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Supplemental information

Photochemically derived 1-aminonorbornanes provide structurally unique succinate dehydrogenase inhibitors with *in vitro* and *in planta* activity

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Supplemental Experimental Procedures

I. General Methods

Unless otherwise noted, all reactions were run under a nitrogen atmosphere in flame-dried glassware. Reactions were stirred using Teflon-coated magnetic stir bars. Reactions were monitored by thin layer chromatography (TLC) using glass-backed plates pre-coated with 230–400 mesh silica gel (250 μm thickness) with fluorescent indicator F254, available from EMD Millipore (cat. #: 1.05715.0001). Plates were visualized by treatment with UV, acidic *p*-anisaldehyde stain, $KMnO_4$ stain, or aqueous ceric ammonium molybdate (Hanessian's stain; CAM) with gentle heating. Products were purified by flash column chromatography using the solvent systems indicated. Silica gel was purchased from SiliCycle, specifically using SilicaFlash P60, 40-63 μm, 230-400 mesh (cat. #: R12030B). Basic alumina was purchased from Acros, basic, Brockmann I, 50-200 μm, 60 Å.

Organic solvents (acetonitrile, dichloromethane, diethyl ether, dimethylformamide, dimethyl sulfoxide, methanol, tetrahydrofuran, toluene) and amine bases (triethylamine, pyridine, N,N-diisopropylethylamine , and diisopropylamine) were purified prior to use by the method of Grubbs and co-workers[1] using a Phoenix Solvent Drying System (for organic solvents, available from JC-Meyer Solvent Systems) or PureSolv Micro amine drying columns (for amine bases, available from Innovative Technology/Inert) under positive argon pressure; all solvents were supplied by Fisher Scientific. Titanium isopropoxide was obtained from Oakwood Chemical, distilled immediately upon receipt, and stored in a clean sure-seal bottle under inert atmosphere. 3-(Trifluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxylic acid (**S55**) and 3-(Difluoromethyl)-1-methyl-1*H*-pyrazole-4-carboxylic acid (**S11**) were ordered from Enamine. Unless otherwise noted, all other reagents were purchased from Sigma-Aldrich, stored as recommended by the supplier, and used without any additional purification.

NMR spectra were measured on a Varian MR400 (^{1}H at 400 MHz, ^{19}F at 376 MHz), Varian INOVA 500 (^{1}H at 500 MHz), a Varian VNMR 500 (^{1}H at 500 MHz, ^{13}C at 126 MHz), or a Varian VNMR 700 MHz (^{1}H at 700 MHz, ^{13}C at 176 MHz) magnetic resonance spectrometer, as noted. ^{1}H chemical shifts are reported relative to the residual solvent peak (chloroform = 7.26 ppm; benzene = 7.16 ppm)[1] as follows: chemical shift (δ) (multiplicity [s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, hept = heptet, br = broad, *app.* = apparent], integration, coupling constant(s) in Hz, proton ID [when available, designated by carbon number]). Deuterated solvents were obtained from Cambridge Isotope Laboratories, Inc. Proton assignments were made via 2D spectroscopy (COSY, HSQC, HMBC, and/or NOESY) and/or analogy to related systems. ^{13}C chemical shifts are reported relative to the residual deuterated solvent ^{13}C signals ($CDCl_3$ = 77.16 ppm, C_6D_6 = 128.1 ppm).[2] Infrared spectra were recorded on either a Perkin-Elmer Spectrum BX or a Nicolet iS50 FT-IR spectrophotometer using an ATR mount with a ZnSe crystal and are reported in wavenumbers (cm^{-1}). Optical rotation data were obtained using a JASCO P-2000 Polarimeter and are reported as $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\boldsymbol{T}}$ (*c* = grams/100 mL), where D indicates the sodium D line (589 nm) and T indicates temperature (all optical rotation values were obtained at ambient operating temperature, ca. 22-28 °C). High resolution mass spectra were obtained using a Micromass AutoSpec Ultima Magnetic Sector mass spectrometer using electrospray ionization (ESI), positive ion mode, or electron impact ionization (EI); we thank Dr. James Windak and Dr. Paul Lennon at the University of Michigan Department of Chemistry instrumentation facility for conducting these experiments.

II. Biological Evaluation

The following presents the specific protocols used in the evaluation of our 1-aminonorbornane (1-aminoNB) SDHI candidates.

II.A. In Vitro Assay Protocols

A radial mycelial growth assay was employed to assess the *in vitro* fungicidal activity of our SDHI candidates. The general protocol is as follows:

Isolates were collected from disease plant tissues in surveys of Michigan field crops and from previous studies.[3,4,5,6] To generate inoculum, isolates were grown on potato dextrose agar (PDA; Acumedia, Lansing, MI), and a 5 mm cork bore was used to cut agar plugs from the growing edge of the colonies. One agar plug was placed mycelial side down in the center of a 100 mm Petri plate for the assay. Assay plates were made with PDA and amended with compounds after autoclaving and cooling the media to 50 °C. Compound stocks were prepared at 10,000 ppm in DMSO, and were diluted in the media to reach a final concentration of 10 ppm. The untreated control was amended with the equivalent amount of DMSO only. Inoculated assay plates were then incubated in the dark at varying temperatures and times best suited for that species (*F. graminearum* 24 °C for 96 hours, *S. sclerotiorum* 25 °C for 42-48 hours, *M. phaseolina* 35 °C for 38-40 hours). Radial growth was measured in two perpendicular directions with a digital caliper (Absolute Digimatic Caliper, model CD-6" AX, Mitutoyo Corp., Sakado 1-Chome, Japan). These two measurements were averaged, and then divided by the average of the untreated control for the same isolate. Each isolate and compound combination was evaluated in at least three separate experiment runs with 1 or 2 technical replicates each run, resulting in 3-6 total replicates (exact number displayed in Table S1 [Section II.C] for each mean).

All data was analyzed and figures created in R (R Core Team, 2018). A linear mixed model was created for each organism individually, with isolate and compound as fixed effects, and experimental run as a random effect. Type III analysis of variance was computed using Satterthwaite's method in order to account for differences in replication. Compound, Isolate, and their interaction had a significant effect ($p < 0.0001$), for all three organisms.

Code for the full analysis is available publicly https://github.com/mikbreunig/NovelSDHI-analysis-.git.

II.B. In Planta Assay Protocols

The greenhouse evaluation of our SDHI candidates on wheat inoculated with *Fusarium graminearum* isolate Ph-1 was performed as follows:

A *Fusarium*-susceptible spring wheat variety (cv. Wheaton) was grown to anthesis in a greenhouse setting prior to treatment. Within a standard treatment hood, a 250 ppm solution of the test compound in acetone was sprayed on wheat heads using a travel-size spray bottle, drawing each spray along the length of the wheat head to ensure dosage across all spikelets. A maximum of 600 μL was applied to each head (four sprays, each spray delivers 125-150 μL), leading to a maximum dose of 0.15 mg per head. Following 24 hr of incubation, each plant was inoculated with *F. graminearum* (isolate Ph-1) by spraying a conidia spore solution. Conidia was prepared by growing isolates on mung bean agar to induce sporulation, after 7 days spores were washed off with sterile water, and a hemocytomer was used to quantify the concentration of spores. Spore solutions were then adjusted to standard concentration of 1×10^5 spores/mL, and applied with a spray bottle (approximately 600 μL per head) including 0.25% tween 20 as a surfactant.

After spore application, plants were covered with clear plastic bags for 72 hrs to increase humidity and encourage spore germination, then allowed to sit in open air for the duration of the experiment. Approximately 21 days after inoculation wheat heads were rated for necrosis (sign of infection) by counting the number of infected spikelets per head. Three pots with at least three plants/pot were used in each experiment, and two runs were completed, with the mean of both runs presented in the main text.

Greenhouse data was analyzed in with a linear mixed model as well, with treatment as a fixed factor and run and replication as random factors. Treatment significantly affected number of diseased spikelets at 21 days post inoculation ($p=0.005$). Comparison of estimated marginal means with Tukey's test did not reveal statistically significant differences in comparison with the novel compounds, due to variability in inoculation success. However, pydiflumetofen was significantly different than the acetone only treatment. Mean of the two experimental runs is presented in Figure 5 in the main text, with bars representing standard error.

II.C. Additional Data Points

The data provided in the main text detailed the majority of the analysis performed on this project, though Figure 2 only disclosed the *in vitro* performance for 5 of the 9 fungal isolates tested. The complete set of *in vitro* data and the associated standard error is presented graphical in Figure S1 and numerically in Table S1:

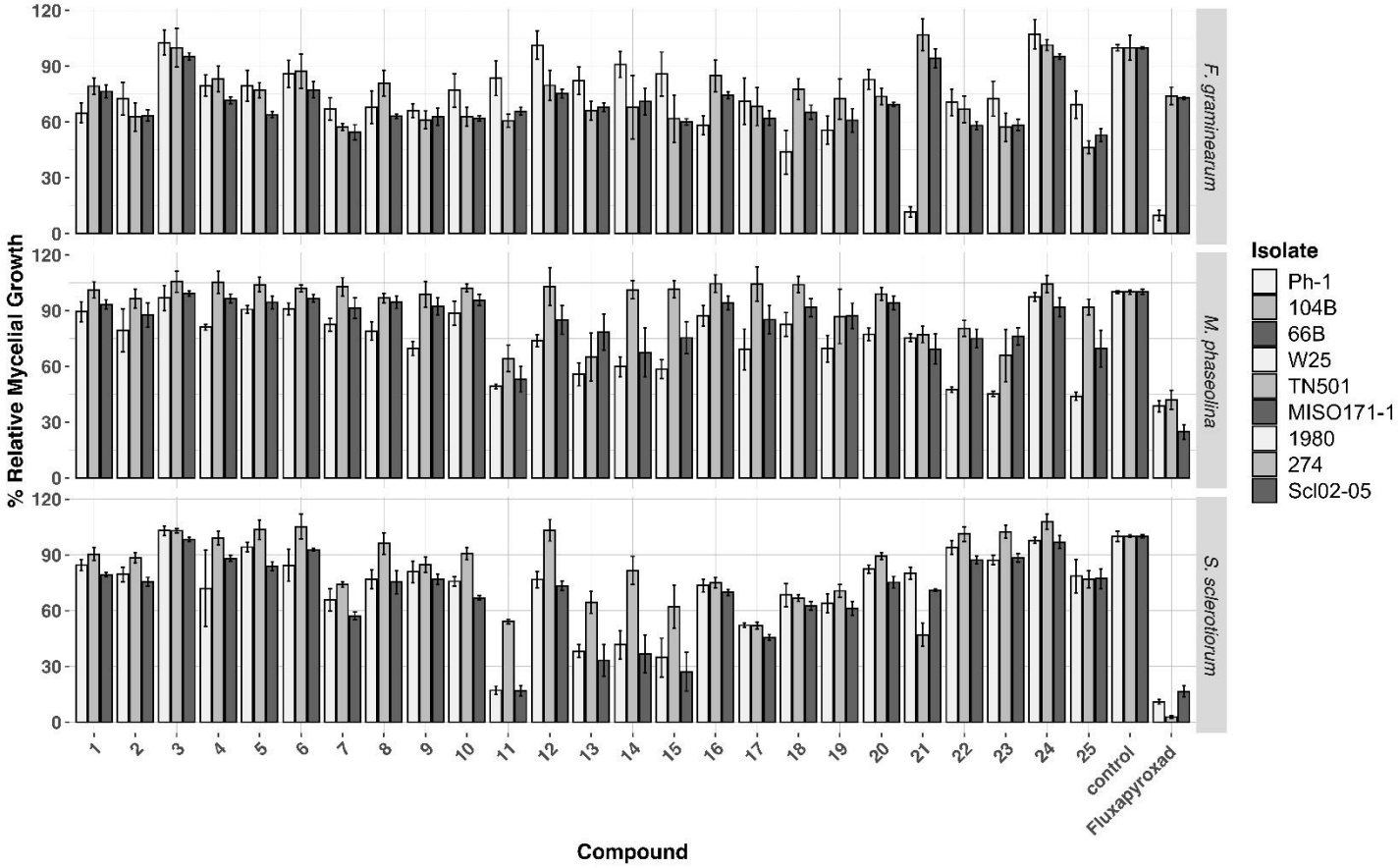


Figure S1. Graphical Compilation of *In Vitro* Fungicidal Activity of 1-AminoNB-Based SDHI Analogs

Table S1. Numerical Compilation of *In Vitro* Fungicidal Activity of 1-AminoNB-Based SDHI Analogs

Compound	Organism	Isolate	*Nominal Mean*	Standard Error	n	Compound	Organism	Isolate	*Nominal Mean*	Standard Error	n
1	*F. graminearum*	104B	***79.0%***	*4.5%*	6	**17**	*F. graminearum*	104B	***68.0%***	*10.3%*	3
1	*F. graminearum*	66B	***76.0%***	*3.3%*	6	**17**	*F. graminearum*	66B	***62.0%***	*4.0%*	3
1	*F. graminearum*	Ph-1	***65.0%***	*5.3%*	7	**17**	*F. graminearum*	Ph-1	***71.0%***	*12.6%*	3
1	*M. phaseolina*	MISO171-1	***93.0%***	*2.5%*	6	**17**	*M. phaseolina*	MISO171-1	***85.0%***	*7.5%*	3
1	*M. phaseolina*	TN501	***101.0%***	*4.4%*	6	**17**	*M. phaseolina*	TN501	***104.0%***	*9.2%*	3
1	*M. phaseolina*	W25	***89.0%***	*5.4%*	7	**17**	*M. phaseolina*	W25	***69.0%***	*10.9%*	4
1	*S. sclerotiorum*	1980	***85.0%***	*2.8%*	7	**17**	*S. sclerotiorum*	1980	***52.0%***	*1.3%*	4
1	*S. sclerotiorum*	205	***79.0%***	*1.2%*	6	**17**	*S. sclerotiorum*	205	***46.0%***	*1.5%*	3
1	*S. sclerotiorum*	274	***90.0%***	*3.5%*	6	**17**	*S. sclerotiorum*	274	***52.0%***	*1.8%*	3
2	*F. graminearum*	104B	***63.0%***	*7.7%*	5	**18**	*F. graminearum*	104B	***78.0%***	*5.7%*	3
2	*F. graminearum*	66B	***63.0%***	*3.0%*	4	**18**	*F. graminearum*	66B	***65.0%***	*3.9%*	3
2	*F. graminearum*	Ph-1	***72.0%***	*8.8%*	5	**18**	*F. graminearum*	Ph-1	***44.0%***	*11.8%*	4
2	*M. phaseolina*	MISO171-1	***87.0%***	*6.5%*	4	**18**	*M. phaseolina*	MISO171-1	***92.0%***	*4.9%*	3
2	*M. phaseolina*	TN501	***96.0%***	*5.0%*	4	**18**	*M. phaseolina*	TN501	***104.0%***	*4.3%*	3
2	*M. phaseolina*	W25	***79.0%***	*11.5%*	5	**18**	*M. phaseolina*	W25	***83.0%***	*6.3%*	4
2	*S. sclerotiorum*	1980	***80.0%***	*3.9%*	5	**18**	*S. sclerotiorum*	1980	***68.0%***	*6.2%*	4
2	*S. sclerotiorum*	205	***76.0%***	*2.4%*	4	**18**	*S. sclerotiorum*	205	***63.0%***	*2.3%*	3
2	*S. sclerotiorum*	274	***88.0%***	*2.8%*	4	**18**	*S. sclerotiorum*	274	***67.0%***	*1.7%*	3
3	*F. graminearum*	104B	***100.0%***	*10.4%*	4	**19**	*F. graminearum*	104B	***72.0%***	*10.9%*	3
3	*F. graminearum*	66B	***95.0%***	*1.9%*	4	**19**	*F. graminearum*	66B	***61.0%***	*6.4%*	3
3	*F. graminearum*	Ph-1	***103.0%***	*6.8%*	5	**19**	*F. graminearum*	Ph-1	***56.0%***	*7.5%*	3
3	*M. phaseolina*	MISO171-1	***99.0%***	*1.4%*	4	**19**	*M. phaseolina*	MISO171-1	***87.0%***	*6.7%*	3
3	*M. phaseolina*	TN501	***106.0%***	*5.7%*	4	**19**	*M. phaseolina*	TN501	***87.0%***	*14.6%*	3
3	*M. phaseolina*	W25	***97.0%***	*6.8%*	4	**19**	*M. phaseolina*	W25	***70.0%***	*7.3%*	4
3	*S. sclerotiorum*	1980	***103.0%***	*2.6%*	5	**19**	*S. sclerotiorum*	1980	***64.0%***	*5.2%*	4
3	*S. sclerotiorum*	205	***98.0%***	*1.3%*	4	**19**	*S. sclerotiorum*	205	***61.0%***	*3.7%*	3
3	*S. sclerotiorum*	274	***103.0%***	*1.2%*	4	**19**	*S. sclerotiorum*	274	***71.0%***	*3.5%*	3
4	*F. graminearum*	104B	***83.0%***	*6.9%*	4	**20**	*F. graminearum*	104B	***74.0%***	*4.5%*	4
4	*F. graminearum*	66B	***72.0%***	*1.9%*	4	**20**	*F. graminearum*	66B	***69.0%***	*1.1%*	4
4	*F. graminearum*	Ph-1	***80.0%***	*5.7%*	4	**20**	*F. graminearum*	Ph-1	***83.0%***	*5.5%*	5
4	*M. phaseolina*	MISO171-1	***97.0%***	*2.4%*	4	**20**	*M. phaseolina*	MISO171-1	***94.0%***	*3.8%*	5
4	*M. phaseolina*	TN501	***105.0%***	*5.9%*	4	**20**	*M. phaseolina*	TN501	***99.0%***	*3.5%*	5
4	*M. phaseolina*	W25	***81.0%***	*1.5%*	5	**20**	*M. phaseolina*	W25	***77.0%***	*3.3%*	5
4	*S. sclerotiorum*	1980	***72.0%***	*20.6%*	5	**20**	*S. sclerotiorum*	1980	***82.0%***	*2.2%*	5
4	*S. sclerotiorum*	205	***88.0%***	*1.6%*	4	**20**	*S. sclerotiorum*	205	***75.0%***	*3.2%*	4
4	*S. sclerotiorum*	274	***99.0%***	*3.6%*	4	**20**	*S. sclerotiorum*	274	***89.0%***	*1.9%*	4
5	*F. graminearum*	104B	***77.0%***	*4.0%*	4	**21**	*F. graminearum*	104B	***107.0%***	*8.5%*	4
5	*F. graminearum*	66B	***64.0%***	*1.7%*	4	**21**	*F. graminearum*	66B	***94.0%***	*5.1%*	4
5	*F. graminearum*	Ph-1	***79.0%***	*8.4%*	5	**21**	*F. graminearum*	Ph-1	***12.0%***	*2.8%*	4
5	*M. phaseolina*	MISO171-1	***94.0%***	*3.3%*	4	**21**	*M. phaseolina*	MISO171-1	***69.0%***	*8.1%*	5
5	*M. phaseolina*	TN501	***104.0%***	*4.0%*	4	**21**	*M. phaseolina*	TN501	***77.0%***	*4.5%*	5
5	*M. phaseolina*	W25	***91.0%***	*1.9%*	5	**21**	*M. phaseolina*	W25	***75.0%***	*2.0%*	4
5	*S. sclerotiorum*	1980	***94.0%***	*2.5%*	5	**21**	*S. sclerotiorum*	1980	***80.0%***	*3.2%*	5
5	*S. sclerotiorum*	205	***84.0%***	*2.3%*	4	**21**	*S. sclerotiorum*	205	***71.0%***	*0.6%*	4
5	*S. sclerotiorum*	274	***104.0%***	*5.2%*	4	**21**	*S. sclerotiorum*	274	***47.0%***	*6.1%*	4
6	*F. graminearum*	104B	***87.0%***	*9.3%*	5	**22**	*F. graminearum*	104B	***67.0%***	*7.3%*	6
6	*F. graminearum*	66B	***77.0%***	*4.4%*	4	**22**	*F. graminearum*	66B	***58.0%***	*2.2%*	6
6	*F. graminearum*	Ph-1	***86.0%***	*7.3%*	5	**22**	*F. graminearum*	Ph-1	***71.0%***	*7.1%*	7
6	*M. phaseolina*	MISO171-1	***97.0%***	*2.0%*	4	**22**	*M. phaseolina*	MISO171-1	***75.0%***	*5.1%*	6
6	*M. phaseolina*	TN501	***102.0%***	*2.0%*	4	**22**	*M. phaseolina*	TN501	***80.0%***	*4.2%*	6
6	*M. phaseolina*	W25	***91.0%***	*3.1%*	5	**22**	*M. phaseolina*	W25	***47.0%***	*1.6%*	7
6	*S. sclerotiorum*	1980	***84.0%***	*8.6%*	5	**22**	*S. sclerotiorum*	1980	***94.0%***	*3.7%*	7
6	*S. sclerotiorum*	205	***93.0%***	*0.6%*	4	**22**	*S. sclerotiorum*	205	***87.0%***	*2.2%*	6
6	*S. sclerotiorum*	274	***105.0%***	*6.8%*	4	**22**	*S. sclerotiorum*	274	***101.0%***	*3.9%*	6
7	*F. graminearum*	104B	***57.0%***	*1.8%*	4	**23**	*F. graminearum*	104B	***57.0%***	*7.6%*	4
7	*F. graminearum*	66B	***55.0%***	*4.0%*	4	**23**	*F. graminearum*	66B	***58.0%***	*3.0%*	4
7	*F. graminearum*	Ph-1	***67.0%***	*6.1%*	5	**23**	*F. graminearum*	Ph-1	***73.0%***	*9.4%*	5
7	*M. phaseolina*	MISO171-1	***91.0%***	*5.5%*	4	**23**	*M. phaseolina*	MISO171-1	***76.0%***	*4.6%*	4
7	*M. phaseolina*	TN501	***103.0%***	*5.0%*	4	**23**	*M. phaseolina*	TN501	***66.0%***	*14.1%*	4
7	*M. phaseolina*	W25	***82.0%***	*3.5%*	4	**23**	*M. phaseolina*	W25	***45.0%***	*1.4%*	5
7	*S. sclerotiorum*	1980	***66.0%***	*6.0%*	5	**23**	*S. sclerotiorum*	1980	***87.0%***	*2.6%*	5
7	*S. sclerotiorum*	205	***57.0%***	*2.0%*	4	**23**	*S. sclerotiorum*	205	***88.0%***	*2.4%*	4
7	*S. sclerotiorum*	274	***74.0%***	*1.5%*	4	**23**	*S. sclerotiorum*	274	***102.0%***	*3.4%*	4
8	*F. graminearum*	104B	***81.0%***	*7.0%*	4	**24**	*F. graminearum*	104B	***101.0%***	*2.8%*	4
8	*F. graminearum*	66B	***63.0%***	*1.1%*	4	**24**	*F. graminearum*	66B	***95.0%***	*1.5%*	4
8	*F. graminearum*	Ph-1	***68.0%***	*8.8%*	4	**24**	*F. graminearum*	Ph-1	***107.0%***	*8.0%*	4
8	*M. phaseolina*	MISO171-1	***94.0%***	*3.3%*	4	**24**	*M. phaseolina*	MISO171-1	***92.0%***	*5.0%*	4
8	*M. phaseolina*	TN501	***97.0%***	*2.6%*	4	**24**	*M. phaseolina*	TN501	***104.0%***	*4.7%*	4
8	*M. phaseolina*	W25	***79.0%***	*4.9%*	5	**24**	*M. phaseolina*	W25	***97.0%***	*2.3%*	5
8	*S. sclerotiorum*	1980	***77.0%***	*5.2%*	5	**24**	*S. sclerotiorum*	1980	***98.0%***	*1.7%*	5
8	*S. sclerotiorum*	205	***75.0%***	*6.1%*	4	**24**	*S. sclerotiorum*	205	***97.0%***	*3.5%*	4
8	*S. sclerotiorum*	274	***96.0%***	*5.8%*	4	**24**	*S. sclerotiorum*	274	***108.0%***	*4.2%*	4

Compound	Organism	Isolate	*Nominal Mean*	Standard Error	n	Compound	Organism	Isolate	*Nominal Mean*	Standard Error	n
9	*F. graminearum*	104B	***61.0%***	*4.8%*	5	**25**	*F. graminearum*	104B	***46.0%***	*3.5%*	4
9	*F. graminearum*	66B	***63.0%***	*4.5%*	4	**25**	*F. graminearum*	66B	***53.0%***	*3.4%*	4
9	*F. graminearum*	Ph-1	***66.0%***	*3.7%*	5	**25**	*F. graminearum*	Ph-1	***69.0%***	*7.3%*	5
9	*M. phaseolina*	MISO171-1	***92.0%***	*4.6%*	4	**25**	*M. phaseolina*	MISO171-1	***70.0%***	*9.9%*	4
9	*M. phaseolina*	TN501	***99.0%***	*6.9%*	4	**25**	*M. phaseolina*	TN501	***92.0%***	*4.2%*	4
9	*M. phaseolina*	W25	***70.0%***	*3.9%*	5	**25**	*M. phaseolina*	W25	***44.0%***	*2.2%*	5
9	*S. sclerotiorum*	1980	***81.0%***	*5.7%*	5	**25**	*S. sclerotiorum*	1980	***79.0%***	*8.9%*	5
9	*S. sclerotiorum*	205	***77.0%***	*2.8%*	4	**25**	*S. sclerotiorum*	205	***77.0%***	*5.3%*	4
9	*S. sclerotiorum*	274	***85.0%***	*4.1%*	4	**25**	*S. sclerotiorum*	274	***77.0%***	*4.6%*	4
10	*F. graminearum*	104B	***63.0%***	*5.2%*	4	**26**	*F. graminearum*	104B	***105.0%***	*0.1%*	2
10	*F. graminearum*	66B	***62.0%***	*1.5%*	4	**26**	*F. graminearum*	66B	***97.0%***	*4.1%*	2
10	*F. graminearum*	Ph-1	***77.0%***	*9.0%*	5	**26**	*F. graminearum*	Ph-1	***99.0%***	*5.1%*	2
10	*M. phaseolina*	MISO171-1	***96.0%***	*3.0%*	4	**26**	*M. phaseolina*	MISO171-1	***97.0%***	*1.0%*	2
10	*M. phaseolina*	TN501	***102.0%***	*2.1%*	4	**26**	*M. phaseolina*	TN501	***100.0%***	*2.7%*	2
10	*M. phaseolina*	W25	***89.0%***	*6.5%*	5	**26**	*M. phaseolina*	W25	***97.0%***	*0.9%*	2
10	*S. sclerotiorum*	1980	***76.0%***	*2.4%*	5	**26**	*S. sclerotiorum*	1980	***97.0%***	*0.7%*	2
10	*S. sclerotiorum*	205	***67.0%***	*1.2%*	4	**26**	*S. sclerotiorum*	205	***97.0%***	*1.0%*	2
10	*S. sclerotiorum*	274	***91.0%***	*3.2%*	4	**26**	*S. sclerotiorum*	274	***103.0%***	*0.3%*	2
11	*F. graminearum*	104B	***61.0%***	*3.6%*	4	**27**	*F. graminearum*	104B	***108.0%***	*1.1%*	2
11	*F. graminearum*	66B	***66.0%***	*2.0%*	4	**27**	*F. graminearum*	66B	***114.0%***	*2.6%*	2
11	*F. graminearum*	Ph-1	***84.0%***	*9.4%*	4	**27**	*F. graminearum*	Ph-1	***106.0%***	*0.4%*	2
11	*M. phaseolina*	MISO171-1	***53.0%***	*6.8%*	5	**27**	*M. phaseolina*	MISO171-1	***99.0%***	*1.7%*	2
11	*M. phaseolina*	TN501	***64.0%***	*7.1%*	5	**27**	*M. phaseolina*	TN501	***97.0%***	*0.5%*	2
11	*M. phaseolina*	W25	***49.0%***	*1.2%*	4	**27**	*M. phaseolina*	W25	***93.0%***	*0.9%*	2
11	*S. sclerotiorum*	1980	***17.0%***	*2.3%*	5	**27**	*S. sclerotiorum*	1980	***102.0%***	*0.5%*	2
11	*S. sclerotiorum*	205	***17.0%***	*2.8%*	4	**27**	*S. sclerotiorum*	205	***103.0%***	*2.5%*	2
11	*S. sclerotiorum*	274	***54.0%***	*1.3%*	4	**27**	*S. sclerotiorum*	274	***101.0%***	*0.3%*	2
12	*F. graminearum*	104B	***80.0%***	*8.2%*	3	**28**	*F. graminearum*	104B	***92.0%***	*2.2%*	2
12	*F. graminearum*	66B	***75.0%***	*2.5%*	3	**28**	*F. graminearum*	66B	***97.0%***	*1.1%*	2
12	*F. graminearum*	Ph-1	***101.0%***	*7.5%*	3	**28**	*F. graminearum*	Ph-1	***57.0%***	*4.5%*	2
12	*M. phaseolina*	MISO171-1	***85.0%***	*7.8%*	3	**28**	*M. phaseolina*	MISO171-1	***98.0%***	*2.8%*	2
12	*M. phaseolina*	TN501	***103.0%***	*10.0%*	3	**28**	*M. phaseolina*	TN501	***99.0%***	*4.8%*	2
12	*M. phaseolina*	W25	***74.0%***	*3.3%*	3	**28**	*M. phaseolina*	W25	***102.0%***	*1.6%*	2
12	*S. sclerotiorum*	1980	***77.0%***	*4.4%*	3	**28**	*S. sclerotiorum*	1980	***91.0%***	*0.4%*	2
12	*S. sclerotiorum*	205	***73.0%***	*2.4%*	3	**28**	*S. sclerotiorum*	205	***86.0%***	*2.4%*	2
12	*S. sclerotiorum*	274	***103.0%***	*5.8%*	3	**28**	*S. sclerotiorum*	274	***91.0%***	*4.0%*	2
13	*F. graminearum*	104B	***66.0%***	*5.2%*	3	**29**	*F. graminearum*	104B	***107.0%***	*2.5%*	2
13	*F. graminearum*	66B	***68.0%***	*2.3%*	3	**29**	*F. graminearum*	66B	***100.0%***	*1.0%*	2
13	*F. graminearum*	Ph-1	***82.0%***	*7.5%*	4	**29**	*F. graminearum*	Ph-1	***102.0%***	*8.0%*	2
13	*M. phaseolina*	MISO171-1	***78.0%***	*9.7%*	3	**29**	*M. phaseolina*	MISO171-1	***102.0%***	*0.6%*	2
13	*M. phaseolina*	TN501	***65.0%***	*13.0%*	3	**29**	*M. phaseolina*	TN501	***104.0%***	*3.4%*	2
13	*M. phaseolina*	W25	***56.0%***	*6.2%*	4	**29**	*M. phaseolina*	W25	***100.0%***	*6.6%*	2
13	*S. sclerotiorum*	1980	***38.0%***	*3.6%*	4	**29**	*S. sclerotiorum*	1980	***96.0%***	*3.7%*	2
13	*S. sclerotiorum*	205	***33.0%***	*8.5%*	3	**29**	*S. sclerotiorum*	205	***99.0%***	*0.8%*	2
13	*S. sclerotiorum*	274	***64.0%***	*5.9%*	3	**29**	*S. sclerotiorum*	274	***98.0%***	*1.5%*	2
14	*F. graminearum*	104B	***68.0%***	*17.1%*	3	**control**	*F. graminearum*	104B	***100.0%***	*6.8%*	8
14	*F. graminearum*	66B	***71.0%***	*7.3%*	3	**control**	*F. graminearum*	66B	***100.0%***	*0.5%*	7
14	*F. graminearum*	Ph-1	***91.0%***	*6.9%*	4	**control**	*F. graminearum*	Ph-1	***100.0%***	*1.8%*	8
14	*M. phaseolina*	MISO171-1	***67.0%***	*13.2%*	3	**control**	*M. phaseolina*	MISO171-1	***100.0%***	*1.4%*	8
14	*M. phaseolina*	TN501	***101.0%***	*4.9%*	3	**control**	*M. phaseolina*	TN501	***100.0%***	*1.1%*	8
14	*M. phaseolina*	W25	***60.0%***	*5.3%*	4	**control**	*M. phaseolina*	W25	***100.0%***	*0.8%*	7
14	*S. sclerotiorum*	1980	***42.0%***	*7.6%*	4	**control**	*S. sclerotiorum*	1980	***100.0%***	*2.7%*	8
14	*S. sclerotiorum*	205	***37.0%***	*10.1%*	3	**control**	*S. sclerotiorum*	205	***100.0%***	*0.8%*	7
14	*S. sclerotiorum*	274	***82.0%***	*7.5%*	3	**control**	*S. sclerotiorum*	274	***100.0%***	*0.7%*	7
15	*F. graminearum*	104B	***62.0%***	*12.6%*	4	**Fluxapyroxad**	*F. graminearum*	104B	***74.0%***	*4.7%*	5
15	*F. graminearum*	66B	***60.0%***	*1.6%*	3	**Fluxapyroxad**	*F. graminearum*	66B	***73.0%***	*0.8%*	5
15	*F. graminearum*	Ph-1	***86.0%***	*11.9%*	5	**Fluxapyroxad**	*F. graminearum*	Ph-1	***10.0%***	*2.7%*	6
15	*M. phaseolina*	MISO171-1	***75.0%***	*8.7%*	5	**Fluxapyroxad**	*M. phaseolina*	MISO171-1	***25.0%***	*3.9%*	6
15	*M. phaseolina*	TN501	***101.0%***	*4.5%*	5	**Fluxapyroxad**	*M. phaseolina*	TN501	***42.0%***	*5.1%*	5
15	*M. phaseolina*	W25	***58.0%***	*5.1%*	6	**Fluxapyroxad**	*M. phaseolina*	W25	***39.0%***	*2.9%*	5
15	*S. sclerotiorum*	1980	***35.0%***	*10.5%*	5	**Fluxapyroxad**	*S. sclerotiorum*	1980	***11.0%***	*1.2%*	6
15	*S. sclerotiorum*	205	***27.0%***	*10.5%*	4	**Fluxapyroxad**	*S. sclerotiorum*	205	***17.0%***	*2.9%*	5
15	*S. sclerotiorum*	274	***62.0%***	*11.7%*	4	**Fluxapyroxad**	*S. sclerotiorum*	274	***3.0%***	*0.7%*	5
16	*F. graminearum*	104B	***85.0%***	*8.6%*	4						
16	*F. graminearum*	66B	***74.0%***	*1.9%*	3						
16	*F. graminearum*	Ph-1	***58.0%***	*5.1%*	4						
16	*M. phaseolina*	MISO171-1	***94.0%***	*3.7%*	5						
16	*M. phaseolina*	TN501	***104.0%***	*4.7%*	5						
16	*M. phaseolina*	W25	***87.0%***	*5.6%*	4						
16	*S. sclerotiorum*	1980	***74.0%***	*3.4%*	5						
16	*S. sclerotiorum*	205	***70.0%***	*1.7%*	4						
16	*S. sclerotiorum*	274	***75.0%***	*2.9%*	4						

Alternative pyrazole carboxamides

A few additional compounds were prepared and evaluated, as seen below. At the outset of the project, additional photochemical procedures developed in the Stephenson lab were employed to generate C5'-haloalkyl-substituted pyrazoles (**26**-**29**; see Figure S2). As seen in Figure S3, these pyrazole variants did not present any obvious improvement in performance relative to the canonical C3'-difluoromethyl pyrazole carboxamide and were thus quickly disregarded.

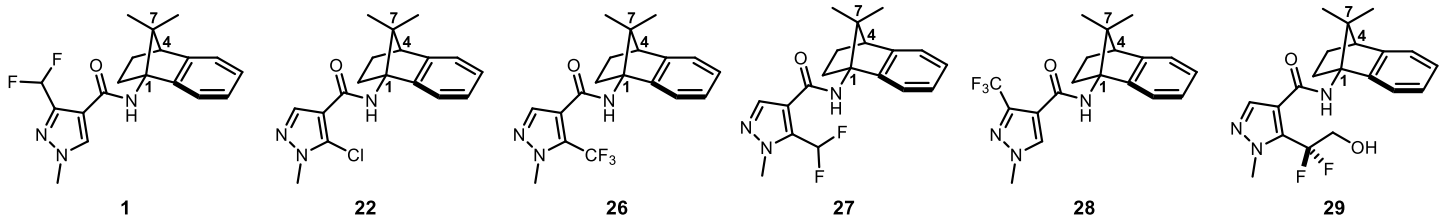


Figure S2. Substrates with Alternative Pyrazole Motifs

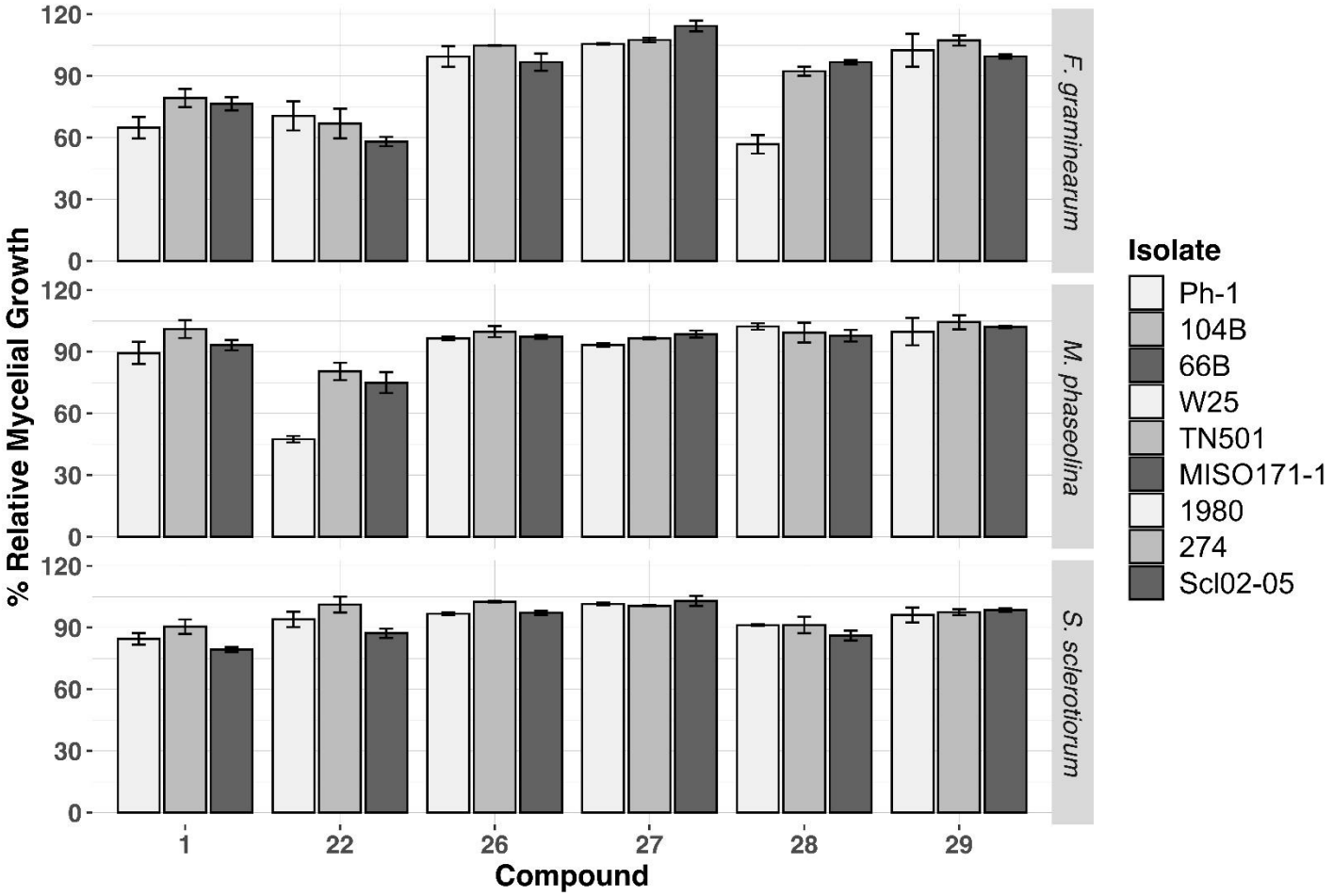


Figure S3. *In Vitro* Data for Substrates with Alternative Pyrazole Motifs

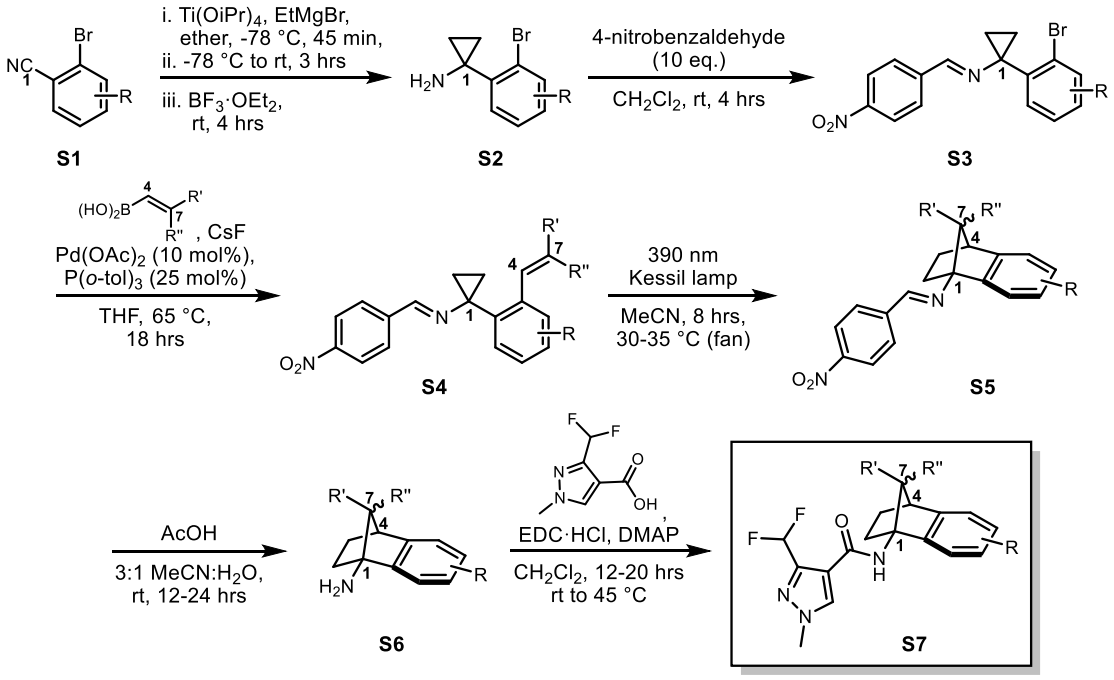
III. General Synthetic Procedures

The following provides a brief summary of the synthetic procedures employed to produce the 1-aminoNB-based SDHI candidates discussed in the main text. This includes procedures from our previously reported method for converting cyclopropylimine species with tethered olefins into Schiff base-protected 1-aminoNBs via a photochemical formal [3+2] cycloaddition[7] as well as procedures to convert the Schiff base-protected 1-aminoNBs into SDHI candidates. Detailed synthetic procedures toward all novel compounds are provided in Section IV.

II.A. General Synthetic Sequence to 1-AminoNBs and SDHI leads

Synthesis of all the SDHI leads detailed in the main text is achieved through a 6-step sequence (generically represented in Scheme S1). Briefly, a Kulinkovich cyclopropanation of the corresponding (2-halo)-aryl nitrile starting material (**S1**) using conditions from Bertus and Szymoniak[8,9] generates the aminocyclopropane motif (**S2**). The Schiff base (**S3**) is formed through simple condensation with 4-nitrobenzaldehyde prior to a Suzuki coupling to generate the photochemistry precursor cyclopropylimine (**S4**). Irradiation with 390 nm light (see Section II.B) affords the desired 1-aminoNB as the Schiff base (**S5**). Solvolysis provides the free bridgehead amine (**S6**), which is readily acylated with the corresponding acid via standard EDC-based coupling conditions to form the final analog (**S7**).

The solvolysis and amide coupling conditions are closely analogous to procedures reported in our initial disclosure of the photochemistry (a generic protocol can be found in Section II.D), but the specific conditions toward each analog is provided below in Section IV. Effectively all cyclopropylimines used to generate 1-aminoNB-based SDHI leads were described in the prior manuscript, including detailed procedures for their synthesis. The reader is directly back to that report as a resource for substrate-specific details, but a general set of procedures is provided in Section II.B for sake of completeness). A handful of SDHI leads required synthetic sequences that deviate from the procedure shown in Scheme S1; brief descriptions of the starting material synthesis for those compounds is supplied with the characterization data for the SDHI lead in question. A representative photochemical procedure is supplied in Section II.C (again, detailed procedures can be found in the prior manuscript).



Scheme S1. General Route toward 1-AminoNB-based SDHI leads

II.B. Generic Procedure for the Synthesis of Cyclopropylimine Precursors

(2-Halo)-aryl nitrile **S1** (1 eq.) was dissolved in dry ether (0.05 M with respect to **S1**) in a dry flask under inert atmosphere, then cooled to -78 °C. Titanium isopropoxide (1.1 eq.) was added in one portion, followed by addition of ethylmagnesium bromide (3.0 M in ether; 2.2 eq.) via syringe, dropwise over the course of 3-5 min. The dark brown-black reaction mixture (clear, colorless at outset of EtMgBr addition) was stirred at -78 °C for 45 min, cold bath was removed, and the reaction was stirred an additional 3 hrs at room temp. BF3·etherate (2.0 eq.) was added dropwise over the course of 2 min, and the reaction mixture was stirred 4 hrs at room temp. The reaction was quenched by carefully pouring in 3:1 mix of sat. Rochelle salt:1 M NaOH in brine (prepared 2x reaction volume, quench

with 1x), followed by 30 min of vigorous stirring at room temp. The biphasic mixture was diluted with the remaining half of the aqueous mixture and ether (2x reaction volume). The phases were separated. The aqueous phase was extracted with three portions of ether (each 1x reaction volume). The combined organics were then washed with 100 mL brine (1x reaction volume), dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under vacuum. The crude residue was purified via flash chromatography over silica using an ethyl acetate:hexanes mobile phase (silica was pre-neutralized with the initial mobile phase + 1% NEt_3; the residue was loaded with PhMe) to afford aminocyclopropane **S2**.

Aminocyclopropane **S2** (1 eq.) was dissolved in dry CH_2Cl_2 (0.15 M with respect to **S2**) under inert atmosphere, followed by addition of 4-nitrobenzaldehyde (2.5 eq.) in one portion. The reaction mixture was stirred at room temp for 4 hrs before concentrating onto celite under vacuum; two portions of pentane (each ~1x reaction volume) were added followed by re-concentration after each. The celite was loaded onto a basic alumina column followed by elution with an ethyl acetate:hexanes mobile phase to afford Schiff base intermediate **S3**.

CsF (5 eq.) was added to flame-dried flask under Ar (with stir bar), the flask was sealed, then flame-dried under vacuum; this flask was stored under vacuum until cool, before purging with N_2. In a separate dry vial under inert atmosphere, $Pd(OAc)_2$ (0.1 eq.) and CyJohnPhos (0.25 eq.) were dissolved in dry, degassed THF (degassed by sparging with Ar through 22 gauge needle for 30 min prior to use, in separate dry flask; total reaction volume was 0.1 M with respect to **S3**, with ~1/6 of the total THF volume being used for this portion of the procedure). The Pd-ligand mix was stirred for 15-20 min at room temp under inert atmosphere. In separate dry vial under inert atmosphere, Schiff base intermediate **S3** (1 eq.) was dissolved in dry, degassed THF (1/3 of total volume) before adding the requisite vinylboronic acid (1.5 eq.) in one portion. The CsF-containing flask received dry, degassed THF (1/3 of total volume), prior to the addition of the starting material and boronic acid mixture via syringe; transfer was quantified with 2 rinses with dry, degassed THF (employing equal portions of the remaining 1/6 of the total volume). Once the Pd^0-phosphine mixture (orange) had stirred for 15-20 min, it was added to the reaction flask via syringe, adding dropwise over 30 seconds. A reflux condenser was attached, the system was flushed with Ar, and the reaction was heated to 65 ºC for 18 hrs, stirring vigorously to prevent CsF from settling. Upon cooling to room temp, the reaction mixture was filtered through a pad of celite, eluting with ethyl acetate (~5x reaction volume) before concentrating under vacuum. The crude residue was purified via flash chromatography over silica using an ethyl acetate:hexanes mobile phase (certain substrates were dry loaded with celite) to generate the cyclopropylimine precursor to the photochemical reaction (**S5**).

II.C. Representative Procedure for Photochemical Production of 1-AminoNBs

Photochemical Equipment and Apparatus

The standard photochemical procedure utilizes a 390 nm LED lamp available from Kessil (PR160-390nm; http://www.kessil.com/photoredox/Products.php). Reactions were cooled with a standard fan (Westpointe, 4 inch personal fan). Reactions were performed behind plastic guards (provided by Ann Arbor Plastics) wrapped in orange film to provide eye protection during prolonged irradiation (film purchased from UV Process Supply, Amber UV filter film; https://www.uvprocess.com/c3/1785-amber-uv-filter-films.html); additional eye protection came in the form of orange safety googles from Uvex (Skyper SCT-orange; this line of protective eyeware has been discontinued, but related amber-tinted safety glasses are available via the Uvex website).

All photochemical reactions were performed in batch in 2 dram vials. The exact apparatus used for each reaction in batch is shown in Figure S4. The PR160-390nm Kessil lamp was clamped such that the reaction mixture lie directly in the center of the beam path. The lamp was tilted at a 60° angle (with respect to the stir plate), positioning the center of the LED lamp 2 cm from the side of the vial. The cooling fan was suspended 5 cm above the top of the reaction vial, centered on the vial. After placing the orange-wrapped shield in front of the setup, the light was turned on, and the system was covered in aluminum foil.

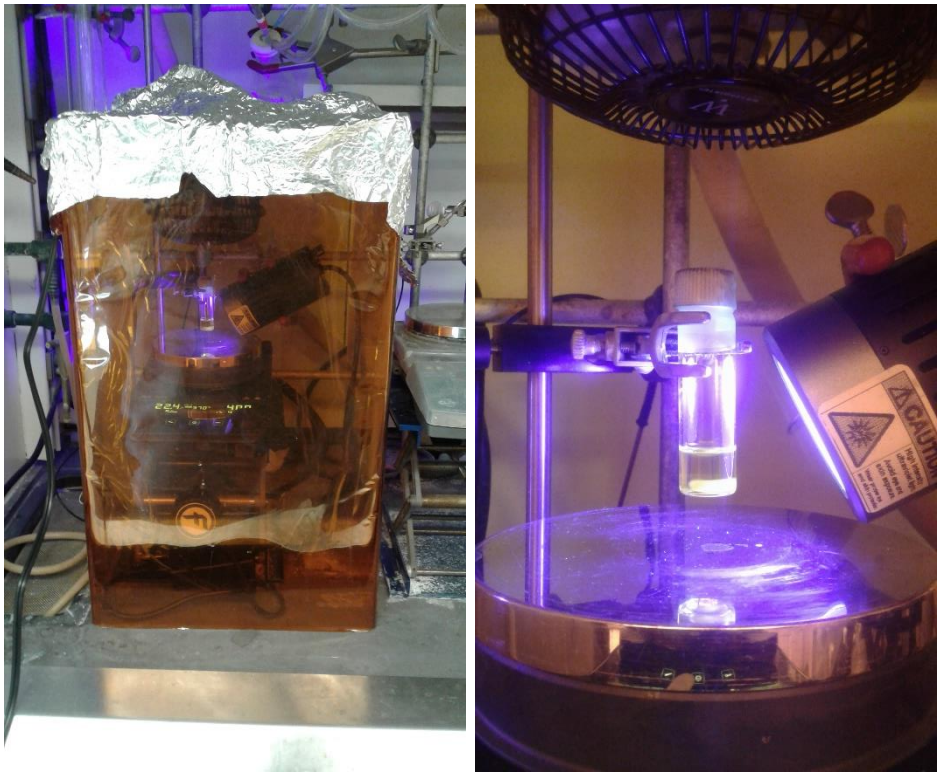
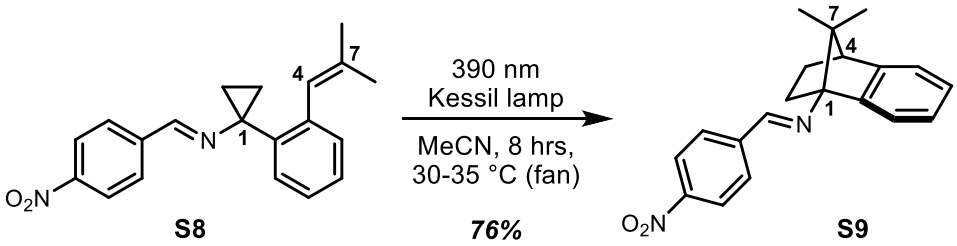


Figure S4. Batch Processing Equipment

Left: Full apparatus in use; Right: Zoom in on lamp orientation while in use (Kessil PR160-390nm pictured).

Representative Procedure



In a dry vial under inert atmosphere, cyclopropylimine **S8** (65.3 mg, 204 μmol) was dissolved in 2.1 mL dry MeCN. Reaction mixture was degassed with three freeze-pump-thaw cycles. The reaction was irradiated with 390 nm light for 8 hrs, using the setup described in Section II.B (temperature maintained between 30-35 °C with a fan). Reaction mixture was dark red. The mixture was poured into 20 mL 1:1 saturated $NaHCO_3$ (aq.):water and diluted with 10 mL ether. Phases were separated, and the aqueous phase was further extracted with 10 mL ether three times. Combined organics were washed with 10 mL brine, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated *in vacuo*. The crude residue was purified via flash chromatography over basic alumina (15% ethyl acetate:hexanes; loaded residue with PhMe). Obtained 49.8 mg (76.3% yield) of a light yellow solid. 1-AminoNB **S9** could be re-crystallized from ether:hexanes to reveal a white solid (no discernable difference in NMR spectrum).

Note: An analogous trial on 78.5 mg (245 μmol) cyclopropylimine **S8** yielded 62.4 mg of 1-aminoNB **S9** (79.5% yield) after 12 hrs of irradiation with 390 nm light. In general, altering the scale of the reaction does not have a large impact on performance as long as the time is adjusted accordingly and the reaction volume can be contained within a vial (one should assume the time will need to scaled exponentially, thus much larger scales will clearly suffer from exceptionally long reaction times, hence the evaluation in flow).

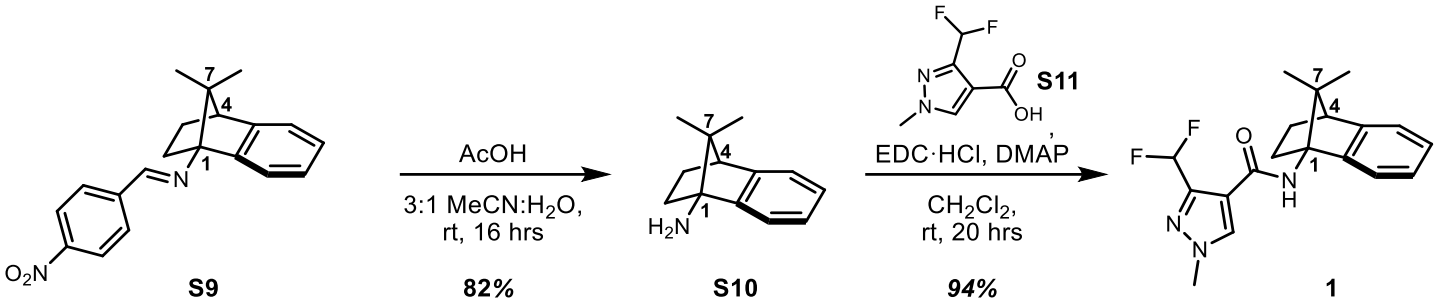
II.D. Generic Procedure for the Synthesis of 1-AminoNB-based SDHI leads

Schiff base-protected 1-aminoNB **S5** (1 eq.) was dissolved in MeCN prior to the addition of HPLC-grade water and glacial acetic acid (3:1:1 MeCN:H_2O:AcOH, collectively totaling 0.1 M with respect to **S5**). The mixture was stirred at room temp for 12-24 hrs. The reaction mixture was diluted with water and 1:1 ether:pentane (each phase 2x reaction volume). Phases were separated. The slightly acidic aqueous phase was washed with two portions of ether (each 2x reaction volume). Aqueous phase was made basic with addition

of 6 M NaOH (aq.) (~1/4 reaction volume or until pH ≥ 14). The basic aqueous phase was extracted with three portions of ether (each 2x reaction volume). The combined organics from the basic extraction were dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen to afford the desired 1-aminoNB **S6**.

1-AminoNB **S6** (1 eq.) was dissolved in dry dichloromethane (0.1-0.2 M with respect to **S6**), followed by addition of the requisite carboxylic acid (1.5 eq.), DMAP (1.5 eq.), and EDC·HCl (1.5 eq.), respectively. The reaction was flushed with Ar, capped, and stirred at room temp 12-20 hrs (see note below). The crude residue was diluted with 1:1 sat. $NaHCO_3$:water (4x reaction volume) and ethyl acetate (2x reaction volume; 1x reaction volume ether can be added to aid separation if necessary). Phases were separated, and the aqueous phase was extracted with 3 portions of ethyl acetate (each 2x reaction volume). The organic phases were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The crude residue was purified with flash chromatography over silica using an ethyl acetate:hexanes mobile phase (silica was pre-neutralized with the initial mobile phase + 1% NEt_3; the residue was loaded with PhMe) to afford the final SDHI candidate **S7**.

Of note, over the course of the SDHI lead library preparation, it was found that sealing the reaction and heating to 40-45 °C generally improved the conversion to product. This will not be found in many of the detailed procedures in Section IV, as the room temp conditions were employed en route to most SDHI analogs prior to this observation. While the room temp conditions are reasonably effective, it is recommended that any future reproductions of this work opt for slight heating in the amide coupling reaction.



S9 **82%** **S10** ***94%*** **1**

Procedure for C7-dimethyl 1-aminoNB analog S12

The following deprotection protocol is taken directly from our prior publication[3] and is included here for completeness.

In a dry vial under inert atmosphere, Schiff base **S9** (95.0 mg, 0.30 mmol) was dissolved in 720 μL dry MeCN, followed by addition of 240 μL water and 240 μL acetic acid. Flushed with Ar, capped, and stirred at room temp for 16 hrs. Diluted with 2 mL ether, then 2 mL 0.5 M HCl (aq.). Phases were separated, and the acidic aqueous phase was washed with 2 mL ether two times. Aqueous phase was then basified with 0.5 mL 6 M NaOH (aq.) and diluted with 2 mL ether. Phases were separated. Extracted basic aqueous phase with three additional portions of 2 mL ether. Combined organics were dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated carefully under a stream of nitrogen. Collected 45.4 mg of 1-aminoNB **S10** (81.8% yield) as a clear, colorless liquid. Note: The final product is modestly volatile; excessive concentration will lead to loss in yield. Note: Starting material is not fully soluble in reaction mixture but will go into solution with time; best results were obtained upon periodically sonicating or swirling in order to suspend residual solid. Partial characterization is provided below:

Partial Characterization Data for C1-NH_2 intermediate:

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.19 (d, 1H, *J* = 7.2 Hz, Ar), 7.16-7.13 (m, 2H, Ar), 7.12-7.09 (m, 1H, Ar), 2.81 (d, 1H, *J* = 4.1 Hz, C4), 2.13-2.08 (m, 1H, C3-eq.), 1.87 (*app*. td, 1H, *J* = 11.1, 4.0 Hz, C2-eq), 1.43 (br s, 2H, -NH_2), 1.32 (ddd, 1H, *J* = 11.4, 9.6, 3.2 Hz, C2-ax), 1.16 (ddd, 1H, *J* = 12.2, 9.3, 4.0 Hz, C3-ax), 1.00 (s, 3H, C7-Me), 0.51 (s, 3H, C7-Me) ppm
R_f = 0.15 (30% ethyl acetate:hexanes + 1% NH_4OH), one red spot, ninhydrin, UV

1-Aminonorbornane **S10** (13.1 mg; 70 μmol) was dissolved in dry dichloromethane (0.75 mL), followed by addition of the carboxylic acid **S11** (18.5 mg; 105 μmol), DMAP (13 mg; 105 μmol), and EDC·HCl (20 mg; 105 μmol), respectively. The reaction was flushed with Ar, capped, and stirred at room temp 14 hrs. The crude residue was diluted with 4 mL water and 2 mL ethyl acetate. Phases were separated, and the aqueous phase was extracted with 3 portions of ethyl acetate, 2 mL each. The organic phases were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The crude residue was purified with flash chromatography over silica (15 to 75% ethyl acetate:hexanes, increasing in 15% increments; loaded residue with PhMe; silica was pre-neutralized with a 15% ethyl acetate:hexanes + 1% triethylamine mobile phase). Obtained 26.7 mg of a slightly yellow solid that was largely pure by ^{1}H NMR analysis, but it was deemed necessary to employ a second round of chromatography (same as above). Collected the desired carboxamide (**1**) as a white solid: 22.8 mg, 94.3% yield.

*Characterization Data for C7-dimethyl 1-aminoNB SDHI candidate **1**:*

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.02 (s, 1H, pyrazole), 7.24-7.21 (m, 1H, Ar), 7.13-7.09 (m, 3H, Ar), 6.82 (t, 1H, J_{HF} = 54.2 Hz, -CHF_2), 6.69 (br s, 1H, -NH), 3.94 (s, 3H, pyrazole -NMe), 2.80 (d, 1H, *J* = 3.7 Hz, C4), 2.41-2.35 (m, 1H, C2-eq.), 2.25-2.19 (m, 2H, C3-eq, C2-ax), 1.32-1.26 (m, 1H, C3-ax), 1.13 (s, 3H, C7-Me), 0.68 (s, 3H, C7-Me) ppm
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 161.9, 146.5, 146.0, 142.1 (t, J_{CF} = 29.3 Hz), 136.2, 126.1, 125.7, 121.4, 120.9, 117.7, 112.5 (t, J_{CF} = 232.3 Hz), 70.7, 59.3, 50.7, 39.6, 30.1, 26.6, 19.8, 19.4 ppm
^{19}F NMR ($CDCl_3$, 376 MHz): δ = -107.4 (*app.* ddd, *J* = 106.4, 54.1, 4.4 Hz) ppm
HRMS (ES+, *m/z)* calculated for $C_{19}H_{22}F_2N_3O^+$: 346.1725, Found: 346.1732.
R_f = 0.35 (70% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

Figure S5: ^{1}H NMR (500 MHz, $CDCl_3$) for 1

Parameter	Value
Title	DS.1997.1H.char
Comment	Proton Spectrum
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Number of Scans	4
Relaxation Delay	0.5000
Acquisition Time	3.5000
Acquisition Date	2018-11-09T09:18:14
Spectrometer Frequency	699.75
Spectral Width	11160.7
Lowest Frequency	-1379.8
Nucleus	1H
Acquired Size	39062
Spectral Size	131072

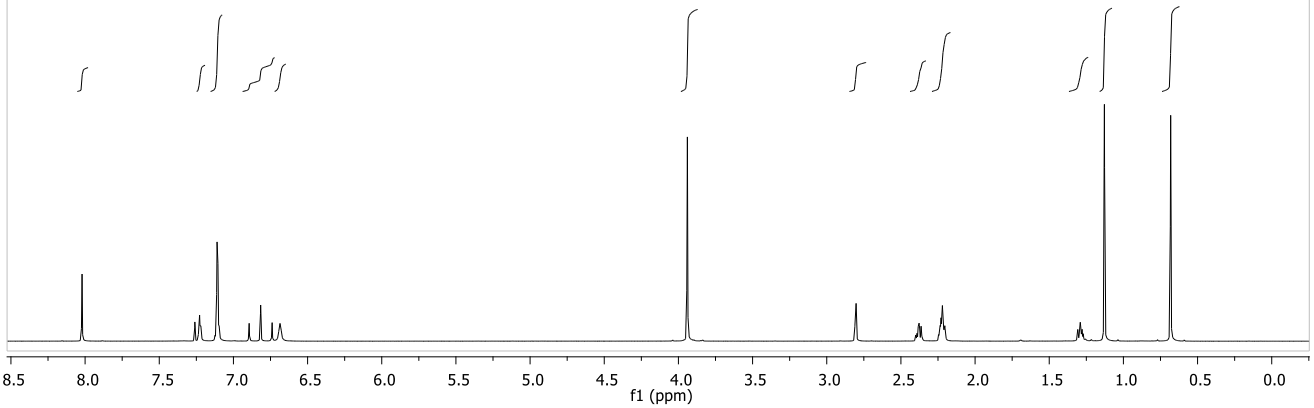


Figure S6: ^{13}C NMR (176 MHz, $CDCl_3$) for 1

Parameter	Value
Title	DS.1997.13C.char
Comment	Carbon-13
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Number of Scans	112
Relaxation Delay	1.5000
Acquisition Time	1.4680
Acquisition Date	2018-11-09T09:19:07
Spectrometer Frequency	175.97
Spectral Width	44642.9
Lowest Frequency	-2966.7
Nucleus	13C
Acquired Size	65536
Spectral Size	131072

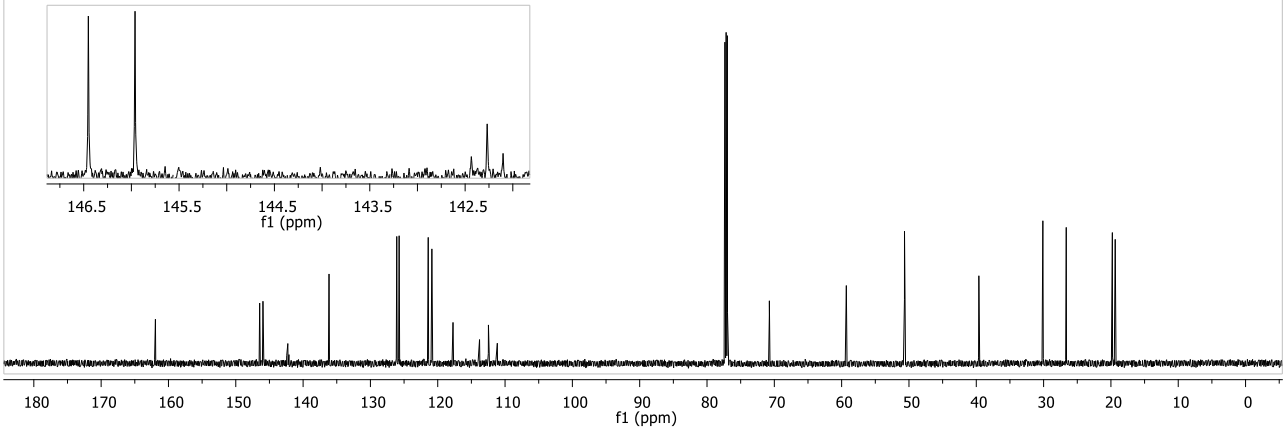
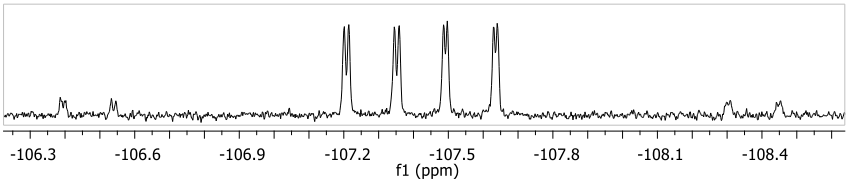
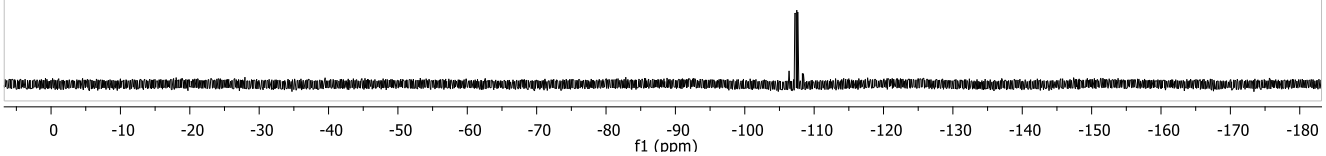
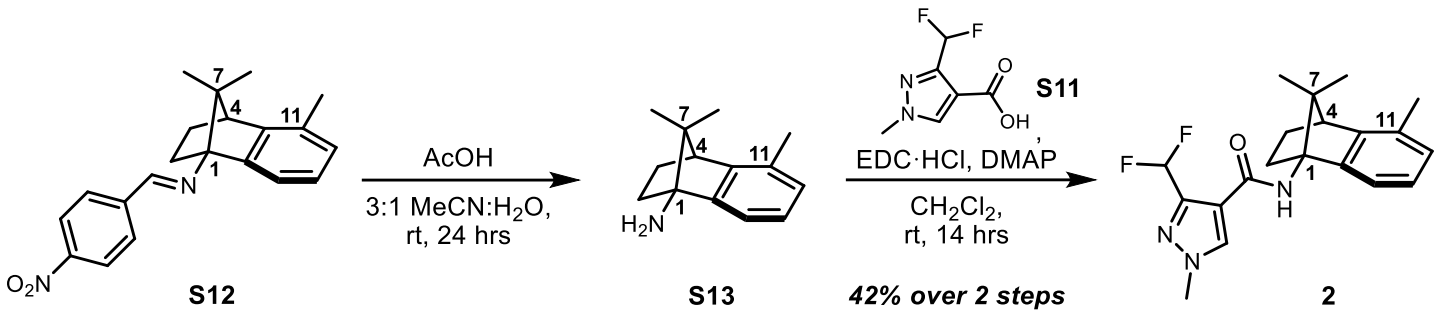


Figure S7: ^{19}F NMR (376 MHz, $CDCl_3$) for 1

Parameter	Value
Title	DS.1997.19F
Comment	Fluorine-19
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Number of Scans	64
Relaxation Delay	1.0000
Acquisition Time	0.7340
Acquisition Date	2018-10-20T18:52:56
Spectrometer Frequency	375.91
Spectral Width	89285.7
Lowest Frequency	-76597.5
Nucleus	19F
Acquired Size	65536
Spectral Size	131072







Procedure for C11-methyl-C7-dimethyl 1-aminoNB analog S13

Removal of the Schiff base protecting group was achieved by dissolving the protected 1-aminonorbornane **S12** (33.9 mg; 0.10 mmol) in a 3:1 MeCN:H_2O mixture (0.75 mL:0.25 mL) before adding acetic acid (0.25 mL). The reaction mixture was flushed with Ar, capped, and stirred at room temp for 24 hrs. The reaction was diluted with 2 mL water and 2 mL ether. The phases were separated, and the slightly acidic aqueous phase was washed with 2 mL ether two additional times. The aqueous phase was made basic through the addition of 0.5 mL of 6 M NaOH (aq.) then diluted with 2 mL ether. Phases were separated, and the aqueous phase was extracted with 3 portions of ether, 2 mL each. The organic phases from the basic extraction were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The desired 1-aminonorbornane **S13** was obtained as a clear, colorless liquid (20.3 mg). Partial characterization is provided below:

*Partial Characterization Data for C1-NH_2 intermediate **S13**:*
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.04 (dd, 1H, *J* = 14.2, 7.0 Hz, Ar), 7.02 (d, 1H, *J* = 6.9 Hz, Ar), 6.93 (d, 1H, *J* = 7.4 Hz, Ar), 2.91 (d, 1H, *J* = 4.1 Hz, C4), 2.26 (s, 3H, C11-Me), 2.12-2.05 (m, 1H, C3-eq), 1.87 (*app.* td, 1H, *J* = 11.4, 3.9 Hz, C2-eq), 1.50 (br s, 2H, -NH_2), 1.30 (ddd, 1H, *J* = 11.6, 9.4, 3.9 Hz, C2-ax), 1.12 (ddd, 1H, *J* = 12.1, 9.4, 4.0 Hz, C3-ax), 1.01 (s, 3H, C7-Me), 0.50 (s, 3H, C7-Me) ppm

1-Aminonorbornane **S13** (20.3 mg; 101 μmol) was dissolved in dry dichloromethane (1.0 mL), followed by addition of the carboxylic acid **S11** (27 mg; 153 μmol), DMAP (18 mg; 147 μmol), and EDC·HCl (29 mg; 151 μmol), respectively. The reaction was flushed with Ar, capped, and stirred at room temp 14 hrs. The crude residue was diluted with 4 mL water and 2 mL ethyl acetate. Phases were separated, and the aqueous phase was extracted with 3 portions of ethyl acetate, 2 mL each. The organic phases were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The crude residue was purified with flash chromatography over silica (15 to 75% ethyl acetate:pentane, increasing in 15% increments; loaded residue with PhMe; silica was pre-neutralized with a 15% ethyl acetate:pentane + 1% triethylamine mobile phase). Obtained 19.3 mg of a slightly yellow solid that was largely pure by ^{1}H NMR analysis, but it was deemed necessary to employ a second round of chromatography (30 to 50 to 100% ethyl acetate:pentane; silica was pre-neutralized with a 30% ethyl acetate:pentane + 1% triethylamine mobile phase). Collected the desired carboxamide (**2**) as a slightly yellow solid: 15.2 mg, 41.7% yield over 2 steps.

*Characterization Data for C11-Me SDHI candidate **2**:*
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.01 (s, 1H, pyrazole), 7.05 (d, 1H, *J* = 7.3 Hz, Ar), 7.01 (*app.* t, 1H, *J* = 7.4 Hz, Ar), 6.93 (d, 1H, *J* = 7.5 Hz, Ar), 6.81 (t, 1H, J_{HF} = 54.2 Hz, -CHF_2), 6.67 (br s, 1H, -NH), 3.95 (s, 3H, pyrazole -NMe), 2.91 (d, 1H, *J* = 3.8 Hz, C4), 2.44-2.39 (m, 1H, C2-eq.), 2.27 (s, 3H, C11-Me), 2.24-2.16 (m, 2H, C3-eq, C2-ax), 1.27-1.22 (m, 1H, C3-ax), 1.13 (s, 3H, C7-Me), 0.68 (s, 3H, C7-Me) ppm
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 161.9, 146.2, 144.1, 142.3 (t, J_{CF} = 29.3 Hz), 136.1, 130.5, 127.3, 125.6, 118.2, 117.8, 112.5 (t, J_{CF} = 232.3 Hz), 70.9, 58.9, 48.3, 39.6, 30.0, 25.8, 19.8, 19.4, 17.9 ppm
^{19}F NMR ($CDCl_3$, 376 MHz): δ = -107.1 (*app.* ddd, *J* = 131.4, 54.9, 4.9 Hz) ppm
HRMS (ESI+, *m/z)* calculated for $C_{20}H_{24}F_2N_3O^+$: 360.1882, Found: 360.1882.
R_f = 0.30 (70% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

Figure S8: ^{1}H NMR (700 MHz, $CDCl_3$) for 2

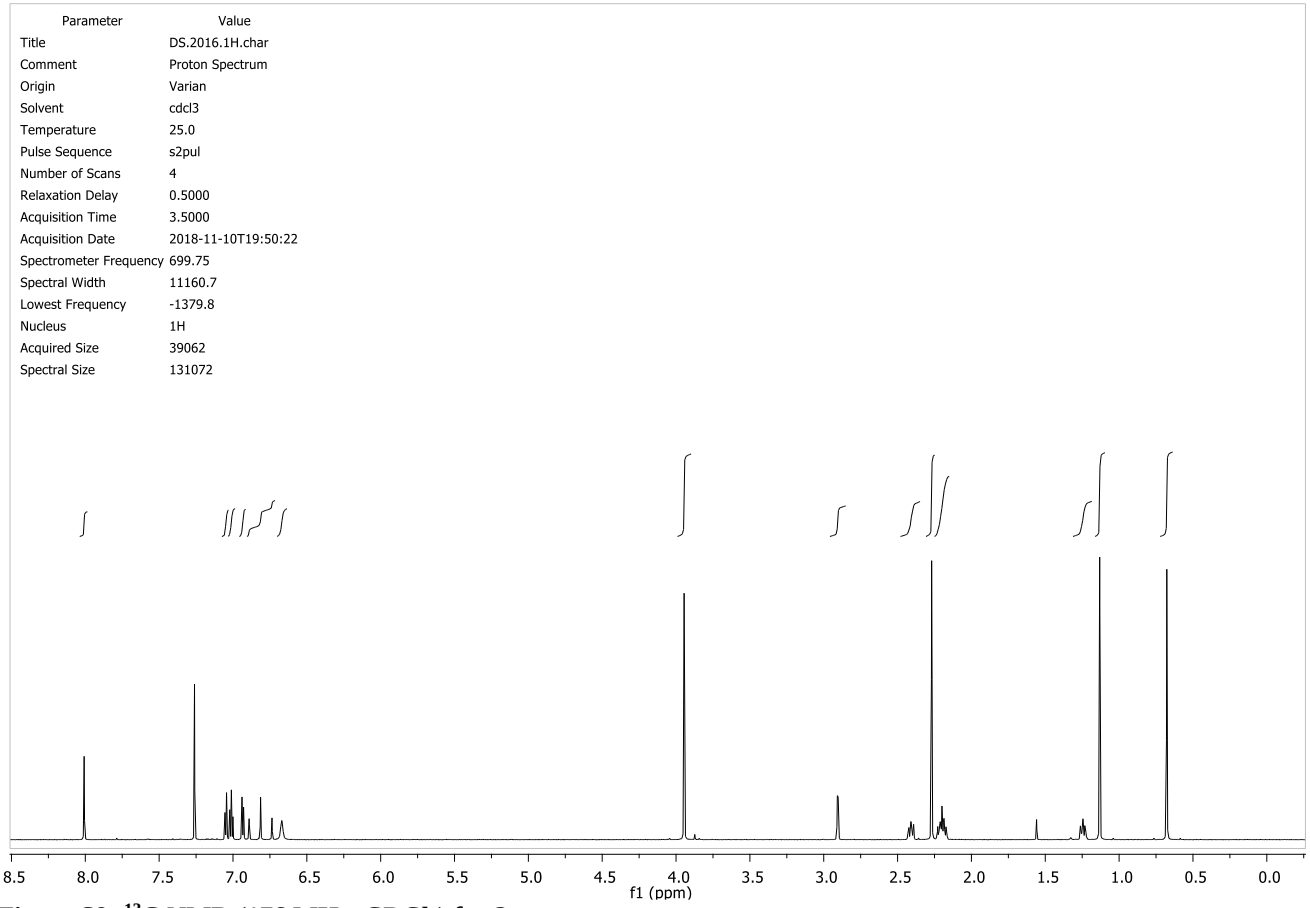


Figure S9: ^{13}C NMR (176 MHz, $CDCl_3$) for 2

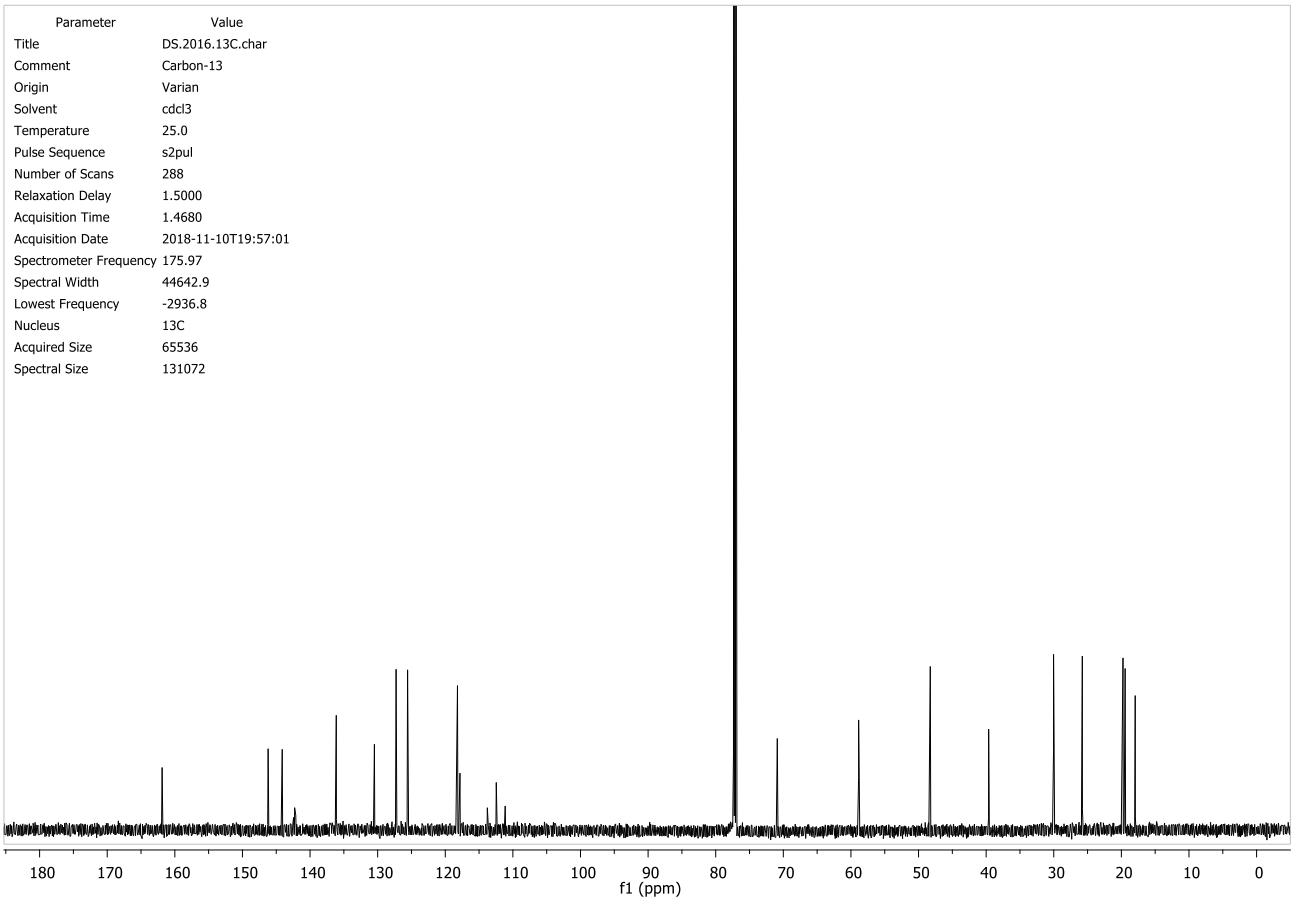
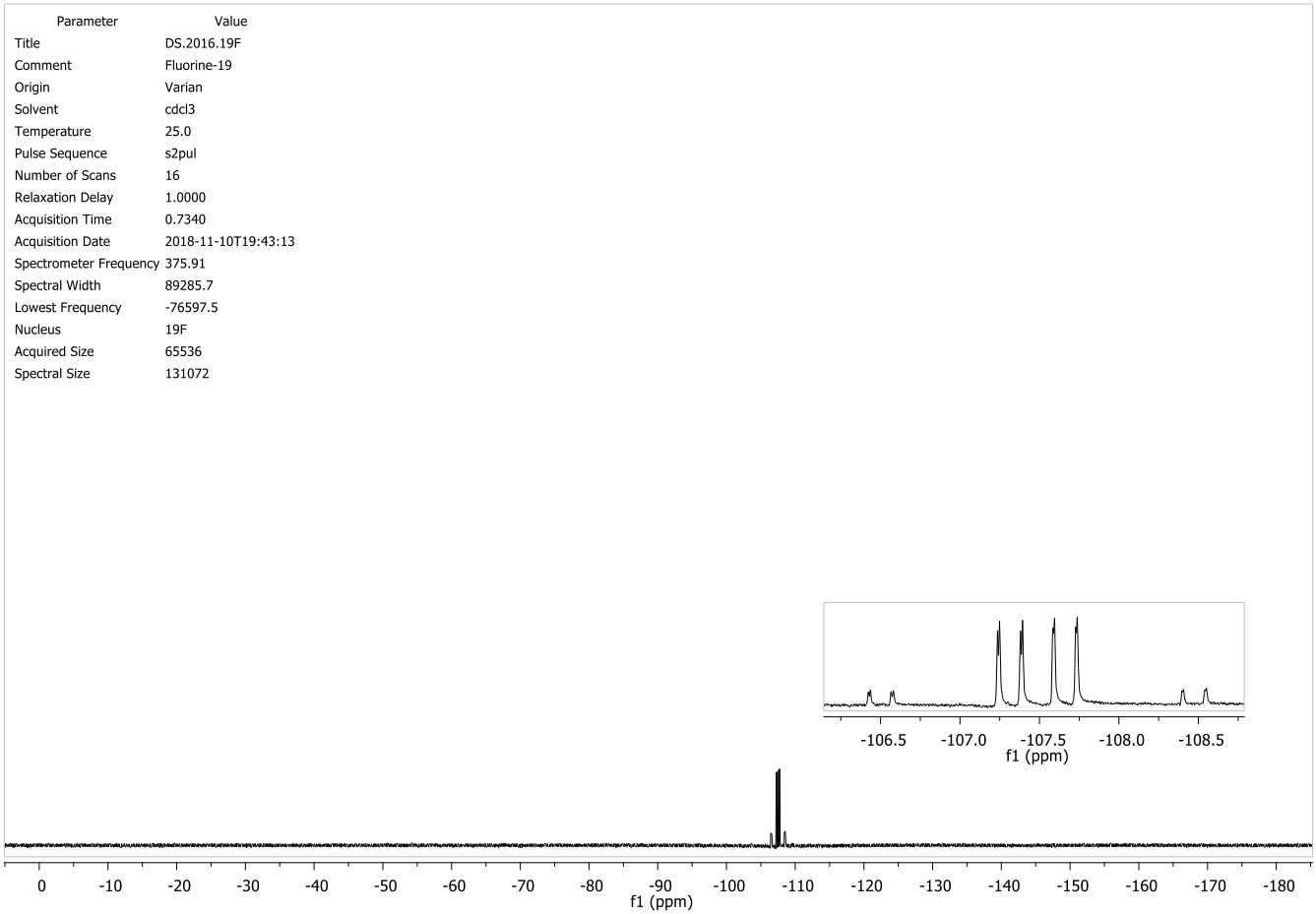
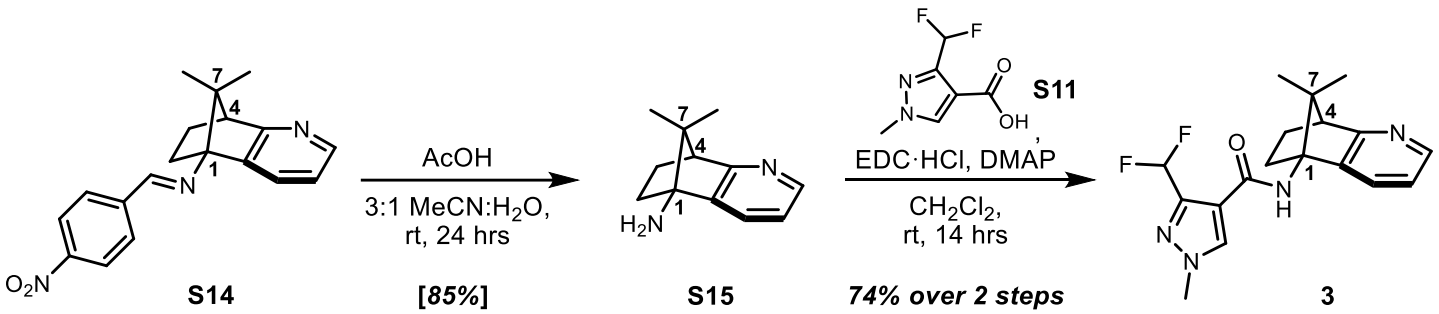


Figure S10: ^{19}F NMR (376 MHz, $CDCl_3$) for 2





Procedure for C11-*aza*-C7-dimethyl 1-aminoNB analog S15

Removal of the Schiff base protecting group was achieved by dissolving the protected 1-aminonorbornane **S14** (46.9 mg; 150 mmol) in a 3:1 MeCN:H_2O mixture (0.9 mL:0.3 mL) before adding acetic acid (0.3 mL). The reaction mixture was flushed with Ar, capped, and stirred at room temp for 24 hrs. The reaction was diluted with 2 mL water and 2 mL ether. The phases were separated, and the slightly acidic aqueous phase was washed with 2 mL ether two additional times. The aqueous phase was made basic through the addition of 0.5 mL of 6 M NaOH (aq.) then diluted with 2 mL ether. Phases were separated, and the aqueous phase was extracted with 3 portions of ether, 2 mL each. The organic phases from the basic extraction were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The desired 1-aminonorbornane **S15** was obtained as a clear, colorless liquid in 84.8% yield (23.3 mg). Partial characterization is provided below:

*Partial Characterization Data for C1-NH_2 intermediate **S15**:*
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.23 (dd, 1H, *J* = 5.2, 1.3 Hz, Ar), 7.45 (d, 1H, *J* = 7.5 Hz, Ar), 7.04 (dd, 1H, *J* = 7.3, 5.3 Hz, Ar), 2.93 (d, 1H, *J* = 4.3 Hz, C4), 2.17 (*app.* ddt, 1H, *J* = 14.4, 10.2, 4.0 Hz, C3-eq), 1.93 (*app.* td, 1H, *J* = 11.1, 4.0 Hz, C2-eq), 1.55 (br s, 2H, -NH_2), 1.36 (ddd, 1H, *J* = 11.5, 9.3, 3.8 Hz, C2-ax), 1.26 (ddd, 1H, *J* = 13.1, 9.3, 4.0 Hz, C3-ax), 1.03 (s, 3H, C7-Me), 0.56 (s, 3H, C7-Me) ppm

1-Aminonorbornane **S15** (12.6 mg; 66 μmol) was dissolved in dry dichloromethane (0.70 mL), followed by addition of the carboxylic acid **S11** (18 mg; 102 μmol), DMAP (12 mg; 98 μmol), and EDC·HCl (19 mg; 99 μmol), respectively. The reaction was flushed with Ar, capped, and stirred at room temp 14 hrs. The crude residue was diluted with 4 mL water and 2 mL ethyl acetate. Phases were separated, and the aqueous phase was extracted with 3 portions of ethyl acetate, 2 mL each. The organic phases were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The crude residue was purified with flash chromatography over silica (30 to 50 to 80 to 100% ethyl acetate:pentane; loaded residue with PhMe; silica was pre-neutralized with a 30% ethyl acetate:pentane + 1% triethylamine mobile phase); multiple column volumes of 100% ethyl acetate were required to fully elute product. Collected the desired carboxamide (**3**) as a slightly yellow solid: 20.0 mg, 87.0% yield (73.8% over two steps).

*Characterization Data for 11-aza SDHI candidate **3**:*
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.23 (dd, 1H, *J* = 5.1, 1.1 Hz, pyridine), 8.01 (s, 1H, pyrazole), 7.52 (d, 1H, *J* = 6.8 Hz, pyridine), 7.01 (dd, 1H, *J* = 7.3, 5.3 Hz, pyridine), 6.80 (t, 1H, J_{HF} = 54.2 Hz, -CHF_2), 6.75 (br s, 1H, -NH), 3.95 (s, 3H, pyrazole -NMe), 2.93 (d, 1H, *J* = 3.2 Hz, C4), 2.32-2.23 (m, 3H, C2-eq, C3-eq, C2-ax), 1.44-1.33 (m, 1H, C3-ax), 1.15 (s, 3H, C7-Me), 0.72 (s, 3H, C7-Me) ppm
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 166.3, 162.0, 146.5, 142.2 (t, J_{CF} = 29.4 Hz), 140.0, 136.3, 129.1, 121.3, 117.2, 112.6 (t, J_{CF} = 232.0 Hz), 69.6, 58.5, 52.7, 39.7, 30.5, 25.1, 19.7, 18.8 ppm
^{19}F NMR ($CDCl_3$, 376 MHz): δ = -107.2 (*app.* ddd, *J* = 54.4, 29.7, 4.6 Hz) ppm
HRMS (ESI+, *m/z)* calculated for $C_{18}H_{21}F_2N_4O^+$: 347.1678, Found: 347.1677.
R_f = 0.25 (10% acetone:dichloromethane + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

Figure S11: ^{1}H NMR (400 MHz, $CDCl_3$) for 3

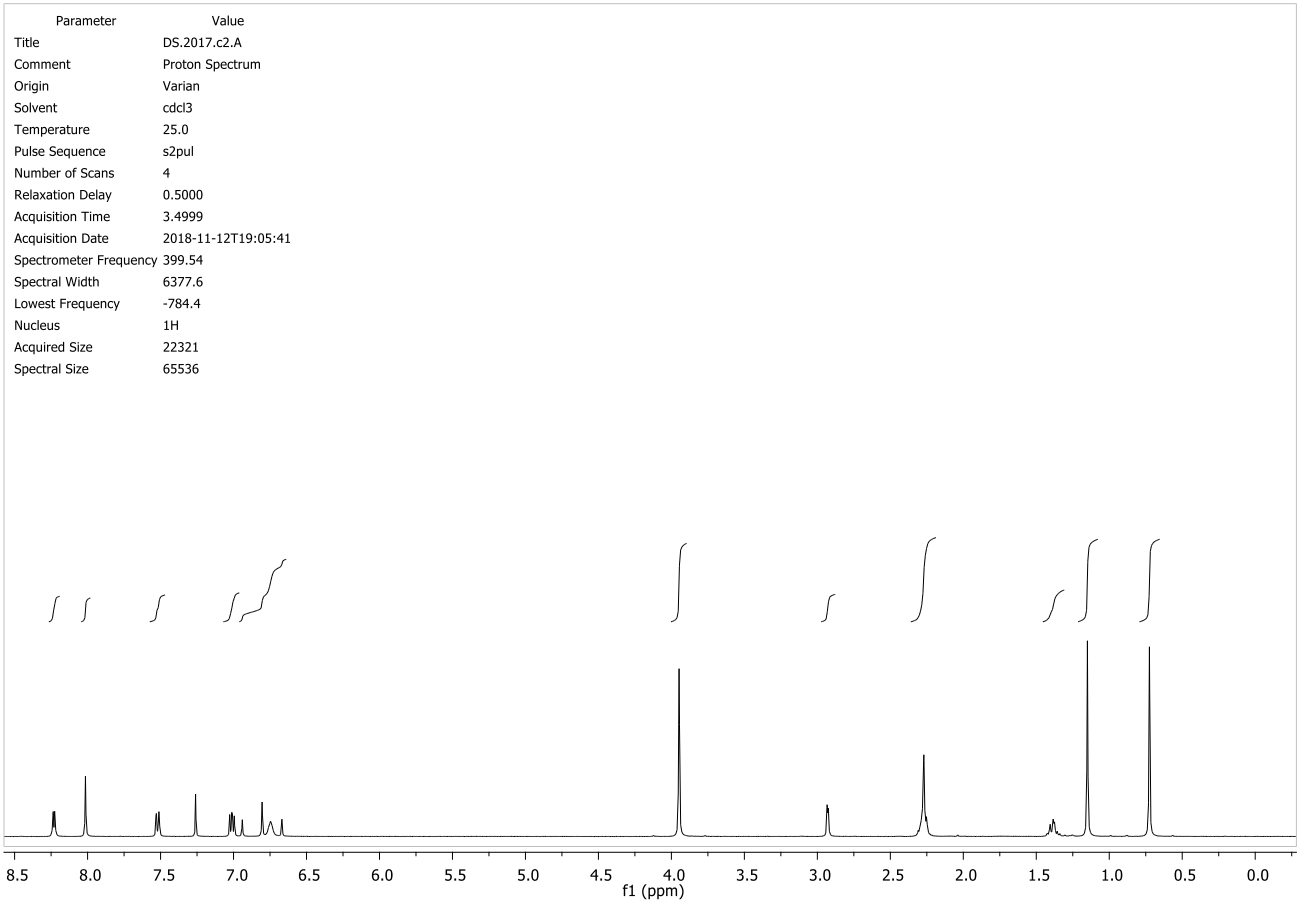


Figure S12: ^{13}C NMR (176 MHz, $CDCl_3$) for 3

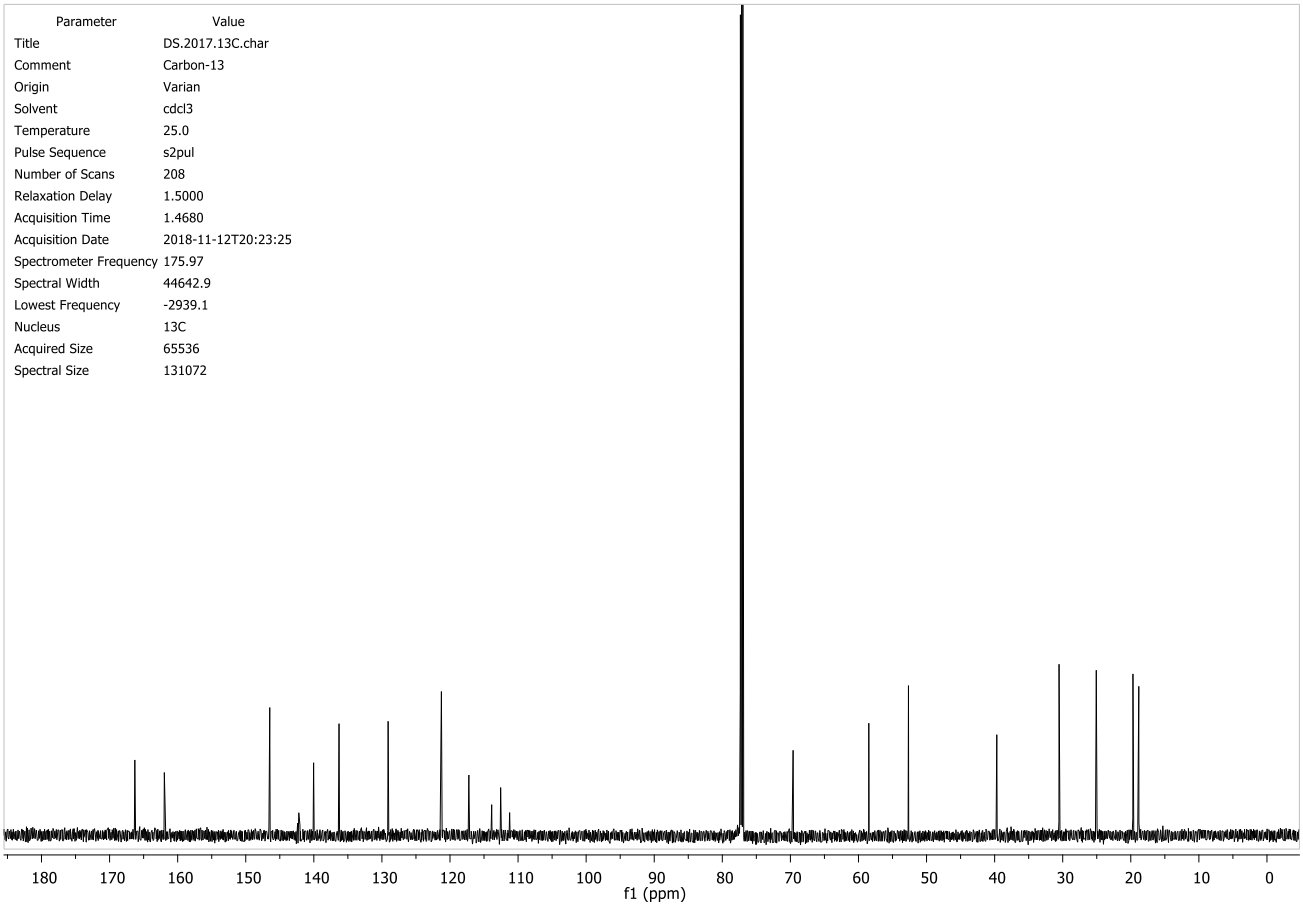
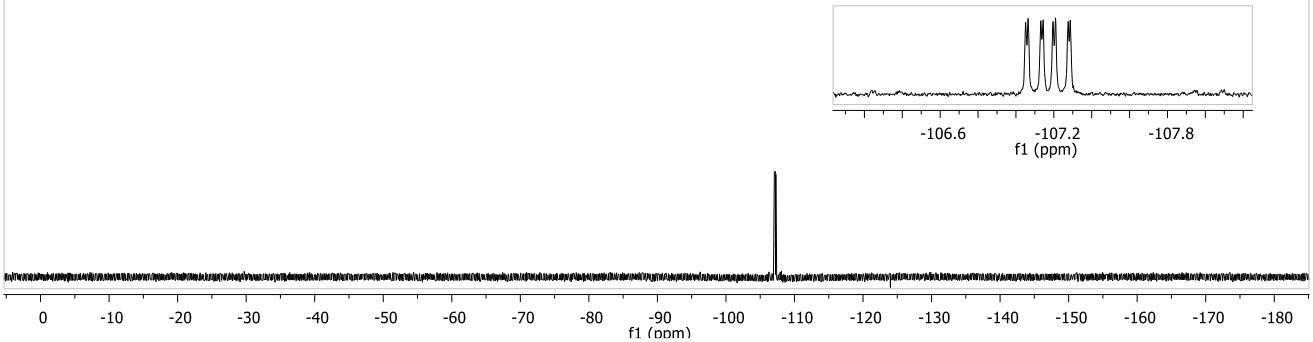
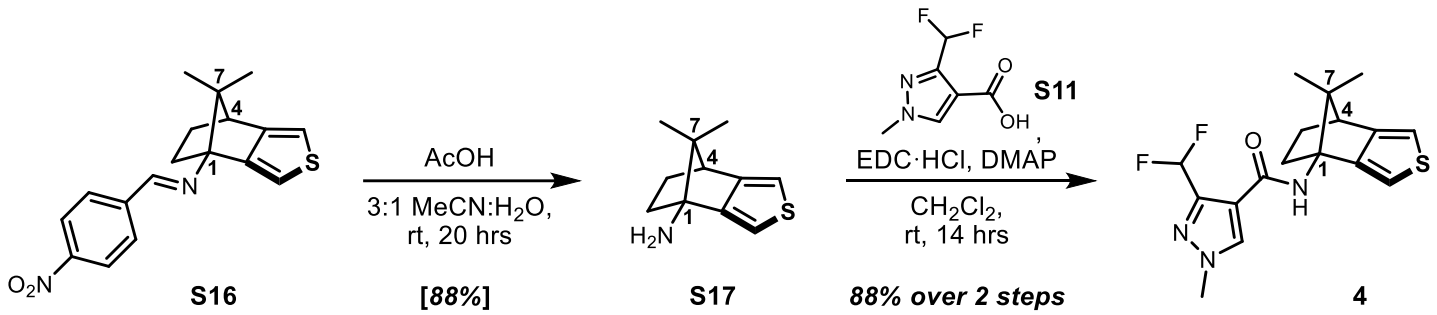


Figure S13: ^{19}F NMR (376 MHz, $CDCl_3$) for 3

Parameter	Value
Title	DS.2017.19F
Comment	Fluorine-19
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Number of Scans	8
Relaxation Delay	1.0000
Acquisition Time	0.7340
Acquisition Date	2018-11-12T19:12:14
Spectrometer Frequency	375.91
Spectral Width	89285.7
Lowest Frequency	-76597.5
Nucleus	19F
Acquired Size	65536
Spectral Size	131072





Procedure for 9-*thio*-C7-dimethyl 1-aminoNB analog S17

Removal of the Schiff base protecting group was achieved by dissolving the protected 1-aminonorbornane **S16** (46.2 mg; 0.14 mmol) in a 3:1 MeCN:H_2O mixture (0.9 mL:0.3 mL) before adding acetic acid (0.3 mL). The reaction mixture was flushed with Ar, capped, and stirred at room temp for 24 hrs. The reaction was diluted with 2 mL water and 2 mL ether. The phases were separated, and the slightly acidic aqueous phase was washed with 2 mL ether two additional times. The aqueous phase was made basic through the addition of 0.5 mL of 6 M NaOH (aq.) then diluted with 2 mL ether. Phases were separated, and the aqueous phase was extracted with 3 portions of ether, 2 mL each. The organic phases from the basic extraction were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The desired 1-aminonorbornane **S17** was obtained as a slightly yellow oil in 87.7% yield (24.0 mg). Partial characterization is provided below:

*Partial Characterization Data for C1-NH_2 intermediate **S17**:*
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.77 (d, 1H, *J* = 1.5 Hz, thiophene), 6.70 (d, 1H, *J* = 2.0 Hz, thiophene), 2.78 (d, 1H, *J* = 4.3 Hz, C4), 2.13-2.06 (m, 1H, C3-eq), 1.88 (*app.* td, 1H, *J* = 11.3, 4.2 Hz, C2-eq), 1.52 (br s, 2H, -NH_2), 1.54-1.48 (m, 1H, C2-ax), 1.12 (ddd, 1H, *J* = 12.3, 9.3, 4.1 Hz, C3-ax), 0.98 (s, 3H, C7-Me), 0.56 (s, 3H, C7-Me) ppm

1-Aminonorbornane **S17** (10.6 mg; 55 μmol) was dissolved in dry dichloromethane (0.60 mL), followed by addition of the carboxylic acid **S11** (15 mg; 85 μmol), DMAP (10 mg; 82 μmol), and EDC·HCl (16 mg; 84 μmol), respectively. The reaction was flushed with Ar, capped, and stirred at room temp 14 hrs. The crude residue was diluted with 4 mL water and 2 mL ethyl acetate. Phases were separated, and the aqueous phase was extracted with 3 portions of ethyl acetate, 2 mL each. The organic phases were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The crude residue was purified with flash chromatography over silica (20 to 100% ethyl acetate:pentane, increasing in 20% increments; loaded residue with PhMe; silica was pre-neutralized with a 20% ethyl acetate:pentane + 1% triethylamine mobile phase). Collected the desired carboxamide **4** as a slightly yellow solid: 19.4 mg, >99% yield (87.7% over two steps).

*Characterization Data for 9-thio SDHI candidate **4**:*
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.00 (s, 1H, pyrazole), 6.90 (d, 1H, *J* = 2.0 Hz, thiophene), 6.80 (t, 1H, J_{HF} = 54.2 Hz, -CHF_2), 6.71 (d, 1H, *J* = 2.1 Hz, thiophene), 6.66 (br s, 1H, -NH), 3.93 (s, 3H, pyrazole -NMe), 2.78 (d, 1H, *J* = 3.9 Hz, C4), 2.34-2.28 (m, 1H, C2-eq), 2.26-2.22 (m, 1H, C3-eq), 2.23-2.18 (m, 1H, C2-ax), 1.43-1.37 (m, 1H, C3-ax), 1.12 (s, 3H, C7-Me), 0.72 (s, 3H, C7-Me) ppm
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 161.8, 149.1, 148.5, 142.2 (t, J_{CF} = 29.3 Hz), 136.2, 117.5, 114.3, 112.5 (t, J_{CF} = 232.2 Hz), 112.4, 69.0, 60.2, 48.0, 39.6, 31.4, 27.3, 20.2, 19.3 ppm
^{19}F NMR ($CDCl_3$, 376 MHz): δ = -107.4 (*app.* ddd, *J* = 54.0, 45.0, 4.5 Hz) ppm
HRMS (ESI+, *m/z)* calculated for $C_{17}H_{20}F_2N_3OS^+$: 352.1290, Found: 352.1291.
R_f = 0.25 (20% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

Figure S14: ^{1}H NMR (700 MHz, $CDCl_3$) for 4

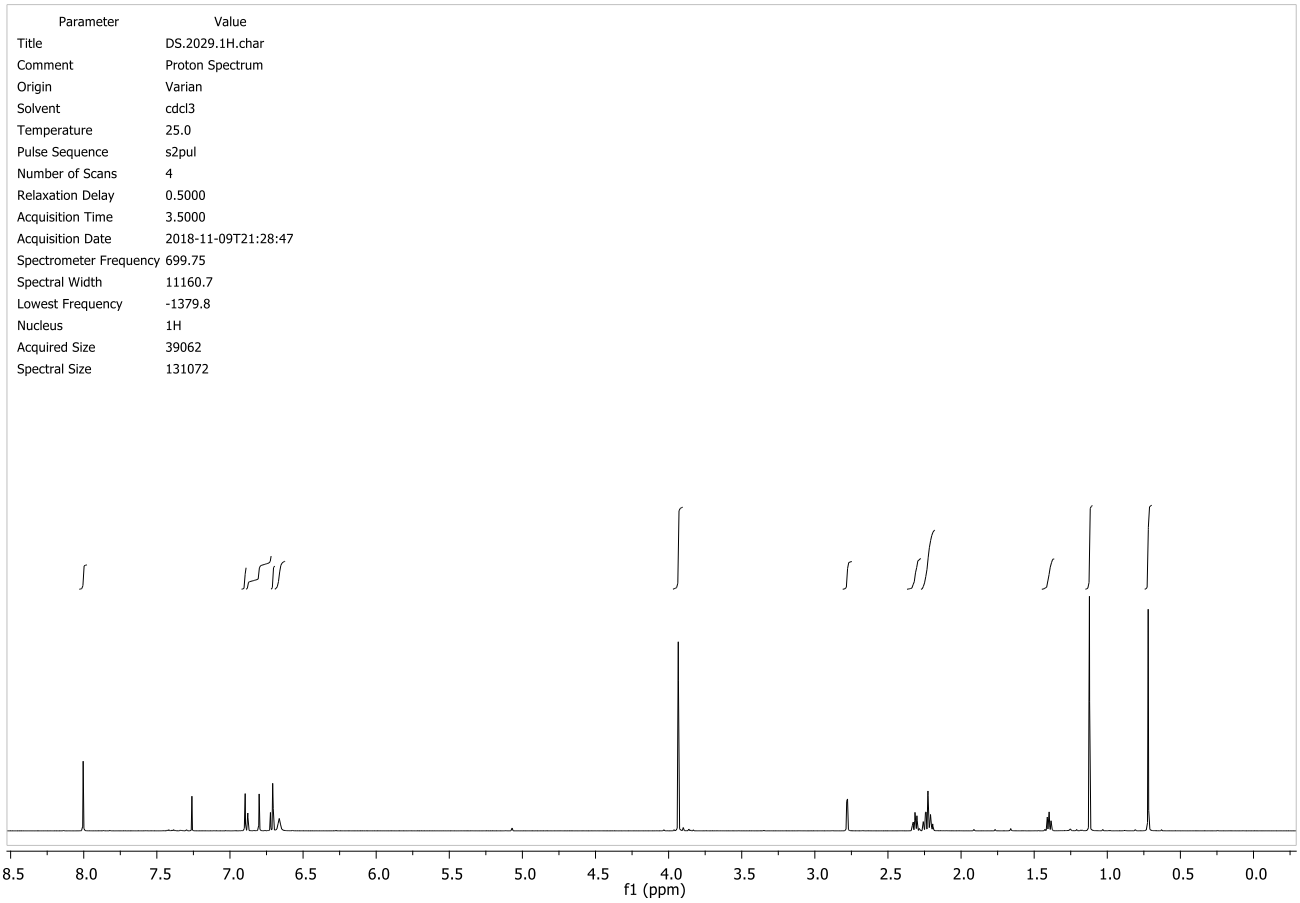


Figure S15: ^{13}C NMR (176 MHz, $CDCl_3$) for 4

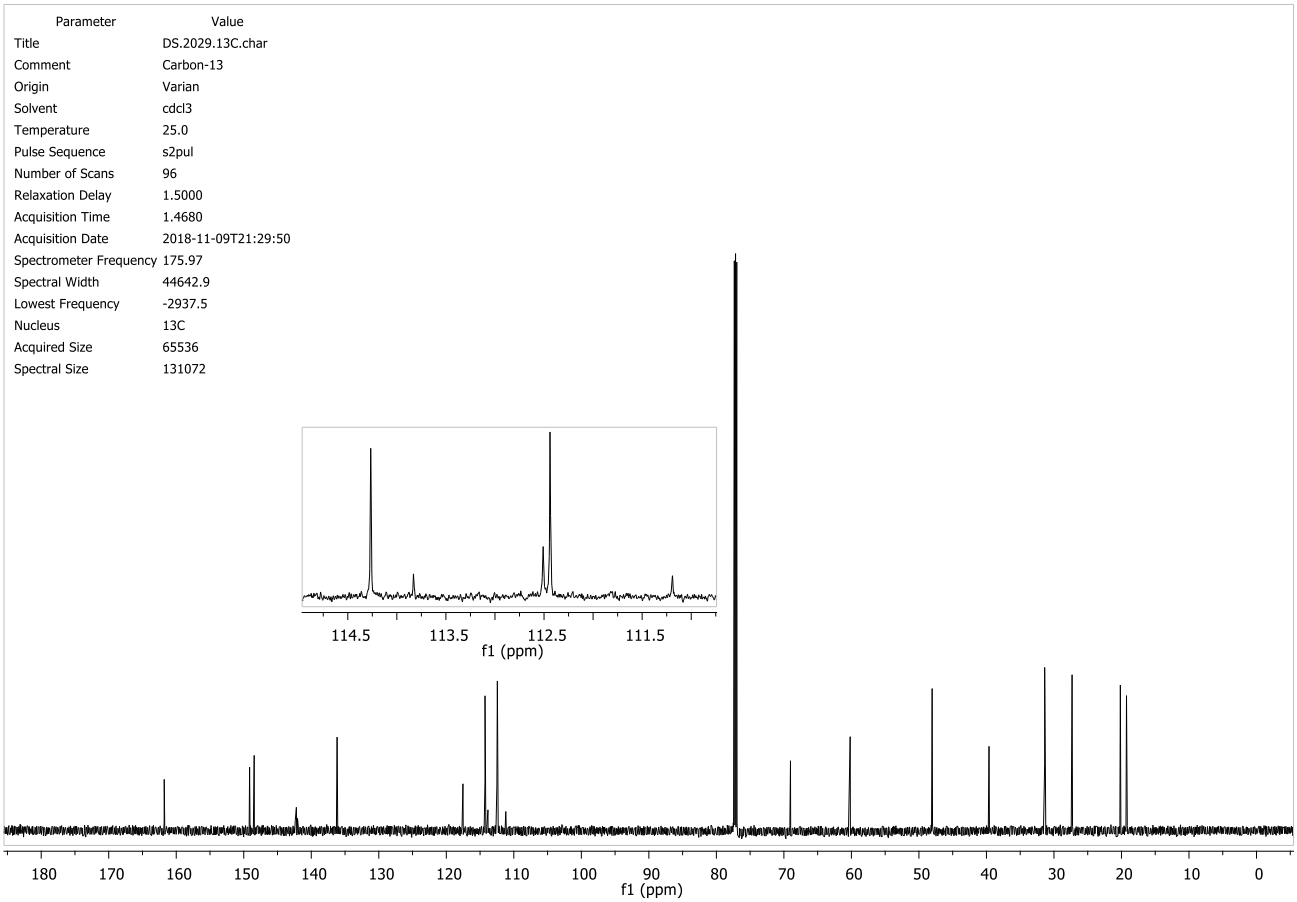
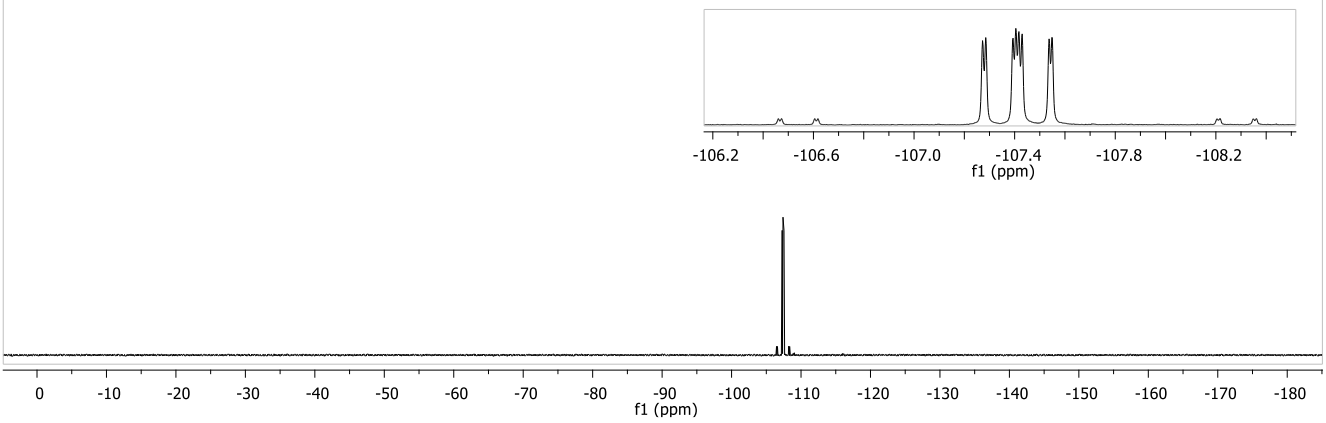
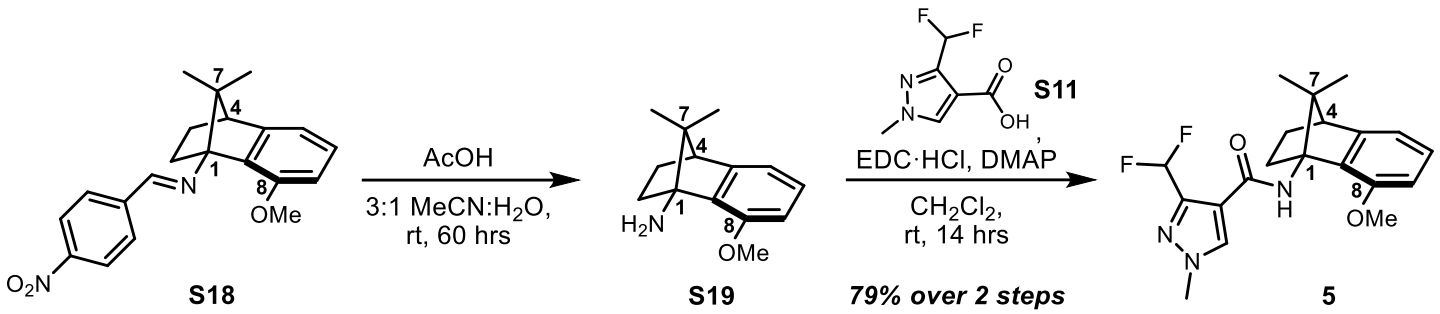


Figure S16: ^{19}F NMR (376 MHz, $CDCl_3$) for 4

Parameter	Value
Title	DS.2029.19F
Comment	Fluorine-19
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Number of Scans	8
Relaxation Delay	1.0000
Acquisition Time	0.7340
Acquisition Date	2018-11-09T17:30:19
Spectrometer Frequency	375.91
Spectral Width	89285.7
Lowest Frequency	-76597.5
Nucleus	19F
Acquired Size	65536
Spectral Size	131072





Procedure for C8-methoxy-C7-dimethyl 1-aminoNB analog S19

Removal of the Schiff base protecting group was achieved by dissolving the protected 1-aminonorbornane **S18** (21.3 mg; 61 μmol) in a 3:1 MeCN:H_2O mixture (0.45 mL:0.15 mL) before adding acetic acid (0.15 mL). The reaction mixture was flushed with Ar, capped, and stirred at room temp for 60 hrs. The reaction was diluted with 2 mL water and 2 mL ether. The phases were separated, and the slightly acidic aqueous phase was washed with 2 mL ether two additional times. The aqueous phase was made basic through the addition of 0.5 mL of 6 M NaOH (aq.) then diluted with 2 mL ether. Phases were separated, and the aqueous phase was extracted with 3 portions of ether, 2 mL each. The organic phases from the basic extraction were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The desired 1-aminonorbornane **S19** was obtained as a yellow oil (14.2 mg). Visible impurities were present in ^{1}H NMR spectrum. Material was moved forward without further purification. Partial characterization is provided below:

*Partial Characterization Data for C1-NH_2 intermediate **S19**:*
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.06 (*app.* t, 1H, *J* = 7.7 Hz, Ar), 6.75 (d, 1H, *J* = 7.1 Hz, Ar), 6.69 (d, 1H, *J* = 8.3 Hz, Ar), 3.81 (s, 3H, C8-OMe), 2.73 (d, 1H, *J* = 4.1 Hz, C4), 2.13-2.06 (m, 1H, C3-eq), 1.86 (*app.* td, 1H, *J* = 11.4, 4.1 Hz, C2-eq), 1.70 (br s, 2H, -NH_2), 1.47 (ddd, 1H, *J* = 11.7, 9.2, 3.9 Hz, C2-ax), 1.26 (ddd, 1H, *J* = 12.2, 9.2, 4.1 Hz, C3-ax), 0.99 (s, 3H, C7-Me), 0.65 (s, 3H, C7-Me) ppm

1-Aminonorbornane **S19** (14.2 mg; at most 61 μmol) was dissolved in dry dichloromethane (0.70 mL), followed by addition of the carboxylic acid **S11** (17 mg; 97 μmol), DMAP (12 mg; 105 μmol), and EDC·HCl (19 mg; 105 μmol), respectively. The reaction was flushed with Ar, capped, and stirred at room temp 14 hrs. The crude residue was diluted with 4 mL water and 2 mL ethyl acetate. Phases were separated, and the aqueous phase was extracted with 3 portions of ethyl acetate, 2 mL each. The organic phases were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The crude residue was purified with flash chromatography over silica (20 to 100% ethyl acetate:pentane, increasing in 20% increments; loaded residue with PhMe; silica was pre-neutralized with a 20% ethyl acetate:pentane + 1% triethylamine mobile phase). Collected the desired carboxamide (**5**) as a slightly yellow solid: 18.1 mg, 79.3% yield over two steps.

*Characterization Data for C8-OMe SDHI candidate **5**:*
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.82 (s, 1H, pyrazole), 7.34 (br s, 1H, -NH), 7.10 (dd, 1H, *J* = 8.1, 7.4 Hz, Ar), 7.00 (t, 1H, J_{HF} = 54.2 Hz, -CHF_2), 6.79 (d, 1H, *J* = 7.2 Hz, Ar), 6.71 (d, 1H, *J* = 8.3 Hz, Ar), 3.96 (s, 3H, pyrazole -NMe), 3.76 (s, 3H, -OMe), 3.16 (ddd, 1H, *J* = 12.1, 10.3, 4.0 Hz, C2-eq), 2.72 (d, 1H, *J* = 4.1 Hz, C4), 1.87 (*app*. ddt, 1H, *J* = 12.1, 10.3, 4.1 Hz, C3-eq), 1.66 (ddd, 1H, *J* = 12.8, 8.4, 3.7 Hz, C2-ax), 1.20 (s, 3H, C7-Me), 1.21-1.18 (m, 1H, C3-ax), 0.73 (s, 3H, C7-Me) ppm
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 161.8, 154.4, 148.6, 143.8 (t, J_{CF} = 26.9 Hz), 133.5 131.8, 127.7, 118.9, 115.0, 111.1 (t, J_{CF} = 232.4 Hz), 109.5, 72.3, 60.5, 55.8, 51.0, 39.7, 27.9, 26.5, 21.2, 20.1 ppm
^{19}F NMR ($CDCl_3$, 376 MHz): δ = -109.9 (*app.* dd, *J* = 307.7, 54.3 Hz), -112.6 (*app.* dd, *J* = 307.7, 53.9 Hz) ppm
HRMS (ESI+, *m/z)* calculated for $C_{20}H_{24}F_2N_3O_2^+$: 376.1831, Found: 376.1829.
R_f = 0.25 (70% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

Figure S17: ^{1}H NMR (700 MHz, $CDCl_3$) for 5

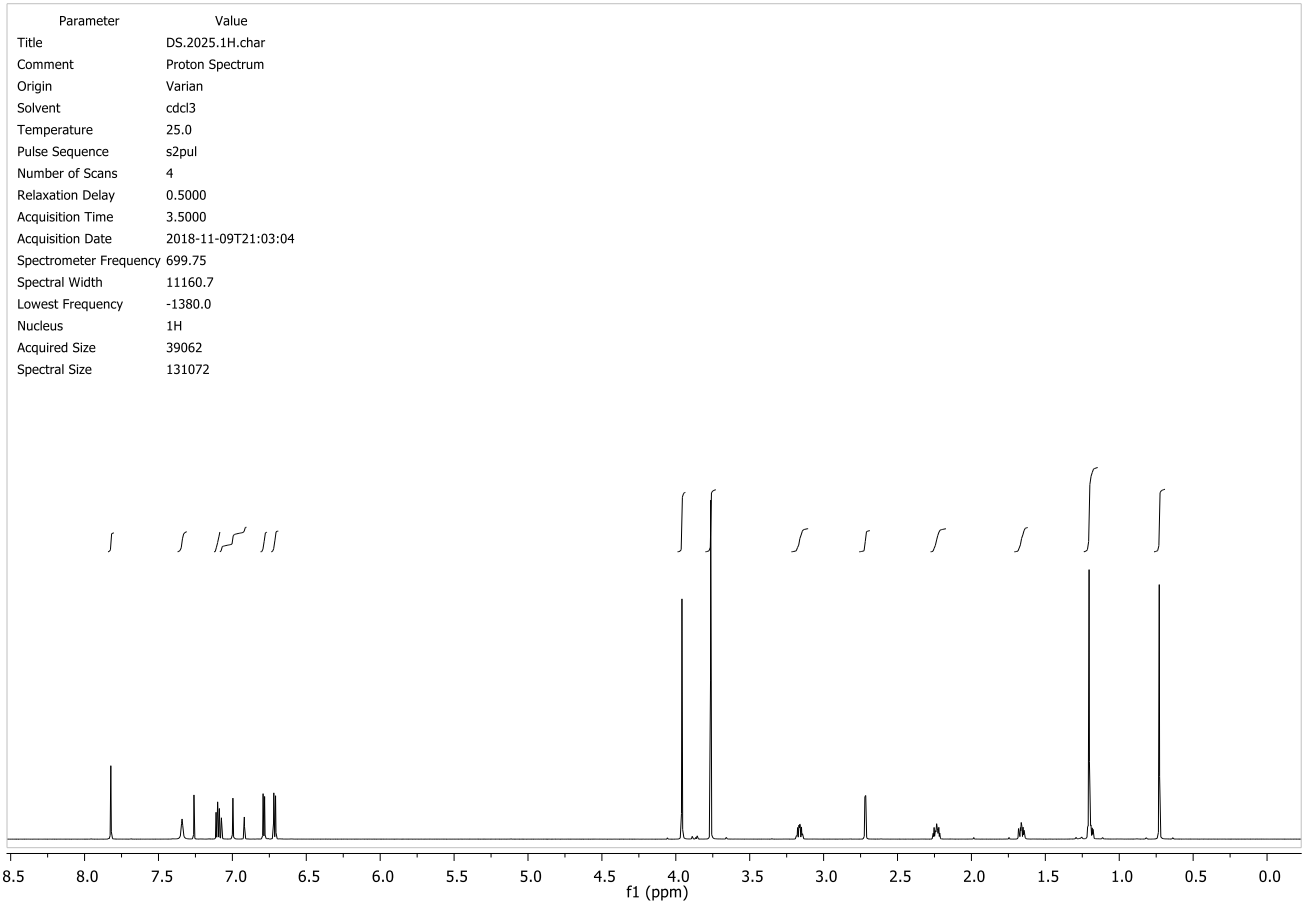


Figure S18: ^{13}C NMR (176 MHz, $CDCl_3$) for 5

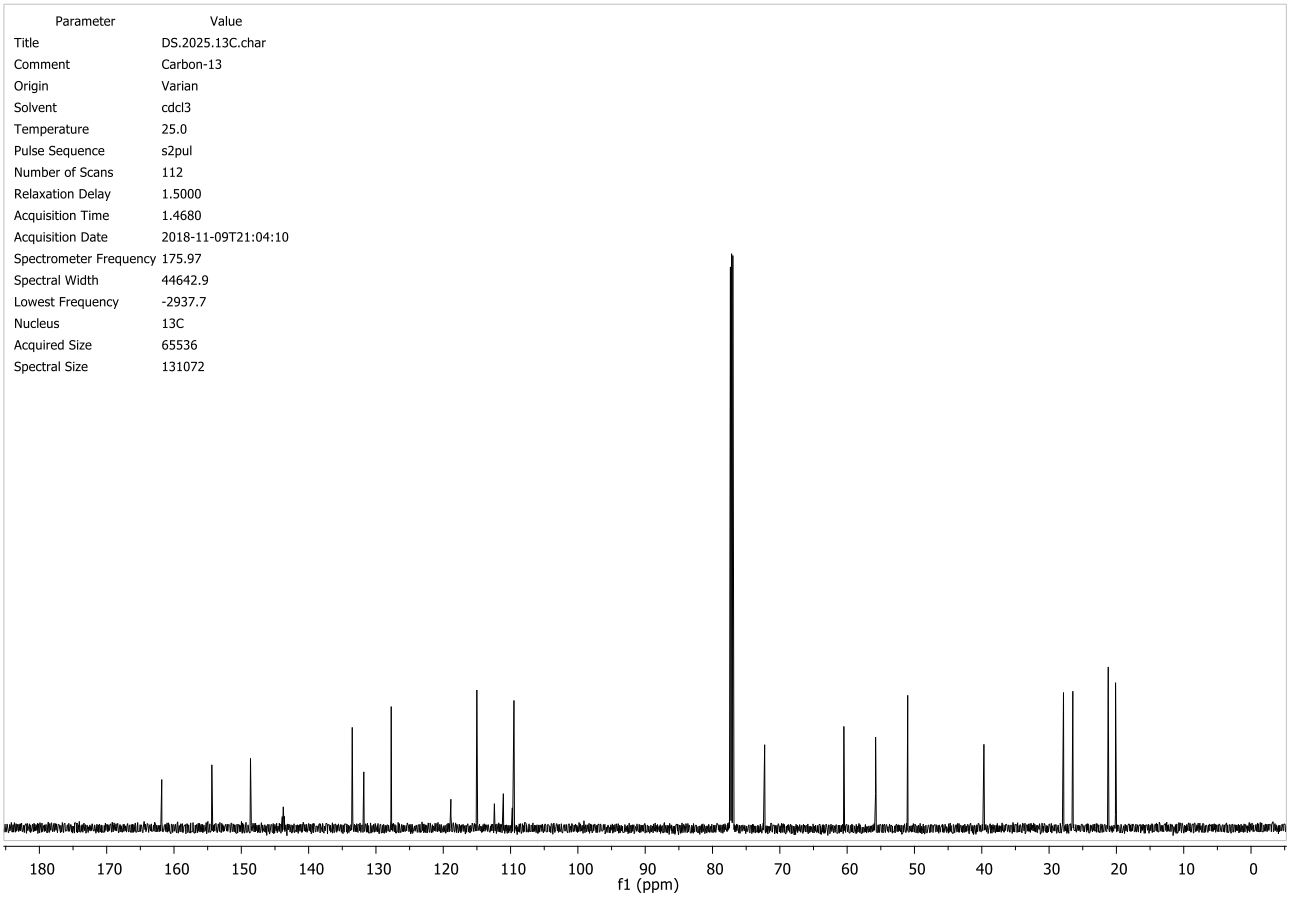
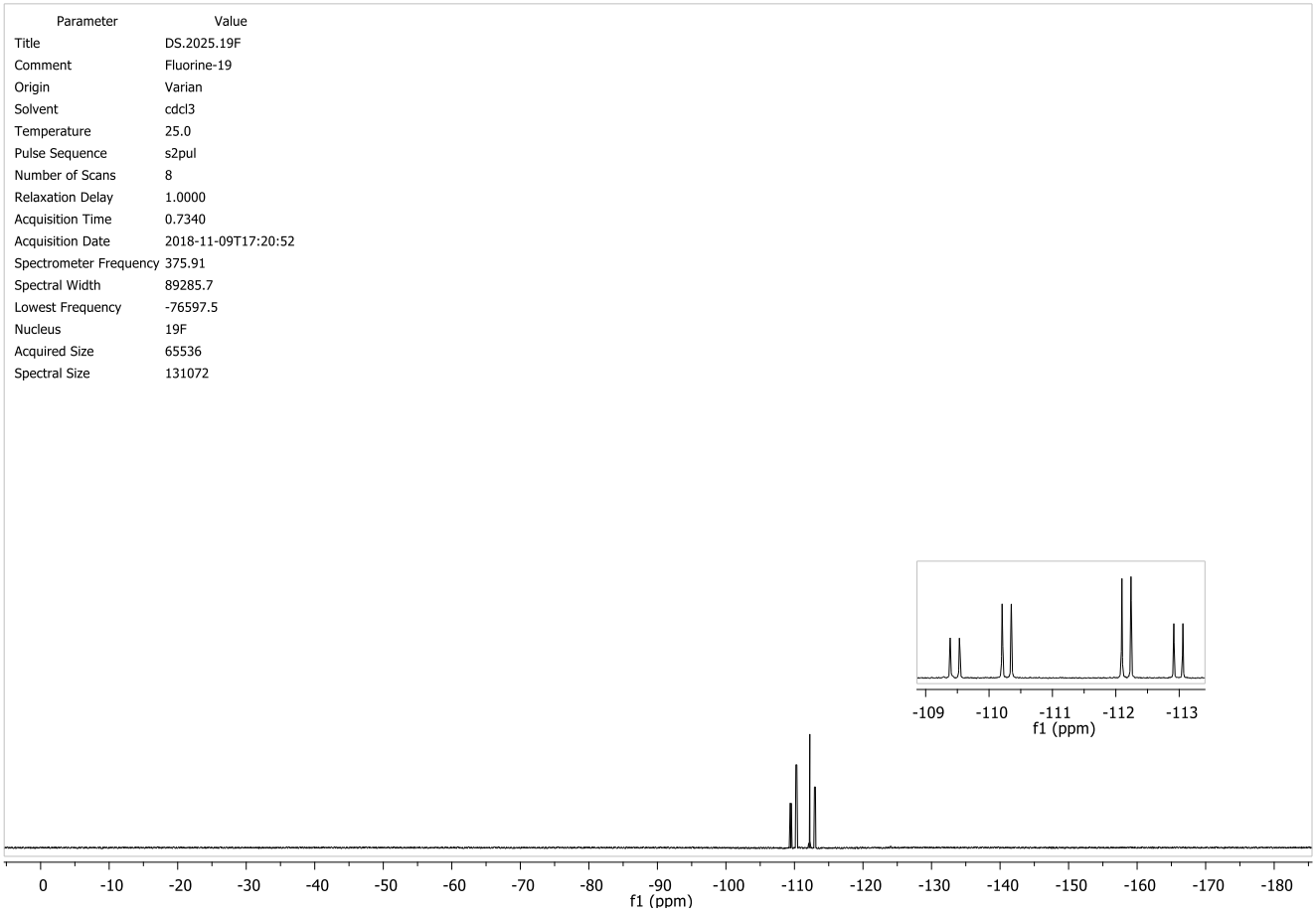
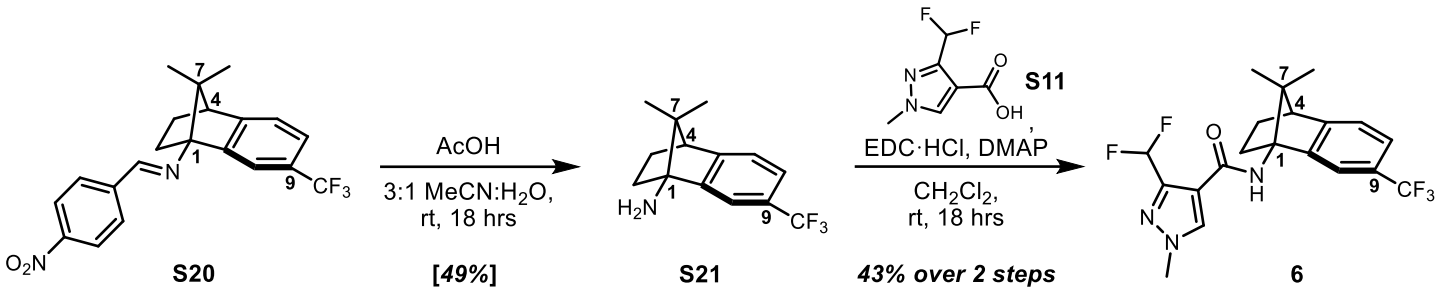


Figure S19: ^{19}F NMR (376 MHz, $CDCl_3$) for 5





Procedure for C9-trifluormethyl-C7-dimethyl 1-aminoNB analog S21

Removal of the Schiff base protecting group was achieved by dissolving the protected 1-aminonorbornane (**S20**; 53.6 mg; 0.14 mmol) in a 3:1 MeCN:H_2O mixture (0.9 mL:0.3 mL) before adding acetic acid (0.3 mL). The reaction mixture was flushed with Ar, capped, and stirred at room temp for 18 hrs. The reaction was diluted with 2 mL water and 2 mL ether. The phases were separated, and the slightly acidic aqueous phase was washed with 2 mL ether two additional times. The aqueous phase was made basic through the addition of 0.5 mL of 6 M NaOH (aq.) then diluted with 2 mL ether. Phases were separated, and the aqueous phase was extracted with 3 portions of ether, 2 mL each. The organic phases from the basic extraction were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The desired 1-aminonorbornane **S21** was obtained as a clear, colorless liquid in 49.4% yield (17.4 mg). Partial characterization is provided below:

*Partial Characterization Data for C1-NH_2 intermediate **S21**:*
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.47-7.44 (m, 1H, Ar), 7.39 (d, 1H, *J* = 7.5 Hz, Ar), 7.19 (d, 1H, *J* = 7.5 Hz, Ar), 2.88 (d, 1H, *J* = 4.2 Hz, C4), 2.15 (*app*. ddt, 1H, *J* = 14.4, 10.2, 4.1 Hz, C3-eq), 1.90 (*app*. td, 1H, *J* = 11.6, 3.9 Hz, C2-eq), 1.46 (br s, 2H, -NH_2), 1.34-1.30 (m, 1H, C2-ax), 1.16 (ddd, 1H, *J* = 12.4, 9.3, 4.1 Hz, C3-ax), 1.02 (s, 3H, C7-Me), 0.51 (s, 3H, C7-Me) ppm

1-Aminonorbornane **S21** (16.5 mg; 65 μmol) was dissolved in dry dichloromethane (0.70 mL), followed by addition of the carboxylic acid **S11** (16 mg; 91 μmol), DMAP (13 mg; 106 μmol), and EDC·HCl (19 mg; 99 μmol), respectively. The reaction was flushed with Ar, capped, and stirred at room temp 18 hrs. The crude residue was diluted with 4 mL water and 2 mL ethyl acetate. Phases were separated, and the aqueous phase was extracted with 3 portions of ethyl acetate, 2 mL each. The organic phases were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The crude residue was purified with flash chromatography over silica (15 to 75% ethyl acetate:pentane, increasing in 15% increments; loaded residue with PhMe; silica was pre-neutralized with a 15% ethyl acetate:pentane + 1% triethylamine mobile phase). Collected the desired carboxamide (**6**) as a slightly yellow solid: 23.1 mg, 86.5% yield (42.7% over 2 steps).

*Characterization Data for C9-CF_3 SDHI candidate **6**:*
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.05 (s, 1H, pyrazole), 7.48 (*app*. s, 1H, Ar), 7.40 (d, 1H, *J* = 7.6 Hz, Ar), 7.21 (d, 1H, *J* = 7.6 Hz, Ar), 6.81 (t, 1H, J_{HF} = 54.2 Hz, -CHF_2), 6.71 (br s, 1H, -NH), 3.95 (s, 3H, pyrazole -NMe), 2.88 (d, 1H, *J* = 3.8 Hz, C4), 2.36-2.31 (m, 1H, C2-eq.), 2.29-2.23 (m, 2H, C3-eq, C2-ax), 1.31-1.25 (m, 1H, C3-ax), 1.14 (s, 3H, C7-Me), 0.68 (s, 3H, C7-Me) ppm
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 161.9, 149.9, 147.3, 142.2 (t, J_{CF} = 29.3 Hz), 136.5, 128.2 (q, J_{CF} = 271.8 Hz), 124.7 (q, J_{CF} = 31.8 Hz), 123.7 (q, J_{CF} = 4.0 Hz), 121.6, 118.3 (q, J_{CF} = 3.8 Hz), 117.4, 112.6 (t, J_{CF} = 232.2 Hz), 70.6, 59.6, 50.6, 39.6, 29.9, 26.3, 19.7, 19.1 ppm
^{19}F NMR ($CDCl_3$, 376 MHz): δ = -107.3 (*app.* ddd, *J* = 89.1, 54.2, 4.6 Hz), -117.0 (dq, *J* = 10.4, 5.2 Hz) ppm
HRMS (ESI+, *m/z)* calculated for $C_{20}H_{21}F_5N_3O^+$: 414.1599, Found: 414.1603
R_f = 0.50 (70% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

Figure S20: ^{1}H NMR (700 MHz, $CDCl_3$) for 6

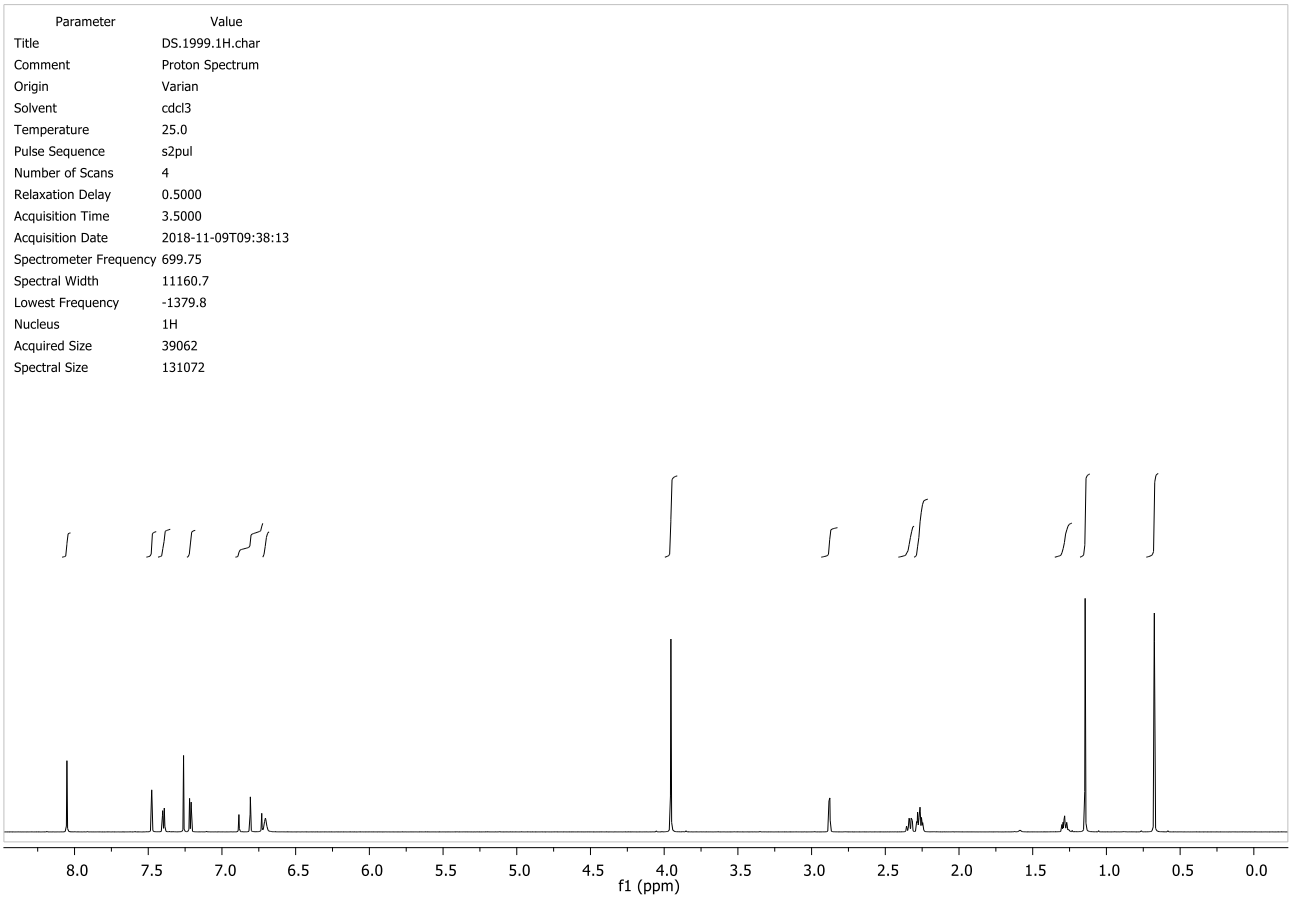


Figure S21: ^{13}C NMR (176 MHz, $CDCl_3$) for 6

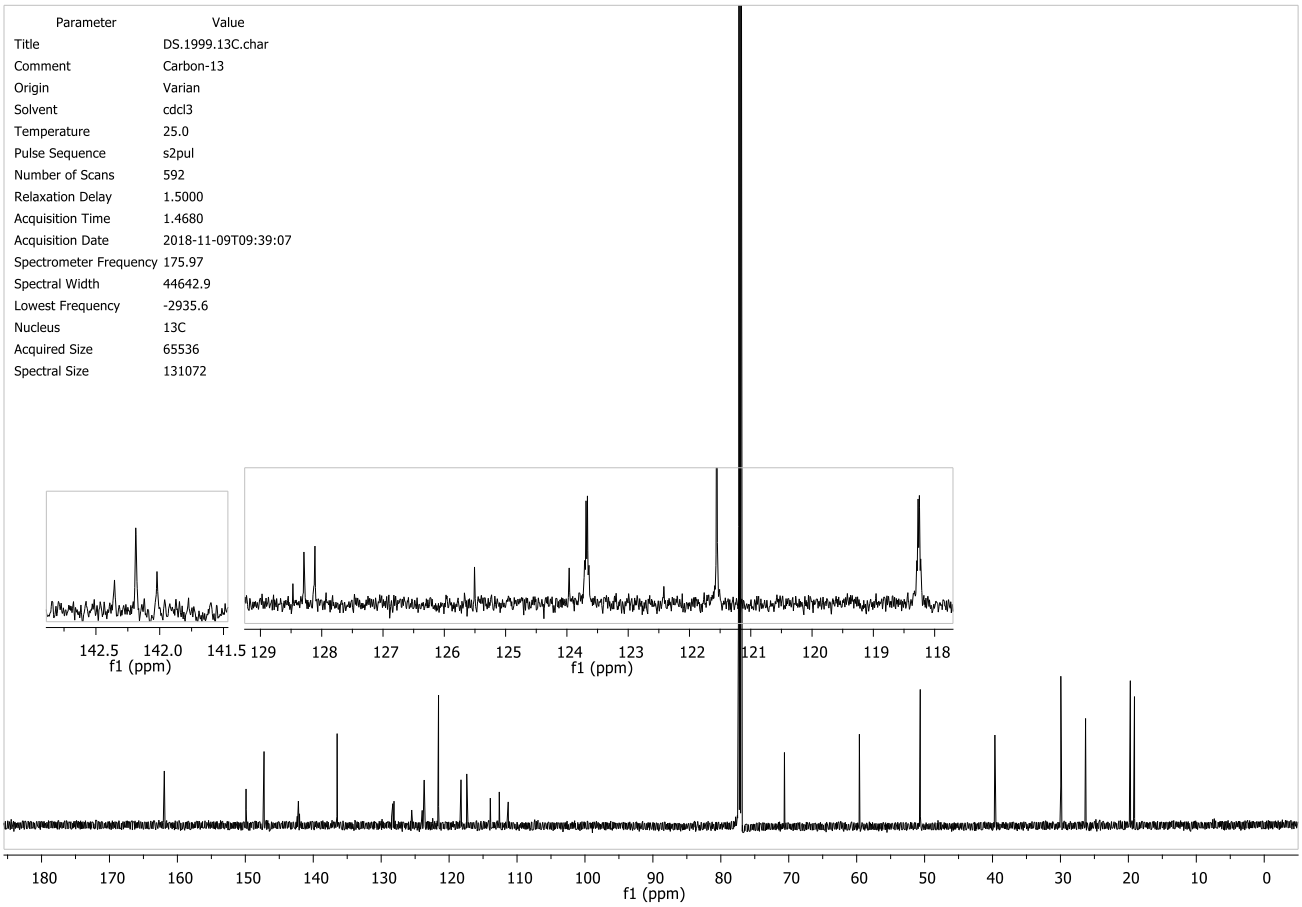
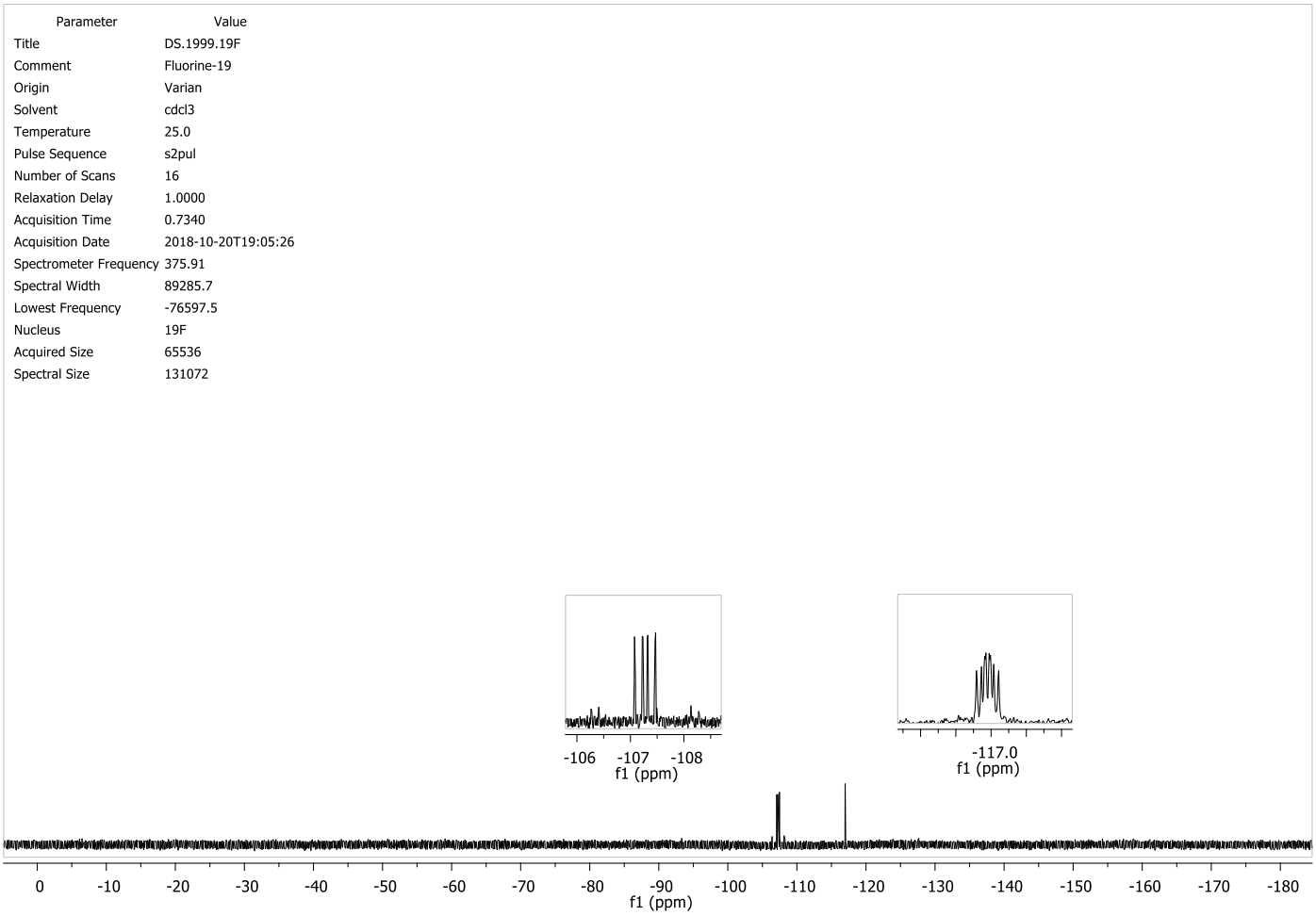
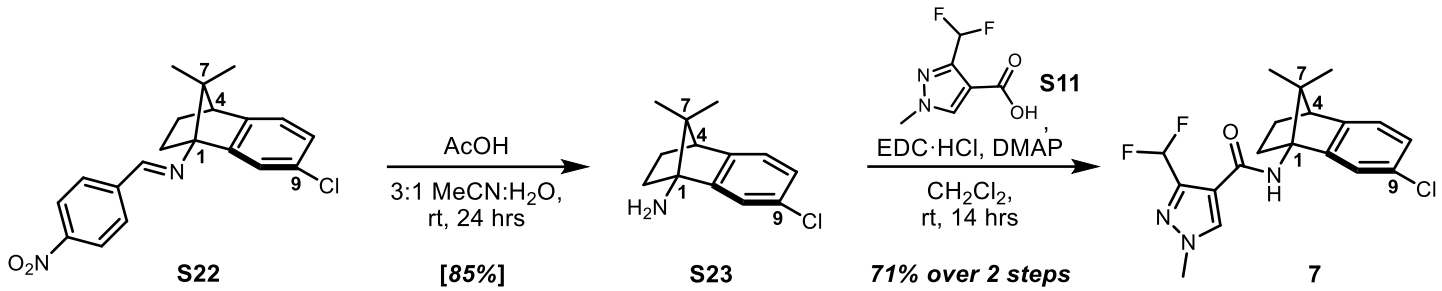


Figure S22: ^{19}F NMR (376 MHz, $CDCl_3$) for 6





S22 **[*85%*]** **S23** ***71% over 2 steps*** **7**

Procedure for C9-chloro-C7-dimethyl 1-aminoNB analog S23

Removal of the Schiff base protecting group was achieved by dissolving the protected 1-aminonorbornane **S22** (40.5 mg; 0.11 mmol) in a 3:1 MeCN:H_2O mixture (0.75 mL:0.25 mL) before adding acetic acid (0.25 mL). The reaction mixture was flushed with Ar, capped, and stirred at room temp for 24 hrs. The reaction was diluted with 2 mL water and 2 mL ether. The phases were separated, and the slightly acidic aqueous phase was washed with 2 mL ether two additional times. The aqueous phase was made basic through the addition of 0.5 mL of 6 M NaOH (aq.) then diluted with 2 mL ether. Phases were separated, and the aqueous phase was extracted with 3 portions of ether, 2 mL each. The organic phases from the basic extraction were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The desired 1-aminonorbornane **S23** was obtained as a clear, colorless liquid in 85.0% yield (21.5 mg). Partial characterization is provided below:

*Partial Characterization Data for C1-NH_2 intermediate **S23**:*
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.20-7.17 (m, 1H, Ar), 7.07 (dd, 1H, *J* = 7.7, 1.9 Hz, Ar), 7.02 (d, 1H, *J* = 7.7 Hz, Ar), 2.80 (d, 1H, *J* = 4.1 Hz, C4), 2.11 (*app.* ddt, 1H, *J* = 14.4, 10.2, 4.0 Hz, C3-eq), 1.87 (*app.* td, 1H, *J* = 11.4, 3.6 Hz, C2-eq), 1.46 (br s, 2H, -NH_2), 1.34-1.28 (m, 1H, C2-ax), 1.16 (ddd, 1H, *J* = 12.2, 9.3, 4.2 Hz, C3-ax), 0.99 (s, 3H, C7-Me), 0.51 (s, 3H, C7-Me) ppm

1-Aminonorbornane **S23** (13.3 mg; 61 μmol) was dissolved in dry dichloromethane (0.70 mL), followed by addition of the carboxylic acid **S11** (16 mg; 91 μmol), DMAP (11 mg; 90 μmol), and EDC·HCl (18 mg; 94 μmol), respectively. The reaction was flushed with Ar, capped, and stirred at room temp 14 hrs. The crude residue was diluted with 4 mL water and 2 mL ethyl acetate. Phases were separated, and the aqueous phase was extracted with 3 portions of ethyl acetate, 2 mL each. The organic phases were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The crude residue was purified with flash chromatography over silica (15 to 75% ethyl acetate:pentane, increasing in 15% increments; loaded residue with PhMe; silica was pre-neutralized with a 15% ethyl acetate:pentane + 1% triethylamine mobile phase). Collected the desired carboxamide (**7**) as a slightly yellow solid: 19.4 mg, 83.4% yield (70.9% over 2 steps).

*Characterization Data for C9-Cl SDHI candidate **7**:*
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.04 (s, 1H, pyrazole), 7.23 (d, 1H, *J* = 1.8 Hz, Ar), 7.08 (dd, 1H, *J* = 7.7, 1.9 Hz, Ar), 7.03 (d, 1H, *J* = 7.7 Hz, Ar), 6.80 (t, 1H, J_{HF} = 54.2 Hz, -CHF_2), 6.67 (br s, 1H, -NH), 3.95 (s, 3H, pyrazole -NMe), 2.80 (d, 1H, *J* = 4.0 Hz, C4), 2.31-2.25 (m, 2H, C2-eq, C3-eq), 2.25-2.19 (m, 1H, C2-ax), 1.27 (ddd, 1H, *J* = 10.9, 7.5, 5.5 Hz, C3-ax), 1.11 (s, 3H, C7-Me), 0.69 (s, 3H, C7-Me) ppm
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 161.9, 148.3, 144.4, 142.2 (t, J_{CF} = 29.6 Hz), 136.4, 131.3, 126.1, 122.6, 121.9, 117.4, 112.6 (t, J_{CF} = 231.9 Hz), 70.7, 59.4, 50.2, 39.6, 30.1, 26.6, 19.7, 19.1 ppm
^{19}F NMR ($CDCl_3$, 376 MHz): δ = -107.1 (*app.* ddd, *J* = 149.7, 54.3, 5.5 Hz) ppm
HRMS (ESI+, *m/z)* calculated for $C_{19}H_{21}ClF_2N_3O^+$: 380.1336, Found: 380.1336.
R_f = 0.35 (70% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

Figure S23: ^{1}H NMR (700 MHz, $CDCl_3$) for 7

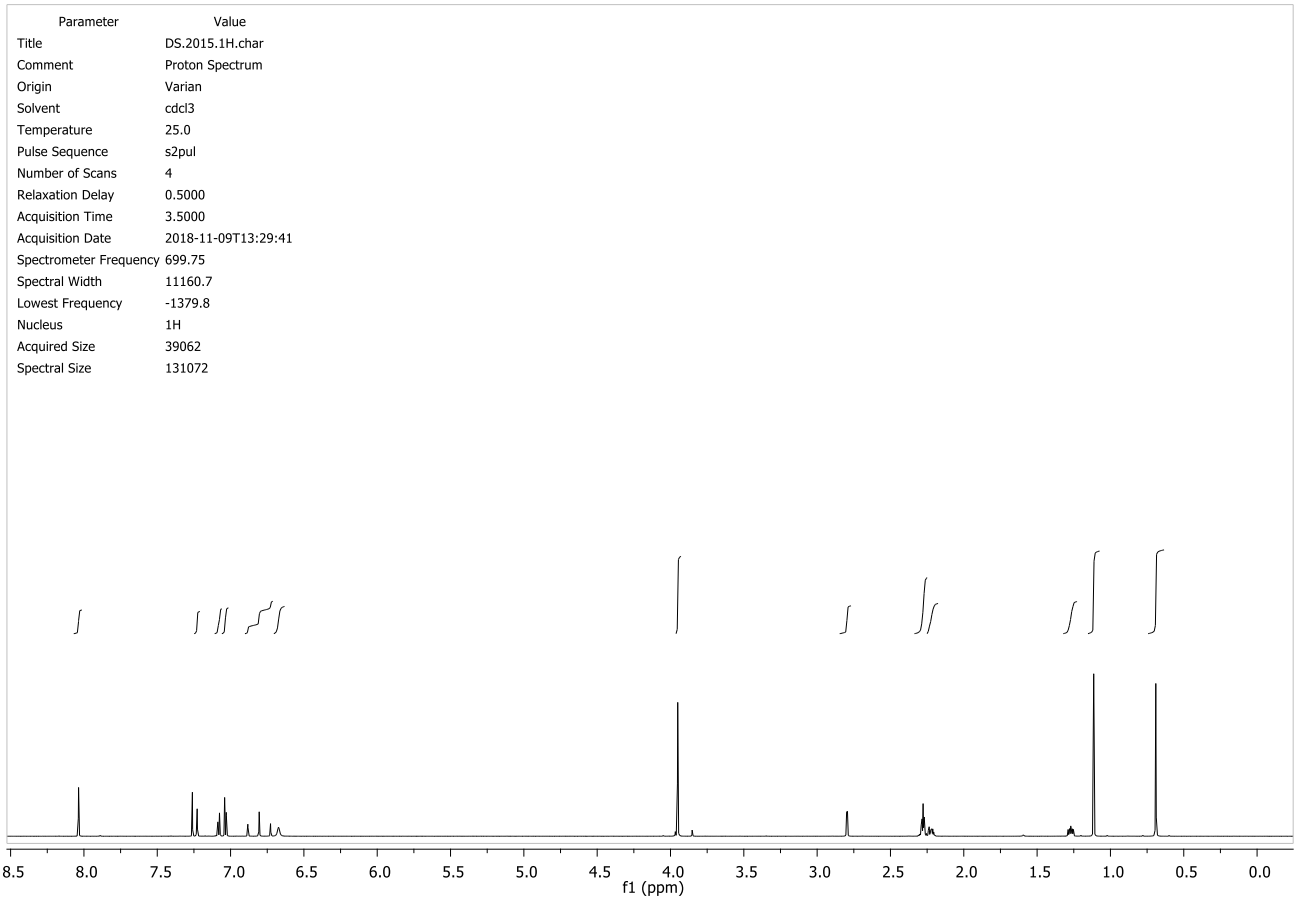


Figure S24: ^{13}C NMR (176 MHz, $CDCl_3$) for 7

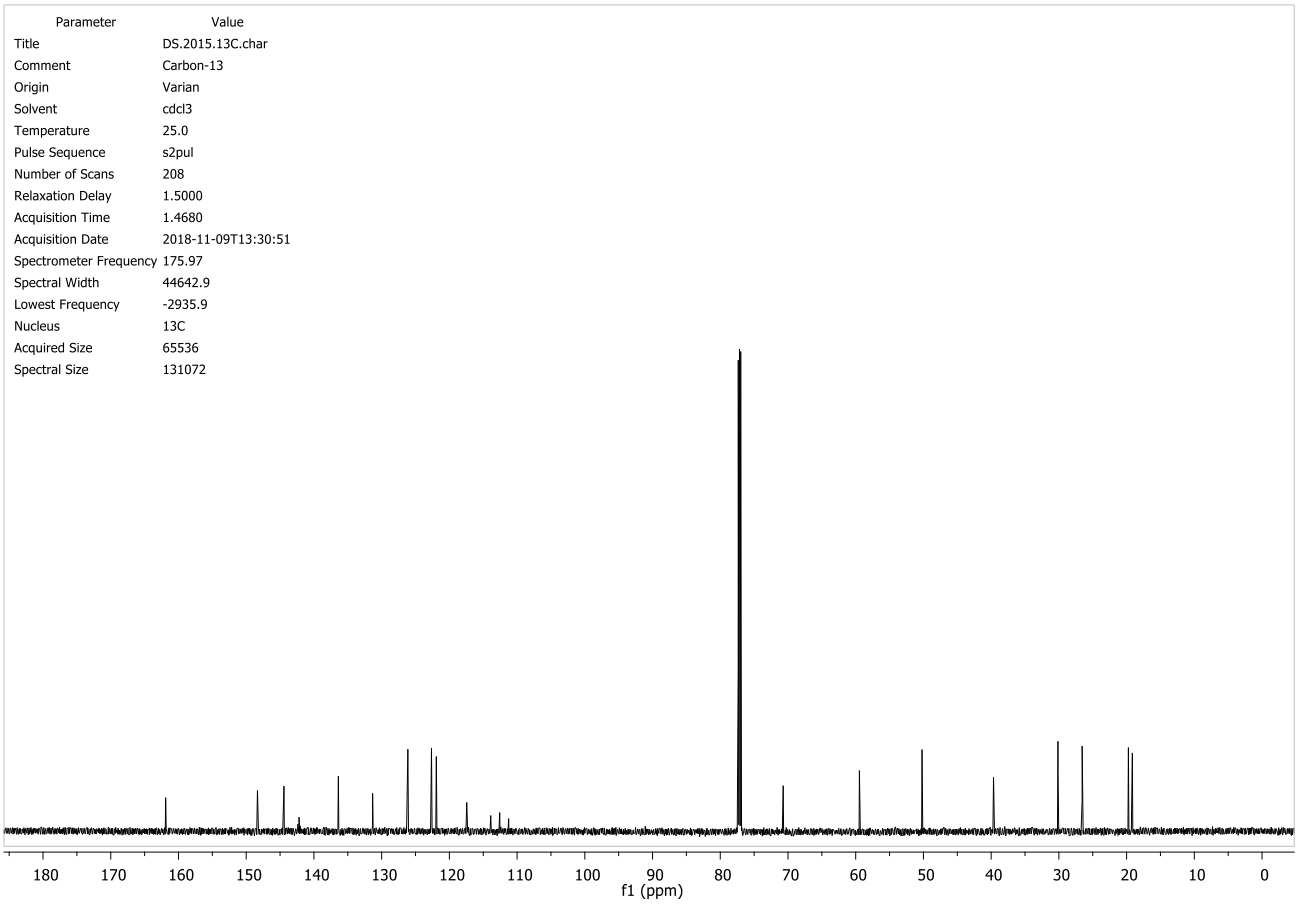
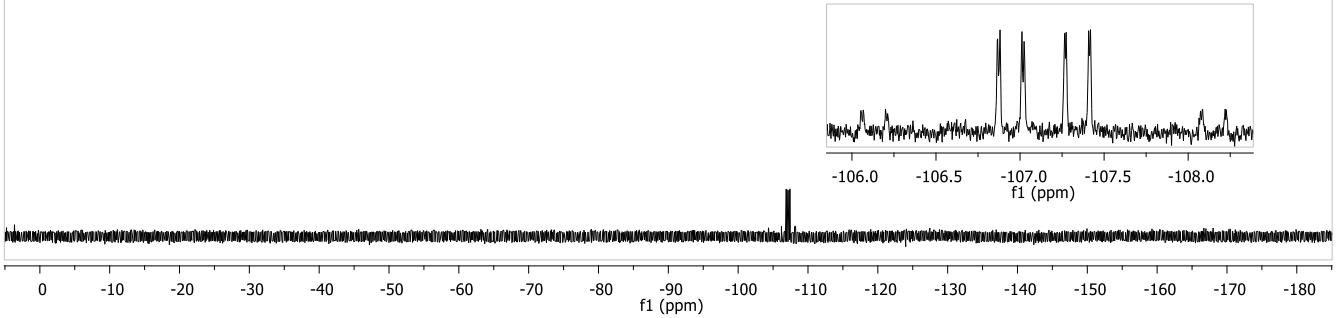
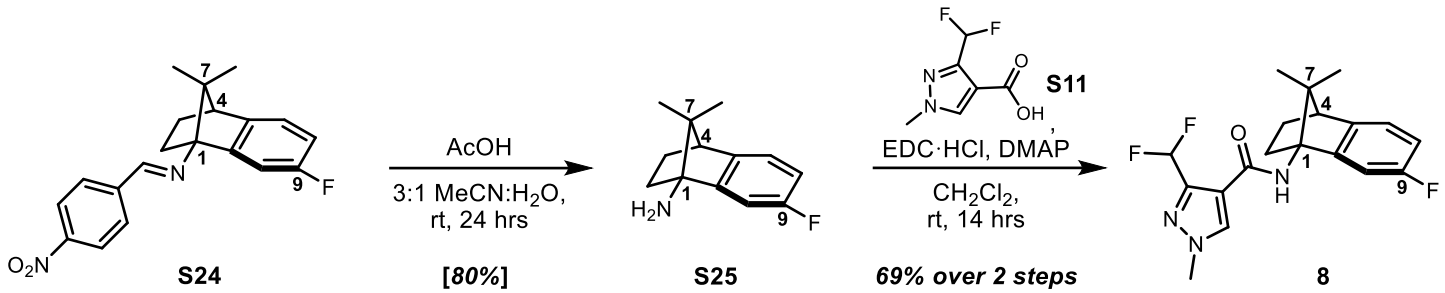


Figure S25: ^{19}F NMR (376 MHz, $CDCl_3$) for 7

Parameter	Value
Title	DS.2015.19F
Comment	Fluorine-19
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Number of Scans	32
Relaxation Delay	1.0000
Acquisition Time	0.7340
Acquisition Date	2018-11-09T20:48:51
Spectrometer Frequency	375.91
Spectral Width	89285.7
Lowest Frequency	-76597.5
Nucleus	19F
Acquired Size	65536
Spectral Size	131072





Procedure for C9-fluoro-C7-dimethyl 1-aminoNB analog S25

Removal of the Schiff base protecting group was achieved by dissolving the protected 1-aminonorbornane **S24** (54.3 mg; 0.16 mmol) in a 3:1 MeCN:H_2O mixture (0.9 mL:0.3 mL) before adding acetic acid (0.3 mL). The reaction mixture was flushed with Ar, capped, and stirred at room temp for 24 hrs. The reaction was diluted with 2 mL water and 2 mL ether. The phases were separated, and the slightly acidic aqueous phase was washed with 2 mL ether two additional times. The aqueous phase was made basic through the addition of 0.5 mL of 6 M NaOH (aq.) then diluted with 2 mL ether. Phases were separated, and the aqueous phase was extracted with 3 portions of ether, 2 mL each. The organic phases from the basic extraction were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The desired 1-aminonorbornane **S25** was obtained as a clear, colorless liquid in 80.4% yield (26.5 mg). Partial characterization is provided below:

*Partial Characterization Data for C1-NH_2 intermediate **S25**:*
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.02 (dd, 1H, *J* = 7.9, 4.9 Hz, Ar), 6.93 (d, 1H, *J* = 8.0 Hz, Ar), 6.81 (ddd, 1H, *J* = 9.9, 8.1, 2.4 Hz, Ar), 2.80 (d, 1H, *J* = 4.0 Hz, C4), 2.14-2.06 (m, 1H, C3-eq), 1.90-1.83 (m, 1H, C2-eq), 1.46 (br s, 2H, -NH_2), 1.34-1.27 (m, 1H, C2-ax), 1.16 (ddd, 1H, *J* = 12.1, 9.4, 4.0 Hz, C3-ax), 0.98 (s, 3H, C7-Me), 0.51 (s, 3H, C7-Me) ppm

1-Aminonorbornane **S25** (12.6 mg; 61 μmol) was dissolved in dry dichloromethane (0.70 mL), followed by addition of the carboxylic acid **S11** (16 mg; 91 μmol), DMAP (11 mg; 90 μmol), and EDC·HCl (18 mg; 94 μmol), respectively. The reaction was flushed with Ar, capped, and stirred at room temp 14 hrs. The crude residue was diluted with 4 mL water and 2 mL ethyl acetate. Phases were separated, and the aqueous phase was extracted with 3 portions of ethyl acetate, 2 mL each. The organic phases were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The crude residue was purified with flash chromatography over silica (15 to 75% ethyl acetate:pentane, increasing in 15% increments; loaded residue with PhMe; silica was pre-neutralized with a 15% ethyl acetate:pentane + 1% triethylamine mobile phase). Obtained 24.0 mg of a slightly yellow solid that was largely pure by ^{1}H NMR analysis, but it was deemed necessary to employ a second round of chromatography (same as above). Collected the desired carboxamide (**8**) as a white solid: 19.2 mg, 86.1% yield (69.2% over 2 steps).

*Characterization Data for C9-F SDHI candidate **8**:*
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.02 (s, 1H, pyrazole), 7.03 (dd, 1H, *J* = 7.9, 4.9 Hz, Ar), 6.98 (dd, 1H, *J* = 8.5, 2.4 Hz, Ar), 6.81 (t, 1H, J_{HF} = 54.2 Hz, -CHF_2), 6.77 (ddd, 1H, *J* = 10.2, 8.1, 2.4 Hz, Ar), 6.68 (br s, 1H, -NH), 3.95 (s, 3H, pyrazole -NMe), 2.79 (d, 1H, *J* = 3.9 Hz, C4), 2.32-2.19 (m, 3H, C2-eq, C3-eq, C2-ax), 1.27 (ddd, 1H, *J* = 12.6, 8.9, 3.7 Hz, C3-ax), 1.11 (s, 3H, C7-Me), 0.69 (s, 3H, C7-Me) ppm
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 161.9, 161.6 (d, J_{CF} = 242.5 Hz), 148.6 (d, J_{CF} = 7.7 Hz), 142.2 (t, J_{CF} = 29.5 Hz), 141.4 (d, J_{CF} = 2.6 Hz), 136.3, 122.3 (d, J_{CF} = 8.2 Hz), 117.5, 112.5 (t, J_{CF} = 232.1 Hz), 112.3 (d, J_{CF} = 22.1 Hz), 109.5 (d, J_{CF} = 23.8 Hz), 70.9, 59.6, 50.0, 39.6, 30.2, 26.7, 19.8, 19.2 ppm
^{19}F NMR ($CDCl_3$, 376 MHz): δ = -107.1 (*app.* ddd, *J* = 105.3, 54.3, 4.5 Hz), -116.8 (*app* td, *J* = 9.2, 4.5 Hz) ppm
HRMS (ESI+, *m/z)* calculated for $C_{19}H_{21}F_3N_3O^+$: 364.1631, Found: 364.1634.
R_f = 0.40 (70% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

Figure S26: ^{1}H NMR (700 MHz, $CDCl_3$) for 8

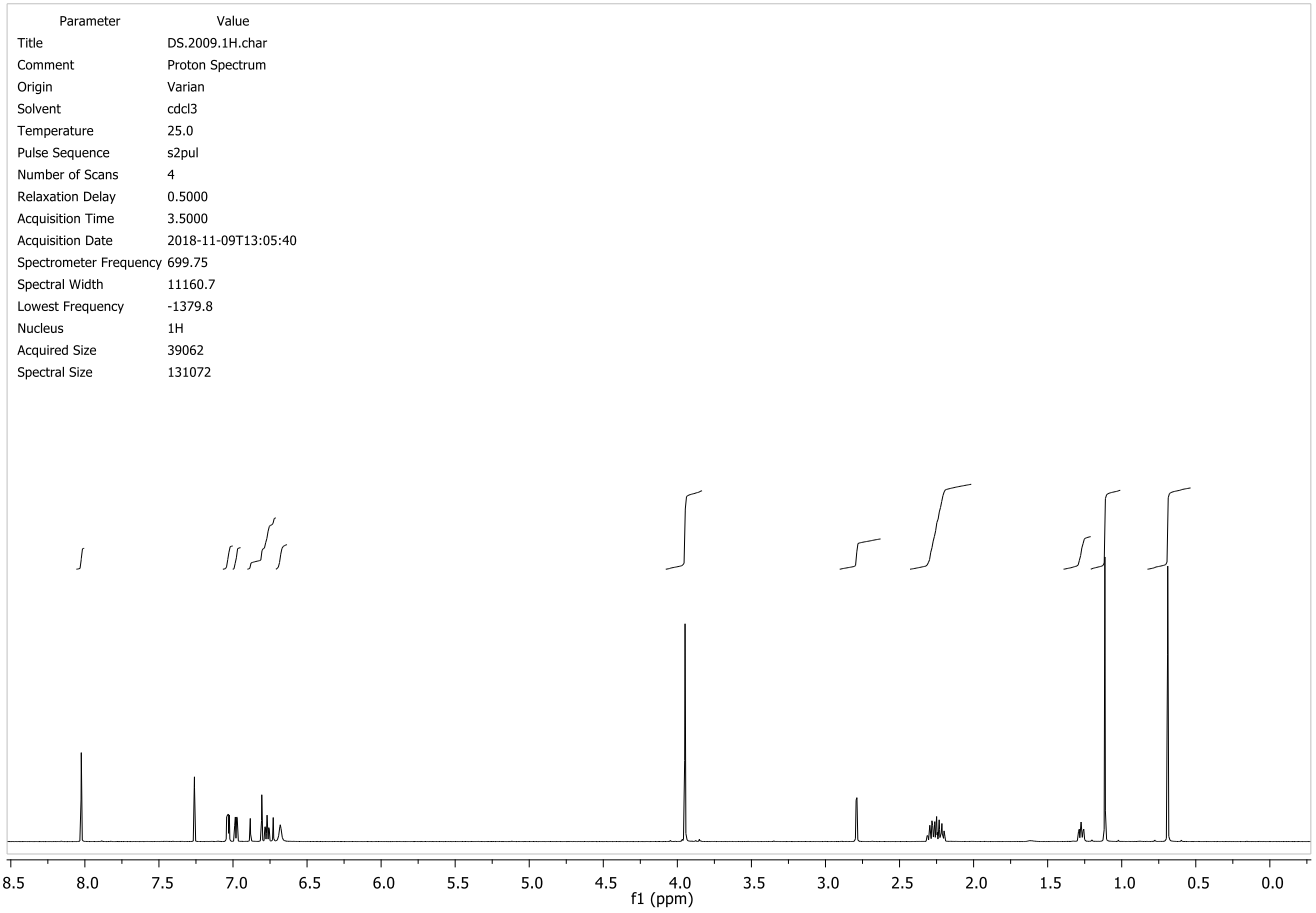


Figure S27: ^{13}C NMR (176 MHz, $CDCl_3$) for 8

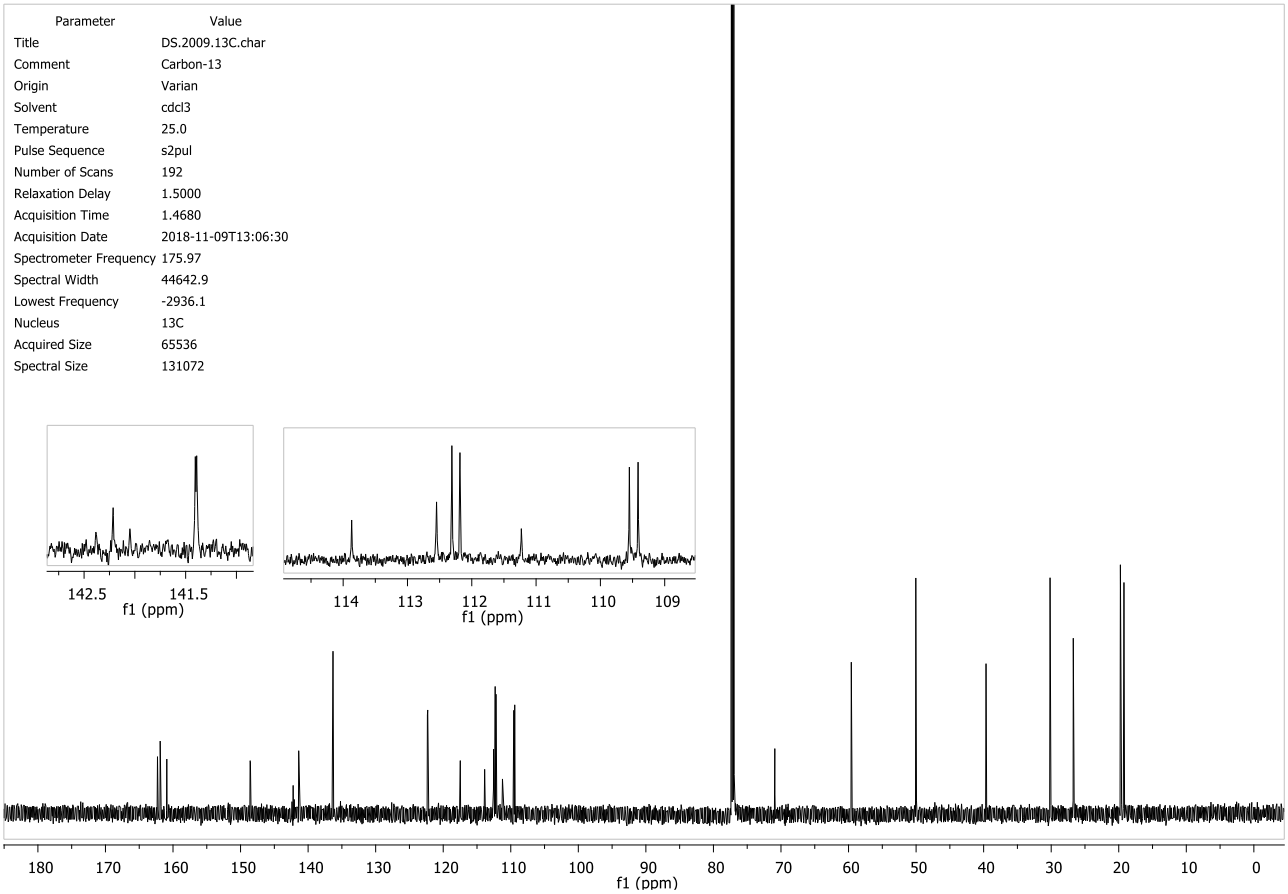
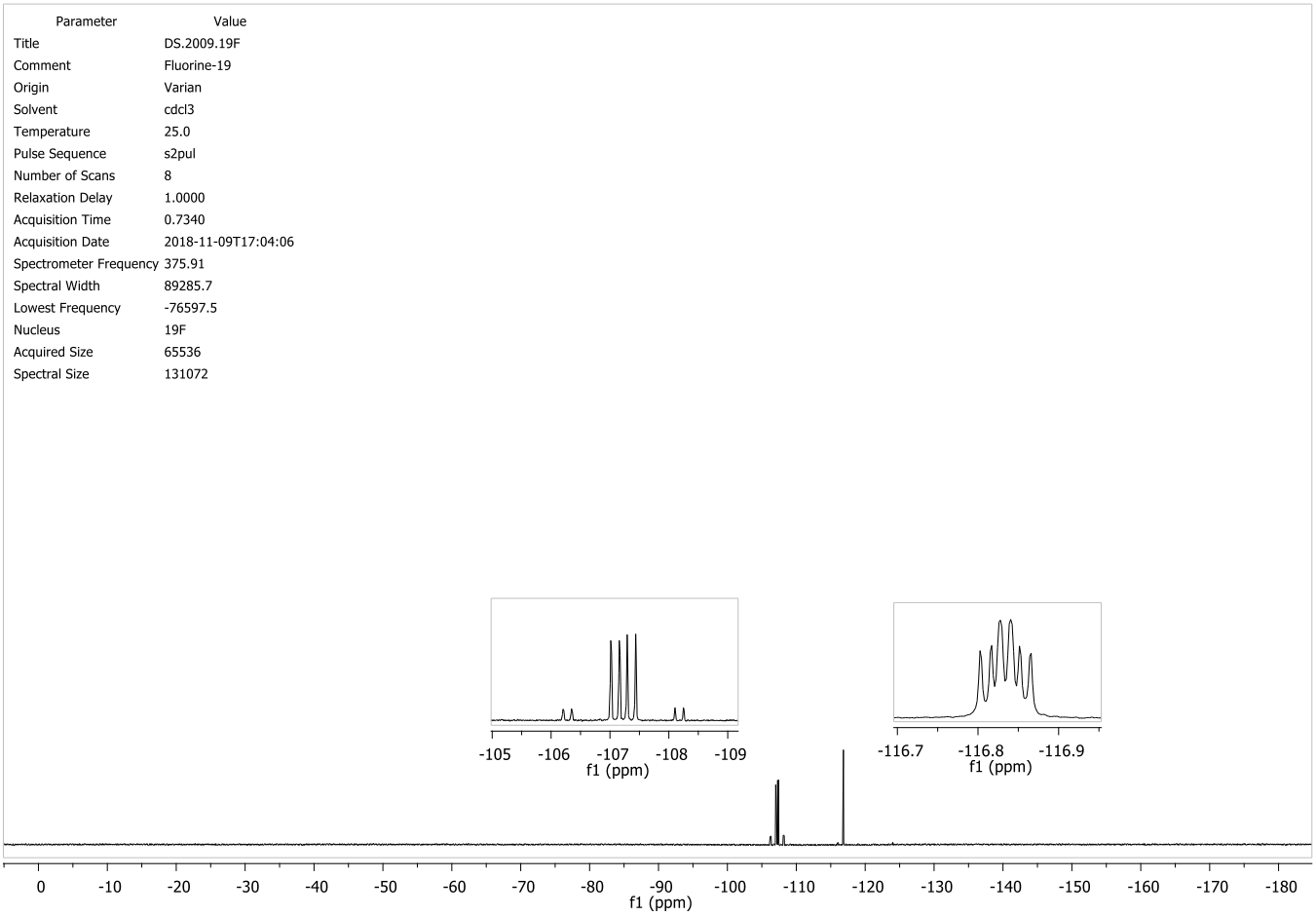
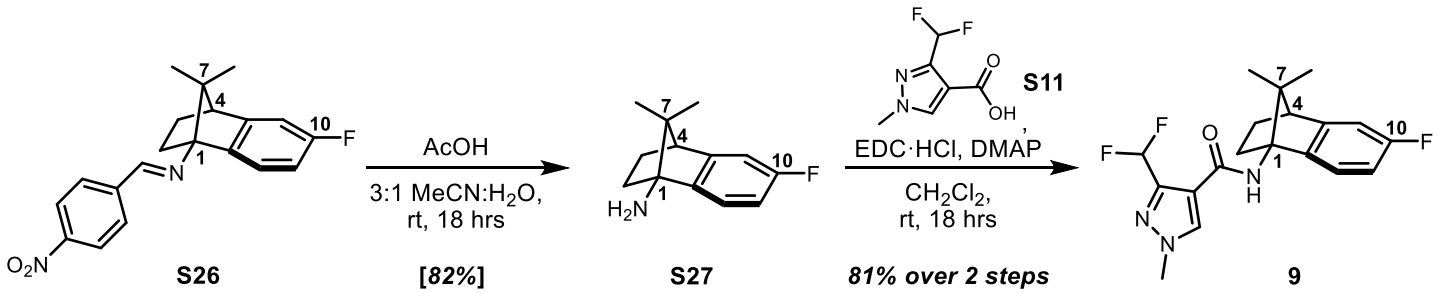


Figure S28: ^{19}F NMR (376 MHz, $CDCl_3$) for 8





Procedure for C10-trifluormethyl-C7-dimethyl 1-aminoNB analog S27

Removal of the Schiff base protecting group was achieved by dissolving the protected 1-aminonorbornane **S26** (47.6 mg; 0.14 mmol) in a 3:1 MeCN:H_2O mixture (0.9 mL:0.3 mL) before adding acetic acid (0.3 mL). The reaction mixture was flushed with Ar, capped, and stirred at room temp for 18 hrs. The reaction was diluted with 2 mL water and 2 mL ether. The phases were separated, and the slightly acidic aqueous phase was washed with 2 mL ether two additional times. The aqueous phase was made basic through the addition of 0.5 mL of 6 M NaOH (aq.) then diluted with 2 mL ether. Phases were separated, and the aqueous phase was extracted with 3 portions of ether, 2 mL each. The organic phases from the basic extraction were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The desired 1-aminonorbornane **S27** was obtained as a clear, colorless liquid in 81.9% yield (23.7 mg). Partial characterization is provided below:

*Partial Characterization Data for C1-NH_2 intermediate **S27**:*
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.13-7.10 (m, 1H, Ar), 6.84 (dd, 1H, *J* = 8.4, 2.2 Hz, Ar), 6.81 (ddd, 1H, *J* = 10.2, 8.0, 2.4 Hz, Ar), 2.80 (d, 1H, *J* = 4.1 Hz, C4), 2.13-2.08 (m, 1H, C3-eq), 1.90-1.84 (m, 1H, C2-eq), 1.45 (br s, 2H, -NH_2), 1.33-1.28 (m, 1H, C2-ax), 1.16 (ddd, 1H, *J* = 12.2, 9.4, 4.1 Hz, C3-ax), 0.99 (s, 3H, C7-Me), 0.51 (s, 3H, C7-Me) ppm

1-Aminonorbornane **S27** (14.0 mg; 68 μmol) was dissolved in dry dichloromethane (0.70 mL), followed by addition of the carboxylic acid **S11** (16 mg; 91 μmol), DMAP (13 mg; 106 μmol), and EDC·HCl (19 mg; 99 μmol), respectively. The reaction was flushed with Ar, capped, and stirred at room temp 18 hrs. The crude residue was diluted with 4 mL water and 2 mL ethyl acetate. Phases were separated, and the aqueous phase was extracted with 3 portions of ethyl acetate, 2 mL each. The organic phases were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The crude residue was purified with flash chromatography over silica (15 to 75% ethyl acetate:pentane, increasing in 15% increments; loaded residue with PhMe; silica was pre-neutralized with a 15% ethyl acetate:pentane + 1% triethylamine mobile phase). Collected the desired carboxamide (**9**) as a slightly yellow solid: 24.6 mg, 99.3% yield (81.3% over 2 steps).

*Characterization Data for cyclopropylimine **9**:*
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.01 (s, 1H, pyrazole), 7.16 (dd, 1H, *J* = 8.1, 5.1 Hz, Ar), 6.85 (dd, 1H, *J* = 8.4, 2.3 Hz, Ar), 6.80 (t, 1H, J_{HF} = 54.2 Hz, -CHF_2), 6.77 (ddd, 1H, *J* = 10.1, 8.1, 2.4 Hz, Ar), 6.68 (br s, 1H, -NH), 3.94 (s, 3H, pyrazole -NMe), 2.80 (d, 1H, *J* = 3.7 Hz, C4), 2.34-2.29 (m, 1H, C2-eq.), 2.25-2.19 (m, 2H, C3-eq, C2-ax), 1.31-1.25 (m, 1H, C3-ax), 1.12 (s, 3H, C7-Me), 0.69 (s, 3H, C7-Me) ppm
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 161.9, 161.8 (d, J_{CF} = 242.5 Hz), 147.9 (d, J_{CF} = 8.0 Hz), 142.2 (t, J_{CF} = 29.4 Hz), 141.9 (d, J_{CF} = 2.5 Hz), 136.2, 122.2 (d, J_{CF} = 8.6 Hz), 117.6, 112.5 (t, J_{CF} = 232.3 Hz), 111.8 (d, J_{CF} = 22.1 Hz), 109.4 (d, J_{CF} = 22.9 Hz), 70.2, 59.5, 50.8, 39.6, 30.3, 26.5, 19.7, 19.2 ppm
^{19}F NMR ($CDCl_3$, 376 MHz): δ = -61.6, -107.1(*app.* ddd, *J* = 132.0, 54.5, 5.6 Hz) ppm
HRMS (ESI+, *m/z)* calculated for $C_{19}H_{21}F_3N_3O^+$: 364.1631, Found: 364.1634.
R_f = 0.35 (70% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

Figure S29: ^{1}H NMR (700 MHz, $CDCl_3$) for 9

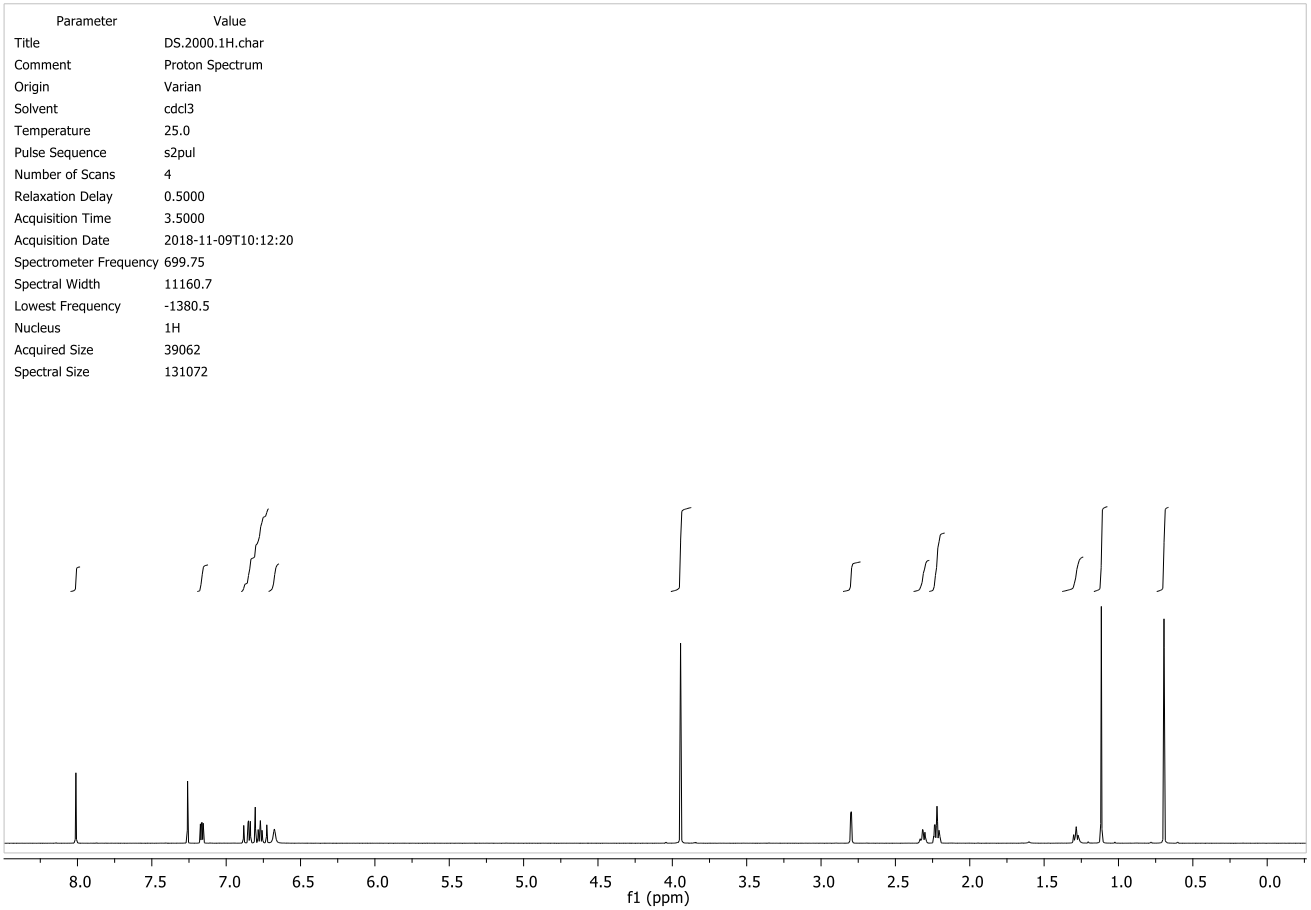


Figure S30: ^{13}C NMR (176 MHz, $CDCl_3$) for 9

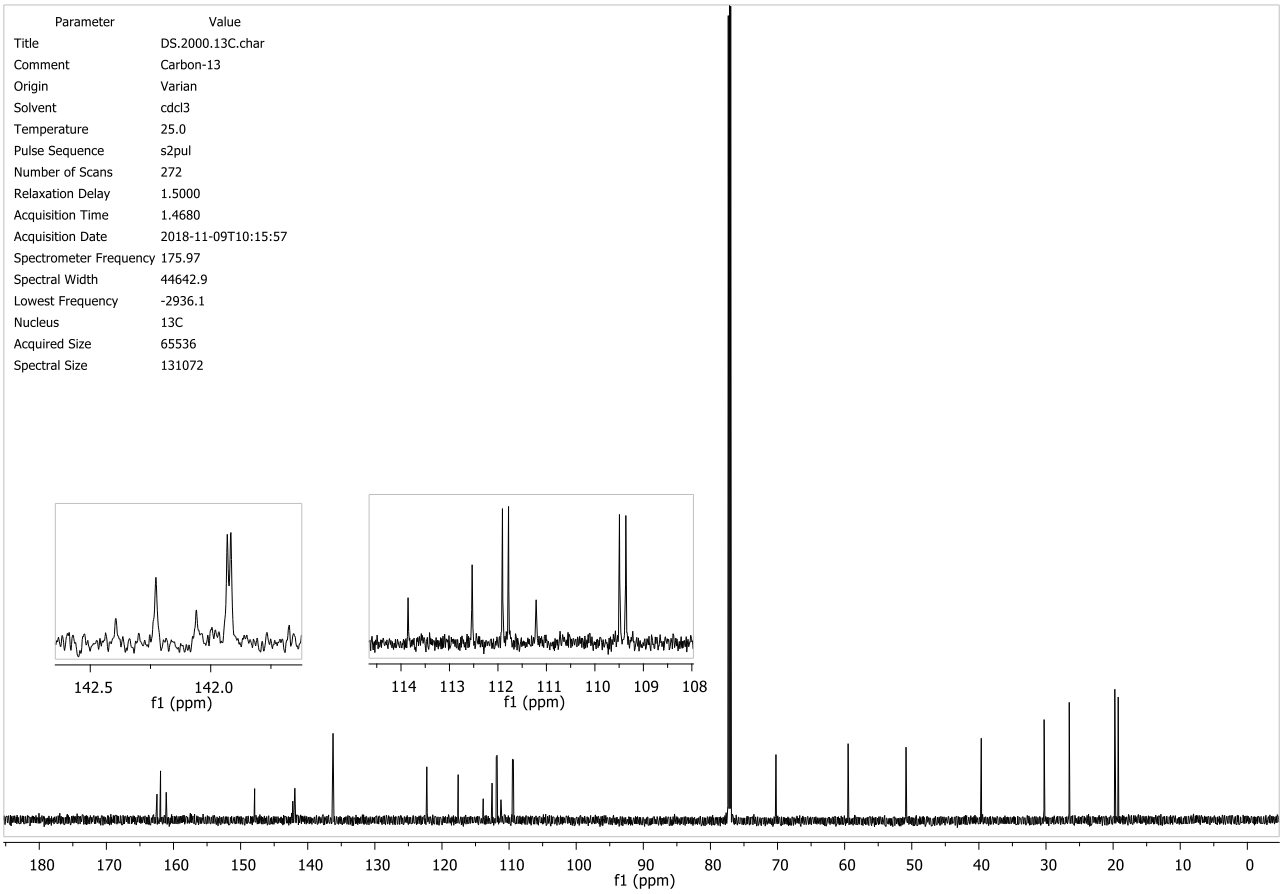
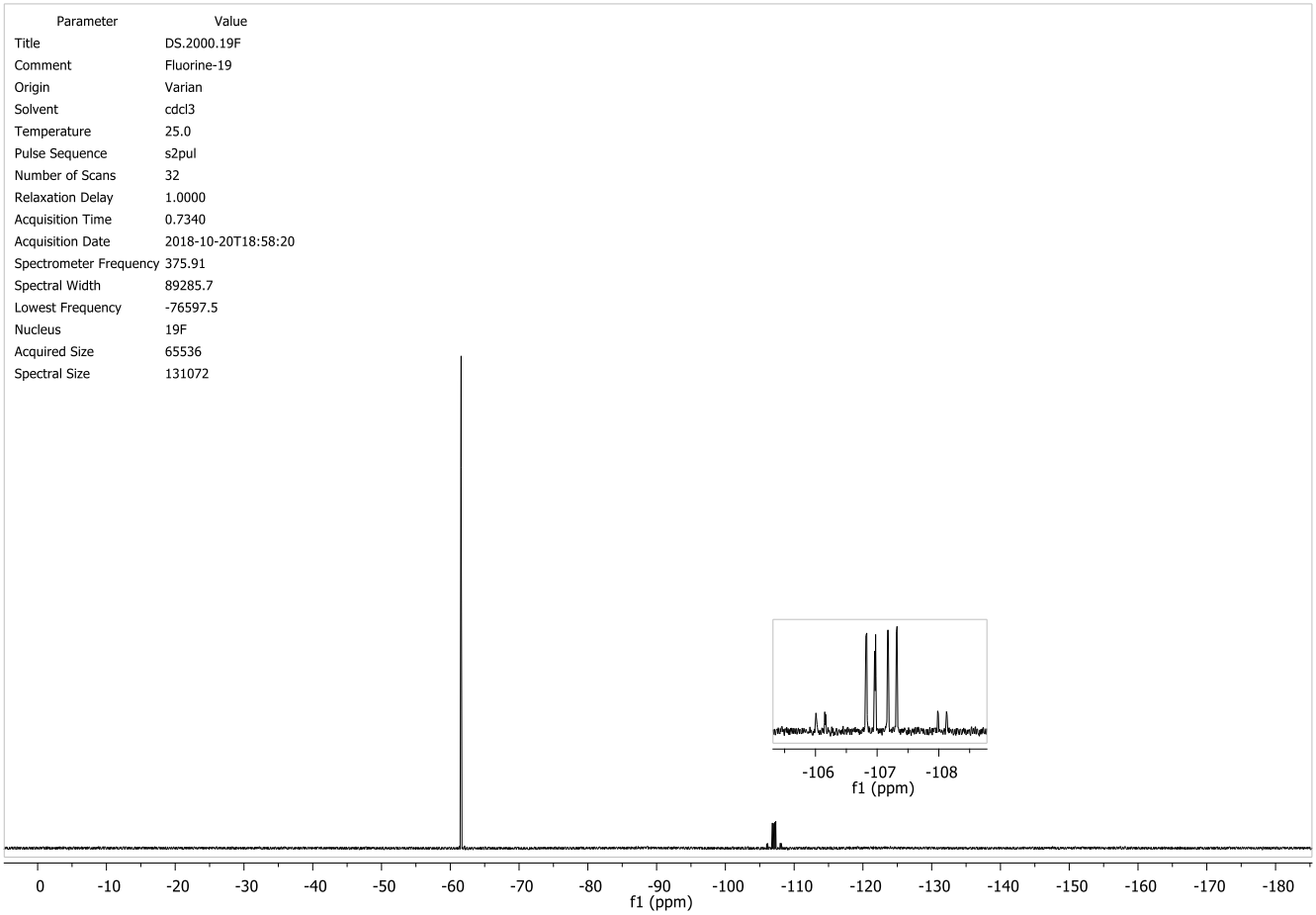
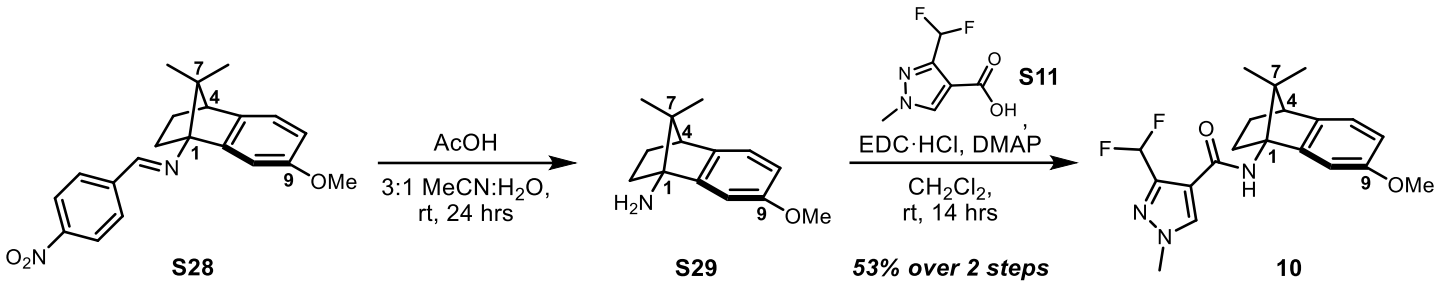


Figure S31: ^{19}F NMR (376 MHz, $CDCl_3$) for 9





Procedure for C9-methoxy-C7-dimethyl 1-aminoNB analog S29

Removal of the Schiff base protecting group was achieved by dissolving the protected 1-aminonorbornane **S28** (37.2 mg; 0.11 mmol) in a 3:1 MeCN:H_2O mixture (0.75 mL:0.25 mL) before adding acetic acid (0.25 mL). The reaction mixture was flushed with Ar, capped, and stirred at room temp for 24 hrs. The reaction was diluted with 2 mL water and 2 mL ether. The phases were separated, and the slightly acidic aqueous phase was washed with 2 mL ether two additional times. The aqueous phase was made basic through the addition of 0.5 mL of 6 M NaOH (aq.) then diluted with 2 mL ether. Phases were separated, and the aqueous phase was extracted with 3 portions of ether, 2 mL each. The organic phases from the basic extraction were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The desired 1-aminonorbornane **S29** was obtained as a clear, colorless liquid (21.3 mg), though minor impurities were still observable by ^{1}H NMR analysis. Material was moved forward without further purification. Partial characterization is provided below:

*Partial Characterization Data for C1-NH_2 intermediate **S29**:*
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.00 (dd, 1H, *J* = 7.9, 4.9 Hz, Ar), 6.84-6.81 (m, 1H, Ar), 6.61 (dd, 1H, *J* = 7.9, 2.4 Hz, Ar), 3.80 (s, 3H, C9-OMe), 2.76 (d, 1H, *J* = 4.0 Hz, C4), 2.12-2.05 (m, 1H, C3-eq), 1.88-1.81 (m, 1H, C2-eq), 1.51 (br s, 2H, -NH_2), 1.35-1.28 (m, 1H, C2-ax), 1.16 (ddd, 1H, *J* = 12.0, 9.5, 3.9 Hz, C3-ax), 0.99 (s, 3H, C7-Me), 0.51 (s, 3H, C7-Me) ppm

1-Aminonorbornane **S29** (18.9 mg from above; at most 87 μmol) was dissolved in dry dichloromethane (0.90 mL), followed by addition of the carboxylic acid **S11** (23 mg; 131 μmol), DMAP (16 mg; 130 μmol), and EDC·HCl (25 mg; 130 μmol), respectively. The reaction was flushed with Ar, capped, and stirred at room temp 14 hrs. The crude residue was diluted with 4 mL water and 2 mL ethyl acetate. Phases were separated, and the aqueous phase was extracted with 3 portions of ethyl acetate, 2 mL each. The organic phases were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The crude residue was purified with flash chromatography over silica (20 to 100% ethyl acetate:pentane, increasing in 15% increments; loaded residue with PhMe; silica was pre-neutralized with a 20% ethyl acetate:pentane + 1% triethylamine mobile phase). Obtained 25.9 mg of a slightly yellow solid that was largely pure by ^{1}H NMR analysis, but it was deemed necessary to employ a second round of chromatography (30 to 50 to 100% ethyl acetate:pentane; silica was pre-neutralized with a 30% ethyl acetate:pentane + 1% triethylamine mobile phase). Collected the desired carboxamide (**10**) as a slightly yellow solid: 21.3 mg, 54.3% yield over 2 steps.

*Characterization Data for C9-OMe SDHI candidate **10**:*
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.01 (s, 1H, pyrazole), 7.01 (d, 1H, *J* = 7.9 Hz, Ar), 6.85 (d, 1H, *J* = 1.5 Hz, Ar), 6.81 (t, 1H, J_{HF} = 54.2 Hz, -CHF_2), 6.64 (br s, 1H, -NH), 6.62 (dd, 1H, *J* = 8.0, 1.9 Hz, Ar), 3.94 (s, 3H, pyrazole -NMe), 3.76 (s, 3H, -OMe), 2.75 (d, 1H, *J* = 3.7 Hz, C4), 2.43-2.38 (m, 1H, C2-eq.), 2.23-2.17 (m, 2H, C3-eq, C2-ax), 1.30-1.25 (m, 1H, C3-ax), 1.11 (s, 3H, C7-Me), 0.69 (s, 3H, C7-Me) ppm
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 161.9, 158.3, 148.1, 142.3 (t, J_{CF} = 29.2 Hz), 138.4, 136.1, 122.0, 117.8, 112.5 (t, J_{CF} = 232.5 Hz), 110.6, 108.0, 71.1, 59.4, 55.5, 49.9, 39.6, 30.0, 27.0, 19.8, 19.5 ppm
^{19}F NMR ($CDCl_3$, 376 MHz): δ = -107.1(*app.* ddd, *J* = 65.5, 54.2 4.2 Hz) ppm
HRMS (ESI+, *m/z)* calculated for $C_{20}H_{24}F_2N_3O_2^+$: 376.1831, Found: 376.1830.
R_f = 0.30 (70% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

Figure S32: ^{1}H NMR (700 MHz, $CDCl_3$) for 10

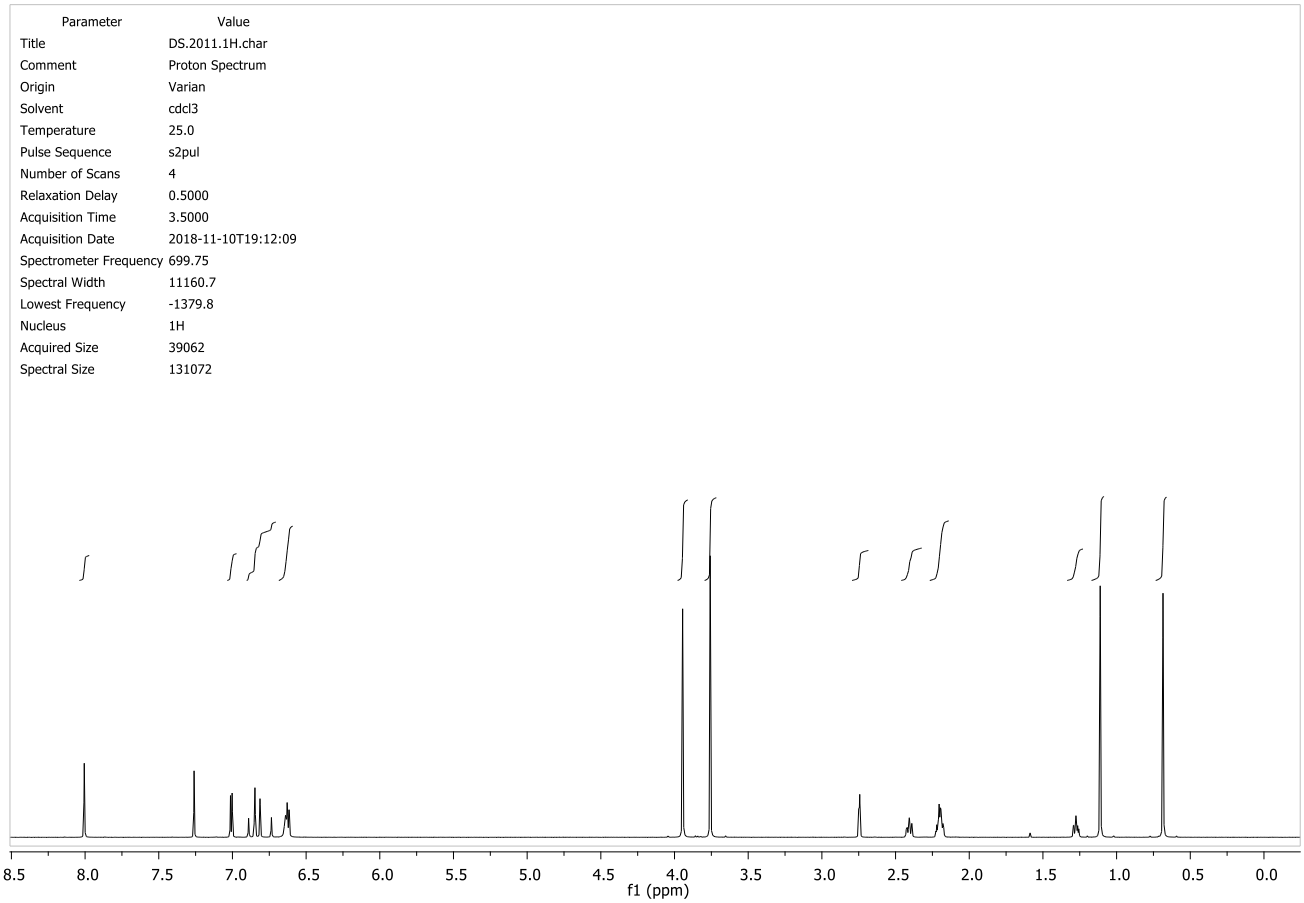


Figure S33: ^{13}C NMR (176 MHz, $CDCl_3$) for 10

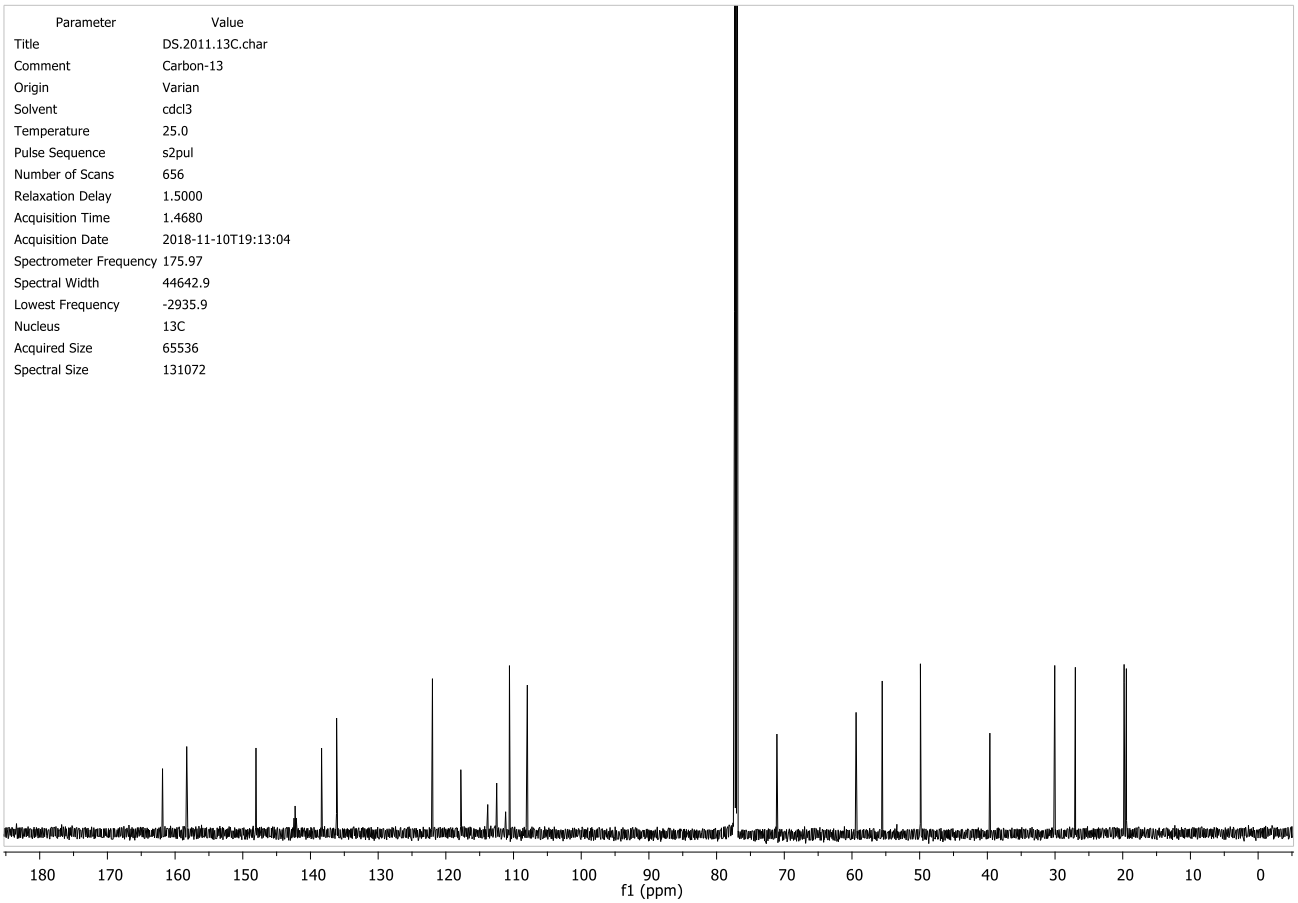
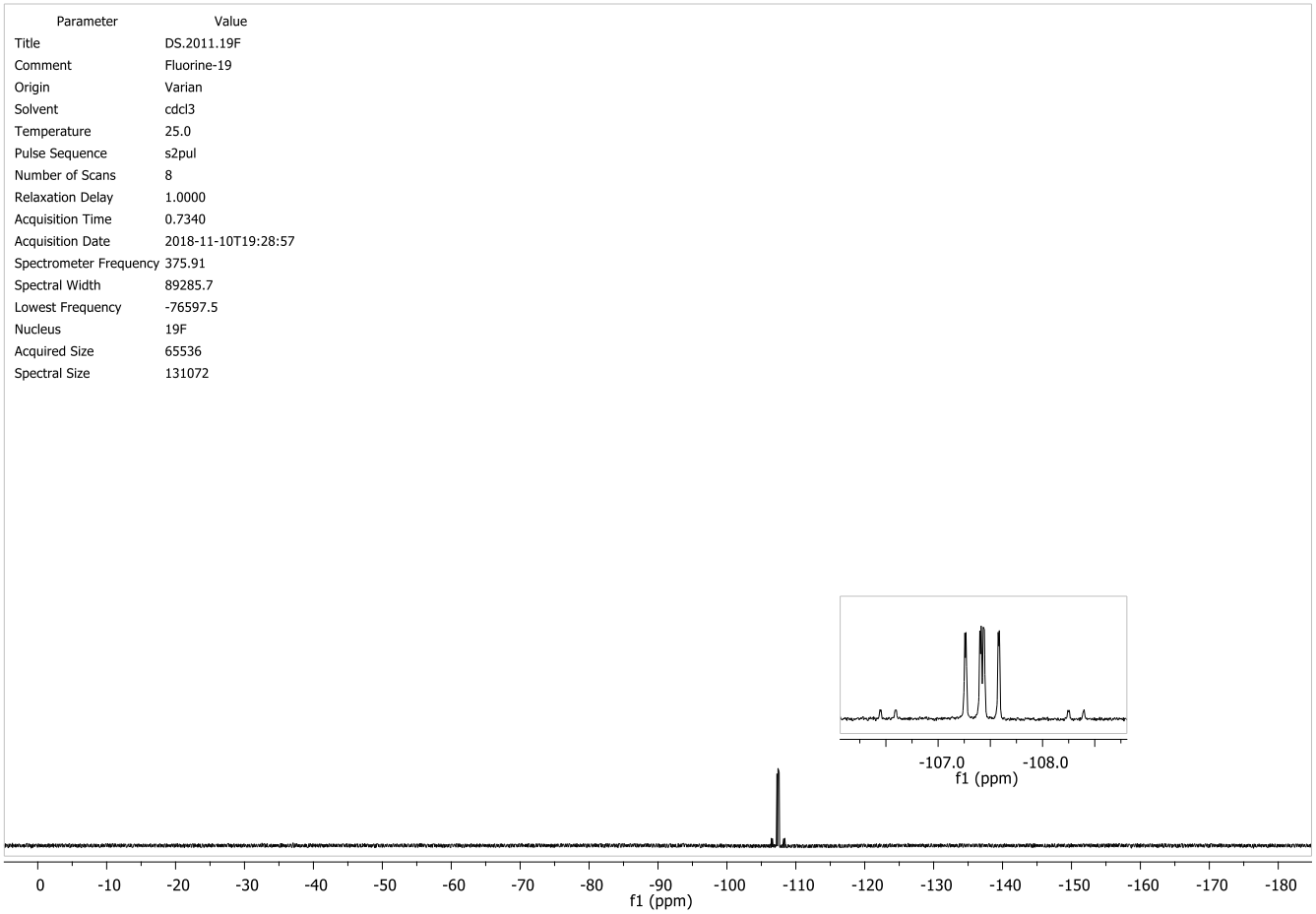
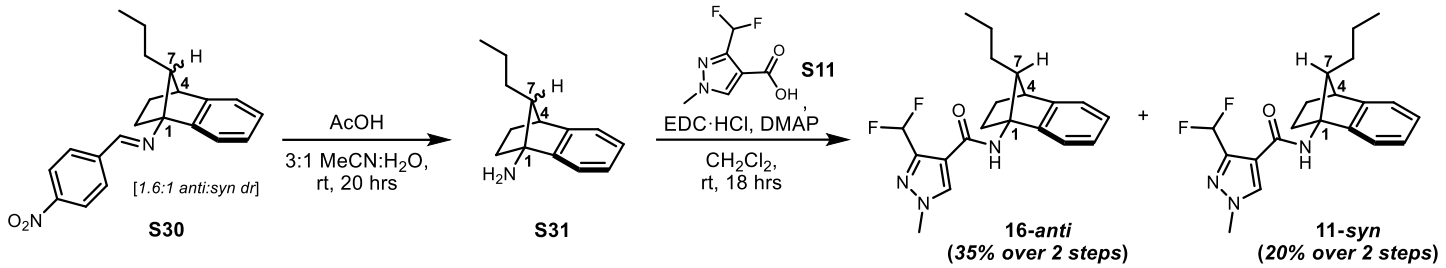


Figure S34: ^{19}F NMR (376 MHz, $CDCl_3$) for 10





Procedure for C7-propyl 1-aminoNB analogs 16-*anti* and 11-*syn*

Removal of the Schiff base protecting group was achieved by dissolving the protected 1-aminonorbornane mix (**S30**; 61.3 mg of a 1.6:1 *anti*:*syn* mixture; 183 μmol) in a 3:1 MeCN:H_2O mixture (1.2 mL:0.4 mL) before adding acetic acid (0.4 mL). The reaction mixture was flushed with Ar, capped, and stirred at room temp for 20 hrs. The reaction was diluted with 2 mL water and 2 mL ether. The phases were separated, and the slightly acidic aqueous phase was washed with 2 mL ether two additional times. The aqueous phase was made basic through the addition of 0.5 mL of 6 M NaOH (aq.) then diluted with 2 mL ether. Phases were separated, and the aqueous phase was extracted with 3 portions of ether, 2 mL each. The organic phases from the basic extraction were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The desired 1-aminonorbornanes (**S31**) were obtained as a slightly yellow oil (30.1 mg) as a 2.2:1 *anti*:*syn* mixture. There were minor impurities present in the ^{1}H NMR spectrum of this mixture, but the material was moved forward without further purification. Partial characterization is provided below.

Diagnostic Data for anti-C7-propyl C1-NH_2 intermediate:
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.06 (d, 1H, *J* = 3.9 Hz, C4), 0.96 (t, 3H, *J* = 7.0 Hz, C7-$CH_2CH_2CH_3$) ppm [*partial line-listing*]

Diagnostic Data for syn-C7-propyl C1-NH_2 intermediate:
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.12 (d, 1H, *J* = 4.0 Hz, C4), 0.80 (d, 3H, *J* = 7.3 Hz, C7-$CH_2CH_2CH_3$) ppm [*partial line-listing*]

1-Aminonorbornane mix **S31** (29.0 mg; at most 144 μmol) was dissolved in dry dichloromethane (1.5 mL), followed by addition of the carboxylic acid **S11** (38 mg; 0.22 mmol), DMAP (26 mg; 0.21 mmol), and EDC·HCl (41 mg; 0.21 mmol), respectively. The reaction was flushed with Ar, capped, and stirred at room temp 18 hrs. The crude residue was diluted with 4 mL water and 2 mL ethyl acetate. Phases were separated, and the aqueous phase was extracted with 3 portions of ethyl acetate, 2 mL each. The organic phases were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The crude residue was purified with flash chromatography over silica (20 to 30 to 40 to 60 to 80 to 100% ethyl acetate:hexanes; loaded residue with PhMe; silica was pre-neutralized with a 20% ethyl acetate:pentane + 1% triethylamine mobile phase). Collected the desired carboxamides **16-*anti*** and **11-*syn*** in three portions: 16.1 mg enriched in **16-*anti***, 9.5 mg of a nearly 1:1 mixture, and 10.3 mg enriched in **11-*syn***. A series of pipet-scale rounds of chromatography over silica was employed to generate pure samples of each isomer (15 to 30 to 50 to 80% ethyl acetate:pentane; silica was pre-neutralized with a 15% ethyl acetate:pentane + 1% triethylamine mobile phase), ultimately affording the products in a distribution across 5 samples:

1. **16-*anti*** only: 13.2 mg, white solid [20.8% over 2 steps]
2. **16-*anti*** enriched: 6.2 mg, off-white solid, 17.7:1 *anti*:*syn* mix
3. middle fractions: 6.8 mg, yellow oily solid, 1:1.3 *anti*:*syn* mix
4. **11-*syn*** enriched: 3.2 mg, light yellow oil, 1:13.9 *anti*:*syn* mix
5. **11-*syn*** only: 5.4 mg, clear, colorless oil [8.5% over 2 steps]

The remaining mixed fraction served as a supply of pure isomers over the evolution of the project. The collect amount of each isomer collected from this reaction is thus: 22.2 mg **16-*anti*** (35.1% over 2 steps) and 12.6 mg **11-*syn*** (19.8% over 2 steps).

*Characterization Data for anti-C7-propyl 1-aminoNB analog **16-anti**:*
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.95 (s, 1H, pyrazole), 7.16-7.14 (m, 1H, Ar), 7.12-7.08 (m, 3H, Ar), 6.87 (t, 1H, J_{HF} = 54.2 Hz, -CHF_2), 6.84 (br s, 1H, -NH), 3.91 (s, 3H, pyrazole -NMe), 3.15 (d, 1H, *J* = 3.6 Hz, C4), 2.57 (dd, 1H, *J* = 10.2, 2.6 Hz, C7), 2.07 (*app.* tt, 1H, *J* = 11.5, 3.9 Hz, C3-eq), 2.00 (*app.* td, 1H, *J* = 10.9, 3.8 Hz, C2-eq), 1.67-1.63 (m, 1H, C2-ax), 1.44-1.38 (m, 1H, C7-$CH_2CH_2CH_3$), 1.36-1.27 (m, 2H, C7-$CH_2CH_2CH_3$, C7-$CH_2CH_2CH_3$), 1.30-1.24 (m, 1H, C3-ax), 1.21-1.14 (m, 2H, C7-$CH_2CH_2CH_3$), 0.92 (t, 1H, *J* = 7.1 Hz, C7-$CH_2CH_2CH_3$) ppm
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 161.0, 147.5, 146.2, 142.7 (t, J_{CF} = 28.8 Hz), 135.7, 126.0, 125.7, 120.9, 118.9, 117.5, 112.2 (t, J_{CF} = 232.7 Hz), 68.4, 61.2, 43.7, 39.6, 30.2, 28.3, 24.9, 21.0, 14.6 ppm
^{19}F NMR ($CDCl_3$, 376 MHz): δ = -108.4 (*app.* dd, *J* = 54.2, 4.2 Hz) ppm
HRMS (ESI+, *m/z)* calculated for $C_{20}H_{24}F_2N_3O^+$: 360.1882, Found: 360.1883.

R_f = 0.50 (70% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

*Characterization Data for syn-C7-propyl 1-aminoNB analog **11-syn**:*
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.98 (s, 1H, pyrazole), 7.21-7.15 (m, 4H, Ar), 6.98 (br s, 1H, -NH), 6.86 (t, 1H, J_{HF} = 54.2 Hz, -CHF_2), 3.94 (s, 3H, pyrazole -NMe), 3.18 (d, 1H, *J* = 3.9 Hz, C4), 2.79 (*app*. td, 2H, *J* = 11.0, 4.1 Hz, C7, C2-eq), 2.13 (*app.* tt, 1H, *J* = 11.2, 4.3 Hz, C3-eq), 1.46 (ddd, 1H, *J* = 11.3, 9.4, 4.4 Hz, C2-ax), 1.30-1.24 (m, 1H, C3-ax), 1.26-1.19 (m, 2H, C7-$CH_2CH_2CH_3$), 1.07-1.02 (m, 1H, C7-$CH_2CH_2CH_3$), 0.77 (t, 1H, *J* = 7.4 Hz, C7-$CH_2CH_2CH_3$), 0.61 (dtd, 1H, *J* = 13.6, 10.2, 5.4 Hz, C7-$CH_2CH_2CH_3$) ppm
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 161.2, 144.6, 144.6, 142.4 (t, J_{CF} = 29.0 Hz), 135.9, 126.6, 126.0, 118.6, 117.7, 112.4 (t, J_{CF} = 232.4 Hz), 69.8, 62.0, 44.8, 39.6, 30.1, 28.0, 27.2, 21.5, 14.5 ppm
Note: Based on analogy to related scaffolds, the 144.6 ppm resonance is assumed to be two overlapping signals.
^{19}F NMR ($CDCl_3$, 376 MHz): δ = -107.8 (*app.* dd, *J* = 54.2, 3.5 Hz) ppm
HRMS (ESI+, *m/z)* calculated for $C_{20}H_{24}F_2N_3O^+$: 360.1882, Found: 360.1885.
R_f = 0.55 (70% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

Figure S35: ^{1}H NMR (700 MHz, $CDCl_3$) for 16-*anti*

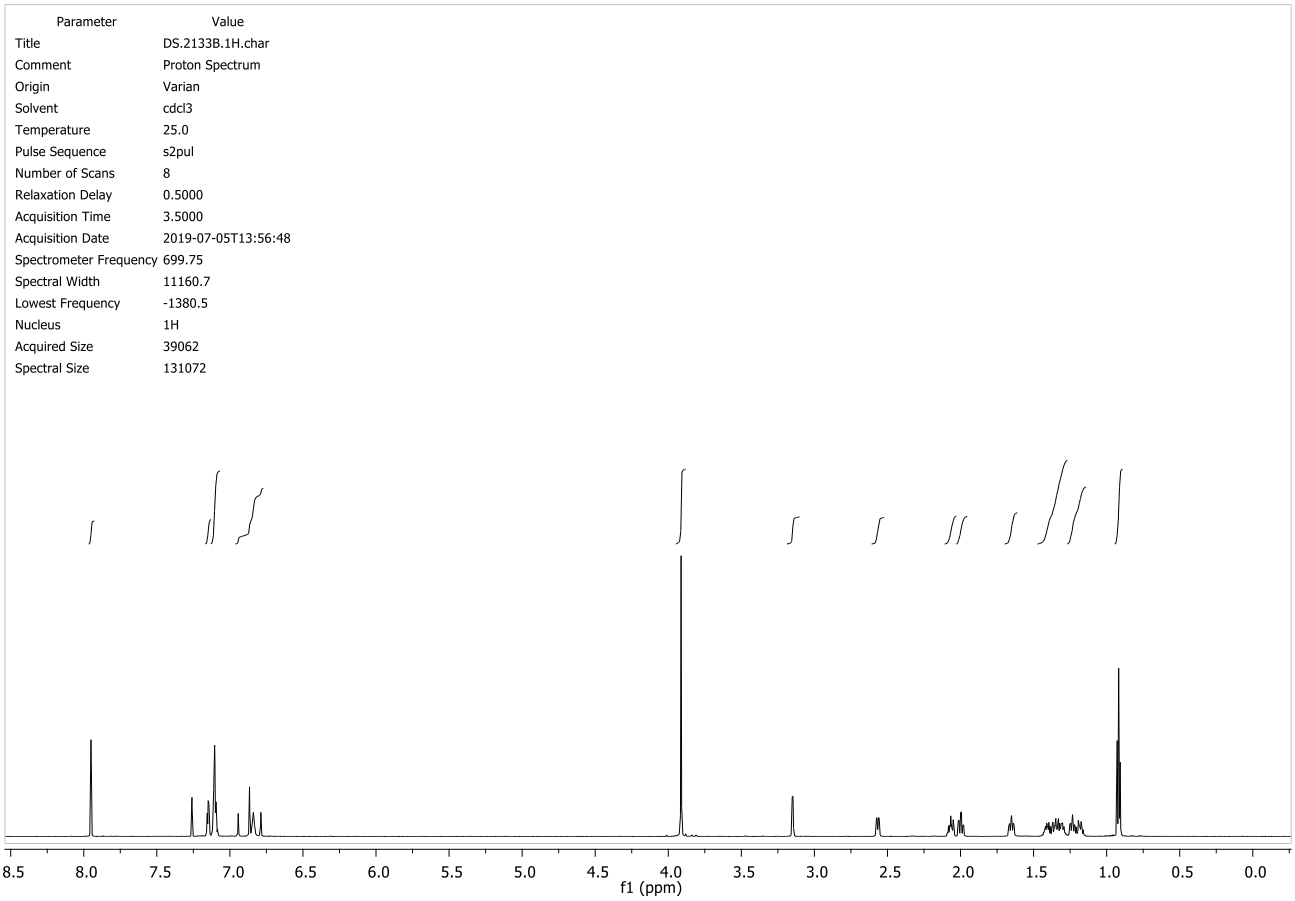


Figure S36: ^{13}C NMR (176 MHz, $CDCl_3$) for 16-*anti*

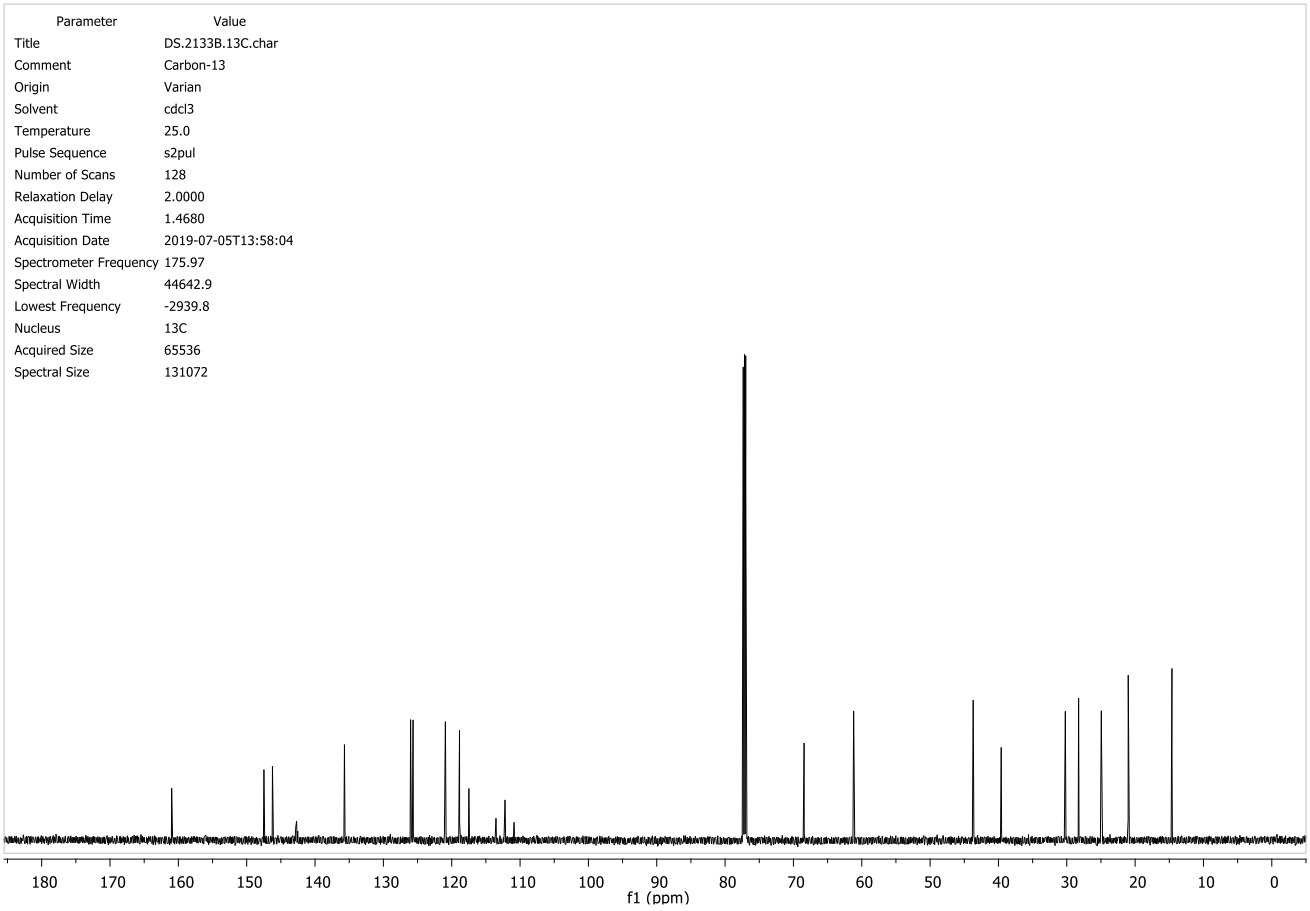


Figure S37: ^{19}F NMR (376 MHz, $CDCl_3$) for 16-*anti*

Parameter	Value
Title	DS.2133B.19F
Comment	Fluorine-19
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Number of Scans	8
Relaxation Delay	1.0000
Acquisition Time	0.7340
Acquisition Date	2019-07-05T15:52:31
Spectrometer Frequency	375.91
Spectral Width	89285.7
Lowest Frequency	-76597.5
Nucleus	19F
Acquired Size	65536
Spectral Size	131072

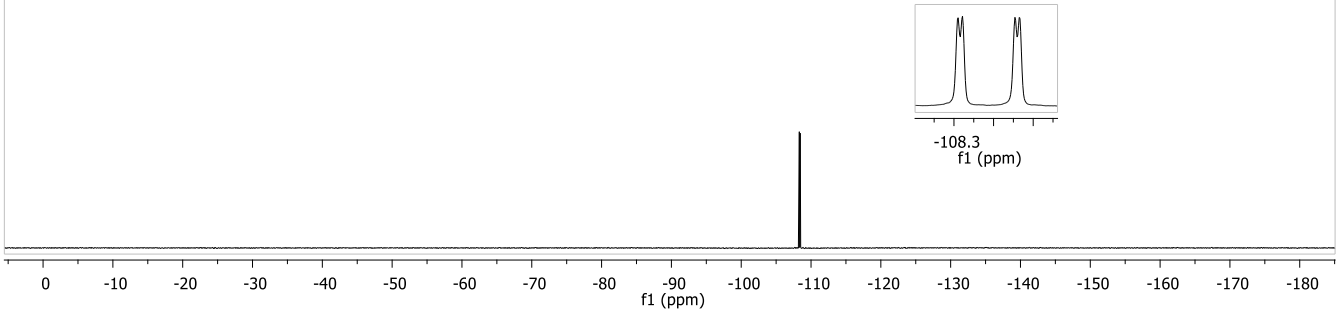


Figure S38: ^{1}H NMR (700 MHz, $CDCl_3$) for 11-*syn*

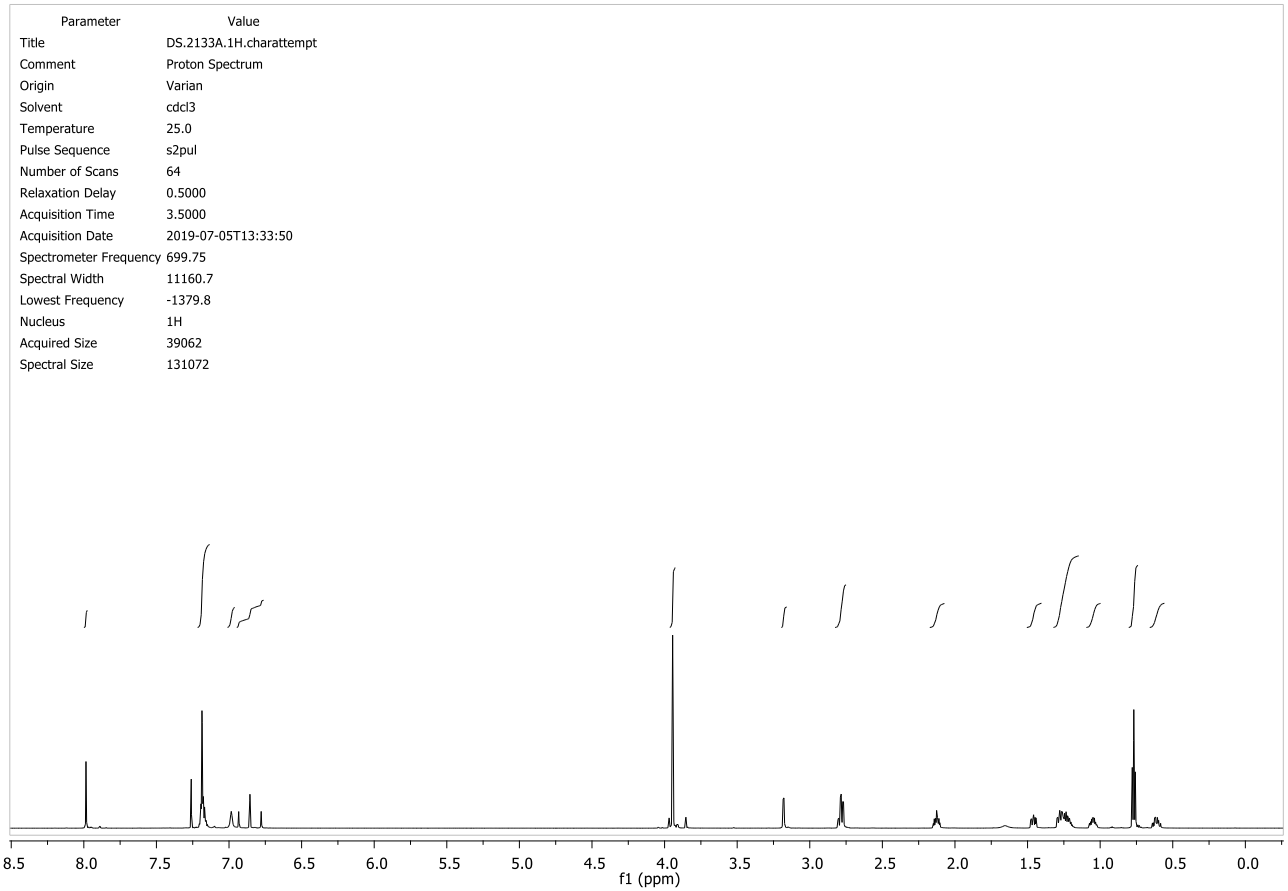


Figure S39: ^{13}C NMR (176 MHz, $CDCl_3$) for 11-*syn*

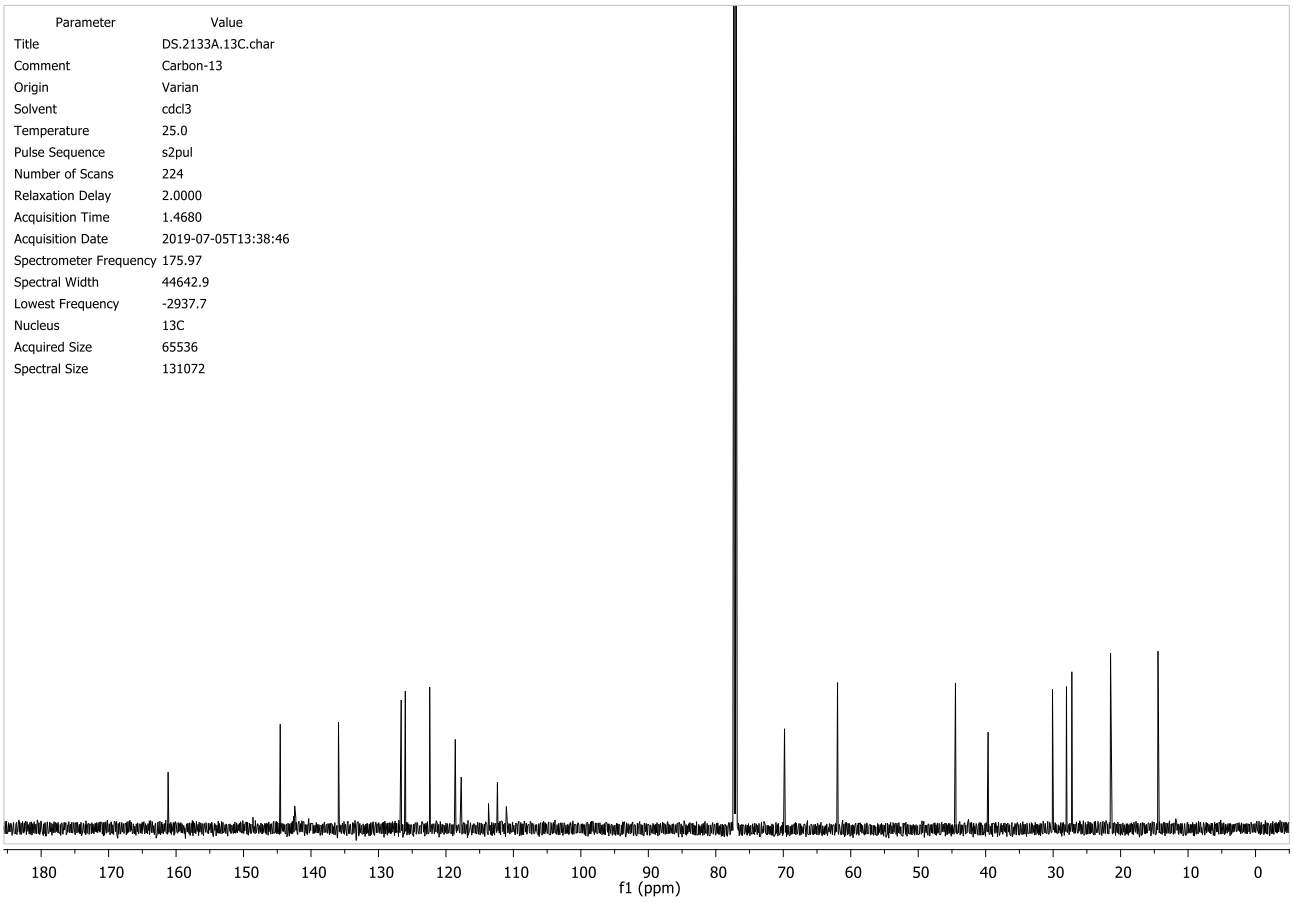
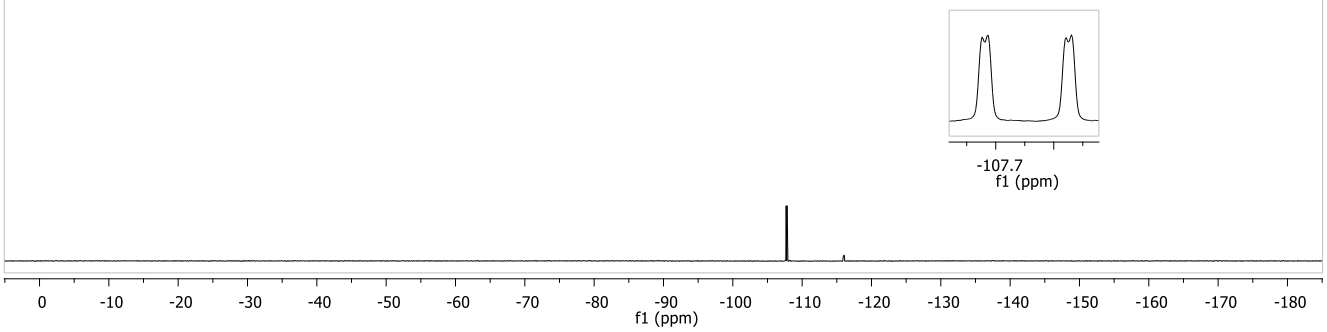
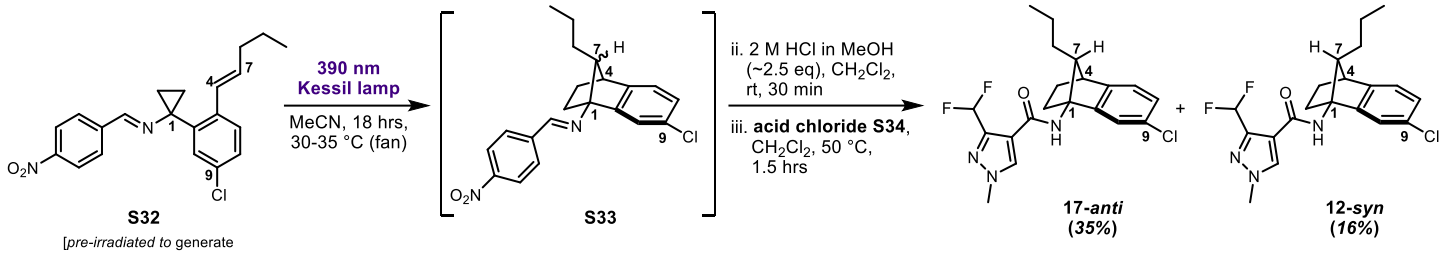


Figure S40: ^{19}F NMR (376 MHz, $CDCl_3$) for 11-*syn*

Parameter	Value
Title	DS.2133A.19F.char1
Comment	Fluorine-19
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Number of Scans	16
Relaxation Delay	1.0000
Acquisition Time	0.7340
Acquisition Date	2019-07-05T15:46:07
Spectrometer Frequency	375.91
Spectral Width	89285.7
Lowest Frequency	-76597.5
Nucleus	19F
Acquired Size	65536
Spectral Size	131072





Procedure for C9-chloro-C7-propyl 1-aminoNB analogs 17-*anti* and 12-*syn*

The requisite Schiff base-protected aminocyclopropane **S32** employed for this procedure was a mixture of the cyclopropylimine and the Schiff base-protected 1-aminonorbornanes **S33** generated in a prior irradiation and isolation procedure; the starting mixture was 38% converted to the 1-aminoNB products **S33**, which were in a 2.0:1 *anti*:*syn* mix (238 mg total; 0.65 mmol total). This material was dissolved in dry acetonitrile (6.5 mL), degassed with three freeze-pump-thaw cycles, and irradiated for 18 hrs while cooling with a fan (using the protocol described in Section II.C).

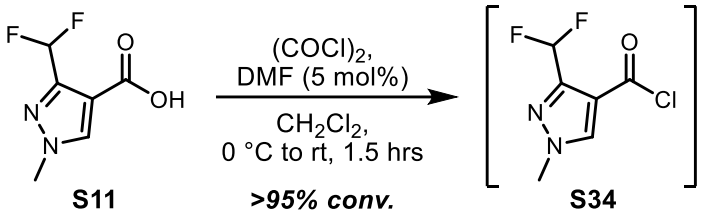
The crude reaction mixture was acidified via the addition of 80 μL 2 M HCl in MeOH (~ 0.2 mmol MeOH and 0.16 mmol HCl; prepared from AcCl and dry MeOH). After 20 min at room temp, a freshly prepared stock of acid chloride **S34** in 4.9 mL CH_2Cl_2 (0.97 mmol; see below for preparation) was added in one portion. The vial was then flushed with Ar and sealed before heating to 50 °C for 1.5 hrs. Upon cooling to room temp, the reaction mixture was quenched by pouring into 50 mL of 1:1 sat. $NaHCO_3$:1 M NaOH, followed by dilution with 25 mL ethyl acetate. The phases were separated. The aqueous phase was extracted with three 25 mL portions of ethyl acetate. The combined organics were then washed with 50 mL brine containing 2 drops 6 M NaOH (aq.), dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under vacuum. The crude residue was purified via flash chromatography over silica (10 to 70% ethyl acetate:hexanes, increasing in 10% increments; loaded crude residue with PhMe; silica was pre-neutralized by treatment with 10% ethyl acetate:hexanes + 1% NEt_3). Collected the products separately: 89.0 mg of carboxamide **17-*anti*** as a white solid (35.0% yield), and 39.5 mg of carboxamide **12-*syn*** as a slightly yellow solid (15.5% yield).

A portion of carboxamide **12-*syn*** was collected as a mixture with the methyl ester by product of the acid chloride reagent **S34**. This material could be recovered by saponification of the methyl ester impurity.

Note: This procedure clearly differs from the other protocols. This was a preliminary attempt at a one-pot, multi-step sequence that is envisioned to facilitate the transition to continuous flow processing. Efforts to optimize this sequence are on-going and will be reported in due course, but this specific reaction scheme is illustrative of the potential.

*Characterization Data for anti-C7-propyl 1-aminoNB analog **17-anti**:*
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.97 (s, 1H, pyrazole), 7.08-7.06 (m, 3H, Ar), 6.85 (t, 1H, J_{HF} = 54.2 Hz, -CHF_2), 6.83 (br s, 1H, -NH), 3.93 (s, 3H, pyrazole -NMe), 3.13 (d, 1H, J = 3.5 Hz, C4), 2.61 (d, 1H, J = 8.5 Hz, C7), 2.06 (*app.* tt, 1H, J = 11.1, 3.8 Hz, C3-eq), 1.96 (*app*. td, 1H, J = 10.9, 3.7 Hz, C2-eq), 1.65-1.59 (m, 1H, C2-ax), 1.44-1.26 (m, 3H, C7-Pr), 1.23-1.10 (m, 1H, C3-ax, C7-C$H_2$$CH_2CH_3$), 0.91 (t, 1H, J = 6.9 Hz, C7-$CH_2CH_2CH_3$) ppm
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 160.9, 149.3, 144.6, 142.6 (t, J_{CF} = 29.1 Hz), 135.9, 131.3, 126.1, 122.2, 119.6, 117.2, 112.3 (t, J_{CF} = 232.6 Hz), 68.4, 61.0, 43.3, 39.6, 30.1, 28.1, 24.7, 20.9, 14.6 ppm
^{19}F NMR ($CDCl_3$, 376 MHz): δ = -108.1 (*app.* dd, J = 54.2, 3.8 Hz) ppm
HRMS (ESI+, *m/z)* calculated for $C_{20}H_{23}ClF_2N_3O^+$: 394.1492, Found: 394.1495.
R_f = 0.40 (50% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

*Characterization Data for syn-C7-propyl 1-aminoNB analog **12-syn**:*
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.99 (s, 1H, pyrazole), 7.17-7.15 (m, 1H, Ar), 7.15-7.08 (m, 2H, Ar), 6.89 (br s, 1H, -NH), 6.85 (t, 1H, J_{HF} = 54.2 Hz, -CHF_2), 3.94 (s, 3H, pyrazole -NMe), 3.16 (d, 1H, J = 3.8 Hz, C4), 2.67 (*app*. td, 2H, J = 11.4, 4.0 Hz, C7, C2-eq), 2.12 (*app.* tt, 1H, J = 11.2, 4.3 Hz, C3-eq), 1.65-1.58 (m, 1H, C2-ax), 1.30-1.16 (m, 3H, C3-ax, C7-CH_2CH_2CH_3), 1.11-1.03 (m, 1H, C7-C$H_2CH_2CH_3$), 0.78 (t, 1H, J = 7.3 Hz, C7-$CH_2CH_2CH_3$), 0.67-0.58 (m, 1H, C7-C$H_2CH_2CH_3$) ppm
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 161.3, 146.6, 143.0, 142.5 (t, J_{CF} = 28.9 Hz), 136.0, 131.6, 126.6, 123.6, 120.1, 117.5, 112.4 (t, J_{CF} = 232.6 Hz), 69.8, 62.5, 44.0, 39.6, 30.4, 27.9, 27.2, 21.4, 14.4 ppm
^{19}F NMR ($CDCl_3$, 376 MHz): δ = -107.6 (*app.* dd, J = 54.2, 3.7 Hz) ppm
HRMS (ESI+, *m/z)* calculated for $C_{20}H_{23}ClF_2N_3O^+$: 394.1492, Found: 394.1497.
R_f = 0.45 (50% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV



S11 ***>95% conv.*** **S34**

Procedure for acid chloride S34

3-(Difluoromethyl)-1-methyl-1H-pyrazole-4-carboxylic acid (**S11**; 321 mg, 1.8 mmol) was dissolved in 9.0 mL dry CH_2Cl_2, then cooled to 0 °C. Oxalyl chloride (150 μL, 1.8 mmol) was added dropwise, followed by the addition of 5 μL dry DMF. The reaction mixture was stirred 10 min at 0 °C before removing the cold bath and stirring an additional 1.5 hrs at room temp; reaction vessel was vented periodically in first 30 min following DMF addition to account for gas evolution. This stock solution was prepared immediate prior to use and is amenable to scaling to larger or smaller scales if needed. A small aliquot can be removed to assess conversion (generally >95% by ^{1}H NMR analysis).

Figure S41: ^{1}H NMR (700 MHz, $CDCl_3$) for 17-*anti*

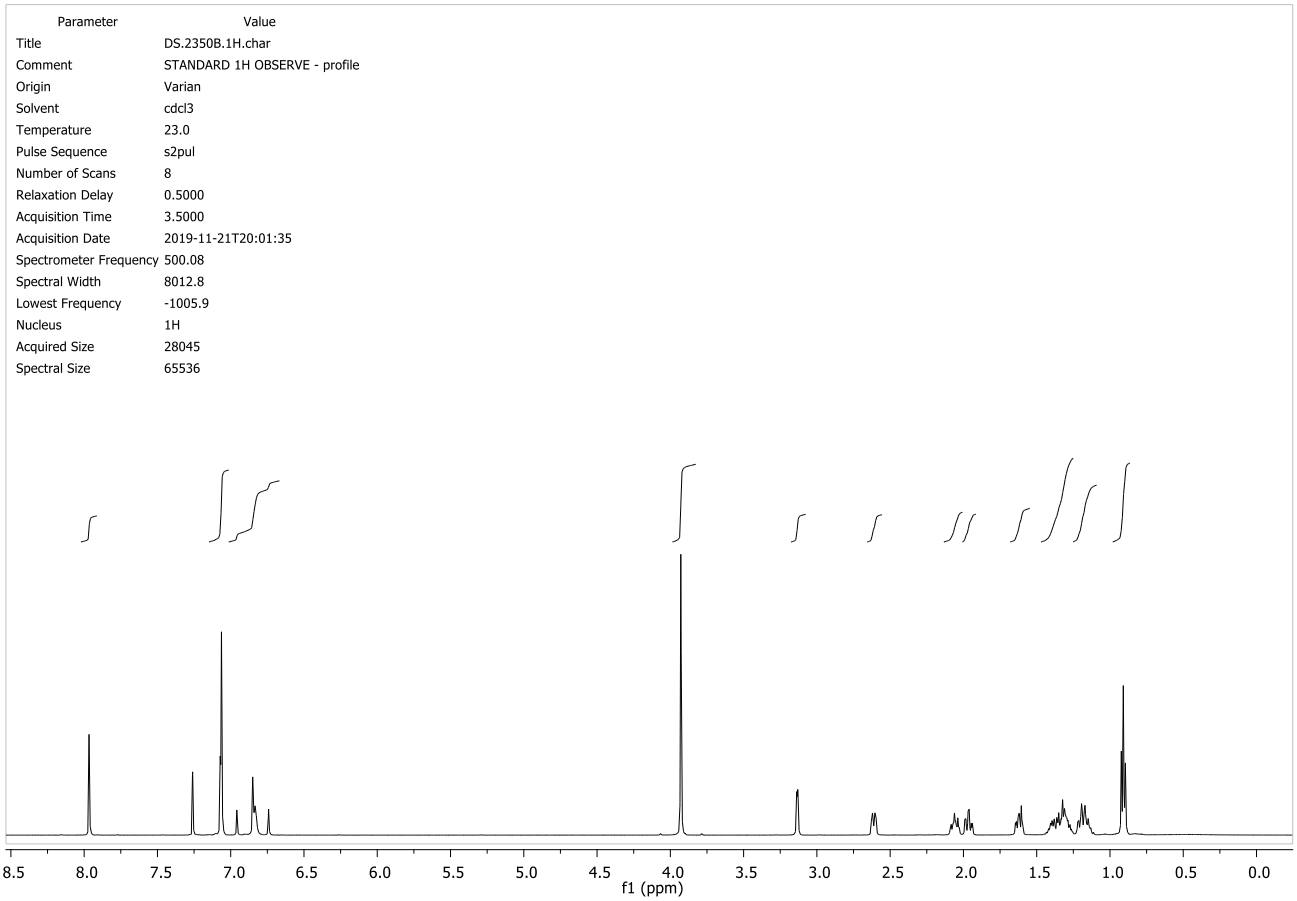


Figure S42: ^{13}C NMR (176 MHz, $CDCl_3$) for 17-*anti*

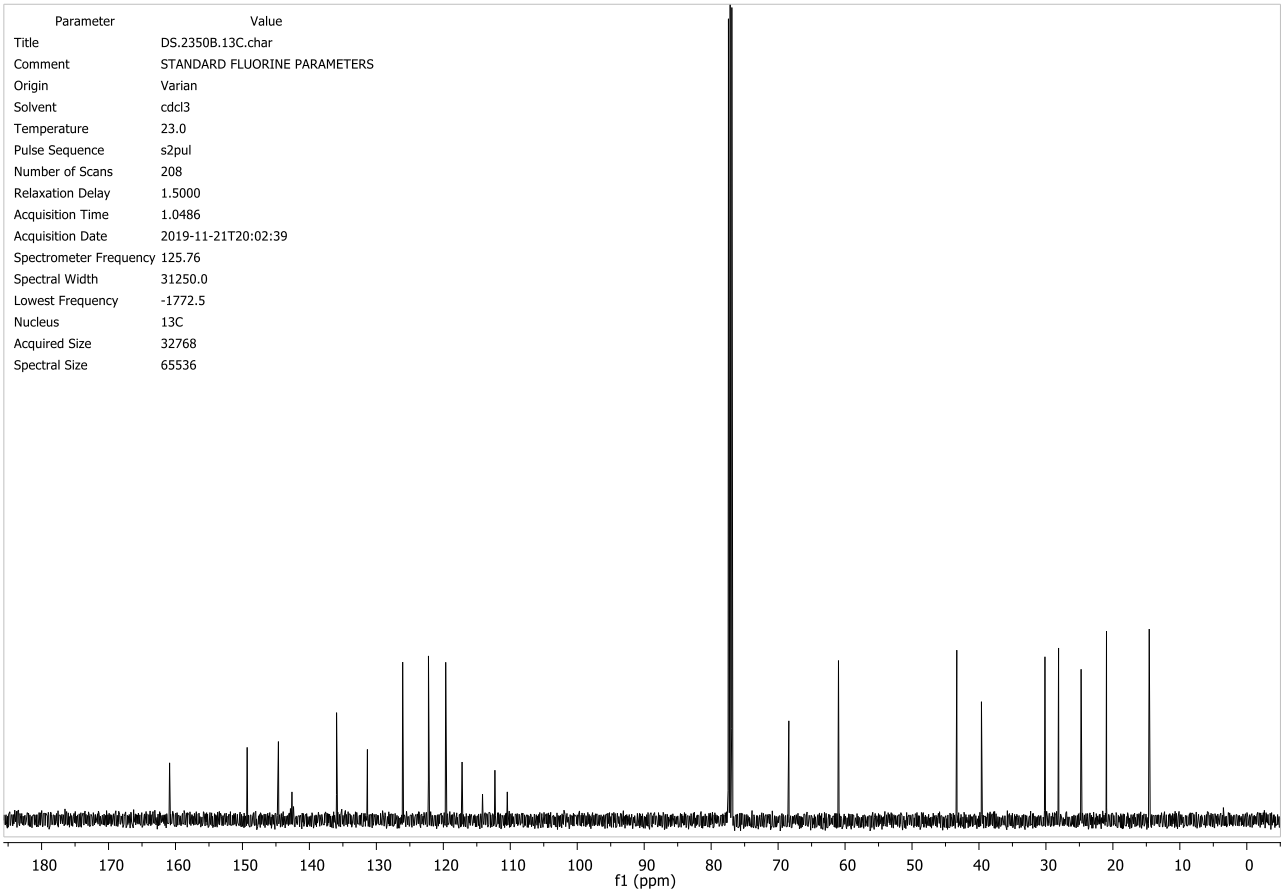


Figure S43: ^{19}F NMR (376 MHz, $CDCl_3$) for 17-*anti*

Parameter	Value
Title	DS.2350B.19F.char
Comment	STANDARD FLUORINE PARAMETERS
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Number of Scans	16
Relaxation Delay	1.0000
Acquisition Time	0.6029
Acquisition Date	2019-11-21T19:57:27
Spectrometer Frequency	470.50
Spectral Width	108695.6
Lowest Frequency	-94344.2
Nucleus	19F
Acquired Size	65536
Spectral Size	131072

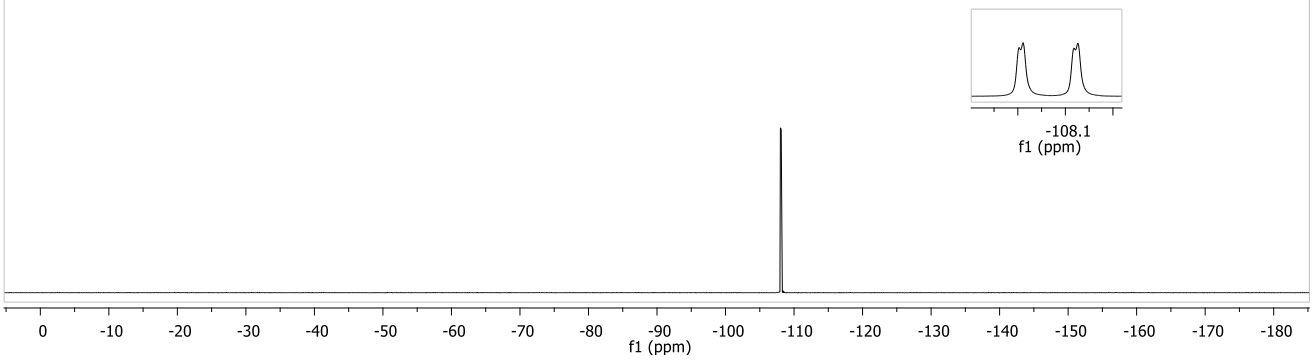


Figure S44: ^{1}H NMR (700 MHz, $CDCl_3$) for 12-*syn*

Parameter	Value
Title	DS.2350A.1H.char
Comment	STANDARD FLUORINE PARAMETERS
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Number of Scans	8
Relaxation Delay	0.5000
Acquisition Time	3.5000
Acquisition Date	2019-11-21T19:43:49
Spectrometer Frequency	500.08
Spectral Width	8012.8
Lowest Frequency	-1005.9
Nucleus	1H
Acquired Size	28045
Spectral Size	65536

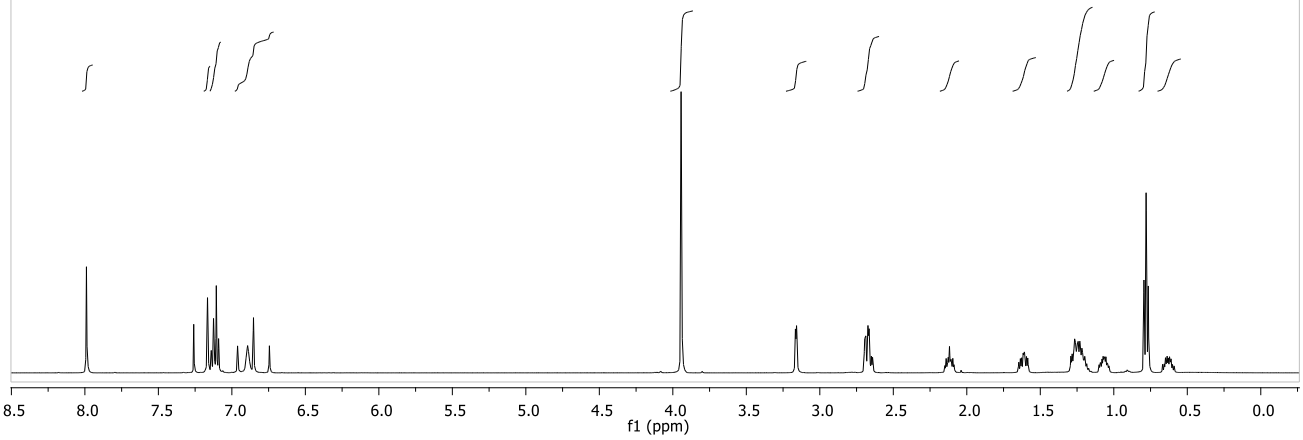


Figure S45: ^{13}C NMR (176 MHz, $CDCl_3$) for 12-*syn*

Parameter	Value
Title	DS.2350A.13C.char
Comment	STANDARD FLUORINE PARAMETERS
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Number of Scans	144
Relaxation Delay	1.5000
Acquisition Time	1.0486
Acquisition Date	2019-11-21T19:45:04
Spectrometer Frequency	125.76
Spectral Width	31250.0
Lowest Frequency	-1772.0
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

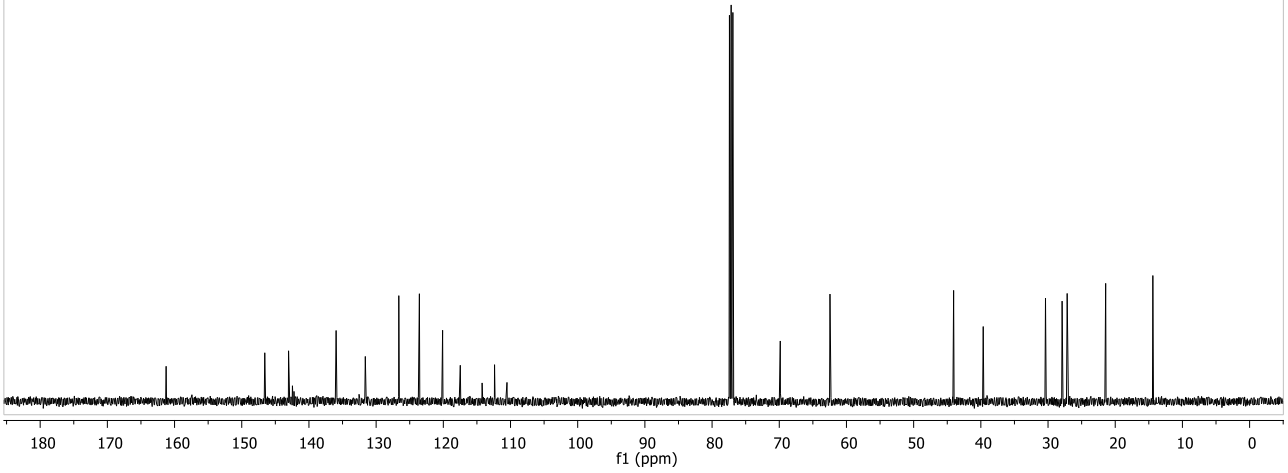
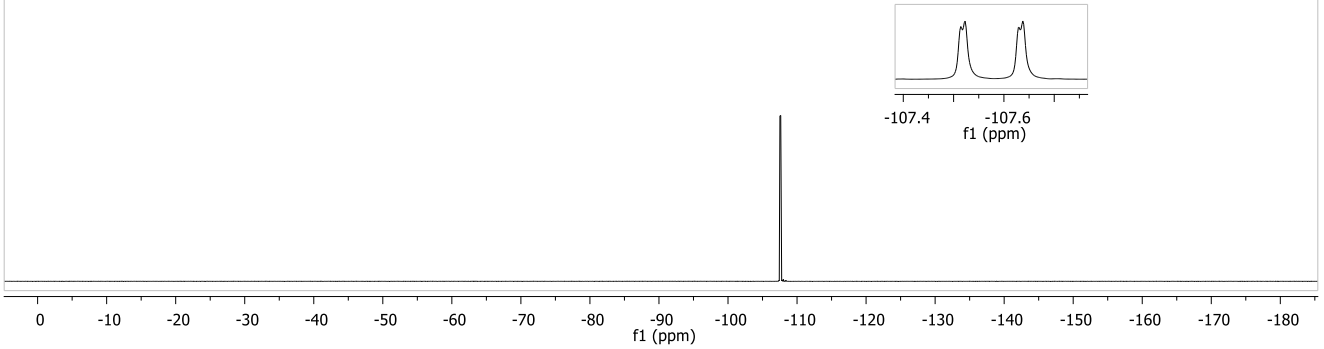
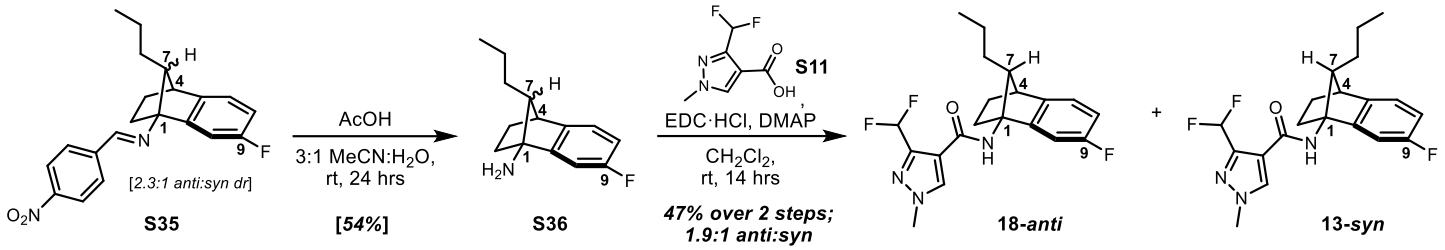


Figure S46: ^{19}F NMR (376 MHz, $CDCl_3$) for 12-*syn*

Parameter	Value
Title	DS.2350A.19F.char
Comment	STANDARD FLUORINE PARAMETERS
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Number of Scans	16
Relaxation Delay	1.0000
Acquisition Time	0.6029
Acquisition Date	2019-11-21T19:52:52
Spectrometer Frequency	470.50
Spectral Width	108695.6
Lowest Frequency	-94344.2
Nucleus	19F
Acquired Size	65536
Spectral Size	131072





Procedure for C9-fluoro-C7-propyl 1-aminoNB analogs 18-*anti* and 13-*syn*

Removal of the Schiff base protecting group was achieved by dissolving the protected 1-aminonorbornane mix (**S35**; 43.2 mg of a 2.3:1 *anti*:*syn* mixture; 123 μmol) in a 3:1 MeCN:H_2O mixture (0.75 mL:0.25 mL) before adding acetic acid (0.25 mL). The reaction mixture was flushed with Ar, capped, and stirred at room temp for 24 hrs. The reaction was diluted with 2 mL water and 2 mL ether. The phases were separated, and the slightly acidic aqueous phase was washed with 2 mL ether two additional times. The aqueous phase was made basic through the addition of 0.5 mL of 6 M NaOH (aq.) then diluted with 2 mL ether. Phases were separated, and the aqueous phase was extracted with 3 portions of ether, 2 mL each. The organic phases from the basic extraction were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The desired 1-aminonorbornanes (**S36**) were obtained as a clear, colorless oil in 53.6% yield (14.4 mg) as a 1.9:1 *anti*:*syn* mixture. Partial characterization provided below.

Diagnostic Data for anti-C7-propyl C1-NH_2 intermediate:
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.05 (d, 1H, *J* = 3.8 Hz, C4), 0.95 (t, 3H, *J* = 7.0 Hz, C7-$CH_2CH_2CH_3$) ppm [*partial line-listing*]
Diagnostic Data for syn-C7-propyl C1-NH_2 intermediate:
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.11 (d, 1H, *J* = 3.9 Hz, C4), 0.81 (d, 3H, *J* = 7.3 Hz, C7-$CH_2CH_2CH_3$) ppm [*partial line-listing*]

1-Aminonorbornane mix **S36** (14.4 mg; 66 μmol) was dissolved in dry dichloromethane (0.70 mL), followed by addition of the carboxylic acid **S11** (17 mg; 97 μmol), DMAP (12 mg; 98 μmol), and EDC·HCl (19 mg; 99 μmol), respectively. The reaction was flushed with Ar, capped, and stirred at room temp 14 hrs. The crude residue was diluted with 4 mL water and 2 mL ethyl acetate. Phases were separated, and the aqueous phase was extracted with 3 portions of ethyl acetate, 2 mL each. The organic phases were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The crude residue was purified with flash chromatography over silica (15 to 75% ethyl acetate:hexanes, increasing in 15% increments; loaded residue with PhMe; silica was pre-neutralized with a 15% ethyl acetate:pentane + 1% triethylamine mobile phase). Collected the desired carboxamides **18-*anti*** and **13-*syn*** as a white solid: 21.9 mg, 88.4% yield (47.4% over two steps).

Subsequent trials of this protocol were exposed to iterative rounds of chromatography over silica as well as trituration from ethyl acetate:hexanes mixtures to generate pure samples of each isomer for biological evaluation.

*Characterization Data for anti-C7-propyl 1-aminoNB analog **18-anti**:*
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.96 (s, 1H, pyrazole), 7.09-7.04 (m, 1H, Ar), 6.84 (t, 1H, J_{HF} = 54.2 Hz, -CHF_2), 6.84-6.80 (m, 1H, Ar), 6.81 (br s, 1H, -NH), 6.79-6.74 (m, 1H, Ar), 3.94 (s, 3H, pyrazole -NMe), 3.14 (d, 1H, *J* = 3.4 Hz, C4), 2.61 (d, 1H, *J* = 9.0 Hz, C7), 2.06 (*app.* tt, 1H, *J* = 11.5, 3.9 Hz, C3-eq), 1.97 (*app*. td, 1H, *J* = 10.6, 2.9 Hz, C2-eq), 1.65-1.59 (m, 1H, C2-ax), 1.44-1.25 (m, 3H, C7-Pr), 1.23-1.11 (m, 1H, C3-ax, C7-$CH_2CH_2CH_3$), 0.92 (t, 1H, *J* = 6.8 Hz, C7-$CH_2CH_2CH_3$) ppm
^{13}C NMR ($CDCl_3$, 126 MHz): δ = 161.6 (d, J_{CF} = 242.5 Hz), 160.9, 149.6 (d, J_{CF} = 7.5 Hz), 142.6 (t, J_{CF} = 28.9 Hz), 141.7 (d, J_{CF} = 2.5 Hz), 135.9, 120.0 (d, J_{CF} = 8.3 Hz), 117.3, 112.3 (d, J_{CF} = 22.3 Hz), 112.3 (t, J_{CF} = 232.5 Hz), 107.1 (d, J_{CF} = 23.4 Hz), 68.6, 61.2, 43.2, 39.6, 30.2, 28.2, 25.0, 21.0, 14.6 ppm
^{19}F NMR ($CDCl_3$, 471 MHz): δ = -108.1 (d, *J* = 54.2 Hz), -116.9 (*app*. td, *J* = 13.5, 8.9 Hz) ppm
HRMS (ESI+, *m/z)* calculated for $C_{20}H_{23}F_3N_3O^+$: 378.1788, Found: 378.1793.
R_f = 0.35 (50% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

*Characterization Data for syn-C7-propyl 1-aminoNB analog **13-syn**:*
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.98 (s, 1H, pyrazole), 7.11 (dd, 1H, *J* = 7.9, 4.9 Hz, Ar), 6.94-6.90 (m, 1H, Ar), 6.90 (br s, 1H, -NH), 6.84 (t, 1H, J_{HF} = 54.2 Hz, -CHF_2), 6.83-6.80 (m, 1H, Ar), 3.95 (s, 3H, pyrazole -NMe), 3.16 (d, 1H, *J* = 3.5 Hz, C4), 2.69 (*app*. td, 2H, *J* = 11.1, 3.9 Hz, C7, C2-eq), 2.12 (*app.* tt, 1H, *J* = 11.2, 4.1 Hz, C3-eq), 1.61-1.54 (m, 1H, C2-ax), 1.31-1.17 (m, 3H, C3-ax, C7-$CH_2CH_2CH_3$), 1.10-1.03 (m, 1H, C7-$CH_2CH_2CH_3$), 0.78 (t, 1H, *J* = 7.3 Hz, C7-$CH_2CH_2CH_3$), 0.67-0.59 (m, 1H, C7-$CH_2CH_2CH_3$) ppm
^{13}C NMR ($CDCl_3$, 126 MHz): δ = 161.8 (d, J_{CF} = 242.8 Hz), 161.2, 146.8 (d, J_{CF} = 7.5 Hz), 142.4 (t, J_{CF} = 29.3 Hz), 139.9 (d, J_{CF} = 2.3 Hz), 136.0, 123.3 (d, J_{CF} = 8.4 Hz), 117.5, 112.8 (d, J_{CF} = 22.1 Hz), 112.4 (t, J_{CF} = 232.5 Hz), 107.5 (d, J_{CF} = 24.0 Hz), 70.1, 62.5, 43.9, 39.6, 30.3, 28.1, 27.2, 21.4, 14.4 ppm
^{19}F NMR ($CDCl_3$, 471 MHz): δ = -107.6 (d, *J* = 54.2 Hz), -116.2 (*app*. dd, *J* = 13.8, 9.0 Hz) ppm

HRMS (ESI+, *m/z)* calculated for $C_{20}H_{23}F_3N_3O^+$: 378.1788, Found: 378.1792.
R_f = 0.45 (50% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

Figure S47: ^{1}H NMR (500 MHz, $CDCl_3$) for 18-*anti*

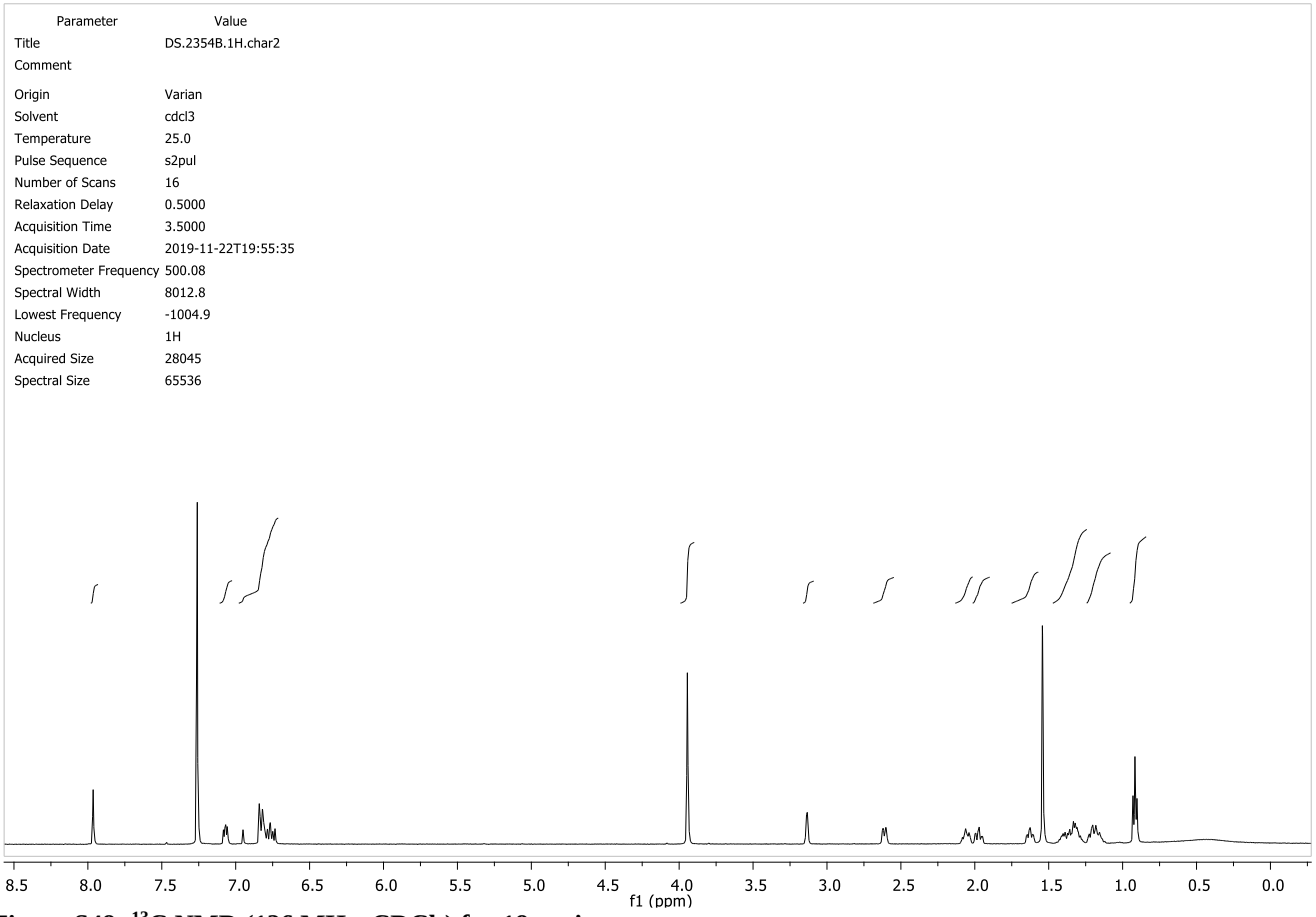


Figure S48: ^{13}C NMR (126 MHz, $CDCl_3$) for 18-*anti*

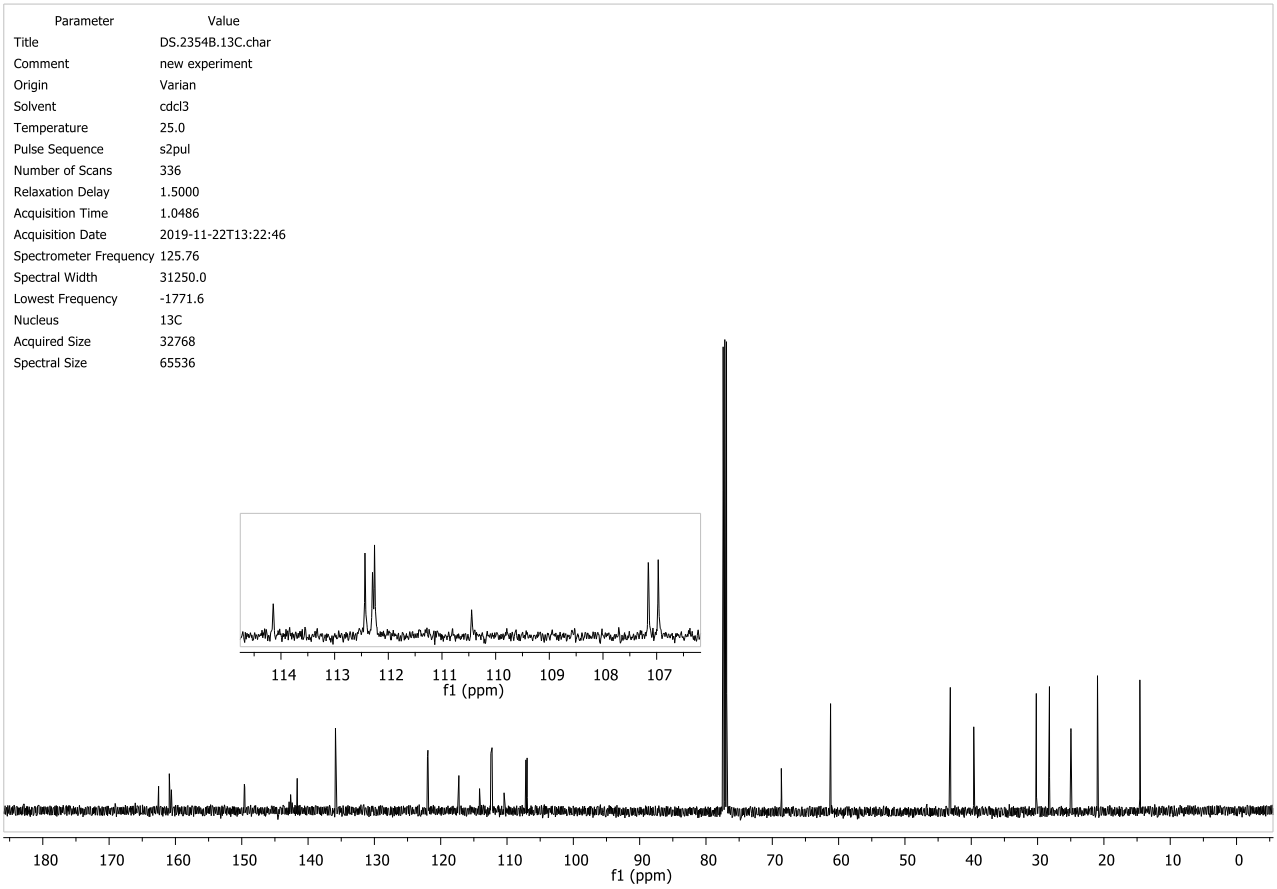


Figure S49: ^{19}F NMR (471 MHz, $CDCl_3$) for 18-*anti*

Parameter	Value
Title	DS.2354B.19F
Comment	STANDARD FLUORINE PARAMETERS
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Number of Scans	8
Relaxation Delay	1.0000
Acquisition Time	0.6029
Acquisition Date	2019-11-22T13:38:42
Spectrometer Frequency	470.50
Spectral Width	108695.6
Lowest Frequency	-94344.2
Nucleus	19F
Acquired Size	65536
Spectral Size	131072

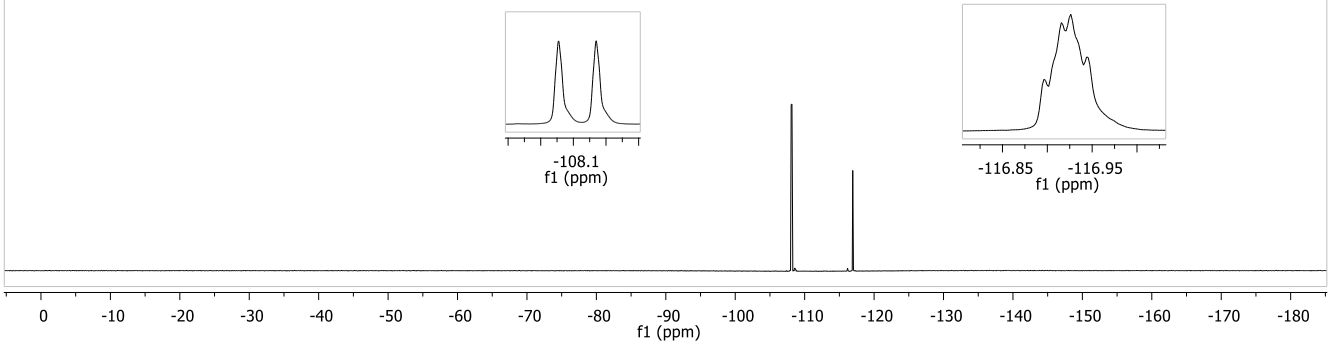


Figure S50: ^{1}H NMR (500 MHz, $CDCl_3$) for 13-*syn*

Parameter	Value
Title	DS.2354A.1H.char2
Comment	new experiment
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Number of Scans	16
Relaxation Delay	0.5000
Acquisition Time	3.5000
Acquisition Date	2019-11-22T19:49:00
Spectrometer Frequency	500.08
Spectral Width	8012.8
Lowest Frequency	-1005.9
Nucleus	1H
Acquired Size	28045
Spectral Size	65536

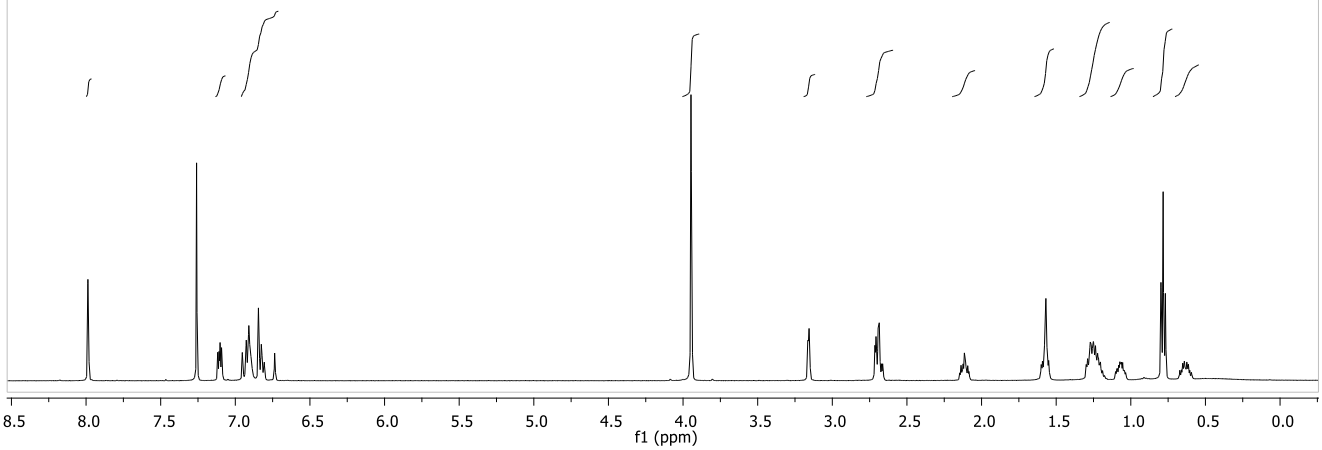


Figure S51: ^{13}C NMR (126 MHz, $CDCl_3$) for 13-*syn*

Parameter	Value
Title	DS.2354A.13C.char
Comment	STANDARD FLUORINE PARAMETERS
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Number of Scans	160
Relaxation Delay	1.5000
Acquisition Time	1.0486
Acquisition Date	2019-11-22T13:10:26
Spectrometer Frequency	125.76
Spectral Width	31250.0
Lowest Frequency	-1772.9
Nucleus	13C
Acquired Size	32768
Spectral Size	65536

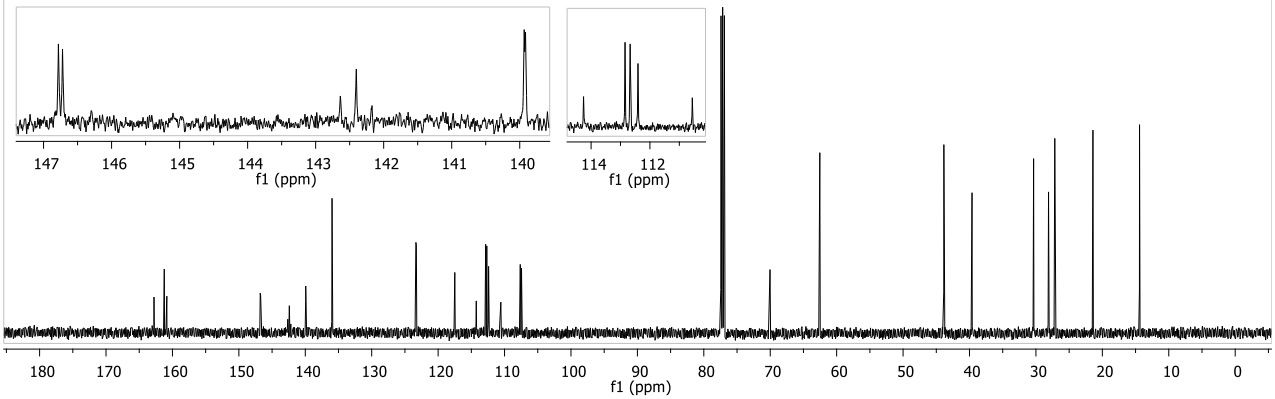
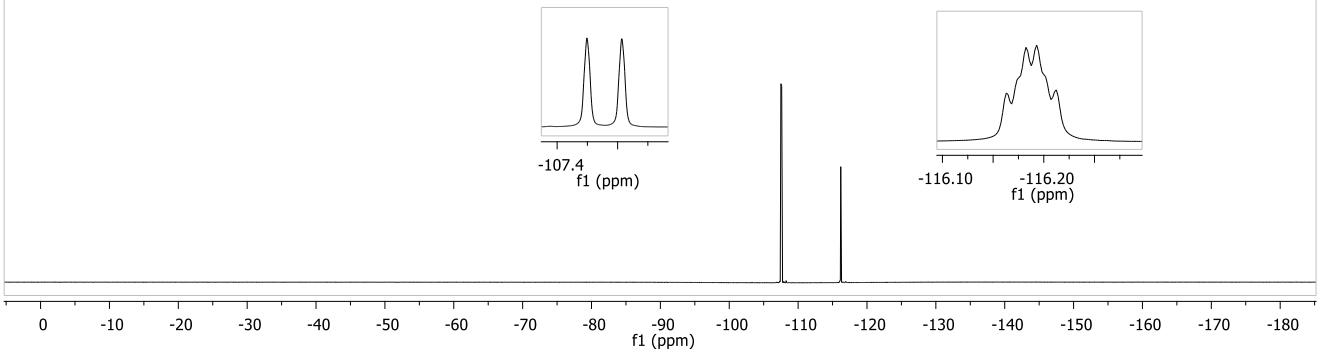
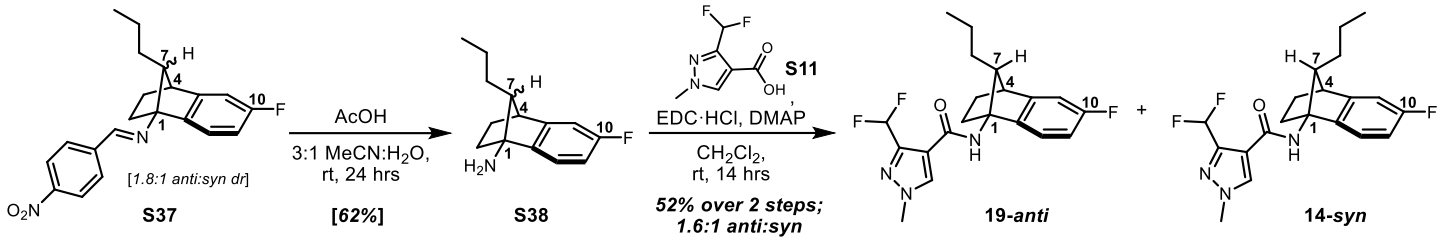


Figure S52: ^{19}F NMR (471 MHz, $CDCl_3$) for 13-*syn*

Parameter	Value
Title	DS.2354A.19F
Comment	STANDARD FLUORINE PARAMETERS
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Number of Scans	8
Relaxation Delay	1.0000
Acquisition Time	0.6029
Acquisition Date	2019-11-22T13:05:10
Spectrometer Frequency	470.50
Spectral Width	108695.6
Lowest Frequency	-94344.2
Nucleus	19F
Acquired Size	65536
Spectral Size	131072





Procedure for C10-fluoro-C7-propyl 1-aminoNB analogs 19-*anti* and 14-*syn*

Removal of the Schiff base protecting group was achieved by dissolving the protected 1-aminonorbornane mix (**S37**; 37.9 mg of a 1.8:1 *anti*:*syn* mixture; 108 μmol) in a 3:1 MeCN:H_2O mixture (0.75 mL:0.25 mL) before adding acetic acid (0.25 mL). The reaction mixture was flushed with Ar, capped, and stirred at room temp for 24 hrs. The reaction was diluted with 2 mL water and 2 mL ether. The phases were separated, and the slightly acidic aqueous phase was washed with 2 mL ether two additional times. The aqueous phase was made basic through the addition of 0.5 mL of 6 M NaOH (aq.) then diluted with 2 mL ether. Phases were separated, and the aqueous phase was extracted with 3 portions of ether, 2 mL each. The organic phases from the basic extraction were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The desired 1-aminonorbornanes (**S38**) were obtained as a clear, colorless oil in 61.5% yield (14.5 mg) as a 1.6:1 *anti*:*syn* mixture. Partial characterization is provided below.

Diagnostic Data for anti-C7-propyl C1-NH_2 intermediate:
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.05 (d, 1H, *J* = 3.9 Hz, C4), 0.95 (t, 3H, *J* = 7.0 Hz, C7-$CH_2CH_2CH_3$) ppm [*partial line-listing*]

Diagnostic Data for syn-C7-propyl C1-NH_2 intermediate:
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.11 (d, 1H, *J* = 4.1 Hz, C4), 0.81 (d, 3H, *J* = 7.3 Hz, C7-$CH_2CH_2CH_3$) ppm [*partial line-listing*]

1-Aminonorbornane mix **S38** (14.5 mg; 66 μmol) was dissolved in dry dichloromethane (0.70 mL), followed by addition of the carboxylic acid **S11** (17 mg; 97 μmol), DMAP (12 mg; 98 μmol), and EDC·HCl (19 mg; 99 μmol), respectively. The reaction was flushed with Ar, capped, and stirred at room temp 14 hrs. The crude residue was diluted with 4 mL water and 2 mL ethyl acetate. Phases were separated, and the aqueous phase was extracted with 3 portions of ethyl acetate, 2 mL each. The organic phases were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The crude residue was purified with flash chromatography over silica (15 to 75% ethyl acetate:pentane, increasing in 15% increments; loaded residue with PhMe; silica was pre-neutralized with a 15% ethyl acetate:pentane + 1% triethylamine mobile phase). Collected the desired carboxamides **19-*anti*** and **14-*syn*** as a white solid: 21.1 mg, 84.6% yield (52.0% over two steps).

Subsequent trials of this protocol were exposed to iterative rounds of chromatography over silica as well as trituration from ethyl acetate:hexanes mixtures to generate pure samples of each isomer for biological evaluation.

*Characterization Data for anti-C7-propyl 1-aminoNB analog **19-anti**:*
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.95 (s, 1H, pyrazole), 7.03 (dd, 1H, *J* = 8.0, 5.0 Hz, Ar), 6.87 (dd, 1H, *J* = 8.4, 2.1 Hz, Ar), 6.85 (t, 1H, J_{HF} = 54.2 Hz, -CHF_2), 6.82 (br s, 1H, -NH), 6.77 (ddd, 1H, *J* = 10.2, 8.2, 2.3 Hz, Ar), 3.93 (s, 3H, pyrazole -NMe), 3.14 (d, 1H, *J* = 3.6 Hz, C4), 2.59 (d, 1H, *J* = 9.8 Hz, C7), 2.10-2.02 (m, 1H, C3-eq), 1.98 (*app*. td, 1H, *J* = 10.8, 3.8 Hz, C2-eq), 1.66-1.58 (m, 1H, C2-ax), 1.44-1.26 (m, 3H, C7-Pr), 1.25-1.19 (m, 1H, C3-ax), 1.20-1.11 (m, 1H, C7-C$H_2$$CH_2CH_3$), 0.91 (t, 1H, *J* = 6.9 Hz, C7-$CH_2CH_2CH_3$) ppm
^{13}C NMR ($CDCl_3$, 126 MHz): δ = 161.0, 161.7 (d, J_{CF} = 242.4 Hz), 148.1 (d, J_{CF} = 7.8 Hz), 142.9 (d, J_{CF} = 2.2 Hz), 142.6 (t, J_{CF} = 29.6 Hz), 135.8, 120.1 (d, J_{CF} = 8.6 Hz), 117.4, 112.3 (t, J_{CF} = 232.5 Hz), 112.0 (d, J_{CF} = 22.4 Hz), 108.8 (d, J_{CF} = 22.9 Hz), 68.0, 61.1, 43.9, 39.6, 30.3, 28.2, 24.8, 21.0, 14.6 ppm
^{19}F NMR ($CDCl_3$, 471 MHz): δ = -108.1 (d, *J* = 54.2 Hz), -117.2 to -117.4 (m) ppm
HRMS (ESI+, *m/z)* calculated for $C_{20}H_{23}F_3N_3O^+$: 378.1788, Found: 378.1792.
R_f = 0.45 (50% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

*Characterization Data for syn-C7-propyl 1-aminoNB analog **14-syn**:*
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.98 (s, 1H, pyrazole), 7.11 (dd, 1H, *J* = 8.0, 4.8 Hz, Ar), 6.94 (br s, 1H, -NH), 6.91 (dd, 1H, *J* = 8.3, 2.3 Hz, Ar), 6.87-6.82 (m, 1H, Ar), 6.84 (t, 1H, J_{HF} = 54.2 Hz, -CHF_2), 3.94 (s, 3H, pyrazole -NMe), 3.17 (d, 1H, *J* = 3.9 Hz, C4), 2.72 (*app*. td, 2H, *J* = 11.1, 4.0 Hz, C7, C2-eq), 2.12 (*app.* tt, 1H, *J* = 11.1, 4.2 Hz, C3-eq), 1.51 (ddd, 1H, *J* = 11.3, 9.5, 4.3 Hz, C2-ax), 1.31-1.18 (m, 3H, C3-ax, C7-CH_2CH_2CH_3), 1.10-1.02 (m, 1H, C7-C$H_2CH_2CH_3$), 0.78 (t, 1H, *J* = 7.3 Hz, C7-$CH_2CH_2CH_3$), 0.67-0.59 (m, 1H, C7-C$H_2CH_2CH_3$) ppm

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 162.1 (d, J_{CF} = 243.4 Hz), 161.2, 146.8 (d, J_{CF} = 7.9 Hz), 142.3 (t, J_{CF} = 29.2 Hz), 140.1 (d, J_{CF} = 2.4 Hz), 136.0, 120.0 (d, J_{CF} = 8.7 Hz), 117.6, 112.5 (t, J_{CF} = 232.4 Hz), 112.2 (d, J_{CF} = 22.4 Hz), 110.4 (d, J_{CF} = 22.8 Hz), 69.3, 62.2, 44.6, 39.6, 30.4, 27.9, 27.2, 21.4, 14.4 ppm
^{19}F NMR ($CDCl_3$, 471 MHz): δ = -107.5 (d, J = 54.2 Hz), -116.3 (*app*. td, J = 9.0, 4.9 Hz) ppm
HRMS (ESI+, *m/z)* calculated for $C_{20}H_{23}F_3N_3O^+$: 378.1788, Found: 378.1796.
R_f = 0.55 (50% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

Figure S53: ^{1}H NMR (500 MHz, $CDCl_3$) for 19-*anti*

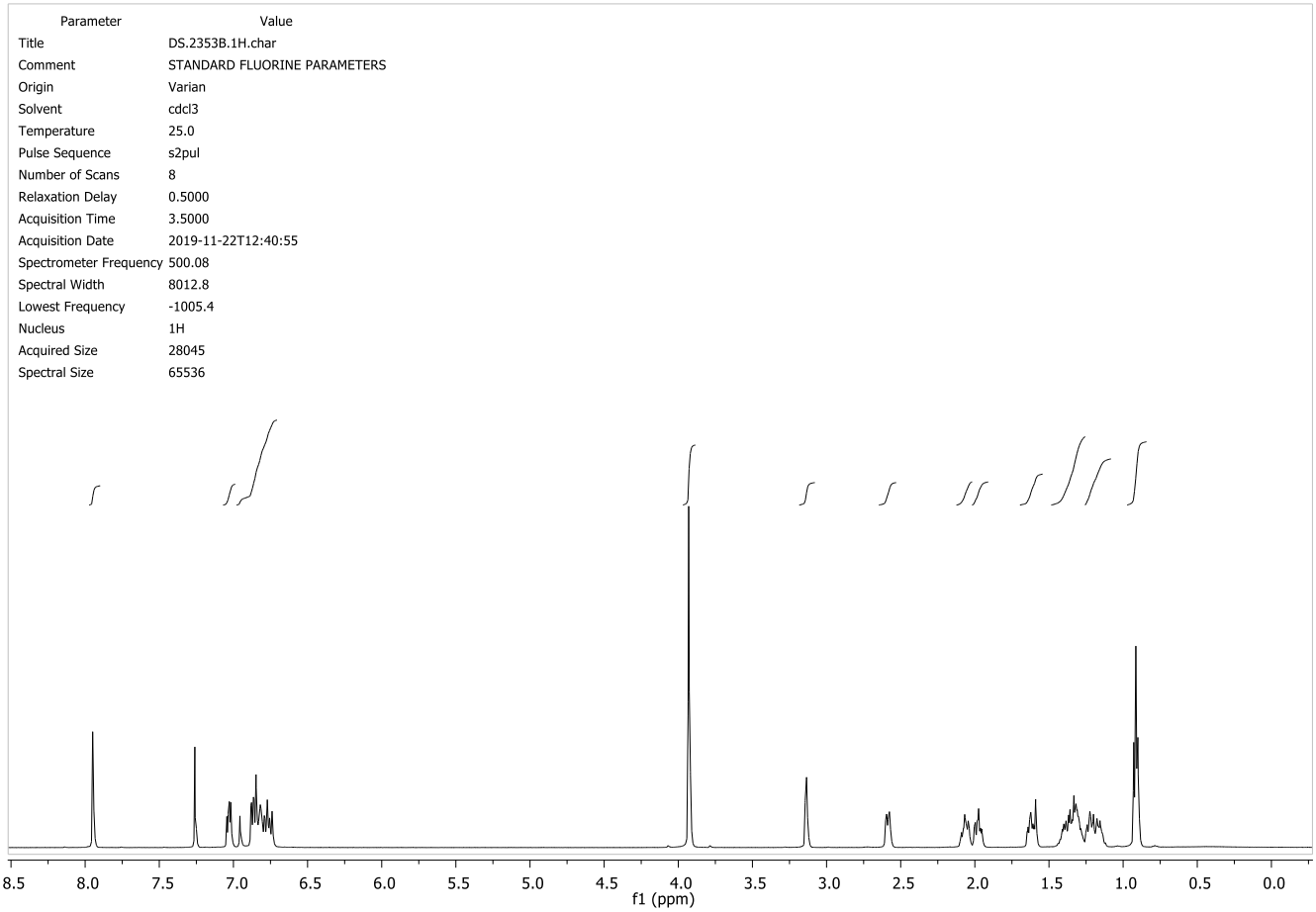


Figure S54: ^{13}C NMR (126 MHz, $CDCl_3$) for 19-*anti*

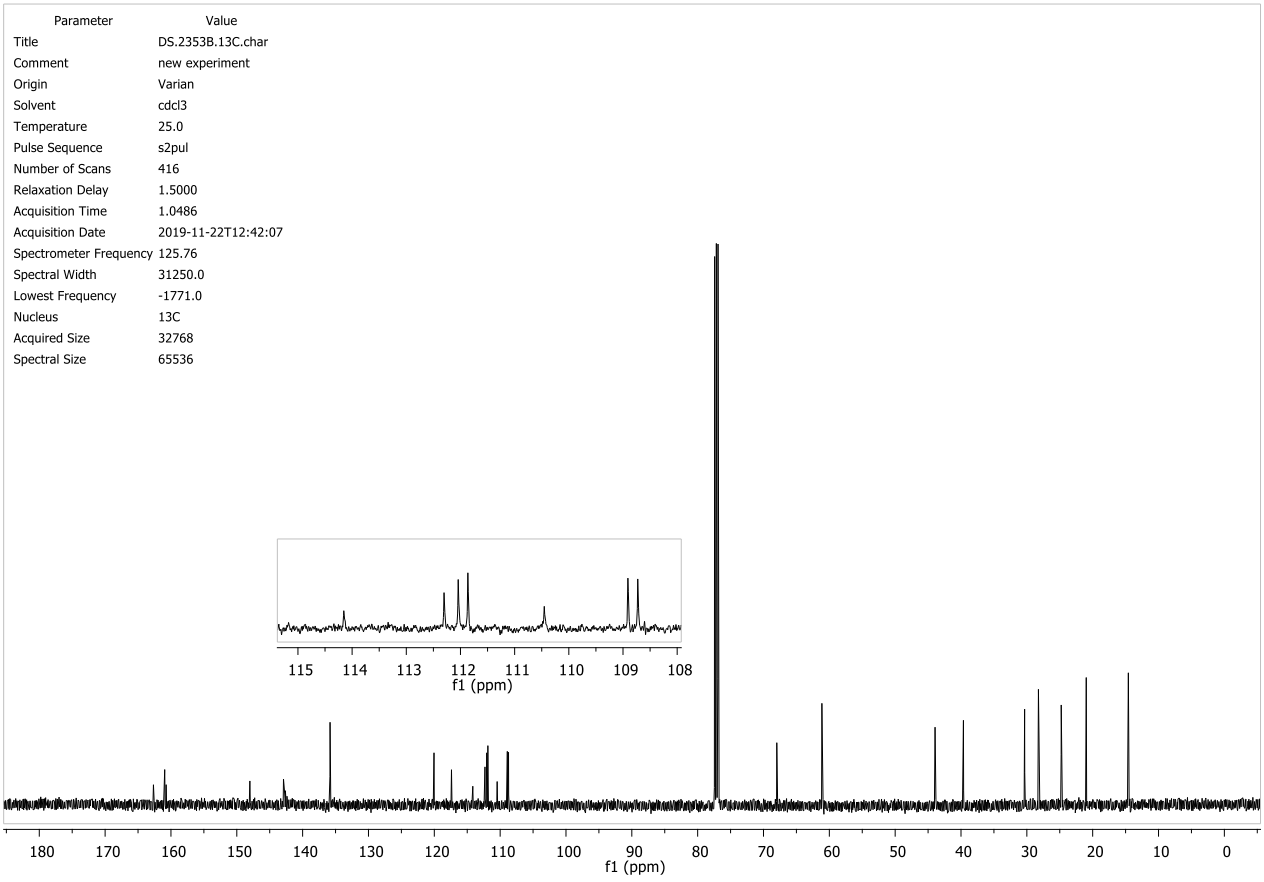


Figure S55: ^{19}F NMR (471 MHz, $CDCl_3$) for 19-*anti*

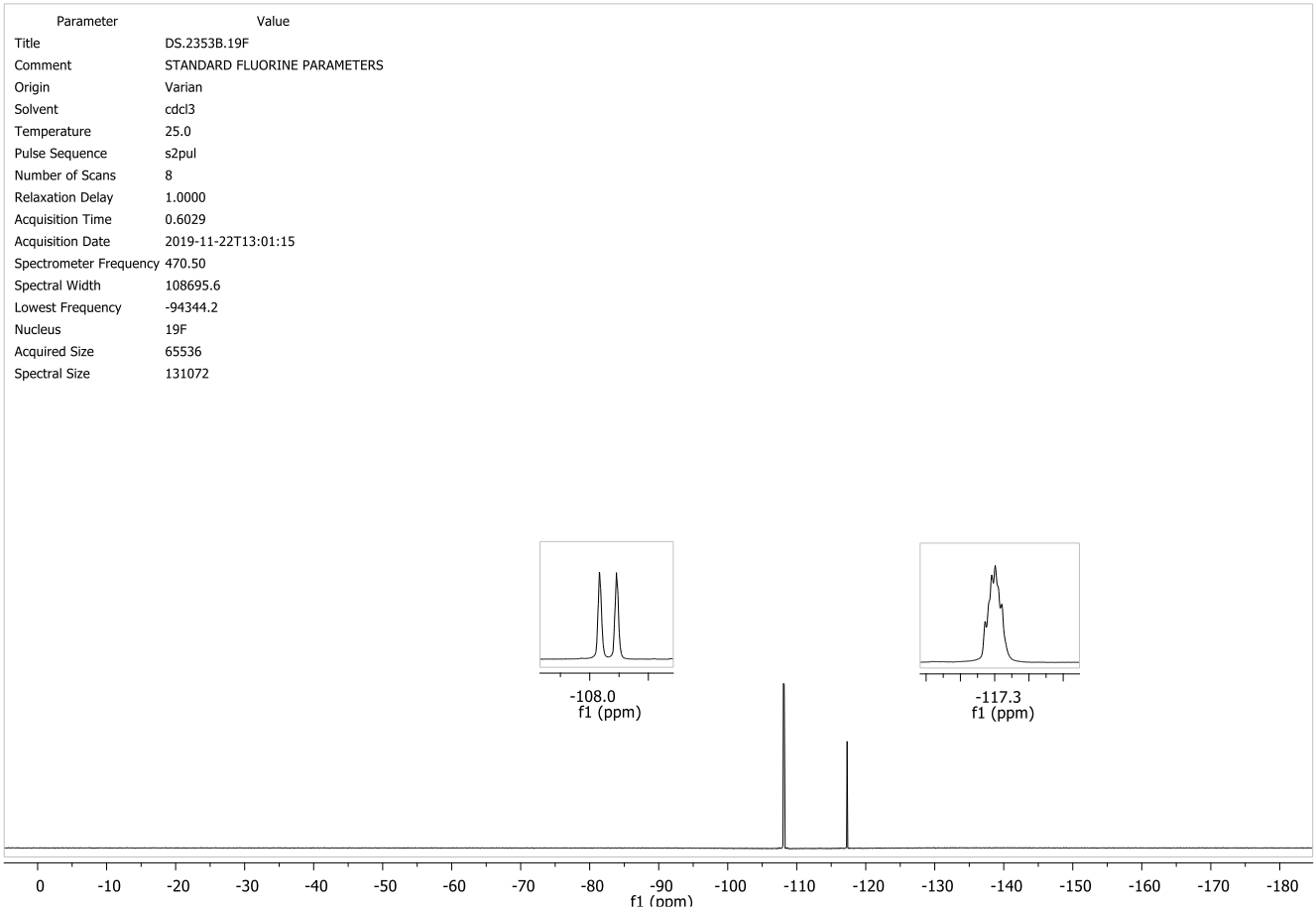


Figure S56: ^{1}H NMR (500 MHz, $CDCl_3$) for 14-*syn*

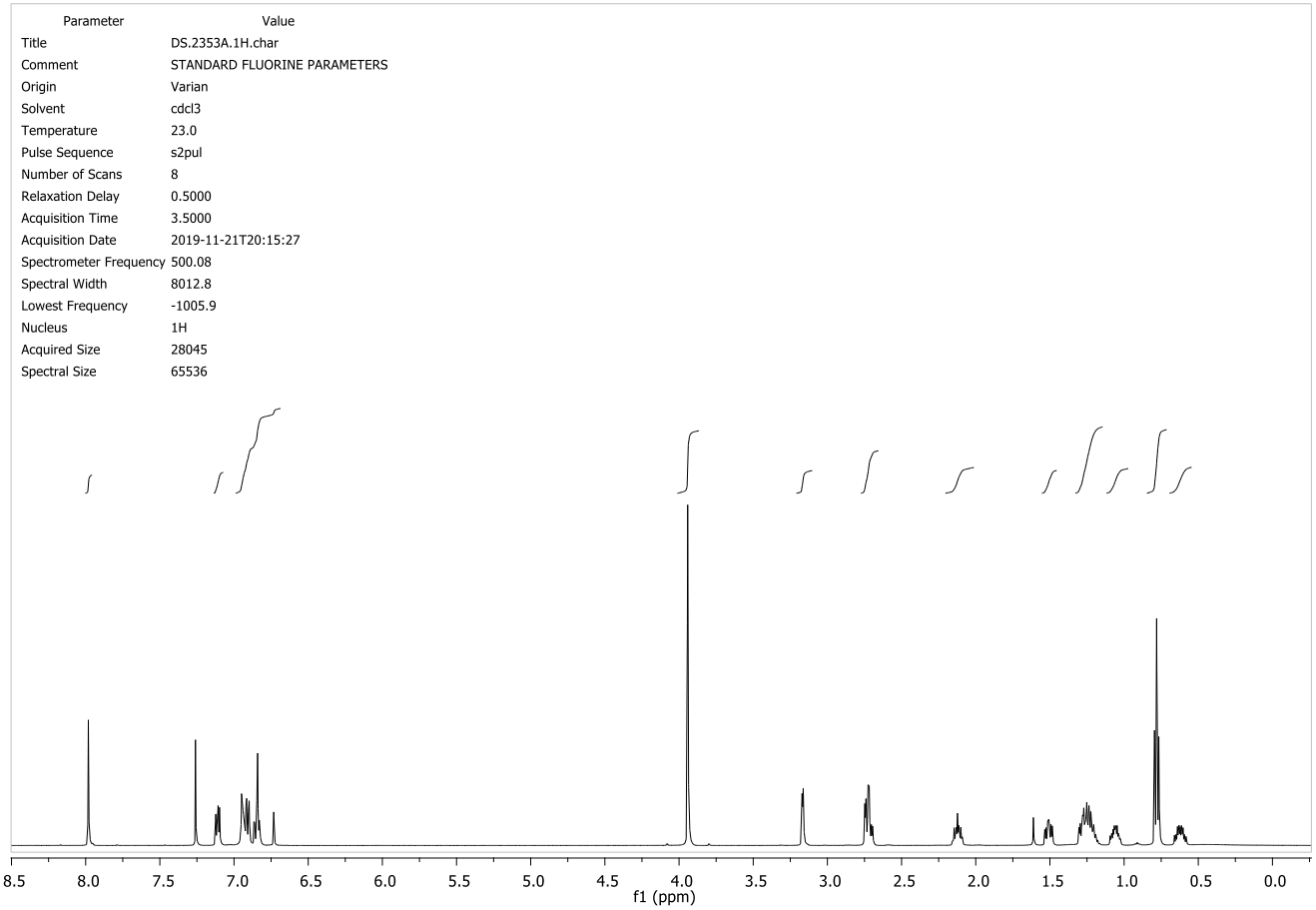


Figure S57: ^{13}C NMR (126 MHz, $CDCl_3$) for 14-*syn*

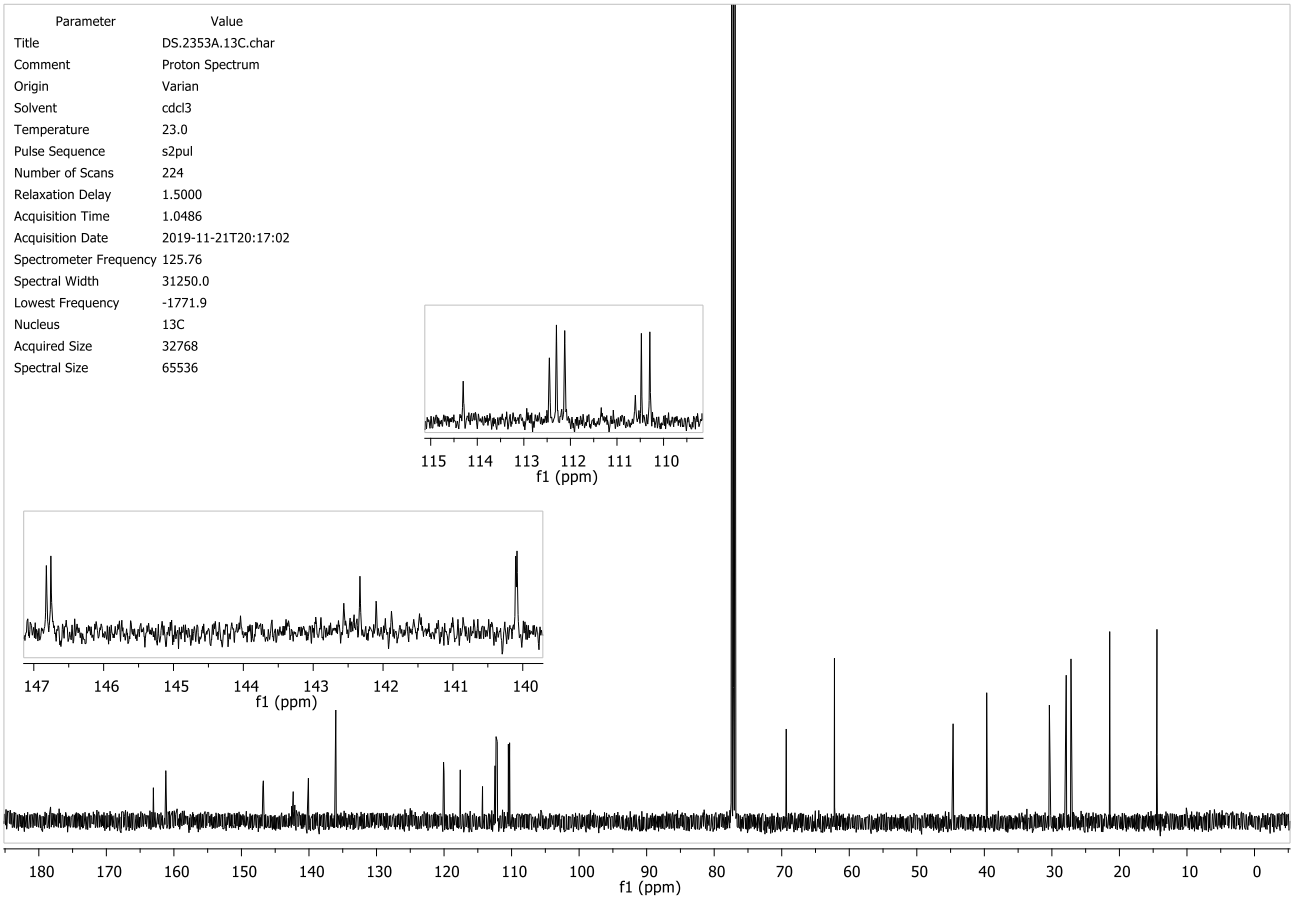
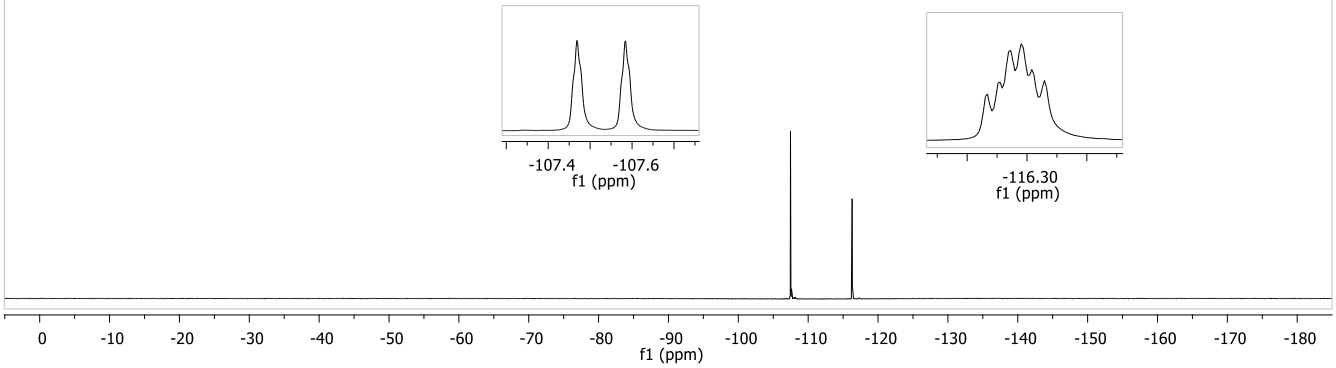
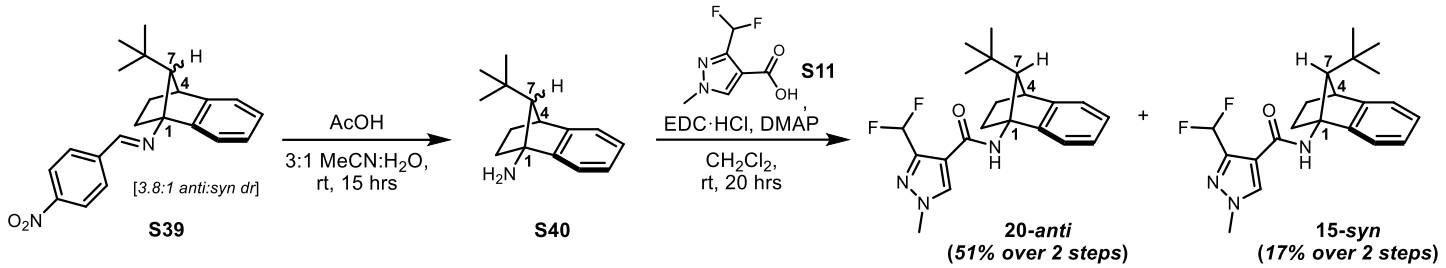


Figure S58: ^{19}F NMR (471 MHz, $CDCl_3$) for 14-*syn*

Parameter	Value
Title	DS.2353A.19F
Comment	STANDARD FLUORINE PARAMETERS
Origin	Varian
Solvent	cdcl3
Temperature	23.0
Pulse Sequence	s2pul
Number of Scans	8
Relaxation Delay	1.0000
Acquisition Time	0.6029
Acquisition Date	2019-11-21T20:27:52
Spectrometer Frequency	470.50
Spectral Width	108695.6
Lowest Frequency	-94344.2
Nucleus	19F
Acquired Size	65536
Spectral Size	131072





Procedure for C7-*tert*-butyl 1-aminoNB analogs 20-*anti* and 15-*syn*

Removal of the Schiff base protecting group was achieved by dissolving the protected 1-aminonorbornane mix (**S39**; 168 mg of a 3.8:1 *anti*:*syn* mixture; 482 μmol) in a 3:1 MeCN:H_2O mixture (3.0 mL:1.0 mL) before adding acetic acid (1.0 mL). The reaction mixture was flushed with Ar, capped, and stirred at room temp for 15 hrs. The reaction was diluted with 50 mL water and 25 mL 1:1 ether:pentane. The phases were separated, and the slightly acidic aqueous phase was washed with 25 mL 1:1 ether:pentane two additional times. The aqueous phase was made basic through the addition of 25 mL of 1 M NaOH (aq.) then diluted with 2 mL ether. Phases were separated, and the aqueous phase was extracted with 4 portions of ether, 25 mL each. The organic phases from the basic extraction were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The desired 1-aminonorbornanes (**S40**) were obtained as a yellow liquid (98.9 mg). This material contained visible impurities in the ^{1}H NMR spectrum, which precluded clean assessment of the *anti*:*syn* ratio. This mixture was moved forward without further purification. Partial characterization is provided below.

Note: analogous procedures for other systems switched to ether only in the 2nd and 3rd washes of the acidic aqueous phase. This switch is critical for removing certain trace impurities and colored byproducts, as evidenced by the lack of purity observed while executing the above deprotection. The ether:pentane mixture is necessary in the initial dilution (some product can be dragged into washes if ether only is employed in initial wash), but to obtain pure C1-NH2 intermediates, the subsequent washes must be ether only.

Diagnostic Data for anti-C7-tert-butyl C1-NH_2 intermediate:
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.27 (d, 1H, *J* = 3.8 Hz, C4), 1.12 (s, 9H, C7-tBu) ppm [*partial line-listing*]

Diagnostic Data for syn-C7- tert-butyl C1-NH_2 intermediate:
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.42 (d, 1H, *J* = 3.6 Hz, C4), 0.66 (s, 9H, C7-tBu) ppm [*partial line-listing*]

1-Aminonorbornane mix **S40** (60.8 mg; at most 282 μmol) was dissolved in dry dichloromethane (2.8 mL), followed by addition of the carboxylic acid **S11** (75 mg; 0.43 mmol), DMAP (52 mg; 0.43 mmol), and EDC·HCl (81 mg; 0.42 mmol), respectively. The reaction was flushed with Ar, capped, and stirred at room temp 20 hrs. The crude residue was diluted with 20 mL water and 10 mL ethyl acetate. Phases were separated, and the aqueous phase was extracted with 3 portions of ethyl acetate, 10 mL each. The organic phases were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The crude residue was purified with flash chromatography over silica (20 to 35 to 50 to 75 to 100% ethyl acetate:hexanes; loaded residue with PhMe; silica was pre-neutralized with a 20% ethyl acetate:hexanes + 1% triethylamine mobile phase). Collected the carboxamide **20-*anti*** as a white solid (56.3 mg, 50.9% yield over 2 steps) and carboxamide **15-*syn*** as a clear, colorless oil (18.9 mg, 17.1% over two steps).

*Characterization Data for anti-C7-propyl 1-aminoNB analog **20-anti**:*
^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.96 (s, 1H, pyrazole), 7.12-7.10 (m, 1H, Ar), 7.09-7.04 (m, 2H, Ar), 7.00-6.98 (m, 1H, Ar), 6.98 (br s, 1H, -NH), 6.88 (t, 1H, J_{HF} = 54.2 Hz, -CHF_2), 3.93 (s, 3H, pyrazole -NMe), 3.32 (d, 1H, *J* = 3.8 Hz, C4), 2.46 (s, 1H, C7), 2.32 (*app.* td, 1H, *J* = 10.9, 3.6 Hz, C2-eq), 2.15 (*app.* tt, 1H, *J* = 10.6, 4.2, C3-eq), 1.60-1.55 (m, 1H, C2-ax), 1.25-1.21 (m, 1H, C3-ax), 1.06 (s, 9H, C7-tBu) ppm
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 160.7, 148.9, 146.6, 142.6 (t, J_{CF} = 28.6 Hz), 135.8, 125.6, 125.2, 120.2, 118.1, 117.7 112.3 (t, J_{CF} = 232.5 Hz), 68.8, 68.8, 44.7, 39.6, 32.5, 32.1, 30.0, 26.3 ppm
^{19}F NMR ($CDCl_3$, 376 MHz): δ = -108.0 (*app.* ddd, *J* = 54.4, 46.8, 4.1 Hz) ppm
HRMS (ESI+, *m/z)* calculated for $C_{21}H_{26}F_2N_3O^+$: 374.2038, Found: 374.2041.
R_f = 0.65 (70% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

*Characterization Data for syn-C7-propyl 1-aminoNB analog **15-syn**:*

^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.99 (s, 1H, pyrazole), 7.23-7.13 (m, 4H, Ar), 7.16 (br s, 1H, -NH), 6.88 (t, 1H, J_{HF} = 54.2 Hz, -CHF_2), 3.94 (s, 3H, pyrazole -NMe), 3.28 (*app*. td, 1H, *J* = 9.9, 2.8 Hz, C2-eq), 3.27 (d, 1H, *J* = 4.3 Hz, C4), 2.74 (d, 1H, *J* = 0.7 Hz, C7), 2.10 (*app.* tt, 1H, *J* = 10.6, 4.2 Hz, C3-eq), 1.19-1.08 (m, 2H, C2-ax, C3-ax), 0.60 (s, 9H, C7-tBu) ppm
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 161.4, 144.9, 144.8, 142.2 (t, J_{CF} = 29.4 Hz), 136.1, 126.8, 126.2, 121.2, 117.9, 116.8, 112.5 (t, J_{CF} = 232.3 Hz), 70.5, 68.8, 44.0, 39.6, 31.7, 30.4, 29.7, 27.8 ppm
^{19}F NMR ($CDCl_3$, 376 MHz): δ = -107.0 (*app.* dd, *J* = 54.2, 4.4 Hz), -107.3 (*app.* dd, *J* = 54.2, 3.8 Hz) ppm
HRMS (ESI+, *m/z)* calculated for $C_{21}H_{26}F_2N_3O^+$: 374.2038, Found: 374.2039.
R_f = 0.70 (70% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

Figure S59: ^{1}H NMR (700 MHz, $CDCl_3$) for 20-*anti*

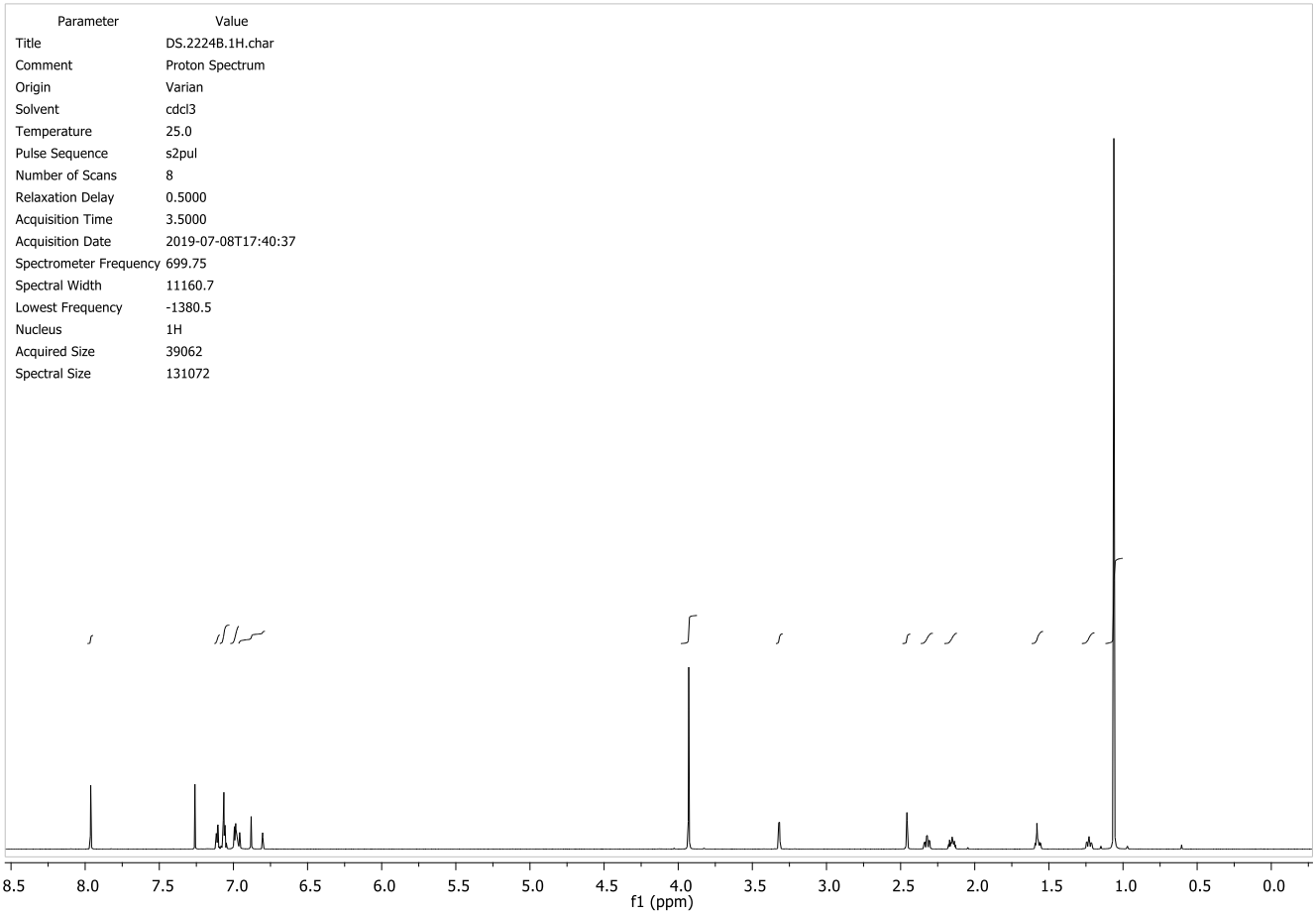


Figure S60: ^{13}C NMR (176 MHz, $CDCl_3$) for 20-*anti*

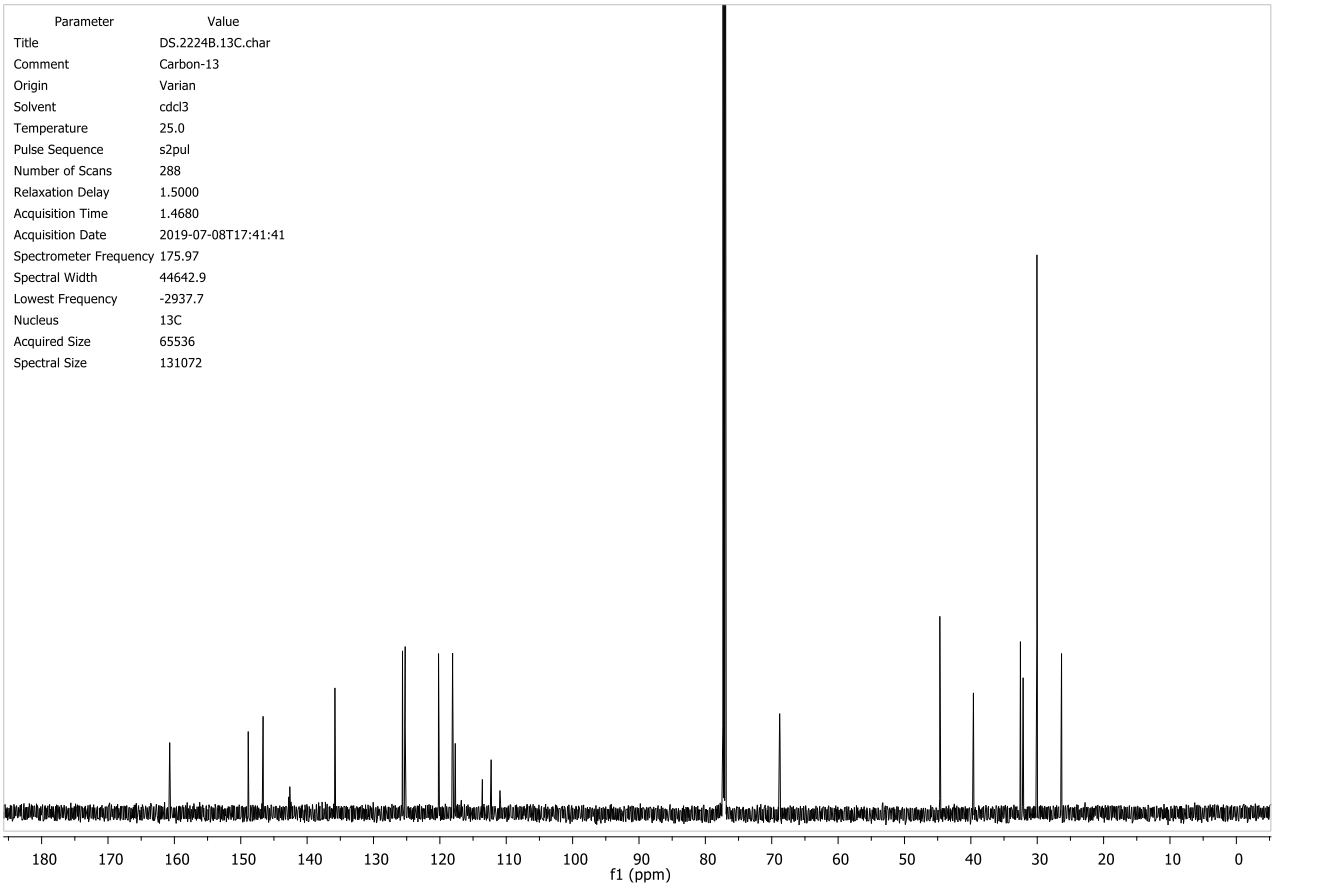


Figure S61: ^{19}F NMR (376 MHz, $CDCl_3$) for 20-*anti*

Parameter	Value
Title	DS.2224B.19F
Comment	Fluorine-19
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Number of Scans	16
Relaxation Delay	1.0000
Acquisition Time	0.7340
Acquisition Date	2019-07-08T19:54:18
Spectrometer Frequency	375.91
Spectral Width	89285.7
Lowest Frequency	-76597.5
Nucleus	19F
Acquired Size	65536
Spectral Size	131072

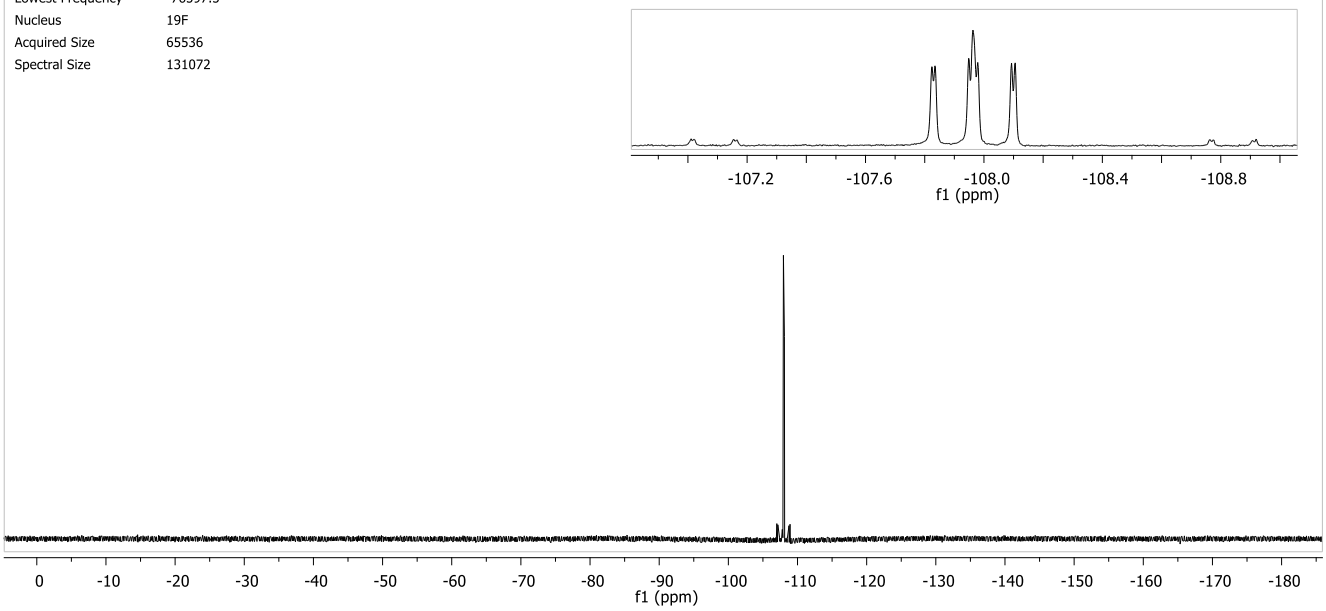


Figure S62: ^{1}H NMR (700 MHz, $CDCl_3$) for 15-*syn*

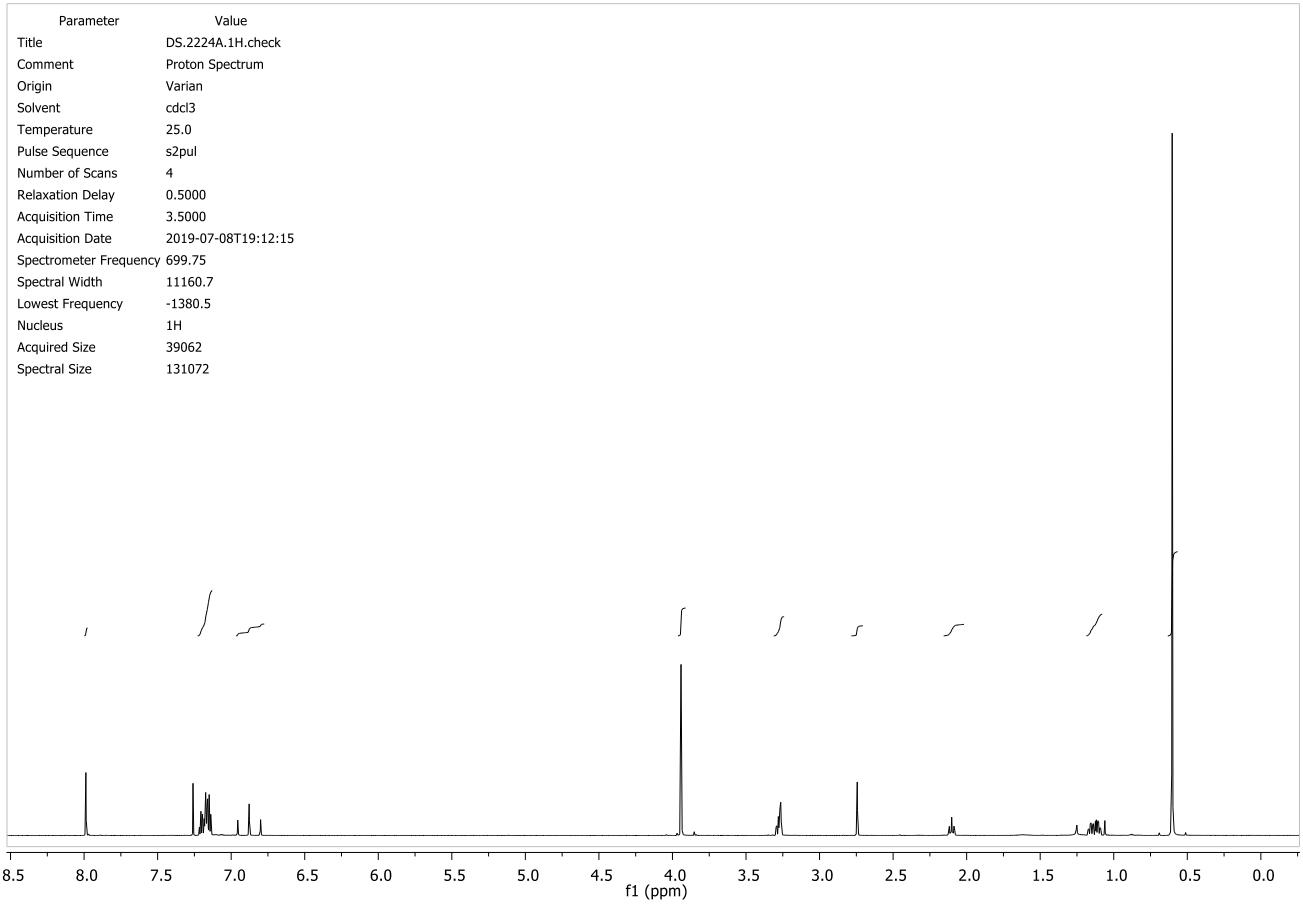


Figure S63: ^{13}C NMR (176 MHz, $CDCl_3$) for 15-*syn*

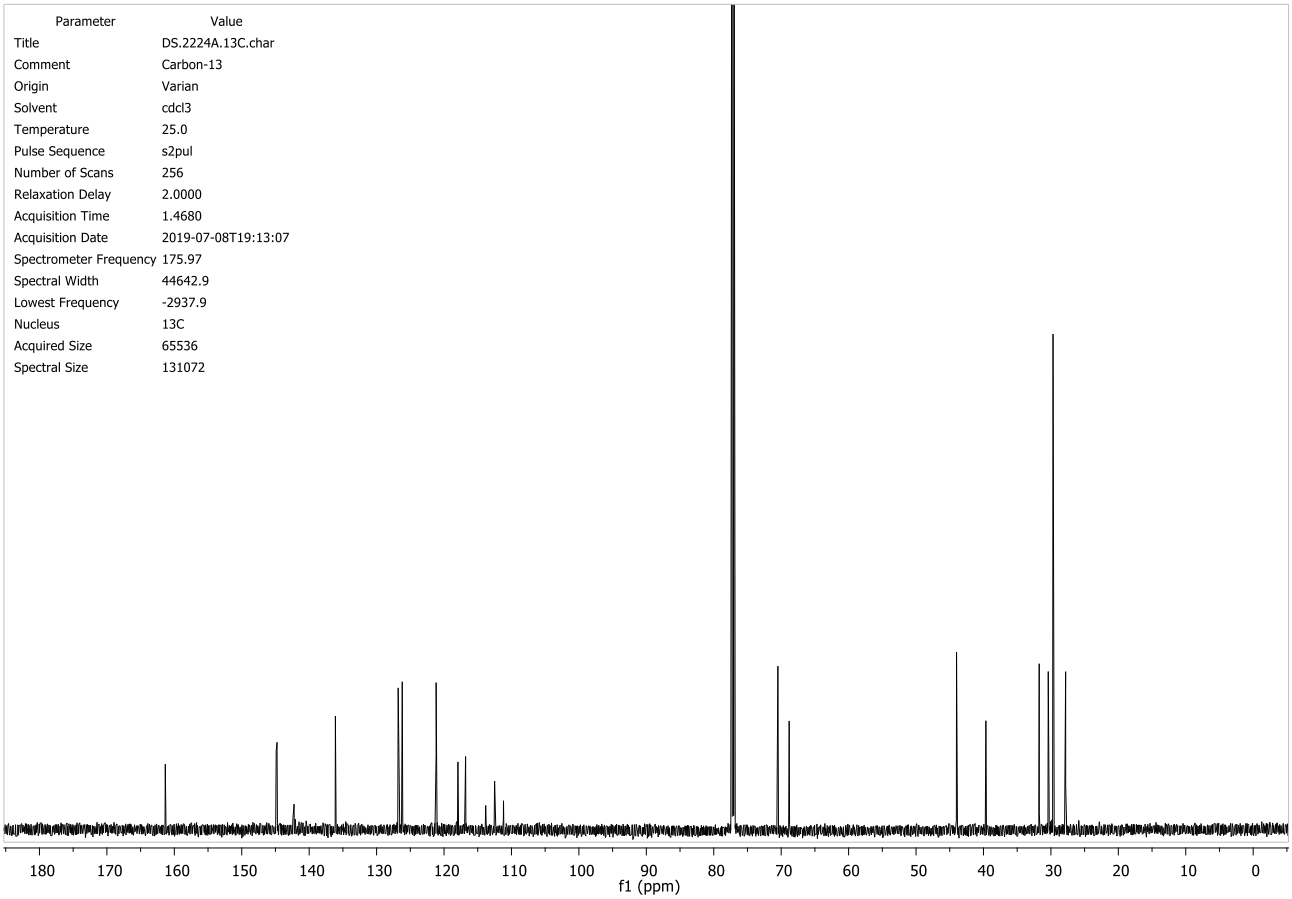
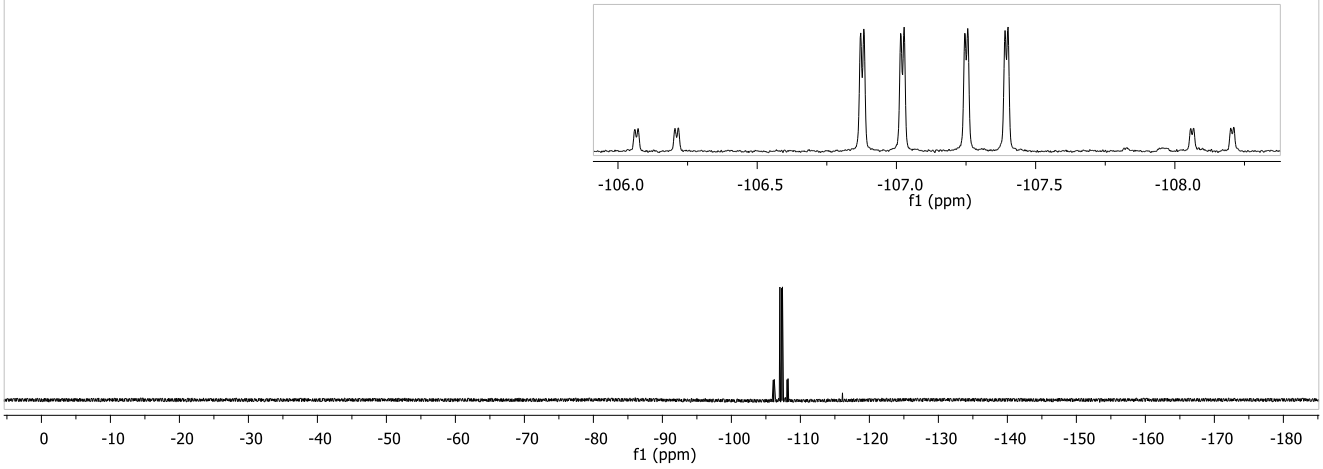
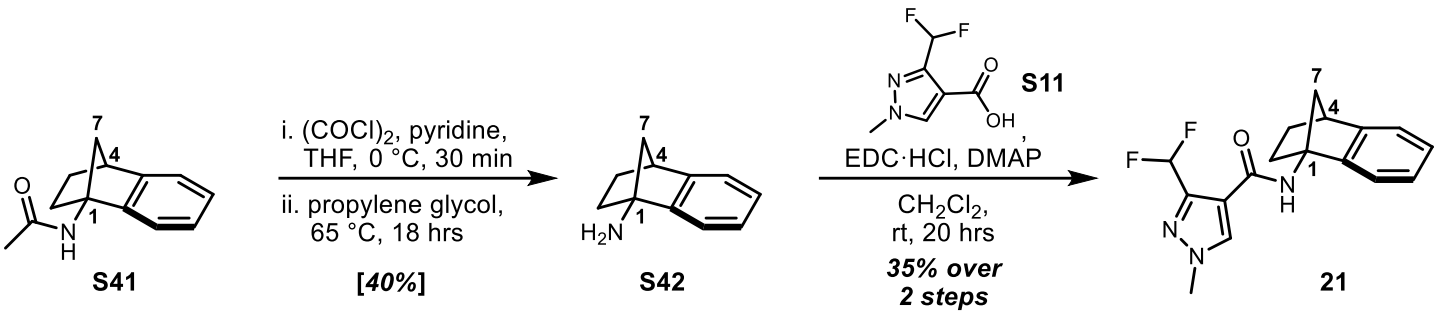


Figure S64: ^{19}F NMR (376 MHz, $CDCl_3$) for 15-*syn*

Parameter	Value
Title	DS.2224A.19F
Comment	Fluorine-19
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Number of Scans	8
Relaxation Delay	1.0000
Acquisition Time	0.7340
Acquisition Date	2019-07-08T19:49:49
Spectrometer Frequency	375.91
Spectral Width	89285.7
Lowest Frequency	-76597.5
Nucleus	19F
Acquired Size	65536
Spectral Size	131072





Procedure for C7-methylene 1-aminoNB analog 21

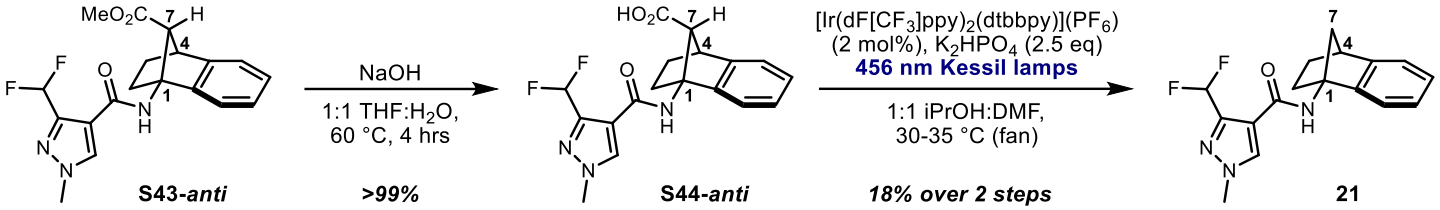
Acetamide **S41** (12.4 mg, 62 μmol) was added to a dry vial under inert atmosphere before dissolving in 0.7 mL dry THF and cooling to 0 °C. Pyridine (12.5 μL, 0.15 mmol) was added prior to the slow addition down side of the vial of oxalyl chloride (10 μL, 0.12 mmol). Stirred vigorously at 0 °C for 30 min with occasional venting to account for gas evolution; reaction mixture turns cloudly. Propylene glycol (30 μL, 0.41 mmol) was added, then the cold bath was removed. Upon warming to room temp, the vial was flushed with Ar, sealed, and the reaction was heated to 65 °C for 18 hrs. Upon cooling to room temp, the reaction mixture was quenched by pouring into 4 mL 0.1 M HCl (aq), then diluting with 1 mL 1:1 ether:pentane. Phases were separated. Aqueous phase was washed with 1 mL 1:1 ether:pentane two times, prior to basifying through the addition of 0.5 mL 6 M NaOH (aq). Basic aqueous phase was extracted with four 1 mL portions of 1:1 ether:pentane. The combined organics were dried over anhydrous magnesium sulfate, filtered to remove solids and carefully concentrated under a gentle stream of nitrogen. Obtained 3.9 mg of a clear, colorless oil, presumed to be 1-aminonorbornane intermediated **S42**. This material was immediately transitioned into the next reaction manifold.

Note: Partially deprotected intermediates could be detected by 1H NMR in the combined organic washes of the acidic aqueous phase (5.9 mg of a yellow oil was collected from this fraction). Re-exposure of this material to the deprotection conditions on this substrate and related acetamides can afford additional deprotected amine material, but these efforts generally are low yielding and contaminated with multiple, previously-undetected byproducts.

1-Aminonorbornane **S42** (3.9 mg; at most 25 μmol) was dissolved in dry dichloromethane (0.5 mL), followed by the addition of carboxylic acid **S11** (6.8 mg; 39 μmol), DMAP (5.4 mg; 44 μmol), and EDC·HCl (7.3 mg; 38 μmol), respectively. The reaction was flushed with Ar, capped, and stirred at room temp 20 hrs. Purified crude residue via pipet-scale chromatography over silica (30 to 50 to 80% ethyl acetate:pentane; silica was pre-neutralized with a 30% ethyl acetate:pentane + 1% triethylamine mobile phase). Collected the desired carboxamide (**21**) in two portions: 5.7 mg of a white solid and 1.1 mg of a slightly yellow solid. Both samples were deemed pure by ^{1}H NMR analysis, bringing the total collection to 6.8 mg, 34.7% yield over two steps.

*Characterization Data for C7-methylene SDHI candidate **21**:*
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.96 (s, 1H, pyrazole), 7.19-7.11 (m, 4H, Ar), 7.06 (br s, 1H, -NH), 6.87 (t, 1H, J_{HF} = 54.2 Hz, -CHF_2), 3.94 (s, 3H, pyrazole -NMe), 3.35 (d, 1H, *J* = 3.9 Hz, C4), 2.39 (*app*. td, 1H, *J* = 11.0, 4.1 Hz, C2-eq), 2.24-2.22 (m, 1H, C7), 2.18-2.16 (m, 1H, C7), 2.19-2.12 (m, 1H, C3-eq), 1.59-1.54 (m, 1H, C2-ax), 1.35-1.29 (m, 1H, C3-ax) ppm
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 161.3, 146.3, 146.0, 142.7 (t, J_{CF} = 29.0 Hz), 135.7 126.4, 126.0, 121.1, 118.2, 117.7, 112.3 (t, J_{CF} = 232.6 Hz), 67.3, 53.1, 41.7, 39.6, 31.2, 28.5 ppm
^{19}F NMR ($CDCl_3$, 376 MHz): δ = -108.3 (dd, *J* = 54.3, 1.6 Hz) ppm
HRMS (ESI+, *m/z)* calculated for $C_{17}H_{18}F_2N_3O^+$: 318.1412, Found: 318.1414.
R_f = 0.40 (70% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

Of note, the C7-methylene SDHI candidate **21** can be directly obtained from the C7-CO_2Me SDHI candidate **S43-*anti*** rather than from acetamide **S41** (a product that was reported in our prior work[3]). Unfortunately, the pyrazole carboxamide appears to be an effective quencher of the photocatalyst in the photochemical decarboxylation (via energy transfer and/or redox pathways), which leads to extremely slow conversions. Alternative decarboxylation methods on this scaffold need to be investigated to improve the throughput of this route. A brief description of this alternative method is provided below.



S43-*anti* **>99%** **S44-*anti*** ***18% over 2 steps*** **21**

The C7-CO_2Me species **S43-*anti*** (46.4 mg) was saponified by dissolving in 0.6 mL THF, diluting with 0.6 mL 2 M NaOH (aq.), and heating to 60 °C for 4 hrs. After cooling to room temp, the crude residue was diluted with 4 mL water and 2 mL 1:1 ethyl acetate:hexanes. Phases were separated, and the basic aqueous phase was washed with 2 portions of 1:1 ethyl acetate:hexanes, 2 mL each. Aqueous phase was acidified to pH ~ 3.5 with 0.7 mL 2 M HCl (aq.), then diluted with 2 mL ethyl acetate. Phases were separated, and the acidic aqueous phase was extracted with 9 portions of ethyl acetate, 2 mL each. The organic phases were combined, dried over anhydrous sodium sulfate, filtered to remove solids, and concentrated under vacuum. Acetone was used to rinse and transfer in these latter steps. Collected 52.9 mg of a white solid (**S44-anti**), clean by ^{1}H NMR save for the various solvent contaminants.

The C7-CO_2H species from the above transformation was dissolved in 0.6 mL isopropanol and 0.6 mL dry DMF prior to adding 2.6 mg of [Ir(dF[CF_3]ppy)$_2$(dtbbpy)](PF_6) and 54 mg potassium phosphate dibasic. The reaction mixture was degassed using three freeze-pump-thaw cycles. The reaction mixture was then irradiated with two 456 nm PR-160 Kessil lamps for 18 hrs while cooling with a fan. The crude reaction mixture was diluted with 4 mL water and 2 mL ethyl acetate. Phases were separated, and the aqueous phase was extracted with 3 portions of ethyl acetate, 2 mL each. The organic phases were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The crude residue was purified with flash chromatography over silica (40 to 70 to 100% ethyl acetate:pentane; loaded residue with PhMe; silica was pre-neutralized with a 40% ethyl acetate:pentane + 1% triethylamine mobile phase). Collected the desired carboxamide **21** as a white solid: 6.9 mg, 17.5% yield over two steps.

Unreacted starting material could be collected by acidifying the basic aqueous mixture and extracting in the manner above. The overall mass balance recovery of this process was generally between 75-85% and was performed iteratively in order to secure additional SDHI candidate **21** for biological purposes.

Figure S65: ^{1}H NMR (500 MHz, $CDCl_3$) for 21

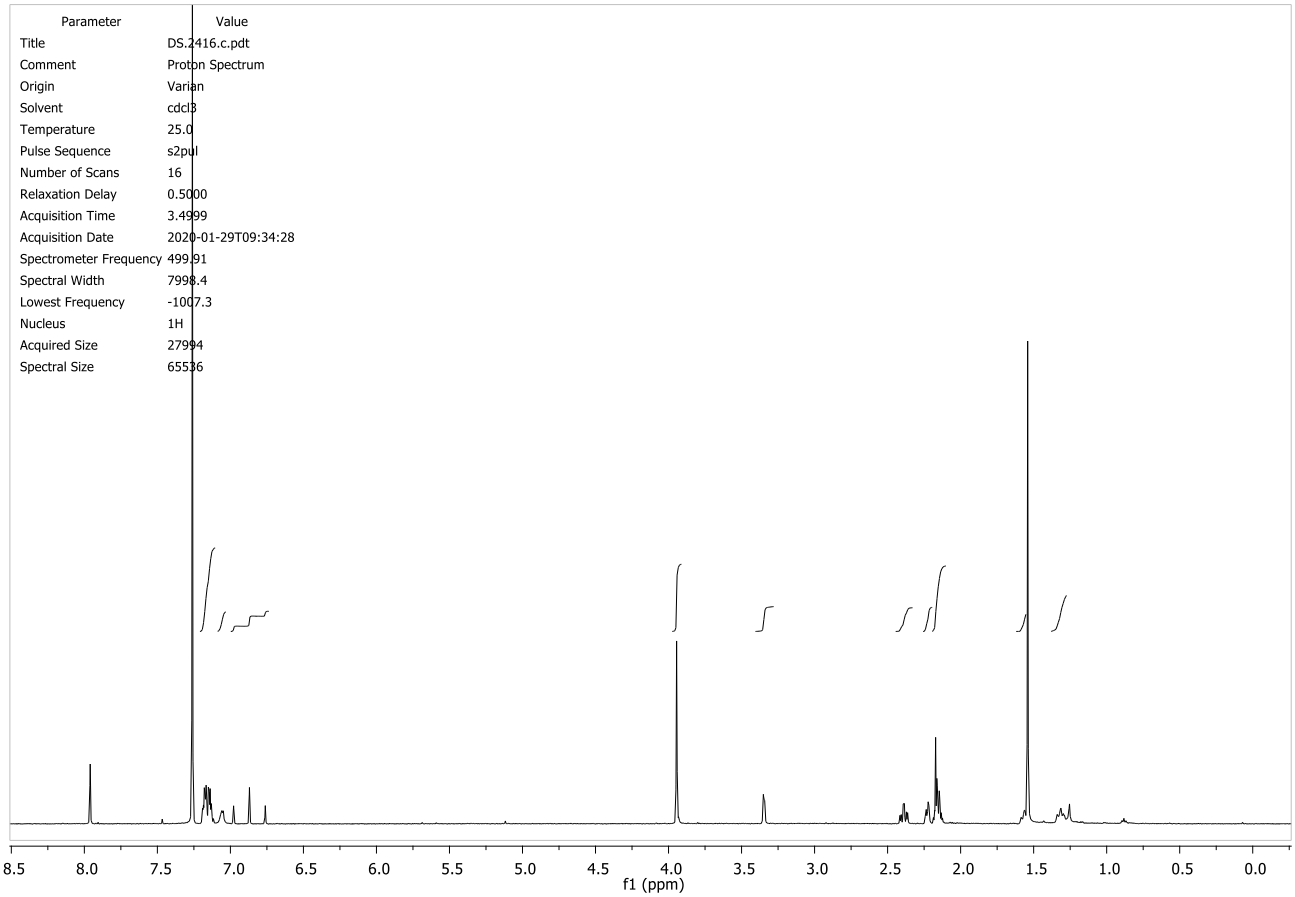


Figure S66: ^{13}C NMR (176 MHz, $CDCl_3$) for 21

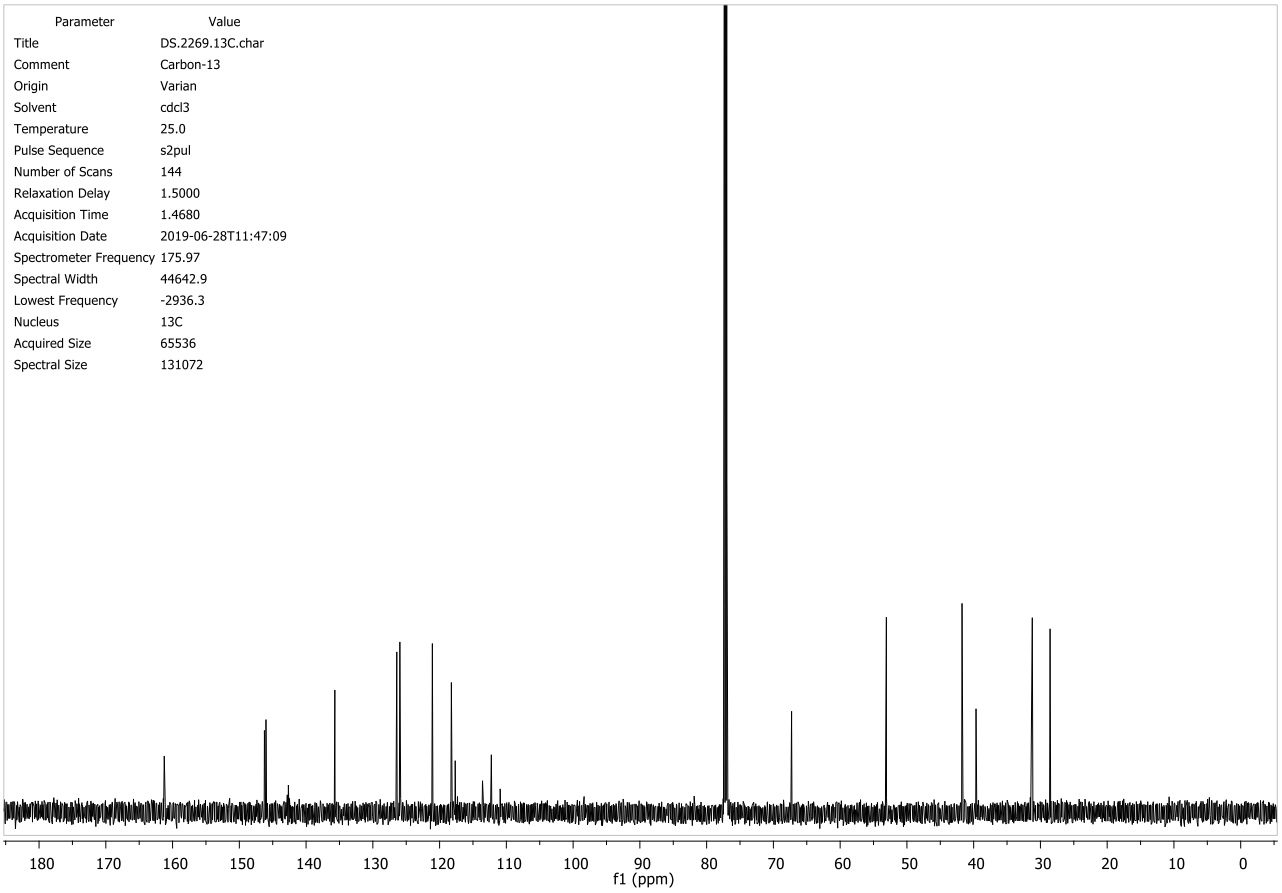
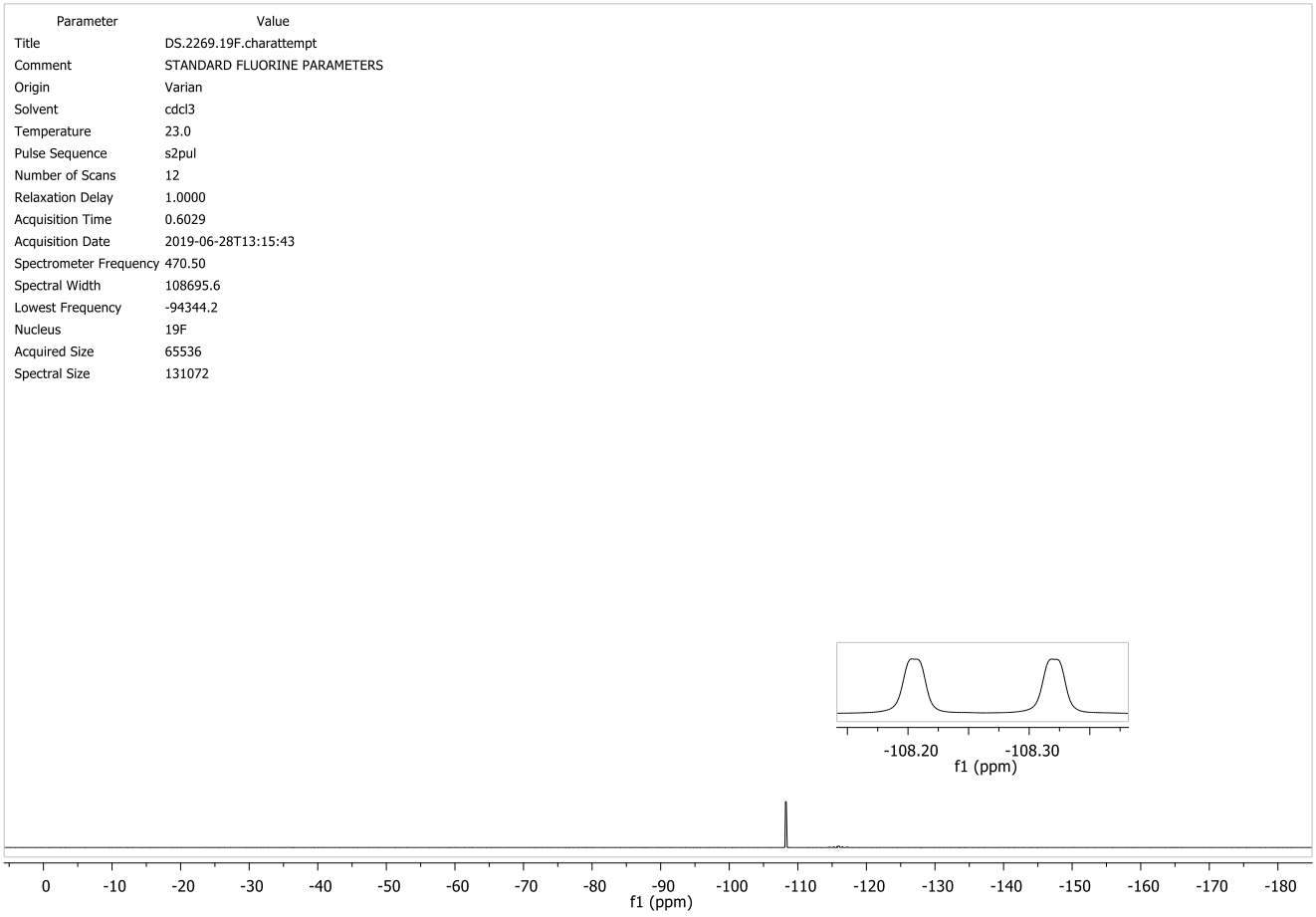
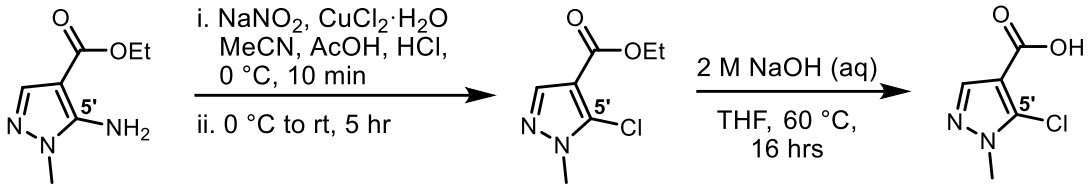


Figure S67: ^{19}F NMR (376 MHz, $CDCl_3$) for 21





S45 ***87%*** **S46** ***42%*** **S47**

Procedure for C5'-chloro pyrazole acid S47

C5'-amino pyrazole ester **S45** (1.06 g, 6.3 mmol) was dissolved in 20 mL dry MeCN in a flask under inert atmosphere. Copper (II) chloride dihydrate (1.6 g, 9.4 mmol) was added in one portion, then cooled to 0 °C. AcOH (2.0 mL) then conc. HCl (aq) (2.0 mL) were added dropwise over 15 s each, respectively. The reaction mixture becomes clear and homogeneous after ~2 min at 0 °C. In a separate beaker, sodium nitrite (1.08 g, 15.7 mmol) was dissolved in 6.0 mL water. The sodium nitrite solution was added to the reaction mixture dropwise over 10 min; gas evolution was visible over the course of the addition, and the reaction mixture became dark red. The reaction mixture was allowed to slowly come to room temp over the course of an hour (monitoring ice bath to ensure gradual warming), then stirred an additional 4 hrs at room temp. An aqueous quench consisting of 3:1 2 M NaOH (aq):sat. $Na_2S_2O_3$ (aq) was prepared in a separatory funnel. A small amount of ice (about enough to fill a 50 mL beaker) was added, followed by the slow addition of the reaction mixture. The quenched mixture was diluted with 50 mL ethyl acetate, and the phases were separated (aq phase pH = 12). The aqueous phase was extracted with three additional portions of ethyl acetate, 50 mL each. The combined organics were washed with 50 mL brine, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under vacuum. The crude residue was purified with flash chromatography over silica (5 to 25% ethyl acetate:pentane, increasing in 5% increments; silica was pre-neutralized with a 5% ethyl acetate:pentane + 1% triethylamine mobile phase). Collected product in two portions: 482 mg of a clear, colorless liquid and 543 mg of a clear, slightly yellow liquid. Both were determined to be pure by ^{1}H NMR analysis, amounting to a total of 1.03 g of C5'-chloro pyrazole ester **S46** (86.7% yield).

*Partial Characterization Data for C5'-chloro pyrazole ethyl ester **S46**:*
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.91 (s, 1H, pyrazole), 4.32 (q, 1H, *J* = 7.1 Hz, -CO_2Et), 3.87 (s, 3H, -NMe), 1.36 (t, 1H, *J* = 7.1 Hz, -CO_2Et) ppm
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 161.8, 141.4, 131.2, 111.2, 60.5, 36.7, 14.4 ppm
HRMS (ES+, *m/z)* calculated for $C_7H_{10}ClN_2O_2^+$: 189.0425, Found: 189.0424
R_f = 0.45 (20% ethyl acetate:hexanes), one spot, UV

Ester **S46** (480 mg, 2.5 mmol) was dissolved in 13 mL dry THF prior to the addition of 13 mL 2 M NaOH (aq) over the course of 2 min. A reflux condenser was attached, the system was flushed with Ar, and then the reaction mixture was heated to 60 °C for 16 hrs while stirring vigorously. Upon cooling to room temp, the reaction mixture was diluted with 20 mL 0.5 M NaOH (aq) and 20 mL ether. The phases were separated, and the basic aqueous phase was washed with two portions of ether, 20 mL each. The aqueous phase was made acidic by the addition of 40 mL 1 M HCl (aq). This led to a pH ~1.5 (beyond desired acidity level) which was increased to pH ~ 3 by addition of 10 mL sat. $NaHCO_3$ (aq). Acidic aqueous phase was extracted with four 20 mL portions of ethyl acetate. Combined organics were washed with mildly acidic brine (20 mL brine + 0.5 mL 1 M HCl (aq)), then dried over anhydrous sodium sulfate, filtered to remove solids, and concentrated under vacuum. Obtained the desired acid **S47** as a white solid, pure by ^{1}H NMR, 170 mg (41.7% yield). Note: A shorter time course and lower temperature is advisable for anyone considering repeating this procedure.

*Characterization Data for C5'-chloro pyrazole acid **S47**:*
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 11.30 (br s, 1H, -CO_2H), 7.98 (s, 1H, pyrazole), 3.90 (s, 3H, -NMe) ppm
^{13}C NMR ($CDCl_3$, 176 MHz): δ = 166.1, 142.2, 132.3, 110.2, 36.9 ppm
HRMS (ES+, *m/z)* calculated for $C_5H_6ClN_2O_2^+$: 161.0112, Found: 161.0117

Figure S68: ^{1}H NMR (500 MHz, $CDCl_3$) for S46

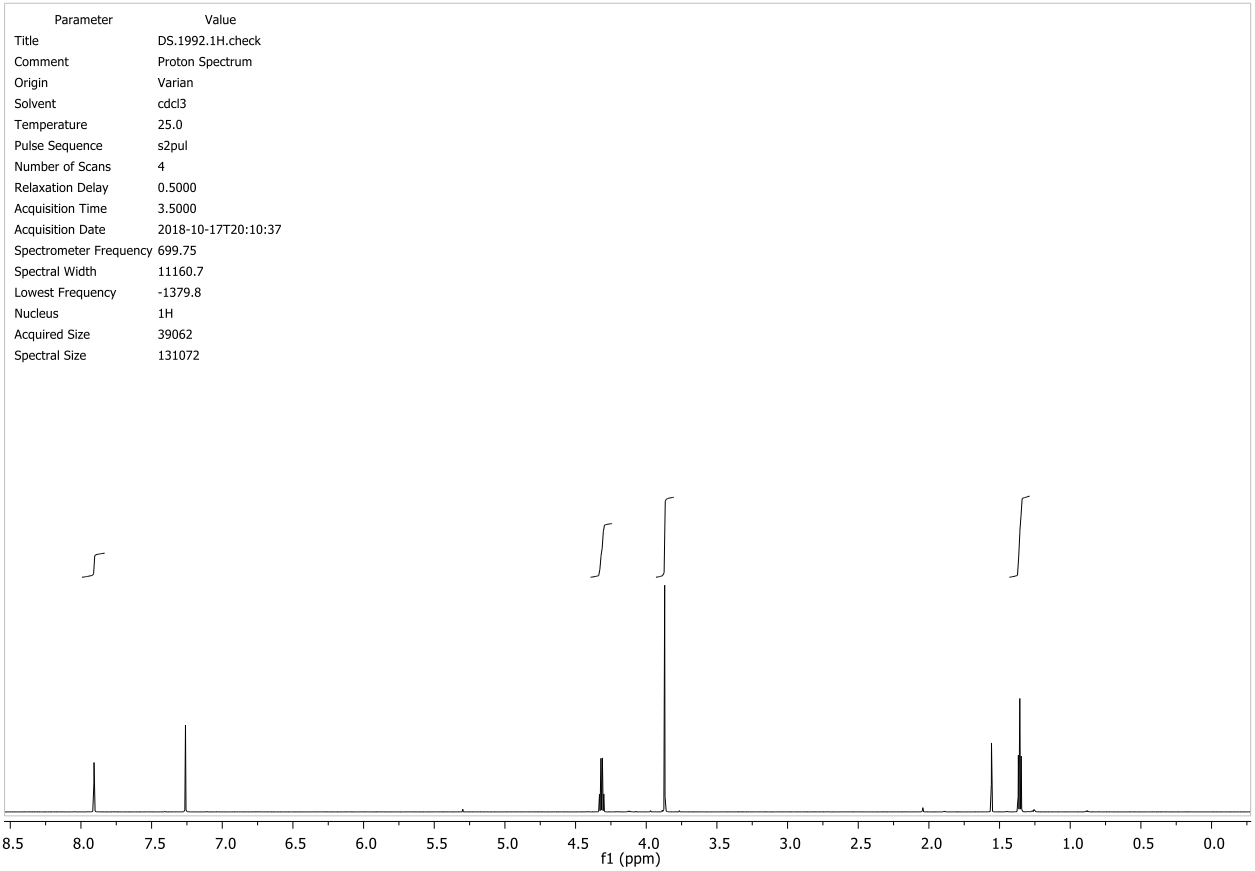


Figure S69: ^{13}C NMR (176 MHz, $CDCl_3$) for S46

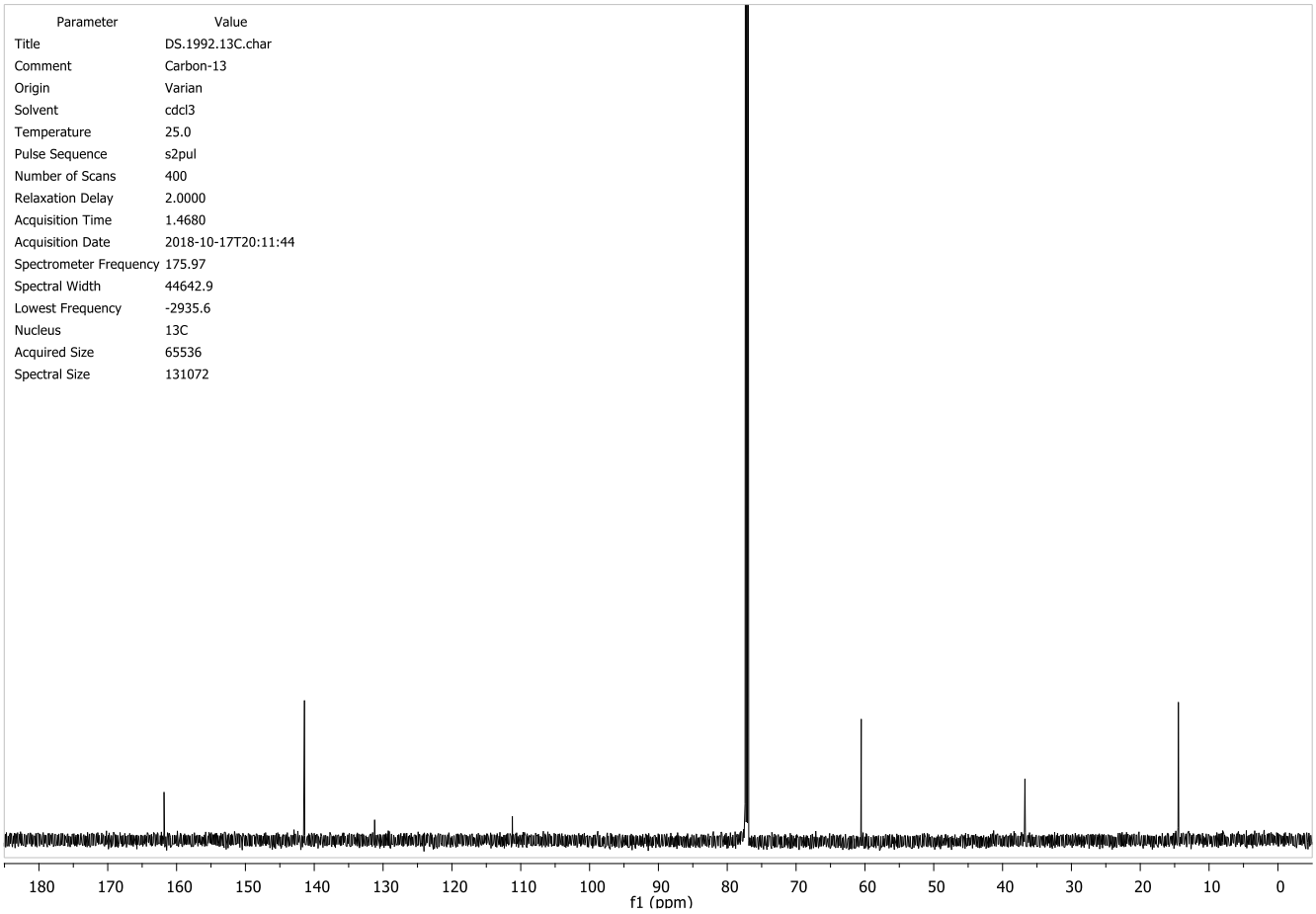


Figure S70: ^{1}H NMR (500 MHz, $CDCl_3$) for S47

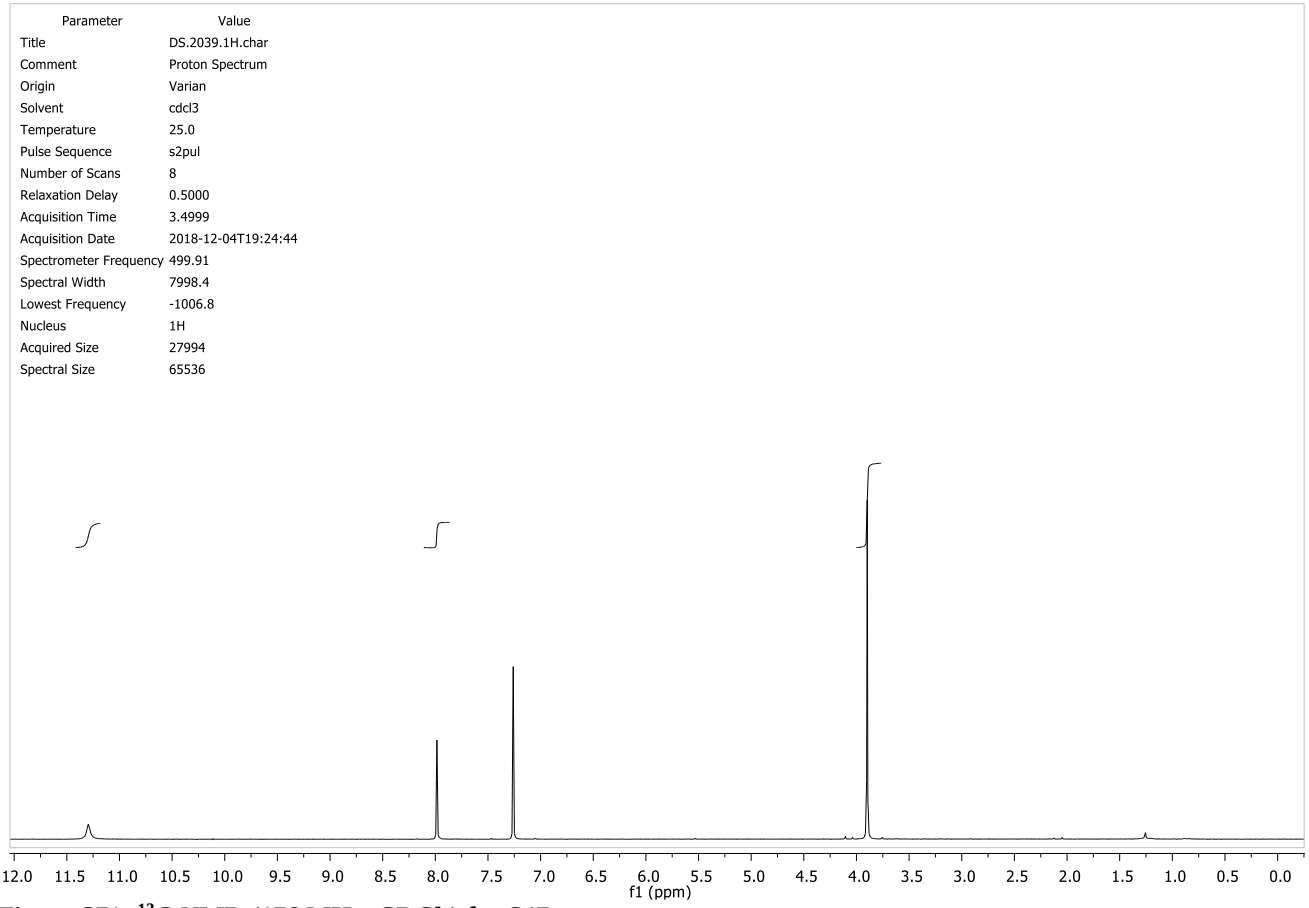
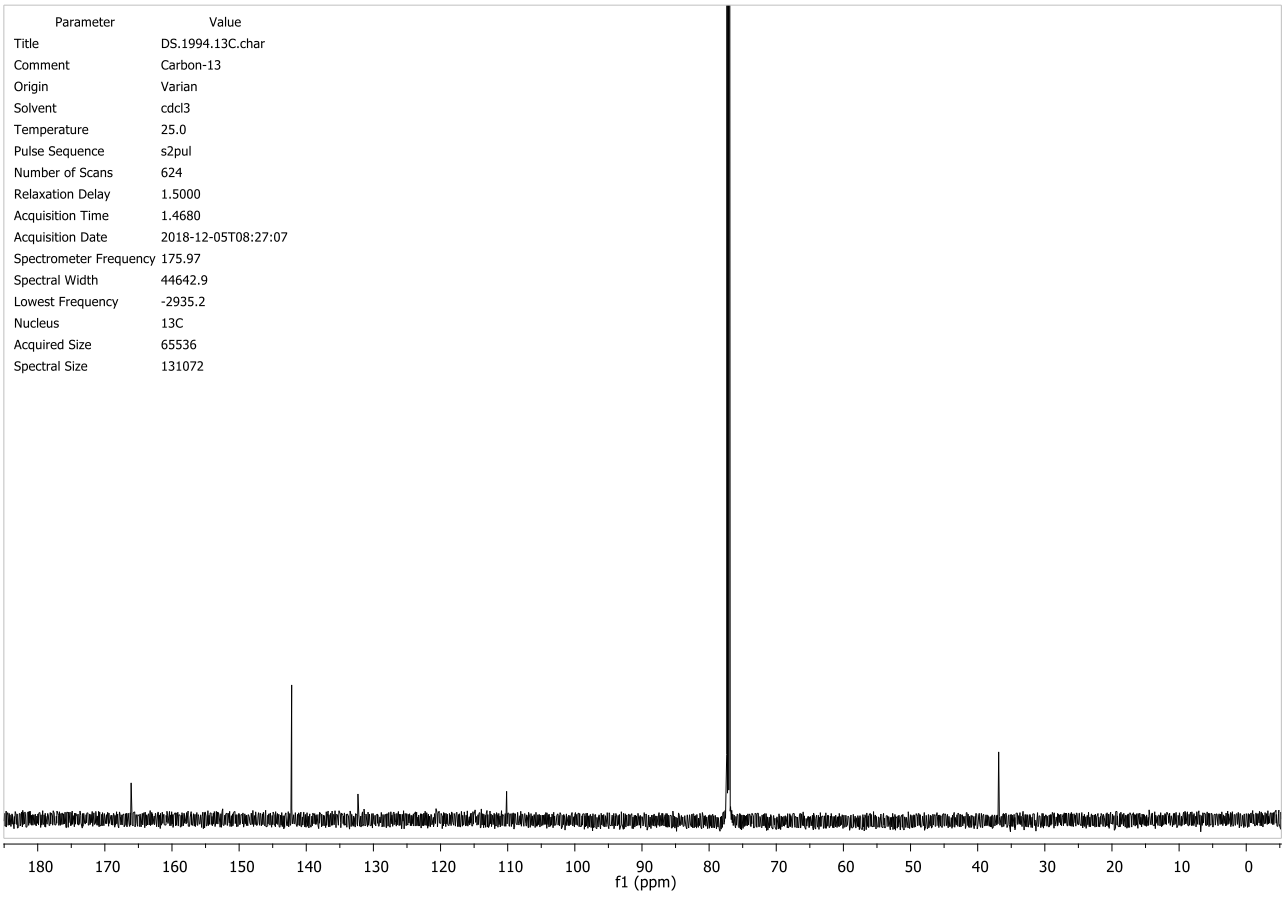
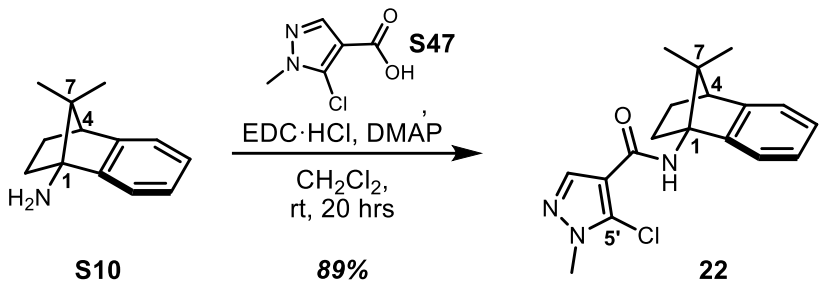


Figure S71: ^{13}C NMR (176 MHz, $CDCl_3$) for S47





Procedure for 5'-Cl C7-dimethyl 1-aminoNB analog 22

1-Aminonorbornane **S10** (14.0 mg; 75 μmol) was dissolved in dry dichloromethane (0.80 mL), followed by addition of carboxylic acid **S47** (18 mg; 112 μmol), DMAP (14 mg; 112 μmol), and EDC·HCl (21.5 mg; 112 μmol), respectively. The reaction was flushed with Ar, capped, and stirred at room temp 14 hrs. The crude residue was diluted with 4 mL water and 2 mL ethyl acetate. Phases were separated, and the aqueous phase was extracted with 3 portions of ethyl acetate, 2 mL each. The organic phases were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The crude residue was purified with flash chromatography over silica (15 to 75% ethyl acetate:pentane, increasing in 15% increments; loaded residue with PhMe; silica was pre-neutralized with a 15% ethyl acetate:pentane + 1% triethylamine mobile phase). Collected the desired carboxamide (**22**) as a white solid in 89.2% yield (22.0 mg).

*Characterization Data for C5'-Cl SDHI candidate **22**:*

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.03 (s, 1H, pyrazole), 7.23-7.20 (m, 1H, Ar), 7.14-7.10 (m, 3H, Ar), 6.39 (br s, 1H, -NH), 3.90 (s, 3H, pyrazole -NMe), 2.83 (d, 1H, *J* = 4.1 Hz, C4), 2.45 (ddd, 1H, *J* = 12.3, 10.2, 4.0 Hz, C2-eq.), 2.26-2.21 (m, 1H, C3-eq), 2.16 (ddd, 1H, *J* = 14.6, 9.2, 4.2 Hz, C2-ax), 1.30 (ddd, 1H, *J* = 12.5, 9.5, 4.1 Hz, C3-ax), 1.15 (s, 3H, C7-Me), 0.70 (s, 3H, C7-Me) ppm

^{13}C NMR ($CDCl_3$, 176 MHz): δ = 161.6, 146.4, 145.9, 141.1, 126.2, 125.8, 125.7, 121.5, 120.7, 115.3, 70.6, 59.3, 50.5, 36.9, 30.0, 26.6, 20.2, 19.7 ppm

HRMS (ESI+, *m/z)* calculated for $C_{18}H_{21}ClN_3O^+$: 330.1368, Found: 330.1374.

R_f = 0.50 (70% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

Figure S72: ^{1}H NMR (500 MHz, $CDCl_3$) for 22

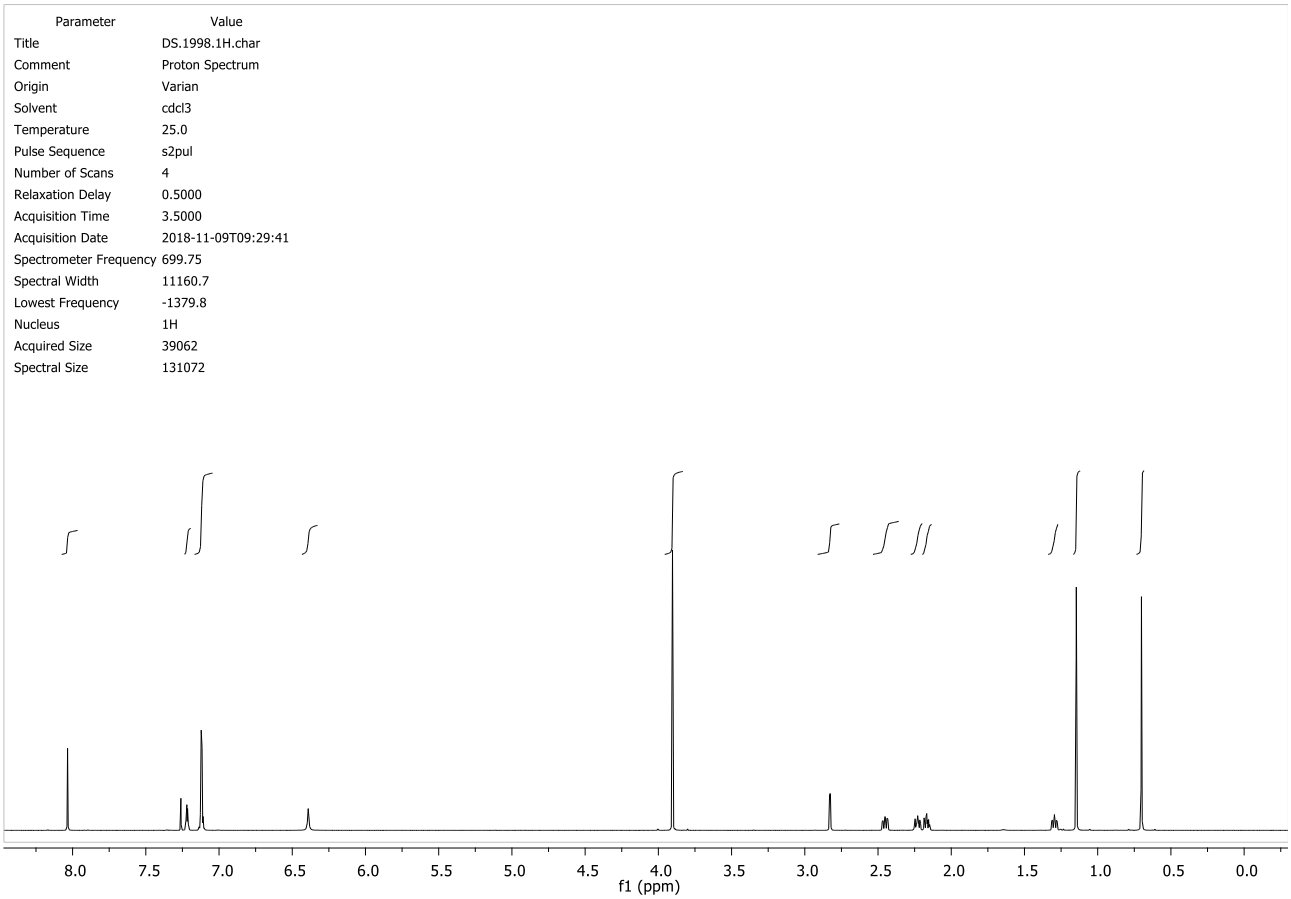
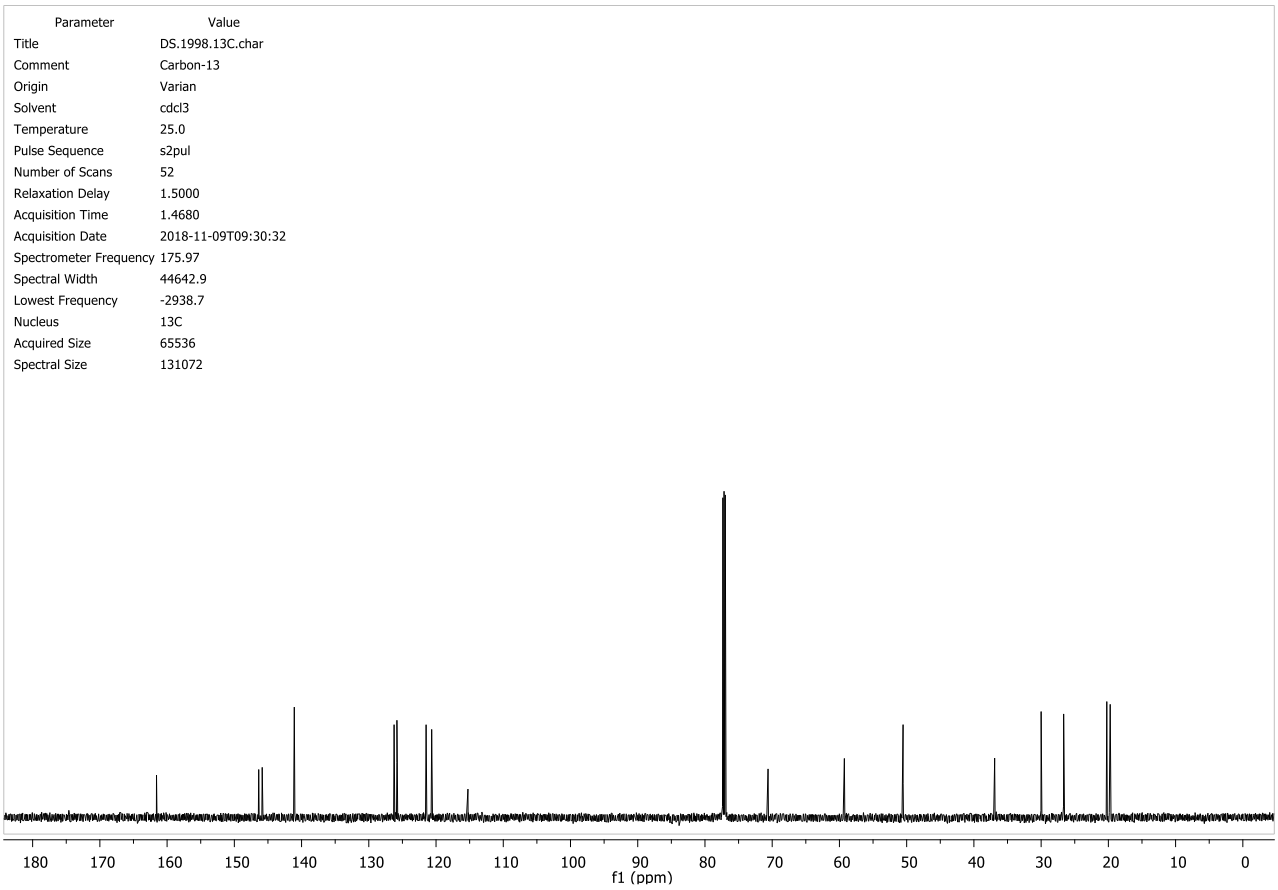
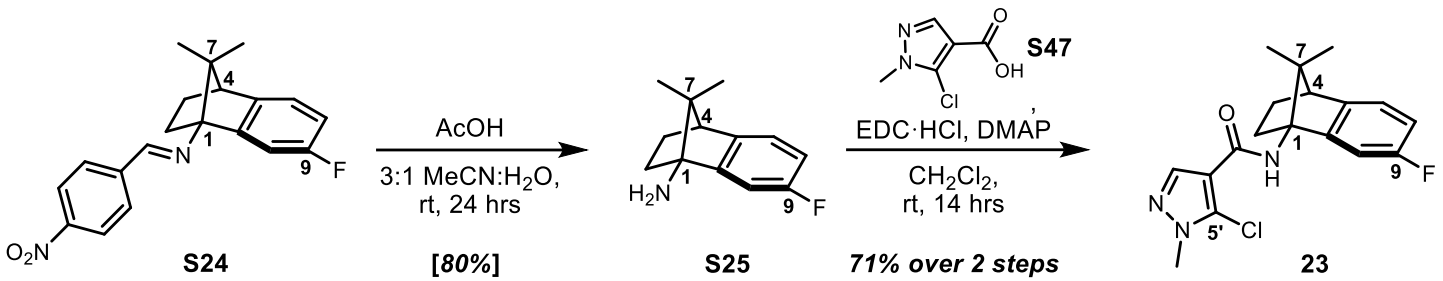


Figure S73: ^{13}C NMR (176 MHz, $CDCl_3$) for 22





Procedure for C5'-chloro-C9-fluoro-C7-dimethyl 1-aminoNB analog 23

1-Aminonorbornane **S25** (14.2 mg; 69 μmol; prepared en route to SDHI candidate **8**) was dissolved in dry dichloromethane (0.70 mL), followed by addition of the carboxylic acid **S47** (17 mg; 106 μmol), DMAP (13 mg; 106 μmol), and EDC·HCl (20 mg; 104 μmol), respectively. The reaction was flushed with Ar, capped, and stirred at room temp 14 hrs. The crude residue was diluted with 4 mL water and 2 mL ethyl acetate. Phases were separated, and the aqueous phase was extracted with 3 portions of ethyl acetate, 2 mL each. The organic phases were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The crude residue was purified with flash chromatography over silica (15 to 75% ethyl acetate:pentane, increasing in 15% increments; loaded residue with PhMe; silica was pre-neutralized with a 15% ethyl acetate:pentane + 1% triethylamine mobile phase). Collected the desired carboxamide (**23**) as a slightly yellow solid: 21.2 mg, 88.1% yield (70.8% over 2 steps).

*Characterization Data for C5'-Cl, C9-F SDHI candidate **23**:*

^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.03 (s, 1H, pyrazole), 7.04 (dd, 1H, *J* = 7.9, 4.9 Hz, Ar), 6.97 (dd, 1H, *J* = 8.4, 2.3 Hz, Ar), 6.80-6.76 (m, 1H, Ar), 6.36 (br s, 1H, -NH), 3.91 (s, 3H, pyrazole -NMe), 2.81 (d, 1H, *J* = 3.7 Hz, C4), 2.37-2.32 (m, 1H, C2-eq.), 2.25-2.19 (m, 2H, C3-eq, C2-ax), 1.30-1.25 (m, 1H, C3-ax), 1.13 (s, 3H, C7-Me), 0.71 (s, 3H, C7-Me) ppm

^{13}C NMR ($CDCl_3$, 176 MHz): δ =161.6 (d, J_{CF} = 242.9 Hz), 161.5, 148.4 (d, J_{CF} = 7.5 Hz), 141.3 (d, J_{CF} = 2.7 Hz), 141.1, 125.8, 122.4 (d, J_{CF} = 8.3 Hz), 115.0, 112.4 (d, J_{CF} = 22.2 Hz), 109.3 (d, J_{CF} = 23.8 Hz), 70.8, 59.5, 49.9, 36.9, 30.1, 26.7, 20.2, 19.6 ppm

^{19}F NMR ($CDCl_3$, 376 MHz): δ = -116.6 (*app* td, *J* = 9.2, 5.2 Hz) ppm

HRMS (ESI+, *m/z)* calculated for $C_{18}H_{20}ClFN_3O^+$: 348.1273, Found: 348.1269.

R_f = 0.50 (70% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

Figure S74: ^{1}H NMR (700 MHz, $CDCl_3$) for 23

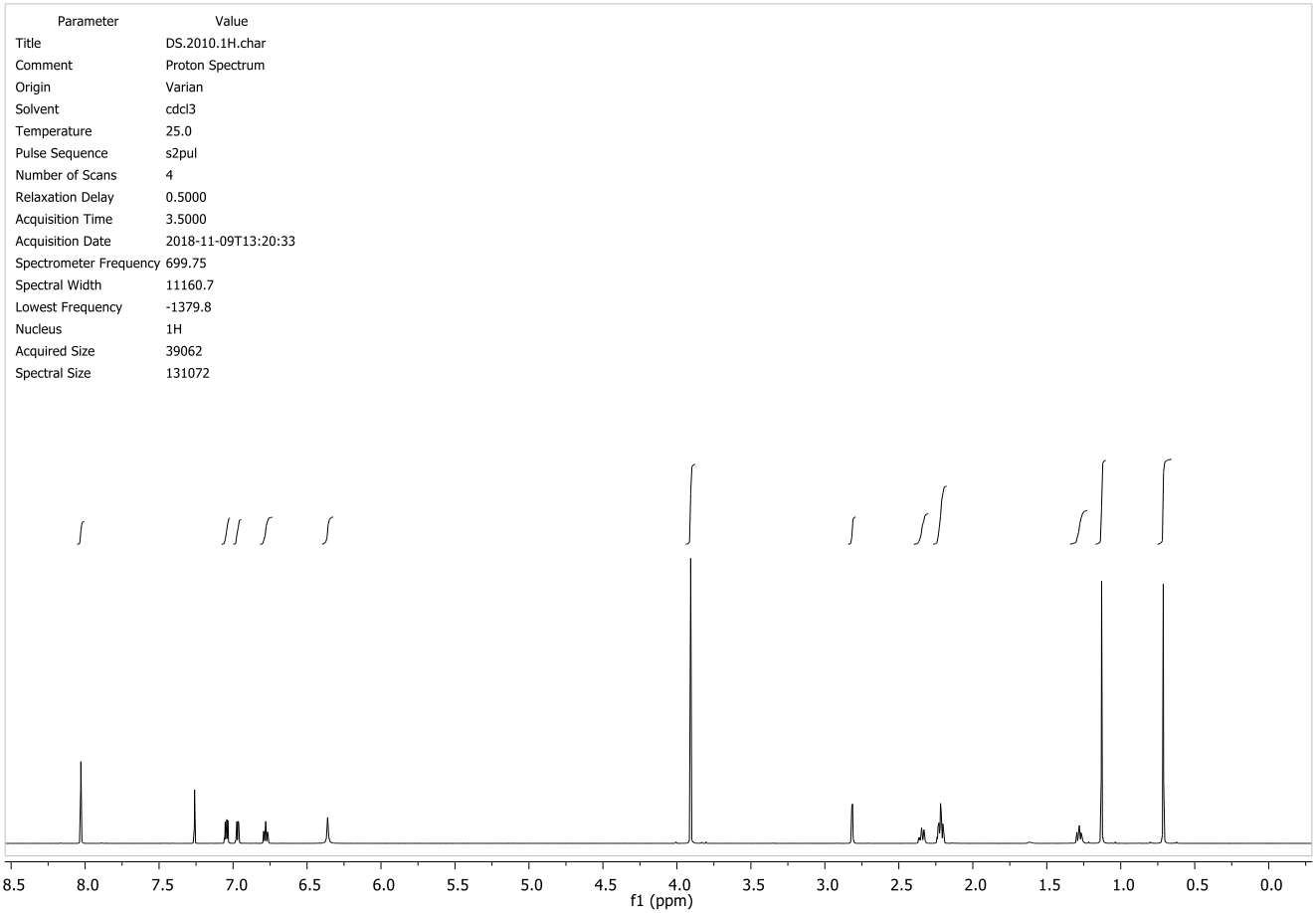


Figure S75: ^{13}C NMR (176 MHz, $CDCl_3$) for 23

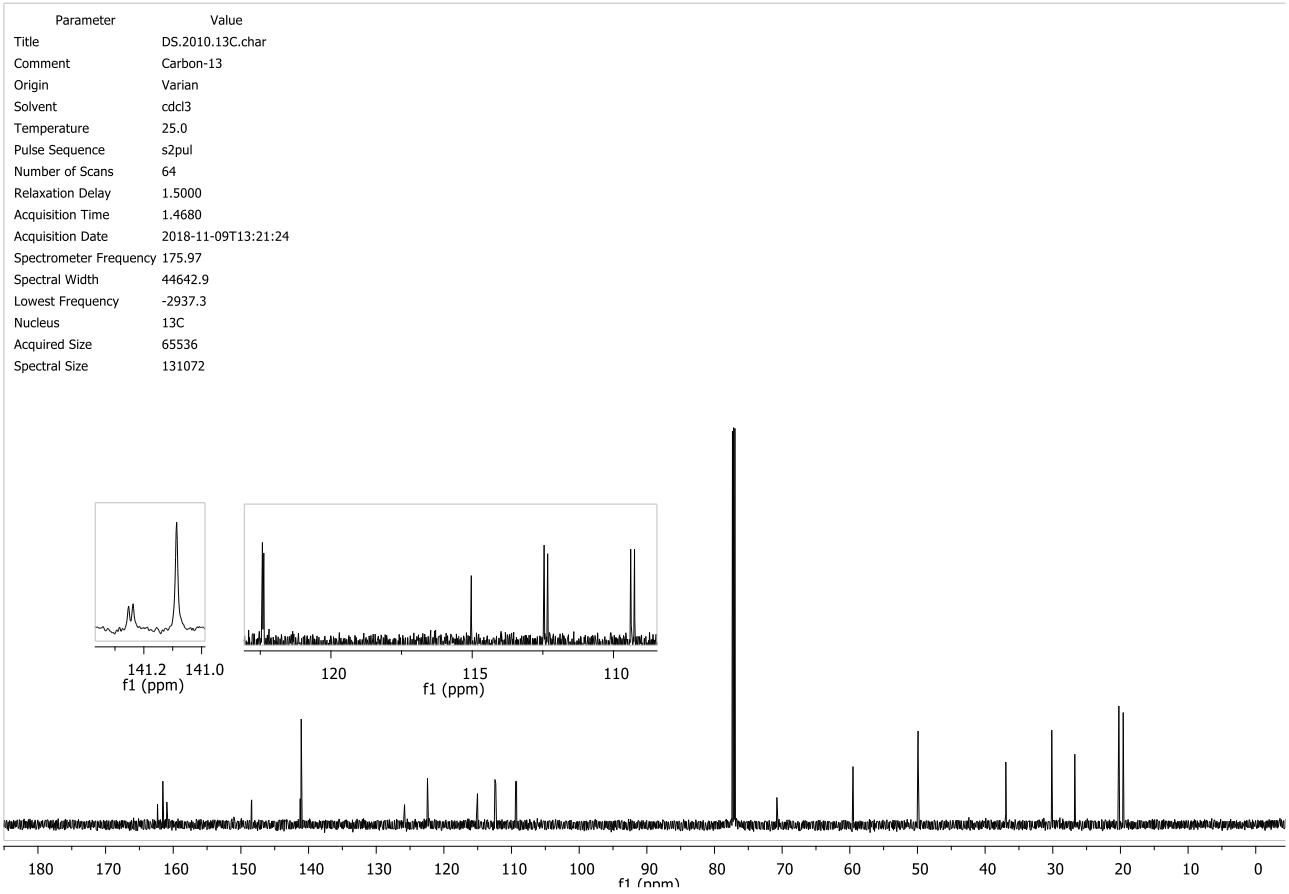
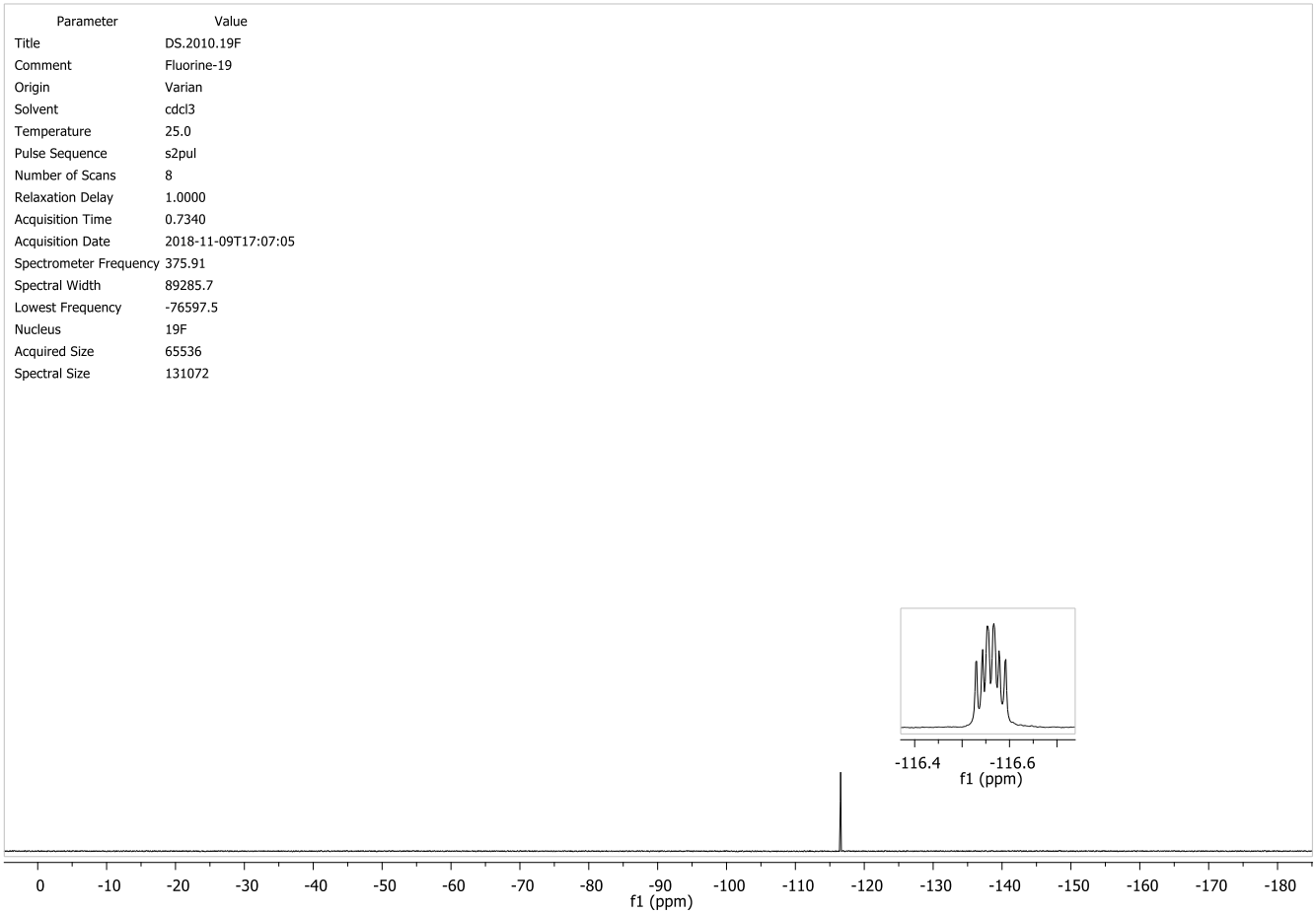
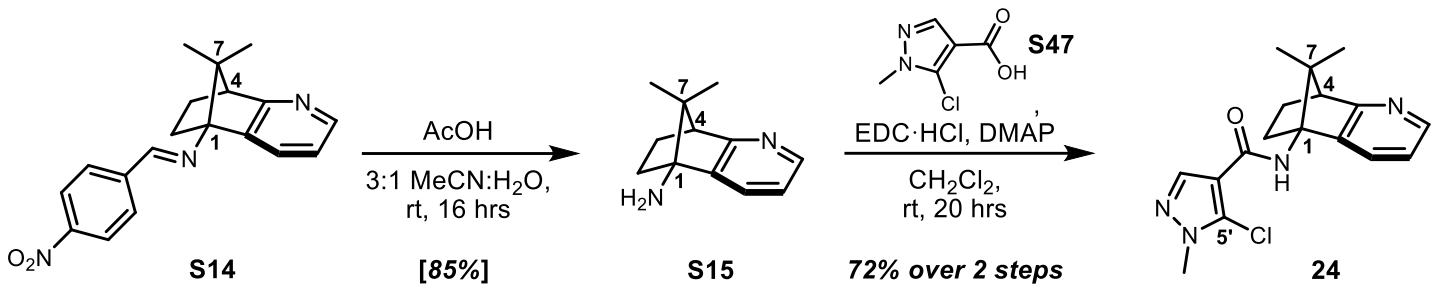


Figure S76: ^{19}F NMR (376 MHz, $CDCl_3$) for 23





Procedure for 11-*aza*-C7-dimethyl 1-aminoNB analog 24

1-Aminonorbornane **S15** (12.4 mg; 66 μmol; prepared en route to SDHI candidate **3**) was dissolved in dry dichloromethane (0.70 mL), followed by addition of the carboxylic acid **S47** (16 mg; 100 μmol), DMAP (12 mg; 98 μmol), and EDC·HCl (19 mg; 99 μmol), respectively. The reaction was flushed with Ar, capped, and stirred at room temp 14 hrs. The crude residue was diluted with 4 mL water and 2 mL ethyl acetate. Phases were separated, and the aqueous phase was extracted with 3 portions of ethyl acetate, 2 mL each. The organic phases were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The crude residue was purified with flash chromatography over silica (5 to 10 to 20 to 30 to 50 to 75% acetone:dichloromethane; silica was pre-neutralized with a 5% acetone:dichloromethane + 1% triethylamine mobile phase). Collected the desired carboxamide (**24**) as a white solid: 18.6 mg, 85.4% yield (72.6% over two steps).

*Characterization Data for C5'-Cl, 11-aza SDHI candidate **24**:*

^{1}H NMR ($CDCl_3$, 700 MHz): δ = 8.24 (dd, 1H, *J* = 5.2, 1.1 Hz, pyridine), 8.03 (s, 1H, pyrazole), 7.53 (d, 1H, *J* = 7.3 Hz, pyridine), 7.02 (dd, 1H, *J* = 7.3, 5.2 Hz, pyridine), 6.43 (br s, 1H, -NH), 3.91 (s, 3H, pyrazole -NMe), 2.96 (d, 1H, *J* = 3.7 Hz, C4), 2.31-2.22 (m, 3H, C2-eq, C3-eq, C2-ax), 1.42-1.37 (m, 1H, C3-ax), 1.17 (s, 3H, C7-Me), 0.75 (s, 3H, C7-Me) ppm

^{13}C NMR ($CDCl_3$, 176 MHz): δ = 166.1, 161.6, 146.6, 141.1, 139.8, 129.2, 125.9, 121.3, 114.8, 69.4, 58.3, 52.6, 37.0, 30.7, 25.1, 20.2, 19.1 ppm

HRMS (ESI+, *m/z)* calculated for $C_{17}H_{20}ClN_4O^+$: 331.1320, Found: 331.1318.

R_f = 0.10 (10% acetone:dichloromethane + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

Figure S77: ^{1}H NMR (700 MHz, $CDCl_3$) for 24

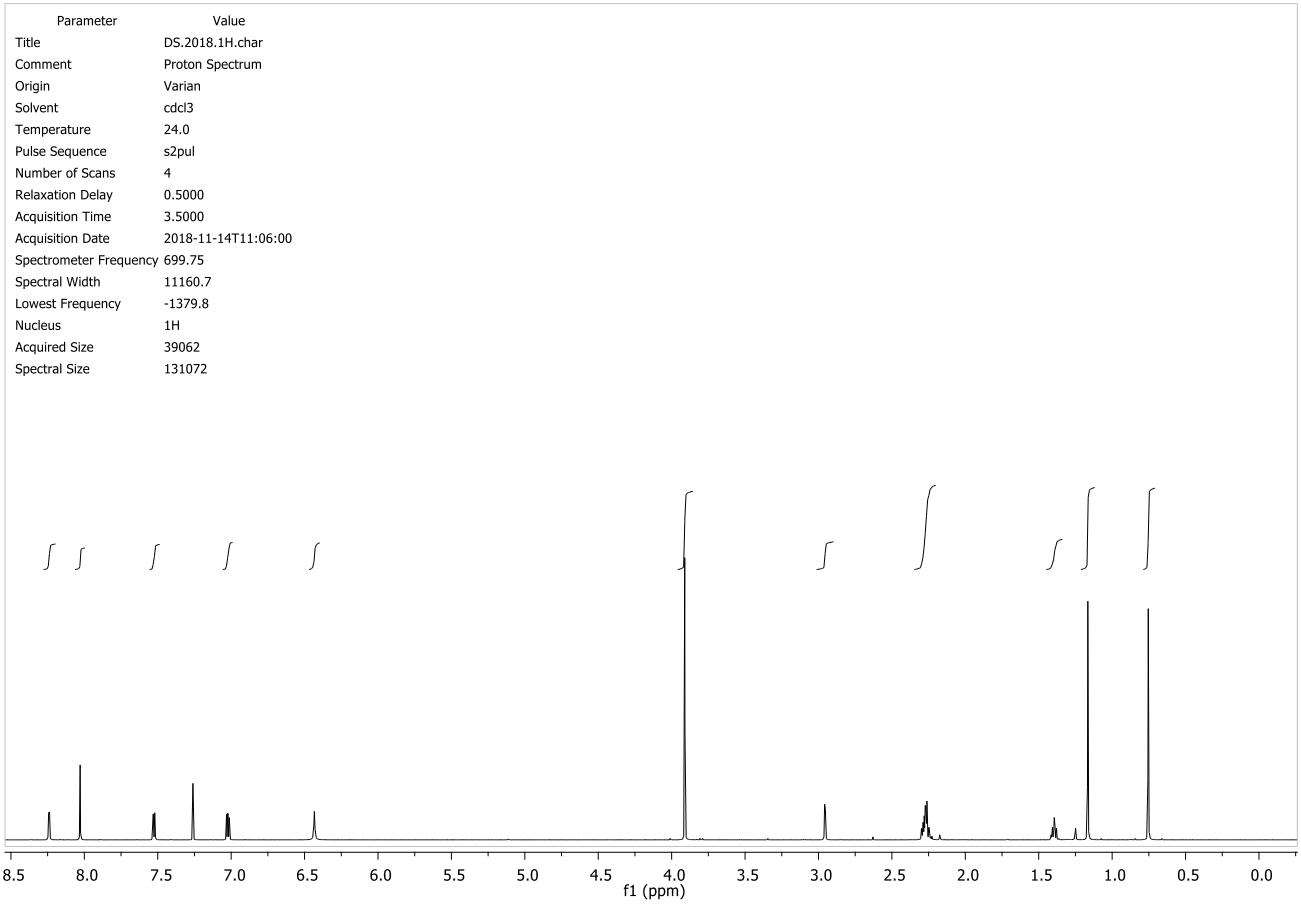
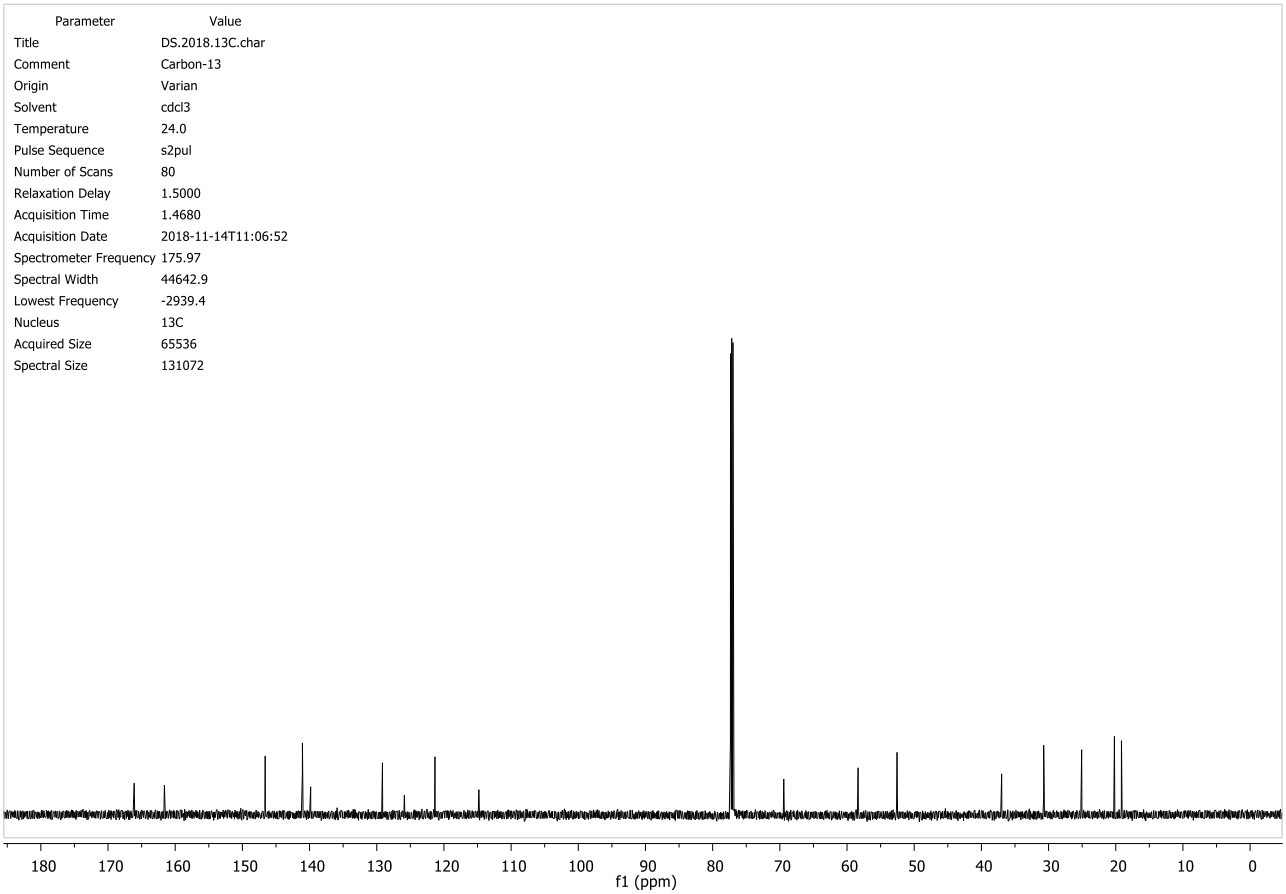
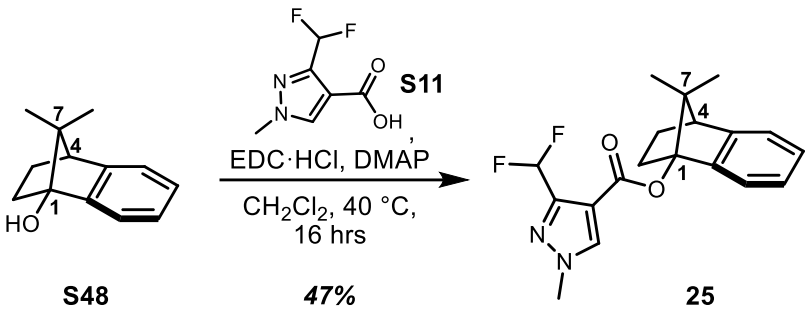


Figure S78: ^{13}C NMR (176 MHz, $CDCl_3$) for 24





Procedure for C7-dimethyl 1-hydroxy analog 25

The 1-hydroxynorbornane **S48** (13.0 mg, 69 μmol; produced from 1-aminoNB **S10**[7]) was dissolved in 1.1 mL dry CH_2Cl_2 in a flame-dried vial under inert atmosphere, followed by the addition of carboxylic acid **S11** (28 mg; 159 μmol), DMAP (19 mg; 156 μmol), and EDC·HCl (30 mg; 156 μmol), respectively. The reaction was flushed with Ar, capped, and stirred at 40 °C for 16 hrs. The crude residue was diluted with 4 mL water and 2 mL ethyl acetate. Phases were separated, and the aqueous phase was extracted with 3 portions of ethyl acetate, 2 mL each. The organic phases were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The crude residue was purified with flash chromatography over silica (3 to 6 to 10 to 15 to 25 to 35 to 50 to 75% ethyl acetate:pentane; loaded residue with PhMe; silica was pre-neutralized with a 3% ethyl acetate:pentane + 1% triethylamine mobile phase). Collected 6.9 mg of recovered starting material as a clear, colorless oil (53% recovery) and 11.3 mg of the desired acylated product **25** as a slightly yellow solid (47.2% yield).

*Characterization Data for 1-acyloxy SDHI candidate **25**:*

^{1}H NMR ($CDCl_3$, 700 MHz): δ = 7.98 (s, 1H, pyrazole), 7.17 (d, 1H, J = 6.9 Hz, Ar), 7.14 (t, 1H, J_{HF} = 54.2 Hz, -CHF_2), 7.14-7.09 (m, 3H, Ar), 4.00 (s, 3H, pyrazole -NMe), 2.79 (d, 1H, J = 4.1 Hz, C4), 2.35 (ddd, 1H, J = 11.8, 9.5, 4.0 Hz, C2-eq), 2.27 (*app*. ddt, 1H, J = 15.9, 11.9, 4.1 Hz, C3-eq), 2.18 (ddd, 1H, J = 11.6, 10.6, 3.9 Hz, C2-ax), 1.35 (ddd, 1H, J = 11.9, 9.8, 3.9 Hz, C3-ax), 1.18 (s, 3H, C7-Me), 0.73 (s, 3H, C7-Me) ppm

^{13}C NMR ($CDCl_3$, 176 MHz): δ = 161.5, 146.2 (t, J_{CF} = 24.6 Hz), 145.6, 144.5, 135.6, 126.4, 125.7, 121.7, 121.4, 113.8 (t, J_{CF} = 3.2 Hz), 109.5 (t, J_{CF} = 236.9 Hz), 93.7, 59.3, 48.6, 39.9, 29.1, 27.0, 20.0, 19.3 ppm

^{19}F NMR ($CDCl_3$, 376 MHz): δ = -114.6 (*app.* dd, J = 309.1, 54.1 Hz), -116.4 (*app.* dd, J = 309.1, 53.9 Hz) ppm

HRMS (ESI+, *m/z)* calculated for $C_{19}H_{21}F_2N_2O_2^+$: 347.1566, Found: 347.1571.

R_f = 0.30 (30% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

Figure S79: ^{1}H NMR (700 MHz, $CDCl_3$) for 25

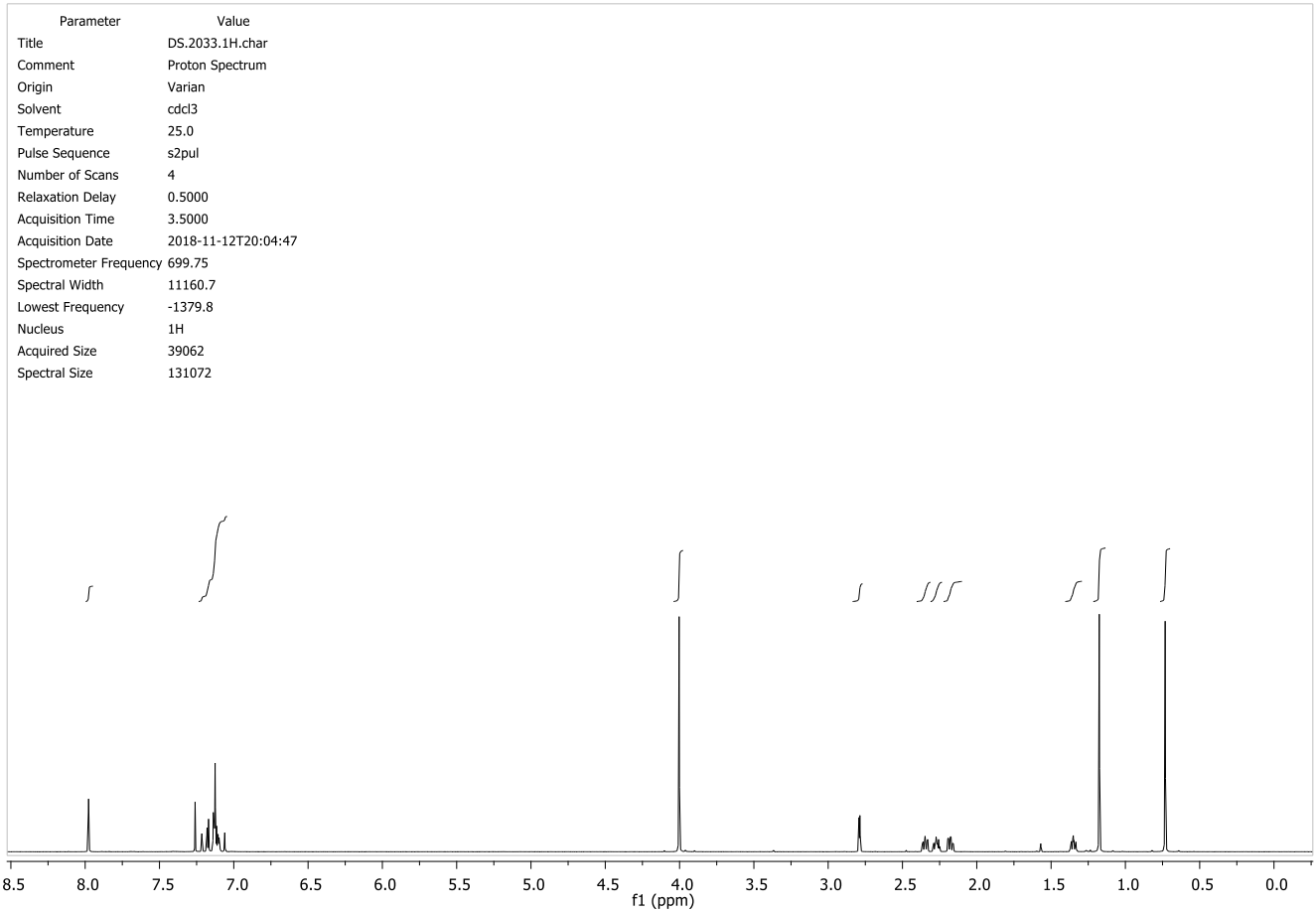


Figure S80: ^{13}C NMR (176 MHz, $CDCl_3$) for 25

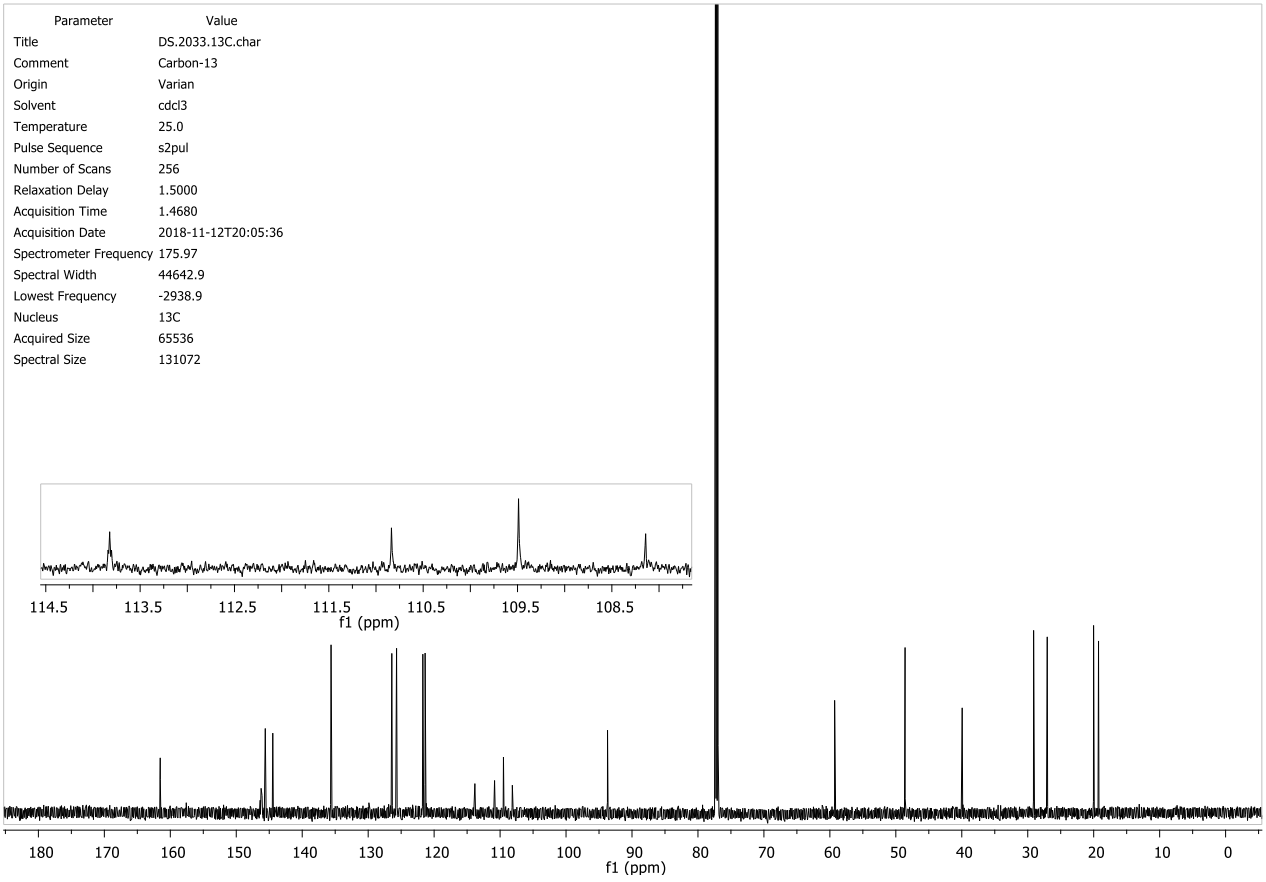
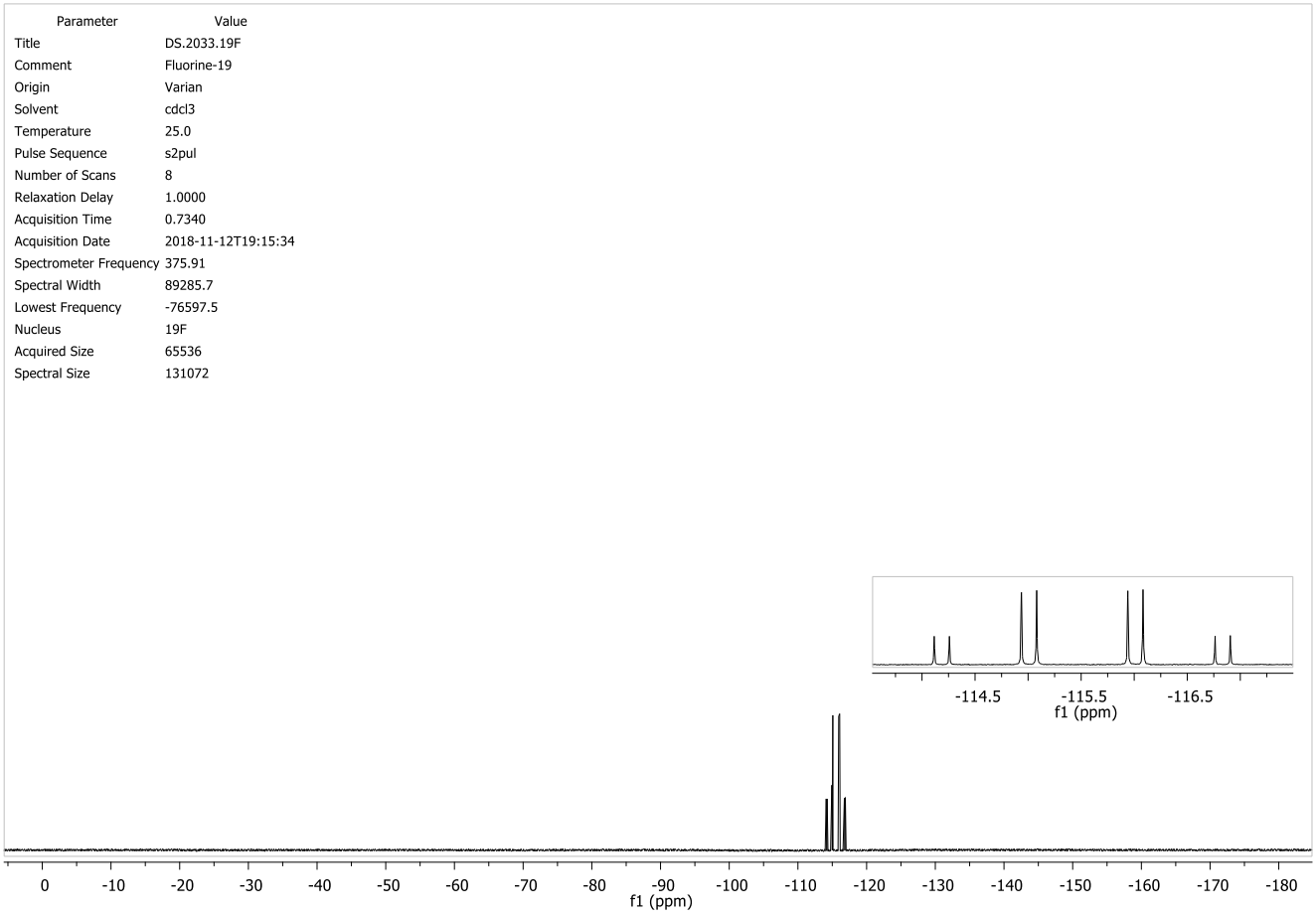
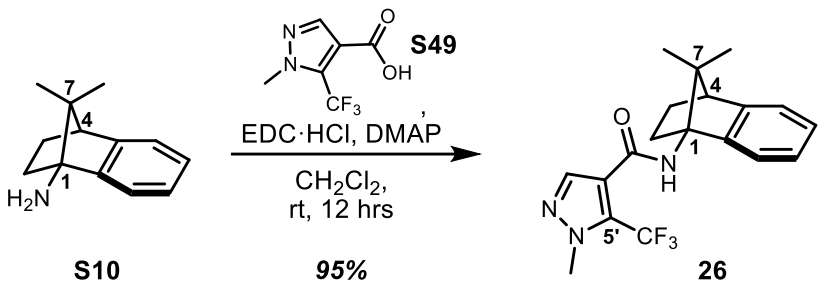


Figure S81: ^{19}F NMR (376 MHz, $CDCl_3$) for 25





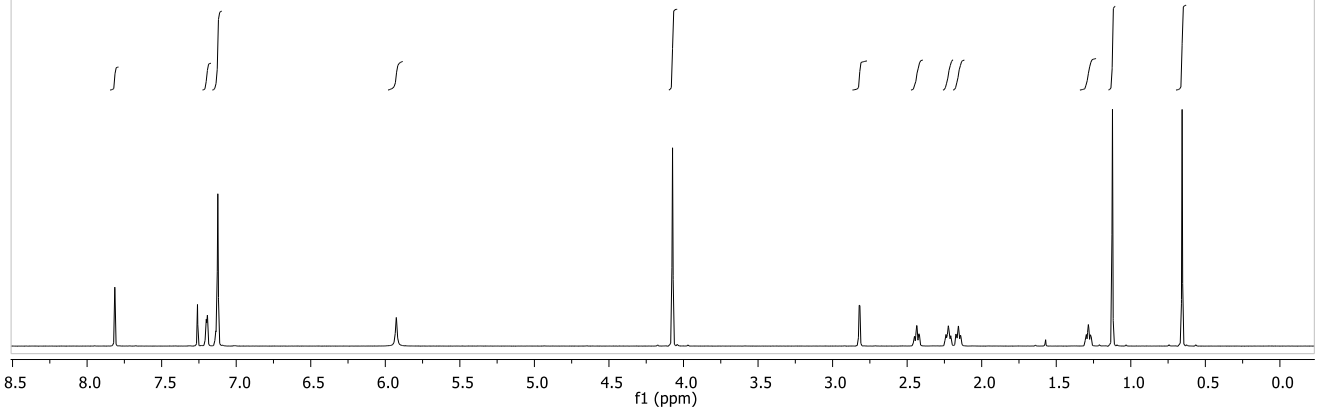
Procedure for C5'-trifluoromethyl C7-dimethyl 1-aminoNB analog 26

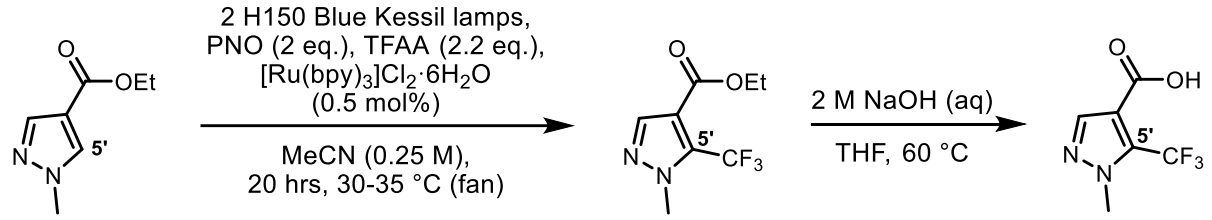
1-Aminonorbornane **S10** (6.0 mg in 0.5 mL CH_2Cl_2; 32 μmol; aliquot taken from a freshly-prepared 6.0 mg/0.5 mL stock solution) was added to a flame-dried vial under inert atmosphere to which carboxylic acid **S49** (11.1 mg; 57 μmol; see preparation below) had already been added. DMAP (5.9 mg; 48 μmol) and EDC·HCl (9.2 mg; 48 μmol) were each added in one portion, respectively. The reaction was flushed with Ar, capped, and stirred at room temp for 12 hrs. The crude residue was diluted with 2 mL 1:1 sat. $NaHCO_3$ (aq):1 M NaOH (aq) and 2 mL ethyl acetate. Phases were separated, and the aqueous phase was extracted with 3 portions of ethyl acetate, 2 mL each. The organic phases were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The crude residue was purified with pipet-scale chromatography over silica (10 to 20 to 40% ethyl acetate:pentane; loaded residue with PhMe; silica was pre-neutralized with a 10% ethyl acetate:pentane + 1% triethylamine mobile phase). Collected 11.0 mg of a white solid, which proved to be pure carboxamide **26** by ^{1}H NMR analysis (94.5% yield).

*Partial Characterization Data for C5'-trifluoromethyl C7-dimethyl 1-aminoNB SDHI candidate **26**:*
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.81 (s, 1H, pyrazole), 7.21-7.18 (m, 1H, Ar), 7.15-7.11 (m, 3H, Ar), 5.93 (br s, 1H, -NH), 4.07 (s, 3H, pyrazole -NMe), 2.82 (d, 1H, *J* = 3.1 Hz, C4), 2.44 (*app.* t, 1H, *J* = 3.1 Hz, C2-eq), 2.22 (*app.* t, 1H, *J* = 3.1 Hz, C3-eq), 2.16 (*app.* t, 1H, *J* = 3.1 Hz, C2-ax), 1.28 (*app.* t, 1H, *J* = 3.1 Hz, C3-ax), 1.12 (s, 3H, C7-Me), 0.66 (s, 3H, C7-Me) ppm
HRMS (ESI+, *m/z)* calculated for $C_{19}H_{21}F_3N_3O^+$: 364.1631, Found: 364.1631.
R_f = 0.25 (30% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

Figure S82: ^{1}H NMR (500 MHz, $CDCl_3$) for 26

Parameter	Value
Title	DS.1754.1H.char
Comment	Proton Spectrum
Origin	Varian
Solvent	cdcl3
Temperature	25.0
Pulse Sequence	s2pul
Number of Scans	4
Relaxation Delay	0.5000
Acquisition Time	3.5000
Acquisition Date	2018-02-13T19:03:15
Spectrometer Frequency	699.75
Spectral Width	11160.7
Lowest Frequency	-1379.8
Nucleus	1H
Acquired Size	39062
Spectral Size	131072





Procedure for C5'-trifluoromethyl pyrazole acid S49

Pyrazole ethyl ester **S50** (212 mg, 1.4 mmol; purchased from Synthonix, re-purified via flash chromatography to a white solid prior to use: $\mathbf{R_f}$ = 0.30 (40% ethyl acetate:hexanes + 1% NH_4OH)) was dissolved in dry MeCN (5.0 mL) prior to the addition of pyridine *N*-oxide (262 mg, 2.8 mmol) and $[Ru(bpy)_3]Cl_2 \cdot 6H_2O$ (5.2 mg, 6.9 μmol), respectively. The reaction mixture was degassed via four freeze-pump-thaw cycles. Trifluoroacetic anhydride (0.30 mL, 3.0 mmol) was added dropwise over 30 sec, prior to sealing the reaction vessel under inert atmosphere. Two Tuna Blue H150 Kessil lamps were positioned on either side of the vial, each 4 cm away, set perpendicular to the sides of the vial (aligned such that the apex of the light should hit the center of the reaction mixture); a cooling fan was positioned 5 cm above the vial (previously shown to maintain temperatures at ~30-35 °C in this apparatus); the mixture was irradiated using this setup for 20 hrs. The reaction mixture had turned dark red. The mixture was quenched with 10 mL 1:1 sat. $NaHCO_3$ (aq):1 M NaOH (aq), then diluted with 10 mL ether. Phases were separated, and the aqueous phase was extracted with 3 portions of ether, 10 mL each. The organic phases were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under vacuum. The crude residue was purified with pipet-scale chromatography over silica (5 to 25% ethyl acetate:hexanes, increasing in 5% increments; loaded residue with PhMe; silica was pre-neutralized with a 5% ethyl acetate:pentane + 1% triethylamine mobile phase). Collected 28.8 mg of a clear, colorless oil, which proved to be pure C5'-trifluoromethyl pyrazole ester **S51** by ^{1}H NMR analysis (9.4% yield).

Note: This method was adapted from photochemistry developed in the Stephenson group (see references below). Clearly, the electronics are not optimally-suited for this particular substrate, but the ability to access the C5' regioisomer was valuable enough to tolerate the low yield. The variation of this methodology that employs 4-Ph-pyridine *N*-oxide did provide higher conversion, but the trifluoromethylated 4-Ph-pyridine byproduct coeluted with the desired pyrazole. For commentary on electronic effects on radical additions to arenes (specific to this mechanism), see commentary in refs c and d. References: a) Beatty, J.; Douglas, J.; Cole, K.; Stephenson, CRJ. *Nat. Commun.* **2015**, 7919; b) Beatty, J.; Douglas, J.; Miller, R.; McAtee, R.; Cole, K.; Stephenson, CRJ. *Chem* **2016**, 456; c) Sun, A.; McClain, A.; Beatty, J.; Stephenson, CRJ. *Org. Lett.* **2018**, 3487; d) McAtee, R.; Beatty, J.; McAtee, C.; Stephenson, CRJ. *Org. Lett.* **2018**, 3491.

*Partial Characterization Data for C5'-trifluoromethyl pyrazole ethyl ester **S51**:*
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.91 (s, 1H, pyrazole), 4.32 (q, 1H, *J* = 7.1 Hz, -CO_2Et), 4.09-4.07 (m, 3H, -NMe), 1.35 (t, 1H, *J* = 7.1 Hz, -CO_2Et) ppm
Note: For this compound, the -NMe is not a sharp single due to long-range HF coupling.
$\mathbf{R_f}$ = 0.75 (40% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

Ester **S51** (28.8 mg, 0.13 mmol) was dissolved in 0.65 mL dry THF prior to the addition of 0.65 mL 2 M NaOH (aq). Flushed vial with Ar, sealed with electrical tape, then heated to 60 °C for 12 hrs while stirring vigorously. Upon cooling to room temp, the reaction mixture was diluted with 2 mL 1 M NaOH (aq) and 2 mL ether. The phases were separated, and the basic aqueous phase was washed with two portions of ether, 2 mL each. The aqueous phase was made acidic by the addition of ~ 2 mL 1 M HCl (aq), halting addition at an aqueous pH ~ 3. Acidic aqueous phase was extracted with four 2 mL portions of ethyl acetate. Combined organics were dried over anhydrous sodium sulfate, filtered to remove solids, and concentrated under vacuum. Obtained the desired acid **S49** as a white solid, pure by ^{1}H NMR, 23.8 mg (94.6% yield).

*Partial Characterization Data for C5'-trifluoromethyl pyrazole acid **S49**:*
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.00 (s, 1H, pyrazole), 4.11 (*app.* d, 3H, J_{HF} = 1.7 Hz, -NMe) ppm
HRMS (ESI-, *m/z)* calculated for $C_6H_4F_3N_2O_2^+$: 193.0230, Found: 193.0224.

Note: For sake of comparison, the C3'-trifluoromethyl pyrazole acid (purchased from Enamine en route to SDHI candidate **28**) has the following line-listing: **^{1}H NMR** ($CDCl_3$, 500 MHz): δ = 8.02 (s, 1H, pyrazole), 4.00 (s, 3H, -NMe) ppm.

Figure S83: ^{1}H NMR (500 MHz, $CDCl_3$) for S51

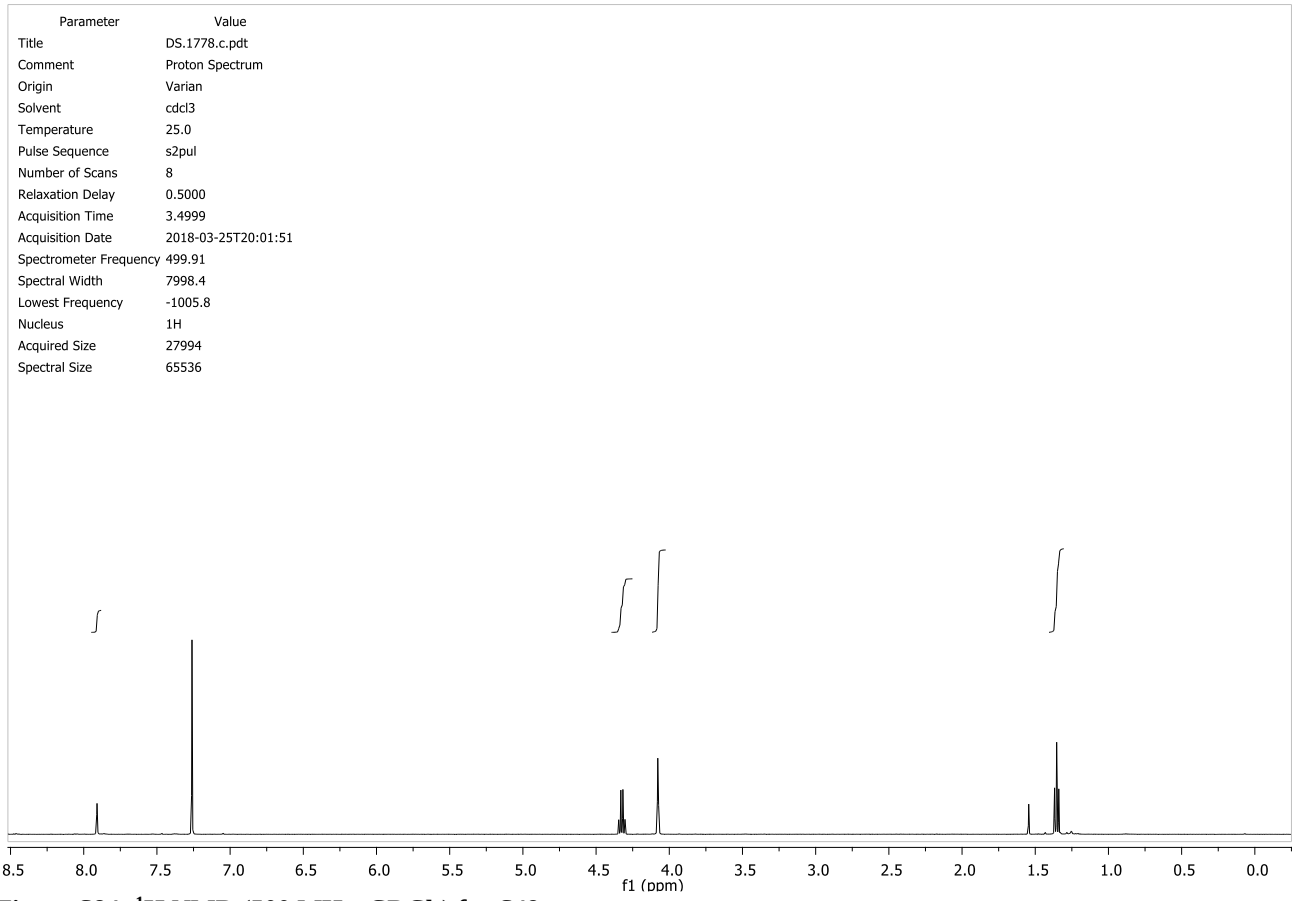
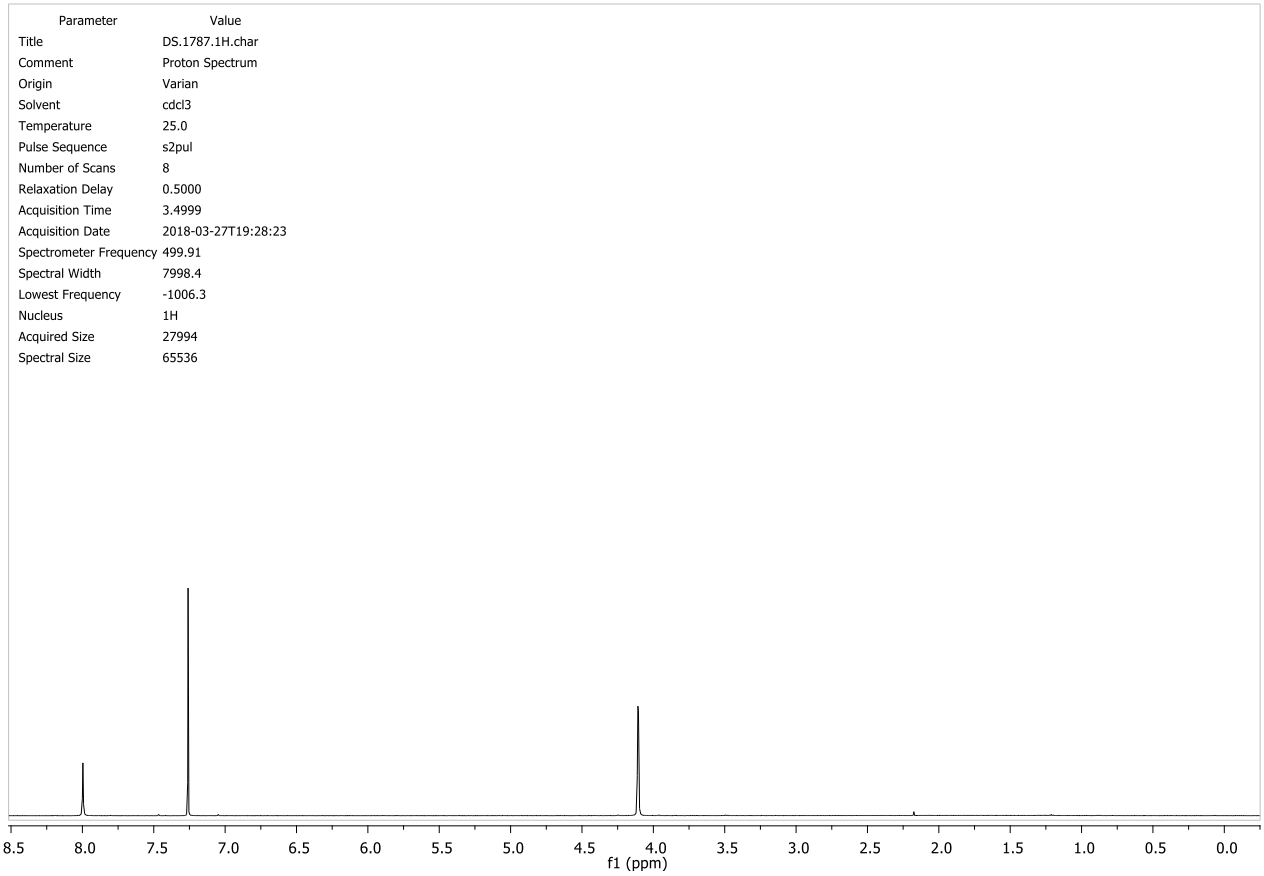
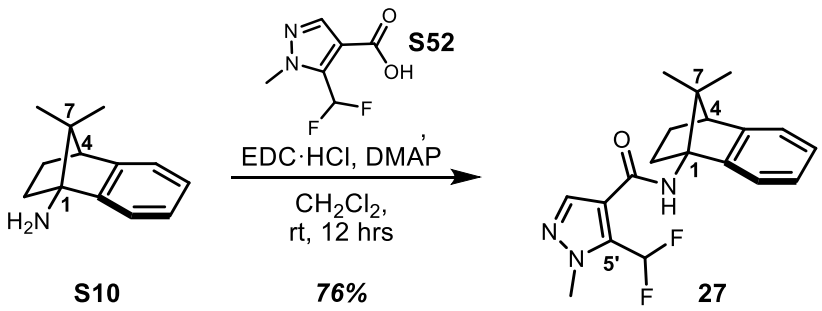


Figure S84: ^{1}H NMR (500 MHz, $CDCl_3$) for S49

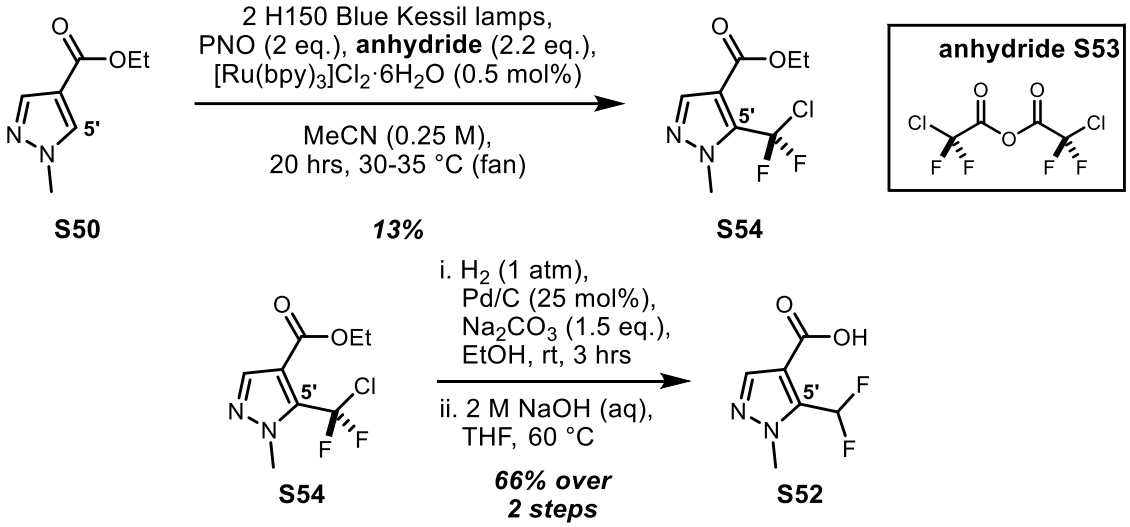




Procedure for C5'-difluoromethyl C7-dimethyl 1-aminoNB analog 27

In a flame-dried vial under inert atmosphere, 1-aminonorbornane **S10** (12.7 mg; 68 μmol) was dissolved in a dichloromethane solution of carboxylic acid **S52** (11.9 mg in 2.2 mL; 68 μmol; see preparation below), followed by the addition of DMAP (12.4 mg; 102 μmol), and EDC·HCl (19.5 mg; 102 μmol) in one portion each, respectively. The reaction was flushed with Ar, capped, and stirred at room temp 12 hrs. The crude residue was diluted with 2 mL 1:1 sat. $NaHCO_3$ (aq):1 M NaOH (aq) and 2 mL ethyl acetate. Phases were separated, and the aqueous phase was extracted with 3 portions of ethyl acetate, 2 mL each. The organic phases were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The crude residue was purified with pipet-scale chromatography over silica (5 to 10 to 15 to 25% ethyl acetate:pentane; loaded residue with PhMe; silica was pre-neutralized with a 5% ethyl acetate:pentane + 1% triethylamine mobile phase). Obtained 17.7 mg of the desired carboxamide (**27**) as a slightly yellow solid (75.6% yield), pure by ^{1}H NMR analysis.

*Partial Characterization Data for C5'-difluoromethyl C7-dimethyl 1-aminoNB SDHI candidate **27**:*
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.67 (t, 1H, J_{HF} = 54.9 Hz, -CHF_2), 7.66 (s, 1H, pyrazole), 7.18-7.12 (m, 4H, Ar), 5.96 (br s, 1H, -NH), 4.10 (s, 3H, pyrazole -NMe), 2.84 (d, 1H, *J* = 4.1 Hz, C4), 2.45 (ddd, 1H, *J* = 12.2, 10.4, 3.9 Hz, C2-eq), 2.26-2.20 (m, 1H, C3-eq), 2.11-2.05 (m, 1H, C2-ax), 1.32-1.24 (m, 1H, C3-ax), 1.13 (s, 3H, C7-Me), 0.70 (s, 3H, C7-Me) ppm
HRMS (ESI+, *m/z)* calculated for $C_{19}H_{22}F_2N_3O^+$: 346.1725, Found: 346.1721.
R_f = 0.65 (40% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV



Procedure for C5'-trifluoromethyl pyrazole acid S52

Pyrazole ethyl ester **S50** (212 mg, 1.4 mmol; purchased from Synthonix, re-purified via flash chromatography to a white solid prior to use: $\mathbf{R_f}$ = 0.30 (40% ethyl acetate:hexanes + 1% NH_4OH)) was dissolved in dry MeCN (5.0 mL) prior to the addition of pyridine *N*-oxide (262 mg, 2.8 mmol) and $[Ru(bpy)_3]Cl_2 \cdot 6H_2O$ (5.2 mg, 6.9 μmol), respectively. The reaction mixture was degassed via four freeze-pump-thaw cycles. Anhydride **S53** (0.53 mL, 3.0 mmol; purchased from Oakwood Chemical) was added dropwise over 30 sec, prior to sealing the reaction vessel under inert atmosphere. Two Tuna Blue H150 Kessil lamps were positioned on either side of the vial, each 4 cm away, set perpendicular to the sides of the vial (aligned such that the apex of the light should hit the center of the reaction mixture); a cooling fan was positioned 5 cm above the vial (previously shown to maintain temperatures at ~30-35 °C in this apparatus); the mixture was irradiated using this setup for 20 hrs. The reaction mixture had turned dark red. The mixture was quenched with 10 mL 1:1 sat. $NaHCO_3$ (aq):1 M NaOH (aq), then diluted with 10 mL ether. Phases were separated, and the aqueous phase was extracted with 3 portions of ether, 10 mL each. The organic phases were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under vacuum. The crude residue was purified with pipet-scale chromatography over silica (2 to 4 to 6 to 10 to 15% ethyl acetate:hexanes; loaded residue with PhMe; silica was pre-neutralized with a 2% ethyl acetate:pentane + 1% triethylamine mobile phase). Collected 42.1 mg of a clear, colorless oil, which proved to be pure C5'-trifluoromethyl pyrazole ester **S51** by ^{1}H NMR analysis (12.8% yield; see mechanistic commentary for acid **S49**).

*Partial Characterization Data for C5'-chlorodifluoromethyl pyrazole ethyl ester **S54**:*
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.88 (s, 1H, pyrazole), 4.34 (q, 1H, J = 7.1 Hz, -CO_2Et), 4.08 (t, 3H, J_{CF} = 2.4 Hz, -NMe), 1.37 (t, 1H, J = 7.1 Hz, -CO_2Et) ppm
Note: For this compound, the -NMe is not a sharp single due to long-range HF coupling.
$\mathbf{R_f}$ = 0.80 (30% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

Chlorodifluoromethylated pyrazole ester **S54** (41.8 mg; 175 μmol) was dissolved in 2.0 mL EtOH (200 proof) under an atmosphere of Ar. Added Pd/C (10 wt% Pd; 15.5 mg, 44 μmol) then sodium carbonate (27.9 mg, 0.26 mmol) in one portion each. Sparged reaction mixture with a balloon of H_2 through a 22 gauge needle (20 gauge outlet needle) for 20 min. Stirred under an atmosphere of hydrogen at room temp for 4 hrs. Sparged with N_2 in the same manner as above for 5 min, then filtered through a plug of celite, eluting with ~5 mL ether. Concentrated filtrate under stream of nitrogen. Collected 26.3 mg of a clear, colorless oil, which was pure difluoromethyl pyrazole ester by ^{1}H NMR (73.5% yield). Note: C-Cl reduction conditions taken from: McAtee, R.; Beatty, J.; McAtee, C.; Stephenson, CRJ. *Org. Lett.* **2018**, 3491.

Partial Characterization Data for C5'-difluoromethyl pyrazole ethyl ester:
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.85 (s, 1H, pyrazole), 7.48 (t, 1H, J_{HF} = 54.8 Hz, -CHF_2), 4.32 (q, 1H, J = 7.1 Hz, -CO_2Et), 4.07 (s, 3H, -NMe), 1.37 (t, 1H, J = 7.1 Hz, -CO_2Et) ppm

The ester synthesized above (26.3 mg, 0.13 mmol) was dissolved in 0.65 mL dry THF prior to the addition of 0.65 mL 2 M NaOH (aq). Flushed vial with Ar, sealed with electrical tape, then heated to 60 °C for 12 hrs while stirring vigorously. Upon cooling to room temp, the reaction mixture was diluted with 2 mL 1 M NaOH (aq) and 2 mL ether. The phases were separated, and the basic aqueous phase was washed with two portions of ether, 2 mL each. The aqueous phase was made acidic by the addition of ~ 2 mL 1 M HCl (aq),

halting addition at an aqueous pH ~ 3. Acidic aqueous phase was extracted with four 2 mL portions of ethyl acetate. Combined organics were dried over anhydrous sodium sulfate, filtered to remove solids, and concentrated under vacuum. Obtained the desired acid **S52** as a white solid, pure by ^{1}H NMR, 20.5 mg (90.4% yield; 66.4% over 2 steps).

*Partial Characterization Data for C5'-difluoromethyl pyrazole acid **S52**:*
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.93 (s, 1H, pyrazole), 7.46 (t, 1H, J_{HF} = 52.7 Hz, -CHF_2), 4.10 (s, 3H, -NMe) ppm
HRMS (ESI-, *m/z)* calculated for $C_6H_5F_2N_2O_2^+$: 175.0325, Found: 175.0321.

Note: For sake of comparison, the C3'-difluoromethyl pyrazole acid (purchased from Enamine en route to SDHI candidate **1**) has the following line-listing: **^{1}H NMR** ($CDCl_3$, 500 MHz): δ = 7.97 (s, 1H, pyrazole), 7.10 (t, 1H, J_{HF} = 53.8 Hz, -CHF_2), 4.00 (s, 3H, -NMe) ppm.

Figure S85: ^{1}H NMR (500 MHz, $CDCl_3$) for S54

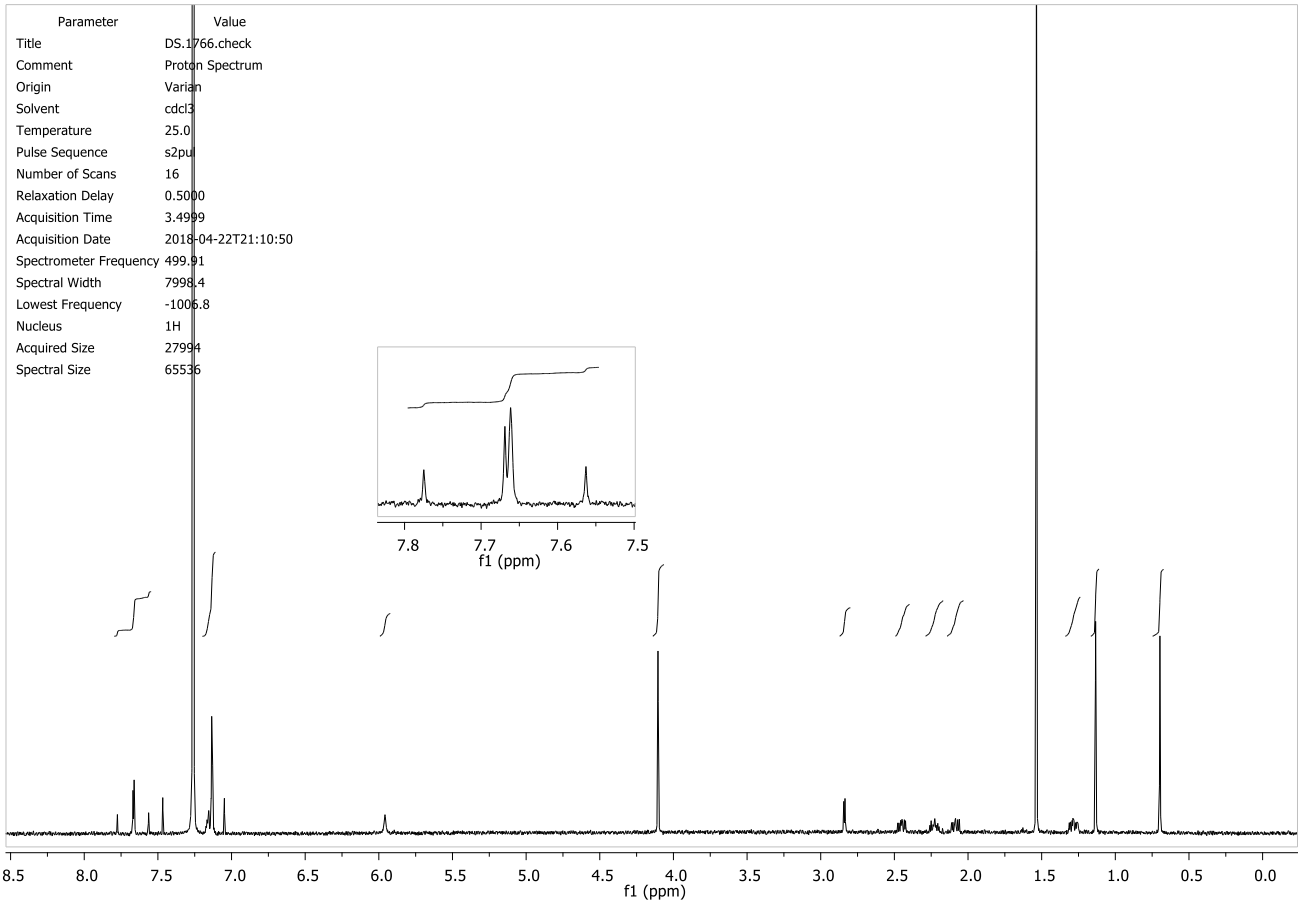


Figure S86: ^{1}H NMR (500 MHz, $CDCl_3$) for Intermediate Ester

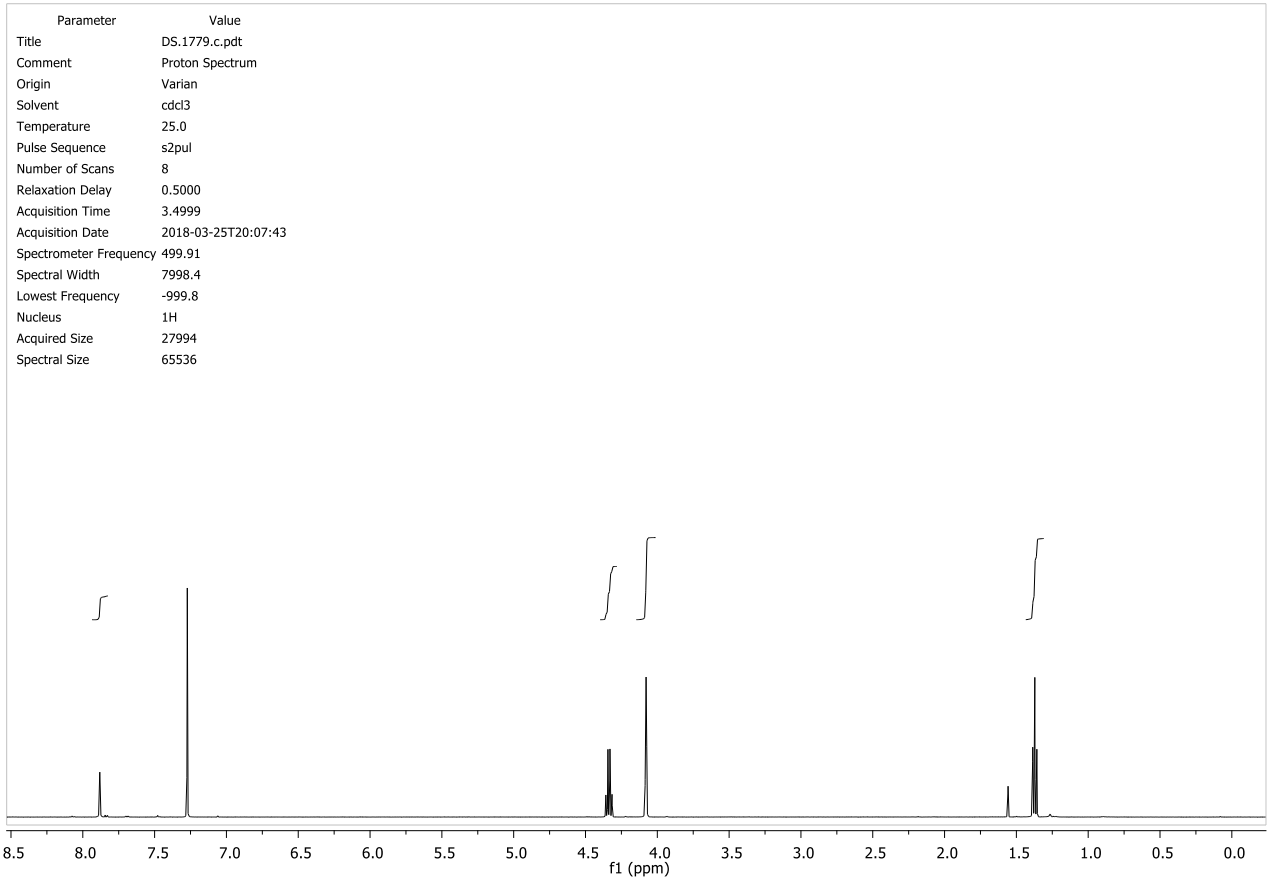
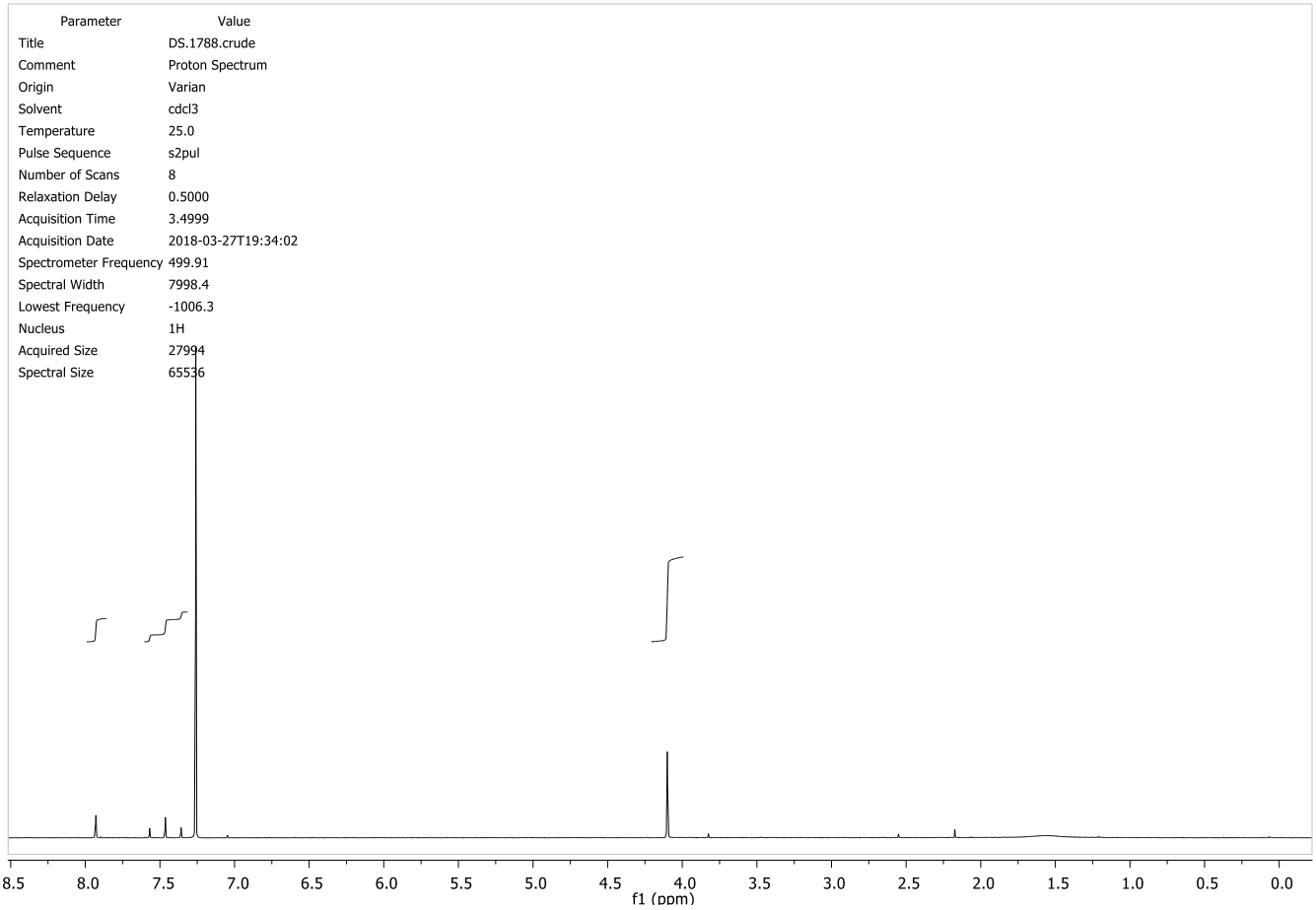
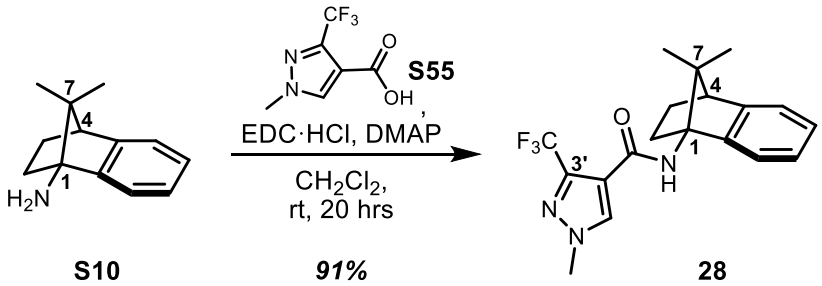


Figure S87: ^{1}H NMR (500 MHz, $CDCl_3$) for S52



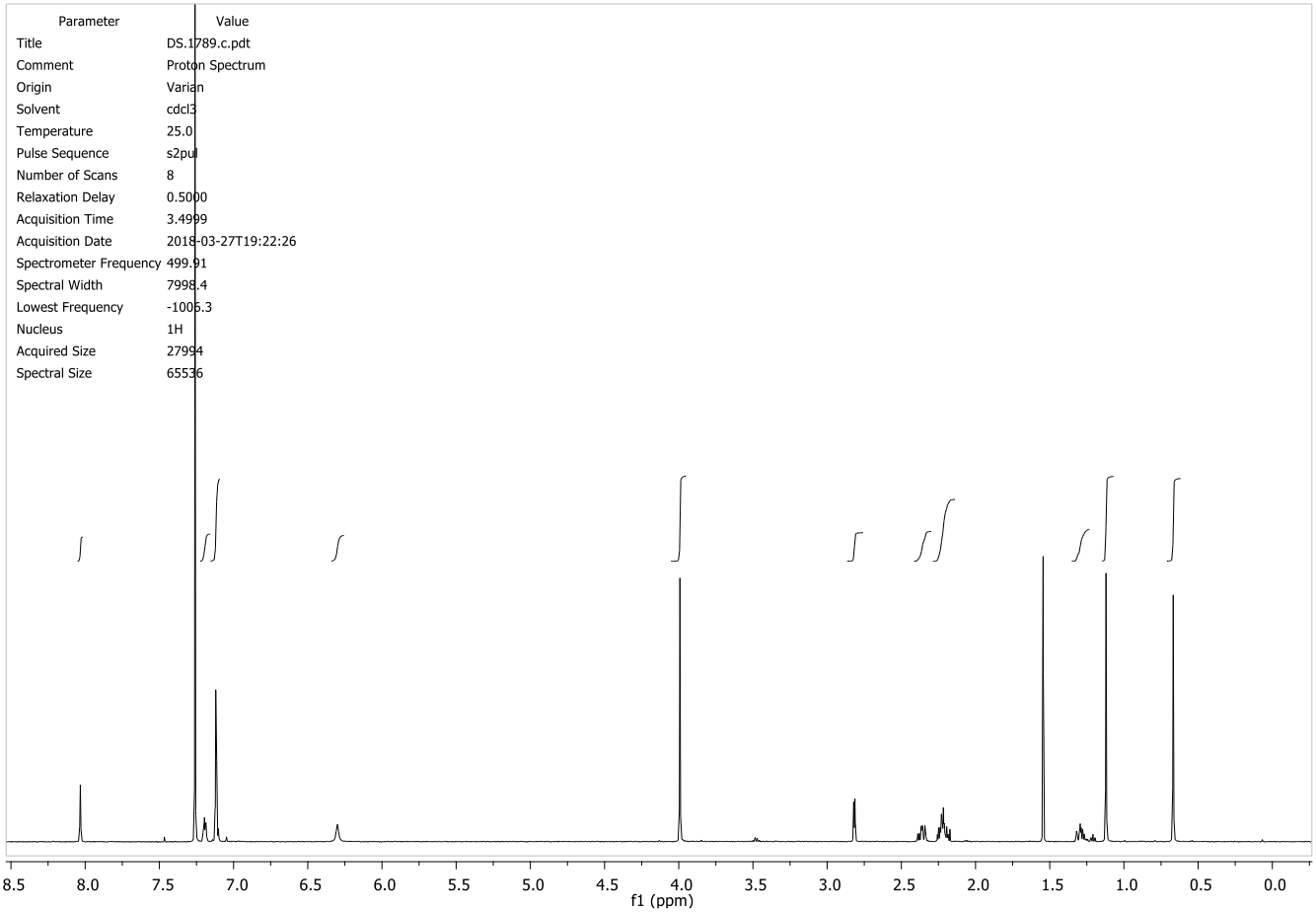


Procedure for C3'-trifluoromethyl C7-dimethyl 1-aminoNB analog 28

1-Aminonorbornane **S10** (10.6 mg; 57 μmol) was dissolved in dry dichloromethane (0.60 mL), followed by addition of the carboxylic acid **S55** (16.5 mg; 85 μmol), DMAP (10.4 mg; 85 μmol), and EDC·HCl (16.3 mg; 85 μmol), respectively. The reaction was flushed with Ar, capped, and stirred at room temp 12 hrs. The crude residue was diluted with 2 mL 1:1 sat. $NaHCO_3$ (aq):1 M NaOH (aq) and 2 mL ethyl acetate. Phases were separated, and the aqueous phase was extracted with 3 portions of ethyl acetate, 2 mL each. The organic phases were combined, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under a stream of nitrogen. The crude residue was purified with pipet-scale chromatography over silica (10 to 25 to 40 to 60% ethyl acetate:pentane; loaded residue with PhMe; silica was pre-neutralized with a 20% ethyl acetate:pentane + 1% triethylamine mobile phase). Obtained 21.0 mg of a slightly yellow solid that was largely pure by ^{1}H NMR analysis, but it was deemed necessary to employ a second round of chromatography (same as above). Collected the desired carboxamide (**28**) in two portions: 15.4 mg as a white solid, and 3.4 mg of a slightly yellow solid; both samples were pure by ^{1}H NMR, combining to total 18.8 mg (91.4% yield).

*Partial Characterization Data for C3'-trifluoromethyl C7-dimethyl 1-aminoNB SDHI candidate **28**:*
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.03 (s, 1H, pyrazole), 7.21-7.18 (m, 1H, Ar), 7.13-7.10 (m, 3H, Ar), 6.30 (br s, 1H, -NH), 3.99 (s, 3H, pyrazole -NMe), 2.82 (d, 1H, *J* = 3.9 Hz, C4), 2.39-2.33 (m, 1H, C2-eq), 2.26-2.17 (m, 2H, C3-eq, C2-ax), 1.33-1.24 (m, 1H, C3-ax), 1.12 (s, 3H, C7-Me), 0.67 (s, 3H, C7-Me) ppm
R_f = 0.40 (50% ethyl acetate:hexanes + 1% NH_4OH), one yellow spot, $KMnO_4$, UV

Figure S88: ^{1}H NMR (500 MHz, $CDCl_3$) for 28



V. Supplemental References

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