

Supporting Information for:

***In silico* Structure-guided Optimization and Molecular Simulation Studies of 3-Phenoxy-4-(3-Trifluoromethylphenyl)pyridazines as Potent Phytoene Desaturase Inhibitors**

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Table S1. The structures, yields, and clog*P* of compounds **2-5**.

compd	R <sup>1</sup>	R <sup>2</sup>	yield/%	clog <i>P</i>
<b>2a</b>	-CH <sub>3</sub>	4-CF <sub>3</sub>	85	5.16
<b>2b</b>	-CH <sub>3</sub>	3-F	60	5.32
<b>2c</b>	-CH <sub>3</sub>	3,4-diF	85	5.44
<b>2d</b>	-CH <sub>3</sub>	3-F,4-Cl	75	6.08
<b>2e</b>	-CH <sub>3</sub>	3-F,4-Br	82	6.23
<b>2f</b>	-CH <sub>3</sub>	3-F,4-CN	75	5.00
<b>2g</b>	-CH <sub>3</sub>	2-F,4-Cl	78	5.85
<b>2h</b>	-CH <sub>3</sub>	3,4,5-triF	65	5.53
<b>3a</b>	-CH <sub>2</sub> CH <sub>3</sub>	4-CF <sub>3</sub>	60	6.70
<b>3b</b>	-CH <sub>2</sub> CH <sub>3</sub>	3-F	60	5.85
<b>3c</b>	-CH <sub>2</sub> CH <sub>3</sub>	3,4-diF	50	5.97
<b>3d</b>	-CH <sub>2</sub> CH <sub>3</sub>	3-F,4-Cl	50	6.61
<b>3e</b>	-CH <sub>2</sub> CH <sub>3</sub>	3-F,4-Br	50	6.76
<b>3f</b>	-CH <sub>2</sub> CH <sub>3</sub>	3-F,4-CN	60	5.52
<b>3g</b>	-CH <sub>2</sub> CH <sub>3</sub>	2-F,4-Cl	55	5.84
<b>3h</b>	-CH <sub>2</sub> CH <sub>3</sub>	3,4,5-triF	50	6.06
<b>3i</b>	-CH <sub>2</sub> CH <sub>3</sub>	4-CN	65	5.33
<b>4a</b>		4-CF <sub>3</sub>	35	6.66
<b>4b</b>		3-F	25	5.81
<b>4c</b>		3,4-diF	25	5.94
<b>4d</b>		3-F,4-Cl	30	6.58
<b>4e</b>		3-F,4-Br	25	6.73
<b>4f</b>		3-F,4-CN	20	5.48
<b>4g</b>		2-F,4-Cl	30	6.35
<b>4h</b>		3,4,5-triF	30	6.03
<b>4i</b>		4-CN	30	5.29
<b>5a</b>		4-CF <sub>3</sub>	40	6.09
<b>5b</b>	-CH(CH <sub>3</sub> ) <sub>2</sub>	3-F	60	5.35
<b>5c</b>	-CH(CH <sub>3</sub> ) <sub>2</sub>	3-F,4-F	60	5.42
<b>5d</b>	-CH(CH <sub>3</sub> ) <sub>2</sub>	3-F,4-Cl	45	6.06
<b>5e</b>	-CH(CH <sub>3</sub> ) <sub>2</sub>	3-F,4-Br	55	6.21
<b>5f</b>	-CH(CH <sub>3</sub> ) <sub>2</sub>	3-F,4-CN	50	4.78
<b>5g</b>	-CH(CH <sub>3</sub> ) <sub>2</sub>	2-F,4-Cl	45	5.86
<b>5h</b>	-CH(CH <sub>3</sub> ) <sub>2</sub>	3,4,5-triF	50	5.49
<b>5i</b>	-CH(CH <sub>3</sub> ) <sub>2</sub>	4-CN	65	6.78

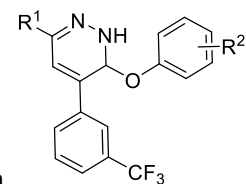


Table S2. The pre-emergence herbicidal activity of compounds **1-5** and diflufenican.

compd	R <sup>1</sup>	R <sup>2</sup>	dosage g ai /ha	ECHCG	DIGSA	SETFA	ABUJU	AMARE	ECLPR
<b>2a</b>	-CH <sub>3</sub>	4-CF <sub>3</sub>	750	8	10	9	5	10	9
			600	8	10	9	1	10	8
			300	7	10	9	1	10	7
			150	3	10	4	1	9	3
<b>2b</b>	-CH <sub>3</sub>	3-F	750	1	4	1	1	3	1
<b>2c</b>	-CH <sub>3</sub>	3,4-diF	750	7	8	4	1	9	5
<b>2d</b>	-CH <sub>3</sub>	3-F,4-Cl	750	2	9	5	1	9	3
<b>2e</b>	-CH <sub>3</sub>	3-F,4-Br	750	3	7	3	1	9	1
<b>2f</b>	-CH <sub>3</sub>	3-F,4-CN	750	2	8	2	1	9	7
<b>2g</b>	-CH <sub>3</sub>	2-F,4-Cl	750	1	1	2	1	8	1
<b>2h</b>	-CH <sub>3</sub>	3,4,5-triF	750	3	10	9	1	9	2
			600	5	10	9	1	8	7
<b>3a</b>	-CH <sub>2</sub> CH <sub>3</sub>	4-CF <sub>3</sub>	750	2	9	5	1	9	3
<b>3b</b>	-CH <sub>2</sub> CH <sub>3</sub>	3-F	750	1	7	2	1	5	1
<b>3c</b>	-CH <sub>2</sub> CH <sub>3</sub>	3,4-diF	750	1	8	8	1	10	1
			600	1	8	7	1	5	1
<b>3d</b>	-CH <sub>2</sub> CH <sub>3</sub>	3-F,4-Cl	750	1	5	2	1	1	1
<b>3e</b>	-CH <sub>2</sub> CH <sub>3</sub>	3-F,4-Br	750	1	1	1	1	1	1
<b>3f</b>	-CH <sub>2</sub> CH <sub>3</sub>	3-F,4-CN	750	1	7	2	1	1	1
<b>3g</b>	-CH <sub>2</sub> CH <sub>3</sub>	2-F,4-Cl	750	1	1	1	1	1	1
<b>3h</b>	-CH <sub>2</sub> CH <sub>3</sub>	3,4,5-triF	750	7	10	9	1	10	6
			600	7	10	8	1	10	5
			300	2	9	3	1	8	3
<b>3i</b>	-CH <sub>2</sub> CH <sub>3</sub>	4-CN	750	2	3	2	1	8	1
<b>4a</b>		4-CF <sub>3</sub>	750	1	7	2	1	7	1
<b>4b</b>		3-F	750	1	1	1	1	1	1
<b>4c</b>		3,4-diF	750	1	1	1	1	1	1
<b>4d</b>		3-F,4-Cl	750	1	1	1	1	1	1
<b>4e</b>		3-F,4-Br	750	1	1	1	1	1	1
<b>4f</b>		3-F,4-CN	750	1	1	1	1	1	1
<b>4g</b>		2-F,4-Cl	750	1	1	1	1	1	1
<b>4h</b>		3,4,5-triF	750	1	8	3	1	8	1
<b>4i</b>		4-CN	750	1	4	1	1	4	2
<b>5a</b>		4-CF <sub>3</sub>	750	1	1	1	1	1	1
<b>5b</b>	-CH(CH <sub>3</sub> ) <sub>2</sub>	3-F	750	1	1	1	1	1	1
<b>5c</b>	-CH(CH <sub>3</sub> ) <sub>2</sub>	3-F,4-F	750	1	1	1	1	1	1
<b>5d</b>	-CH(CH <sub>3</sub> ) <sub>2</sub>	3-F,4-Cl	750	1	1	1	1	1	1
<b>5e</b>	-CH(CH <sub>3</sub> ) <sub>2</sub>	3-F,4-Br	750	1	1	1	1	1	1
<b>5f</b>	-CH(CH <sub>3</sub> ) <sub>2</sub>	3-F,4-CN	750	1	1	1	1	1	1
<b>5g</b>	-CH(CH <sub>3</sub> ) <sub>2</sub>	2-F,4-Cl	750	1	1	1	1	1	1

<b>5h</b>	-CH(CH <sub>3</sub> ) <sub>2</sub>	3,4,5-triF	750	1	1	1	1	1	1
<b>5i</b>	-CH(CH <sub>3</sub> ) <sub>2</sub>	4-CN	750	1	1	1	1	1	1
<b>1</b>	-CH <sub>3</sub>	4-CN	750	5	5	5	10	10	7
diflufenican			750	7	10	8	1	10	2
			600	10	10	8	1	9	2
			300	10	10	8	1	9	1
			150	10	10	7	1	9	1

<sup>a</sup>Abbreviation: *Echinochloa crus-galli*: ECHCG; *Digitaria sanguinalis*: DIGSA; *Setaria faberii*: SETFA; *Abutilon juncea*: ABUJU; *Eclipta prostrata*: ECLPR; *Amaranthus retroflexus*: AMARE; <sup>b</sup>Rating scale of herbicidal activity: 10, 100%; 9, 99–90%; 8, 89–80%; 7, 79–70%; 6, 69–60%; 5, 59–50%; 4, 49–40%; 3, 39–30%; 2, 29–20%; 1, 19–0%.

Table S3. Calculated binding free energies (kcal/mol) of **2a** with *Synechococcus* PDS.

compd	$\Delta E_{\text{ele}}$	$\Delta E_{\text{VDW}}$	$\Delta E_{\text{MM}}$	$\Delta G_{\text{sol}}$	$\Delta E_{\text{bind}}$	$-T\Delta S$	$\Delta G_{\text{bind}}^a$
<b>2a</b>	-12.95±2.28	-52.04±1.93	-64.99±2.66	35.54±2.71	-29.45 ± 2.48	10.08±2.43	-19.37±2.46

<sup>a</sup> $\Delta G_{\text{bind}} = \Delta E_{\text{ele}} + \Delta E_{\text{vdw}} + \Delta G_{\text{sol}} + (-T\Delta S)$ .

## 1 General method

### 1.1 General method to synthesize intermediates 7-12.

#### 1.1.1 Preparation of ethyl 2-(3-(trifluoromethyl)phenyl)acetate (7).

H<sub>2</sub>SO<sub>4</sub> (0.5 mL) was added to a solution of 2-oxo-3-(3-(trifluoromethyl)phenyl)propanoic acid **6** (20.0 g, 98 mmol) and C<sub>2</sub>H<sub>5</sub>OH (100 mL) at room temperature and then heated to 80 °C for 12 h. Then, the reaction cooled to 25 °C and concentrated in vacuo. The resulting residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (150 mL), and the organic layer was washed with H<sub>2</sub>O (100 mL) and saturated Na<sub>2</sub>CO<sub>3</sub> solution (100 mL), dried over magnesium sulfate and filtrated. The filtrate was concentrated to give 18.2 g yellow oil of intermediate **7**. Yield, 80%, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.57 – 7.42 (m, 4H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.67 (s, 2H), 1.26 (t, *J* = 7.2 Hz, 3H).

#### 1.2 Preparation of ethyl 2-bromo-2-(3-(trifluoromethyl)phenyl)acetate (8)

A solution of ethyl 2-(3-(trifluoromethyl)phenyl)acetate **7** (10.0 g, 32 mmol), *N*-bromosuccinimide (NBS, 6.3 g, 35.2 mmol), and azobisisobutyronitrile (AIBN, 5.2 g, 3.2 mmol) was heated to reflux for 10 h with stirring. Then, the reaction solution was cooled to 25 °C. The resulting undissolved substance was removed by filtration. The filtrate was concentrated and purified by column chromatography to afford 7.1 g of orange oil **8**. Yield, 70%, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.81 (s, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 5.36 (s, 1H), 4.31 – 4.21 (m, 2H), 1.29 (t, *J* = 7.2 Hz, 3H).

#### 1.3 The synthetic methods for intermediates 9-12 were the same as our previous work.

*6-methyl-4-(3-(trifluoromethyl)phenyl)pyridazin-3(2H)-one (11a)*. Yellow soild, 50% yield; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 11.77 (s, 1H), 8.10 (d, *J* = 7.6 Hz, 1H), 8.02 (s, 1H), 7.69 (d, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.32 (s, 1H), 2.42 (s, 3H).

*6-ethyl-4-(3-(trifluoromethyl)phenyl)pyridazin-3(2H)-one (11b)*. Yellow soild, 50% yield; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.98 (s, 1H), 8.32 (s, 1H), 8.27 (d, *J* = 7.6 Hz, 1H), 7.96 (d, *J* = 7.6 Hz, 1H), 7.82 (s, 1H), 7.79 (t, *J* = 7.6 Hz, 1H), 2.98 (q, *J* = 7.6 Hz, 2H), 1.19 (t, *J* = 7.6 Hz, 3H).

*6-cyclopropyl-4-(3-(trifluoromethyl)phenyl)pyridazin-3(2H)-one (11c)*. Yellow soild, 30% yield; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 12.99 (s, 1H), 8.30 (s, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.70 (t, *J* = 7.8 Hz, 1H), 7.61 (s, 1H), 2.01 (tt, *J* = 8.3, 5.0 Hz, 1H), 0.97 – 0.85 (m, 4H).

*6-isopropyl-4-(3-(trifluoromethyl)phenyl)pyridazin-3(2H)-one (11d)*. Yellow soild, 35% yield; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 13.04 (s, 1H), 8.31 (s, 1H), 8.18 (d, *J* = 7.6 Hz, 1H), 7.79 (d, *J* = 10.0 Hz, 2H), 7.69 (t, *J* = 7.6 Hz, 1H), 3.01 – 2.93 (m, 1H), 1.22 (d, *J* = 6.8 Hz, 6H).

*3-chloro-6-methyl-4-(3-(trifluoromethyl)phenyl)pyridazine (12a)*. White soild, 50% yield; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.77 (d, *J* = 7.6 Hz, 1H), 7.73 (s, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.35 (s, 1H), 2.78 (s, 3H).

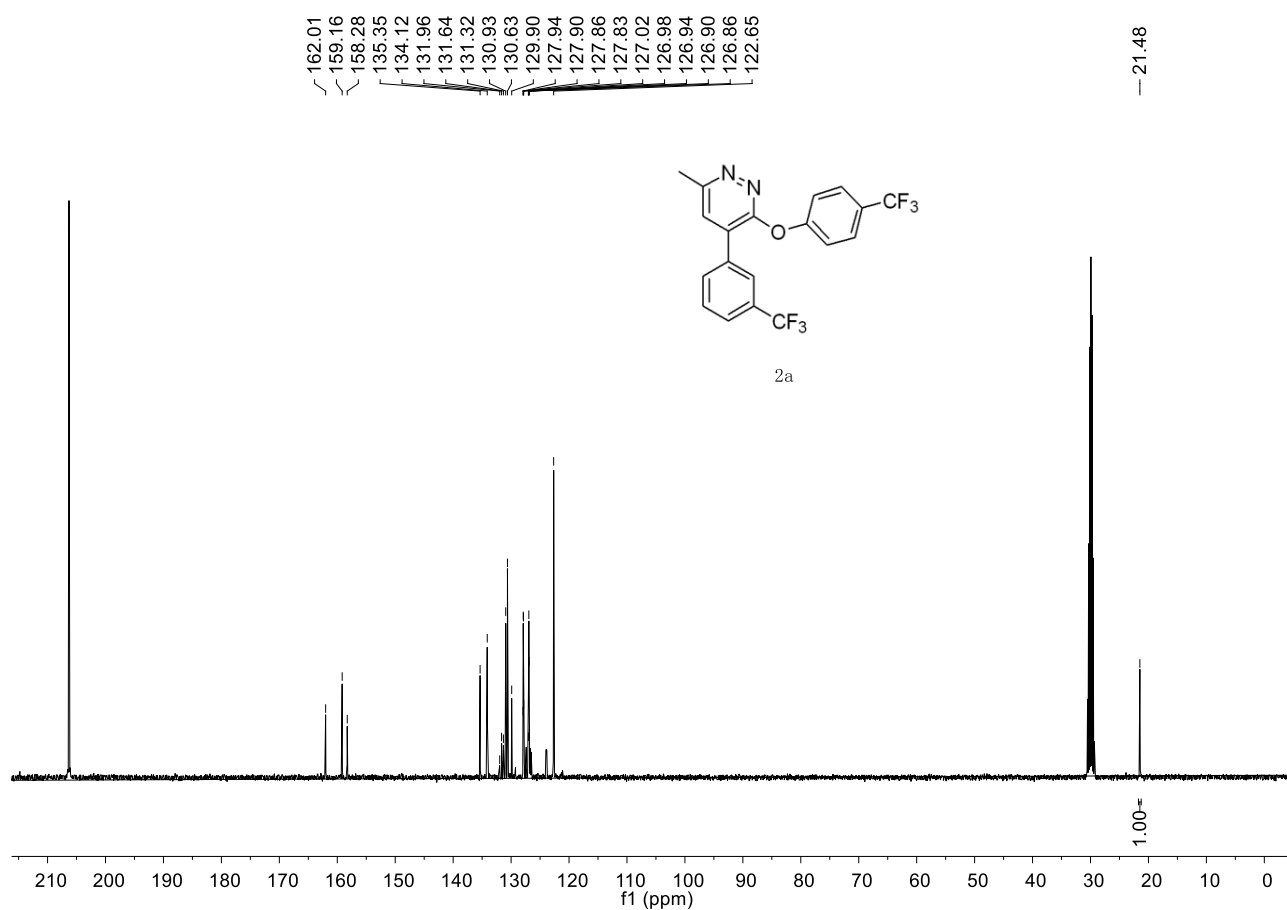
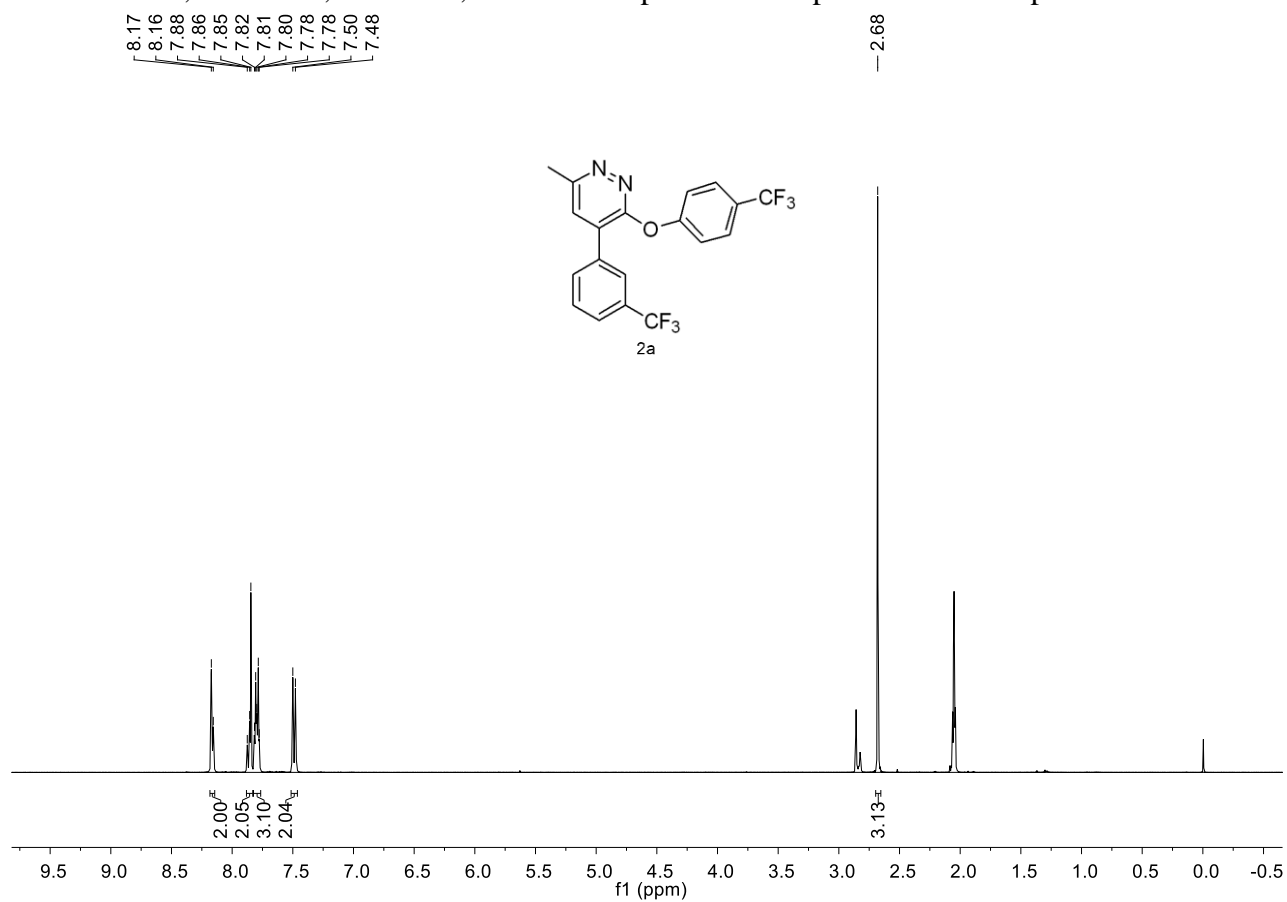
*3-chloro-6-ethyl-4-(3-(trifluoromethyl)phenyl)pyridazine (12b)*. Yellow soild; 70% yield; <sup>1</sup>H NMR (400 MHz, DMSO) δ 8.26 (s, 1H), 8.15 (d, *J* = 7.9 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 1H), 7.78 (s, 1H), 7.72 (t, *J* = 7.9 Hz, 1H), 2.62 (q, *J* = 7.5 Hz, 2H), 1.12 (t, *J* = 7.5 Hz, 3H).

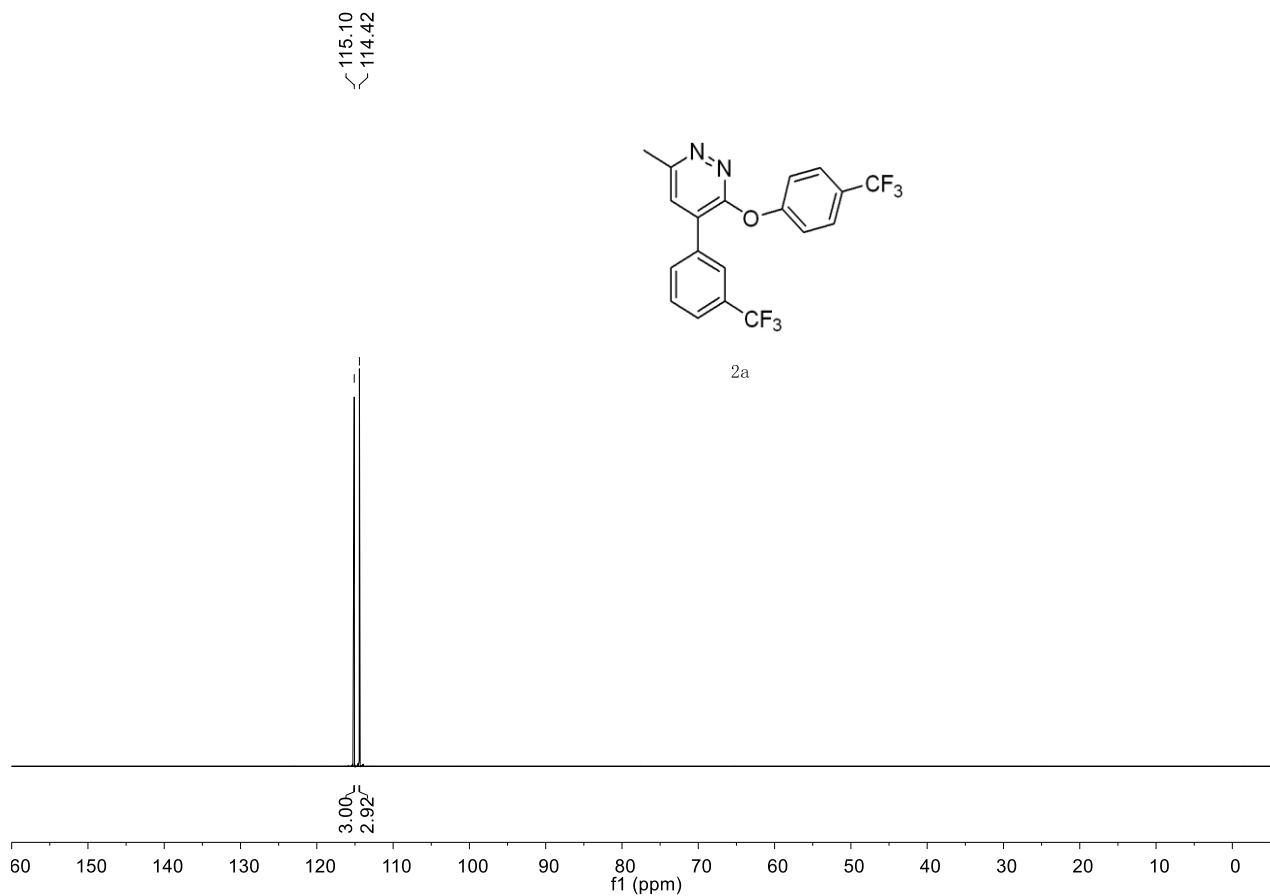
*3-chloro-6-cyclopropyl-4-(3-(trifluoromethyl)phenyl)pyridazine (12c)*. Yellow soild; 30% yield; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>) δ 8.00 (s, 1H), 7.95 – 7.88 (m, 2H), 7.79 (t, *J* = 7.6 Hz, 1H), 7.74 (s, 1H), 2.34

(tt,  $J = 7.6, 5.2$  Hz, 1H), 1.24 – 1.10 (m, 4H).

*3-chloro-6-isopropyl-4-(3-(trifluoromethyl)phenyl)pyridazine* (**12d**). Yellow oil, 70% yield;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.78 – 7.71 (m, 2H), 7.69 (d,  $J = 8.0$  Hz, 1H), 7.64 (t,  $J = 7.6$  Hz, 1H), 7.32 (s, 1H), 3.40 – 3.32 (m, 1H), 1.39 (d,  $J = 7.2$  Hz, 6H).

The  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR,  $^{19}\text{F}$  NMR, and HRMS spectrum of representative compounds.

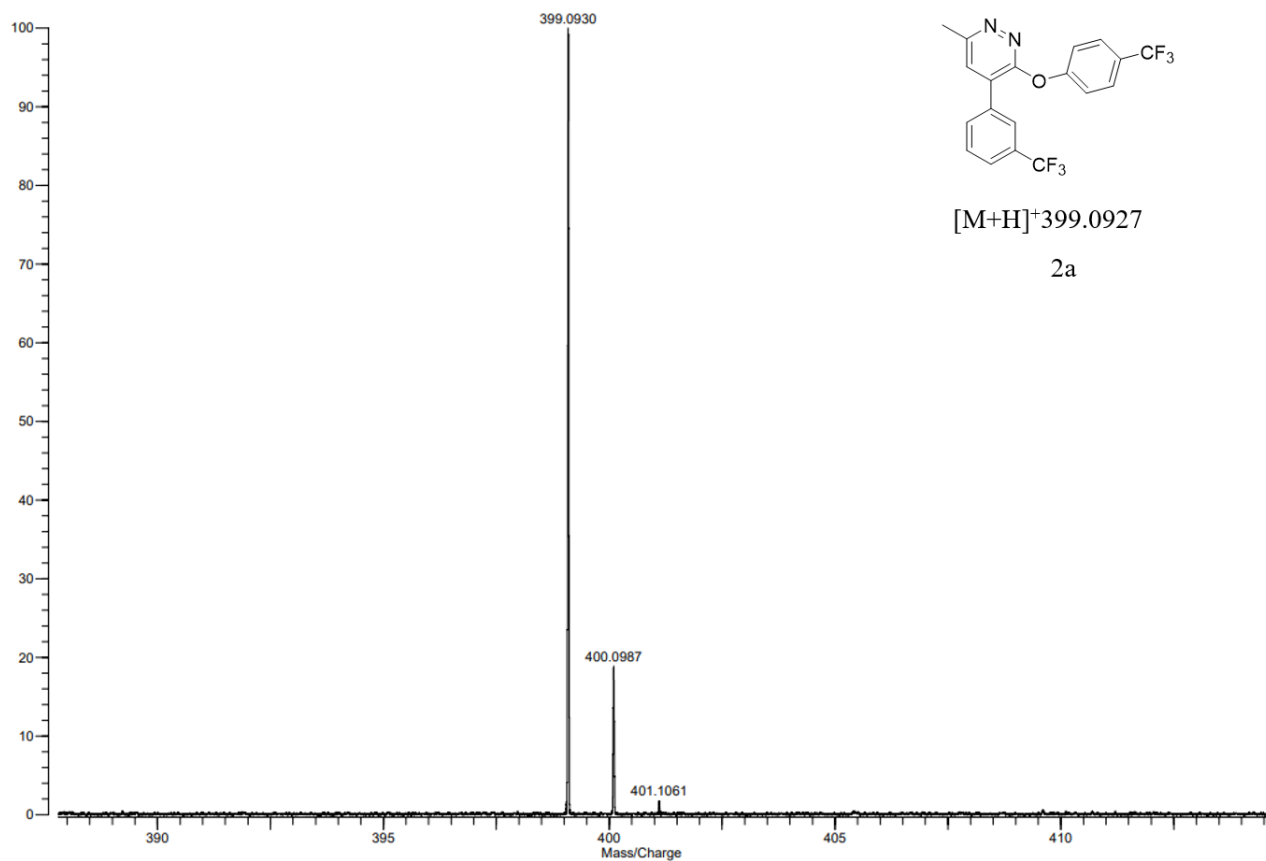




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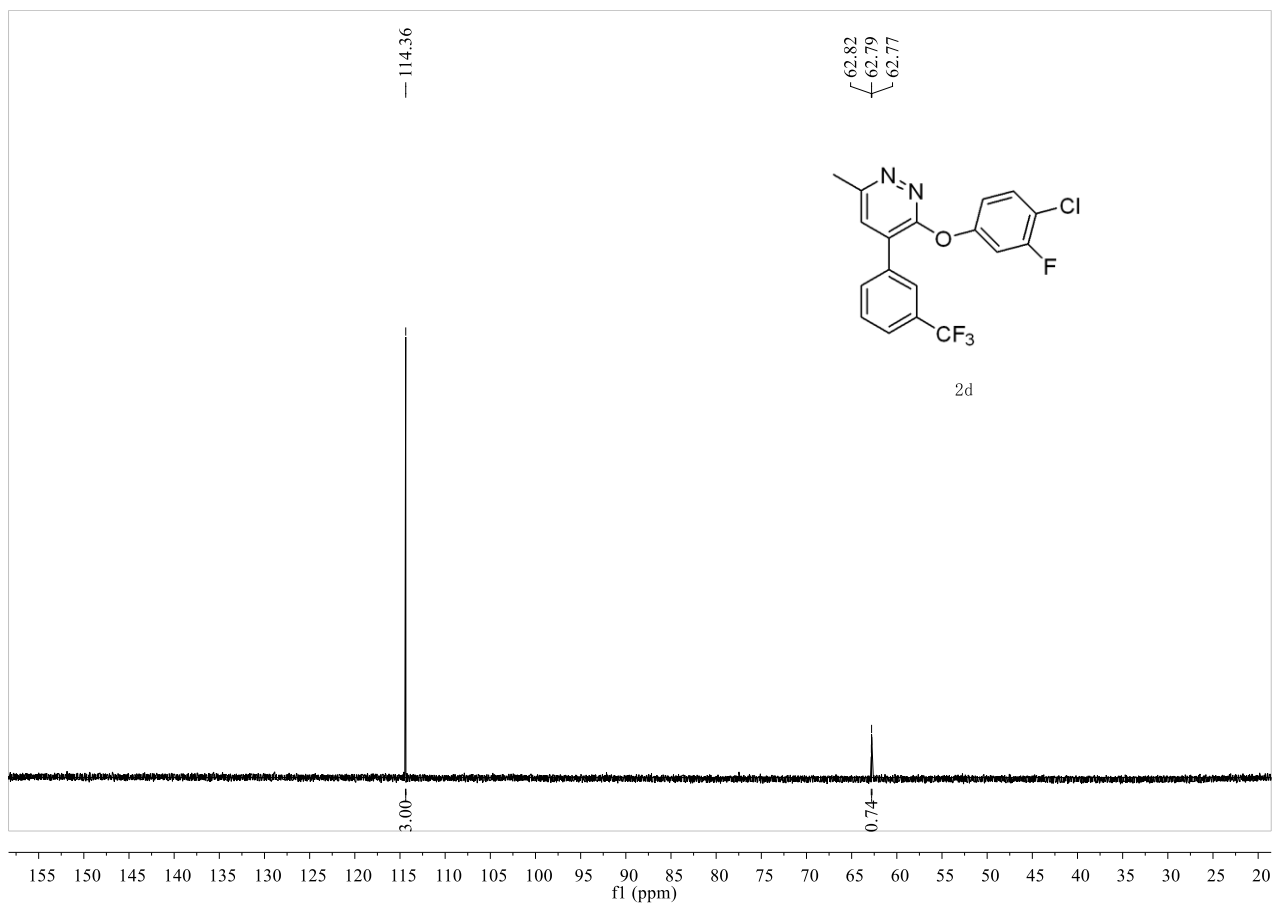
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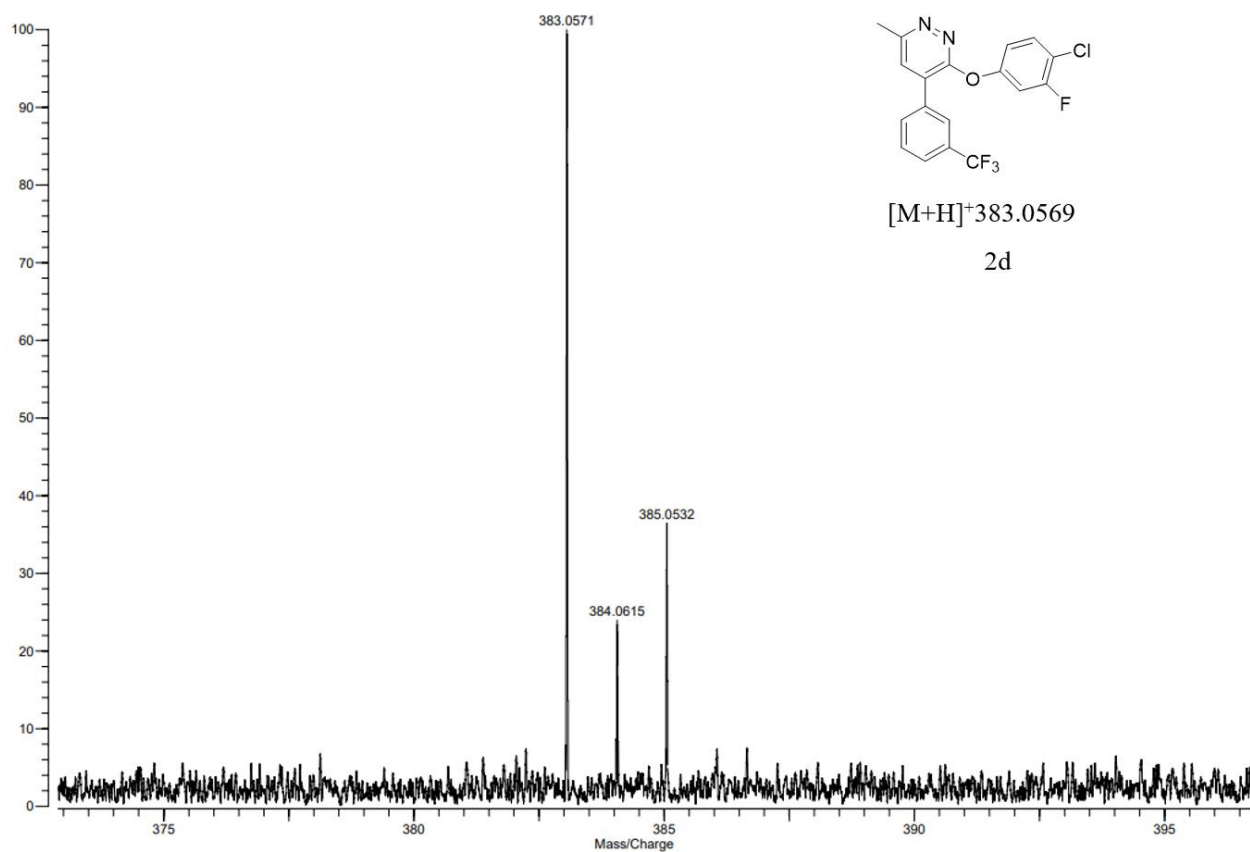


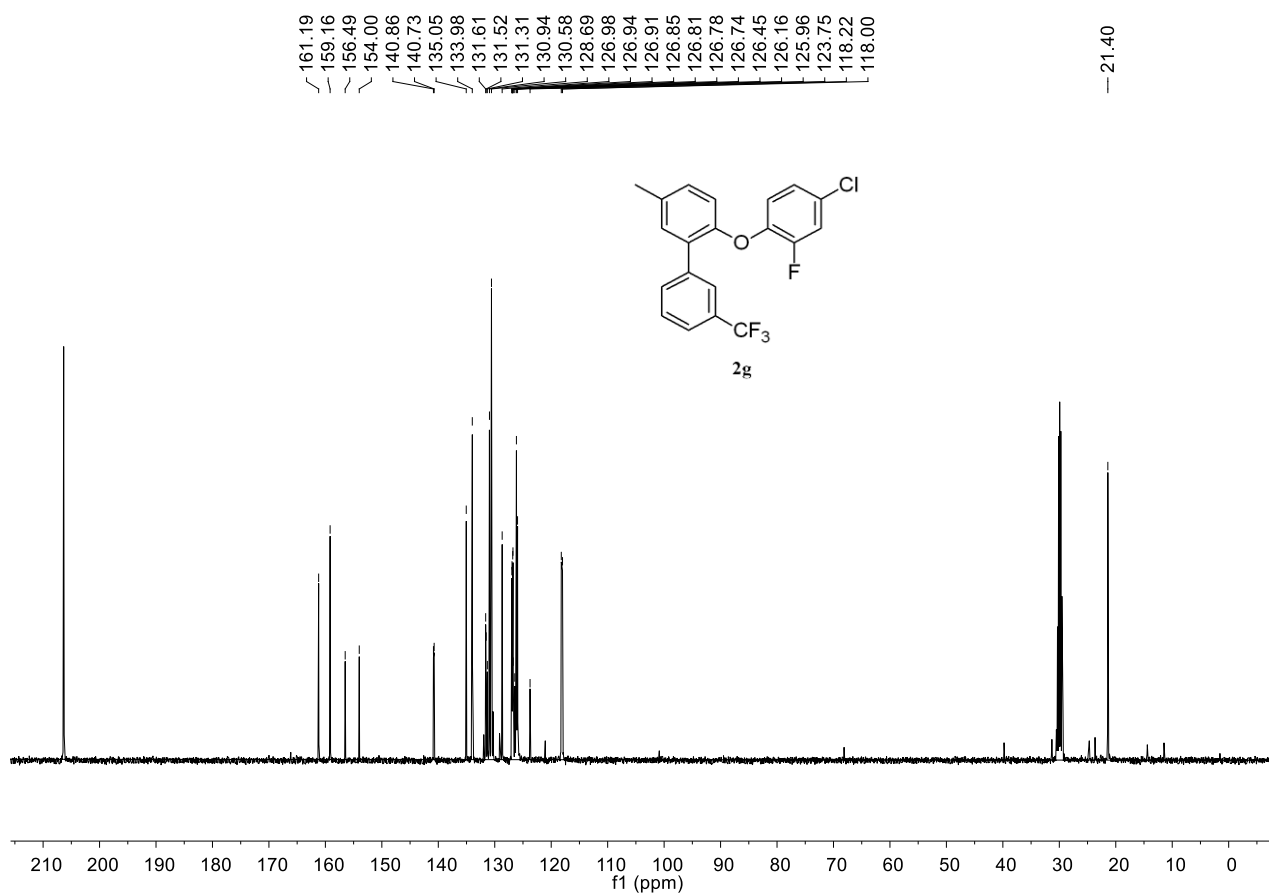
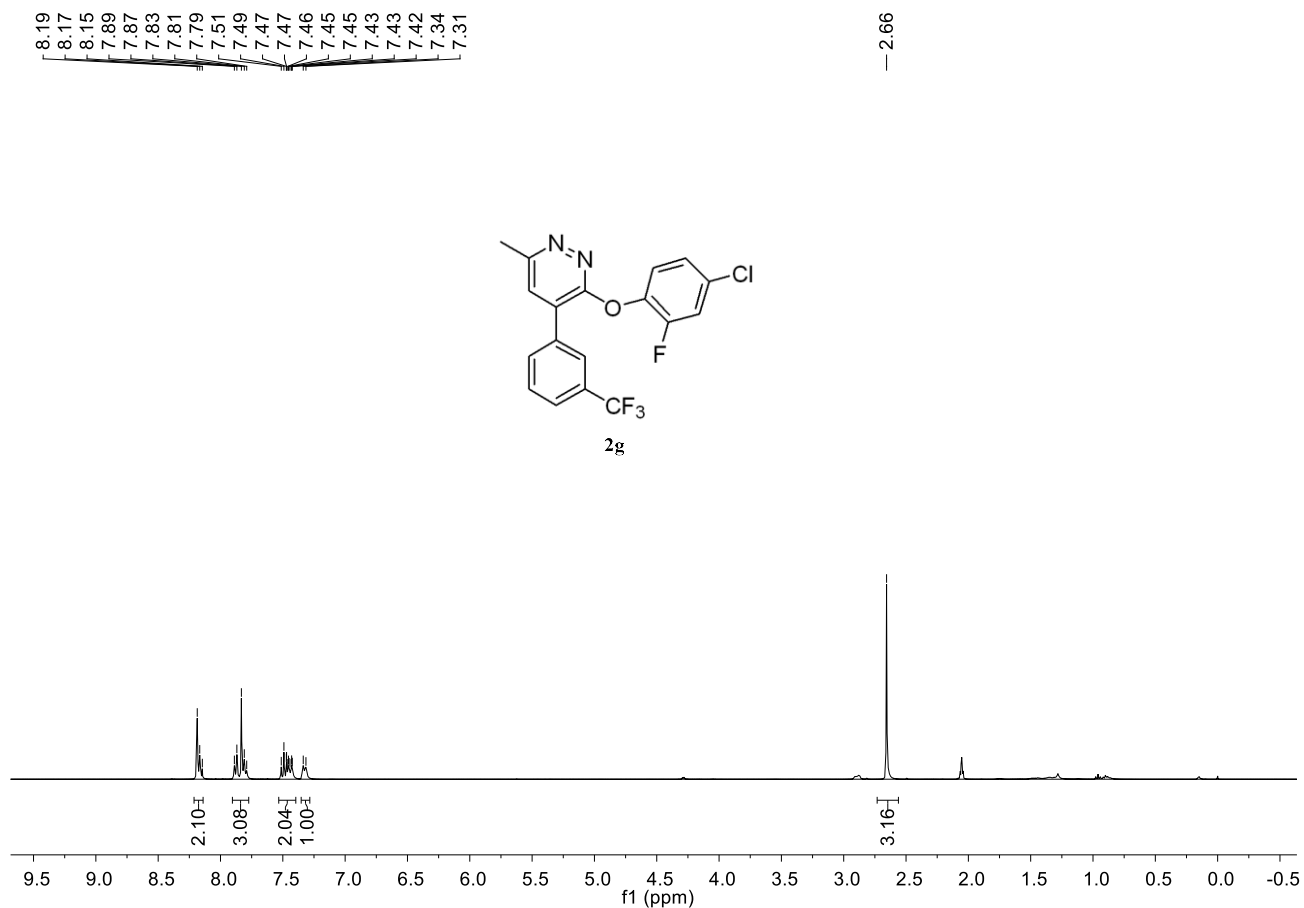


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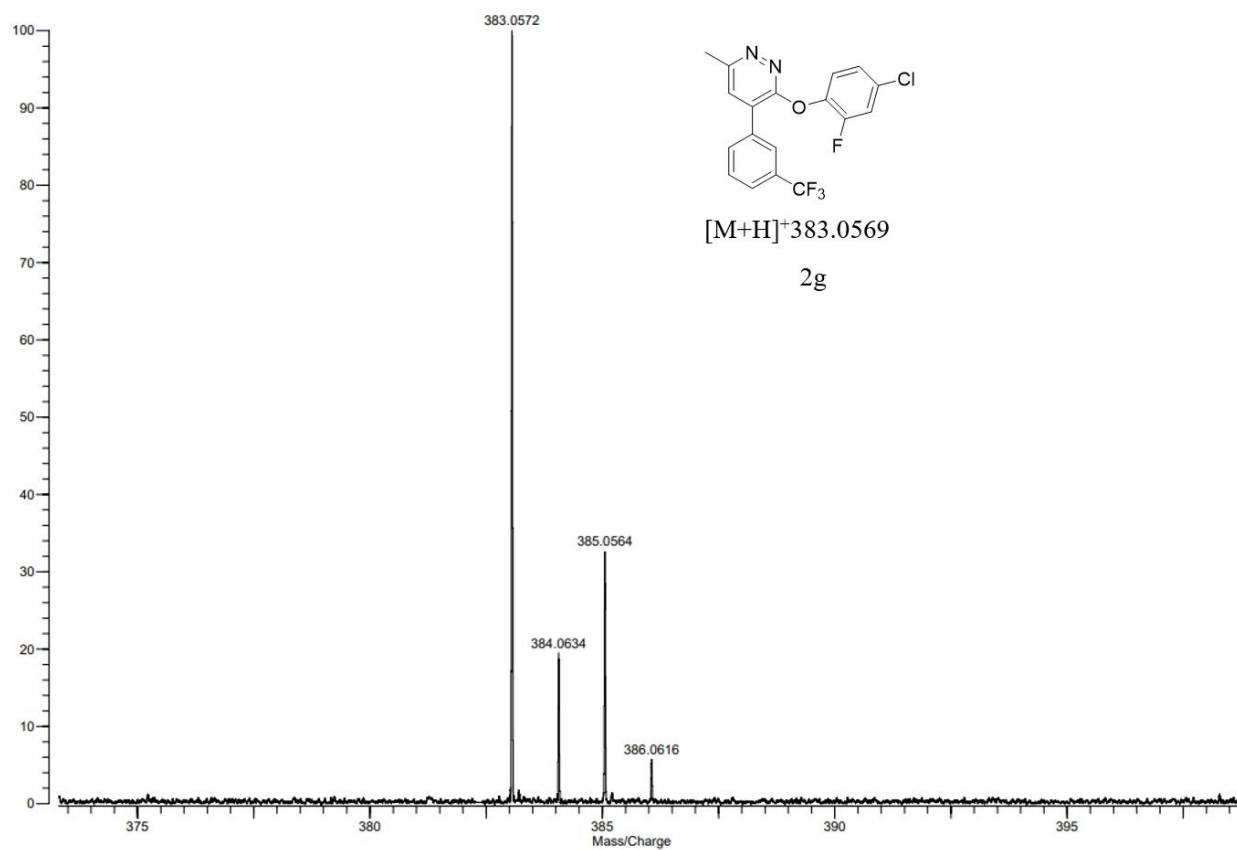


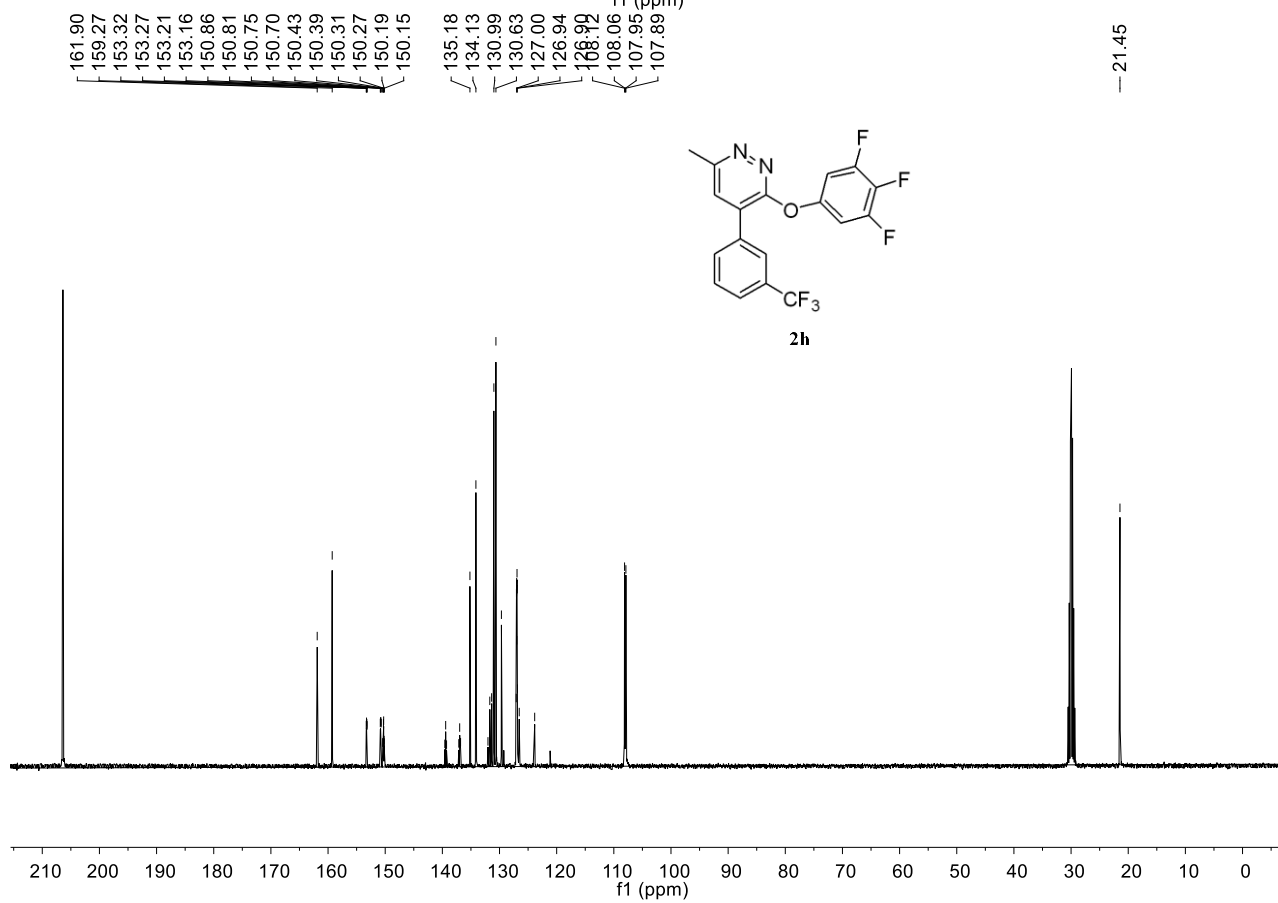
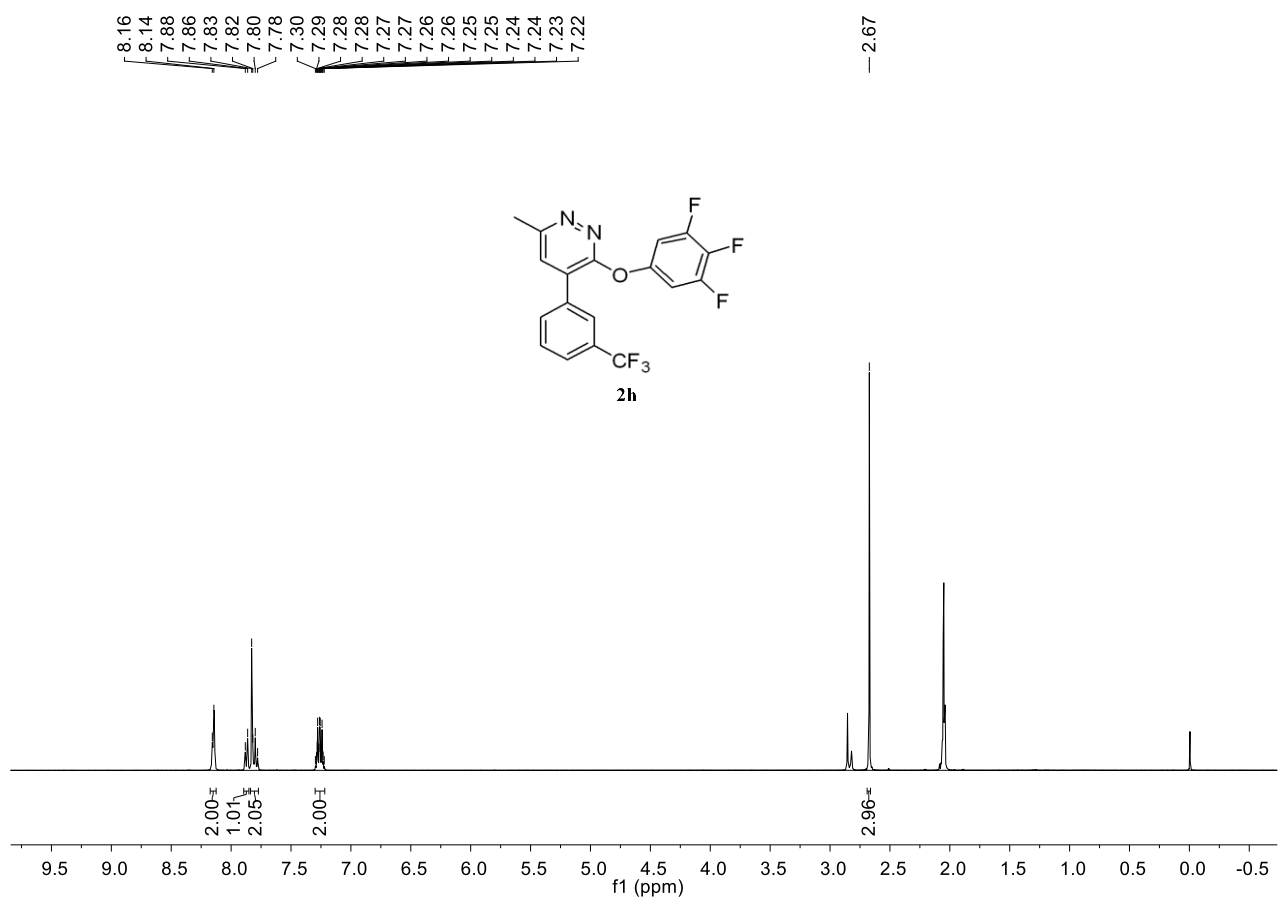


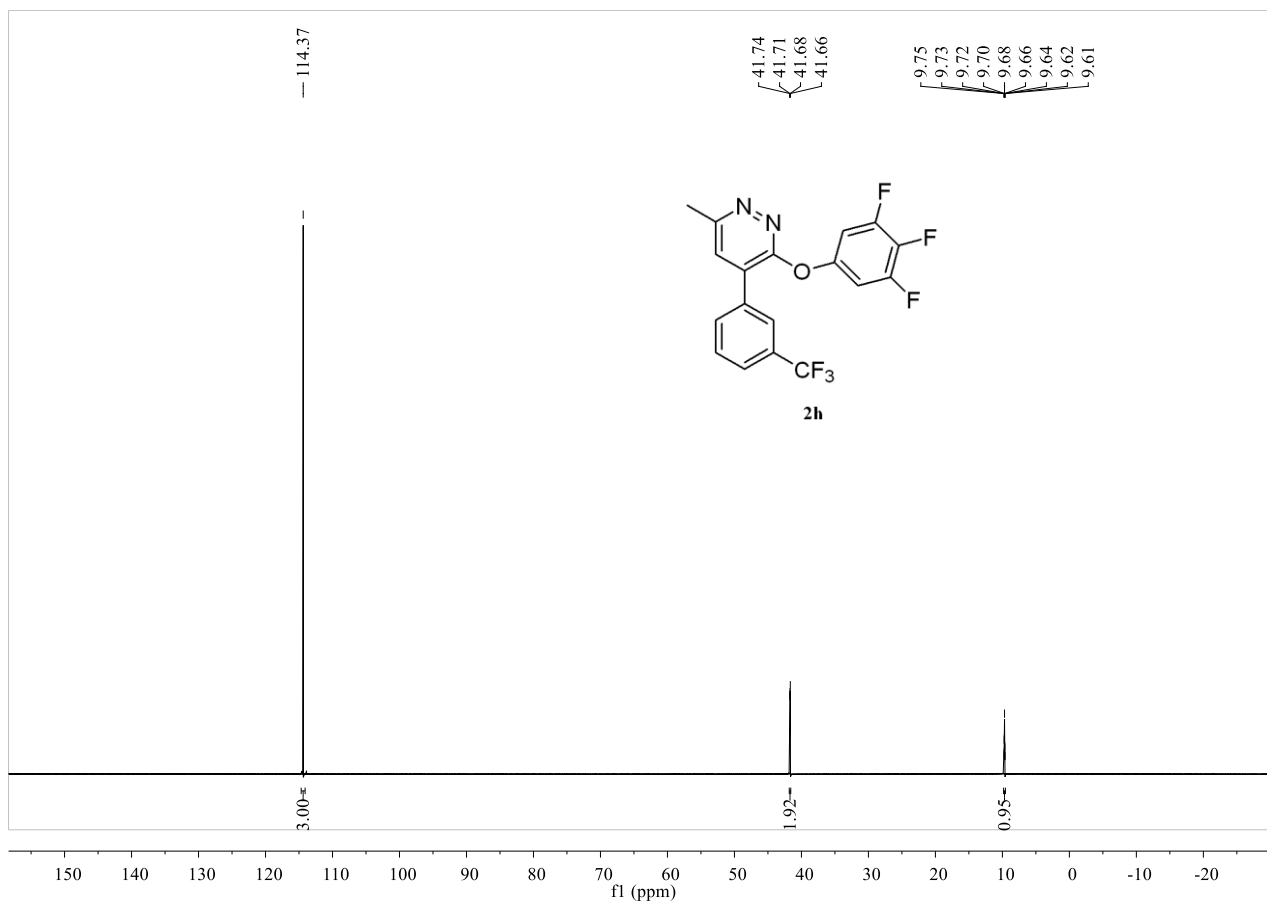
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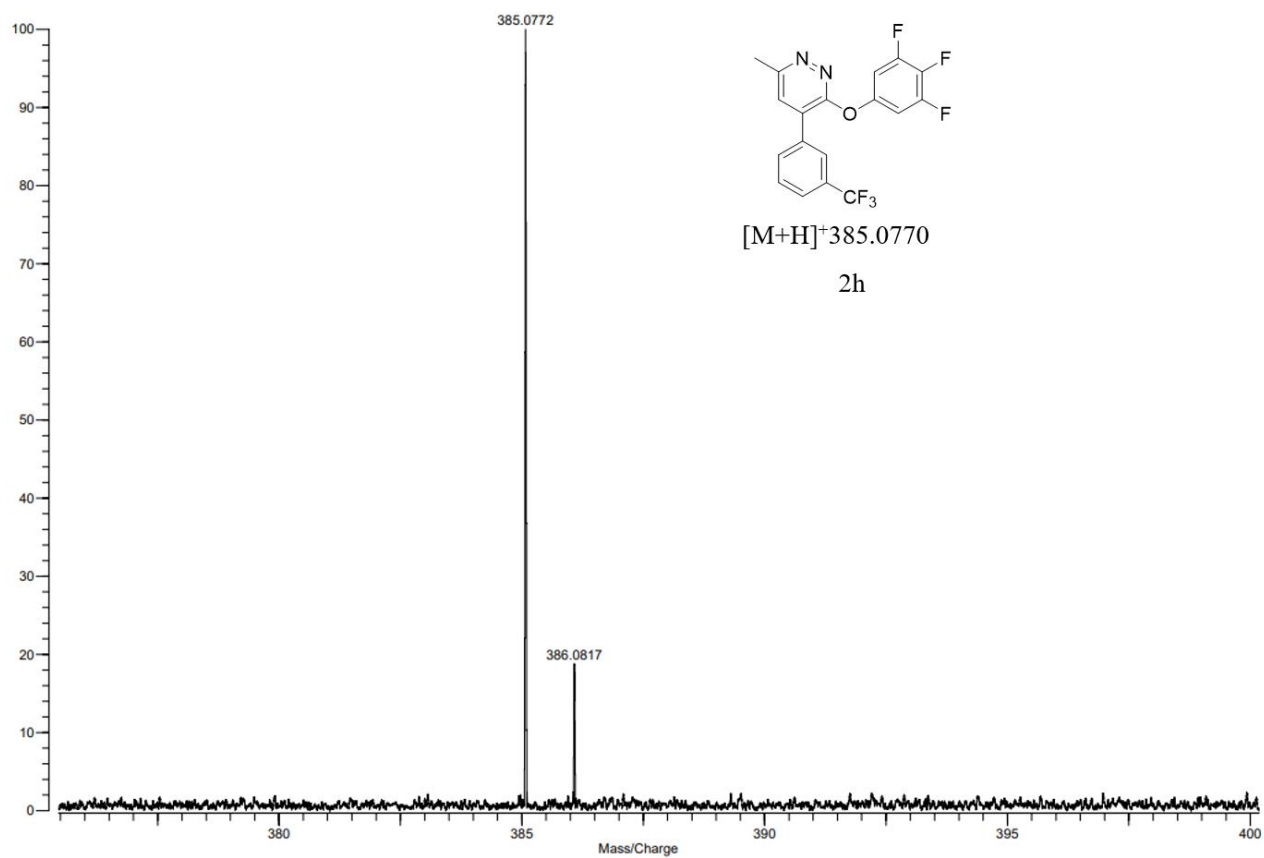


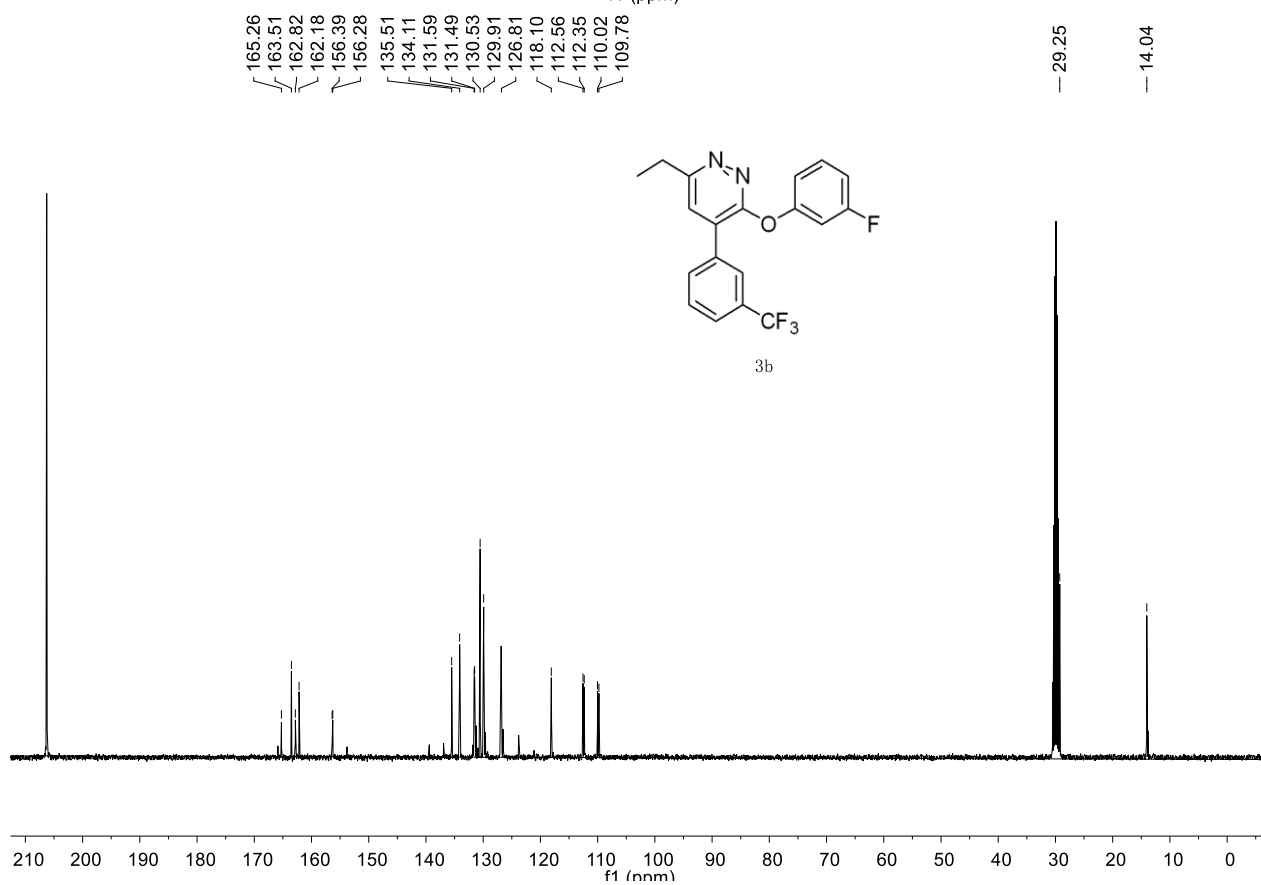
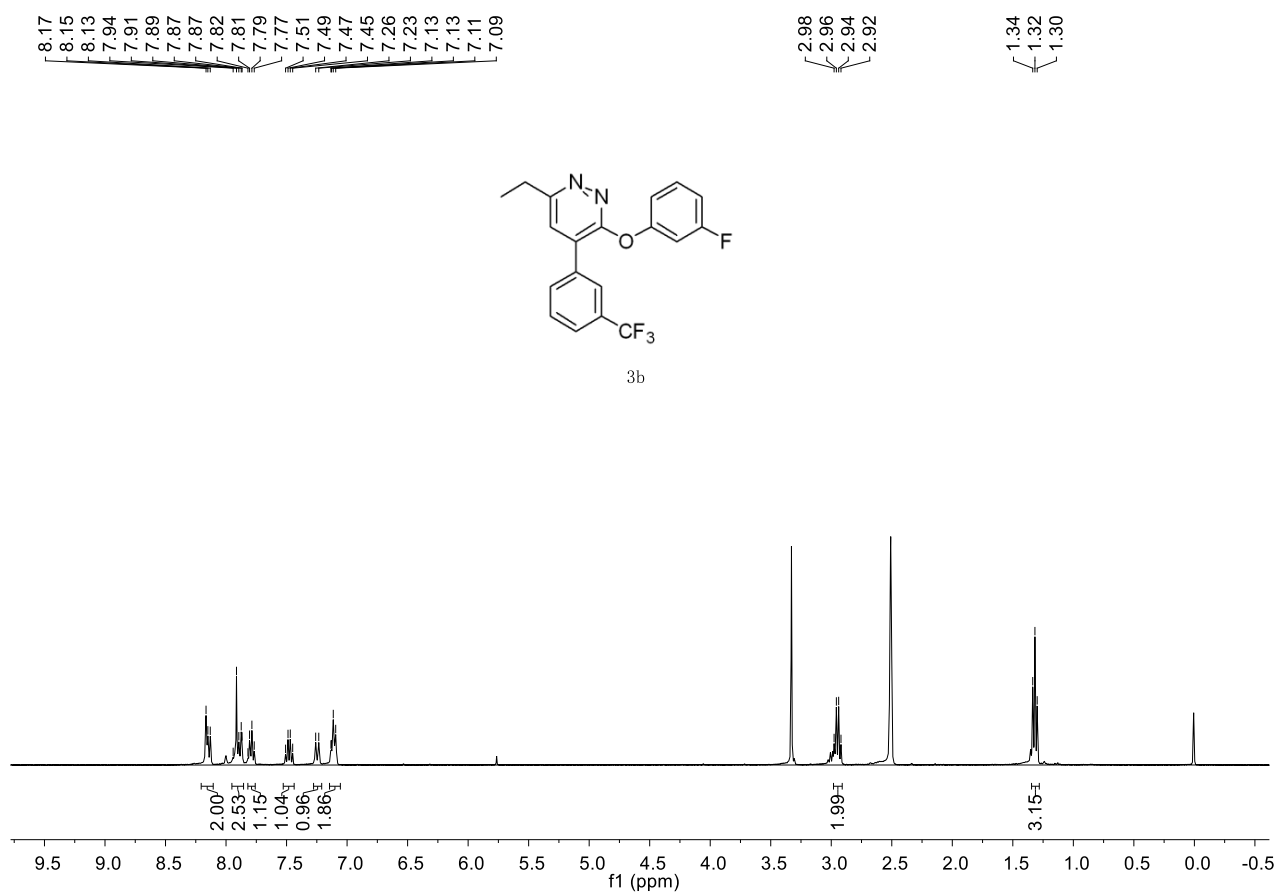


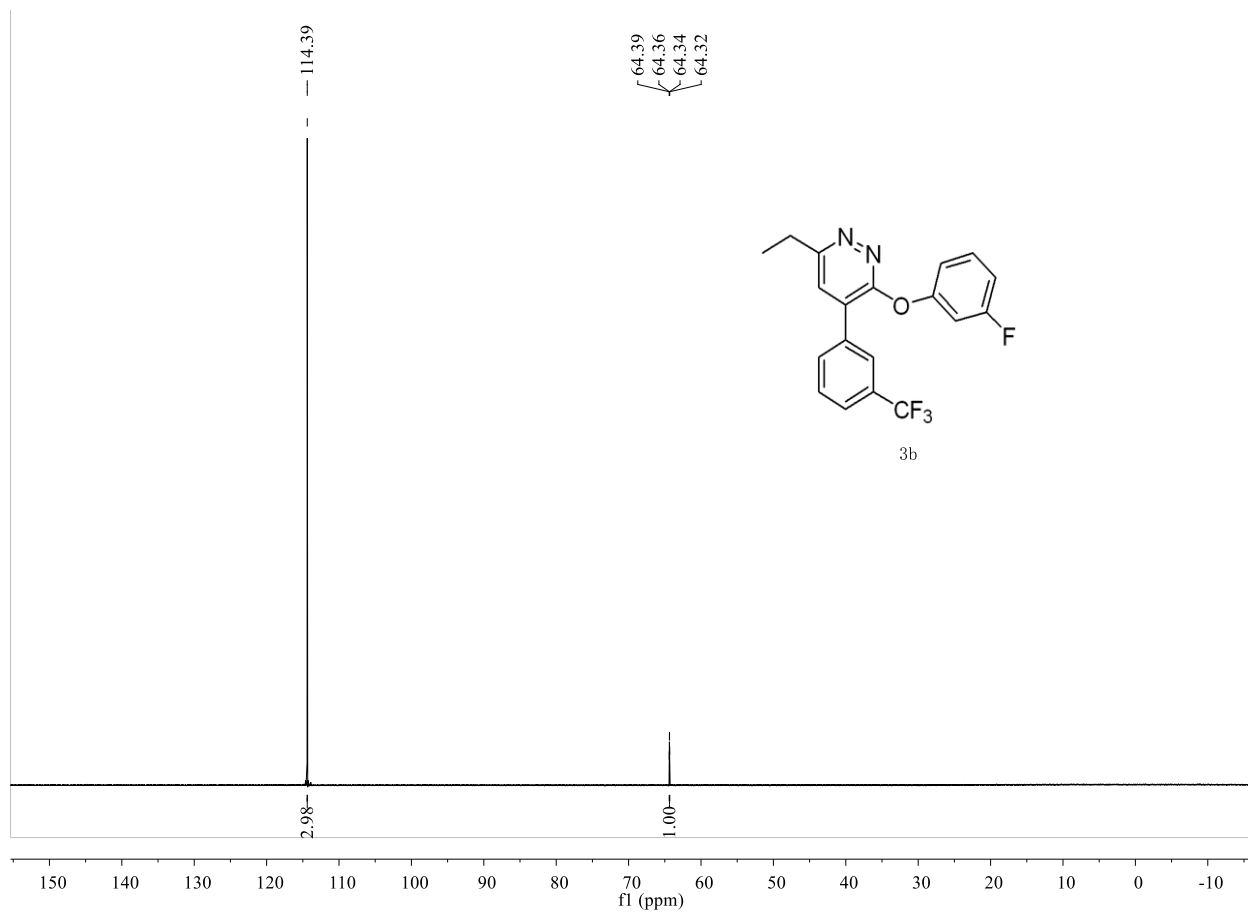
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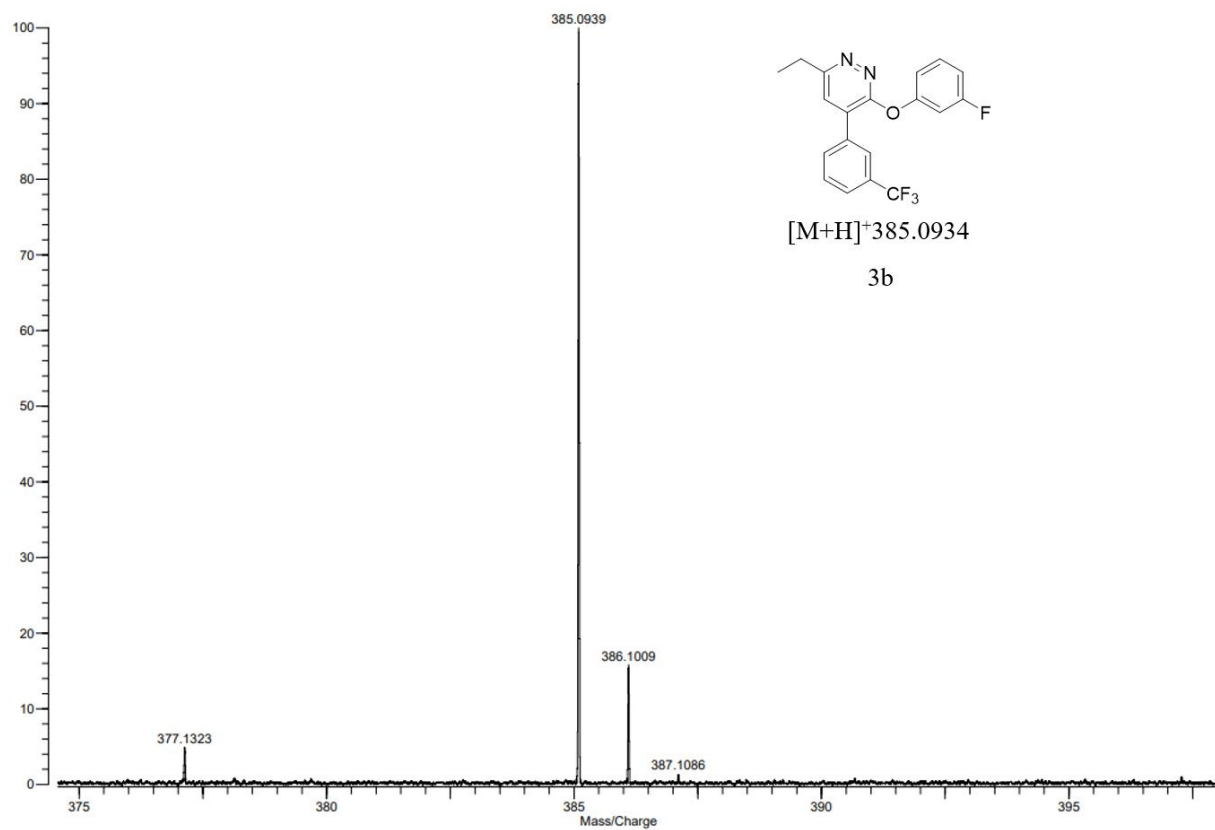




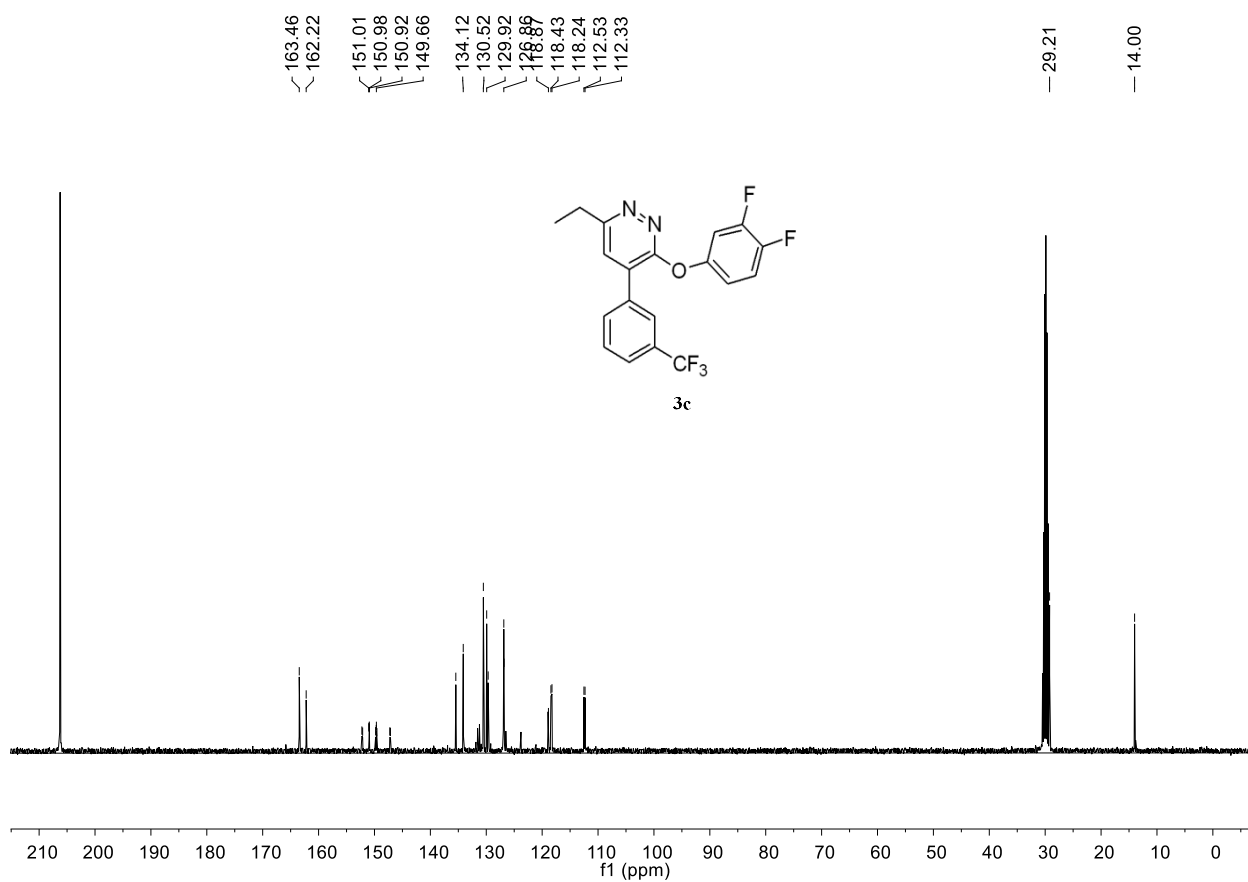
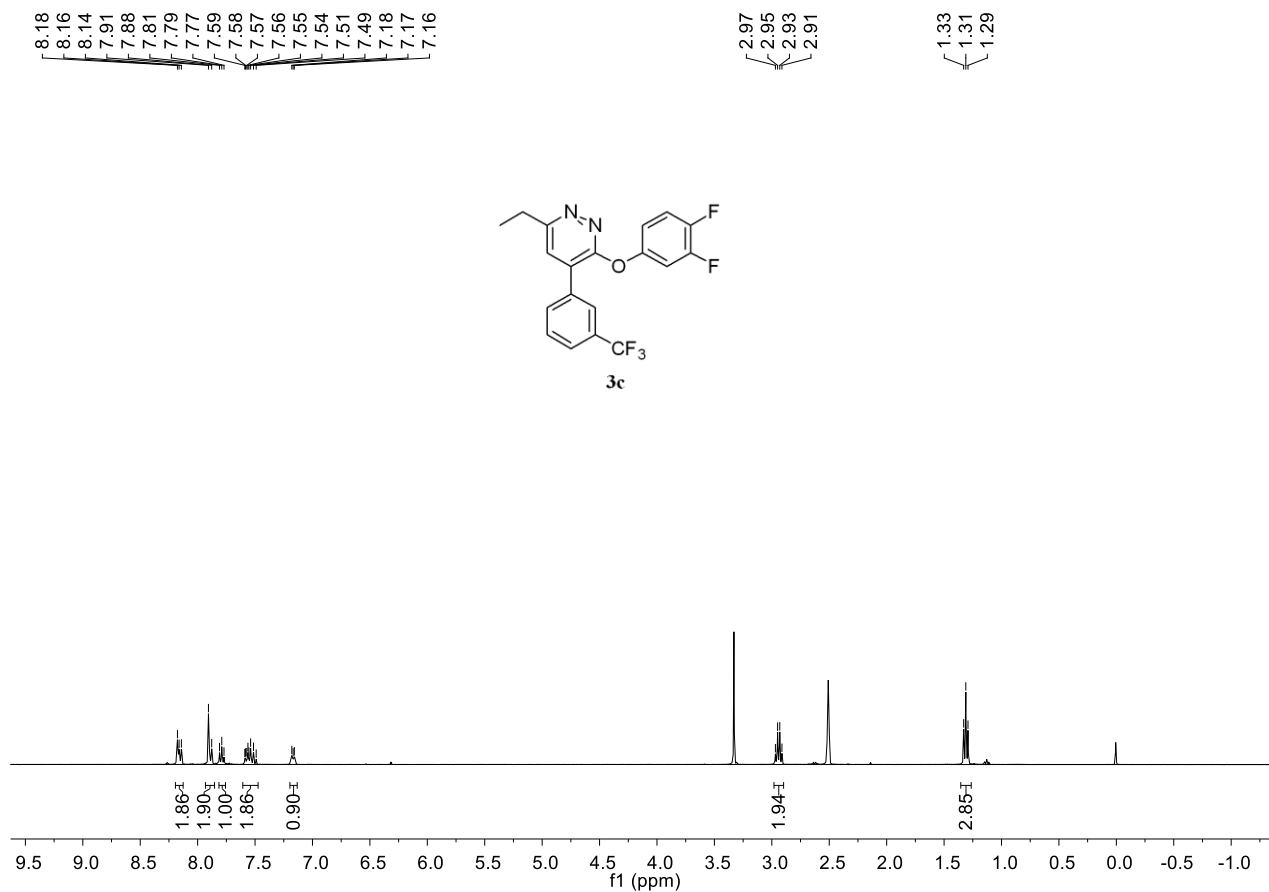
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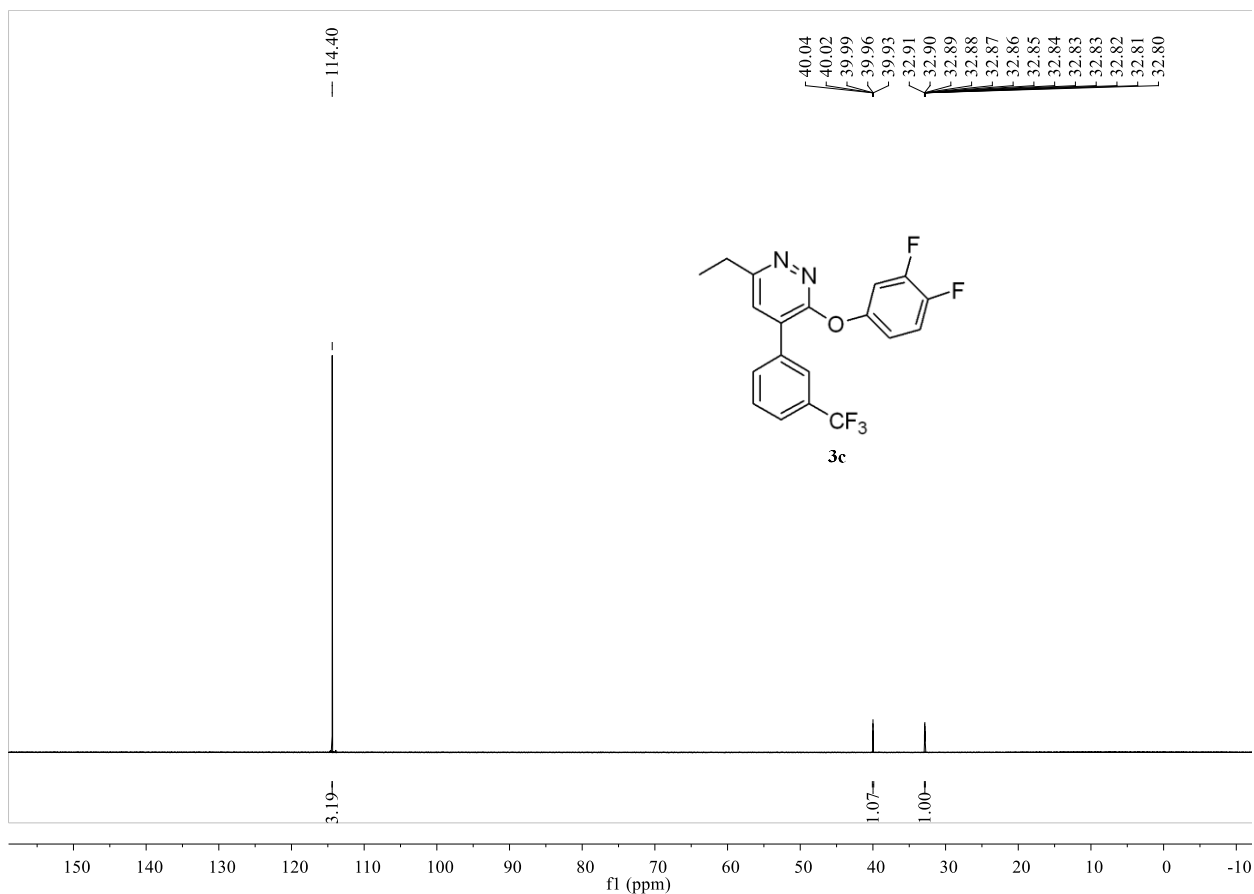
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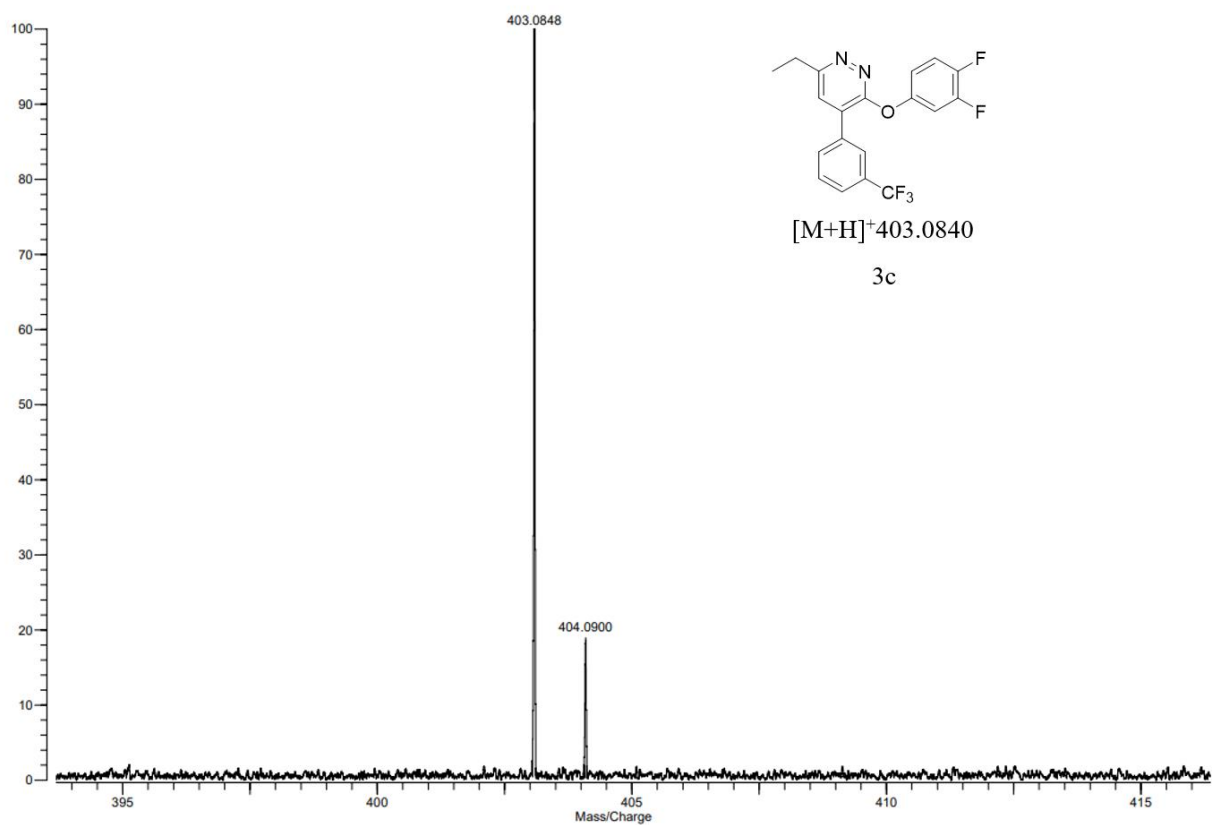


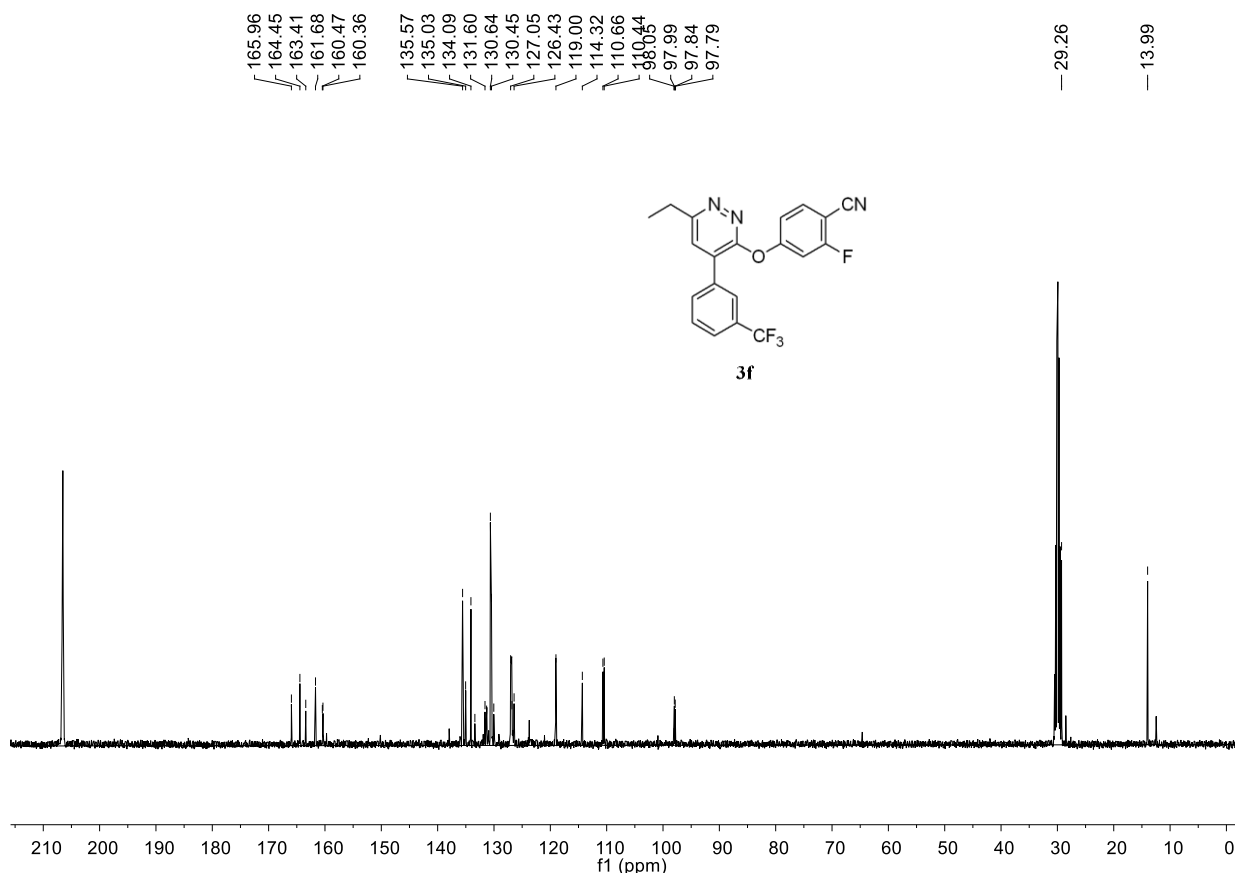
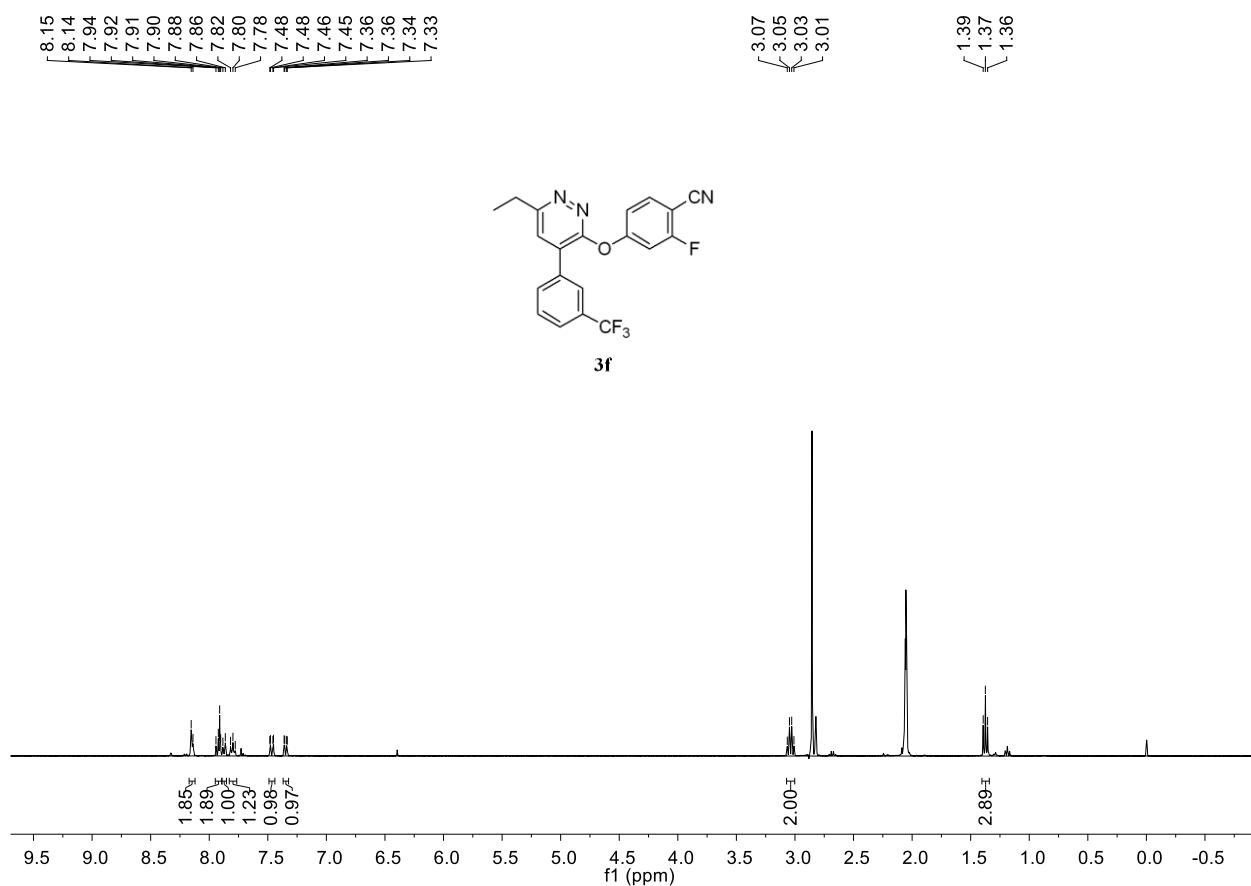


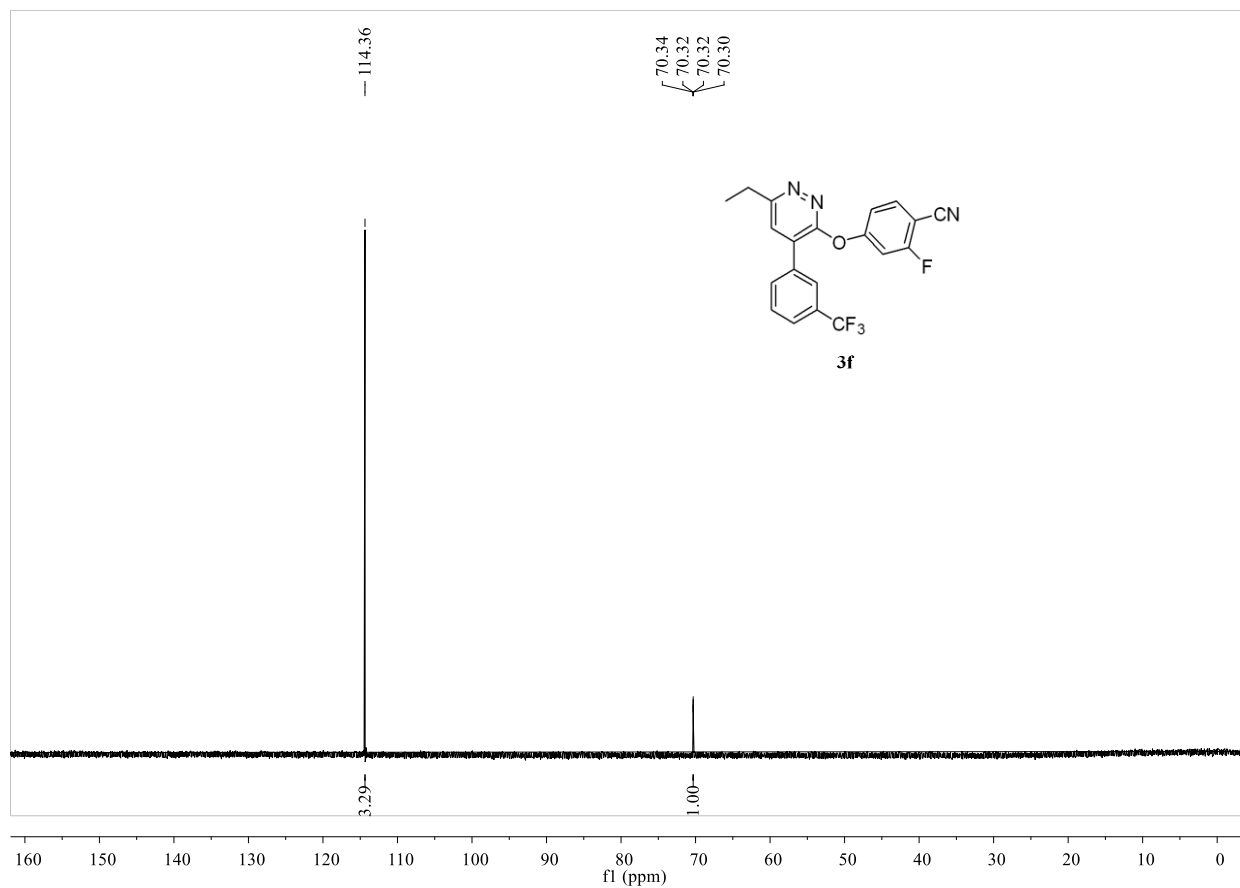
Varian QFT-ESI  
File: Y402\_ESI.trans

Mode: Positive  
Scans: 1

Date: 03-MAR-2021  
Time: 11:54:55  
Scale: 21.5532



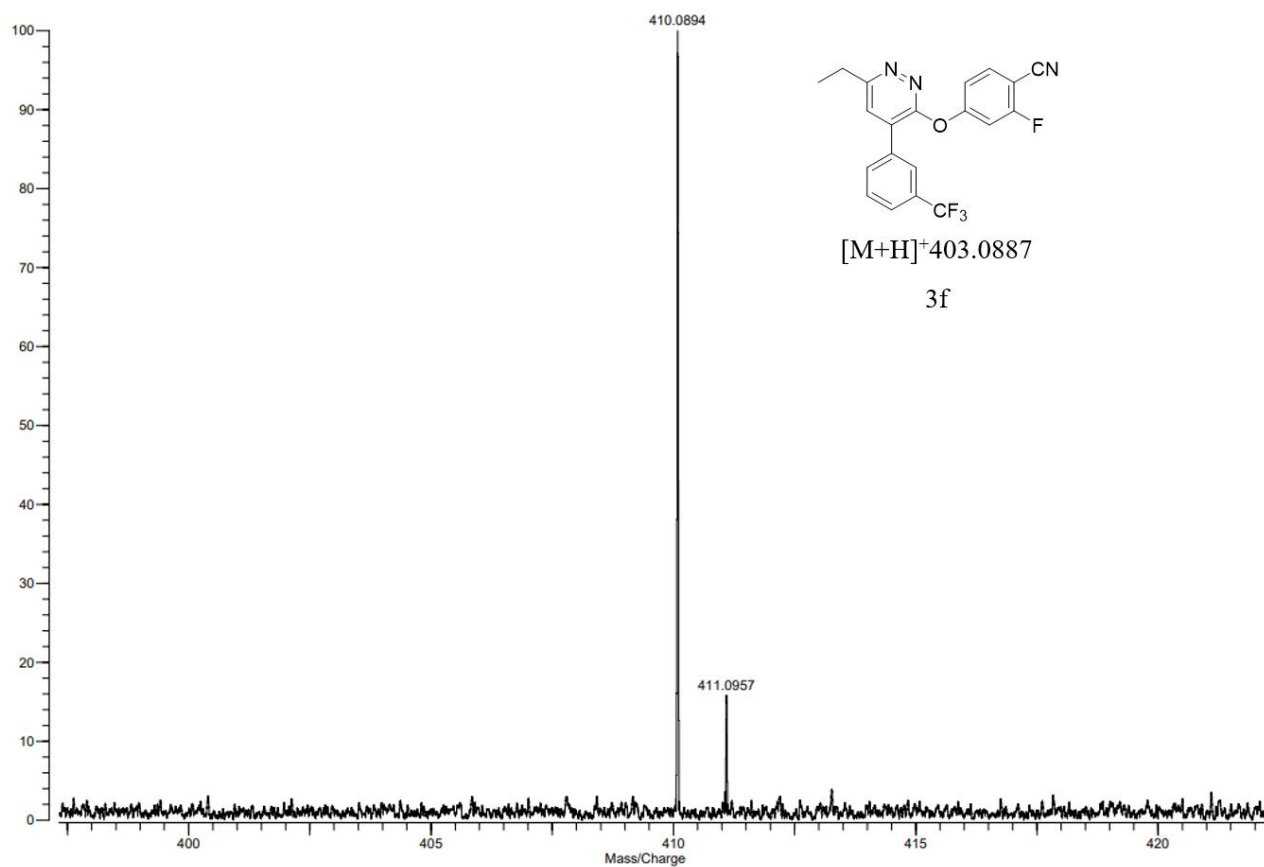




Varian QFT-ESI  
File: Y418\_ESI.trans

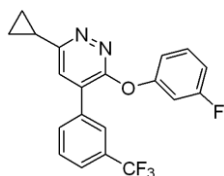
Mode: Positive  
Scans: 1

Date: 03-MAR-2021  
Time: 11:38:48  
Scale: 33.9367

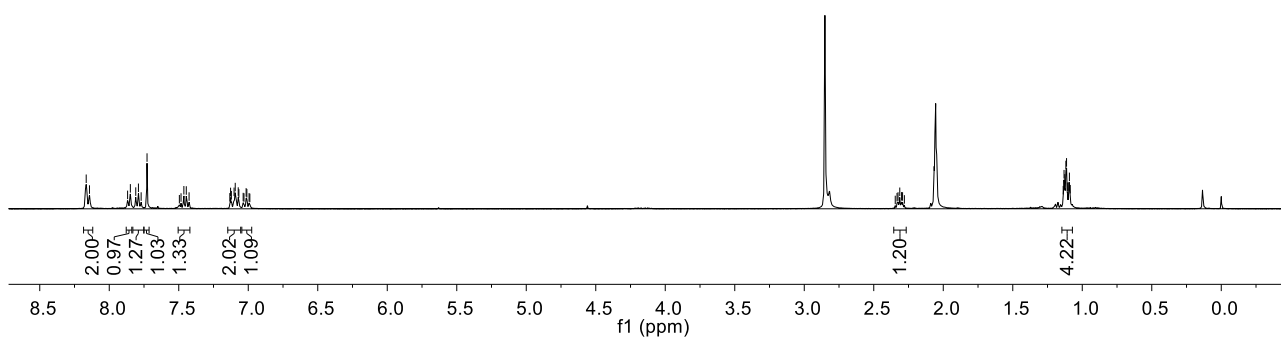


8.17  
8.14  
7.87  
7.85  
7.81  
7.79  
7.77  
7.73  
7.50  
7.48  
7.46  
7.45  
7.43  
7.13  
7.13  
7.12  
7.10  
7.09  
7.07  
7.07  
7.04  
7.03  
7.02  
7.01  
6.99

2.35  
2.33  
2.33  
2.31  
2.30  
2.29  
2.28  
1.14  
1.13  
1.13  
1.12  
1.11  
1.11  
1.10  
1.09  
1.09

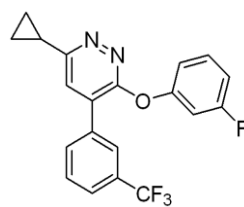


**4b**

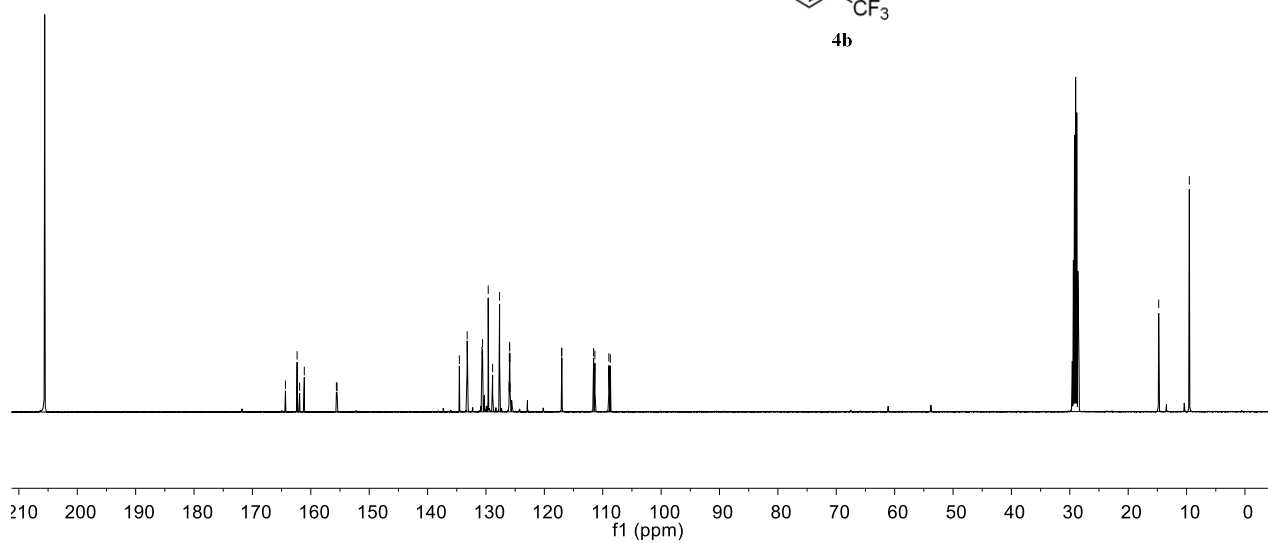


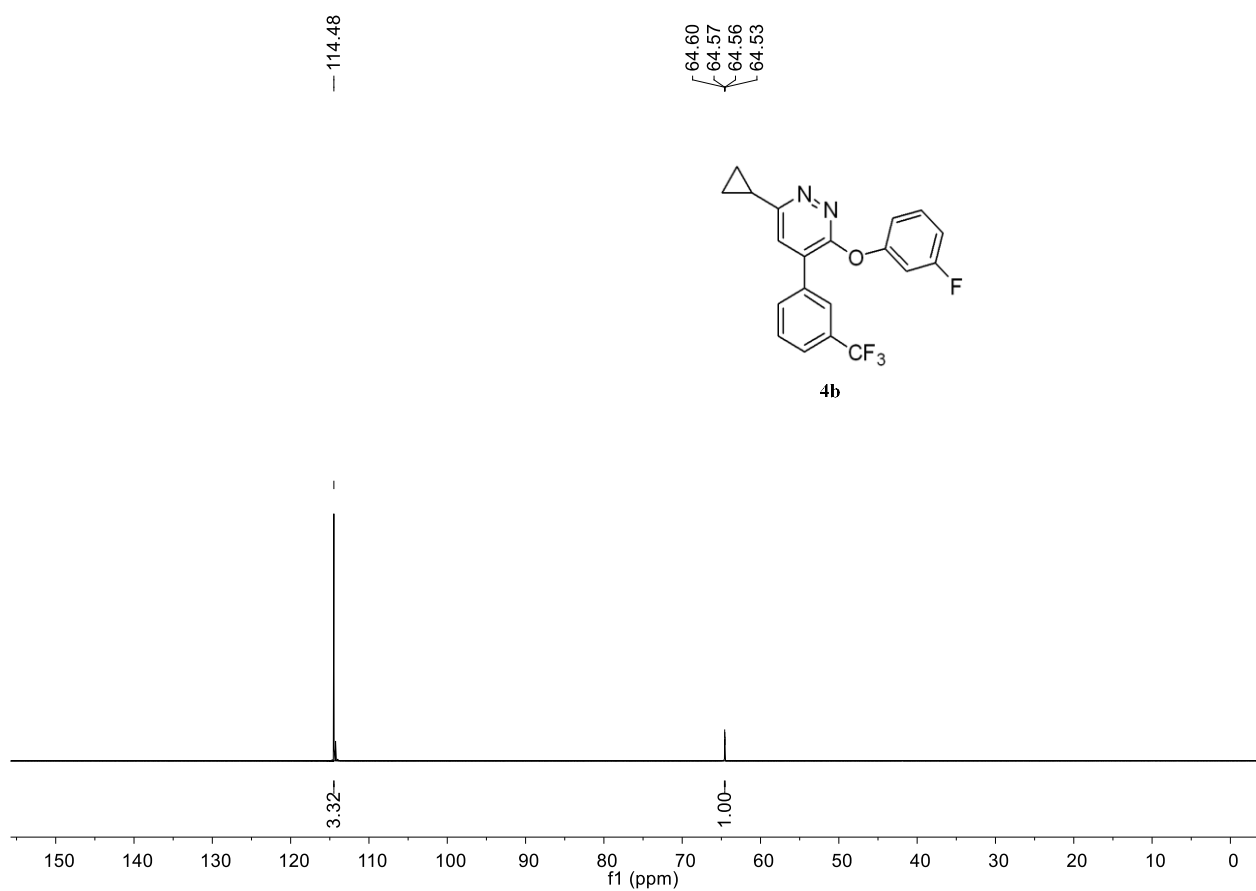
164.35  
162.35  
161.91  
161.11  
155.62  
155.51  
133.22  
130.69  
130.59  
129.61  
127.67  
125.97  
125.62  
125.02  
117.01  
111.56  
111.34  
108.94  
108.70

14.77  
9.53



**4b**

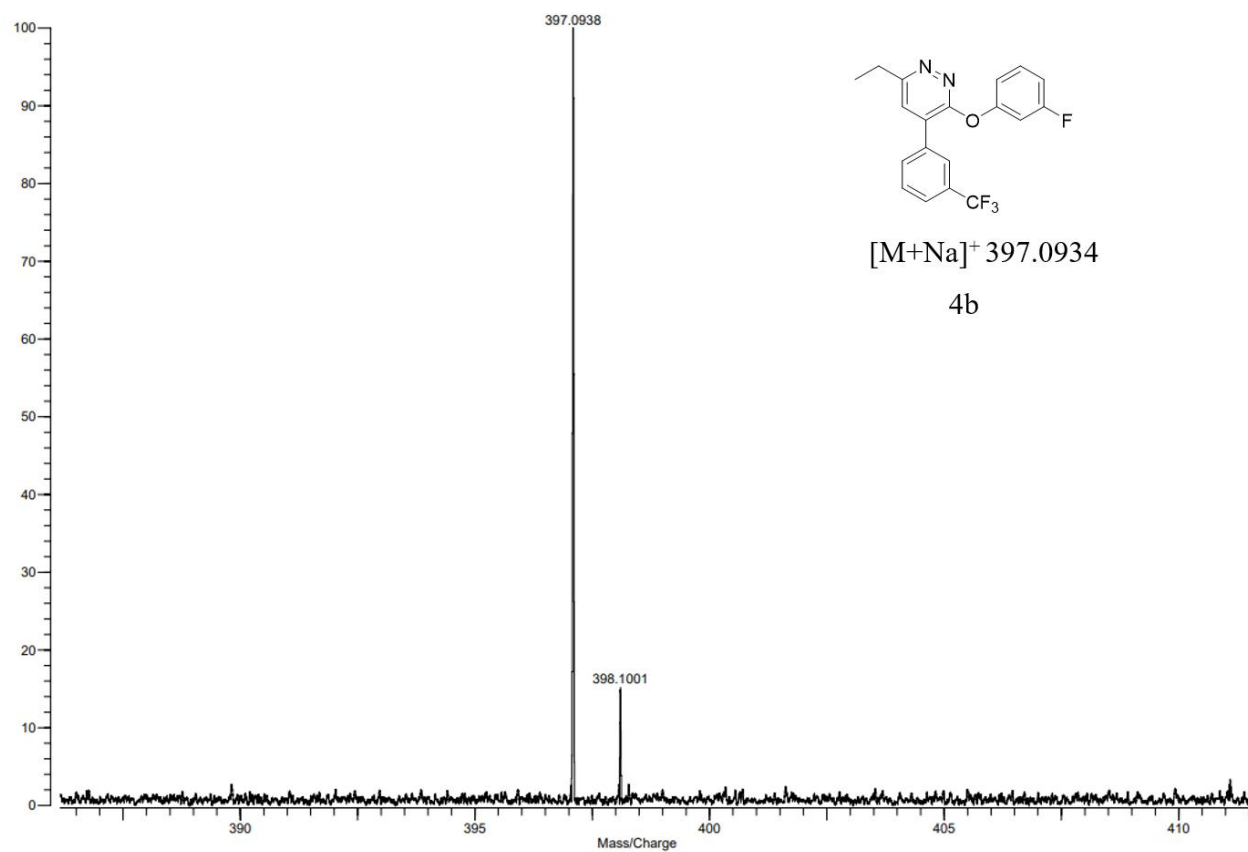


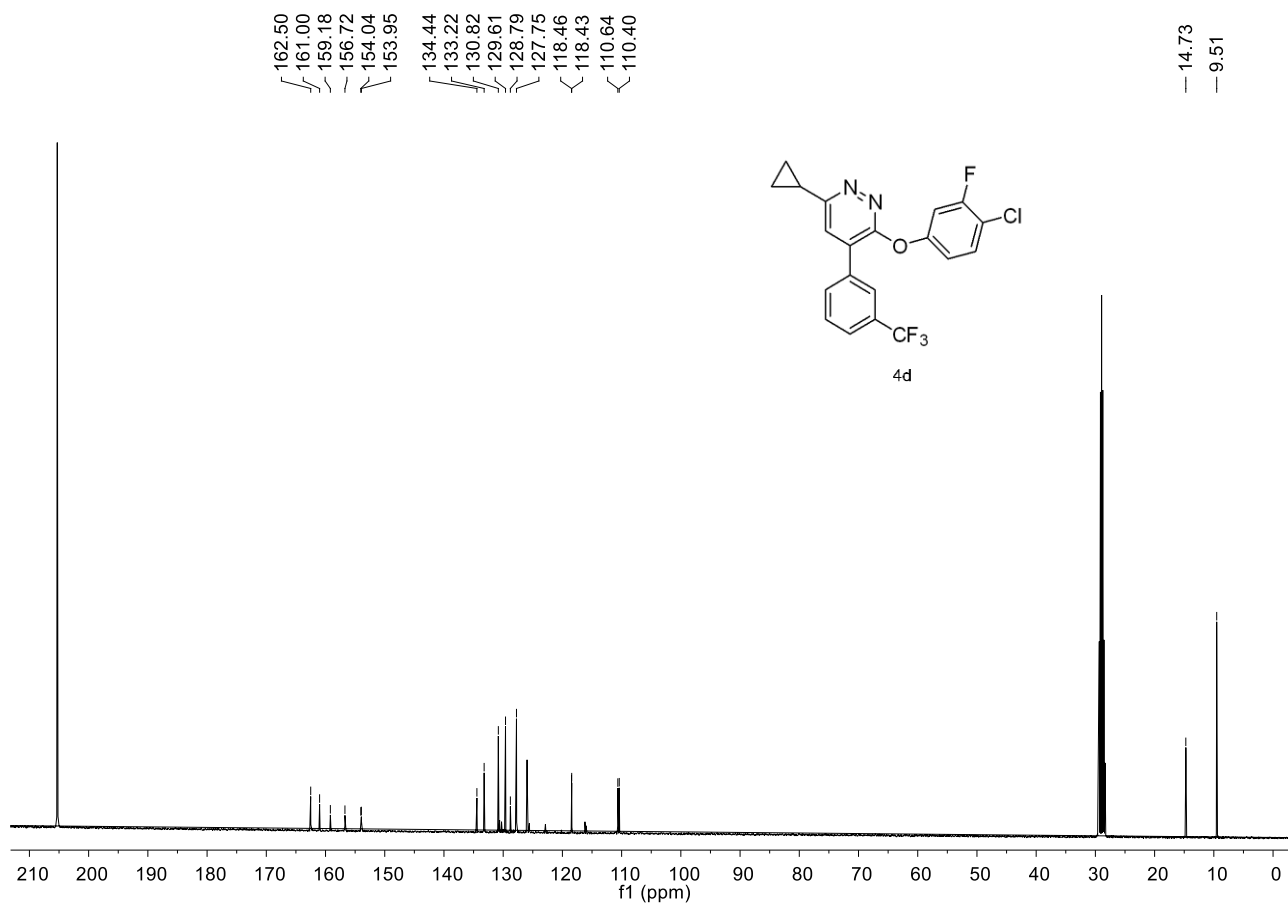
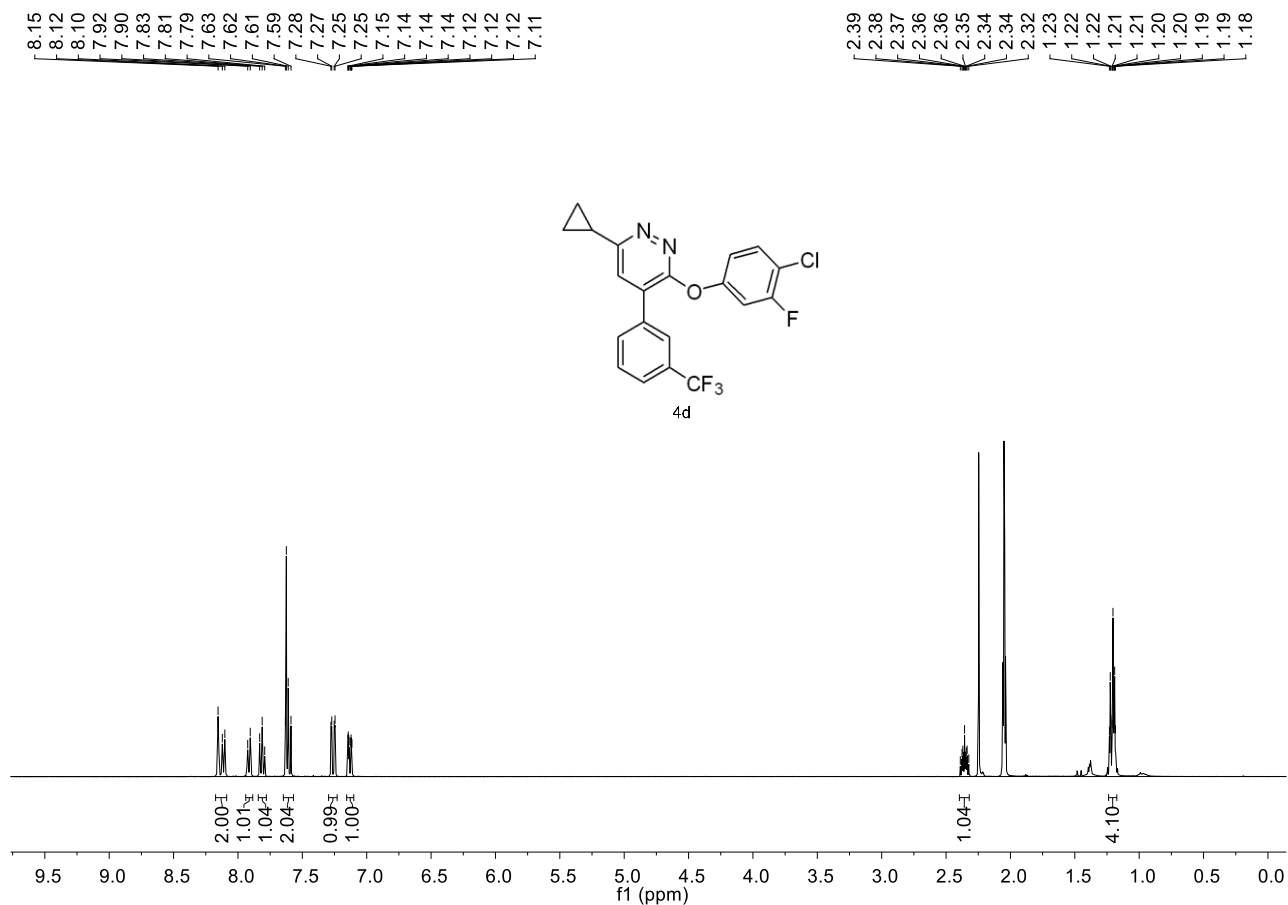


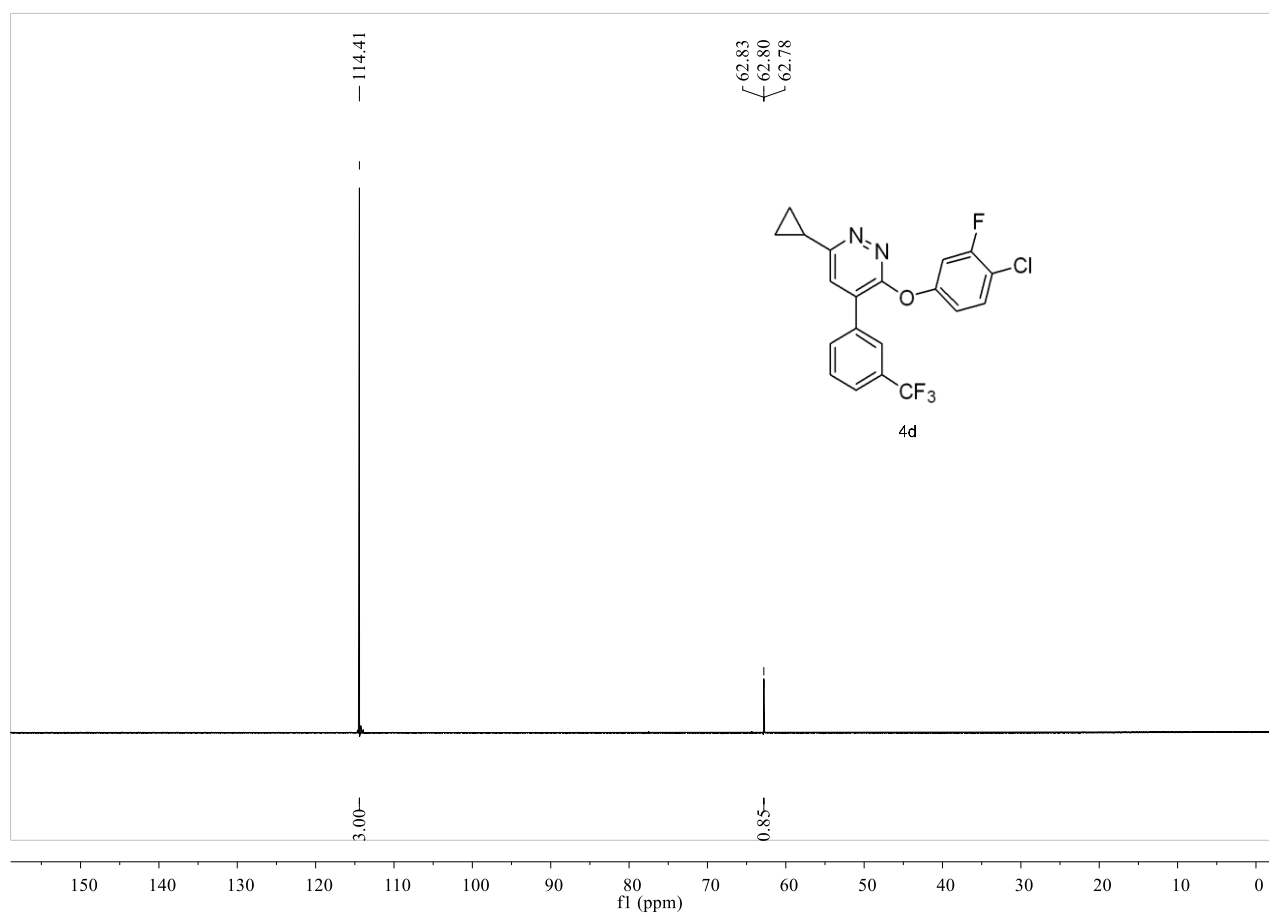
Varian QFT-ESI  
File: Y320\_ESI.trans

Mode: Positive  
Scans: 1

Date: 03-MAR-2021  
Time: 10:25:03  
Scale: 24.9858

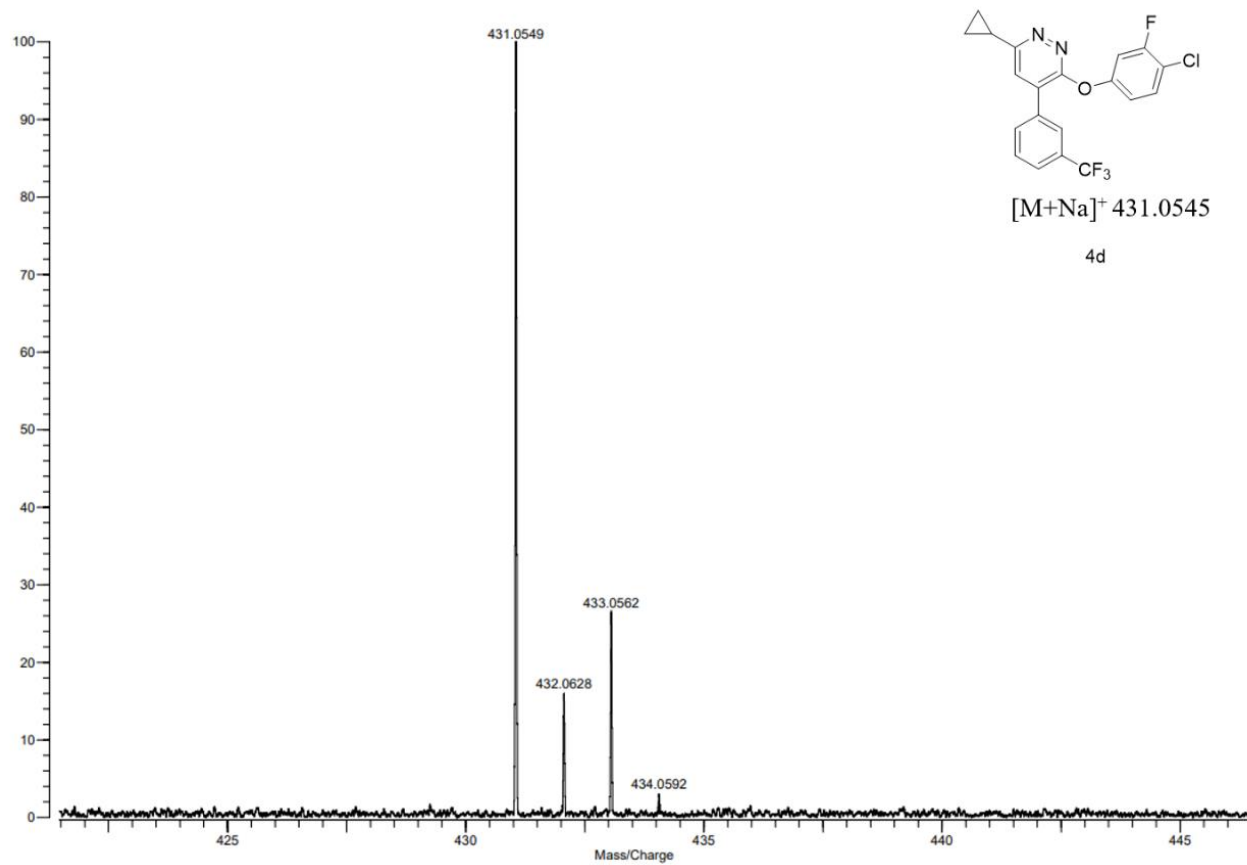




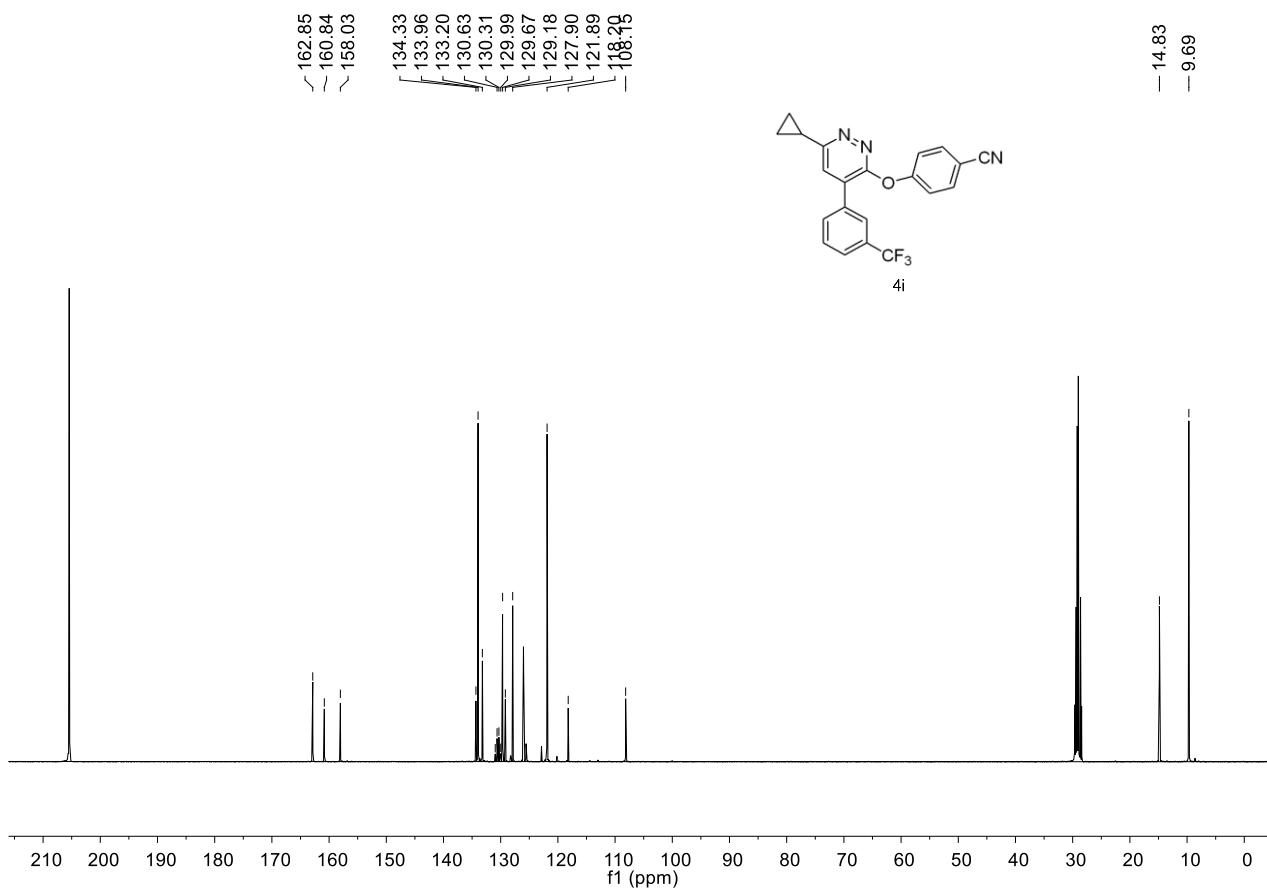
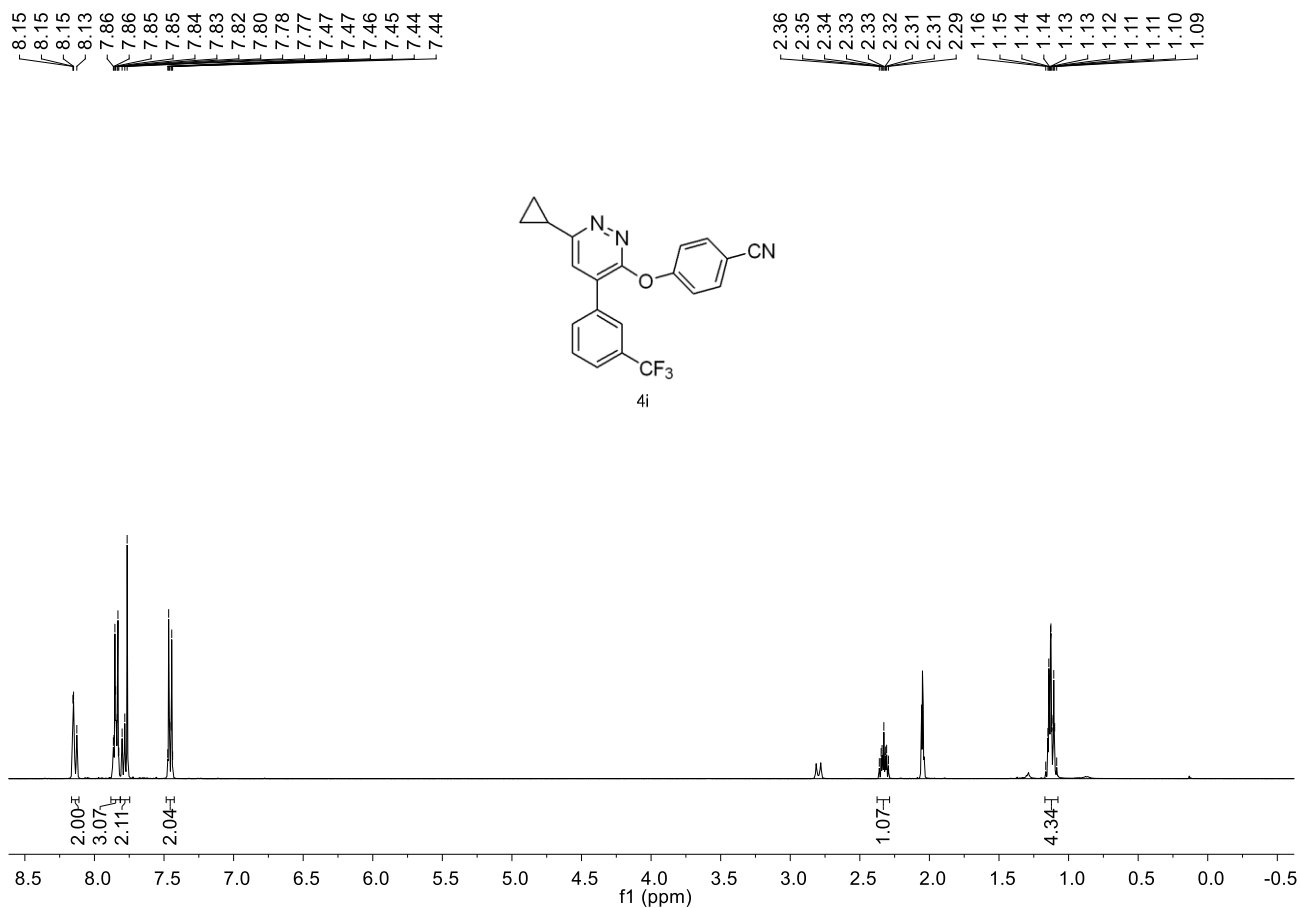


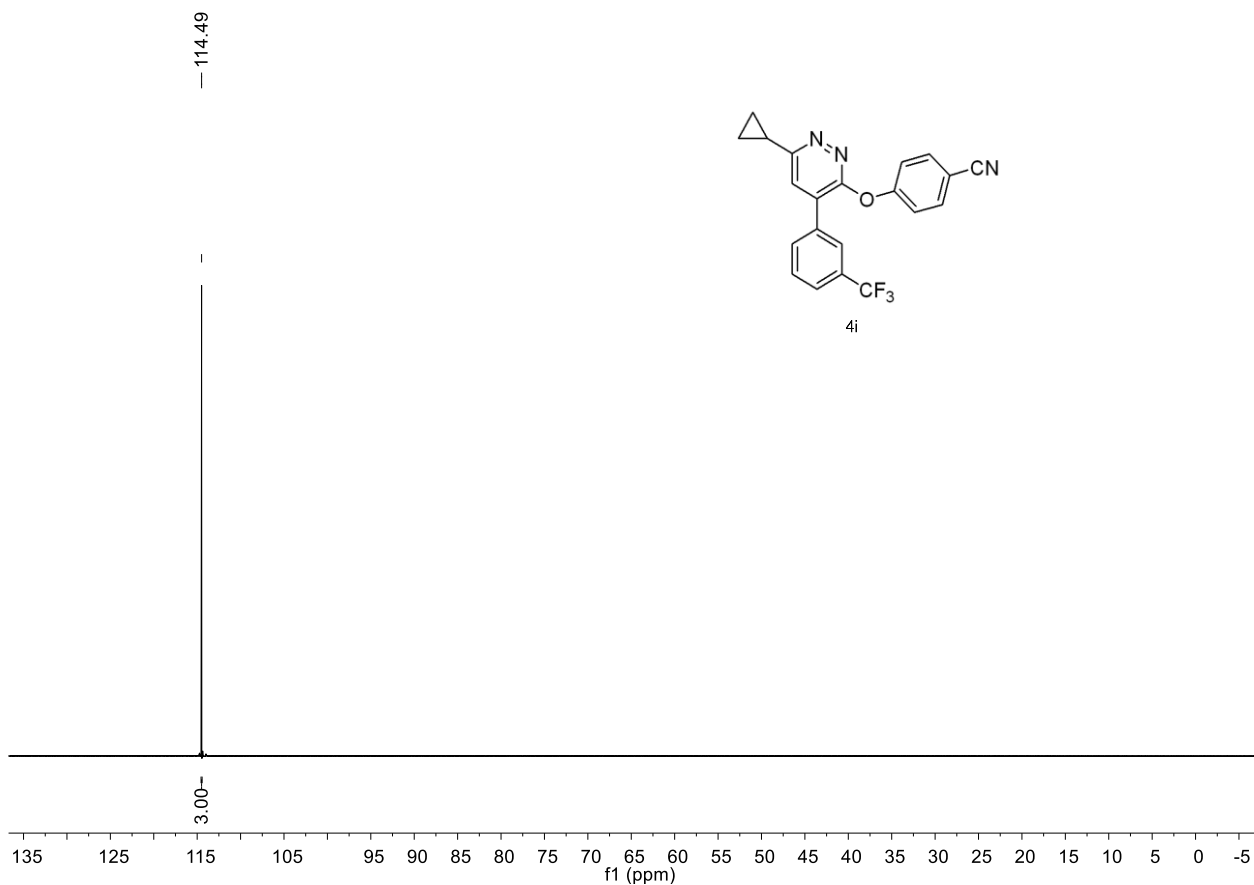
Mode: Positive  
Scans: 1

Date: 03-MAR-2021  
Time: 10:34:15  
Scale: 16.4096



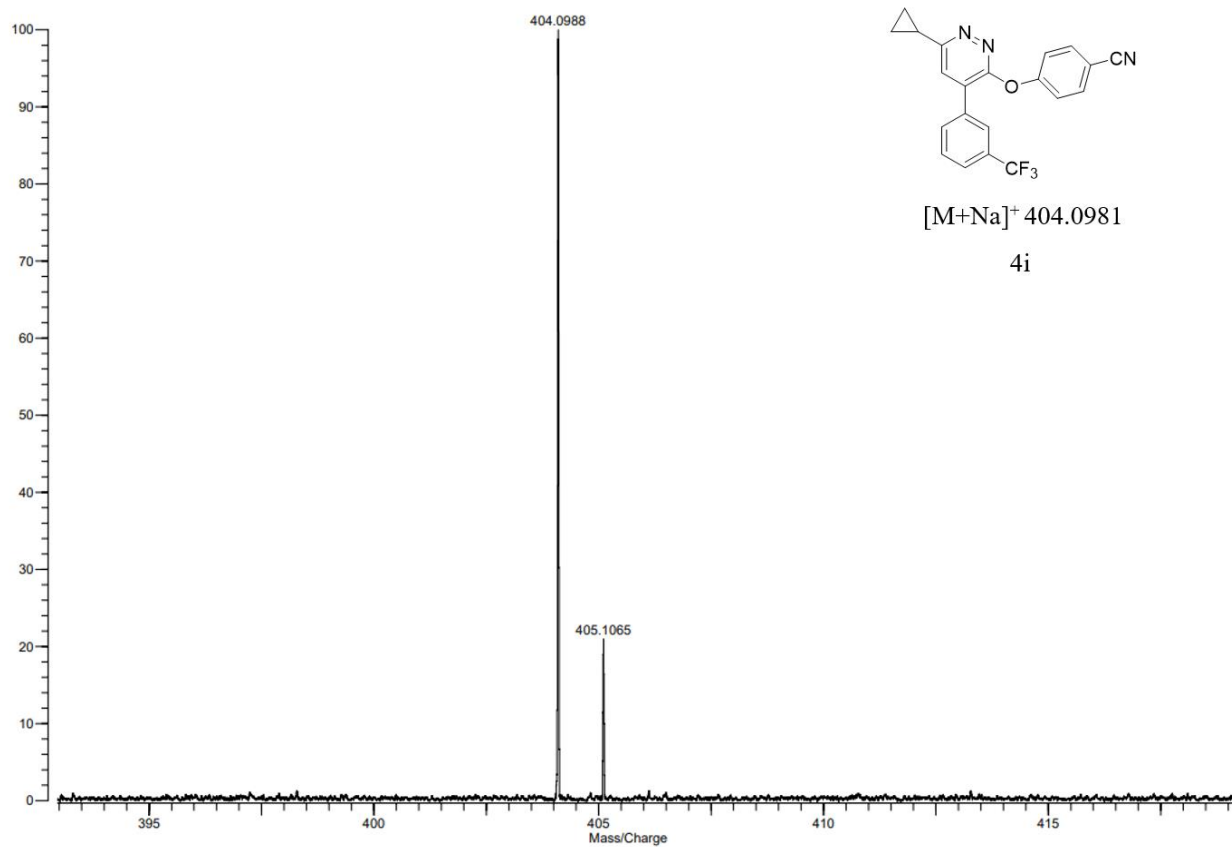


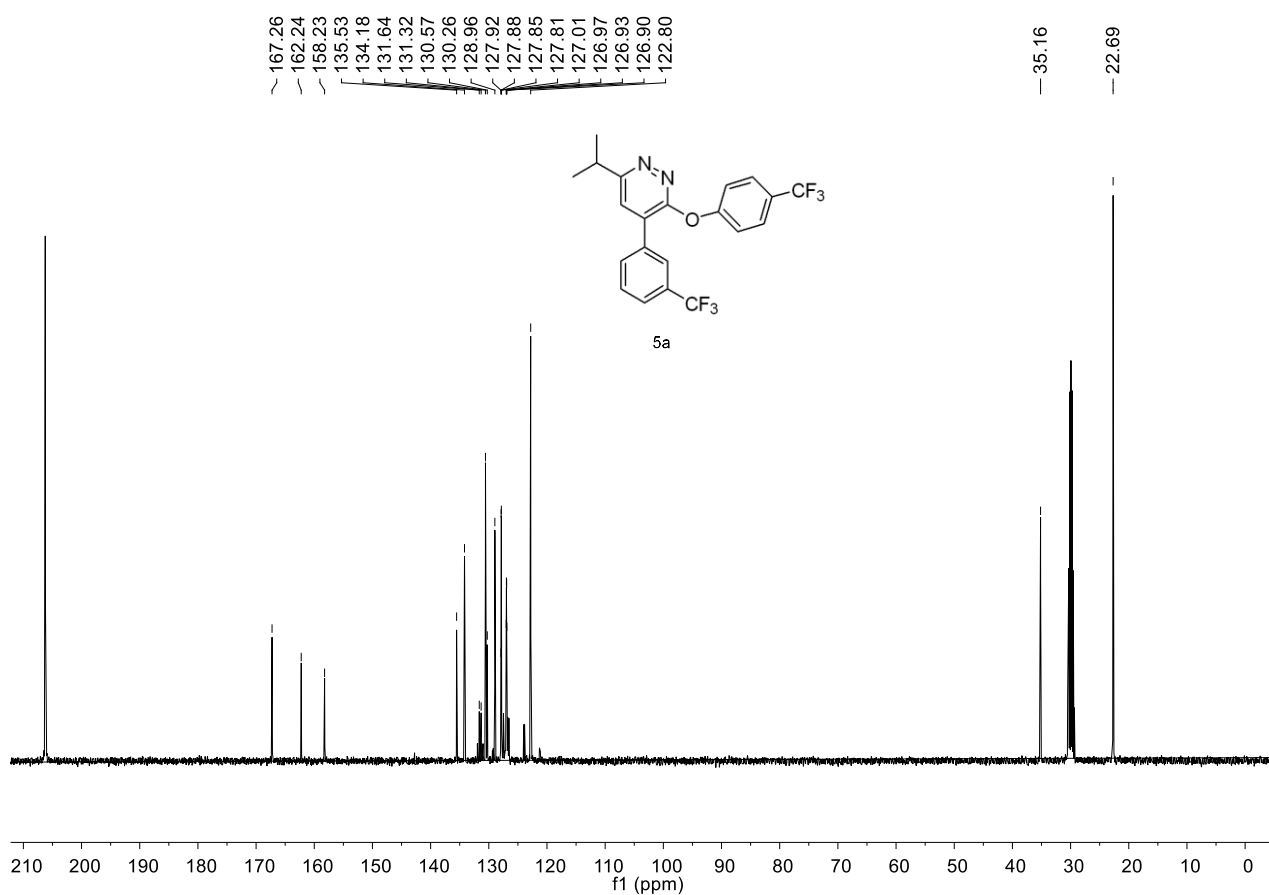
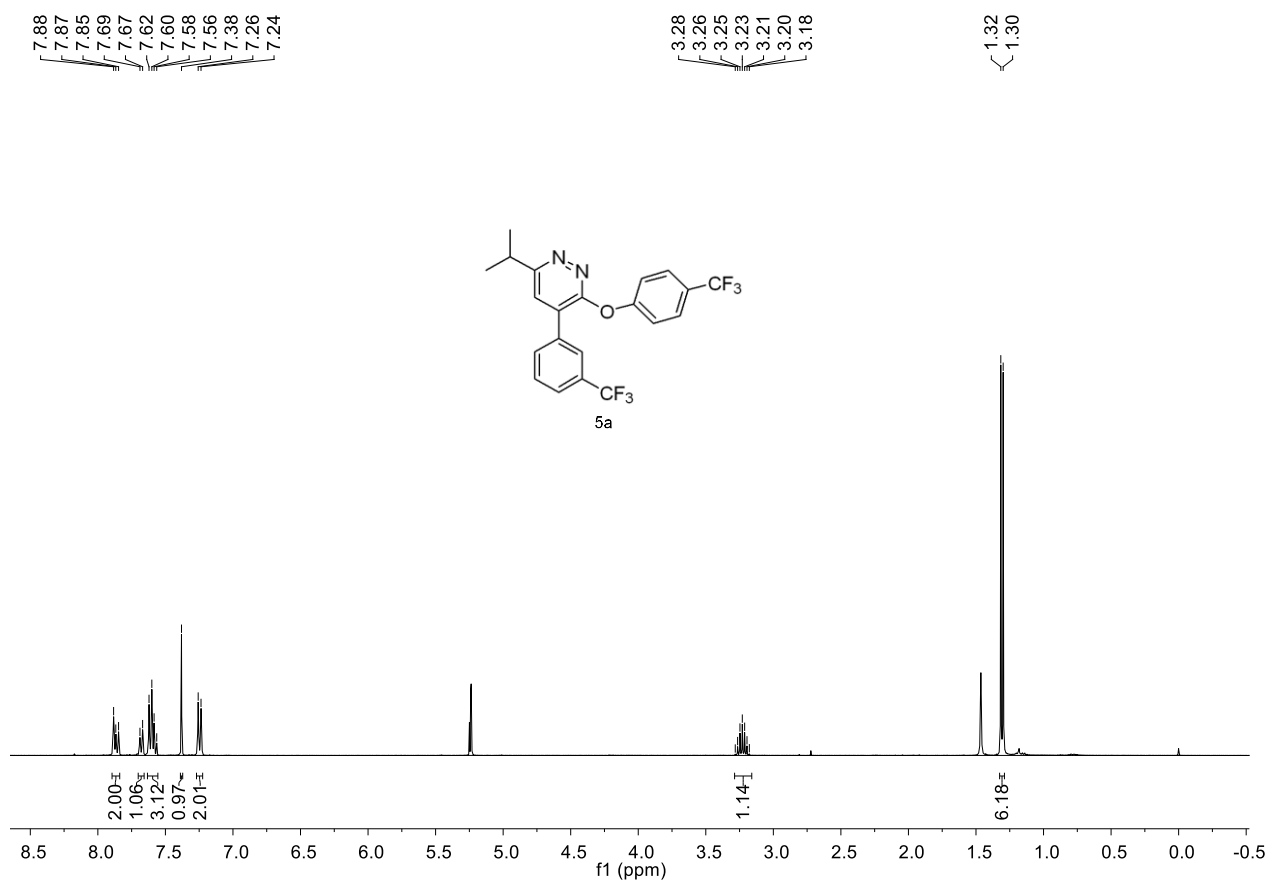


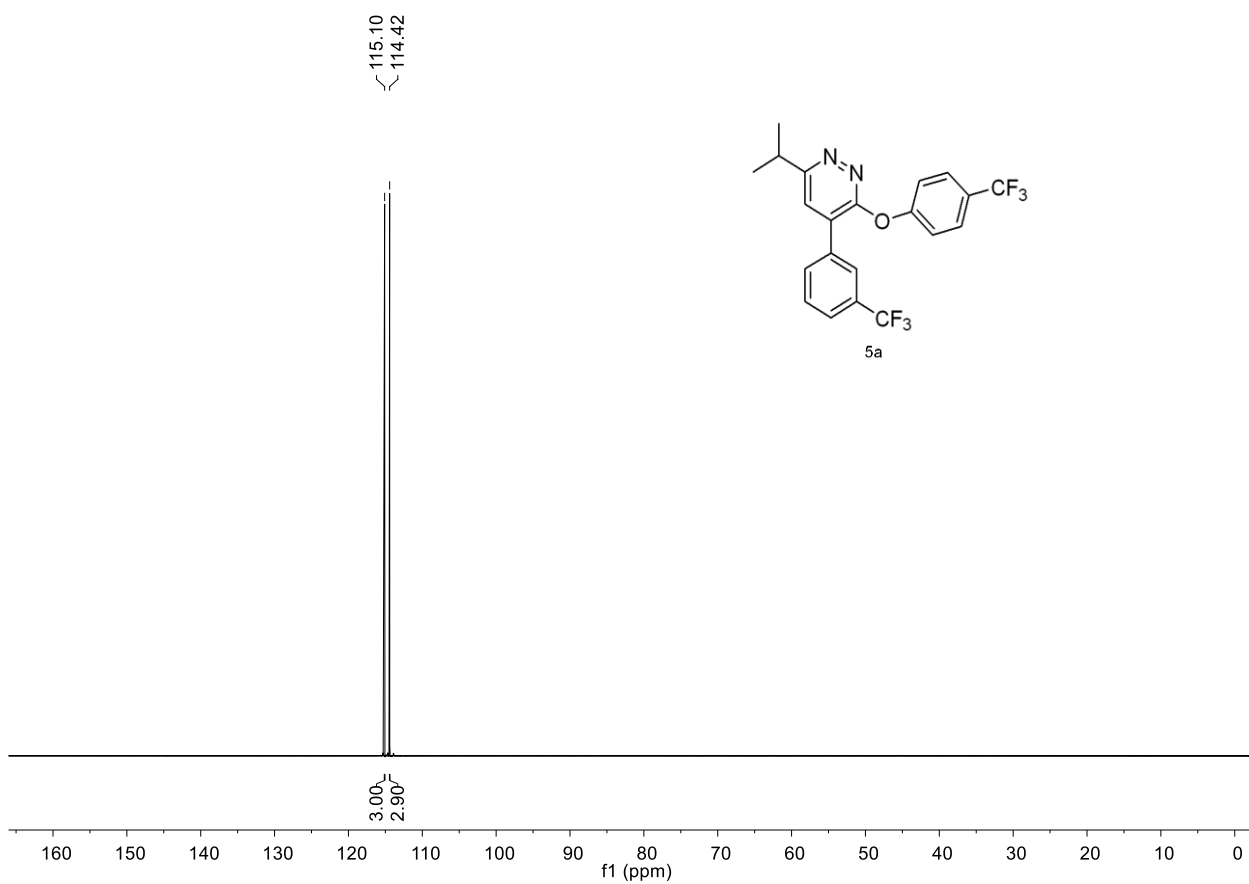


Varian QFT-ESI  
File: Y301\_ESI.trans

Mode: Positive Date: 03-MAR-2021  
Scans: 1 Time: 09:27:54  
Scale: 10.7201



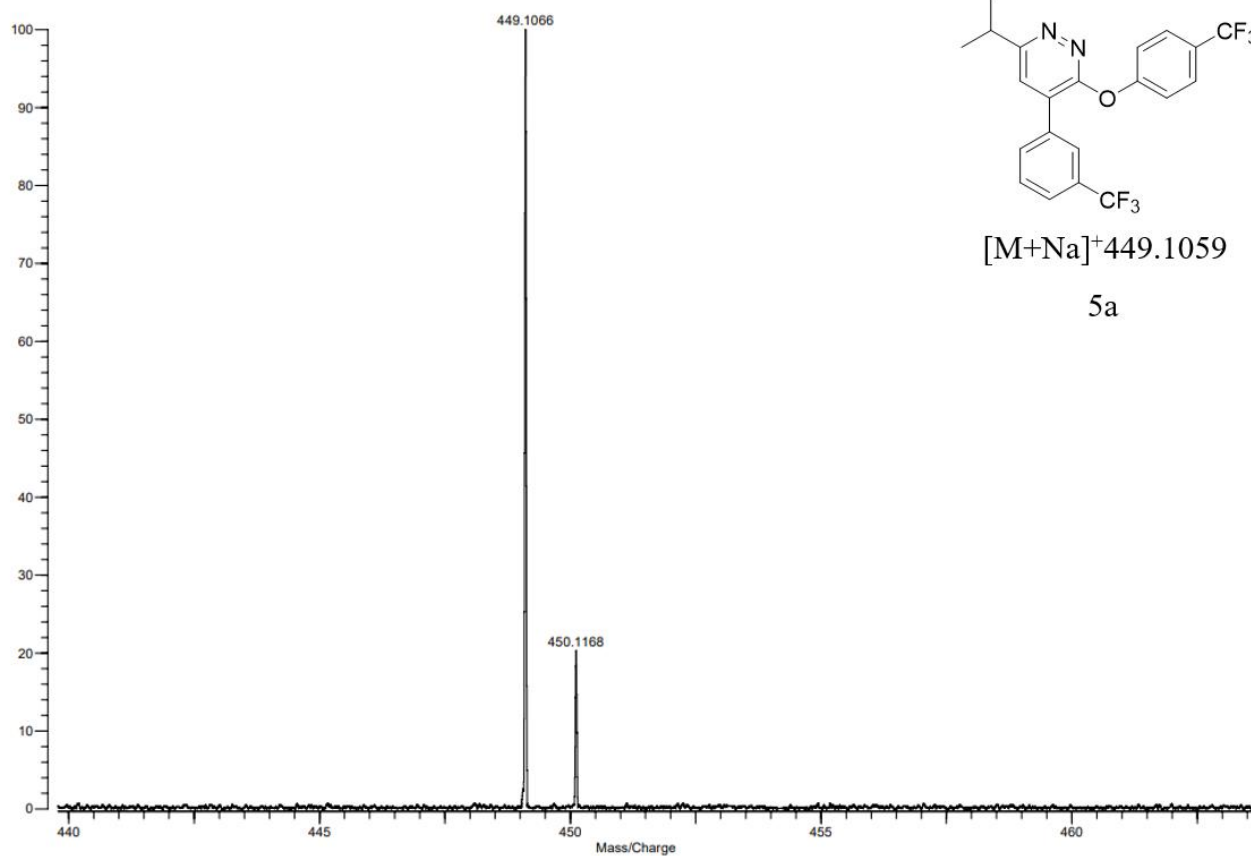


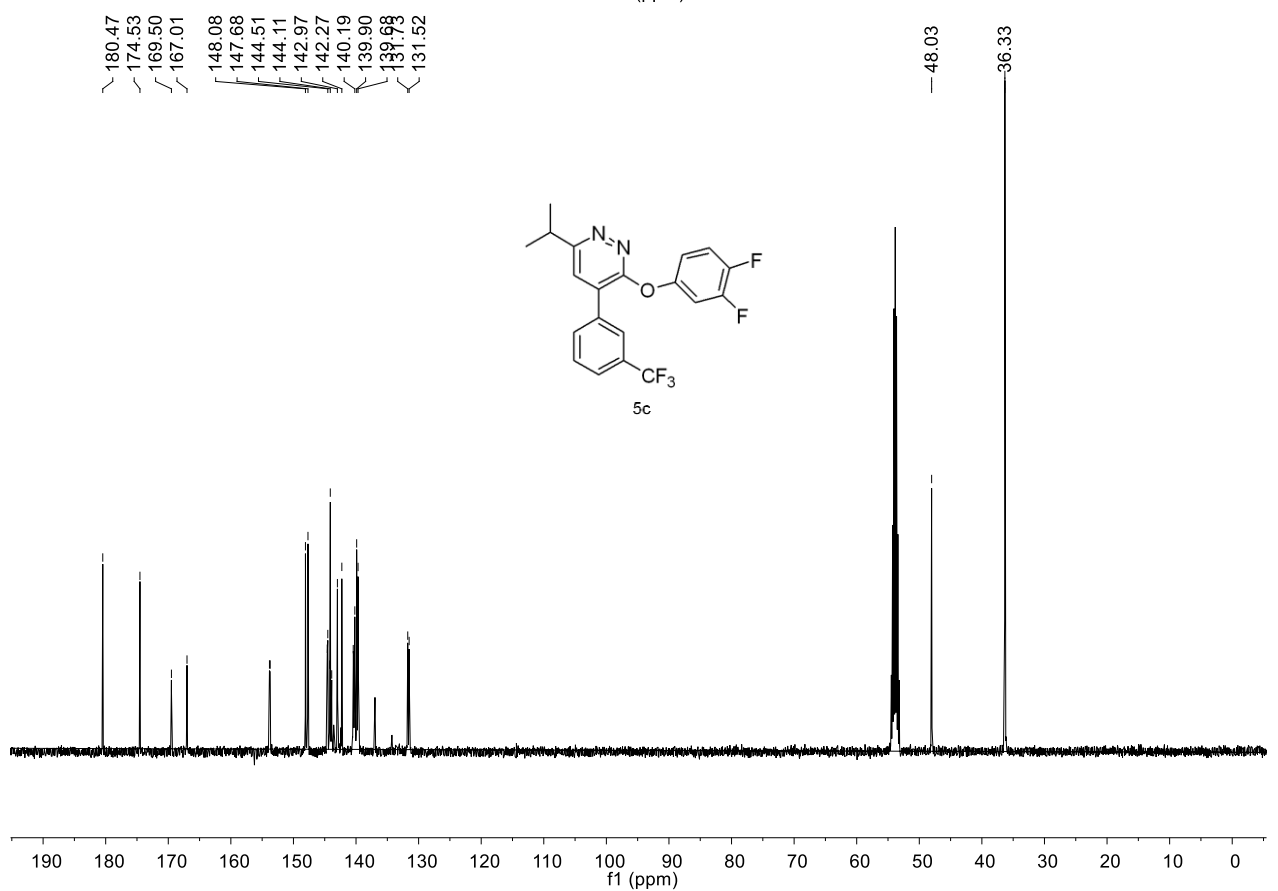
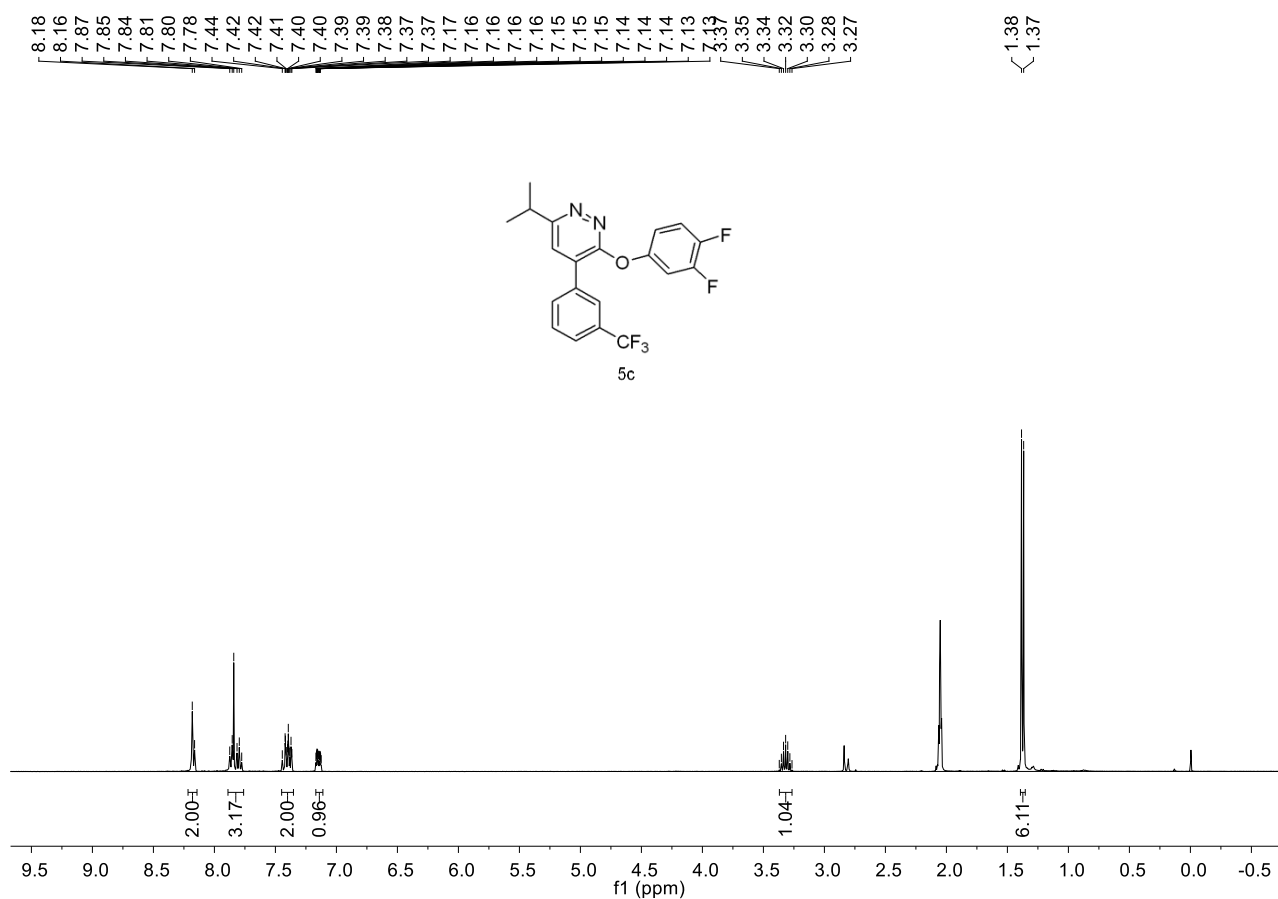


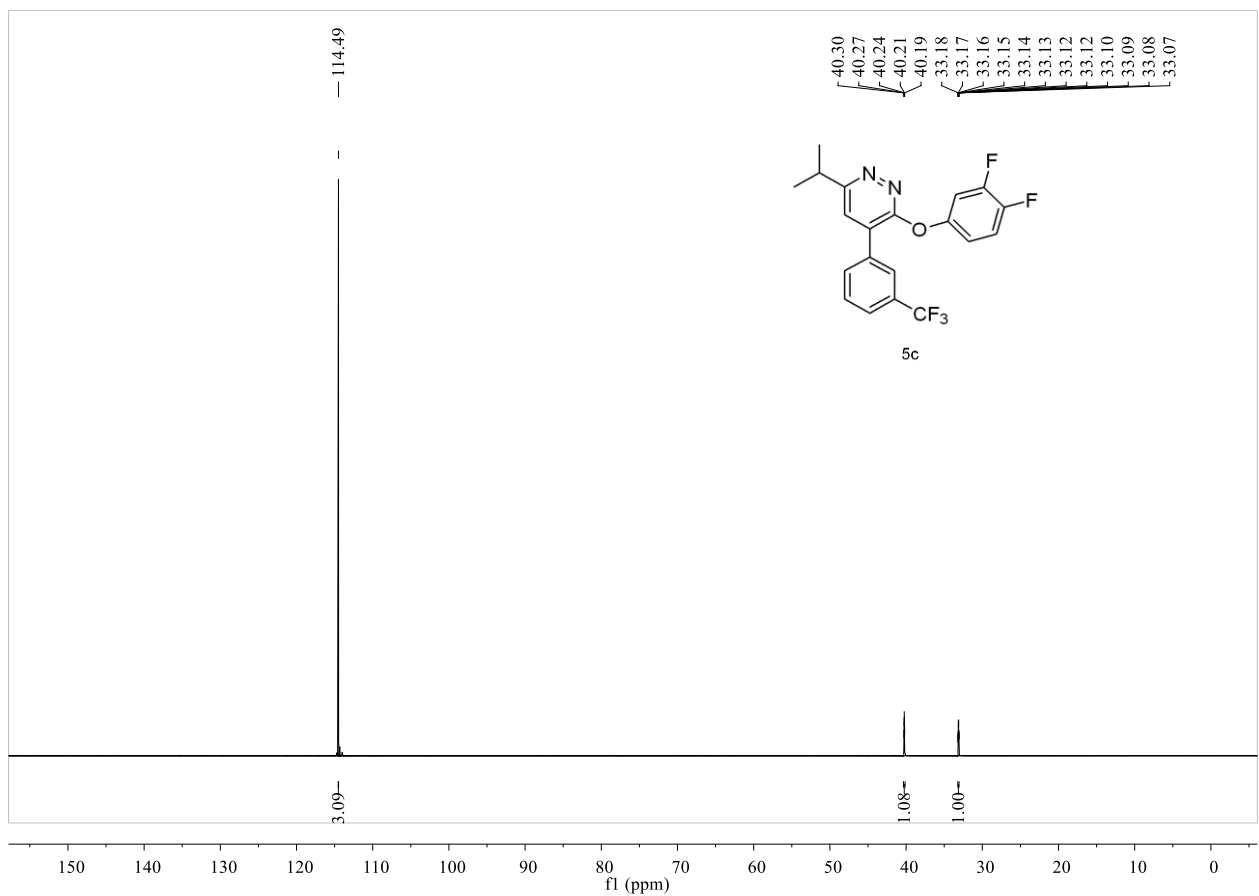
Varian QFT-ESI  
File: Y209\_ESI.trans

Mode: Positive  
Scans: 1

Date: 03-MAR-2021  
Time: 09:05:57  
Scale: 7.6681

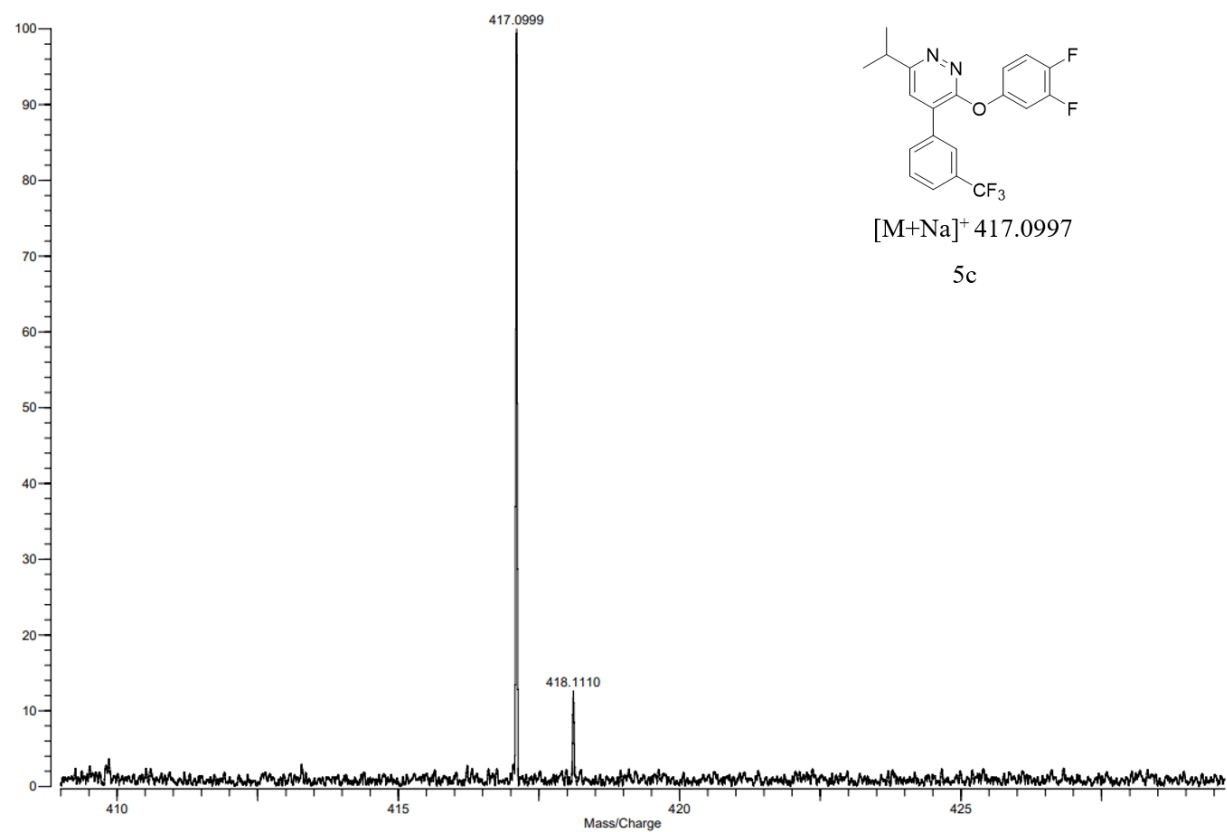


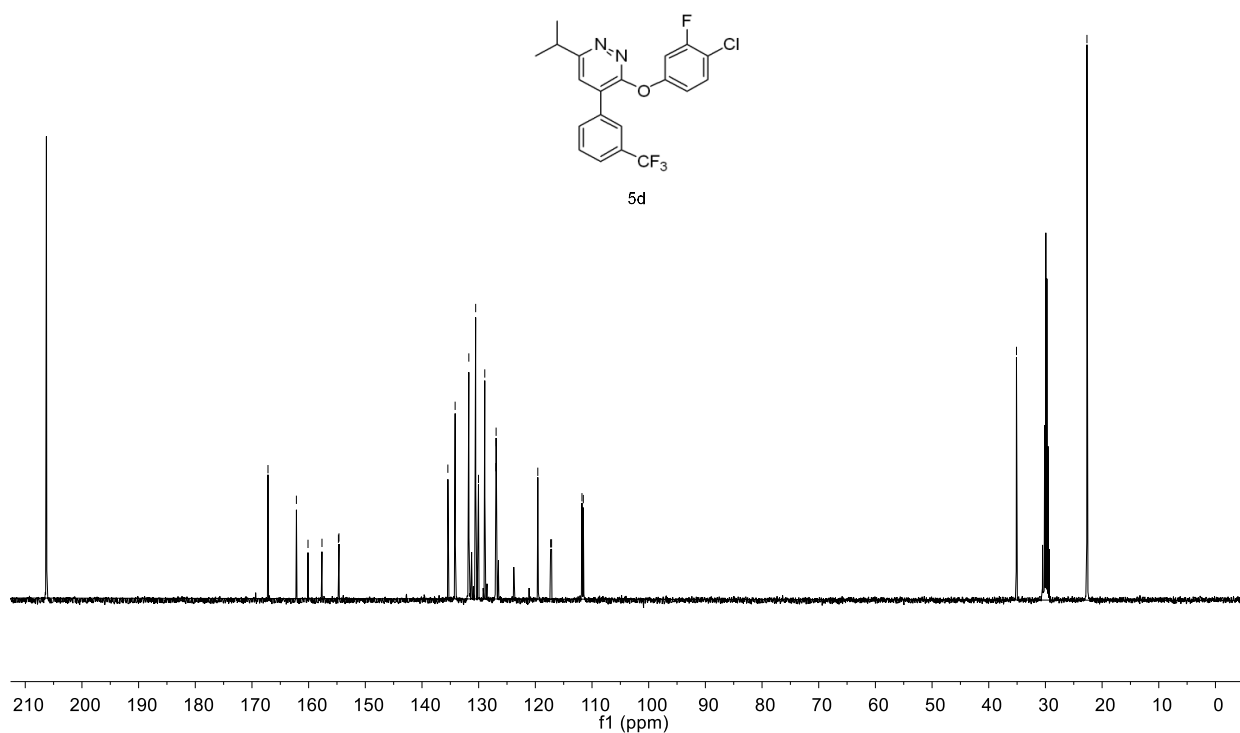
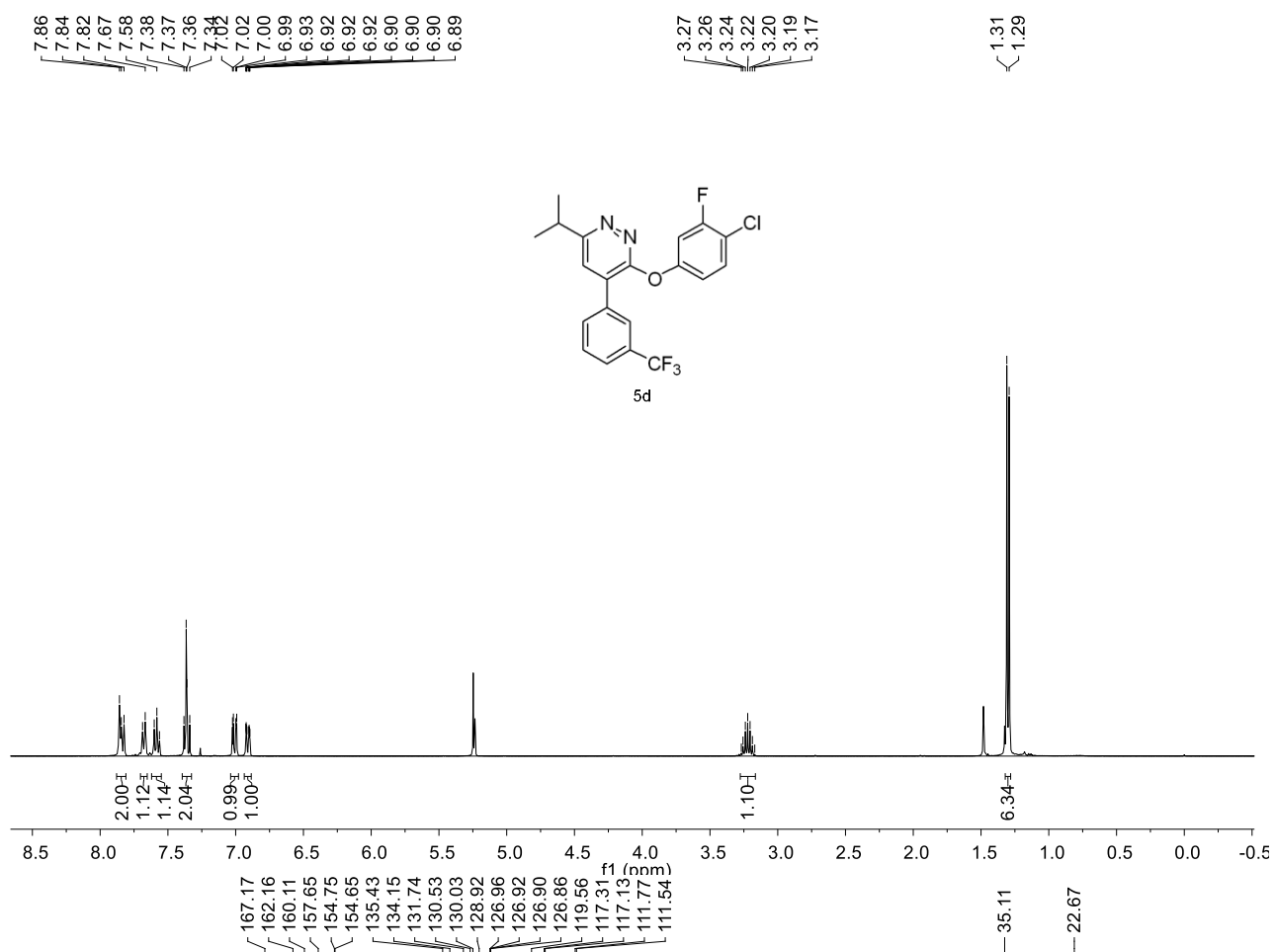


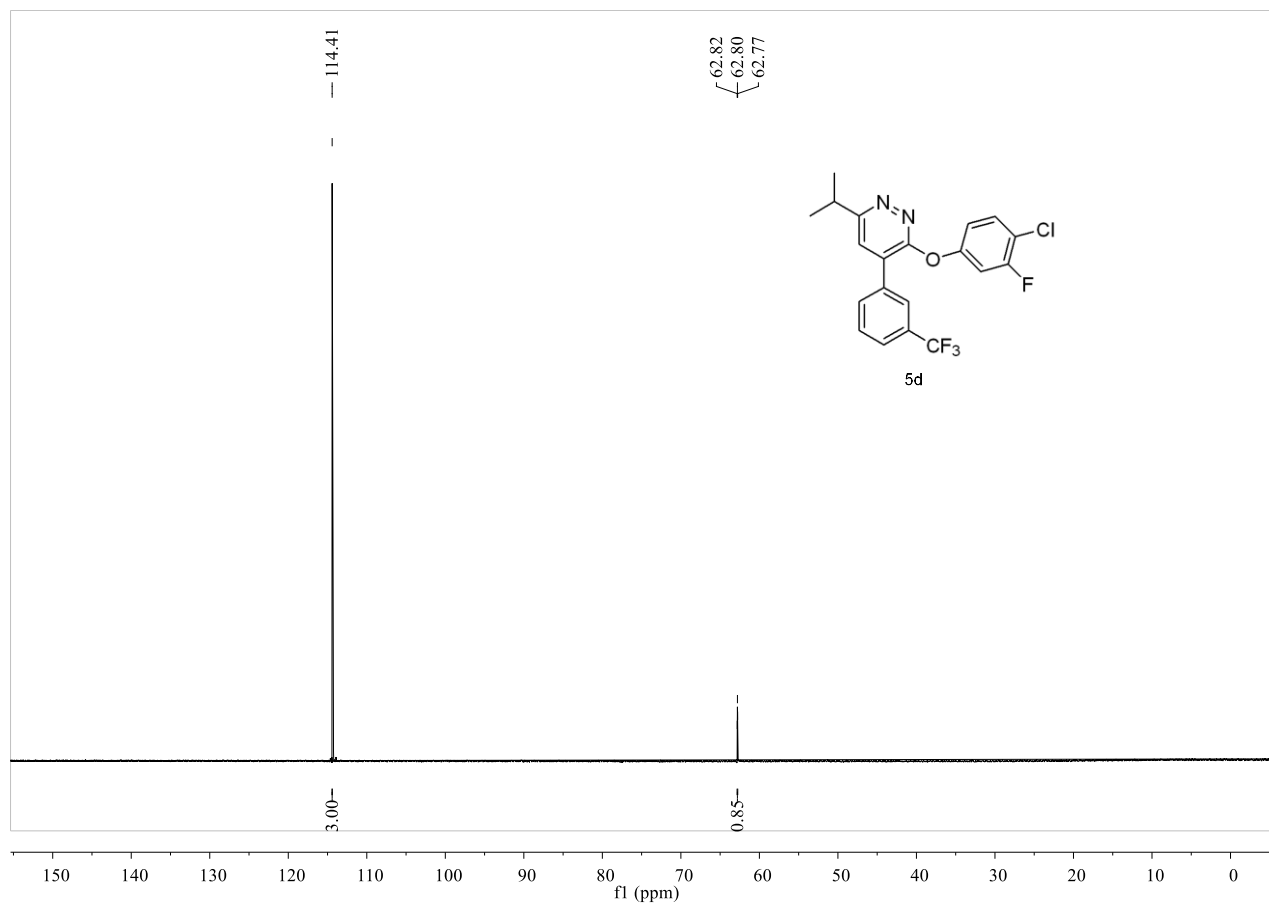


Varian QFT-ESI  
File: Y202\_ESI.trans

Mode: Positive  
Scans: 1  
Date: 03-MAR-2021  
Time: 09:02:18  
Scale: 30.2196







Varian QFT-ESI  
File: Y230\_ESI.trans

Mode: Positive  
Scans: 1

Date: 03-MAR-2021  
Time: 09:11:10  
Scale: 15.3644

