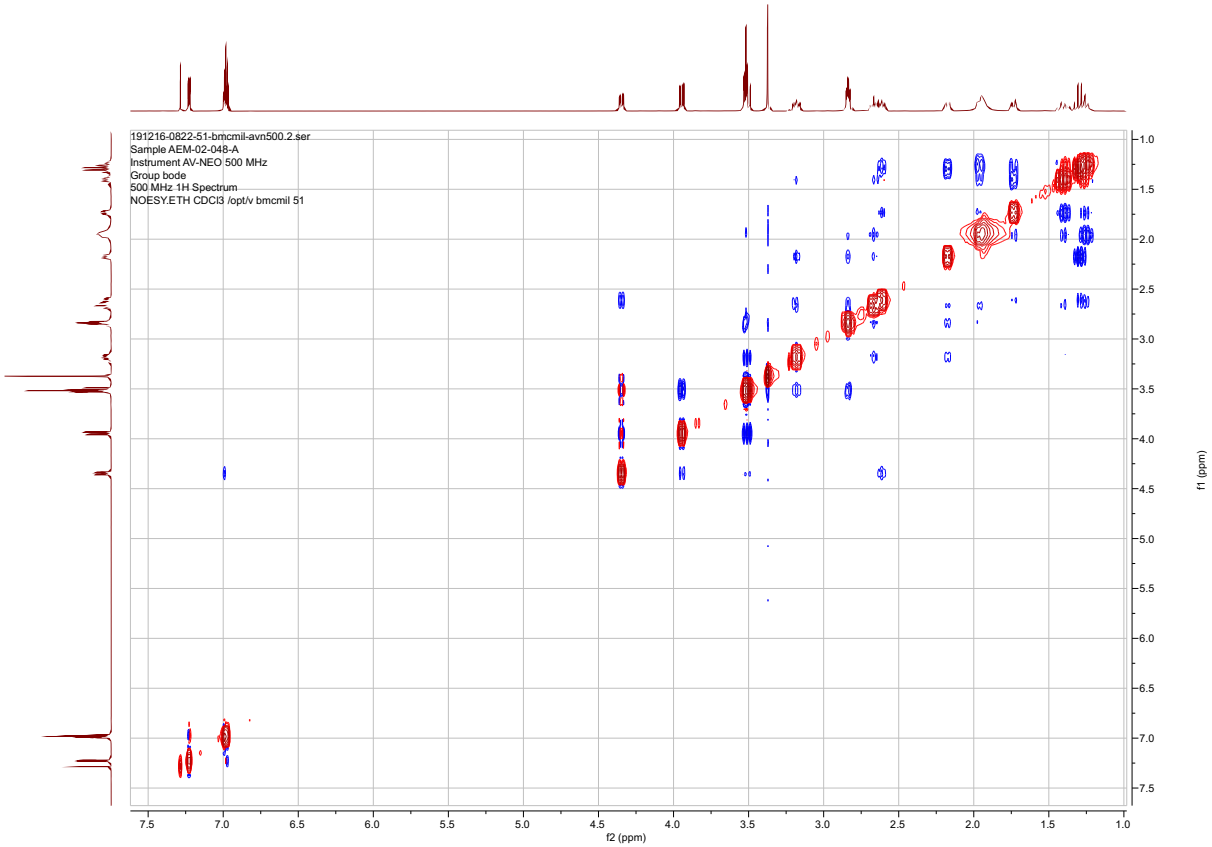

**Crystallization of Compound 31**

Compound 31 was crystalized using slow evaporation in EtOAc. (CCDC 2169554)

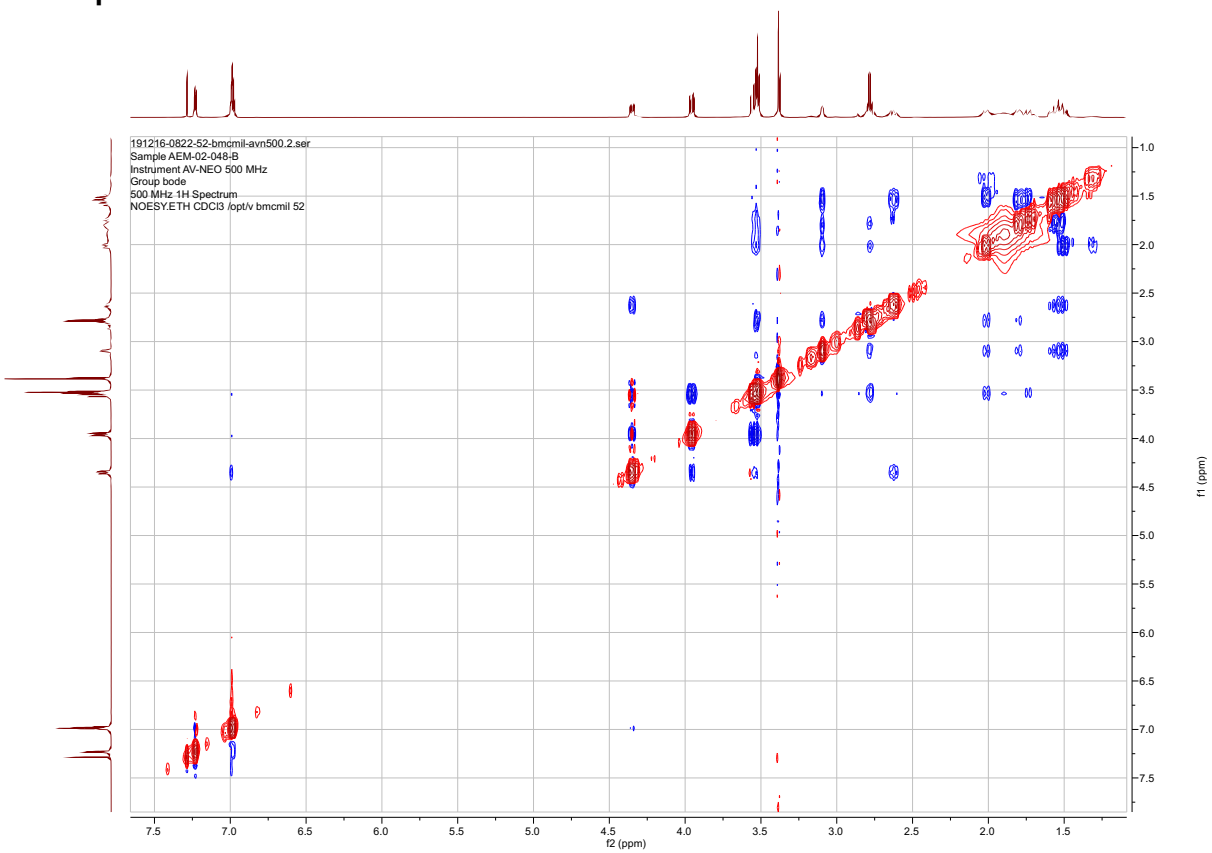


## NOE NMR Spectra

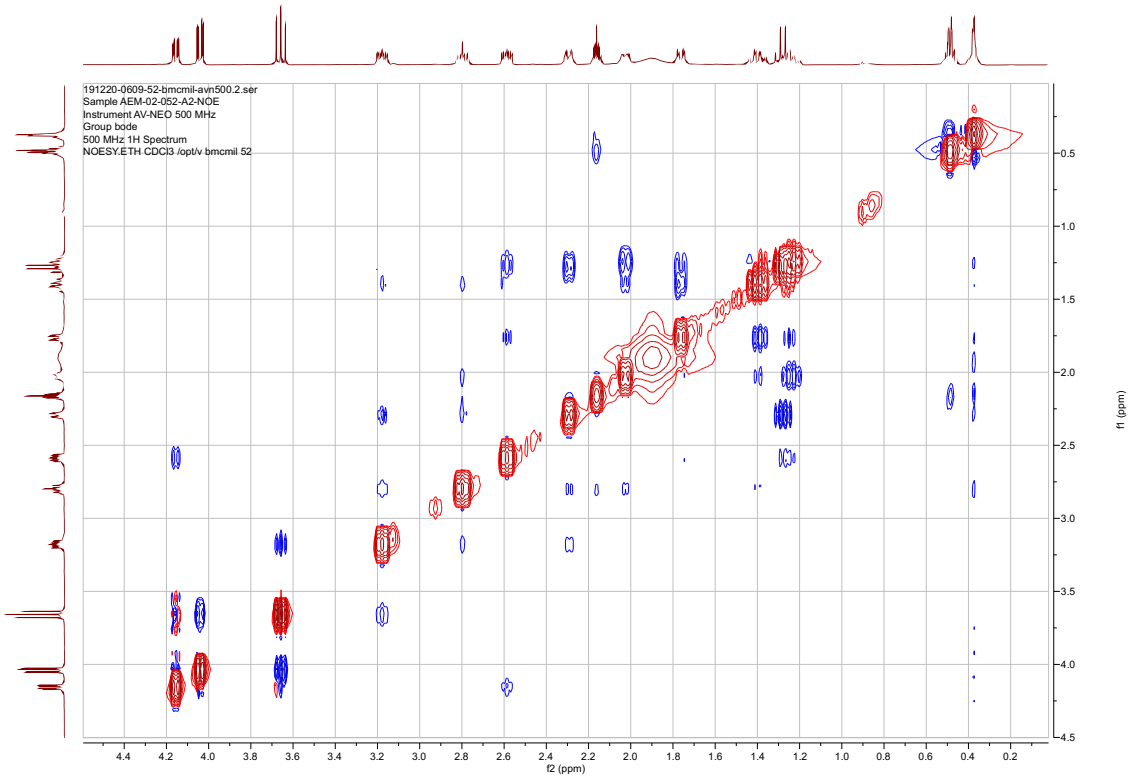
### NOE Spectrum of 5 DiaA



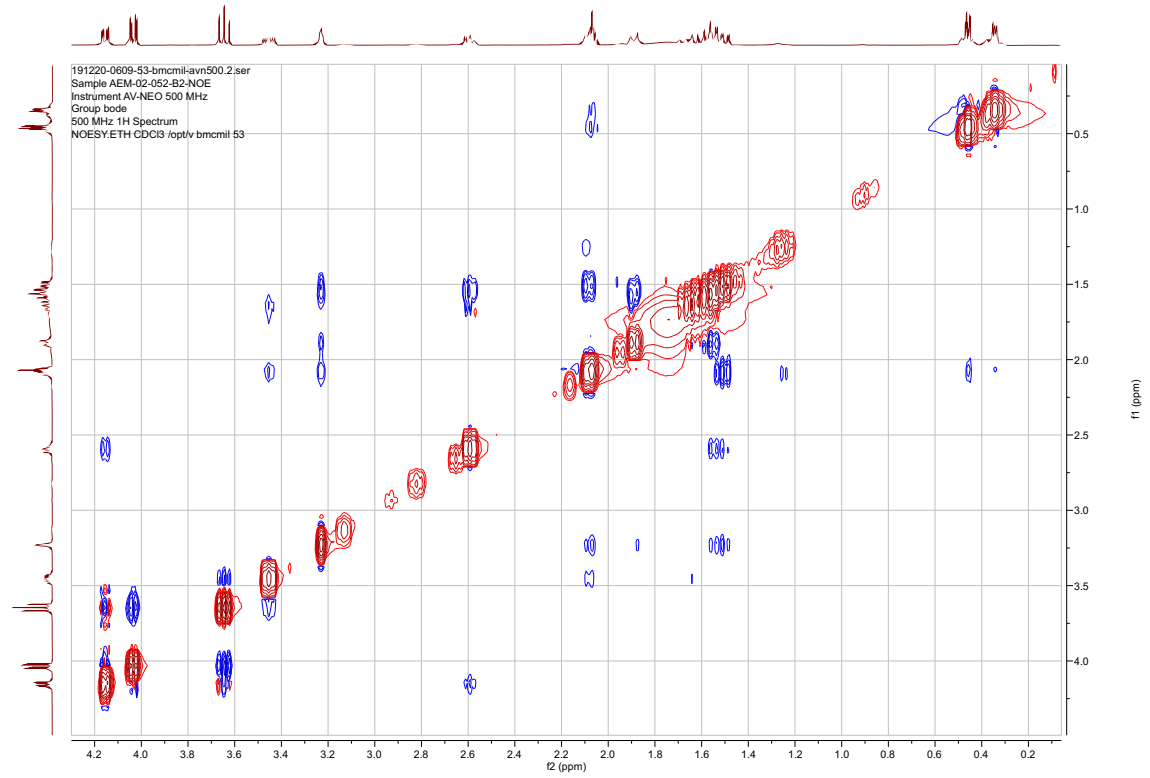

### NOE Spectrum of 5 DiaB



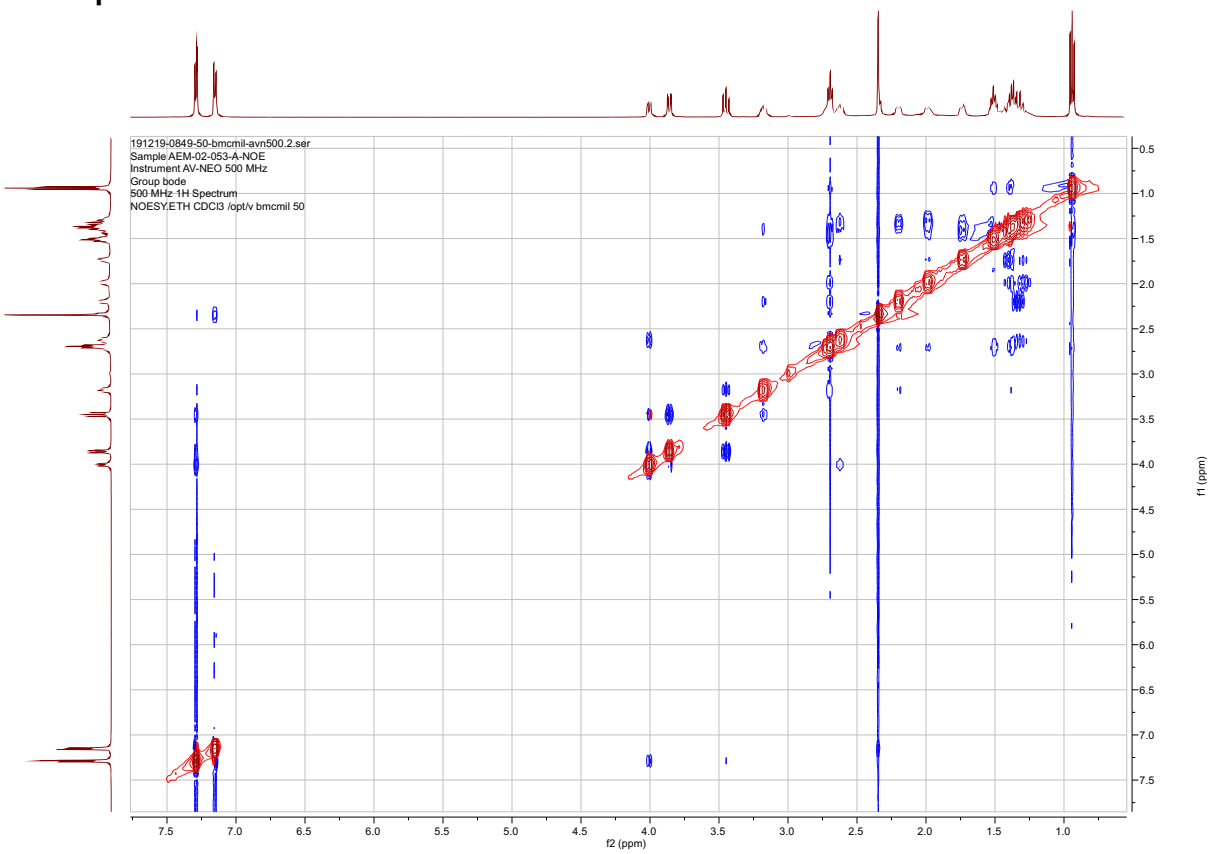
## NOE Spectrum of 6 DiaA



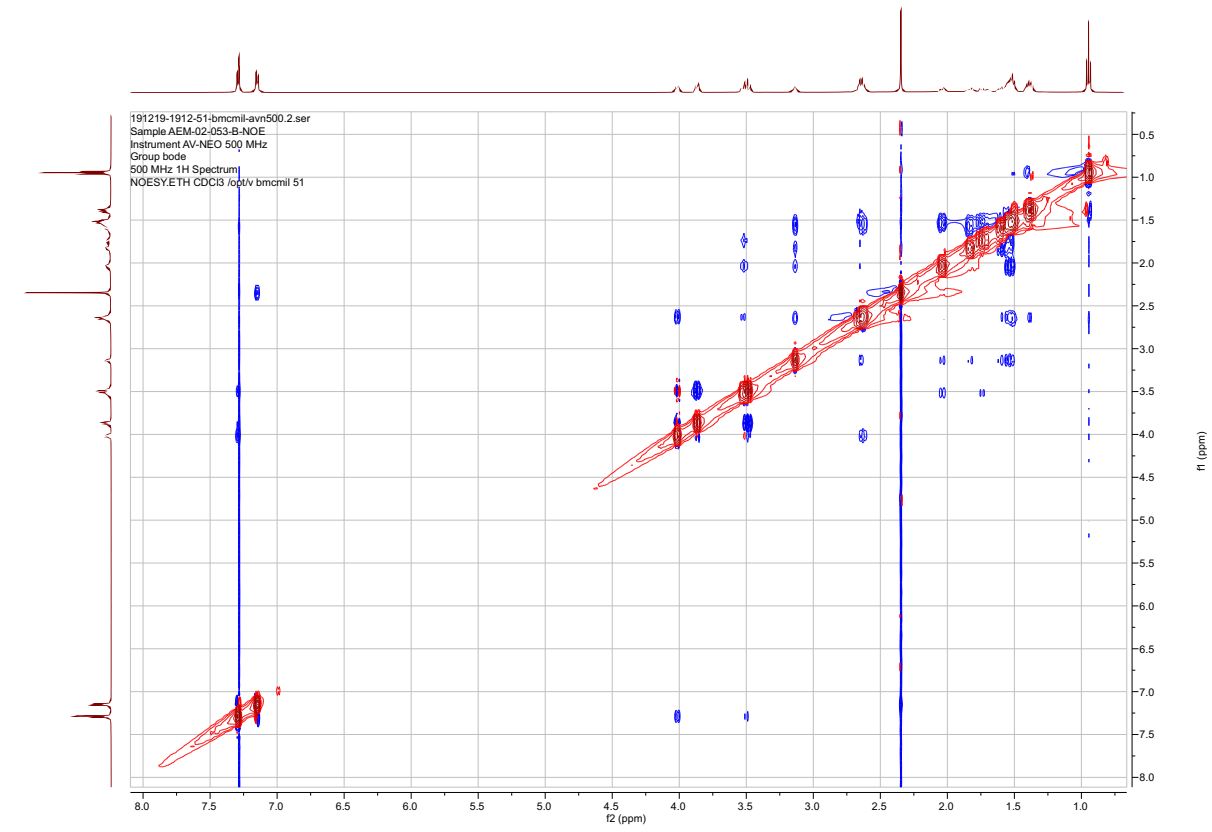

## NOE Spectrum of 6 DiaB



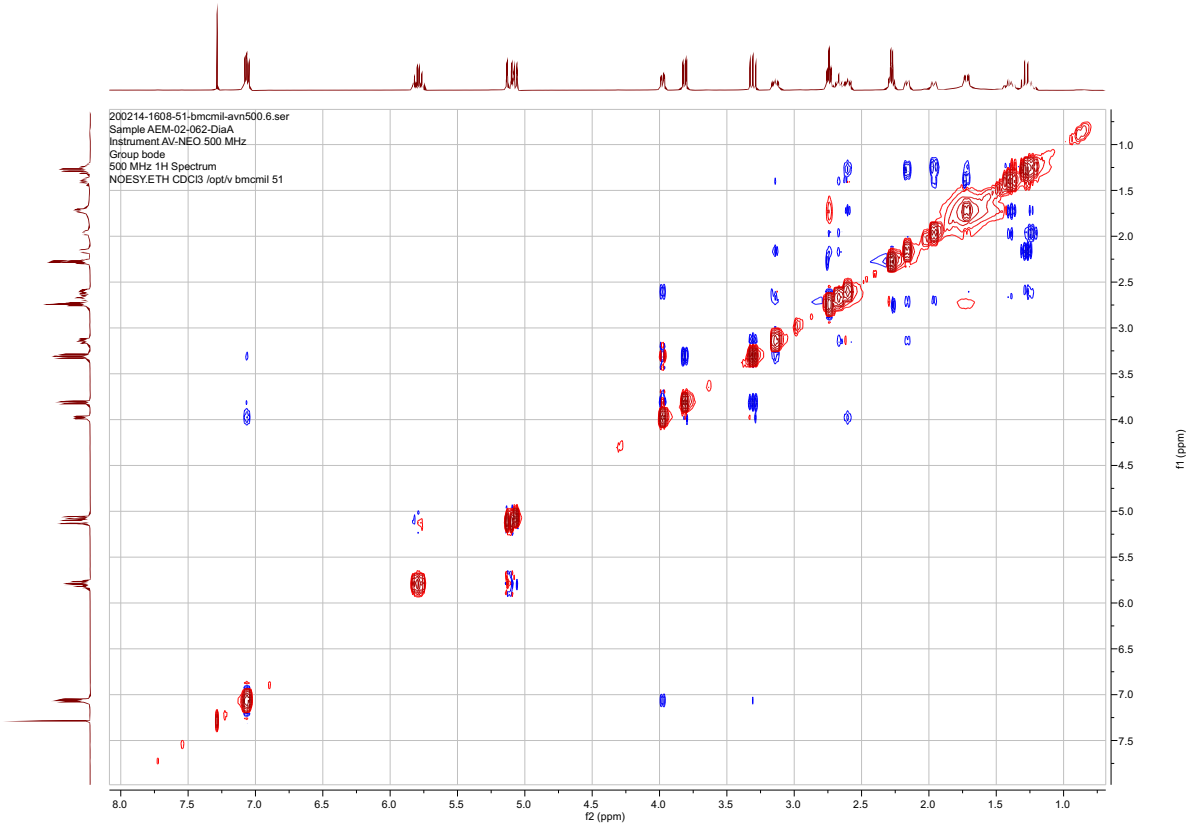
## NOE Spectrum of 7 DiaA



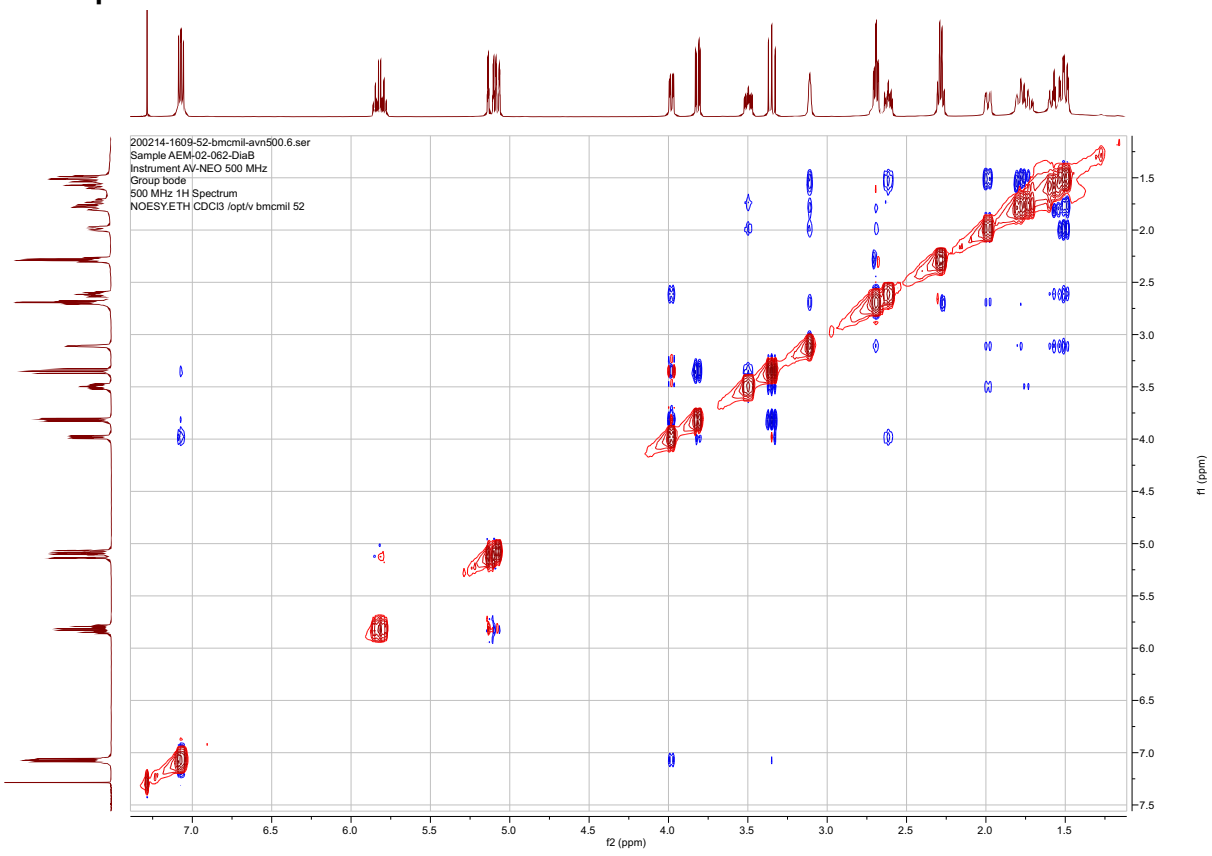

## NOE Spectrum of 7 DiaB



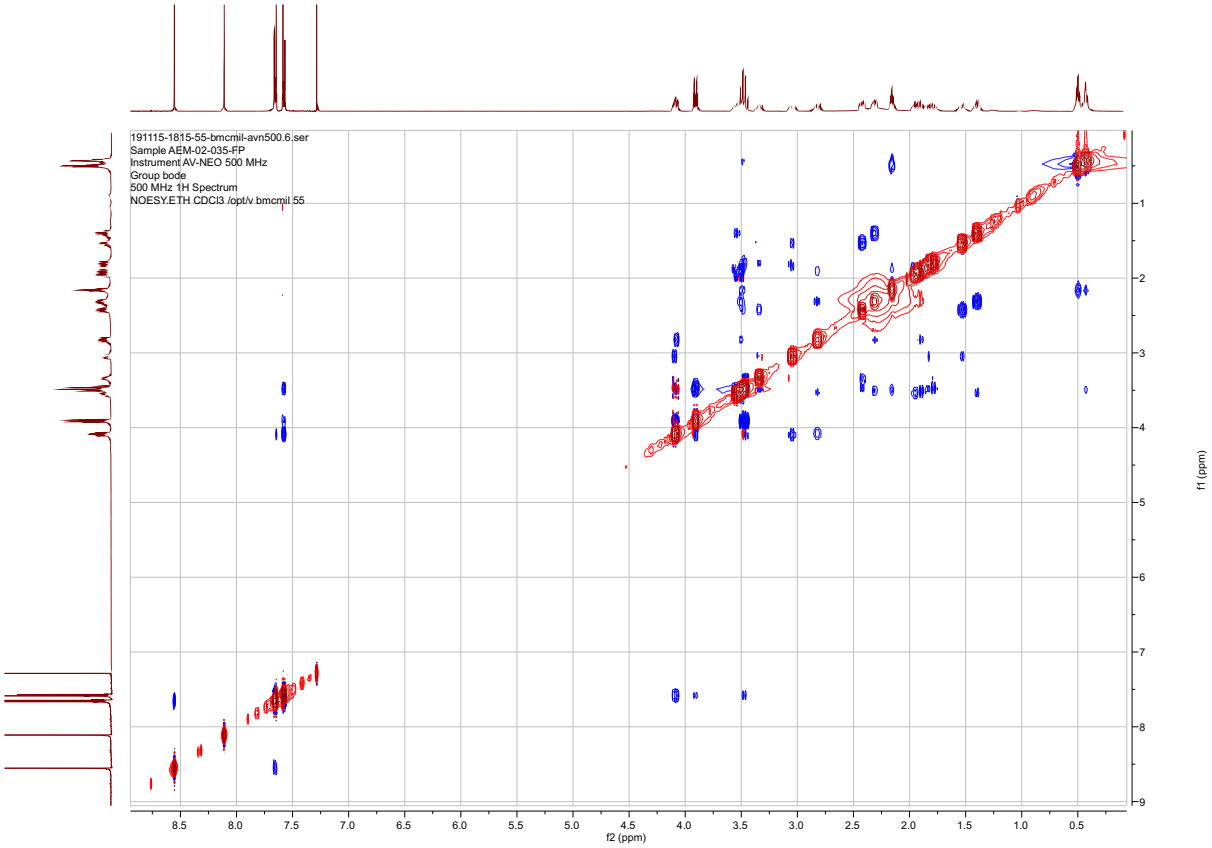
## NOE Spectrum of 8 DiaA




## NOE Spectrum of 8 DiaB

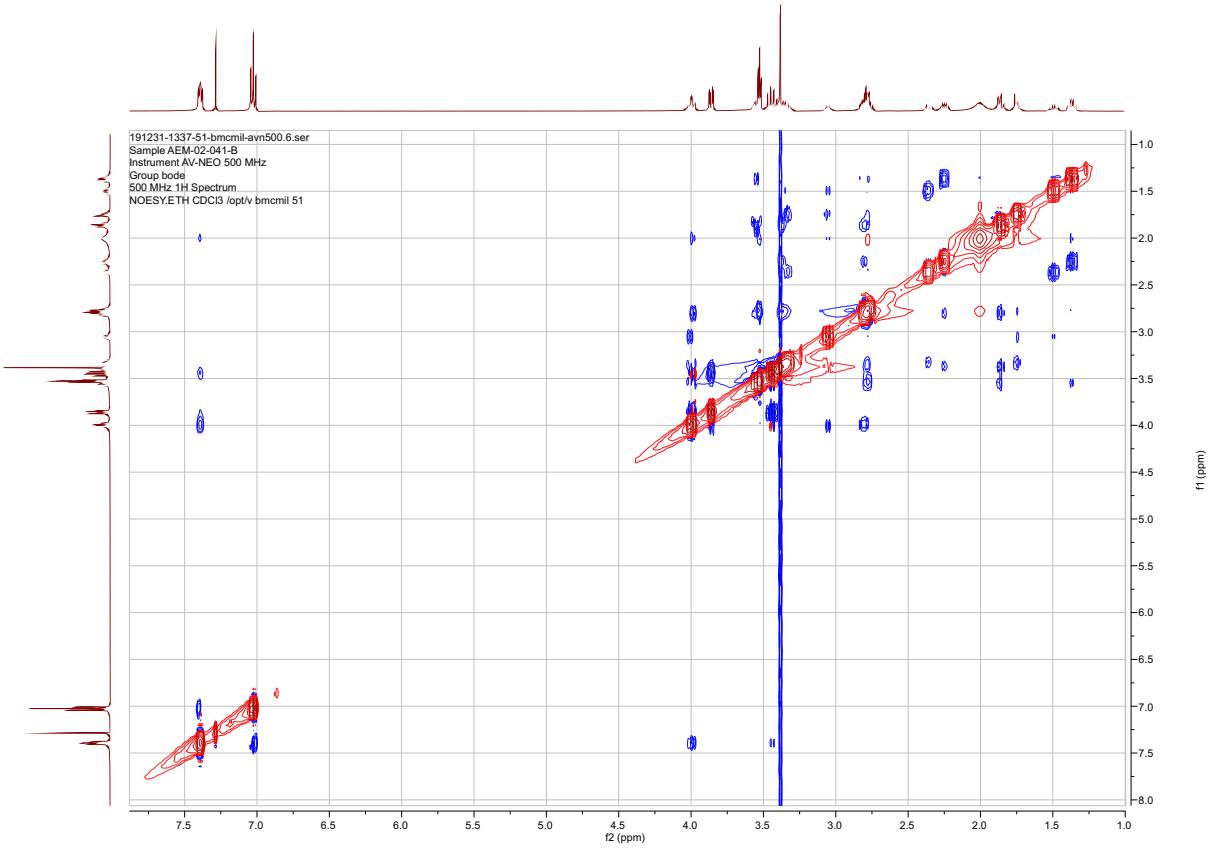


## NOE Spectrum of 9

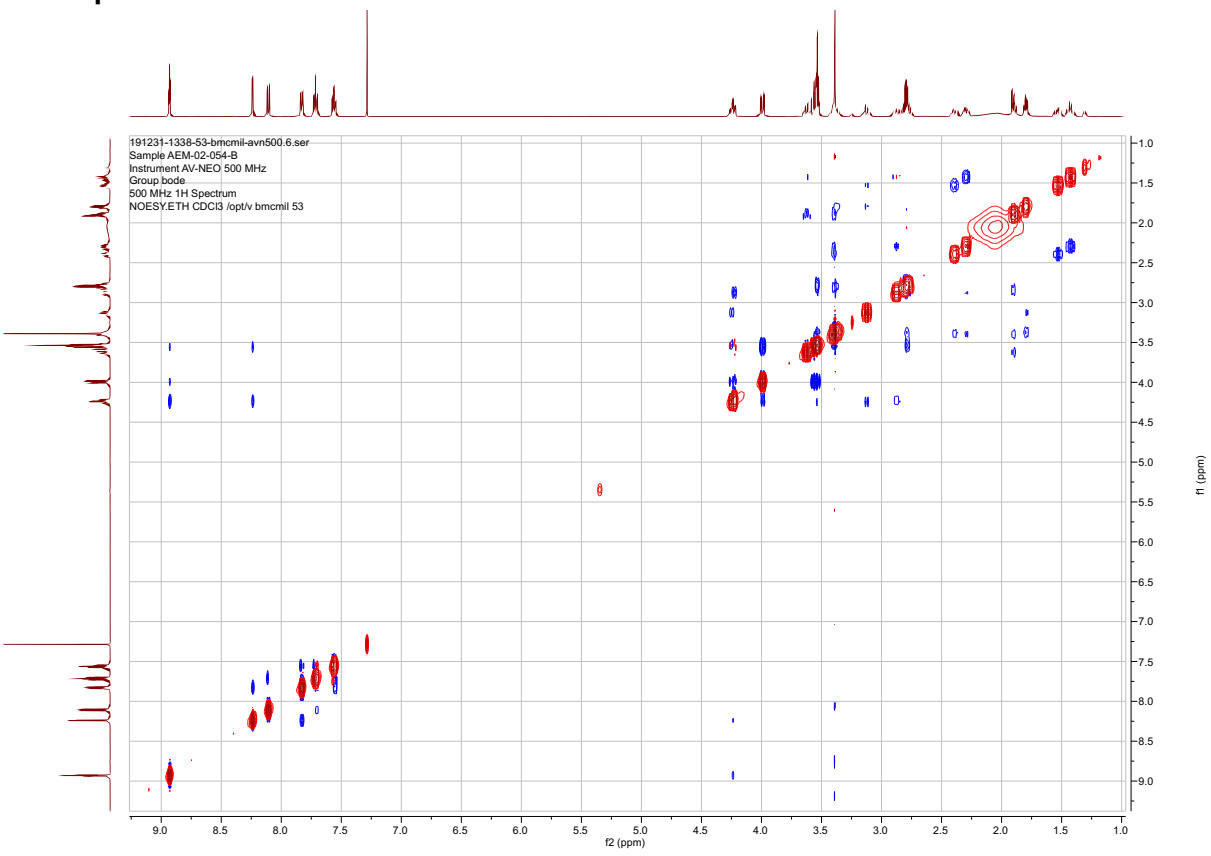



## NOE Spectrum of 10

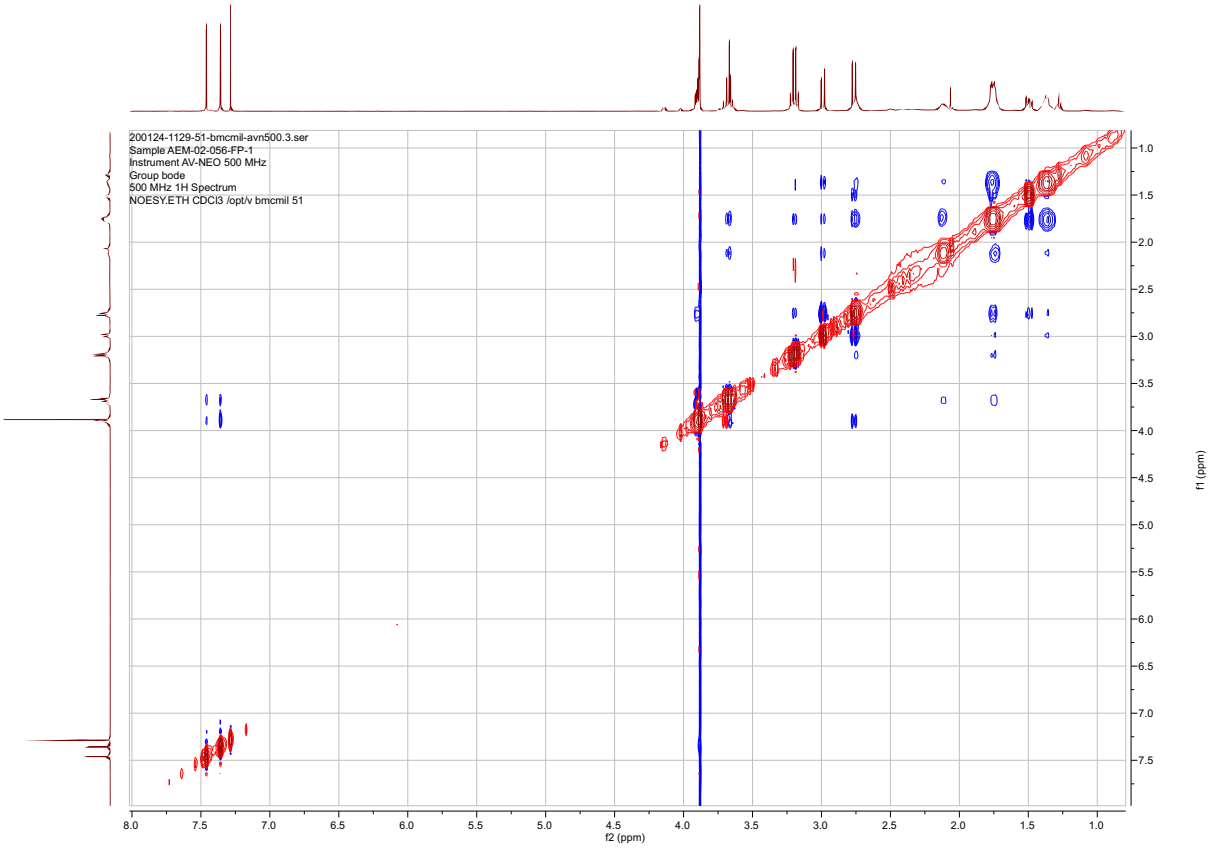
## NOE Spectrum of 11



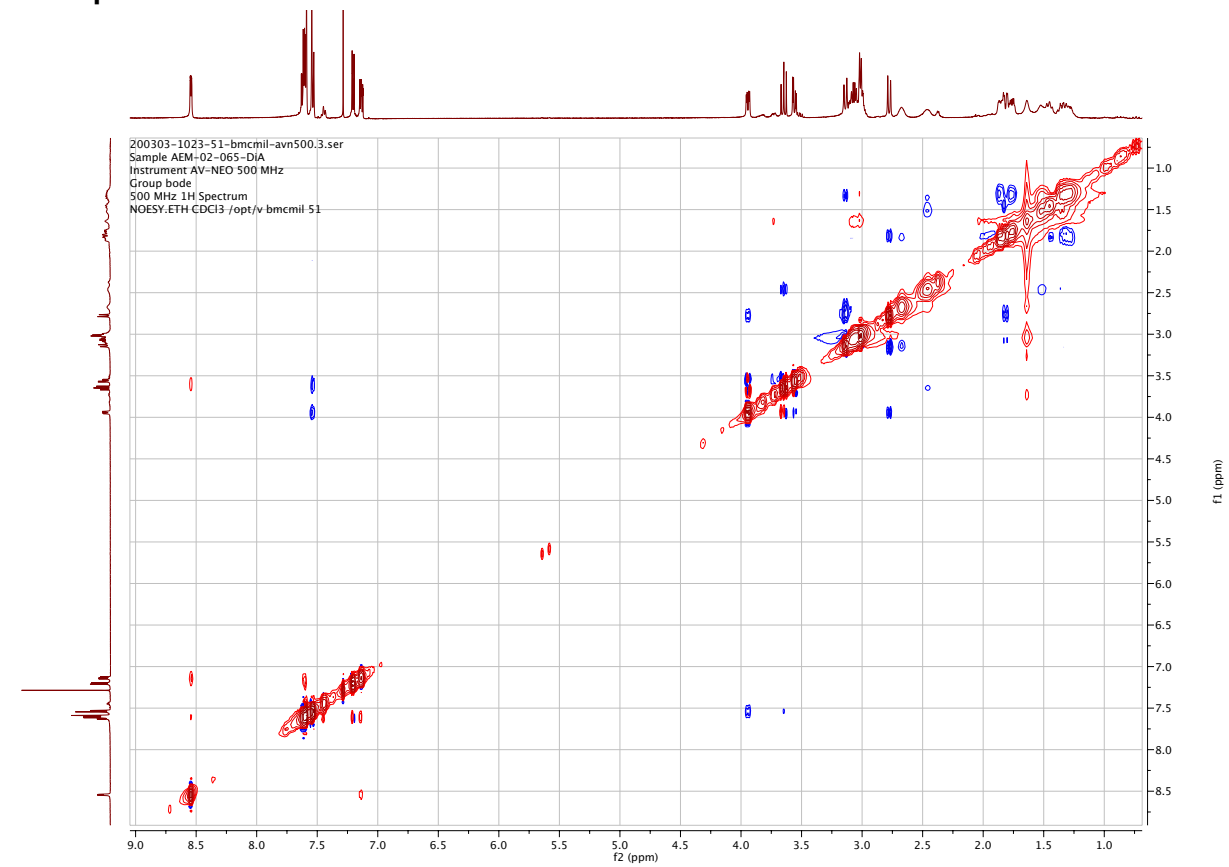

## NOE Spectrum of 12



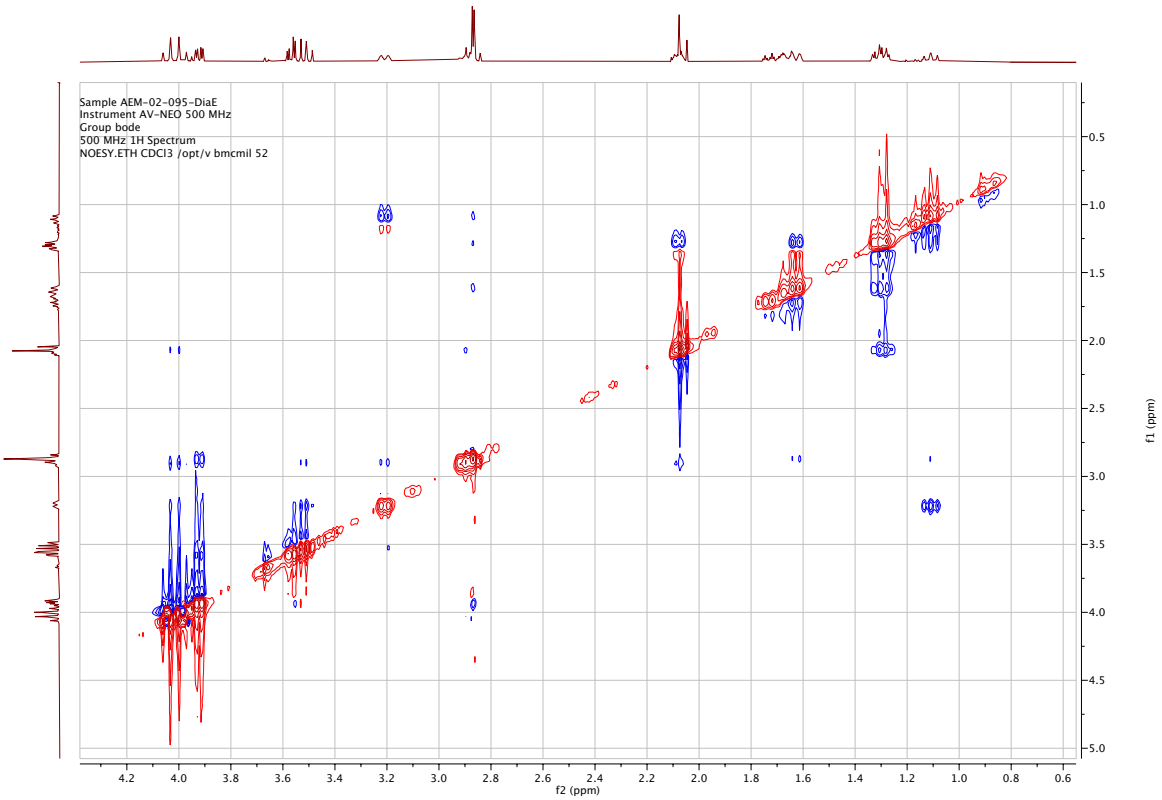
## NOE of Spectrum 24



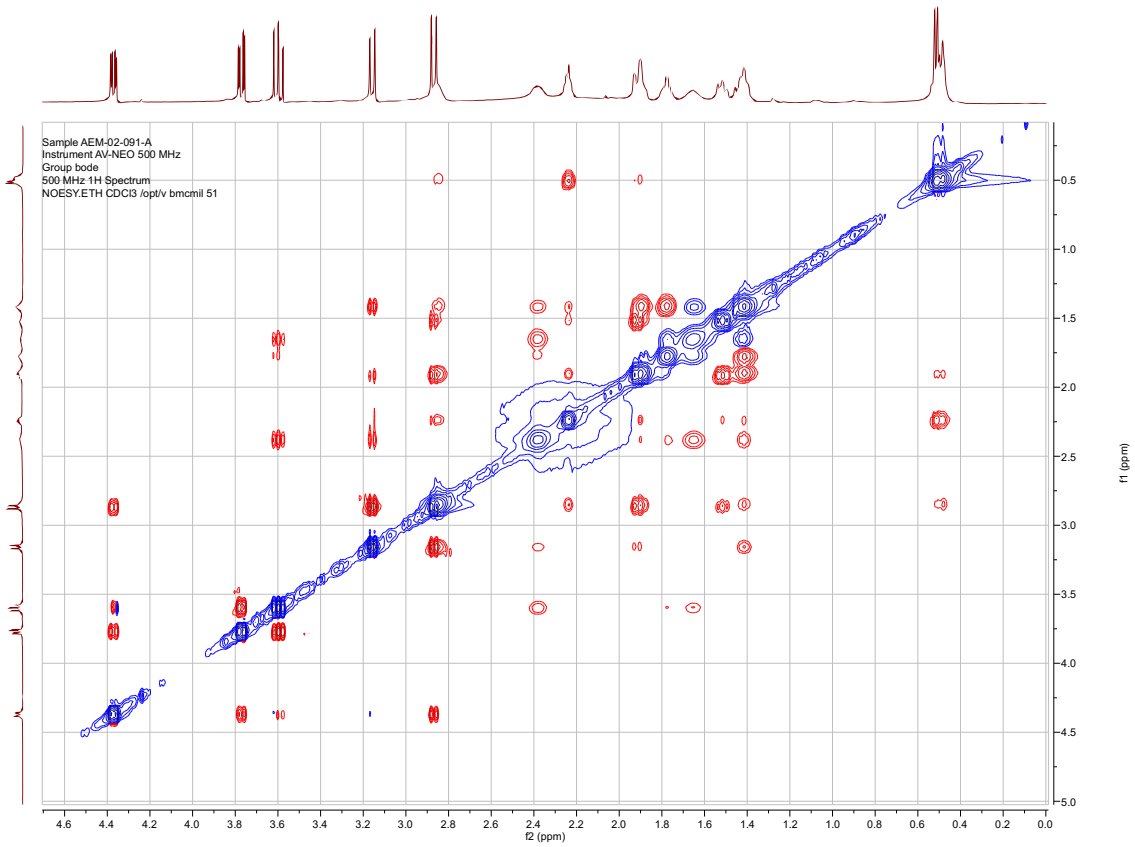

## NOE Spectrum of 25



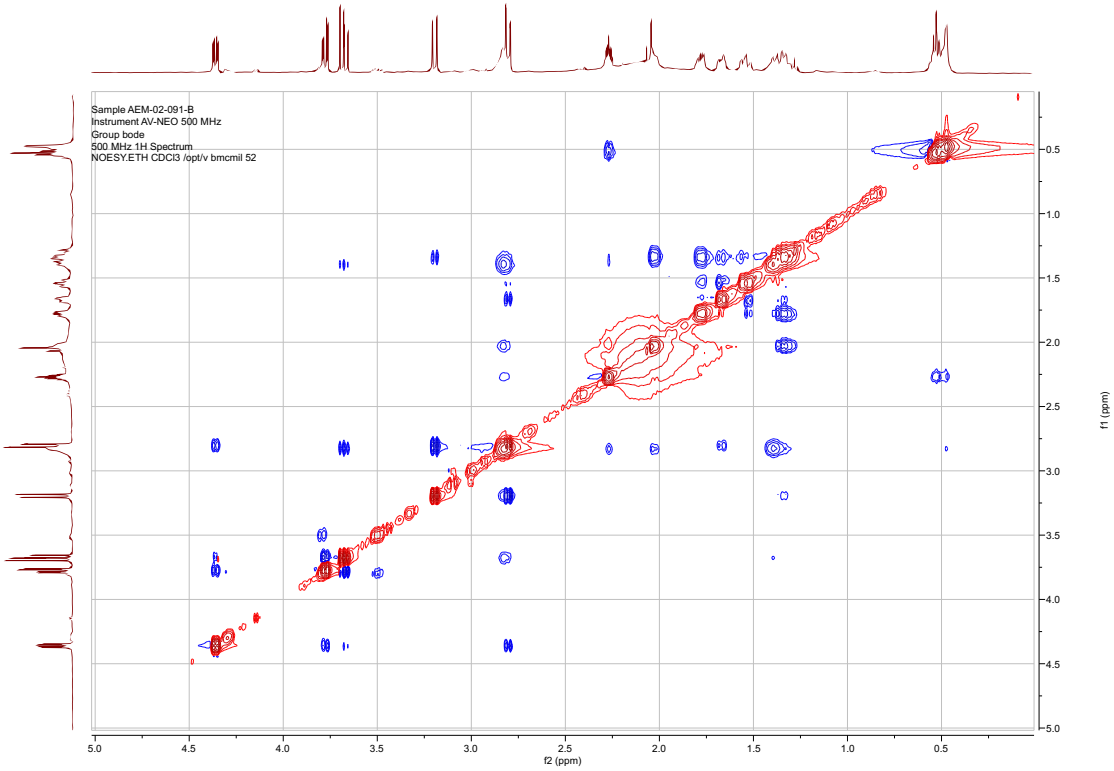
## NOE Spectrum of 26



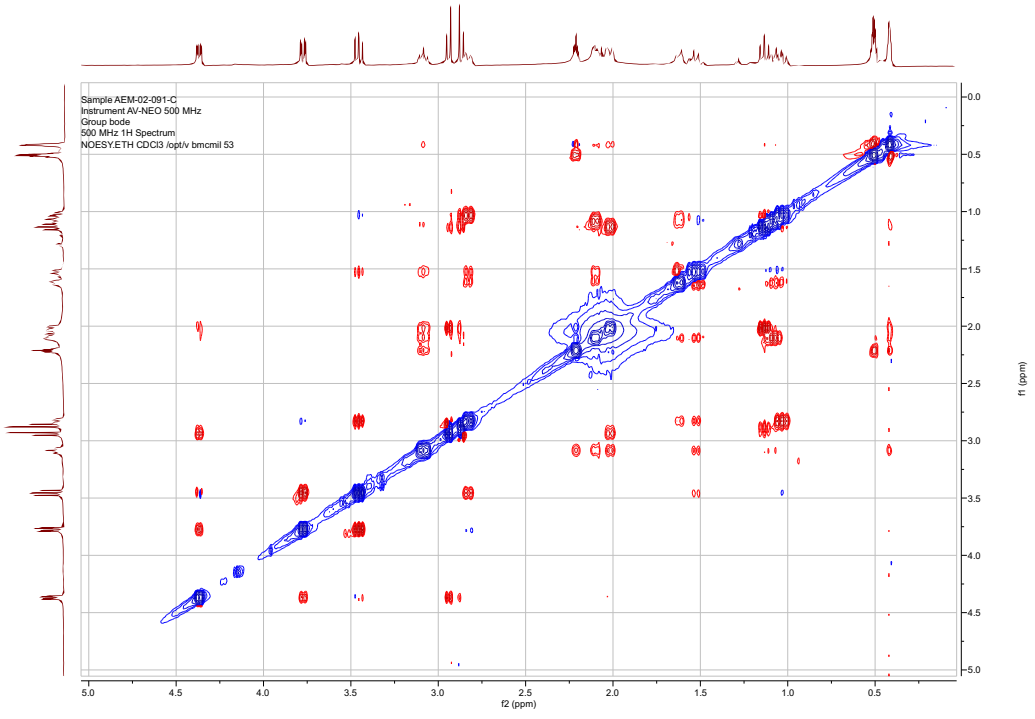

## NOE Spectrum of 27 DiaA



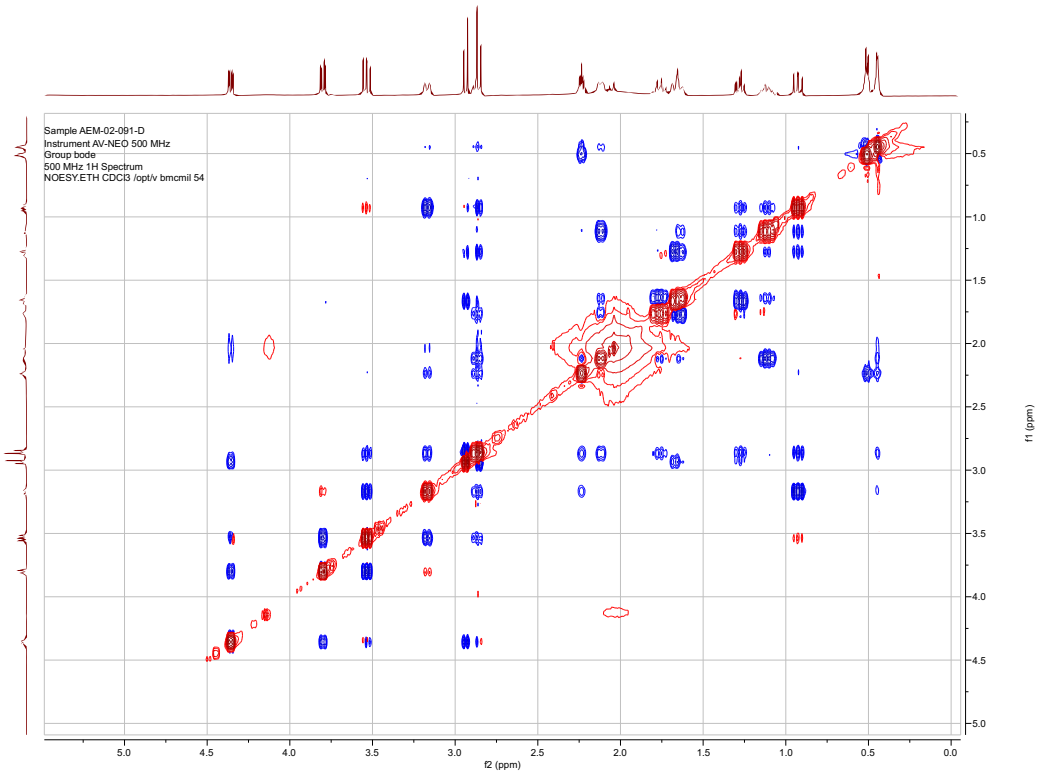
## NOE Spectrum of 27 DiaB




## NOE Spectrum of 27 DiaC



## NOE Spectrum of 27 DiaD



**Computational Procedures**

Conformational analysis was performed using the MacroModel package.[15] All molecular mechanics calculations were carried out using the OPLS4 force field.[16] Geometry optimizations and NMR predictions were performed using the Jaguar package.[17,18] Conformers were subjected to density functional theory (DFT) geometry optimizations at the B3LYP/6-311G** level of theory with an "ultrafine" integration grid using the polarizable continuum model (PCM) with chloroform as a solvent.

**$^{13}$C NMR Predictions**

Conformer searching was performed using torsional sampling.[19] Selected conformers were subject to DFT geometry optimization and NMR prediction as described above. The resulting NMR chemical shifts were Boltzmann weighted and used for comparison to experimental values using corrected mean average error (CMAE).

**$^{1}$H NMR Predictions**

The lowest energy conformer was found using force field minimization and subject to DFT geometry optimization and NMR prediction as described above. The predicted chemical shifts were directly compared to experimental values without further manipulation.

[15] Schrödinger Release 2022-3: MacroModel, Schrödinger, LLC, New York, NY, 2021.

[16] C. Lu, C. Wu, D. Ghoreishi, W. Chen, L. Wang, W. Damm, G. A. Ross, M. K. Dahlgren, E. Russell, C. D. Von Bargen, R. Abel, R. A. Friesner, E. D. Harder, *J. Chem. Theory Comput.*, 2021, **17**, 4291.

[17] Schrödinger Release 2022-3: Jaguar, Schrödinger, LLC, New York, NY, 2021.

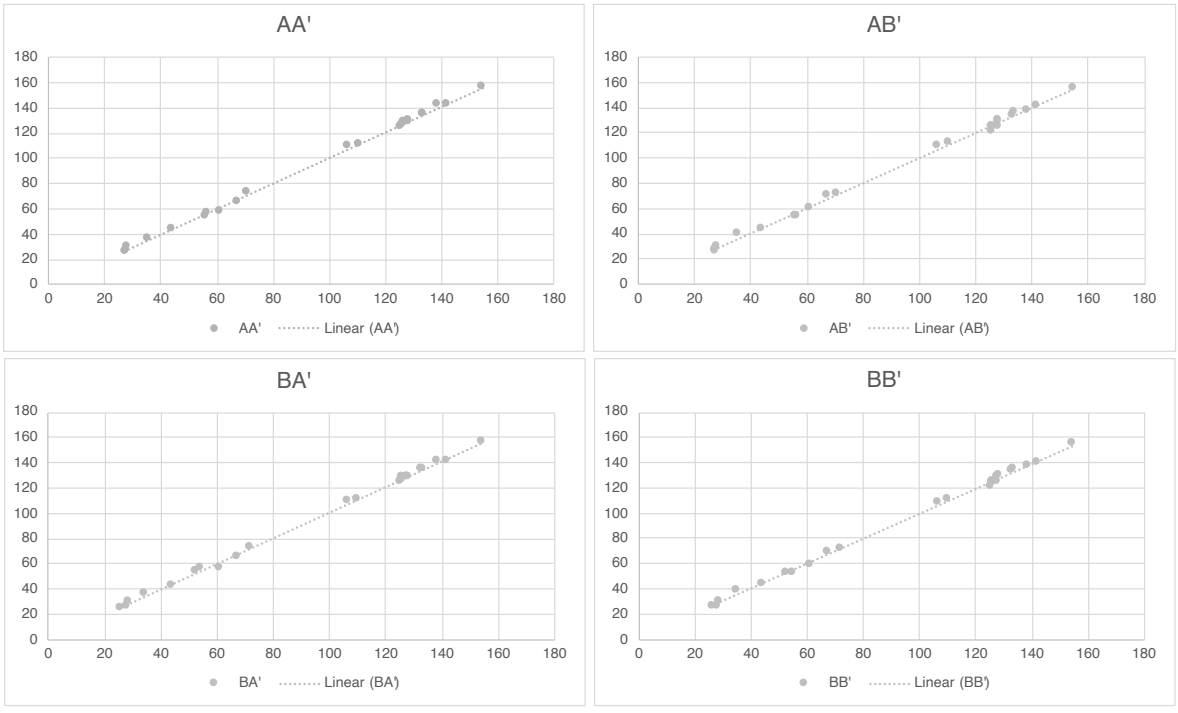
[18] A. D. Bochevarov, E. Harder, T. F. Hughes, J. R. Greenwood, D. A. Braden, D. M. Philipp, D. Rinaldo, M. D. Halls, J. Zhang, R. A. Friesner, *Int. J. Quantum Chem.*, 2013, **113**, 2110.

[19] P. H. Willoughby, M. J. Jansma, T. R. Hoye, *Nature Protocols*, 2014, **9**, 643.

## Compound 15 $^{13}$C NMR Prediction

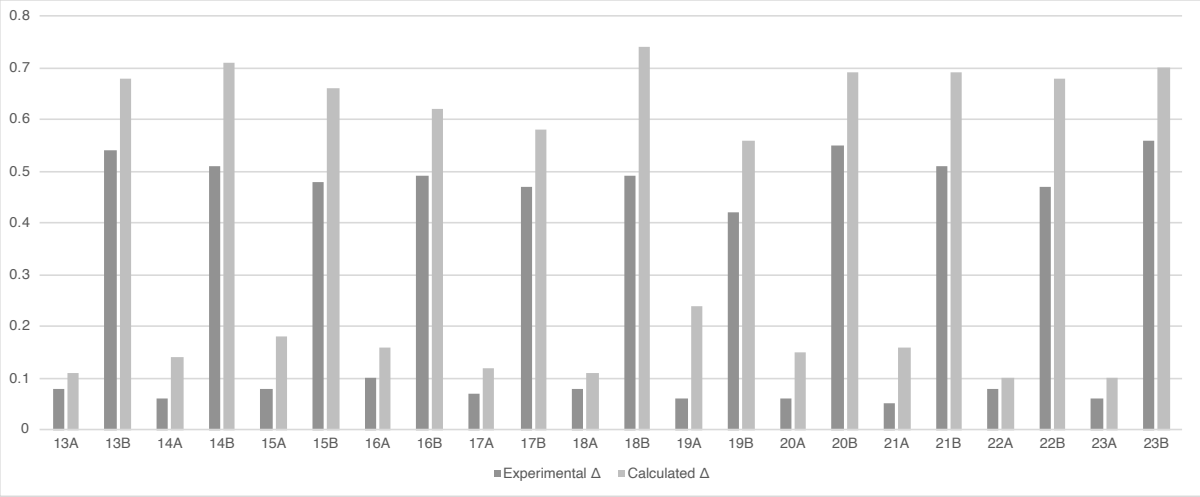
| Experimental 13C NMR (ppm) | | Predicted 13C NMR (ppm) | |
|---|---|---|---|
| **DiaA** | **DiaB** | **A'** | **B'** |
| 154.36 | 154.61 | 156.44 | 155.25 |
| 141.69 | 141.79 | 142.05 | 140.71 |
| 138.3 | 138.33 | 141.91 | 136.98 |
| 133.41 | 133.41 | 134.63 | 135.29 |
| 133.06 | 133.06 | 134.51 | 133.35 |
| 128.05 | 128.04 | 129.22 | 129.36 |
| 127.83 | 127.84 | 128.74 | 128.61 |
| 127.67 | 127.67 | 128.47 | 124.82 |
| 126.11 | 126.11 | 128.18 | 124.75 |
| 125.8 | 125.8 | 126.32 | 124.51 |
| 125.66 | 125.73 | 126.27 | 124.12 |
| 125.46 | 125.47 | 124.67 | 120.96 |
| 110.11 | 110.15 | 110.52 | 111.43 |
| 106.54 | 106.73 | 109.75 | 108.73 |
| 70.33 | 71.9 | 73.04 | 71.66 |
| 66.94 | 67.5 | 65.3 | 69.45 |
| 60.92 | 61.07 | 57.15 | 59.59 |
| 56.11 | 54.61 | 56.76 | 53.22 |
| 55.86 | 52.71 | 53.45 | 52.96 |
| 43.45 | 43.84 | 42.88 | 43.33 |
| 35.23 | 34.69 | 36.23 | 39.4 |
| 27.71 | 28.58 | 30.18 | 29.92 |
| 27.47 | 28.2 | 26.27 | 26.57 |
| 26.97 | 26.04 | 25.52 | 26.03 |

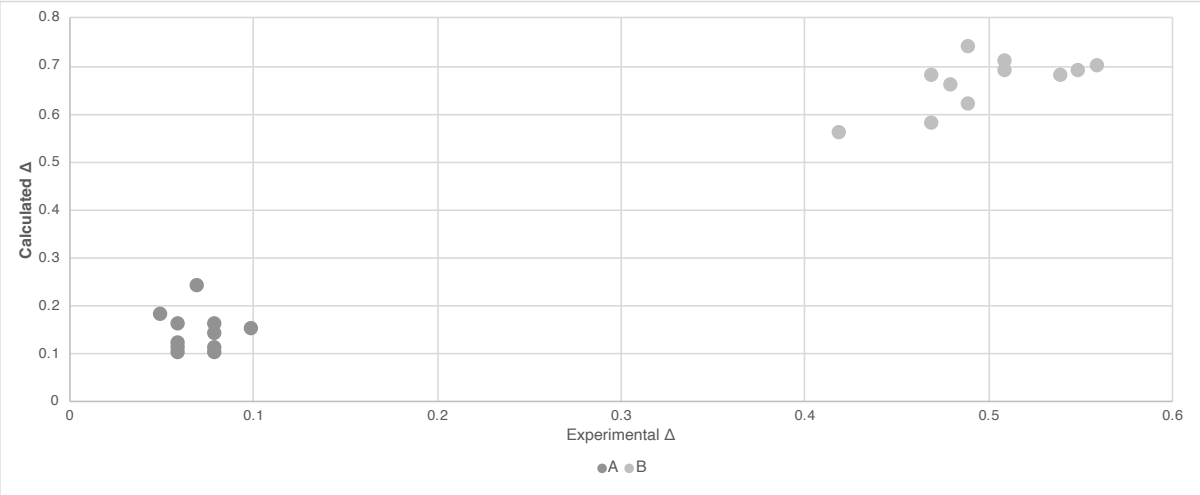
| **Assignment** | AA' | AB' | BA' | BB' |
|---|---|---|---|---|
| **CMAE** | 1.39 | 1.73 | 1.90 | 1.66 |



## Compounds 13-23 $^{1}$H NMR Prediction

| Compound | Experimental Proton 1 | Experimental Proton 2 | Experimental Δ | Calculated Proton 1 | Calculated Proton 2 | Calculated Δ |
|---|---|---|---|---|---|---|
| 13A | 2.85 | 2.77 | 0.08 | 2.93 | 2.82 | 0.11 |
| 13B | 3.25 | 2.71 | 0.54 | 3.41 | 2.73 | 0.68 |
| 14A | 2.86 | 2.8 | 0.06 | 3.03 | 2.89 | 0.14 |
| 14B | 3.25 | 2.74 | 0.51 | 3.33 | 2.62 | 0.71 |
| 15A | 2.95 | 2.87 | 0.08 | 2.91 | 2.73 | 0.18 |
| 15B | 3.29 | 2.81 | 0.48 | 3.51 | 2.85 | 0.66 |
| 16A | 2.9 | 2.8 | 0.1 | 3.03 | 2.87 | 0.16 |
| 16B | 3.26 | 2.77 | 0.49 | 3.48 | 2.86 | 0.62 |
| 17A | 2.96 | 2.89 | 0.07 | 2.93 | 2.81 | 0.12 |
| 17B | 3.31 | 2.84 | 0.47 | 3.58 | 3 | 0.58 |
| 18A | 2.85 | 2.77 | 0.08 | 2.96 | 2.85 | 0.11 |
| 18B | 3.22 | 2.73 | 0.49 | 3.48 | 2.74 | 0.74 |
| 19A | 2.82 | 2.76 | 0.06 | 2.95 | 2.71 | 0.24 |
| 19B | 3.15 | 2.73 | 0.42 | 3.34 | 2.78 | 0.56 |
| 20A | 2.86 | 2.8 | 0.06 | 2.96 | 2.81 | 0.15 |
| 20B | 3.26 | 2.71 | 0.55 | 3.47 | 2.78 | 0.69 |
| 21A | 2.85 | 2.8 | 0.05 | 2.99 | 2.83 | 0.16 |
| 21B | 3.22 | 2.71 | 0.51 | 3.48 | 2.79 | 0.69 |
| 22A | 2.87 | 2.79 | 0.08 | 2.94 | 2.84 | 0.1 |
| 22B | 3.21 | 2.74 | 0.47 | 3.44 | 2.76 | 0.68 |
| 23A | 2.87 | 2.81 | 0.06 | 2.94 | 2.84 | 0.1 |
| 23B | 3.27 | 2.71 | 0.56 | 3.46 | 2.76 | 0.7 |



## Workflow comparisons

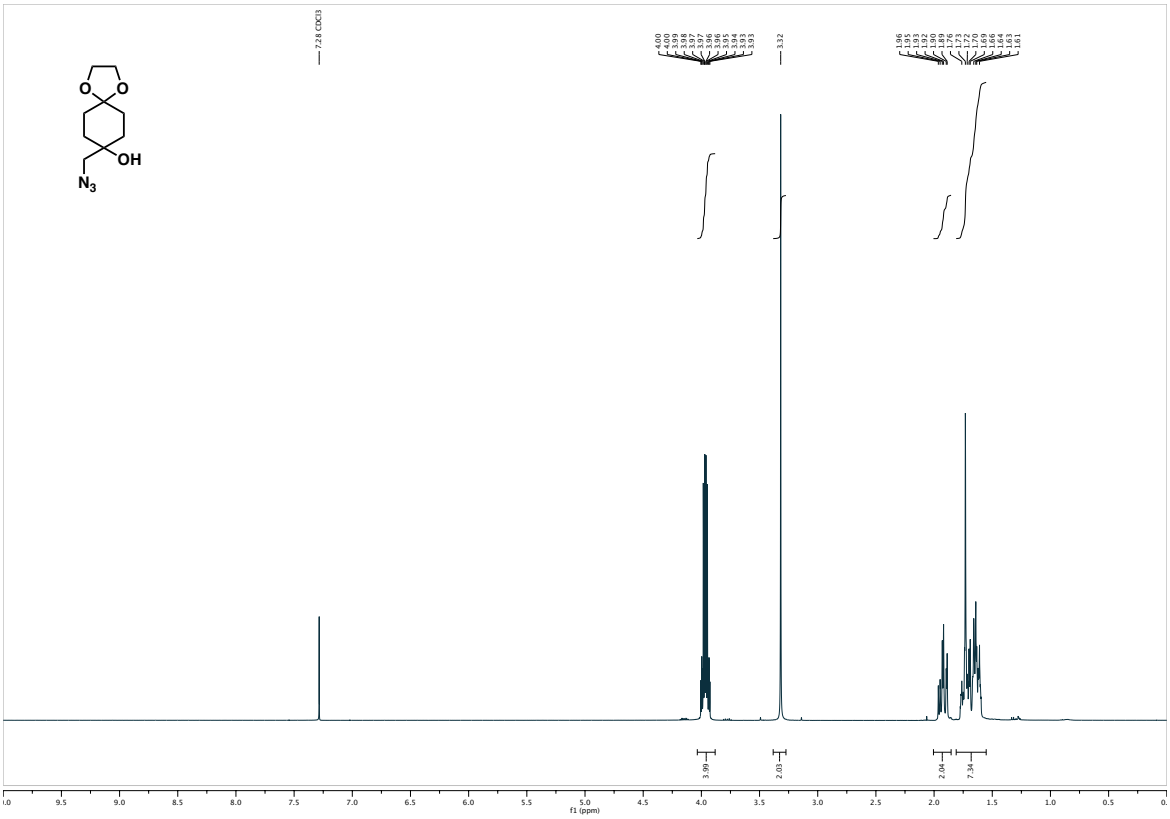
| Standard Autoamted Workflow | | | |
|---|---|---|---|
| Operation | Time min (h) | Time max (h) | User Involvment (yes/no) |
| Weigh out starting material | 0.1 | | Yes |
| Insert capsule and start reaction | 0.05 | | Yes |
| Automated SnAP and Ketone deprotection | 15.5 | 22.5 | No |
| Concentrate ketone | 0.3 | | Yes |
| Add amine, insert capsule and start reductive amination | 0.15 | | Yes |
| Automated Reductive Amination | 3 | 12 | No |
| Dry product | 0.3 | | No |
| Optional add IS and crude NMR | 0 | 0.5 | Yes |
| Preparative HPLC | 1 | | No |
| Optional freebasing | 0 | 0.5 | Yes |
| Dry Product | 1 | | No |
| Characterise Product | 1 | | No |
| Total hours | 22.4 | 38.4 | |
| Total User Hours | 0.6 | 1.6 | |
| Molecules | 4 | 2 | |
| **User Hours per Molecule** | **0.15** | **0.80** | **Average = 0.5** |

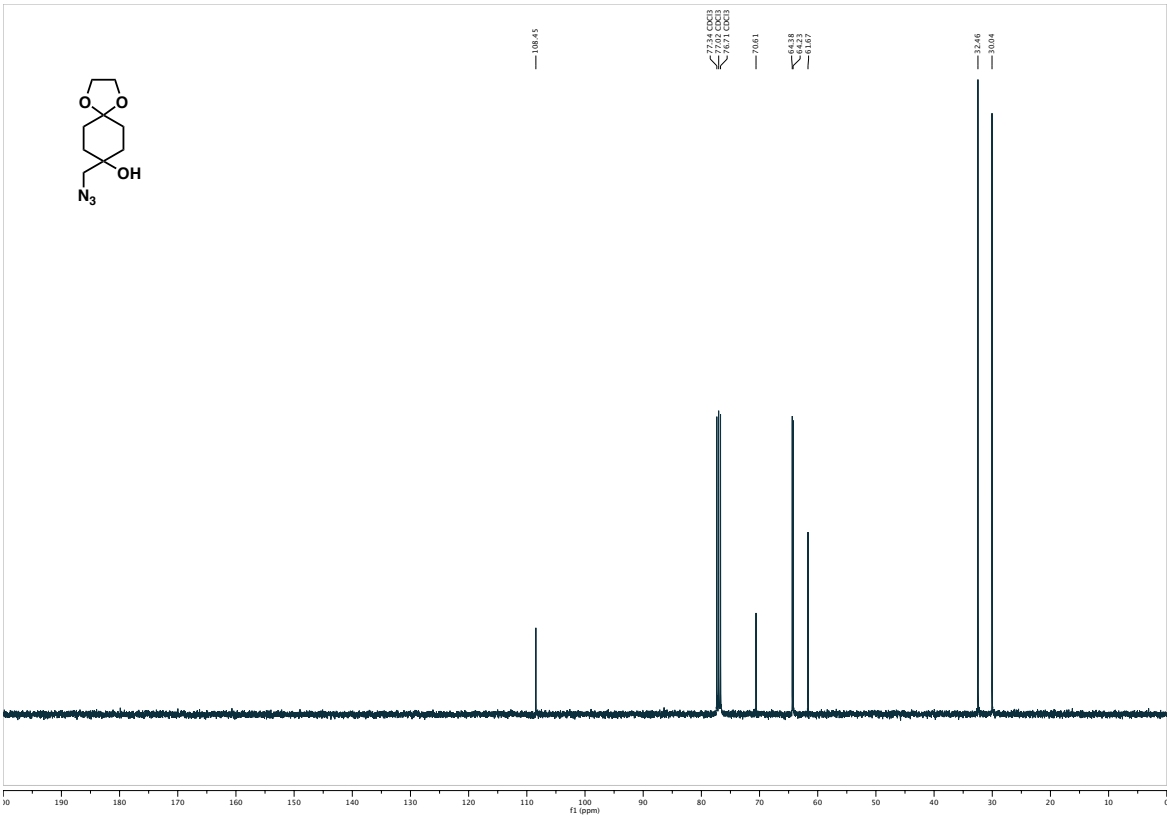
| Automated Workflow with plate Diversification | | | |
|---|---|---|---|
| Operation | Time min (h) | Time max (h) | User Involvment (yes/no) |
| Weigh out starting material | 0.1 | | Yes |
| Insert capsule and start reaction | 0.05 | | Yes |
| Automated SnAP and Ketone deprotection | 15.5 | 22.5 | No |
| Concentrate ketone | 0.3 | | Yes |
| Disolve and pipette starting materials | 1 | | Yes |
| Automated Reductive Amination | 3 | 12 | No |
| Contrafuge and concentrate | 1 | | No |
| Analysis | 1.5 | | No |
| Total Hours | 22.45 | 38.45 | |
| Total User Hours | 1.45 | 1.45 | |
| Molecules | 40 | 20 | |
| **User Hours per Molecule** | **0.04** | **0.07** | **Average = 0.06** |

| Manual Workflow | | | |
|---|---|---|---|
| Operation | Time min (h) | Time max (h) | User Involvment (yes/no) |
| Weigh out starting material | 0.5 | | Yes |
| Set up imine formation | 0.5 | | Yes |
| Imine formation | 5 | | No |
| Filter molecular sieves | 0.5 | | Yes |
| Weigh out and pre-form SnAP catalyst | 0.5 | | Yes |
| SnAP reaction | 5 | | No |
| SnAP workup | 1 | | Yes |
| SnAP column | 2 | | Yes |
| Dry product | 1 | | No |
| Set up acetal deprotection | 0.5 | | Yes |
| Acetal deprotection | 5 | 12 | No |
| Work up acetal deprotection | 1 | | Yes |
| Optional Column Ketone | 2 | | Yes |
| Dry ketone | 1 | | No |
| Set up reductive amination | 0.5 | | Yes |
| Reductive Amination | 3.00 | 12 | No |
| Work up reductive amination | 1 | | Yes |
| Dry product | 1 | | No |
| Optional add IS and crude NMR | 0.5 | | Yes |
| Preparative HPLC | 1 | | No |
| Optional freebasing | 0 | 0.5 | Yes |
| Dry product | 1 | | No |
| Characterise Product | 1 | | No |
| Total Hours | 34.50 | 50.5 | |
| Total User Hours | 10.5 | 11 | |
| Molecules | 4 | 2 | |
| **User Hours per Molecule** | **2.63** | **5.5** | **Average = 4.1** |

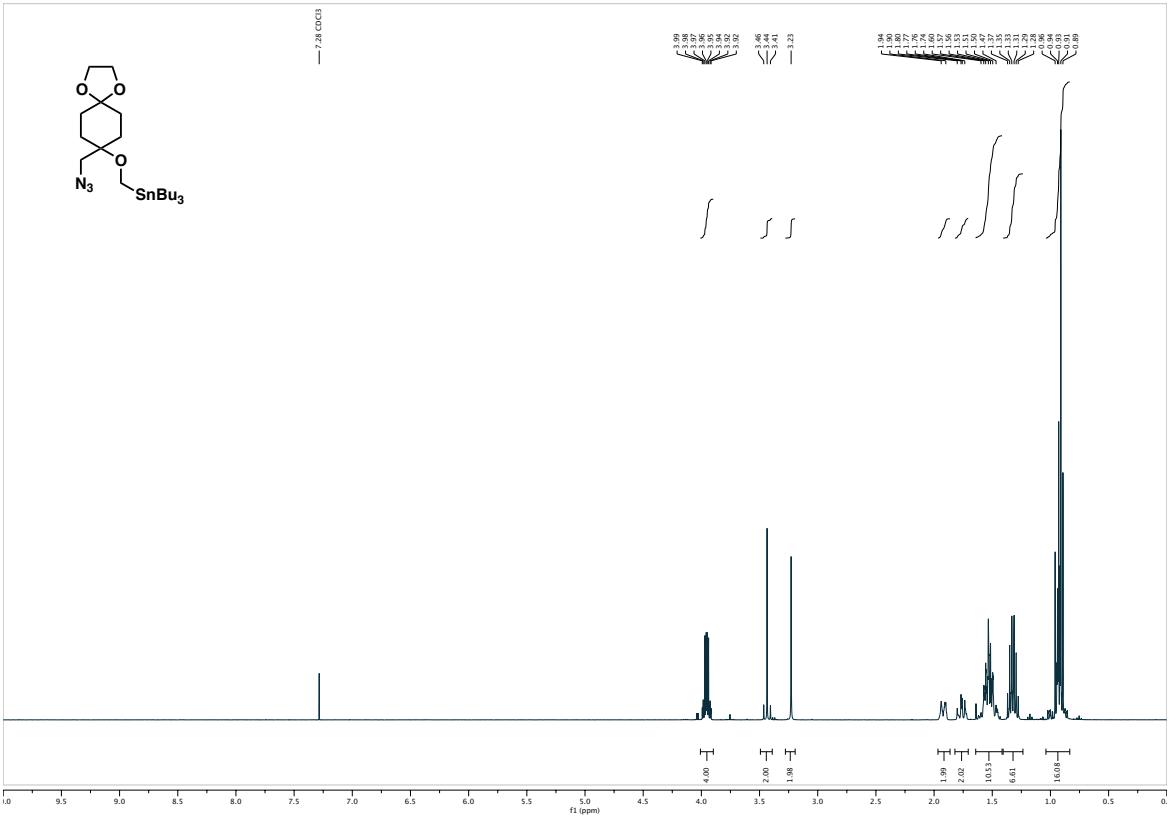
## NMR Spectra

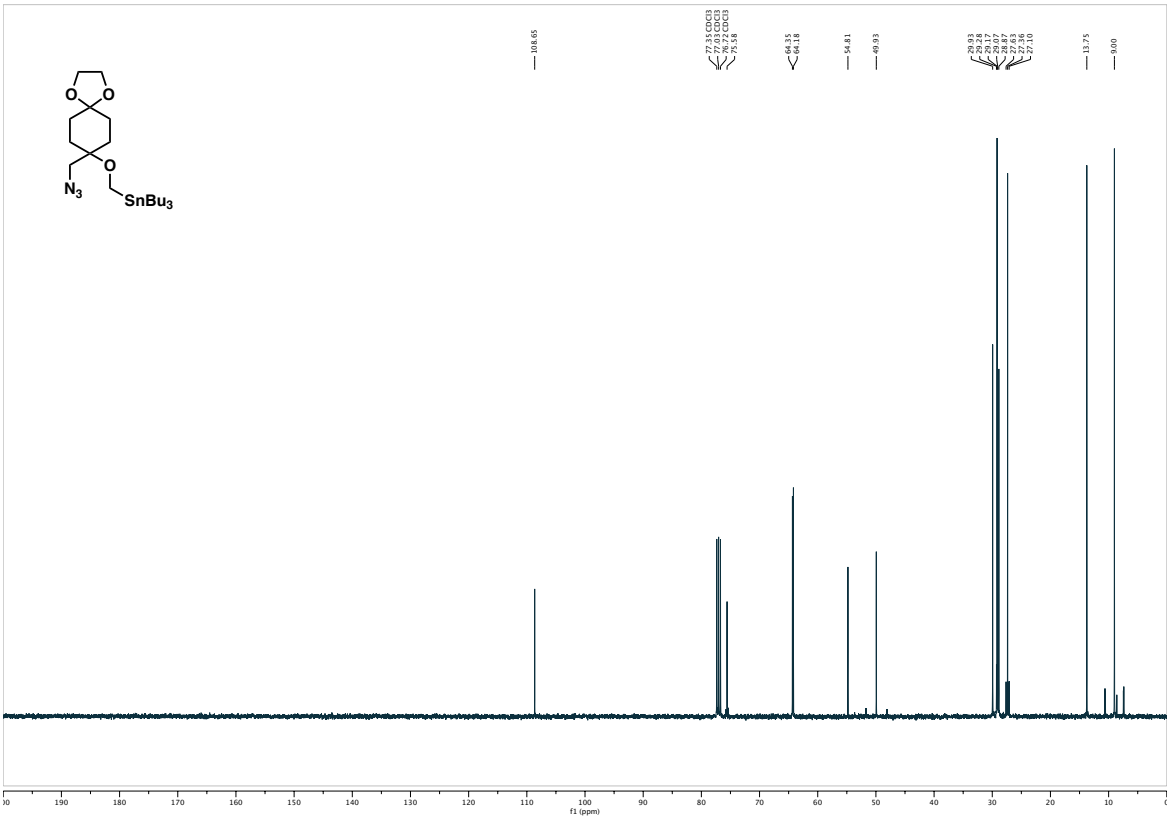
### 1-1



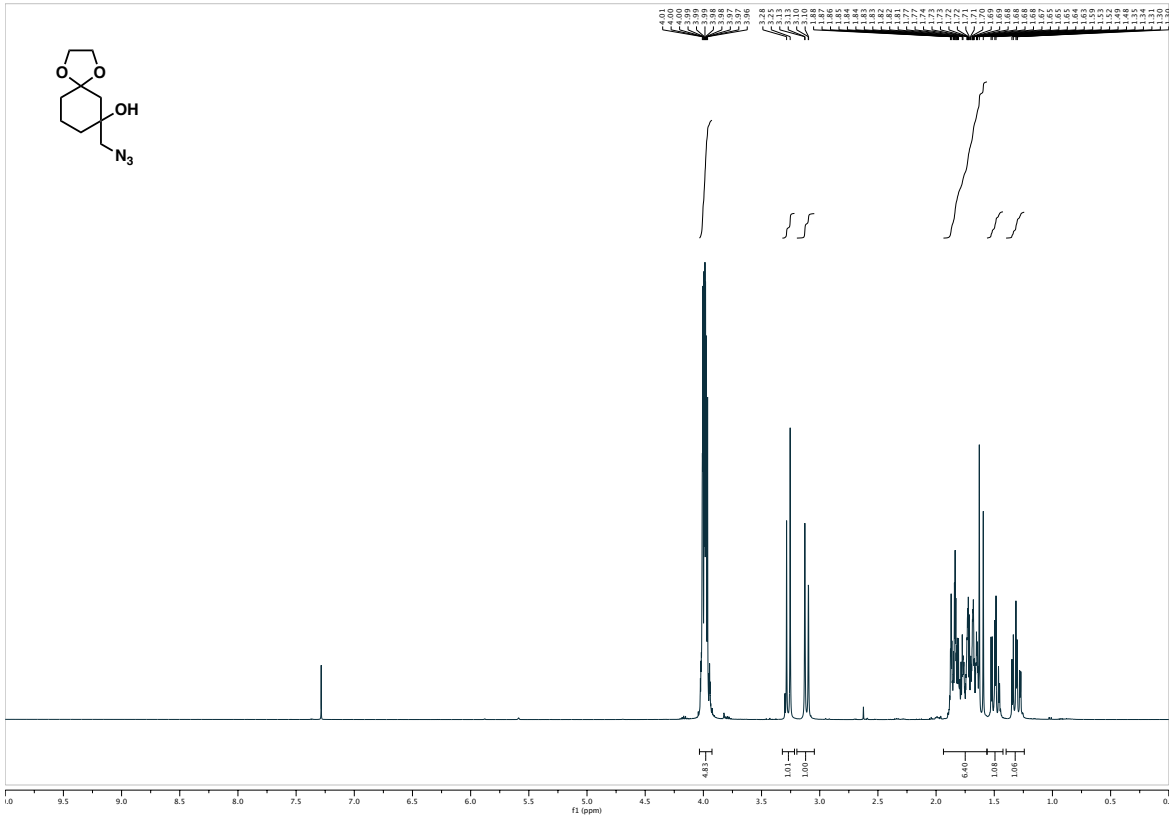



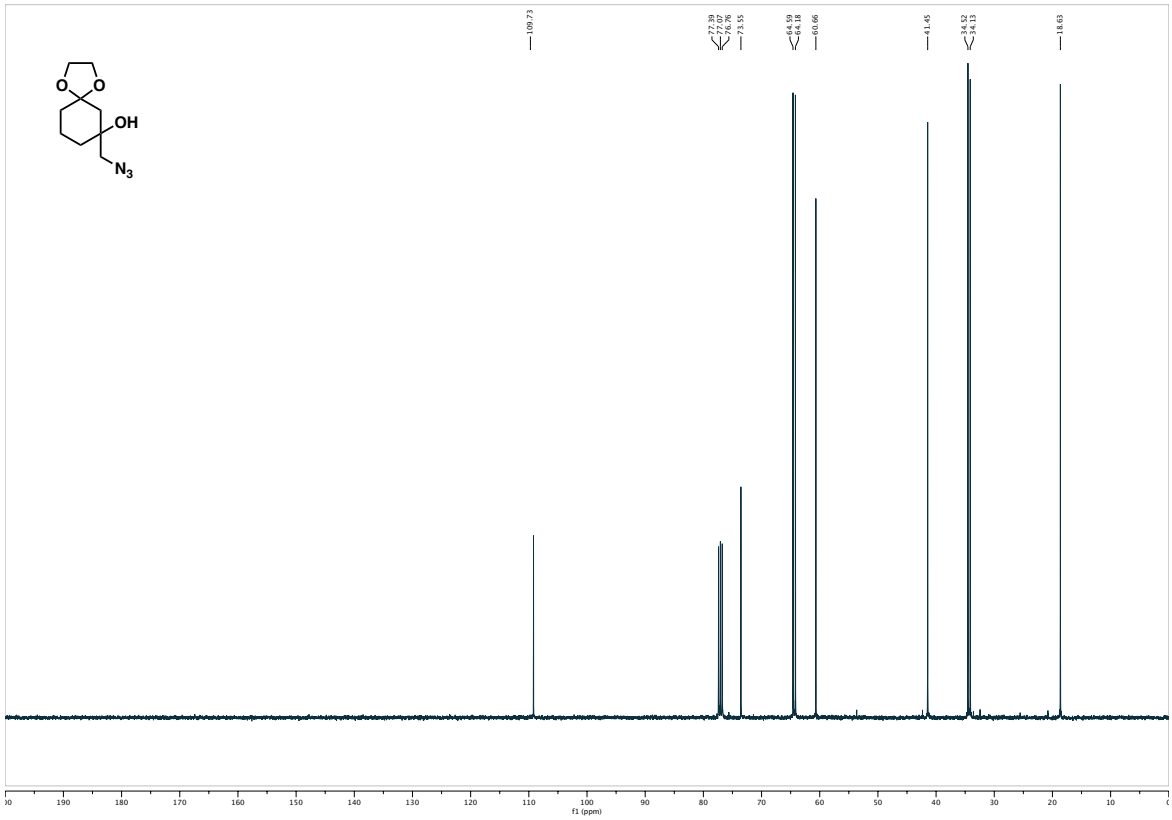
**1-2**


7.28 CDCl3
3.99
3.98
3.97
3.96
3.95
3.94
3.93
3.92
3.46
3.44
3.41
3.23
1.94
1.90
1.89
1.77
1.76
1.74
1.60
1.57
1.56
1.53
1.51
1.50
1.47
1.37
1.35
1.33
1.31
1.29
1.28
0.96
0.94
0.93
0.91
0.89
4.00
2.00
1.98
1.99
2.02
10.53
6.61
16.08
f1 (ppm)
O
O
O
N3
SnBu3

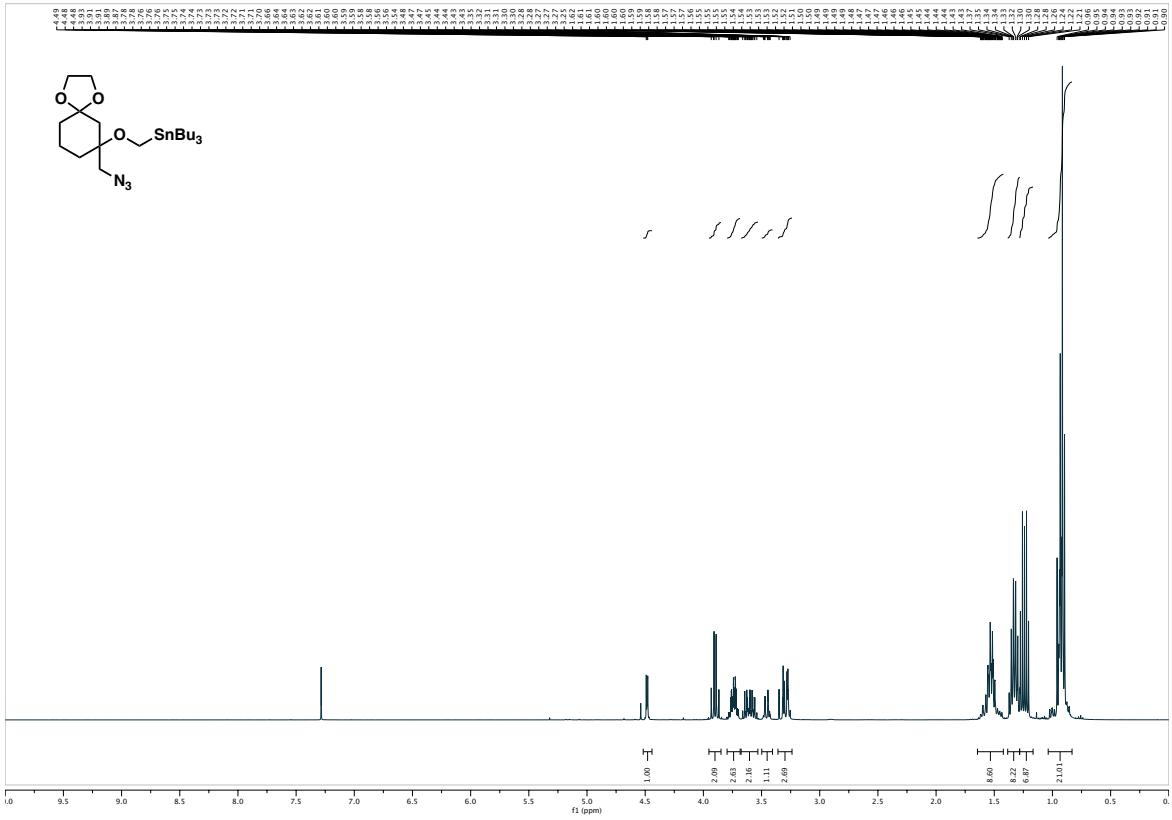

108.65
77.35 CDCl3
77.03 CDCl3
76.72 CDCl3
75.58
64.35
64.18
54.81
49.93
29.38
29.36
29.17
29.07
28.97
27.63
27.56
27.10
13.75
9.00
f1 (ppm)
O
O
O
N3
SnBu3

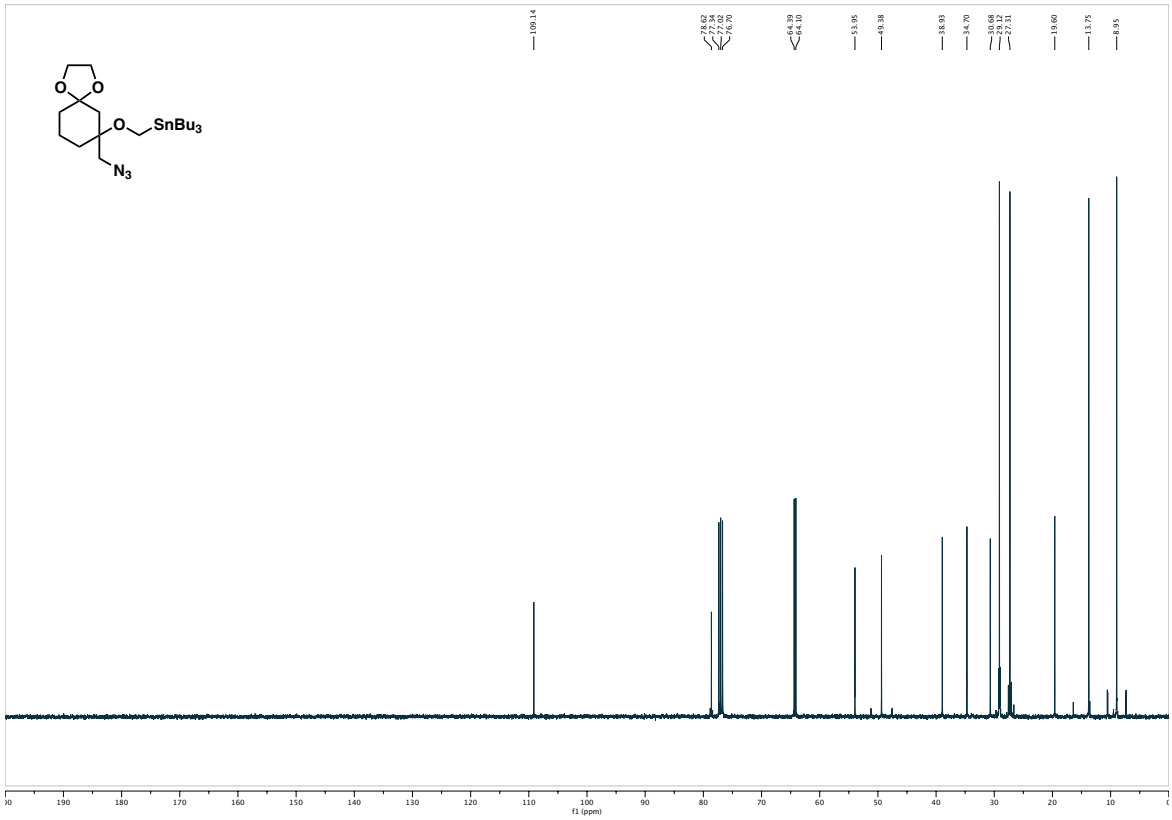
**2-1**



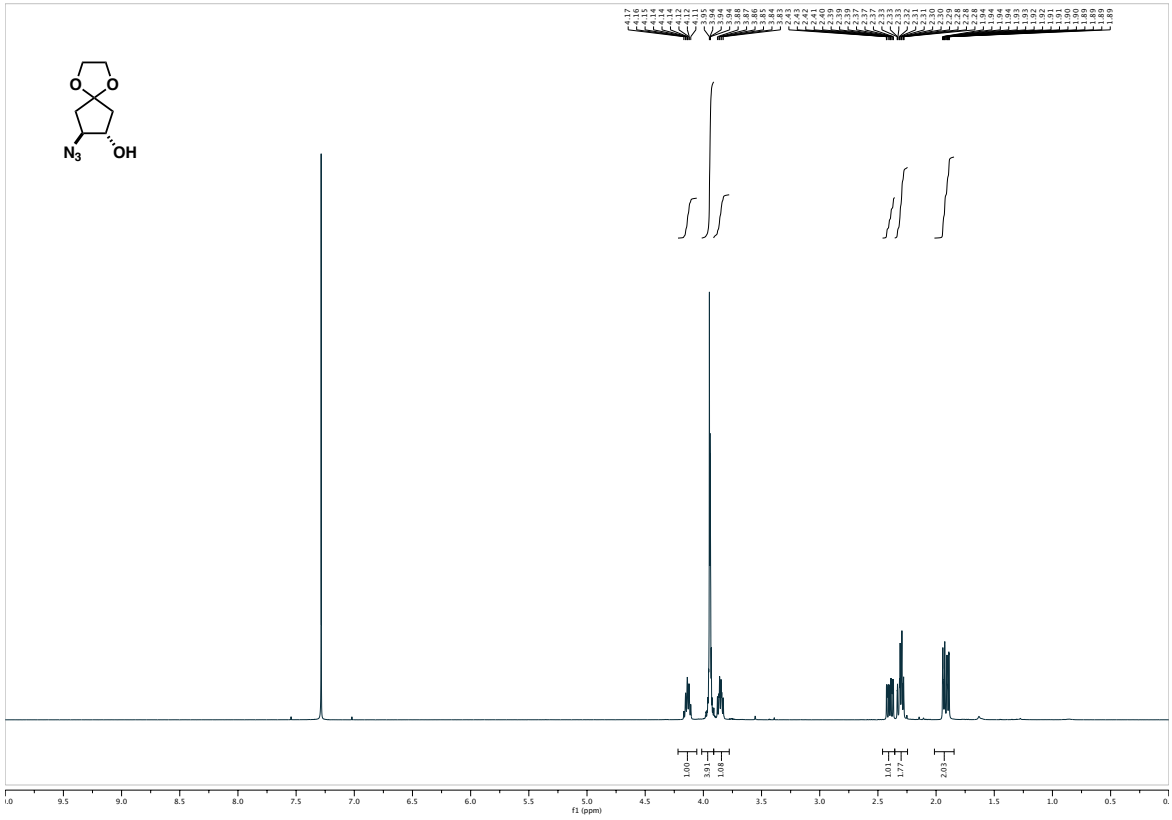



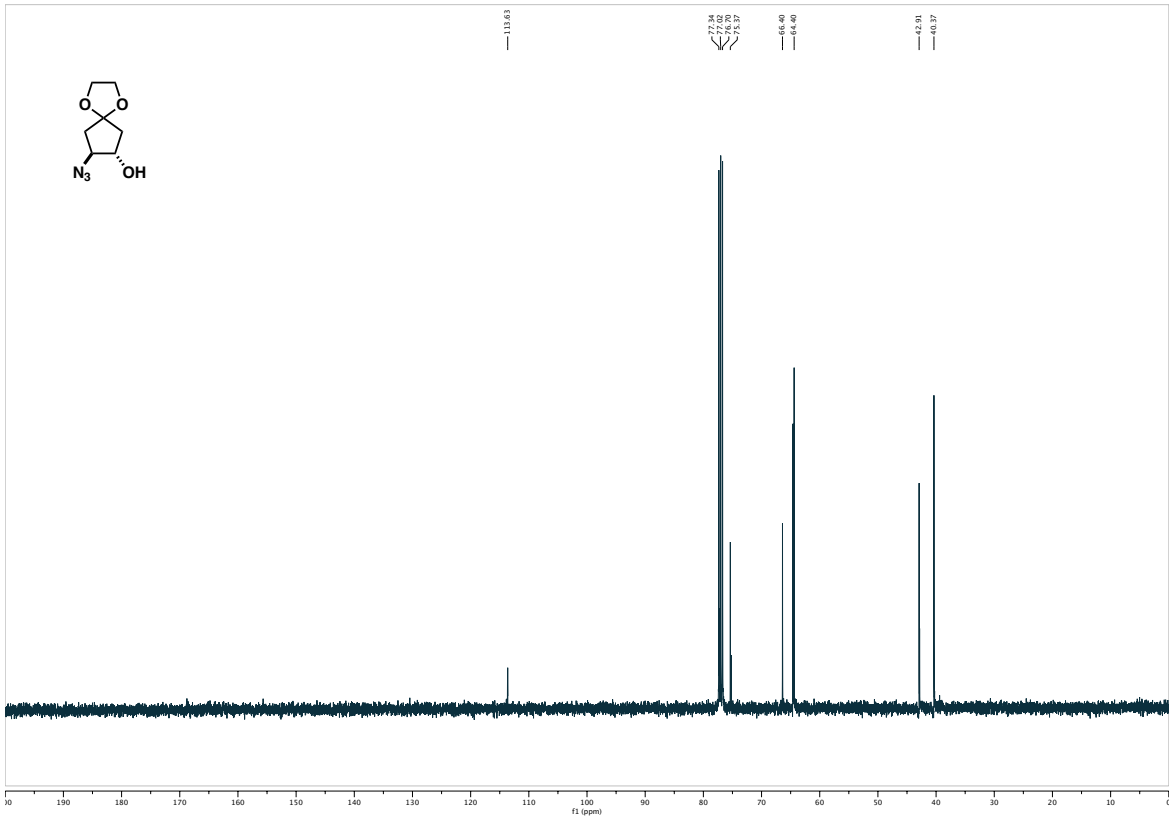
## 2-2


SnBu3
N3
1.00
2.09
2.63
2.16
1.11
2.69
8.60
8.22
6.87
2.01
f1 (ppm)

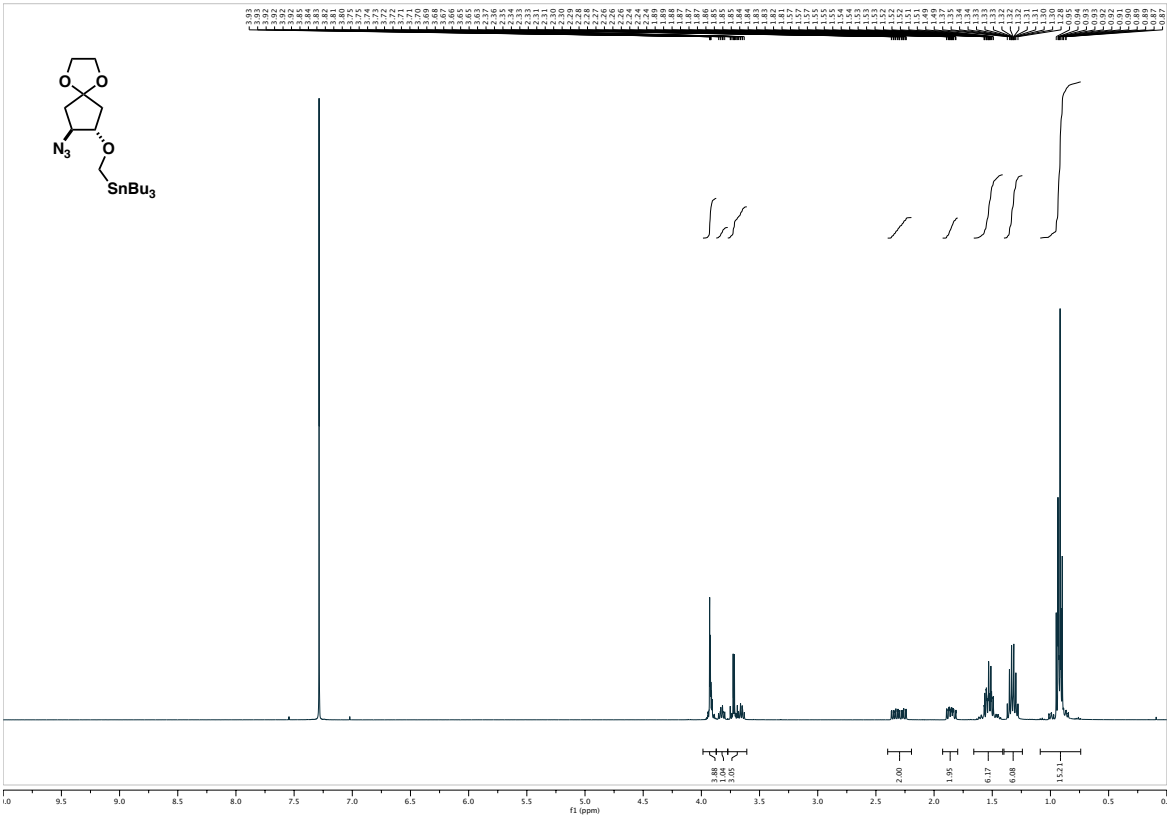

SnBu3
N3
109.14
78.62
77.34
77.02
76.70
64.39
64.10
53.95
49.38
38.93
34.70
30.68
29.12
27.32
19.60
13.75
8.95
f1 (ppm)

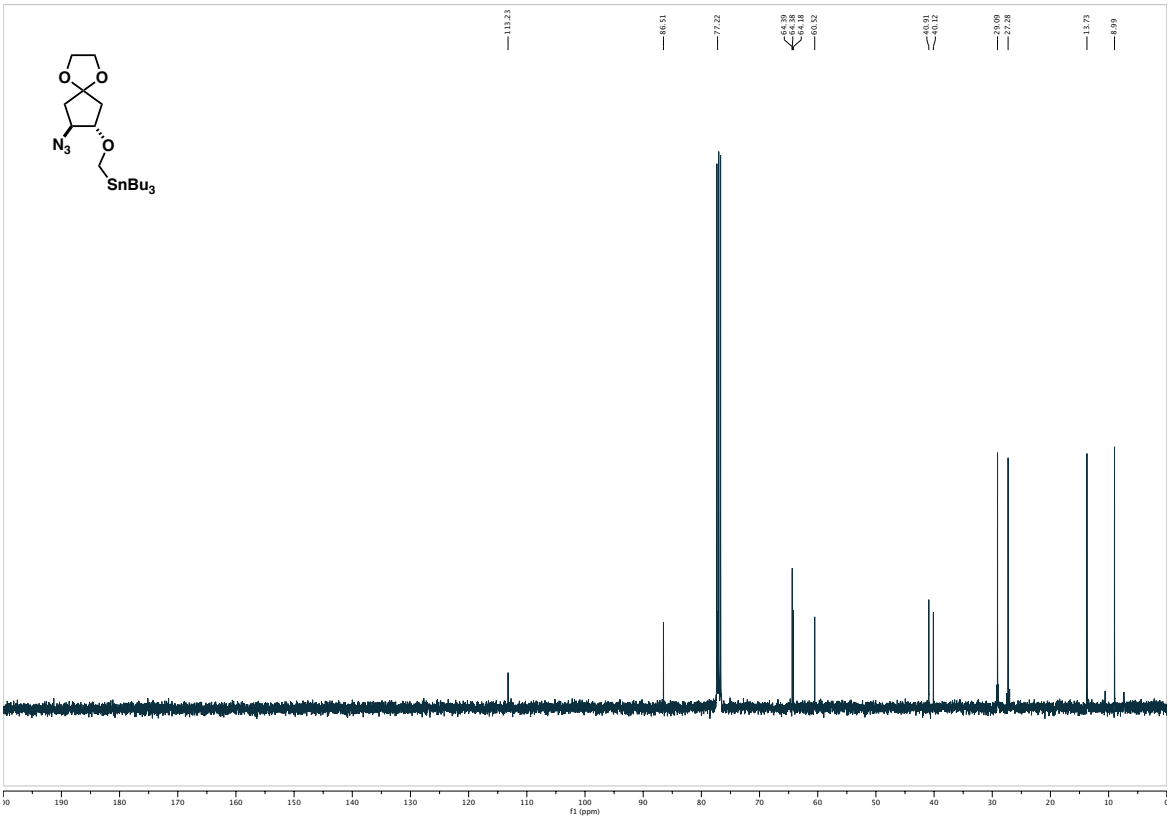
**3-1**


O
O
N3
OH
1.00
3.91
1.08
1.01
1.77
2.03
f1 (ppm)

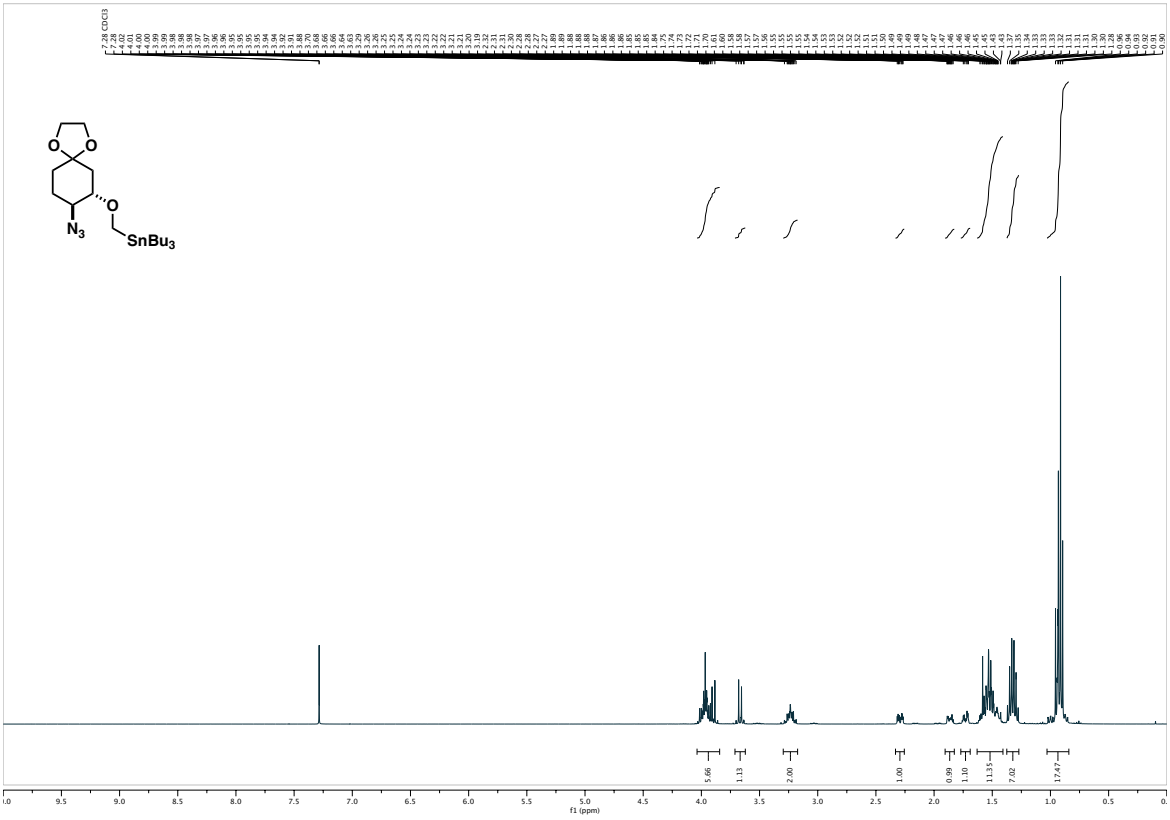

O
O
N3
OH
113.63
77.34
77.00
76.65
75.37
66.40
64.40
42.91
40.37
f1 (ppm)

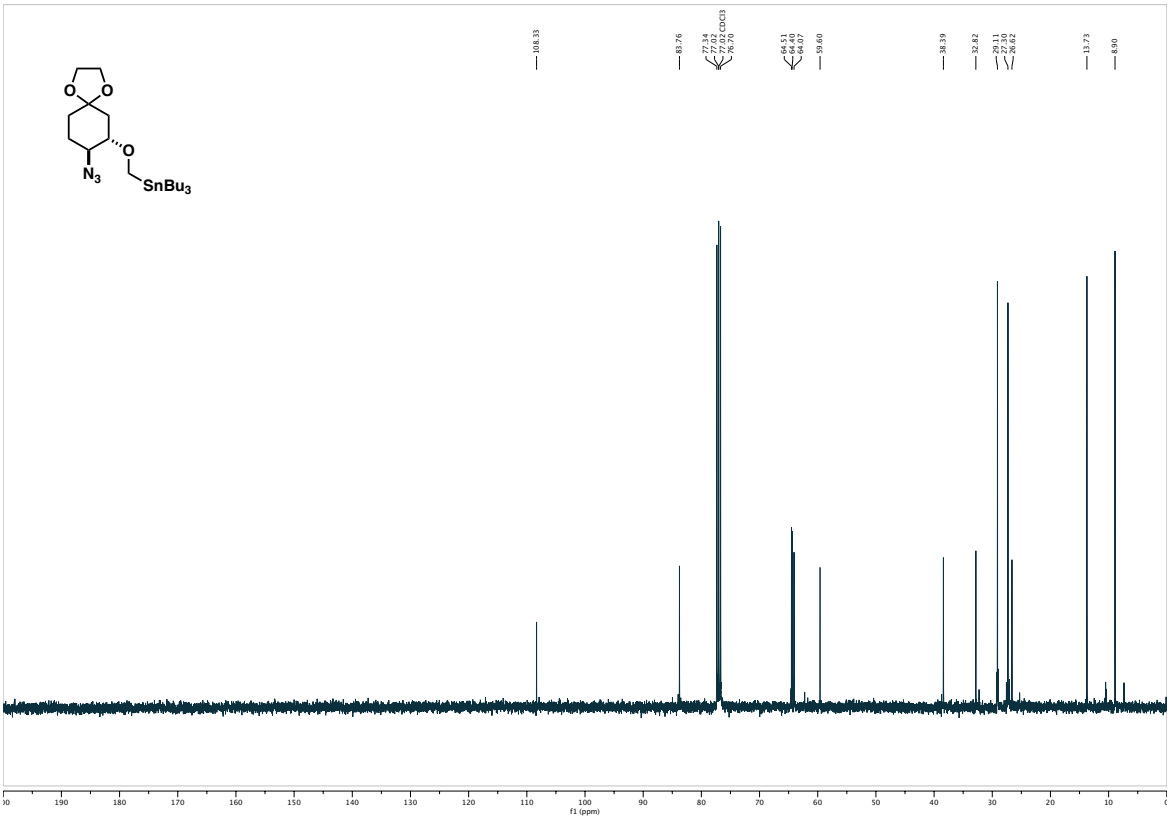
**3-2**


O
O
N3
O
SnBu3
3.88
1.04
3.05
2.00
1.95
6.17
6.08
15.21
f1 (ppm)

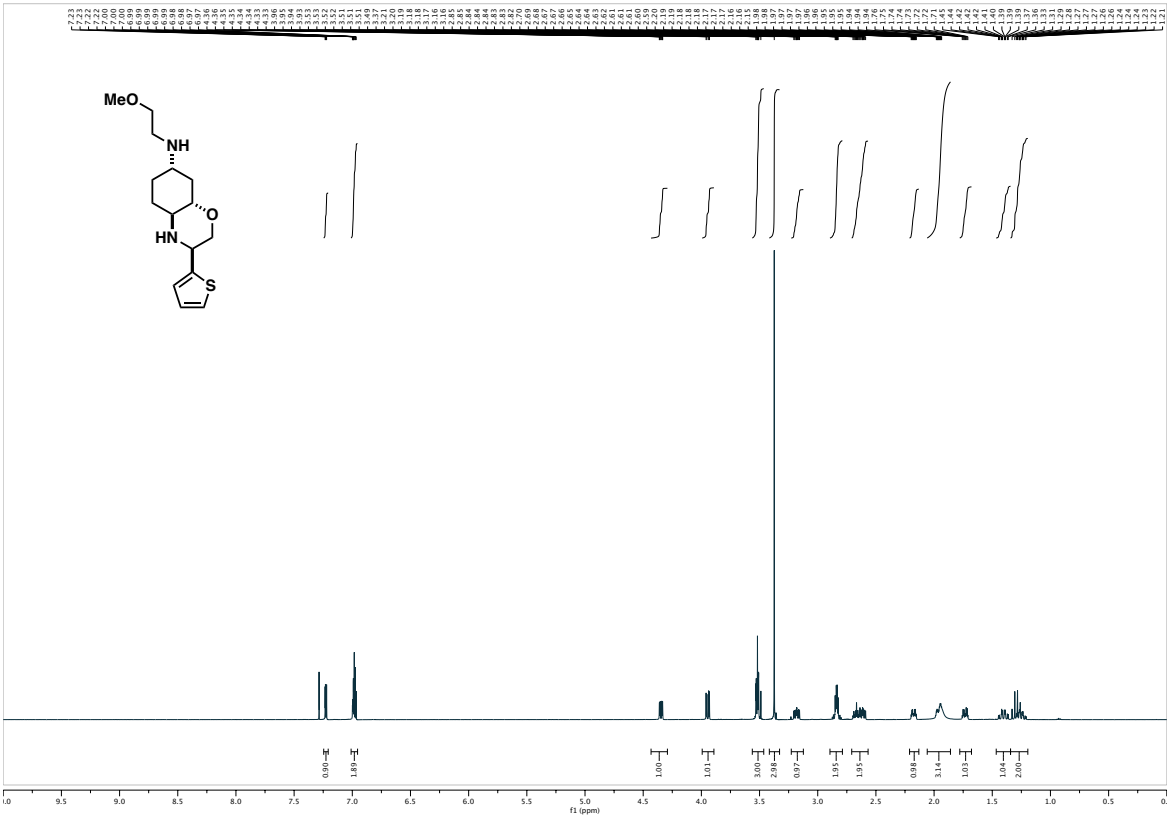

O
O
N3
O
SnBu3
113.23
86.51
77.22
64.39
64.38
64.18
60.52
40.01
40.12
29.09
27.28
13.73
8.99
f1 (ppm)

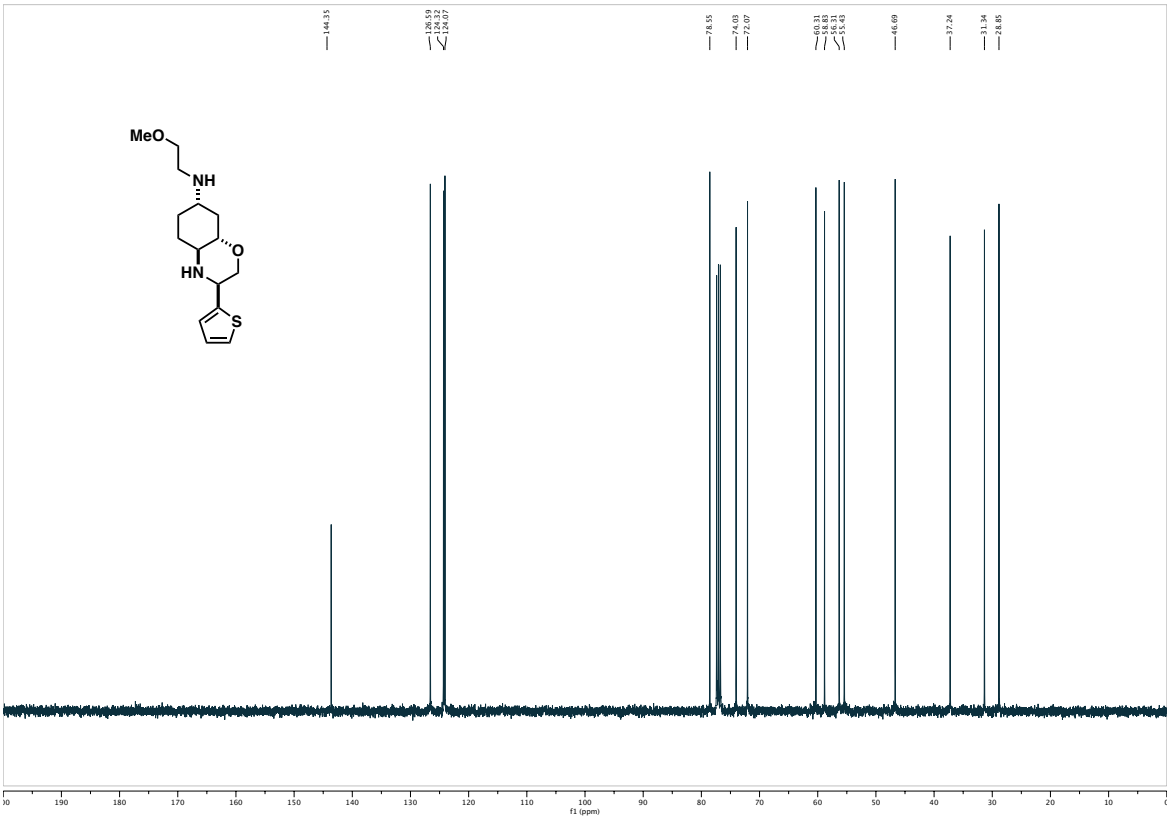
**4-1**


O
O
O
N3
SnBu3
5.66
1.13
2.00
1.00
0.99
1.10
1.135
7.02
17.47
f1 (ppm)

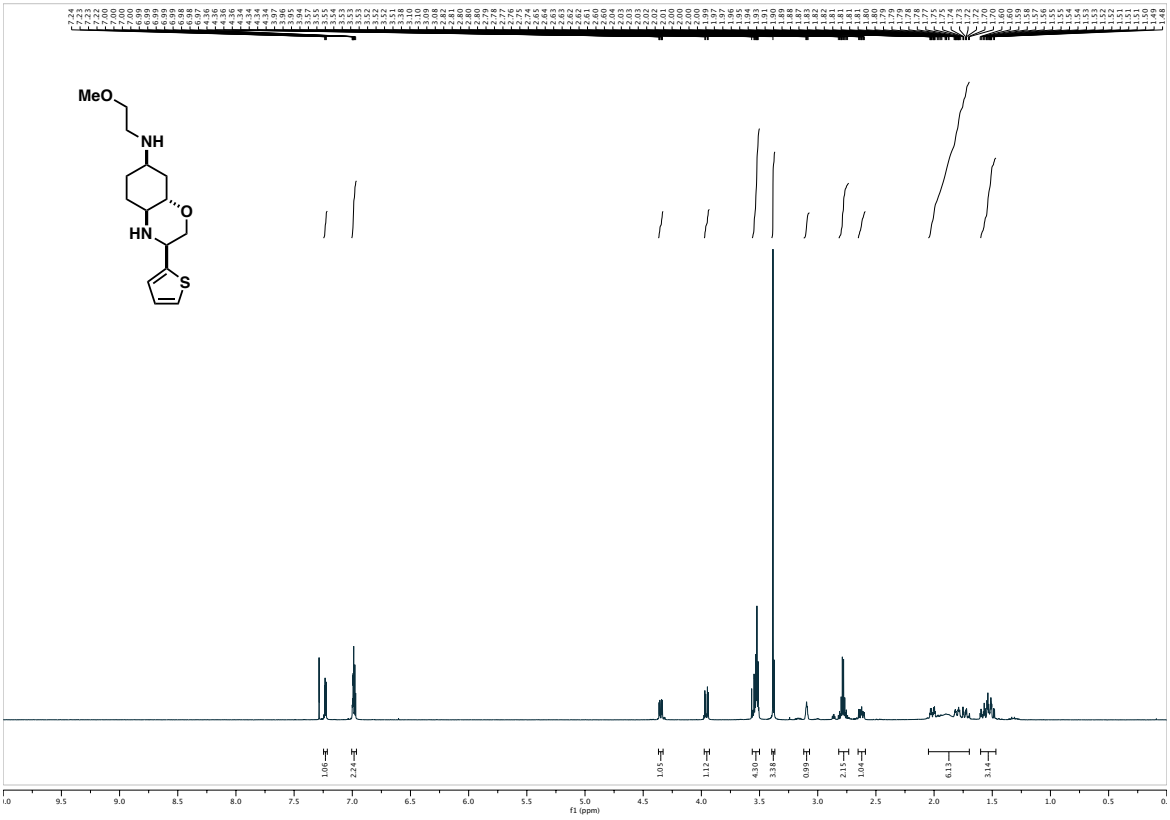

O
O
O
N3
SnBu3
108.33
83.76
77.34
77.02
77.02 CDCl3
76.70
64.51
64.40
64.07
59.60
38.39
32.82
29.11
27.30
26.62
13.73
8.90
f1 (ppm)

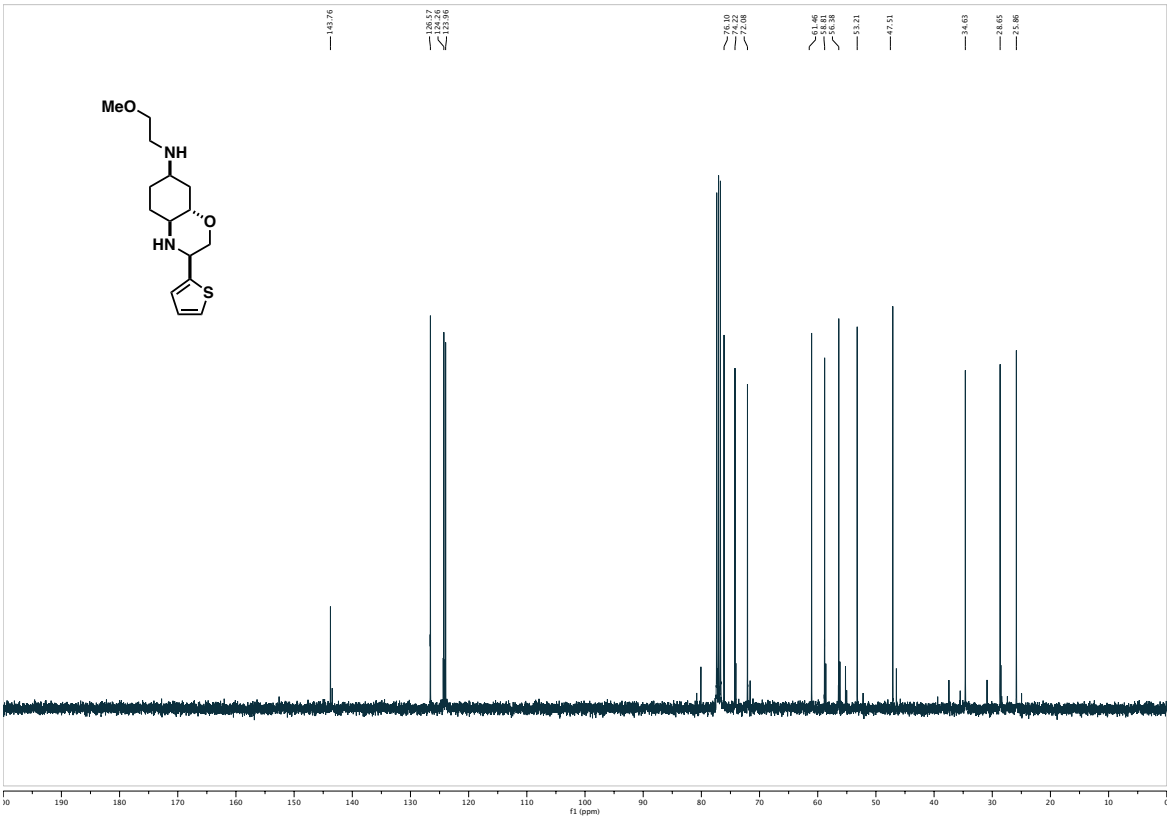
## 5-DiaA



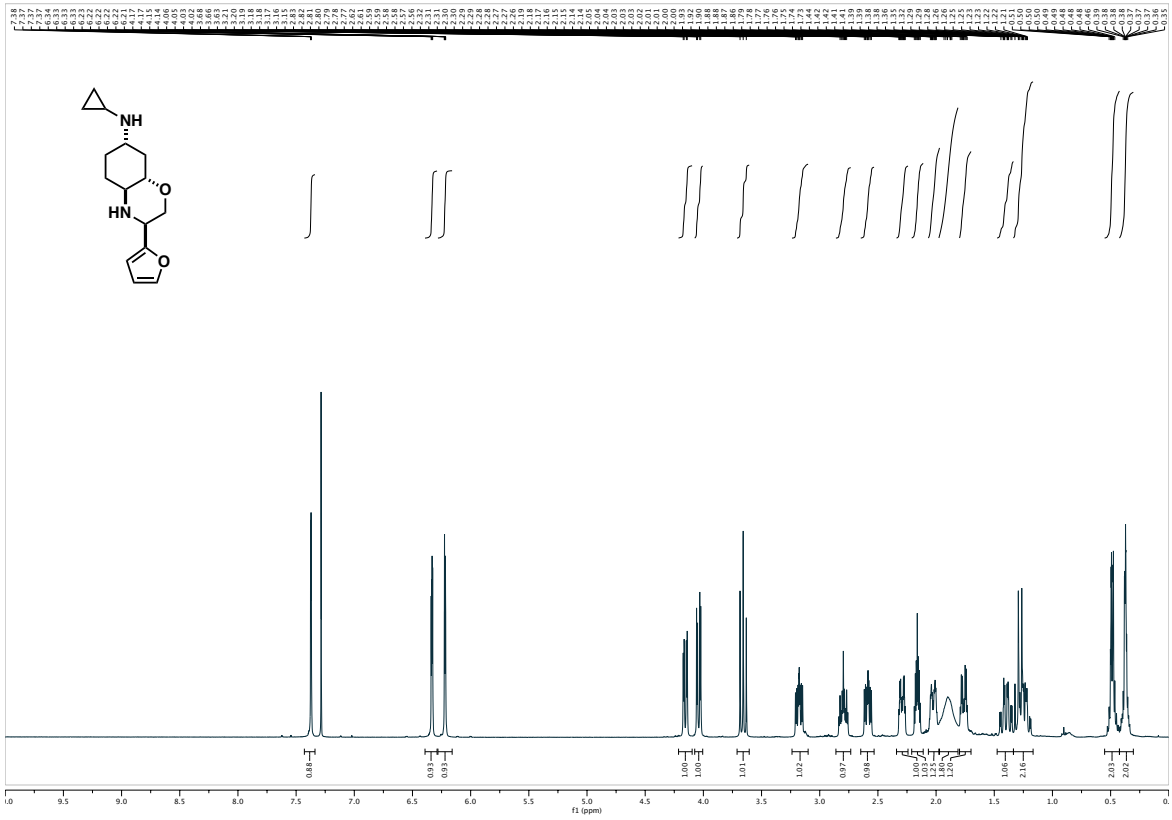



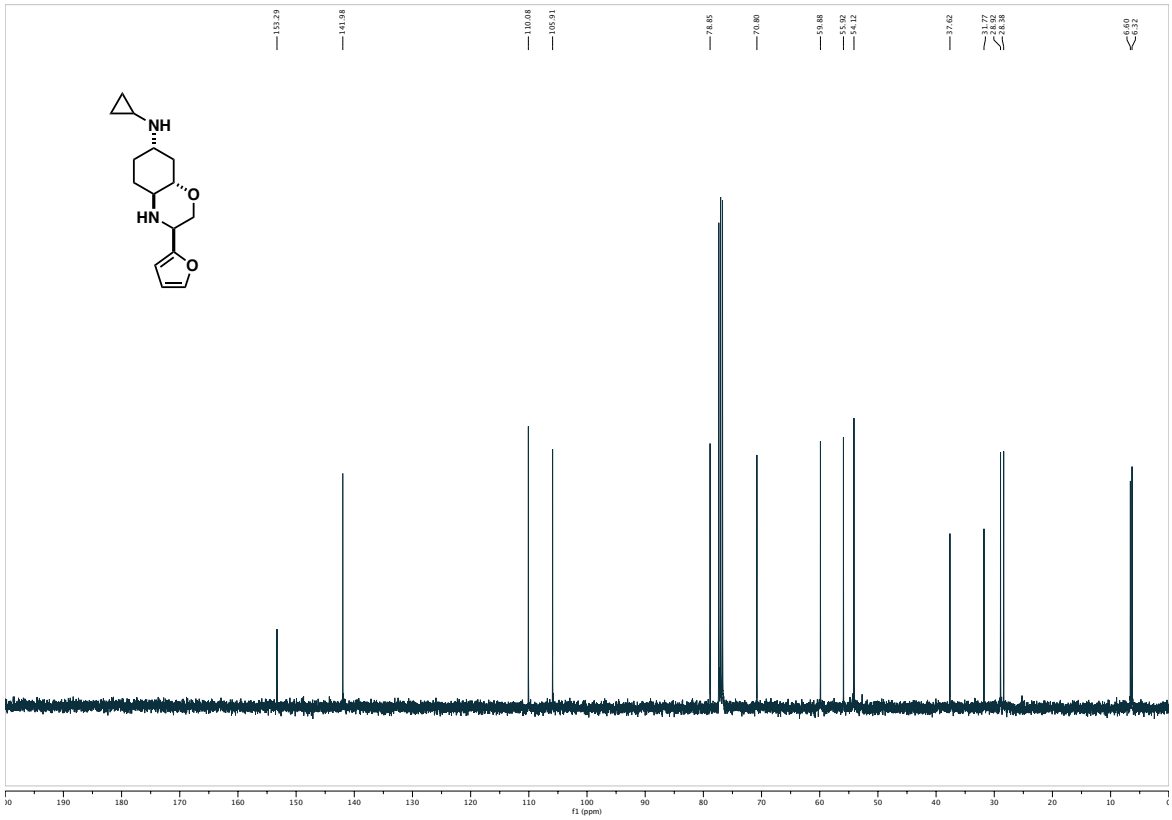
## 5-DiaB


MeO
NH
O
HN
S
1.06
2.24
1.05
1.12
4.30
3.38
0.99
2.15
1.04
6.13
3.14
f1 (ppm)

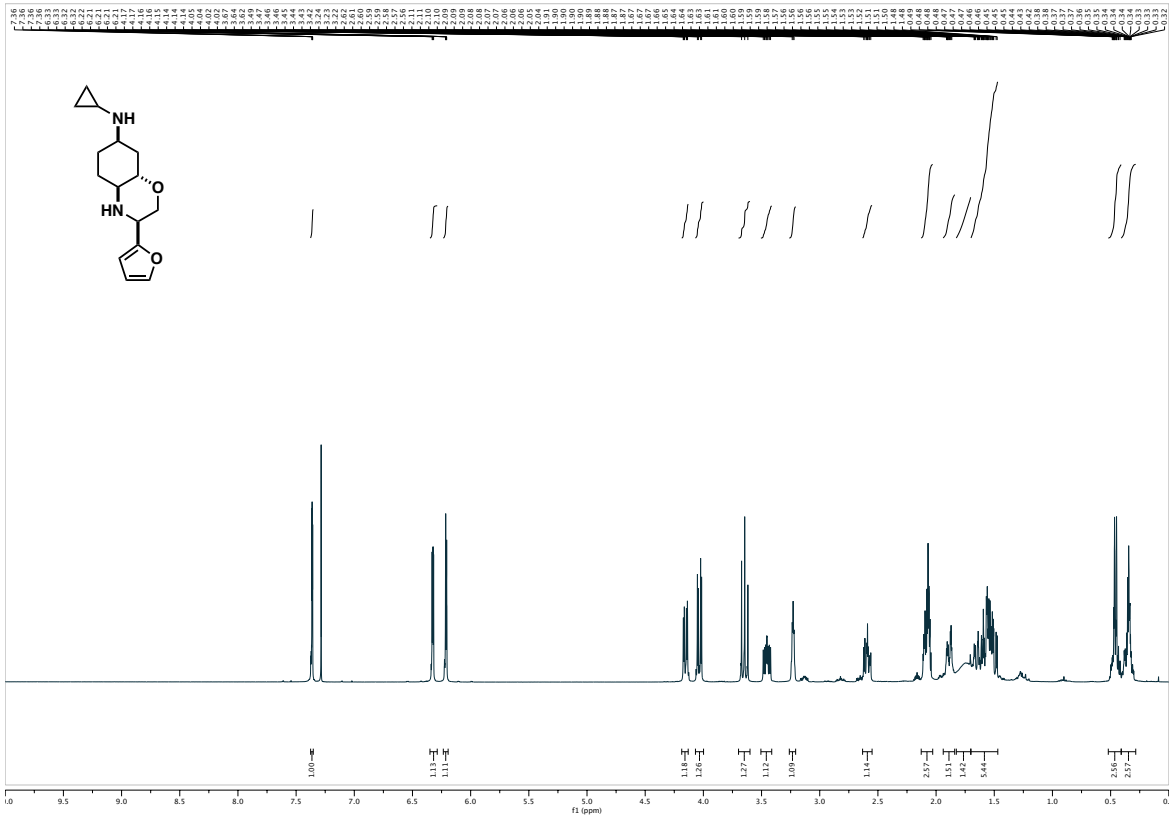

143.76
126.57
124.46
120.46
76.10
74.22
72.08
61.46
59.81
56.38
53.21
47.51
34.63
28.65
25.86
MeO
NH
O
HN
S
f1 (ppm)

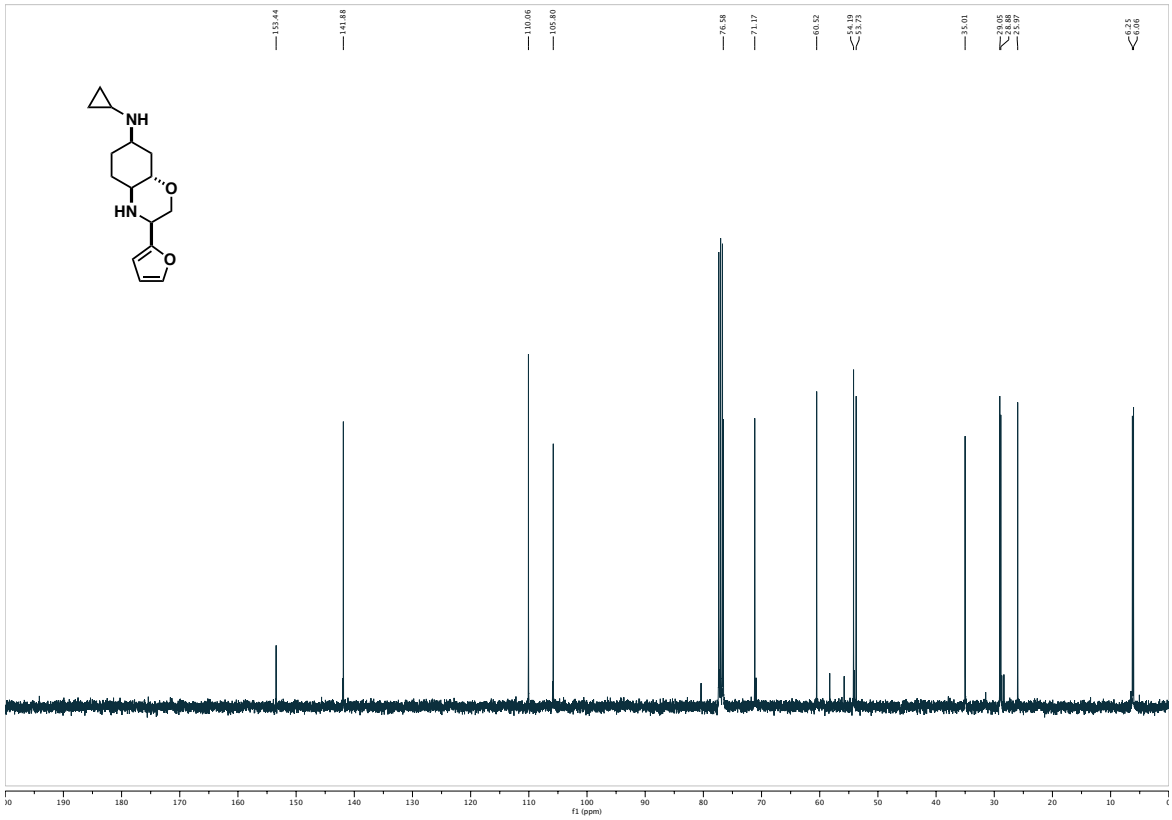
## 6-DiaA


NH
O
HN
O
f1 (ppm)

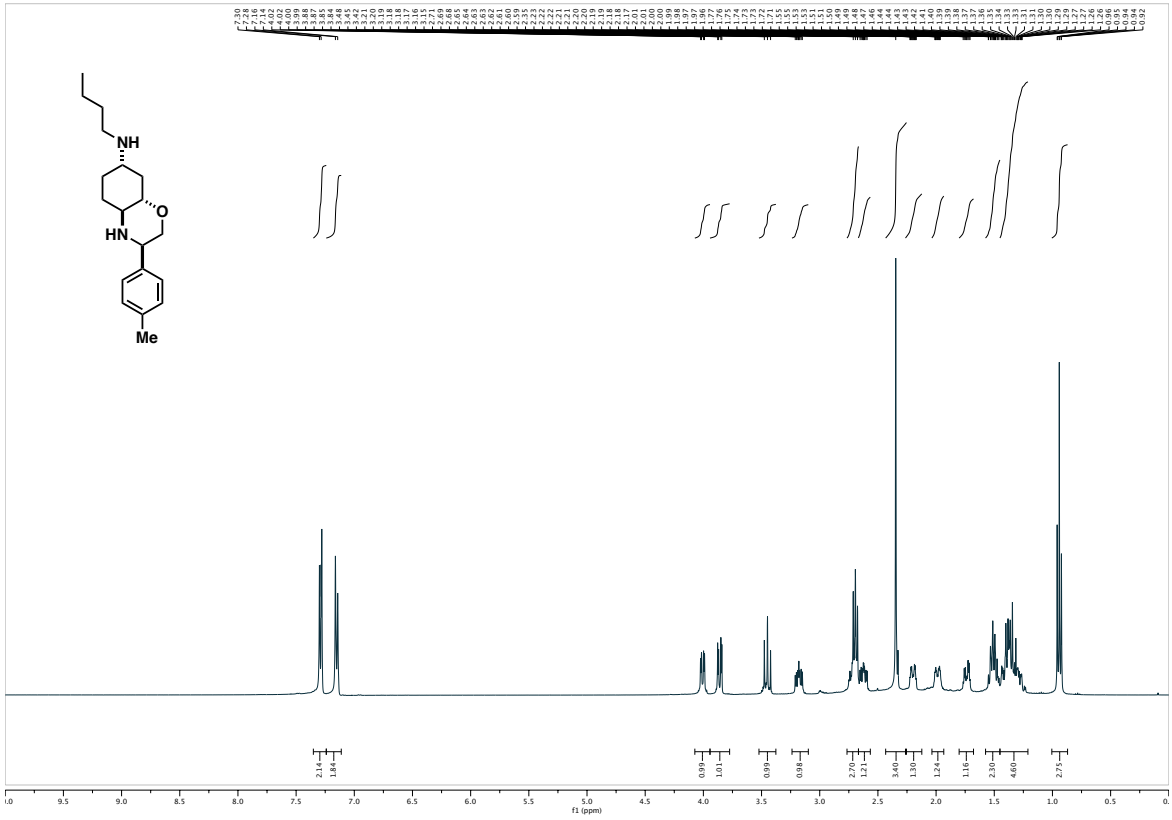

153.29
141.98
110.08
105.91
78.85
70.80
59.88
55.92
54.12
37.62
31.77
24.92
18.38
6.60
6.32
NH
O
HN
O
f1 (ppm)

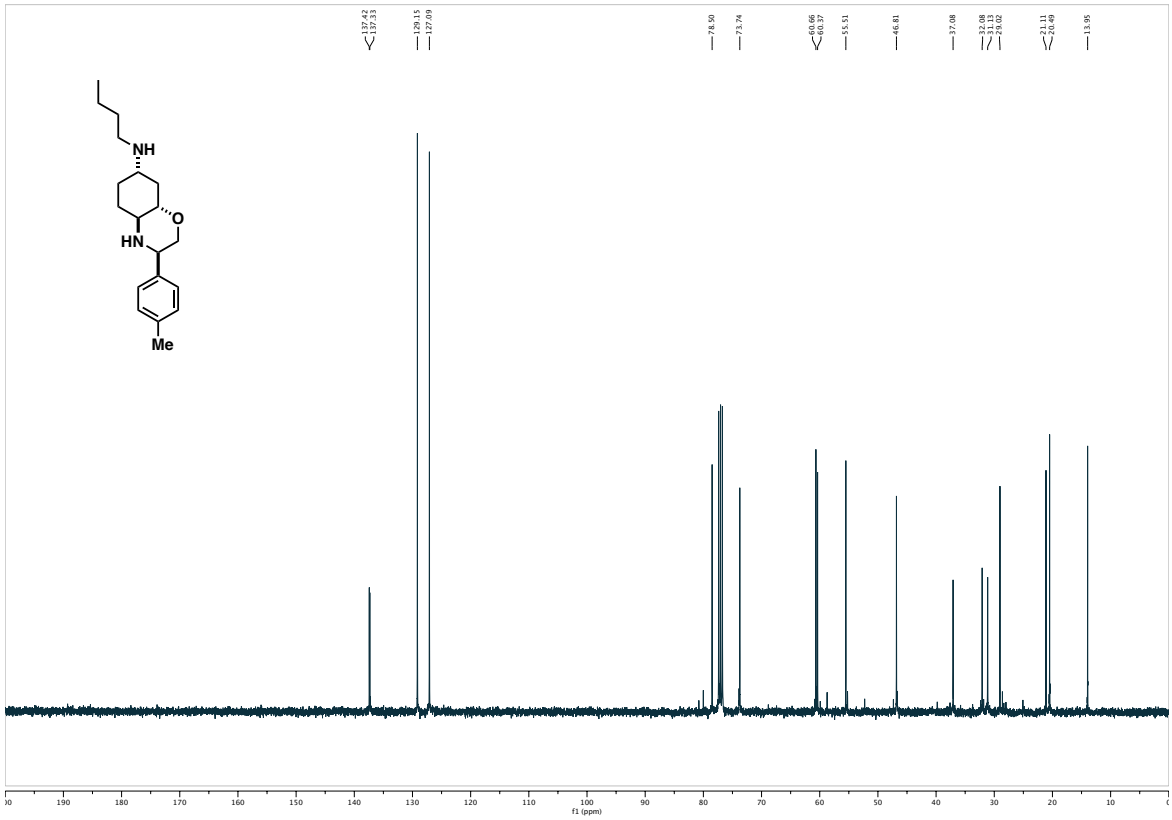
## 6-DiaB



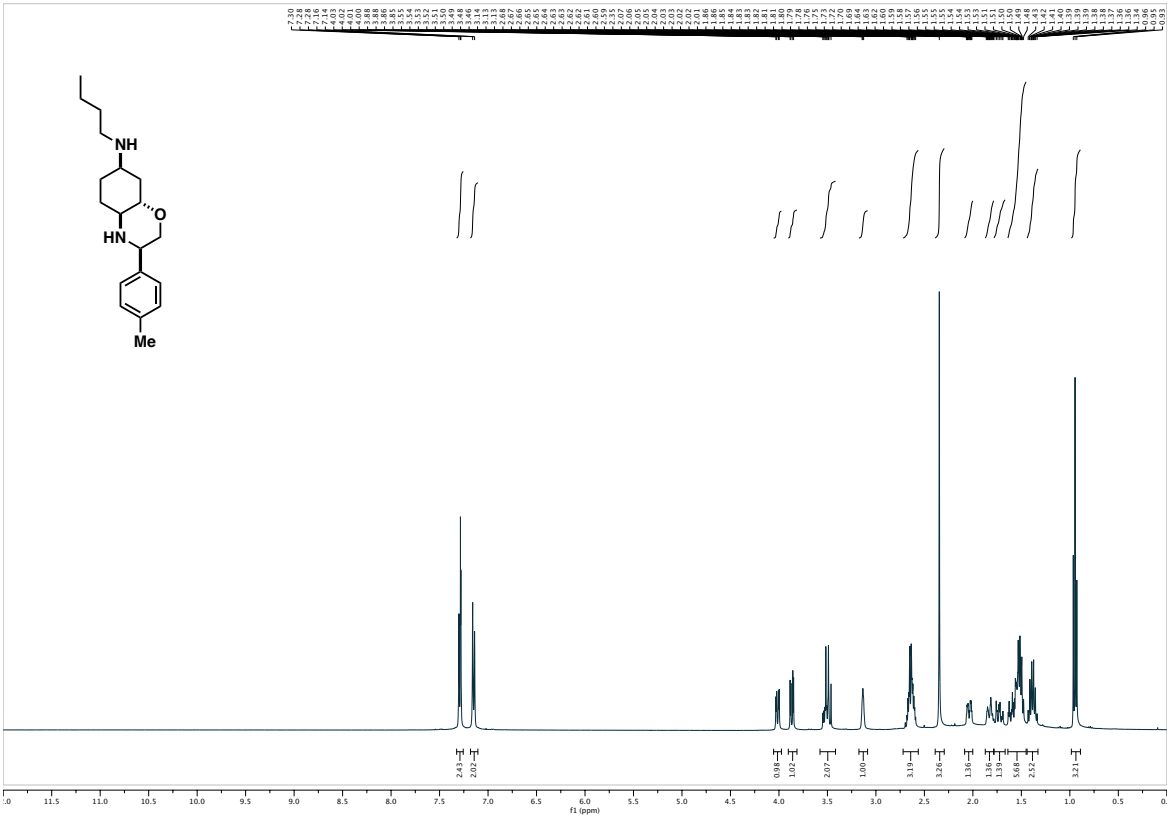



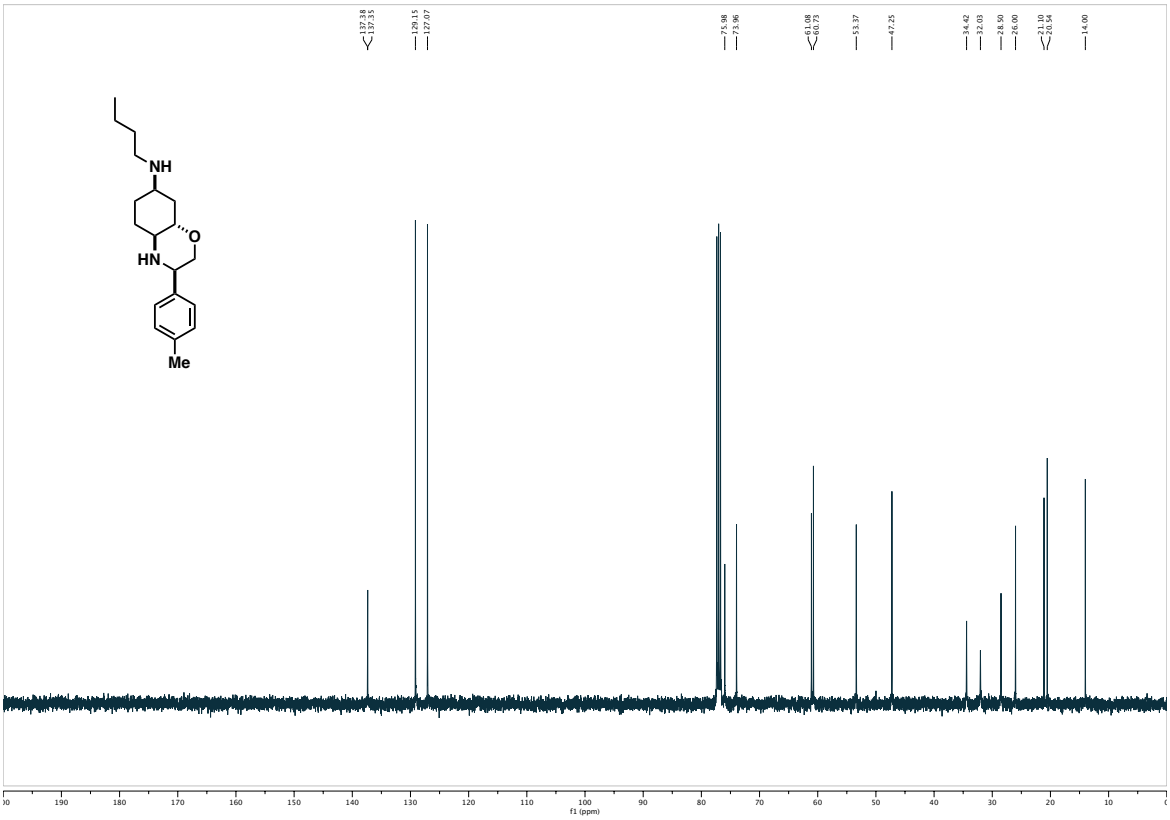
## 7-DiaA



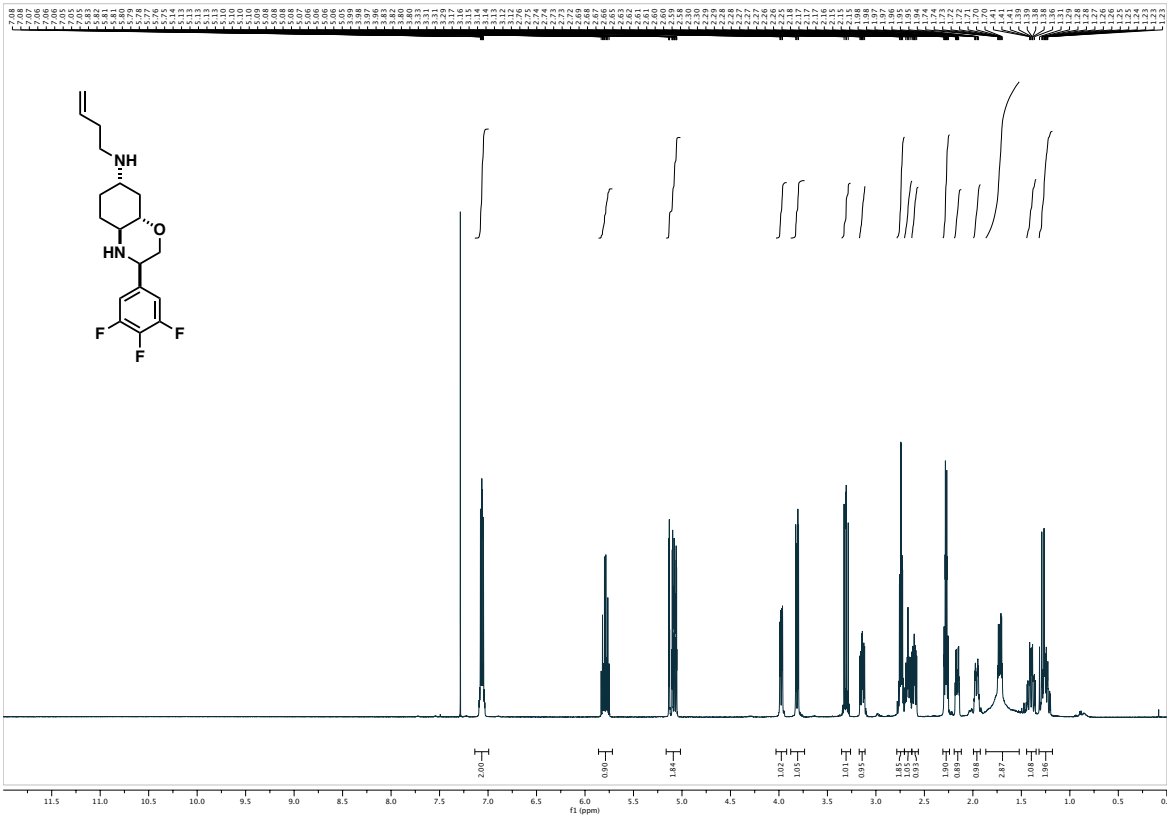



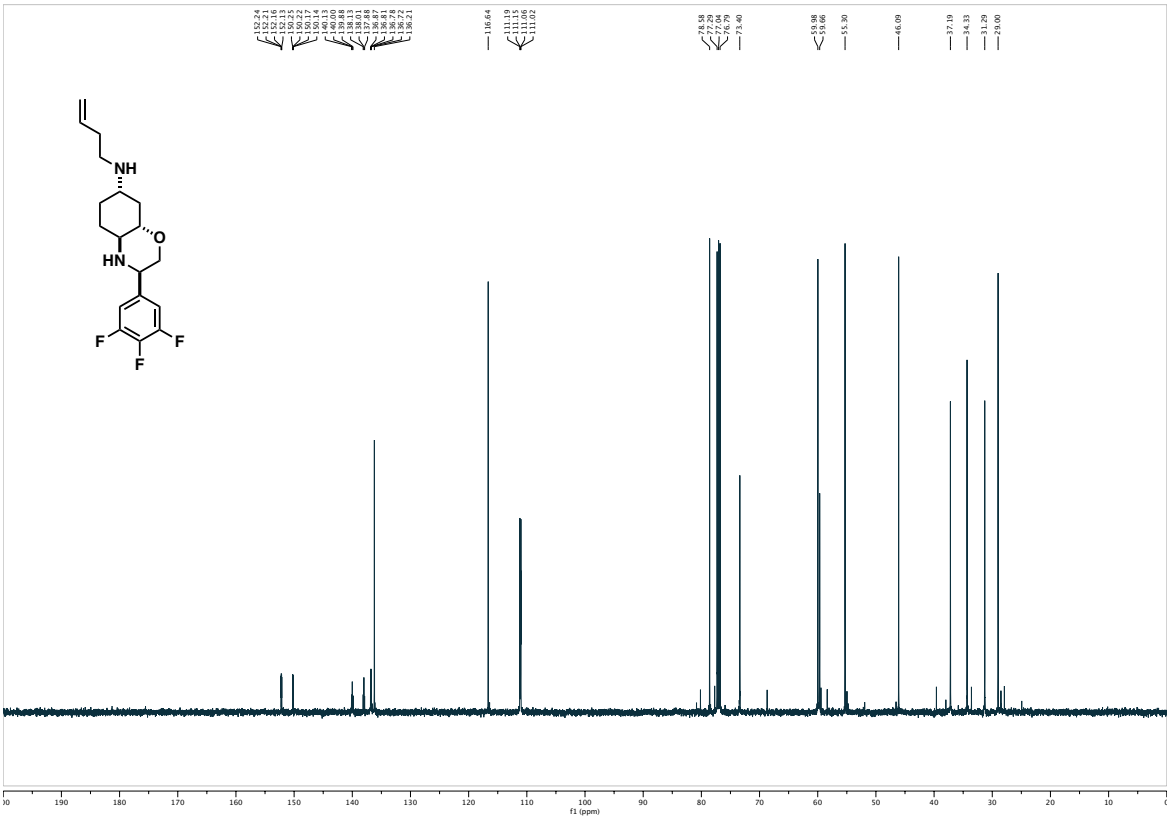
## 7-DiaB



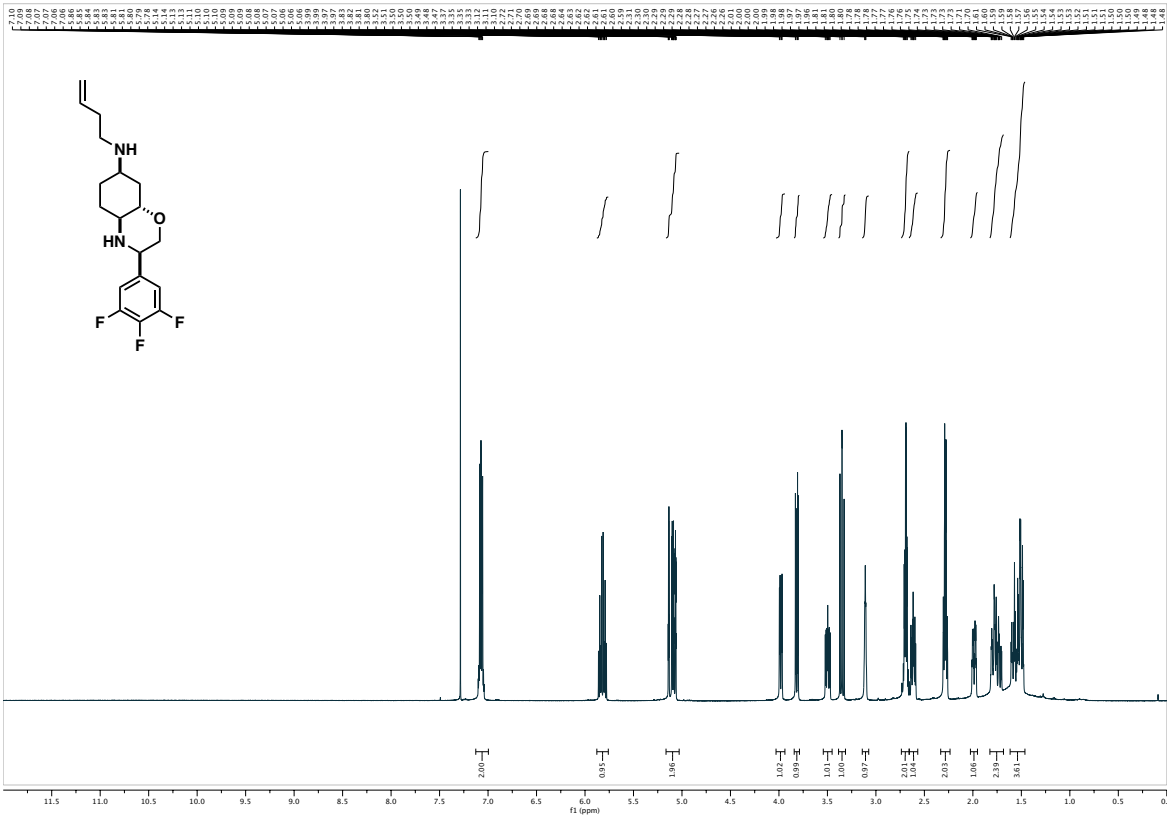



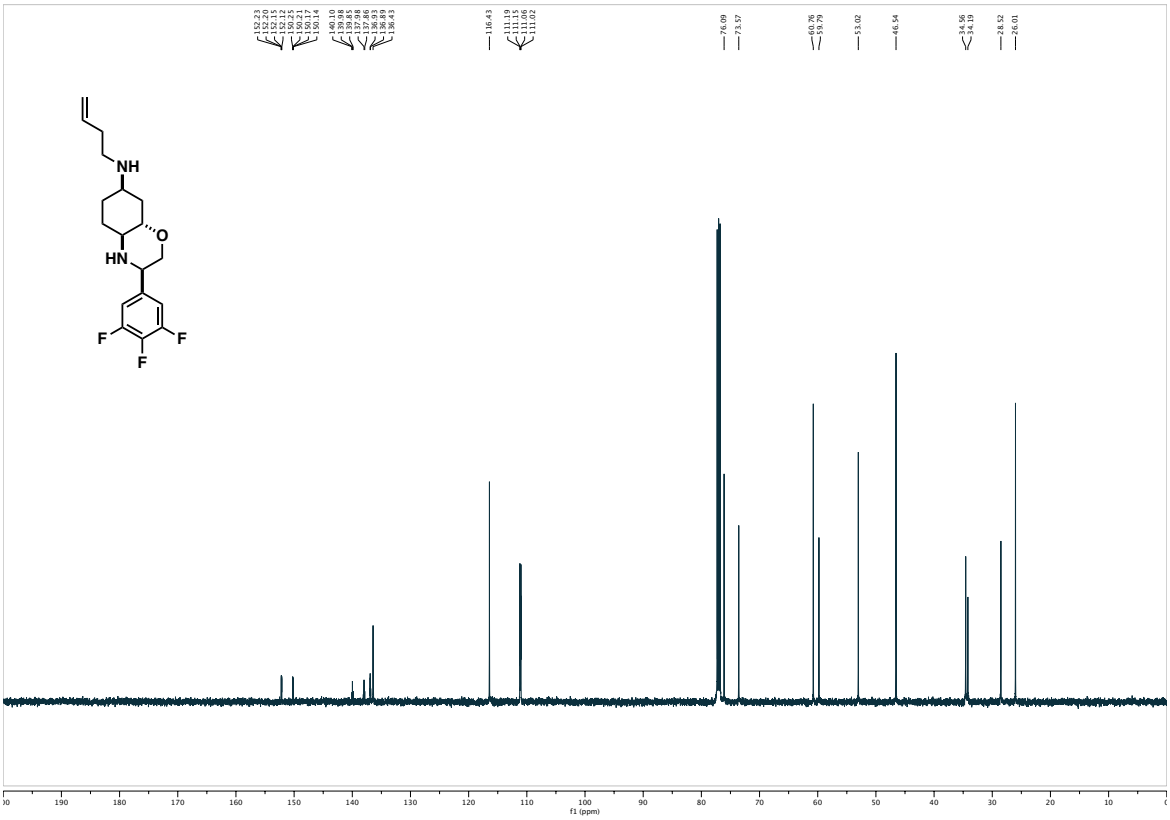
## 8-DiaA



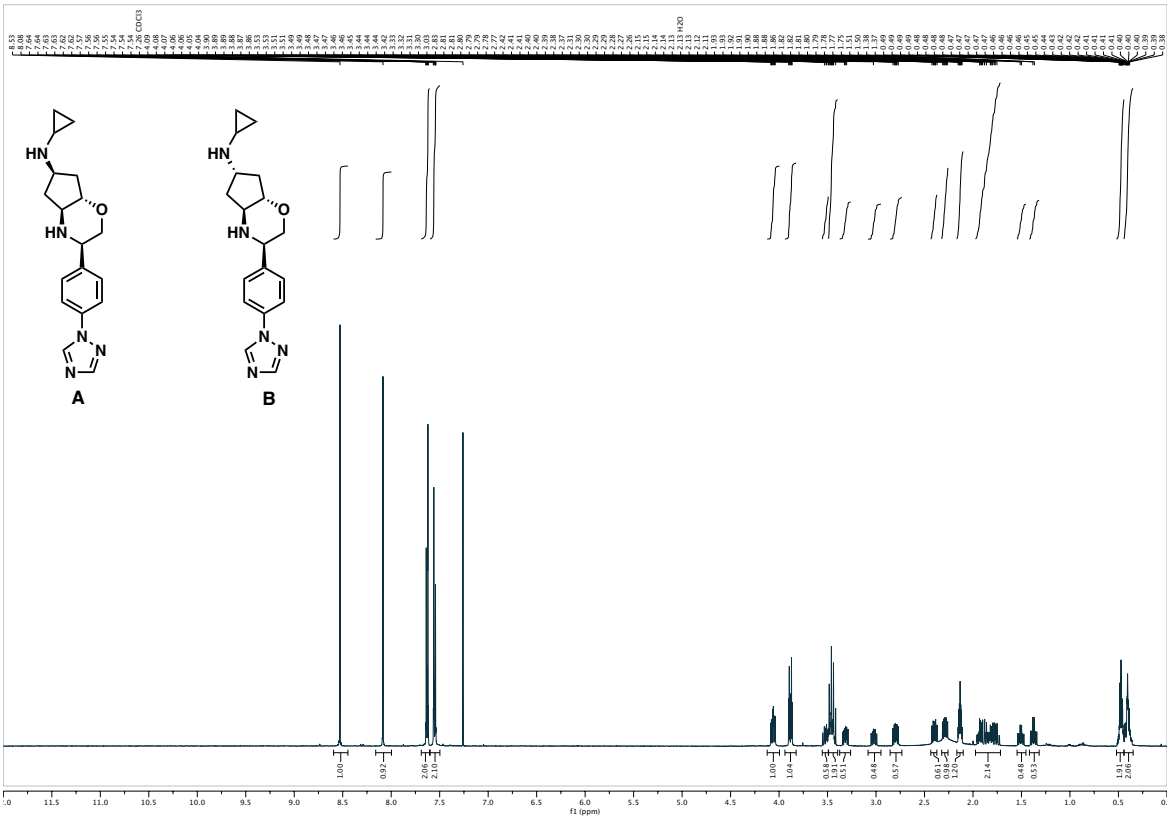



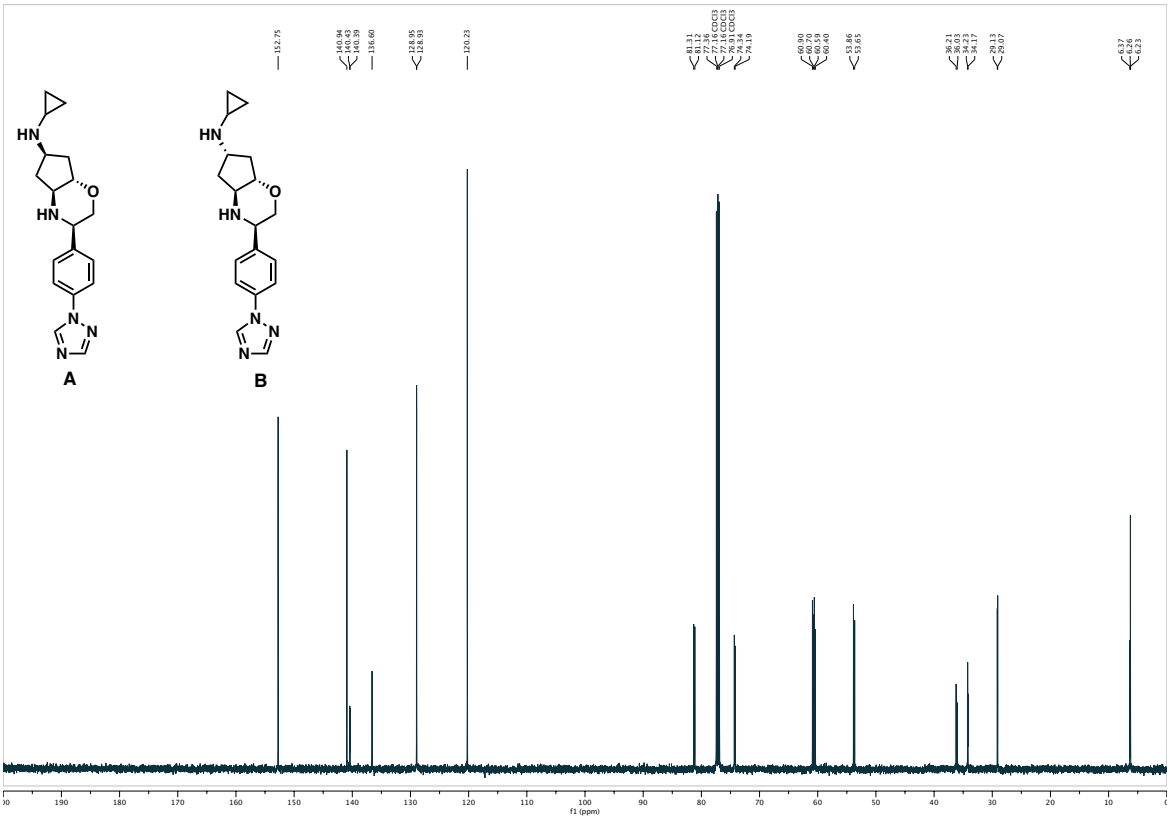
## 8-DiaB



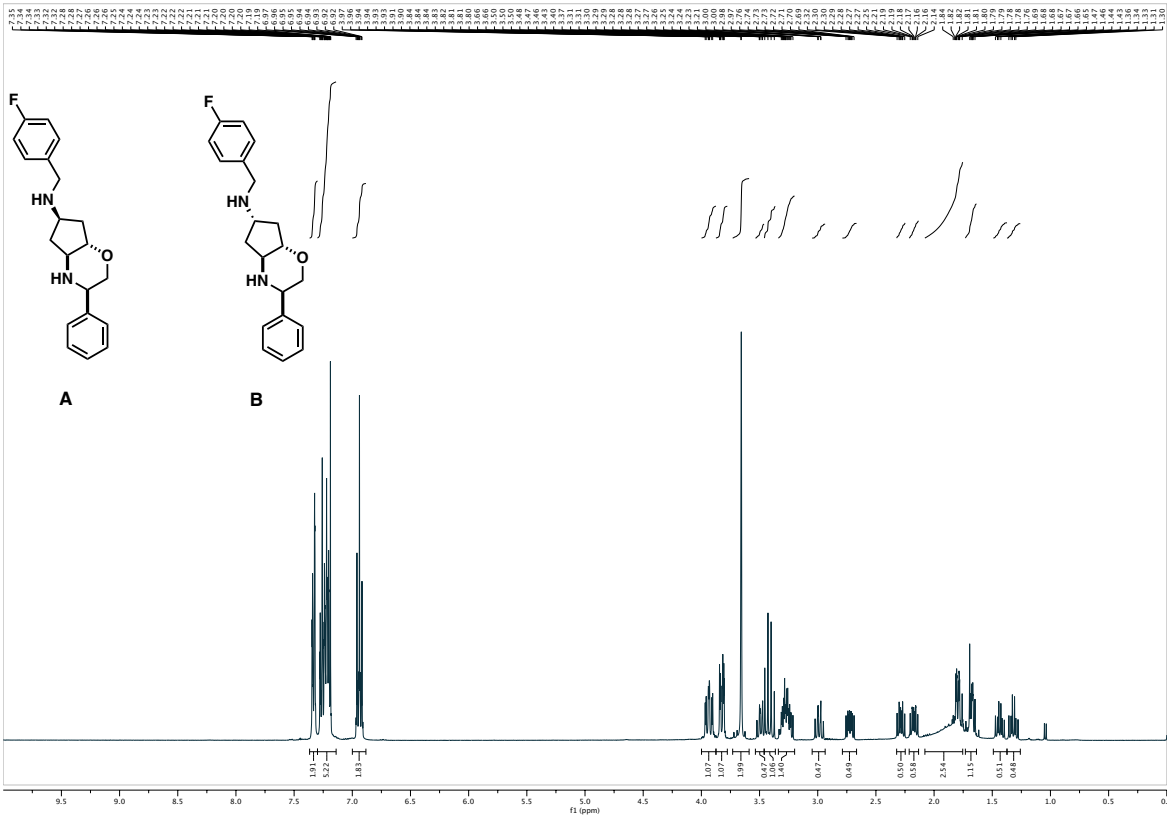



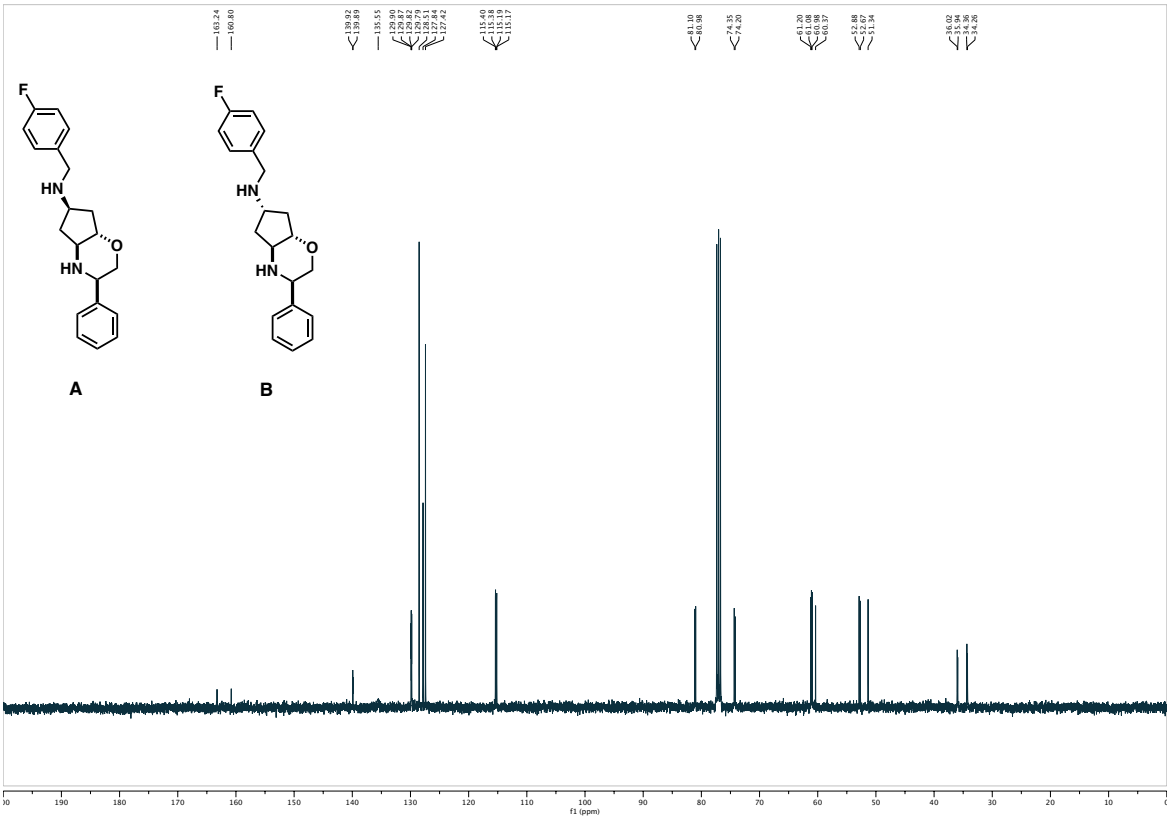
**9**



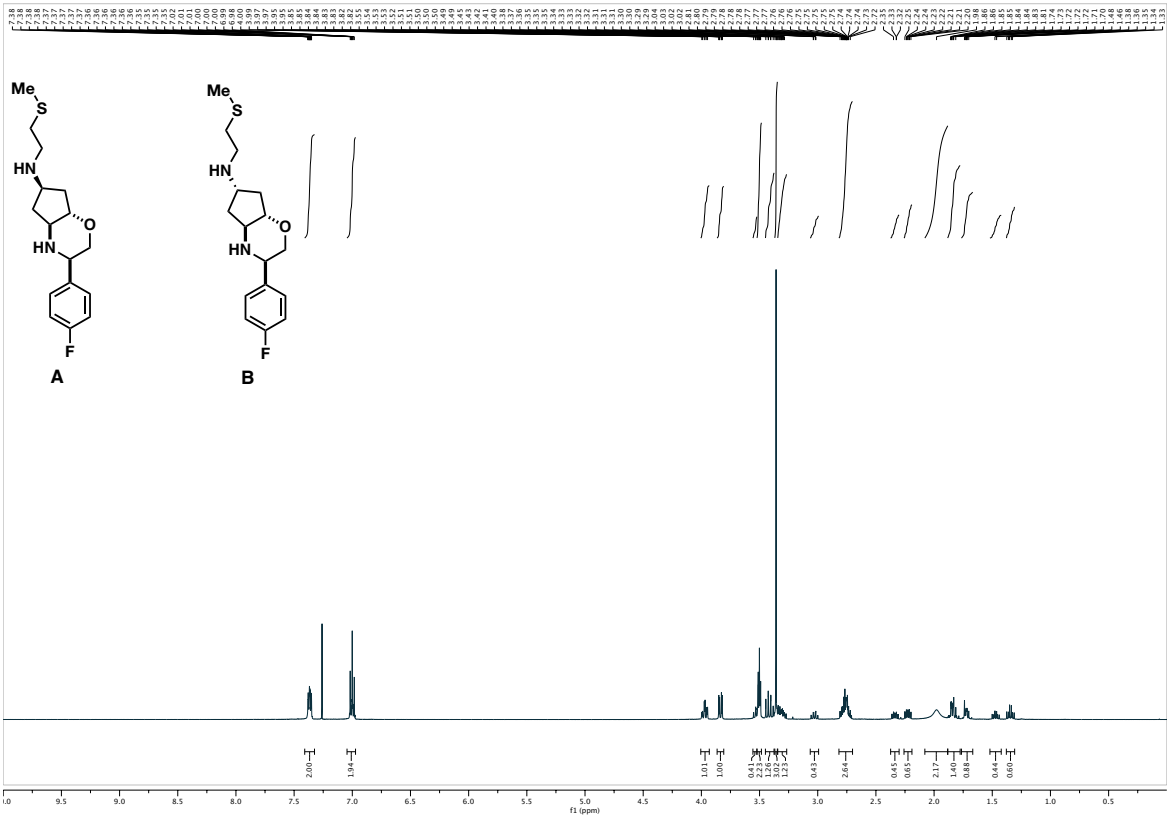



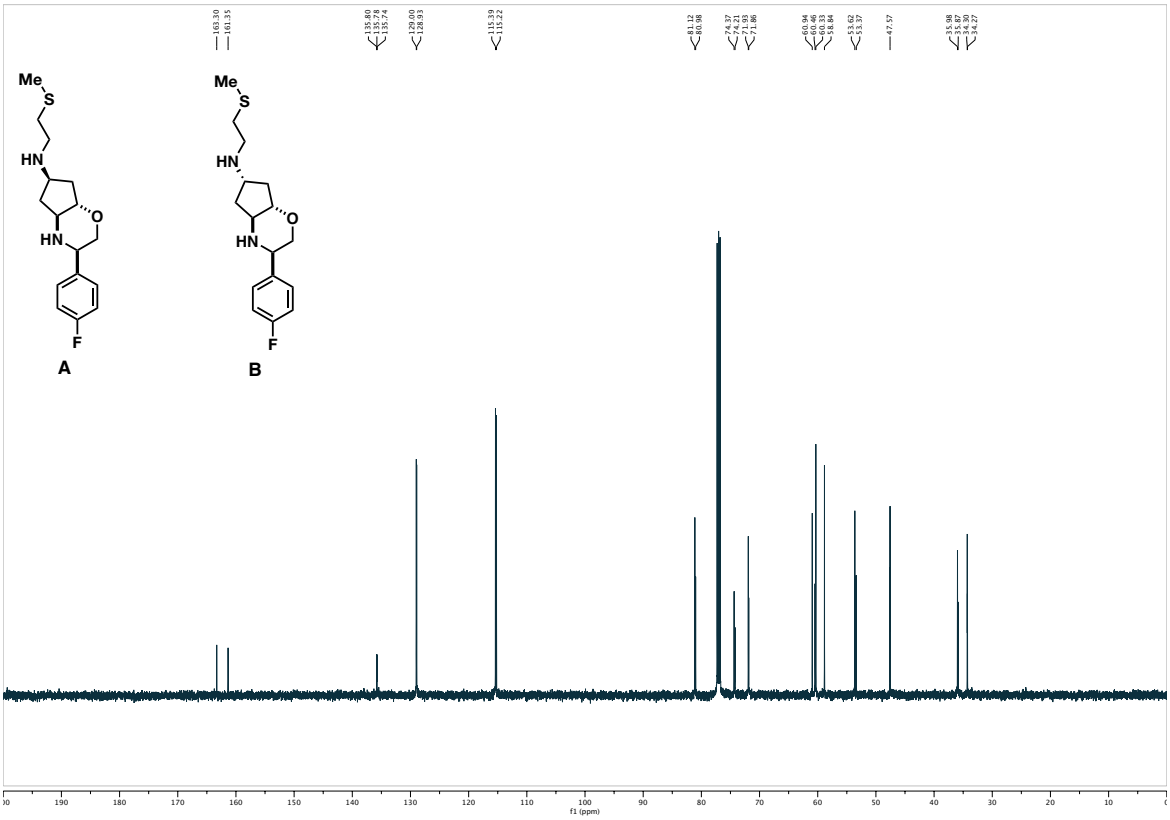
**10**



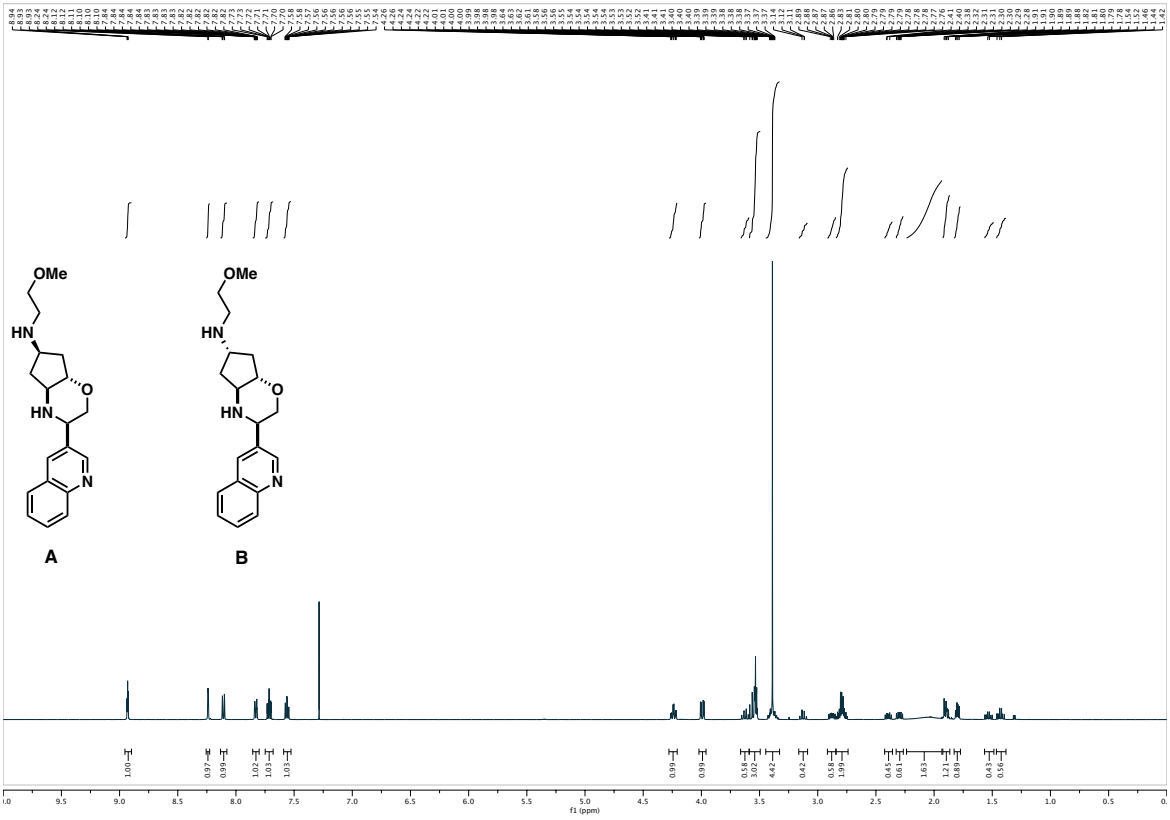



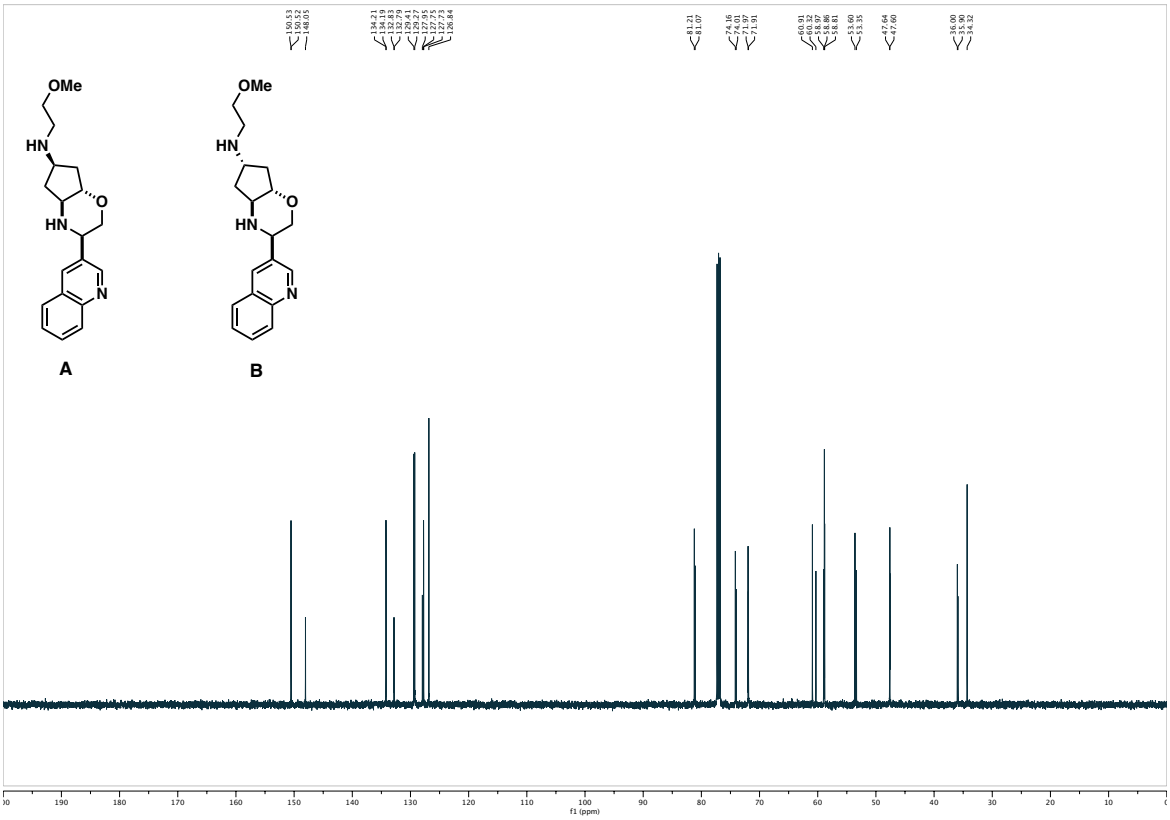
**11**



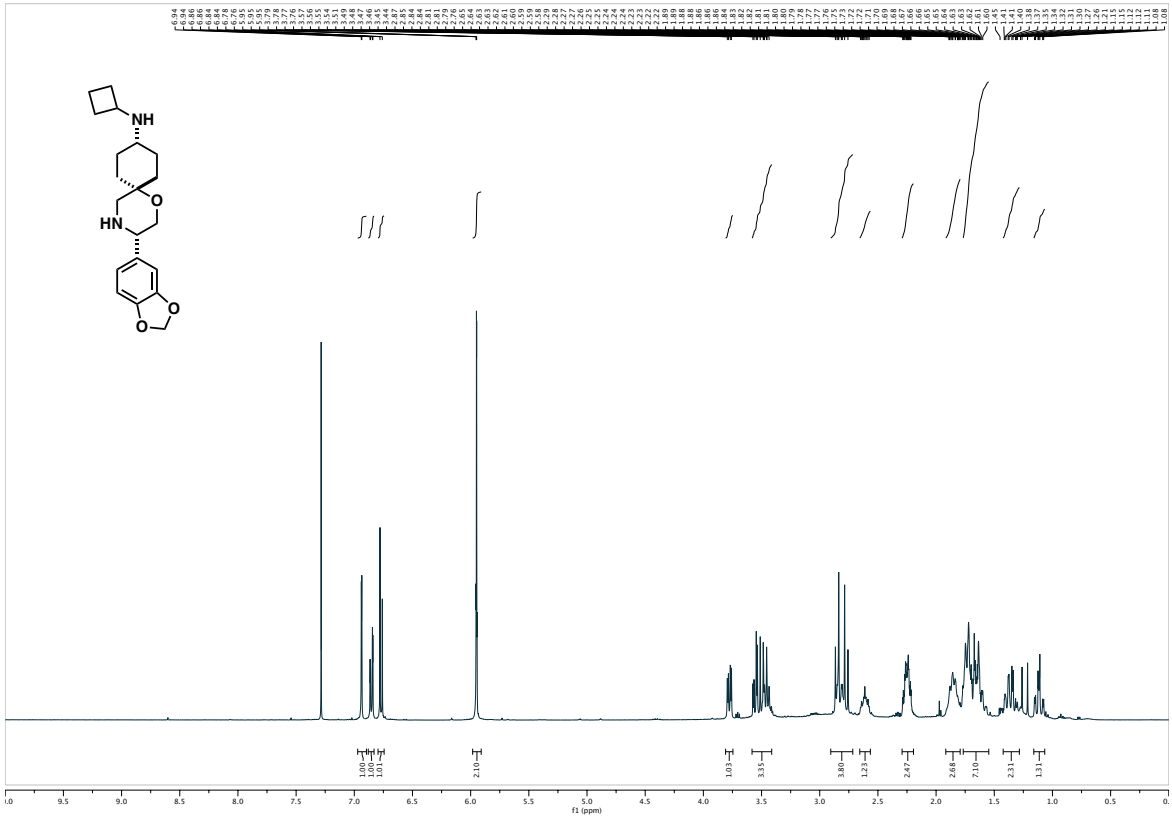



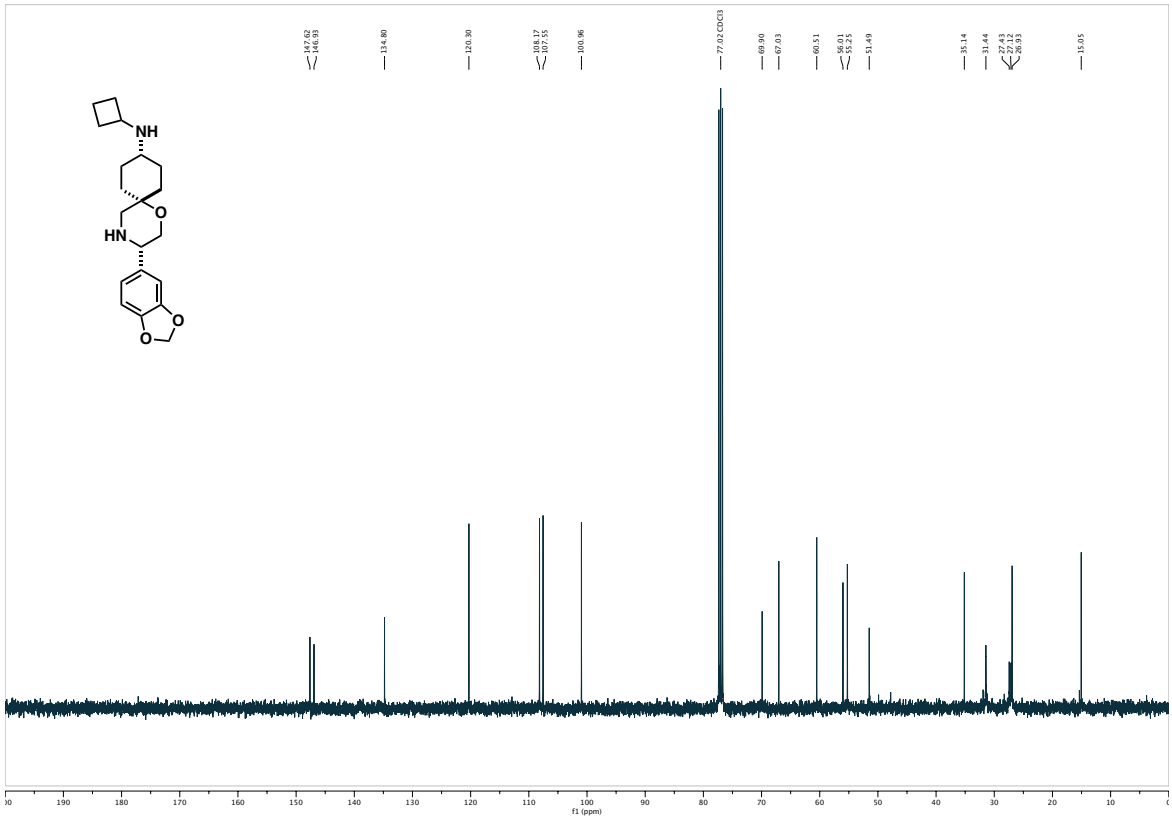
**12**



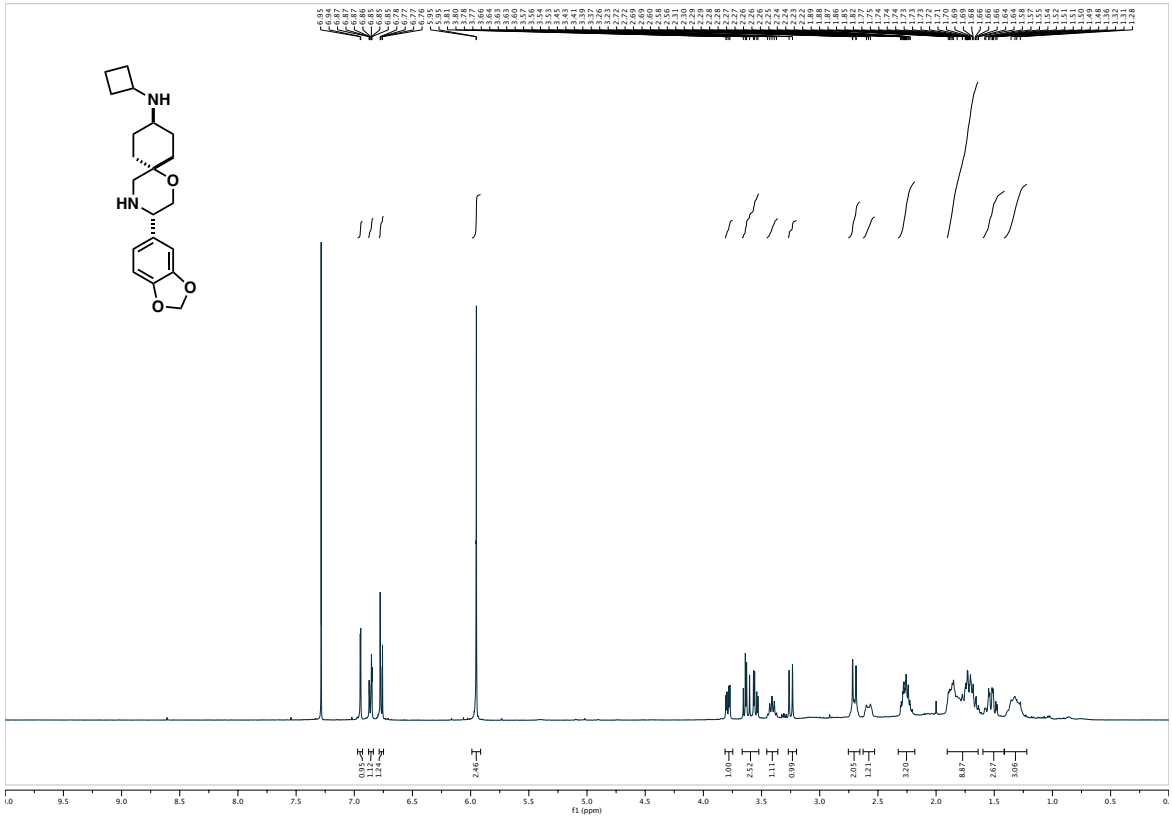



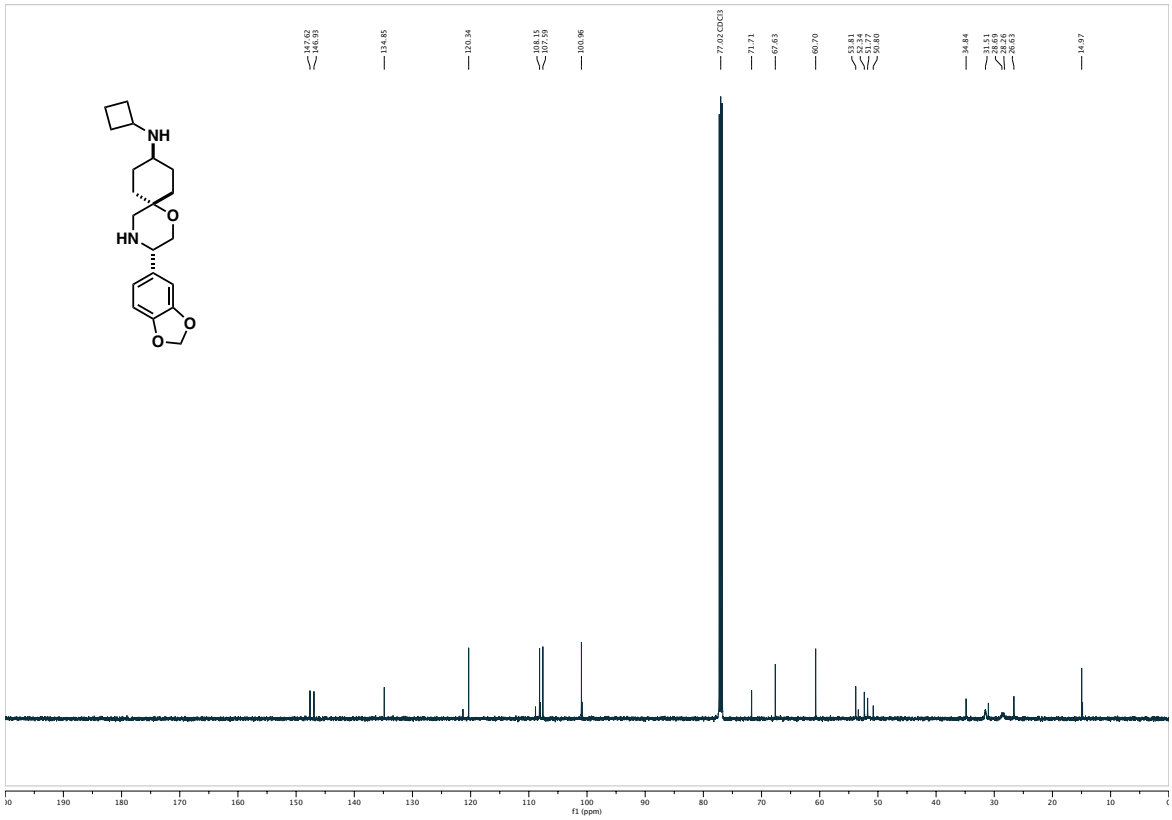
## 13-DiaA


NH
O
HN
O
O
f1 (ppm)

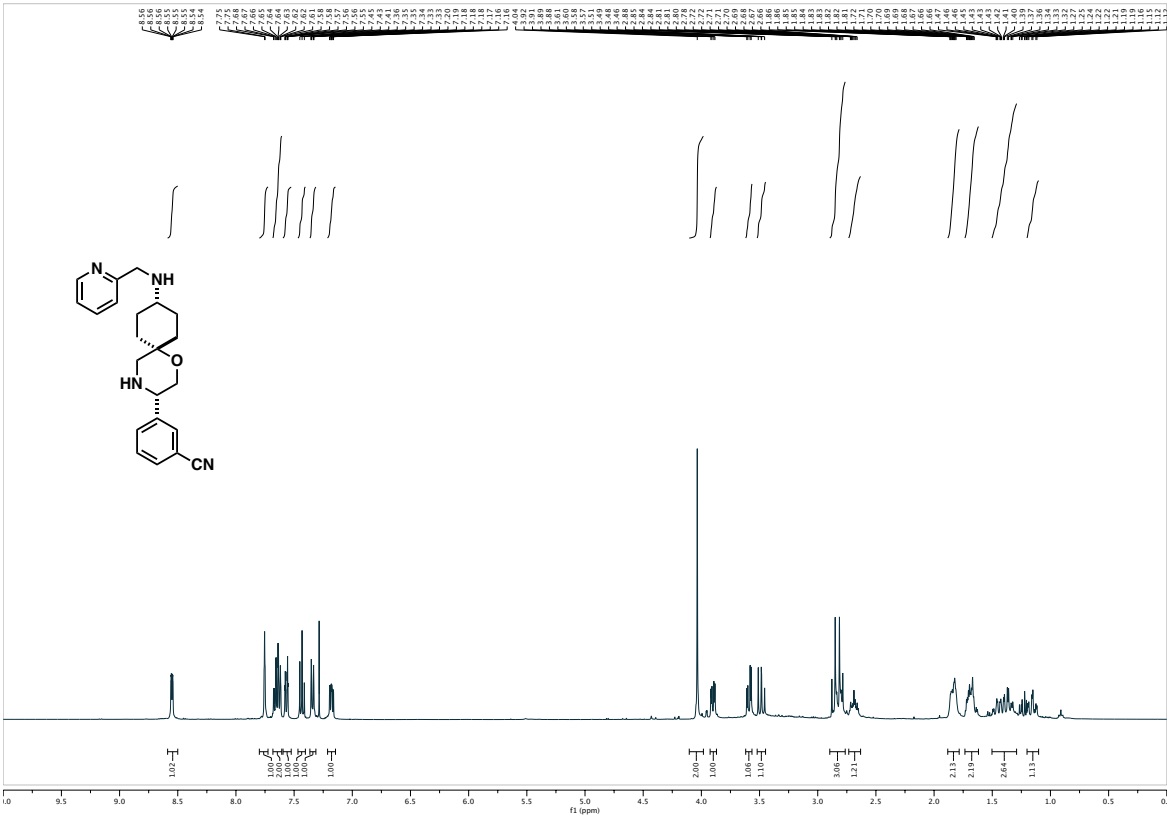

147.62
146.93
134.80
120.30
108.17
107.55
100.96
77.02 CDCl3
69.90
67.03
60.51
56.01
55.25
51.49
35.14
31.44
27.43
27.12
26.93
15.05
NH
O
HN
O
O
f1 (ppm)

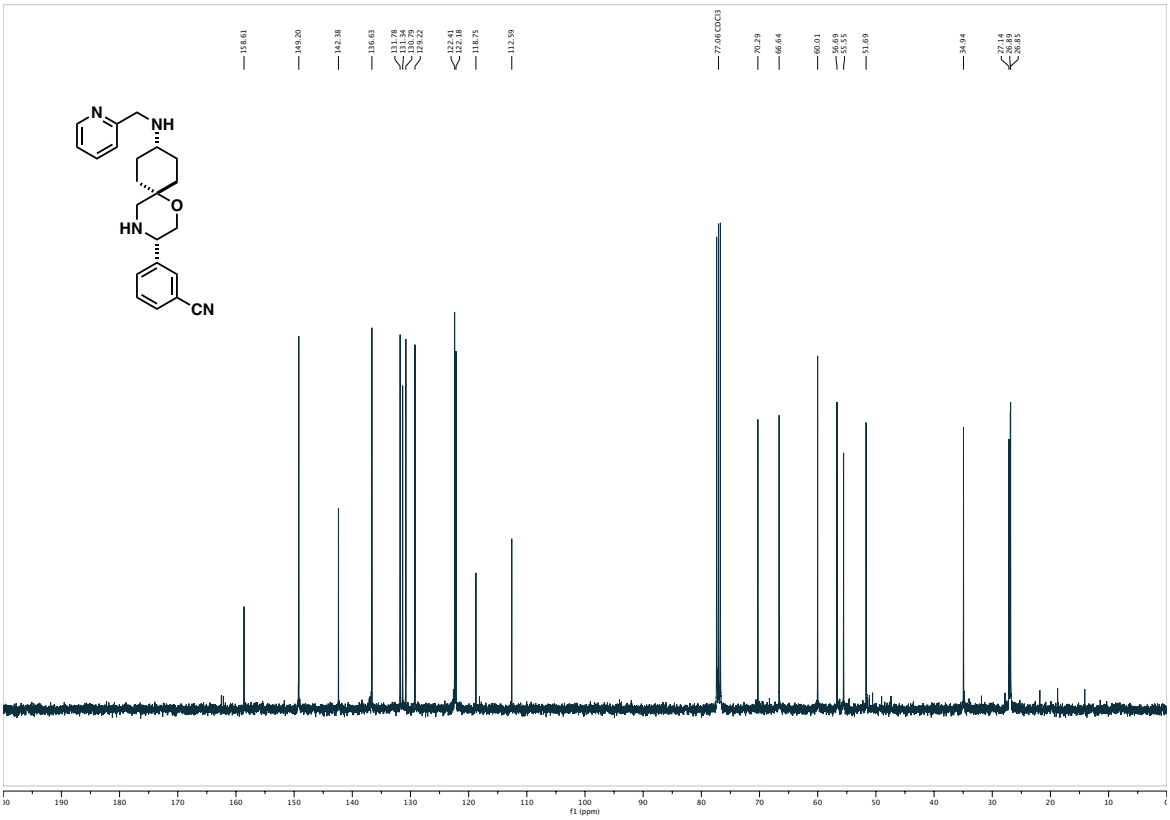
## 13-DiaB



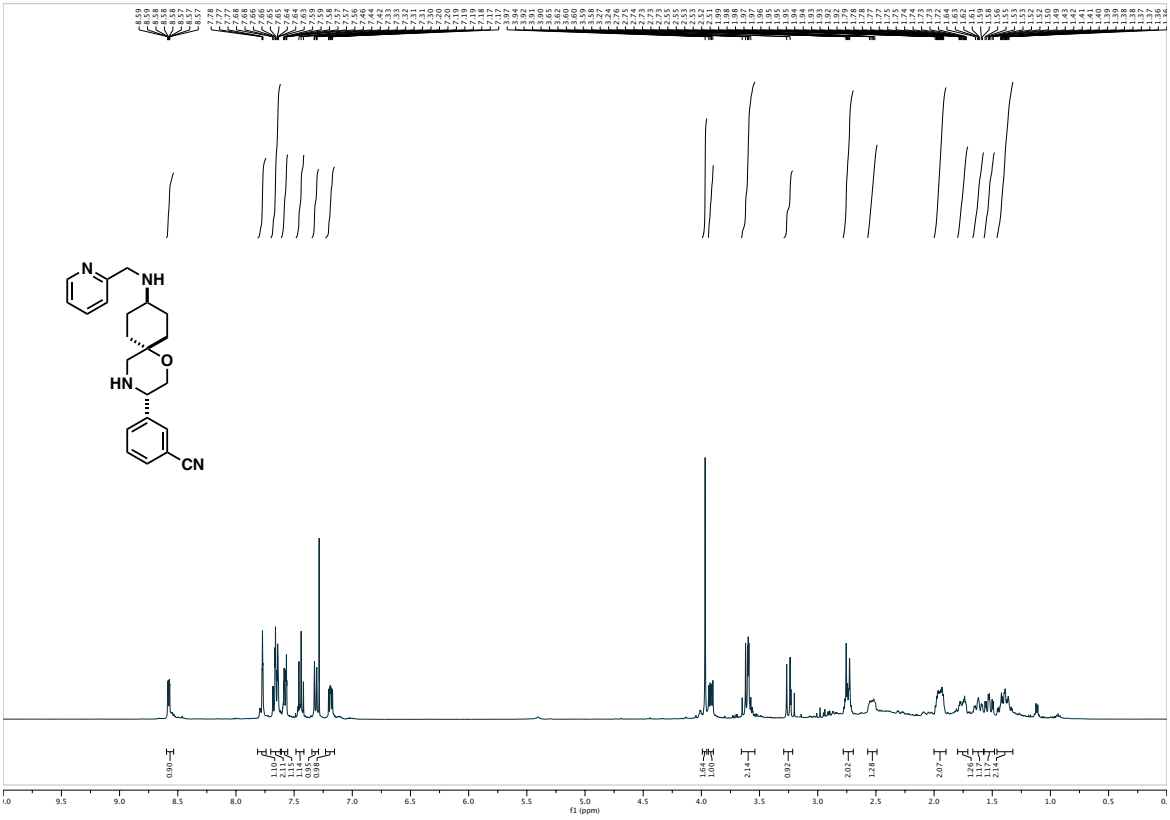



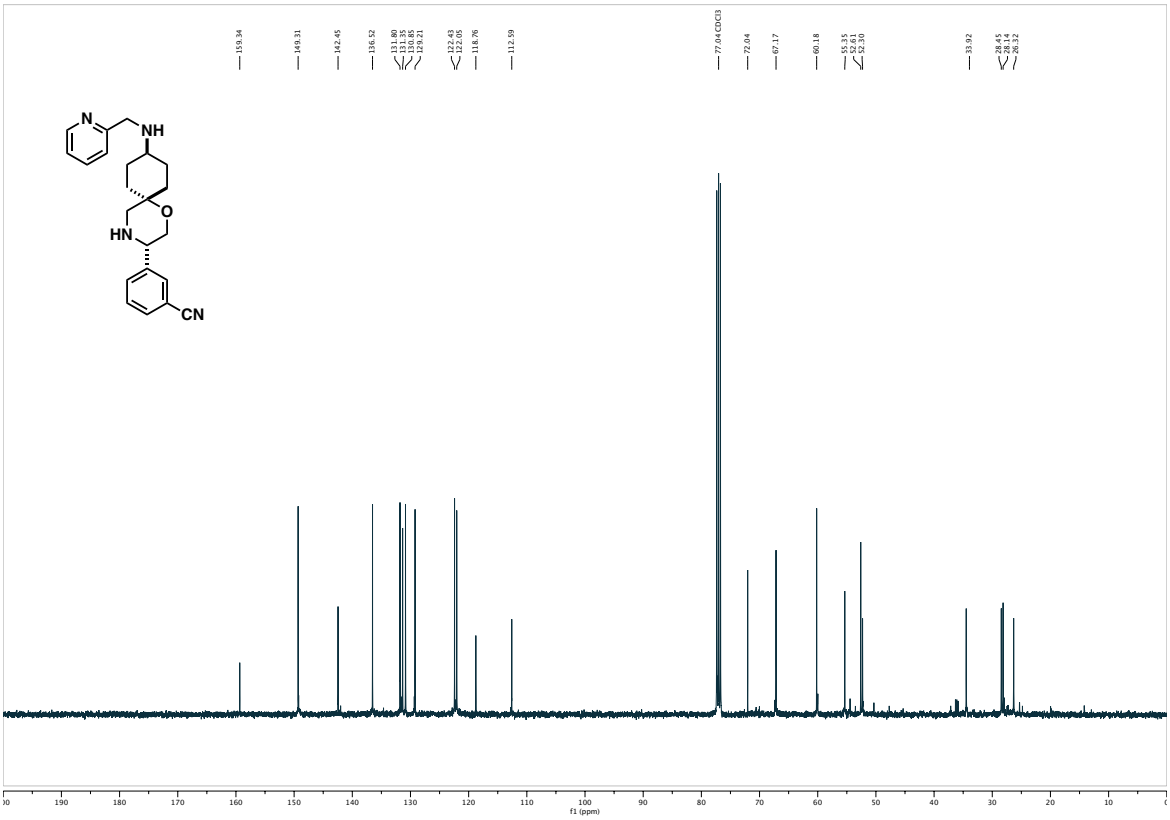
## 14-DiaA


N
NH
O
HN
CN
f1 (ppm)

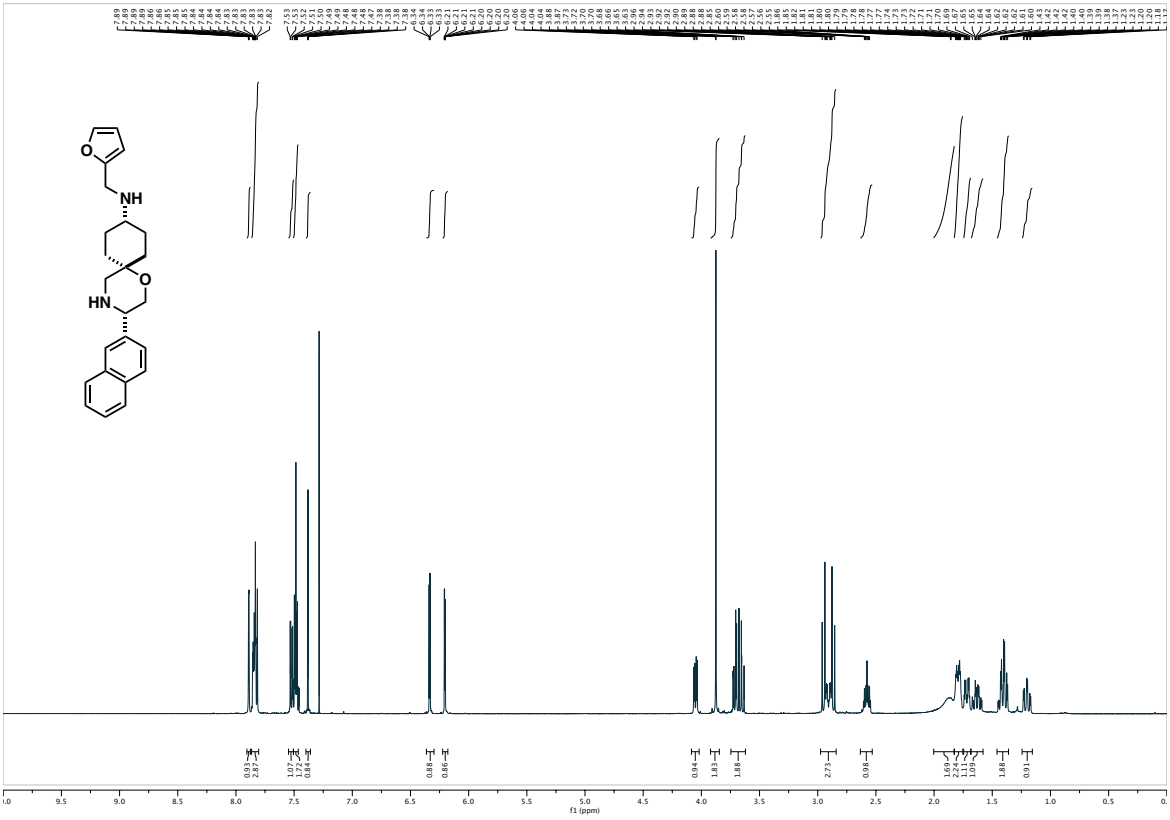

158.61
149.20
142.38
136.63
131.78
131.34
130.79
129.22
127.41
122.18
118.75
112.59
77.06 CDCl3
70.29
66.64
60.01
56.69
55.55
51.69
34.94
27.14
26.69
26.85
N
NH
O
HN
CN
f1 (ppm)

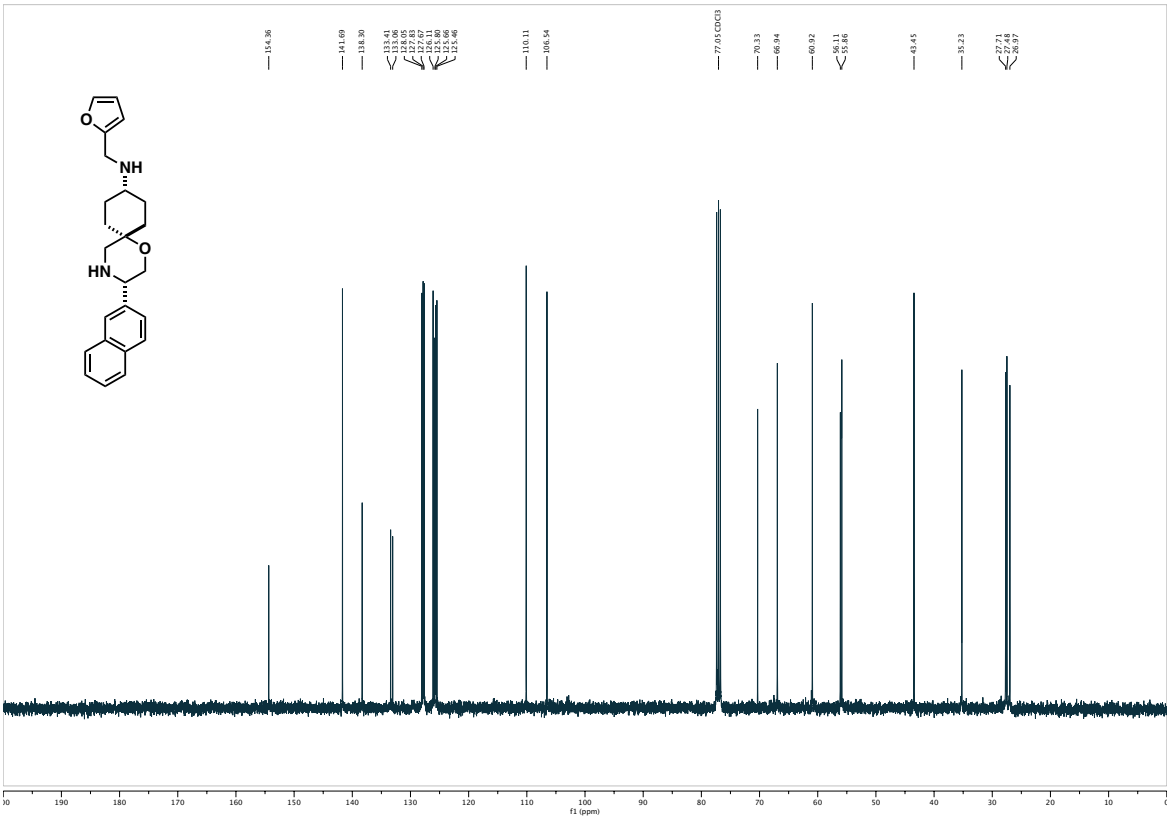
## 14-DiaB


N
NH
O
HN
CN
f1 (ppm)

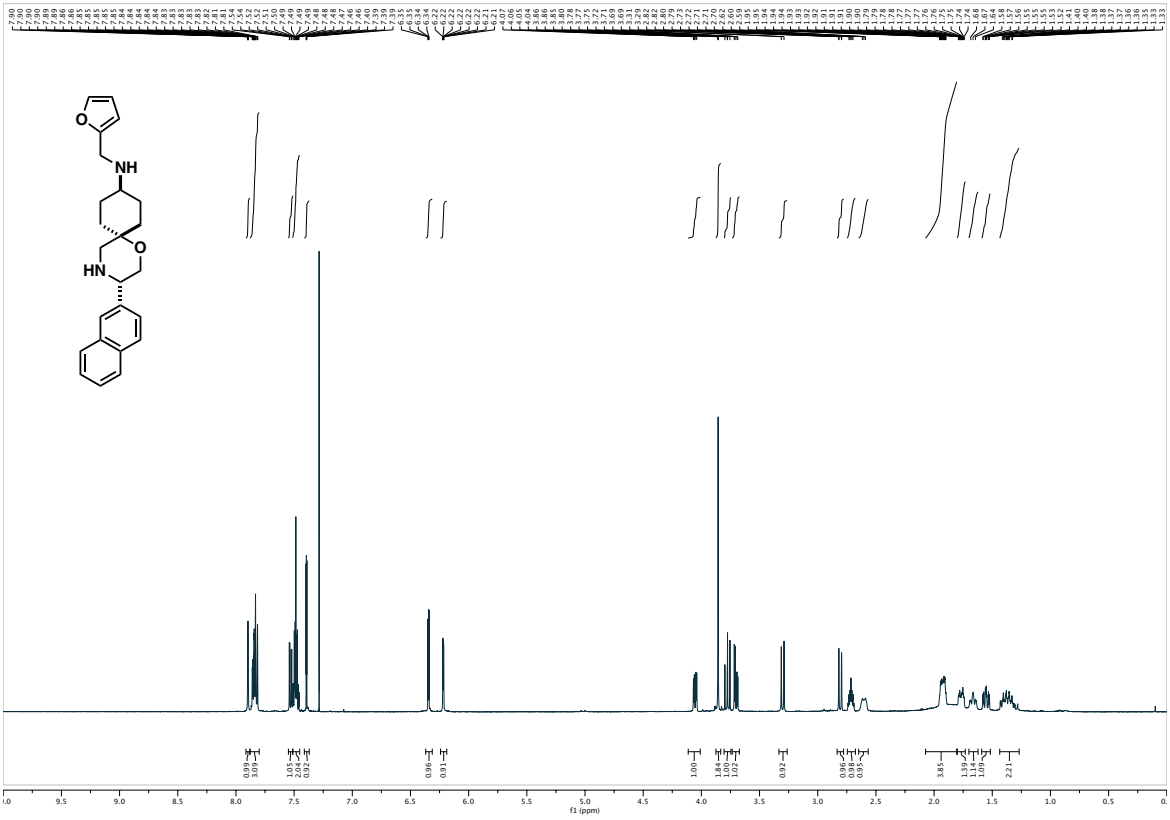

159.34
149.31
142.45
136.52
131.80
131.35
130.85
129.21
122.43
122.05
118.76
112.59
77.04 CDCl3
72.04
67.17
60.18
55.35
52.61
52.30
33.92
28.45
28.14
26.32
N
NH
O
HN
CN
f1 (ppm)

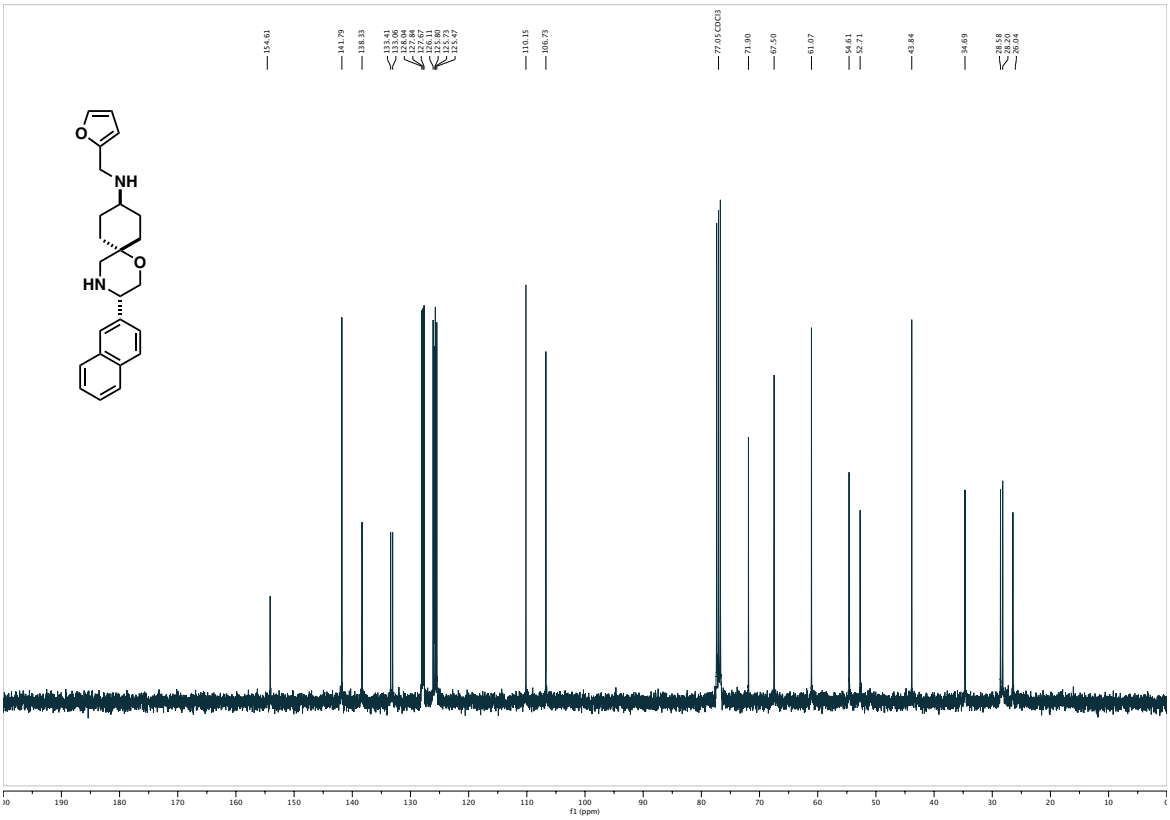
## 15-DiaA



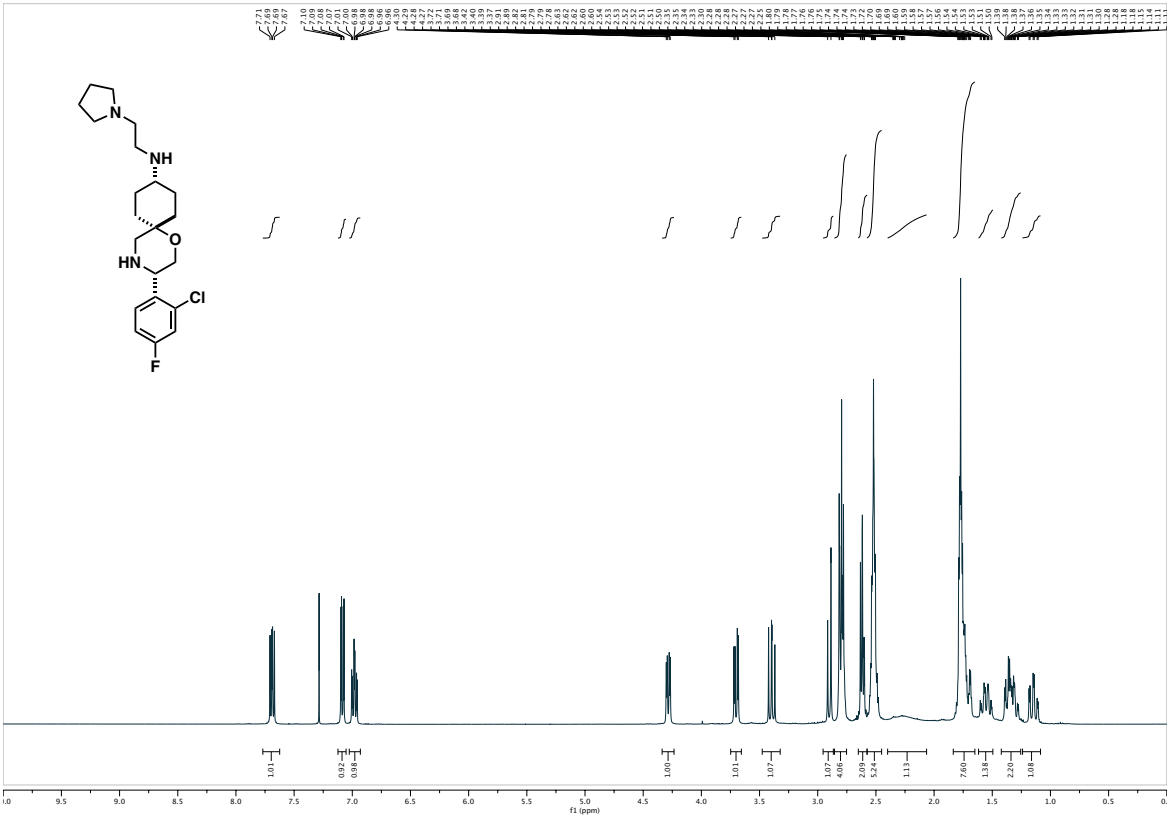



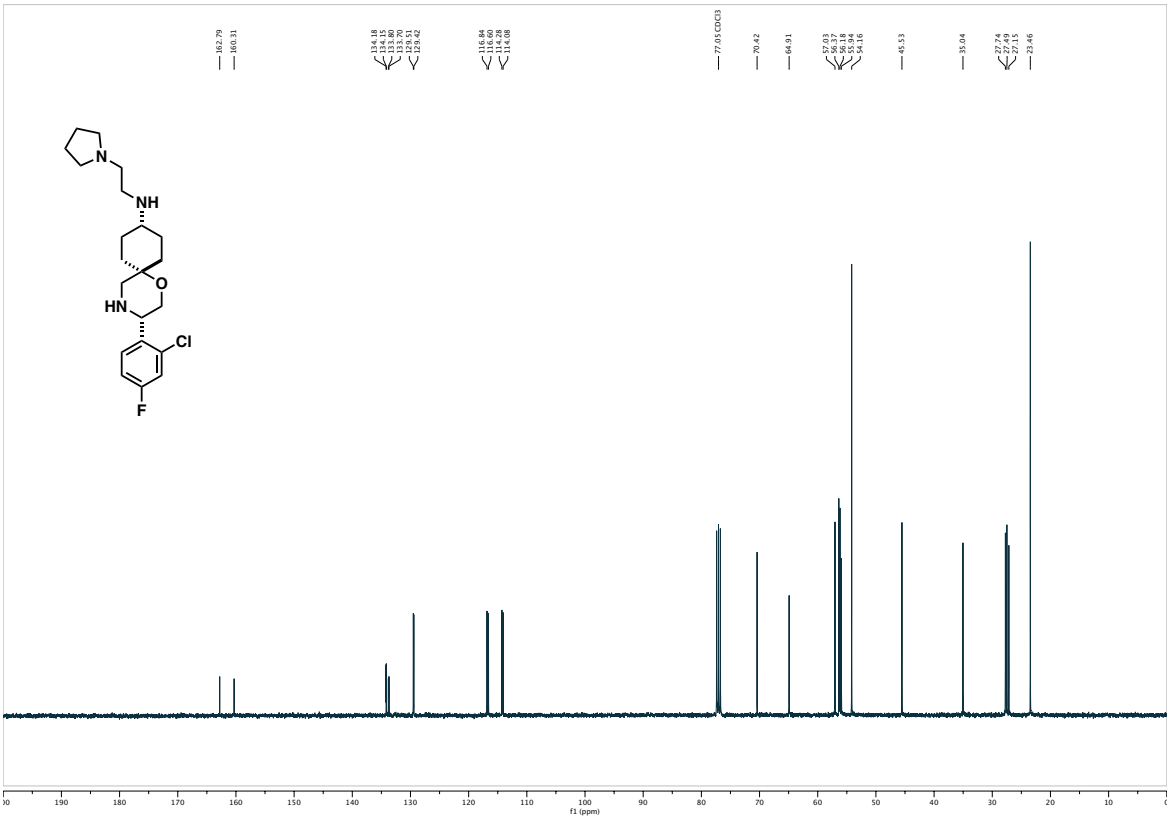
## 15-DiaB



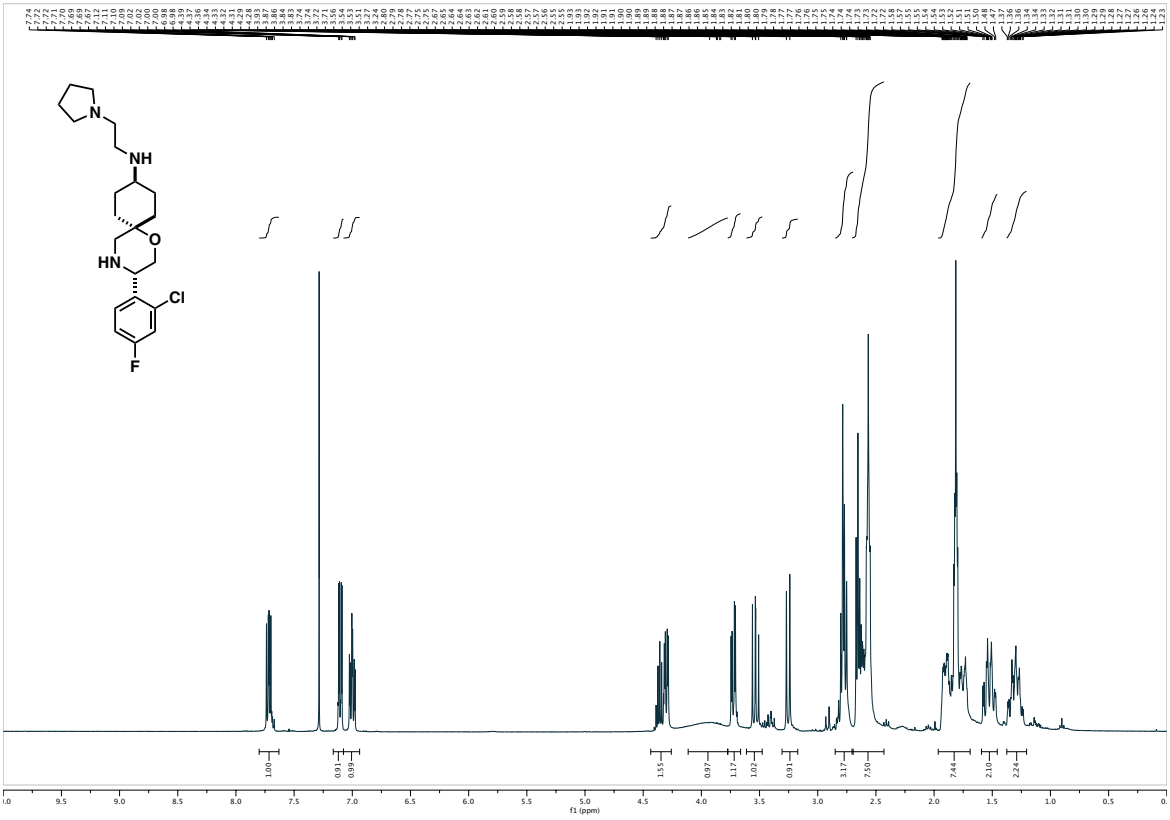


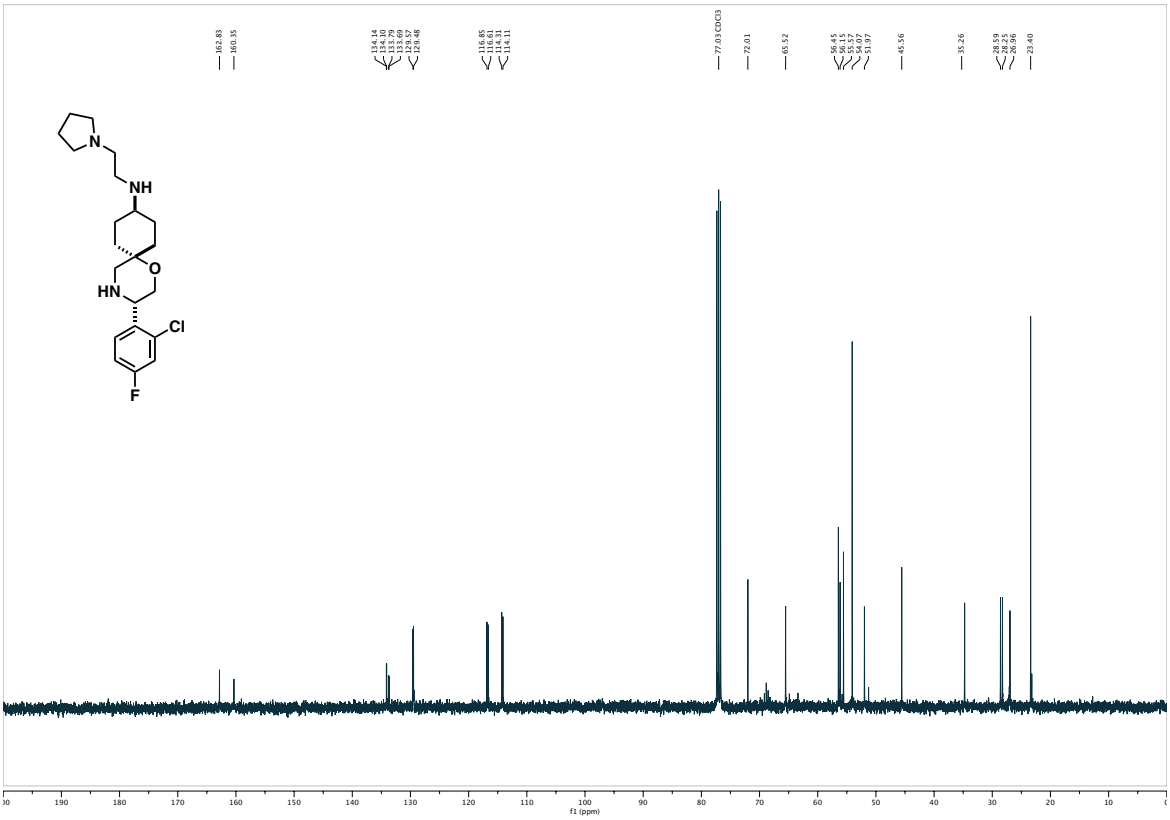
## 16-DiaA



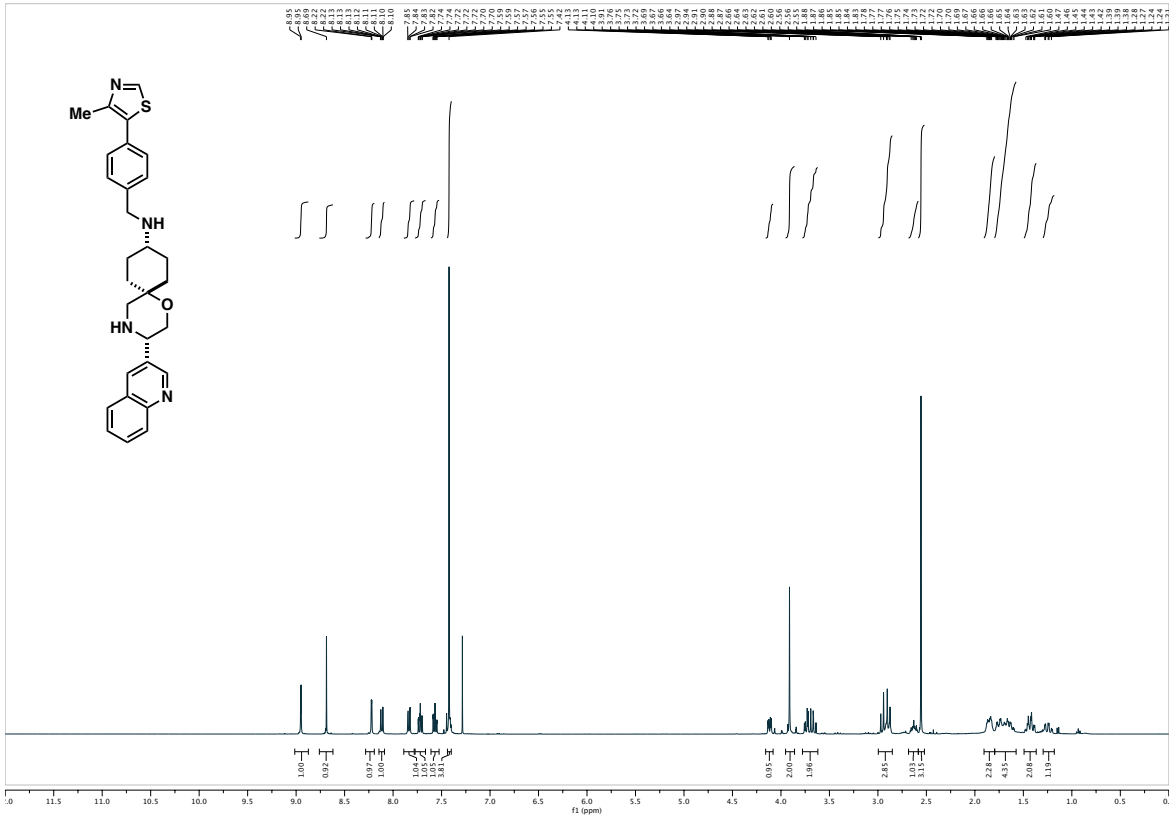



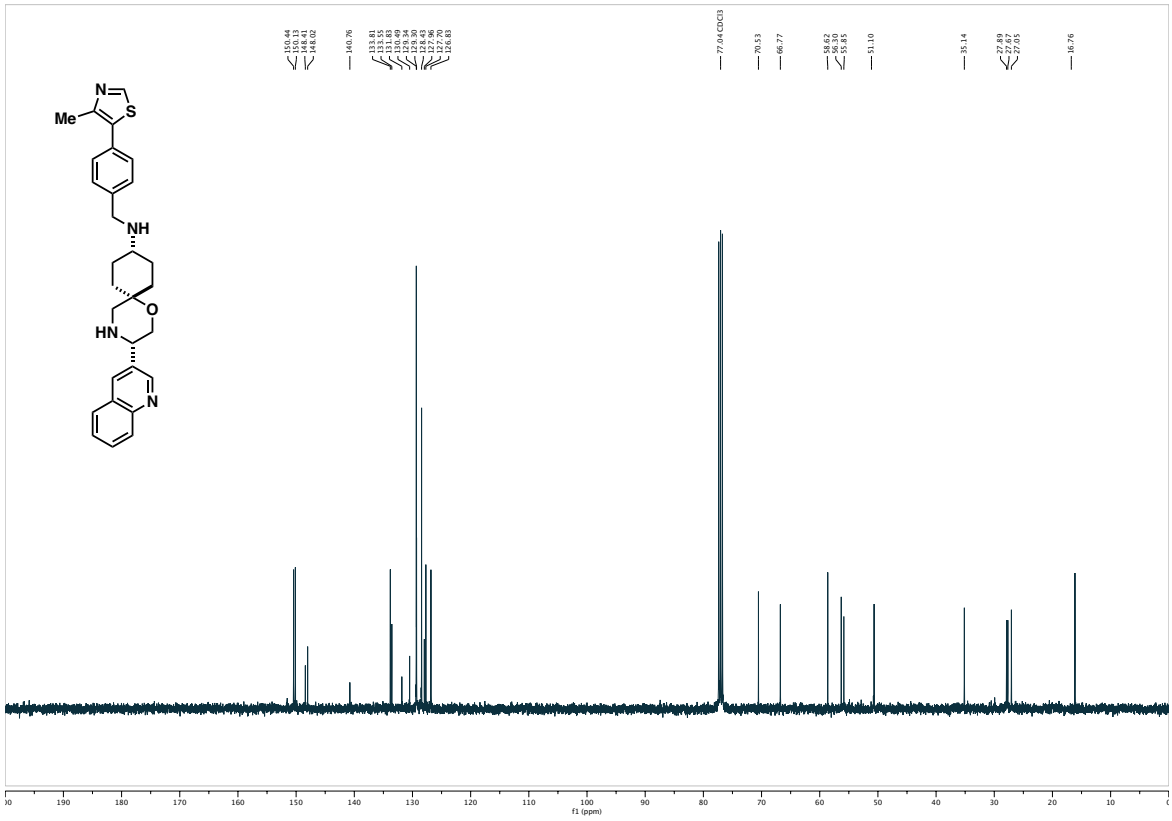
## 16-DiaB



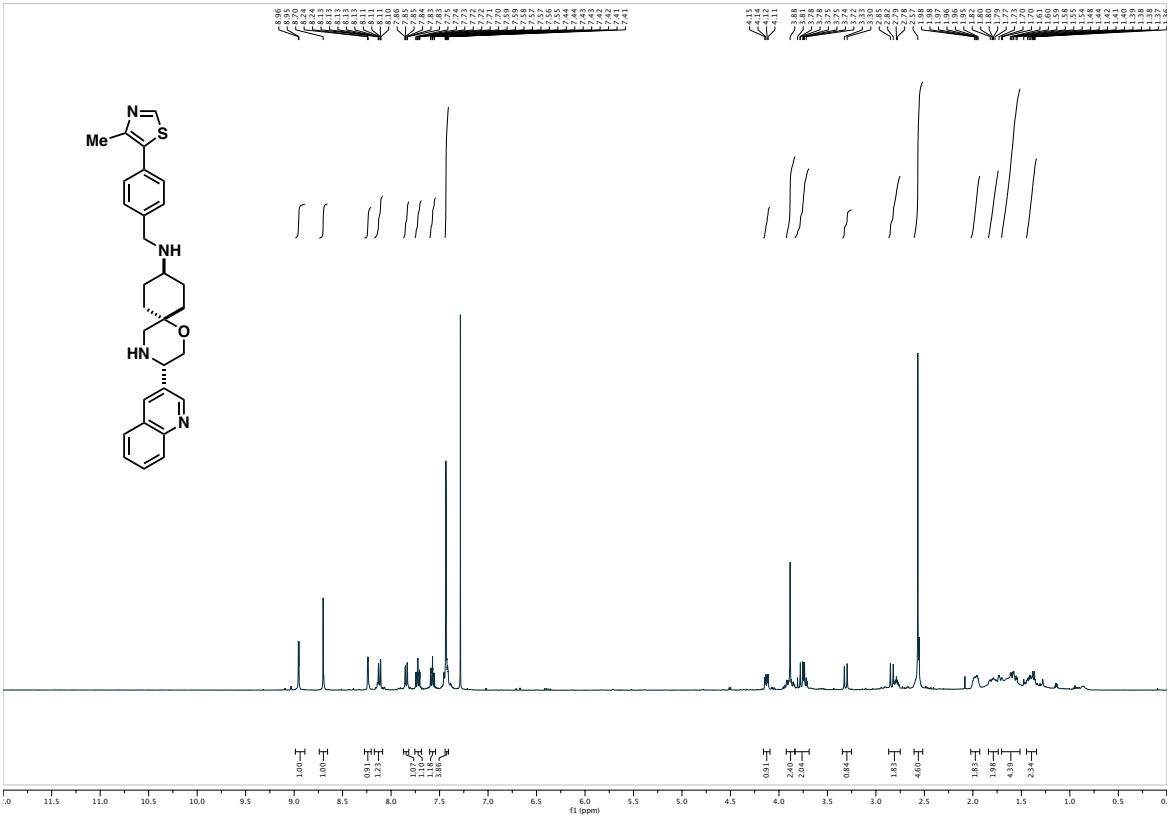



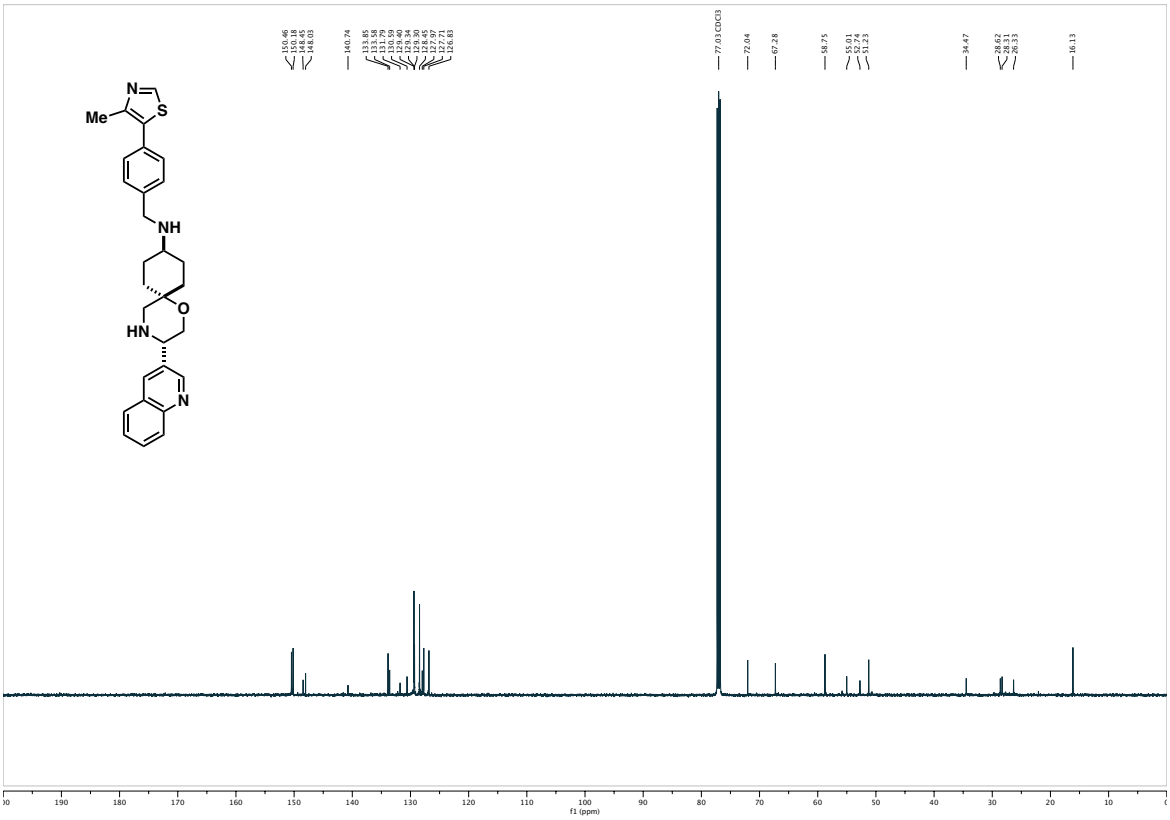
## 17-DiaA


Me
NH
HN
O
N
f1 (ppm)

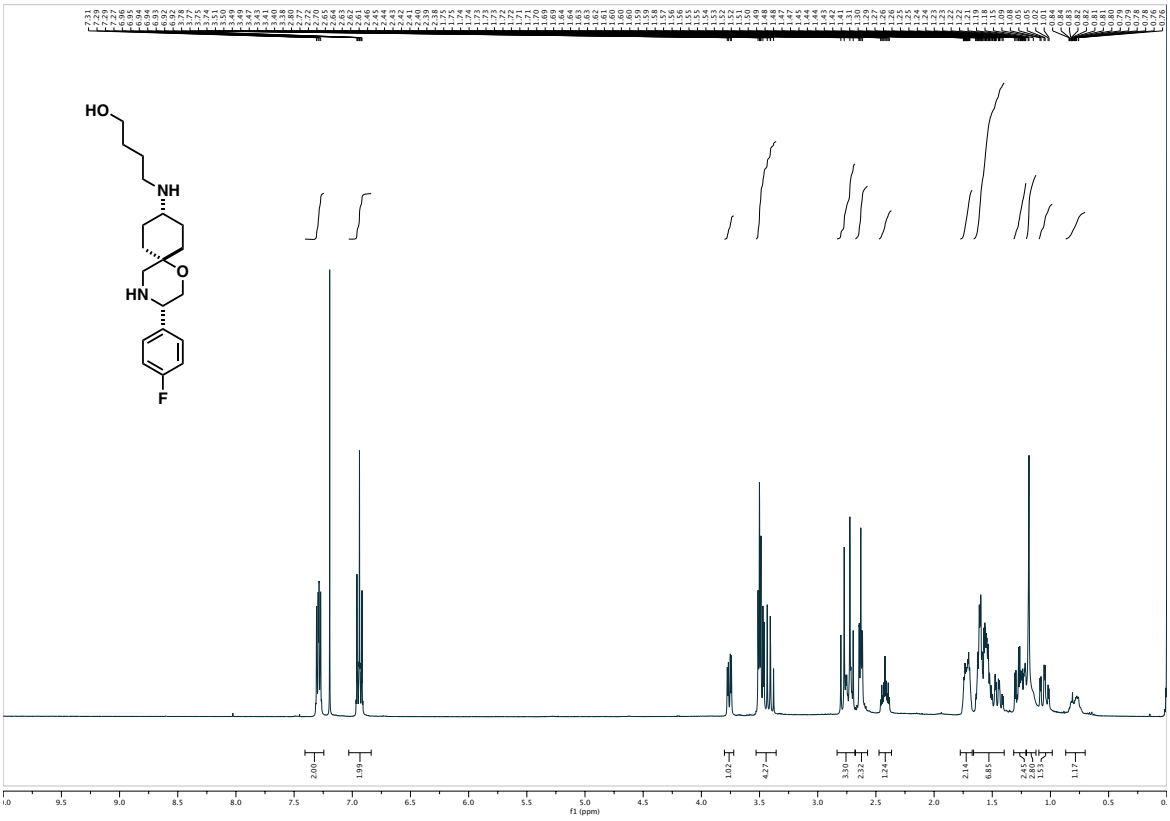

Me
NH
HN
O
N
77.04 CDCl3
70.53
66.77
58.62
56.30
55.85
51.10
35.14
27.89
27.67
27.05
16.76
f1 (ppm)

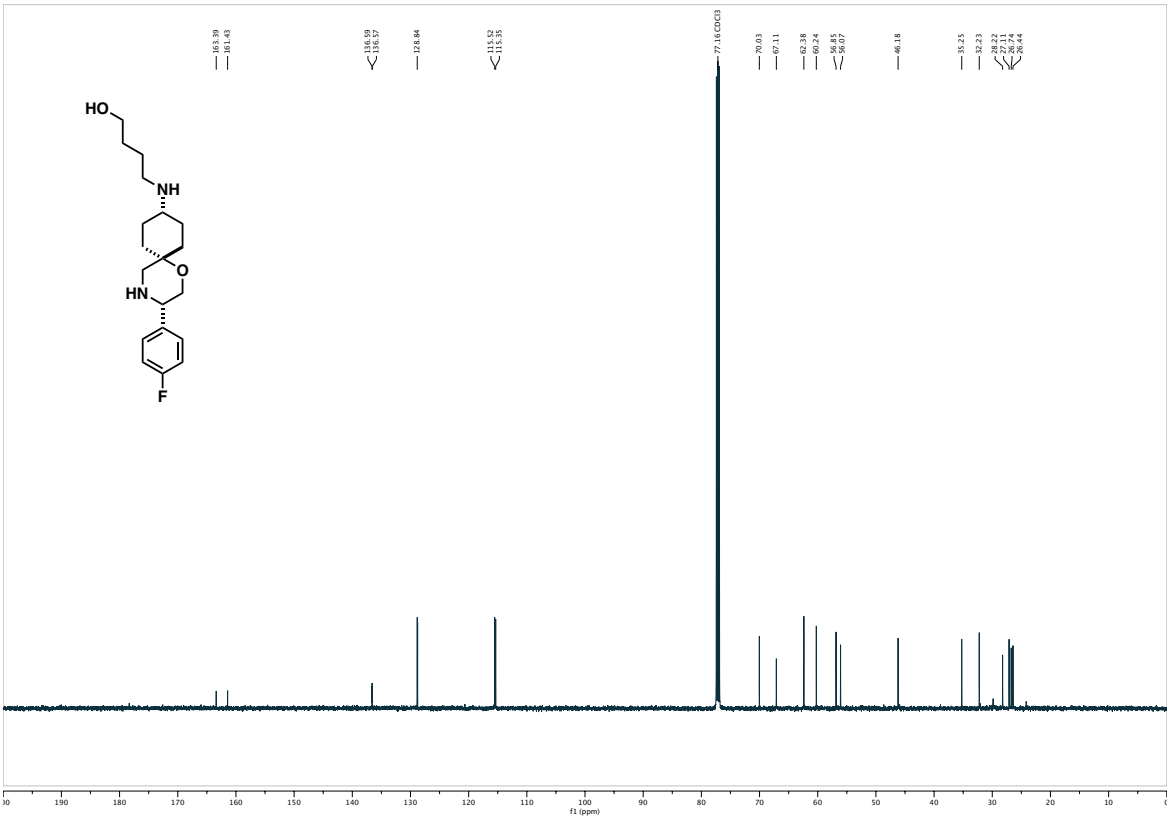
## 17-DiaB



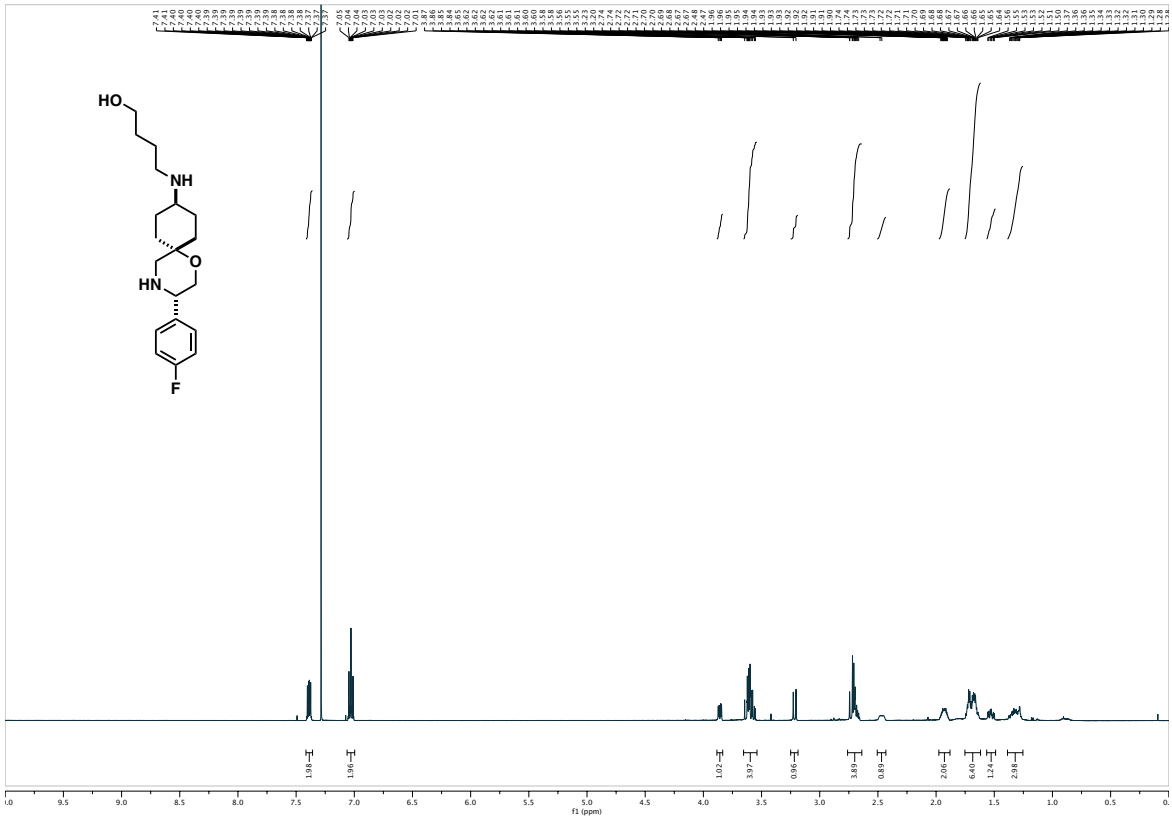



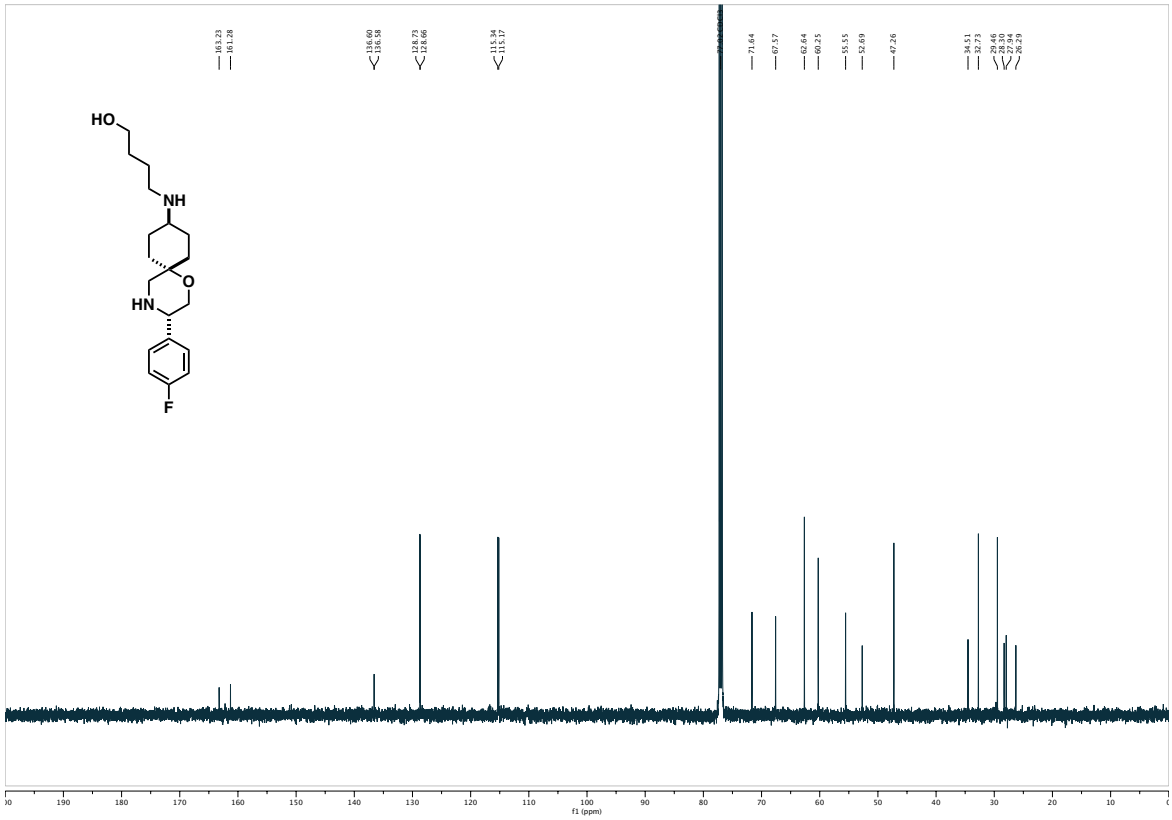
## 18-DiaA



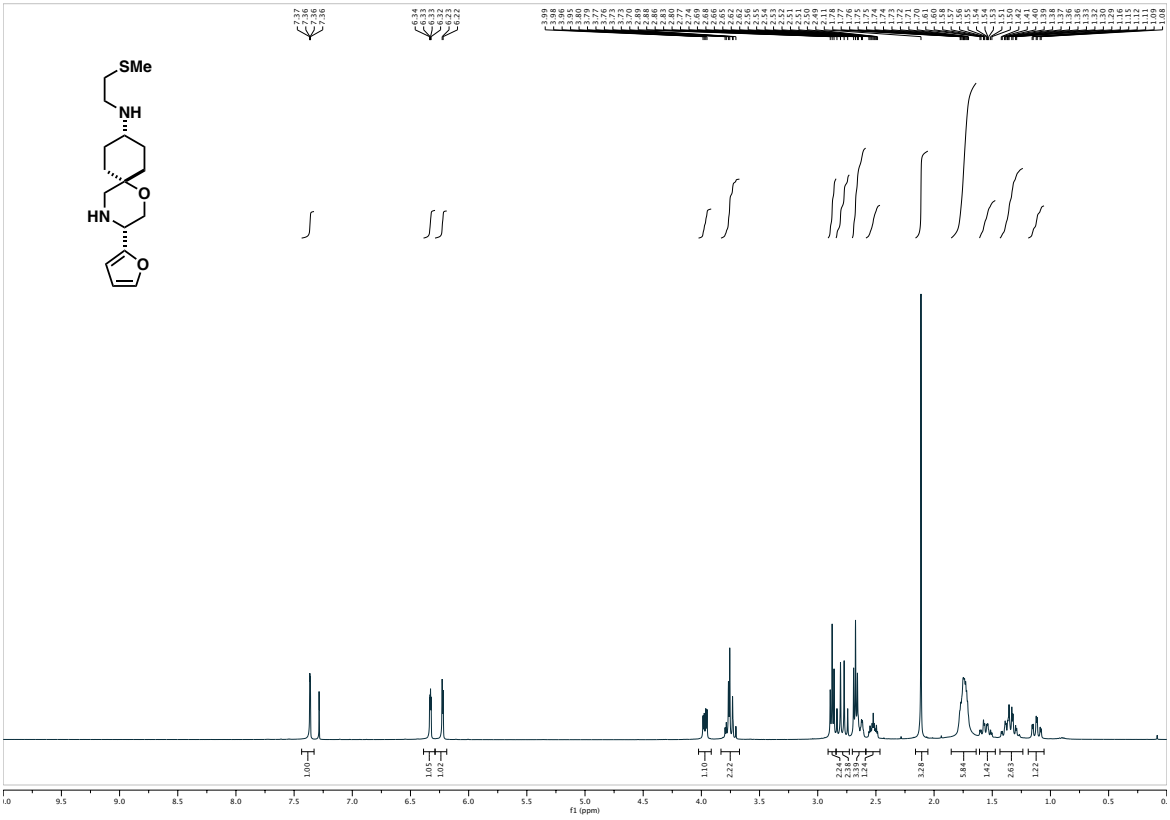



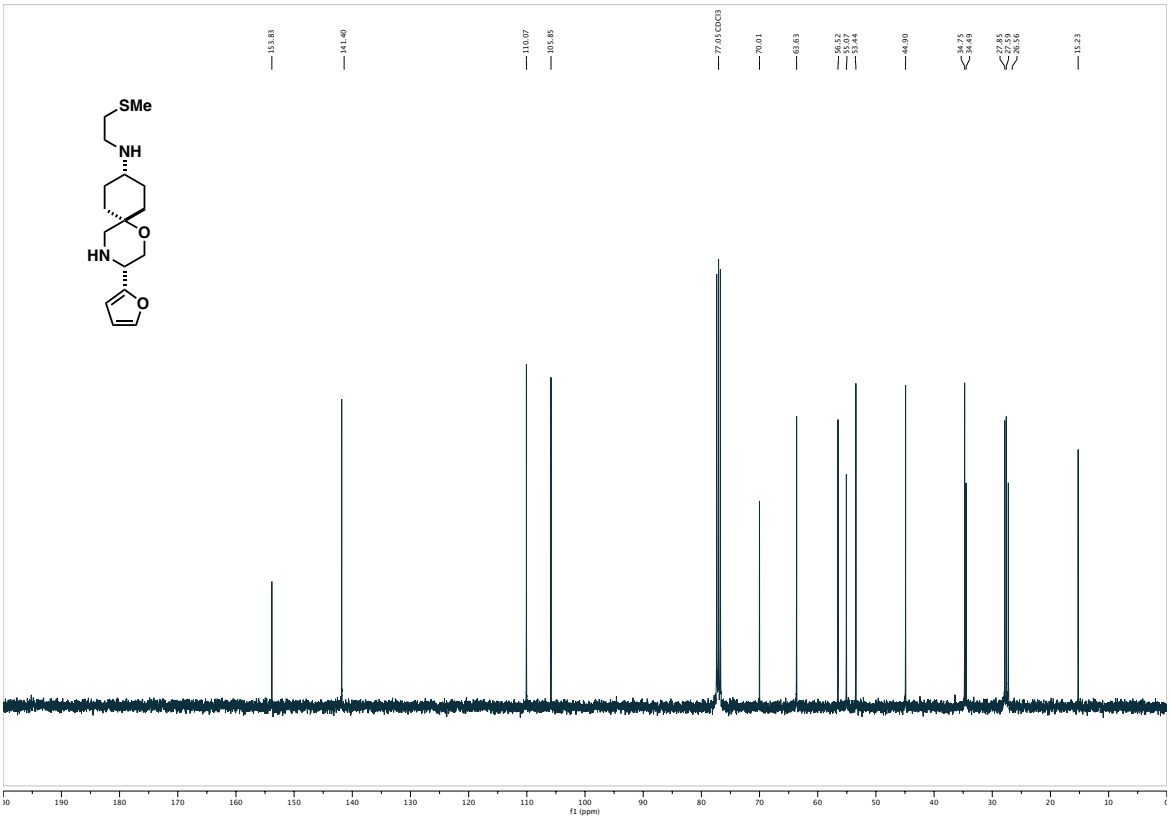
## 18-DiaB



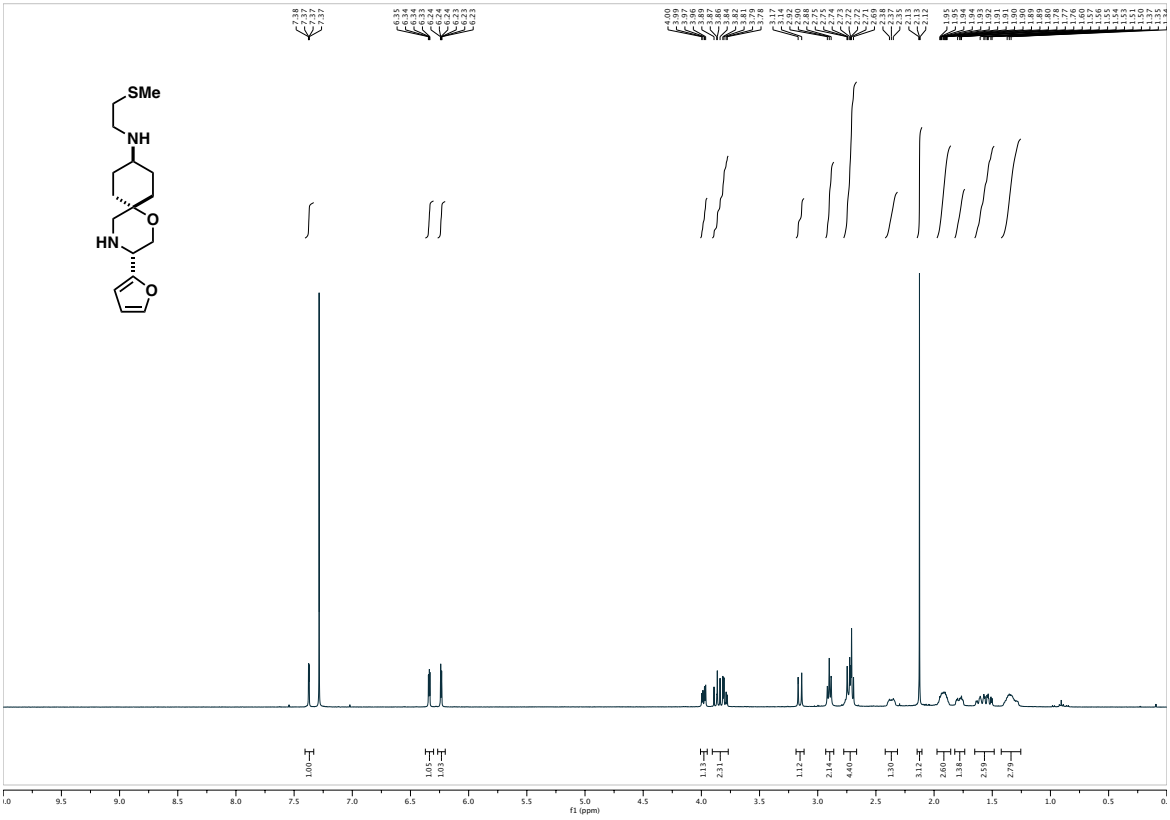



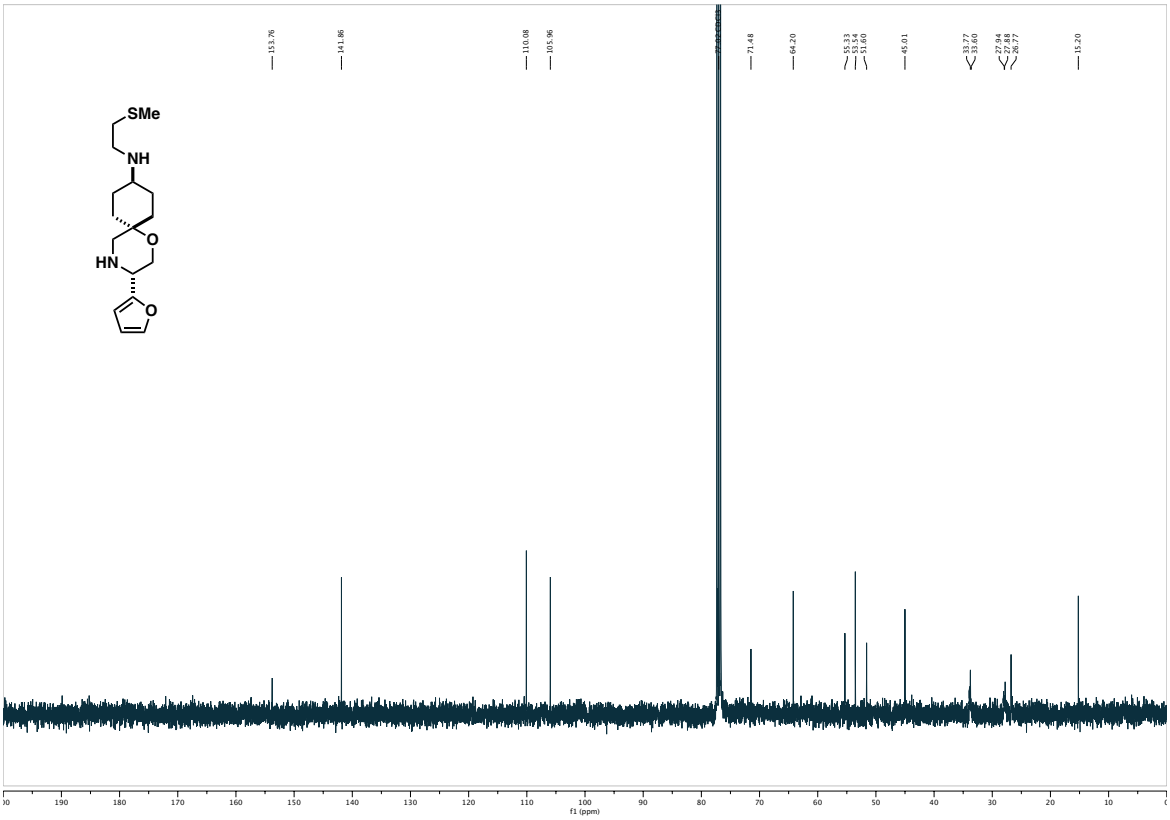
## 19-DiaA



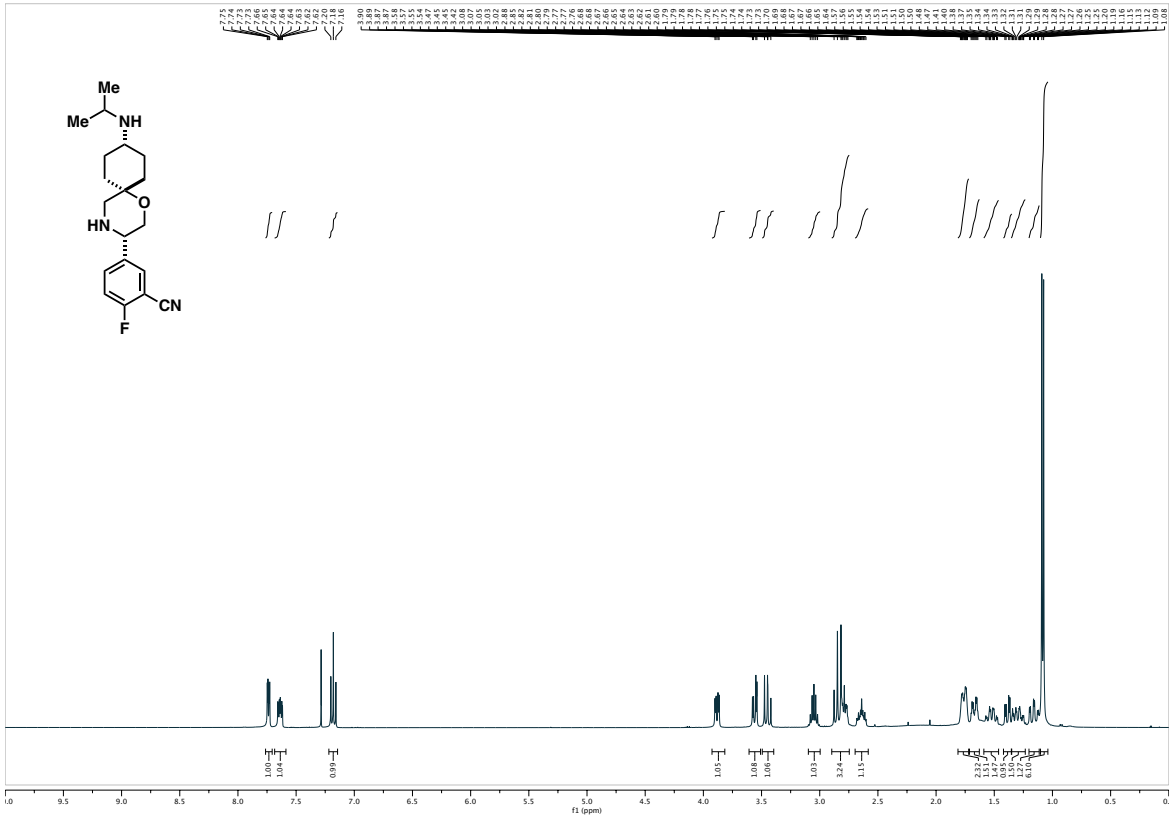



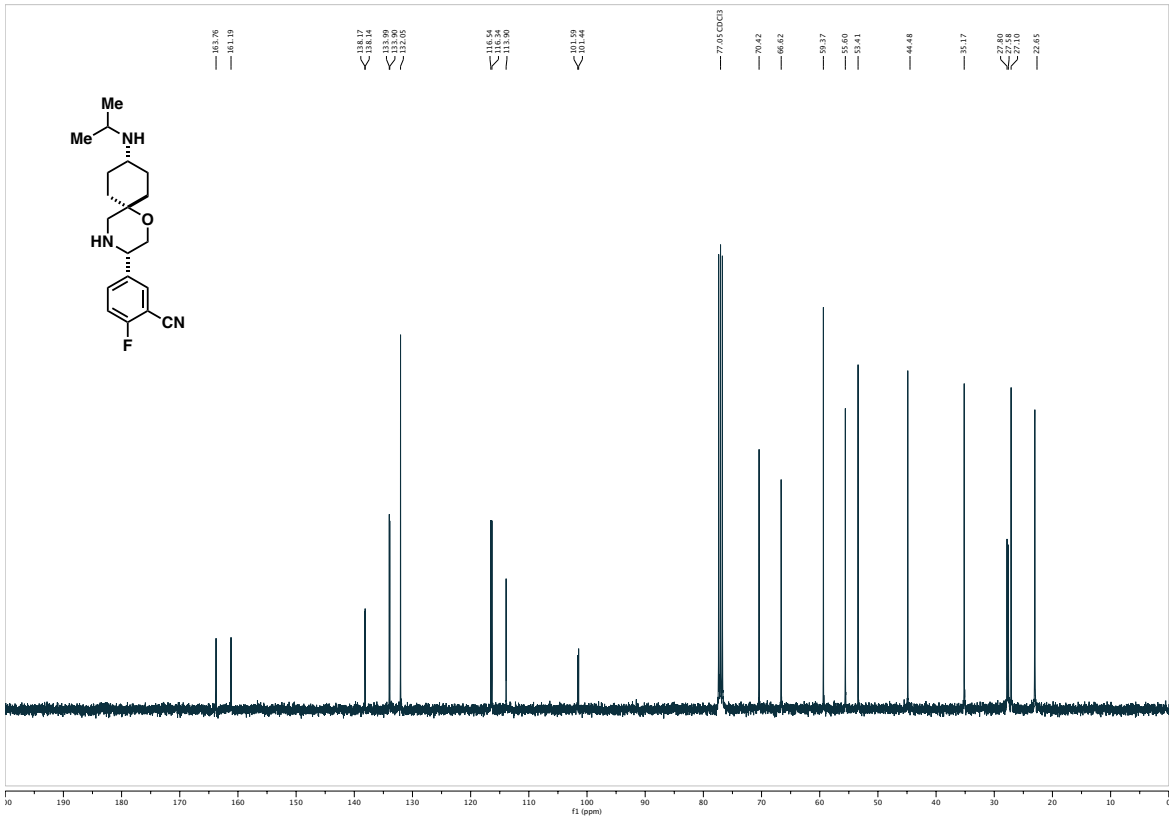
## 19-DiaB



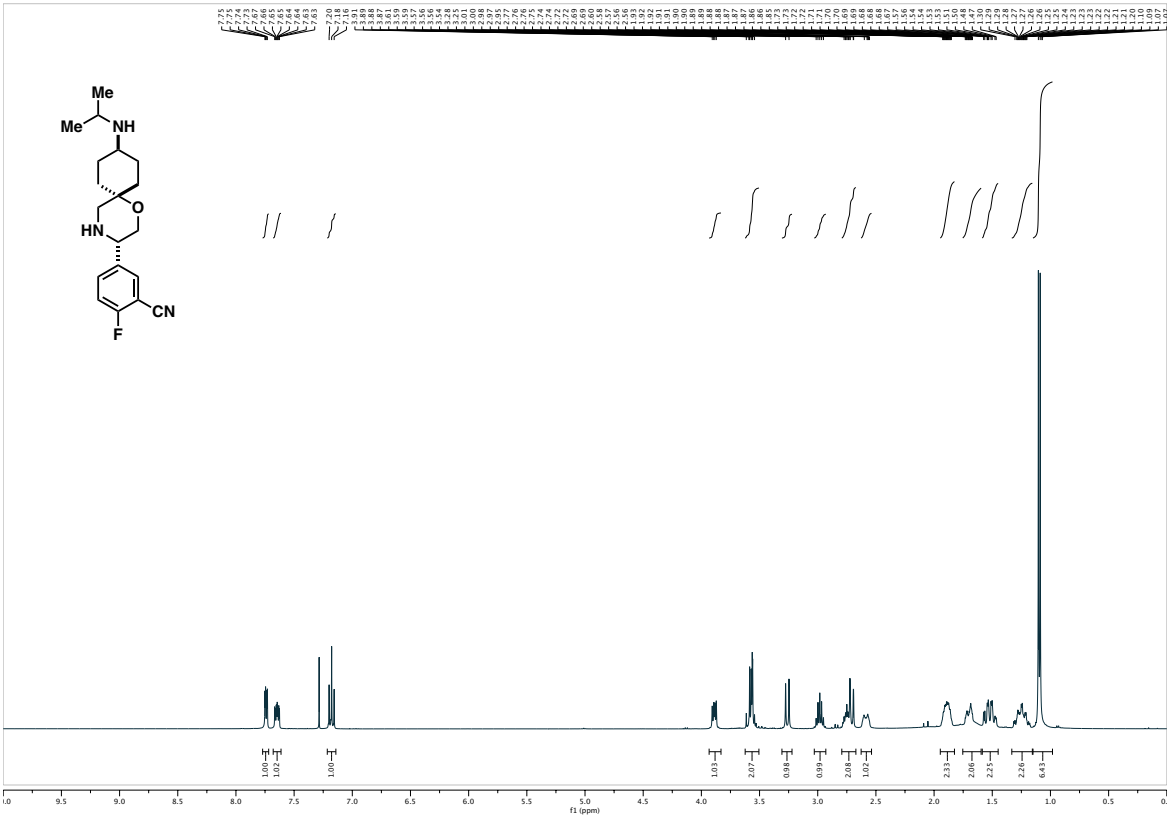



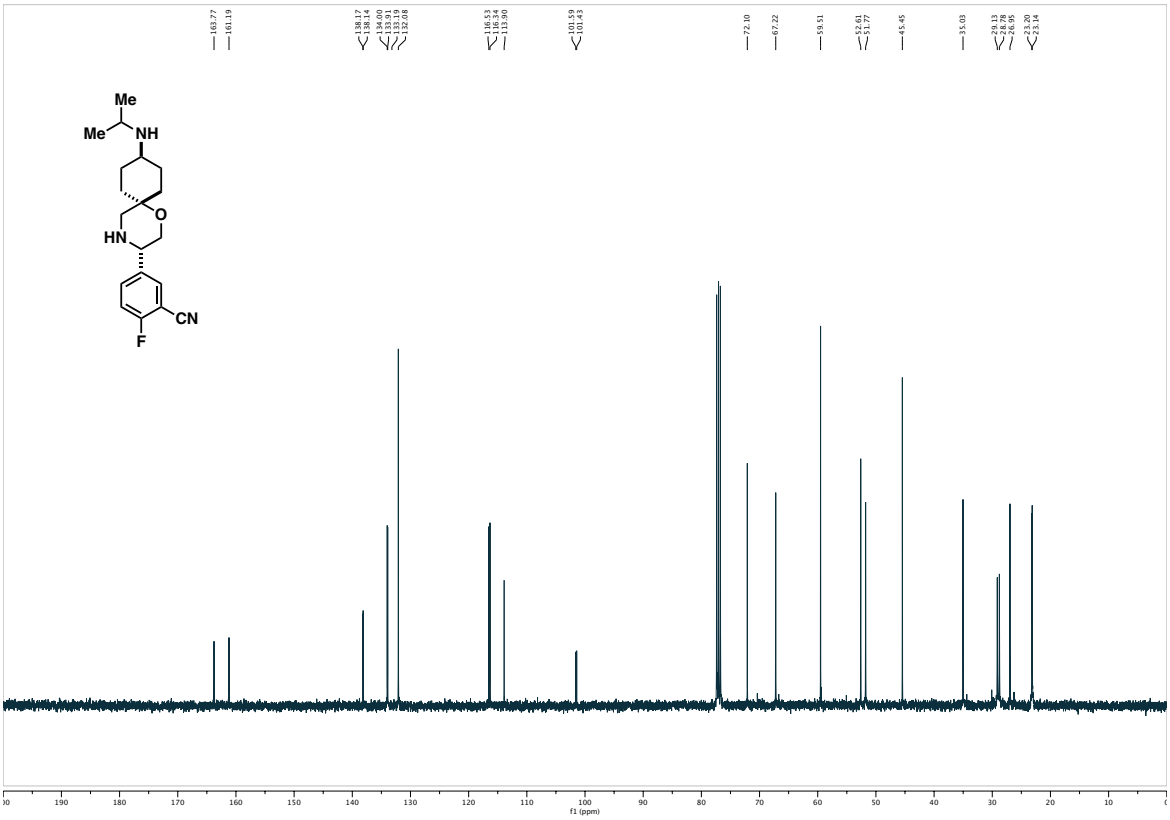
## 20-DiaA



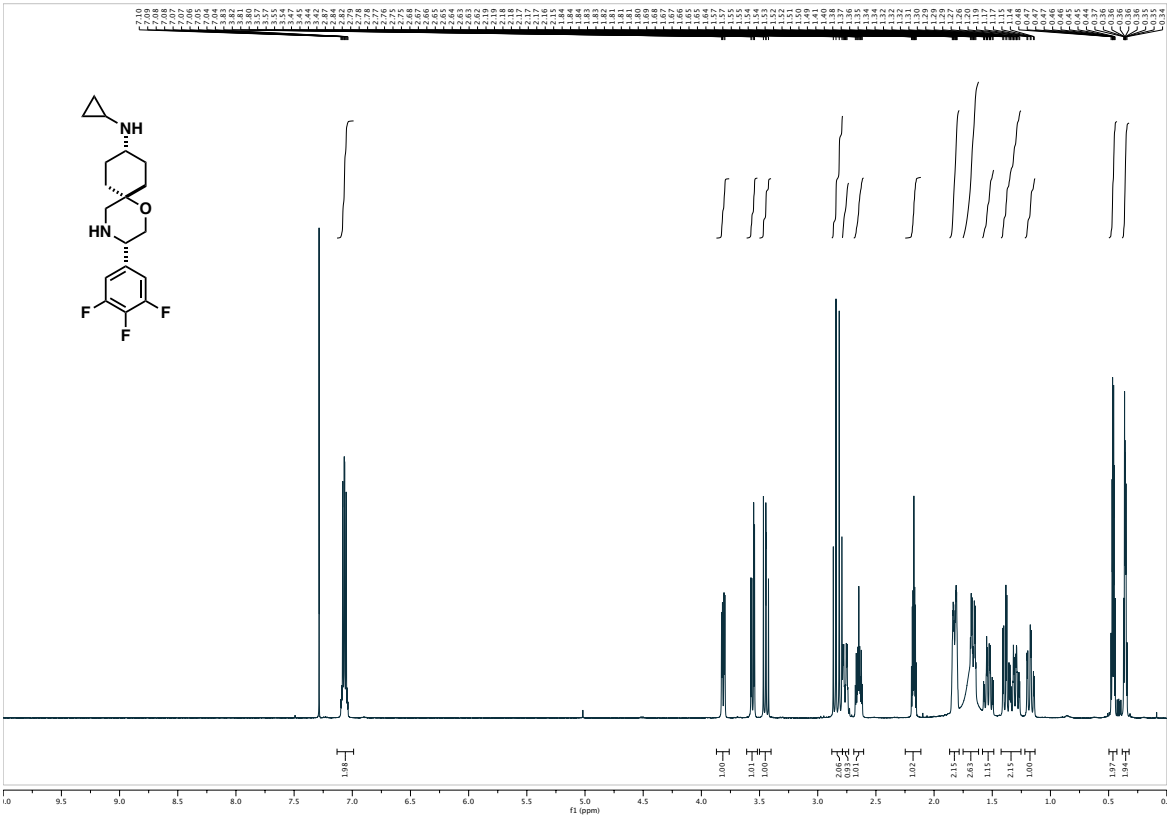



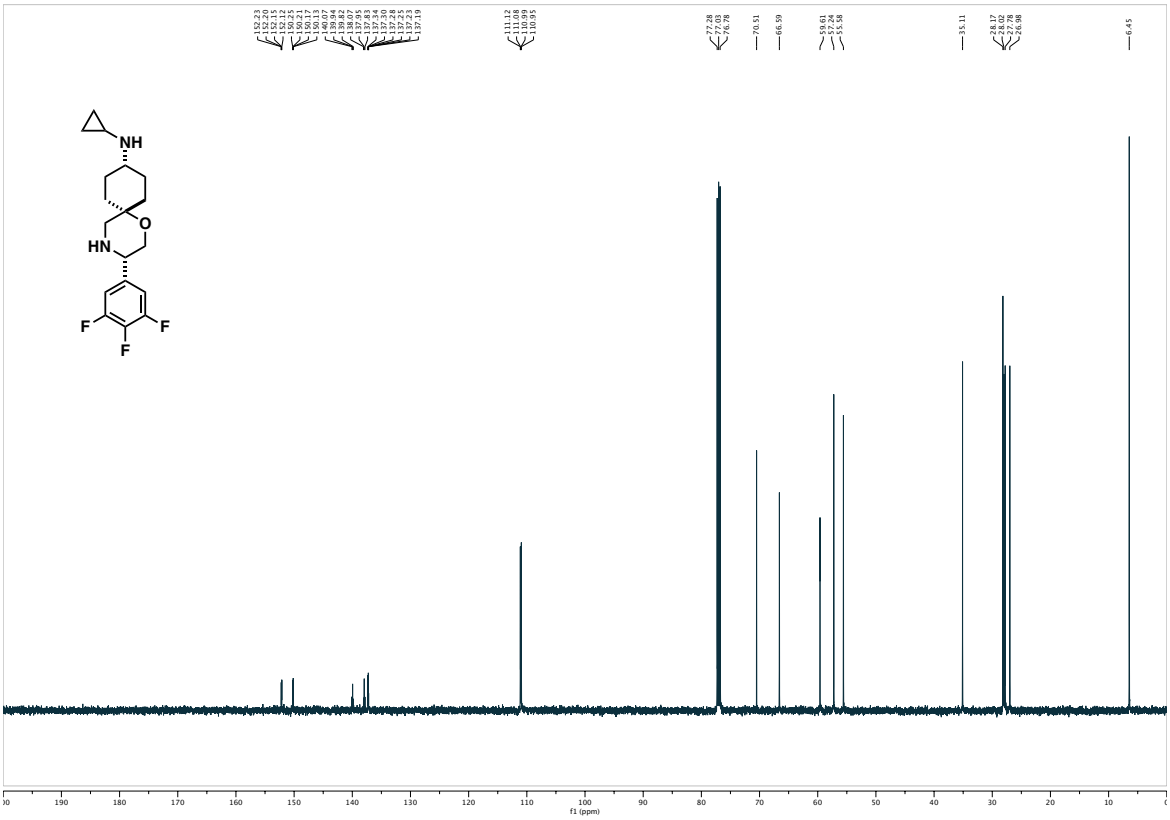
## 20-DiaB



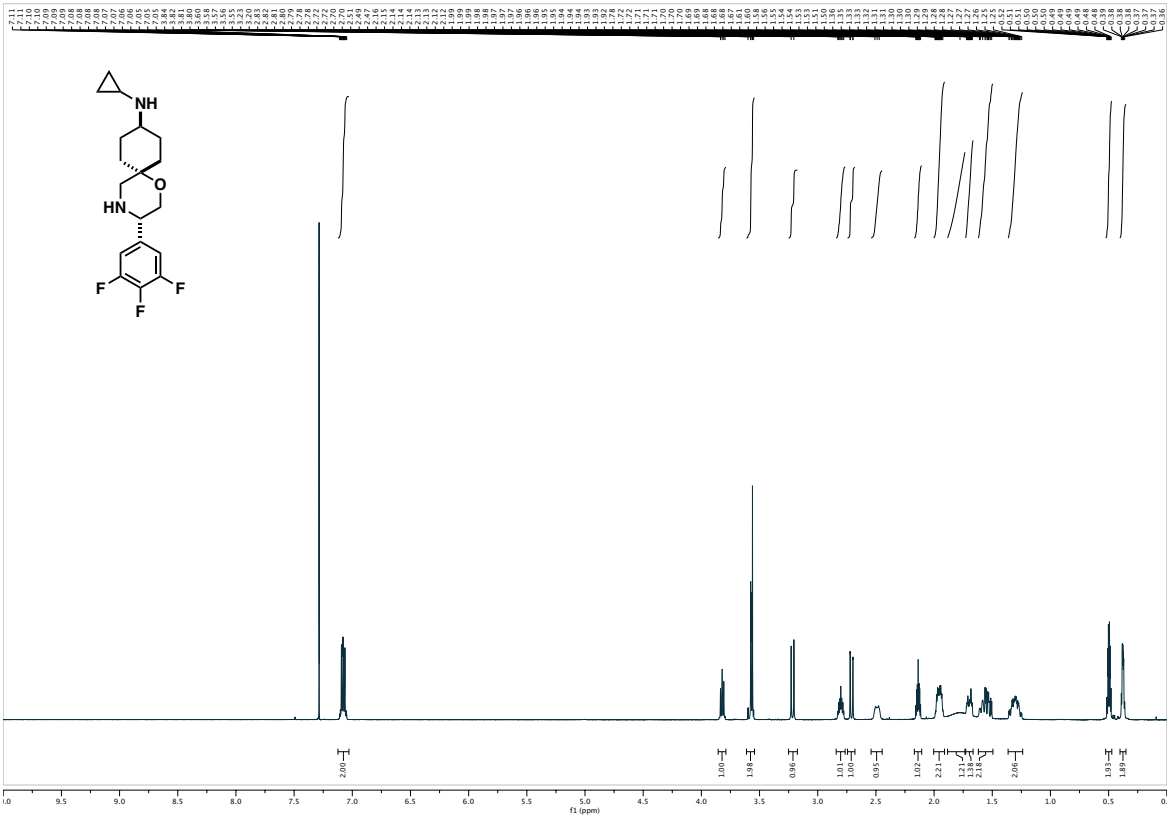



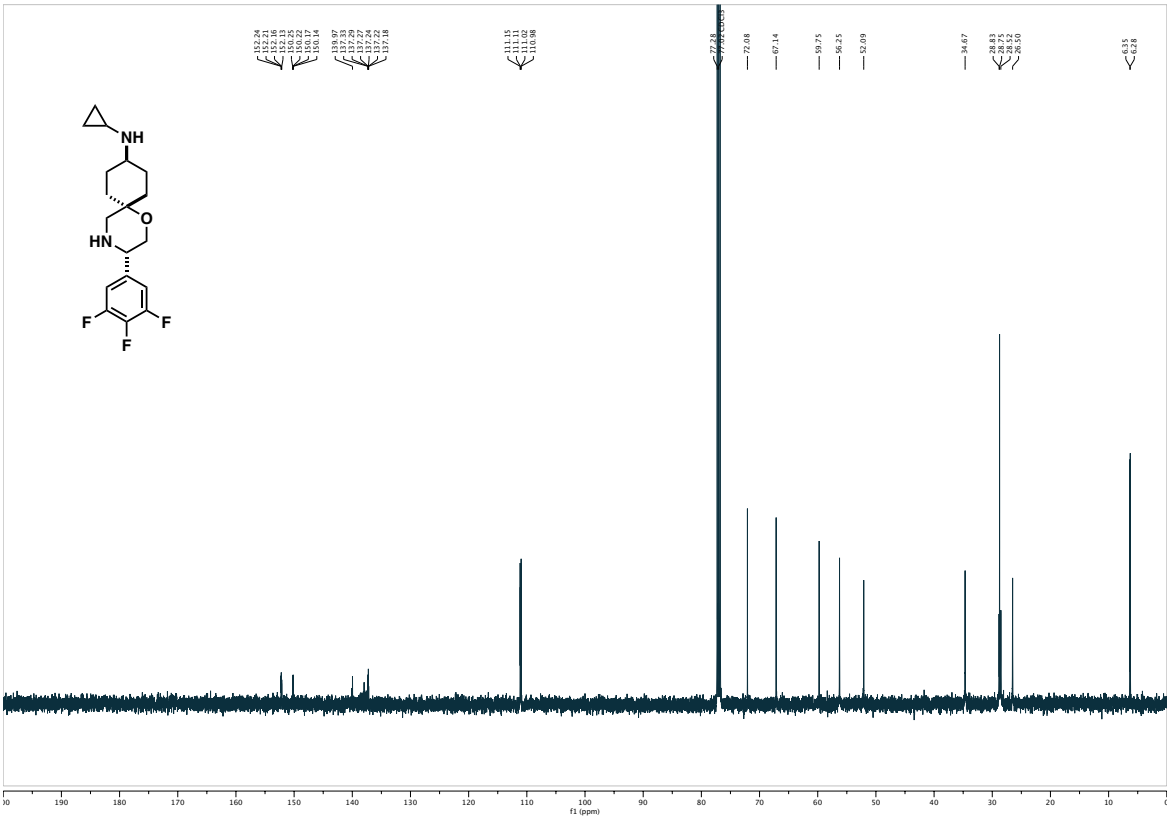
## 21-DiaA



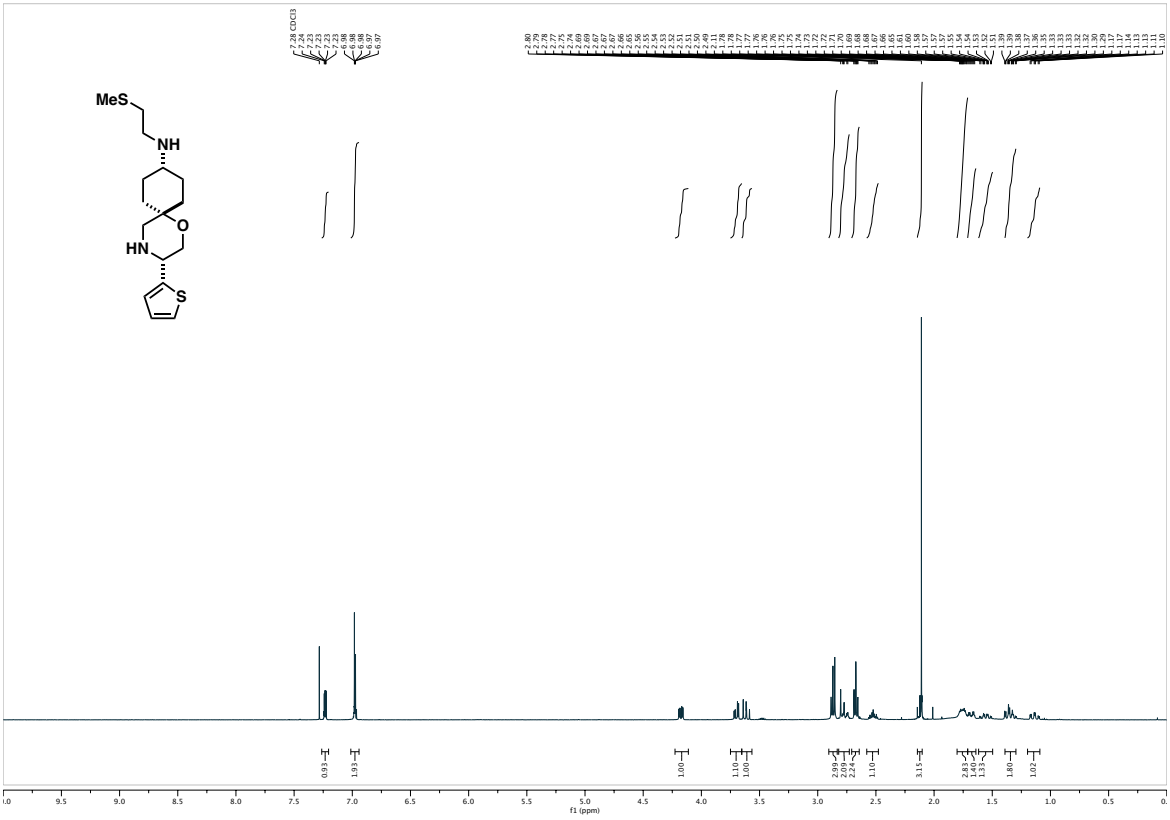



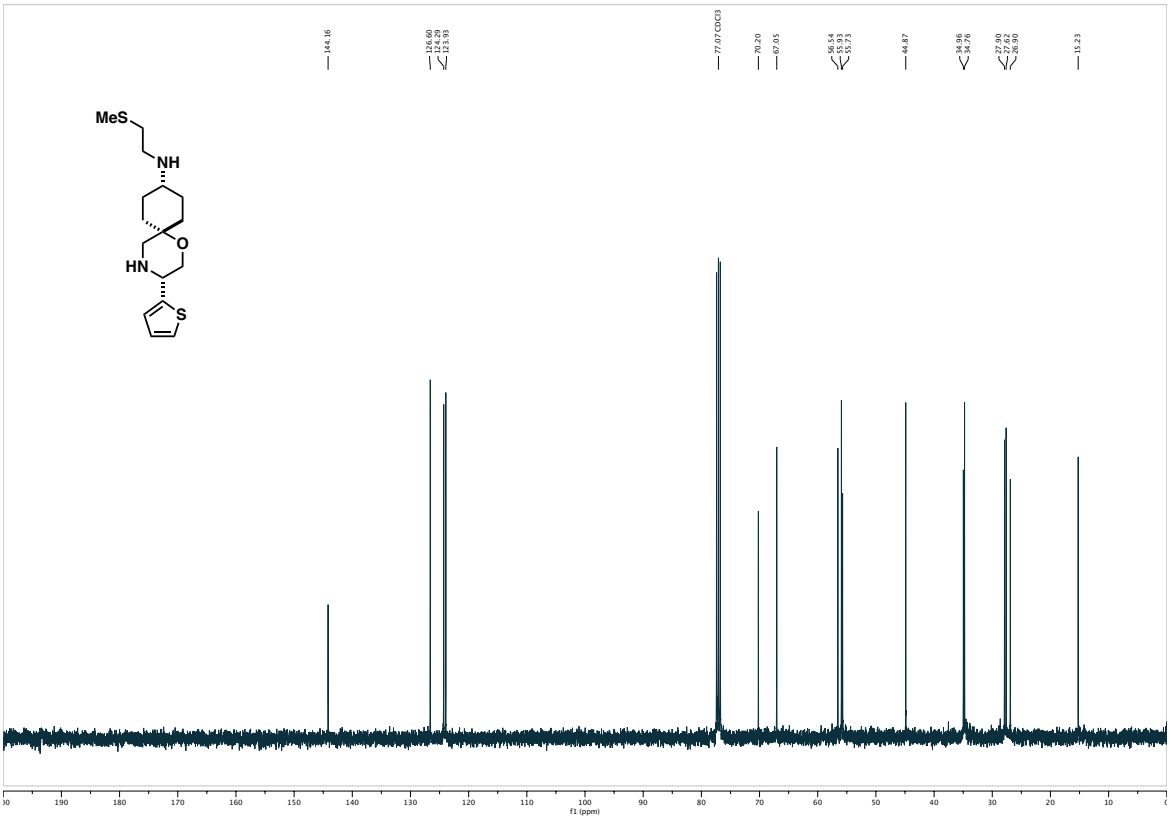
## 21-DiaB



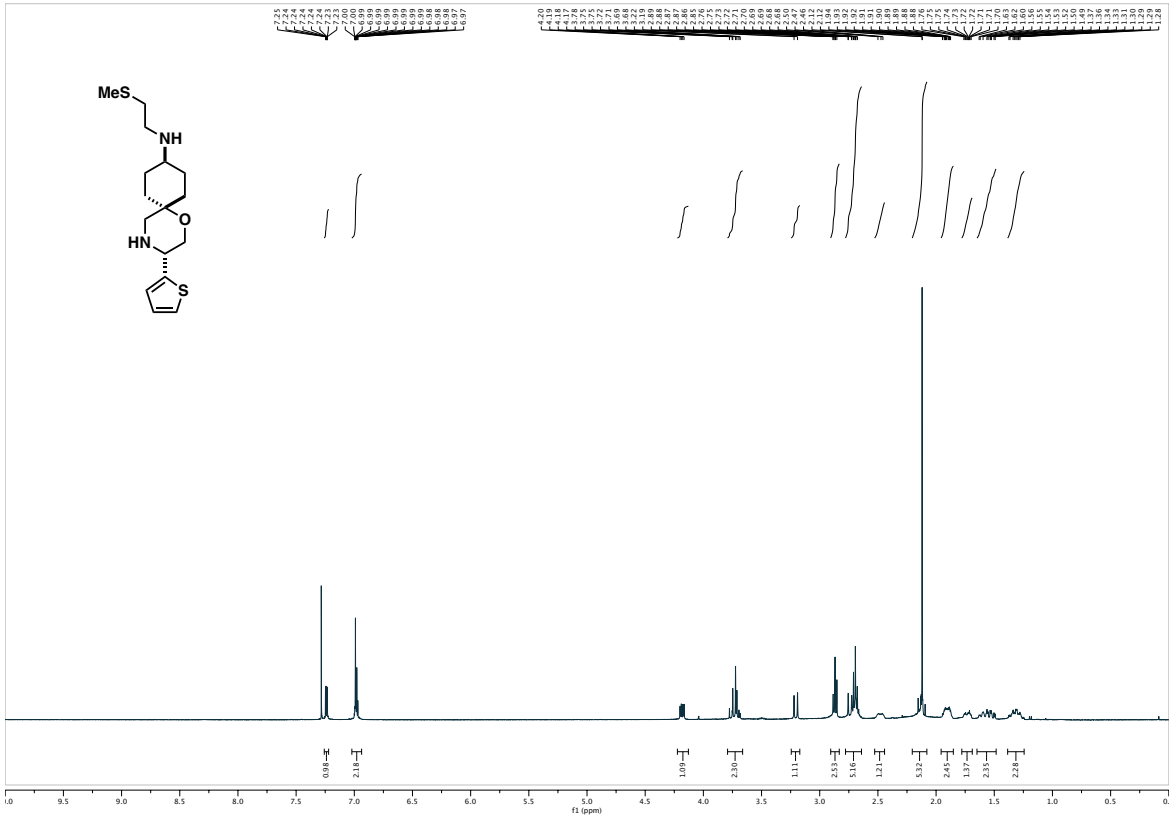



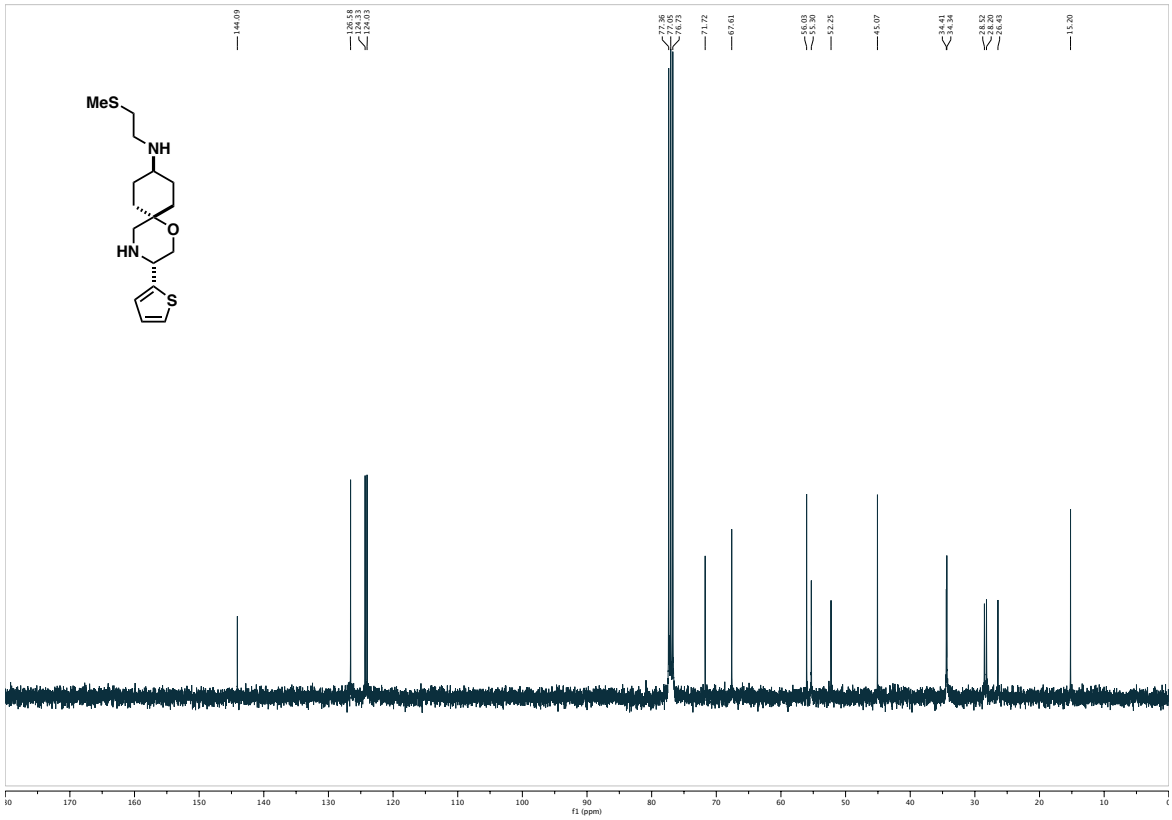
## 22-DiaA



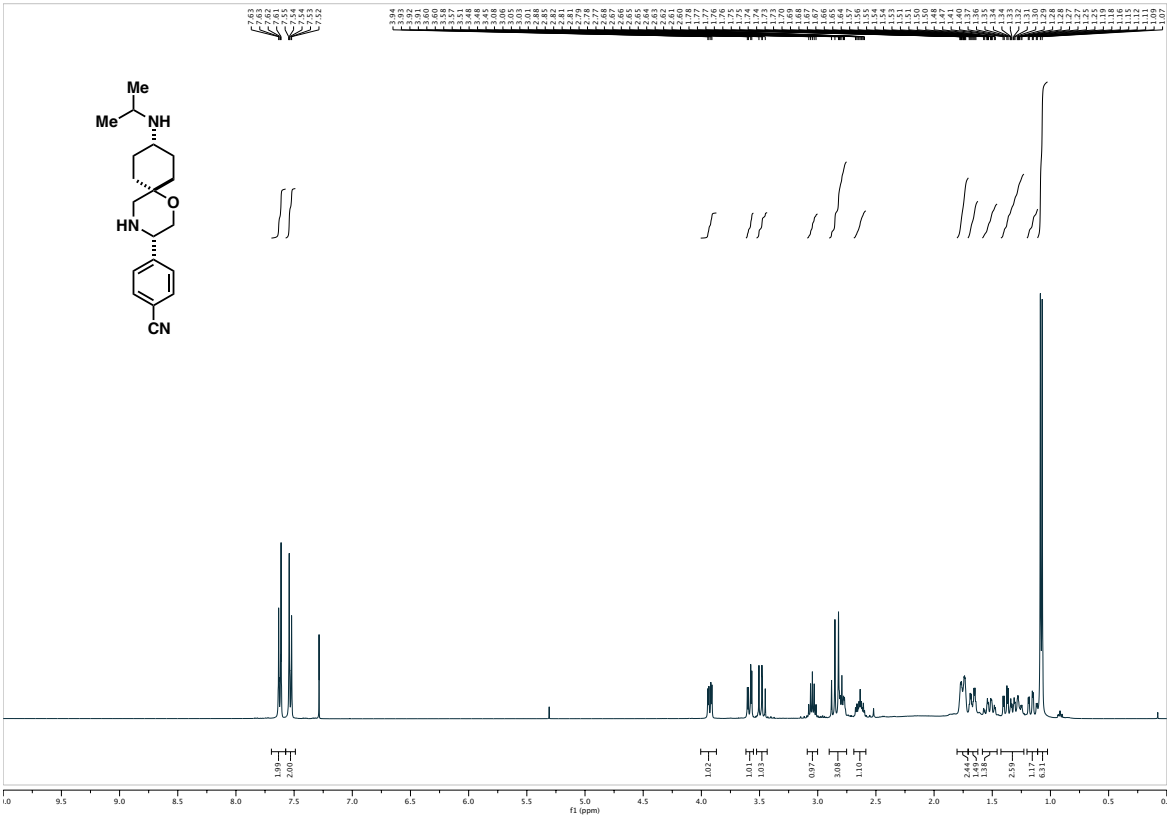



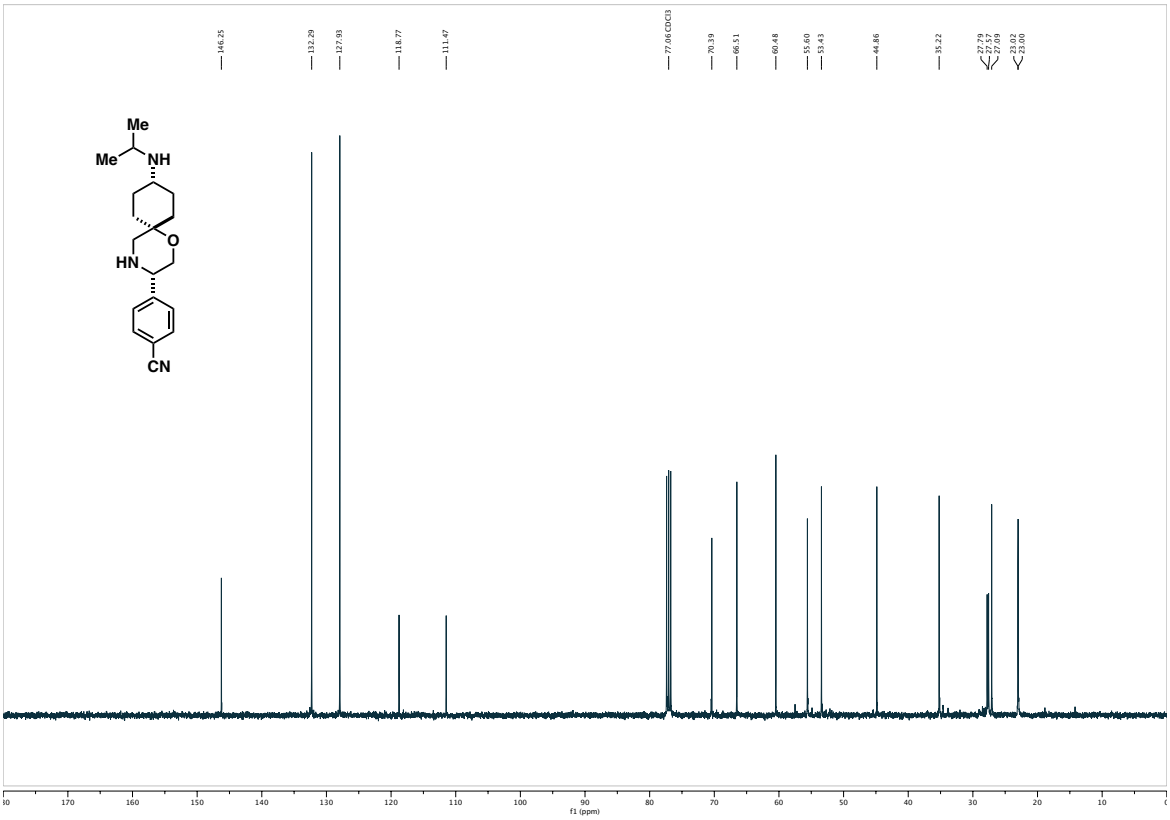
## 22-DiaB



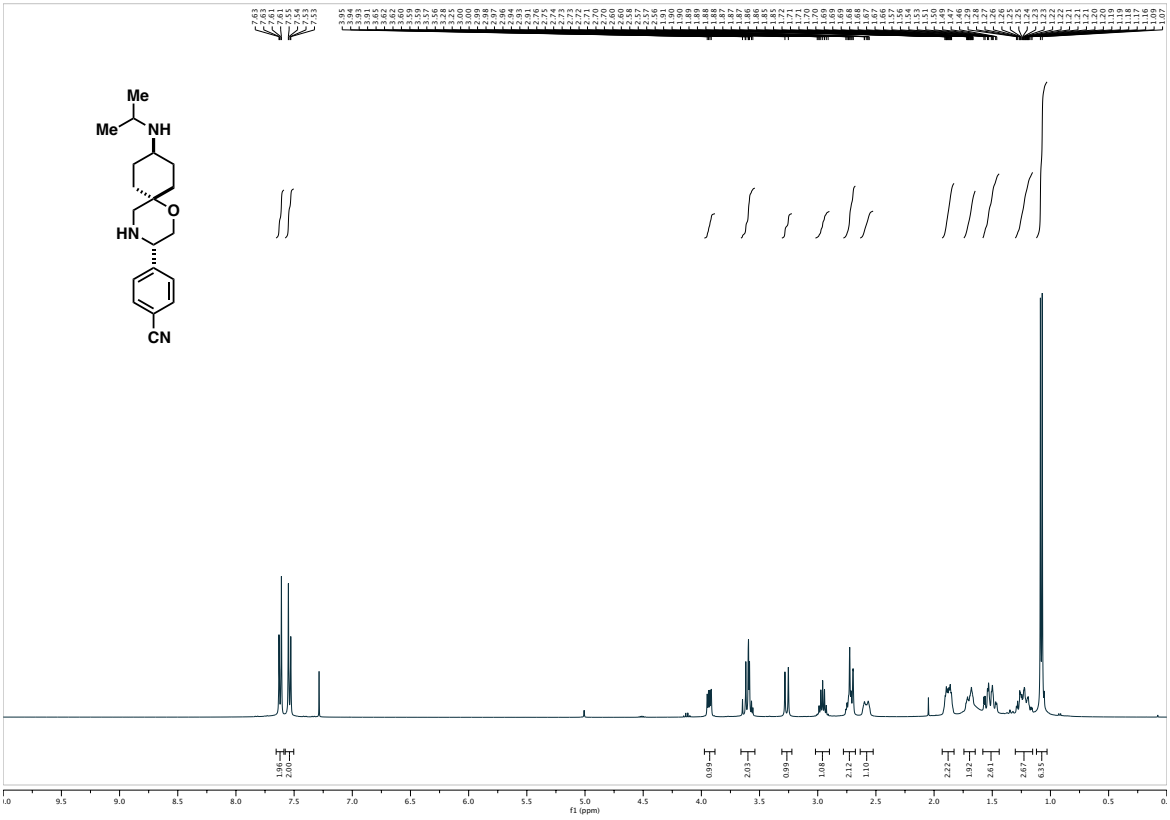



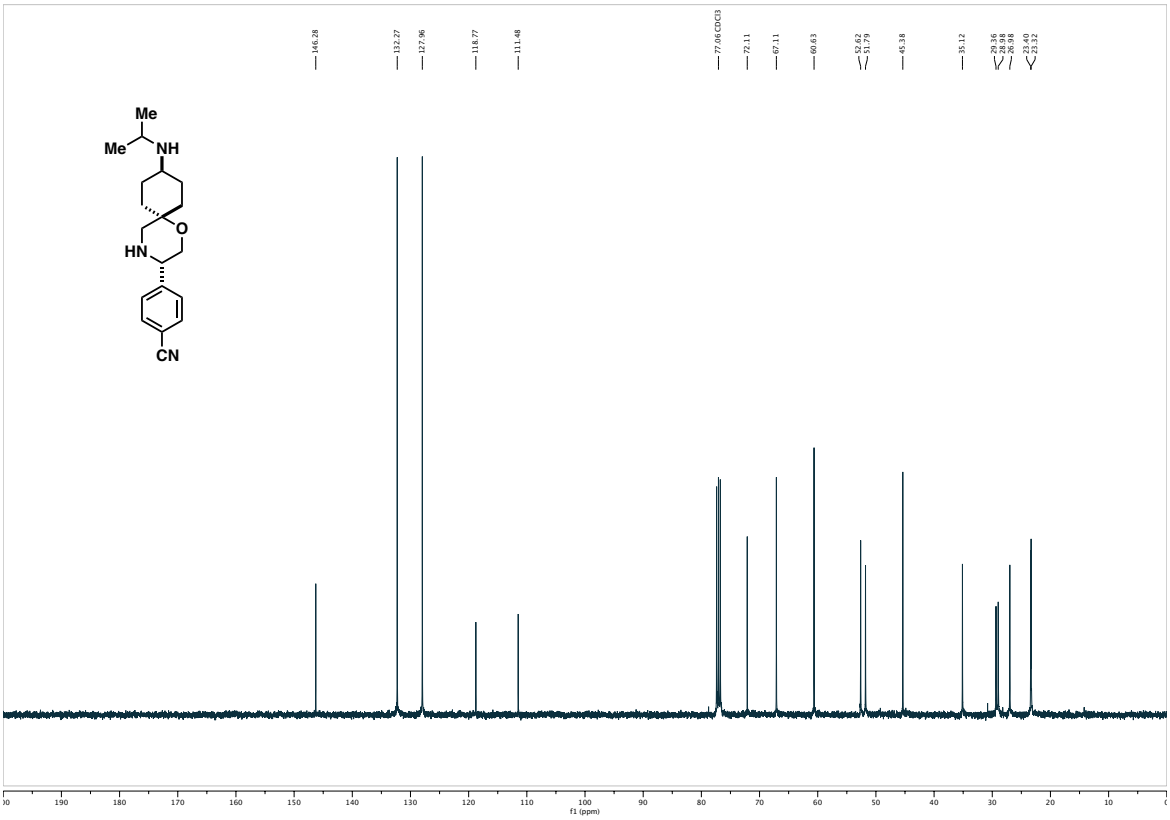
## 23-DiaA



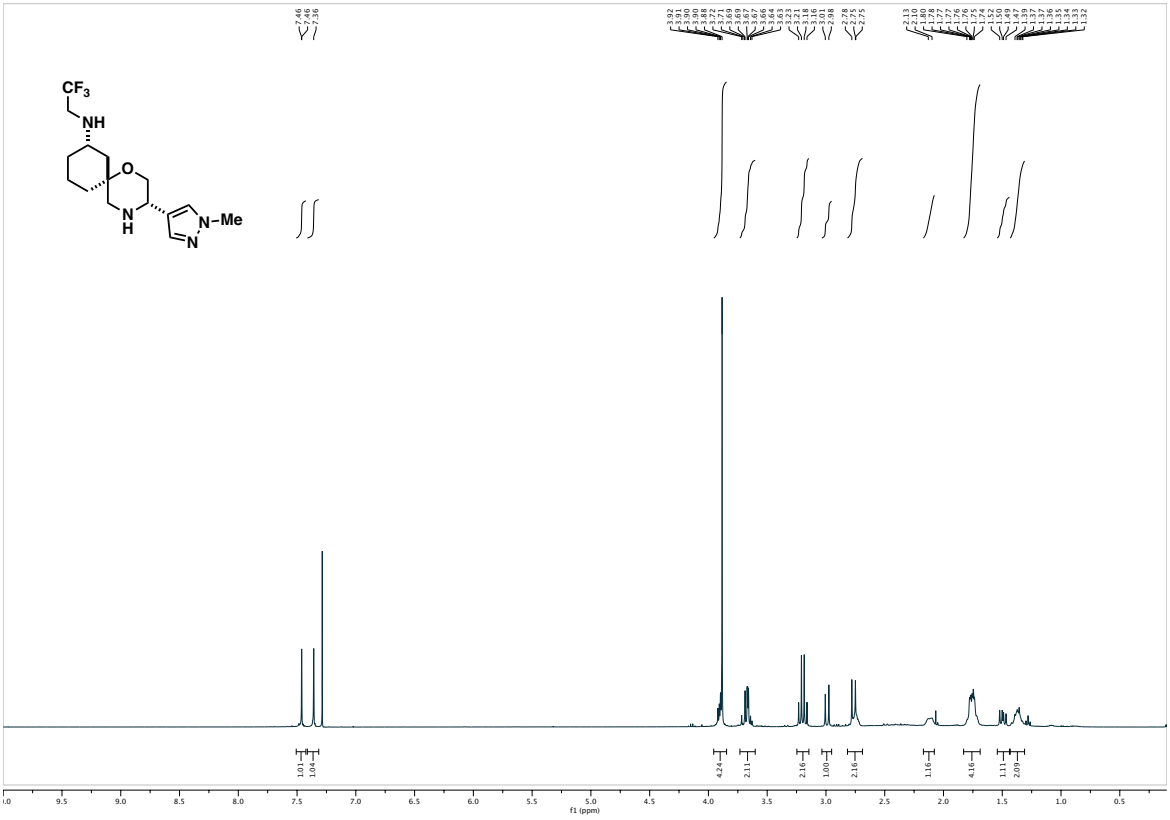



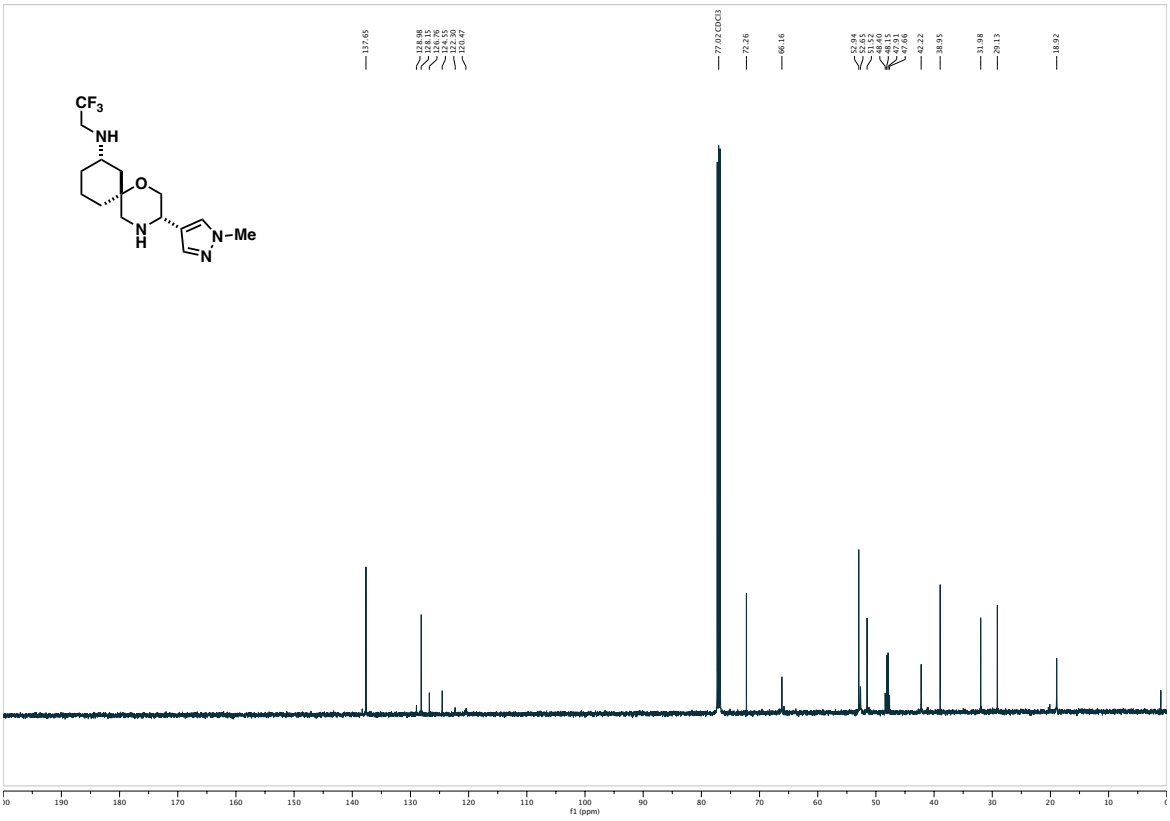
## 23-DiaB



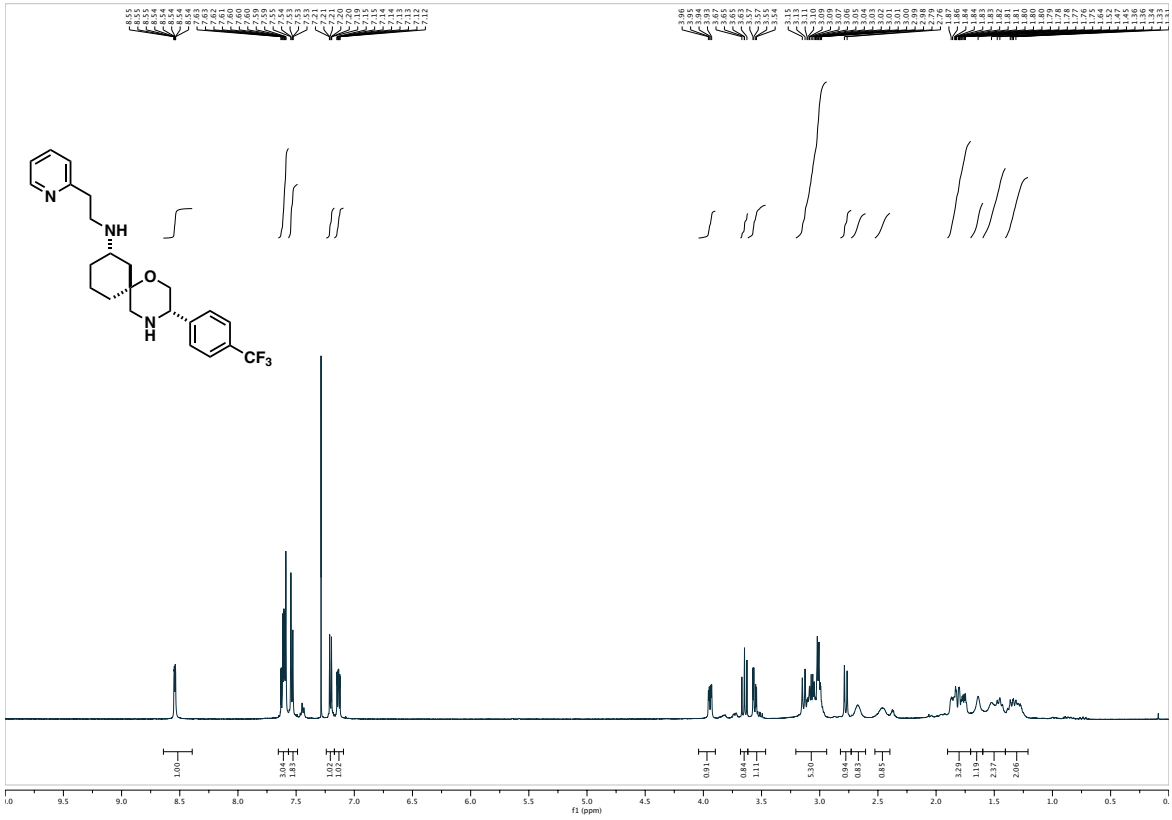



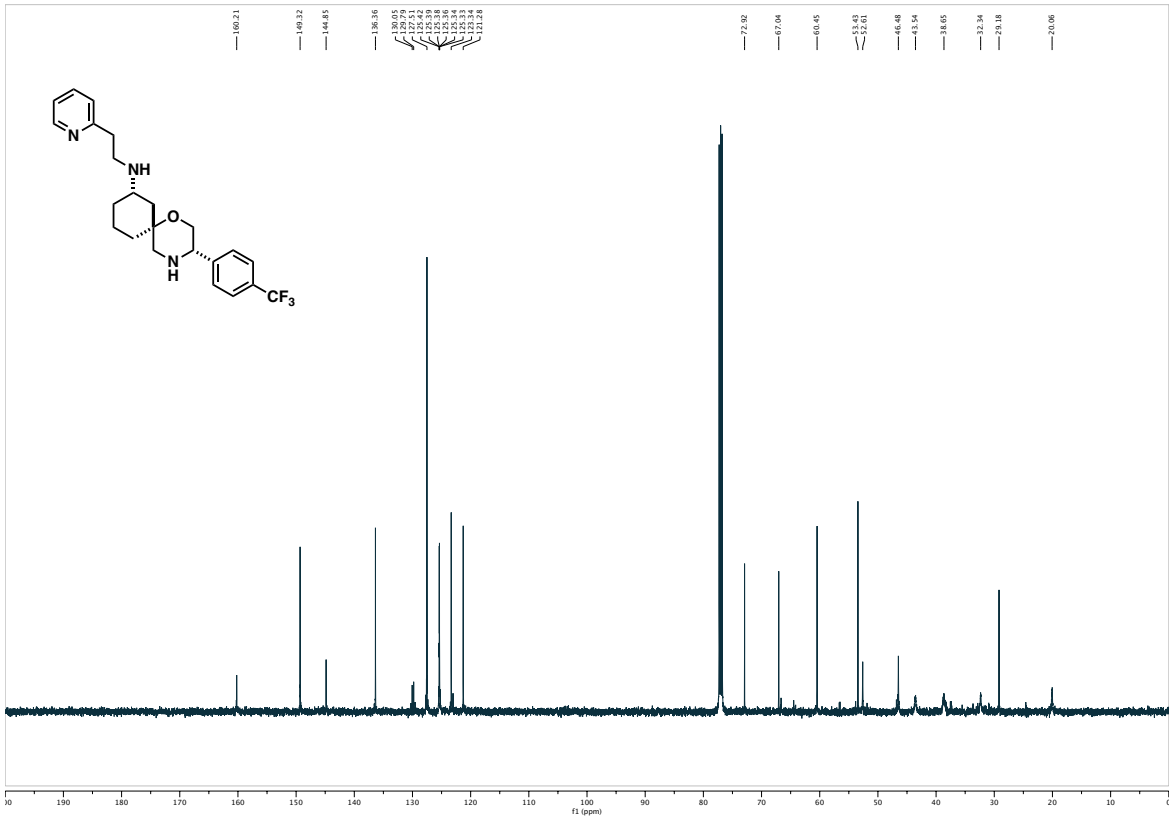
## 24-DiaA



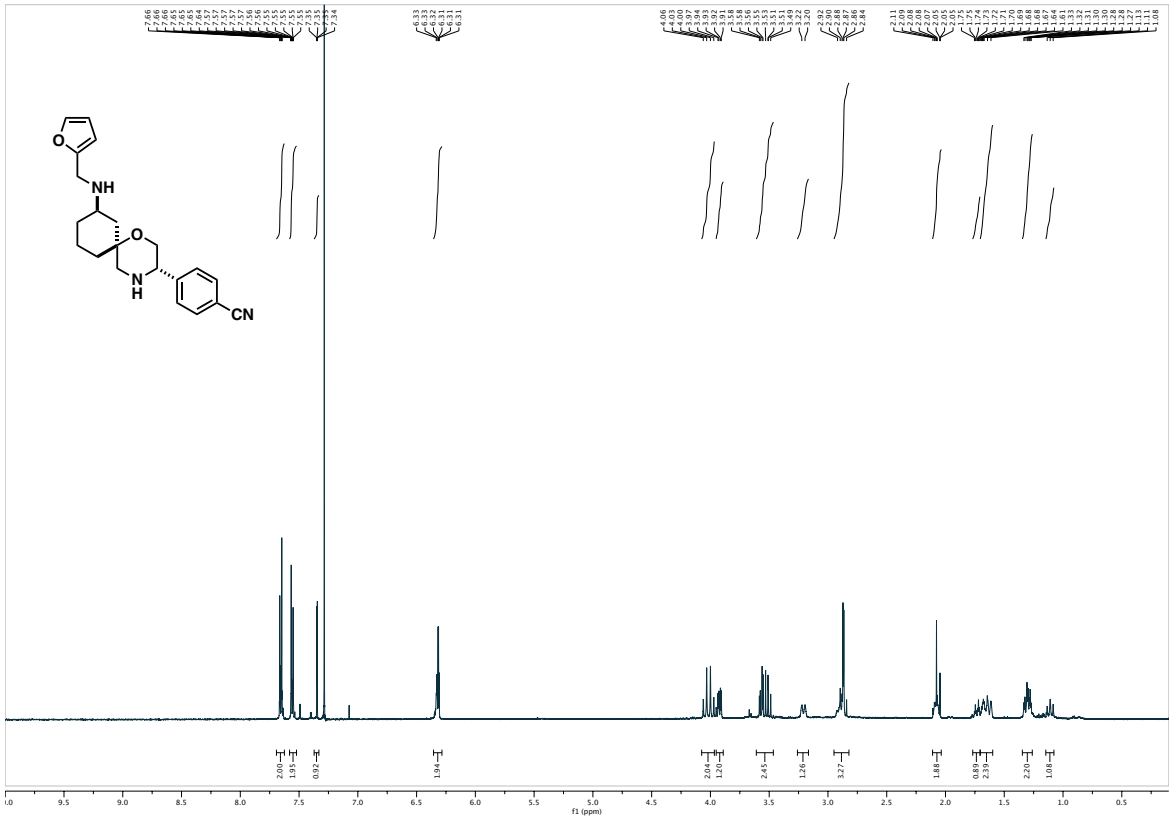



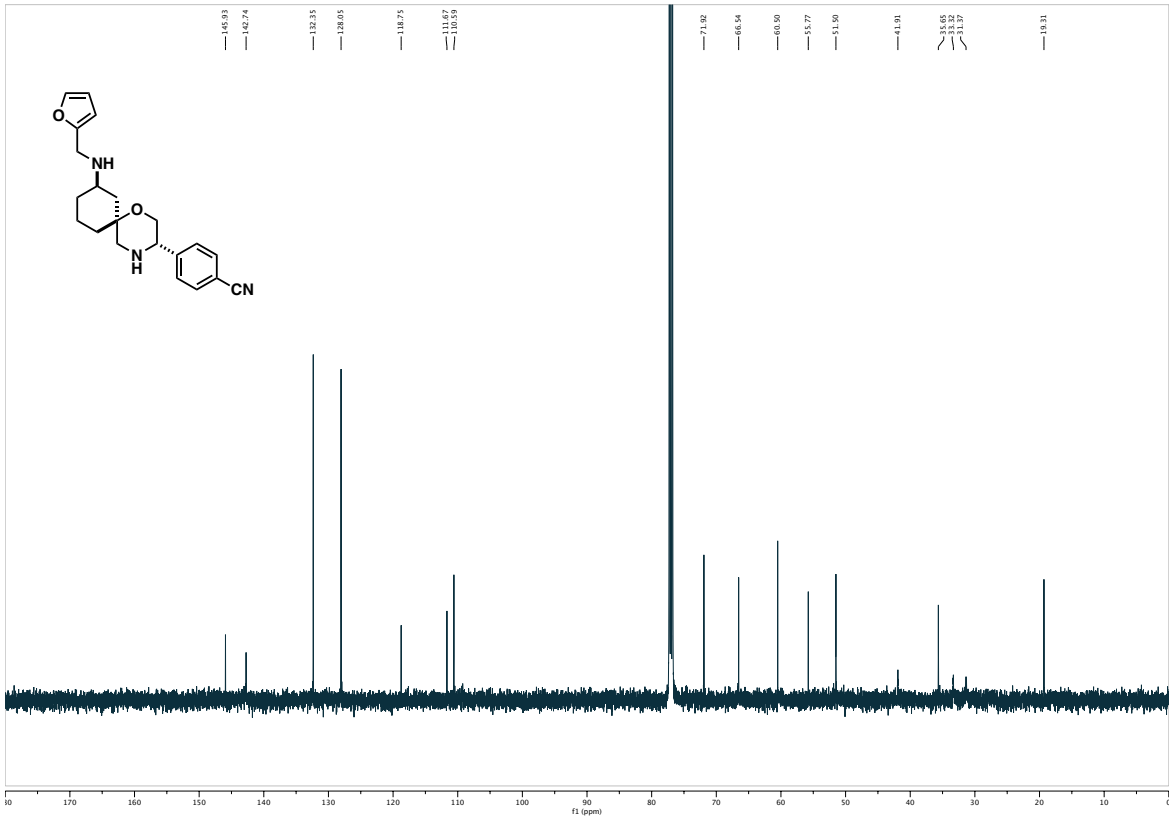
## 25-DiaA



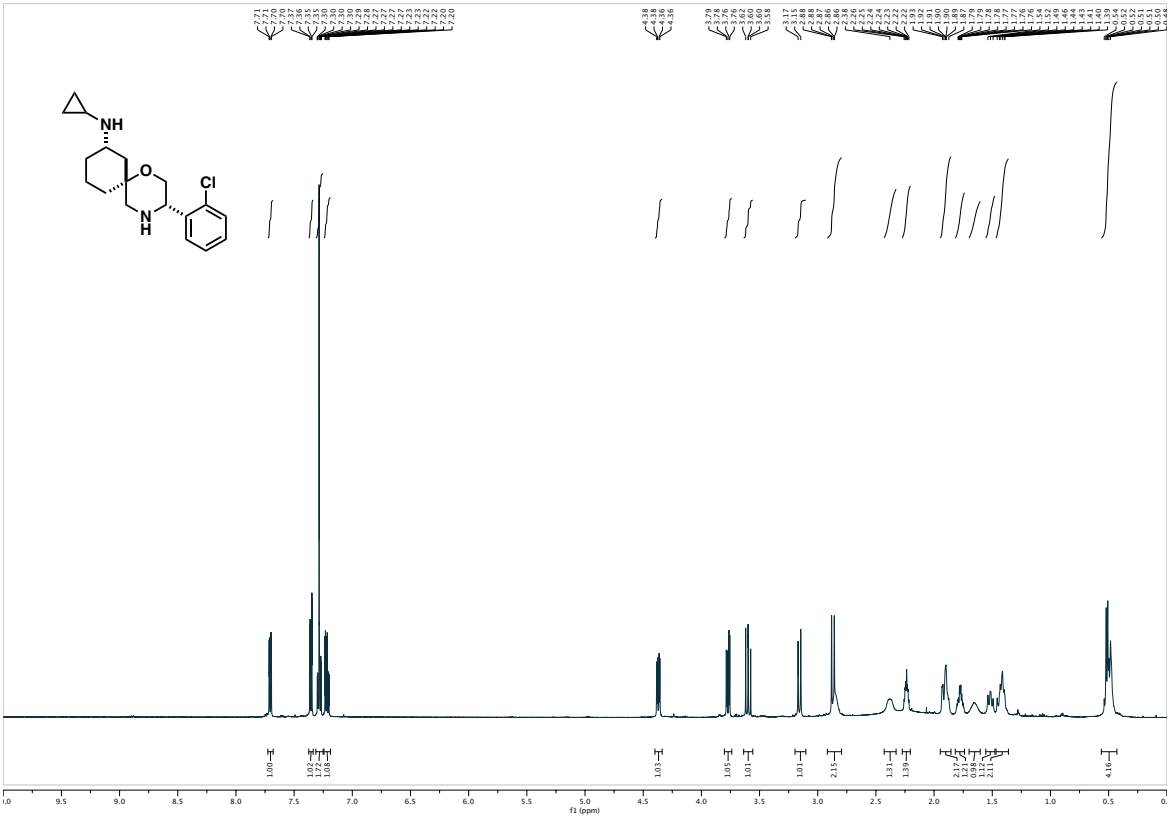



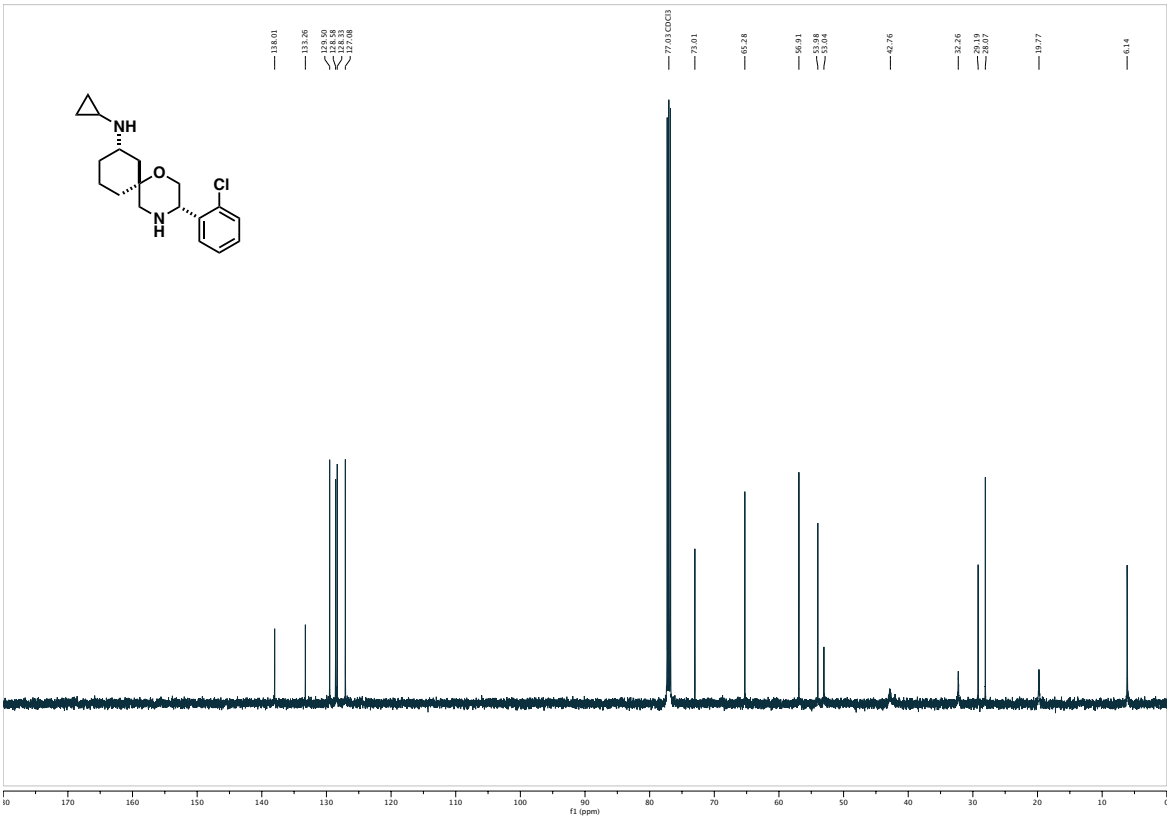
## 26-DiaD



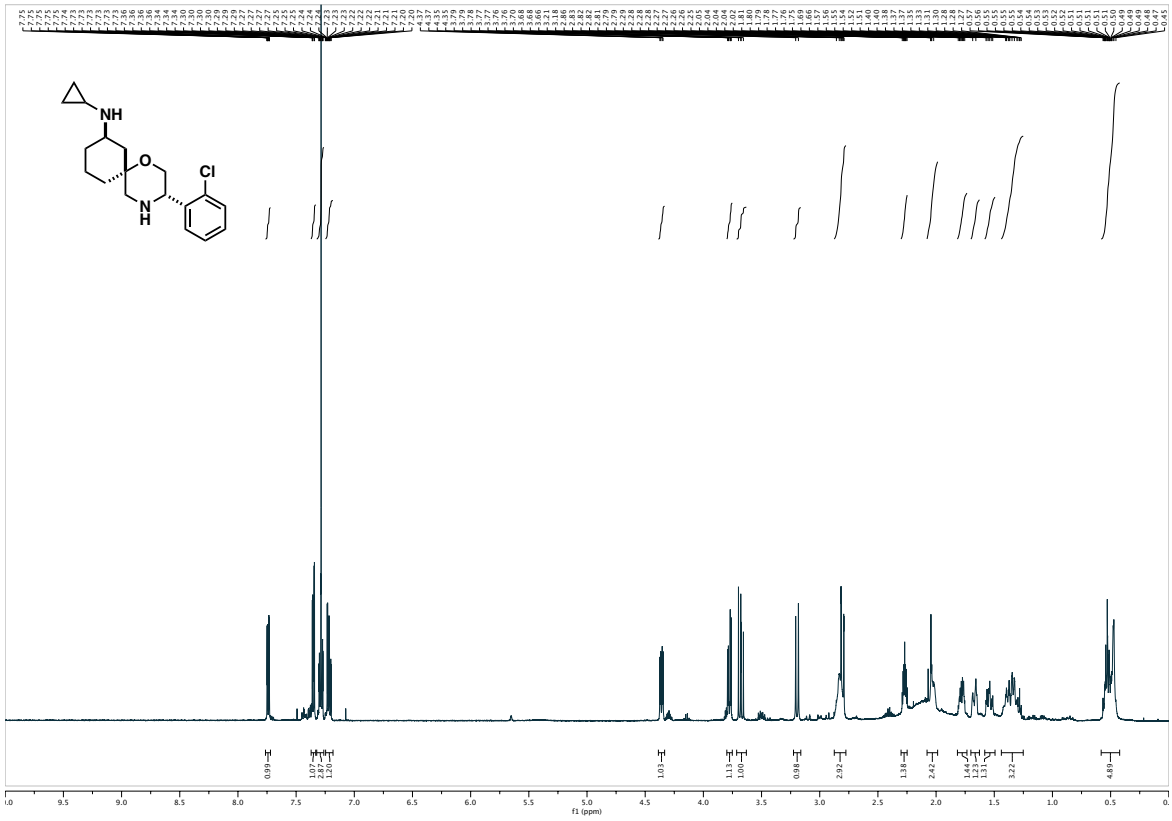



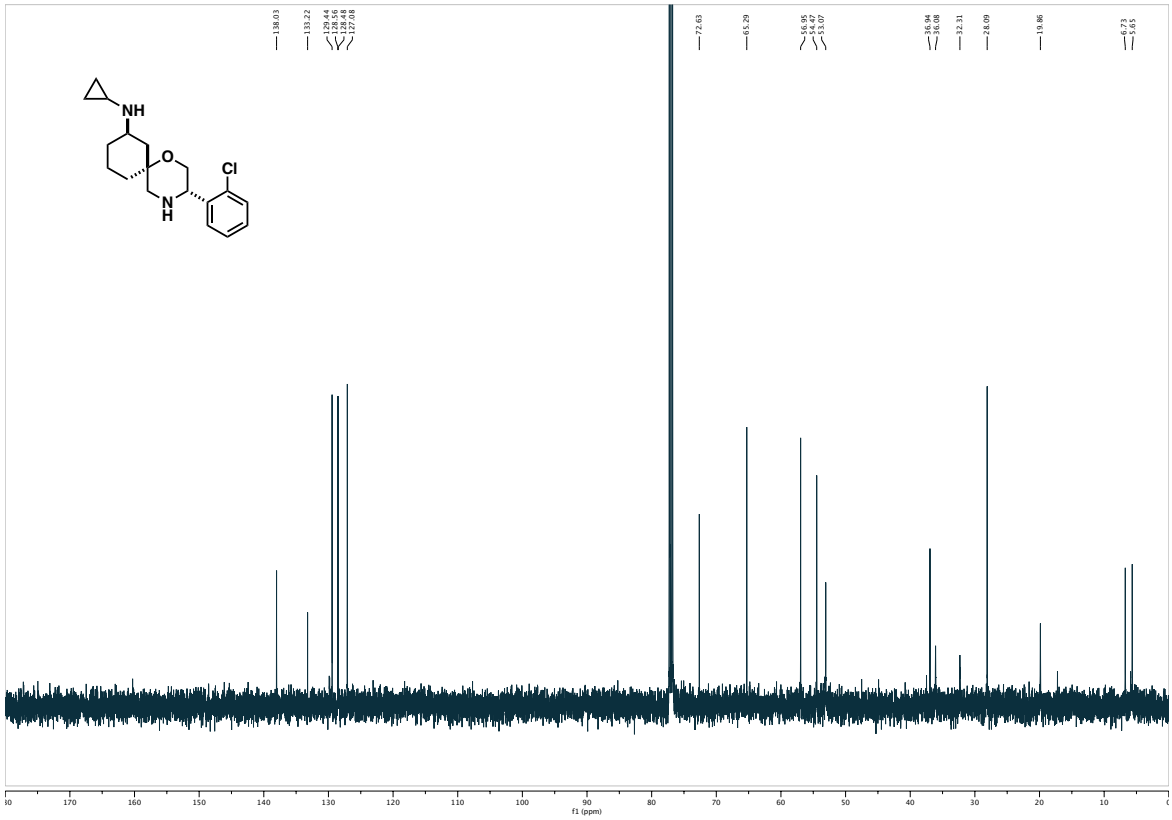
## 27-DiaA



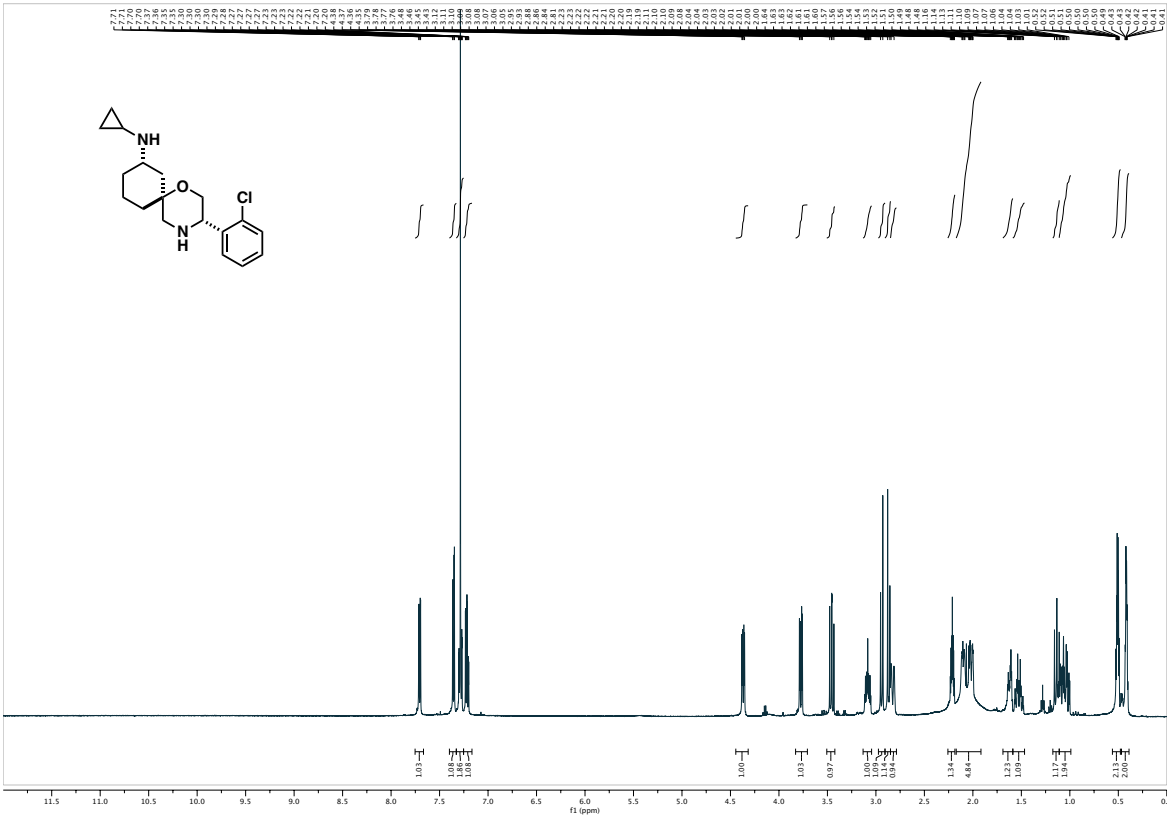



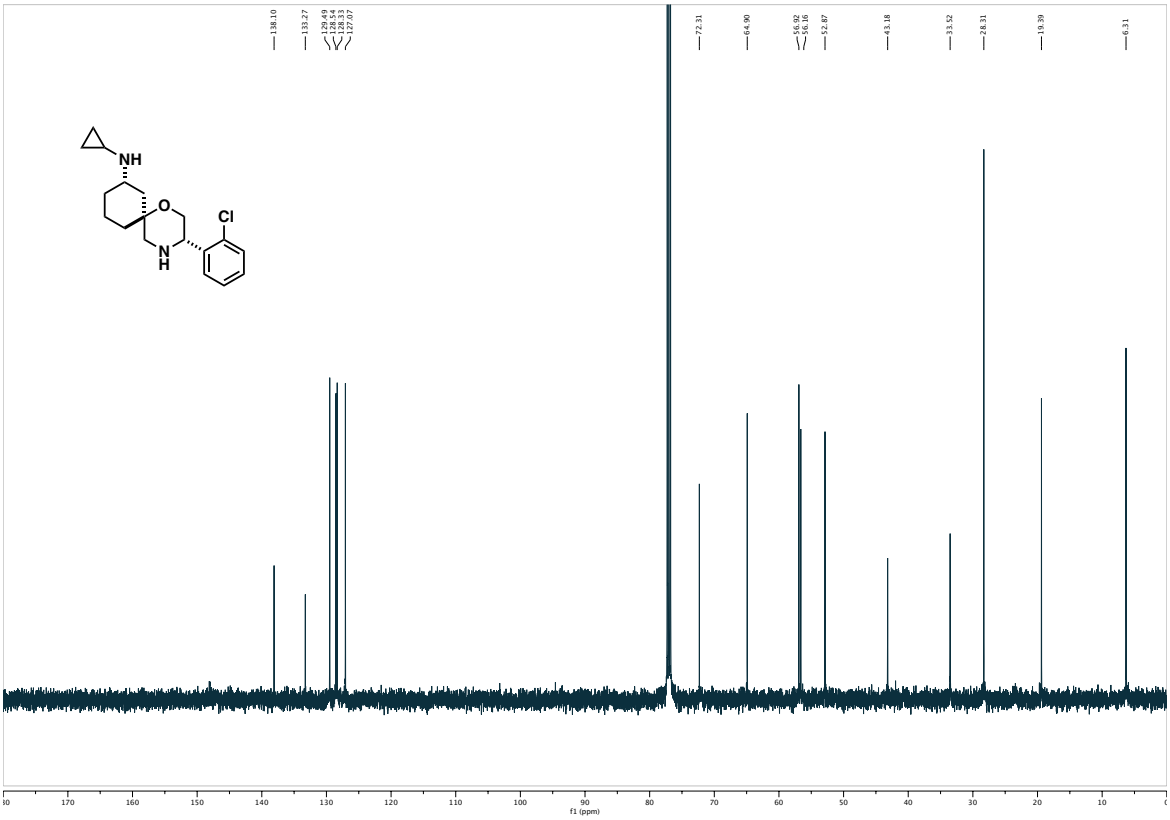
## 27-DiaB



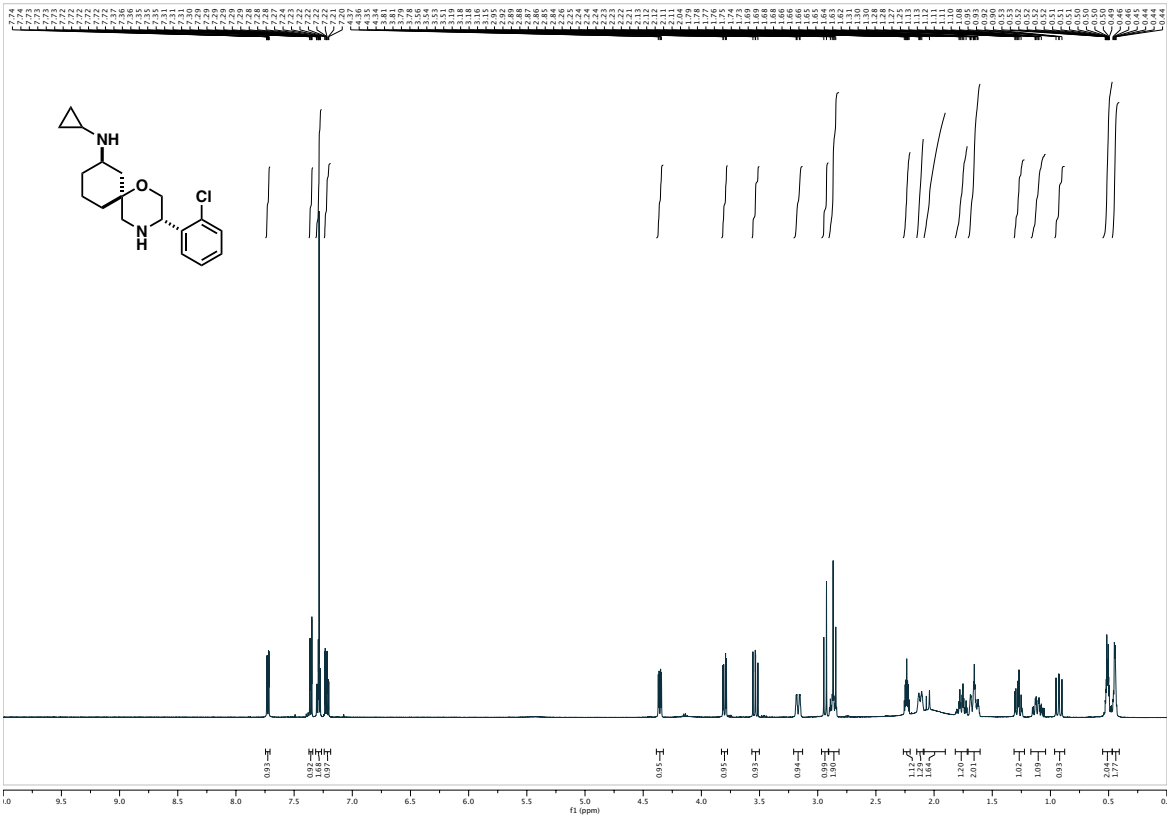



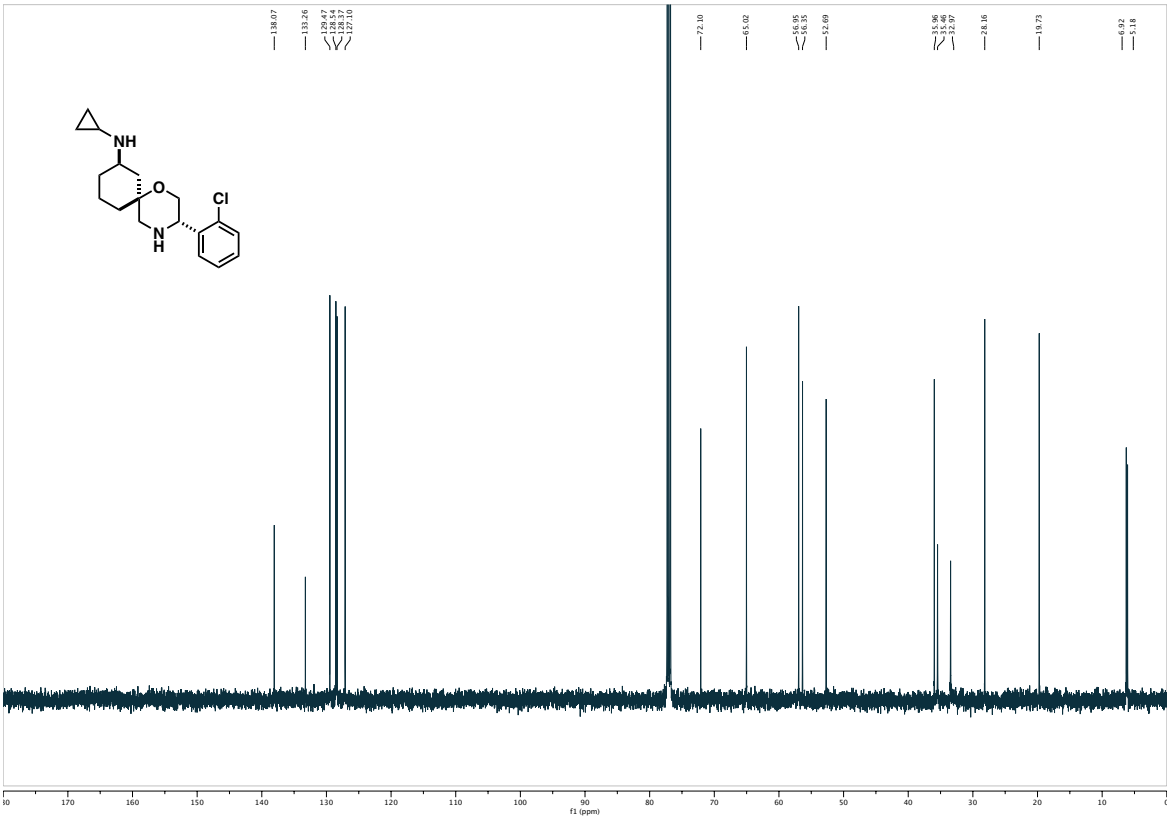
## 27-DiaC



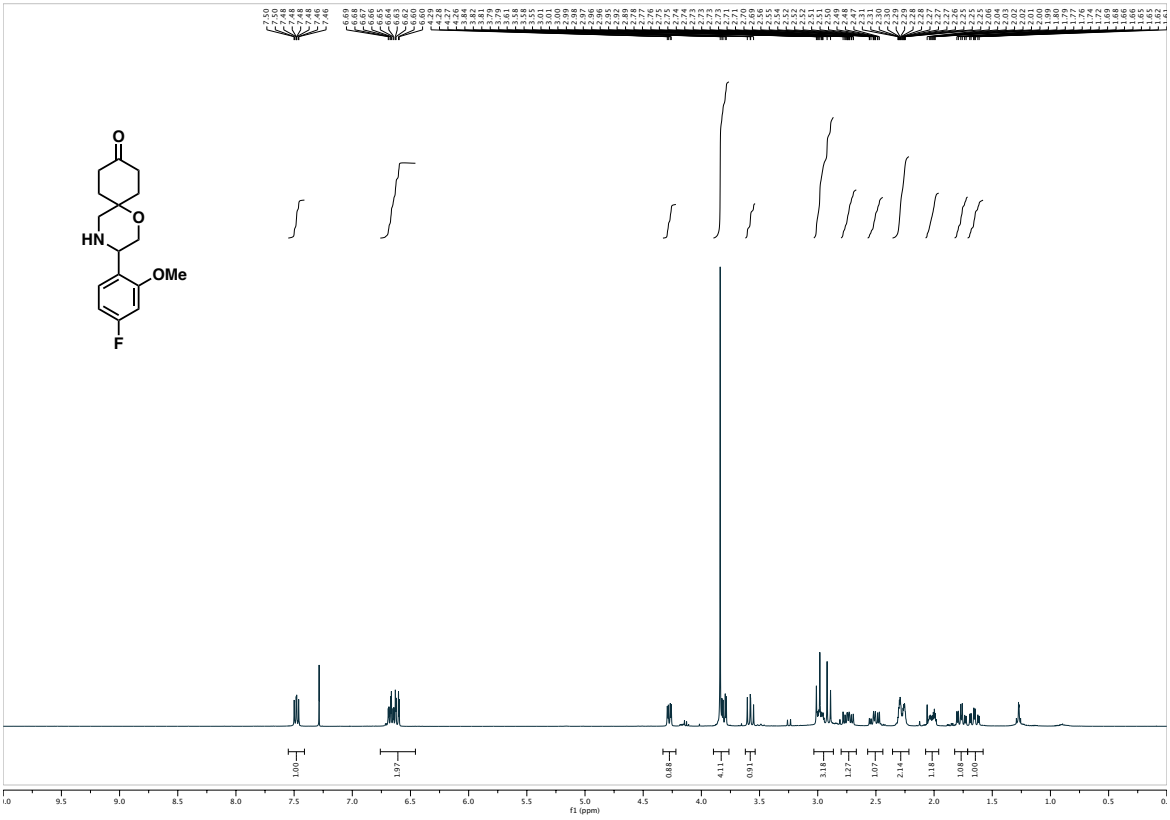



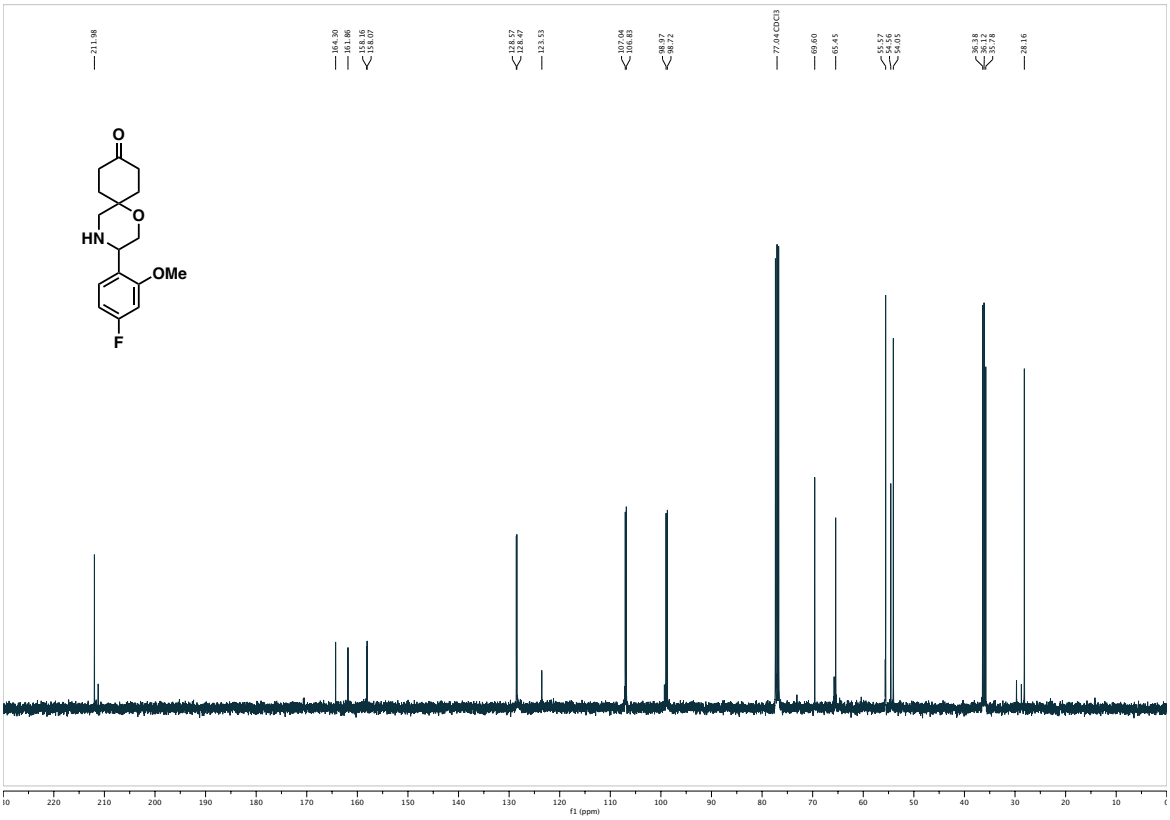
## 27-DiaD



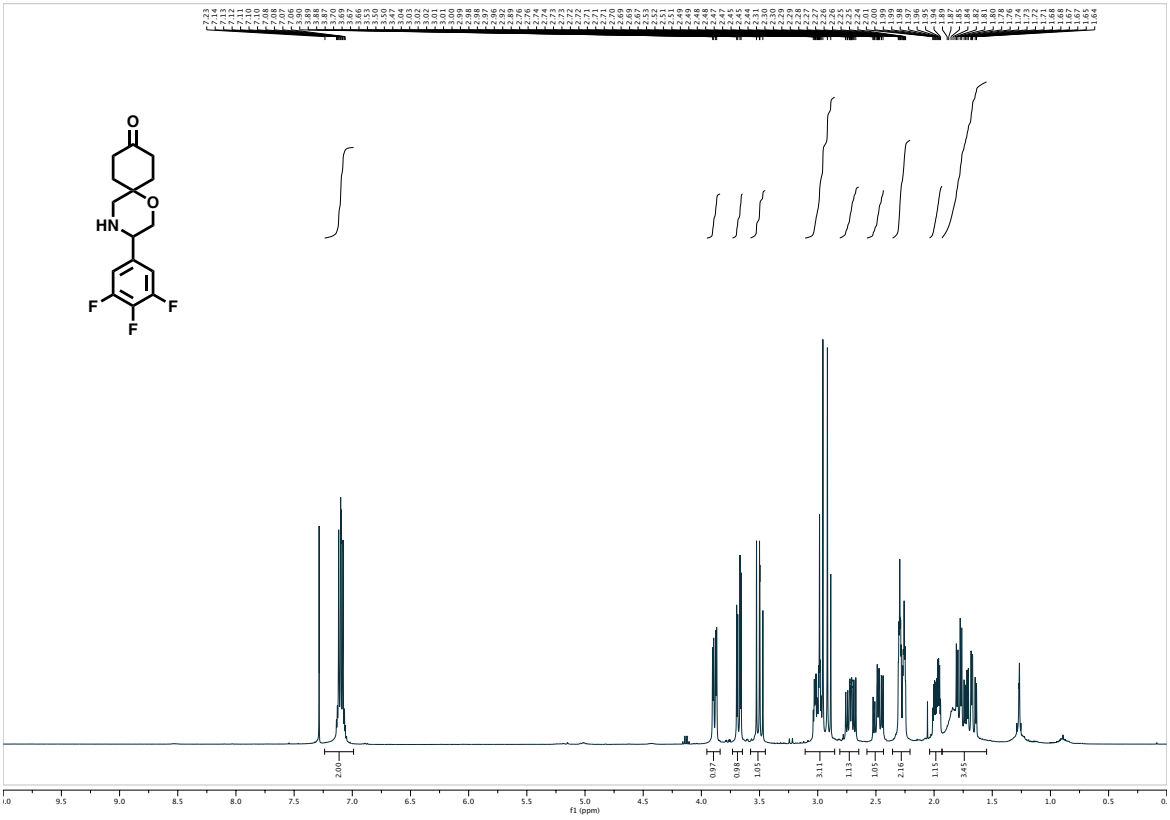



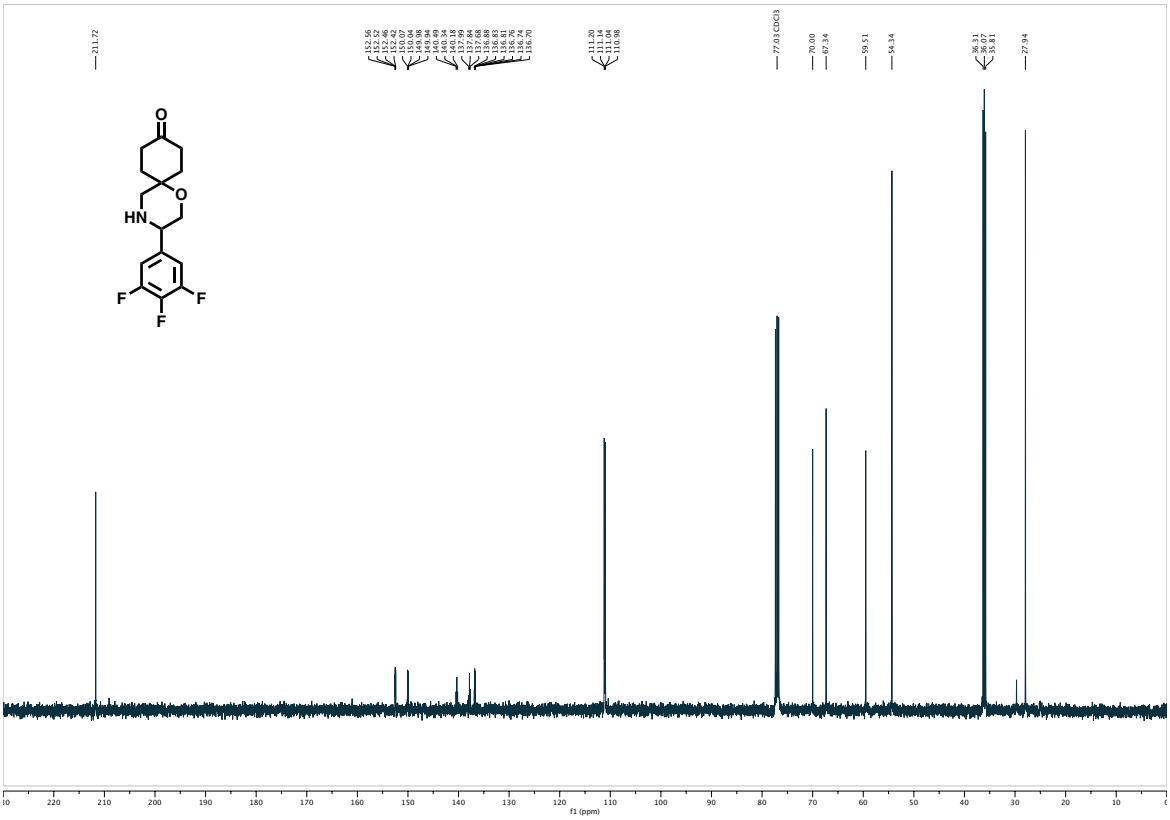
**28**



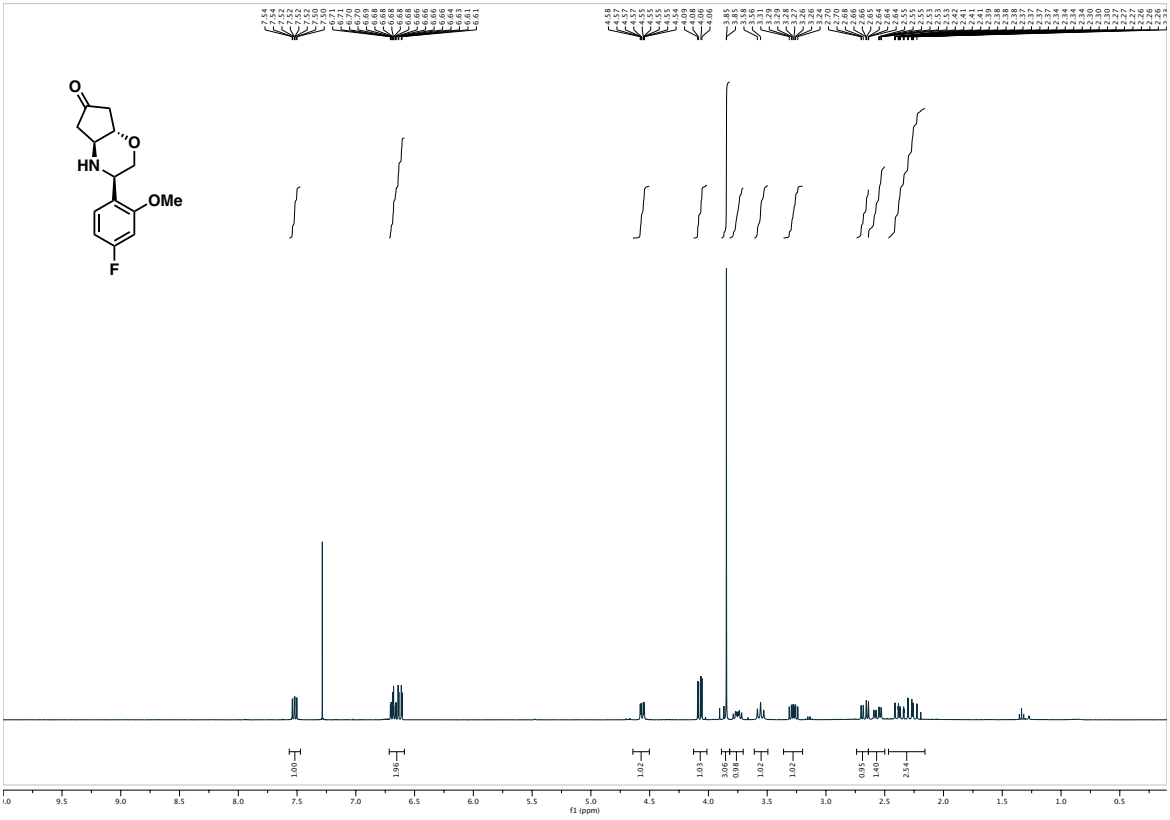



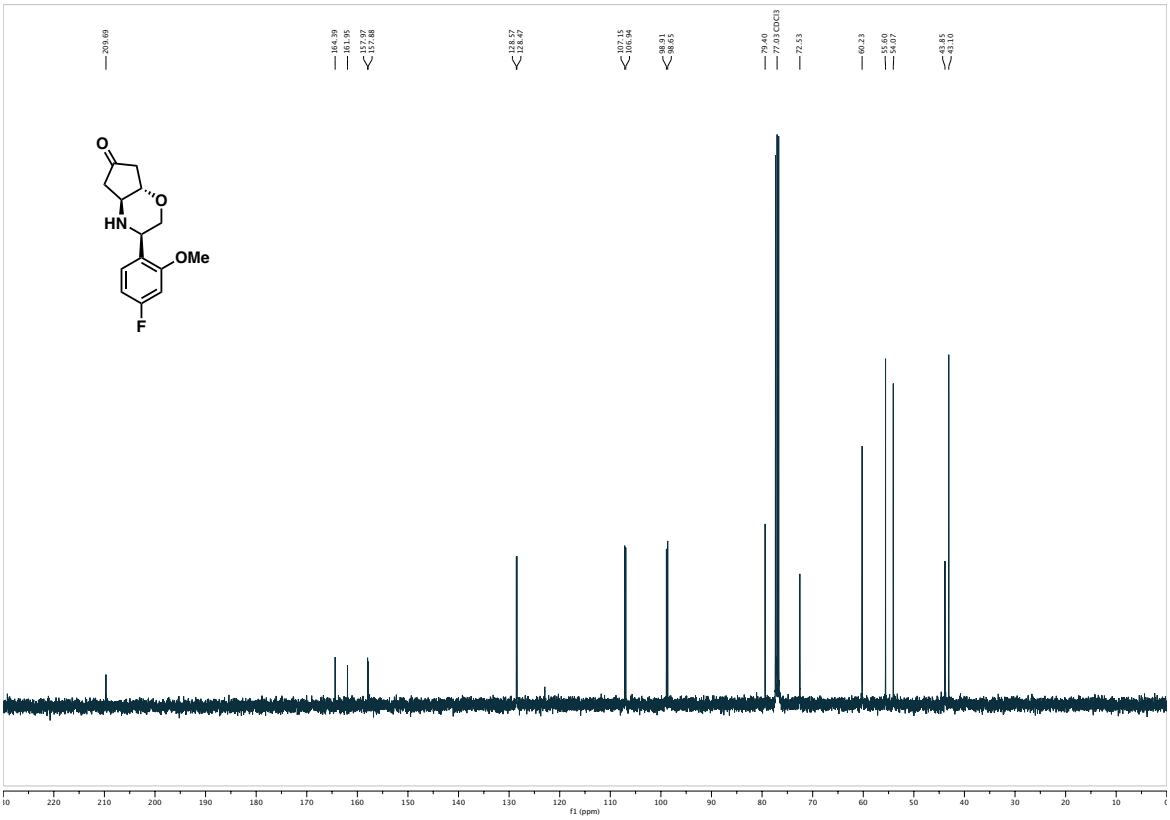
**29**


O
O
HN
F
F
F
2.00
0.97
0.98
1.05
3.11
1.13
1.05
2.16
1.15
3.45
f1 (ppm)

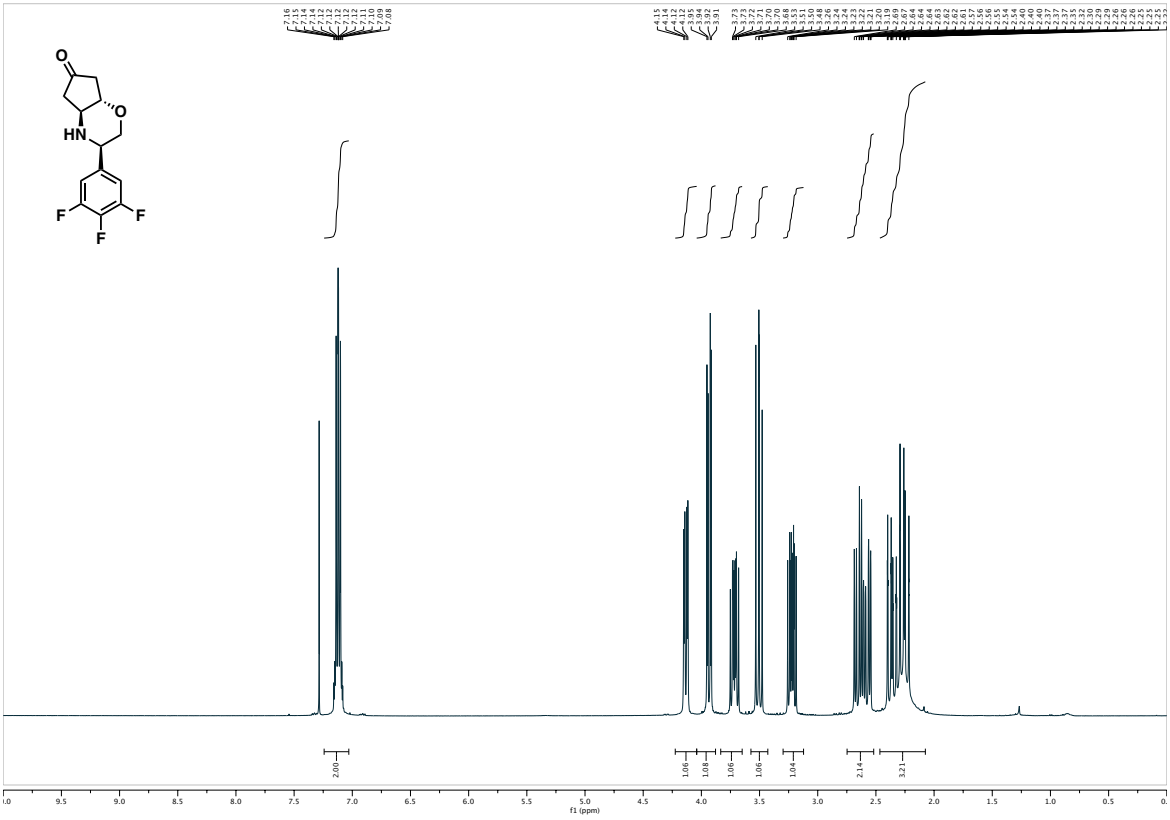

211.72
152.56
152.42
152.46
152.42
150.07
150.04
149.98
149.94
149.89
140.94
140.69
137.84
137.80
136.88
136.83
136.81
136.76
136.74
136.70
111.20
111.14
111.04
110.98
77.03 CDCl3
70.00
67.34
59.51
54.34
36.31
36.07
35.84
27.94
O
O
HN
F
F
F
f1 (ppm)

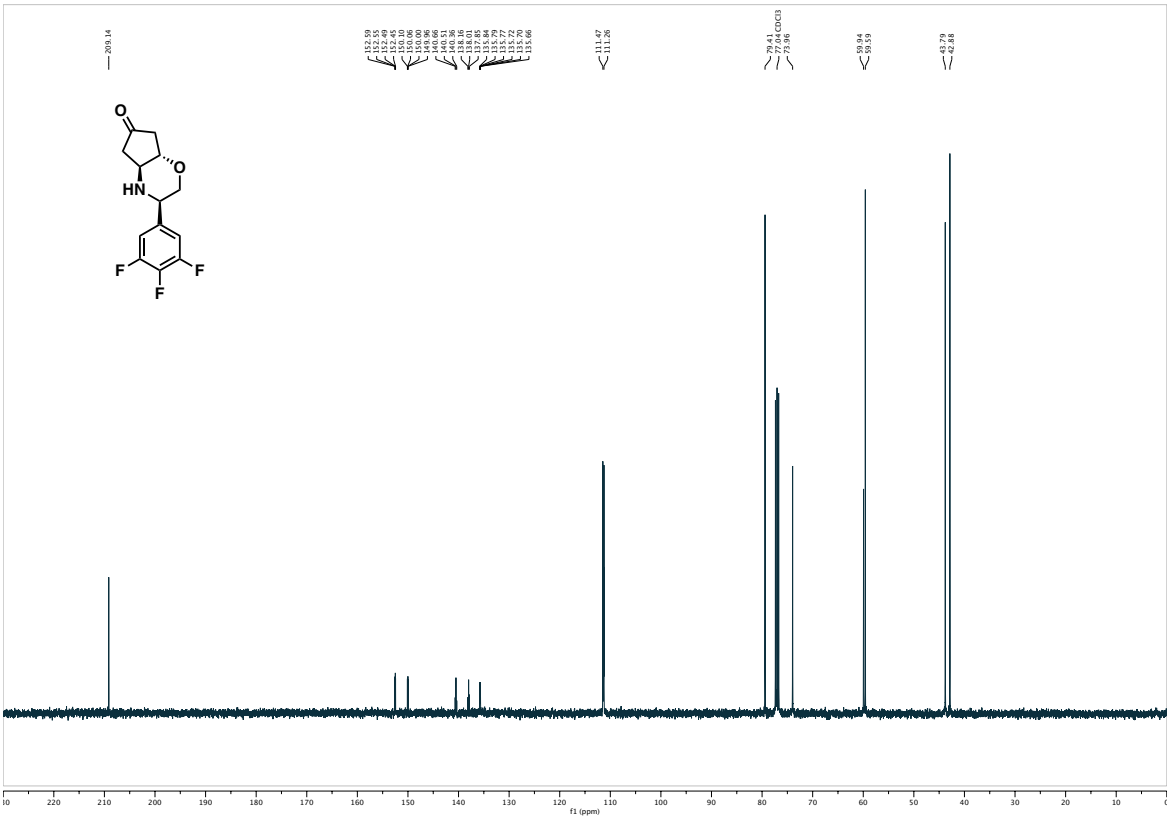
**30**



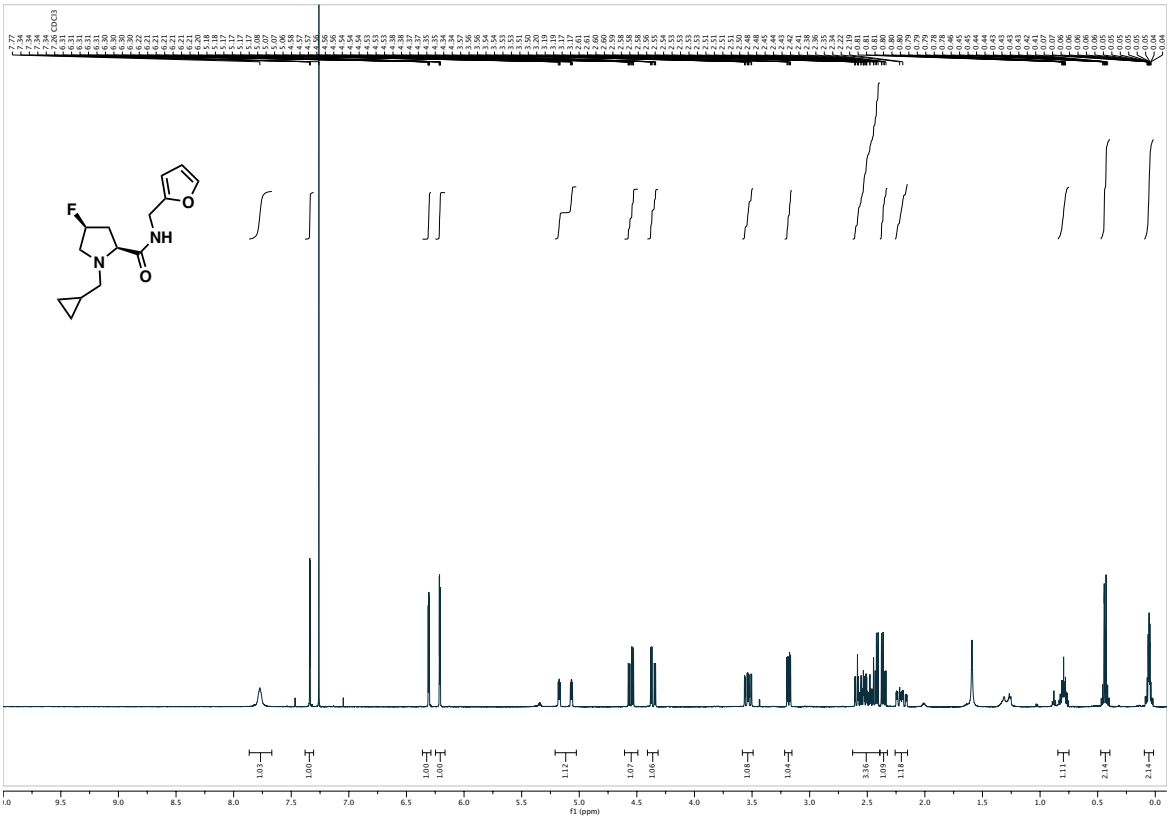



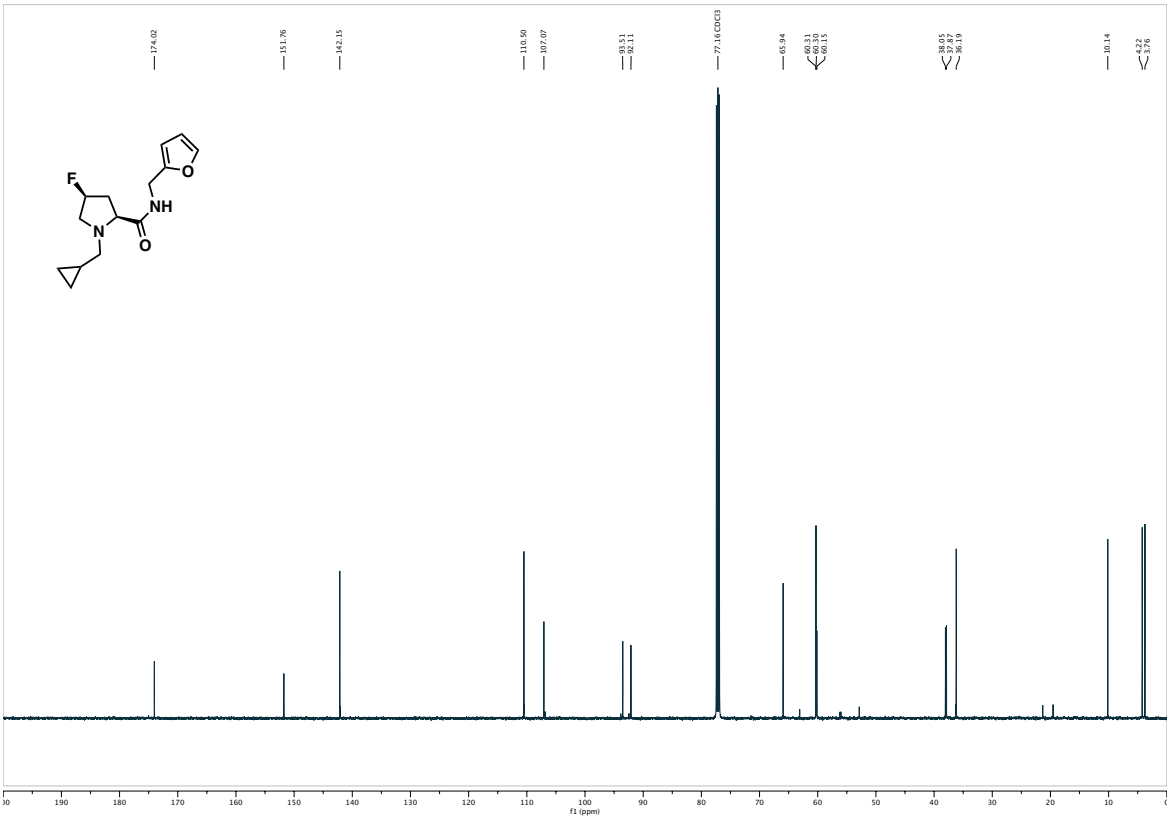
**31**



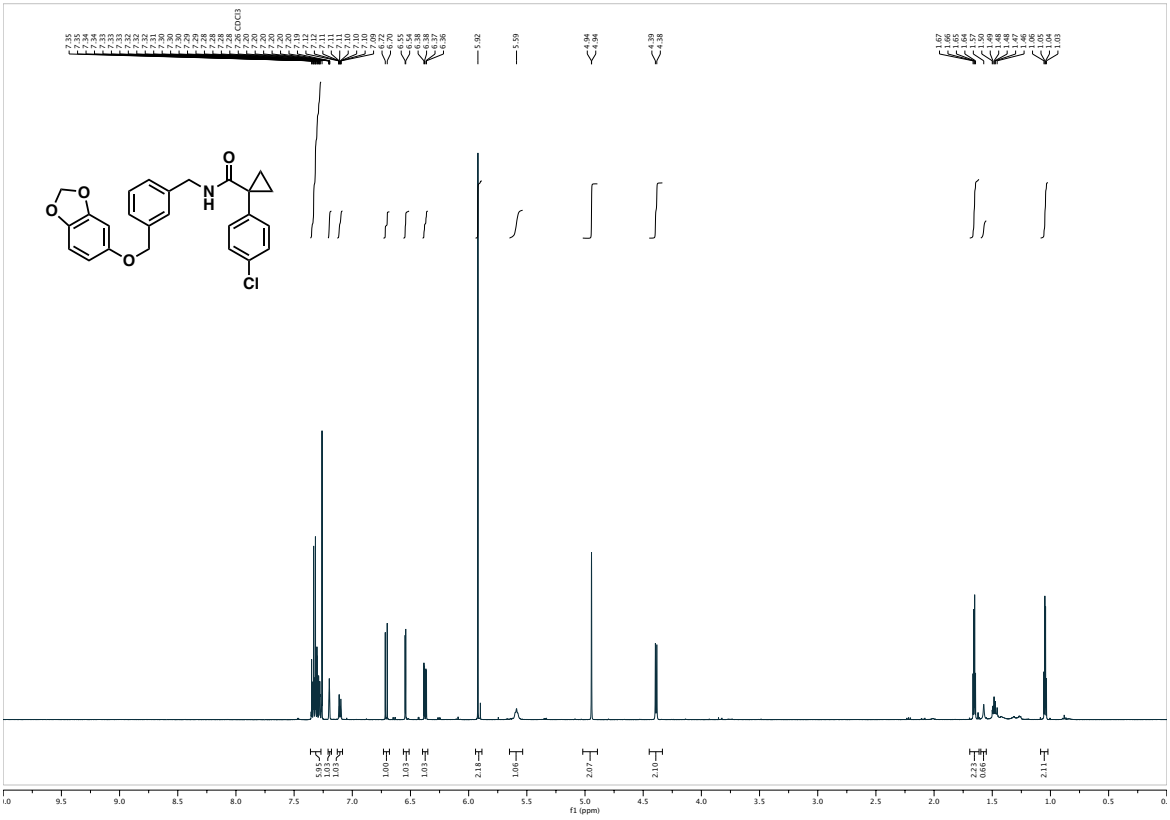



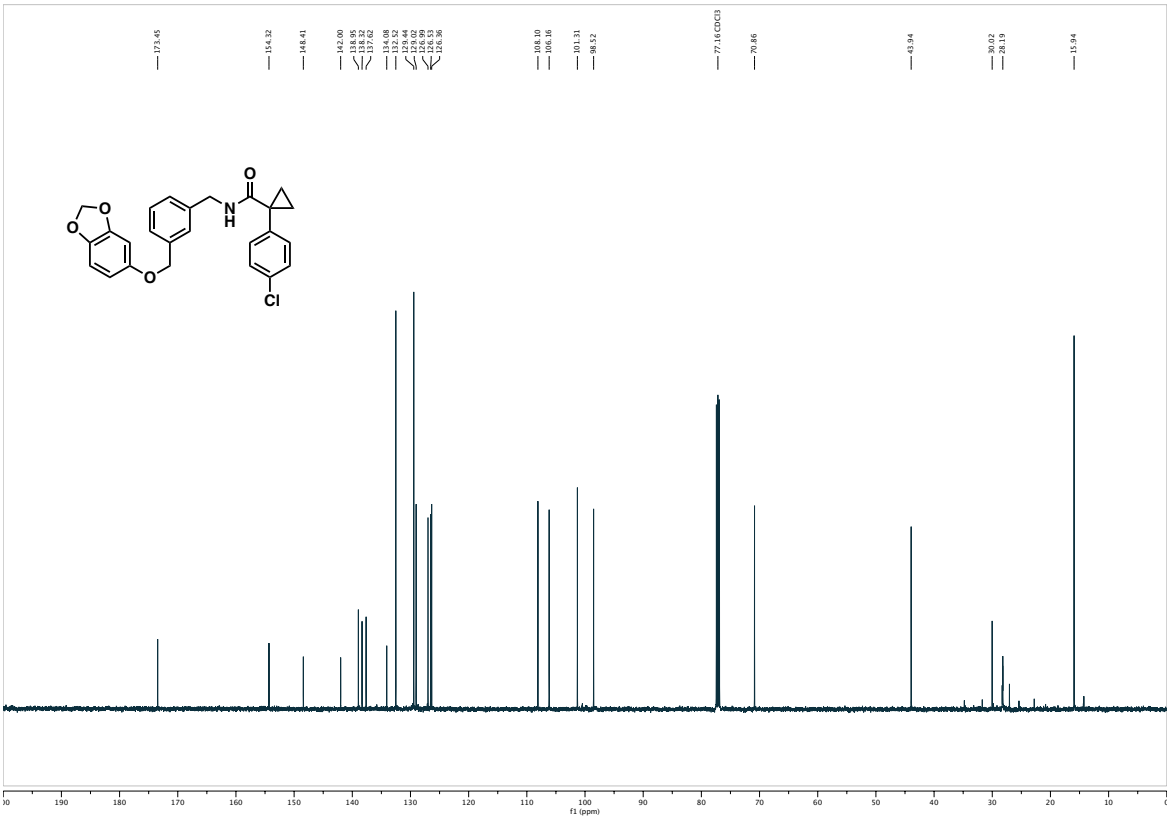
**32**


F
O
NH
N
O
f1 (ppm)


174.02
151.76
142.15
110.50
107.07
93.51
92.11
77.16 CDCl3
65.94
60.31
60.30
60.15
38.05
36.19
10.14
4.22
3.76
F
O
NH
N
O
f1 (ppm)

**33**



**34**