A Chemical Probe Strategy for Interrogating Inhibitor Selectivity Across the MEK kinase Family

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Supporting Information

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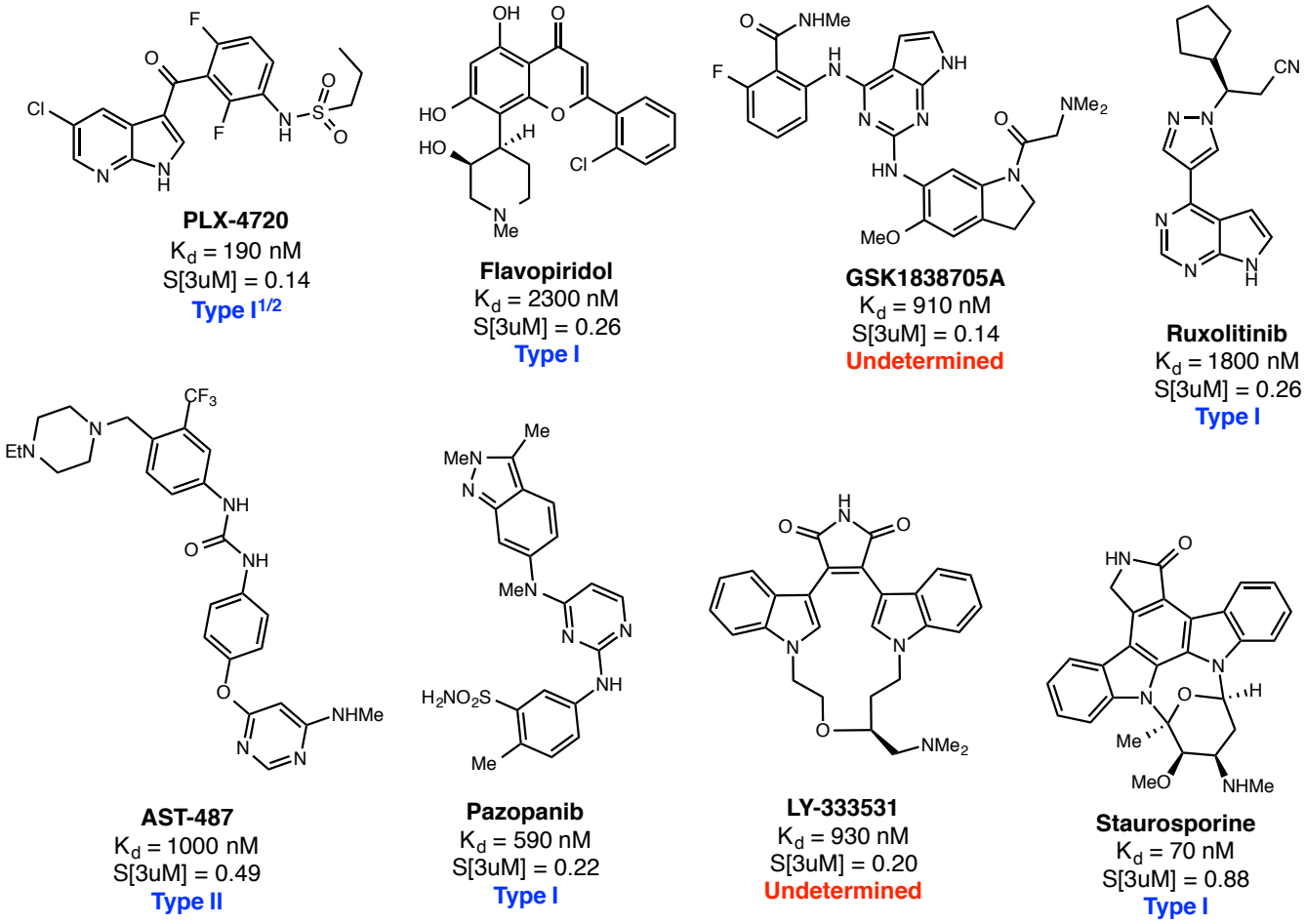


Figure S1. Known kinase inhibitors (plus staurosporine used as assay validation) tested and major criteria used from the literature for selecting compounds. K_d of compound to MEK4, S[3uM] is the global kinome selective score at 3uM and various modes of binding.

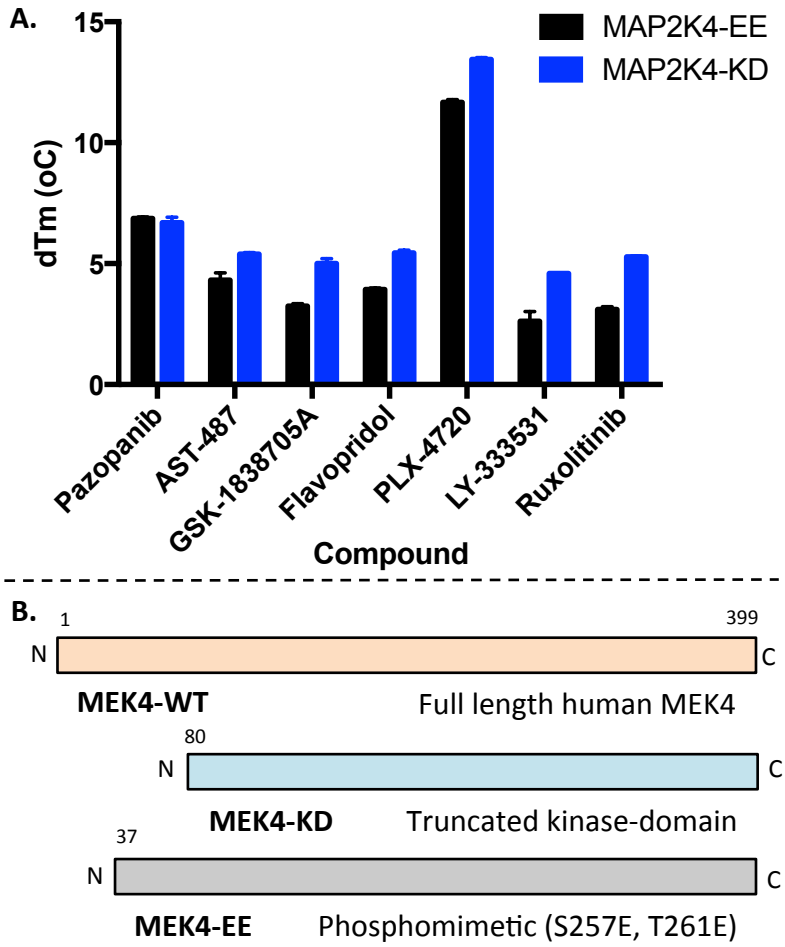


Figure S2. Secondary binding assay to determine binding mode of compounds to MEK4. A) Fluorescence thermal shift (FTS) assay comparing inactive kinase domain and constitutively active domain. B) Recombinant MEK4 constructs used in binding assay.

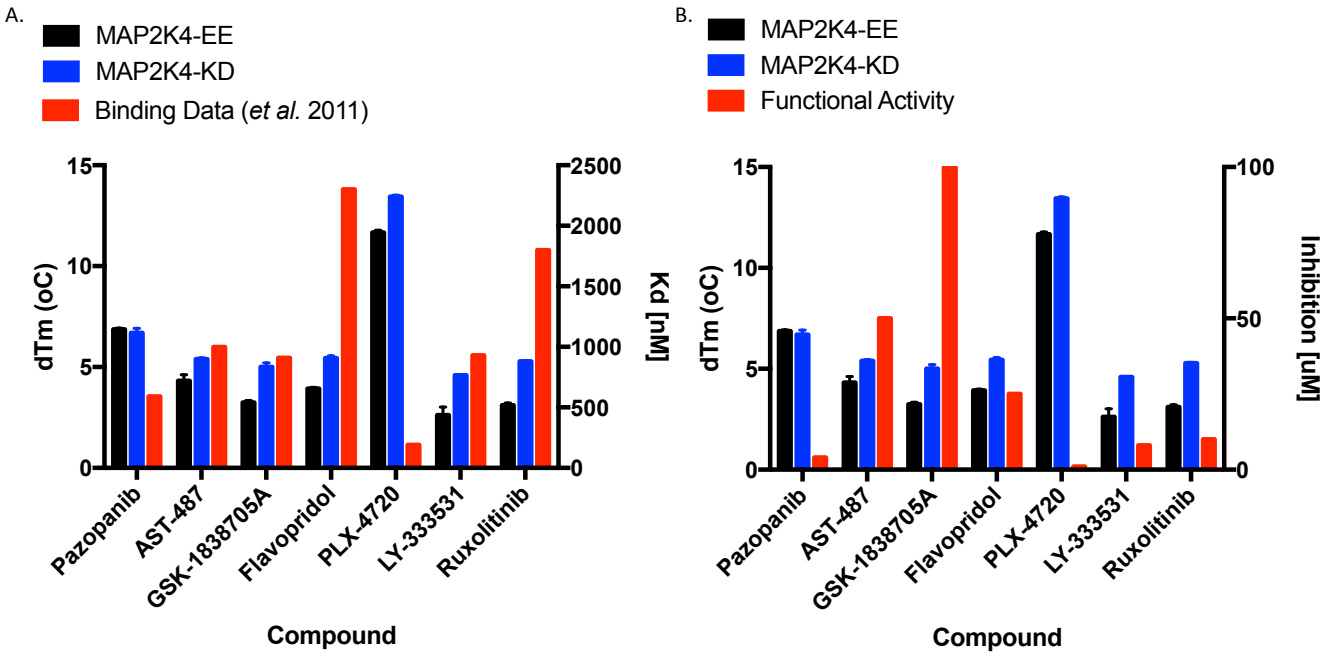


Figure S3. A) FTS binding data for both MEK4-EE and KD constructs compared to published binding data. B) FTS binding data for both MEK4-EE and KD constructs compared to functional activity data of MEK4.

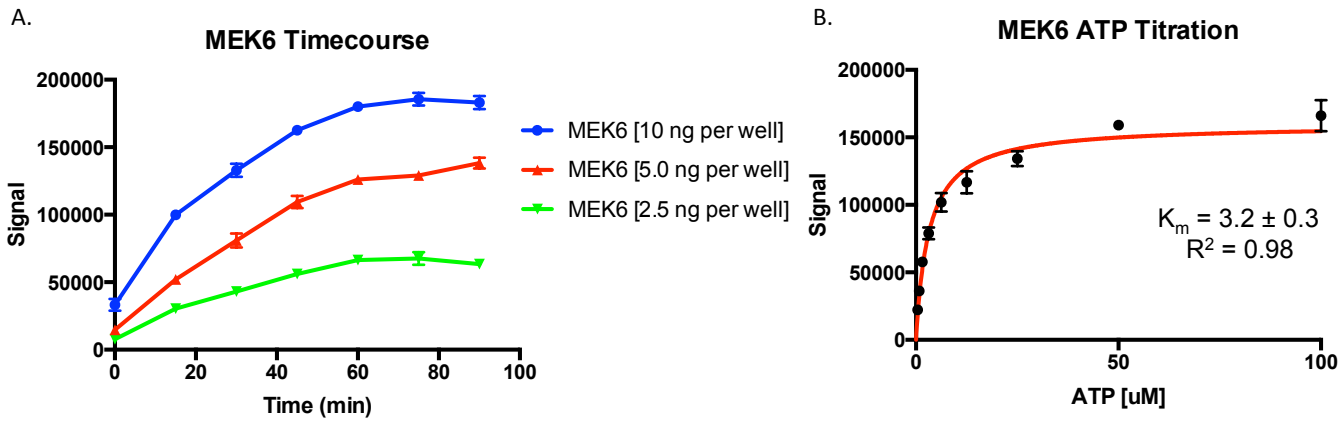


Figure S4. Representative graphs from MEK6 assay optimization. A) Timecourse at various concentrations to ensure linear range was chosen and B) ATP-titration for calculation of K_d.

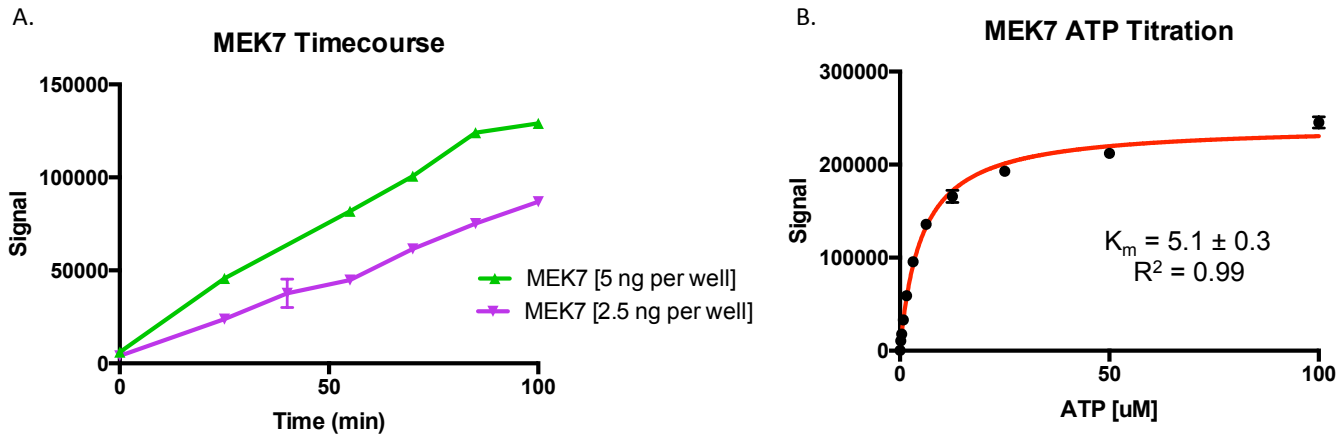


Figure S5. Representative graphs from MEK7 assay optimization. A) Time course at various concentrations to ensure linear range was chosen and B) ATP-titration for calculation of K_d.

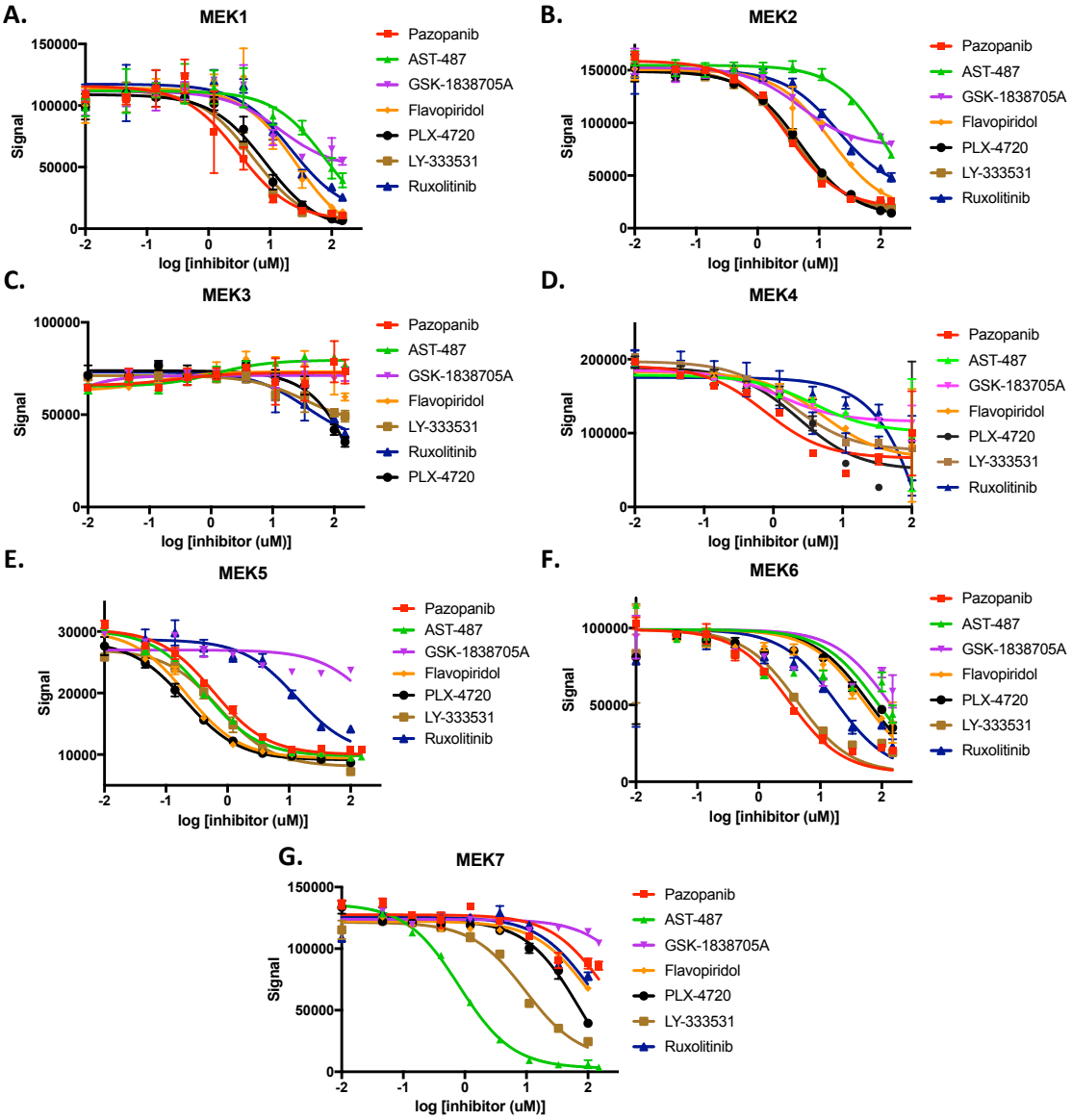


Figure S6. IC_{50} curves for MEK kinase isoforms and their ability to inhibit phosphorylation of their downstream substrate against selected compounds. **MEK-substrate systems:** A) MEK1-ERK2. B) MEK2-ERK2. C) MEK3-p38. D) MEK4-p38 E) MEK5-ERK5. F) MEK6-p38. G) MEK7-JNK1. *Sample size n=2 run in triplicate.*

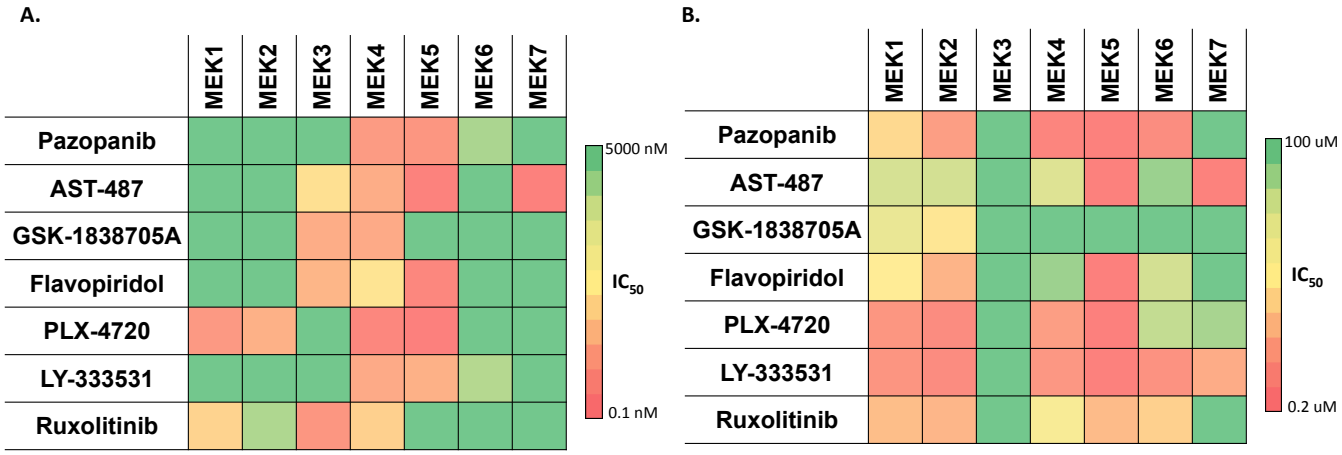


Figure S7. Comparison of binding and functional data. A) Heat map of binding affinity (K_d) data from literature on all MEK isoforms against selected inhibitors. B) Functional inhibition activity data of inhibitors against MEK isoforms.

A.

	MEK1	MEK2	MEK4	MEK6	MEK7
MEK7	41	41	54	45	100
MEK6	44	43	60	100	
MEK4	43	44	100		
MEK2	89	100			
MEK1	100				

B.

	MEK1	MEK2	MEK3	MEK4	MEK5	MEK6	MEK7
MEK7	39.9	40.1	48.6	52.9	44.8	51.8	100
MEK6	47.4	43.9	64.1	61.7	55.6	100	
MEK5	52.7	51.2	52.2	49.5	100		
MEK4	39	39	53.8	100			
MEK3	49.4	47.4	100				
MEK2	86.4	100					
MEK1	100						

Figure S8. Comparison of structural and sequence homology of MEK isoforms. A) Structural homology of MEK isoforms. B) Sequence homology of MEK isoforms.

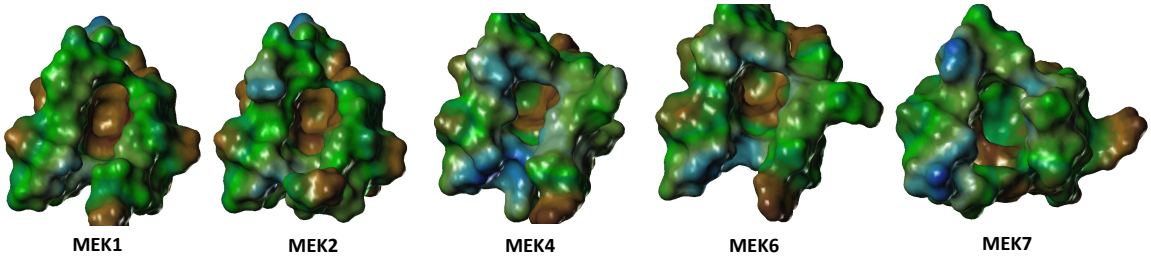
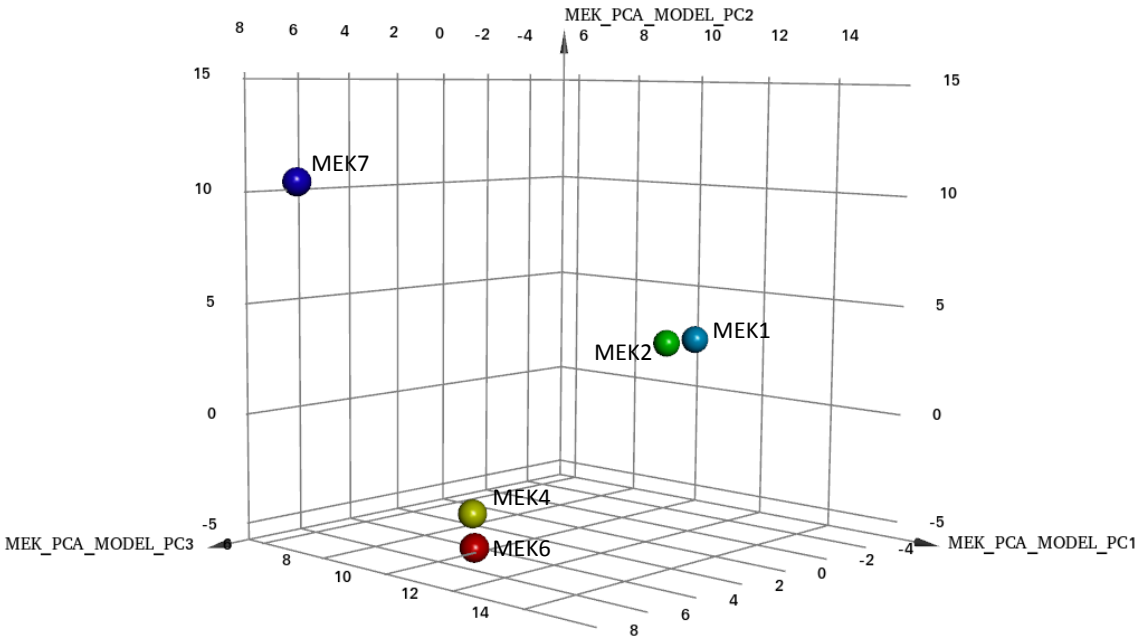


Figure S9. Lipophilic potential maps of MEK1, MEK2, MEK4, MEK6 and MEK7. *Brown: Lipophilic (like oil/fat); Blue-Green: Hydrophilic (like water).



Isoform	PCA_Model_PC1	PCA_Model_PC2	PCA_Model_PC3
MEK1	9.91	2.26	-5.65
MEK2	9.40	2.06	-5.01
MEK4	8.96	-4.68	3.26
MEK6	9.73	-5.77	4.18
MEK7	5.42	10.29	6.07

Figure S10. 3D-PCA plot of MEK isoforms utilizing 148 parameters computed. MEK1 and MEK2 are both in quadrant (+ + -) and MEK4 and MEK6 occupy quadrant (+ - +) while MEK 7 is in a very different location, quadrant (+ + +).

Table S1. ATP binding pocket domain amino acids sequence comparison of MEK1, 2, 4, 6 and 7 of residues with in a 5Å from ATP centroid.

MEK1	M143EHMDVLGSQDKSNCDDALVKGVAGGGNV
MEK2	M147EHMDVLGSQDKSNCDDALVKAVAGGGNT
MEK4	M178ELMSVTLCSKNDSKDDAIKVGSSRGGYA
MEK6	M129ELMDVLTCDSNSKDKDAKVLGSRGGYA
MEK7	M212ELMGTCVLCNSKEKDAVKWVGCFGMGGT

Blue: hinge residues; Orange: gatekeeper residue separating active site and back hydrophobic pocket; Red: gatekeeper-2 residue; Purple: MEK4 and MEK6 sequence similarity

Table S2. Protomols in the ATP binding pocket domain.

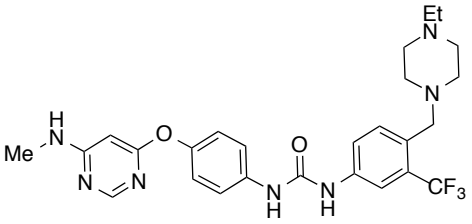
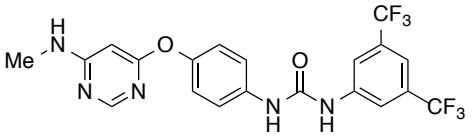
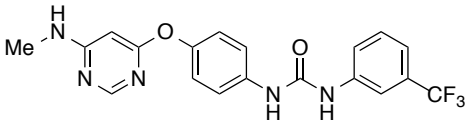
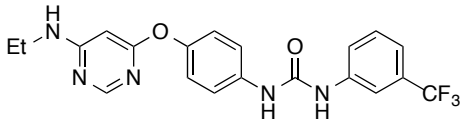
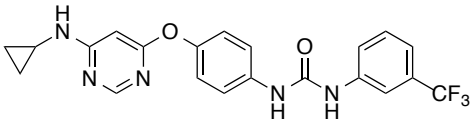
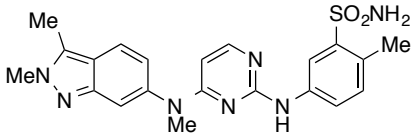
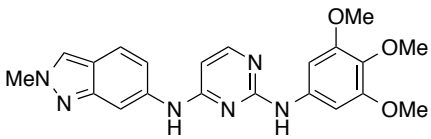
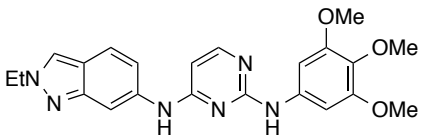
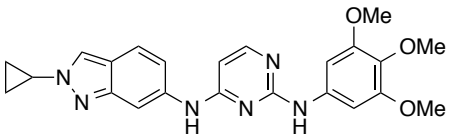
Isoform	Hydrophobic	HB acceptor	HB donor
MEK1	70	19	14
MEK2	69	19	15
MEK4	63	23	14
MEK6	63	23	13
MEK7	82	13	15

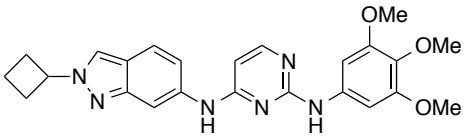
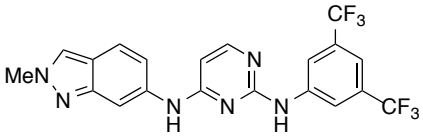
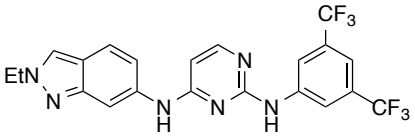
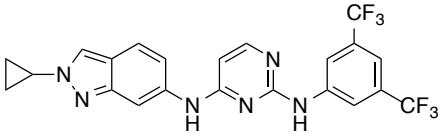
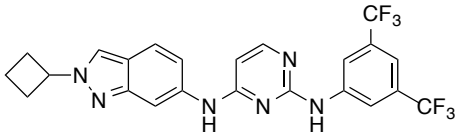
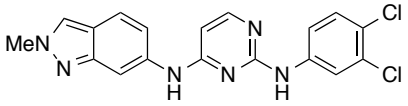
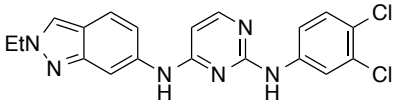
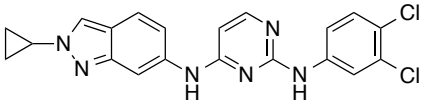
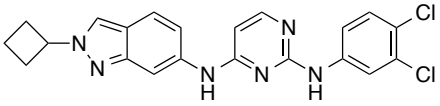
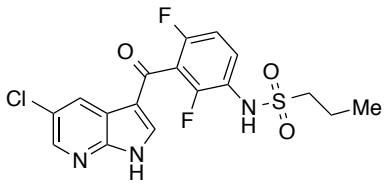
Table S3. In silico docking results.

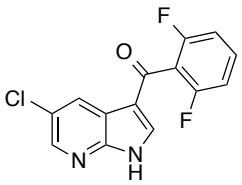
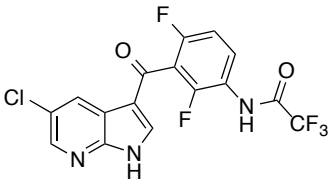
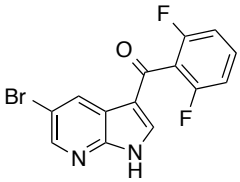
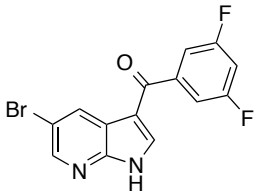
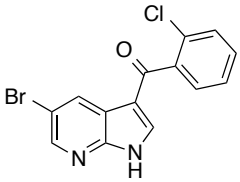
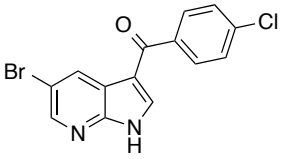
Compound	MEK1		MEK2		MEK4		MEK6		MEK7	
	BA[1] in µM	Score[2]	BA[1] in µM	Score[2]	BA[1] in µM	Score[3]	BA[1] in µM	Score[2]	BA[1] in µM	Score[2]
AST-487	5	5.14	5	5.54	1	6.62	5	5.46	0.027	8.86
GSK-1838705A	5	4.11	5	5.68	0.91	7.12	5	5.19	5	5.51
PLX-4720	0.55	6.99	1.1	6.56	0.19	7.91	5	4.37	5	6.19
Pazopanib	5	5.52	5	5.87	0.59	6.96	4.1	6.12	5	5.27

** **1** BA = Binding Affinity (K_d) (where 5.0 means >/= 5.0 uM BA, upper cutoff point) **2** Score = Total docked score is a function of apparent $pK_d = -\log K_d$ **3** Score = Apparent pK_d obtained through Induced Fit Docking*

Table S4. Analog list. **IC_{50} values are in μM Assays performed in triplate and reproduced for an n = 2.*

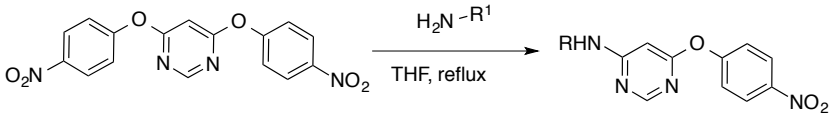
Compound	Structure	MEK4 (IC_{50})	MEK6 (IC_{50})	MEK7 (IC_{50})
AST-487 (1)		44.8 ± 5.2	>75.0	0.81 ± 0.003
1a		33.7 ± 3.1	---	74.0 ± 13.5
1b		27.2 ± 0.91	---	5.4 ± 0.23
1c		21.3 ± 1.4	---	5.9 ± 0.19
1d		19.1 ± 0.52	---	15.2 ± 0.24
Pazopanib (2)		1.5 ± 0.03	3.1 ± 0.09	>100
2a		10.5 ± 0.65	10.0 ± 0.17	---
2b		4.6 ± 0.21	7.4 ± 0.04	---
2c		4.2 ± 0.25	6.9 ± 0.08	---

2d		2.0 ± 0.17	2.7 ± 0.04	---
2e		> 75.0	---	---
2f		> 75.0	---	---
2g		> 75.0	---	---
2h		> 75.0	---	---
2i		8.1 ± 1.2	---	---
2j		20.4 ± 2.4	---	---
2k		17.9 ± 4.3	---	---
2l		15.4 ± 3.6	---	---
PLX4720 (3)		6.6 ± 1.2	60 ± 6.0	> 75.0

3a		6.9 ± 3.9	75.1 ± 7.3	---
3b		3.8 ± 0.11	33.8 ± 6.4	---
3c		1.4 ± 0.03	2.5 ± 1.0	---
3d		27 ± 1.3	> 100	---
3e		3.7 ± 0.04	1.2 ± 0.56	---
3f		26.1 ± 0.63	71.8 ± 20.7	---

General Information

All reactions were carried out under a nitrogen atmosphere in oven-dried glassware with magnetic stirring. Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and ceric ammonium nitrate stain or potassium permangenate stain followed by heating. ^{1}H NMR spectra were recorded on AVANCE III 500MHz w/ direct cryoprobe (500 MHz) spectrometer and are reported in ppm using solvent as an internal standard. Data are reported as (ap = apparent, s = singlet, d = doublet, t = apparent triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration.) Proton-decoupled ^{13}C NMR spectra were recorded on an AVANCE III 500 MHz w/ direct cryoprobe (125 MHz) spectrometer and are reported in ppm using solvent as an internal standard. Mass spectra were obtained on a WATERS Acquity-H UPLC-MS with a single quad detector (ESI).

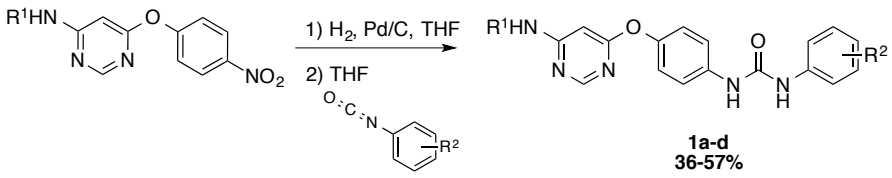


General procedure for the synthesis of compounds 4a-c: Into a round bottom flask was added 4,6-bis-(4-nitrophenoxy)pyrimidine[1] (14.11 mmol), amine (70.6 mmol), and THF (Volume: 17.21 ml). The mixture was heated to 30°C and stirred for an additional 16 hours. A solution of NaOH (5 g) and water (500 mL) was charged over 30 minutes while maintaining the mixture at room temperature. The mixture was cooled to 0°C and stirred for an additional hour. Product was collected by filtration, rinsed with water and dried overnight under high vacuum to afford compound **4a-c** (26-79 % yield) as solids.

N-methyl-6-(4-nitrophenoxy)pyrimidin-4-amine (4a): Yield: 79%. Matched previously reported characterization.[1]

N-ethyl-6-(4-nitrophenoxy)pyrimidin-4-amine (4b): Yield: 45%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.25 (d, *J* = 9.2 Hz, 2H), 8.21 (s, 1H), 7.37 – 7.13 (m, 2H), 5.88 (s, 1H), 5.12 (bs, 1H), 3.31 (s, 2H), 1.28 (t, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.72, 164.76, 158.23, 158.10, 144.53, 125.45, 121.68, 36.56, 14.42. LRMS (ESI): Mass calcd for C12H12N4O3 $[M+H]^+$: 261; found 261.

N-cyclopropyl-6-(4-nitrophenoxy)pyrimidin-4-amine (4c): Yield: 26%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.29 (d, *J* = 9.1 Hz, 2H), 8.22 (s, 1H), 7.30 (d, *J* = 9.1 Hz, 2H), 6.28 (s, 1H), 5.68 (s, 1H), 2.55 (bs, 1H), 0.93 – 0.82 (m, 2H), 0.68 – 0.60 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.81, 166.29, 158.15, 157.90, 144.59, 125.44, 121.77, 87.51, 23.34, 7.56. LRMS (ESI): Mass calcd for C13H12N4O3 $[M+H]^+$: 273; found 273.



[1] Prasad, K. et al. *Organic Process Research Development* **2008**, 12, 1146-1155.

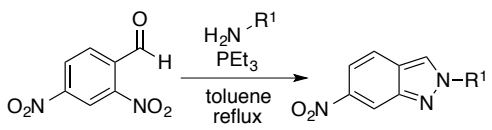
General procedure for the synthesis of compounds 1a-d: 10% Palladium on carbon (0.026 mmol) was added to a solution of N-alkyl-6-(4-nitrophenoxy)pyrimidin-4-amine **4** (0.257 mmol) in MeOH (Volume: 1286 µl), and the mixture was stirred under hydrogen atmosphere at room temperature for 12 hours. The catalyst was removed by filtration/celite and washed with MeOH. The filtrate and washings were combined and the solvent was distilled off under reduced pressure to give crude 6-(4-aminophenoxy)-N-alkylpyrimidin-4-amine. To a stirring solution of crude 6-(4-aminophenoxy)-N-alkylpyrimidin-4-amine (0.257 mmol) in THF (Volume: 1.5 mL) was added 1-isocyanato-4-nitrobenzene (0.257 mmol) slowly. The mixture was allowed to stir for 6 hours and then concentrated and purified via flash chromatography to afford compound **1a-d** (36-57 % yield).

1-(3,5-bis(trifluoromethyl)phenyl)-3-(4-((6-(methylamino)pyrimidin-4-yl)oxy)phenyl)urea (1a): Yield: 36%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.45 (s, 0H), 8.23 (s, 0H), 7.88 (s, 0H), 7.81 (d, *J* = 1.5 Hz, 1H), 7.45 (s, 0H), 7.29 – 7.17 (m, 1H), 6.96 (d, *J* = 8.3 Hz, 1H), 5.61 (s, 0H), 5.47 (d, *J* = 5.4 Hz, 0H), 2.88 (d, *J* = 4.7 Hz, 1H).^{13}C NMR (125 MHz, $CDCl_3$) δ 171.39, 165.59, 157.89, 153.15, 148.61, 140.27, 135.44, 132.06, 124.20, 122.00, 118.68, 116.13, 28.37. LRMS (ESI): Mass calcd for C20H15F6N5O2 $[Me+H]^+$: 472; found 472.

1-(4-((6-(methylamino)pyrimidin-4-yl)oxy)phenyl)-3-(3-(trifluoromethyl)phenyl)urea (1b): Yield: 57%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.05 (s, 1H), 8.84 (s, 1H), 8.13 (s, 1H), 8.01 (s, 1H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.51 (dd, *J* = 12.4, 8.2 Hz, 3H), 7.29 (dd, *J* = 17.3, 6.3 Hz, 2H), 7.07 (d, *J* = 8.6 Hz, 2H), 5.73 (s, 1H), 3.32 (s, 2H). ^{13}C NMR (125 MHz, DMSO) δ 153.03, 147.94, 141.06, 136.86, 130.37, 130.10, 129.85, 125.76, 123.59, 122.32, 120.26, 118.49, 114.56. LRMS (ESI): Mass calcd for C19H16F3N5O2 $[Me+H]^+$: 404; found 404.

1-(4-((6-(ethylamino)pyrimidin-4-yl)oxy)phenyl)-3-(3-(trifluoromethyl)phenyl)urea (1c): Yield: 55%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.05 (s, 1H), 8.85 (s, 1H), 8.02 (d, *J* = 2.0 Hz, 1H), 7.63 – 7.56 (m, 1H), 7.58 – 7.45 (m, 3H), 7.35 – 7.23 (m, 2H), 7.13 – 7.01 (m, 2H), 1.10 (t, *J* = 7.2 Hz, 3H).^{13}C NMR (125 MHz, DMSO) δ 164.86, 153.03, 147.93, 141.06, 136.87, 130.38, 122.34, 120.27, 118.49, 114.58, 35.51, 14.97. LRMS (ESI): Mass calcd for C20H16F3N5O2 $[M+ACN+H]^+$: 460; found 460.

1-(4-((6-(cyclopropylamino)pyrimidin-4-yl)oxy)phenyl)-3-(3-(trifluoromethyl)phenyl)urea (1d): Yield: 67%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.07 (s, 1H), 8.86 (s, 1H), 8.02 (d, *J* = 2.0 Hz, 1H), 7.66 – 7.55 (m, 1H), 7.55 – 7.41 (m, 3H), 7.43 – 7.28 (m, 1H), 7.15 – 7.02 (m, 2H), 0.70 (dt, *J* = 6.8, 3.3 Hz, 2H), 0.53 – 0.38 (m, 2H). ^{13}C NMR (125 MHz, DMSO) δ 153.03, 147.87, 141.07, 136.85, 130.37, 125.76, 123.59, 122.37, 120.19, 118.48, 114.58, 30.06, 23.55, 6.95. LRMS (ESI): Mass calcd for C21H18F3N5O2 $[M+H]^+$: 430; found 430.



5a-d
45-80%

General synthesis of compound 5a-d: 2,4-dinitrobenzaldehyde (5.10 mmol) was dissolved in toluene (Volume: 25.5 ml) and there to was added alkylamine (5.61 mmol) and the mixture was refluxed under heating. After the solution was stirred for 3 hours it was kept standing to cool to room temperature and the solvent was distilled off *in vacuo*. To the residue was added triethyl phosphite (26.8 ml, 153 mmol) and the residue was heated to 150° C. After the residue was stirred for 4 hours, it was kept standing to

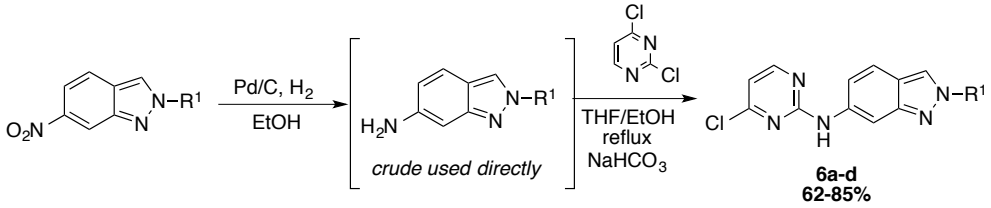
cool to room temperature, and the residue was purified by the silica gel column chromatography affording the crude product. To the crude product was added hexane (2 ml), and the precipitated material was collected by filtration as the compound **5a-d** (45-80% yield).

2-methyl-6-nitro-2H-indazole (5a): Yield: 80%. Matched previously reported characterization.[2]

2-ethyl-6-nitro-2H-indazole (5b): Yield: 72%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 8.06 (s, 1H), 7.89 (d, *J* = 10.3 Hz, 1H), 7.76 (d, *J* = 10.3 Hz, 1H), 4.55 (q, 2H), 1.68 (t, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.80, 146.46, 124.38, 122.87, 121.33, 115.70, 115.52, 49.41, 15.73. LRMS (ESI): Mass calcd for C9H9N3O2 $[M+H]^+$: 192; found 192.

2-cyclopropyl-6-nitro-2H-indazole (5c): Yield: 77%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.67 (s, 1H), 8.13 (s, 1H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.72 (d, *J* = 9.7 Hz, 1H), 4.02 (m, 1H), 1.44 (m, 2H), 1.26 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.53, 124.12, 123.81, 121.19, 115.81, 115.49, 35.47, 7.69. LRMS (ESI): Mass calcd for C10H9N3O2 $[M+H]^+$: 204; found 204.

2-cyclobutyl-6-nitro-2H-indazole (5d): Yield: 45%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.70 (s, 1H), 8.06 (s, 1H), 7.86 (d, *J* = 9.5 Hz, 1H), 7.71 (d, *J* = 8.6 Hz, 1H), 5.09 (m, 1H), 2.71 (m, 2H), 2.62 (m, 2H), 1.99 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.73, 146.48, 124.12, 122.00, 121.39, 115.70, 115.64, 57.57, 30.54, 14.97. LRMS (ESI): Mass calcd for C11H11N3O2 $[M+H]^+$: 218; found 218.



General synthesis of compound 6a-d: 10% Palladium on carbon (0.113 mmol) was added to a solution of 2-alkyl-6-nitro-2H-indazole **5** (1.129 mmol) in EtOH (Volume: 5645 µl), and the mixture was stirred under hydrogen atmosphere at room temperature for 12 hours. The catalyst was removed by filtration/celite and washed with ethanol. The filtrate and washings were combined and the solvent was distilled off under reduced pressure to give crude 2-alkyl-2H-indazol-6-amine.

To a stirred solution of the crude amine (1.129 mmol) and $NaHCO_3$ (3.39 mmol) in ethanol (5.6 mL) was added 2,4-dichloropyrimidine (3.39 mmol) at room temperature. After the reaction was stirred for 6 h at 85˚C, the suspension was cooled to room temperature, filtered and washed thoroughly with DCM. The filtrate was concentrated under reduced pressure to give compounds **6a-d** (62-85% yield).

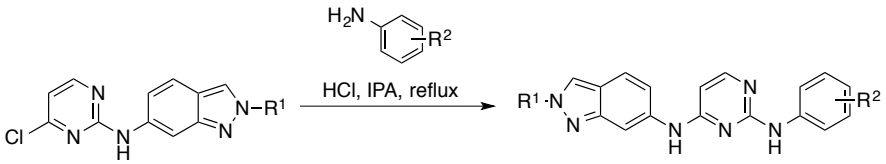
N-(2-chloropyrimidin-4-yl)-2-methyl-2H-indazol-6-amine (6a): Yield: 78%. Matched previously reported characterization.[2]

N-(2-chloropyrimidin-4-yl)-2-ethyl-2H-indazol-6-amine (6b): Yield: 85%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.08 (d, *J* = 6.5 Hz, 1H), 7.94 (s, 1H), 7.70 – 7.63 (m, 2H), 7.41 (s, 1H), 6.93 (d, *J* = 8.6 Hz, 1H), 6.65 (d, *J* = 6.5 Hz, 1H), 4.47 (q, 2H), 1.64 (t, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.82, 160.83, 158.03, 148.76, 134.63, 122.42, 121.81, 120.07, 119.17, 110.51, 102.43, 48.70, 15.83. LRMS (ESI): Mass calcd for C13H12ClN5 $[M+H]^+$: 274; found 274.

[2] Stafford, J.A. et al. *J. Med. Chem.* **2008**, 51, 4632-4640.

N-(2-chloropyrimidin-4-yl)-2-cyclopropyl-2H-indazol-6-amine (6c): Yield: 79%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.08 (d, *J* = 6.1 Hz, 1H), 8.00 (s, 1H), 7.68 – 7.59 (m, 2H), 7.36 (s, 1H), 6.92 (dd, *J* = 1.6, 1.0 Hz, 1H), 6.64 (d, *J* = 5.4 Hz, 1H), 3.99 – 3.89 (m, 1H), 1.40 – 1.31 (m, 2H), 1.21 – 1.14 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.75, 160.84, 158.05, 148.56, 134.80, 123.41, 121.74, 119.76, 119.28, 110.34, 102.46, 34.64, 7.24. LRMS (ESI): Mass calcd for C14H12ClN5 $[M+H]^+$: 286; found 286.

N-(2-chloropyrimidin-4-yl)-2-cyclobutyl-2H-indazol-6-amine (6d): Yield: 62%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.09 (d, *J* = 6.3 Hz, 1H), 7.97 (s, 1H), 7.70 – 7.63 (m, 2H), 7.31 (s, 1H), 6.93 (d, *J* = 10.3 Hz, 1H), 6.66 (d, *J* = 6.7 Hz, 1H), 5.05 (m, 1H), 2.72 (m, 2H), 2.62 (m, 2H), 1.97 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.75, 160.85, 158.06, 148.69, 134.64, 121.90, 121.54, 119.79, 119.12, 110.45, 102.43, 56.96, 30.55, 14.93. LRMS (ESI): Mass calcd for C15H14ClN5 $[M+H]^+$: 300; found 300.



2a-l
43-95%

General synthesis of compound 2a-l: To a solution of N-(2-chloropyrimidin-4-yl)-2-alkyl-2H-indazol-6-amine **6** (0.154 mmol) and aniline (0.154 mmol) in isopropanol (Volume: 1328 µl) was added 4 drops of concentrated HCl, and the mixture was heated to reflux with stirring overnight. The mixture was allowed to cool to room temperature and the resulting precipitate was collected via filtration and washed with Et_2O to yield compounds **2a-l** (43-95% yield).

N4-(2-methyl-2H-indazol-6-yl)-N2-(3,4,5-trimethoxyphenyl)pyrimidine-2,4-diamine (2a): Yield: 54%. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.04 (s, 1H), 7.90 (d, *J* = 5.7 Hz, 1H), 7.54 (d, *J* = 9.2 Hz, 1H), 7.14 (d, *J* = 8.4 Hz, 1H), 6.95 (s, 2H), 6.18 (d, *J* = 5.4 Hz, 1H), 4.12 (s, 3H), 3.69 (s, 3H), 3.61 (s, 6H). ^{13}C NMR (125 MHz, MeOD) δ 162.80, 161.16, 156.38, 154.32, 150.62, 139.40, 138.15, 134.09, 126.16, 121.64, 120.09, 119.77, 106.43, 99.83, 98.89, 61.24, 56.32, 49.85, 40.07. LRMS (ESI): Mass calcd for C21H22N6O3 $[M+H]^+$: 407; found 407.

N4-(2-ethyl-2H-indazol-6-yl)-N2-(3,4,5-trimethoxyphenyl)pyrimidine-2,4-diamine (2b): Yield: 65%. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.21 (d, *J* = 7.0 Hz, 1H), 8.19 (d, *J* = 9.1 Hz, 1H), 8.03 (d, *J* = 6.3 Hz, 1H), 7.85 (s, 1H), 7.65 (s, 1H), 7.18 (s, 1H), 6.90 (s, 2H), 6.31 (d, *J* = 6.8 Hz, 1H), 4.46 (q, 2H), 3.75 (s, 3H), 3.64 (s, 6H), 1.59 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, MeOD) δ 161.61, 156.72, 153.25, 148.75, 136.72, 134.46, 134.27, 123.38, 120.65, 119.05, 118.22, 106.78, 99.17, 98.83, 59.80, 54.98, 14.88. LRMS (ESI): Mass calcd for C22H24N6O3 $[M+H]^+$: 422; found 422.

N4-(2-cyclopropyl-2H-indazol-6-yl)-N2-(3,4,5-trimethoxyphenyl)pyrimidine-2,4-diamine (2c): Yield: 45%. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.31 (s, 1H), 8.23 (s, 1H), 8.02 (s, 1H), 7.85 (d, *J* = 6.5 Hz, 1H), 7.61 (d, *J* = 10.2 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 6.91 (s, 2H), 6.32 (d, *J* = 6.9 Hz, 1H), 4.09 – 3.93 (m, 1H), 3.77 (s, 3H), 3.63 (s, 6H), 1.37 – 1.25 (m, 2H), 1.25 – 1.08 (m, 2H). ^{13}C NMR (125 MHz, MeOD) δ 165.78, 161.56, 156.51, 153.19, 148.56, 136.81, 123.96, 120.59, 118.78, 118.34, 106.71, 99.06, 98.81, 59.83, 54.98, 33.81, 6.16. LRMS (ESI): Mass calcd for C23H24N6O3 $[M+H]^+$: 433; found 433.

N4-(2-cyclobutyl-2H-indazol-6-yl)-N2-(3,4,5-trimethoxyphenyl)pyrimidine-2,4-diamine (2d): Yield: 43%. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.17 (s, 63H), 8.06 (s, 2H), 7.95 (d, J = 6.6 Hz, 1H), 7.58 (d, J = 9.2 Hz, 36H), 7.16 (d, J = 10.4 Hz, 2H), 6.22 (d, J = 5.8 Hz, 1H), 5.07 (m, 1H), 3.73 (s, 3H), 3.63 (s, 6H), 2.69 (m, 2H), 2.58 (m, 2H), 1.97 (m, 2H). ^{13}C NMR (125 MHz, MeOD) δ 162.80, 161.16, 156.44, 154.34, 150.50, 139.36, 138.17, 134.06, 123.61, 121.83, 119.80, 119.64, 106.74, 99.84, 98.81, 61.24, 57.86, 56.29, 31.43, 15.59. LRMS (ESI): Mass calcd for C24H26N6O3 $[M+H]^+$: 447; found 447.

N2-(3,5-bis(trifluoromethyl)phenyl)-N4-(2-methyl-2H-indazol-6-yl)pyrimidine-2,4-diamine (2e): Yield: 95%. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.37 (s, 2H), 8.09 (d, J = 17.2 Hz, 3H), 7.61 (s, 1H), 7.40 (s, 1H), 7.19 (s, 1H), 6.35 (s, 1H), 4.18 (s, 3H). ^{13}C NMR (125 MHz, MeOD) δ 161.42, 159.22, 155.10, 149.22, 142.87, 137.86, 131.60, 131.34, 124.76, 122.50, 120.36, 118.72, 117.91, 113.07, 104.84, 100.01, 47.59, 38.66. LRMS (ESI): Mass calcd for C20H14F6N6 $[M+H]^+$: 453; found 453.

N2-(3,5-bis(trifluoromethyl)phenyl)-N4-(2-ethyl-2H-indazol-6-yl)pyrimidine-2,4-diamine (2f): Yield: 87%. ^{1}H NMR (500 MHz, Chloroform-d) δ 8.37 (s, 1H), 8.15 (s, 0H), 8.06 (s, 0H), 7.62 (s, 0H), 7.40 (s, 1H), 7.18 (s, 0H), 6.35 (s, 0H), 4.45 (s, 0H), 1.60 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.86, 160.61, 156.52, 150.48, 144.27, 139.18, 132.77, 126.07, 124.66, 123.91, 121.89, 119.44, 114.47, 106.47, 101.41, 16.26. LRMS (ESI): Mass calcd for C21H16F6N6 $[M+H]^+$: 467; found 467.

N2-(3,5-bis(trifluoromethyl)phenyl)-N4-(2-cyclopropyl-2H-indazol-6-yl)pyrimidine-2,4-diamine (2g): Yield: 76%. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.39 (s, 2H), 8.21 (s, 2H), 7.61 (s, 1H), 7.42 (s, 1H), 7.18 (s, 1H), 6.36 (s, 1H), 3.99 (s, 1H), 1.31 (s, 2H), 1.21 (s, 2H). ^{13}C NMR (125 MHz, MeOD) δ 161.39, 159.22, 155.11, 148.98, 142.88, 137.98, 131.61, 124.67, 123.82, 122.50, 120.43, 118.16, 117.91, 113.03, 104.82, 100.06, 33.59, 6.03. LRMS (ESI): Mass calcd for C22H16F6N6 $[M+H]^+$: 479; found 479.

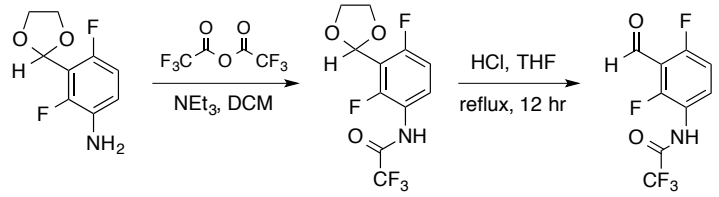
N2-(3,5-bis(trifluoromethyl)phenyl)-N4-(2-cyclobutyl-2H-indazol-6-yl)pyrimidine-2,4-diamine (2h): Yield: 78%. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.35 (s, 2H), 8.19 (s, 1H), 8.06 (s, 2H), 7.61 (s, 1H), 7.40 (s, 1H), 7.17 (s, 1H), 6.34 (s, 1H), 5.08 (s, 1H), 2.69 (s, 2H), 2.58 (s, 2H), 1.98 (td, J = 10.0, 5.6 Hz, 2H). ^{13}C NMR (125 MHz, MeOD) δ 162.84, 160.38, 156.09, 150.44, 144.13, 139.11, 133.04, 126.04, 123.88, 123.59, 121.99, 119.76, 119.50, 114.61, 106.70, 101.42, 57.86, 31.43, 15.58. LRMS (ESI): Mass calcd for C23H18F6N6 $[M+H]^+$: 493; found 493.

N2-(3,4-dichlorophenyl)-N4-(2-methyl-2H-indazol-6-yl)pyrimidine-2,4-diamine (2i): Yield: 66%. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.23 (s, 3H), 8.13 (s, 2H), 8.00 (s, 1H), 7.95 (s, 2H), 7.64 (s, 1H), 7.53 (s, 2H), 7.32 (s, 1H), 7.19 (s, 3H), 6.29 (s, 1H), 4.19 (s, 14H). ^{13}C NMR (125 MHz, MeOD) δ 161.52, 158.79, 154.17, 149.13, 140.32, 137.59, 131.66, 129.72, 124.83, 123.78, 120.44, 118.96, 118.83, 118.41, 105.71, 99.01, 38.72. LRMS (ESI): Mass calcd for C18H14Cl12N6 $[M+H]^+$: 386; found 386.

N2-(3,4-dichlorophenyl)-N4-(2-ethyl-2H-indazol-6-yl)pyrimidine-2,4-diamine (2j): Yield: 57%. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.22 – 8.12 (m, 1H), 8.04 – 7.95 (m, 3H), 7.66 (d, J = 8.8 Hz, 1H), 7.56 (dd, J = 8.8, 2.6 Hz, 1H), 7.31 (d, J = 8.9 Hz, 1H), 7.19 (dd, J = 8.9, 1.8 Hz, 1H), 6.30 (d, J = 5.9 Hz, 1H), 4.47 (q, J = 7.3 Hz, 2H), 1.62 (t, J = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, MeOD) δ 161.52, 154.42, 149.00, 140.38, 137.52, 129.71, 123.26, 120.52, 120.37, 118.80, 118.39, 105.98, 98.97, 14.90. LRMS (ESI): Mass calcd for C19H16Cl12N6 $[M+H]^+$: 400; found 400.

N4-(2-cyclopropyl-2H-indazol-6-yl)-N2-(3,4-dichlorophenyl)pyrimidine-2,4-diamine (2k): Yield: 68%. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.22 (s, 3H), 7.99 (s, 1H), 7.96 (s, 3H), 7.64 (s, 1H), 7.53 (s, 1H), 7.31 (s, 1H), 7.16 (s, 1H), 6.29 (s, 1H), 3.99 (s, 0H), 1.32 (s, 1H), 1.18 (s, 2H). ^{13}C NMR (125 MHz, MeOD) δ 161.49, 158.68, 153.99, 148.84, 140.25, 137.61, 131.67, 129.74, 123.90, 120.50, 118.92, 118.50, 105.91, 99.07, 33.69, 6.29, 6.09. LRMS (ESI): Mass calcd for C20H16Cl12N6 $[M+H]^+$: 412; found 412.

N4-(2-cyclobutyl-2H-indazol-6-yl)-N2-(3,4-dichlorophenyl)pyrimidine-2,4-diamine (2l): Yield: 49%. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.23 (s, 1H), 8.14 (s, 3H), 7.95 (s, 3H), 7.68 (s, 1H), 7.52 (s, 1H), 7.33 (s, 1H), 7.16 (s, 1H), 6.32 (s, 1H), 5.11 (s, 1H), 2.71 (s, 2H), 2.59 (s, 2H), 2.00 (s, 2H). ^{13}C NMR (125 MHz, MeOD) δ 163.82, 161.61, 157.50, 151.83, 148.84, 139.58, 136.94, 131.78, 129.86, 124.57, 122.34, 120.99, 120.78, 119.38, 118.80, 118.42, 106.96, 56.55, 30.05, 14.20. LRMS (ESI): Mass calcd for C21H18Cl12N6 $[M+H]^+$: 426; found 426.

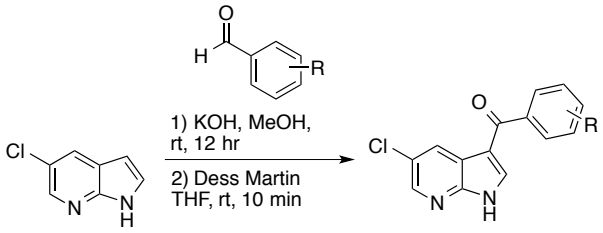


7 **93%** **8** **84%**

Preparation of N-(2,4-difluoro-3-formylphenyl)-2,2,2-trifluoroacetamide: 3-(1,3-dioxolan-2-yl)-2,4-difluoroaniline (520mg, 2.58 mmol, prepared based off previous literature[3]) was dissolved in DCM (10 mL). Triethylamine (360 µL, 2.58 mmol) was added slowly and the mixture was cooled to 0°C. Slowly, trifluoroacetic anhydride was added portion-wise. The mixture was allowed to stir for 3 hours and then diluted with DCM (30mL) and washed with sat. $NaHCO_3$, brine and water. The organic layers were combined and dried over sodium sulfate and concentrate *in vacuo* to afford fairly pure product N-(3-(1,3-dioxolan-2-yl)-2,4-difluorophenyl)-2,2,2-trifluoroacetamide **7** at 715 mg, 93% yield. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.31 – 8.16 (m, 1H), 7.99 (s, 1H), 6.96 (t, 1H), 6.23 (s, 1H), 4.27 – 4.16 (m, 2H), 4.10 – 3.99 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.56, 157.55, 154.87, 154.56, 152.75, 150.68, 123.37, 111.99, 96.82, 66.02, 45.67, 8.51. LRMS (ESI): Mass calcd for C11H8F5NO3 $[M+H]^+$: 298; found 298.

The protected trifluoroacetamide 7 (700 mg, 2.355mmol) was added to a small round bottom flask and dissolved in THF (10mL). At room temperature 6N HCl was added and the mixture was headed to 65°C and stirred for 2 hours. After completion of the reaction, ethyl acetate (15 mL), water (10 mL) was charged and stirred for 15 minutes. Organic layer and aqueous layers were separated, aqueous layer was back extracted with ethyl acetate (2 x 10mL), combined organic layer was successively washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate and concentrated under vacuum. The crude was purified by flash chromatography to afford N-(2,4-difluoro-3-formylphenyl)-2,2,2-trifluoroacetamide 8 (500 mg, 84% yield). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 10.35 (s, 1H), 8.58 – 8.37 (m, 1H), 8.04 (s, 1H), 7.18 – 7.01 (m, 1H). ^{13}C NMR (125 MHz, Chloroform-*d*) δ 183.43 (t, J = 4.3 Hz), 161.31 (d, J = 5.8 Hz), 159.22 (d, J = 5.4 Hz), 156.46 – 154.01 (m), 153.64 (d, J = 5.9 Hz), 151.54 (d, J = 5.6 Hz), 128.42 (d, J = 10.6 Hz), 120.91 (dd, J = 10.1, 4.0 Hz), 116.46 , 114.37 – 113.82 (m), 112.82 (dd, J = 22.0, 4.4 Hz). LRMS (ESI): Mass calcd for C9H4F5NO2 $[M+ACN+Na]^+$: 317; found 317.

[3] Chava, S. et al., Novel Processes for the Preparation of Vemurafenib Patent WO2015/75749 A1, 2015.



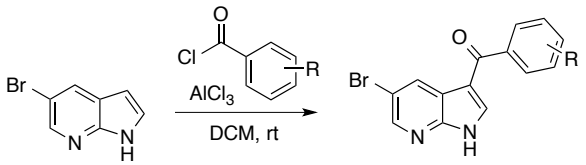
3a,b
54-78%

General procedure for the synthesis of 3a,b: Into a round bottom flask was added 5-chloro-lH-pyrrolo[2,3-b]pyridine (0.328 mmol, prepared as described previously in the literature[4]) in methanol (3 mL). Potassium hydroxide (1.31mmol) and substituted benzaldehyde (0.328 mmol) were added and the reaction mixture was stirred overnight. The reaction mixture was poured into 1N HCl and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and crystallized from ethyl acetate to give crude material which was used directly in oxidation reaction.

Into a round bottom flask was added crude in tetrahydrofuran (3 mL). Dess-Martin periodinane (0.355 mmol) was added in portions. The reaction mixture was stirred at ambient temperature for 10 minutes, then poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, concentrated and purified by silica gel chromatography to give compounds **3a** and **3b** (78% and 54% yield, respectively).

(5-chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)(2,6-difluorophenyl)methanone (3a): Yield: 78%. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.57 (s, 1H), 8.37 (s, 1H), 7.93 (s, 2H), 7.58 (s, 1H), 7.15 (s, 1H). ^{13}C NMR (125 MHz, MeOD) δ 182.41, 160.49, 147.51, 143.35, 138.11, 132.02, 129.01, 126.61, 118.71, 116.00, 111.75, 111.55. LRMS (ESI): Mass calcd for C14H17ClF2N2O $[M+H]^+$: 293; found 293.

N-(3-(5-chloro-1H-pyrrolo[2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl)-2,2,2-trifluoroacetamide (3b): Yield: 54%. ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.58 (s, 1H), 8.37 (s, 1H), 7.99 (s, 2H), 7.76 (s, 1H), 7.22 (s, 1H). ^{13}C NMR (125 MHz, MeOD) δ 181.06, 147.55, 143.46, 138.43, 129.04, 126.70, 118.69, 115.76, 111.77, 68.89, 48.10. LRMS (ESI): Mass calcd for C16H17ClF5N3O2 $[M+H]^+$: 404; found 404.



3c-f
9-44%

General procedure for the synthesis of 3c-f: 5-Azaindole (0.51 mmol) was added to a stirred suspension of $AlCl_3$ (2.54 mmol) in dichloromethane (10 mL). After the mixture was stirred at room temperature for 1 h, substituted benzoyl chloride (2.54 mmol) was added dropwise and the resulting mixture stirred for 8 h. MeOH (2 mL) was added cautiously to quench the reaction, the solvents were removed under vacuum, and the residual solid was purified by silica gel chromatography using a mixture of EtOAc and MeOH (10:1) as eluent to afford the acylated products **3c-f** (9-44% yield).

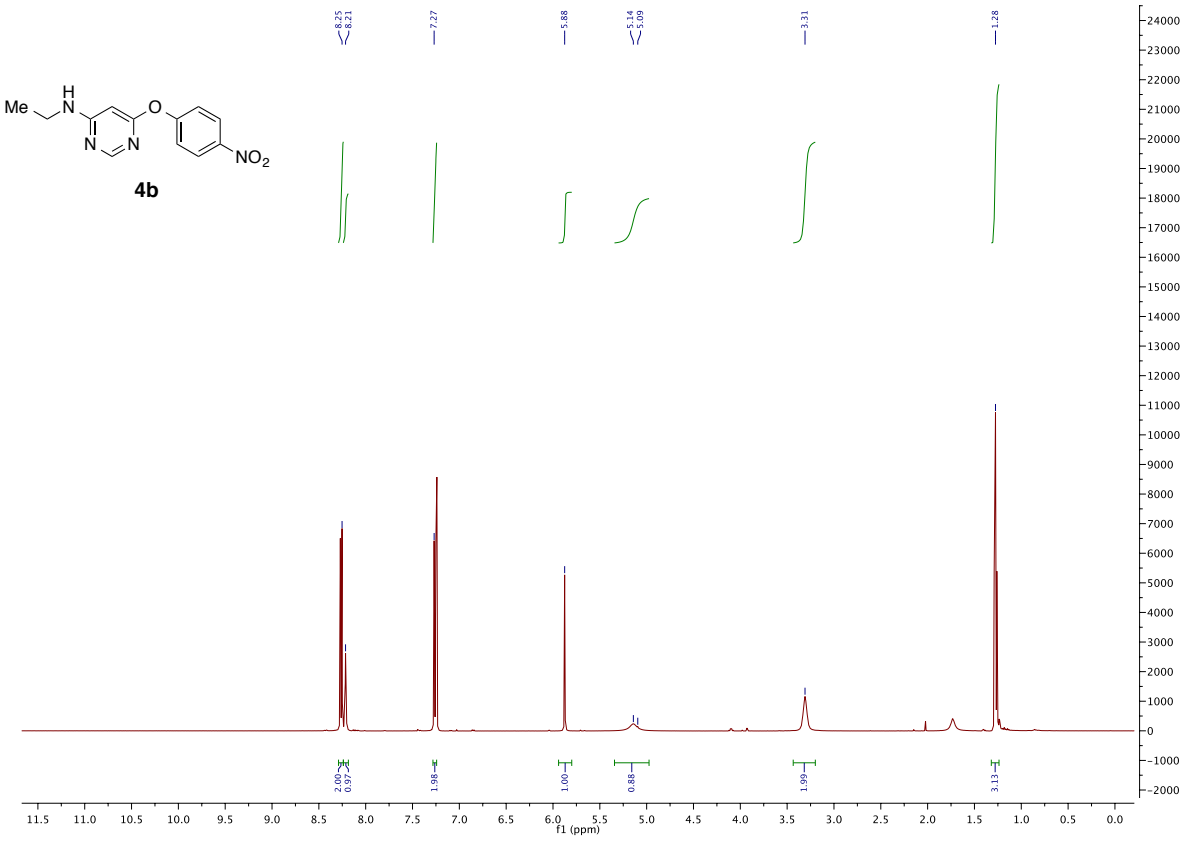
[4] Bollag, G. et al. *PNAS*, **2008**, 105, 3041-3046.

(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)(2,6-difluorophenyl)methanone (3c): Yield: 34%. ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.99 (d, *J* = 1.9 Hz, 1H), 7.74 (s, 1H), 7.47 – 7.44 (m, 2H), 7.04 – 7.00 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.99, 162.23, 160.61, 160.18, 158.61, 146.69, 143.97, 136.29, 135.08, 133.36, 131.82, 116.77, 112.34, 112.14, 111.94. LRMS (ESI): Mass calcd for C14H17BrF2N2O $[M+H]^+$: 338; found 338.

(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)(3,5-difluorophenyl)methanone (3d): Yield: 44%. ^{1}H NMR (500 MHz, DMSO) δ 8.65 (d, *J* = 2.3 Hz, 1H), 8.49 (d, *J* = 2.3 Hz, 1H), 8.34 (s, 1H), 7.65 – 7.42 (m, 4H). ^{13}C NMR (125 MHz, DMSO) δ 163.72, 161.65, 148.10, 145.41, 138.83, 131.94, 120.70, 114.30, 112.93, 107.39. LRMS (ESI): Mass calcd for C14H17BrF2N2O $[M+H]^+$: 338; found 338.

(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)(2-chlorophenyl)methanone (3e): Yield: 9%. ^{1}H NMR (500 MHz, DMSO) δ 8.53 (d, *J* = 2.3 Hz, 1H), 8.48 (d, *J* = 2.3 Hz, 1H), 7.94 (s, 1H), 7.63 – 7.54 (m, 3H), 7.49 (ddd, *J* = 8.1, 6.8, 1.3 Hz, 1H). ^{13}C NMR (125 MHz, DMSO) δ 188.73, 148.18, 145.41, 139.48, 138.90, 130.41, 130.11, 129.37, 127.71, 119.96, 114.57, 114.40. LRMS (ESI): Mass calcd for C14H18BrClN2O $[M+H]^+$: 336; found 336.

(5-bromo-1H-pyrrolo[2,3-b]pyridin-3-yl)(4-chlorophenyl)methanone (3f): Yield: 11%. ^{1}H NMR (500 MHz, DMSO) δ 8.65 (d, *J* = 2.2 Hz, 1H), 8.48 (d, *J* = 2.4 Hz, 1H), 8.24 (s, 1H), 7.92 – 7.79 (m, 2H), 7.68 – 7.58 (m, 2H). ^{13}C NMR (125 MHz, DMSO) δ 188.81, 147.97, 145.27, 138.25, 137.95, 136.97, 131.99, 130.93, 129.15, 120.82, 114.15, 113.37. LRMS (ESI): Mass calcd for C14H18BrClN2O $[M+H]^+$: 336; found 336.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H
N
O
N
N
NO2
4b
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8.21
7.27
5.88
5.14
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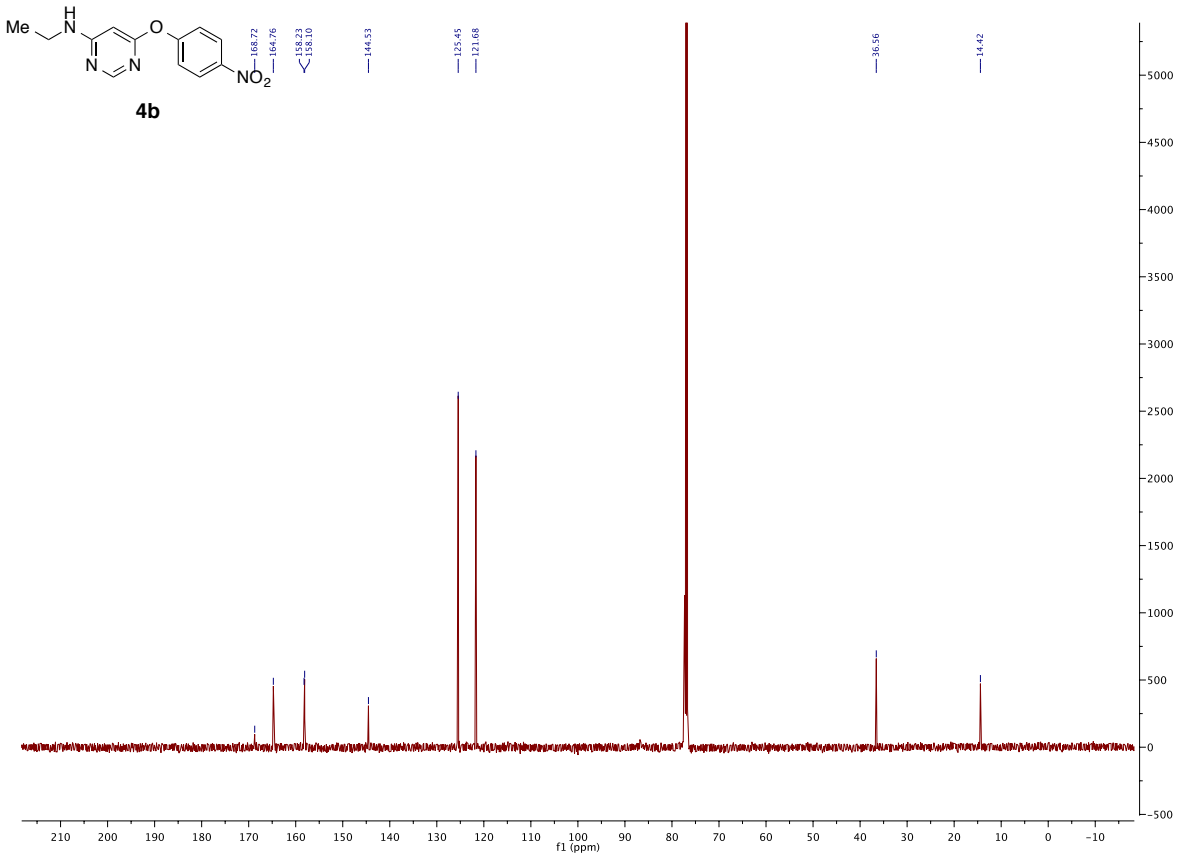
1.28
2.00
0.97
1.98
1.00
0.88
1.99
3.13
f1 (ppm)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H
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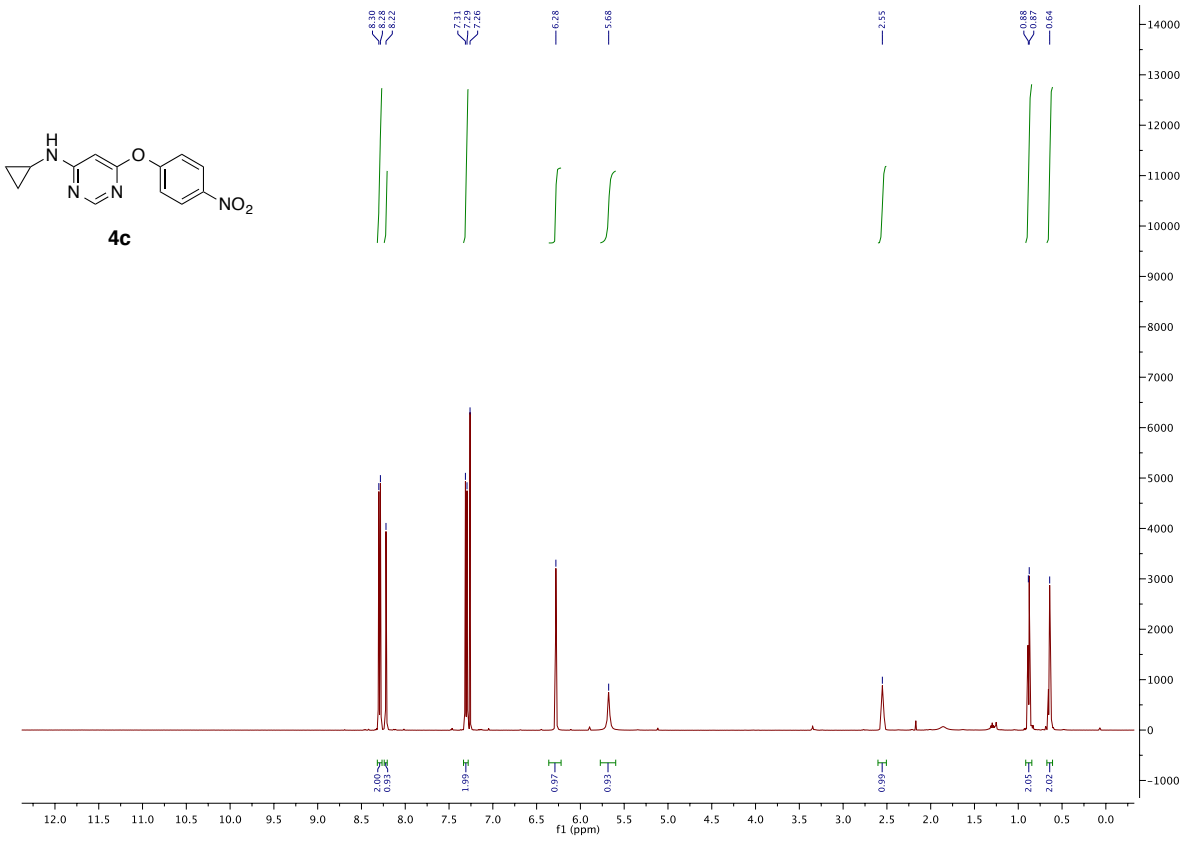
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1.99
0.97
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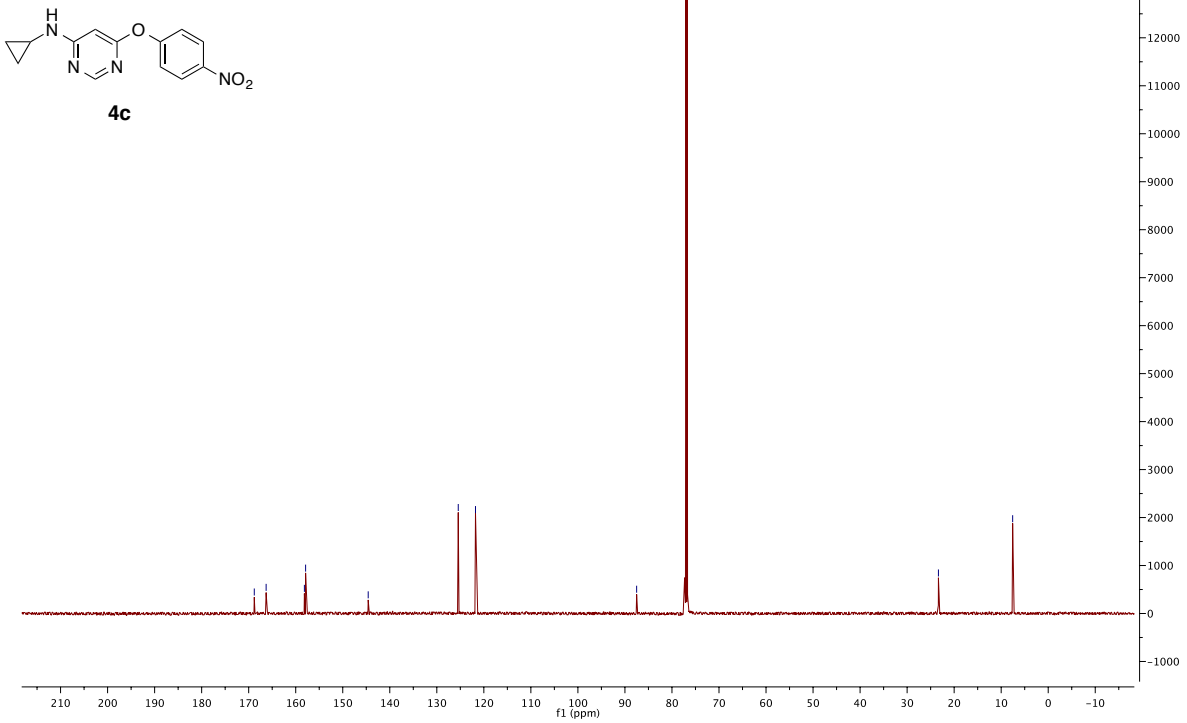
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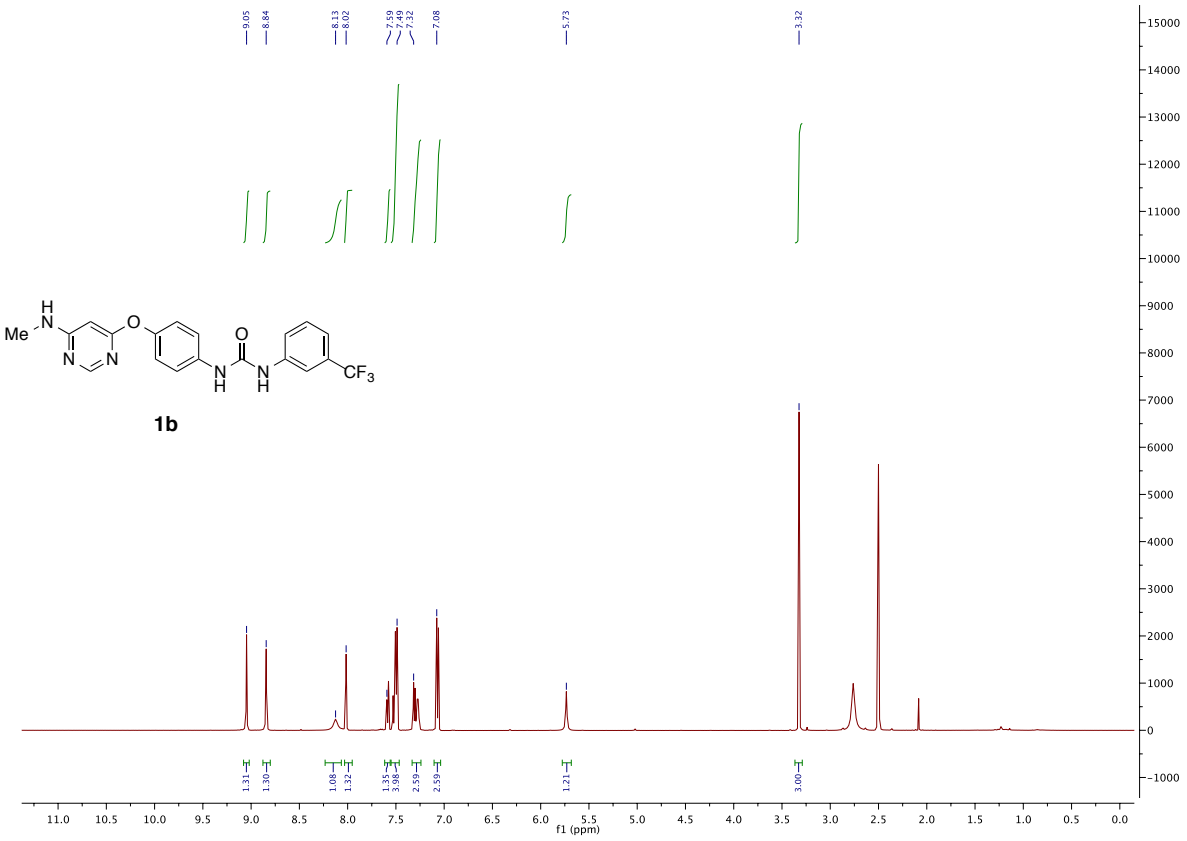
4c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2.59
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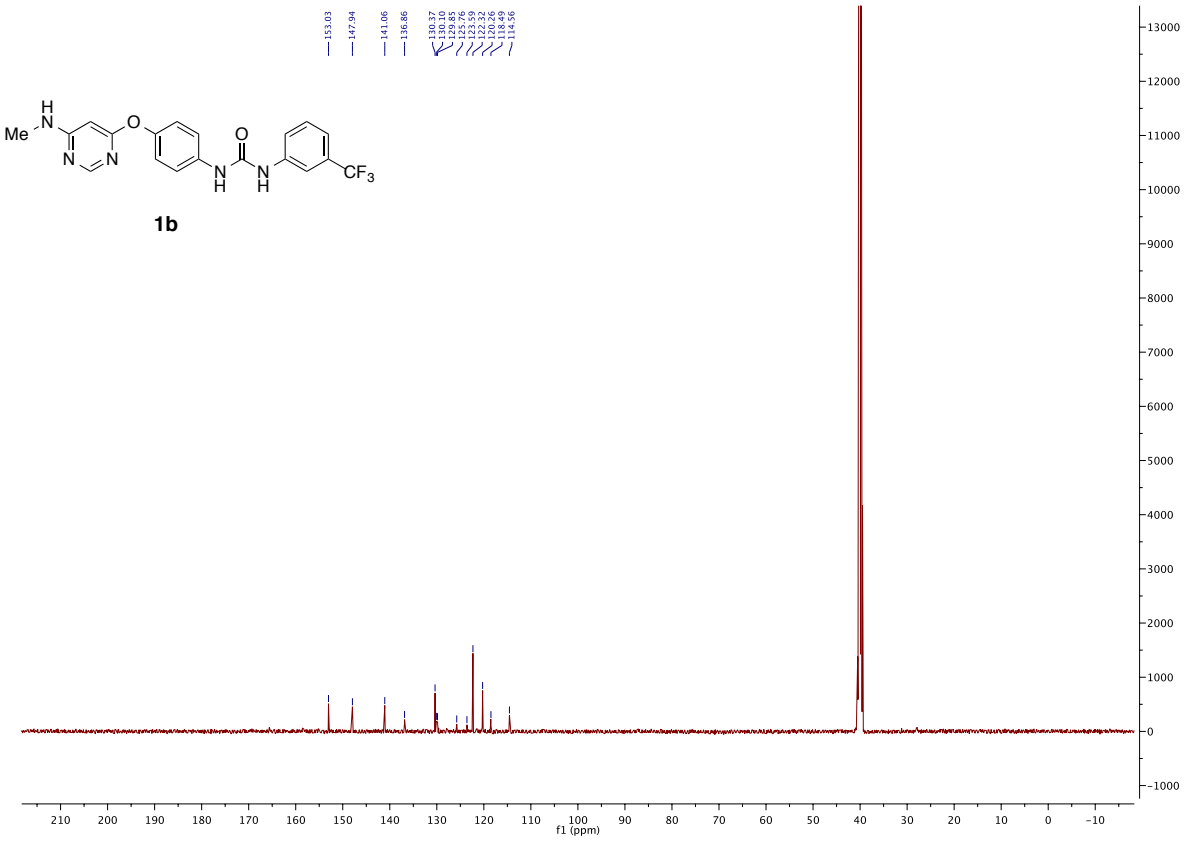
3.00
f1 (ppm)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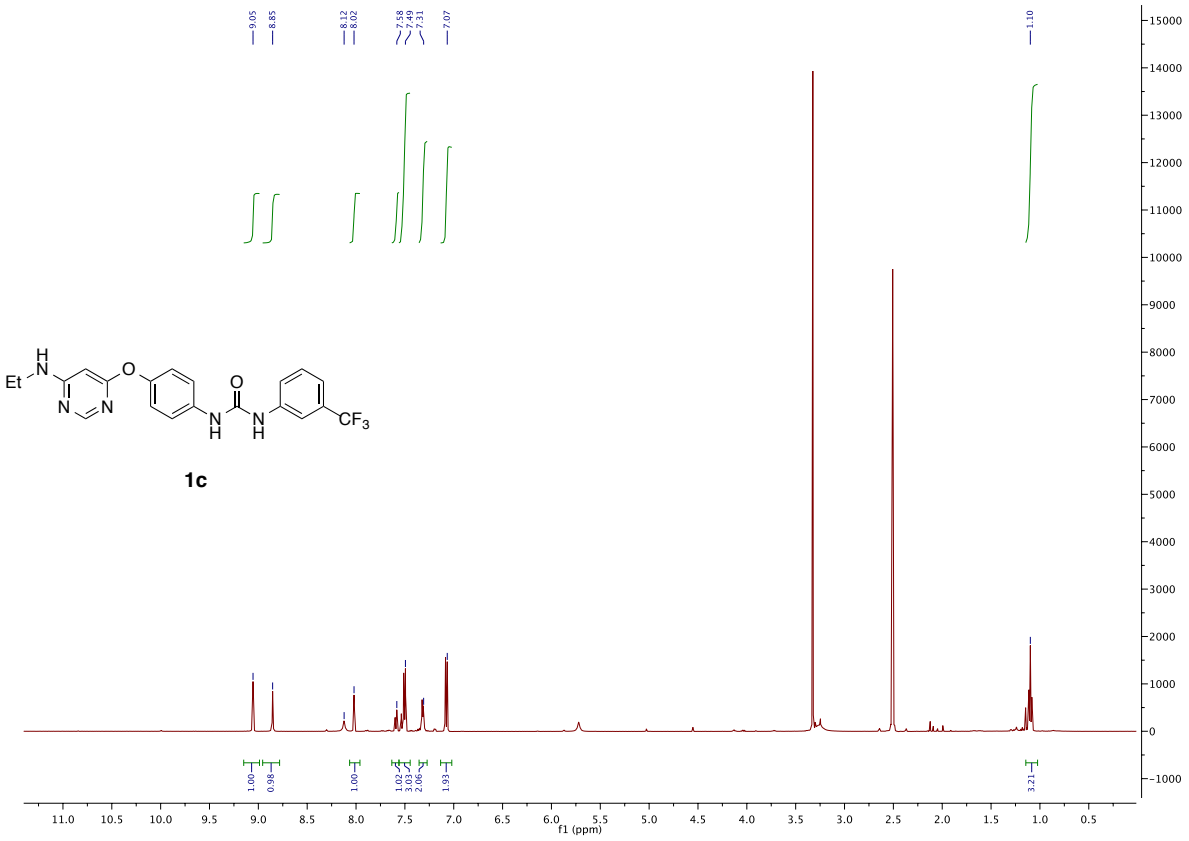
f1 (ppm)

1b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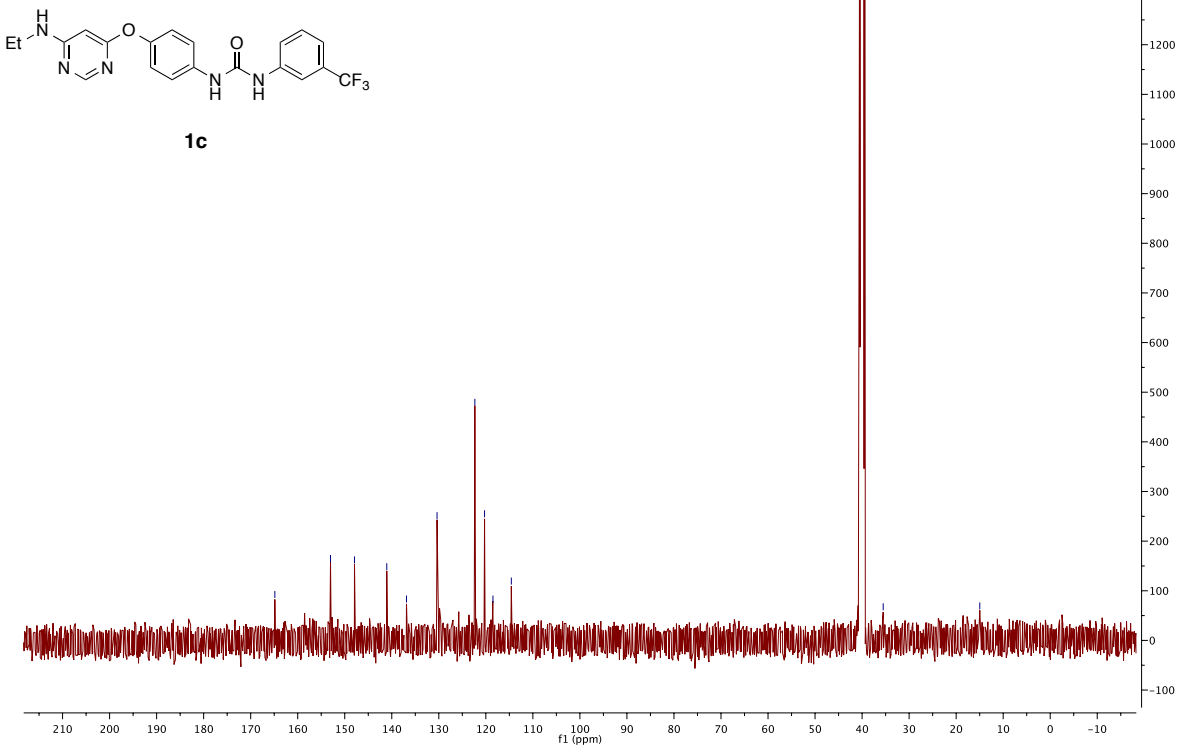
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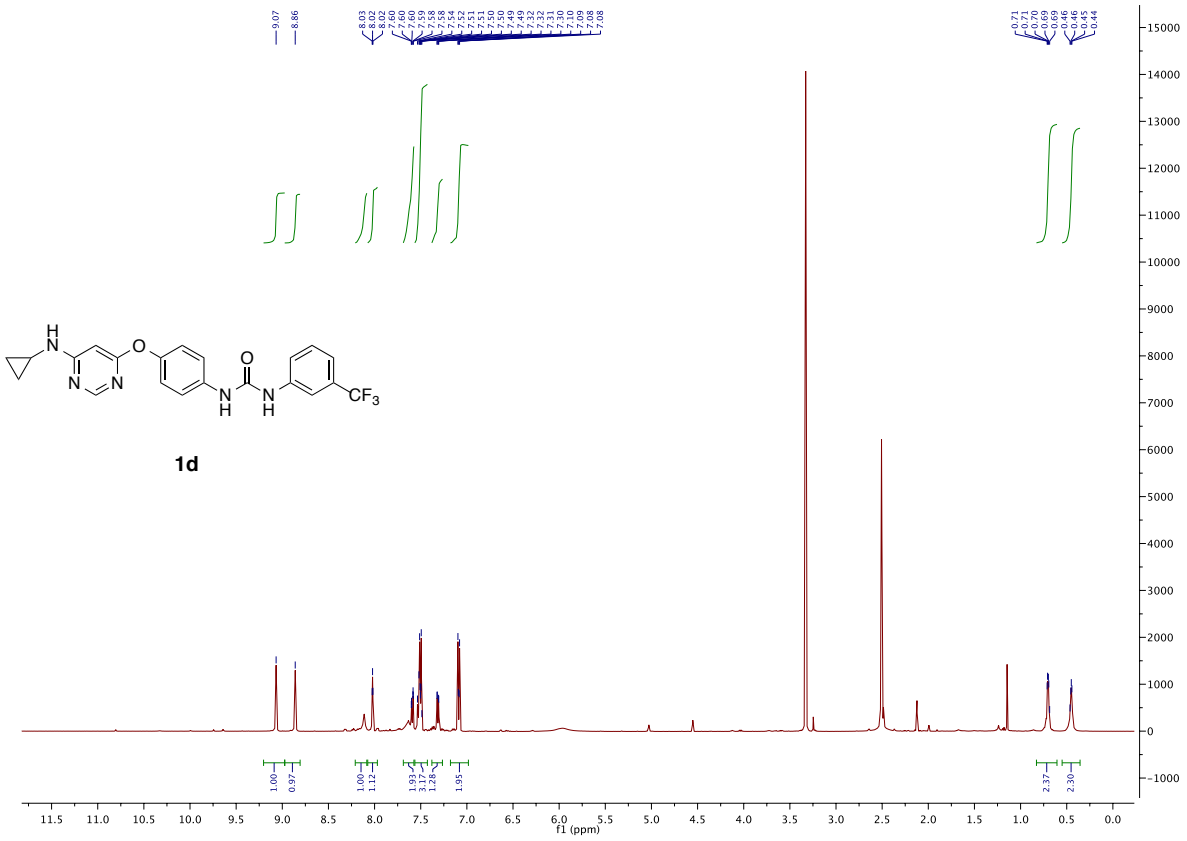
1c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7.32
7.32
7.31
7.10
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7.08
7.08
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0.70
0.69
0.69
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0.45
0.45
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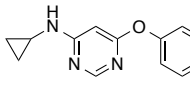
f1 (ppm)



1d

153.03
147.87
141.07
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130.37
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118.48
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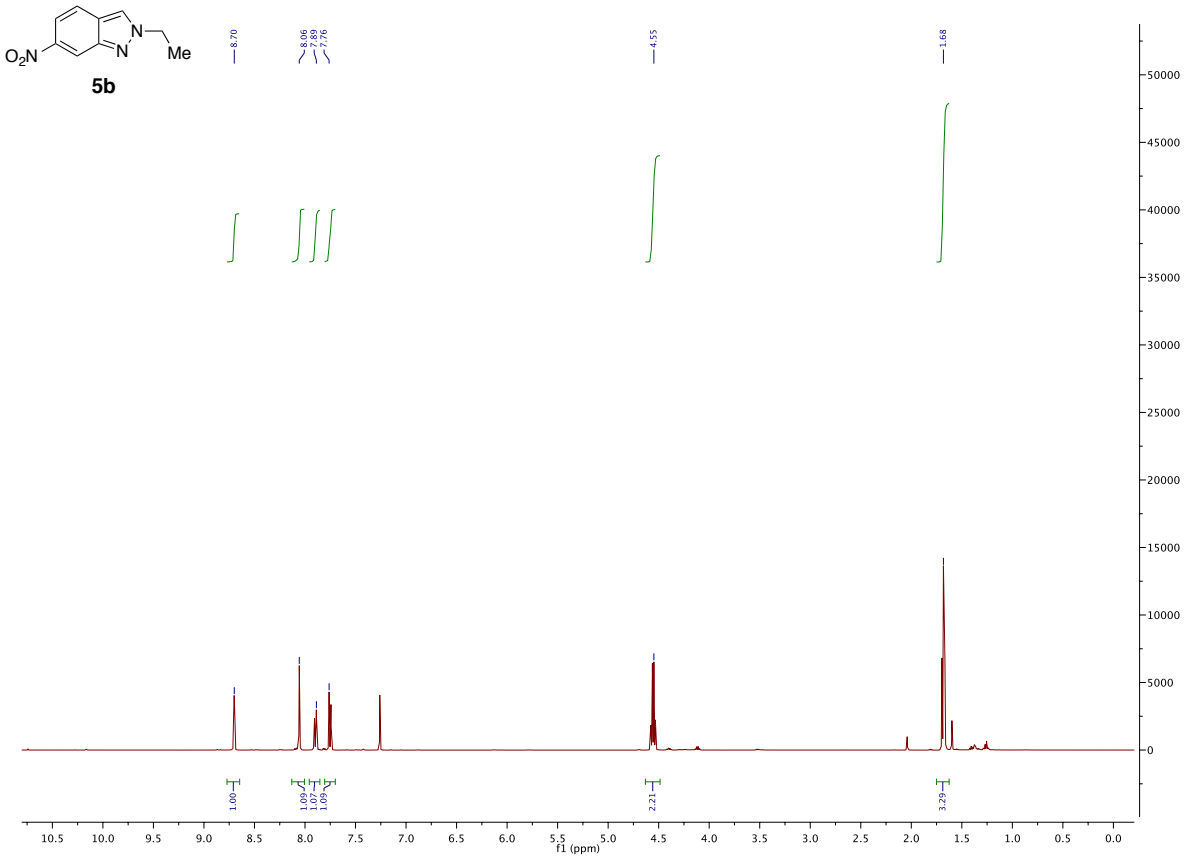
30.06
23.55
6.95
f1 (ppm)

1d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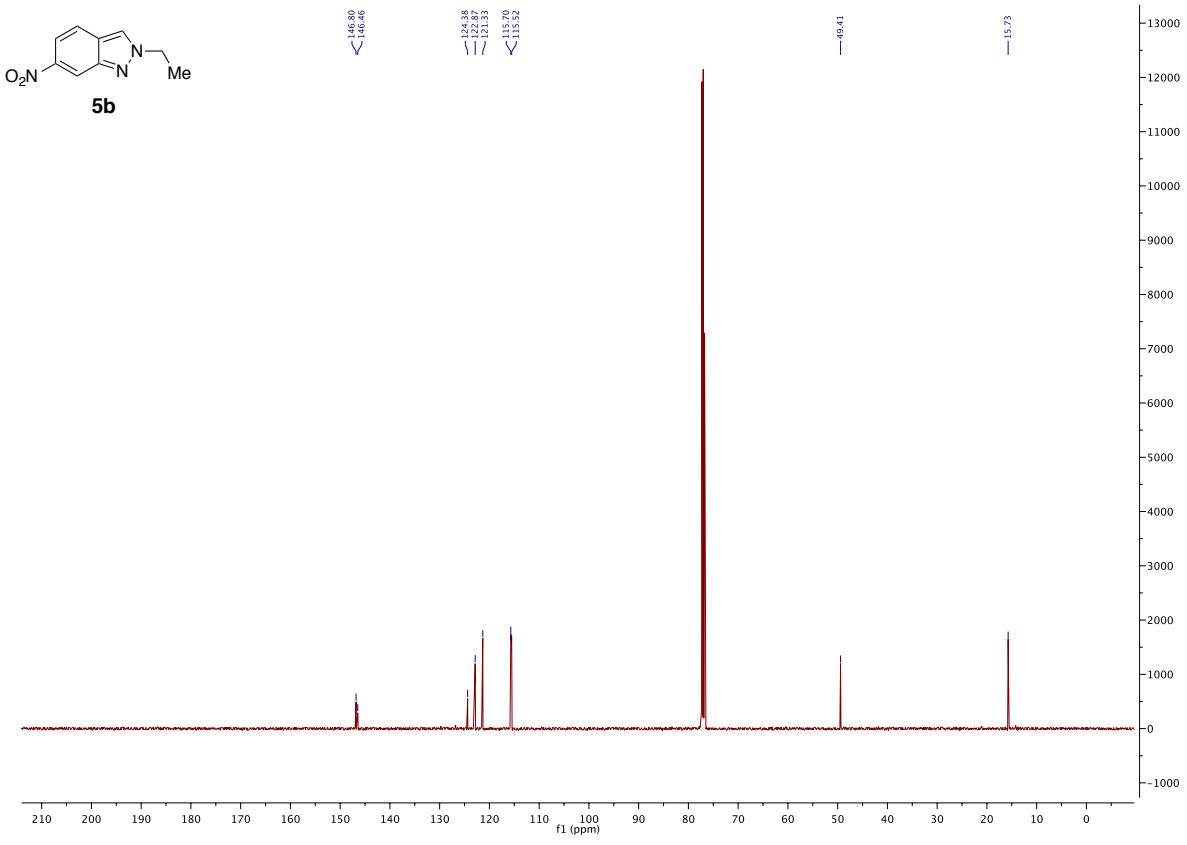
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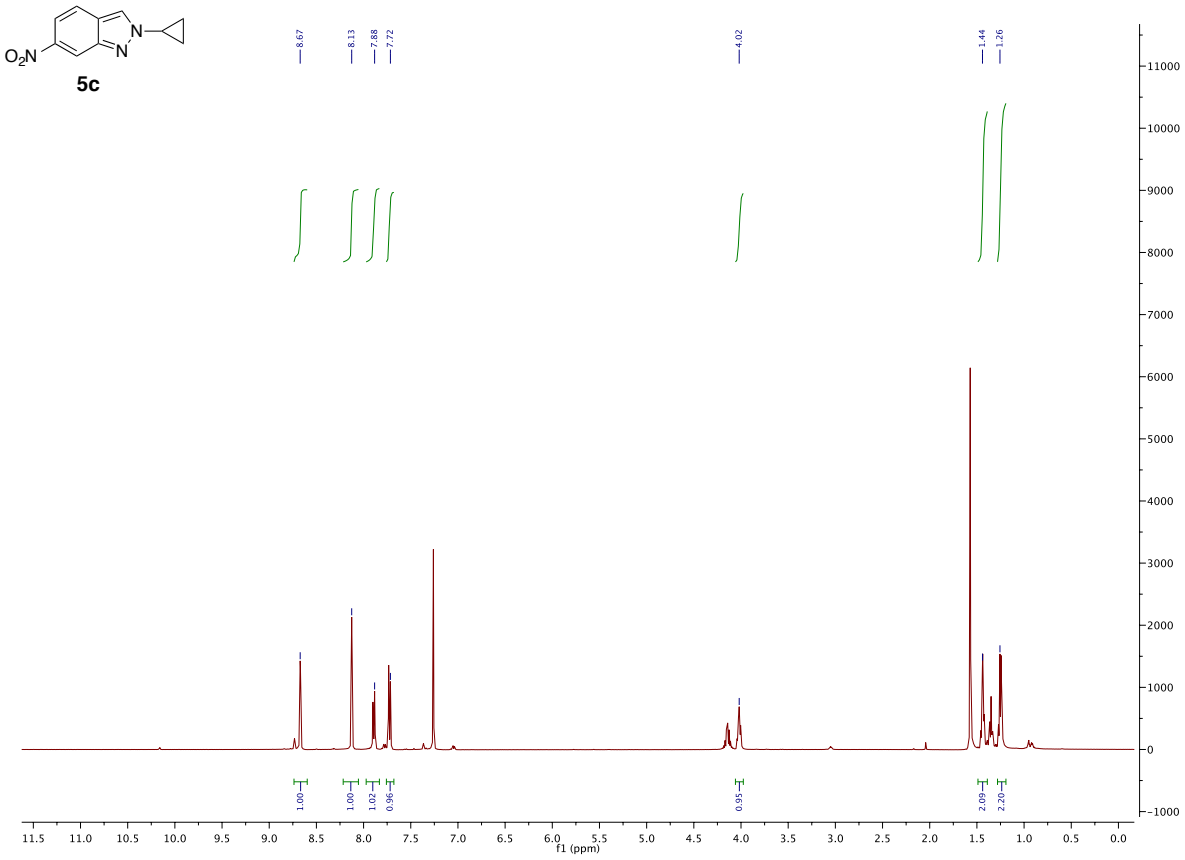
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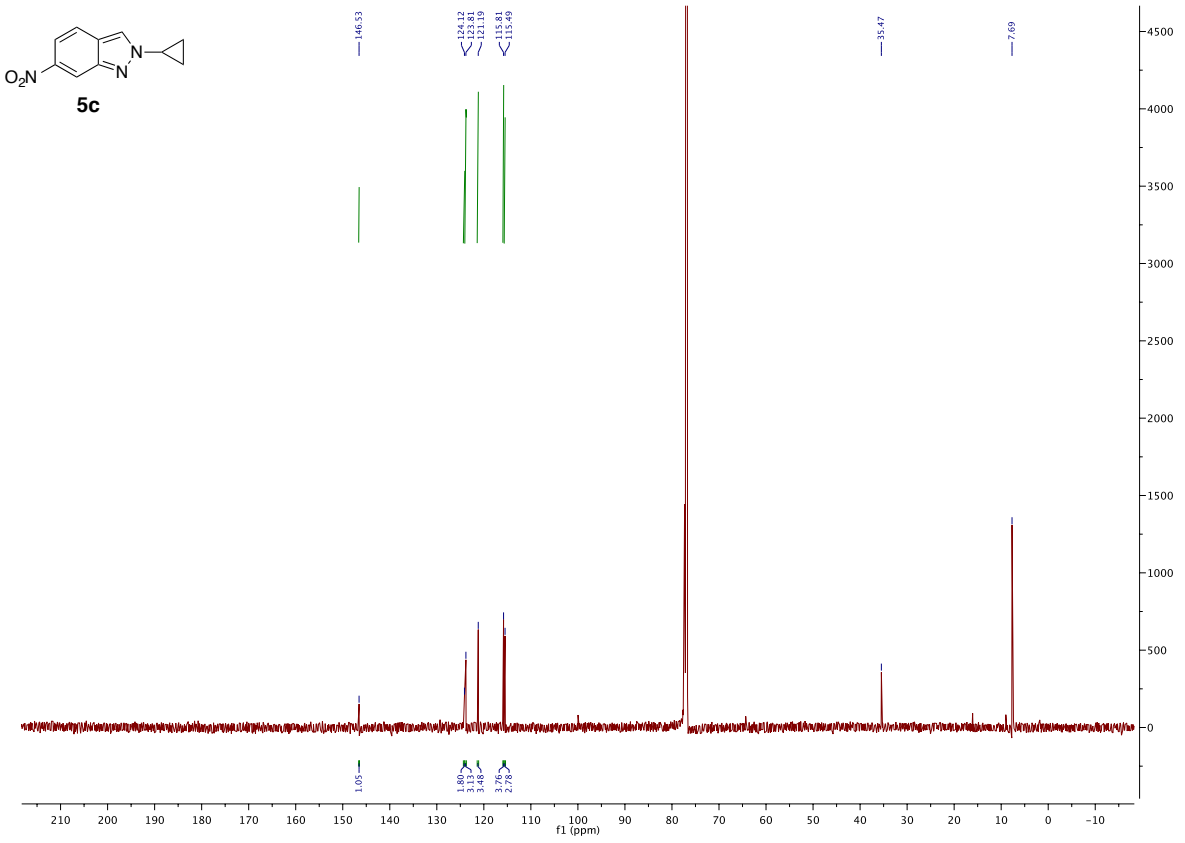
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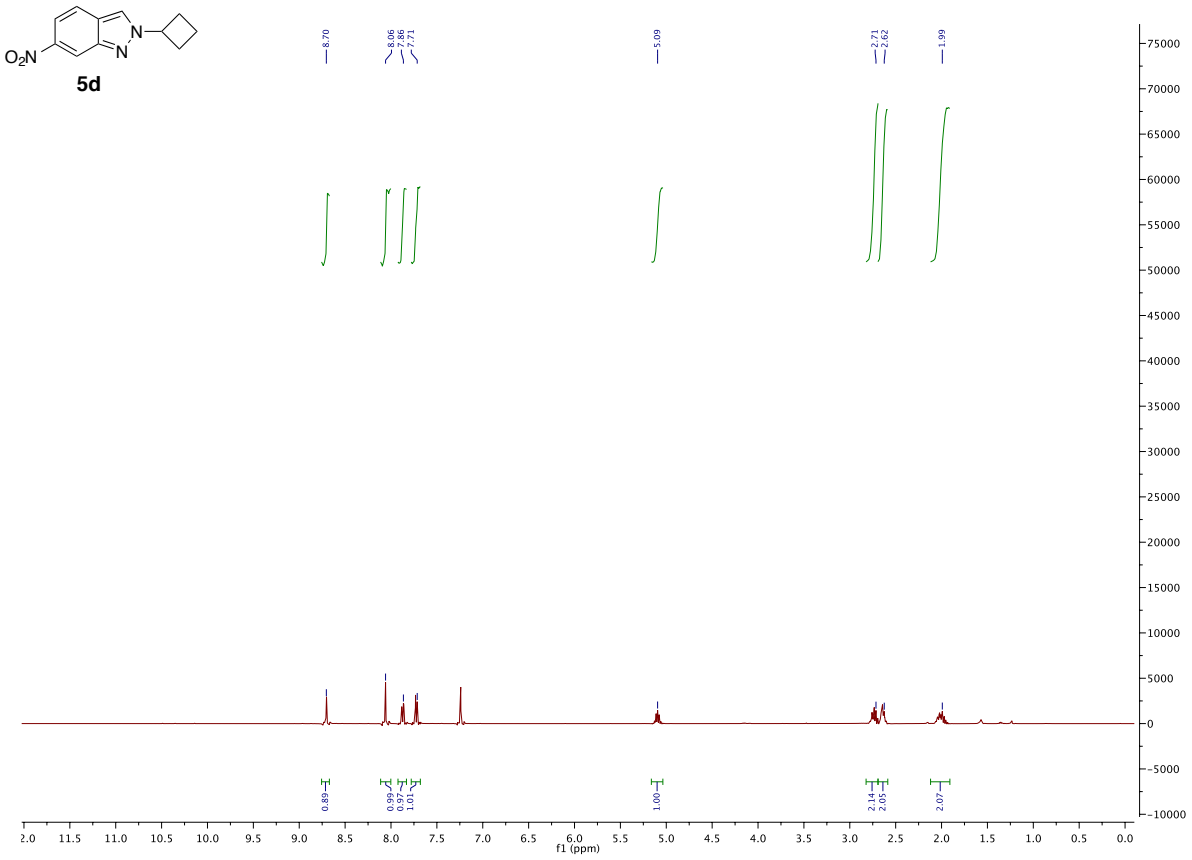
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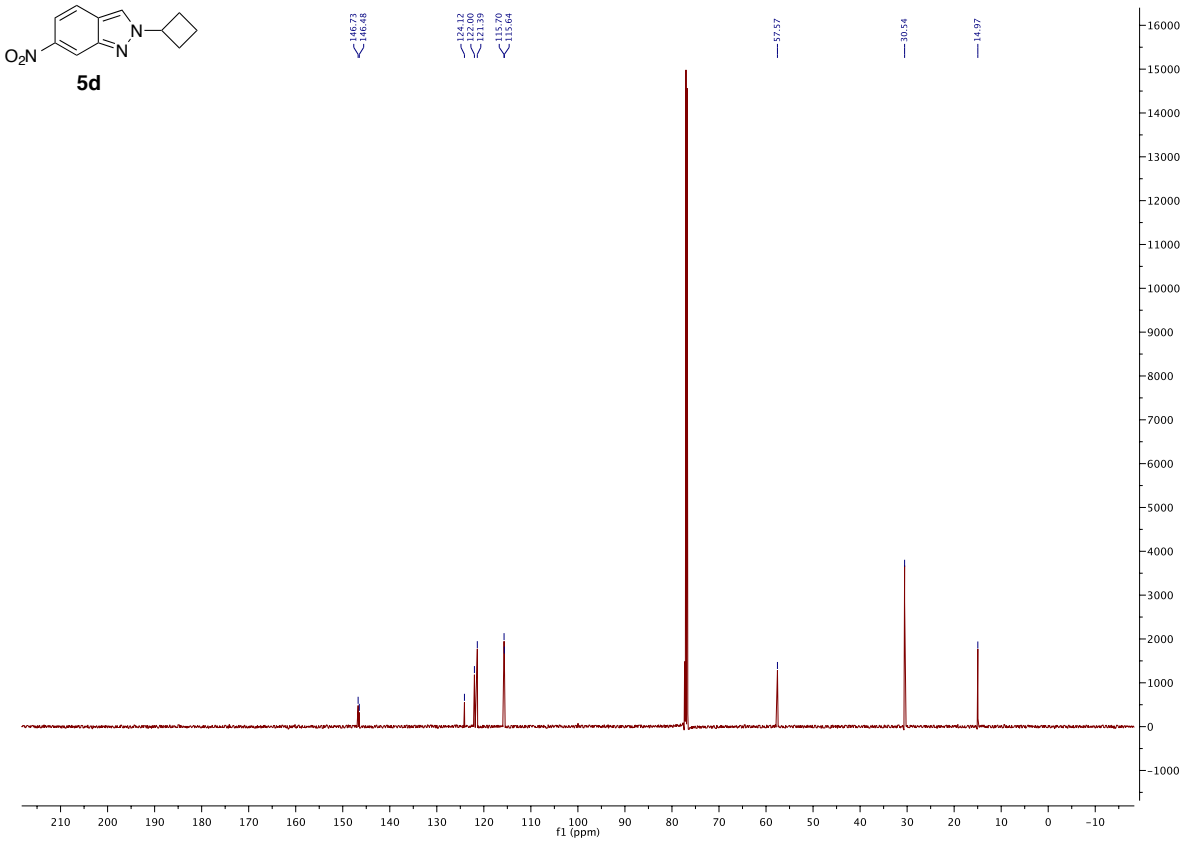
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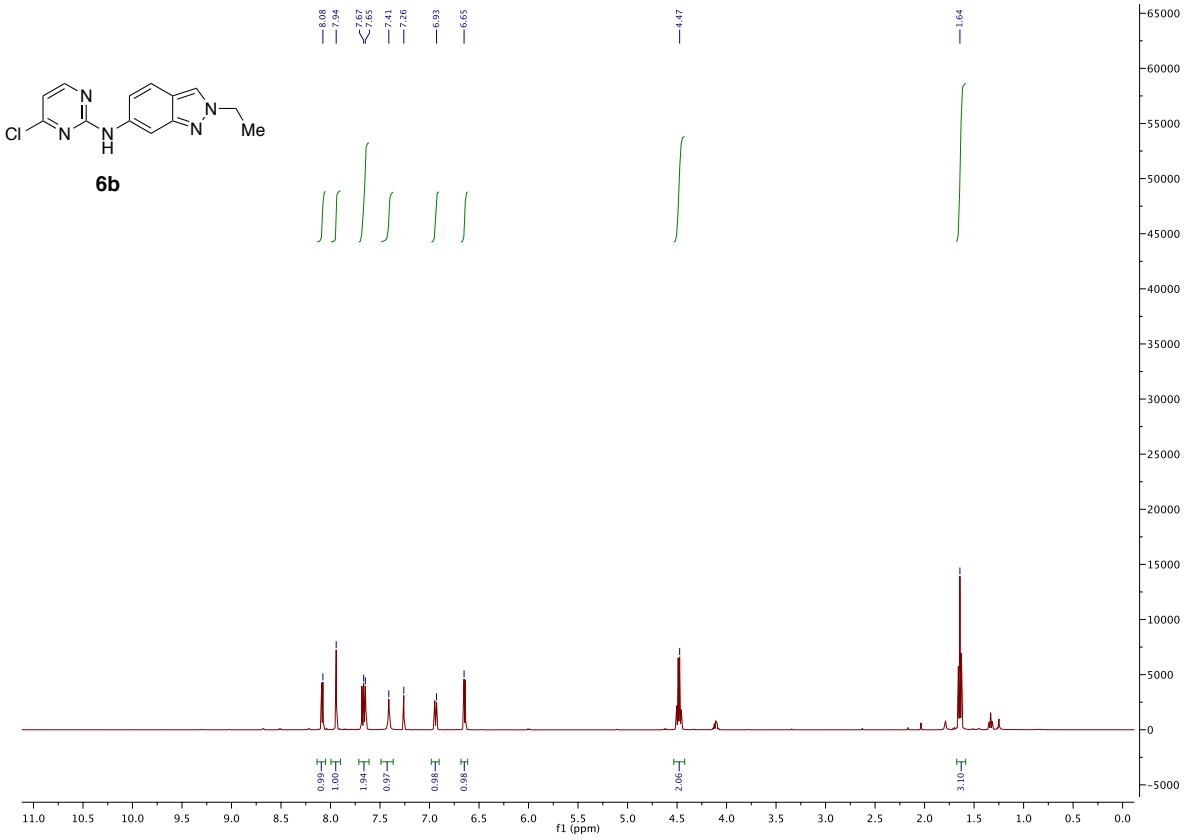
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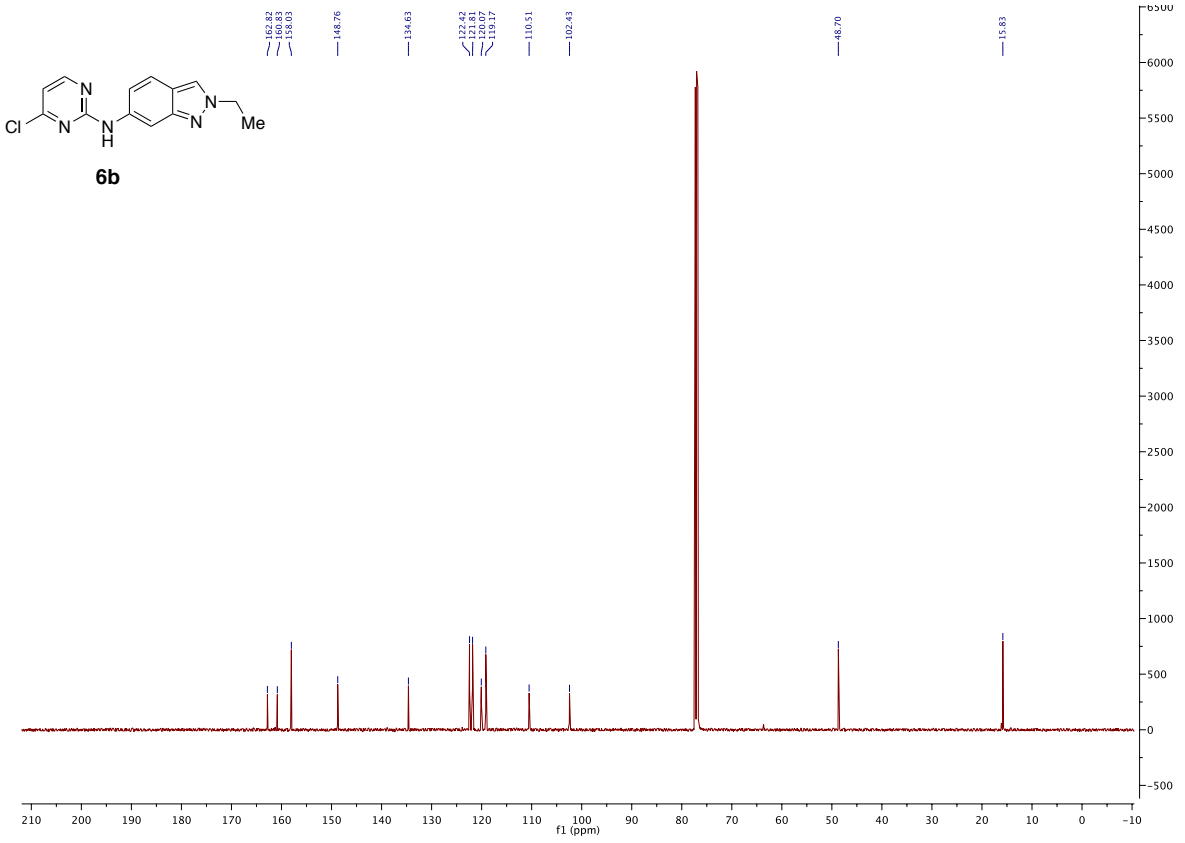
6b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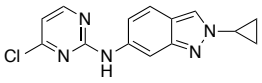
6b



6c

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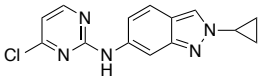

6c

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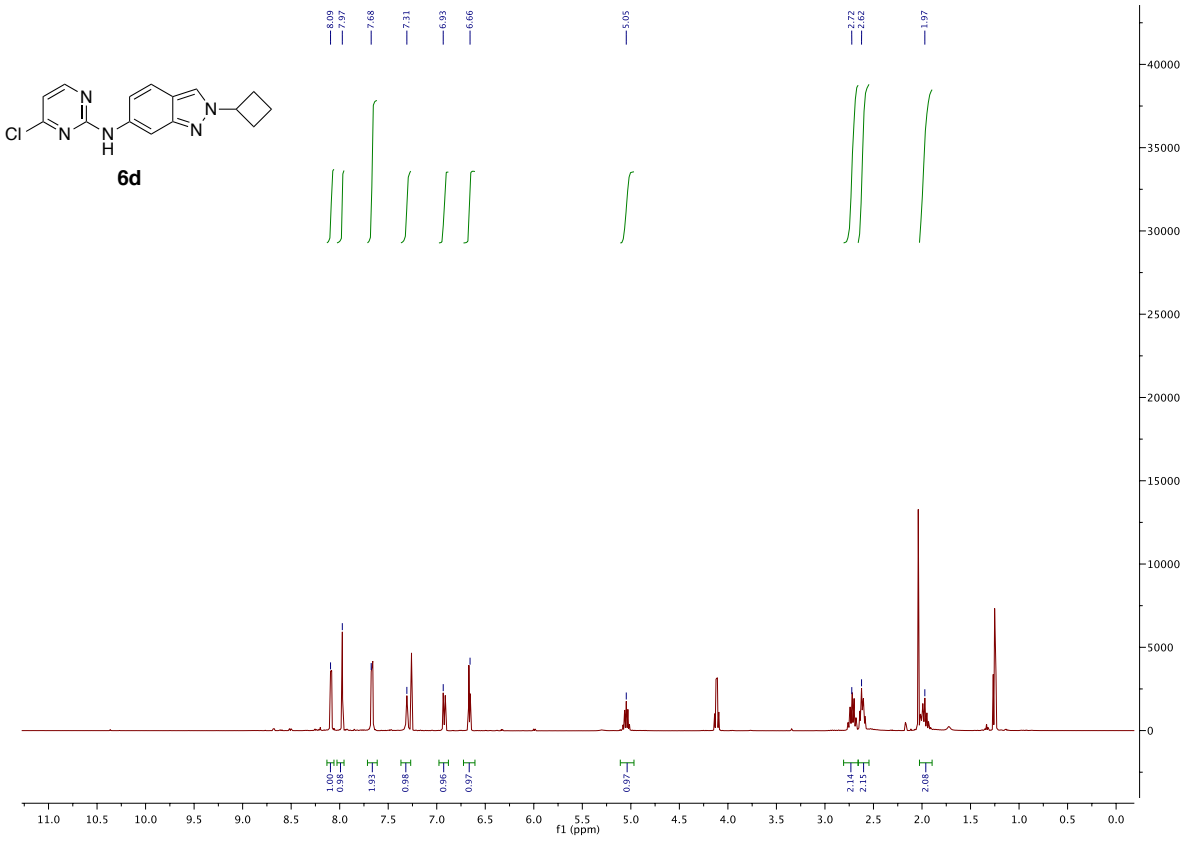
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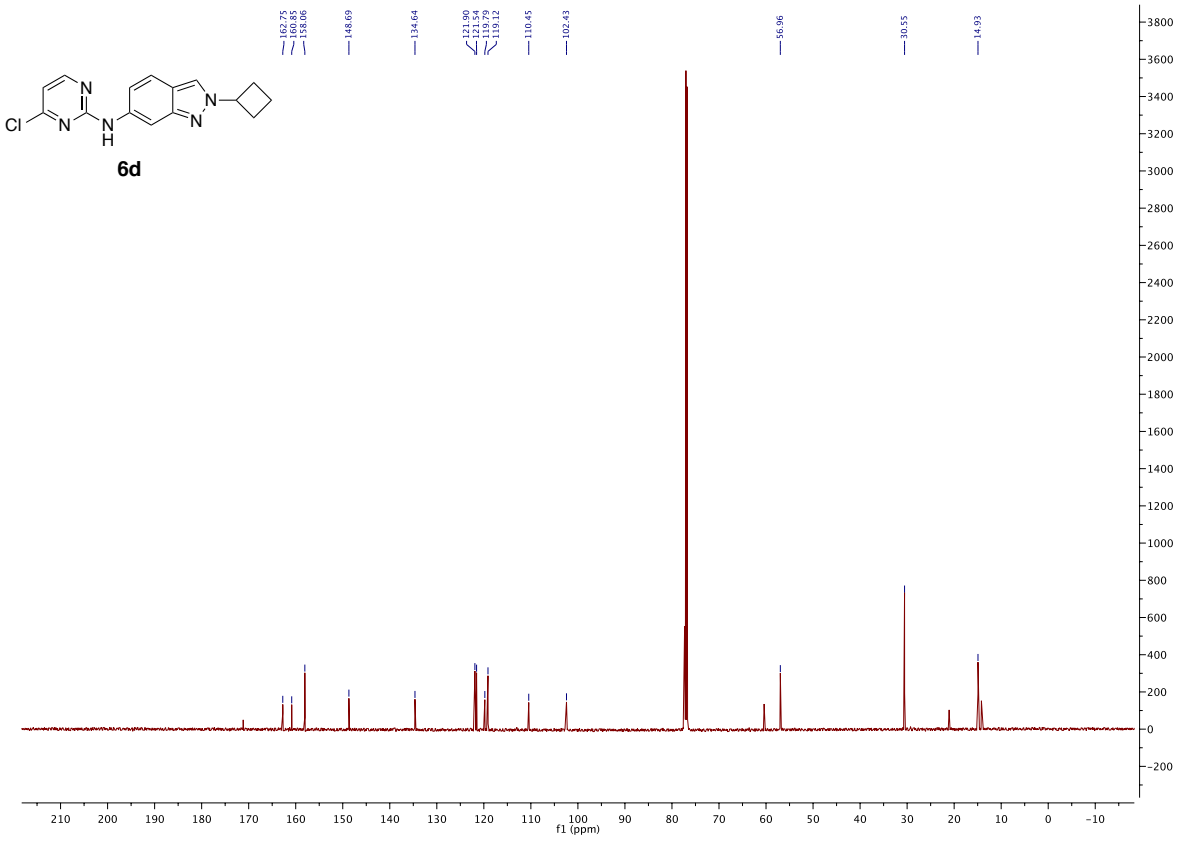
6d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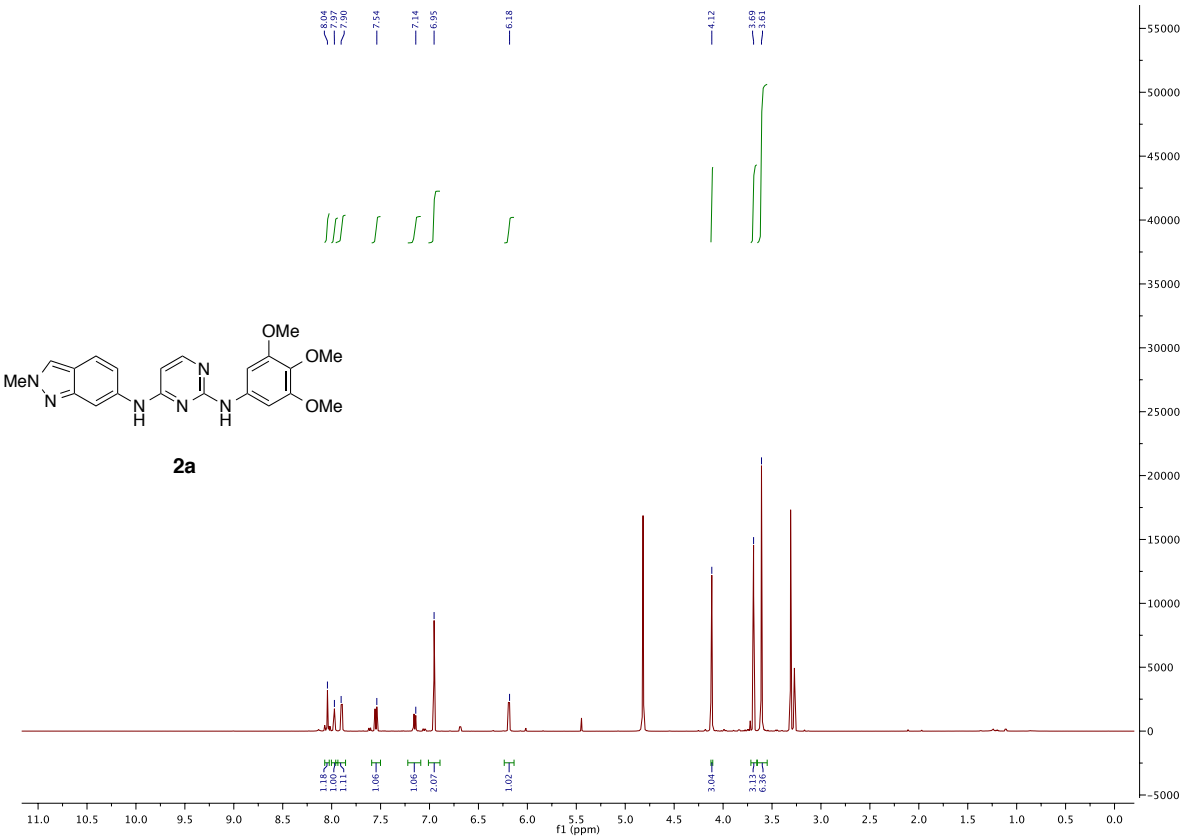
6d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N
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2a
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1.09
1.11
1.06
1.06
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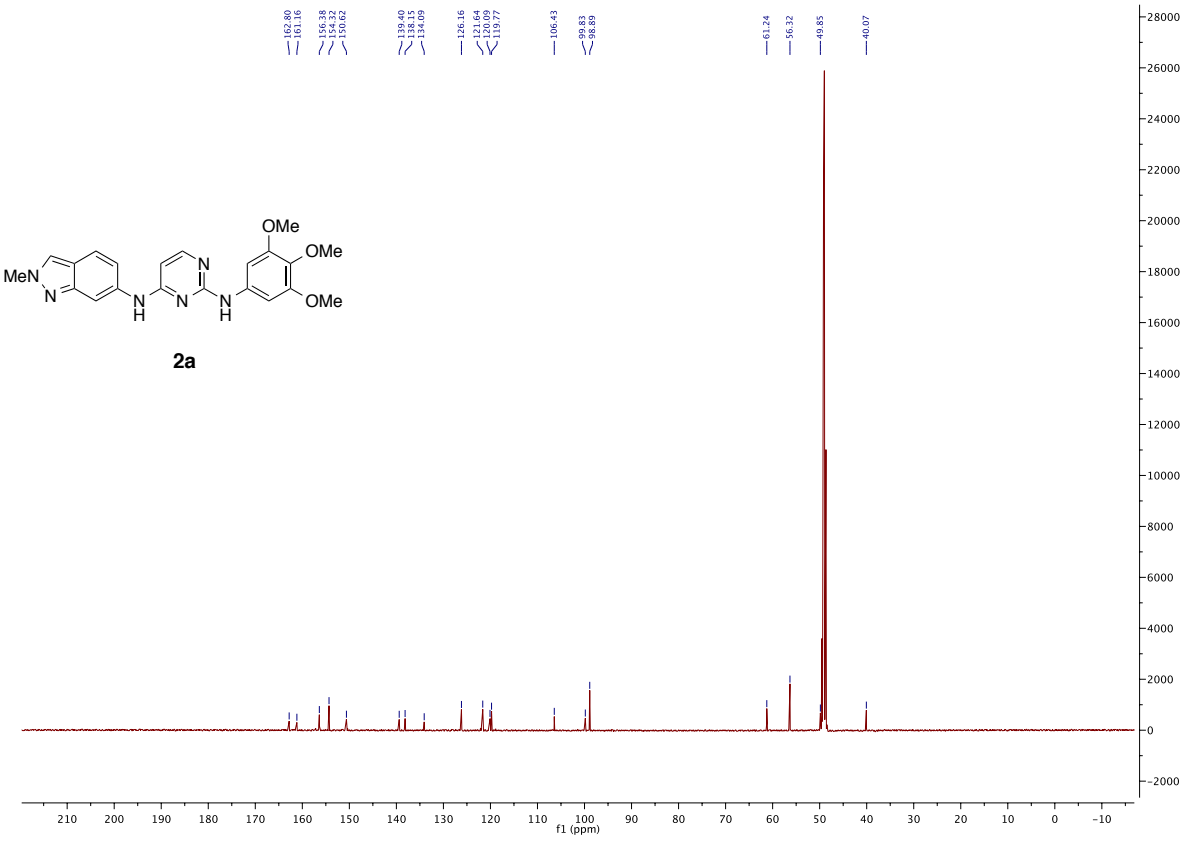
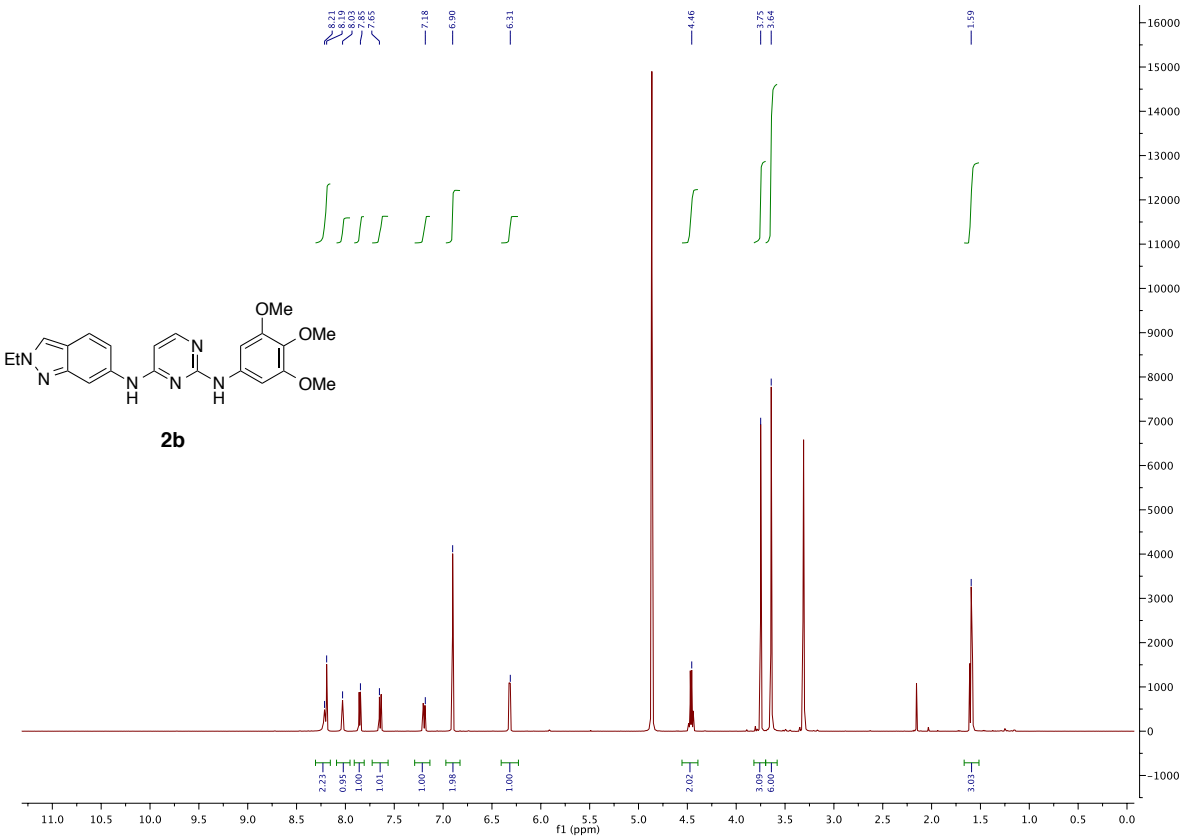
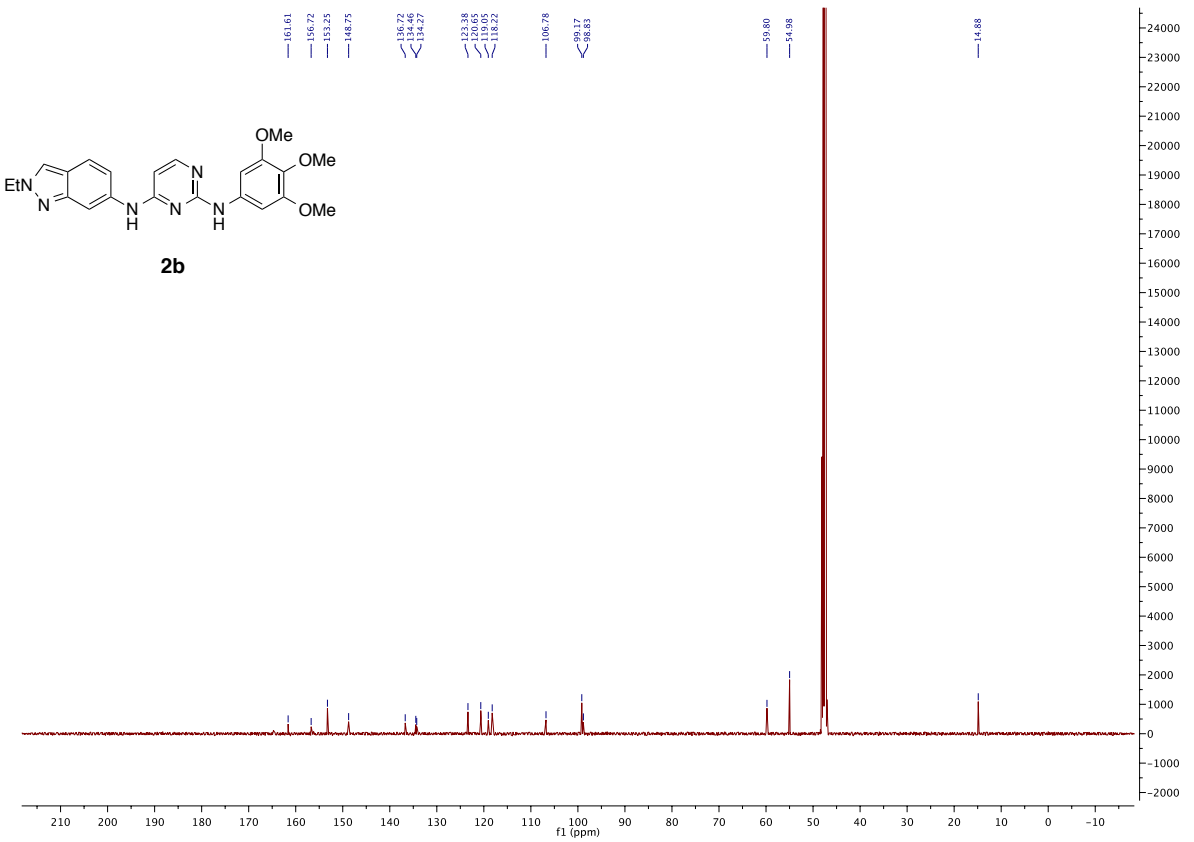
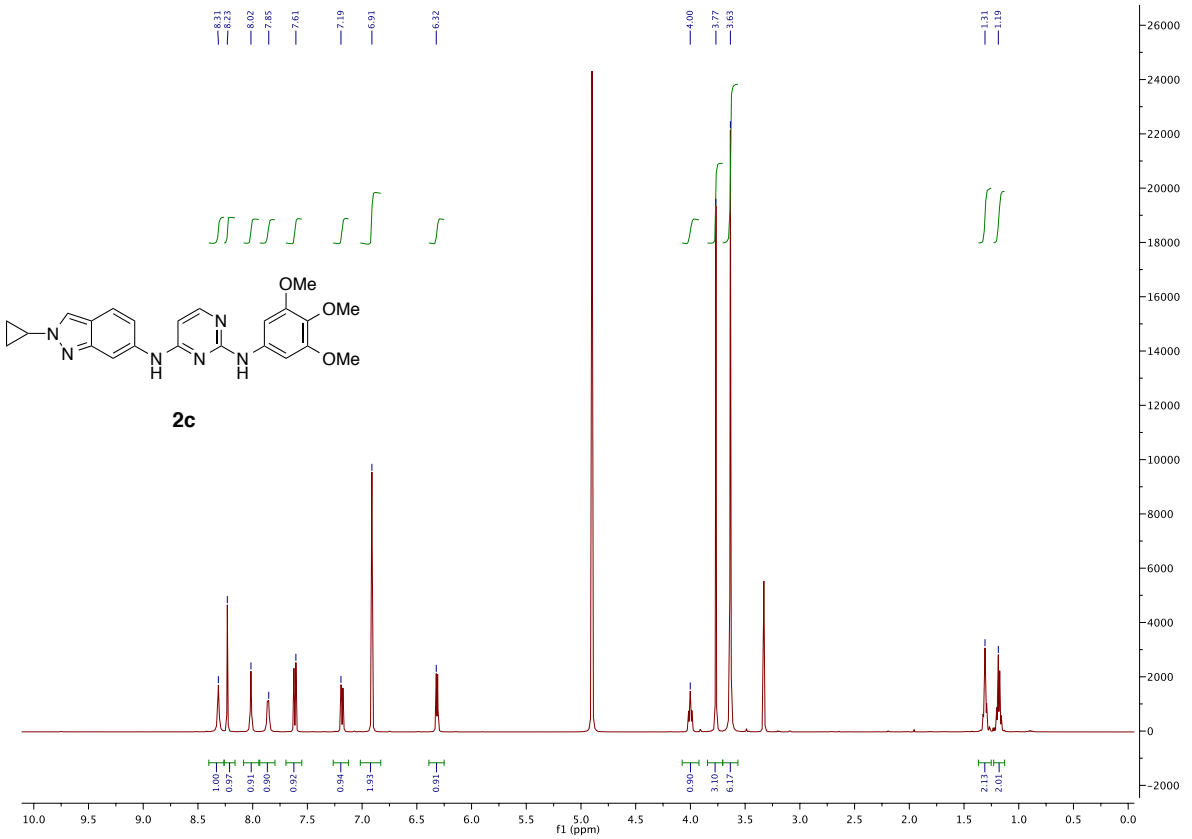
1.02
3.04
3.13
6.36
f1 (ppm)

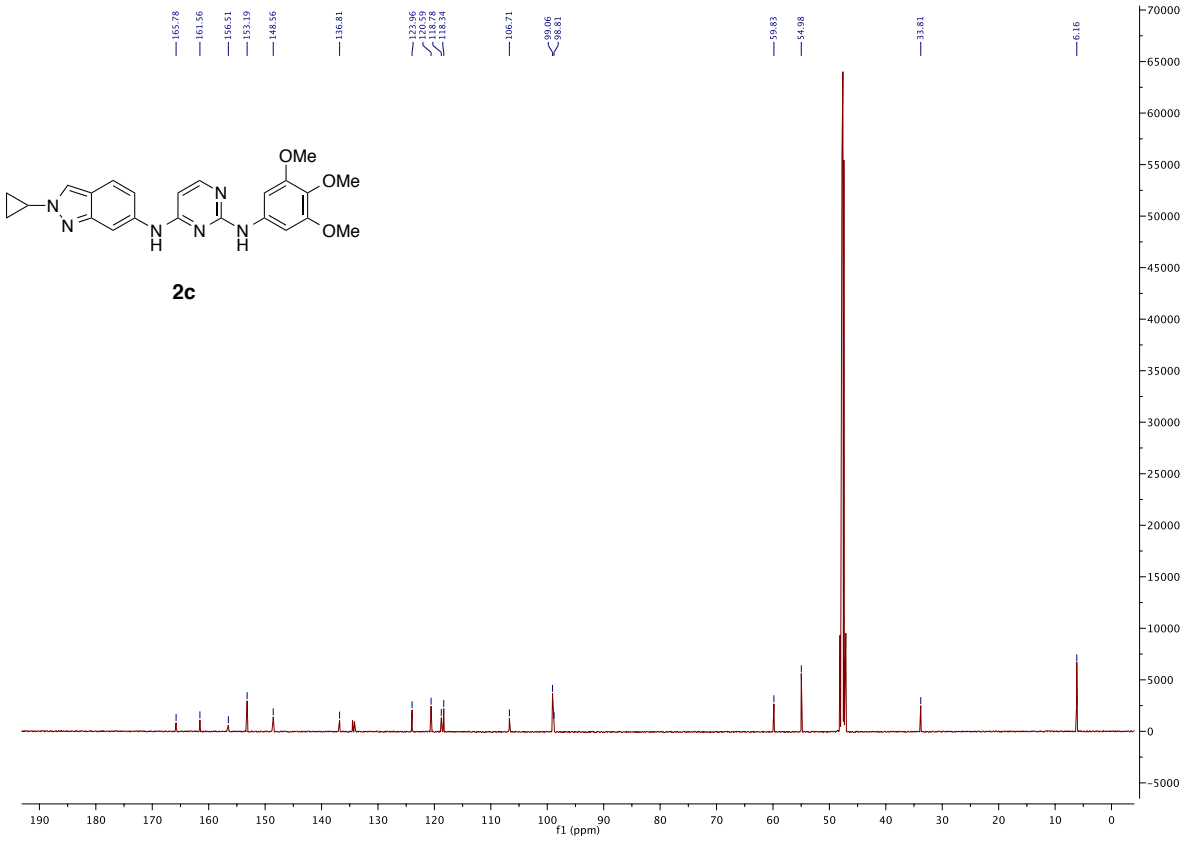

162.80
161.16
156.38
154.22
150.62
139.40
138.15
134.09
126.16
121.64
120.09
119.77
106.43
99.83
98.89
61.24
56.32
49.85
40.07
OMe
OMe
OMe
MeN
N
N
H
N
N
H
2a
f1 (ppm)

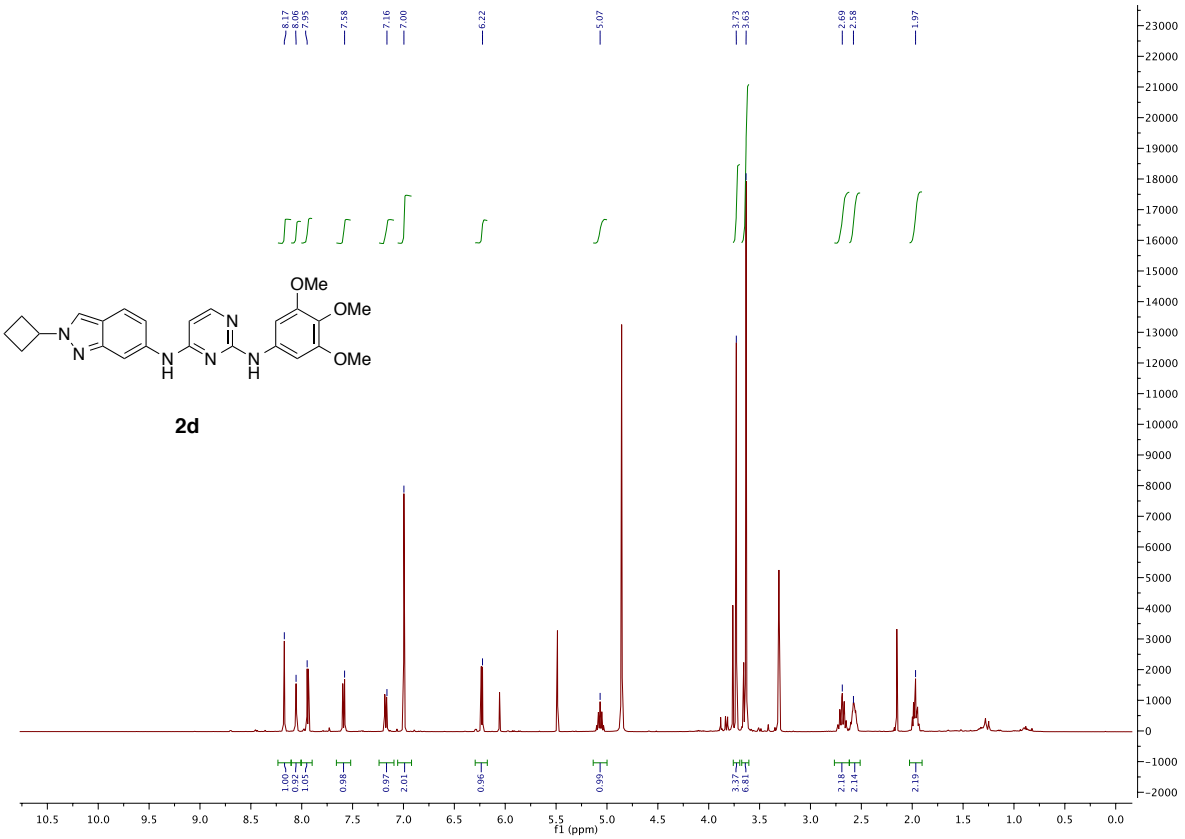

8.21
8.19
8.03
7.85
7.65
7.18
6.90
6.31
4.46
3.75
3.64
1.59
2.23
0.95
1.00
1.01
1.00
1.98
1.00
2.02
3.09
6.00
3.03
f1 (ppm)


161.61
156.72
153.25
148.75
136.72
134.46
134.27
123.38
120.65
119.55
118.22
106.78
99.17
98.83
59.80
54.98
14.88
f1 (ppm)

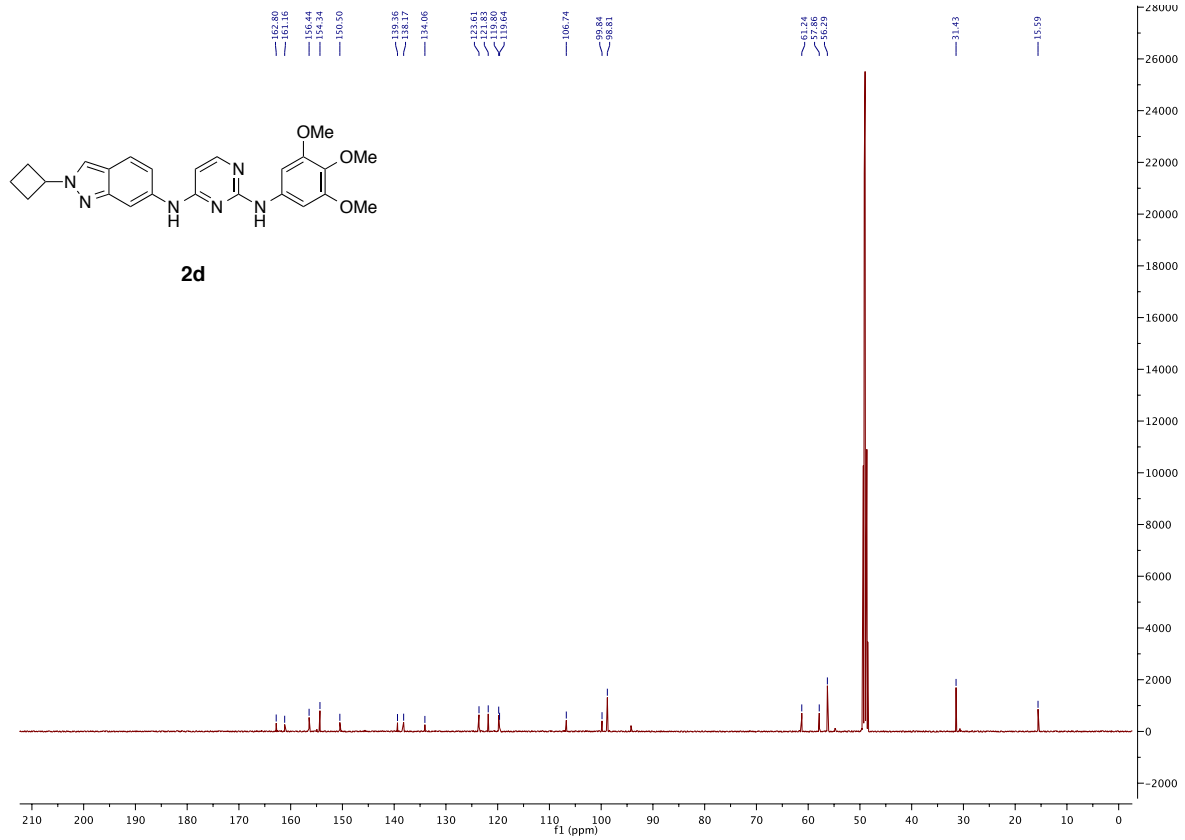
2b


8.31
8.23
8.02
7.85
7.61
7.19
6.91
6.32
4.00
3.77
3.63
1.31
1.19
OMe
OMe
OMe
N
N
N
N
N
H
H
2c
1.00
0.97
0.91
0.90
0.92
0.94
1.93
0.91
0.90
3.10
6.17
2.13
2.01
f1 (ppm)

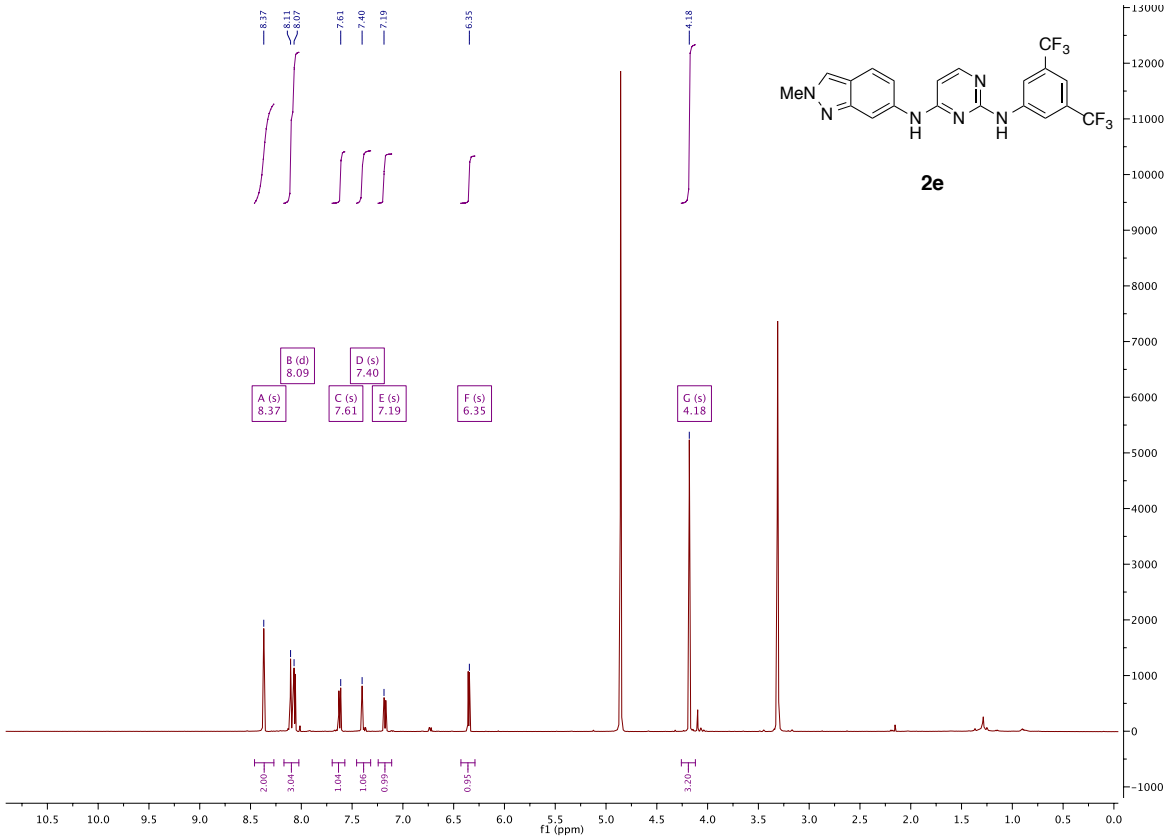

165.78
161.56
156.51
153.19
148.56
136.81
123.96
120.59
118.78
118.34
106.71
90.06
88.81
59.83
54.98
33.81
6.16
OMe
OMe
OMe
N
N
N
N
N
H
H
2c
f1 (ppm)

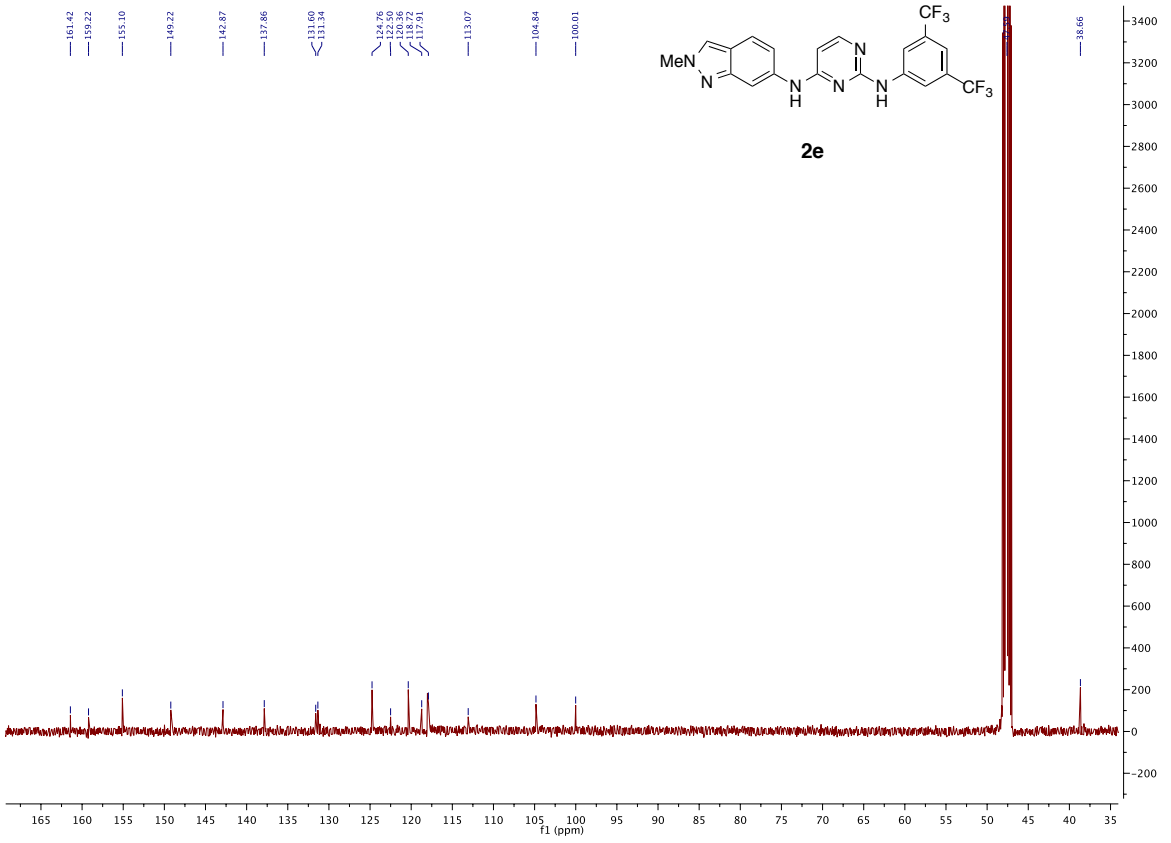

8.17
8.06
7.95
7.58
7.16
7.00
6.22
5.07
3.73
3.63
2.69
2.58
1.97
OMe
OMe
OMe
N
N
N
N
H
N
H
1.00
0.92
1.05
0.88
0.97
2.01
0.96
0.99
3.37
6.81
2.18
2.14
2.19
f1 (ppm)

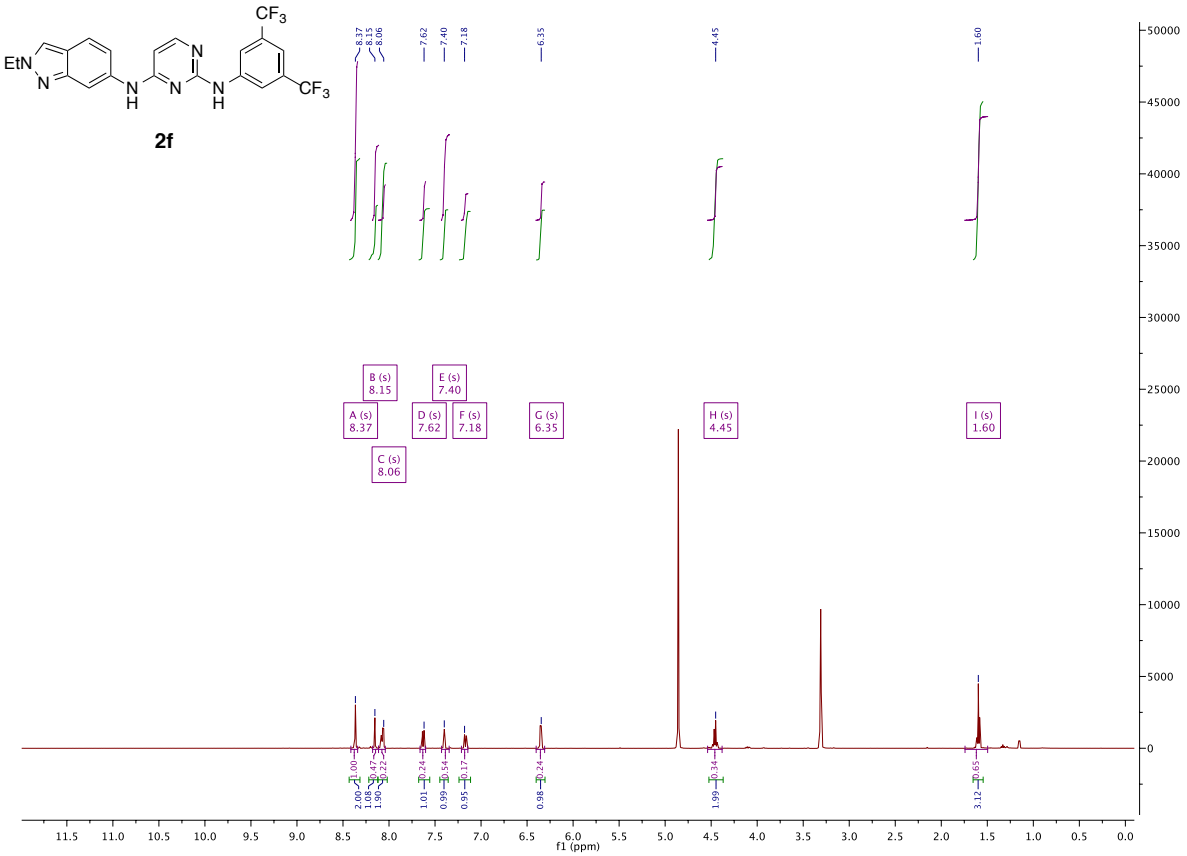
2d

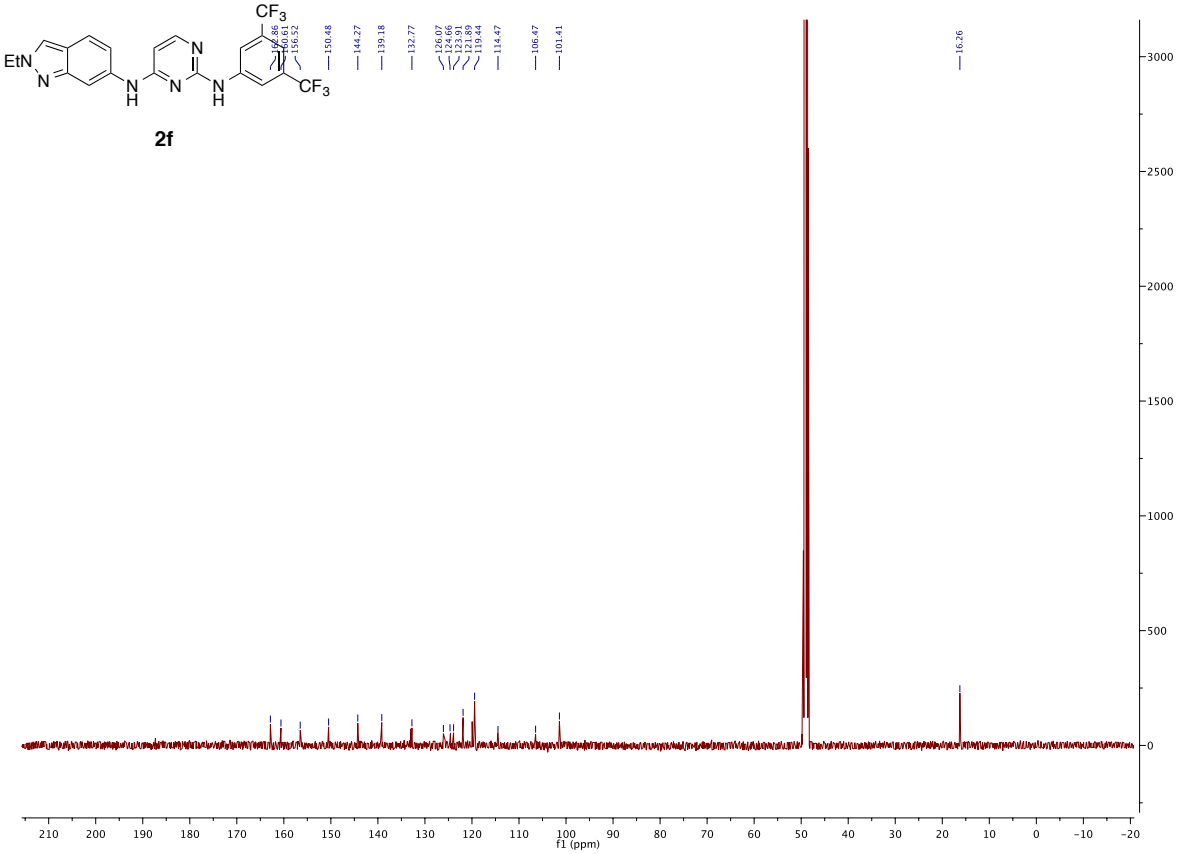

162.80
161.16
156.44
154.34
150.50
139.36
138.17
134.06
123.61
121.83
119.80
119.64
106.74
99.84
98.61
61.24
57.86
56.29
31.43
15.59
OMe
OMe
OMe
N
N
N
N
H
N
H
f1 (ppm)

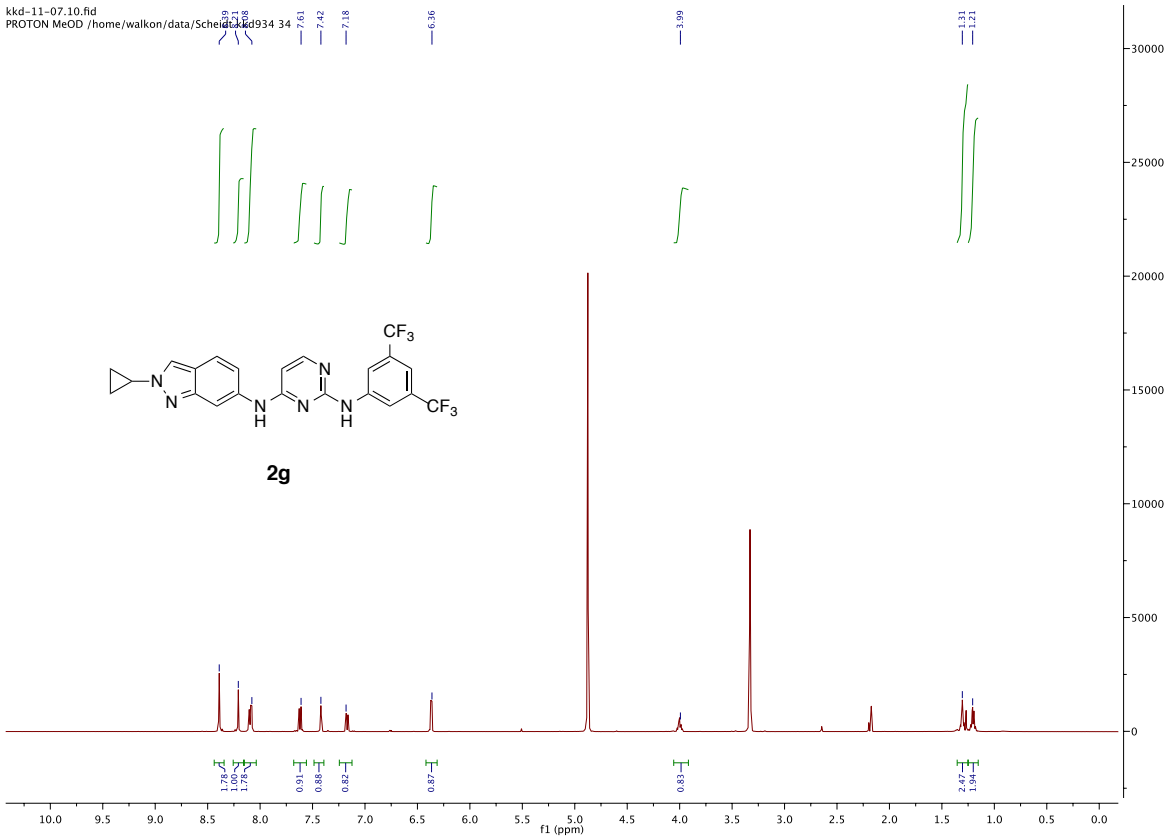
2d

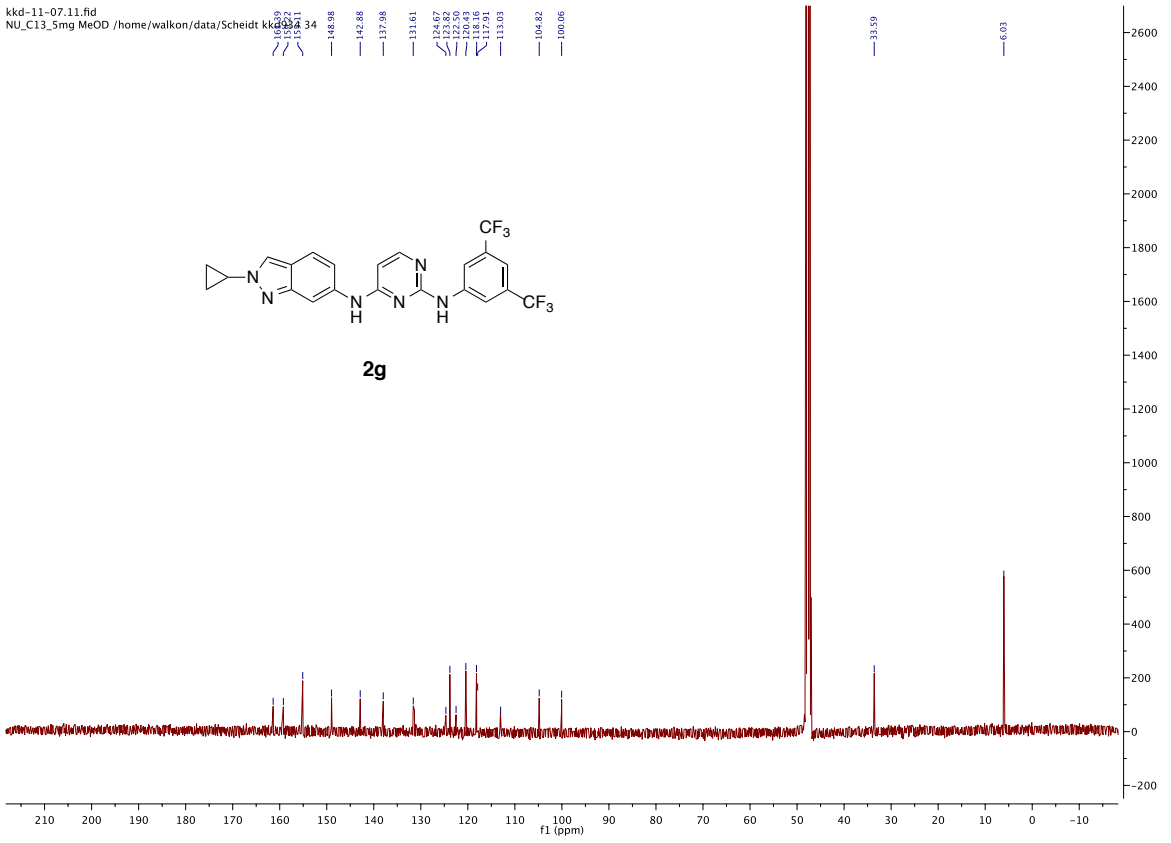

8.37
8.11
8.07
7.61
7.40
7.19
6.35
4.18
B (d) 8.09
D (s) 7.40
A (s) 8.37
C (s) 7.61
E (s) 7.19
F (s) 6.35
G (s) 4.18
2.00
3.04
1.04
1.06
0.99
0.95
3.20
f1 (ppm)
MeN
N
H
CF3
2e

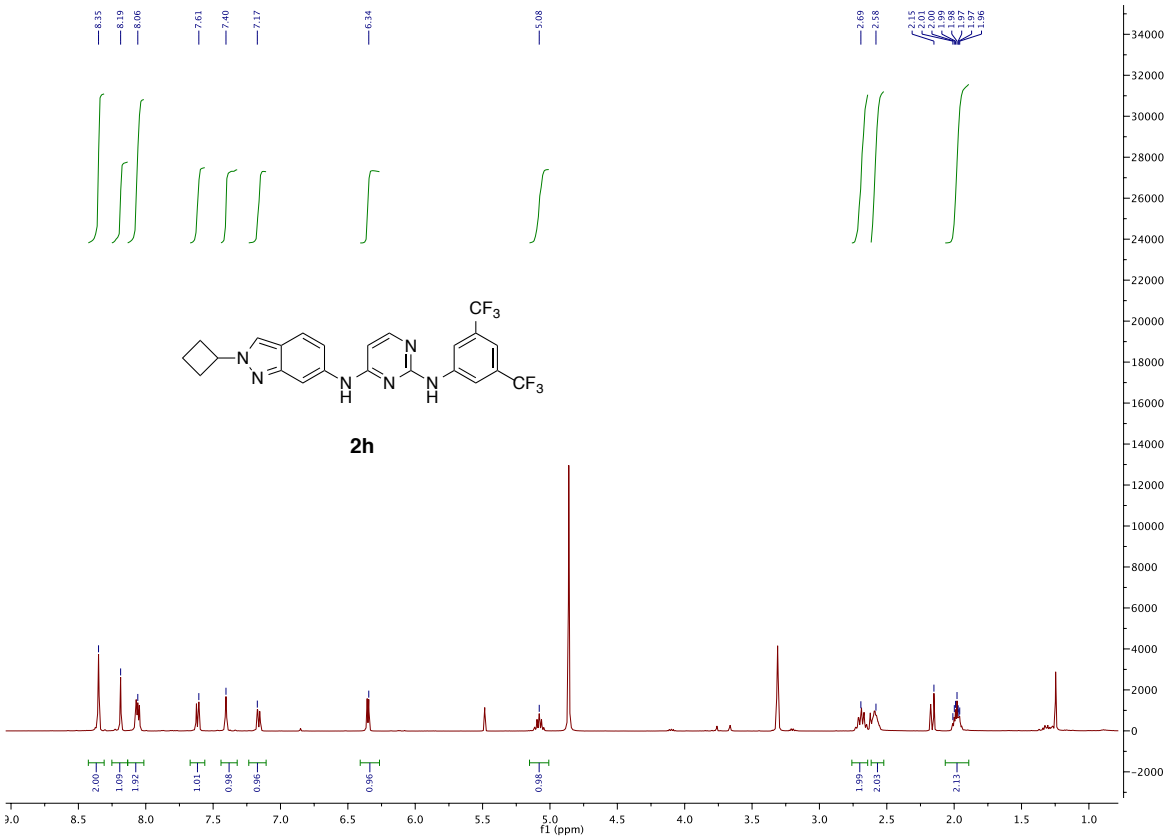

161.42
159.22
155.10
149.22
142.87
137.86
131.60
131.34
124.76
122.50
120.36
118.72
117.91
113.07
104.84
100.01
38.66
f1 (ppm)
MeN
N
H
CF3
2e

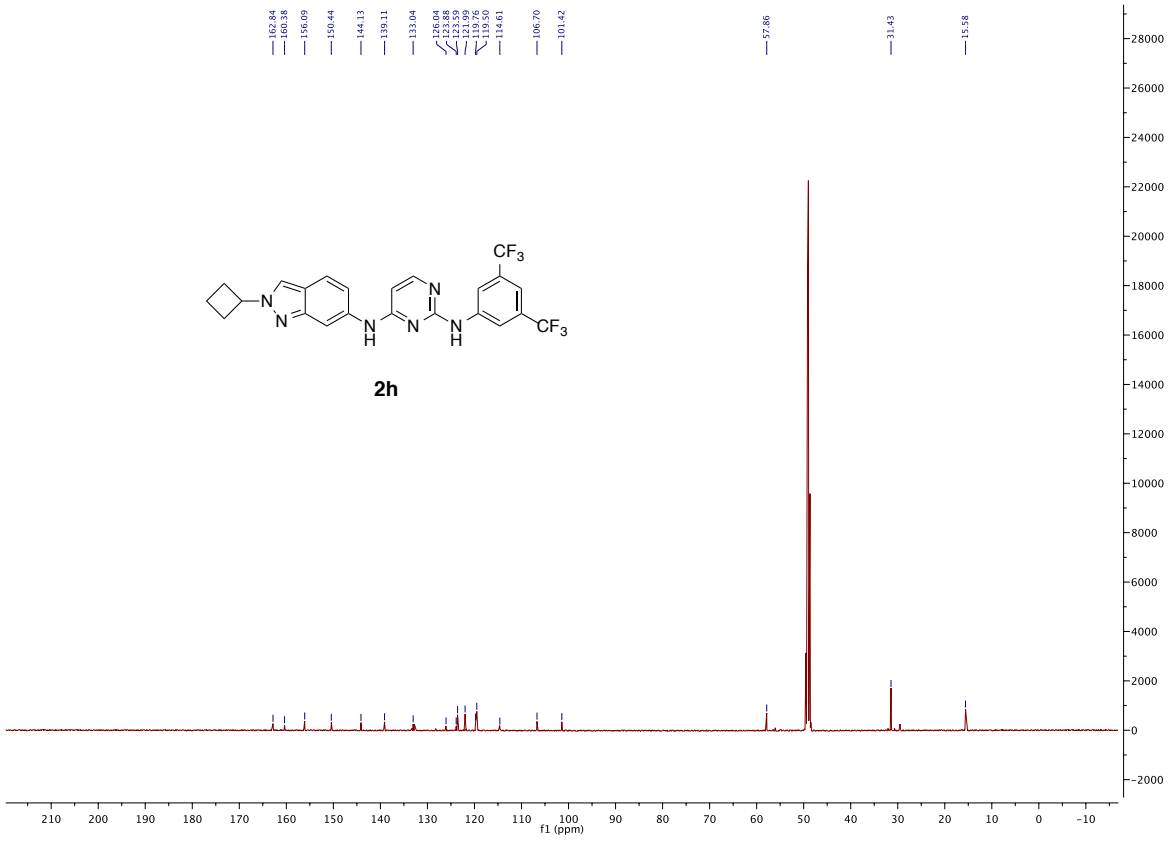

2f
A (s) 8.37
B (s) 8.15
C (s) 8.06
D (s) 7.62
E (s) 7.40
F (s) 7.18
G (s) 6.35
H (s) 4.45
I (s) 1.60
f1 (ppm)


2f
f1 (ppm)

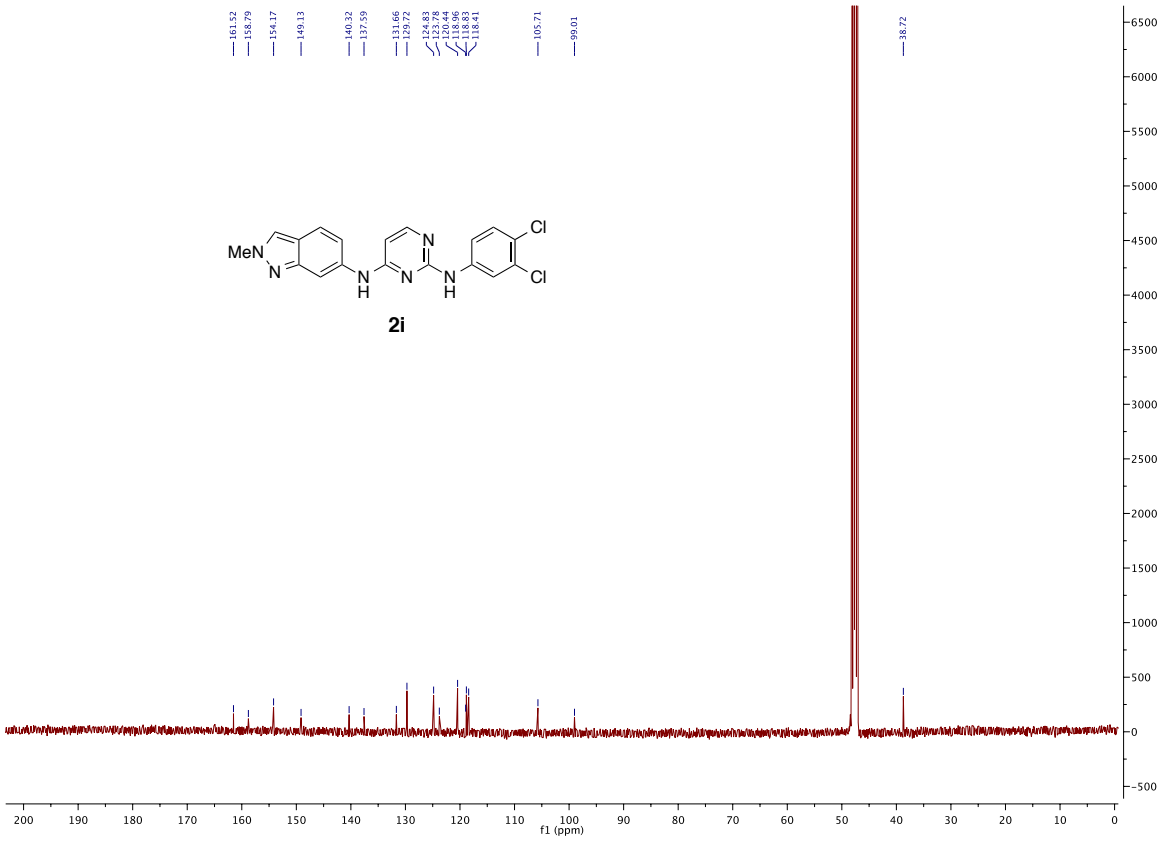

kkd-11-07.10.fid
PROTON MeOD /home/walkon/data/Scheidt/kkd934 34
7.61
7.42
7.18
6.36
3.99
1.31
1.21
CF3
CF3
N
H
2g
f1 (ppm)

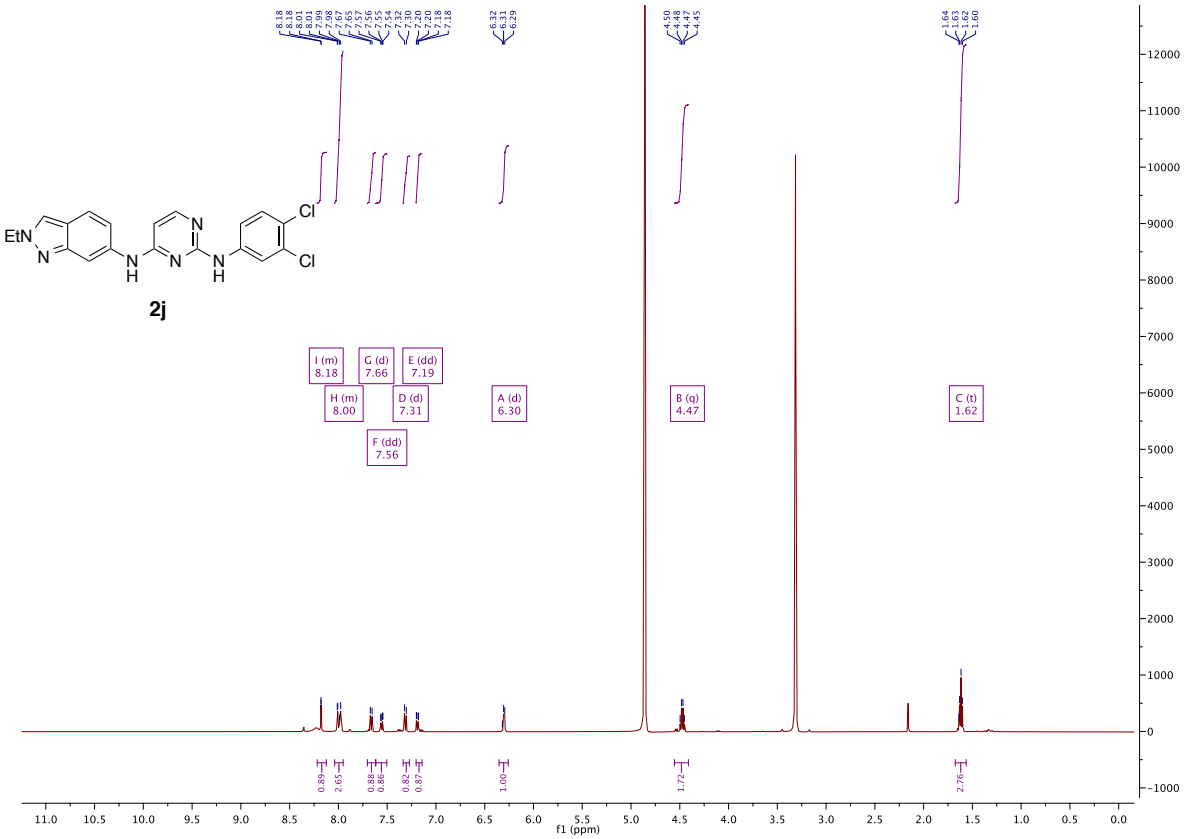

kkd-11-07.11.fid
NU_C13_5mg MeOD /home/walkon/data/Scheidt kkd934 34
148.98
142.88
137.98
131.61
124.67
123.82
122.69
120.43
118.16
117.91
113.03
104.82
100.06
33.59
6.03
CF3
CF3
N
H
2g
f1 (ppm)

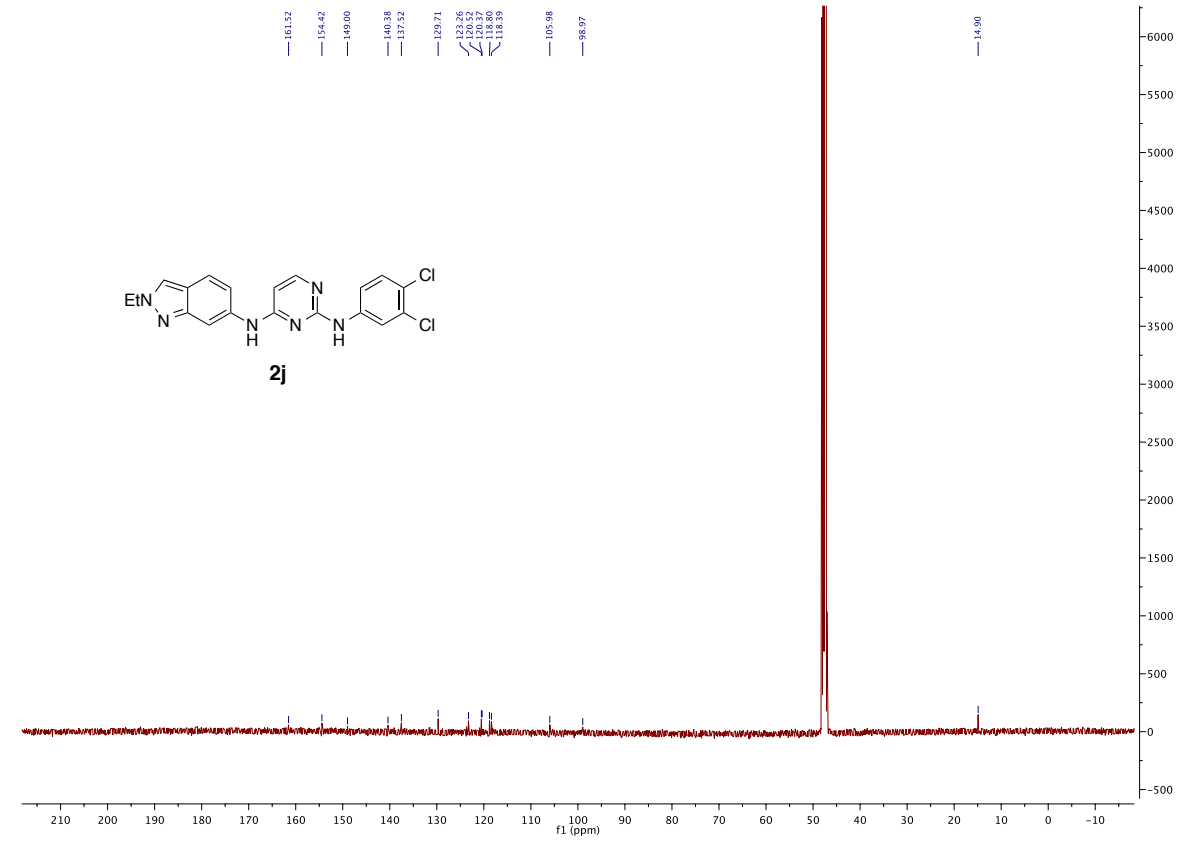

8.35
8.19
8.06
7.61
7.40
7.17
6.34
5.08
2.69
2.58
2.15
2.01
2.00
1.99
1.98
1.97
1.96
CF3
CF3
N
N
N
N
N
H
H
2h
2.00
1.09
1.92
1.01
0.98
0.96
0.96
0.98
1.99
2.03
2.13
f1 (ppm)

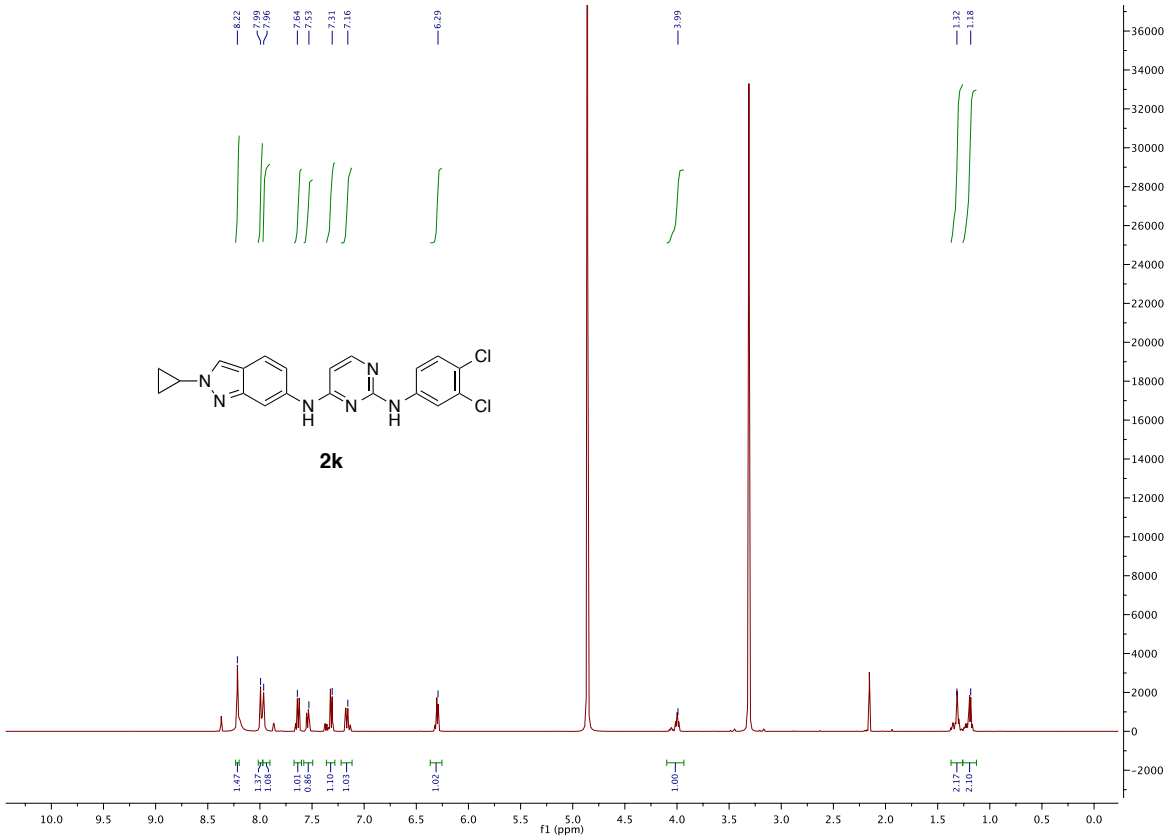

162.84
160.38
156.09
150.44
144.13
139.11
133.04
126.04
123.88
123.59
121.99
119.76
119.50
114.61
106.70
101.42
57.86
31.43
15.58
CF3
CF3
N
N
N
N
N
H
H
2h
f1 (ppm)

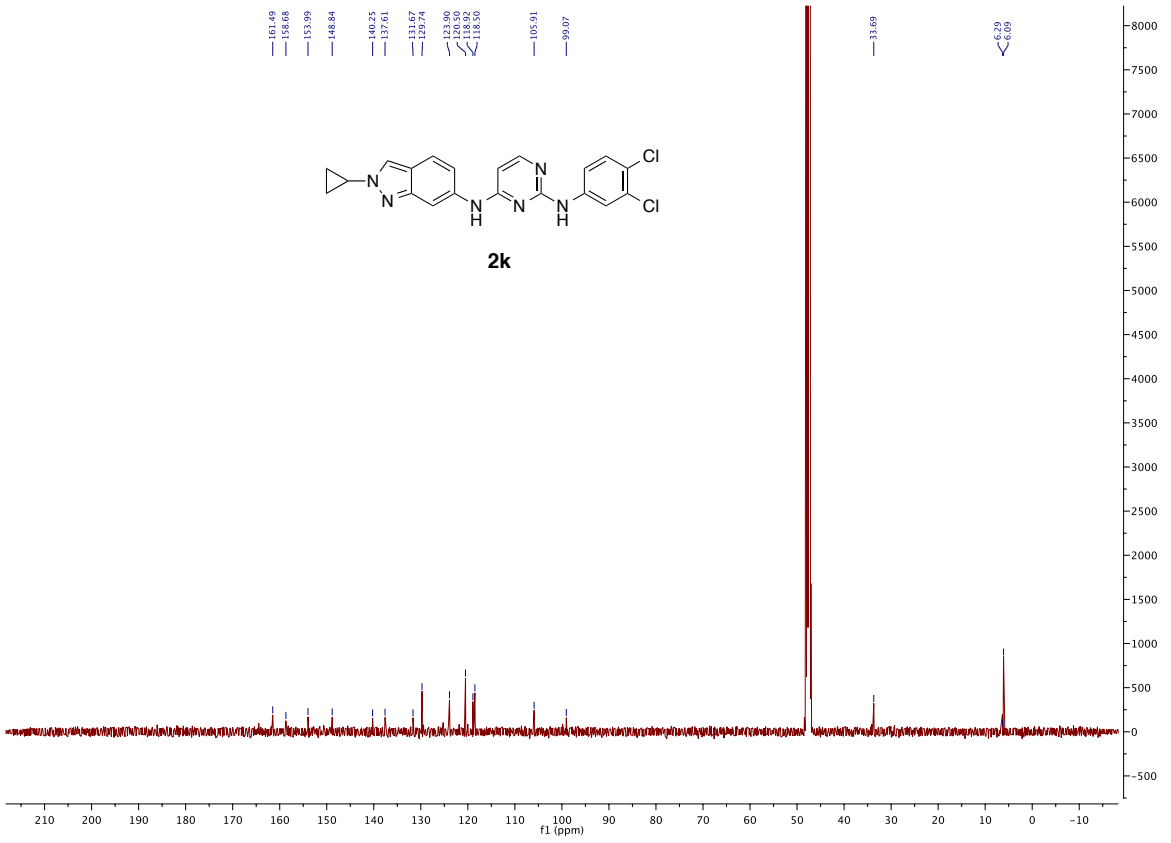

kkd-11-21.20.fid
PROTON MeOD /home/walkon/data/Scheidt kkd934 1
8.23
8.13
8.00
7.95
7.64
7.53
7.32
7.19
6.29
4.19
J (s) 8.23
H (s) 7.95
D (s) 7.32
G (s) 8.00
E (s) 7.64
C (s) 7.19
A (s) 6.29
B (s) 4.19
I (s) 8.13
F (s) 7.53
3.44
2.18
1.41
2.29
1.08
1.86
1.10
2.74
1.00
14.04
f1 (ppm)
MeN
N
N
H
N
N
H
Cl
Cl
2i

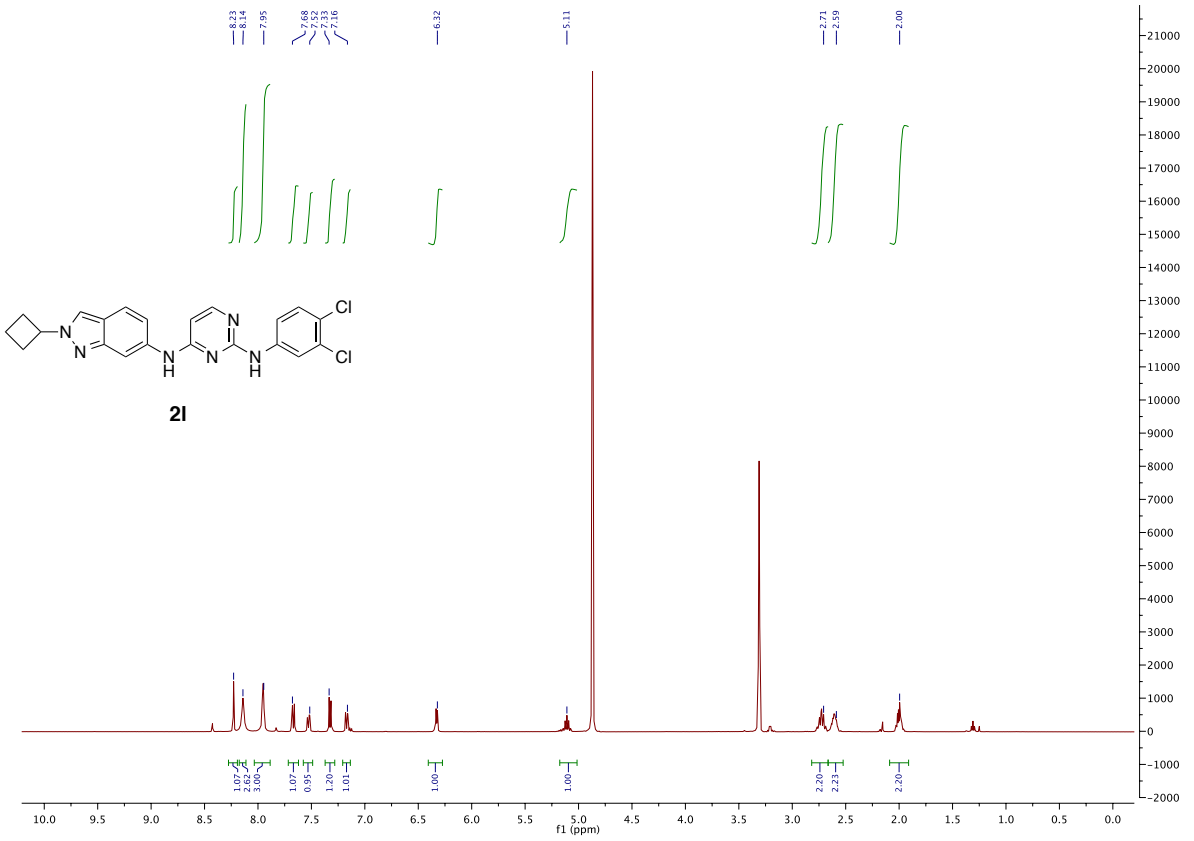

161.52
158.79
154.17
149.13
140.32
137.59
131.66
129.72
124.83
123.78
120.44
118.96
118.83
118.41
105.71
99.01
38.72
f1 (ppm)
MeN
N
N
H
N
N
H
Cl
Cl
2i

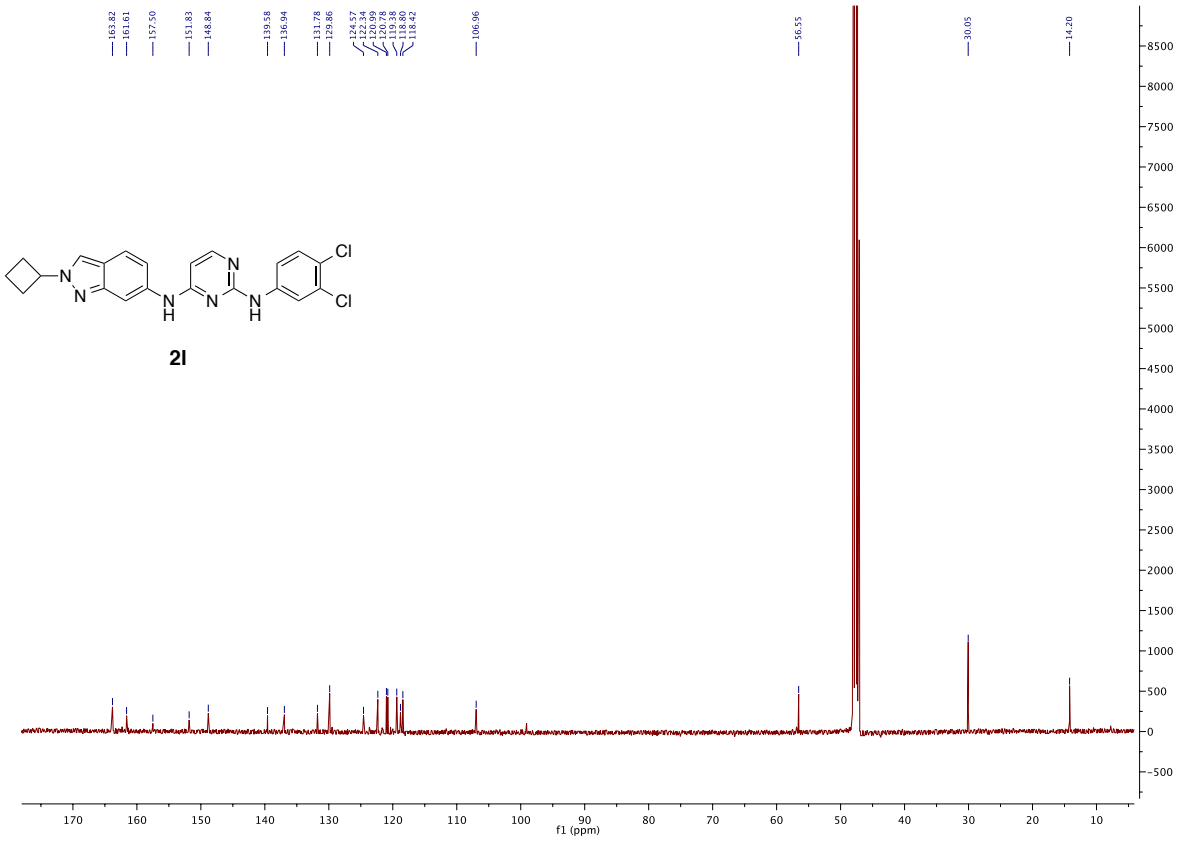

2j
I (m) 8.18
H (m) 8.00
G (d) 7.66
F (dd) 7.56
E (dd) 7.19
D (d) 7.31
A (d) 6.30
B (q) 4.47
C (t) 1.62
f1 (ppm)

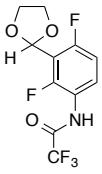

2j
161.52
154.42
149.00
140.38
137.52
129.71
123.26
120.52
120.37
118.80
118.59
105.98
98.97
14.90
f1 (ppm)


8.22
7.99
7.96
7.64
7.53
7.31
7.16
6.29
3.99
1.32
1.18
Cl
Cl
2k
1.47
1.37
1.08
1.01
0.86
1.10
1.03
1.02
1.00
2.17
2.10
f1 (ppm)


161.49
158.68
153.99
148.84
140.25
137.61
131.67
129.74
123.90
120.55
118.92
118.50
105.91
99.07
33.69
6.29
6.09
Cl
Cl
2k
f1 (ppm)

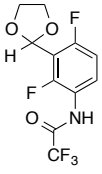

8.23
8.14
7.95
7.68
7.52
7.33
7.16
6.32
5.11
2.71
2.59
2.00
Cl
Cl
2l
f1 (ppm)


163.82
161.61
157.50
151.83
148.84
139.58
136.94
131.78
129.86
124.57
122.34
120.98
120.78
119.38
118.60
118.42
106.96
56.55
30.05
14.20
Cl
Cl
2l
f1 (ppm)



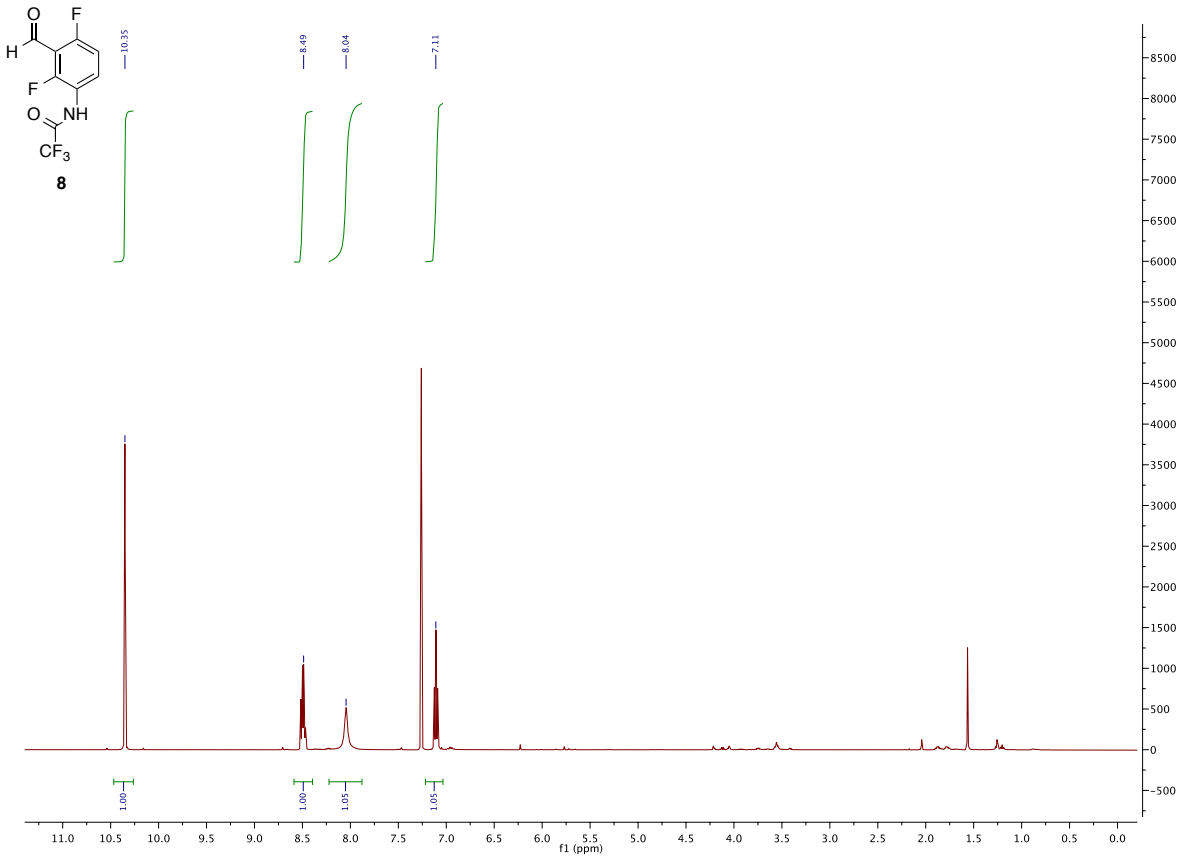
7

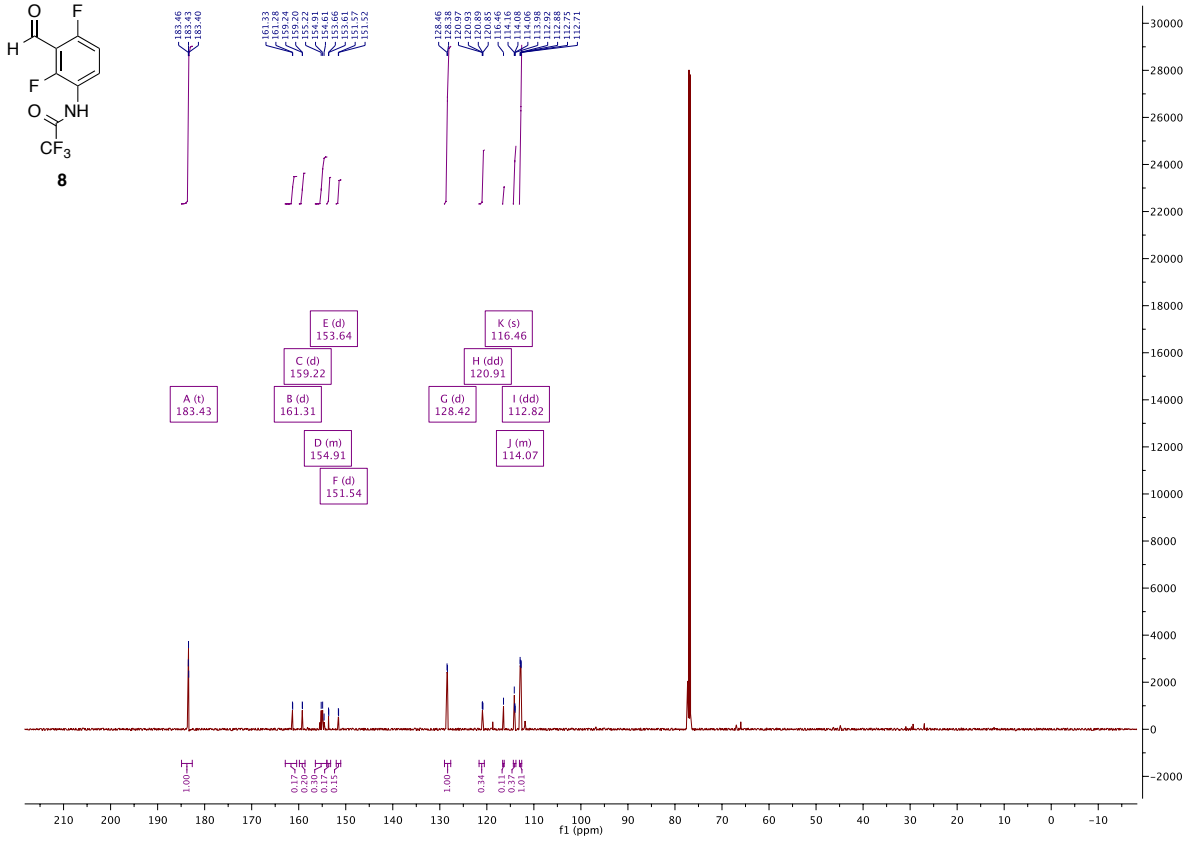
8.23
7.99
6.96
6.23
4.22
4.05
1.05
0.97
1.05
1.00
2.15
2.21
f1 (ppm)

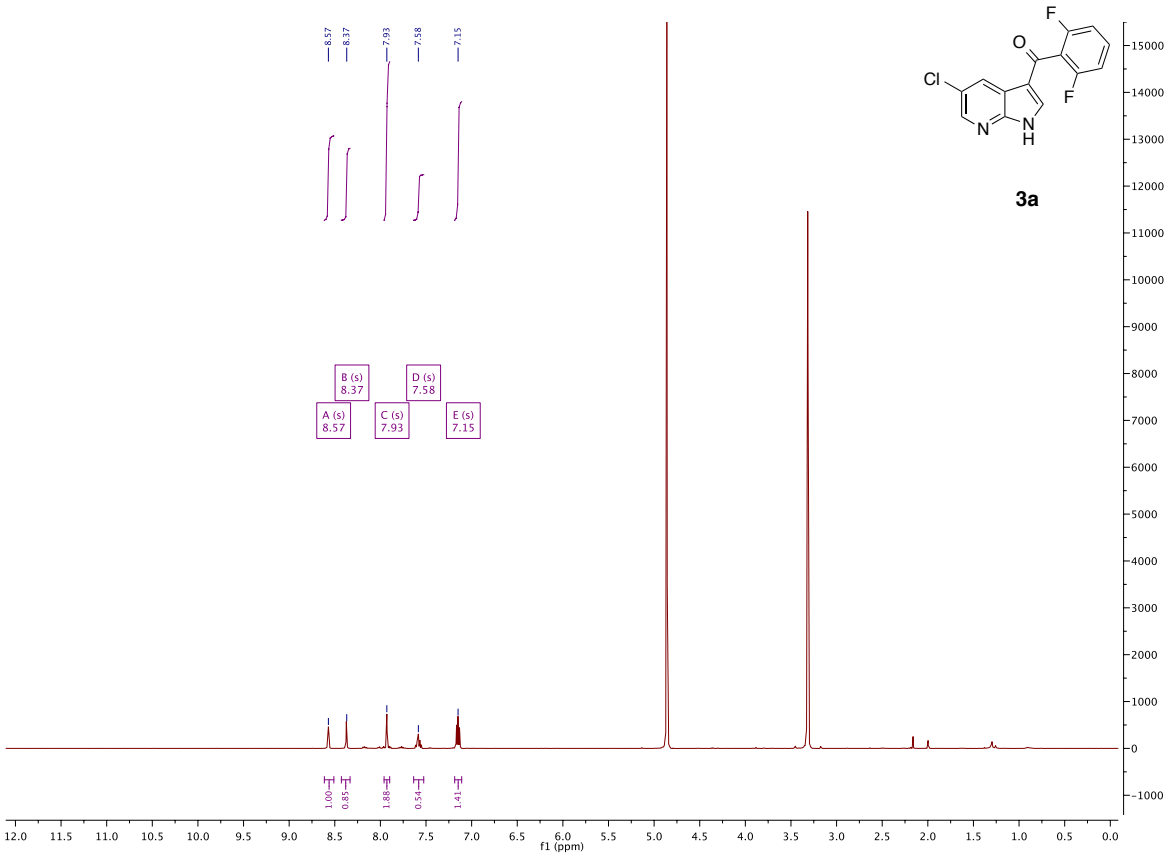


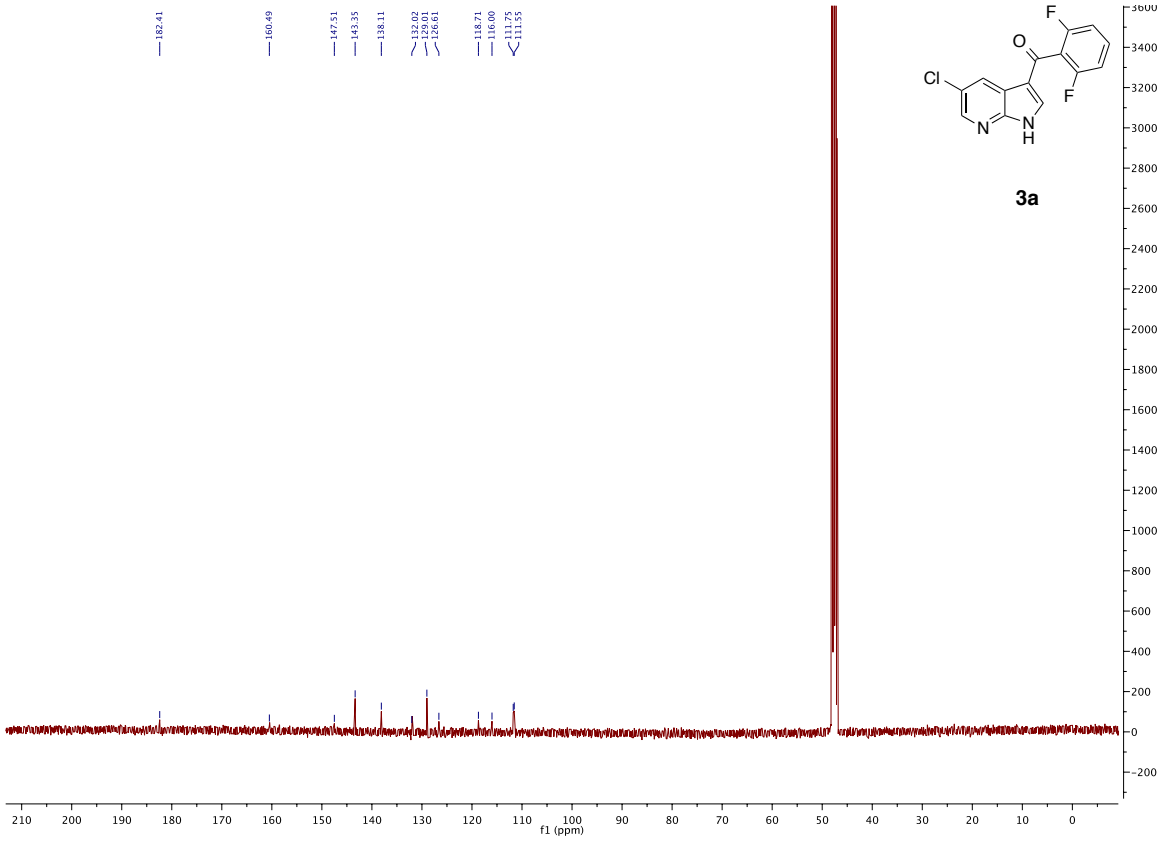
7

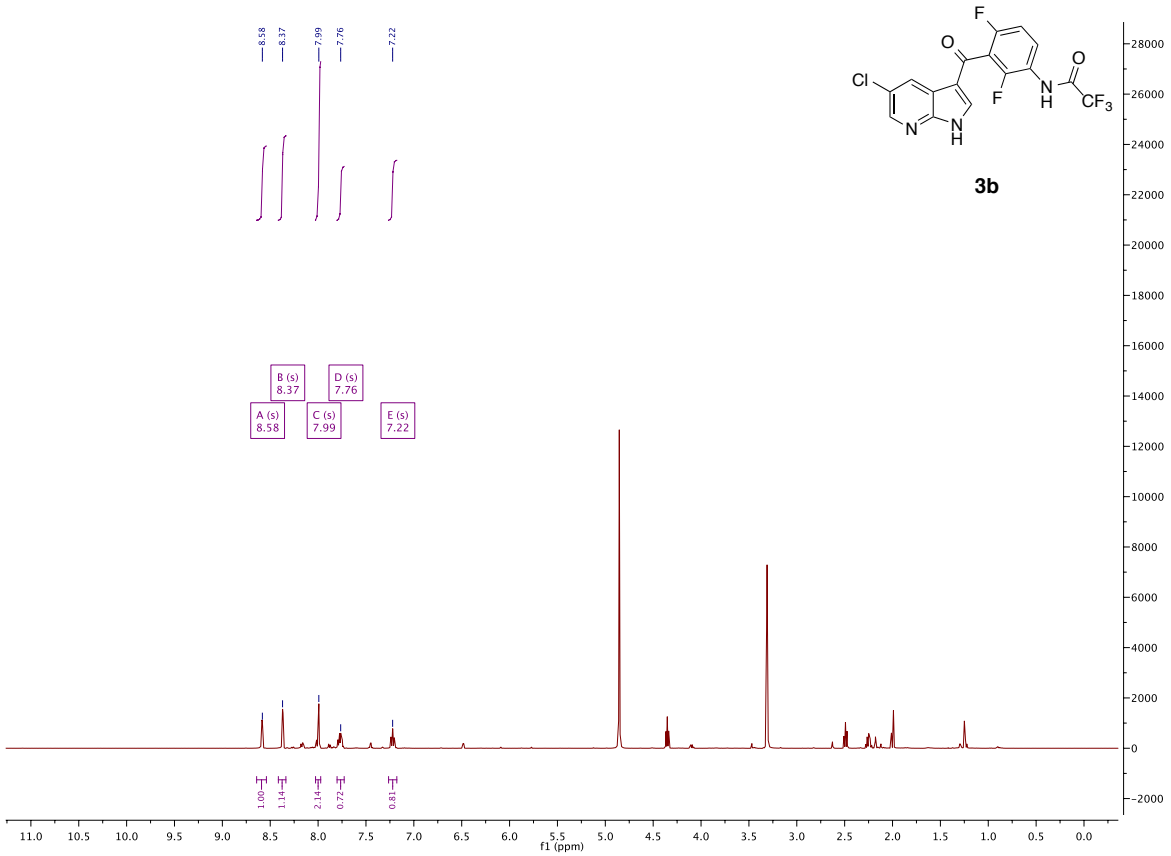
159.56
157.55
154.87
154.56
123.75
150.68
123.37
111.99
96.82
66.02
45.67
8.51
f1 (ppm)

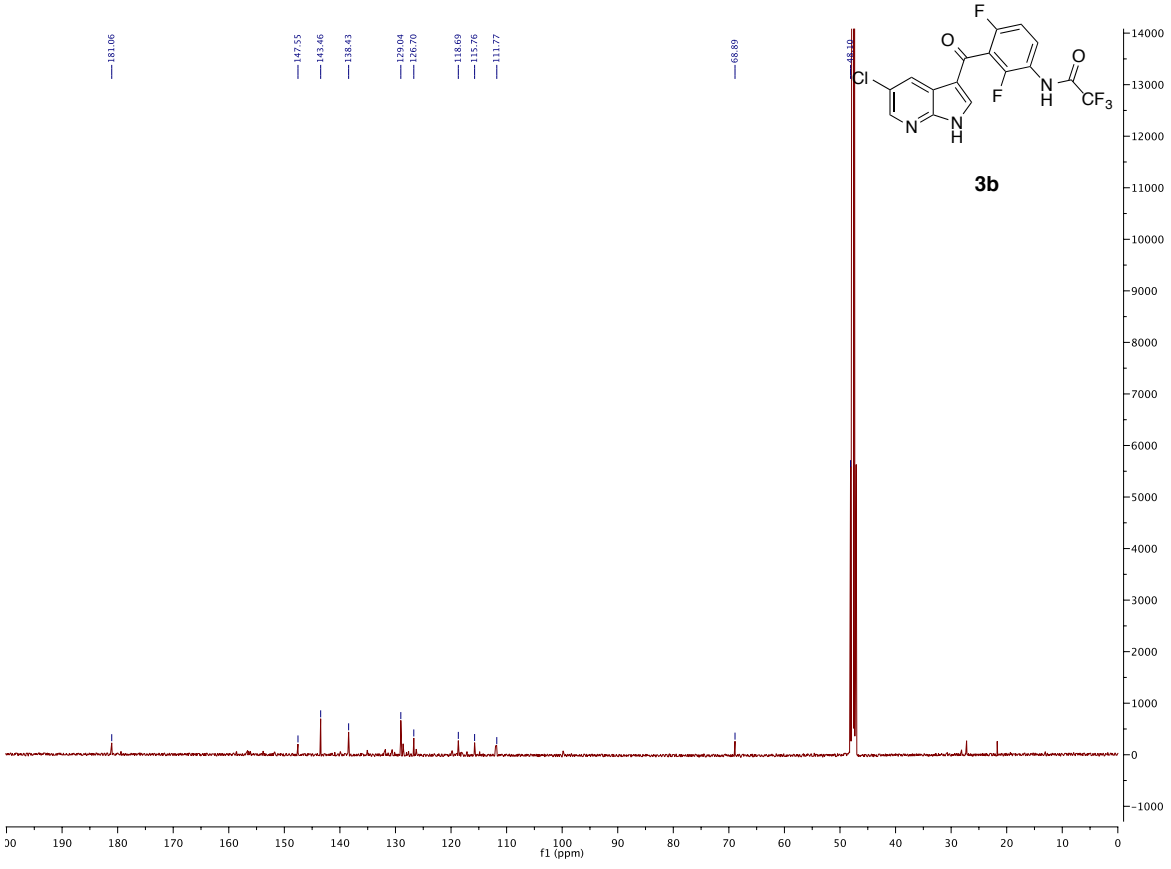

8
10.35
8.49
8.04
7.11
1.00
1.00
1.05
1.05
f1 (ppm)

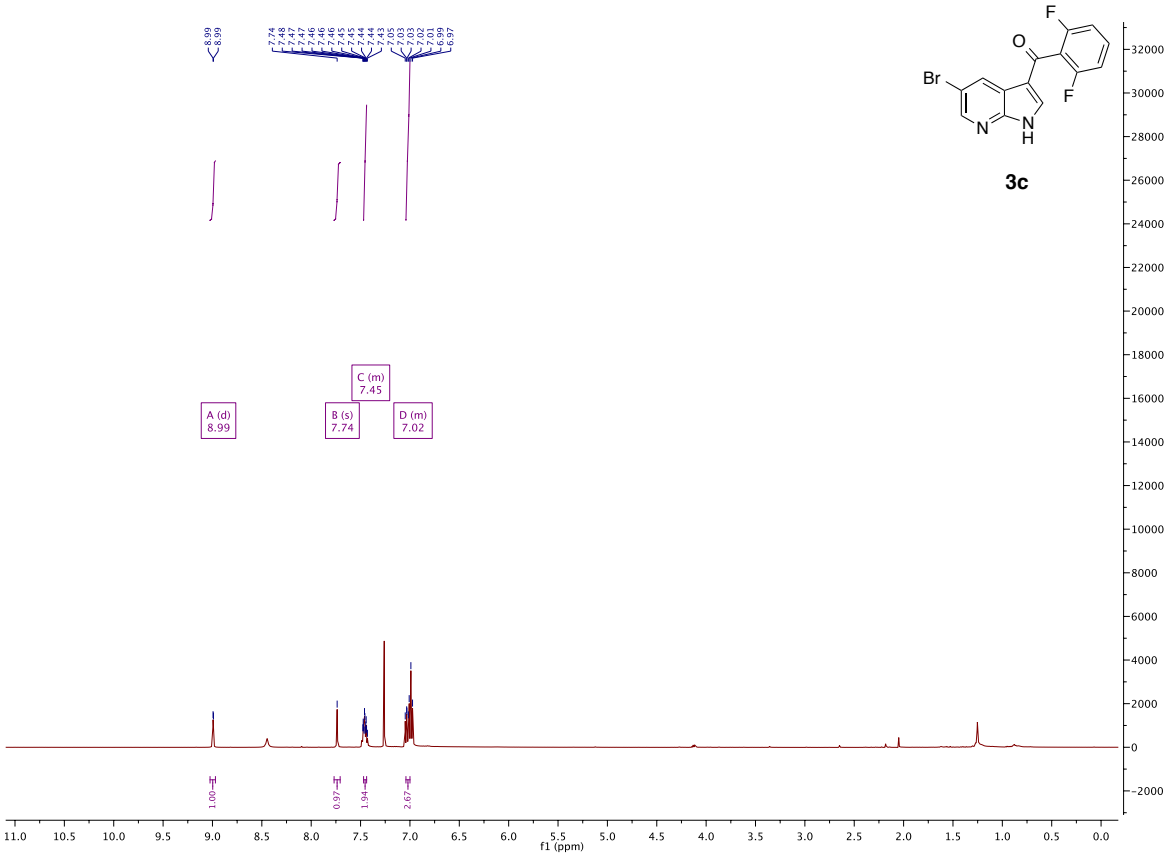

8
A (t) 183.43
B (d) 161.31
C (d) 159.22
D (m) 154.91
E (d) 153.64
F (d) 151.54
G (d) 128.42
H (dd) 120.91
I (dd) 112.82
J (m) 114.07
K (s) 116.46
f1 (ppm)

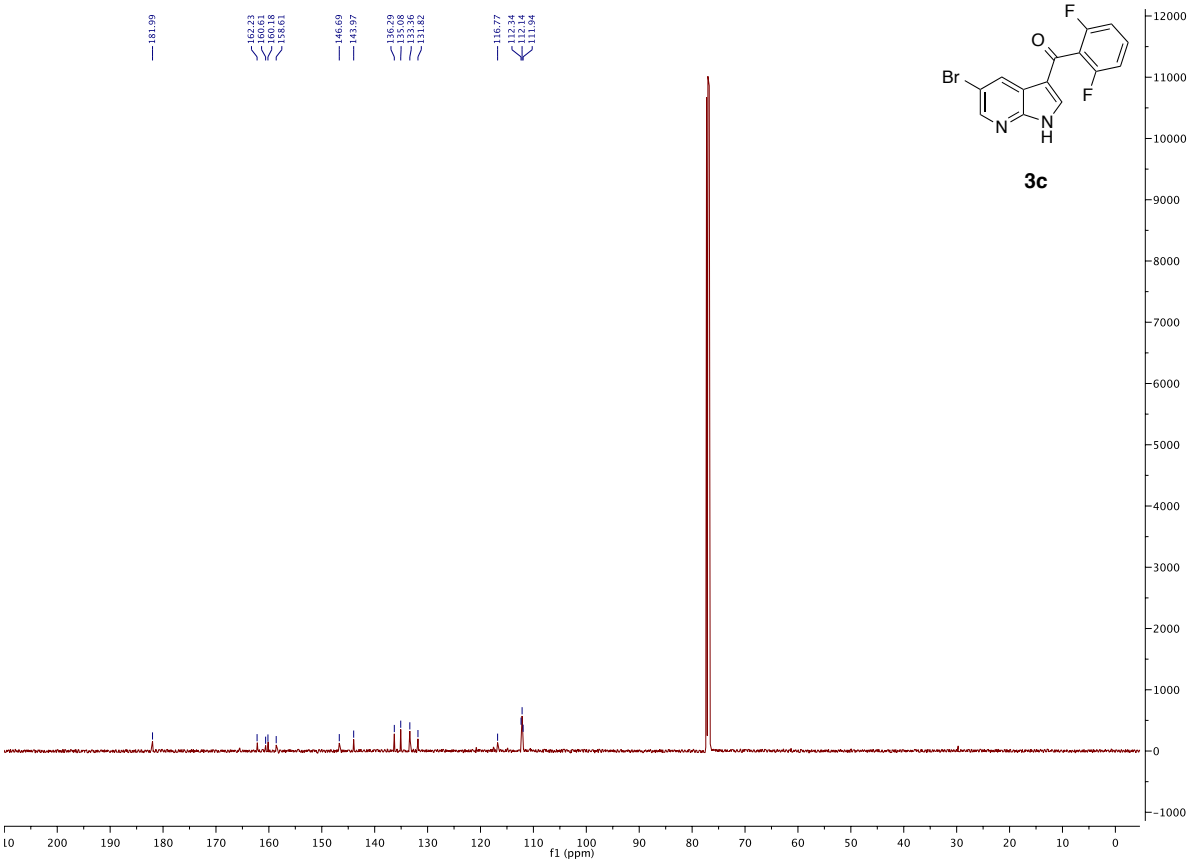

8.57
8.37
7.93
7.58
7.15
B (s) 8.37
D (s) 7.58
A (s) 8.57
C (s) 7.93
E (s) 7.15
1.00
0.85
1.88
0.54
1.41
f1 (ppm)
3a

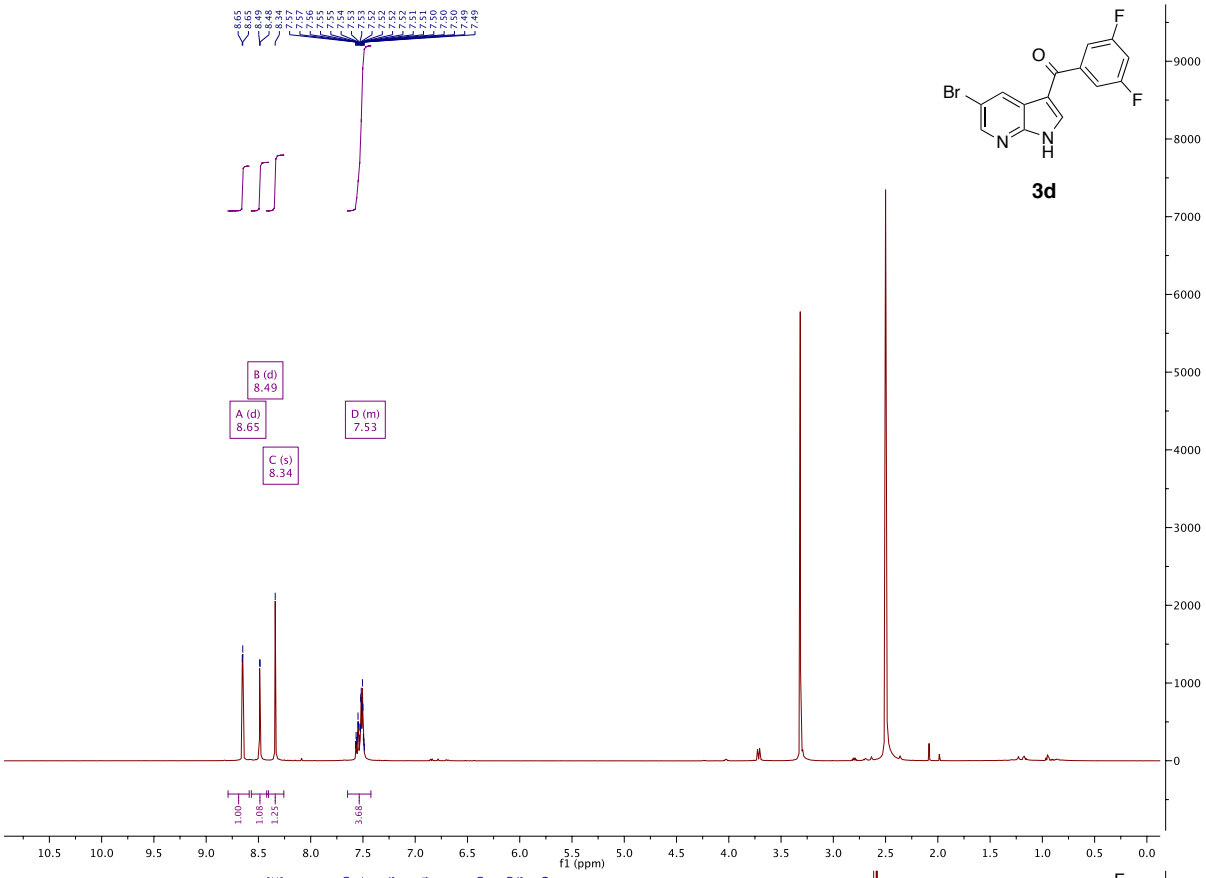

182.41
160.49
147.51
143.35
138.11
132.02
129.01
126.61
118.71
116.00
111.75
111.55
f1 (ppm)
3a

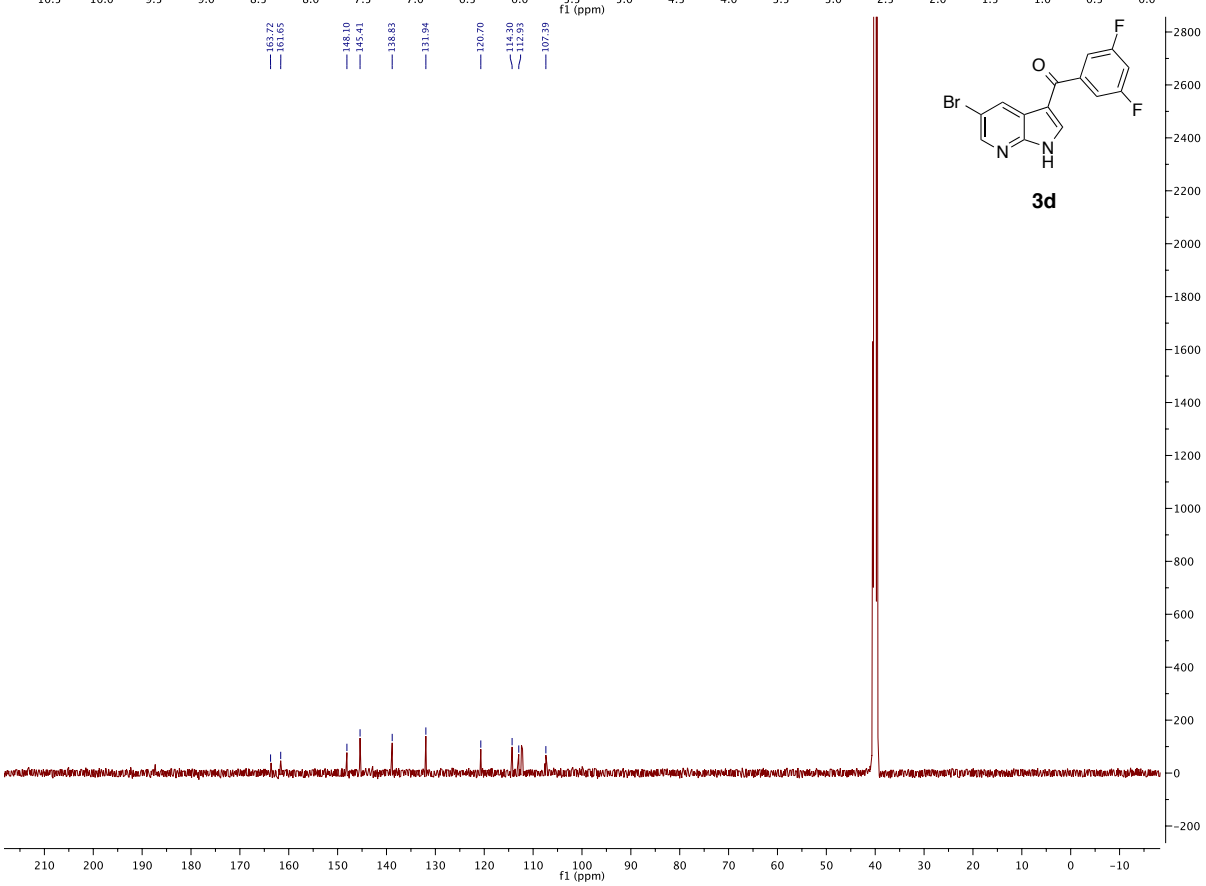

8.58
8.37
7.99
7.76
7.22
B (s) 8.37
D (s) 7.76
A (s) 8.58
C (s) 7.99
E (s) 7.22
1.00
1.14
2.14
0.72
0.81
f1 (ppm)
3b

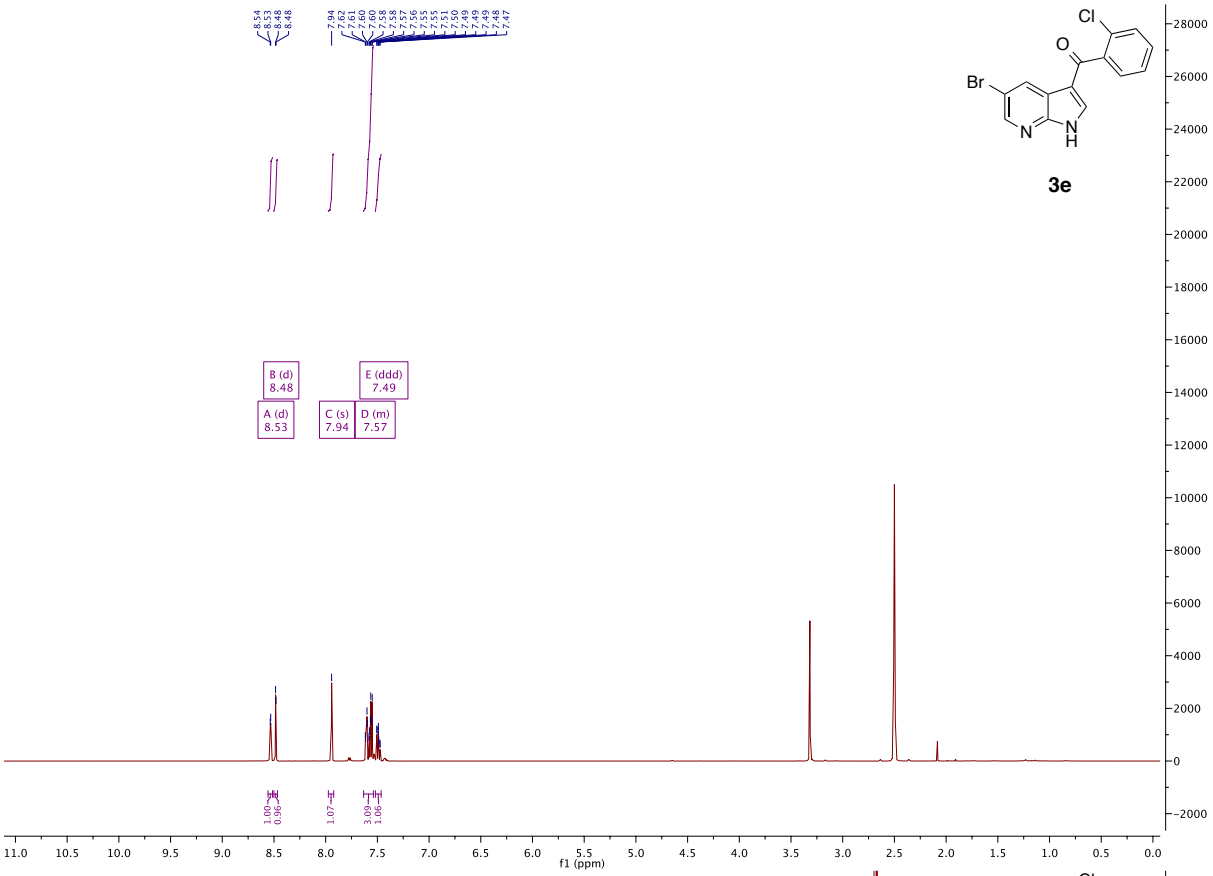

181.06
147.55
143.46
138.43
129.04
126.70
118.69
115.76
111.77
68.89
f1 (ppm)
3b

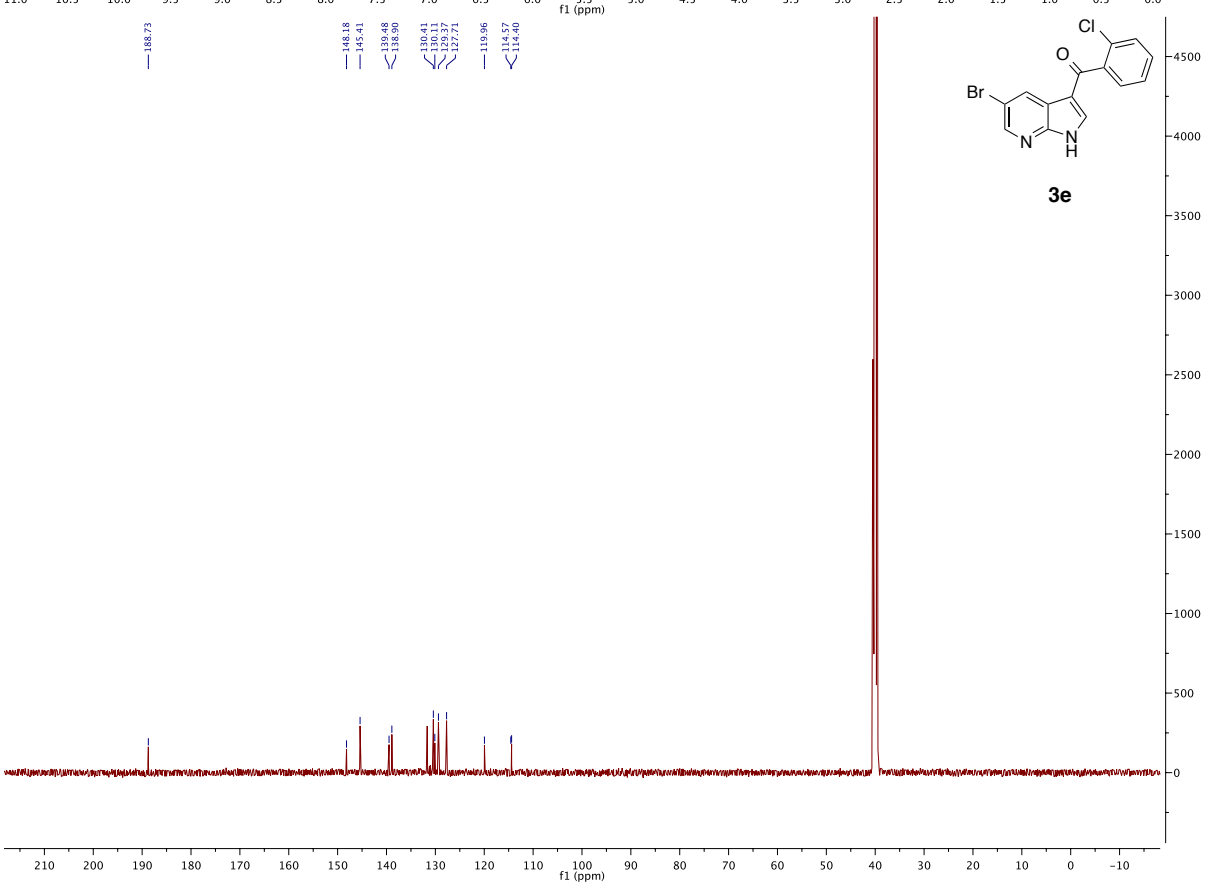

3c
A (d) 8.99
B (s) 7.74
C (m) 7.45
D (m) 7.02
f1 (ppm)

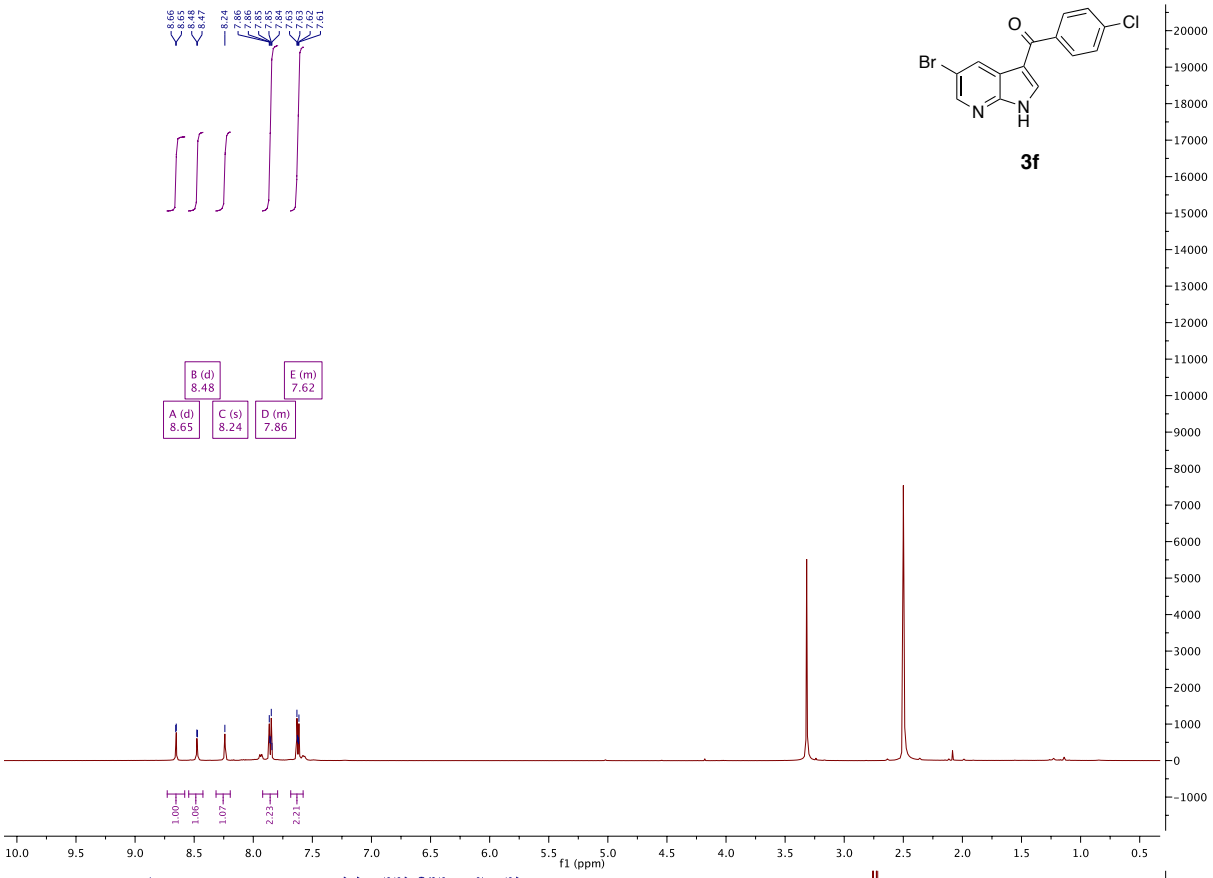

3c
f1 (ppm)


8.65
8.65
8.49
8.48
8.34
7.57
7.57
7.56
7.55
7.55
7.54
7.53
7.53
7.52
7.52
7.52
7.51
7.51
7.50
7.50
7.49
7.49
B (d)
8.49
A (d)
8.65
C (s)
8.34
D (m)
7.53
1.00
1.08
1.25
3.68
f1 (ppm)
Br
O
F
F
N
H
3d


163.72
161.65
148.10
145.41
138.83
131.94
120.70
114.30
112.93
107.39
f1 (ppm)
Br
O
F
F
N
H
3d

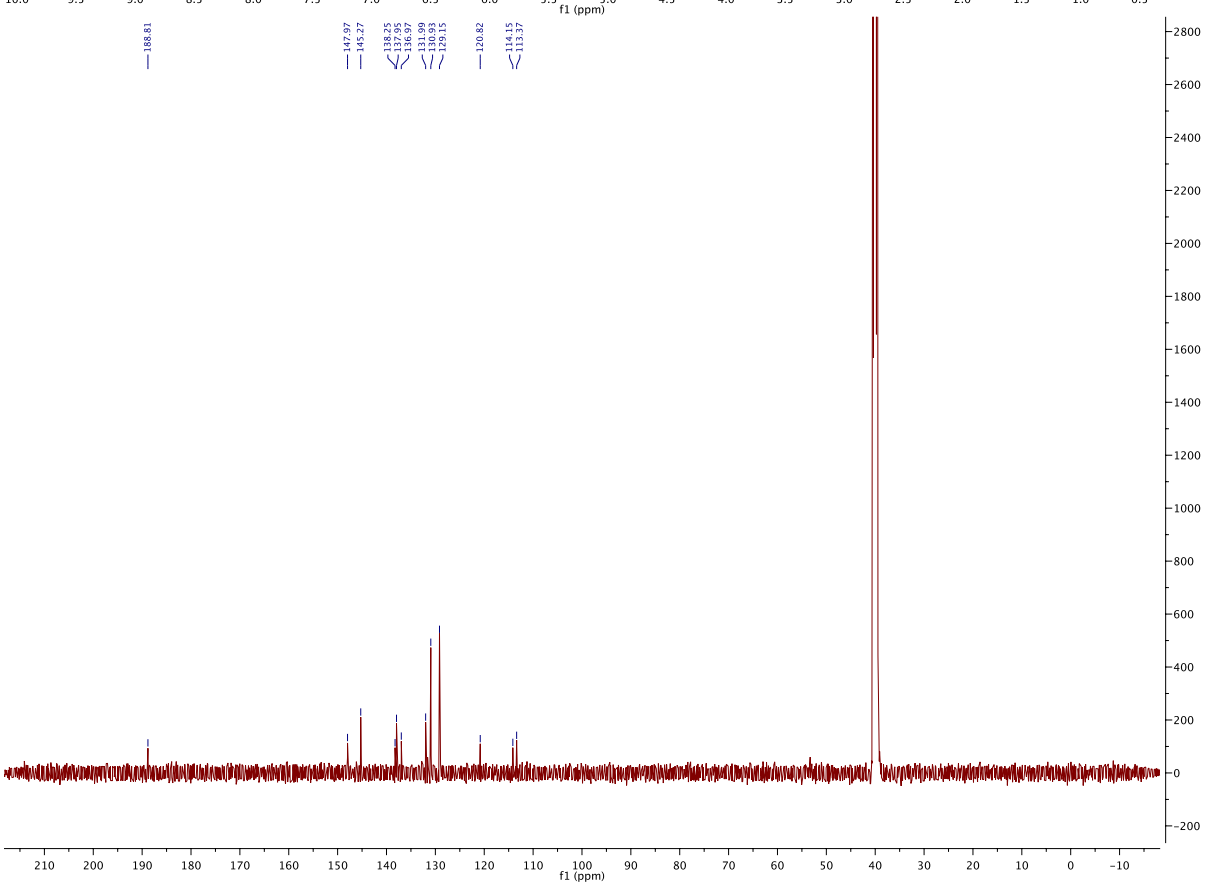

8.54
8.53
8.48
8.48
7.94
7.62
7.61
7.60
7.60
7.58
7.58
7.57
7.56
7.55
7.55
7.51
7.50
7.49
7.49
7.49
7.48
7.47
B (d) 8.48
E (ddd) 7.49
A (d) 8.53
C (s) 7.94
D (m) 7.57
1.00
0.98
1.07
3.09
1.06
f1 (ppm)
Cl
O
Br
N
H
3e

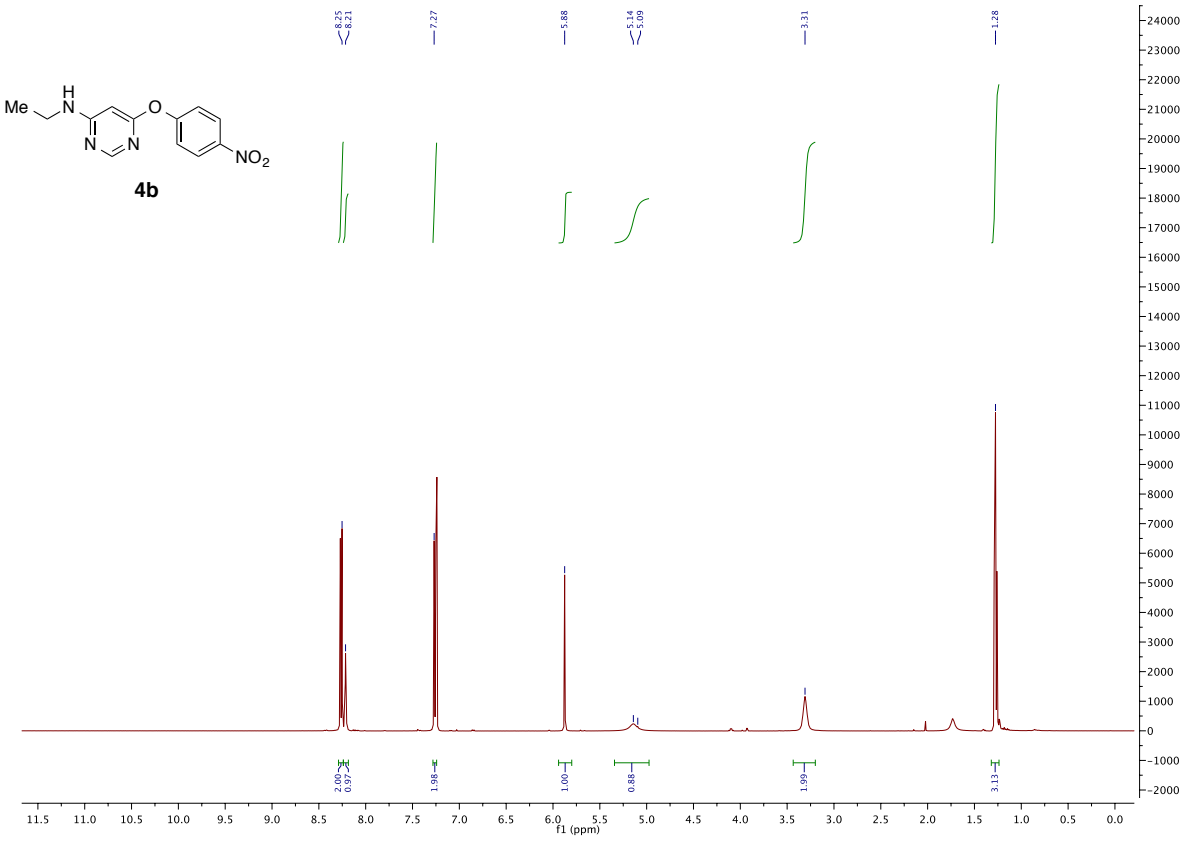

188.73
148.18
145.41
139.48
138.90
130.41
130.11
129.37
127.71
119.96
114.57
114.40
f1 (ppm)
Cl
O
Br
N
H
3e

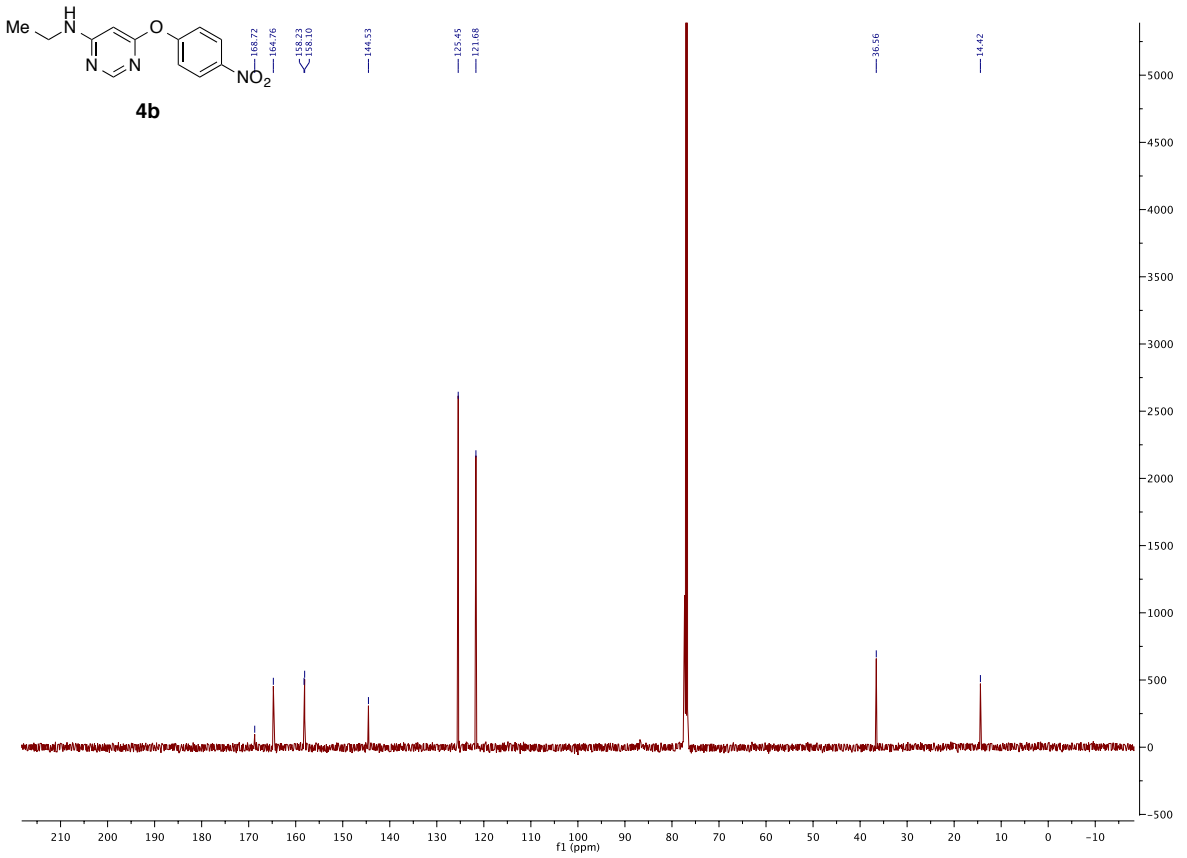

8.66
8.65
8.48
8.47
8.24
7.86
7.85
7.85
7.84
7.63
7.62
7.61
B (d)
8.48
E (m)
7.62
A (d)
8.65
C (s)
8.24
D (m)
7.86
1.00
1.06
1.07
2.23
2.21
f1 (ppm)

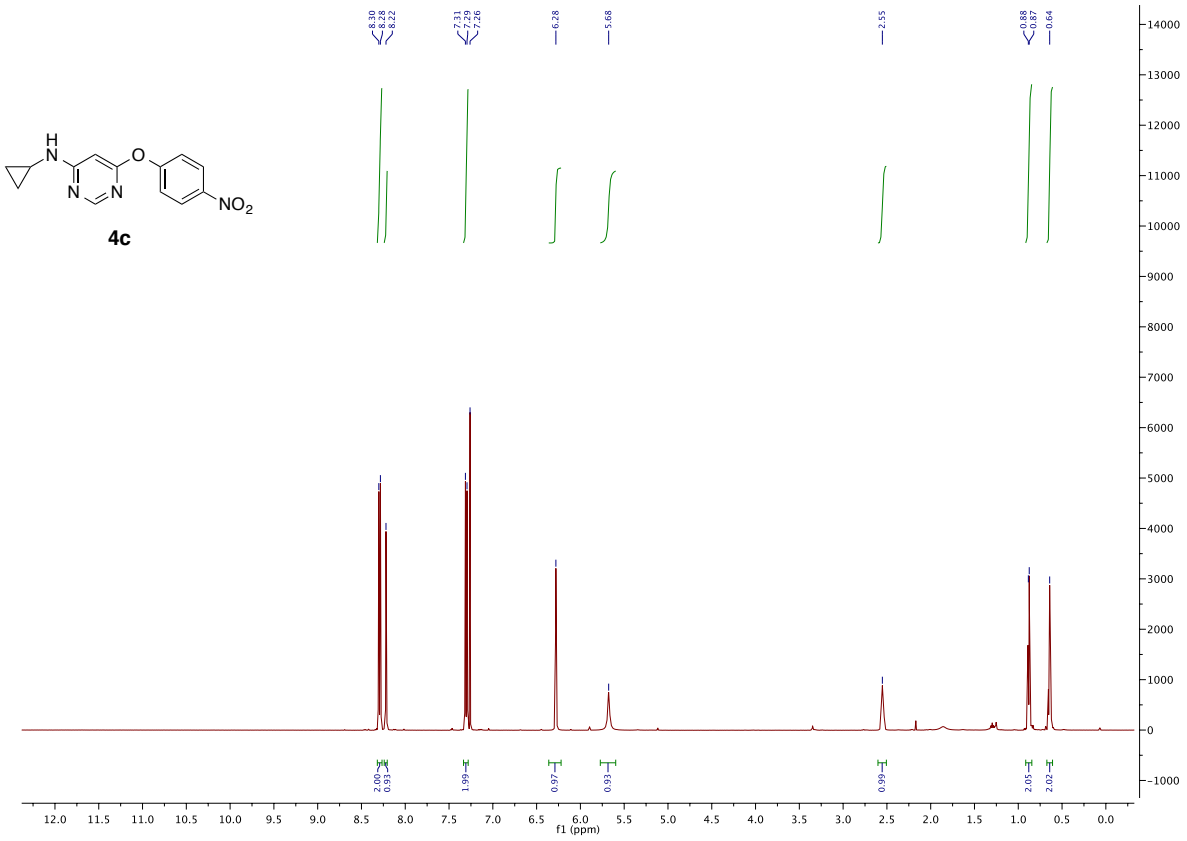
O
Cl
Br
N
N
H

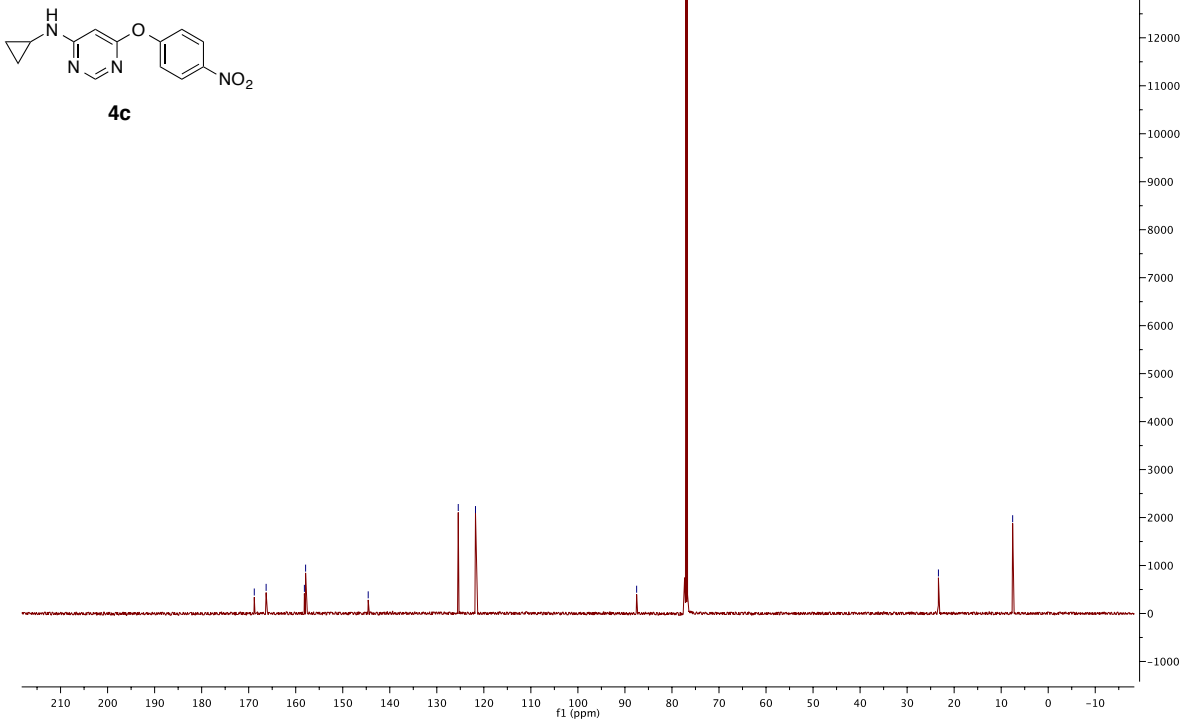
3f


188.81
147.97
145.27
138.25
137.95
136.97
131.99
130.38
129.15
120.82
114.15
113.37
f1 (ppm)

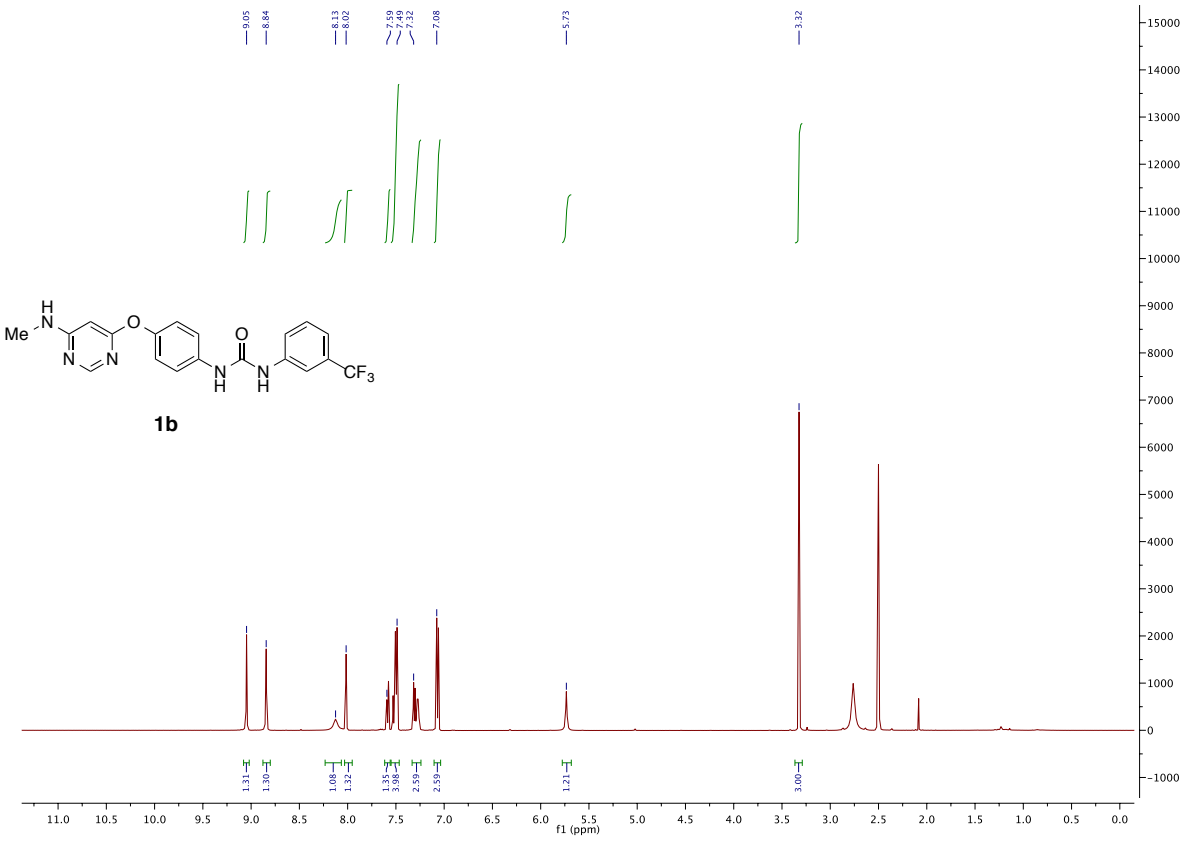

Me
H
N
O
N
N
NO2
4b
8.25
8.21
7.27
5.88
5.14
5.09
3.31
1.28
2.00
0.97
1.98
1.00
0.88
1.99
3.13
f1 (ppm)

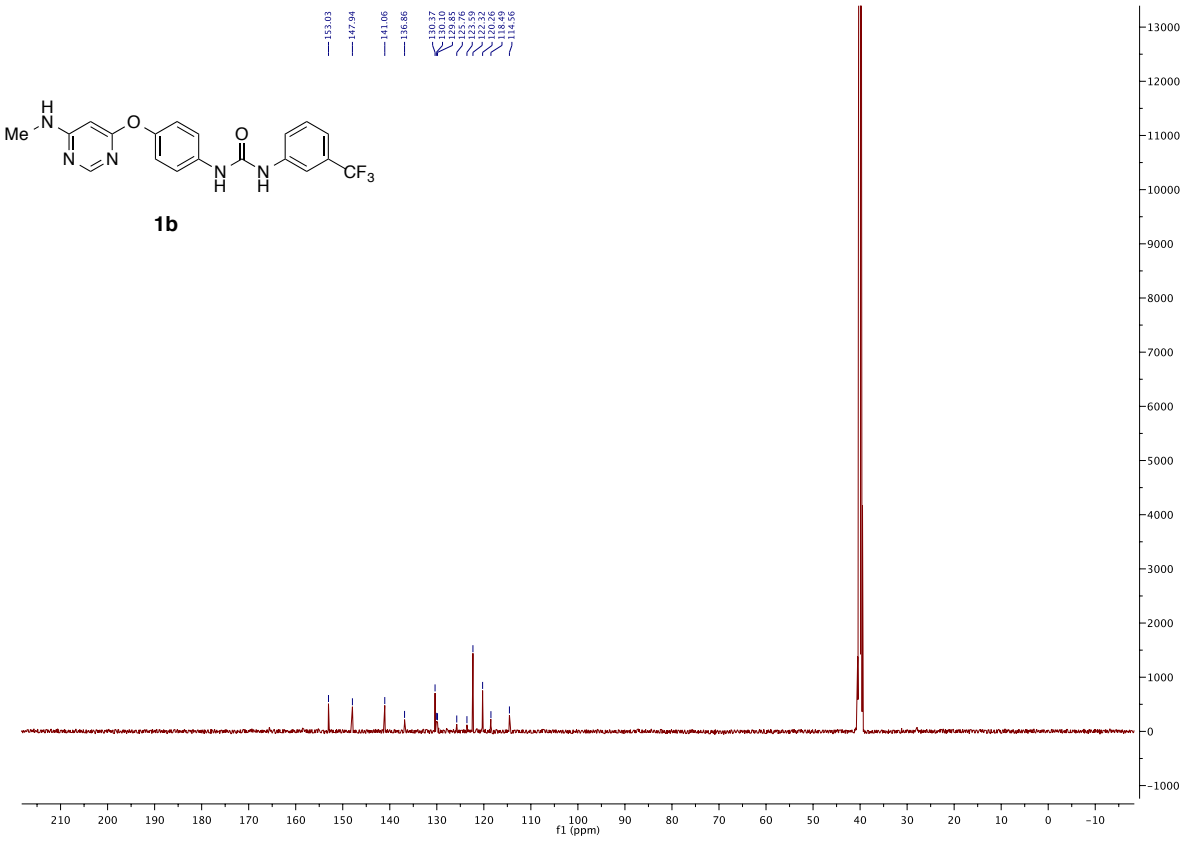

Me
H
N
O
N
N
NO2
4b
168.72
164.76
158.23
158.10
144.53
125.45
121.68
36.56
14.42
f1 (ppm)


8.30
8.28
8.22
7.31
7.29
7.26
6.28
5.68
2.55
0.88
0.87
0.64
2.00
0.93
1.99
0.97
0.93
0.99
2.05
2.02
f1 (ppm)

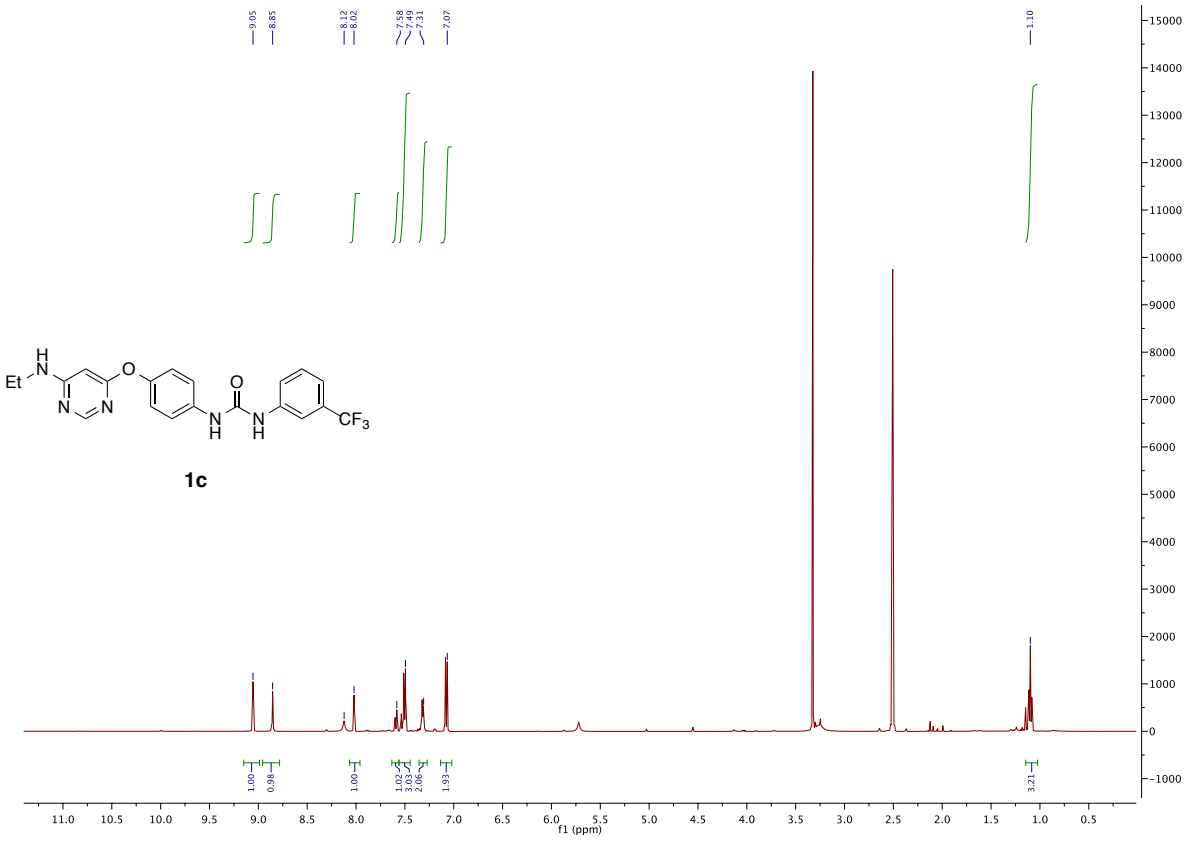

168.81
166.29
158.15
157.90
144.59
125.44
121.77
87.51
23.34
7.56
f1 (ppm)

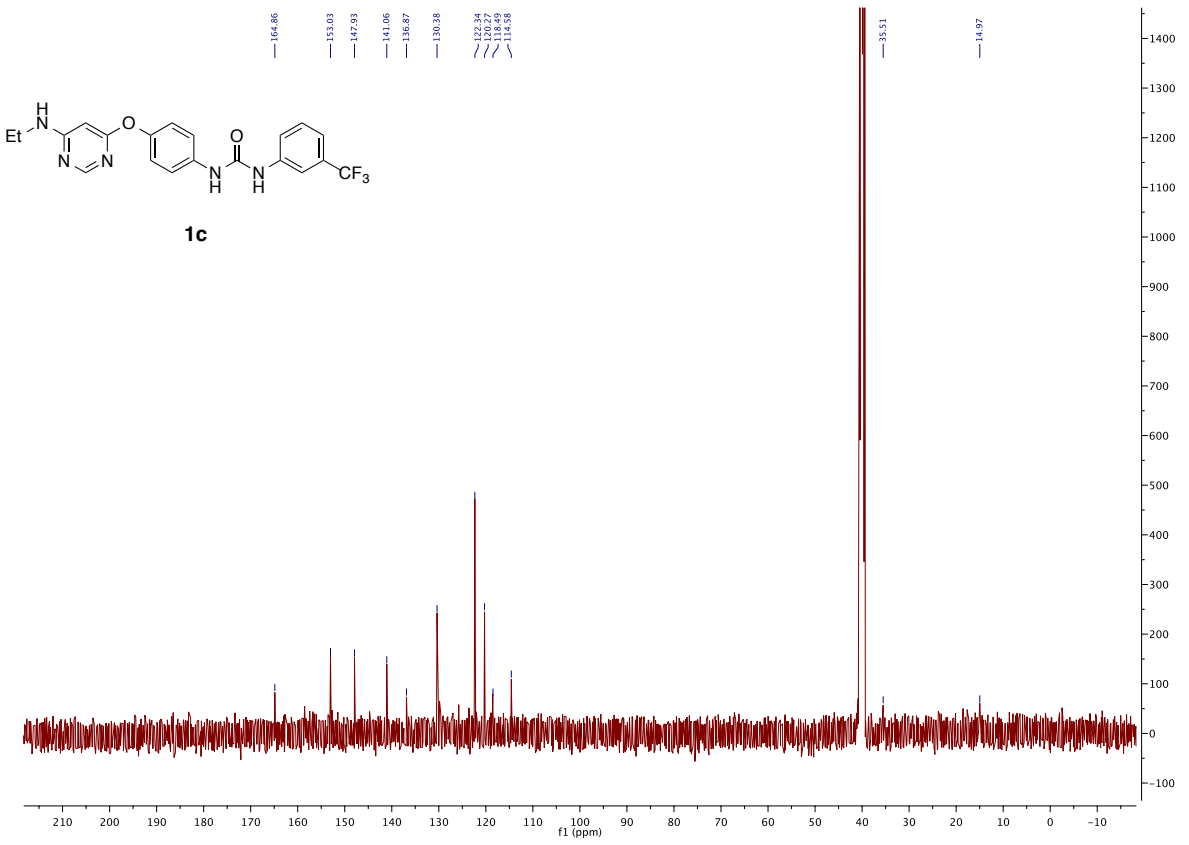
4c


9.05
8.84
8.13
8.02
7.59
7.49
7.32
7.08
5.73
3.32
1.31
1.30
1.08
1.32
1.35
3.98
2.59
2.59
1.21
3.00
f1 (ppm)

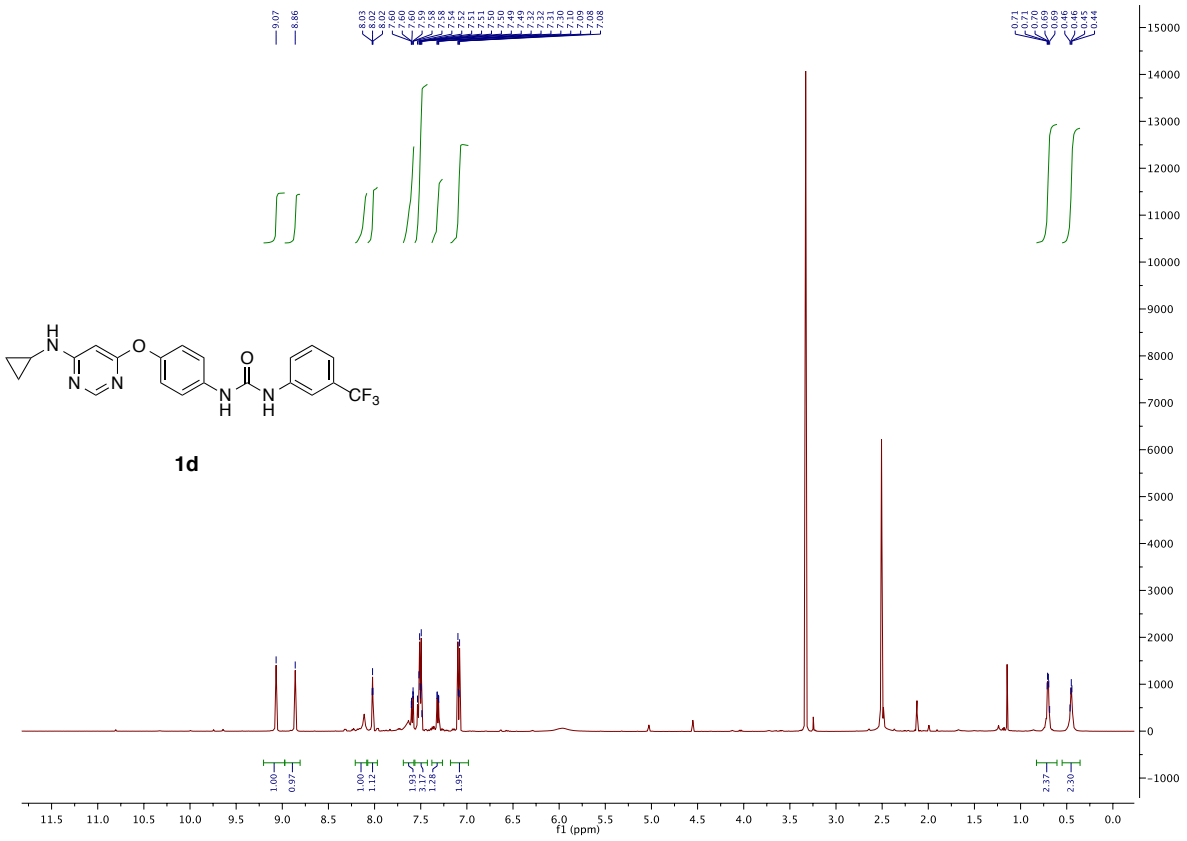

153.03
147.94
141.06
136.86
130.37
130.10
129.85
125.76
123.59
122.32
120.26
118.49
114.56
f1 (ppm)

1b

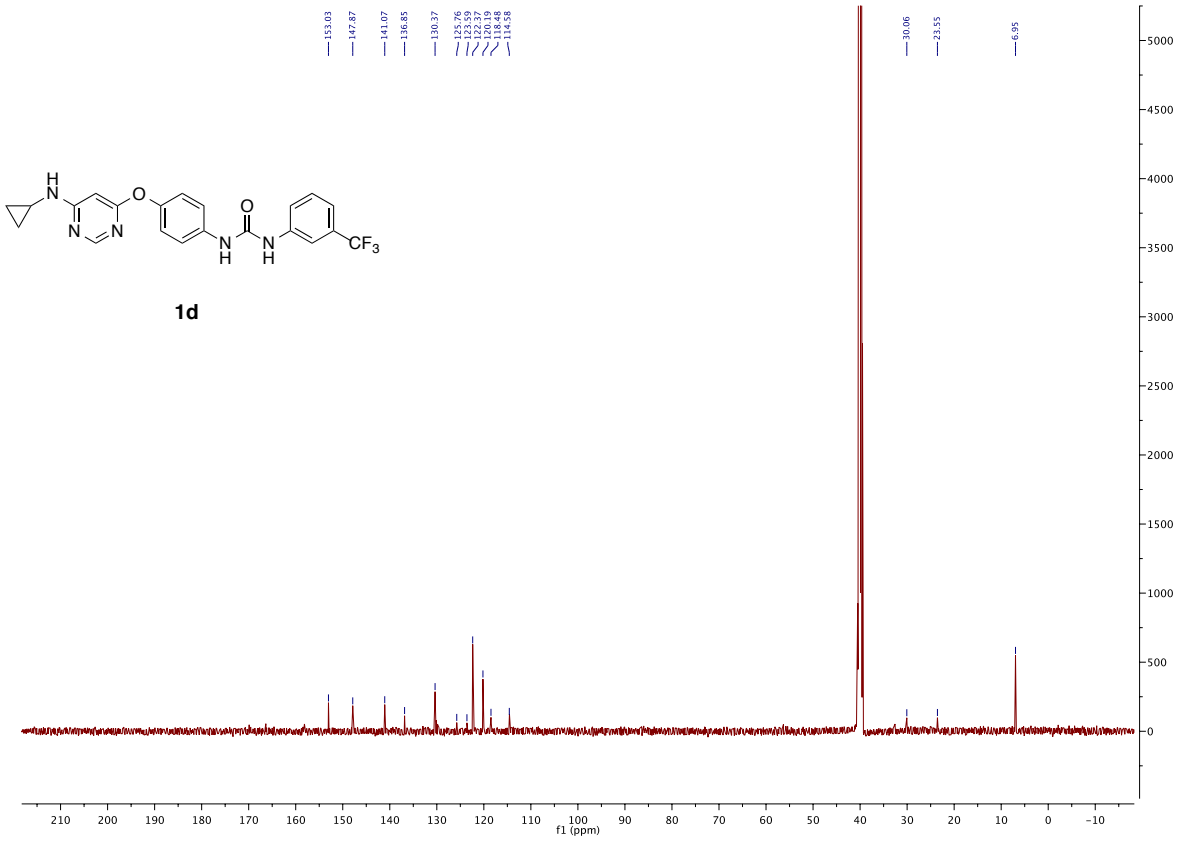

9.05
8.85
8.12
8.02
7.58
7.49
7.31
7.07
1.10
1.00
0.98
1.00
1.02
3.03
2.06
1.93
3.21
f1 (ppm)


164.86
153.03
147.93
141.06
136.87
130.38
122.34
120.27
118.49
114.58
35.51
14.97
f1 (ppm)

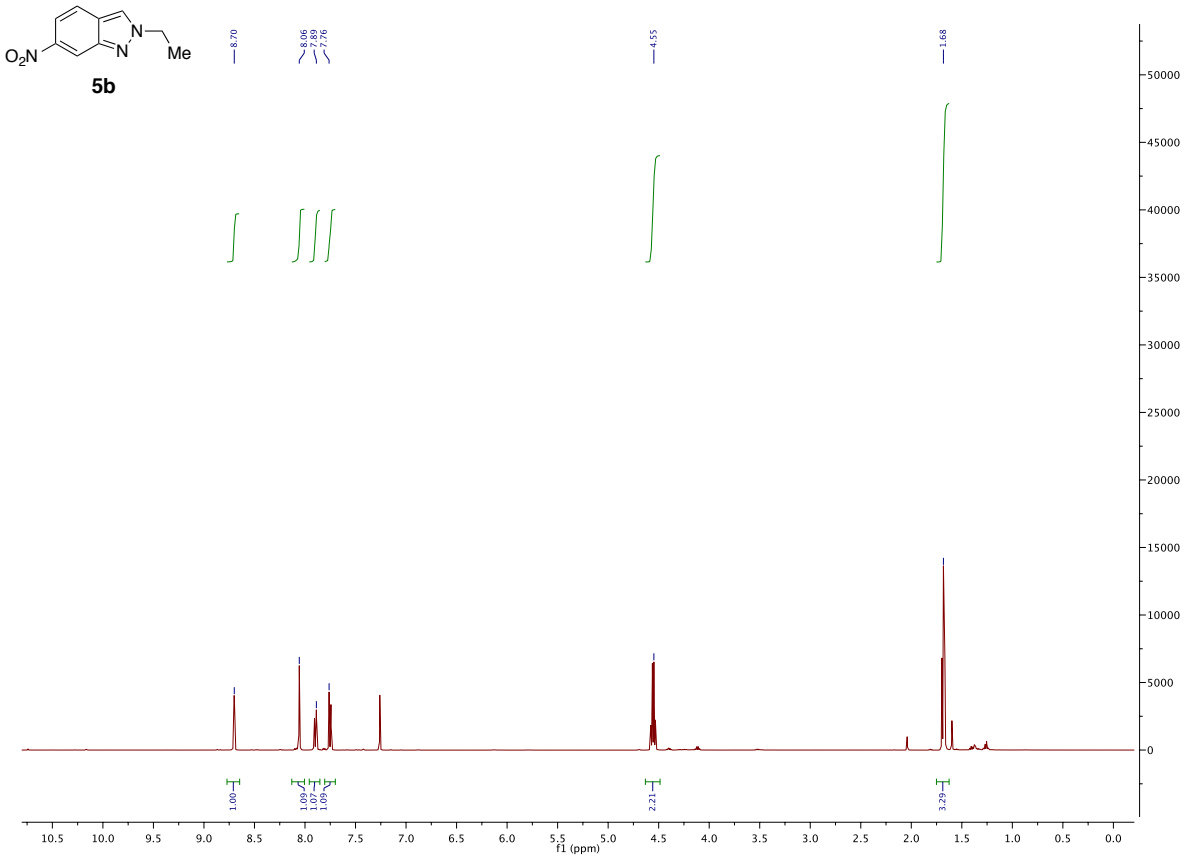
1c

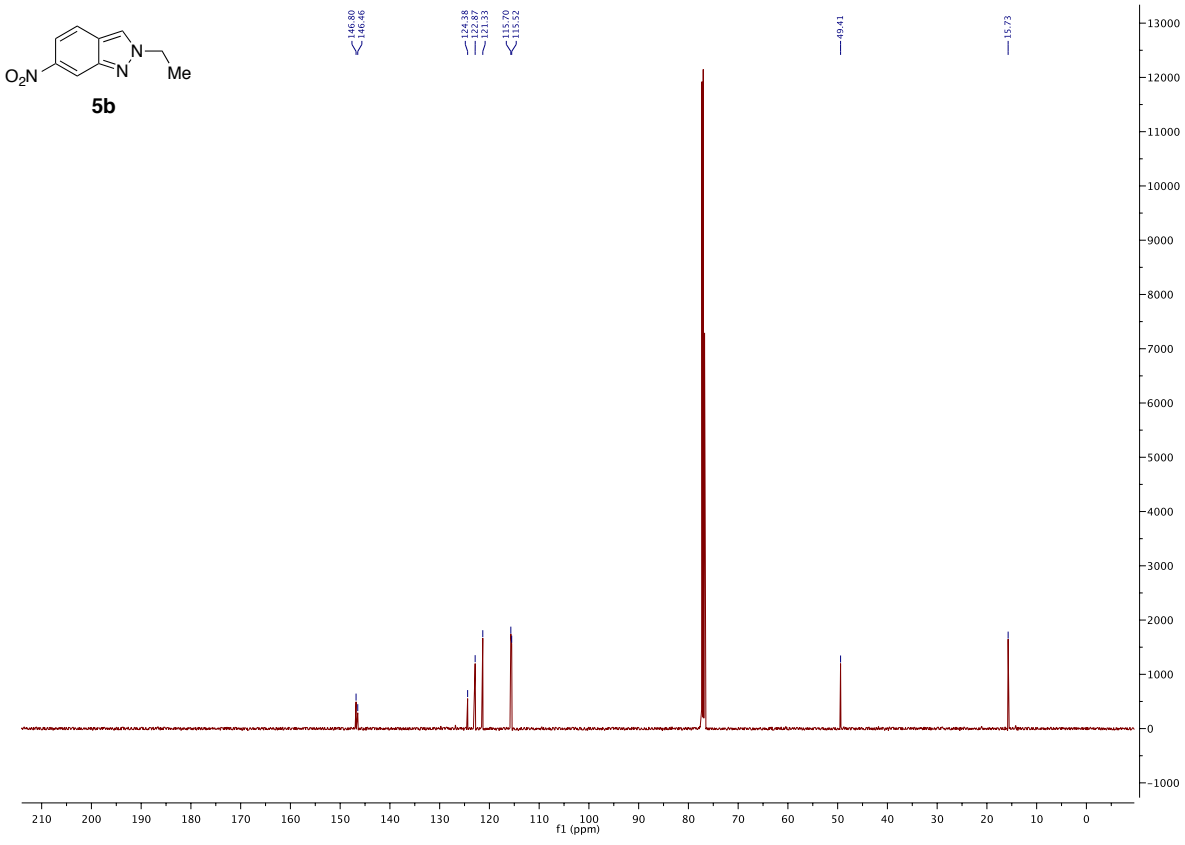

9.07
8.86
8.03
8.02
8.02
8.02
7.60
7.60
7.60
7.60
7.59
7.58
7.58
7.58
7.54
7.52
7.51
7.51
7.50
7.50
7.50
7.49
7.49
7.32
7.32
7.31
7.30
7.10
7.09
7.08
7.08
0.71
0.71
0.70
0.70
0.69
0.69
0.46
0.46
0.45
0.45
0.44
1.00
0.97
1.00
1.12
1.93
3.17
1.28
1.95
2.37
2.30
f1 (ppm)

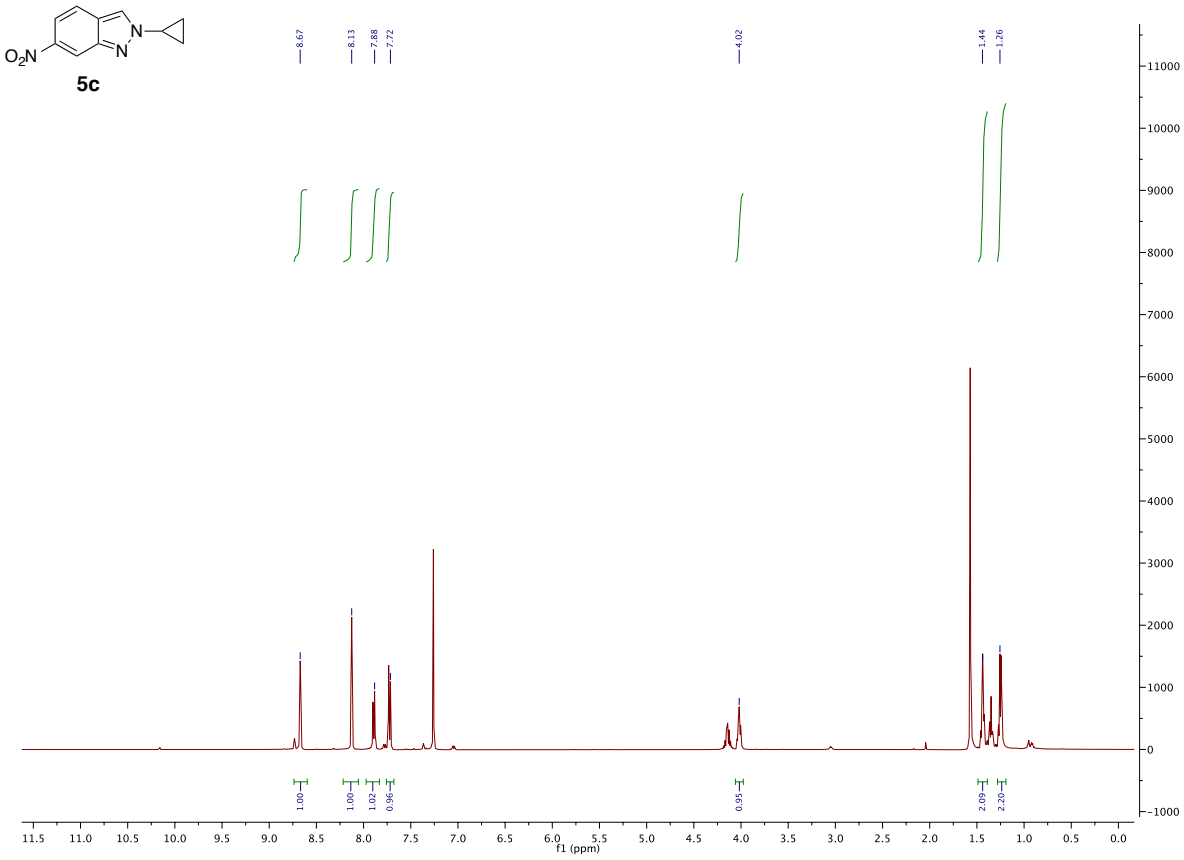
1d

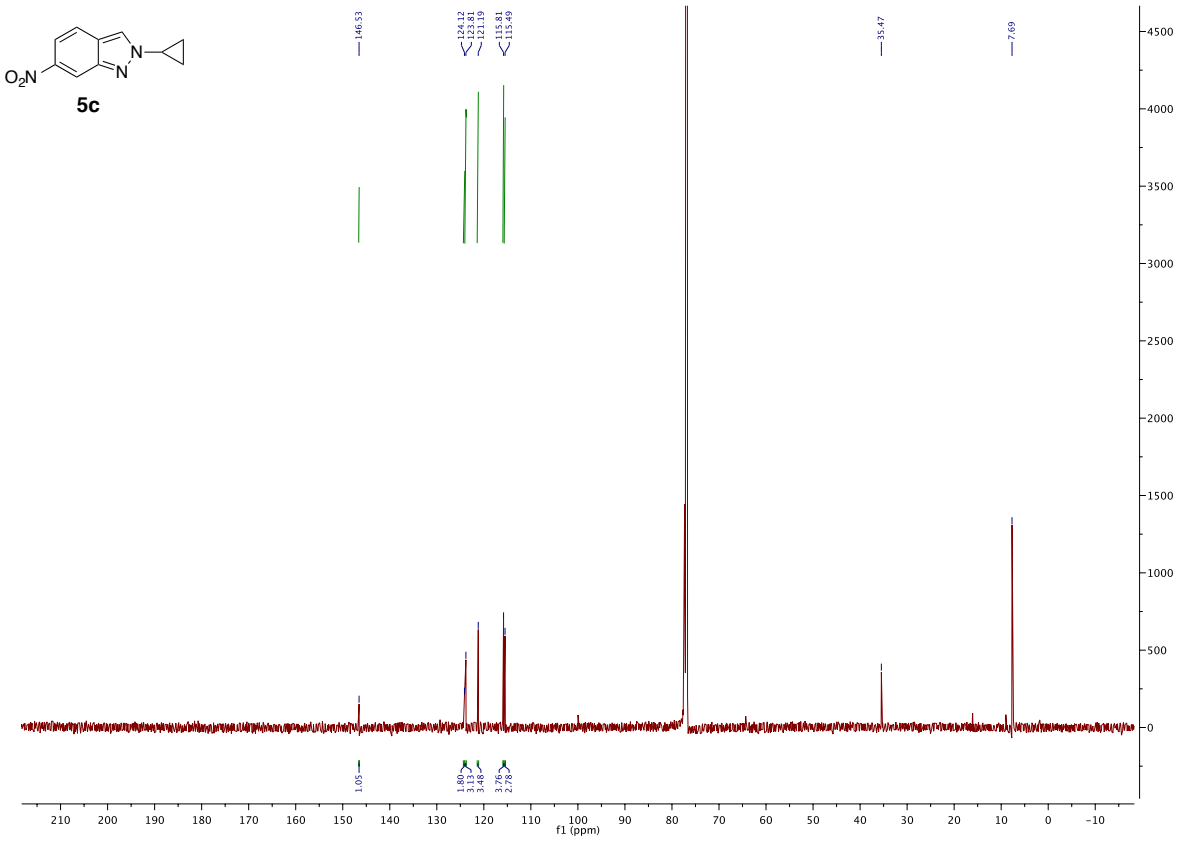

153.03
147.87
141.07
136.85
130.37
125.76
123.59
122.37
120.19
118.48
114.58
30.06
23.55
6.95
f1 (ppm)

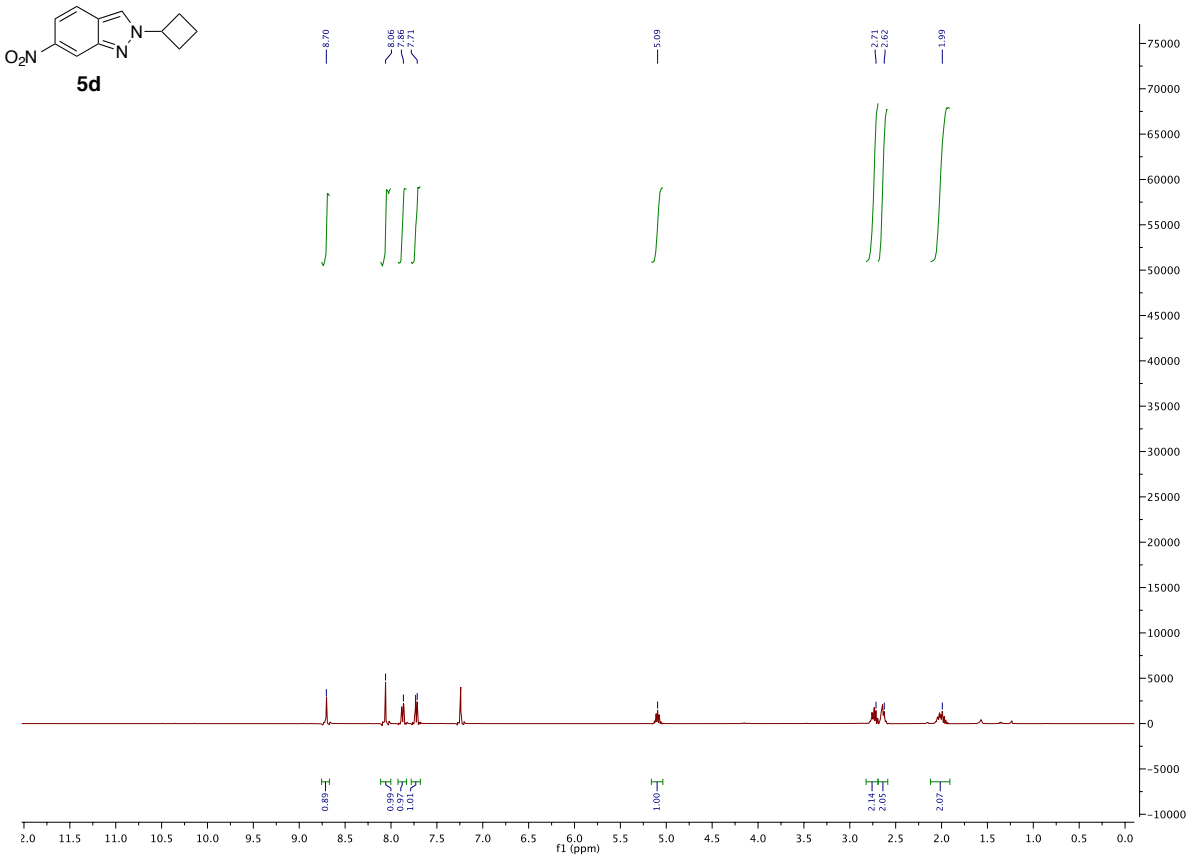
1d

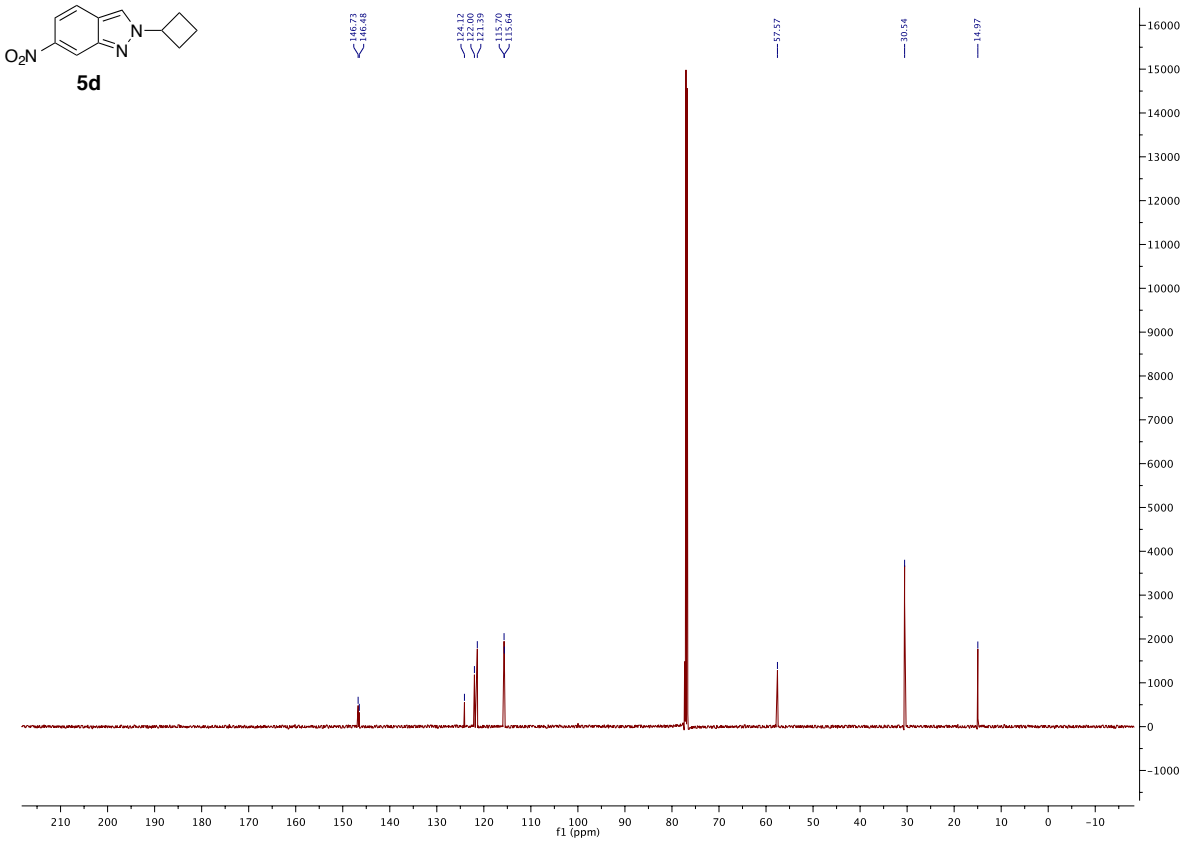

O2N
N
N
Me
5b
8.70
8.06
7.89
7.76
4.55
1.68
1.00
1.09
1.07
1.09
2.21
3.29
f1 (ppm)

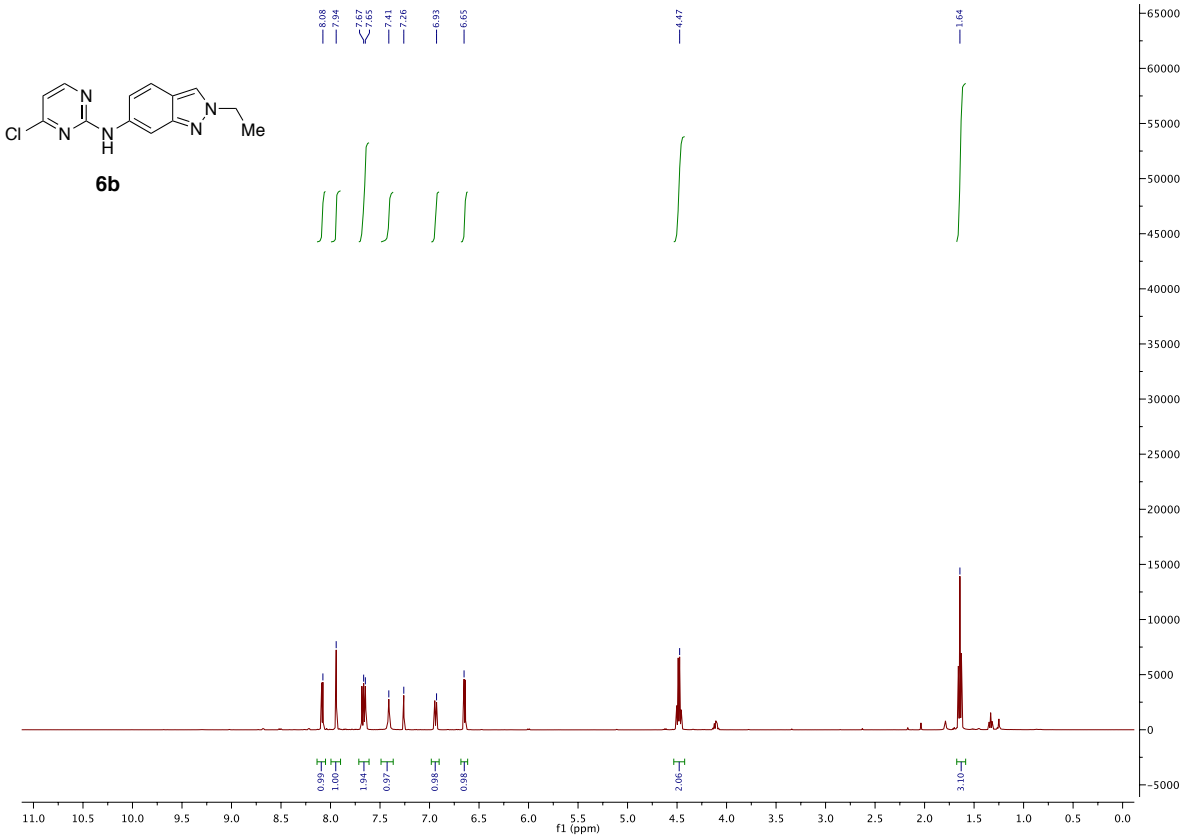

O2N
N
N
Me
5b
146.80
146.46
124.38
122.87
121.53
115.70
115.52
49.41
15.73
f1 (ppm)


O2N
5c
8.67
8.13
7.88
7.72
4.02
1.44
1.26
1.00
1.00
1.02
0.96
0.95
2.09
2.20
f1 (ppm)

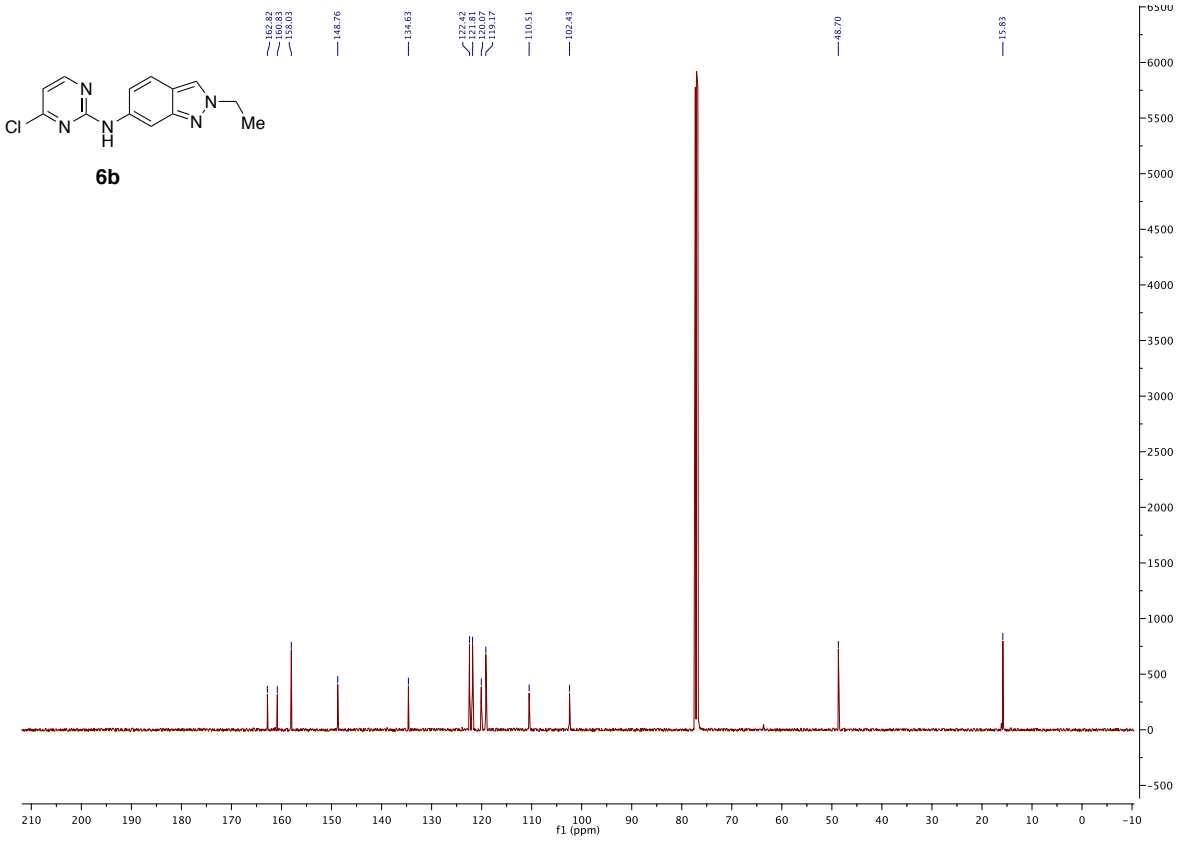

O2N
5c
146.53
124.12
124.83
121.19
115.81
115.49
35.47
7.69
1.05
1.80
3.13
3.48
3.76
2.78
f1 (ppm)


O2N
5d
8.70
8.06
8.06
7.71
5.09
2.71
2.62
1.99
0.89
0.99
0.97
1.01
1.00
2.14
2.05
2.07
f1 (ppm)

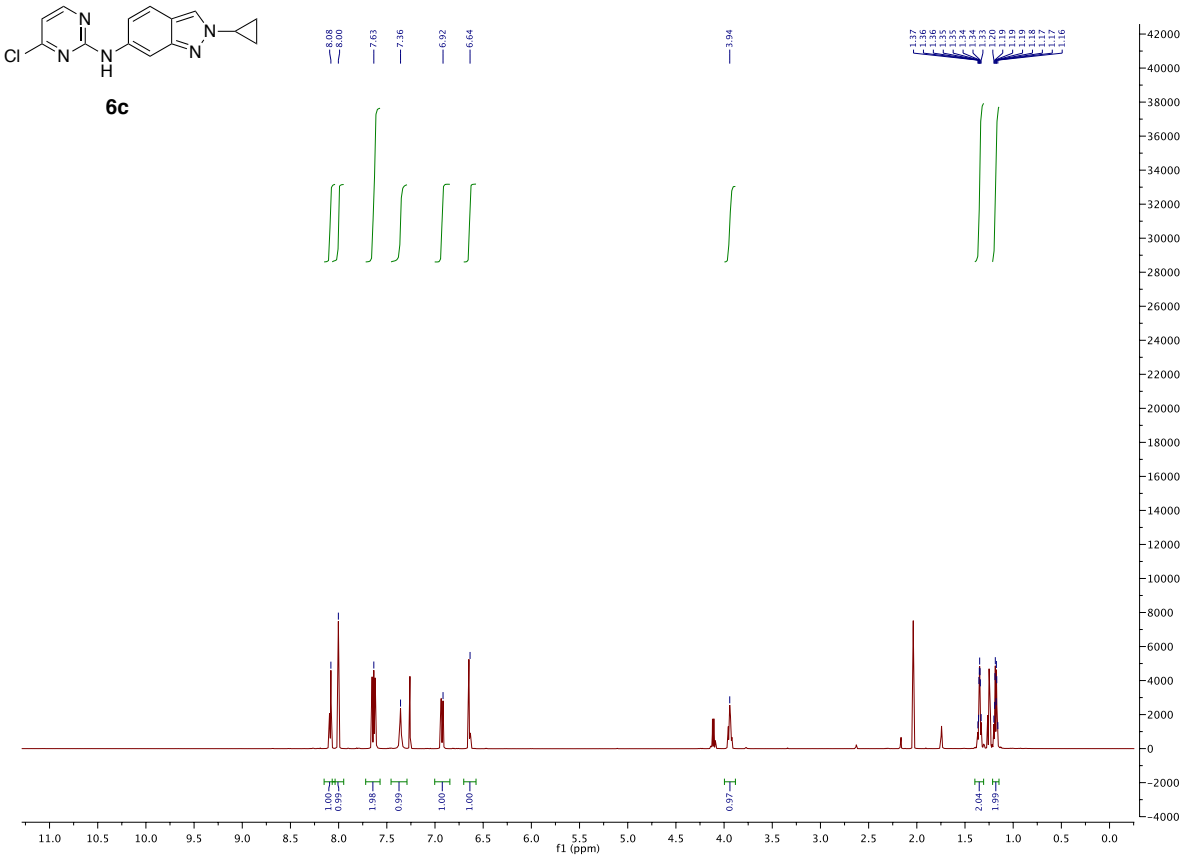

O2N
5d
146.73
146.48
124.12
122.00
121.39
115.70
115.64
57.57
30.54
14.97
f1 (ppm)

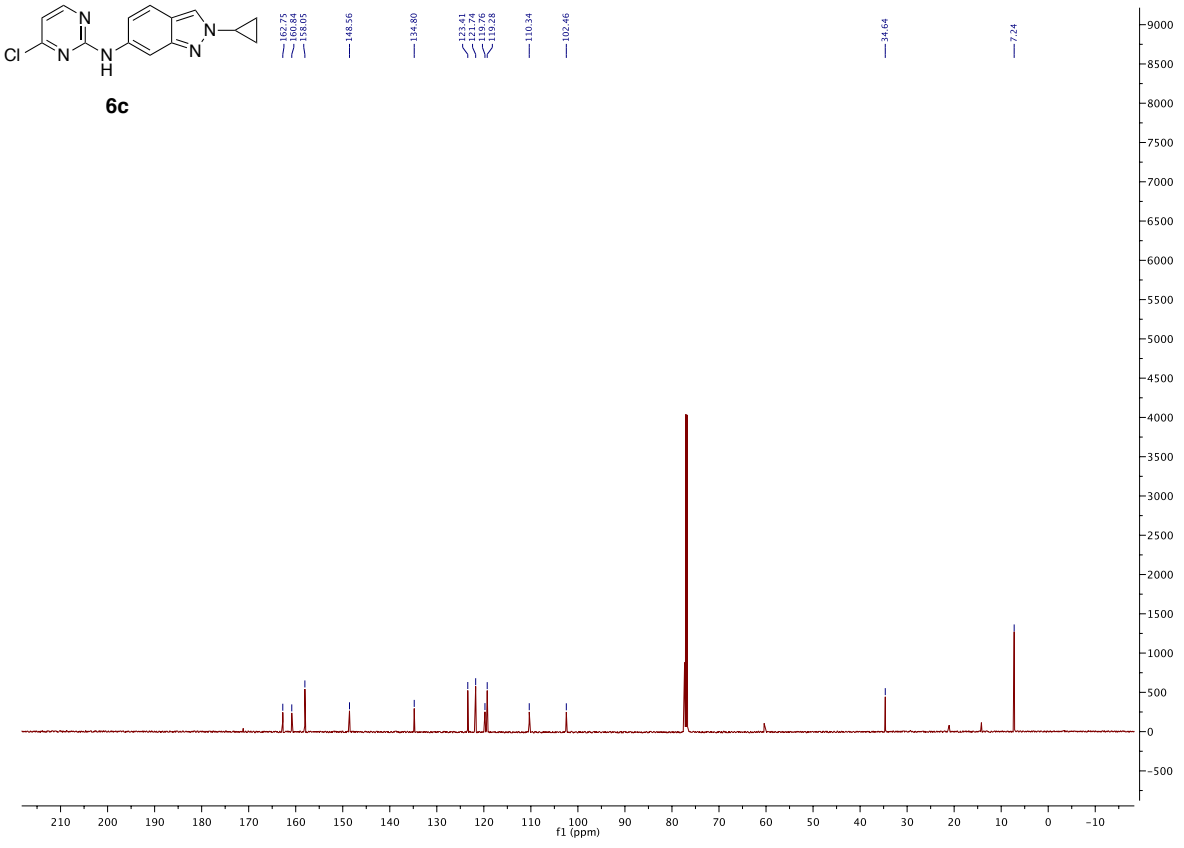

8.08
7.94
7.67
7.65
7.41
7.26
6.93
6.65
4.47
1.64
0.99
1.00
1.94
0.97
0.98
0.98
2.06
3.10
f1 (ppm)

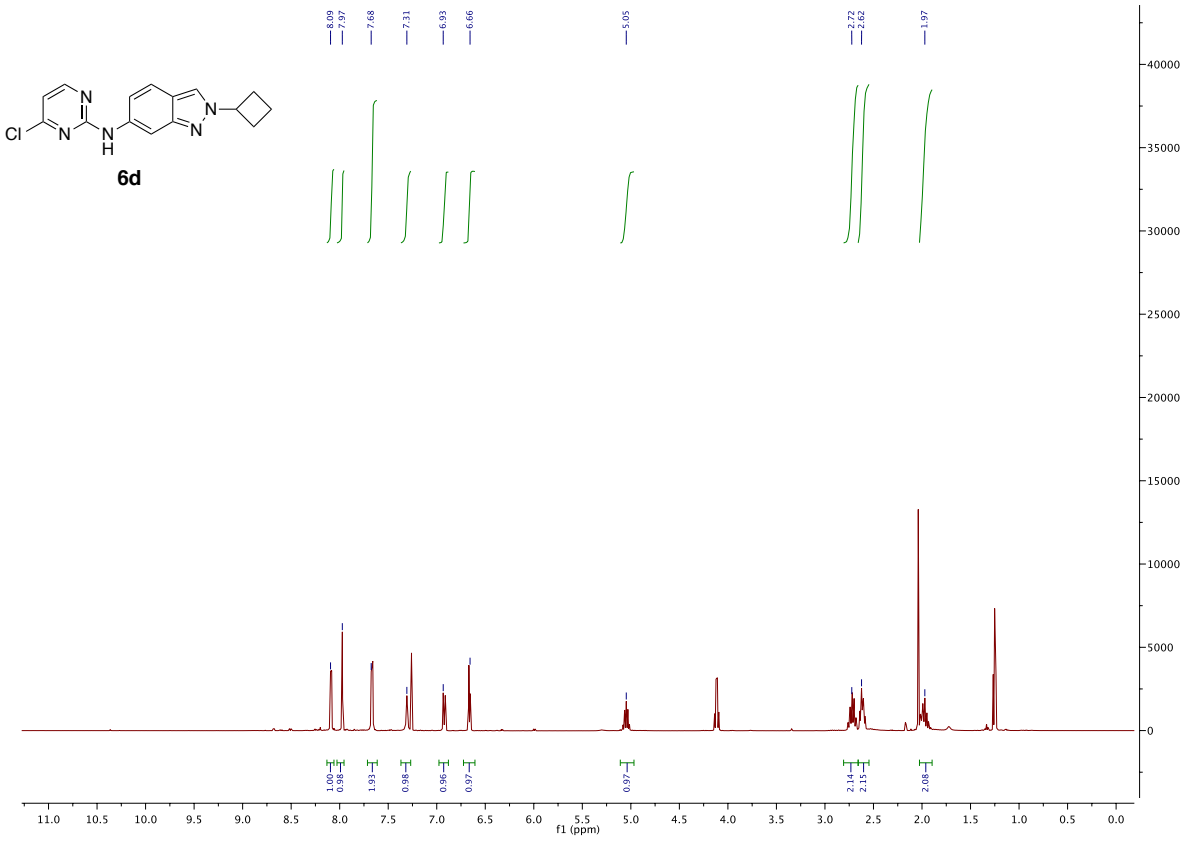
6b


162.82
160.83
158.83
148.76
134.63
122.42
121.81
120.07
119.17
110.51
102.43
48.70
15.83
f1 (ppm)

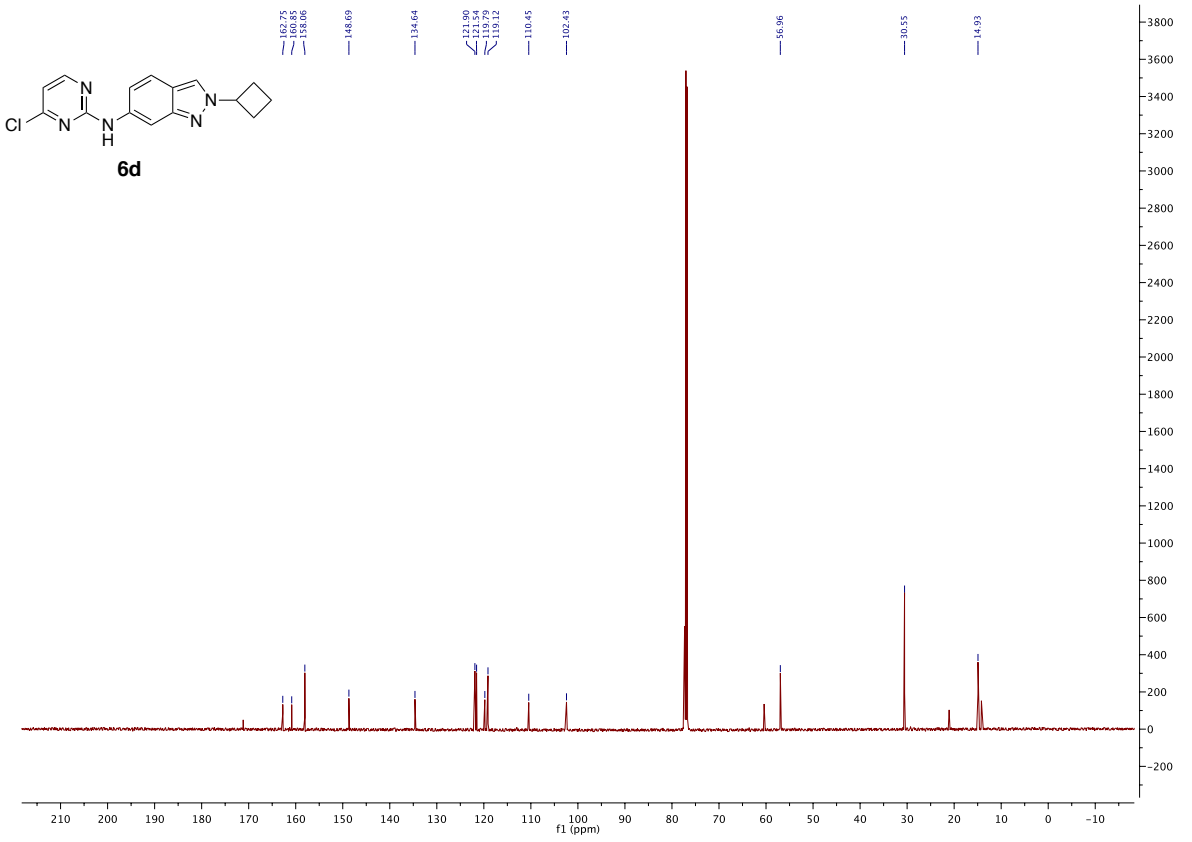
6b


6c
8.08
8.00
7.63
7.36
6.92
6.64
3.94
1.37
1.36
1.36
1.35
1.35
1.34
1.34
1.33
1.20
1.19
1.19
1.18
1.17
1.17
1.16
1.00
0.99
1.98
0.99
1.00
1.00
0.97
2.04
1.99
f1 (ppm)

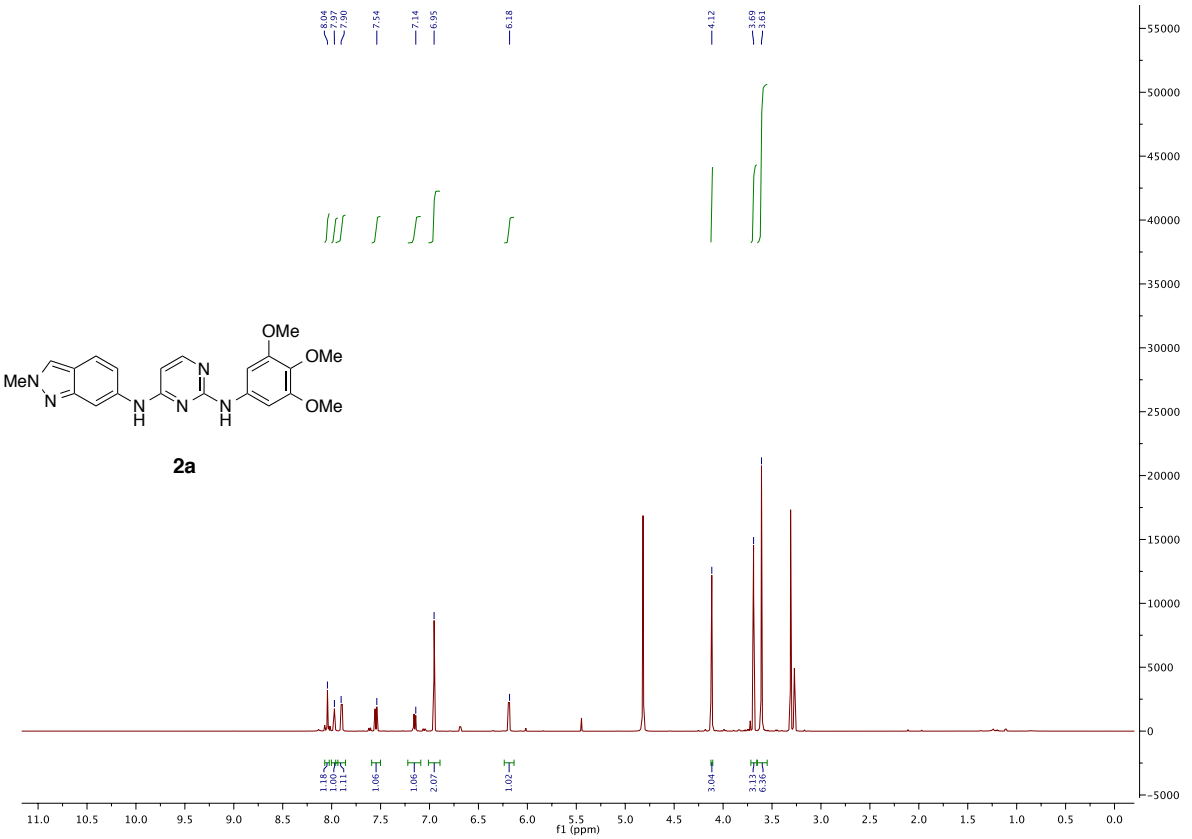

6c
162.75
160.84
158.65
148.56
134.80
123.41
121.74
119.76
119.28
110.34
102.46
34.64
7.24
f1 (ppm)

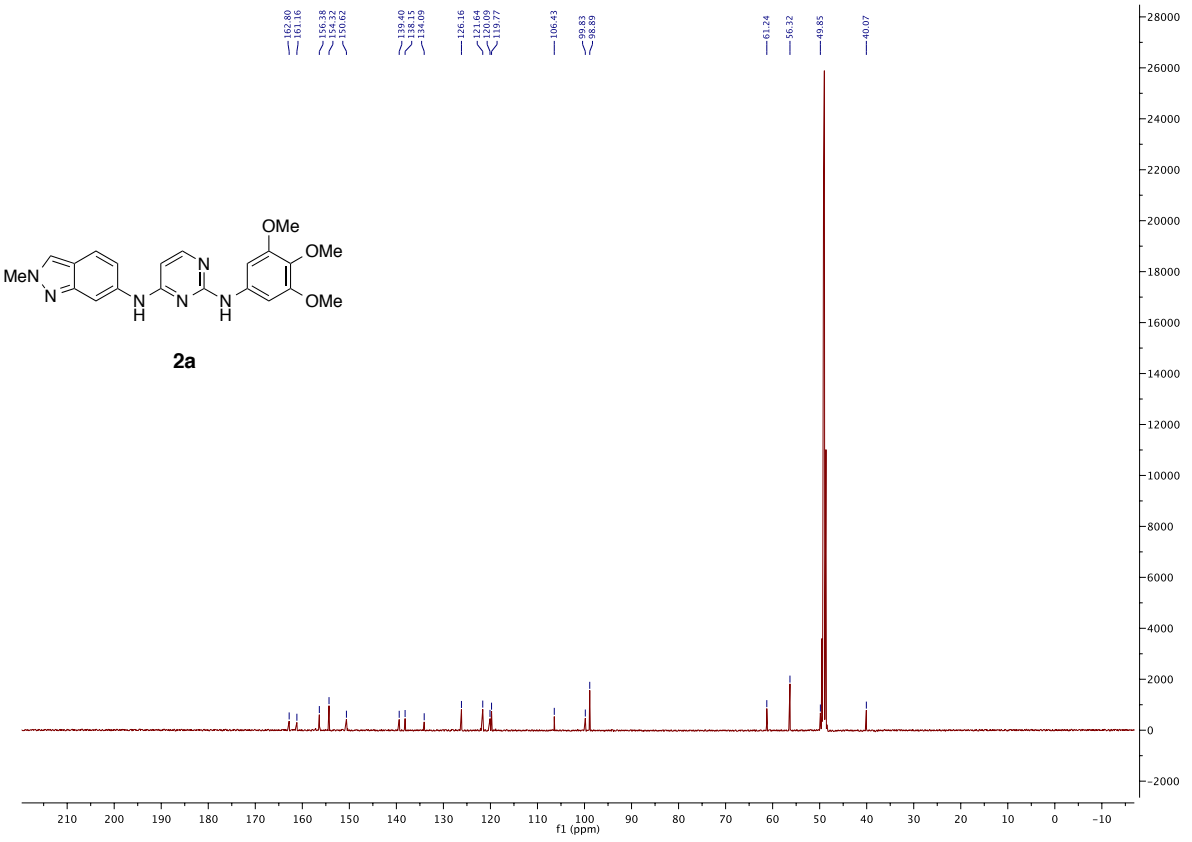

8.09
7.97
7.68
7.31
6.93
6.66
5.05
2.72
2.62
1.97
1.00
0.98
1.93
0.98
0.96
0.97
0.97
2.14
2.15
2.08
f1 (ppm)

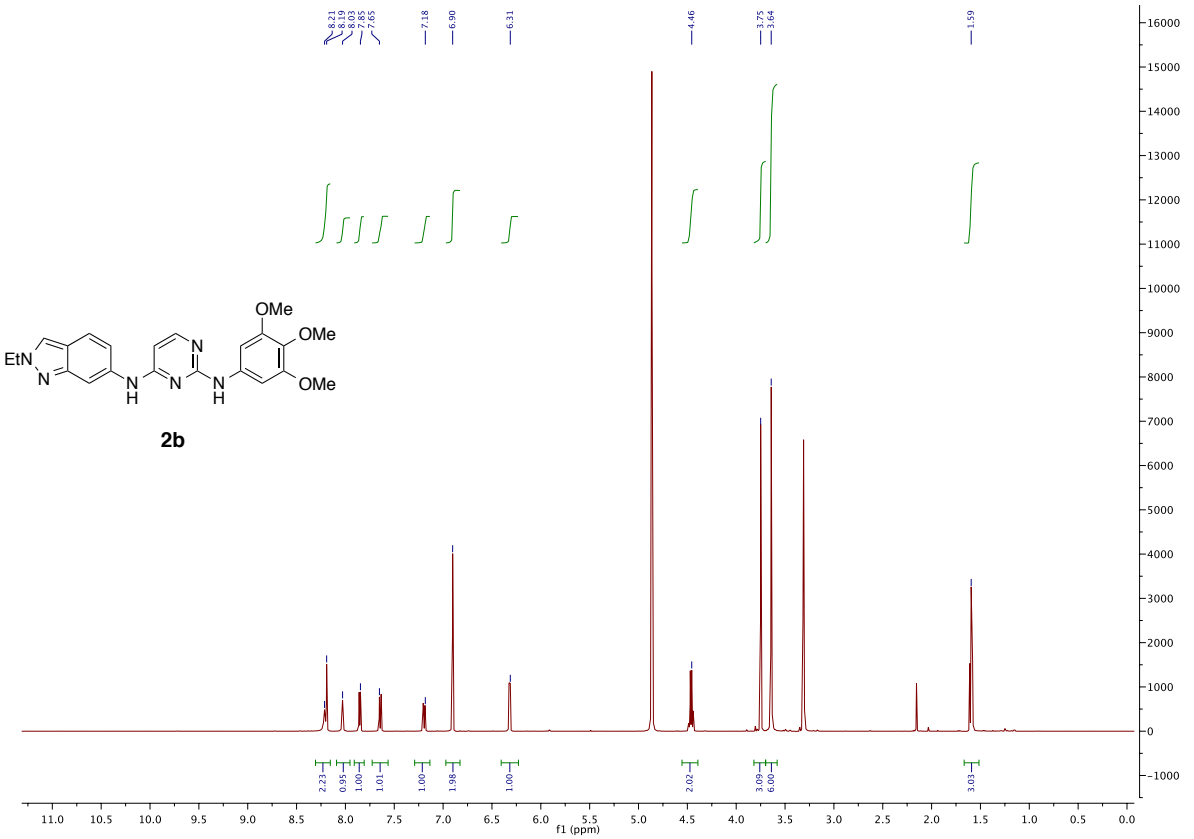
6d


162.75
160.65
158.06
148.69
134.64
121.90
121.54
119.29
119.12
110.45
102.43
56.96
30.55
14.93
f1 (ppm)

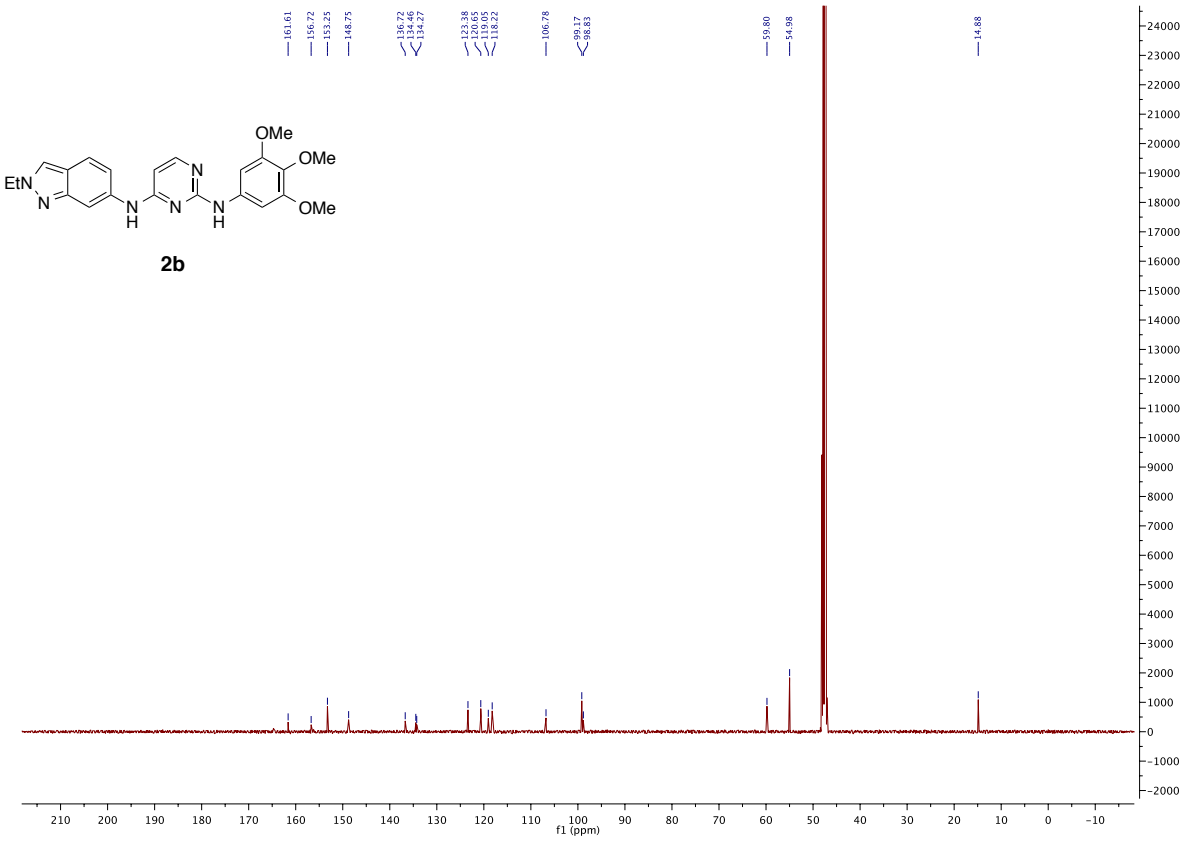
6d


8.04
7.97
7.90
7.54
7.14
6.95
6.18
4.12
3.69
3.61
OMe
OMe
OMe
MeN
N
N
N
H
N
H
2a
1.18
1.09
1.11
1.06
1.06
2.07
1.02
3.04
3.13
6.36
f1 (ppm)

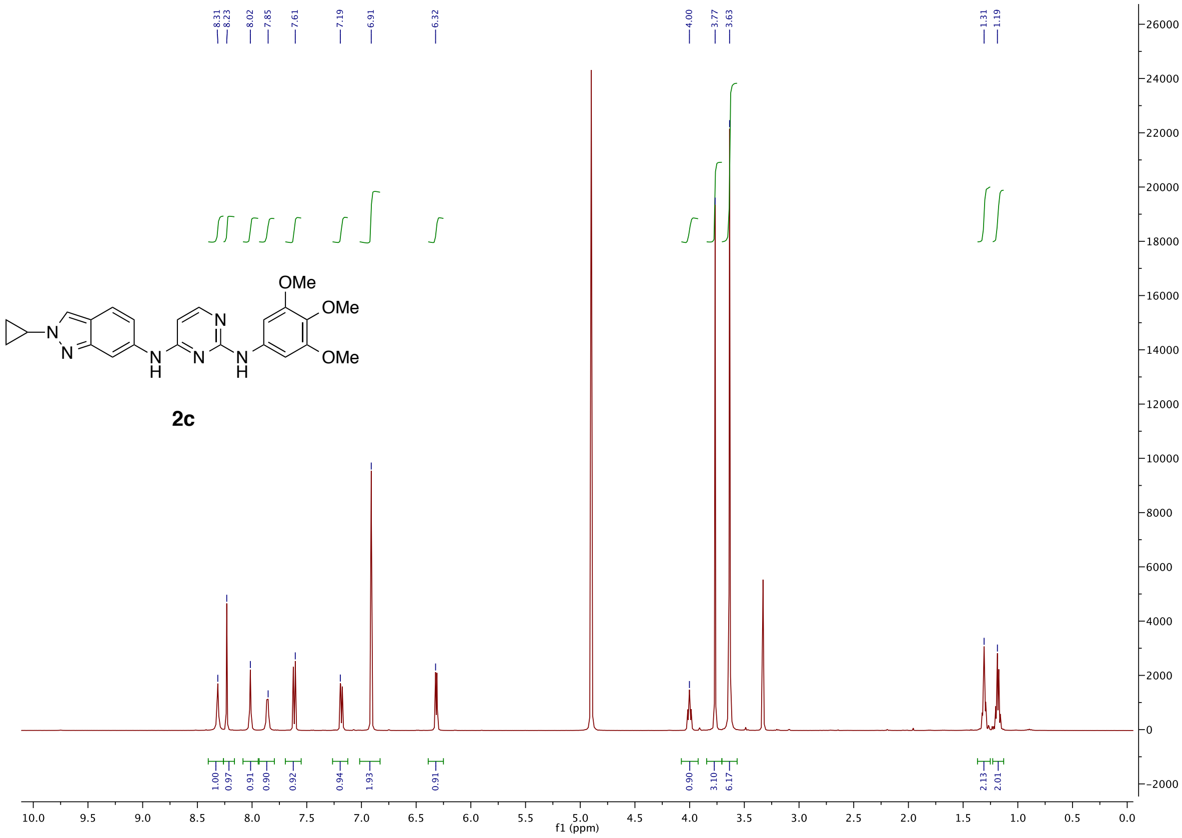

162.80
161.16
156.38
154.22
150.62
139.40
138.15
134.09
126.16
121.64
120.09
119.77
106.43
99.83
98.89
61.24
56.32
49.85
40.07
OMe
OMe
OMe
MeN
N
N
N
H
N
H
2a
f1 (ppm)

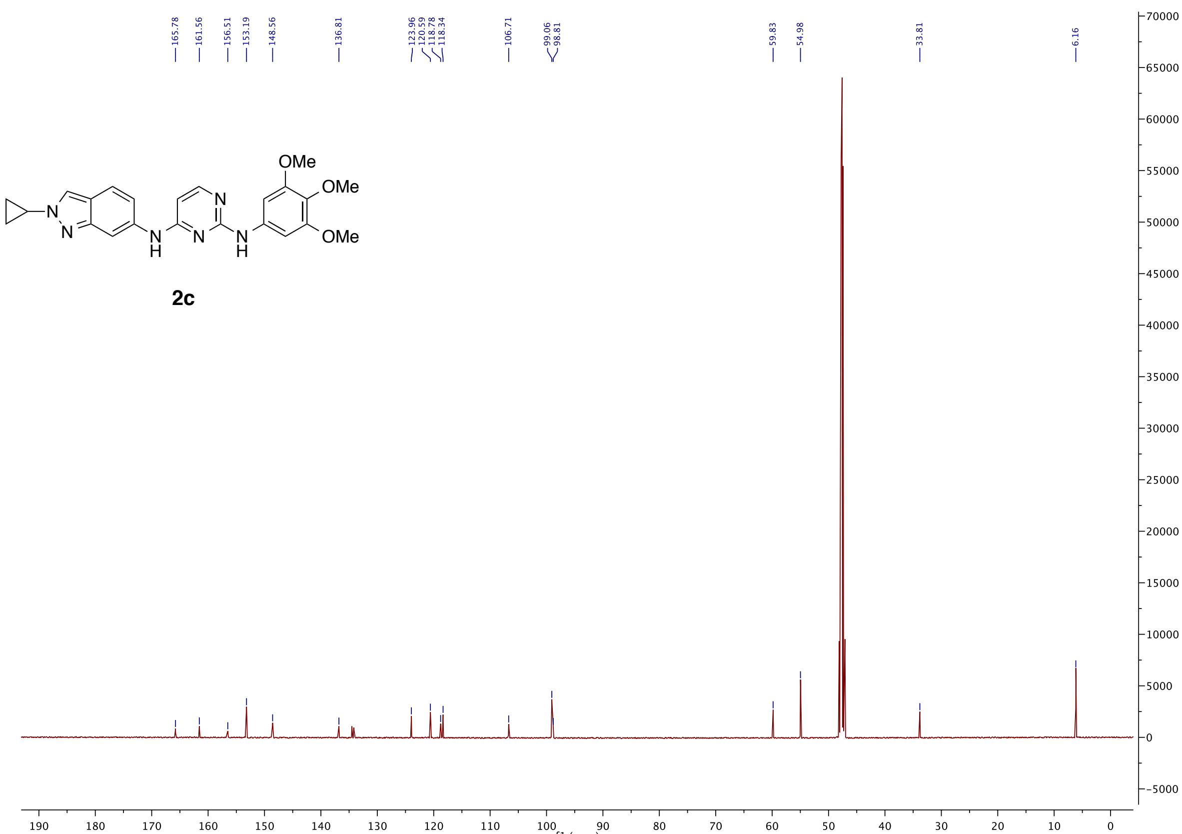

8.21
8.19
8.03
7.85
7.65
7.18
6.90
6.31
4.46
3.75
3.64
1.59
OMe
OMe
OMe
EtN
N
N
N
N
H
N
H
2.23
0.95
1.00
1.01
1.00
1.98
1.00
2.02
3.09
6.00
3.03
f1 (ppm)

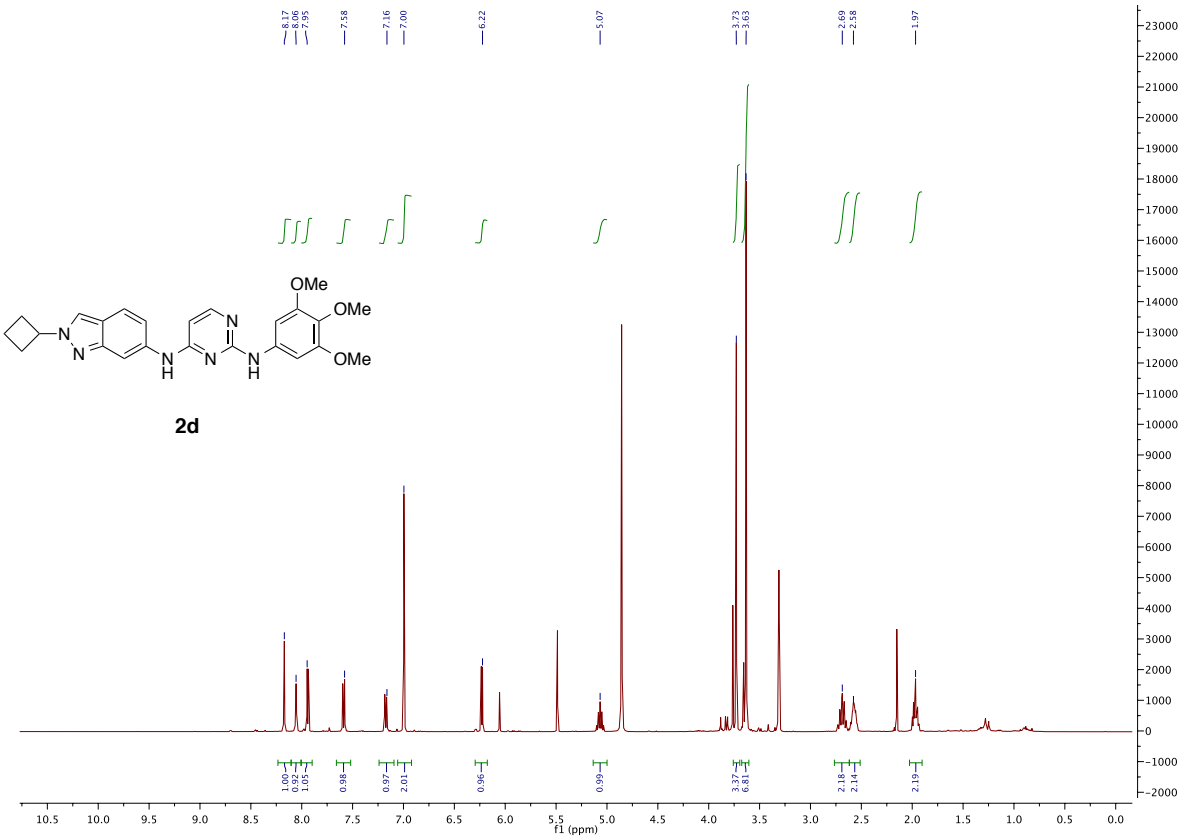
2b


161.61
156.72
153.25
148.75
136.72
134.46
134.27
123.38
120.65
119.55
118.22
106.78
99.17
98.83
59.80
54.98
14.88
OMe
OMe
OMe
EtN
N
N
N
N
H
N
H
f1 (ppm)

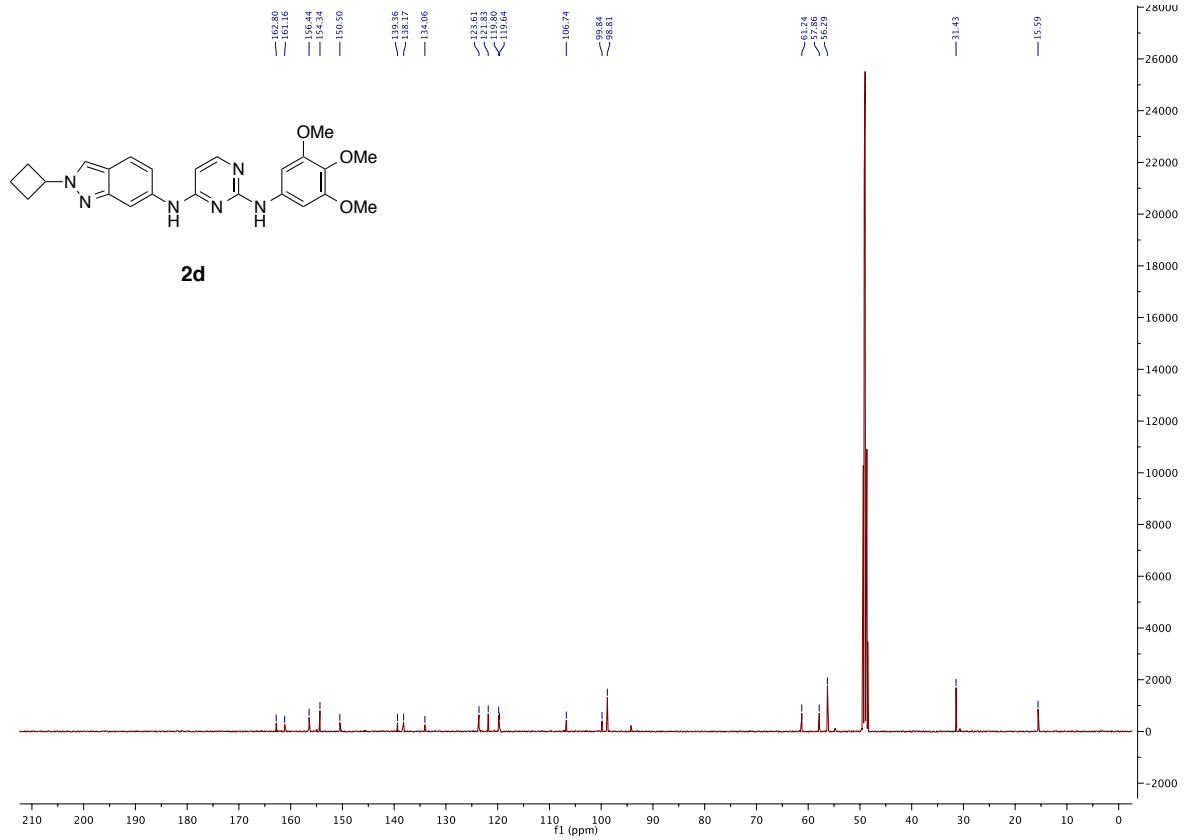
2b


8.31
8.23
8.02
7.85
7.61
7.19
6.91
6.32
4.00
3.77
3.63
1.31
1.19
1.00
0.97
0.91
0.90
0.92
0.94
1.93
0.91
0.90
3.10
6.17
2.13
2.01
OMe
OMe
OMe
N
N
N
N
H
N
N
H
2c
f1 (ppm)

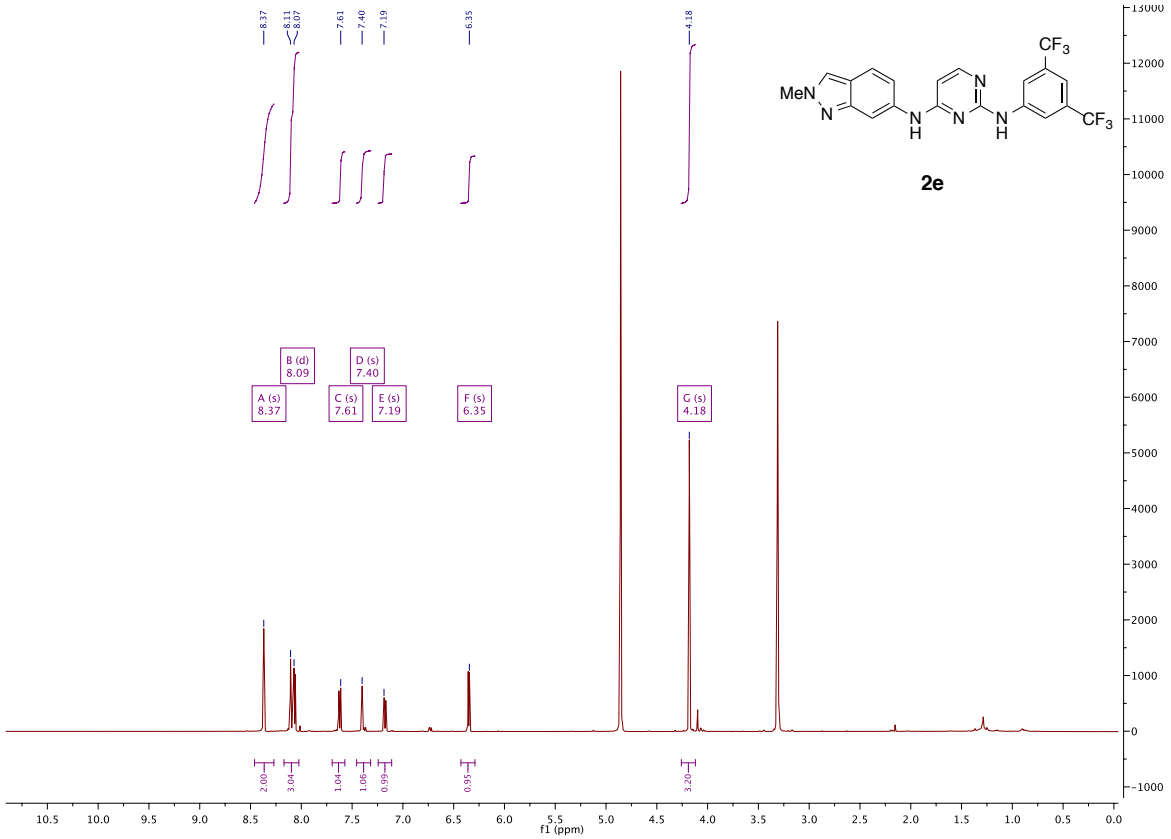

165.78
161.56
156.51
153.19
148.56
136.81
123.96
120.59
118.78
118.34
106.71
99.06
98.81
59.83
54.98
33.81
6.16
OMe
OMe
OMe
N
N
N
N
H
N
N
H
2c
f1 (ppm)

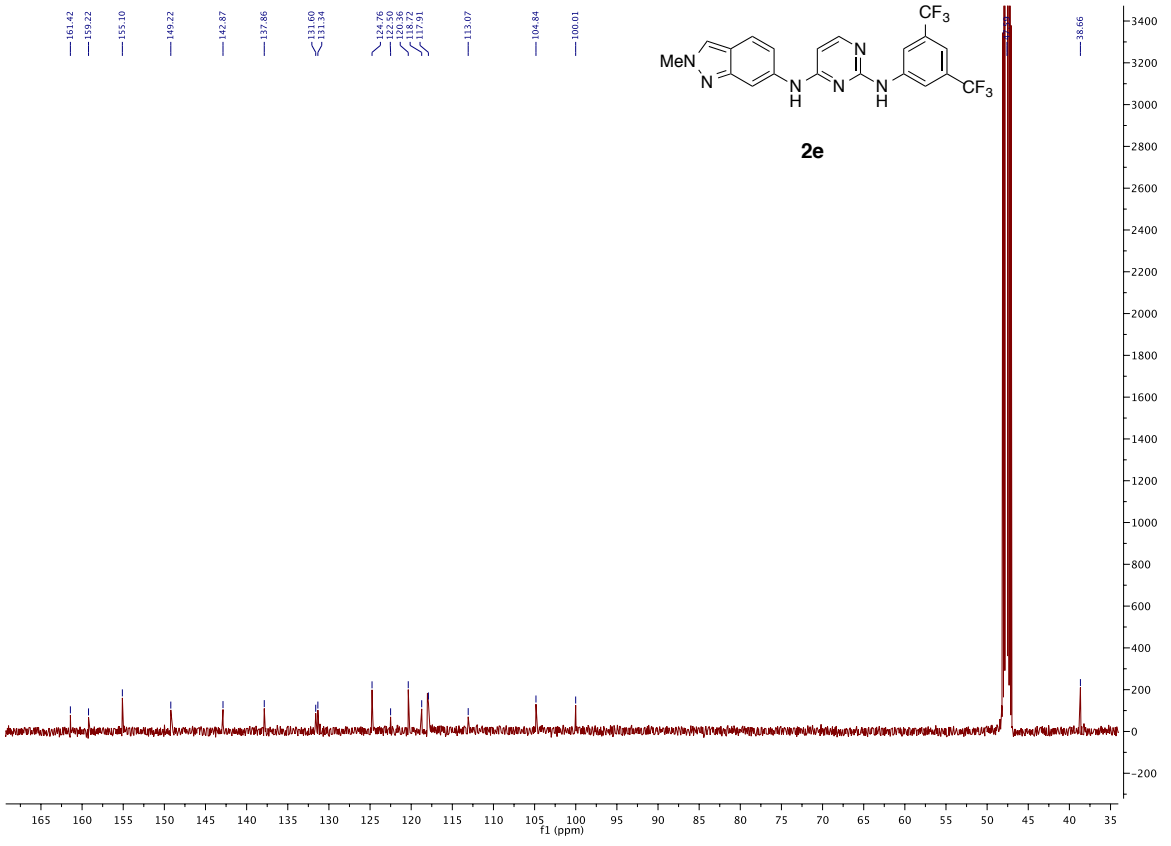

8.17
8.06
7.95
7.58
7.16
7.00
6.22
5.07
3.73
3.63
2.69
2.58
1.97
OMe
OMe
OMe
N
N
N
N
H
N
H
1.00
0.92
1.05
0.88
0.97
2.01
0.96
0.99
3.37
6.81
2.18
2.14
2.19
f1 (ppm)

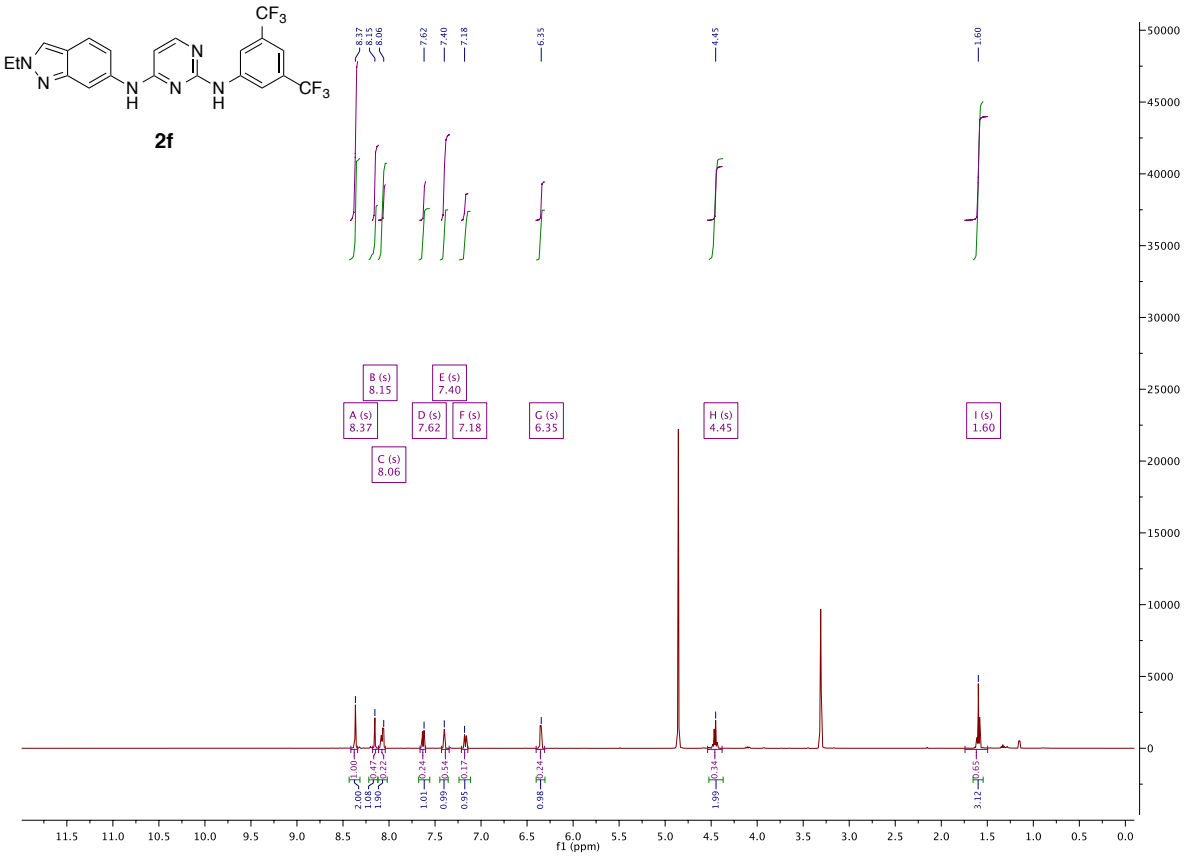
2d

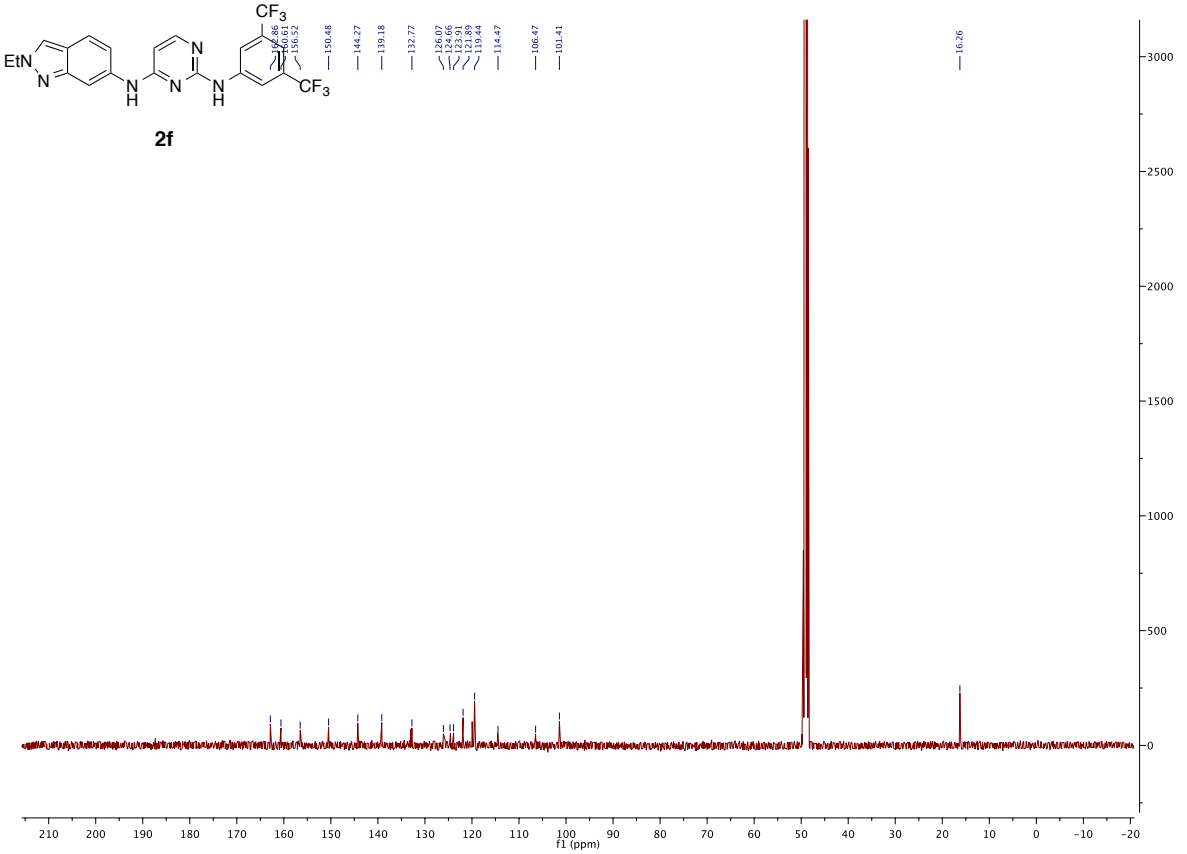

162.80
161.16
156.44
154.34
150.50
139.36
138.17
134.06
123.61
121.83
119.80
119.64
106.74
99.84
98.61
61.24
57.86
56.29
31.43
15.59
OMe
OMe
OMe
N
N
N
N
H
N
H
f1 (ppm)

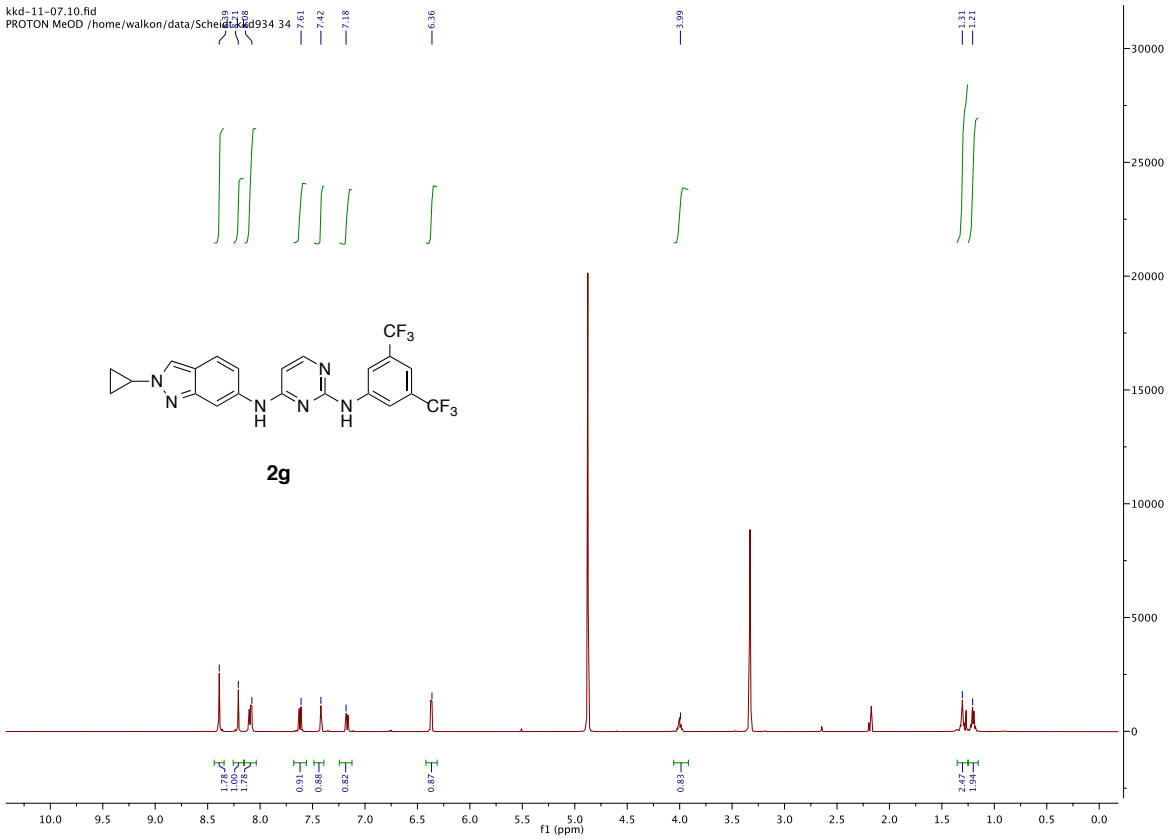
2d

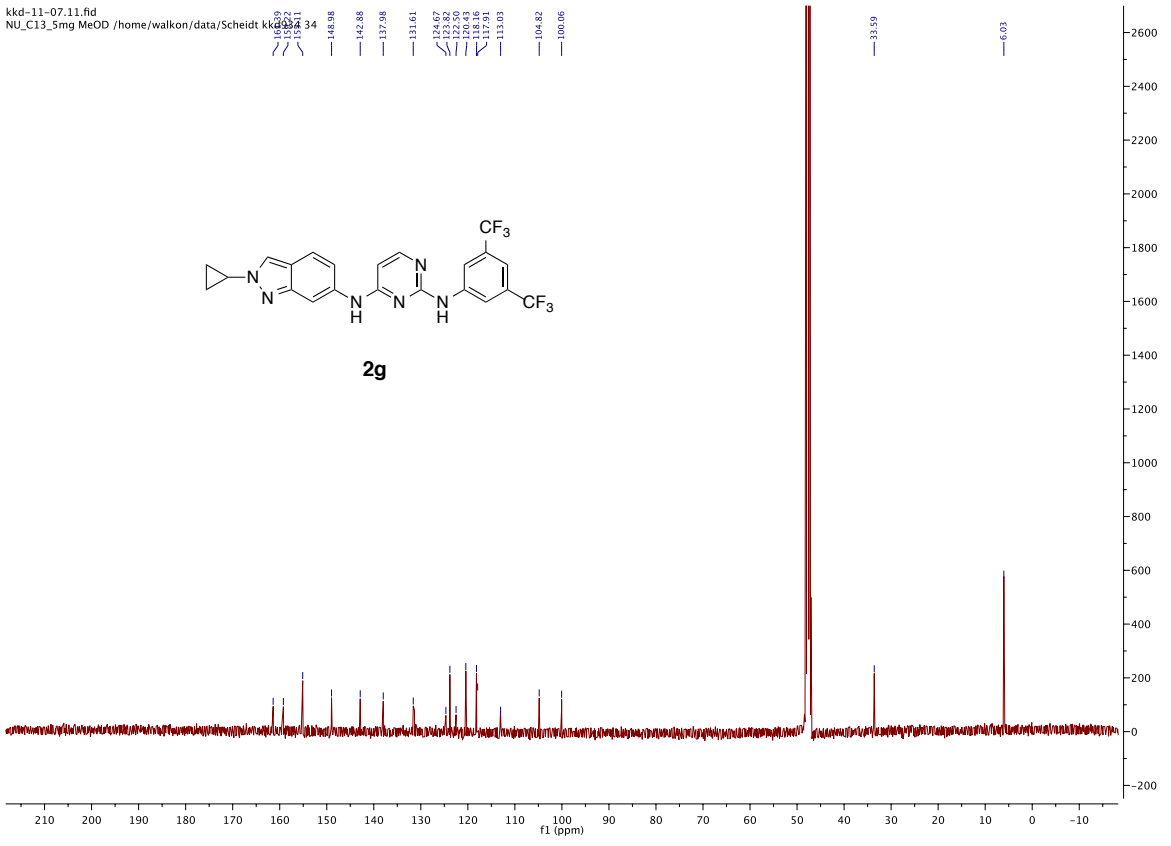

8.37
8.11
8.07
7.61
7.40
7.19
6.35
4.18
B (d) 8.09
D (s) 7.40
A (s) 8.37
C (s) 7.61
E (s) 7.19
F (s) 6.35
G (s) 4.18
2.00
3.04
1.04
1.06
0.99
0.95
3.20
f1 (ppm)
MeN
N
N
H
N
N
N
H
CF3
CF3
2e

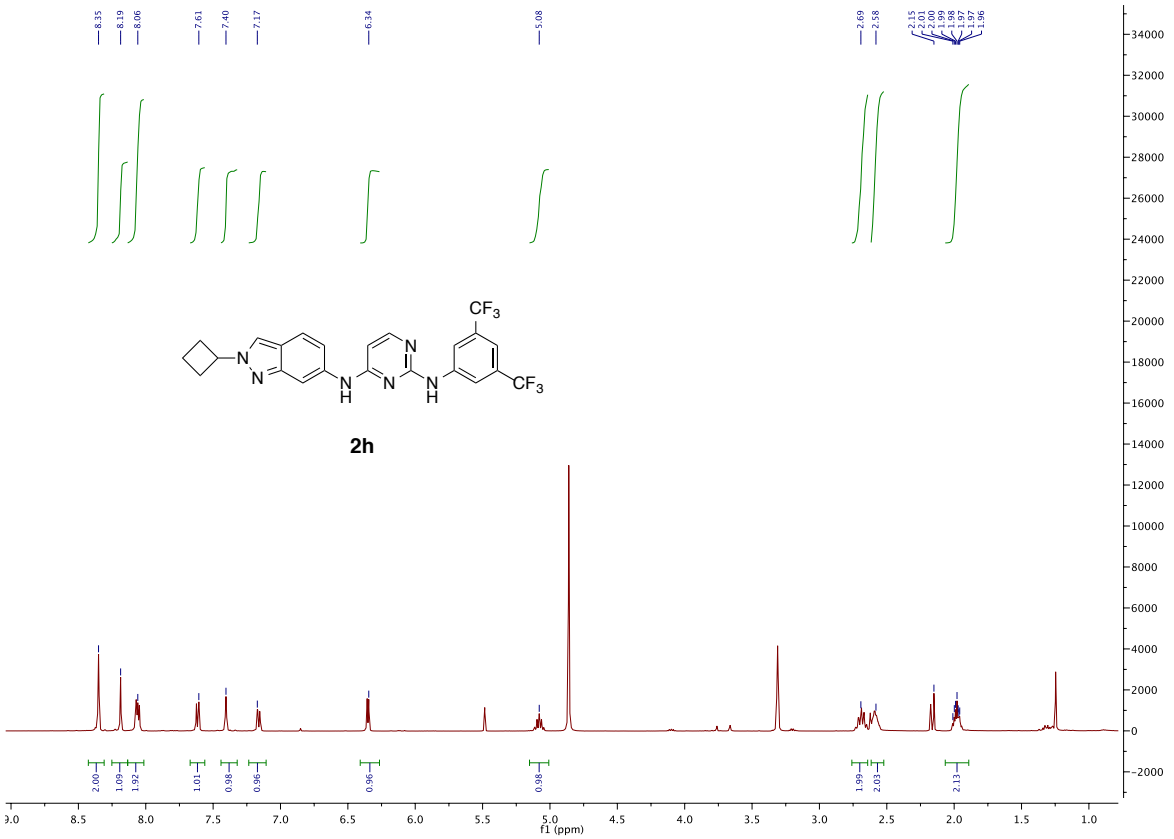

161.42
159.22
155.10
149.22
142.87
137.86
131.60
131.34
124.76
122.50
120.36
118.72
117.91
113.07
104.84
100.01
38.66
f1 (ppm)
MeN
N
N
H
N
N
N
H
CF3
CF3
2e

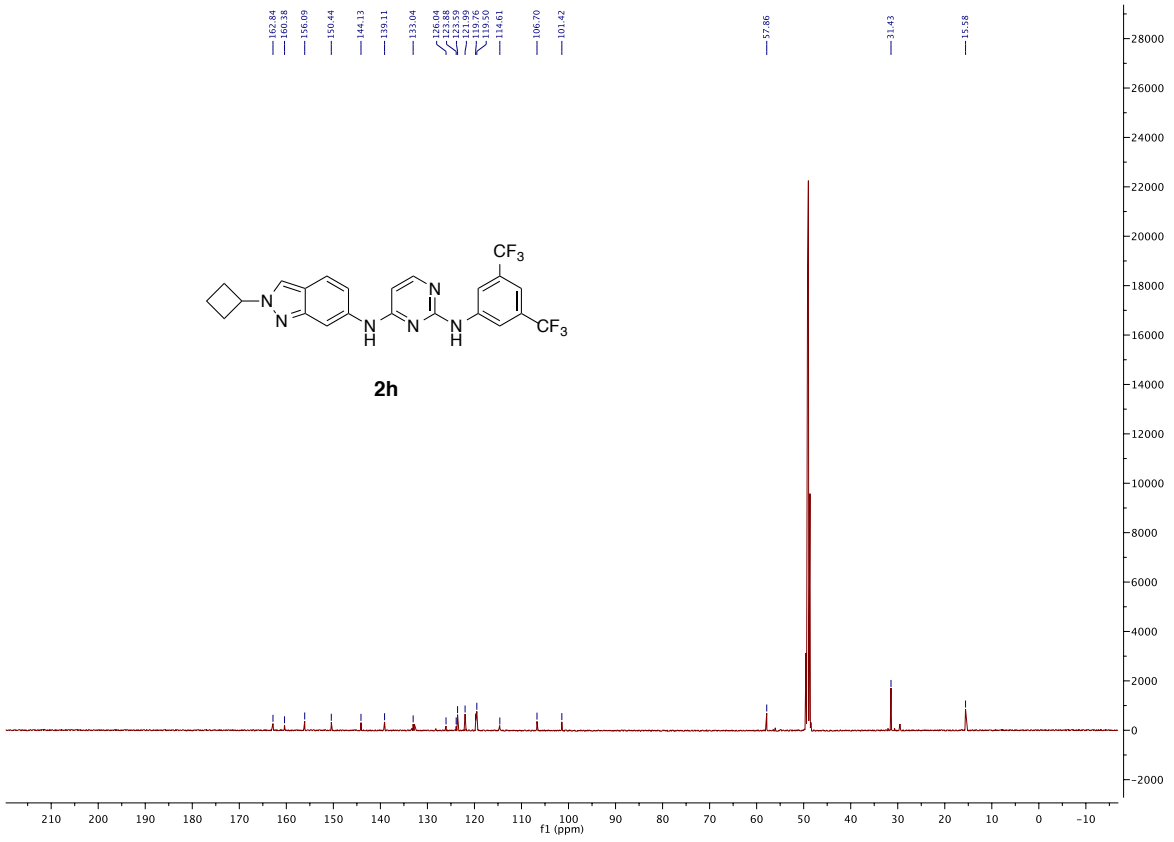

CF3
EtN
N
N
N
H
N
N
H
CF3
2f
8.37
8.15
8.06
7.62
7.40
7.18
6.35
4.45
1.60
B (s) 8.15
E (s) 7.40
A (s) 8.37
D (s) 7.62
F (s) 7.18
G (s) 6.35
H (s) 4.45
I (s) 1.60
C (s) 8.06
f1 (ppm)


CF3
EtN
N
N
N
H
N
N
H
CF3
2f
160.86
160.61
156.52
150.48
144.27
139.18
132.77
126.07
124.66
123.31
121.89
119.44
114.47
106.47
101.41
16.26
f1 (ppm)

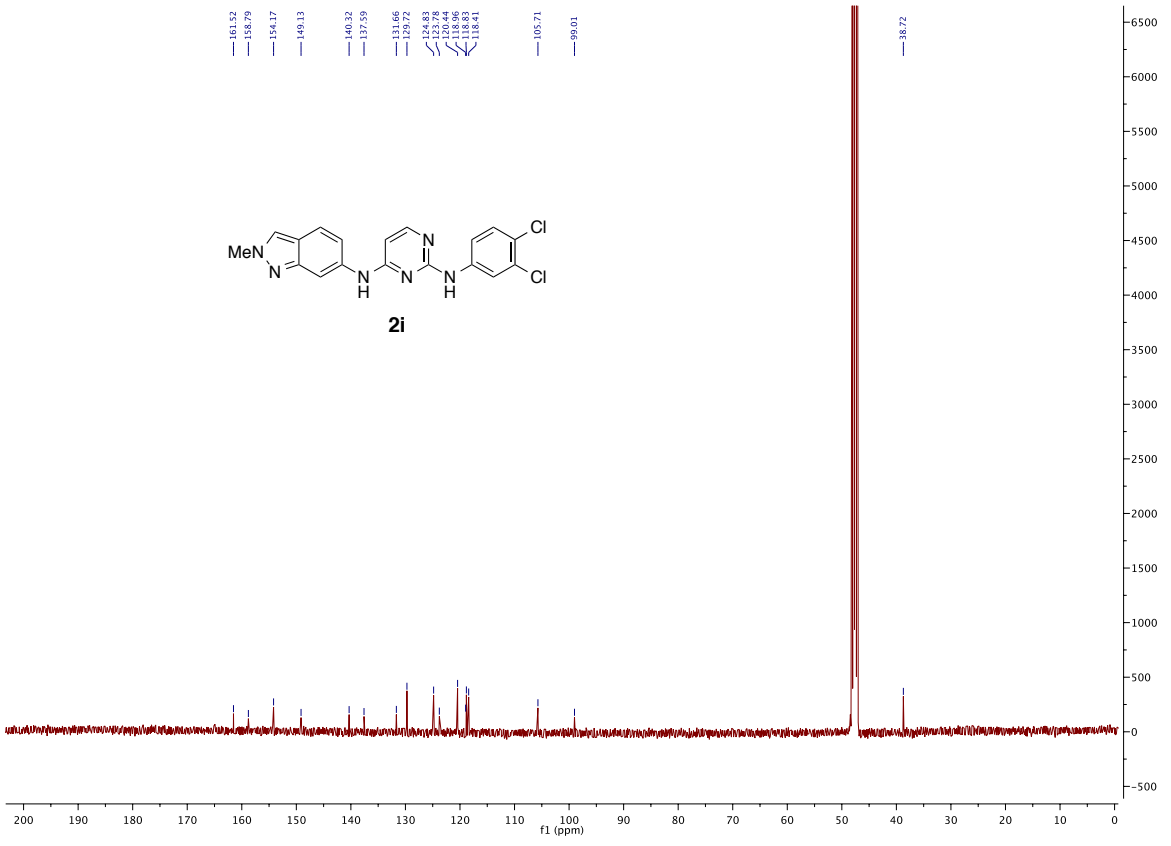

kkd-11-07.10.fid
PROTON MeOD /home/walkon/data/Scheidt/kkd934 34
7.61
7.42
7.18
6.36
3.99
1.31
1.21
CF3
CF3
N
N
N
H
N
N
H
2g
f1 (ppm)

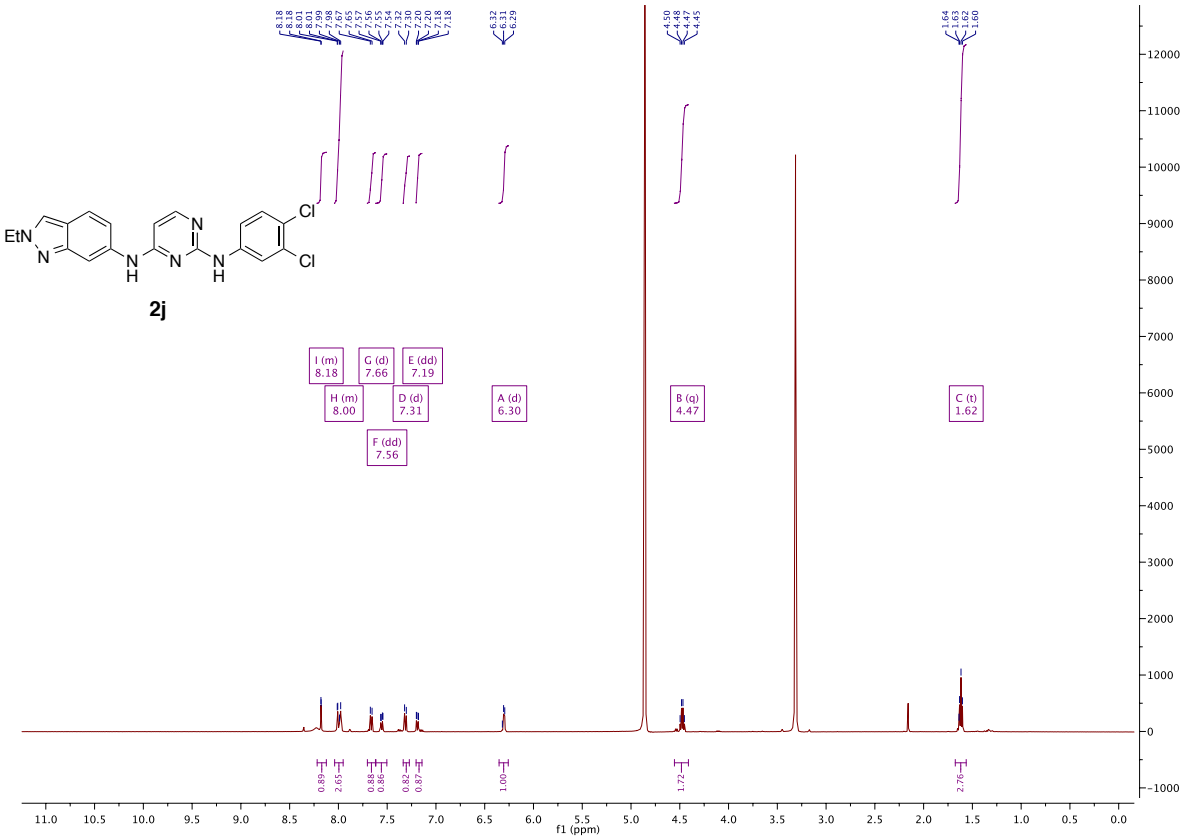

kkd-11-07.11.fid
NU_C13_5mg MeOD /home/walkon/data/Scheidt kkd934 34
148.98
142.88
137.98
131.61
124.67
123.82
122.69
120.43
118.16
117.91
113.03
104.82
100.06
33.59
6.03
CF3
CF3
N
N
N
H
N
N
H
2g
f1 (ppm)

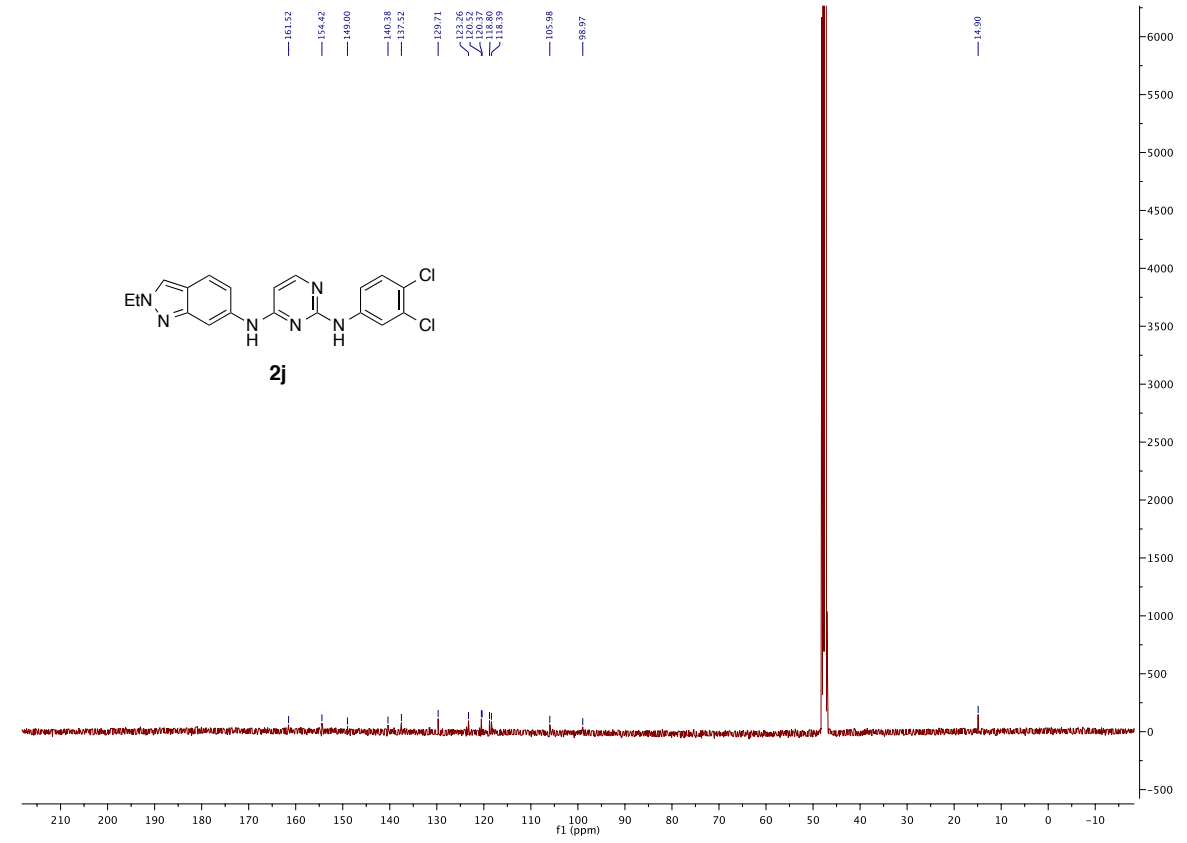

8.35
8.19
8.06
7.61
7.40
7.17
6.34
5.08
2.69
2.58
2.15
2.01
2.00
1.99
1.98
1.97
1.96
CF3
CF3
N
N
N
N
N
H
H
2h
2.00
1.09
1.92
1.01
0.98
0.96
0.96
0.98
1.99
2.03
2.13
f1 (ppm)

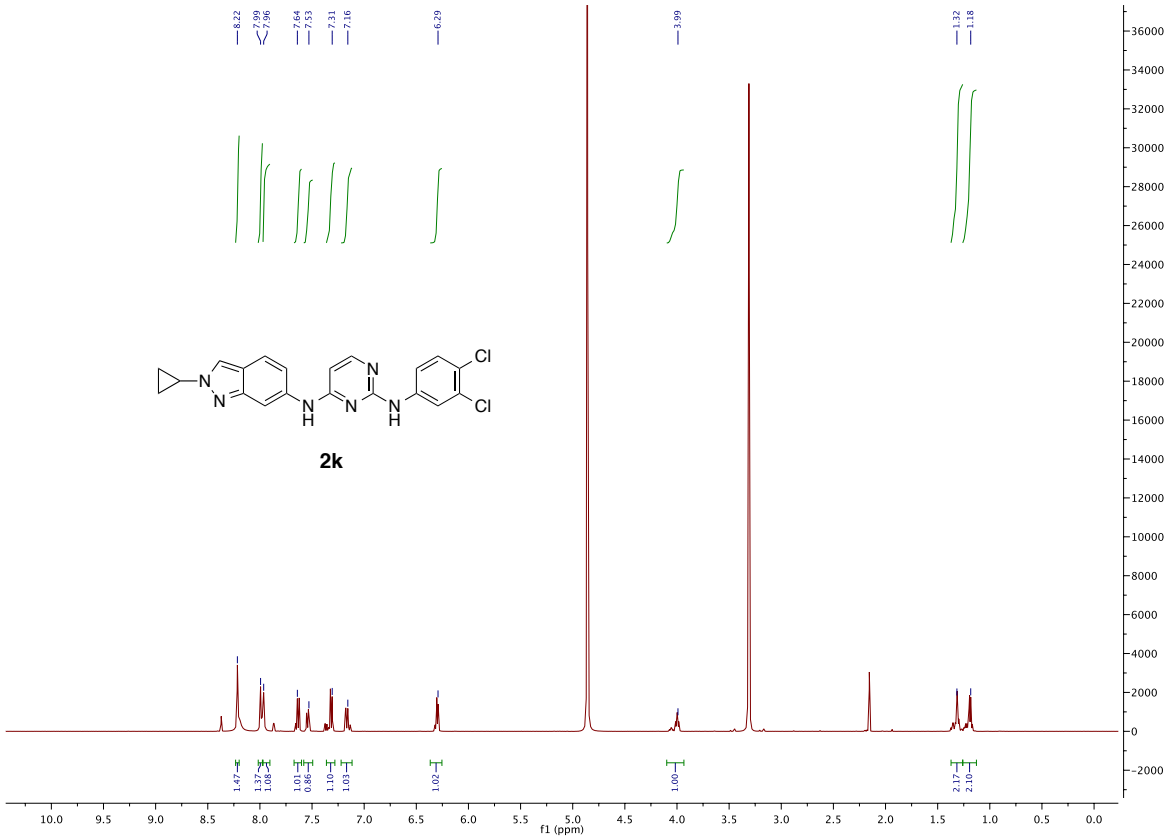

162.84
160.38
156.09
150.44
144.13
139.11
133.04
126.04
123.88
123.59
121.99
119.76
119.50
114.61
106.70
101.42
57.86
31.43
15.58
CF3
CF3
N
N
N
N
N
H
H
2h
f1 (ppm)

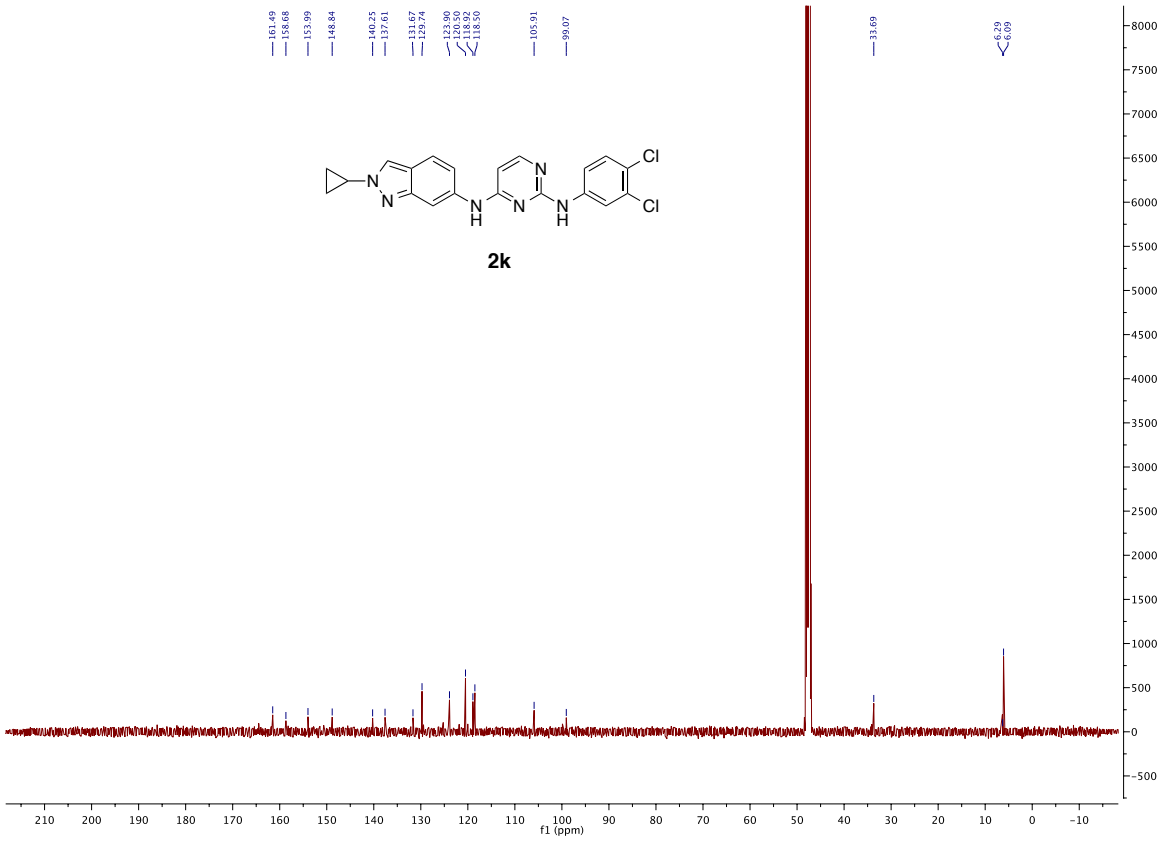

kkd-11-21.20.fid
PROTON MeOD /home/walkon/data/Scheidt kkd934 12
8.23
8.13
8.00
7.95
7.64
7.53
7.32
7.19
6.29
4.19
J (s) 8.23
H (s) 7.95
D (s) 7.32
G (s) 8.00
E (s) 7.64
C (s) 7.19
A (s) 6.29
B (s) 4.19
I (s) 8.13
F (s) 7.53
3.44
2.18
1.41
2.29
1.08
1.86
1.10
2.74
1.00
14.04
f1 (ppm)
MeN
N
N
H
N
N
H
Cl
Cl
2i

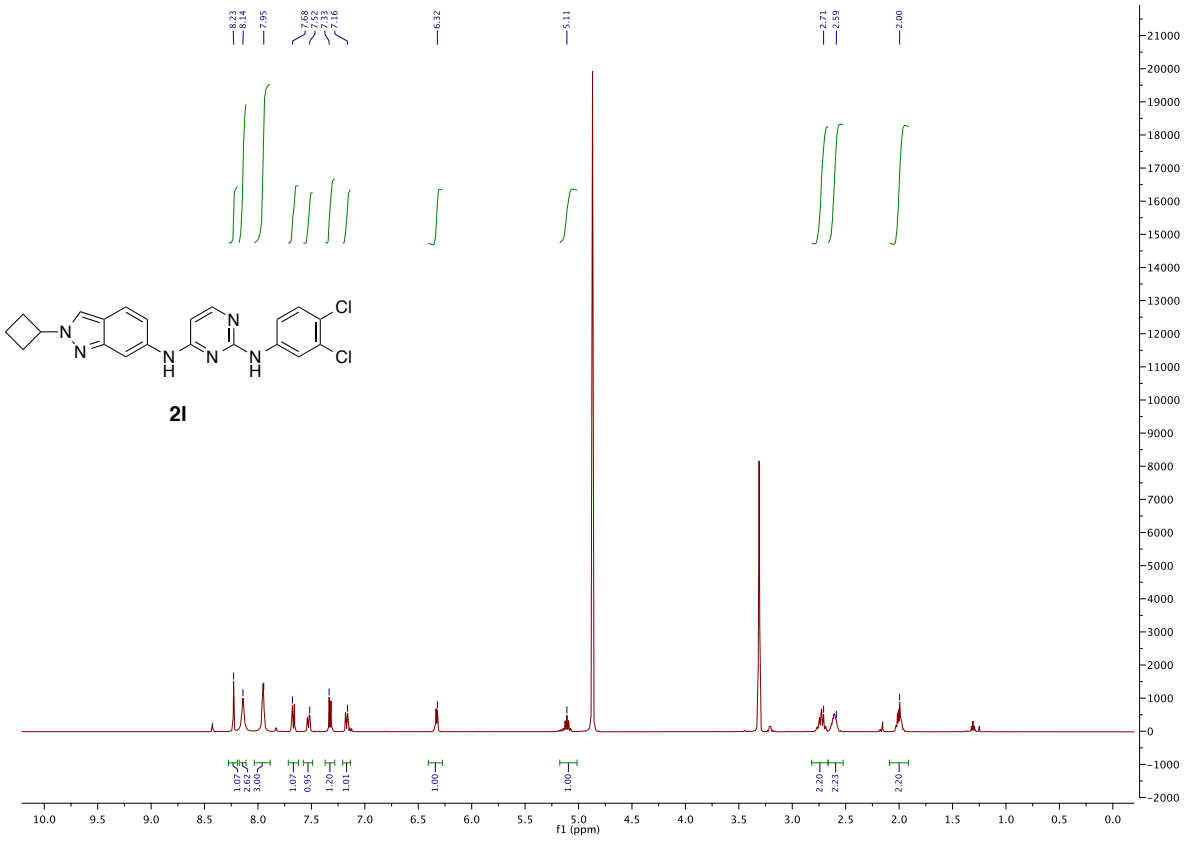

161.52
158.79
154.17
149.13
140.32
137.59
131.66
129.72
124.83
123.78
120.44
118.96
118.83
118.41
105.71
99.01
38.72
f1 (ppm)
MeN
N
N
H
N
N
H
Cl
Cl
2i


2j
I (m) 8.18
H (m) 8.00
G (d) 7.66
F (dd) 7.56
E (dd) 7.19
D (d) 7.31
A (d) 6.30
B (q) 4.47
C (t) 1.62
f1 (ppm)

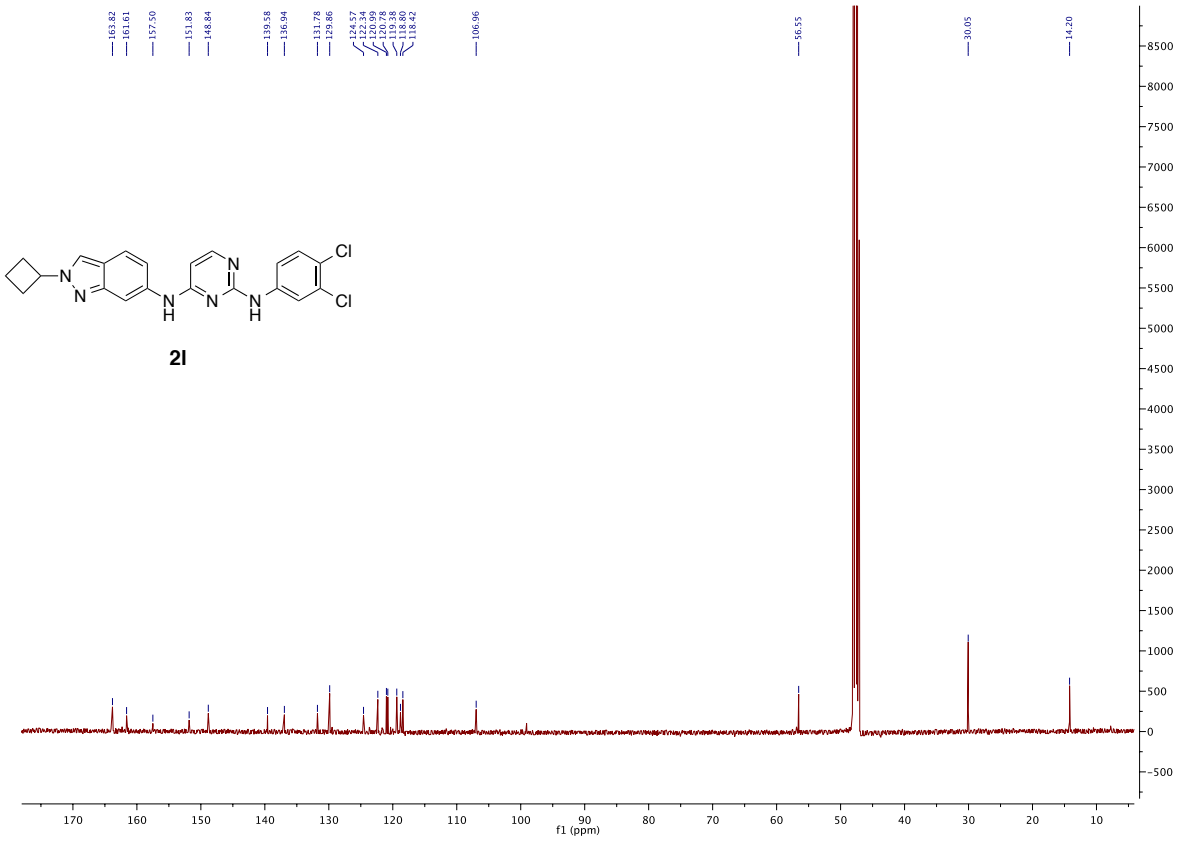

2j
f1 (ppm)


8.22
7.99
7.96
7.64
7.53
7.31
7.16
6.29
3.99
1.32
1.18
Cl
Cl
2k
1.47
1.37
1.08
1.01
0.86
1.10
1.03
1.02
1.00
2.17
2.10
f1 (ppm)

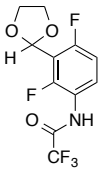

161.49
158.68
153.99
148.84
140.25
137.61
131.67
129.74
123.90
120.55
118.92
118.50
105.91
99.07
33.69
6.29
6.09
Cl
Cl
2k
f1 (ppm)


8.23
8.14
7.95
7.68
7.52
7.33
7.16
6.32
5.11
2.71
2.59
2.00
1.07
2.02
3.00
1.07
0.95
1.20
1.01
1.00
1.00
2.20
2.23
2.20
Cl
Cl
f1 (ppm)

2l

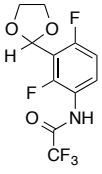

163.82
161.61
157.50
151.83
148.84
139.58
136.94
131.78
129.86
124.57
122.34
121.98
120.78
119.38
118.60
118.42
106.96
56.55
30.05
14.20
Cl
Cl
f1 (ppm)

2l



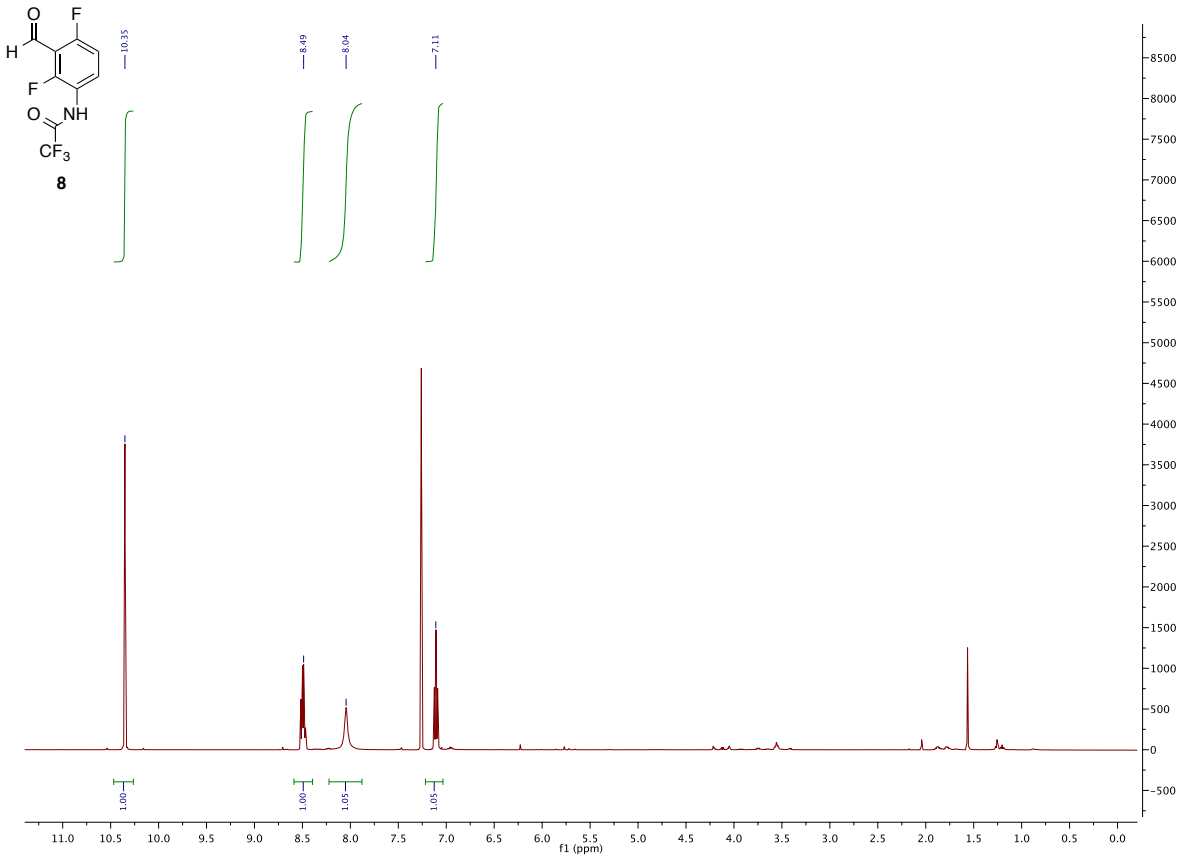
7

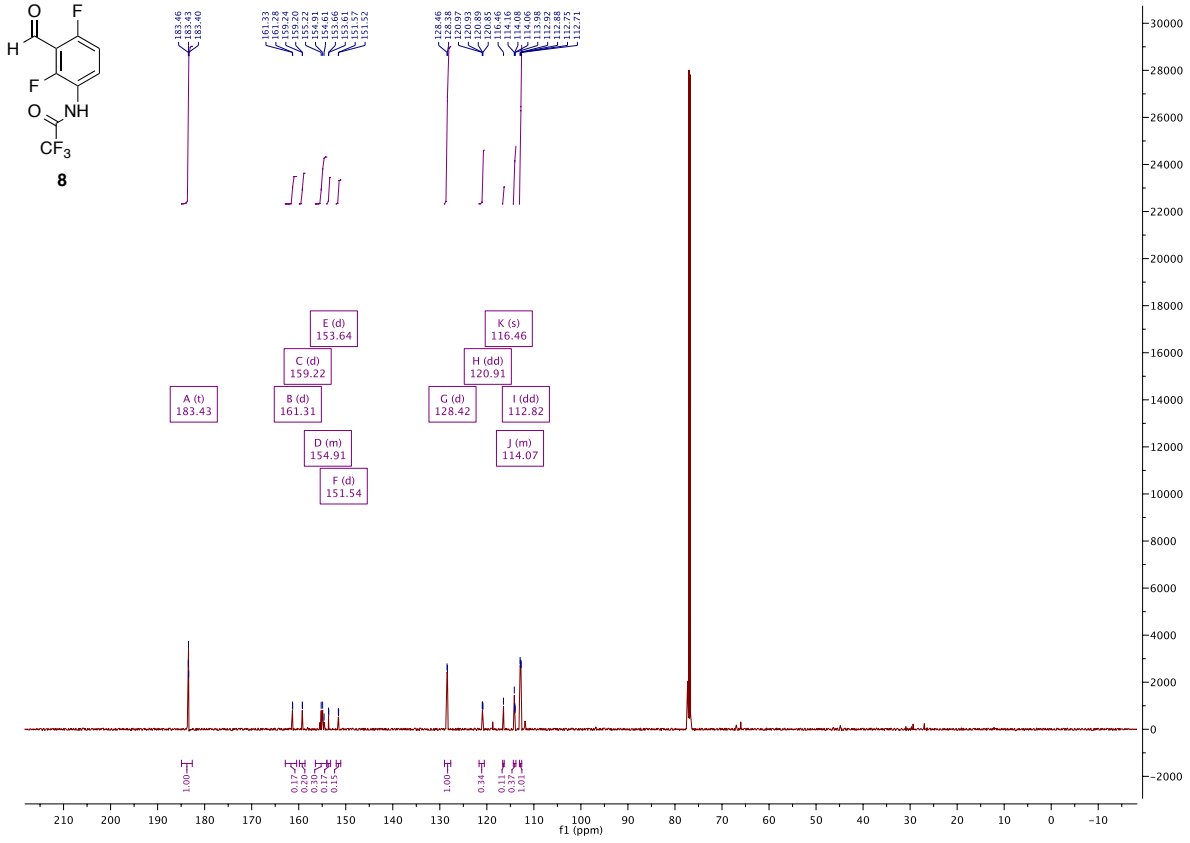
8.23
7.99
6.96
6.23
4.22
4.05
1.05
0.97
1.05
1.00
2.15
2.21
f1 (ppm)

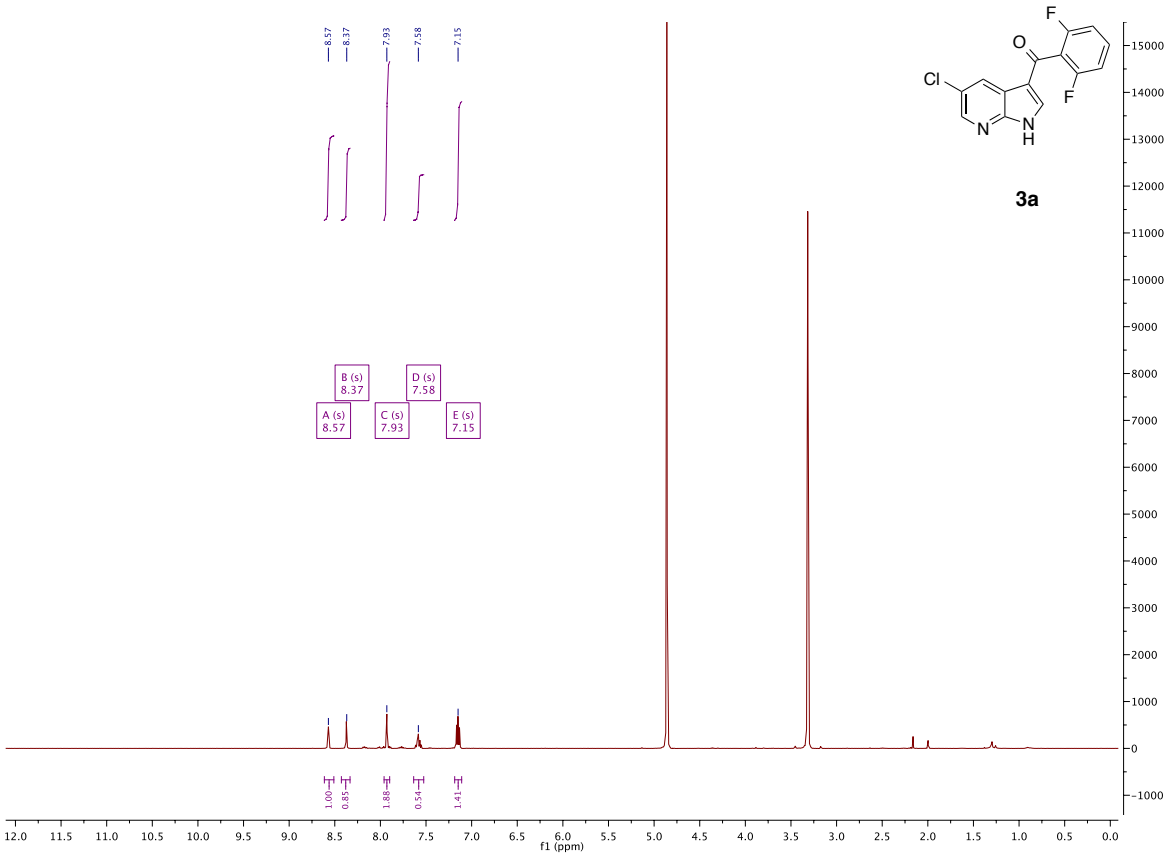


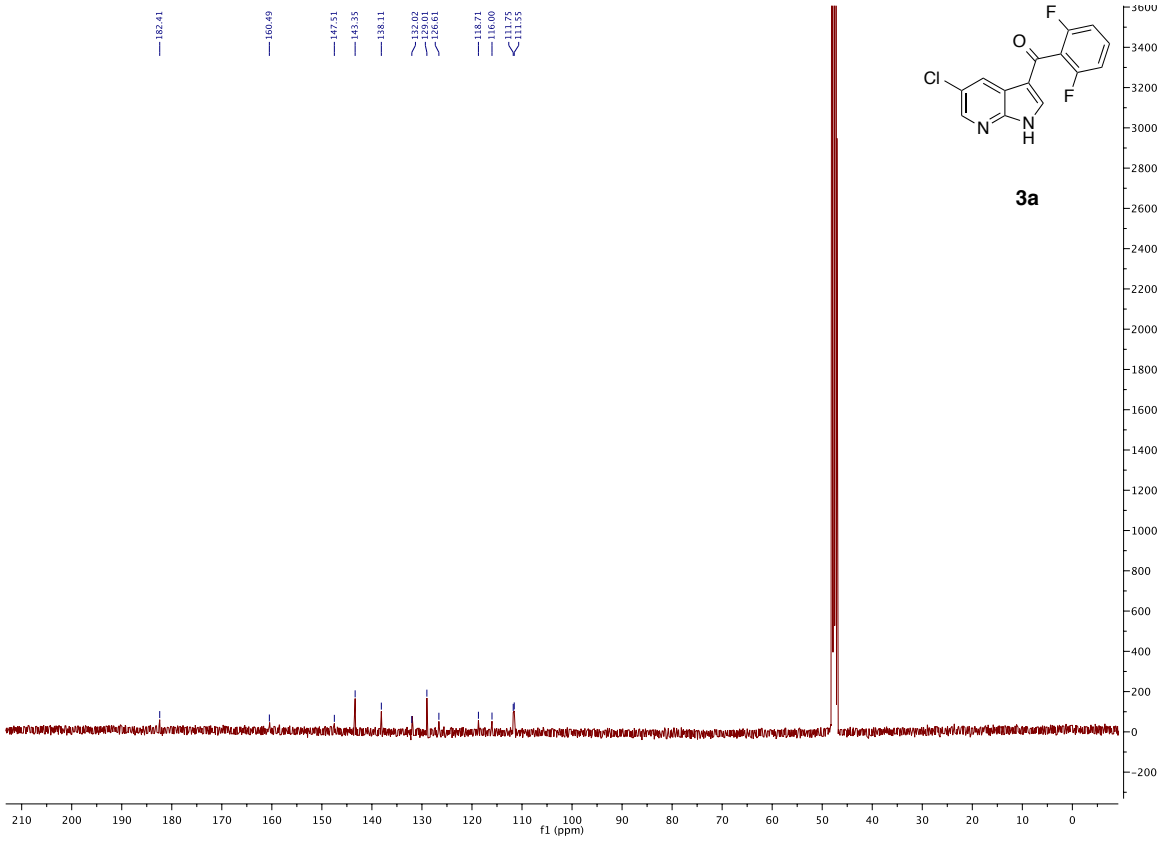
7

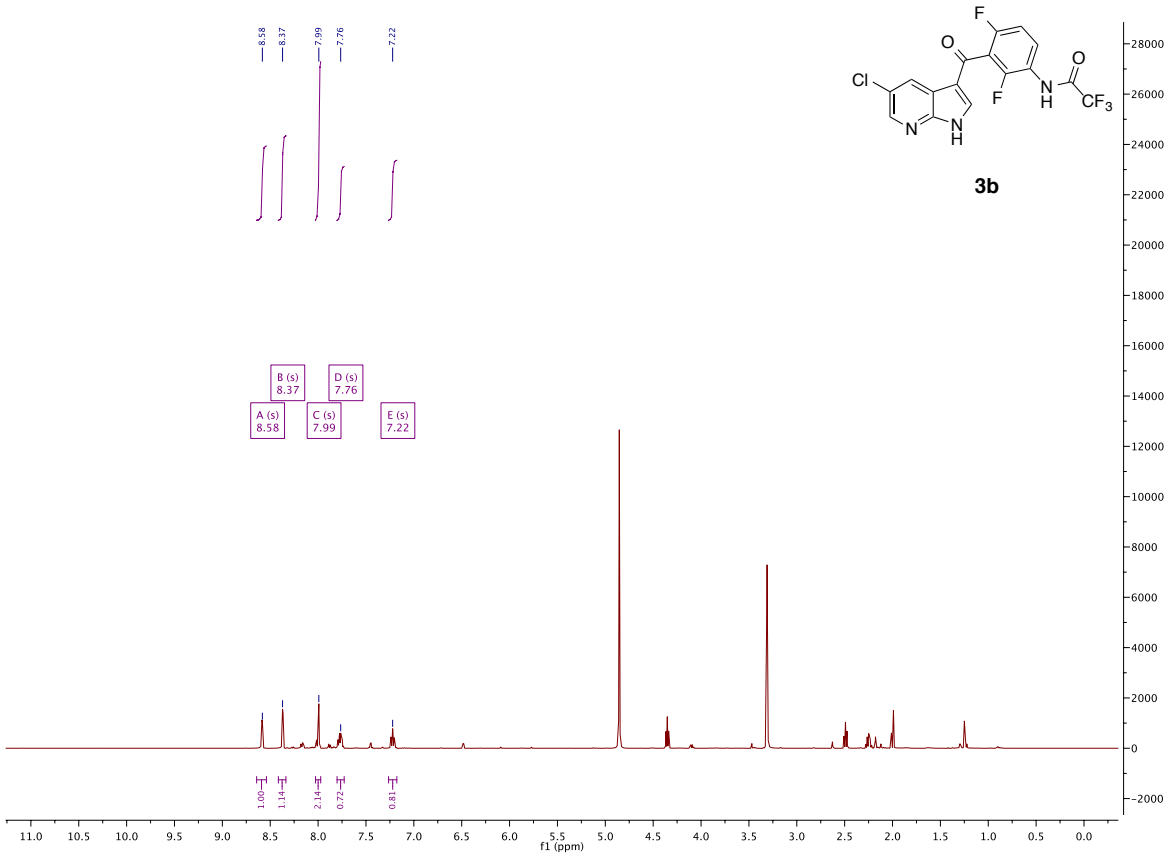
159.56
157.55
154.87
154.56
123.75
150.68
123.37
111.99
96.82
66.02
45.67
8.51
f1 (ppm)

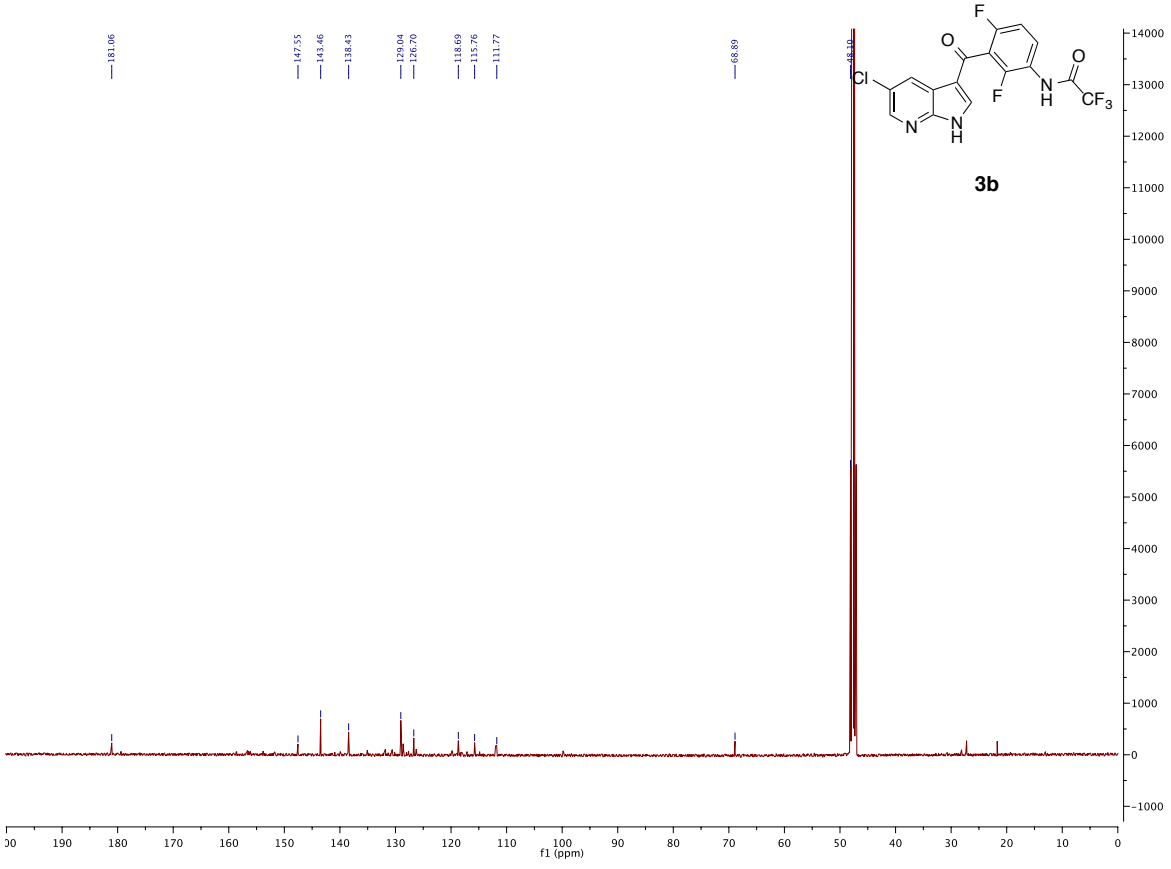

8
10.35
8.49
8.04
7.11
1.00
1.00
1.05
1.05
f1 (ppm)

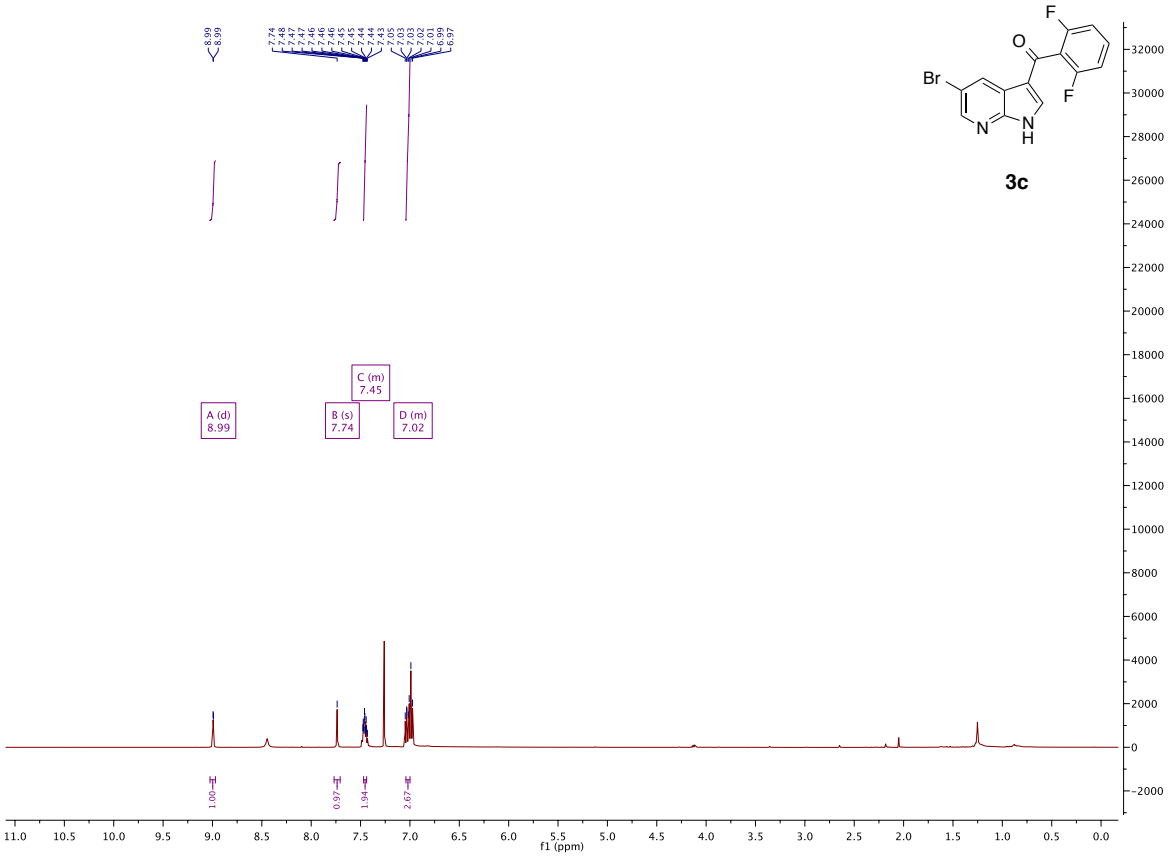

8
A (t) 183.43
B (d) 161.31
C (d) 159.22
D (m) 154.91
E (d) 153.64
F (d) 151.54
G (d) 128.42
H (dd) 120.91
I (dd) 112.82
J (m) 114.07
K (s) 116.46
f1 (ppm)

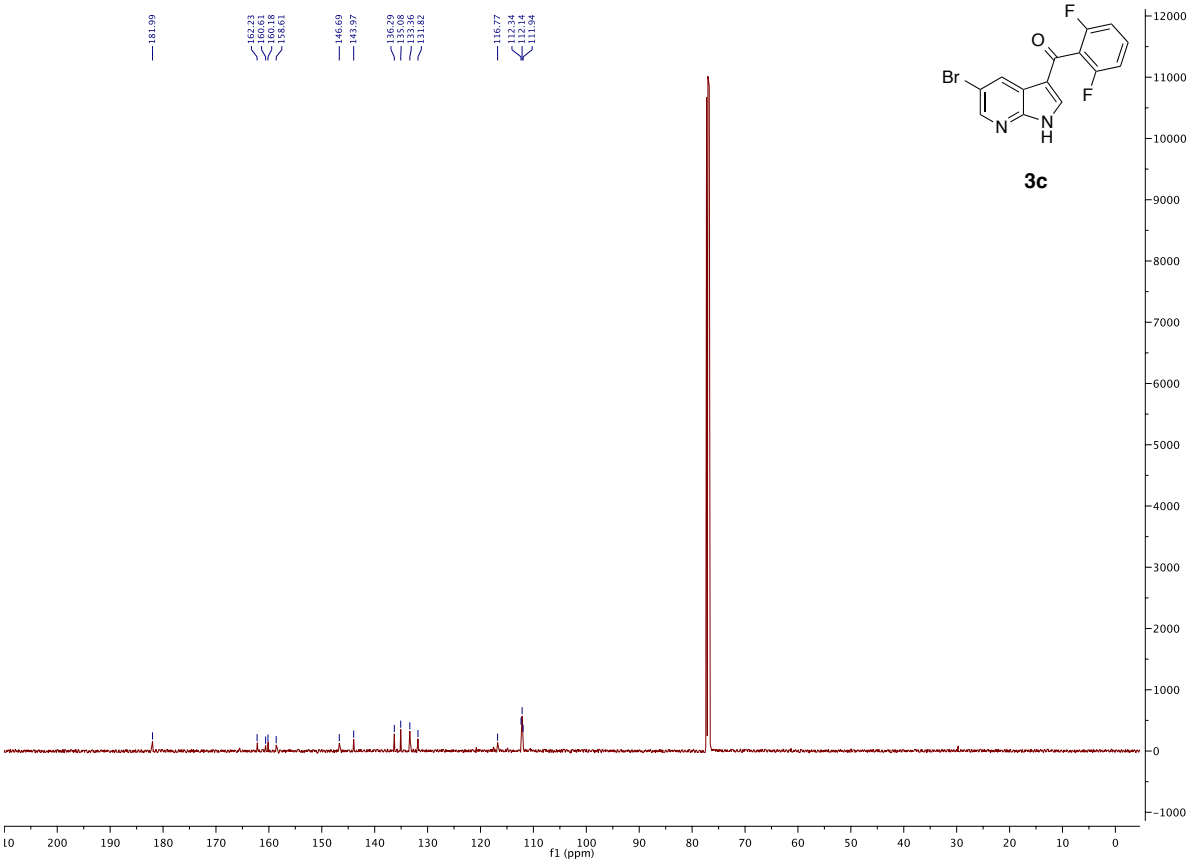

8.57
8.37
7.93
7.58
7.15
B (s) 8.37
D (s) 7.58
A (s) 8.57
C (s) 7.93
E (s) 7.15
1.00
0.85
1.88
0.54
1.41
f1 (ppm)
3a

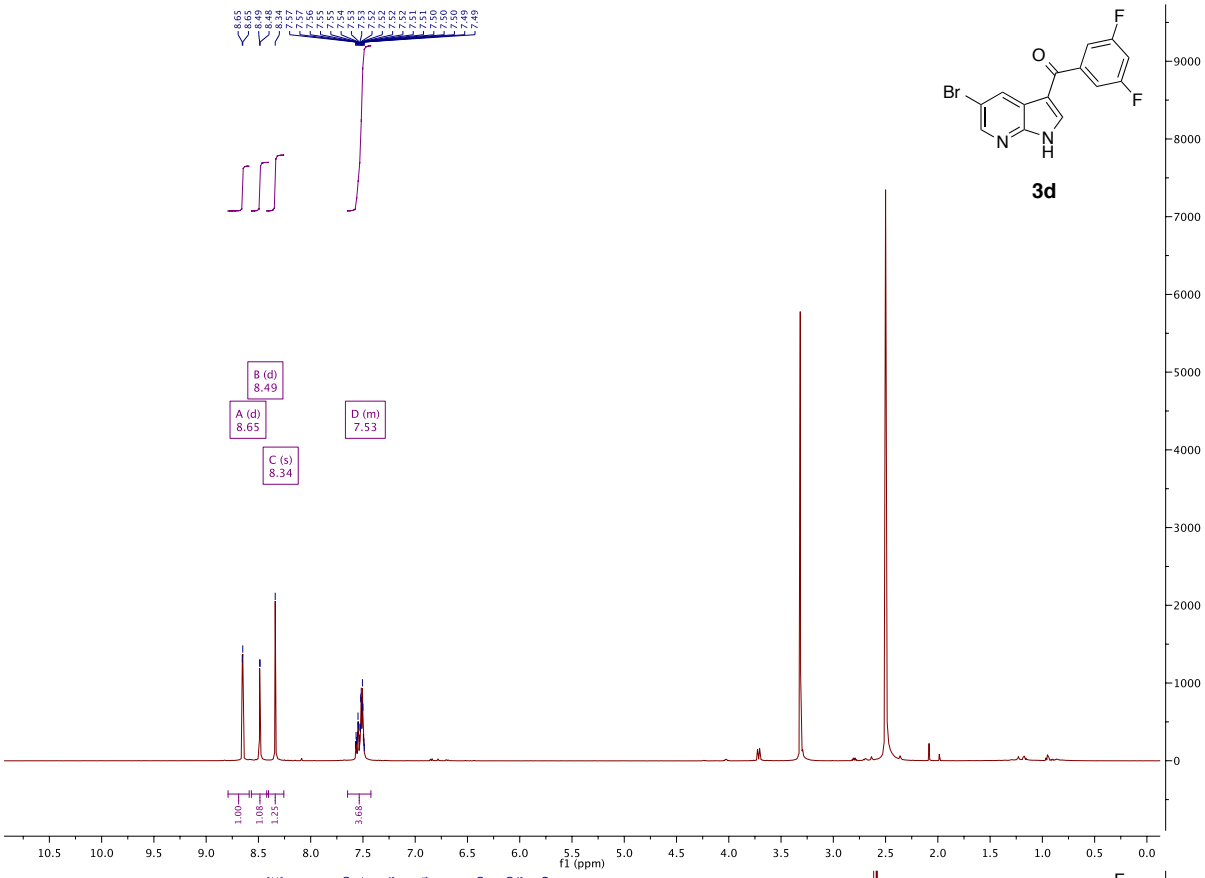

182.41
160.49
147.51
143.35
138.11
132.02
129.01
126.61
118.71
116.00
111.75
111.55
f1 (ppm)
3a

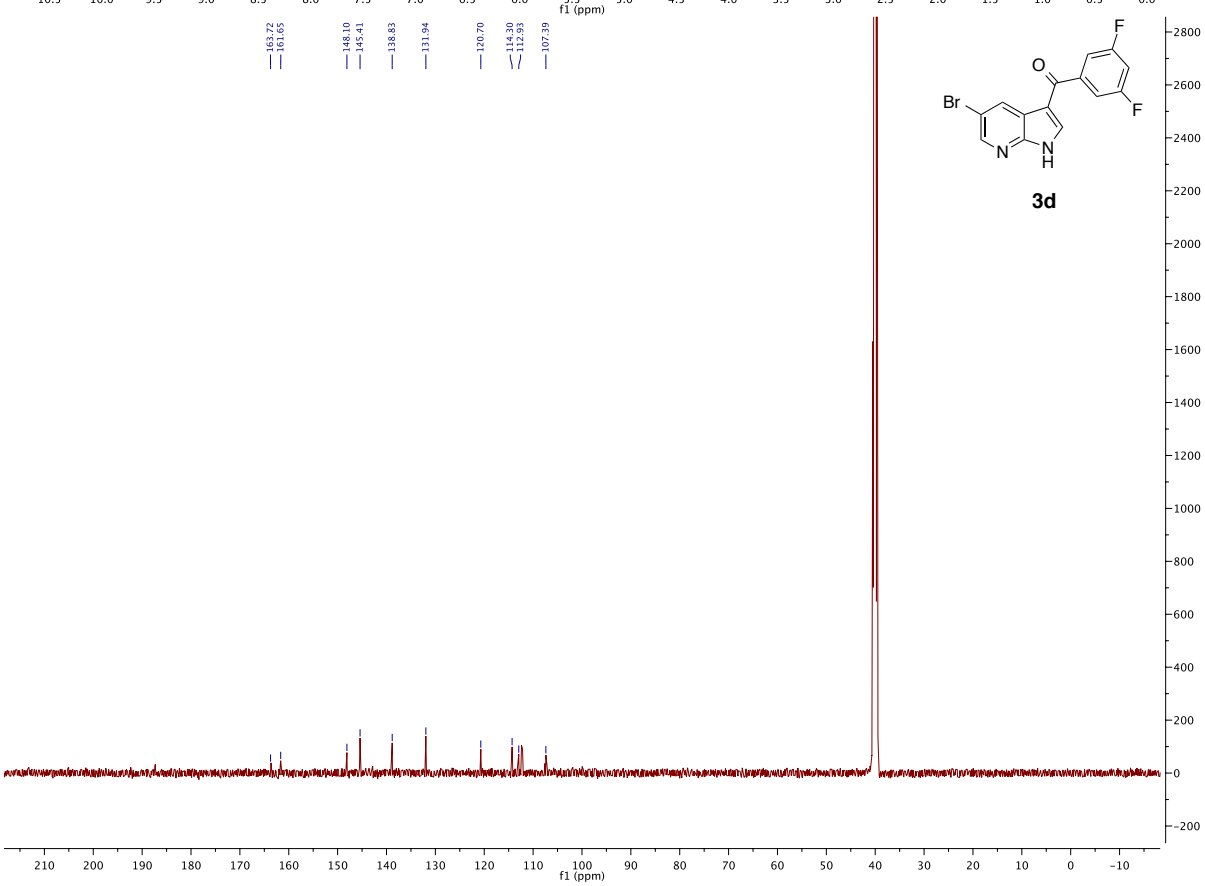

8.58
8.37
7.99
7.76
7.22
B (s) 8.37
D (s) 7.76
A (s) 8.58
C (s) 7.99
E (s) 7.22
1.00
1.14
2.14
0.72
0.81
f1 (ppm)
3b

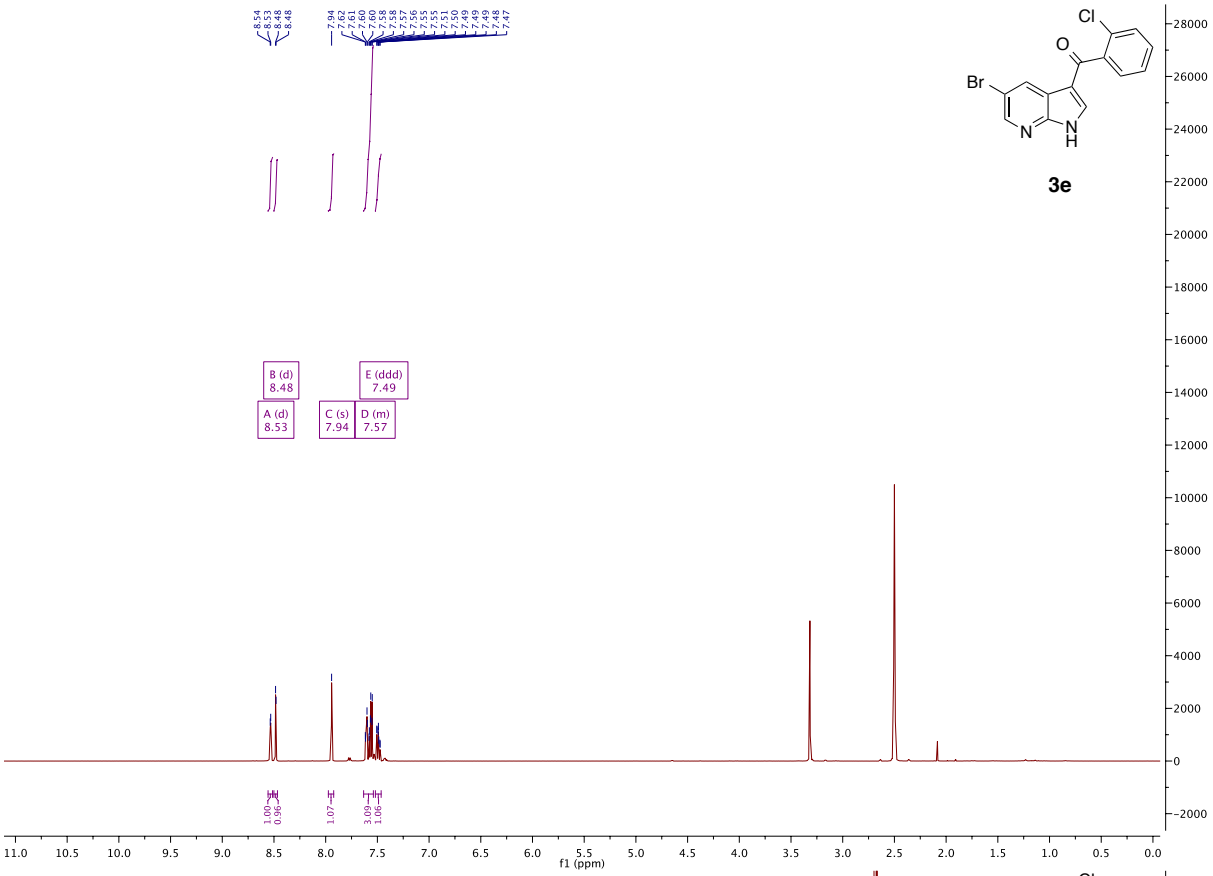

181.06
147.55
143.46
138.43
129.04
126.70
118.69
115.76
111.77
68.89
f1 (ppm)
3b

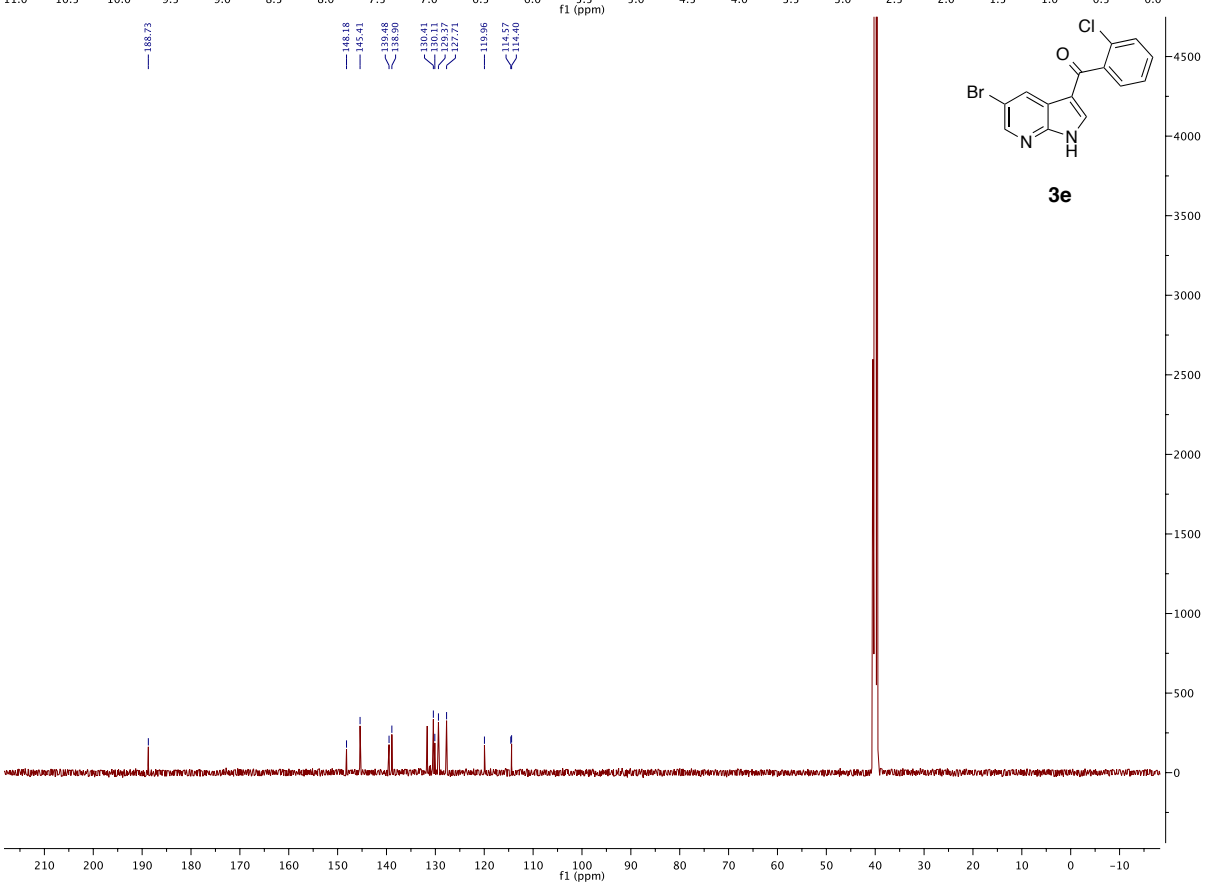

3c
A (d) 8.99
B (s) 7.74
C (m) 7.45
D (m) 7.02
f1 (ppm)

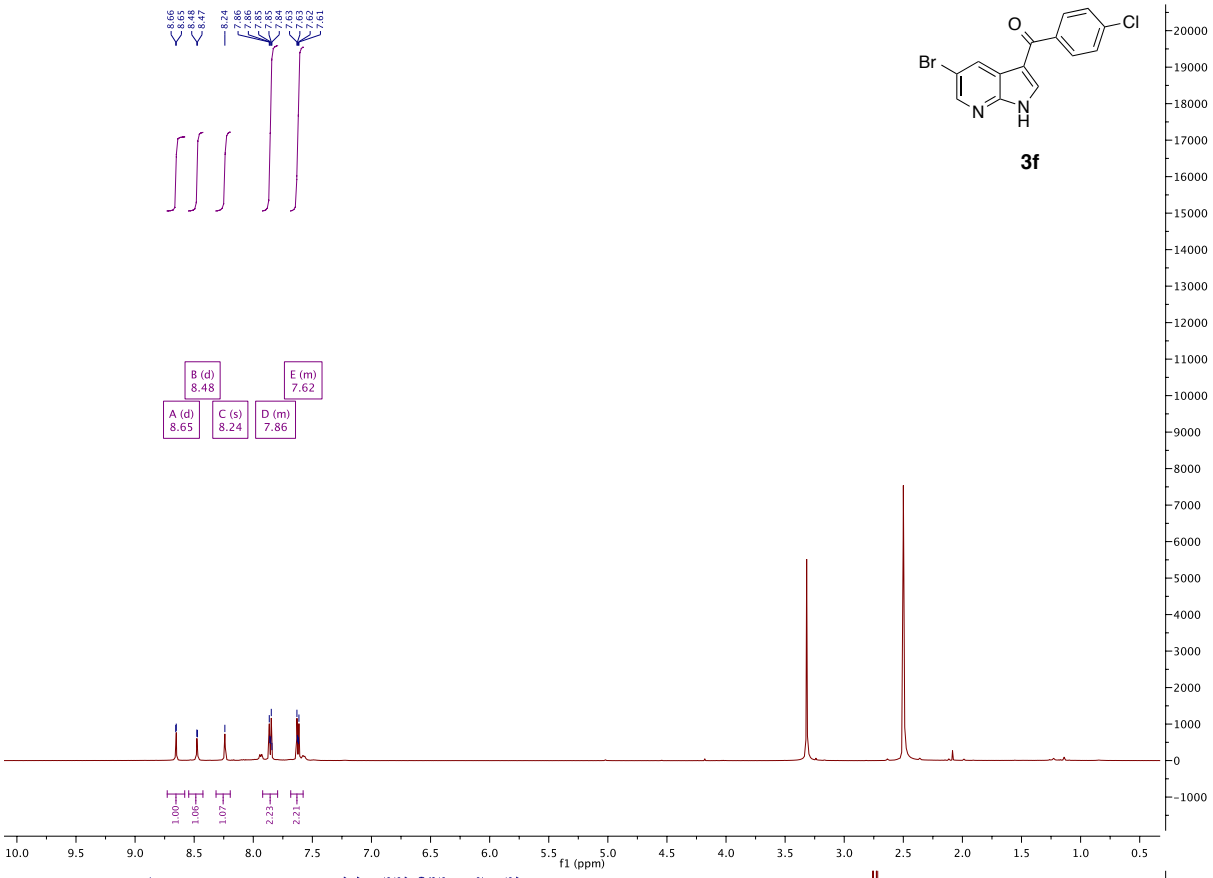

3c
f1 (ppm)

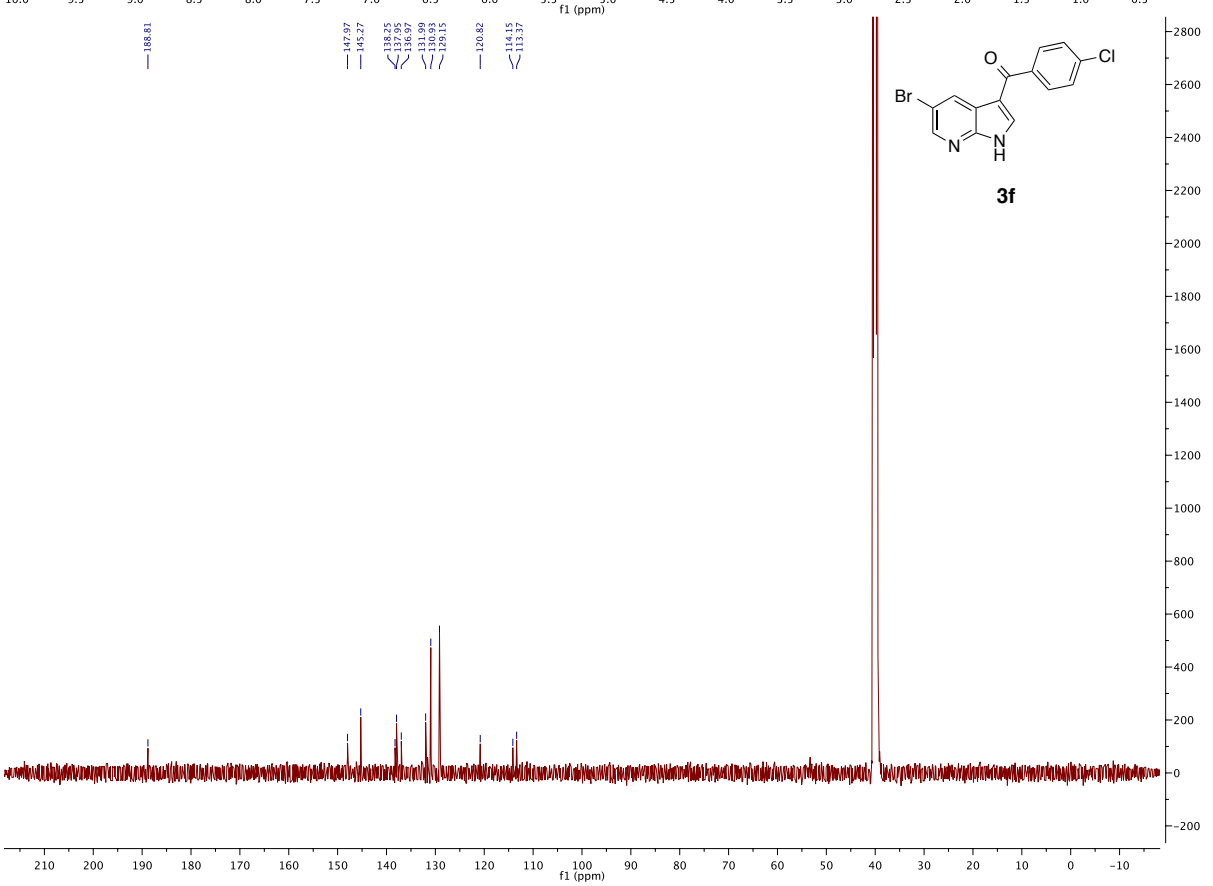

8.65
8.65
8.49
8.48
8.34
7.57
7.57
7.56
7.55
7.55
7.54
7.53
7.53
7.52
7.52
7.52
7.51
7.51
7.50
7.50
7.49
7.49
B (d)
8.49
A (d)
8.65
C (s)
8.34
D (m)
7.53
1.00
1.08
1.25
3.68
f1 (ppm)
F
O
Br
F
N
N
H
3d


163.72
161.65
148.10
145.41
138.83
131.94
120.70
114.30
112.93
107.39
f1 (ppm)
F
O
Br
F
N
N
H
3d


8.54
8.53
8.48
8.48
7.94
7.62
7.61
7.60
7.60
7.58
7.58
7.57
7.56
7.55
7.55
7.51
7.50
7.49
7.49
7.49
7.48
7.47
B (d) 8.48
E (ddd) 7.49
A (d) 8.53
C (s) 7.94
D (m) 7.57
1.00
0.98
1.07
3.09
1.06
f1 (ppm)
Cl
O
Br
N
H
3e


188.73
148.18
145.41
139.48
138.90
130.41
130.11
129.37
127.71
119.96
114.57
114.40
f1 (ppm)
Cl
O
Br
N
H
3e


8.66
8.65
8.48
8.47
8.24
7.86
7.85
7.84
7.63
7.62
7.61
B (d)
8.48
E (m)
7.62
A (d)
8.65
C (s)
8.24
D (m)
7.86
1.00
1.06
1.07
2.23
2.21
f1 (ppm)
Br
Cl
O
N
H
3f


188.81
147.97
145.27
138.25
137.95
136.97
131.99
130.38
129.15
120.82
114.15
113.37
f1 (ppm)
Br
Cl
O
N
H
3f